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Article

ARTICLE

Cost-Effectiveness Analysis of Lung Cancer Screening Accounting for the Effect of Indeterminate Findings

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Abstract

Background: Numerous health policy organizations recommend lung cancer screening, but no consensus exists on the optimal policy. Moreover, the impact of the Lung CT screening reporting and data system guidelines to manage small pulmonary nodules of unknown significance (a.k.a. indeterminate nodules) on the cost-effectiveness of lung cancer screening is not well established.
Methods: We assess the cost-effectiveness of 199 screening strategies that vary in terms of age and smoking eligibility criteria, using a microsimulation model. We simulate lung cancer-related events throughout the lifetime of US-representative current and former smokers. We conduct sensitivity analyses to test key model inputs and assumptions.
Results: The cost-effectiveness efficiency frontier consists of both annual and biennial screening strategies. Current guidelines are not on the frontier. Assuming 4% disutility associated with indeterminate findings, biennial screening for smokers aged 50–70 years with at least 40 pack-years and less than 10 years since smoking cessation is the cost-effective strategy using $100 000 willingness-to-pay threshold yielding the highest health benefit. Among all health utilities, the cost-effectiveness of screening is most sensitive to changes in the disutility of indeterminate findings. As the disutility of indeterminate findings decreases, screening eligibility criteria become less stringent and eventually annual screening for smokers aged 50–70 years with at least 30 pack-years and less than 10 years since smoking cessation is the cost-effective strategy yielding the highest health benefit.
Conclusions: The disutility associated with indeterminate findings impacts the cost-effectiveness of lung cancer screening. Efforts to quantify and better understand the impact of indeterminate findings on the effectiveness and cost-effectiveness of lung cancer screening are warranted.

Lung cancer is the leading cause of cancer deaths in the United States (1). The US Preventive Services Task Force (USPSTF) recommends lung cancer screening (LCS) with low-dose computed tomography (LDCT) for asymptomatic individuals at high risk for lung cancer (2), based on the results of the National Lung Screening Trial (NLST) (3). Numerous other health policy organizations, including the Centers for Medicare & Medicaid Services (CMS), endorse LCS; however, no consensus exists on the optimal screening policy (2,4–8).

A main challenge facing LCS is the management of positive screening findings of unknown significance (hereon referred to as "indeterminate findings"). Small, predominantly benign lung nodules regularly appear on lung computed tomography (CT) exams of current and former smokers (9,10). However, their malignancy probability, albeit low, necessitates further surveillance with serial CT to assess their clinical significance, thereby inducing anxiety and distress (11,12). To reduce the high false-positive rates observed in the NLST (3) and standardize the

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diagnostic workup for indeterminate findings, the American College of Radiology developed the Lung CT screening reporting and data system (Lung-RADS), a standardized system for reporting and following up LDCT findings (13). A retrospective analysis of Lung-RADS to the NLST reports statistically significant reduction in the false-positive rate of LCS (14). However, Lung-RADS can introduce prolonged periods of uncertainty, thereby affecting individuals' quality of life.

Although cost-effectiveness analyses of LCS have been published (15–19), these analyses do not consider the quality-of-life effects of lung cancer screening, nor the benefits and harms of Lung-RADS. Consequently, the net effect on quality of life incurred by patients with indeterminate findings and the impact of Lung-RADS on the effectiveness and cost-effectiveness of LCS are not known. In this study, we assess the cost-effectiveness of LCS after incorporating the Lung-RADS guidelines to manage indeterminate findings for the US population.

Methods

We compared the health benefits and costs associated with LCS using a validated microsimulation model, developed within the Cancer Intervention and Surveillance Modeling Network, previously used to inform the USPSTF recommendation for LCS (20,21). We evaluated screening outcomes on the general US population born in 1950 because it represents the current targeted population, similar to the USPSTF analysis (2,20). We tested the cost-effectiveness of LCS on males and females separately and derived population estimates by aggregating our sex-specific results, using the single payer/insurer perspective.

Lung Cancer Risk and Disease Progression

We estimated individual's annual risk of lung cancer incidence using a lung carcinogenesis model, which translates smoking duration and intensity to annual lung cancer risk (22). We obtained US-representative smoking histories and smoking-specific other-causes mortalities using a validated smoking history generator (23,24). For every lung cancer case, we simulated sex-specific disease progression of various lung cancer subtypes (adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, and small-cell carcinoma) using a published and tested natural history model of lung cancer (25). As previously described, our microsimulation model was calibrated and validated on data from NLST and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial and matched the observed sex-specific lung cancer US mortality and incidence rates for the 1950 birth cohort obtained from the US Surveillance, Epidemiology, and End Results program (26) (Supplementary Figure 1, available online).

Screening Strategies

We superimposed the screening program of interest onto the natural history of the disease and simulated lung cancer-related events in the life history of 1 million men and women, separately. A simplified flowchart depicting the screening and diagnostic process is presented in Figure 1. We assessed the cost-effectiveness of annual and biennial screening strategies by varying the starting and stopping ages of screening between 50 and 65, and 70 and 80 years, respectively, with 5-year increments, and smoking exposure between 20, 30, and 40 pack-years, and 10, 15, and 20 years since smoking cessation for former smokers. For brevity, we denote a screening strategy as "screening interval"-"age start screening"-"age stop screening"-"smoking pack-years"-"years since quit"; for example, the USPSTF strategy is denoted as A-55-80-30-15.

Lung-RADS Implementation

For this analysis, our microsimulation model was updated to incorporate the latest version of the Lung-RADS guidelines, which has been developed and optimized for annual LCS (13). To mirror Lung-RADS for annual screening strategies, we considered a screening exam negative if assessed as Lung-RADS category 1 or 2; otherwise, the exam was considered positive. An individual with an indeterminate finding that was not assessed as lung cancer during follow-up returned to the general population and underwent screening while screen eligible. When investigating biennial strategies, we examined two different implementations of Lung-RADS: 1) original Lung-RADS and 2) modified Lung-RADS guidelines. In the latter, to address the higher lung cancer risk in individuals with indeterminate findings, we required at least two negative follow-up exams before an indeterminate case returned to biennial screening. A detailed description of our implementation of Lung-RADS is available in the Supplement (available online).

Also, we evaluated the counterfactual scenario whereby all indeterminate findings were assessed as Lung-RADS category 2 findings (hereon referred to as "Lung-RADS Category 2 Only" scenario). The rate of false-positive findings for the Lung-RADS Category 2 Only scenario was assumed to be negligible (27). This scenario is analyzed solely for comparison purposes because it provides a reference point that allows us to estimate the overall effect of indeterminate findings by removing both the beneficial effects accrued from following-up indeterminate findings (ie, increase in life-years) and the harmful effects of indeterminate findings (ie, disutility—a metric quantifying the negative consequences associated with an event—and cost of follow-up).

Health Utilities

We relied on literature-derived utilities associated with health states and interventions considered in our analysis (Table 1) (15,28). We defined diagnostic utilization rates based on expert opinion (AL) and treatment utilization rates based on data from the NLST (Supplementary Table 1, available online) (3). We assumed that lung cancer patients surviving more than five years after primary diagnosis with no further lung cancer events returned to normal health-state utilities.

Although several studies agree that the long-term effects of indeterminate findings are insignificant, they report differing impact on quality of life over the short-term (11,12,29–31). For our base-case analysis, we compared two values for the short-term disutility associated with indeterminate findings, specifically, 0% and 4%, as reported in the studies of Gareen et al. and van den Bergh et al., respectively (30,12). We assumed that the disutility persisted up to the first follow-up exam or death, whichever occurred first, and assumed to be negligible henceforth. For example, the 4% disutility associated with an indeterminate finding, when applied for 6 months, is equivalent to loss of approximately 7 days per individual per indeterminate finding.

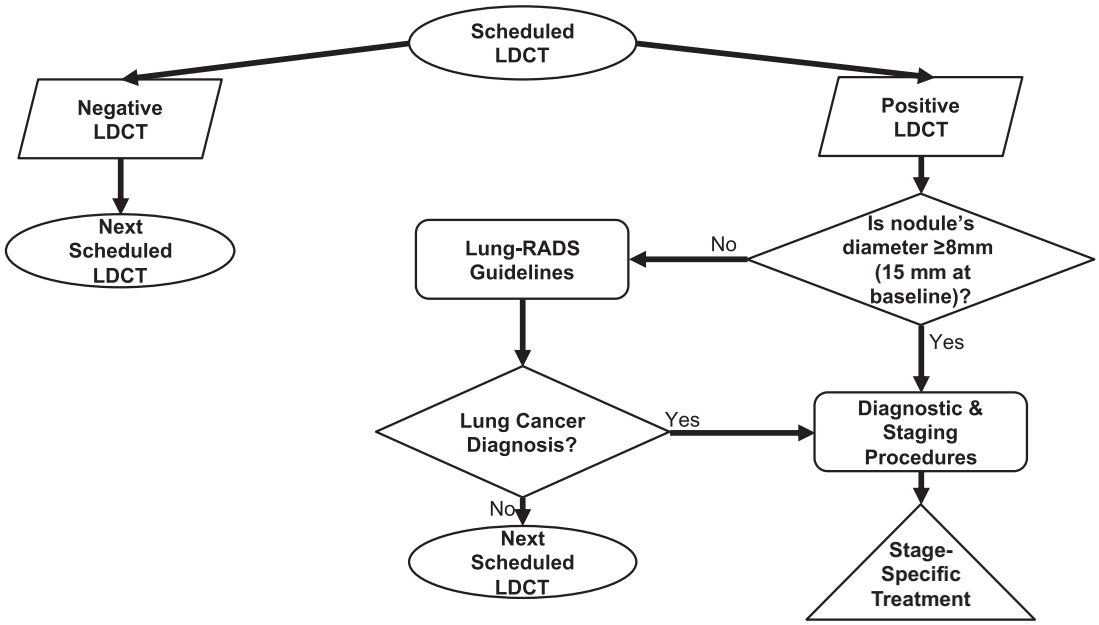

Figure 1. Flowchart of key clinical screening events. LDCT = low-dose computed tomography; Lung-RADS = Lung CT screening reporting and data system.

Costs

Costs associated with screening and diagnostic procedures were obtained from the Medicare reimbursement rates (32). Downstream treatment costs were allocated into three phases of care: initial (6 months from diagnosis), continuing (remaining life time between initial and terminal phases), and terminal (last 6 months of life). We obtained phase-specific cost estimates from related literature (33,34) (Table 1). We considered only direct medical costs related to screening and diagnostic LDCT exams, diagnostic workup, and treatment interventions, and omitted productivity and travel costs from our analysis. All costs were represented in 2018 US dollars.

Outcome Measures

Primary outcome measures included the incremental cost-effectiveness ratio (ICER), gained quality-adjusted life-years (QALYs), and costs relative to no screening; all outcomes were discounted at a 3% annual rate. We applied the two commonly used willingness-to-pay (WTP) thresholds of $50 000 and $100 000 per QALY saved to determine whether an intervention is cost-effective (35). Secondary outcome measures included lung cancer mortality reduction, rate of overdiagnosed cases (defined as the screen-detected cases that would not have been detected in the absence of screening), and number of false-positive findings.

Sensitivity Analyses

We tested the robustness of our findings through univariate sensitivity analyses. We varied the models' input parameters within a range (±20%, unless specified otherwise) around their base-case values (Table 1). Considering the high prevalence of indeterminate findings, we performed univariate sensitivity analysis around the disutility of indeterminate findings ranging its value between 0% and 8% (11,29,30). Also, we varied the false-positive rate of LCS (within ±50%) around the base-case value, based on the observed rates reported in the American College of Radiology Lung Cancer Screening Registry (36). Given the lack of empirical evidence around the false-positive rate in biennial strategies, we examined the cost-effectiveness of biennial screening strategies varying their false-positive rate (±20%) around their base-case value while keeping the false-positive rate for annual strategies fixed.

Results

We assessed the cost-effectiveness of 100 annual and 99 biennial (each under two Lung-RADS implementations) clinically relevant screening strategies. We followed individuals for their entire lifetime after excluding patients diagnosed with lung cancer before age 50 years.

Base-Case Analysis

With no disutility associated with indeterminate findings, the cost-effectiveness efficiency frontier was comprised of six annual and four biennial strategies (Figure 2A, Table 2). Using a WTP threshold of $100 000/QALY, all biennial and two annual strategies of the frontier were cost-effective relative to the strategy preceding them on the frontier. The most effective (ie, highest health benefit) cost-effective strategy was annual screening for smokers aged 50–70 years, with at least 30 pack-years and no more than 10 years since smoking cessation for former smokers, denoted A-50-70-30-10. It screened 21% of the US population, yielded 6% lung cancer-specific mortality reduction, and produced 2.8 million screening exams per 1 million individuals from the general population. Among the screening exams, 6% were positive, among which 94% were indeterminate findings and 92% were false-positive findings. Furthermore, 3% of the true-positive findings were overdiagnosed cases. The main cost driver for the A-50-70-30-10 strategy was the downstream treatment (53% of the total cost), followed by the cost of terminal care (34%), cost of detection (13%), and cost of shared decision making (<1%).

Table 1. Procedure rates, health state utilities, disutilities due to screening and treatment, and cost of alternative interventions included in our analysis

Input parameter	Base case	Sensitivity analysis range	Source
Health state			
Age, y			
50–59	0.861 (M), 0.837 (F)*		
60–69	0.840 (M), 0.811 (F)*	Not varied	(28)
70–79	0.802 (M), 0.771 (F)*		
≥80	0.782 (M), 0.724 (F)*		
Early-stage NSCLC			(15)
Screen detected	0.83*	0.66–0.99	
Otherwise detected	0.73*	0.58–0.88	
SCLC or advanced stage NSCLC	0.66*	0.53–0.79	(15)
Terminal year	0.62*	0.50–0.74	(17)
Surgery†	0.82*	0.78–0.86	(15)
Chemotherapy/radiation†	0.86*	0.83–0.89	(15)
Indeterminate finding‡	0.96*	0.92–1.00	(11, 12, 29, 30)
Screening outcomes			
False-positive rate	12.8% at baseline screen	5–20%	(14)
	5.3% for subsequent screens	1–10%	(14)
Invasive diagnostic procedure§	35%	28–42%	Expert opinion
False-positive findings referred to invasive procedures	2.7%	2.2–3.2%	(3)
Surgical mortality	1%	0–3%	(3)
Discounting			
Costs	3%	0–5%	(31)
Life-years	3%	0–5%	(31)
Cost of interventions‖			
Low-dose screening CT exam	242	194–291	(32)
Shared decision-making session	29	23–35	(32)
Diagnostic CT	242	194–291	(32)
Invasive diagnostic procedure	436	349–524	(32)
PET	1410	1128–1692	(32)
Surgery (monthly)			
First month from surgery	30 999	24 799–37 199	(33)
Initial phase of care	1046	837–1255	(33)
Continuing phase of care	1464	1172–1757	(33)
Chemotherapy, monthly			
Initial phase of care	7167	5734–8601	(33)
Continuing phase of care	5123	4098–6147	(33)
Radiation therapy, monthly			
Initial phase of care	5228	4182–6274	(33)
Continuing phase of care	2233	1786–2680	(33)
Chemotherapy and radiation, monthly			
Initial phase of care	7838	6270–9405	(33)
Continuing phase of care	3976	3181–4771	(33)
Best supporting care, monthly			
Initial phase of care	2155	1724–2586	(33)
Continuing phase of care	2210	1768–2652	(33)
Palliative care, monthly			
Death from lung cancer	13 377	10 701–16 052	(33)
Death from other causes	10 574	8459–12 689	(33)
Death due to lung cancer surgery	48 448	38 758–58 138	(34)

*Base case utility value for quality adjustment (sex). CT = computed tomography; F = female; M = male; NSCLC = non-small cell lung cancer; PET = positron emission tomography; SCLC = small cell lung cancer.

†Time frame: 1 month for surgery, 90 days for chemotherapy and radiation therapy.

‡Time frame: up to the first negative follow-up exam or death, whichever comes first.

§Based on expert opinion (AL).

‖Base case and sensitivity analysis range values are in 2018 US$.

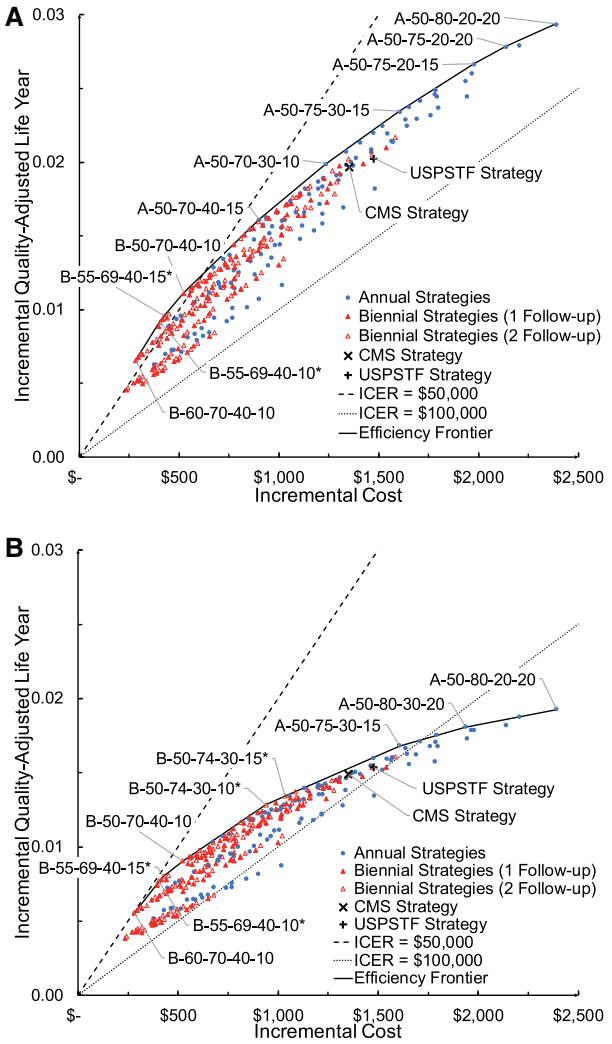

Figure 2. Cost-effectiveness efficiency frontier of lung cancer screening with low-dose computed tomography in asymptomatic individuals when the disutility associated with indeterminate findings is applied up to the first negative follow-up exam and is equal to **A)** 0% and **B)** 4%. X-S-E-P-Q represents efficient screening strategies where X = screening frequency (annual [A] and biennial [B]); S = starting age; E = stopping age; P = pack-years; Q = years since smoking cessation; X-S-E-P-Q* denotes strategies with modified Lung CT screening reporting and data system as their follow-up management for indeterminate findings. CMS = Centers for Medicare & Medicaid Services; ICER = incremental cost-effectiveness ratio; USPSTF = US Preventive Services Task Force.

With a 4% disutility associated with indeterminate findings, the cost-effectiveness efficiency frontier was comprised of three annual and six biennial strategies (Figure 2B, Table 2). However, only biennial strategies were cost-effective using a $100 000 WTP threshold: biennial screening for smokers aged 50–70 years, with at least 40 pack-years and less than 10 years since quit, denoted B-50-70-40-10, coupled with the original Lung-RADS guidelines, yielded the highest health benefit among the cost-effective strategies of the efficiency frontier. The B-50-70-40-10 strategy screened 14% of the population, resulted in 3% lung cancer-specific mortality reduction, and resulted in 920 000 screening exams per 1 million individuals from the general population.

The CMS and USPSTF guidelines were not on the efficiency frontier. The CMS and USPSTF strategies screened approximately 20% of the US population and yielded 8% and 9% lung cancer-specific mortality reduction, respectively. For the CMS and USPSTF guidelines, among all screens, 6% were positive and among all-positive screens, 92% were indeterminate cases, 89% were false-positive, and 5% of the screen-detected lung cancer cases were overdiagnosed. Interestingly, when we assumed no disutility associated with indeterminate findings, the CMS and USPSTF strategies were strongly dominated by other strategies included in our analysis. For higher levels of the disutility associated with indeterminate findings, current guidelines were not strongly dominated by other strategies, but were not cost-effective relative to no screening (Table 3).

When the health benefit accrued from LCS was based on unadjusted life-years, annual screening was cost-effective under $100 000 WTP threshold with notable reduction in the ICERs and less stringent eligibility criteria (Supplementary Figure 2, Supplementary Table 2, available online). Incremental cost-effectiveness analyses stratified by sex showed that LCS was more cost-effective in women compared to men (Supplementary Figure 3, Supplementary Tables 3–4, available online).

Effect of the Disutility Associated with Indeterminate Findings

We compared the efficiency frontiers for a range of values for the disutility of indeterminate findings (0%, 1%, 2%, 4%, 6%, 8%) and found that they differed substantially (Figure 3A; Supplementary Figure 4, Supplementary Table 5, available online). When the disutility of indeterminate findings were less than or equal to 1%, biennial screening was the cost-effective strategy with the highest health benefit under $50 000 per QALY WTP threshold, whereas, for the $100 000 per QALY WTP threshold, annual screening was the cost-effective strategy with the highest health benefit. As the disutility of indeterminate findings increased above 2%, the cost-effective strategy, regardless of the WTP threshold used, with the highest health benefit was based on biennial screening. Interestingly, the Lung-RADS Category 2 Only analysis produced an efficiency frontier that was comparable to the frontier with 2% disutility for indeterminate findings, although the strategies on the cost-effectiveness frontiers varied (see Figure 3A caption).

Figure 3B presents the percentage change in health benefit under different disutility levels associated with indeterminate findings, relative to our base-case disutility value of 4%, for the base-case efficient strategies. Comparing our base-case's efficient strategies with their counterpart using Lung-RADS Category 2 Only, we found that the health benefit accrued from biennial screening strategies reduced, whereas for annual screening strategies, it increased relative to our base-case analysis.

Also, we examined the effect of indeterminate findings when the false-positive rate associated with screening was plus or minus 50% around our base-case value (Supplementary Figure 5A, Supplementary Table 6, available online). The false-positive rate did not have a large effect on the cost-effectiveness efficiency frontier when the disutility of indeterminate findings was 0%. In contrast, when the disutility of indeterminate findings were 4%, the false-positive rate affected the efficiency frontier. In particular, when we increased the false-positive rate by 50%, the eligibility criteria for the cost-effective strategies were more stringent than the efficient strategies obtained from the base-case analysis, whereas when we

Table 2. Incremental cost-effectiveness ratios, screening outcomes, and costs associated with the efficient strategies resulting in our base-case analyses (assuming 0% and 4% disutility associated with indeterminate findings) for every 1 million individuals sampled from the general US population

No disutility associated with indeterminate findings											
Outcome	No screening	B-60-70-40-10	B-55-69-40-10*	B-55-69-40-15*	B-50-70-40-10	A-50-70-40-15	A-50-70-30-10	A-50-75-30-15	A-50-75-20-15	A-50-75-20-20	A-50-80-20-20
Incremental cost per person relative to no screening	NA	$282	$403	$426	$522	$903	$1236	$1607	$1980	$2140	$2391
Incremental QALY per person relative to no screening	NA	0.0065	0.0092	0.0096	0.0111	0.0161	0.0199	0.0235	0.0267	0.0279	0.0294
ICER relative to no screening	NA	$43 118	$43 993	$44 348	$46 873	$55 968	$62 154	$68 472	$74 175	$76 788	$81 387
ICER relative to the strategy preceding it on the frontier	NA	$43 118	$46 166	$51 940	$62 582	$76 279	$88 717	$103 485	$115 803	$136 226	$166 074
No. (%) people ever screened	NA	106 858 (12%)	119 101(13%)	124 620 (14%)	128 415 (14%)	131 997 (15%)	186 295 (21%)	195 314 (22%)	269 374 (30%)	279 021 (31%)	279 416 (31%)
LDCT screens	NA	502 328	695 099	756 081	921 002	1 910 921	2 819 754	3 519 883	4 614 854	5 110 738	5 531 169
Positive screenings	NA	40 614	52 061	55 937	65 818	118 980	172 302	214 584	280 464	308 426	335 122
Follow-up exams	NA	34 639	90 149	97 278	57 992	110 545	162 585	200 850	264 935	291 971	314 985
False-positives	NA	33 500	44 354	47 878	56 658	108 080	159 668	196 642	260 125	286 863	308 620
Overdiagnosed cases	NA	207	194	210	232	307	328	632	708	762	1224
Mortality reduction, %	NA	3	3	3	3	5	6	8	9	9	11
Deaths avoided	NA	1327	1555	1626	1805	2517	2959	4091	4667	4911	5891
Interval LC cases*	NA	14 633	12 203	11 931	12 665	11 401	9869	14 710	12 738	11 830	17 779
Early stage	NA	3876	3163	3075	3251	2960	2522	3805	3234	2971	4511
Advanced stage	NA	10 757	9040	8856	9413	8440	7346	10 906	9504	8859	13 268
Screen-detected LC cases	NA	6746	7511	7852	8738	10 124	11 703	16 499	18 661	19 729	24 124
Early stage	NA	6063	6854	7164	7971	9511	11 004	15 527	17 555	18 568	22 701
Advanced stage	NA	683	658	688	767	613	700	972	1106	1161	1423
Shared decision-making cost, million $	NA	3	3	4	4	4	5	6	8	8	8
Detection cost, million $	49	134	186	197	231	421	616	723	937	1025	1073
Screening LDCT	NA	79	120	130	169	349	533	634	836	919	964
Diagnostic LDCT	NA	6	16	18	12	22	31	37	49	54	56
Other non-invasive diagnostic procedures	5	5	5	5	5	5	5	5	5	5	5
Invasive diagnostic procedures	0	0	0	0	1	1	2	2	2	3	3
Staging	44	44	44	44	44	44	45	45	45	45	46
Treatment cost, million $	1988	2132	2190	2198	2249	2392	2495	2700	2815	2867	3021
Cost of terminal care, million $	1552	1573	1572	1573	1576	1584	1586	1606	1611	1615	1638

(continued)

4% disutility associated with indeterminate findings										
Characteristic	No screening	B-60-70-40-10	B-55-69-40-10*	B-55-69-40-15*	B-50-70-40-10	B-50-74-30-10*	B-50-74-30-15*	A-50-75-30-15	A-50-80-30-20	A-50-80-20-20
Incremental cost per person relative to no screening	NA	$282	$403	$426	$522	$940	$1033	$1607	$1936	$2391
Incremental QALY per person relative to no screening	NA	0.0055	0.0077	0.0080	0.0090	0.0128	0.0134	0.0168	0.0181	0.0193
ICER relative to no screening	NA	$50 905	$52 458	$53 149	$57 690	$73 195	$76 909	$95 592	$107 153	$124 147
ICER relative to the strategy preceding it on the frontier	NA	$50 905	$56 455	$69 758	$92 561	$110 293	$156 999	$169 749	$261 829	$382 838
No. (%) people ever screened	NA	106 858 (12%)	119 101 (13%)	124 620 (14%)	128 415 (14%)	187 640 (21%)	194 591 (22%)	195 314 (22%)	200 262 (22%)	279 416 (31%)
LDCT screens	NA	502 328	695 099	756 081	921 002	1 608 904	1 789 418	3 519 883	4 140 661	5 531 169
Positive screenings	NA	40 614	52 061	55 937	65 818	110 457	121 443	214 584	252 559	335 122
Follow-up exams	NA	34 639	90 149	97 278	57 992	196 177	216 373	200 850	234 862	314 985
False-positives	NA	33 500	44 354	47 878	56 658	96 770	106 745	196 642	229 340	308 620
Overdiagnosed cases	NA	207	194	210	232	424	460	632	1077	1224
Mortality reduction, %	NA	3	3	3	3	5	6	8	10	11
Deaths avoided	NA	1327	1555	1626	1805	2808	3004	4091	5122	5891
Interval LC cases*	NA	14 633	12 203	11 931	12 665	15 635	14 817	14 710	20 487	17 779
Early stage	NA	3876	3163	3075	3251	3951	3710	3805	5300	4511
Advanced stage	NA	10 757	9040	8856	9413	11 684	11 108	10 906	15 187	13 268
Screen-detected LC cases	NA	6746	7511	7852	8738	13 298	14 254	16 499	21 189	24 124
Early stage	NA	6063	6854	7164	7971	12 195	13 071	15 527	19 946	22 701
Advanced stage	NA	683	658	688	767	1103	1183	972	1243	1423
Shared decision-making cost, million $	NA	3	3	4	4	5	6	6	6	8
Detection cost, million $	49	134	186	197	231	385	418	723	810	1073
Screening LDCT	NA	79	120	130	169	296	326	634	715	964
Diagnostic LDCT	NA	6	16	18	12	38	41	37	42	56
Other non-invasive diagnostic procedures	5	5	5	5	5	5	5	5	5	5
Invasive diagnostic procedures	0	0	0	0	1	1	1	2	2	3
Staging	44	44	44	44	44	45	45	45	45	46
Treatment cost, million $	1988	2132	2190	2198	2249	2458	2506	2700	2887	3021
Cost of terminal care, million $	1552	1573	1572	1573	1576	1586	1588	1606	1630	1638

Any nonscreen-detected case. ICER = incremental cost-effectiveness ratio; LC = lung cancer; LDCT = low-dose computed tomography; NA = not applicable; QALYs = quality-adjusted life-years; X-S-E-P-Q represents efficient screening strategies where X = screening frequency (annual [A] and biennial [B]); S = starting age; E = stopping age; P = pack-years; Q = years since smoking cessation; X-S-E-P-Q denotes strategies with the modified Lung CT screening reporting and data system as their follow-up management for indeterminate findings.

Table 3. Incremental cost-effectiveness ratios of the CMS and USPSTF recommendations relative to no screening

Strategy	Disutility associated with indeterminate findings, %	Incremental cost relative to no screening	Incremental LY relative to no screening	ICER relative to no screening using LY	Incremental QALY relative to no screening	ICER relative to no screening using QALY
A-55-80-30-15 (USPSTF)	0 (No disutility)	$1476	0.0308	$42 819	0.0203	$72 745
	1	$1476	0.0308	$42 819	0.0190	$77 469
	2	$1476	0.0308	$42 819	0.0178	$82 849
	4	$1476	0.0308	$42 819	0.0153	$96 213
	6	$1476	0.0308	$42 819	0.0129	$114 718
	8	$1476	0.0308	$42 819	0.0104	$142 036
	Lung-RADS Category 2 Only*	$1320	0.0262	$50 430	0.0166	$79 607
A-55-77-30-15 (CMS)	0 (No disutility)	$1353	0.0297	$40 845	0.0197	$68 629
	1	$1353	0.0297	$40 845	0.0185	$73 075
	2	$1353	0.0297	$40 845	0.0173	$78 136
	4	$1353	0.0297	$40 845	0.0149	$90 702
	6	$1353	0.0297	$40 845	0.0125	$108 084
	8	$1353	0.0297	$40 845	0.0101	$133 708
	Lung-RADS Category 2 Only*	$1232	0.0252	$48 873	0.0161	$76 354

*All indeterminate findings are assessed as Lung-RADS Category 2 findings; thus, no disutility is associated with such findings for this specific scenario. CMS = Centers for Medicare & Medicaid Services; ICER = incremental cost-effectiveness ratio; Lung-RADS = Lung CT screening reporting and data system; QALYs = quality-adjusted life-years; LY = life-year; USPSTF = US Preventive Services Task Force

reduced the false-positive rate by 50%, LCS eligibility criteria relaxed.

Sensitivity Analyses of ICER to Input Parameters

We assessed the sensitivity of the ICERs, relative to no screening, to changes in input parameters for the most effective cost-effective strategies from our base-case analyses, namely, A-50-70-30-10 and B-50-70-40-10 strategies (Figure 4). The parameters that affected the ICER of the A-50-70-30-10 strategy, from most to least influential, were the disutility of indeterminate findings, the discounting factor, and the utility of screen-detected early stage lung cancer. The ICER of the B-50-70-40-10 strategy was most sensitive to the discounting factor, the utility of screen-detected early-stage lung cancer, and the disutility of indeterminate findings. Sensitivity analyses on the CMS and USPSTF guidelines are presented in Supplementary Figure 6 (available online).

When we assumed 20% higher false-positive rates for the biennial screening strategies relative to the annual strategies, annual screening for smokers aged 55–70 years, with at least 40 pack-years and no more than 10 years since smoking cessation was the cost-effective screening strategy yielding the highest health benefit in our analysis using 4% disutility associated with indeterminate findings (Supplementary Figure 5B, Supplementary Table 7, available online). The false-positive rate for the biennial screening strategies had very little effect on the results of our analysis assuming no disutility associated with indeterminate findings.

Discussion

We evaluated the cost-effectiveness of alternative LCS strategies that incorporate the Lung-RADS guidelines for the management of indeterminate findings. We show that LCS is cost-effective, but existing guidelines are not optimal in terms of cost-effectiveness. Interestingly, among all health utilities, the cost-effectiveness of LCS is most sensitive to the disutility of indeterminate findings.

Even though long-term disutility effects associated with indeterminate findings are reported as negligible (29), our findings demonstrate that the short-term disutility affects the cost-effectiveness of screening. Because the duration of these effects is not well established (12), we took a conservative approach and applied the disutility of indeterminate findings only until the first follow-up examination. Even so, as the disutility of indeterminate findings increases, screening eligibility criteria for the cost-effective strategies become more stringent. We show that if the disutility of indeterminate findings is about 2% (equivalent to loss of approximately 4 days per indeterminate finding), the net health benefit incurred from the diagnostic management per Lung-RADS is comparable to the decrement in QALYs because of the negative effects associated with indeterminate findings.

CMS requires patient-physician communication regarding the benefits and harms of LCS as part of a shared decision-making process for screening (7), but this can offer little comfort upon an indeterminate finding. Our findings suggest that reducing the false-positive rate of LCS and/or shortening the duration of the effects following an indeterminate finding would enhance the cost-effectiveness of LCS. The alternative disutility levels associated with indeterminate findings allow us to infer the impact of the duration of its effects; for example, 2% disutility up to the first negative follow-up exam provides a good approximation to the scenario where 4% disutility is applied for half as long. Hence, an adjunctive diagnostic biomarker to LCS could enhance the effectiveness of screening by reducing the false-positive rates and by shortening the duration of the disutility associated with indeterminate findings. However, an analysis that considers the benefits and harms of LCS when combined with an adjunctive diagnostic biomarker would be needed to assess overall effectiveness of such a strategy.

Recent findings from the European NELSON trial demonstrate impressive mortality reduction benefit from LCS for individuals with even lighter smoking exposure than the NLST and show clinically important differences between men

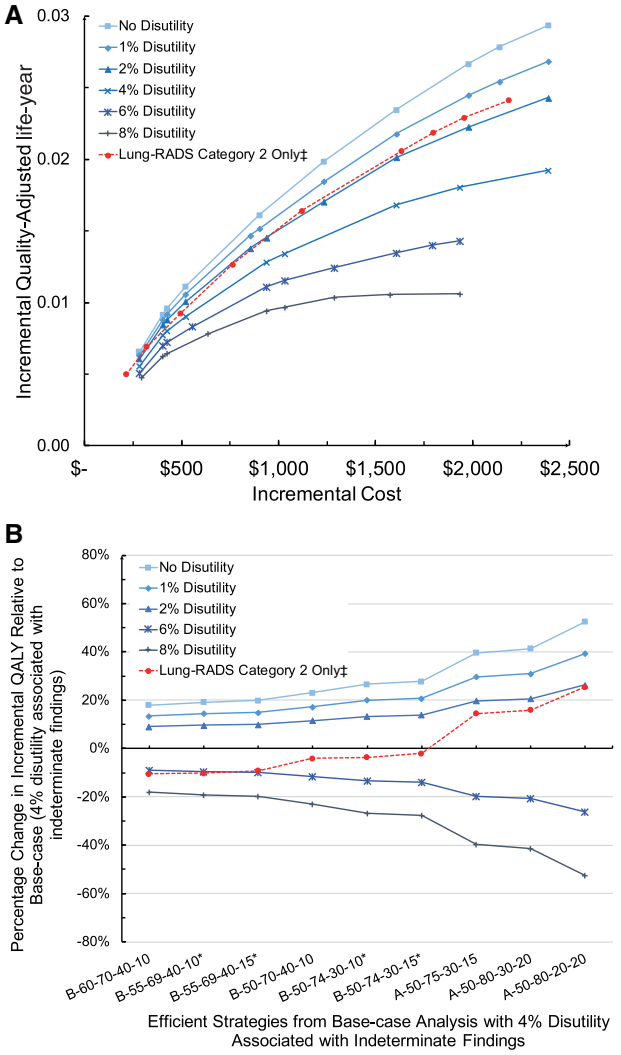

Figure 3. Effect of the disutility associated with indeterminate findings. **A)** Effect of disutility associated with indeterminate findings on the cost-effectiveness efficiency frontier of lung cancer screening in asymptomatic individuals when the disutility associated with indeterminate findings is 4% and applied up to the first negative follow-up exam. The following strategies, given in ascending order of their cost, are forming the efficiency frontiers under each scenario: Lung CT screening reporting and data system (Lung-RADS) Category 2 Only‡: B-60-70-40-10 (cost-effective with $50K/QALY WTP threshold), B-55-69-40-10, B-50-70-40-20, A-50-70-40-10, A-50-70-30-10 (cost-effective with $100K/QALY WTP threshold), A-50-75-20-10, A-50-75-20-15, A-50-75-20-20, A-50-80-20-20; No disutility: B-60-70-40-10, B-55-69-40-10* (cost-effective with $50K/QALY WTP threshold), B-55-69-40-15*, B-50-70-40-10, A-50-70-40-15, A-50-70-30-10 (cost-effective with $100K/QALY WTP threshold), A-50-75-30-15, A-50-75-20-15, A-50-75-20-20, A-50-80-20-20; 1% disutility: B-60-70-40-10, B-55-69-40-10* (cost-effective with $50K/QALY WTP threshold), B-55-69-40-15*, B-50-70-40-10, B-50-70-30-15*, A-50-70-40-15 (cost-effective with $100K/QALY WTP threshold), A-50-70-30-10, A-50-75-30-15, A-50-75-20-15, A-50-75-20-20, A-50-80-20-20; 2% Disutility: B-60-70-40-10 (cost-effective with $50K/QALY WTP threshold), B-55-69-40-10*, B-55-69-40-15*, B-50-70-40-10, B-50-70-30-15* (cost-effective with $100K/QALY WTP threshold), B-50-74-30-10*, A-50-70-30-10, A-50-75-30-15, A-50-75-20-15, A-50-80-20-20; 4% disutility: B-60-70-40-10, B-55-69-40-10*, B-55-69-40-15*, B-50-70-40-10 (cost-effective with $100K/QALY WTP threshold), B-50-74-30-10*, B-50-74-30-15*, A-50-75-30-15, A-50-80-30-20, A-50-80-20-20; 6% disutility: B-60-70-40-10, B-55-69-40-10*, B-55-69-40-15* (cost-effective with $100K/QALY WTP threshold), B-50-70-40-10*, B-50-74-30-10*, B-50-74-30-15*, B-50-80-30-20*, A-50-75-30-15, A-50-80-30-15, A-50-80-30-20; 8% disutility: B-60-70-40-10*, B-55-69-40-10* (cost-effective with $100K/QALY WTP threshold), B-55-69-40-15*, B-55-75-40-15*, B-50-74-30-10*, B-50-74-30-15*, B-50-80-30-20*, A-55-80-30-20, A-50-80-30-20. **B)** Percentage change in incremental QALYs per person accrued from the efficient strategies comprising the cost-effectiveness efficiency frontier of our base-case analysis with the disutility associated with indeterminate findings set at 4% (baseline represents the QALYs accrued when the disutility level associated with indeterminate findings is set at 4%) under various levels of the disutility associated with indeterminate findings and the Lung-RADS Category 2 Only follow-up management ([QALY of screening strategy tested – QALY of base-case screening strategy]/QALY of base-case screening strategy). QALYs = quality-adjusted life-years; WTP: willingness-to-pay; X-S-E-P-Q represents efficient screening strategies where X = screening frequency (annual [A] and biennial [B]); S = starting age; E = stopping age; P = pack-years; Q = years since smoking cessation; X-S-E-P-Q* denotes biennial strategies with modified Lung-RADS follow-up management for indeterminate findings.

‡All indeterminate findings are assessed as Lung-RADS Category 2 findings.

and women (37). Based on our findings, a population-wide LCS policy (either annual or biennial) similar to the NELSON's eligibility criteria (ie, smokers aged 50–75 years, with at least 15 or 10 cigarettes per day for more than 25 and 30 years, respectively, and no more than 10 years since smoking cessation) would be on the cost-effectiveness efficiency frontier if the disutility associated with indeterminate findings is small. Our sex-specific analyses demonstrate that screening is more cost-effective among women, consistent with previous findings (18,38).

Beyond the screening eligibility criteria, the disutility of indeterminate findings has implications on the frequency of screening. By including utilities, we found that annual strategies are not cost-effective when the disutility associated with indeterminate findings is at least 2%. Our findings suggest that if the disutility of indeterminate findings is relatively high, then the reduction in harms associated with indeterminate findings in biennial screening outweigh the reduction in the number of lung cancer deaths avoided, a finding that supports existing literature proposing that biennial screening may be more cost-effective (39,40). On the contrary, the analysis of ten Haaf et al. reported that biennial screening strategies are dominated by annual strategies, but it was optimized for Ontario, Canada (not the United States), did not incorporate Lung-RADS, and the health benefit was not adjusted for the quality of life (41).

LCS uptake remains extremely low [estimated at 2–4% (42)]. It is reported that the main reasons for the low uptake of LCS is the lack of knowledge regarding the benefits and costs associated with LCS. We show that LCS is cost-effective; however, it is sensitive to the disutility associated with indeterminate findings, which warrants further evaluation. Our findings can be used to guide decision makers and educate primary care physicians about the value of LCS.

Our analysis has several limitations. First, we assume perfect adherence to the screening program, thereby overestimating the costs and benefits of screening. The effect of imperfect adherence on the health benefits of LC screening is studied elsewhere (43). Second, we limit our analysis to a single birth cohort. Third, our analysis does not consider implications introduced into the screening process by comorbidity status of the population at risk. Fourth, our analysis is limited by the natural history model, which models solely solid tumors, ignoring progression for nodules with ground-glass opacity observed in CT screening (25). However, it is reported that the majority of ground-glass opacity nodules demonstrate an indolent clinical course (44,45). Finally, incidental findings (ie, diagnosis of pulmonary diseases other than lung cancer) as well as the positive effects of indeterminate findings (ie, improvements in patients, lifestyle, eg, smoking

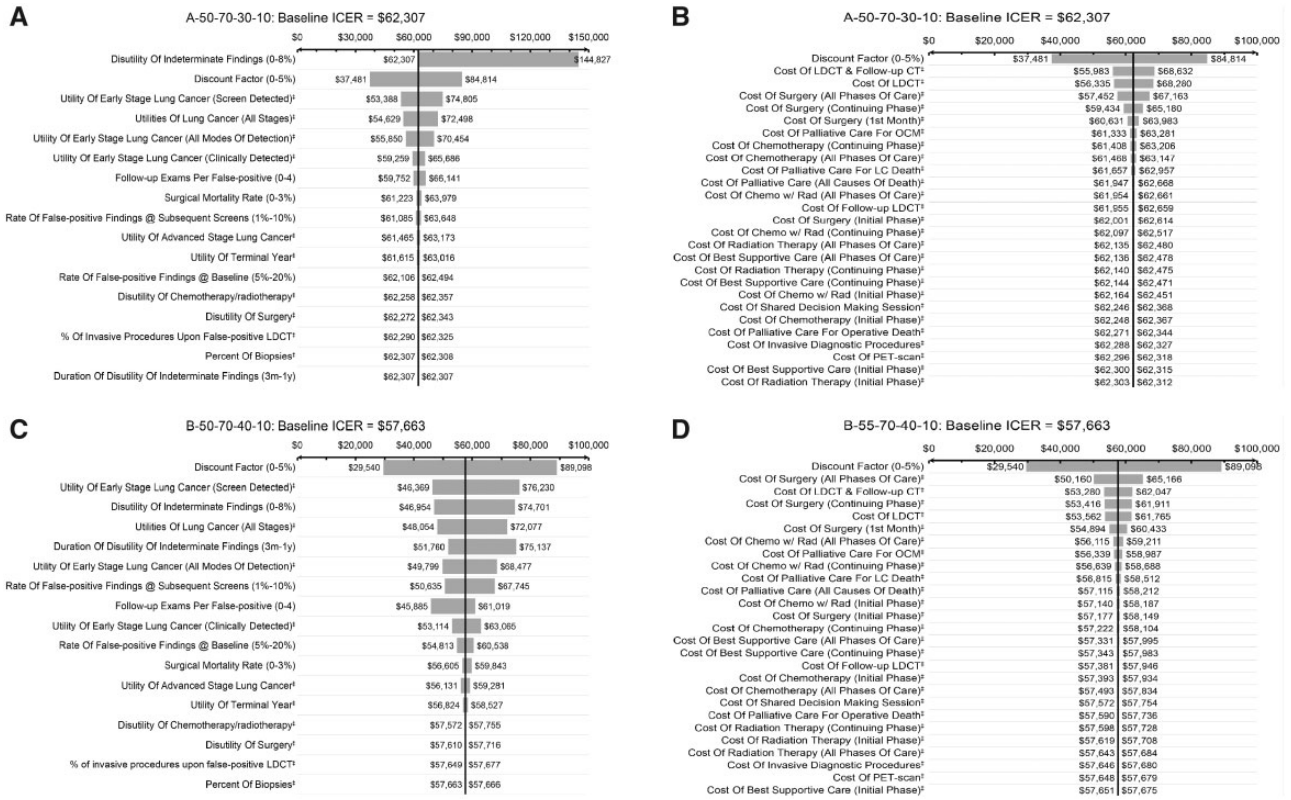

Figure 4. Sensitivity analysis relative to "No Screening" strategy. Sensitivity analysis of the ICER for **A)** A-50-70-30-10 strategy (with no disutility associated with indeterminate findings) on changes in health utility inputs, **B)** A-50-70-30-10 strategy (with no disutility associated with indeterminate findings) on changes in cost inputs, **C)** B-50-70-40-10 strategy (with 4% disutility associated with indeterminate findings) on changes in health utility inputs, and **D)** B-50-70-40-10 strategy (with 4% disutility associated with indeterminate findings) on changes in cost inputs, relative to no screening for the US general population born in 1950. Initial phase is defined as the first year after diagnosis; continuing phase is defined as the time after 1 year from diagnosis and 1 year before death; terminal care is provided for the last year of a person's life; X-S-E-P-Q represents the efficient screening strategy where X = screening frequency (annual [A] and biennial [B]); S = starting age; E = stopping age; P = pack-years; Q = years since smoking cessation. Chemo = chemotherapy; ICER = incremental cost-effectiveness ratio; LDCT = low-dose computed tomography; PET = positron emission tomography; rad = radiation therapy.

‡Unless specified otherwise, the range of the parameter value was defined by plus or minus 20% around their baseline value shown in Table 1.

cessation) (17,46) were not considered in our analysis, thus underestimating the health benefit accrued from screening.

Our findings provide evidence that LCS is cost-effective even when the health benefit is adjusted for quality of life. The disutility of indeterminate findings affects the cost-effectiveness of LCS, favoring biennial screening when this disutility increases; hence, the effects of this disutility should be considered when optimizing LCS strategies.

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