Institution: University of Liverpool		
Unit of Assessment: Uo1: Clinical Medicine		
Title of case study: Lung Cancer Screening: Improving early detection of the commonest cause of cancer death through the UK Lung Cancer Screening (UKLS) trial catalysing implementation and unique risk modelling		
Period when the underpinning research was undertaken: 2000 – present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Professor John K Field	**Role(s) (e.g. job title):** Clinical Professor Molecular Oncology	**Period(s) employed by submitting HEI:** 1986-present
Period when the claimed impact occurred: Aug 2013 - present		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Identification of early-stage lung cancer saves lives. Liverpool's lung cancer risk-model has provided the UK with a clinically-efficient, cost-effective method for targeted referral of high-risk individuals. Liverpool led the only random clinical trial to demonstrate that this risk-based approach can be successfully used to identify patients for lung cancer screening. The findings played an essential role in establishing the potential of lung cancer screening for early diagnosis in the UK, with adopted protocols enabling early intervention now being used to inform approaches in Europe and China. Notably, our work underpins introduction of the first NHS England (NHSE) lung screening programme (>GBP70,000,000 between 2019 and 2023), delivering lung health-checks in seventeen localities utilising Liverpool's risk model, as a model for national upscaling. NHSE predicts identification of 3,400 cancers for early intervention by 2023.

2. Underpinning research

The Liverpool Lung Project (LLP) Risk Model was developed from the LLP_{v1} case control and cohort population (LLP_{v1}, JK-Field-PI) (3.1). The LLP risk model was validated in two international case-control studies UK cohort (Area-Under-the-Curve (AUC0.82) (3.1). The risk model has been recently validated in the 76,000 UK Lung Cancer Screening (UKLS) responders to the first questionnaire (AUC-0.81). The risk model has evolved and been updated to LLP_{v3}, using sex and age specific incidence for the whole of England, providing a better estimate of absolute lung cancer risk (3.3). LLP_{v2} was used to select high-risk individuals for the UKLS trial-2011 (JK-Field Chief-Investigator) (3.2). It was the largest clinical UK trial on the lung NCRI Portfolio (2011). LLP_{v3} has been recommended for implementation in the large NHSE lung screening programme (3.3).

The UKLS trial: true population-based trial, including all Indices of Multiple Deprivation with 250,000 individuals approached (3.4); barriers to uptake were analysed; high-risk population identified utilising the LLP_{v2} (5% risk over 5 years) (3.1); unique set of findings; volumetric assessment of pulmonary lung nodules used in Radiology Reporting. UKLS trial had well-defined Care Pathway for the clinical management of patients with CT detected nodules; 67% were early-stage lung cancer (T1A/B N0) (3.5); a very high proportion of the lung cancer patients identified by CT screening were suitable for surgical intervention (83% vs 20% in routine clinical practice) (3.5) (3.4); low benign resection rate 10%; psychological impact was found to be transitory; smoking cessation was successfully implemented (3.5); integrated smoking cessation with screening (3.6); UKLS cost-effectiveness providing cost per QALY of screening, resulting in an estimate of around GBP8,500 per QALY gained for screening, well within the NICE guidelines (3.4).

Implementation. The UKLS trial outcomes were immediately taken-up by the Liverpool CCG and setup of a Service Evaluation of lung cancer screening in the hard-to-reach areas in the Liverpool region (JK-Field on Liverpool Healthy Lung Project (LHLP) Steering Committee and joint evaluation with Queen Mary London). The Liverpool CCG invested GBP3,000,000 into the LHLP. 2,591 patients were recruited in Liverpool, utilising the LLP_{v2} risk model and demonstrated 2% lung cancers.

The UKLS publication stimulated similar early lung cancer screening projects in Manchester, Nottingham, London and Yorkshire. In January 2019, NHSE announced a GBP70,000,000 investment into 'Targeted Screening for Lung Cancer with Low Radiation Dose Computed Tomography'. The Protocol for the Targeted Lung Health Checks Programme was prepared by NHSE Lung Cancer Screening Advisory Group (JK-Field Task & Finish Group).

3. References to the research

[3.1] Raji OY, Duffy SW, Agbaje OF, Baker SG, Christiani DC, Cassidy A, **Field JK**. 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: 242-250. https://doi.org/10.7326/0003-4819-157-4-201208210-00004

[3.2] Fiona E. McRonald, Ghasem Yadegarfar, David R. Baldwin, Anand Devaraj, Kate E. Brain, Tim Eisen, John A. Holemans, Martin Ledson, Nicholas Screaton, Robert C. Rintoul, Christopher J. Hands, Kate Lifford, David Whynes, Keith M. Kerr, Richard Page, Mahesh Parmar, Nicholas Wald, David Weller, Paula R. Williamson, Jonathan Myles, David M. Hansell, Stephen W. Duffy and **John K. Field**. The UK Lung Screen (UKLS): Demographic Profile of First 88,897 Approaches Provides Recommendations for Population Screening. *Cancer Prev Res* March 1 2014 (7) (3) 362-371; http://dx.doi.org/10.1158/1940-6207.CAPR-13-0206

[3.3] **Field JK**, Vulkan D, Davies MPA, Duffy SW, Gabe R. Liverpool Lung Project lung cancer risk stratification model: calibration and prospective validation. Thorax 2021;76:161–168. http://dx.doi.org/10.1136/thoraxjnl-2020-215158 (first published 20 October 2020)

[3.4] **Field JK**, Duffy SW, Baldwin DR, Brain KE, Devaraj A, Eisen T, Green BA, Holemans JA, Kavanagh T, Kerr KM, Ledson M, Lifford KJ, McRonald FE, Nair A, Page RD, Parmar MK, Rintoul RC, Screaton N, Wald NJ, Weller D, Whynes DK, Williamson PR, Yadegarfar G, Hansell DM. 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: 1-146. https://doi.org/10.3310/hta20400

[3.5] Brain K, Lifford KJ, Carter B, Burke O, McRonald F, Devaraj A, Hansell DM, Baldwin D, Duffy SW, **Field JK**. Long-term psychosocial outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised controlled trial. *Thorax*. 2016 Nov;71(11):996-1005. http://dx.doi.org/10.1136/thoraxjnl-2016-208283

[3.6] Brain K, Carter B, Lifford KJ, Burke O, Devaraj A, Baldwin DR, Duffy S, **Field JK**. Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK Lung Cancer Screening Trial. Thorax 2017;72:912-918. http://dx.doi.org/10.1136/thoraxjnl-2016-209690

4. Details of the impact

Context. Lung cancer accounts for more deaths than any other cancer (21% for the UK between 2015 and 2017). There are 1,740,000 deaths per annum worldwide (projected to rise to 2,890,000 by 2030) with 25% of those occurring in Europe. In 2012 Oxford health economists estimated that the cost to the UK economy was GBP2,400,000,000 per annum, higher than for any other cancer. Although late-stage lung cancer has a very poor prognosis, early-stage cancer can be successfully treated by surgical intervention if diagnosed early. Therefore, an effective method of detecting early-stage cancer has the potential for significant long-term economic and clinical impact.

Equivocal data from the 2011 NLST US lung screening trial did not prompt implementation of screening programmes [5.1]. A major barrier in the UK and Europe was the expense of large-scale referral for lung screening [5.1]. The Liverpool LLP risk model introduced a more targeted framework of pre-selection for screening, enabling high-risk individuals to be identified, thereby providing a clinically efficient and cost-effective approach to saving lives [5.1]. The Liverpool-led UK Lung Cancer Screening (UKLS) study supplied robust new

evidence, which accelerated implementation of lung screening programmes [5.2], as acknowledged by the UK Lung Cancer Coalition [5.3].

UK screening implementation and policy planning. The Liverpool-led UKLS directly led to five other local health providers introducing screening projects [5.2], and the NHS England (NHSE) lung screening programme (GBP70,000,000 investment, 2019-2023), incorporating the Liverpool LLP risk model in screening programmes in ten additional sites [5.4]. NHSE is now delivering expanded lung health checks in seventeen localities [5.4]. NHSE predicts identification of 3,400 cancers for early intervention by 2023 [5.4]. In addition, the LLP risk model is being used to inform progress in policy and planning at EU-level [5.4, 5.10]. NHSE's programme is intended for future UK upscaling [5.5]. The NHSE Senior Programme Manager, NHS England & NHS Improvement stated that 14,000,000 high-risk individuals are projected to be screened for lung cancer by 2028 [5.5]. Wales and Scotland are also now exploring implementation of lung screening referencing UKLS and LHLP and JK-Field is an advisor to this work [5.5].

The Independent Review of Adult Screening programmes in England (2019) references Liverpool's role in the rationale for the new lung screening programme [5.3]. CEO of the Roy Castle Lung cancer Foundation acknowledged the contribution of LLP and UKLS to the NHSE programme [5.6].

Health economics and patient benefits. The initial Liverpool-led UKLS study demonstrated to UK government the financial feasibility of a programme of lung screening. Independent health-economic analysis established a quality adjusted life year (QALY) cost of GBP8,466, well within NICE guidelines [5.7]. Significantly, Liverpool has a disproportionately high incidence of lung cancer and UKLS demonstrated an effective way to tackle this [5.2]. Prompting immediate implementation (2016) of the UK's first, and to date largest, lung screening pilot, 'Liverpool Healthy Lung Project' (LHLP), with an investment of GBP3,000,000 by the Liverpool CCG to tackle local health inequality. Evaluation of 'Liverpool Healthy Lung Project' (LHLP) in 2018 showed that 1 death was avoided for every 300 scans and 86% of diagnoses were early-stage, with 193 confirmed new Chronic Obstructive Pulmonary Disorder diagnoses, and 18% of current smokers agreeing referral to a cessation clinic [5.2]. Results from the NELSON lung cancer screening trial study in the Netherlands (2020) further confirm the merits of lung screening, achieving 24% mortality gains.

International implementation. As a measure of the extended reach of Liverpool's impact in the field of lung cancer screening, a European expert on lung screening and recent Senior Editor of the British Journal of Radiology has commented that UKLS had "a major impact" on implementation of a UK programme, and notes JK-Field's "inexhaustible drive" to support international uptake, through major contributions to the International Association for the Study of Lung Cancer, and in interpretation of key European trial results [5.6]. JK-Field was also invited to review lung screening in China, resulting in ten recommendations (2019) and is cited in China's lung screening guidelines [5.8]. His Nature review of lung cancer screening (2020) presents international colleagues with a framework for further international implementation [5.9].

The UKLS trial was the only RCT to demonstrate that a risk-based approach can be successfully used to identify patients for lung cancer CT screening. Together with the nodule management approach, that risk-based approach has been recommended for adoption into policy by the European screening professions and EU Commission [5.10]. JK-Field is called on to advise European countries [5.10], in particular the utilisation of the LLP_{v3} risk model in Germany [5.2]. JK-Field led the European Commission policy on lung cancer screening [5.10], led a roundtable discussion of European experts and also co-developed the 'European Position Statement on Lung Cancer Screening' [5.10].

5. Sources to corroborate the impact

[5.1] Catalysing impact; avoiding a standstill ahead of NELSON results – UKLS showing clinical-efficiency and cost-effectiveness
Ruparel M, Janes SM. Thorax 2016;71:103– 104. http://dx.doi.org/10.1136/thoraxjnl-2015-208210. Table 1 shows relatively high detection versus other studies (2.1%). Discussion of how UKLS addressed barriers to UK/Europe implementation regarding clinical efficiency and cost-effectiveness. Also see http://dx.doi.org/10.1136/thoraxjnl-2011-200351 for summary of IASLC concerns with NLST.
'Call for lung cancer screening in UK', 11 September 2014. www.bbc.co.uk/news/health-29142822. Highlighting UK NSC 2014 concerns with existing evidence and looking to UKLS results before deciding on action.

[5.2] Implementation Projects, attribution to LLP/ and impact of (as a table)
These local projects reference UKLS as a stimulus and/or use the risk model, e.g. Manchester's Lung Health Check Pilot, Report. See 'Why did we do it?' p.4; West London, note LLP advantages over PCLO, as per the *Lung Cancer* 2020; 148:12-19 reference; Yorkshire protocol uses LLP risk model and references UKLS. Nottingham followed UKLS and LHLP (in 2017), with Roy Castle (an LHLP collaborator) funding.
Liverpool, the first of these local projects, includes reference to UKLS and connection with University of Liverpool in its project materials; evaluation of the project by Ghimire B, Maroni R, Vulkan D, et al. (2019) 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.
Germany: use of LLP model in HANSE study for LC Screening in Northern Germany (email), October 2020

[5.3] Attributions of NHSE programme to LLP and UKLS
e.g. **UK Lung Cancer Coalition**, October 2016, '25 by 25: A Ten-Year Strategy to Improve Lung Cancer Survival Rates', e.g. p.12 "Whilst the UK National Screening Committee are yet to make a decision on lung cancer until the results from the NELSON trial are published...the United Kingdom Lung Cancer Screening (UKLS) trial…commissioned by the Department of Health's Technology Assessment Programme, showing positive results in 2016 to support the case for a national programme"
https://www.uklcc.org.uk/files/UKLCC%2025%20by%2025%20FINAL.pdf
e.g. Report of The Independent Review of Adult Screening Programmes in England. (Oct 2019) p.21 discussing NHSE programme implementation cites sources which highlight the Liverpool role. https://www.england.nhs.uk/wp-content/uploads/2019/02/report-of-the-independent-review-of-adult-screening-programme-in-england.pdf

[5.4] NHSE lung screening programme implementation 2019, Liverpool attributions
Protocol**:** NHS England, National Cancer Programme (2019) *Targeted Screening for Lung Cancer with Low Radiation Dose Computed Tomography: Standard Protocol prepared for the Targeted Lung Health Checks Programme.* On use of LLP risk model, see section 3.3, p.12-13 https://www.england.nhs.uk/wp-content/uploads/2019/02/targeted-lung-health-checks-standard-protocol-v1.pdf 3.3.2 p.12.
3400 lives figure reported: https://www.england.nhs.uk/contact-us/privacy-notice/how-we-use-your-information/our-services/evaluation-of-the-targeted-lung-health-check-programme/
Lee R, Nair A, Stacey C, et al. S21 Developing NHS England's national targeted lung health check pilot. Thorax 2019;74:A14. Overview of programme and states "The Standard Protocol is already being used by several European countries as a template for local protocol development." http://dx.doi.org/10.1136/thorax-2019-BTSabstracts2019.27

[5.5] Wales and Scotland, planned extension of England implementation:
i. Wales Cancer Network, Lung Health Check Scoping Review Project, Wales www.walescanet.wales.nhs.uk/lung-health-check - Wales steps towards implementation; report: https://collaborative.nhs.wales/networks/wales-cancer-network/wcn-documents/lung-health-scoping-report/, discusses UKLS, LHLP and cites work by JK-Field.

ii. Scotland Lung Cancer Screening Advisory Committee: 'How should Scotland respond to the challenge of lung cancer screening? A mixed-methods feasibility study', JK-Field membership of Expert Steering Group (p.14), citations of JK-Field UKLS and LHLP work (references). 'Support builds for lung screening in Scotland' Emma Morris, 5 February 2020 /https://pharmafield.co.uk/healthcare/support-builds-for-lung-cancer-screening-in-scotland/
iii. Planned England extension: NHS Long Term Plan, 7 January 2019 https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/ p.61 'Milestones for cancer' box "By 2022 the lung health check model will be extended"; 14,000,000 figure from NHSE Senior Programme Manager, presentation slide 7 (contact 3); extension to a further seven sites noted in letter to Cancer Alliances Leadership teams from NHS Cancer Programme Director, 6 April 2020, Annex, p.5 "From April 2020, funding will also be available to support the seven existing projects we will be bringing into the national programme."

[5.6] Testimonial/ Quotes from key stakeholders
Testimonial from European Professor/radiology expert (contact 1)
Roy Castle Foundation CEO quote on Liverpool work as springboard for NHSE implementation (contact 2):
https://www.roycastle.org/much-needed-but-much-still-to-do-our-response-to-nhs-englands-announcement-for-lung-health-checks/

[5.7] Independent health economist evaluation
Whynes DK. Could CT screening for lung cancer ever be cost effective in the United Kingdom? *Cost Eff Resour Alloc* 2008;6:5. Cost-effectiveness points also summarised by Ruparel and Jannes (2016), mentioning in discussion of UKLS e.g. p.103, "this is the first time actual expenditure from LDCT screening in the UK has been evaluated".
https://www.roycastle.org/much-needed-but-much-still-to-do-our-response-to-nhs-englands-announcement-for-lung-health-checks/

[5.8] China impact:
Cheng, YI., Davies, MPA., Dan Liu, D., Li, W., and Field, JK. Implementation planning for lung cancer screening in China. Review. Precision Clinical Medicine, 2019, 1–32. https://doi.org/10.1093/pcmedi/pbz002. Details ten recommendations for China lung cancer screening, p.24, 'Panel 1'.
Zhou Q, Fan Y, Wang Y, Qiao Y, Wang G, Huang Y, Wang X, Wu N, Zhang G, Zheng X, Bu H, Li Y, Wei S, Chen L, Hu C, Shi Y, Sun Y. China National Lung Cancer Screening Guideline with Low-dose Computed Tomography (2018 version). Zhongguo Fei Ai Za Zhi. 2018 Feb 20;21(2):67-75. Chinese (abstract and references in English). https://doi.org/10.3779/j.issn.1009-3419.2018.02.01. Cites Field (references 8 and 13).

[5.9] SPIRAL framework in Nature Review:
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 (2020). https://doi.org/10.1038/s41571-020-00432-6

[5.10] European Impact
Policy: Field JK, Zulueta J, Veronesi G, Oudkerk M, Baldwin D, R, Holst Pedersen J, Paci E, Horgan D, de Koning H, J: EU Policy on Lung Cancer CT Screening 2017. Biomed Hub 2017;2(suppl 1):1-8. https://doi.org/10.1159/000479810
Roundtable: Field JK, de Koning H, et al. Implementation of lung cancer screening in Europe: challenges and potential solutions: summary of a multidisciplinary roundtable discussion. ESMO Open 2019;4:e000577. https://doi.org/10.1136/esmoopen-2019-000577
Position statement: Oudkerk M, Devaraj A, Vliegenthart R, Henzler T, Prosch H, Heussel CP, Bastarrika G, Sverzellati N, Mascalchi M, Delorme S, Baldwin DR, Callister ME, Becker N, Heuvelmans MA, Rzyman W, Infante MV, Pastorino U, Pedersen JH, Paci E, Duffy SW, de Koning H, Field JK. European position statement on lung cancer screening. Lancet Oncol. 2017 Dec;18(12):e754-e766. https://doi.org/10.1016/S1470-2045(17)30861-6