1 **Estimating the cost-effectiveness of lung cancer screening with low dose computed**

2 **tomography for high risk smokers in Australia**

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1 **Abstract**

2 **Background**: Health economic evaluations of lung cancer screening with low dose computerised

3 tomography (LDCT) that are underpinned by clinical outcomes are few.

4 **Methods**: We assessed the cost-effectiveness of LDCT lung screening in Australia by applying

5 Australian cost and survival data to the outcomes observed in the U.S. National Lung Screening Trial

6 (NLST), in which a 20% lung cancer mortality benefit was demonstrated for three rounds of annual

7 screening among high-risk smokers aged 55-74 years. Screening-related costs were estimated from

8 Medicare Benefits Schedule reimbursement rates (2015); lung cancer diagnosis and treatment costs

9 from a 2012 Australian, hospital-based study; lung cancer survival rates from the New South Wales

10 Cancer Registry (2005-2009); and other-cause mortality from Australian life tables, weighted by

11 smoking status. Health utility outcomes, screening participation and lung cancer rates were those

12 observed in the NLST. Incremental cost effectiveness ratios (ICERs) were calculated for a ten-year

13 time horizon.

14 **Results**: LDCT lung screening was estimated at AU$138,000 (80% CI, AU$84,700-$353,000)/life-

15 year gained and AU$233,000 (80% CI, AU$128,000-$1,110,000)/quality-adjusted life year (QALY)

16 gained. The ICER was more favourable when all-cause mortality and the costs of incidental findings

17 were estimated in sensitivity analyses: AU$157,000/QALY gained This can be compared to an

18 indicative willingness-to-pay threshold in Australia of AU$30,000-$50,000/QALY.

19 **Conclusions**: LDCT lung screening using NLST selection and implementation criteria is unlikely to be

20 cost-effective in Australia. Future economic evaluations should consider alternate screening eligibility

21 criteria, intervals, nodule management, the impact and costs of new therapies, investigations of

22 incidental findings, and incorporating smoking cessation interventions.

23 (247 of 250 words)

1 **Introduction**

2 Lung cancer is the leading cause of cancer-related death, both in Australia and worldwide,[1] and

3 population-based lung cancer screening has the potential to save many lives. In 2011, a 20% (95% CI

4 6.8%-26.7%) relative reduction in mortality from lung cancer was observed among long-term, heavy

5 smokers aged 55-74 years screened annually for 3 years with low dose computed tomography

6 (LDCT) in the U.S. National Lung Screening Trial (NLST).[2] As a consequence, many organisations

7 are now recommending annual lung screening with LDCT with variations of the NLST eligibility criteria

8 (i.e., those aged 55-74 years with 30 or more pack-years smoking history including those who quit

9 within the past 15 years).[3-8] A health economic evaluation of the NLST found that LDCT screening

10 was associated with an incremental cost-effectiveness ratio (ICER) of US$52,000/life-year (LY)

11 gained or US$81,000/quality-adjusted life-year (QALY) gained.[9] Many other U.S. based cost-

12 effectiveness analyses have reported estimates considered favourable.[10, 11] Outside the U.S.

13 however, lung cancer screening has not been systematically introduced, in part because many

14 questions remain with regard to cost-effectiveness in different settings. Further, all cost-effectiveness

15 analyses to date have been based on preliminary assumptions regarding screening effectiveness,

16 with the exception of the NLST health economic evaluation.[9]

17 These developments have prompted an urgent need for evidence on the harms, benefits and cost-

18 effectiveness of lung cancer screening in the Australian setting where trial data are few.[12] An early

19 evaluation found that LDCT screening was likely to be expensive (~AU$88,000-$105,000/QALY).[13]

20 The evaluation was based on a hypothetical cohort of current, heavy smokers aged 60-64 years in

21 Australia for the period 2002-2003, and assumed a screening-related mortality reduction of 27%. We

22 now provide an updated cost-effectiveness estimate for Australia that is grounded in strong evidence,

23 by applying Australian costs and Australian lung cancer survival estimates to the outcomes observed

24 in the NLST over a ten-year horizon.

25 **Methods**

26 We calculated the life-expectancy and costs associated with 3 annual LDCT lung screens compared

27 to usual care in a hypothetical scenario in which the trial population and lung cancer outcomes

28 observed in the NLST were applied to Australian population-based survival rates, with Australian cost

29 estimates. The benefits to participants are given as expected LYs or QALYs, up to a ten-year time

30 horizon from entry into screening (i.e., at randomisation). The ICER (the ratio of incremental cost to

31 incremental health benefit) for the comparison of LDCT screening to a no-screening strategy was

32 calculated for a base-case, with sensitivity analyses for selected inputs and assumptions. Bootstrap

33 resampling was used to determine 80% confidence intervals (CI) for incremental costs, benefits and

34 ICERs for our base-case (95% CIs were not calculated because they contained the origin in some

35 results). Each bootstrap sample included a resample of all NLST participants to estimate the mean

36 benefits and costs by screening strategy, sex, age and smoking status. We also generated a cost-

37 effectiveness acceptability curve, whereby the probability of cost-effectiveness is plotted against a

38 willingness-to-pay threshold.[14]

1   **Data inputs**

2   *NLST Trial Population*

3   The NLST was a randomised trial of lung screening among people aged 55-74 years, with 30 or more

4   pack-years smoking and 15 years or less since quitting. Details of the trial protocol are reported

5   elsewhere,[15] but briefly, 53,452 participants were randomised to receive 3 annual screens with either

6   LDCT or chest radiography (Aug 2002-Apr 2004), and followed up for 5 years to December 2009.

7   Outcomes derived from the NLST for this analysis were: 1) Number screened at each screening

8   round and number with a positive screen; 2) Number with lung cancer by stage and histological sub-

9   type; 3) Number of deaths due to lung cancer or other causes by the end of the study period. These

10   outcomes were directly extracted from the NLST dataset which was obtained from the National

11   Cancer Institute and calculated separately for each sex by smoking status (current/former) within 5-

12   year age strata. As in the original NLST cost-effectiveness analysis,[9] the outcomes of the chest

13   radiography arm were assumed equivalent to a no-screening arm given that chest radiography had no

14   effect on lung cancer mortality in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

15   (PLCO) in the US.[16] We reanalysed original line data from the trial for 53,171 participants after

16   excluding 204 participants who were deemed ineligible in the dataset and 77 participants who were

17   lost to follow-up within one day.

18   *Australian Survival Rates*

19   **Lung cancer cases**

20   For each participant in the NLST with a lung cancer diagnosis during the trial period (i.e., 3 annual

21   screens plus 5 years of follow-up) who was still alive at the end of follow-up, beyond-screening LYs

22   were estimated using relative, stage-specific survival data from the New South Wales Cancer Registry

23   (NSWCR; 2005-2009),[17] which receives all notifications of primary cancer diagnoses for residents of

24   NSW. We assumed that stage-specific survival rates were equivalent for LDCT-screened and

25   unscreened cases (i.e., screening did not preferentially detect less indolent tumours). Specifically,

26   expected LYs are given by the number of years alive within the trial study period (observed) and

27   added to the expected beyond-trial LYs based on Australian survival probabilities by age, sex and

28   stage of disease. Extent of disease classification reported in the NSWCR is broadly similar to the

29   SEER summary staging system.[18] Where SEER summary stage was not recorded in the NLST,

30   extent of disease was imputed using the tumour-node-metastasis (TNM) cancer staging system as

31   described in **Appendix A** (see **Tables S1-S4**). Where multiple lung cancer diagnoses were reported

32   for a participant (86 cases), only the first diagnosis of lung cancer was used to inform survival.

33   **Those without lung cancer**

34   For those without a lung cancer diagnosis, beyond-trial LYs were estimated from Australian life tables

35   (2012-2014),[19] adjusted for smoking status using the relative risk of all-cause mortality associated

1 with smoking in the U.S.,[20] similar to the original NLST evaluation. For the base-case, we assumed

2 that LDCT screening had no effect on mortality from causes other than lung cancer. Specifically, we

3 did not make assumptions regarding the number and type of potential clinically relevant incidental

4 findings, which were not sufficiently documented in the NLST. We restricted the base-case estimate

5 to lung cancer outcomes and allowed for all-cause mortality benefits in sensitivity analyses. Thus, for

6 all participants, LYs were calculated by taking observed survival in the "no screening" arm (i.e., chest

7 radiography) of the NLST and adding them to the beyond-trial Australian life-expectancy calculations

8 to derive a 10-year horizon from randomisation (see **Appendix B** for details). For the base-case, we

9 also assumed that 1) screening had no impact on beyond-trial risk of lung cancer, and 2) there was

10 no potential for radiation-induced cancer from screening, which is considered to be low in the 55-74

11 age group.[21]

12 *Australian Costs*

13 All costs were assumed for the year 2015 from a health services perspective. Any costs given in

14 earlier years were inflated using the ABS' weighted average of capital cities Consumer Price Index for

15 Health series,[22] and reported in Australian dollars.

16 The cost for a LDCT screen was based on the existing price of the test as listed in the Medicare

17 Benefits Schedule (MBS; $295 undiscounted in 2015) for a CT scan of the chest. The direct medical

18 costs involved in diagnostic follow-up for a true-positive screen or for cancer detected by usual care

19 (no screening), staging investigations, treatment, clinician consultations, treatment interventions, and

20 hospitalisation were estimated using data from an Australian study of new cases of lung cancer

21 presenting at two hospitals in NSW, Dec 2005-Dec 2006.[23] Costs were accumulated from first

22 consultation until final follow-up at Oct 31, 2008. Infrastructure, staff and non-medical costs were

23 excluded, and data were not available for the cost of general practitioner (GP) consultations prior to

24 diagnosis. Costs were reported as the overall mean cost of diagnosis and treatment in Australian

25 dollars by stage and histology (i.e., NSCLC: Stage I $8,235; II $17,007; III $13,678; IV $13,959;

26 SCLC: Limited stage $20,277; Extensive stage $12,966, undiscounted in 2005).[23] The cost of

27 diagnostic work-up for false-positive LDCT screens was taken from the previous Australian

28 evaluation, which was calculated from relevant MBS items at an average of $899.41 (undiscounted in

29 2002, and inflated to 2015).[13] A discount rate of 5% (with sensitivity analyses on 0-7%) was used for

30 both costs and expected LYs, consistent with Australian recommendations from the beginning of the

31 screening period.[24] The cost of lung cancer was discounted as though the cost was incurred at the

32 time of diagnosis.

33 *Utility Weights*

34 Quality of life was approximated by a utility, which is a measure of preference for a given health state

35 rated on a scale where 0 equals death and 1 equals perfect health. QALYs were calculated using the

36 utility weights associated with screening in the NLST.[9] The baseline utilities for men and women that

37 completed the Short Form Health Survey SF-36 were 0.76 and 0.74 respectively. We assumed a drop

1 in utility of 0.02 at the age of 75, as observed in the U.S. National Health Measurement Study.[25] Utility

2 weights for those with lung cancer were estimated from the same dataset by TNM stage for two time

3 periods: < 12 months, and ≥ 12 months from the date of diagnosis (as was done for the NLST[9], see

4 **Appendix B**). We assumed that the utility weight assigned at ≥ 12 months from diagnosis continued

5 unchanged for the remainder of the survival calculation.

6 Quality of life was not measurably affected by a positive or negative screening result in the NLST,

7 therefore we did not apply one in our base-case. However, to account for a potentially negative

8 impact of positive scans on quality of life, we performed a one-way sensitivity analysis where a drop in

9 utility occurred for two months following a positive screen, with a range of 0-0.05 (similar to sensitivity

10 analyses in the NLST evaluation).[9]

11 **Sensitivity analyses**

12 *Accounting for all-cause mortality*

13 To account for the 6.7% relative reduction in all-cause mortality in the LDCT arm of the NLST, the

14 LDCT group was assigned the observed survival in the LDCT arm and assumed an average of 0.19

15 incidental findings per screenee (based on a previous report [26]) in a sensitivity analysis. A recent

16 study noted a wide variety of "clinically actionable" incidental findings in relation to lung screening in

17 the Veteran's Health Administration, including emphysema and coronary artery calcifications.[27] To our

18 knowledge there has not been a systematic costing study of incidental findings in relation to lung

19 screening and so we applied a preliminary estimate of $2000 per incidental finding (values between

20 $0 -$2500 were used in the NLST[9]), discounted such that 80% of findings occurred at the baseline

21 scan and 20% spread evenly over the two incidence scans.

22 *Variation in cost assumptions*

23 One-way sensitivity analyses were conducted on a range of values for 1) the cost per screen, 2) the

24 cost of diagnostic follow-up for a false positive, and 3) the cost of diagnosis, staging and treatment for

25 lung cancer. We varied the cost per screen from $221 (75% of the base-case value) to $590 (double

26 the base-case value), reasoning that LDCT testing may be subject to an economy of scale if a full

27 national screening program is implemented, making each screen cheaper, or alternatively, that the

28 screening program may incur additional costs if multiple readings are required. The impact of varying

29 false-positive follow-up was assessed over the range of ±20% of the base-case value. The impact of

30 varying the combined diagnosis and treatment cost was assessed by 1) ±20% of the base-case value

31 for all cancer cases, and 2) increasing the cost of stage III/IV NSCLC cases by +100% to explore the

32 potential for increased costs associated with newer targeted therapies and mutation testing.

33 *Survival weighted by the demographic profile of the Queensland Lung Cancer Screening Study*
34 *(QLCSS)*

1   The screening outcomes from the NLST were compared to an Australian feasibility study of lung

2   screening that replicated the NLST protocol for the LDCT arm (the Queensland Lung Cancer

3   Screening Study, 2007-2014; QLCSS).[28, 29] Specifically, participants aged 60-74 years were recruited

4   via advertisements and media press release.[28] After excluding those aged <60 years at

5   randomisation, we calculated the estimated LYs in Australia by weighting the LYs of individuals in the

6   NLST according to the proportion of QLCSS participants within each 5-year age-group, sex, and

7   smoking status strata.

8   *Variation in the estimated time horizon*

9   A one-way sensitivity analysis examined a lifetime horizon as compared to the 10-year base-case

10   calculation for LYs.

11   *Variation in nodule management and definition of a positive scan*

12   In the NLST, any LDCT-detected nodule that was greater than 4 mm was considered a positive scan,

13   and the false-positive rate (FPR) was 24%. Attempts at reducing the FPR have come from more

14   recent nodule management protocols such as the British Thoracic Society guidelines and Lung-RADS

15   (FPR 13% using NLST data).[30, 31] Adopting this definition would change the positive predictive value

16   (proportion of criteria positive participants with cancer) of a screening program. Thus, we performed a

17   one-way analysis of varying the number of false-positive LDCT outcomes by ±20% on the second and

18   third rounds of screening.

19   *Restrict the definition of screening eligibility*

20   We evaluated current and past smokers separately, as well as evaluating an eligibility criterion of 40

21   pack-years smoking history as an alternative to the 30 pack-year NLST criteria (similar to previous

22   studies).[32-34]

23   **Results**

24   The number of lung cancers and lung cancer deaths observed in the NLST are reproduced in

25   **Appendix A** (**Table S4**). Overall, there were 934 non-small cell lung cancers (NSCLC) and 142 small-

26   cell (SCLC) in the LDCT arm; and 802 NSCLC and 161 SCLC in the 'no screening' arm. There were

27   214 more localised NSCLC diagnosed in the LDCT arm than in the no-screening arm, comparable

28   numbers diagnosed at regional disease stage, and 87 fewer distant disease cases. The proportions of

29   SCLC by stage of disease at diagnosis were almost identical across the two arms.

30   Mean LYs and QALYs were greater in the LDCT arm than the no-screening arm, both within the trial

31   (observed) and at the ten-year time horizon (**Table 1**). The incremental expected LYs of LDCT-

32   screened individuals with a lung cancer diagnosis was 0.54 years over the ten-year period using

33   Australian lung cancer survival rates (compared to 1.6 years incremental benefit over a lifetime

34   reported in the NLST[9]).

1   In the base-case, the average cost per person was higher in the LDCT scenario than the no screening

2   scenario, primarily due to the cost of the screen itself and diagnostic workup of positive results (**Table**

3   **2**). Screening with LDCT cost an additional $1,564 (80% CI, $1,525-$1,604) per person compared

4   with no screening (discounted from the beginning of the screening period), and provided an additional

5   0.0113 (80% CI, 0.0045-0.0181) LYs per person and 0.00670 (80% CI, 0.0014-0.0120) QALYs per

6   person (**Table 3**). The corresponding ICERs were $138,000 (80% CI, $84,700-$353,000) per life-year

7   gained and $233,000 (80% CI: $128,000-$1,110,000) per QALY gained. The ICERs by current and

8   former smoking status were $123,000 and $1,480,000 per QALY gained, respectively. The cost-

9   effectiveness acceptability curve is shown in **Figure 1a**, where the probability of a cost-effective

10   screening scenario increases as the willingness to pay threshold (horizontal axis) increases,

11   approaching 98.4% probability of cost-effectiveness. A threshold analysis for the cost of a LDCT

12   screen demonstrated that even at very low screening costs, lung screening would not be cost-

13   effective under the base-case assumptions tested here (see **Figure 1b**).

14   **Sensitivity Analyses**

15   Variation in base-case parameters resulted in ICER estimations that varied from $127,000 to

16     $509,000 per QALY gained and is presented in **Table 4** and **Figure 2**. The largest ICER was due to

17   the degree of disutility assigned to a false positive screen result. Specifically, in the worst case, where

18   a disutility of 0.05 was assigned to the 2 months following a false positive scan, the ICER was

19     $509,000 per QALY gained. The smallest (most favourable) ICER was observed when all-cause

20   mortality was factored into the survival benefit. Specifically, including the mortality benefit observed in

21   the LDCT arm from causes other than lung cancer resulted in an ICER of $127,000 per QALY gained.

22   When the cost of incidental findings (estimated at $2000 per finding) was also included in the

23   calculation the ICER increased to $157,000 per QALY gained.

24   Of the main input costs assessed, the cost per screen had the greatest impact on the ICER, ranging

25   from $204,000 to $351,000 per QALY gained, followed by the cost of following up false positives

26   ($211,000 to $256,000 per QALY gained). Varying the mean cost of treatment ±20% had a very

27   minimal impact on the ICER. Increasing the cost of stage III/IV lung cancers by 100% resulted in a

28   slightly more favourable ICER ($223,000/QALY gained) than the base-case.

29   The time-horizon for survival benefit was tested in the range of 10 years up to a lifetime, with the

30   resulting incremental LYs shown in **Figure 3**. The change in additional LYs (and QALYs) gained by

31   LDCT screening increases as the horizon approaches ≈14 years, towards a maximum of 0.0127 LYs

32   (0.0075 QALYs), with a corresponding ICER of $210,000 per QALY gained. When the horizon was

33   extended further than 14 years, the incremental LYs gained by screening decreased towards a

34   minimum of 0.0096 LYs (0.0049 QALYs) at the lifetime horizon, with a corresponding ICER of

35     $319,000 per QALY gained.

36   Varying the discount rate from 0-7% increased the ICER from $212,000 to $262,000 per QALY

37   gained over the 10-year time horizon. Changing the expected number of false positives in incidence

1   scans to reflect potential differences in positive predictive value (PPV), also resulted in a relatively

2   small change in ICER. The observed PPV for second or third round (incidence) screens in the trial

3   was 5.9%. A 20% decrease in PPV resulted in a cost per person in the LDCT group of $1,659,

4   corresponding to a 6% increase to the additional cost of LDCT per person. A 20% increase in PPV

5   resulted in a ~4% decrease in the additional cost per person.

6   Differences in the distribution of participants in the NLST compared to those in the QLCSS by age,

7   sex, and smoking status are presented in **Table S5**. Lung-cancer incidence was similar in the QLCSS

8   compared to the same age range in the LDCT arm of the NLST (121, 95% CI, 66-202 vs. 85 cases

9   per 10,000 person-years, respectively). Weighting the results by the demographic profile of QLCSS

10   participants decreased the ICER to $154,000 per QALY gained. The reduction in ICER from that of

11   the base-case was mostly due to the exclusion of people aged less than 60 years at randomisation.

Discussion

By applying Australian cost and population-based survival data to the NLST outcomes, we estimated that lung cancer screening with LDCT would cost AU$233,000/QALY gained, and AU$138,000/LY gained over a 10-year time horizon. Our base-case estimates were higher than the previous Australian estimate of AU$105,090 per QALY gained in 2002.[13] This is not surprising given the wide range of ICERs we observed in sensitivity analyses, and illustrates the importance of model parameters and assumptions. For example, the previous Australian estimate was based on a hypothetical cohort of current smokers and was more similar to the ICER for current smokers in our analysis (i.e., AU$123,000/QALY gained). However, even the lower ICER estimates in our study were more than double what would be considered cost-effective in the Australian context (i.e., the current 'willingness-to-pay' threshold is ~AU$30,000-50,000/QALY gained).[35]

The NLST reported a statistically significant, 6.7% (95% CI, 1.2-13.6) mortality benefit of LDCT screening on deaths from any cause (3.2% due to deaths other than lung cancer).[2] This result suggests that lung screening may capture clinically significant abnormalities other than lung cancer that are detected during the screening examination (e.g., heart, abdomen). One study reported that "actionable" conditions such as coronary artery calcification or emphysema occurred in 19% of LDCT lung screens, including 'severe' findings that merited immediate attention in 0.8% of cases.[26] Given the smoking history of those eligible for lung screening, it is not surprising that incidental findings are common. We applied the rate of 19% actionable incidental findings in a sensitivity analysis, assigning 0.19 incidental findings per LDCT participant at a cost of $2000 per finding. When we combined these (most likely conservative) costs with the other-cause mortality benefit, the ICER of LDCT was more favourable than the base-case. Thus, including non-lung cancer survival benefits in cost-effectiveness evaluations might improve ICERs, although the potential for overtreatment and complications in relation to these conditions would also need consideration. We also did not factor in a smoking cessation intervention, which would increase the cost of a screening program but may reduce morbidity and the long-term health costs of smoking, thereby improving cost-effectiveness.[33, 36]

Two recent systematic reviews of cost-effectiveness evaluations of LDCT screening have highlighted that many factors impact on ICER estimates and demonstrate the difficulties inherent in comparing ICERs across evaluations with different underlying assumptions.[10, 11] While not directly comparable, our base-case ICER is higher than that reported for the original NLST evaluation (US$81,000/QALY gained[9]). This is due to differences in the model assumptions, health system costs, value of the dollar, and survival rates across the two populations. The reviews also reported that ICERs for LDCT lung screening were highly sensitive to aspects of screening program design and implementation, including the definition of the target screening group, the cost of a LDCT screen, and the proportion of lung cancers detected at an early stage.[10, 11] Our analysis was consistent with these findings. For example, varying the cost of a LDCT scan had a large impact on our ICER estimates. The cost of a screen could potentially be reduced if trained radiographers are utilised in conjunction with experienced thoracic radiologists,[37] or in conjunction with an accurate computerised vision tool

1   (computer aided detection).[38] Similar to previous reports, this highlights the importance of factors

2   impacting the number of screens within a program (e.g., the optimal screening interval and the

3   definition of screening results requiring follow-up scans).[32, 34] One of the biggest factors impacting

4   both the number of scans and the cost-effectiveness of lung screening is the criteria used for

5   screening eligibility.

6   The eligibility criteria for the NLST was age (55-74 years) and smoking history (≥30 pack years; <15

7   years quit), and almost all trials to date have used some variation of these criteria. Although mostly

8   underpowered, trials utilising less conservative eligibility criteria (e.g., ≥20 pack years) have not

9   replicated the lung cancer mortality benefit demonstrated in the NLST.[39, 40] Restricting eligibility

10   criteria to individuals with ≥40 pack years, or to current smokers alone, improved cost-effectiveness in

11   our sensitivity analyses similar to findings elsewhere.[32, 33, 41] However, data demonstrating that the

12   balance of harms, benefits, and costs can be optimised with the use of lung cancer risk prediction

13   tools are mounting.[42, 43] These tools are now being incorporated into trial eligibility criteria,[44-46] and are

14   expected to improve screening effectiveness.

15   The recommended age range for lung screening is also critical in terms of the risk of radiation-

16   induced lung cancer. For younger age groups (<50 years), or those with lower risk of lung cancer, the

17   radiation risks are likely to outweigh the benefit of screening, especially for women.[21] In the NLST, it

18   was predicted that approximately one cancer death may be caused by radiation from imaging per

19   2,500 people screened. Based on these estimates, the benefit in preventing lung cancer deaths in the

20   NLST is greater than the radiation risk, which may present 10-20 years later. We did not account for

21   radiation-induced cancers, given that the typical lag between radiation exposure and cancer diagnosis

22   is 1 to 2 decades or more.[47] Thus, leaving out radiation-induced cancers altogether was not likely to

23   impact our results. In the NLST it was estimated that ICERs were only slightly less favourable over an

24   estimated range of radiation-induced lung cancer deaths.[9]

25   We demonstrated that the ICER was particularly sensitive to the degree of disutility assigned to the

26   short-term psychological impact of screening results. Indeed, the highest ICER we observed in

27   sensitivity analyses was when a two-month disutility weighting for false positive scans was included,

28   resulting in an ICER of AU$509,000/QALY gained. In the NLST no loss in utility was detected by the

29   SF-36 after a false positive screen, which was justified by noting that the information regarding the

30   frequency and clinical significance of false positive results before study entry may have prevented

31   distress.[9] In the NELSON trial, scores on the SF-12 similarly did not show any clinically relevant

32   changes across the trial, however the Impact of Event Scale (IES; measuring lung-cancer-specific

33   distress) detected significant differences 2 months after a screening result.[48] That is, participants with

34   an 'indeterminate result' requiring 3 months surveillance responded with higher distress scores

35   compared to baseline. Both the number and management of false positive results appear to be critical

36   factors for cost-effectiveness, however very few data on utilities in LDCT lung screening and for lung

37   cancer management have been published.[49] Thus, psychological and health-related quality of life in

38   relation to both screening and lung cancer management represent a significant evidence gap,

1   especially in the Australian context. Furthermore, the quality of the screening information given to

2   participants and risk communication is critical to reducing distress, thereby improving cost-

3   effectiveness.

4   In addition to the potential for psychological harms in relation to false positives screens, the ICER is

5   also sensitive to costs involved in following up false positive scans. The number and cost of false

6   positive screens depends on the definition of a positive scan and the nodule management strategy

7   employed. The proportion of positive results (both false and true positive) has been shown to vary

8   with the age of the cohort and the number of screens.[33, 34] In the NLST, more than 20% of LDCT

9   participants required follow-up after their first screen and in ~25% of surgical procedures, the nodule

10   was determined to be benign.[2] Since the NLST, there have been advances in nodule management

11   strategies that aim to reduce the number of false positives in a screening program.[31] In our sensitivity

12   analyses, varying the cost of false positive follow-up had a greater impact on the ICER than varying

13   the cost of lung cancer treatment itself. To date, there is no consensus on the definition of a screen-

14   detected suspicious nodule nor on the management of 'potentially malignant' screen-detected

15   nodules. However, research on using nodule risk calculators to optimise sensitivity and specificity in

16   this domain is underway.[44]

17   The cost of lung cancer treatment used in our analysis came from a 2005-2008, hospital-based

18   costing study.[23] These costs did not include routine blood tests, hospital department infrastructure,

19   staff, and out-of-hospital costs such as GP or community-based care costs. The main cost

20   components were due to hospitalisation and chemotherapy, and only two patients were treated with

21   tyrosine kinase inhibitors.[23] New lung cancer therapies continue to be added to the Australian

22   pharmaceutical benefits scheme (i.e., all government-subsidised medicines), such as those that target

23   epidermal growth factor receptor and anaplastic lymphoma kinase mutation positive NSCLC, and

24   immune check point inhibitors. These new therapies can be expensive, and uptake of these drugs

25   and related technologies are increasing.[50] Although the cost of these therapies were not captured in

26   our base-case, increasing the cost of stage III/IV lung cancers by 100% resulted in a slightly more

27   favourable ICER (AU$223,000/QALY gained). As the use of these therapies become a part of routine

28   care, the benefits of early detection will increase.

29   An important limitation of our study is the use of population–based lung cancer survival rates to

30   estimate benefits to participants. The survival rates, taken from the NSW population, included lung

31   cancer survival among low-risk and never-smokers (~15%). Further, in the NLST, stage-specific

32   survival was significantly greater for screened vs. unscreened cases (data not shown), which could be

33   due to a combination of lead time bias, screen-detected indolent or minimally invasive disease, and

34   within stage survival benefits due to earlier detection. Thus, population-based survival rates do not

35   account for a potential screening-related survival benefit. Given these considerations, the life-year

36   calculations in our analysis may be overestimated for non-screen-detected cases given this is a

37   sample of heavy smokers, yet underestimated in screen-detected cases given the potential for a

38   screening-related survival benefit.

Cost-effectiveness estimates of lung screening are highly sensitive to the proportion of cancers detected at an early stage,[10] and our ICER estimates are contingent on the number of lung cancers detected in the NLST. Our estimates may, therefore, differ somewhat to what might be observed for a population-based screening scenario. This is because the distribution of disease and the types of people who are likely to present themselves for a population-based screening program are potentially different to that of a trial scenario. Indeed, QLCSS participants were not representative of the Australian population, with a higher proportion having tertiary education.[29] In Australia, participation in existing population-based cancer screening programs is known to be lower among sub-groups with a high prevalence of smoking, such as those living in lower socioeconomic areas (e.g.,[51]) Engaging sub-groups of the population with high smoking rates (the 'hard to reach') in lung screening is likely to be a challenge in Australia, and will be an important factor for optimising the proportion of cancer detected at an early stage. We did not include any recruitment or program costs that would be needed for an equitable, population-based program in which referral to screening would need to be embedded in the health system.

Although this analysis finds that lung cancer screening based on the NLST protocol is not yet likely to be cost-effective in Australia, investment in reducing the lung cancer burden in Australia remains an imperative. Total expenditure on lung cancer grew by 33%, from 2000–01 to 2004–05, and this increase was higher than the increase in the expenditure for all cancers (31%) and all diseases (20%).[52] Primary prevention through tobacco control is likely to be the most effective and cost-effective long-term strategy for reducing the burden of lung cancer. However, given the 20-30 year lag between tobacco exposure and lung cancer incidence, the full benefits of these interventions will not be realised for many years to come, and there is room for secondary prevention to have a significant impact.

Given that significant reductions in lung cancer mortality can be achieved with LDCT screening, it is important that future economic evaluations consider alternate screening eligibility criteria, intervals, nodule management, the impact and costs of new therapies, investigations of incidental findings, and incorporating smoking cessation interventions. There is also a need for more systematic data on the identification and treatment of incidental findings, the impact of screening on psychological well-being and the potentially mitigating effects of effective risk communication. Reducing uncertainty in these areas will allow for more reliable and possibly more favourable cost-effectiveness estimates for Australia.

1 **Acknowledgements**

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1   **Figure Legends**

2   **Figure 1**. a) Scatter plot of bootstrap resampled estimates of the incremental costs ($) versus

3   incremental benefits (QALYs), solid line indicates where the expected base-case ICER lies in the

4   benefit-cost plane. b) Corresponding estimated cost-effectiveness acceptability curve, given by the

5   bootstrap resampled ICER distribution, for the LDCT screening strategy.

6   **Figure 2.** Estimated ICERs in sensitivity analyses in relation to the base case estimate (dotted vertical

7   line). Variation in ICER is one-to-one (monotonic) with respect to the change in each sensitivity

8   parameter for all analyses except for the calculation of the time horizon for expected LY.

9   **Figure 3.** Estimated incremental LYs by variation in time horizon, starting from the base case of 10

10   years from randomisation, up to a maximum of 45 years from randomisation or until age 100

11   (whichever occurs first).

Table 1. Life-years (LY) and quality adjusted life-years (QALY) per person from date of randomisation by NLST arm, estimated from Australian data sources.

Time Horizon	Life Expectancy (life-year)		Quality-Adjusted Life Expectancy (QALY)	
	LDCT	No Screening*	LDCT	No screening*
Within trial (observed)	5.459	5.452	4.093	4.089
Participants with lung cancer	4.684	4.391	3.366	3.167
Participants without lung cancer	5.492	5.492	4.123	4.123
10-year horizon (estimated)**	7.462	7.451	5.589	5.583
Participants with lung cancer	5.568	5.027	3.980	3.600
Participants without lung cancer	7.542	7.542	5.657	5.657

*Observed outcomes for the 'no screening' scenario were derived from the chest radiography arm of the NLST, but assumed equivalent to a no-screening arm given that chest radiography had no effect on lung cancer mortality as a screening intervention in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.[16]

** Life-years were discounted at 5% and are defined as follows: within-trial life-years were calculated from the date of randomization in the NLST to the date of death or December 31, 2009 if the patient was alive. For participants assumed alive at the end of the trial period, 10-year life expectancy for lung cancer cases was estimated on the basis of the participants' age and stage at diagnosis, sex, and histological subtype from relative survival probabilities derived from the New South Wales Cancer Registry (2005-2009). For participants alive at the end of the trial without lung cancer, 10-year life expectancy was estimated with the use of 201X Australian Life Tables, adjusted for smoking status.

Table 2. Mean per person cost of lung cancer by screening strategy

Cost	LDCT Screening	No screening
Total	$2,205	$640
Screening	$790	$0
False positive workup	$745	$0
Treatment*	$670	$640
NSCLC	$554	$511
SCLC	$115	$130

* includes diagnostic workup for true positive screen or usual care.

Table 3. Estimated incremental cost effectiveness ratio (ICER) of LDCT screening to no screening

Strategy		Cost	Benefit	Incremental Cost	Incremental Benefit	ICER
Overall	**LDCT Screening**	$2,205		$1,564		
	Life-years		7.459		0.0113	$138,000
	QALY		5.587		0.0067	$233,000
	No screening	$640		-		
	Life-years		7.447		-	-
	QALY		5.580		-	-
Current Smokers	**LDCT Screening**	$2,358		$1,526		
	Life-years		7.364		0.0190	$80,500
	QALY		5.514		0.0124	$123,000
	No screening	$832		-		
	Life-years		7.345		-	-
	QALY		5.502		-	-
Past Smokers	**LDCT Screening**	$2,063		$1,601		
	Life-years		7.547		0.0038	$423,000
	QALY		5.654		0.0011	$1,480,000
	No screening	$461		-		
	Life-years		7.543		-	-
	QALY		5.653		-	-

Table 4. Sensitivity analyses of variations in base case assumptions

Scenario	Value	Strategy	Cost ($)	Benefit (QALY)	Incremental cost ($)	Incremental benefit (QALY)	ICER ($/QALY)
Base case	5% discount rate	LDCT	2,205	5.587	1,564	0.0067	233,000
		No screening	640	5.580			
Other-cause mortality benefit of LDCT screening included	Participants without lung cancer given 0.0053 additional QALYs (observed)	LDCT	2,205	5.592	1,564	0.0124	127,000
		No screening	640	5.580			
Cost of incidental findings included	$2000 per incidental finding, 0.19 findings per screenee	LDCT	2,582	5.587	1,942	0.0067	290,000
		No screening	640	5.580			
Other-cause mortality and cost of incidental findings combined		LDCT	2,582	5.592	1,942	0.0124	157,000
		No screening	640	5.580			
NLST trial population weighted by QLCSS population and excluded age 55-59 years		LDCT	2,446	5.518	1,644	0.0107	154,000
		No screening	802	5.508			
Cost per LDCT screen	$221 (-25% base case)	LDCT	2,006	5.587	1,366	0.0067	204,000
		No screening	640	5.580			
	$590 (+100%)	LDCT	2,994	5.587	2,354	0.0067	351,000
		No screening	640	5.580			
Cost of false positive follow-up	$1379 (-20%)	LDCT	2,056	5.587	1,415	0.0067	211,000
		No screening	640	5.580			
	$2068 (+20%)	LDCT	2,354	5.587	1,714	0.0067	256,000
		No screening	640	5.580			
Disutility for false positive scans	-0.05 for 2 months following screening	LDCT	2,205	5.583	1,564	0.00307	509,000
		No screening	640	5.580			
Definition of positive nodules on incidence screens (T1/T2)	0.047 (-20% observed)	LDCT	2,300	5.587	1,659	0.0067	248,000
		No screening	640	5.580			
	0.071 (+20% observed)	LDCT	2,142	5.587	1,501	0.0067	224,000
		No screening	640	5.580			
Discount rate	0%	LDCT	2,430	7.139	1,682	0.00793	212,000
		No screening	748	7.131			
	7%	LDCT	2,143	5.119	1,540	0.00589	262,000
		No screening	604	5.113			
Cost of lung cancer diagnosis/treatment	-20%	LDCT	2,071	5.587	1,559	0.0067	233,000
		No screening	512	5.580			
	+20%	LDCT	2,339	5.587	1,570	0.0067	234,000
		No screening	767	5.580			
Cost of Stage III/IV NSCLC diagnosis/treatment	+100%	LDCT	2,444	5.587	1,492	0.0067	223,000
		No screening	952	5.580			
Increased time horizon for expected life-years	Lifetime	LDCT	2,205	8.964	1,564	0.0049	319,000
		No screening	640	8.960			
Restricted to participants with 40 pack-years smoking history	N = 39,510	LDCT	2,362	5.544	1,596	0.00779	205,000
		No screening	766	5.536			

Figure 1. a) Scatter plot of bootstrap resampled estimates of the incremental costs ($) versus incremental benefits (QALYs), solid line indicates where the expected base-case ICER lies in the benefit-cost plane. b) Corresponding estimated cost-effectiveness acceptability curve, given by the bootstrap resampled ICER distribution, for the LDCT screening strategy.
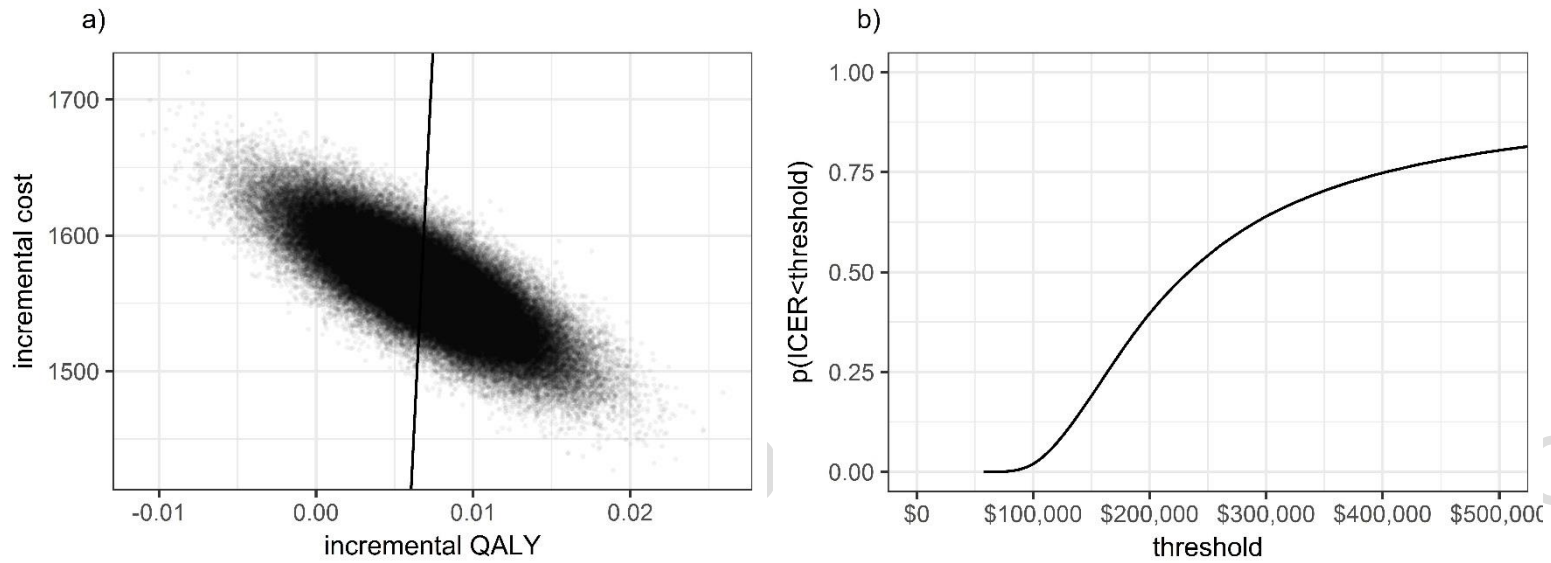
Figure 2. Estimated ICERs in sensitivity analyses in relation to the base case estimate (dotted vertical line). Variation in ICER is one-to-one (monotonic) with respect to the change in each sensitivity parameter for all analyses except for the calculation of the time horizon for expected LY.
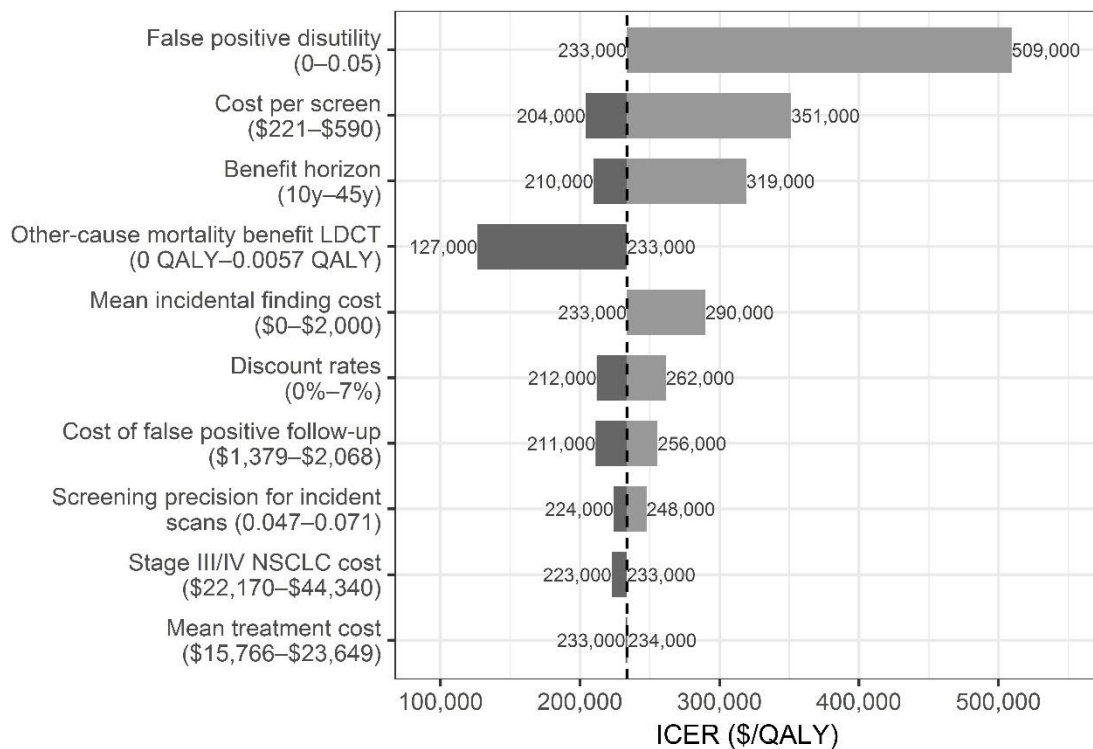
Figure 3. Estimated incremental LYs by variation in time horizon, starting from the base case of 10 years from randomisation, up to a maximum of 45 years from randomisation or until age 100 (whichever occurs first).

Appendix A
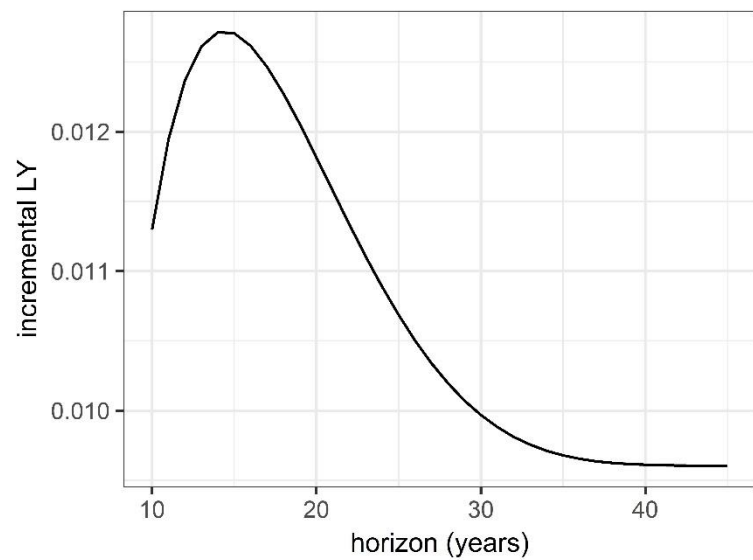
Classifying extent of disease for non-small cell lung cancers

Extent of disease in the NLST dataset was classified using the 7th edition of the tumor-node-metastasis (TNM) staging system,[1] and by SEER summary stage in a sub-set of participants (n = 18,714) summarised in Table S1. Extent of disease is recorded in the New South Wales Cancer Registry (NSWCR) by a similar classification system to SEER summary stage (however it should be noted that staging information is sometimes missing for cases that were not hospitalised, and classified as unknown stage of disease). In order to estimate stage-specific life expectancy and life-years using the Australian survival rates, we classified NLST (TNM-staged) cases according to the NSWCR staging system. Specifically, we assigned TNM stage IA cases the survival rates associated with 'localised disease' in the NSWCR, and TNM stage IV cases were assigned survival rates for 'distant disease'. TNM stage IIB—IIIA outcomes were assigned survival rates for 'regional disease' in the NSWCR. TNM stages IB and IIIB were considered in closer detail to determine if there were simple predictors in the clinical and pathological T, N and M values to differentiate between the localised and regional cases for stage IB, and the regional and distant cases for stage IIIB.

For TNM stage IB, clinical T1a and T1b cases were assigned NSWCR survival rates for 'regional disease', and all other cases were considered localised. When we tested this assumption on the sub-set of NLST cases that had both TNM and SEER summary stage classification, 38 out of the 54 observations were accurately classified. Although not perfect, this approach was marginally better than assuming all TNM stage IB were localised disease, which was correct for 31 of the 54 observations.

TNM stage IIIB was assumed to be 'distant disease' according to the NSWCR system if either clinical or pathological N stage was N3, otherwise it was assumed to be 'regional disease'. These assumptions correctly predicted 33 out of the 42 observations, which was a better approach than assuming all cases were 'distant disease' (i.e., 22 of the 42).

Any missing TNM data was imputed using a random forest algorithm[2] and then mapped as described above to NSWCR extent of disease at diagnosis. The out-of-bag error rates for imputed values of the TNM, pathological, and clinical N stage were less than 2%, while the out-of-bag error rate for values of clinical T stage was 26%. The error in the imputed clinical T stage values may affect the classification of 53 out of the 220 TNM stage IB cancers.

Veterans Administration Lung Cancer Study Group (VALCSG) stage for small-cell lung cancer

To determine a mapping from TNM to VALCSG classification of small-cell lung cancer[3] the data from all NLST sites were utilised. The cross-tabulation of VALCSG and TNM stage is presented in **Table S2**. Given the small numbers of small-cell lung cancers, only a simple mapping of TNM stage was possible. TNM stage IA—IIIB were assumed to be classified as limited disease, whereas stage IV was assumed extensive. Any missing values of TNM stage (7th ed.)

were imputed using the same random-forest procedure as for non-small-cell lung cancer, then mapped to a VALCSG stage.

The inferred extent of disease distribution for those with imputed TNM data compared to those whose TNM was known is presented in **Table S3** for both trial arms. There was no significant difference in the number of missing cases across the trial arms, however the imputed values were more likely to be distant disease than the known TNM data in both indicating that the missing data mechanism is not completely random.

Table S1. Distribution of non-small cell lung cancer TNM stages in the NLST by recorded SEER summary stage.

SEER summary stage	TNM Stage						
	IA	IB	IIA	IIB	IIIA	IIIB	IV
Localised	246	31	2	4	1	1	0
Regional	3	23	37	24	85	20	4
Distant	0	2	1	1	6	22	207
Unknown	4	0	0	0	3	0	0

Table S2. Distribution of small cell lung cancer TNM stages in the NLST by recorded VALCSG stage.

SEER summary stage	TNM Stage						
	IA	IB	IIA	IIB	IIIA	IIIB	IV
Limited	10	5	3	4	31	20	7
Extensive	0	0	0	0	3	2	149
Missing	8	2	5	0	11	6	28

Table S3. Inferred extent of disease by imputation status in the NLST

Extent	LDCT		CXR	
	Known TNM n (%)	Imputed TNM n (%)	Known TNM n (%)	Imputed TNM n (%)
Localised	444 (44%)	15 (25%)	248 (27%)	6 (12%)
Regional	289 (28%)	21 (34%)	284 (31%)	17 (35%)
Distant	282 (28%)	25 (41%)	382 (42%)	26 (53%)

Table S4. Distribution of lung cancer incidence and mortality by stage and sub-type in the National Lung Screening Trial (NLST; 2002-2009)

Extent	Incidence		Mortality	
	LDCT n (%)	No screening* n (%)	LDCT n (%)	No screening* n (%)
Non-small cell lung cancer				
Localised	452 (48%)	238 (30%)	61 (18%)	45 (11%)
Regional	270 (29%)	265 (33%)	119 (35%)	115 (28%)
Distant	212 (23%)	299 (37%)	163 (48%)	254 (61%)
Total	934	802	343	414
Small cell lung cancer				
Limited	54 (38%)	63 (39%)	33 (32%)	32 (29%)
Extensive	88 (62%)	98 (61%)	69 (68%)	79 (71%)
Total	142	161	102	111

Appendix B

Expected life-years (LYs) and quality adjusted life-years(QALYs)

To estimate the incremental benefit of LDCT screening versus no screening, the difference in the expected LYs from randomisation (entry to screening) between the two trial arms is estimated;

$$LY_{\mathrm{LDCT}} - LY_{\mathrm{CXR}}.$$

The estimates of the expected LYs for each arm, LY_{LDCT} and LY_{CXR}, are given by the weighted sums of the expected LYs for participants with ($LY_{\mathrm{arm,LC}}$) and without ($LY_{\mathrm{arm,\sim LC}}$) lung cancer, weighted by the number in each category within each arm ($N_{\mathrm{arm,LC}}$ and $N_{\mathrm{arm,\sim LC}}$). For the LDCT arm;

$$LY_{\mathrm{LDCT}} = \frac{1}{N_{\mathrm{LDCT,LC}} + N_{\mathrm{LDCT,\sim LC}}} \left(N_{\mathrm{LDCT,LC}} LY_{\mathrm{LDCT,LC}} + N_{(\mathrm{LDCT,\sim LC})} LY_{\mathrm{LDCT,\sim LC}} \right),$$

with a similar expression for the chest X-ray arm. Note that in the base case analysis, we simply replace $LY_{\mathrm{LDCT,\sim LC}}$ with $LY_{\mathrm{CXR,\sim LC}}$ in the above so that those without lung cancer receive no benefit from LDCT.

The two expected LY values in the preceding expression are given by the mean of the estimated expected LYs from randomisation up to a time horizon for each such participant from the NLST. In the following sections we describe how we calculate the estimate for each individual.

Participants without a lung cancer diagnosis

The estimated LYs for a participant without a diagnosis of lung cancer in the trial was either the LYs observed in the trial if the participant's death is confirmed within the trial period, or estimated by the time of the last follow-up since randomisation plus additional expected LYs up to a horizon of ten years. The additional expected LYs is determined by Australian population mortality hazard data adjusted for smoking status. This does not factor in the pack-year history of the participants, however this may be partially offset by the healthy volunteer effect in the trial.[4] The beyond-trial hazard does not depend upon trial arm, as we assume that there is no impact on future chance of lung cancer or other-cause mortality from having a LDCT screen.

Smoking status-adjusted mortality-hazard at any age a is given by;

$$\mu_{\mathrm{S,G}}(a) = \mu_{\mathrm{N,G}}(a) HR_{\mathrm{S,G}}(a)$$

for smoking status $\mathrm{S} \in \{\mathrm{N, F, C}\}$ (never, former and current smoker respectively), sex $\mathrm{G} \in \{\mathrm{M, F}\}$ (male and female respectively) and the mortality-hazard ratio of smoking status S to never smokers $HR_{\mathrm{S,G}}(a)$ given by a pooled-cohort analysis of studies conducted in the years 2000—2010 in the U.S.[5]. The values of $\mu_{\mathrm{N,G}}(a)$ are found by solving at each age;

$$\mathbb{P}(D|G \cap \text{age} = a) = \sum_{S}\left(1 - e^{-\mu_{N,G}(a)HR_{S,G}(a)}\right)\mathbb{P}(S|G \cap \text{age} = a)$$

given Australian smoking prevalence by birth and age, $\mathbb{P}(S|G \cap \text{age} = a)$, from household survey data[6], and the annual probability of death, $\mathbb{P}(D|G \cap \text{age} = a)$, from life-tables for the Australian population[7].

The case where death is recorded at $t = F$ (all times in years) is described first. The discounted LYs with discount rate $D > 0$ is

$$LY(F) = \frac{1}{D}(1 - e^{-DF}).$$

For those alive at final follow-up, the discounted life expectancy from randomisation at time $t = 0$, given smoking status, a time-horizon $t = \text{T}$ (assumed to be 10 years for all analyses), and age a_r at randomisation is

$$LY_{\text{S},G,a_r}(\text{T}, F) = \int_{0}^{T} S_{\text{S},G,a_r}(t; F)e^{-Dt}\text{d}t\,,$$

where $S_{\text{S},G,a_r}(t; F)$ is the survival function given follow-up F;

$$S_{\text{S},G,a_r}(t; F) = \begin{cases} 1, & t < F, \\ \exp\left(-\int_{F}^{t}\mu_{\text{S},G}(a_r + \tau)\,\text{d}\tau\right), & t \geq F, \end{cases}$$

for $0 \leq t \leq T$. In the base case, the expected QALYs is given by multiplying the expected LY expressions above by the baseline utility $U_{\text{base},G}$, with the adjustment required for age greater than 75 easily derived from the above.

Participants with a lung cancer diagnosis

We model all-cause relative survival given a lung cancer diagnosis with a reflected and translated gamma distribution function;

$$RS_{\text{G},\text{E},\bar{a}_d}(\tau) = 1 - \frac{\gamma\left(\alpha_{\text{G},\text{E},\bar{a}_d}, \tau\beta_{\text{G},\text{E},\bar{a}_d}\right)}{\Gamma\left(\alpha_{\text{G},\text{E},\bar{a}_d}\right)}, \qquad \tau > 0,$$

where τ is the time in years since diagnosis ($\tau \equiv t - d$), and $\bar{a}_d$ and E are the age (in groups) and extent of disease at diagnosis respectively. γ and Γ are the lower incomplete and standard gamma functions respectively.

This model was fitted to data at 1 and 5 years following diagnosis stratified by sex, age at diagnosis (in age-groups 55-64, 65-74, and 75+), and extent of disease at diagnosis estimated by the NSWCR[8]. Relative survival at 1 and 5 years by all three co-variates was estimated by assuming that the effects of the co-variates are independent. The values of $\alpha_{\text{G},\text{E},\bar{a}_d}$ and $\beta_{\text{G},\text{E},\bar{a}_d}$ were uniquely solved for given the two data points available per sex, age and extent at diagnosis. The absolute all-cause hazard, $\mu_{\text{G},\text{E},a_d}(t)$, at time t since diagnosis for age at diagnosis (in years, rather than grouped) a_d, was then calculated using Australian life-table data and the approximation that the population without lung cancer in each age group had a uniform age distribution within the age group.

Due to conflicting evidence of an effect, we did not incorporate smoking status at diagnosis in the estimation of overall survival due to lung cancer. In retrospective cohort studies of NSCLC, smoking status has been shown to be both predictive[9-14] and non-predictive[15] of overall survival. The histological type of cancer has been shown to influence whether smoking status is predictive of survival[16], contrary to previous findings[11]. An additional reason for not including smoking status is the lack of Australian studies of lung cancer survival which account for it.

The equation for discounted expected LYs if death is recorded at final follow-up is the same as for without a lung cancer diagnosis. For those alive at final follow-up the equation is;

$$LY_{G,E,a_d}(T; t_d, F) = \int_0^T S_{G,E,a_d}(t; t_d, F)e^{-Dt}dt.$$

The associated survival function is;

$$S_{G,E,a_d}(t; t_d, F) = \begin{cases} 1, & t < F, \\ \exp\left(-\int_F^t \mu_{G,E,a_d}(\tau - t_d)\,d\tau\right), & t \geq F. \end{cases}$$

Quality of Life Adjustment

If the participant had a diagnosis of lung cancer at time $t = t_d$ then the utility will vary over the life of the participant. TNM stage-specific utilities were estimated for two time periods following diagnosis in the NLST[4], these are; (1) the first twelve months of cancer since diagnosis, and (2) living beyond twelve months with cancer and was assumed to be unchanged until death.

Let $U_{base,G}$, $U_{<12,E}$, and $U_{\geq12,E}$ be, respectively, the utilities at baseline by sex, G, less than twelve months from diagnosis and twelve months or greater from diagnosis by stage of disease E. The expression for the quality adjusted life expectancy for $D > 0$ is, after taking out a common factor of e^{-Dt_d};

$$QALY_{G,E} \times e^{Dt_d} = \frac{U_{base,G}}{D}(e^{Dt_d} - 1) + \frac{U_{<12,E}}{D}\left(1 - e^{-D\min(1,F-t_d)}\right) + \frac{e^{-D\min(1,F-t_d)}U_{\geq12,E}}{D}\left(1 - e^{-D\max(F-t_d+1,0)}\right).$$

Discounted QALYs

The discounted quality-adjusted life expectancy is the sum of each health state-utility weighted by the expected (discounted) LYs in that health state. To avoid unnecessary subscripts in the expression, we denote $S(t) = S_{G,E,a_d}(t; t_d, F)$, and let $U_{base} = U_{base,G}$, $U_{<12} = U_{<12,E}$, and $U_{\geq12} = U_{\geq12,E}$. The expression for the discounted quality-adjusted life expectancy until time-horizon T is, after taking out a common factor of e^{-Dt_d};

$$QALY \times e^{Dt_d} = U_{base}\frac{e^{Dt_d} - 1}{D} + U_{<12}\int_0^1 S(t + t_d)e^{-Dt}dt + U_{\geq12}\int_1^T S(t + t_d)e^{-Dt}dt,$$

for follow-up $F < 1 + t_d$, and

$$QALY \times e^{Dt_d} = U_{\text{base}} \frac{e^{Dt_d} - 1}{D} + \frac{U_{<12}(1 - e^{-D})}{D} + U_{\geq 12} \left(\frac{e^{-D} - e^{-D(F-t_d)}}{D} + \int_F^T S(t)e^{-Dt}\mathrm{d}t \right),$$

for $F \geq 1 + t_d$.

Expressions for quality-adjusted life expectancy incorporating age-related decline of quality of life, where all utilities drop by 0.02 at age 75, can be derived from expressions given.

Appendix C

Comparison of NLST with QLCSS

Table S5. Distribution of participants in the National Lung Screening Trial (NLST; 2002-2009) and the Queensland Lung Cancer Screening Study (QLCSS; 2007-2014) by age, sex and smoking status

Characteristic	NLST	QLCSS	NLST (age 60-74)
	n (%)	n (%)	n (%)
Age			
55-59	22,738 (43%)	-	-
60-64	16,294 (31%)	139 (55%)	16,294 (54%)
65-69	9,477 (18%)	90 (35%)	9,477 (31%)
70-74	4,662 (9%)	26 (10%)	4,662 (15%)
Sex			
Male	31,376 (59%)	170 (67%)	18,385 (60%)
Female	21,795 (41%)	85 (33%)	12,048 (40%)
Smoking status			
Current	25,616 (48%)	108 (42%)	13,351 (44%)
Former	27,555 (52%)	147 (58%)	17,082 (56%)
Total	53,248	255	30,453

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