

IMPLEMENTATION OF LUNG CANCER
SCREENING:
LESSONS FROM A LOCAL LUNG
CANCER SCREENING PILOT

Dr Emily C Bartlett
Department of Radiology
Royal Brompton Hospital
London

A thesis submitted to Imperial College London,
for the Degree of Doctor of Philosophy

2021

STATEMENT OF ORIGINALITY

I declare that this thesis is my own original work. Any data, images, or text resulting from the published or unpublished work of others are fully identified as such within the work, and attributed to their originator.

The copyright of this thesis rests with the author. Unless otherwise indicated, its contents are licensed under a Creative Commons Attribution-NonCommercial 4.0 International Licence (CC BY-NC).

Under this licence, you may copy and redistribute the material in any medium or format. You may also create and distribute modified versions of the work. This is on the condition that: you credit the author and do not use it, or any derivative works, for a commercial purpose.

When reusing or sharing this work, ensure you make the licence terms clear to others by naming the licence and linking to the licence text. Where a work has been adapted, you should indicate that the work has been changed and describe those changes.

Please seek permission from the copyright holder for uses of this work that are not included in this licence or permitted under UK Copyright Law.

ABSTRACT

Growing evidence from screening trials suggests that computed tomography (CT) screening for lung cancer reduces lung cancer mortality, but lung cancer screening has not yet been approved by the UK national screening committee.

This thesis sought to answer questions about how lung screening might be implemented outside a trial setting. Clinical questions included how to maximise participant uptake and attendance for screening, how risk models used in UK pilots to select participants for screening compare in identifying individuals at high risk of cancer, and the downstream consequences of the detection of incidental findings during screening for primary and secondary care. From a radiological angle, workforce requirements for population-based screening are unknown and questions surround the optimisation of nodule management protocols for screening, and how consistent, high-quality reporting can be achieved.

The West London pilot confirmed that with use of risk-based prediction models, lung cancer can be detected with a prevalence of >2.0%. Whilst screening has been advocated as a means to detect undiagnosed cardiovascular and respiratory disease, data from the West London pilot have demonstrated that despite a *potential* benefit of the identification of such disease, future work will be required to maximise *actual* benefits, with few participants referred to primary or secondary care having a subsequent change in management.

A study of radiologist reading times demonstrated that lung screening scans can ordinarily be reported in <5 minutes. Radiologist adherence to nodule management guidelines is, however, crucial. The development of a tabulated algorithm and subsequently a mobile phone application to assist radiologists demonstrated that greater adherence to protocols can be achieved than when following flow chart

algorithms. A small interobserver agreement study involving clinicians involved in screening from other UK screening centres indicated the need for amendments to the current nodule management guidelines for several challenging nodule management scenarios.

ACKNOWLEDGEMENTS

There are several people who I would like to thank for their support and assistance. First and foremost, I am grateful to Professor Anand Devaraj for his supervision, guidance and time over the past three years, and for innumerable conversations, debates and written comments which have helped to clarify and improve the contents of this thesis. The combination of brilliance and humility are rarely encountered, and I consider it a great privilege to have worked for three years with such a supervisor. I am also indebted to Dr Samuel Kemp, as my second supervisor, who helped me to see the bigger picture and wider ramifications of the work contained within this thesis. This, alongside great attention to detail when reviewing this thesis, also substantially improved the final work.

Several radiologists and physicians have contributed to work contained within this thesis, to whom I am also grateful. Dr Carole Ridge, Dr Saeed Mirsadraee, Professor Simon Padley and Professor Sujal Desai have provided helpful and constructive comments to me during the development of the mobile phone application used within the West London pilot. Dr Mario Silva provided radiologist reading times data from the bioMILD trial in Italy and I am grateful to him and his radiology colleagues, Dr Gianluca Milanese and Dr Margherita Ruggirello, for this. Dr Carole Ridge, Professor Sujal Desai and Professor Devaraj also kindly allowed me to use their reading times for the same chapter. Dr Arjun Nair, Dr Hasti Robbie, Dr Mike Darby, Dr James Shambrook and Dr Samuel Kemp participated in the interobserver agreement study within this thesis, and I am grateful for their time and input.

David Butler developed the mobile phone application in use in the West London screening pilot; his attention to detail and timely edits have helped me enormously.

My parents, the Rev. Brian Blackshaw and Dr Pat Munday, have showed unwavering support and encouragement through many years of education. Lastly, and above all, I am hugely indebted to my husband, John, for his love and support.

TABLE OF CONTENTS

STATEMENT OF ORIGINALITY	2
ABSTRACT.....	3
ACKNOWLEDGEMENTS	5
TABLE OF CONTENTS.....	7
LIST OF TABLES.....	18
LIST OF FIGURES.....	21
ACRONYMS, ABBREVIATIONS AND SYMBOLS.....	24
CHAPTER 1: INTRODUCTION.....	28
1.1 Background to lung cancer	28
1.1.1 Incidence, mortality and survival	28
1.1.2 Aetiology and risk of lung cancer	29
1.1.3 Histological classification and staging of lung tumours	31
1.1.4 Treatment of lung cancer	36
1.2 Background to lung cancer screening	39
1.2.1 General principles of screening	39
1.2.2 Performance characteristics of screening tests	41
1.2.2.1 Statistical principles.....	41
1.2.2.2 Biases associated with screening tests	42
1.2.2.3 Outcome measures	44
1.2.3 History of lung cancer screening	45
1.2.3.1 Screening with chest radiographs and sputum analysis.....	45

1.2.3.2 Non-randomised trials including single arm studies	47
1.2.3.3 Randomised controlled trials	48
1.2.4 Principles of screening applied to lung cancer screening	52
1.3 Patient selection for lung cancer screening.....	57
1.3.1 Risk models for patient selection for screening.....	58
1.4 Lung cancer screening through targeted lung health checks (LHCs)	63
1.4.1 UK pilot studies using a lung health check model	63
1.4.2 Participant uptake for screening.....	66
1.5 Technical considerations related to CT scanning	67
1.5.1 Principles of CT scanning	67
1.5.2 CT radiation dose	68
1.5.3 Low dose CT (LDCT) scanning.....	70
1.6 CT reporting in lung cancer screening.....	71
1.6.1 Lung nodule terminology.....	71
1.6.2 Detection and measurement of pulmonary nodules on CT.....	73
1.6.3 CT Reading times with CAD.....	75
1.6.4 Benign and malignant pulmonary nodules.....	76
1.6.5 Management of pulmonary nodules	80
1.6.6 Reporting incidental findings detected at LDCT screening	82
1.6.7 Standardised reporting and quality assurance	84
1.7 Aims of thesis.....	85
CHAPTER 2: GENERAL METHODS.....	87

2.1 Overview of the West London targeted lung screening pilot.....	87
2.1.1 Rationale, funding and governance of the screening pilot.....	87
2.1.2 Identification of clinical commissioning groups for participant recruitment	87
2.1.3 Governance structure of the West London targeted lung screening pilot.....	88
2.2 Participant eligibility, identification and invitation strategy	89
2.3 Lung health checks	90
2.3.1 Personnel and staff training.....	90
2.3.2 Data collection during LHCs.....	91
2.3.2.1 Clinical data and red flag symptoms.....	91
2.3.2.2 Spirometry	93
2.3.2.3 Low dose CT eligibility, risk scores and interpretation and validation of risk calculators	93
2.3.3 Data storage	96
2.4 CT acquisition, transfer and storage	96
2.4.1 CT scanning protocol	96
2.4.2 CT image transfer and storage	97
2.4.3 Quality assurance for image acquisition and transfer	98
2.5 CT reporting.....	99
2.5.1 Baseline scan reporting	99
2.5.2 Follow-up scan reporting.....	101
2.5.3 Nodule management protocols	102
2.5.4 Reporting of incidental findings.....	105

2.5.6 Radiologist training and quality assurance	107
2.5.5 CT reporting templates	107
2.6 Communication of results	109
2.6.1 Participants who did not attend a LHC.....	109
2.6.2 Participants ineligible for, or declining, LDCT screening.....	110
2.6.3 CT screened participants.....	110
2.6.3.1 Positive, indeterminate and negative CT screening scans at baseline	110
2.6.3.2 Communication of results to GPs and participants	111
2.6.3.3 CT incidental findings and management protocol for incidental findings	111
2.6.4 Spirometry results	113
2.7 Results letter generation and InfoFlex® quality assurance process	113
2.8 Significant unexpected events.....	114
2.9 Data analysis and statistical analysis.....	114
2.9.1 Data extraction from InfoFlex®	114
2.9.2 Screening metrics.....	114
2.9.2.1 Participant uptake	114
2.9.2.2 Participant attendance.....	114
2.9.2.3 CT screening outcomes.....	115
2.9.2.4 Recall rate.....	115
2.9.2.5 False positive cases.....	116
2.9.3 Participant satisfaction surveys	116
2.9.4 Statistical analyses	117

CHAPTER 3: RESULTS	119
3.1 Introduction	119
3.2 Baseline results of the West London targeted lung screening pilot	119
3.2.1 Invitations sent and response rates.....	119
3.2.1.1 Letters to potential participants	119
3.2.1.2 Uptake from the first invitation letters, second invitation letters and phone calls	120
3.2.2 Demographic profile of LHC participants.....	121
3.2.3 Overall attendance and non-attendance rates	123
3.2.3.1 Confirmation of eligibility for a LHC upon attendance	124
3.2.4 Risk profile of LHC participants who had a risk score calculated.....	126
3.2.5 LDCT scans performed at baseline	128
3.2.5.1 Baseline scan doses	128
3.2.6 LDCT scan outcomes	129
3.2.6.1 Positive, negative and indeterminate scans, recall rates and false positive rates	129
3.2.6.2 Lung cancer diagnoses and treatment.....	131
3.2.6.3 Non-lung neoplasms and significant incidental findings.....	133
3.2.6.4 Non-urgent incidental findings detected at LDCT.....	134
3.2.7 Time from baseline scan to CT report and results letter	136
3.2.8 Time from CT to PET-CT scan.....	136
3.2.9 Referrals to primary and secondary care following the LHC appointment....	137
3.2.9.1 Referrals to primary care	137

3.2.9.2 Referrals to secondary care.....	137
3.2.10 Significant unexpected and adverse events.....	138
3.2.11 Discussion.....	139
3.3 Comparison of mobile scanner and fixed (hospital) site scanner.....	142
3.3.1 Uptake for a LHC at the mobile and fixed site scanner	142
3.3.2 Non-attendance at the mobile and fixed site scanner.....	142
3.3.3 Demographic and socioeconomic comparison of participants invited to the mobile and fixed site scanner.....	143
3.3.4 Distance travelled to scanner for participants invited to the mobile and fixed site scanner.....	146
3.3.5 Participant satisfaction surveys at the mobile and fixed sites	148
3.3.6 Discussion	149
3.4 Summary	151
CHAPTER 4: DOWNSTREAM CONSEQUENCES OF IDENTIFYING INCIDENTAL AND OTHER NON-LUNG CANCER FINDINGS FROM THE WEST LONDON TARGETED LUNG SCREENING PILOT.....	153
4.1 Introduction	153
4.2 Methods.....	154
4.2.1 Primary care data collection	155
4.2.2 Secondary care data collection	156
4.2.3 Primary care costs resulting from LHC recommendations	156
4.3 Results	158

4.3.1 Summary of all non-lung cancer referrals to primary and secondary care arising from the LHC.....	158
4.3.2 Primary care referrals	159
4.3.2.1 Coronary artery calcification (CAC) for QRISK assessment	160
4.3.2.2 Cardiac valve calcification and/or aortic or pulmonary artery dilatation, for echocardiogram or CT angiography	161
4.3.2.3 Suspected COPD – for community COPD or respiratory review	162
4.3.2.4 Miscellaneous referrals for incidental imaging findings.....	163
4.3.2.5 Red flag symptoms	163
4.3.2.6 Summary of outcomes of primary care referrals following identification of non-lung cancer findings.....	164
4.3.3 Secondary care referrals	166
4.3.3.1 Participants referred to secondary care as a result of findings detected at LDCT.....	167
4.3.3.2 Participants ineligible for a LDCT scan and referred to secondary care for red flag symptoms	169
4.3.3.3 Summary of outcomes of secondary care referrals for non-lung cancer findings	173
4.3.4 Primary care costs	174
4.3.4.1 Modelled primary care costs based on patients attending primary care .	174
4.3.4.2 Modelled anticipated costs resulting from closer adherence to the NHSE protocol.....	174
4.4 Discussion.....	177

4.5 Summary	181
CHAPTER 5: READING TIMES IN LUNG CANCER SCREENING	184
5.1 Introduction	184
5.2 Methods.....	185
5.2.1 Reading times	185
5.2.1.1 CT reading times in the West London Screening Pilot.....	185
5.2.1.2 IRCCS Istituto Nazionale Tumori di Milano, Milan, reading times.....	188
5.2.2 Statistical analysis	189
5.3 Results	189
5.3.1 Reading times for 6 radiologists.....	189
5.3.2 Relationship between reading times and the number of nodules and incidental findings reported	190
5.4 Discussion.....	191
5.5 Summary	194
CHAPTER 6: INTERSCAN VARIABILITY IN VOLUMETRIC MEASUREMENTS OF SMALL PULMONARY NODULES <150mm³ – IMPLICATIONS FOR LUNG CANCER SCREENING	196
6.1 Introduction	196
6.2 Methods.....	198
6.2.1 Participant recruitment.....	198
6.2.3 Scanning protocol and nodule analysis	199
6.2.4 Statistical analysis	200
6.3 Results	201

6.4 Discussion.....	204
6.5 Summary	209
CHAPTER 7: RADIOLOGIST ADHERENCE TO NODULE MANAGEMENT GUIDELINES IN LUNG CANCER SCREEING.....	210
7.1 Introduction	210
7.2 Methods.....	212
7.2.1 Development of the RBH L-RADS mobile phone application.....	212
7.2.2 Evaluation of radiologist compliance with the West London nodule management algorithms.....	214
7.2.3 Evaluation of reliability of the RBH L-RADS mobile phone application	214
7.2.4 Statistical analysis	216
7.3 Results	216
7.3.1 Radiologist compliance with the nodule management flow chart.....	216
7.3.2 Radiologist compliance with the tabulated L-RADS algorithm.....	217
7.3.3 Radiologist compliance with the RBH L-RADS mobile phone application.....	219
7.3.4 Accuracy and inclusiveness of the RBH L-RADS mobile phone application...	220
7.4 Discussion.....	221
7.5 Summary	224
CHAPTER 8: RADIOLOGIST AGREEMENT ON MANAGEMENT OF COMPLEX NODULE SCENARIOS IN LUNG SCREENING	225
8.1 Introduction	225
8.2 Methods.....	226
8.2.1 Case selection and distribution	227

8.2.2 Statistical analysis	229
8.3 Results	230
8.4 Discussion.....	232
8.5 Summary	236
CHAPTER 9: CONCLUSION.....	237
REFERENCES.....	244
Appendix A: Members of the West London targeted lung screening pilot steering group and operations group	270
Appendix B: Invitation letter and accompanying patient information leaflet.....	272
Appendix C: CT scan patient information leaflet	276
Appendix D: West London targeted lung screening pilot nodule management protocol	278
Appendix E: RBH L-RADS nodule management protocol	282
Appendix F: Protocol for reporting incidental imaging findings in the West London targeted lung screening pilot.....	285
Appendix G: Example results letters to participants and GPs.....	286
Appendix H: Protocol for referral of participants to primary or secondary care according to spirometry results in the West London targeted screening pilot.....	289
Appendix I: Participant satisfaction survey developed by the West London pilot project operations group in conjunction with Ipsos MORI.	290

Appendix J: Nodule management scenarios distributed to radiologists and clinicians for interobserver agreement study	294
---	------------

LIST OF TABLES

Chapter 1

1.1	Reclassification of bronchioalveolar carcinoma according to the 2011 IASLC/ATS/ERS publication.....	32
1.2	TNM8 for lung cancer.....	35
1.3	ECOG performance status.....	36
1.4	Ten principles of screening.....	40
1.5	Ten criteria for lung cancer screening.....	41
1.6	Inclusion criteria, screening protocols and outcomes of major randomised controlled trials to date.....	49
1.7	Summary of eligibility criteria and variables included in a number of frequently cited risk prediction models.....	60
1.8	Patient eligibility, uptake and baseline results of UK-based pilot studies and trials using a LHC model.....	66
1.9	Adjustable CT parameters affecting dose.....	69

Chapter 3

3.1	Baseline demographic data for all participants who opted in for a LHC appointment.....	122
3.2	Demographic characteristics of attendees and non-attendees.....	124
3.3	Demographic profile and risk profile of 1542 participants who attended a LHC and had a risk score calculated.....	127
3.4	Summary of baseline scan doses at the mobile and fixed sites.....	128

3.5	Clinical and pathological details of the 29 participants with lung cancer detected, including PLCO _{m2012} and LLP _{v2} risk scores of each participant diagnosed with cancer.....	133
3.6	Non-lung malignancies and significant incidental findings detected during the screening pilot.....	134
3.7	Imaging investigations carried out within the screening pilot for benign diagnoses.....	138
3.8	Significant unexpected and adverse events during the lung screening pilot...	139
3.9	Demographic and socioeconomic characteristics of participants booking LHC appointments at the two sites.....	143
3.10	Comparison of participant satisfaction survey results between fixed site and mobile site scanner locations.....	148

Chapter 4

4.1	Areas where the West London targeted lung screening pilot referral protocol deviates from the current NHS England referral protocol.....	157
4.2	Outcomes of incidental non-urgent imaging findings detected at LDCT in participants who were referred to primary care.....	163
4.3	Diagnosis and treatment of participants with undiagnosed ILAs who attended secondary care for follow-up.....	168
4.4	Diagnoses and treatment given to participants having normal CT scans to investigate chronic cough and outcomes following treatment.....	171
4.5	Costs of GP and community respiratory appointments, subsequent imaging studies and secondary care referrals following recommendations from the West London targeted lung screening pilot.....	174

4.6	Modelled additional primary care costs resulting from closer adherence to the current NHSE protocol.....	176
-----	--	-----

Chapter 5

5.1	Median reporting times for 6 radiologists.....	189
5.2	Number of reported cases with 0-4 nodules and 0-4 incidental findings.....	190
5.3	Spearman's rank correlation (Rs) between the number of nodules reported, number of incidental findings reported and reading times for 6 radiologists.....	191

Chapter 6

6.1	A model to demonstrate the implications of assuming stability for solid nodules growing 15-24% in 3 months.....	208
-----	---	-----

Chapter 7

7.1	Short excerpt from a decision table provided to the software developer.....	213
-----	---	-----

Chapter 8

8.1	Nodule management scenarios selected for distribution to reporting radiologists in other screening centres.....	228
8.2	Management recommendations of 5 clinicians for the 12 cases.....	231

LIST OF FIGURES

Chapter 1

1.1	Computed tomography (CT) image of histologically proven invasive mucinous adenocarcinoma showing typical radiological features of consolidation containing air bronchograms.....	33
1.2	Population of a 2 x 2 table to calculate sensitivity (A/A+C) and specificity (D/D+C) of a diagnostic test.....	42
1.3	Sensitivity, specificity and positive predictive values in two populations with a differing disease prevalence.....	42
1.4	Lung nodules with differing composition.....	72
1.5	Morphological features of nodules.....	72

Chapter 2

2.1	Smoking prevalence in North West London CCGs 2014/2015.....	88
2.2	Clinical datapoints collected at the LHC.....	92
2.3	Management of participants presenting with red flag symptoms.....	93
2.4	Datapoints required to calculate PLCO _{m2012} and LLP _{v2} risk scores for participants, as recorded in InfoFlex®	94
2.5	PLCO _{m2012} risk calculator in InfoFlex® system.....	95
2.6	An example of a small solid nodule as identified by Veolity™ software.....	99
2.7a	A juxtavascular nodule not identified by Veolity™ software.....	100
2.7b	Segmentation of the juxtavascular nodule following identification of nodule by the reporting radiologist.....	100

2.8	Example of a report exported to the PACS system from Veolity™, documenting the size (both diameter and volume) and location of a solid nodule.....	101
2.9	Example Veolity™ report from a follow-up study.....	102
2.10	Excerpt from baseline PACS reporting template.....	108
2.11	Excerpt from the PACS screening reporting template updated with RBH L-RADS data entry points.....	109

Chapter 3

3.1	Reasons for ineligibility for a LHC at the telephone triage stage.....	120
3.2	Reason for ineligibility for a LHC upon attendance.....	124
3.3	Participant pathway to the point of receiving a lung LHC.....	125
3.4	Outcomes following the LHC risk score calculation and subsequent LDCT scans.....	129
3.5a	IMD profile of all participants invited to the fixed site.....	144
3.5b	IMD profile of all participants invited to the mobile site.....	144
3.6a	IMD profile of all responders and non-responders invited to the fixed site...	145
3.6b	IMD profile of all responders and non-responders invited to the mobile site..	145
3.7a	Histogram demonstrating distance from home (km) to the fixed site for all 1047 participants who booked a LHC at the fixed site.....	147
3.7b	Histogram demonstrating distance from home (km) to the mobile site for 702 participants who booked a LHC at the mobile site.....	147

Chapter 4

4.1	Summary of non-urgent primary and secondary care referrals resulting from the West London targeted lung screening pilot for non-lung cancer findings	159
4.2	Summary of primary care attendances following referral from the LHC pilot.....	160

4.3	Summary of reasons for referral to secondary care from the West London targeted lung screening pilot.....	167
-----	---	-----

Chapter 5

5.1	Anonymised AuditTrail extract from Veolity™, demonstrating the opening time and closing time for a study and reporting radiologist.....	186
5.2	Excerpt from baseline scan report in the West London Screening Pilot.....	187
5.3	Histogram of reading times for 120 scans.....	190

Chapter 6

6.1	Volumetric measurements of 100 nodules on first and second scans.....	202
6.2	Absolute volume difference (mm ³) between volume measurements on the first and second scans, plotted against the mean nodule volume (mm ³).....	203
6.3	Relative difference in nodule volumes (%) plotted against the mean nodule volume (mm ³).....	204

Chapter 7

7.1	Example of output from the RBH L-RADS mobile phone application.....	215
-----	---	-----

Chapter 8

8.1	New tab (within the red box) in mobile phone application added during the second phase of the pilot.....	226
8.2	Example of one nodule management scenario included amongst the 12 cases provided to radiologists, together with the management options given in each case.....	229

ACRONYMS, ABBREVIATIONS AND SYMBOLS

LUNG CANCER SCREENING TRIALS AND STUDIES

COSMOS	Continuous Observation of Smoking Subjects
DANTE	Detection and screening of early lung cancer with Novel Imaging Technology and Molecular Essays
DLCST	Danish Lung Cancer Screening Trial
ELCAP	Early Lung Cancer Action Program
I-ELCAP	International Early Lung Cancer Action Program
ITALUNG	Italian Lung Cancer Screening Trial
JHLP	John Hopkins Lung Project
LLP	Liverpool Lung Project
LSUT	Lung Screen Uptake Trial
LUSI	Lung Cancer Screening Intervention
MILD	Multicentric Italian Lung Detection
MLP	Mayo Lung Project
MSKCC	Memorial Sloane Kettering Cancer Centre
NELSON	Nederlands–Leuvens Longkanker Screenings Onderzoek
NLST	National Lung Screening Trial
NY-ELCAP	New York Early Lung Cancer Action Program
PLCO	Prostate, Lung, Colorectal, Ovarian
UKLS	UK Lung Cancer Screening

ORGANISATIONS

ATS	American Thoracic Society
CCG	Clinical Commissioning Group
CIMS	Chameleon Information Management Services
CSU	Commissioning Support Unit
ECOG	Eastern Co-operative Oncology Group
ERS	European Respiratory Society
IASLC	International Association for the Study of Lung Cancer
NHS	National Health Service

NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
PSSRU	Personal Social Services Research Unit
RBH	Royal Brompton Hospital
RCR	Royal College of Radiologists
RMH	Royal Marsden Hospital
RMP	Royal Marsden Partners
USPSTF	United States Preventative Services Taskforce
WHO	World Health Organisation

HISTOPATHOLOGICAL TERMS

AAH	Atypical adenomatous hyperplasia
AIS	Adenocarcinoma in situ
BAC	Bronchoalveolar cancer
MIA	Minimally invasive adenocarcinoma
NSCLC	Non small cell lung cancer
SCLC	Small cell lung cancer
TNM	Tumour Node Metastasis

CT AND IMAGING TERMINOLOGY

AEC	Automatic exposure control
ALARA	As low as reasonably achievable
CAD	Computer Aided Detection
CT	Computed Tomography
CTDI	Computed Tomography Dose Index
CTDI _{vol}	Volume Computed Tomography Dose Index
CTDI _w	Weighted Computed Tomography Dose Index
DICOM	Digital Imaging and Communications in Medicine
DLP	Dose-length product
GGN	Ground-glass nodule
IPLN	Intrapulmonary lymph node

IR(ME)R	Ionising Radiation (Medical Exposure) Regulations
kV	kilovolts
kVp	Peak kilovoltage
LDCT	Low-Dose Computed Tomography
mSv	millisieverts
MRI	Magnetic Resonance Imaging
PACS	Picture Archiving and Communication System
PET	Positron Emission Tomography
PET-CT	Positron Emission Tomography-Computed Tomography
pGGN	Pure ground-glass nodule
PSN	Part-solid nodule
SSN	Sub-solid nodule
VDT	Volume doubling time

STATISTICAL TERMS AND SYMBOLS

CI	Confidence Interval
HR	Hazard ratio
IQR	Interquartile range
κ	Fleiss Kappa
NNT	Number needed to treat
PPV	Positive predictive value
RR	Rate ratio
R_s	Spearman's Rank
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
χ^2	Chi-squared

MISCELLANEOUS

CAC	Coronary Artery Calcification
CBE	Coffee Break Experiment
COPD	Chronic Obstructive Pulmonary Disease
EBUS	Endobronchial ultrasound

FEV1	Forced Expiratory Volume in 1 second
FVC	Forced vital capacity
GP	General Practitioner
ICER	Incremental cost effectiveness ratio
ILA	Interstitial lung abnormality
ILD	Interstitial lung disease
IMD	Index of Multiple Deprivation
LHC	Lung health check
MDT	Multi-disciplinary team
PPFE	Pleuro-parenchymal fibroelastosis
QALY	Quality-adjusted life year
SABR	Stereotactic ablative radiotherapy
VATS	Video Assisted thorascopic surgery

CHAPTER 1: INTRODUCTION

1.1 Background to lung cancer

1.1.1 Incidence, mortality and survival

The International Agency for Research on Cancer reported an estimated 2.2 million new cases of lung cancer globally in 2020, making lung cancer the most common primary malignancy worldwide [1]. According to the latest available data from England, there were 38888 new diagnoses of lung and bronchial cancer in 2017, comprising 12.7% of all malignancies diagnosed that year [2]. Across all age groups, it is the second most common cancer for men and women, second to prostate cancer (in men) and breast cancer (in women) [2]. However in those over the age of 75 lung cancer is the most common primary malignancy [3].

Although second to prostate and breast cancer in overall incidence, lung cancer is the most common cause of cancer related mortality both globally and within the UK [1]. Responsible for 1.8 million deaths globally in 2020, lung cancer mortality was almost double that of colorectal cancer, the second most common cause of cancer mortality [1]. In the UK, malignant neoplasms of the trachea, bronchus and lung comprised 5.6% of all deaths in 2019, remaining the most common cause of cancer mortality [4].

One-year survival from lung cancer is low at only 37.1% for men and 44.5% for women [5]. Lung cancer may remain asymptomatic until the disease is at an advanced stage; between 2012 and 2016, 50.3% of men had Stage IV disease at diagnosis, and the 1-year age-standardised survival of this cohort is only 16.7% [6]. By contrast, 1-year survival of patients diagnosed with Stage 1 disease exceeds 85% [6]. In recognition of the disparity between survival with early- and late-stage disease, there

has been significant interest for nearly 50 years in how to detect early lung cancer, to improve survival and reduce lung cancer mortality.

1.1.2 Aetiology and risk of lung cancer

Although postulated as early as the 1930s, the link between tobacco consumption and lung cancer incidence was firmly established in the 1950s, with the publication of 3 studies from the UK and the United States of America (USA) [7-9]. Tobacco became widely commercially available at the beginning of the 20th Century and large-scale cigarette production coupled with advertising resulted in increased tobacco consumption [10]. In the UK the peak smoking prevalence amongst males was in the period following the Second World War when as many as 75% of males smoked [10]. This was followed by a peak in smoking prevalence for women, which was both later (around 1970) and lower (approximately 50%) [10]. Throughout most of the twentieth century, smoking prevalence was higher in men than women, but over time, the gender gap progressively narrowed, largely as a result of a more rapidly declining prevalence amongst males. By 2000, the smoking prevalence was similar amongst males (28.5%) and females (25.5%) [11]. By 2019, smoking rates had fallen to 15.8% overall in the UK [11].

The prevalence of lung cancer and lung cancer mortality has closely mirrored tobacco consumption, peaking in 1979 in males, with a time lag of approximately 30 years. At that time, the mortality rate from lung cancer amongst males was almost 170/100000 [12]. Lung cancer mortality rates in females gradually increased through the period 1980-2010 to approximately 50/100000 and may have peaked in recent years [12]. Although lung cancer remains the most common cause of cancer related mortality today, it is likely that the incidence and prevalence will gradually decline over time with the reduction in smoking prevalence.

Alongside smoking, numerous other factors have been postulated to cause lung cancer or contribute to lung cancer risk including genetic susceptibility, occupational exposure to carcinogens, diet, air pollution, radiation exposure and chronic inflammation from infections.

Genome wide association studies have looked at genetic influences in susceptibility to lung cancer, as well as genes which may affect smoking behaviour and susceptibility to chronic obstructive pulmonary disease (COPD) – the latter associated with an increased risk of lung cancer. A number of regions on chromosomes associated with the development of lung cancer, known as susceptibility loci, have been identified [13]. Some loci are specific to particular demographic cohorts, such as a locus on chromosome 3q, known to increase the risk of lung cancer in non-smoking Asian females [13].

The importance of occupational exposures has been quantified by Rushton *et al.* who estimated that in 2005, 14.5% of lung cancers in the UK were attributable to occupational exposures, including exposure to asbestos, mineral oils, silica, radon and heavy metals [14]. A recent systematic review and meta-analysis of dietary factors affecting lung cancer risk suggested a decreased risk of lung cancer (8%-18%) with higher consumption of fruit and vegetables. However, the magnitude of this risk reduction was decreased when adjustments were made for smoking status [15]. Red meat consumption (particularly well-cooked red meat) may also increase lung cancer risk [13]. Previous lung infection, including infection with both tuberculosis and chlamydia pneumoniae [16], or chronic inflammation of the lung may also increase the lung cancer risk [13].

Although various environmental factors, including those described above, are thought to increase an individual's risk of lung cancer, smoking is, without doubt, the

most important amongst these. Several of these factors have now been incorporated into lung cancer risk prediction models, which are discussed further in Section 1.3.1.

1.1.3 Histological classification and staging of lung tumours

The fourth edition of the World Health Organisation (WHO) Classification of Tumours of the Lung, Pleura, Thymus and Heart was published in 2015 [17]. This was an updated version of the 2004 classification with changes reflecting advances in immunohistochemical and molecular tests. The recently published 2021 update to the Classification of Tumours adds a small number of new entities and some additional information on molecular findings associated with different tumour types [18].

Lung tumours are classified as either epithelial tumours, mesenchymal tumours, lymphohistiocytic tumours, tumours of ectopic origin or metastatic tumours. The most common primary tumours are epithelial in origin. Amongst the epithelial tumours, non-small cell lung cancers (NSCLCs), including adenocarcinoma and squamous cell carcinoma, are most common. In 2018, NSCLCs comprised 88.6% of histologically confirmed lung cancers diagnosed in England and Wales, Guernsey and Jersey [19]. Small cell lung cancers (SCLCs) are neuroendocrine tumours and are much less common than NSCLCs, comprising only 9.7% of histologically confirmed tumours in the same cohort [19]. Other rarer neuroendocrine tumour types include large cell neuroendocrine carcinoma and carcinoid tumours.

In recognition of significant advances in the areas of oncology, pathology, radiology and surgery, in 2011 the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) recommended a number of changes to the way in which adenocarcinoma is classified, including when this diagnosis is made from small biopsy or resection specimens or from cytology [20]. The term “bronchioloalveolar cancer” had historically been used to

describe a variety of tumours with widely differing prognoses; the updated 2011 guidelines therefore sought to reclassify adenocarcinoma in a way which better reflected the differing survival rates associated with different tumour subtypes. In addition, the availability of new chemotherapeutic agents meant that specific molecular testing was recommended to enable targeted therapy for some patients with particular molecular abnormalities in tumours.

Categories of New Adenocarcinoma Classification where Former BAC Concept was Used
1. Adenocarcinoma in situ (AIS), which can be non-mucinous and rarely mucinous
2. Minimally invasive adenocarcinoma (MIA), which can be non-mucinous and rarely mucinous
3. Lepidic predominant adenocarcinoma (non-mucinous)
4. Adenocarcinoma, predominantly invasive with some non-mucinous lepidic component (includes some resected tumours, formerly classified as mixed subtype and some clinically advanced adenocarcinomas formerly classified as non-mucinous BAC)
5. Invasive mucinous adenocarcinoma (formerly mucinous BAC)

Table 1.1 Reclassification of bronchioalveolar carcinoma according to the 2011 IASLC/ATS/ERS publication. Adapted from Travis *et al* [21]. BAC, bronchioloalveolar carcinoma.

Preinvasive lesions include atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS); the former representing “a localized, small (usually 0.5 cm or less) proliferation of mildly to moderately atypical type II pneumocytes and/or Clara cells lining alveolar walls and sometimes, respiratory bronchioles” [21] and the latter representing a small lesion (<3cm) with pure lepidic (non-invasive) growth. These are associated with 100% disease-specific survival if surgically resected [21]. Minimally

invasive adenocarcinoma (MIA) refers to small lesions (<3cm) with less than 5mm of invasion. These also have near to 100% disease-specific survival if surgically resected [21]. The diagnoses of AIS and MIA can only be made from completely resected tumours. In the event that a biopsy sample demonstrates lepidic growth, this may represent either AIS, MIA or a larger invasive tumour with some lepidic growth.

Larger invasive non-mucinous adenocarcinomas can be a mixture of histologic subtypes and should be classified according to their predominant subtype. These should be separated from invasive mucinous tumours which show distinctive histopathological and radiological features. Radiologically, invasive mucinous tumours often show a lobar or multi-lobar distribution and may comprise multiple nodular or consolidative opacities. They may contain air bronchograms (Figure 1.1) [21].



Figure 1.1 Computed tomography (CT) image of histologically proven invasive mucinous adenocarcinoma showing typical radiological features of consolidation containing air bronchograms.

Staging of malignancies has been historically carried out using a TNM system. In lung cancer, staging reflects the extent of the primary tumour (T stage), nodal (N

stage) and metastatic (M stage) spread of the disease. Once a tumour is classified by T, N and M, a less detailed numeric staging value is given to the tumour, grouping various T, N and M combinations together. This staging system ranges between I and IV, where I corresponds to small, localised tumours (the least advanced disease) and IV corresponds to cancer with metastatic spread (the most advanced disease).

The 8th edition of TNM staging was based upon a global database collated by the IASLC of over 94000 patients from 16 countries worldwide who were diagnosed with lung cancer between 1999 and 2010 [22]. TNM 8 (Table 1.2) has been used globally since January 2017 [22]. Whilst staging systems are relatively stable over time, the treatment landscape for lung cancer has significantly altered over the past twenty years and thus prognosis in relation to staging varies with treatment availability and continues to change. However, survival remains strongly related to pathological staging. In England, one-year survival for Stage I lung cancer in adults diagnosed between 2013-2017 was 87.7%, 73% for Stage II disease, 48.7% for Stage III disease and 19.3% for Stage IV disease [23].

Descriptor	Definition
T descriptor	
TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma <i>in situ</i>
T1	Tumour ≤ 3cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)
T1mi	Minimally invasive adenocarcinoma
T1a	Tumour ≤ 1cm in greatest dimension
T1b	Tumour >1cm but ≤ 2cm in greatest dimension
T1c	Tumour >2cm but ≤ 3cm in greatest dimension
T2	Tumour >3cm but ≤ 5cm or tumour with any of the following features: involvement of a main bronchus regardless of the distance from the carina; invasion of the visceral pleura; associated with partial or complete lung atelectasis or pneumonitis
T2a	Tumour >3cm but ≤ 4cm in greatest dimension
T2b	Tumour >4cm but ≤ 5cm in greatest dimension
T3	Tumour >5cm but ≤ 7cm in greatest dimension or one that directly invades any of the following structures: parietal pleura, chest wall (including superior sulcus tumours), phrenic nerve, parietal pericardium; or separate tumour nodule(s) in the same lobe
T4	Tumour measuring >7cm in greatest dimension that invades any of the following structures; mediastinum, diaphragm, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; or separate tumour nodule or nodules in a different lobe of the same lung
N descriptor	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M descriptor	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule or nodules in contralateral lung; malignant pleural effusion or pleural thickening or nodules or masses; malignant pericardial effusion or pericardial thickening or nodules or masses
M1b	Single distant (extrathoracic) metastasis in a single organ
M1c	Multiple distant (extrathoracic) metastases in a single organ or multiple organs

Table 1.2 TNM8 for lung cancer. From Staging Manual in Thoracic Oncology 2nd edition [24].

1.1.4 Treatment of lung cancer

Treatment of lung cancer depends upon the histological subtype of the cancer, tumour location and staging, patient fitness and patient preference. A full discussion of the treatment options for all stages of lung cancer is beyond the scope of this thesis. As the intention of screening is to detect early-stage (I and II) disease, this is covered in more depth in the forthcoming discussion; only brief consideration is given to the treatment of late-stage (III and IV) disease. The National Institute for Health and Care Excellence (NICE) has recently updated treatment guidelines and these are outlined below, together with the evidence to support these guidelines [25].

Patient fitness is usually assessed by performance status. In the UK, the Eastern Co-operative Oncology Group performance status is most commonly used, with a scale ranging from 0-5 (Table 1.3), with a score of 0 denoting no symptoms and a score of 5 representing death [26]. In metastatic NSCLC (i.e. Stage IV disease) performance status predicts survival [27] and is an important factor in influencing treatment options.

ECOG Scale	Score
Fully active, able to carry on all pre-disease performance without restriction	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work	1
Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	2
Capable of only limited selfcare, confined to bed or chair for more than 50% of waking hours	3
Completely disabled. Can not carry on any selfcare. Totally confined to bed or chair	4
Dead	5

Table 1.3 ECOG performance status, from Oken *et al*, 1982 [26].

Non-small cell lung cancer (NSCLC)

Patients with early-stage NSCLC (I-IIA) are offered treatment with surgery and/or radiotherapy with curative intent. A randomised trial of lobectomy versus limited

resection in the 1990s demonstrated increased locoregional recurrence with limited resection (either wedge resection or segmentectomy), but similar survival [28], and for this reason lobectomy and systematic lymph node dissection have been the surgical treatment of choice for early-stage (I and II) lung cancer for over two decades. With the advent of computed tomography (CT) screening for lung cancer and the resultant identification of more early-stage and therefore small lung cancers, new interest emerged in sub-lobectomy as an option for surgical treatment. A later prospective trial by Okada *et al.* demonstrated that lobectomy offered no survival advantage over extended segmentectomy in selected patients with tumours <2cm in size [29]. The importance of tumour size was reiterated in a later publication by the same group, in which segmental resection was associated with survival comparable to lobectomy in selected patients with node negative disease and tumours <2cm in size [30]. The role of sub-lobar resection versus lobectomy for small tumours remains contested, and the outcomes of two large clinical studies in Japan and North America are still awaited [31]. However, in the interim, lobectomy remains the recommended surgical procedure for operable NSCLC. Segmentectomy is reserved for those who decline lobectomy, or for those who lack physiological reserve.

Stereotactic ablative radiotherapy (SABR) is a further alternative to sub-lobectomy for those unable to tolerate surgery, or who decline it [25]. SABR is a non-invasive treatment in which highly focused radiation beams are delivered to tumours over 1-5 treatments delivered over the course of 1-2 weeks [32, 33]. A meta-analysis of observational studies demonstrated a survival advantage of SABR over conventional radiotherapy [34], and two randomised controlled trials (RCTs) have also demonstrated improved local disease control and reduced toxicity for SABR compared to conventional radiotherapy in inoperable Stage I NSCLC [35, 36]. Consequently, this is now recommended in preference to conventional or hyperfractionated radiotherapy [33].

The role of SABR in the treatment of medically operable patients with early-stage lung cancer remains uncertain [37], and at present SABR is offered only to those who are unable to undergo surgery after consideration of surgery, rather than as a first-choice treatment option.

Combination treatment (surgery, radiotherapy and chemotherapy) is recommended for those with Stage IIB and III disease, dependent upon surgical resectability, nodal disease and patient factors.

Historically, the treatment of advanced-stage (IIIB-IV) NSCLC has been with platinum-based chemotherapy [38]. However, treatment of advanced-stage disease has changed over the past twenty years with the discovery of specific molecular abnormalities in tumours amenable to targeted therapy. Such treatment can be directed towards specific genetic alterations detected in tumours. For example, tyrosine kinase inhibitors are now first line treatment for those with EGFR, ALK and ROS1 mutations, seen primarily in adenocarcinomas [25]. In addition to targeted therapy, immunotherapy with immune checkpoint blockers has emerged as a further treatment option improving overall and progression-free survival in some groups [38].

Small cell lung cancer (SCLC)

First line treatment for limited-stage (non-metastatic) small cell lung cancer is with cisplatin-based combination chemotherapy [25]. For those with a good performance status (ECOG-WHO 0-1), radiotherapy is offered as a concurrent treatment if the disease can be encompassed within a radiotherapy field. When concurrent radiotherapy is given, this should be offered before the third cycle of chemotherapy [39]. For those who are unfit for concurrent radiotherapy, sequential radiotherapy can be offered to those who respond to first line chemotherapy [25]. Prophylactic cranial irradiation has been newly recommended for those with limited-

stage disease and a good performance status, who have not progressed on first line treatment [25]. Surgery in small cell lung cancer can be considered for those with Stage I disease, but in view of the aggressive nature of the disease, this is rarely the case at presentation. Although three early RCTs [40-42] demonstrated no statistically significant survival benefit for surgery in small cell lung cancer [43], in a pooled retrospective analysis of 41297 patients, surgical resection was associated with superior overall survival for Stage I disease [44].

Those with extensive-stage (metastatic) small cell lung cancer should be offered platinum-based combination chemotherapy [25]. Thoracic radiation with prophylactic cranial irradiation is now recommended for those with extensive disease who have a partial or full response to first line treatment, and prophylactic cranial irradiation alone for those with a performance status of 0-2 who have responded to first line chemotherapy [25]. At present targeted therapies and immunotherapy are not recommended for the treatment of small cell lung cancer.

1.2 Background to lung cancer screening

1.2.1 General principles of screening

In 1968, Wilson and Jungner published their seminal work "Principles and Practices for Screening for Disease" [45]. This document, commissioned by the WHO, contained 10 principles for screening, documented in Table 1.4.

1.	The condition sought should be an important health problem
2.	There should be an accepted treatment for patients with recognised disease
3.	Facilities for diagnosis and treatment should be available
4.	There should be a recognisable latent or early symptomatic stage
5.	There should be a suitable test or examination
6.	The test should be acceptable to the population
7.	The natural history of the condition, including development from latent to declared disease, should be adequately understood
8.	There should be an agreed policy on whom to treat as patients
9.	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as whole
10.	Case-finding should be a continuing process and not a "once and for all" project

Table 1.4 Ten principles of screening [45].

Since the 1960s, over 50 lists of different screening criteria have been proposed, attempting to revise these criteria to apply to particular diseases, or to account for advances in diagnostic science, for example in the area of genomic medicine [46]. The original principles, however, have largely stood the test of time and share the idea that screening should detect early, treatable disease in asymptomatic individuals.

In 2001, Obuchowski *et al.* proposed their own 10 criteria for screening, applied specifically to lung and colorectal cancer (Table 1.5) [47]. Before evaluating how these principles apply to lung cancer screening in the present day, a discussion of the performance characteristics of screening tests, as well as the design and results of previous screening trials is warranted.

1.	The disease has serious consequences
2.	The screening population has high prevalence of a detectable preclinical phase
3.	Screening detects little pseudodisease
4.	The screening test has high accuracy for detecting the detectable preclinical phase
5.	Screening detects disease before a critical point
6.	The screening test causes little morbidity
7.	The screening test is affordable and available
8.	Treatment exists
9.	Treatment is more effective when applied before symptoms begin
10.	Treatment is not too risky or toxic

Table 1.5 Ten criteria for lung cancer screening [47].

1.2.2 Performance characteristics of screening tests

1.2.2.1 Statistical principles

The ability of a test to predict disease is defined by sensitivity, specificity and positive predictive value (PPV). With reference to Figure 1.2, sensitivity describes the proportion of people with a disease who are correctly identified by the screening test ($A/A+C$). Specificity describes the proportion of people without the disease who are correctly identified as not having the disease by the test ($D/D+B$). In an ideal screening test, sensitivity and specificity would both be very high. Thus, most people with the disease would be identified by the test, and most people without the disease would be correctly identified as not having the disease.

	Disease Present	Disease Absent
Test Positive	A (True positives)	B (False positives)
Test Negative	C (False negatives)	D (True negatives)

Figure 1.2 Population of a 2 x 2 table to calculate sensitivity ($A/A+C$) and specificity ($D/D+C$) of a diagnostic test. A, B, C, D represent the number of patients in each category.

The PPV of a test is the proportion of individuals with a positive test result who have the disease ($A/A+B$). Unlike sensitivity and specificity, the positive predictive value of a test is dependent upon disease prevalence. A simple mathematical calculation (Figure 1.3) demonstrates that for a disease with low prevalence, the PPV of the test is low despite a high sensitivity and specificity. In the hypothetical examples given, assuming a test sensitivity and specificity of 80%, the PPV of a screening test for a disease with a prevalence of 5% and 20%, is 17% and 50% respectively. Therefore, in a screened population where a disease is very common, the PPV of the test will be higher than in populations where the disease is very rare.

	Disease Present	Disease Absent
Test +	4 (A)	19 (B)
Test -	1 (C)	76 (D)

	Disease Present	Disease Absent
Test +	16 (A)	16 (B)
Test -	4 (C)	64 (D)

Disease prevalence in the population = $5/100 = 0.05$ (5%)	Disease prevalence in the population = $20/100 = 0.2$ (20%)
Sensitivity = $4/5 = 0.8$ (80%)	Sensitivity = $16/20 = 0.8$ (80%)
Specificity = $76/95 = 0.8$ (80%)	Specificity = $64/80 = 0.8$ (80%)
PPV = $4/23 = 0.17$ (17%)	PPV = $16/32 = 0.5$ (50%)

Figure 1.3 Sensitivity, specificity and positive predictive values in two populations (left- and right-hand columns) with a differing disease prevalence.

1.2.2.2 Biases associated with screening tests

The preclinical phase is the time between tumour onset and symptom development. Screening aims to detect patients during this preclinical stage of disease.

The time between diagnosis and the appearance of symptoms is known as the lead time [48]. When assessing the efficacy of a screening test, a common fallacy is to attribute improved duration of survival to early diagnosis and treatment. In reality, length of survival may simply reflect earlier diagnosis, a phenomenon known as "lead time bias".

"Overdiagnosis" refers to the detection of disease which progresses sufficiently slowly such that death is caused by other causes prior to symptom development from the screened disease [49, 50]. When survival of the screened group is attributed to treatment, this is erroneous, since the disease would not have caused death. Overdiagnosis can be associated with significant morbidity, not least that associated with invasive tests, but also with anxiety associated with being given a cancer diagnosis. One way to estimate the overdiagnosis rate is to compare the rate of cancer diagnosis in a screened and unscreened arm of a RCT. Assuming the underlying prevalence of cancer in the screened and unscreened arms is the same, after a sufficiently long period of follow-up (allowing for any symptoms to develop), the number of cancers diagnosed in both arms should equalise [51]. If this is not the case, this suggests that the excess cases in the screened arm have been over-diagnosed.

"Length time bias" is caused by the differential progression of different types of the disease. Some tumours, such as lung adenocarcinomas, can be slow growing, whilst others, such as small cell tumours, progress much more rapidly [52]. The former are more likely to be detected at screening by virtue of having a longer pre-clinical phase, whereas the latter are more likely to present as interval cancers, presenting clinically between screening rounds. Length time bias refers to the incorrect attribution of improved survival to early diagnosis and treatment because of screening when, in reality, survival of those with slow growing tumours detected at screening would be naturally longer by virtue of the more indolent biological behaviour of the disease [48].

“Selection bias”, also known as “volunteer bias” [48], occurs when the cohort of participants undergoing screening does not have the same risk of cancer-specific mortality as the background unscreened population or cohort. For example, if a screened cohort happens to have a slightly lower risk of mortality from lung cancer by virtue of the characteristics of that cohort (such as age, gender or smoking status), the lower mortality in the screened group is incorrectly attributed to the benefit of screening, rather than the inherent lower risk of mortality in this cohort.

1.2.2.3 Outcome measures

“Disease specific survival” describes the percentage of people in a screened or unscreened group who have not died from the specific disease at the end of a defined period of follow-up. This measure is widely used, but is influenced by lead time bias, length time bias, selection bias and overdiagnosis [48]. Participants who die from other causes are excluded from analyses of disease specific survival.

“Disease specific mortality” describes the mortality rate (usually per 100000 individuals) associated with a specific disease divided by the number of people at risk and can be compared in screened and non-screened cohorts. This measure is unaffected by both lead time bias and length time bias [48]; however, disease specific mortality is not sensitive to benefits associated with treatment which might increase the duration of survival but not prevent death [47]. Disease specific mortality requires accurate documentation of cause of death, and this is a significant limitation of this measure, particularly in patients who are likely to have multiple comorbidities which may contribute to death. For this reason, “overall mortality” or “overall survival” can be used, but both require very large sample sizes to be adequately powered to detect mortality reductions associated with screening [51], and consequently, these measures are less commonly used in cancer screening studies.

Absolute risk reduction, relative risk reduction and number needed to screen are further measures to describe the efficacy of screening. *Absolute risk reduction* is calculated as the mortality rate in the unscreened (control) group, minus the mortality rate in the screened group. *Relative risk reduction* divides the absolute risk reduction by the disease specific mortality rate in the control group. If an individual has an absolute risk of dying from lung cancer of 2% in the next 10 years and, if screened, has a 10-year risk of dying from lung cancer of 1%, the absolute risk reduction is 1% (2%-1%) and the relative risk reduction is 50% (2%-1%/2%). It is argued that absolute risk reduction is a better measure of screening efficacy than relative risk reduction as the latter does not convey any information about an individual's baseline risk [50]. The *number needed to treat (NNT)* to prevent one death is the reciprocal of the absolute risk reduction. In the example above, the NNT is $1/0.01 = 100$ people.

1.2.3 History of lung cancer screening

1.2.3.1 Screening with chest radiographs and sputum analysis

In the 1970s, four RCTs took place assessing the value of chest radiography in detection of lung cancer. Two of these, the John Hopkins Lung Project (JHLP) [53] and the Memorial Sloane Kettering Cancer Centre (MSKCC) trial [54] had an identical study design, comparing participants randomised to receive an annual chest radiograph (the control, single screen group) with participants receiving an annual chest radiograph and 4 monthly sputum cytology over a period of 5-8 years (the intervention, dual screen group). In a third American study, the Mayo Lung Project (MLP), participants were randomised to have either a 4- monthly chest radiograph and sputum cytology (the intervention group) or to a control group, who were recommended at the beginning of the study to have a yearly chest radiograph and sputum cytology [55]. A contemporaneous Czechoslovakian study randomised participants to receive a chest radiograph and sputum cytology every 6 months for 3 years (the intervention group)

or to a chest radiograph and sputum cytology at the beginning and end of three years (the control group). At the end of the three years, both groups were offered an annual chest radiograph each year until year 6 [56].

Neither the MSKCC nor JHLP trials demonstrated any difference in the number of lung cancers detected, nor in the lung cancer mortality rate, between the intervention and control groups. In contrast, the MLP and Czechoslovakian trials both showed a larger number of cancers detected in the intervention group, as well as more early-stage cancers. However, neither demonstrated an improvement in lung cancer mortality in the intervention group. Since publication, these four trials have been subject to significant scrutiny. In particular, proponents of screening with chest radiographs have noted that none of these early trials involved a non-intervention control group and that the sample sizes in all of these studies were inadequate [57]. In spite of the limitations of these studies, there was a long period of lost interest in lung cancer screening through the 1980s and 1990s.

In 2002 one further RCT, the Prostate, Lung, Colorectal and Ovarian (PLCO) trial, enrolling over 150000 individuals, was conducted in the USA. This large trial aimed to ascertain whether screening could reduce mortality caused by four common cancers, namely those of the prostate, lung, colorectum and ovary. For lung cancer, a comparison was made between participants screened with an annual chest radiograph (the intervention group) and a control group receiving no chest radiograph [58]. Unlike the earlier trials in the 1970s, a significant proportion of recruited participants in the PLCO trial were non-smokers, and the control arm was a zero-intervention arm. The trial found no difference in lung cancer mortality amongst the screening and control arms, even allowing for smoking status.

1.2.3.2 Non-randomised trials including single arm studies

Two of the larger non-randomised trials of CT screening for lung cancer are discussed below.

Early Lung Cancer Action Project (ELCAP)

Recognising both the limitations and results of earlier screening studies with chest radiographs, the Early Lung Cancer Action Project (ELCAP) was initiated in the early 1990s. This study enrolled 1000 asymptomatic smokers with a 10 pack-year history of smoking, for a chest radiograph and low dose computed tomography (LDCT) scan to screen for lung cancer [59]. Of the 1000 smokers, 27 had CT detected lung cancer; only 7 of these were visible on the contemporaneous chest radiograph. Furthermore, all but one of these cancers was amenable to surgical resection [59]. A number of potential issues were highlighted, not least the high prevalence of mostly benign CT detected pulmonary nodules, which were found in almost 25% of the 1000 participants. Nonetheless, the results of this cohort study were sufficient to revive interest in screening for lung cancer, in particular, screening with CT.

Pan Canadian Early Detection of Lung Cancer (PanCan) Study

The PanCan study was a multicentre single arm study, recruiting 2537 ever-smokers aged 50-75 to screening at baseline, year 1 and year 4. The study was designed specifically to prospectively assess validity of a participant selection model for screening, the PanCan risk model, a precursor of the 2009 and 2012 PLCO risk models, discussed below [60]. Median follow-up for the study was 5.5 years and the primary outcome was lung cancer incidence. After 5.5 years of follow-up, the cumulative lung cancer incidence per 10000 person years follow-up was 6.5%. Furthermore, 77% of the cancers diagnosed were early-stage cancers [61].

1.2.3.3 Randomised controlled trials

Table 1.6 summarises the inclusion criteria (age, gender, smoking history), screening protocols and outcomes (cancer detection rate and mortality reductions) of RCTs to date.

RCT (date of recruitment)	Inclusion criteria	Screening protocol	Baseline cancer detection rate (%)
DANTE [62] (2001-2006)	60-75 yrs of age, males only, ≥ 20 pack yr smoking history, stopped smoking < 10 yrs earlier	Annual LDCT for 4 yrs versus no screen	2.2
NLST [63] (2002-2004)	55-74 yrs of age, males and females, ≥ 30 pack yr smoking history, stopped smoking < 15 yrs earlier	Annual LDCT versus chest radiograph for 3 yrs	1.0
DEPISCAN [64] (2002-2004)	50-75 yrs of age, asymptomatic males and females, current or former cigarette smoking history of ≥ 15 cigarettes/day for ≥ 20 yrs, stopped smoking < 15 yrs earlier	Annual LDCT versus chest radiograph for 2 yrs	2.4
NELSON [65] (2003-2006)	50-74 yrs of age, males and females, > 10 cigarettes per day for > 30 yrs or > 15 cigarettes/day for > 25 yrs, stopped smoking ≤ 10 yrs ago.	LDCT screening at baseline, yr 1, yr 2, yr 4 and yr 6.5 versus no screen	0.9
DLCST [66] (2004-2006)	50-70 yrs of age, males and females, ≥ 20 pack yr smoking history, quit smoking < 10 yrs earlier, FEV1 ratio $> 30\%$, able to climb two flights of stairs without pausing	Annual LDCT for 5 yrs versus usual care	0.8
ITALUNG [67] (2004-2006)	55-69 yrs of age, males and females, ≥ 20 pack yr smoking history	Annual LDCT for 4 yrs versus no screen	1.5
MILD [68] (2005-2011)	> 49 yrs of age, males and females ≥ 20 pack yr smoker, stopped smoking < 10 yrs earlier, no cancers within past 5 yrs	No screen versus annual LDCT versus biennial LDCT	0.5 (biennial) 1.0 (annual)
LUSI [69] (2007-2011)	50-69 yrs of age, males and females, ≥ 25 yrs smoking of ≥ 15 cigarettes/day <i>or</i> ≥ 30 yrs smoking of ≥ 10 cigarettes per day	Annual low-dose CT and smoking cessation for 5 yrs versus smoking cessation alone	1.1
UKLS [70] (2011-2014)	50-75 yrs of age, males and females, $\geq 5\%$ lung cancer risk according to LLP _{v2} risk score	Single LDCT screen versus no screen	1.7

Table 1.6 Inclusion criteria, screening protocols and outcomes of major randomised controlled trials to date. LDCT = low dose CT; RCT = randomised controlled trial; FEV1 = forced expiratory volume in 1 second.

National Lung Screening Trial (NLST)

This large RCT carried out in the United States of America recruited 53454 smokers and ex-smokers aged 55-74 with a 30+ pack year history of smoking, who were current smokers or had stopped smoking <15 years prior to the study. Between 2002 and 2004, participants were randomised to LDCT screening or chest x ray for 3 years [63]. The trial was powered to detect a 21% decrease in mortality in the LDCT group compared to the group screened by chest radiograph. The results, published in 2011, demonstrated a 20% reduction in lung cancer mortality (95% Confidence Interval (CI) 6.8-26.7; $p=0.004$) in the CT screened arm [63]. Two hundred and seventy cancers were detected in 26309 patients screened by LDCT at baseline (1.0%). Almost 70% of CT detected cancers diagnosed in the NLST trial were Stage I and II, and 92.5% of the Stage IA and IB cancers detected by low dose CT were treated with surgery with curative intent [63].

Shortly after the publication of the NLST results in 2011, the United States Preventative Services Task Force (USPSTF) recommended CT screening for lung cancer amongst a high-risk cohort of smokers and ex-smokers aged 55-80 with the same smoking history as those recruited for the NLST trial (Table 1.6), and screening commenced in the USA in 2015 [71, 72].

European randomised controlled trials

The largest European trial, Netherlands–Leuven Longkanker Screenings Onderzoek (Dutch acronym: NELSON), recruited 15792 participants, randomising participants to an intervention arm, with LDCT screening at baseline and then 1 year, 3 years and 5.5 years from baseline, or to a control arm with no screening. Participants were eligible for screening if they were smokers or ex-smokers (≤ 10 years since cessation), with a significant smoking history (>15 cigarettes/day for 25 years, or >10

cigarettes/day for 30 years). This trial was powered to detect a 25% reduction in lung cancer mortality over 10 years in males through CT screening. In 2020, the 10-year follow-up results of the NELSON trial were published, demonstrating a cumulative rate ratio for death from lung cancer of 0.76 in men (95% CI 0.61-0.94, $p=0.01$) and 0.67 (95% CI 0.38-1.14) in women, in the CT screened arm compared to the control arm. The mortality results in women lacked statistical significance because of the small number of women enrolled in the trial (2534/15789, 16.0%) [73]. Importantly, the NELSON trial also demonstrated a shift in stage at diagnosis: 58.6% of the cancers detected in the screening arm were Stage I at diagnosis, compared to 13.5% of cancers in the control arm, who were unscreened [73]. The lung cancer detection rate overall in the NELSON trial was 0.9% [73].

Alongside the NELSON trial, several small RCTs, each recruiting fewer than 5000 participants, took place in Europe. These included the Italian Detection and screening of early lung cancer with Novel Imaging (DANTE) trial [62], the French DEPISCAN trial [64], the Danish Lung Cancer Screening Trial (DLCST) [66], the Italian Lung Cancer Screening Trial (ITALUNG) [67], the Multicentric Italian Lung Detection (MILD) trial [68], the German Lung Cancer Screening Intervention (LUSI) trial [69] and the UK Lung Cancer Screening (UKLS) trial [70]. Frequency of lung cancer at baseline was between 0.5% and 2.4% in these trials [74]. None of these trials were initially powered to detect mortality reductions [75]. Nonetheless, 10-year follow-up results from the Italian MILD study demonstrated a 39% reduction in lung cancer mortality (Hazard Ratio (HR) 0.61; 95% CI 0.39-0.95, $p=0.017$) amongst the CT screened group compared to the control arm without CT screening [76]. The German LUSI trial demonstrated a statistically significant reduction in lung cancer mortality in CT screened women (HR = 0.31; 95% CI 0.10-0.96, $p=0.04$) but not in men (HR = 0.94; 95% CI 0.54-1.61, $p=0.84$) compared to a control (unscreened) group [77]. The ITALUNG study demonstrated a non-

statistically significant reduction in lung cancer mortality in the CT screened group of 30% (Rate ratio (RR)=0.70; 95% CI 0.47-1.03, p=0.07), compared to a non-screened control arm [78]. Neither the DLCST nor DANTE trials detected a statistically significant lung cancer mortality reduction in the CT screened arms of the trials. The DEPISCAN trial, comparing screening with LDCT and chest radiograph, found eight times as many lung cancers in the CT screened arm at the baseline screen; no mortality reduction data has been reported from this trial [64]. The UKLS mortality results are as yet unpublished [75].

The largest UK randomized controlled trial was the UKLS trial. Unlike the NELSON, NLST and other European trials, the recruitment strategy of the UKLS trial did not initially approach only smokers or ex-smokers. Instead, 247354 individuals aged 50-74, were selected at random from National Health Service (NHS) records and sent a letter and postal questionnaire. Seventy-five thousand nine hundred and fifty-eight individuals (30.7%) responded to the questionnaire, and the responses to the questionnaire were used to identify individuals at high risk of lung cancer, using a validated lung cancer risk model (LLP_{v2}, with a threshold of $\geq 5.0\%$) (see Section 1.3.1) [70]. Four thousand and fifty-five eligible (1.6%) participants meeting this risk threshold were randomised to either a single screen LDCT or usual care (no CT) [70]. Baseline lung cancer prevalence amongst the LDCT cohort was 1.7%, greater than both the NLST and NELSON trials (1.0% and 0.9% respectively). In addition, 85.7% were Stage I or II at diagnosis, compared to 68.7% in the NLST trial [63, 70].

1.2.4 Principles of screening applied to lung cancer screening

Obuchowski's 10 principles will now be discussed in turn, with specific reference to lung cancer screening.

Principle 1: The disease has serious consequences.

That lung cancer is a disease with serious consequences is not in dispute. Mortality statistics have already been reported (Section 1.1) and lung cancer remains the leading cause of cancer related mortality globally.

Principle 2: The screening population has high prevalence of a detectable preclinical phase.

Data from previous lung cancer screening trials and local projects have demonstrated that approximately 0.5-3.0% of participants screened will have undiagnosed asymptomatic lung cancer at a baseline screen [74, 79]. This figure depends upon the underlying risk of the screened cohort, which is related to a several factors including patient age, gender and smoking history. The criteria used to select the screened population also determines the prevalence of disease. Both NSCLC and SCLC are diagnosed on lung cancer screening studies.

Principle 3: Screening detects little pseudodisease.

Pseudodisease refers to any disease which is not true disease. Obuchowski *et al.* use the term “pseudodisease” to encompass both disease which is felt to represent lung cancer, but is not lung cancer (called “type I pseudodisease”) and that which is sufficiently slowly progressing that it would never cause death (called “type II pseudodisease”) and is therefore investigated and treated unnecessarily [47]. Elsewhere in the literature, the term “false positive” is used for the discovery and investigation of type I pseudodisease, whereas the term “overdiagnosis” describes type II pseudodisease.

There is no doubt that lung cancer screening detects pseudodisease of both types. The false positive rates of previous screening trials have been variable, but this has largely depended upon how a “false positive” screen has been defined within the protocol of the screening trial. For example, in the largest screening trial to date, the

National Lung Screening Trial (NLST), a positive screening test was defined as a low dose CT (LDCT) scan revealing any non-calcified nodule 4mm or greater in diameter (or a chest radiograph with a noncalcified nodule or mass). Enlarged lymph nodes could also be classified as a positive result. As a result, 39.1% of participants in the CT screened arm of the trial had at least one positive screening result, and the majority of these (96.4%) were not cancer and therefore false positive results [63]. However, within this trial, fewer than 3% of participants went on to have a surgical biopsy or procedure to determine a diagnosis; the majority of participants underwent imaging follow-up. By contrast, in the NELSON trial, a false positive result was defined as those who were referred to a respiratory physician for further diagnostic investigation which was subsequently negative for malignancy [73, 80]. In this trial, only 264/22600 (1.2%) CT screened participants had a false positive test result [73]. Thus, false positive rates are largely dependent upon the definition of “false positive” within the screening trial.

Overdiagnosis of lung cancer is of equally great concern. Over investigation and treatment of indolent tumours is associated with unnecessary anxiety and cost. However, with modern nodule management protocols (as discussed further in Section 2.5.3) this can be minimised. Attempts have been made to quantify overdiagnosis in previous screening trials. By comparing lung cancer incidence in the chest radiograph and LDCT arms of the NLST and following up patients for 5 years, Patz *et al.* estimate that 18.5% of all lung cancers were over-diagnosed [81]. However, with extended follow-up of a median of 11.3 years, there was no significant difference in the incidence of lung cancer in the two arms of the trial [82]. Furthermore, by virtue of age and comorbidities, participants eligible for lung cancer screening have high mortality from cardiovascular and respiratory disease [63, 73], and these competing causes of mortality may also to contribute to overdiagnosis in lung screening. Ongoing research and modelling is being carried out in this area.

Principle 4: The screening test has high accuracy for detecting the detectable preclinical phase.

An important distinction should be made here between NSCLC and SCLC. In a retrospective analysis of the cases of SCLC diagnosed in the NLST, Thomas *et al.* report a test sensitivity of 76.5% for SCLC compared to 95.3% for NSCLC [83]. SCLC is more likely to present as an interval cancer, that is to say, a cancer detected between screening rounds. This raises the question of whether SCLC is harder to identify than NSCLC (i.e. missed on a previous screening study), or simply more rapidly progressing (not being present on a prior study). Some data support the former suggestion; in the same cohort of patients, 8.1% of the diagnosed SCLCs were not within the lung parenchyma. Instead, these were found at other sites, including at the lung hilum, within the carina or a main stem bronchus, or in the mediastinum [83]. Previous analyses of missed lung cancers at screening, which have not reported the histological subtypes of the missed tumours, have reported that endobronchial and nodal tumours can be overlooked at lung cancer screening, emphasising this point [84, 85].

Principle 5: Screening detects disease before a critical point.

The transition between Stage III and Stage IV disease, at the time of metastasis of a cancer, is usually considered to be the “critical point” after which treatment is less effective in reducing mortality [47]. However, as the 1-year survival of lung cancer drops from over 70% for Stage II disease, to 48.7% for Stage III disease [23], this may be the “critical point” for lung cancer. A distinction can be made here between SCLC and NSCLC. In NLST 80% of SCLCs were diagnosed by screening at Stage III/IV [83], beyond the so-called “critical point” where treatment may be of benefit. By contrast, 64% of NSCLC was Stage I or II at diagnosis [83].

Principle 6: The screening test causes little morbidity.

Screening by CT involves radiation exposure; however, in most LDCT protocols, this is considered negligible. This is discussed at greater length in Section 1.5.2. Anxiety related to attendance at screening appointments, including concerns about undergoing CT imaging, fear of interaction with doctors and medical settings [86] and concerns regarding indeterminate screening findings or positive test results, are recognised potential harms. Other causes of morbidity include intervention for benign disease, including biopsy and surgery, both of which can be minimised with nodule management protocols to minimise overdiagnosis. Detection of incidental findings may be an unwanted outcome of screening if incidental findings result in unnecessary interventions for benign disease, or anxiety resulting from long term surveillance, but these also can be minimised with an appropriate protocol for incidental findings.

Principle 7: The screening test is affordable and available.

Low dose CT is widely available in the NHS setting within the UK. CT screening has been advocated as being affordable based on cost-effectiveness and costs per quality-adjusted life year (QALY). Cost effectiveness is traditionally evaluated using an incremental cost effectiveness ratio (ICER), which quantifies the change in costs between an intervention and no-intervention, divided by the change in the effects that the intervention might cause. According to NICE guidelines, in the UK interventions with an ICER <£20000/QALY are considered affordable [87]. The UKLS trial was estimated to have a ICER (assuming screen detected cancers compared to symptomatic detection) of £6325 per life-year gained (95% CI £4109 -£9430) or £8466 per QALY gained (95% CI £5516-£12634) [70], and at present lung cancer screening in the UK is therefore considered to be affordable.

Principles 8, 9 and 10: Treatment exists. It is more effective when applied before symptoms begin. Treatment is not too risky or toxic.

Treatment for lung cancer exists and has been discussed (Section 1.1.4). Emergency symptomatic presentation of lung cancer is associated with increased short-term mortality and more advanced disease [88]. Treatment for lung cancer is not without morbidity and risk but can be given with curative intent for early-stage disease.

Overall, the evidence suggests that screening for SCLC is unlikely to improve disease specific mortality, and as such, screening for lung cancer should be considered primarily a screening tool for NSCLC.

1.3 Patient selection for lung cancer screening

Targeted screening for lung cancer is preferable to population wide screening for the following reasons:

- Lung cancer prevalence within the population is variable. As the PPV of a screening test is directly related to disease prevalence, the PPV of screening will be increased by screening individuals at high risk of lung cancer. Patients should therefore be carefully selected for screening according to their risk of lung cancer.
- The cost-effectiveness of screening has been demonstrated to increase with lung cancer risk [89].
- Screening for lung cancer is not without harm. Risks include cumulative radiation dose and those associated with overdiagnosis and the detection and investigation of false positive LDCT results.
- Screening has been shown to reduce the greatest number of lung cancer deaths amongst those of highest risk [90].

Consequently, identification of a high-risk population for screening is of great importance.

Early lung cancer screening trials selected participants based on age and cumulative smoking history. A number of risk models are now available to stratify

participants according to risk, in order to maximise the efficiency and cost effectiveness of screening. These models incorporate multiple risk factors, including smoking history, family history and occupational exposures.

1.3.1 Risk models for patient selection for screening

Table 1.7 summarises the characteristics of a number of risk models which have been derived to estimate risk of lung cancer amongst specified cohorts.

Various measures are used to evaluate the performance characteristics of screening models. Calibration refers to the ability of a model to assign an accurate probability of disease to an individual [91]. Discrimination describes the ability of the model to distinguish those with cancer from those without cancer and is measured by calculating the area under the receiver operator characteristic curve (AUROC). The value of the area under the curve is given by the c-statistic which ranges from 0.5 (indicating that discrimination is no better than chance) to 1.0 (indicating perfect discrimination) [92].

Risk Model	Model prediction	Eligibility criteria	Risk factors/variables included
African American model [93]	Risk of lung cancer in 5 years	African Americans. No other eligibility restrictions	Smoking status, pack-years smoked, age at smoking cessation (former smokers), number of years since smoking cessation (former smokers), self-reported PMH COPD or hay fever and exposures to asbestos or wood dusts
Bach Model [94]	Risk of lung cancer within 1 year (iterative to 10 years)	45-69 years, ever smokers, ≥ 20 pack year history, quit within 15 years	Age, sex, smoking duration, smoking intensity (cigarettes/day), time since quitting (yrs), asbestos exposure
Hoggart model [95]	Risk of lung cancer over any time window 1-5 years	Individuals aged 40-65	Age, Age started smoking, average smoking intensity, age started smoking and, for former smokers, duration of smoking
Liverpool Lung Project (LLP) model [96]	Risk of lung cancer within 5 years	Model derived from data from a case-control study enrolling individuals aged 20-80 years	Age, sex, smoking duration, PMH cancer or pneumonia, FH lung cancer, asbestos exposure
LLP_{v2} model [70, 96]	Risk of lung cancer within 5 years	Individuals aged 50-79 years	As above, except i) includes PMH bronchitis, emphysema, COPD, TB (as well as pneumonia) ii) treats smokers of pipes and cigars as conferring equal risk to cigarette smokers
LLP_{v3} model [97]	Risk of lung cancer within 5 years	Validated on a dataset of patients aged 50-75	As LLP _{v2} , but recalibrated with age- and sex-specific UK population wide lung cancer incidence data
Lung cancer risk assessment tool (LCRAT) [98]	Risk of lung cancer within 1-10 years	Ever smokers, 55-74 years	Age, sex, race/ethnicity, education, BMI, emphysema, FH lung cancer, pack-years smoked, cigarettes/day, smoking duration (yrs), time since quitting (yrs).
Muller model [99]	Risk of lung cancer in 2 years	Model derived primarily from individuals aged 40-70	Age, sex, cigarette smoking status, previous cancer diagnosis, FH lung cancer, PMH asthma, allergy, eczema, emphysema or bronchitis, maximum FEV1, smoking intensity (cigarettes/day), age stopped smoking, difficult not smoking for 1 day
PLCO model [100]	Risk of lung cancer in 9 years	Two models – one for general population and one for	Age, socioeconomic status (education), BMI, FH of lung cancer, PMH COPD, recent chest x-ray, smoking status (never, former, or current), pack-years smoked and smoking duration. Ever

		ever smokers, aged 55-74	smokers model also included time since quitting (yrs)
PCLO_{m2012} model [101]	Risk of lung cancer in 6 years	Ever smokers, ≥ 30 pack-year history and quit smoking within 15 years	Age, ethnicity, socioeconomic status (education), body mass index, FH lung cancer, PMH COPD, smoking status (never, former or current), smoking duration (yrs)
Two stage clonal expansion lung cancer incidence model [102]	Risk of lung cancer in 1 year	Nurses health study, Health Professionals Follow up Study	Age, gender, smoking status, smoking duration, smoking intensity, time since quitting (yrs)

Table 1.7 Summary of eligibility criteria and variables included in a number of frequently cited risk prediction models. PMH= past medical history; FH= family history; TB= tuberculosis; BMI= body mass index; COPD= chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second.

Several studies have sought to compare the performance of these difference lung cancer risk models [92, 103-105]. D'Amelio *et al.* compare the discriminatory power, accuracy (namely the positive and negative predictive values) and clinical utility of the LLP, Bach and Spitz models when applied to a cohort of 1066 participants with lung cancer and 677 control participants without lung cancer enrolled in an American case control study [104]. They found that the LLP and Spitz models had comparable discriminatory power (0.69), significantly better than Bach model (0.66, $p=0.02$) [104]. At a risk threshold of 2.5% the LLP model had the highest false positive rate of the three models. At all risk thresholds the LLP model correctly identified a greater proportion of patients with lung cancer than the other two tests, but also incorrectly identified a higher proportion of the controls. The wider applicability of these findings is limited by the small sample size and by their specific application to Caucasian populations (for which they were originally designed) in this study [104]. Li *et al.* externally validated 4 risk prediction models (the LLP, Bach, Spitz and PLCO_{m2012} models) with participants from a German population based prospective cohort study, European Prospective Investigation of

Cancer and Nutrition (EPIC) [103]. They found that the PLCO_{m2012} model showed the highest discriminatory power (0.81) as well as the highest sensitivity, specificity and positive predictive value, but that superiority over the Bach and LLP models was only modest.

In a population based prospective study, Katki *et al.* applied nine risk prediction models to a sample over 400000 ever-smokers in America, comparing the number of individuals selected for screening using each model and assessing the calibration and discrimination of the models [105]. They found that the Bach model, PLCO_{m2012} model, LCRAT, and a similar model, the Lung Cancer Death risk assessment tool (LCDRAT) [98], were the best calibrated models, with higher calibration than 5 other models, including the original LLP model. AUCs for these four models were in the range of 0.75-0.79 [105]. In a retrospective validation study, Ten Haaf *et al.* compared the performance characteristics of nine established risk prediction models using data from the American NLST and PLCO trials. They found that discriminatory power of the models was variable and was higher for lung cancer mortality than lung cancer incidence. Overall, the discriminative performance of the models was higher for the PLCO_{m2012} model, the Bach model and the two-stage clonal expansion lung cancer incidence model than for other models. They concluded that the PLCO_{m2012} model performed best of all the nine tested models across a number of different performance measures [92].

It is noteworthy that the LLP model had a lower discriminatory value than other models in both the above analyses [92, 105]. This may be related to the ability to apply the LLP model, validated in the UK, to American screening cohorts. The LLP model includes asbestos exposure and the age of lung cancer diagnosis in first degree relatives; these data are not captured in either of the datasets from the PLCO or NLST trials. Consequently, Ten Haaf *et al.* assume no asbestos exposure and that when a family history of lung cancer had been reported, this had been diagnosed over the age of 60,

rather than at a young age. This may have limited the application of the LLP models to these cohorts, potentially biasing results.

Despite the differences in the performance of the models compared in these studies and reviews, these risk models offer better sensitivity and most offer better specificity than the inclusion criteria used for NLST, based only on age and smoking duration, and to the similar criteria currently recommended for screening in the USA [90, 92, 98].

In view of this, the current recommendation from European experts and in the NHS England (NHSE) screening protocol is that either or both of the LLP_{v2} or PLCO_{m2012} models should be used for patient selection for lung cancer screening [80]. This recommendation is based upon the findings of the previous reviews and studies and also on the fact that only the LLP_{v2} and PanCan models (a precursor of PLCO_{m2012}) have been used prospectively to date for patient selection for randomised and non-randomised controlled studies [106].

Ongoing questions surround the optimum risk threshold for the LLP_{v2} model. This is determined not only by theoretical measures such as sensitivity and specificity, but also upon cost-analysis. Use of a high eligibility threshold (such as 5%) decreases sensitivity but increases specificity, perhaps offering a more cost-effective approach to screening, whilst a lower threshold increases sensitivity at the expense of specificity. Based on various modelling studies, a threshold of 2.5% may be the optimum threshold to optimise sensitivity and specificity [96, 104, 107, 108], and this is currently the threshold recommended in the NHSE lung cancer screening guidelines [109].

The recently published LLP_{v3} model recalibrated age- and sex-specific risk factors within the LLP_{v2} model to account for differences in the incidence of lung cancer in the populations of Liverpool (from which the original LLP model had been derived) and the

wider UK population [97]. The LLP_{v3} model was recalibrated with updated UK population-wide lung cancer incidence data. In the LLP_{v3} model, a LLP_{v2} risk threshold of 2.5% equates to a LLP_{v3} risk threshold of 1.33%. Although the authors recommend that the LLP_{v3} model at a threshold of 2.5% should be utilised in lung cancer screening programmes in the UK going forward (corresponding to a higher LLP_{v2} score), this change is yet to be implemented in NHSE guidelines.

1.4 Lung cancer screening through targeted lung health checks (LHCs)

1.4.1 UK pilot studies using a lung health check model

In the past 5 years several pilot studies and trials have commenced in the UK seeking to answer questions about patient recruitment, uptake and selection [79, 110-112]. In common with the UKLS trial, most pilot studies and trials in the UK have selected participants for CT screening using multivariate risk prediction models (either the LLP_{v2} model, the PLCO_{m2012} model or both) to determine eligibility for CT. USPSTF criteria for lung cancer screening (current or ex-smokers (quit ≤ 15 years ago) with ≥ 30 pack-year smoking history) are also being used in 2 screening trials in conjunction with multivariate risk models [110, 111]. Table 1.8 summarises the participant eligibility, participant uptake and baseline results of a number of UK pilot studies and trials to date. A unique feature of the UK pilot studies has been that participants have been invited to a targeted “lung health check” (LHC) involving a nurse-led respiratory consultation, spirometry and calculation of a risk score determining eligibility for a LDCT.

By inviting patients to LHCs, “cancer screening” is not emphasised. Rather, a holistic approach to lung and cardiovascular health is taken, which might include smoking cessation advice or assessment for COPD, as well as screening for lung cancer. These additional assessments or interventions may increase the cost-effectiveness of lung cancer screening and are considered add-on benefits of the LHC model. For example, COPD is under-diagnosed in the primary care setting [113, 114]. It contributes to 1 in 8

emergency hospital admissions, is associated with cardiovascular events, including myocardial infarction [115], and preventative treatment of acute exacerbations prevents hospital admissions. Therefore, the identification and treatment of undiagnosed COPD in a high-risk cohort of smokers and ex-smokers through a LHC may be a significant benefit of lung cancer screening. Amongst 2525 LHC attendees in a pilot study in Manchester who performed spirometry during the LHC appointment, 944 (37.4%) had obstructive spirometry ($FEV_1/FVC < 0.7$), of whom 250/944 (26.4%) were symptomatic with no known prior diagnosis of COPD [116]. Similarly, in the London-based Lung Screen Uptake Trial (LSUT), 560/967 (56.7%) participants having spirometry assessment had airflow obstruction, of whom 147/560 (26.3%) were symptomatic but not known to have COPD [117]. Whilst a theoretical benefit of detecting COPD exists, no data are available to show that reporting of undiagnosed suspected COPD to primary care results in a meaningful positive outcome for patients, such as referral to pulmonary rehabilitation or initiation of pharmacological treatment.

Pilot study or trial	Liverpool Healthy Lung Programme [112]	Manchester [79]	Lung Screen Uptake Trial [111]	Yorkshire Lung Screening Trial [110]	SUMMIT trial [118, 119]
Participants invited	11526 Ever smokers aged 58-70 (subsequently 58-75), or those with a diagnosis of COPD	Ever smokers aged 55-74	2012 smokers or ex-smokers (quit within previous 7 years) aged 60-75. Randomised to one of two invitation strategies	Ever smokers aged 55-80; intention to invite 62980 individuals and randomise to a LHC or usual care (1:1)	Ever smokers aged 55-75; target recruitment 25000
Uptake from invitation	4566 patients (40% of invited patients)	2827 patients (28.5% of eligible patients invited)	1058 (52.6% of eligible participants invited)	Not reported	Not reported
Eligibility criteria for CT	LLP _{v2} ≥5%	PLCO _{m2012} ≥ 1.51	LLP _{v2} ≥ 2.5% or PLCO _{m2012} ≥1.51% or eligible by USPSTF criteria	LLP _{v2} ≥ 5.0% or PLCO _{m2012} ≥1.51% or eligible by USPSTF criteria	PLCOM2012 ≥1.3% or eligible by USPSTF criteria
% of participants having LHC eligible for CT	43% [†]	56.2%	89.9% (77.1% underwent LDCT)	Not reported	Not reported
Lung cancer prevalence	1.9% (25 cancers, in first 21 months)	3% (42 cancers, detected following baseline or 3-month follow-up scan)	4.7% (36 cancers after median of 1044 days of follow-up)	Not reported	Not reported
% Lung cancers Stage I/II	76%	80.4%	72.2%	Not reported	Not reported
Cancer patients treated with curative intent	Not reported	89.1%	75.0%	Not reported	Not reported

Nodule management protocol	Based on nodule diameter	on	Based on nodule diameter and BTS nodule management guidelines [120]	on	Based on nodule volume and BTS nodule management guidelines [120]	on	Based on nodule volume and BTS nodule management guidelines [120]	on	Based on nodule volume and BTS nodule management guidelines [120]
-----------------------------------	--------------------------	----	---	----	---	----	---	----	---

Table 1.8 Patient eligibility, uptake and baseline results of UK-based pilot studies and trials using a LHC model. *Data reported are percentage of attendees consenting to data-sharing who qualified for CT. BTS = British Thoracic Society

1.4.2 Participant uptake for screening

Despite the USPSTF recommendation that eligible patients should be screened, and although Medicare offer to reimburse screening, only 3.5% of eligible Americans participated in lung cancer screening in 2015 [121]. Although uptake at UK pilot studies has been significantly better at approximately 20-50%, uptake is significantly lower than that for other screening programmes. By comparison, in 2017, uptake for breast cancer screening in the UK was 71.1% [122]. In light of this, considerable work has been carried out to understand barriers to uptake in UK pilot studies.

The Manchester screening pilot was the first UK based lung cancer screening pilot study to offer participants community based LHCs and scans in a mobile unit, with the intention of "*reducing barriers to participation*" by offering a "*convenient, community based LHC*" [79]. A qualitative study in Manchester, based around discussions in 6 focus groups, found that whilst most individuals reported a "*general positivity*" for lung cancer screening, this did not always equate to uptake intention. Various push and pull factors were explored including practicalities of attending screening, fear of potential results, stigma associated with active smoking and more positively, desires to know about lung health and the potential benefits of early diagnosis of lung cancer [86].

The LSUT sought to investigate whether participant uptake amongst difficult to reach individuals, particularly current smokers from socioeconomically deprived

backgrounds, can be improved by a targeted invitation strategy [123]. Patients were randomised to one of two groups, being offered different information in the invitation letters. Both the control and intervention group received an invitation letter to a LHC on behalf of their general practitioner (GP), a subsequent reminder letter and a prescheduled appointment for a LHC within two weeks. In the intervention group, participants received a leaflet specifically designed to minimise "*fear, fatalism and stigma*" [123, 124]. The control group received a leaflet similar to that provided for other NHS cancer screening programmes (such as cervical screening) [123]. The trial demonstrated overall uptake at 52.6%, with no difference between the intervention (52.3%) and control groups (52.9%) [124]. The authors attribute the high uptake in this trial to the LHC approach, primary care endorsement of the pilot, the invitation strategy which included both a preliminary and reminder letter, as well as scheduled appointments, with the last of these being unique to the LSUT trial.

1.5 Technical considerations related to CT scanning

This section outlines CT acquisition, radiation dose in relation to CT, LDCT scanning, and image quality required for lung cancer screening. As NHSE have now provided guidelines for CT scanning of screening patients in lung cancer screening programmes, these will be discussed specifically.

1.5.1 Principles of CT scanning

The technology involved in CT scanning has advanced significantly since the 1970s when CT scanning was first used. In modern day CT, an x-ray tube, collimator and detectors rotate at speed on a donut-shaped gantry around a patient. The patient is moved through the scanner on a table. By convention, the direction of movement of the table is along the z-axis. X-rays are produced continually, and the detectors on the CT scanner measure the attenuation of the x ray beam, determined by the density of the structures through which it passes. Images are usually reconstructed through a

process of filtered back projection or iterative reconstruction. Each image is made up of numerous voxels (typically approximately 1mm^3 in size) which are given a CT number, or Hounsfield unit (HU), corresponding to the average linear attenuation coefficient of the tissues within the voxel [125].

Most modern-day scanners are multi-slice helical scanners. Helical scanners allow for the continuous rotation of the gantry and therefore the uninterrupted acquisition of data. Multiple narrow detector rows allow for true isotropic (i.e. equal in all three dimensions) reconstruction of images and improved resolution. Scanning times are also reduced by using helical multidetector scanners.

1.5.2 CT radiation dose

A number of measures are used to describe dose in relation to CT scanning including the absorbed dose, CT Dose Index (CTDI), dose length product (DLP) and effective dose. The absorbed dose (measured in grays (Gy) ($1\text{Gy} = 1\text{J kg}^{-1}$) describes the energy deposited per unit mass within an object [126]. It does not take into account the differing radiation sensitivity of different body organs, nor is it able to give a whole body dose [126]. The CTDI is a measure of dose from a single rotation of the gantry, measured using a pencil ionisation chamber with a perspex phantom [125]. It is frequently used to compare doses between different scanners [125] or at different scanning parameter settings [126]. A weighted CTDI (CTDI_w) is a weighted average of dose across a single slice taking measurements from the centre of a phantom and the periphery, whereas CTDI volume (CTDI_{vol}) is the CTDI_w divided by the beam pitch (the latter being the movement of the tabletop per rotation divided by the collimator length). The dose-length product (DLP) is the product of the CTDI_{vol} and the total scan length (in cm) (estimated from the movement of the table) and is therefore a good indication of the radiation dose of an entire CT scan. During helical scanning, or scanning with multidetector scanners, estimating scan length from the movement of the table

underestimates the true scan length, due to some over-scanning at the beginning and end of the scan, and this should be adjusted for.

The effective dose of a scan, given in millisieverts (mSv), is calculated by multiplying the DLP by a weighting factor specific for each organ and adjusted according to the radiation sensitivity of the organ [126]. It is calculated based on an “average” individual, who is assumed to weigh 70kg. This measure is most frequently used to compare radiation doses for scans of different parts of the body.

Dose in CT scanning is determined by various adjustable factors documented in Table 1.9.

Adjustable CT parameter	Definition	Relationship of adjustable parameter to CT dose
Tube current (mA)		Dose is directly proportional to mA
Tube rotation time (s)	Time taken for 1 rotation of the gantry	Dose is directly proportional to rotation time
Tube current-time product (mAs)	Tube current multiplied by exposure time	Dose is directly proportional to tube current-time product
X ray tube anode-cathode voltage (kV) (sometimes stated as peak kilovoltage (kVp))	Energy of the x-ray beam	Dose is proportional to kVp raised to an exponential power between 2 and 3
Pitch	Movement of the table-top per rotation/collimator length (in multislice CT)	Dose is inversely proportional to pitch

Table 1.9 Adjustable CT parameters affecting dose, adapted from Maldijan and Goldman, 2013 [127]. kV = kilovolts, mAs = milliampere-seconds.

Automatic exposure control (AEC) is a dose reduction technique available on most modern CT scanners. AEC works by reducing the current (mA) from the x-ray tube to compensate for variations in attenuation within patients (and between patients) in order to maintain a prespecified image quality throughout the scan.

In addition to these adjustable factors, there are a number of non-adjustable parameters which will affect dose including scanner geometry and patient build.

Radiation exposure confers a risk to the individual exposed (and when scanning those of reproductive age, to their descendants). Some radiation effects are deterministic, i.e. not occurring below a threshold dose [125]. These include the risk of cataracts or skin erythema. More significant are the stochastic effects, which are those occurring by chance, but with a greater likelihood with increasing radiation exposure. These include the risk of cancer development related to CT radiation exposure. The total lifetime cancer risk associated with receiving a given dose of radiation is dependent on age and gender. For a male between the age of 60-69, the lifetime cancer risk resulting from a CT of the chest, is approximately 0.0024%/mSv of radiation [128]. A typical standard dose CT of the chest may have an effective dose of 5.8-6.6mSv [128].

1.5.3 Low dose CT (LDCT) scanning

In view of the risks associated with radiation discussed above, the as low as reasonably achievable (ALARA) principle should be adopted for all studies involving ionising radiation. The inherent differences between the attenuation of the lung parenchyma and the attenuation of the soft tissue of the mediastinum and the pulmonary vasculature allow for a LDCT of the thorax to be performed with a low tube current. For example, a LDCT scan of the thorax using a fixed low tube current of 40mAs delivers an effective dose of between 1-1.5mSv/CT [129], approximately 1/4 to 1/6 of the dose of a standard thoracic CT, with a corresponding increased lifetime risk of malignancy of approximately 0.002-0.004% in a 60-69 year old male [128].

Other methods used to further reduce dose in thoracic CT, include AEC [126, 127] and the use of iterative reconstruction algorithms, as opposed to filtered back projection [130, 131].

1.6 CT reporting in lung cancer screening

1.6.1 Lung nodule terminology

A lung nodule is a "*rounded or irregular opacity, well or poorly defined, measuring up to 3cm in diameter*" [132]. Nodules are described according to their size, location, composition or density, morphology and internal characteristics.

Size. Lesions greater than 3cm in size are described as lung masses. A nodule <3mm in size is described as a micronodule [132]. Nodules are routinely measured by diameter in mm (in one or two axes) in clinical practice. However, in CT screening a number of previous trials, including both the NELSON and UKLS trials, have used nodule follow-up protocols based on nodule volume measurements in mm³.

Location. The location of a nodule includes the lobe in which a nodule is found and the position within the lung parenchyma (subpleural, peri-fissural or juxta-pleural, peribronchovascular or centrilobular).

Composition. Lung nodules are either solid or sub-solid (Figure 1.3a-c). Solid nodules have a homogeneous soft tissue density [132]. Sub-solid nodules (SSNs) may be either pure ground-glass nodules (pGGNs) or part-solid nodules (PSNs). Pure GGNs are, by definition, of lower attenuation than the pulmonary vasculature. On an unenhanced CT scan, pulmonary vessels and bronchioles traversing a ground-glass lesion can be clearly identified. Part-solid nodules have ground-glass and solid components. Nodules can also contain fat or calcification.

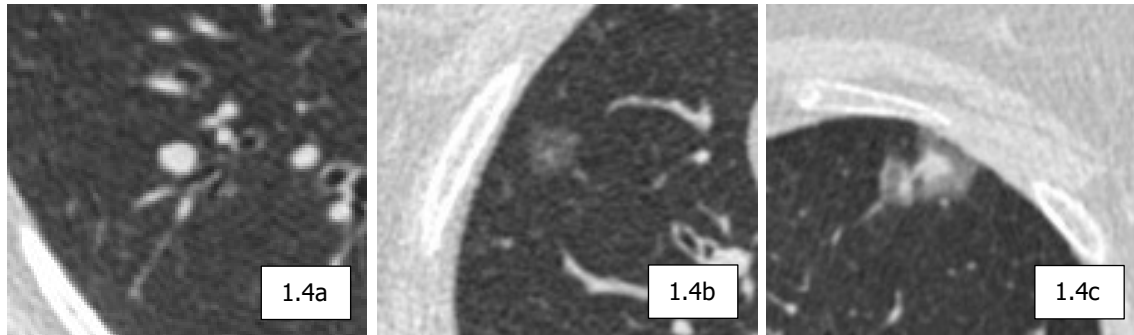


Figure 1.4 Lung nodules with differing composition. Solid (1.4a), part-solid (1.4b) and pure ground-glass (1.4c) lung nodules.

Morphology. The contour of a nodule may be described as smooth, spiculated (Figure 1.4a) or lobulated (Figure 1.4b). Nodules and masses may contain bubble like lucencies (Figure 1.4c) or air bronchograms (Figure 1.4d). In addition, nodules may cause pleural indentation or retraction of a fissure (Figure 1.4e).

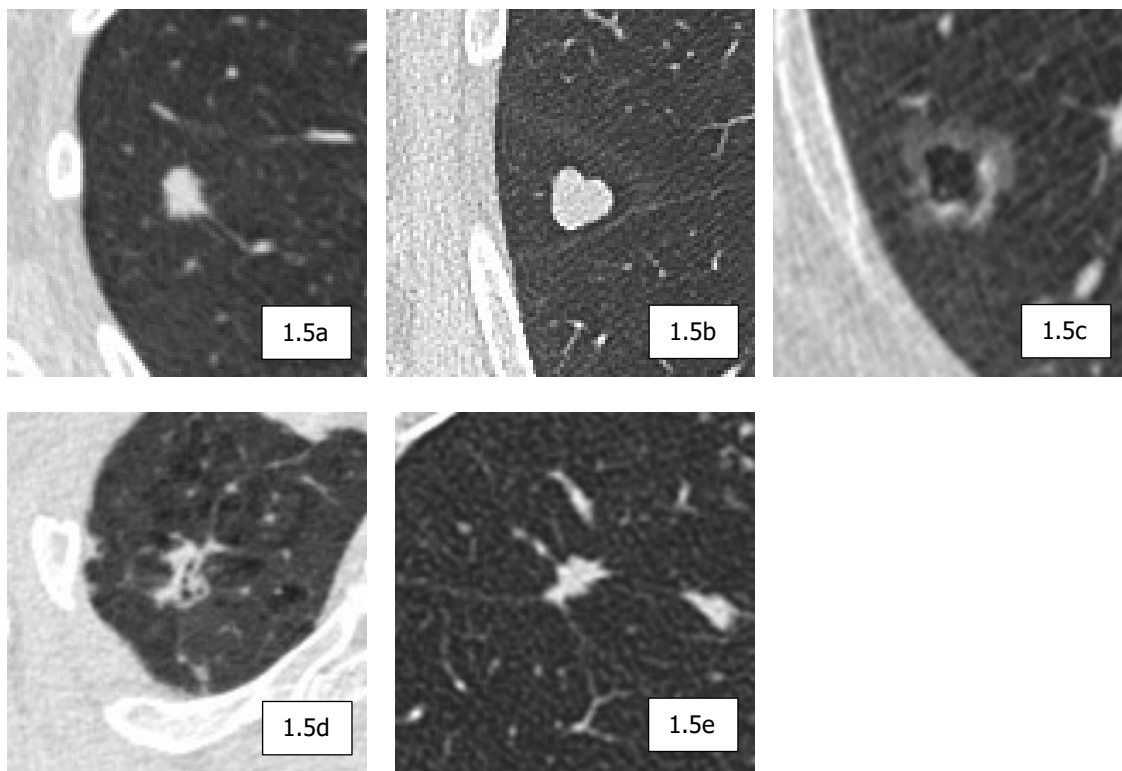


Figure 1.5 Morphological features of nodules. Spiculated (1.5a) and lobulated (1.5b) lung nodules. A nodule containing a bubble-like lucency (1.5c), an air bronchogram (1.5d) and causing retraction of a fissure (1.5e).

1.6.2 Detection and measurement of pulmonary nodules on CT

The inherent difference between the low attenuation of normal lung parenchyma and higher attenuation of pulmonary nodules enables most nodules to be readily identified on CT. Post-processing techniques, such as maximum intensity projection (MIP) reconstructions, can be used to identify very small nodules in the lungs [133]. In a MIP algorithm, only the highest attenuation voxels along a stack of images in the z-axis direction are visible in the final images, displayed as thin slabs, drawing attention to small or inconspicuous nodules [134]. However, even in spite of MIP algorithms, lung nodules can be missed. Double reporting of CT scans has been shown to improve nodule detection rates [135], though it should be noted that double reporting usually requires a third reader to perform arbitration for discrepant readings.

Since the late 1980s, computer aided detection (CAD) systems have been developed to aid radiologists and clinicians in detecting abnormalities within imaging studies (CAdE systems), as well as in interpreting or characterising findings detected on imaging (CAdx systems) [136]. In thoracic CT, particular interest has arisen in the use of CAD systems for the detection and characterisation of lung nodules. CAdx systems are able, for example, to distinguish benign from malignant lesions, based on imaging characteristics [137]. CAD systems have five main steps: image acquisition, image pre-processing (to improve image quality), image segmentation (separation of the lungs from other organs and tissues), nodule detection and elimination of false positives [136]. CAD systems are not only able to detect lung nodules, but also calculate lung nodule diameters and volumes, allowing nodules to be compared across serial scans in time. A previous study, involving analysis of 400 scans from the NELSON study database, demonstrated that the use of CAD software was more sensitive than double reading of scans by two radiologists in detecting lung nodules [138]. However, CAD software sensitivity is affected by the composition of lung nodules (being less sensitive for

pGGNs), the location of lung nodules (being less sensitive for juxtavascular and juxtapleural nodules) and nodule size (being less sensitive for very small nodules below 3mm in diameter) [139].

Computer software is also essential to measure the volume of pulmonary nodules. Volumetry, the measurement of a nodule volume, has been used in previous screening studies to assess the growth of pulmonary nodules between interval scans [65, 68, 70, 140]. The accuracy of volumetry is dependent upon satisfactory segmentation of the lung nodule, the particular volumetry software package technique for measurement [141], CT acquisition and reconstruction methods [142], characteristics of the lung nodule (being better for solid than PSNs) and the location of pulmonary nodules, amongst other factors [143]. Thus, as far as is possible in clinical practice, scanning parameters and the software used for scans should be kept the same between scans, so as to reduce inaccuracy. Previous studies have demonstrated up to 25% variability in nodule measurements performed on two consecutive (same day) scans using volumetry software [144, 145]. However, such studies have evaluated metastatic nodules and have not specifically evaluated small pulmonary nodules <150mm³. The ability of volumetric software to reliably determine growth of such small nodules is unknown. This is relevant for lung cancer screening, where small nodules may warrant imaging follow-up after baseline or subsequent (incident round) screening scans.

Volume doubling times (VDTs) are calculated using the following formula [143, 146]:

$$\frac{\ln(\text{natural logarithm})2 \times \text{Days Between Scans}}{\ln(\text{Volume on Second Scan/Volume on Baseline Scan})}$$

This model assumes that cells double at a constant rate, resulting in exponential growth of the nodule. Others have suggested that, in reality, malignant nodules may show a decrease in growth rate, following an initial period of exponential growth [147]. Lindell *et al.* plotted growth curves of 18 lung cancers screened over a 4-year period and found

that lung cancer growth could not be predicted by an exponential model [148]. However, nodule volume was calculated from nodule diameter measurements taken from thick slice CTs and calculated nodule volumes are likely to be less accurate than volumetric measurements taken directly from thin slice CTs. A recent study, however, analysing the VDT of 47 lung cancers diagnosed after three screening rounds in the NELSON trial, demonstrated that these small tumours grew with exponential growth and that the use of a VDT model is appropriate, particularly for the assessment of small nodules [149].

1.6.3 CT Reading times with CAD

The development of CAD software has raised the question of how the software can be most efficiently integrated into the workflow of the CT reader. CAD software can be used as a concurrent or second reader. When used as a concurrent reader, imaging is first presented to the CAD software. Nodules marked by the CAD are presented to a radiologist, who evaluates the findings of the CAD and performs an independent search. In the second reader mode, the radiologist first evaluates the scan and then presents the imaging to the CAD software. Various studies have evaluated reading times of thoracic CTs using CAD [150, 151], some comparing reading times in the concurrent and second reader modes [152].

Previous studies have differed in their methods and case selection. Beigelman-Aubry *et al.* evaluated reading times to identify nodules on lung cancer screening studies, comparing reporting times using a clinical workstation (without CAD) to reporting with CAD [151]. The study involved reading paired LDCT screening scans, comparing nodules on a current and prior scan. The study found no significant difference in reading times between the clinical and CAD workstations (mean reading times between 4 and 5.5 minutes). Importantly, this study did not record the time to evaluate incidental findings on the scan [151] and therefore is unlikely to reflect the time required to report screening scans in real-life practice. Beyer *et al.* compared reading times using CAD as a concurrent

and second reader, and reading times without CAD, but did not state whether the time taken included the time required to write a report [152]. They found that mean reading times were significantly shorter when using CAD as a concurrent reader (274 seconds), compared to without CAD (294 seconds; $p=0.04$), or use of CAD as a second reader (337 seconds; $p<0.001$) [152]. Brown *et al.* describe reading times using a CAD system with an integrated reporting functionality, whereby a report generates automatically with results detected by the CAD system, comparing reading times with and without CAD [150]. They found a 7-44% reduction in reading times across three CT readers, using CAD technology compared to without CAD [150]. However, such systems, with integrated automatically produced reports, are not in routine use. At present, no data are available to indicate the time taken to report lung cancer screening studies, including documentation of findings in an appropriate report.

1.6.4 Benign and malignant pulmonary nodules

Lung nodules are extremely common, being found in as many of 20-50% of high-risk patients undergoing CT screening [120]. In the NLST trial, nodule prevalence amongst participants aged 55-74 with a 30 pack year smoking history was 25.9%, but lung cancer was present in only 1.0% [63]. The causes of nodules are numerous and include benign and malignant (including metastatic) lesions. Common benign causes of nodules include lung inflammation and infection (including tuberculosis, sarcoidosis, fungal infection and rheumatoid arthritis), intrapulmonary lymph nodes (IPLNs) and benign neoplastic nodules (such as hamartomas). The histopathology of malignant lung lesions has already been discussed in Section 1.1.3.

The challenge of lung cancer screening is to distinguish benign from malignant nodules. Clinical and radiological factors affect the likelihood of a nodule being benign or malignant. Clinical factors include age, smoking status (current or former), smoking

pack-year history and previous history of cancer [120]. The radiological factors are discussed below.

Benign pulmonary nodules.

Morphology: Certain morphological characteristics of nodules allow for them to be disregarded as definitely benign and these are well documented. Specific patterns of calcification, including diffuse, central, laminated or popcorn patterns, are suggestive of a benign aetiology [120]. On occasion, a combination of morphological features allow for a confident specific benign diagnosis. For example, macroscopic fat, with “popcorn” calcification, is typical of a benign hamartoma [153]. Benign IPLNs can be identified through a combination of their contour (smooth), shape (triangular or lentiform) composition (solid) and location (within 1cm of the pleura, more commonly in the lower than upper lobes) [120, 154], as well as their connection to pulmonary veins (and specifically not to pulmonary arteries) [154].

Size: In the earliest lung cancer screening studies, nodules were measured by diameter rather than volume. An early study, assessing very small (<5mm) nodules detected in the ELCAP screening trial, demonstrated that nodules of this small size are highly likely to be benign, or if malignant, too small to demonstrate meaningful growth or perform intervention, earlier than 1 year later [155]. This led to the introduction of a 5mm threshold for follow-up of screen detected nodules on baseline imaging in subsequent ELCAP screening patients in New York (NY-ELCAP) and internationally (I-ELCAP) [156]. Subsequent studies looked at the implication of raising the threshold for follow-up of nodules to 6-9mm, using data from the NLST and I-ELCAP trials, and the proportion of participants who would have had a corresponding delay to lung cancer diagnosis with higher size thresholds for follow-up. As might be expected, these studies demonstrated an increasing proportion of participants who might have a delay to lung

cancer diagnosis as the threshold for nodule follow-up increased at 1mm increments [156, 157]. Later, data from the NELSON screening trial, using volumetry rather than diameter measurements, demonstrated that screened participants with nodules <5mm in diameter/<100mm³ volume did not have an increased risk of malignancy compared to screened participants without any lung nodules [158]. On this basis, a recommendation was made that nodules <100mm³ do not require interval CT follow-up in screening studies. The British Thoracic Society (BTS) nodule management guidelines, discussed further in Section 1.6.5, take a more cautious approach, recommending a threshold of <80mm³, in recognition of the fact that there may be variability in nodule volume measurements between software packages [120, 141, 159].

Nodule growth: A lack of nodule growth is considered a good indicator of benignity. In a retrospective analysis of VDTs of nodules detected over two screening rounds in the NELSON trial, Horeweg *et al.* report that the risk of malignancy in solid nodules with a VDT of >600 days was only 0.8% [160]. The BTS guidelines therefore recommend that solid nodules with a VDT of more than 600 days can be regarded as benign [120].

Malignant pulmonary nodules

Callister *et al.* analysed 30 studies evaluating the clinical and radiological characteristics of benign versus malignant nodules. They found that 5 radiological features were predictive of malignancy in two or more studies using multivariate analyses. Recognised features predictive of malignancy were nodule size, upper lobe location [161], spiculation, pleural indentation and a rapid VDT (<400 days) [120]. Features of SSNs associated with malignancy include a bubble-like appearance, and pleural retraction or indentation [120]. However, none of these features alone are specific for malignancy.

The VDT of malignant nodules is highly variable, ranging from fewer than 40 days, to more than 400 days [52, 162-165]. VDTs are recognised to be faster for SCLC than NSCLC [52] and slower for SSNs than solid nodules [163, 164]. Malignant SSNs, usually on the adenocarcinoma spectrum, can have long VDTs. In an analysis of 19 GGNs diagnosed as cancers in a screening study, Hasegawa *et al.* found that the mean VDT for these cancers was 813 days [163]. Tumours with such indolent behaviour might be regarded as over-diagnosed cases, for which aggressive treatment may not be appropriate.

Various risk models have been proposed and validated to assess risk of malignancy in pulmonary nodules. The Brock model (also known as the PanCan model), incorporates clinical factors (age, gender and family history of lung cancer) and radiological factors (presence of emphysema, nodule size – measured by diameter, nodule count, location, type and spiculation) to give an estimated risk of malignancy in an indeterminate nodule. This model was derived from a screening cohort (in the PanCan study) and validated externally initially in the British Columbia Cancer Agency dataset [166]. It has subsequently been externally validated in a number of studies [167-170], although not always studies of screening detected nodules [171].

The Herder score calculates a risk of malignancy in a nodule following a positron emission tomography (PET) scan [172]. This model incorporates clinical factors (age, smoking history, history of previous extra-thoracic cancer), radiological factors (nodule size, location, spiculation) and fluorodeoxyglucose (FDG) avidity of a nodule on a PET scan. It should be noted that both the Brock and Herder risk models incorporate spiculation as a morphological feature predictive of malignancy. A study looking at interobserver variability in the characterisation of lung nodules by 107 thoracic radiologists found significant interobserver variability for characterising a nodule as spiculated (Fleiss kappa (κ)= 0.353) [173] and this raises questions about the extent to

which such calculations should incorporate morphological features for which there is significant interobserver variation.

1.6.5 Management of pulmonary nodules

In practice, although there are characteristic features associated with benign nodules, when these are not present, nodules remain indeterminate. Various factors influence the investigation and management of such nodules and comprehensive guidelines have been written by a number of societies including the Fleischner Society [174], the American College of Chest Physicians [175] and the BTS [120]) to assist radiologists and physicians. The Lung-RADS™ nodule management algorithm was developed in the USA in 2014 specifically to assist clinicians in the management of screening-detected nodules; a subsequent update to the algorithm was published in 2019 [176, 177]. The purpose of the Lung-RADS™ algorithm was to simplify and standardise nodule management in screening and to base ongoing management recommendations on lung cancer risk. This algorithm is now widely used for lung cancer screening in the USA. Although the various nodule management guidelines above differ in their applicability and scope, for the purposes of the forthcoming discussion, only the BTS guidelines are discussed, as these are currently the guidelines recommended for nodule management in lung cancer screening in the UK.

In recognition of the high prevalence of benign solid nodules even within high-risk screening cohorts, fundamental principles of screening protocols include reducing the over-investigation of nodules which are likely to be benign and lowering false positive rates. This can in part be achieved through nodule management protocols which minimise recall rates (i.e. the proportion of individuals having a baseline scan who are recalled for further scans or invasive investigations before the next screening round). Investigation of such nodules results in patient anxiety, increased cost and unnecessary investigations, which should be minimised as much as possible.

The BTS guidelines divide solid and sub-solid nodules, with separate management algorithms for each type. In the solid nodule algorithm, small solid nodules ($<5\text{mm}$ in size/ $<80\text{mm}^3$) and nodules showing clearly benign features, require no further follow-up or surveillance due to their low risk of malignancy. This is based on data previously discussed from the NELSON trial [160]. For larger ($>8\text{mm}/>300\text{mm}^3$) solid nodules, with a risk of malignancy of $>10\%$ according to the Brock model, PET-CT is recommended, and further investigation or CT surveillance is based on risk. For solid nodules which fit into neither of these categories, CT surveillance is recommended at 12 months, with or without CT surveillance at 3 months depending on nodule size. At 3 or 12 months, VDTs should be calculated to establish growth rates, and the further guidelines for the investigation of nodules are based on VDTs [120].

New solid nodules appearing on incident round scans (12 months or more after a baseline scan) are known to have an increased risk of malignancy [178]. Although not currently incorporated within the BTS nodule management guidelines, the BTS Quality Standards Guideline recommends that new small solid nodules appearing on incident round scans warrant imaging follow-up [179]. At present, how radiologists manage such nodules in the screening setting is unknown.

Sub-solid nodules are treated as a distinct entity in the BTS guidelines. Previous screening studies have demonstrated that between 31 and 45% of pGGNs resolved during follow-up [180, 181], whilst Lee *et al.* showed that 69.8% of PSNs were transient in a Korean screening programme [182]. For this reason, the BTS guidelines recommend a three-month follow-up scan for all SSNs, recognising that many will resolve.

Whilst SSNs are more likely than solid nodules to be malignant, these have a better prognosis than solid nodules [120, 183]. In a retrospective analysis of 117 SSNs which were persistent at 3 months of follow-up or resected in 108 participants in the

NELSON screening trial, 28 of 33 resected SSNs were pre-invasive, and none of the remaining 84 non-resected SSNs progressed to clinically significant invasive malignancy after a median follow-up time of 95 months [184]. Nonetheless, the development of a solid component in a previously pGGN, or growth (>2mm) of a small solid component of a PSN, or a change in morphology of a SSN is suggestive of malignancy, and on these grounds, the BTS guidelines currently recommend resection of these lesions [120].

1.6.6 Reporting incidental findings detected at LDCT screening

Incidental findings are defined as imaging abnormalities detected which are unrelated to the indication for the CT scan. In the context of LDCT screening for lung cancer, this includes any incidental findings other than lung nodule or lung cancer identification. The identification of relevant incidental findings may be of benefit to patients, through the discovery of asymptomatic pathology for which intervention and/or treatment is available. For example, the discovery of an early renal or breast malignancy may reduce morbidity and mortality, and early diagnosis could be cost effective. The counterargument is that many incidental findings are not clinically significant, and that the investigation of such findings causes significant anxiety to patients and increases the cost of screening programmes. Unnecessary additional tests for incidental findings generated from screening may also increase waiting times for diagnostic tests for patients outside of screening programmes. In an Irish screening study involving 449 participants, MacRedmond *et al.* reported no incidentally found extra-thoracic malignancies, but incidental non-malignant pathology was reported in 61.5% of patients [185]. Only one extra-pulmonary malignancy was identified in 1929 patients undergoing baseline scanning in the NELSON trial [186]. By contrast, in a retrospective analysis of the screening scans of 5201 patients involved in an Italian pilot screening study, the Continuous Observation of Smoking Subjects (COSMOS) study, Rampinelli *et al.* report 27 extra-pulmonary malignancies (0.5%) [187].

Aside from incidental malignancies, previous studies have reported a highly variable rate of significant or potentially significant incidental findings, varying from 8% to over 50% [185, 186], with high rates even when radiologists were instructed to report only incidental findings requiring follow-up or further evaluation [188]. These differences can be accounted for by differing definitions of what is considered significant, different selection criteria for patients, and differing CT scan fields and scanning techniques. No consensus has yet been reached on what should be considered significant and what should be reported. One pragmatic approach is to report incidental findings only when there is an established outcome or intervention related to the finding which would benefit the patient.

Urgent non-malignant incidental findings are uncommon but include significant aortic dilatation or focal aortic aneurysms. Other non-urgent findings which may warrant primary or secondary care referral include interstitial lung disease, heavy coronary artery calcification (CAC), cardiac valve calcification, or significant bronchiectasis.

At the time of commencement of the West London targeted lung screening pilot, no formal guidelines had been made available by NHSE regarding how incidental findings should be reported and managed in the lung screening setting. Initial NHSE guidelines for reporting incidental findings, published in January 2019, stated that reported incidental findings should be "*clinically significant*", "*reviewed at [a] LDCT Review MDT*" and that there should be an agreement between screening programmes and primary care physicians about "*the nature and benefit of ...recommended interventions*" [109]. More recently, guidance for reporting and onward referral of specific incidental findings has been provided by NHSE in order to standardise the reporting and management of incidental findings in screening [189].

1.6.7 Standardised reporting and quality assurance

A specific CT reporting template for screening is not provided in NHSE guidelines. However, recommendations are made within the guidelines about how nodules should be reported (including site, volume, morphology (solid/ground-glass/part solid), benign features) and the NHSE guidelines specify that a narrative report should not be used [109]. Radiologists reporting screening studies should be familiar with thoracic CT reading, nodule volumetry software and BTS guidelines for nodule management, as well as regularly attending or leading a local lung cancer MDT.

NHSE guidelines recommend that quality assurance processes should be in place for lung cancer screening reporting. Examples of such processes include experienced readers reviewing the first 50 screening studies of new readers, periodically reviewing the reports of readers, and evaluation of recall rates, false positive and negative rates of readers, with appropriate feedback [109]. Similar recommendations, including training and supervision of radiologists beginning screening reporting, are in place in Canada [190].

To date, few studies report radiologist compliance with nodule management protocols. A study of 834 radiologists' compliance with Fleischner society nodule management guidelines in the USA, demonstrated that nodule management recommendations by radiologists for three specific nodule scenarios followed the published guidelines in only 34.7-60.8% of cases [191]. However, this study was not specific to the lung screening setting. In the UK, the Royal College of Radiologists (RCR) audit guidelines stipulate that for incidentally detected lung nodules, radiologists' compliance with BTS nodule management protocols should exceed 95% [192]. Unanswered questions remain about whether radiologists adhere to nodule management guidelines in the screening setting.

1.7 Aims of thesis

The aims of this thesis are to examine currently unanswered diverse questions that may inform the future implementation of CT screening for lung cancer in the UK, based on analysis of data from one of the first pilot lung cancer screening projects in the UK in West London:

1. To report the baseline results and feasibility of the West London targeted lung screening pilot, including participant, screening protocol and radiological parameters. This will include patient demographics, uptake for lung cancer screening, lung cancer yield and lung cancer stage. Participant eligibility and lung cancer using two different risk models (LLP_{v2} and PLCO_{m2012}) will be compared. Radiological parameters described will include CT dose, recall rates, lung cancer yield, false positive rates and turnaround times.
2. To evaluate the potential benefit of community-based mobile screening units to improve uptake and attendance for lung cancer screening compared to a fixed-site hospital-based scanner, and to explore factors which may influence uptake and attendance (or non-attendance) for screening, including through participant satisfaction surveys.
3. To establish the downstream consequences of LHCs and LDCT screening for primary and secondary care. Specifically, to establish the additional workload for primary and secondary care resulting from incidental findings of LHCs or LDCT scans, and to establish whether recommendations related to non-cancer findings made following LHCs and CT screening result in meaningful interventions for patients in primary and secondary care.
4. To investigate 5 specific unanswered radiological questions relating to CT screening reading and nodule management that may influence lung screening implementation:

- i. How long does it take for radiologists to read CT screening scans using up-to-date reading protocols?
- ii. What increase in small nodule size (volume) on sequential CT represents true growth as opposed to interscan measurement variability?
- iii. What is radiologist compliance to the study's nodule management protocol?
- iv. Can novel techniques be used to improve radiologist compliance to the study's nodule management protocol?
- v. To what extent do radiologists agree on the management of complex nodule management scenarios not currently covered by BTS nodule management guidelines?

CHAPTER 2: GENERAL METHODS

2.1 Overview of the West London targeted lung screening pilot

2.1.1 Rationale, funding and governance of the screening pilot

The purpose of the West London targeted lung screening pilot was to offer low dose CT screening to individuals at high risk of lung cancer in West London, with a view to detecting early lung cancer and to answer questions relating to the practical implementation of lung cancer screening in an NHS setting. The pilot was fully funded through the Cancer Transformation Fund from NHSE. Data were collected as part of a service evaluation with due consideration given to ethical and data protection requirements [193, 194]. Funding was allocated to the project via the Royal Marsden Partners (RMP), who have a memorandum of understanding with the Royal Brompton Hospital (RBH) who, in conjunction with RMP, designed and set up the pilot.

2.1.2 Identification of clinical commissioning groups for participant recruitment

Research commissioned by and carried out by RMP in 2017 and 2018 identified two clinical commissioning groups (CCGs) in North West London from which to invite participants: The London Borough of Hillingdon, and the London Borough of Hammersmith and Fulham. The London borough of Hillingdon was identified as having the lowest 1-year survival (28%, 2013) for lung cancer [195] and the highest proportion of lung cancer patients diagnosed with Stage III and IV disease (71.0%, 2014-2017), compared to all other North West London CCGs over the same period [196]. Smoking rates in the London borough of Hammersmith and Fulham were higher (19.6%, 2014/2015) than all other in North West London CCGs, and above the national average (18.4% in England, 2014/2015) (personal correspondence, RMP Cancer Alliance, 26th February 2019) (Figure 2.1).

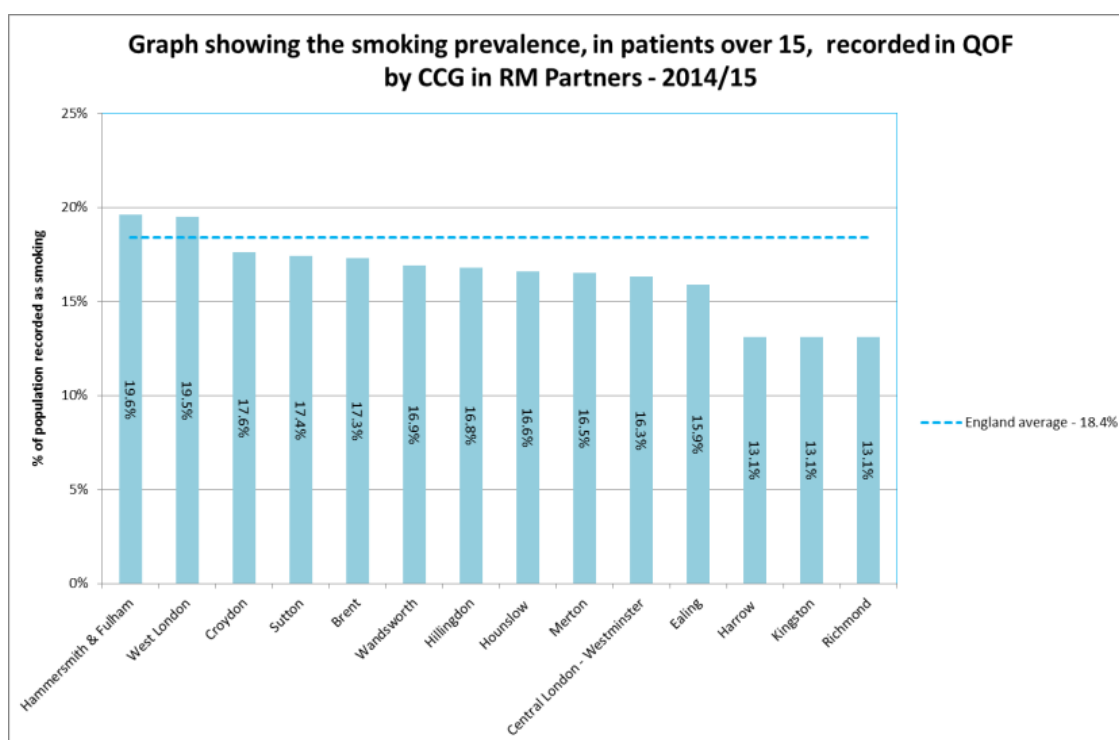


Figure 2.1 Smoking prevalence in North West London CCGs 2014/2015. Image provided by RMP Cancer Alliance.

2.1.3 Governance structure of the West London targeted lung screening pilot

Decisions regarding the overall design and delivery of the pilot, and associated research studies, were made by a project operations group comprising clinical staff from the Royal Brompton Hospital, GP representatives from both West London CCGs and individuals from the RMP West London Cancer Alliance (documented in Appendix

A).

A smaller operations group (Appendix A) included members of the operations group and individuals involved in service delivery and research in the Royal Brompton Hospital, including information technology (IT) staff, radiology management and research staff associated with the project. This group met on a fortnightly basis between August 2018-April 2019 to discuss operational issues surrounding project activity, service delivery, staffing and project finances.

2.2 Participant eligibility, identification and invitation strategy

An expression of interest email was sent to all GP practices within Hammersmith and Fulham in January 2018. Nine GP practices in Hammersmith and Fulham, and 8 GP practices in Hillingdon enrolled in the pilot.

The target population comprised current and ever-smokers, who had stopped smoking over the age of 40, aged 60-75 in these two CCGs. Potential participants were identified from SystmOne and EMIS, two secure electronic clinical databases used in Hammersmith and Fulham CCG and Hillingdon CCG respectively. Participant data (name, age, sex, ethnicity (where available), participant address, GP name and practice address, smoking status, diagnosis of existing COPD, diagnosis of existing malignancy and NHS number) were collated by the NW London Commissioning Support Unit (CSU) and securely transferred to project staff at the RBH.

Potential participants were subsequently invited by letter, on behalf of their GPs, to attend a LHC at one of two sites. Those living within the Hillingdon CCG were invited to a mobile scanning unit located in a supermarket car park initially in West Drayton and subsequently in Hayes, Middlesex. Potential participants in the Hammersmith and Fulham CCG were invited to a LHC at the RBH, hereafter referred to as the “fixed site”.

The invitation letter was accompanied by a patient information leaflet briefly stating the purpose of the LHC (Appendix B). The content of the letter and accompanying leaflet was intended to be minimal, so as to prevent fear and reduce stigma. The format of the letter and leaflet were similar to that used in previous pilot studies [123] and approved by a patient advisory group prior to commencing the pilot. Although the possibility of having a lung CT was discussed in the leaflet, no mention of lung cancer detection or smoking cessation was made in either the initial invitation letter or accompanying leaflet. Participants were invited to opt in by calling a dedicated clinic booking line, staffed by trained administrative staff.

Upon telephoning, participants were screened for eligibility. Those outside the specified age range (60-75), never smokers, former smokers who quit under the age of 40, those with active malignancy or on the palliative care register, those with a WHO performance status of 3 or 4 and those who had received a thoracic CT in the previous 2 years, were excluded from the study at the point of telephoning. Eligible participants were offered a LHC appointment.

After an initial invitation letter, two strategies were attempted to improve participant uptake. A second invitation letter was sent to 23.7% potential participants and a telephone call was made to 11.4% of non-responders, based on availability and optimisation of administrative staff resources.

2.3 Lung health checks

2.3.1 Personnel and staff training

Over the course of the pilot, LHCs were carried out by a variety of trained health care professionals, primarily three band 6 nurses, as well as two junior doctors and a radiographer from the RBH.

Staff received training about how to consent invitees to participate in the LHC. For those eligible for a LDCT scan, LHC staff explained the associated radiation dose, the possibility of finding a lung nodule, and the implications of both positive and negative scans. These participants were also shown a patient information leaflet about CT scans (Appendix C). Staff were also expected to be able to perform spirometry, and dedicated spirometry training was provided to staff when this had not previously been a part of their routine clinical or research work.

Data were entered by the clinical staff into a project database (discussed in Section 2.3.2). Specific training was given to staff about how to interpret clinical questions and responses relating to participant symptoms, smoking history, interpretation of spirometry results and how to accurately record data within the

database. This training was provided by the author, following operations group discussions with the Respiratory Lead and Radiology Clinical Lead (hereafter referred to as the Clinical Lead) of the project. Participants who were current smokers at their LHC appointment were offered a referral to local smoking cessation services, and an online referral to local smoking cessation services in each London borough was made at the time of the LHC for those accepting an offer of referral.

All staff were initially observed carrying out a LHC by the Clinical Lead and/or the author before performing LHCs independently.

2.3.2 Data collection during LHCs

Due to the absence of suitable commercially available databases designed specifically for lung screening, a custom-made electronic database was designed to record the clinical data, scan results and outcomes of participants who received LHCs. The database was built by Chameleon Information Management Services (CIMS) in conjunction with staff from RMP and the author, within an information management system (InfoFlex®) already in use in the RBH. Data points to be collected for each participant were determined by the project operations group.

2.3.2.1 Clinical data and red flag symptoms

In addition to lung cancer risk factors (Section 2.3.2.3 below) a number of clinical questions were asked during the LHC and recorded on the InfoFlex® database (Figure 2.2). COPD history was documented in order to determine participants who would subsequently require referral to primary care for respiratory investigations (Section 2.6.4).

Participants who presented with symptoms of an acute intercurrent respiratory tract infection, an acute cough, a fever, or those taking antibiotics for an acute respiratory tract infection, were ineligible for a LHC at that time and were offered another appointment for a LHC 6 weeks later.

- Lung Health Check

Is the patient on a COPD register?	✓	✗	▼
Does the patient have a known COPD diagnosis?	✓	✗	▼
Current respiratory infection?	✓	✗	▼
Current cough?	✓	✗	▼
Current fever?	✓	✗	▼
Currently on antibiotics?	✓	✗	▼
Delay Lung Health Check for 6 weeks	✓	✗	▼
Date of next Health Check			
Known haemoptysis?	✓	✗	▼
Last episode of haemoptysis			
Is this symptom being investigated elsewhere?			

- Self-reported Symptoms

No. of chest infections in the last 12 months	+	-	
Unexplained appetite loss	✓	✗	▼
Unexplained fatigue	✓	✗	▼
Unexplained chest pain	✓	✗	▼
Unexplained weight loss	✓	✗	▼
How much weight lost?			
MRC dyspnoea score			▼
Any other self reported symptoms			

Figure 2.2 Clinical datapoints collected at the LHC.

Participants were specifically asked about current or recent haemoptysis, a NICE red flag symptom warranting urgent referral to secondary care [197]. Those presenting with acute haemoptysis were referred directly to the respiratory clinic, for a respiratory consultation and CT scan. These individuals were ineligible for a LHC and LDCT in view of their symptoms.

Other red flag symptoms for lung cancer that were self-reported, were also recorded (Figure 2.2) The management of participants presenting with red flag symptoms is shown in Figure 2.3.

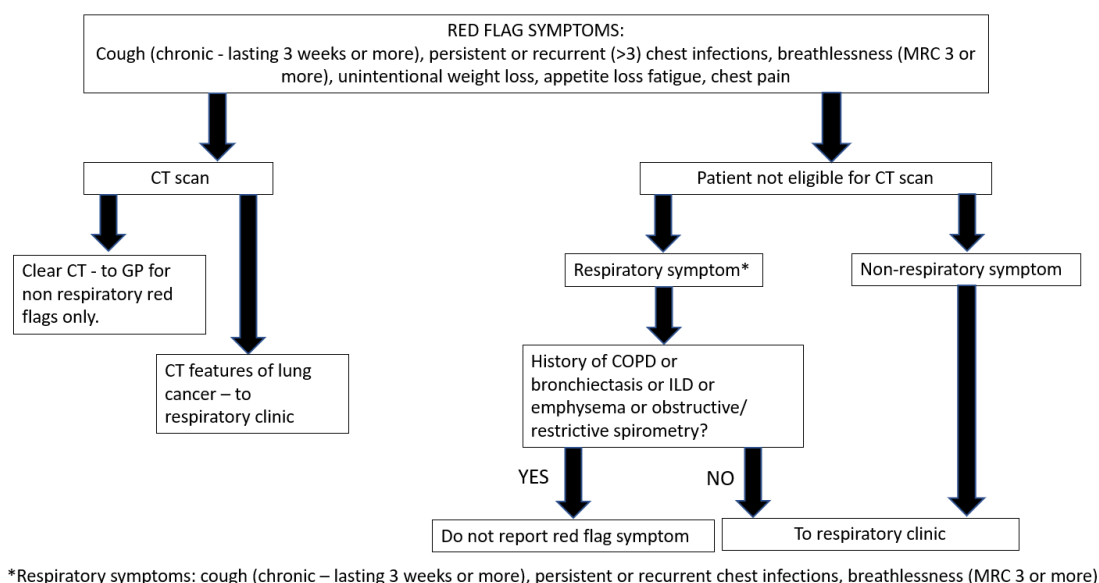


Figure 2.3 Management of participants presenting with red flag symptoms.

In the West London targeted lung screening pilot, some participants with CAC on LDCT were subsequently referred to primary care for a QRISK® assessment with a view to commencing lipid-lowering therapy, if appropriate, according to a protocol described in Section 2.6.3.3. This was done following the LDCT scan and correlated with current statin use and a history of ischaemic heart disease, which were also recorded at the time of the LHC.

2.3.2.2 Spirometry

All participants were offered spirometry, unless there was a clinical contraindication to performing spirometry. Spirometry results were interpreted by the LHC staff in line with the BTS COPD consortium guidelines [198] and recorded within the InfoFlex® programme.

2.3.2.3 Low dose CT eligibility, risk scores and interpretation and validation of risk calculators

A PLCO_{m2012} risk calculator (in a Microsoft Excel document) is freely available online [199]. An unlocked version of this Excel document was replicated by the author,

using formulae available within the original publication [101] and provided to CIMS to build within the InfoFlex® data management system. The LLP_{v2} risk score calculator in Microsoft Excel was provided directly by the chief investigator of the LLP_{v2} derivation study [96] (Personal communication, Professor John Field, University of Liverpool) and also provided to CIMS to incorporate within InfoFlex®. These risk calculators were tested 50 times within InfoFlex® with different clinical data and compared to the online calculators, to ensure that risk scores were accurately calculated. Later, the Infoflex® risk calculators were also used to validate a synthetic dataset of 100 risk scores provided by NHSE.

With participant agreement, clinical data were acquired to allow for the calculation of PLCO_{m2012} and LLP_{v2} risk scores (Figure 2.4). Upon entry of the relevant clinical data in Infoflex®, the LLP_{v2} and PLCO_{m2012} risk scores were automatically calculated. The PLCO_{m2012} risk score calculator is demonstrated in Figure 2.5.

Did the patient agree to a Risk Score calculation? ☐ ☒ ☐ ☐			
Lung Cancer Risk Assessment		Smoking	
Education		Current smoking status	
Height		Age started smoking	
Weight		Age when quit	
BMI		If restarted, age restarted smoking	
Personal history of cancer?	☒ ☐	Number of years smoking cigarettes	
Undergoing active treatment for malignancy?		Number of years smoking other only (e.g. exclusively smoking a pipe or cigars etc)	
Family History of lung cancer?		Smoking duration	
Ethnic Group (PAS)	NK - Not Known	If current smoker, difficulty not smoking for 1 day	
Ethnicity (PLCO)		Average no. of cigarettes per day	
Occupation (current or prior)		Years ago quit smoking	
Any job with asbestos exposure?			
Ever lived with anyone that worked with asbestos?	☒ ☐		
Health Check			
Prior TB?		Known IHD?	☒ ☐
Prior pneumonia?		On Statin?	☒ ☐
Chronic bronchitis?		Known bronchiectasis?	☒ ☐
Known emphysema?		History of asthma?	☒ ☐
Known ILD?	☒ ☐	History of allergy and/or eczema?	☒ ☐
Calculated Risk Scores			
PLCO ₂₀₁₂ Risk Score		Above threshold for PLCO?	
LLP v2 Risk Score		Above threshold for LLP?	

Figure 2.4 Datapoints required to calculate PLCO_{m2012} and LLP_{v2} risk scores for participants, as recorded in InfoFlex®.

PLCO 2012 Risk Score				
Age (when event created)	67	+ -	Age Coefficient Contribution	0.9346416
Education			Education Coefficient Contribution	
Height	. cm	+ -		
Weight	. kg	+ -		
BMI			BMI Coefficient Contribution	
Does the patient have a known COPD diagnosis?		✓ ✗		
Known emphysema?		✓ ✗		
Prior bronchitis?		✓ ✗		
Lung Condition			Lung Condition Coefficient Contribution	
Personal history of cancer?		✓ ✗	Personal History Coefficient Contribution	
Family History of lung cancer?			Family History Coefficient Contribution	
Ethnicity (PLCO)			Ethnicity Coefficient Contribution	
Current smoking status			Smoking Status Coefficient Contribution	
Average number of cigarettes per day			Cigarettes per day Coefficient Contribution	
Smoking Duration in years (cigarettes only)	Years	+ -	Duration Smoked Coefficient Contribution	
Age when quit				
Years ago quit smoking			Years Ago Quit Smoking Coefficient Contribution	
			EXP(xb)	
			PLCO2012 Risk Score	
			Above threshold for PLCO?	

Figure 2.5 PLCO_{m2012} risk calculator in InfoFlex[®] system.

The PLCO_{m2012} risk calculator was derived from data acquired during the PLCO screening trial carried out in the USA. Demographic data collected for this trial therefore related to the North American population enrolled in this trial and are not comparable to a UK population, as outlined below.

Education level was measured in the following six categories in the original PLCO model: 1=less than high-school graduate; 2=high-school graduate; 3=some training after high school; 4=some college; 5=college graduate and 6=postgraduate or professional. In the West London pilot, education level was categorised as follows: 1=<GCSE level; 2=GCSE level; 3=A Level; 4=Some university; 5=Degree; 6=postgraduate.

Ethnicity, classified in the following categories in the original PLCO model (White, Black, Hispanic, Asian, American Indian or Alaskan Native, Native Hawaiian or Pacific Islander) was classified as follows: White, Black, Hispanic, Asian, Native Hawaiian/Pacific Islander, American Indian/Alaskan Native, Other, Prefer not to say. Participants self-reported ethnicity: those describing themselves as mixed race, or another ethnicity, were recorded as "Other". At the time of commencing the West London targeted lung screening pilot, a PLCO_{m2012} risk score excluding the race/ethnicity parameter was not

available. Therefore, in view of the absence of any published data about the risk of mixed-race participants, or participants of other ethnicities, at the time of building the Infoflex[®] system, these participants were considered to carry the same risk as the “reference group” [101], i.e. the same as the White population.

Participants who did not smoke cigarettes, for example, smokers of pipes or cigars, did not have a PLCO_{m2012} risk score calculated, in view of the fact that the original PLCO_{m2012} calculator specifically refers to smokers of cigarettes. Although a history of cigar smoking is captured in the original PLCO dataset [200], cigar smoking was not incorporated into the PLCO_{m2012} model. Consequently, a decision was taken that for this cohort of participants, who had never smoked cigarettes, only a LLP_{v2} risk score was calculated.

Participants with either a PLCO_{m2012} score of ≥ 1.51 [100], or an LLP_{v2} score of ≥ 2.0 were eligible for a CT scan and were offered a same-day LDCT scan by the LHC staff. At the time of planning the West London pilot, a LLP_{v2} threshold of between 2.0 and 3.0 was thought to offer the best balance between sensitivity (which increases at lower risk thresholds), and specificity and cost effectiveness, both of which improve at higher risk thresholds [107].

2.3.3 Data storage

Access to the specific InfoFlex[®] data management system for this pilot was available only to members of the clinical team participating in the project.

2.4 CT acquisition, transfer and storage

2.4.1 CT scanning protocol

Participants were scanned on a 128-slice Siemens Edge CT scanner at the fixed site between August 2018 and April 2019, or on a 128-slice GE Healthcare Optima CT660 scanner at the mobile site between October 2018 and March 2019. The scanner at the

mobile site was provided by an independent private company, Alliance Medical Limited (Warwick, UK).

Participants were scanned from the lung apices to the lung bases, with a breath hold and without the administration of contrast medium. Weight based scanning parameters were used. AEC was enabled on both scanners; this resulted in alterations of the tube current (mAs) for different sized individuals in order to maintain a consistent image quality at the lowest dose. Tube voltage (kV) was pre-set and adjusted for participant weight (<50kg, 50-80kg, 80+kg). Images were reconstructed with filtered back projection and a soft tissue reconstruction kernel [142], the latter being manufacturer specific, but closely matched between the two scanners. On the fixed site scanner, the image slice thickness was 1mm with a slice increment of 0.7mm. On the mobile scanner, the slice thickness was 1.25mm, with a slice increment of 1.25mm. Images were provided to radiologists as a single reformat as lung windows (window width 1500, level -500).

Nodule follow-up scans for participants who were originally scanned at the mobile site were carried out at Harefield Hospital. Participants were scanned on a 128-slice GE Revolution™ CT Evo scanner, with AEC enabled. As with the mobile scanner, the slice thickness was 1.25mm, with a slice increment of 1.25mm, and the image protocol was closely matched to the mobile GE scanner. Image reconstruction was with filtered back projection, as at the mobile and fixed site scanners.

2.4.2 CT image transfer and storage

Transfer of images acquired on the fixed site scanner to the hospital Picture Archiving and Communication System (PACS) (Impax, Agfa Healthcare NV, Belgium) occurred immediately after the scan was performed. Imaging acquired at the mobile unit was transferred to the RBH PACS system as encrypted Digital Imaging and Communications in Medicine (DICOM) images across a 4G network, using a third party,

Visbion Innovative Imaging management solutions (Surrey, UK). Upon arrival within the RBH PACS system, the images were also transferred automatically to a commercial nodule volumetry software programme, Veolity™, provided by MeVis Medical Solutions (Bremen AG, Germany).

2.4.3 Quality assurance for image acquisition and transfer

Evaluation of CT dose

Dose data were reviewed for the first 50 scans performed in the project, to ensure that the median effective dose was below 2mSv, as recommended by NHSE [189] and approximately 6-monthly thereafter.

Image acquisition and reconstruction

Errors in image acquisition included incomplete imaging, for example when the lung bases were missed, or inadequate scan quality, for example due to movement artefact. Radiologists were able to report these errors in the scan reports and would recommend a repeat scan for re-evaluation.

Errors in image reconstruction were reported within 48 hours to the radiology services manager at the fixed site and to the head of CT clinical services at Alliance Medical Limited, when scans had been performed on the mobile unit. Radiographers were advised of errors to prevent repetition.

Image transfer

Although image transfer from the mobile scanner was by 4G, all LDCTs were also transferred to compact discs and transported to the fixed site as a safety mechanism in case of data loss.

A list of all participants scanned at the mobile scanner each week was provided by the LHC team to the author. Throughout the project, whilst scanning was being performed at the mobile site, this list was cross checked with the scans which had been uploaded to PACS, to ensure that no scans were lost or unreported.

2.5 CT reporting

2.5.1 Baseline scan reporting

All baseline scans were reported by 1 of 5 consultant thoracic radiologists at the RBH, all with >8 years of experience in thoracic CT reporting. All imaging was reviewed with CAD software, using Veolity™, a software package available from MeVis medical solutions. The Veolity™ CAD system was used as a concurrent reader [201], whereby the scan was first presented to the CAD software and subsequently reviewed by the reporting radiologist.

In the first instance, the CAD software identified, segmented and measured all solid nodules (Figure 2.6).

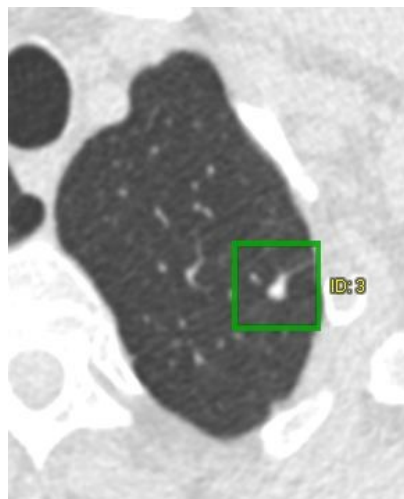


Figure 2.6 An example of a small solid nodule as identified by Veolity™ software.

An initial click of the mouse resulted in the software automatically identifying any lung nodules and highlighting these on the scan with a box, as shown in Figure 2.6. A second click on the box resulted in the automatic segmentation and measurement of the nodules. Each nodule was presented to the radiologist, who could either save or discard the identified nodule based on the study's nodule management protocol (discussed in Section 2.5.2). The Veolity™ software also allowed the radiologist to manually alter the segmentation of a nodule if required. After the CAD reading and subsequent evaluation of nodules, the radiologist re-reviewed the scan to look for any nodules missed by

Veolity™, for example, those adjacent to vascular structures (Figure 2.7a and b), the pleura or the hilum, and any PSNs or pGGNs. A mouse-click on these nodules selected the nodule, which was subsequently classified by the radiologist as solid, part solid or ground-glass, and segmented and measured by the Veolity™ system. Finally, the radiologist reviewed the remainder of the scan for significant incidental findings.

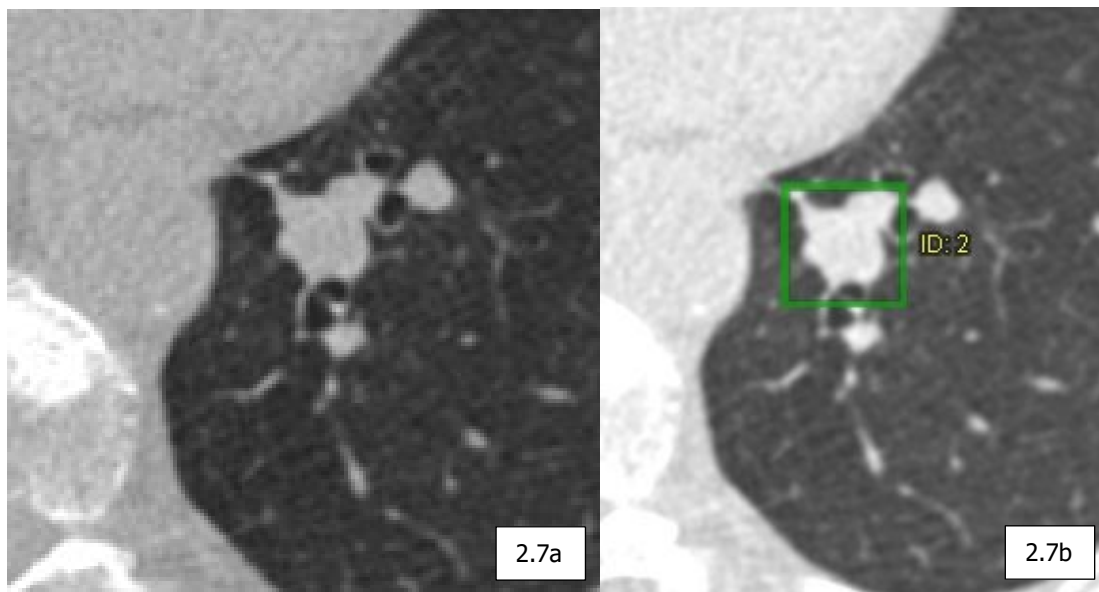


Figure 2.7a and b A juxtavascular nodule not identified by Veolity™ software (2.7a). Segmentation of the juxtavascular nodule following identification of nodule by the reporting radiologist (2.7b).

Upon reading and signing off the CT study on Veolity™ a report of any nodules selected by the reporting radiologist was automatically transferred to the hospital PACS system (Figure 2.8).

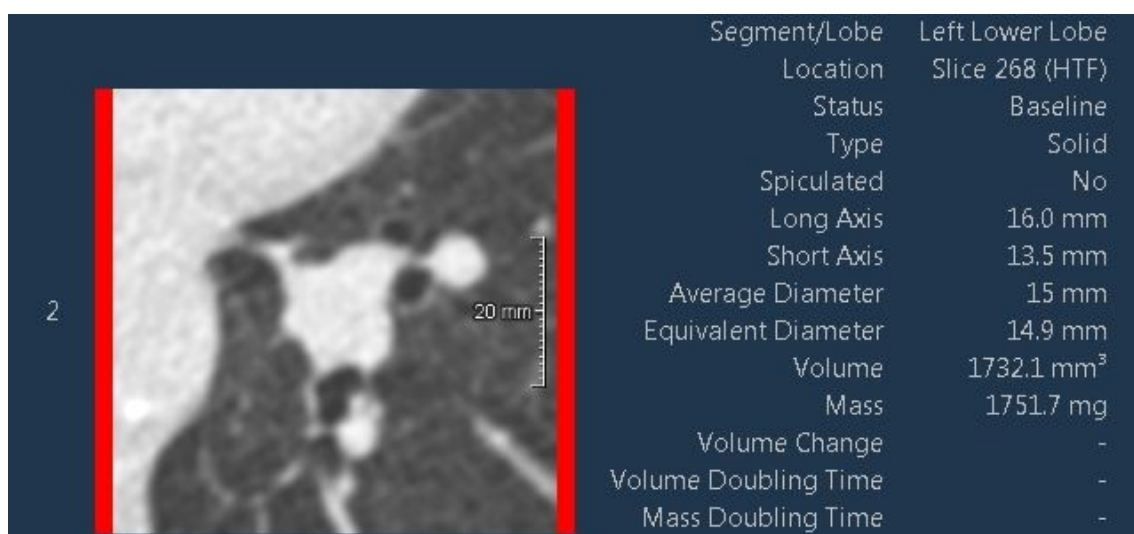


Figure 2.8 Example of a report exported to the PACS system from Veolity™. The size (both diameter and volume) and location of a solid nodule are documented.

2.5.2 Follow-up scan reporting

Follow-up CT scans at 6 weeks, 3 months, 6 months and 12 months were required for participants with pulmonary nodules in accordance with the reporting protocols for solid and sub-solid nodules discussed in Section 2.5.3.

Upon opening a follow-up scan within the Veolity™ programme, the CAD system matched the follow-up scan to the baseline scan for the same patient and automatically identified the nodules which had previously been saved on the baseline scan. A mouse-click resulted in the measurement of the nodule and a calculation of any change in volume (%) and VDT for solid nodules. An example report showing the volume change and VDT of a solid nodule is shown in Figure 2.9.

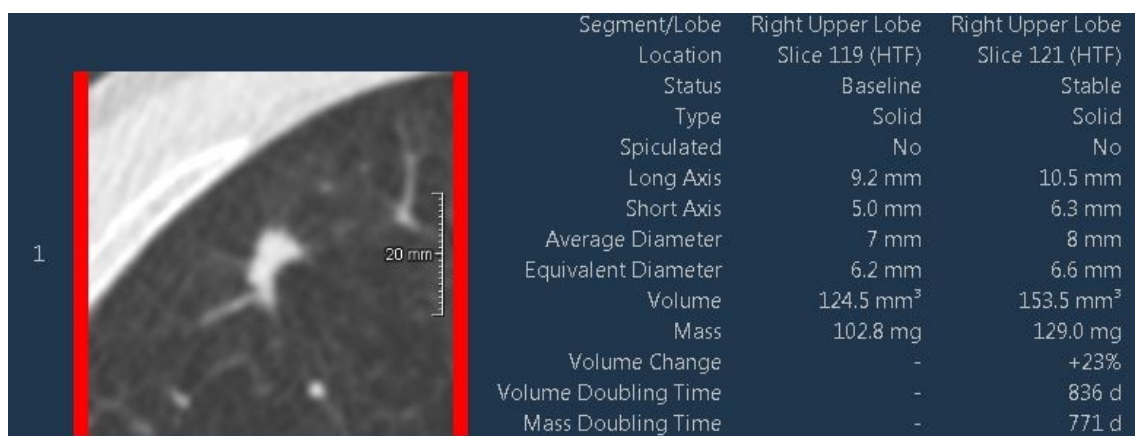


Figure 2.9 Example Veolity™ report from a follow-up study. This shows, in the middle column, the results from the baseline scan and, in the right-hand column, the results from the follow-up scan, including a calculation of a % volume change and volume doubling time (VDT) from the previous scan.

After evaluating the nodules which had been identified on the baseline scan, the CAD software was then used to search for any new or missed nodules. Finally, a review of the scan for any new incidental findings was performed. The radiologist then transferred a report of the follow-up scan generated by Veolity™ to the RBH PACS system.

Interval CT scans were reported by the same 5 consultant radiologists. In addition, two radiology Clinical Fellows, including the author, also reported interval CT scans, under the supervision of the Clinical Lead. All scans reported by the Clinical Fellows were reviewed and signed off by a consultant radiologist throughout the pilot.

2.5.3 Nodule management protocols

At the outset of the West London targeted lung screening pilot, the management of nodules was determined by two algorithms for solid and sub-solid nodules (Appendix D), in a similar flow-chart format to the BTS nodule management guidelines [120]. These management algorithms were based on the BTS guidelines but adapted as follows:

1. Participants with solid nodules $\geq 80\text{mm}^3$ and $< 125\text{mm}^3$ ($\geq 5\text{mm}$ - $< 6\text{mm}$) were invited for a CT scan 6 months from baseline (rather than 3 months from

baseline, as in BTS guidelines). This more conservative approach was taken to allow for meaningful growth which might be detected at a 6-month scan. A similar approach has been taken by other screening groups [176, 202].

2. Participants with solid nodules growing with a volume doubling time (VDT) of ≤ 400 days, or with $\geq 25\%$ volume growth were only investigated with a PET-CT scan if the nodule in question was $\geq 200\text{mm}^3$ (corresponding to a diameter of approximately 7.25mm). This was to prevent the over-investigation of small but growing nodules that may be below the threshold for PET-CT resolution [203], that potentially have a significant likelihood of benignity based on size. Such nodules also are at the threshold for acceptable diagnostic yield for percutaneous biopsy.
3. Participants with pGGNs 5mm to $\leq 30\text{mm}$, without any associated altered morphology (such as pleural retraction, or associated bubble like lucencies), were invited for a CT scan 12 months from baseline (rather than 3 months from baseline, as in BTS guidelines). A significant proportion of such nodules found in screening trials are inflammatory and resolve [180]. Persistent pGGNs demonstrate a higher likelihood of malignancy than solid nodules [204], but demonstrate indolent biological behaviour, giving support to an active surveillance approach [180, 184, 205]. A 12-month scan is currently thought to be a safe approach to the management of pGGNs in the screening setting and is also used in other UK screening trials [118].
4. Participants with PSNs of any size were followed up with a 3-month CT, in line with BTS guidelines [120]. However, at three months, further investigation with PET-CT was only performed for persistent PSNs only in the following circumstances: for nodules with altered morphology; for nodules with a solid component $> 8\text{mm}$; or for nodules with a solid component $< 8\text{mm}$, provided that

the solid component had grown >2mm since the previous scan. In contrast, the BTS guidelines suggest using the Brock model at 3 months to evaluate risk of malignancy and to guide further management [120]. Although persistent PSNs have a high likelihood of malignancy [204], the behaviour of such nodules is frequently indolent and investigation and treatment of these nodules may represent overdiagnosis and overtreatment [118, 206, 207].

5. The BTS nodule management guidelines do not provide any recommendation as to how to manage consolidation or inflammatory appearing opacities, instead recommending that they are referred for further investigation [120]. To minimise over-investigation, these participants were offered a 3-month scan if the radiologist categorised the opacity as inflammatory (referred to as “nodular consolidation” in the reporting template (Section 2.5.5)). In early 2019, a change in protocol was implemented, so that radiologists could choose to recommend follow-up scans after 6 weeks rather than 3 months to match the recommendations for consolidation identified on chest radiographs in clinical practice [208].
6. Participants with suspicious nodules in the following categories were referred directly for PET-CT scans, rather than to a lung cancer or nodule MDT:
 - i. A solid nodule $\geq 300\text{mm}^3$ ($\geq 8\text{mm}$) with a Brock score [166] $>10\%$ at baseline. The calculation of a Brock score was made by the reporting radiologist at the time of reporting. The required data points, including family history of lung cancer, were available from the PACS reporting system, having been added to the CT request form by the LHC team members requesting LDCT scans.
 - ii. A solid nodule with $\geq 25\%$ volume growth, a VDT ≤ 600 days (or unequivocal growth, only when volumetry was not possible) and an absolute size of $\geq 200\text{mm}^3$ on a follow-up scan at any time point.

- iii. A persistent part-solid nodule with altered morphology, namely pleural retraction or associated bubble-like lucencies on a follow-up scan at any time point.
- iv. A pGGN $\geq 30\text{mm}$ in size, with or without altered morphology, on any follow-up scan.

This approach, used in previous European screening trials, was used to reduce the time taken to investigation and diagnosis [62, 209].

In late 2019 the screening pilot was extended to include an incident round of screening 18-24 months after the baseline scan. The original flow-chart algorithms (Appendix D) were modified to include the management of new nodules arising on incident round scans, including small nodules $\geq 30\text{mm}^3$, and the long-term management of SSNs identified in the first round of screening. In view of the increasing complexity and length of the new flow chart algorithms, the author, in conjunction with the Clinical Lead, simplified the nodule management recommendations by converting the BTS-based flow charts into a tabulated format based on a nomenclature used in Lung-RADS™, hereafter termed RBH L-RADS (Appendix E). The new tabulated categorised RBH L-RADS document was distributed to radiologists in late 2019 for use from January 1st 2020 at the outset of the second (incident) round of screening. Thereafter, radiologists reporting for the West London targeted lung screening pilot were asked to report a RBH L-RADS score for every nodule reported on a screening scan (up to a maximum of 4 nodules), as well as the highest RBH L-RADS score on a given scan, with a corresponding follow-up recommendation.

2.5.4 Reporting of incidental findings

The protocol for reporting incidental findings was agreed by the project operations and steering groups. In line with the principles of available guidelines at the time of planning the pilot [210], the following incidental findings were routinely reported

on the basis that health interventions may be available which might improve participant prognosis:

1. Bronchiectasis was reported if it was moderate or severe, as determined subjectively by the reporting radiologist. In one previous study, interobserver agreement for the classification of the severity of bronchiectasis on HRCT was been shown to be good ($\kappa=0.78$); disagreement between radiologists occurred only in cases of mild bronchiectasis and never in severe disease [211].
2. Interstitial lung abnormalities (ILAs) ($>5\%$), as assessed visually by the reporting radiologist. Examples of ILAs include non-dependent ground-glass opacification or reticulation, honeycomb cysts and traction bronchiectasis [212, 213]. Participants with $>5\%$ ILAs have been shown to be more likely to have restrictive lung function than those without ILAs involving 5% or more of the lung [212].
3. Emphysema was reported if $>15\%$, as assessed visually by the reporting radiologist [214].
4. Coronary artery calcification (CAC) was reported if it was considered by the reporting radiologist to be moderate-severe. Chiles *et al.* demonstrated that visual classification of CAC into mild, moderate or severe correlates well with the Agatston score based on density (HU) of CAC, with good interobserver agreement between readers (weighted Kappa (κ_w)=0.85) [215].

The rationale for reporting these incidental findings is discussed in Section 2.6.3.3.

Other incidental findings were reported at the discretion of the reporting radiologist based on the understanding that the finding should be significant and associated with a beneficial intervention (such as a breast mass). Benign incidental findings (such as likely hepatic cysts) were not reported.

2.5.6 Radiologist training and quality assurance

All consultant radiologists were trained in the use of Veolity™ software. Training on the use of Veolity™ and interpretation of the nodule management protocols was provided by the Clinical Lead and author (following training by the Clinical Lead) and by MeVis medical solutions. The first 20 screening scans reported by each radiologist were reviewed for accuracy and signed off by the Clinical Lead. Subsequently, all five radiologists reported independently.

All radiologists had the option of referring cases to the RBH nodule MDT for a second opinion. This was documented on the scan report and required a radiology alert to be added to the report, which ensured that cases were referred to the MDT.

2.5.5 CT reporting templates

All scans were reported in a reporting template in PACS by the radiologist (Figure 2.10). A similar PACS template was available for follow-up scans but modified to enable reporting of growth of nodules and volume doubling times. Radiologists were required to report up to 4 pulmonary nodules on baseline or follow-up scans. Incidental findings were deleted from the pre-populated list on the report template when not present.

Solid nodules were reported by volume (in mm³). PSNs and pGGNs were reported by diameter (in mm). For a part-solid nodule, the size of the solid component and ground-glass component were both measured and recorded, for example, "4mm(solid)/13mm(ground-glass)", or "4mm/13mm". In some instances, where the reporting radiologist felt that the CAD software inaccurately segmented the nodules, long axis diameter (mm) was measured with electronic callipers.

Note to radiologist: Please delete as appropriate below or enter data where required:

Scan timepoint

Baseline scan:

Nodule 1

Lobe:

Slice:

Type (solid/GGN/PSN/nodular consolidation//IPLN):

Size (mm³) if volumetry used:

Size (mm) if diameter used:

Brock Score (if appropriate):

Recommendations for follow-up for Low Dose Team:

1) For scans requiring nodule surveillance or nodule discharge:

- No further scan:
- 6 weeks from baseline CT [if CT is non-diagnostic]:
- 3 months from baseline CT:
- 6 months from baseline CT:
- 9 months from baseline CT:
- 12 months from baseline CT:
- For longer term surveillance (please specify):

2) For scans requiring PET/CT and/or nodule MDT [Note (1) above must be empty]

- PET/CT and then nodule MDT [requires RADAlert]:
- Nodule MDT for second opinion [requires RADAlert]:

3) Significant other unexpected findings requiring immediate further investigation:

- Non-pulmonary cancer, for MDT [requires radalert] – please specify recommendations:
- Other – please specify recommendations [requires radalert]:

4) Significant other unexpected findings requiring non-urgent review:

- Significant bronchiectasis (Respiratory Review):
- Interstitial Lung Disease 5-10% (Requires correlation with LFTs):
- Interstitial Lung Disease >10% (Respiratory Review):
- Emphysema >15% (Primary Care/smoking cessation):
- Moderate coronary calcification (Primary care/Q Risk):
- Severe coronary calcification (Primary care/Q Risk):
- Other (Please specify recommendation)

Figure 2.10 Excerpt from baseline PACS reporting template.

When the RBH L-RADS algorithm was introduced in 2020, minor amendments to the PACS reporting templates were made to incorporate RBH L-RADS categorisations (Figure 2.11).

<u>Nodule 1</u> Lobe: Slice: Type (solid/GGN/PSN/nodular consolidation//IPLN): Size (mm³) if volumetry used: Size (mm) if diameter used: RBH L-RADS: <u>Recommendations for follow-up for Low Dose Team:</u> 1) <i>For scans requiring nodule surveillance or nodule discharge:</i> • No further scan: • 6 weeks from baseline CT [if CT is non-diagnostic OR nodular consolidation]: • 3 months from baseline CT: • 6 months from baseline CT: • 9 months from baseline CT: • 12 months from baseline CT: RBH L-RADS [Highest RBH L-RADS score of all nodules reported]:

Figure 2.11 Excerpt from the PACS screening reporting template updated with RBH L-RADS data entry points (highlighted).

2.6 Communication of results

Results letters were sent to all participants and their GPs (with participant consent) who had booked a LHC.

2.6.1 Participants who did not attend a LHC

Participants who did not attend their LHC were telephoned by the administration team and offered another appointment. If a participant could not be contacted, they received a letter with contact details to rebook an appointment. If a participant did not attend an appointment a second time, they received a “did not attend” letter, with contact details to rebook if they still wished to attend. GPs were also informed by letter that their patients had missed an appointment.

2.6.2 Participants ineligible for, or declining, LDCT screening

Participants who did not meet the risk threshold for CT, or who declined CT screening despite meeting the threshold, received a results letter reporting the presence of any symptoms (including red flag symptoms as per the protocol in Figure 2.3) and spirometry results. Participants with unexplained red flag symptoms for lung cancer were advised to visit their GP to discuss the symptom(s). Symptomatic participants with a chronic cough or breathlessness and obstructive spirometry, without a known diagnosis of COPD, were referred to their GPs for a community respiratory/COPD review to discuss further testing and treatment [216]. A participant was considered to have a history of COPD either if self-reported, or if the data originally extracted by the CSU from electronic health records indicated that the participant was already on the COPD register. With participant consent, results letters with the same information, as well as the PLCO_{m2012} and LLP_{v2} risk scores, were sent to GPs.

2.6.3 CT screened participants

2.6.3.1 Positive, indeterminate and negative CT screening scans at baseline

Positive scan:

Participants with positive scans were those referred to the lung cancer MDT for consideration of invasive investigations or treatments [217].

Indeterminate scan:

Participants with indeterminate scans were those that required surveillance LDCT scans at 6 weeks, 3 months, 6 months and/or 12 months and/or a PET-CT scan within the nodule management protocol.

Negative scan:

A participant was deemed to have a negative scan if no nodules were present on the scan or if one or more of the following types of nodules were present:

- Nodules with unequivocal benign features, including intrapulmonary lymph nodes or fat and calcium containing nodules, presumed to represent benign pulmonary hamartomas.
- Solid nodules $<80\text{mm}^3$ (or $<5\text{mm}$ in diameter where segmentation and volumetric measurements of the nodule were not accurate).
- pGGNs $<5\text{mm}$.
- Non-nodular opacities, including scars or atelectasis.

2.6.3.2 Communication of results to GPs and participants

Participants and GPs received a letter with the results of the LHC and scan within 2 weeks of their LHC. Participants with suspicious lung nodules (Section 2.5.3; point 6) were telephoned by a consultant respiratory physician to inform them of their need for a PET-CT scan and/or biopsy. GPs were also contacted by telephone by the LHC staff in these circumstances.

Those with indeterminate scans received appointments for follow-up scans. Participants and GPs were also informed of the results of their interval scans by letter within 2 weeks of the scan.

2.6.3.3 CT incidental findings and management protocol for incidental findings

As discussed, bronchiectasis, ILAs, emphysema and coronary calcification were routinely reported on screening studies (Appendix F).

Participants with previously undiagnosed bronchiectasis of at least moderate severity were referred to secondary care in order to determine the aetiology of the bronchiectasis, offer appropriate advice regarding antibiotic therapy in the event of infection, and to refer to physiotherapy services for sputum clearance exercises.

Participants without known interstitial lung disease (ILD) and with ILAs $>10\%$ were referred to secondary care for further assessment of the likely aetiology of their

interstitial disease and for further investigations and therapy as deemed necessary. Participants with 5-10% ILAs were referred to secondary care only if the participant had restrictive spirometry at their LHC. ILAs 5-10% were not reported to participants or GPs other than in these circumstances.

Participants with emphysema >15%, who were also current smokers, were informed of “smoking related damage” on their CT scan. The GP was also informed of emphysema on the scan. For these participants, the participant letter reinforced the importance of smoking cessation.

Coronary calcification was reported to participants as a “hardening of the arteries of your heart”, and participants were advised to visit their GP to discuss this. This information was provided only when participants had denied statin use and a history of ischaemic heart disease. GPs were informed of the presence of CAC and were advised to perform a QRISK® calculation to assess 10-year cardiovascular risk as per NICE guidelines [218].

Management of urgent incidental findings, including suspected malignancy, were co-ordinated by the author. Participants were contacted directly by phone by a consultant respiratory physician. GPs were also telephoned to inform them of these findings. Letters were subsequently sent to participants and GPs with this information (Appendix G).

Other incidental findings requiring further investigation were managed on a case-by-case basis, following radiology recommendations, or in the event of uncertainty, following ad hoc discussions between radiologists. The decision to investigate an incidental finding in primary or secondary care was determined by the reporting radiologist and/or project clinical team.

Non-urgent incidental findings requiring further investigation were managed within the low dose project, or were referred to primary care, depending on the proximity of the participant to the Royal Brompton Hospital.

2.6.4 Spirometry results

Reporting of spirometry results was correlated with symptoms and, when relevant, findings on the CT scan (Appendix H).

2.7 Results letter generation and InfoFlex® quality assurance process

The InfoFlex® programme was designed so that all results letters were automatically generated. The contents of the results letters were determined by the fields populated within InfoFlex® at the LHC, as well as the CT report. Templates were written by the author containing specific algorithms to determine the contents of results letters. In the early stages of the project, in excess of 40 permutations of possible results and outcomes were tested to ensure that the letters were accurate. In addition, all generated letters (other than DNA letters) were reviewed by the author prior to sending for the first 3 months and intermittently thereafter. Corrections of the algorithms was performed whenever inaccuracies were identified once the system was live.

A Microsoft Excel database was created to record all letters sent to participants and GPs and was maintained by the author. This was cross checked with a list generated from InfoFlex® documenting any participants who had not received letters. Specifically, for participants who had undergone a CT scan, a monthly check was made of InfoFlex® to check that all participants who had undergone a CT scan had also received results.

A database of all participants with lung nodules requiring follow-up was also created in Microsoft Excel and stored on a secure RBH trust drive and maintained by the author. This list was compared with a list automatically generated from InfoFlex® of all participants requiring nodules on a monthly to 6-weekly basis, to ensure that all

participants needing a follow-up scan had undergone a scan (or were otherwise accounted for).

2.8 Significant unexpected events

Any significant unexpected events surrounding LHCs, scans, participant complaints or results letters were documented within the hospital DATIX system and online incident reporting system within use in the Royal Brompton Hospital. These were subsequently investigated.

2.9 Data analysis and statistical analysis

2.9.1 Data extraction from InfoFlex®

The InfoFlex® system was utilised to extract data regarding participant demographics (age, gender, smoking status, ethnicity, socioeconomic status, home postcode), attendance at LHCs, results of LHCs (including spirometry), risk scores, scan outcomes (when performed), incidental findings and referrals to primary and secondary care. Various search 'queries' were set up within InfoFlex® by the author, which enabled quick data extraction. These could be modified as required to answer specific clinical questions. Training was provided by CIMS to enable the author to extract data from the InfoFlex® database as required.

2.9.2 Screening metrics

2.9.2.1 Participant uptake

In line with prior UK-based screening pilots, uptake is reported as a proportion of potentially eligible attendees opting in for a LHC, following removal of those with exclusion criteria for a LHC (see Section 2.2) [79, 111, 123].

2.9.2.2 Participant attendance

All participants attending a LHC are reported as attendees. Attendance is reported as those attending a LHC as a proportion of those who responded to a LHC

invitation and had a LHC appointment booked. Participants attending an initial LHC with an acute illness had a LHC rebooked 6 weeks later. For the purposes of uptake, these participants are considered to be attendees, rather than non-attendees, as they attended an initial appointment, even if a subsequent appointment was not attended.

2.9.2.3 CT screening outcomes

Definitions of positive, indeterminate and negative CT screening tests at baseline are described in Section 2.6.3.1. Those participants with indeterminate baseline scans underwent subsequent CT and, in some cases, PET-CT imaging. Following this participants were either:

- i. Referred to the lung cancer MDT for invasive investigations, thereby becoming “positive” cases.
- ii. Discharged from nodule follow-up because of either volumetric stability of a solid nodule at 1 year of follow-up, or resolution of any nodule, thereby becoming “negative” cases.
- iii. Maintained within the lung cancer screening programme, being indeterminate nodules requiring long term follow-up beyond 1 year. This category included participants with stable SSNs requiring 4 years of follow-up according to BTS guidelines and those with solid nodules not amenable to volumetry, requiring 2 years of follow-up according to BTS guidelines [120].

2.9.2.4 Recall rate

The recall rate encompasses all those who required further diagnostic investigation for suspected lung cancer prior to an anticipated second screening round, including both those undergoing surveillance LDCT, PET-CT or invasive investigation.

2.9.2.5 False positive cases

Previous screening trials have varied in the way in which they have reported false-positive cases and a wide range of false-positive rates are therefore described in the literature. The previous NLST trial reported all participants undergoing any CT follow-up for screen-detected nodules who did not have cancer as a false positive case [63]. The European position statement recommends that the term “false-positive” should describe the proportion of individuals who required a further investigation, namely a PET-CT scan or invasive procedure, or who were referred to a pulmonologist with suspected lung cancer, who subsequently did not have a diagnosis of lung cancer [80]. An alternative approach, taken by one European study, is to define false positive cases as those having a positive LDCT result without a subsequent diagnosis of lung cancer following invasive investigation (namely biopsy or surgery) [219]. In the West London targeted lung screening pilot, PET-CT scans are incorporated into the nodule management protocol and did not automatically trigger a clinical referral. Consequently, only those participants with positive scans as defined above who were found to have benign disease after invasive investigations, were considered false positive cases. False positive cases are reported both as a proportion of all those deemed to have a positive scan and, additionally, as a proportion of all participants undergoing baseline LDCT.

2.9.3 Participant satisfaction surveys

To analyse participant satisfaction at the fixed site and mobile site, a participant satisfaction survey was developed by the project operations group in conjunction with Ipsos MORI (London, UK), an independent market research company [217] (Appendix I). The survey was evaluated and approved by a patient advisory group, prior to use. The survey was offered to all participants upon completion of a LHC at both sites and participation was optional. The survey recorded basic demographic data and comprised 20-30 questions (depending on scan eligibility), 4 of which directly pertained to suitability

of the venue and ease of access to the scanner. Survey completers recorded their response using a five-point Likert scale. All data analysis was carried out by the author.

2.9.4 Statistical analyses

Specific methods of statistical analysis used in this thesis are discussed in the relevant chapters. Statistical analysis depended upon the data extracted from the InfoFlex® system. Data extracted were either categorical (in distinct groups) or numerical (when having a specifically numeric value). Categorical data were nominal (in non-ordered groups, such as gender or smoking status) or ordinal (in an ordered group, such as socioeconomic status, discussed further in Chapter 3, Section 3.3.2). Numerical data were either discrete (taking a specific whole number) or continuous (taking any value).

Comparisons of different groups of participants, for example, attendees and non-attendees, or participants at the mobile site and those at the fixed site, depended upon the specific data parameter or characteristic of the group to be investigated and whether the data were categorical or nominal.

The Chi-Squared (χ^2) test was used to compare proportions in two independent categorical groups. This test is used to assess whether the proportion of individuals with a particular (binary) characteristic is the same within two independent groups, or whether there is a significant difference between the expected and observed proportions of individuals with a characteristic in the two groups. The null hypothesis for the χ^2 test is that the proportions of individuals with a specific characteristic is the same within the two groups.

The analysis of numerical data were based upon whether the data were parametric (normally distributed) or non-parametric (non-normally distributed). In this thesis, groups were always independent (i.e. unrelated, or unpaired). The unpaired (two-sample) t-test was used to compare the mean and distribution of two groups of

parametric data. The Mann-Whitney U test was used to compare means from two groups when the data were non-parametric. All statistical analysis was carried out in SPSS (IBM SPSS Statistics for Windows, Version 26.0, 2019, Armonk, NY: IBM Corp.)

CHAPTER 3: RESULTS

3.1 Introduction

The first part of this chapter (Section 3.2) discusses the overall results of the West London targeted lung screening pilot, including baseline expression of interest, uptake and attendance of potential participants, the demographic profile and baseline risk of participants, baseline scan outcomes including cancer diagnoses, nodule recall rates and incidental findings. The second part of the chapter (Section 3.3) compares uptake, attendance (and non-attendance) of participants at the mobile and fixed site (hospital) scanners and evaluates socioeconomic and demographic factors which may have influenced participant uptake.

3.2 Baseline results of the West London targeted lung screening pilot

3.2.1 Invitations sent and response rates

3.2.1.1 Letters to potential participants

Nine thousand seven hundred and ninety-one potential participants from Hammersmith and Fulham and Hillingdon CCGs were invited with an initial letter for a LHC appointment. Of these, 546 letters (5.6%) were returned, indicating participants were no longer resident at the address. A further 879 participants (9.0%) were not eligible for LHCs at the stage of telephone triage. Reasons for ineligibility are shown in Figure 3.1.

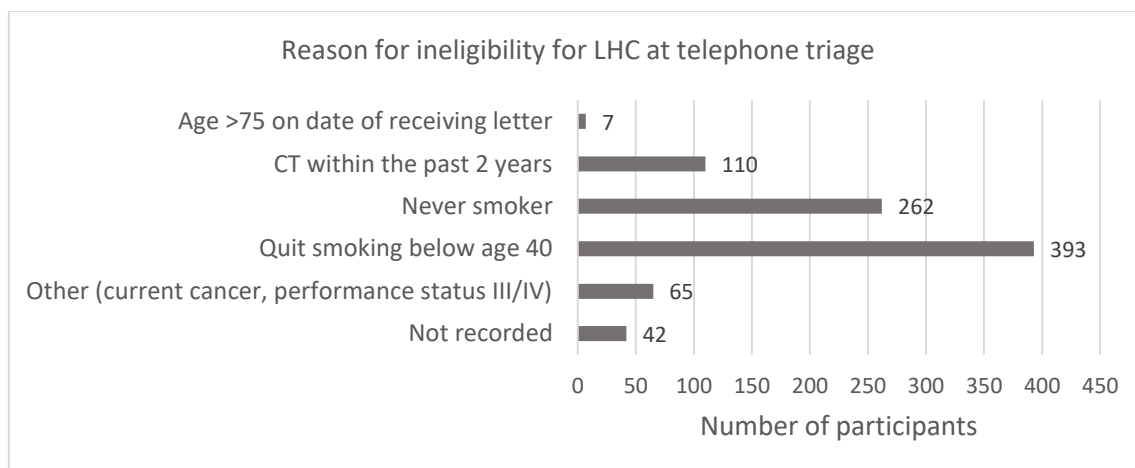


Figure 3.1 Reasons for ineligibility for a LHC at the telephone triage stage.

Overall, excluding those participants for whom letters were returned and the ineligible participants, 8366 potential participants were invited for a LHC [217].

3.2.1.2 Uptake from the first invitation letters, second invitation letters and phone calls

As per precedent, uptake is reported as a proportion of all potentially eligible participants (Section 2.9.2.1) [79]. Of the 8366 potentially eligible participants, 1590 (19.0%) individuals responded to the first invitation letter and were offered a LHC appointment. Of 2322 potential participants sent a second letter, 78/2322 (3.4%) responded and made an appointment for a LHC. Of the participants who received a second letter, 1003/2322 (43.2%) were also telephoned and offered an appointment, and 67/1003 (6.7%) made an appointment for a LHC. In addition, 114 participants who had not received a second appointment letter were telephoned, of whom 14/114 (12.3%) made an appointment for a LHC. Consequently, a total of 159 participants took up a LHC only after a second invitation letter or phone call. Therefore, in total, 1749/8366 (20.9%) participants made appointments for LHCs [217].

In view of low uptake from second letters and telephone calls, a decision was taken by the project operations group to discontinue second invitations and redirect resources to the initial invitation and appointment letter [217].

3.2.2 Demographic profile of LHC participants

The baseline demographic characteristics of all participants opting in for a LHC are shown in Table 3.1.

The Index of Multiple Deprivation (IMD) is an overall measure of deprivation, combining seven different domains of deprivation (income deprivation, employment deprivation, education skills and training deprivation, health deprivation, crime, barriers to housing and services, living environment deprivation) [220]. It is widely used as a surrogate measure of socioeconomic status in the UK.

Within England there are 32844 defined neighbourhood areas, which are ranked between 1 (the most deprived) and 32844 (the least deprived). These are divided into 10 equally sized groups, with decile 1 representing the 10% of most deprived areas in the country and decile 10 representing the least deprived areas in the country. IMD scores are, by convention, reported in quintiles rather than deciles [112, 221]. A publicly accessible database is available online, through which IMDs and corresponding deciles can be obtained using a postcode search tool [222].

Total number of individuals responding to invitation to LHC		1749
Age:		
Mean age (SD)		67.4 (4.46)
Median age (Range)		67 (60-76 ¹)
Gender (%):		
Female		795 (45.5)
Male		954 (54.5)
Smoking status (%):		
Never smoker		3 ² (0.2)
Ex-smoker		1322 (75.6)
Current smoker (cigarettes)		404 (23.1)
Current smoker (other – e.g. cigars)		17 (1.0)
Not recorded		3 ³ (0.2)
Ethnicity (%):		
White		1309 (74.8)
Black (non-hispanic)		45 (2.6)
Hispanic		7 (0.4)
Asian		107 (6.1)
Other (includes mixed race)		70 (4.0)
Prefer not to say		6 (0.3)
Unknown		205 ⁴ (11.7)
Prior diagnosis of COPD (%):		
Yes		150 (8.6)
No		1406 (80.4)
Unknown		193 ⁴ (11.0)
IMD Quintile (%):		
1 (most deprived)		179 (10.2)
2		475 (27.2)
3		438 (25.0)
4		348 (19.9)
5 (least deprived)		308 (17.6)
IMD not available		1 (<0.1)

Table 3.1 Baseline demographic data for all participants who opted in for a LHC appointment.

¹ Eligibility for a LHC was determined by the participants age at the data of CSU data extraction. If participants advised the administrative team on the telephone prior to the appointment that they had turned 76 years of age, they were not offered an appointment. However, a number of participants attended appointments having recently turned 76, despite the telephone triage. Between August 2018 and February 2019, upon attending, these participants were told that they were not eligible for a LHC. In February 2019, the protocol was changed such that if these participants attended LHCs, a LHC should be carried out. This accounts for the upper age of 76.

² At telephone triage, these participants should not have been offered a LHC appointment; however, due to smoking status not being confirmed at the telephone triage stage, these three participants attended LHCs, but did not undergo a LHC after confirming that they were never smokers.

³ These three participants did not attend their appointment, therefore smoking status was not confirmed.

⁴ These participants either did not attend their appointment or attended their appointment and were subsequently found to be ineligible for a LHC.

3.2.3 Overall attendance and non-attendance rates

One thousand six hundred and five of 1749 (91.8%) participants booking an appointment attended a LHC. Of these, 54/1605 (3.4%) were acutely unwell upon attendance with a respiratory tract infection (n=25), acute cough (n=22) or acute cough and respiratory tract infection (n=7) and were offered a LHC 6 weeks later. Forty-three of the 54 participants (79.6%) reattended six weeks later. The remaining 11/54 (20.4%) participants received a non-attendance letter after missing their follow-up appointment but did not book another appointment.

One hundred and forty-four participants of 1749 responding to an invitation to a LHC did not attend their LHC appointment (8.2%). The demographic characteristics of attendees compared to non-attendees are shown in Table 3.2. Attendees were more likely than non-attendees to be ex-smokers ($p<0.001$) and of higher socioeconomic status ($p<0.001$). Considering only the 159 participants who took up the offer of a LHC after a second letter or phone call, 29/159 participants (18.2%) did not attend their appointment. Participants who booked an appointment after a second letter or phone call were more likely to be non-attendees than those who booked after the initial letter ($p<0.01$).

	Attendees Number (%)	Non-attendees	<i>p</i> value
All attendees	1605	144	
Gender:			
Female	723 (45.0)	72 (50.0)	0.25
Male	882 (55.0)	72 (50.0)	
Age:			
Median age (IQR)	67 (63-69)	66 (63-67)	0.10
Smoking status (%):			
Ex-smoker/Never smoker	1240 (77.3)	85 (59.0)	<0.001
Current smoker	365 (22.7)	56 (38.9)	
Unknown (all non-attendees)	0 (0)	3 (2.1)	
IMD:			
Median (IQR)	16279 (10236-23651)	12535(8812-18122)	<0.001
IMD quintile (median)	3	2	

Table 3.2 Demographic characteristics of attendees and non-attendees. IQR = Interquartile range

3.2.3.1 Confirmation of eligibility for a LHC upon attendance

Upon attendance, 52/1749 (3.0%) participants were ineligible for a LHC. Telephone triage had failed to exclude these participants prior to booking an appointment. The reasons for ineligibility for a LHC are shown in Figure 3.2.

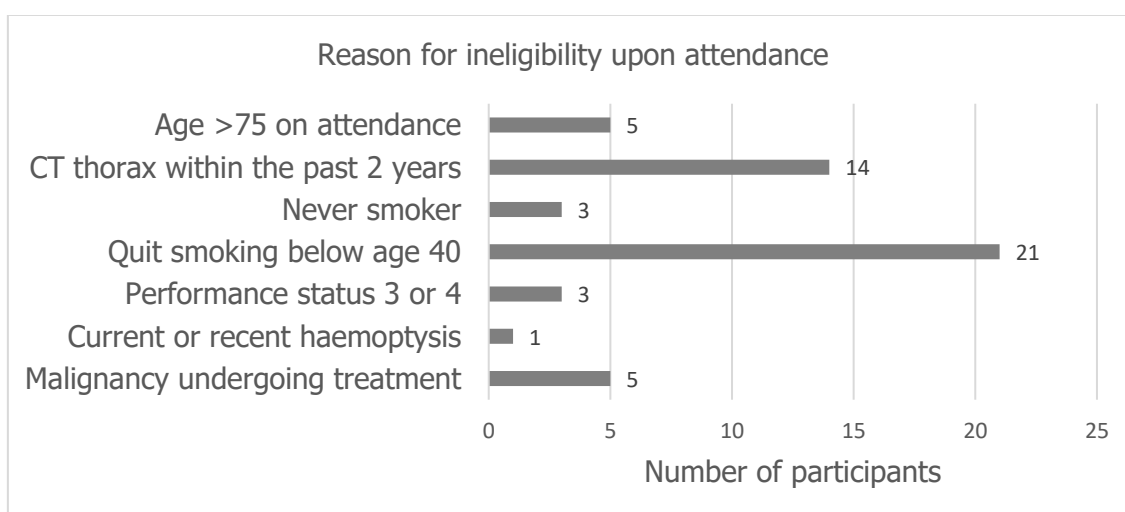


Figure 3.2 Reason for ineligibility for a LHC upon attendance.

One participant with haemoptysis was referred directly to a respiratory clinic. The remaining participants were discharged without having a LHC. Excluding the 11 participants who were acutely unwell and did not attend a 6-week follow-up appointment and the 52 participants who were not eligible upon attendance, 1542 participants attended LHCs and had a risk score calculation. Figure 3.3 summarises the participant pathway to the point of receiving a LHC.

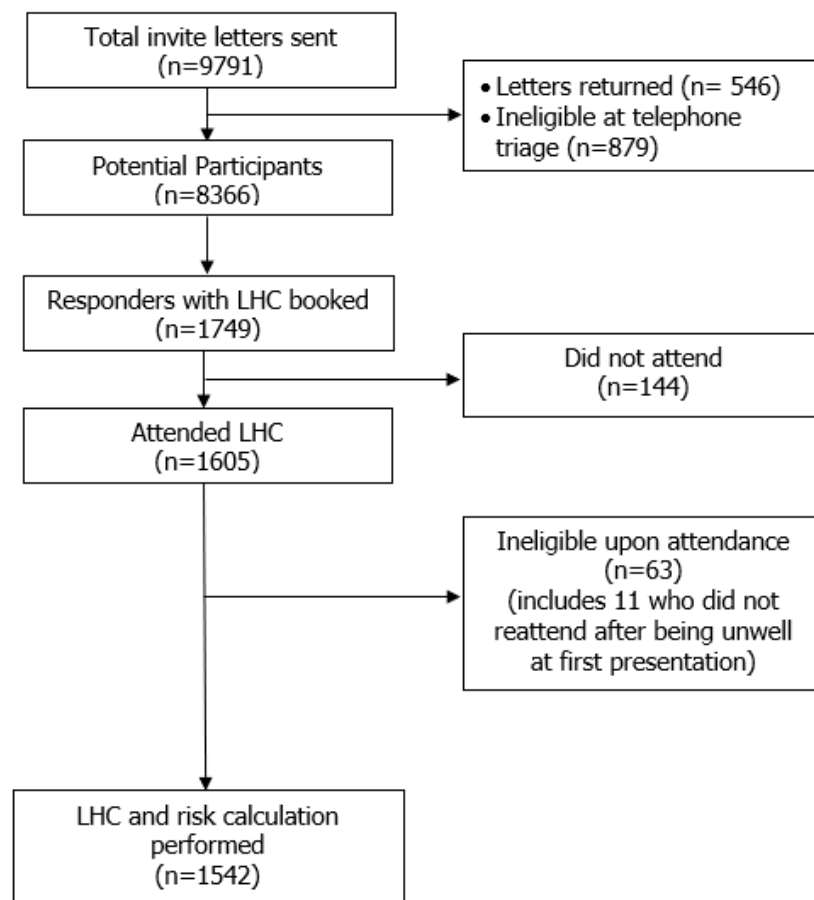


Figure 3.3 Participant pathway to the point of receiving a lung LHC (adapted from [217]).

3.2.4 Risk profile of LHC participants who had a risk score calculated

All 1542 participants who attended and were eligible for a LHC agreed to a risk score calculation. A summary of the risk profile, including the demographic characteristics pertaining to the $PLCO_{m2012}$ and LLP_{v2} risk scores of the 1542 participants for whom a risk score was calculated, is shown in Table 3.3.

In total, 1506/1542 (97.7%) participants had a $PLCO_{m2012}$ risk score calculated. Twenty of the remaining 36 participants had never smoked cigarettes and therefore did not obtain a $PLCO_{m2012}$ risk score. The remaining 16 participants had incomplete $PLCO_{m2012}$ datapoints in the LHC database resulting in only a LLP_{v2} score being calculated.

One thousand, one hundred and fifty-nine of 1542 (75.2%) participants who had a risk score calculated were eligible for a LDCT scan. Six hundred and thirty-seven of 1159 eligible participants (55.0%) met both the $PLCO_{m2012}$ and LLP_{v2} risk thresholds. Seventy-one participants of the 1159 eligible participants (6.1%) qualified for a scan only by meeting the $PLCO_{m2012}$ risk score; 451/1159 (38.9%) of participants qualified for a scan only by meeting the LLP_{v2} threshold. Fourteen of the 1159 participants (1.2%) eligible for a CT scan declined the offer of a scan.

Participant demographic variable	Relevant risk model	Participant response	Result
Age: Mean age, years (SD)	PLCO and LLP		67.4 (4.5)
Personal history of cancer: Number (%)	PLCO and LLP	Yes	200 (13.0)
Family history of lung cancer: Number (%)	PLCO and LLP	Yes – early onset ≤60 Yes – late onset >60 No	95 (6.2) 199 (12.9) 1248 (80.1)
Ethnicity: Number (%)	PLCO	White Black (non-Hispanic) Hispanic Asian Other (includes mixed race) Prefer not to say	1307 (84.8) 45 (2.9) 7 (0.5) 107 (6.9) 70 (4.5) 6 (0.4)
Education level†: Number (%)	PLCO	<O-Level O-Level A-Level Some university Degree Postgraduate Not recorded	311 (20.2) 325 (21.1) 273 (17.6) 179 (11.6) 284 (18.4) 169 (11.0) 1 (0.1)
BMI: Median (IQR)	PLCO		27.2 (24.2-30.1)
Smoking status: Number (%)	PLCO	Ex-smoker Current smoker	1188 (77.0) 354 (23.0)
Average number of cigarettes smoked/day*: Mean (SD)	PLCO		16.8 (11.6)
Duration smoked, years (cigarettes only): Mean (SD)	PLCO		34.6 (12.3)
Years ago quit smoking (all participants): Mean (SD)	PLCO		11.7 (10.3)
History of COPD, emphysema or chronic bronchitis: Number (%)	PLCO	Yes	265 (17.2)
History of COPD, emphysema, bronchitis, TB or pneumonia: Number (%)	LLP	Yes	449 (29.1)
Gender: Number (%)	LLP	Male Female	844 (54.7) 698 (45.3)
Asbestos exposure: Number (%)	LLP	Yes	171 (11.1)
Duration smoked, years : Number (%)	LLP	1-19 20-39 40-59 60 or more	106 (6.9) 819 (53.1) 608 (39.4) 9 (0.6)
Lung cancer risk PLCO: Median (IQR)* PLCO: Median: participants with lung cancer only (IQR) PLCO ≥1.51%: (Number (%))* LLP: Median (IQR) LLP: Median: participants with lung cancer only (IQR) LLP ≥ 2.0%: Number (%) PLCO ≥1.51% and/or LLP ≥ 2.0%: Number (%)			1.37 (0.52-3.07) 3.77 (1.53-7.76) 707/1506 (46.9) 3.41 (1.81-6.39) 8.54 (4.22, 11.0) 1088/1542 (70.6) 1159/1542 (75.2)

Table 3.3 Demographic profile and risk profile of 1542 participants who attended a LHC and had a risk score calculated. Adapted from [217]. *Data are for 1522 cigarette

smokers. Non-cigarette smokers (n=20) and those missing PLCO_{m2012} data parameters (n=16) did not receive a PLCO_{m2012} score. *PLCO_{m2012} scores were calculated for 1506 participants. SD= standard deviation; IQR = interquartile range.

3.2.5 LDCT scans performed at baseline

In total 1145/1542 participants (74.3%) underwent CT at baseline. One thousand and eighty-two of 1145 participants (94.5%) had a LDCT scan on the same day as their completed LHC (range 0-58 days). Those who had a 6-week delay to their LHC because of acute illness upon first presentation are regarded as having had a completed LHC at their second attendance and are not included amongst those who did not have a same day LDCT. Sixty-three of 1145 screened participants (5.5%) did not have a scan on the same day as their completed LHC. The median delay amongst these 63 participants was 7 days (Interquartile range (IQR) 2-15 days, range 1-58 days). Reasons for not having a CT scan on the same day as a LHC were not recorded but included unwillingness to wait for a CT scan at the fixed site, difficulty in registering patients remotely at the mobile site on the hospital requesting system and a technical failure of the mobile CT scanner on one day.

3.2.5.1 Baseline scan doses

Effective doses for baseline scans performed on the Siemens Edge CT scanner at the RBH fixed site scanner and the GE Optima 660 CT scanner at the mobile unit are shown in Table 3.4. At both sites, the median effective doses were well below 2mSv recommended by NHSE [109].

Scanner (Location)	Median effective dose (mSv)	Interquartile range
Siemens Edge (Fixed site)	0.86	0.74-1.00
GE Optima 660 (Mobile)	1.47	0.96-2.09

Table 3.4 Summary of baseline scan doses at the mobile and fixed sites.

3.2.6 LDCT scan outcomes

3.2.6.1 Positive, negative and indeterminate scans, recall rates and false positive rates

Data pertaining to scan outcomes is summarised in Figure 3.4.

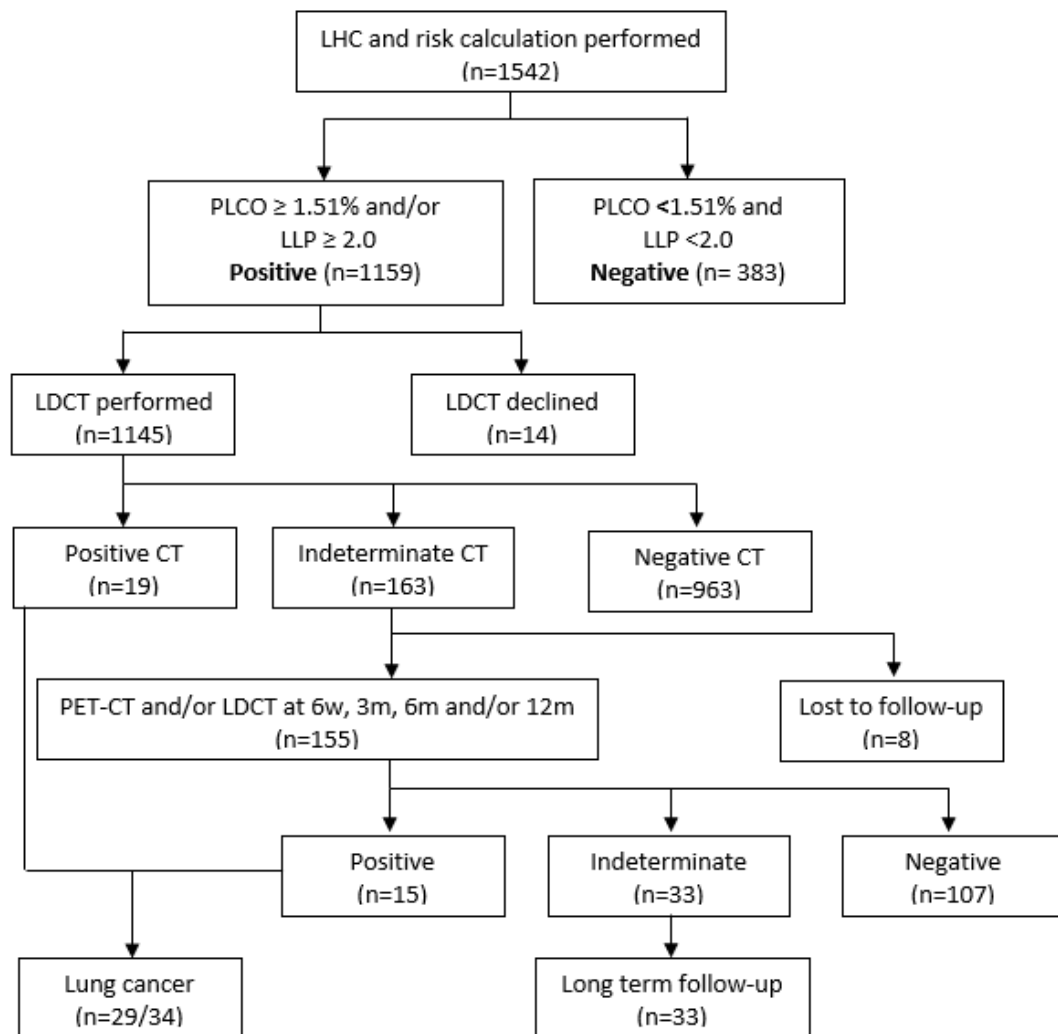


Figure 3.4 Outcomes following the LHC risk score calculation and subsequent LDCT scans (edited from [217]).

Positive scans

To reiterate, a baseline scan was considered positive if the scan resulted in a referral to the lung MDT for consideration of invasive investigations or treatment (Section 2.6.3.1). At baseline, 19/1145 (1.7%) participants had a positive scan resulting in further

invasive investigations or treatment for lung cancer. Of these, 16 participants had a PET-CT scan showing FDG activity suspicious for lung cancer (Brock score >10%). One participant was referred to the lung MDT with suspected multifocal indolent lung cancers characterised by SSNs, but did not undergo PET-CT; one participant was referred directly to the respiratory clinic with suspected lung cancer, for pleural aspiration. One participant declined PET-CT and was lost to follow-up.

In addition to the 19 positive baseline scans, 15/1145 (1.3%) participants had a positive scan result at a 6-week, 3-month, 6-month or 12-month follow-up LDCT. Therefore, a total of 34/1145 (3.0%) participants were referred to the lung MDT for consideration of further diagnostic investigation. Of these, 29/34 (85.2%) were subsequently diagnosed with lung cancer, discussed below.

Negative scans

Nine hundred and sixty-three of 1145 scanned participants (84.1%) had negative baseline scans, requiring no further follow-up. A further 107/1145 (9.3%) participants were discharged after 6-week, 3-month, 6-month or 12-month of follow-up imaging following resolution of nodules, or because of confirmed volumetric stability of nodules at 12 months of follow-up.

Indeterminate scans

At baseline, 163/1145 (14.2%) scanned participants had an indeterminate nodule requiring imaging follow-up. Eight participants were lost to follow-up. One hundred and twenty-two participants were subsequently reclassified as positive (n=15) or negative (n=107) cases following imaging follow-up. At 12 months of follow-up, 33 participants remained in the screening programme for ongoing surveillance of SSNs requiring long term follow-up (n=31) or because of solid lesions not amenable to volumetric analysis at 12 months of follow-up (n=2).

Recall rate

The total recall rate was 182/1145 scanned participants (15.9%) [217]. This included 19 participants with a positive CT at baseline, who underwent subsequent invasive investigations and 163 participants recalled for imaging follow-up following an indeterminate baseline CT.

False positives

As previously described (Section 2.9.2.5), false positive cases were individuals undergoing invasive investigation following positive LDCT scans and/or PET-CT imaging, who were not subsequently diagnosed with lung cancer. Five participants who were not subsequently diagnosed with lung cancer were investigated with PET-CT (n=4), ultrasound guided aspiration of the thorax (n=1), bronchoscopy +/- biopsy or endobronchial cryobiopsy (n=3), endobronchial ultrasound (EBUS) (n=2), percutaneous CT guided biopsy (n=2) and video-assisted thorascopic surgery (VATS) (n=1). Consequently, 5 of the 34 (14.7%) participants referred to the MDT for invasive investigation for suspected lung cancer were false positive cases. This comprised 5/1145 (0.4%) of participants having an initial baseline scan.

3.2.6.2 Lung cancer diagnoses and treatment

Details of all lung cancers detected during the LDCT pilot are given in Table 3.5.

ID	Sex	Age	PS	TNM(8)	Stage	Pathological type	Outcome	PLCO _{m2012}	LLP _{v2}
1	F	68	1	pT1bN0M0	IA2	Large cell neuroendocrine	Surgery	19.32	15.61
2	M	73	0	pT1bN0M0	IA2	Adenocarcinoma	Surgery	7.63	13.42
3	F	74	1	cT2bN2M0	IIIA	Adenocarcinoma	Systemic therapy and radiotherapy	10.42	6.02
4	F	74	0	cT4N2M1a	IVA	Small cell carcinoma	Systemic therapy ^(P)	1.23	3.91
5	F	74	1	cT2a(m)N0M0	IB	Adenocarcinoma	Microwave ablation and surveillance	1.58	18.06
6	M‡	71	1	cT4N2M0	IIIB	Small cell carcinoma	Systemic therapy ^(P)	25.34	35.92
7	F	69	0	pT1bN0M0	IA2	Adenocarcinoma	Surgery	1.52	2.97
8	M	66	0	cT4N3M0	IIIC	Small cell carcinoma	Systemic therapy	2.15	4.84
9	M‡	75	0	pT1b(2)N0M0	IA2	Adenocarcinoma	Surgery and Microwave ablation	4.77	8.54
10	M	74	0	pT2aN0M0	IB	Adenocarcinoma	Surgery	3.68	12.12
11	M	75	0	pT1bN0M0	IA2	Adenocarcinoma	Surgery	1.05	11.00
12	M	74	0	cT2aN1M0	IIB	Squamous cell carcinoma	Systemic therapy – declined	11.39	24.34
13	F	75	0	cT3N1M1a	IVA	Non-small cell cancer (not otherwise specified)	Systemic therapy ^(P)	1.45	4.22
14	F	63	2	cT3N3M0	IIIC	Adenocarcinoma	Unsuitable for treatment in view of PS	6.75	9.57
15	F	69	0	pT4N0M0	IIIA	Adenocarcinoma	Surgery + adjuvant systemic therapy	3.73	3.68
16	F	74	1	pT1cN0M0	IA3	Squamous cell carcinoma	Surgery	2.05	7.40
17	M	73	0	cT2aN1M1b	IVA	Squamous cell carcinoma	Systemic therapy ^(P)	1.04	8.54
18	M	65	0	pT1b(m)N0M0	IA2	Adenocarcinoma	Surgery	NA	8.69
19	M‡	67	0	cT1bN2M1b	IVA	Adenocarcinoma	Systemic therapy	3.80	9.91
20	F‡	67	0	N/A	IE	Pulmonary marginal zone lymphoma of MALT origin	Surgery	1.25	3.79
21	M‡	69	0	cT1aN0M0	IA1	Clinical	Surveillance (patient choice)	3.91	4.06

22	M‡	63	0	pT1bN0M0	IA2	Adenocarcinoma	Surgery	4.60	4.02
23	M‡	72	0	pT2aN2M0	IIIA	Adenocarcinoma	Surgery + adjuvant systemic therapy	8.15	11.67
24	F‡	72	0	pT2aN0M0	IB	Adenocarcinoma	Surgery	1.53	9.96
25	M‡	75	0	cT1a(2)N0M0	IA1	Adenocarcinoma	Surgery	8.17	9.95
26	F‡	64	0	cT1aN0M0	IA1	Clinical	Surveillance (patient choice/co- morbidity)	2.64	4.98
27	F	70	0	cT4N3M1b	IVA	Adenocarcinoma	Systemic therapy ^(P)	12.55	8.67
28	F‡	73	0	pT1bN0M0	IA1	Carcinoid, no atypical features	Surgery	4.65	6.39
29	F‡	73	0	pT1miN0M0	IA1	Adenocarcinoma	Surgery	1.08	3.90

Table 3.5 Clinical and pathological details of the 29 participants with lung cancer detected, including PLCO_{m2012} and LLP_{v2} risk scores of each participant diagnosed with cancer. PS, performance status. ^(P) palliative treatment ‡Diagnosed at 6-week, 3-month or 12-month follow-up scan. Updated from [217].

The stage distribution of lung tumours diagnosed in the West London targeted lung screening pilot was as follows: Stage I (17/29, 58.6%), Stage II (1/29, 3.4%), Stage III (6/29, 20.7%), Stage IV (5/29, 17.2%).

3.2.6.3 Non-lung neoplasms and significant incidental findings

Non-lung neoplasms and significant or urgent incidental findings, as well as their treatment are documented in Table 3.6.

ID	Diagnosis	Route of detection	Treatment	Outcome
	Non-lung neoplasms			
1	Follicular lymphoma	LDCT and subsequent PET-CT scan and CT biopsy for paraspinal masses	Chemotherapy	In remission at time of follow-up (11 months post diagnosis)
2	Anterior mediastinal mass	LDCT and subsequent PET-CT scan	None	Undergoing annual MRI imaging surveillance
3	Anterior mediastinal mass	LDCT and subsequent MRI scan	None	Pericardiac recess
4	Anterior mediastinal mass	LDCT	Keyhole resection following CT and PET-CT scan at 1 year demonstrating growth	Histopathology demonstrated a benign thymic cyst
5	Anterior mediastinal mass	LDCT and PET-CT	None	Undergoing annual MRI imaging surveillance
6	Breast lesion	LDCT and PET-CT	Wide local excision	Grade II ductal carcinoma in situ; in remission
	Significant incidental findings			
6	6.0 cm aneurysm of the ascending aorta	LDCT	Aortic valve, aortic root and ascending aorta replacement	Under ongoing surveillance following surgery

Table 3.6 Non-lung malignancies and significant incidental findings detected during the screening pilot.

3.2.6.4 Non-urgent incidental findings detected at LDCT

Incidental imaging findings initially managed within the screening pilot

Further imaging investigations within the screening pilot were carried out on 7/1145 participants who had incidental findings detected at LDCT as documented in

Table 3.7. Of these 7 participants, 3 were subsequently referred to primary or secondary care for further diagnostic investigations.

ID	Investigation	Finding	Diagnosis	Subsequent referral to primary or secondary/tertiary care
1	Renal ultrasound	Renal lesion	Simple cyst	No
2	Adrenal MRI	Adrenal lesion	Lipid poor adrenal adenoma	Primary care for biochemical tests
3	Adrenal CT	Adrenal lesion	Adrenal myelolipoma	Primary care with a view to urology referral
4	Liver ultrasound and contrast enhanced CT	Liver lesion	No diagnosis made	Secondary care: Diagnosed as atypical haemangioma
5	PET-CT scan	Anterior mediastinal lesion	Suspected thymic or thyroid cyst	No
6	MRI thorax	Anterior mediastinal lesion	Pericardial recess	No
7	3-month and 12-month interval CT	Lymph node enlargement	Benign intrathoracic nodal enlargement –radiological diagnosis of sarcoidosis	No

Table 3.7 Imaging investigations carried out within the screening pilot for benign diagnoses.

Incidental imaging findings referred to primary care

Sixty-five participants with moderate or heavy coronary calcification were referred to their GP with a recommendation to perform a QRISK® score. Twenty-one participants with other cardiac or vascular findings were referred to primary care with a recommendation for an echocardiogram (n=18) or with a view to a cardiology referral from primary care (n=3). Eight participants were referred to primary care for other miscellaneous findings on their LDCT scan, including diffuse bone sclerosis (n=1), hepatic and renal lesions (n=2), adrenal lesions (n=3), a chest wall cyst (n=1) and

infective consolidation (n=1). The decision to investigate some participants within the screening pilot, and refer others to primary care, was based upon the location of the participant and proximity to the RBH. Including those for whom initial work-up was carried out within the screening pilot, a total of 97/1145 (8.5%) participants were referred to primary care for further investigation of imaging findings detected on their LDCT scan.

Incidental imaging findings referred to secondary care

Forty-two of 1145 (3.6%) CT-screened participants were referred to secondary care, for non-urgent incidental findings detected on their LDCT, or subsequent follow-up scans. Indications for referral were ILAs (n=23), moderate or severe bronchiectasis (n=15; one participant had both an ILA and bronchiectasis), and miscellaneous imaging findings namely tracheal narrowing (from a thyroid goitre) (n=1), pleural thickening (n=1), an unexplained pleural effusion (n=1), suspected eosinophilic pneumonia (n=1) and an indeterminate liver lesion (n=1).

3.2.7 Time from baseline scan to CT report and results letter

One thousand one hundred and fourteen of 1145 (97.2%) scans were reported within 7 days of the LDCT (range 0-15 days). The median time until a report was provided was 2 days (IQR 1-3 days). One thousand one hundred and eleven of 1145 (97.0%) participants were sent a results letter within 2 weeks of their LDCT.

3.2.8 Time from CT to PET-CT scan

Twenty-seven of 1145 participants undergoing a baseline LDCT required a PET-CT scan following a baseline scan for findings suspicious of lung cancer. The median number of days between the baseline LDCT and PET-CT scan was 8 days (range 2-22 days).

3.2.9 Referrals to primary and secondary care following the LHC appointment

This section outlines the referrals to primary and secondary care as a direct result of the LHC appointment, rather than the LDCT scan. The outcomes of all referrals to primary and secondary care, including those related to imaging findings, are discussed in Chapter 4.

3.2.9.1 Referrals to primary care

Of 1542 participants having a LHC, 56 (3.6%) participants with obstructive spirometry and symptoms, namely chronic cough or breathlessness with no known diagnosis of COPD, were referred to primary care for a COPD assessment. In addition, 17/1542 (1.1%) participants (two of who had also been referred to secondary care for other reasons) were advised to visit their GP for non-respiratory red flag symptoms, as defined by NICE suspected cancer recognition and referral guidelines [197], following a negative LDCT screen. Ten participants reported fatigue, 4 participants reported chest pain and 3 participants reported weight loss.

3.2.9.2 Referrals to secondary care

One participant with haemoptysis was referred urgently to clinic for a contrast enhanced CT scan and clinical review, without having a full LHC.

Twenty-nine of 383 (7.6%) participants who were not eligible for a LDCT scan according to the LLP_{v2} or PLCO_{m2012} risk thresholds presented with red flag symptoms for lung cancer and were reviewed in clinic for these symptoms. Of these 22 had a chronic cough, 2 had cough and chest pain, 1 had cough and fatigue, 1 had fatigue, 1 had breathlessness, 1 had fatigue and breathlessness and 1 had recurrent infections.

3.2.10 Significant unexpected and adverse events

Table 3.8 documents details of unexpected and adverse events which took place during the pilot, including the resultant harms, and actions taken to prevent these from recurring.

Date and site	Adverse event	Resultant harm	Actions taken
Image acquisition: Unintended radiation exposure			
05/09/18 RBH	Extra scan performed due to failure to scan lung bases	Additional effective radiation dose: 0.3mSv	Radiographer advised and aware at the time
10/01/19 Harefield Hospital	Extra scan performed as a duplicate scan request had inadvertently been made	Additional effective radiation dose: 4.9mSv	Phone call to patient to apologise for error. Incident reporting form (DATIX) completed
Image acquisition: delay in image acquisition			
06/02/19 Mobile	Fire at mobile scanner: 4 patients required to return at a later date	Inconvenience to patient	Apology to patients
12/2/19 Mobile	Patient not scanned due to spinal fixation rods. Recalled for scan	Inconvenience to patient	Radiographer informed
Delay or failure to transfer images from mobile unit to the RBH			
13/02/19 Mobile	Failure of transfer of images to MeVis, due to failure at mobile to give patient a hospital number	Two-week delay in CT report	Safety check to ensure that all patients scanned had CT report
14/02/19 Mobile	Failure of transfer of images to PACS/MeVis or compact disc. Patient assumed to have not had a scan	13-day delay in CT report	Feedback to Alliance to ensure all patients imaged have remote transfer of imaging and image transfer to compact disc
Communication of results			
27/11/18 RBH	Failure to send results letter to patient due to incorrect data entry on Infoflex®	Delay to patient receiving results	Phone call to patient. Incident (DATIX) form completed. Education provided to nurses regarding safe use of Infoflex®

Table 3.8 Significant unexpected and adverse events during the lung screening pilot.

3.2.11 Discussion

Data from the West London targeted lung screening pilot adds to evidence that lung cancer screening is both effective in detecting early lung cancer and feasible to deliver. Specifically, the West London pilot has showed that lung cancer screening can be delivered from a mobile site, as well as a fixed site, with near-immediate remote transfer of imaging from a remote unit and rapid turnaround times for reporting scans and results letters. Furthermore, with nodule management protocols incorporating PET-CT scans, these can be expedited without requiring MDT discussion or clinic attendance. Data from the West London pilot can be combined with that from other pilots to demonstrate the efficacy of screening. Although feasibility has been demonstrated in West London, elsewhere this will depend on local factors, including access to imaging (CT and PET-CT), reporting capacity, and LHC and administrative staffing levels, all of which contribute to rapid turn-around times and overall efficiency of pilots.

Overall prevalence of lung cancer in the West London targeted lung screening pilot was 2.5%, similar to other UK studies in which prevalence has ranged from 1.9% to 4.7% [79, 111, 112, 217]. Fifty-nine percent of lung cancers diagnosed within the West London pilot were Stage I at diagnosis, compared to 15% of lung cancers identified in the general population in England [223]. By comparison, 82.2% lung cancers presenting in Hillingdon between 2012-2018 were Stage III or IV at diagnosis [196]. Staging in the West London pilot was comparable to other similar studies in Europe [62, 78, 224].

Overall uptake for the West London targeted screening pilot was lower than in similar pilot studies carried out elsewhere within the UK. Uptake in a pilot in Manchester was 26.3% [79], and in the UKLS trial was 30.7% [70], both higher than the West London pilot. In Liverpool, uptake was 40% [112] and in the London-based Lung Screen Uptake Trial (LSUT), 52.6% [111, 124]. The invitation strategy and material used in the

West London pilot were similar to other LHC-based programmes in the UK, using an invitation sent on behalf of primary care practitioners, together with a patient information booklet [79]. The invitation strategy for the LSUT differed from the West London pilot with pre-invitations sent to participants as well as scheduled appointments [124]. Scheduled appointments meant that participants did not therefore have to opt-in to a LHC [124] and this may have contributed to high attendance. Strategic public engagement events in Manchester and Liverpool preceded the invitation letter for a LHC, and this may explain the high uptake in these pilots. For example, in Liverpool, “breathe easy” public events involving promotion of the Liverpool Healthy lung project were attended by over 2000 members of the public [225]. Similar events did not take place in London prior to the start of the first phase of the West London pilot. Ghimire *et al.* also reported significant uptake as a result of a second invitation letter and phone call. Sixty-five percent of attendees attended only after a second invitation letter or phone call [112]. This differed significantly from the West London pilot; only 159/1749 (9.1%) of participants opting in for a LHC in the West London pilot did so as a result of a second letter or phone call. Furthermore, in West London, this cohort were also statistically more likely to be non-attendees than those who had booked unprompted by a second reminder. Reasons for this are unknown; it is possible that those booking only for a LHC after a second letter or call were less interested and therefore more likely to be non-attendees.

Eligibility for a CT scan was higher in the West London targeted lung screening pilot than in a number of UK based previous trials including UKLS, Manchester and Liverpool, but comparable to the London-based LSUT trial. Participants in the UKLS and Liverpool pilots were eligible for a scan if they met or exceeded a 5% threshold for LLP_{V2} [70]; those in the Manchester pilot were eligible for a scan if they met the 1.51% threshold for $PLCO_{m2012}$ [79]. Participants in the LSUT were eligible for a scan if they met

the PLCO_{m2012} threshold of 1.51%, the LLP_{v2} threshold of 2.5% or USPSTF screening criteria [111]. The West London pilot used a LLP_{v2} threshold of $\geq 2\%$ and a PLCO_{m2012} of $\geq 1.51\%$, with participants being eligible for a scan if they met the threshold for either risk score. Analysis of the West London data showed that the LLP_{v2} threshold of $\geq 2\%$ was very much more permissive than the PLCO_{m2012} threshold of $\geq 1.51\%$, with 451/1159 (38.9%) participants eligible for a scan by virtue of meeting the LLP_{v2} threshold of $\geq 2.0\%$, but not meeting the PLCO_{m2012} threshold of $\geq 1.51\%$ [217]. By contrast, 71/1159 (6.1%) participants eligible for a LDCT met the PLCO_{m2012} only. Of importance, 6/29 (20.7%) participants with lung cancer were not eligible for a LDCT scan according the PLCO_{m2012} threshold of 1.51%, raising the question of the suitability of the use of PLCO_{m2012} risk model in isolation in a UK population. Although similar data regarding scan eligibility for participants with lung cancer has not been reported from the London-based LSUT, the median PLCO_{m2012} score in participants with lung cancer in that trial was higher (5.68%) than in the West London pilot (3.77%) [111]. This is likely to reflect the invitation strategy of the LSUT; participants were required to have stopped smoking within the previous 7 years (compared to age over 40 in the West London pilot). This difference in recruitment strategy is likely to be responsible for the higher median PLCO_{m2012} score for all participants in that trial.

NHSE screening guidelines propose use of the LLP_{v2} model with a threshold of $\geq 2.5\%$ to determine eligibility for a scan, in conjunction with the PLCO_{m2012} model (with a threshold of 1.51%) [109]. Had this LLP_{v2} threshold been utilised, 88 of 1145 (7.7%) participants who had a scan by virtue of having a LLP_{v2} risk threshold ≥ 2 and < 2.5 (and not meeting the PLCO_{m2012} risk threshold), would not have been eligible for a scan. With a LLP_{v2} threshold of 2.5, 1057/1145 participants would have been scanned and 29 cancers diagnosed, corresponding to 2.7% of those scanned. This equates to a reduction in the number needed to scan at baseline/lung cancer from 39.4 participants to 36.4

participants. An associated cost saving of just under 8% on baseline scans would have been achieved, with no cancers being missed.

A recent modelling study assessed the performance (calibration and discrimination) of eight risk models, including LLP_{v2}, LLP_{v3} and PCLO_{m2012}, in over 270000 current and former smokers enrolled in three longitudinal population studies in the UK [226-229]. All 8 models showed calibration >1, indicating that the models predicted more lung cancer cases (or deaths) than were observed over the time period specified for the risk prediction model. Comparing the performance of PCLO_{m2012}, LLP_{v2} and LLP_{v3} in this study, LLP_{v3} was best calibrated amongst the largest of the three cohorts of participants analysed (expected lung cancers/observed lung cancers 1.20). Discrimination ranged between AUC 0.77-0.84, depending on which longitudinal study cohort was analysed and with which model. Although the overall difference in discrimination was considered modest, discrimination was higher for PCLO_{m2012} than LLP_{v2} or LLP_{v3} [226]. Further prospective studies will therefore be required to assess the performance of LLP_{v2}, LLP_{v3} and PCLO_{m2012} models in the UK population.

3.3 Comparison of mobile scanner and fixed (hospital) site scanner

3.3.1 Uptake for a LHC at the mobile and fixed site scanner

Eight thousand three hundred and sixty-six potentially eligible participants were invited for LHCs at the two sites. Of these 5135/8366 (61.4%) were invited to the fixed site and 3231/8366 (38.6%) were invited to the mobile scanner. One thousand and forty-seven of 5135 (20.4%) participants responded to an invitation to the fixed site, compared to 702/3231 (21.7%) of participants invited to the mobile site (p=0.14) [217].

3.3.2 Non-attendance at the mobile and fixed site scanner

One hundred and forty-four of the 1749 (8.2%) participants did not attend their booked LHC appointment. Of these, 96/1047 (9.2%) did not attend their appointment

at the fixed site and 48/702 (6.8%) did not attend their appointment at the mobile site (p=0.08).

3.3.3 Demographic and socioeconomic comparison of participants invited to the mobile and fixed site scanner

Table 3.9 shows some demographic characteristics of participants booking appointments at the mobile site and fixed site scanners. Responders at the fixed site were of lower socioeconomic status and were more likely to be current than ex-smokers [217].

	Fixed site	Mobile site	<i>p</i> value
Total number responders (%)	1047 (59.9)	702 (40.1)	
Age:			
Median (IQR)	67 (63-71)	68 (64-72)	0.006
Gender (%):			
Female	555 (53.0)	399 (56.8)	0.115
Male	492 (47.0)	303 (43.2)	
Smoking status (%):			
Ex-smoker/Never smoker	775 (74.0)	550 (78.3)	0.049
Current smoker	269 (25.7)	152 (21.7)	
Unknown (all non- attendees)	3 (0.3)	0	
IMD			
Median (IQR)	12535.5 (8587-17239)	24011(15789-28997)	<0.001
IMD quintile (median)	2	4	

Table 3.9 Demographic and socioeconomic characteristics of participants booking LHC appointments at the two sites [217]. IQR = interquartile range.

Figures 3.5a and b show the IMD distribution of all responders (who booked a LHC) and non-responders at the two sites.

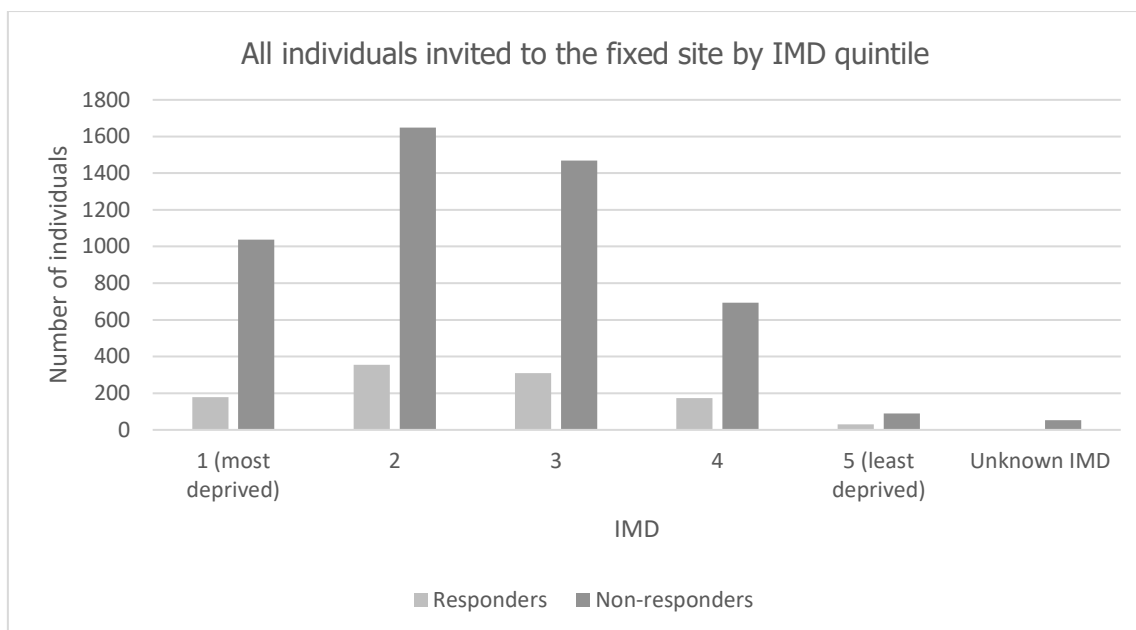


Figure 3.5a IMD profile of all participants invited to the fixed site.

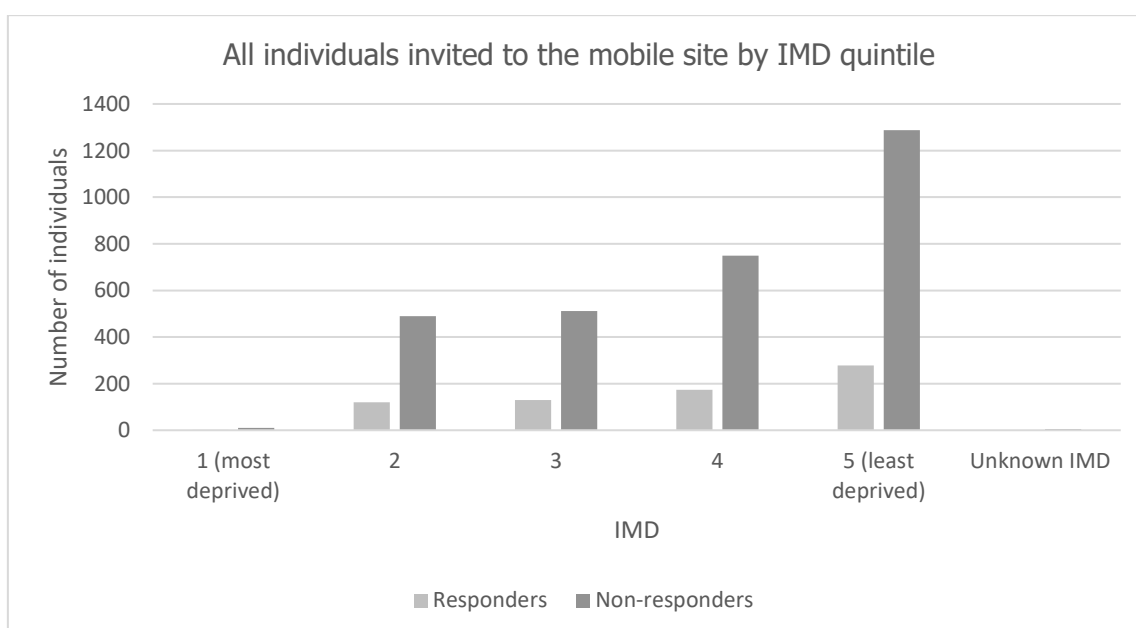


Figure 3.5b IMD profile of all participants invited to the mobile site.

IMD data were available for all but 59 participants invited for LHCs. Postcodes of these 59 participants were unavailable (n=9) or not recognised by the available online calculator (n=50) [222]. These individuals were excluded from statistical analysis. Figures 3.4a and b demonstrate that the socioeconomic profile of the potential participants invited to the fixed site and mobile site were very different. Almost 2/3

(66.3%) of those invited to the mobile scanner were within quintiles 4 and 5, whereas 53.3% of those invited to the fixed site scanner were within quintiles 1 and 2.

Uptake as a proportion of all those invited is shown in Figures 3.6a and b.

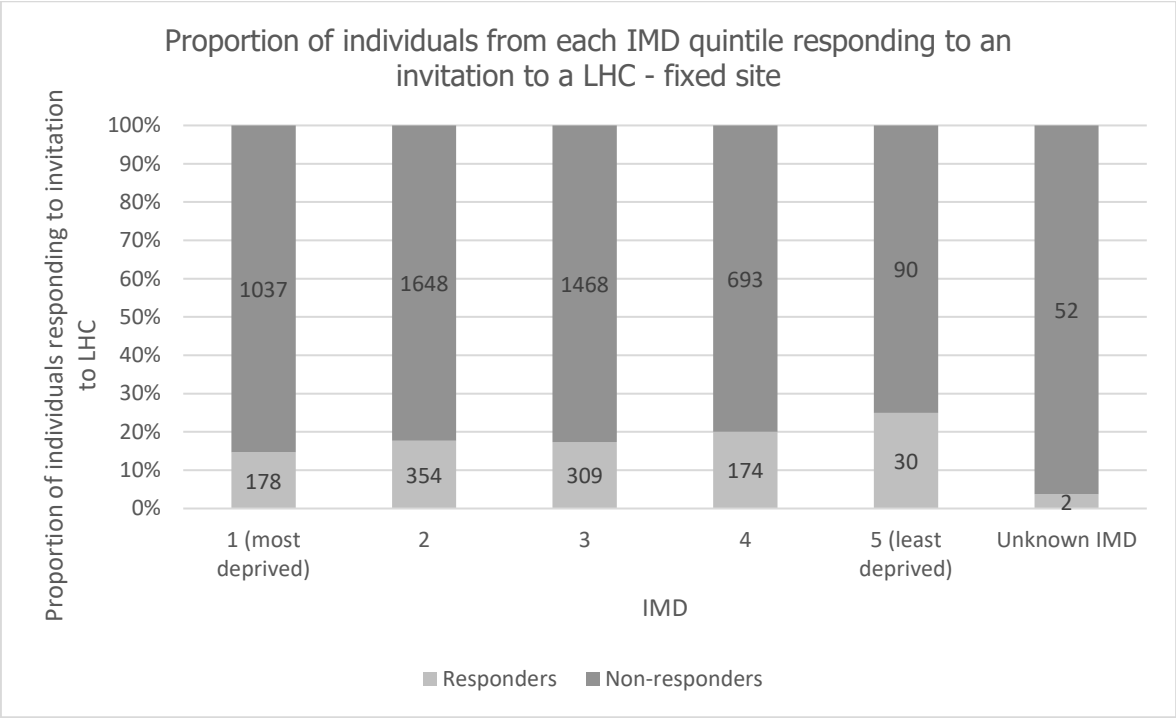


Figure 3.6a IMD profile of all responders and non-responders invited to the fixed site.

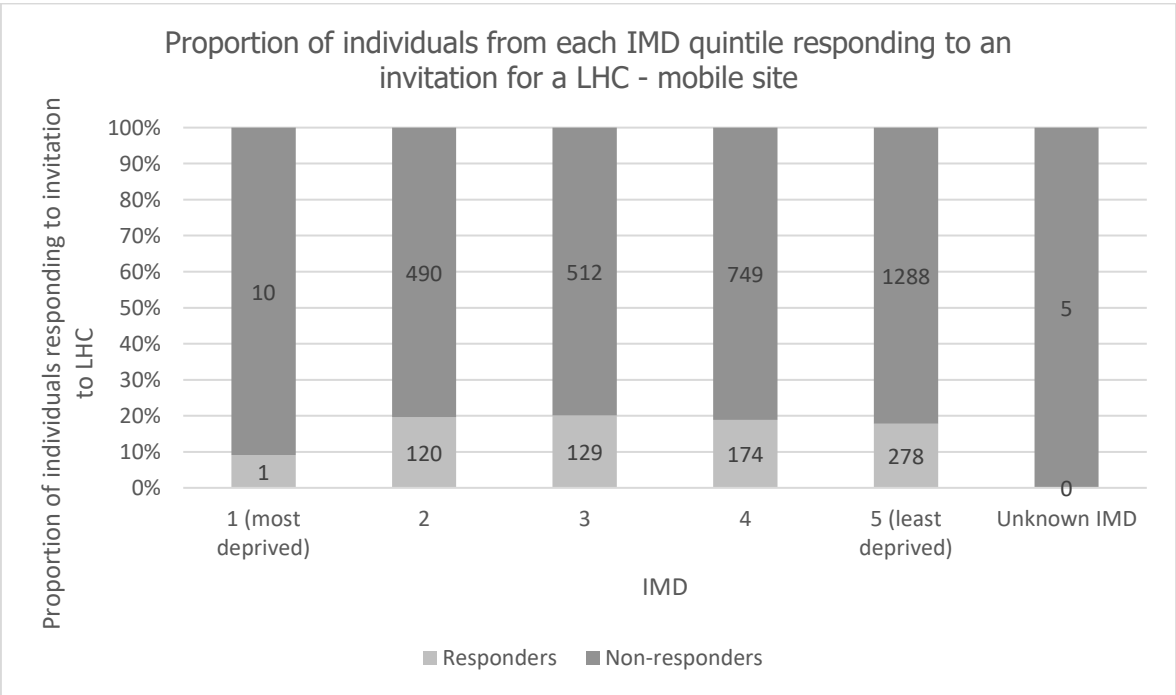


Figure 3.6b IMD profile of all responders and non-responders invited to the mobile site.

Small numbers of invitees in IMD quintile 1 at the mobile site preclude statistical comparison of uptake between the two sites within this socioeconomic group. However, when combining uptake in IMD quintile 1/2 across the two sites, there is no statistical difference in uptake between the mobile and fixed sites ($p=0.07$). Similarly, within IMD quintiles 3 and 4, no statistically significant difference in uptake was observed. Only in the least deprived IMD quintile (5) were participants invited to the fixed site more likely to respond positively to an invitation for a LHC than those invited to the mobile site ($p=0.048$).

At the fixed site, a positive response to invitation rose with an increase in socioeconomic status (χ^2 test for trend, $p=0.01$), but this was not true for the mobile site (χ^2 test for trend, $p=0.22$).

3.3.4 Distance travelled to scanner for participants invited to the mobile and fixed site scanner

The distance needed to travel to a LHC appointment was calculated as the distance from the postcode of a participants' GP (as a surrogate for home address) and the postcode of the site appointment [217]. The median (IQR) distance needed to travel to the fixed site was 3.3km (2.6-4.1km), compared to 6.4km (4.2-8.6km) to the mobile scanner ($p<0.01$) [217]. Histograms of the distance needed to travel by participants to the hospital and mobile sites are shown in Figures 3.7a and b. Fifteen participants who needed to travel more than 11km to the fixed site were erroneously given appointments at the fixed site despite living in the London Borough of Hillingdon, of whom 3 did not attend their appointments.

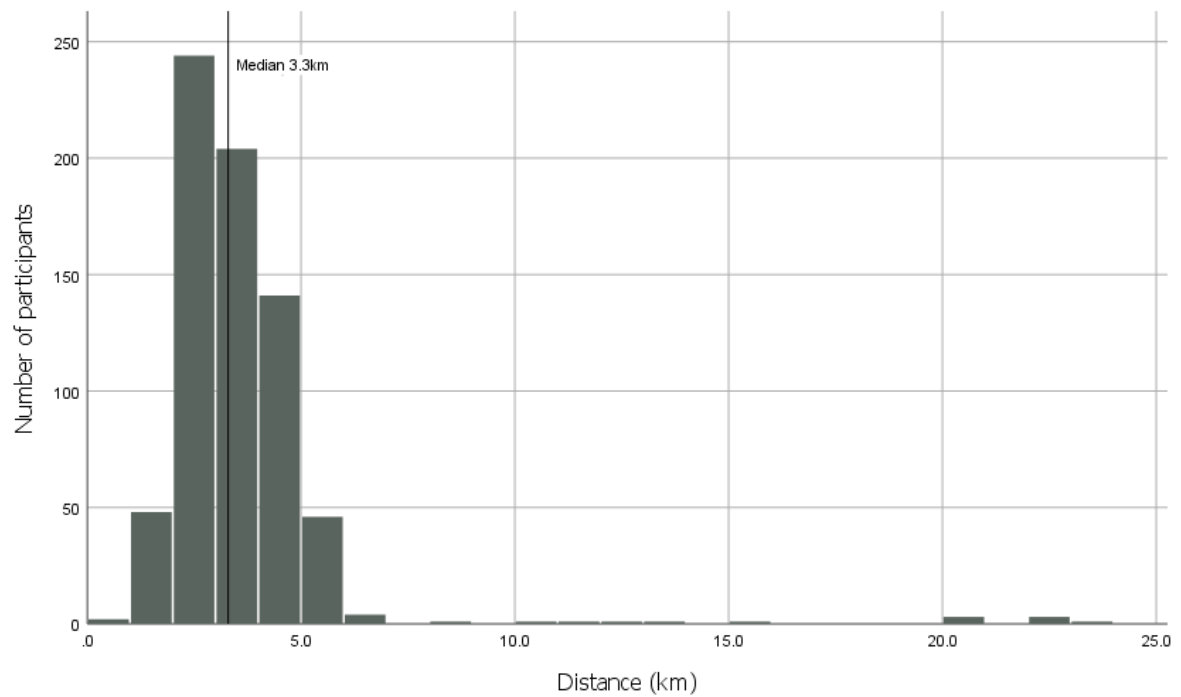


Figure 3.7a Histogram demonstrating distance from home (km) to the fixed site for all 1047 participants who booked a LHC at the fixed site.

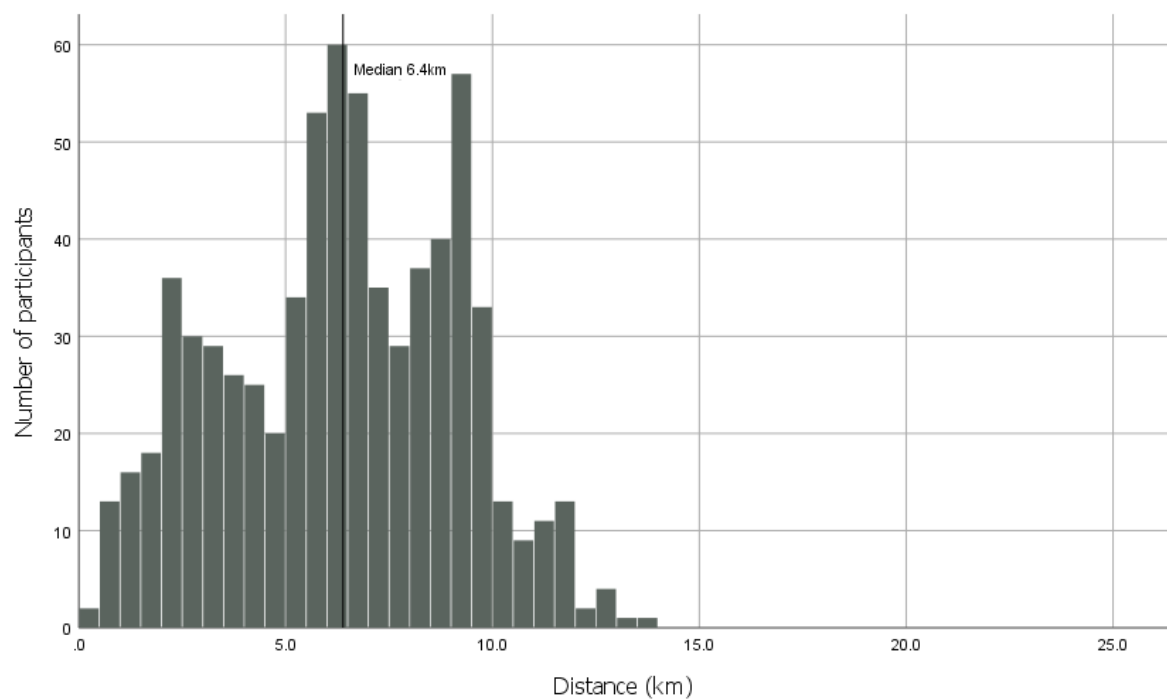


Figure 3.7b Histogram demonstrating distance from home (km) to the mobile site for 702 participants who booked a LHC at the mobile site.

3.3.5 Participant satisfaction surveys at the mobile and fixed sites

Of 1542 participants who attended and completed a LHC, 418 (27.1%) completed the feedback questionnaire developed by IPSOS MORI in conjunction with the project operations group. Of these 364/418 (87.1%) completed the survey fully; the remaining 54/418 (12.9%) participants did not include the site of their LHC on their survey response (n=19/54, 35.2%) or did not answer all questions relating to the suitability of the venue or access to the venue (n=35/54, 64.8%) [217].

Two hundred and seventy-four of 911 (30.1%) attendees at the fixed site who were eligible for a LHC completed the survey, compared to 90/631 (14.3%) at the mobile site ($p < 0.01$) [217]. Table 3.10 shows satisfaction survey responses relating to the LHC and CT scanner location.

Survey question	Participant response	Mobile Site (Proportion (%))	Fixed site (Proportion (%))	<i>p</i> value
The venue was easy to get to	Strongly Agree/Agree	81/90 (90.0)	262/274 (95.6)	0.05
	Don't know [‡] , Disagree or Strongly Disagree	9/90 (10.0)	12/274 (4.4)	
The venue felt like the right place to have a health check	Strongly Agree/ Agree	86/90 (95.6)	265/274 (96.7)	0.61
	Don't know, Disagree or Strongly Disagree	4/90 (4.4)	9/274 (3.3)	
I had enough privacy at the venue	Strongly Agree/ Agree	88/90 (97.8)	268/274 (97.8)	0.98
	Don't know, Disagree or Strongly Disagree	2/90 (2.2)	6/274 (2.2)	
I had enough space at the venue	Strongly Agree/ Agree	86/90 (95.6)	270/274 (98.5)	0.09
	Don't know [‡] , Disagree or Strongly Disagree [‡]	4/90 (4.4)	4/274 (1.5)	

Table 3.10 Comparison of participant satisfaction survey results between fixed site and mobile site scanner locations. [‡]indicates no responses in that category (from [217]).

3.3.6 Discussion

Mobile screening units have been advocated as a means to increase uptake for lung cancer screening [79, 230]. Mobile units are widely used for other screening programmes including breast and cervical cancer screening in Europe and the USA [231]. Various potential benefits of mobile screening have been described, including increasing convenience, reducing travel times for participants [79], reaching remote populations who would otherwise not have access to screening, and offering flexible hours of operation [231]. A lack of willingness to visit a hospital has also been reported as a reason for non-participation in lung cancer screening [232].

Results from a questionnaire-based analysis of reasons for participation in the second round of the Manchester pilot, showed that almost three quarters of participants felt that scanner location was an important factor in their decision to attend screening, and 23% reported that they would be less likely to attend a hospital-based setting compared to a mobile scanner [230]. However, those questioned had already previously attended screening in a mobile unit and might be considered to be highly engaged in the screening process, having returned for a second round of scans. Therefore, those interviewed are likely to have represented a cohort biased towards community-based screening simply by having previously engaged with it. The West London targeted lung screening pilot is the first lung cancer screening programme to prospectively compare uptake and attendance in a community-based and hospital setting. No statistically significant difference in either uptake or attendance were demonstrated in this pilot. Additionally, our patient satisfaction survey indicated that over 95% of participants attending a LHC at both sites felt that the location was the "right place for a health check". However, two important differences between these two cohorts in the West London pilot merit further discussion.

Firstly, the socioeconomic status of those invited to the mobile and fixed site scanners was very different; almost 2/3 of those invited to the mobile scanner were of high socioeconomic status (IMD quintiles 4 and 5). The previous UKLS study showed that those of low socioeconomic status were less likely to engage with screening; the positive response rate in the UKLS study ranged from 19.6% (IMD quintile 1) to 34.2% (IMD quintile 5) [221]. In the West London pilot, there was a small but statistically significant increase in uptake with increasing socioeconomic status at the fixed site, ranging from 14.7% in IMD quintile 1, to 25% in IMD quintile 5. The magnitude of the improvement in uptake was less than that shown in the UKLS study [221]. No improvement in uptake with increasing socioeconomic status was observed at the mobile site. Uptake amongst those of the highest socioeconomic status (IMD quintile 5) at the mobile site was only modest at 17.8%, compared to 34.2% in this cohort in the UKLS study. Uptake in quintile 5 at the mobile site was lower than quintiles 2 (19.7%) and 3 (20.1%). Comparing uptake within each IMD quintile across the two sites, no significant improvement was seen in uptake at the mobile site, compared to the fixed site. In this regard, the evidence from the West London pilot does not support the argument that uptake is significantly improved by use of a mobile scanning unit.

Secondly, invitations to participants in the London Borough of Hillingdon covered a larger geographical area than those in the London Borough of Hammersmith and Fulham, explaining the increased distance needed to travel by participants to the mobile site. Ali *et al.* in their analysis of factors affecting uptake in the UKLS trial, found that “travel”, including distance, lack of public transport and the cost of transport or parking, was the most frequently cited reason for non-participation [217, 232]. Furthermore, even those of high socioeconomic status, who were more likely to participate in screening than those of lower socioeconomic status, were deterred by travel issues [232]. Similarly, Maheswaran *et al.* reported a small decrease in uptake for breast screening associated

with increasing driving distance to a mobile site [217, 233]. In the West London pilot, a greater proportion of participants attending the fixed site scanner agreed with the statement "The venue was easy to get to" ($p=0.05$), likely reflecting frequent and reliable public transport links in central West London. This was in spite of the scarcity of public parking at the fixed site. One limitation is that travel times to the mobile and fixed sites were not compared, as these are likely to vary significantly depending upon mode of transport used and the time of day of attendance for a LHC. Overall, comparison of both uptake and attendance and participant satisfaction surveys suggests that geography, travelling distance and ease of access may be more important factors in influencing uptake than the scanner location in a fixed or mobile site *per se*.

In practice, a multitude of factors are likely to determine willingness to attend lung cancer screening. These may include car parking availability for car drivers, the cost of taxi or lift services for the immobile, and public transport proximity and frequency. A straightforward analysis comparing distance travelled to the scanner does not adequately convey the nuances of accessibility to transportation for either cohort. A future analysis might compare absolute travel time and travel cost from home to either scanner; this data might be obtained from participants at the time of the LHC. Similarly, knowledge of mode of transport used to attend an appointment would be informative. A potential benefit of use of a mobile unit is that scanning capacity is immediately available, which may not always be the case within a NHS hospital setting.

3.4 Summary

- The West London targeted lung screening pilot adds to previous evidence showing that targeted lung cancer screening through a LHC model, with use of risk-based prediction models, can identify lung cancer with a prevalence of $>2.0\%$ and is capable of identifying participants with early-stage disease most amenable to curative therapy.

- The West London pilot demonstrates the low risk of harm related to lung cancer screening. Using a low-dose CT protocol results in low radiation related risk. With volumetry-based nodule management protocols, recall rates for indeterminate nodules can be kept low and invasive investigations for benign disease and false positive tests can be minimised.
- The LLP_{v2} risk model (at a threshold of either 2.0% or 2.5%) is a more permissive risk model than the PLCO_{m2012} model in selecting participants for screening in a UK population. Data from the West London pilot suggest that the PLCO_{m2012} may not perform adequately in isolation from a second risk model in the UK setting, with 20.7% of participants with lung cancer in the West London pilot, being below threshold for a LDCT scan according to PLCO_{m2012}.
- Similar levels of uptake, attendance and satisfaction were demonstrated at a mobile and fixed site scanner, suggesting that participant attendance may be driven by factors in addition to CT scanner location. Distance and ease of access to the scanner may be more important factors in determining uptake than the location of the CT scanner, *per se*. In an urban setting, a community based mobile scanner may be of little additional value, where distances travelled to the scanner are likely to be shorter.
- Overall uptake for lung cancer screening in the West London pilot was lower than in other similar pilots. Further work is needed to explore reasons for this and devise strategies to engage hard-to-reach cohorts.

CHAPTER 4: DOWNSTREAM CONSEQUENCES OF IDENTIFYING INCIDENTAL AND OTHER NON-LUNG CANCER FINDINGS FROM THE WEST LONDON TARGETED LUNG SCREENING PILOT

4.1 Introduction

Lung cancer screening, when implemented through a LHC model, provides an opportunity to identify wider health issues in a cohort of smokers and former smokers. By virtue of age and smoking history, those attending LHCs are known to be at high risk of not only lung cancer, but also cardiovascular and respiratory disease [63, 73]. Additional health interventions resulting from the LHC are assumed to increase the cost-effectiveness of lung cancer screening [109], but to date, the cost of the further investigation or management of these wider health issues identified has not been quantified.

Two different aspects of the LHC enable identification of participants who may benefit from additional health interventions. Firstly, during the clinical consultation, symptomatic individuals (including those with red flag symptoms for lung cancer) and those with abnormal spirometry are identified. Secondly, for those eligible for LDCT, potentially significant incidental imaging findings may be identified, for which participants may require further investigation or clinical care. However, no previous studies from the UK have evaluated the downstream consequences of the LHC model for primary and secondary care. Specifically, little is known about the outcomes of referrals to primary and secondary care, whether recommendations made by screening pilots are implemented, or whether changes are made to patient management in the primary or secondary care setting which might influence patient prognosis.

The protocol for referring participants to primary and secondary care from the West London targeted lung screening pilot is described in Chapter 2.6.3. This is similar

to the subsequently published NHSE protocol and quality assurance guidelines [109, 189]. The number and proportion of participants referred to primary and secondary care were reported in Chapter 3 (Sections 3.2.6.3, 3.2.6.4 and 3.2.6.8) and these are reiterated in brief below.

The aims of this chapter are as follows:

- 1) To quantify the participant attendance rate at primary and secondary care appointments, following the LHC appointment.
- 2) To establish the implementation rate of recommendations for further investigations in primary care.
- 3) To quantify the number and proportion of participants referred to secondary care, following primary care appointments and investigations.
- 4) To quantify the proportion of participants undergoing a change in management initiated by primary or secondary care practitioners.
- 5) To estimate initial primary care costs resulting from recommendations made in LHC results letters in the West London pilot, including the cost of initial primary care appointments, investigations and subsequent secondary care referrals.
- 6) To estimate anticipated additional primary care costs which might have resulted from closer alignment to the NHSE protocol in areas where the West London pilot deviated from the NHSE protocol.

4.2 Methods

Follow-up of participants was performed as a service evaluation project and was registered accordingly at the Royal Brompton Hospital [234], with due consideration given to data protection requirements in line with Healthcare Quality Improvement Partnership guidelines [194]. Consent to contact participants following their LHC to discuss the outcomes of recommendations made to primary care was obtained during

the LHC and recorded in Infoflex®. Non-consenters were excluded from the analysis of outcomes of primary care referrals (Section 4.3.1).

4.2.1 Primary care data collection

Recommendations for further investigation or management of incidental clinical or imaging findings during the LHC were made in the LHC results letter to GPs, within 2 weeks of the LHC appointment. Participants similarly received results letters and were advised to visit their GP to discuss incidental clinical and imaging findings. The content and phrasing of the results letters to primary care and participants were approved by the project steering group and patient advisory group at the outset of the pilot study.

Between 3 and 9 months after the LHC appointment, primary care records of consenting participants were reviewed by the author in conjunction with primary care staff. Participants who had died or had moved out of area in the time between the LHC and primary care follow-up were considered 'lost to follow-up'. Where specific recommendations had been made to primary care, the following data were collected [234]:

- 1) Patient attendance rate in primary care following a LHC recommendation.
- 2) Implementation rate by primary care of recommendations arising from the LHC.
- 3) Proportion of participants with changes to management following investigations (including pulmonary rehabilitation or pharmacotherapy).
- 4) Subsequent secondary care referrals made by GPs either directly as recommended, or independently made by the GP.

Additionally, data were collected (GP attendances, investigations performed and outcomes) for participants who had been referred to GPs for red flag symptoms [234].

Although specific recommendations had been made for further investigations and referrals, data were also collected regarding additional referrals made or investigations requested which resulted indirectly from the LHC letter.

4.2.2 Secondary care data collection

Participants were referred directly to secondary care in accordance with the protocols described in Section 2.3.2.1 and Figure 2.2 (for red flag symptoms) and Section 2.6.3.3 (for incidental imaging findings). In summary, participants were referred directly to secondary care if they had i) any unexplained red flag symptoms for lung cancer and were ineligible for a LDCT scan, or ii) severe bronchiectasis on LDCT without a known diagnosis of bronchiectasis, or iii) interstitial lung abnormalities (ILAs) (>10% in extent) on LDCT without a known diagnosis of ILD, or iv) ILAs 5-10% in extent in association with restrictive spirometry.

Electronic hospital records were reviewed 12-18 months after referral to secondary care to ascertain:

- 1) Participant attendance rate at secondary care appointments.
- 2) New diagnoses resulting from secondary care.
- 3) Percentage of participants with changes to management following LHC recommendations.

4.2.3 Primary care costs resulting from LHC recommendations

Primary care costs for GP appointments and investigations were estimated from published sources, namely the Personal Social Services Research Unit (PSSRU) and NHS England Tariffs (2018/2019) [235] and Reference costs (2017/2018) [236]. Assistance in cost calculations were sought from a healthcare economics consultancy company (JB Medical Consultancy, Sudbury, UK). In the absence of a specific tariff for a community COPD review or community respiratory review, the cost incurred by the GP was based

on the cost of 'Respiratory Physiology – Full lung function testing' [236]. When a participant attended a primary care appointment, a single GP appointment was assumed.

Costs were also included if primary care physicians organised tests or made referrals as a result of the LHC outcome letter, even if the specific advice for recommendations made in the results letter was not followed exactly, to reflect real world practice. The cost of subsequent investigations performed in secondary care following the initial referral are not included in this analysis, which focuses on initial costs that can be attributed to a specific primary care practitioner.

An estimate is also provided of additional primary care costs which might result from closer alignment with the NHSE protocol. Areas where primary care costs might be expected to increase because of closer adherence to the protocol are shown in Table 4.1.

Clinical scenario	West London targeted lung screening pilot protocol	Recommended NHSE protocol
Moderate or severe bronchiectasis on LDCT	Secondary care referral	Primary care or secondary care referral (at discretion of local lung screening pilot) [189]
Red flag symptoms – ineligible for LDCT	Secondary care referral	Management according to NICE Guidelines (NG12): Suspected cancer recognition and referral 1) Chest radiograph +/- 2) 2 week wait referral [109]
Abnormal spirometry	Primary care referral only if obstructive spirometry associated with symptoms	All patients with abnormal spirometry to be referred to primary care [109]
Emphysema on CT	Inform patient of smoking related damage in results letter if emphysema >15%	Consider referral to local community respiratory team if emphysema >25%. Smoking cessation advice [189]

Table 4.1 Areas where the West London targeted lung screening pilot referral protocol deviates from the current NHSE referral protocol.

Modelled costs are based on a) the actual number of participants referred to secondary care in the West London pilot, who might otherwise have been sent to primary care physicians and b) those who were not referred to primary care in the West London pilot who may have been referred to primary care under closer adherence to the NHSE protocol. In modelling the additional cost to primary care which might arise from closer adherence to the current NHSE protocol, the following assumptions are made:

- 1) A similar proportion of participants would have attended primary care appointments as those who did attend primary care appointments in the West London pilot.
- 2) All participants with red flag symptoms, except haemoptysis, would have undergone a chest radiograph, organised from primary care. LHC attendees with haemoptysis would continue to be referred directly to secondary care from the screening pilot.

4.3 Results

4.3.1 Summary of all non-lung cancer referrals to primary and secondary care arising from the LHC

Figure 4.1 summarises all the non-urgent referrals to primary and secondary care resulting from the LHC or LDCT scan. In total, 233/1542 participants (15.1%) were referred to primary or secondary care for 241 indications.

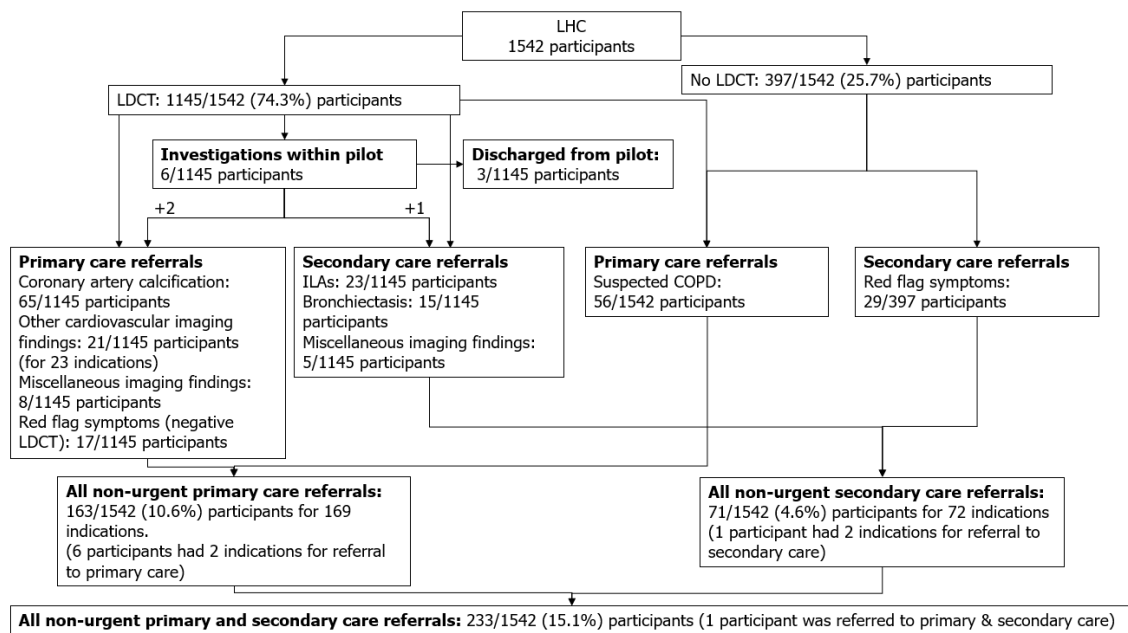


Figure 4.1 Summary of non-urgent primary and secondary care referrals resulting from the West London targeted lung screening pilot for non-lung cancer findings.

In addition to these non-urgent referrals, three urgent referrals were made directly to secondary care for participants with haemoptysis, a dilated aortic root and marked gastric wall thickening.

4.3.2 Primary care referrals

This section discusses all the outcomes of primary care referrals, categorised into the reason for referral. Four participants (4/163, 2.5%) referred to primary care did not consent to follow-up and therefore outcome data pertain to the remaining 159 participants consenting to follow-up [234]. Figure 4.2 summarises the number of referrals to, and attendances in, primary care amongst the 159 participants consenting to follow-up.

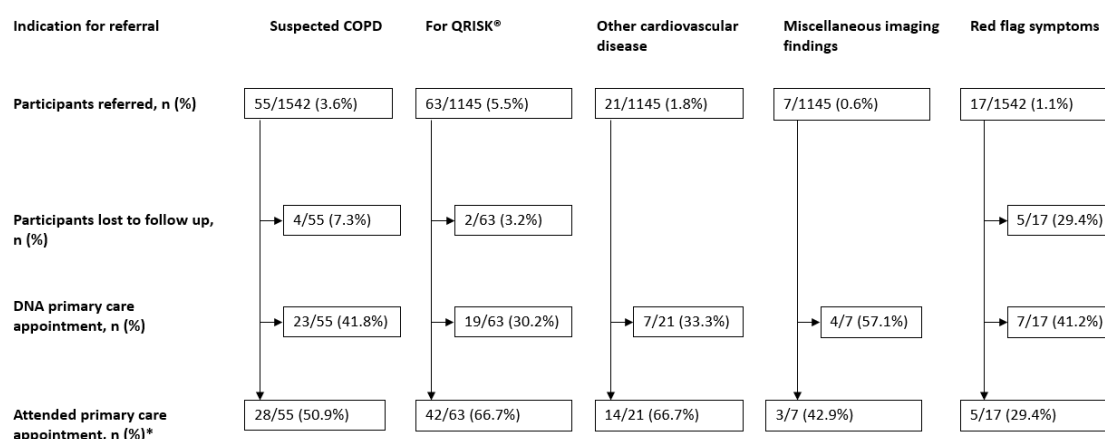


Figure 4.2 Summary of primary care attendances following referral from the LHC pilot [234].

4.3.2.1 Coronary artery calcification (CAC) for QRISK assessment

Sixty-five of 1145 (5.7%) CT-screened participants with moderate or severe CAC were referred to primary care with a recommendation to perform a QRISK® assessment (Section 2.6.3.2). Of 63 participants consenting to follow-up, 2/63 (3.2%) participants were lost to follow-up having moved out of area. Primary care records showed that 9/63 (14.3%) were already taking lipid lowering therapy at the time of their LHC, although this had been denied during the LHC appointment. One of these participants made an appointment with their GP despite already taking lipid lowering therapy. The remaining 8 did not visit their GP.

Forty-one of 63 (65.1%) participants not already taking lipid lowering therapy were reviewed in primary care as recommended. Of these, 30/41 (73.2%) had a QRISK® score calculated [234]. The median (range) QRISK score was 20 (11.2 - 43.3). All forty-one participants were offered statin therapy. Twenty-three of 41 (56.1%) participants who attended primary care appointments started or restarted statin therapy initiated by the GP, 8 of whom did so without having a QRISK® calculation at their GP appointment. One participant started statin therapy following a referral to a rapid access chest pain

clinic, independent of the LHC recommendation. Sixteen of 41 (39.0%) participants declined statin therapy offered to them.

In addition to the eight participants already taking a statin, who were not reviewed in primary care, a further eleven of 63 (17.5%) participants who were not taking a statin had not been reviewed in primary care despite the recommendation in the GP and patient letters.

Although a recommendation was made for a QRISK®, 4 participants were also referred for cardiology assessment from primary care. The cardiologist commenced statin and aspirin therapy for one participant. Further outcomes for the remaining 3 participants are unknown.

In summary, of 63 consenting participants referred to their GP for a QRISK® score, 42/63 (66.7%) attended GP appointments, 30/63 (47.6%) had a QRISK® score and 24/63 (38.1%) commenced new pharmacotherapy as a result of the LHC [234].

4.3.2.2 Cardiac valve calcification and/or aortic or pulmonary artery dilatation, for echocardiogram or CT angiography

Twenty-one of 1145 (1.8%) CT screened participants were referred to primary care for suspected cardiovascular disease on LDCT not related to CAC [234]. All participants consented to GP follow-up. Eighteen echocardiograms were recommended for participants with cardiac valve abnormalities, mild aortic dilatation or suspected pulmonary hypertension. Three non-urgent secondary care referrals were recommended in participants with moderate aortic dilatation (n=2) and heavy aortic valve calcification (n=1).

Fourteen participants (14/21, 66.7%) attended a GP appointment. Echocardiograms were performed in 8/18 (44.4%) participants, one of whom was subsequently referred to cardiology due to critical aortic stenosis. Of the three

participants in whom non-urgent secondary care referrals were recommended, two (with aortic dilatation) were referred to cardiothoracic or vascular surgeons; both underwent CT imaging. The third participant with heavy aortic valve calcification had an echocardiogram, but not a secondary care referral.

Two out of the 18 (11.1%) participants for whom echocardiography was recommended were referred to cardiology in secondary care, although this had not been the recommendation from the LHC team; one participant went on to have a CT coronary angiogram rather than an echocardiogram.

4.3.2.3 Suspected COPD – for community COPD or respiratory review

Fifty-six of 1542 (3.6%) participants who had a LHC were referred for a community COPD or respiratory review in view of obstructive spirometry and respiratory symptoms. All had denied a previous diagnosis of COPD in their LHC. One participant did not consent to GP follow-up. Fifty-five participants are therefore included in the forthcoming analysis.

Four of 55 (7.3%) participants were lost to follow-up and 28/55 participants (50.9%) attended GP appointments. The remaining 23/55 (41.8%) were not reviewed in primary care [234]. Of the 55 participants referred, 5/55 (9.1%) already had a diagnosis of COPD or asthma which had been denied by participants during the LHC.

Of the twenty-eight who visited their GP, 21/28 (75.0%) had a subsequent community COPD review; 14/55 participants referred to primary care (25.5%) received a new diagnosis of COPD, 2/55 (3.6%) were newly diagnosed with asthma [234] and 3/55 (5.5%) were deemed not to have COPD following further investigations. Two of the participants who visited their GP were amongst the five participants who already had a diagnosis of COPD or asthma. Of the 16 participants diagnosed with a new respiratory diagnosis, 6/16 (37.5%) began pharmacotherapy and 1/16 (6.3%) began pulmonary

rehabilitation [234]. A change in management therefore occurred in 7/55 (12.7%) of those referred.

4.3.2.4 Miscellaneous referrals for incidental imaging findings

Eight referrals and recommendations were made to primary care regarding incidental imaging findings; one participant did not consent to GP follow-up. Of the remaining 7 referrals, 2 of these participants had already undergone some further imaging investigations within the LHC pilot and were subsequently referred to primary care. The reasons for referral and outcomes are shown in Table 4.2.

LDCT finding	Recommendation	GP action	Outcome
<i>Participants referred directly to GP</i>			
Diffuse bone sclerosis	PSA, renal function and full blood count	Blood tests performed	No ongoing referral or treatment
Suspected chest infection	Primary care review for consideration of antibiotic treatment	Reviewed	No treatment given
Suspected polycystic liver and kidney disease	Liver and renal function tests	Not seen by GP	No ongoing referral or treatment
Suspected chest wall cyst	Ultrasound	Not seen by GP	
Adrenal lesion – likely adrenal myelolipoma	For urology referral	Referred to urology	No further action
<i>Participants initially investigated in the LDCT project and subsequently referred to the GP</i>			
Adrenal lesion – suspected lipid poor adenoma (MRI)	Biochemical testing	Not seen by GP	No ongoing referral or treatment
Adrenal lesion – suspected adrenal myelolipoma (Adrenal protocol CT)	Referral to endocrine surgeons for assessment	Not seen by GP	No ongoing referral or treatment

Table 4.2 Outcomes of incidental non-urgent imaging findings detected at LDCT in participants who were referred to primary care.

4.3.2.5 Red flag symptoms

Seventeen participants with red flag symptoms for lung cancer and a LDCT not demonstrating lung cancer were referred to primary care [234]. Five participants (5/17,

29.4%) attended GP appointments. Of these, 1 was referred for a colonoscopy and breast screen. The remaining 4 had no further investigations. None of the participants reviewed in primary care were diagnosed with cancer. Upon contacting 7 of the remaining 12 participants, 2 denied previously reporting the red flag symptom, and 4 considered the symptom not of significance and had not attended a GP appointment. One participant sought private medical care and was diagnosed with a neurological condition. Five participants could not be contacted and were lost to follow-up.

4.3.2.6 Summary of outcomes of primary care referrals following identification of non-lung cancer findings

Overall attendance in primary care

One hundred and sixty-three of 1542 participants undergoing a LHC (10.6%) were advised to visit their GP following the LHC for 169 indications. Four participants did not consent to follow-up. Outcome data were therefore sought for 159 participants. Sixty-eight participants (42.8%) did not attend or communicate with primary care regarding the specific indication with the LHC letter. Ninety-one of 159 participants attended primary care appointments (2 participants for 2 indications) and therefore attendance rate at primary care following LHC recommendations was 57.2% [234].

Implementation rate of recommendations

One hundred and forty-eight specific recommendations (for QRISK® n=63; respiratory review n=55; echocardiograms n=18; secondary care referrals n=4, miscellaneous tests or reviews for other imaging findings n=8) were made in one hundred and forty-two participants referred to primary care, who consented to follow-up. Additionally, seventeen participants were advised to visit their GP for red flag symptoms. Of the one hundred and forty-eight specific recommendations, 46/148 (31.1%) were actioned as suggested in the LHC letter.

Changes in patient management resulting from primary care referrals

Amongst the 159 participants consenting to follow-up, one hundred and eighteen referrals in 115 participants were made for either CAC detected on LDCT, or for a community COPD review. These 118 referrals comprised over 70% (118/165, 71.5%) of the referrals to primary care, in 115/159 (72.3%) participants consenting to follow-up. Of these, 30 participants (30/115, 26.1%) began pharmacotherapy for COPD or elevated cardiovascular risk. One participant referred for a community COPD review began pulmonary rehabilitation.

Twenty-one of 159 (13.2%) participants were referred for valvular heart disease or vascular disease. Amongst this cohort, one participant was subsequently referred via cardiology for aortic valve surgery following a non-urgent referral to primary care for an echocardiogram. Four participants remain in long term follow-up following GP initiated secondary care referrals for vascular disease (aortic dilatation) (n=2) or following echocardiograms (n=2). None of the seven participants referred with other incidental imaging findings had long term patient management changes.

Amongst the 17 participants referred to primary care for red flag symptoms, no long-term changes to patient management were made, except in one participant diagnosed, through private medical care, with a neurological condition.

A change in patient management therefore occurred in 37/159 (23.3%) participants following recommendations to primary care from the West London pilot. This comprised 2.4% (37/1542) of participants attending a LHC.

Secondary care referrals independently initiated by primary care following LHC recommendations

Six cardiology referrals were made by primary care although specific recommendations for referral to secondary care had not been made. Specific outcomes of these secondary care referrals are unknown.

4.3.3 Secondary care referrals

Seventy-five referrals to secondary care were made directly from the LHC pilot in 74/1542 participants (4.8%), 1 of whom had two reasons for referral (interstitial lung abnormalities and bronchiectasis). Three participants were referred for urgent follow-up; the remaining 71 participants were referred for non-urgent appointments. Section 3.2.6.4 and 3.2.8.2 of the previous chapter quantified the number of non-urgent referrals to secondary care as a result of the LDCT scan and LHC appointment respectively, and these are summarised in Figure 4.3. This chapter reports attendance rates, diagnoses and outcomes for participants referred directly to primary care from the LHC pilot. The further investigation of these participants was at the discretion of the respiratory physician or other secondary care consultant reviewing the participant and was not stipulated in the protocol for the LHC pilot.

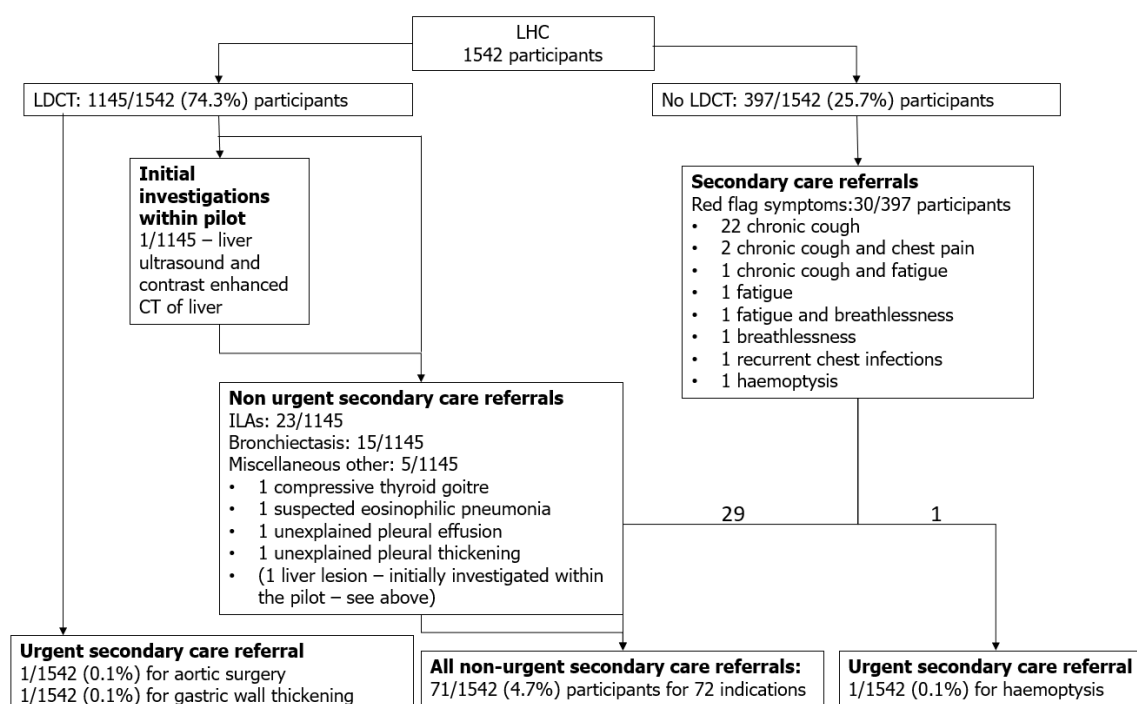


Figure 4.3 Summary of reasons for referral to secondary care from the West London targeted lung screening pilot for non-lung cancer findings.

4.3.3.1 Participants referred to secondary care as a result of findings detected at LDCT *Interstitial lung abnormalities (ILAs)*

Twenty-three of 1145 (2.0%) CT-screened participants with ILAs, who did not report a prior diagnosis of ILD or lung fibrosis at the LHC, were referred to secondary care. Two participants subsequently reported having a previous diagnosis of an ILD, which they had not reported at the time of the LHC and were discharged from secondary care without further investigation. One participant did not attend a clinic appointment and was lost to follow-up. The diagnoses and treatment of the remaining 20 participants is given in Table 4.3.

Patient number	Diagnosis	Management
1	Idiopathic pulmonary fibrosis	Pharmacotherapy
2-3	Idiopathic pulmonary fibrosis	Pulmonary rehabilitation
4-6	Idiopathic pulmonary fibrosis	Surveillance
7	NSIP	Surveillance
8	Sarcoidosis	Pharmacotherapy
9	Chronic hypersensitivity pneumonitis	Pharmacotherapy
10-12	Smoking-related ILD	Smoking cessation advice
13	Smoking-related ILD	Surveillance
14	Unclassifiable ILA likely related to gastro-oesophageal reflux	Pharmacotherapy
15-20	Unclassifiable subclinical ILAs	Surveillance

Table 4.3 Diagnosis and treatment of participants with ILAs who attended secondary care for follow-up.

In summary, 4 participants referred with ILAs are taking pharmacotherapy, and 2 participants had pulmonary rehabilitation. All 20 participants remain under long-term follow-up within secondary care.

Bronchiectasis

Fifteen participants with bronchiectasis on their LDCT were referred directly to secondary care for investigation and management. One of these participants also had an ILA (Table 4.3, patient 14) and was managed with pharmacotherapy. One participant did not attend an appointment and was lost to follow-up. Of the remaining 13 participants with bronchiectasis, 1 was treated with pharmacotherapy, 2 with pharmacotherapy and a course of pulmonary rehabilitation and 6 with chest physiotherapy. Lifestyle advice was given to two participants, and one participant was advised to have an annual flu and pneumococcal vaccination. One participant had no specific treatment or advice given to them.

Other incidental imaging findings requiring secondary care follow-up

Five participants were referred to secondary care for non-urgent follow-up of incidental imaging findings. One participant with a compressive thyroid goitre was

reviewed in secondary care, was found to be asymptomatic and was discharged without further investigations. One participant with flitting ground-glass opacities on serial CTs was investigated with bronchoalveolar lavage. No definite diagnosis was made, and the participant remains under follow-up without treatment. One participant with diffuse bilateral pleural thickening was referred to clinic; this was found to be longstanding after retrieval of historical imaging from another institution and the participant was discharged without treatment. One participant was reviewed due to unilateral pleural thickening; this was attributed to previous infection and not further investigated. Finally, one participant with a focal liver lesion was investigated initially by the LHC team with ultrasound and contrast enhanced CT. As the lesion remained indeterminate following these investigations, the participant was referred to a hepatobiliary centre for further assessment. Subsequent imaging investigations concluded that the lesion was likely to represent an atypical benign haemangioma. No treatment was given.

Two participants with incidental imaging findings were referred for urgent secondary care follow-up. One participant was referred due to aortic root dilatation. Following further CT imaging, this participant underwent an aortic root replacement and valve replacement. A second patient was referred to a gastroenterologist for stomach thickening. An endoscopy found no significant abnormalities and no malignancy.

In summary, of the 7 participants referred to secondary care for incidental LDCT imaging findings other than ILAs or bronchiectasis, four had further investigations, whilst one required surgical treatment. One participant remains under ongoing follow-up.

4.3.3.2 Participants ineligible for a LDCT scan and referred to secondary care for red flag symptoms

Chronic cough

Participants who were ineligible for a CT scan were most commonly referred directly to clinic because of chronic cough, with or without other symptoms, including chest pain or fatigue (25/30, 83.3%). Participants with chronic cough were investigated by chest radiograph (n=4), thoracic CT (n=22), blood tests (n=8), lung function tests (n=7), an echocardiogram (n=1), an ECG (n=1) and oesophageal manometry (n=1).

Of the 3 participants who did not have a CT scan, 2 participants had chest radiographs, and 1 had no additional imaging. Cough was attributed to reflux in two cases and mild bronchiectasis in 1 participant. Of these 3 participants, 1 was offered pulmonary rehabilitation (but declined), 1 was given lifestyle advice, and 1 was discharged without advice or treatment.

In 5/22 (22.7%) participants who had a CT, a possible cause of chronic cough was identified on imaging: interstitial lung disease (pleuro-parenchymal fibroelastosis (PPFE)) was detected in one participant, mild bronchiectasis in three participants and a large hiatus hernia presumed to be causing reflux in one participant. Of those diagnosed with bronchiectasis, one was treated with pharmacotherapy, and one was treated with physiotherapy and pharmacotherapy; the third participant was not offered treatment. Lifestyle modifications were recommended for the participant with a large hiatus hernia and presumed reflux. The participant with PPFE was referred onwards to the interstitial lung disease department for further management. There were no subsequent changes to patient management. In the remaining 17 participants imaged with CT, no cause of cough was demonstrated on imaging.

Five of 17 participants who had a normal CT scan did not attend subsequent clinic appointments and were lost to follow-up. The remaining 12 participants were reviewed in clinic. Cough was most commonly attributed to reflux (5 additional participants), post-nasal drip or nasal congestion (2 participants), bronchitis (2

participants) or laryngeal hypersensitivity (1 participant). Treatment offered to these participants is detailed in Table 4.4. No cause of cough was recorded in 1 participant. One further participant had a historic diagnosis to account for their chronic cough and had no change in management. None of the 25 participants referred to secondary care with chronic cough were diagnosed with lung cancer.

ID	Suspected cause of cough	Treatment offered or recommended	Outcome
1	Reflux	Chest physiotherapy	Did not attend physiotherapy. Discharged
2	Reflux	Pharmacotherapy	Did not take prescribed medication. Discharged
3	Reflux	Pharmacotherapy	Declined medication. Discharged
4	Reflux	Lifestyle advice only	Discharged
5	Reflux	No specific advice or treatment	Discharged
6	Post-nasal drip	Steroid nasal spray	Discharged
7	Nasal congestion	Lifestyle advice	Discharged
8	Bronchitis	Pharmacotherapy	Discharged
9	Bronchitis	Over the counter nasal decongestant	Discharged
10	Laryngeal hypersensitivity	No specific advice or treatment	Discharged

Table 4.4 Diagnoses and treatment given to participants having normal CT scans to investigate chronic cough and outcomes following treatment.

In summary, of 25 participants referred to clinic for chronic cough (with or without a second red flag symptom), 16 participants were given a diagnosis for, or explanation for, their cough. Although 13 of these participants were offered treatment or lifestyle advice, only 5 accepted treatment (pharmacotherapy +/- physiotherapy) and 4 received lifestyle advice. A change in management or potential positive health benefit (through lifestyle advice) occurred in 9/25 (36%) participants referred to secondary care for chronic cough.

Fatigue and breathlessness

Two participants were reviewed with fatigue, one of whom also had shortness of breath. One participant was offered a CT, which did not explain either the fatigue or breathlessness. The participant was discharged with a recommendation for the GP to further investigate chronic fatigue. The second participant was investigated with lung function and blood tests, both of which were unremarkable. This participant was discharged with a recommendation to lose weight. One participant with breathlessness alone had a CT demonstrating cardiomegaly. Breathlessness was attributed to cardiac pathology, and the participant was already under the care of the cardiology team. No new diagnoses were made, and no treatment was given to these three participants.

Recurrent chest infections

One participant with recurrent chest infections had a CT which did not demonstrate any underlying abnormality to account for the infections. A 5mm nodule was detected on her CT scan; the participant was discharged from follow-up after 1 year of CT imaging demonstrating no growth of the nodule, indicating benignity. No explanation for the recurrent chest infections was given, and this participant received no treatment from secondary care.

Haemoptysis

One participant was referred urgently to clinic with haemoptysis. A CT was performed demonstrating no evidence of lung cancer. The participant declined bronchoscopy; no treatment was given.

In summary, of 30 participants who were ineligible for a LDCT scan but reported red flag symptoms in their LHC, 26 were subsequently investigated with a CT. Malignancy was not detected in any of these participants. Those not investigated with a CT had a full respiratory history, lung function testing, +/- a chest radiograph (n=2) and blood

tests (n=1). At 1 year of follow-up, only 1 participant with newly detected interstitial lung disease (PPFE) remains under ongoing follow-up in secondary care.

4.3.3.3 Summary of outcomes of secondary care referrals for non-lung cancer findings

Overall attendance in secondary care

Of 74 participants referred to secondary care, 7 participants failed to attend clinic appointments, although 5 of 7 did undergo a CT scan. Overall attendance at secondary care clinic appointment was therefore 67/74 (90.5%).

Pharmacological or other non-surgical treatment resulting from all secondary care referrals

Although pharmacotherapy was offered to fifteen participants, only 13/74 (17.6%) took medications for conditions diagnosed in secondary care, primarily for cough, ILAs or bronchiectasis. Eleven of 73 participants (15.1%) were offered pulmonary rehabilitation or physiotherapy following secondary care referrals, and 9/73 (12.3%) attended such appointments. As four participants had both pulmonary rehabilitation or physiotherapy, and pharmacological treatment, in total only 18/74 (24.3%) participants had management changes following secondary care review, comprising only a small proportion of those referred to secondary care. Potential health benefits may also be realised through lifestyle changes recommended in 13 participants, including stopping smoking in 7 participants.

Surgical treatment resulting from secondary care referrals

One participant underwent an aortic root replacement surgery following an urgent secondary care referral.

4.3.4 Primary care costs

4.3.4.1 Modelled primary care costs based on patients attending primary care

Table 4.5 shows estimated costs resulting from primary care referrals in the West London targeted lung screening pilot. Inputted costs are from published sources, namely the Personal Social Services Research Unit (PSSRU)[237] and NHS England Tariffs (2018/2019)[235] and Reference costs (2017/2018)[236]. Overall, the mean initial cost attributable to primary care was £55.19/consenting patient referred to primary care (n=159) or £5.69/patient attending a LHC (n=1542).

Activity or investigation	Cost/unit	Number performed	Total cost
GP appointment	£33.00 [237]	91	£3003.00
Community COPD review	£139.00 [236]	21	£2919.00
Direct access echocardiogram	£64.00 [235]	9	£576.00
Cardiology referral	£157.00 [235]	7	£1099.00
Outpatient colonoscopy	£406.00 [236]	1	£406.00
Urology referral	£142.00 [235]	1	£142.00
Cardiac surgery referral	£296.00 [235]	2	£592.00
Mammogram	£39.00 [236]	1	£39.00
			£8776.00

Table 4.5 Costs of GP and community respiratory appointments, subsequent imaging studies and secondary care referrals following recommendations from the West London targeted lung screening pilot.

4.3.4.2 Modelled anticipated costs resulting from closer adherence to the NHSE protocol

Closer adherence to the NHSE protocol would have resulted in a larger number of participants being referred to primary care, for the reasons outlined in Section 4.2.4.

Referrals resulting from abnormal clinical symptoms or spirometry during the LHC

Closer adherence to the NHSE protocol would have resulted in an additional 380 asymptomatic participants with abnormal spirometry (obstructive spirometry, n= 263;

restrictive spirometry, n=117) and no known diagnosis of COPD or asthma being referred to primary care.

In the West London pilot, 29 participants reported respiratory red flag symptoms (other than haemoptysis) who were ineligible for a LDCT scan according to the LLP_{v2} and PLCO_{m2012} risk thresholds. Alignment with the NHSE protocol would result in these participants being referred to primary care rather than secondary care for further assessment.

In total, therefore, an additional 409 referrals would have been made to primary care as a result of abnormal spirometry or clinical symptoms resulting from the LHC.

Referrals resulting from abnormal LDCT findings

Emphysema was reported on LDCT scans if involving >15% of the lung parenchyma in line with the West London targeted lung screening pilot protocol. NHSE suggest referral of participants with >25% emphysema on their CT scan. Modelling therefore uses the >15% emphysema threshold recorded, rather than the 25% threshold of emphysema. In the West London pilot, there were 25 additional participants with emphysema >15% on their scan, with normal spirometry and no known diagnosis of COPD, who would have been referred to primary care for a respiratory review.

Additionally, 15 participants were referred to secondary care for bronchiectasis detected on LDCT scans. The NHSE protocol allows screening pilots to refer to primary or secondary care in these instances. Modelling assumes that these participants are referred first to primary care.

Modelled costs

Assuming all of the above referrals were made to primary rather than secondary care, an additional 449 referrals would have been made to primary care in the West

London pilot in approximately 29.1% (449/1542) of LHC attendees. Modelled costs of these referrals are shown in Table 4.6. A total of 612 referrals would have been made to primary care, comprising 39.7% of LHC attendees (612/1542).

Assuming 57% primary care attendance overall (as in the West London targeted lung screening pilot) and the assumptions given above, additional primary care referrals would have cost an additional £9144.00. This would increase the overall cost to primary care to £17920.00, or £11.62/LHC attendee (n=1542), or £29.28/participant referred from the LHC programme to primary care (n=612). The limitations of this modelling are discussed further below. Modelled costs, however, are assumed to be the minimum costs attributable to primary care practitioners as a result of alignment to the NHSE protocol.

Indication for referral	No. cases referred to secondary care in West London Pilot	Modelled attendance rate in primary care (57%)	Cost of first primary care appointment (£) (£33.00/ appointment)	Cost of chest radiograph (£) (£39.00/radiograph)	Cost of subsequent secondary care (respiratory referral (£) (£208.00/ appointment)	Total Cost for clinical condition/ referral indication (£)
<u>Resulting from LHC</u>						
Red flag symptoms	29	17	561.00	663.00	Unknown	1224.00
Abnormal spirometry	380	217	7161.00		Unknown	7161.00
<u>Resulting from LDCT</u>						
Bronchiectasis	15	9	297.00	Unknown	Unknown	297.00
Emphysema	25	14	462.00		Unknown	462.00
Total						9144.00

Table 4.6 Modelled additional primary care costs resulting from closer adherence to the current NHSE protocol.

4.4 Discussion

In the West London targeted lung screening pilot, a strict protocol guided referrals to primary care for non-lung cancer findings, which meant only a small proportion (163/1542, 10.6%) of LHC participants were referred to primary care for further management or investigation. Closer alignment to the NHSE protocol would have increased this to approximately 40% of participants, a marked increase on the number of referrals made during the West London pilot.

There was a significant difference in the proportion of participants who attended primary care appointments (91/159, 57.2%) and secondary care appointments (67/74, 90.5%) ($p < 0.001$). Reasons for this are unknown, but this may reflect perceived severity of disease, with those referred to secondary care perceiving that the referral indicated a more severe disease. Alternatively, low attendance may reflect the fact that participants were given scheduled appointments in secondary care but were asked to book appointments in primary care.

Low attendance for follow-up in primary care was unexpected, given that participants had opted-in to the pilot, indicating some interest in personal health [234]. Reasons for not attending NHS health checks have been previously described and include participants not understanding the purpose of the primary care referral, or having difficulty in obtaining a GP appointment [234, 238]; these reasons for non-attendance may equally apply to participants attending LHCs. In some instances, participants made a deliberate choice not to attend primary care appointments. On the part of GPs, this may reflect lack of engagement with the recommendations in letters, the clinical judgement of the GPs, or time constraints [234].

Previous screening trials have reported the potential benefits that might be achieved through LHC-based lung cancer screening. Ruparel *et al.* report that, in a lung

cancer screening programme, 98% of those attending screening qualified for lipid-lowering therapy, according to a QRISK2[®] score (>10%) carried out as part of a LHC, although less than 50% were currently taking such medication [239]. Similarly, Balata *et al.* report that amongst a screening cohort in Manchester, 93% of participants, not already known to have cardiovascular disease, had a QRISK2[®] score >10%, and almost half (47%) were not taking a statin [240]. Neither study, however, report the subsequent changes to patient management resulting from the high QRISK2[®] score. Two important findings in the West London pilot are noted. Firstly, amongst those referred for a QRISK[®] score, a minority (9/63, 14.3%) were already taking a statin or other lipid lowering therapy, which they had denied in the LHC, possibly indicating a lack of awareness of prescribed medications. Secondly, of the majority who were reviewed in primary care, almost 40% declined statin therapy offered to them. This was unexpected and may be a significant barrier to the potential benefits of a LHC. Positively, the LHC was a prompt to a small number of participants (n=9) to restart statin therapy who had previously stopped, and a further 15 participants started statin therapy *de novo*. Nonetheless, only 24/63 (38.1%) of participants referred to primary care for a QRISK[®], and 2.1% of those scanned within the pilot, commenced lipid lowering therapy directly as a result of the LHC, indicating limited benefits to patients as a whole for a number of complex reasons. These results highlight that any proposed theoretical benefits of highlighting incidental findings in lung screening may not routinely result in practical benefit.

The opportunity to detect undiagnosed COPD during LHCs is now well recognised; Balata *et al.* report that 37.4% of attendees at LHCs in the Manchester lung screening pilot had obstructive spirometry, of whom almost one half had no known diagnosis of COPD [116]. In the London-based Lung Screening Uptake Trial, 57% of screening participants had spirometry consistent with COPD, of whom 67% were not known to have a diagnosis of COPD [117]. Amongst these participants, 50.4% of those

with suspected undiagnosed COPD were symptomatic with cough or dyspnoea [117]. Similarly, amongst screening attendees at the Liverpool Healthy Lung Project, abnormal lung function was demonstrated in 25% of participants who were not known to already have COPD [112]. Ghimire *et al.* postulate that, based on local clinical experience in Liverpool, 1/3 of these participants might subsequently be diagnosed with, and treated for, COPD. However, data on actual outcomes in primary care in these pilots are not provided. In the Liverpool Healthy Lung project all participants with abnormal spirometry (FEV1/FVC <0.7) were referred to primary care. Similarly, in Manchester, abnormal spirometry results were communicated to primary care practitioners with a recommendation for further assessment [112, 116]. The West London targeted lung screening pilot protocol was more selective; although all spirometry results were provided to primary care, a recommendation for a formal COPD assessment was made only for symptomatic participants not known to have asthma or COPD in line with NICE guidelines [216]. Consequently, this resulted in only 56/1542 (3.6%) participants being referred to primary care from the West London pilot. In total, only 16/55 (29.1%) participants referred to primary care (for whom follow-up data were available) received a new respiratory diagnosis, reflecting relatively low GP attendance, as well as the fact that a small number of patients already had a diagnosis of COPD, of which they were unaware. Although electronic data originally extracted from primary care at the outset of the pilot included whether a participant was known to be on the COPD register, primary care patient records occasionally described COPD whilst the patient was not recorded as being on the COPD register. This infrequent occurrence (in <10% participants referred) reflects inaccuracies of electronic health care records, a problem which has been previously identified in research studies [241]. Furthermore, only 7/55 participants (12.7%) referred to primary care for this indication had a change in

management, representing a very small proportion 7/1542 (0.5%) of those attending a LHC.

The NHSE standard protocol suggests referral of those with abnormal spirometry to primary care [109] and the Quality Assurance document suggests referral of those with moderate (>25%) or more severe emphysema on a CT scan to primary care [189]. The protocol does not currently recommend integration of clinical symptoms with spirometry results, as recommended by NICE. As demonstrated by modelling from the West London pilot, the majority of additional GP referrals arising because of closer adherence to the NHSE protocol would arise from these indications. This approach would consequently significantly increase primary care workload, particularly if lung cancer screening is rolled out more widely than the current NHSE pilot sites in the UK. The impact of this additional workload in primary care needs to be carefully considered and further investigated, given that only 12.7% of participants referred to primary care for possible COPD had a change in management following primary care referral [234]. Further work is also needed to better understand the reasons for lack of engagement at primary care and participant level, so these may be addressed to maximise the potential benefits of LHCs.

Modelled initial costs to primary care in the West London targeted lung screening pilot were £5.69/LHC attendee [234]. Had the pilot been more closely aligned to NHSE protocol, costs to primary care would significantly increase to £11.62/LHC attendee. A number of limitations to this cost analysis are noted. Firstly, only initial costs falling upon a specific primary care practitioner have been included. Inevitably, those participants who were referred to secondary care underwent a number of other investigations and treatments, the cost of which would also fall upon a CCG. These data, however, were not available, as participants were referred to a number of hospitals within the West London area and investigations and procedures performed are unknown. This analysis

was not intended as a cost-effectiveness analysis, rather a cost-burden analysis, given the complexities of quantifying cost-benefits for several different interventions in a small number of participants. It is, however, assumed that costs incurred by primary care would be offset by benefits obtained through diagnosis and health interventions, although the extent of such benefits are not currently established. Secondly, a single GP appointment was assumed for each attendee in primary care, likely underestimating costs. Thirdly, data were not collected on further investigations that might result from commencing statin therapy including serial laboratory tests (such as lipid profile) which would marginally increase costs. Finally, costs arising from additional primary care referrals to secondary care, following spirometry or abnormal chest radiographs performed in primary care, are unknown but are likely to increase costs to primary care.

4.5 Summary

Lung cancer screening is thought to be an opportunity to identify wider health issues in a high-risk screening population. No previous studies in the UK have reported actual changes to patient diagnoses or management as a result of LHC-based screening. The following conclusions can be drawn from the West London targeted lung screening pilot.

- With adherence to a strict referral protocol identifying those of highest risk of concurrent cardiovascular disease, or serious or significant incidental findings, referrals to primary and secondary care can be minimised. In total, 237/1542 (15.4%) of LHC attendees in the West London pilot were referred on to primary or secondary care.
- Subsequent attendance within primary care (91/159, 57.2%) was significantly less than that in secondary care (67/74, 90.5%) ($p < 0.001$).

- Significant or serious incidental findings resulting from the LHC and referred via primary or secondary care were uncommon; only 2 participants referred to primary or secondary care required urgent or semi-urgent cardiovascular surgery.
- None of the participants referred to primary or secondary care with red flag symptoms were found to have a diagnosis of cancer.
- The majority of participants referred to secondary care in the West London pilot were discharged within 1 year of the LHC. Those with ILAs or ILD are an exception, with all remaining in long term follow-up in secondary care. The NHSE protocol recommends direct referral of those with interstitial lung abnormalities to secondary care, and this appears appropriate. Those with bronchiectasis could be managed within primary care in the first instance, given that all participants were discharged from secondary care services within 1 year.
- Closer adherence to NHSE protocol would have resulted in a substantial increase to the proportion of participants referred to primary care (612/1542, 39.7%). This increase can largely be attributed to asymptomatic participants who might be referred for abnormal spirometry results. Closer alignment of the NHSE protocol with NICE guidelines, recommending investigation of symptomatic participants for COPD, would substantially decrease referrals to primary care.
- Costs of primary care referrals overall were low at £5.69/LHC attendee [234]. Closer alignment to the NHSE protocol would have increased primary care costs to £11.62/LHC attendee, but with only a small consequent reduction in secondary care workload and costs.
- Although previous LHC studies have demonstrated a clear *potential* benefit of identification of cardiovascular and respiratory disease, future work will be required to maximise *actual* benefits. Few participants referred to primary care (37/159, 23.3%) or secondary care (19/74, 25.7%) had a change in management as a result

of LHC recommendations, together comprising 56/1542 (3.6%) LHC attendees, although other benefits may be derived from lifestyle advice given at such appointment, not fully captured in this analysis.

CHAPTER 5: READING TIMES IN LUNG CANCER SCREENING

5.1 Introduction

The gradual roll-out of lung cancer screening pilots in the UK is expected to generate an additional 86000 baseline CT examinations over the next 2 years (Dr Arjun Nair, personal correspondence), which will require an increase in radiologist reporting capacity. NHSE quality assurance guidelines for lung cancer screening stipulate that participants should receive the results of LHCs and LDCT scans within 4 weeks of the LHC appointment, requiring a rapid reporting turnaround time [189]. Determining whether national CT screening is feasible in the UK therefore requires an understanding of lung screening reporting times. At present, little is known about reporting times for lung cancer screening studies. The RCR estimate that an uninterrupted consultant radiologist might reasonably report 3-6 CT examination/hour [242]. However, these figures are not specific to LDCT lung cancer screening studies.

NHSE stipulate that lung cancer screening studies should be reported using volumetry for nodule measurements; the use of CAD software is not mandated [189]. The use of narrative or descriptive reports is also discouraged, and use of prespecified reporting templates is stipulated [109]. A number of previous studies have explored the use of CAD software in reporting thoracic CT scans. These have focused on the sensitivity of CAD software in detecting nodules [151, 152], the influence of the particular method of using CAD (for example as a concurrent or second reader of scans) on reading times [152], or on the time benefits of integrating CAD software within a radiology workflow, with the automatic generation of reports [150]. Previous studies, however, have not included the time required to actually report the scan once nodules have been detected by CAD [152], or have not included time which would ordinarily be taken to review other areas within the scanning field, such as the mediastinum, chest wall, or upper abdomen [151, 201]. No previous studies have reported 'real-life' reading times for lung cancer

screening studies, encapsulating all elements of CT reading including opening of studies on worklists, reading the study using CAD software, reviewing of incidental findings and finally the generation of a non-narrative, structured, template-based report. The aim of this chapter is therefore to provide data on real-life reporting times for lung cancer screening studies, which might be used for modelling radiology reporting capacity for national lung cancer screening.

5.2 Methods

This study was performed as a service evaluation, in order to assess the performance and efficiency of consultant radiologists in reading and reporting lung cancer screening studies, and was registered as such at the RBH.

5.2.1 Reading times

To avoid institutional bias, reading time data from consecutive cases were collected from 2 institutions in the UK and Italy, with >10 years' experience in delivering lung cancer screening.

5.2.1.1 CT reading times in the West London Screening Pilot

Three thoracic radiologists, each with at least 8 years of thoracic radiology experience, read 20 consecutive baseline LDCT screening studies, performed between 30th January 2019 and 8th February 2019. Data were collected prospectively, and radiologists were informed that reading times data would be collected, in advance of CT reading. As described in Section 2.5.1, CAD software (Veolity™ (MeVis Medical Solutions, Bremen, Germany)) was used as a concurrent reader, whereby the scan was first read by the CAD software and subsequently reviewed by the reporting radiologist. Radiologists were instructed to first open and read the CT imaging using Veolity™ CAD software, report the scan in PACS (Impax, Agfa HealthCare NV, Belgium) using a prespecified reporting template, and then authorize the study in Veolity™. In so doing,

the time of opening and closing the scan, recorded within the Veolity™ software programme, represented the total time to report the scan.

Data were extracted from Veolity™ using the “AuditTrail” function, with access provided by the PACS team to the Clinical Lead and author. An example of data extracted using the AuditTrail function is shown in Figure 5.1. The date of the report, opening time (denoted by “open”), sign off time (denoted by “close”) and reporting radiologist (denoted by initials “ad” in Figure 5.1) were recorded. The time recorded was to the nearest second.

```
2020-07-23 14:59:36.817,ad158,impaxw7_ds22 (192.168.84.17),open,[participant  
name],1.3.51.0.1.1.192.168.90.77.100002661642.2661679,1.3.12.2.1107.5.1.4.83206.30000020072208361096900012  
661,succeeded  
  
2020-07-23 15:00:53.045,ad158,impaxw7_ds22 (192.168.84.17),close,[participant  
name],1.3.51.0.1.1.192.168.90.77.100002661642.2661679,1.3.12.2.1107.5.1.4.83206.30000020072208361096900012  
661,succeeded;signed off
```

Figure 5.1 Anonymised AuditTrail extract from Veolity™, demonstrating the opening time and closing time for a study and reporting radiologist.

Radiologists reported a maximum of 4 lung nodules, selecting the largest nodules in cases where >4 nodules were present. Reporting of benign lung nodules, or intrapulmonary lymph nodes, was not mandatory. Specific incidental findings were sought on each scan, including emphysema, bronchiectasis, interstitial lung disease and coronary calcification. Radiologists could choose to report other significant incidental findings at their discretion, if they were deemed to be serious or of high clinical significance, in line with NHSE guidelines [109].

Reporting in PACS required the radiologist to open a pre-loaded PACS reporting template and transcribe the specific features of nodules, namely the location, slice on the scan, type of nodule and size, from the Veolity™ scan report into the reporting

template. An excerpt of the baseline scan report template is provided in Figure 5.2. A free text space was available for incidental findings. Manual deletion of areas of the report which were not applicable to the scan being reported was required. All reports required a recommendation for further management.

Scan timepoint

Baseline scan:

Nodule 1

Lobe:

Slice:

Type (solid/GGN/PSN/nodular consolidation//IPLN):

Size (mm³) if volumetry used:

Size (mm) if diameter used:

Recommendations for follow-up for Low Dose Team:

1) For scans requiring nodule surveillance or nodule discharge:

- No further scan:
- 6 weeks from baseline CT [if CT is non-diagnostic OR nodular consolidation]:
- 3 months from baseline CT:
- 6 months from baseline CT:
- 9 months from baseline CT:
- 12 months from baseline CT:

2) For scans requiring PET/CT and/or nodule MDT [Note (1) above must be empty]

- PET/CT and then nodule MDT [requires RADAlert]:
- Nodule MDT for second opinion [requires RADAlert]:

3) Significant other unexpected findings requiring immediate further investigation:

- Non-pulmonary cancer, for MDT [requires RADAlert] – please specify recommendations:
- Other – please specify recommendations [requires RADAlert]:

4) Significant other unexpected findings requiring non-urgent review:

- Significant bronchiectasis (Primary care):
- Smoking related ILD (SR-ILD) (No further action):
- Interstitial Lung Abnormalities <5% (No further action):
- Interstitial Lung Abnormalities 5-10% (Requires correlation with LFTs):
- Interstitial Lung Abnormalities >10% (Respiratory Review):
- Emphysema >15% (Primary Care/smoking cessation):
- Moderate coronary calcification (Primary care/Q Risk):
- Severe coronary calcification (Primary care/Q Risk):
- Other (Please specify recommendation):

Figure 5.2 Excerpt from baseline scan report in the West London Screening Pilot.

5.2.1.2 IRCCS Istituto Nazionale Tumori di Milano, Milan, reading times

Data were collected retrospectively on 20 consecutive cases read as part of the bioMILD screening trial in Italy between 8th February 2014 and 10th February 2015 [76] and provided by Dr Mario Silva (IRCCS Istituto Nazionale Tumori di Milano). Reading times data were collected from 3 thoracic radiologists, each reporting twenty consecutive LDCT studies. The reading time, measured in seconds, represented the time between opening the LDCT screening study and the signature on the screening report. This was recorded by an independent observer using a stopwatch.

The CT reading protocol in the bioMILD trial was as follows: images were first reviewed using maximum intensity projection (MIP) reformats of the lungs, to detect lung nodules and then subsequently with dedicated CAD software for nodule detection (LungCARE, Oncology, Syngovia, Siemens Healthineers, Forchheim, Germany) as a second reader.

A structured report was written on a dedicated information technology platform, created by the National Cancer Institute in Milan. The platform also served a database for the bioMILD screening trial. For each screening CT, the volume and longest diameter of the 4 largest solid or PSNs were reported in the structured report. The density and size of up to 4 pGGNs were also reported. Various morphological features associated with nodules (for example spiculation and calcification) were recorded for each nodule. The following incidental findings were also specifically sought: coronary calcification, pleural effusions, pericardial effusion, non-nodular abnormalities of the lung parenchyma, abnormalities of the neck, mediastinum, breasts, abdomen or bones or 'other abnormalities', with 'yes/no' drop down boxes or free text boxes for manual population. A final summary outcome with recommended follow-up was also required within the report.

5.2.2 Statistical analysis

Reading times for all radiologists are reported in seconds (median, IQR). A post-hoc analysis using Spearman's rank correlation was performed to investigate the relationship between radiologist reading times and i) number of nodules/CT, and ii) incidental findings reported/CT for each radiologist. Statistical analysis was performed with SPSS (IBM SPSS Statistics for Windows, Version 26.0, 2019, Armonk, NY: IBM Corp.).

5.3 Results

5.3.1 Reading times for 6 radiologists

The median reading time for the 120 reported scans was 226 seconds (IQR 178 – 282 seconds) (Figure 5.3). Median reporting times for individuals ranged from 159 seconds to 269 seconds. Of the 120 scans, 96 (80.0%) were reported in under 300 seconds (5 minutes), and only 3 scans (2.5%) took >10 minutes to report.

Reporting times for the 6 radiologists are demonstrated in Table 5.1.

Radiologist (Location)	Median reporting time, secs (IQR)
1 (West London)	212 (165-245)
2 (West London)	269 (238-447)
3 (West London)	159 (127-323)
4 (Italy)	227 (203-284)
5 (Italy)	184 (118-258)
6 (Italy)	247 (199-280)

Table 5.1 Median reporting times for 6 radiologists.

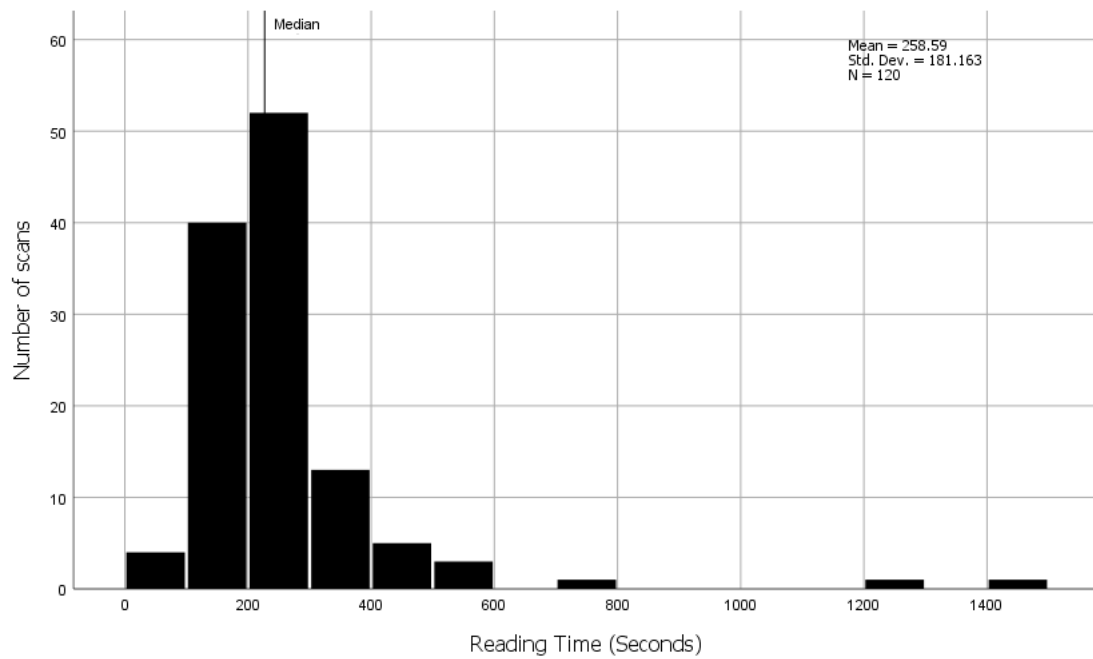


Figure 5.3 Histogram of reading times for 120 scans.

5.3.2 Relationship between reading times and the number of nodules and incidental findings reported

Table 5.2 shows the number of nodules and incidental findings reported on the 120 cases.

Number of nodules	Number of cases	Number of incidental findings	Number of cases
0	68	0	46
1	29	1	46
2	10	2	18
3	7	3	9
4	6	4	1
TOTAL	120	Total	120

Table 5.2 Number of reported cases with 0-4 nodules and 0-4 incidental findings.

There was a positive correlation between the number of nodules reported and reading time across all scans (r_s 0.495, $p < 0.001$). This was also true for each individual radiologist (Table 5.3). A similar relationship between the number of incidental findings

reported and reading times was not demonstrated either across all scans (r_s 0.089, $p=0.33$) or for individual radiologists (Table 5.3).

Radiologist	1	2	3	4	5	6
Relationship between reading times and number of nodules reported						
Rs	0.577	0.636	0.62	0.895	0.818	0.575
p value	<0.001	<0.01	<0.01	<0.001	<0.001	<0.01
Relationship between reading times and number of incidental findings reported						
Rs	0.058	0.142	0.238	0.192	0.025	0.003
p value	0.809	0.5511	0.313	0.4166	0.9158	0.9889

Table 5.3 Spearman's rank correlation (Rs) between the number of nodules reported, number of incidental findings reported and reading times for 6 radiologists.

5.4 Discussion

Questions have been raised about the capacity of thoracic radiologists to report increasing numbers of imaging studies should lung cancer screening be rolled out more widely [243, 244]. This is an initial study to explore actual reading times for lung cancer screening studies which may contribute to workforce and capacity modelling for the future.

Data collected from two institutions in the UK and Italy have shown that most studies can be reported in <5 minutes, and almost all studies were reported in <10 minutes. Importantly data were obtained from 6 different radiologists, indicating that these reporting times are likely to be reproducible amongst other thoracic radiologists with a similar level of expertise. Unlike most previous studies on CT reporting times, reporting times in this study included the time to construct and complete the semi-structured report. Brown *et al.* report reading times for lung CT studies from the time of opening the report to closing the report [150]. They sought to demonstrate whether time reductions for reporting could be achieved by the automatic population of CAD measurements (of nodules, the aortic diameter and pleural effusions) within a fully integrated reporting system, compared to manual measurements of the same. In

contrast to this study, the cases were pre-selected for the number of nodules on each scan, and radiologists were not required to assess the whole scan (for example mediastinal structures and lymph nodes). Whilst a meaningful time saving was achieved through the fully automatic integration of CAD detections within an automated report, the results of the study by Brown *et al.* are not easily generalisable to the screening setting, as currently few fully integrated CAD and reporting systems are widely commercially available. Brown *et al.* reported CAD-assisted reading times ranging between a mean of 151 seconds for the quickest reader and 525 seconds for the slowest reader [150]. However, the reading times achieved in this cannot be directly compared to reading times achieved in a real-life screening setting, as the radiologist was not required to assess the whole scan.

Fast reporting times were achieved despite slightly differing reporting protocols and software systems in the two institutions. Both institutions, however, used CAD software and semi-structured reporting, essential for quick turnover of studies. The NHSE standard protocol for lung cancer screening advises use of automated structured reporting, and the quality assurance document provided by NHSE offers an example of a standard reporting proforma [109, 189]. Use of volumetric software is mandated [109].

Unsurprisingly, reporting times were positively correlated with the number of nodules reported; this is likely a reflection of the time taken to segment and document the features of a nodule. Three studies took more than 10 minutes to report, all of which had 3 or more nodules reported. Upon retrospective review of the imaging available for two of these cases, it is apparent that numerous nodules were present. Although the radiologist was required to report only the largest 4 nodules, the act of selecting the largest 4 may have added additional time. However, such cases are infrequent. More than >80% of the studies had either no nodules or 1 lung nodule, requiring less time to report. The lack of relationship between the number of incidental findings and reading

times is also not unexpected; identification of incidental findings, for example coronary calcification or emphysema, can be performed and reported quickly and do not require measurements or detailed analysis.

The speed at which new studies are loaded is an important factor influencing overall reporting times. One limitation of this study is that it did not include the time taken between cases for new studies to open. Radiologists did not necessarily report all 20 screening studies in the same sitting. Furthermore, this study only assessed reading times for new baseline studies. Follow-up studies require comparison of nodules to those previously detected and the calculation of volume doubling times for growing nodules. These might therefore be expected to be more time consuming to report. Further studies are required to evaluate the additional reading time required for follow-up screening studies. Finally, all radiologists involved in this study were experienced thoracic radiologists, and less experienced radiologists are likely to take longer to report screening scans in the early stages of screening reporting.

Despite these limitations, some important implications for the national screening programme and radiology provision can be made. The RCR estimate that an uninterrupted consultant might report 3-6 CT scans/hour. Data from the West London and bioMILD trials suggest that as many as 15 CT screening scans might be reported within one hour. However, reporting at this rate is unlikely to be sustainable over a number of hours due to the repetitive nature of the reporting and radiologist fatigue; fast reporting might only be achieved through reporting in small batches. Additionally, radiologist training time, PACS cycling time, additional reporting time required for complex follow-up cases and multidisciplinary team time have not been assessed. Therefore, quantifying the implications of this for radiology provision is complex. However, assuming that the expansion of lung cancer screening requires an additional 86000 scans over the next two years and estimating that 6-10 scans might therefore

reasonably be reported/hour, allowing for MDT time and complex cases, approximately 4300-7200 additional reporting hours of radiologist time will be required annually. This corresponds to between 1075-1800 programmed activities (each 4 hours) for radiologists each year. As radiologists are unlikely to be reporting lung cancer screening scans full time, this will need to be spread across the radiology workforce; therefore, additional programmed activities required will not equate precisely to additional radiology posts. Consequently, even with rapid reporting of LDCT screening, there will be a requirement to substantially expand reporting capacity to enable the delivery of screening on this scale, as these scans will be additional to normal NHS workload, which has also rapidly expanded over recent years [245].

5.5 Summary

- This study sought to ascertain real-life reading times for lung cancer screening studies. Reading times were obtained from 6 thoracic radiologists reading a total of 120 low dose CT scans in two institutions in the UK and Italy. Data demonstrate that almost all baseline screening studies are reported in <10 minutes and 80% in less than 5 minutes.
- Reporting times (median 224 seconds/scan) were shown to be faster than estimated by the RCR for CT reporting (3-6 scans/hour). Allowing for additional time for training radiologists and MDT discussion, as well as for reporting complex and follow-up cases, it is estimated that 6-10 screening scans might be performed/hour. These data may influence calculations for additional radiologists with expertise in screening to support the expansion of lung cancer screening over the coming years.
- Despite differing reading methods in two institutions, both institutions used CAD software, volumetric measurements of nodules and semi-automated structured non-narrative reporting, all of which are required for rapid reporting.

- A positive relationship between reading times and the number of nodules reported/scan was demonstrated, but a similar relationship was not shown between reading times and incidental findings reported. However, more than 80% of screening studies had no nodules or 1 nodule, accounting for overall fast reading times.

CHAPTER 6: INTERSCAN VARIABILITY IN VOLUMETRIC MEASUREMENTS OF SMALL PULMONARY NODULES <150mm³ – IMPLICATIONS FOR LUNG CANCER SCREENING

6.1 Introduction

Volumetric measurements of nodules are now considered the "*preferred measurement method of nodules*" [120] in both clinical practice and the screening setting. Volumetry has been shown to be a more accurate and reproducible measure of nodule size than diameter measurements and a more sensitive measure of volume growth as determined by volume doubling times [246-248]. Consequently, volumetry can be used to both confirm stability and establish definite growth of pulmonary nodules.

In the screening setting, including in the West London screening pilot, trial protocols using volumetric measurements of nodules have stipulated a threshold of 25% volume growth to signify true growth of a nodule over a period of 3 or more months [66, 68, 111, 217, 249], as recommended in the BTS nodule management guidelines [120]. This threshold is based upon previous in vivo studies measuring the interscan variability in volume measurements of the same nodule on two scans performed on the same day, known as "coffee break experiments" (as the patient has a short 'coffee-break' between serial scans) [144, 145, 250, 251]. Using a Bland-Altman method of determining agreement between the two measured volumes [252], these studies have demonstrated that interscan variability in nodule measurements to be approximately 25% of the estimated 'true' nodule volume, the latter calculated as the mean of the two nodule volume measurements [141, 144, 251]. This value is now widely used in clinical practice for the management of incidental pulmonary nodules [120] and also in the lung cancer screening setting as a threshold for determining growth [66, 111, 217]. This inter-scan variability in nodule volume measurements has been attributed to slight variability in the segmentation of nodules, including those which are irregular in shape, or attached to

pleural surfaces or vessels [250] and to patient factors, such as level of patient inspiration or pulsation of the heart [144, 145, 253].

Most previous in vivo studies examining inter-scan variability have, however, recruited participants with known lung metastases [141, 144, 250, 251]. Nodules in these previous studies have ranged in size from $<10\text{mm}^3$ to almost 5000mm^3 , therefore many of the nodules analysed in these previous studies are much larger than incidental nodules normally detected in the lung cancer screening setting. Furthermore, in one study by Gietema *et al.*, almost half (106/218, 48.6%) of the metastatic nodules measured were spherical, a feature not necessarily typical of primary lung cancers [144].

Theoretically, smaller nodules might be expected to show greater variability in nodule volume measurements than larger nodules. As previously described (Section 1.5.1), a CT image is composed of numerous voxels each with an attenuation value (in Hounsfield Units) corresponding to the average attenuation coefficient of the voxel. In smaller nodules, with a greater surface area: volume ratio, more voxels on the periphery of a nodule will contain only a part of the nodule, rather than being completely filled with nodule. Volumetry software analyses adjacent voxels containing air and makes a subsequent volume correction for the nodule based on this analysis. Smaller nodules may therefore show greater variability than larger nodules in volume measurements because of this partial volume effect. However, there are limited data evaluating inter-scan variability in volume measurements for small nodules, and previous studies have shown conflicting results [144, 145, 250, 251]. Understanding inter-scan variability and identifying an accurate measure of true growth in small nodules is especially relevant at the incident round of screening, at which point in time nodules as small as 30mm^3 may warrant CT follow-up [179, 254]. It is also hypothesised that non-metastatic nodules, which might be more irregular in shape than metastatic nodules, may show greater interscan variability than metastatic nodules.

Therefore, given the importance of the 25% threshold for stipulating growth of a nodule in the BTS guidelines as well as in numerous screening nodule management protocols, the conflicting results in previous studies relating to the interscan variability for nodules of different sizes, and the reliance on examining larger lung metastases in prior studies, the purpose of this study was to perform a same day test-retest analysis (coffee-break experiment) to establish whether the approximately 25% interscan variability demonstrated in previous studies applied to small ($<150\text{mm}^3$) non-metastatic nodules which might be commonly be detected in the lung screening setting and to establish the limits of agreement which might apply to such nodules.

6.2 Methods

Ethical approval for this study was granted by the NHS London Brent Research Ethics Committee (REC; reference 19/LO/02020) on 8th February 2019. Approval was obtained via the Integrated Research Application System (IRAS; reference 254778) and site-specific approval was granted by the RBH Research and Development Department and by the Sponsor, Imperial College London.

6.2.1 Participant recruitment

Between March 2019 and January 2021, adults with known solid pulmonary nodules measuring $<150\text{mm}^3$, who were scheduled to undergo surveillance CT for lung nodules, were invited to participate in a coffee break study involving two low dose CT scans performed in quick succession. Potential participants were identified from a database of participants awaiting nodule surveillance CT in the West London screening pilot, maintained by the author, from patients in nodule follow-up under the nodule MDT at the RBH, or from booked CT scanning requests at the RBH containing the word “nodule”. The most recent CT imaging was reviewed by the author for the presence of suitably sized nodules and participants were sent an participant information sheet and invitation to participate in this study two weeks prior to their next scheduled follow-up

CT. No individuals with a known non-lung primary tumour were invited to participate in the study. Participants with SSNs were not included in this study, as the established limits of agreement previously published do not apply to SSNs and growth of such nodules is determined by calliper rather than volumetric measurements. Written informed consent to participate in this study was obtained from all participants at the time of attendance for the patient's clinically indicated nodule surveillance CT.

6.2.3 Scanning protocol and nodule analysis

All participants were scanned on a 128-slice Siemens Edge CT scanner at the RBH using the LDCT screening protocol described in Chapter 2.4.1, utilising weight-based scanning parameters and with AEC enabled. Following acquisition of the clinically indicated nodule surveillance thoracic CT, images were immediately reviewed by the author to ensure that nodules previously identified had not resolved or substantially grown. A second scan was then performed with identical scanning parameters within 15 minutes. All participants stood up between the two scans and were subsequently repositioned on the CT scanning table before a second scan.

Axial images from the CT scanner were reconstructed using a soft tissue reconstruction kernel, as for the West London screening pilot. Data from both scans were transferred from the CT scanner to a PACS reporting workstation, and semi-automated nodule volumetric analysis was performed using SyngoVia™ software (Syngo.Via Client 5.1, SyngoVia™, Siemens Healthineers, Germany, 2009-2018). Images were displayed in the SyngoVia™ software with a window width of 1500HU and level of -500HU. A mouse click was used for the identification of nodules, and nodules were subsequently automatically segmented and measured by the software. No manual correction of volumetric measurements was performed; if segmentation was judged to be poor, for example because of attachment to an adjacent vessel or the pleura, nodules were excluded from analysis. This method reflects real life practice, where nodules felt to be

inadequately segmented by volumetric software in the screening would be measured by diameter. Analysis of all nodules was performed by the author.

All nodules present on one or both scans measuring 30mm³-150mm³ were included in this study. This size threshold of 30mm³ was chosen in view of the recommendation from the BTS Quality Standards that small new nodules not present on a previous CT scan within the previous 2 years should undergo surveillance [179]. This in turn was based on data from the NELSON trial that demonstrated an increased risk of malignancy in new solid nodules ($\geq 27\text{mm}^3$) presenting on incident round scans [178].

The author recorded the lobe in which each measured nodule was found. Nodules were characterised as being spherical or non-spherical. Non-spherical nodules were further sub-categorised as having a smooth or an irregular margin. If applicable, nodules were also recorded to be juxtapleural, juxtafissural or juxtavascular if abutting the chest wall, a fissure or a blood vessel respectively.

6.2.4 Statistical analysis

The inter-scan variability of volumetric nodule measurements was assessed using the Bland-Altman method of assessing agreement [252]. Since the true volume of any given nodule is not known, the mean of the two measured volumes ($(V_1+V_2)/2$, V_{mean}) is assumed to represent the true nodule volume [144, 251, 255, 256]. The absolute difference in the measured nodule volumes (V_1-V_2 , mm³) is plotted against the mean nodule volume. The difference in nodule volume is also reported as a proportion of the mean nodule volume ($(V_1-V_2/V_{\text{mean}})*100$, %), to provide a measure of the relative difference in volumes between the two scans. The upper and lower limits of agreement are calculated as the range of 95% of the observed absolute and relative differences in the two volume measurements (1.96 standard deviations above and below the mean

difference). The limits of agreement were also calculated by the same method for the subset of nodules abutting the vasculature or pleura.

Linear regression was used to assess for proportional bias, namely whether the limits of agreement for the relative difference of nodule volumes varied with the mean nodule volume. The values of the relative difference in nodule volumes (%) were converted to absolute values (removing negative signs) and regressed against the mean nodule volume [257].

All statistics were carried out in SPSS (IBM SPSS Statistics for Windows, Version 26.0, 2019, Armonk, NY: IBM Corp.).

6.3 Results

Forty-nine participants were recruited for the study, and all underwent an initial LDCT scan. In four participants the nodule previously identified in the patient had either resolved (n=2), or had appreciably decreased in size (n=2), and the participants were not scanned a second time. Forty-five participants underwent two consecutive low dose CT scans. A total of 107 small nodules were identified in these participants. Four nodules were found to be marginally $>150\text{mm}^3$ on the volumetric measurements on both the initial and second scans, and one nodule was just under 30mm^3 on both scans. Two nodules were poorly segmented by the volumetry software; one was irregular in contour and juxtavascular, and the second nodule was irregular but not abutting the vasculature or pleura. All seven nodules were excluded from analysis. Therefore, a total of 100 non-calcified nodules in 41 participants (23 males, mean age 65 years, range 37-84 years) were finally evaluated. The mean time between the two scans for the 41 participants was 307 seconds (range 128 seconds – 763 seconds).

Forty-seven nodules were present in 21 participants undergoing follow-up in the West London screening pilot, and 53 nodules were found in 20 patients undergoing follow-up in the clinical service at the RBH. Nodules were in the left upper lobe (n=21),

left lower lobe (n=26), right upper lobe (n=26), right middle lobe (n=6), right lower lobe (n=21). Twenty-eight nodules were spherical with a smooth margin. A further 7 nodules were non-spherical (primarily polygonal) with a smooth margin. The remaining 65 nodules were non-spherical with an irregular margin. Two nodules were juxtaleural, 5 nodules were juxtafissural, and 13 nodules were juxtavascular.

Nodules volumes on the first scan ranged from 31-158mm³ (mean 80.5mm³, SD 36.5mm³) and on the second scan from 28-170mm³ (mean 81.6mm³, SD 37.6mm³) (Figure 1).

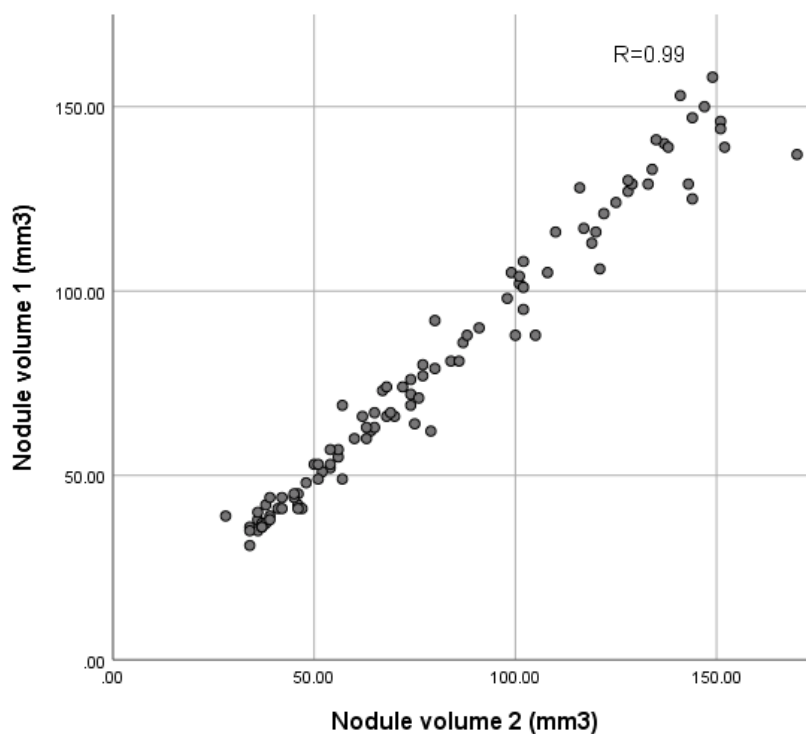


Figure 6.1 Volumetric measurements of 100 nodules on first and second scans. R=Spearman's Rho ($p < 0.001$).

The mean absolute volume difference between the two scans was -1.09mm³ (95% CI -2.42 to 0.24), range -33mm³ to 12mm³. The lower and upper limits of agreement were -14.2mm³ and 12.0mm³ (Figure 6.2). The mean relative difference in nodule volumes was -0.90%, range -24.1% to 32.8%. The lower and upper limits of agreement were -16.4 and 14.6% respectively (Figure 6.3). Lower and upper limits of

agreement for 58 nodules with a mean volume of 30-<80mm³ were -16.8% to 16.2%, with a mean relative volume difference of -0.3% (95% CI -2.51 to 1.91%). For the 42 larger nodules, 80-150mm³, the upper and lower limits of agreement were -15.8% to 12.3%, with a mean relative volume difference of -1.7% (95% CI -3.96 to 0.50%).

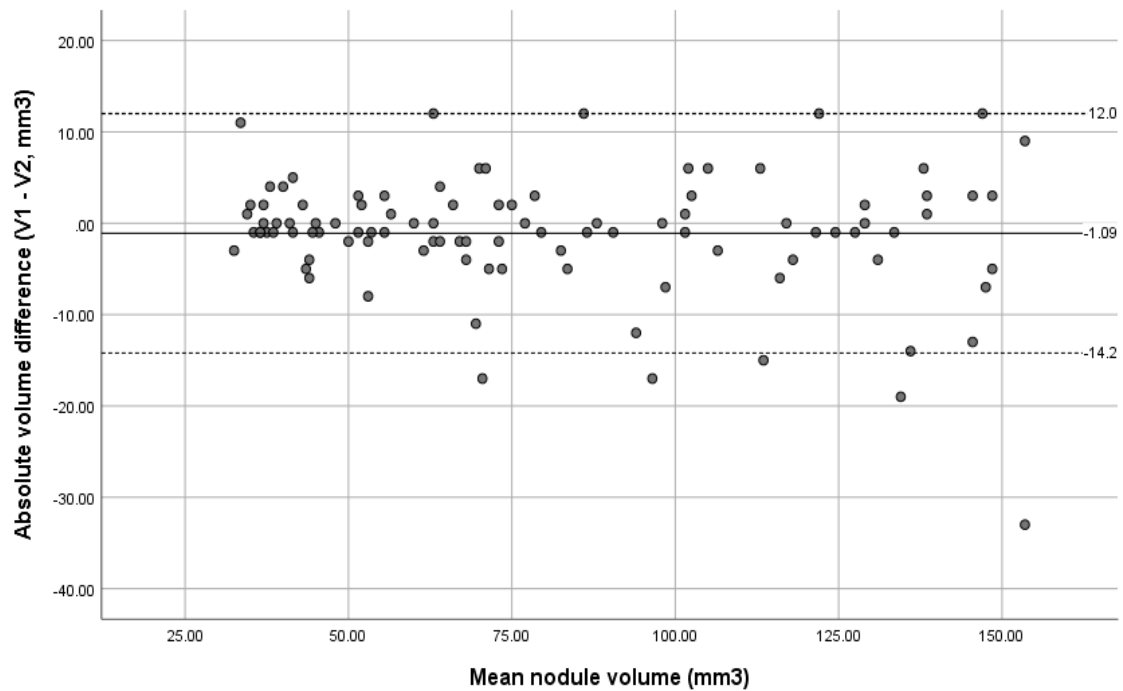


Figure 6.2 Absolute volume difference (mm³) between volume measurements on the first and second scans, plotted against the mean nodule volume (mm³). Solid line demonstrates the mean absolute volume difference, and dashed lines show the upper and lower limits of agreement.

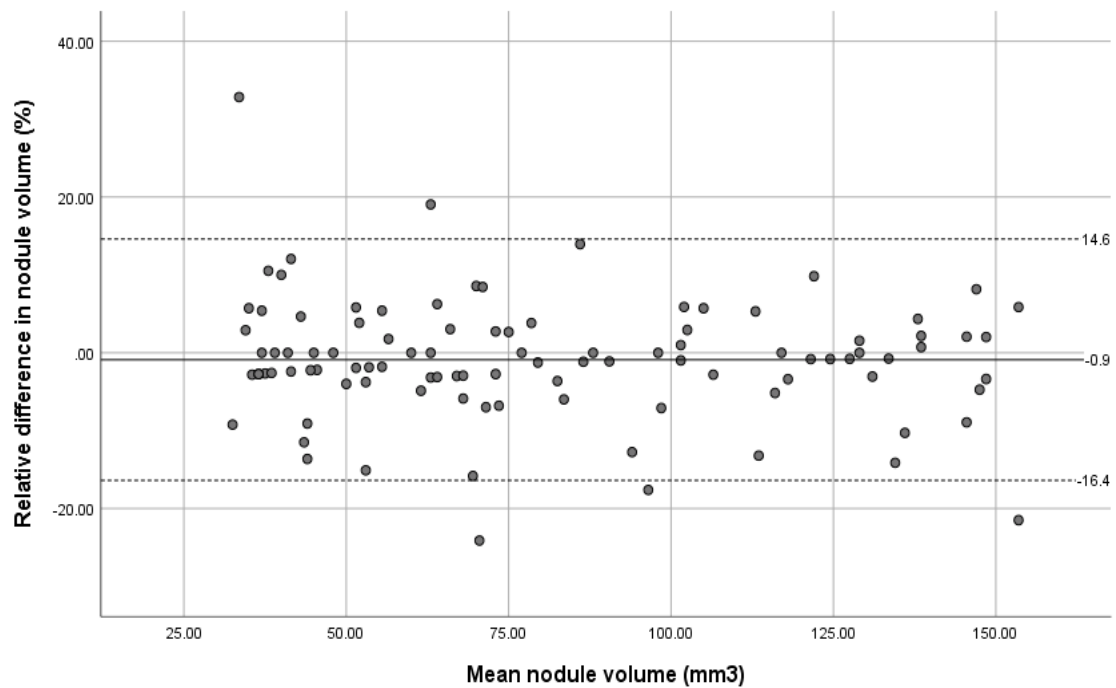


Figure 6.3 Relative difference in nodule volumes (%) plotted against the mean nodule volume (mm^3). The solid line demonstrates the mean relative volume difference, and dashed lines show the upper and lower limits of agreement.

In view of the wider limits of agreement for the smaller nodules $<80\text{mm}^3$ than the larger nodules $80\text{-}150\text{mm}^3$, linear regression was used to assess for proportional bias. This demonstrated no significant relationship between the relative difference in nodule volume and the mean nodule volume ($p=0.66$).

In a sub-analysis of the 15 nodules abutting the vasculature or pleura, the mean relative volume difference between the two scans was -2.17% (95% CI -5.90% to 1.57%) and the lower and upper limits of agreement were -15.4% and 11.1% respectively.

6.4 Discussion

This study sought to establish the reproducibility of volumetric software in measuring small non-metastatic pulmonary nodules $<150\text{mm}^3$. Given the effects of partial voluming on CT and the non-spherical nature of many nodules detected in the screening setting, the limits of agreement were expected to be wider than published in

previous similar studies involving metastatic nodules. Unexpectedly, this study demonstrated narrower limits of agreement, 15.5% either side of the mean relative difference in nodule volume. This may reflect advances in volumetry software over the past 15 years, differences in volumetry software packages and advances in CT scanner technology.

The importance of the nodule size in the interscan variability of nodule volumes has been explored in previous studies with conflicting results. Wormanns *et al.* demonstrated similar interscan variability in nodule volumes, for a cohort of 151 pulmonary nodules between 7.3mm³ and 4833mm³ and a subset of these nodules with diameters <10mm in size (corresponding to a volume of approximately <525mm³) [250]. In a study of 218 nodules, Gietema *et al.* found that the limits of agreement overall were -21.2 to 23.8% either side of the mean nodule volume and that the overall nodule volume did not significantly affect variability in nodule measurements [144]. Goodman *et al.* reported the standard deviation of the mean nodule volume for 43 nodules in 3 size categories (diameter <6mm, 6-9mm and >9mm) and found that the 95% confidence limits on these standard deviations were less for nodules ≥9mm in size (+/- 17.9%) compared to those 6-<9mm in size (+/- 31.4%) implying that smaller nodules had greater variability in measurements [145]. De Hoop *et al.* likewise found that interscan volume variability for nodules ≥8mm in diameter was significantly less than for nodules <8mm in diameter, when assessed with 5 of 6 different volumetry software packages [141]. By contrast, Talwar *et al.* found slightly lower interscan volume variability for nodule measurements in nodules <500mm³ (-24.8% to 23.7%) compared to those over 500mm³ (-28.9% to +24.7%) [251]. This study has demonstrated no evidence that the relative difference in nodule volumes (%) varies in relation to the absolute size of the nodule for small nodules between 30-150mm³.

Previous studies have investigated the impact of nodule outline on volume variability. This is important because metastases are not necessarily morphologically similar to nodules detected in lung cancer screening. Gietema *et al.* found that the interscan variability in the volume of non-spherical nodules was up to 30%, more than double that of spherical nodules [144]. Almost 50% of the nodules in that study were spherical as might be expected for a study containing only metastatic nodules, compared to 28% in the study within this thesis. Nodules abutting vasculature or the pleura were excluded in this study. Goodman *et al.* studied 43 nodules, of which 26 (60.4%) had “well defined edges” (smooth or lobulated margins), and 17 (39.5) were irregular or spiculated [145]. They showed no significant difference in the standard deviation of the mean nodule volumes for these small cohorts of irregular versus smooth nodules.

The study within this thesis also demonstrated narrower limits of agreement than previously reported by Wormanns *et al.* [250]. In Wormanns’ *et al.* study, the relative difference in nodule volume between the two scans (%) was calculated as $(V_1 - V_{\text{mean}})/V_{\text{mean}} * 100$, rather than $(V_1 - V_2)/V_{\text{mean}} * 100$, a method halving the limits of agreement, compared to the method used in this thesis. Therefore, using comparable methods to this thesis, Wormanns *et al.* found limits of agreement between -38.6% to 40.8%, for a subset of 105 nodules <10mm in diameter (which are broadly comparable in size to the nodules studied within this thesis). The authors attribute the interscan variability of nodule measurements to nodules abutting the pleura or vessels, although they do not report how many nodules in their study had this characteristic. In the current study, although only a very small proportion of all nodules analysed (15/100) abutted the vasculature or pleura, narrower limits of agreement were found in this subset of nodules indicating that this was not a factor broadening the limits of agreement. Therefore, it is likely that the wider limits of agreement reported in that study may reflect advances in CT technology or volumetric software since publication almost 20 years ago.

The current study was unique in recruiting participants not known to have metastatic nodules. Other strengths of the study include that all individuals were scanned with an identical low dose scanning protocol on the same scanner, and analysis was performed using a modern volumetry software package. Therefore, the conditions and scanning protocol with which this study was performed are likely to mirror scanning parameters in a screening programme and therefore the results of this study can be extrapolated to a lung screening cohort.

Results from the current study may have implications for the management of small pulmonary nodules in screening. The BTS guidelines define growth as a 25% increase in nodule volume for solid segmentable nodules. However, the data from this study suggest that a smaller threshold for defining growth may be appropriate. The impact on nodule management depends on a number of factors, including nodule size and the time interval to the next surveillance scan.

Table 6.1 models the impact of narrower limits of agreement on growth assessment of small nodules of different sizes and the implications of these narrower limits of agreement for the timing of subsequent follow-up scans or further investigations, assuming further investigation (PET and biopsy) is reserved for nodules $\geq 200\text{mm}^3$ [80, 118, 217].

Nodule volume (mm ³) at baseline	Nodule volume at 3m assuming 15%-24% growth (mm ³)	Ongoing management as determined by current BTS guidelines	Nodule volume (mm ³) at 12m assuming VDT 296-456 days*	Time at which intervention would be warranted	Implication of assuming stability at <25% growth
30	34.5-37.2	Assumed stable; perform 12m scan	52.5-70.9	27-42 months	No change in management at 12m
50	57.5-99.2	Assumed stable; perform 12m scan	87.5-118.2	21-30 months	No change in management at 12m
80	92-99.2	Assumed stable; perform 12m scan	139.9-189.1	15-21 months	No change in management at 12m
115	132.3-142.6	Assumed stable; perform 12m scan	201.1-271.9	9-12 months	Up to 3m delay in investigation
130	149.5-161.2	Assumed stable; perform 12m scan	227.4-307.3	6-12 months	Up to 6m delay in investigation
150	172.5-186	Assumed stable; perform 12m scan	262.3-354.6	6-9 months	Up to 6m delay in investigation

Table 6.1 A model to demonstrate the implications of assuming stability for solid nodules growing 15-24% in 3 months. *A VDT of 296-456 days corresponds to between 15-24% growth over a period of three months.

This modelling indicates that for the cohort of nodules measuring 115-150mm³ the assumption of nodule stability if a nodule is growing at <25% between serial scans may result in a delay to further investigation of nodules in this size range by up to six months. The findings of the current study therefore suggest that closer surveillance may be appropriate for nodules between 115-150mm³ apparently growing between 15% and 25% in the first three months of follow-up. These cannot be assumed to be stable, and consideration should be given to short-term imaging follow-up, for example, at 3-month interval. Provided a minimum volume threshold of 200mm³ is maintained prior to invasive

or further investigation, little harm is expected to result from closer surveillance, since in all cases, at least one additional scan would be required to confirm ongoing growth.

In conclusion, this study has shown that the interscan variability in volumetric measurements of small non-metastatic pulmonary nodules $<150\text{mm}^3$ may be smaller than reported in previous studies that have focused on metastatic nodules with a greater range of sizes. This may have implications for scanning intervals for small pulmonary nodules detected in screening. Further studies would be of benefit using different volumetry software on a similar cohort of patients to validate the findings of the current study.

6.5 Summary

This study sought to investigate the interscan variability in nodule volumes for small non-metastatic nodules $30\text{-}150\text{mm}^3$ in size, using a Bland-Altman statistical method, as determined by limits of agreement.

- At the outset of the study, it was hypothesised that the limits of agreement might be broader for small non-metastatic nodules than metastatic nodules.
- Unexpectedly, the results of this study demonstrated narrower limits of agreement than previous studies, in the region of $\pm 16\%$ of the mean nodule volume. This may reflect improvements in volumetry software, CT technology, or other differences in patient cohorts between this study and previous studies.
- The implications of this study are primarily for the management of small pulmonary nodules growing between $15\text{-}25\%$ between serial scans. Such nodules would under current guidelines be regarded as stable; however, this study suggests that $>15\%$ growth might reflect true growth. This has management implications for nodules between $115\text{-}150\text{mm}^3$. A more cautious approach is therefore suggested for the management of growing nodules in this size range.

CHAPTER 7: RADIOLOGIST ADHERENCE TO NODULE MANAGEMENT GUIDELINES IN LUNG CANCER SCREEING

7.1 Introduction

Several guidelines have been produced to ensure standardised reporting and management of nodules detected on CT imaging [120, 174, 175, 177]. Standardised reporting of LDCT screening cases is important to ensure consistent and appropriate management of participants with pulmonary nodules and to prevent over-investigation of nodules or overdiagnosis of lung cancer, whilst minimising delayed diagnosis. The BTS nodule management guidelines recommend using the same management algorithms for nodules detected in screening as those detected incidentally in a clinical setting [120]; consequently, the BTS guidelines have been used by a number of screening pilot studies and trials in the UK [79, 110, 111, 118, 217, 258]. In Europe, no specific screening nodule management protocol has been published, although an expert group has recommended a volumetry-based nodule management protocol broadly based on BTS guidelines [80]. In the USA, the Lung-RADS™ nodule management protocol was developed specifically for management of nodules detected in the screening setting, shortly after the USPSTF taskforce recommended population-based screening and has been in use since 2014 [176, 177].

Despite the publication of various nodule management guidelines, radiologist adherence to guidelines in clinical practice has been shown to be variable. One study of radiologist compliance with Fleischner society guidelines for incidentally detected nodules demonstrated that the recommendations of radiologists followed guidelines in 81% of cases [259]. In larger surveys of radiologists' adherence to Fleischner Society guidelines has varied between 27-82%, with a tendency towards recommending over-investigation of nodules in these studies [191, 260, 261]. Very little data are available, however, on radiologist compliance to BTS guidelines in the UK, although results of local

audits suggest considerable variability in conformity to guidelines [262, 263]. Reasons for this may include lack of awareness of guidelines, or the lack of immediate availability of guidelines for reference [260], and consequently standardisation of radiology reports has been suggested as a means to improve compliance [259, 264, 265]. In the setting of screening, few studies have evaluated radiologist compliance with nodule management protocols [266]. No published data are currently available regarding radiologist compliance to nodule management protocols in screening in the UK.

Although the complexity and length of nodule management guidelines has been cited as one reason for poor compliance to guidelines [267], the BTS guidelines are summarised in four simple flow-chart algorithms for the management of pulmonary nodules [120] and are regarded as simple and intuitive to use [268].

The nodule management algorithms used in the West London pilot were modified during the course of the programme as described in Section 2.5.3. To summarise in brief, the original nodule management algorithm developed was based on BTS guidelines, with similar flow-chart algorithms for nodule management (Appendix D). Subsequently, in preparation for an incident round of screening, this was modified to a simplified tabulated format, with nodule categorisations similar to the Lung-RADS™ algorithm, referred to as RBH L-RADS (Appendix E).

In late January 2020, following feedback from reporting radiologists using the tabulated RBH L-RADS algorithm, a mobile phone application was developed, with the assistance of a software developer, to further facilitate radiologists' use of the RBH L-RADS algorithm. Radiologists had described challenges in quickly identifying the correct scenario for a given nodule using the tabulated algorithm. Therefore, the author aimed to develop a functional mobile phone application that would readily generate the appropriate management recommendation. This was made available to radiologists at

the RBH at the beginning of June 2020 for beta testing and was used thereafter for reporting.

The aims of this study were as follows: Firstly, to evaluate radiologist compliance with the pilot study's nodule management algorithm using a) flow-charts based on the BTS guidelines (Appendix D) versus b) a tabulated algorithm based on the RBH L-RADS categorisation system (Appendix E) versus c) the tabulated RBH L-RADS categorisation system with the assistance of a mobile phone application. Secondly, given the novel approach of developing a mobile phone application, to evaluate how comprehensive the mobile phone application was, by identifying the frequency of nodule management scenarios not catered for by the mobile application.

7.2 Methods

This study was performed as a service evaluation of radiologist compliance with the West London nodule management protocol using different reporting aids and was registered accordingly at the Royal Brompton Hospital.

7.2.1 Development of the RBH L-RADS mobile phone application

A series of decision tables for every nodule scenario at each screening interval were written by the author. The nodule management outcomes (RBH L-RADS score and corresponding follow-up interval) were documented within the decision tables. A short excerpt from one of these decision tables (for nodules detected on a baseline scan) is shown in Table 7.1. These decision tables were provided to a software developer (David Butler; <https://www.nimisis.com>) who produced a mobile phone application available for beta testing. This was reviewed by the author and minor functional changes were made to the mobile phone application to improve ease of use.

SCENARIO	1	2	3	4	5
Nodule Type					
Solid	1	0	1	0	1
Endobronchial	0	1	0	1	0
Pure Ground-glass	0	0	0	0	0
Part-solid	0	0	0	0	0
Nodular consolidation	0	0	0	0	0
Benign lung nodules	0	0	0	0	0
Intrapulmonary lymph node	0	0	0	0	0
Non-nodular opacity	0	0	0	0	0
No lung nodules	0	0	0	0	0
Size (volume)					
<50mm ³	1	1	0	0	0
≥ 50mm ³ to <80mm ³	0	0	1	1	0
≥ 80mm ³ to <125mm ³	0	0	0	0	1
≥ 125mm ³ to <300mm ³	0	0	0	0	0
≥300mm ³	0	0	0	0	0
OR Size (diameter)					
<3mm	1	1	0	0	0
≥ 3mm to <5mm	0	0	1	1	0
≥ 5mm to <6mm	0	0	0	0	1
≥ 6mm to <8mm	0	0	0	0	0
≥ 8mm	0	0	0	0	0
≥ 30mm	NA	NA	NA	NA	NA
<5mm	NA	NA	NA	NA	NA
≥ 5mm to <30mm	NA	NA	NA	NA	NA
Brock Score					
≤10%	NA	NA	NA	NA	NA
>10%	NA	NA	NA	NA	NA
RBH L-RADS	1	1	2	2	3C
	Return to next screening round	Return to next screening round	Return to next screening round	Return to next screening round	Follow-up CT in 6 months
Management					

Table 7.1 Short excerpt from a decision table provided to the software developer.

7.2.2 Evaluation of radiologist compliance with the West London nodule management algorithms

To assess radiologist compliance with the original flow chart nodule management algorithm (Appendix D), consecutive LDCT reports after 1st January 2019 were reviewed retrospectively by the author for reports containing lung nodules, until 75 scans containing nodules had been reviewed. The scan follow-up recommendation was reviewed by the author to assess whether the correct follow-up recommendation had been made based on the West London nodule management algorithm. Where multiple nodules were present on a scan, radiologists were expected to recommend follow-up at the earliest interval required by any lung nodule reported on the scan.

For assessment of radiologist compliance with the tabulated RBH L-RADS algorithm (Appendix E), consecutive LDCT reports after 1st January 2020 were retrospectively reviewed by the author. The following were evaluated: i) the frequency of correct RBH L-RADS categorisations for each nodule reported, and ii) the frequency of correct overall management based on the RBH L-RADS score of all reported nodules. Seventy-five LDCT reports containing lung nodules were reviewed.

Radiologists were asked to report scans using the RBH L-RADS mobile phone application from 2nd June 2020. The same review process was repeated for 75 LDCT scans reported after this time, to assess radiologist nodule management compliance.

In view of the fact that the mobile phone application was novel and under testing, as a quality assurance process, all scan outcomes with nodules were re-reviewed by the author shortly after radiologist reporting.

7.2.3 Evaluation of reliability of the RBH L-RADS mobile phone application

The reliability of the mobile phone application was evaluated by reviewing the cases in which an incorrect RBH L-RADS nodule categorisation was made in the 75 cases

reported with the mobile phone application. In each circumstance, an assessment was made as to whether i) the RBH L-RADS categorisation in the mobile phone application was incorrect, when compared to the BTS-based RBH L-RADS nodule management tabulated algorithm (Figure 7.1) or ii) the mobile phone application was not programmed to give a RBH L-RADS categorisation in the given scenario. The mobile phone application was subsequently amended to correct errors or incorporate scenarios not catered for within the initial application design.

<
Follow up

Scan interval	Follow up
Follow up interval ?	3 months
Is nodule new?	No
Nodule type ?	Solid
Stable? ?	Growing
Size ☐ Volume: $\geq 125\text{mm}^3$ to $< 200\text{mm}$	

RBH L-RADS: **4A**
Management:
Follow up CT in 3 months

Figure 7.1 Example of output from the RBH L-RADS mobile phone application.

In the event where the RBH L-RADS score was deemed to be incorrect in a LDCT report, the mobile phone application was reviewed for the RBH L-RADS score as well as corresponding management recommendation.

7.2.4 Statistical analysis

For evaluation of the radiologist compliance with the original nodule management flow chart, management recommendation accuracy is reported as a proportion of all scans reported, together with a description of any outcome errors made.

For evaluation of the radiologist compliance with the tabulated RBH-LRADS algorithm and mobile phone application, nodule RBH L-RADS categorisation accuracy is reported as a proportion of all nodules given a RBH-LRADS score. Additionally, the accuracy in scan outcomes are reported as a proportion of the 75 scans assessed for both the tabulated algorithm and mobile phone application.

Reliability of the mobile phone application is evaluated through calculating the proportion of nodules for which i) the outcome recommendation in the mobile phone application was incorrect, and ii) no outcome was available in the mobile phone application.

7.3 Results

7.3.1 Radiologist compliance with the nodule management flow chart

Ninety-four lung nodules were reported on 75/260 (28.9%) scans performed between 01/01/2019 and 26/02/2019. Of 75 scans, 62 (82.7%) were baseline screening scans, and 13 (17.3%) were follow-up screening scans. In 65/75 (86.7%) cases, the recommended follow-up interval corresponded to the nodule management algorithm as written in the flow chart (Appendix D).

In 10/75 (13.3%) cases the recommended follow-up interval did not correspond to the nodule management algorithm as written in the flow chart (Appendix D). In 3/10 of these cases, the error identified was deemed to be a transcription error, where a radiologist had inadvertently given two management outcomes on the PACS report. In all three of these cases, the intended follow-up interval was clear from the description

of the nodule in written report and participants were given correct outcome results letters.

In 6/10 cases, the nodule management interval recommended by the reporting radiologist was earlier than recommended by the nodule management protocol. In 4 of these 6 cases, this applied to solid nodules for which nodule follow-up was recommended at 6 weeks (1 case) or 3 months (3 cases), instead of 3 months and 6 months respectively. In the remaining 2/6, this applied to GGNs for which follow-up was recommended at 3 months instead of 12 months.

Finally, in the tenth case the nodule follow-up recommendation was given for 6 months of follow-up, rather than 3 months of follow-up, as the reporting radiologist had made a recommendation based on a different nodule (requiring later follow-up) on the scan. In this case, this did not result in a delay to diagnosis of a lung malignancy; the nodule was subsequently deemed to be benign at 1 year of follow-up.

In summary, of the 75 reported cases evaluated, overall accuracy of follow-up recommendations was 86.7%.

7.3.2 Radiologist compliance with the tabulated L-RADS algorithm

One hundred and thirty-one lung nodules were reported on 75/193 (38.9%) LDCT screening scans performed between 1st January 2020 and 2nd March 2020. Of the 75 scans with nodules, 23 (30.7%) were baseline screening scans, 50 (66.7%) were follow-up screening scans, and 2 (2.7%) were incident round screening scans. One hundred and twenty-one of 131 (92.4%) RBH L-RADS nodule categorisations were correct according to the RBH L-RADS tabulated algorithm. However, in only three of the ten nodule categorisations which were incorrect, the final follow-up recommendation on the scan report was incorrect. In 2/3 cases, the scan recommendation was for a follow-up scan at 6 months rather than 3 months. In neither case did this delay in the follow-

up scan result in a delayed diagnosis of lung cancer. In the third case, a reporting error would have resulted in the premature discharge of a patient with a stable lung nodule (not amenable to volumetric measurements) at 12 months, rather than 24 months of follow-up. This error was detected at the time of reporting and the management outcome altered.

In the remaining seven cases with an incorrect RBH L-RADS classification, the final follow-up recommendation was correct, despite the classification error. This was either because the final follow-up recommendation was determined by a different nodule reported on the scan (3/7), or because the management recommendation was correct, despite the incorrect RBH L-RADS categorisation (4/7), possibly indicating transcription errors in recording RBH L-RADS scores.

In addition to the three outcome errors resulting from incorrect RBH L-RADS categorisations, one further incorrect scan outcome recommendation was detected, which was deemed to be a transcription error, where despite the correct RBH L-RADS categorisation, the reporting radiologist had written an ambiguous outcome recommendation. In this case, the reporting radiologist had recommended both a 12-month follow-up scan and a PET-CT scan, when the participant should have been discharged from follow-up according to the RBH-LRADS categorisation given. This was also reviewed at the time of reporting and corrected.

In summary therefore, on a per nodule basis, 121/131 (92.4%) RBH-LRADS categorisations were correct. However, overall outcome accuracy was 94.7% with the correct follow-up recommendation made in 71/75 cases. Of the four errors, three were caused by incorrect RBH-LRADS classifications.

7.3.3 Radiologist compliance with the RBH L-RADS mobile phone application

One hundred and two lung nodules were reported on 75/543 (13.8%) LDCT screening scans performed between 2nd June 2020 and 11th November 2020. Of the 75 scans with nodules, 29 (38.7%) were baseline screening scans, 27 (36.0%) were follow-up screening scans, and 19 (25.3%) were incident round screening scans.

Overall accuracy of RBH L-RADS nodule categorisations was 97/102 (95.1%). One nodule was not given an RBH L-RADS classification, as the reporting radiologist felt that the mobile phone application did not cater for the clinical scenario (discussed further in Section 7.3.4); a follow-up recommendation was made based on discussions with the Clinical Lead. Four of 102 (3.9%) of RBH-LRADS categorisations were incorrect. In these cases, the radiologist accurately described the nodule in the report, but entered the wrong RBH-LRADS classification on the report. This was despite the correct outcome recommendation being visible within the mobile phone application. However, these RBH L-RADS categorisation errors resulted in only one incorrect final scan outcome recommendation. In the remaining three cases, the correct outcome recommendation was reported despite the wrong RBH L-RADS categorisation. In 1 of these 3 cases, the scan outcome was determined by a different nodule on the scan, although in this case, the mobile phone application was also found to not cater for the particular nodule scenario (discussed in Section 7.3.4). In the second case, the correct outcome had been written on the report, suggesting that the nodule RBH L-RADS categorisation may have been a transcription error. In the third case, the final outcome was the same (namely, "Return to next screening round"), despite the incorrect RBH L-RADS categorisation.

In addition to the one case where the incorrect L-RADS classification resulted in an incorrect outcome recommendation, there were a further 5 cases where the incorrect follow-up recommendation was reported, despite the correct RBH L-RADS classification. In 3/5 cases, this was due to a reporting radiologist misunderstanding how the mobile

phone application should be interpreted, immediately after the mobile phone application had been introduced. In 1/5 cases, no follow-up recommendation was given, and in 1/5 cases the wrong recommendation was given despite the right RBH L-RADS categorisation. These cases were felt likely to be transcription errors.

In summary, 95.1% (97/102) RBH L-RADS categorisations were accurate, and 92% (69/75) management recommendations were correct. However, only one management recommendation error was related to an incorrect RBH L-RADS classification.

7.3.4 Accuracy and inclusiveness of the RBH L-RADS mobile phone application

No scenarios were identified in the mobile phone application in which the incorrect L-RADS score or management recommendation was given for the described nodule. Only two scenarios were identified during the review of cases reported with the mobile phone application where application did not deliver a RBH L-RADS recommendation. The scenarios were as follows:

- 1) A participant with “nodular consolidation” on a baseline screening scan, returned for CT follow-up after a 6-week interval. On the 6-week interval scan, the nodular consolidation had completely resolved, revealing a small 188mm³ discrete solid nodule, which had grown 52% since the earlier scan 6 weeks earlier (when segmented retrospectively on the earlier scan), with a volume doubling time of 70 days. The mobile phone application did not cater for the scenario in which a nodule became apparent at this particular time interval (6 weeks of follow-up). After discussion with the Clinical Lead, a further follow-up scan was performed 3 months after the 6-week follow-up scan.
- 2) The second case concerned a participant in whom a solid nodule was detected on an incident round scan (performed at 19 months from baseline scan). With

retrospect, the reporting radiologist noted that the nodule had been present on the baseline screening scan 19 months earlier. The nodule was not amenable to segmentation using the Veolity™ software and a diameter measurement had to be used. The incident round algorithm within the mobile phone application catered only for old stable solid nodules amenable to volumetry; a corresponding recommendation for diameter measurements had not been programmed.

7.4 Discussion

The purpose of this study was to evaluate radiologist compliance with the West London pilot nodule management protocol using different radiology aids. Radiologist compliance with the nodule management algorithm, as assessed by final scan outcome recommendations, was lowest at 86.7% when using the flow chart algorithms during the first phase of the West London pilot. Although radiologist transcription errors appeared to account for incorrect outcomes in 3/10 cases in which the management recommendation was incorrect, there were a further 7 cases where this was not clearly the case. It is noteworthy that in 5 of these 7 cases, the recommendation made by the reporting radiologist directly followed the BTS guidelines [120], rather than the modified form of the guidelines used in the West London pilot nodule management protocol. This suggests that radiologists may have made nodule management recommendations from memory, based on BTS guidelines, without reference to the flow chart algorithm.

Fewer outcome errors were made by radiologists when using the tabulated RBH L-RADS algorithm (4/75, 5.3%) and the mobile phone application (6/75, 8.0%), corresponding to overall correct management recommendations in 94.7% and 92% of cases respectively. In these scenarios, outcome errors were more frequently related to an incorrect RBH L-RADS categorisation when using the tabulated form of RBH-LRADS (3/4 cases, 75%) than when using the mobile phone application (1/6 cases, 16.7%),

likely reflecting the ease of identifying the correct RBH L-RADS score when using the mobile phone application.

It is noted that on a per nodule basis, correct categorisation of nodules was made in only 121/131 nodules (92.4%) with the tabulated RBH L-RADS algorithm; however, some errors did not affect the final management outcome for cases because of multiple nodules present. Under different circumstances, had these nodules been the only nodules present on the scan, these incorrect categorisations may have influenced final management recommendations. On a per nodule basis RBH L-RADS categorisation was better with the mobile phone application than the tabulated algorithm with 97/102 (95.1%) categorisations correct, again probably reflecting the ease of identification of the particular RBH L-RADS score using the mobile phone application.

In the UK, the RCR provide audit standards to assess adherence to BTS nodule management guidelines and suggest a threshold of 95% adherence to guidelines as an appropriate audit standard [192, 262]. This standard was not met in this study, although when using the RBH-LRADS algorithm both in a tabulated format and in the mobile phone application, correct management recommendations were made in >90% cases. Two local audits performed in UK hospitals for compliance with BTS nodule management guidelines outside of the screening setting have demonstrated 30.8% and 94% compliance to guidelines [263], but other data from the UK are lacking. One small study in the USA documented 94% of LDCT screening studies contained a Lung-RADS™ categorisation and follow-up recommendation, following a local quality improvement project introducing a revised radiology reporting template [266]. The authors do not report however whether the follow-up recommendation corresponded with the L-RADS categorisation in this study. In a survey of 120 radiologists' self-reported adherence to published nodule management guidelines in the USA, 94% reported adhering to guidelines either "very" or "fairly often" in the screening setting [269]. This, however,

was a survey of self-reported familiarity with guidelines and personal practice and not an analysis of actual screening reports.

Apparent transcription errors in reports were identified in a number of cases reported using all three reporting methods (the algorithm, tabulated RBH L-RADS algorithm and the mobile phone application). The format of the PACS report required radiologists to delete management outcomes which were not applicable at the bottom of the report, and in some cases it was apparent that radiologists had not done this correctly. Transcription errors might only be avoided with a fully automated system in which management recommendations are automatically generated by a computer system once nodules have been identified and measured. However, reporting systems of this nature are not in routine use in NHS pilot studies in the UK at present. Alternatively, a PACS reporting with a drop-down outcome box would reduce this particular error, as radiologists would be forced to select a single outcome.

A second purpose of this study was to evaluate the mobile phone application developed to facilitate reporting in the West London pilot. This study showed that it was feasible to develop a mobile phone application to aid radiologist nodule management recommendations. No errors were detected in the mobile phone application management recommendations, but there were two clinical scenarios, as described above, in which the mobile phone application did not produce a RBH L-RADS recommendation. Verbal feedback from reporting radiologists also indicated that the mobile phone application facilitated ease of reporting.

7.5 Summary

This study sought to establish radiologist adherence to the West London nodule management protocol using both a flow chart algorithm and a categorical system similar to Lung-RADS™ (RBH L-RADS), provided in a tabulated format and subsequently in a mobile phone application.

- Radiologist compliance with the nodule management protocol improved with the use of the RBH L-RADS categorisation system when assessed by the final outcome recommendation on the scan, compared to when using a flow chart (BTS style) algorithm.
- Overall outcome recommendations were close to the BTS audit standard of 95% correct recommendations only when using the tabulated RBH L-RADS algorithm (94.7%). However, on a per nodule basis, the correct RBH L-RADS classification was made more frequently using the mobile phone application than the tabulated algorithm.
- The study has demonstrated that the bespoke mobile phone application developed for use in the West London screening pilot can be used as a safe and reliable adjunct to reporting in lung cancer screening. Feedback from reporting radiologists indicated that the use of the mobile phone application was preferable to a tabulated algorithm, in terms of accessibility, speed and ease of use.
- Irrespective of the nodule management algorithm used to report screening scans, errors in transcription in PACS reports were not infrequently observed. Errors related to multiple outcomes could be reduced through a fully automated reporting system, for example within the CAD software, or by use of a drop-down menu in radiology reports. Further studies could assess whether the use of a drop-down menu or other forms of report automation reduces reporting errors.

CHAPTER 8: RADIOLOGIST AGREEMENT ON MANAGEMENT OF COMPLEX NODULE SCENARIOS IN LUNG SCREENING

8.1 Introduction

Throughout the West London pilot, it became apparent that there were several nodule management scenarios in screening for which clear guidelines on management were not available in the BTS nodule management algorithm. In these scenarios, reporting radiologists referred patients to the RBH nodule MDT for further discussion to determine ongoing management. A number of these scenarios involved the initial or subsequent management of new small solid nodules detected on incident round screening, or solid nodules retrospectively deemed to have been present on earlier scans but growing on incident round scans. These scenarios were not catered for within the “follow-up” tab in the mobile phone algorithm. In view of this, the Clinical Lead and author developed a protocol for the follow-up of such nodules, and this was also subsequently programmed into a new tab within the mobile phone application in mid-November 2020 (Figure 8.1). As with the development of the original mobile phone application, the same software developer was provided with a series of decision tables which were programmed into the mobile phone application.

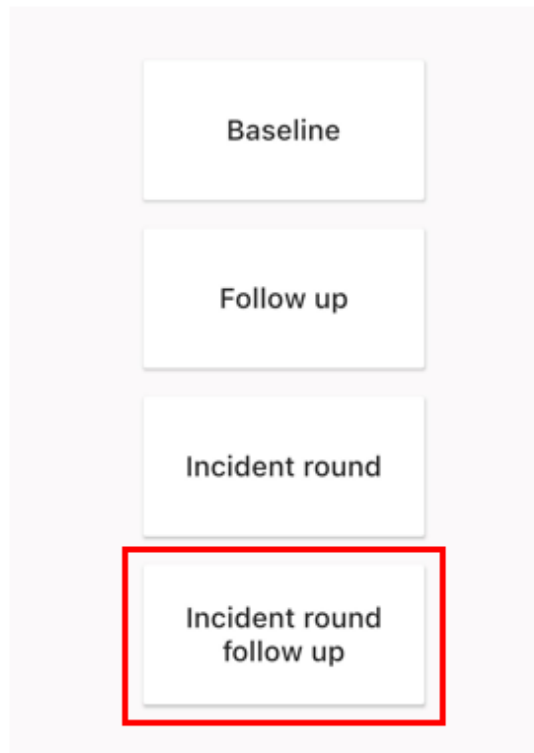


Figure 8.1 New tab (within the red box) in mobile phone application added during the second phase of the pilot.

The aims of this study were two-fold. Firstly, to establish how thoracic radiologists from other UK screening centres manage selected complex nodule scenarios that were identified by the author and Clinical Lead as not being catered for by the BTS nodule management guidelines, and to compare recommendations of radiologists and MDTs from other screening programmes to the management recommended by a member of the RBH nodule MDT. Secondly, to compare interobserver agreement for nodule management in these challenging scenarios with interobserver agreement for a series of nodules scenarios currently catered for within BTS guidelines.

8.2 Methods

This study was carried out as a service evaluation and registered accordingly at the RBH in the context of evaluating nodule management decision reproducibility of the RBH nodule MDT.

8.2.1 Case selection and distribution

Seven complex nodule management scenarios were selected for this study. Four scenarios were identified relating to the management of incident round nodules or nodules at follow-up. Three scenarios related to nodule management at baseline. These latter cases were chosen as the BTS guidelines do not offer management recommendations for these specific situations. Additionally, 5 nodule management cases were identified that were regarded by the author as being non-complex, as they were catered for by the BTS guidelines. Overall, there were 12 scenarios outlined in Table 8.1.

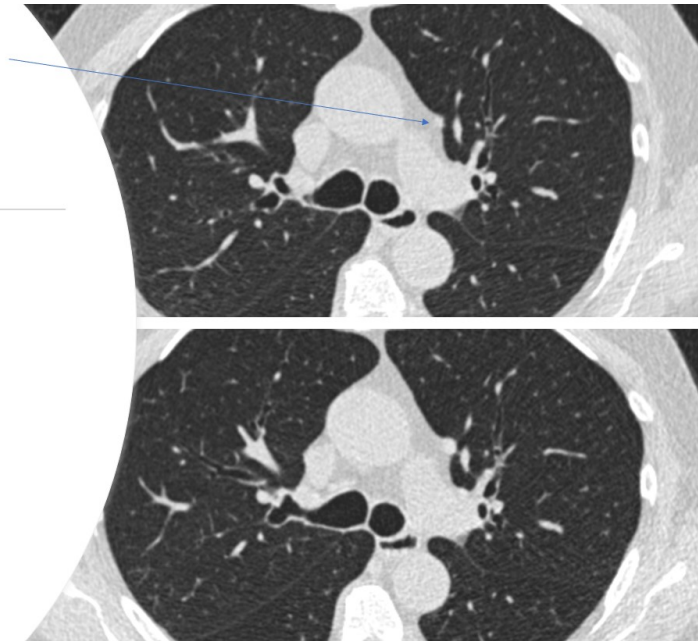
A Microsoft® PowerPoint® (Microsoft 365 Apps for Enterprise, 2017) presentation was distributed by email to 4 radiologists from three other UK screening programmes at UCLH London, Southampton and Leeds, as well as to a member of the RBH nodule MDT. The presentation contained a description of each nodule scenario and 1-2 anonymised LDCT images of the nodule for reference (Figure 8.2; all cases are shown in Appendix J). Reviewers were asked to choose one management option from a list provided (Figure 8.2). Options were identical in all nodule management scenarios, although free text boxes were provided if a reviewer wished to offer an alternative management suggestion, such as a scan at an interval not specified, or for further investigation. Management recommendations were mutually exclusive. All reviewers recorded their responses independently. Completed PowerPoint presentations were returned to the author.

Nodule management scenarios	
Complex scenarios (not covered in BTS guidelines)	
1.	Incident round scan with a solid nodule of 42mm ³ that, in retrospect, was visible on a baseline round scan, then measuring 14mm ³ (VDT 466 days)
2.	Incident round scan with a new solid nodule of 30mm ³ that subsequently grew to 76mm ³ 3 months later
3.	Incident round scan with a new small solid nodule measuring 35mm ³
4.	12-month follow-up scan showing a small solid nodule of 125mm ³ that, in retrospect, had been present 12 months earlier, then measuring 62mm ³ (VDT 362 days)
5.	Baseline scan with a cluster of nodules; the largest nodule measures 1350mm ³
6.	Baseline scan with a cyst with irregular wall thickening
7.	Baseline scan with consolidation measuring 922mm ³
Scenarios covered by BTS guidelines	
8.	Baseline scan with spiculated solid nodule (655mm ³ ; Brock 45%)
9.	Baseline scan with an 8mm ground-glass nodule
10.	3-month from baseline follow-up scan with a solid nodule measuring 597mm ³ , previously 199mm ³ at baseline (VDT 58 days)
11.	Baseline scan with a part solid nodule (solid component 3mm, total size 13mm)
12.	12-month follow-up scan with a 13mm ground-glass nodule (unchanged from baseline)

Table 8.1 Nodule management scenarios selected for distribution to reporting radiologists in other screening centres.

Scenario 4

- Left upper lobe nodule abutting mediastinum not reported at time 0.
- 12 months later the nodule measures **125mm³**
- Retrospective review of old imaging suggests that the nodule measured **62mm³** 12 months earlier.
- VDT is 362 days.



Management

- What management would you choose for this nodule?

- ☐ Discharge to next screening round
- ☐ 3 month follow up scan
- ☐ 12 month follow up scan
- ☐ Follow up scan at other interval (please specify)

(If follow up scan at other interval please specify here)

- ☐ Further investigation (please specify)

(If further investigation – please type here)

Figure 8.2 Example of one nodule management scenario included amongst the 12 cases provided to radiologists, together with the management options given in each case.

8.2.2 Statistical analysis

Overall interobserver agreement for the management recommendation of the twelve nodules was calculated using multirater Fleiss' κ statistics. The κ values were interpreted as follows: poor ($0.00 < \kappa \leq 0.20$); fair ($0.21 < \kappa \leq 0.40$); moderate

($0.41 < \kappa \leq 0.60$); good ($0.61 < \kappa \leq 0.80$); very good ($0.81 < \kappa \leq 1.00$) [270], these are given with 95% CIs. A p value of <0.05 was regarded as statistically significant. All statistics were carried out in SPSS (IBM SPSS Statistics for Windows, Version 26.0, 2019, Armonk, NY: IBM Corp.)

8.3 Results

All 5 reviewers made management recommendations in all 12 cases, giving a total of 60 management selections for the 12 nodules. Where “further investigation” was selected by reviewers, this involved PET-CT in all cases (+/- referral to a multidisciplinary team). The option to perform a “follow-up scan at [an]other interval” was rarely used (4/60 recommendations), by three different reviewers. Reviewer responses are summarised in Table 8.2.

Overall interobserver agreement for management of all twelve nodule scenarios was fair ($\kappa=0.322$, 95% CI 0.319-0.325, $p<0.0005$). However, for the 7 challenging scenarios (not incorporated in BTS guidelines) interobserver agreement was poor ($\kappa=0.170$, 95% CI 0.126-0.175, $p=0.01$). Interobserver agreement was moderate ($\kappa=0.491$, 95% CI 0.485-0.496, $p<0.0005$) in the recommendations for the management of the five scenarios to which the BTS guidelines would apply directly.

Scenario	Reviewer recommendations				
	Discharge	3-month follow-up scan	12-month follow-up scan	Follow-up at other interval	PET-CT and/or MDT
1. Incident round scan with a solid nodule of 42mm ³ that, in retrospect, was visible on a baseline round scan, then measuring 14mm ³ (VDT 466 days)	1/5	1/5	2/5*	1/5	0/5
2. Incident round scan with a new solid nodule of 30mm ³ that subsequently grew to 76mm ³ 3 months later	0/5	5/5*	0/5	0/5	0/5
3. Incident round scan with a new small solid nodule measuring 35mm ³	2/5	1/5	2/5*	0/5	0/5
4. 12-month follow-up scan showing a small solid nodule of 125mm ³ that, in retrospect, had been present 12 months earlier, then measuring 62mm ³ (VDT 362 days)	0/5	2/5	0/5	0/5	3/5*
5. Baseline scan with a cluster of nodules; the largest nodule measures 1350mm ³	2/5	2/5	0/5	1/5*	0/5
6. Baseline scan with a cyst with irregular wall thickening	0/5	1/5	4/5*	0/5	0/5
7. Baseline scan with consolidation measuring 922mm ³	0/5	3/5	0/5	1/5	1/5*
8. Baseline scan with spiculated solid nodule (655mm ³ ; Brock 45%)	0/5	0/5	0/5	0/5	5/5*
9. Baseline scan with an 8mm ground-glass nodule	0/5	3/5*	2/5	0/5	0/5
10. 3-month from baseline follow-up scan with a solid nodule measuring 597mm ³ , previously 199mm ³ at baseline (VDT 58 days)	0/5	1/5	0/5	0/5	4/5*
11. Baseline scan with a part solid nodule (solid component 3mm, total size 13mm)	0/5	4/5*	0/5	1/5	0/5
12. 12-month follow-up scan with a 13mm ground-glass nodule (unchanged from baseline)	1/5	0/5	4/5*	0/5	0/5

Table 8.2 Management recommendations of 5 clinicians for the 12 cases. *Response given by the member of the RBH nodule MDT.

In only 2 cases (cases 2 and 8, Table 8.2) did all 5 reviewers make the same management recommendation. Of the 5 'easier' scenarios in which BTS guidelines applied directly, there was perfect agreement in one case (case 8), and in 3 of the remaining 4 scenarios, only 1 reviewer disagreed with the consensus view of the remaining 4 reviewers. By contrast, in the 7 more challenging scenarios, there was perfect agreement in one case (case 2), but in 3 cases (cases 1, 3 and 5) there was no majority opinion. The greatest variability for management recommendations was seen in case 1 where four different management recommendations were made by the reviewers. In cases 4 and 7, two reviewers disagreed with the majority view held by the other reviewers, and in case 6, one reviewer disagreed with the majority view held by the other reviewers.

In all scenarios, except for scenario 5 and scenario 7, the response of the RBH nodule MDT reviewer was the same as at least one other reviewer. In 4 cases, the representative of the RBH nodule MDT agreed with 3 other reviewers, in 2 cases with 2 other reviewers and in 2 cases with 1 other reviewer.

8.4 Discussion

The purpose of this post hoc analysis was to establish how screening experts would manage several difficult nodule management scenarios compared to a member of the RBH nodule MDT and to assess agreement between 5 expert reviewers whose routine work involved the management of lung cancer screening patients.

This study found that there is considerable variation in the management recommendation for nodules amongst a series of challenging nodule management scenarios. In a large international interobserver agreement study of nodule characterisation and subsequent management recommendations, Nair *et al.* found that amongst 107 radiologists categorising 69 nodules and making subsequent management

recommendations, interobserver agreement on management strategies for nodules was only fair ($\kappa = 0.296$, 95% CI 0.294-0.298) and that 20.6% of radiologists disagreed with the management recommendation given by the majority of radiologists [173], results not dissimilar to the current small interobserver study. The disagreement in management recommendations in the current study was not unexpected, as experienced screening radiologists in the West London pilot had been uncertain about nodule management recommendations, referring several of the cases distributed in this study to the RBH nodule MDT for discussion and consensus opinion. The current NHSE Standard Protocol for lung screening recommends that nodule management should be based on the BTS nodule management guidelines [109, 120]. However, there are no specific guidelines for new or growing small nodules within the BTS guidelines at present, which will inevitably lead to some variability in management of nodules detected at incident screening rounds. These nodule management difficulties will become increasingly frequent as more UK screening programmes carry out incident rounds of screening.

Nodule management after incident round scans is complex due to the lower size threshold for follow-up of new solid nodules after an incident round scan. Walter *et al.* evaluate the risk of malignancy in newly detected nodules at incident round scans which persist after a period of follow-up, using data from the NELSON trial [271]. The authors find that using a VDT of <590 days (measured from the time of identification of the nodule to the first scan after the incident round scan) gives a sensitivity and PPV of lung cancer of 92.0% and 30.7% respectively. Using either VDT of <590 days or a volume of 200mm³ on an incident round follow-up scan (i.e. the first scan after an incident round scan) improves sensitivity to 100.0%, but with a small decrease in the positive predictive value of the test (to 27.2%). In the nodule follow-up protocol of the NELSON trial, all new nodules measuring 50-500mm³ underwent a follow-up scan at 6-8 weeks, after which management was determined by VDT. This protocol, however, is problematic for

small nodules ($50\text{-}80\text{mm}^3$), which are unlikely to warrant intervention at such a short interval given absolute size, therefore likely resulting in further serial scans rather than intervention.

Follow-up recommendations at incident rounds should reflect both the size of the nodule, the (retrospective) presence or absence of the nodule on any previous scans and the VDT when previously present. For very small new nodules ($30\text{-}50\text{mm}^3$), a 3-month follow-up scan may be inappropriate. If a nodule of this small size has a doubling time of 45 days - a rare occurrence in only the most aggressive lung tumours such as small cell tumours - at a 3-month interval, the nodule would measure only $120\text{-}200\text{mm}^3$ and may be too small to consider further investigation or intervention. Therefore, in these cases, a 6-month interval scan might be considered more appropriate, to allow for growth, particularly as the majority of lung tumours will have a much longer VDT.

Similar questions arise at the point of an incident round follow-up scan (i.e. a scan performed 3-6 months after the detection of a new solid nodule on an incident round scan). Ongoing management should be determined by a combination of the absolute size of the nodule and the growth of the nodule with early interval follow-up scans for growing nodules over a particular size threshold (such as 125mm^3), reserving further investigation for only large nodules (for example $>200\text{mm}^3$). Using variable time intervals for follow-up, such as 3 months and 6 months in different circumstances, inevitably adds complexity to nodule management guidelines. Although such complexity was easily incorporated within the RBH L-RADS mobile phone application, these complexities would be more difficult to manage within a flow chart algorithm, similar to the current BTS guidelines.

In two of the twelve scenarios (cases 5 and 7) there may have been ambiguity about whether nodules appeared inflammatory or malignant. In BTS guidelines, large

nodules or opacities measuring 300mm^3 are further risk stratified with the Brock score, with many such opacities warranting a PET-CT scan at baseline and subsequent investigation [120]. In a retrospective review of the screening scans of 3800 patients in a screening programme in the USA, inflammatory or infectious opacities were found in 331/3800 (8.7%) patients, with consolidation in 14/331 (4.2%) of these cases, or 41/3800 (1.1%) of those imaged. Finding malignancy in only 2 participants in this study (both of whom had consolidation, rather than other inflammatory appearing opacities such as a tree in bud pattern), the authors recommend imaging follow-up in 3 months only for those participants with consolidation specifically [272]. In the current post hoc analysis, differing responses from reviewers reflected variability in the management of inflammatory opacities in cases 5 and 7 in the screening setting. Management recommendations varied from discharge to interval scan (at different intervals), or PET-CT scan in these two scenarios. The current protocol used in the West London pilot and also in the SUMMIT study [118] is to discharge participants with opacities regarded as definitely inflammatory by the reporting radiologist, such as those with a clustered “tree-in-bud” pattern on a background of airways disease, but to offer an interval scan at 6 weeks to participants with nodular consolidation ($>300\text{mm}^3$), when there is uncertainty about inflammation versus malignancy. This approach is similar to that proposed by Mendoza *et al.* in their recent analysis [272]. The benefit of an approach involving a short-term follow-up scan is that PET-CT scans and subsequent biopsies might be avoided for participants with inflammatory consolidation which resolves within 6 weeks.

Interobserver agreement for the 5 non-complex scenarios was better than for the 7 challenging scenarios, but there were nonetheless one or two reviewers who disagreed with the majority opinion in 4 of the 5 cases. This likely reflects variations to the BTS guidelines used in local screening pilots. For example, in the case of the baseline scan with an 8mm pGGN, the management recommendation of two radiologists (to

perform a 12-month follow-up scan rather than a 3-month follow-up scan) almost certainly reflects a conservative approach to pGGNs in other screening programmes, as would also have been the recommendation within the West London screening pilot. This indicates that local screening pilots may be adapting BTS guidelines in a similar manner to the West London pilot, in order to reduce over-investigation. This approach is also supported by data from both the NELSON and MILD trials, demonstrating the safety of active surveillance of pGGNs [184, 205].

8.5 Summary

- Over the course of the Incident Round of the West London pilot, a number of nodule management scenarios became apparent for which guidelines are not currently available. In particular, this was the case for determining the initial and subsequent follow-up of small new nodules arising on incident round scans.
- A post hoc analysis seeking to establish how radiologists would manage a variety of challenging nodules scenarios in the screening setting, including small new nodules on incident round scans as well as baseline nodule management scenarios not covered by the current BTS guidelines, found poor interobserver agreement ($\kappa=0.170$) between 5 expert reviewers from different UK screening centres. Interobserver agreement for management of scenarios currently covered by the BTS guidelines was moderate ($\kappa=0.491$).
- There is a need for further formal guidance on nodule management relating to the management of nodules newly detected on incident round scans, as well as for some scenarios at baseline not currently covered by BTS guidelines, such as possibly inflammatory appearing opacities characterised by consolidation.

CHAPTER 9: CONCLUSION

Despite improvements in treatment options for lung cancer over recent years, lung cancer remains the leading cause of cancer related mortality worldwide [1] due to the late presentation of individuals with the disease. Early scepticism regarding the value of screening with chest radiographs has been gradually replaced with growing enthusiasm for lung cancer screening following the findings of two large RCTs demonstrating significant mortality reductions associated with screening, as well as a stage shift at diagnosis [63, 73]. In most of Europe, lung cancer screening remains in a “(pre)planning phase” [273]. However, in the UK, several regional programmes have commenced pilot studies [79, 110, 111, 217, 258] in anticipation of the gradual rollout of lung cancer screening over the coming years.

The West London pilot was an early NHSE funded lung cancer screening pilot seeking to answer a number of questions about the feasibility and practical implementation of lung cancer screening. Chapter 2 described the governance structure and methods used in the West London pilot. The development of a custom-built computer database (in Inflex[®]) was essential to the smooth running of the pilot. This database, in which all data pertaining to the LHC were stored, enabled rapid data extraction, the calculation of risk scores for patients through integrated PLCO_{m2012} and LLP_{v2} risk calculators and a means to generate personalised results letters based on clinical parameters and scan results from the LHC. During the course of this pilot, the risk calculators within the West London screening pilot Inflex[®] database were used to validate the risk calculators later developed by NHSE for use in pilot studies elsewhere in the country, as described in Chapter 2.

At the time of commencing the West London targeted lung cancer screening pilot in August 2018, the West London pilot was one of the earliest NHS funded pilots, delivered through a LHC model. The results of Chapter 3 showed that **lung cancer**

screening can detect lung cancer at a prevalence of >2.0% on a baseline screen, using appropriate risk-based models for participant selection and that screening is capable of identifying participants with early-stage disease.

Furthermore, **rapid turn-around times for scan reporting, investigation of potential lung cancer and results' letter generation can be achieved.** Chapter 3

also sought to compare the two risk models (PLCO_{m2012} and LLP_{v2}) which are currently recommended for use in NHSE pilots across the country. An important finding of this thesis was that in the West London cohort, **the PLCO_{m2012} risk model underestimated overall lung cancer risk compared to the LLP_{v2} model** with 1 in 5 participants diagnosed with lung cancer in this pilot being ineligible for a scan according to this risk model (PLCO <1.51%, but LLP_{v2} >2.5%). Data from pooled studies selecting participants using both risk models will be required to establish whether this a function of local demographic factors and the small overall number of cancers in this study, or whether this model underestimates risk more widely in the UK population. Furthermore, although current NHSE guidelines suggest recruitment with an LLP_{v2} of 2.5% [109], a recent recommendation of the LLP authors has been to consider recruitment with a more selective LLP_{v3} model, at the same 2.5% threshold [97]. In this regard, analysis of data from UK pilots comparing the new LLP_{v3} model and the LLP_{v2} model at a threshold of 2.5% will be informative. Given the slight differences in recruitment criteria used in phase 1 of the West London pilot and the current NHSE protocol, namely that participants who had stopped smoking <40 years of age were excluded from the West London pilot, future research will also evaluate the lung cancer yield and cost effectiveness of screening amongst those who stopped smoking under 40 years of age.

One local pilot study in Manchester suggested that uptake for lung cancer screening might be improved through the use of a mobile community-based scanning unit [79]. It was proposed that a mobile unit provides a safe, non-clinical and non-

intimidating environment for individuals who might be unprepared to attend a hospital environment. The West London pilot compared uptake and attendance at a hospital and mobile scanner in a prospective study. In Chapter 3, it was reported that **the West London pilot was unable to demonstrate the benefits of a mobile scanning unit in improving uptake or attendance for lung cancer screening compared to a hospital site**. Convenience and easy access to screening may be more important than the location of the CT scanner. Use of mobile scanners comes at a high cost and without providing definite benefits in terms of participant uptake compared to hospital scanners. However, such scanners do provide additional capacity which is unlikely to be easily accommodated within NHS hospitals in a normal working week. A mixed model, allowing local pilots to determine the scanner location depending on ease of access to a scanner and overall cost, may be appropriate.

A number of other recent UK-based studies have reported on the prevalence of undiagnosed COPD and CAC in screening cohorts, identifying a potential benefit to patients through diagnosis and treatment of COPD and elevated cardiovascular risk [116, 117, 239, 240]. The protocol of the West London screening pilot had a high threshold for referral to primary care in recognition of the finite capacity of primary care to absorb downstream referrals and to minimise overall cost to primary care. Closer adherence to the current NHSE protocol would have resulted in almost 40% of lung screening participants being referred to primary care, almost four times as many as were actually referred in the West London pilot. It may be appropriate to revise NHSE guidelines to reflect NICE guidelines for the investigation of COPD [216], resulting in fewer referrals focused on symptomatic participants.

To the author's knowledge, the West London pilot has been the first UK pilot to evaluate whether the identification of COPD, CAC and other incidental imaging and clinical findings in screening results in an *actual* change in patient management.

Unexpectedly, it was found in Chapter 4 that **almost 50% of participants referred to primary care were not subsequently reviewed in primary care** and that **fewer than 1/4 of those referred to primary care had a change in clinical management as a result of the LHC recommendation**. If the potential additional benefits of lung cancer screening related to identification and treatment of respiratory and cardiovascular diseases are to be realised, further work must involve close collaboration between lung screening pilots and primary care and future research should explore reasons for low subsequent attendance in primary care.

The latter part of this thesis (Chapters 5-8) had a radiological focus. In Chapter 5, implications for radiology workforce planning were explored, through an analysis of CT reading times in lung cancer screening. Using reading time data from the West London pilot and from the MILD trial in Italy, it was demonstrated that using an appropriate volumetry-based CAD reporting system and a non-narrative report, **reporting of baseline LDCT scans can be carried out in <5 minutes in 80% of cases**. Whilst this is reassuringly rapid, there remains a recognised radiology workforce capacity challenge, particularly in the UK [274]. Although not necessarily optimal, the gradual roll out of local pilot projects, with ongoing quality assurance processes, may be an interim solution until infrastructure and a workforce are in place to support a national screening programme.

Chapter 6 looked at the inter-scan variability in nodule volume measurements of small pulmonary nodules $<150\text{mm}^3$. Given the BTS recommendation to follow small new nodules found on incident round scans, it was felt important to establish what interscan variability might be expected for such small nodules, in order that growth over the short term, or indeed stability over 1 year, can be determined with confidence. Unexpectedly, the results of this study demonstrated **narrower limits of agreement than previous studies, in the region of $\pm 16\%$ of the mean nodule volume**. As explored in

Chapter 6, this may have implications for the follow-up of small nodules growing 15-25% over a period of three months, which may require closer surveillance than the BTS criteria currently suggest.

The West London screening pilot nodule management protocol was based on the BTS nodule management guidelines, with some modifications to minimise over-investigation of small nodules and overdiagnosis of indolent ground-glass tumours. However, during the first round of the screening pilot, and subsequently with the roll out of an incident round of screening, various nodule management scenarios were identified which are not covered in the BTS nodule management guidelines at present. Furthermore, in Chapter 8, it was demonstrated that, **even amongst screening experts from a number of UK screening pilots, management of complex nodule scenarios differed**, indicating a need for updated guidelines, particularly for the management of very small nodules newly detected or growing on incident round scans.

A comprehensive nodule management protocol must, however, be accompanied by a radiology workforce competent to follow such guidelines. Reassuringly, the findings of Chapter 7 confirmed **overall good adherence to the West London nodule management protocol**. One outcome of the work in this study has been to alter the PACS reporting proforma within the Royal Brompton for screening such that only one management outcome recommendation can be selected from a drop-down menu, with the aim to reduce transcription errors and improve overall accuracy of reporting. **The development of a mobile phone application facilitated reporting and improved adherence to the West London pilot nodule management protocol** in the second phase of the pilot. On a typical screening reporting list in a well-established screening programme, a combination of baseline, follow-up and incident round scans might be intermixed, and the mobile phone application allows radiologists to identify the right

follow-up interval for nodules detected at different screening intervals, without needing to refer to several written nodule management guidelines.

Since the outset of the West London pilot, the onset of the SARS-CoV-2 (COVID-19) pandemic has brought about new challenges for screening programmes. There are specific problems for lung screening programmes, for example how spirometry can be safely performed in the setting of circulating SARS-CoV-2 infection in the community and how participants with new chronic cough related to a lung cancer might be distinguished from those with long-COVID. The latter problem may in part account for the dramatic reduction in the number of participants referred as a two-week wait referral from primary care to secondary care throughout the pandemic. In the CCGs involved in this pilot, between 16th March 2020 and 2021, weekly two week wait referrals for suspected lung cancer were up to 85.7% lower than in a baseline comparison period between 7th October – 29th December 2019 (pre-COVID-19) [275]. Recent modelling has suggested that delays in diagnosis and treatment may result in an additional 1235-1372 lung cancer deaths over 5 years in the UK, an increase of 4.8-5.3% [276].

How the COVID-19 pandemic will influence uptake for lung screening in the long term is currently unknown; one study in the USA has demonstrated a significant decline in attendance rates for lung cancer screening amongst young, female, African-American current smokers since the outset of the pandemic [277]. Whilst virtual LHCs are providing an interim solution allowing some screening programmes to recommence screening, ongoing work will be required to provide reassurance to participants and safe environments in which participants can attend LDCT scans, and this is likely to be an important area of research in the short term.

The outcomes of recent national trials have confirmed the benefits of lung cancer screening in reducing lung cancer mortality through early diagnosis. The success of lung cancer screening in the future is predicated upon the delivery of high-quality screening

which is likely to be delivered for the foreseeable future through a growing workforce operating through local programmes. Although there remain a number of unanswered questions (such as optimisation of participant selection through risk models) and areas for further investigation (such as whether overall mortality and the cost effectiveness of screening can be improved through identification *and management* of incidental findings such as coronary calcification), real-world implementation programmes including the West London Pilot have demonstrated that screening can proceed and expand cautiously whilst these questions are answered in real-time.

REFERENCES

1. World Health Organization. International Agency for Research on Cancer. Global Cancer Observatory. Lung cancer fact sheet. Available from <https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf> Last accessed 12 March 2021.
2. Office for National Statistics. Cancer registration statistics, England: 2017. Release date 26 Apr 2019. Available from <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/condition sanddiseases/bulletins/cancerregistrationstatisticsengland/2017> Last accessed 12 Mar 2021.
3. Office for National Statistics. Cancer registration statistics, England. Release date 26 Apr 2019, last updated 16 May 2019. Available from <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/condition sanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland> Last accessed 12 Mar 2021.
4. Office for National Statistics. Deaths registered in England and Wales, 2019. Release date 1 Jul 2020. Available from <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/de aths/datasets/deathsregisteredinenglandandwalesseriesdrreferencetables> Last accessed 12 Mar 2021.
5. Office for National Statistics. Cancer survival in England: adult, stage at diagnosis and childhood - patients followed up to 2018. Release date 12 Aug 2019. Available from <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/condition sanddiseases/bulletins/cancersurvivalinengland/stageatdiagnosisandchildhoodpatientsf ollowedupto2018> Last accessed 12 Mar 2021.
6. Office for National Statistics. Cancer survival in England: national estimates for patients followed up to 2017. Release date 24 Jan 2019. Available from <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/condition sanddiseases/bulletins/cancersurvivalinengland/nationalestimatesforpatientsfollowedup to2017> Last accessed 12 Mar 2021.
7. Doll R, Hill AB. Smoking and carcinoma of the lung; preliminary report. Br Med J. 1950;2(4682):739-48.
8. Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma; a study of 684 proved cases. J Am Med Assoc. 1950;143(4):329-36.

9. Schrek R, Baker LA, et al. Tobacco smoking as an etiologic factor in disease; cancer. *Cancer Res.* 1950;10(1):49-58.

10. Graham H. Smoking prevalence among women in the European community 1950-1990. *Soc Sci Med.* 1996;43(2):243-54.

11. Office for National Statistics. Adult smoking habits in Great Britain. Release date 7 Jul 2020. Available from <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/drugusealcoholandsmoking/datasets/adultsmokinghabitsingreatbritain> Last accessed 16 Mar 2021.

12. Cancer Research UK. Lung cancer mortality statistics. Available from <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/mortality#heading=Two> Last accessed 16 Mar 2021.

13. Malhotra J, Malvezzi M, Negri E, La Vecchia C, Boffetta P. Risk factors for lung cancer worldwide. *Eur Respir J.* 2016;48(3):889-902.

14. Rushton L, Hutchings SJ, Fortunato L, Young C, Evans GS, Brown T, et al. Occupational cancer burden in Great Britain. *Br J Cancer.* 2012;107:S3.

15. Vieira AR, Abar L, Vingeliene S, Chan DSM, Aune D, Navarro-Rosenblatt D, et al. Fruits, vegetables and lung cancer risk: a systematic review and meta-analysis. *Ann Oncol.* 2015;27(1):81-96.

16. Zheng W, Blot WJ, Liao ML, Wang ZX, Levin LI, Zhao JJ, et al. Lung cancer and prior tuberculosis infection in Shanghai. *Br J Cancer.* 1987;56(4):501-4.

17. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG (Eds.) WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. 4th edition. Lyon: International Agency for Research on Cancer; 2015.

18. WHO Classification of Tumours editorial board (Eds.) WHO Classification of Tumours, 5th edition, Volume 5, Thoracic Tumours. Lyon: International Agency for Research on Cancer; 2021.

19. Royal College of Physicians. National Lung Cancer Audit annual report (for the audit period 2018) Version 2. London: Royal College of Physicians; 2021.

20. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International association for the study of lung cancer/american thoracic

society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 2011;6(2):244-85.

21. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma. J Thorac Oncol. 2011;6(2):244-85.

22. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. Chest. 2017;151(1):193-203.

23. Office for National Statistics. Cancer survival in England - adults diagnosed (2013-2017). Release date 12 Aug 2019. Available from <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/condition sanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed> Last accessed 17 Mar 2021.

24. Rami-Porter R. (Ed.) IASLC Staging Manual in Thoracic Oncology, 2nd edition. North Fort Myers, FL: Editorial Rx Press; 2016. 2016.

25. National Institute for Health and Care Excellence (NICE), Lung cancer: diagnosis and management (NG122). 2019. Available from <https://www.nice.org.uk/guidance/ng122> Last accessed 19 Jun 2019.

26. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

27. Simmons CP, Koinis F, Fallon MT, Fearon KC, Bowden J, Solheim TS, et al. Prognosis in advanced lung cancer--A prospective study examining key clinicopathological factors. Lung Cancer. 2015;88(3):304-9.

28. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg. 1995;60(3):615-22; discussion 22-3.

29. Okada M, Yoshikawa K, Hatta T, Tsubota N. Is segmentectomy with lymph node assessment an alternative to lobectomy for non-small cell lung cancer of 2 cm or smaller? Ann Thorac Surg. 2001;71(3):956-60; discussion 61.

30. Okada M, Nishio W, Sakamoto T, Uchino K, Yuki T, Nakagawa A, et al. Effect of tumor size on prognosis in patients with non-small cell lung cancer: the role of segmentectomy as a type of lesser resection. J Thorac Cardiovasc Surg. 2005;129(1):87-93.

31. Landreneau RJ, Schuchert MJ. Is segmentectomy the future? *J Thorac Dis.* 2019;11(1):308-18.
32. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA.* 2010;303(11):1070-6.
33. SABR UK Consortium. Stereotactic Ablative Body Radiation Therapy (SABR): A Resource. v6.1. 2019. Available from <https://www.sabr.org.uk/wp-content/uploads/2019/04/SABRconsortium-guidelines-2019-v6.1.0.pdf> Last accessed 12 March 2021.
34. Grutters JP, Kessels AG, Pijls-Johannesma M, De Ruyscher D, Joore MA, Lambin P. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother Oncol.* 2010;95(1):32-40.
35. Nyman J, Hallqvist A, Lund J, Brustugun OT, Bergman B, Bergström P, et al. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol.* 2016;121(1):1-8.
36. Ball D, Mai GT, Vinod S, Babington S, Ruben J, Kron T, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. *Lancet Oncol.* 2019;20(4):494-503.
37. Jones GS, Baldwin DR. Recent advances in the management of lung cancer. *Clin Med (Lond).* 2018;18(Suppl 2):s41-s6.
38. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. *Nature.* 2018;553(7689):446-54.
39. Waqar SN, Morgensztern D. Treatment advances in small cell lung cancer (SCLC). *Pharmacol Ther.* 2017;180:16-23.
40. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. *Lancet.* 1973;2(7820):63-5.
41. Lad T, Piantadosi S, Thomas P, Payne D, Ruckdeschel J, Giaccone G. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. *Chest.* 1994;106(6 Suppl):320s-3s.

42. Liao M, Zhao J, Zhou Y. [Multimodality therapy of late stage lung cancer]. *Zhonghua Zhong Liu Za Zhi*. 1995;17(5):384-6.
43. Barnes H, See K, Barnett S, Manser R. Surgery for limited-stage small-cell lung cancer. *Cochrane Database Syst Rev*. 2017;4:Cd011917.
44. Liu T, Chen Z, Dang J, Li G. The role of surgery in stage I to III small cell lung cancer: A systematic review and meta-analysis. *PLoS One*. 2018;13(12):e0210001.
45. Wilson JMG, Jungner G. *Principles and practices of screening for disease*. Geneva, Switzerland: World Health Organization; 1968. Available from <http://www.who.int/bulletin/volumes/86/4/07-050112BP.pdf> Last accessed 13 Jan 2021.
46. Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull World Health Organ*. 2008;86(4):317-9.
47. Obuchowski NA, Graham RJ, Baker ME, Powell KA. Ten criteria for effective screening: their application to multislice CT screening for pulmonary and colorectal cancers. *AJR Am J Roentgenol*. 2001;176(6):1357-62.
48. Alibhai SM. Cancer screening: the importance of outcome measures. *Crit Rev Oncol Hematol*. 2006;57(3):215-24.
49. Carter JL, Coletti RJ, Harris RP. Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. *Bmj*. 2015;350:g7773.
50. Black WC. Computed tomography screening for lung cancer: review of screening principles and update on current status. *Cancer*. 2007;110(11):2370-84.
51. Pinsky PF. Principles of Cancer Screening. *Surg Clin North Am*. 2015;95(5):953-66.
52. Sone S, Nakayama T, Honda T, Tsushima K, Li F, Haniuda M, et al. CT findings of early-stage small cell lung cancer in a low-dose CT screening programme. *Lung Cancer*. 2007;56(2):207-15.
53. Frost JK, Ball WC, Jr., Levin ML, Tockman MS, Baker RR, Carter D, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. *Am Rev Respir Dis*. 1984;130(4):549-54.

54. Melamed MR, Flehinger BJ, Zaman MB, Heelan RT, Perchick WA, Martini N. Screening for early lung cancer. Results of the Memorial Sloan-Kettering study in New York. *Chest*. 1984;86(1):44-53.
55. Fontana RS, Sanderson DR, Taylor WF, Woolner LB, Miller WE, Muhm JR, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic study. *Am Rev Respir Dis*. 1984;130(4):561-5.
56. Kubik A, Polak J. Lung cancer detection. Results of a randomized prospective study in Czechoslovakia. *Cancer*. 1986;57(12):2427-37.
57. Bach PB, Kelley MJ, Tate RC, McCrory DC. Screening for lung cancer: a review of the current literature. *Chest*. 2003;123(1 Suppl):72s-82s.
58. Oken MM, Hocking WG, Kvale PA, Andriole GL, Buys SS, Church TR, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. *JAMA*. 2011;306(17):1865-73.
59. Henschke CI. Early lung cancer action project: overall design and findings from baseline screening. *Cancer*. 2000;89(11 Suppl):2474-82.
60. Tammemagi MC, Schmidt H, Martel S, McWilliams A, Goffin JR, Johnston MR, et al. Participant selection for lung cancer screening by risk modelling (the Pan-Canadian Early Detection of Lung Cancer [PanCan] study): a single-arm, prospective study. *Lancet Oncol*. 2017;18(11):1523-31.
61. Marshall HM, Yang IA, Bowman RV, Fong KM. Editorial on PanCan study. *Transl Lung Cancer Res*. 2018;7(Suppl 1):S57-s9.
62. Infante M, Lutman FR, Cavuto S, Brambilla G, Chiesa G, Passera E, et al. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. *Lung Cancer*. 2008;59(3):355-63.
63. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395-409.
64. Blanchon T, Bréchet JM, Grenier PA, Ferretti GR, Lemarié E, Milleron B, et al. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). *Lung Cancer*. 2007;58(1):50-8.

65. van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R, et al. Management of lung nodules detected by volume CT scanning. *N Engl J Med*. 2009;361(23):2221-9.
66. Pedersen JH, Ashraf H, Dirksen A, Bach K, Hansen H, Toennesen P, et al. The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence round. *J Thorac Oncol*. 2009;4(5):608-14.
67. Lopes Pegna A, Picozzi G, Mascalchi M, Maria Carozzi F, Carrozzi L, Comin C, et al. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. *Lung Cancer*. 2009;64(1):34-40.
68. Pastorino U, Rossi M, Rosato V, Marchiano A, Sverzellati N, Morosi C, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev*. 2012;21(3):308-15.
69. Becker N, Motsch E, Gross ML, Eigentopf A, Heussel CP, Dienemann H, et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. *J Cancer Res Clin Oncol*. 2012;138(9):1475-86.
70. Field JK, Duffy SW, Baldwin DR, Brain KE, Devaraj A, Eisen T, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health Technol Assess*. 2016;20(40):1-146.
71. Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive services task force recommendation. *Ann Intern Med*. 2013;159(6):411-20.
72. Aberle DR. Implementing lung cancer screening: the US experience. *Clin Radiol*. 2017;72(5):401-6.
73. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. *N Engl J Med*. 2020;382(6):503-13.
74. Silva M, Pastorino U, Sverzellati N. Lung cancer screening with low-dose CT in Europe: strength and weakness of diverse independent screening trials. *Clin Radiol*. 2017;72(5):389-400.
75. Oudkerk M, Liu S, Heuvelmans MA, Walter JE, Field JK. Lung cancer LDCT screening and mortality reduction - evidence, pitfalls and future perspectives. *Nat Rev Clin Oncol*. 2021;18(3):135-51.

76. Pastorino U, Silva M, Sestini S, Sabia F, Boeri M, Cantarutti A, et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial: new confirmation of lung cancer screening efficacy. *Ann Oncol*. 2019;30(7):1162-9.
77. Becker N, Motsch E, Trotter A, Heussel CP, Dienemann H, Schnabel PA, et al. Lung cancer mortality reduction by LDCT screening-Results from the randomized German LUSI trial. *Int J Cancer*. 2020;146(6):1503-13.
78. Paci E, Puliti D, Lopes Pegna A, Carrozzi L, Picozzi G, Falaschi F, et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. *Thorax*. 2017;72(9):825-31.
79. Crosbie PA, Balata H, Evison M, Attack M, Bayliss-Brideaux V, Colligan D, et al. Implementing lung cancer screening: baseline results from a community-based 'Lung Health Check' pilot in deprived areas of Manchester. *Thorax*. 2019;74(4):405-9.
80. Oudkerk M, Devaraj A, Vliegenthart R, Henzler T, Prosch H, Heussel CP, et al. European position statement on lung cancer screening. *Lancet Oncol*. 2017;18(12):e754-e66.
81. Patz EF, Jr., Pinsky P, Gatsonis C, Sicks JD, Kramer BS, Tammemagi MC, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med*. 2014;174(2):269-74.
82. Team NLSTR. Lung Cancer Incidence and Mortality with Extended Follow-up in the National Lung Screening Trial. *J Thorac Oncol*. 2019;14(10):1732-42.
83. Thomas A, Pattanayak P, Szabo E, Pinsky P. Characteristics and Outcomes of Small Cell Lung Cancer Detected by CT Screening. *Chest*. 2018;154(6):1284-90.
84. Scholten ET, Horeweg N, de Koning HJ, Vliegenthart R, Oudkerk M, Mali WP, et al. Computed tomographic characteristics of interval and post screen carcinomas in lung cancer screening. *Eur Radiol*. 2015;25(1):81-8.
85. Devaraj A. Missed cancers in lung cancer screening--more than meets the eye. *Eur Radiol*. 2015;25(1):89-91.
86. Tonge JE, Attack M, Crosbie PA, Barber PV, Booton R, Colligan D. "To know or not to know..." Push and pull in ever smokers lung screening uptake decision-making intentions. *Health expectations : an international journal of public participation in health care and health policy*. 2019;22(2):162-72.

87. National Institute for Health and Care Excellence (NICE). 2014. Developing NICE guidelines: the manual. Process and Methods (PMG20). Available from <https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation> Last accessed 10 June 2020.
88. McPhail S, Elliss-Brookes L, Shelton J, Ives A, Greenslade M, Vernon S, et al. Emergency presentation of cancer and short-term mortality. *Br J Cancer*. 2013;109(8):2027-34.
89. Black WC, Gareen IF, Soneji SS, Sicks JD, Keeler EB, Aberle DR, et al. Cost-effectiveness of CT screening in the National Lung Screening Trial. *N Engl J Med*. 2014;371(19):1793-802.
90. Kovalchik SA, Tammemagi M, Berg CD, Caporaso NE, Riley TL, Korch M, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med*. 2013;369(3):245-54.
91. Gray EP, Teare MD, Stevens J, Archer R. Risk Prediction Models for Lung Cancer: A Systematic Review. *Clin Lung Cancer*. 2016;17(2):95-106.
92. Ten Haaf K, Jeon J, Tammemagi MC, Han SS, Kong CY, Plevritis SK, et al. Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. *PLoS Med*. 2017;14(4):e1002277.
93. Etzel CJ, Kachroo S, Liu M, D'Amelio A, Dong Q, Cote ML, et al. Development and validation of a lung cancer risk prediction model for African-Americans. *Cancer Prev Res (Phila)*. 2008;1(4):255-65.
94. Bach PB, Kattan MW, Thornquist MD, Kris MG, Tate RC, Barnett MJ, et al. Variations in lung cancer risk among smokers. *J Natl Cancer Inst*. 2003;95(6):470-8.
95. Hoggart C, Brennan P, Tjonneland A, Vogel U, Overvad K, Ostergaard JN, et al. A risk model for lung cancer incidence. *Cancer Prev Res (Phila)*. 2012;5(6):834-46.
96. Cassidy A, Myles JP, van Tongeren M, Page RD, Liloglou T, Duffy SW, et al. The LLP risk model: an individual risk prediction model for lung cancer. *Br J Cancer*. 2008;98(2):270-6.
97. Field JK, Vulkan D, Davies MPA, Duffy SW, Gabe R. Liverpool Lung Project lung cancer risk stratification model: calibration and prospective validation. *Thorax*. 2021;76(2):161-8.

98. Katki HA, Kovalchik SA, Berg CD, Cheung LC, Chaturvedi AK. Development and Validation of Risk Models to Select Ever-Smokers for CT Lung Cancer Screening. *JAMA*. 2016;315(21):2300-11.
99. Muller DC, Johansson M, Brennan P. Lung Cancer Risk Prediction Model Incorporating Lung Function: Development and Validation in the UK Biobank Prospective Cohort Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35(8):861-9.
100. Tammemagi CM, Pinsky PF, Caporaso NE, Kvale PA, Hocking WG, Church TR, et al. Lung cancer risk prediction: Prostate, Lung, Colorectal And Ovarian Cancer Screening Trial models and validation. *J Natl Cancer Inst*. 2011;103(13):1058-68.
101. Tammemagi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, et al. Selection criteria for lung-cancer screening. *N Engl J Med*. 2013;368(8):728-36.
102. Meza R, Hazelton WD, Colditz GA, Moolgavkar SH. Analysis of lung cancer incidence in the Nurses' Health and the Health Professionals' Follow-Up Studies using a multistage carcinogenesis model. *Cancer Causes Control*. 2008;19(3):317-28.
103. Li K, Husing A, Sookthai D, Bergmann M, Boeing H, Becker N, et al. Selecting High-Risk Individuals for Lung Cancer Screening: A Prospective Evaluation of Existing Risk Models and Eligibility Criteria in the German EPIC Cohort. *Cancer Prev Res (Phila)*. 2015;8(9):777-85.
104. D'Amelio AM, Jr., Cassidy A, Asomaning K, Raji OY, Duffy SW, Field JK, et al. Comparison of discriminatory power and accuracy of three lung cancer risk models. *Br J Cancer*. 2010;103(3):423-9.
105. Katki HA, Kovalchik SA, Petito LC, Cheung LC, Jacobs E, Jemal A, et al. Implications of Nine Risk Prediction Models for Selecting Ever-Smokers for Computed Tomography Lung Cancer Screening. *Ann Intern Med*. 2018;169(1):10-9.
106. Field JK, Heuvelmans MA, Devaraj A, Heussel CP, Baldwin DR, Vliegenthart R, et al. Low-dose CT for lung cancer screening - Authors' reply. *Lancet Oncol*. 2018;19(3):e135-e6.
107. Ten Haaf K, De Koning H, Field J. P2.13-025 Selecting the Risk Cut off for the LLP Model. *J Thorac Oncol*. 2017;12(11):S2174.
108. Raji OY, Duffy SW, Agbaje OF, Baker SG, Christiani DC, Cassidy A, et al. Predictive accuracy of the Liverpool Lung Project risk model for stratifying patients for computed tomography screening for lung cancer: a case-control and cohort validation study. *Ann Intern Med*. 2012;157(4):242-50.

109. NHS England - National Cancer Programme. Targeted Screening for Lung Cancer with Low Radiation Dose Computed Tomography. Standard Protocol prepared for the Targeted Lung Health Checks Programme. 2019. Available from <https://www.england.nhs.uk/wp-content/uploads/2019/02/targeted-lung-health-checks-standard-protocol-v1.pdf> Last accessed 25 Jun 2021.
110. Crosbie PA, Gabe R, Simmonds I, Kennedy M, Rogerson S, Ahmed N, et al. Yorkshire Lung Screening Trial (YLST): protocol for a randomised controlled trial to evaluate invitation to community-based low-dose CT screening for lung cancer versus usual care in a targeted population at risk. *BMJ Open*. 2020;10(9):e037075.
111. Ruparel M, Quaife SL, Dickson JL, Horst C, Tisi S, Hall H, et al. Lung Screen Uptake Trial: results from a single lung cancer screening round. *Thorax*. 2020;75(10):908-12.
112. Ghimire B, Maroni R, Vulkan D, Shah Z, Gaynor E, Timoney M, et al. Evaluation of a health service adopting proactive approach to reduce high risk of lung cancer: The Liverpool Healthy Lung Programme. *Lung Cancer*. 2019;134:66-71.
113. Bednarek M, Maciejewski J, Wozniak M, Kuca P, Zielinski J. Prevalence, severity and underdiagnosis of COPD in the primary care setting. *Thorax*. 2008;63(5):402-7.
114. Kaplan A, Thomas M. Screening for COPD: the gap between logic and evidence. *Eur Respir Rev*. 2017;26(143).
115. Wedzicha JA, Singh R, Mackay AJ. Acute COPD exacerbations. *Clin Chest Med*. 2014;35(1):157-63.
116. Balata H, Harvey J, Barber PV, Colligan D, Duerden R, Elton P, et al. Spirometry performed as part of the Manchester community-based lung cancer screening programme detects a high prevalence of airflow obstruction in individuals without a prior diagnosis of COPD. *Thorax*. 2020;75(8):655-60.
117. Ruparel M, Quaife SL, Dickson JL, Horst C, Tisi S, Hall H, et al. Prevalence, Symptom Burden and Under-Diagnosis of Chronic Obstructive Pulmonary Disease in a Lung Cancer Screening Cohort. *Ann Am Thorac Soc*. 2020.
118. Horst C, Dickson JL, Tisi S, Ruparel M, Nair A, Devaraj A, et al. Delivering low-dose CT screening for lung cancer: a pragmatic approach. *Thorax*. 2020;75(10):831-2.
119. SUMMIT trial protocol. Available from <https://clinicaltrials.gov/ct2/show/NCT03934866> Last accessed 18 Jun 2021.

120. Callister ME, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax*. 2015;70 Suppl 2:ii1-ii54.
121. Jemal A, Fedewa SA. Lung Cancer Screening With Low-Dose Computed Tomography in the United States-2010 to 2015. *JAMA Oncol*. 2017;3(9):1278-81.
122. Jenkins J. Breast screening performance report shows we are detecting cancers early but uptake is falling. 2018. Available from <https://phescreening.blog.gov.uk/2018/02/06/breast-screening-performance-report-shows-we-are-detecting-cancers-early-but-uptake-is-falling/> Last accessed 17 Mar 2021.
123. Quaife SL, Ruparel M, Beeken RJ, McEwen A, Isitt J, Nolan G, et al. The Lung Screen Uptake Trial (LSUT): protocol for a randomised controlled demonstration lung cancer screening pilot testing a targeted invitation strategy for high risk and 'hard-to-reach' patients. *BMC Cancer*. 2016;16:281.
124. Quaife SL, Ruparel M, Dickson JL, Beeken RJ, McEwen A, Baldwin DR, et al. Lung Screen Uptake Trial (LSUT): Randomized Controlled Clinical Trial Testing Targeted Invitation Materials. *Am J Respir Crit Care Med*. 2020;201(8):965-75.
125. Allisy-Roberts P WJ. *Farr's Physics for Medical Imaging*. 2 ed. London: Elsevier Ltd; 2008 2008.
126. Lee CH, Goo JM, Ye HJ, Ye SJ, Park CM, Chun EJ, et al. Radiation dose modulation techniques in the multidetector CT era: from basics to practice. *Radiographics*. 2008;28(5):1451-9.
127. Maldjian PD, Goldman AR. Reducing radiation dose in body CT: a primer on dose metrics and key CT technical parameters. *AJR Am J Roentgenol*. 2013;200(4):741-7.
128. Wall BF, Haylock R, Jansen JTM, Hillier MC, Hart D, Shrimpton PC. Radiation risks from medical x-ray examinations as a function of the age and sex of the patient. Health Protection Agency Report HPA-CRCE-028, 2011. Chilton, UK: Health Protection Agency; 2011. Available from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/340147/HPA-CRCE-028_for_website.pdf Last accessed 20 May 2021.
129. Saltybaeva N, Martini K, Frauenfelder T, Alkadhi H. Organ Dose and Attributable Cancer Risk in Lung Cancer Screening with Low-Dose Computed Tomography. *PLoS One*. 2016;11(5):e0155722.
130. Murugan VA, Kalra MK, Rehani M, Digumarthy SR. Lung Cancer Screening: Computed Tomography Radiation and Protocols. *J Thorac Imaging*. 2015;30(5):283-9.

131. de Margerie-Mellon C, de Bazelaire C, Montlahuc C, Lambert J, Martineau A, Coulon P, et al. Reducing Radiation Dose at Chest CT: Comparison Among Model-based Type Iterative Reconstruction, Hybrid Iterative Reconstruction, and Filtered Back Projection. *Acad Radiol*. 2016;23(10):1246-54.
132. Hansell DM, Bankier AA, MacMahon H, McCloud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology*. 2008;246(3):697-722.
133. Napel S, Rubin GD, Jeffrey RB. STS-MIP: A New Reconstruction Technique for CT of the Chest. *J Comput Assist Tomogr*. 1993;17(5):832-8.
134. Gruden JF, Ouanounou S, Tigges S, Norris SD, Klausner TS. Incremental Benefit of Maximum-Intensity-Projection Images on Observer Detection of Small Pulmonary Nodules Revealed by Multidetector CT. *American Journal of Roentgenology*. 2002;179(1):149-57.
135. Wormanns D, Ludwig K, Beyer F, Heindel W, Diederich S. Detection of pulmonary nodules at multirow-detector CT: effectiveness of double reading to improve sensitivity at standard-dose and low-dose chest CT. *Eur Radiol*. 2005;15(1):14-22.
136. Cai J, Xu D, Liu S, Cham MD. The Added Value of Computer-aided Detection of Small Pulmonary Nodules and Missed Lung Cancers. *J Thorac Imaging*. 2018;33(6):390-5.
137. Firmino M, Morais AH, Mendoca RM, Dantas MR, Hekis HR, Valentim R. Computer-aided detection system for lung cancer in computed tomography scans: review and future prospects. *Biomed Eng Online*. 2014;13:41.
138. Zhao Y, de Bock GH, Vliegenthart R, van Klaveren RJ, Wang Y, Bogoni L, et al. Performance of computer-aided detection of pulmonary nodules in low-dose CT: comparison with double reading by nodule volume. *Eur Radiol*. 2012;22(10):2076-84.
139. Al Mohammad B, Brennan PC, Mello-Thoms C. A review of lung cancer screening and the role of computer-aided detection. *Clin Radiol*. 2017;72(6):433-42.
140. Saghir Z, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. *Thorax*. 2012;67(4):296-301.
141. de Hoop B, Gietema H, van Ginneken B, Zanen P, Groenewegen G, Prokop M. A comparison of six software packages for evaluation of solid lung nodules using semi-automated volumetry: what is the minimum increase in size to detect growth in repeated CT examinations. *Eur Radiol*. 2009;19(4):800-8.

142. Wang Y, de Bock GH, van Klaveren RJ, van Ooyen P, Tukker W, Zhao Y, et al. Volumetric measurement of pulmonary nodules at low-dose chest CT: effect of reconstruction setting on measurement variability. *Eur Radiol*. 2010;20(5):1180-7.
143. Devaraj A, van Ginneken B, Nair A, Baldwin D. Use of Volumetry for Lung Nodule Management: Theory and Practice. *Radiology*. 2017;284(3):630-44.
144. Gietema HA, Schaefer-Prokop CM, Mali WP, Groenewegen G, Prokop M. Pulmonary nodules: Interscan variability of semiautomated volume measurements with multisection CT-- influence of inspiration level, nodule size, and segmentation performance. *Radiology*. 2007;245(3):888-94.
145. Goodman LR, Gulsun M, Washington L, Nagy PG, Piacsek KL. Inherent variability of CT lung nodule measurements in vivo using semiautomated volumetric measurements. *AJR Am J Roentgenol*. 2006;186(4):989-94.
146. Collins VP, Loeffler RK, Tivey H. Observations on growth rates of human tumors. *Am J Roentgenol Radium Ther Nucl Med*. 1956;76(5):988-1000.
147. Xu XL. The biological foundation of the Gompertz model. *Int J Biomed Comput*. 1987;20(1-2):35-9.
148. Lindell RM, Hartman TE, Swensen SJ, Jett JR, Midthun DE, Mandrekar JN. 5-year lung cancer screening experience: growth curves of 18 lung cancers compared to histologic type, CT attenuation, stage, survival, and size. *Chest*. 2009;136(6):1586-95.
149. Heuvelmans MA, Vliegenthart R, de Koning HJ, Groen HJM, van Putten M, Yousaf-Khan U, et al. Quantification of growth patterns of screen-detected lung cancers: The NELSON study. *Lung Cancer*. 2017;108:48-54.
150. Brown M, Browning P, Wahi-Anwar MW, Murphy M, Delgado J, Greenspan H, et al. Integration of Chest CT CAD into the Clinical Workflow and Impact on Radiologist Efficiency. *Acad Radiol*. 2019;26(5):626-31.
151. Beigelman-Aubry C, Raffy P, Yang W, Castellino RA, Grenier PA. Computer-aided detection of solid lung nodules on follow-up MDCT screening: evaluation of detection, tracking, and reading time. *AJR Am J Roentgenol*. 2007;189(4):948-55.
152. Beyer F, Zierott L, Fallenberg EM, Juergens KU, Stoeckel J, Heindel W, et al. Comparison of sensitivity and reading time for the use of computer-aided detection (CAD) of pulmonary nodules at MDCT as concurrent or second reader. *Eur Radiol*. 2007;17(11):2941-7.

153. Siegelman SS, Khouri NF, Scott WW, Jr., Leo FP, Hamper UM, Fishman EK, et al. Pulmonary hamartoma: CT findings. *Radiology*. 1986;160(2):313-7.
154. Barnett J, Pulzato I, Wilson R, Padley S, Nicholson AG, Devaraj A. Perinodular Vascularity Distinguishes Benign Intrapulmonary Lymph Nodes From Lung Cancer on Computed Tomography. *J Thorac Imaging*. 2019;34(5):326-8.
155. Henschke CI, Yankelevitz DF, Naidich DP, McCauley DI, McGuinness G, Libby DM, et al. CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. *Radiology*. 2004;231(1):164-8.
156. Henschke CI, Yip R, Yankelevitz DF, Smith JP. Definition of a positive test result in computed tomography screening for lung cancer: a cohort study. *Ann Intern Med*. 2013;158(4):246-52.
157. Yip R, Henschke CI, Yankelevitz DF, Smith JP. CT screening for lung cancer: alternative definitions of positive test result based on the national lung screening trial and international early lung cancer action program databases. *Radiology*. 2014;273(2):591-6.
158. Horeweg N, Scholten ET, de Jong PA, van der Aalst CM, Weenink C, Lammers JW, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. *Lancet Oncol*. 2014;15(12):1342-50.
159. Zhao YR, van Ooijen PM, Dorrius MD, Heuvelmans M, de Bock GH, Vliegenthart R, et al. Comparison of three software systems for semi-automatic volumetry of pulmonary nodules on baseline and follow-up CT examinations. *Acta Radiol*. 2014;55(6):691-8.
160. Horeweg N, van Rosmalen J, Heuvelmans MA, van der Aalst CM, Vliegenthart R, Scholten ET, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. *The Lancet Oncology*. 2014;15(12):1332-41.
161. Byers TE, Vena JE, Rzepka TF. Predilection of lung cancer for the upper lobes: an epidemiologic inquiry. *J Natl Cancer Inst*. 1984;72(6):1271-5.
162. Wilson DO, Ryan A, Fuhrman C, Schuchert M, Shapiro S, Siegfried JM, et al. Doubling times and CT screen-detected lung cancers in the Pittsburgh Lung Screening Study. *Am J Respir Crit Care Med*. 2012;185(1):85-9.

163. Hasegawa M, Sone S, Takashima S, Li F, Yang ZG, Maruyama Y, et al. Growth rate of small lung cancers detected on mass CT screening. *Br J Radiol*. 2000;73(876):1252-9.
164. Henschke CI, Yankelevitz DF, Yip R, Reeves AP, Farooqi A, Xu D, et al. Lung cancers diagnosed at annual CT screening: volume doubling times. *Radiology*. 2012;263(2):578-83.
165. Heuvelmans MA, Oudkerk M, de Bock GH, de Koning HJ, Xie X, van Ooijen PM, et al. Optimisation of volume-doubling time cutoff for fast-growing lung nodules in CT lung cancer screening reduces false-positive referrals. *Eur Radiol*. 2013;23(7):1836-45.
166. McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med*. 2013;369(10):910-9.
167. Winkler Wille MM, van Riel SJ, Saghir Z, Dirksen A, Pedersen JH, Jacobs C, et al. Predictive Accuracy of the PanCan Lung Cancer Risk Prediction Model -External Validation based on CT from the Danish Lung Cancer Screening Trial. *Eur Radiol*. 2015;25(10):3093-9.
168. Nair VS, Sundaram V, Desai M, Gould MK. Accuracy of Models to Identify Lung Nodule Cancer Risk in the National Lung Screening Trial. *Am J Respir Crit Care Med*. 2018;197(9):1220-3.
169. Al-Ameri A, Malhotra P, Thygesen H, Plant PK, Vaidyanathan S, Karthik S, et al. Risk of malignancy in pulmonary nodules: A validation study of four prediction models. *Lung Cancer*. 2015;89(1):27-30.
170. Zhao H, Marshall HM, Yang IA, Bowman RV, Ayres J, Crossin J, et al. Screen-detected subsolid pulmonary nodules: long-term follow-up and application of the PanCan lung cancer risk prediction model. *Br J Radiol*. 2016;89(1060):20160016.
171. Winter A, Aberle DR, Hsu W. External validation and recalibration of the Brock model to predict probability of cancer in pulmonary nodules using NLST data. *Thorax*. 2019;74(6):551-63.
172. Herder GJ, van Tinteren H, Golding RP, Kostense PJ, Comans EF, Smit EF, et al. Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglucose positron emission tomography. *Chest*. 2005;128(4):2490-6.
173. Nair A, Bartlett EC, Walsh SLF, Wells AU, Navani N, Hardavella G, et al. Variable radiological lung nodule evaluation leads to divergent management recommendations. *Eur Respir J*. 2018;52(6).

174. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. *Radiology*. 2017;284(1):228-43.
175. Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e93S-e120S.
176. American College of Radiology. Lung-RADS™ (v1.0) Assessment Categories. 2014. Available from https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADS_AssessmentCategories.pdf Last accessed 27 Jan 2021.
177. American College of Radiology. Lung-RADS™ (v1.1) Assessment Categories. 2019. Available from <https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf> Last accessed 27 Jan 2021.
178. Walter JE, Heuvelmans MA, de Jong PA, Vliegenthart R, van Ooijen PMA, Peters RB, et al. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. *Lancet Oncol*. 2016;17(7):907-16.
179. Baldwin D, Callister M, Akram A, Cane P, Draffan J, Franks K, et al. British Thoracic Society quality standards for the investigation and management of pulmonary nodules. *BMJ Open Respir Res*. 2018;5(1):e000273.
180. Silva M, Sverzellati N, Manna C, Negrini G, Marchiano A, Zompatori M, et al. Long-term surveillance of ground-glass nodules: evidence from the MILD trial. *J Thorac Oncol*. 2012;7(10):1541-6.
181. Felix L, Serra-Tosio G, Lantuejoul S, Timsit JF, Moro-Sibilot D, Brambilla C, et al. CT characteristics of resolving ground-glass opacities in a lung cancer screening programme. *Eur J Radiol*. 2011;77(3):410-6.
182. Lee SM, Park CM, Goo JM, Lee CH, Lee HJ, Kim KG, et al. Transient part-solid nodules detected at screening thin-section CT for lung cancer: comparison with persistent part-solid nodules. *Radiology*. 2010;255(1):242-51.
183. Callister ME, Baldwin DR. How should pulmonary nodules be optimally investigated and managed? *Lung Cancer*. 2016;91:48-55.

184. Scholten ET, de Jong PA, de Hoop B, van Klaveren R, van Amelsvoort-van de Vorst S, Oudkerk M, et al. Towards a close computed tomography monitoring approach for screen detected subsolid pulmonary nodules? *Eur Respir J*. 2015;45(3):765-73.
185. MacRedmond R, Logan PM, Lee M, Kenny D, Foley C, Costello RW. Screening for lung cancer using low dose CT scanning. *Thorax*. 2004;59(3):237-41.
186. van de Wiel JC, Wang Y, Xu DM, van der Zaag-Loonen HJ, van der Jagt EJ, van Klaveren RJ, et al. Neglectable benefit of searching for incidental findings in the Dutch-Belgian lung cancer screening trial (NELSON) using low-dose multidetector CT. *Eur Radiol*. 2007;17(6):1474-82.
187. Rampinelli C, Preda L, Maniglio M, Sirica L, Travaini LL, Veronesi G, et al. Extrapulmonary malignancies detected at lung cancer screening. *Radiology*. 2011;261(1):293-9.
188. Kinsinger LS, Anderson C, Kim J, Larson M, Chan SH, King HA, et al. Implementation of Lung Cancer Screening in the Veterans Health Administration. *JAMA Intern Med*. 2017;177(3):399-406.
189. NHS England - National Cancer Programme. Targeted Screening for Lung Cancer with Low Radiation Dose Computed Tomography. Quality Assurance Standards prepared for the Targeted Lung Health Checks Programme. 2019. Available from <https://www.england.nhs.uk/wp-content/uploads/2019/02/targeted-screening-for-lung-cancer-quality-assurance-standard.pdf> Last accessed 25 Jun 2021.
190. Canadian Association of Radiologists. Guide on CT Screening for Lung Cancer. 2016. Available from <https://car.ca/wp-content/uploads/CT-Screening-for-Lung-Cancer-2017.pdf> Last accessed 12 Jan 2021.
191. Eisenberg RL, Bankier AA, Boiselle PM. Compliance with Fleischner Society guidelines for management of small lung nodules: a survey of 834 radiologists. *Radiology*. 2010;255(1):218-24.
192. Royal College of Radiologists. Compliance with the British Thoracic Society guidelines for follow-up of indeterminate pulmonary nodules on CT. 2013. Available from <https://www.rcr.ac.uk/audit/compliance-british-thoracic-society-guidelines-follow-indeterminate-pulmonary-nodules-ct> Last accessed 14 Jan 2021.
193. NHS Health Research Authority and Medical Research Council. Is my study research? 2017. Available from <http://www.hra-decisiontools.org.uk/research/> Last accessed 13 Oct 2020.

194. Healthcare Quality Improvement Partnership. HQIP guide for clinical audit, research and service review. 2011. Available from <https://www.hqip.org.uk/resource/hqip-guide-for-clinical-audit-research-and-service-review/#.X7aDvOVxc2z> Last accessed 19 Nov 2020.
195. Office for National Statistics. Index of cancer survival for Clinical Commissioning Groups in England: Adults diagnosed 1998-2013 and followed up to 2014. Release date 26 Feb 2016. Available from <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/condition sanddiseases/bulletins/indexofcancersurvivalforclinicalcommissioninggroupsinengland/adultsdiagnosed19982013andfollowedupto2014#breast-colorectal-and-lung-cancer-1-year-survival> Last accessed 16 Mar 2021.
196. National Cancer Registration and Analysis Service. Stage breakdown by CCG. Release date Feb 2019, version 3. Available from http://www.ncin.org.uk/publications/survival_by_stage Last accessed 17 Mar 2021.
197. National Institute for Health and Care Excellence (NICE), Suspected cancer: recognition and referral (NG12). 2017. Available from <https://www.nice.org.uk/guidance/ng12> Last accessed 8 Oct 2019.
198. BTS COPD Consortium. Spirometry in practice. A practical guide to using spirometry in primary care. 2005. Available from <https://www.clinicalscience.org.uk/wp-content/uploads/2015/03/BTS-spirometry-in-practice.pdf> Last accessed 17 Mar 2021.
199. Brock University. Lung Cancer Risk Calculators. Lung cancer risk prediction model for smokers only (PLCOM2012). Available from <https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/> Last accessed 17 Mar 2021.
200. National Institute of Health, National Cancer Institute. Cancer Data Access System. Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Baseline questionnaire for female participants (BQF3). Version date 10/99. Available from <https://cdas.cancer.gov/static/cdas/documents/studies/plco/forms/BQF3.f6fa09686904.pdf> Last accessed 17 Mar 2021.
201. Nair A, Screaton NJ, Holemans JA, Jones D, Clements L, Barton B, et al. The impact of trained radiographers as concurrent readers on performance and reading time of experienced radiologists in the UK Lung Cancer Screening (UKLS) trial. *Eur Radiol*. 2018;28(1):226-34.
202. Rzyman W, Didkowska J, Dziedzic R, Grodzki T, Orlowski T, Szurowska E, et al. Consensus statement on a screening programme for the detection of early lung cancer in Poland. *Adv Respir Med*. 2018;86(1):53-74.

203. Madsen PH, Holdgaard PC, Christensen JB, Høilund-Carlsen PF. Clinical utility of F-18 FDG PET-CT in the initial evaluation of lung cancer. *Eur J Nucl Med Mol Imaging*. 2016;43(11):2084-97.
204. Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley D, Miettinen OS. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. *AJR Am J Roentgenol*. 2002;178(5):1053-7.
205. Silva M, Prokop M, Jacobs C, Capretti G, Sverzellati N, Ciompi F, et al. Long-Term Active Surveillance of Screening Detected Subsolid Nodules is a Safe Strategy to Reduce Overtreatment. *J Thorac Oncol*. 2018;13(10):1454-63.
206. Yankelevitz DF, Yip R, Smith JP, Liang M, Liu Y, Xu DM, et al. CT Screening for Lung Cancer: Nonsolid Nodules in Baseline and Annual Repeat Rounds. *Radiology*. 2015;277(2):555-64.
207. Yip R, Yankelevitz DF, Hu M, Li K, Xu DM, Jirapatnakul A, et al. Lung Cancer Deaths in the National Lung Screening Trial Attributed to Nonsolid Nodules. *Radiology*. 2016;281(2):589-96.
208. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax*. 2009;64 Suppl 3:iii1-55.
209. Veronesi G, Bellomi M, Mulshine JL, Pelosi G, Scanagatta P, Paganelli G, et al. Lung cancer screening with low-dose computed tomography: a non-invasive diagnostic protocol for baseline lung nodules. *Lung Cancer*. 2008;61(3):340-9.
210. Kauczor HU, Bonomo L, Gaga M, Nackaerts K, Peled N, Prokop M, et al. ESR/ERS white paper on lung cancer screening. *Eur Radiol*. 2015;25(9):2519-31.
211. Diederich S, Jurriaans E, Flower CD. Interobserver variation in the diagnosis of bronchiectasis on high-resolution computed tomography. *Eur Radiol*. 1996;6(6):801-6.
212. Washko GR, Hunninghake GM, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. *N Engl J Med*. 2011;364(10):897-906.
213. Hatabu H, Hunninghake GM, Richeldi L, Brown KK, Wells AU, Remy-Jardin M, et al. Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. *Lancet Respir Med*. 2020;8(7):726-37.

214. Papaioannou AI, Kostikas K, Papaporfyriou A, Angelakis L, Papathanasiou E, Hillas G, et al. Emphysematous Phenotype is Characterized by Low Blood Eosinophils: A Cross-Sectional Study. *Copd*. 2017;14(6):635-40.
215. Chiles C, Duan F, Gladish GW, Ravenel JG, Baginski SG, Snyder BS, et al. Association of Coronary Artery Calcification and Mortality in the National Lung Screening Trial: A Comparison of Three Scoring Methods. *Radiology*. 2015;276(1):82-90.
216. National Institute for Health and Care Excellence (NICE), Chronic obstructive pulmonary disease in over 16s: diagnosis and management (NG115). 2018. Available from www.nice.org.uk/guidance/ng115 Last accessed 10 Oct 2019.
217. Bartlett EC, Kemp SV, Ridge CA, Desai SR, Mirsadraee S, Morjaria JB, et al. Baseline Results of the West London lung cancer screening pilot study - Impact of mobile scanners and dual risk model utilisation. *Lung Cancer*. 2020;148:12-9.
218. National Institute for Health and Care Excellence (NICE), CVD risk assessment and management. 2019. Available from <https://cks.nice.org.uk/cvd-risk-assessment-and-management> Last accessed 13 Jan 2021.
219. Veronesi G, Maisonneuve P, Spaggiari L, Rampinelli C, Pardolesi A, Bertolotti R, et al. Diagnostic performance of low-dose computed tomography screening for lung cancer over five years. *J Thorac Oncol*. 2014;9(7):935-9.
220. Ministry of Housing, Communities and Local Government. The English Indices of Deprivation Research Report. 2019. Available from <https://www.gov.uk/government/publications/english-indices-of-deprivation-2019-research-report> Last accessed 6 Jan 2020.
221. McRonald FE, Yadegarfar G, Baldwin DR, Devaraj A, Brain KE, Eisen T, et al. The UK Lung Screen (UKLS): demographic profile of first 88,897 approaches provides recommendations for population screening. *Cancer Prev Res (Phila)*. 2014;7(3):362-71.
222. Department for Communities and Local Government. English indices of deprivation 2015. 2015. Available from <http://imd-by-postcode.opendatacommunities.org/imd/2019> Last accessed 26 Mar 2021.
223. Lung cancer incidence statistics, Cancer Research UK. Available from <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-Three>. Last accessed 7 May 2020.
224. Wille MM, Dirksen A, Ashraf H, Saghir Z, Bach KS, Brodersen J, et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. *Am J Respir Crit Care Med*. 2016;193(5):542-51.

225. Liverpool Clinical Commissioning Group (Dr Edward Gaynor). Liverpool Healthy Lung Project Presentation. Available from https://www.cancerresearchuk.org/sites/default/files/edward_gaynor.pdf Last accessed 4 Dec 2020. .
226. Robbins HA, Alcala K, Swerdlow AJ, Schoemaker MJ, Wareham N, Travis RC, et al. Comparative performance of lung cancer risk models to define lung screening eligibility in the United Kingdom. *Br J Cancer*. 2021;124(12):2026-34.
227. Swerdlow AJ, Jones ME, Schoemaker MJ, Hemming J, Thomas D, Williamson J, et al. The Breakthrough Generations Study: design of a long-term UK cohort study to investigate breast cancer aetiology. *Br J Cancer*. 2011;105(7):911-7.
228. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779.
229. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr*. 2002;5(6b):1113-24.
230. Balata H, Tonge J, Barber PV, Colligan D, Elton P, Evison M, et al. Attendees of Manchester's Lung Health Check pilot express a preference for community-based lung cancer screening. *Thorax*. 2019;74(12):1176-8.
231. Greenwald ZR, El-Zein M, Bouten S, Ensha H, Vazquez FL, Franco EL. Mobile Screening Units for the Early Detection of Cancer: A Systematic Review. *Cancer Epidemiol Biomarkers Prev*. 2017;26(12):1679-94.
232. Ali N, Lifford KJ, Carter B, McDonald F, Yadegarfar G, Baldwin DR, et al. Barriers to uptake among high-risk individuals declining participation in lung cancer screening: a mixed methods analysis of the UK Lung Cancer Screening (UKLS) trial. *BMJ Open*. 2015;5(7):e008254.
233. Maheswaran R, Pearson T, Jordan H, Black D. Socioeconomic deprivation, travel distance, location of service, and uptake of breast cancer screening in North Derbyshire, UK. *J Epidemiol Community Health*. 2006;60(3):208-12.
234. Bartlett EC, Belsey J, Derbyshire J, Morris K, Chen M, Addis J, et al. Implications of incidental findings from lung screening for primary care: data from a UK pilot. *NPJ Prim Care Respir Med*. 2021;31(1):36.
235. NHS England, NHS Improvement. National tariff payment system. 2017. Annex A: 2017/18 and 2018/19 National Tariff: currencies and prices. Available from

https://improvement.nhs.uk/documents/6580/2017-19_NTPS.zip Last accessed 4 May 2020.

236. NHS England, NHS Improvement. Reference Cost Collection: National Schedule of Reference Costs - Year 2017-18 - NHS trust and NHS foundation trusts. Available from https://improvement.nhs.uk/documents/6468/201718_reference_costs_data_and_guidance.zip Last accessed 5 May 2020.

237. Personal Social Sciences Research Unit (PSSRU). Unit costs of health and social care. 2019. Available from <https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/>. Last accessed 3 Apr 2020.

238. Harte E, MacLure C, Martin A, Saunders CL, Meads C, Walter FM, et al. Reasons why people do not attend NHS Health Checks: a systematic review and qualitative synthesis. *Br J Gen Pract*. 2018;68(666):e28-e35.

239. Ruparel M, Quaife SL, Dickson JL, Horst C, Burke S, Taylor M, et al. Evaluation of cardiovascular risk in a lung cancer screening cohort. *Thorax*. 2019;74(12):1140-6.

240. Balata H, Blandin Knight S, Barber P, Colligan D, Crosbie EJ, Duerden R, et al. Targeted lung cancer screening selects individuals at high risk of cardiovascular disease. *Lung Cancer*. 2018;124:148-53.

241. Whittaker H, Quint JK. Using routine health data for research: the devil is in the detail. *Thorax*. 2020;75(9):714-5.

242. The Royal College of Radiologists. Clinical Radiology Workload: guidance on radiologists' reporting figures. London: The Royal College of Radiologists; 2012. Available from [https://www.rcr.ac.uk/system/files/publication/field_publication_files/BFCR\(12\)12_workload_0.pdf](https://www.rcr.ac.uk/system/files/publication/field_publication_files/BFCR(12)12_workload_0.pdf) Last accessed 16 Apr 2021.

243. van der Aalst CM, Ten Haaf K, de Koning HJ. Lung cancer screening: latest developments and unanswered questions. *Lancet Respir Med*. 2016;4(9):749-61.

244. McCartney M, Fell G, Finnikin S, Hunt H, McHugh M, Gray M. Why 'case finding' is bad science. *J R Soc Med*. 2020;113(2):54-8.

245. NHS England. NHS Long Term Plan. 2019. Available from <https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf> Last accessed 12 Oct 2020. .

246. Ko JP, Berman EJ, Kaur M, Babb JS, Bomsztyk E, Greenberg AK, et al. Pulmonary Nodules: growth rate assessment in patients by using serial CT and three-dimensional volumetry. *Radiology*. 2012;262(2):662-71.
247. Revel MP, Merlin A, Peyrard S, Triki R, Couchon S, Chatellier G, et al. Software volumetric evaluation of doubling times for differentiating benign versus malignant pulmonary nodules. *AJR Am J Roentgenol*. 2006;187(1):135-42.
248. Gierada DS, Rydzak CE, Zei M, Rhea L. Improved Interobserver Agreement on Lung-RADS Classification of Solid Nodules Using Semiautomated CT Volumetry. *Radiology*. 2020;297(3):675-84.
249. Xu DM, Gietema H, de Koning H, Vernhout R, Nackaerts K, Prokop M, et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. *Lung Cancer*. 2006;54(2):177-84.
250. Wormanns D, Kohl G, Klotz E, Marheine A, Beyer F, Heindel W, et al. Volumetric measurements of pulmonary nodules at multi-row detector CT: in vivo reproducibility. *Eur Radiol*. 2004;14(1):86-92.
251. Talwar A, Willaime JMY, Pickup LC, Enescu M, Boukerroui D, Hickes W, et al. Pulmonary nodules: Assessing the imaging biomarkers of malignancy in a "coffee-break". *Eur J Radiol*. 2018;101:82-6.
252. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1(8476):307-10.
253. Kostis WJ, Reeves AP, Yankelevitz DF, Henschke CI. Three-dimensional segmentation and growth-rate estimation of small pulmonary nodules in helical CT images. *IEEE Trans Med Imaging*. 2003;22(10):1259-74.
254. Walter JE, Heuvelmans MA, Oudkerk M. Small pulmonary nodules in baseline and incidence screening rounds of low-dose CT lung cancer screening. *Transl Lung Cancer Res*. 2017;6(1):42-51.
255. Patton N, Aslam T, Murray G. Statistical strategies to assess reliability in ophthalmology. *Eye (Lond)*. 2006;20(7):749-54.
256. Wang Y, van Klaveren RJ, van der Zaag-Loonen HJ, de Bock GH, Gietema HA, Xu DM, et al. Effect of nodule characteristics on variability of semiautomated volume measurements in pulmonary nodules detected in a lung cancer screening program. *Radiology*. 2008;248(2):625-31.

257. Ludbrook J. Confidence in Altman-Bland plots: a critical review of the method of differences. *Clin Exp Pharmacol Physiol*. 2010;37(2):143-9.
258. Grover H, Ross T, Fuller E. Implementation of targeted screening for lung cancer in a high-risk population within routine NHS practice using low-dose computed tomography. *Thorax*. 2020;75(4):348-50.
259. Wiener RS, Gould MK, Slatore CG, Fincke BG, Schwartz LM, Woloshin S. Resource use and guideline concordance in evaluation of pulmonary nodules for cancer: too much and too little care. *JAMA Intern Med*. 2014;174(6):871-80.
260. Esmaili A, Munden RF, Mohammed TL. Small pulmonary nodule management: a survey of the members of the Society of Thoracic Radiology with comparison to the Fleischner Society guidelines. *J Thorac Imaging*. 2011;26(1):27-31.
261. Mets OM, de Jong PA, Chung K, Lammers JJ, van Ginneken B, Schaefer-Prokop CM. Fleischner recommendations for the management of subsolid pulmonary nodules: high awareness but limited conformance - a survey study. *Eur Radiol*. 2016;26(11):3840-9.
262. Ward E, Beattie A. Do radiology reports follow BTS guidelines for pulmonary nodules? Poster presentation. Available from https://www.rcr.ac.uk/sites/default/files/bts_guidelines_pulmonary_nodules.pdf Last accessed 3 Feb 2021.
263. Kweka M, Alex J. Compliance with the BTS guidelines for follow-up of indeterminate pulmonary nodule on CT. 2018. Poster Presentation. Available from <https://www.eposters.net/poster/compliance-with-the-bts-guidelines-for-follow-up-of-indeterminate-pulmonary-nodule-on-ct> Last accessed 3 Feb 2021.
264. Goldberg-Stein S, Walter WR, Amis ES, Jr., Scheinfeld MH. Implementing a Structured Reporting Initiative Using a Collaborative Multistep Approach. *Curr Probl Diagn Radiol*. 2017;46(4):295-9.
265. Woloshin S, Schwartz LM, Dann E, Black WC. Using radiology reports to encourage evidence-based practice in the evaluation of small, incidentally detected pulmonary nodules. A preliminary study. *Ann Am Thorac Soc*. 2014;11(2):211-4.
266. Cubillos L, Brenner AT, Birchard K, Henderson LM, Molina PL, Pignone M, et al. Multidisciplinary quality improvement initiative to standardize reporting of lung cancer screening. *Transl Lung Cancer Res*. 2018;7(Suppl 3):S297-s301.

267. Loverdos K, Fotiadis A, Kontogianni C, Iliopoulou M, Gaga M. Lung nodules: A comprehensive review on current approach and management. *Ann Thorac Med*. 2019;14(4):226-38.
268. Baldwin DR. Management of pulmonary nodules according to the 2015 British Thoracic Society guidelines. Key messages for clinical practice. *Pol Arch Med Wewn*. 2016;126(4):262-74.
269. Gould MK, Altman DE, Creekmur B, Qi L, de Bie E, Golden S, et al. Guidelines for the Evaluation of Pulmonary Nodules Detected Incidentally or by Screening: A Survey of Radiologist Awareness, Agreement, and Adherence From the Watch the Spot Trial. *J Am Coll Radiol*. 2021;18(4):545-53.
270. Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. *Bmj*. 1992;304(6840):1491-4.
271. Walter JE, Heuvelmans MA, Ten Haaf K, Vliegenthart R, van der Aalst CM, Yousaf-Khan U, et al. Persisting new nodules in incidence rounds of the NELSON CT lung cancer screening study. *Thorax*. 2019;74(3):247-53.
272. Mendoza DP, Chintanapakdee W, Zhang EW, Gilman MD, Lennes IT, Frank AJ, et al. Management and Outcomes of Suspected Infectious and Inflammatory Lung Abnormalities Identified on Lung Cancer Screening CT. *AJR Am J Roentgenol*. 2020.
273. van der Aalst CM, Ten Haaf K, de Koning HJ. Implementation of lung cancer screening: what are the main issues? *Transl Lung Cancer Res*. 2021;10(2):1050-63.
274. Silvestrin, C. Europe's looming radiology capacity challenge. 2016. Available from https://www.telemedicineclinic.com/wp-content/uploads/2016/11/Europes_looming_radiology_capacity_challenge-A_comparitive_study Last accessed 19 Mar 2021.
275. NHS Digital. NHS e-referral service open data. 2021. Available from <https://digital.nhs.uk/dashboards/ers-open-data> Last accessed 15 Apr 2021.
276. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. *Lancet Oncol*. 2020;21(8):1023-34.
277. Van Haren RM, Delman AM, Turner KM, Waits B, Hemingway M, Shah SA, et al. Impact of the COVID-19 Pandemic on Lung Cancer Screening Program and Subsequent Lung Cancer. *J Am Coll Surg*. 2021;232(4):600-5.

Appendix A: Members of the West London targeted lung screening pilot steering group and operations group

Steering Group Name	Role
Professor Anand Devaraj	Consultant Radiologist/Clinical Lead
Dr Thomas Newsom-Davis	Med Oncologist/RMP Clinical Lead
Professor Stan Kaye	Professor of Medical Oncology & Research Director, RM Partners
Dr Peter Wills	Consultant Chest Physician
Dr Sarah Whiteside	Macmillan GP
Dr Stephen Vaughan-Smith	Lead GP
Sam Agboola	CCG Rep
Toby Hyde	CCG Rep
Afsana Safa	NWL STP Clinical Lead
Professor Sanjay Popat	Consultant Thoracic Medical Oncologist and BTOG Chair
John Pearcey	Assistant General manager lung division, Royal Brompton Hospital
Christine Peacock	Radiology services manager, Royal Brompton Hospital
Professor Pallav Shah	Consultant Chest Physician
Dr Samuel Kemp	Consultant Chest Physician
Dr Ranil De Silva	Preventative cardiologist
Shikha Sharma	Public Health Consultant
Steve Hajioff	Director of Public Health
Dr Michelle Chen	Research and Development Manager, RM Partners
Katie Morris	Project Lead, RM Partners
Anita McWhirter	Pharmacist
Jane Derbyshire	Senior Project Support, RM Partners
Dr Emily Bartlett	Clinical Research Fellow, Radiology
James Addis	Project Manager

Operations Group Name	Role
Professor Anand Devaraj	Consultant Radiologist
Professor Simon Padley	Consultant Radiologist
John Pearcey	Assistant General Manager lung division, Royal Brompton Hospital
Christine Peacock	Radiology services manager, Royal Brompton Hospital
Dr Samuel Kemp	Consultant Chest Physician
Dr Emily Bartlett	Clinical Research Fellow, Radiology
Sara Shaheen	Senior Research Co-ordinator
Adam Bell	I&T Imaging Services Manager
Tracey Yarker	Clinical Technology Director
Chris Japhtha	Head of Procurement, Member of the Chartered Institute of Procurement and Supply (MCIPS)
Katie Morris	Project Lead, RM Partners
Michelle Chen	Research and Development Manager, RM Partners
Jane Derbyshire	Senior Project Support, RM Partners

Appendix B: Invitation letter and accompanying patient information leaflet

GP letter head

Dear xxxx,

Free Lung Health Check

We are pleased to invite you to a new free NHS service to check your lung health.

Our GP practice has been selected to take part in this pilot service and an invitation is being sent to all of our patients who have ever been regular smokers and are aged between 60 and 75 years.

What will happen if I choose to make an appointment?

You can expect your appointment with the respiratory nurse to last around 30 minutes. At the appointment you will be asked questions about your general health, lungs and breathing and will be offered further tests if you wish to have them. The enclosed leaflet provides further information about the check.

Booking an appointment

The Lung Health Check will take place in a special mobile clinic located in the car park of Sainsbury's Hayes (see travel details on the reverse of this letter). Places are limited so please call **0330 128 8121 ext: 84973/84974** as soon as possible to book your appointment and don't miss out.

If you need an interpreter or any special arrangements, please inform the team when booking your appointment.

You are welcome to bring somebody along with you on the day.

If you have any queries about whether to take part or have any other unanswered questions about the service please call **0330 128 8121 ext: 84973/84974**.

Yours sincerely,

GP practice name

Getting to your health check:

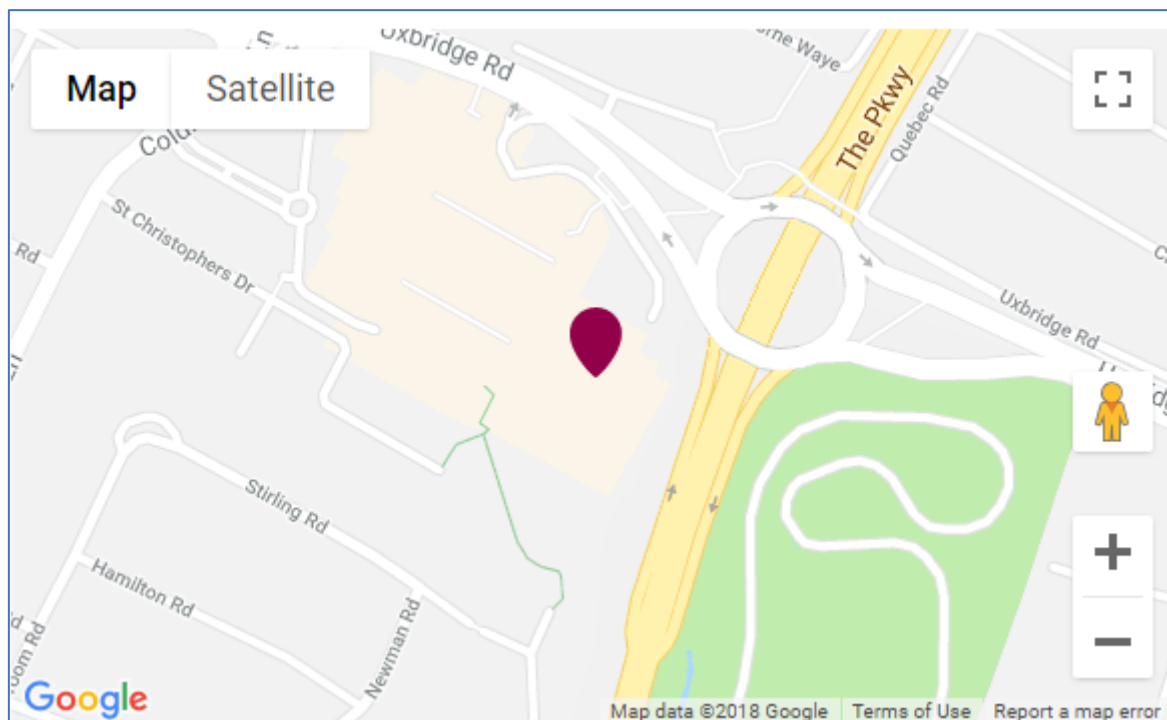
The following information will provide you with full details on how to get to your health check:

Lombardy Retail Park
Coldharbour Lane
Hayes
UB3 3HG

How to get to the mobile unit:

See here for directions: <https://stores.sainsburys.co.uk/directions/0630/hayes>

The mobile unit is next to the multi storey car park, accessed via the pathway between GAME and Sainsbury's.



Free Lung Health Check



A new NHS service

Your GP practice is taking part in this pilot service and is inviting people who:

- **Are a smoker or ex-smoker (that gave up after the age of 40) and**
- **Are aged between 60 and 75**

If both of these apply to you, then you can have a free Lung Health Check.

What is a Lung Health Check?

The Lung Health Check will look for a range of breathing and respiratory conditions so any treatment, if necessary, can be offered earlier. Your appointment will take approximately 30 minutes but may take a bit longer if you need a lung scan.

What will happen?

You will be welcomed by a respiratory nurse and asked some questions about your general health, breathing and lungs.

You will then be invited to take part in a number of tests such as blowing into a machine called a spirometer which tests how well your lungs are working, and measuring your height and weight.

With your permission, your risk of getting lung cancer during the next few years will also be calculated and, depending on the results, you may be offered a lung scan.

You will also be offered the opportunity to participate in research that we are carrying out into improving lung health. You can decide about participating in this on the day, or later, and will be given plenty of time to ask questions.

What will happen after the Lung Health Check?

The nurse will share your results with you and offer you advice about lung health. You may be advised to go and see your GP, who will be sent a copy of your results after the check is completed.

If you are advised to have a lung scan

A CT (computerised tomography) scan is a special X-ray that takes a series of detailed images of the body. The nurse will talk you through the scan and answer any questions that you may have.

If you decide to have a scan this can happen on the same day, or if more convenient, can be booked for soon after. The lung scan will take approximately 15 minutes.

The scan can spot lung problems early – often before you notice anything, when treatment could be simpler and more successful. Results from the scan will be available within 2 weeks and you will be contacted by telephone or letter, where next steps will be discussed.

‘This is fantastic new opportunity for local residents to give their lungs a full MOT’

*Dr Sarah Whiteside, GP
Hammersmith and Fulham*

Next steps

You can book a Lung Health Check by calling the clinic booking line on **0330 128 8121 ext: 84973/84957**. Please let them know if you have had a CT scan in the last two years.

Places on this pilot service are limited so please book your appointment as soon as possible.

If you need an interpreter or any special arrangements, please inform the team when booking your appointment.

If you have any questions about the project, please telephone **0330 128 8121 ext: 84973/84957** to speak to a member of the Lung Health Check Team.

With thanks to Liverpool CCG Healthy Lung Programme, Manchester Cancer Improvement Partnership and UCLH Respiratory for their support in developing our resources.

Appendix C: CT scan patient information leaflet



A lifetime of specialist care

Royal Brompton & Harefield **NHS**
NHS Foundation Trust

CT scan consent form

Today we have offered you a computed tomography (CT) scan of your lungs.

What is a computed tomography (CT) scan?

A CT scan is a 5-10 minute scan to take a detailed picture of your lungs. You will not be required to have an injection or to fast (stop eating) before the scan. There is no tunnel involved. Rather, going in the scanner is like passing through a polo mint.

The scan involves radiation with x-rays. You are exposed to background radiation in your normal day to day life. The CT scan we are offering will be low dose; this means that the radiation dose is about equal to the normal background radiation you would receive normally over 6 months living in the UK.

Why are we offering you this scan?

The main purpose of the scan is to detect early lung cancer before you get symptoms, so that a small cancer can be treated early. We know that the smaller a lung cancer is detected, the better the outcome for you.

What might be found on the scan?

Sometimes a CT scan detects small nodules in your lungs. Pulmonary (lung) nodules are very small shadows that show up on the CT scan as a small "spot". They are common and very occasionally can be cancerous. However the vast majority of nodules are benign (non-cancerous) and are caused by other things, such as scarring from a previous infection.

If your scan does show a pulmonary nodule then, just as a precaution, we will arrange for you to have a follow-up CT scan to make sure the nodule does not grow. If over time we find that the nodule does change or grow then we may arrange further tests or scans.

Can anything else be found on my scan?

This scan is not intended as a thorough assessment of your heart or lungs. Although this scan is being offered to detect early lung cancer, occasionally there are findings on your scan which may require follow-up with your GP or another hospital specialist. We would refer you onwards for these. You would be informed if that were the case.

What is nothing is found on my scan?

If your scan is negative, this does not mean that you will not get cancer in the future. If you develop a persistent cough, cough up blood, or you have other symptoms which worry you in relation to your lung health, you should see your GP. They can arrange further tests for you as appropriate.

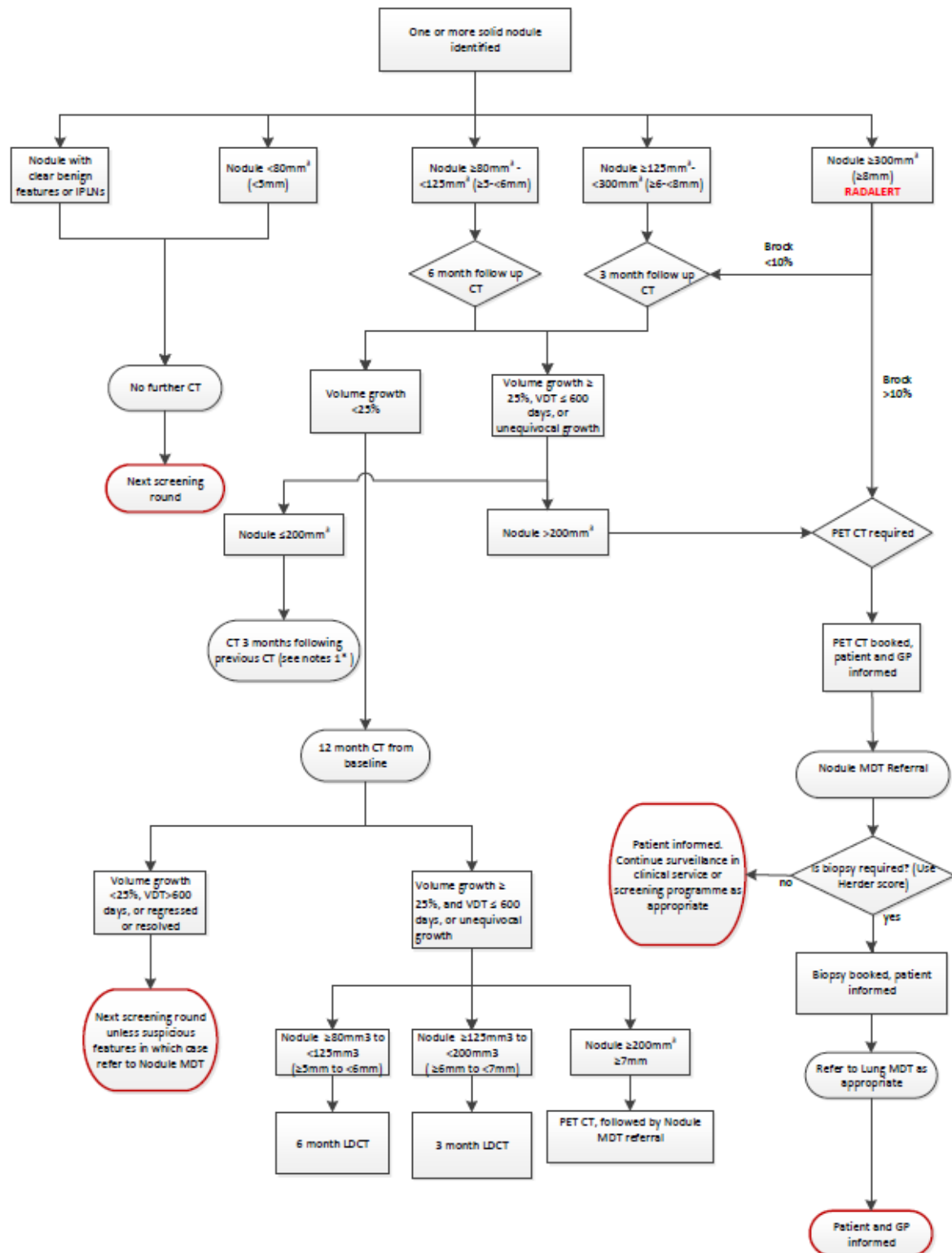
When will I get my scan results?

The results of your scan will be posted to you within 2-3 weeks of your scan. The results of your scan will also be sent to your GP.

Please ask the nurse if you have any further queries.

Appendix D: West London targeted lung screening pilot nodule management protocol

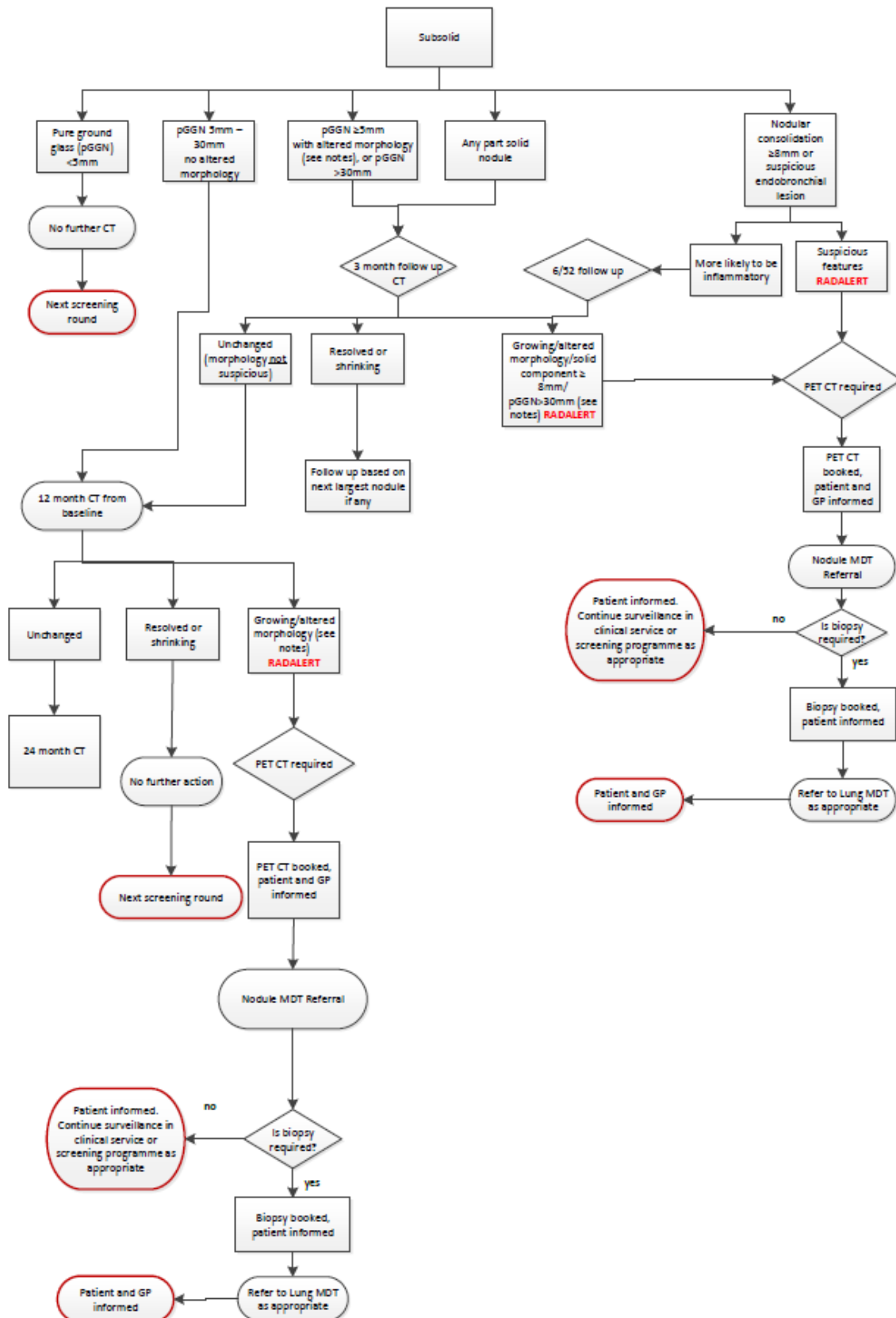
Solid nodules



SOLID NODULES: Supplementary notes

- A maximum of 4 nodules are to be recorded at baseline, which should be the largest 4. Management is based on the largest nodule. IPLNs do not have to be recorded.
- Growing nodules should be $>200\text{mm}^3$ (or 8mm if volume not calculated) before referral to MDT. If nodules are growing $>25\%$ at 3 months but $\leq 200\text{mm}^3$, repeat CT in 3 months.
- New nodules found on a 3-month follow-up scan should be managed according to the baseline (Y0) algorithm.
- Nodular consolidation $>8\text{mm}$ or endobronchial lesions or other nodules $>8\text{mm}$ that appear more likely to be inflammatory, but where malignancy is a consideration, may be scanned again at 6 weeks (see SSN algorithm). If unchanged or growing at the 6-week scan, these should be referred to MDT. Opacities that are clearly inflammatory (e.g. tree-in-bud or endobronchial mucous) and where malignancy is not a consideration do not require follow-up.
- In cases where volumetry is not possible and diameter measurements are made, a VDT should not be calculated (even if extrapolated from diameter). Assessment should be based on unequivocal growth (as per BTS).
- **AT ANY TIME POINT:** radiologists can upgrade to next level of management if nodules are felt to have suspicious features and recommended management is felt not to be sufficient. In cases of uncertainty, radiologists can refer to MDT for discussion.
- Notes 1*: Nodule to be managed according to VDT compared to baseline ($>$ or $\leq$ 600 days) and absolute size ($>$ or $\leq 200\text{mm}^3$). Those with shrinking nodules at this stage should be discharged to the next screening round.
- Unilateral pleural effusions, or pleural thickening should be referred to the MDT. Significant lymph node enlargement should undergo repeat 3-month CT or MDT referral at the radiologists discretion based on overall appearances.

Subsolid nodules



SUBSOLID NODULES: Supplementary notes

- A maximum of 4 nodules are to be recorded, which should be the largest 4. Management is based on the largest nodule. IPLNs do not need to be recorded.
- New nodules found on a 3-month follow-up scan should be managed according to the baseline algorithm.
- SSNs with growing morphology refers to a new or increasing solid component or a growing pGGN >30mm. SSNs with altered morphology refers to bubble like lucencies or pleural retraction. If there is an increase in density or solid component and the solid component is still <8mm, then the increase should be at least 2mm since the previous CT or observed on two CTs before MDT referral. Otherwise continue to next round.
- Nodular consolidation >8mm or endobronchial lesions or other nodules >8mm that appear more likely to be inflammatory, but where malignancy is a consideration, may be scanned again at 6 weeks. If unchanged or growing at the 6-week scan, these should be referred to MDT. Opacities that are clearly inflammatory (e.g. tree-in-bud or endobronchial mucous) and where malignancy is not a consideration do not require follow-up.
- If part solid nodule and solid component is >90% of nodule size, then consider as per solid nodule.
- **AT ANY TIME POINT:** radiologists can upgrade to next level of management if nodules are felt to have suspicious features and the recommended management felt not to be sufficient. In cases of uncertainty, radiologists can refer to MDT for discussion. Radiologists should note that the recommended algorithm for SSNs takes into account efforts to minimize overdiagnosis.

Appendix E: RBH L-RADS nodule management protocol

Category Descriptor	Score	Descriptor	Management: Imaging time from current scan
Incomplete	0	Part or all of lungs cannot be evaluated	6-week LDCT
Negative	1	<u>At any scan:</u> No lung nodules <i>AND/OR</i> Benign lung nodules: specific calcifications – complete, central, popcorn, concentric rings and fat containing nodules <i>AND/OR</i> Intrapulmonary lymph nodes <i>AND/OR</i> Non nodular opacities (e.g. atelectasis, scars, vessel confluence, definitely inflammatory nodules) <i>OR</i> <u>At baseline:</u> Micronodules <50mm³ (<3mm) (do not require documentation) <i>OR</i> <u>At ≥12-month scan</u> New nodule <30mm³ (<2mm) (do not require documentation) <i>OR</i> <u>At any follow-up scan:</u> Resolved nodules (solid, part-solid or ground-glass or nodular consolidation)	Continue with/return to next LDCT screening round
Indeterminate nodule: Very likely benign or indolent	2	Solid nodule(s) <u>At baseline:</u> ≥50mm³ to <80mm³ (≥3mm to <5mm) <i>OR</i> <u>At 6-week, 3-month or 6-month scan:</u> Resolving/shrinking nodules <i>OR</i> <u>At ≥12-month scan:</u> Nodule stable or shrinking by volumetric measurements⁵ <i>AND/OR</i> Growing nodule with VDT >600 days. <i>OR</i> <u>At 24-month scan:</u> Old nodule stable by visual assessment when volumetry not possible PSN(s): <u>At any follow-up scan:</u> Resolving/shrinking nodule <i>OR</i> <u>At 24-month scan:</u> Stable and solid component <8mm <i>OR</i> Nodule with solid component growing <2mm since earliest scan and <8mm pGGN(s): <u>At any time:</u> <5mm <i>OR</i> <u>At any follow-up scan:</u> Resolving/shrinking nodule Nodular consolidation <u>At 6-week follow-up scan:</u> Resolving nodular consolidation	Continue with/return to next LDCT screening round
Indeterminate nodule: Likely benign or indolent	3A	Solid: <u>At 12-month scan:</u> Stable by visual assessment when volumetry not possible PSN(s): <u>At 12-month scan:</u>	12-month LDCT

⁵ Stability defined by <25% growth in volume at up to 1 year or no clear visual growth if volumetry not possible.

		Stable and solid component <8mm <i>OR</i> Nodule with solid component growing <2mm since earliest scan and <8mm pGGN(s): <u>At any time</u> ≥5mm - ≤30mm with no altered morphology⁶	
	3B	Solid nodule(s): <u>At 3-month scan:</u> Stableⁱ or old nodule growing >25% with VDT ≤600 days and ≥80mm³ to < 125mm³ (≥5mm to <6mm). PSN(s): <u>At 3-month scan:</u> Stable and solid component <8mm <i>OR</i> Nodule with solid component growing <2mm since earliest scan and <8mm	9-month LDCT
	3C	Solid nodule(s): <u>At baseline:</u> ≥80mm³ to < 125mm³ (≥ 5mm to <6mm) <i>OR</i> <u>At 6-month scan:</u> Stableⁱ or old nodule growing >25% with VDT ≤600 days and ≥80mm³ to < 125mm³ (≥5mm to <6mm). <i>OR</i> <u>At follow-up scan at ≥12 months only:</u> New nodule ≥30mm³ to < 80mm³ (≥2mm to <5mm) <i>OR</i> Old nodule: Volume growth ≥25% and VDT ≤600 days and nodule ≥80mm³ to <125mm³ (≥5mm to <6mm)	6-month LDCT
Suspicious	4A	Solid nodule(s): <u>At baseline:</u> ≥125mm³ to <300mm³ (≥ 6mm to <8mm) <i>OR</i> Nodule ≥300mm³ (≥ 8mm) with Brock score <10% <i>OR</i> <u>At follow-up scan:</u> Old nodule: Volume growth ≥25% and VDT ≤600 days and nodule ≥125 to <200mm³ (≥6mm to < 7mm) <i>OR</i> <u>At 12-month scan or incident round scan</u> New nodules ≥80 to <300mm³ (≥ 5mm to <8mm) PSN(s): <u>At baseline:</u> Nodule any size, with any size solid component. <i>OR</i> <u>At follow-up scan</u> New nodule, any size, with any size solid component. pGGN(s) <u>At baseline:</u> Nodule ≥30mm <i>OR</i> Nodule any size, with altered morphologyⁱⁱ <i>OR</i> <u>At follow-up scan:</u> New nodule ≥30mm <i>OR</i> New nodule, any size, with altered morphologyⁱⁱ	3-month LDCT
	4B	Nodular consolidation: <u>At any scan:</u> When not clearly inflammatory or malignant	6-week LDCT
Very Suspicious	4C	Solid nodule(s): <u>At baseline:</u> ≥ 300mm³ (≥8mm) with Brock score >10% <i>OR</i> <u>At follow-up scan:</u> Old nodule with ≥25% volume growth and VDT ≤ 600 days (or unequivocal growth⁷) and nodule ≥200mm³ (≥7mm) <i>OR</i> New nodule (≥12 months) ≥300mm³ (≥8mm)	PET-CT and MDT referral

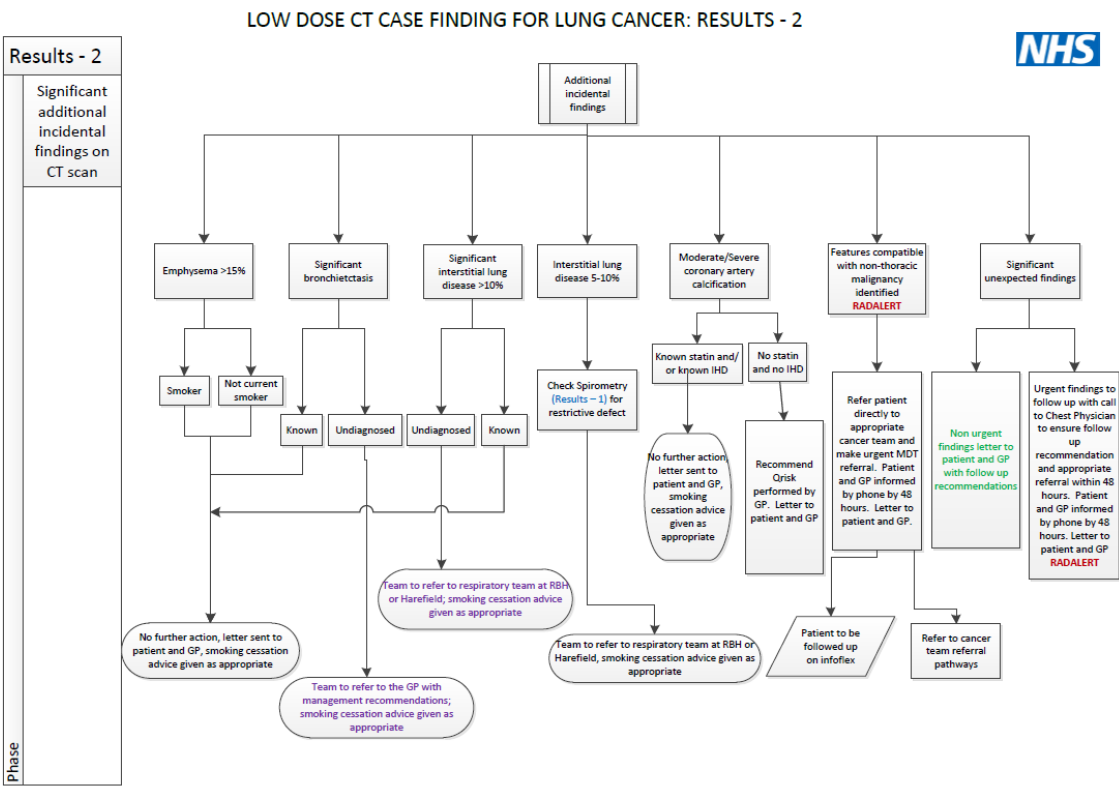
⁶ Altered morphology: includes pleural retraction, bubble like lucencies.

⁷ Unequivocal growth – only when volumetry not accurate/unable to segment nodule.

		PSN(s): <u>At follow-up scan:</u> Persistent nodule, any size with altered morphologyⁱⁱ <i>OR</i> Old nodule with ≥2mm growth in solid component since earliest scan <i>OR</i> Any nodule with solid component ≥8mm pGGN(s): <u>At follow-up scan:</u> Nodule ≥30mm and persistent +/- altered morphology or old nodule 5-30mm and persistent with altered morphology. Nodular consolidation: <u>At baseline:</u> Highly suspicious for malignancy <i>OR</i> <u>At 6-week scan</u> Non-resolving or growing	
	4X	Category 2, 3 or 4 nodules or non-nodular opacities, with additional features or imaging findings that increase the suspicion of malignancy including cysts with irregular thickened or nodular walls <i>OR</i> Suspicious endobronchial nodule⁸ At follow-up scan when persistent	For PET-CT or MDT referral

⁸ At baseline, any endobronchial nodule should be treated like a solid nodule of the same size.

Appendix F: Protocol for reporting incidental imaging findings in the West **London targeted lung screening pilot**



Appendix G: Example results letters to participants and GPs

GP letter

Royal Brompton & Harefield 
NHS Foundation Trust

GP
GP ADDRESS
XXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXX

Monday-07-January-2019

Dear Doctor XXXXX,

Re: PATIENT NAME NHS No: PATIENT NHS NO D.O.B: PATIENT DOB

Your patient was seen as part of the RM Partners (RMP) Lung Low Dose CT Case Finding Project on XXXXXXXX. This involved a lung health check, which included a lung cancer risk assessment and low dose CT scan, if indicated. As part of the health check we discussed the spirometry, lung risk score and CT scan and what various results would mean and the patient was happy to proceed. Please find below the results from the appointment, including all follow-up actions and recommendations.

Results from the lung health check:

Height:XXXXX Weight: XXXXX BMI: XXXXX

Current smoking status: Ex-Smoker

Spirometry:
FEV1: 2.15 L (96 % predicted)
FVC: 2.49 L (88 % predicted)
FEV1/FVC ratio: 086.3 %
Exhaled CO 02.00 ppm
PLCOm 2012 risk score: 0.18118 %
LLP (version 2) risk score: 3.09693 %

These are the results of the appointment:

Spirometry findings and follow-up actions and recommendations:

Non-diagnostic spirometry performed was normal:

Spirometry results are provided for information only and no further specific action is required at this time.

Lung Cancer Risk Assessment and CT Scan Results:

Based on the patient's lung cancer risk score, a CT scan was performed. This showed no features to suggest lung cancer. However, this does not completely exclude the possibility of developing lung cancer in the future and therefore the importance of recognizing and reporting future symptoms of lung cancer was discussed with the patient.

CT Incidental Findings:

The scan showed significant coronary artery calcification and the patient is not known to have ischaemic heart disease and the patient does not report being on lipid lowering therapy. Therefore we would recommend that a QRISK assessment is performed, if not previously carried out.

Your patient is now discharged from the RMP Lung Low Dose CT Case Finding Project.

Yours sincerely,

NAME OF NURSE
JOB TITLE

Participant letter

PATIENT NAME
PATIENT ADDRESS
XXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXX

Monday-07-January-2019

Dear NAME OF PATIENT

Thank you for attending your lung health check on DATE OF APPOINTMENT. At your appointment we discussed the blowing test (spirometry), lung risk score and CT scan and what various results would mean for you and you were happy to go ahead. Please find below the results from your appointment, including all follow-up actions and recommendations. A copy of the results has also been sent to your GP.

Your lung function test was within the normal range for someone of your age and height and you do not need any treatment following your health check.

I am pleased to let you know that your scan was **negative** and did **not** show evidence of any lung cancer. However, this does not completely exclude the possibility of developing lung problems in the future and therefore if you have any new or persistent chest symptoms, please see your GP or practice nurse to get this checked.

Your scan has shown some hardening of the arteries of your heart. Because of this we recommend that you book an appointment to see your GP.

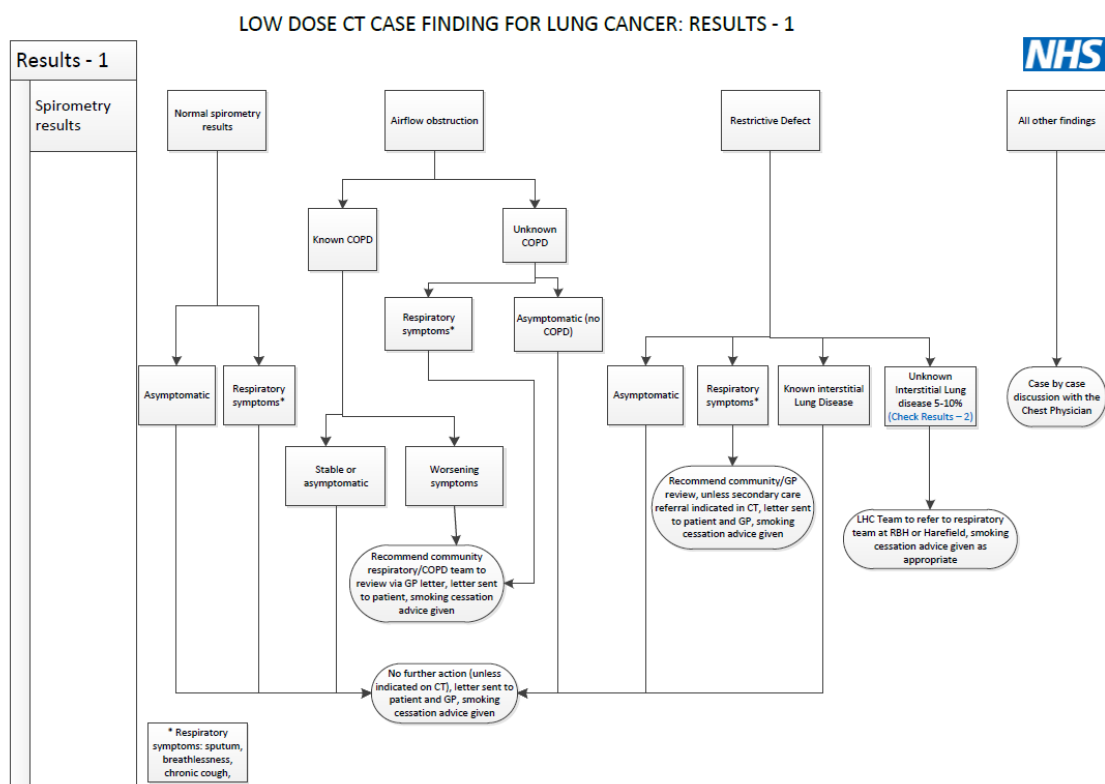
You are now discharged from the RMP Lung Low Dose CT Case Finding Project.

If you have any questions about your Lung Health Check, please telephone 0330 128 8121 ext 84973/84974 to speak to a member of the Lung Health Check team.

Yours sincerely,

NAME OF NURSE
JOB TITLE

Appendix H: Protocol for referral of participants to primary or secondary care according to spirometry results in the West London targeted screening pilot



Appendix I: Participant satisfaction survey developed by the West London pilot project operations group in conjunction with Ipsos MORI.

How was your experience of the Lung Health Check?

The Lung Health Check is a new service that we are trialling. Completing this form about your experience will help us to decide if this would be a useful service to continue and develop further. All personal information you provide will remain confidential. It will not be linked to your name, address, NHS or hospital number.

The findings from this questionnaire will be for evaluation purposes and shared with other NHS healthcare organisations. It will not be possible to identify you in any results that may be published.

If you have any queries relating to this survey or require any assistance to complete the survey please contact the Lung Health Team on **0330 128 8121 ext: 84973/84974.**

Please return the completed questionnaire to the Reception staff of the Lung Health Check, or directly to the Lung Health Nurse. If you would like to post us back your survey, please use the stamped addressed envelope provided at your earliest convenience.

Only complete the survey if you are the patient or if you are completing the survey on behalf of the patient (e.g. a carer or family member).

Please complete the questions as best as you can and where relevant write using block capitals.

Please tick ✓ your answers below and give one answer per question only.

Booking your appointment

Did you have enough information about why you had been invited for a Lung Health Check?					
☐ Yes	☐ No – further verbal information required				
☐ I did not want/need any information	☐ No – further written information required				
	☐ No – no information was provided				
When booking your appointment, how clear, or not, was the information you were given about:					
	Very clear	Fairly clear	Not very clear	Not at all clear	
What the invite was about	☐	☐	☐	☐	
What would happen at the check	☐	☐	☐	☐	
How to book an appointment	☐	☐	☐	☐	
Support and advice available for you and your family	☐	☐	☐	☐	
Your Lung Health Check with the nurse					
Thinking about where the health check was held...					
	Strongly agree	Agree	Disagree	Strongly disagree	
The venue was easy to get to	☐	☐	☐	☐	
The venue felt like the right place to have a health check	☐	☐	☐	☐	
I had enough privacy at the venue	☐	☐	☐	☐	
I had enough space at the venue	☐	☐	☐	☐	
Thinking about your conversation with the nurse during your health check...					
	Strongly agree	Agree	Disagree	Strongly disagree	Don't know
The nurse considered any stress I was facing	☐	☐	☐	☐	☐
I feel better about my lung health after meeting the nurse	☐	☐	☐	☐	☐
The nurse was concerned about my well-being	☐	☐	☐	☐	☐
The appointment lasted for the right amount of time	☐	☐	☐	☐	☐
How satisfied, or not, were you with the following:					
	Very satisfied	Satisfied	Dissatisfied	Very dissatisfied	
The conversation you had about lung health	☐	☐	☐	☐	
The conversation you had about smoking cessation/healthy lifestyles	☐	☐	☐	☐	
The tests that were carried out	☐	☐	☐	☐	
The way your risk of lung cancer was explained	☐	☐	☐	☐	

The decision on whether to refer you for a CT scan		☐	☐	☐	☐
Your CT scan (uses X-rays and a computer to create detailed images of inside the body)					
When did you have your scan?					
Straight after my health check		Within two weeks of my health check			
☐		☐			
Later the same day of my health check		Later than two weeks after my health check			
☐		☐			
How do you feel about the length of time you had to wait for your CT scan?					
☐ The scan was done sooner than I thought		☐ The scan should have been done a bit sooner			
☐ The scan was done as soon as I thought was necessary		☐ The scan should have been done a lot sooner			
☐ I do not know/I cannot remember					
Thinking about your scan...					
Did you have the opportunity to ask all the questions you wanted before the scan?					Yes ☐
Did you have the opportunity to ask all the questions you wanted after the scan?					Yes ☐
How satisfied, or not, were you with the following:					
	Very satisfied	Satisfied	Dissatisfied	Very dissatisfied	Don't know
The information given before your scan	☐	☐	☐	☐	☐
The way your CT was performed	☐	☐	☐	☐	☐
The time it took to receive your results	☐	☐	☐	☐	☐
The information provided with your CT results	☐	☐	☐	☐	☐
The explanation of what would happen next	☐	☐	☐	☐	☐
Support and advice available for you and your family	☐	☐	☐	☐	☐
Your overall experience of the health check					
If a friend asked you if they should go to lung health check/CT, would you encourage them or discourage them?					
Strongly encourage	☐	Strongly discourage	☐		
Encourage	☐	Discourage	☐		
		Neither	☐		
How would you rate your overall experience of the health check/CT?					
Very satisfied	☐	Very dissatisfied	☐		

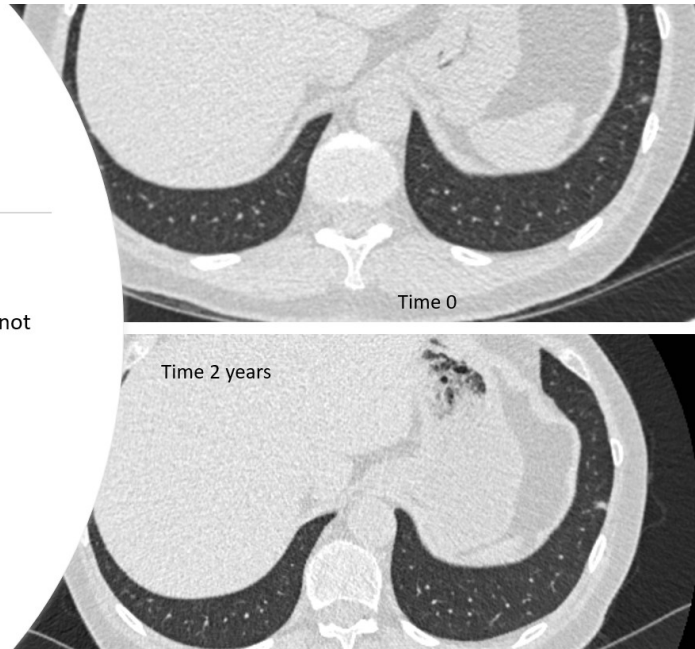
Satisfied ☐	Dissatisfied ☐ Neither ☐
Please explain: 	
About you	
Are you: ☐ Male ☐ Female ☐ Prefer not to say	What is your age group: ☐ 60-65 ☐ 66-70 ☐ 71-75 ☐ Prefer not to say
How would you describe your ethnic origin? ☐ Asian or Asian British ☐ Black African, Caribbean or Black British ☐ Mixed, multiple ethnicities ☐ Other ethnic group ☐ White ☐ Prefer not to say	

Thank you for taking the time to complete this survey.
Please return this form directly to the Lung Health Check team or in the stamped addressed envelope provided.

Appendix J: Nodule management scenarios distributed to radiologists and clinicians for interobserver agreement study

Scenario 1

- Scan performed 2 years apart
- At time 0: 14mm³ solid (or part solid) nodule in the left costophrenic recess (not reported).
- At time 2 years: solid 42mm³.
- VDT 466 days

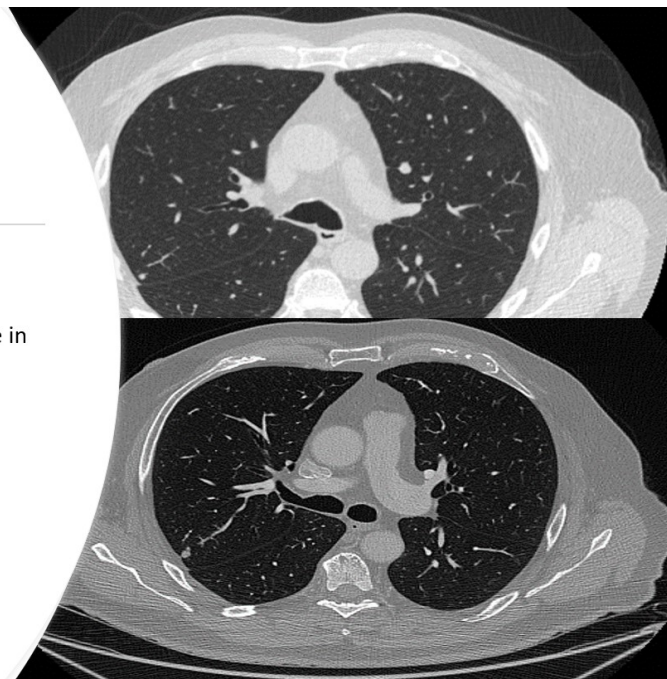


Scenario 2

No nodules on scan at time 0.

24 months later: **New 30mm³** solid nodule in RUL (top image).

Imaged elsewhere (breathless – CTPA): 3 months later: nodule now **78mm³**

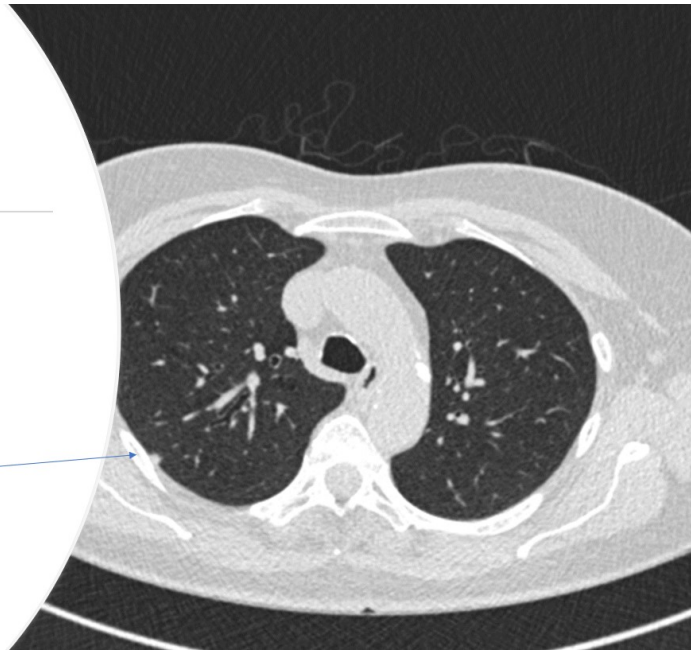


Scenario 3

Incident round scan

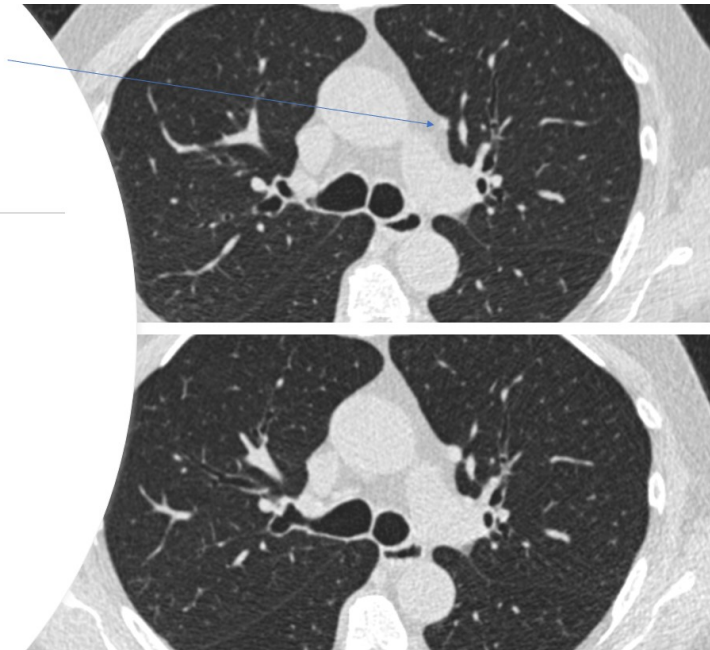
No nodule on baseline scan 2 years earlier

New nodule **35mm³**



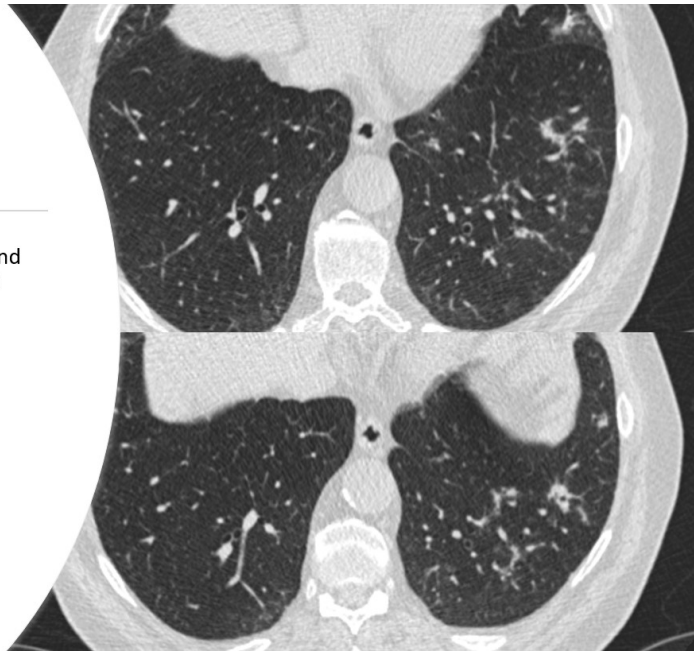
Scenario 4

- Left upper lobe nodule abutting mediastinum not reported at time 0.
- 12 months later the nodule measures **125mm³**
- Retrospective review of old imaging suggests that the nodule measured **62mm³** 12 months earlier.
- VDT is 362 days.



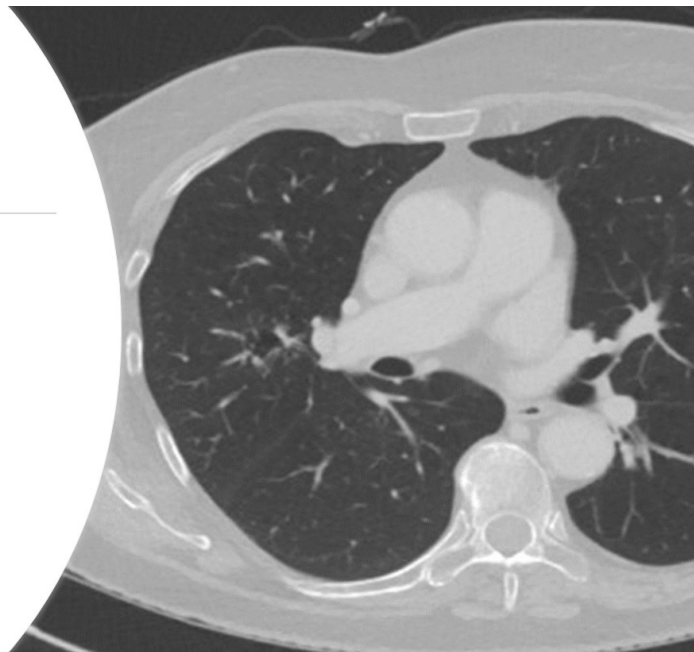
Scenario 5

Cluster of nodules in the left lower lobe and lingula; the largest measures **1350mm³** at baseline



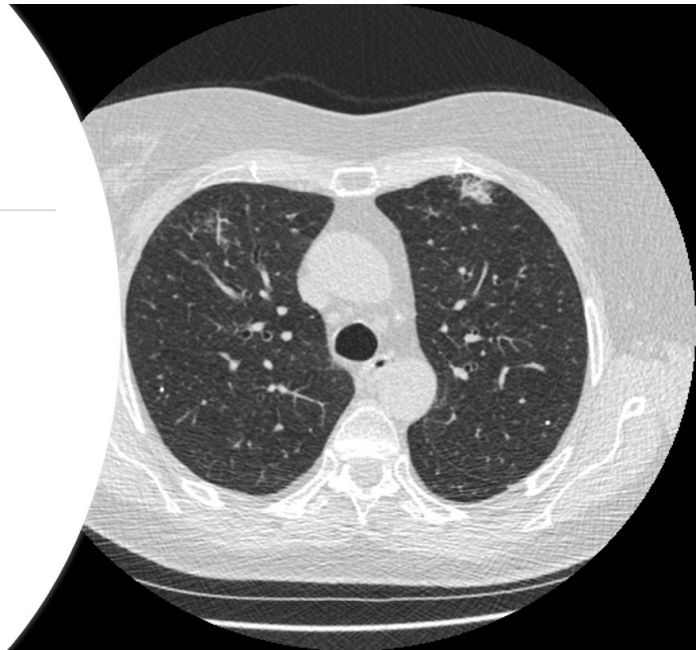
Scenario 6

- Pericystic thickening right upper lobe
- Baseline scan



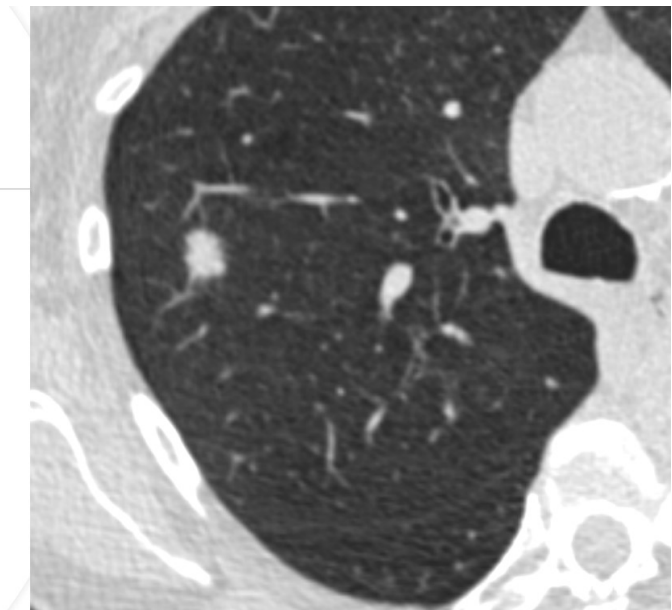
Scenario 7

Opacity in left upper lobe
922mm³, 19mm
No prior imaging available



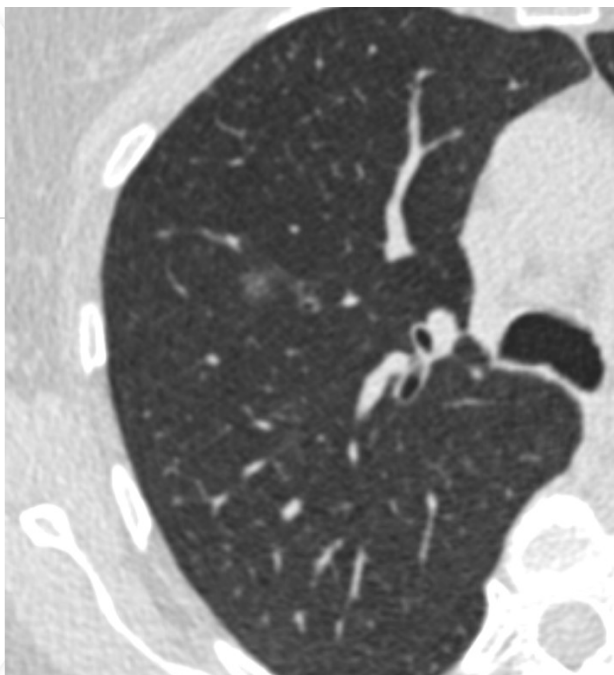
Scenario 8

Baseline scan
Solid nodule 655mm³
Brock 45%



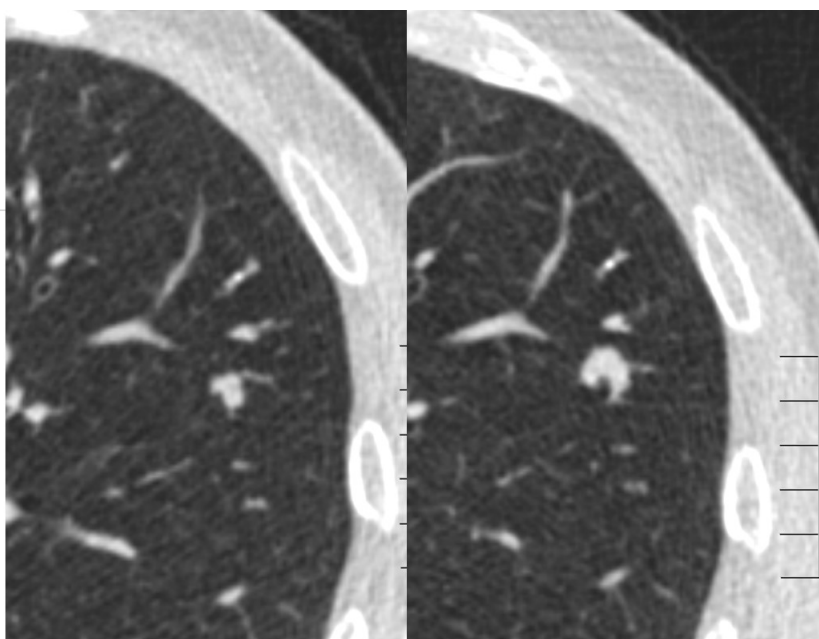
Scenario 9

Baseline scan
8mm pure GGN



Scenario 10

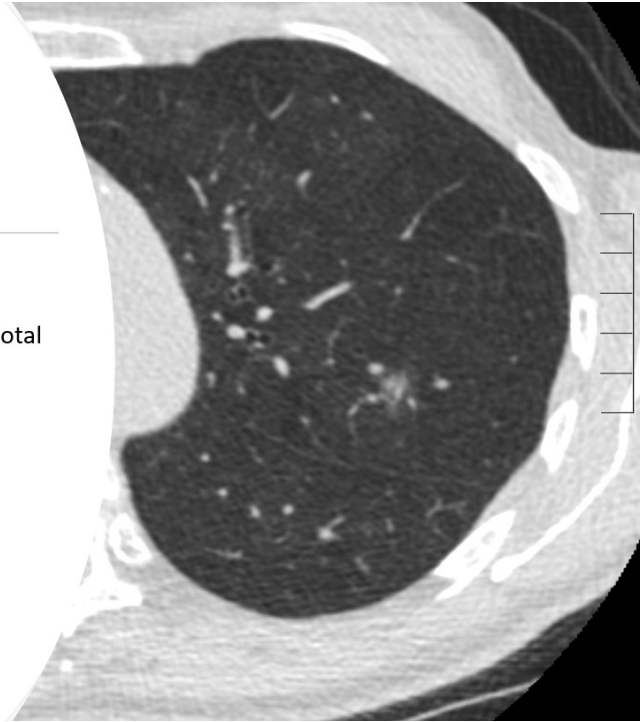
LUL nodule
Baseline 199mm³
3 month follow up 597mm³
VDT 58 days



Scenario 11

Baseline scan.

Part solid nodule (solid component 3mm, total size 13mm)



Scenario 12

- Right upper lobe pure GGN
- 13mm at baseline
- 13mm at year 1

