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Implementing low-dose computed tomography screening for lung cancer in Canada: implications of alternative at-risk populations, screening frequency, and duration

W.K. Evans MD,* W.M. Flanagan BM,† A.B. Miller MD,‡ J.R. Goffin MD,* S. Memon MBBS MPH,§ N. Fitzgerald MA,§ and M.C. Wolfson PhD‖

ABSTRACT

Background   Low-dose computed tomography (LDCT) screening has been shown to reduce mortality from lung cancer; however, the optimal screening duration and "at risk" population are not known.

Methods   The Cancer Risk Management Model developed by Statistics Canada for the Canadian Partnership Against Cancer includes a lung screening module based on data from the U.S. National Lung Screening Trial (NLST). The base-case scenario reproduces NLST outcomes with high fidelity. The impact in Canada of annual screening on the number of incident cases and life-years gained, with a wider range of age and smoking history eligibility criteria and varied participation rates, was modelled to show the magnitude of clinical benefit nationally and by province. Life-years gained, costs (discounted and undiscounted), and resource requirements were also estimated.

Results   In 2014, 1.4 million Canadians were eligible for screening according to NLST criteria. Over 10 years, screening would detect 12,500 more lung cancers than the expected 268,300 and would gain 9200 life-years. The computed tomography imaging requirement of 24,000–30,000 at program initiation would rise to between 87,000 and 113,000 by the 5th year of an annual NLST-like screening program. Costs would increase from approximately $75 million to $128 million at 10 years, and the cumulative cost nationally over 10 years would approach $1 billion, partially offset by a reduction in the costs of managing advanced lung cancer.

Conclusions   Modelling various ways in which LDCT might be implemented provides decision-makers with estimates of the effect on clinical benefit and on resource needs that clinical trial results are unable to provide.

Key Words   Lung cancer, screening, low-dose computed tomography, modelling, NLST, Canada

INTRODUCTION

Lung cancer was diagnosed in 26,100 people in Canada in 2014[1]. Only approximately 17% of those patients will survive to 5 years, largely because most (75%) present with advanced, incurable disease[2,3]. However, when lung cancer is detected early, surgical resection can cure up to 70% of patients[4]. In 2006, the Early Lung Cancer Action Program investigators in the United States reported results from a study of 31,567 asymptomatic people at risk for lung cancer.

Low-dose computed tomography (LDCT) identified lung cancer in 484, 85% of whom had clinical stage I cancer[5]. Unfortunately, the Early Lung Cancer Action Program was not designed to assess the effect of screening on lung cancer mortality. More recently, the U.S. National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality at 6 years for LDCT compared with chest radiography screening in more than 50,000 participants[6].

The foregoing results have generated enthusiasm for population-based screening, and numerous guidelines

recommending LDCT screening programs have been published[7–11]. A 2013 Cochrane review[12] and a systematic review[13] have also supported the U.S. Preventive Services Task Force recommendation on LDCT screening[14]. Cancer Care Ontario published a guideline recommending LDCT screening[15], and the Canadian Task Force on Preventive Health Care also recently published recommendations supportive of annual LDCT screening for up to 3 consecutive years in an at-risk population identical to that of the NLST population[16].

Nevertheless, the NLST trial left many unanswered questions with respect to how best to implement a population-based screening program. Those questions include the optimal frequency and duration of a program and the best target population to screen.

Although ongoing trials are comparing LDCT with usual care, none are as large as the NLST, and it is highly unlikely that future trials of sufficient size will set out to address important questions such as the cost-effectiveness of annual screening, the effects of using alternative risk factors and different screening frequencies, and the inclusion of a smoking cessation program. To assist provincial policymakers considering the implementation of a lung cancer screening program, we used the Cancer Risk Management Model for lung cancer (CRMM-LC) developed and maintained by the Canadian Partnership Against Cancer (CPAC) to model the potential benefits and costs of various implementation strategies.

In an earlier publication, we demonstrated that implementation of an NLST-like program in the Canadian context had an incremental cost-effectiveness ratio (ICER) of $52,000 per quality-adjusted life year (QALY)[17]. When smoking history was modelled for 20 or 40 pack–years, the ICERs generated were, respectively, $62,000 and $43,000 per QALY. The addition of a smoking cessation program that improved the quit rate by 22.5% with a one-time intervention improved the ICER to $24,000 per QALY.

The foregoing cost-effectiveness data provide the economic basis to support introduction of a LDCT screening program, but the practical implications by province in Canada are lacking. In particular, factors such as the total budgetary impact, the actual potential life-years gained (LYGS) by province, and the number of computed tomography (CT) scans needed for implementation and over time are important factors that policymakers have to consider. The present paper provides the CRMM outputs for those factors and others that could be important for provincial decision-makers.

METHODS

Development of the CRMM-LC

The CRMM was developed by a multidisciplinary team in collaboration with Statistics Canada. A detailed description of the CRMM and some of its outputs was reported previously[18,19]. Briefly, the CRMM simulates large representative samples of the Canadian population, one individual at a time, from birth to death. The simulated individuals are subject to equations and probabilities derived from empirical data that shape their demographic profile, labour force characteristics, risk factor exposures, risk of developing cancer, health status, and risk of death. Life histories unfold

in a continuous-time, discrete-event Monte Carlo microsimulation with explicit competing risks. The model is similar to a comprehensive longitudinal health, demographic, and economic survey of the population that includes future years. The CRMM-LC is based on Canada's lung cancer incidence and diagnostic data and treatment approaches. An annualized hazard of developing lung cancer during each year of a simulated person's life is estimated based on risks related to smoking and radon exposure, applied to a background lung cancer incidence rate. The background rates were fitted to Canadian Cancer Registry data for 2005 by age, sex, and province, while controlling for smoking and radon exposure. The simulated number of new cancer cases was assessed for fit against other years of cancer registry data. Simulated people developing lung cancer have a stage-specific survival based on published data[20,21]. Simulations are performed at the individual level for millions of synthetic cases representative of the Canadian population and aggregated to determine effects on health outcomes and costs to the health care system. Individuals interested in greater detail about the model structure can refer to prior publications[18,19] and to version 2.1 of the CRMM-LC, which is available on the CPAC Web site, at http://www.cancerview.ca/cancerriskmanagement[22].

The CRMM-LC has undergone internal and external validation to ensure that all components—including demographics, risk factors, cancer incidence, and diagnostic and treatment approaches—are acceptable to Canadian lung cancer experts and that cause-specific mortality reproduces observed levels[22].

Development of a Screening Module Based on NLST Data

The screening module utilized data from the NLST, including rates of screen-detected cancers, the stage of non-small-cell lung cancers, the stage distributions for screen-detected cancers, and stage-specific survival. The module also incorporated NLST data concerning cancers detected in the intervals between annual screens and cancers detected in the post-screening period. Data from NLST relating to the increased lung cancer incidence and decreased lung cancer mortality with LDCT screening compared with chest radiography alone, and the number of positives (true and false) and negatives (true and false) based on the screening round and the 1-year interval after screening were used to develop estimates of the sensitivity and specificity of LDCT.

The target screening population for the base-case scenario was defined using the NLST eligibility criteria for age (55–74 years), smoking history (30 pack–years), smoking status (current smokers and former smokers who quit within 15 years of starting screening), and health status (no prior history of lung cancer). The scenario assumed 60% participation reached in a linear fashion over 10 years, with 70% adherence.

To confirm that the CRMM-LC reproduces the NLST screening results, a calibration and assessment exercise was undertaken[22]. The simulated mortality reduction from LDCT screening was 23% compared with 20% in the NLST. The difference in the number of lung cancer cases between the CRMM-LC and the NLST over 6 years varied by 2.3% at

most, and the difference in cumulative incidence at 6 years was less than 1%. The estimate for overdiagnosed cases was 6 percentage points higher than the 18.5% estimated for the NLST[23].

Costs reported here are expressed in 2008 Canadian dollars. The costs were increased annually by 1% to reflect economic growth as applicable to wages (estimated by Canada's Chief Actuary[24]) and assumed to apply to the health sector. Life-years gained were adjusted for health-related quality based on Canadian population preferences[25–27], and LYGs and costs were discounted at 3% annually[28]. A smoking cessation program is not included in the base-case scenario, but was modelled; the effects will be reported in a separate publication. Biennial screening has also been modelled and will be separately reported.

RESULTS

Size of the Eligible Canadian Population
Applying the NLST criteria to Statistics Canada's data for provincial age distribution and smoking rates, approximately 1.4 million screen-eligible individuals were estimated to be living in Canada in 2014. Using a 10-year time horizon for cost analyses, the screen-eligible population would decrease to 1.2 million by 2023. To calculate ICERs and capture the full impact of screening on future health care costs and outcomes, a lifetime horizon was applied.

Table I shows the number of people eligible to enter the screening program at baseline (2014) and the incremental numbers of new eligible people in 2015, 2020, and 2023 according to smoking history. The incremental numbers in a given year cannot simply be added to the baseline number, because people eligible in 2014 might not be eligible for screening in 2020 because of screen-ineligibility or death. The initial number of screening candidates would be 23% greater if eligibility for screening were to be expanded to include people with a 20 pack-year history, and 27% smaller if eligibility were to be restricted to people with a 40 pack-year history.

Table II shows the estimated number of screen-eligible people by province and territory (using the NLST eligibility criteria) and the percentage of each province's population that would be screen-eligible. On average, 4.1% of Canadians are eligible, ranging from 3.3% in Alberta to 5.3% in Newfoundland and Labrador. Table II also shows the maximum number of eligible people who could enter the first year of the program and the average incremental number of potential new eligible people per year over the subsequent 10 years. The incremental numbers represent individuals who become eligible for screening because they have reached 55 years of age. The table also shows the average number of people screened annually in the time period 2014–2023, given the specified assumptions concerning participation and adherence, and decline in eligibility over time.

Estimates of New Lung Cancer Cases

Base-Case Scenario Annual Screening
Without screening, the model projects that, in the 10 years from 2014 to 2023, a total of 268,300 new lung cancer cases will be diagnosed in Canada. Table III shows the number of new incident cases at two time points and cumulatively over 10 years for annual screening for different age ranges, smoking histories, and participation rates.

Given an annual screening program focused on a population similar to that enrolled in the NLST, 280,800 lung cancer cases would be diagnosed, representing a 4.8% increase (approximately 13,000 additional cases). Many of the additional cases would be cancers detected early by screening and potentially curable. However, some will also be overdiagnosed—that is, cancers that would not have been detected during the lifetime of the individual in the absence of screen detection.

Estimates of Lung Cancers Detected According to Smoking History, Age, and Participation
If the number of pack–years for screen eligibility were to be decreased to 20 from 30, the incremental number of screen-detected new lung cancer cases would increase by 1700 over 10 years; increasing the pack–year requirement to 40 would result in 2600 fewer cases. If screening were to target individuals 50–69 years of age, the number of lung cancers detected by screening would be 3600 fewer; however, if the age limits were to be 55–84 years, 5400 more cases would be detected. If a participation rate of 20% was achieved only gradually over 10 years (that is, 2% increase per year over 10 years), 8400 fewer cases would be detected compared with the base-case scenario (60% participation achieved over 10 years).

Table IV shows the benefits of LDCT screening compared with no screening, measured in cumulative LYGs over 10 and 20 years, according to the various scenarios. The number of LYGs by 10 years is relatively modest. For the base-case scenario, the gain is 9200, but that number rises with the inclusion of a broader age range and higher participation. By 20 years, the LYGs are substantially greater. Health-related QALYs are negative in the early years of the screening program, being mostly negative for participants with the smallest number of pack–years (Figure 1). The same effect is evident for various participation rates and age ranges (data not shown).

Table V shows QALYs gained cumulatively over 20 years according to the various scenarios.

Resource Utilization
The total number of CT scans required for a pan-Canadian screening program—inclusive of additional diagnostic CT

TABLE I Annual screening baseline and incremental number of screen-eligible individuals in Canada, by year and smoking history

Smoking history (pack–years[a])	Screen-eligible individuals[b]			
	Baseline (2014)	2015	2020	2023
20	1,768,300	119,500	90,600	86,700
30	1,436,300	79,600	55,200	52,300
40	1,043,800	56,100	37,700	34,300

[a] Average number of packs of cigarettes smoked daily multiplied by the number of years of smoking at that rate.
[b] Rounded to nearest 100.

TABLE II Screen-eligible individuals and individuals screened on average[a] during 2014–2023 based on an annual screening scenario, by province

Province	Provincial population (2014)	Eligible for screening (2014)		Average eligible to be screened (incremental *n*) annually (2015–2023)	Average (*n*) screened annually (2014–2023)
		(%)	(*n*)		
British Columbia	4,832,700	3.6	174,900	7,300	37,800
Alberta	3,814,100	3.3	126,800	6,000	28,200
Saskatchewan	1,027,000	4.2	42,800	2,200	10,000
Manitoba	1,273,800	3.7	47,400	2,200	10,600
Ontario	14,039,100	3.6	510,900	27,300	117,000
Quebec	7,771,200	5.2	403,400	16,900	89,900
Nova Scotia	1,002,600	4.9	49,100	2,100	11,000
New Brunswick	801,100	5	40,300	2,100	9,300
Newfoundland and Labrador	567,000	5.3	30,000	1,400	6,800
Prince Edward Island	152,200	5	7,700	300	1,800
NWT and Nunavut	80,00	2.2	1,800	100	400
Yukon	35,700	3.9	1,400	100	300
TOTAL	35,396,800	4.1	1,436,300	67,900	323,200

[a] Age 55–74, 30-year smoking history; rounded to nearest 100.
NWT = Northwest Territories.

TABLE III Estimated incident lung cancer cases in Canada by screening scenario in 2014 and 2023, and cumulatively over 10 years[a]

Scenario	Incident cases (*n*)		
	2014	2023	2014–2023
No screening	25,000	28,600	268,300
Annual screening, age 55–74[b]	25,800	30,400	280,800
20 Pack–years	26,000	30,700	282,500
40 Pack–years	25,700	30,000	278,200
Age 55–69	25,600	29,700	276,500
Age 55–79	26,000	31,000	284,200
Age 55–84	26,100	31,300	286,200
Age 50–69	25,700	29,800	277,200
20% participation	25,300	29,300	272,400
40% participation	25,600	29,800	276,500
70% participation	26,000	30,600	282,800
80% participation	26,100	30,800	284,700

[a] Values rounded to nearest 100.
[b] Annual screening and age 55–74 is the base-case scenario characterized by a smoking history of 30 pack-years and 60% participation rate. The other scenarios vary in the aspect subsequently shown.

scans to diagnose screen-detected abnormalities—is approximately 3.2 million over 10 years. That estimate takes account of the frequency of screening, participation and adherence rates, and the frequency with which diagnostic and follow-up CT scans occur, as observed in the NLST[6].

Although the annual incremental number of CT scans for most provinces is modest, the two most populous provinces would see potential increases in CT scan requirements of 24,000–30,000 in the first year, rising to 87,000–113,000 by the 5th year. The number of invasive procedures required to investigate screen-detected abnormalities would initially (in 2014) be approximately 1400 in total across Canada, but that number would increase over time. By 2023, the number of procedures in the annual screening cohort is estimated to be 6700. Eligibility based on smoking history and participation also influence the number of invasive procedures required.

Budget Impact

In the absence of a screening program, the cost of diagnosing and treating lung cancer in Canada over the next decade is estimated to be $5.7 billion. Table VI presents the total discounted costs to implement a LDCT screening program in Canada and to manage lung cancer over 10 years. At start-up, the annual cost of screening is estimated at $75 million, rising to $128 million in 10 years. The total discounted cost of screening over 10 years approaches $1 billion. Overall, on an annual basis, the cost of treating lung cancer is close to $600 million and decreases by approximately $12 million with the implementation of annual screening. However, those estimates do not include the costs of promoting the program, additional overhead or infrastructure costs, or setting up the information systems necessary to monitor the effects of the program.

Cost of Overdiagnosis

The percentage of overdiagnosed cases, calculated as the net increase in the number of lung cancer cases in the screen arm as a percentage of all screen-detected cancers after an average of 6.5 years of follow-up, is 24.8% in the CRMM-LC. All the excess cases would be stage I, so that the costs of their diagnosis and treatment can be estimated using the costs applied in the CRMM-LC overall. We estimate that 7400 people would be overdiagnosed over 10 years, at a cost of $116 million (undiscounted) and $98 million (discounted). If we had used the NLST overdiagnosis rate
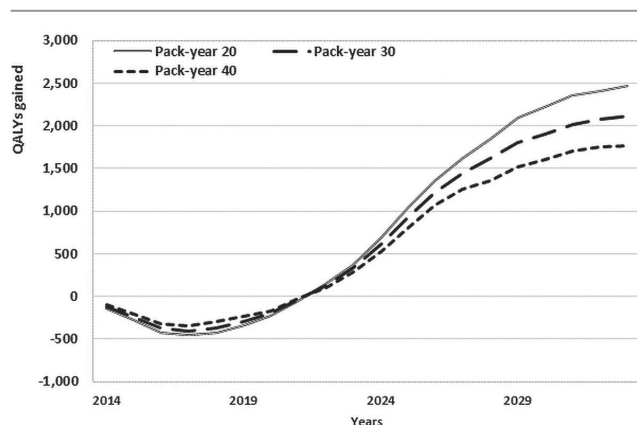
TABLE IV Cumulative life-years gained and costs, by scenario, over 10 and 20 years compared with "no screening"[a]

| Scenario | Cumulative life-years gained | | Costs (2008 CA$, millions) | | | | | |
| | | | Overall | | For screening | | For treatment | |
	2014–2023	2014–2033	2014–2023	2014–2033	2014–2023	2014–2033	2014–2023	2014–2033
No screening			5,700.6	10,926.7	0.0	0.0	5,700.6	10,926.7
Annual, screening 55–74 years[b]	9,200	51,300	6,838.0	13,097.5	945.7	1,868.7	5,892.3	11,228.8
20 Pack–years	10,300	59,400	7,155.9	13,918.0	1,238.3	2,629.6	5,917.7	11,288.4
40 Pack–years	7,300	41,400	6,512.4	12,413.3	658.9	1,255.6	5,853.5	11,157.8
Age 55–69	6,400	34,900	6,572.4	12,482.6	744.2	1,368.0	5,828.2	11,114.6
Age 55–79	11,300	63,000	7,012.0	13,562.3	1,067.4	2,228.2	5,944.6	11,334.1
Age 55–84	12,100	67,900	7,100.9	13,830.8	1,125.2	2,427.3	5,975.7	11,403.5
Age 50–69	7,000	38,700	6,764.3	12,800.6	927.1	1,675.9	5,837.1	11,124.7
20% participation	3,100	16,900	6,121.9	11,701.5	358.8	671.6	5,763.1	11,029.9
40% participation	6,100	34,300	6,477.8	12,399.9	652.2	1,270.9	5,825.6	11,129.0
70% participation	10,400	59,400	7,017.3	13,452.2	1,092.6	2,167.7	5,924.7	11,284.5
80% participation	11,800	67,500	7,194.3	13,798.2	1,238.8	2,465.5	5,955.4	11,332.7

[a]   Life-years rounded to nearest 100. All costs discounted at 3%.
[b]   Annual screening and age 55–74 is the base-case scenario characterized by a smoking history of 30 pack-years and 60% participation rate. The other scenarios vary in the aspect subsequently shown.

FIGURE 1 Quality-adjusted life-years (QALYs) gained with annual screening, by pack–year history. All values discounted 3%.

cancer and have recommended its implementation[7,9,10,14]. The challenge now is to determine the most cost-effective way to screen in a population-based program.

To introduce a new screening program, policymakers require reasonable estimates of the potential benefits and harms of screening, a good understanding of the resources required to mount the program, and estimates of its cost-effectiveness and budget impacts. A well-done screening trial can answer only some of those questions. Modelling is essential to estimate the long-term effects of various program options and to project overall cost-effectiveness.

Fortunately, the CRMM-LC can project the benefits of the NLST beyond 3 annual screens and can evaluate the effects of a variety of scenarios related to age at entry, pack–years smoked, duration of screening, and participation at a national or provincial level. Provincial analysts can access the model and run scenarios using various age and smoking history criteria[22].

Using population demographic data from Statistics Canada and data from surveys about smoking, it has been possible to estimate the number of potential candidates for screening in each province.

The NLST recruited volunteers who were younger than those who would have to be reached in a population-based program in Canada. They were also well educated, and their high participation and adherence indicate that they were highly motivated. It can be anticipated that the participation rate in Canada would initially be lower than that in the NLST. Although many former smokers are individuals of higher socioeconomic status and educational attainment, those who continue to smoke now represent those most addicted and perhaps least likely to attend a screening program. They are also typically of lower socioeconomic status and a challenge to reach[36]. We have therefore modelled low rates of participation, including 20% and 40%. We believe that such rates are realistic during the start-up

(18.5%), the number of overdiagnosed individuals would be 5500, for a cost of $86 million (undiscounted) and $73 million (discounted).

DISCUSSION

The NLST demonstrated that screening for lung cancer with LDCT is efficacious. Ideally, before mounting population-based screening programs, consistent data should be available from a number of high-quality trials. Although a number of trials are ongoing, all are smaller than the NLST[29–35]. They also have entry criteria different from those of the NLST. It is highly unlikely that another trial the size of the NLST will ever be conducted to address the outstanding questions. Nonetheless, several organizations have already concluded that LDCT is efficacious in screening for lung

years of a lung screening program, because that was the level of participation seen with colorectal screening in a similar-age population in Canada[37]. It is notable that a breast screening rate of 60% has only recently been attained after 20 years in the Ontario provincial program[38].

As noted in Table II, the number of new individuals entering the program each year and the total number in the program are expected to decline over time, primarily because of lower smoking rates in the younger-age population in Canada.

The results of modelling the NLST data over a 20-year period are encouraging from the clinical perspective, because LDCT screening is projected to result in 51,000 health-related QALYs gained, with an ICER of about $50,000 per QALY[17]. Other estimates of the cost-effectiveness of LDCT screening have fallen within a similar range[39–41]. However, even "cost-effective" interventions can have a major budget impact, which is why the CRMM-LC is of particular value to provincial decision-makers who can now be informed

TABLE V Cumulative quality-adjusted life-years gained, by province and scenario, over 20 years (2014–2033) compared with "no screening"[a]

Scenario	Province or territory											
	BC	AB	SK	MB	ON	QB	NS	NB	NL	PEI	NWT, NU[b]	YK[b]
Annual screening, 55–74 years[c]	1,290	1,420	380	690	4,180	4,410	870	520	240	150	__	__
20 Pack–years	1,580	1,710	350	730	5,180	4,570	1,060	570	370	160	__	__
40 Pack–years	870	1,050	250	580	3,270	4,510	630	520	270	100	__	__
Age 55–69	790	930	380	510	3,380	2,940	720	410	230	140	__	__
Age 55–79	1,540	1,480	360	830	5,040	5,190	870	620	200	170	__	__
Age 55–84	1,560	1,520	420	840	5,020	5,360	860	560	200	140	__	__
Age 50–69	1,120	1,050	410	630	3,920	3,480	720	500	190	130	__	__
20% participation	320	370	-10	130	1,630	1,790	170	70	140	80	__	__
40% participation	890	950	250	510	3,000	3,020	540	60	50	130	__	__
70% participation	1,350	1,740	440	790	4,830	4,910	1,030	630	300	170	__	__
80% participation	1,690	1,940	500	910	5,540	5,290	1,160	650	330	210	__	__

[a]   Values rounded to nearest 10 and discounted at 3%.
[b]   Values not shown because of small sample size.
[c]   Annual screening and age 55–74 is the base-case scenario characterized by a smoking history of 30 pack-years and 60% participation rate. The other scenarios vary in the aspect subsequently shown.

TABLE VI Total discounted costs (3%) of annual screening, by province at implementation, and cumulative costs over 10 years[a]

Province	Cost (2008 CA$, millions)						
	Of screening			Of treatment			Of screening plus treatment 2014–2023 Total
	2014	2023	2014–2023 Total	2014	2023	2014–2023 Total	
Canada	75.3	128.0	945.8	596.2	584.3	5892.3	6838.0
British Columbia	9.2	14.4	110.6	72.5	70.9	711.7	822.3
Alberta	6.6	11.1	82.6	49.8	53.3	521.6	604.2
Saskatchewan	2.3	4.0	29.2	16.8	17.9	174.3	203.5
Manitoba	2.5	4.2	31.3	21.9	22.3	209.2	240.5
Ontario	26.6	47.2	342.8	204.1	200.1	2036.6	2379.4
Quebec	21.2	35.5	262.6	172.0	163.8	1662.7	1925.3
New Brunswick	2.2	3.8	27.4	10.2	12.1	133.0	160.4
Nova Scotia	2.6	4.3	32.0	27.7	26.7	266.3	298.5
Prince Edward Island	0.4	0.7	5.3	2.5	3.1	27.9	33.2
Newfoundland and Labrador	1.6	2.6	19.8	13.0	13.8	134.3	154.1
NWT and Nunavut	0.1	0.1	1.1	0.8	0.4	5.0	6.0
Yukon	0.1	0.1	0.9	0.4	0.3	4.0	4.9

[a]   Scenario: 55–74 years of age, 30-year smoking history. Values are rounded to nearest 100,000. The costs of treating lung cancer without low-dose computed tomography screening are estimated to be $584.5 million in 2014, $560.2 million in 2023, and $5,700.6 million cumulatively for 2014–2023.
NWT = Northwest Territories.

about the costs of implementation by year and cumulatively over time to assess the feasibility of implementing such a program.

Screening has a short-term negative effect on QALYS (Figure 1). That effect reflects the detection of more lung cancer cases in the early screening years, which results in patients receiving treatment and incurring treatment-related toxicities. Overdiagnosis also contributes to the decline in health-related utilities. Patients whose disease has been found at a curable stage contribute to the increasing number of QALYS saved over the long term.

Concerns about a large demand for CT imaging and diagnostic investigations to work up screen-detected lung nodules are largely unfounded if the modelling assumptions are correct: namely, that participation ramps up at an annual rate of 6%–7%, achieving 60% participation at 10 years and adherence of 70%. For most provinces, the estimate of the annual incremental number of CT scans is generally modest. That information is key for provincial ministries of health, which have to estimate the incremental resource and funding requirements for the jurisdiction.

A large proportion of screen-detected abnormalities are subsequently determined to be false positives. In the NLST, 96.4% of the abnormalities initially detected subsequently proved not to be cancer. Nonetheless, once nodules are identified, they require either follow-up imaging or invasive diagnostic procedures, and harms potentially follow from those interventions. We estimated the number of repeat imaging and needle aspiration biopsies on the basis of the NLST data and data from a pan-Canadian CT study[42]. The incremental number of invasive procedures is quite low, although additional diagnostic CT imaging is more frequent. A recent report on the use of a biomarker—a plasma-based microRNA signature classifier—during the MILD LDCT screening trial[34] demonstrated that the combination of the microRNA signature classifier and LDCT reduced the false-positive rate to 3.7%[43]. If a microRNA signature classifier or another biomarker is confirmed to be effective in reducing false-positive screen rates, it would, in many cases, avoid the need for follow-up CT imaging and unnecessary invasive procedures and would reduce costs.

By applying the NLST eligibility criteria and participation and adherence rates within the CRMM, the cost-effectiveness of a pan-Canadian LDCT screening program has been estimated[17]. Compared with no screening, LDCT resulted in an ICER of $52,000 per QALY[17]. Changes in participation rates altered the number of LYGs and the total cost, but not the ICER. The ICER was sensitive to changes in the adherence rate. However, the LDCT ICER remained below $100,000 per QALY gained even with varying smoking histories and age eligibilities, among other factors[17].

Overdiagnosis

Screening results in overdiagnosis and incremental costs that cannot be avoided. The precise magnitude of overdiagnosis from LDCT screening is uncertain. A modelling study performed for the U.S. Preventive Services Task Force estimated the proportion of overdiagnosis to be 10%–12%[14]. In the CRMM-LC, our own computations were applied to the data obtained from the NLST investigators, deriving an estimate of 18.5% from 3 screens over the average of 6.5 years

of follow-up. That finding was confirmed by Patz *et al.*[23]. However, it is important to note that this degree of overdiagnosis was based on comparing LDCT with chest radiography screening, and considerable overdiagnosis can result from chest radiography screening alone. Another factor that might not be taken fully into account in our model is deaths from long-term complications of treatment in overdiagnosed lung cancers. Early deaths from overtreatment were incorporated into the estimates of efficacy in the NLST, because any death regarded by the death reviewers as resulting from screening for, or treatment of, lung cancer was regarded as a lung cancer death[44]; however, deaths after long term follow-up would not have been included.

Given the range of overdiagnosis rates in the literature, we estimated the costs that might occur, assuming that such patients all present with stage I non-small-cell lung cancer. Based on the CRMM-LC estimates of 24.8% at 6.5 years, the cost of overdiagnosis would be $116 million (undiscounted) or $98 million (discounted at 3% per annum). Using the NLST rate of 18.5% at 6.5 years, the cost would be $72.8 million dollars to treat approximately 5500 overdiagnosed individuals.

Other Considerations

The NLST was undertaken with considerable rigour. Only 33 U.S. sites were involved, all radiologists were skilled in the reading of CT images, the CT imaging equipment had to meet a high standard as defined in the study protocol, and a rigorous quality assurance program was in place[45]. The investigation of detected abnormalities was undertaken in sophisticated hospitals and cancer treatment centres. For Canadian jurisdictions to achieve results equivalent to those in the NLST, it will be necessary that they have similar or higher levels of expertise and resources, including high-quality CT imaging equipment, appropriately trained technologists and radiologists, and sufficient resources to undertake the investigation of any abnormalities found.

As with any model, assumptions have had to be made, the most critical of which are the sensitivity and specificity of LDCT scanning. Values were estimated to be consistent with the NLST findings for 3 annual screens, but are unknown for the additional screens envisaged for population-based screening programs. The NLST results suggested improved sensitivity in the 3rd and final screen compared with the 2nd screen, which we assumed would not be plausible in a population-based setting. We therefore conservatively assumed that the sensitivity estimated for the 2nd screening round from NLST data (87%) would be perpetuated for the 3rd and all subsequent rounds. Specificity also improved on the 3rd screening round; however, in this case, it seemed plausible that the cumulative knowledge from earlier screens could lead to better specificity in later rounds of screening. We assumed a specificity of 84% for the 3rd and all subsequent screens, consistent with NLST findings.

The costs for screening and management of lung cancer are largely based on Ontario practices and costs, which we assume are generally similar to those elsewhere in Canada. The Ontario Case Costing Initiative and the Ontario Health Insurance Plan Schedule of Benefits and Fees were used for payments to physicians and for technical services[46] and the costs to deliver radiotherapy and chemotherapy were

derived from individual institutions[47,a]. Costs for end-of-life care were obtained from Manitoba[48]. The clinical practices for lung cancer management were current when planning was initiated in 2008, but the treatment of lung cancer has since evolved, particularly for advanced disease. New and expensive agents such as pemetrexed and various molecularly targeted therapies are now routinely used. Those treatment approaches are not currently part of the model. However, if they were to be added, screening would be anticipated to be even more cost-effective because the number of advanced cases would be reduced. Further, newer surgical approaches and comprehensive integrated care have reduced postoperative hospitalization, substantially reducing costs.

In Canada, approximately 4.4 million CT scans were performed in 2012[49]. Although capacity has been further increased since then, there are shortages of interventional radiologists and significant waits to access CT imaging. Although screening will result in additional demand for access to CT and for investigation of screen-detected abnormalities, the CRMM can quantify the magnitude of the additional resource requirements so that appropriate planning for the necessary physical and human resources can be undertaken.

CONCLUSIONS

The CRMM-LC screening model is able to project the number of new lung cancer patients that will be diagnosed over a 10-year period (and beyond), with and without a screening program, and can generate lifetime outcomes. It can estimate the number of eligible candidates for a LDCT screening program and the LYGS, based on a variety of eligibility criteria, smoking histories, ages of entry, and participation rates. It can provide provinces with very practical information, such as the anticipated incremental number of CT scans and invasive procedures that will be required. Importantly, the cost-effectiveness and budget requirements under a variety of implementation strategies can be estimated. It is anticipated that this information will prove useful to those charged with decisions related to the implementation of LDCT screening across Canada.

CONFLICT OF INTEREST DISCLOSURES
We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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^a Meeke S, Juravinski Cancer Centre. Chemotherapy preparation and administration costs. Personal communication.

AUTHOR AFFILIATIONS
*McMaster University, Hamilton, ON; †Statistics Canada, Ottawa, ON; ‡Dalla Lana School of Public Health, Toronto, ON; §Canadian Partnership Against Cancer, Toronto, ON; ‖University of Ottawa, Ottawa, ON.

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