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Risk Model–Based Lung Cancer Screening: A Cost-Effectiveness Analysis

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Abstract

Background: In their 2021 lung cancer screening recommendation update, the US Preventive Services Task Force (USPSTF) evaluated strategies that select individuals based on their personal lung cancer risk (risk model-based strategies), highlighting the need for further research on the benefits and harms of risk model-based screening.

Objective: To evaluate and compare the cost-effectiveness of risk model-based lung cancer screening strategies vs. the USPSTF recommendation and to explore optimal risk thresholds.

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Access to Data and Data Analysis
IT and SSH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Design: Comparative modeling analysis.

Data Sources: National Lung Screening Trial; Surveillance, Epidemiology, and End Results program; US Smoking History Generator.

Target Population: 1960 US birth cohort.

Time Horizon: 45 years.

Perspective: US health care sector.

Intervention: Annual low-dose computed tomography in risk model-based strategies that start screening at age 50 or 55, stop screening at age 80, with 6-year risk thresholds between 0.5% −2.2% using the PLCOm2012 model.

Outcome Measures: Incremental cost-effectiveness ratio (ICER) and cost-effectiveness efficiency frontier connecting strategies with the highest health benefit at a given cost.

Results of Base-Case Analysis: Risk model-based screening strategies were more cost-effective than the USPSTF recommendation and exclusively comprised the cost-effectiveness efficiency frontier. Among the strategies on the efficiency frontier, those with a 6-year risk threshold of 1.2% or greater were cost-effective with an ICER less than $100,000 per quality-adjusted life year (QALY). Specifically, the strategy with a 1.2% risk threshold had an ICER of $94,659 (model-range: $72,639-$156,774), yielding more QALYs for less cost than the USPSTF recommendation, while having a similar level of screening coverage (person ever-screened 21.7% versus USPSTF's 22.6%).

Results of Sensitivity Analyses: Risk model-based strategies were robustly more cost-effective than the 2021 USPSTF recommendation under varying modeling assumptions.

Limitations: Risk models were restricted to age, sex, and smoking-related risk predictors.

Conclusion: Risk model-based screening is more cost-effective than the USPSTF recommendation, thus warranting further consideration.

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Introduction

In 2021, the US Preventive Services Task Force (USPSTF) issued their updated recommendation on lung cancer screening that lowers the starting age from 55 to 50 years and the minimum cumulative smoking exposure from 30 to 20 pack-years relative to its 2013 recommendation.(1) As part of their lung cancer screening update, the USPSTF reviewed the performance of strategies that select individuals based on their personal lung cancer risk (hereon referred to as risk model-based strategies)(1, 2), in addition to strategies that select individuals based on categorical age and smoking history (hereon referred to as categorical age-smoking strategies) such as their final recommendation. Risk model-based strategies use validated risk prediction models to estimate the personal lung cancer risk of individuals within a prespecified time horizon, based on a set of risk factors associated with lung cancer.(3–5)

Several prior studies have evaluated the performance of risk model-based screening for lung cancer.(2, 4, 6–13) To inform the 2021 USPSTF recommendation update, the Cancer Intervention and Surveillance Modeling Network (CISNET) Lung Working Group conducted a comparative modeling study and reported that risk model-based strategies avert more lung cancer deaths and result in fewer radiation-related deaths than categorical age-smoking strategies.(2, 14) Interim findings from the International Lung Screening Trial demonstrated that risk model-based lung cancer screening programs improve sensitivity versus categorical age-smoking strategies.(15) Several international trials and pilot studies announced their plans to evaluate the feasibility of risk model-based screening strategies for lung cancer, with some of them reporting encouraging preliminary findings.(15–20)

Despite the potential for risk-model based screening to improve screening performance, comprehensive evaluations of the cost-effectiveness of risk-model based screening programs have been largely lacking. Prior studies have estimated the cost-effectiveness of categorical age-smoking strategies for lung cancer.(21–25) Kumar and colleagues conducted an analysis comparing the cost-effectiveness across different subgroups stratified by estimated risk scores,(26) but was limited to the National Lung Screening Trial (NLST) study population, thus not generalizable to the U.S. population. The cost-effectiveness of risk model-based screening was evaluated for the UK,(27) Canada,(28) and Australia,(29) but no study to date has compared the cost-effectiveness of risk-model based screening versus the 2021 USPSTF recommendations.

The cost-effectiveness of risk model-based screening could depend on the risk threshold used to select individuals for screening given the differences in health outcomes associated with screening individuals from different risk strata.(3, 4) Several studies evaluated the effectiveness of risk model-based screening programs by assessing lung cancer mortality reduction or life-years gained.(15, 16, 30–34) These studies used the PLCOm2012 model and considered specific risk thresholds (e.g., 6-year risk of 1.3%, 1.5%, or 1.7%) that were shown to yield similar sensitivity or eligibility as compared to past screening trials or to the USPSTF recommendations. However, the optimality of these risk threshold from a cost-effectiveness perspective cannot be determined.

In this study, we evaluated and compared the cost-effectiveness of risk model-based strategies versus the 2021 USPSTF recommendation using a range of clinically meaningful risk thresholds discussed in the literature or implemented in contemporary international lung cancer screening programs(4, 15, 16, 34).

Methods

We used a comparative modeling approach involving four validated microsimulation models of the CISNET Lung Working Group that informed the USPSTF recommendations on lung cancer screening, to assess the cost-effectiveness of risk model-based screening strategies (Supplemental Table 1).(2, 14, 35)

CISNET Model Description

Four microsimulation models of the CISNET Lung Working Group [the Microsimulation Screening Analysis (MISCAN)-Lung Model from Erasmus University Medical Center,(36) the Lung Cancer Policy Model from Massachusetts General Hospital,(37) the Lung Cancer Outcomes Simulation from Stanford University,(38, 39) and the model from University of Michigan(40)] were independently developed to evaluate lung cancer screening strategies. Because the models differ in modeling assumptions and mathematical formulation of lung cancer development and progression, the comparative analysis allows us to assess the impact of model specification uncertainty. All models were calibrated to lung cancer incidence and mortality data from the NLST and the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial.(41) An overview of the models and their assumptions is provided in Supplemental Methods, Supplemental Table 2 and the literature.(14, 35, 41, 42)

Study Population and Smoking Histories

Lung cancer related events for 1 million men and women were simulated separately, using smoking patterns of the 1960 U.S. birth cohort that is representative of the U.S. population targeted by screening. Smoking histories and age at death from competing causes of death were obtained from the CISNET’s smoking history generator (Supplemental Methods).(43–45) Simulated individuals entered the study at age 45 and were followed until age 90 or death, whichever occurred first, corresponding to a study horizon between 2005–2050.(2, 21)

Risk Prediction Models

We assessed individuals’ lung cancer risk using the PLCOm2012 risk prediction model and the Lung Cancer Death Risk Assessment Tool (LCDRAT).(12, 46) We selected these models since they are ranked among the best performing externally validated risk prediction models for lung cancer and allowed evaluation of screening programs that select individuals based on their risk of being diagnosed with lung cancer (PLCOm2012) versus risk of dying from lung cancer (LCDRAT).(4, 11) We used simplified versions for both models restricted to age, sex, and smoking-related risk predictors to estimate the personal risk of ever-smoked individuals, which maintained high predictive performance (Supplemental Methods, Supplemental Tables 3–4).(4, 30) We considered a set of clinically meaningful 6-year lung cancer risk thresholds ranging from 0.5%−2.2%, because programs within that range yielded a positive net benefit versus the NLST eligibility criteria.(2, 4, 15, 16, 30, 34) Individuals were eligible to undergo annual lung cancer screening if they satisfied the age eligibility criteria and their risk was above the 6-year risk threshold specified by each screening strategy.

Health Utility and Cost Inputs

We evaluated the cost-effectiveness of screening programs using the U.S. health care sector perspective.(21, 23) We adjusted the remaining life-years of simulated individuals for quality of life using published health utilities associated with aging, lung cancer screening, screening findings, lung cancer stage at diagnosis, and terminal care (Supplemental Table 5).(47–50)

Costs associated with screening and diagnostic procedures were obtained from the 2020 Centers for Medicare and Medicaid Services reimbursement rates based on their corresponding Current Procedural Terminology code (Supplemental Table 6). Downstream treatment costs associated with specific phases of lung cancer treatment were adopted from a published analysis of SEER/Medicare data and converted to 2020 U.S. dollars using a 3% annual inflation rate (Supplemental Table 7).(23, 51) Health utilities and costs were standardized, discounted using a 3% annual rate, and shared across the four models.

Outcome Measures

Primary outcome measures included: (1) the cost-effectiveness efficiency frontier, i.e., the line segments connecting strategies that yield the highest health benefit at a given level of cost, and (2) the incremental cost-effectiveness ratios (ICER) of each screening strategy relative to the strategy preceding it on the efficiency frontier.

Each model estimated the sex-specific health benefits and costs associated with each strategy. We normalized the results to 100,000 individuals alive at age 45 with no history of lung cancer and derived the overall population outcomes for each of the CISNET models by aggregating the sex-specific results. We calculated the arithmetic mean for the costs and quality-adjusted life-years (QALYs) for each screening strategy from the model-specific results for the overall population, and then estimated the ICER of strategy i relative to strategy j as follows:

$$ICER_{ij} = \frac{Cost_i - Cost_j}{QALY_i - QALY_j}$$

where strategy i corresponds to the strategy that is being evaluated, and strategy j denotes the reference strategy.

Screening strategies were considered cost-effective if they (i) were on the cost-effectiveness efficiency frontier and (ii) had an ICER less than $100,000 vs the preceding strategy on the efficiency frontier(52–54).

Secondary outcomes included lung cancer mortality reduction, life-years gained from screening, number of LDCT screening exams, overdiagnosis rates, and strategies' net monetary benefit(55). Results are presented per 100,000 individuals from the general population (including individuals who were ineligible for screening, e.g. never-smoking individuals) alive at age 45 with no history of lung cancer, unless stated otherwise.

Base-case and Sensitivity Analyses

For the base-case analysis, we used the PLCOm2012 and LCDRAT risk models to estimate the lung cancer risk of ever-smoked individuals(12, 46). We assigned a one-time disutility of 0.01 (3.65 days)(22) per indeterminate finding (that is a Lung-RADS category 3 or 4A finding(56)) applied from the time of detection up until the next follow-up exam, and a one-time disutility of 0.001 (8.75 hours)(50) per LDCT exam assuming perfect adherence to screening.

For practicality, all sensitivity analyses were conducted using the PLCOm2012 risk model. We examined the robustness of our findings to changes on the disutility levels associated with indeterminate findings (disutility range: 0.005–0.02(22)) and regular LDCT exams (disutility range: 0–24 hours(50)). We evaluated the cost-effectiveness of screening assuming age-specific adherence rates observed in current clinical practice (Supplemental Table 8).(57) To incorporate potential implementation challenges associated with risk model-based programs, we also considered a scenario with lower adherence rates for the risk model-based strategies relative to the adherence rate used for categorical age-smoking strategies (Supplemental Methods). To reflect current practice that discourages screening for high comorbid individuals, we evaluated the cost-effectiveness of risk model-based strategies when individuals with short life expectancy (less than 5 years from the time of the LDCT screening exam assessed annually) were ineligible for screening.(2, 21) Also, we evaluated the cost-effectiveness of screening accounting for the additional cost associated with the risk assessment (Supplemental Table 6). Finally, univariate, and probabilistic sensitivity analyses were conducted to assess the sensitivity of our findings to changes in the values of key model input parameters (Supplemental Methods).

Results

Base-Case Analysis

The results of our base-case analysis using the PLCOm2012 are shown in Tables 1 and Figure 1A. Risk model-based screening strategies were more cost-effective than the 2021 USPSTF recommendation. Notably, all the categorical age-smoking strategies—including the 2021 and the 2013 USPSTF recommendations—were strongly dominated (i.e., more costly yet yielded fewer QALYs) by risk model-based strategies. The cost-effectiveness efficiency frontier derived from the analysis using the PLCOm2012 model included 12 risk model-based strategies that started screening at age 50 years. Among the 12 strategies on the cost-effectiveness efficiency frontier, the 6 strategies with a 6-year risk threshold of 1.2% or greater were cost-effective (i.e., an ICER less than $100,000). Notably, the strategy using a 1.2% 6-year threshold yielded the highest health benefit among the cost-effective strategies (ICER=$94,659 per QALY gained; on the frontier of 3 out of 4 models, ICER range across models: $72,639-$156,774) (Supplemental Tables 9–12). The 1.2% PLCOm2012 strategy yielded higher reduction in lung cancer mortality than the 2021 USPSTF recommendation (12.4% vs. 11.7%), while maintaining a similar level of screening coverage (21.7% vs 22.6% individuals ever screened) (Table 2).

The analysis using the LCDRAT model—that predicts the risk of 6-year lung cancer mortality (vs. 6-year lung cancer incidence in PLCOm2012)—yielded findings similar to the PLCOm2012, although the cost-effective screening strategy that yielded the highest QALYs used a 1.1% 6-year LCDRAT risk threshold (vs. 1.2% risk threshold with the PLCOm2012) with an ICER of $97,284 per QALY gained (ICER range across models: $67,728-$143,125) (Figure 1B and Table 3).

Model-specific results showed that the efficiency frontiers were still comprised of only risk model-based strategies across all CISNET models, although the range of cost-effective risk thresholds varied across the models from 0.9% or greater to 2.2% or greater for the

PLCOm2012 model (Supplemental Tables 9–12) and from 1.0% or greater to 2.2% or greater for the LCDRAT model (Supplemental Tables 13–16).

Our findings using the net monetary benefit (to replace the ICERs) are presented in Supplemental Tables 17–18.

Sex-specific analyses showed that the efficiency frontiers were still comprised of only risk model-based strategies, and both risk model-based and categorical age-smoking strategies were more cost-effective for women than for men (Supplemental Tables 19–20). The analysis performed using unadjusted life-years (versus QALY) with the PLCOm2012 model yielded similar results to the base-case (Supplemental Table 21).

Sensitivity Analyses

When we assumed maximum disutility values associated with LDCT exams and indeterminate findings, the efficiency frontier was still comprised only of risk model-based strategies that initiate screening at age 50 years (Supplemental Table 22, Supplemental Figure 1). However, among the strategies on the efficiency frontier, only risk model-based strategies with a 6-year risk threshold (PLCOm2012) of 2.0% or greater (versus 1.2% or greater in the base-case) remained cost-effective under the maximum disutility values. Specifically, the strategy with a 2.0% 6-year risk threshold was cost-effective and yielded the highest health benefit with a mean ICER of $84,113 (on the frontier of all models, ICER range: $53,951-$980,439). When directly compared against the 2021 USPSTF strategy, the 2.0% risk model-based strategy was estimated to screen fewer people (15.8% vs 22.6% of the general population ever screened), requiring about half the screening exams compared with the USPSTF (1.9 million vs. 4.0 million LDCT per 100,000 people) but yielded lower lung cancer mortality reduction (9.8% vs. 11.8%) (Table 3).

When we incorporated imperfect adherence rates into screening (see Supplemental Methods), the efficiency frontier was still comprised only of risk model-based strategies and the range of cost-effective risk threshold remained unchanged even when the risk model-based strategies were assumed to have lower adherence (up to 85% level) than the USPSTF recommendations (Supplemental Tables 23–26). When we used the lower and upper bounds for the age-specific adherence rates, the strategies on the efficiency frontier remained unchanged but the range of cost-effective risk thresholds changed, with cost-effective screening programs becoming more inclusive (i.e. using lower risk thresholds) as adherence rates decreased (Supplemental Tables 27–28). Sensitivity analyses that excluded individuals with limited life expectancy from screening (see Methods) showed improved cost-effectiveness, with overall lower ICERs (Supplemental Table 29) compared to the base-case analysis (Table 2); the cost-effectiveness efficiency frontier was still comprised of risk model-based strategies, thus dominating the 2021 USPSTF recommendation. The analyses that directly compared each strategy including individuals with low life-expectancy versus the same strategy excluding them are presented in Supplemental Table 30. The sensitivity analyses that incorporated the costs associated with annual risk assessment showed that risk model-based strategies remained cost-effective versus the 2021 USPSTF recommendation, especially when the risk assessment costs were incurred by individuals who previously didn't undergo screening and satisfied the age eligibility criteria (Supplemental Tables 31–32).

The univariate sensitivity analyses for the risk model-based strategy that starts screening at age 50 with 6-year PLCOm2012 risk threshold of 1.2%—which was chosen as the most cost-effective strategy in the base-case analysis using the PLCOm2012 model—showed that the ICERs were sensitive to changes to the values of the health utility associated with Stage I non-small cell lung cancer, and the discounting factor (Figure 2, Supplemental Tables 33–50). The probabilistic sensitivity analysis demonstrated that the strategy with 1.2% 6-year risk threshold was cost-effective relative to the 1.3% 6-year risk threshold strategy with 31% probability using $100,000 willingness-to-pay threshold (Supplemental Figure 2).

Discussion

In this study, we evaluated the cost-effectiveness of risk model-based lung cancer screening strategies that use validated risk prediction models to select individuals for screening. We found that risk model-based screening strategies consistently yielded more QALYs and cost savings compared to the 2021 USPSTF recommendation. The cost-effectiveness efficiency frontier included only risk model-based screening strategies that start screening at age 50 regardless of whether the risk assessment was based on lung cancer incidence or mortality. Among the strategies on the efficiency frontier, the strategies with a 6-year risk threshold of 1.2% or greater (with the PLCOm2012) were cost-effective under the base-case analysis. Particularly, the strategy with a 1.2% PLCOm2012 risk threshold yielded more QALY for less cost than the USPSTF recommendation, while having a similar level of screening coverage (person ever-screened 21.7% for the 1.2% PLCOm2012 versus 22.6% for the 2021 USPSTF recommendation).

Of note, risk model-based screening strategies were consistently more cost-effective than the 2021 USPSTF recommendation under varying modeling assumptions, including when a minimum of 5-year life expectancy was included as an eligibility criterion and when imperfect adherence was implemented. However, the range of cost-effective risk thresholds for selecting individuals for screening was sensitive to the risk models used, to the adherence rate, and to the disutility levels associated with regular screening LDCT exams and indeterminate findings. For example, when we used the LCDRAT model that predicts 6-year lung cancer mortality (vs. 6-year lung cancer incidence using PLCOm2012), the cost-effective risk model-based strategies used a 6-year risk threshold of 1.1% or greater (1.2% or great in PLCOm2012). Discrepancies in the optimal risk-thresholds between PLCOm2012 and LCDRAT highlight the importance for lung cancer screening programs to use model-specific risk-thresholds. Further, when we assumed the maximum disutility levels for LDCT screening and indeterminant findings, the cost-effective risk model-based screening strategies used more stringent 6-year risk thresholds (2.0% PLCOm2012 or greater versus 1.2% or greater in the base-case). However, the maximum disutility levels (i.e., 24 hours for LDCT screening and 2% for indeterminant findings) used for our sensitivity analyses may be regarded as conservative compared to the literature.(22, 58, 59) Furthermore, using the cost-effective risk thresholds of 2.0% or greater estimated under the maximum disutility assumption would lead to reduced screening coverage versus the 2021

USPSTF recommendation (person ever-screened 15.8% vs. 22.6%) and lower lung cancer mortality reduction (9.8% vs. 11.8%). If expanded eligibility is one of the key considerations in implementing lung cancer screening programs, the range of cost-effective PLCOm2012 risk thresholds of 1.2% or greater (that include the range of 2.0% or greater) estimated under the base-case—with more moderate but realistic levels of disutility (8 hours for LDCT screening(50) and 1% for indeterminant findings(22))—could present a reasonable solution. The strategy with a 6-year PLCOm2012 risk threshold of 1.2% could lead to a similar level of screening coverage as the USPSTF recommendation (person ever-screened 21.7% vs. 22.6% according to the 2021 USPSTF recommendation), with greater lung cancer mortality reduction (12.4% vs. 11.8%). Ultimately, optimal risk thresholds must be tailored to specific settings based on practical considerations, benefits and harms trade-offs, and resource constraints.

This study is the first to comprehensively evaluate the cost-effectiveness of risk model-based lung cancer screening relative to the 2021 USPSTF recommendation for the US. Although our modeling study that informed the 2021 USPSTF recommendation on lung cancer screening showed that risk model-based strategies offer a modicum of life-year benefit relative to categorical age-smoking programs,(2, 14) in this study we showed that when we consider the quality-adjusted life-years gained from screening and the costs of screening, diagnostic, and treatment modalities then risk model-based screening strategies offer a substantially higher benefit relative to the categorical age-smoking strategies. The comparative modeling approach and comprehensive sensitivity analyses conducted proved the robustness of the main study findings under varying modeling assumptions. We showed that risk model-based lung cancer screening programs despite generally shifting screening eligibility to older ages when lung cancer risks, as well as comorbidity risks, are higher,(2, 4) remain more cost-effective than the 2021 USPSTF recommendation. Findings from this study are aligned with prior studies, which demonstrated the need to use risk-thresholds that are specific to the risk model used,(4, 30) that lung cancer screening is more cost-effective in women than men,(21–23, 25) and that the cost-effectiveness of lung screening programs is sensitive to the disutility of indeterminate findings.(22) Exploring optimal risk thresholds from a cost-effectiveness perspective identified a range of risk thresholds that could be used as a potential guide for the development of cost-effective risk model-based lung cancer screening policies under different settings and healthcare resources.

Our study has limitations. We used simplified versions of the risk prediction models to assess the lung cancer risk of individuals as done in prior CISNET studies.(2, 4) Consequently, we may have underestimated the cost-effectiveness of risk model-based screening strategies as the full models would be expected to better identify high risk individuals. Modeling additional covariates for the risk assessment (such as family history or race/ethnicity) is challenging because it requires their joint simulation at the population level, accounting for their correlations and time trends(60). We assumed that adherence to annual screening was independent of sex, race/ethnicity, and socioeconomic status.(61–64) Our current models do not incorporate potential issues regarding availability of resources to satisfy the expected increase in the number of LDCT exams,(5, 65–67) nor contemporary treatment modalities. We used the health care sector perspective and ignored productivity loss, impact on the quality of life of caregivers, and physician and facility costs. We assessed the cost-effectiveness of lung cancer screening for the general US population, but the recommended risk-threshold may not be the optimal for every region/state/heath system given potential differences in the prevalence of lung cancer, sociodemographic risk factors, and practice patterns. Lastly, we did not consider the benefit of offering smoking cessation interventions at the time of lung cancer screening, which have been shown to improve the cost-effectiveness of screening programs(68–71), and assumed that lung cancer risk and false-positive rates were independent(72).

In conclusion, lung cancer screening strategies that select individuals based on their personal lung cancer risk are robustly more cost-effective than the 2021 USPSTF recommendations. Risk model-based screening is cost-effective under a wide range of risk-thresholds, offers flexibility for implementation across different settings, and warrants further consideration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reproducible Research Statement:

- Study protocol: Not available.
- Statistical code: Not available.
- Data set: Key model inputs are posted as a data supplement on Annals website. Inputs obtained from the CISNET's Smoking History Generator can be obtained from the CISNET's Resource page at https://resources.cisnet.cancer.gov/projects/#shg/tce/summary. Results from the sensitivity analyses using the Lung Cancer Death Risk Assessment Tool (LCDRAT) and the PLCOm2012 model with life expectancy are available from the authors upon request.

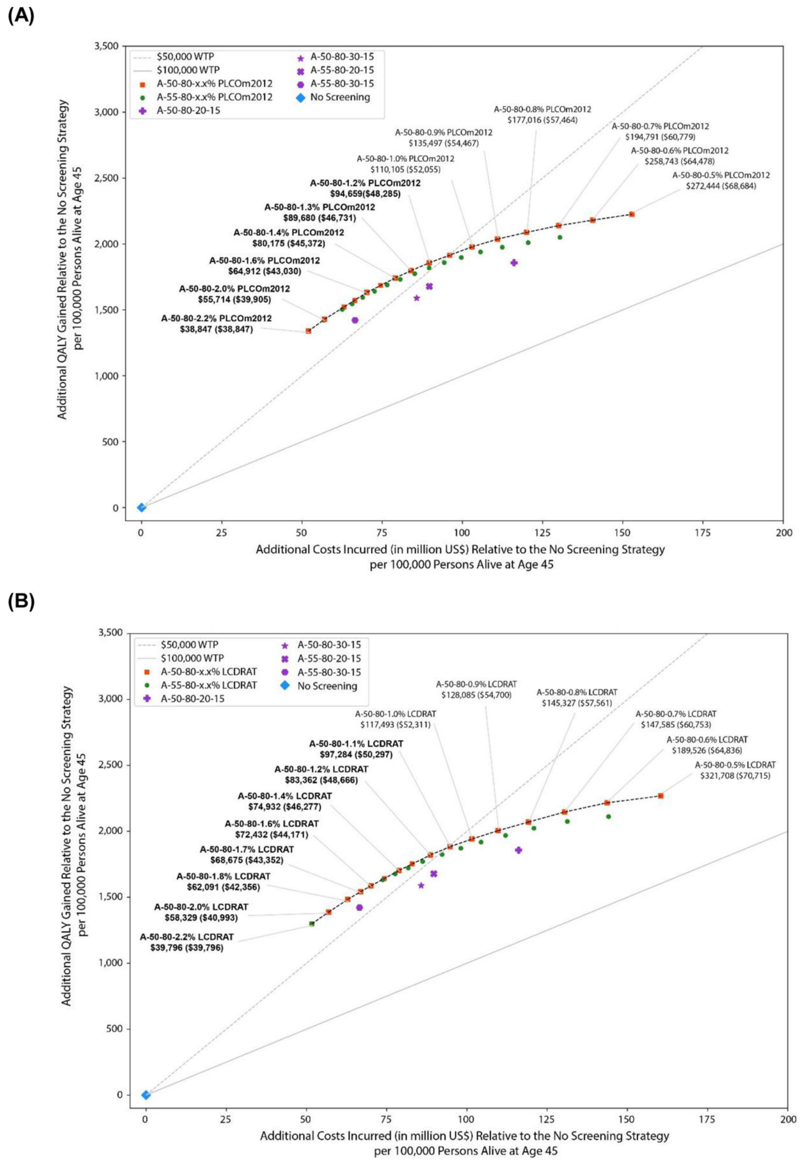

Figure 1.

Additional Total Health Benefits (Measured Using QALY) Gained and Costs Incurred Associated With Categorical Age-Smoking and Risk Model-Based Screening Strategies Relative to the No Screening Strategy Based on the Mean Values Across the 4 CISNET Models under the base-case analysis Using (A) the PLCOm2012 Risk Prediction Model and (B) the Lung Cancer Death Risk Assessment Tool (LCDRAT) Risk Prediction Model.

¶The screening strategies are labeled as follows: For categorical age-smoking strategies, frequency (A–annual)–age start–age stop–minimum pack-years–maximum years since quitting; For risk model-based strategies, frequency (A–annual)–age start–age stop–6-year lung cancer risk threshold per the risk prediction model specified

*Strategies in bold text are the cost-effective strategies (defined as those strategies with an ICER lower than $100,000) relative to the strategy that precedes it on the efficiency frontier.

†All outcomes are discounted at a 3% annual rate.

Abbreviations: QALY, quality-adjusted life-years; USPSTF, U.S. Preventive Services Task Force; WTP, willingness-to-pay threshold; CISNET, Cancer Intervention and Surveillance Modeling Network.

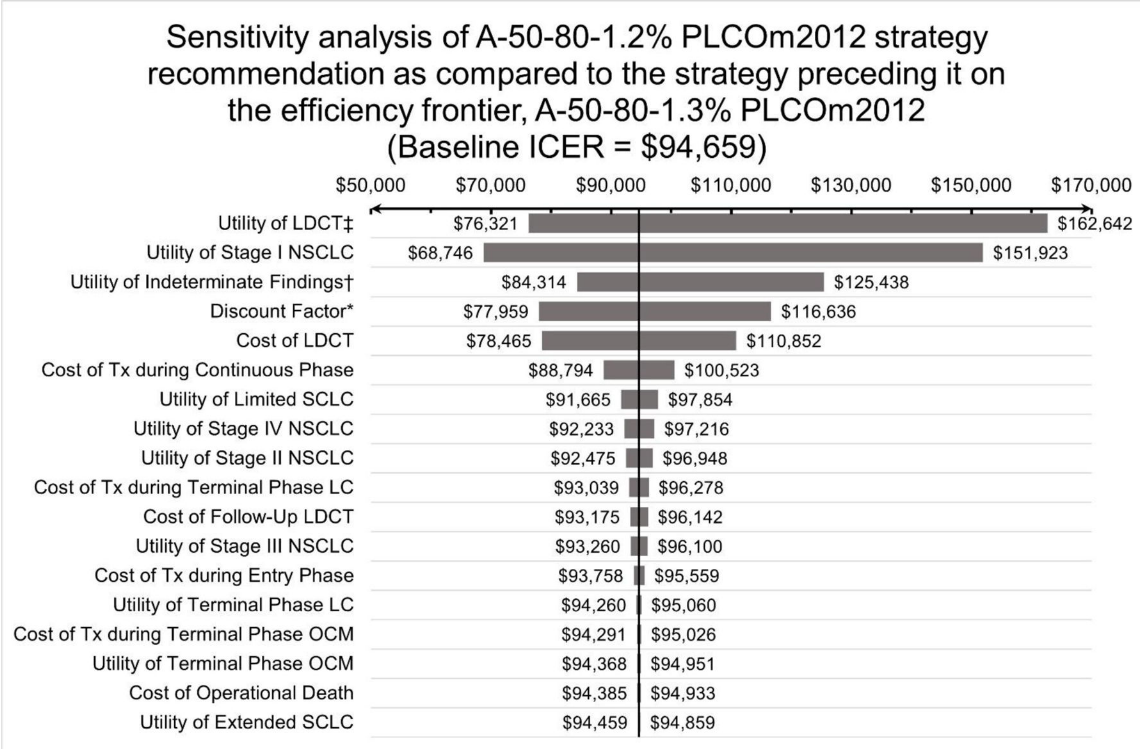

Figure 2.

Univariate Sensitivity Analyses (±25% of their base-case value unless otherwise indicated) of the 1.2% 6-year PLCOm2012 risk strategies that start screening at age 50 years relative to their preceding strategy on the efficiency frontier (1.3% 6-year PLCOm2012 risk strategy) from the base-case analysis.

‡minimum utility was −1 day per LDCT exam; maximum utility was 0 days per LDCT exam

†minimum utility was −0.02 per indeterminate finding; maximum utility was −0.005 per indeterminate finding

*minimum discounting factor was 1%; maximum discounting factor was 5%

The screening strategies are labeled as follows: frequency (A–annual)–age start–age stop–6-year lung cancer risk threshold per the risk prediction model specified

Abbreviations: ICER, incremental cost-effectiveness ratio; PLCO, Prostate, Lung, Colorectal and Ovarian Screening Trial, LDCT, low-dose computed tomography; NSCLC, non-small cell lung cancer; Tx, treatment; LC, lung cancer; SCLC, small cell lung cancer; OCM, other causes of mortality.

Table 1.

Base-Case Analysis Using the PLCOm2012 Risk Prediction Model.

Additional health benefits gained, and costs incurred from risk model-based screening strategies Using the PLCOm2012 Risk Prediction Model relative to the No Screening strategy per 100,000 individuals alive at age 45 with no prior lung cancer diagnosis and their respective incremental cost effectiveness ratios (ICERs) based on the average values across the 4 CISNET models.

Strategies denoted in bold text comprised the cost-effectiveness efficiency frontier.

Screening Strategy	Additional Costs Incurred to the No Screening Strategy, million 2020 US $ (model range)	Additional QALYs Accrued from Screening Relative to the No Screening Strategy, n (model range)	ICER (based on QALY) vs No Screening, 2020 US $ per QALY gained (model range)	ICER (based on QALYs) vs. Strategy Preceding it on the Efficiency Frontier, 2020 US $ per QALY gained (model range)
No Screening	$0	0	NA	NA
A-55-80-2.2% PLCOm2012	$51,931,287	1,336	$38,865	Weakly Dominated ($38,865)
A-50-80-2.2% PLCOm2012	**$52,002,812**	**1,338**	**$38,847**	**$38,847**
A-55-80-2.0% PLCOm2012	$56,810,234	1,420	$39,993	Weakly Dominated ($58,743)
A-50-80-2.0% PLCOm2012	**$56,992,252**	**1,428**	**$39,905**	**$55,714**
A-55-80-1.8% PLCOm2012	$62,528,608	1,503	$41,586	Weakly Dominated ($73,454)
A-50-80-1.8% PLCOm2012	$63,078,811	1,521	$41,446	Weakly Dominated ($64,919)
A-55-80-1.7% PLCOm2012	$65,623,264	1,544	$42,479	Weakly Dominated ($74,014)
A-50-80-1.7% PLCOm2012	$66,468,174	1,571	$42,298	Weakly Dominated ($66,164)
A-55-80-30-15 (2013 USPSTF)	$66,519,606	1,421	$46,795	Strongly Dominated (−$1,425,040)
A-55-80-1.6% PLCOm2012	$68,905,550	1,593	$43,235	Weakly Dominated ($71,976)
A-50-80-1.6% PLCOm2012	**$70,233,361**	**1,632**	**$43,030**	**$64,912**
A-55-80-1.5% PLCOm2012	$72,587,371	1,641	$44,231	Weakly Dominated ($264,953)
A-50-80-1.5% PLCOm2012	$74,507,098	1,685	$44,210	Weakly Dominated ($80,480)
A-55-80-1.4% PLCOm2012	$76,532,995	1,689	$45,306	Weakly Dominated ($110,399)
A-50-80-1.4% PLCOm2012	**$79,037,632**	**1,741**	**$45,372**	**$80,175**
A-55-80-1.3% PLCOm2012	$80,622,944	1,731	$46,569	Strongly Dominated ($−147,302)
A-50-80-1.3% PLCOm2012	**$83,982,177**	**1,797**	**$46,731**	**$89,680**
A-55-80-1.2% PLCOm2012	$85,130,409	1,774	$47,977	Strongly Dominated ($−50,475)
A-50-80-30-15	$85,736,541	1,588	$53,966	Strongly Dominated ($−8,417)
A-55-80-1.1% PLCOm2012	$89,611,084	1,818	$49,282	Weakly Dominated ($265,843)
A-55-80-20-15	$89,674,227	1,678	$53,435	Strongly Dominated ($−47,851)
A-50-80-1.2% PLCOm2012	**$89,681,756**	**1,857**	**$48,285**	**$94,659**

Screening Strategy	Additional Costs Incurred to the No Screening Strategy, million 2020 US $ (model range)	Additional QALYs Accrued from Screening Relative to the No Screening Strategy, n (model range)	ICER (based on QALY) vs No Screening, 2020 US $ per QALY gained (model range)	ICER (based on QALYs) vs. Strategy Preceding it on the Efficiency Frontier, 2020 US $ per QALY gained (model range)
A-55-80-1.0% PLCOm2012	$94,357,570	1,858	$50,777	Weakly Dominated ($5,050,396)
A-50-80-1.1% PLCOm2012	$96,027,274	1,914	$50,163	Weakly Dominated ($111,445)
A-55-80-0.9% PLCOm2012	$99,648,273	1,897	$52,526	Weakly Dominated ($250,616)
A-50-80-1.0% PLCOm2012	**$102,964,181**	**1,977**	**$52,055**	**$110,105**
A-55-80-0.8% PLCOm2012	$105,619,756	1,939	$54,467	Strongly Dominated (−$68,364)
A-50-80-0.9% PLCOm2012	**$110,941,735**	**2,036**	**$54,467**	**$135,497**
A-55-80-0.7% PLCOm2012	$112,417,377	1,974	$56,922	Strongly Dominated (−$23,828)
A-50-80-20-15 (2021 USPSTF)	$116,109,362	1,857	$62,514	Strongly Dominated (−$28,783)
A-50-80-0.8% PLCOm2012	**$119,980,323**	**2,087**	**$57,464**	**$177,016**
A-55-80-0.6% PLCOm2012	$120,487,811	2,009	$59,957	Strongly Dominated (−$6,477)
A-50-80-0.7% PLCOm2012	**$130,042,132**	**2,139**	**$60,779**	**$194,791**
A-55-80-0.5% PLCOm2012	$130,389,883	2,049	$63,614	Strongly Dominated (−$3,869)
A-50-80-0.6% PLCOm2012	**$140,582,980**	**2,180**	**$64,478**	**$258,743**
A-50-80-0.5% PLCOm2012	**$152,844,752**	**2,225**	**$68,684**	**$272,444**

[*] The screening strategies are labeled as follows: For categorical age-smoking strategies, frequency (A–annual)–age start–age stop–minimum pack-years–maximum years since quitting; For risk model-based strategies, frequency (A–annual)–age start–age stop–6-year lung cancer risk threshold per the risk prediction model specified.

Note: The efficiency frontier comprises of the strategies denoted in bold text.

Abbreviations: QALY, quality-adjusted life-years; USPSTF, U.S. Preventive Services Task Force; ICER, incremental cost-effectiveness ratio; CISNET, Cancer Intervention and Surveillance Modeling Network; PLCOm2012, Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial modified 2012 risk prediction model.

Table 2.

Screening Outcomes and Utilization Rates Using the PLCOm2012 Risk Prediction Model.

Clinical outcomes and utilization of LDCT by screening programs based on the average across the 4 CISNET models for a cohort of 100,000 persons alive at age 45 years, with no prior lung cancer diagnosis. Strategies denoted in bold text comprised the cost-effectiveness efficiency frontier under the base-case analysis.

Screening Strategy	Persons ever-screened, %	LDCT Screens, n	Total Lung Cancer Cases, n	Screen-detected Lung Cancer Cases, n	Overdiagnosis[†], %	Total Lung Cancer Deaths, n	Lung Cancer Deaths Averted, n	Lung Cancer Mortality Reduction, %
No Screening	NA	NA	5,075	NA	NA	3,988	NA	NA
A-50-80-20-15 (2021 USPSTF)	22.6	420,553	5,152	1,295	5.9	3,521	467	11.7
A-50-80-30-15	15.0	291,575	5,138	1,068	5.9	3,608	380	9.5
A-50-80-0.5% PLCOm2012	**32.0**	**637,426**	**5,180**	**1,710**	**6.2**	**3,374**	**614**	**15.4**
A-50-80-0.6% PLCOm2012	**30.0**	**577,395**	**5,178**	**1,665**	**6.2**	**3,395**	**593**	**14.9**
A-50-80-0.7% PLCOm2012	**28.2**	**526,150**	**5,176**	**1,622**	**6.2**	**3,413**	**576**	**14.4**
A-50-80-0.8% PLCOm2012	**26.6**	**479,972**	**5,174**	**1,582**	**6.3**	**3,430**	**559**	**14.0**
A-50-80-0.9% PLCOm2012	**25.1**	**438,777**	**5,171**	**1,540**	**6.3**	**3,449**	**540**	**13.5**
A-50-80-1.0% PLCOm2012	**23.9**	**403,254**	**5,170**	**1,501**	**6.3**	**3,464**	**525**	**13.2**
A-50-80-1.1% PLCOm2012	22.7	372,216	5,168	1,463	6.4	3,480	508	12.7
A-50-80-1.2% PLCOm2012	**21.7**	**344,519**	**5,166**	**1,427**	**6.4**	**3,496**	**493**	**12.4**
A-50-80-1.3% PLCOm2012	**20.7**	**319,642**	**5,165**	**1,388**	**6.5**	**3,510**	**478**	**12.0**
A-50-80-1.4% PLCOm2012	**19.8**	**298,086**	**5,163**	**1,356**	**6.5**	**3,524**	**464**	**11.6**
A-50-80-1.5% PLCOm2012	19.0	278,448	5,162	1,322	6.6	3,538	451	11.3
A-50-80-1.6% PLCOm2012	**18.3**	**260,797**	**5,160**	**1,289**	**6.6**	**3,550**	**438**	**11.0**
A-50-80-1.7% PLCOm2012	17.6	245,264	5,159	1,257	6.7	3,565	423	10.6
A-50-80-1.8% PLCOm2012	17.0	230,814	5,157	1,226	6.7	3,577	412	10.3
A-50-80-2.0% PLCOm2012	**15.8**	**205,802**	**5,154**	**1,169**	**6.8**	**3,599**	**389**	**9.8**
A-50-80-2.2% PLCOm2012	**14.7**	**184,998**	**5,151**	**1,116**	**6.8**	**3,620**	**368**	**9.2**
A-55-80-20-15	20.6	331,326	5,151	1,234	6.2	3,553	435	10.9
A-55-80-30-15 (2013 USPSTF)	14.1	228,348	5,137	1,016	6.1	3,635	354	8.9
A-55-80-0.5% PLCOm2012	31.4	562,664	5,180	1,656	6.4	3,402	586	14.7
A-55-80-0.6% PLCOm2012	29.5	511,319	5,178	1,614	6.4	3,422	566	14.2

Screening Strategy	Persons ever-screened, %	LDCT Screens, n	Total Lung Cancer Cases, n	Screen-detected Lung Cancer Cases, n	Overdiagnosis†, %	Total Lung Cancer Deaths, n	Lung Cancer Deaths Averted, n	Lung Cancer Mortality Reduction, %
A-55-80-0.7% PLCOm2012	27.7	468,778	5,176	1,575	6.4	3,437	551	13.8
A-55-80-0.8% PLCOm2012	26.2	434,033	5,174	1,540	6.4	3,452	537	13.5
A-55-80-0.9% PLCOm2012	24.8	403,164	5,172	1,504	6.4	3,468	520	13.0
A-55-80-1.0% PLCOm2012	23.7	376,792	5,170	1,470	6.5	3,480	508	12.7
A-55-80-1.1% PLCOm2012	22.6	353,236	5,168	1,438	6.5	3,492	496	12.4
A-55-80-1.2% PLCOm2012	21.6	331,516	5,166	1,406	6.5	3,506	482	12.1
A-55-80-1.3% PLCOm2012	20.6	310,395	5,164	1,372	6.5	3,518	470	11.8
A-55-80-1.4% PLCOm2012	19.8	291,482	5,163	1,343	6.6	3,530	458	11.5
A-55-80-1.5% PLCOm2012	19.0	273,801	5,161	1,312	6.6	3,543	445	11.2
A-55-80-1.6% PLCOm2012	18.3	257,667	5,160	1,281	6.7	3,555	433	10.9
A-55-80-1.7% PLCOm2012	17.6	243,228	5,159	1,251	6.7	3,568	420	10.5
A-55-80-1.8% PLCOm2012	17.0	229,535	5,157	1,222	6.7	3,578	410	10.3
A-55-80-2.0% PLCOm2012	15.8	205,393	5,154	1,167	6.8	3,600	388	9.7
A-55-80-2.2% PLCOm2012	14.7	184,889	5,151	1,116	6.8	3,621	368	9.2

* The screening strategies are labeled as follows: For categorical age-smoking strategies, frequency (A–annual)–age start–age stop–minimum pack-years–maximum years since quitting; For risk model-based strategies, frequency (A–annual)–age start–age stop–6-year lung cancer risk threshold per the risk prediction model specified.

† Overdiagnosis was defined as the excess lung cancer cases in the screening vs. the no screening scenario, divided by the number of screen-detected lung cancer cases in the screening scenario

Abbreviations: LDCT, low-dose computed tomography; USPSTF, U.S. Preventive Services Task Force; CISNET, Cancer Intervention and Surveillance Modeling Network.

Table 3.

Base-Case Analysis Using the LCDRAT Model.

Additional health benefits gained, and costs incurred from risk model-based screening strategies Using the LCDRAT Risk Prediction Model relative to the No Screening strategy per 100,000 individuals alive at age 45 with no prior lung cancer diagnosis and their respective incremental cost effectiveness ratios (ICERs) based on the average values across the 4 CISNET models.

Strategies denoted in bold text comprised the cost-effectiveness efficiency frontier.

Screening Strategy	Additional Costs Incurred to the No Screening Strategy, million 2020 US $ (model range)	Additional QALYs Accrued from Screening Relative to the No Screening Strategy, n (model range)	ICER (based on QALY) vs No Screening, 2020 US $ per QALY gained (model range)	ICER (based on QALYs) vs. Strategy Preceding it on the Efficiency Frontier, 2020 US $ per QALY gained (model range)
No Screening	$0	0	NA	NA
A-55-80-2.2% LCDRAT	**$51,661,619**	**1,298**	**$39,796**	**$39,796**
A-50-80-2.2% LCDRAT	$51,661,619	1,298	$39,796	Weakly Dominated ($39,796)
A-50-80-2.0% LCDRAT	**$56,887,368**	**1,387**	**$40,993**	**$58,329**
A-55-80-2.0% LCDRAT	$56,888,295	1,387	$40,994	Strongly Dominated ($−24,180)
A-55-80-1.8% LCDRAT	$62,829,047	1,483	$42,359	Weakly Dominated ($62,214)
A-50-80-1.8% LCDRAT	**$62,842,162**	**1,483**	**$42,356**	**$62,091**
A-55-80-30-15 (2013 USPSTF)	$66,519,605	1,421	$46,795	Strongly Dominated ($−59,192)
A-50-80-1.7% LCDRAT	**$66,848,407**	**1,541**	**$43,352**	**$68,675**
A-55-80-1.7% LCDRAT	$66,861,638	1,540	$43,391	Strongly Dominated ($−12,304)
A-55-80-1.6% LCDRAT	$69,907,510	1,582	$44,167	Weakly Dominated ($74,962)
A-50-80-1.6% LCDRAT	**$70,083,155**	**1,586**	**$44,171**	**$72,432**
A-55-80-1.5% LCDRAT	$73,766,904	1,631	$45,215	Weakly Dominated ($82,158)
A-50-80-1.5% LCDRAT	$74,248,144	1,641	$45,227	Weakly Dominated ($75,667)
A-55-80-1.4% LCDRAT	$77,646,789	1,676	$46,301	Weakly Dominated ($83,728)
A-50-80-1.4% LCDRAT	**$78,824,273**	**1,703**	**$46,277**	**$74,932**
A-55-80-1.3% LCDRAT	$81,713,928	1,721	$47,460	Weakly Dominated ($156,573)
A-50-80-1.3% LCDRAT	$82,957,510	1,752	$47,332	Weakly Dominated ($83,720)
A-50-80-30-15	$85,736,540	1,588	$53,966	Strongly Dominated ($−60,331)
A-55-80-1.2% LCDRAT	$86,204,812	1,770	$48,692	Weakly Dominated ($110,001)
A-50-80-1.2% LCDRAT	**$88,600,638**	**1,820**	**$48,666**	**$83,362**
A-55-80-20-15	$89,674,226	1,678	$53,435	Strongly Dominated ($−7,540)
A-55-80-1.1% LCDRAT	$92,258,356	1,823	$50,589	Weakly Dominated ($1,171,649)

Screening Strategy	Additional Costs Incurred to the No Screening Strategy, million 2020 US $ (model range)	Additional QALYs Accrued from Screening Relative to the No Screening Strategy, n (model range)	ICER (based on QALY) vs No Screening, 2020 US $ per QALY gained (model range)	ICER (based on QALYs) vs. Strategy Preceding it on the Efficiency Frontier, 2020 US $ per QALY gained (model range)
A-50-80-1.1% LCDRAT	**$94,746,515**	**1,883**	**$50,297**	**$97,284**
A-55-80-1.0% LCDRAT	$98,097,694	1,871	$52,407	Strongly Dominated ($−281,819)
A-50-80-1.0% LCDRAT	**$101,584,480**	**1,941**	**$52,311**	**$117,493**
A-55-80-0.9% LCDRAT	$104,409,660	1,918	$54,434	Strongly Dominated ($−118,437)
A-50-80-0.9% LCDRAT	**$109,685,029**	**2,005**	**$54,700**	**$128,085**
A-55-80-0.8% LCDRAT	$112,030,313	1,968	$56,908	Strongly Dominated ($−64,129)
A-50-80-20-15 (2021 USPSTF)	$116,109,362	1,857	$62,514	Strongly Dominated ($−43,448)
A-50-80-0.8% LCDRAT	**$119,182,025**	**2,070**	**$57,561**	**$145,327**
A-55-80-0.7% LCDRAT	$120,884,274	2,023	$59,741	Strongly Dominated ($−36,160)
A-50-80-0.7% LCDRAT	**$130,415,640**	**2,146**	**$60,753**	**$147,585**
A-55-80-0.6% LCDRAT	$131,289,693	2,074	$63,301	Strongly Dominated ($−12,036)
A-50-80-0.6% LCDRAT	**$143,738,815**	**2,216**	**$64,836**	**$189,526**
A-55-80-0.5% LCDRAT	$144,141,879	2,111	$68,252	Strongly Dominated ($−3,837)
A-50-80-0.5% LCDRAT	**$160,443,427**	**2,268**	**$70,715**	**$321,708**

* The screening strategies are labeled as follows: For categorical age-smoking strategies, frequency (A–annual)–age start–age stop–minimum pack-years–maximum years since quitting; For risk model-based strategies, frequency (A–annual)–age start–age stop–6-year lung cancer risk threshold per the risk prediction model specified.

Note: The efficiency frontier comprises of the strategies denoted in bold text.

Abbreviations: QALY, quality-adjusted life-years; USPSTF, U.S. Preventive Services Task Force; ICER, incremental cost-effectiveness ratio; CISNET, Cancer Intervention and Surveillance Modeling Network; LCDRAT, Lung Cancer Death Risk Assessment Tool risk prediction model.