

ORIGINAL ARTICLE

Cost-Effectiveness of CT Screening in the National Lung Screening Trial

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ABSTRACT

BACKGROUND

The National Lung Screening Trial (NLST) showed that screening with low-dose computed tomography (CT) as compared with chest radiography reduced lung-cancer mortality. We examined the cost-effectiveness of screening with low-dose CT in the NLST.

METHODS

We estimated mean life-years, quality-adjusted life-years (QALYs), costs per person, and incremental cost-effectiveness ratios (ICERs) for three alternative strategies: screening with low-dose CT, screening with radiography, and no screening. Estimations of life-years were based on the number of observed deaths that occurred during the trial and the projected survival of persons who were alive at the end of the trial. Quality adjustments were derived from a subgroup of participants who were selected to complete quality-of-life surveys. Costs were based on utilization rates and Medicare reimbursements. We also performed analyses of subgroups defined according to age, sex, smoking history, and risk of lung cancer and performed sensitivity analyses based on several assumptions.

RESULTS

As compared with no screening, screening with low-dose CT cost an additional \$1,631 per person (95% confidence interval [CI], 1,557 to 1,709) and provided an additional 0.0316 life-years per person (95% CI, 0.0154 to 0.0478) and 0.0201 QALYs per person (95% CI, 0.0088 to 0.0314). The corresponding ICERs were \$52,000 per life-year gained (95% CI, 34,000 to 106,000) and \$81,000 per QALY gained (95% CI, 52,000 to 186,000). However, the ICERs varied widely in subgroup and sensitivity analyses.

CONCLUSIONS

We estimated that screening for lung cancer with low-dose CT would cost \$81,000 per QALY gained, but we also determined that modest changes in our assumptions would greatly alter this figure. The determination of whether screening outside the trial will be cost-effective will depend on how screening is implemented. (Funded by the National Cancer Institute; NLST ClinicalTrials.gov number, NCT00047385.)

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N Engl J Med 2014;371:1793-802.

DOI: 10.1056/NEJMoa1312547

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LUNG CANCER IS THE LEADING CAUSE OF cancer-related deaths in the United States¹; however, until recently, no method of screening had been shown to reduce mortality from lung cancer. The National Lung Screening Trial (NLST) showed that screening with low-dose helical computed tomography (CT) of the chest in patients at high risk for lung cancer was associated with a 20% reduction in lung-cancer mortality.² Several major medical societies have since recommended screening with low-dose CT for patients with a similarly high risk of lung cancer.³ The U.S. Preventive Services Task Force has released a grade B recommendation for low-dose CT screening,⁴ which means that private insurers must cover the cost of screening.⁵

One major consideration for policymakers is the cost-effectiveness of this screening intervention.⁶ Before publication of the NLST results, several cost-effectiveness analyses reported results ranging from very favorable^{7,8} to unfavorable.^{9,10} This variation reflected both the uncertainty regarding the effectiveness of screening with low-dose CT for lung cancer and the use of different methods of analysis. At the inception of the NLST, the investigators planned to use the results of the trial to conduct cost-effectiveness analyses and planned the data collection accordingly.^{2,11-13} The primary focus of this report is the cost-effectiveness of screening with low-dose CT as performed in the NLST. The report includes an extensive sensitivity analysis, which is relevant to extrapolation beyond the NLST findings (see Section 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

METHODS

NLST POPULATION

The NLST was a joint effort of the American College of Radiology Imaging Network (ACRIN) and the Lung Screening Study (LSS). From August 2002 through April 2004, a total of 53,452 persons were enrolled and randomly assigned to undergo three annual screenings with either low-dose CT or chest radiography.² Participants were followed through December 31, 2009. Major eligibility criteria included an age between 55 and 74 years and a smoking history of at least 30 pack-years. The study protocol was approved by the

institutional review board at each of 33 screening centers (23 ACRIN centers and 10 LSS centers), and written informed consent was obtained from each participant before randomization.

Vital status was based on questionnaires administered semiannually (ACRIN) or annually (LSS); for participants lost to follow-up, status was based on data from the National Death Index. Medical records were obtained from participants who had received positive screening results, a diagnosis of lung cancer, or both, and information related to diagnostic procedures and lung-cancer staging and treatment was abstracted with the use of forms that were harmonized across ACRIN and LSS. More detailed information related to diagnostic procedures and lung-cancer treatment was collected from ACRIN sites to inform the cost-effectiveness analysis^{14,15} (see Section 6 in the Supplementary Appendix). In addition, data on health-related quality of life were collected from participants at 16 of the ACRIN screening centers.

SCREENING STRATEGIES AND STUDY DESIGN

We compared three strategies: screening with low-dose CT, screening with radiography, and no screening. For the two screening strategies, cost and health outcomes were based directly on trial data. For the strategy of no screening, we assumed that health outcomes would be the same as those in the radiography group and that costs would equal those in the radiography group minus the costs of screening examinations and workups for false positive results. We based these assumptions on the results of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial,¹⁶ which showed no significant reduction in lung-cancer mortality or overdiagnosis in the group randomly assigned to screening with chest radiography.

The analysis conformed to the reference-case recommendations of the U.S. Panel on Cost-Effectiveness in Health and Medicine.¹² Assuming that screening would affect only the costs and health benefits related to lung-cancer screening and treatment, we conducted the analysis from a societal perspective, in which all health effects and changes in resource use were included.¹⁷ We considered both a within-trial time horizon (with the effects of screening observed through December 31, 2009) and a lifetime horizon. For each strat-

egy, we estimated life expectancy and quality-adjusted life expectancy (QALE) from the time of randomization (assumed for the sake of simplicity to be January 1, 2009, for all participants). We reported costs and life-years on a present-value basis, with an annual discount rate of 3%.

LIFE EXPECTANCY

We assumed that screening did not affect life expectancy in participants who did not receive a diagnosis of lung cancer and that it did not incur costs beyond those involved in the workup for a patient with a positive examination result (with the exception of potentially clinically significant incidental findings and the occurrence of radiation-induced lung cancer in the low-dose CT group after the trial⁴) (see Table S7-5 in the Supplementary Appendix). During the trial, there were 116 more lung cancers diagnosed in the CT group than in the radiography group. We also assumed that all these additional cases resulted from overdiagnosis, so that participants in the radiography group without a diagnosis of lung cancer at the end of the trial had the same future risk of lung cancer as those in the CT group. This assumption is justified by the near convergence of lung-cancer incidence in the two groups in the last 3 years of the trial (Table S2-2 and Fig. S2-1 in the Supplementary Appendix). Given these assumptions, the life expectancies of participants without a diagnosis of lung cancer are equal in the two groups (with the exception of the radiation-induced lung cancers occurring only in the low-dose CT group). The life expectancy associated with each screening strategy was equal to a weighted average of the life expectancies of participants with and those without lung cancer.

We excluded 150 of the 53,452 patients who underwent randomization: 100 were lost to follow-up within 1 day after randomization or after their first screening examination (46 in the CT group and 54 in the radiography group), 48 had missing data with respect to lung cancer (i.e., there were not enough data to predict survival [33 in the CT group and 15 in the radiography group]), and 2 were younger than 50 years of age at study entry (1 patient in each group). For each of the remaining 53,302 participants (26,642 in the CT group and 26,660 in radiography group), 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 the patient was deceased (as was the case with 3964 patients); to December 31, 2009, if the patient was alive; or to the latest date on which the patient was known to be alive if data on vital status were missing on December 31, 2009. For the 49,338 participants not known to be deceased on December 31, 2009, we estimated beyond-trial life-years on the basis of their age on the date they were last known to be alive, sex, smoking status at study entry, and lung-cancer stage, if any, using 2009 U.S. Life Tables¹⁸ adjusted for smoking status and stage-specific annual probabilities of dying from lung cancer (Sections 3 and 4 in the Supplementary Appendix).

We used the observed NLST stage-specific mortality from lung cancer to estimate life expectancy for the first 5 years after diagnosis. For subsequent years, for which NLST data were sparse, we adjusted the observed NLST mortality specific to disease stage to account for the decline in the hazard of death from lung cancer with increased time from the time of diagnosis that was observed in the Surveillance, Epidemiology, and End Results Program¹⁹ and that has been observed with long-term follow-up of patients with stage I lung cancer detected on CT screening.²⁰

To adjust life expectancy for quality, we used utilities derived from the Short Form Health Survey SF-36,²¹ which was administered to 11,696 participants from 16 of 23 ACRIN screening sites. At baseline, the mean utilities (a measure of quality of life on a scale of 0 [death] to 1 [perfect health]) were 0.76 and 0.74 for men and women, respectively, and did not differ by age (Section 5 in the Supplementary Appendix). We also adjusted for lung-cancer stage and time of diagnosis. Because there was no significant difference in utilities between those with false positive screening results and those with true negative screening results, we did not adjust for screening results in the base case.¹⁴ (The base case reflects several assumptions made to reduce the complexity of our analysis and minimize the use of variables for which there are no reliable estimates. For example, we assumed that all 116 additional cases diagnosed in the CT group were due to overdiagnosis and that there was no reduction in quality of life after a positive screen. See the Supplementary Appendix for further details.)

COSTS

We estimated the expected per-person cost related to lung cancer for the same cohort of 53,302 participants used in the estimation of life expectancy. Total per-person costs were calculated as the sum of direct medical costs and indirect costs. We based direct medical costs on utilization related to the screening examination, diagnostic workup for positive screening results and signs or symptoms of lung cancer, and lung-cancer treatment, and we calculated these costs for each participant each year after randomization, using 2009 Medicare prices.²² The frequency of screening was based on records indicating adherence to screening with CT or radiography. In the ACRIN subgroup, medical utilization related to diagnostic workup and treatment of lung cancer was obtained directly by means of medical-record abstraction (Section 6 in the Supplementary Appendix). We obtained utilization data from 5133 of the 18,840 participants in the ACRIN subgroup, including almost all those who had a positive screening result, a diagnosis of lung cancer, or both, and imputed costs for LSS participants and ACRIN participants without cost data using variables for which data had been collected for all participants. We based indirect medical costs on time and travel for the participant and caregiver, using 2009 U.S. pricing for hourly earnings²³ and automobile-mileage reimbursement.²⁴ In the base case, we assigned an effective total cost of \$500 for a participant with at least one potentially clinically significant incidental finding (Section 6.7 in the Supplementary Appendix), and we included medical care (during and after the trial) for lung cancers diagnosed during the trial and for future hypothetical cases of lung cancer induced by radiation from CT screening.

STATISTICAL ANALYSIS

The three screening strategies were organized according to their baseline costs (from high to low). Incremental costs, life expectancies, QALEs, and incremental cost-effectiveness ratios (ICERs) were calculated for each strategy after the exclusion of any strategy that cost more but provided no benefit as compared with another strategy. We estimated the statistical uncertainty of our results by calculating equal-tail 95% bootstrap confidence intervals.^{25,26}

We performed analyses in subgroups defined

according to age (in 5-year age groups), sex, smoking status (current vs. former), and quintiles for the risk of lung cancer that were based on a recently validated model.²⁷ To assess the internal validity of our analysis, we dropped three of our base-case assumptions: the assumption that screening with low-dose CT did not affect mortality from causes other than lung cancer, the assumption that all excess cases in the low-dose CT group were overdiagnoses (and instead considering the possibility that up to half of the excess cases were not overdiagnoses),^{28,29} and the assumption that screening with chest radiography was ineffective in reducing lung-cancer mortality as compared with no screening (Section 7 in the Supplementary Appendix). In addition, because of the large disparity across groups in the numbers of participants with stage IA non-small-cell lung cancer who were alive at the end of the trial (324 in the CT group vs. 140 in the radiography group) and because of the uncertainty regarding their survival more than 5 years after diagnosis, we repeated the analysis on the basis of optimistic and pessimistic assumptions about their long-term survival (Section 4 in the Supplementary Appendix). We also performed sensitivity analyses of the quality of life after receipt of a positive screening result and after a diagnosis of lung cancer, of radiation-induced lung-cancer deaths,⁴ and of overdiagnosis in the radiography group. Such overdiagnosis would have violated our base-case assumptions with regard to the group that received no screening.

To assess the generalizability of our results, we performed sensitivity analyses of surgical mortality and of the costs of the low-dose CT screening examinations, follow-up CT examinations, surgical resection, chemotherapy, radiation therapy, time and travel, management of incidental findings, and future medical care.

RESULTS

DIAGNOSES AND DEATHS

Among the 53,302 participants in our analysis, 1076 in the CT group and 978 in the radiography group received a diagnosis of lung cancer (Table S2-1 in the Supplementary Appendix). Among those in the CT group who had lung cancer, 469 died from lung cancer and 49 died from other causes; among those in the radiography group

Table 1. Life-Years and Quality-Adjusted Life-Years per Person.*

Time Horizon	Life Expectancy		Quality-Adjusted Life Expectancy	
	CT	Radiography	CT	Radiography
	<i>life-yr</i>		<i>QALY</i>	
Within trial	5.7846	5.7775	4.3390	4.3351
Participants with lung cancer	4.9013	4.6029	3.5603	3.3596
Participants without lung cancer†	5.8228	5.8228	4.3728	4.3728
Lifetime	14.7386	14.7071	10.9692	10.9491
Participants with lung cancer	8.4792	6.8479	6.0521	4.8981
Participants without lung cancer†	15.0097	15.0103	11.1821	11.1825

* Life-years were discounted at 3% and are defined as follows: within-trial life-years were calculated from the date of randomization to the date of death if the patient was deceased; to December 31, 2009, if the patient was alive; or to the latest date on which the patient was known to be alive if data on vital status were missing on December 31, 2009. For participants not known to be deceased by that date, beyond-trial life-years were estimated on the basis of the participants' age on the date they were last known to be alive, sex, smoking status at study entry, and lung-cancer stage, if any, with the use of 2009 U.S. Life Tables,¹⁸ adjusted for smoking status and stage-specific annual probabilities of dying from lung cancer. For further details see Sections 3 and 4 in the Supplementary Appendix. The results for participants who underwent no screening were assumed to be the same as for those who underwent radiographic screening.

† For participants without lung cancer, outcomes were assumed to be the same for those who underwent CT screening and those receiving radiographic screening except for an adjustment for the occurrence of radiation-induced lung cancer after the trial.

who had lung cancer, 552 died from lung cancer and 35 died from other causes. These numbers represent data from the time of study entry through December 31, 2009.

LIFE EXPECTANCY AND QALE

Discounted life expectancy and QALE were higher in the CT group than in the radiography group, and the between-group differences were greater when these variables were projected over a lifetime horizon rather than a within-trial horizon because the lifetime horizon accounted for life-years saved after the trial (Table 1). For the approximately 4% of patients with a diagnosis of lung cancer, the incremental life expectancy was 1.6 years.

COSTS AND INCREMENTAL COST-EFFECTIVENESS

Discounted per-person costs were much higher in the CT group than in the radiography group (Table 2), mainly because of the cost of the screening examination and the much higher Medicare reimbursement for a CT scan of the chest (without the administration of contrast material) than for a chest radiograph (\$285 vs. \$24).²² Per-person costs for diagnostic workups and surgery were also higher in the CT group,

but the per-person costs of chemotherapy and radiation therapy were lower than those in the radiography group. Future medical costs, which were calculated only in the sensitivity analysis, were slightly higher in the CT group because a

Table 2. Costs per Person.*

Cost	CT	Radiographic	No
	Screening	Screening	Screening
	<i>U.S. \$</i>		
Total	3,074	1,911	1,443
Screening	1,130†	336	0
Workup	835	645	512
Treatment	1,106	931	931
Surgery	736	470	470
Chemotherapy	282	351	351
Radiation therapy	88	110	110
Radiation-induced lung cancer	3	0	0

* Costs include those for time and travel, which were \$101 for each screening visit, each workup visit, and each surgical visit. The cost for time and travel for each radiation therapy visit was \$175 and for each chemotherapy visit, \$381.

† The cost of CT screening includes that of addressing potentially clinically significant incidental findings.

Table 3. Incremental Cost-Effectiveness.*

Strategy	Cost	Life Expectancy	QALE	Incremental Costs†	Incremental Life Expectancy	Incremental QALE	Cost per Life-Yr U.S. \$ (95% CI)	Cost per QALY U.S. \$ (95% CI)
	U.S. \$	life-yr	QALY	U.S. \$	life-yr	QALY		
CT screening	3,074	14.7386	10.9692	1,631	0.0316	0.0201	52,000 (34,000–106,000)	81,000 (52,000–186,000)
Radiographic screening	1,911	14.7071	10.9491	469	0	0	NA	NA
No screening‡	1,443	14.7071	10.9491	—	—	—	—	—

* All costs were calculated for the base case, which reflects several assumptions made to reduce the complexity of the analysis and minimize the use of variables for which there are no reliable estimates. NA denotes not applicable, QALE quality-adjusted life expectancy, and QALY quality-adjusted life-year.

† Incremental costs are in reference to the strategy of no screening because the radiography strategy cost more but provided no incremental health benefit as compared with no screening.

‡ The cost of the strategy of no screening included the cost of the diagnosis and treatment of lung cancer without low-dose CT or radiographic screening.

higher proportion of participants were still alive at the end of the trial. We assumed that per-person costs in the group undergoing no screening were the same as those in the group undergoing radiography minus the costs for screening

and for the workup of false positive screening results.

In our base case, screening with radiography was more expensive than no screening but provided no health benefit (Table 3). As compared with no screening, screening with low-dose CT cost an additional \$1,631 (95% confidence interval [CI], 1,557 to 1,709) per person and provided an additional 0.0316 life-years per person (95% CI, 0.0154 to 0.0478) and 0.0201 QALYs per person (95% CI, 0.0088 to 0.0314); the corresponding ICERs were \$52,000 per life-year gained (95% CI, 34,000 to 106,000) and \$81,000 per QALY gained (95% CI, 52,000 to 186,000).

SUBGROUP AND SENSITIVITY ANALYSES

The incremental costs were relatively stable among subgroups, with a range of \$1,453 to \$1,905 (Table 4). However, the range for incremental QALYs was much wider (0.0027 to 0.0515), with the highest QALY value up to nearly 20 times as high as the lowest; consequently, the range for ICERs was just as wide (\$32,000 to \$615,000 per QALY gained). The ICER was much lower for women than for men (\$46,000 vs. \$147,000 per QALY gained), for current smokers than for former smokers (\$43,000 vs. \$615,000 per QALY gained), for the three oldest age groups than for the youngest age group, and for the two quintiles with the highest risk of lung cancer than for the three quintiles with the lowest risk.

Our results were highly sensitive to several of

Table 4. Incremental Costs According to Subgroups.

Characteristic	No. of Participants	Incremental Costs	Incremental QALYs	Cost per QALY
		U.S. \$	QALY	U.S. \$
Sex				
Male	31,446	1,683	0.0115	147,000
Female	21,856	1,557	0.0340	46,000
Age at entry				
55–59 yr	22,773	1,541	0.0101	152,000
60–64 yr	16,333	1,520	0.0320	48,000
65–69 yr	9,504	1,900	0.0351	54,000
70–74 yr	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
Risk of lung cancer				
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

our base-case assumptions (Table 5). The ICER fell to \$54,000 per QALY gained when the reduction in mortality from causes other than lung cancer was included, to \$55,000 per QALY gained when only half rather than all the excess lung cancers in the CT group were attributed to overdiagnosis, and to \$62,000 per QALY gained when the risk of death from lung cancer after screening with chest radiography as compared with no screening was reduced to 0.94. However, the ICER approached or exceeded \$100,000 per QALY gained when future health care costs were included; when costs for the screening examination, follow-up, or surgery were increased; when the pessimistic expectations of survival with stage IA non-small-cell lung cancer were assumed; and when small reductions in quality of life related to positive screening results and a diagnosis of stage IA lung cancer were included. The ICER rose slightly with the inclusion of deaths from radiation-induced lung cancer.

DISCUSSION

Our base-case estimates of the ICERs for screening with low-dose CT versus no screening — \$81,000 per QALY gained and \$52,000 per life-year gained — fall between the two estimates reported since the intervention was proven effective in the NLST and fall below \$100,000 per QALY gained, a threshold level that some experts consider to be a reasonable value in the United States.³⁰ Much of the difference between our estimate of ICER and the substantially higher estimate reported by McMahon et al.³¹ can be explained by the difference in the number of follow-up CT scans per positive screening examination — approximately one observed in the NLST,³² as compared with four assumed in the study by McMahon et al. Much of the difference between our estimate and the lower estimate reported by Pynson et al.³³ can be explained by their assumption that the reduction in mortality from lung cancer that resulted from screening would be higher than the 20% observed in the NLST.

The estimated cost-effectiveness of screening with low-dose CT varied widely in the subgroup analysis. Screening with low-dose CT was much more cost-effective among women than among men and among the groups with a higher risk of lung cancer than among those with a lower risk,

findings that are consistent with two recent reports showing the greater effectiveness among women³⁴ (probably related to different distributions of lung cancer according to histologic type) and among persons at higher risk³⁵ in the NLST. Screening with low-dose CT was also more cost-effective for current smokers than for former smokers and for the older groups than for the youngest group, findings that are probably due to the higher risk of lung cancer among current smokers and older patients. However, the trends related to age and risk were not uniform, probably because the numbers of lung cancers reported in the subgroups in our study were smaller than the numbers in the total sample.

The ICERs reported in our study were highly sensitive to several of our base-case assumptions. The ICER fell substantially when we excluded our assumptions that CT screening did not affect mortality from causes other than lung cancer, that all excess lung cancers in the CT group were due to overdiagnosis, and that screening with chest radiography was ineffective. The ICER rose substantially when we included future health care costs of survivors that were unrelated to lung cancer, but we did not include these costs in our base case because their inclusion is controversial¹² and because they have not been included in prior cost-effectiveness analyses of lung-cancer screening.^{7-10,31,33,35} The ICER also rose substantially when we increased the costs of the screening examination, follow-up, and surgery and when we reduced the quality of life related to positive screening results and to a diagnosis of stage IA lung cancer.

We observed no loss of utility in our generic instruments after a report of positive results, a finding that is consistent with another trial, in which false positive screening mammograms were reported³⁶; however, distress in response to a positive result (and relief on learning of true negative results) were observed in the NELSON trial (Current Controlled Trials number, ISRCTN63545820) when these emotions were measured with disease-specific instruments measuring quality of life.³⁷ All participants in the NLST were provided with detailed information about the frequency and clinical significance of false positive results before study entry, and patients with positive screening results received additional information, which may have reduced their distress.

Table 5. Results of Sensitivity Analyses.

Scenario	Cost per QALY
	U.S. \$
Base case*	81,000
Inclusion of non-lung-cancer deaths	54,000
Relative risk of screening with radiography vs. no screening (1.0)	
0.8	40,000
0.94†	62,000
1.1	171,000
No. of future excess cases (0)‡	
29	66,000
58	55,000
Survival for stage IA non-small-cell lung cancer (intermediate)	
Low	67,000
High	108,000
Cost of screening with low-dose CT (\$285)	
100	56,000
500	110,000
Multiplier for no. of follow-up screenings with low-dose CT (1)	
0.5	78,000
5	110,000
Multiplier for cost of surgery (1 = \$22,000)	
0.5	73,000
3	114,000
Surgical mortality (1.2%)	
0.0%	79,000
8.0%	96,000
Future health care costs (0 after CT; 0 after no screening)	
\$171,018 after CT screening	120,000
\$170,248 after no screening	
Reduction in quality of life after positive screen (0)	
0.05	116,000
Reduction in quality of life after diagnosis of stage IA lung cancer (0.03)	
0.07	101,000
Cost of managing potentially significant incidental finding (\$500)	
0	78,000
\$2,500	96,000
Radiation-induced lung-cancer deaths per lung-cancer death prevented (0.046)	
0	79,000
0.092	83,000

* The base case reflects several assumptions made to reduce the complexity of the analysis and minimize the use of variables for which there are no reliable estimates. The base-case value for each variable is given in parentheses.

† The point estimate is for the subgroup of the Prostate, Lung, Colorectal, and Ovarian Cancer-Screening Trial that was eligible for the National Lung Screening Trial.¹⁶

‡ Future excess cases represent the additional number of lung cancers diagnosed after the trial in the radiography group as compared with the CT group.

Although the NLST results suggest that screening with low-dose CT costs less than \$100,000 per QALY gained, screening conducted outside the trial may be more costly, depending on the variables that we considered in our sensitivity analyses and on the way in which screening is implemented. One of the most important factors is the cost of the low-dose CT screening examination. Costs could also increase considerably if patient counseling and follow-up are properly accounted for. As the true cost of screening approaches \$500, the cost becomes prohibitive. The cost could also become prohibitive if the number of follow-up CT scans were to increase. However, the American College of Radiology has developed a reporting system that will raise the positivity threshold that was used in the NLST and could substantially decrease the number of follow-up CTs obtained.³⁸

There are several additional limitations to our analysis that deserve consideration. First, we excluded 150 NLST participants from our analysis, 48 of whom had lung cancer but for whom we did not have adequate information to project their survival. Because 47 of these participants were known to be alive at the end of the trial and more of these participants were in the CT group than in the radiography group, their exclusion probably led to a small bias against screening with low-dose CT. Second, we assumed that screening with low-dose CT did not affect smoking status after the time of entry into the NLST.³⁹ To the extent that screening caused current smokers to become former smokers, we underestimated the cost-effectiveness of screening with low-dose CT. Finally, we did not consider numerous factors that relate to the generalizability of our results outside the NLST, such as the high quality of care provided at NLST screening centers and the stringent selection criteria. However, the Cancer Intervention and Surveillance Modeling Network (CISNET) recently reported an analysis that includes eligibility criteria and screening intervals.⁴⁰

In conclusion, we estimate that screening with low-dose CT for lung cancer as performed in the NLST costs less than \$100,000 per QALY gained. The determination of whether screening performed outside the trial will be cost-effective will depend on exactly how screening is implemented.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dennis G. Fryback, Ph.D., for his advice during the initial planning phase of the cost-effectiveness analysis and the subsequent analysis phase regarding quality of life; Care Communications, which was involved in the planning of the study and the abstraction of the medical records; the following members of the NLST Cost-Effectiveness Analysis Biostatistics Analytic Team for their contributions to the data analysis: Stavroula Chrysanthopoulou, Ph.D., Sarah Demello, M.S., Pratikumar Desai, M.P.H., and Erin Greco, M.S., all at

the ACRIN Biostatistics Center, Brown University, Providence, RI; the NLST-ACRIN Research Team and their research associates, who obtained all the information required for the cost-effectiveness analysis; Suzanne B. Lenz, study coordinator for NLST at Dartmouth-Hitchcock Medical Center, for her contributions to the data-collection efforts of the NLST-ACRIN Research Team; the screening-center investigators and the staff of the NLST; and the study participants, whose contributions made this study possible.

REFERENCES

- Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62:10-29.
- Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395-409.
- Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA* 2012;307:2418-29.
- Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014;160:330-8.
- Patient Protection and Affordable Care Act. August 28, 2013 (<http://www.gpo.gov/fdsys/pkg/PLAW-111publ148/content-detail.html>).
- Sox HC. Better evidence about screening for lung cancer. *N Engl J Med* 2011; 365:455-7.
- Marshall D, Simpson KN, Earle CC, Chu C. Potential cost-effectiveness of one-time screening for lung cancer (LC) in a high risk cohort. *Lung Cancer* 2001;32: 227-36.
- Wisnivesky JP, Mushlin AI, Sicherman N, Henschke C. The cost-effectiveness of low-dose CT screening for lung cancer: preliminary results of baseline screening. *Chest* 2003;124:614-21.
- Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *JAMA* 2003;289:313-22.
- Manser R, Dalton A, Carter R, Byrnes G, Elwood M, Campbell DA. Cost-effectiveness analysis of screening for lung cancer with low dose spiral CT (computed tomography) in the Australian setting. *Lung Cancer* 2005;48:171-85.
- Aberle DR, Berg CD, Black WC, et al. The National Lung Screening Trial: overview and study design. *Radiology* 2011; 258:243-53.
- Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost-effectiveness in health and medicine. Oxford, England: Oxford University Press, 1996.
- Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value Health* 2005;8:521-33.
- Gareen IF, Duan F, Greco EM, et al. Impact of lung cancer screening results on participant health-related quality of life and state anxiety in the National Lung Screening Trial. *Cancer* 2014; 10.1002/cncr.28833.
- Gareen IF, Sicks JD, Molene D, et al. Identifying and collecting pertinent medical records for centralized abstraction in a multi-center randomized clinical trial: the model used by the American College of Radiology arm of the National Lung Screening Trial. *Contemporary Clinical Trials* 2013;24:36-44.
- Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. *JAMA* 2011;306:1865-73.
- Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. *JAMA* 1996;276:1172-7.
- Arias E. United States life tables, 2009. *Natl Vital Status Rep* 2014;62(7):1-63.
- Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence — SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2012 Sub (1973-2010 varying), April 2013 (<http://www.seer.cancer.gov/data/seerstat/nov2012>).
- Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;355:1763-71.
- Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;21:271-92.
- Centers for Medicare and Medicaid Services. Physician Fee Schedule look-up tool. March 1, 2011 (http://www.cms.hhs.gov/pfslookup/02_PFSsearch.asp).
- Department of Labor. Employer costs for employee compensation — December 2009. March 10, 2010 (http://www.bls.gov/news.release/archives/ecec_03102010.pdf).
- General Services Administration. Privately owned vehicle (POV) mileage reimbursement rates. 2012.
- Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. *Health Econ* 1997;6:327-40.
- Stinnett AA. Adjusting for bias in C/E ratio estimates. *Health Econ* 1996;5:470-2.
- Tammemägi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. *N Engl J Med* 2013;368:728-36.
- Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst* 2010;102:605-13.
- Veronesi G, Maisonneuve P, Bellomi M, et al. Estimating overdiagnosis in low-dose computed tomography screening for lung cancer: a cohort study. *Ann Intern Med* 2012;157:776-84.
- Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness — the curious resilience of the \$50,000-per-QALY threshold. *N Engl J Med* 2014;371:796-7.
- McMahon PM, Kong CY, Bouzan C, et al. Cost-effectiveness of computed tomography screening for lung cancer in the United States. *J Thorac Oncol* 2011;6: 1841-8.
- Church TR, Black WC, Aberle DR, et al. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med* 2013;368:1980-91.
- Pyenson BS, Sander MS, Jiang Y, Kahn H, Mulshine JL. An actuarial analysis shows that offering lung cancer screening as an insurance benefit would save lives at relatively low cost. *Health Aff (Millwood)* 2012;31:770-9.
- Pinsky PF, Church TR, Izmirlan G, Kramer BS. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. *Cancer* 2013;119:3976-83.
- Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med* 2013;369:245-54.
- Tosteson AN, Fryback DG, Hammond CS, et al. Consequences of false-positive screening mammograms. *JAMA Intern Med* 2014;174:954-61.
- van den Bergh KA, Essink-Bot ML, Borsboom GJ, et al. Short-term health-related quality of life consequences in a

- lung cancer CT screening trial (NELSON). *Br J Cancer* 2010;102:27-34.
38. American College of Radiology. Lung Imaging Reporting and Data System (Lung-RADS). April 29, 2014 (<http://www.acr.org/Quality-Safety/Resources/LungRADS>).
39. van der Aalst CM, van Klaveren RJ, van den Bergh KA, Willemsen MC, de Koning HJ. The impact of a lung cancer computed tomography screening result on smoking abstinence. *Eur Respir J* 2011; 37:1466-73.
40. de Koning HJ, Meza R, Plevritis SK, et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. *Ann Intern Med* 2014;160:311-20.

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