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Risk-targeted lung cancer screening: A cost effectiveness analysis

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Abstract

Background: Targeting low-dose computed tomography (LDCT) for lung cancer screening to those at highest risk for lung cancer mortality has been suggested to improve screening efficiency.

Objective: Quantify the value of risk-targeted selection for lung cancer screening compared to National Lung Screening Trial (NLST) eligibility criteria.

Design: Cost-effectiveness analysis using multi-state prediction model

Data Source: NLST

Target Population: Current and former smokers eligible for lung cancer screening

Time Horizon: Lifetime

Perspective: Healthcare sector

Intervention: Risk-targeted versus NLST-based screening.

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Outcome Measures: Incremental 7-year mortality, life-expectancy, quality adjusted life years (QALY), costs and cost-effectiveness of screening with LDCT versus chest X-ray at each decile of lung cancer mortality risk.

Results of Base-Case Analysis: Higher lung cancer mortality risk participants were older with greater comorbidities and higher screening-related costs. The incremental lung cancer mortality benefits over the first 7 years ranged from 1.2 to 9.5 lung cancer deaths prevented per 10,000 person-years, for the lowest and highest risk deciles respectively (extreme decile ratio=7.9). The gradient of benefits across risk groups was attenuated in terms of life years (extreme decile ratio=3.6) and quality adjusted life years (extreme decile ratio=2.4). The incremental cost-effectiveness ratios (ICERs) were similar across risk deciles (\$75,000/QALY (lowest risk decile) to \$53,000/QALY (highest risk decile)). Payers willing to pay \$100,000/QALY would pay for LDCT screening for all decile groups.

Results of Sensitivity Analysis: Alternative assumptions did not substantially alter our findings

Limitation: Our model did not account for all correlated differences between lung cancer mortality risk and quality of life.

Conclusion: While risk-targeting can improve screening efficiency in terms of early lung cancer mortality per person screened, the gains in efficiency are attenuated and modest in terms of life years, QALYs and cost-effectiveness.

Background

The National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer deaths when screening with low-dose computed tomography (LDCT) versus chest X-ray(1). NLST participants were between the ages of 55 and 74, with at least 30 pack-year smoking history and former smokers had no more than 15 years of smoking abstinence(1). Most subsequent guidelines, including the US preventative services task force (USPSTF), have largely adopted the NLST eligibility criteria when recommending who should receive lung cancer screening(2–4).

A retrospective analysis of the NLST showed that 60% of participants at highest predicted risk of lung cancer death accounted for 88% of all screening prevented lung cancer mortality(5). Other influential studies have also suggested that utilizing multiple risk factors to select the participants at the highest predicted risk of either developing or dying from lung cancer would greatly improve the efficiency and yield of lung cancer screening(6–10). A generalized limitation of these studies is that the benefits of screening with LDCT is measured in terms of reduced lung cancer mortality over the short term, generally the first 5 to 7 years per patient screened, and do not account for differences in long term survival or costs in higher versus lower risk patients.

In this analysis, we applied a novel multi-state model to calculate each NLST participant's predicted lifetime benefits and costs of screening with LDCT versus chest X-ray. We use these estimates to examine the value of applying an individualized risk-targeted approach to

participant selection for screening over the broader NLST inclusion criteria at common willingness to pay thresholds.

Methods

Model Overview

Using data from the NLST(1), we derived a multi-state regression model(11,12) to predict health state transitions as a function of an individual participant's baseline characteristics and the lung cancer screening technology used (chest X-ray or LDCT). The rationale for using a multi-state model is described in the Appendix. This technique jointly estimates the baseline hazards and the effects of risk factors on four transitions between the four health states shown in Figure 1: 1-alive without cancer, 2-alive with lung cancer, 3-dead due to other causes or 4-dead due to lung cancer. The resulting equation provided individualized predictions, under each screening condition, of the probability of being in each of the four states at any given point in time. These predictions were used to risk stratify the population and also to predict individualized lung cancer mortality benefits of LDCT screening at 7-years. Extrapolations of the baseline hazards were used to project the probability of being in each of the 4 states beyond 7-years, in order to estimate individualized lifetime health benefits. Individualized costs were estimated using utilization data from the NLST and linear regression prediction models, plus assumptions to estimate lifetime medical costs. For the purposes of presentation, we stratified participants into deciles (10% cohorts) based on their 7-year risk of lung cancer mortality when screened with chest X-ray. Finally, we calculated the incremental net monetary benefit (iNMB) for each participant to summarize the value of a risk-stratified screening strategy compared to the NLST inclusion criteria at common willingness to pay (WTP) thresholds of \$50,000/QALY and \$100,000/QALY(13,14).

Model derivation and validation

The NLST enrolled 53,454 participants and randomly assigned them to undergo three consecutive annual screenings from randomization (years 0, 1 and 2) with either LDCT (26,722) or the control screening method of chest X-ray (26,732). The trial had a median follow up period of 6.5 years. Our multi-state regression model included 8 baseline variables for each NLST participant (age, sex, race, family history in a first degree relative, body mass index (BMI), smoking exposure (pack-years), years since smoking cessation and self-reported history of emphysema). We selected these variables based on a previously published model(5). We excluded 368 NLST participants with missing data for any of these variables. Since the transition from smoker to lung cancer did not satisfy the proportional hazard assumption, as the difference in lung cancer diagnoses between screening conditions occurred mostly within the first year post randomization, participants were stratified on initial screening assignment. The proportional hazards assumption was also checked for all other included variables over each of the 4 transitions by examining the correlation of the Schoenfeld residuals with time. Proportionality in the 7-year follow-up data was generally not rejected, nor was there any evidence of a consistent non-significant trend for diminishing or strengthening predictor effects over time.

To evaluate model performance, we constructed calibration plots under each screening condition for the observed proportions of outcome events against the predicted risks for individuals grouped by quintiles (20% cohorts) of risk. We used the concordance statistic (c-statistic) to assess model discrimination. All analyses were performed using R version 3.3.2 and SAS 9.3 (SAS institute, Cary NC).

Benefits

We estimated benefits for each participant as the incremental model-projected health outcomes following LDCT screening compared to chest X-ray screening. We used the multi-state model to project potential outcomes for each subject through year-7 post-randomization. We extrapolated subsequent survival conditional on survival to year-7 using a Weibull distribution (Appendix Figure 1). Health outcomes included life expectancy and quality-adjusted life expectancy under each screening condition for each individual. We computed the expected quality-adjusted life years (QALYs) as the sum of each health state's contribution. Each state's contribution was equal to the product of the expected years lived in that state and the state's utility weight. The utility weights used were: 1.0 (equivalent to 1-year of perfect health) for the initial state of being alive without lung cancer, 0.77 for alive with lung cancer (the average utility for metastatic and non-metastatic lung cancer reported in a meta-analysis(15)) and 0.0 (equivalent to death).

Costs

Components of costs included the costs of initial screening, medical care utilization including diagnosis and management following a positive screening result and age-stratified background medical costs (Appendix Table 1 and 2)(14). We estimated initial screening costs and costs associated with a positive screening as the product of utilization data and unit prices (using 2016 Medicare reimbursement(16)). Utilization estimates came directly from the NLST, which recorded for each participant diagnostic and procedure codes pertinent to the screening, diagnosis and treatment of lung cancer. We focused on codes likely to have the greatest impact on incremental costs i.e. codes with frequency differences of 10 or more across the two arms of the trial. Our analysis included 35 diagnostic procedures, 13 treatment codes and 5 complication codes, in addition to costs for screening (Appendix Table 1).

These empirically derived incremental costs were used in a generalized linear regression equation, based on 9 characteristics (the 8 variables included in the risk model plus treatment arm (LDCT versus chest X-ray), to predict each individual patient's expected incremental costs (expected cost with LDCT *minus* expected cost with chest x-ray).

Analysis

Cost-effectiveness analyses assessed the comparative value of screening with LDCT versus chest X-ray for each participant using incremental cost effectiveness ratios (ICER). We calculated the ICER for each patient as the predicted incremental cost of screening with LDCT compared to X-ray divided by the predicted incremental benefits of LDCT. All analyses were performed from the healthcare sector perspective and all future life-years and costs were discounted at 3%(17).

We calculated the iNMB of a risk targeted screening strategy compared to the best strategy applied to all participants enrolled in the NLST. The iNMB provides a useful summary of both the health and the economic gains of an intervention by expressing them on the same scale, converting net health benefits into monetary terms (multiplying incremental QALYs by the WTP threshold(18)). Here, in addition to determining the “conversion rate” for a QALY, the WTP threshold also determines the lung cancer mortality risk threshold at which the more expensive screening technology (LDCT) is deemed cost effective. Risk targeting improves cost-effectiveness by switching those patients above or below this risk threshold to (or from) LDCT for whom the switch accrues a positive iNMB (i.e. for whom the switch is cost-effective at a given WTP threshold). We used the commonly applied WTP thresholds of \$50,000 or \$100,000 per QALY(13). The per-patient iNMB is the aggregate gain across all switched individuals divided by the number of individuals screened.

Sensitivity Analyses

We assessed the influence of alternative assumptions on the model-projected cost-effectiveness: 1-LDCT provides continually accruing lung cancer mortality gains by extrapolating the reduced hazard of lung cancer mortality throughout the patient’s lifetime (Appendix Figure 1); 2-removal of age-specific background medical costs; and 3. assign utility weights of 0.57 or 1.0 following a diagnosis of lung cancer (base case=0.77)(15).

Results

Multi-state Prediction Model and Study Population

Appendix Table 3 summarizes the multistate regression model; risk factors and their associated hazard ratios are shown for lung cancer incidence, lung cancer death and competing causes of death. Transition-specific discrimination measured by the c-statistic ranged from 0.61 (95% CI 0.59–0.63) for lung cancer to death to 0.70 (95% CI 0.68–0.72) for progression from the healthy state to a diagnosis of lung cancer. There was excellent agreement between model-predicted outcomes (including lung cancer diagnosis, lung cancer mortality and non-lung cancer mortality) and those observed within the trial period (Appendix Figure 2).

After stratifying the 53,086 NLST participants by their baseline risk of lung cancer mortality, the highest-risk versus lowest-risk quintile participants were on average 8-years older; more likely to be white; be male; have a positive family history of lung cancer; be a current smoker with a 30 pack-year or greater exposure and have an underlying diagnosis of emphysema (Table 1).

Health Benefit

The lung cancer mortality benefit from LDCT screening (compared to chest X-ray screening) increased with increasing baseline risk of death from lung cancer (Figure 2). For the lowest risk (decile 1), LDCT screening prevented 1.2 deaths from lung cancer per 10,000 person-years compared to 9.5 deaths from lung cancer per 10,000 person-years for patients at the highest risk (decile 10). Benefits also increased across increasing risk deciles when expressed as LYs gained (decile 1=0.015, decile 10=0.056) and QALYs gained (decile

1=0.011, decile 10=0.028)(Figure 2). Comparing the benefit gradient across risk groups, the extreme (highest to lowest) decile ratio was greatest in terms of lung cancer mortality benefits in the first seven years (ratio=7.9); the extreme decile ratio greatly attenuated when comparing LYs gained (ratio=3.6), with further attenuation when comparing QALYs gained (ratio=2.4)(Figure 2).

Costs and Incremental Cost-Effectiveness

Screening with LDCT increased lifetime costs by \$1089 versus screening with chest X-ray, yielding an ICER for LDCT of \$37,000/LY gained or \$60,000/QALY gained in the overall NLST cohort.

When examined across risk-strata, incremental costs for LDCT increased with rising baseline lung cancer mortality risk (Appendix Figure 3). Among patients with the lowest lung cancer mortality risk, the incremental cost of LDCT largely reflected the difference in the cost of screening (\$254 for LDCT and \$42 for X-ray). In contrast, besides the higher costs associated with more lung cancer diagnoses, higher risk patients had more invasive testing following a positive screen, generating additional costs (Appendix Table 4). Among higher risk patients, the higher incremental costs (\$1500 for decile 10 compared to \$890 for decile 1) offset the higher incremental benefits to yield similar ICERs across risk deciles. For the lowest risk decile, the ICER was \$75,000/QALY, compared to \$53,000/QALY for the highest risk decile (Figure 2).

Because no participant generated an ICER above \$100,000/QALY, screening all participants with LDCT was cost-effective at this threshold. Conversely, no participant generated an ICER below \$50,000/QALY, so LDCT screening was not cost-effective for any participant at this lower threshold. At both thresholds using either the risk targeted approach or the NLST inclusion criteria screening strategy yield identical decisions, with no aggregate savings (i.e. iNMB=0).

Sensitivity Analyses

When extrapolating ongoing benefits of screening with LDCT beyond year-7, the overall ICER for LDCT decreases; LDCT becomes the preferred screening strategy at the \$50,000/QALY threshold. A risk-stratified approach yields the same screening decision, generating no savings above the NLST inclusion criteria at both WTP thresholds (Table 2). Removal of background costs or removal of disutility (utility weight=1.0) for LDCT screening also improved the overall cost-effectiveness of LDCT (to \$43,000/QALY and \$37,000/QALY respectively), making it the preferred screening strategy at the \$50,000/QALY threshold. Risk-stratification identified some low risk participants who were not cost-effective to screen with LDCT under these scenarios at the lower WTP threshold (22% in the former and 15% in the latter case). Nevertheless, the per patient iNMB were relatively modest, indicating that the savings from avoiding LDCT in these low risk patients were similar in value to the QALYs lost (Table 2). At the \$100,000/QALY threshold, LDCT remained cost-effective in these scenarios. When assigning a utility of 0.57 following a diagnosis of lung cancer, screening with LDCT was more cost effective in the low risk patients compared to the high risk patients, but was not cost effective for any participant at either WTP thresholds.

The iNMB for risk targeting remains low for all two- and three-way sensitivity analyses (Appendix Table 5).

Discussion:

Consistent with prior findings(5–7), we demonstrated that participants at the highest baseline risk of death from lung cancer gained the greatest benefit in terms of LDCT-prevented lung cancer deaths in the first 7 years following screening initiation; 80% of lives saved can be obtained by targeting the highest risk 60%. However, higher risk participants were older with greater smoking exposure and more likely to have a pre-existing diagnosis of COPD, the gradient of benefit across risk strata was greatly attenuated when expressed as life-years and QALYs over a lifetime time horizon. Additionally, participants who were at higher risk of lung cancer also generated higher lung cancer screening costs owing to more invasive testing following a positive screen. Thus, the cost-effectiveness of screening lower risk patients meeting NLST criteria was similar to screening higher risk participants. An individualized risk-targeted approach to participant selection for screening proved no more cost-effective than the broader NLST inclusion criteria at common WTP thresholds of \$50,000 and \$100,000 per QALY gained.

When testing our model assumptions, in most scenarios, the cost-effectiveness of NLST-based screening and individualized (risk-based) screening strategies yielded the same decisions, either screen all with LDCT or screen all with chest X-ray, depending on the WTP threshold. Even in sensitivity analyses in which LDCT screening was cost-effective for some high-risk participants and not for low-risk participants, individualizing decisions did not yield substantial benefits, because the trade-offs involved exchanging costs and QALYs that were near-equivalent in value. Under the sensitivity analysis applying lower utility weights after a diagnosis of lung cancer reduced the health benefits of cancer detection, high-risk participants actually were less cost effective to screen than low-risk participants.

When making their screening recommendations, both the USPSTF(2) and the American Cancer Society(3) have largely adopted the inclusion criteria of the NLST to determine screening eligibility. Several analyses using a variety of pre-screening risk-prediction models have argued that individual risk-based selection of participants would substantially improve efficiency compared to the broader screening approach applying the NLST or the USPSTF criteria(5–8). Katki *et al.* demonstrated that applying a risk-prediction model similar to the one examined in our study to preferentially screen the highest-risk participants could lead to a 20% increase in the number of lung cancer deaths prevented over a 5-year period without any increase in the number of patients screened(6). These authors assumed that the short-term benefits seen in terms of LDCT-prevented lung cancer deaths translate into long-term survival benefits. However, our analysis demonstrates that each older, higher risk person with greater co-morbidities surviving lung cancer because of screening accrues fewer additional life-years compared to each younger, healthier, lower risk survivor. Additionally, because a lung cancer diagnosis has a substantial impact on the quality of life among survivors, the absolute magnitude of the benefit gradient between higher and lower risk participants is smaller when expressed as QALYs. Our analysis did not account for reductions in quality of life due to the greater burden of non-lung-cancer disease in higher

risk participants (such as COPD and non-pulmonary tobacco-related comorbidities); if included, we anticipate further attenuation of the gradient of benefit of screening high risk participants compared to low risk participants.

Although the overall estimate of the ICER from our study of \$60,000/QALY is lower than the \$81,000/QALY seen in a prior economic analysis by Black *et al.*(19), their analysis compared LDCT with no screening. When adjusting their estimates for the incremental cost of screening with chest X-ray their ICERs are almost identical to ours. When Black *et al.* attempted to apply a validated lung cancer risk model(5) to their trial-based empirical economic evaluation, their results were too unstable to produce reliable cost effectiveness estimates in the risk strata, due to the low and imprecisely estimated mortality rates in 5 risk subgroups and two treatment arms. Our multi-state model was designed to address this instability(20,21).

Currently, implementation of lung cancer screening requires a clinician to identify a high-risk smoker, counsel the patient on the harms and benefits of screening in addition to smoking cessation counseling to maximize screening benefits(22). Implementation of screening has been shown to be limited(23), with concerns raised that using risk models to determine screening eligibility may further complicate and impede screening implementation(24,25). Our analysis suggests that the gains from such risk-based eligibility are likely to be small when extrapolated over the longer term, assuming perfect implementation of the two competing strategies.

Proposed as a general approach to examine heterogeneity of effects for better treatment targeting(26,27), risk-stratification has been demonstrated to increase the absolute risk difference of the primary outcome in many trials across a wide variety of conditions (higher risk patients generally obtain more absolute benefit)(5–6,28–30). Our analysis provides a caution that this strategy may have limitations when benefits beyond the primary outcome of the study are evaluated, especially across a lifetime time horizon(31). When risk factors for the primary outcome (in this case lung cancer mortality) impact mortality from other causes, the attenuation of the gradient of benefit seen across risk will likely occur. Risk-modeling provides an important strategy for examining heterogeneity of treatment effects to optimize treatment decisions(28); our analysis suggests this approach will not always substantially improve cost-effectiveness, even when absolute treatment benefits appear to be heterogeneous within the trial, so the specifics of each analysis will matter greatly.

Limitations

Our findings regarding the similar cost-effectiveness of screening NLST-high-risk and NLST-low-risk participants depend on certain model assumptions. Our model relies on the conventional assumption of a constant relative effect across risk groups; while this appears empirically justified(5), we acknowledge that the NLST was under-powered to precisely estimate screening effectiveness in every subgroup, particularly those at low risk. While our prediction model has not been externally validated, any decrease in model performance is likely to further attenuate the gradient between the highest and lowest risk participants, further degrading the usefulness of risk-targeting. Additionally, our model did not account

for different tumor types, grades and stage. While it has been empirically shown that the effectiveness (in terms of relative risk reduction of lung cancer mortality) appears not to differ between risk strata(5), and we estimated risk-specific costs, we could not account for risk-correlated differences in tumor type, grade and stage that may differentially affect quality of life for the lung cancer diagnosis. We also did not account for the impact of non-cancer-related illness on utility weights, which would make high-risk patients relatively less favorable to screen compared to low risk patients. Nevertheless, aside from quality of life estimates, our model rigorously incorporated the relevant differences between higher and lower risk participants for each aspect of the analysis (i.e. short-term benefits, life expectancy and costs). The importance of congruent levels of granularity for these analyses has recently been emphasized(31).

There are also limitations to our overall estimate of cost-effectiveness. Our findings are based on data from the NLST, which compared LDCT to chest x-ray. The Prostate Lung Colorectal and Ovarian (PLCO) cancer screening trial has previously demonstrated that chest X-ray as a screening modality does not effectively reduce lung cancer mortality(32). Hence, our ICERs may be more favorable than they otherwise would have been if we had compared LDCT to no screening at all. Second, our ICER estimates do not extrapolate outside the NLST population and reflect the NLST screening protocol, which calls for three annual screens; whereas the current USPSTF recommendations broaden the inclusion criteria in terms of age and duration of annual screening(2). Finally, our estimates do not reflect quality of life gains from the diagnosis and treatment of incidental findings, such as emphysema and coronary artery calcification, the true costs and benefits of which have not yet been determined. Despite enrollment into the NLST starting in 2002, we believe that the findings continue to be generalizable, particularly given the strength of the exposure-response relationship between the heavy tobacco use required for enrollment and both lung cancer and cardio-pulmonary mortality(33).

Conclusion:

We confirmed prior work that demonstrate increased number of early lung cancer deaths can be averted per patient screened by applying more granular risk targeting than the overall inclusion criteria of the NLST. However, higher risk patients are more costly to screen and also have a lower life-expectancy should they survive lung cancer. Thus, applying such a risk model is unlikely to lead to substantial improvement in the cost-effectiveness of LDCT screening in terms of quality adjusted life years gained per unit cost.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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IRB Approval: This study was approved for exemption by the Tufts Institutional Review Board.

Appendix A

Appendix Table 1:

Screening, Diagnosis, Treatment and Complication Costs

NLST Dataset Code	Screening Procedure	Total Cost (\$)
Study arm: 2 = CXR	Posteroanterior chest x-ray	42.25
Study arm: 1 = CT	Spiral CT	254.57
NLST Dataset Code	Diagnostic Procedure	Total Cost (\$)
1	Biopsy - Endobronchial	403.87
2	Biopsy - Percutaneous liver	369.86
9	Biopsy - Open Surgical	502.33
10	Biopsy - Transbronchial	403.87
11	Radiograph - Bone	64.81
13	Radiograph - Chest	27.93
14	Clinical Evaluation	78.05
15	Radiograph - Comparison with historical images	11.10
17	CT - Abdomen and pelvis	313.29
23	CT - Chest, limited thin section of nodule	277.13
25	Cytology - Sputum	16.47
29	Lymphadenectomy/lymph node sampling	475.48
31	MRI - Bone	386.87
32	MRI - Brain	159.45
33	MRI - Chest	487.18
39	Pulmonary function tests/spirometry	42.50
43	Resection	10687.00
46	Thoracotomy	10687.00
49	Thoracoscopy	321.16
50	Biopsy - Thoracoscopic	393.85
53	Biopsy - Percutaneous transthoracic yielding histology	458.30
54	Bronchoscopy without biopsy or cytology	182.60
55	CT - Abdomen (or liver)	264.24
56	CT - Chest, plus nodule densitometry	277.13
57	CT - Diagnostic chest	277.13
58	Cytology - Bronchoscopic	322.60
61	Echocardiography	199.25
62	MRI - Abdomen (or liver)	434.07
63	Radionuclide scan - FDG-PET scan *	1220.00

NLST Dataset Code	Screening Procedure	Total Cost (\$)
66	Radionuclide scan - Ventilation/perfusion lung	349.81
68	Radionuclide scan - Fusion PET/CT scan	1220.00
69	CT - Chest, low dose spiral	254.57
70	CT - Chest limited thin section of entire lung	277.13
71	CT - Chest and abdomen	463.31
72	CT - Chest, abdomen, and pelvis	691.03
NLST Dataset Code	Treatment Procedure	Total Cost (\$)
101	Radiation of Primary Chest Tumor and/or Regional Nodes	3843.68
102	Radiation of Hilar/Mediastinal Lymph Nodes	3843.68
103	Radiation of Prophylactic Brain	3843.68
104	Radiation of Therapeutic Brain	3843.68
203	Lobectomy	10687.00
205	Pneumonectomy	10687.00
206	Wedge Resection	10687.00
208	Lymphadenectomy/Lymph Node Sampling	475.48
212	Multiple Wedge Resections	10687.00
214	Thoracotomy	10687.00
215	Thoracoscopy (VATS)	321.16
216	Thoracoscopy (VATS) with conversion to Thoracotomy	11008.16
300	Systemic Chemotherapy	15826.92
NLST Dataset Code	Complication	Total Cost (\$)
1	Acute respiratory failure	9895.00
17	Hospitalization post procedure	4744.00
23	Pneumothorax requiring tube placement	14273.00
29	Bronchial stump leak requiring tube thoracostomy or other drainage for >4 days	29522.00
31	Injury to vital organ or vessel	9895.00

The estimation of costs were based on 2016 Medicare reimbursement values for International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes, Current Procedural Terminology (CPT) procedural codes, and Medical Severity Diagnosis Related Groups (MS-DRG) codes that were documented by the NLST investigators during the course of the trial. Our analysis focused on codes with greater than 10 difference in frequency between chest X-ray and LDCT.

*- 2016 National Medicare price listing was not available for PET scan, thus price listed is institution specific reimbursement for PET scan and similar in values to prior published US cost estimates for PET scan(17).

Appendix Table 2:

Background Costs

Age Range	Average annual health expenditure
0 – 24 years	\$1828/year
25 – 34 years	\$2728/year
45 – 54 years	\$5039/year
55 – 64 years	\$7780/year

Age Range	Average annual health expenditure
65 – 74 years	\$9814/year
75 – 99 years	\$12037/year

Appendix Table 3:

Transitional Hazard Ratios for the Multistate Prediction Model.

	Transition 1: Smoker to Lung Cancer (n=53,086) [*]	Transition 2: Smoker to non- lung cancer death (n=53,086) [*]	Transition 3: Lung cancer to non-lung cancer death (n=2079) [*]	Transition 4: Lung Cancer to lung cancer death (n=2079) [*]
Risk Factor	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age	1.084 (1.075–1.092)	1.086 (1.079–1.094)	1.053 (1.009–1.099)	1.008 (0.996–1.021)
Body Mass Index (BMI)				
- Normal BMI	0.923 (0.865–0.985)	0.840 (0.809–0.873)	0.888 (0.694–1.138)	0.964 (0.902–1.030)
- Elevated BMI	1.001 (1.000–1.002)	1.003 (1.002–1.004)	1.002 (0.998–1.006)	1.001 (1.000–1.002)
Male Sex	0.994 (0.908–1.08)	1.787 (1.642–1.944)	2.079 (1.259–3.432)	1.296 (1.134–1.482)
Family History of Lung Cancer	1.237 (1.145–1.337)	1.010 (0.938–1.087)	0.876 (0.577–1.330)	0.963 (0.860–1.079)
Smoking Exposure (Per Pack Year)	1.009 (1.008–1.011)	1.006 (1.005–1.007)	0.995 (0.986–1.004)	1.002 (0.999–1.004)
Years since smoking cessation	0.685 (0.648–0.725)	0.739 (0.706–0.774)	0.864 (0.649–1.151)	0.809 (0.744–0.880)
Diagnosis of Emphysema	1.576 (1.391–1.785)	1.638 (1.470–1.825)	0.779 (0.400–1.519)	1.072 (0.903–1.272)
Ethnicity				
- White	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
- Black	1.278 (1.045–1.561)	1.897 (1.640–2.194)	0.909 (0.325–2.542)	0.861 (0.641–1.156)
- Hispanic	0.498 (0.309–0.803)	1.025 (0.770–1.365)	0.981 (0.134–7.162)	0.601 (0.268–1.346)
- Other	0.890 (0.702–1.128)	1.074 (0.891–1.294)	0.293 (0.040–2.123)	1.028 (0.724–1.460)

The proportional hazards assumption was met for all risk factors. For transition 1, smoking to lung cancer, further stratification was performed with separate hazard ratio (HR) based on screening with either low dose CT (LDCT) or chest x-ray.

^{*} The sample sizes correspond to the number of participants at risk of the health state transition over the trial period. The outcomes for each transition over the trial period were: Transition 1 - Smoker to Lung Cancer: N=2079; Transition 2- Smoker to non-lung cancer death: N=2830; Transition 3 - Lung cancer to non-lung cancer death: N=82; and Transition 4 - Lung Cancer to lung cancer death: N=1082.

[†]- Body Mass Index (BMI) was centered at 25 and the hazard ratios are for increase of 5.

Appendix Table 4:

Positive Screen Rate, Investigation Methods and Lung Cancer Diagnosis according to quintiles of risk

Variable	Q1		Q2		Q3		Q4		Q5	
	n=5314	%	n=5314	%	n=5314	%	n=5314	%	n=5313	%
Positive Screen	1462	28	1640	30.8	1721	32.3	1809	34	2155	41
Lung Cancer	56	1	106	2	148	2.8	238	4.5	407	7.7

Variable	Q1		Q2		Q3		Q4		Q5	
	n=5314	%	n=5314	%	n=5314	%	n=5314	%	n=5313	%
Method of investigation		% Positive Screen		% Positive Screen		% Positive Screen		% Positive Screen		% Positive Screen
Clinical Evaluation or Plain radiographs	1256	85.9	1441	87.9	1522	88.4	1611	89.1	1972	91.5
CT	1171	80.1	1336	81.5	1373	79.8	1440	79.6	1757	81.5
MRI	54	3.7	62	3.8	69	4.0	87	4.8	117	5.4
PET-CT	193	13.2	221	13.5	249	14.5	342	18.9	527	24.5
Close Biopsy	43	2.9	58	3.5	60	3.5	105	5.8	173	8.0
Invasive Procedure	111	7.6	146	8.9	168	9.8	249	13.8	384	17.8

21,269 participants included in our analysis underwent screening with Low dose CT (LDCT) in the National Lung Screening Trial (NLST). Each participant was stratified into quintiles (Q1 (lowest risk) to Q5 (highest risk)) based on their baseline 7-year risk of lung cancer mortality according to our multi-state model. Using empirically derived data from the NLST, participants at the highest risk quintile (Q5) were more likely to have a LDCT screen classified as 'positive' according to the NLST protocol. High-risk participants were more likely to receive a diagnosis of lung cancer (both screen and non-screening detected). High-risk participants were also more likely to have more invasive testing as a follow up for a positive screen.

Appendix Table 5:

Expanded Sensitivity analyses with combination of multiple parameters

	Removal of Background costs	Sustained mortality benefits of LDCT post year-7	Utility weight following cancer diagnosis	Average ICER (\$/QALY)	Lowest Risk Decile ICER	Highest Risk Decile ICER	% screened with LDCT at \$50K per QALY threshold	iNMB per patient at \$50K per QALY threshold	% screened with LDCT at \$100K per QALY threshold	iNMB per patient at \$100K per QALY threshold
One-way sensitivity analyses										
Base Case	No	No	0.77	\$60,000	\$75,000	\$53,000	0%	\$0	100%	\$0
Sustained mortality benefits of LDCT post year 7	No	Yes	0.77	\$24,000	\$28,000	\$22,000	100%	\$0	100%	\$0
Removal of Background Costs	Yes	No	0.77	\$43,000	\$62,000	\$31,000	78%	\$20	100%	\$0
Utility weight 1.0 following lung cancer diagnosis	No	No	1	\$37,000	\$57,000	\$27,000	85%	\$12	100%	\$0
Utility weight 0.57 following lung cancer diagnosis	No	No	0.57	\$125,000	\$102,000	\$365,000	0%	\$0	0%	\$0
Two-way sensitivity analyses										
	Yes	Yes	0.77	\$8,500	\$14,000	\$5,800	100%	\$0	100%	\$0
	Yes	No	1	\$27,000	\$47,000	\$16,000	3%	\$0.51	100%	\$0
	Yes	No	0.57	\$90,000	\$84,000	\$210,000	0%	\$0	87%	\$47
	No	Yes	1	\$17,000	\$21,000	\$16,000	100%	\$0	100%	\$0
	No	Yes	0.57	\$34,000	\$38,000	\$36,000	100%	\$0	100%	\$0
Three-way sensitivity analyses										
	Yes	Yes	1	\$6,200	\$11,000	\$4,000	100%	\$0	100%	\$0
	Yes	Yes	0.57	\$12,000	\$19,000	\$9,300	100%	\$0	100%	\$0

iNMB= incremental net monetary benefit

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Figure 1: Structure of the multi-state model

All patients enter the multi-state model as high risk smokers defined by the entry criteria for the National Lung Screening Trial (NLST). The multi-state model consists of 4 health states with 4 possible transitions. The figure describes the number of illness-death multi-state transitions over the trial period.

A:

Extreme Decile Ratios

B:

Figure 2: Mortality, Life Expectancy, Quality of Life benefits and ICER according to risk

Participants were stratified by pre-screening risk of lung cancer mortality, decile 1 representing the lowest risk 10% of the screening cohort. A: Over the initial 7-year period of the study the difference in mortality benefits (number of prevented deaths per 10,000 person year follow up), life expectancy (LY) and quality of life (QALY) between screening with low dose CT versus chest X-ray was calculated. Participants with the greatest pre-screening risk of lung cancer mortality had the greatest benefit in mortality when screened with LDCT (extreme decile ratio of 7.9), however the gradient of benefit was attenuated when accounting for life expectancy (extreme decile ratio of 3.6) and quality of life (extreme decile ratio of 2.4). B: The incremental cost-effectiveness ratio (ICER) is calculated by the ratio of difference in costs and difference in incremental improvement in LY and QALY between screening with low dose CT versus chest X-ray. The ICER remains between \$100,000/QALY and \$50,000/QALY for all deciles of risk.

Table 1:

Baseline characteristics of patients according to quintiles of risk of death from lung cancer.

Characteristics	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
	N=10617	N=10617	N=10617	N=10617	N=10618
Age - yr					
Mean +/- SD	58.3 +/- 3.0	59.6 +/- 4.1	60.4 +/- 4.6	62.4 +/- 4.5	66.4 +/- 4.5
Interquartile Range	56–60	56–63	57–63	59–65	63–70
Sex					
Male (%)	5655 (53)	5858 (55)	6217 (59)	6565 (62)	7064 (67)
BMI					
Mean +/- SD	30.2 +/- 5.4	29.1 +/- 4.9	27.6 +/- 4.7	26.8 +/- 4.4	25.8 +/- 4.4
Interquartile Range	26.4–33.1	25.8–31.8	24.4–30.0	23.7–29.2	23.0–28.1
Race					
White (%)	9183 (86)	9555 (90)	9643 (91)	9627 (91)	9731 (92)
Black (%)	270 (2.5)	424 (4.0)	518 (4.9)	603 (5.7)	530 (4.9)
Hispanic (%)	686 (6.5)	153 (1.4)	50 (0.5)	27 (0.2)	16 (0.1)
Other or unspecified (%)	478 (4.5)	485 (4.6)	406 (3.8)	360 (3.4)	341 (3.2)
No. of first degree relatives					
0 (%)	8873 (84)	8695 (82)	8432 (79)	8001 (75)	7501 (71)
1 (%)	1580 (15)	1700 (16)	1892 (18)	2208 (21)	2462 (23)
2 (%)	164 (1.5)	222 (2.1)	293 (2.8)	408 (3.8)	655 (6.1)
Pack Years of Smoking					
Mean +/- SD	45.3 +/- 14.3	48.6 +/- 17.0	52.4 +/- 18.5	59.4 +/- 21.7	74.1 +/- 32.2
Interquartile Range	34.5 – 52.5	37.0–58.0	39.6–61.5	43–72	50–90
Year Since Smoking Cessation					
<1 or current (%)	457 (4.3)	4291 (40)	6650 (63)	7502 (71)	8574 (81)
1–4.9 (%)	2082 (20)	2686 (25)	1846 (17)	1594 (15)	1338 (13)
5 (%)	8078 (76)	3640 (34)	2121 (20)	1521 (14)	706 (6.6)
Emphysema					
Yes (%)	106 (1.0)	256 (2.4)	425 (4.0)	886 (8.3)	2412 (23)

Table 2:

Sensitivity Analyses

	Average ICER/QALY	Lowest Risk Decile ICER	Highest Risk Decile ICER	% Screened with LDCT at \$50,000 threshold	iNMB per patient at \$50,000 per QALY Threshold	% Screened with LDCT at \$100,000 threshold	iNMB per patient at \$100,000 per QALY Threshold
Base Case	\$60,000	\$75,000	\$53,000	0%	\$0	100%	\$0
Sustained mortality benefits of LDCT post year 7	\$24,000	\$28,000	\$22,000	100%	\$0	100%	\$0
Removal of Background Costs	\$43,000	\$62,000	\$31,000	78%	\$20	100%	\$0
Utility Weight of 1.0 following lung cancer diagnosis	\$37,000	\$57,000	\$27,000	85%	\$12	100%	\$0
Utility Weight of 0.57 following lung cancer diagnosis	\$125,000	\$102,000	\$365,000	0%	\$0	0%	\$0

iNMB= incremental net monetary benefit