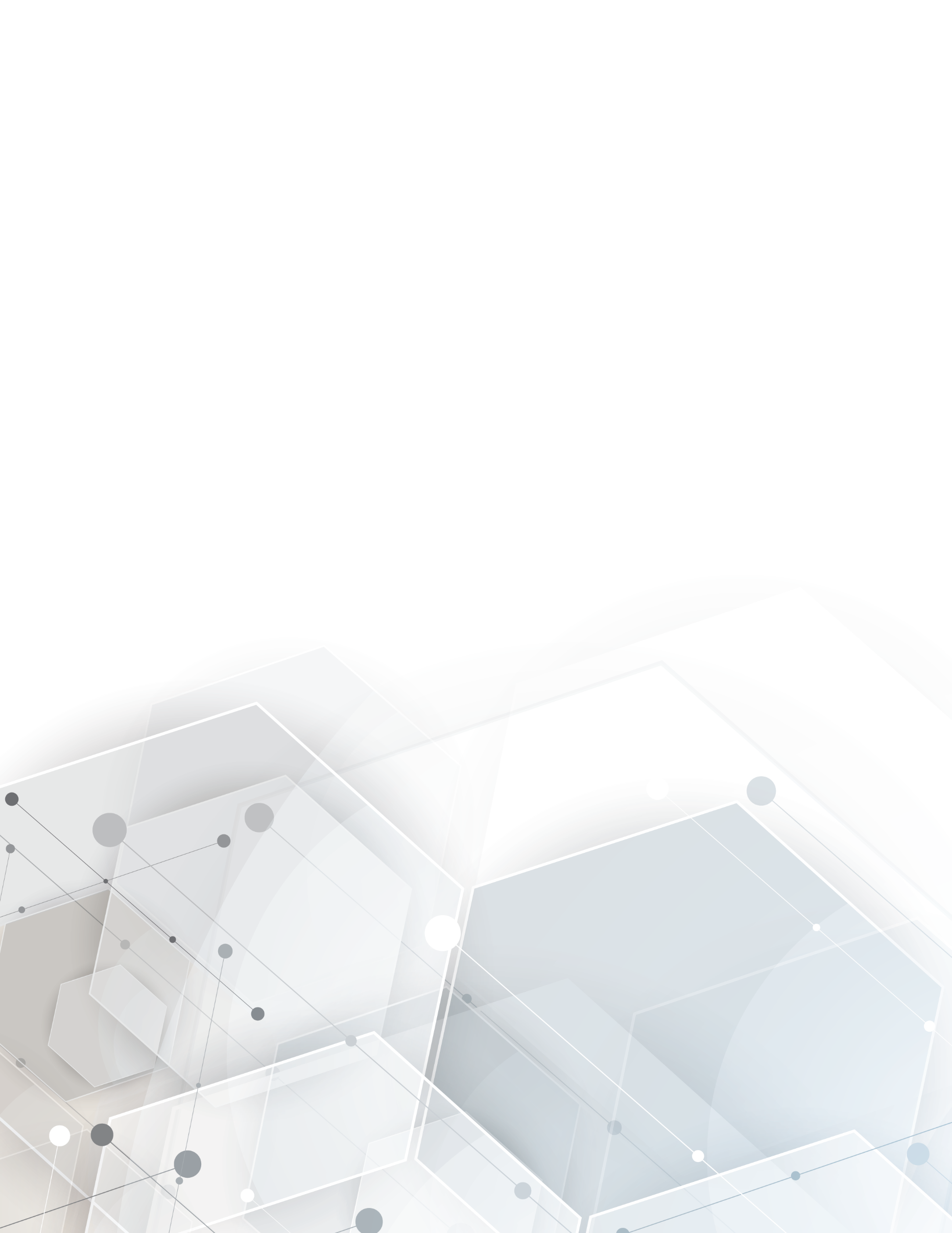


Version 1.1 – March 2020

**GUIDANCE FOR BUSINESS**

**CASE DEVELOPMENT**



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About this document

As the steward of the Canadian Strategy for Cancer Control (the Strategy), the Canadian Partnership Against Cancer (the Partnership) has a mandate to advance work on cancer control for all Canadians. The [Strategy](https://www.partnershipagainstcancer.ca/cancer-strategy/) places a priority on the early detection of cancer, and specifically calls for action to advance lung cancer screening in Canada. Lung cancer screening with low-dose computed tomography has been shown to reduce lung cancer mortality by 20%-24% in two large randomized clinical trials.1,2 Given the efficacy of lung cancer screening, the Partnership’s role is to work across all jurisdictions and accelerate lung cancer screening implementation within the Canadian health care system.

On behalf of cancer programs across the country, the Partnership engaged the Toronto Health Economics and Technology Assessment (THETA) Collaborative to develop a general business case for lung cancer screening that could be adopted by jurisdictional partners across Canada. A working group comprised of representatives appointed by provincial and territorial cancer programs ([Appendix 1](#_Appendix_1._List)) was established to advise on the particular elements that should be covered in this document and at what level of detail.This report, prepared by the collaborative efforts of the working group, the Partnership and THETA, provides comprehensive guidance with respect to key considerations in the development of jurisdiction-specific business proposals for an evidence-informed lung cancer screening program using low-dose computed tomography to screen individuals at high-risk for the disease.

The report contains background information, environmental scans of lung cancer screening policies, both domestically and internationally, and the evidentiary basis for a lung cancer screening program. This business case incorporates new evidence that has emerged from research studies and new modelling capabilities that have become available to help inform implementation considerations.

Throughout the document, red text has been added to highlight areas where the text can be tailored by users of the business case to accurately describe their jurisdictional context. As lung cancer screening programs are anticipated to vary across the country, these sections should be filled with jurisdiction-specific content.

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# List of Abbreviations

|  |  |
| --- | --- |
| CI | Confidence interval |
| CT | Computed tomography |
| CTFPHC | Canadian Task Force on Preventive Health Care |
| EU | European Union |
| HR | Hazard ratio |
| ICER | Incremental cost-effectiveness ratio |
| LDCT | Low-dose computed tomography |
| LC | Lung cancer |
| LY | Life years |
| NRT | Nicotine replacement therapy |
| RCT | Randomized controlled trial |
| RR | Relative risk |
| QALY | Quality adjusted life years |
| SES | Socio-economic status |
| THETA | Toronto Health Economics and Technology Assessment |

# Executive Summary

#### Background

Lung cancer is the most commonly diagnosed cancer among Canadians. In 2019, the Canadian Cancer Statistics Advisory Committee estimated that annually 29,300 Canadians are diagnosed with lung cancer and 21,000 die from it.3 Lung cancer kills more Canadians than [colon](https://www.cancer.org/cancer/colon-rectal-cancer.html), breast, and prostate cancers combined. In fact, 26% of all cancer-related deaths are attributable to lung cancer.3 Less than 19% of Canadians with lung cancer survive more than five years after diagnosis.3

Lung cancer might be considered an excellent candidate for screening since 70% of all lung cancers are diagnosed at advanced stages (III and IV)3 and, in many cases, the disease progresses over a number of years – providing opportunities for clinical intervention. Five-year survival for advanced-stage lung cancer is less than 20%. If found in the earliest stage (Stage 1A), the 5-year survival is more than 80%. This has significant implications on reducing mortality and decreasing health care utilization through early detection.

With the development of low-dose computed tomography (LDCT), early detection for lung cancer has become feasible and has been shown to be clinically effective. Indeed, two of the largest randomized controlled trials (RCTs) (NLST: n= 53,454 and NELSON: n = 13, 195) have shown a reduction in lung cancer related mortality by 20-24% with LDCT screening.1,4

Furthermore, the number needed to screen (NNS) to prevent one death was estimated to be 2555 for LDCT, which is considerably lower compared to other screening programs already implemented in Canada. As such, the NNS to prevent one breast cancer death varies from 645 to 1,724 in each age decade from 40 to 79 years for mammography6 and the NNS to prevent one colorectal cancer death is 850 for flexible sigmoidoscopy.7

Lung cancer screening is expected to be cost effective, and economic modelling shows that it is on par with other population-based screening strategies and within accepted economic thresholds. The Partnership’s OncoSim model[[1]](#footnote-2) projects that at a national level, over a 20-year time frame, lung cancer screening with LDCT is projected to detect 8,000 to 17,000 more lung cancer cases at Stage I, leading to 6,000 to 14,000 fewer cases at Stage IV and 5,000 to 13,000 fewer lung cancer deaths. Compared to no screening, lung cancer screening would cost $20,000-$40,000 per QALY gained and is projected to be cost-effective at the cost-effectiveness threshold of $50,000 per QALY gained[[2]](#footnote-3) and comparable to the cost-effectiveness of Canadian breast cancer screening programs.8

Smoking cessation remains the most important preventive measure for lung cancer and related deaths. Unfortunately, quit rates among long-term heavy smokers are poor. Moreover, heavy smokers remain at high risk of developing lung cancer even years after smoking cessation. Therefore, LDCT screening is the only feasible intervention to lower mortality among those who have already stopped smoking. Considering the fundamental role of smoking in lung cancer, LDCT screening paired with smoking cessation will have greater potential to reduce cancer related morbidity and mortality than either intervention alone.

In 2016, the Canadian Task Force on Preventive Health Care (CTFPHC) recommended lung cancer screening with LDCT for individuals at high-risk for lung cancer. An organized lung cancer screening program with LDCT will target a small population of high-risk individuals who meet specific eligibility criteria. This differs from other recommended screening for breast, cervical and colorectal cancers which target larger, “average-risk” populations. The CTFPHC and the Canadian Association of Radiologists recommended that screening should be performed in a centre with expertise in early detection and management of lung cancer.9,10 Lung cancer is one of four cancers for which screening is recommended by the CTFPHC. Organized screening programs exist across the country for the other three cancers (breast, cervical and colorectal), but organized lung cancer screening programs have not yet been implemented in Canada.

|  |
| --- |
| The Canadian Task Force on Preventive Health Care (2016) recommends\* |
| * LDCT annual screening up to 3 consecutive times† * for people 55-74 years * current or former (quit ≤15 years) smokers * with ≥30 pack-year smoking history |

LDCT: low-dose computed tomography

\* At the time the recommendations were made, risk assessment tools were not included in the model used to assess the costs and consequences of screening for lung cancer in Canada. At that time, the CTFPHC acknowledged this as a gap and noted in their recommendation that further research was needed to determine whether risk assessment tools could be incorporated into the clinical algorithm.9 Since the publication of this recommendation, evidence has demonstrated the value of a risk-based approach to lung cancer screening.11

†At the time the recommendations were made, there was only RCT evidence on three annual screens. Since the publication of this recommendation, new evidence has emerged to show the benefit of extending the duration of screening.12

#### Current Situation

Currently, there are no organized lung cancer screening programs in Canada. However, some provinces and territories have started working towards the development of lung cancer screening program, such as preparing business cases and assembling advisory committees.13 Two research studies have been initiated in Alberta and British Columbia, and one pilot trial has been launched in Ontario. These studies aimed to identify any operational issues that need to be addressed for provincial roll-out of the organized screening program. Preliminary results from these research studies and pilots are highly favourable and demonstrate that lung cancer screening is feasible and effective in a Canadian context.14

Five provinces and one territory (AB, BC, MB, ON, NS, NT) have reported that opportunistic (ad hoc) lung cancer screening is occurring in their jurisdictions. The CTFPHC guidelines recommend against opportunistic screening since the harms associated with screening outside guideline recommendations appear to outweigh the benefits. The main reasons why opportunistic screening may be harmful are15:

* Screening is recommended only for a small segment of the population who have an increased risk of developing lung cancer. Screening of lower-risk individuals can cause net harm and waste valuable health care resources.
* Patients referred to opportunistic screening may receive a diagnostic CT instead of LDCT and hence get four times higher radiation exposure than would be ideal. If LDCT is used, there may not be standardized low-dose protocols in a region, also resulting in people receiving a higher than recommended radiation dose.16
* Since there may be a lack of expertise in interpreting screening CT outside organized settings, individuals with suspicious findings (incidentally detected pulmonary nodules) may undergo unnecessary imaging, biopsy procedures, or surgery with associated potential complications including mortality.
* There is no mechanism to help facilitate follow-up of abnormal results, rescreening or referral to diagnostic work-up.
* There are no mechanisms to assess and monitor the effectiveness and safety of opportunistic screening, which will be critical for outcome evaluation.

An organized screening program could mitigate these identified harms by:

* Following strict eligibility criteria for defining a high-risk population who would benefit the most.
* Setting optimal screening frequency.
* Supporting implementation of low-dose protocols along with annual quality assurance to minimize radiation exposure.
* Supporting implementation of nodule management protocols and diagnostic pathways to minimize the risk of false positive screens, the number of unnecessary procedures and related complications.[[3]](#footnote-4)
* Providing developed program performance indicators for quality assurance and quality improvement, and monitoring system performance and screening outcomes.[[4]](#footnote-5)
* Providing expertise in evaluating new evidence as it comes forward on ideal screening indications, intervals, and duration.

#### Recommended solution

Opportunistic screening is already happening. It is likely incurring more costs and negative impacts to individuals than would occur if screening was implemented in a programmatic fashion. Thus, the choice health departments have is whether to invest in an organized screening program or to continue to fund opportunistic screening in an unorganized, unevaluated and uncontrolled manner.

Population-based organized screening programs for breast, cervical and colorectal cancer have been implemented across Canada. Most provinces also have experience with LDCT lung cancer screening through participation in Pan-Canadian Early Lung Cancer Detection Study (AB, BC, NS, NL, ON, QC), ongoing research studies (AB, BC) and pilot trials (ON). Hence, an opportunity exists to build on these assets and expertise to effectively implement organized LDCT screening in Canadian provinces and territories.

#### Proposed program description

The program will target 55-74 year old individuals, who have a [2% risk of developing lung cancer within 6-year period[[5]](#footnote-6)]. Individuals will be offered [three annual scans/a baseline screen with subsequent annual or biennial screens for up to three scans based on findings of scans/a baseline screen with subsequent annual or biennial screens until the age of 74 based on findings of the baseline and subsequent LDCT].

#### Estimated impact on system capacity

To estimate the net impact of a screening program on system capacity, a “no screening” strategy was selected as a comparator, which provided the most conservative estimate. Assuming a [40%/30%] participation rate and a 10-year program phase-in period, approximately [XXX] individuals per year may be eligible for screening and approximately [XXX] LDCT scans may be required per year. Overall, approximately [XXX] new lung cancer cases would be screen-detected per year.

The cancer detection rate has been estimated to be [6-15] per 1,000 scans. As a comparison, the cancer detections rates are around 5 per 1,000 tests for mammography.17

The most conservative estimates suggest that the incremental budget required to run LDCT screening program is [$$$] per year. It should be noted that comparing the organized program to “no screening” overestimates the volume of resources required, which will be offset by the reduction in opportunistic screening.

|  |  |
| --- | --- |
|  | Per year |
| Eligible (high-risk) population (n) |  |
| Total screens (n) |  |
| Diagnostic procedures (n)   * Invasive * Non-invasive |  |
| Screen-detected new lung cancer (n) |  |
| TOTAL COST\* ($)   * Screening costs * Provincial/territorial program costs * Diagnostic workup costs * Smoking cessation program costs * Incidental finding costs * Cancer treatment costs |  |

All estimates in the table are annual incremental relative to [no screening/opportunistic screening], average over 20 years.

\*Screening costs include costs of LDCT screening and radiologist reading;

Diagnostic workup costs include costs for respirologist consultation, costs for invasive (biopsy, bronchoscopy, mediastinoscopy, mediastinotomy, thoracoscopy thoracotomy) and noninvasive procedures (chest CT, FDG PET-CT, chest x-ray) for those who have suspicious nodules;

Cancer treatment costs include costs for surgery, radiation, chemotherapy, immunotherapy, and palliative care;

Incidental finding costs include costs for investigation and treatment of incidental findings;

Smoking cessation costs include costs for nicotine replacement therapy, pharmacotherapy and counselling;

Provincial/territorial program costs include costs for promotion, patient recruitment, results communication, salaries for clinical and non-clinical staff, equipment etc.

More details on input parameters are provided in the Technical Appendix.

When successfully implemented, it is projected that the net costs of the program will be [$$$] for each quality adjusted life year saved.

Policy and decision makers often use cost-effectiveness thresholds to guide adoption and funding decisions on healthcare technologies. Though there is no single threshold recommended for Canada, $50,000 per QALY has been the most commonly used threshold in health economics18,19 with a range of $20,000 to $100,000.20 Interventions in oncology seem to be adopted at higher thresholds of acceptability.19 Considering a [$50,000/$100,000] willingness to pay threshold, this investment is considered to be cost-effective.

The main cost drivers were screening costs, followed by the operating costs of the program. By leveraging existing assets and structures for other organized screening programs, jurisdictions could optimize allocation of operating costs that could further reduce budget impact and the costs per life years gained.

# Context

# Description of the Health Problem

## Lung cancer incidence, staging and mortality

Lung cancer is the malignant growth of cells in the lung that destroys nearby tissue and may spread (metastasize) to other parts of the body. Lung cancer is the most commonly diagnosed cancer among Canadians. In 2019, the Canadian Cancer Statistics Advisory Committee estimated that annually 29,300 Canadians are diagnosed with lung cancer, representing 13% of all new cancer cases in Canada.3 In [Province/Territory A, X number] people were diagnosed with lung cancer in [2019].Lung cancer is the leading cause of cancer related deaths in Canada. Annually, there are 21,000 deaths due to lung cancer, accounting for 26% of all cancer deaths.3 In fact, lung cancer kills more Canadians than [colon](https://www.cancer.org/cancer/colon-rectal-cancer.html), breast, and prostate cancer combined. The same is true for [Province/Territory A, where X number] of deaths in [year] were from lung cancer, making it the leading cause of cancer related deaths in this jurisdiction. The five-year net survival is 19% for lung cancer, compared to 93% for prostate cancer, 88% for breast cancer, and 65% for colorectal cancer.3 Table 1 summarizes lung cancer statistics by jurisdiction.

**Table 1.** The estimated number (2019) of new lung cancer and all cancer cases as well as cancer related deaths in Canadian provinces and territories

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Province/  Territory | LC incident cases | All incident cancer cases | % of all cases | LC deaths | All cancer deaths | % of all cancer deaths |
| AB&NT | 2,400 | 20,600 | 12% | 1,710 | 7,000 | 24% |
| BC&YT | 3,250 | 26,900 | 12% | 2,500 | 10,900 | 23% |
| MB | 950 | 6,900 | 14% | 680 | 2,950 | 23% |
| NB | 820 | 5,100 | 16% | 610 | 2,100 | 29% |
| NL | 510 | 3,750 | 14% | 420 | 1,590 | 26% |
| NS | 1,050 | 6,700 | 16% | 800 | 2,900 | 28% |
| ON | 10,400 | 87,700 | 12% | 6,900 | 29,700 | 23% |
| PE | 155 | 970 | 16% | 115 | 380 | 30% |
| QC | 8,900 | 55,600 | 16% | 6,600 | 22,100 | 30% |
| SK | 810 | 5,900 | 14% | 610 | 2,400 | 25% |
| NT\* | 14 | 111 | 13% | 12 | 45 | 26% |
| NU\*\* | 19 | 60 | 32% | NA | NA | NA |
| YT\*\*\* | 22 | 153 | 14% | 18 | 62 | 30% |
| All | 29,300 | 220,400 | 13% | 21,000 | 82,100 | 26% |

LC: lung cancer

Source: [Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2019. Toronto, ON: Canadian Cancer Society; 2019](https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics%20supplementary%20information/2019/province-specific-statistics.pdf?la=en).

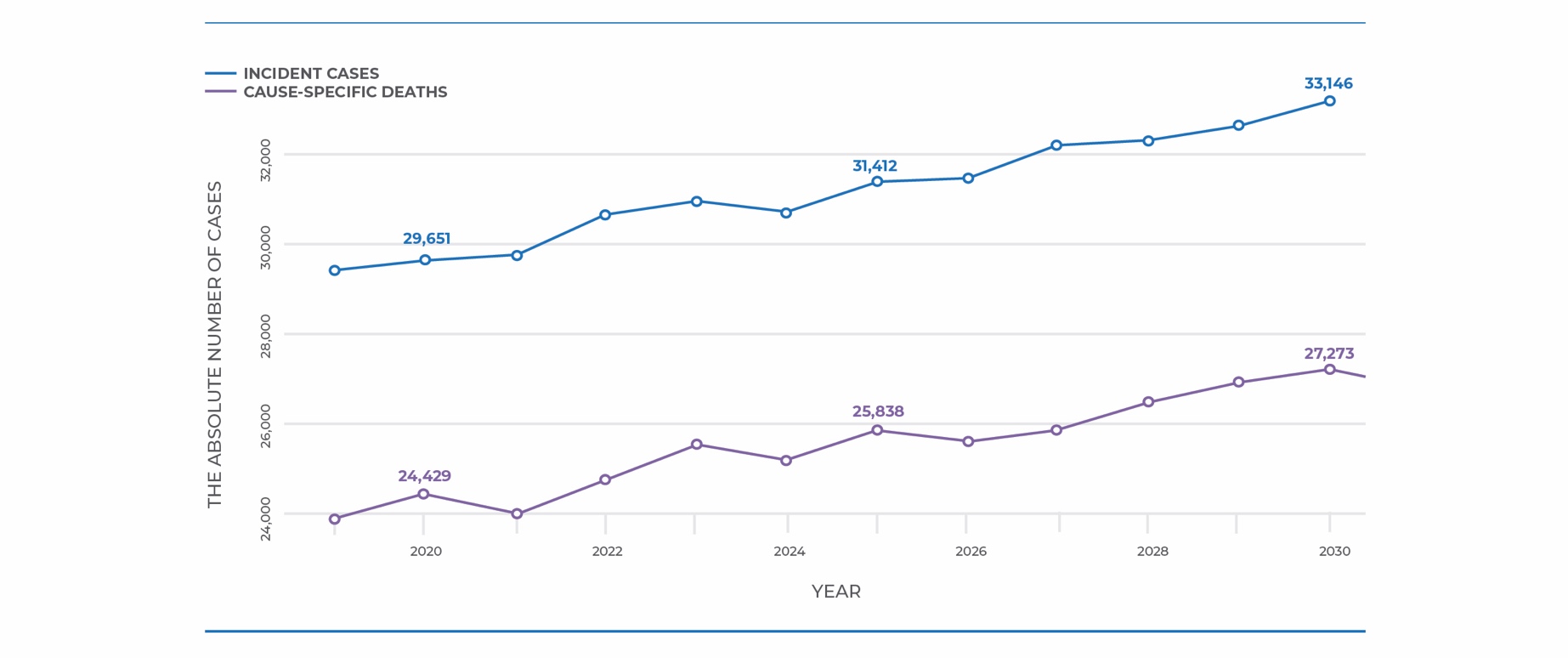
\*Data on NT cancer incidence were obtained from 2001-2010 annual average estimates, and on cancer mortality from 2000-2009 annual average estimates.21

\*\*Data on NU cancer incidence were obtained from 1999-2011 annual average estimates.22

\*\*\*Data on YT cancer incidence were obtained from 2009-2016 annual average estimates, and on cancer mortality from 2009-2013 annual average estimates.23,24

Although the incidence rate of lung cancer is declining (due to successes in reducing population levels of smoking in the past few decades), the number of new cases of lung cancer and cause-specific deaths is still

projected to increase in Canada by 2030 due to population growth and aging (Figure 1). This will have important implications for the health care system, and for managing health care resources.

**Figure 1.** Ten-year projections of new cases of lung cancer and disease-specific deaths in Canada.

Source: Data projected using OncoSim model, version 3.1.1.

In its early stages, lung cancer is usually asymptomatic, with the absence of pain, cough and shortness of breath. However, once a person experiences symptoms, the cancer has very likely progressed to an advanced stage. About 70% of lung cancer cases are diagnosed at advanced stages[[6]](#footnote-7) (Stages III and IV) when the cancer has already spread into the surrounding area and distant sites (i.e. metastasized).3 Only 30% of lung cancer cases are diagnosed at earlier stages (I and II) ([Table 2](#Table_2)).

If diagnosed earlier, lung cancer progression may be delayed, which would improve prognosis, decrease health care utilization and reduce the number of deaths due to lung cancer. Treatment options also differ for early and late stage cancers. At an earlier stage, surgery with intent to cure is possible, but not at later stages. The five-year survival for Stage I lung cancer is 68% - 92%, while for Stage IV the 5-year survival is 0-10% ([Table 2](#Table_2)), meaning that no more than 10% of patients diagnosed with Stage IV cancer survive 5 years.

In addition, direct health care costs for providing treatment for patients with early stage lung cancer are substantially lower than for patients with advanced stages.25 The annual course of recent immunotherapies for advanced lung cancer may cost as much as $140,000 per patient.26,27

**Table 2.** The stage distribution and survival for lung cancer

|  |  |  |  |
| --- | --- | --- | --- |
| Stage | Stage distribution | 2-year survival | 5-year overall survival |
| Stage I | 21% | 87-97 % | 68-92% |
| Stage II | 9% | 72-79 % | 53-60% |
| Stage III | 20% | 24-55 % | 13-36% |
| Stage IV | 50% | 10-23 % | 0-10% |

Data source for stage distribution: Canadian Cancer Registry from Statistics Canada.

There are no survival statistics available for the different stages of lung cancer for Canada. The information comes from the Lung Cancer Staging Project 28 and the most recent TNM 8th edition on lung cancer stage classification.29

Variation in 2 and 5-year survival estimates depends on sub-stage of lung cancer.

Thus, an effective organized screening program would allow for the detection of lung cancer cases at earlier stages, improve

patient outcomes, decrease the number of individuals with advanced lung cancer who require intensive treatment and care such as immunotherapies, and reduce use of additional healthcare resources.

|  |
| --- |
| Highlights   * Lung cancer is the most commonly diagnosed cancer and kills more Canadians than [colon](https://www.cancer.org/cancer/colon-rectal-cancer.html), breast, and prostate cancer combined. * About 70% of lung cancer cases are diagnosed at advanced stages. * Lung cancer often does not give rise to any symptoms in its early stages. * If found earlier, lung cancer may be cured, which would decrease health care utilization, treatment costs and reduce mortality. |

## Smoking as a major risk factor

Smoking remains one of the main causes of lung cancer and accounts for 85% of cases.30 A recent meta-analysis including a sample of over 7 million individuals showed that smoking increases risk of lung cancer both among men (relative risk (RR) = 7.33; 95% confidence interval (CI): 4.90 to 10.96) and women (RR = 6.99; 95% CI: 5.09 to 9.59).31

Lung cancer risk increases with the number of packs smoked and years of smoking. Smoking history is often measured in pack-years. One pack-year is the equivalent of smoking one pack (20 cigarettes) per day for one year (e.g., if person smoked 10 cigarettes per day for six years, then their smoking history is three pack-years).Between 2001 and 2018, smoking rates declined substantially from 26% to 16% in Canada as a result of comprehensive tobacco control efforts.32 The national target is to achieve less than 5% tobacco use by 2035 with the efforts of Canada’s Tobacco Strategy.33

Smoking rates vary geographically within Canada. In 2018, smoking rates in the provinces varied from 13% in British Columbia to 21% in Newfoundland and Labrador ([Table 3](#Table_3)). In the Territories, smoking rates were 20%, 35% and 63% in Yukon, Northwest Territories and Nunavut, respectively. In [Province/Territory A], smoking rates are [higher than/lower than/close to] the national average.

**Table 3.** Smoking prevalence (%) by province or territory in Canada (2001-2018)

|  |  |  |  |
| --- | --- | --- | --- |
| PROVINCE/TERRITORY | 2001 | 2010 | 2017-2018 |
| AB | 28 | 23 | 16 |
| BC | 21 | 17 | 13 |
| MB | 25 | 19 | 17 |
| NB | 26 | 23 | 14 |
| NL | 29 | 23 | 21 |
| NS | 28 | 23 | 18 |
| NT | 47 | 42 | 35 |
| NU | 57 | 54 | 63 |
| ON | 25 | 19 | 15 |
| QC | 30 | 23 | 18 |
| PE | 28 | 24 | 17 |
| SK | 28 | 23 | 20 |
| YT | 34 | 28 | 20 |
| CANADA | 26 | 21 | 16 |

Source: Canadian Community Health Survey (2001, 2010 and 2017-2018)

Smoking cessation remains the most important preventive measure for lung cancer and related deaths. A recent analysis of 216,917 adults in the US National Health Interview Survey (NHIS) showed that individuals who quit smoking at ages 55-64 had three times less risk of dying due to lung cancer than those who continue smoking.34

Although smoking cessation is the most effective form of primary prevention, support for quitting smoking is not universally available to patients and the general population, and cessation aid coverage varies widely across jurisdictions.

Furthermore, smoking cessation is a complex process; it may take an average 5-30 attempts over a smokers’ lifetime to quit successfully,35 which is why smoking cessation and relapse prevention programs with adequate and long-term public

coverage of nicotine replacement therapy (NRT), pharmacotherapy and evidence-

based counselling are important supports for current and recent smokers.

Unfortunately, heavy smokers remain at high risk of developing lung cancer even years after smoking cessation. In fact, in previous research studies in Canada, nearly 40% of people attending for screening had already stopped smoking,11 leaving LDCT screening the only further step available to them to reduce their risk of dying from lung cancer.

Therefore, lung cancer screening paired with smoking cessation has greater potential to reduce cancer related morbidity and mortality than either intervention alone and recurring screening provides additional opportunities for systematic smoking cessation. Having a reciprocal referral mechanism between lung cancer screening and smoking cessation programs that are available both to the general population (e.g., quit-lines) and for cancer patients in particular (e.g., within cancer treatment settings) will help to coordinate efforts across the healthcare system and provide continuous support to patients throughout their quit journey. Economic analyses have shown that integration of smoking cessation therapies alongside LDCT screening significantly improves the cost-effectiveness of the lung screening program.36,37

|  |
| --- |
| **Highlights**   * In Canada, nearly 40% of people attending for screening had already stopped smoking and the other 60% are current smokers. * Heavy smokers remain at high risk of developing lung cancer even years after smoking cessation, leaving LDCT screening the only further step available to them to reduce their risk of dying from lung cancer. * Lung cancer screening paired with smoking cessation have greater potential to reduce cancer related morbidity and mortality than either intervention alone. |

# Description of Technology under Assessment

## Screening for lung cancer

Screening is a process of applying a test to detect a potential disease or condition in a person who has no known signs or symptoms of that disease or condition. The decision to utilize a test for cancer screening involves a complex interplay of factors related to the selection of the target population, the effectiveness of the test, the benefits and harms associated with screening, availability of effective treatments to extend lifespan, and healthcare related costs.

Lung cancer is an excellent candidate for screening. Lung cancer is a significant health issue, and 70% of all lung cancers are currently diagnosed at advanced stages. The disease has a long, asymptomatic phase that presents opportunities for regular testing to find early cancers that have a greater chance of successful treatment. As an example, it typically takes about 8 years for a squamous cell carcinoma to grow to a size when it is commonly diagnosed (30 mm). By the time the individual becomes symptomatic, the risk of metastasis is considerable.38 The challenge, until recently, had been the lack of an effective screening test. Over the past several decades, chest radiography and sputum cytology were extensively studied for their potential as lung cancer screening tests. However, neither of these has been found to reduce mortality in randomised controlled trials,39 likely due to the fact that neither of the tests had enough sensitivity to detect cancer at the earlier stages, where it is more likely to be cured.

Computed tomography (CT) scanning is a diagnostic test that uses x-rays to generate multiple cross-sectional images of internal organs. LDCT uses less ionizing radiation (dose of ≤ 1.6 mSv)40,41 than a conventional CT scan (dose of 8.2 mSv).42 As a comparison, in Canada, the average annual dose of background radiation is 1.8 mSv,43 so properly done, LDCT provides a radiation dose similar to these annual background rates experienced by all Canadians. It produces images of better quality at a lower radiation dosage. Furthermore, it requires no contrast and hence reduces risks to patients, simplifies scheduling and reduces related costs.

The two largest RCTs of LDCT screening have shown a reduction in lung cancer mortality of 20-24% (NLST: n= 53,454 and NELSON: n = 13,195).1,2 Among women, the NELSON trial found a 33% reduction in lung cancer mortality (n=2,594). The number needed to screen (NNS) to prevent one death was estimated to be 2555 for LDCT, which is considerably lower compared to other screening programs already implemented in Canada. For context, the NNS to prevent one breast cancer death varies from 645 to 1,724 in each age decade from 40 to 79 years for mammography6 and the NNS to prevent one colorectal cancer death is 850 for flexible sigmoidoscopy.7

In 2016, the Canadian Task Force on Preventive Health care ([CTFPHC](https://canadiantaskforce.ca/guidelines/published-guidelines/lung-cancer/)) recommended screening with LDCT for a high-risk population. An organized lung cancer screening program with LDCT will target a small population of high-risk individuals who meet specific eligibility criteria. As recommended by CTFPHC and the Canadian Association of Radiologists, screening should be conducted in health care settings with expertise in early diagnosis and treatment of lung cancer (i.e. “centres with qualified radiologists and radiologic technologists, with examinations and diagnostic follow-up guidelines”).9,10

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| The Canadian Task Force on Preventive Health Care recommends\* |
| * LDCT annual screening up to 3 consecutive times† * for people 55-74 years * current or former (quit ≤15 years) smokers * with ≥30 pack-year smoking history |

LDCT: low-dose computed tomography

\*At the time the recommendations were made, risk assessment tools were not included in the model used to assess the costs and consequences of screening for lung cancer in Canada. At that time, the CTFPHC acknowledged this as a gap and noted in their recommendation that further research was needed to determine whether risk assessment tools could be incorporated into the clinical algorithm.9 Since the publication of this recommendation, evidence has demonstrated the value of a risk-based approach to lung cancer screening.11

†At the time the recommendations were made, there was only RCT evidence on three annual screens. Since the publication of this recommendation, new evidence has emerged to show the benefit of extending the duration of screening.12

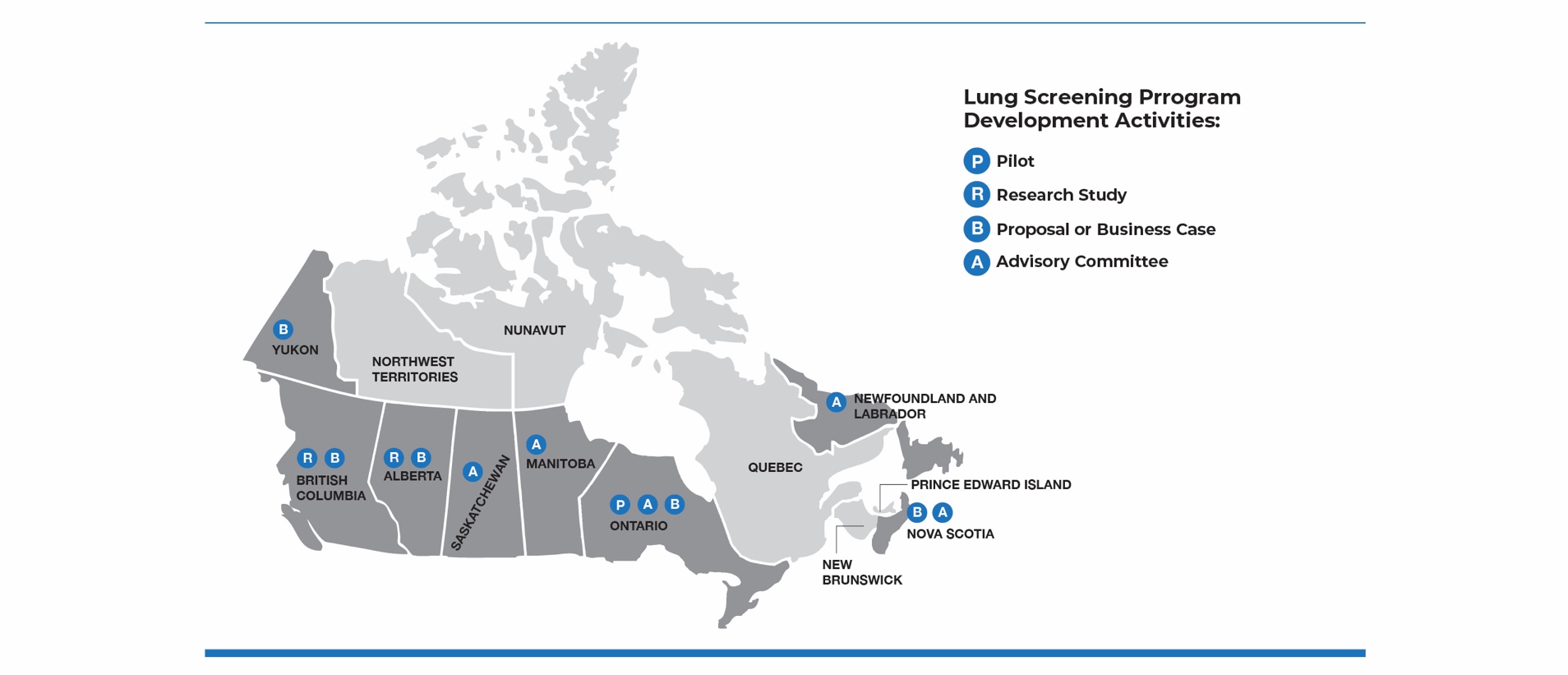
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| **Highlights**  Given the scientific evidence, CTFPHC recommendations and availability of technology, the implementation of lung cancer screening programs represents a key tool to build on existing tobacco cessation efforts and reduce lung cancer mortality. Organized lung cancer screening is also an opportunity to decrease the number of Canadians with advanced cancers that require expensive treatment. |

## Status of organized screening across Canada

An organized cancer screening program ensures the provision and promotion of screening tests to the eligible population and a pathway to diagnosis for persons with an abnormal screening result. The screening program collects data to support appropriate patient rescreening and follow-up, monitors patient experience and outcome, and reports on system performance.

Currently there are no province/territory-wide organized lung cancer screening programs in Canada. However some provinces and territories have started working towards the development of a lung cancer screening program, such as preparing business cases, assembling advisory committees and conducting research or pilot studies (Figure 2).13

* In 2017, Cancer Care Ontario launched a pilot of organized lung-cancer screening for high-risk individuals. The pilot was initiated in three sites in June 2017 with expansion to four sites in 2019.
* Three lung cancer screening research studies have been initiated: two research studies are ongoing in Alberta and British Columbia, and the Pan-Canadian study has been completed ([Table 4](#Table_4)). The research studies in Alberta and British Columbia aim to refine screening inclusion criteria, prospectively evaluate of lung nodule management protocols and evaluate of the role of computer-aided diagnostic tools in radiologists’ workflow.
* Business cases have been created or submitted to health ministries in five provinces and territories.
* Advisory committees for lung cancer screening have been formed, or are in development, in five provinces.
* The Pan-Canadian Lung Cancer Screening Network (PLCSN) was established in 2012 to support the implementation of lung cancer screening in Canada. The following projects have been advanced by the PLCSN:
* Development of a Lung Cancer Screening Framework – outlines consensus recommendations for key components of a quality lung cancer screening program.
* Development of National Lung Cancer Screening Quality Indicators – provides consensus on pan-Canadian indicators that should be reported on by all programs to measure system performance.
* Activities towards development of national-level lung cancer screening database – outlines considerations related to enabling performance reporting across programs.

**Figure 2.** Lung Cancer Screening related strategies in Canada (July 2018)

Source: [Canadian Partnership Against Cancer. Environmental Scan. 2018](https://www.partnershipagainstcancer.ca/topics/lung-cancer-screening-environmental-scan-2018/)

­The Pan-Canadian Early Detection of Lung Cancer trial, conducted at eight centres across Canada (Vancouver, Calgary, Toronto, Hamilton, Ottawa, Quebec City, Halifax and St. John’s), demonstrated that identification of high-risk individuals for lung cancer screening is feasible in a Canadian context.11 The Pan-Canadian study, along with ongoing research studies in Alberta and British Columbia and the pilot in Ontario, helped to build expertise in LDCT screening for lung cancer across Canada. The acquired practical experience and approach can inform the implementation of organized LDCT screening in Canadian provinces and territories.

**Table 4.** Summary of piloted screening programs/studies in Canada

|  |  |  |
| --- | --- | --- |
| Study, years, sample size | Eligibility | Screening frequency |
| Pan-Can Study (2008-2016),  n = 2,537 (completed)11 | ≥50-75 years &  ≥2% LC risk in 6 years\* | Baseline, at 1 and 4  years post-baseline |
| British Columbia Lung Screen Trial44  (2016-2021),  n=4,800 (expected) | ≥55-80 years &  ≥1.5% LC risk in 6 years\* or  ≥30 years of smoking history & smoking cessation ≤15yrs | Baseline, then based on Pan-Canadian lung nodule management protocol (annual or biennial scans based on detected nodule malignancy risk) |
| Alberta Lung Cancer Screening Study45  (2015-ongoing),  n=800 (recruitment completed) | ≥55-74 years &  ≥1.5% LC risk in 6 years\*  or  ≥30 pack-year smoking &  smoking cessation ≤ 15yrs | Three annual scans |
| Ontario Lung Cancer Screening Pilot46 (2017-2021),  n=3,000 (expected) | ≥55-74 years &  ≥2% LC risk in 6 years\* &  ≥20 years of smoking history | The screening frequency is based on the Lung-RADs score47 (see [Appendix 4](#_Appendix_4._Lung-RADS)) and can differ from annual recall (for negative scans) to 3-month follow up (for suspicious scans). |

\*the LC risk is calculated using PLCOm2012 criteria5

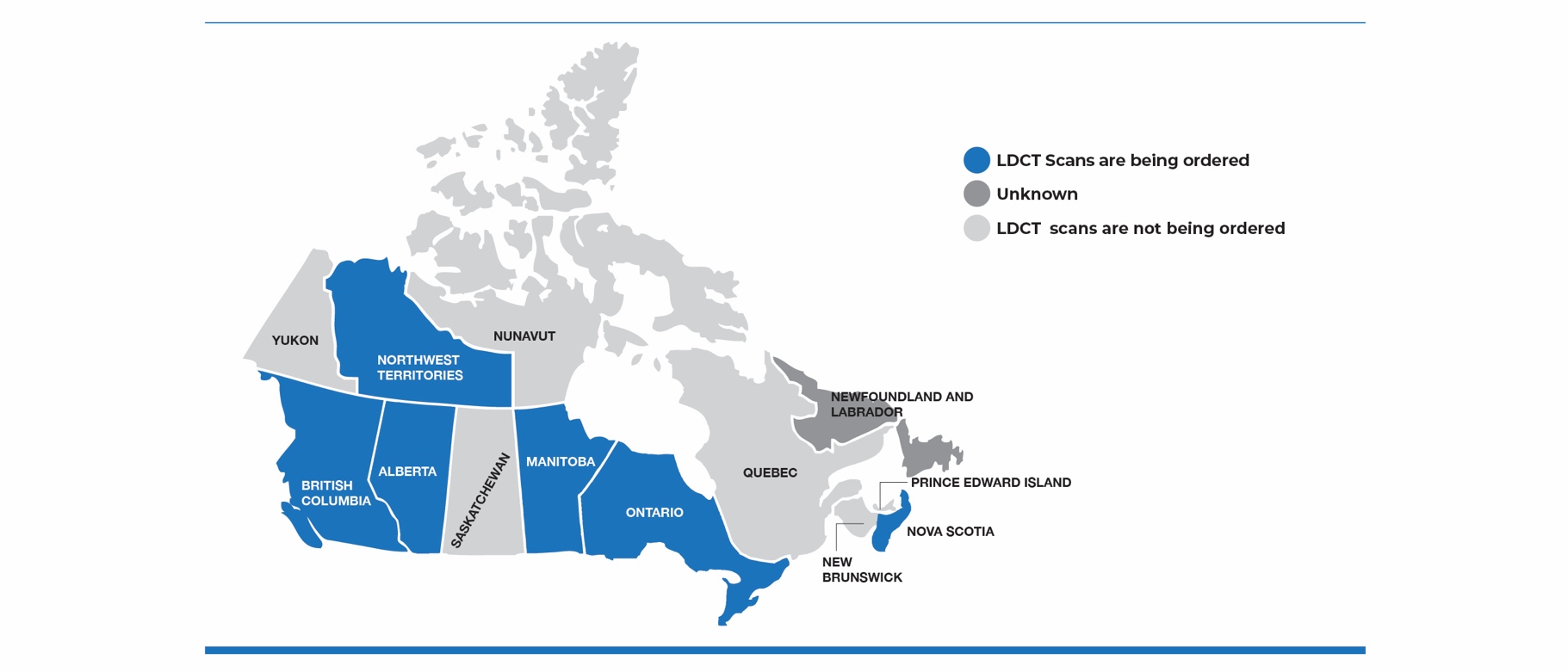
## Status of opportunistic screening across Canada

Opportunistic screening is the “ad hoc” screening of asymptomatic individuals outside an organized program setting in an unevaluated and uncontrolled manner. The CTFPHC guidelines (2016) recommend against opportunistic screening since the harms associated with screening outside of a programmatic setting appear to outweigh the benefits. Below are the main reasons why opportunistic screening may be harmful.

* The patient referred to opportunistic screening may receive a diagnostic CT instead of LDCT and hence may receive four times higher radiation exposure.
* Since there may be a lack of expertise in interpreting screening CT outside organized settings, individuals with incidentally detected pulmonary nodules may undergo unnecessary imaging, invasive diagnostic procedures or surgery with associated potential complications including mortality.
* Since screening is recommended only for a small segment of the population who have a high risk of developing lung cancer, screening of lower-risk individuals can cause net harm (unnecessary radiation, invasive procedures etc.) and waste valuable health care resources.
* Screening programs help facilitate appropriate follow up of abnormal results, rescreening, and in the case of lung cancer screening, connection to appropriate, evidence-based smoking cessation supports.
* Screening programs collect data to support continuous quality improvement. People participating in ad hoc screening do not benefit from the quality assurance and quality improvement activities offered through a programmatic approach.

In the absence of organized lung cancer screening programs, five provinces and one territory (AB, BC, MB, ON, NS, NWT) reported that they aware of opportunistic screening for lung cancer with LDCT. However, the amount of opportunistic screening remains largely unknown (Figure 3). A study of ad-hoc screening conducted at the McGill University Health Centre found that only 49% of individuals screened ad hoc met screening guidelines, and only 8% of scans performed were low-dose.48 The BC Lung Cancer Screen Trial identified that 15% of ever-smokers who would otherwise be eligible for LDCT screening had already had chest CT within the last 2 years. In [Province/Territory A], private clinics are offering opportunistic lung cancer screening services with physicians’ referrals.

**Figure 3**. Opportunistic Lung Cancer Screening in Canada



Source: Canadian Partnership Against Cancer. Environmental Scan. 2018

## Status of screening worldwide

Some countries have already begun implementing lung cancer screening and issuing recommendations. In the United States, as of February 2015, Medicare covers LDCT annual screening for people aged 55 to 77 years who are either current smokers or have quit smoking within the last 15 years.49

Since 2010, China offers screening to smokers age 50-74 with ≥30 pack-years smoking history. Since July 2019, the South Korean government offers LDCT biennial screening to smokers age 55 to 75 years with ≥30 pack-years smoking history.

In the United Kingdom, the Manchester Lung Health Check pilot launched in 2016 to screen individuals in deprived areas aged 55-74 with a 6-year lung cancer risk greater than 1.5%.50 They have shown that LDCT screening using mobile units can reach high-risk individuals and detect cancer at early, curable stages. Prior to the study, 48% of lung cancer cases were diagnosed at Stage IV and 11% at Stage I. During the study, only 11% of cases were diagnosed at Stage IV and 68% at Stage I.

In 2019, the National Health Service announced extension of the Lung Health Check program, deploying more mobile CT.51 Due to its success, NHS England has announced the funding of ten additional sites across the country at a cost of around £70 million over four years.52 The Queensland Lung Cancer Screening Study (QLCSS) assessed the feasibility of lung cancer screening implementation for current or past smokers ((≥30 pack-years, current or quit within the past 15 years) aged 60-74 in Australia. The study demonstrated that the benefits are similar to the NLST results, and that it would be feasible to implement.53

In addition to the CTFPHC, other organizations have also issued recommendations for lung cancer screening with LDCT that are summarized in [Table 5](#Table_5).

**Table 5.** Guidelines for lung cancer organized screening with LDCT

|  |  |  |
| --- | --- | --- |
| Organization, Country | Eligibility | Screening frequency |
| CTFPHC, Canada9 | ≥55–74 years &  ≥30 pack-year smoking &  smoking cessation ≤15years; | Three annual screens |
| The United States Preventive Services Task Force, US54 | ≥50-80 years &  ≥30 pack-year smoking &  smoking cessation ≤15years | Annual screening |
| The National Comprehensive Cancer Network, US55 | ≥55–74 years &  ≥30 pack-year smoking &  smoking cessation ≤15years;  or  ≥50 years &  ≥1.3% LC risk in 6-years &  ≥20 pack-years of smoking | Frequency and duration were not specified |
| The American Cancer Society, US56 | ≥55–74 years &  ≥30 pack-year smoking &  smoking cessation ≤15years; | Annual screening until the age of 74 |
| American Association for Thoracic Surgery, US57 | ≥55–79 years &  ≥30 pack-year smoking  or  ≥50-79 years &  ≥20 pack-year smoking &  ≥5% LC risk in 6-years | Annual screening until the age of 79 |
| EU position statement, Europe58 | Planning for LDCT screening throughout Europe | Frequency and duration were not specified |
| Japanese Imaging Guidelines, Japan59 | ≥50-80 years &  ≥30 pack-year smoking &  smoking cessation ≤ 15years | Frequency and duration were not specified |

LC: lung cancer; CTFPHC: Canadian Task Force on Preventive Health Care; EU: European Union; LDCT: low-dose computed tomography

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| **Highlights**   * LDCT is the only screening test that has potential to detect lung cancer in its earlier stages, decrease the number of advanced cancers that require expensive treatment and improve survival. * The acquired practical experience from the Pan-Canadian and other ongoing research studies and pilots can inform the implementation of organized LDCT screening in Canadian provinces and territories. * CTFPHC recommendations on organized lung cancer screening for high risk individuals have been released.   + CTFPHC recommends against opportunistic screening, since harms might outweigh benefits.   + Six jurisdictions have already reported that opportunistic screening is occurring. * The choice for health systems is whether to invest in an organized screening program, or continue to fund opportunistic screening in an unorganized, unevaluated and uncontrolled manner, and spending resources to screen individuals who may not benefit. |

# Health Technology Assessment

# Summary of Clinical Evidence on LDCT Screening

*In the section below, we provide a brief overview of clinical evidence, effectiveness and safety of LDCT for screening for lung cancer. We summarize the effectiveness primarily with respect to mortality-related outcomes.*

## What are the benefits of LDCT screening?

### Pan-Canadian OncoSim modelling

The Partnership’s OncoSim model projects that at a national level, over a 20-year time frame, lung cancer screening with LDCT is projected to detect 8,000 to 17,000 more lung cancer cases at Stage I, leading to 6,000 to 14,000 fewer cases at Stage IV and 5,000 to 13,000 fewer lung cancer deaths. Compared to no screening, lung cancer screening would cost $20,000-$40,000 per QALY gained and is project to be cost-effective at the cost-effectiveness threshold of $50,000 per QALY gained[[7]](#footnote-8) and comparable to the cost-effectiveness of breast cancer screening programs.8

### Overview of randomized control trials

Seven large-scale RCTs (NLST, DANTE, DLCST, MILD, NELSON, ITALUNG and LUSI) have published the results on effectiveness of LDCT screening on mortality related outcomes ([Appendix 2](#_Appendix_3._Mortality)). The sample size of these trials ranged from 2,811 to 53,434. All seven studies recruited high-risk populations, though the definition of “high-risk” varied between trials. Most of the trials reported annual screening intervals up to five rounds, but the Italian MILD trial reported annual screening intervals up to 10 times. All trials but one compared LDCT with usual care (i.e. no screening). The NLST trial compared LDCT with chest X-ray. The two largest and best quality RCTs (NLST, NELSON) demonstrated a substantial reduction in lung cancer related mortality with LDCT screening at long term follow-up. In 2011, NLST found a 20% reduction at over 6.5 years of follow-up1 and NELSON found a 24% reduction at 10 years.2 The updated analysis of NLST trial released in 2019 extended to over 12 years of follow-up and reaffirms the original findings.60

MILD and ITALUNG studies also demonstrated borderline reduction in mortality at >9 years of follow-up. Both studies showed greater survival benefits beyond 4-5th year of screening.12,61

The LUSI trial reported a 69% reduction in lung cancer mortality among women but not among men.62 The NLST, MILD and ITALUNG trials also reported reduction in all-cause mortality with borderline significance.4,12,61 Two other studies (DANTE, DLCST) did not find any differences in lung cancer-related or all-cause deaths between LDCT screening and no screening arms.63,64

All seven trials showed that lung cancers detected in the LDCT screening arms were more likely to be early stage (I and II) than those in the control arms. For example, in the NELSON trial, among the screen-detected cases in the intervention arm, 58.6% were diagnosed at stage I, whereas only 13.5% of cases were diagnosed at stage I in the control arm.2

**NELSON Trial: Summary of Mortality Results**

Results

The NELSON randomized lung cancer screening trial comparing low-dose computed tomography versus no screening was published in the New England Journal of Medicine in February 2020.

A total of 13,195 men and 2,594 women between the ages of 50-74 participated in the study. Participants in the screening arm underwent low-dose computed tomography (LDCT) screening at baseline (T0), year 1, year 3 and year 5.5. Participants in the control arm did not receive screening. Each participant was followed up for a minimum of 10 years.

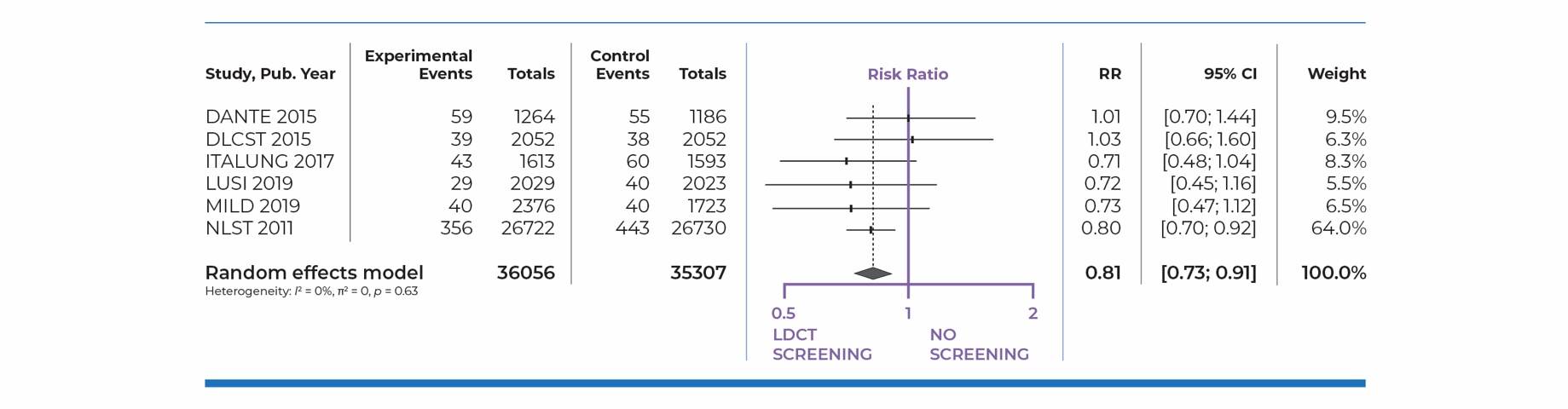
The study confirms a significant 24% reduction in lung cancer mortality in men (rate ratio for death from lung cancer at 10 years = 0.76 (95% confidence interval [CI], 0.61-0.94) and 33% reduction in women (rate ratio for death from lung cancer at 10 years = 0.67 (95% confidence interval [CI], 0.38-1.14) with LDCT screening. Lung cancer mortality was 2.5 deaths per 1000 person-years in the screening group and 3.30 deaths per 1000 person-years in the control group.

Interpretation

The results of the NELSON trial study confirm the effectiveness of LDCT screening in reducing mortality from lung cancer. NELSON is the second large randomized trial that shows a significant benefit of lung cancer screening using LDCT, following the publication of the NLST in 2011.

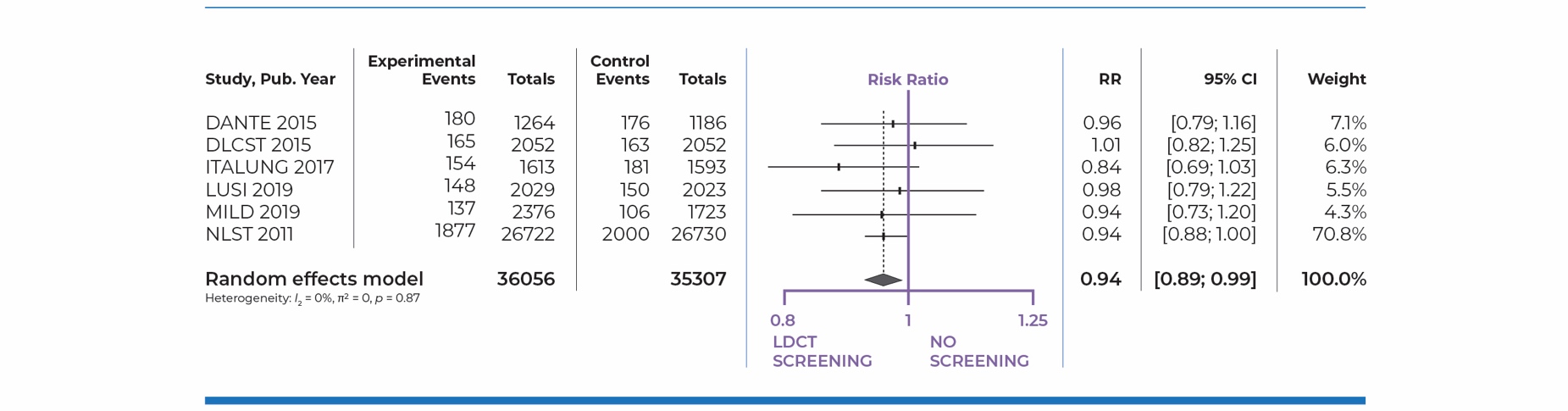
### Meta-analysis of RCTs

THETA collaborative conducted a meta-analysis assessing the effectiveness of LDCT on mortality. Since the NELSON trial results had not yet been published at the time this meta-analysis was conducted, the meta-analysis included six trials (NLST, DANTE, DLCST, MILD, ITALUNG and LUSI). The results demonstrated that LDCT is associated with a statistically significant 19% reduction in lung-cancer mortality (pooled RR = 0.81; 95% CI: 0.73 to 0.91) (Figure 4).



**Figure 4:** Meta-analysis of lung-cancer related deaths[[8]](#footnote-9)

The pooled findings also showed that LDCT screening reduces all-cause mortality (pooled RR = 0.94; 95% CI: 0.89 to 0.99) (Figure 5)



**Figure 5:** Meta-analysis of all-cause deaths[[9]](#footnote-10)

As stated earlier, the meta-analysis did not incorporate the outcomes from the NELSON trial, which, given the trial’s success, would further shift the pooled results in favor of LDCT screen

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| Highlights  The overview of clinical studies provides definitive evidence that:   * Lung cancer could be diagnosed at an earlier stage, if LDCT screening were implemented. * Beyond stage shift, LDCT screening reduces lung cancer-related mortality in high-risk individuals. LDCT is the only test that has been shown to sufficiently increase early detection of lung cancer to result in fewer deaths. |

Studies demonstrated heterogeneity in screening frequency, and in the definition of high-risk population and abnormal scan. All these parameters may substantially impact the screening volume, number of lung cancers found as well as false positive outcomes. The Pan-Canadian Early Lung Cancer Detection Study provides some insights on these issues.

### Canadian Early Lung Cancer Detection Study

The Pan-Canadian trial (2008-2016) was an observational study aiming to assess efficacy of the risk-based PanCan model in selecting individuals for lung cancer screening.11 It was conducted at eight centres (Vancouver, Calgary, Toronto, Hamilton, Ottawa, Quebec City, Halifax and St. John’s) and enrolled 2,537 individuals aged 50 – 75 years. As opposed to age and smoking history criteria applied in the RCTs described above, the Pan-Canadian trial selected individuals using a risk-based approach. The study included patients with at least a 2% 6-year risk of developing lung cancer and followed them for a median of 5.5 years.

The PanCan study found that:

* Risk-based screening can identify a larger proportion of individuals with early stage cancer than screening based on age and smoking history criteria alone.
  + Compared with 57% of lung cancers observed in NLST, 77% of lung cancers in the Pan-Canadian study were early stage (I or II).11
* Risk-based recruitment identifies relatively higher number of individuals who are subsequently diagnosed with lung cancer than screening based on age and smoking history criteria.
  + The incidence of lung cancer in Pan-Canadian study was higher than that of in NLST (6.5% vs 4.0%).11
  + The number needed to screen to detect one cancer and avert cancer-related death is smaller with the application of risk-based recruitment than with recruitment based on age and smoking history criteria.5,65

PanCan study investigators took further steps and developed a nodule risk calculator (nodule management protocols) that differentiates an abnormality as benign, intermediate or malignant.66,67 This substantially reduces the necessity in subsequent diagnostic procedures and may also be used to guide screening frequency ([Appendix 3](#_Appendix_5._PanCan)).

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| **Highlights**   * *Risk-based recruitment* and *nodule management protocols* eliminate unnecessary exposure of lower risk individuals, reduce the overall screening volumes, and reduce amount of diagnostic downstream services required. * The number needed to screen to identify one cancer and prevent one lung cancer death is lower if nodule management protocols are employed than that reported in NLST trial. * Lung nodule management protocols should therefore be considered in the implementation of lung cancer screening to maximize the benefits and minimize the budgetary impact of the program. |

## What are the potential harms of LDCT screening?

A major challenge with any screening procedure is that no test is completely accurate. Below is a list of potential harms associated with LDCT screening and mitigation strategies. Since the NLST and NELSON studies were conducted, other research has been done that has demonstrated how harms could be reduced. Effective tools have been developed, such as lung nodule risk calculators and lung nodule management frameworks, to improve the effectiveness and efficiency of lung cancer screening.

#### False positive findings

False positive findings are one of the most common adverse effects of any screening program. Patients with positive screening results may undergo additional diagnostic procedures, incur additional healthcare costs and experience unnecessary complications.

In the NELSON trial, 2.1% of scans (467 out of 22,600) were positive. Among those who were screen-positive, 43.5% were confirmed to have lung cancer. The false discovery rate (defined as the proportion of false positive screens among all positive screens) was 56.5% (264/467). Overall, only 1.2% (264 of 22,600) of the total scans performed had a false-positive result. Approximately 23% (67 out of 293) of participants with false-positive screen results underwent an invasive procedure, including surgeries or transthoracic biopsies68 comprising <1% (67 out of 7,582) of all screened participants. In the NLST, the false positive rate (defined as the proportion of positive screens among those who did not have cancer) was 23% and the false discovery rate was 96.4%. Roughly 2.2 % of all patients with a positive screen had undergone an invasive surgical procedure or biopsy.1,4

Current nodule management protocols (e.g. PanCan calculator, Lung-RADS,) differ from the NLST protocol in important ways to mitigate this issue ([Appendices 3](#_Appendix_5._PanCan), [4](#_Appendix_6._Lung-Rads)). They apply certain risk criteria (based on size and other nodule characteristics) to define an abnormality as potentially malignant, benign or indeterminate, which can substantially reduce the number of false-positive findings and the subsequent need for additional invasive procedures.47,66 Both PanCan and Lung-RADS nodule detection protocols showed good performance in discriminating benign nodules from malignant ones in the Alberta Lung Cancer Screening Study.69

#### Major complications following positive LDCT test result

The rate of major complications for patients undergoing invasive diagnostic procedures varies between 10.7% in NELSON68 to 28.6% in DANTE70 and 37.5% in DLCST.71 In the NLST trial the rate of major complications was 12% for patients with confirmed lung cancer and 2.4% without confirmed lung cancer.1,4 Postoperative death within 60 days of surgery was 1.6% and 0.1% for patients with and without confirmed lung cancer respectively.1,4

Within an organized screening program, standardized diagnostic workup protocols will limit unnecessary procedures and related complications.

#### Overdiagnosis

Apart from detecting aggressive cancers, screening would also detect slow-growing tumors that would otherwise have remained silent, regressed, or would not cause clinical symptoms and death. Hence, overdiagnosis may lead to overtreatment, related complications and incur unnecessary harms to the patient and costs to the system. In the NLST study, the estimated rate of overdiagnosis was 3%.60 As suggested earlier, both PanCan and Lung-RADS nodule detection protocols perform better than NLST protocols in discriminating nodules, which would further reduce this rate.

#### Radiation exposure

LDCT uses ionizing radiation (dose of ≤ 1.6 mSv) per screen.40,41 As a comparison, the average annual dose of radiation per Canadian is 1.8 mSv.43 No studies reported on radiation-related patient outcomes (e.g. radiation-induced lung cancer) at long-term follow-up. Based on the NLST results, Bach et al. estimated the lifetime risk to develop fatal cancer caused by radiation to be equal to 1: 2,500.72 Considering that the lifetime cancer risk in general population is 1:2 this additional risk is negligible. Within an organized screening program, low dose protocols and routine quality control will ensure the maintenance of low dose levels of radiation.

#### Incidental findings

Clinically significant abnormalities (cardiovascular, thyroid, adrenal findings, extrapulmonary cancers) unrelated to lung cancer are often detected in LDCT screening participants.

However, the impact of incidental findings on morbidity and mortality remains unknown and warrants further research. People eligible for lung cancer screening are at elevated risk of cardiovascular disease. Therefore, timely diagnosis and preventive treatments can further improve survival of these patients.73

It has been shown that only 7-20% of incidental findings require further investigation, mainly non-invasive testing or additional consultation.74-76 The rate of incidental findings with major clinical implications is less than 1%.

In the subgroup analysis of NLST (n = 17,309), incidental findings were found in 59% of participants; 20% were identified as clinically important, with the highest prevalence reported for cardiovascular findings (8.5%). Extrapulmonary malignancies were uncommon and found in 0.4% of participants. Authors concluded that indiscriminatory follow-up of incidental findings may significantly increase direct healthcare cost with little benefit, since detected extrapulmonary malignancies were rare.75,77

Similarly, in a subgroup analysis of NELSON participants (n=1,929), 129 (7%) had clinically relevant findings. Of those 118 (91%) required further diagnostic workup, mainly ultrasound. Only 21 (1%) participants had findings with clinical implications, including one patient with malignancy. Based on these results, the authors advised against systematically searching for incidental findings in lung cancer screening studies using LDCT.74

A Canadian study retrospectively assessed the prevalence of incidental findings among 4,073 LDCT screens. The authors found 782 (19%) subjects had incidental findings, of those 486 (62%) required further diagnostic workup. Seven patients had findings requiring immediate attention.76

When distributed over the total number of screening participants, the estimated cost of investigation due to incidental findings is about $12 per screen.76,78 However, when the cost for therapeutic interventions is included, nearly half (46.2%) of the screening related expenses (~$800 per screened individual that includes costs for LDCT scan, consultation, subsequent diagnostic testing and treatment) was attributable to the evaluation and treatment of incidental findings.77

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| **Highlights**   * Organized screening programs should use standardized algorithms for reporting on incidental findings. * Recent guidelines recommend classifying incidental findings into not clinically relevant (no investigation is required), possibly clinically relevant (further investigation, clinical judgement might be required) and concerning (therapeutic intervention is indicated) to avoid unnecessary diagnostic procedures while maintaining optimal clinical care.79 |

## How could organized screening programs mitigate harms?

The CTFPHC guidelines (2016) recommend that screening should only be carried out in health care settings with expertise in early diagnosis and treatment of lung cancer. Opportunistic screening is not recommended since the harms associated with screening outside of guideline recommendations appear to outweigh the benefits. An organized screening program could mitigate the harms associated with screening in a number of ways, which are described below:

1. Following strict eligibility criteria for defining a high-risk population who would benefit the most.

Unlike other cancer-screening programs (breast, cervical, colon) targeted for an average-risk population, lung cancer screening is recommended for only a small segment of the population who have an increased risk of developing lung cancer. Screening of lower or average-risk individuals could cause net harm to those individuals and increase associated costs. In Canada, the ongoing studies/pilot have strictly defined eligibility criteria with slight variation across the studies ([Table 4](#Table_4)). Opportunistic screening cannot ensure enrollment of high-risk individuals only, hence will generate a high number of false positive results, lead to inappropriate and costly diagnostic workup, and waste valuable healthcare resources. As family doctors and other primary care providers play an important role in initiating the lung cancer screening process, integration of primary care into an organized program would help to ensure that only eligible individuals are screened.

1. Setting optimal screening frequency and duration.

Screening frequency is one of the key factors to maximize benefits and manage costs. It is expected to vary across the provinces and territories. In Ontario and Alberta, annual screening is recommended, while British Columbia is using a nodule management protocol (PanCan), where screening frequency is based on detected nodule malignancy risk.80,66,67 The PanCan protocol is the only protocol that recommends a biennial screen instead of an annual screen for individuals with very low risk of lung cancer for the next 24 months based on the findings of the baseline LDCT. The CTFPHC recommends three annual screens, which reflects NLST protocol. Extended follow-up of NLST participants showed a dilution of the screening effect with time after three rounds of LDCT. However, some programs may consider a longer screening duration beyond three rounds as participants entering the screening program at a younger age are still at risk of lung cancer after three annual screens. Given significant costing implications on healthcare system, the optimal duration is yet to be determined. Organized screening programs are best positioned to capture data on process and outcomes that could be used to inform future screening recommendations. With ad hoc, or opportunistic screening, the ability to function as a learning health system is diminished, as each practitioner makes their own decisions as new literature appears.

1. Supporting development and implementation of low dose protocols along with annual quality assurance to minimize radiation exposure.

LDCT uses radiation dose of ≤ 1.6 mSv per screen.1 However, scan protocols vary depending on individual machine capacities. The organized screening program will support development of standardized technical protocols, while quality assurance check-ups will ensure that low radiation exposure protocol is maintained. An example of this is the Radiology Quality Assurance Program developed for the Ontario lung cancer screening pilot to ensure LDCT is performed and interpreted in a uniform manner across participating pilot sites.81 Similarly, quality strategies developed for breast cancer screening by the Canadian Association of Radiologists could be employed as a possible model for quality assurance for lung cancer screening programs.82 In an opportunistic setting, maintaining low dose radiation across individual machines is less likely, and more patients may receive a diagnostic CT instead of LDCT (four times higher radiation exposure).

1. Supporting development and implementation of nodule management protocols to minimize the risk of false positive and false negative results and overdiagnosis.

Not all lung nodules require follow up. Current nodule management protocols employed in Ontario (Lung-RADS nodule management protocol),47 and British Columbia and Alberta (Pan-Can lung nodule management protocol)66 apply certain criteria to define an abnormality as potentially malignant, benign or indeterminate, which can substantially reduce the number of false-positive findings and the subsequent need for additional diagnostic procedures ([Appendices 3](#_Appendix_5._PanCan), [4](#_Appendix_6._Lung-Rads)). The organized program would ensure that qualified radiologists with expertise in early detection will be involved with interpretation of the screening results.

1. Supporting development and implementation of patient management/diagnostic pathways to minimize the number of unnecessary procedures.

As indicated earlier, not all nodules required further diagnostic workup. Due to the lack of expertise in interpreting screening CT outside organized settings, individuals with incidentally detected pulmonary nodules may undergo unnecessary repeat imaging procedures, invasive diagnostic procedures or surgery with associated potential complications, including mortality. Within an organized screening program, standardized diagnostic workup protocols could limit unnecessary procedures and related possible complications.

To support optimal management of screen-detected lung nodules, the Partnership is facilitating the development of a lung nodule management framework aimed at advancing standardized practices in lung cancer screening to ensure patient safety and effective, high-quality screening. The framework will provide evidence-based best practice guidance for specialists to manage screen-detected lung nodules and include a sample of a patient-friendly screening radiology report.

1. Providing developed program performance indicators to support quality assurance and quality improvement, and monitoring system performance and screening outcomes.

The Pan-Canadian Lung Cancer Screening Network (2017) developed quality indicators to monitor the outcomes of the screening program.83 The National Data Working Group, assembled in 2016, summarized options for the management of lung cancer screening data in Canada. Eight provinces and one territory (AB, BC, NB, NL, NS, NT, ON, PE, QC) currently employ synoptic reporting (i.e. standardized electronic report) for lung cancer pathology.

|  |
| --- |
| **Highlights**   * Organized screening will ensure that appropriate populations are screened at the recommended interval, as well as receive appropriate and timely diagnostic workup for abnormal findings. * The implementation of nodule management frameworks will limit unnecessary invasive and non-invasive procedures. * It will also enable quality monitoring, management and evaluations of screening program outcomes. |

# Summary of Economic Evidence on LDCT Screening

A standard approach of assessing value for money of any medical intervention, and weighing benefits versus harms, is cost-effectiveness analysis. Cost-effectiveness analyses often employ the metric of incremental cost per quality adjusted life-year (QALY) gained. The QALY is a universal measure of health and health gain, and incorporates both length and quality of life. The use of cost-effectiveness thresholds to support adoption and funding decisions on healthcare technologies is widespread. Though there is no single threshold recommended for Canada, a threshold of $50,000 per QALY (i.e. the value of one year in good health) gained has been the most commonly used threshold for health economics18,19 with a range of $20,000 to $100,000.20 Interventions in oncology seem to be adopted at higher thresholds of acceptability.19

Our literature search identified two systematic reviews on economic evaluations for LDCT screening for lung cancer, and four Canadian and one UK cost-effectiveness study that were published after the systematic reviews. Studies are summarized in [Appendix 5](#_Appendix_7._Summary).

Results from a systematic review that included 13 economic studies on LDCT screening vs. no screening found wide variation in reported incremental cost-effectiveness ratios. Cost per QALY gained varied from $28,000 - $243,000 for annual screening and from $1,500 – $151,000 for one-time screening.84 A study that tested population-based screening in Ontario identified an optimal scenario of screening 55-75 year old individuals with smoking history of >40 pack-years, with an incremental cost of $41,136 per each additional QALY gained.25 Only two studies factored in the cost of incidental findings in the economic evaluation.80,85 Across all studies, the major determinants of cost-effectiveness were i) appropriate selection of high-risk population, ii) costs and frequency of the LDCT screening, iii) integration of smoking cessation therapies, and iv) sensitivity and specificity of LDCT.

In conclusion, the cost-effectiveness of a lung cancer screening program will depend on how the program is implemented. The following factors need to be considered when defining optimal screening strategies:

* Appropriate selection of high-risk individuals
  + Selection criteria using risk prediction tools such as the PLCOm2012 are more sensitive and cost-effective than age and pack-years criteria.5,86,87
* Appropriate screening frequency is defined
  + The UK study showed 3 consecutive annual screens always resulted in a better cost-effectiveness ratio compared to annual, biennial, or one-time scans.88 The Italian MILD study and NELSON trial did not find more interval cancers or deleterious stage shift with biennial screening. The ILST study shows lower-risk individuals (about 80% of the participants) can be screened biennially instead of annually. The MILD study also showed it took 10 annual or 5 biennial screenings to see a significant reduction of lung cancer mortality in their small study.
* Protocols for nodule management and incidental findings are in place
  + Current nodule management protocols define screening frequency based on screening results.66,67
* Integration of a cessation program alongside LDCT screening program
  + The integration of smoking cessation therapies alongside LDCT screening significantly improves the cost-effectiveness of the program.36,37
  + A study assessed the impact of integrating smoking cessation alongside LDCT screening in Canada and estimated that integrating smoking cessation would offer further clinical impact. Assuming a conservative quit rate of 2.5% per attempt, smoking cessation in the context of LDCT screening would prevent 12 more lung cancer and save 200 more life-years per 1000 smokers screened, and would be cost-effective, when compared to screening alone.89

|  |
| --- |
| **Highlights**   * Whether a population-based screening program will be cost-effective depends on how the program is implemented * The major determinants of cost-effectiveness are  1. Appropriate selection of high-risk population, 2. Costs and frequency of the LDCT screening, 3. Protocols in place for nodule management and incidental findings, and 4. Integration of smoking cessation therapies for current smokers |

# Ethical, Social and Equity Considerations Related to LDCT Screening

As with any screening program, LDCT screening may raise concerns about equity. Smoking is strongly associated with socioeconomic status (SES), with higher smoking rates seen amongst individuals with lower SES, with smoking onset at younger ages. The Canadian Community Health Survey (2017) reported that 22% of surveyed individuals in households in the lowest income quintile were smokers compared with 12% of individuals in households in the highest income quintile.90 This means that socio-economically disadvantaged individuals are more likely to be affected by lung cancer and would benefit significantly from lung cancer screening.

People experiencing low SES may have significant barriers to access preventive health services, such as transportation issues, cost of parking, or difficulties obtaining time off work. The cost of smoking cessation interventions and inequities in access may place these individuals at increased disadvantage. Therefore, it is of utmost importance that any organized lung screening program is set up to be inclusive of all high-risk individuals and does not perpetuate or increase health inequalities across socioeconomic groups or jurisdictions.

LDCT screening may have a potential to reduce health inequities if the implementation of the program is accessible to these individuals at higher risk of lung cancer. The Manchester Lung Health Check pilot, through implementation of mobile CT scanners and increasing service accessibility, showed that participation in screening services was high in individuals with low SES. The majority of recruited individuals were in the most deprived decile.50

Additional equity concerns may arise from eligibility criteria for the screening program. Unlike risk prediction tools that take SES and ethnicity into account, NLST-like eligibility criteria determine eligibility using only age and smoking history. NLST-like criteria may create equity concerns by denying preventive health services for individuals who do not meet the age and smoking history criteria, but who may have a similar or higher risk of lung cancer. Risk-based enrollment can take other factors such as ethnicity and SES into account and avoid exacerbating disparities. The ongoing Canadian studies are now employing risk-based enrollment, which should be recommended in light of these equity considerations.

In many regions, Indigenous peoples have higher rates of smoking, lung cancer incidence and lung cancer mortality compared to non-Indigenous individuals.91,92 Lung cancer screening approaches should be accessible, culturally safe and involve engagement with Indigenous communities in cases where lung cancer screening programs have been identified as a health priority by First Nations, Inuit and Métis people.

#### Public involvement

Focus group discussion with patient groups in the UK revealed that overall people at high risk of lung cancer were supportive of the lung cancer screening program. Patients acknowledged that receiving a diagnosis of lung cancer would affect their quality of life in the short-term, but they felt empowered to have more time for planning and making the best use of the remaining time. They considered the level of radiation risk and false positive results associated with the screening acceptable given the survival benefits.88

# Program Implementation

# Recommended Approach

Across Canada, population-based screening programs exist for detecting breast cancer (implemented across 12 jurisdictions; not implemented in NU), cervical cancer (implemented in 8 jurisdictions; not implemented in QC, PE, YT, NT and NU) and colorectal cancer (implemented in 10 jurisdictions; not implemented in QC, NT and NU). Each jurisdiction has designated institutions/agencies that plan, deliver, and oversee the implementation of organized screening programs. In addition, Pan-Canadian Cancer Screening Networks hosted by the Partnership leverage the expertise and best practices across the country to support policy decisions and guide implementation of new programs in Canadian jurisdictions.

Hence, an opportunity exists to build on these assets and expertise and effectively implement organized LDCT screening for high-risk populations in Canadian provinces and territories. To maximize the benefits of lung cancer screening, it must be implemented as an organized, population-based approach, following the models used for other screening programs in the country and internationally. Additionally, equity considerations that are implemented for lung cancer screening can be leveraged to benefit underserved individuals in the other population-based screening programs. This is a unique opportunity to increase equity in screening across all organized programs.

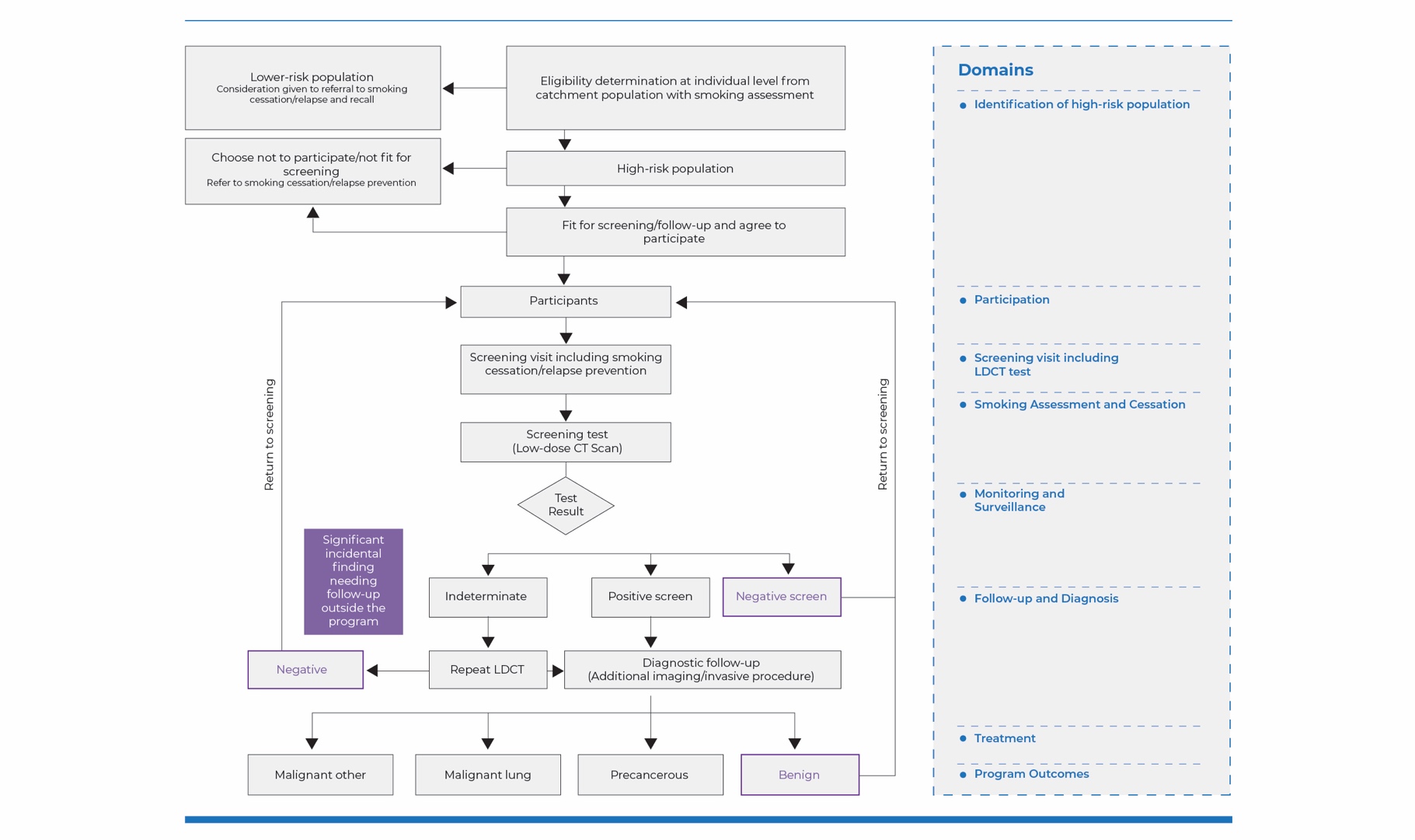
## Program description

The proposed screening program would provide [three annual] LDCT screening to individuals aged [55-74] years who had at least [2% estimated 6-year risk] of developing lung cancer [alternative: with at least a 30 pack-year smoking history, who currently smoke or quit less than 15 years ago]. Individuals would be managed according to LUNG-RADS [PanCan lung] nodule management protocols.

|  |  |
| --- | --- |
| Component | Description  [not all the components may be applicable to a specific jurisdiction] |
| Risk assessment /recruitment | Recruitment will be broad – participants will be able to enter the program through self-referral, referral from [primary care provider/healthcare provider], referral from smoking cessation program.  Individuals aged [55-74] will receive risk-assessment questionnaires; those identified as high-risk would receive invitation to screening. [Individuals aged 55-74 will be encouraged to use online tool to evaluate their eligibility for the screening program].  A [nurse navigator/physician] will perform eligibility evaluation.  Eligible high-risk patients will [not] require physician referral to proceed with the screening.  All current smokers [will be referred to/will receive] evidence-based smoking cessation program [using an opt-out approach]. |
| LDCT screening | Eligible patients will be screened at [specify centre, ex., medical imaging units] according to low dose protocols.  Qualified radiologist with expertise in early diagnosis will interpret the LDCT images.  [Vendor software will be used to calculate the malignancy risk for identified lung nodules.]  Recommendation for diagnostic workup investigation or next screening will be based on nodule management protocols. |
| Diagnosis | Nurse navigators [physicians] will communicate [both negative and] positive results, schedule specialist physician consultation and further diagnostic workup.  [Negative results will be communicated by mail].  If biopsy is performed, the results will be captured [by synoptic reporting] and forwarded to designated agency. |
| Re-screening | Designated agency will send reminders to already screened individuals. |
| Program evaluation & monitoring | The program [designated body] will collect record-level data, including demographics, risk factors, screening test date & results, diagnostic test dates & results, surgical procedure date & results, [smoking cessation uptake and outcome]. The data will be shared for analysis at the pan-Canadian level.  Local cancer agencies/programs will conduct program evaluation using quality indicators and data from [indicate data source]. |

The lung cancer screening pathway is displayed in Figure 6.

**Figure 6.** Lung cancer screening pathway



## Estimated program volume and impact on system capacity

Opportunistic (ad hoc) screening is already occurring in [Province/Territory A]. Numerous smokers and ex-smokers receive requisitions for chest x-ray, CT, or LDCT examinations from their primary care providers. However, the amount of opportunistic screening remains unknown. Therefore, to estimate the net impact of a screening program on system capacity, a “no screening” strategy was selected as a comparator. This comparator will also provide the most conservative estimate for the budget impact and mitigate any concerns for under-planning. [(*For provinces and territories where the amount of opportunistic screening is known)* In [Province/Territory A], about [30%] of screenings do not meet criteria and are occurring opportunistically. Therefore, we estimated the impact of screening choosing the opportunistic screening as a comparator in additional scenario analyses.]

We used the Partnership’s OncoSim37,93,94 microsimulation model[[10]](#footnote-11) to compare health benefits, healthcare services volume, costs and cost-effectiveness in the presence and absence of organized lung cancer screening. The net impact was then calculated by comparing the outcomes of “no screening” [or ad-hoc screening] to “organized screening” over a ten-year time horizon.

The Lung Cancer Screening Business Case Working Group identified key scenarios that are the most realistic and feasible to implement [in Province/Territory A]. Scenarios were focused on differing eligibility criteria for the LDCT screening, as well as screening program frequency and duration. Jurisdiction specific scenarios, key assumptions and their corresponding outputs for each jurisdiction are summarized in an excel file.

Table 6 below summarizes the estimated volume for diagnostic and treatment services over the first 3-year program period for the base-case scenario, considering [40%/30%] program uptake and 10-year roll-out in period.

**Table 6.** Projected annual incremental volume of health services attributable to the screening program (average over 20 years), vs. [no screening/opportunistic screening]

|  |  |
| --- | --- |
| Volume | Per year |
| Eligible population |  |
| Total individuals screened |  |
| Total scans |  |
| Diagnostic procedures   * Invasive * Non-Invasive |  |
| Screen-detected lung cancer |  |
| False positives |  |

*Note:* Estimates for each jurisdiction will be circulated separately in an Excel file.

### LDCT services

Considering the population age structure in the [province/territory] and smoking prevalence, in total approximately [XXX] individuals may be eligible for screening and approximately [XXX] LDCT scans may be required during the first three years of the program.

The volume of opportunistic screening would decrease with the implementation of an organized program. The reduction in ad hoc scans would offset the increased volume in LDCT scans within the organized program and healthcare system resources would be targeted to those who can most benefit from the services. Therefore, comparing the organized program to “no screening” overestimates the volume of resources required, which will be offset by the reduction in opportunistic screening.

Currently there are [XXX] CT scanners across the [province/territory] that can perform the LDCT screening. The current CT units can [cannot] accommodate the screening volume. The existing code for CT of the chest could [not] be used for LDCT screening as well. LDCTs for lung screening do not require contrast. Therefore, LDCTs can be scheduled outside of core operating hours and do not require “real-time” radiologists reads.

*Future considerations:* Explore the impact on wait-times, alternative delivery models (utilizing existing capacity, purchasing additional CT scans, adding mobile units, etc.)

### Smoking cessation services

Approximately two thirds of screened individuals may be current smokers. All current smokers undergoing screening will be referred to a smoking cessation program, which may include counselling, NRT, or varenicline. A number of leading [tobacco cessation programs](https://www.partnershipagainstcancer.ca/topics/leading-practices-clinical-smoking-cessation/) are available across all the jurisdictions in Canada,95 which could be considered to be integrated within screening setting.

*Future consideration:* Explore the opportunity to add NRT and/or pharmacotherapy to counselling services, to provide on-site programs etc., if not currently funded.

### Diagnostic workup

The amount of diagnostic services (both invasive and non-invasive) is expected to increase initially, with a greater increase in non-invasive services such as chest CT and PET-CT. It must be noted that true positive individuals would utilize most of these services anyway, at later stages of their disease, hence the overall impact on the system should level off as the program stabilizes.

Approximately [XXX] samples may be sent for analysis. The current pathologist capacity is adequate and can process [XXX] additional specimen annually.

### Lung cancer management

On average, approximately [XXX] new cases of lung cancer may be screen-detected per year. The cancer detection rate is estimated to be [6-9] per 1,000 scans. As a comparison, the cancer detections rates are around 4 per 1,000 tests, for breast, cervical or colorectal cancer screening programs.96 Due to the small number of additional lung cancer detected per year, screening is expected to have minimal impact on demand for surgery and medical oncologist.

### Providers affected

An organized provincial or territorial screening program requires a multidisciplinary team. Increased volume of healthcare services associated with the screening, diagnostic and treatment pathways may affect waiting times for the following providers or require additional staff:

* Family physicians and other primary care providers play an important role in supporting cancer screening,97 and will likely be involved with lung cancer screening programs. However, the degree of impact will depend on the structure of the program, their role in recruiting, referring eligible patients to the screening program, as well as in communicating screening test results. Depending on the program structure, an organized screening program can potentially reduce the requirements on primary care providers by facilitating some navigation functions. As the screening program becomes established, primary care physicians will be seeing fewer patients with advanced lung cancer who need symptom management, emergency visits, hospitalization or palliative care.
* Qualified radiologists with expertise [(e.g. performed minimum # screening reads)] in early detection will be involved with interpretation of the screening results. In the [province/territory], approximately [XXX] radiologists are currently actively practicing at adequate [near] capacity. Lung cancer screening would [not] require additional radiologists to manage the predicted volume. The number of radiologists that would be required depends on the screening program uptake and eligibility criteria. Some of the workload will be offset by a reduction in imaging required for monitoring treatment outcomes every three to six months after initiation of chemotherapy, targeted therapy and or immunotherapy, and by re-aligning resources currently consumed by opportunistic screening. Furthermore, the number of radiologists participating in the program could be limited to those with specific expertise, or who meet specific criteria established by the program or other body.
* Respirologists will consult screen-positive patients and arrange/provide further diagnostic workup such as endoscopic ultrasound biopsies for diagnosis and staging. The impact on respirologists’ workload would depend on nodule management protocols and thresholds used for screens evaluation as suspicious, or indeterminate or negative.
* Pathologists will be involved to analyze lung biopsy specimens. The increased workload (average [XXX] samples annually) may [not] require additional pathologists to manage predicted volume. The volume of biopsies will be offset by existing biopsies for advanced cancers.
* Physicians will be involved with conducting invasive diagnostic interventions including endoscopies, biopsies as well as nodule resections. Currently physicians in the [province/territory] are working at their full [near] capacity. Increased volume of surgeries, biopsies would potentially require additional surgical staff.
* Smoking cessation counsellors (depending on design of the program).

## Budget impact analysis

Following the model above, the net budget impact for each year was calculated by subtracting incurred costs of “screening” strategy from the costs of “no screening” strategy, or in some cases, “opportunistic screening”.

The following key cost categories were identified: i) screening costs, ii) diagnostic costs, iii) lung cancer management/treatment costs, iv) program costs, v) capital costs, vi) smoking cessation costs, and vii) cost of incidental findings.

*Screening costs* included the costs of LDCT test and radiologist interpretation.

*Diagnostic costs* included costs for [respirologist/specialist physician] consultations and non-invasive and invasive procedures performed after positive screen.

*Cancer management costs* included treatment-related costs such as radiation therapy, chemo-immunotherapy, surgery and palliative care.

*Provincial/Territorial program costs* assumed compensation for the clinical leads, nurse navigators, non-clinical roles (program coordinators, screen registry staff, IT staff) and other non-staffing program costs (promotion, education, patient recruitment, result communication, etc.), which may vary across jurisdictions. Lung cancer screening program implementation presents an opportunity to create efficiencies by building on and leveraging what exists in other population-based screening programs.

*Capital costs* included one-time costs related to purchase of different software for structured reporting, malignancy risk calculators and other IT related projects. Capital costs were depreciated during 5-year period on a straight-line basis, assuming 5 years of useful life for the software.

*Smoking cessation costs* included the costs for counselling, NRT and pharmacotherapy.

*Incidental finding costs* were incurred due to further investigation of incidental findings

Table 7 below present the screening program net costs over the ten-year time horizon.

**Table 7.** Projected incremental budget impact attributable to the screening program (2019 dollars) vs. [no screening/opportunistic screening] (annual average over 20 years)

|  |  |
| --- | --- |
|  | Incremental cost per year |
| Screening costs |  |
| Provincial/Territorial program costs |  |
| Diagnostic workup costs |  |
| Smoking cessation program costs |  |
| Incidental finding costs |  |
| Cancer treatment costs |  |
| TOTAL COST |  |

The incremental budget required to run LDCT screening program for high risk patients was estimated at [$$$] per year for the first 20 years.

## Cost-effectiveness analysis

To estimate the cost-effectiveness of the proposed LDCT screening we compared costs and quality-adjusted life-years (QALYs) in the presence and absence of an organized screening program. Details on cost-effectiveness methodology are provided in [Appendix 6](#_Appendix_8._Methodology).

Results:The results for identified scenarios are provided in Table 8.

Compared to no screening [opportunistic screening]:

* Scenario 1 and Scenario 2 screening detects [XXX] and [XXX] cases of lung cancer, preventing [XXX] and [XXX] cancer deaths, translating to [XXX] and [XXX] additional QALYs, respectively.
* The resulting additional cost per additional QALY is [$$$] for up to 3 rounds of annual screening and [$$$] for up to 10 rounds of biennial screening (for those with very low malignancy risk after the baseline screen).

**Table 8**. Incremental lifetime outcomes of a cohort of individuals eligible for screening in the next 20 years (2020-2039), vs. [no screening/opportunistic screening]

|  |  |  |
| --- | --- | --- |
| Scenario | [name of scenario 1] | [name of scenario 2] |
| Lung cancer cases diagnosed at stage I & II |  |  |
| Lung cancer deaths avoided |  |  |
| Additional healthcare costs\* |  |  |
| Quality-adjusted life-years (QALYs) gained\* |  |  |
| Incremental cost per QALY gained |  |  |

\*Discounted at 1.5% per year

The main cost drivers were [cost of screening, followed by operational cost of the program, and cost of smoking cessation].

#### Conclusion:

When compared with no screening [opportunistic screening], scenario I costs [$$$] per QALY gained and scenario II costs [$$$] per QALY gained. Organized lung cancer screening is cost effective considering the [$100,000/$50,000] threshold.

# Implementation Plan

## Screening program operational models

Jurisdictions may consider various models to deliver the provincial or territorial program. Below is experience from BC with description of two operational designs, which might be potentially applicable to other jurisdictions.

1. Hub and Spoke model
2. Hub and Spoke model with mobile CT

Hub and Spoke model: The hub clinics provide full screening services from image acquisition to reporting. A “spoke” clinic performs CT scans only, whileimage interpretation and reading occurs at the hub clinic by a trained radiologist. The key advantage is that this model utilizes existing CT capacity and information systems and therefore requires minimal capital investment. However, for population in rural areas travel might be required, which would potentially limit program uptake. Assisted travel for these patients might increase the access to the program.

Hub and Spoke model with mobile CT: This model implies addition of a mobile CT unit to the alternative described above. The mobile CT unit for general use would improve health services delivery in remote communities for different conditions. This mobile unit could potentially be used for a lung cancer screening. Similar to a “spoke” clinic, the mobile unit performs CT scans only, whileimage interpretation and reading occurs at a hub clinic. This alternative would increase access to the program, particularly for population residing in rural areas. This model has been implemented in the UK, where LDCT scans offered in mobile vans to a high-risk population in Manchester resulted in a lung cancer screening stage shift in the screened population.98 LDCT scans can also be integrated with other health services. For example, mobile LDCT can be used to identify those at high risk of coronary heart disease, COPD, osteoporosis, and fatty liver. These comprehensive services are not readily accessible in underserved areas.

## Integration of smoking cessation interventions in lung cancer screening setting

Current guidelines strongly recommend integration of smoking cessation interventions within the context of lung cancer screening programs.99,100 Likewise, Canada’s Lung Cancer Screening Framework, developed by the Pan-Canadian Lung Cancer Screening Network, identifies tobacco cessation as a core component of any Canadian lung cancer screening program.101 Lung cancer screening programs should provide culturally relevant smoking cessation supports to lung cancer screening participants. Studies have shown that smoking cessation integrated into lung cancer screening programs would further prevent lung cancer and all-cause deaths; it is cost-effective and significantly improves the cost-effectiveness of lung cancer screening.36,37,89

Emerging experience from Canadian pilots/studies have shown that an adjunct smoking cessation program can be successfully implemented in the LDCT screening setting and might have the potential to increase the effectiveness of smoking cessation. Early data from Ontario’s Lung Cancer Screening Pilot for People at High Risk demonstrated high uptake of smoking cessation programs. Around 85% of eligible current smokers attended hospital-based smoking cessation services during their baseline LDCT screening. The effectiveness of the program will be evaluated in fiscal year 2020/21.102

The Alberta Lung Cancer Screening Study evaluated the effectiveness of smoking cessation interventions offered within the context of a LDCT screening program. The overall quit rate was 13%, which was more than double the background cessation rate of 5% in the Canadian general population.

A number of leading [tobacco cessation programs](https://www.partnershipagainstcancer.ca/topics/leading-practices-clinical-smoking-cessation/) are available across all the jurisdictions in Canada.95 NRT is available without prescription in most jurisdictions. However, pharmacotherapy requires a prescription that may not be publicly funded.95 Improving access and funding of NRT and pharmacotherapy may increase the smoking cessation rate and should be considered in future programs. In fact, Canada’s Lung Cancer Screening Framework calls for tobacco cessation services to be advanced prior to, or in conjunction with, the development of lung cancer screening programs.101

[Appendix 7](#_Appendix_7._Summary_1) provides the summary on two recent systematic reviews103,104 on the effectiveness of smoking cessation programs alongside LDCT screening.

|  |
| --- |
| **Highlights**   * Integrating smoking cessation into LDCT screening would further prevent lung cancer and all-cause deaths, and is cost-effective, when compared to screening alone. * Given the availability of smoking cessation programs in Canada and feasibility of their integration, jurisdictions are encouraged to implement of smoking cessation strategies in a LDCT screening setting. * A combination of smoking cessation interventions including counselling, NRT and pharmacotherapy should be integrated into lung cancer screening programs. |

## Critical dependencies

Below, we list potential critical dependencies that might [not] be applicable to jurisdictions.

* Accessing web-based risk assessment tool to assess patient eligibility
* Development and implementation of radiology quality standards
  + Training of qualified radiologists
  + Quality assurance of CT facilities and included equipment
* Implementation of structured reporting for LDCT screening at reading sites
* Implementation of synoptic reporting at pathology labs
* Development and maintenance of screening registry
* Procurement of additional CT scans, mobile units if applicable
* [NRT and/or Pharmacotherapy provision and access to evidence-based counselling support]

## Implementation risks and mitigation strategies

Below we identify potential implementation risks and proposed mitigation strategies.

|  |  |
| --- | --- |
| Description of risk | Risk-mitigation strategy |
| Unable to recruit high-risk population | Leverage experience from other screening programs currently ongoing in the jurisdiction.  Involve family physicians to support recruitment.  Raise public awareness of high-risk lung cancer screening through multiple communication channels.  Adopt best practices from other jurisdictions.  Engage members of underserved communities and Indigenous communities to inform development and implementation of accessible, culturally safe screening. |
| Unable to accommodate required screening volume | Develop phased roll out plan.  Reconsider eligibility criteria and prioritize screening of population with greater risk who would benefit the most.  Expand existing CT operations (hours and days of operations).  Schedule CT exams during off-hours.  Consider adding CT units, mobile units etc. |
| [Unable to provide access/equity;  Unable to increase human resources;  Unable to implement program due to loss of resource commitments;  Unable to provide funded smoking cessation programs;  Unable to provide travel support] |  |

## Program effectiveness measures

Below we list national lung cancer screening quality indicators to measure success of the screening program at its earlier stages of implementation.83

* Early reassessment rate
* Invasive procedure rate
* Positive predictive value
* Cancer detection rate out of those screened
* Cancer detection rate out of those biopsied
* Proportion of lung cancers detected at early stage
* Non-malignant nodule biopsy/resection rate
* Resection rate
* 30-day mortality following an invasive diagnostic procedure
* 30-day mortality following surgical procedure

Some other potential success measures that could be considered are:

* Program uptake rate
* Abnormal LDCT rate
* Wait time from abnormal LDCT to definitive diagnosis
* Wait time from diagnosis to treatment
* Smoking quit rate in the screened participants

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# Appendices

## Appendix 1. List of working group members

|  |  |  |  |
| --- | --- | --- | --- |
| Name | Title | Organization | Province/  Territory |
| Huiming Yang | Medical Director, Screening Programs | Alberta Health Services | AB |
| Lisa Kan | Senior Director, Screening Program | British Columbia Cancer Agency | BC |
| Kelly Bunzeluk | Director of Screening Programs | Cancer Care Manitoba | MB |
| Grlica Bolesnikov | Acting Director of Operations | New Brunswick Cancer Network | NB |
| Eshwar Kumar | Co-Chief Executive Officer, New Brunswick Department of Health | New Brunswick Cancer Network | NB |
| Janet Templeton | Director, Provincial Cancer Program | Eastern Health | NL |
| Krista Rigby | Director, Community & Population Oncology | Nova Scotia Health Authority Cancer Care Program | NS |
| Eileen Kilfoil | Operations Manager, Cancer Screening Programs | Nova Scotia Health Authority Cancer Care Program | NS |
| Melissa Coulson | Director, Implementation, Cancer Screening | Cancer Care Ontario | ON |
| Gillian Bromfield\* | Director, Program Design, Cancer Screening | Cancer Care Ontario | ON |
| Jessica Moffatt | Group Manager, Evidence Integration & Primary Care, Program Design, Cancer Screening, Prevention & Cancer Control | Cancer Care Ontario | ON |
| Jennifer Jelley | Provincial Lung Cancer Prevention and Screening Coordinator | Health PEI | PE |
| Marla Delaney | Provincial Cancer Coordinator | Health PEI | PE |
| Gailyne MacPherson | Director, Diagnostic Imaging | Health PEI | PE |
| Marie-Noëlle Vallée | Director of Screening Services and Clinical Support | Health and Social Services | QC |
| Laurence Eloy | Cancer Screening Medical Coordinator | Health and Social Services | QC |
| Mireille Chinas Ugalde | Conseillère aux services de dépistage et soutien clinique | Health and Social Services | QC |
| Kevin Wilson | VP Population Health, Quality & Research | Saskatchewan Cancer Agency | SK |
| Karen Efthimiou | Director, Early Detection | Saskatchewan Cancer Agency | SK |
| Diane Lamothe | Implementation Manager, Colorectal Screening program | Health and Social Services | YT |

\*Participated March-June 2019

## Appendix 2. Mortality related outcomes: summary of randomized controlled trials

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study, country,  sample size | Eligibility | Intervention | Screening  frequency | Duration of follow-up | Mortality |
| NLST4,  USA,  n=53,452  NLST60 ,  USA,  n=53,452 | 55-74 years &  ≥30 pack-year smoking | LDCT vs CXR | 3 annual scans | > 6.5 years  median 12.3 years | LC related mortality  RR = 0.84 (0.75 to 0.95)  All-cause mortality  RR = 0.93 (0.88 to 1.00)  LC related mortality  RR = 0.89 (0.80 to 0.99)  All-cause mortality  RR = 0.97 (0.94 to 1.01) |
| NELSON2, Netherlands/Belgium,  n=13,195 (men), 2,594 (women) | 55-75 years &  ≥15 pack-years  smoking | LDCT vs  no screening | 4 scans  (years 0, 1, 3, 5.5) | > 10 years | LC related mortality  RR (men) = 0.76 (0.61 to 0.94)  RR (women) = 0.67 (0.38 to  1.14)  All-cause mortality  RR=1.01 (0.92 to 1.11) |
| DLCST64,71,  Denmark,  N=4,104 | 50-70 years &  ≥20 pack-years smoking | LDCT vs  no screening | 5 annual scans | median 9.8 years | LC related mortality  HR = 1.03 (0.66 to 1.60)  All-cause mortality  HR = 1.02 (0.82 to 1.27) |
| MILD12,  Italy,  n=4,099 | >49 years &  ≥20 pack-years smoking | LDCT vs  no screening | 10 annual scans or  5 biennial scans | > 10 years | LC related mortality  HR = 0.61 (0.39 to 0.95)  All-cause mortality  HR = 0.80 (0.62 to 1.03) |
| DANTE63,  Italy,  N=2,450 | 60 -74 years &  ≥20 pack-years smoking | LDCT vs  no screening | 4 annual scans | median 8.4 years | LC related mortality  HR = 0.99 (0.69 to 1.43)  All-cause mortality  HR = 0.95 (0.77 to 1.17) |
| ITALUNG61,  Italy,  N=3,206 | 55 -69 years &  ≥20 pack-years smoking | LDCT vs  no screening | 4 annual scans | median 9.3 years | LC related mortality  RR = 0.70 (0.47 to 1.03)  All-cause mortality  RR = 0.83 (0.67 to 1.03) |
| LUSI62,  Germany,  N=4,052 | 50 - 69 years &  ≥15 cigarettes/day for ≥25 years or ≥10 cigarettes/day for ≥30 years | LDCT vs  no screening | 5 annual scans | median 8.8 years | LC related mortality  HR = 0.74 (0.46 to 1.19)  Men:  HR = 0.94 (0.54–1.61),  Women:  HR = 0.31 (0.10–0.96)  All-cause mortality  HR = 0.99 (0.79 to 1.25) |

HR: hazard ratio; LC: lung cancer, LDCT: low-dose computed tomography; CXR: chest X-ray; RR: rate ratio;

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## Appendix 3. PanCan nodule management protocol

|  |  |  |
| --- | --- | --- |
| Category | LDCT finding | Action plan |
| 1 | Normal finding, benign calcification, perifissural nodule, hamartoma  Nodule risk index <1.5% | Consider biennial screening |
| 2 | Low risk of malignancy  Nodule risk index <1.5% to <6% | Schedule annual repeat screening |
| 3 | Moderate risk of malignancy  Nodule risk index <6% to <30% | Rescreen in 3 months:   * If no growth, annual screening * If interval growth, refer for definitive diagnosis * May consider definitive diagnosis for nodule risk index between 10% to <30% after discussion between the clinician and patients |
| 4 | High risk of malignancy  Nodule risk index ≥30% | Refer for definitive diagnosis |
| 5 | Suspicious for lung cancer: Mass lesion with a non-infectious cause; mediastinal or hilar lymphadenopathy irrespective of nodule size | Refer for definitive diagnosis |

Source: Martin C Tammemagi and Stephen Lam BMJ 201466

## Lung-RADS nodule management protocol – Version 1.1 (Assessment Category Release Date: 2019)Appendix 4. Lung-RADS nodule management protocol – Version 1.1 (Assessment Category Release Date: 2019)

**Source:** American College of Radiology: <https://amgrad.org/RADS/lungrads.pl>

## Appendix 5. Summary of economic evidence on LDCT screening

|  |  |  |  |
| --- | --- | --- | --- |
| Author, year | Population | Intervention | Key findings |
| Systematic reviews of cost-effectiveness studies | | | |
| Puggina et al, 2016105  Search period:  To March 2015 | High risk population | LDCT vs  no screening  2 studies compared one time screening, and 7 studies - annual screening | * 9 studies were included * Five studies reported that LDCT is cost-effective at threshold of US$50,000 per QALY gained and seven studies were cost-effective at threshold of US$100,000 per QALY gained. * Two studies reported that integration of smoking cessation may significantly reduce the ICER |
| Raymakers et al, 201684  Search period:  Jan 2000 to  Dec 2014 | High-risk population | LDCT vs  no screening  4 studies compared one time screening, and 7 studies – annual screening | * 13 studies we included * Cost per QALY gained varied from $28,000 - $243,000 for annual screening and from $1,500 – $151,000 for one-time screening * Integration of smoking cessation interventions may significantly reduce the ICER * The results were sensitive to the cost of LDCT, appropriate identification of high-risk population, lead time bias and smoking cessation |
| Recent cost-effectiveness evaluations not included in the above listed systematic reviews | | | |
| Goffin et al, 2015\*, Canada93 | High risk population | LDCT vs  no screening  3 annual screenings | * Cost per QALY gained was C$52,000 * Integration of smoking cessation reduce the ICER to C$24,000/QALY * The results were sensitive to appropriate identification of high-risk population and adherence rates |
| Goffin et al, 2016\*, Canada37 | High risk population | Annual LDCT vs  biennial LDCT | * Cost per QALY gained varied from C$54,000–$4.8 million * Integration of smoking cessation interventions may significantly reduce the ICER * Results were sensitive to sensitivity and specificity of LDCT and stage shift |
| Haaf et al, 2017,  Canada25 | High risk population | Annual vs biennial vs no screening | * Annual screening was more cost-effective than biennial screening * The optimal scenario was the annual screening of current and former (≤10 years since quitting) smokers (≥40 pack-years) between ages 55-75 resulting in an ICER of $41,136/QALY * Scenarios with higher exposure to smoking history were more cost-effective |
| Cressman et al,  Canada85 | High risk population | LDCT vs. CXR | * Cost per QALY gained was C$20,724 * Cost effectiveness was driven primarily by non-lung cancer outcomes |
| Snowsill et al, 2018, UK88 | High risk population | Single vs triple vs annual vs biennial vs no screening | * In all scenarios triple screen was more effective and less costly than annual or biennial screens * In all scenarios triple screen resulted in the most QALYs * The ICERs of triple screening were varied between £36,181 to £42,254 per QALY * Results were sensitive to the natural history of lung cancer, the cost of LDCT screening |

\*These studies used the OncoSim tool for the modeling.

ICER: incremental cost-effectiveness ratio; LDCT: low-dose computed tomography; QALY: quality adjusted life years

## Appendix 6. Methodology on economic evaluation of LDCT screening in Canada

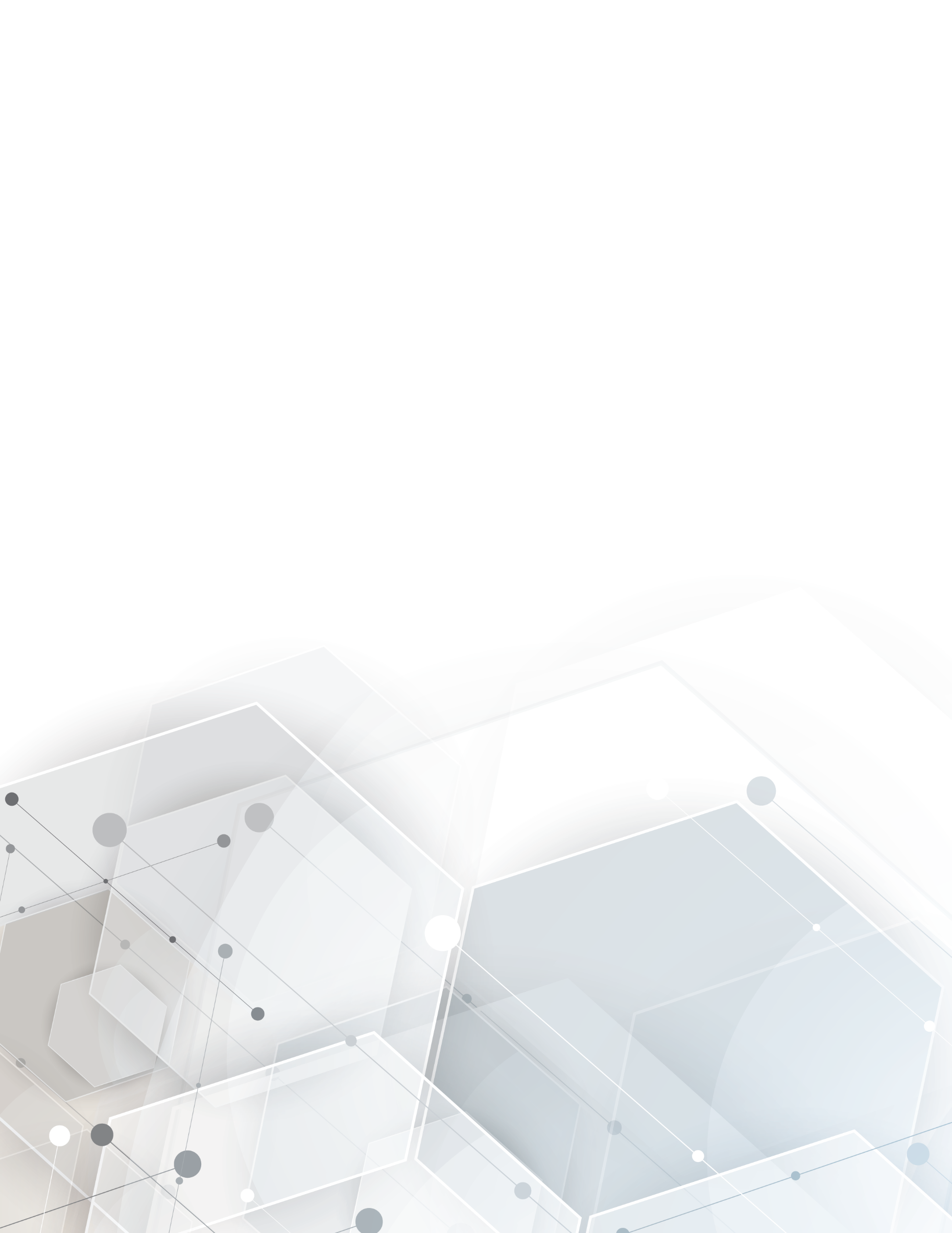
|  |  |
| --- | --- |
| Design | * A cost utility analysis using the OncoSim microsimulation model |
| Target population | * Base-case scenario: the model screened [current and former (≤15 years since quitting) smokers (≥35 pack-years) between ages 55-74]. * [Alternative eligibility criteria were tested in scenario analyses] |
| Intervention | * Base-case scenario: [three annual screens] were compared to current practices (no organized screening). * [Alternative frequency and duration were tested in scenario analyses] |
| Perspective | * Healthcare payer perspective |
| Time horizon | * Lifetime |
| Data source | * In the OncoSim model, data was derived from Statistics Canada, health surveys, Canadian cancer registry data, published literature and expert opinion when necessary * LDCT screening implied Lung-RADS protocol. * Screening program operational costs were obtained from each jurisdiction |
| Outcomes | * Life years, quality adjusted life years, direct healthcare costs |
| Discount | * 1.5% per CADTH guideline recommendations |
| Costing Year | * 2019 CAD |
| Assumptions | * Model assumptions are summarized in Technical Appendix |
| Validation | * Cancer incidence and mortality data have aligned well with cancer registry data, have been internally validated and compared with other models with good face validity106 |

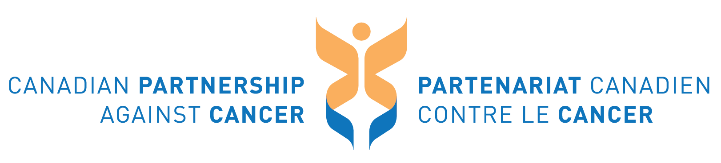
More details on model assumptions, data sources and input parameters are provided in the Technical Appendix.

## Appendix 7. Summary of RCTs and observational studies on implementation of smoking cessation strategies along LDCT screening

|  |  |  |  |
| --- | --- | --- | --- |
| Author | Population | Intervention | Outcome |
| Randomized controlled trials | | | |
| Clark et al. 2004, US107 | ≥50 years smokers with ≥20 pack-year history of smoking | Written self-help manuals (n = 86) *vs.* a list of internet sites (n=85)  Both sources provided smoking cessation information including information on related medications | 1-year of follow-up: There were no statistically significant differences in 7-day point prevalence quit rates (10% standard vs. 5% internet), respectively (p = 0.166). The quit rates were comparable to that of the general population. |
| van der Aalst et al 2012, Netherlands108 | ≥50 years smokers (male only) who smoked > 15 cigarettes a day for >25 years or > 10 cigarettes a day for 30 years | Self-help brochure (SHB) (n = 642) vs*.* computer tailored intervention (CTI) (n = 642). During CTI participants completed an individual questionnaire and received tailored advice | 2 years of follow-up: There were no statistically significant differences at 7-day point prevalence abstinence (13.2% CTI vs.15.9% SHB); prolonged smoking abstinence (12.5% CTI vs. 15.6% SHB), and continued smoking abstinence (12.1%T vs. 15.1% S). Only 23% in CTI group completed the questionnaire and hence received the tailored advice |
| Ferketich et al. 2012, US109 | ≥50 years smokers with ≥20 pack-year history of smoking | Cessation program offered *after* LDCT (n=9) *vs. before* LDCT (n=9). The program included oncologist advice to quit smoking, pharmacotherapy, and a referral to a 12-week telephone counseling by a nurse | Results suggested that receiving the intervention *before* compared to *after* LDCT could result in a higher abstinence rates at 4 months post-treatment (33.3% vs. 22.2%), and at 6 months post-treatment (22.2% vs. 11.1%).  No statistical tests were performed |
| Marshal et al. 2016, Australia110 | Individuals who smoke median 25 cigarettes a day | Face to face counselling session with take home audio materials, printed materials and phone helpline referral vs. printed materials and phone helpline referral | No significant differences in quit rates at 12 months between intervention (14.3%) and control (18.5%) group (p=0.74) |
| Taylor et al 2017, US111 | ≥20 pack-years smokers | Six weekly counselling calls and resource list (booklet, website, contact information for helpline) vs resource list only | Higher abstinence at 3 months in intervention group (17.4% vs 4.3 % p = 0.04) |
| Observational studies | | | |
| Filippo et al. 2015, Italy112 | ≥55 years current or former (≤15 years) smokers with ≥30 pack-year history of smoking | Pharmacotherapy + counseling (n=71).  No comparison group | 57.1% patients quit smoking after the treatment and were abstinent at 6 months follow-up; |
| Pozzi et al. 2015, Italy113 | 49–75 years with ≥20 pack-year history of smoking | Pharmacotherapy + counseling (n=187). | 1-year follow-up: Overall rate of continuous abstinence of 19.8%. |
| Park et al. 2015, US114 | 55–74 year with ≥30 pack-year history of smoking | 5A’s intervention: Ask, Advise, Assess, Assist, and Arrange, offered *after* the screening. No comparison group. | 1 year after the screening: Delivering the first three steps (Ask, Advise, and Assess) was not significantly associated with quitting. However, Assist was associated with a 40% increase in the odds of quitting (adjusted OR, 1.40; 95% CI, 1.21–1.63), and Arrange with a 46% increase in the odds of quitting (adjusted OR, 1.46; 95% CI, 1.19–1.79) |
| Bade et al. 2016, Germany115 | ≤20 cigarettes a day (55%)  >20 cigarettes a day (45%)  ≤35 years (40%)  >35 years (60%) | Attendance to smoking cessation therapy offered within LDCT screening context vs non-attendance | Higher smoking cessation rates who attended vs not-attended counselling at 1 year (14.6% vs 6.7%, p<0.001) and 2 years (12.9% vs 7.6%, p<0.002) |
| Luh et al. 2016,  Taiwan116 | Age started smoking ≤20 (57%) and >20 years (43%) | Clinician provided counselling vs leaflet | Patients who received counselling had greater odds in readiness to quit ( OR = 2.27, 95% CI:1.07-4.84) |
| Zeliadt et al. 2017, US117 | ≥30 pack-years smokers | Telephone counselling vs Information on helpline and tobacco treatment services | No significant differences in 7day abstinence at 4weeks between intervention (19%) and control (4%) group (p=0.1) |

Note: Studies listed in Appendix 2 were included in two recent systematic reviews. Both reviews concluded that the optimal strategy of smoking cessation within a lung cancer screening program remains uncertain.103,104





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1. OncoSim is led and supported by the Canadian Partnership Against Cancer, with model development by Statistics Canada, and is made possible through funding by Health Canada. [↑](#footnote-ref-2)
2. The estimate of <$20,000 per QALY gained does not include screening program cost. The cost includes costs for LDCT and reading, follow-up diagnostics, incidental findings, smoking cessation, and accounts for cost-savings from averting advanced stage treatments, such as immunotherapy. [↑](#footnote-ref-3)
3. The Partnership is facilitating the development of a lung nodule management framework aimed at advancing standardized practices in lung cancer screening to ensure patient safety and effective, high-quality screening. The framework will provide evidence-based best practice guidance for specialists to manage screen-detected lung nodules and include a sample of a patient-friendly screening radiology report. [↑](#footnote-ref-4)
4. In 2017, the Pan-Canadian Lung Cancer Screening Network (2017) developed quality indicators to monitor the outcomes of the screening program. [↑](#footnote-ref-5)
5. Risk is computed using PLCOm2012 risk prediction model (Tammemägi et al, 2013) [↑](#footnote-ref-6)
6. The lung cancer stage is classified according to international TNM staging system, where T represents the size of the tumor, N represents the involvement of lymphatic nodes and M represents the presence of distant metastasis. [↑](#footnote-ref-7)
7. The estimate of <$20,000 per QALY gained does not include screening program cost. The cost includes costs for LDCT and reading, follow-up diagnostics, incidental findings, smoking cessation, and accounts for cost-savings from averting advanced stage treatments, such as immunotherapy. [↑](#footnote-ref-8)
8. NELSON trial results are not included in this meta-analysis. The meta-analysis was completed in 2019, prior to the publication of the NELSON trial mortality results. [↑](#footnote-ref-9)
9. NELSON trial results are not included in this meta-analysis. The meta-analysis was completed in 2019, prior to the publication of the NELSON trial mortality results. [↑](#footnote-ref-10)
10. OncoSim is led and supported by the Canadian Partnership Against Cancer, with model development by Statistics Canada, and is made possible through funding by Health Canada. [↑](#footnote-ref-11)