Lung Cancer

Economic impact of using risk models for eligibility selection to the International Lung Screening Trial

--Manuscript Draft--

Manuscript Number:	LUNGCANCER-D-22-01224R1
Article Type:	Research paper
Keywords:	Lung screening; lung cancer screening; cost-effectiveness; economic impact; equity impact; health equity; risk model; PLCOm2012; USPSTF2013; eligibility criteria; screening selection
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	Materials and Methods The cost-effectiveness of using PLCOm2012 versus USPSTF-2013 was evaluated with a decision analytic model based on the ILST and other screening trials. The primary outcomes were costs in 2020 International Dollars ($), quality-adjusted life-years (QALY) and incremental net benefit (INB, in $ per QALY). Secondary outcomes were selection characteristics and cancer detection rates (CDR). Results Compared with the USPSTF-2013 criteria, the PLCOm2012 risk model resulted in $355 of cost savings per 0.2 QALYs gained (INB=$4294 at a willingness-to-pay threshold of $20 000/QALY (95%CI: $4205–$4383). Using the risk model was more cost-effective in females at both a 1.5% and 1.7% 6-year risk threshold (INB=$6616 and $6112, respectively), compared with males ($5221 and $695). The PLCOm2012 model selected more females, more individuals with fewer years of formal education, and more people with other respiratory illnesses in the ILST. The CDR with the risk model was higher in females compared with the USPSTF-2013 criteria (Risk Ratio=7.67, 95% CI: 1.87–31.38). Conclusion The PLCOm2012 model saved costs, increased QALYs and mitigated socioeconomic and sex-based disparities in access to screening.

Highlights

- Using the PLCOm2012 risk model to determine eligibility for lung screening saves costs, and improves outcomes compared with age-smoking history categorical methods
- The risk model mitigated gender-based and socioeconomic disparities in access to lung screening
- The PLCOm2012 risk model was most cost-effective for females and at a 1.5%/6 year threshold for both sexes
- Our findings call for deeper inquiry into screening eligibility processes through a sex and gender plus-based lens

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Economic impact of using risk models for eligibility selection to the International Lung Screening Trial

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Abstract

Objectives

Using risk models as eligibility criteria for lung screening can reduce race and sex-based disparities. We used data from the International Lung Screening Trial (ILST; NCT02871856) to compare the economic impact of using the PLCOm2012 risk model or the US Preventative Services' categorical age-smoking history-based criteria (USPSTF-2013).

Materials and Methods

The cost-effectiveness of using PLCOm2012 versus USPSTF-2013 was evaluated with a decision analytic model based on the ILST and other screening trials. The primary outcomes were costs in 2020 International Dollars ($), quality-adjusted life-years (QALY) and incremental net benefit (INB, in $ per QALY). Secondary outcomes were selection characteristics and cancer detection rates (CDR).

Results

Compared with the USPSTF-2013 criteria, the PLCOm2012 risk model resulted in $355 of cost savings per 0.2 QALYs gained (INB=$4294 at a willingness-to-pay threshold of $20 000/QALY (95%CI: $4205–$4383). Using the risk model was more cost-effective in females at both a 1.5% and 1.7% 6-year risk threshold (INB=$6616 and $6112, respectively), compared with males ($5221 and $695). The PLCOm2012 model selected more females, more individuals with fewer years of formal education, and more people with other respiratory illnesses in the ILST. The CDR with the risk model was higher in females compared with the USPSTF-2013 criteria (Risk Ratio=7.67, 95% CI: 1.87–31.38).

Conclusion

The PLCOm2012 model saved costs, increased QALYs and mitigated socioeconomic and sex-based disparities in access to screening.

1. Introduction

Three large randomized trials have shown that lung cancer screening with low-dose computed tomography (LDCT) can reduce lung cancer mortality by more than 20%.[1-3] In 2013 the US Preventative Services Task Force (USPSTF) gave lung screening a grade "B" recommendation for individuals between ages 55–80, with at least 30 pack-years of smoking history and ≤15 years of smoking abstinence.[4] The recommendation supported reimbursement of lung screening exams for insured individuals who met this criterion. Recent findings suggest that defining eligibility by such categorical age-smoking criteria, however, inadvertently introduces disparity in access to screening for Black African Americans and for females who may fall below the cut-points for eligibility, despite having a high lung cancer risk.[5,6]

To mitigate race and sex-based disparities in access to lung screening, the USPSTF has recently reduced the minimum age of screening eligibility to 50 years and lowered the smoking pack-years requirement from 30 to 20 years.[7,8] Modelling studies have since shown that not only do these newer USPSTF-2021 criteria fail to mitigate disparity in access to screening, but the new criteria further exacerbate racial disparity since white participants would gain significantly more years of life from lung screening.[9] The potential for such "intervention-generated inequities" in lung cancer screening calls for evaluations that simultaneously consider who gains and who loses from lung cancer screening selection methods.[10] A methodology from health economics known as distributional cost-effectiveness is gaining momentum in mainstream evaluative research as a way to simultaneously quantify cost-effectiveness and equity impacts resulting from large-scale public health decisions, such as cancer screening.[11] Of particular concern for the area of lung screening is the measure of forgone investment from investing in policy alternatives which provide benefits that are more evenly distributed across the population.

Lung cancer risk models provide an alternative to the USPSTF's categorical age-smoking history-based eligibility criteria. Through their ability to simultaneously account for tobacco smoke exposure, comorbidities, cancer history and socioeconomic characteristics, risk

models give additional weight to the most established predictors of lung cancer compared with age and smoking history considerations alone. When compared to categorical risk-factor-based methods of selection, risk models have been found superior in their ability to identify Black Americans with lung cancer in the US and can mitigate disparity in the number of life-years gained from screening for both Black participants and females. [9,12–14] Prospective trials from multiple countries have shown that risk models such as the PLCOm2012 can reduce the number of participants needed to screen to detect early-stage lung cancer with a high ratio of curable lung cancer among those selected.[15,16]

The International Lung Screening Trial (ILST; NCT02871856) was designed to prospectively compare early lung cancer detection rates for the PLCOm2012 risk model versus the USPSTF-2013 categorical age-smoking criteria method of determining screening eligibility and the economic implications. The study recruited 5819 participants in Canada, the UK, Australia, Spain, and Hong Kong, between 2015-2020 to analyse the effectiveness and cost-effectiveness of selecting participants with the PLCOm2012 risk model.[17] Early results suggest that the PLCOm2012 model offers more cumulative years of life and is a more accurate predictor of lung cancer risk than the USPSTF-2013 method of determining eligibility.[18] The study found that female participants would gain significantly more years of life from screening if selected with the PLCOm2012 method and that the cancer detection rate was higher for ILST participants who scored positive with the PLCOm2012 risk model. We, therefore, hypothesize that risk models enable more cost-effective screening programs compared to the categorical age-smoking history-based methods of determining eligibility. This study aims to compare the characteristics of ILST participants selected with the PLCOm2012 risk model versus those with the USPSTF-2013 criteria, and to quantify the cost-effectiveness of the two competing selection methods.

2. Methods

2.1. Model overview

We developed a probabilistic simulation model to compare the PLCOm2012 method of determining lung cancer screening eligibility with the USPSTF-2013 criteria. In the base-case scenario, the total costs and total quality-adjusted life years (QALYs) gained from lung screening with the PLCOm2012 risk model were compared with the USPSTF-2013 categorical age-smoking based eligibility criteria, over the average lifetime horizon of ILST participants (*i.e.* years 2020–2040). The risk threshold used for selection based on the PLCOm2012 score was ≥1.70%/6 years in the base-case scenario. This value was selected because it led to similar numbers of participants eligible in both study arms of the ILST. The economic modelling followed a semi-Markov framework, relaxing the memoryless Markovian property and allowing for time-dependent events (*i.e.* cancer incidence and increasing mortality rates with age) to change. In the intervention and comparator arms of the analysis, costs, health state transitions and long-term outcomes were simulated according to the probability that ILST participants will be stratified into "screen" or "no screen" branches of the model, depending on the eligibility criteria used (Figure 1). Long-term screening outcomes were simulated based on a previous version of the model built from the NLST trial data (Table 2). Full details are provided in the supplementary material. All future costs and QALYs were discounted at a rate of 3% per year and expressed in 2020 International Dollars (~1 US, 1.34 Canadian or 1.45 Australian Dollars, in 2020). The currency conversion used purchasing power parity indicators from the World Health Organization and we followed international guidelines for discounting in economic evaluations.[19] The uncertainty from key parameters and assumptions was evaluated deterministically and the combined effect of uncertainty for all parameters was evaluated probabilistically. The incremental cost-effectiveness ratio (ICER) was linearized at a willingness to pay (WTP) threshold of $20 000 /QALY to yield the incremental net monetary benefit (INB) statistic for accurate comparison of cost-effectiveness across different scenarios.[20] We assumed the perspective of the universal healthcare payer, which is similar to the societal perspective regarding

decisions about how to determine eligibility for lung cancer screening. The WTP threshold for lung screening is indicative of cost-effectiveness in Canada and Australia, but not a deciding factor; we, therefore, selected this value as a nominal threshold for comparison with other early detection health services.[21,22]

2.2. Participants

Participant data from the ILST were used to determine the probability of screening and cancer incidences. Between August 25, 2016, to November 21, 2020, individuals who were above age 55 and with at least 20 years of smoking history were recruited for participation in the ILST by radio, television, newspaper, paid social media advertisements, mail-out invitations and/or through general practice clinics in both countries. This analysis included the Australia and Canada study sites of the ILST, which recruited approximately the same number of participants from each country. Eligibility for participation was considered if individuals had either a PLCOm2012 lung cancer risk score of at least 1.51%/6 years or if they met the USPSTF-2013 criteria (≥30 pack-years; smoked within 15 years, age between 55 and 80); individuals who met either selection criteria were invited for an LDCT screening exam according to the study protocol.[17]

2.3. Parameters and Assumptions

2.3.1 Screening outcomes

The model considered lung cancer incidences from the ILST and all other outcomes from the previously published simulation model from the NLST (cancer progression rates, cancer incidences in no-LDCT screen scenario, and mortality by lung cancer or any cause). Long-term incidence and mortality rates were standardized for age and sex with Canadian life and cancer incidence tables, assuming similar trends in Canada and Australia.[23,24] The cancer detection rate (CDR) was the number of ILST participants with lung cancer detected within one year of their last annual screening exam for either the PLCOm2012 or USPSTF-2013 method, divided by the total number who were assessed for risk, deemed eligible and screened. The CDR in the

ILST was used to calculate transition probabilities to either curable or non-curable lung cancer for each selection strategy, by sex. Stage data (using the American Joint Committee on Cancer TNM system—8th edition) were assigned for all participants with any clinically confirmed lung cancer in the ILST and used to classify the detected lung cancer as curable versus not curable. Any resectable stage IIIA or lower lung cancer was considered "curable" and any non-resectable stage IIIA, stage IIIB or stage IV lung cancer was considered "non-curable". To account for health status during screening, no-screening, treatment and relapse, we used screening utility values from participants published in the literature (Table 2). We assumed that for the "no-screen" pathway, participants would not experience disutility from potential screening harms (*i.e.* false-positive results, anxiety, benign resections), that utility was similar across demographic subgroups of the cohort, and that screening-eligible participants would not improve their health status for any reason.

2.3.2 Costs

The resource utilization data from the ILST were not uniformly collected at all study sites, therefore we reference a detailed prospective analysis of resource utilization rates for Canadian lung screening participants.[25] A retrospective Australia study shows similar resource utilization rates and costs associated with screening.[26] Full details of the costing method are in the supplementary material. Briefly, a review of the Pharmaceutical Benefits Scheme schedule in Australia and health technology assessments in Canada was undertaken and the annual costs for all new treatments were calculated per list price and dosing requirements on the FDA label, considering the restricted mean duration of progression-free survival from the pivotal drug approval trials. Costs for a five-minute telephone-based risk assessment by a navigator were applied to the intervention arm regardless of whether or not a participant was deemed eligible by the risk model and an additional 35 minutes of navigator time was applied to those who were PLCO-positive. Cost data were evaluated annually for each health state. A separate analysis of the first-year rates and costs of physician services, imaging exams, invasive investigations, follow-up CT

exams, and adverse events was undertaken for screening participants who did not have lung cancer detected (*i.e.* costs for false-positive examinations), disaggregated by sex.

2.4 Sensitivity analysis

The impact of lowering or increasing the risk threshold applied to the PLCOm2012 model from the ≥1.7%/6 years threshold in the base-case scenario was tested deterministically. Male and female incidence and mortality data were disaggregated and the cost-effectiveness for both sexes was analyzed separately in the deterministic sensitivity analysis. The deterministic sensitivity analysis assessed basic modelling parameters including discount rate assumptions, individual variations in all costs, utilities and transition probabilities in the model. Alternate scenarios included WTP thresholds between zero and $50 000/QALY and the assumption that risk-model selected cohorts could have 10% higher rates of mortality due to greater age, comorbidities, or adverse socioeconomic reasons or 10% lower rates of mortality due to smoking cessation being provided along with lung screening or prescriptions of statins from incidental coronary findings. For the probabilistic sensitivity analysis (PSA) we ran 100 000 Monte Carlo simulations, accounting for uncertainty from the data on costs with gamma distributions around the mean and beta distributions around the mean for annual transition probabilities and health utility inputs (Table 2).

2.5. Statistical analysis

We used fisher's exact tests to detect differences in proportions and t-tests for differences in means. A comparison of the demographic characteristics for PLCOm2012 versus USPSTF-2013 selected groups in the ILST was performed with tests of statistical significance using p-values from two-sided tests and any threshold < 0.1 was considered relevant for potentially significant findings. The statistical analyses and modelling inputs were prepared with StataMP version 10, and the model was programmed with TreeAgePro version 2020.

3. Results

The ILST recruited 10 983 individuals in Canada and Australia who had an interest in lung cancer screening. Of these, 4062 were deemed eligible by either the PLCOm2012 or USPTF-2013 criteria and enrolled in the study (Table 1). There were 774 (19%) participants who were PLCOm2012-positive with the ≥1.7% threshold applied but were USPSTF-2013-negative; 797 (20%) who were PLCOm2012-negative and USPSTF-2013-positive; and 2491 (61%) participants were selected by both criteria. Participants excluded by the USPSTF-2013 criteria had an elevated lung cancer risk according to the PLCOm2012 model (3.25% (95% CI:3.11-3.39)). Compared to the USPTF-2013-negative portion of the ILST, the USPSTF-2013 criteria selected a significantly higher proportion of male participants, as well as those with younger age, higher educational attainment, and fewer co-morbidities. There was no significant difference in the proportion of males and females selected with the PLCOm2012 model (p=0.84); however, the risk model selected a higher proportion of individuals with fewer years of formal education, more co-morbid respiratory illnesses, personal history of cancer or family history of lung cancer, and a lower proportion of males and post-secondary graduates (Table 1). Over 90% of the ILST participants who enrolled were white, thereby limiting our ability to report on racial differences attributed to the eligibility criteria. White participants who were eligible by either criterion were more likely to enroll than eligible participants who reported to be of another race (Supplementary Table S.1.).

Of the 97 individuals with screen-detected lung cancer, 89 were selected with the PLCOm2012 model, and 71 were selected with the USPSTF-2013 criteria. The risk ratio (RR) for screen-detected lung cancer (CDR) was significantly higher in the PLCO-positive portion of the ILST compared with participants who scored negative with the PLCOm2012 selection method (RR: 3.31; 95%CI: 1.61–6.79), whereas the proportion of participants with screen-detected lung cancer did not differ between the USPSTF-2013 positive and negative

subgroups (RR: 0.79; 95%CI: 0.50-1.22), for both sexes combined. The CDR was greater for individuals scoring positive by PLCOm2012, but it was not significant in males, (females: RR 7.67, 95% CI:[1.87–31.38]; males: RR: 1.86, 95%CI:[0.79–4.48]). Female ILST participants had a slightly younger mean age than males (64 vs 65) and more females enrolled in the 55-59 age group than males (29% versus 26%).

Non-curative treatment costs for lung cancer have increased substantially over the past five years. Specifically, the costs for systemic therapy increased 9.4-fold in Canada and 7.5-fold in Australia due to new treatments for non-small cell lung cancer (Supplementary Material). The rate of false-positive investigations for participants who did not have lung cancer was low overall, however, the rate of false-positive invasive investigations per person (*i.e.* needle biopsies and bronchoscopy exams for participants who did not have lung cancer) was slightly higher in females compared with males, (0.05 *vs.* 0.03, p=0.06), and the mean cost for these unnecessary invasive investigations was significantly higher ($83 *vs.* $41; p<0.05).

In the base-case scenario, risk-model selection resulted in $355 of cost savings per 0.20 QALYs gained over the USPSTF-2013 strategy. At a willingness-to-pay threshold of $20 000/QALY, the mean incremental net benefit (INB) was $4294(95%CI: $4205–$4383). The probabilistic sensitivity analysis showed that 90% of the simulations were considered cost-effective at $20 000/QALY, and 80% of the simulations resulted in cost-savings if the WTP threshold was $0/QALY; the risk model delivered more QALYs and saved costs (See supplementary material, Figure S.4). The INB of using the PLCOm2012 model for selection in males was $695(95%CI: $608–$781); in females, using the risk model was more cost-effective: (INB= $6616, 95%CI: $6436–$6796). Lowering the threshold to ≥1.5%/6 years increased the INB to $4876(95%CI: $4782–$4969) for both sexes, while the INB for females was unaffected ($6112(95%CI: $6419–$6803) but improved substantially for males: $5221(95%CI: $5124–$5318). The risk model was most cost-effective at the ≥1.5/6 years threshold (INB: $4876). When this threshold was applied, 379 (9%) more ILST participants were eligible for screening and four additional cases of lung cancers would be detected compared to the base-case ≥1.7%/6 years threshold. At the ≥1.3%/6 years threshold there would be 538 more participants eligible compared to the base case scenario, and six

additional cases of lung cancer would be detected however the INB was less favorable as this threshold is nearly equivalent to the USPSTF-2013 criteria. Increasing the risk threshold to ≥1.9%/6 years also diminished the cost-savings effect of using the risk model (INB =-$1089, 95% CI:-$1173 to -$1005) in comparison with the USPSTF-2013 criteria, a finding related to older ages selected at this risk threshold. In alternate scenarios where the background mortality rate was increased by 10% in the PLCOm2012 arm only, the PLCOm2012(≥1.7%/6 years risk threshold) method remained the cost-saving strategy for determining eligibility, INB= $1034(95% CI: $947–$1221). Reducing mortality in the PLCOm2012 arm to the same degree (feasibly through effective smoking cessation treatment or prescribing life-saving statins for incidentally discovered coronary disease) had the most favourable economic impact (INB: $7736, 95%CI: $7642–$7830) (Figure 2).

4. Discussion

Using prospective data from the ILST we found that the PLCOm2012 risk model saved costs and QALYs compared with the USPSTF-2013 risk factor criteria. The CDR was higher with the PLCOm2012 risk model method of selection compared with the USPSTF-2013 criteria and the risk model improved access to screening for females and individuals with fewer years of formal education. When the risk threshold was lowered to ≥1.5%/6 years, the cost-effectiveness improved for both males and females, however in the ILST selection with the risk model method was less cost-effective if the risk threshold applied was broadened to ≥1.3%/6 years or narrowed to the 1.9%/6 years threshold. The efficiency of using the PLCOm2012 risk model was most pronounced among females, a finding driven by the pronounced difference in the observed cancer detection rate.

This finding is important because there are sex-based differences in enrollment in randomized controlled trials.[1,2] Selection criteria that do not favour enrolling females, therefore, limit the potential impact of screening by design. Furthermore, the risk model may reduce exposure to potentially higher screening harms for females who have a low risk of developing lung cancer. It may be rationalized that with greater rates of false-positive invasive investigations, and significantly higher CDR, females are at a higher risk of

screening harms from overdiagnosis; while gender and other social groupings have established relationships with tobacco use, lung cancer and screening behaviour.[10,31] Our results call for the use of sex and gender-plus-based plus analysis to continue measuring efficiency and equity in the implementation of lung screening.[32]

We found the choice of the risk threshold used with a risk model could optimize the economic impact of screening in the ILST cohort. The choice of which threshold value to use may vary in different populations and policy settings. For example, the Ontario Lung Screening Pilot study uses a ≥ 2.00%/6-year risk threshold with the PLCOm2012 model.[33] The Australian and UK governments recommend using the ≥1.51%/6-year threshold for their future screening program.[21,34] The UK program will also use a risk model developed by the Liverpool Lung Project (LLP) and future participants may enroll if they reach the chosen threshold with either risk model. Other studies suggest that risk models should be validated in the specific population that they are used and that "living" assessments of risk should be maintained from linked administrative databases to monitor changes over time.[35,36]

Evidence from participants in screening trial cohorts is essential due to the anticipated inconsistency between the population at risk and those who are more likely to participate in a lung screening program[37] Observational studies however are limited in their reliance on screening participation, thus underrepresenting the true racial, ethnic and gender diversity in population-based settings. The availability of methods to evaluate screening utility or disutility further limits the available economic evidence available for lung screening[38,39] In addition, there are limitations on the evidence available to inform willingness-to-pay threshold assumptions. All of these limitations render our main findings likely to be an underestimate of the efficiency and equity of lung screening selection methods in population settings.

When potential participants are fully informed of the risks (potential screening harms) and benefits (reduced lung cancer mortality) of screening, risk models offer an additional layer of information that can support decisions, particularly for individuals with a high risk of developing lung cancer. Our findings show that lung screening results are heterogenous when

disaggregated by sex and other indicators of social position. If health equality is an implied social value, then the costs of interventions aimed at reducing inequities in access to screening should be considered. The costs associated with the decision to use, or continue using, the alternative, age-smoke history categorical method of determining lung screening eligibility are paid by members of the population with social disadvantages.

5. Acknowledgement

We thank the following individuals for their support: Anne Dybuncio, John Spinelli, Stuart Peacock, Penelope Brasher, and Craig Mitton. We thank the National Cancer Institute for providing access to data collected for the National Lung Screening Trial. The statements contained herein are solely those of the authors and do not represent or imply concurrence or endorsement by the National Cancer Institute.

6. Funding Statement

The International Lung Cancer Screening Trial was funded by the Terry Fox Research Institute, the Vancouver General Hospital and University of British Columbia Hospital Foundation, the BC Cancer Foundation, the Australian National Health and Medical Research Council and the Medical Futures Fund. The funders enabled access to the health services used in the study and in-kind contributions. The funders were not involved in the design, analysis or interpretation of the results of this study.

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Conflict of Interest Statements

SC developed the cost-effectiveness model used in the study. The code for the model is available free of charge to non-commercial users, upon request. Commercial users will need to establish an information-sharing agreement with Simon Fraser University and receive approval by the International Lung Screening Trial scientific steering committee. SC has not received money for the use of the economic model and does not anticipate any payments in the future. SC and RMy held grants from Michael Smith Health Research and the Social Sciences and Humanities Council of Canada to support community-engaged research on the topic of access to lung health services. AM received travel or accommodation support for meetings by Roche, Olympus and the International Association for the study of Lung Cancer, KMF received travel support for several medical and scientific meeting organizers and received additional grants or contracts from Olympus and Australian Medical Research Future Fund and MeVis Medical Solutions AG/Health Inc; and payments or honoraria for lectures, presentations or speaker's fees and is the unpaid Chair for Lung Cancer Consultative Group and a Council member. AT received consultancy fees from Olympus Respiratory America and additional grants or contracts from Biodesix Inc and Arch Biomedical Inc.

Figure 1

Click here to access/download;Figure;Figure_1_model_concept.docx

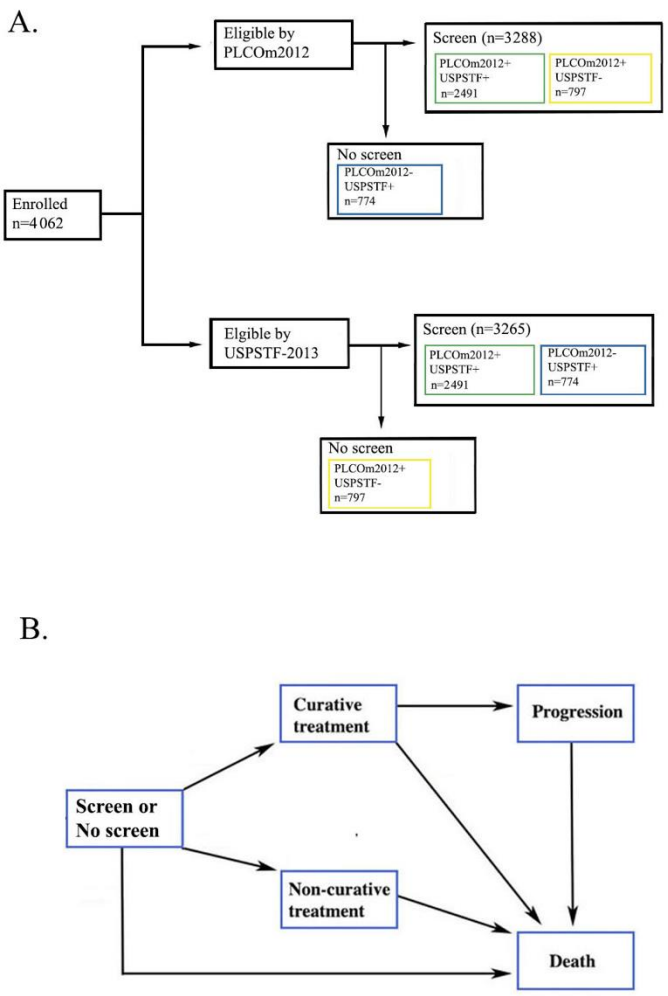

Figure 1. Model Structure. Comparison arms and screening strategies for the cost-effectiveness analysis (A) and Markov health states (B) defining the screening strategy (*i.e.* LDCT-based screening or not screening), Curable lung cancer (i.e. resectable stage IIIA or lower lung cancer), lung cancer progression (after resection), Non-curable Stage IIIA or higher and non-resectable lung cancer.

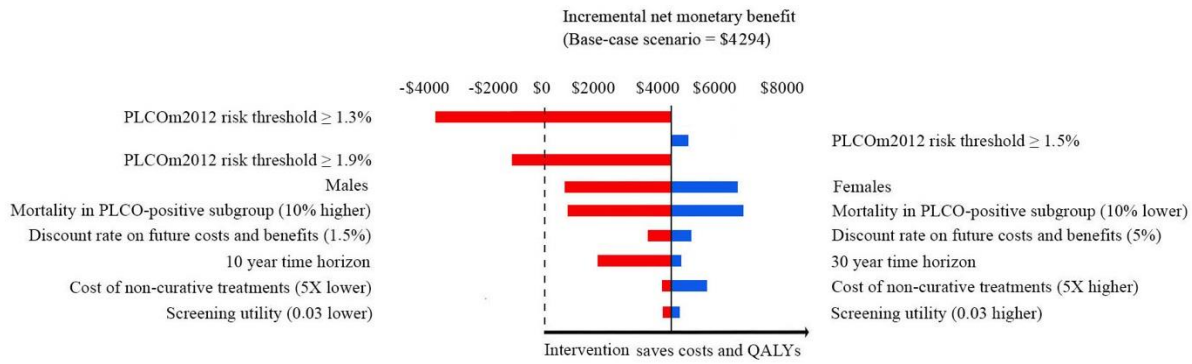

Figure 2. Deterministic sensitivity analysis. The base-case scenario compares the cost-effectiveness of lung screening eligibility selection using the PLCOm2012 risk model, 1.7% with determining eligibility with the USPSTF-2013 criteria. The red and blue bars show the impact that individual parameter variations have on the incremental net benefit result. Higher INB (blue) indicates that the scenario is more cost-effective than the base-case scenario; red bars indicate reduced cost savings relative to the base-case scenario. Unless specified the scenarios are for males and females combined.

Table 1: Participant characteristics by selection method and screening eligibility

		PLCOm2012, ≥ 1.7%/6-year risk threshold		USPSTF-2013 criteria	
		Screen	No screen	Screen	No screen
		N=3265	N=797	N=3288	N=774
Age	Years	65.7 (65.5–65.9)	58.7 (58.5–58.9)**	63.0 (62.8–63.2)	69.8 (69.4–70.2)**
Age groups	55-69	602 (18.4%)	521 (65.3%)**	1078 (32.8%)	45 (5.8%)**
	60-64	865 (26.5%)	224 (28.1%)	989 (30.1%)	100 (12.9%)**
	65-69	879 (26.9%)	48 (6.0%)**	726 (22.1%)	201 (26.0%)*
	70-74	619 (19.0%)	4 (0.5%)**	379 (11.5%)	244 (31.5%)**
	75-79	284 (8.7%)	0 (0.0%)**	113 (3.4%)	171 (22.0%)**
	≥80	16 (0.5%)	0 (0.0%)*	3 (0.1%)	13 (1.7%)**
Sex	Female	1546 (47.4%)	380 (47.7%)	1510 (45.9%)	416 (53.8%)**
Ethnicity	White	3010 (92.2%)	683 (85.7%)**	2988 (90.9%)	705 (91.1%)
	East Asian	94 (2.9%)	66 (8.3%)**	137 (4.2%)	23 (3.0%)
	Others	161 (4.9%)	48 (6.0%)	163 (5.0%)	46 (6.0%)
Education	Grade 8 or lower	124 (3.9%)	5 (0.6%)**	100 (3.1%)	29 (3.8%)
	Grades 9-11	690 (21.1%)	81 (10.2%)**	623 (19.0%)	148 (19.1%)
	High school degree	762 (23.3%)	122 (15.3%)**	706 (21.5%)	178 (23.0%)
	Technical degree	514 (15.8%)	122 (15.3%)	523 (15.8%)	113 (14.6%)
	Associate degree	528 (16.2%)	182 (22.8%)**	581 (17.7%)	129 (16.7%)
	Bachelor's degree	424 (13.0%)	189 (23.7%)**	509 (15.5%)	104 (13.4%)
	Advanced degree	223 (6.8%)	96 (12.0%)**	246 (7.5%)	73 (9.4%)*
Country	Australia	1664 (51.0%)	365 (45.8%)**	1614 (49.1%)	419 (54.1%)**
	Canada	1601(49.0%)	432 (54.2%)**	1674 (50.9%)	355 (45.9%)**
Health status	PLCOm2012 risk score	4.8 (4.6–4.9)	1.2 (1.2–1.2)**	4.3 (4.1–4.4)	3.3 (3.1–3.4)**
	Currently smoking	1728 (52.9%)	261 (32.8%)**	1768 (53.8%)	221 (28.6%)**
	Pack years	48.2 (47.5–48.9)	39.0 (38.3–39.7)**	48.7 (48.1–49.3)	36.6 (35.3–38.0)**
	Family history of lung cancer	991 (30.4%)	62 (7.8%)**	773 (22.3%)	320 (41.3%)**
	Personal history of cancer	488 (15.0%)	25 (3.1%)**	399 (10.3%)	174 (22.5%)**
	Body-mass index	27.0(26.9–27.2)	29.35 (29.0–29.7)**	27.69 (27.5–27.9)	26.56 (26.2–26.9)**
Comorbid conditions[b]	Chronic obstructive pulmonary disease	571 (17.5%)	23 (2.5%)**	449 (13.7%)	145 (18.7%)**
	Chronic bronchitis	327 (10.0%)	23 (2.9%)**	264 (8.0%)	86 (11.1%)**
	Emphysema	353 (10.8%)	14 (1.8%)**	285 (8.7%)	82 (10.6%)*
Life expectancy[c]	Males	31.0%	43.7%	43.6%	11.2%
	Females	37.7%	65.9%	43.9%	22.1%

Data are mean (95% confidence interval), n(%), median (interquartile range), or n/N(%), unless otherwise stated

[a]p-value from tests for differences between the "screen" and "no-screen" groups for either the PLCOm2012 or USPSTF-2013 criteria, denoted ** for $p<0.05$ and * if $0.05<p<0.1$

[b] Self-reported history at baseline

[c]20-year life expectancy from age at enrollment to ILST

Table 2: Parameters and assumptions

Parameter		Selection result	Years	Risk model (Intervention)		Categorical age-smoking selection (Comparator)		Source data/Reference
				Males	Females	Males	Females	
Transition probabilities[a]	Probability of selection	Screen	2020	0.81	0.80	0.83	0.78	ILST
		No screen	2020	0.20	0.20	0.17	0.22	ILST
	Curative CDR	Screen	2020–2040	0.01 (λ=2.43 x 10^{-4}; γ=0.66)	0.02 (λ=2.94 x 10^{-4}; γ=0.70)	0.01 (λ=2.93 x 10^{-4}; γ=0.61)	0.01 (λ=9.98 x 10^{-5}; γ=0.81)	ILST
	Non-curative CDR		2020–2040	0.00 (λ=8.48 x 10^{-5}; γ=0.53)	0.00 (λ=1.57 x 10^{-4}; γ=0.46)	0.00 (λ=2.47 x 10^{-5}; γ=0.64)	0.002 (λ=1.61 x 10^{-4}; γ=0.46)	ILST
	Non-lung cancer mortality		2020–2040	0.00 (λ=1.34 x 10^{-6}; γ=0.49)	0.00 (λ=1.34 x 10^{-6}; γ=0.49)	0.00 (λ=1.34 x 10^{-6}; γ=0.49)	0.004 (λ=1.34 x 10^{-6}; γ=0.49)	NLST (LDCT arm)[27]
	Progression incidence		2020–2040	0.05 (λ=1.92 x 10^{-4}; γ=0.95)	0.05 (λ=1.92 x 10^{-4}; γ=0.95)	0.05 (λ=1.92 x 10^{-4}; γ=0.95)	0.05 (λ=1.92 x 10^{-4}; γ=0.95)	
	Curative mortality		2020–2040	0.05 (λ=6.39 x 10^{-4}; γ=0.73)	0.05 (λ=6.39 x 10^{-4}; γ=0.73)	0.05 (λ=6.39 x 10^{-4}; γ=0.73)	0.05 (λ=6.39 x 10^{-4}; γ=0.73)	
	Non-curative mortality		2020–2040	0.43 (λ=6.99 x10^{-3}; γ=0.74)	0.43 (λ=6.99 x 10^{-3}; γ=0.74)	0.43 (λ=6.99 x 10^{-3}; γ=0.74)	0.43 (λ=6.99 x 10^{-3}; γ=0.74)	
	Progression mortality		2020–2040	0.36 (λ=1.62 x 10^{-3}; γ=0.95)	0.36 (λ=1.62 x 10^{-3}; γ=0.95)	0.36 (λ=1.62 x 10^{-3}; γ=0.95)	0.36 (λ=1.62 x 10^{-3}; γ=0.95)	
	Background mortality[b]		2025–2040	2.08 x10^{-2}	1.40 x10^{-2}	1.37 x10^{-2}	8.70 x10^{-3}	Statistics Canada[24]
	Background CIR (Curable)[c]		2025–2040	1.42 x10^{-3}	1.24 x10^{-3}	1.42 x10^{-3}	1.24 x10^{-3}	Canadian Cancer Society[23]
	Background CIR (Non-Curable)[c]		2025–2040	1.83 x10^{-3}	8.14 x10^{-4}	1.83 x10^{-3}	8.14 x10^{-4}	Canadian Cancer Society[23]
	Curative CDR	No screen	2020–2040	0.20 x10^{-2} (λ=1.81 x 10^{-5}; γ=0.83)		0.90 x10^{-2} (λ=9.85 x 10^{-5}; γ=0.76)		NLST (CXR arm)[27]
	Non-curative CDR		2020–2040	0.20 x10^{-2} (λ=4.03 x 10^{-6}; γ=1.04)		0.70 x10^{-2} (λ=2.70 x 10^{-5}; γ=0.94)		
	Non-lung cancer mortality[a]		2020–2040	0.30 x10^{-2} (λ=4.81 x 10^{-7}; γ=1.47)		0.80 x10^{-2} (λ=1.94 x 10^{-6}; γ=1.41)		
	Progression incidence		2020–2040	11.4 x10^{-2} (λ=9.97 x 10^{-4}; γ=0.82)		9.40 x10^{-2} (λ=6.71 x 10^{-4}; γ=0.85)		
	Curative mortality rate		2020–2040	1.16 x10^{-2} (λ=4.81 x 10^{-7}; γ=1.46)		9.40 x10^{-2} (λ=1.92 x 10^{-3}; γ=0.70)		
	Non-curative mortality		2020–2040	0.50 (λ=4.89 x 10^{-3}; γ=0.84)		0.51 (λ=5.80 x 10^{-3}; γ=0.82)		
	Progression mortality		2020–2040	0.45 (λ=4.34 x 10^{-3}; γ=0.84)		0.50 (λ=6.43 x 10^{-3}; γ=0.79)		
	Background mortality[b]		2025–2040	8.90 x10^{-3}	5.50 x10^{-3}	3.50 x10^{-2}	1.40 x10^{-2}	Statistics Canada[24]
	Background CIR (Curable)[c]		2025–2040	5.37 x10^{-4}	4.60 x10^{-4}	2.70 x10^{-3}	1.24 x10^{-3}	Canadian Cancer Society[23]
	Background CIR (Non-Curable)[c]		2025–2040	7.98 x10^{-4}	3.55 x10^{-4}	2.73 x10^{-3}	8.14 x10^{-4}	Canadian Cancer Society[23]
Costs (SD)	Risk assessment	Screen	2020	$15 ($5)		$6 ($2)		Assumption
		No screen	2020	$6 ($2)		$6 ($2)		
	Screening costs	Screen	2020	$450 ($44)				Cressman *et al*, 2014[25] with updates to 2020[d]
			2021	$238($26)				
			2022	$204 ($29)				
			2023	$135 ($18)				
			2024–2035	$326 ($47)				
			2036–2040	$0				Assumption
		No screen	2020–2040	$0				Assumption
	Curative treatment for lung cancer	Screen and no screen	2020	$22 552 ($1814)				Cressman *et al*, 2014[25]

					with updates to 2020[d]
			2021	$752 ($71)	
			2022	$503 ($81)	
			2023	$584 ($145)	
			2024–2033	$483 ($140)	
			2033–2040	$0	Assumption
	Non-curative treatment	Screen and no screen	2020	$68 603 ($7377)	
			2021	$20 868 ($7137)	
			2022–2040	$9 703 ($3459)	
	Progression after curative treatment	Screen and no screen	2020	$35 111 ($8385)	
			2021	$10 365 ($5763)	
			2022–2040	$20 746 ($19 249)	
Utility (SD)	Screen (no lung cancer)		2020–2040	0.85 (0.03)	Cressman *et al*, 2014[25]
	No screen (no lung cancer)		2020–2040	0.87 (0.03)	Ngo *et al*, 2022[27]
	Curative treatment for lung cancer	Screen and no screen	2020–2040	0.82 (0.16)	Tramontano *et al* 2015[29]
	Non-curative treatment	Screen and no screen	2020	0.78 (0.18)	Tramontano *et al* 2015[29]
		Screen and no screen	2021–2040	0.5 (0.18)	Tramontano *et al* 2015[29]
	Progression after curative treatment	Screen and no screen	2020	0.69 (0.24)	Jang *et al* 2010[30]
		Screen and no screen	2021–2040	0.75 (0.20)	Jang *et al* 2010[30]

Abbreviations: NLST= National Lung Cancer Screening Trial, LDCT= Low Dose Computed Tomography, CXR= Chest Radiography, ILST= International Lung Screening Trial, PanCan=Pan-Canadian Early Detection of Lung Cancer Trial, CDR= cancer detection rate, CIR= cancer incidence rate

[a] λ= shape and is the slope of the Weibull survival model, it is used for estimating the value of parameters that change over time. Transition probabilities were calculated from 2.3 years of follow-up in the ILST or a previous analysis of 6.4 years of follow-up from the NLST (25); the initial probability of transition for year 1 is provided.

[b]Age-adjusted background mortality from any cause added to the NLST or ILST-derived transition probabilities starting in 2025 according to the median age in the ILST and life tables from Statistics Canada[24]

[c]Age-adjusted background incidences of stage 1-3 lung cancer (curable) or stage 4 (non-curable), added to the NLST or ILST-derived transition probabilities starting in 2025 according to the median age in the ILST and incidence rates from the Canadian Cancer Society[25]

[d]See supplementary materials

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Credit Author Statement

SC, MFW, KMF, SL, KC, MCT conceived the study. SC, MFW, PJN, AT, SW, RMa, ES, SA-K, DK, CH, SBH, MC, AF, JYW, HMM, KMF, SL, KC, and MCT contributed to data curation. SA-K, AF, JYW, SL and MCT verified the raw data. SC, MFW, PJN, SW, SA-K, DK, CH, SBH, MC, AF, JYW, HMM, KMF, SL, KC and MCT analyzed the data. SC, MFW, AT, ES, JM, JY, KMF, KC, and SL contributed to funding acquisition. SC, MFW, PN, SW, SL and MCT wrote the first draft of the manuscript. All authors critically reviewed the manuscript and agreed with the decision to submit it for publication. All authors had full access to all the data in the study and SC, MFW, and SA-K take responsibility for the integrity of the data and the accuracy of the data analysis.