International Lung Cancer Screening Trial Protocol

PROJECT TITLE: Prospective Evaluation of Selection Criteria for Lung Cancer Screening with Low-dose Thoracic Computed Tomography and Standardized System for Nodule Management – An International Study

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AREA OF FOCUS: Lung Cancer, Early Detection

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Project Summary

Background. The cost-effectiveness of a population-based lung cancer screening program with low-dose computed tomography (LDCT) to reduce lung cancer mortality is strongly influenced by the sensitivity and specificity of the selection criteria for screening. Retrospective analysis by Tammemagi and co-workers showed that the PLCOm2012 lung cancer risk prediction model using 7 non-smoking and 4 smoking variables detects 7.6% more lung cancer and samples 8.7% fewer people compared to the US Preventive Services Task Force (USPSTF) screening inclusion criteria based on age and smoking history alone. The sensitivity and specificity of PLCOm2012 versus USPSTF screening criteria to select smokers for lung cancer screening has not been prospectively evaluated in the general population.

1.0 Primary Objectives:

(1.1) Define the optimal selection criteria for LDCT screening.

(1.2) Evaluate a standardized system for lung nodule identification, classification, and management.

2.0 Secondary Objectives (optional sub-studies):

(2.1) Evaluate outdoor and household air pollution as a lung cancer risk factor.

(2.2) Evaluate the role of blood biomarkers for assessment of lung cancer risk and malignancy potential of lung nodules

(2.3) Evaluation of quality of life

3.0 Study Plan:

(3.1) Compare the relative sensitivity of the PLCO m2012 ≥1.51% over 6 years lung cancer risk screening threshold versus the USPSTF screening criteria (55-80 years of age who had smoked at least 30 pack-years and former smokers who had stopped smoking for less than 15 years) in newly diagnosed lung cancer patients.

(3.2) Recruit 8,000 ever smokers between the age of 55 to 80 years from Canada, Australia, Denmark and Italy and prospectively evaluate the sensitivity, specificity and positive predictive value of the PLCOm2012 and USPSTF selection criteria, in two phases:

Phase I – Canada and Australia (4000 participants)

Phase II - Italy and Denmark (4000 participants)

(3.3) Prospectively evaluate the PanCan lung nodule malignancy risk prediction tool and Lung-RADS for management of lung nodules detected by screening LDCT.

Significance: This project addresses the important issues of identifying optimal risk selection criteria for LDCT lung cancer screening in the general population as well as the accuracy of the PanCan Lung Nodule Malignancy Risk prediction tool for management of LDCT detected lung nodules.

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Study Protocol

A. Background

The well powered, randomized National Lung Screening Trial (NLST) showed that screening of high-risk smokers with low dose computed tomography can reduce death from lung cancer by about 20% compared to screening with chest radiography.[1,2] Recently the United States Preventive Services Task Force (USPSTF) published recommendations on low dose computed tomography (LDCT) screening for lung cancer.[3-5]

It recommended annual CT screening of people aged 55-80 years who had smoked at least 30 pack-years (e.g., one pack of cigarettes per day for 30 years) and discontinuing (or not starting) screening after 15 years of smoking abstinence. Following the final decision on February 5, 2015, by the Centers of Medicare and Medicaid Services to cover lung CT screening of Americans aged 55-77 years who had smoked at least 30 pack-years,[6] lung cancer screening is being implemented in the U.S. health care system and many other jurisdictions, including several provinces in Canada and Australia, are considering similar paths.

Very recently, the Canadian Task Force for Preventive Health Care recommended screening of high-risk smokers (55 to 74 years who had smoked at least 30 pack-years within the past 15 years annually for 3 consecutive years.[7]

Several research questions remain in translating CT screening from a clinical trial setting to the population level such as identifying the optimal method for selecting enrolees into screening programs and optimal protocol for management of lung nodules found at screening.

The Pan-Canadian Early Detection of Lung Cancer Study funded by the Terry Fox Research Institute and the Canadian Partnership Against Cancer has recently published an accurate lung nodule malignancy risk calculator to provide a lung nodule management guideline that can significantly reduce the number of follow-up scans and other investigations for suspicious or indeterminate lung nodules.[8,9]

The PanCan lung nodule malignancy risk calculator is recommended by the American College of Radiology Lung-RADS[10] and the British Thoracic Society Guideline[11] for investigation and management of

pulmonary nodules found by screening LDCT. However, prospective evaluation of the PanCan lung nodule management protocol versus other protocol such as Lung-RADS is yet to be performed.

A1. Predicting the Risk of Lung Cancer.

Lung cancer screening is most effective when applied to people at high risk.[12,13] The use of an accurate risk prediction model that incorporates risk factors besides age and smoking history is more efficient at identifying people who will develop lung cancer and die from the disease and will likely lead to a more cost-effective screening program (lung cancers deaths averted per screen) than the NLST criteria.[12,13]

Currently, at least 17 lung cancer risk prediction models exist. These risk models have been summarized by in a recent publication.[8] The Tammemagi PLCOm2011, PLCOm2012 and PLCOall2014 models and the Hoggart European Prospective Investigation into Cancer and Nutrition (EPIC) model are the only models that are based on large prospectively followed population-based samples not limited to people at high risk of lung cancer[12,14-16] and they show high discrimination and calibration in smokers.

Quesionnaire-based approaches do not require direct contact because risk can be assessed by telephone or online. This approach is relatively simple, has broad coverage, and is less time consuming and costly than the clinic-based approach that requires direct contact with the participants. When the threshhold for screening in the PLCOm2012 prediction model[12] was set to give the same proportion screened from the PLCO trial as the NLST criteria, it had 11.9% ($p<0.001$) greater sensitivity (83.0% vs 71.1%) in identifying those who would be diagnosed with lung cancer in six years of follow-up and 41.3% fewer future lung cancers were missed (17.0% vs 28.9%). Using an earlier version of the PLCOm2011 risk assessment tool[14] for recruitment of participants into the Pan-Canadian Early Detection of Lung Cancer Study, the risk prediction tool was found to be very accurate. The average six-year lung cancer risk in 2,537 participants recruited in 8 centers across Canada was 4.5%. The percentage of confirmed lung cancer cases was 6.5% after a median follow-up of 3.8 years. In a subsequent study,

Tammemagi and colleagues estimate from the PLCOm2012 risk prediction model that a threshold of 1.51% for 6-year lung cancer risk (65th percentile of risk) can identify 80% of ever smokers who will

have lung cancer.[15] This threshold was chosen because lung cancer mortality in the LDCT arm consistently dropped below that in the chest x-ray arm. Although the PLCOm2012 risk assessment tool and risk threshold is the only quantitatively defined method to select high risk smokers for LDCT screening, to what extent it can be applied to the general population in western countries is not known.

In Canada, for example, a significantly higher proportion of the Canadian population are non-White (Table 1) while the PLCO cohort (where the risk prediction model was derived from) is predominantly American White Caucasian.[12,14,15] The proportion of current smokers in the general Canadian population is also lower especially in the west coast where only 8% of adults age 55 to 75 still smokes (Table 1).

To transition from a clinical trial setting to population screening, the effectiveness of the PLCOm2012 ≥0.0151 threshold or the USPSTF criteria to select high risk individuals for LDCT screening in the Canadian setting and other jurisdictions needs to be validated. In the United States, emerging data suggests less than 40% of the lung cancer patients would meet the USPSTF screening criteria (55-80 years who had smoked at least 30 pack-years and not starting screening after 15 years of smoking abstinence) had screening were available prior to diagnosis.[17] A head-to-head comparison between USPSTF and PLCOm2012 selection criteria has not been performed.

A2. Importance of Accurrate Selection Criteria for Lung Cancer Screening

Experience with current screening programs such as screening mammography and colorectal screening, the participation rate is between 50% to 70%. Lung cancer screening with LDCT will have net benefit only in those with sufficient risk for lung cancer.[3] In NLST, screening 60% of highest risk subjects prevented 88% of the lung cancer deaths while the false-positive per preventable lung cancer death was the highest among those with lower risk.[13] In a retrospective analysis of the PLCO ever smokers cohort, the PLCOm2012 prediction tool was found to have significantly higher sensitivity, specificity and positive predictive value of 83%, 62.9% and 4.0 respectively compared to 71.1%, 62.7% and 3.4 respectively using the NLST criteria.[12] In a recent study by one of us (Tammemagi), compared with NLST/USPSTF criteria, selection of individuals for screening using high-quality risk models should lead to fewer individuals being screened, more cancers being detected, and fewer false positives.

More lives will be saved with greater cost-effectiveness.[18] Using the NLST chest x-ray group as a comparison, a cost-effectiveness analysis of the Pan-Canadian Early Detection of Lung Cancer Study that used an earlier version of the PLCOm2011 risk prediction tool to enrol screenees showed an ICER of $10,212/QALY.[19] In NLST using age and smoking as selection criteria, the ICER was $81,000/QALY.[20]

In addition to cost-effectiveness, the impact of lung cancer screening at the population level is strongly dependent on the proportion of at risk subjects potentially reached by the screening selection criteria. For example, if the sensitivity of identification of persons at risk of lung cancer is 80% and the participation rate is 70%, 56% of the at risk population could be reached. On the other hand, if the sensitivity is 40%, only 28% of the at risk population would be reached. If a poor sensitivity of selection is coupled with a low screening uptake rate such as 50%, the impact at the population level would be only 20%. Therefore, to achieve a cost-effective lung screening program at the population level, a selection tool with high sensitivity and specificity is required.

A3. Web Risk Assessment Tool (http://www.brocku.ca/lung-cancer-risk-calculator) [12,14,15]

An innovative web-based lung cancer risk assessment tool (to determine who is eligible for screening) developed by Dr. Martin Tammemagi has been tested for subject selection and recruitment in the Pan Canadian Early Detection of Lung Cancer Study (PanCan) (Figure 1). This tool can be integrated into a physician's electronic medical record system, available as an iPhone or iPad app or accessed online. This tool has been updated that can automatically display the lung cancer risk using the PLCOm2012 prediction model and whether a person is eligible for LDCT screening according to the PLCOm2012-risk≥0.0151 selection criteria or the USPSTF criteria (Figure 2). It will be used for recruitment in this project.

A4. Outdoor and Household Pollution as Lung Cancer Risk Predictor

In the fall of 2013, IARC determined that there was sufficient evidence to conclude that outdoor air pollution and one of its major components, particulate matter, are carcinogens and important causes of lung cancer.[21,22] They estimated that worldwide, 223,000 deaths from lung cancer were attributable to outdoor air pollution in 2010. The most recent estimates from the Global Burden of Disease estimate 387,000 lung cancer deaths attributable to outdoor air pollution in 2013 (24% of all lung cancer deaths).[23,24] IARC also concluded that there is sufficient evidence for a causal link between

indoor emissions from household combustion of coal and lung cancer (Group 1).[25,26] In addition, combustion of biomass fuel (mainly wood) and high-temperature frying are probably carcinogenic to humans (both Group 2A).[26] Roughly half of the world's population, mostly in low- and medium-resource countries use solid fuels for heating or cooking or both, frequently in poorly ventilated spaces.[26] The World Health Organization considers indoor smoke from combustion of solid fuels as one of the top ten risks for the global burden of disease.[26] The Global Burden of Disease estimates 128,000 lung cancer deaths attributable to household air pollution in 2013.[23,24] A meta-analysis of 7 studies of lung cancer in Chinese and Taiwanese never-smoking females found a relative risk associated with indoor coal and wood burning of 2.66 (95% CI 1.39-5.07) and with cooking oil vapours of 2.12 (95% CI 1.39-5.07)[27] and large case-control studies of lung cancer and indoor coal and wood burning in never-smokers from Europe[28] (both sexes) and from Canada[29] (significant for women only) found relative risks of 1.22 (95% CI 1.04-1.44) and 2.5 (95% CI 1.5-3.6), respectively. Another important environmental lung carcinogen is radon and its decay products.[30,31] Radioactive radon is a naturally ocurring inert gas which can move from soil and rock, and human exposures primarily occur in mining activities and residential basements. The odds ratio for lung cancer from exposure to radon at a concentration of 100 Bq/m^3 (becquerels = radon disintegrations per second per cubic meter) occurring 5 to 30 years before the date of diagnosis was 1.12 (95% confidence interval (CI) 1.00-1.28).[32] A pooled analysis of case-control studies in North America (n=7) and Europe (n=13) estimate that 10% and 9% of lung cancers are attributable to radon exposure.[32,33] Predictive mapping for radon risk is available in some regions of the world such as British Columbia[34] with more qualitative data from other countries such as China.[35] The actual indoor exposure is difficult to quantify due to lack of measurement data from individual homes.

Although outdoor and household air pollution account for an estimated 29% of lung cancer deaths worldwide, none of the 17 lung cancer risk prediction models published so far has included outdoor and/or household pollution as one of the risk variables. A prospective analysis of data from 17 cohort studies (312,944 participants) based in nine European countries by the European Study of Cohorts for Air Pollution Effects showed a statistically significant association between the risk for lung adenocarcinoma and PM_{10} (hazard ratio [HR] of 1·51 (1·10-2·08) per 10 μg/m^3) and HR of 1·55 (1·05-2·29) per 5 μg/m^3 for $PM_{2.5}$.[36] In Canada, a case-control study of 2390 incident lung cancers from eight different provinces, estimated an elevated odds ratio of 1.29 (95% confidence interval = 0.95-1.76) per

per 10 μg/m^3 increase in $PM_{2.5}$.[37] Worldwide, around 2.4 billion people use traditional biomass fuels for household cooking or heating. The ORs for lung cancer risk with biomass for cooking and/or heating were 1.21 (95% CI 1.05 to 1.39) for men and 1.95 (95% CI 1.16 to 3.27) for women in studies with adequate adjustment and a clean reference category.[38] With global migration patterns and a multi-ethnic society, it is important to examine the role of outdoor and household air pollution as part of a lung cancer risk prediction model. The Canadian Partnership Against Cancer Expert Panel on Identifying Individuals at High Risk for Lung cancer Screening made the recommendation that air pollution should be considered for inclusion in existing lung cancer risk prediction models.[39] As an optional study, we will offer the participants to answer a detailed epidemiologic questionnaire to collect information on outdoor and household air pollution exposures in addition to history regarding smoking habits, family history of lung cancer, personal history of cancer, chronic obstructive pulmonary disease, occupation, symptoms and medications (Appendix 1).

A5. Role of Biomarkers in Lung Cancer Screening

There has been intense international interest in developing biomarkers for lung cancer screening for several important applications: (a) Selection of high-risk individuals for LDCT screening; (b) Diagnosis of benign versus malignant lung nodules; and (c) Differentiation between indolent (slow growing) versus aggressive screen-detected lung cancers (rapid growth, high metastatic potential). These studies involve analysis of blood[40-50], sputum[51-53], exhaled breath[54] and bronchoscopic specimens.[55-56] As a tool to pre-screen people for lung cancer screening, few of the reported biomarkers have reached prospective screening Phase IV clinical trial. Of the ones that has undergone prospective Phase IV clinical validation, such as EarlyCDT-test for which our team was involved,[42,43] the test performance (sensitivity <20% at a specificity of 90% in a screening population, S. Lam *et al*, unpublished data) was insufficient as a pre-screening test. Many of the biomarker studies are limited by small sample size and hence over-fitting of estimates to data, retrospective case-control study versus prospective study designs, use of pre-diagnostic sprcimens collected from patients with a high prevalence of lung cancer rather than that expected a screening population, and use of unreliable/expensive technology platform.

As part of the Pan-Canadian Screening Study, we have collected blood samples from 2,537 high-risk former and current smokers. Pro-surfactant protein B was confirmed by our team to have net benefit for

lung cancer risk prediction in a model consisting of age, sex, BMI, personal history of cancer, family history of lung cancer, adult pneumonia, FEV1% Pred, smoking - cigs/day & duration using the Pan-Canadian Early Detection of lung Cancer Study blood samples from 2,537 participants.[41,57] In collaboration with the National Taiwan University, the usefulness of Pro-surfactant protein B as a biomarker for lung cancer risk assessment in a never smoker LDCT screening cohort is currently on-going. An international consortium coordinated by Dr. Sam Hanash in MD Anderson Cancer Center is being formed to validate Pro-surfactant protein B and other candidate biomarkers for lung cancer screening. Blood specimens will be obtained from the participants in this study for future biomarker studies. Separate REB submissions will be made to access these banked specimens.

A6. Lung Nodule Management

Currently, there is no universally accepted protocol for management of screening LDCT detected lung nodules. The only evidence-based lung nodule risk calculator is the one published by the PanCan study team.[8,9] The accuracy of this lung nodule risk calculator was validated in two recently published studies in Europe and UK.[58,59] A recent study at the Radboud University in the Netherlands suggests the PanCan nodule risk predictor may have superior sensitivity and specificity than the Lung-RADS classification[60] (Figures 3 & 4). The PanCan lung nodule malignancy risk calculator is recommended by the American College of Radiology Lung-RADS[10] and the British Thoracic Society Guideline[11] for investigation and management of pulmonary nodules found by screening LDCT. Prospective evaluation of the PanCan lung nodule management and Lung-RADS has not been performed but is one of the objectives of the current study.

A6. Frequency and Duration of LDCT Screening

The optimal frequency and duration of LDCT screening has not been defined. NLST has 3 rounds of screening one year apart.[1,2] The current USPSTF recommendation is annual LDCT screening until the age of 80 if the person is healthy and fit for surgery if early lung cancer is found. Screening will be discontinued after 15 years of smoking abstinence.[3-5] The UK Lung Cancer Screening Trial has a single round of CT screening.[61] Data from the PanCan study suggests that screenees with no lung nodules greater than 1 mm or a lung nodule malignancy risk <1.5% in the largest nodule (if more than one lung nodule) has very low risk for lung cancer within 2 years (Figure 5). We will offer a second round of LDCT screening in 24 months to those without lung nodule or the lung nodule malignancy score is <1.5%.[8,9]

Those with lung nodules with a risk score ≥1.5% will be followed for 2 years (solid nodules) and up to 5 years (sub-solid nodules) according to current clinical practice. All participants will be prospectively followed by phone, letter or personal interview for a minimum of 6 years to determine occurrence of incident lung cancer. If evidence warrants, the follow-up protocol will be amended.

B. Specific Aims and Hypothesis

We hypothesize that:

1. The proportion of lung cancers detected by PLCOm2012-risk ≥0.0151 threshold is greater than by USPSTF criteria and the proportion of overall sample selected at high-risk by PLCOm2012 is smaller than by USPSTF criteria.
2. The PanCan lung nodule malignancy risk tool accurately defines the frequency of repeat imaging study and the need for biopsy for lung nodules found by screening LDCT.

Specific Aims:

Aim 1: Compare the sensitivity of the PLCOm2012-risk ≥0.0151 threshold versus USPSTF lung cancer screening selection criteria.

Aim 2: Prospective evaluation of the PanCan algorithm for management of screening LDCT detected lung nodules.

Aim 3 (optional): Collect additional air pollution exposure information and blood specimens for ancillary studies.

Aim 3 (optional): Collect blood specimens to evaluate the role of blood biomarkers for assessment of lung cancer risk and malignancy potential of lung nodules

Aim 4 (optional): Evaluate the impact of LDCT screening on quality of life.

C. Research Plan

C1. Study Schema

The flow diagram of the study is shown in Figures 6 and 7 below:

Figure 6. Participant Recruitment Flow Diagram

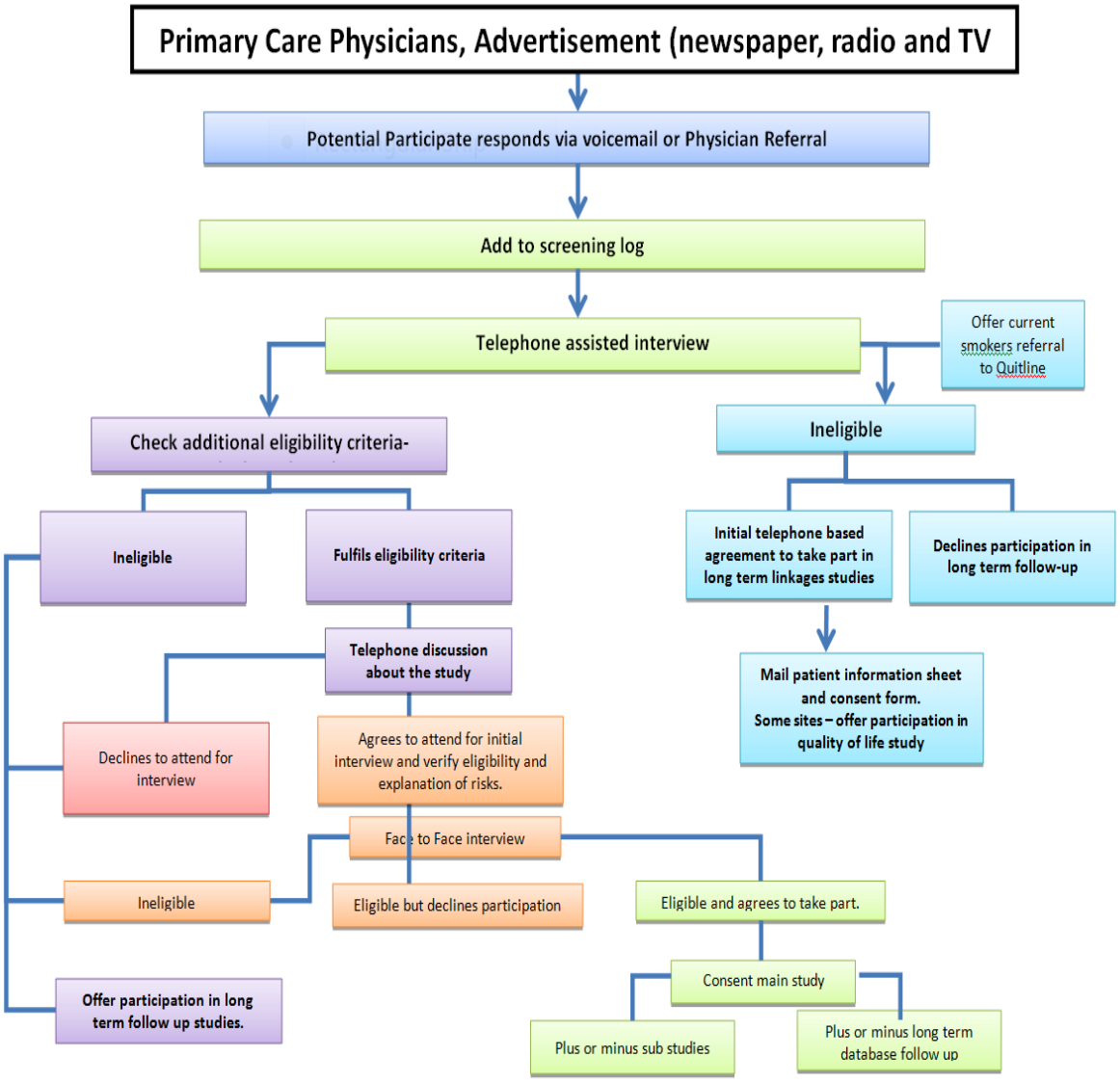
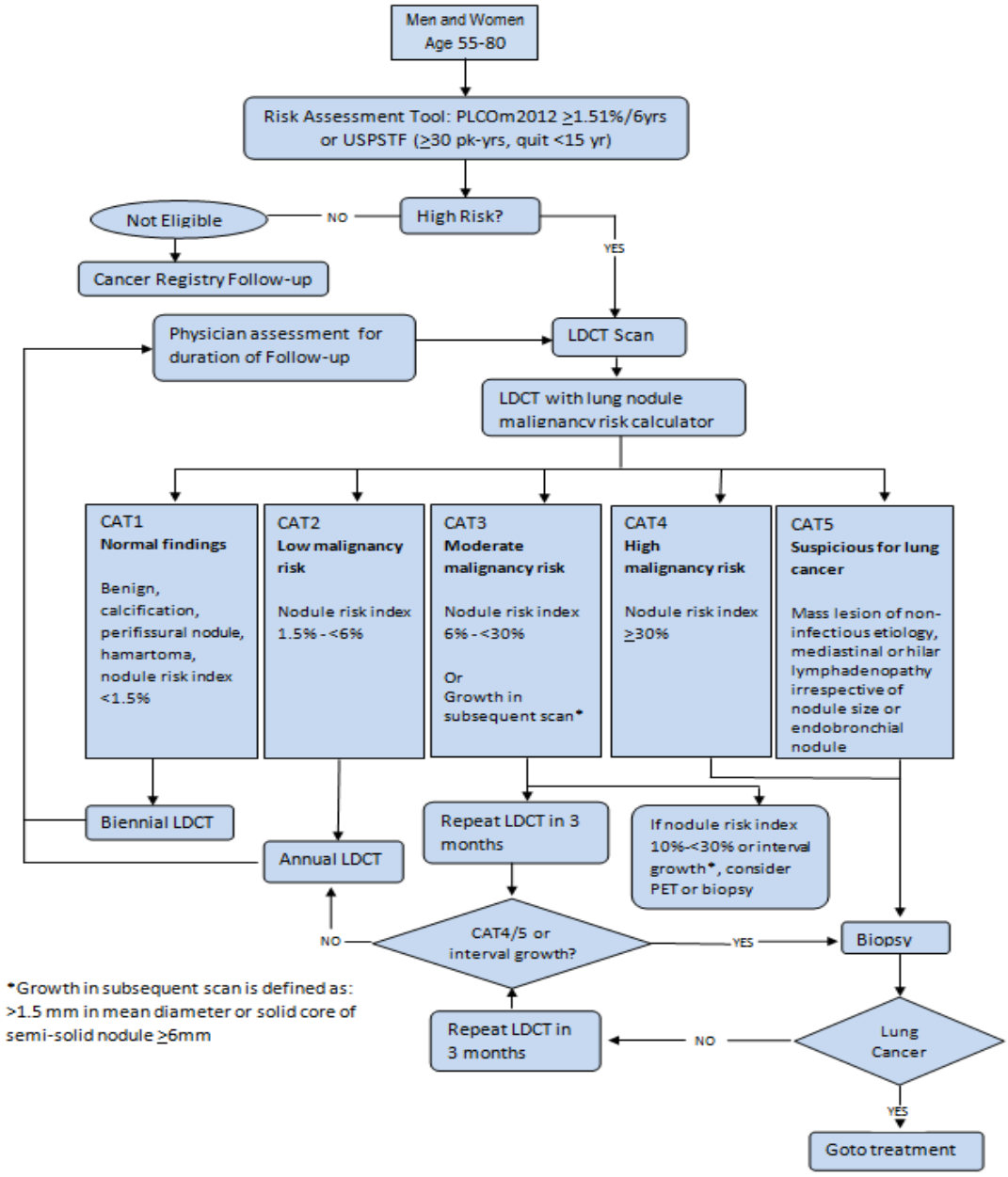


Figure 7. Lung Nodule Management Protocol



C2. Participant Inclusion and Exclusion Criteria

C2.1 Inclusion Criteria

- Women or men age 55 to 80 years.
- Current or former smokers. A former smoker is defined as one who has stopped smoking for one or more years.
- An estimated 6-year lung cancer risk of ≥1.51% based on the PLCOm2012 risk prediction model or ≥ 30 pack-years smoking history (pack-year is defined as number of pack of cigarettes smoked per day multiply by the number of years smoked. If a participant stopped smoking for 6 months or more and then restarted smoking again, the time will be subtracted from the total duration of smoking in 0.5-year increments)
- ECOG performance status 0 or 1.
- Capable of providing, informed consent for screening procedures (low dose spiral CT)

C2.2 Exclusion Criteria

- Clinical symptoms suspicious for lung cancer e.g., hemoptysis, chest pain, weight loss
- Any medical condition, such as severe heart disease (e.g. unstable angina, chronic congestive heart failure), acute or chronic respiratory failure, home oxygen therapy, bleeding disorder, that in the opinion of the investigator could jeopardize the subject's safety during participation in the study or unlikely to benefit from screening due to shortened life-expectancy from the co-morbidities
- Have been previously diagnosed with lung cancer
- Have had other non-curatively treated cancer outside the lung.
- Pregnancy
- Pneumonia or bronchitis requiring antibiotic treatment within the last 12 weeks
- Unwilling to have a spiral chest CT
- Chest CT within 2 years
- Does not fit into CT scanner table due to gross obesity
- Cannot lie on CT scanning table on the back with arms over the head
- Received chemotherapy or cytotoxic drugs within the last 6 months
- Unwilling to sign a consent

C3. Number of Participants

2,000 participants will be accrued from Vancouver and 2,000 participants will be accrued from 4

centers in Australia (Brisbane, Sydney, Melbourne, Perth) over 24 months. Pending institutional approval, it is anticipated that an additional 4,000 participants will be recruited from Denmark and Italy for a total of 8,000 participants. Both men and women and members of all races and ethnic groups are eligible for this trial. The rationale for the sample size is described below.

C4. Recruitment

C4.1 Recruitment strategies

Participants between the ages of 55 to 80 will be recruited using several strategies:-

Strategy	**Canada**	**Australian sites**			
		Brisbane	**Sydney**	**Melbourne**	**Perth**
C4.1.1 Network of primary care physicians who see patients with lung cancer	X				
C4.1.2 Social media, newspaper, radio, television	X	X	X	X	X
C4.1.3 Department of Human Services mail out (invitation)				X	

C4.1.1 In Canada, BCCA is collaborating with a Network of primary care physicians who have historically demonstrated provision of care to lung cancer patients. The Study will invite members of the primary care network to advertise to identify potentially eligible patients and refer them to the Vancouver General Hospital Lung Cancer Screening Centre.

C4.1.2 Social media, newspapers, radio and television. As previously used in the Queensland Lung Cancer Screening Study and the Pan-Canadian Early Detection of Lung Cancer Study, this study will utilize existing organizational platforms for advertising the study to the general community through these public accessible media vehicles using electronic social media announcements, public service messages, media releases and targeted advertisement to appropriate parties.

The core information is shown below. Minor modifications will be made to reflect the local situation as needed:

Could you be at risk of developing lung cancer?

Are you:

- *A smoker or recent former smoker?*
- *Aged between 55 and 80?*
- *In good general health?*

If you answered yes to these questions, you may be eligible to take part in a research study conducted by International Consortium XXXX at XXXX Hospital.

Eligible persons are invited to have a low- dose CT scan to see if this could be a useful way of detecting early lung cancer in healthy people at risk.

If you are interested in participating, please contact the research team at XXX Hospital on (0X) XXX XXXX for more information.

C4.1.3 Department of Human Services mail out (Melbourne).

Once ethics approval has been obtained, we will apply to Department of Human Services (DHS) to conduct a mail out to people aged 55 to 80 living in areas close to the study centre. The mail out will be conducted by DHS on behalf of the organisation conducting the study. Participants who are aged 55 to 80 living in pre-selected regions based on post codes will be randomly selected from the DHS Medicare database. DHS will conduct the mail out on our behalf so that identifiable data is not provided to us directly. The mail out will include study information and an invitation to take part along with telephone contact details and a reply-paid envelope.

C4.2 Eligibility assessment process (Figure 2)

C4.2.1 People interested in participating in the study will telephone the study centre (free call number) and speak with the research coordinator/assistant or will leave contact details for return calls. People approached through direct mail out will also be given a telephone number to call or will be provided with a written form (including contact details) and reply-paid envelope to return to the study centre. The research coordinator at each study centre will conduct an initial telephone eligibility assessment using an innovative web-based lung cancer risk assessment tool (PLCOm2012 developed by Dr Martin

Tammemagi). This tool is available as an iPhone app or iPad app or accessed online. This tool can automatically display the lung cancer risk and indicate whether a person is eligible for LDCT screening according to the PLCOm2012-risk≥0.0151 selection criteria or the USPSTF criteria (Figure 2).

C4.2.2 Those who meet the PLCOm2012 1.51%/6 years lung cancer risk criteria or the USPSTF screening criteria (current smokers who have smoked at least 30 pack-years and former smokers who have smoked 30 pack-years and who have stopped smoking for less than 15 years) will be asked a further series of questions to assess eligibility based on all inclusion/exclusion criteria. Those who are eligible will be invited for a face-to-face meeting to verify smoking history and smoking status (for former smokers by urinary cotinine or exhaled carbon monoxide), inclusion/exclusion criteria, explanation of the risks and benefits of LDCT screening. Participants who are unable to travel twice will have their smoking status verified on the day of the CT scan. Informed consent will be obtained for the main study and for optional studies (e.g., outdoor and household air pollution exposure and blood specimen collection) before the CT scan.

C4.2.3 A study number will be assigned. Those not eligible for screening will be assigned a study number with additional code to denote ineligibility.

C4.2.4 Informed consent will be obtained using the attached study patient information and consent forms (Appendix XXX)

C4.2.4.1 Eligible participants who have provided informed consent will be invited to undergo CT screening and will be invited to consent to be involved in sub-studies.

C4.2.2.2 Non eligible people who expressed an interest to be screened but do not meet either screening inclusion criteria or are excluded for other reasons will be asked to take part in long term follow up.

C4.2.2.3 In addition, those who are eligible for screening but decline to take part after a discussion about the risks and benefits will be offered participation in long term follow up.

We will seek consent for long term linkages studies on these groups (C4.2.2.2 and C4.2.2.3) of participants using an opt-out process.

In Australia, consent will be sought to link participant data with state-based cancer registries and the National Death Index and MBS records in order to determine the incidence of lung cancer in those who do not fulfill the screening inclusion criteria and also to assess whether those who are not eligible subsequently undergo CT scanning outside of the study.

In Canada, consent will be sought to link participant data with the Cancer Registry.

Participants will be offered the opportunity to opt out at any time including at the time of the telephone interview, those who do not opt out at this point will be sent a participant information sheet and opt out form and asked to return to the study centre by pre-paid envelopes if **they do not** wish to take part in the linkages study. They will be asked to return the form within 3 weeks and if a form has not been received within that time frame it will be assumed that they do not object to participation in the linkages study.

Consent may also be sought for participation in Optional Sub-studies such as air pollution surveys, biomarkers and quality of life.

C5.0 Optional Sub-Study at the Vancouver Site

The modified Pan-Canadian Early Detection of Lung Cancer risk assessment questionnaire (Figure 2) plus an outdoor and domestic air pollution exposure questionnaire (Appendix 1) will be administered to all newly diagnosed lung cancer patients (estimated to be 1,400 patients over two years) who will be attending the Vancouver Cancer Center of the BC Cancer Agency or the Thoracic Surgery Department of the Vancouver General Hospital (VGH). The VGH Thoracic Surgery Unit is one of four thoracic surgery centers for surgical treatment of lung cancer patients in the entire 4.6 million population in British Columbia. From the risk assessment tool, we will determine the relative sensitivity of the PLCOm2012-risk ≥1.51% threshold versus the USPSTF screening criteria to identify lung cancer patients who are ever smokers.

C6.0 Blood specimen collection (optional)

Blood samples will be collected on the day of registration after signing informed consent to collect blood annually for up to five years. For subjects found to have lung cancer, a blood specimen will be obtained prior to treatment and 3 to 6 months post treatment (for those who will be given treatment

with curative intent) to determine whether the biomarkers decrease after treatment with curative intent. Blood samples will be drawn without regard to fasting status or time of day, although the time of day and approximate time of last meal will be recorded on the sample collection form.

The first one mL blood contain contaminating substances from epithelial cells will be discarded. One 9 mL blood sample (obtained from a 10 cc Red uncoated blood tube) will be drawn and processed into serum and clot. One 9 ml blood sample obtained from a 10 cc yellow-top ACD tube and one 9 ml blood sample obtained from a lavender-top 10 mL potassium EDTA tube will be drawn and processed into plasma for the biomarkers measurements. Part of the buffy coat will be used for cell sorting to study the composition of the immune cells with the remaining stored for DNA-based biomarker assessments. The time between blood collection and storage will be recorded.

Samples that are more than 2 hours between collections, processing and storage will be repeated. A unique identifier will be associated with each specimen and linked to the patient data in the CC database management office. The samples will be stored at -80^{o}C.

C7. Thoracic Low-dose Computed Tomography (LDCT)

A multi-detector row CT scanner with minimum section collimation of ≤1 mm and minimum number of data acquisition channels ≥ 16 will be employed. The CT scans will be performed at 120 kV, 40-50 mA (automatic modulation based on patient size), pitch 1:0, gantry rotation time ≤0.5 seconds (total scan times <15 seconds). The scan length will be from the lung apices to the adrenals. Low radiation dose acquisitions using less than ≤1.5 mSv effective dose will be obtained using reduced mA and a minimum gantry rotation time. The CT dose index volume (CTDIvol) will be ≤3.0 mGy (32cm) for a standard sized patient (170 cm, 70 Kg, BMI = 24). Images will be acquired in a single inspiratory breath hold with the subject in the supine position with arms overhead. No intravenous or oral contrast will be used. Images will be reconstructed using 1 mm or less section thickness and ≤1 mm spacing. Two image reconstruction algorithms will be employed, a high spatial frequency algorithm for lung parenchyma (e.g. bone (GE) or B60 (Siemens)) and an intermediate spatial frequency algorithm for mediastinal structures (e.g. standard (GE) or B35 (Siemens)). The mediastinal reconstruction algorithm will be useful to provide lower noise images on these reduced dose images. Images will be archived to the hospital/screening center based PACS server with full annotation and stored in local site for clinical use if needed. A second image file will be saved with an anonymized study number. The file with the anonymized study number will be sent to the central study data server.

Calibration scans will be performed at all participating sites using the body calibration phantoms and spatial resolution supplied with the CT scanners at each site. These calibration scans will be performed using the same technical parameters as proposed in the low dose CT protocol (kVp 120, 40 mAs, rotation time 1 second or less, 32 cm field of view reconstruction, intermediate and high spatial frequency reconstruction algorithm). Spatial resolution and image noise will be measured on the submitted images and used for standardization of each site. Reference scans will be repeated on a yearly basis. Dr. John Mayo and Dr. John Aldrich, the VGH Radiation Protection Officer and Medical Physicist will review the data to ensure adequate scanner performance at each of the sites.

C8. LDCT Reading and Reporting

The LDCTs will be processed by computer assisted detection (CAD) software (Philips or the Mevis Veolity system). The software will automatically identify lung nodules ≥3 mm in diameter, determine the location, define the nodule type (solid, semisolid, non-solid, perifissural), measure the short and long axis, volume and calculate the nodule malignancy risk score according to the PanCan calculator.[8] A trained radiology technician will review the CAD marks. The technician reviewed the processed cases and the annotated markings of abnormalities by the CV software. CAD marks on true nodules will be accepted and false positives CADS marks deleted. The technician then reviews the scans and manually marked any additional nodules and other abnormalities that are not identified by the CAD software. The LDCT scans will be read by a chest radiologist who has read at least 300 chest CTs in the last 3 years. On alternate days, the radiologist will either report the scans with the CAD marks displayed or first report the findings without the CAD marks displayed and then with the CAD marks displayed. The time taken to generate a report with the CAD marks displayed, without the CAD marks will be automatically tracked by the computer. Changes in the report for scans that are read without the CAD marks displayed first will be recorded. A standardized report will be made similar to that in Figure 8. The report will be sent to the Screening Center Physician and the participants' primary care physicians. The report will contain a recommendation for follow-up or referral to a respirologist/thoracic surgeon in the screening program for further investigation.

C9. Management of Abnormal Scans

CT scan follow up protocol will be determined by the schema in Section C1 (Figure 7). Participants with no abnormality on the baseline exam or lung nodule with a maximum malignancy risk

score <1.5% will have a repeat scan in 24 months. For participants with a maximum nodule malignancy risk score of 1.5% to <6% will have a repeat LDCT annually for 2 years (for solid nodules) and up to 5 years (for sub-solid nodules). Those with malignancy score 6% to 10% will have a repeat LDCT in 3 months organized by the study navigator. Participants with a nodule malignancy risk score ≥10% will be considered suspicious for lung cancer. A nodule that grows on two consecutive scans (>1.5 mm in mean diameter, volume change (≥100% for nodules <5 mm; ≥30% >5 mm but ≤10mm and ≥20% for nodules ≥10 mm), volume doubling time between 30 to 400 days or development of a solid core ≥5 mm in a sub-solid nodule) will also be considered to be suspicious for lung cancer. They will be seen by the study physician/surgeon. A shared decision will be made regarding additional imaging studies (repeat LDCT or PET/CT) or a biopsy (bronchoscopic transbronchial biopsy or CT guided transthoracic needle/core biopsy). Further diagnostic procedure may include serology for cryptococosis and histoplasmosis or wedge resection. The overall aim will be to establish a pathologic or cytologic diagnosis and perform definitive treatment. Any confirmed diagnosis of lung cancer and other abnormality on the CT in the surrounding soft tissue of the chest and abdomen will be treated or followed up according to standard of care in the institution as directed by the medical team and the local study radiologist.

C10. Smoking Cessation

Smoking cessation will be offered to all current smokers whether they are eligible or not eligible for the study. Although randomized controlled trials did not find a statistically significant difference between individuals who were screened with CT and individuals who were not screened,[62-,64] a three to five times higher smoking cessation rate was observed compared with spontaneous quit rate in the general population which is generally between 2% to 3%.[64,65] In the multi-center PanCan study of 2,537 participants, the smoking cessation rate (confirmed by urine cotinine) was 21% at the end of 12 months and 25% at the end of 24 months. Only 5% of the former smokers re-started smoking. The higher smoking cessation rates in a CT screening program were often attributed to a "teachable moment". It was found that participants who were presented with abnormal CT results had a higher smoking cessation rate than those with normal scan.[62,66,67] The differences in smoking prevalence between those with abnormal screen versus normal screen were present up to 5 years after the last screen.[67] Personal perception of increased health risk from visualization of abnormalities on a CT scan may improve smoking cessation rate compares to conventional approach using counseling with and without pharmacotherapy. Since the information from a screening CT can be readily extracted, we will use a

combination of counseling (Canadian Quit Now Smoking Cessation Program or Quitline in Australia) with nicotine replacement and other smoking cessation drug such as buproprion or varenicline as needed; plus use of personalized CT images of lung nodules, emphysema and or coronary artery calcification. The CT scans will be analyzed by the VIDA Diagnostic software to generate a 3D image display of the severity of their emphysema (Figure 9). Pulmonary nodules and coronary artery calcification will be extracted from their CT scans (Figures 10 and 11). The abnormal findings will be explained to the smokers. They will receive a hard copy of the relevant images. The participants will be followed up in person 3, 6 and 12 months after intervention to assess their smoking status. Smoking cessation will be confirmed by urinary cotinine measurement or exhaled carbon monoxide. Resumption of smoking among former smokers will be monitored using urine cotinine monitoring at baseline and the annual visits.

C11. *Outcome Evaluation*

The outcomes of interest in this study are:

- the number needs to be screened to detect one cancer with the PLCOm2012 versus the USPSTF selection criteria
- proportion of participants who do not meet either the PLCOm2012 or USPSTF screening selection criteria but develop lung cancer
- cancer detection rate
- the number of interval lung cancer cases
- recall rate
- Invasive procedure rate
- Non-malignant biopsy/surgery rate
- adverse events (morbidity related to bronchoscopy, biopsies, surgery or other treatments)
- resection rate
- stage distribution of the lung cancers
- Mortality (lung cancer, all causes)
- smoking cessation rate (for current smokers)
- rate of detection of other incidental significant treatable diseases
- type and costs of downstream investigation and treatment related to abnormalities found by the screening procedures whether the final diagnosis is lung cancer or not

- identify logistics/barriers for an early detection program

The participants will be followed regularly at annual intervals for four years either by telephone or personal visits, and details of all outpatient visits and use of allied health services related to lung cancer diagnosis or treatment will be obtained. Additional information regarding development of lung cancer or death from lung cancer beyond 4 years will be obtained from Cancer Registries and Death Registries. Change in smoking status will be monitored annually using urinary cotinine/exhaled carbon monoxide.

Diagnostic procedures related to the early detection procedures will be tracked by the site study coordinator. The lung cancer cases will be evaluated by the Steering Committee. The histology cell type, TNM stage, treatment procedures, length of hospital stay, type of hospital ward (Intensive Care, step-down unit, general ward), physician visits etc. will be tracked by the site study coordinator and submitted to the CC database. For lung cancer cases (both prevalent and interval) that are not managed by the site investigators, the site coordinator will obtain the procedure and pathology reports as well as the tissue blocks from the outside facility for review.

C12. Incremental value of including air pollution in the PLCOm2012 lung cancer risk prediction tool to identify high-risk individuals for LDCT screening (Vancouver Site)

A detailed epidemiologic questionnaire (see appendix) will be administered to participants who consent to this optional study. The questionnaire is a modified version of the *Health and Lifestyle Core Questionnaire For Women and Men* (HLCQ) used in the Canadian Partnership for Tomorrow Projects (CPTP). This questionnaire is particularly thorough in collecting data on personal history and family history of cancer, smoking exposure, alcohol consumption and anthropometric measurement. These represent exposures that are active areas of lung cancer prediction research. For example, it is unclear how to optimally code family history of lung cancer in prediction models. Can prediction be improved by including number of family members with lung cancer (or other cancers) and should early age versus older age of onset be included? Personal history of cancer was an important predictor of lung cancer and PLCO analysis suggested that it might be a useful predictor in never-smokers. However, what components of personal history of cancer are important is unclear - which previous cancer types and which cancer treatment(s) are important are yet to be identified. Some of our recent analyses suggested

that very heavy alcohol use might be predictive of lung cancer independent of detailed adjustment for smoking exposure. But this exposure has not been included in any lung cancer risk prediction model to date. Body mass index has repeatedly been found to be inversely associated with lung cancer and has been included in several lung cancer risk prediction models, including all three PLCO models. However, the nature of the relationship is unknown, and if the underlying association can be more optimally measured for prediction is unknown. The PLCO cohort has 88% White, 5.2% Black, 1.9% Hispanic, 3.8% Asian, 0.6% Pacific Islander and 0.25% American Indian[14]. Black race is a predictor in two of the U.S.-based PLCO models[12,14]. The impact of race/ethnicity on lung cancer risk prediction in the BC population with different minority group is unknown. The proposed study will clarify these and additional relationships and help improve risk prediction.

A unique feature of this study is the ability to collect detailed residential history within Canada and prior residence outside of Canada (for foreign born immigrants) as well as household exposures from cooking and heating with solid fuels such as coal. From a full address, or just a city or street name – a coordinate value will be obtained from Google Maps (www.maps.google.ca) for each place of residence. The coordinates will be used for mapping of the long term air pollution exposure level ($PM_{2.5}$) using satellite observations. We have previously developed global high resolution models of outdoor air pollution levels that have been successfully applied to epidemiologic analyses including cancer mortality in China and Canada.[68-71] A time weighted air pollution exposure index will be developed from the intensity and duration of exposure similar to tobacco smoke exposure. We will also use our questionnaire to identify those who used solid fuels for cooking or heating and to generate exposure duration for household air pollution exposure. Since information on radon exposure based upon measurements from individual homes is usually lacking, we will test inclusion in the prediction model of estimated radon exposure based on risk prediction maps in a sensitivity analysis only.

C13. *Statistical Considerations*

C13.1 In the PLCO intervention arm smokers, the mean PLCOm2012 estimated 6-year lung cancer risk was 3.9%. This suggests that in a similar sample of 4000 smokers screened and followed for six years, 155 lung cancers would be detected. Assuming that 85.3% and 77.8% of the samples will be positive by the USPSTF criteria and PLCOm2012 risk>1.51% criteria, respectively, and that the sensitivity to detect

lung cancer are 83.8% and 94.3%, respectively, our sample size of 4000 will have greater than 90% power to demonstrate that compared to the USPSTF criteria, the PLCOm2012 criteria selects a significantly smaller proportion of individuals and detects a significantly higher proportion of lung cancers. Our study will have a 39% power to demonstrate that the positive predictive power for PLCOm2012 (4.2%) is significantly greater than observed for the USPSTF (3.4%). The numbers used in these calculations come directly from PLCO data. A two-sided alpha error of 0.05 was applied. The correlation between the two criteria was -.222. Power calculations were performed using STATA MP 14.1 software (College Station, Texas) using bootstrap resampling methods and the *power pairedproportions* program based on McNemar's test.

C13.2 For screening CT detected lung nodules, the retrospective analysis by van Riel et al suggest the PanCan nodule management protocol may have better sensitivity and specificity than Lung-RADS .[10,60] (Figure 3, 4). Each management schema has unique harms and benefits with possible costs differences so we will undertake a prospective comparison of the PanCan probabilistic strategy and the LungRADS nodule classification. Since the Lung-RADS also recommend using the PanCan nodule protocol for class 4 findings, a randomized trial comparing the two would not be meaningful. We will determine their effect on the frequency of additional imaging, biopsies, surgical resection, and outcomes of these procedures (diagnosis, False positives, False negatives). Through an iterative process, the management protocols will be evaluated every six months to determine if revision is warranted).

C13.3 To determine the incremental value of air pollution for lung cancer risk assessment versus the PLCOm2012 model, newly diagnosed lung cancer patients (both ever-smokers and never-smokers) and the Lung Screening Study participants (ever-smokers) in the Vancouver site will be used to test if there is a significant difference in the pollution index between those with and without lung cancer and those who meet the PLCOm2012 6-year lung cancer risk threshold ≥0.0151 versus those who don't. We will externally validate any resultant risk prediction model using the Canadian Partnership for Tomorrow Project (CPTP) cohorts, the Canadian Communities Health Survey (CCHS) data linked to provincial cancer cancer incidence registries (Table 2), as well as the on-going 10,000 screening cohort from the National Taiwan University to determine the predictive performance (discrimination and calibration) of the model overall, and where numbers permit, in subsets and ethnic subgroups of the population. The CPTP and CCHS data linked to cancer registry outcomes provide ideal data for our efforts to validate the PLCO risk models and lung cancer screening selection criteria in Canadian settings, and to

potentially improve them. These data include prospective follow-up data which provide estimation of true risks based on incidence data (probability of lung cancer in a defined population at risk per defined time period).

We anticipate well over 1,700 lung cancers from the CPTP and CCHS cohorts. To minimize over-fitting of any new model, a rule of thumb suggests that 10-20 outcomes be present per predictor variable in the model. We expect all new models to have 15 or fewer predictors and thus do not expect serious problems with over-fit.[72] We will also use bootstrap methods to estimate model *optimism*.[73]

If the PLCOm2012 model performs in the Canadian population as well as in the PLCO cohort (AUC 0.80), it may be difficult to find significant incremental improvement in AUC from the addition of new predictor(s) to the model.[74] Net Reclassification Improvement (NRI) is a method that is more sensitive at identifying prediction improvements at important decision-making thresholds.[75] The NRI has been criticized recently and as a response it has been recommended that the number of risk categories for decision-making be kept small and risk boundaries are clinically relevant.[76] We will apply these guideline in our application of NRI.

The predictive performance of the PLCO models will be assessed by AUC, a measure of discrimination or ability to classify correctly, and assessing calibration (do model-estimated probabilities correspond to observed probabilities). Calibration will be evaluated graphically by plotting observed risk versus model-estimated risk by deciles of model risk. Calibration will also be evaluated by assessing the magnitude of the mean and 90th percentile absolute error (observed minus predicted risks[72]), and by applying Cox recalibration (logistic recalibration).[77] The efficiencies of the PLCOm2012 risk ≥0.0151 and the USPSTF criteria to select high risk smokers for LDCT screening will be compared by applying these criteria to the prospective data and determining the number that are criteria-positive, sensitivity, specificity and PPVs. Confidence intervals for proportions will be prepared using the exact binomial method.[78] Statistical measures of performance fail to estimate clinical benefit of one method over another. We will apply *decision curve anaysis* to compare net benefit diferences between the diferent models and criteria.[79]

C14. *Health Economics Analysis*

C14.1 Lung Cancer Natural History Model

The economic analysis will be undertaken with the use of a natural history microsimulation model of lung cancer that is being developed in parallel with the LDCT trial by Prof Canfell and her team at Cancer Council NSW (CCNSW). The development of the lung cancer model is part of a broader and separate program of work and will serve as tool for assessing the outcomes of the LDCT trial. The CCNSW team has successfully built and implemented a natural history model for cancer of the cervix, which was used to evaluate the effectiveness of different cervical screening interventions within the framework of a screening trial in the UK.[80] Similar methodology will be used to assess the effectiveness and cost-effectiveness of the proposed LDCT screening strategies for this trial.

Specifically, a lung cancer natural history model will be constructed to simulate lung cancer incidence and mortality in the Australian population and will be built, validated, and calibrated using representative datasets, and a large, population-based Australian cohort study (the 45 and Up Study).[81] It will be an individual-based (microsimulation) model developed using a discrete-event simulation framework implemented in C++ and will consist of several core components (e.g., lung cancer natural history, diagnosis, treatment, and survival), including a 'smoking history generator'. The smoking history generator will simulate individual life/smoking histories and will be similar to that developed by the National Cancer Institute's Cancer Intervention and Surveillance Modelling Network (CISNET) that serves as input for similar lung cancer models in the US.[82,83] CISNET (http://cisnet.cancer.gov) is a consortium of investigators that uses mathematical modeling to assess the impact of cancer control interventions on population trends in incidence and mortality for a variety of cancer sites, and the team at CCNSW is currently a member (for cervical cancer). Although detailed tobacco exposure by age, sex and birth cohort will *not* be simulated for the Canadian, Italian and Danish trial participants, the model will be adapted for these sites to incorporate historical tobacco exposure for each country as previously done for CISNET. Specifically, published data for the US-CISNET model will be used in conjunction with a review of smoking in each country, to adapt the background and tobacco exposure assumptions in the trial population.

To assess the effectiveness of the various screening strategies within the trial, a simulated cohort of individuals who match trial participants (age, smoking status, etc.) will be configured. As trial data become available (T_0, T_1, T_2), successive validation exercises will be performed using the demographic, participation, cost, and outcomes data from trial participants. The modelled health resource utilisation and health outcome predictions for the simulated cohort will be compared to the

observed data as in previous work.[80] Following completion of this validation step, and in order to perform health economic evaluation of LDCT screening as performed in the trial, projections of 10-year and lifetime outcomes and costs for trial participants will then be performed.

C14.2 Ascertaining cost data

Health care resource utilization rates within the trial will be prospectively reported from each of the study centres via an electronic case report form. The method of capturing direct medical costs will vary depending on the setting. In Australia, costs will be ascertained from utilisation data within the trial, including the costs of screening itself, out-of-hospital medical services funded under the Medicare Benefits Schedule and/or the Department of Veteran Affairs, public hospital utilization, and patient diaries as per the Queensland Lung Cancer Screening Study.[84] Other Australian datasets, such as the 45 and Up Study, will be used to supplement these cost data with information regarding emergency department presentations, private hospital admissions, and prescription pharmaceuticals subsidised by the Pharmaceutical Benefit Scheme.

Societal cost data will be ascertained from questionnaires administered to a subgroup of participants and to consenting lung cancer patients receiving treatment at the BC Cancer Agency.[85] The questionnaires will be used to calculate costs to screening participants and will be calculated on a per-visit basis with consideration to the average travel time, distance and modality used to attend screening or non-curative treatment appointments in Vancouver, BC or in Australia as well as the employment status and out-of-pocket expenses to attend screening or lung cancer treatment appointments.

D. TIME LINE By Year

1 Ethics, DSM appointment, site coordination /activation at all sites, commence recruitment and LDCT screening for all cohorts, begin collation of data at all sites.

2 Continue recruitment and screening at all sites. Complete screening by mid-year. Follow-up of cohort and outcomes of screening throughout year, begin collation of data at all sites.

3 Follow-up of cohort and outcomes throughout year; continue collation of data at all sites and collation of findings across cohorts, begin economic evaluation. CAD substudy evaluation.

4 Follow-up, interim reports; continue economic evaluation.

5 Completion of follow-up, finalise collation of data across all sites, finalise economic evaluation, presentation and publication of reports

E. PROJECT MANAGEMENT

E1. Organizational Aspects

The overall operational organization of the consortium is described in Table 4.

E2. Integration and Communications

A **Team Website** updated weekly by the Central Coordination Center, will communicate research activities, progress, and achievements of the Team. It will also allow message posting for internal communication of the Team. **Monthly Teleconference** will serve as the forum for updating progress, identifying barriers in subject recruitment and exchange of results, material and techniques. **Executive Committee Meetings** will be held quarterly to monitor progress, resource allocation and all reporting responsibilities. An annual meeting of the team will be held along with other investigators to exchange ideas.

E3. Monitoring Of Milestones

Our goal is to recruit 4,000 subjects over 24 months. With 5 centers (Vancouver, Brisbane, Sydney, Melbourne, Perth), an average of 167 subjects needs to be enrolled each month. With an active primary care physicians' network, advertising campaign and an anticipated high acceptance rate similar to our previous studies, we believe 167 subjects per month is a realistic figure.

Accrual will be monitored continuously. Weekly inputting of data and plotting accrual will establish individual site and overall progress. Monthly teleconference of the study coordinators in the network will be held to address recruitment/retention issues and how best to overcome them. Variations in accrual are expected. Quarterly accrual rates, cumulative accrual rates and trend are important parameters the steering committee will be monitoring closely to detect significant deviation from the target enrollment.

E4. Data Sharing Agreement

- Each Collaborator shall agree to permit use of the anonymized Multi-Party Data from the clinical trial by any other Collaborator in sub-projects or publications that are approved by the Executive Committee.

- Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to consortium parties. All data made available will comply with HIPAA regulations.
- Any manuscripts, abstracts or press releases reporting the results of this clinical trial must be approved by the Executive Committee.

F. TABLES

Table 1. Clinical Trial versus General Population Demographics Age 55 to 75

	PLCO N= 85,717[1]	NLST N= 53,452[2]	Canada[3]	British Columbia[3]
Male : Female	**58% : 42%**	**59% : 41%**	**49% : 51%**	**45% : 55%**
Race/Ethnicity				
Non-White	**17%**	**10%**	**19%**	**45%***
Education				
≤HS	**31%**	**30%**	**37%**	**41%**
≥ College	**69%**	**70%**	**63%**	**59%**
Current Smokers	**20%**	**48%**	**12%**	**8%**
Median Pack-years	**29**	**48**	**42**	**38**

[1]Prostate Lung Colorectal and Ovarian Cancer Screening Trial (reference #13)

[2]National Lung Screening Trial (reference #1)

[3]Stat Canada 2011 statistics

http://www12.statcan.ca/nhs-enm/2011/as-sa/99-010-x/2011001/tbl/tbl2-eng.cfm#a3

*47% in Toronto

Table 2. Ever Smoker Population Cohorts for Evaluation of Additional Risk Factors

	CPTP	CCHS
Numbers	**48,504**	**71,514**
Male: Female	**46%:54%**	**NA**
Ethnicity **White** **Non-white**	**94%** **6%**	**NA**
Current: Ex Smokers	**17%:83%**	**39%:61%**
Education **≤HS** **≥ College**	**28%** **72%**	**52%** **48%**
Projected # lung cancers for analysis in 3 years	**1,000**	**770**

CPTP = Canadian Partnership Tomorrow Generation Project

CCHS = Canadian Community Health Survey

Table 3. Project Organization

International Consortium Co-Directors: Dr. Stephen Lam (Canada)
Dr. Kwun Fong (Australia)

Site	Site Lead Investigator	Radiologist
Vancouver General Hospital	Dr. John Yee	Dr. John Mayo
UQTRC, TPCH, RBWH	Dr Henry Marshall	Dr Karin Steinke
Sydney, NSW	Dr Emily Stone	TBD
Melbourne, VIC	Dr Rene Manser	TBD
Perth, WA	Drs McWilliams/Brims	TBD

Lung Cancer Risk Modeling:

Martin Tammemagi (Brock University, Canada)

John Spinelli (BC Cancer Agency, Canada)

Health Economics:

Luke Conolly, Karen Canfell, and Marianne Weber (Australia)

Sonya Cressman (BC Cancer Agency, Canada)

Martin Tammemagi (Brock University, Canada)

Executive Committee (EC) will be responsible for the overall scientific direction of the Team; it will include the Co-Directors, the site lead investigators, and the project manager. The EC is responsible for strategic planning and monitoring of progress to ensure the study will be completed in a timely manner.

G. Figures

Figure 1. Screen shot of on-line lung cancer risk assessment and lung nodule management tools Available as Apps from Apple Store. Android versions will become available as well.

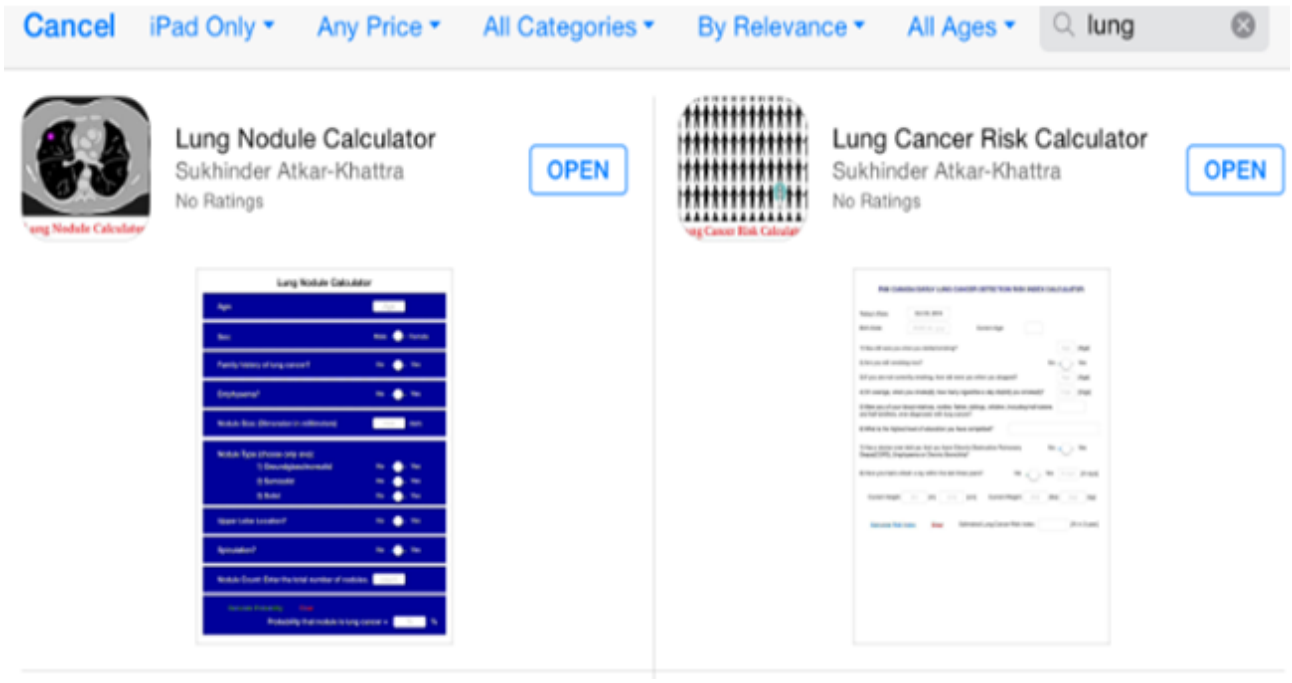
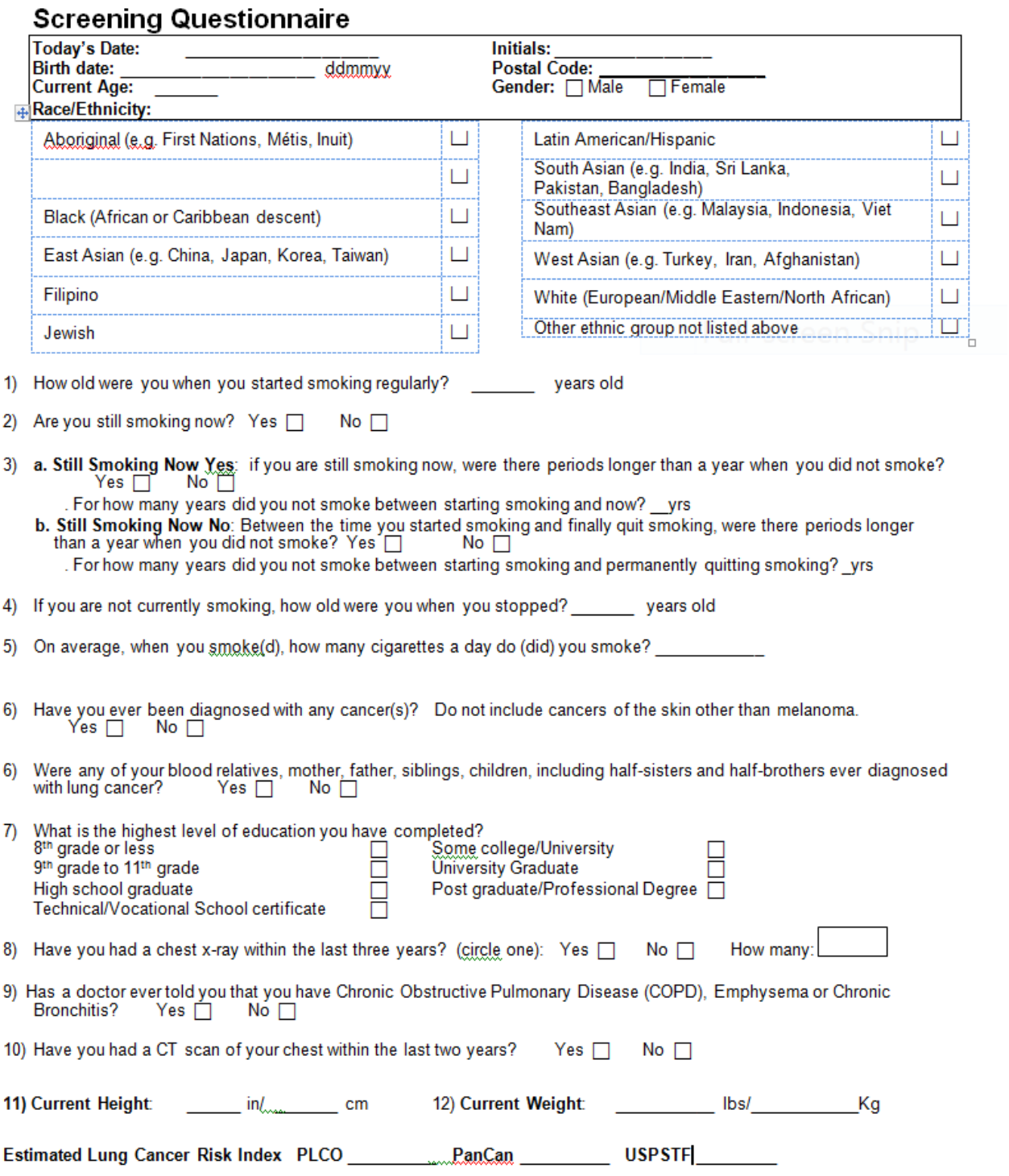


Figure 2. Updated Web based risk assessment tool for LDCT screening study recruitment



Screening Questionnaire

Today's Date: _____ **Initials:** _____
Birth date: _____ ddmmyy **Postal Code:** _____
Current Age: _____ **Gender:** ☐ Male ☐ Female
Race/Ethnicity:

Aboriginal (e.g. First Nations, Métis, Inuit)	☐	Latin American/Hispanic	☐
	☐	South Asian (e.g. India, Sri Lanka, Pakistan, Bangladesh)	☐
Black (African or Caribbean descent)	☐	Southeast Asian (e.g. Malaysia, Indonesia, Viet Nam)	☐
East Asian (e.g. China, Japan, Korea, Taiwan)	☐	West Asian (e.g. Turkey, Iran, Afghanistan)	☐
Filipino	☐	White (European/Middle Eastern/North African)	☐
Jewish	☐	Other ethnic group not listed above	☐

1) How old were you when you started smoking regularly? _____ years old

2) Are you still smoking now? Yes ☐ No ☐

3) **a. Still Smoking Now Yes**: if you are still smoking now, were there periods longer than a year when you did not smoke?
Yes ☐ No ☐
. For how many years did you not smoke between starting smoking and now? __yrs
b. Still Smoking Now No: Between the time you started smoking and finally quit smoking, were there periods longer than a year when you did not smoke? Yes ☐ No ☐
. For how many years did you not smoke between starting smoking and permanently quitting smoking? _yrs

4) If you are not currently smoking, how old were you when you stopped? _____ years old

5) On average, when you smoke(d), how many cigarettes a day do (did) you smoke? _____

6) Have you ever been diagnosed with any cancer(s)? Do not include cancers of the skin other than melanoma.
Yes ☐ No ☐

6) Were any of your blood relatives, mother, father, siblings, children, including half-sisters and half-brothers ever diagnosed with lung cancer? Yes ☐ No ☐

7) What is the highest level of education you have completed?

8th grade or less	☐	Some college/University	☐
9th grade to 11th grade	☐	University Graduate	☐
High school graduate	☐	Post graduate/Professional Degree	☐
Technical/Vocational School certificate	☐		

8) Have you had a chest x-ray within the last three years? (circle one): Yes ☐ No ☐ How many: ☐

9) Has a doctor ever told you that you have Chronic Obstructive Pulmonary Disease (COPD), Emphysema or Chronic Bronchitis? Yes ☐ No ☐

10) Have you had a CT scan of your chest within the last two years? Yes ☐ No ☐

11) Current Height: _____ in/_____ cm 12) **Current Weight**: _____ lbs/_____Kg

Estimated Lung Cancer Risk Index PLCO _____ **PanCan** _____ **USPSTF**_____

Figure 3. Lung-RADs Classification (http://www.acr.org/Quality-Safety/Resources/LungRAD**)**

Lung-RADS for nodules at baseline	Findings	Management
Category 1	Nodules with benign calcification pattern	LDCT 12 mo
Category 2	Solid nodule <6mm	
	Part-solid nodule <6mm total diameter	
	Non-solid nodule <20mm	
Category 3	Solid nodule ≥6mm to <8mm	LDCT 6 mo
	Part-solid nodule ≥6mm total with solid core <6mm	
	Non-solid nodule ≥20mm	
Category 4A	Solid nodule ≥8mm to <15mm	LDCT 3 mo / PET-CT
	Part-solid nodule ≥6mm with solid core ≥6mm to <8mm	
Category 4B	Solid nodule ≥15mm	contrast CT / PET-CT / biopsy
	Part-solid nodule with solid core ≥8mm	

Figure 4: PanCan lung nodule risk calculator versus Lung-RADs

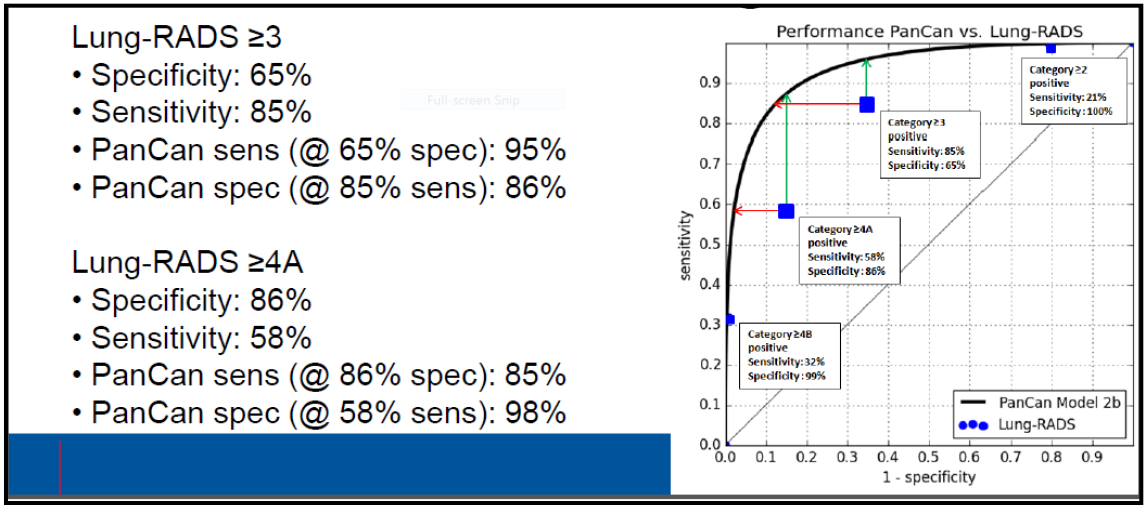
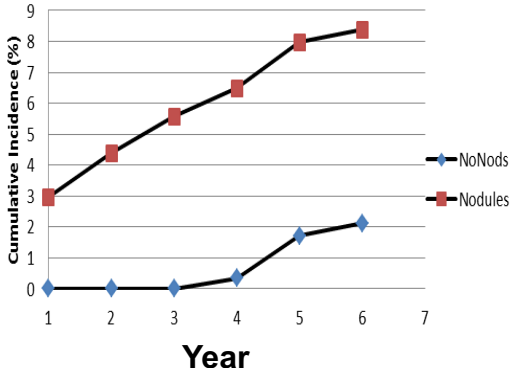
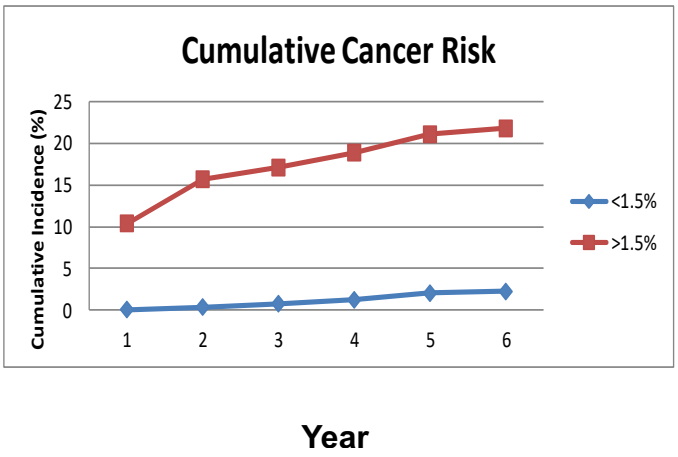


Figure 5: Different Lung Cancer Risks Depending on Nodule vs No nodule or Nodule Risk Score (Data from Pan-Canadian Early Detection of Lung Cancer Study). The results suggest annual screening is not needed in those without lung nodules or nodules with low malignancy risk



No Nodule ≥1mm:23% cohort



<1.5% Risk Score:78% cohort

Figure 6 & 7 in Section C1

Figure 8. Sample Standardized Report

Name	3348
Sex	F
Age	60
ID	3348
Visit	Visit 3
CT Scan Date	Nov 30, 2009
Signed off by	Vancouver-user
Comments	

LungRADS Assessment Category 2 based on nodule ID 2. Management: continue annual screening with LDCT in 12 months

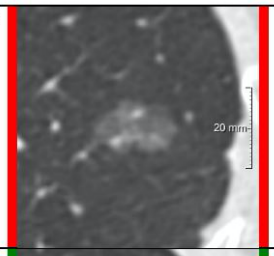
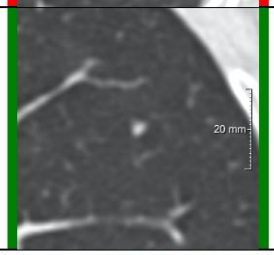
			Finding	Baseline Dec 10, 2007	Visit 2 Jan 07, 2009	Visit 3 Nov 30, 2009	Comments
1			Location	Slice 58	Slice 58	Segment L1/2, Slice 62	
			Status	New	Old	Old	
			Result		Growing	Growing	
			Type	GroundGlassOpacity	GroundGlassOpacity	GroundGlassOpacity	
			Equivalent Diameter	13.0 mm	16.3 mm	17.7 mm	
			Mass	348.2 mg	626.4 mg	886.5 mg	
			Axis long/short	14.4 / 10.4 mm	20.3 / 13.3 mm	23.6 / 12.6 mm	
			Description			Well defined	
			Volume doubling time		401 d	941 d	
			Mass doubling time		465 d	653 d	
			Malignancy probability	12.54%	23.08%	43.83%	
2			Location	Slice 107	Slice 109	Slice 118	
			Status	New	Old	Old	
			Result		Smaller	Growing	
			Type	Solid	Solid	Solid	
			Equivalent Diameter	3.5 mm	3.3 mm	3.6 mm	
			Mass	12.0 mg	12.7 mg	16.1 mg	
			Axis long/short	2.8 / 1.1 mm	3.8 / 3.1 mm	3.8 / 2.7 mm	
			Description				
			Volume doubling time		-1873 d	988 d	
			Mass doubling time		4817 d	955 d	
			Malignancy probability	0.06%	0.23%	0.23%	
		Lymph Node Involvement	Present	No	No	No	
		Coronary Artery Calcification	LMLAD	None	None	None	
			CIR	None	None	None	
			RCA	None	None	None	
Emphysema		Extent	Mild (5-25%)	Trivial (<5%)	Mild (5-25%)		
		Type	Centrilobular	Centrilobular	Centrilobular		
		Distribution	Diffuse	Diffuse	Diffuse		
Airway Wall Thickening		Present	No	No	No		

Figure 9. Increasing severity of emphysema detected by CT scan

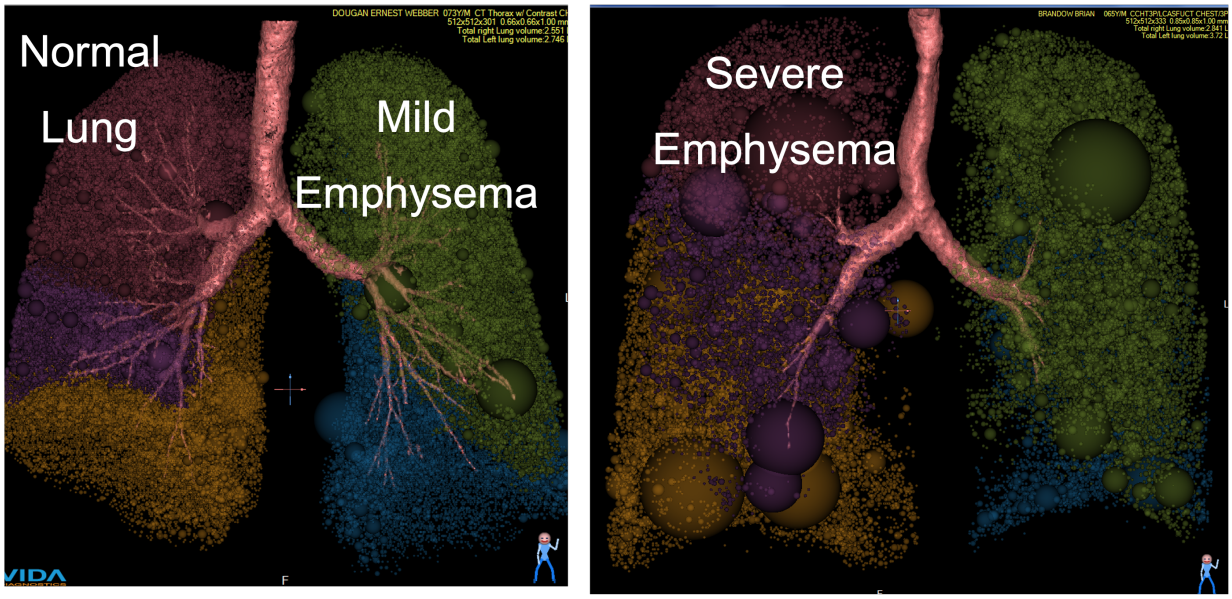


Figure 10. Lung nodule detected by screening CT Scan (arrow)

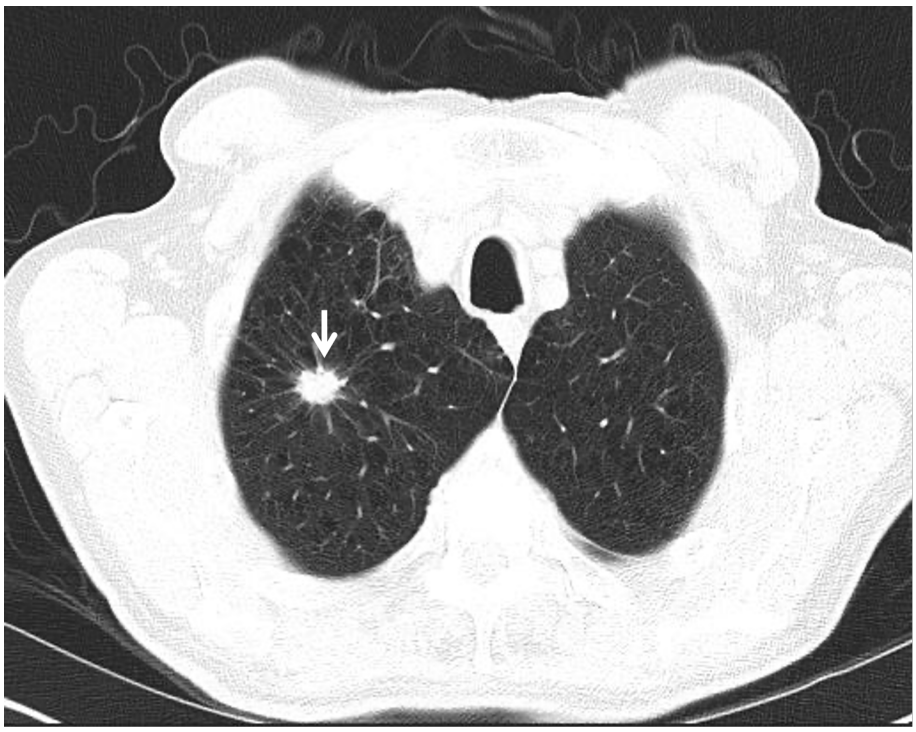
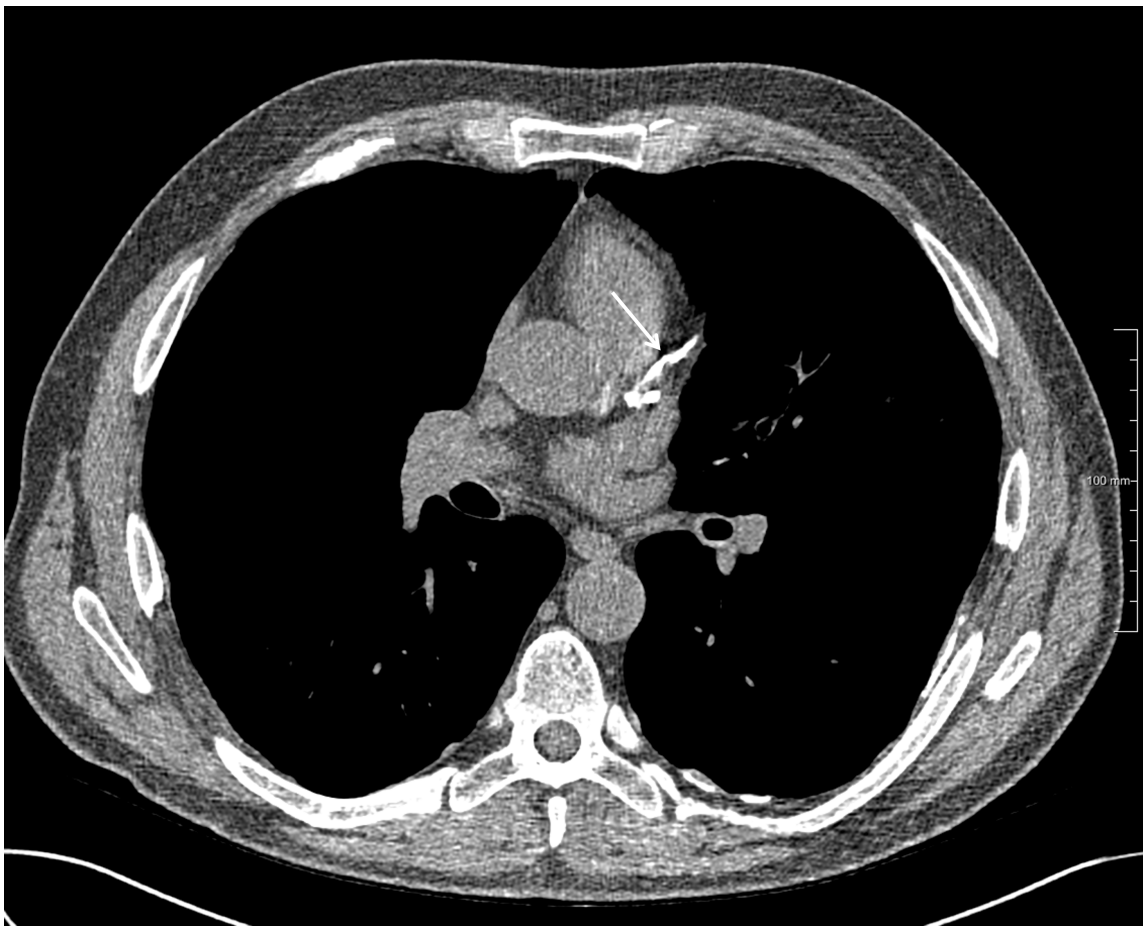


Figure 11. Coronary artery calcification found on CT Scan (arrows)



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