ORIGINAL RESEARCH

Annals of Internal Medicine

Cost-Effectiveness Analysis of Lung Cancer Screening in the United States

A Comparative Modeling Study

Steven D. Criss, BS; Pianpian Cao, MPH; Mehrad Bastani, PhD; Kevin ten Haaf, PhD; Yufan Chen, MPH; Deirdre F. Sheehan, MPH; Erik F. Blom, MD; Iakovos Toumazis, PhD; Jihyoun Jeon, PhD; Harry J. de Koning, MD, PhD; Sylvia K. Plevritis, PhD; Rafael Meza, PhD; and Chung Yin Kong, PhD

Background: Recommendations vary regarding the maximum age at which to stop lung cancer screening: 80 years according to the U.S. Preventive Services Task Force (USPSTF), 77 years according to the Centers for Medicare & Medicaid Services (CMS), and 74 years according to the National Lung Screening Trial (NLST).

Objective: To compare the cost-effectiveness of different stopping ages for lung cancer screening.

Design: By using shared inputs for smoking behavior, costs, and quality of life, 4 independently developed microsimulation models evaluated the health and cost outcomes of annual lung cancer screening with low-dose computed tomography (LDCT).

Data Sources: The NLST; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SEER (Surveillance, Epidemiology, and End Results) program; Nurses' Health Study and Health Professionals Follow-up Study; and U.S. Smoking History Generator.

Target Population: Current, former, and never-smokers aged 45 years from the 1960 U.S. birth cohort.

Time Horizon: 45 years.

Perspective: Health care sector.

Intervention: Annual LDCT according to NLST, CMS, and USPSTF criteria.

Outcome Measures: Incremental cost-effectiveness ratios (ICERs) with a willingness-to-pay threshold of $100 000 per quality-adjusted life-year (QALY).

Results of Base-Case Analysis: The 4 models showed that the NLST, CMS, and USPSTF screening strategies were cost-effective, with ICERs averaging $49 200, $68 600, and $96 700 per QALY, respectively. Increasing the age at which to stop screening resulted in a greater reduction in mortality but also led to higher costs and overdiagnosis rates.

Results of Sensitivity Analysis: Probabilistic sensitivity analysis showed that the NLST and CMS strategies had higher probabilities of being cost-effective (98% and 77%, respectively) than the USPSTF strategy (52%).

Limitation: Scenarios assumed 100% screening adherence, and models extrapolated beyond clinical trial data.

Conclusion: All 3 sets of lung cancer screening criteria represent cost-effective programs. Despite underlying uncertainty, the NLST and CMS screening strategies have high probabilities of being cost-effective.

Primary Funding Source: CISNET (Cancer Intervention and Surveillance Modeling Network) Lung Group, National Cancer Institute.

Ann Intern Med. 2019;171:796-804. doi:10.7326/M19-0322 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 5 November 2019.

The National Lung Screening Trial (NLST) demonstrated that screening high-risk smokers with low-dose computed tomography (LDCT) could reduce lung cancer mortality by 20% versus chest radiography (1). On the basis of the NLST's findings, lung cancer screening was recommended by the U.S. Preventive Services Task Force (USPSTF) in 2013 and the U.S. Centers for Medicare & Medicaid Services (CMS) in 2015, ensuring private insurance and Medicare coverage, respectively. The guideline eligibility criteria match the enrollment criteria of the NLST (current or former smokers aged 55 to 74 years; smoking history of at least 30 pack-years; and for former smokers, fewer than 15 years since quitting), except the USPSTF and CMS recommend screening up to age 80 and 77 years, respectively (1–3).

The USPSTF chose criteria that are likely to maximize the benefits and minimize the harms of lung cancer screening, without explicitly considering cost factors in its decision making (4). However, the estimated number of persons eligible for lung cancer screening may range from 7 million to 12 million (5–7), so understanding the lung cancer and cost outcomes of the screening alternatives is essential as it becomes more commonly used in the United States.

Previous studies evaluated the cost-effectiveness of lung cancer screening in the United States and elsewhere, although the specific screening strategies evaluated, assumptions used, and respective results have varied widely (7–17). In these studies, lung cancer screening resulted in incremental cost-effectiveness ratios (ICERs) ranging from $11 000 per quality-adjusted life-year (QALY) to $207 000 per QALY (7–11, 13, 15, 16). However, in these analyses, either a single lung

See also:

Editorial comment 851

Web-Only
Supplement

cancer screening program was compared with no screening or the screening programs evaluated were not consistent with current U.S. guidelines, because many of these analyses predate the CMS and USPSTF recommendations.

To compare current screening eligibility criteria in the United States, our comparative modeling study used standardized model inputs and allowed different models to produce independent results for possible cross-validation (18). By using 4 independent, validated models (from Erasmus Medical Center, Harvard Medical School–Massachusetts General Hospital, University of Michigan, and Stanford University) in the CISNET (Cancer Intervention and Surveillance Modeling Network) Lung Group of the National Cancer Institute (NCI), this study estimated cost, effectiveness, and cost-effectiveness outcomes for a no-screening and 3 screening strategies based on the NLST, CMS, and USPSTF eligibility criteria from the perspective of the U.S. health care sector.

METHODS

Population

To account for age, period, and cohort effects in estimating each person's lifetime smoking exposure history, the 4 microsimulation models simulated outcomes from each screening strategy for 1 million individual men and 1 million individual women from the 1960 U.S. birth cohort from age 45 to death or to a maximum age of 90 years, as defined later. Study of the target population began at age 45 to provide sufficient time for prevalent lung cancers to develop before screening age, allowing the simulated populations to better mimic the likely existing pool of persons in a screening program. Smoking histories for each person were simulated by the CISNET Lung Group's Smoking History Generator (SHG) (19–22), which was developed to provide stochastic simulation of smoking history and other-cause mortality inputs specific to age, birth cohort, and sex (more information may be found at https://cisnet.cancer.gov/lung). Standardized inputs from the SHG include rate of smoking initiation, smoking intensity, rate of smoking cessation, and non–lung cancer death (corrected for smoking behavior) (19–25). The SHG allows the models to account for the elevated risk for death from various smoking-related comorbid conditions, such as congestive heart failure and stroke, among others.

Screening

Three screening strategies—the NLST, CMS, and USPSTF criteria—that assumed a 100% rate of adherence to screening were evaluated against a scenario in which no screening occurred. The NSLT screening eligibility criteria included persons aged 55 to 74 years who had a smoking history of at least 30 pack-years and either currently smoked or quit smoking within the previous 15 years. The CMS and USPSTF criteria were similar but increased the upper age limit for screening eligibility to 77 and 80 years, respectively.

Model Descriptions, Calibration, and Validation

Whereas randomized trials, such as the NLST, establish efficacy, modeling can complement those data by exploring starting and stopping ages for screening as well as screening frequencies, which would be impractical in trials. The various approaches to developing the 4 microsimulation models allowed a robust assessment of alternative screening guidelines (**Table 1**). Each model simulated individual-level lung cancer histories, including age and stage at diagnosis, whether screening was performed, earlier diagnosis and stage shifts related to screening, histologic subtype, rate of disease progression, and survival after diagnosis (26–29). The Erasmus, Michigan, and Stanford models each used a 2-stage clonal expansion model, which simulates the biological growth of cancer cells from initiation of precancerous cells to malignant transformation, to relate individual smoking history to age-specific lung cancer incidence or mortality risk (22, 30–32). The Harvard–Massachusetts General Hospital model used logistic regression models and Gompertz functions for tumor initiation and progression, respectively, to simulate individual lung cancer history (32, 33).

Each model was calibrated extensively to reproduce observed lung cancer incidence and mortality data from U.S. epidemiologic studies (**Table 1**) (26, 34–37). First, the models were calibrated to the lung cancer incidence and mortality data from the NLST, then they were validated by using data from participants in the PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial who would have been eligible for screening in the NLST (26). The PLCO lung cancer incidence and mortality curves used years since randomization, with follow-up data collected between 2002 and 2010. The models were calibrated further to enable extrapolation to persons in the PLCO data set who did not meet NLST eligibility criteria (never-smokers and light smokers) (26). Detailed calibration and validation methods for each model were described previously (26, 35–37). **Supplement Figures 1** to **5** (available at Annals.org) provide model outcomes for the composition of smoker type, lung cancer incidence, cumulative lung cancer cases, lung cancer mortality, and cumulative lung cancer deaths.

Costs

The 4 models also shared standardized cost inputs to enhance their comparability. Two types of costs were used—those related to screening and diagnostic procedures and those related to lung cancer treatment. Relevant procedures included chest radiography, screening LDCT, follow-up LDCT, bronchoscopy, mediastinoscopy, needle biopsy, video-assisted thoracoscopic surgery, and positron emission tomography/CT. Procedure costs were sourced from the CMS by using Current Procedural Terminology codes (**Supplement Table 2**, available at Annals.org) (38). Methods for determining lung cancer treatment costs were based on a primary data analysis of the SEER (Surveillance, Epidemiology, and End Results)–Medicare data set (39, 40). Treatment costs were converted to 2018 U.S. dollars by

adjusting Part A claims using the CMS Prospective Payment System hospital price index and Part B claims using the Medicare economic index (39, 41, 42). Procedure costs were sourced from the CMS at 2018 prices (38). **Supplement Table 2** describes the SEER–Medicare cost analysis and cost input parameters.

Base-Case Outcomes

Primary study outcomes were the ICERs for each screening strategy, calculated as the incremental cost divided by incremental QALYs gained, where QALYs adjusted survival for standardized age-based quality-of-life utilities and disutilities associated with the different stages of lung cancer progression (**Supplement Table 3**, available at Annals.org) (43–45) to account for quality-of-life reductions due to age-related comorbid conditions and to cancer. To calculate aggregate cost, the total number of procedures and total life-years spent in each phase of cancer care were multiplied by their respective costs. Life-years, QALYs, and costs were discounted at an annual rate of 3% (46, 47). We considered ICERs falling below a societal willingness-to-pay (WTP) threshold of $100 000 per QALY to be cost-effective (48). Secondary outcomes included mortality reduction and overdiagnosis (49). Results reflect the averaged results from the 4 models standardized to 100 000 persons alive at age 45 years from the 1960 birth cohort.

Sensitivity Analyses

Scenario-based sensitivity analyses explored the effect of 4 plausible alternative cases for certain model parameters. The first 2 scenarios varied cost by 15% for total LDCT examinations and cumulative costs in the continuation phase of lung cancer treatment, because they were the largest components of the procedure and treatment cost categories, respectively. The third scenario varied treatment costs for persons younger than 65 years by 15% to address uncertainty regarding costs for these underrepresented persons in the SEER–Medicare data set. The fourth scenario reduced screening adherence from 100% to 45%, with each person having a 45% probability of attending each screening LDCT examination each time (6). Additional sensitivity analyses that excluded persons with limited life expectancy and varied incidence rates may be found in the **Supplement** (available at Annals.org).

Probabilistic sensitivity analysis involved sampling the value of all cost and quality-of-life (utility) variables from their probability distributions and reevaluating the screening strategies in 100 000 iterations (details in **Supplement Tables 3** to **5**, available at Annals.org). Because including natural history parameters would be computationally prohibitive and because each model uses them differently, we excluded natural history parameters from the probabilistic sensitivity analysis.

Role of the Funding Source

The funding source had no role in the design of the study; the collection, analysis, and interpretation of the data; or the decision to approve publication of the finished manuscript.

RESULTS

No Screening

For 100 000 persons alive at age 45 years, the 4 models projected that a no-screening scenario would result in 5370 (range, 4170 to 6690) lung cancer diagnoses (**Table 2** and **Supplement Figure 6**, available at Annals.org) and 4230 (range, 3190 to 5480) lung cancer deaths by age 90 (**Table 2** and **Supplement Figure 7**, available at Annals.org) at an aggregated cost of $295 million (range, $249 million to $337 million), with 8% due to procedure costs and 92% to treatment costs.

Table 1. Overview of Microsimulation Models

Variable	Erasmus (MISCAN-Lung)	Harvard-MGH (Lung Cancer Policy Model)	University of Michigan	Stanford (Lung Cancer Outcomes Simulator)
Data sources used for calibration	NHS/HPFS, SEER, NLST, PLCO	SEER, NLST, PLCO	NHS/HPFS, NLST, PLCO, U.S. lung cancer mortality data	NHS/HPFS, SEER, NLST, PLCO
Central smoking dose–response module	2-stage clonal expansion model	Probabilistic by histology	2-stage clonal expansion model	2-stage clonal expansion model
Lung cancer stages modeled	IA, IB, II, IIIA, IIIB, IV	IA1, IA2, IB, II, IIIA, IIIB, IV	IA1, IA2, IB, II, IIIA, IIIB, IV	Early (I–II) and advanced (III–IV)
Stage progression	Markov state transition by histology	Based on tumor volume and metastatic burden	Backward model based on histology and stage at lung cancer incidence	Based on tumor volume and metastatic burden
Lung cancer survival	By sex, histology, and stage; based on SEER 18 (2004–2010)	Calibrated to SEER 18 (2004–2013)	By sex, histology, stage, and age at diagnosis; based on SEER 18 (2005–2012)	Based on SEER 18 (1988–2003)
Screening sensitivity model	By stage and histology	By size (millimeters) and location in lung (central or peripheral)	By stage and histology	By size (millimeters) and histology
General mechanism of screening effect	Cure model	Earlier-stage detection from the natural history model	Earlier-stage detection and cure model	Implicit, stage-shift model
Follow-up procedures algorithm	Implicit, based on NLST	Explicit, based on Fleischner and Lung-RADS guidelines	Implicit, based on NLST	Explicit, based on Lung-RADS guidelines

Lung-RADS = Lung Imaging Reporting and Data System; MGH = Massachusetts General Hospital; MISCAN = Microsimulation Screening Analysis; NHS/HPFS = Nurses' Health Study/Health Professionals Follow-up Study; NLST = National Lung Screening Trial; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SEER = Surveillance, Epidemiology, and End Results.

Table 2. Summary of Averaged Clinical Outcomes and Cost-Effectiveness Results*

Strategy†	Lung Cancer Cases, *n*		Lung Cancer Deaths, *n*	Overdiagnosis Rate, %‡	Total Cost, *$ (million)*	Life-Years, *n (million)*	QALYs, *n (million)*	ICER, *$*	
	Total	Screen Detected						Per Life-Year	Per QALY
No screening	**5370**	–	**4230**	–	**295**	**2.79834**	**2.32753**	–	–
Minimum	4170	–	3190	–	249	2.78528	2.31784	–	–
Maximum	6690	–	5480	–	337	2.81018	2.33669	–	–
NLST (stop at age 74)	**5410**	**941**	**3900**	**6**	**382**	**2.80099**	**2.32952**	**36 400**	**49 200**
Minimum	4180	208	3050	4	342	2.78637	2.31865	28 400	36 300
Maximum	6750	1490	5040	9	452	2.81422	2.33958	52 100	70 000
CMS (stop at age 77)	**5430**	**1110**	**3840**	**6**	**388**	**2.80115**	**2.32962**	**42 600**	**68 600**
Minimum	4190	227	3030	5	347	2.78643	2.31869	35 600	54 300
Maximum	6770	1750	4970	10	461	2.81444	2.33973	57 100	92 300
USPSTF (stop at age 80)	**5450**	**1250**	**3800**	**7**	**393**	**2.80124**	**2.32967**	**51 900**	**96 700**
Minimum	4190	244	3010	5	352	2.78647	2.31871	45 200	74 800
Maximum	6790	1970	4910	11	467	2.81458	2.33981	66 400	122 000

CMS = Centers for Medicare & Medicaid Services; ICER = incremental cost-effectiveness ratio; NLST = National Lung Screening Trial; QALY = quality-adjusted life-year; USPSTF = U.S. Preventive Services Task Force.
* For a cohort of 100 000 persons alive at age 45 years. Boldface signifies the averaged result from the 4 models.
† *Minimum* and *Maximum* refer to minimum and maximum estimates among the 4 models, respectively.
‡ The overdiagnosis rate up to age 90 years 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 (49).

Life expectancy per person at age 45 averaged 36.6 years (range, 36.4 to 36.9 years) (Supplement Figure 8, available at Annals.org) and quality-adjusted life expectancy averaged 23.3 QALYs (range, 23.2 to 23.4 QALYs).

Screening Results

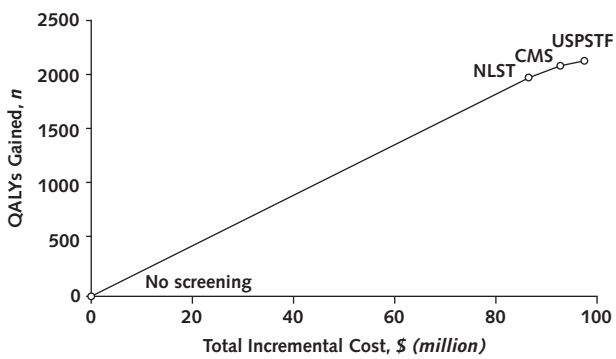
Primary Outcomes

Each of the 4 models predicted that all 3 screening strategies would be on the efficient frontier (Figure 1 and Table 2). For 100 000 persons alive at age 45 (Table 2), screening based on NLST eligibility criteria diagnosed 44 (range, 19 to 59) additional lung cancers and prevented 331 (range, 144 to 457) lung cancer deaths versus no screening, leading to an additional 2650 life-years (range, 1090 to 4040 life-years) and 1990 QALYs (range, 815 to 3160 QALYs) gained. The averaged aggregate cost for NLST screening (with 19% due to procedure costs and 81% to treatment costs) was $86 million (range, $57.0 million to $115 million) higher than no screening, producing an average cost-effective ICER of $49 200 (range, $36 300 to $70 000) per QALY versus no screening.

Compared with the NLST strategy, the CMS screening eligibility criteria yielded 16 (range, 3 to 22) additional cases of lung cancer diagnosed and 51 (range, 19 to 72) lung cancer deaths avoided, with 160 life-years (range, 61 to 220 life-years) and 100 QALYs (range, 38 to 141 QALYs) gained per 100 000 persons, respectively. The averaged aggregate cost on the basis of the CMS criteria was estimated to be $6.36 million (range, $3.48 million to $9.05 million) per 100 000 persons higher than that of the NLST strategy, with total procedure and treatment costs making up 20% and 80%, respectively. Each model predicted that screening based on the CMS criteria would achieve an ICER below the WTP threshold compared with screening based on the NLST criteria, with an average ICER of $68 600 (range, $54 300 to $92 300) per QALY.

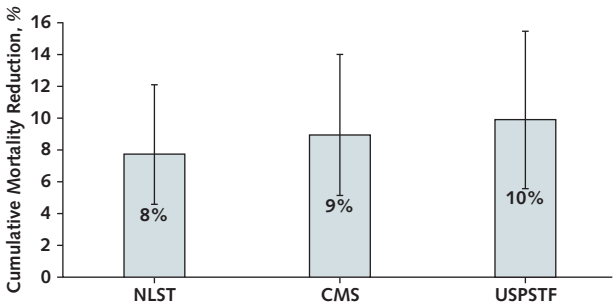
Relative to the CMS strategy, the USPSTF eligibility criteria diagnosed 18 (range, 4 to 28) additional lung cancer cases and prevented 42 (range, 15 to 61) lung cancer deaths, yielding an additional 93 life-years (range, 38 to 141 life-years) and 51 QALYs (range, 21 to 85 QALYs) gained per 100 000 persons. The averaged aggregate cost was $4.56 million (range, $2.52 million to $6.37 million) higher than that of the CMS strategy,

Figure 1. Efficient frontier for no screening and for the NLST, CMS, and USPSTF screening strategies.



The figure shows the average incremental cost per QALY per 100 000 persons alive at age 45 years. *Efficient frontier* represents successive strategies that provide the greatest incremental effectiveness per incremental cost (the incremental cost-effectiveness ratio being the inverse of the slope between 2 points on the frontier). CMS = Centers for Medicare & Medicaid Services; NLST = National Lung Screening Trial; QALY = quality-adjusted life-year; USPSTF = U.S. Preventive Services Task Force.

Figure 2. Cumulative mortality reduction by screening strategy.



Kaplan–Meier survival curves, by strategy, are provided in Supplement Figure 9 (available at Annals.org). Error bars indicate the range of estimates by the 4 models; they are not CIs. CMS = Centers for Medicare & Medicaid Services; NLST = National Lung Screening Trial; USPSTF = U.S. Preventive Services Task Force.

with procedure and treatment costs comprising 20% and 80%, respectively. The 4 models projected that ICERs for the USPSTF versus the CMS criteria would fall just below the WTP threshold, with an average ICER of $96 700 (range, $74 800 to $122 000) per QALY.

Additional Outcomes

Cumulative lung cancer mortality increased when screening was stopped at younger ages; therefore, compared with no screening, the reduction in mortality rose as the maximum age for screening eligibility increased: 8% (range, 5% to 12%) with the NLST, 9% (range, 5% to 14%) with the CMS, and 10% (range, 6% to 16%) with the USPSTF criteria (**Figure 2** and lung cancer–specific Kaplan–Meier survival curves in **Supplement Figure 9**, available at Annals.org). Fewer women than men were screening-eligible smokers; therefore, women had a lower reduction in mortality with screening (**Supplement Table 6**, available at Annals.org). Overdiagnosis rates increased along with maximum age for screening eligibility, averaging 6% (range, 4% to 9%) for the NLST (to age 75), 6% (range, 5% to 10%) for the CMS (to age 77), and 7% (range, 5% to 11%) for the USPSTF criteria (to age 80) (**Table 2**).

Cost Outcomes

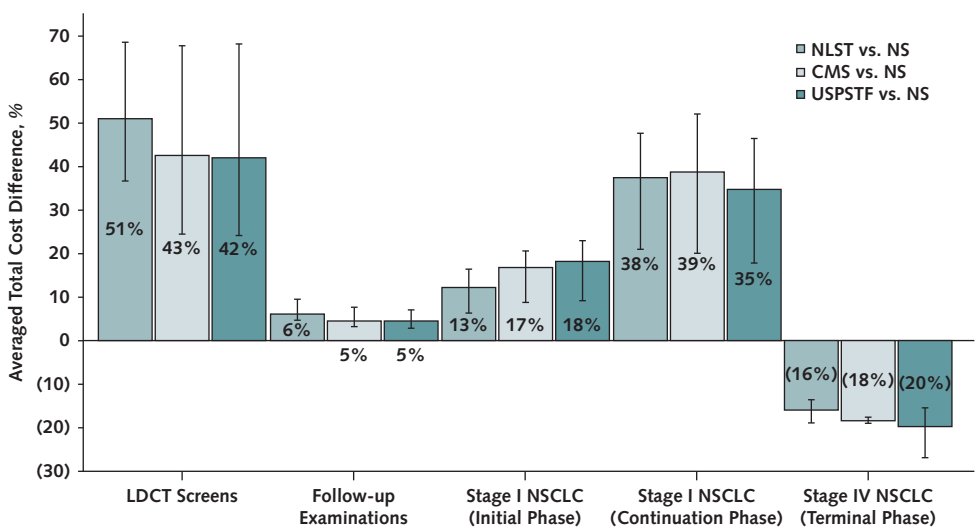
The items that constituted the greatest proportions of total cost difference between screening and no screening were increases in LDCT screening, follow-up scans, initial-phase treatment of stage I non–small cell lung cancer (NSCLC), and continuation-phase NSCLC stage I treatment, as well as decreases in terminal-phase NSCLC stage IV treatment for those who died of lung cancer (**Figure 3**). **Supplement Figures 10** and **11** (available at Annals.org) show cost components as a share of total procedure and treatment costs, respectively. **Supplement Table 7** (available at Annals.org) provides results from the use of screening and diagnostic procedures.

Sensitivity Analyses

Scenario-Based Sensitivity Analyses

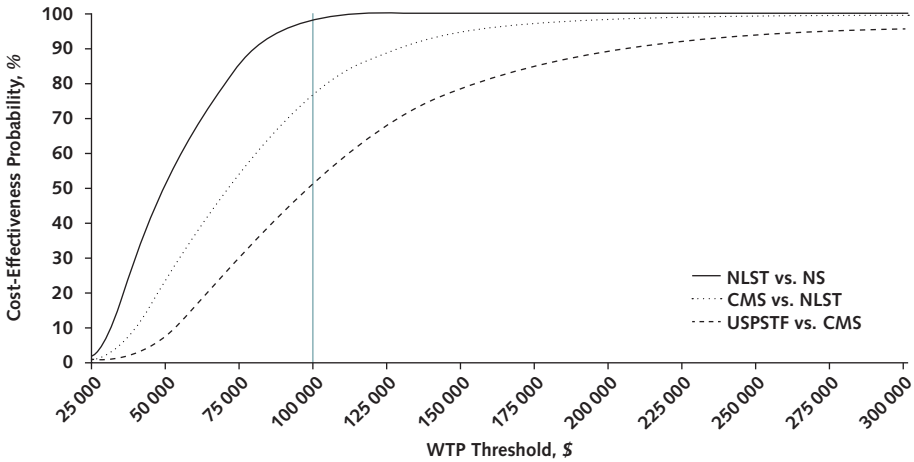
Although varying the cost of LDCT examinations increased or decreased the average ICER for the 3 screening strategies by only $4000 to $7000 per QALY for the 4 models (**Supplement Tables 8** and **9**, available at Annals.org), the ICER for the USPSTF strategy crossed the WTP threshold (at $103 000 per QALY) when the cost of LDCT increased by 15%. Varying the cost of continuation-phase treatment for all persons

Figure 3. Averaged percentage of total cost differences among screening strategies.



Cost components selected represent the 5 greatest contributors to total cost difference. Error bars indicate the range of estimates by the 4 models; they are not CIs. CMS = Centers for Medicare & Medicaid Services; LDCT = low-dose computed tomography; NLST = National Lung Screening Trial; NS = no screening; NSCLC = non-small cell lung cancer; USPSTF = U.S. Preventive Services Task Force.

Figure 4. Probabilistic sensitivity analysis for base-case:cost-effectiveness acceptability curves for the screening strategies.



The vertical line marks the WTP threshold used in this study. CMS = Centers for Medicare & Medicaid Services; NLST = National Lung Screening Trial; NS = no screening; USPSTF = U.S. Preventive Services Task Force; WTP = willingness-to-pay.

had a similar effect on the ICERs for the strategies (Supplement Tables 10 and 11, available at Annals.org), with the ICER for the USPSTF strategy again surpassing the WTP threshold—at $102 000 per QALY—with a 15% increase in treatment cost. Adjusting treatment costs by 15% for persons younger than 65 years altered the ICERs for each strategy by less than $2000 per QALY (Supplement Tables 12 and 13, available at Annals.org). When we decreased the screening adherence rate to 45%, the ICER for each strategy decreased by $4000 to $7000 per QALY (Supplement Table 14, available at Annals.org). If screening could be stopped when life expectancy fell below 5 years, or if cancer incidence increased by 40%, the ICERs decreased by $3000 to $12 000 per QALY for the NLST, $14 900 to $15 500 per QALY for the CMS, and $18 700 to $19 500 per QALY for the USPSTF criteria, to an ICER of $77 200 to $78 000 per QALY in sensitivity analyses (Supplement Tables 15 and 17, available at Annals.org). If cancer incidence fell by 40%, the ICERs increased by $22 300 per QALY for the NLST, $24 900 per QALY for the CMS, and $39 300 per QALY for the USPSTF strategy, to an ICER of $136 000 per QALY (Supplement Table 16, available at Annals.org).

Probabilistic Sensitivity Analysis

In the probabilistic sensitivity analysis, the NLST screening strategy remained on the efficient frontier in 89% (range, 74% to 97%), the CMS strategy in 94% (range, 84% to 100%), and the USPSTF strategy in 99% (range, 96% to 100%) of 100 000 iterations. At the WTP threshold of $100 000 per QALY, the NLST screening strategy had a 98% (range, 95% to 100%) probability of being cost-effective, whereas the CMS and USPSTF strategies had a 77% (range, 54% to 91%) and 52% (range, 22% to 74%) probability, respectively (Figure 4).

DISCUSSION

In evaluating the cost-effectiveness of current lung cancer screening guidelines with different upper age criteria—NLST, CMS, and USPSTF—our 4 CISNET models showed that all 3 strategies resulted in ICERs below the commonly referenced U.S. WTP threshold of $100 000 per QALY. All 4 models estimated that the NLST and CMS screening criteria would be cost-effective, and 2 models predicted that the USPSTF screening criteria would be cost-effective. Increasing the upper age for screening resulted in a greater reduction in mortality but also led to higher procedure and treatment costs and overdiagnosis rates.

The agreement among 4 independently developed models with standardized inputs demonstrates the robustness of the conclusion that both the NLST and CMS criteria are cost-effective strategies. The models did not come to a consensus regarding the cost-effectiveness of the USPSTF screening strategy; however, the averaged ICER for this strategy was in the cost-effective range. The borderline cost-effectiveness of the USPSTF criteria points to the importance of critically assessing the upper age limit for a screening program. Because the USPSTF strategy extends screening to age 80, additional costs are incurred without commensurate gains in QALYs. The USPSTF strategy's elevated ICER is explained primarily by the shorter life expectancy and lower quality of life of persons older than 77 years at diagnosis because of increased mortality due to smoking-related comorbid conditions and fewer available treatment options.

Sensitivity analyses provided support for the robustness of the results with regard to input parameters. Varying the cost of LDCT examinations and continuation-phase treatment led to moderate changes in the averaged ICERs for the 3 strategies, with the ICER for the USPSTF strategy increasing to $103 000 and $102 000

per QALY when LDCT examination and continuation-phase treatment costs, respectively, were increased by 15%. Such changes may be expected given that LDCT scans and continuation-phase costs make up the greatest proportion of procedural and overall treatment costs, respectively (**Supplement Figures 10** and **11**, available at Annals.org). Adjusting treatment costs for persons younger than 65 years had a minimal effect on the cost-effectiveness outcomes. A decrease in the assumed adherence rate led to modestly lower ICERs for each screening strategy. In the probabilistic sensitivity analysis in which only quality-of-life and cost input parameters were varied, the NLST and CMS screening strategies had high probabilities of remaining cost-effective at the $100 000 per QALY WTP threshold (NLST, 98%; CMS, 77%), whereas the USPSTF strategy had a lower probability of being cost-effective (52%).

Other modeling analyses from the literature have drawn mixed conclusions regarding the cost-effectiveness of certain screening strategies (8–12, 50, 51). These studies, however, cannot be directly compared with the results of our analysis, because they did not specifically model the NLST, CMS, and USPSTF screening strategies as competing choices on the same efficient frontier, and in some cases they assessed the cost-effectiveness of screening in different populations. The cost-effectiveness of screening in the NLST was studied by Black and colleagues (8), who found that LDCT screening based on the NLST criteria was cost-effective, albeit at a higher ICER than our study estimates ($81 000 per QALY). However, this analysis pertained only to a cross-sectional sample of persons in the NLST and did not assess the criteria when applied to a U.S. birth cohort with follow-up to age 90 (8). Moreover, our study was performed from the health care sector perspective, whereas Black and colleagues (8) used the societal perspective; therefore, their screening costs included time lost, transportation, and caregiver expenses, leading to a higher ICER compared with no screening.

Our study had limitations. First, we assumed a 100% screening adherence rate to project outcomes in the case of perfect clinician and population adherence to a screening program. Other cancer screening programs have estimated adherence rates ranging from 46.4% to 85.8% (52), suggesting that 100% may not be a likely expectation for lung cancer screening adherence. We studied the effect of a more achievable adherence rate by performing a sensitivity analysis with 45% adherence (6). Second, the results from NELSON (Dutch–Belgian Randomized Lung Cancer Screening Trial) showing decreased lung cancer mortality due to CT screening were released recently (53); however, our analysis does not include the screening criteria used in NELSON because the smoking eligibility criteria, categorization of findings, and nodule management differed from those currently used in the United States. We also do not have complete information on the number of LDCTs performed and the downstream effects of this program, because this study has yet to be published in full. The NELSON study showed a greater reduction in lung cancer mortality than that observed in the NLST, which may have led to improved cost-effectiveness; however, at this time we cannot accurately predict the costs of such a program or the drivers that led to a greater decrease in mortality. Third, we did not include risk-based screening strategies in our study. Because neither the CMS nor the USPSTF have issued recommendations regarding risk-based screening, patients who qualify for risk-based screening yet fall outside currently recommended screening guidelines would not have mandated Medicare or private insurance coverage. In addition, no strong consensus exists regarding which of the many risk-based prediction models would be recommended for implementation. For these reasons, we plan to address the cost-effectiveness of risk-based screening in future CISNET projects. Existing studies suggest that targeting high-risk smokers might make screening more efficient, although higher-risk patients are more costly to screen and have a shorter life expectancy (7, 13). Finally, in extrapolating the NLST's results to older age groups, questions may arise regarding how the models captured the tradeoffs between higher lung cancer risk in older age groups (potentially leading to greater benefit) and shorter life expectancy or lower quality of life (likely attenuating that benefit). By using QALYs to measure effectiveness and the well-validated SHG to more accurately simulate competing causes of death in older persons, our models explicitly examined the interplay of these tradeoffs for higher-risk persons.

In conclusion, this comparative analysis suggests that the NLST, CMS, and USPSTF screening strategies represent cost-effective programs based on a common U.S. WTP threshold, with the USPSTF criteria yielding the most benefit but also the highest cost. When all the uncertainties in quality of life and cost inputs are considered, the NLST and CMS screening strategies have high probabilities of being cost-effective, with the CMS strategy yielding the greatest increase in life-years and QALYs gained and the greatest reduction in lung cancer mortality.

From Massachusetts General Hospital, Boston, Massachusetts (S.D.C., Y.C.); University of Michigan, Ann Arbor, Michigan (P.C., J.J., R.M.); Stanford University School of Medicine, Stanford, California (M.B., I.T., S.K.P.); Erasmus University Medical Center, Rotterdam, the Netherlands (K.T., E.F.B., H.J.D.); Massachusetts General Hospital, Boston, Massachusetts, and Broad Institute, Cambridge, Massachusetts (D.F.S.); and Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (C.Y.K.).

Acknowledgment: The authors thank E.J. Feuer for scientific input and critical review of the work.

Grant Support: This study is based on research conducted by the NCI's CISNET (NCI grant U01-CA199284).

Disclosures: Dr. ten Haaf reports nonfinancial support from the International Association for the Study of Lung Cancer Strategic Screening Advisory Committee, grants from Sunnybrook Health Sciences (Toronto, Canada) and the University of Zurich, and grants and nonfinancial support from the

NELSON screening program outside the submitted work. Ms. Sheehan reports grants from the NCI during the conduct of the study. Dr. Blom reports grants from National Institutes of Health (NIH)/NCI during the conduct of the study and grants and nonfinancial support from the NELSON screening program outside the submitted work. Dr. de Koning reports grants from the NIH during the conduct of the study and was a principal investigator for NELSON. Dr. Plevritis reports grants from the NCI during the conduct of the study and has been a scientific consultant to Grail. Dr. Meza reports grants from the NIH during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-0322.

Reproducible Research Statement: *Study protocol*: Model details are available in Table 1; additional details may be found on the CISNET Web site (https://cisnet.cancer.gov/lung/profiles.html). *Statistical code*: An earlier version of the SHG is available by request (e-mail, shg-distrib@lung.cisnet-group.org). *Data set*: Smoking prevalence, initiation, cessation, and intensity rates are available in the publications listed under "Smoking History Generator" at https://resources.cisnet.cancer.gov/projects/#.

Corresponding Author: Chung Yin Kong, PhD, Institute for Technology Assessment, Massachusetts General Hospital, 101 Merrimac Street, Suite 1010, Boston, MA 02114; e-mail, joey@mgh-ita.org.

Current author addresses and author contributions are available at Annals.org.

References

1. **Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team.** Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395-409. [PMID: 21714641] doi:10.1056/NEJMoa1102873
2. **Moyer VA; U.S. Preventive Services Task Force.** Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160:330-8. [PMID: 24378917] doi:10.7326/M13-2771
3. **Jensen TS, Chin J, Ashby L, et al.** Decision Memo for Screening for Lung Cancer With Low Dose Computed Tomography (LDCT) (CAG-00439N). Baltimore: Centers for Medicare & Medicaid Services; 2015.
4. **U.S. Preventive Services Task Force.** USPSTF and Cost Considerations. Accessed at www.uspreventiveservicestaskforce.org/Page/Name/uspstf-and-cost-considerations on 30 September 2019.
5. **Jemal A, Fedewa SA.** Lung cancer screening with low-dose computed tomography in the United States–2010 to 2015 [Letter]. JAMA Oncol. 2017;3:1278-1281. [PMID: 28152136] doi:10.1001/jamaoncol.2016.6416
6. **Criss SD, Sheehan DF, Palazzo L, et al.** Population impact of lung cancer screening in the United States: projections from a microsimulation model. PLoS Med. 2018;15:e1002506. [PMID: 29415013] doi:10.1371/journal.pmed.1002506
7. **Cressman S, Peacock SJ, Tammemägi MC, et al.** The cost-effectiveness of high-risk lung cancer screening and drivers of program efficiency. J Thorac Oncol. 2017;12:1210-1222. [PMID: 28499861] doi:10.1016/j.jtho.2017.04.021
8. **Black WC, Gareen IF, Soneji SS, et al; National Lung Screening Trial Research Team.** Cost-effectiveness of CT screening in the national lung screening trial. N Engl J Med. 2014;371:1793-802. [PMID: 25372087] doi:10.1056/NEJMoa1312547
9. **Villanti AC, Jiang Y, Abrams DB, et al.** A cost-utility analysis of lung cancer screening and the additional benefits of incorporating smoking cessation interventions. PLoS One. 2013;8:e71379. [PMID: 23940744] doi:10.1371/journal.pone.0071379
10. **McMahon PM, Kong CY, Bouzan C, et al.** Cost-effectiveness of computed tomography screening for lung cancer in the United States. J Thorac Oncol. 2011;6:1841-8. [PMID: 21892105] doi:10.1097/JTO.0b013e31822e59b3
11. **Mahadevia PJ, Fleisher LA, Frick KD, et al.** Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. JAMA. 2003;289:313-22. [PMID: 12525232]
12. **Ten Haaf K, Tammemägi MC, Bondy SJ, et al.** Performance and cost-effectiveness of computed tomography lung cancer screening scenarios in a population-based setting: a microsimulation modeling analysis in Ontario, Canada. PLoS Med. 2017;14:e1002225. [PMID: 28170394] doi:10.1371/journal.pmed.1002225
13. **Kumar V, Cohen JT, van Klaveren D, et al.** Risk-targeted lung cancer screening: A cost-effectiveness analysis. Ann Intern Med. 2018;168:161-169. [PMID: 29297005] doi:10.7326/M17-1401
14. **Tomonaga Y, Ten Haaf K, Frauenfelder T, et al.** Cost-effectiveness of low-dose CT screening for lung cancer in a European country with high prevalence of smoking–A modelling study. Lung Cancer. 2018;121:61-69. [PMID: 29858029] doi:10.1016/j.lungcan.2018.05.008
15. **Yang SC, Lai WW, Lin CC, et al.** Cost-effectiveness of implementing computed tomography screening for lung cancer in Taiwan. Lung Cancer. 2017;108:183-191. [PMID: 28625633] doi:10.1016/j.lungcan.2017.04.001
16. **Field JK, Duffy SW, Baldwin DR, et al.** UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. Thorax. 2016;71:161-70. [PMID: 26645413] doi:10.1136/thoraxjnl-2015-207140
17. **Pyenson BS, Henschke CI, Yankelevitz DF, et al.** Offering lung cancer screening to high-risk Medicare beneficiaries saves lives and is cost-effective: an actuarial analysis. Am Health Drug Benefits. 2014;7:272-82. [PMID: 25237423]
18. **National Cancer Institute, Cancer Intervention and Surveillance Modeling Network.** Comparative Modeling. Accessed at https://cisnet.cancer.gov/modeling/comparative.html on 30 September 2019.
19. **Holford TR, Meza R, Warner KE, et al.** Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. JAMA. 2014;311:164-71. [PMID: 24399555] doi:10.1001/jama.2013.285112
20. **Holford TR, Levy DT, McKay LA, et al.** Patterns of birth cohort-specific smoking histories, 1965-2009. Am J Prev Med. 2014;46:e31-7. [PMID: 24439359] doi:10.1016/j.amepre.2013.10.022
21. **Jeon J, Meza R, Krapcho M, et al.** Chapter 5: Actual and counterfactual smoking prevalence rates in the U.S. population via microsimulation. Risk Anal. 2012;32 Suppl 1:S51-68. [PMID: 22882892] doi:10.1111/j.1539-6924.2011.01775.x
22. **Jeon J, Holford TR, Levy DT, et al.** Smoking and lung cancer mortality in the United States from 2015 to 2065: A comparative modeling approach. Ann Intern Med. 2018;169:684-693. [PMID: 30304504] doi:10.7326/M18-1250
23. **Feuer EJ, Levy DT, McCarthy WJ.** Chapter 1: the impact of the reduction in tobacco smoking on U.S. lung cancer mortality, 1975-2000: an introduction to the problem. Risk Anal. 2012;32 Suppl 1:S6-S13. [PMID: 22882893] doi:10.1111/j.1539-6924.2011.01745.x
24. **Anderson CM, Burns DM, Dodd KW, et al.** Chapter 2: birth-cohort-specific estimates of smoking behaviors for the U.S. population. Risk Anal. 2012;32 Suppl 1:S14-24. [PMID: 22882884] doi:10.1111/j.1539-6924.2011.01703.x
25. **Rosenberg MA, Feuer EJ, Yu B, et al.** Chapter 3: cohort life tables by smoking status, removing lung cancer as a cause of death. Risk Anal. 2012;32 Suppl 1:S25-38. [PMID: 22882890] doi:10.1111/j.1539-6924.2011.01662.x

26. **Meza R, ten Haaf K, Kong CY, et al.** Comparative analysis of 5 lung cancer natural history and screening models that reproduce outcomes of the NLST and PLCO trials. Cancer. 2014;120:1713-24. [PMID: 24577803] doi:10.1002/cncr.28623
27. **McMahon PM, Meza R, Plevritis SK, et al.** Comparing benefits from many possible computed tomography lung cancer screening programs: extrapolating from the National Lung Screening Trial using comparative modeling. PLoS One. 2014;9:e99978. [PMID: 24979231] doi:10.1371/journal.pone.0099978
28. **Han SS, Ten Haaf K, Hazelton WD, et al.** The impact of overdiagnosis on the selection of efficient lung cancer screening strategies. Int J Cancer. 2017;140:2436-2443. [PMID: 28073150] doi:10.1002/ijc.30602
29. **de Koning HJ, Meza R, Plevritis SK, et al.** Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. Ann Intern Med. 2014;160:311-20. [PMID: 24379002] doi:10.7326/M13-2316
30. **Hazelton WD, Clements MS, Moolgavkar SH.** Multistage carcinogenesis and lung cancer mortality in three cohorts. Cancer Epidemiol Biomarkers Prev. 2005;14:1171-81. [PMID: 15894668]
31. **Meza R, Hazelton WD, Colditz GA, et al.** Analysis of lung cancer incidence in the Nurses' Health and the Health Professionals' Follow-Up Studies using a multistage carcinogenesis model. Cancer Causes Control. 2008;19:317-28. [PMID: 18058248]
32. **McMahon PM, Hazelton WD, Kimmel M, et al.** Chapter 13: CISNET lung models: comparison of model assumptions and model structures. Risk Anal. 2012;32 Suppl 1:S166-78. [PMID: 22882887] doi:10.1111/j.1539-6924.2011.01714.x
33. **McMahon PM, Kong CY, Weinstein MC, et al.** Adopting helical CT screening for lung cancer: potential health consequences during a 15-year period. Cancer. 2008;113:3440-9. [PMID: 18988293] doi:10.1002/cncr.23962
34. **Oken MM, Hocking WG, Kvale PA, et al; PLCO Project Team.** Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA. 2011;306:1865-73. [PMID: 22031728] doi:10.1001/jama.2011.1591
35. **Caverly TJ, Cao P, Hayward RA, et al.** Identifying patients for whom lung cancer screening is preference-sensitive: a microsimulation study. Ann Intern Med. 2018;169:1-9. [PMID: 29809244] doi:10.7326/M17-2561
36. **Han SS, Erdogan SA, Toumazis I, et al.** Evaluating the impact of varied compliance to lung cancer screening recommendations using a microsimulation model. Cancer Causes Control. 2017;28:947-958. [PMID: 28702814] doi:10.1007/s10552-017-0907-x
37. **Ten Haaf K, van Rosmalen J, de Koning HJ.** Lung cancer detectability by test, histology, stage, and gender: estimates from the NLST and the PLCO trials. Cancer Epidemiol Biomarkers Prev. 2015;24:154-61. [PMID: 25312998] doi:10.1158/1055-9965.EPI-14-0745
38. **Centers for Medicare & Medicaid Services.** Physician Fee Schedule Look-Up Tool. Accessed at www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PFSlookup/index.html on 30 September 2019.
39. **Sheehan DF, Criss SD, Chen Y, et al.** Lung cancer costs by treatment strategy and phase of care among patients enrolled in Medicare. Cancer Med. 2019;8:94-103. [PMID: 30575329] doi:10.1002/cam4.1896
40. **National Cancer Institute, Division of Cancer Control and Population Sciences.** SEER-Medicare Linked Database. Accessed at https://healthcaredelivery.cancer.gov/seermedicare on 30 September 2019.
41. **Centers for Medicare & Medicaid Services.** Market Basket Data. Accessed at www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/MedicareProgramRatesStats/MarketBasketData.html on 30 September 2019.
42. **Centers for Medicare & Medicaid Services.** Trustees Report and Trust Funds. Accessed at www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/ReportsTrustFunds/index.html on 30 September 2019.
43. **Hanmer J, Lawrence WF, Anderson JP, et al.** Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Med Decis Making. 2006 Jul-Aug;26:391-400. [PMID: 16855127]
44. **Tramontano AC, Schrag DL, Malin JK, et al.** Catalog and comparison of societal preferences (utilities) for lung cancer health states: results from the Cancer Care Outcomes Research and Surveillance (CanCORS) study. Med Decis Making. 2015;35:371-87. [PMID: 25670839] doi:10.1177/0272989X15570364
45. **van den Hout WB, Kramer GW, Noordijk EM, et al.** Cost-utility analysis of short- versus long-course palliative radiotherapy in patients with non-small-cell lung cancer. J Natl Cancer Inst. 2006;98:1786-94. [PMID: 17179480]
46. **Sanders GD, Neumann PJ, Basu A, et al.** Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. JAMA. 2016;316:1093-103. [PMID: 27623463] doi:10.1001/jama.2016.12195
47. **Neumann PJ, Sanders GD, Russell LB, et al.** Cost-Effectiveness in Health and Medicine. New York: Oxford Univ Pr; 2017.
48. **Neumann PJ, Cohen JT, Weinstein MC.** Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. N Engl J Med. 2014;371:796-7. [PMID: 25162885] doi:10.1056/NEJMp1405158
49. **Patz EF Jr, Pinsky P, Gatsonis C, et al; NLST Overdiagnosis Manuscript Writing Team.** Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med. 2014;174:269-74. [PMID: 24322569] doi:10.1001/jamainternmed.2013.12738
50. **Raymakers AJN, Mayo J, Lam S, et al.** Cost-effectiveness analyses of lung cancer screening strategies using low-dose computed tomography: a systematic review. Appl Health Econ Health Policy. 2016;14:409-418. [PMID: 26873091] doi:10.1007/s40258-016-0226-5
51. **Pyenson BS, Sander MS, Jiang Y, et al.** An actuarial analysis shows that offering lung cancer screening as an insurance benefit would save lives at relatively low cost. Health Aff (Millwood). 2012;31:770-9. [PMID: 22492894] doi:10.1377/hlthaff.2011.0814
52. **Clarke TC, Soler-Vila H, Fleming LE, et al.** Trends in adherence to recommended cancer screening: the US population and working cancer survivors. Front Oncol. 2012;2:190. [PMID: 23293767] doi:10.3389/fonc.2012.00190
53. **de Koning HJ, Van Der Aalst CM, ten Haaf K, Oudkerk M.** Effects of volume CT lung cancer screening: mortality results of the NELSON randomised-controlled population based trial [Abstract]. Presented at IASLC 19th World Conference on Lung Cancer, Toronto, Ontario, Canada, 23-26 September 2018. Abstract no. PL02.05.

Current Author Addresses: Mr. Criss and Mr. Chen: Massachusetts General Hospital, 101 Merrimac Street, Suite 1010, Boston, MA 02114.
Ms. Cao and Drs. Jeon and Meza: University of Michigan School of Public Health, 1415 Washington Heights, SPH-II 5533, Ann Arbor, MI 48109.
Drs. Bastani, Toumazis, and Plevritis: Stanford University, 318 Campus Drive, S255, Stanford, CA 94305.
Drs. ten Haaf, Blom, and de Koning: Erasmus MC University Medical Center, PO Box 2040, 3000 CA Rotterdam, the Netherlands.
Ms. Sheehan: Broad Institute, 415 Main Street, Cambridge, MA 02142.
Dr. Kong: Institute for Technology Assessment, Massachusetts General Hospital, 101 Merrimac Street, Suite 1010, Boston, MA 02114.

Author Contributions: Conception and design: S.D. Criss, M. Bastani, I. Toumazis, S.K. Plevritis, R. Meza, C.Y. Kong.
Analysis and interpretation of the data: S.D. Criss, P. Cao, M. Bastani, K. ten Haaf, Y. Chen, D.F. Sheehan, E.F. Blom, I. Toumazis, J. Jeon, H.J. de Koning, S.K. Plevritis, R. Meza, C.Y. Kong.
Drafting of the article: S.D. Criss, D.F. Sheehan, R. Meza, C.Y. Kong.
Critical revision for important intellectual content: S.D. Criss, K. ten Haaf, E.F. Blom, H.J. de Koning, S.K. Plevritis, R. Meza, C.Y. Kong.
Final approval of the article: S.D. Criss, P. Cao, M. Bastani, K. ten Haaf, Y. Chen, D.F. Sheehan, E.F. Blom, I. Toumazis, J. Jeon, H.J. de Koning, S.K. Plevritis, R. Meza, C.Y. Kong.
Provision of study materials or patients: S.D. Criss, S.K. Plevritis, C.Y. Kong.
Statistical expertise: M. Bastani, K. ten Haaf, Y. Chen, H.J. de Koning, S.K. Plevritis, R. Meza, C.Y. Kong.
Obtaining of funding: H.J. de Koning, S.K. Plevritis, R. Meza, C.Y. Kong.
Administrative, technical, or logistic support: S.D. Criss, R. Meza, C.Y. Kong.
Collection and assembly of data: S.D. Criss, K. ten Haaf, D.F. Sheehan, I. Toumazis, R. Meza, C.Y. Kong.