Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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APPENDIX 1

Assumptions

In our CEA, we made several assumptions to reduce the complexity of our analysis and minimize the use of variables for which there are no reliable estimates. In Table S1, we list our base case assumptions and plausible alternative assumptions. In addition, we estimate the magnitude of the effect that replacing the base case assumption with the alternative assumption would have had on our base case estimate of the quality-adjusted ICER ($81,000 per QALY gained). For example, changing the assumption that all excess cases of lung cancer (116) in low-dose CT group were due to overdiagnosis to the alternative assumption would lower the ICER by $25,000/QALY.

Table S1-1. Potential effects of replacing base case assumptions with alterative assumptions on the cost per QALY gained of low-dose CT screening versus no screening.

Base case assumption	**Alternative assumption**	**Change from base case ($81,000/QALY)**	**ICER with alternative assumption**
Conservative assumptions	**ICER with Alternative would be smaller, so screening would be more efficient**	**($/QALY)**	**($/QALY)**
Screening with low-dose CT did not decrease non-lung cancer deaths as observed in NLST.	Screening with low-dose CT decreased non-lung cancer deaths as observed in NLST. (see 7.4.1).	27,000	54,000
All excess cases of lung cancer (116) in low-dose CT group were due to overdiagnosis.	Only one-half of excess cases of lung cancer (58) in low-dose CT group were due to overdiagnosis (see Table S7-3).	26,000	55,000
Radiographic screening compared to no-screening would have had no effect on lung cancer mortality, RR = 1.00.	Radiographic screening compared to no-screening would have reduced lung cancer mortality, RR = 0.94 [1](see Table S7-2).	19,000	62,000
Negative screening exams did not increase quality of life.	Negative screening exams did increase quality of life by 0.012 QALYs (see Table S7-8).	15,000	66,000
No costs or effects of taking care of family members with cancer	CT had more early stage cancer, but CXR had more advanced cancer and deaths, which would have more caretaker involvement	Small net effect	

Optimistic Assumptions	**ICER with alternative assumptions would be bigger so screening would be less efficient**		
No inclusion of future health care costs unrelated to lung cancer diagnosed in trial*	Inclusion of future health care costs due to longer lives (ongoing cancer costs already in analysis)(see Table S7-20)	39,000	120,000
Positive screening exams did not reduce quality of life.	Positive screening exams did reduce quality of life by 0.03 QALYs (see Table S7-8).	18,000	99,000
There was no overdiagnosis of lung cancer in the radiography group (proportion of screen detected lung cancer overdiagnosed = 0)	There was over-diagnosis of lung cancer in the radiography group (proportion of screen detected lung cancer overdiagnosed = 0.1)(See Table S7-4)	5,000	86,000
No inclusion of other long term harms or costs of screening that emerge after the trial ends.	Inclusion of these costs (unknown)	Small	
NLST participants have average age, sex adjusted smoker mortality following the trial.	NLST participants have higher smoker related mortality due to greater smoking history but lower other cause mortality due to healthy volunteer effect	Unknown	
Exclusion of costs unrelated to lung cancer or incidental findings during the trial.	Inclusion of these costs (unknown)	Unknown	

*Inclusion of future medical costs is controversial [2], many prior CEAs have not included them [3], and none of the prior CEAs pertaining to lung cancer screening have included them [4-9].

Table S1-2. Potential effects of changing conditions from NLST to the community for or against CT screening.

Condition in NLST	Condition in community	Effect on ICER estimate	
		Impact on value of screen	Magnitude ($/QALY)
Strict eligibility criteria for screening, e.g. >=30 pack-yrs, age 55-74	Less strict eligibility requirement, e.g., fewer pack-yrs.	Against	Large
	More strict eligibility requirement, e.g., only current smokers.	For	Large
False positive rate about 24%	Higher false positive rate due to less experience or fear of malpractice	Against	Moderate
.	Lower false positive rate with incorporation of Lung-RADS [10].	For	Moderate
Modest degree of overdiagnosis	Higher degree of overdiagnosis due to improvements in image quality or fear of malpractice.	Against	Moderate
	Lower degree of overdiagnosis with incorporation of Lung-RADS	For	Moderate
Healthy volunteer effect	No healthy volunteer effect	Against	Moderate
High level of provider skill in diagnosis and treatment	Lower level of provider skill in diagnosis and treatment	Against	Variable
Rigorous consent process and follow-up of positive screens	Less rigorous consent process and follow-up of positive screens leads to more anxiety	Against	Variable
Higher Medicare prices at academic centers	Lower Medicare prices in community	For	Small
Higher Medicare prices for chest CT in 2009 ($285)	Lower Medicare prices for chest CT in 2014 ($193)	For	*13,000

*See Table S7-10

APPENDIX 2

Study Population

Table S2-1. Lung cancer diagnoses and deaths in NLST[11].

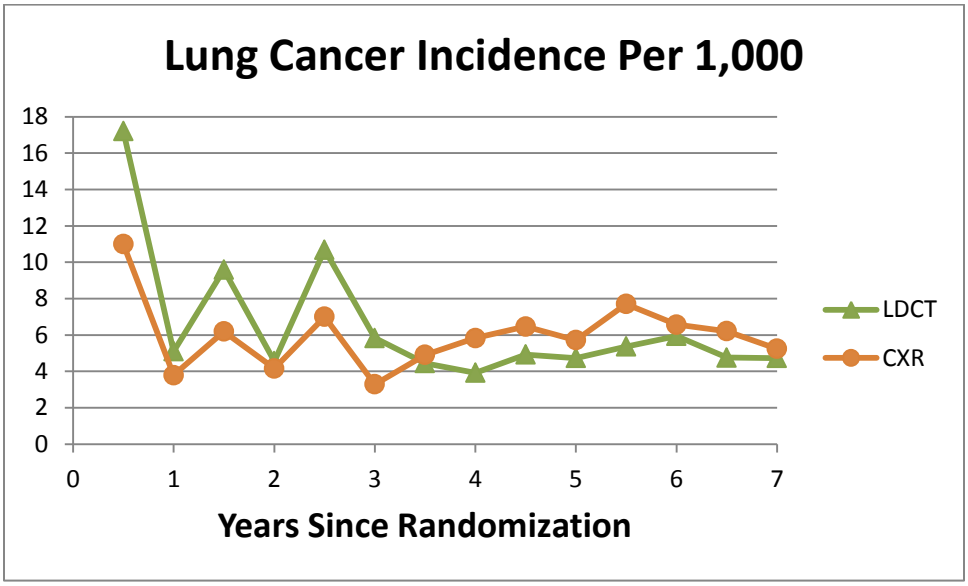
	CT	CXR	Total
All participants in full NLST	26,722	26,730	53,452
With lung cancer diagnosis*	1,109	993	2,102
All exclusions from CEA	80	70	150
Lost to FU within 1 day	46	54	100
Missing lung cancer information	33	15	48
Less than 50 years of age	1	1	2
All participants in NLST CEA	26,642	26,660	53,302
With lung cancer diagnosis	1,076	978	2,054
All deaths	1,920	2,044	3,964
Deaths from lung cancer**	469	552	1,021
All deaths from other causes	1,451	1,492	2,943
Deaths from other causes and lung cancer diagnosis	49	35	84
Alive*** at end of trial	24,722	24,616	49,338
Alive*** at end of trial with lung cancer diagnosis	558	391	949
Alive*** at end of trial without lung cancer diagnosis	24,164	24,225	48,389

* The numbers are higher than those previously reported [11] because they include lung cancers diagnosed at time of death and a later data cut date (1/31/2011 vs 9/28/2010).
** The numbers are higher than those previously reported [11] because they result from a later censor date (12/31/2009 vs 1/15/2009) and a later data cut date (1/31/2011 vs 9/28/2010).
***includes those lost to follow-up before 12/31/09.

Table S2-2. Lung cancer incidence by study group and years since randomization.

	Low-dose CT			Radiography			
Years	**Lung Cancers**	**Person-Years**	**Incidence per 1000 per-yrs**	**Lung Cancers**	**Person-Years**	**Incidence per 1000 per-yrs**	**Incidence Difference per 1000 per-yrs**
0.5	228	13,246	17.21	146	13,269	11.00	6.21
1.0	67	13,143	5.10	50	13,188	3.79	1.31
1.5	125	13,038	9.59	81	13,085	6.19	3.40
2.0	59	12,944	4.56	54	12,986	4.16	0.40
2.5	137	12,814	10.69	90	12,860	7.00	3.69
3.0	74	12,691	5.83	42	12,748	3.29	2.54
3.5	56	12,583	4.45	62	12,622	4.91	-0.46
4.0	49	12,488	3.92	73	12,512	5.83	-1.91
4.5	61	12,372	4.93	80	12,359	6.47	-1.54
5.0	58	12,262	4.73	70	12,229	5.72	-0.99
5.5	65	12,110	5.37	93	12,060	7.71	-2.34
6.0	70	11,773	5.95	77	11,718	6.57	-0.62
6.5	40	8,412	4.76	52	8,377	6.21	-1.45
7.0	19	4,016	4.73	21	4,007	5.24	-0.51
7.5	1	486	2.06	2	491	4.07	-2.02

Figure S2-1. Lung cancer incidence by study group and years since randomization.



APPENDIX 3

Annual Probability of Dying

3.1 Derivation of probabilities without lung cancer diagnosis

For participants without a diagnosis of lung cancer during the trial, we estimated beyond trial life years per participant based on each participant's age on the date last known to be alive, sex, and smoking status (current versus former) at entry using mortality rates from the 2009 U.S. mortality tables [12] with adjustment for smoking status [13, 14].

R_X = Risk of death in group X [12]
P_Z = Prevalence of group Z [15]
$RR_{X/Y}$ = Relative risk in group X versus group Y
G = General population
CS = Current smoker
FS = Former smoker
NS = Never smoker
where X, Y = G, CS, FS, or NS and Z= CS, FS, or NS.

$$R_G = P_{NS} * R_G * RR_{NS/G} + P_{FS} * R_G * RR_{FS/G} + P_{CS} * R_G * RR_{CS/G}$$

Divide by R_G

$$1 = P_{NS} * RR_{NS/G} + P_{FS} * RR_{FS/G} + P_{CS} * RR_{CS/G}$$

Substitute $RR_{FS/NS} * RR_{NS/G}$ for $RR_{FS/G}$ and $RR_{CS/NS} * RR_{NS/G}$ for $RR_{CS/G}$

$$1 = P_{NS} * RR_{NS/G} + P_{FS} * RR_{FS/NS} * RR_{NS/G} + P_{CS} * RR_{CS/NS} * RR_{NS/G}$$

Solve for $RR_{NS/G}$

$$1 = (RR_{NS/G})(P_{NS} + P_{FS} * RR_{FS/NS} + P_{CS} * RR_{CS/NS})$$

$RR_{NS/G} = 1 / [P_{NS} + P_{FS} * RR_{FS/NS} + P_{CS} * RR_{CS/NS}]$

Note: Values for P_{NS}, P_{FS} and P_{CS} are in Table S4 Values for $RR_{FS/NS}$ and $RR_{CS/NS}$ are in Table S5.

Calculate Risks for FS and CS from General population

$R_{NS} = R_G * RR_{NS/G}$

$R_{FS} = R_{NS/} * RR_{FS/NS}$

$R_{CS} = R_{NS} * RR_{CS/NS}$

Table S3-1. Smoking prevalence by age and sex [15].

Age	Men			Women		
	Never Smoker (NS)	Former smoker (FS)	Current smoker (CS)	Never smoker (NS)	Former smoker (FS)	Current smoker (CS)
45-64	0.416	0.340	0.245	0.565	0.231	0.204
65-74	0.336	0.535	0.129	0.579	0.309	0.112
> 75	0.378	0.559	0.063	0.672	0.274	0.055

Table S3-2. Relative risks (RR) compared to never smokers of death from all causes†.

Age	Men		Women	
	Current smoker (CS)	Former smoker (FS)	Current smoker (CS)	Former smoker (FS)
50-54	2.86	1.40	1.94	1.21
55-59	3.02	1.50	2.24	1.24
60-64	2.76	1.51	2.30	1.27
65-69	2.65	1.58	2.35	1.37
70-74	2.50	1.54	2.13	1.27
75-79	2.12	1.37	1.88	1.38
80-84	1.94	1.35	1.73	1.23
>85	1.33	1.11	1.27	1.08

†Age and sex-specific relative risks of death by smoking status above were provided for this analysis by the American Cancer Society Epidemiology Research Program and were calculated using the first 6 years of follow-up of the CPS-II population as described in Thun [13].

We assumed that the participants alive without a diagnosis of lung cancer at the end of a trial experienced death rates equal to smokers generally. In other words, we assumed that the higher risk due to the 30 pack-year history of smoking in NLST participants would be offset by the healthy screenee effect and the lower risk of lung cancer death in the vast majority of NLST participants who screened negative.

Life table calculations

For NLST participants, we estimated the probability of dying within one year from all causes based on the q_x value from the 2009 US life table (Table S3-3), where x is a single year of age (R_G). We let $RR_{CS/NS}$ and $RR_{FS/NS}$ represent the relative risks of current and former smokers compared to never smokers, respectively. For a 60 year-old male current smoker, for example, we calculated the probability of dying within one year from all causes (R_{CS}) as follows:

$$R_{CS} = R_{NS} * RR_{CS/NS}$$
$$= R_{NS} * 2.76$$
$$R_{NS} = R_G * RR_{NS/G}$$
$$= 0.01122 * RR_{NS/G}$$
$$RR_{NS/G} = 1 / [P_{NS} + P_{FS} * RR_{FS/NS} + P_{CS} * RR_{CS/NS}]$$
$$= 1/ [0.416 + 0.340 *1.51 + 0.245*2.76]$$
$$= 0.6228$$
$$R_{CS} = 0.01122 * 0.6228* 2.76$$
$$= 0.0193$$

Table S3-3. 2009 US Life Table for 60-year old male [12].

Age	mx	qx	ax	lx	dx	Lx	Tx	ex
60	0.01128	0.01122	0.5	85651	961	85170	1846968	21.56

3.2 Derivation of probabilities with lung cancer diagnosis

For surviving participants with a diagnosis of lung cancer during the trial, we estimated beyond trial life years as for the non-lung cancer participants but with the addition of mortality related to their lung cancer diagnosis. To avoid double-counting cancer deaths, we needed an estimate of their projected non-lung cancer death rates, PrDieNLC|LC, which can be partly based on 2009 U.S. life tables [12] adjusted for smoking (Table S3-2). In the NLST, the proportion of all deaths

that were not due to lung cancer was 0.74 (2,943/3,964). We assumed the same proportion would hold for the general smoker death estimates PrDieALL|S (equals R_{CS} or R_{FS} for current or former smokers described in previous section of participants without lung cancer) and that survivors with lung cancer diagnosis would have the same hazards of deaths not due to lung cancer as smokers generally. With these assumptions,

PrDieNLC|LC = 0.74* PrDieALL|S

For short time periods, overall probabilities of dying (PrDie|LC), assuming additive hazards, can be calculated from the probabilities of dying from lung cancer given a lung cancer diagnosis (PrDieLC|LC) and of dying from other causes given a lung cancer diagnosis (PrDieNLC|LC).

PrDie|LC = PrDieLC|LC + PrDieNLC|LC – [PrDieLC|LC * PrDieNLC|LC]

PrDieLC|LC was based on stage-specific survival statistics for lung cancer (see Appendix 3) while PrDieNLC|LC was estimated from (PrDieALL/S).

PrDie|LC = PrDieLC|LC + 0.74 *PrDieALL|S (1– PrDieLC|LC)

3.3 Life expectancy

We assumed that screening did not affect life expectancy in those not diagnosed with lung cancer and did not incur costs beyond those for workup of a positive exam. To estimate life expectancy for the low-dose CT (LE_{CT}) and radiography (LE_{Rad}) strategies, we excluded 150 of the 53,452 randomized in the NLST, 80 from CT group and 70 from radiography group. We excluded 100 because they were lost to follow-up within 1 day of randomization or their first screen (46 from CT group, 54 from radiography group), 48 because of missing lung cancer data needed to project survival beyond their observation period (33, 15) and 2 because of age less than 50 years at entry (1, 1).

We used the remaining 53,302 participants (26,642 in CT group, 26,660 in radiography group) to estimate LE_{CT} and LE_{Rad} by multiplying the life expectancies of those with lung cancer (LELC) and those without (LENLC) by the proportions of those with lung cancer (PLC) and those without (1-PLC) in the full NLST (to adjust for the small differences in the proportions

before and after exclusion of the 150 participants). In addition, we assumed that participants without a lung cancer diagnosis at the end of the trial in the radiography group had the same future risk for developing lung cancer as those in the CT group. This latter assumption is justified by the convergence of lung cancer incidence in the two groups in the last two years of the trial (Figure S1). With these assumptions the life expectancies of those without a diagnosis of lung cancer in the two groups are equal. Thus, the life expectancy for each screening strategy was equal to a weighted average of the life expectancies of those with and without lung cancer.

$$LE_{CT}=LELC_{CT}*PLC_{CT}+LENLC*(1-PLC_{CT})$$

$$LE_{Rad}=LELC_{Rad}*PLC_{Rad}+LENLC*(1-PLC_{Rad})$$

where PLC_{CT} =0.042 (1,109/26,722) and PLC_{Rad}=0.037 (993/26,730).

For each of the remaining 53,302, we estimated life years by adding beyond trial life years to within trial life years. We calculated within trial life-years from the date of randomization to the date of death if deceased (3,964), to 12/31/09 if still alive, or to the latest date they were known to be alive if vital status was missing on 12/31/09. For the 49,338 participants not known to be deceased on 12/31/09, we estimated beyond trial life years based on age on the date they were last known to be alive, sex, smoking status at entry, and lung cancer stage, if any, using 2009 U.S. life tables [12] adjusted for smoking status and annual probabilities of dying from lung cancer (see Appendix 4).

APPENDIX 4

Lung cancer survival

The observed stage-specific lung cancer survival was higher in the NLST than in SEER [16]. This difference was most likely due to stage migration, healthy volunteer effect, and possibly better treatment. (We considered lung cancer patients diagnosed in 1998 or later [N=158,250] and fit Cox proportional hazards survival curves separately by stage to compare SEER survival with NLST survival. The SEER stage was based on AJCC 3rd edition, modified.)

The observed NLST stage-specific lung cancer survival was used to estimate life expectancy for the first 5 years after diagnosis. For subsequent years, the NLST data were sparse. To estimate the survival beyond 5 years, we considered both NLST hazards before 5 years and SEER hazards before and after 5 years to account for the change in hazards over time. Because the surgical mortality was extremely low in NLST, only 1%, we used the stage-specific average annual hazard during years 3, 4, and 5 to project future survival. In SEER and in studies of long term survival in Stage I lung cancer [17-19], the hazards declined after 5 years. In SEER, the decline was such that the stage-specific ratios of the average annual hazard for years 5 through 10 to the average annual hazard for years 3 through 5 were 0.48, 0.47, 0.34, and 0.29 for Stages I, II, III, and IV NSCLC, respectively. To estimate the hazard at x years, $x > 5$, in the base case, we multiplied the average annual hazard during years 3, 4, and 5 in NLST by the stage-specific ratio of decline in SEER at year x.

We developed smooth baseline hazard models for non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) using the observed NLST data and the methods of Royston [20]. The NSCLC model was stratified by stage (IA1, IA2, IB, II, III, IV) and included the following covariates: sex, age (5-year interval), histology (squamous cell, bronchioloalveolar carcinoma (BAC), and adenocarcinoma plus other NSCLC), and lesion size. For SCLC, only stage and age were significant predictors of survival in the Cox model. Consequently, the SCLC model was simpler and included only stage and age (continuous) as covariates. For both models, we estimated baseline hazards (6 baseline hazards for NSCLC, one for each stratum, and 1 for SCLC). We used the baseline hazards and hazard ratios for the covariates to estimate the annual probability of dying from lung cancer for all NSCLC and SCLC participants who were alive on 12/31/09 (including those 16 lung cancer participants who were lost to follow-up). Carcinoid tumors are not included in the IASLC NSCLC or SCLC survival models. For the 6 participants with carcinoid tumors, all of which were localized, we derived an annual probability of surviving

lung cancer from the reported 5-year survival of 84% (annual probability of surviving = (0.84)^(1/5) = 0.966) [21].

Among the participants still alive on 12/31/09, there were many more diagnosed with Stage IA NSCLC in the low-dose CT group than in the radiography group, 324 versus 140, while there were similar numbers diagnosed with Stages IB-IV NSCLC in the two groups, 195 versus 203. Therefore, we performed a sensitivity analysis on survival after 5 years for Stage IA NSCLC. In the base case, we assumed hazards equal to the product of the average annual multivariate hazard during years 3, 4, and 5 in NLST and the ratio of decline in SEER. In the optimistic scenario (most favorable to screening), we assumed all the lung cancer participants were subject to a constant hazard of dying from lung cancer of 0.01 per year after surviving 5 years. This hazard is slightly greater than the expected annual hazard for those randomized to the radiography group (the observed lung cancer mortality in the radiography group was 309/100,000 person years [11] and according to SEER age-specific lung cancer mortality peaks in age group 80-84 years at three fold the age-specific mortality in age group 60-64 years, 382 versus 120/100,000 [22]). In the pessimistic scenario (most unfavorable to screening), we assumed all the lung cancer participants were subjected to constant NLST hazards without any adjustment for the observed decline in hazards over time seen in SEER. Unlike in SEER, most of the early stage lung cancers in the low-dose CT group of NLST were screen detected, so it is possible that future early-stage lung cancer hazards will not fall in NLST as they did in SEER. However, in a large international study of patients with Stage I lung cancer detected by CT screening [17], the survival curves are nearly flat after 5 years, suggesting that the hazards did fall close to zero in that study. Figure S2 shows the base case, optimistic and pessimistic estimates for survival in Stage IA1 NSCLC in NLST. The smoothed estimate from SEER is based on the weighted Cox model with weights, w, equal to the ratio of the proportion of participants in each age group from NLST and SEER.

$$w = \frac{Proportion\ of\ participants\ in\ age\ group\ in\ NLST}{Proportion\ of\ participants\ in\ age\ group\ in\ SEER}$$

In order to illustrate the difference between the base case, optimistic and pessimistic scenarios, Table S4-1 below presents the average annual hazards for stage IA1 NSCLC by sex, age, and histology for years 6 through 10. The annual hazard is the probability of a participant dying from lung cancer in the next year given the participant is still alive at the beginning of the year. We used the median lesion size, for stage IA1 NSCLC, 13.5mm. A larger size would lead to

a larger hazard. The hazard is presented here rather than the commonly seen hazard ratio since the ratio requires a comparison between two groups and we are providing the hazard for only a single group at a time. For comparative purposes, the observed (KM) average annual hazard during years 3-5 was 0.035 for all stage IA1 NLST participants.

We analyzed survival for Stages IA2 NSCLC in the same manner that we analyzed Stage IA1 NSCLC. These survival curves can be seen in Figure S4-3. For stages IB through IV and small cell cancer we used only the base case survival estimates.

Table S4-1. Stage IA1 NSCLC average annual hazards for years 6 through 10 after diagnosis adjusted for sex, age, histology, and lesion size.

Sex	Age	Histology	Lesion Size	Base Case Scenario	Optimistic Scenario	Pessimistic Scenario
Male	55-59	Adeno+	13.5mm	0.024	0.010	0.049
		BAC	13.5mm	0.010	0.010	0.021
		Squamous	13.5mm	0.019	0.010	0.040
	60-64	Adeno+	13.5mm	0.025	0.010	0.053
		BAC	13.5mm	0.011	0.010	0.023
		Squamous	13.5mm	0.020	0.010	0.043
	65-69	Adeno+	13.5mm	0.026	0.010	0.054
		BAC	13.5mm	0.011	0.010	0.024
		Squamous	13.5mm	0.021	0.010	0.044
	70-74	Adeno+	13.5mm	0.034	0.010	0.071
		BAC	13.5mm	0.015	0.010	0.031
		Squamous	13.5mm	0.027	0.010	0.057
Female	55-59	Adeno+	13.5mm	0.020	0.010	0.041
		BAC	13.5mm	0.009	0.010	0.018
		Squamous	13.5mm	0.016	0.010	0.033
	60-64	Adeno+	13.5mm	0.021	0.010	0.044
		BAC	13.5mm	0.009	0.010	0.019
		Squamous	13.5mm	0.017	0.010	0.039
	65-69	Adeno+	13.5mm	0.022	0.010	0.046
		BAC	13.5mm	0.009	0.010	0.020
		Squamous	13.5mm	0.018	0.010	0.037
	70-74	Adeno+	13.5mm	0.028	0.010	0.059
		BAC	13.5mm	0.012	0.010	0.026
		Squamous	13.5mm	0.023	0.010	0.048

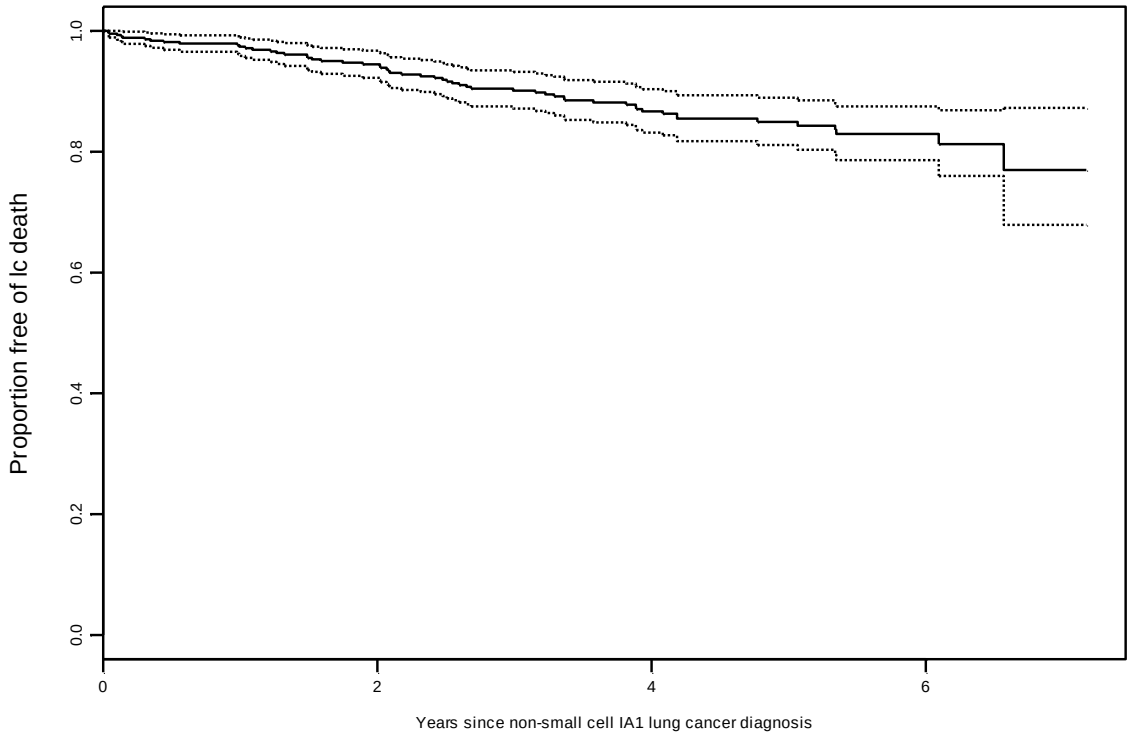


Figure S4-1: Lung cancer specific survival for Stage IA1 NSCLC (both groups). Upper and lower curves represent 95% confidence intervals.

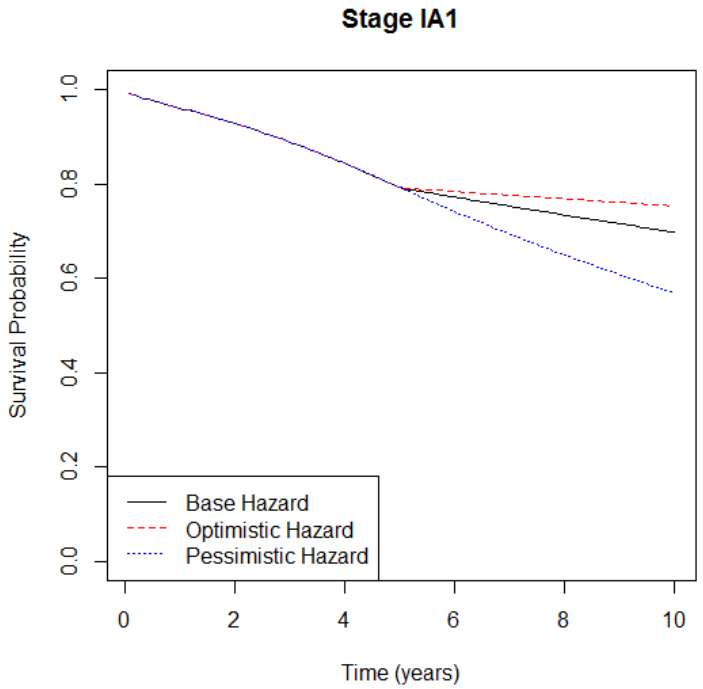


Figure S4-2: Non-small cell lung cancer stage IA1. Survival function for a 60-64 year old male participant with 13.5mm adeno plus lung cancer.

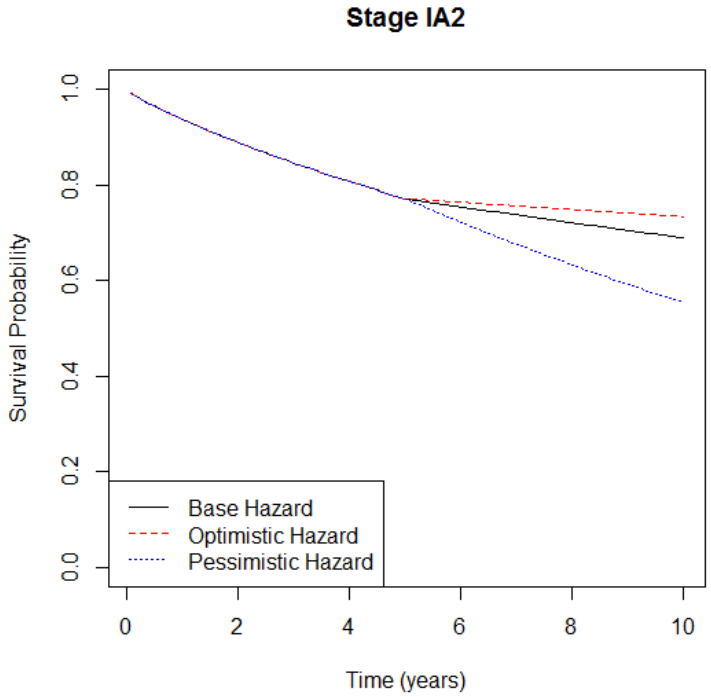


Figure S4-3: Non-small cell lung cancer stage IA2. Survival function for a 60-64 year old male participant with 25mm adeno plus lung cancer.

APPENDIX 5

Quality of life adjustment

To estimate quality adjusted life expectancy for each screening strategy, we used utilities derived from the Short Form (SF)-6D, a subset of the SF-36, which was collected at 16 of 23 ACRIN screening sites. All participants at these sites received the SF-36 at baseline and a subset of these participants completed additional SF-36 forms at later time points, including after their screening exams and lung cancer diagnoses. At baseline, the mean utilities were 0.76 and 0.74 for men and women, respectively and did not differ by age. We subtracted 0.02 after age 75 for both men and women as this age-related decline was observed in a recent large U.S. study of health related quality of life, which included the SF-6D [23].

We also adjusted for lung cancer stage and time of diagnosis. In the ACRIN participants, the mean utilities increased from 0.652 to 0.752 between 1 month and 3 years (Table S5-1) but the confidence intervals after the first year overlapped. Therefore, we estimated the stage-specific utilities for the first year after diagnosis as a weighted average of the utilities at 1 and 6 months and the stage-specific utilities thereafter as a weighted average of the utilities at 12, 18, 24, 30, and 36 months (Table S5-2). For Stage IA lung cancer, utility increased from a mean of 0.70 during the first year to a mean of 0.72 beyond (Table S5-2). These findings are consistent with a recent study of health related quality of life among Stage I NSCLC survivors [24], in whom the Physical Health Component of their SF-36v2 score was reduced by a mean of 2.43 (which can be converted to a reduction of 0.02 on the SF-6D [25]) at a mean of 3.5 years after resection. Although there was no consistent relationship between stage and utility in the ACRIN participants (Table S5-2), probably because of the small sample size and lower compliance among those with advanced stages, a recent meta-analysis of lung cancer utilities revealed a strong inverse relationship between stage and utility [26]. Therefore, after subtracting 0.01 from the observed utility in Stage IV during the first year (Table S5-2) to account for two probable outliers in the radiography group (Table S5-1) and using the observed utility in Stage IA, we linearly interpolated the utilities for the intermediate stages to estimate the utilities for the base case (Table S5-3).

Table S5-1. Observed utilities (SF-6D scores) for lung cancer by stage, group and time since diagnosis.

		Time since diagnosis													
		1 Month		*6 Month*		*12 Month*		*18 Month*		*24 Month*		*30 Month*		*36 Month*	
		SF-6D Index		*SF-6D Index*		*SF-6D Index*		*SF-6D Index*		*SF-6D Index*		*SF-6D Index*		*SF-6D Index*	
		N	*Mean*	*N*	*Mean*	*N*	*Mean*	*N*	*Mean*	*N*	*Mean*	*N*	*Mean*	*N*	*Mean*
Study Arm	*Stage*														
Spiral CT	*IA*	28	0.659	32	0.714	19	0.732	24	0.724	16	0.681	11	0.718	7	0.744
	IB	4	0.714	5	0.747	3	0.701	4	0.751	3	0.674	1	0.738	1	0.780
	II	1	0.465	1	0.923	2	0.762	2	0.746	2	0.678	1	0.572	.	.
	III	7	0.604	8	0.558	5	0.587	4	0.667	4	0.700	3	0.706	2	0.764
	IV	7	0.591	4	0.578	4	0.611	2	0.568	2	0.614	1	0.731	1	0.696
X-Ray	*IA*	11	0.705	13	0.724	11	0.740	10	0.684	8	0.705	7	0.730	3	0.763
	IB	.	.	1	0.687	.	.	1	0.595	.	.	.	.	.	.
	II	2	0.552	2	0.554	1	0.577	1	0.639	.	.	.	.	.	.
	III	6	0.634	6	0.682	4	0.748	5	0.795	3	0.782	4	0.726	2	0.766
	IV	2	0.755	.	.	0	.	.	.	.	.	.	.	.	.
Total		68	0.652	72	0.688	49	0.707	53	0.712	38	0.692	28	0.717	16	0.752

Table S5-2. Observed utilities for lung cancer by stage over time.

	Years since diagnosis	
Stage	<12 months	12 months +
IA	0.696	0.718
IB	0.727	0.711
II	0.600	0.684
III	0.614	0.716
IV	0.612	0.623

Table S5-3. Base case utilities for lung cancer by stage over time.

	Years since diagnosis	
Stage	<12 months	12 months +
IA	0.700	0.720
IB	0.675	0.695
II	0.650	0.670
III	0.625	0.645
IV	0.600	0.620

Because the sample sizes were small and decreased over time and the confidence intervals around the utility values were wide, especially for advanced stages, we performed sensitivity analyses on these values (Tables S7-6, S7-7).

We did not observe any difference in utilities between those with positive versus negative screening results, conditional on lung cancer diagnosis, and therefore did not include screening results in our quality adjustment in the base case. However, because positive and negative screening results have been shown to increase and decrease lung cancer specific distress in the NELSON trial [27], we performed a two-way sensitivity analysis on the utilities following positive and negative screening results (Table S7-8).

APPENDIX 6

Costs

Estimation of costs

In the design of the NLST, the ACRIN centers planned to collect detailed cost information, including International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes and Current Procedural Terminology (CPT) procedure codes for services rendered and dates of service, whereas the LSS centers planned to collect only that information pertinent to the diagnosis and treatment of potential lung cancers. For this analysis, the ACRIN investigators decided to use only the benefits and costs related to lung cancer in the primary analysis. For the purposes of this paper, the NLST investigators agreed to estimate the missing costs in the LSS subset from the ACRIN subset based on common related data elements.

We estimated the expected per subject cost related to lung cancer for each screening strategy as we estimated life expectancy using the same proportions of participants with (PLC) and without (1-PLC) a diagnosis of lung cancer in each group and using the same 53,302 non-excluded participants. Thus, the expected per subject cost for each screening strategy (C_{CT}, C_{rad}) was equal to a weighted average of expected per subject costs of those with (CLC_{CT}, CLC_{rad}) and without (CNLC) lung cancer.

$C_{CT}=CLC_{CT}*PLC_{CT} + CNLC*(1-PLC_{CT})$
$C_{rad}=CLC_{rad}*PLC_{rad} + CNLC*(1-PLC_{rad})$
where PLC_{CT} =0.042 (1,109/26,722) and PLC_{Rad}=0.037 (993/26,730).

In addition, we assumed that the cost associated with no screening would be the same as that associated with radiography screening minus the costs of the radiography screening exams ($C_{rad-SCR}$) and workup of false positive radiography screening exams ($C_{rad-FPWU}$).

$C_{NOSCR}=C_{rad}-C_{rad-SCR}- C_{rad-FPWU}$

We did not subtract the costs of workup for true positive, false negative radiography screening exams (with symptoms), or lung cancer treatment because we assumed that there was no radiography overdiagnosis and that these costs would have occurred without screening.

The total per subject costs for each strategy were calculated as the sum of direct medical costs and indirect costs for each subject, the latter of which included time and travel expenses for participants and caregivers, divided by the number of participants. All costs were based on 2009 US dollar pricing for Medicare [28], hourly earnings [29], and automobile mileage reimbursement [30] and date of entry into the trial for each subject was equated with Jan 1, 2009. Costs were discounted annually at different rates, 3% in the base case.

Direct medical

In the primary analysis, direct medical costs were based on the frequency of medical utilization related to the screening exam, diagnostic work-up for positive screening results and signs or symptoms of lung cancer, and lung cancer treatment and calculated for each subject each year after randomization. The frequency of screening was based on screening low-dose CT and radiography compliance records in both the ACRIN and LSS populations. In the ACRIN participants with complete medical abstraction records, the frequency of medical utilization related to diagnostic work-up and treatment of lung cancer was directly obtained from their abstraction records, which included dates, CPT codes, and other variables used for MS-DRG coding.

CPT codes

The medical abstraction records in the ACRIN subset contained frequencies for 1,837 unique CPT codes. Among these, 164 had been identified as potentially relevant to the CEA before the trial was completed based on discussions by the NLST Executive Committee and the NLST CEA writing team, which included clinical experts in chest radiology, pulmonary medicine, and medical oncology. To determine if any of the remaining 1,673 CPT codes were relevant we counted only those for which the product of the difference between frequencies between groups and global Medicare reimbursement exceeded $30,000, a threshold above which the code could start to affect the ICER (the $30,000 threshold corresponds to an increase in the ICER of about $85/LY). Only one procedure, myocardial perfusion imaging (CPT 78465), met this criterion and we added it to the list of relevant procedures. To avoid double counting, we did not count CPTs that occurred during hospitalizations or that were related to outpatient chemotherapy or radiation therapy (see below). Among the remaining 111 relevant procedures, some, such as PET/CT, were always counted as relevant while others, such as abdominal CT, were only counted if they occurred within 60 days after a positive screen or between 60 days

before and any time after a diagnosis of lung cancer based on consensus of the writing team (Table S10).

We used the 2009 Physician Fee Schedule [28] for both professional and technical components of all outpatient procedures included in the Physician Fee Schedule except for PET/CT, for which the technical component is contracted locally. We assigned PET/CT a total cost of $1284 based on Medicare reimbursement to Dartmouth-Hitchcock Medical Center.

Table S6-1. Relevant Current Procedural Terminology (CPT) procedures.

CPT Description	CPT Code	Price†	Count
FNA W/O IMAGE	10021	126.95	Always
FNA W/IMAGE	10022	130.20	Always
ENDOBRONCHIAL US ADD-ON	31620	263.29	Always
DX BRONCHOSCOPE/WASH	31622	296.11	Always
DX BRONCHOSCOPE/BRUSH	31623	323.52	Always
DX BRONCHOSCOPE/LAVAGE	31624	300.80	Always
BRONCHOSCOPY W/BIOPSY(S)	31625	324.60	Always
BRONCHOSCOPY/LUNG BX, EACH	31628	389.52	Always
BRONCHOSCOPY/NEEDLE BX, EACH	31629	595.46	Always
BRONCHOSCOPY DILATE/FX REPAIR	31630	200.17	Always
BRONCHOSCOPY/LUNG BX, ADDL	31632	73.58	Always
BRONCHOSCOPY/NEEDLE BX ADDL	31633	88.00	Always
BRONCHOSCOPY W/FB REMOVAL	31635	333.98	Always
BRONCHOSCOPY, BRONCH STENTS	31636	220.01	Always
BRONCHOSCOPY, STENT ADD-ON	31637	78.26	Always
BRONCHOSCOPY, REVISE STENT	31638	245.25	Always
BRONCHOSCOPY W/TUMOR EXCISE	31640	256.79	Always
DIAG BRONCHOSCOPE/CATHETER	31643	172.76	Always
BRONCHOSCOPY, CLEAR AIRWAYS	31645	290.70	Always
DRAIN CHEST	32421	151.12	Always
TREAT COLLAPSED LUNG	32422	190.79	Always
INSERT PLEURAL CATHETER	32422	190.79	Always
INSERT CHEST TUBE	32422	190.79	Always
REMOVE/TREAT LUNG LESIONS	32141	1416.34	Always
NEEDLE BIOPSY CHEST LINING	32400	145.35	Always
BIOPSY, LUNG OR MEDIASTINUM	32405	100.27	Always
PUNCTURE/CLEAR LUNG	32420	110.36	Always
THORACOSCOPY, DIAGNOSTIC	32606	462.37	Always

THORACOSCOPY, SURGICAL	32657	775.07	Always
BIOPSY/REMOVE LYMPH NODES	38500	288.17	Always
NEEDLE BIOPSY, LYMPH NODES	38505	120.10	Always
BIOPSY/REMOVE LYMPH NODES	38510	464.90	Always
BIOPSY/REMOVE LYMPH NODES	38525	383.39	Always
LAPAROSCOPY, LYMPH NODE BIOPSY	38570	528.02	Always
REMOVE LYMPH NODES, NECK	38720	1199.21	Always
REMOVE THORACIC LYMPH NODES	38746	258.60	Always
IDENTIFY SENTINEL NODE	38792	38.23	Always
EXPLORE CHEST	39010	775.79	Always
VISUALIZE CHEST	39400	478.96	Always
NEEDLE BIOPSY LIVER	47000	306.57	Always
BIOPSY, ABDOMINAL MASS	49180	162.30	Always
CT HEAD/BRAIN W/O DYE	70450	218.56	Always
CT HEAD/BRAIN W/DYE	70460	282.40	Always
CT HEAD/BRAIN W/O & W/DYE	70470	341.91	Always
MRI BRAIN W/O DYE	70551	569.85	Always
MRI BRAIN W/DYE	70552	637.30	Always
MRI BRAIN W/O & W/DYE	70553	852.61	Always
CHEST X-RAY	71010	23.80	Always
CHEST X-RAY	71020	31.74	Always
CHEST X-RAY	71021	38.23	Always
CHEST X-RAY	71022	45.80	Always
CHEST X-RAY AND FLUOROSCOPY	71023	66.00	Always
CHEST X-RAY	71030	46.17	Always
CHEST X-RAY	71035	33.90	Always
DIAGNOSTIC CT W/O CONTRAST	71250	284.93	Always
DIAGNOSTIC CT W/ CONTRAST	71260	341.91	Always
DIAGNOSTIC CT W/O THEN W/ CONTRAST	71270	422.34	Always
CT LOW DOSE HELICAL SCREENING CT EXAM	71250	284.93	Always

CT THORAX W/O DYE	71250	284.93	Always
CT THORAX W/DYE	71260	341.91	Always
CT THORAX W/O & W/DYE	71270	422.34	Always
CT ANGIOGRAPHY, CHEST	71275	519.00	Always
MRI CHEST W/O DYE	71550	613.85	Always
MRI CHEST W/O & W/DYE	71552	944.58	Always
CT PELVIS W/O DYE	72192	271.22	Within 60 days
CT PELVIS W/DYE	72193	324.60	Within 60 days
CT PELVIS W/O & W/DYE	72194	413.68	Within 60 days
MRI LOWER EXTREMITY W/O DYE	73718	552.54	Within 60 days
MRI LWR EXTREMITY W/O&W/DYE	73720	851.53	Within 60 days
MRI JNT LWR EXTRE W/O DYE	73721	541.36	Within 60 days
MRI JOINT LWR EXTR W/DYE	73722	592.21	Within 60 days
MRI JOINT LWR EXTR W/O&W/DYE	73723	813.30	Within 60 days
MR ANG LWR EXT W OR W/O DYE	73725	602.31	Within 60 days
CT ABDOMEN W/O DYE	74150	273.38	Within 60 days
CT ABDOMEN W/DYE	74160	363.55	Within 60 days
CT ABDOMEN W/O & W/DYE	74170	475.72	Within 60 days
CT ANGIO ABDOM W/O & W/DYE	74175	529.10	Within 60 days
MRI ABDOMEN W/O DYE	74181	510.34	Within 60 days
MRI ABDOMEN W/DYE	74182	676.61	Within 60 days
MRI ABDOMEN W/O & W/DYE	74183	858.02	Within 60 days
X-RAYS, BONE SURVEY	76062	27.77	Within 60 days
CT SCAN FOR NEEDLE BIOPSY	77012	200.53	Within 60 days
BONE IMAGING, LIMITED AREA	78300	97.30	Within 60 days
BONE IMAGING, MULTIPLE AREAS	78305	98.30	Within 60 days
BONE IMAGING, WHOLE BODY	78306	99.30	Within 60 days
BONE IMAGING, 3 PHASE	78315	100.30	Within 60 days
BONE IMAGING (3D)	78320	101.30	Within 60 days
BONE MINERAL, SINGLE PHOTON	78350	102.30	Within 60 days

BONE MINERAL, DUAL PHOTON	78351	103.30	Within 60 days
HEART IMAGE (3D), MULTIPLE	78465	485.10	Within 60 days
LUNG PERFUSION IMAGING	78580	205.22	Within 60 days
LUNG V/Q IMAGE SINGLE BREATH	78584	156.53	Within 60 days
LUNG V/Q IMAGING	78585	338.67	Within 60 days
AEROSOL LUNG IMAGE, MULTIPLE	78587	196.56	Within 60 days
PERFUSION LUNG IMAGE	78588	313.06	Within 60 days
VENT IMAGE, MULT PROJ, GAS	78594	219.28	Within 60 days
LUNG DIFFERENTIAL FUNCTION	78596	364.27	Within 60 days
BRAIN IMAGING, LTD STATIC	78600	170.23	Within 60 days
BRAIN IMAGING (PET)	78609	73.94	Within 60 days
TUMOR IMAGING (PET), LIMITED	78811	1284.00	Always
TUMOR IMAGE (PET)/SKULL-THIGH	78812	1284.00	Always
TUMOR IMAGE (PET) FULL BODY	78813	1284.00	Always
TUMOR IMAGE PET/CT, LIMITED	78814	1284.00	Always
TUMOR IMAGE PET/CT SKULL-THIGH	78815	1284.00	Always
TUMOR IMAGE PET/CT FULL BODY	78816	1284.00	Always
ECHO TRANSTHORACIC	93350	211.71	Within 60 days
BREATHING CAPACITY TEST	94010	32.82	Within 60 days
EVALUATE WHEEZING	94060	57.71	Within 60 days
VITAL CAPACITY TEST	94150	22.36	Within 60 days
LUNG FUNCTION TEST (MBC/MVV)	94200	22.36	Within 60 days
PULMONARY STRESS TEST/SIMPLE	94620	71.77	Within 60 days

† All prices based on 2009 national pricing for Medicare [28] except for PET imaging (CPTs 78811-78816), which were based on Medicare payment at Dartmouth-Hitchcock Medical Center, because no national prices existed.

MS-DRG price calculations

The medical abstraction records in the ACRIN subset contained frequencies for 443 unique Medical Severity Diagnosis Related Groups (MS-DRG) codes, among which 16 had been identified as potentially relevant to the CEA before the trial was completed based on discussions by the NLST Executive Committee and the NLST CEA writing team, which included clinical experts in chest radiology, pulmonary medicine, and medical oncology. After reviewing all the MS-DRG codes frequencies, we added 9 MS-DRGs because they were empirically more common in the low-dose CT group than the radiography group and were judged by clinical experts on the writing team to be related to a lung cancer diagnosis. Thus, we allowed a total of 25 unique MS-DRGs (Table S6-2). Certain hospitalizations, such as major chest procedures (MS-DRG 163-165), were always counted as related to treatment, while others, such as chemotherapy (MS-DRG 847), were only counted if the associated discharge date was later than the lung cancer diagnosis date based on consensus of the writing team.

Table S6-2. Relevant Medical Severity Diagnosis Related Groups (MS-DRGs).

MS-DRG Description	Code	Weight	Price*	Count**
Trach w MV 96+ hrs or PDX exc face, mouth & neck w/o maj O.R.	4	11.1366	$81,627	After
Nervous system neoplasms w MCC	54†	1.5860	$11,625	After
Nervous system neoplasms w/o MCC	55†	1.0828	$7,936	After
Major chest procedures w MCC	163†	4.9978	$36,632	Always
Major chest procedures w CC	164†	2.5953	$19,022	Always
Major chest procedures w/o CC/MCC	165†	1.8036	$13,220	Always
Other resp system O.R. procedures w MCC	166†	3.6912	$27,055	Always
Other resp system O.R. procedures w CC	167†	2.0264	$14,853	Always
Other resp system O.R. procedures w/o CC/MCC	168†	1.3433	$9,846	Always
Respiratory neoplasms w MCC	180†	1.6950	$12,424	Always
Respiratory neoplasms w CC	181†	1.2316	$9,027	Always
Respiratory neoplasms w/o CC/MCC	182†	0.8736	$6,403	Always
Respiratory system diagnosis w ventilator support 96+ hours	207	5.1055	$37,422	After
Respiratory system diagnosis w ventilator support <96 hours	208	2.1801	$15,979	After
Chemotherapy w/o acute leukemia as secondary diagnosis w MCC	846†‡	2.1272	$15,592	After
Chemotherapy w/o acute leukemia as secondary diagnosis w CC	847†	0.9421	$6,905	After
Chemotherapy w/o acute leukemia as secondary diagnosis w/o CC/MCC	848†‡	0.7970	$5,842	After
Radiotherapy	849†	1.2094	$8,864	After
Septicemia or severe sepsis w MV 96+ hours	870	5.7258	$41,968	After
Septicemia or severe sepsis w/o MV 96+ hours w MCC	871	1.8222	$13,356	After
Septicemia or severe sepsis w/o MV 96+ hours w/o MCC	872	1.1209	$8,216	After
Complications of treatment w MCC	919‡	1.5223	$11,158	After
Complications of treatment w CC	920	0.9234	$6,768	After
Complications of treatment w/o CC/MCC	921‡	0.6109	$4,478	After
Other factors influencing health status	951†	0.7616	$5,582	After

*Price = Weight x $7,329.64 (Weights have been rounded to 4 decimal places).
**"Always" counted or counted only if discharge date was "After" lung cancer diagnosis.
†Selected as relevant before review of abstracted records.
‡There were no occurrences of these allowed MS-DRGs in the medical abstraction,

For the hospital component of inpatient care, we calculated each 2009 MS-DRG payment as the product of the MS-DRG weight [31] and a multiplier, $7,329.64. The multiplier was based on the formula for calculating Hospital Specific DRG Payments [32]:

Multiplier = [(Standardized Labor Share x Operating Wage Index) + (Standardized Non-Labor Share)] x (1 + Operating IME + Operating DSH Adjustment Factor) + (Standard Federal Rate) x (GAF) x (1 + DSH Adjustment Factor + IME Adjustment Factor)

The standardized amounts are shown in Table S6-3.

Table S6-3. Standardized amounts for 2009 for DRG calculator.

Standardized Labor Share	$3,574.50
Standardized Non-Labor Share	$1,553.91
Standard Federal Rate	$424.17

See Tables 1A and 1D at http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Acute-Inpatient-Files-for-Download-Items/CMS1247872.html

The impact factors (Operating Wage Index, Operating IME, Operating DSH Adjustment Factor, GAF, DSH Adjustment Factor, IME Adjustment Factor) were obtained from a convenience sample of 43 hospitals (at least one from each NLST screening center) weighted by recruitment numbers and the 2009 historical impact file [33], which adjusts for labor costs, indirect medical education, and disproportionate share of low-income patients.

For the professional component of inpatient care, we assumed that it was equal to 13% of the MS-DRG-specific payment based on the billings records for MS-DRGs 163-165 at two of the NLST sites (Dartmouth-Hitchcock Medical Center and Medical University of South Carolina).

6.2 Imputation of missing CPT and MS-DRG costs

For LSS participants (and ACRIN participants with missing medical abstraction records) with more than 2.5 years of follow-up since randomization we imputed costs over one-year time intervals defined by screening rounds T0, T1, and T2 from ACRIN participants with known costs using variables collected on all participants. For workup and hospitalization, we first matched on screening year and result, group, lung cancer stage (0, IA, IB, II, III, IV), vital status, and certain procedures (chest CT, PET, biopsy, and chest surgery) and then used a random hot deck method for imputation. We matched 97.7% of the time intervals on the first attempt. After we removed screening year and result from the match requirement, we matched 2.3% of the remaining time

intervals on the second attempt. We matched the remaining 0.12% of the time intervals on chest CT, PET, and chest surgery.

The above approach would underestimate CPT and DRG costs for those lost to follow-up because their costs would not include costs due to lung cancer diagnosis and procedures occurring after they were lost to follow-up. To minimize the underestimation of costs for participants lost to follow-up without a lung cancer diagnosis, those with 2.5 years or less of follow-up were divided into 4 categories based on duration of follow-up: 1) <= 2 days after randomization or first screen; 2) > 2 days, <= 6 months; 3) > 6 months, <=1.5 years; 4) > 1.5 years, <=2.5 years. Of the 102 participants in category 1, 100 (46 low-dose CT, 54 radiography) were excluded from the analysis (the remaining 2 were known to have died and were included in the analysis). For the participants in categories 2-4, costs were imputed after matching over the same length of follow-up, study group, and smoking status. For example, a subject lost to follow-up after 1 year without a lung cancer diagnosis would have his costs estimated from participants without a lung cancer diagnosis after 1.5 years, some of whom would subsequently incur costs for a lung cancer diagnosis occurring during the trial but more than 1.5 years after randomization. For participants lost to follow-up after a lung cancer diagnosis, we matched on year following lung cancer diagnosis, study group, smoking status and lung cancer stage.

6.3 Chemotherapy cost estimation

The cost of outpatient chemotherapy was based on the ACRIN subset of participants with lung cancer, for whom specific agents and start dates of treatment were abstracted (inpatient chemotherapy under MS-DRG 847 accounted for only 2% of the total chemotherapy costs). In this subset, 61 unique regimens (combinations of up to 3 agents) were abstracted. We (AN) estimated the costs for a 12-week course (3 cycles of 28 days or 4 cycles of 21 days) for any regimen used more than once, which accounted for about 95% of all treatments. The costs were based on 2012 Medicare reimbursements in the Los Angeles area for the agents themselves and the expected associated anti-emetics, other supportive drugs, infusions, office visits, and laboratory tests an adjustment for locality and year. These costs were multiplied by 0.824, the ratio of the national payment for an outpatient office visit (CPT 99211) in 2009, $18.75, to Los Angeles payment for the same visit in 2012, $22.77. In the base case, we initially assumed that participants received two 12-week courses over an estimated 14 visits based on the number of visits for each of the regimens and their frequencies. For example, one of the more commonly used regimens was Carboplatin/ Ectopicide, for which we estimated 9 visits per 12-week course or18 visits per two courses. However, because we observed only 9.5 chemotherapy visits in the

low-dose CT group and 9.3 chemotherapy visits in the radiography group of the ACRIN subset, we adjusted the chemotherapy cost downward by 9.5/14 in low-dose CT group and 9.3/14 in radiography group. Chemotherapy costs for LSS participants and ACRIN participants with missing records were estimated from the cost in the ACRIN subset after matching on stage (IV versus other), histology (small cell lung cancer versus other histology), vital status, and follow-up time after diagnosis (less than versus greater than or equal to 180 days). The mean discounted total (direct and indirect) cost of chemotherapy for the 971 participants receiving chemotherapy was approximately $17,000, about $3,000 of which was for time and travel.

6.4 Radiation therapy cost estimation

The cost of outpatient radiation therapy was based on the ACRIN subset of participants who received at least one radiation therapy procedure for lung cancer based on CPT coding in the medical record abstraction (inpatient radiation therapy under MS-DRG 849 accounted for less than 1% of the total radiation therapy costs). The mean non-discounted direct cost was $3,880, which we applied to all participants in NLST who had received radiation therapy for lung cancer. We also assumed that each participant receiving radiation therapy had 30 visits. There is a wide variation in the direct costs of different therapies, ranging up to about $25,000 for intensity-modulated radiation therapy (IMRT). However, we did not include any cost variation because in the comparison between low-dose CT screening and no screening the absolute value of the incremental cost of XRT was less than 1% of the total incremental cost of low-dose CT. The mean discounted total (direct and indirect) cost of radiation therapy for the 623 participants receiving radiation therapy was approximately $8,000, about $4,600 of which was for time and travel.

6.5 Indirect costs

Indirect medical costs were based on time and travel for the subject and caregiver using a previously reported methodology for colon cancer screening [34]. Time costs were based on total subject and caregiver time expended for workup and treatment of lung cancer and the mean hourly total compensation costs for civilian workers in 2009, $29.37 [29]. The cost of travel included estimated time and round trip mileage at the U.S. government automobile reimbursement rate per mile, $0.55 [30]. We assumed a 50 mile round trip for each medical encounter given that the mean trip distance measured from the home zip code to the screening center in the ACRIN subset was 56 miles. Using this approach, the non-discounted costs of time

and travel for each screening, workup and surgical visit was $101, for each radiation therapy visit, $175, and for each chemotherapy visit, $381.

6.6 Discounting

As with life-years and QALYs, we discounted costs 3% annually starting in the second year. For screening costs, we assumed that the T0, T1, and T2 exams were performed during first, second, and third years since randomization. For CPT and DRG costs, we used the abstracted dates of the procedures and hospital discharges in the ACRIN subset to determine the year since randomization during which the service was provided. For chemotherapy costs, we assumed that these services were provided at 2.82 years in the low-dose CT group and 3.23 years in the radiography group based on the mean lengths of time between randomization and the start of these treatments in the study population. Similarly, for radiation therapy costs, we assumed that these services were provided at 2.90 years in the low-dose CT group and 3.31 years in the radiography group.

6.7 Additional cost of significant incidental findings

There is no reliable information on the costs of managing potentially significant incidental findings, however, two recent studies of lung cancer screening with CT in Italy and Canada reported radiologic costs of $129 [35] and $95 [36] per finding. In a study of incidental findings in CT colonography in the US, total medical costs were about $1,600 per finding, only about one-thirds of which was due to radiologic imaging. For the base case, we assumed that 15% of participants in the low-dose CT group had at least one potentially significant incidental finding [11] and the total (direct and indirect) cost of managing the findings was $500 per participant. We incorporated this cost into the cost of the low-dose CT screening exam (we did not include this cost in the radiography or no screening groups). Given that participants in the low-dose CT group had on average about 2.8 screening exams, we added $26.68 ($500*0.15/2.8) to the cost of each low-dose CT screening exam. In the sensitivity analysis (Table S7-19), we varied the proportion of participants with these findings and the costs of managing them.

APPENDIX 7

Statistical analyses

7.1 LEs, QALEs, and expected costs

To obtain the point estimates of the LEs, QALEs, and expected costs for each group, we subdivided the groups by lung cancer status and weighed the components by the proportions with lung cancer (PLC) and without (1-PLC) within the full NLST population (53,452). For example:

$$LE_{CT}=LELC_{CT}*PLC_{CT}+LENLC*(1-PLC_{CT}) \quad \text{Eq 1}$$

$$LE_{rad}=LELC_{rad}*PLC_{rad}+LENLC*(1-PLC_{rad}) \quad \text{Eq 2}$$

where PLC_{CT} =0.042 (1,109/26,722) and PLC_{rad}=0.037 (993/26,730).

We used these weights because more participants with lung cancer were excluded from the low-dose CT group (33) than from the radiography group (15) in the NLST CEA sample (53,302). Also note that we assumed that the LE in the derived no screening group (LE_{NO}) was equal to LE_{rad}. Next, we calculated the quality adjusted life-expectancies (QALEs) for the low-dose CT and no screening groups in the exact same manner. We calculated the expected costs for the low-dose CT, C_{CT}, and no screening, C_{NO}, groups using the same weights but we estimated the costs in the no screening group to be equal to those for the radiography group minus the costs of the screening exams and the workup for false positive results. To obtain the ICERs, we divided the incremental costs and incremental health effects as follows:

$$\$/LY = (C_{CT}-C_{NO})/(LE_{CT}-LE_{NO}) \quad \text{Eq 3}$$

$$\$/QALY = (C_{CT}-C_{NO})/(QALE_{CT}-QALE_{NO}) \quad \text{Eq 4}$$

7.2 Bootstrap confidence intervals

We estimated the bootstrap 95% confidence interval for the ICERs using the following four step process [37].

1) We drew a random sample of size n_{CT}=26,642 with replacement from the low-dose CT group and calculated the LEs, QALEs, and costs using the same weights as in Eqs 1 and 2.

2) We drew a random sample of size n_{NO}=26,660 with replacement from the no screening group and calculated the LEs, QALEs, and costs using the same weights as in Eqs 1 and 2.

3) We calculated the bootstrap estimates of the LEs, QALEs, expected costs and the ICERs using Eqs 3 and 4.

4) We repeated the bootstrap B=10,000 iterations. To account for a few negative or extremely large ICER estimates related to a few iterations with negative or near-zero incremental health effects, we replaced the negative ICERs with positive values equal to 1 plus the highest positive values and winsorized the distribution by replacing the 10 smallest ICER estimates with the 11th smallest and replacing the 10 largest ICER estimates with the 11th largest [38]. From this winsorized distribution of 10,000 bootstrap replicates, we found the 2.5th and 97.5th percentile values and set these as the 95% bootstrapped confidence interval.

Bias

We also calculated the bootstrap estimator of the bias in using the observed ICER as an estimate of the true underlying ICER. That bias can be estimated as the difference between the mean of the winsorized 10,000 bootstrap estimates of the ICER and the point estimate of the ICER [37]. The estimated bias of the quality-adjusted ICER equaled $9,600 (90,807 - 81,206) per QALY gained and was 23% of the estimated standard error (9,600 / 41,211). For this reason, following the recommendation in Efron and Tibshirani [39] we did not adjust for bias in either the point estimate or the confidence intervals). Had we done so, the unbiased estimate of the ICER would have been $81,206- $9,600 = $71,606 per QALY gained.

7.3 Subset analyses

We performed subset analyses based on gender, 5-year age groups between 55-59 years old and 70-74 years old at entry, smoking status (current versus former), and quintiles of lung cancer risk based on a recently validated model [40]. We estimated the QALEs and expected costs for each subset within the NLST CEA sample (N=53,302) in the same manner that we estimated these outcomes for the full sample except that we used the proportions of lung cancer in each respective subset within the full NLST population (N=53,452). For example, in the estimation of QALEs for men, we subdivided the 31,446 male participants (Table S13) by group and lung cancer status and applied Eqs S1 and S2 using the proportions of lung cancer among the men in the full NLST population, PLC_{CT} =0.0424 and PLC_{rad}=0.0373.Then we used Eqs 3 and 4 to estimate the cost per QALY gained among men. As detailed below, we included the effects of radiation induced lung in estimating the incremental costs and QALYs accounting for different risk factors related to age, sex, and smoking status [41]. One of the risk factors for developing a radiation induced lung cancer is the risk of developing non-radiation induced lung cancer and we assumed that former smokers had a 6.6 relative risk compared to never smokers [42].

Table S7-1. Subset analyses.

Subset	**Number of participants**	**Incremental costs**	**Incremental QALYs**	**$/QALY**
Gender				
Men	31,446	$1,683	0.0115	147,000
Women	21,856	$1,557	0.0340	46,000
Age (years at entry)				
55-60	22,773	$1,541	0.0101	152,000
60-65	16,333	$1,520	0.0320	48,000
65-70	9,504	$1,900	0.0351	54,000
70-75	4,685	$1,905	0.0163	117,000
Smoking status				
Former	27,643	$1,661	0.0027	615,000
Current	25,659	$1,601	0.0369	43,000
Lung cancer risk				
First quintile	10,660	$1,453	0.0086	169,000
Second quintile	10,661	$1,454	0.0118	123,000
Third quintile	10,660	$1,651	0.0061	269,000
Fourth quintile	10,661	$1,672	0.0515	32,000
Fifth quintile	10,660	$1,851	0.0354	52,000

Sensitivity analyses

7.4.1. Inclusion of deaths from causes other than lung cancer

In the base case scenario, we chose to consider only lung cancer deaths and assume that any reduction in non-lung cancer deaths was due to chance alone. At the end of the trial, there were 83 fewer lung cancer deaths and 41 fewer deaths from other causes in the low-dose CT group than in the radiography group (Table S2-1), possibly due to management of incidental findings, misclassification of death, chance, or some combination. Had we included all deaths in our analysis and assumed the same health benefit for preventing non-lung cancer and lung cancer deaths, the incremental health effect for the low-dose CT group compared the no screening group would have been approximately 124/83 times larger than 0.0201 or 0.0300. The ICER would be $54,000 ($1,631/0.0300) per QALY gained.

Effectiveness of chest radiography screening

To assess the internal validity of our analysis, we relaxed our assumption that radiography screening (compared to no screening) had no effect on lung cancer mortality and considered relative risks ranging from 0.80 to 1.1. The PLCO recently reported a relative risk of 0.94 (95% CI: 0.80-1.15) for the NLST eligible subset [1]. We assumed that the relative risk of low-dose CT screening to no screening ($RR_{CT/NO}$) is equal to the product of the relative risk of low-dose CT screening to radiography screening ($RR_{CT/rad}$) and the relative risk of radiography screening to no ($RR_{rad/NO}$). Based on the most recent reporting of lung cancer mortality reduction in NLST, $RR_{CT/rad} = 0.84$[43].

$$RR_{CT/NO}=RR_{CT/rad}* RR_{rad/NO}$$

$$RR_{CT/NO}=0.84* RR_{rad/NO}$$

Since relative risk reduction (RRR) = 1-RR,

$$RRR_{CT/NO} =1 – 0.84* RR_{rad/NO}$$

We also assumed that the incremental gain in QALYs between low-dose CT screening and no screening (ΔQ) would be directly proportional to $RRR_{CT/NO}$.

$$\Delta Q = k*RRR_{CT/NO}$$

In the base case, $RR_{rad/NO} = 1$ and $\Delta Q = 0.0201$ QALYs so

$RRR_{CT/NO}$ $=1 - 0.84 = 0.16$ and

k $=0.0201/0.16 = 0.1256$

Since we are assuming a fixed incremental cost of low-dose CT screening versus no screening, $1,631,

$\Delta C/\Delta Q$ $= \$1631/[0.1256*(1 - 0.84*RR_{rad/NO})]$

Table S7-2. $/QALY versus $RR_{rad/NO}$.

$RR_{rad/NO}$	$/QALY
0.80	40,000
0.85	45,000
0.90	53,000
0.94	62,000
0.95	64,000
1.00	**81,000**
1.05	110,000
1.10	171,000

Future excess lung cancers in radiography group

We also relaxed our assumption that all excess lung cancers in the low-dose CT group were due to overdiagnosis and considered the possibility that there would be future excess cases in the radiography group. We chose a range from 0 to 58 given that there were 116 more lung cancers diagnosed in the low-dose CT group than in the radiography group through the end of the trial (Table S2-1), some overdiagnosis of lung cancer was expected on the basis of previous studies[44, 45] but that there was an excess lung cancer incidence in the radiography group of about 1.0 per 1,000 person-years during the last 1.5 years of the NLST and modeling has shown that about one-half of the cumulative excess in NSCLC in the low-dose CT group would disappear with lifetime follow-up [46]. We assumed that participants with future lung cancers in the radiography group would have the same QALE and lung cancer costs from the end of the

trial, as did the observed lung cancer participants in the radiography group from the start of the trial.

Participants in the radiography group without lung cancer alive at the end of the trial had a discounted QALE of 7.20 QALYs from the end of the trial. Participants in the radiography group with lung cancer diagnosed after the screening phase had a non-discounted QALE of 3.13 QALYs from diagnosis. The non-discounted cost of lung cancer management in the no screening group is $31,873. Assuming excess lung cancers in the radiography group have the same outcomes and are diagnosed on average 2 years after the end of the trial (average follow-up in trial 6.4 years), each excess case in the radiography group would lose 3.41 QALYs after discounting(7.20 - 0.75/(1.03)^(6.4) - 0.75/(1.03)^(7.4) 3.13/(1.03)^(8.4)). In addition, each excess case would gain $24,865 ($31,873/(1.03)^(8.4)) in costs. Consequently, the ICER falls from $81,000 per QALY gained to $55,000 per QALY gained as the number of excess cases increase to 58.

Table S7-3. $/QALY versus number of future excess lung cancer in radiography group.

Excess cases	Lost Q_{rad}	Added cost	ΔC	ΔQ	$/QALY
0	**0.0000**	**0**	**$1,631**	**0.0201**	**81,000**
29	0.0042	30	$1,602	0.0243	66,000
58	0.0084	60	$1,572	0.0285	55,000

7.4.2 Survival for stage IA NSCLC

Because of the large disparity across groups in the numbers of participants with stage IA non-small cell lung cancer (NSCLC) alive at the end of the trial, 324 in CT versus 140 in radiography, and the uncertainty in survival beyond 5 years from diagnosis, we repeated the analysis for optimistic and pessimistic assumptions about the long term hazards of dying from lung cancer. In the optimistic scenario, we used a constant hazard of 0.01 per year, which is slightly greater than the observed annual hazard for all those randomized to the radiography group. This change increased the incremental QALE to 0.0242 and decreased the ICER from the base case to $67,000 per QALY gained. For the pessimistic scenario, we used a constant covariate-specific hazard equal to that observed for stage IA NSCLC during years 2 through 5 of the trial (see Table S4-1). This change decreased the incremental QALE to 0.0151 and increased the ICER from the base case to $108,000 per QALY gained.

7.4.3 Relative risk adjustment for smoking

In the base case scenario, we assumed that the all-cause mortality for participants without lung cancer would be the same as for the general US population after adjustment for smoking. However, the adjustment for smoking is based on the general population of smokers in the US population while the NLST population had much greater smoking history, greater than or equal to 30 pack years. To assess the potential impact of a higher relative risk due to smoking or other cause, we multiplied the age and sex-specific relative risks of death by smoking status in the general population (Table S3-2) by a factor of 2, which decreased the incremental QALE from 0.0201 to 0.0171 and increased the ICER to $95,000 per QALY gained.

Overdiagnosis in chest radiography group

In the base case scenario, we assumed that there was no overdiagnosis in the radiography group based on the recent findings in the NLST-eligible subset of the PLCO (N=30,321), who were randomized to 4 annual screens with chest radiography versus no screening [1]. After 6 years, the rate ratio for a lung cancer diagnosis in the radiography screening group versus the no screening group was 1.00 (In the full cohort, N=154,901, the RR was 1.02 after 6 years). However, overdiagnosis with chest radiography has been observed in previous trials of screening with chest radiography. In the Mayo Lung Cancer Project [47](MLP) (N=9,211), 90 lung cancers were screen detected in the screened group and 46 more lung cancers were diagnosed in the screening group yielding an overdiagnosis rate of 51% (46/90). However, screening in MLP was performed 3 times per year for 6 years and 16 lung cancers were diagnosed by sputum cytology alone.

To assess the potential impact of overdiagnosis in the radiography group of NLST, we start with the following assertions:

- 26,730 subjects in the radiography group
- 279 of the lung cancers in radiography group were detected by screening
- The base case incremental cost of low-dose CT versus no screening is $1,631.
- The base case incremental QALE of low-dose CT versus no screening is 0.0201.
- 90% of overdiagnosis cases were stage IA, 10% stage IB (At the end of the trial, the excess in the low-dose CT group was much greater for Stage IA, 416 versus 196, than for stage B, 104 versus 93) .
- Incremental harm of overdiagnosis per case = 0.67 QALYs based on Table S5-3.

- Incremental cost of overdiagnosis vs no lung cancer per case (IC) = mean cost of lung cancer in no screening group = $31,873

If P is the proportion of the 279 screened detected lung cancers in the chest radiography group that were overdiagnosed, then

- QALE in the no screening group was underestimated by P*(279/26730)*0.67
- Per subject cost in the no screening group was overestimated by P*(279/26730)*IC
- $\Delta C/\Delta Q$ = [$1,631 + P*(279/26730)*IC]/[0.0201 - P*(279/26730)*0.67]

We chose 0 for the base case estimate because, compared to the MLP, the PLCO is much more recent, more than 3 times as large, and far more comparable to the NLST with regard to study population and intervention.

Table S7-4. $/QALY versus proportion of lung cancers overdiagnosed in radiography group.

Proportion	$/QALY
0	**81,000**
0.1	86,000
0.2	91,000
0.3	96,000
0.4	102,000
0.5	108,000

Radiation induced lung cancer deaths

There is a small theoretical risk of radiation induced lung cancer death associated with low-dose chest CT beginning about 10 years after exposure. It has been estimated that with continued annual screening from age 55 to 80 in a US cohort of 100,000 adults there would be 24 induced lung cancer deaths compared to 521 prevented lung cancer deaths [48].

To assess the potential impact of radiation induced lung cancer in the low-dose CT group of NLST, we start with the following assumptions:

- Before consideration of radiation effects, the incremental QALE of low-dose CT versus no screening is 0.0205.
- Before consideration of radiation effects, the incremental per person cost of low-dose CT versus no screening, is $1,628.
- The ratio of radiation induced lung cancer deaths to lung cancer deaths prevented is 24/521 = 0.046 [48].

- The lag time from the first low-dose screening CT to the diagnosis of radiation induced lung cancer >= 10 years.
- In the NLST, the mean age at entry was 61.
- For a 61 year old smoker, the mean years of (discounted) lost life from radiation induced lung cancer is 4.2 years based on method of Berrington [41].
- There were 83 fewer lung cancer deaths in the low-dose CT group (N=26,722) than in the radiography group (Table S2-1).
- The mean utility at the start of the trial was 0.75
- The incremental cost of managing each lung cancer during the trial is $31,873.
- The incremental cost of managing each lung cancer after the trial is $24,428 = $31,873/(1.03)^9.

Given the above assumptions,

- After adjustment of radiation effects, the incremental QALE of low-dose CT versus no screening = 0.0205 - 0.046*(83/26722)*4.2*0.75 = 0.0201
- After adjustment of radiation effects, the incremental cost of low-dose CT versus no screening = $1,628 + 0.046*(83/26722)*$24,428 = $1,631.

Table S7-5. $/QALY versus ratio of radiation-induced to prevented lung cancer deaths.

Radiation risk ratio	$/QALY
0	79,000
0.023	80,000
0.046	**81,000**
0.069	82,000
0.092	83,000

Quality of life following lung cancer diagnosis

In the base case scenario, we used the stage and time dependent utilities based on SF-6D results in NLST and a recent meta-analysis (Table S5-3). Although the base case utilities were slightly different than the observed utilities (Table S5-2), they both resulted in an ICER of $81,000 per QALY gained. Because the utility values for lung cancer in NLST were higher than previously reported for advanced stages, we subtracted 0.05 to 0.25 from the stage IV lung cancer utilities (stage IV), fixed the stage IA utilities and re-interpolated the remaining utilities for stages

IB, II, and III. Table S7-6 shows that the $/QALY decreases slightly with the utilities for stage IV.

Table S7-6. $/QALY versus decrease in offstage IV lung cancer utilities.

Decrease in utilities for Stage IV	$/QALY
0	**81,000**
0.05	81,000
0.10	81,000
0.15	80,000
0.20	80,000
0.25	80,000

In addition, because there was a large excess of stage IA in the low-dose CT group, we varied the utilities for stage IA by adding 0.02 to subtracting 0.05 to the baseline values. Table S7-7 shows that the $/QALY increases from the base case as stage IA utilities are decreased.

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Table S7-7. $/QALY versus change in stage IA lung cancer utilities.

Change in utilities for Stage IA	$/QALY
+0.02	74,000
0.00	**81,000**
-0.02	90,000
-0.04	101,000

Quality of life following screening CT

In the base case scenario, we assumed that the CT screening results did not affect quality of life based on the SF-6D and EQ-5D questionnaires completed by NLST participants. However, the NELSON investigators reported a statistically significant increase in lung-cancer specific distress after a positive screen on the IES total score [27] and a statistically significant decrease after a negative screen, about 40% as large as the increase. They also reported a clinically insignificant decrease on the EQ-5D, VAS of 0.04. Although disease-specific quality of life instruments do not provide utilities for cost-effectiveness analysis, we explored the effects of changes in quality of life following positive and negative screens. To assess the potential impact of positive and negative screening results, we start with the following assertions:

- 24% of all CT screens were positive [11]
- 76% of all CT screens were negative.
- The average duration of effect was 6 months.
- Baseline utility value was 0.75 (see Appendix 5)
- The base case incremental QALE of low-dose CT versus no screening is 0.0201.
- The decrease (P) in QOL after a positive ranges from 0 to 0.05.
- The increase (Q) in QOL after a negative ranges from 0 to 0.02

We then vary the proportional decrease and increase over these ranges and note:

- The decrease in QALE from all positive screens = P*0.24*0.5= P *0.12
- The increase in QALE from all negative screens = Q*0.76*0.5= Q* 0.38
- The net change in QALE from all screens = -P *0.12 + Q*0.38

$\Delta C/\Delta Q$ =1631/(0.0201 - P *0.12 + Q*0.38).

Table S7-8. $/QALY by changes in utilities associated with screening results.

		Increase after negative screen				
Decrease after positive screen	**0**	0.004	0.008	0.012	0.016	0.02
0	**81,000**	75,000	71,000	66,000	62,000	59,000
0.01	86,000	80,000	74,000	70,000	65,000	62,000
0.02	92,000	85,000	79,000	73,000	69,000	65,000
0.03	99,000	91,000	84,000	78,000	72,000	68,000
0.04	107,000	97,000	89,000	82,000	76,000	71,000
0.05	116,000	105,000	95,000	87,000	81,000	75,000

Surgical mortality

To assess the impact of surgical mortality on the cost effectiveness of low-dose CT screening versus no screening, we assumed that those receiving surgery in the low-dose CT group have a QALE of 10.0 QALYs if they survive surgery and a QALE of 0 if they do not. The QALE of those without lung cancer was 11.18 QALYs (see Table 1) and the 5-year survival for participants with stage I lung cancer in the low-dose CT group was about 90%. The surgical mortality in the NLST was 1.2% [11] and 124 more participants in the low-dose CT group than is the radiography group received surgery (MS-DRG codes 163-168). The observed the incremental gain in QALYs (ΔQ) was 0.0201. Thus,

$\Delta Q = 0.0201 - ((M-1.2)/100)*124*(10/26722)$,

where M is the surgical mortality (%).

Table S7-9. $/QALY versus surgical mortality.

Surgical mortality (%)	$/QALY
0	$79,000
1	**$81,000**
2	$83,000
3	$85,000
4	$87,000
5	$89,000
6	$91,000
7	$94,000
8	$96,000
9	$99,000
10	$102,000

Cost of low-dose CT screening exam

We replaced the base case Medicare price of $285 (Table S6-2), with multiples of $100 ranging from $0 to $800 and recomputed the costs for the low-dose CT group (with discounting based on the year of the exam).

Table S7-10. $/QALY versus cost of low-dose CT screening exam.

Cost of CT exam	$/QALY
$0	42,000
$100	56,000
$200	70,000
$285	**81,000**
$300	83,000
$400	97,000
$500	110,000
$600	124,000
$700	138,000
$800	151,000

Cost of time and travel for screening

We multiplied our base case estimate of $101 by a factor of 0.5 to 3 and recomputed the costs for the low-dose CT and no screening groups (with discounting based on the year of the travel).

Table S7-11. $/QALY versus cost of time and travel for screening.

Factor	$/QALY
0.5	74,000
1	**81,000**
2	95,000
3	109,000

Cost of CT follow-up exam and PET-CT

We multiplied the Medicare prices, $285 for CT and $1,284 for PET-CT (Table S6-2), by a factor of 0.5 to 5 and recomputed the costs for the low-dose CT group (with discounting based on the year of the exam).

Table S7-12. $/QALY versus cost of CT follow-up exam.

Factor	$/QALY
0.5	79,000
1	**81,000**
2	87,000
3	93,000

Table S7-13. $/QALY versus cost of PET-CT exam.

Factor	$/QALY
0.5	80,000
1	**81,000**
2	84,000
3	86,000
4	89,000
5	91,000

Number of follow-up CT exams

We multiplied the number of follow-up CT exams by a factor of 0.5 to 5 and recomputed the costs for the low-dose CT group (with discounting based on the year of the exam).

Table S7-14. $/QALY versus number of follow-up CT exams.

Factor	$/QALY
0.5	78,000
1	**81,000**
2	88,000
3	96,000
4	103,000
5	110,000

Cost of surgical resection

We multiplied the non-discounted cost of surgery, $22,258 ($19,697 based on the Medicare price of MS-DRGs 163-165 (Table S6-2) weighted by their frequency in NLST plus 13% professional component) by a factor of 0.5 to 3 and recomputed the costs for the low-dose CT and no screening groups (with discounting based on the year of the surgery).

Table S7-15. $/QALY versus cost surgical resection.

Factor	$/QALY
0.5	73,000
1	**81,000**
2	98,000
3	114,000

Cost of time and travel for workup and surgical treatment

We multiplied our base case estimate of $101 by a factor of 0.5 to 3 and recomputed the costs for the low-dose CT and no screening groups (with discounting based on the year of the travel).

Table S7-16. $/QALY versus cost of time and travel for workup.

Factor	$/QALY
0.5	80,000
1	**81,000**
2	84,000
3	87,000

Cost of chemotherapy

We multiplied our base case estimate based on two 12- week courses (mean total discounted cost about $17,000 per case), by a factor of 0 to 3, corresponding to the number of 12-week courses and recomputed the costs for the low-dose CT and no screening groups.

Table S7-17. $/QALY versus number of chemotherapy courses.

# of courses	$/QALY
0	85,000
1	83,000
2	**81,000**
3	79,000
4	78,000
5	76,000
6	74,000

Cost of radiation therapy

We multiplied our base case estimate (mean total discounted cost about $8,000 per case), by a factor of 0 to 5 and recomputed the costs for the low-dose CT and no screening groups (with discounting based on the year of the treatment).

Table S7-18. $/QALY versus radiation therapy factor.

Factor	$/QALY
0	82,000
1	**81,000**
2	80,000
3	79,000
4	78,000
5	77,000

Cost of significant incidental findings

To assess the impact of potentially significant incidental findings on the cost effectiveness of low-dose CT screening versus no screening, we assumed that their detection had no impact on LE or QALE and considered only their cost as a function of the proportion of participants in the low-dose CT group that had at least one potentially significant incidental findings (P_{SIF}) and their average total, direct and indirect costs (C_{SIF}).

In the base case, we set P_{SIF} to 0.15 [11] and $C_{SIF}$to $500 (see Section 6.7). We also considered doubling P_{SIF} and varying C_{SIF} from 0 to $2,500.

Table S7-19. $/QALY versus proportion with and cost of significant incidental finding (SIF).

	Proportion with SIF	
Cost per SIF	0.15	0.3
$0	78,000	78,000
$500	**81,000**	85,000
$1,000	85,000	92,000
$1,500	88,000	99,000
$2,000	92,000	107,000
$2,500	96,000	114,000

Cost of medical care after trial

To assess the impact of future health care costs beyond the trial (unrelated to lung cancers diagnosed during the trial or induced by radiation from CT screening), we added these costs to those participants alive and the end of the trial as a function of their age and per capita total health care costs in 2004 [49] multiplied by the ratio of national health care expenditure in 2009 to 2004, 1.32.[50](Table S7-20). The future costs per person were $171,018 for the low-dose CT group and $170,248 for no screening (and radiography) groups because there was a higher proportion of participants alive in the low-dose CT than the radiography group at the end of the trial. Consequently, the incremental cost per person increased from the base case $1,631 to $2,402 and the $/QALY increased from the base case to $120,000.

Table S7-20. Total per capital health care costs by age [49].

Age Group	2004	2009
55-64	$7,787	$10,279
65-74	$10,778	$14,227
75-84	$16,389	$21,633
85+	$25,691	$33,912

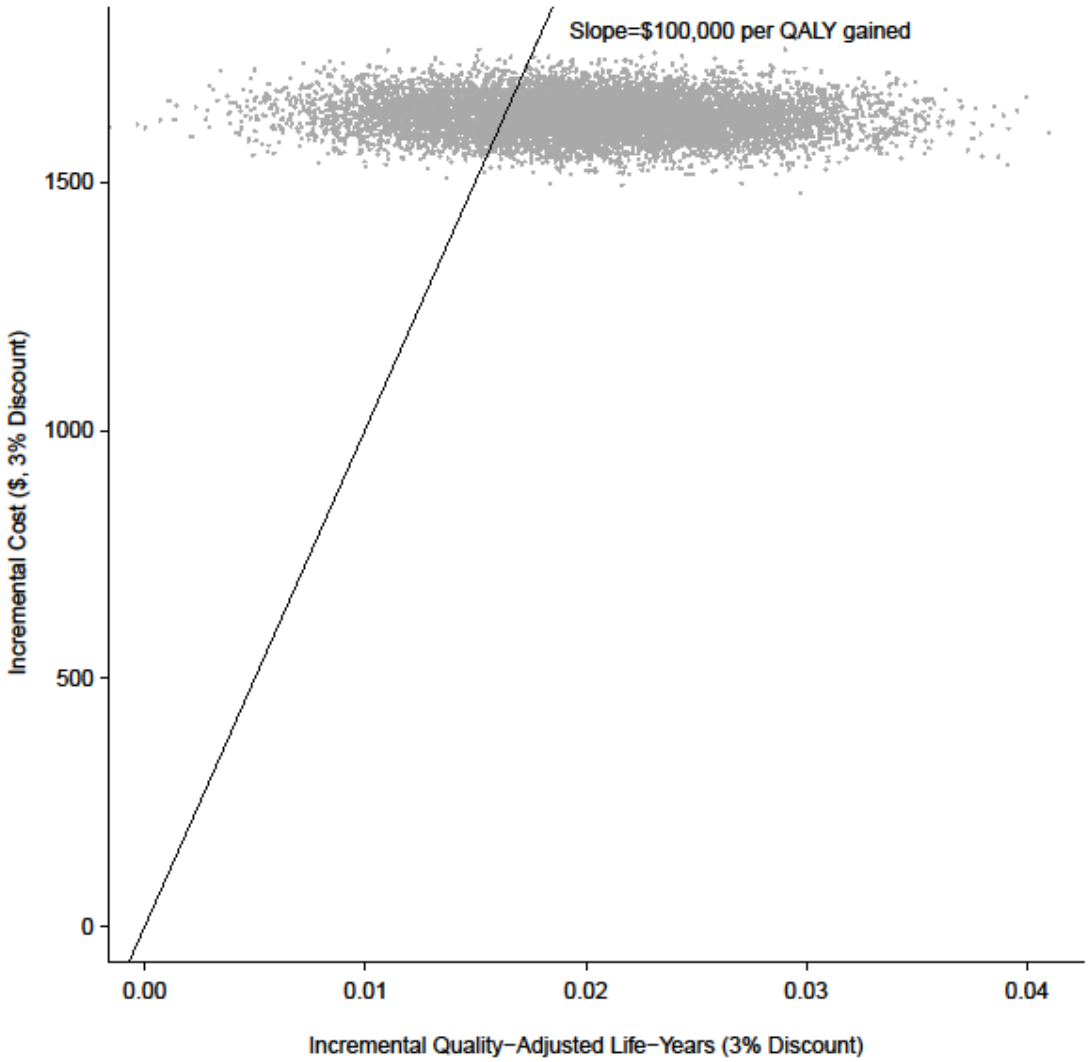

Figure S7-1. Scatterplot of incremental quality-adjusted life years and incremental cost obtained by 10,000 bootstrap samplings.

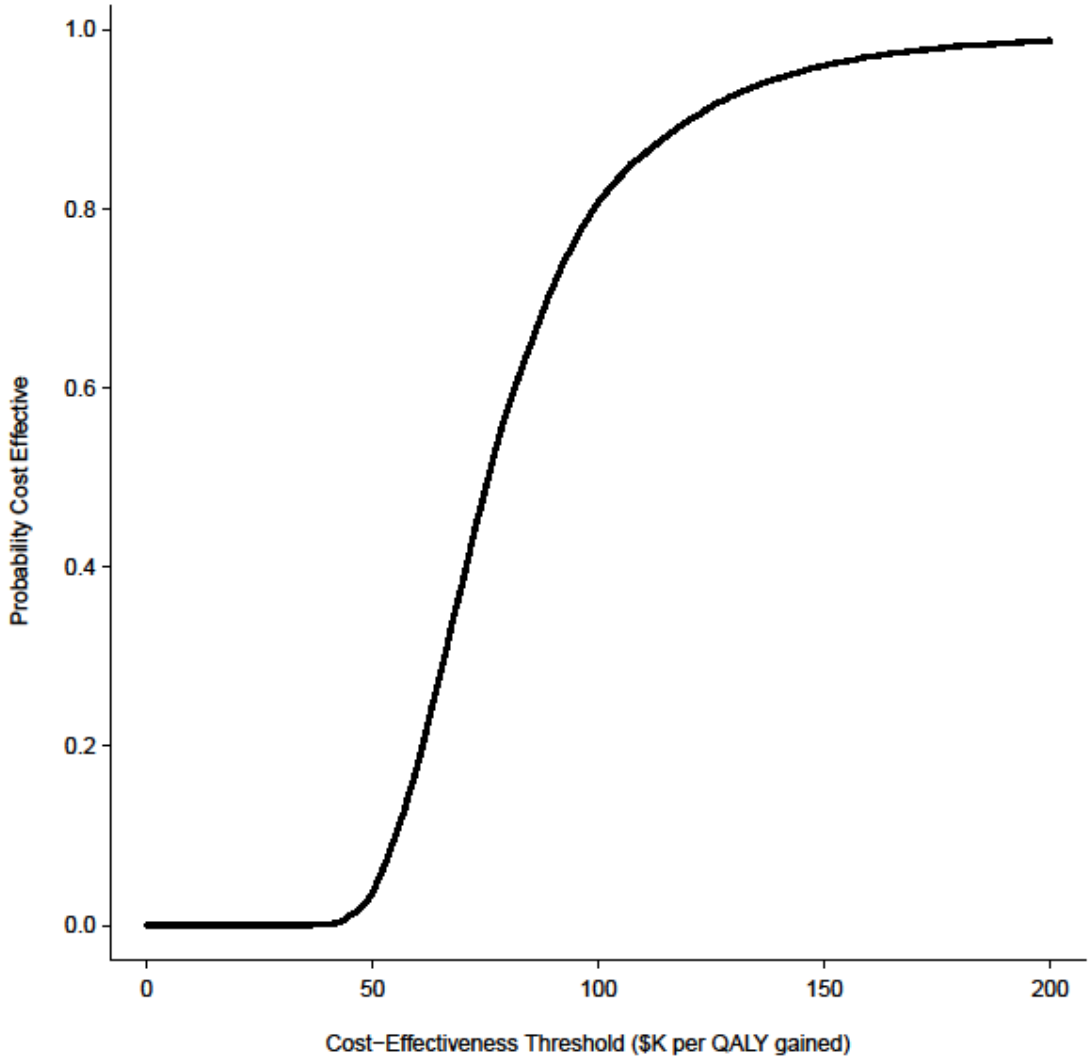

Figure S7-2. Cost-effectiveness acceptability curve (CEAC). As the cost-effectiveness threshold increases, the probability that CT screening for lung cancer is cost-effective also increases.

APPENDIX 8

NLST-ACRIN Research Team

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