



Editorial

Low-dose Computed Tomography Screening: The (Other) Lung Cancer Revolution

C. Horst^{*}, M.E.J. Callister[†], S.M. Janes^{*}^{*}Lungs for Living, UCL Respiratory, University College London, London, UK[†]Department of Respiratory Medicine, Leeds Teaching Hospitals NHS Trust, St James's University Hospital, Leeds, UK

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The advent of immune checkpoint inhibitors for the treatment of metastatic non-small cell lung cancers has been a bright spot in the otherwise bleak landscape of the UK's deadliest cancer. In a disease where two-thirds of those who present with a new diagnosis will be dead within a year, and survival outcomes have changed little in the last four decades [1], the potential to extend progression-free and overall survival by, on average, 4 months [2] is noteworthy. Immunotherapy may play a starring role in the future of lung cancer treatment but there is a more revolutionary approach to improving lung cancer outcomes: low-dose computed tomography (LDCT) screening. Lung cancer screening (LCS) with LDCT demonstrates considerable lung cancer and all-cause mortality risk reduction [3,4]. LCS and effective and embedded smoking cessation interventions show synergy, with the mortality reduction of screening essentially doubled by prolonged cessation [5]. However, when it comes to LDCT screening, there is still a hearts-and-minds battle to be won (see Table 1).

Evidence (and Reticence)

LDCT screening for lung cancer arrived in 2011, with the publication of the National Lung Screening Trial's (NLST) mortality results: the large American trial ($n = 53\,454$) showed that, compared with annual chest radiographs, LDCT screening reduced lung cancer mortality by 20%, and all-cause mortality by 7% [3]. Smaller studies in the UK have reinforced the benefits of LDCT screening, showing a stage-shift of disease to stages I and II when screening is carried out in high-risk populations [6,7]. Early mortality data from the NELSON trial ($n = 15\,822$) show a 26% lung cancer mortality risk reduction in men screened with LDCT

compared with standard of care (no screening); the reduction may be even greater in women [4].

In February 2019, as part of the National Health Service (NHS) Long Term Plan, it was announced that more lung health checks and same-day LDCT scans would be offered to those at highest risk of lung cancer [8]. These lung health checks will take the form of 10 discrete pilot schemes in the areas of England with the worst lung cancer outcomes [9]. However, the UK National Screening Committee (NSC) is yet to endorse a national LCS programme, and until it does, provision of LDCT screening will be limited to pilots and research studies, meaning many lives that could be saved will be lost.

The NSC must assess the evidence of efficacy and determine the health economics of such a new service, as well as working with the Government and Royal Colleges in managing infrastructure and workforce implications. Alternatively, LDCT may not fulfil the criteria to be assessed by the NSC. This seems odd, after all it is called LDCT screening across the world. However, there is the suggestion that LDCT screening is simply 'early diagnosis in a high-risk cohort'. If the NSC decides not to assess LDCT screening then the work will fall to the National Institute for Health and Care Excellence (NICE); meaning, if approved, there would be no national programme but rather locally implemented efforts in delivery, similar to the current situation in the USA.

Challenges to Lung Cancer Screening

The UK LCS community has three specific challenges to address, summarised by Wilson and Jungner [10] over half a century ago. First, 'to bring to treatment those with previously undetected disease [uptake]'; second, 'to avoid harm to those persons not in need of treatment [minimising harms]'; and third, to ensure that 'the cost of case-findings

Author for correspondence: C. Horst, Lungs for Living, UCL Respiratory, University College London, 5 University Street, London, WC1E 6JF, UK.

E-mail address: carolyn.horst@ucl.ac.uk (C. Horst).

Table 1
Summary of randomised lung cancer screening studies. Adapted from [24]

Study	Recruitment period	Recruitment criteria	Screening methods	Sample size (number screened)	Nodule threshold	Mortality benefit	Cancer detection rate
NLST [3]	2002–2004	Age 55–74 years, ≥ 30 pack-years, quit <15 years ago	Annual LDCT or CXR for 3 years	53 454 (26 722)	4 mm	20% RR LCM 6.7% RR ACM	1.0%
MILD [25]	2005–2011	Age > 49 years, ≥ 20 pack-years, quit <10 years ago, no recent cancer within last 5 years	3 groups: no screen versus annual LDCT versus biennial LDCT for 5 years	4099 (2376)	60 mm ³	Yes (NS) 30% RR LCM 17% RR ACM	0.7%
ITALUNG [26]	2004–2006	Age 55–69 years, ≥ 20 pack-years	Annual LDCT for 4 years versus no screen	3206 (1406)	5 mm	Yes 39% RR LCM 20% RR ACM	1.4%
DANTE [27]	2001–2006	Age 60–75 years, ≥ 20 pack-years, quit <10 years ago, male	Annual LDCT for 4 years versus no screen	2472 (1276)	5 mm	No	2.2%
DEPISCAN [28]	2002–2004	Age 50–75 years, ≥ 15 pack-years	Annual LDCT versus annual CXR for 2 years	765 (336)	5 mm	Not reported	2.4%
DLCST [29]	2004–2006	Age 50–70 years, ≥ 20 pack-years, quit <10 years ago, FEV1 > 30%, able to climb 2 flights of stairs, excluded if recent cancer/terminal illness	Annual LDCT versus usual care for 5 years	4104 (2052)	5 mm	No	0.8%
NELSON [4,30]	2003–2006	Age 50–75 years, ≥ 15 pack-years	LDCT screen at 0, 1, 3 and 5.5 years versus no screen	15 822 (7155)	50 mm ³	Yes 26% RR LCM (men) 39% RR LCM (women)	0.9%
UKLS [31]	2011–2013	Age 50–75 years, $\geq 5\%$ 5-year lung cancer risk as calculated by LLPv2 score	Single LDCT screen versus no screen	4061 (1994)	≥ 15 mm ³ /3 mm: 12-month scan. ≥ 50 mm ³ : 3-month scans	Not reported	2.1%

ACM, all cause mortality, CXR, chest X-ray, FEV1, forced expiratory volume in 1 second, LCM, lung cancer mortality, LDCT, low-dose computed tomography, LLPv2, Liverpool lung project risk model version 2, RR, risk reduction.

(including diagnosis and treatment) ... be economically balanced in relation to possible expenditure on medical care as a whole [cost-effectiveness]’.

In terms of uptake, ‘apathy’ in smokers and ex-smokers about their health has been raised as a barrier to effective engagement. In the USA, where LDCT screening is paid for by state-sponsored Medicare and Medicaid programmes, uptake has been inconsistent: it is estimated that only 4% of those eligible have undergone screening [11,12]. This disappointing response is a result of the provision of healthcare, relying on family practitioners being aware of LCS — many are not — and having access to centres that provide it [11]. Importantly, the evidence from UK screening studies and pilot programmes show a more positive picture when LDCT screening is approached with a systematic, population-based invitation strategy. Initial figures from the Lung Screen Uptake Trial in London show that when high-

risk populations identified in primary care databases are approached with an invitation from their general practitioners to participate in a lung health check, response rates are over 50% [13].

The second challenge is perceived harms to those screened, specifically over-diagnosis (where a true cancer is identified that would not have harmed that person in their lifetime); false-positive results, where unnecessary investigations or interventions are undertaken for a person who does not, ultimately, have a cancer; and the (over) management of incidental, non-lung cancer findings, which may or may not have caused the individual harm if left undetected.

The initial estimate of over-diagnosis in NLST was 18.5% (measured 6 years from trial entry) [14]. However, with longer follow-up (up to 12 years), rates dropped considerably to 3.1%. Interestingly, rates of over-diagnosis remained

high (79%) for broncho-alveolar cell carcinomas [15]. These lesions, now largely referred to as adenocarcinoma *in situ*, tend to correspond to pure ground glass nodules on computed tomography scans; contemporary strategies encourage surveillance only, reflecting their very indolent course. For context, breast screening quotes an overdiagnosis rate of 19% [16].

Reported rates of false-positive screens vary considerably. The NLST published a rate of 23.3% (centres in the USA have reported rates as high as 58% [17]); the UK Lung Screening trial and NELSON both quote 3.6%. This variability reflects different definitions of ‘positive findings’; e.g. in excluding nodules that require a repeat scan in 3 months’ time, the rate of ‘false positives’ (and associated harms) reduces substantially. Only those nodules of size significance, increasing growth or changing morphology are invasively investigated.

LDCT screening also requires a unified approach when it comes to incidental findings; unlike in breast or bowel screening, where only the target area is imaged, LDCT screening captures the entire thoracic cavity. Recommendations for further investigation or management should be evidence based in order to prevent unnecessary and unhelpful intervention [18], while providing the best possible outcomes for patients. Data gathered from LDCT trials currently underway in the UK will go some way to providing support for comprehensive guidelines.

Yes, but is it Worth the Cost?

Having maximised participation and minimised harms, the final challenge is demonstrating the cost-effectiveness of screening and justifying the very considerable investment required to set up a comprehensive UK-wide screening programme while the NHS struggles with a limited budget and ever-increasing demands on existing services.

There has been, to date, no published estimate of the probable total cost of a nationwide LCS programme, but informal estimates have ranged from £100 million to £200 million per annum. Analysis from the Health Economics Unit at York University allows an estimation of these opportunity costs [17]. A LCS programme costing between £100 million and £200 million may result in the loss of between 2330 and 4659 life-years (and 7733 and 15 465 quality-adjusted life-years) elsewhere in the NHS [19]. There would need to be clear demonstration that the expected gains from LCS justify this displacement of resource. Cost-effectiveness analyses from both the UK Lung Screening pilot and the Manchester Lung Health Check programme show favourable incremental cost-effectiveness ratios, where the anticipated gains would clearly exceed the opportunity costs described above [6,20]. A modelling study produced for the Health Technology Authority showed a cost-effectiveness assessment less favourable and closer to the supposed ‘NICE threshold’ [21]. However, this analysis pre-dated publication of both the NELSON results (showing a greater reduction in mortality

than NLST) and more mature data from NLST showing low rates of overdiagnosis. Re-evaluation of cost-effectiveness incorporating the latest data is required.

It is frequently commented that consideration of a national screening programme while the UK as a whole disinvests in smoking cessation interventions (the annual spend on smoking cessation services in England reduced from £128 million in 2013/14 to £89 million in 2017/18 [22]) makes little sense. Smoking cessation interventions represent one of the most cost-effective interventions in the whole of healthcare, and there is therefore urgent need to reinvest in these services. However, to use this disinvestment as a reason not to fund a LCS programme seems perverse. If all novel tests or treatments being considered for implementation in the NHS were required to show better cost-effectiveness than smoking cessation interventions, then few if any would come into clinical practice. However, the close link between smoking cessation and LCS offers an opportunity to embed one within the other, improving the cost-effectiveness of the overall bundle of activity. Modelling studies that project doubling of smoking cessation rates through the screening episode show a halving of the incremental cost-effectiveness ratio [23]. Delivering smoking cessation interventions co-located with LCS is being pursued in many of the UK lung health check programmes.

Lung Cancer Screening and the Future

With two large randomised trials showing reduced lung cancer mortality, and newer data showing significantly lower harms than originally reported, the arguments in favour of LCS at a participant level are difficult to ignore. Debate will continue about the health economic assessment of LCS and whether this represents value for money. Much will depend on the risk threshold at which people are invited for LCS. The higher the lung cancer risk required to enter a screening programme, the greater the yield of cancer (per person screened) and the more cost-effective a programme would be. Yet by limiting LCS to a higher-risk cohort, the overall number of cancers detected, and therefore lives saved, would be reduced. Ongoing studies comparing risk thresholds will be critical in informing this debate.

The UK NSC is optimally placed to make these assessments, and provide the infrastructure required for any possible future nationwide programme. Only with the rigour of data collection and quality assurance alongside workforce expansion and training can we be assured that the impressive results from screening studies be replicated in centres across the country. Without such an approach we may face another postcode lottery of implementation and miss out on the considerable benefits that LCS has to offer. With immunotherapy extending life after diagnosis for those with late-stage disease, a comprehensive high-quality LDCT screening programme preventing many people from reaching late-stage disease, and smoking cessation embedded at all steps of the pathway, we may finally start to see a turnaround in lung cancer outcomes.

Conflicts of Interest

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References

- [1] Lung cancer statistics. Cancer Research UK. Available at: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/survival#heading-Zero>.
- [2] Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018;378(22):2078–2092, <https://doi.org/10.1056/NEJMoa1801005>.
- [3] Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365(5):395–409, <https://doi.org/10.1056/NEJMoa1102873>.
- [4] De Koning H, Van Der Aalst C, Ten Haaf K, Oudkerk M. Effects of volume CT lung cancer screening: mortality results of the NELSON randomised-controlled population based trial. *J Thorac Oncol* 2018;13(10):S185, <https://doi.org/10.1016/j.jtho.2018.08.012>.
- [5] Tanner NT, Kanodra NM, Gebregziabher M, Payne E, Halbert CH, Warren GW, et al. The association between smoking abstinence and mortality in the National Lung Screening Trial. *Am J Respir Crit Care Med* 2016;193(5):534–541.
- [6] Field JK, Duffy SW, Baldwin DR, Whyne DK, Devaraj A, Brain KE, et al. UK lung cancer RCT pilot screening trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. *Thorax* 2016;71(2):161–170.
- [7] Ruparel M, Dickson J, Quaife S, Sophie T, Hall H, Horst C, et al. Results from a prevalence round of LDCT screening for lung cancer in the Lung Screen Uptake Trial. *Lung Cancer* 2019;127:S22–S23, [https://doi.org/10.1016/S0169-5002\(19\)30100-X](https://doi.org/10.1016/S0169-5002(19)30100-X).
- [8] Alderwick H, Dixon J. The NHS long term plan. *BMJ* 2019;364:58–59.
- [9] NHS to rollout lung cancer scanning trucks across the country. NHS England; 2019.
- [10] Wilson JMG, Jungner G. *Principles and practice of screening for disease*. WHO Public Paper 34. Geneva: WHO; 1968. Available at: https://apps.who.int/iris/bitstream/handle/10665/37650/WHO_PHP_34.pdf?sequence=17&isAllowed=y.
- [11] 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, <http://oncology.jamanetwork.com/article.aspx?doi=10.1001/jamaoncol.2016.6416>.
- [12] Bryan L, Westmaas L, Alcaraz K, Jemal A. Cigarette smoking and cancer screening underutilization by state: BRFSS 2010. *Nicotine Tob Res* 2014;16:1183–1189, <https://doi.org/10.1093/ntr/ntu047>.
- [13] Ruparel M, Quaife S, Dickson J, Bhowmik A, Taylor M, Shaw P, et al. Identification and attendance of a high-risk cohort in a lung cancer screening demonstration pilot. *Thorax* 2017;72(Suppl. 3):A10.
- [14] Patz EF, Pinsky P, Gatsonis C, Sicks JD, Kramer BS, Tammemägi MC, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med* 2014;174(2):269, <http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2013.12738>.
- [15] Black WC, Chiles C, Church TR, Gareen IF, Gierada DS, Mahon I, et al. Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial National Lung Screening Trial Writing Team 1. *J Thorac Oncol* 2019, <https://linkinghub.elsevier.com/retrieve/pii/S1556086419304733>.
- [16] Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. *Br J Cancer* 2013;108(11):2205–2240, <https://doi.org/10.1038/bjc.2013.177>.
- [17] Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technol Assess* 2015;19(14):1–503.
- [18] 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–e766, [https://doi.org/10.1016/S1470-2045\(17\)30861-6](https://doi.org/10.1016/S1470-2045(17)30861-6).
- [19] Opportunity cost calculator, Centre for Health Economics, University of York. Available at: <https://www.york.ac.uk/che/research/teehta/thresholds/>.
- [20] Hinde S, Crilly T, Balata H, Bartlett R, Crilly J, Barber P, et al. The cost-effectiveness of the Manchester 'lung health checks', a community-based lung cancer low-dose CT screening pilot. *Lung Cancer* 2018;126:119–124, <https://doi.org/10.1016/j.lungcan.2018.10.029>.
- [21] Snowsill T, Yang H, Griffin E, Long L, Varley-Campbell J, Coelho H, et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. *Health Technol Assess* 2018;22(69):1–276.
- [22] Tobacco Advisory Group. *Hiding in plain sight: treating tobacco dependency in the NHS*. Royal College of Physicians; 2018. Available at: <https://www.rcplondon.ac.uk/file/10116/download?token=K05kvT-7>.
- [23] McMahon PM, Kong CY, Bouzan C, Weinstein MC, Cipriano LE, Tramontano AC, et al. Cost-effectiveness of computed tomography screening for lung cancer in the United States. *J Thorac Oncol* 2011;6(11):1841–1848, <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L51602384%5Cn>, <https://doi.org/10.1097/JTO.0b013e31822e59b3>.
- [24] Ruparel M. *Implementing CT screening in the UK: finding an evidence base for practical strategies*. Doctoral thesis, University College London; 2018. Available at: <http://discovery.ucl.ac.uk/10056414/>.
- [25] 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. *Ann Oncol* 2019;30(7):1162–1169.
- [26] 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:

- 825–831, <http://thorax.bmj.com/lookup/doi/10.1136/thoraxjnl-2016-209825>.
- [27] 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):355–363.
- [28] 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):50–58.
- [29] Wille MMW, 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;193:542–551.
- [30] Horeweg N, Scholten ET, de Jong PA, van der Aalst CM, Weenink C, Lammers JWJ, 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):1341–1350.
- [31] Field JK, Duffy SW, Baldwin DR, Whyne DK, Devaraj A, Brain KE, et al. UK lung cancer RCT pilot screening trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. *Thorax* 2015;71(2):161–170.