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Resource Utilization and Costs during the Initial Years of Lung Cancer Screening with Computed Tomography in Canada

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Background: It is estimated that millions of North Americans would qualify for lung cancer screening and that billions of dollars of national health expenditures would be required to support population-based computed tomography lung cancer screening programs. The decision to implement such programs should be informed by data on resource utilization and costs.

Methods: Resource utilization data were collected prospectively from 2059 participants in the Pan-Canadian Early Detection of Lung Cancer Study using low-dose computed tomography (LDCT). Participants who had 2% or greater lung cancer risk over 3 years using a risk prediction tool were recruited from seven major cities across Canada. A cost analysis was conducted from the Canadian public payer's perspective for resources that were used for the screening and treatment of lung cancer in the initial years of the study.

Results: The average per-person cost for screening individuals with LDCT was $453 (95% confidence interval [CI], $400–$505) for the initial 18-months of screening following a baseline scan. The screening costs were highly dependent on the detected lung nodule size, presence of cancer, screening intervention, and the screening center. The mean per-person cost of treating lung cancer with curative surgery was $33,344 (95% CI, $31,553–$34,935) over 2 years. This was lower than the cost of treating advanced-stage lung cancer with chemotherapy, radiotherapy, or supportive care alone, ($47,792; 95% CI, $43,254–$52,200; $p = 0.061$).

Conclusion: In the Pan-Canadian study, the average cost to screen individuals with a high risk for developing lung cancer using LDCT and the average initial cost of curative intent treatment were lower than the average per-person cost of treating advanced stage lung cancer which infrequently results in a cure.

Key Words: Lung cancer screening, Cost analysis, Cost-effectiveness.

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The National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer-specific mortality by screening high-risk current or former smokers in the United States using low-dose computed tomography (LDCT).[1] The NLST is the first randomized trial with adequate power and duration of follow-up to demonstrate the absolute benefits of LDCT screening. Incorporating results of the trial, the U.S. Preventive Services Task Force gave a grade B recommendation for lung cancer screening using LDCT in the United States.[2]

The potential impact that lung cancer screening may have at the population-level is profound. It is estimated that in 2013, over 300,000 North Americans were diagnosed with lung cancer and approximately 200,000 died from the disease.[3,4] With such high incidence and mortality rates, screening individuals for lung cancer with LDCT has the potential to save thousands of lives. Approximately 8.6 million individuals in the United States meet the criteria for enrolment in the NLST, based on their age and smoking history.[5] The cost of national screening programs could be significant, potentially reaching billions of dollars of national expenditure.[6] It is against this backdrop that an understanding of the costs associated with population-based LDCT screening becomes essential in order to estimate the budget impact of lung cancer screening programs.

Cost-effectiveness evidence in the literature for lung cancer screening with LDCT is inconclusive. Some models predict that LDCT-based screening is highly likely to be considered cost-effective while others conclude the opposite.[7] There are no models that use cost data from the actual experience of screening participants and little is known about the cost implications of screening, even in the idealized clinical trial setting. Screening costs may, for example, be skewed toward different individuals for a variety of reasons including their general health and the availability of local healthcare resources.[8] Diagnostic imaging rates and invasive procedures triggered by "positive" screening results can vary substantially between the different screening studies.[9] The proportion of screened subjects affected by this uncertainty is considerable as data from both of the existing large randomized screening trials, (the NLST and the Dutch-Belgian Randomized Lung Cancer Screening trials) show that 20% or greater of those screened require at least one additional follow-up LDCT scan after their first baseline screening exam.[10,11] The screening programs are driven by the hypothesis that lung cancer may be cured if the disease is detected at an early stage and that the benefits of doing so not only include reduced lung cancer mortality but also the possibility of averting potentially expensive treatment courses that are associated with low success rates in the advanced stage setting.

The Pan-Canadian Early Detection of Lung Cancer Study was established with the objective of developing an affordable screening strategy for reducing lung cancer deaths within Canadian health care systems. The study selected individuals using a Web-based lung cancer risk prediction tool.[12] If that risk was 2% or more over 3 years, the participants were invited for an interview by a study coordinator at the screening center for inclusion in the study. In this article, we describe the resources utilized and the costs associated with the initial years of this screening study and 2 years of follow-up after the treatment of screen-detected lung cancer. Our intent is to improve the evidence base that is available for cost-effectiveness modeling.

MATERIALS AND METHODS

The Pan-Canadian Study

Between September 2008 and December 2011, participants in the Pan-Canadian study were recruited by newspaper, radio, and physician office advertisements in seven major cities across Canada. The advertisements were directed to Canadians at the risk of developing lung cancer due to their age and smoking history. Inclusion/exclusion criteria and study methods have been reported previously.[13]

Following approval by the ethics review board at each of the recruiting institutions, 2537 eligible participants were enrolled and scheduled for screening with at least two annual LDCT screening tests (CT-S-1 and CT-S-2). The first half of the Pan-Canadian cohort also received a baseline autofluorescence bronchoscopy (AFB) screening exam. Lung nodules that were deemed suspicious for lung cancer were referred for further investigation, which may have included diagnostic imaging, bronchoscopy, percutaneous biopsy, or a surgical procedure.

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Lung Nodule Follow-Up Protocol

Subjects with baseline scans (CT-S-1) with no nodules or with the largest solid nodule measuring less than 5 mm in diameter or nonsolid (ground glass) nodules, measuring less than 8 mm in diameter, were to undergo a follow-up examination in 12 months' time (CT-S-2). If there were nodules on CT-S-1 or CT-S-2 but no new nodules and no growth of existing nodules on CT-S-2, a 24-month scan (CT-S-3) was performed. The subject was then discharged from the study at 12 months following CT-S-2 if there were no nodules at 24 months, if there was no growth of existing solid nodules and no development of new nodules. Subjects with any semi-solid or solid nodule 5 to 10 mm or nonsolid nodules 8 to 10 mm were to receive an additional limited or low-dose full chest scan at 3 months (CT-S-n-FU).

A subject with growth of an existing nodule, development of a solid component in a nonsolid nodule or a new nodule was to receive an additional scan at 3 months with a decision on successive scans, biopsy, or excision biopsy to be made at the discretion of the study physician and radiologist. A nodule that grew on two consecutive scans, a nonsolid opacity showing development of a solid component and any nodule greater than 10 mm in diameter would be considered as suspicious for lung cancer and the lesion was managed based on the practice patterns of the local institution. Any other abnormality on the CT in the surrounding soft tissue of the chest and abdomen was followed according to the standard of care in the institution as directed by the medical team and the local study radiologist.

Resource Utilization Data

Study coordinators recorded demographic information, screening test results, and resource utilization data for enrolled participants on an electronic case report form. All direct medical healthcare resources used for early detection, diagnosis, staging, and treatment of lung cancer or any other type of cancer were recorded chronologically from the point of enrollment in the study to the point of data censoring described in the "screening-phase parameters" section. The resources were defined as any medical appointment, investigation or procedure, hospital admission, lung cancer treatment including chemotherapy, radiation therapy, surgery, or blood product used in the investigation or treatment of lung cancer and its sequelae. Resources used for clinical correlation of abnormal screening results, for complications arising from diagnostic tests, for lung cancer treatment or further screening were also included. Data on resources used to investigate or treat non-cancer incidental findings such as coronary artery calcification or emphysema were collected for a separate publication, but were not included in this cost analysis.

Screening Resources

Under the Pan-Canadian Study protocol, each participant was scheduled to receive at least two annual CT screening tests (CT-S-1 and CT-S-2). CT-S-1 was the first (baseline) screening exam and CT-S-2 was the second annual screening exam, occurring 12 months after CT-S-1. CT scans were classified as screening CT exams if they were undertaken according to the screening protocol (i.e., <1.5 mSv effective radiation dose, performed in the absence of a proven malignancy, without intravenous contrast media, and conducted at least 60 days after the previous screening CT). The follow-up screening exams were accounted for cumulatively; that is, the first follow-up screening LDCT triggered by CT-S-1 was termed CT-S-1-FU-1, and the second was CT-S-1-FU-2.

Screening-Phase Parameters

Resource utilization data for the screening phase commenced upon the date of CT-S-1 and continued for 18 months for the participants who did not have cancer. Data for participants who had cancer were classified as "screening-phase" data until a cancer diagnosis was confirmed by biopsy or surgical excision or 18 months of time from CT-S-1 had passed, whichever occurred first. A diagnosis of cancer needed to be documented within 30 months of CT-S-1 and before December 31, 2012 to be captured in this analysis.

Treatment-Phase Resources

Resource utilization data for the treatment of lung cancer were analyzed separately as treatment-phase resources. The data were divided into four sub-phases of treatment: diagnostic workup, first-line treatment, follow-up year 1 and follow-up year 2. The data were sorted further according to the modality of first-line treatment (i.e., surgery or nonsurgical management) in order to represent the policy decision problem related to treating lung cancer with a curative intent. Resource utilization data for the diagnostic workup phase began at CT-S-1 and continued up to the date of the first chemotherapy or radiotherapy treatment, date of surgery, or the date on which a decision was made for management by supportive care only. Resources utilized during the first-line treatment-phase were collected starting from the date of surgery or first chemotherapy or radiotherapy treatment and continued until the final day of first-line treatment, or 30 days after the surgery. Resources for complications were included in the first-line treatment phase until the complication resolved or the patient died, whichever occurred first. First-line treatment costs for patients who received supportive care only were set to zero and any subsequent resource utilization data were accounted for in the annual follow-up phases of treatment. Annual follow-up transitions occurred 365 days after the previous transition and resource utilization data for each completed phase of treatment including any relapsed lung cancer were included before December 31, 2012.

Cost Analysis

Resource utilization rates were multiplied by their calculated unit cost and divided by the number of participants in the cohort to determine the mean per-person cost. The unit costs for resource utilization were based on the provincial 2013 reimbursement schedules from the Medical Service Plan in the province of British Columbia. Physician fees and reimbursement for clinical services within Canada do not vary greatly for different provinces. Chemotherapy drug costs were referenced from Canadian wholesale drug prices. Hospitalizations for surgical resections, surgical pathology, chemotherapy, radiotherapy, palliative care, ambulatory

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TABLE 1. Demographic, Study, and Clinical Characteristics

	Frequency-Discrete Variables (%)	Median-Continuous Variables (SD)
Demographic		
All	2059 (100)	
Age at CT-S-1, per year[a]		62.9 (5.8)
Female sex	915 (44.4)	
White ethnicity	1999 (97.1)	
Education, per level (1–7)		Level 4 (1.7)
Quality of life at baseline (EQ5D visual analogue scale, <60% vs. ≥60%)	297 (14.4)	
Study-specific		
Screening study site		
1	438 (20.1)	
2	339 (16.5)	
3	191 (9.3)	
4	264 (12.8)	
5	202 (9.8)	
6	362 (17.6)	
7	263 (12.7)	
Screening status		
18-months completed, no cancer	1845 (89.6)	
Lost to follow-up	106 (5.1)	
Positive for lung cancer	83 (4.0)	
Other cancer	15 (0.7)	
Deceased	10 (0.5)	
Use of AFB-screening intervention (LDCT + AFB vs. LDCT alone)	1184 (57.5)	
Number of chest radiographs in the 1 year before enrolment		0 (0.7)
Number of CT exams in the past 3 years before enrollment		0 (0.2)
Screening phase (start-up phase [pre-2010] vs. full functioning phase [2010])	1278 (62.1)	
Risk factors		
Pack years		50 (23.4)
Smoking status, current vs. former	1281 (62.2)	
Family history, first degree relative with cancer	722 (35.1)	
Number of listed comorbidities		3 (2.3)
Presence of coronary heart disease	150 (7.2)	
Presence of COPD	228 (11.1)	
Number of lung cancer symptoms		3 (2.1)
Presence of low lung function (predicted FEV1 <80% vs. ≥80%)	912 (44.3)	
CT-S-1 test results		
Number of nodules (per-person)		3 (3.9)
Nodule size		
1–4.9 mm nodule	1560 (75.8)	
5.0–9.9 mm nodule	827 (40.2)	
10.0–14.9 mm nodule	143 (7.0)	
Nodule(s) ≥15 mm	85 (4.1)	
Nodule characteristics		
≥1 Calcified nodule	398 (19.3)	
≥1 PFN	49 (2.4)	
≥1 GGO	521 (25.3)	
≥1 Semisolid	194 (9.4)	
≥1 Solid nodule	1520 (73.8)	
Emphysema observed on CT-S-1	1195 (58.0)	

[a]Baseline CT scan (CT-S-1).

LDCT, low-dose computed tomography; AFB, autoflourescence bronchoscopy; CT, computed tomography; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 sec; PFN, perifissural nodule; GGO, ground glass opacity.

care, and complications resulting from the procedures were accounted for on a per-person basis using hospital data from the province of Ontario and professional fees from the Medical Service Plan (see supplementary material, Supplemental Digital Content, http://links.lww.com/JTO/A661). All costs were inflated to 2013 Canadian dollars. One Canadian dollar was approximately equal to one U.S. dollar in 2013.

Statistical Analysis

Two regression models were built to investigate the impact of study variables (listed in Table 1) on screening resources. Model 1 is a logistic regression model to investigate the factors that influence the use of CT-S-1-FU-1. The first follow-up CT exam was considered a representative additional screening resource that would be required beyond annual LDCT scans. Model 2 is a linear regression model with per-person screening costs as the dependent variable. The same independent variables were included in both the regression models. Clustering of data within study sites was handled in regression modeling by treating them as fixed effects and including them in all the models as indicator variables. Postmodel building, interactions amongst regression variables was tested. Variables that were considered clinically relevant were included in the models (Table 3). Mann–Whitney significance tests were applied to investigate statistically significant cost differences between treatment modalities. All statistical analyses were conducted with STATA version MP12.1.

RESULTS

Study Cohort

Two thousand fifty-nine participants of the 2537 pan-Canadian participants were included in this analysis according

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to the inclusion/exclusion criteria (Fig. 1). The number of individuals who did not have lung cancer detected was 1961 and their median follow-up time was 547 days (interquartile range [IQR], 546–549). After 375 median days (IQR, 105.5–546.8), 107 individuals were lost to follow-up. The main reasons for loss from the study were that the participants had moved, developed other medical conditions or loss of interest when the prior LDCT did not show any suspicious abnormality. During the screening study period, 83 individuals (4%) had a lung cancer diagnosis confirmed within 244 median days (IQR, 78.5–522.0) following CT-S-1. Eighty-five percent (1751) individuals who had CT-S-1 returned for CT-S-2 within 370 median days (IQR, 361–385). Nine individuals died of nonlung cancer causes.

Screening-Phase Resources

The majority of screening-phase resources used in this study were LDCT screening exams: 32.5% of all screened individuals had at least one follow-up LDCT. Follow-up LDCT rates after CT-S-2 (i.e., CT-S-2-FU-1) were low (6.6%) and occurred within 98 median days following CT-S-2 (IQR, 91–126), suggesting that most suspicious nodules are found on the initial baseline scan. Eighty-five percent of the individuals who had CT-S-1 returned for CT-S-2 within 18 months; thus, less CT-S-2 resources were utilized. The lower rate of CT-S-2 utilization resulted in a lower contribution to the mean per-person cost over the 18-month screening period (Table 2). There were low rates of complications and low rates of invasive investigations during the screening phase. Physician and diagnostic resources were rarely utilized for screening that did not result in a cancer diagnosis and screening occurred mostly outside of the primary care setting. There were 14 physician appointments per 100 persons screened overall, contributing an average $20 to the mean per-person cost of the entire cohort. Individuals who had lung cancer had an average of 1.4 physician appointments before their lung cancer was confirmed.

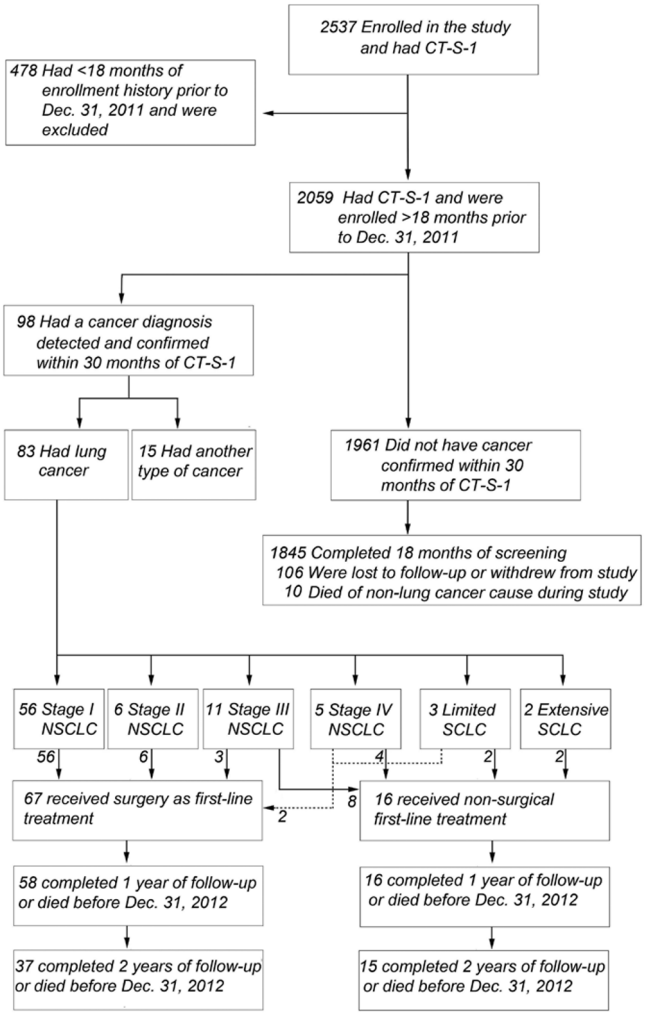

FIGURE 1. Economic analysis of the Pan-Canadian Early Detection of Lung Cancer Study. NSCLC, non–small-cell lung cancer; CT, computed tomography.

The mean per-person cost of screening individuals who did not have a lung cancer diagnosis was $453 (95% confidence interval [CI], $400–505) for individuals screened with LDCT. For individuals who were screened with AFB and LDCT, the average screening cost was significantly higher as a result of the high unit cost of AFB resources.

The use of AFB screening interventions did not affect the use of the most commonly used resource, CT-S-1-FU-1, but it was a statistically significant contributor to increased screening costs ($p < 0.001$), as shown in models 1 and 2 (Table 3). Study site, screening adherence status, smoking status and the number, size, and character of the nodules were significantly independent variables associated with CT-S-1-FU-1 rates and/or increased screening cost ($p < 0.05$). All study sites showed significant differences from the reference site according to the use of CT-S-1-FU-1 resources and four of six study sites had significantly higher cost coefficients than the reference site.

Treatment-Phase Resources

There were 83 lung cancer cases detected and confirmed within 30 months of CT-S-1. Sixty-seven percent of these cases were stage IA non–small-cell lung cancer (NSCLC), and 75% were early-stage (I or II) NSCLC (Fig. 1). The average per-person cost to find and diagnose lung cancer was not statistically significantly different between individuals who had first-line surgery versus nonsurgical treatment ($p = 0.74$) nor were the treatment-phase costs different between the two groups ($p = 0.13$; Table 4). Bronchoscopy, physician and imaging resource utilization rates drove the average cost higher ($p < 0.05$) in the nonsurgical diagnosis and treatment phases and the mean cost to treat serious complications was higher for the patients treated with first-line surgery ($p < 0.05$). The chemotherapy drug costs in this study were only for cytotoxic, nontargeted agents (see supplementary material, Supplemental Digital Content, http://links.lww.com/JTO/A661).

The annual follow-up costs were statistically significantly lower for the individuals who received first-line surgery when compared with those who received nonsurgical treatment for the advanced-stage disease in years 1 and 2 ($p < 0.001$ and $p < 0.05$, respectively). The cumulative, mean per-person cost for individuals diagnosed with cancer who completed all

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TABLE 2. Mean Per-Person Cost (SE) for Screening-Phase Costs

Resource	All Screened (Cancer Detected + No Cancer Detected)	No Cancer Detected		Lung Cancer Detected	Other Cancer Detected
		AFB + CT Screened	CT Screened		
Number	2059	1140	821	83	15
CT-S-1[a]	$193 (0)	$193 (0)	$193 (0)	$193 (0)	$193 (0)
CT-S-2[b]	$165 (2)	$180 (1)	$154 (3)	$77 (10)	$77 (25)
Follow-up LDCT[c]					
CT-S-1-FU-1	$44 (2)	$49 (2)	$33 (2)	$77 (9)	$53 (20)
CT-S-1-FU-2	$6 (1)	$7 (1)	$3 (1)	$22 (7)	$11 (11)
CT-S-1-FU-3	$1 (0)	$1 (0)	—	$4 (3)	$0 (0)
CT-S-2-FU-1	$11 (1)	$13 (1)	$7 (1)	$15 (5)	$32 (17)
CT-S-2-FU-2	$0 (0)	$0 (0)	$0 (0)	$0 (0)	$0 (0)
Screening AFB	$427 (8)	$742 (1)	—	$358 (42)	$201 (89)
Non-invasive investigations					
Diagnostic imaging	$44 (6)	$15 (5)	$13 (4)	$711 (92)	$302 (134)
Physician	$20 (2)	$16 (2)	$6 (1)	$192 (25)	$162 (43)
Cardiopulmonary exams	$3 (1)	$1 (0)	$0 (0)	$58 (13)	$9 (6)
Invasive investigations					
Endoscopy	$36 (4)	$26 (5)	$11 (4)	$302 (57)	$625 (228)
Percutaneous biopsy	$20 (3)	$4 (2)	$3 (2)	$384 (61)	$185 (101)
Surgery (benign lesion)	$26 (12)	$27 (16)	$29 (21)	n/a[d]	n/a[d]
Complications					
Minor	$1 (1)	$2 (1)	—	$7 (5)	$0 (0)
Intermediate	$5 (3)	—	—	$208 (111)	$0 (0)
Hospitalization	$9 (9)	—	—	—	$1212 (1212)
Average cost (per-person)	$1011 (22)	$1275 (21)	$452 (27)	$2606 (178)	$3062 (1176)

[a]Base line scan (CT-S-1).
[b]12-month annual scan (CT-S-2).
[c]3-month follow-up scan (CT-S-n-FU-n).
[d]Not applicable because surgery for proven malignant lesions are classified as treatment-phase resources.
SE, standard error; AFB, autoflourescence bronchoscopy; CT, computed tomography.

four phases of treatment (diagnostic workup, treatment, follow-up year 1 and follow-up year 2) or died was $33,244 (95% CI, $31,553–34,935), for individuals who received surgery as their first-line treatment (n = 38). Eighteen percent (6 of 33) of individuals who completed all four phases of treatment and had early-stage NSCLC (<stage III) had radiographic and/or pathologic evidence of recurrent or second primary lung cancer within 2 years of their surgery. The cumulative cost of treating individuals with surgery over all the four treatment phases was lower than the cumulative cost of treating advanced-stage lung cancer with chemotherapy, radiotherapy, or supportive care alone (n = 15) ($47,796; 95%CI, $43,258–52,265) ($p$ = 0.061, comparing the two costs).

DISCUSSION

This is the first prospective resource utilization and cost analysis of a lung cancer screening study that may be used to inform program evaluation and cost-effectiveness analyses (CEAs). We noted that nodule management differed between the study sites, which contributed significantly to the cost of follow-up after the baseline CT scan and to increased screening costs at some of the study sites. Our results project the expected 18-month screening costs for an LDCT-based study of 1000 people to be $434,427 to screen participants who do not have lung cancer at the baseline or within 18 months of follow-up. If the cancer detection rates and treatment decisions were similar to those observed in the Pan-Canadian study (i.e., 4% screen-detected lung cancer, 81% receiving first-line surgery, 19% receiving nonsurgical first-line treatment for advanced disease), the expected cost for the treatment of screen-detected lung cancer would total over $1.4 million dollars. The entire program, including both LDCT-based screening and treatment costs for 1000 subjects, would cost approximately $1.9 million dollars or $1880 per person. This excludes the initial costs of setting up the screening program infrastructure and its promotion through the general practice and wider community. Recruitment costs were not included in our cost analysis although the centers were provided with a research budget of $20,000 to use toward advertising or other recruitment strategies. Recruitment in the NLST was reported to cost an average $130 (USD) per-person.[14]

When the findings of the Pan-Canadian study are compared with the NLST, the same low rate of invasive investigations and complications is observed in screened individuals without lung cancer.[10,15] However, in the Canadian study, there is a slightly higher rate of follow-up CT exams than in the

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TABLE 3. Regression Modeling: Covariates Associated with the Use of CT-S-1-FU-1 (Model 1) and Increased Screening-Phase Cost (Model 2)

Model variables	Model 1	Model 2
Dependent variables	Odds ratio (SE)	Cost coefficient (SE)
Outcomes	CT-S-1-FU-1	Screening-phase cost
Independent variables		
Demographic		
Age at CT-S-1, per year	n.s.	n.s.
Female sex	n.s.	n.s.
White ethnicity	n.s.	n.s.
Education, per level	n.s.	n.s
Quality of life at baseline, EQ5D visual analog scale <60% vs. ≥60%	n.s.	n.s.
Study-specific		
Screening study site		
1	Reference	Reference
2	2.18 (0.33)***	$303*** (81)
3	2.62 (0.35)***	n.s.
4	2.71 (0.34)***	$175* (79)
5	2.37 (0.37)***	n.s.
6	2.40 (0.29)***	$217** (70)
7	1.16 (0.32)***	$156* (79)
Screening status		
18-months completed, no cancer	Reference	Reference
Lost to follow-up	−0.98* (0.49)	−$226* (93)
Positive for lung cancer	−1.24** (0.36)	$1340*** (112)
Other cancer	−1.74* (0.74)	$2089*** (245)
Deceased	−3.86* (1.52)	n.s.
Use of AFB screening intervention (LDCT + AFB vs. LDCT alone)	n.s.	$700*** (50)
Number of chest radiographs in the 1 year before enrolment	n.s.	n.s.
Number of CT exams in the past 3 years before enrollment	n.s.	n.s.
Screening phase (start-up phase [pre-2010] vs. full functioning phase [2010])	n.s.	n.s.
Risk factors		
Pack years	n.s.	n.s.
Smoking status, current vs. former	0.34 (0.17)**	n.s
Family history, first degree relative with cancer	n.s.	n.s.
Number of listed comorbidities	n.s.	n.s.
Presence of coronary heart disease	n.s.	n.s.
Presence of COPD	n.s.	n.s.
Number of lung cancer symptoms	n.s.	n.s.
Presence of low lung function (predicted FEV1 <80% vs. ≥80%)	n.s.	n.s.
CT-S-1 test results		
Number of nodules (per-person)	0.12 (0.03)***	n.s.
Nodule size		
1–4.9 mm nodule	−0.53*** (0.28)	n.s.
5.0–9.9 mm nodule	3.6*** (0.21)	n.s.
10.0–14.9 mm nodule	3.0*** (0.31)	$500*** (82)
nodule(s) ≥15 mm	1.6*** (0.36)	$542* (108)
Nodule characteristics		
≥1 Calcified nodule	−0.88*** (0.23)	n.s.
≥1 PFN	n.s.	n.s.
≥1 GGO	−0.52** (0.19)	−$154** (54)
≥1 Semi-solid	n.s.	n.s.
≥1 Solid nodule	0.92** (0.29)	$136* (69)
Emphysema observed on CT-S-1	n.s.	n.s.

($p \geq 0.05$, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

n.s., not significant; SE, standard error; AFB, autoflourescence bronchoscopy; LDCT, low-dose computed tomography; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 sec; PFN, perifissural nodule; GGO, ground glass opacity.

NLST after the first (baseline) LDCT (32.5% versus 21%), yet the rates of follow-up CT exams that occurred after CT-S-2 were similar, 6.6% and 7.1%, for the Canadian and NLST studies, respectively. A recently reported lung nodule malignancy risk calculator has the potential to reduce variability in workup at screening sites and substantially reduce the number of CTs after the first screening LDCT.[13]

Our data also show that treatment costs are a substantial component of any lung cancer screening program and should be considered in detail in CEA, particularly as new chemotherapeutic agents emerge and drive late-stage treatment costs higher.[16] In Canada, cancer treatments generally cost less than in the United States and the price of patented drugs in Canada is contained by the government regulation, which ensures that new drugs are not sold at a price higher than the mean price in comparable member countries of the Organization for Economic Co-operation and Development.[17]

There has been considerable debate surrounding the issue of cost-effectiveness of lung cancer screening, due largely to the absence of evidence of a mortality benefit before the NLST. Some studies have found that lung cancer screening is likely to be cost-effective.[18–21] Others, including post-NLST simulations, have found that screening with LDCT would be highly unlikely to be considered cost-effective, even under the most conservative parameter inputs.[22,23] Smoking cessation interventions can improve the cost-effectiveness of screening programs.[19,23] None of the studies to date have considered real world screening study data. The current challenge in health care delivery is how to exploit new technologies to improve patient outcomes and improve health care access, while keeping the costs under control. The number of deaths that potentially could be prevented and the number of life years gained

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TABLE 4. Mean Per-Person Cost (SE) for Short-Term Treatment of Screen-Detected Lung Cancer by First-Line Surgery or Nonsurgical Treatment of Advanced Disease

Treatment Phase Completed	Diagnostic Workup		First-Line Treatment		Follow-Up Year 1		Follow-Up Year 2		All Phases	
First-Line Treatment	**Surgical**	**Nonsurgical**	**Surgical**	**Nonsurgical**	**Surgical**	**Nonsurgical**	**Surgical**	**Nonsurgical**	**Surgical**	**Nonsurgical**
Number	67	16	67	16	58	15	37	8	38	15
Screening exams										
CT-S-1	$193 (0)	$193 (0)	—	—	—	—	—	—	$193 (0)	$193 (0)
CT-S-2	$89 (12)	$36 (19)	—	—	—	—	—	—	$31 (12)	$26 (18)
CT-S-3	$26 (8)	$24 (17)	—	—	—	—	—	—	$5 (5)	$13 (13)
Screening AFB	$389 (46)	$321 (94)	—	—	—	—	—	—	$494 (59)	$343 (98)
Follow-up screening LDCT										
CT-S-1-FU-1	$88 (10)	$30 (16)	—	—	—	—	—	—	$67 (12)	$32 (17)
CT-S-1-FU-2	$19 (6)	$20 (14)	—	—	—	—	—	—	$17 (8)	$21 (14)
CT-S-1-FU-3	$2 (2)	$10 (10)	—	—	—	—	—	—	$4 (4)	$11 (11)
CT-S-2-FU-1	$23 (9)	$10 (10)	—	—	—	—	—	—	$13 (7)	$11 (11)
CT-S-2-FU-2	$14 (6)	—	—	—	—	—	—	—	$4 (4)	—
CT-S-3-FU-1	$2 (2)	—	—	—	—	—	—	—	—	—
CT-S-3-FU-2	$2 (2)	—	—	—	—	—	—	—	—	—
Noninvasive investigations										
Diagnostic imaging	$1528 (92)	$1548 (141)	$68 (21)	$308 (116)	$541 (76)	$930 (169)	$496 (97)	$519 (293)	$2487 (197)	$3096 (373)
Physician	$403 (35)	$442 (83)	$84 (11)	$464 (145)	$556 (42)	$763 (171)	$264 (29)	$579 (246)	$1307 (102)	$1990 (376)
Cardio/ pulmonary exams	$141 (32)	$116 (45)	$1 (1)	$5 (5)	$43 (14)	$18 (18)	$15 (7)	$3 (3)	$157 (47)	$89 (30)
Invasive investigations										
Bronchoscopy	$417 (75)	$1102 (152)	—	$49 (49)	$58 (30)	—	$75 (43)	—	$526 (109)	$1144 (144)
Percutaneous biopsy	$592 (75)	$346 (119)	—	—	$66 (39)	—	$57 (39)	—	$645 (97)	$370 (125)
Treatment										
Surgery	—	—	$18,083 (948)	$937 (937)	$757 (435)	—	$323 (323)	—	$19,753 (1568)	$1000 (1000)
Chemotherapy/ radiotherapy	—	—	—	$10,059 (2242)	$657 (231)	$3161 (1375)	$57 (57)	$9273 (7405)	$624 (250)	$16,829 (4103)
Hospitalizations for progressive disease	—	—	—	—	—	$13,096 (6238)	$553 (553)	$9323 (4314)	$538 (538)	$18,069 (6744)
Complications										
Minor	$23 (11)	—	—	$31 (31)	—	—	—	—	$20 (12)	$33 (33)
Intermediate	$155 (86)	$625 (610)	$213 (150)	$2267 (1537)	$259 (178)	—	—	$62 (62)	$519 (290)	$3118 (1690)
Serious	—	—	$4202 (2327)	$1197 (707)	$264 (185)	$124 (121)	—	—	$5836 (4007)	$1398 (746)
Average per-person cost	$4108 (195)	$4824 (814)	$22,188 (2818)	$15,272 (3490)	$3210 (887)	$18,089 (6456)	$1842 (766)	$19,758 (8177)	$33,244 (5005)	$47,792 (8053)

SE, standard error; AFB, autoflourescence bronchoscopy; LDCT, low-dose computed tomography.

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with lung cancer screening using LDCT is greater than any new treatment modality offered over the last 2 decades. If expensive targeted therapies become widespread in the treatment of advanced, inoperable lung cancer, a screening program could potentially become cost saving while at the same time improving patient outcomes.

Continuing care for stage III and IV lung cancer is higher than early-stage lung cancer on a monthly basis, even when chemotherapy costs are excluded.[24] Data from the Canadian National Ambulatory Care Reporting System in Canada also suggest high costs of care to manage advanced lung cancer specifically due to the use of acute inpatient, intensive care, and emergency department resources in the last month of life.[25] The Canadian data also shows that the number of deaths that occur in an acute care hospital is nearly three times higher for lung cancer than for any other type of cancer.

Shifting lung cancer management toward a "curative intent" paradigm would have cost consequences such as the additional treatment of overdiagnosed lung cancer and the treatment for relapsed or second primary lung cancer, following a curative intent resection. Overdiagnosis of individuals who would not have died of the disease is estimated to be approximately 13%.[26] Surgical failure rates for early-stage NSCLC, as measured by recurrence or second lung primaries were 18% over the first 2 years, which were included in our study. However, the rate could potentially reach 40% over 5 years, and add costs to individuals who were treated initially with surgery.[27] The collection of individual cost and outcomes data in pilot screening studies is essential as screening guidelines, risk stratification and evidence to inform cost-effectiveness estimates develop in the post-NLST era.

The Pan-Canadian study has potential limitations. The majority of the study participants were of Caucasian ethnicity and able to attend screening appointments at major Canadian cities. Depending on how rural and minority groups are reached, the actual program cost may be higher. In Canada, 19% of the population lives outside of an urban community and 16% of the total population is a visible minority,[28,29] possibly affecting screening adherence rates and out-of-pocket expenditures that are not covered by Canada's healthcare programs. These costs were not included in this analysis. The impact of screening on the quality of life or other health outcomes and noncancer incidental findings was not part of this analysis and we did not compare our results to a screen-free comparative cohort. The Pan-Canadian study was conducted prospectively through a multicenter, interdisciplinary network of lung cancer specialists in a healthcare system based on universal coverage. A population-based program may have higher costs and worse outcomes if screening does not involve a team that is experienced in the management of screen-detected lung nodules and treatment of early lung cancer. Reimbursement deficiencies could be problematic to patients in other health care systems if the patients have medical coverage for lung cancer screening but not for the treatment of detected disease.

The Pan-Canadian study has potential strengths. The risk prediction tool used in the Pan-Canadian study for recruitment resulted in a reduction in the number of people needed to be screened to detect one lung cancer compared with NLST criteria. The risk prediction tool used in this study was subsequently found to have 11.9% greater sensitivity in identifying those who would be diagnosed with lung cancer in the 6 years of follow-up when compared with the NLST criteria.[30] Screening of higher risk individuals may also improve cost-effectiveness by reducing the number of false positives per prevented lung cancer death.[31]

As program planning unfolds in publicly funded healthcare systems or private screening clinics, robust CEA modeling from both the public payer and societal perspective are necessary. The importance of building CEA models with reference to population-level data cannot be overstated. Lung cancer screening is going to be a major policy issue and accurate information on the costs and benefits of screening are urgently needed to inform future cost-effectiveness models and the overarching policy debate.

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