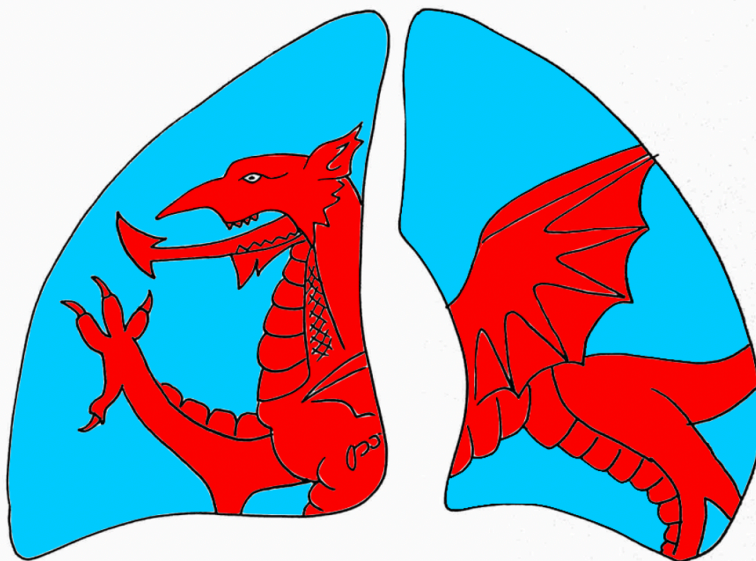


# LUNG HEALTH CHECK



**WALES**

## SCOPING REPORT

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## INTRODUCTION

Over recent years the body of evidence in favour of targeted lung cancer screening with low-dose CT has grown, accompanied by enthusiasm for its introduction as part of a broader “Lung Health Check”. Major developments in the last eighteen months have included the publication of a second large randomised controlled trial demonstrating a reduction in lung cancer mortality with targeted low-dose CT screening, and Lung Health Check programmes commencing in England following promising pilot projects.

There is currently no Lung Health Check or lung cancer screening activity underway in Wales. In 2019, the Cancer Implementation Group commissioned a scoping project to review the evidence on lung cancer screening and Lung Health Checks, to learn from activities already underway in England, and to consider the challenges of commencing a Lung Health Check programme in Wales.

The scoping project commenced in September 2019 and proceeded at pace during its first six months, with the team attending several screening conferences and events, holding a stakeholder engagement day at the Life Sciences Hub in Cardiff Bay in December 2019, and developing links with key contacts in the lung cancer screening community elsewhere in the UK. Unfortunately the COVID-19 pandemic has disrupted several further activities that were planned: visits to Lung Health Check sites in England were cancelled as their programmes were put on hold, and members of the scoping team had to prioritise pandemic-related work during the peak of the crisis.

Nevertheless, the reasons for undertaking this scoping project remain highly relevant. Lung cancer is a major health burden in Wales, and a proactive approach to finding cases at an earlier stage is needed in order to improve outcomes. This scoping report describes the current health burden of lung cancer in Wales, the evidence surrounding lung cancer screening and Lung Health Checks, the potential impact and challenges of delivering a national Lung Health Check programme in Wales, and some suggestions for the next steps to be taken.

## DECLARATION OF INTERESTS

Dr Sinan Eccles is a Consultant Respiratory Physician at Royal Glamorgan Hospital. He has no relevant financial or non-financial conflicts of interest to declare relating to this work.

Claire Wright and Roya Yadollahi have no conflicts of interest to declare.

## EXECUTIVE SUMMARY

1. Lung cancer is the leading cause of cancer death in Wales. The majority of cases present with late-stage disease. Lung cancer outcomes are worse in Wales than the rest of the UK and much of Europe.
2. The National Lung Screening Trial (NLST) and NELSON are two large randomised controlled trials demonstrating a 20% or greater relative reduction in lung cancer mortality with low-dose CT (LDCT) screening in high-risk individuals. NLST also found a 6.7% relative reduction in all-cause mortality: this is the only randomised controlled trial focussed on a single cancer site to find a difference in all-cause mortality with screening.
3. NLST raised concerns regarding high rates of overdiagnosis and false-positive findings with LDCT screening. Modern protocols for the surveillance of indeterminate pulmonary nodules reduced the overdiagnosis rate in NELSON to less than 10% at 11 years of follow-up, and only 1.2% of participants had a false-positive scan result.
4. The UK Lung Screening Trial was a smaller randomised controlled trial not powered to detect differences in mortality. Over 85% of the lung cancers detected by LDCT screening were stage 1 or 2, and 83% underwent surgical treatment. In comparison, only 29% of lung cancers in Wales present with stage 1 or 2 disease.
5. Lung Health Checks (LHCs) are a targeted health intervention which include LDCT screening for lung cancer, case-finding of chronic obstructive pulmonary disease (COPD) with spirometry, and smoking cessation interventions for current smokers. Co-delivering these interventions to high-risk individuals is likely to be more cost-effective than delivering them separately.
6. LHC pilot projects undertaken in England have had promising results, including a large proportion of the lung cancers detected being at an early stage and undergoing surgical resection. The inclusion criteria and delivery of these programmes has varied.
7. In 2019, NHS England began a Targeted LHC programme in multiple areas of England. Men and women aged 55-74 years who have ever smoked are identified from primary care records and invited for a LHC. Risk tools are used to determine an individual's future risk of lung cancer, with those at highest risk offered a LDCT scan. Participants are invited for a scan two years after the baseline scan, and for intervening scans if indeterminate pulmonary nodules are found on the baseline scan. The programme was due to complete in 2023, though this is likely to be delayed in light of the COVID-19 pandemic.
8. Historically, the National Screening Committee (NSC) has made recommendations on population-based screening and NICE has made recommendations on targeted screening. There had been some debate as to which group LHCs/lung cancer screening would fall into. An independent review of screening programmes in 2019 recommended the formation of a new body to make recommendations on both population-based and targeted screening, with LHCs highlighted as a specific topic that the new body should consider.

9. There is limited evidence on the cost-effectiveness of LHCs, though most assessments based on the UK healthcare system have been favourable at usual thresholds used for decision-making. A cost-effectiveness modelling study has been commissioned by the NSC, and is likely to influence future recommendations following its planned publication in summer 2021.
10. LHC programme delivery has varied with differences including: the age range for invitation; the criteria for LDCT; whether smoking status is established from primary care records or by contacting the whole population in the target age range; whether participants are assessed by phone initially or if all participants are invited for a face-to-face LHC; and whether additional interventions such as assessment of cardiovascular risk are also undertaken. A programme with wider inclusion criteria and a greater number of interventions will cost more, though could be more cost-effective overall.
11. To be successful, a LHC programme must adhere to the principles of a high-quality screening programme including having robust systems for call and recall systems, governance, quality assurance, data management, and ongoing evaluation.
12. A national LHC programme in Wales using the same parameters as the NHS England programme would have a target population of approximately 380,000 people aged 55-74 years who have ever smoked. Based on modelling data for the first two years, a national programme with 50% uptake would generate approximately 5,000 LDCT scans per month and find approximately 4,100 lung cancers over two years, half of which would undergo surgical treatment. A programme with 50% uptake could prevent over 500 lung cancer deaths during the first 5 years, whilst one with an uptake of 75% could prevent over 800 lung cancer deaths during the first 5 years.
13. The greatest challenges of delivering a national LHC programme in Wales would include: determining how to accurately identify the target population based on their smoking status; engaging and recruiting the target population; providing the reporting capacity for the large number of LDCT scans that would be generated; and ensuring that downstream pathways are prepared to manage the increased case-load and altered case-mix of lung cancer diagnoses. It may be desirable to use different parameters to the NHS England programme in order to manage the volume of LDCT scans generated and ensure that the programme can be delivered successfully.
14. Delivery of a LHC programme in the climate of the COVID-19 pandemic is challenging as cleaning of equipment, social distancing, and the aerosol generation from spirometry would all greatly reduce the number of participants who could be seen each day, thus reducing the cost-effectiveness of the programme. As COVID-19-related restrictions are eased, effective delivery of LHCs should be possible as they were prior to the pandemic.
15. It is likely to be several years before the NSC/proposed new screening body makes recommendations on LHCs/LDCT screening for lung cancer. Whilst awaiting this, it would be desirable for Wales to commence some pilot LHC activity in order to prepare for the implementation of a future national programme.

## WHAT IS THE CURRENT HEALTH BURDEN OF LUNG CANCER IN WALES?

Lung cancer is the most common cause of cancer death worldwide, responsible for over 1.6 million deaths annually.<sup>(1)</sup> In Wales, lung cancer is the third most common cancer in men and the second most common cancer in women, but is the leading cause of cancer death overall accounting for more deaths than breast and colorectal cancer combined (figure 1).<sup>(2)</sup>

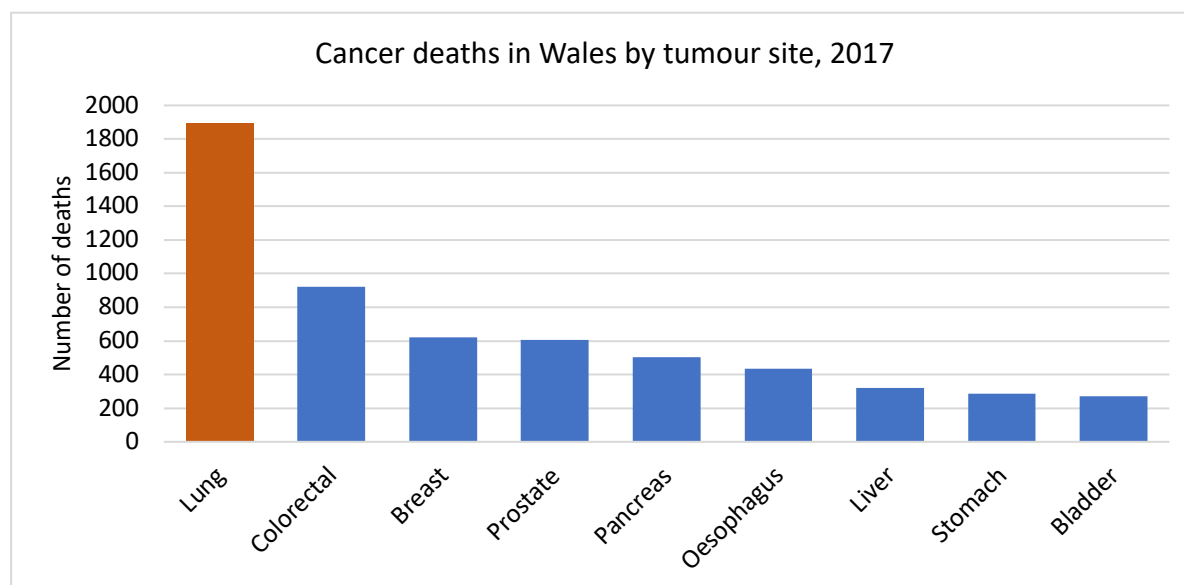


Figure 1: Comparison of deaths due to common cancers in Wales, 2017.

The incidence of lung cancer in Wales is falling in men and rising in women, reflecting the later peak of smoking prevalence in women in the 20<sup>th</sup> century.<sup>(2,3)</sup> The combined age-standardised rate of lung cancer per 100,000 population in Wales has remained stable over recent years,<sup>(2)</sup> but the number of diagnoses per year is rising (figure 2).<sup>(4)</sup>

Lung cancer prognosis is strongly linked to stage of disease at diagnosis (figure 3). Between 2013-2017 there were almost 11,000 lung cancer diagnoses in Wales.<sup>(4)</sup> Over 8000 of these (71%) had stage 3 or 4 disease where curative treatment is rarely possible. One-year survival for patients with stage 4 lung cancer was 15% in the same period. In comparison, only 17% of cases were diagnosed with stage 1 lung cancer which offers the best chance of curative treatment; one-year survival for this group was 78%.

Survival from lung cancer is poor in comparison to almost all other types of cancer.<sup>(2)</sup> In Wales, approximately half of people with lung cancer die within six months of diagnosis, and almost three-quarters die within twelve months.<sup>(2)</sup> Only 6.5% of patients are alive five years after diagnosis. Survival from lung cancer in the UK is poor compared to other high-income countries,<sup>(5)</sup> with little improvement seen over the last 40 years.<sup>(6)</sup> Wales consistently has a lower survival rate than other parts of the UK,<sup>(2)</sup> and in the Eurocare 5 study Wales ranked 28<sup>th</sup> out of 29 European countries for lung cancer survival.<sup>(7)</sup>

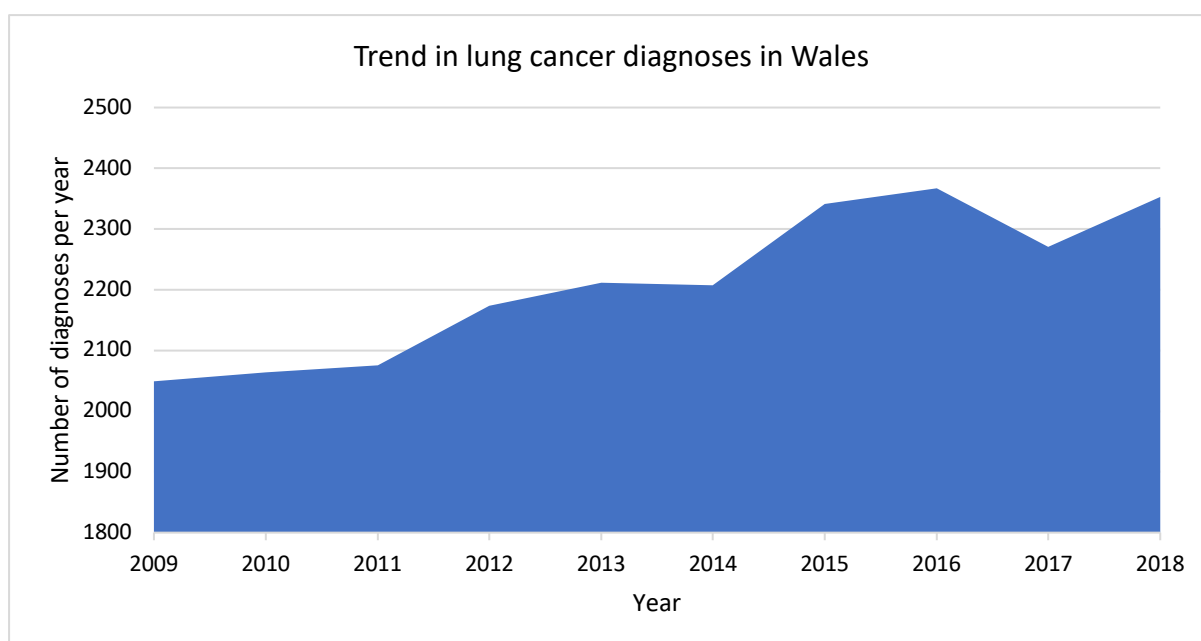


Figure 2: Trend in lung cancer diagnoses in Wales over ten years.

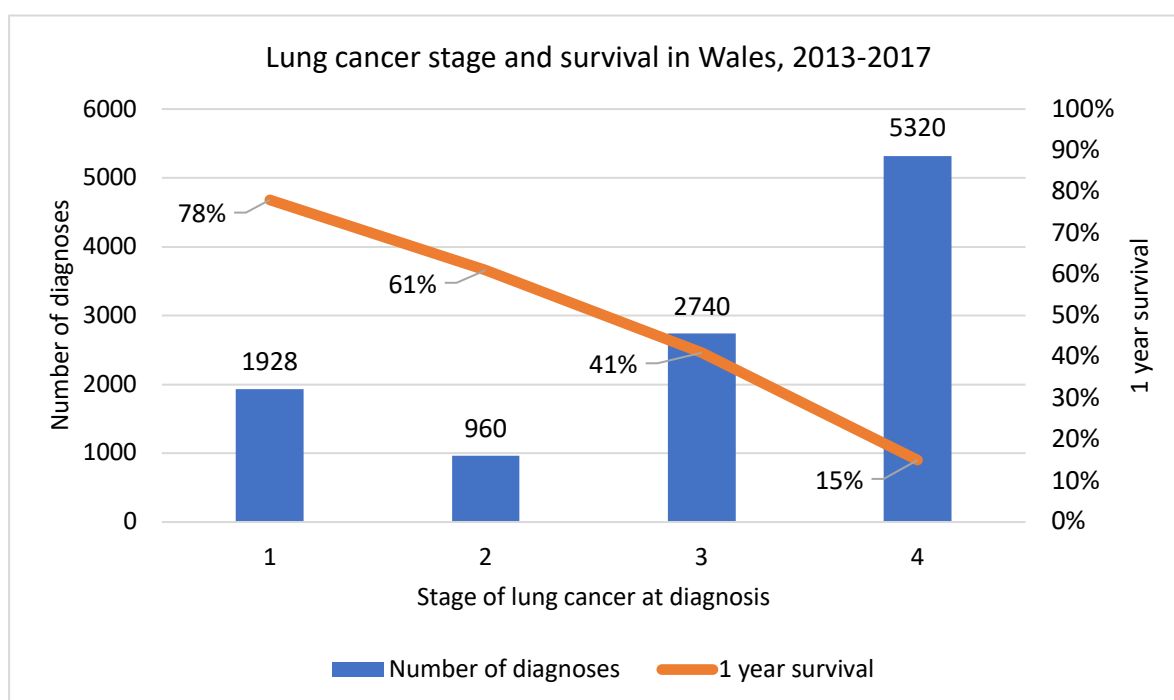


Figure 3: Frequency of diagnoses of lung cancer by stage and 1-year survival in Wales, 2013-2017.

Of the most common cancer types, lung cancer has the widest cancer death inequality, with a gradient of higher mortality in increasingly deprived areas. The size of the differences in mortality between more and less deprived areas has increased over time.(2) The reasons for this are likely to be multifactorial, including a higher prevalence of smoking in deprived areas, differences in attitude to health, and access to healthcare services.

The costs of treating late-stage lung cancer are higher than for treating early-stage lung cancer. In 2014, a report prepared for Cancer Research UK stated that treatment of stage 1 lung cancer cost £7,952 on average per patient, whilst stage 4 treatment cost £13,078.(8) The difference is likely to be wider now due to the development of new expensive treatments for late-stage lung cancer.

New treatments for late-stage lung cancer are lengthening life-expectancy in suitable patients,(9) but rely on tumour-related factors such as expression of PD-L1 or other genetic markers, and on patients with metastatic disease having a well-maintained performance status. Campaigns to raise awareness of the symptoms of lung cancer have been undertaken but have had little impact on outcomes in Wales,(10,11) likely due to symptoms of lung cancer being non-specific and early-stage lung cancer rarely causing symptoms.(12) The only strategies likely to lead to a significant reduction in lung cancer mortality are reducing the prevalence of smoking, and the introduction of a screening programme to detect more lung cancers at an early stage.

## WHAT IS THE EVIDENCE FROM RANDOMISED CONTROLLED TRIALS ON LUNG CANCER SCREENING?

Many of the characteristics of lung cancer suggest that screening could be an effective strategy to improve outcomes.<sup>(13)</sup> It is a common health condition with high rates of morbidity and mortality, has a pre-symptomatic phase, and treatment is more effective in the early stages of disease. Known risk factors, particularly smoking, can allow targeting of a high-risk subgroup of the population to improve efficiency.

Lung cancer screening trials in the 20<sup>th</sup> century focusing on chest x-ray and sputum cytology did not demonstrate any survival benefit. In the 1990s, interest in lung cancer screening was renewed after single arm studies on low-dose CT (LDCT) detected a large proportion of lung cancers at an early stage.<sup>(14–17)</sup> Following these promising results, randomised controlled trials (RCTs) were needed to overcome the biases inherent in non-randomised screening studies.<sup>(13)</sup>

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### NATIONAL LUNG SCREENING TRIAL (NLST)

The largest RCT on lung cancer screening with LDCT is the National Lung Screening Trial (NLST), performed in the USA with results reported in 2011.<sup>(18)</sup> NLST randomised 53,454 participants to either annual LDCT or annual chest x-ray for three years. Participants were men and women aged 55 to 74 years who either currently smoked or had stopped within the last 15 years, with at least a 30 pack-year smoking history. The trial was stopped early after an interim analysis found significant benefit in the LDCT arm, including a relative reduction in lung cancer deaths of 20% (absolute reduction in lung cancer deaths of 62 per 100,000 person years), and a 6.7% relative reduction in all-cause mortality (absolute reduction of 74 deaths per 100,000 person-years). For those undergoing at least one screen, the number needed to screen to prevent one lung cancer death was 320.

One thousand and sixty lung cancers were diagnosed in the LDCT arm, with 649 of these diagnosed after a “positive” scan, 44 after a negative scan, and 367 who either did not attend for their screening scan or were diagnosed during follow-up after screening had completed. Of the cancers detected by LDCT, 63.0% were at stage 1 and 7.2% at stage 2 (70.2% stage 1 or 2 combined). Most early-stage cancers were surgically resected. During the second and third years of screening fewer late-stage cancers were detected in the LDCT group, suggesting that detection of lung cancers in earlier screening rounds had reduced the number of late-stage cancers subsequently detected.

NLST used a very broad definition of a “positive” scan, including any scan with a non-calcified nodule  $\geq 4$ mm in diameter. This led to a high rate of positive scans (24.2%), with 96% of these not having lung cancer and therefore being considered “false-positives”. The management of small pulmonary nodules and the definition of a “positive” scan has evolved over time, meaning most of these “false-positives” would not be considered positive scans in later studies. NLST also reported a high proportion of resections for benign disease at 21%. This is higher than in subsequent studies and pilots, reflecting the aggressive approach taken to managing small nodules in NLST.

NLST reported a higher number of cancers diagnosed in the LDCT arm compared to the chest x-ray arm, suggesting overdiagnosis, i.e. the detection of clinically insignificant disease. The initial results of NLST suggested that 18% of cancers in the LDCT arm were overdiagnosed. However, extended follow-up of the NLST cohort found that the incidence of lung cancer in the chest x-ray arm “caught up” over time, suggesting that many of the cases that appeared to have been overdiagnosed after 4.5 years follow-up would have later

become clinically apparent. After extended follow-up (median 11.3 years), the overdiagnosis rate in the LDCT arm had reduced to 3.1%.(19) Most overdiagnosed cases were classified as “bronchoalveolar carcinoma”, a term now superseded by “lepidic adenocarcinoma” or “adenocarcinoma *in situ*”. These are minimally invasive cancers or pre-cancerous lesions that are often seen as subsolid pulmonary nodules on LDCT. Guidelines now recommend a conservative approach to management of most subsolid nodules unless there is clear evidence of progression.(20) More recent pilots have reported much lower resection rates for lepidic adenocarcinoma, suggesting that implementation of modern pulmonary nodule management guidelines can reduce overdiagnosis. In the extended analysis, a significant reduction in lung cancer mortality was maintained, and the number needed to screen to prevent one lung cancer death remained similar at 303.

In summary, NLST demonstrated that LDCT can detect early-stage lung cancer and reduce lung cancer-specific and all-cause mortality, but raised concerns regarding the potential harms associated with false-positive results and overdiagnosis. Following publication of NLST, in 2013 the US Preventive Services Task Force (USPSTF) began recommending annual screening with LDCT in adults aged 55-80 years who currently smoke or had stopped within the past 15 years with at least a 30 pack-year history.(21) In the UK and Europe a more cautious view was taken due to uncertainty regarding whether the benefits of LDCT clearly outweighed the risks, whether the benefits of screening would be seen in a European population and healthcare system, and whether screening could successfully be undertaken in a cost-effective manner. Much emphasis was placed on the outcome of a large European-based RCT: NELSON.

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## NELSON

NELSON is the second-largest RCT on lung cancer screening with LDCT, and is the only RCT other than NLST adequately powered to detect a reduction in lung cancer mortality. NELSON was initiated in 2000 in the Netherlands and Belgium, verbally reported results in 2018 and formally published in early 2020.(22) NELSON randomised 13,195 men (primary cohort) and 2594 women (separate subgroup analysis) aged 50 to 74 years who were current smokers or had stopped within the last 10 years and had smoked >15 cigarettes a day for >25 years, or >10 cigarettes a day for >30 years, to either a screening protocol with LDCT or no screening. The screening protocol consisted of four screening rounds with LDCT with increasing time intervals of 1, 2 and 2.5 years between rounds, and follow-up to 10 years from baseline. In men, screening reduced lung cancer mortality from 3.30 deaths per 1000 person-years to 2.50 per 1000 person-years, a 24% relative reduction at 10 years. Of the cancers in men occurring in the screening arm in whom the stage was recorded, 43% were at stage 1 and 9% were stage 2 (52% stage 1 or 2). This is a smaller proportion than in other studies as it includes cancers detected during an extended follow-up period when screening was not ongoing and cancers were more likely to present with stage 4 disease; for screen-detected cancers in the screening arm, 67.9% were stage 1 or 2. The incidence of lung cancer was 0.9% over the four screening rounds. In the smaller subgroup of women, the relative reduction in lung cancer mortality was 33% at 10 years which did not reach statistical significance, though at years 7, 8 and 9 a statistically significant relative reduction was seen of 48-59%. NELSON was not powered to detect a difference in all-cause mortality, and no significant difference was seen.

Three-hundred and four lung cancers were detected in the control arm and 342 in the screening arm, an excess diagnosis rate of 14% with screening that could suggest overdiagnosis. However, the incidence curves between groups converged over time, suggesting the overdiagnosis rate could be lower than this over a longer follow-up period: at 11 years of follow-up the overdiagnosis rate had fallen to 8.9%. Over the four screening rounds, 2.1% of participants had a “positive” scan requiring additional investigation other than an earlier interval CT, just under half of whom were subsequently diagnosed with lung cancer. In total, 1.2% of screened participants had a “false-positive” scan not resulting in a diagnosis of lung cancer. Over the four screening rounds, 9.2% of scans had an indeterminate finding requiring an early interval scan, usually to monitor

pulmonary nodules. The rate of indeterminate scans was highest at the baseline screening round (19.7%), falling to between 1.9% and 6.7% in subsequent screening rounds. The rate was lower in later rounds partly because some nodules would already have been known to be stable from previous screening rounds.

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## UK LUNG SCREENING TRIAL (UKLS)

The UK Lung Screening Trial pilot (UKLS) randomised 4,055 participants to a single screening LDCT or usual care.<sup>(23)</sup> A larger second phase of the trial was planned but did not receive funding. Due to its limited size, the pilot study was not sufficiently powered to detect differences in mortality between the intervention and control arms.

UKLS had several important differences to NLST and NELSON. Firstly, these studies had used age and smoking history alone to determine eligibility for CT; UKLS used the Liverpool Lung Project (LLPv2) risk model to determine 5-year risk of lung cancer, and included participants aged 50-75 years with a 5-year risk of lung cancer of  $\geq 5\%$ . This model incorporates additional risk factors including previous asbestos exposure, family history of lung cancer and personal history of certain respiratory diseases. This was done with the aim of enriching the lung cancer prevalence in the cohort to improve screening efficiency, and resulted in a high lung cancer detection rate: 2.1% in the screening arm (1.7% at baseline, 0.4% following interval scans) compared to 1.0% at baseline in NLST and 0.9% at baseline in NELSON). Secondly, UKLS was a true population-based study, identifying nearly 250,000 potential participants within the specified age range from local Primary Care Trust records, then filtering via response to an approach letter and a subsequent questionnaire to determine risk of lung cancer. Thirdly, protocol-driven radiology pathways utilising volumetric analysis of nodules were used resulting in a low rate of intervention for benign disease (10% benign surgical resection rate, vs. 21% in NLST).

Of the 249,988 population in Liverpool and Cambridgeshire and surrounding areas aged 50-75 years who were identified from primary care trust records, 75,958 (30.7%) responded positively to an invitation letter, of whom 8,729 (11.5% of responders) were determined to be at high risk of lung cancer. Those who responded were more likely to be ex-smokers than current smokers, and tended to be of higher socioeconomic status.<sup>(24)</sup> Of the high-risk responders, 4,055 were randomised to either a single screening LDCT or usual care. Further CT scans for nodules requiring follow-up were arranged, meaning that some participants in the screening arm underwent more than one LDCT during the study.

A total of 1994 participants underwent a screening LDCT. Sixty-four participants (3.2%) had a nodule suspicious of lung cancer and were referred to the local lung cancer MDT of whom 32 (50% of positive scans) had lung cancer. The prevalence of lung cancer at baseline was 1.7%. A very low threshold for interval scanning was used including nodules as small as 3mm, leading to a high interval imaging rate: approximately half of participants in the screening arm underwent a follow-up CT scan at either 12 months, or 3 and 12 months. Of those undergoing a 12 month scan only, only additional 1 lung cancer was detected (0.2%). For those undergoing scans at 3 +/- 12 months, a further 9 lung cancers were detected (1.9%). The overall prevalence of lung cancer including those detected at baseline and following interval scans was 2.1%. Of the lung cancers detected, 66.7% were stage 1 and 19.0% stage 2 (85.7% stage 1 or 2 combined). Surgical resection was the primary treatment for 83%.

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## OTHER EUROPEAN TRIALS

Smaller European RCTs (<5000 participants) on LDCT for lung cancer screening have had mixed results. The Detection and Screening of Early Lung Cancer by Novel Imaging Technology trial (DANTE), performed in Italy, compared annual CT with clinical review for four years.(25) More lung cancers were found in the CT arm with a greater proportion having early-stage disease, but no survival benefit was seen. The Danish Lung Cancer Screening Trial (DLCST) compared annual CT for 5 years with usual care, finding more lung cancers in the CT arm with a greater proportion at an early stage, but no difference in late-stage lung cancer or survival.(26) The ITALUNG trial in Italy compared annual LDCT for four years to usual care.(27) A similar number of lung cancers were found in the LDCT and control arms, with a larger proportion of early-stage disease and non-significant trends towards improved lung cancer-specific and overall survival with LDCT. The Multicentric Italian Lung Detection (MILD) trial randomised participants to either usual care, annual, or biennial LDCT. More lung cancers were found in the LDCT arms with a large proportion at an early stage. Whilst no mortality benefit with LDCT was seen after 5 years of follow-up,(28) a statistically significant reduction in lung cancer-specific and overall mortality was seen after 10 years.(29) The German Lung Cancer Screening Intervention (LUSI) trial randomised participants to either usual care or annual LDCT for 5 years, with a larger proportion of early-stage lung cancers detected in the LDCT arm.(30) Lung cancer-specific mortality was 26% lower in the LDCT arm though this did not reach statistical significance. When analysed by sex, a larger reduction in lung cancer-specific mortality was seen in women which was statistically significant.

Differences in the results of these smaller trials are likely to be due to a mixture of factors including: different inclusion criteria; variable screening intervals, durations of screening and follow-up; differing geographical areas; and variable management of abnormal findings such as indeterminate pulmonary nodules. These trials were individually underpowered to detect differences in mortality. Results from RCTs that reported mortality outcomes have been subject to a meta-analysis as discussed on p20.

## WHAT ARE LUNG HEALTH CHECKS?

Whilst awaiting publication of NELSON and for the National Screening Committee to make recommendations on LDCT screening for lung cancer, the ongoing high lung cancer mortality rates in the UK and the positive results from NLST led to the development of several pilot programmes in England. Much of this pilot activity has been in the form of “Lung Health Checks” (LHCs) which invite current and ex-smokers for an assessment of future lung cancer risk, offer LDCT to those at high risk, and include other components such as spirometry and smoking cessation.

There are two main advantages of delivering targeted lung cancer screening via LHCs. Firstly, people may find the idea of attending for a “Lung Health Check” less daunting than attending for “lung cancer screening”. Fatalistic beliefs and fear of death associated with a cancer diagnosis are well-recognised, are more prevalent in those at highest risk, and may reduce participation in a programme that focusses on lung cancer.(31–33) Participating in a LHC may be seen as doing something positive for health, whereas being screened for lung cancer could be perceived as only looking for a negative finding. Secondly, LHCs can provide an opportunity to identify and address other problems common in the target population such as smoking, COPD and coronary artery disease. Delivering multiple interventions through a single programme has the potential to improve cost-effectiveness.

## UK LUNG HEALTH CHECK ACTIVITY

### MANCHESTER LUNG HEALTH CHECK

A pilot programme in Manchester offered targeted lung cancer screening with LDCT as part of a one-stop community-based LHC in a mobile unit located next to local shopping centres.(34) People aged 55-74 years were identified from GP records and invited for a LHC if they had ever smoked. The LHC included an assessment of respiratory symptoms, spirometry, smoking cessation advice for current smokers and an assessment of lung cancer risk. Lung cancer risk was assessed using the PLCO<sub>M2012</sub> risk assessment tool, which includes age, socioeconomic status, body mass index (BMI), ethnicity, sex, family history of lung cancer, personal history of any cancer, history of respiratory disease and smoking duration and intensity. Those with a lung cancer risk of  $\geq 1.51\%$  over 6 years were offered annual screening with LDCT over two screening rounds, with the first LDCT performed at the time on the mobile unit.

Demand exceeded capacity for LHC appointments, with 2,541 people attending for a LHC. The population targeted were from deprived areas. Of those who attended, 1,429 (56.2%) were above the risk threshold for LDCT, with 1,384 undergoing LDCT. Of these, 81 (5.9%) had a positive scan requiring referral to a lung cancer clinic, of whom 42 had lung cancer (3.0% of those undergoing LDCT, 1.7% of those attending for a LHC). Forty-six lung cancers were diagnosed: three patients had  $>1$  lung cancer. The majority of cancers were early-stage: 63% at stage 1 and 17.4% at stage 2 (80.4% stage 1 or 2 combined). Surgical resection was performed in 65.2% and curative intent treatment was offered in 89.1%.

The false-positive rate (i.e. referred to lung cancer clinic but not diagnosed with lung cancer) was 2.8% of those undergoing LDCT. Negative scans were defined as those with no nodules, nodules with benign appearances or known to be stable, or nodules  $<6\text{mm}$ . This accounted for 82.6% of scans performed. According to current guidelines, solid nodules 5-6mm in size would undergo a 12-month interval scan. In this programme, scans containing nodules of this size were included in the negative scan group, as with annual screening they did not

require different management to those with no nodules. However, this means that the high rate of negative scans in this pilot would not be applicable if a screening interval of >12 months were used. In that case, 24.9% of the “negative” scans would be reclassified as indeterminate and require a 12-month interval scan. Three-month interval scans were performed in 12.7%, mostly for surveillance of nodules.

People who were eligible for LDCT were invited for a second scan 12 months later; 1194/1323 (90%) attended.<sup>(35)</sup> There were no interval cancers (i.e. no patients with a negative baseline scan were diagnosed with lung cancer prior to the second screening round). Thirty scans at 12-months were positive (2.5%), of whom 29 attended lung cancer clinic (one declined). Of these, 19/29 (65.5%) were diagnosed with lung cancer, equating to an incidence of lung cancer in the second screening round of 1.6%. Seventy-nine percent of cancers in this screening round were stage 1, with no stage 2 cancers diagnosed. Surgical resection was performed in 42%, and curative intent treatment was offered in 79%.

The false-positive rate for the second screening round was 0.8% of those scanned. One patient underwent surgery for benign disease. The majority of scans were negative, with only 71/1194 (5.9%) deemed indeterminate and requiring a 3-month interval scan. The second screening round saw a significantly lower number of positive and indeterminate scans than the first round. This is likely to be partly due to the availability of a baseline scan for comparison, allowing stable nodules to be ignored.

The Manchester pilot improved on the performance of previous lung cancer screening trials in several areas. Firstly, over the two screening rounds 4.4% of those screened were diagnosed with lung cancer, equivalent to one cancer for every 23 people screened. This is high in comparison to the incidence of lung cancer in the first two screening rounds of NLST and NELSON, and may be due to the use of a risk assessment tool for lung cancer together with targeting of a particularly deprived, high-risk population. Secondly, the benign resection rate was markedly lower than in any reported trials, likely due to different thresholds for investigation and intervention for small pulmonary nodules being adopted in line with modern pulmonary nodule guidelines, and an aggressive approach being taken to biopsying nodules to confirm malignancy prior to resection.

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## LIVERPOOL HEALTHY LUNG PROGRAMME

The Liverpool Healthy Lung Programme consisted of two sequential phases: the first was a series of public engagement events in Liverpool aimed at promoting positive messages about lung health and addressing fears and fatalism related to lung cancer diagnosis and treatment; the second involved inviting people for a LHC.<sup>(36,37)</sup>

People aged 58-75 years were identified from GP records. Those recorded on the GP record as having ever smoked or having a diagnosis of COPD were invited for a LHC based in a community health hub. The LHC included spirometry for those without a previous diagnosis of COPD, smoking cessation advice and offer of referral to a local NHS smoking cessation service, and a risk assessment for lung cancer. As in UKLS, the Liverpool Lung Project (LLPv2) risk model was used with those with a 5-year risk of  $\geq 5\%$  referred to a local hospital for a LDCT.

A total of 11,526 invitations were sent with 4,566 (40%) attending for a LHC, of whom 3,591 (79%) consented to data sharing. Only 1,264 (35%) took part following the first invitation letter; 43% and 22% participated after a second reminder letter and a subsequent telephone call respectively. Of those who attended and agreed to data sharing, 1,548/3,591 (43%) were above the risk threshold for LDCT, with 1,318 undergoing LDCT (85% of those in whom LDCT was recommended).

Results for Liverpool were presented in a different way to the Manchester programme, with 119/1,318 (9%) having a “finding requiring further investigation”. This definition included immediate referrals to lung cancer clinic, 3-month interval scans or 12-month interval scans. This therefore includes what were considered positive and indeterminate scans by Manchester, and some scans that would have been considered “negative” by Manchester as they contained small nodules requiring a 12-month scan only. Of these, 25 were diagnosed with lung cancer (1.9% of those undergoing LDCT, 0.7% of those attending for a LHC), and a further 11 (0.8% of those undergoing LDCT) were still undergoing investigation for a suspicious lesion at the time of publication of the report. The majority of cancers were early-stage: 64% at stage 1 and 12% at stage 2 (76% stage 1 or 2 combined). Surgical resection was performed for 74% of lung cancers diagnosed.

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#### NOTTINGHAM LUNG HEALTH MOT

In the Nottingham “Lung MOT” pilot, people aged 60-75 years from five GP practices with a positive smoking history in the last 5 years were invited for a LHC.(38) Of 1020 eligible people, 25% attended for a LHC at their GP practice which included taking a medical and smoking history, spirometry, smoking cessation advice for current smokers, and calculation of lung cancer risk using the QCancer risk score. Those with a 2-year risk of lung cancer of  $\geq 0.68\%$  (equivalent to the 5% of the population at highest risk of lung cancer) were offered a LDCT in a mobile scanner located close to the GP practice within 4 weeks of the LHC. Of those invited, 323 (27%) attended for a lung MOT, 166 (51% of attenders) were recommended to have a LDCT, and 157 (49% of attenders, 95% of those recommended) had a LDCT. Scans with no nodules or nodules  $< 5\text{mm}$  in size were considered negative. Scans with nodules 5-6mm in size were considered indeterminate, with a 12-month interval scan organized. Nodules larger than this were referred for further investigation. These are again slightly different definitions of positive and indeterminate scans compared to other trials and pilots. Eleven patients (7%) had a scan requiring further investigation, of whom three (2%) had lung cancer, two of which were stage 1 and underwent surgical resection (66.7%), with the other having stage 4 disease at diagnosis. Following the pilot programme a wider rollout was funded and took place in 2018, results from which are awaited.

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#### NHS ENGLAND TARGETED LUNG HEALTH CHECK PROGRAMME

In early 2019, NHS England announced £70 million funding for fourteen Targeted Lung Health Check (TLHC) projects to run in 10 cancer alliances across England between 2019 and 2023 (figure 4).(39) The programme exists entirely within NHS England as a “targeted health intervention” rather than as a population-based screening programme which would usually involve both NHS England and Public Health England. This roll-out of more widespread lung cancer screening activity prior to formal publication of the NELSON trial results or a recommendation from the National Screening Committee has been subject to some criticism.(40,41)

A standard protocol specifies various aspects of the programme including the assessment process, LDCT acquisition and reading, management of findings, and clinical governance procedures.(42) The protocol does allow some variation in delivery, which is hoped to inform optimal models for a future wider roll-out. Participants invited are aged 55-74 years who have ever smoked as recorded on their GP record. The LHC includes spirometry, smoking cessation advice for current smokers, and assessment of lung cancer risk using both the PLCO<sub>M2012</sub> (threshold  $\geq 1.51\%$  risk over 6 years) and LLPv2 ( $\geq 2.5\%$  risk over 5 years) risk assessment tools. Those who are above the threshold for either risk assessment tool have a LDCT.

Protocols for management of pulmonary nodules, incidental findings and quality assurance standards have also been developed.(43) Most sites are utilising mobile CT scanners rather than existing or new static site scanners. In 2020 it was announced that seven existing LHC projects would come under the umbrella of the NHS England programme to allow more robust quality assurance and data gathering. The variables of some of these projects differ from the NHS England standard protocol, such as the target age range, risk calculator(s) and threshold for LDCT, and the screening interval following a normal baseline LDCT. It is planned to utilise this heterogeneity during evaluation of the projects to help inform the optimal model for a future national programme.

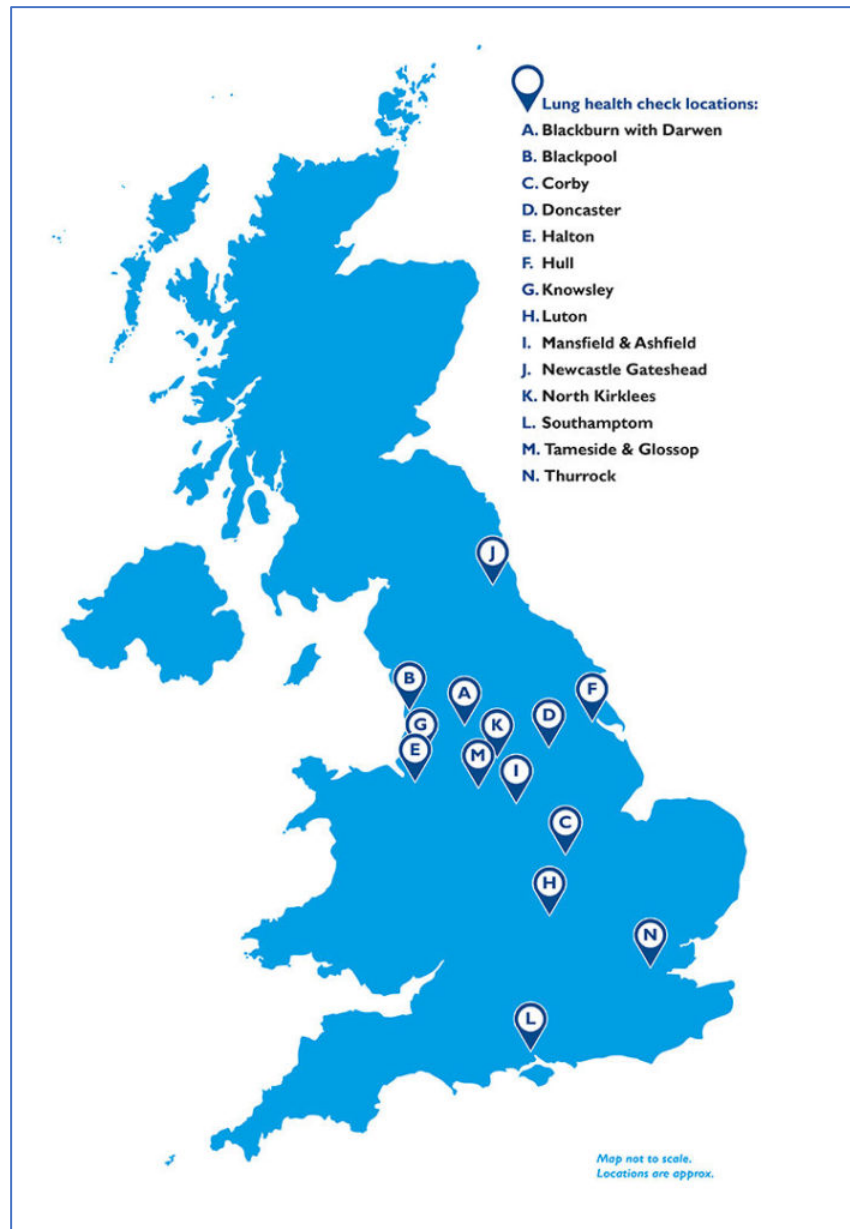


Figure 4: Original fourteen NHS England Targeted Lung Health Check Programme sites prior to expansion.

## OTHER UK LUNG HEALTH CHECK ACTIVITY

### LUNG SCREEN UPTAKE TRIAL (LSUT)

The Lung Screen Uptake Trial (LSUT) was an RCT based at UCL, London, focused on optimising uptake of lung cancer screening.(38,44) Participants aged 60-75 years with a positive smoking history within the last 5 years were identified from GP records, with the aim of recruiting and randomising 2000 participants. Those in the control arm were sent a pre-invitation letter for a LHC and a standard information booklet followed by an invitation letter with a scheduled appointment, and a second invitation letter if they did not attend. Those in the intervention arm were invited in the same way, but sent “targeted, stepped and low-burden” information designed to reduce fear, fatalism and stigma associated with lung cancer instead of the standard information booklet. LHCs took place in hospital and included spirometry, a carbon monoxide breath test, referral to smoking cessation and other local health promotion services where appropriate, and assessment of lung cancer risk. Lung cancer risk was assessed using both the LLPv2 ( $\geq 2.5\%$  five-year risk threshold) and PLCO<sub>M2012</sub> ( $\geq 1.51\%$  six-year risk threshold) models, with those above either risk threshold referred for LDCT. In 2019 it was reported that there had been no difference in uptake between the two arms, but that uptake overall had been higher than previous clinical and real-world studies.(45)

### YORKSHIRE LUNG SCREENING TRIAL (YLST)

YLST is an ongoing RCT running from 2017 to 2024 aiming to perform up to 7000 LHCs in Leeds in people aged 55-80 years who are current or ex-smokers.(46) If the target for recruitment is met, YLST will be the third largest RCT on LDCT screening after NLST and NELSON. Participants are randomised to usual care or invited for a LHC; those randomised to usual care are not informed that they are participating in the trial. Initial assessment for those in the intervention arm is done by telephone. LHCs occur in a mobile community-based unit with on-site LDCT, with only those determined to be eligible for LDCT during the telephone phase invited for a face-to-face LHC. Lung cancer risk is assessed using three criteria: the PLCO<sub>M2012</sub> and LLPv2 risk assessment tools, and the USPSTF criteria for lung cancer screening. Two screening rounds with an interval of two years are planned. The study is due to conclude in 2024 and publish results in 2025.

### SUMMIT

SUMMIT is a prospective observational cohort study aimed at clinically validating a blood test for the early detection of multiple types of cancer, and to deliver LDCT screening for lung cancer.(47) It aims to enroll 50,000 participants in London aged 50-77 years, with half at high risk and half at low risk of lung cancer based on USPSTF criteria and PLCO<sub>M2012</sub> risk assessment. Both groups will provide a blood sample, whilst those at high risk will also undergo a LHC and have a LDCT at baseline. Those with a negative baseline CT will return for a further LHC at 12 months and be further randomised to either a further LDCT or no further LDCT. The study is planned to run from 2019 until 2023, with follow-up completing in 2030.

### OTHER UK ACTIVITY

LHC pilots have taken place elsewhere in the UK, including in London (affiliated with the Royal Brompton and Harefield hospitals)(48) and Salford (49) amongst others. Some private healthcare companies within the UK offer assessment of lung cancer risk and LDCT as a service to clients.

## EVIDENCE SUMMARY ON LDCT SCREENING AND LUNG HEALTH CHECKS

For screening activity to be useful the benefits must outweigh the harms, and the activity must be deliverable at an acceptable level of cost. Evidence for mortality reduction with LDCT screening has been available since 2011 with publication of NLST, but there had been concerns regarding the harms including overdiagnosis and the number of false-positive results. In addition, even if the benefits outweighed the harms it was unclear whether a programme could be delivered at an acceptable level of cost; cost-effectiveness estimates based on the American healthcare system have been unfavourable compared to the usual thresholds applied in the UK. Since then the body of evidence has grown, with refinements to the screening process reducing overdiagnosis and false-positive rates, improved selection of participants making screening more efficient, and pilots in England suggesting that LHCs can be delivered cost-effectively within the UK healthcare system.

### BENEFITS

#### DETECTION OF EARLY-STAGE LUNG CANCER

Studies and pilots have consistently demonstrated “stage-shift” of lung cancer with LDCT screening, with the majority of cases being detected at stage 1 or 2 rather than stage 3 or 4 as through usual pathways. Detecting a greater proportion of lung cancers at an early stage offers a better chance of curative treatment, most commonly by surgical resection. In Wales only 29% of lung cancers are diagnosed at stage 1 or 2.<sup>(4)</sup> With LDCT screening up to around three-quarters of lung cancers are diagnosed at stage 1 or 2 (figure 5).<sup>(4,18,22,23,35,37)</sup> The proportion of lung cancers detected at an early stage may rise in screening rounds after the initial screening round due to treatment of early-stage lung cancer in the initial screening round reducing late-stage disease in subsequent rounds. The screening interval is also important: in NELSON, more early-stage lung cancers were detected with one- and two-year screening intervals than after a 2.5-year interval.<sup>(50)</sup>

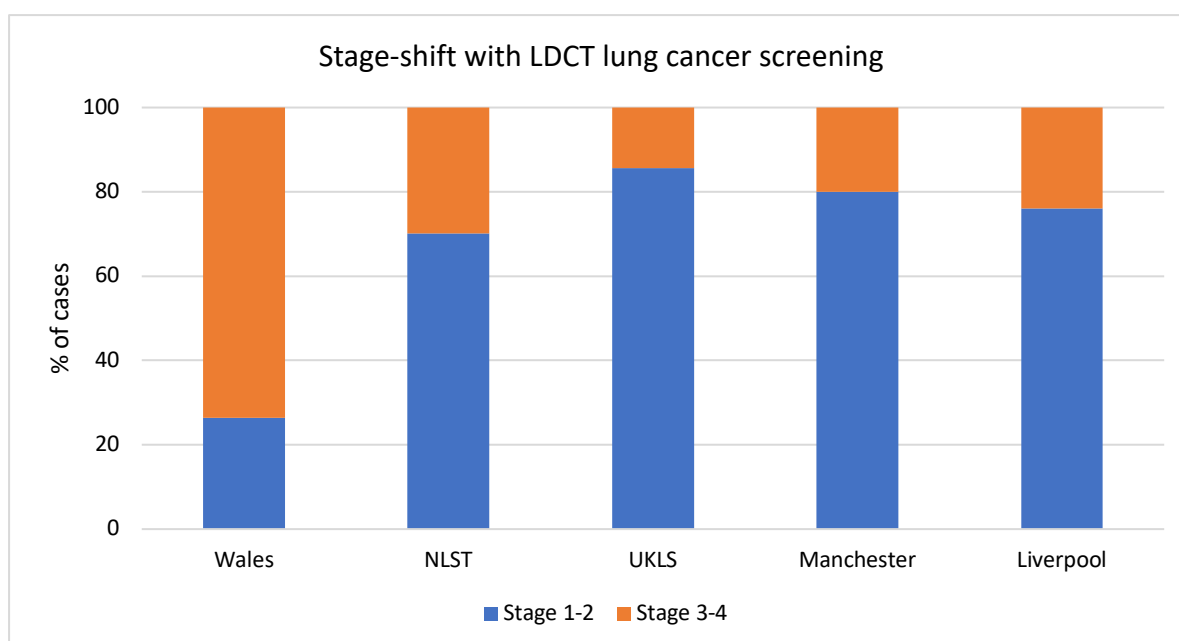


Figure 5: Stage-shift in trials and pilots compared to presentation via usual care in Wales. NELSON results are complex to interpret due to the prolonged follow-up period during which there was not ongoing screening and the increasing screening interval between rounds, so are described separately here: 67.9% of screen-detected lung cancers were stage 1 or 2; of all lung cancers detected in the screening arm (including those diagnosed in follow-up period after screening had ceased), 48.8% were stage 1 or 2. In the control arm, 23.4% of lung cancers were stage 1 or 2.

## REDUCTION IN MORTALITY

Stage-shift alone is insufficient evidence to support LDCT screening. If many of the lung cancers diagnosed at an early stage are “overdiagnoses” (i.e. inconsequential cancers detected by screening that would not have been detected prior to death from another cause), then stage-shift can occur without benefit, or indeed cause net harm due to interventions that would not have otherwise occurred.<sup>(13)</sup> Disease-specific mortality is generally accepted as the primary outcome for large randomised controlled screening trials, as this compensates for the problems of overdiagnosis and lead-time bias.<sup>(13,51)</sup> The only trials powered to detect a reduction in lung cancer mortality have been NLST and NELSON, both of which demonstrated statistically significant reductions (tables 1 and 2). A statistically significant reduction in all-cause mortality is difficult to achieve even with very large sample sizes, as the disease in question is only likely to cause a small proportion of the total deaths.<sup>(51–53)</sup> NLST is the only randomised screening trial examining a single type of cancer to demonstrate a significant reduction in all-cause mortality.<sup>(53)</sup>

Table 1: Mortality reduction in NLST.

NLST	LDCT	Chest x-ray	Absolute reduction in deaths (95% CI); and relative reduction	P value
	Deaths/100,000 persons			
Lung cancer mortality	1308	1620	312 (106-518); 20%	0.003
All-cause mortality	7024	7482	457 (18-896); 6.7%	0.04

Table 2: Mortality reduction in NELSON.

NELSON		Screened arm	Control arm	Cumulative rate ratio for death from lung cancer at 10 years (95% CI)
		<i>Deaths/1000 person-years</i>		
Lung cancer mortality	Men	2.50	3.30	0.76 (0.61-0.94)
	Women			0.67 (0.38-1.14)
All-cause mortality	Men	13.93	13.76	1.01 (0.92-1.11)
	Women			Not reported

Both NLST and NELSON reported a relative reduction in lung cancer mortality of 20% or greater with LDCT screening. This did not reach statistical significance for the smaller cohort of women in NELSON at 10 years of follow-up, though was statistically significant at 7, 8 and 9 years of follow-up. These two large randomised controlled trials provide strong evidence that LDCT screening is effective at reducing lung cancer mortality, with NLST also providing evidence of reduction in all-cause mortality.

The duration of follow-up is important when considering mortality outcomes in screening trials. Even if screening reduces cancer deaths, this may not be captured if the follow-up period is too short or too long. It appears that some lung cancers have a lead-time (the period when they are detectable by screening prior to usual presentation) of many years. In the MILD trial, no difference in mortality was seen after 5 years of follow-up, but by ten years of follow-up a significant relative reduction in lung cancer mortality of 39% was seen (hazard ratio 0.61, 95% confidence interval 0.39-0.95).(29) The trend for all-cause mortality was in the same direction favouring the screened arm, but did not reach statistical significance (hazard ratio 0.80, 95% confidence interval 0.62-1.03).

A meta-analysis of LDCT screening trials published in 2020 pooled lung cancer mortality and all-cause mortality results from seven RCTs including NLST and NELSON, totaling almost 85,000 participants.(54) The pooled results showed a 17% reduction in lung cancer mortality with LDCT screening (risk ratio 0.83, 95% confidence interval 0.76-0.91). A relative reduction of overall mortality of 4% was seen with LDCT screening, which was borderline for statistical significance (risk ratio 0.96, 95% confidence interval 0.92-1.00).

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## SMOKING CESSATION

Participation in lung cancer screening is associated with a positive impact on smoking cessation which carries many health benefits. This is discussed in more detail in the “Other potential Lung Health Check components” section (p24).

## HARMS

### RADIATION

Lung cancer screening is usually performed using LDCT without intravenous contrast. Exposure to ionising radiation through CT scanning can increase the risk of solid tumours and leukaemia, though the risk associated with low dose exposure is disputed.<sup>(55)</sup> The mean effective radiation dose from a single LDCT for lung cancer screening is 1.4 mSv, which is similar to 1 year of background radiation and significantly less than the 7 mSv of a standard dose diagnostic CT thorax.<sup>(56)</sup> The cumulative dose of radiation with multiple scans is also important, as participants in an ongoing programme will have multiple LDCTs over time in addition to diagnostic CT scans, PET scans and CT-guided biopsies if abnormalities are found. Whilst the radiation dose will be higher in people with abnormal findings, these individuals also have the greatest potential to benefit from these tests. The mean lifetime attributable risk of malignancy due to radiation in people undergoing diagnostic work up and radical treatment for lung cancer has been estimated at 0.059%.<sup>(57)</sup>

Estimates of the likely impact of radiation on populations undergoing lung cancer screening with LDCT suggest that the benefits are likely to outweigh the risks. It has been estimated that a ten-year programme incorporating over 42,000 LDCTs and subsequent investigations such as diagnostic CT and PET would cause 1.5 radiation induced lung cancers and 2.4 other major cancers.<sup>(58)</sup> One major radiation-induced cancer would be expected for every 108 lung cancers detected through screening.

The Manchester programme utilised ultra-low dose CT (ULDCT, also called very low dose CT). There is no universally agreed definition of what constitutes a ULDCT, though the radiation dose is usually <1mSv and comparable to that of a two-view chest x-ray. Due to the high contrast difference between pulmonary nodules and background lung tissue on CT, ULDCT appears to be comparable to LDCT for detection and measurement of pulmonary nodules, though less effective at detecting other abnormalities such as emphysema.<sup>(59–61)</sup> Detection of other abnormalities on CT can do good or harm, and where the benefits of identifying and acting on incidental findings do not clearly outweigh the risks, reduced detection may actually be preferable.

### FALSE-POSITIVES

A “false-positive” finding is a LDCT finding that is reported as abnormal but is ultimately not of any relevance, and most commonly refers to pulmonary nodules that do not represent invasive malignancy. Early-stage lung cancer can appear on LDCT as a pulmonary nodule, however, pulmonary nodules are common and the vast majority are benign. False-positive nodules can cause harm due to additional radiological investigations and exposure to radiation, risks associated with invasive procedures such as CT-guided biopsy and surgical resection of benign disease, and by causing anxiety and psychological harm. A high false-positive rate within a screening programme can cause wider harm by inappropriately diverting resources away from those with true disease.

The definition of what constitutes a “positive” finding in lung cancer screening has evolved over time. NLST defined any non-calcified nodule  $\geq 4\text{mm}$  in diameter as “positive” and reported a high rate of positive scans at 24.2%, with 96% of these described as false-positives (i.e. 23.3% of the screened population).<sup>(18)</sup> The management of pulmonary nodules has moved on since NLST: it is now recognised that nodules <5mm in diameter are unlikely to be malignant and routine follow-up imaging is not recommended.<sup>(20)</sup> Nodules with the characteristic appearance of a benign intraparenchymal lymph node or hamartoma also require no routine follow-up imaging. Subsolid pulmonary nodules rarely represent invasive malignancy and can be followed up

with an interval LDCT. Solid nodules 7-8mm in diameter are now followed up with an interval scan at 3 months from baseline, and nodules 5-6mm in diameter are followed up with a 12-month scan.

More recent studies have separated what previously constituted a “positive” finding in NLST into “positive” and “indeterminate” findings. A “positive” finding is one that requires immediate further assessment such as a PET scan or biopsy, with a “false-positive” being such a case that does not result in a diagnosis of cancer. An indeterminate finding refers to a nodule that does not require immediate further assessment but does require surveillance imaging.

Even with this separation of definitions there has been variation in where the line between “indeterminate” and “positive” has been drawn. Having a higher threshold for defining a positive finding will reduce the false-positive rate,<sup>(62)</sup> but risks delaying some diagnoses of cancer. The Manchester programme defined positive results as nodules  $\geq 8$ mm in diameter with a BROCK score (a tool for predicting probability of lung cancer in pulmonary nodules on CT) of  $\geq 10\%$  at baseline, or nodules that demonstrated growth on follow-up CT with a volume doubling time (VDT) of  $< 400$  days. Using these criteria, the Manchester programme reported a positive scan rate of 5.9% and a false-positive rate of 2.8% of the screened population. NELSON and UKLS used similar criteria other than using a nodule diameter of  $\geq 10$ mm, and reported positive scan rates of 6.0% and 5.7%, and false-positive rates of 3.6% and 3.6% respectively.

Information regarding false-positive rates in UK LDCT screening activity were presented at the British Thoracic Oncology Group Lung Cancer Screening Update meeting in 2019. This included combining results from UKLS, Manchester, Liverpool and London screening activity. Of 7659 LDCTs performed, 347 (4.5%) had a positive finding requiring referral to a lung cancer clinic. 177 (2.3%) had lung cancer, giving a false-positive rate of 2.2% of those screened. An early interval CT was required for 1004 participants (13.3%). Physical harm caused by false-positives was extremely rare: 45 participants (0.6%) underwent invasive testing for benign disease, seven (0.1%) underwent surgical resection for benign disease, and no major complications or deaths resulted from invasive testing or treatment of benign disease. This very low benign resection rate reflects the progress made in the management of pulmonary nodules over time, in contrast to the 24.4% benign resection rate in NLST.

The false-positive rate can be reduced by following modern guidance on the management of pulmonary nodules as described above, including use of volumetric analysis and risk assessment tools such as the BROCK calculator.<sup>(20)</sup> Reporting of scans by experienced thoracic radiologists with the confidence to dismiss nodules with benign characteristics and avoid “over-reporting” can help reduce the positive and false-positive scan rates. Artificial intelligence (AI)-aided reporting may have a greater role in reducing false-positive rates in the future by helping determine whether nodule characteristics suggest a benign or malignant aetiology, though at present the primary use of AI is to facilitate detection and reporting of pulmonary nodules.

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## OVERDIAGNOSIS

Overdiagnosis refers to disease detected by screening that would not be clinically relevant within a participant’s lifetime, e.g. detection of a lung cancer that would not have caused harm or been detected prior to death from another cause. The rate of overdiagnosis in lung cancer screening trials can be estimated by comparing incidence of lung cancer in LDCT and control arms of the trials; an excess incidence in the LDCT arm may suggest overdiagnosis. The apparent overdiagnosis rate has varied widely between different trials and pilots. Reasons for this may include different definitions of overdiagnosed cases, the management of subsolid and small solid pulmonary nodules evolving over time,<sup>(20)</sup> and different durations of follow-up before reporting of results.

Most lung cancers considered overdiagnosed in earlier trials such as NLST were bronchoalveolar carcinomas, a term now superseded by “lepidic adenocarcinoma” or “adenocarcinoma *in situ*”. These lesions are usually recognised on LDCT as subsolid pulmonary nodules, have an excellent cancer-specific prognosis, and are usually managed conservatively unless radiological surveillance suggests evidence of progression.(20,63)

Duration of follow-up in trials can influence the overdiagnosis rate. Lung cancers detected by screening which would not have become clinically relevant during the follow-up period but would have during prolonged follow-up may incorrectly appear to be an overdiagnosed case. This is seen where the incidence of lung cancer is higher in a screening arm of a trial and no lung cancer-specific mortality benefit is seen during a shorter period of follow-up, but a longer period of follow-up does reveal a benefit. This occurred in both the ITALUNG and MILD trials.(27,29) In NLST the overdiagnosis rate reduced from 18% to 3.1% with prolonged follow-up.(19) The overdiagnosis rate in NELSON fell over time, standing at 8.9% after 11 years of follow-up.(22)

It has been estimated that for every overdiagnosed case of lung cancer, 3-5 lung cancer deaths would be prevented.(64) In contrast, estimates for breast cancer screening suggest that one breast cancer death would be prevented for every 3-5 overdiagnosed cases.

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## PARTICIPANT DISTRESS

A systematic review of the psychological impact of LDCT screening suggested that participating in screening may be associated with some short-term psychological discomfort but did not significantly affect distress, worry, or health-related quality of life, whilst false-positive results were associated with some short-term increases in distress.(65) A further study evaluated a subset of participants who had positive and negative scans in NLST and found no difference in health-related quality of life or anxiety at 1 or 6 months in those with false-positive screens or with significant incidental findings.(66) In UKLS, no clinically significant long-term psychosocial impact was seen in participants in the LDCT arm compared to the control arm.(67) The concept of a LHC may be more acceptable to patients than lung cancer screening, though a direct comparison of the psychological effects of lung cancer screening and LHCs has not been conducted.

## POTENTIAL BENEFIT OR HARM

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### INCIDENTAL DETECTION OF OTHER DISEASE

LDCT is not a focused test. In addition to the lungs, areas including the heart, adrenal glands, lymph nodes, liver and spleen will all undergo some imaging meaning that some incidental findings are inevitable. These findings may or may not be of clinical significance, and their detection may be of net benefit or harm. A screening programme must endeavor to only report incidental findings that are likely to be of clinical significance and where intervention is likely to be beneficial, as reporting and acting on inconsequential incidental findings may cause harm to the individual and carry costs to the healthcare system.

The prevalence of incidental findings has varied in LDCT screening activity to date, largely driven by different criteria for reporting incidental findings. Whilst there has been some analysis of the relevance of reporting incidental findings, the true balance between benefits and harms for specific findings is unknown.(68–71) As part of their quality assurance guidance, the NHS England programme has produced a protocol for the reporting of incidental findings such as emphysema, coronary artery calcification, interstitial lung disease, mediastinal abnormalities, thoracic aneurysms and adrenal nodules amongst others.(43)

## UNCERTAINTIES AND GAPS IN THE EVIDENCE

There do remain some gaps in the evidence on LDCT screening. Firstly, women have been under-represented in the larger trials, representing 41% of the NLST cohort and analysed only as a separate subgroup in NELSON accounting for only 16% of the total cohort. Nevertheless, NLST, NELSON and LUSI all reported a statistically significant reduction in lung cancer mortality in women despite the smaller sample sizes, with the reduction in lung cancer mortality larger in women than men in all three trials.(22,30,72)

Secondly, there had been some concern that no reduction in lung cancer mortality had been seen in smaller European trials prior to NELSON. These trials were underpowered to detect a statistically significant difference in lung cancer mortality and some may have had follow-up periods insufficient to detect a difference: the MILD trial did not reveal a reduction in lung cancer mortality at the end of the planned 5 years of follow-up, but did when follow-up was extended to 10 years.(29) Pooling of results from these trials with NLST and NELSON has confirmed a significant reduction in lung cancer mortality with LDCT screening.(54)

Thirdly, there has been discussion about the lack of effect on all-cause mortality in NELSON. A very large sample size is required to detect a significant difference in all-cause mortality, as only a small proportion of the study population will die of lung cancer and many more will die of other causes; it is therefore difficult for a reduction in lung cancer mortality to have a major effect on all-cause mortality.(51–53) The largest trial to date, NLST, did report a statistically significant reduction in all-cause mortality, whilst all-cause mortality was almost identical between both arms of NELSON. A meta-analysis of results from LDCT screening trials has shown a trend towards a reduction in all-cause mortality, even when the neutral result from NELSON is included.(54) There has been much debate about whether a reduction in all-cause mortality in randomised controlled trials is needed to justify roll-out of a screening programme. Most existing screening programmes, such as for bowel cancer, have been rolled out on the basis of evidence of reduction of cancer-specific, and not all-cause mortality; NLST is the only randomised screening trial on any single cancer site to demonstrate a significant reduction in all-cause mortality to date.

## OTHER POTENTIAL LUNG HEALTH CHECK COMPONENTS

### SMOKING CESSATION

Smoking is one of the leading cause of premature death and preventable morbidity in the UK,(73) placing a huge burden on NHS resources. It has been estimated that in the UK, smoking is responsible for 19% of all deaths and 12% of all disability-adjusted life-years lost, with a direct cost to the NHS in 2005-06 of £5.2 billion.(74) Smoking cessation offers many health benefits, particularly reduction in risk of cancers, respiratory and cardiovascular diseases.

There had been concerns that LDCT screening/LHCs could reassure patients that if smoking-related disease developed it would be detected and managed, and would give them a “license to smoke”. This has not been the case in the trials and pilots to date. Current smokers who participate in lung cancer screening may be more motivated to accept smoking cessation interventions,(75) and LHCs offer a “teachable moment” to trigger a quit attempt. American guidelines that have recommended lung cancer screening have highlighted the importance of incorporating smoking cessation interventions into their programmes.(21) Lung cancer screening trials have reported variable proportions of participants who considered a quit attempt and who reported that they had quit at follow-up. Nevertheless, quit rates have generally been higher in participants in lung cancer screening than background population quit rates.

Amongst the health benefits offered by smoking cessation is a reduction in the risk of lung cancer which could theoretically make a LHC programme less cost-efficient over time. However, lung cancer screening with LDCT and prolonged abstinence from smoking appear to have a synergistic effect on lung cancer mortality, offering approximately double the benefit to lung cancer mortality reduction: a secondary analysis of NLST found that ex-smokers who had abstained for 7 years in the control arm had a 20% reduction in lung cancer mortality, equal to the 20% reduction in the screening arm overall, whilst those who underwent screening and had abstained for 15 years had a 38% reduction in lung cancer mortality.(76)

In NLST, one year after the third annual screen 24% of smokers in both arms (who had both undergone screening, with either LDCT or chest x-ray) had quit.(77) In a subgroup analysis, current smokers with a positive screen (lung cancer or nodule) were more likely to stop smoking, whilst consistently negative screens were not associated with smoking relapse in ex-smokers or smokers who stopped following their initial screen. In NELSON, the smoking quit rate was 14.5% in the screening arm and 19.1% in the control arm, compared to a background quit rate of 6.7%.(78) UKLS reported a 24% quit rate at 2 years in the intervention group, compared to 4% in the background population.(79) Those with a negative screen were more likely to quit than controls, and those requiring additional investigations following screening were much more likely to quit.

The smoking cessation interventions in most lung cancer screening and LHC activity have been of low intensity, usually including written information on smoking cessation and available services together with brief counselling. It is uncertain whether more intensive interventions such as an on-site counsellor, immediate prescription or provision of nicotine replacement therapy or other medication, or more intense follow-up support is more effective or cost-effective in this setting. UK LHC programmes with an on-site smoking cessation counsellor have generally had more smoking cessation contacts and more quit dates set. For example, in Wakefield 26% of attendees who were current smokers accepted a referral to Yorkshire Smokefree, whilst three-quarters of current smokers in the Yorkshire Enhanced Stop Smoking study (YESS) saw a smoking cessation counsellor who was located on-site.(BTOG screening update, 2019)

The cost-effectiveness of smoking cessation interventions is difficult to estimate as the wide range of long-term benefits smoking cessation offers are difficult to capture in an economic model. Simple interventions such as brief opportunistic advice cost very little per life-year gained. Adding self-help material or offering specialist smoking cessation counselling increases the cost but also substantially increases the number of people who quit and the number of life-years gained. Pharmacotherapy can be added to these interventions and increases the quit rate further.(80–88) Nicotine replacement therapy increases the probability of a quit attempt being successful by 50-60% regardless of setting,(85) and has been estimated to cost between £494 and £3,554 per QALY gained.(88) Varenicline (Champix) is effective at increasing the chances of a quit attempt being successful, is more effective than a single delivery method of NRT, though not more effective than a combination of NRT delivery methods.(86) Varenicline is estimated to cost between £950 and £1,140 per QALY gained. Bupropion (Zyban) is also effective at increasing the success of smoking cessation, though evidence suggests it is less effective than varenicline.(80) In addition, different approaches may be required for different groups; for example, more intensive behavioral support may be required for older, more deprived people who smoke.(89)

Eight studies in the USA are testing various smoking cessation strategies under the umbrella of the “Smoking cessation within the context of lung cancer screening” (SCALE) collaboration.(90) Factors being examined include use of quitlines, medication, integrated care, training toolkits, and web and text message-based resources amongst others. These studies are ongoing, with some due to complete in 2022. In the UK, the YESS study is testing the effect of giving patients personalised risk information including pictures of emphysema or coronary artery calcification from their own LDCT on smoking cessation.(91) YESS is due to complete in 2021.

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## CASE-FINDING OF COPD

It is estimated that between one-third and one-half of people living with COPD have not been diagnosed.(92,93) There has been considerable debate about the value of case-finding in COPD.(94). In favour, earlier diagnosis and treatment may reduce the risk of future complications such as exacerbations and pneumonia, lessen the burden of breathlessness, reduce the risk of comorbidities associated with physical inactivity, and incentivise smoking cessation. Against, a COPD diagnosis is associated with costs such as inhaled therapy and regular reviews by healthcare professionals, and case-finding is only of use if earlier intervention is of definite benefit. The NSC do not recommend population-based screening for COPD, but do state that identifying COPD in people with symptoms (i.e. case-finding as opposed to screening) is cost-effective.(95) The NICE COPD guideline recommends suspecting a diagnosis of COPD in people over 35 who have a risk factor such as a history of smoking, together with at least one symptom including exertional breathlessness, chronic cough, regular sputum production, frequent winter “bronchitis” or wheeze.(96) NICE recommend using the MRC dyspnoea scale to assess breathlessness, performing spirometry at diagnosis, and using post-bronchodilator spirometry to confirm a diagnosis of COPD. The GOLD COPD guideline advocates active case-finding in symptomatic and/or at-risk groups, therefore a broader group than the NICE guidelines as this would include asymptomatic individuals.(97)

Participants in LHC programmes are at high risk of COPD due to their age and smoking history. Performing spirometry in all participants regardless of symptoms would be in keeping with GOLD guidance, whilst limiting spirometry to those who are symptomatic would be in keeping with NICE guidance. Those with a pre-existing diagnosis of airways disease such as COPD or asthma would not necessarily need to undergo spirometry as demonstrating airflow obstruction on spirometry in this group would not aid diagnosis, though participants may still be keen to know the severity of airflow obstruction as part of their “Lung Health Check”. Most LHC programmes that have included spirometry have done so without giving a bronchodilator, therefore those with airflow obstruction should ideally undergo further assessment including post-bronchodilator spirometry to confirm the diagnosis of COPD. This could be done in primary care, potentially with added support as part of the LHC programme, or within the LHC programme itself.

The proportion of participants in a LHC programme identified as having a possible new diagnosis of COPD will be influenced by what proportion of participants undergo spirometry as part of their LHC, what proportion have COPD, and in what proportion the diagnosis of COPD is already known. In Manchester 22% of participants had a prior diagnosis of COPD and 37% had airflow obstruction on spirometry.(34) The proportion of patients with a new diagnosis of COPD was not reported (and will not necessarily be the difference between these two percentages). In Liverpool 23% of participants had a prior diagnosis of COPD, 63% of participants underwent spirometry and 37% of those had an abnormal result, usually due to airflow obstruction.(37) It was anticipated that 10% of those participants who did not have a prior diagnosis of COPD would be diagnosed with COPD as a result of undergoing a LHC, 65% of whom would have mild airflow obstruction. An analysis of a representative subgroup of males who underwent spirometry in the NELSON trial revealed airflow obstruction in 38%, with 63% having mild airflow obstruction.(98) The proportion with a prior diagnosis of COPD was not reported. In an analysis of participants in the COPDGene Study, which enrolled smokers with and without COPD to investigate genetic factors causing COPD and includes LDCT as part of the study, 61% of participants had a prior diagnosis of COPD, 44% had radiological emphysema, and 7% received a new diagnosis of COPD.(99) In the Yorkshire Lung Screening Trial, all participants attending for a face-to-face LHC undergo spirometry but only those with symptoms and at least moderate airflow obstruction are highlighted for further action.

A modelling study in 2019 suggested that active case-finding of COPD every 3 years using a symptom questionnaire followed by spirometry in individuals who reported symptoms would have a cost per QALY of £16,596.(100) This model did not factor in the potential benefits of enhanced smoking cessation rates with

case-finding. The model made many assumptions, including a small beneficial effect on mortality of case-finding an earlier treatment which has not convincingly been demonstrated in randomised controlled trials. The model of triennial case-finding being cost-effective suggests that assessment of symptoms +/- spirometry if symptomatic could be done at regular intervals within a LHC programme rather than just at an initial LHC.

Radiological emphysema, which can be detected on CT, can occur in the absence of airflow obstruction. Whilst case-finding of COPD is recommended, identifying radiological emphysema without airflow obstruction is not of proven benefit and some LHC programmes have chosen not to report its presence.

Both the presence of airflow obstruction (usually due to COPD) and radiological emphysema (with or without airflow obstruction) are independent risk factors for the development of lung cancer.(101,102) Incorporating the presence or absence of these findings from the initial LHC into the assessment of lung cancer risk at subsequent screening rounds has been discussed (103) but has not yet been implemented in practice.

There has been little discussion on how best to manage other abnormal findings on spirometry, such as restrictive defects which can have a wide range of causes. Five percent of participants undergoing spirometry in the Liverpool programme had restrictive spirometry. Severe obesity may cause restrictive spirometry, and information regarding body mass index (BMI) could be available as it forms part of the PLCO<sub>M2012</sub> lung cancer risk assessment tool. Some other causes such as interstitial lung disease may be identified by LDCT, though depending on the structure of the LHC programme some people who undergo spirometry may not also undergo LDCT. Algorithms for how to deal with abnormal spirometry results would need to be put in place, with more complex results interpreted by a clinician incorporating other information. Some LHC programmes have chosen not to report spirometry abnormalities other than airflow obstruction.

In summary, accepting the differences in populations and methods in the results described above, approximately one-third of LHC attendees are likely to have evidence of airflow obstruction on spirometry most of whom will have COPD, and around 10% of those attending for a first LHC may have a new diagnosis of COPD. This is likely to be reduced to <5% if those with mild airflow obstruction only are excluded. Some who do not have airflow obstruction on spirometry at their initial LHC may go on to develop COPD during the duration of a long-term programme, so performing spirometry at subsequent rounds could also be of value. The incidence of new COPD diagnoses would be likely to be lower during subsequent LHC rounds, as most “latent” undiagnosed cases would be found during the first LHC round.

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## CORONARY ARTERY DISEASE

Coronary artery disease shares risk factors with lung cancer including age and smoking history, and was the leading cause of death in the NLST cohort.(18) NICE guidance on cardiovascular risk assessment recommends annual estimation of risk for people over the age of 40 years.(104) Those estimated to have a 10-year risk of cardiovascular disease of  $\geq 10\%$  should undergo a formal risk assessment using the QRISK2 risk assessment tool, with statin therapy recommended for those with a formal 10-year risk of  $\geq 10\%$ . Systematic assessment is not uniform across Wales meaning that many people at high risk of cardiovascular disease will not have had their risk factors adequately addressed. Therefore, identification of cardiovascular disease during LHCs could address an unmet need.

Coronary artery calcification (CAC) is readily detected on LDCT, and in asymptomatic individuals indicates subclinical coronary artery disease. CAC is a strong predictor of future coronary events and related mortality,(105) and CT assessment for CAC to improve risk stratification in individuals at intermediate risk of coronary artery disease is recommended by various groups including the American College of Cardiology/American Heart Association and the European Society of Cardiology.(106,107) However, offering

statin therapy on the basis of detection of CAC alone is not currently recommended given the lack of prospective evidence to support this. A dedicated gated cardiac CT is usually the investigation of choice for CT assessment of coronary artery calcification, the protocol for which differs from that of LDCT for lung cancer screening. However, there does appear to be good correlation between the results of dedicated cardiac CT and LDCT used for lung cancer screening.(104,105) Severity and extent of calcification can be measured by several methods, including formal computer-aided calculation scores such as the Agatston score, a simpler score of 0-3 based on each main coronary artery to give a total score of 0-12, or a very simple overall visual assessment of absent/mild/moderate or heavy coronary artery calcification.(105)

The relevance of coronary artery calcification on LDCT detected during lung cancer screening has been investigated retrospectively in participants in NLST and NELSON.(108,109) Coronary artery calcification was a strong independent risk factor for cardiovascular events, with an increasing hazard ratio for events with higher calcification scores. In a retrospective analysis of NELSON where a randomly selected subgroup of participants' LDCTs were assessed for coronary artery calcification, 10% had a previous history of cardiovascular disease.(108) Of those remaining, 24% had no coronary artery calcification, 29% had mild calcification, 30% moderate and 17% severe based on the scoring system used. Of those in the moderate and severe groups, 48-64% were not on statin treatment.

The relationship between the presence of CAC on LDCT and QRISK2 score has been evaluated in LSUT.(110) In this UK cohort, aged 60-75 years who had been coded as a current smoker within the past 5-7 years and underwent LDCT after risk assessment at a LHC, 11% had a previous history of cardiovascular disease. Of those remaining, 61.9% had evidence of CAC on LDCT with heavy CAC in 7.2%. QRISK2 score estimated without measurement of serum cholesterol was  $\geq 10\%$  in 98% of participants. Of these, 56.8% did not report a history of statin use. These findings suggest that almost all participants in lung cancer screening with LDCT would be eligible for statin therapy according to current NICE guidance regardless of the presence or absence of CAC, which would make its presence or absence irrelevant. Given the strong relationship between CAC and cardiovascular events, an unanswered question is whether the presence or absence of CAC in this setting could help refine risk stratification, identifying lower risk individuals less likely to benefit from statin therapy and very high-risk individuals in whom more intense intervention strategies may be beneficial. Some LHC pilots such as in Liverpool have formally assessed QRISK2 as part of the LHC process.

Given these uncertainties, there has been much debate about the value of reporting CAC on LDCT for lung cancer screening. Given the near ubiquitous high QRISK2 scores in those in LSUT, the strategy of reporting moderate to severe CAC in order to highlight those who should undergo formal QRISK2 assessment would seem to add little value if cardiovascular risk stratification was already taking place. However, those with both a high QRISK2 score and CAC are likely to be at the highest risk and prioritising primary protection strategies in this group is likely to offer the greatest benefits, though this has not been confirmed prospectively. It has also been suggested that awareness of the presence of CAC may motivate patients and healthcare professionals to address risk factors more promptly and may overcome patient-related barriers to statin therapy such as concerns about side effects.(110) This would need to be balanced against the potential downsides: assessing coronary artery calcification on LDCT would increase the time required for radiology reporting (though AI reporting may aid this in future); additional work would be required to convey the results to the patient and their GP; and reporting of the findings would generate additional work for primary care and cardiology services. One so far unexplored option is to co-deliver Lung and Cardiovascular health checks through a unified programme. This would be logistically challenging, as cardiovascular health checks are for a wider age range (starting age 40 years), and would not be limited to ever-smokers.

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## ATRIAL FIBRILLATION

In the Manchester programme an electronic device was used to detect atrial fibrillation (AF) as part of the LHC. This has not been a feature of other LHC programmes, and results regarding this aspect of the Manchester programme have not been published to date. The NSC do not currently recommend systematic population screening for AF, though noted that the Screening for Atrial Fibrillation with ECG to Reduce Stroke (SAFER) trial is in progress and will provide further evidence. The incidence of AF in the UK is predicted to rise over time, and earlier identification and treatment with anticoagulation could reduce the incidence of stroke.<sup>(111)</sup> However, anticoagulation carries significant risks, and the benefits of earlier detection have not been demonstrated in randomised controlled trials. It is therefore uncertain whether the risks of overdiagnosis and treatment with anticoagulation outweigh the benefits.

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## OTHER POTENTIAL ADDITIONAL COMPONENTS

Some LHC programmes have included measurement of HbA1C, and of cholesterol to formally calculate QRISK2 scores. The argument for these additional components is that people eligible for lung cancer screening are at high risk of morbidity and mortality from other conditions that could be detected at the time of a LHC. A broader approach to LHCs could offer additional health benefits, though the clinical and cost-effectiveness of these additional components is unproven. It is possible that these additional components could do more harm than good, either due to harms to individuals by overdiagnosis and further assessments, or by diverting resources to address them away from other more effective interventions.

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## BIOMARKERS

There has been much research aimed at identifying biomarkers in blood or breath tests that could help improve risk stratification of who should undergo LDCT and at what intervals, and to help determine whether detected nodules are likely to be malignant or not. At present, definitive evidence to support the use of any specific biomarker is lacking – all require further clinical validation and reproduction of results.

The Early detection of Cancer of the Lung Scotland trial (ECLS) randomised 12,209 people in Scotland aged 50 to 75 years at high risk of lung cancer (either current or ex-smokers with at least a 20 pack-year history, or less than 20 pack-year history but with a family history of lung cancer in a first degree relative) to either no intervention or to an EarlyCDT-Lung blood test.<sup>(112,113)</sup> The blood test is designed to detect autoantibodies to abnormal cell surface proteins, which may allow earlier detection of cancer. Those with a negative blood test underwent no further tests, whilst those with a positive blood test underwent intense surveillance including five CT scans over two years. The results were presented in 2019, reporting that 41.1% of participants who underwent the blood test and were diagnosed with lung cancer had stage 1 or 2 disease, compared to 26.8% in the control arm. The reporting that use of the blood test led to more early-stage lung cancers being detected has been criticised, as CT scanning is known to detect more early-stage lung cancers than usual care and those in the control arm did not undergo routine CT scanning, therefore making it impossible to determine how much of the effect was due to the blood test and how much was due to CT scanning.

Ongoing research into the role of biomarkers includes the SUMMIT trial which aims to clinically validate a blood test used to detect cell-free nucleic acids. SUMMIT is due to complete in 2030.

## COST EFFECTIVENESS

Estimates of the cost-effectiveness of LDCT screening have varied widely. Factors that influence the cost-effectiveness of a LDCT screening programme include eligibility criteria, diagnostic pathways and follow-up protocols, population characteristics including smoking prevalence, and healthcare system characteristics and costs. Cost-effectiveness estimates rely on many assumptions within their models, have used different methodologies, and have been based on different programme designs. Estimates made for other countries may not be applicable to the UK. In addition, the cost-effectiveness of lung cancer screening in isolation may not reflect the cost-effectiveness of a broader LHC programme.

In June 2020 a cost-effectiveness modelling study was commissioned by the National Screening Committee and is expected to report in summer 2021.

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### COST EFFECTIVENESS OF LDCT SCREENING

Estimates of cost-effectiveness using data from NLST and based on the American healthcare system have been unfavourable. Based on NLST and when compared to no screening, LDCT screening has been estimated to cost an additional \$1,631 per person, with an incremental cost-effectiveness ratio (ICER) of \$52,000 per life-year gained and \$81,000 per QALY gained.<sup>(114)</sup> The authors noted that modest alterations to the assumptions in the model led to large changes in the estimates.

A further retrospective analysis of participants in NLST examined the effect of applying the PLCO<sub>M2009</sub> risk calculator (a earlier version to PLCO<sub>M2012</sub>) using a threshold of  $\geq 2\%$  over 6 years to determine eligibility for screening.<sup>(115)</sup> Only 19.7% of participants in NLST were above this risk threshold. Applying this risk assessment to determine eligibility for LDCT and comparing it to usual care, there was an average gain of 0.032 QALYs at a cost of Can\$668 (Canadian dollars). Based on 2017 (time of publication) exchange rates, this equates to approximately £12,400 per QALY gained. Using the risk calculator reduced the estimated overall cost of screening by excluding low-risk participants, though had little effect on the cost-effectiveness of LDCT in this model as cost-effectiveness was largely driven by non-lung cancer outcomes including mortality reductions or improvements in quality of life related to smoking cessation and management of incidental findings. The authors suggested that overall, lung cancer screening would be likely to be cost-saving based on the American healthcare model due to the high costs of non-curative treatments such as chemotherapy and immunotherapy.

The cost-effectiveness of various screening scenarios using NLST- and NELSON-like selection criteria (based on age and smoking history without use of a risk calculator) has been estimated based on the Swiss healthcare system and population using a simulation model.<sup>(116)</sup> Compared to usual care, all screening scenarios led to an increased number of lung cancers being detected and a reduction in lung cancer mortality. Cost-effectiveness estimates ranged from €35,674 to €69,099 per QALY gained (£31,000 to £60,000 based on 2017 exchange rates). Annual screening led to a greater reduction in mortality than screening at 2- or 3-year intervals, but at greater cost and with greater harms (including rates of false-positive scans, overdiagnosis and invasive procedures). The most cost-effective scenario was to screen individuals aged 60-75 years with a >40 pack-year smoking history who currently smoked or had stopped within the last ten years, with a screening interval of three years. This scenario cost €24,972 per life-year gained. In all scenarios, the number of lung cancer deaths prevented was greater than the number of overdiagnosed cases at a ratio of 2-3:1.

UKLS included a cost-effectiveness analysis as part of study.<sup>(23)</sup> The cost-effectiveness of a single screening round compared to usual care was estimated at £8,466 per QALY. This estimate included costs of screening,

interval scans, investigations for those with suspicious findings, and diagnostic work-up and treatment for detected cancers. The estimated cost per lung cancer detected was £13,464. The total programme cost to screen approximately 2000 people, including modelling of an invitation protocol, was £754,877. If costs associated with treatment of cancers that would otherwise have been treated via usual care are offset, the net programme cost was £565,498.

A cost-effectiveness analysis of the Manchester pilot programme estimated a cost of £10,069 per QALY.(117) This analysis was based on a reconstruction of the UKLS cost-effectiveness trial analysis using data from the Manchester pilot. This estimate included costs of conducting the screening programme and of investigating and treating true- and false-positive results. Additional factors such as case-finding of COPD, the need to increase capacity of downstream services, costs beyond interval scans at 3 months, and one-off costs associated with initiating the programme (such as scoping evidence, rather than costs associated with the programme itself) were not included.

The cost-effectiveness of the Liverpool and Nottingham pilots was estimated as part of the ACE (Accelerate, Coordinate, Evaluate) project.(118) The cost per QALY was estimated at £13,087 and £19,453 for Liverpool at Nottingham respectively. These estimates included consideration of smoking cessation and case-finding of COPD, but the report notes that the large number of assumptions made in generating the estimates severely limit their robustness. The Liverpool pilot was larger than the Nottingham pilot, spent a larger amount on community engagement, and referred participants to local hospitals for CT scans rather than using a mobile unit.

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## COST-EFFECTIVENESS OF A LUNG HEALTH CHECK PROGRAMME

The individual core components of LHCs, namely targeted lung cancer screening, case-finding of COPD and smoking cessation interventions, appear to be cost-effective at usual thresholds used by NICE when delivered separately in the UK healthcare system. Co-delivering these components through a single programme to a high-risk population is likely to be more cost-effective than delivering them separately. In addition, some components have synergistic effects on others, for example, participating in lung cancer screening activity appears to have a positive effect on smoking cessation, and prolonged abstinence from smoking has a synergistic effect with LDCT screening on lung cancer mortality (figure 6).(76)

The cost of a LHC programme must be considered in comparison to the opportunity cost, i.e. the benefits that are lost by displacement of resources. One frequently discussed comparison is whether the investment required for a LHC programme would be more effectively spent on upscaling smoking cessation services. It has been commented that using the cost-effectiveness of smoking cessation services as the threshold for introduction for a LHC programme is an unfair bar to set, and one that is not applied to other new interventions.(119) Furthermore, LHC programmes are likely to result in increased smoking cessation rates, and modelling studies suggest that if a programme could double the smoking cessation rate compared to background quit rates the incremental cost-effectiveness ratio roughly halves.(120)

LHC programmes are likely to be cost-effective at the usual thresholds set by NICE. However, the total cost of a programme can vary widely whilst still being cost-effective. For example, annual or biennial LDCT screening may have similar levels of cost-effectiveness, but a programme screening annually will cost significantly more. In any resource-limited setting it is important for a LHC programme to both be cost-effective and to have a total cost that is acceptable within the wider healthcare system.

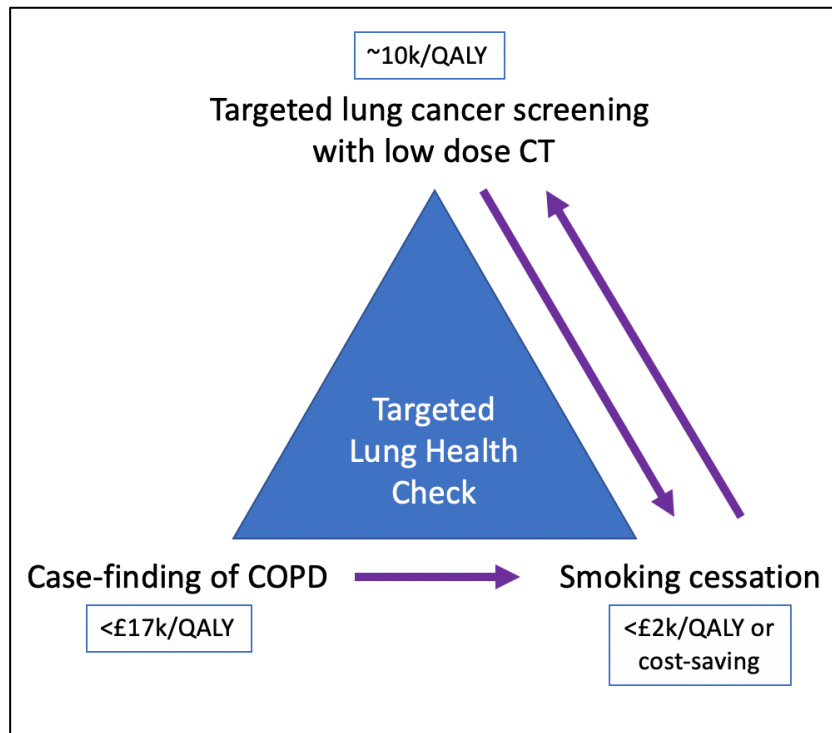


Figure 6: Cost-effectiveness of the components of targeted LHCs, and synergistic effects (arrows).

## WHERE COULD LUNG HEALTH CHECKS FIT INTO THE HEALTHCARE SYSTEM IN WALES?

Screening is defined by the UK National Screening Committee (NSC) as “the process of identifying healthy people who may have an increased chance of a disease or condition. The screening provider then offers information, further tests and treatment. This is to reduce associated problems or complications.”(121) The use of LDCT to identify people with asymptomatic early-stage lung cancer is consistent with this definition, and therefore constitutes screening. Until recently there had been much debate as to whether LDCT screening for lung cancer would be a “systematic population-based” or “targeted” screening activity. The NSC advises ministers on systematic population-based screening that applies to whole segments of the population, usually defined by age and/or sex only, whilst the National Institute for Health and Care Excellence (NICE) makes recommendations on programmes that are targeted at high risk groups, for example, targeted screening of women at high risk of breast cancer due to genetic mutations. This distinction has been blurred by the NSC making recommendations on diabetic eye screening, which only applies to the subgroup of the population with diabetes. The NSC lists the criteria for what it considers to be systematic population-based screening, and the contentious point for lung cancer screening has been that “there should be an effective means of identifying and contacting the whole cohort to be offered screening”. It is argued that GP records are an effective means of identifying all people with diabetes, but are not an effective means of identifying those with a sufficiently heavy smoking history to be eligible for lung cancer screening.

In October 2019, an independent review of adult screening programmes in England was published.(122) The report acknowledged the growth of targeted screening, which has traditionally fallen outside the remit of the NSC, and described the distinction as “an unhelpful historical anomaly”. The report recommended that a single advisory body be established, bringing together the functions of the NSC on population-based screening and NICE on targeted screening. This recommendation was accepted by Matt Hancock, Secretary of State for Health and Social Care. It is currently uncertain whether this will be achieved by extending the remit of the NSC or by forming an entirely new body. Nevertheless, LDCT screening and LHCs were specifically named as screening activity that did not clearly fall within the NSC’s current remit but would be appropriate for review by the proposed new body.

Prior to this development, the potential paths to implementation for a national LHC programme were complex (figure 7). A national LHC programme could have developed as a systematic population-based screening programme if recommended by the NSC, as a targeted screening programme following a recommendation by NICE, or as a “targeted health intervention” delivered outside of the usual structure for screening programmes. The third option is effectively where the current NHS England programme operates, though this commenced prior to any review by the NSC or NICE. Following the independent review of screening programmes, there is now a clearer potential path to implementation (figure 8).

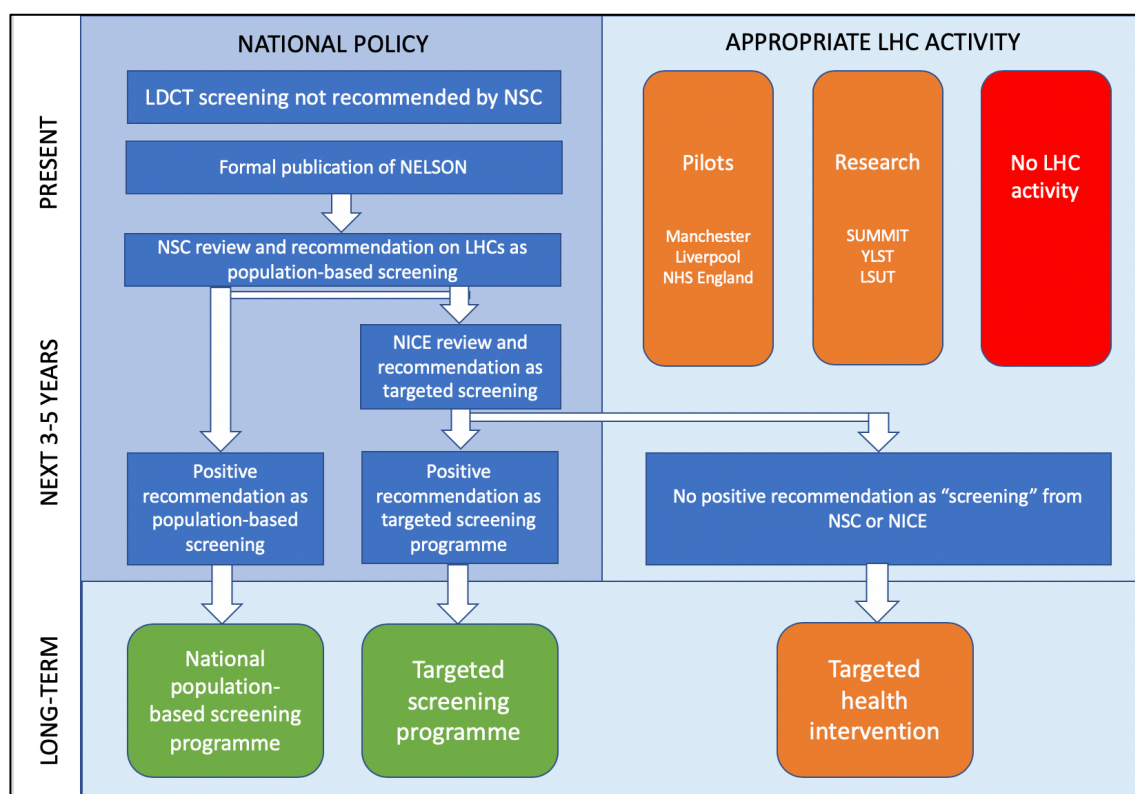


Figure 7: Potential paths to implementation for LHC programmes prior to the independent review on screening programmes.

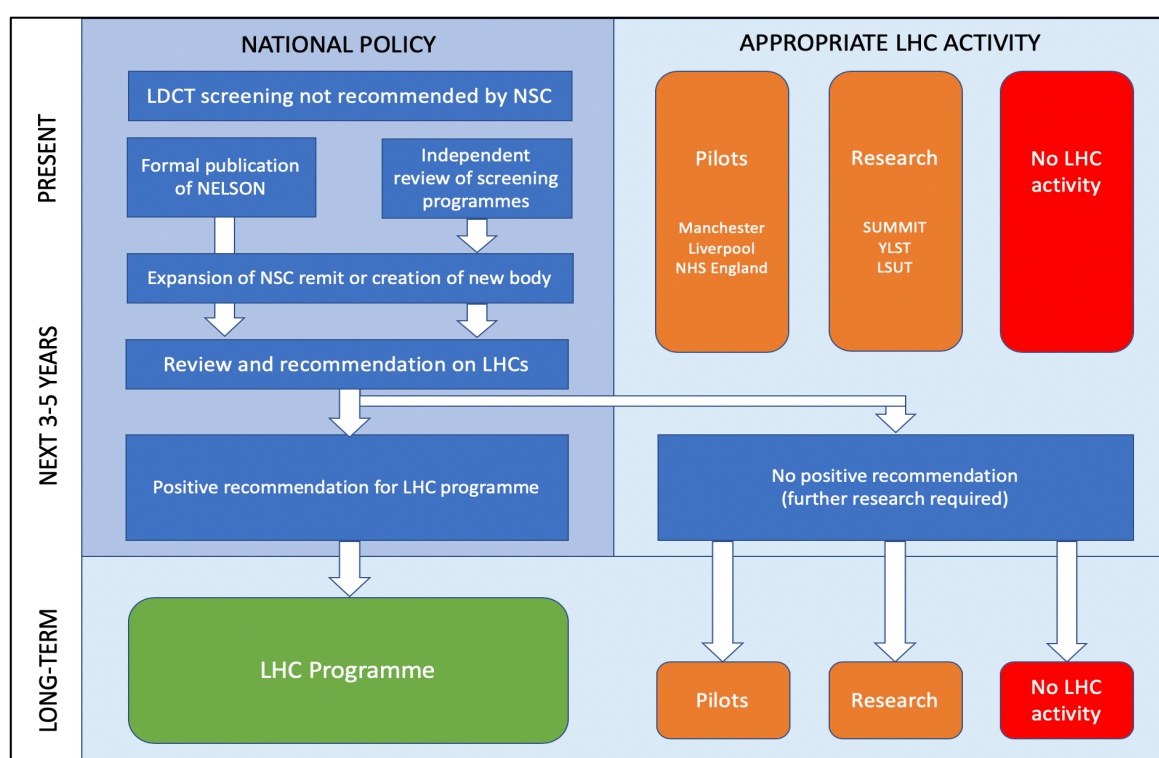


Figure 8: Potential path to implementation for LHC programmes following the independent review on screening programmes.

Now that there is a more clearly defined path to implementation it is sensible for any future national programme in Wales to be developed in line with this, rather than as a targeted health intervention operating outside of screening infrastructure as the NHS England programme currently does. However, it is important to note that the proposed new body does not yet exist, so its formation and review on LDCT screening/LHCs is likely to take some time.

The proposed changes have created some uncertainty as to how future screening programmes will be managed and funded. One of the problems highlighted by the independent review of screening programmes was the disparity between population-based and targeted screening programmes with regards to this. For population-based screening, in Wales the findings of the NSC inform the Welsh Screening Committee who advise Welsh Assembly Government (WAG). WAG mandates Public Health Wales (PHW) to commission, plan, deliver and quality assure population-based screening programmes. In contrast, delivery of targeted screening programmes is the responsibility of local health boards, with PHW providing support for call and recall, monitoring of the population and quality assurance for certain programmes. In England, the independent review also recommended that population-based and targeted screening programmes should come under a single body in future rather than being separated between NHS England and Public Health England. There is not a clear equivalent structure in Wales, and a LHC programme would differ from existing programmes as it falls somewhere between the previous definitions of population-based and targeted screening. It is important for PHW to be heavily involved in the planning, delivery and quality assurance of any future national LHC programme in Wales, as their expertise and experience will be vital to ensure that the programme is delivered to the high standards required for screening activity to be beneficial.

## IS A POSITIVE RECOMMENDATION FOR A LUNG HEALTH CHECK PROGRAMME LIKELY?

Previous concerns regarding whether LHCs or LDCT screening represent systematic population-based or targeted screening should no longer be an issue if the recommendations of the independent report on screening are implemented. As the proposed new body to make recommendations on all aspects of screening is yet to form it is uncertain what their review process will be, though it is likely to involve examining the benefits, harms and cost-effectiveness of screening interventions in line with the usual process of the NSC.

The evidence-base on LDCT screening suggests that the benefits of stage-shift, reduction in lung cancer mortality, and the positive effect on smoking cessation outweigh the risks of overdiagnosis, false-positives, radiation exposure and anxiety/participant distress. There are still some gaps and flaws in the evidence-base including heterogeneity in the definition of false-positive scans in the trials, under-representation of women, difficulties identifying the target population for screening from GP records, how best to engage the target population, and how best to deliver smoking cessation interventions alongside LDCT screening. However, the confirmation of a reduction in lung cancer mortality in a second large RCT together with UK pilots demonstrating that LHCs can be delivered successfully in the UK healthcare setting both add weight to the possibility of a positive recommendation.

If the NSC/new body take the view that the benefits outweigh the risks, the key remaining question is whether a LHC programme can be delivered at an acceptable level of cost. Estimates of cost-effectiveness in the UK healthcare system have been favourable, but there has not yet been a robust assessment of the expected cost-effectiveness and total cost of a large-scale systematic national programme. A cost-effectiveness modeling study was commissioned in summer 2020 and is due to report to the NSC in summer 2021.

Even if LHC programmes are cost-effective, they will still require investment: they are unlikely to be cost-saving or cost-neutral despite the likelihood of some reduction in expensive treatments used for late-stage disease. The variables selected for the programme such as the age range, criteria for LDCT and delivery structure would have major effects on the cost of the programme. The total cost of implementing the programme would need to be considered against the opportunity-cost, i.e. if that money was spent elsewhere, could it do more good overall. With regards to lung cancer, the only two interventions likely to make a significant difference to lung cancer mortality are LDCT screening and reducing the prevalence of smoking amongst the population. However, these two interventions will benefit populations at different time-points: LDCT screening could benefit the population in the short- and medium-term, whilst reducing smoking rates would have a beneficial effect primarily in the longer term. It is therefore unlikely that any other intervention would be more effective than a LHC programme at reducing lung cancer mortality in the at-risk population over the short- and medium-term.

There is little chance that the NSC/new body will make a positive recommendation for a national LHC programme to be implemented until the cost-effectiveness modelling study has been completed and its findings can be considered, which will be late 2021 at the earliest. There is a possibility that the NSC/new body will defer any decisions until the NHS England programme has also run its course and been evaluated. The programme was due to complete in 2023, though this may be delayed due to the COVID-19 pandemic.

One possible outcome of the NSC/new body's review is a recommendation for a LHC programme that is limited to targeting geographical areas with the highest incidence of lung cancer, where benefits are likely to be greatest. This would be akin to the current NHS England programme, which has selected areas with the highest burden of lung cancer. This would be more cost-effective than providing a LHC programme to the entire population and would limit the total cost of the programme, but could lead to concerns about inequity and a "postcode lottery" for LHCs. However, as lung cancer is more common in deprived communities it could be argued that targeting such areas would help to reduce health inequality overall.(123)

## WHAT ARE THE POTENTIAL MODELS AND RESOURCES REQUIRED FOR A NATIONAL LUNG HEALTH CHECK PROGRAMME IN WALES?

There is not currently a single “best” model for a LHC programme. If a national programme is taken forward in Wales then certain aspects of the programme may be mandated by the NSC/new body, whilst others would be left to the implementation team to decide.

The first decision would be whether to implement a LDCT screening programme alone or a broader LHC programme. The latter is likely to be the better option in order to co-deliver other beneficial interventions and improve cost-effectiveness, and because the concept of a LHC is likely to be more acceptable to the target population and therefore may improve uptake, particularly in those at highest risk. Co-delivery of a greater number of interventions could increase the cost-effectiveness of the programme, but would also increase the total cost of the programme. In a resource-limited setting, a more stream-lined programme that costs less may be preferable to a broader programme with a higher level of cost-effectiveness but an unacceptably high total cost. (figure 9).

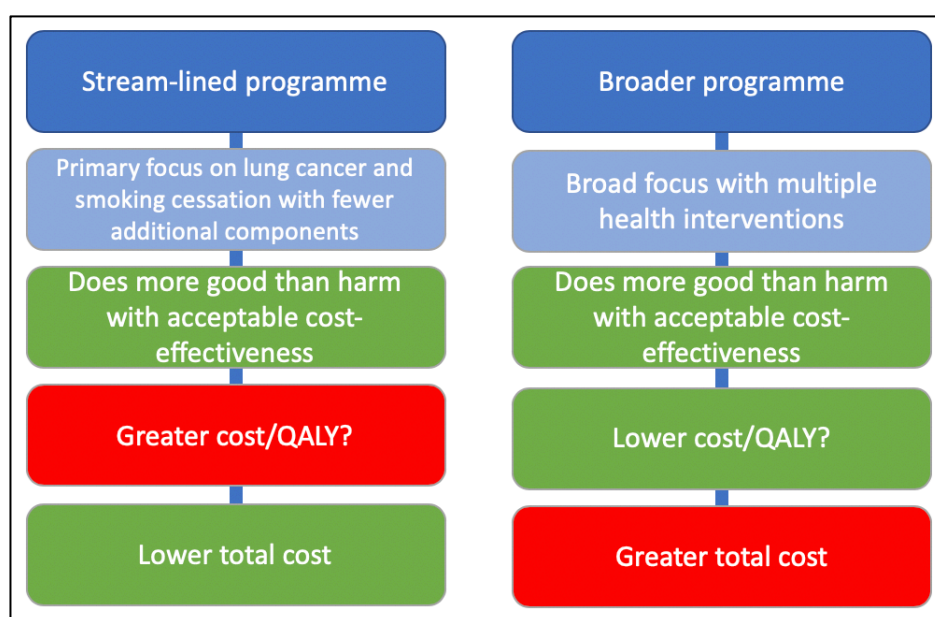


Figure 9: Stream-lined vs broader LHC programmes and the cost implications.

Other decisions would include the target age range, in what format and location to undertake the LHCs, and how to undertake the sieving process to identify those eligible for LDCT screening. A wide range of approaches to this have been taken in trials and LHC activity to date (table 3). The options selected for the NHS England programme were largely selected based on expert opinion rather than strong supportive evidence.

Table 3: Age ranges and filtering process from whole population to LDCT in screening and LHC activity to date.  
cpd = cigarettes per day.

	Age range (years)	Starting population	Invited for LHC	LHC location	LDCT inclusion criteria	LDCT location
<b>NLST</b>	55-74	-	-	-	30+ pack-year smoking history, + current smoker or quit within last 15 years	US screening centres
<b>NELSON</b>	50-75	-	-	-	15 cpd for 25 years or 10 cpd for 30 years, + current smoker or quit within last 10 years	University medical centres/hospitals
<b>UKLS</b>	50-75	All in age range	Based on postal questionnaire assessing lung cancer risk	-	LLP $\geq$ 5%/5yrs	Hospital-based
<b>YLST</b>	55-80	GP record all current and ex-smokers	All from starting population invited for telephone-based LHC, only those eligible for LDCT invited for face-to-face LHC	Community-based mobile unit	PLCO <sub>M2012</sub> $\geq$ 1.51%/6yrs or LLPv2 $\geq$ 2.5%/5yrs or 30+ pack-year smoking history + current smoker or quit within last 15 years	Community-based mobile unit
<b>Manchester</b>	55-74	All in age range	Invitation letter to phone to book LHC if current or ex-smoker	Community-based mobile unit	PLCO <sub>M2012</sub> $\geq$ 1.51%/6yrs	Community-based mobile unit
<b>Liverpool</b>	58-75	GP record all current and ex-smokers	All current and ex-smokers	Community health hub	LLPv2 $\geq$ 5%/5yrs	Hospital-based
<b>NHS England programme</b>	55-74	GP record all current and ex-smokers	All current and ex-smokers	Variable	PLCO <sub>M2012</sub> $\geq$ 1.51%/6yrs or LLPv2 $\geq$ 2.5%/5yrs	Mobile or fixed-site

## AGE RANGE

Lung cancer diagnoses in Wales follow an approximately normal distribution for age, with a peak at 71-75 years (figure 10).(4) The further the lower limit for age is extended from the peak age for lung cancer incidence, the more lung cancers will be detected, but the number needed to screen per diagnosis of lung cancer will be greater. The younger the population that is invited, the more likely it is that cancers will be detected in people of better performance status and with fewer co-morbidities who are fit for radical treatment. Younger patients have more additional life expectancy to gain if they are radically treated, and may benefit more from other aspects of LHCs such as earlier smoking cessation. However, as the number needed to screen per lung cancer diagnosis increases due to the lower incidence of lung cancer in younger people, the programme will become less cost-effective.

Most LHC activity has used a lower age limit of between 50 and 60 years (table 4), with the NHS England programme selecting 55 years. In UKLS, very few participants aged 60 years or under were eligible for LDCT using the LLPv2 risk model with a threshold of  $\geq$ 5%/5yrs, and few people under 55 years of age engaged in the recruitment process.(124)

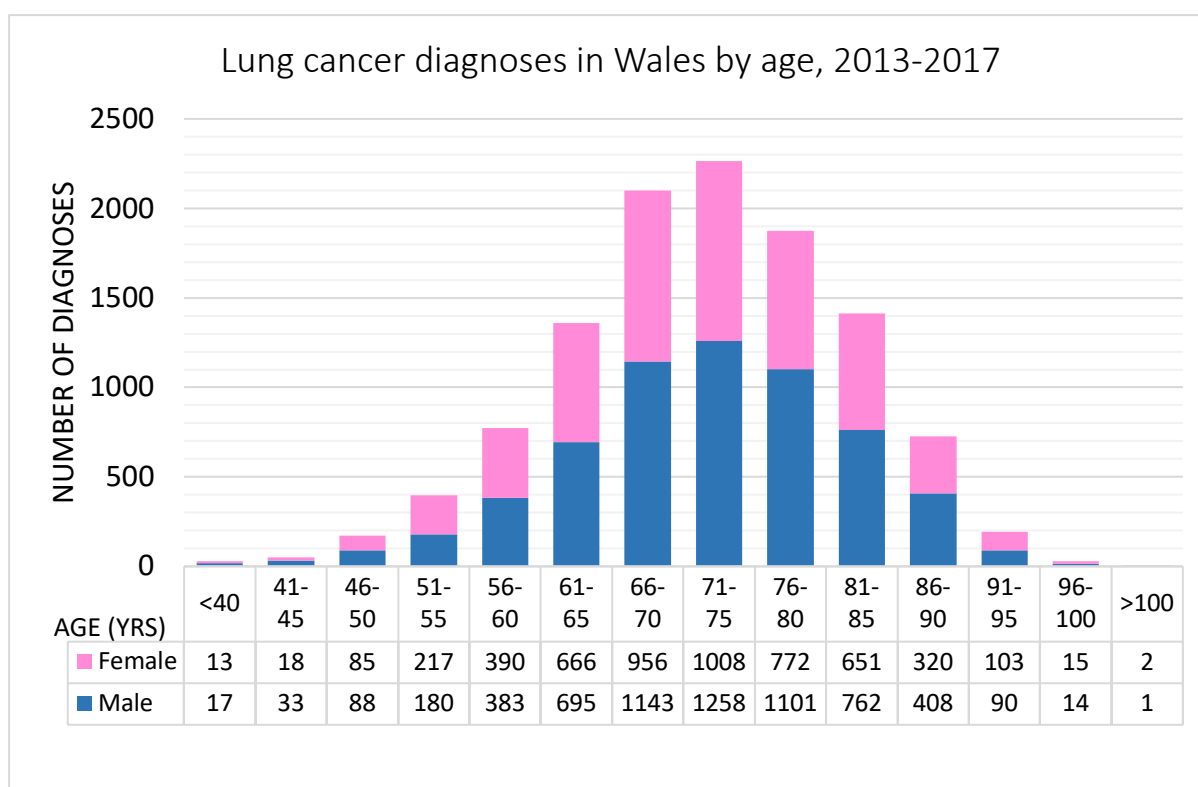


Figure 10: Age distribution of lung cancer diagnoses in Wales.

Trial/programme	Age range (years)
NHS England Lung Health Check Programme	55-75
NLST (US)	55-74
NELSON (Netherlands/Belgium)	50-75
UK Lung Screening Trial	50-75
Liverpool	58-75
Manchester	55-74
Nottingham	50-75
Lung Screen Uptake Trial (London)	60-75
Yorkshire Lung Screening Trial	55-80
SUMMIT	50-77

Table 4: Age ranges invited to LDCT/LHC activity.

Lung cancer is common in people above the upper age limits used in trials and programmes to date. Older people are more likely to have comorbidities or be of poorer performance status which may make them unsuitable for radical treatment if lung cancer is detected, and will have less life expectancy to gain from screening compared to younger people. As such, the target age range for LHCs has usually been weighted towards younger age groups up to and including the peak age range for lung cancer incidence. Screening up to a certain age could reasonably be expected to have a protective effect for several years after cessation of screening as early-stage lung cancers will have been identified and treated before they would have presented symptomatically. The key trials showing a mortality benefit (NLST and NELSON) did not include participants over the age of 75 years, hence there is no RCT evidence to strongly support LDCT screening above this age.

The NHS England programme selected an age range of 55-74 years. These were pragmatic cut-offs based on a mixture of evidence and expert opinion. It was initially planned to use an upper age limit of 80 years, but this was lowered based on modelling of how many additional LDCTs this would generate. Just over half (56%) of lung cancers in England occur in people aged 55-74 years. Informal discussions have suggested that the scale of the NHS England projects, particularly with regards to LDCT reporting, is proving challenging. The upper limit of 74 years (and 364 days) looks to be a sensible upper limit cut-off supported by evidence from trials and aligning with the peak incidence for lung cancer, but the lower limit could be varied to manage capacity. For example, Wales could choose to narrow the age range to 60-74 years, at least initially, in order to limit the resource implications for the programme. The exact impact this of this is difficult to accurately predict: it could reduce the target population and therefore the number of LHCs by around 25%, but more people towards the upper end of the age range would be eligible for LDCT so the reduction in LDCTs will be less than this, perhaps 10-15%.

## SIEVING PROCESS

Screening programmes perform a “sieving” function that filters those that require intervention from the wider population.<sup>(13)</sup> For LDCT screening, the starting point is all people registered at GP practices within the target age range. The final filtered group is those with findings on LDCT suspicious of lung cancer requiring urgent further investigation. This group are then referred to their local lung cancer service, with this point marking the line between the programme and downstream services.

The sieving process can be performed in different ways, with different resource implications. The steps in the process for a LHC programme are shown in figure 11.

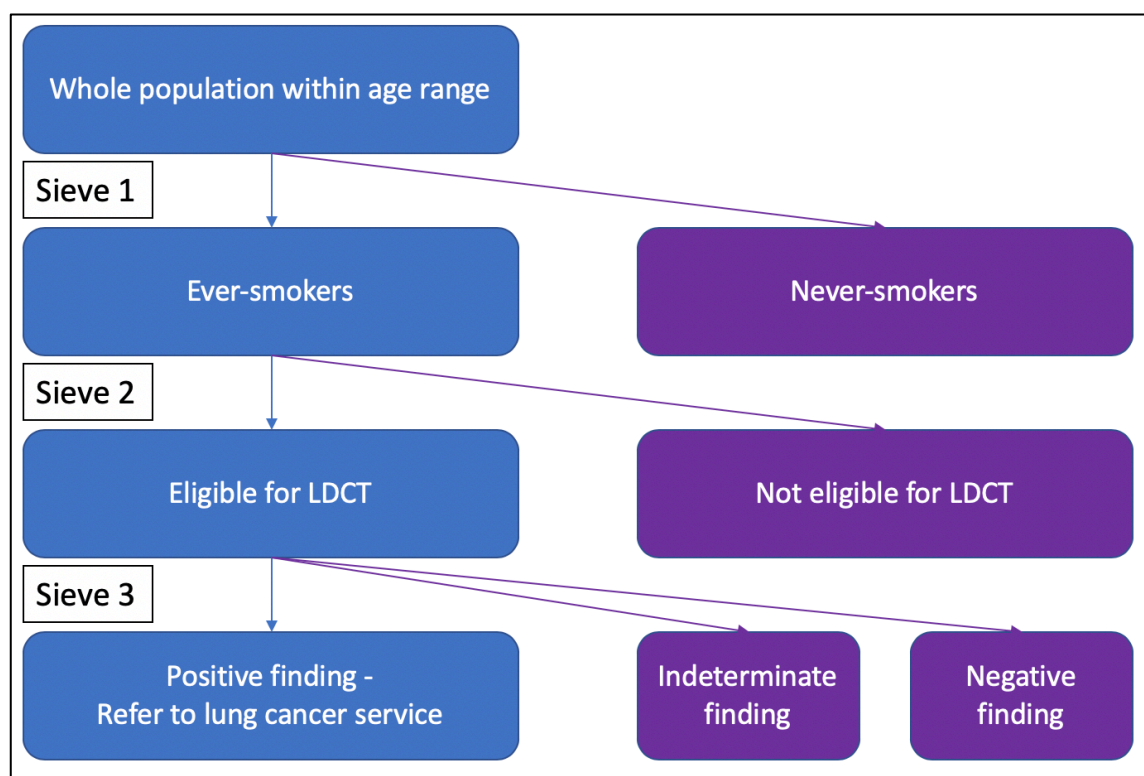


Figure 11: Sieving process for a LHC programme.

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## SIEVE 1

After identifying the broad target population based on age from GP records, two main options have been used for Sieve 1, which filters the population down to ever-smokers. Smoking data is held within GP records, and this has been used to identify ever-smokers in most LHC activity in England to date. The main exception is the Manchester programme, where all people within the target age range were contacted by letter and invited to book a LHC if they were an ever-smoker, thus not relying on the smoking data recorded on the GP record. Smoking status is not currently a Quality and Outcomes Framework (QOF) indicator, so there is not a financial incentive for GP practices to ensure smoking data is complete or up to date. The Manchester programme did not feel that the smoking data held on GP records was accurate or complete enough to rely on, hence contacting the whole population within the target age range.

The accuracy of the smoking data held on GP records as a whole across Wales is uncertain. It is likely that most people who are recorded as current or ex-smokers will have smoked at some point for this positive recording to have been made. There is a possibility that some people will be recorded as never-smokers either inaccurately at the time, because they have never been asked, or will have become smokers since the information was recorded. Smoking statuses that were recorded further in the past may be less accurate than those recorded more recently. From discussion with a small number of practices in different parts of Wales, the percentage of patients in the target age group with any smoking status recorded (with no indication of the accuracy of what is recorded) has varied from around 95% to as low as 60% in one practice. Publications in the USA have suggested that smoking status recorded in medical records is frequently inaccurate,<sup>(125)</sup> though also that there is variation in reported smoking history when taken directly from patients at different time-points.<sup>(126)</sup> Using GP records to determine smoking status costs less than contacting all participants, but if the records are not sufficiently accurate then it will undermine the effectiveness of the programme. If GP records are used as the source for smoking status, a project to update the data at participating GP practices prior to performing Sieve 1 could be undertaken. Similar projects have been funded by Public Health Wales to improve the data quality in GP records on immunization status prior to programmes being undertaken.

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## SIEVE 2

After filtering the population down to ever-smokers in the target age range, the next sieve is to identify those eligible for LDCT. This step has varied widely between programmes, both in terms of the criteria used for LDCT eligibility and the setting for the sieving process.

Many programmes including Manchester and the NHS England programme have invited all ever-smokers in the target age range for a face-to-face LHC and have performed the second sieve as part of it. It is estimated that in the NHS England programme 56% of those attending for a face-to-face LHC will be eligible for LDCT; therefore almost double the number of face-to-face LHCs will be performed compared to LDCTs, with associated resource implications. In contrast, YLST and SUMMIT have used telephone triage for the second sieve. YLST identifies ever-smokers in the target age range from GP records and invites them for an initial telephone-based LHC which includes confirmation of smoking status and questions to determine eligibility for LDCT. Only those who are eligible for LDCT are invited for a face-to-face LHC, which reduces the number of face-to-face LHCs performed compared to other programmes. This means that ever-smokers who are not eligible for LDCT may not have access to the other aspects delivered at face-to-face LHCs, though alternative arrangements can be put in place such as direct referral to smoking cessation services from the telephone-based LHC.

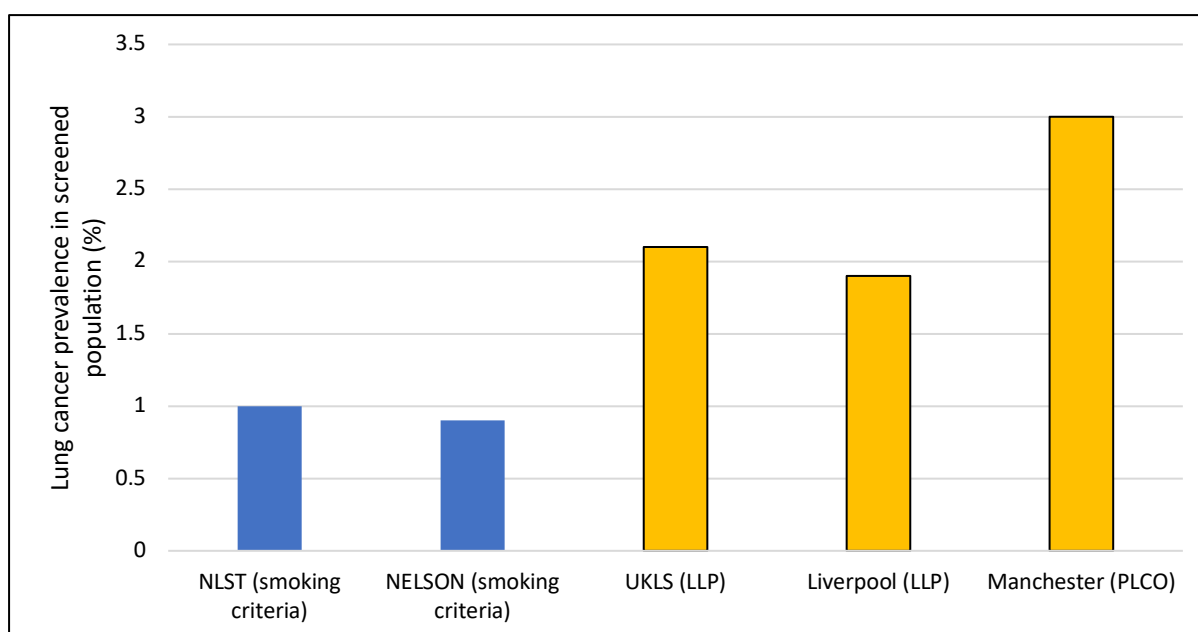
The eligibility criteria for LDCT have evolved over time. NLST and NELSON both determined eligibility for LDCT based on aspects of the smoking history alone (table 3, p38). However, the prevalence of lung cancer in the screened population was relatively low leading to attempts to enrich the prevalence of lung cancer in the screened population and improve the efficiency and cost-effectiveness of screening. This has been done by using risk assessment tools that estimate future risk of lung cancer. The main tools that have been used are the LLPv2 and PLCO<sub>M2012</sub> risk assessment tools (table 5).

*Table 5: Comparison of lung cancer risk assessment tools.*

<b>Tool</b>	<b>LLPv2</b>	<b>PLCO<sub>M2012</sub></b>
<b>Components</b>	<ul style="list-style-type: none"> <li>• Age</li> <li>• Gender</li> <li>• Smoking duration</li> <li>• History of pneumonia/COPD/emphysema/bronchitis/TB</li> <li>• Occupational asbestos exposure</li> <li>• Previous history of malignancy</li> <li>• Previous family history of lung cancer; relative's age at onset (&lt;60 y or &gt;60 years) and whether first degree relative</li> </ul>	<ul style="list-style-type: none"> <li>• Age</li> <li>• Education level</li> <li>• Body mass index</li> <li>• History of COPD/chronic bronchitis/emphysema</li> <li>• Personal history of lung cancer</li> <li>• Family history of lung cancer</li> <li>• Ethnicity</li> <li>• Smoking status</li> <li>• Average number of cigarettes smoked per day</li> <li>• Duration smoked (years)</li> <li>• Years having ceased smoking</li> </ul>
<b>Time-period future risk of lung cancer applies to</b>	5 years	6 years
<b>Thresholds used</b>	<ul style="list-style-type: none"> <li>• NHS England; <math>\geq 2.5\%</math></li> <li>• UKLS; <math>\geq 5\%</math></li> <li>• Liverpool; <math>\geq 5\%</math></li> <li>• YLST; <math>\geq 5\%</math></li> </ul>	<ul style="list-style-type: none"> <li>• NHS England; <math>\geq 1.51\%</math></li> <li>• Manchester; <math>\geq 1.51\%</math></li> <li>• YLST; <math>\geq 1.51\%</math></li> </ul>

Application of these tools has successfully enriched the prevalence of lung cancer in screened populations (figure 12) and their use is now generally considered to be best practice for the sieving process.

YLST is using three sets of criteria for the second sieve, including LLPv2, PLCO<sub>M2012</sub> and the US Preventive Services Task Force (USPTF) criteria for LDCT screening (which is based on the NLST smoking criteria with a broader age range). One of the planned outcomes of the trial is a comparison of the effectiveness of these criteria. The LLPv2 components can be fully determined by telephone. One of the components of PLCO<sub>M2012</sub> is body mass index (BMI): self-reported BMI is used at the telephone stage and is confirmed at the face-to-face LHC in YLST, which carries the risk of some patients initially being incorrectly categorised as being at high or low risk if their self-reported weight and height are inaccurate.



*Figure 12: Increased lung cancer prevalence in screened populations with the use of lung cancer risk assessment tools. Note that the number of screening rounds and screening intervals were not uniform between studies/programmes which may have contributed to the differences.*

Based on data from a survey in Yorkshire, the proportion of the population aged 55-80 who would be eligible for LDCT screening based on different eligibility criteria has been estimated (table 6).(127)

*Table 6: Proportion of population eligible for LDCT using various eligibility criteria, based on data from Yorkshire population.*

Eligibility criteria for LDCT	Proportion of population age 55-80 years who are eligible for LDCT	95% confidence interval
NLST criteria	11.9%	10.6-13.2
USPTF criteria	13.3%	12.0-14.7
PLCO <sub>M2012</sub> $\geq 1.51\%/6\text{yrs}$	20.7%	19.1-22.3
LLPv2 $\geq 5\%/5\text{yrs}$	15.8%	14.4-17.3

The NHS England programme assesses risk using both LLPv2 (threshold  $\geq 2.5\%/5$  yrs) and PLCO<sub>M2012</sub> (threshold  $\geq 1.51\%/6$  yrs) and offers LDCT to people above either risk threshold. The thresholds selected in the NHS England programme are based on evidence, modelling studies and expert opinion.(128,129) UKLS and Liverpool both used LLPv2 with a higher threshold of  $\geq 5\%$ . Lowering the threshold to  $\geq 2\%$  was considered for the NHS England programme as this was modelled to maximise the detection rate of lung cancer. However, this would have led to a substantial increase in the number of LDCT scans through the programme, so a pragmatic decision was made to use a threshold of  $\geq 2.5\%$ . Whilst relatively low thresholds for LDCT have been selected in the NHS England programme in order to maximise the number of lung cancer detected, using a higher threshold for LDCT eligibility such as LLPv2  $\geq 5\%/5\text{yrs}$  is one option to limit the number of LDCTs performed if capacity for LDCT reporting is a concern. Publication regarding an updated version of LLP (v3) is due in late 2020. The impact of applying LLPv3 to a LHC programme population is not yet known.

## LUNG HEALTH CHECK DELIVERY

Some programmes have delivered LHCs in two stages: an initial telephone-based LHC to determine eligibility for LDCT, followed by a face-to-face LHC only for those eligible for LDCT. Others have invited all ever-smokers for a face-to-face LHC, with only a proportion of those attending going on to have a LDCT.

Face-to-face LHCs have been delivered in different settings. Manchester, Leeds, and most projects in the NHS England programme have used mobile community-based units with on-site LDCT. The Manchester mobile LHC unit, provided by Cobalt and Siemens Healthineers, consists of three lorries which connect together to form a single large unit containing areas for consultations, spirometry, blood tests for research projects, a waiting area, a staff room and a LDCT scanner. Various configurations of mobile units have been developed depending on the needs of different programmes.

An alternative model is to perform the face-to-face LHC in a static setting such as a GP practice or community health hub, with those eligible for LDCT sent to either a mobile LDCT scanner or referred to their local hospital for the scan. It may be that a mixture of approaches would be best for a national programme in Wales. Existing hospital-based CT scanners are unlikely to be able to provide the additional scanning capacity required for a LHC programme, so additional scanners would be needed. Mobile CT scanners are expensive to run, costing around £2500-£3500/day for 12-hour days. A larger dedicated LHC unit would cost more and would require a larger location, but would avoid the need to find separate locations to perform both the face-to-face LHC and the LDCT. There is a significant cost of moving and setting up mobile units at a new site. In more densely populated urban areas with good transport links such as in Cardiff or Swansea centrally located static-site LDCT scanners could provide better value, whilst mobile units may be a more effective strategy for rural areas.

The target population for LHCs can be difficult to engage, particularly those at highest risk.<sup>(32)</sup> Participants in the LHC programme in Manchester expressed a preference for a community-based location over hospital-based, with the preference strongest in current smokers and those in the most deprived socio-economic groups.<sup>(130)</sup> Travel was highlighted as an important barrier to participation.

Most programmes have developed a “LHC Hub” where much of the programme activity other than the face-to-face LHCs occurs. This could host the telephone-based component of LHCs, booking of face-to-face LHCs, assimilation and communication of results, and the management and governance aspects of the programme.

## LUNG HEALTH CHECK COMPONENTS

Of the potential additional components that can be included in a LHC programme beyond LDCT screening, smoking cessation interventions in current smokers are likely to have the greatest positive impact and be the most cost-effective add-on. There are different levels of intervention that can be included, ranging from simple advice through to an on-site counselor and provision of NRT. Providing the strongest possible intervention such as an on-site counsellor at the face-to-face LHC is likely to be the best option in order to maximise the opportunity to trigger successful quit attempts. The counsellor could have the opportunity to see multiple current smokers every day making it an efficient use of time, and commencing the “quit journey” when motivation is likely to be raised will lead to more quit attempts. If a telephone-based component is included then smoking cessation advice could be included as part of this, advising that quitting with help and medication offers the best chance of stopping and providing referral to smoking cessation services with participants having the option to opt-out.

All UK LHC programmes have included case-finding of COPD with spirometry. There have been differences in how this has been delivered, particularly with regards to what thresholds are used for further action. Many participants will have mild and/or asymptomatic airflow obstruction, and it is not clear that identifying these cases will be of significant benefit. In Leeds, only symptomatic participants with at least moderate airflow obstruction are highlighted for review by a community COPD team. Asymptomatic and/or mild airflow obstruction is recorded on the LHC reports but no specific action is recommended. Limiting the number of participants highlighted for further action will reduce the additional work generated by the programme.

LHC programmes have included a variety of other components such as estimating cardiovascular risk, HbA1c and AF screening. Those with a greater number of additional components have argued that the target population for LHCs are at risk of a myriad of other health problems, that identifying and intervening in these problems may improve overall life expectancy, and that this would therefore reduce the overdiagnosis rate of the programme as competing causes of death would be reduced. The arguments against include the cost of additional components, and that by screening for multiple conditions there is a greater risk that the activity may not occur in a well-planned, quality-assured manner. Including a large number of additional components also risks the core messages and objectives of a LHC programme getting diluted or lost within a broader programme.

## LDCT REPORTING

Capacity for LDCT reporting is one of the greatest challenges for a national LHC programme, and is discussed in detail later in this report (p61).

For a LHC programme to be successful it is vital that the LDCT reporting is of high quality. It is important that sensitivity for detecting pulmonary nodules requiring urgent investigation or surveillance is high in order to maximise the benefits, but also to avoid excessive investigation or surveillance for findings that are unlikely to be clinically significant in order to minimise harms. Radiologists with adequate experience in reading thoracic CTs who have undergone specific training on reporting LDCT screening scans and who participate in lung cancer MDTs are likely to be best placed to maximise the sensitivity and specificity of LDCT findings. AI software to aid nodule detection and reporting is also likely to improve the sensitivity and efficiency of reporting.

Standardised reporting criteria for suspected lung cancers, pulmonary nodules and incidental findings should be set and a standardised reporting template used. A “positive findings” meeting has been a feature of some LHC programmes, where detected abnormalities are discussed by a group of radiologists to increase confidence to dismiss clinically insignificant findings.

## DOWNSTREAM PATHWAYS

When an individual’s LHC and LDCT are complete the findings need to be reported, communicated and acted on. Standardised protocols defining which findings should be reported and highlighted would be required. Findings suspicious of lung cancer would be referred directly to the local lung cancer service, with care “handed over” from the programme at this point. It would be important to track cases referred from the programme for evaluation purposes. There has been some discussion as to whether a contrast-enhanced CT should be performed as the next step for all cases with findings suspicious of lung cancer. This is probably best left to local teams to decide on a case-by-case basis, as in some cases non-contrast-enhanced LDCT may reveal obvious metastatic disease and a contrasted scan would not alter management.

Around 15% of participants undergoing LDCT will have an “indeterminate” scan due to the finding of a pulmonary nodule which is not suspicious enough to warrant urgent referral to the local lung cancer service, but also not low risk enough to disregard. The NHS England standard protocol recommends that monitoring such nodules is done within the LHC programme rather than handed back to local teams, and that the interval for surveillance should be as defined by the BTS guidelines on pulmonary nodules.(20) The high-level participant pathway from the NHS England programme, which would be an acceptable model for a national programme in Wales, is shown in figure 13.

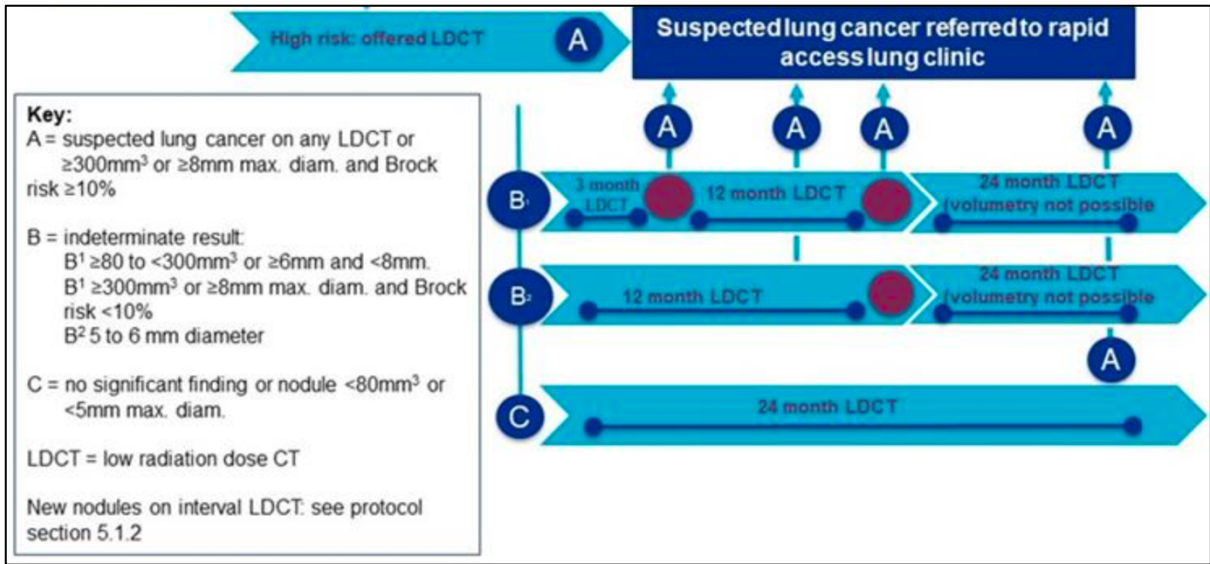


Figure 13: Participant pathway for NHS England TLHC programmes.

The NHS England programme has developed an “incidental findings” reporting protocol (43) that could be adapted for use in Wales. Important findings requiring secondary care input should be referred directly from the programme rather than requesting for this to be done by primary care.

The downstream pathway for smoking cessation input would be dependent on what is provided during the LHC. For current smokers who do not see a smoking cessation counsellor in person, advice and referral to local smoking cessation service with the option to opt-out could be provided either from the telephone-based or face-to-face LHC.

For spirometry, algorithms with actions based on results would need to be developed or adapted from other LHC programmes. Participants who fit certain criteria would be highlighted for a further review, which could be conducted in an enhanced primary care clinic with support from community respiratory nurses. The actions taken in YLST based on spirometry results are shown in table 7.

A report in a standardised format should be generated and sent to the participant’s GP. The report should clearly highlight the most important findings, the actions being taken, and any actions required by primary care. Ideally a copy of the report should also be made available through a widely accessible system such as Welsh Clinical Portal.

Table 7: Actions taken in YLST based on spirometry results

FEV <sub>1</sub> /FVC	FEV <sub>1</sub> % predicted	COPD symptoms	Action
<70%	Any	Absent	Spirometry results sent to GP with comment that this is obstructive spirometry, but that the participant is either asymptomatic or the reduction in lung function is mild so no referral has been made to Community Respiratory Team. No specific action required other than smoking cessation interventions in current smokers.
<70%	≥100%	Present	
<70%	80-100%	Present	
<70%	<80%	Present	Suggestive of COPD; referred to Community Respiratory Team.

## LONG-TERM MODEL

There has so far been little discussion on how a LHC programme should operate over the longer-term. Important aspects that would need to be decided include the interval between LDCTs following a normal scan, whether a full LHC is performed at subsequent rounds or a LDCT only, and how to manage individuals who do not meet the criteria for LDCT initially but may cross the risk threshold before reaching the upper age limit for the programme.

It is clear that ongoing screening within the target age range is required to reduce lung cancer mortality. NLST performed annual LDCT, whilst NELSON used increasing screening intervals of 1 year, 2 years and 2.5 years. In NELSON a greater proportion of the lung cancers found after the 2.5 year screening interval were late-stage compared to with shorter screening intervals, suggesting that a 2.5 year interval is too long.<sup>(50)</sup> Modelling studies suggest that annual LDCT screening is likely to be more cost-effective than biennial or triennial screening,<sup>(116)</sup> but the total cost of the programme would be significantly greater. The NHS England programme pragmatically decided on a two-year interval for participants with a normal baseline LDCT, which would be a reasonable model for Wales based on current evidence.

If a two-year LDCT screening interval is used, the next question is whether additional LHC components should be re-delivered during subsequent rounds. Some people will continue to smoke meaning smoking cessation interventions may continue to have value. The value of performing spirometry at each subsequent LHC is likely to diminish as most “latent” cases of COPD will be discovered during the first LHC round. Some people will go on to develop COPD during the duration of their participation in the programme, so there could be some value in repeating spirometry at later rounds, but whether the benefits would be worth the time and cost is uncertain. One option is for a more comprehensive LHC on entering the programme followed by more stream-lined subsequent rounds to include LDCT, questions to assess for new symptoms, signposting and referral to smoking cessation services, and spirometry only in selected cases.

Some ever-smokers who are not above the risk-threshold for LDCT will become eligible for LDCT over time as lung cancer risk increases with age. At the initial LHC, it should be possible to estimate participants’ risk at that time and project whether they would be above the risk threshold at an older age assuming other parameters remain the same. Most existing programmes are only planned to operate for a finite period of time, so participants are discharged if they are not above the risk threshold at the initial LHC. For a long-term programme a system to recall people who will pass the risk threshold in future would be desirable.

## DATA MANAGEMENT AND SOFTWARE

Data management systems would be needed for various aspects of a LHC programme. Ideally, a single integrated system would be developed that contains information about each participant and allows tracking of appointments, outcomes, reports and referrals. Databases for screening programmes in Wales are usually developed and run by the Public Health Wales informatics team, with a single national database for each programme. Development of such a database takes significant time and resources. It may be that separate software would be used for other functions such as capturing data from the telephone LHC and LDCT reports, that integrates with the screening programme database. Table 8 lists some of the systems that would be required to operate a LHC programme.

*Table 8: Data management systems and software required for a LHC programme.*

	<b>Description</b>
<b>Participant database</b>	Master database to manage call and recall, record results, referrals and outcomes.
<b>Front-end software for LHC</b>	To record symptoms, smoking status and components of lung cancer risk assessment. Integrated calculation of lung cancer risk. Links to booking system for face-to-face LHC/LDCT. System to guide “Lung Health Checker” through telephone consultation, limit answer inputs to plausible values, provide prompts for discussion and referrals e.g. smoking cessation. Recording of spirometry results at face-to-face LHC.
<b>LDCT reporting tool</b>	Template for LDCT reporting: structure and limit inputs based on reporting protocols (e.g. limit opportunities for free text, specify datasets for nodules and suspected cancers, prompt review for incidental findings and limit reporting to defined significant findings). Integrated calculation of Brock score (indicating malignancy risk of pulmonary nodule) based on nodule characteristics and information from the LHC. Link reports to participant database.
<b>AI reporting</b>	Software for computer-aided detection of pulmonary nodules. Aids radiologists to detect and more efficiently report LDCT findings. The main software programmes used in existing LHC programmes have been Veolity (131) and Veye Chest (Aidence) (132).
<b>LHC reporting</b>	Much of an individual’s LHC report could be generated by software that extracts information and applies algorithms to the LHC, spirometry results and LDCT reports. This would require the data to be held in standardised formats. Human reporting could be limited to situations that do not fit into the defined algorithms.
<b>Virtual positive findings meeting</b>	A positive LDCT findings meeting where radiologists review scans with possible abnormalities could be held by video-conference.
<b>Imaging repository</b>	LDCT images are likely to be of value in clinical practice, for example if a patient is subsequently admitted to hospital. A central repository for image storage would be needed. Radiologists would need to be able to access both LDCT screening scans and previous scans done in Wales to determine if findings are new or old.

## QUALITY ASSURANCE

Quality assurance is vital to the success of a screening programme. The essence of quality assurance for a screening programme is to set objectives and standards for each aspect of the programme, establish systems for achieving them, to monitor performance, and to take action to improve performance where necessary. The NHS England programme has produced a Quality Assurance Standards document (43) that could be adapted for use in Wales. The areas covered include standards for:

- Lung cancer screening nurses and radiologists
- Radiology hardware and software
- Patient Administration System software
- Data management
- LHC programme pathways
- Participant and General Practice communications
- Smoking cessation
- Participant experience
- LDCT referral, performance and reporting
- External quality assurance of radiologists

## GOVERNANCE

Clear lines of responsibility are important to ensure effective running of a LHC programme. Each project in the NHS England programme utilises the clinical governance structure shown in figure 14. A national LHC programme in Wales could use a similar structure, with a Responsible Assessor and Responsible Radiologist reporting to a Clinical Director of Programme. A national LHC programme would feed into multiple lung cancer services across Wales so there would be a number of responsible clinicians based in different geographical areas. A detailed description of the responsibilities of these roles are given in the NHS England programme standard protocol (42), which could be adapted for use in a national programme in Wales.

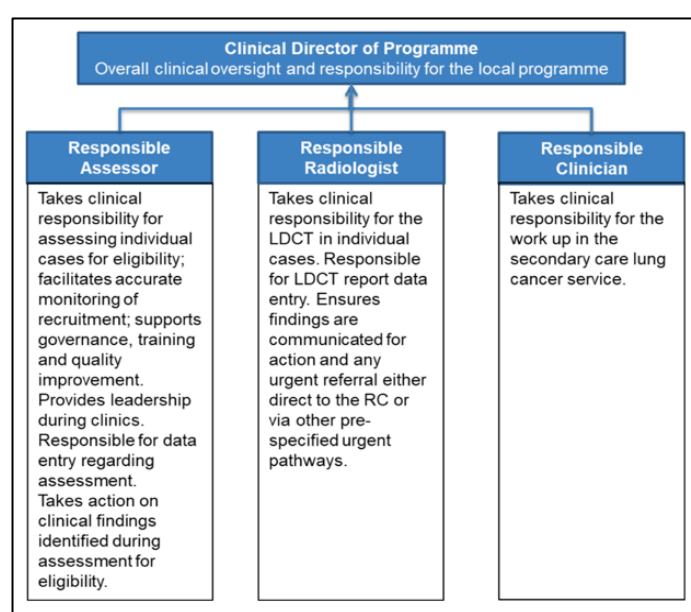


Figure 14: Structure for clinical governance within the NHS England LHC programme.

## EVALUATION

Evaluation of a LHC programme should include a review of lung cancer and pulmonary nodule diagnoses and outcomes, COPD diagnoses, assessment of uptake of the programme, and assessment of whether those at highest risk are being reached. As there are still uncertainties regarding the best way to implement a LHC programme, alterations to the programme may be needed based on evaluation findings or emerging evidence. Areas of particular interest for evaluation would include how to identify those at highest risk, the impact of the programme on downstream services and their capacity to deal with findings from the programme, and long-term trends in lung cancer mortality following the implementation of the programme.

Evaluation of pilot LHC activity would not necessarily be focused on the same areas as for a national programme. Pilot evaluation would be more focused on testing processes, whilst a national programme would be more concerned with evaluating outcomes. The NHS England programme is being externally evaluated by Ipsos MORI. Health Technology Wales is a body that could potentially evaluate a LHC pilot in Wales.

## COMMUNICATION STRATEGIES

### INVITATIONS

Existing LHC programmes have found that participants respond well to invitations for a “FREE Lung Health Check” that are framed as being from their GP practice, utilising their letter style and logo, but replacing practice contact details with those of the LHC programme. Uptake has generally been poor after a first invitation letter alone; a series of invitations has been associated with improved uptake (figure 15).

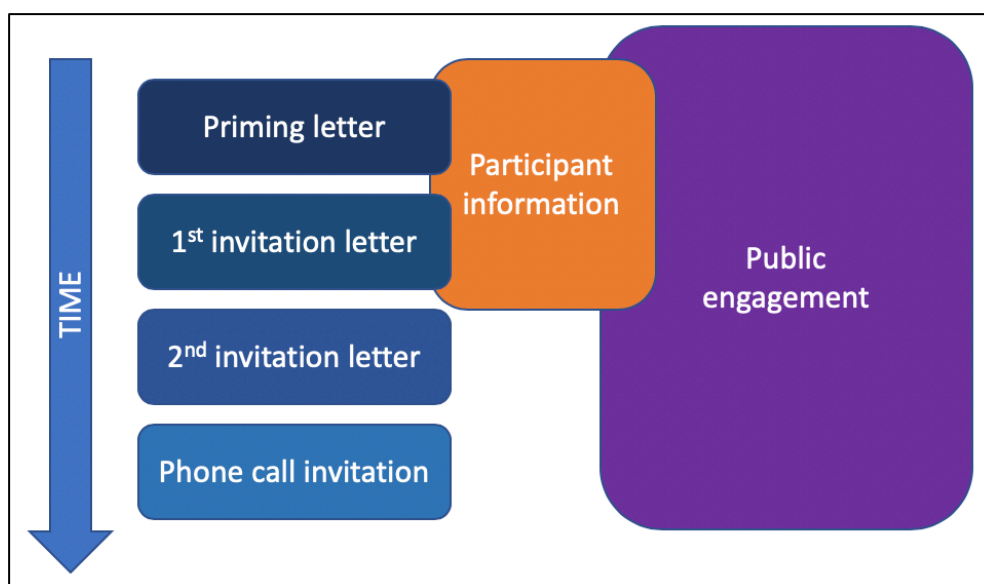


Figure 15: Invitation process for LHCs.

## PARTICIPANT INFORMATION

Written information on LHCs has usually been provided alongside the first invitation letter, with additional information available via a website or by phone. The NHS England programme created a patient information booklet detailing what LHCs involve, information on lung cancer, and on the benefits and risks of LDCT screening (figure 16); a similar document could be used for a programme in Wales. Providing a “low-burden” information leaflet regarding LHCs at the time of invitation, with more detailed information on the benefits and risks of LDCT screening delayed until the face-to-face LHC, did not lead to greater uptake in the Lung Screen Uptake Trial.(45)

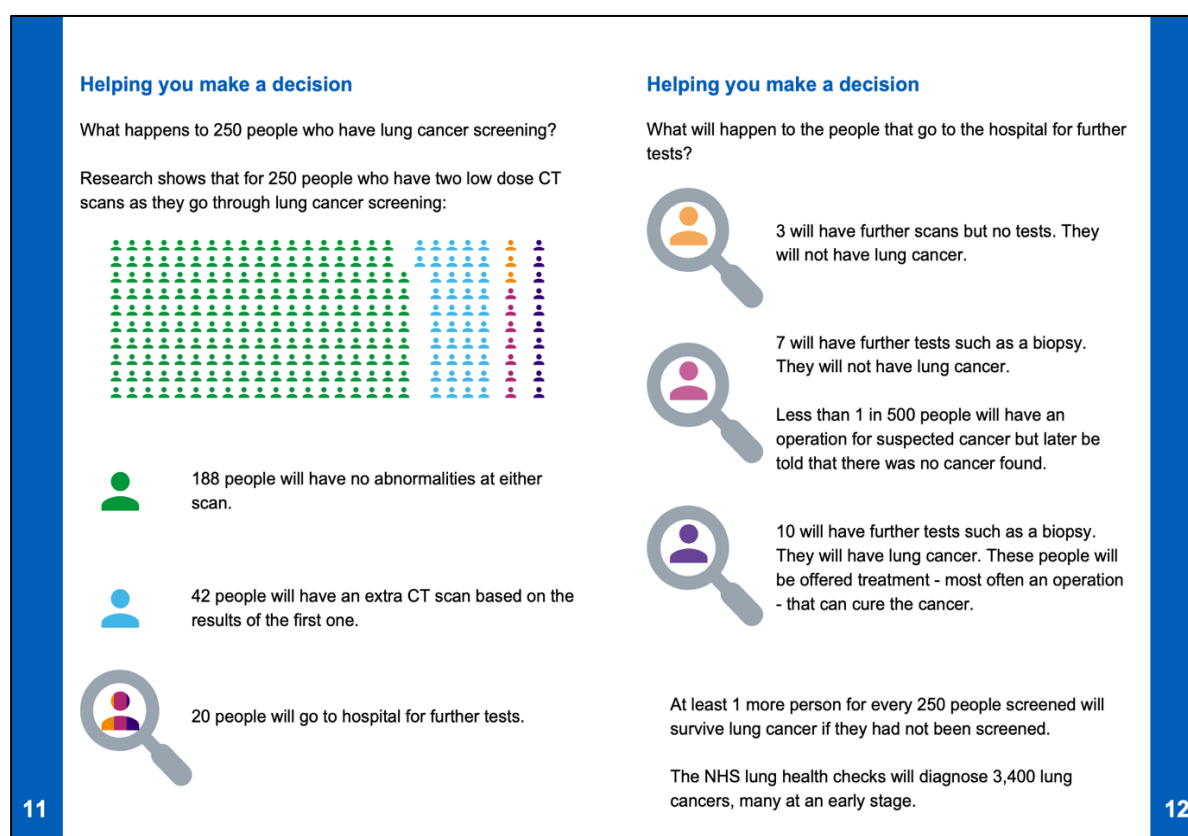


Figure 16: Excerpt from NHS England programme participant information booklet.

How much information participants should be given on prior to LDCT, and how obtain consent to proceed, has been debated. Much LHC/LDCT screening activity has taken place in a research settings where a detailed consent process is necessary. The framing of statistics is important, as the same statistics communicated in different ways can make screening appear very effective or ineffective. The NHS England programme standard protocol includes a list of key information that should be relayed to potential participants including the purpose of the LDCT scan, the downstream processes following the LDCT, and the potential benefits and risks of undergoing LDCT in broad terms. There is not currently agreement on whether written consent is required.

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## RESULTS AND REFERRALS

In Manchester, every participant who undergoes a LDCT is telephoned to inform them of their results. Most other programmes have relayed the majority of results (such as normal scans or scans with small nodules requiring surveillance only) via standardised letters. In the NHS England programme a letter is also used to inform participants if there has been a finding that requires further investigation, with details of where they are being referred and a contact number for if they have further questions. Urgent or serious findings should be communicated by telephone or in person where possible.

A report of the findings of the LHC and LDCT should be sent to the participant's GP. This should be structured to clearly highlight findings that are important or require further action from the GP. Additional information such as spirometry results not requiring further action should be provided with clear guidance that this is the case. Much of the report could be generated automatically using algorithms if results are recorded in a standardised format.

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## ENGAGEMENT

Manchester and Liverpool both spent considerable resources on raising public awareness of their LHC programmes. This included adverts in local press, on local radio stations, on television and on social media. Posters were placed in public areas such as bus stops and at GP practices, and there was a presence at local events and in community settings such as at local clubs and supermarkets. The aims were to encourage attendance, to convey positive messages regarding lung health, and to overcome fears and fatalism surround the diagnosis and treatment of lung cancer, giving the message that "if you find it early, something can be done".

## WORKFORCE AND TRAINING

The workforce to deliver a LHC programme would need to be recruited and undergo relevant training. The size of the workforce would be dependent on the scale of the programme. Some of the key members of the workforce needed are listed in Table 9.

Each project in the NHS England programme covering a population of up to 55,000 people had funding for the following core staff:

- Medical consultant – 1 whole-time equivalent (WTE)
- Band 6 Specialist Lung Health Check Nurse – 1 WTE
- Band 6 Practice Nurse – 1 WTE
- Band 4 PACS support – 2 WTE
- Band 3 Administrator – 1 WTE
- Band 8a Project Manager – 1 WTE

Governance roles, radiographers and radiology reporting were considered separately, with scaled funding based on the projected number of CT scans during the lifetime of the programme. No specific funding was allocated for a smoking cessation counsellor – projects were expected to link to local services. Projects with larger populations were allocated additional funding for additional project management support.

Table 9: Key members of a Lung Health Check programme workforce (table continued on following page)

<b>Governance team</b>	Including a Clinical Director of Programme, Responsible Assessor and Responsible Radiologist as described on p49. The Responsible Clinician would be the local Lung Cancer service lead; for a national programme there would be multiple Responsible Clinicians for different geographical areas.
<b>Lung Health Checkers</b>	<p>The workforce who deliver LHCs have varied from band 3 staff in Yorkshire through to band 8 staff in Manchester. In most programmes, Lung Health Checkers have undertaken a mixture of tasks including organising appointments, assessing participants over the phone and/or face-to-face and recording relevant data, offering some basic counselling regarding smoking cessation, undertaking spirometry tests, and dealing with results including contacting patients, organising referrals and creating reports to send to primary care. The Responsible Assessor (usually a physician with an interest in lung cancer), would oversee this work and be available for support and trouble-shooting.</p> <p>Training would depend on the exact role and previous experience, but may include communication skills, training in smoking cessation counselling and in delivering spirometry tests. If responsible for requesting CT scans, Ionising Radiation Medical Exposure Regulations (IRMER) training would also be required.</p>
<b>Smoking cessation counselors</b>	Ideally a LHC programme would have an on-site smoking cessation counselor. An alternative model is to refer to existing services. The National Centre for Smoking Cessation and Training provides online training modules for new practitioners.
<b>Radiographers</b>	Required to facilitate LDCT scanning. Some companies that provide mobile CT scanners will also provide radiographer staff as part of their service.
<b>Radiologists</b>	Radiologists with an interest in thoracic radiology are needed to report LDCT scans. Specific training on reporting of pulmonary nodules and LDCT undertaken for screening purposes would be required, such as the course provided by the British Society of Thoracic Imaging.
<b>Administration team</b>	Administrative support would be needed to manage appointments, result letters and reports, for co-ordination of aspects such as “positive findings” meetings, and to manage rotas and leave for staff.
<b>Other</b>	Various other staff would be required to facilitate the day-to-day running of the programme including IT support, cleaners, maintenance support for the LHC unit, etc.

## EQUIPMENT

Most LHC programmes have utilised a mobile LHC unit where LHCs take place, and had a separate “LHC Hub” where other aspects are managed including booking appointments, undertaking telephone assessments and dealing with results generated by the LHC.

Equipment required for a LHC programme includes:

- Office space for the LHC Hub (including computers, telephones etc)
- LHC unit (usually a mobile unit containing space for a face-to-face LHCs, spirometry, smoking cessation counselling and a mobile LDCT scanner, though other set-ups are possible such as static sites or a static site coupled with a mobile scanner)
- Portable spirometers
- Computers and software for data collection
- Materials for invitations, patient information leaflets, result letters and reports

## COST

The cost of a LHC programme is dependent on the set-up and scale of the programme. A national LHC programme with a wide target age range using a low risk threshold for LDCT, delivered in a mobile LHC unit by band 8 staff and offering multiple additional LHC components, will clearly cost more than a stream-lined approach utilising telephone triage, delivered by band 3 staff and using a higher risk threshold for LDCT.

With so many variables, it is difficult to offer a realistic estimate of what a national LHC programme would cost at present. Hopefully the work commissioned by the NSC to examine the cost-effectiveness of LHCs may offer some stronger indicators. The limited data available to inform future cost estimates is discussed below.

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## NHS ENGLAND TARGETED LUNG HEALTH CHECKS

The NHS England programme, consisting of 14 projects across 10 cancer alliances, is planned to receive £70m funding. This is to allow the programme to run between 2019-2023, with a single two-year screening cycle occurring during this time. The projects received £328,000 each, plus £264 per expected CT scan.

In total, the projects are expected to cover an eligible population of 600,000 people aged 55-74 years. A comparison of the expected numbers in the NHS England programme and national figures for Wales are shown in table 10.

Table 10: Comparison of projected populations for NHS England programme and for population of Wales over a two-year cycle, applying NHS England programme criteria for LHCs and LDCT.

	NHS England TLHC programme	Wales
<b>Population aged 55-74 years</b>	600,000	761,422
<b>Number of Lung Health Checks to be performed</b> (assuming 50% ever-smokers, all ever-smokers invited for a LHC, with 50% uptake)	150,000	175,127
<b>Number undergoing initial LDCT</b> (assuming 92% of those above risk threshold undergo LDCT)	81,000	95,129

The eligible population in Wales is approximately 25% greater than the eligible population for the NHS England programme. However, this does not mean that the cost of delivering a rolling 2-year LHC programme in Wales would simply be 25% greater than the funding for the NHS England programme. Firstly, the NHS England programme may yet prove to cost more or less than the funding it has been allocated. Secondly, the NHS England programme is running as separate projects across ten cancer alliances, whereas some aspects in Wales could be centrally coordinated such as LDCT provision, radiology reporting and data management. Thirdly, the costs associated with a long-term programme are different to those of running a programme over a single cycle: for example, it may be more cost-efficient to rent a mobile scanner for a finite project, whilst purchasing a mobile or static scanner may be more cost-effective for an ongoing programme. Fourthly, a LHC programme with a different model of delivery such as using initial telephone triage to reduce the number of face-to-face LHCs, or by using a higher risk threshold for LDCT, could significantly alter the cost of the programme. Finally, the rurality of much of Wales could increase the cost of delivering the programme successfully in comparison to the mostly urban areas covered in the NHS England programme.

## MANCHESTER

The Manchester Lung Health Check pilot programme cost £663,076. A total of 2,541 LHCs were delivered, with 1,384 going on to have a LDCT. Whilst 16,402 invitations to participate were sent out, demand exceeded availability of LHC appointments so the cost does not reflect what would be required to cover a population of this size. The cost figure included recruitment, performing of LHCs and LDCT, LDCT reporting, and any 3-month interval LDCTs required. An additional estimated “non-recurrent” cost of £315,000 funded a programme office tasked with exploring evidence and designing the pilot programme, and was not included in the cost figure.

## DOWNSTREAM SERVICES

In addition to the costs of running the programme itself, it should be noted that a LHC programme will cause an increase in workload for several downstream services such as for PET, respiratory departments (including MDT and outpatient work), radiology-guided biopsy, bronchoscopy and EBUS, thoracic surgery, stereotactic radiotherapy, and other services impacted by incidental findings including primary care. Most cost estimates have included the costs of a LHC programme, but not of ensuring that downstream services can increase capacity to meet demand.

## WHAT IS THE POTENTIAL IMPACT OF A NATIONAL LUNG HEALTH CHECK PROGRAMME?

The potential impact of a national LHC programme is dependent on factors such as the age range invited, the risk thresholds used for LDCT, the uptake of the programme, whether downstream services have adequate capacity to deal with findings of the programme, and whether the benefits of LDCT screening seen in RCTs can be realised in the real-world setting.

### NHS ENGLAND MODELLING TOOL

As part of the development of the NHS England programme, a model was created to predict the throughput of the projects within the programme during their 2-year cycle. The model is largely based on outcomes from the Manchester pilot, and requires inputs including the number of people in the target population aged 55-74 years and the percentage of these who are ever-smokers. This data is available for the population of Wales: there are just over 760,000 people aged 55-74 years, with 50.0% of those in this age range having ever smoked, which when fed into the model predicts the throughput of the programme as detailed in table 11. These results are also shown broken down by health board, assuming that the impact would be proportionate to the relative population size of each health board. Additional calculations such as the number of radiology reporting sessions per week for LDCTs and lung cancer figures for Wales in 2018 are also displayed for comparison.

There are many reasons to believe that this model is unlikely to be an accurate prediction of the impact of introducing a national LHC programme. Firstly, the tool assumes that 50% of those eligible for a LHC will book one, of whom 92% will attend. Downstream calculations vary widely depending on programme uptake: a programme with an uptake of 30% or 70% would have massively different resource implications and impact. Secondly, the parameters and structure of the NHS England programme represent one of many options for how a LHC programme can be performed: factors such as the age range, risk threshold for LDCT, filtering process from whole population to LHC to LDCT, and protocols for surveillance of nodules will all affect the number of LHCs and LDCT scans performed. Changing any of these variables could have a large effect on the throughput of the programme. Thirdly, the downstream effects are largely based on data from Manchester, which targeted a particularly high-risk population with high levels of deprivation, smoking prevalence and lung cancer mortality. Such areas are likely to have more people above the risk threshold for LDCT and will detect more lung cancers, so extrapolating these figures across the whole population is unlikely to be representative. Finally, the number of individuals requiring investigation or being diagnosed with lung cancer is weighted towards initial screening rounds, when more latent cases will be detected. Rounds following the initial 2-year cycle would be expected to generate fewer cases requiring investigation.

Health Board	Betsi	Powys	H Dda	Swansea	CTM	AB	C&V	Wales
<b>TARGET POPULATION FOR LUNG HEALTH CHECKS</b>								
Total population	698,369	132,447	132,447	389,372	445,190	591,225	496,413	<b>3,138,631</b>
Age 55-74	181,308	39,794	106,703	90,673	104,463	140,736	97,745	<b>761,422</b>
55-74 ever-smokers (50.0%)	90,654	19,897	53,352	45,337	52,232	70,368	48,873	<b>380,711</b>
<b>LUNG HEALTH CHECKS (LHCs) AND CTs</b>								
LHCs booked (50%)	45,327	9,949	26,676	22,668	26,116	35,184	24,436	<b>190,356</b>
LHCs performed (92%)	41,701	9,153	24,542	20,855	24,026	32,369	22,481	<b>175,127</b>
Above risk threshold for CT (56% of LHCs)	23,352	5,125	13,743	11,679	13,455	18,127	12,590	<b>98,071</b>
Initial CT performed (97% of those indicated)	22,652	4,972	13,331	11,328	13,051	17,583	12,212	<b>95,129</b>
Scans per month over 2-year cycle with roaming programme (including 3- and 12-month interval CTs for nodules)	890-1340	170-250	490-740	500-740	570-850	750-1130	630-950	<b>4000-6000</b>
Radiology reporting sessions required per week for CTs	15.4	2.9	8.5	8.6	9.8	13.0	10.9	<b>69.2</b>
<b>INVESTIGATIONS, CANCERS AND TREATMENTS FOLLOWING LHCs</b>								
Investigation required after 0,3- or 12-month CT (5.9%)	1,254	238	692	699	799	1061	891	<b>5,635</b>
Cancers found following 0, 3- or 12-month CT (50.8% of those requiring investigation)	637	121	352	355	406	539	453	<b>2,863</b>
Investigation required at 24-month CT - start of 2 <sup>nd</sup> screening round (2.4% of CTs)	421	80	233	235	269	357	299	<b>1,893</b>
Cancers found at 24-month CT (65.5% of those requiring investigation)	276	52	152	154	176	234	196	<b>1,240</b>
Total cancers @ 2yrs (following baseline, 3- and 12-month interval CTs for nodules, and at start of second screening round at 24 months)	913	173	504	509	582	773	649	<b>4,103</b>
Cancers per year @ 2yrs	456	87	252	255	291	386	324	<b>2,052</b>
Surgery only (51%) <i>per year @ 2yrs</i>	233	44	129	130	148	197	165	<b>1,046</b>
Surgery + adjuvant chemotx (7.7%) <i>per year @ 2yrs</i>	35	7	19	20	22	30	25	<b>158</b>
SABR (12.2%) <i>per year @ 2yrs</i>	56	11	31	31	35	47	40	<b>250</b>
Chemo-radiation (9.1%) <i>per year @ 2yrs</i>	41	8	23	23	26	35	29	<b>187</b>
Radiotherapy only (9.1%) <i>per year @ 2yrs</i>	41	8	23	23	26	35	29	<b>187</b>
SACT only (4.6%) <i>per year @ 2yrs</i>	21	4	12	12	13	18	15	<b>94</b>
Best supportive care (6.1%) <i>per year @ 2yrs</i>	28	5	15	16	18	24	20	<b>125</b>
<b>CURRENT CANCERS, STAGES AND TREATMENTS</b>								
Lung cancers 2018	540	N/A	299	301	459	434	305	<b>2,338</b>
Stage 1-2	141	N/A	70	78	113	155	107	<b>664</b>
Stage 3-4	399	N/A	229	223	346	279	198	<b>1,674</b>
Surgery	82	N/A	52	50	55	53	49	<b>341</b>

*Table 11: Potential impact of a national LHC programme based on NHS England modelling tool. Population figures from <https://stats.wales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates/Local-Health-Boards/populationestimates-by-lhb-age>. Ever-smokers data extrapolated from report prepared by Rebecca Hughes, Information analyst at Public Health Wales; 15.6% current smokers, 34.3% ex-smokers, 50.0% ever-smokers. Current smokers are based on current smoker % across Wales applied to health board populations, not individual health board data. Lung Health Check attendance assumes 50% will respond and book a LHC, of whom 92% will attend, of whom 56% will be above risk threshold for CT, of whom 97% will undergo initial LDCT. Scans per month over 2 years based on roaming programme addressing different GP practices within health board at different time-points during 2-year cycle. Based on NHS England projection toolkit scans per month for all-Wales programme, extrapolated to health board populations, rounded to nearest 10. Radiology reporting sessions required based on 20 LDCT reports per session, using upper estimate of scans per month. Less patients require investigation following 24-month scan than baseline scan and a larger proportion have cancer, as many nodules will now be known stable/benign nodules in the scanned population. Current cancers, stages and treatments based on data submitted to Lung Cancer Peer Review 2019, combining MDTs within health boards. Where <2% of stages missing, those missing assumed stage 3-4. Peer review data contains a small number (<5%) of mesotheliomas cases.*

Despite the limitations of these predictions, some useful observations can still be made. The results highlight that if Wales were to introduce a LHC programme using the same parameters as the NHS England programme it would have major resource implications. Over 380,000 people in Wales would be eligible for a LHC if they were offered to all ever-smokers in the target age range. The model assumes an uptake of 50% amongst the eligible population which would result in around 175,000 LHCs being performed in the first cycle, though clearly this number would be higher with greater uptake. In the NHS England programme only a proportion of those invited for a LHC are eligible for CT, though this would still result in almost 100,000 first-round CTs being performed. The model suggests many more cancers would be found in the first programme cycle than would be found through usual routes of presentation, with a large proportion of these undergoing surgical resection. Indeed, the figures suggest that the number of surgical resections would be more than three times the number currently performed per year during the first two years of the programme. For the reasons discussed above this is likely to be an overestimate, but nevertheless highlights that a marked increase in surgical resections for lung cancer would be a likely consequence of introducing a national LHC programme.

## AGE AND RISK THRESHOLD MODELLING

As discussed previously (p40), narrowing the age range used from 55-74 years to 60-74 years would reduce the number of ever-smokers eligible for LHCs by approximately 25%. The number eligible for LDCT would also reduce, but not by the same percentage as a greater proportion of older people would be above the risk threshold for LDCT; the reduction would likely be around 10-15%.

Raising the risk threshold for LDCT, for example by using LLPv2  $\geq 5\%/5$  years rather than PLCO<sub>M2012</sub>  $\geq 1.51\%/6$  yrs or LLPv2  $\geq 2.5\%/5$  yrs, would also reduce the number of LDCTs. If modelling from Yorkshire (127) is extrapolated for the population of Wales, a programme with 50% uptake would lead to around 60,000 LDCTs in the first round, as opposed to nearly 100,000 using the NHS England criteria. Both figures could vary widely depending on uptake of the programme.

## POTENTIAL IMPACT ON LUNG CANCER MORTALITY

Unfortunately the lung cancer mortality reduction of 20% or greater seen in larger RCTs with LDCT screening does not mean that introduction of a national LHC programme in Wales would result in a 20% reduction in lung cancer mortality across the population. The best that could be hoped for is a 20% or greater reduction in lung cancer mortality *in the screened population*. Just over half of lung cancers occur in the 55-74 year old age group; there will be no opportunity for screening to reduce mortality in those below the lower age limit, though a protective effect for a number of years after screening ceases at the upper age limit is likely. Within the target age range, a proportion of lung cancers will occur in those outside the inclusion criteria for screening: around 15% of lung cancers occur in never-smokers, and some will occur in ever-smokers who are below the risk threshold for LDCT. Amongst those who are eligible for LDCT, only those who actually undergo LDCT screening can potentially benefit – the impact of the programme is dependent on uptake by the eligible population. Finally, effects seen in tightly managed RCTs are not always seen when applied at scale in the real world. All of these factors can dilute the apparent headline figures in screening trials if a national programme is implemented. A more realistic estimate is that a national LHC programme could reduce lung cancer mortality by 20% or more in the eligible population who attend, and by 5-10% across the entire population. The true figures could be higher than this in the longer-term due to increased smoking cessation rates and the lasting protective effect after screening has ceased at the upper age limit.

Table 12 outlines what the potential impact of a national LHC programme in Wales could be, factoring in the points discussed above. Clearly such an estimate has to make many assumptions and changes in any of the variables could alter the estimates significantly. The cost-effectiveness model due to report to the NSC in 2021 may be able to utilise more data to create a more accurate prediction of the impact on mortality across the population.

*Table 12: Potential reduction in deaths with a national LHC programme in Wales*

	(Projected) Cases over 5 years
Deaths from lung cancer in Wales over 5 years (2013-2017)	9537
56% of lung cancer diagnoses occur 55-74 year olds. (assume that number of deaths approximately correlates with number of diagnoses)	5341
Assume 80% of lung cancers in 55-74 year olds occur in those eligible for LDCT screening based on smoking history and risk assessment	4273
Number of lung cancer deaths prevented If lung cancer mortality is reduced by 25% in those who undergo LDCT screening, with 50% uptake by those eligible	534 (5.6% reduction across whole population)
Number of lung cancer deaths prevented If lung cancer mortality is reduced by 25% in those who undergo LDCT screening, with 75% uptake by those eligible	801 (8.4% reduction across whole population)

## OTHER POTENTIAL IMPACTS

Publications on LHC activity to date have focussed primarily on lung cancer detection. There is limited data available describing the potential impact of a LHC programme on other areas such as smoking cessation, COPD case-finding and identification of coronary artery calcification. Table 13 offers some estimates of the potential impact of a national LHC programme for Wales on non-lung cancer outcomes. As for the lung cancer figures, these estimates are based on limited data and rely on several assumptions.

Health Board	Betsi	Powys	H Dda	Swansea	CTM	AB	C&V	Wales
<b>SMOKING CESSATION</b>								
Current smokers age 55-74 in population	28,284	6,208	16,646	14,145	16,296	21,955	15,248	<b>118,782</b>
Expected quitters after attending LHC	1,202	264	708	601	692	933	648	<b>5,049</b>
Expected quitters without LHC programme	520	114	306	260	300	404	281	<b>2,186</b>
Potential additional quitters due to LHCs	682	150	402	341	392	529	367	<b>2,863</b>
<b>COPD</b>								
New COPD diagnoses due to LHCs (10%)	2,752	604	1,620	1,376	1,586	2,136	1,484	<b>11,559</b>
Number of GP practices in health board	109	16	51	50	50	79	62	<b>421</b>
New COPD diagnoses per practice	25	38	32	28	32	27	24	<b>27</b>
<b>CORONARY ARTERY CALCIFICATION (CAC)</b>								
Moderate or severe CAC without known IHD not currently taking a statin	3,935	864	2,316	1,968	2,267	3,054	2,121	<b>16,525</b>
As above, per GP practice	36	54	46	40	46	39	34	<b>39</b>

*Table 13: Potential non-lung cancer impact of a national LHC programme. Smoking cessation: figures are based on those attending LHCs, with a 4% background quit rate and a 14% quit rate for LHC attenders (based on quit rate in screened arm in UKLS). COPD case-finding: based on approximately 10% of LHC attendees having a new diagnosis of COPD (Liverpool and extrapolated Manchester data). Figure based on symptomatic airflow obstruction without a known diagnosis of airways disease in those undergoing spirometry; does not include radiological emphysema without airflow obstruction. GP practice numbers based on old ABMU and Cwm Taf boundaries adjusted for Swansea Bay and Cwm Taf Morgannwg boundaries. CAC numbers based on 10% having known IHD, 30% having moderate and 17% having severe CAC, and 48-64% of moderate to severe group not being on a statin - average 56% (based on NELSON trial data – similar UK data not available).*

## WHAT WOULD BE THE GREATEST CHALLENGES IN DELIVERING A NATIONAL LUNG HEALTH CHECK PROGRAMME?

### IDENTIFICATION OF TARGET POPULATION

As described previously (p40), a LHC programme must perform several “sieves” of the population down to those with findings suggestive of lung cancer on LDCT. A key step in the process is identifying people who are current or ex-smokers. Two main approaches have been taken in LHC activity to date: (1) contacting all people in the target age range and inviting them for a LHC if they are an ever-smoker; or (2) utilising information held on GP records to identify ever-smokers. The latter approach has been used in most LHC activity in England including the NHS England programme, but there are concerns as to whether the smoking data on GP records is complete or accurate enough to be used for this purpose.

Data from a small number of GP practices in Wales has revealed highly variable completeness of smoking status data. Most practices contacted had a smoking status recorded for around 90-95% of people aged 55-74 years, whilst one practice had data for only 60%. Even if a smoking status is recorded, it is unclear what proportion of these are accurate. Robust population-based screening relies on the existence of a robust database of the eligible population. One reason LHCs have generally been considered targeted rather than population-based screening is doubts over whether GP records are a robust source to identify ever-smokers.

One option that has not yet been explored is to systematically assess and update the smoking data held on GP records prior to the invitation process. This could be done by providing funding for GP practices to contact people without recent smoking data recorded, or cases where the smoking data is felt unlikely to be accurate. Such a project should be strongly considered if LHC activity goes ahead in Wales.

### LDCT REPORTING CAPACITY

The single biggest challenge in delivering a large-scale LHC programme in Wales would be ensuring there is sufficient radiology reporting capacity for the LDCTs generated by the programme. If the parameters used in the NHS England programme were used for a national programme in Wales with 50% uptake this would generate 4000-6000 LDCT scans per month, requiring approximately 70 sessions of consultant thoracic radiologist time per week for reporting alone, not accounting for additional time such as positive findings meetings, training and quality assurance processes. This additional reporting capacity does not currently exist; in fact, there are already concerns that the radiology workforce is insufficient to cope with existing demand. The Royal College of Radiologists annual census (133) reports that:

- There is a shortfall of consultant radiologists across the UK with thoracic radiology highlighted as a subspecialty of particular concern,
- Demand for diagnostic imaging, particularly complex imaging such as CT and MRI, is rising at a much faster rate than the workforce is growing,
- Wales has the lowest ratio of consultant radiologists to 100,000 population across the UK
- At least 10% of consultant radiologist posts in Wales are unfilled, and
- Outsourcing costs are rising year-on-year to close the gap between demand and supply for reporting.

Options to address the challenge of creating capacity to report LDCTs in a LHC programme are discussed below.

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## REDUCE LDCT SCANS

The NHS England programme standard protocol sets out parameters for its programme such as the target age range and risk threshold for LDCT. These were based on available evidence and expert opinion at the time, but many of the variables could be altered to manipulate the number of scans generated by the programme.

Discussions with those involved in the NHS England programme have confirmed that ensuring adequate LDCT reporting capacity is proving challenging. Whilst these projects have employed various strategies to try to meet demand such as paying consultant radiologists extra sessions to report LDCTs outside of their job plan or outsourcing reporting to external companies, it is not clear that these solutions would be viable to manage demand in a large-scale national programme. If the reporting capacity cannot be created, then limiting the number of LDCTs may be necessary, at least until additional capacity can be created. A similar situation was faced in bowel screening, where the threshold for additional investigations has varied in order to manage demand for endoscopy.

The two main options for limiting the number of LDCTs is by narrowing the target age range or by raising the risk threshold for LDCT eligibility.

Narrowing the target age range from 55-74 years to 60-74 years is one option to reduce the number of LDCTs. Whilst this would reduce the number of people undergoing risk assessment by around 25%, the reduction in the number of LDCTs would be less: perhaps 10-15%. This is because a smaller proportion of the 55-59 year old group will be above the risk threshold for LDCT, as age is an important factor in the calculation. Younger people have more to gain from earlier diagnosis of lung cancer as their life expectancy is greater than that of older people, so curative treatment of a lung cancer that would have caused premature death will lead to a greater number of life-years gained. However age is a continuous variable for risk, so some lung cancers will always occur in people below whatever lower age limit is chosen, and some limit must be selected.

Lowering the upper age limit could cause a greater reduction in the number of LDCTs but would not be an attractive strategy as this is around the peak age for lung cancer incidence. Excluding this group from screening would reduce the number of lung cancer diagnoses and increase the number needed to screen per lung cancer diagnosis, reducing the cost-effectiveness of the programme.

The NHS England programme uses two assessment tools to predict the future risk of lung cancer and offer LDCT if either threshold is exceeded. Raising the threshold for LDCT would reduce the number of LDCTs performed by limiting them to those at highest risk. For example, a threshold of  $\geq 2.5\%$  risk of lung cancer over 5 years is used for the LLPv2 tool in the NHS England programme, whilst the threshold was  $\geq 5\%$  in the Liverpool pilot and in UKLS. Modelling work from Liverpool suggested that lowering the threshold below 5% would increase the number of lung cancer diagnoses in proportion to the increase in LDCTs (i.e. lowering the threshold would not increase the number needed to screen per diagnosis), and recommended considering lowering the threshold below 5% in future.(37)

An inevitable negative effect of reducing the number of LDCTs is that a greater proportion of lung cancers will occur outside of the screened population. This can give the impression that the programme is failing to “do its job”. There are already concerns that engaging those at high risk of lung cancer in screening is difficult, so negative perceptions about the programme could exacerbate this.

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## IN-HOUSE RADIOLOGISTS

There are currently insufficient consultant radiologists who specialise in thoracic radiology to deliver the reporting required for a national LHC programme alongside their existing workload. The NHS England programme sets out quality standards for radiologists reporting LDCTs which include attendance at a British Society of Thoracic Imaging Lung Nodule Workshop, reporting of 500 thoracic CTs per annum, and regular attendance at a thoracic MDT meeting as part of their routine clinical work. This would exclude most “general” radiologists from contributing to reporting.

Options for maximising the contribution of the existing pool of thoracic radiologists in Wales include:

- Providing or paying for training on screening LDCT reporting
- Paying for screening scans to be reported outside of usual job plan at Additional Duty rates
- Reorganising jobs plans so sessions are dedicated to reporting screening LDCTs with the displaced work covered by outsourcing or recruitment of additional radiologists or reporting radiographers
- Actively recruiting additional thoracic radiologists to contribute to the screening service.

LHC activity in England has employed a mixture of approaches. Manchester actively recruited additional consultant radiologists to increase capacity for reporting screening LDCTs and for the lung cancer service as a whole. Some sites have paid radiologists to report LDCTs as extra sessions, including radiologists from neighbouring regions when internal capacity has been insufficient. Organising reporting in this way is unlikely to be sustainable for a large-scale ongoing national programme – limited size programmes have been able to borrow reporting capacity from elsewhere, but if screening is occurring across the country then this is no longer an option. A LHC programme could aim to recruit radiologists specifically for the programme to report LDCTs. However, a job plan entirely consisting of LDCT reporting is unlikely to be attractive and would be difficult to recruit into. If possible, the best strategy would be to increase the number of thoracic radiologists in Wales, with most thoracic radiologists having part of their job plan dedicated to screening reporting. This may be viable if the number of screening LDCTs is less than that projected based on modelling from the NHS England programme; to report 4000-6000 scans per month would need approximately 70 sessions of reporting time, assuming a rate of 20 scans per session. This does not take into account annual leave or requirement for other non-reporting sessions in job plans. Sessions would also be needed for training, positive-finding meetings and contributions to local lung cancer services including MDT meetings. To provide this number of reports, Wales would probably require at least 12-14 additional whole-time equivalent thoracic radiologists. Recruitment to meet this demand would be extremely challenging and would likely take an extended period of time.

Nevertheless, there would be major advantages to keeping reporting in-house within Wales. Quality assurance of an in-house service would be more straight-forward. Having a pool of reporting radiologists would allow a positive findings meeting to be organised, which is a recommended feature of the NHS England programme. Radiologists would still have to review and prepare cases to discuss at lung cancer MDTs, so being involved in the discussion of these scans prior to this will make this more efficient.

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## RADIOGRAPHERS

There has been some limited exploration into whether radiographers could take on reporting of screening LDCTs. A small study found significant variation in the results of two reporting radiographers in this setting, with the conclusion that this strategy for reporting could not be recommended.<sup>(134)</sup> It is possible that performance could improve with additional training and experience. At present, an important role of reporting radiographers could be in taking on work displaced from thoracic radiologists in order to free up time for LDCT screening reporting.

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## OUTSOURCING

Several radiology reporting outsourcing companies offer reporting of LDCT screening scans. Outsourcing comes with some disadvantages – it will be more difficult to quality assure, will reduce efficiency of subsequent discussions at positive findings and lung cancer MDT meetings, and carries risks for the long-term future of the programme as the cost of reporting will be subject to market forces. Current quotes for the cost of reporting screening LDCTs are around £40/scan. Based on the projected number of scans using the NHS England model with 50% uptake, the cost of outsourcing reporting would be approximately £2.9 million/year. In addition to this, additional consultant radiologist sessions would still be required to discuss positive findings and run other aspects of the programme.

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## ARTIFICIAL INTELLIGENCE

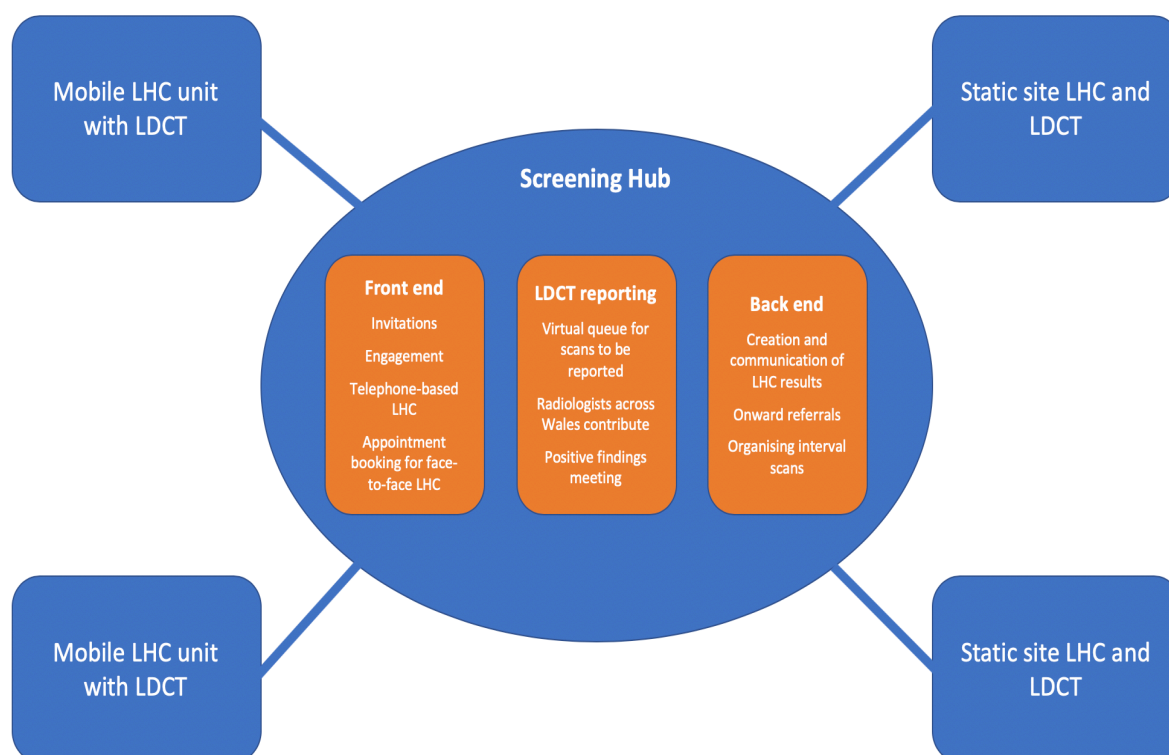
Given the challenge of reporting the large volume of LDCT scans, there has been much interest in the development of Artificial Intelligence (AI) software to improve the efficiency of reporting.

The majority of AI software currently available focuses on Computer-Aided Detection (CADe) of pulmonary nodules. This software provides some automated functions such as detecting nodules, measuring nodule size, and calculating the volume doubling time for nodules at interval scans. These programmes have usually been used as a “second read” for scans, helping to avoid missing important nodules following the “first read” by a radiologist. Veye Chest (Aidence) and Veolity are the main software packages that have been used in English LHC projects. Feedback from users suggests that whilst this software is helpful for detecting nodules, it will not always detect larger masses, and is not designed to detect other important findings such as thoracic aneurysms or adrenal masses. There is ongoing research in Computer-Aided Diagnosis (CADx) programmes, which aim to accurately predict malignant findings rather than nodules *per se*. An example is a programme in development by Google which uses “deep learning” to refine the accuracy of its findings.<sup>(135)</sup> Some positive results from retrospective analysis of scans have been published, but further prospective validation is needed before this is ready for use in practice.

There is likely to be significant progress in this field over the next 5-10 years, with a major aim being the development of software that can differentiate a “normal” LDCT that does not require review by a radiologist from a “potentially abnormal” scan that requires human reporting. This would allow the number of LDCTs requiring reporting by radiologists to be vastly reduced.

## CENTRALISED REPORTING

Centralised co-ordination of LDCT reporting across Wales is likely to be a better option for a national LHC programme than relying on individual health boards to provide reporting capacity for their own populations. Recruitment to some areas in Wales is more difficult than others, and a screening programme must be able to offer an equitable service across the country. Whilst not utilised in the NHS England programme, a “reporting hub” model has been discussed as an option for future programmes. This would involve a pool of radiologists who contribute to reporting. They would not necessarily need to be in a single location – this could be a “virtual hub” where scans are queued to be reported, with videoconferencing software to facilitate a positive finding meeting, where findings such as nodules or significant incidental findings are discussed with colleagues for a second opinion, rather than every scan undergoing a second read by a radiologist. This model is likely to reduce false-positive or irrelevant incidental findings on LDCT reports, as a second opinion could increase confidence to dismiss an equivocal finding and reduce unnecessary further investigations or follow-up. Screening scans across Wales could feed in to one or more reporting hubs, in a “hub and spoke” model. A physical hub could also host other functions of the programme such as the initial telephone-based LHCs, reporting of LHC results to GPs and patients, and administration related to the programme (Figure 17).



*Figure 17: Centralised screening hub for reporting and other aspects of a LHC programme, with “spoke” sites for face-to-face LHCs and LDCT.*

## DOWNSTREAM CAPACITY

The success of a cancer screening programme depends not just on identifying cases, but also on ensuring that identification of cases leads to an improvement in outcomes. Downstream pathways that a screening programme feeds into must be well-prepared to deal with positive findings.

Lung cancer services across Wales are organised into MDTs, with one or more MDTs serving the population of each health board (excluding Powys). Patients with suspected lung cancer are referred to their local MDT for investigation and treatment. The “National Optimal Cancer Pathway” (NOCP) for suspected and confirmed lung cancer describes the usual diagnostic pathway for patients presenting via usual routes including GP referrals, incidental findings on scans done for other indications, and emergency presentations. It is anticipated that patients undergoing LHCs who have findings suspicious of lung cancer would feed into the pathway alongside the other routes of entry.

The delivery of the NOCP for lung cancer within the recommended timeframe targets is already extremely challenging, with most MDTs in Wales achieving this in around 75% of cases at Peer Review in 2019. Particular pressure points in the pathway where capacity is stretched includes PET, diagnostic procedures such as EBUS and the associated pathology reporting required, and thoracic surgery. The workload for respiratory physicians who provide lung cancer services in Wales alongside other clinical commitments has also been highlighted as an area of concern.

The introduction of a LHC programme would add pressure to downstream services for several reasons. Firstly, the total number of lung cancers detected would be greater than previously. Data from NELSON suggests that due to overdiagnosis, over an extended period of time approximately 10% more lung cancers would be seen compared to the current incidence. Secondly, a “surge” of suspected lung cancers could be expected during the first screening round. This is because the first screening round would detect both lung cancers that would have presented in the near future and more indolent cancers that may not have been detected for several years. This was seen in NELSON where the incidence of lung cancer was highest in the first screening round, with the incidence in the control arm “catching up” slowly over many years of follow-up (figure 18). If a national programme were to commence simultaneously across Wales, downstream services would need to be prepared for a surge of suspected lung cancer cases during the first screening round, followed by a steadier rate of cases in subsequent rounds.

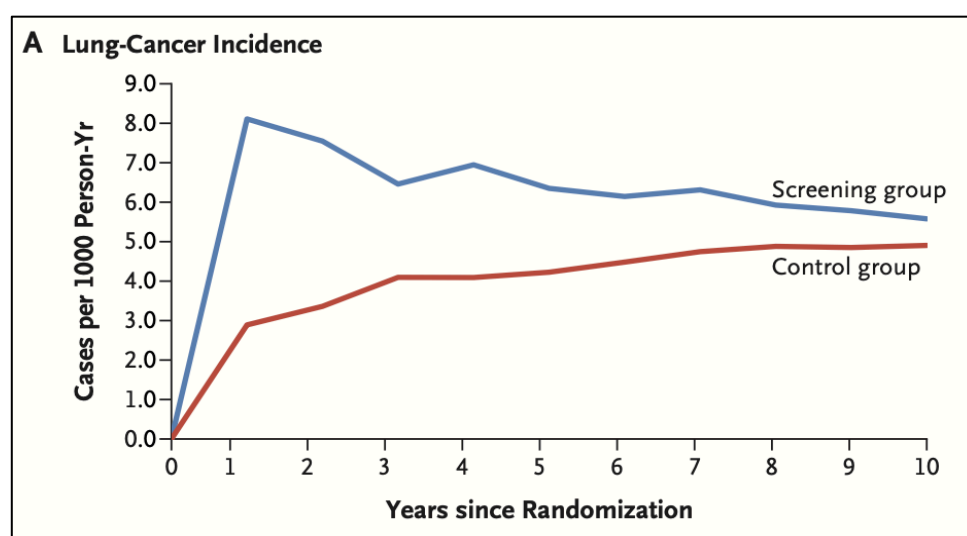


Figure 18: Incidence of lung cancer in NELSON trial over time.(22)

The third effect on downstream services would be due to the stage-shift seen with screening. A greater proportion of stage 1 and 2 cases would be expected, which would alter the balance of downstream investigations being done (table 14). For example, a greater number of PET scans and lung function tests would be needed to investigate suspicious pulmonary nodules, and a greater number of CT-guided biopsies of small nodules would be needed to reduce the risk of surgical resection of benign disease. Thoracic surgery and stereotactic radiotherapy would see an increase in demand. There would also likely be an increase in demand for lung cancer clinic appointments, other diagnostic/staging procedures such as EBUS, and on pathology services who report on CT-guided biopsy, EBUS and surgical specimens. There may be a modest reduction in demand for some services such as biopsies from sites of metastatic disease and systemic therapy. However, due to the number of patients who would still present via non-screening routes and the fact that some patients with metastatic disease detected via screening may be of better performance status than if they had later presented symptomatically, it is possible that no reduction in demand for these aspects would be seen.

	Predicted effect on demand		
	++	+	+/-
<b>Downstream services</b>	PET Thoracic surgery Stereotactic radiotherapy CT-guided biopsy of small nodules Lung function	Lung cancer outpatient clinics EBUS Pathology	Biopsies from metastases Systemic anti-cancer treatment

Table 14: Predicted effects of screening on demand for downstream services

## PET

The PET scanning service in South Wales has been provided by a single scanner in Cardiff until July 2020, when a second PET scanner in Singleton Hospital, Swansea began operating. The PET service for North Wales is provided by a visiting mobile scanner in Wrexham.

Figure 19 demonstrates the increase in demand for PET over recent years, and the projected acceleration of that trend in future excluding the effect of a LHC programme being introduced. The Welsh NHS PET workload was approximately 2,900 scans for 2019-2020, with demand projected to rise to over 4,000 scans by 2022-23.(136) This is due to the increasing incidence of some cancers and expansion of clinical indications for PET scanning. Lung requests accounted for almost 40% of PET scans in 2019-2020.

It is difficult to accurately predict the additional demand that a LHC programme would generate on PET services. The NHS England modelling tool suggested that over 5,000 people in Wales could require investigation during the first 12 months of the programme, with over 1,500 undergoing radical treatment. The number of PET scans required would therefore be somewhere between these two numbers. Some of these cases would have presented through normal channels in the absence of a LHC programme, so not all would be additional cases. It is also likely that the NHS England modelling tool overestimates the number of cases that would be seen given the demographics of the population the modelling tool was based on in comparison to the population across Wales. Nevertheless, there would almost certainly be a surge in PET requests due to the large number of nodules detected in the first screening round, with a lower number in subsequent rounds.

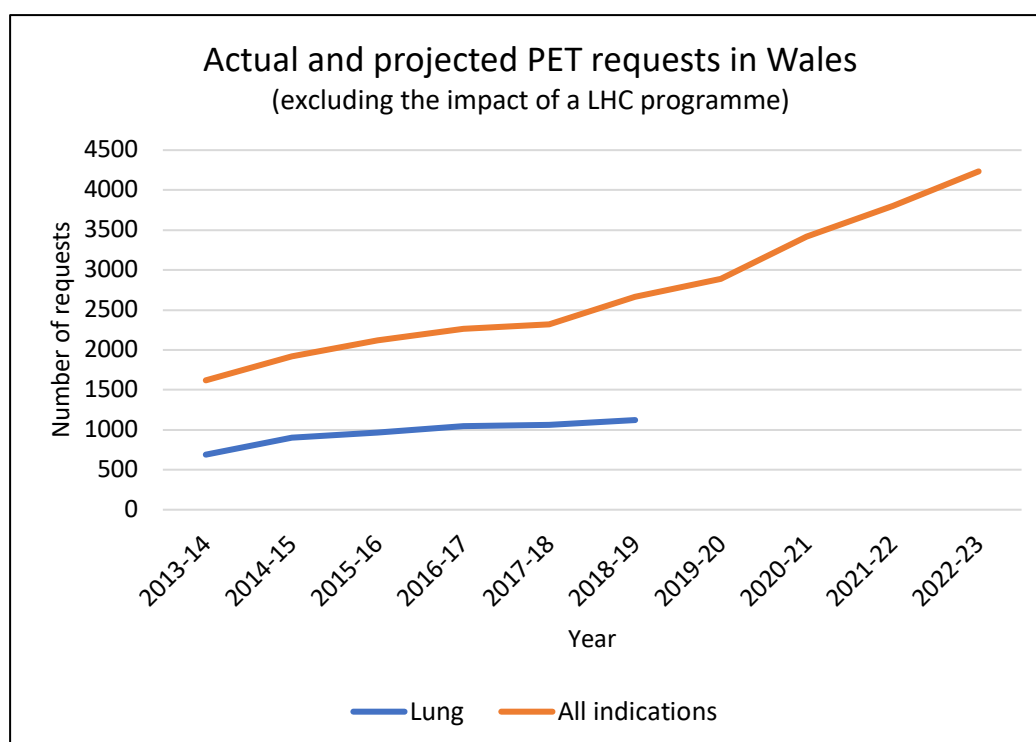


Figure 19: PET requests in Wales. Actual data up to 2018-19 and projected data for subsequent years. Excludes the possible impact of the introduction of a LHC programme. (136)

## THORACIC SURGERY

Thoracic surgery in South Wales is currently provided at University Hospital of Wales, Cardiff, and Morriston Hospital, Swansea. In North Wales, patients are referred to Liverpool Heart and Chest Hospital. Following an independent review by the Royal College of Surgeons in 2018, a recommendation was made for thoracic surgery services in South Wales to be consolidated to a single site, which was selected as Morriston Hospital. Implementation planning is ongoing regarding this, with no definitive date for implementation at present.

In 2018, 341 patients from Wales underwent surgical resection for lung cancer. The NHS England modelling tool suggests that there could be over 1,000 surgical resections performed per year during the first 2-year cycle of a LHC programme. For the reasons described above, this is likely to be an overestimate, but it is nonetheless clear that there would be a surge in demand for surgical resections particularly during the first cycle of the programme. Without increasing thoracic surgery capacity in Wales, patients are likely to face longer waits for surgery. A prolonged wait between a positive screening test and definitive treatment is likely to cause anxiety. Even for early-stage lung cancers, modest delays in surgical treatment are independently associated with increased risk of upstaging of disease and reduced survival.(137–139)

Surgical capacity could be increased by increasing the operating time available, by increasing the efficiency of theatre turnover time, or by utilising surgical techniques to minimise operating time and length of stay.(140) Minimally invasive approaches such as video-assisted thoracic surgery (VATS) are associated with improved quality of life and reduced post-operative pain for patients.(141,142) Robotic thoracic surgery is not currently available in Wales but may offer further efficiency advantages.(143) One debate likely to gain further attention in future is whether screen-detected early-stage lung cancers can be effectively treated by sub-lobar resection. Lobectomy has been the standard of care for lung cancer resections for over 20 years following an RCT where more limited resections did not confer significant benefits but were associated with a higher rate of

recurrence and death.<sup>(144)</sup> However, much has changed in the diagnosis and management of lung cancer since then and limited resections for very small screen-detected lung cancers is an attractive option to potentially reduce operating times and length of stay. Preserving lung capacity is likely to be beneficial to patients, including affording a better chance of being suitable for radical treatment in the significant proportion who will develop a second lung cancer in their lifetime. Results from ongoing RCTs in Japan and the USA comparing lobectomy to limited resection are eagerly awaited.

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## STEREOTACTIC RADIOTHERAPY

Stereotactic ablative radiotherapy (SABR) is the preferred treatment for patients with early-stage non-small cell lung cancer who decline surgery or in whom surgery is contraindicated.<sup>(145)</sup> Surgery has been the first-line radical treatment choice when possible, though this view has been challenged in recent years,<sup>(146)</sup> and with several RCTs ongoing the role of SABR may become more prominent in future. The number of lung cancer cases treated with SABR in Wales is increasing year on year, with approximately 60 cases treated in South Wales and 25 cases in North Wales in 2019. Many screen-detected lung cancers will be suitable for surgical or SABR treatment, and patient factors and/or choice may lead to a significant increase in demand for SABR if a national LHC programme commences.

Currently SABR is only available at a single site in Wales: Velindre Cancer Centre in Cardiff. NHS England have stated that SABR should be rolled out to all English radiotherapy centres by April 2021. Currently patients in South West Wales have access to the SABR service in Cardiff, and patients in North Wales are referred to the Clatterbridge Cancer Centre, Wirral. In both instances there can be lengthy travel times for patients. Plans for local SABR services in South West and North Wales are both in development.

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## OTHER EFFECTS

All aspects of the diagnostic and treatment pathways would be affected in some way by the introduction of a LHC programme. The services discussed above are delivered at a limited number of sites servicing multiple health boards. Other aspects of the pathway such as lung cancer outpatient clinics, lung function testing, CT-guided biopsies and bronchoscopy/EBUS procedures are usually delivered by each MDT or health board, so capacity would have to be considered for each MDT across Wales. The National Lung Cancer Audit and the Peer Review system for cancer services in Wales offer frameworks for this. In particular, provision of CT-guided biopsies is important to consider. In order to minimise the number of surgical resections performed for benign disease, it is desirable to obtain histological confirmation of malignancy prior to surgery. The Manchester Lung Health Check programme achieved extremely low benign resection rates by aggressively biopsying small suspicious nodules. Doing this requires experienced and confident radiologists who are willing to take on tricky cases for biopsy.

For all lung cancer services across Wales to develop their services to meet the targets set by the NOCP will be challenging, and will be even an even greater challenge if demand is increased by a national LHC programme. Consideration should be given as to whether different models of delivering the NOCP could be better placed to achieve this, such as the development of diagnostic hubs serving multiple MDTs or health boards where expertise on CT-guided biopsies and bronchoscopic procedures can be concentrated in order to improve efficiency and diagnostic yield, whilst improving the equity of access across different regions.

## IMPLICATIONS OF THE COVID-19 PANDEMIC

### IMPACT ON LUNG HEALTH CHECK PROGRAMMES

The COVID-19 pandemic has had a profound effect on healthcare systems and society as a whole. Established screening programmes were paused in spring 2020, as was all LHC activity in England. LHCs within YLST and Manchester recommenced in July and August 2020 respectively. Plans at other LHC sites are variable: some are due to resume activity in autumn 2020, whilst others have deferred their programmes until at least April 2021.

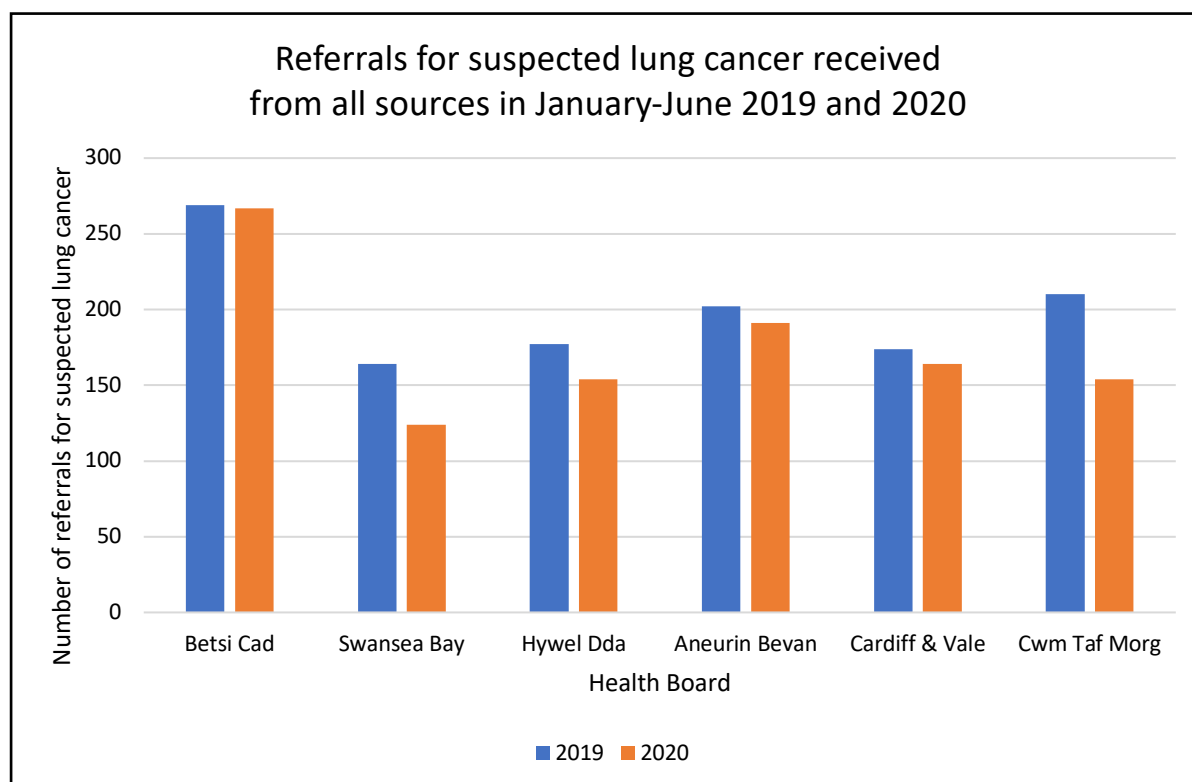
The COVID-19 pandemic is likely to have lasting effects on the operation of LHC programmes. Many of these issues are being worked through by projects in England at present:

- Participants may be reluctant to attend public areas or healthcare facilities due to the perceived risk of COVID-19 exposure. Feedback from Leeds and Manchester suggests that participants are happy to attend community-based LHC units but are extremely reluctant to attend hospital sites.
- Patient-facing materials have been updated to include information regarding COVID-19, personal protective equipment, and social distancing in waiting areas.
- Most projects are now planning to perform the initial assessment by telephone or video consultation rather than face-to-face.
- Public transport links may be less accessible than previously.
- Symptom or temperature checks on arrival may require additional staff and time.
- Social distancing and scanner cleaning protocols will reduce the number LHCs that can be performed per day.
- Spirometry and blood pressure measurements have been deferred.
- There is ongoing discussion as to whether on-site smoking cessation counselling should continue or be switched to brief advice and referral to services where this was not already the case.
- Downstream services such as CT, PET, lung function testing, outpatient clinics, etc. have often been operating with reduced capacity.

The timeline trajectories for completion and evaluation of the NHS England programme will require revision to account for the pause in delivery and the slower run rates, which is likely to delay the possibility of a wider roll-out. New projects may face challenges securing mobile CT scanners, as most of those available have been secured by NHS England to help clear the backlog of diagnostic scans that accumulated during the suspension of routine services.

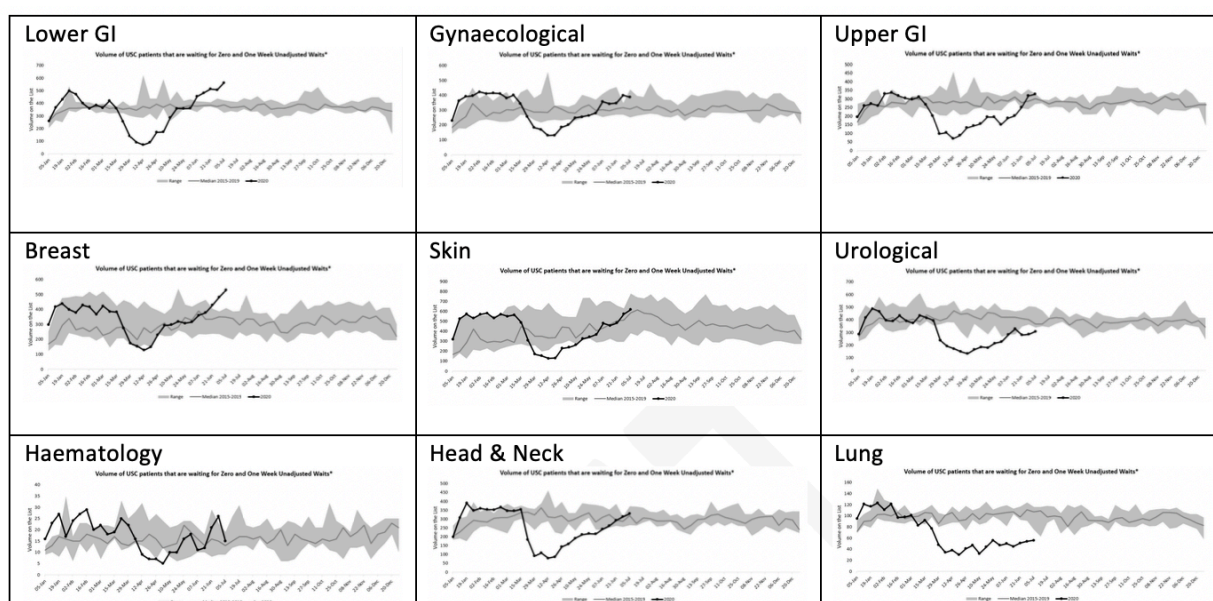
## IMPACT ON LUNG CANCER DIAGNOSES

A feature of the COVID-19 pandemic has been a reduction in the number of suspected cancer referrals. In January-June 2020, there were 12% less referrals for suspected lung cancers compared to the corresponding months in 2019. There were less referrals across all health boards, though the magnitude of the reduction ranged from 1% in Betsi Cadwaladr to 27% in Cwm Taf Morgannwg (figure 20).(4)



*Figure 20: Referrals for suspected lung cancer in 2020 compared to 2019. Difference in conversion rates (the percentage of referrals that go on to be diagnosed with cancer) mean that these figures may not reflect the number of lung cancer diagnoses between years or health boards.*

A reduction in referrals for all cancer types was seen, but this recovered back to usual levels for most cancer types by July 2020. Some such as lower GI and breast cancer services have seen a rebound effect with an above average number of suspected cancer referrals in June and July 2020. The exception to this has been lung cancer where referrals have remained significantly below normal levels (figure 21).



*Figure 21: Illustration of number of patients on cancer diagnostic pathways in Wales in 2020 (solid line) compared to usual number over preceding five years (grey). All cancer types saw a reduction in referrals as the pandemic escalated during the second quarter of 2020, but most had recovered to a “usual” level by July 2020 with the exception of lung cancer. (Data provided by Wales Cancer Network)*

There are likely to be multiple factors contributing to the sustained reduction in suspected lung cancer referrals. There are few symptoms specific enough to trigger a suspected lung cancer referral, so many referrals come following abnormal chest x-rays done for relatively non-specific indications. There has been a large reduction in the number of primary care referrals for chest x-rays, with public health and government advice for people with new respiratory symptoms to stay at home and isolate. Patients have been reluctant to attend GP surgeries and hospitals even when appointments have been scheduled due to the risk of contracting COVID-19. A proportion of lung cancer referrals and diagnoses occur due to incidental findings on routine CT scans for other indications or on surveillance scans for small pulmonary nodules, and such routine work has largely been put on hold. Finally, many people at highest risk of lung cancer have been instructed to “shield” due to the high prevalence of cardiac, respiratory and other disease in this group. Shielding will result in less exposure to other people, which will reduce the number of respiratory infections occurring, which in turn will result in less consultations with healthcare professionals and less opportunity for lung cancer to be suspected or detected on examination or imaging. There has been some discussion within the Wales Cancer Network as to whether a specific intervention is needed in order to recover lung cancer detection rates back to their usual levels going forward.

There are several areas in which major developments could occur in the near future that would alter the delivery of LHC programmes.

Finding better ways to identify high-risk individuals who will benefit from LDCT is an area of much research. Further refinements to risk assessment tools may help with this: an updated “LLPv3” tool has been developed with further information on its use due to be published in autumn 2020. Better sensitivity and specificity of risk tools may help reduce the number of LDCTs generated by a LHC programme, making the programme more efficient and cost-effective.

The search for a biomarker to help risk-stratify for LDCT is ongoing. The nature of this research means that a major breakthrough with sufficient clinical validation to alter practice is likely to be 10 years away or more. Biomarkers or genetic evaluation could also offer a mechanism to identify people at risk of lung cancer who have never smoked. This group are not eligible for LHCs based on current criteria but account for over 15% of lung cancer diagnoses in the UK, with this percentage rising over time.

A so-far under-researched area is whether it is possible to identify people who are most likely to benefit if a lung cancer diagnosis is made. A large number of lung cancer diagnoses occur in people aged over 75, but co-morbidities and performance status mean that many may be unsuitable for aggressive treatment or are likely to die from other conditions before doing so from their lung cancer. A mechanism to identify fitter older patients who are still likely to benefit from LDCT screening could lead to many more lung cancers being diagnosed and actively treated through the programme.

An area with the potential for major development in the next 5-10 years is AI-assisted LDCT reporting. If software can progress to the point that some “normal” scans no longer require reporting by a radiologist, this would address the issue of LDCT reporting capacity which would currently be one of the main rate-limiting steps in the development of a large-scale LHC programme.

## WHAT SHOULD WALES DO NEXT?

### FACTORS TO CONSIDER

In deciding the next steps for Wales regarding LHCs, there are two main issues to consider: (1) the plans for the NSC/proposed new screening body to review and make recommendations on lung cancer screening/LHCs, and (2) Wales' readiness to commence LHC activity particularly in the context of COVID-19 pandemic.

### REVIEW AND RECOMMENDATIONS BY NSC/NEW SCREENING BODY

The path to implementation for a national LHC programme was uncertain prior to Sir Mike Richards' review of screening programmes, with ongoing discussion as to whether it should follow a recommendation from the NSC or NICE, or if LHCs would be implemented as a "targeted health intervention" rather than as a screening programme. Following the review there should be a more clearly defined path to implementation: recommendations on whether a programme should be implemented should come from the proposed new screening body.

Given that this path to implementation has now been put forward, it makes sense for a future national LHC programme in Wales to be created in line with this. However, it is likely to be several years before the NSC/new body makes recommendations on lung cancer screening/LHCs. Firstly, the proposed new body does not yet exist, and it is yet to be determined whether it will be an entirely new body or created by expansion of the NSC's remit. Creating and recruiting to the new group, and deciding its terms of reference and protocols, will take some time. Secondly, the cost-effectiveness modelling study on LHCs that has been commissioned by the NSC is due to report in summer 2021 and will form a key part of the NSC/new body's considerations. Thirdly, when the new screening body has been formed and the cost-effectiveness modelling study is available, the process of reviewing evidence and making recommendations will take some time. Fourthly, the screening body may choose to defer making recommendations on a national programme until further information is available from the NHS England programme, which was due to complete in 2023 but is now likely to take until at least 2024 due to the impact of COVID-19.

### WALES' READINESS FOR LHC ACTIVITY

Many healthcare services across Wales were already stretched prior to the COVID-19 pandemic. The imbalance between the rising number of lung cancer cases and the resources available was highlighted as an issue for lung cancer services during Peer Review in 2019. Referrals for suspected lung cancer have fallen acutely during the pandemic, but services are currently ill-prepared for the predictable flood of cases that a LHC programme would generate. Capacity for diagnostic CT scanning, lung function tests, outpatient clinics, bronchoscopy, surgery and radiotherapy have all fallen due to lack of staff, introduction of social distancing measures and cleaning protocols. Primary care has also undergone large-scale change over recent months, on a background of already being stretched. Both primary and secondary care have large backlogs of work to catch up on, with Respiratory medicine hit particularly hard due to being at the fore-front of the secondary care response to COVID-19. It is likely to take several years for services to recover to their previous capacity and waiting times.

## RECOMMENDED COURSE OF ACTION

There are three broad options for what Wales could do next with regards to LHCs: (1) plan and implement a national LHC programme from now, (2) do nothing at this point in time, or (3) plan and commence some limited LHC activity in the first instance.

Taking the issues described above into account, it does not appear that implementation of a national LHC programme for Wales would be the best course of action at this moment in time. It would be more prudent for this to be done in conjunction with recommendations made by the NSC/new screening body, and when healthcare services are in a stronger position to manage the output of a LHC programme.

However, taking no action at this point is also likely to be a poor option for Wales. The arguments in favour of LHC development remain valid: lung cancer is a major health burden, outcomes in Wales are poor, and the evidence supporting the benefits outweighing the risks has grown over time. Cost-effective delivery in UK healthcare settings has been demonstrated in pilot studies in England.

The third option of planning and commencing some limited LHC activity in the short-to-medium-term is likely to be the best option at present. It can take many years for a national screening programme to be rolled out, and smaller projects can provide important experience and learning that can help lay the foundations for subsequent larger-scale programmes. Limited LHC activity in selected areas is also likely to do more good than harm at an acceptable level of cost as shown in the pilot projects in England. These points formed the rationale for the development of the current NHS England LHC programme in selected areas prior to any recommendation from the NSC.

Given the uncertainty of how the COVID-19 pandemic will proceed and the need for existing services to recover, it would be sensible for a fully operational LHC pilot in Wales to plan to commence no sooner than the second half of 2021. The impact of COVID-19 on winter 2020 is of particular concern, so making firm plans to proceed during or immediately after this would be difficult. However, there are still activities that could be undertaken over the next 12 months to increase readiness for LHC activity. Monitoring the recovery of lung cancer services and the implications of COVID-19 will be important, and learning from resumption of the NHS England programme will be helpful. Preparation projects prior to a fully operational pilot could be undertaken with minimal disruption to the recovery of healthcare services: for example, a project could be undertaken to analyse, validate and improve the smoking status records at GP practices in parallel with other preparations for a LHC pilot project.

## PROPOSED TIME-LINE FOR NEXT STEPS

### NEXT 12 MONTHS

- Ongoing learning from LHC projects in England
- Monitor recovery of respiratory, lung cancer and screening services
- Monitor implications of COVID-19 pandemic on existing LHC activity
- Keep abreast of new evidence and developments relevant to LHCs
- Plan and commence a project to assess, validate and improve smoking status data at a number of GP practices
- Make plans for a LHC pilot project in Wales

### IN 12-24 MONTHS

- Commence a LHC pilot project in Wales
- Review cost-effectiveness evidence emerging from the modelling study commissioned by the NSC
- Monitor plans of the NSC/new screening body
- Update projections of the impact and resources required for a national programme based on emerging data

### IN 3-5 YEARS

- Expand pilot activity based on learning from first pilot project and NHS England programme results
- Be prepared to plan implementation of a national LHC programme if a positive recommendation is made by the NSC/new screening body

## SMOKING STATUS DATA PROJECT

The lack of a comprehensive database of current and ex-smokers has not been satisfactorily addressed in LHC activity to date. A project to analyse, validate and improve the smoking status data held on GP records could create the required database, rather than relying on incomplete or potentially inaccurate data as the NHS England programme has done.

A number of GP practices could be selected based on potential sites for a LHC pilot. A protocol could be developed to identify missing smoking data in people within and coming up to the target age range. For those who have data recorded, a sample could be contacted to verify the accuracy of the data. Where data is less likely to be accurate, such as if smoking status was last recorded many years ago, patients could be contacted to update their smoking history. This would improve the accuracy of the data held and allow analysis to see whether inaccurate data can be predicted based on sex, age, time since smoking status was last recorded, number of times the smoking status has ever been recorded, co-morbidities and so on. This would be an important piece of work to inform the process for a national programme in Wales and across the UK, as well as being the first step in preparing for a pilot. Such a project could be undertaken with limited resources and would not impair the recovery of healthcare services from the COVID-19 pandemic. The project would require planning, a small administration team to contact patients and record the data, and analysis and evaluation of the results.

## PRINCIPLES OF A LHC PILOT IN WALES

If the short- to medium-term plan in Wales is to proceed with a pilot LHC project, its development should adhere to the following principles:

- Aim to maximise the ratio of good to harm in the most cost-effective way possible
- Start small to maximise the chances of successful delivery and limit costs
- Be based on a model that could be scaled up for a larger programme
- Address particular challenges and barriers that need to be overcome for a LHC programme to be successfully delivered in Wales.

Considering these principles, a list of recommendations for pilot activity in Wales is given below. Many of the recommendations are aligned with NHS England LHC programme standard protocol, whilst others are based on evidence and modelling discussed elsewhere in this report.

## LHC PILOT RECOMMENDATIONS

### PILOT SITE LOCATION

1. Commence pilot LHC activity in a deprived area with a high incidence of lung cancer, where the likelihood of doing more good than harm will be greatest. Areas to consider include Merthyr Tydfil, Rhondda Cynon Taf or Neath Port Talbot.
2. Consider a second pilot site to run concurrently or sequentially to the first site, to develop aspects of the programme that could be centrally delivered. Areas to consider include Wrexham, Flintshire or Denbighshire in North Wales, or Llanelli in West Wales.

### PILOT PROGRAMME DELIVERY

3. Raise awareness of upcoming LHC activity amongst the general public and healthcare professionals prior to the programme commencing, including informing potential participants prior to their invitation.
4. Identify potential participants aged 60-74 from GP records. Undertake a project to improve the completeness and accuracy of smoking status data prior to or as part of the pilot.
5. Invite potential participants for an initial telephone-based LHC by letter. Follow-up non-responders with a further invitation letter, followed by a telephone call. Invitations should be designed as being from the participant's GP practice.
6. At the telephone-based LHC, ask questions to determine future risk of lung cancer using risk calculators. Screen for exclusion criteria for LDCT. Those above the risk threshold are invited for a face-to-face LHC, with a firm appointment agreed for this during the telephone call. Written information regarding the date, time, location and public transport links to the face-to-face LHC should be sent to the participant, as well as information about LHCs and LDCT screening.
7. A tool such as LLPv2 should be used to assess lung cancer risk and determine eligibility for LDCT. Consider using LLPv3 if this is available, selecting a threshold depending on modelling of the number of LDCTs generated. A threshold of  $\geq 2.5\%/5$  years should be used.
8. The telephone-based LHC should also enquire about symptoms of lung cancer and COPD, existing respiratory diagnoses, and smoking status. Brief advice should be given to current smokers and a referral made to smoking cessation services unless the participant opts out. Participants not above the lung cancer risk thresholds may still be referred or sign-posted to local services if they have red-flag symptoms or suspected COPD without a prior diagnosis.
9. The face-to-face LHC could be delivered either in a mobile community-based unit with on-site LDCT, or in a fixed facility with and adjacent mobile LDCT unit. Existing hospital CT scanners are unlikely to have the capacity to accommodate the programme.
10. The face-to-face LHC should consist of confirmation of key information gathered at the telephone-based LHC, information and consent for LDCT screening, spirometry, and LDCT. Additional potential components such as assessment of cardiovascular risk, AF and HbA1c should not be included in the pilot.

11. Smoking cessation interventions should be a core component of the LHC. The strongest available intervention should be included, such as an on-site counsellor and immediate access to NRT when possible.
12. Participants attending for a face-to-face LHC should undergo targeted spirometry where results will be helpful. Protocols for who to offer spirometry and how results are communicated to participants and primary care should be in place. Obstructive spirometry in participants with symptoms of COPD without a prior diagnosis should be highlighted for further action. An enhanced primary care clinic supported by community-based respiratory nurses could be implemented to deliver this.
13. LDCT should be performed without intravenous contrast. CT equipment, image acquisition and reconstruction should be as per the parameters for the NHS England programmes. Radiation exposure should be kept as low as possible whilst maintaining good image quality, with an effective radiation dose well below 2mSV.

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## LDCT REPORTING & OUTCOMES

14. LDCT reporting should ideally be undertaken by thoracic radiologists in Wales by adjustment of job plans or as additional duty sessions for the pilot activity. They would not necessarily need to be based locally to the pilot site. The reporting radiologists should undergo specific training in LDCT/nodule reporting, and report using a standardised template.
15. Computer-aided detection software should be used to aid nodule detection and reporting.
16. Quality assurance processes for LDCT reporting should be in place. A regular meeting of reporting radiologists should occur (remotely if necessary) to discuss positive findings on LDCTs.
17. Participants with findings on LDCT suspicious of lung cancer should be informed by telephone or face-to-face and referred from the programme to the local lung cancer MDT.
18. Participants with pulmonary nodules on LDCT should be informed by letter with the option of further discussion by phone, and informed of the arrangements for their next surveillance CT. Surveillance CTs should be managed, conducted and reported within the programme, with nodules showing concerning features referred to the local lung cancer MDT. Surveillance CT intervals should be as per the NHS England programmes. Timing of availability of the mobile CT unit to provide surveillance scans at later dates should be considered if planning to utilise the mobile unit across multiple sites. Where this is not possible arrangements may need to be made for surveillance CTs to be conducted at local hospitals, but these scans should still be organised, reported and acted on by the LHC programme.
19. Incidental findings on LDCT should only be reported when likely to be of clinical relevance. Guidance on the reporting and management of incidental findings should be developed. Relevant results and planned actions should be communicated to participants by letter or telephone as appropriate.
20. A LHC report should be sent to the GP. Key information including significant findings and actions required should be prominently displayed on the front page. This LHC report should also be made available on Welsh Clinical Portal.

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## PROGRAMME GOVERNANCE & WORKFORCE

21. Systems should be in place to ensure robust call and recall, data collection, collection and storage of LDCT images and reports, and to generate largely automated LHC reports from the information collected.
22. A management team will be needed including a clinical lead, a programme manager and a lead radiologist. A plan for workforce, training and equipment should be developed depending on the budget and planned scale of the project.

## PILOT SITE LOCATION(S)

Commencing pilot activity at two geographically separate sites rather than a single site would increase the complexity of pilot activity, but would be better placed to lay the foundations for a larger scale future programme. So far most pilot activity in England has taken place in limited geographical areas within a single cancer alliance, linked to a single lung cancer service. Each of these pilots have developed their own programme infrastructure which has been self-contained within that cancer alliance. However, to deliver LHCs on a larger scale there are significant advantages to centralising some aspects of the programme. For example, the capacity to report LDCTs would be a major challenge for a national programme. If each health board in Wales were required to recruit additional radiologists to support their local LHC activity this would be extremely difficult. For a larger scale LHC programme in Wales to be robust, it would be preferable for Wales to have a centralised pool of radiologists contributing to the service rather than relying on individual health boards to provide them. This pool of radiologists could be based in a limited number of locations, or could be a network of radiologists linked across Wales. Quality assurance and evaluation are other aspects that would benefit from centralised delivery. Running two pilot sites would allow links across Wales to be developed and lay the foundations for centrally run aspects of a larger future LHC programme. In order for these links to be tested, the pilot sites should be in different health boards.

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## SOUTH WALES PILOT

One pilot site should be in an area of South Wales which is socially deprived and has a high health burden due to lung cancer. It would be best for the pilot to be conducted outside of central Cardiff or Swansea; pilots in England have demonstrated that LHC programmes can be effective when conducted adjacent to large thoracic oncology centres, so having the programme geographically removed from these services would allow evaluation of whether LHC programmes can successfully develop links from a LHC programme to the local lung cancer MDTs, then on to regional surgical and oncology centres.

An ideal pilot site in South Wales would have a high incidence and mortality from lung cancer in order for enough cases to be detected to do more good than harm, and to test flow through downstream systems. It would also require engagement and enthusiasm from the local lung cancer service and primary care. A higher smoking prevalence and a higher incidence of lung cancer in people below the upper age limit for the programme would also be desirable. There is relatively little variation in proportion of cases presenting with early or late-stage in different areas of Wales, so this is not a helpful factor to take into consideration.

Of the health boards in Wales, Cwm Taf (prior to including Bridgend and become Cwm Taf Morgannwg) has consistently had the highest lung cancer incidence and mortality overall, the highest incidence of lung cancer in people aged under 75 years, and the highest smoking prevalence (table 15).

*Table 15: Lung cancer statistics in Cwm Taf (prior to becoming Cwm Taf Morgannwg), compared to Wales average.*

	<b>Cwm Taf</b>	<b>Wales average</b>
Lung cancer incidence (per 100,000 population per year)	91.4	80.7
Lung cancer mortality (per 100,000 population per year)	74.3	62.1
Smoking prevalence (2013-14 QOF data)	22.1%	20.4%

When broken down by local authority, Merthyr Tydfil has had the highest incidence and mortality from lung cancer in recent years both within Cwm Taf and across Wales (table 16).

*Table 16: Top 5 local authorities for lung cancer incidence and mortality in Wales, 2013-2017. EASR = European Age Standardised Rate per 100,000*

<b>Rank</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>Wales average</b>
Lung cancer incidence (2013-17, EASR/100,000)	Merthyr Tydfil (106.4)	Rhondda Cynon Taff (94.3)	Neath Port Talbot (93.6)	Newport (90.5)	Caerphilly (88.0)	(80.7)
Lung cancer mortality (2013-2017 EASR/100,000)	Merthyr Tydfil (86.1)	Neath Port Talbot (74.0)	Rhondda Cynon Taff (71.3)	Newport (70.4)	Caerphilly (67.2)	(62.1)

Some older data from 2009-2013 is available from an analysis published in 2015 by the Welsh Cancer Intelligence & Surveillance Unit which breaks down lung cancer statistics by GP cluster. Within Cwm Taf at this time, North Rhondda had the highest lung cancer incidence, followed by South Rhondda, South Cynon and South Merthyr Tydfil. For lung cancer diagnoses in people aged under 75 years, the incidence was highest in males in North Rhondda followed by South Cynon and South Rhondda, and in females was South Rhondda followed by North Cynon and North Rhondda. Within Cwm Taf, Merthyr Tydfil had a greater proportion of lung cancer diagnoses in people aged over 75 years.

There is not a single “best” location to pilot LHCs in South Wales based on this data, which also does not take into account the engagement needed from lung cancer services and primary care. Cwm Taf is the health board with the highest lung cancer mortality, and GP clusters within Merthyr Tydfil or Rhondda Cynon Taf look to fulfil most of the desirable criteria for a South Wales pilot site.

## NORTH OR SOUTH WEST WALES PILOT

If a second pilot site goes ahead, it should be located in a different health board in order to develop systems for centrally delivered components. An unanswered question from pilots in England to date is whether LHCs can be successfully delivered in more rural settings. As such, the second site could be located in North or South West Wales, should target areas with a high health burden due to lung cancer, and include rural areas within its scope.

Looking at similar data to that discussed above for the South Wales pilot, Betsi Cadwaladr has a similar lung cancer incidence to the Wales average, whilst Hwyl Dda's lung cancer incidence is slightly below the average (table 17). However, both health boards cover large geographical areas including areas with a relatively low health burden due to lung cancer, so more detailed assessment of smaller localities is required to inform the best site for a pilot.

*Table 17: Lung cancer statistics in North and West Wales.*

	<b>Betsi Cadwaladr</b>	<b>Hwyl Dda</b>	<b>Wales average</b>
Lung cancer incidence (per 100,000 population per year)	80.2	74.7	80.7
Lung cancer mortality (per 100,000 population per year)	62.7	56.4	62.1
Smoking prevalence (2013-14 QOF data)	20.4%	18.9%	20.4%

Several local authorities in North Wales have a numerically higher lung cancer incidence and mortality than the Wales average, though not to the level of statistical significance. Other local authorities in North Wales, and all those in South West Wales were numerically below the Wales average. The areas with the highest lung cancer incidence and mortality across North and South West Wales are shown in table 18.

*Table 18: Lung cancer statistics by local authority for North and West Wales only, 2013-2017.*

<b>Rank for North or South West Wales</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>Wales average</b>
Lung cancer incidence (2013-17, EASR/100,000)	Wrexham (86.5; 7 <sup>th</sup> /22 local authorities in Wales)	Flintshire (84.3; 8 <sup>th</sup> /22)	Denbighshire (82.7; 9 <sup>th</sup> /22)	(80.7)
Lung cancer mortality (2013-2017 EASR/100,000)	Wrexham (66.8)	Denbighshire (65.5)	Flintshire (63.9)	(62.1)

Within North Wales, when broken down by GP cluster based on 2009-2013 data, North Denbighshire had the highest lung cancer mortality (105.7/100,000/year) followed by Conwy East. North Denbighshire also had the highest lung cancer incidence for men and women aged under 75 years, and the highest smoking prevalence at 24.2%, followed by Wrexham town (23.1%).

Within South West Wales, the GP cluster with the highest lung cancer incidence was Llanelli (97.2/100,000/year), which also had the highest smoking prevalence in the area (20.7%). For age under 75 years, Llanelli was ranked second for lung cancer incidence in both men (after Amman/Gwendraeth) and women (after South Pembrokeshire).

Again, there are many factors to take into consideration, but areas that fulfil many of the desirable criteria for a second pilot site include Wrexham or North Denbighshire in North Wales, and Llanelli in South West Wales.

If a North Wales site on the border between Wales and England is selected (within areas of Wrexham or Flintshire), this may add some complexities for people living in England but registered with a Welsh GP practice. Assessing impact on downstream services such as thoracic surgery and oncology may also be more difficult for a North Wales site, as some of these services are provided in England which could make access to data and separating effects from England and Wales challenging.

## PILOT PROJECT SCALE

Depending on the resources available, the size of a LHC pilot project in Wales could be determined by the number of GP practices selected to participate, the target age range chosen, and the risk threshold selected for LDCT. After selecting these variables, the number of LDCTs undertaken could still vary widely depending on the uptake of the programme.

Table 19 demonstrates how the uptake of a pilot project would alter the throughput of a pilot programme using a narrow age range and a high threshold for LDCT and the North Rhondda GP cluster as an example. Based on these figures, a pilot using an age range of 60-74 years and a high risk threshold for LDCT could recruit from around four GP practices of this size in order to scan approximately 500 people if the uptake of from the target population was 50%. Using the same variables, if the entire GP cluster of five practices was included then around 720 to 1000 people would be scanned if the uptake was 50-70%.

Table 19: Throughput of a pilot LHC project with a narrow target age range and high threshold for LDCT, with 30%, 50% and 70% uptake of the target population. All figures are approximate and based on extrapolation of data from various sources.

		Tylorstown Surgery, Tylerstown	St Davids Surgery, Ton Pentre	Ferndale Medical Centre, Ferndale	Forest View, Treorchy	Ty Newydd Surgery, Treherbert	Total
<b>Registered patients</b>		6,017	4,970	7,609	10,332	6,429	35,357
Age 55-74		1,460	1,206	1,846	2,507	1,560	8,578
Age 60-74		1,095	904	1,384	1,880	1,170	6,433
<b>Age 60-74, ever-smokers</b>		547	452	692	940	585	3,217
<b>Telephone LHC</b>	30% uptake	164	136	208	282	175	965
	50% uptake	274	226	346	470	292	1,608
	70% uptake	383	316	485	658	409	2,252
<b>Eligible for LDCT using NHS England criteria</b>	30% uptake	92	76	116	158	98	540
	50% uptake	153	127	194	263	164	901
	70% uptake	215	177	271	368	229	1,261
<b>Eligible for LDCT using higher threshold e.g. LLPv2≥5%/5yrs</b>	30% uptake	74	61	93	126	79	432
	50% uptake	123	101	155	211	131	721
	70% uptake	172	142	217	295	183	1,009

Based on approximate figures extrapolated from the NHS England modelling tool, a pilot that aimed to undertake 1000 telephone LHCs and 500 initial LDCTs would lead to 30-40 patients requiring investigation after their initial, 3-month or 12-month LDCT, with 15-20 cancers likely to be found, of whom 10-15 would undergo surgery.

If 60 telephone LHCs and 30 LDCTs were undertaken per week, it would take 16 weeks for a cohort of 1000 LHCs/500 LDCTs to be completed. As the LDCTs would have to be undertaken following the telephone LHCs, commencing LDCT scanning 4 weeks after the telephone LHCs would give a duration of 20 weeks for the first phase of the project. Plans would need to be made to provide 3-month and 12-month interval scans for participants who required them due to indeterminate findings. Approximately 50-100 new diagnoses of COPD would be expected to be found.

The cost of a pilot would depend on its size and variables. Linking much of the activity to existing services such as smoking cessation and community respiratory teams could help to limit costs. The main costs would be use of LDCT scanners and reporting of LDCTs, and employment of Lung Health Checkers and a management/governance/clinical team. Once the variables and/or budget of a pilot have been determined, a more detailed implementation plan could be produced.

## CONCLUSIONS

Notwithstanding the impact of the COVID-19 pandemic, evidence has been growing in favour of LDCT screening for lung cancer, and LHC activity has been accelerating at pace in England with the development of the NHS England Targeted LHC programme. Whether a positive recommendation is forthcoming from screening bodies in the near future or not, LHC activity is likely to continue to grow with England aiming for a national programme to be established within the next 10 years. Lung cancer is the leading cause of cancer death in Wales, with outcomes lagging behind those of the other nations within the UK as well as much of Europe. Whilst the time is not yet right to commit to a full national LHC programme in Wales, there is a risk of Wales falling further behind in lung cancer care and outcomes unless some action is taken in the short- and medium-term. This report proposes aiming to commence a LHC pilot in Wales within the next 12-24 months. In addition, a project to improve smoking status data held on GP records could be undertaken whilst the pilot is being planned, which would make a valuable contribution to the pilot and to the development of future LHC activity throughout the UK.

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