Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series #15-10

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Screening High-Risk Populations for Lung Cancer

H. Roberts, C. Walker-Dilks, K. Sivjee, Y. Ung, K. Yasufuku, A. Hey, N. Lewis, and the Lung Cancer Screening Guideline Development Group

Report Date: April 18, 2013

EBS 15-10 is comprised of 3 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1436

Section 1:	**Guideline Recommendations**
Section 2:	**Evidentiary Base**
Section 3:	**Development Methods, Recommendations Development and External Review Process**

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Roberts H, Walker-Dilks C, Sivjee K, Ung Y, Yasufuku K, Hey A, et al. Screening high-risk populations for lung cancer. Toronto (ON): Cancer Care Ontario; 2013 April 18. Program in Evidence-based Care Evidence-Based Series No.: 15-10.

Journal Citation (Vancouver Style): Roberts H, Walker-Dilks C, Sivjee K, Ung Y, Yasufuku K, Hey A, et al. Screening high-risk populations for lung cancer: guideline recommendations. J Thorac Oncol. 2013 Oct;8(10):1232-7.

Evidence-Based Series #15-10

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Screening High-Risk Populations for Lung Cancer

Table of Contents

Evidence-Based Series #15-10: Section 1

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Screening High-Risk Populations for Lung Cancer: Guideline Recommendations

H. Roberts, C. Walker-Dilks, K. Sivjee, Y. Ung, K. Yasufuku, A. Hey, N. Lewis, and the Lung Cancer Screening Guideline Development Group

Report Date: April 18, 2013

BACKGROUND

Lung Cancer and Screening

Lung cancer is the most common cause of cancer death in Ontario. Contributing to the high mortality rate is a lack of an effective evidence-based screening method. Utilizing the two tests commonly used to screen for lung cancer, chest radiography (CXR) and sputum cytology, has not demonstrated a reduction in mortality. Screening for lung cancer using low-dose computed tomography (LDCT) has been the subject of research studies since the 1990s (1-3). In the intervening years, much has been learned about the detection of lung nodules using LDCT, the characterization of early lung cancers, and, more recently, the effect of LDCT on disease-specific mortality. The National Lung Screening Trial (NLST) compared LDCT with CXR in high-risk populations and found a 20% reduction in lung cancer mortality at 6 years with LDCT after an initial scan and two annual rounds of screening (4). The NLST is the first randomized controlled trial (RCT) to show a mortality benefit with lung cancer screening.

Some knowledge gaps still exist regarding the use of LDCT for lung cancer screening including the balance of benefit and harm, the optimal group of at-risk individuals to screen, the frequency and duration of screening, and the cost-effectiveness across various health environments. Thus, LDCT screening is not yet part of the standard of care, and no formal process currently exists in Ontario for lung cancer screening. However, physicians and patients are aware of the technique, and it has begun to be used without official guidelines. Injudicious use of LDCT can potentially cause more harm than benefit, including exposure of healthy persons to ionizing radiation and subsequent invasive procedures for ultimately benign lesions. When used correctly, however, LDCT screening has the potential to save lives.

Population-based Screening Programs

CCO uses the following criteria in deciding whether or not to recommend to the government that a publicly funded, organized population-based screening program be implemented:

- Burden of disease
- Clinical effectiveness and safety of screening
    - Short-term benefits (effectiveness and safety) of screening should outweigh harms

    - Long-term benefits (effectiveness and safety) of screening should outweigh harms
- Screening tests are acceptable to individuals
- Cost effectiveness
- Resource availability (e.g., system capacity required to implement screening; system capacity required to support diagnostic testing for individuals with an abnormal screening test result; resources required to implement quality assurance for every component of the screening pathway)

Purpose of this Guideline

Guidelines on the appropriate use of LDCT for lung cancer screening are urgently needed for physicians and patients to avoid the ad hoc adoption of LDCT screening for lung cancer by hospitals and diagnostic centres and to minimize the risks associated with LDCT scanning (e.g., false positives leading to unnecessary invasive follow-up, overdiagnosis, and increased radiation exposure). This guideline focuses on clinical effectiveness and safety considerations. Specifically, this guideline provides advice on the use of LDCT screening for lung cancer, including the definition of a population at risk, the definition and follow-up of a positive scan result, and the duration and interval of screening. Beyond the scope of this guideline are several key issues, including: acceptability of LDCT to individuals, feasibility of implementing LDCT, cost-effectiveness of LDCT screening, an analysis of resource availability, high prevalence of lung nodules in the target population (high false-positive rate), and definition of a "positive" screening result. These and other issues will need to be addressed by CCO.

In the guideline development process, evidence from existing trials and guidelines from relevant organizations have been reviewed. Wherever possible, information collected has been applied to the Ontario environment. Where there are discrepancies in the literature (e.g., the definition of high risk), the panel arrived at a consensus. Where there is insufficient evidence in the literature (e.g., overall duration of screening), recommendations have been based on the Working Group's best judgement at the current time, and adjustments may be made when new evidence is available.

The supporting evidence for this guideline is primarily contained in a systematic review from a collaboration of the American Cancer Society, the American College of Chest Physicians, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network (5). Data from the original publications of the primary studies were extracted when details not reported in the systematic review were required to address specific questions in the current guideline.

GUIDELINE OBJECTIVES

To determine the appropriate use, if any, of LDCT in the screening of high-risk populations for lung cancer, including:

Patient considerations

- Patient characteristics that define a high-risk population

Test considerations

- The necessary elements involved in defining a positive result on LDCT and follow-up of a positive result
- The appropriate screening interval
- The appropriate screening duration

Structural considerations that affect effectiveness and safety

- Organized versus opportunistic screening

TARGET POPULATION

Men and women considered at high risk for lung cancer based on their age and smoking history.

INTENDED USERS

This guideline is intended for provincial policy makers, primary care physicians, nurse practitioners, radiologists, respirologists, thoracic surgeons, thoracic oncologists, and any health professionals involved with patients who may be at risk for developing lung cancer.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Screening High-risk Populations for Lung Cancer:

The Working Group is in favour of screening high-risk individuals for lung cancer with LDCT. The primary evidence base for this proposal is the NLST, a large (>50,000 participants) RCT that compared LDCT screening with CXR and showed a 20% decrease in death from lung cancer in high-risk persons (4).

The primary benefit associated with LDCT screening is a statistically significant reduction in mortality, both lung cancer specific and all cause. LDCT can identify smaller nodules than can CXR and thus can detect lung cancer at an earlier stage when a cure is more possible. Under current circumstances, most lung cancer patients are diagnosed at an advanced stage, and lung cancer accounts for more than a quarter of all cancer deaths (6).

LDCT screening is not without risk. CT scanning, with its acquisition of multiple images, exposes an individual to a greater radiation dose than does CXR and may place patients at increased risk of lung and breast cancer. Based on models from official bodies and commissioned studies of estimates of harm from radiation, Bach et al estimate using the NLST data that one cancer death may be caused by radiation from imaging per 2500 persons screened (5). The serial CT scans required as part of a screening program necessitate judicious and efficient use of the technology with strict rules pertaining to quality control and training. The information obtained from a CT scan of the chest provides more precise visualization of lung nodules leading to a higher rate of detection of lung nodules. Although the majority of these nodules (>90%) will be benign, the detection of these nodules may lead to further imaging and follow-up that can involve invasive diagnostic procedures and possibly to harmful and unnecessary treatment. Completely addressing the clinical and cost implications of this high false-positive rate [e.g., in the NLST, 27% of scans were positive, and 96% of those were false positive (4)] is critical and remains a challenge. In the interim, the Working Group endorses a strict application of screening to only a high-risk targeted population.

In general, the recommendations below reflect the parameters of the NLST (4). Where there are deviations from those parameters, we provide justification. While there are still ongoing trials comparing LDCT with usual care, none are as large (and therefore as statistically powerful) as the NLST, and it is unlikely that another trial the size of the NLST will be undertaken. Some aspects of the ongoing trials may affect the recommendations once their results are known, and we have qualified our recommendations to acknowledge these uncertainties.

RECOMMENDATIONS AND SPECIFIC EVIDENCE

Main Recommendation

Recommendation 1: Screening for lung cancer with LDCT is recommended in high-risk populations defined as persons 55 to 74 years of age with a minimum smoking history of ≥30 pack-years* who currently smoke or have quit within the past 15 years and are disease free at the time of screening.

*Pack-years = number of cigarette packs smoked per day x the number of years smoked.

Key Evidence

- Among the studies in the collaborative review, the age for initiation of screening ranged from 47 to 60 years in the RCTs and from 40 to 60 years in the single-arm studies (5).
- The upper age for screening ranged from 69 to 80 years in the RCTs and 73 to 85 years in the single-arm studies (5). The NLST initiated screening in persons ≥55 years of age and stopped at age 75 years (4).
- The minimum smoking history in the RCTs ranged from ≥15 to ≥30 pack-years, and in the single-arm studies from ≥10 to ≥20 pack-years (5). The NLST enrolled persons with a smoking history of ≥30 pack-years and former smokers who had quit within the previous 15 years (4).
- Seven RCTs reported previous cancer history in the eligibility criteria, stipulating a minimum numbers of years disease free since a previous cancer diagnosis. These ranged from 5 years to an indefinite period with variations for different types of cancers. Among 11 single-arm studies, this criterion was described as a minimum of 5 years since a previous cancer diagnosis, any previous lung cancer, any known pulmonary metastases, and any previous cancer diagnosis (5). In the NLST, exclusion criteria were a previous diagnosis of lung cancer, a previous diagnosis of other cancer within the previous 5 years, chest CT scan within 18 months before enrollment, haemoptysis, or unexplained weight loss >6.8 kg in the preceding year (4).

Justification

- There is no evidence to support a specific age to initiate screening, a specific age to cease screening, or a specific screening-frequency interval. The highest quality and most compelling evidence is from the NLST. As such, the parameters used in this trial were endorsed by the Working Group as clinically reasonable. Patient acceptability, cost-effectiveness, feasibility, and system capacity may influence whether or not these parameters are reasonable and implementable.
- Smoking history is a subjective risk factor, and we acknowledge that it cannot be precisely measured. If smoking is begun in early adulthood (i.e., early 20s) as it commonly is, by age 50 to 55, most people will have exceeded 20 pack-years. Although the NLST enrolled participants with a minimum smoking history of 30 pack-years, several other studies used a threshold of 20 pack-years or less. These studies had lung cancer detection rates similar to those of the NLST. It is anticipated that an increased detection rate would lead to a mortality reduction. The Working Group agreed on a 30 pack-year smoking history threshold to recommend lung cancer screening, aligning with that study entry criterion in the NLST. The panel will update this recommendation when the results of the NELSON trial (which had a 15 pack-year requirement) are published.
- It is reasonable to define the screening population by age and smoking history, but there is currently insufficient evidence to include participants based on other risk

factors such as family history, passive smoking, occupational exposure, radon exposure, previous cancer, and other diseases.

Qualifying Statements

Screening may be a reasonable option in persons with a smoking history of <30 pack-years. However, as this risk group was not included in the NLST, an explicit recommendation in favour of screening such persons cannot be made at this time. A current trial (NELSON) includes patients with a minimum smoking history of 15 pack-years and may provide additional data to determine the minimum smoking history appropriate for screening.

Defining a Positive Result on LDCT and Follow-up of a Positive Result

Recommendation 2: Positive Result and Follow-up

- **Screening modality: Screening for lung cancer should be done using an LDCT multi-detector scanner with the following parameters: 120 to 140 peak kilovoltage (kVp), 20 to 60 milliampere seconds (mAs), with an average effective dose ≤1.5 millisieverts (mSv).**
- **Collimation should be ≤2.5 mm.**
- **Definition of a positive result: A nodule size of ≥5 mm found on LDCT indicates a positive result and warrants a 3-month follow-up CT. Nodules ≥15 mm should undergo immediate further diagnostic procedures to rule out definitive malignancy.**
- **Appropriate follow-up of a positive result: Follow-up CT of a nodule should be done at 3 months as a limited LDCT scan (i.e., only a slab covering the nodule will be scanned, not the entire chest). The Lung Cancer Diagnosis Pathway should be consulted for guidance on clinical work-up.**

Key Evidence

- Most of the studies published since 2008 used multi-detector CT scanners. The voltage ranged from 100 to 140 kVp, with all but one study using 120 to 140 kVp. The current ranged from 20 to 100 mAs, with all but one study not exceeding 60 mAs. The average effective dose was reported in 5 studies and ranged from 0.6 to 1.5 mSv (5). The NLST used multi-detector scanners with a minimum of 4 channels, 120 to 140 kVp, 20 to 30 mAs, and an average effective dose of 1.5 mSv (4).
- Among the studies, collimation ranged from 0.75 to 10 mm (5). Collimation in the NLST was ≤2.5 mm (4).
- Nodule size found on LDCT warranting further investigation ranged from a minimum size of any diameter to a maximum of >15 mm (5). In the NLST, nodules measuring ≥4 mm received further work-up (4).
- Nine studies defined tumour growth. Growth can be determined with calliper measurements of diameter (6 studies) or 3-dimensional volume measurements (4 studies). One RCT and one single-arm study described significant growth as an increase in tumour diameter of ≥1 mm. Three single-arm studies described significant growth as an increase in diameter in at least 1 dimension. Two RCTs described growth as a change in tumour volume of ≥25%. One single-arm study defined growing lesions as those with volume-doubling time between 30 and 400 days, and another used tumour volume and time between high-resolution CT scans to calculate doubling time (5). A definition of growth was not reported in the NLST.

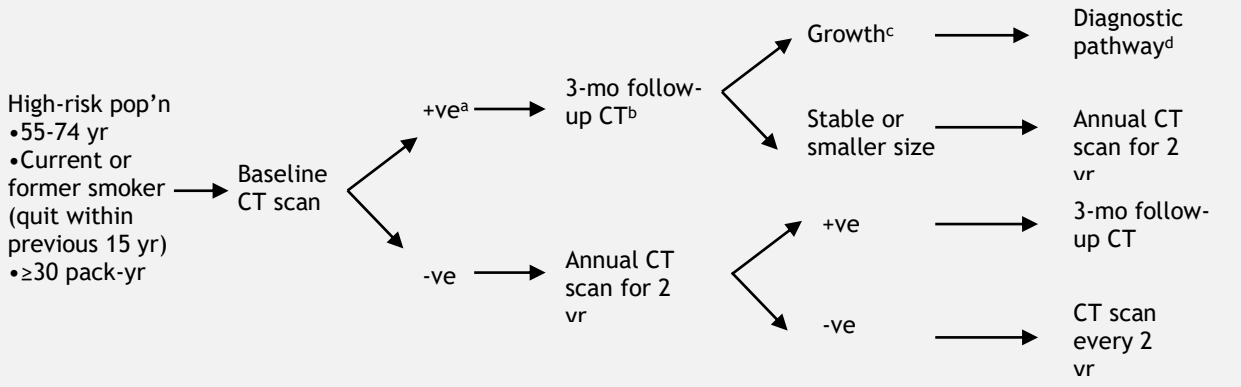
- Guidance on the presentation and clinical work-up of a lung cancer diagnosis is detailed in the CCO Lung Cancer Diagnosis Pathway (7).

Justification

- For screening modality, the parameters listed in the recommendations are derived from the NLST and ongoing studies.
- With respect to collimation, newer scanners are able to provide 1-mm collimation with a short breath-hold time, but a large amount of images are produced making scrolling and reading cumbersome. At the current time, the collimation used in the NLST is recommended.
- With respect to nodule size warranting further investigation, the recommendation deviates from the parameters of the NLST. In general, the smaller the nodule that defines a positive scan, the larger the number of positive scans, and the larger the number of false-positive results and unnecessary investigations for benign nodules. Based on a 4-mm threshold, 7191 of 26,309 (27.3%) scans in the NLST were positive; 6921 (96%) of the positive results were false positive. A 5-mm threshold will lower the rate of false-positive results, and if nodules between 4 and 5 mm are assessed on an annual scan, it is unlikely a significant finding will be missed. A prospective study of 1035 high-risk individuals found that nodules <5 mm identified by LDCT could be safely monitored at 1-year intervals (8). A retrospective study of two cohorts of patients (n=1000 and n=1897) determined that had no immediate attention been given to nodules between 3 and 5 mm until the first annual repeat screening, immediate further work-up would have been recommended in only 13% of patients rather than the 28% that received diagnostic interventions (9). Raising the threshold for a positive scan from a diameter of 4 mm to a diameter of 5 mm will help lower the false-positive rate without sacrificing the early detection of curable lung cancers. A recent study has suggested that increasing the threshold for a positive scan to 7 or 8 mm may decrease further work-up without delaying diagnosis (10). This will be revisited in future versions of this guideline when more information becomes available.
- The recommended follow-up is based on common standard of care actions in the presence of positive findings. Short-term follow-up CT scans are recommended in the event of a positive-screening CT scan to assess the growth of a parenchymal nodule. These CT scans do not need to cover the entire chest; it is sufficient to limit the scan to the location of a nodule (i.e., a slab of a few centimetres covering the location of the nodule). This can substantially decrease the radiation exposure to the patient.

LDCT Screening Interval

Recommendation 3: Persons at high risk for lung cancer should commence screening with an initial LDCT scan followed by annual screens for 2 consecutive years, and then once every 2 years after each negative (-ve) scan.



[a]A positive (+ve) test is defined as a solid nodule ≥5 mm or a non-solid nodule (part solid or ground glass) ≥8 mm.
[b]If the nodule appearance dictates a different approach (e.g., bronchoscopy or PET), this can be chosen at the discretion of the reading physician.
[c]Doubling time of between 30 and 400 days.
[d]Lung Cancer Diagnosis Pathway (7).

Key Evidence

- LDCT was done on an annual basis in 18 studies; on years 1, 2, and 4 in one study; every 6 months in one study; and after 2 years in one study (5). The NLST conducted LDCT screens annually for 3 years (4).
- The MILD trial did not demonstrate a shift to higher stage disease with biennial screening compared with annual screening. Of 49 lung cancers, 20 were detected in the biennial group and 29 in the annual group (11).

Justification

- The current evidence stems from research studies on lung cancer screening, which by definition have a beginning and an end (e.g., in the case of the NLST, three rounds of screening). This guideline, however, extends this evidence to a screening program, which does not have a defined end. The annual to biennial approach is based on best evidence balancing expected benefit from regular scanning with accumulated harms from costs, radiation, and burden on the health care system.
- The current evidence is not sufficient to confirm the benefit of a specific screening interval. The recommendation of annual screening for 3 years is subject to change when longer term trial evidence or further stratification methods become available from the NELSON trial.

Organized Versus Opportunistic Screening

The decision to implement an organized, population-based screening program involves many factors, not just the existence of supportive RCT clinical evidence. However, because the benefit of screening to date has only been demonstrated in the context of an organized screening effort (i.e., a randomized clinical trial that compared two types of screening

technology), it is the opinion of the Working Group that screening should be conducted in a manner similar to the NLST trial: that is, in an organized fashion. The ASCO guideline [(5) supplementary online content] also supports screening of high-risk individuals, but only in the settings that can deliver comprehensive care such as that provided to NLST participants. The NLST authors themselves advise restraint in contemplating lung cancer screening recommendations on the basis of the NLST findings claiming the need for rigorous analysis of the cost-effectiveness of LDCT, and the weighing of the reduction in mortality against the harms of positive screening results, overdiagnosis, and cost (4). However, we are aware that these issues would be examined by provincial policy makers before screening policy decisions were made and approved.

Because of the potential harms that may arise with LDCT screening done contrary to the recommendations above, a program is required that explicitly describes the target population that will benefit the most, the referral process, the frequency and duration of screening, the locations where screening may take place, the personnel involved in performing and interpreting the scans, and the precise criteria that define a positive scan. The inclusion of smoking-cessation counseling within the screening program is crucial. If elements of data collection and monitoring, quality assurance, and evaluation are built into the screening program from the start, it can be modified while in operation.

Opportunistic screening takes the form of CT scans applied to individuals who are asymptomatic, may not qualify for the test, or are referred on an ad hoc basis outside of a programmatic structure. These scans often include contrast, are not done with the low-dose technique, and lack appropriate follow-up of detected lung nodules. This type of screening results in unnecessarily high radiation to the individual, potential side effects from contrast, and invasive procedures for potentially benign lesions. The Working Group believes strongly that screening outside a centre with experience and expertise in identifying the high-risk population, interpreting results and counselling patients, and performing the appropriate diagnostic techniques is ill advised. Such ad hoc screening will lead to an increase in the false-positive rate and in peri-procedure morbidity and mortality, and will threaten to mitigate some or all of the benefits of the screening process.

Next Steps

The Lung Cancer Screening Working Group believes that the benefits of screening high-risk populations for lung cancer with LDCT outweigh the harms. The benefits stem from the documented improvement in mortality observed in the NLST showing that LDCT can not only detect small, early-stage lung cancers, but it can also facilitate curing an individual of lung cancer. The harms stem from the investigation itself (radiation exposure) and the sequelae from the false-positive results (detection of lung nodules that ultimately turn out to be benign), and the risk associated with diagnostic evaluation [in the NLST, the frequency of death within 60 days of a diagnostic evaluation was 8 per 10,000 individuals screened by LDCT and 5 per 10,000 screened by CXR (4)].

We address the concern over radiation exposure by recommending a low-dose regimen and by increasing the screening interval to every 2 years after three negative annual scans. We also suggest that the follow-up CT of a suspicious nodule be done as a limited scan to further reduce the radiation exposure.

We address the impact of false-positive results by the definition of a positive CT scan: we intentionally deviated from the parameters of the NLST in this instance. In the NLST, the threshold for a positive result was a nodule ≥4 mm in diameter. At baseline, >27% of the screening tests were positive and 96% of those were false-positive results. By increasing the threshold of a positive test to 5 mm, the rate of positive baseline scans can be reduced to

<20% while still detecting early-stage, curable lung cancers. We also recommend a follow-up algorithm of CT-detected nodules that is simple and straightforward based on size and growth, and results in an extremely low rate of invasive procedures for benign lesions (12).

Lung cancer screening with LDCT is recommended and can be most effectively and safely offered through an organized screening program and administered by specialized centres with multidisciplinary care teams.

To determine whether or not a population-based screening program is appropriate for Ontario will require the CCO Prevention and Cancer Control division to investigate the other criteria relevant to the decision-making process. Priorities include:

- Safety and effectiveness (long-term)
- Cost effectiveness
- Resources available

JOURNAL REFERENCE

A practice guideline has been published in the peer-reviewed journal, *Journal of Thoracic Oncology* (http://journals.lww.com/jto/pages/default.aspx):

- Roberts H, Walker-Dilks C, Sivjee K, Ung Y, Yasufuku K, Hey A, et al. Screening high-risk populations for lung cancer: guideline recommendations. J Thorac Oncol. 2013 Oct;8(10):1232-7.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Updating

All PEBC documents are maintained and updated as described in the PEBC Document Assessment and Review Protocol at http://www.cancercare.on.ca/.

Contact Information

For information about the PEBC and the most current version of all reports,
please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail:ccopgi@mcmaster.ca

REFERENCES

1. Naidich DP, Marshall CH, Gribbin C, Arams RS, McCauley DI. Low-dose CT of the lungs: preliminary observations. Radiology. 1990;175(3):729-31.
2. Kaneko M, Eguchi K, Ohmatsu H, Kakinuma R, Naruke T, Suemasu K, Moriyama N. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology. 1996;201(3):798-802.
3. Mori K, Tominaga K, Hirose T, Sasagawa M, Yokoyama K, Moriyama N. Utility of low-dose helical CT as a second step after plain chest radiography for mass screening for lung cancer. J Thorac Imag. 1997;12(3):173-80.
4. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409.
5. Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry D, Brawley OW, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA. 2012;307(22):2418-29.
6. Canadian Cancer Society, National Cancer Institute of Canada. Canadian Cancer Statistics 2012. Toronto (Canada): National Cancer Institute of Canada; 2012.
7. Cancer Care Ontario Disease Pathway Management Secretariat. Lung Cancer Diagnosis Pathway. Version 2012.2 [cited July 2012]. Available from: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=124606
8. Bellomi M, Veronesi G, Rampinelli C, Ferretti S, De Fiori E, Maisonneuve P. Evolution of lung nodules < or =5 mm detected with low-dose CT in asymptomaticsmokers. Br J Radiol. 2007;80(957):708-12.
9. Henschke CI, Yankelevitz DF, Naidich DP, McCauley DI, McGuinness G, Libby DM, et al. CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. Radiology. 2004 ;231(1):164-8.
10. Henschke CI, Yip R, Yankelevitz DF, Smith JP; International Early Lung Cancer Action Program Investigators. Definition of a positive test result in computed tomography screening for lung cancer: a cohort study. Ann Intern Med. 2013 Feb19;158(4):246-52.
11. Pastorino U, Rossi M, Rosato V, Marchianò A, Sverzellati N, Morosi C, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. Eur J Cancer Prev. 2012;21(3):308-15.
12. Wagnetz U, Menezes RJ, Boerner S, Paul NS, Wagnetz D, Keshavjee S, Roberts HC. CT screening for lung cancer: implication of lung biopsy recommendations. AJR Am J Roentgenol. 2012;198(2):351-8.

Evidence-Based Series #15-10: Section 2

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Screening High-Risk Populations for Lung Cancer: Evidentiary Base

H. Roberts, C. Walker-Dilks, K. Sivjee, Y. Ung, K. Yasufuku, A. Hey, N. Lewis, and the Lung Cancer Screening Guideline Development Group

Report Date: April 18, 2013

OBJECTIVE

To determine the appropriate use, if any, of low-dose computed tomography (LDCT) in the screening of high-risk populations for lung cancer, including:

- Patient characteristics that define a high-risk population
- The necessary elements involved in defining a positive result on LDCT and follow-up of a positive result
- The appropriate screening interval
- Organized versus opportunistic screening

INTRODUCTION

Screening is a process that is intended to detect a disease or a condition in apparently healthy people. Screening is performed to detect disease in its early stages, before symptoms are present, when the condition or disease is more easily treatable. A screening test is not a diagnostic test, and positive screening test results must be confirmed by definitive diagnostic tests followed by treatment of confirmed cases.

The benefits of screening include mortality reduction through early detection and treatment of disease in asymptomatic individuals, and the use of interventions that are usually easier and less expensive to perform than are diagnostic interventions. The harms of screening include incorrectly identifying people as having the condition when they do not (false positives), detecting relatively indolent disease that would not cause problems during a person's lifetime (overdiagnosis), and not detecting disease when it is present (false negatives) (Table 1). These are substantial concerns, as incorrect identification may lead to anxiety and unnecessary investigations and potentially hazardous treatment resulting from false positives and overdiagnosis, and missed opportunities for early treatment resulting from false negatives.

Table 1. Relation between screening test result and presence of cancer.

		Cancer present	
		Yes	No
Screening test result	Positive	a	b
	Negative	c	d

a) True positive: those with a positive screening test and confirmed cancer
b) False positive: those with a positive screening test and no confirmed cancer
c) False negative: those with a negative screening test and confirmed cancer
d) True negative: those with a negative screening test and no confirmed cancer

Screening may be conducted in an ad hoc, opportunistic fashion, or through an organized program. Opportunistic screening is often the result of a single patient request or physician recommendation made during a routine medical consultation for unrelated conditions or on the basis of a possible increased risk for developing the disease of interest. Opportunistic screening does not involve systematically inviting the whole target population. It does not allow for evaluation of the benefits and possible harms of the screening intervention, and is more likely to result in variability in the participants' characteristics and the quality of the screening process (1,2). In the case of lung cancer screening, opportunistic screening may involve the use of higher-than-necessary doses of radiation or intravenous contrast enhancement with CT scans, or the nonsystematic follow-up of nodules resulting in potentially unnecessary invasive procedures for ultimately benign lesions.

Organized screening generally targets asymptomatic people in a specific age range or in a specific high-risk group. Screening programs should only be implemented when there is good evidence of reduced cancer-specific mortality, and the benefits of screening outweigh the harms. Screening programs usually include specific mechanisms (e.g., invitations) to encourage participation and follow-up if necessary.

Ontario currently operates screening programs for three types of cancers: colorectal, breast and cervical. Cancer Care Ontario collects fecal occult blood test, mammogram, and cervical screening data provincially. No screening program currently exists for lung cancer.

BACKGROUND

Lung cancer is the leading cause of cancer death in Canada, and it is estimated there will be 25,600 new cases and 20,100 deaths from lung cancer in 2012 (3). In Ontario, there were 6200 lung cancer deaths in 2007 with a death rate (per 100,000) of 39.7, compared with death rates for the three other most common cancers: prostate 19.8, colon and rectum 19.0, and breast 12.1 (4). About 75% of lung cancer patients are diagnosed at stage III or stage IV (5). Screening helps identify cancer earlier than disease symptoms normally present and offers the potential for curative treatment. However, screening may also detect non-malignant abnormalities or tumours that will not progress within a patient's lifetime, causing anxiety and may result in unnecessary aggressive treatment. The two tests commonly used to screen for lung cancer have been chest radiography (CXR) and sputum cytology, but a reduction in lung cancer mortality has not been demonstrated with utilization of these tests. Screening with LDCT increases the detection rate of smaller nodules in the lung, thus offering an opportunity to remove and cure the cancer. Until recently, studies evaluating lung cancer screening generally found that screening increased the early detection rate of lung cancer, but this did not translate into a decrease in mortality. The National Lung Screening Trial (NLST) was the first randomized controlled trial (RCT) to show a reduction in death from lung cancer in persons screened with LDCT (6). Given the encouraging results of the NLST, the implementation of LDCT on a broader scale is inevitable. It is, therefore, important to ensure

that lung cancer screening is implemented in a way that will maximize the lifesaving potential and minimize the harms of screening with LDCT.

This document is intended to provide guidance to health professionals and policy makers on lung cancer screening using LDCT. The advice focuses primarily on determining the target population that would benefit most from screening (i.e., those at high risk of developing lung cancer), providing technical parameters for LDCT imaging and the definition of a positive screening CT, and describing the necessary components for an effective lung cancer screening initiative. For guidance on the presentation and clinical work-up of a lung cancer diagnosis, we refer readers to the CCO Lung Cancer Diagnosis Pathway (7).

METHODS

The primary evidence base for this guideline is contained in a systematic review from a collaboration of the American Cancer Society, the American College of Chest Physicians (ACCP), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) (8). A clinical practice guideline was published in an online supplement to the systematic review and is available on the ASCO website (9). The collaborative systematic review was reviewed by a Research Coordinator from the PEBC and the Working Group of the Lung Cancer Screening Guideline Development Group (Appendix 1). The Working Group considered the collaborative review to be a comprehensive presentation of the current evidence on lung cancer screening in high-risk populations and employed it as the evidence base for this clinical practice guideline. The scores on the Assessment of Multiple Systematic Reviews (AMSTAR) tool (10) for the collaborative systematic review are listed in Appendix 2, and the Appraisal of Guidelines Research and Evaluation (AGREE) II scores (11) are in Appendix 3.

The search strategy used in the systematic review (8) was re-run in MEDLINE and EMBASE in May 2012 to retrieve any studies published since April 2012. A search was also done for relevant abstracts from the ASCO Annual Meeting.

METHODS OF THE COLLABORATIVE REVIEW BY BACH ET AL (8)

Literature Search Strategy

Searches were conducted using MEDLINE (1996 to 1 April 2012), EMBASE (1996 to April 2012), and the Cochrane Library (April 2012). References of relevant papers were reviewed for additional studies. The search strategy combined MeSH and Emtree terms and related text words that described lung cancer, population screening, and LDCT. eAppendix 1 and eAppendix 3 in Bach et al describe the literature search strategy and study selection process.

Study Selection Criteria

Studies were eligible for inclusion if they were RCTs that compared LDCT screening with another form of screening or no screening, or were noncomparative studies in which all participants were screened with LDCT. Outcomes of lung cancer-specific mortality and all-cause mortality were only considered from RCTs. At least one of the following other outcomes of interest had to be included in the LDCT arm of RCTs or a single-arm study to be eligible: mortality from the evaluation of suspected lung cancer, the likelihood of nodule detection at initial screening test and/or at repeat screening, the frequency of invasive diagnostic procedures among those with suspected cancer, the frequency of follow-up imaging tests, and the rate of smoking cessation or smoking re-initiation.

Studies were excluded if the screening population had a primary risk factor other than smoking, if they were published in a language other than English, or if they reported outcomes only in patients diagnosed with lung cancer through screening.

RESULTS OF THE COLLABORATIVE REVIEW BY BACH ET AL (8)

Literature Search Results

The review included three randomized controlled trials (RCTs) comparing LDCT screening with chest radiography (CXR), five RCTs comparing LDCT screening with usual care (no screening), and 13 single-arm studies of LDCT. The number of participants ranged from 190 to 53,454 in the RCTs and from 60 to 5201 in the single-arm studies. The publication years ranged from 2002 to 2011 in the RCTs and from 2001 to 2010 in the single-arm studies. The rate of adherence to screening was high among the RCTs, ranging from 87% to 100% at baseline, 86% to 96% in the first year of screening after baseline (4 trials), and 90% and 90% in the second year of screening (2 trials). Among the cohort studies, adherence to screening ranged from 96% to 100% at baseline, 47% to 97% in year 1 (12 studies), and 20% to 84% in year 2 (6 studies). Several studies are ongoing, and their results were only from the baseline round of screening.

The risk-of-bias quality-criterion elements assessed were: appropriate question, reproducible methodology, adequate randomization, concealed allocation, sufficient sample size, comparable groups, blinding, validated and reliable measures, adequate follow-up, acceptable loss to follow-up, appropriate analyses, accurate results, and conflict of interest. Risk of bias was found to be variable among the RCTs [eTable 1 in Bach et al (8)]. Many of the quality criterion elements were not applicable, such as blinding, or not specified where there was insufficient detail or unknown risk of bias. Among the single-arm studies, the risk of bias was high in many cases, such as not providing justification for the sample size, not declaring a prespecified endpoint, or not reporting the sources of funding. The NLST (6) and Danish Lung Cancer Screening Trial (DLCST) (12) had low risk of bias. The NLST met all quality criterion elements with the exception of concealed allocation, which was not specified. Blinding was deemed not applicable for studies of screening.

Outcomes

The systematic review was designed to conduct a thorough evaluation of LDCT screening. A set of questions was developed with the objective of determining the benefits and harms of LDCT screening:

1. What are the potential benefits of screening individuals at elevated risk of developing lung cancer using LDCT?
2. What are the potential harms of screening individuals at elevated risk of developing lung cancer using LDCT?
3. Which groups are most likely to benefit or not benefit from screening?
4. In what setting is screening likely to be effective?

Benefits

Three of the RCTs reported data on the effect of LDCT screening on lung cancer-specific mortality. The NLST was the largest (n=53,454) of the RCTs identified and included three annual rounds of screening and a median of 78 months of follow-up (6). Patients in the LDCT group had a 20% decrease in lung cancer-specific mortality compared with patients in the CXR group [relative risk (RR) 0.80, 95% CI 0.73 to 0.93, p=0.004]. The number needed to screen (NNS) with LDCT to prevent one death from lung cancer was 320. The ongoing Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular

Essays (DANTE) (13) and DLCST (12) had much smaller sample sizes (n=2811 and n=4104, respectively) and compared five annual rounds of LDCT screening with usual care. At a median follow-up of 34 months, the DANTE trial showed a statistically nonsignificant decrease of 3% in lung cancer-specific mortality with LDCT compared with usual care (RR 0.97, 95% CI 0.71 to 1.32, p=0.84) (13). The DLCST also reported no difference between groups (RR 1.15, 95% CI 0.83 to 1.61, p=0.43) (14). A pooled analysis of the three trials provided a combined odds ratio of 0.82 (95% CI 0.72 to 0.94) [eFigure 4 in Bach et al (8)].

All three trials also reported all-cause mortality. The NLST showed a statistically significant decrease in death from any cause with LDCT screening (RR 0.93, 95% CI 0.86 to 0.99, p=0.02) (6), while the difference between groups in the DANTE trial (RR 0.97, 95% CI 0.80 to 1.20, p=0.84) (13) and the DLCST (RR 1.19, 95% CI 1.01 to 1.40, p=0.059) was not statistically significant (14).

The effect on smoking behaviour was examined in the systematic review because there is concern that a tendency exists with LDCT screening for smokers to continue smoking, and former smokers to return to smoking when screening results are negative. These concerns have been expressed previously in the literature. None of the studies in the systematic review addressed whether public statements regarding the benefits of LDCT affected smokers' behaviours. Of the few studies that examined quit rates or resumption of smoking rates, none showed significant changes in patients screened with LDCT. An analysis of the ELCAP data examined whether consistently negative screening results are associated with less cessation and more relapse over a 6-year period, and found patients who received negative CT scan results had a 28% lower likelihood of achieving point abstinence at one or more follow-ups than did those with a positive result (15). However, the study also found that a consistently negative result was not associated with a reduced long-term smoking abstinence or increased relapse back to smoking.

Harms

Potential harms of LDCT screening identified in the systematic review included the high rate of noncancerous nodule detection (false-positive results) (90% to 97%), the frequency of repeat diagnostic imaging (2% to 58%) and invasive procedures (1.3% to 8% per screened individual), the risk for overdiagnosis (the detection of relatively indolent histologically confirmed lung tumours that would not have been detected or caused symptoms or disease during a patient's lifetime), which can have a negative effect on quality of life, and increased radiation exposure due to repeat scans required after the detection of an abnormality.

The reporting of false-positive rates varied across studies, depending on the threshold described in a given study (0, ≥4, ≥5 mm) and the denominator used (all nodules over the threshold or all patients tested). Denominators were further affected by whether they were determined per screening round or per person year.

In the NLST, a positive screening-test result was defined as the detection of a noncalcified nodule measuring ≥4 mm in any diameter and that was deemed suspicious for lung cancer. The rate of a positive test result across the three screening rounds was 24% in the LDCT group compared with 6.9% in the CXR group. Diagnostic follow-up occurred for >90% of the positive test results, usually consisting of further imaging. Of the positive test results, 96.4% were false positive in the LDCT group and 94.5% were false positive in the CXR group (6).

The effective dose of radiation from LDCT was about 1.5 mSv per screen. In the NLST, the dose was about 8 mSv per participant over 3 years, including screening and diagnostic follow-up tests (6). From the NLST data, it was predicted that for every 2500 persons screened, 1 cancer death may be caused by radiation from imaging.

The NLST was the only study to report on complications resulting from LDCT screening. The frequency per 10,000 persons screened of a major complication occurring during a diagnostic evaluation of a detected finding was 33 in the LDCT group and 10 in the CXR group. The frequency of death occurring within 60 days of a diagnostic evaluation of a detected finding was 8 per 10,000 persons screened with LDCT and 5 per 10,000 persons screened with CXR. Among the patients who had nodules detected by LDCT that were determined to be benign, death within 60 days occurred in 11 patients (0.06%), and major complications occurred in 61 patients (0.36%). Most of the major complications occurred after surgical procedures (6).

Groups Likely to Benefit/not Benefit

The systematic review sought to determine which groups of patients would and would not benefit from LDCT screening.

a. Age and duration of screening

Among the eight RCTs included in the collaborative systematic review, the lower age limit to commence lung cancer screening ranged from 47 years to 60 years. The upper age limit ranged from 69 years to 80 years. Among the 13 single-arm studies, the lower age limit ranged from 40 years to 60 years. The upper age limit ranged from 73 years to 85 years.

b. Smoking history

Among the eight RCTs, the minimum number of pack-years ranged from ≥15 to ≥30. In the seven RCTs reporting these data, the number of years since quitting in former smokers was ≤10 in five trials and ≤15 in two trials. Among the 13 single-arm studies, the minimum number of pack-years ranged from ≥10 to ≥20. In the five studies reporting these data, the number of years since quitting in former smokers was <0.5 in one study and ≤10 in four studies.

c. Previous cancer history and other risk factors

Among the seven RCTs reporting these inclusion criteria, two trials stated a minimum of 5 years since a previous cancer diagnosis, one trial stated 10 years since previous cancer treatment (5 years for early laryngeal or skin cancer), one trial stated a minimum of 5 years since diagnosis of lung cancer and exclusion of any past renal or breast cancer or melanoma, one trial excluded patients with any previous lung cancer or current treatment for any cancer, and two trials excluded patients with any previous cancer diagnosis. Among the 11 single-arm studies reporting these criteria, two studies stated a minimum of 5 years since a previous cancer diagnosis, one study excluded patients with any previous lung cancer, one study excluded patients with any known pulmonary metastases, and seven studies excluded patients with any previous cancer diagnosis.

The NLST was the only study to show a benefit of LDCT screening in terms of reducing the risk of death from lung cancer (6). The patients enrolled in the trial were between 55 and 74 years of age at the time of randomization, had a history of cigarette smoking of ≥30 pack-years, and if they were former smokers, had quit within the past 15 years. Patients were excluded if they had previously been diagnosed with lung cancer, had a chest CT scan within the past 18 months, had haemoptysis, or had an unexplained weight loss of >6.8 kg in the past year. The minimum length of time permitted since a previous cancer diagnosis was 5 years. A family history of lung cancer in any first-degree relative was 22%; in ≥2 first-degree relatives, the rate was 3.3%. The patient characteristics covered a broad range of lung cancer risk. It was estimated that the median NLST patient (a current smoker about 62 years of age with a 50 pack-year smoking history) had a risk of being diagnosed with lung cancer over the next 10 years of 10%. In contrast, the patient who met the minimum entry criteria (a former smoker 55 years of age with a 30 pack-year smoking history) had a 10-year lung cancer risk of about 2%.

Effective Settings

The 33 study sites of the NLST were all high-volume academic medical centres, most with >400 hospital beds and several with subspecialty training programs in thoracic radiology and thoracic surgery. Patient compliance was also high, with 93% to 95% adherence to the screening protocol across three rounds of screening. Furthermore, extensive quality control measures were taken in terms of ensuring the technical standards of the equipment, the training and education of the radiology personnel, and the interpretation of the test results. One single-arm study maintained that the early diagnosis or screening of lung cancer is best pursued as an interdisciplinary activity (16). Given the strictness of the NLST study parameters, the systematic review cautioned that the effectiveness of LDCT screening might differ substantially if it were adopted more broadly by community facilities with less expertise in radiology and in the diagnosis and treatment of lung cancer.

Few studies included a smoking-cessation component in the LDCT screening intervention. In two of the eight RCTs, participants in both the LDCT group and comparison group had access to smoking cessation counseling (17,18). In one single-arm study smoking cessation was recommended and facilitated (19,20).

We also sought to determine the necessary elements involved in defining and following up a positive result on LDCT and the appropriate screening interval. The details for each study for LDCT collimation, nodule size warranting work-up, and screening interval are shown in Tables 1 and 2 of the collaborative systematic review (8), and the details for nodule growth, CT follow-up, other diagnostic tests, and incidental findings are listed in Appendix 4 of this report.

Defining a Positive Result on LDCT and Follow-up of a Positive Result

a. Screening modality

All studies used LDCT. The voltage ranged from 100 to 140 peak kilovoltage (kVp) in the eight RCTs, and from 120 to 140 kVp in 12 single-arm studies. The current exposure time ranged from 20 to 60 milliampere seconds (mAs) in the RCTs, and from 20 to 60 mAs in the single-arm studies. Pitch ranged from 1.25 to 2. The average effective radiation dose was reported in five studies and ranged from 0.6 to 1.5 millisieverts (mSv).

The voltage used in the NLST was 120 to 140 kVp, the current time varied from 20 to 30 mAs, and the average effective radiation dose was 1.5 mSv. All CT and chest radiographic equipment had to meet the published standards of the American College of Radiology. Platform-specific image-acquisition charts were developed to ensure standardized image quality at all study sites.

b. Collimation

Among the eight RCTs, the collimation ranged from 0.75 mm to 5 mm. Among the 13 single-arm studies, collimation ranged from 1 mm to 10 mm. Collimation in the NLST was ≤2.5 mm.

c. Nodule size

Among the eight RCTs, the nodule size warranting additional imaging (CT and/or PET) ranged from any size to >5 mm, and the nodule size warranting diagnostic testing (e.g., biopsy, bronchoscopy, thoracotomy) ranged from ≥6 to >15 mm. Among the 13 single-arm studies, the nodule size warranting additional imaging ranged from any size to >5 mm, and the nodule size warranting diagnostic testing ranged from ≥6 to ≥15 mm.

In the NLST, noncalcified nodules measuring ≥4 mm in any diameter were classified as positive, suspicious for lung cancer.

Most of the studies reported a detection rate of benign nodules (false-positive rate) of >90%. A detected nodule usually prompted further imaging, but the rates varied from 1% to 45% across the studies.

d. Growth

Three RCTs defined tumour growth: two trials described growth as a change in tumour volume of ≥25% and one trial described growth as an increase in mean nodule diameter of ≥1 mm.

Seven single-arm studies defined growth: three studies described growth as an increase in nodule diameter in at least one dimension, one study described growth as an interval increase in diameter in any direction, one study described growth as an increase in tumour diameter of at least 20% or 1 mm or the transformation of a semi-solid nodule into a solid nodule, one study described it as a volume doubling time between 30 and 400 days, and one study used the tumour volumes and the time between high resolution CT screens to calculate the doubling time of the tumour.

A definition of growth was not reported in the NLST. The Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial used semi-automated volumetry software to calculate the percentage change in volume and volume-doubling time (21). This strategy decreased the rate of positive results requiring further follow-up. Whether this translates to decreased lung cancer mortality in the screened group is unknown until the final results of the trial are available.

e. CT follow-up

One study implemented spiral thin-section CT limited to the area of interest and 3-dimensional analysis within 1 month for any noncalcified lesions >5 mm (22). In another study, additional limited thin-section LDCT covering a maxiumum of 50 mm in the craniocaudal axis was done within 2 weeks to more precisely characterize pulmonary nodules (23).

f. Other diagnostic tests

A diagnostic protocol was followed in six of the eight RCTs, although specific details on adherence to or deviation from the protocol or the procedures used were not provided for three of them. Among the single-arm studies, a diagnostic protocol was in place in all but one study. A detected nodule invariably prompted further imaging, but few studies reported sufficient details to ascertain specific types of tests and rates of patients requiring them.

No single diagnostic algorithm was employed across the NLST study centres; diagnostic assessment was done outside the context of the NLST. However, patients who had positive results on a screening LDCT received follow-up recommendations from NLST radiologists. Some centres developed guidelines for subsequent evaluation of abnormalities suspicious for lung cancer on the basis of current best practices (24).

g. Incidental findings

Incidental findings were discussed and/or a follow-up procedure was reported in four RCTs and six single-arm studies. These included respiratory disorders and abnormalities outside the lungs or bronchi, and follow-up could include referral for treatment and further diagnostic work-up.

In the NLST, abnormalities suggesting conditions other than lung cancer were noted and flagged for follow-up to be done by participants' personal physicians (6).

LDCT Screening Interval

Among the eight RCTs, LDCT was done on an annual basis in seven trials and on years 1, 2, and 4 in one trial. Among the 13 single-arm studies, LDCT was done annually in 11 studies, every 6 months in one study, and after 2 years in one study. The NLST conducted LDCT screens annually for 3 years (6). The NELSON study also had three rounds of screening, but on years 1, 2, and 4 (21).

CONCLUSIONS OF THE COLLABORATIVE REVIEW BY BACH ET AL (8)

The collaborative review concluded that screening with LDCT was beneficial in persons at high risk for lung cancer. The evidence of a statistically significant benefit is found in one RCT, and uncertainty exists about the generalizability of results. Across all studies, there was marked variability in the frequency of nodule detection, follow-up investigations, biopsies, and invasive procedures. High false-positive rates were found across all studies. The NLST was the predominate study in the systematic review, with the largest sample size, the lowest risk of bias, and a statistically significant decrease in lung cancer mortality, and it currently provides the most compelling evidence on the topic of lung cancer screening.

UPDATE SEARCH APRIL 2013

The search strategy from the collaborative systematic review was re-run in April 2013 to retrieve any relevant studies published since the previous search. The update search identified two relevant papers (25,26).

A systematic review with meta-analysis included six RCTs, all of which were included in the collaborative systematic review (25). The trials were pooled and provided summary odds ratios for detection of stage I non–small-cell lung cancer (3.9, 95% CI 2.1 to 7.4), total non–small-cell lung cancer (5.5, 95% CI 3.1 to 9.7), detection of false-positive nodules (3.1, 95% CI 2.6 to 3.7), and rate of thoracotomy for benign lesions (0.37, 95% CI 0.36 to 0.39).

The encouraging results of the single-arm study by Pastorino et al (included in the collaborative systematic review) prompted the launch of the MILD trial (26), which randomized 4099 participants to LDCT screening (n=2376) or usual care (n=1723), and further randomized the LDCT arm to be screened every 12 months (annual, n=1190) or every 24 months (biennial, n=1186). All patients received a smoking-cessation intervention and underwent pulmonary function tests and blood sample collection. The median follow-up was 4.4 years. Forty-nine lung cancers were detected by LDCT screening (29 in the annual group and 20 in the biennial group), and 20 lung cancers were detected in the control group. Ten lung cancers were not detected by LDCT screening (interval cancers): five in the annual group and five in the biennial group. The 5-year cumulative lung-cancer incidence was 620 per 100,000 in the annual LDCT screening group, 457 per 100,000 in the biennial LDCT screening group, and 311 per 100,000 in the control group (p=0.036). The incidence was greater in the LDCT group than in the control group (p=0.025), but the annual and biennial groups did not differ (p=0.24). The difference between the screening (annual and biennial combined) and control groups for lung cancer mortality (hazard ratio [HR] 1.52, 95% CI 0.63 to 3.65) or all-cause mortality (HR 1.39, 95% CI 0.83 to 2.34) was not statistically significant. After adjustment for age and smoking, the HRs were 1.64 (95% CI 0.67 to 4.01) and 1.40 (95% CI 0.82 to 2.38), respectively.

EXISTING GUIDELINE DOCUMENTS

Since the release of the NLST findings, numerous organizations have begun to issue position statements and practice guidelines advising on the use of LDCT in lung cancer screening.

ACCP/ASCO

The ACCP and ASCO issued a joint guideline that accompanied the collaborative systematic review (8,9). It recommended that for smokers and former smokers who are age 55 to 74 years and who have smoked for 30 pack years or more and either continued to smoke

or quit within the past 15 years, annual screening with low-dose CT should be offered over both annual screening with chest radiograph or no screening, but only in settings that can deliver the comprehensive care provided to NLST participants. Additional remarks included:

1. Counseling should include a complete description of potential benefits and harms so the individual can decide whether or not to undergo LDCT screening;
2. Screening should be conducted in a centre similar to those where the NLST was conducted, with multi-disciplinary coordinated care and a comprehensive process for screening, image interpretation, management of findings, and evaluation and treatment of potential cancers;
3. A number of important questions about screening could be addressed if individuals who are screened for lung cancer are entered into a registry that captures data on follow-up testing, radiation exposure, patient experience, and smoking behaviour;
4. Quality metrics should be developed such as those in use for mammography screening, which could help enhance the benefits and minimize the harm for individuals who undergo screening;
5. Screening for lung cancer is not a substitute for stopping smoking. The most important thing patients can do to prevent lung cancer is to not smoke;
6. The most effective duration or frequency of screening is not known.

ACCP/ASCO does not recommend LDCT screening in persons younger than age 55 years or older than age 74 years, persons with less than 30 pack-year smoking history, persons who had quit smoking more than 15 years ago, or persons with severe comorbid conditions that would preclude potentially curative treatment or limit life expectancy.

NCCN

The NCCN recommended LDCT screening in high-risk individuals defined as: Age 55 to 74 years; 30 or more pack-year history of smoking tobacco; and, if former smoker, have quit within 15 years (27). This is a category 1 recommendation (based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate), because these individuals are selected based on the NLST inclusion criteria. Annual screening is recommended for these high-risk individuals until they are 74 years of age based on the NLST. However, uncertainty exists about the appropriate duration of screening and the age at which screening is no longer appropriate.

NCCN also recommended screening in persons age 50 years or older; 20 or more pack-year history of smoking tobacco, and one additional risk factor including cancer history, lung disease history, family history of lung cancer, radon exposure, or occupational exposure.

NCCN does not recommend LDCT screening in moderate-risk individuals (age 50 or older and a 20 or more pack-year history or second hand smoke exposure, but no additional lung cancer risk factors) or low-risk individuals (age less than 50 years and/or a smoking history of less than 20 pack-years).

American Lung Association

In response to the results of the NLST, and acknowledging that a number of issues concerning screening in the general population could not be addressed by the NLST, the American Lung Association produced a set of interim recommendations (28). LDCT screening was recommended in persons who matched the NLST patient criteria: current or former smokers 55 to 74 years of age, smoking history of ≥30 pack-years, and no history of lung cancer. Smoking cessation should be continuously emphasized to persons being screened. It was also emphasized that a CXR should not be done for lung cancer screening, and that the best prevention for lung cancer is to quit or never start smoking.

International Association for the Study of Lung Cancer

The International Association for the Study of Lung Cancer (IASLC) published a position statement in July 2011 outlining factors to be considered for the implementation of lung cancer screening (29) and followed with a workshop to further develop approaches (30). Based on the NLST results, the statement indicated that it is appropriate for heavy smokers aged 55 to 74 years to discuss relevant lung cancer screening with their physicians to assist them in deciding whether to undergo LDCT screening. It acknowledged that while the NLST is the first RCT to demonstrate a significant reduction in lung cancer mortality through early detection, further research is required for additional information on mortality advantage, cost effectiveness, and the clinical management outcomes of lung cancer screening. It emphasized the need for multidisciplinary groups of trained specialists in screening implementation, screening trials and tobacco-control programs.

The workshop convened the international expertise of radiologists, respirologists, surgeons, pathologists, and cancer screening experts, and specific working groups were formalized: the Core Task Force and Screening Implementation Group, plus expert groups for radiology, respirology, surgery, and pathology. Each working group held discussions, and a number of considerations were raised concerning aspects of CT screening implementation. These included the development of uniform radiology standards, the classification of a positive screen, the follow-up of nodules screened positive, the surgical aspects of CT screening, the handling of pathology specimens from CT-screened patients, and the role of industry in terms of the availability of screening management systems and image datasets for validation. The IASLC set up a Strategic CT Screening Advisory Committee to engage professional organizations worldwide to focus on the following areas: Identification of high-risk persons for lung cancer CT-screening programs, development of radiological guidelines for lung cancer CT-screening programs, development of guidelines for the follow-up of indeterminate nodules detected on CT-screening scans, development of guidelines for pathology reporting of nodules from lung cancer CT-screening scans, development of recommendations for surgical and therapeutic interventions of suspicious nodules detected on lung cancer CT-screening scans, and integration of smoking cessation endeavors into lung cancer CT-screening programs.

Canadian Partnership Against Cancer

In 2011, the Canadian Partnership Against Cancer (CPAC) convened an expert panel to review the current evidence regarding lung cancer screening using LDCT and issued an anticipatory science document (31). The document is not intended to provide clinical or policy recommendations. It summarizes the existing RCTs, discusses the risks and benefits of LDCT screening, and presents issues surrounding policy, education, resources, and follow-up investigation and treatment that should be considered if lung cancer screening is implemented at the population level.

CPAC hosted a Pan-Canadian Forum in November 2011 to enable Canadian cancer control leaders and policy makers to develop an informed approach to lung cancer screening. During this forum, participants discussed the issues pertaining to lung cancer screening, including the eligibility and identification of the target population, management of abnormal screening results, smoking cessation, and resources and costing. The issue of organized versus opportunistic screening was also discussed.

A second forum was held in February 2012 to follow up priorities identified in the previous forum and discuss new information. Participants were updated on the Cancer Risk Management Lung Cancer Model, available from www.cancerview.ca (32) and the pan-Canadian Early Lung Cancer Detection study, which aims to validate a lung-cancer risk-

assessment strategy. Information was also presented on Canadian cancer registries, CT-scanning services capacity across Canada, and radiation exposure concerns about LDCT. The Ontario Breast Screening Program was presented as an example of a current screening practice and highlighted the criteria to be met for a facility to qualify as a high-risk screening centre, target population characteristics, roles for primary care providers, and quality management elements.

International Early Lung Cancer Action Program (I-ELCAP)

I-ELCAP is an international collaborative group of lung cancer experts pursuing the early diagnosis, treatment, and ultimate cure of lung cancer through the rapid dissemination and advancement of research (33). Included among its research endeavors, I-ELCAP has developed a protocol for lung cancer screening (34). The protocol outlines the steps to be followed in diagnosing lung cancer in a screening regimen, including image production, image reading, screening frequency, follow-up of scan results, assessment of growth, communication of results, and biopsy procedure. The protocol also describes the I-ELCAP web-based management system, quality assurance procedures, and smoking cessation as part of lung cancer screening.

The IASLC, CPAC, and I-ELCAP documents mentioned above are not practice guidelines, but they present and summarize essential details that should be taken into consideration during any discussion about establishing a lung cancer screening program.

Ongoing Trials

Table 2. Ongoing trials.

Investigator	Title	Identifier	Status
P Vedsted, University of Aarhus	The Effect of Direct Referral for Fast CT Scan in Early Lung Cancer Detection in General Practice	NCT01527214	Recruiting
S Arnold, University of Kentucky	Early Detection of Lung Cancer in a High-Risk Population Defined by PFT, Biomarkers, and CT Scanning	NCT00596310	Ongoing, not recruiting
AK Ganti, University of Nebraska	CT Scans in Screening for Lung Cancer in Current and Former Smokers	NCT00625690	Unknown
RV LaRocca, Kentuckiana Cancer Institute	Chest X-Ray or Chest CT Scan in Patients at High Risk of Developing Lung Cancer	NCT00006087	Unknown
S Lam, British Columbia Cancer Agency	Screening Methods in Finding Lung Cancer Early in Current or Former Smokers (Pan Canadian Study)	NCT00751660	Ongoing, not recruiting
H Roberts, University Health Network, Toronto	Early Lung Cancer Detection Using Computed Tomography (I-ELCAP)	NCT00188734	Recruiting
RJ van Klaveren, Erasmus Medical Centre (Netherlands)	Dutch Belgian randomised lung cancer screening trial (NELSON)	ISRCTN 63545820	Ongoing
O Wiestler, German Cancer Research Centre Heidelberg, Germany	Spiral computed tomography scanning for the early detection of lung cancer (LUSI)	ISRCTN 30604390	Completed

JH Pedersen, Gentofte University Hospital, Hellerup, Denmark	Danish Lung Cancer Screening Trial (DLCST)	NCT00496977	Unknown
J Field, Roy Castle Lung Cancer Research Programme, University of Liverpool	United Kingdom Lung Cancer Screening Trial (UKLS)	www.hta.ac.uk/2382	In progress

DISCUSSION

The risk of dying from lung cancer is substantial among a subset of smokers and former smokers, because under current practices, lung cancer is commonly detected at an advanced stage. Detection of lung cancer at an earlier stage would make it more likely that surgical resection would be possible and lead to cure. It is reasonable to assume that screening targeted to persons at high risk for lung cancer would result in decreased mortality from the disease. Until recently, however, studies testing methods of screening for lung cancer have been not designed to observe an effect on lung cancer mortality. The NLST is the first study to show a mortality benefit with screening with LDCT.

The foundation of this evidentiary base is a collaborative systematic review produced by the ACCP, ASCO, and NCCN (8). The review included eight RCTs and 13 single-arm studies of LDCT screening for lung cancer. Three of the RCTs assessed lung cancer mortality: two compared LDCT with usual care and showed statistically nonsignificant differences (13,14), whereas the largest RCT with >53,000 participants showed a significant decrease of 20% at 6 years with LDCT compared with CXR (6). Meta-analysis of the three trials showed a combined odds ratio of 0.82 (95% CI 0.72 to 0.94). The systematic review also revealed harms associated with LDCT screening. In most studies more than 90% of nodules detected were noncancerous nodules, and any detected nodule usually prompted further imaging and potentially more invasive procedures. The NLST had a false-positive rate of 96%.

Currently, only the NLST provides evidence of the benefits of LDCT screening for lung cancer. Nevertheless, it is a large rigorous controlled trial with low risk of bias, and we believe the evidence is compelling and supports the introduction of lung cancer screening if delivered to patients and in settings similar to those of the NLST.

With respect to the target population, we agree with offering lung cancer screening to individuals meeting the inclusion criteria of the NLST, that is, men and women 55 to 74 years of age with a smoking history of ≥30 pack-years who continue to smoke or have quit within the past 15 years.

We deviate slightly from the parameters of the NLST in the definition of a positive CT scan, and maintain that lung nodules of ≥5 mm should trigger follow-up imaging rather than 4 mm (35,36).

The optimum frequency of screening is unknown. Most of the studies in the systematic review followed an annual screening interval, including the NLST, but yearly screening for an indefinite period of time may not be feasible or necessary.

Screening for lung cancer with LDCT has been shown to be successful within the confines of a carefully controlled clinical trial. To be effective on a broader scale, screening will require similarly rigorous implementation criteria that are more likely to be achieved through an organized screening program. Such a program should only be considered when there is strong evidence of reduced cancer-specific mortality and a population-level benefit achieved with a balance of benefits and harms (31). The UK National Screening Committee

adapted the principles for population screening developed by Wilson and Jungner in 1968 (37), and refined the previous criteria to focus on four questions for determining the viability of a screening program: Do we understand the natural history of the disease? Is there a good screening test? Is there an effective treatment? Is the program acceptable to the population? The UK National Screening Committee's criteria for the initiation of a screening program are shown in Appendix 5. It is the opinion of the Working Group that screening for early lung cancer in high-risk populations meets the requirements for an organized screening program. The NNS of 320 to prevent one lung cancer death attained in the NLST should be considered in the context of other screening programs: for mammography an NNS of 1339 women aged 50 to 59 years to prevent one breast cancer death (38) and for flexible sigmoidoscopy an NNS of 489 to prevent one colorectal cancer death (39).

The importance of smoking cessation in reducing the risk of lung cancer is well understood. No LDCT screening program should be mounted without being tightly linked to a smoking-cessation program for individuals who still smoke (40). Participants in a screening program need to be made aware of the pronounced benefits of stopping smoking and the harms associated with continuing to smoke, even after a normal screening result. There is concern that negative results from LDCT screening will provide smokers with a justification to continue smoking. Another view is that screening creates an environment in which people are more receptive to positive behaviour changes. The studies in the collaborative review that examined the smoking behaviour of LDCT-screened persons did not find a substantial effect on quit rates or relapse rates. However, a recent systematic review of the literature on the effect of CT screening on the smoking behaviours of current smokers showed that participants in lung screening programs were motivated to quit smoking (41). Smoking-cessation interventions should be intensive and sustained over several months.

CONCLUSIONS

Lung cancer screening with LDCT has great promise to address the dismal prognosis of lung cancer if it is performed in a standardized fashion with controlled scanning, reporting, and follow up in individuals at a defined risk. This report has reviewed the evidence on the clinical effectiveness and safety of LDCT screening for lung cancer and provided guidance on defining the population at risk, the follow-up of a positive scan result, and the duration and interval of screening. It proposes that effective screening for lung cancer is best achieved through an organized screening program.

Research continues with planned analyses of the NLST and ongoing RCTs in Europe. As new information on LDCT lung cancer screening emerges, this document will be updated.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, the provincial Lung Cancer Disease Site Group (DSG) and Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Four authors declared they had no conflicts of interest, and two (HR and KY) declared conflicts.

HR reported she was a principal investigator of the ELCAP study and the Pan-Canadian Lung Cancer Screening Study, and has given talks to community hospitals interested in lung cancer screening. Furthermore, her department is pursuing collaborations with third parties to perform lung cancer screening.

KY reported he has received educational and research grants from Olympus Medical Systems.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca

ACKNOWLEDGEMENTS AND AUTHORSHIP

CCO Prevention and Cancer Control would like to acknowledge the following participants in the guideline development process:

The Lung Cancer Screening Guideline Development Group would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Laurie Elit, Sheila McNair, Hans Messersmith, Rebecca Wong, Stephen Lam, and Heather Bryant for providing feedback on draft versions.
- Harkanwal Randhawa for conducting a data audit.
- Saira Akram and Bruce Histed for copy editing.

A complete list of the members of the Lung Cancer Screening Guideline Development Group, with their affiliations, is provided in Appendix 1.

REFERENCES

1. Segnan N, Patnick J, von Karsa L (eds). European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis, 1st Ed. Luxembourg: Publications Office of the European Union; 2010.
2. Espinas JA, Aliste L, Fernandez E, Argimon JM, Tresserras R, Borras JM. Narrowing the equity gap: the impact of organized versus opportunistic cancer screening in Catalonia (Spain). J Med Screen. 2011;18(2):87-90.
3. Canadian Cancer Society, National Cancer Institute of Canada. Canadian Cancer Statistics 2012. Toronto (Canada): National Cancer Institute of Canada; 2012.
4. Cancer Care Ontario. Cancer Surveillance. Incidence and Mortality in Ontario [cited July 2012]. Available from: https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=121950#two-tab
5. Cancer Quality Council of Ontario. Lung Cancer in Ontario – Surveillance [cited July 2012]. Available from: http://www.csqi.on.ca/cancer_in_ontario/lung/
6. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011 ;365(5):395-409.
7. Cancer Care Ontario Disease Pathway Management Secretariat. Lung Cancer Diagnosis Pathway. Version 2012.2 [cited July 2012]. Available from: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=124606
8. Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA. 2012 ;307(22):2418-29.
9. American Society of Clinical Oncology. The role of CT screening for Lung Cancer in clinical practice. The evidence based practice guideline of the American College of Chest Physicians and the American Society for Clinical Oncology. 2012 [cited July 2012]. Available from: http://www.asco.org/ASCOv2/Practice+%26+Guidelines/Guidelines/Clinical+Practice+Guidelines/The+role+of+CT+screening+for+Lung+Cancer+in+clinical+practice.+The+evidence+based+practice+guideline+of+the+American+College+of+Chest+Physicians+and+the+American+Society+for+Clinical+Oncology
10. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.
11. The Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument. AGREE II. (YEAR) [cited July 2012]. Available from: http://www.agreetrust.org/
12. Pedersen JH, Ashraf H, Dirksen A, Bach K, Hansen H, Toennesen P, et al. The Danish randomized lung cancer CT screening trial-overall design and results of the prevalence round. J Thorac Oncol. 2009;4(5):608-14.
13. Infante M, Cavuto S, Lutman FR, Brambilla G, Chiesa G, Ceresoli G, et al; DANTE Study Group. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med. 2009 1;180(5):445-53.
14. Saghir Z, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. Thorax. 2012;67(4):296-301.
15. Anderson CM, Yip R, Henschke CI, Yankelevitz DF, Ostroff JS, Burns DM. Smoking cessation and relapse during a lung cancer screening program. Cancer Epidemiol Biomarkers Prev. 2009 Dec;18(12):3476-83

16. Picozzi G, Paci E, Lopez Pegna A, Bartolucci M, Roselli G, De Francisci A, et al. Screening of lung cancer with low dose spiral CT: results of a three year pilot study and design of the randomised controlled trial "Italung-CT". Radiol Med. 2005;109(1-2):17-26.
17. Lopes Pegna A, Picozzi G, Mascalchi M, Maria Carozzi F, Carrozzi L, Comin C, et al; ITALUNG Study Research Group. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. Lung Cancer. 2009;64(1):34-40.
18. Garg K, Keith RL, Byers T, Kelly K, Kerzner AL, Lynch DA, et al. Randomized controlled trial with low-dose spiral CT for lung cancer screening: feasibility study and preliminary results. Radiology. 2002;225(2):506-10.
19. MacRedmond R, Logan PM, Lee M, Kenny D, Foley C, Costello RW. Screening for lung cancer using low dose CT scanning. Thorax. 2004;59(3):237-41.
20. MacRedmond R, McVey G, Lee M, Costello RW, Kenny D, Foley C, et al. Screening for lung cancer using low dose CT scanning: results of 2 year follow up. Thorax. 2006;61(1):54-6.
21. van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med. 2009;361(23):2221-9.
22. Pastorino U, Bellomi M, Landoni C, De Fiori E, Arnaldi P, Picchio M, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet. 2003;362(9384):593-7.
23. Diederich S, Wormanns D, Semik M, Thomas M, Lenzen H, Roos N, et al. Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. Radiology. 2002;222(3):773-81.
24. National Lung Screening Trial Research Team, Aberle DR, Berg CD, Black WC, Church TR, Fagerstrom RM, Galen B, et al. The National Lung Screening Trial: overview and study design. Radiology. 2011;258(1):243-53.
25. Gopal M, Abdullah SE, Grady JJ, Goodwin JS. Screening for lung cancer with low-dose computed tomography: a systematic review and meta-analysis of the baseline findings of randomized controlled trials. J Thorac Oncol. 2010;5(8):1233-9.
26. Pastorino U, Rossi M, Rosato V, Marchianò A, Sverzellati N, Morosi C, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. Eur J Cancer Prev. 2012;21(3):308-15.
27. Wood DE, Eapen GA, Ettinger DS, Hou L, Jackman D, Kazerooni E, et al. Lung cancer screening. J Natl Compr Canc Netw. 2012;10(2):240-65.
28. Samet JM, Crowell R, Estepar RSJ, et al. Lung Cancer Screening Committee. Providing Guidance for Lung Cancer Screening: The American Lung Association Interim Report on Lung Cancer Screening. 2012 [cited July 2012]. Available from: http://www.lung.org/about-us/our-impact/top-stories/guidance-on-ct-lung-cancer.html
29. International Association for the Study of Lung Cancer. IASLC's 2011 Statement on CT Screening for Lung Cancer [cited July 2012]. Available from: http://iaslc.org/policies/statement-on-ct-screening/
30. Field JK, Smith RA, Aberle DR, Oudkerk M, Baldwin DR, Yankelevitz D, Pedersen JH, Swanson SJ, Travis WD, Wisbuba II, Noguchi M, Mulshine JL; IASLC CT Screening Workshop 2011 Participants. International Association for the Study of Lung Cancer Computed Tomography Screening Workshop 2011 report. J Thorac Oncol. 2012;7(1):10-9.
31. Canadian Partnership Against Cancer, Lung Cancer Screening Expert Panel. Lung Cancer Screening Expert Panel: Summary of Existing and New Evidence. Toronto: Canadian Partnership Against Cancer; 2011 [cited July 2012]. Available from: http://www.cancerview.ca/idc/groups/public/documents/webcontent/cpac_lung_cancer_screening_fin.pdf

32. Canadian Partnership Against Cancer. Cancer Risk management Lung Cancer Model [cited July 2012]. Available from: http://www.cancerview.ca/cv/portal/Home/QualityAndPlanning/QPProfessionals/SystemPlanning/CancerRiskManagementModel/CRMMModelProfile?_afrLoop=1250522809449000&lang=en&_afrWindowMode=0&_adf.ctrl-state=fbqfkdaai_4
33. International Early Lung Cancer Action Program [cited July 2012]. Available from: http://www.ielcap.org/ielcap/about.html
34. Henschke CI. International Early Lung Cancer Action Program: Enrollment and Screening Protocol. 2011 [cited Jun 28]. Available from: http://www.ielcap.org/professionals/protocols.html
35. Bellomi M, Veronesi G, Rampinelli C, Ferretti S, De Fiori E, Maisonneuve P. Evolution of lung nodules < or =5 mm detected with low-dose CT in asymptomaticsmokers. Br J Radiol. 2007;80(957):708-12.
36. Henschke CI, Yankelevitz DF, Naidich DP, McCauley DI, McGuinness G, Libby DM, et al. CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. Radiology. 2004;231(1):164-8.
37. Wilson JMG, Jungner JJ. Principles and practice of screening for disease. Geneva: World Health Organization, 1968.
38. US Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;151(10):716-26, W-236.
39. Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, Parkin DM, Wardle J, Duffy SW, Cuzick J; UK Flexible Sigmoidoscopy Trial Investigators. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375(9726):1624-33.
40. Evans WK, Wolfson MC. Computed tomography screening for lung cancer without a smoking cessation program–not a cost-effective idea. J Thorac Oncol. 2011;6(11):1781-3.
41. Poghosyan H, Kennedy Sheldon L, Cooley ME. The impact of computed tomography screening for lung cancer on smoking behaviors: a teachable moment? Cancer Nurs. 2012;35(6):446-75.
42. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Clapp JD, Clingan KL, Gareen IF, Lynch DA, Marcus PM, Pinsky PF. Baseline characteristics of participants in the randomized national lung screening trial. J Natl Cancer Inst. 2010 Dec 1;102(23):1771-9.
43. van Iersel CA, de Koning HJ, Draisma G, Mali WP, Scholten ET, Nackaerts K, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). Int J Cancer. 2007 ;120(4):868-74.
44. Gohagan J, Marcus P, Fagerstrom R, Pinsky P, Kramer B, Prorok P; Writing Committee, Lung Screening Study Research Group. Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of the National Cancer Institute. Chest. 2004;126(1):114-21.
45. Gohagan JK, Marcus PM, Fagerstrom RM, Pinsky PF, Kramer BS, Prorok PC, et al; LUNG SCREENING STUDY RESEARCH GROUP. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. Lung Cancer. 2005;47(1):9-15.
46. Blanchon T, Bréchot JM, Grenier PA, Ferretti GR, Lemarié E, Milleron B, et al; Dépiscan Group. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). Lung Cancer. 2007;58(1):50-8.

47. Veronesi G, Bellomi M, Mulshine JL, Pelosi G, Scanagatta P, Paganelli G, et al. Lung cancer screening with low-dose computed tomography: a non-invasive diagnostic protocol for baseline lung nodules. Lung Cancer. 2008;61(3):340-9.
48. Veronesi G, Bellomi M, Scanagatta P, Preda L, Rampinelli C, Guarize J, et al. Difficulties encountered managing nodules detected during a computed tomography lung cancer screening program. J Thorac Cardiovasc Surg. 2008;136(3):611-7.
49. Wilson DO, Weissfeld JL, Fuhrman CR, Fisher SN, Balogh P, Landreneau RJ, et al. The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan. Am J Respir Crit Care Med. 2008;178(9):956-61.
50. Menezes RJ, Roberts HC, Paul NS, McGregor M, Chung TB, Patsios D, et al. Lung cancer screening using low-dose computed tomography in at-risk individuals: the Toronto experience. Lung Cancer. 2010;67(2):177-83.
51. Sobue T, Moriyama N, Kaneko M, Kusumoto M, Kobayashi T, Tsuchiya R, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. J Clin Oncol. 2002;20(4):911-20.
52. Swensen SJ, Jett JR, Hartman TE, Midthun DE, Sloan JA, Sykes AM, et al. Lung cancer screening with CT: Mayo Clinic experience. Radiology. 2003;226(3):756-61.
53. Swensen SJ, Jett JR, Sloan JA, Midthun DE, Hartman TE, Sykes AM, et al. Screening for lung cancer with low-dose spiral computed tomography. Am J Respir Crit Care Med. 2002;165(4):508-13.
54. Henschke CI, Naidich DP, Yankelevitz DF, McGuinness G, McCauley DI, Smith JP, et al. Early lung cancer action project: initial findings on repeat screenings. Cancer. 2001;92(1):153-9.
55. Henschke CI, Yankelevitz DF, Libby DM, McCauley D, Pasmantier M, Altorki NK, et al. Early lung cancer action project: annual screening using single-slice helical CT. Ann N Y Acad Sci. 2001;952:124-34.
56. Bastarrika G, García-Velloso MJ, Lozano MD, Montes U, Torre W, Spiteri N, et al. Early lung cancer detection using spiral computed tomography and positron emission tomography. Am J Respir Crit Care Med. 2005;171(12):1378-83.
57. Diederich S, Thomas M, Semik M, Lenzen H, Roos N, Weber A, et al. Screening for early lung cancer with low-dose spiral computed tomography: results of annual follow-up examinations in asymptomatic smokers. Eur Radiol. 2004;14(4):691-702.
58. Diederich S, Wormanns D, Lenzen H, Semik M, Thomas M, Peters PE. Screening for asymptomatic early bronchogenic carcinoma with low dose CT of the chest. Cancer. 2000;89(11 Suppl):2483-4.
59. Novello S, Fava C, Borasio P, Dogliotti L, Cortese G, Crida B, et al. Three-year findings of an early lung cancer detection feasibility study with low-dose spiral computed tomography in heavy smokers. Ann Oncol. 2005;16(10):1662-6.
60. Callol L, Roig F, Cuevas A, de Granda JI, Villegas F, Jareño J, et al. Low-dose CT: a useful and accessible tool for the early diagnosis of lung cancer in selected populations. Lung Cancer. 2007;56(2):217-21.

Appendix 1. Lung Cancer Screening Guideline Development Group

Members of the Working Group

Dr. Heidi Roberts	Medical Imaging, Women's College Hospital, Toronto, Ontario
Dr. Khalil Sivjee	Division of Respirology, Sunnybrook Health Sciences, Toronto, Ontario
Dr. Yee Ung	Radiation Oncology, Sunnybrook Health Sciences, Toronto, Ontario
Dr. Kazuhiro Yasufuku	Division of Thoracic Surgery, Toronto General Hospital, Toronto, Ontario
Dr. Amanda Hey	Regional Primary Care Lead, Hôpital régional de Sudbury Regional Hospital, Sudbury, Ontario
Ms. Cindy Walker-Dilks	Program in Evidence-Based Care, McMaster University, Hamilton, Ontario
Dr. Nancy Lewis	Prevention and Cancer Control, Cancer Care Ontario

Members of the Expert Panel

Dr. Lawrence Paszat	Institute for Clinical Evaluative Sciences, Toronto, Ontario
Dr. Anthony Miller	Dalla Lana School of Public Health, University of Toronto
Dr. Linda Rabeneck	Prevention and Cancer Control, Cancer Care Ontario
Dr. Bill Evans	Lung Cancer DSG, Juravinski Cancer Centre, Hamilton
Dr. Swati Kulkarni	Lung Cancer DSG, Windsor Regional Cancer Centre
Dr. Andrew Robinson	Lung Cancer DSG, Sudbury Regional Hospital
Dr. Ronald Feld	Lung Cancer DSG, Princess Margaret Hospital, Toronto
Dr. Andrew Pearce	Lung Cancer DSG, Sudbury Regional Hospital
Dr. Conrad Falkson	Lung Cancer DSG, Cancer Centre of Southeastern Ontario, Kingston General Hospital
Dr. John Goffin	Lung Cancer DSG, Juravinski Cancer Centre, Hamilton
Dr. Richard Gregg	Lung Cancer DSG, Cancer Centre of Southeastern Ontario, Kingston General Hospital
Dr. Edward Yu	Lung Cancer DSG, London Regional Cancer Program
Dr. Peter Ellis	Lung Cancer DSG, Juravinski Cancer Centre, Hamilton
Dr. Natasha Leighl	Lung Cancer DSG, Princess Margaret Hospital, Toronto

Appendix 2. AMSTAR Rating of the Systematic Review by Bach et al (8).

1. Was an 'a priori' design provided?	**Yes**
2. Was there duplicate study selection and data extraction?	**Yes**
3. Was a comprehensive literature search performed?	**Yes** -MEDLINE, EMBASE, and Cochrane Library search strategies provided; consulted reference lists of related papers and relevant review articles
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	**Yes** -Non-English was excluded
5. Was a list of studies (included and excluded) provided?	**Yes/No** -only included studies were listed
6. Were the characteristics of the included studies provided?	**Yes**
7. Was the scientific quality of the included studies assessed and documented?	**Yes** -only RCTs or cohort studies in which all participants were screened
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	**Yes**
9. Were the methods used to combine the findings of studies appropriate?	**Not applicable**
10. Was the likelihood of publication bias assessed?	**Not applicable**
11. Was the conflict of interest stated?	**No**

Appendix 3. AGREE II Scores for the ACCP/ASCO Clinical Practice Guideline (9).

Number of reviewers: 3

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigor:	Clarity Presentation:	Applicability:	Editorial Independence:
74.1%	81.5%	67.4%	83.3%	33.3%	77.8%

Appendix 4. LDCT Study Characteristics.

Study	Risk	Defining a positive scan & follow-up actions				Planned screening interval and duration	Smoking-cessation program
	Previous cancer history	Growth	CT follow-up technique (limited scan?)	Other tests	Incidental findings	Interval	
RCTs							
Aberle 2011 (6) Aberle 2010 (42) (NLST)	Previous cancer and family history of lung cancer (42, table 5) Minimum length of time since diagnosis of previous cancer: 5 yr (42, pg 1773)		CT procedures included abdomen/pelvis, brain, chest (limited thin section of nodule), abdomen (or liver), chest plus contrast-enhanced nodule densitometry, diagnostic chest, chest (low-dose helical), chest (limited thin section of entire lung), chest/abdomen, chest/abdomen/pelvis (Suppl, pg 34)	Diagnostic follow-up investigations (no protocol): clinical procedure, CXR, chest CT, PET, trans- or extra-thoracic biopsy, bronchoscopy, mediastinoscopy, mediastinotomy, thoracoscopy, thoracotomy (6, pg 401) Full list (Suppl, pg 34-5)	Abnormalities suggesting conditions other than lung cancer were noted. Pathology reports obtained for other reported cancers to exclude possibility that such tumours represented lung metastases (6, pg 397-8)	3 rounds of screening, 1 yr apart (baseline, yr 1, yr 2) (6, pg 397)	
Infante 2009 (13) (DANTE)	Minimum length of time since previous cancer treatment: 10 yr (early laryngeal and non-melanoma skin cancer, 5 yr) (pg 446)			Diagnostic follow-up investigations: 2nd-line LDCT/high resolution CT, PET, VATS, thoracotomy (pg 449, Table 4)	Significant abnormalities of the heart, aorta, or mediastinal structures were reported (pg 452)	5 rounds of screening, 1 yr apart (baseline, yr 1 to yr 4) (pg 446)	
vanKlaveren 2009 (21) vanIersel2006 (43) (NELSON)	Current or past renal or breast cancer or melanoma excluded. Minimum length of time since diagnosis of lung cancer: 5 yr. Lung cancer diagnosed >5 yr ago but still under treatment excluded (43, pg 870)	Change in volume ≥25% between 1st/2nd or 2nd/3rd scans. Growing nodules classified according to volume-doubling time (<400, 400-600, >600 days) (21, pg 2222) (Suppl, Fig 1, pg 2)		Diagnostic follow-up investigations: Flexible bronchoscopy, FNA, CT (Suppl, Table 1) Clinical evaluation, recall chest CT, CXR, PET/PET-CT, MRI, lung function test, bronchoscopy, FNA, invasive procedure (lung biopsy or wedge resection, VATS, thoracotomy,		3 rounds of screening (baseline, yr 1, yr 3) (21, pg 2222)	

Study	Risk	Defining a positive scan & follow-up actions				Planned screening interval and duration	Smoking-cessation program
	Previous cancer history	Growth	CT follow-up technique (limited scan?)	Other tests	Incidental findings	Interval	
				mediastinoscopy, mediastinotomy) (Suppl, Tbl 2)			
Pedersen 2009 (12) (DLCST)	Patients with previous treatment for lung or breast cancer, malignant melanoma, or hypernephroma excluded. Minimum length of time since diagnosis of any other previous cancer: 5 yr (pg 609)	Growth was defined as an increase in volume ≥25%. Growing nodules were considered category 5 (pg 610)		PET-CT or contrast-enhanced CT, invasive procedures (bronchoscopy, transthoracic needle aspiration biopsy, endoscopy US, endobronchial US, and/or mediastinoscopy, VATS (pg 610)	Incidental findings on CT outside lungs or bronchi were referred for relevant work-up and treatment (pg 610)	5 rounds of screening, 1 yr apart (baseline, yr 1 to yr 4) (pg 609)	
LopesPegna 2009 (17) (ITALUNG)	Patients with previous cancer other than non-melanoma skin cancer were excluded (pg 35)	Significant growth defined as increase of ≥1 mm in mean diameter in solid nodule or increase of the solid component in a part-solid nodule (pg 36)		Follow-up LDCT, PET, FNA, CT-guided FNA, fibre-optic bronchoscopy (pg 36)	If screening detected focal abnormalities consistent with inflammatory disease, antibiotic treatment and a 1-mo follow-up CT was recommended (pg 36)	4 rounds of screening, 1 yr apart (baseline, yr 1 to yr 3) (pg 35,36)	Both screening and no-screening groups had access to smoking cessation program (pg 35)
Garg 2002 (18)			All nodules classified as being non-benign after the baseline CT were fully evaluated with diagnostic thin-section CT. Scanning started from the lung apices and extended inferiorly to include the adrenals (pg 508)	Dynamic contrast-enhanced CT, PET, and/or biopsy; percutaneous, bronchoscopic, or surgical tissue evaluation (pg 508)		2 rounds of screening (baseline, yr 1) (pg 507)	Current smokers in both groups had access to smoking cessation program (pg 507)
Gohagan 2004 (44) Gohagan 2005 (45) (LSS)	History of lung cancer or current treatment for any cancer other than non-melanoma skin cancer was excluded (44, pg			Diagnostic follow-up (no protocol): comparison with previous CT or CXR, clinical evaluation, follow-up chest CT, follow-up CXR,		2 rounds of screening (baseline, yr 1) (44, pg 115)	

Study	Risk	Defining a positive scan & follow-up actions				Planned screening interval and duration	Smoking-cessation program
	Previous cancer history	Growth	CT follow-up technique (limited scan?)	Other tests	Incidental findings	Interval	
	115)			pulmonary function tests, invasive procedures (bronchoscopy, lung biopsy or resection, thoracotomy, thoracoscopy, mediastinotomy, mediastinoscopy (44, Table 3, pg 118)			
Blanchon 2007 (46) (DEPISCAN)	History of malignancy was excluded (pg 52)			Diagnostic follow-up: PET and/or histologic diagnosis, invasive procedures (pg 52)		3 rounds of screening, 1 yr apart (baseline, yr 1, yr 2) (pg 52)	
Single Arm Studies							
Veronesi 2008a (47) Veronesi 2008b (48)	Diagnosis of malignant disease (other than non-melanoma skin cancer) in previous 5 yr excluded (47, pg 341)	Growing lesions defined as those with volume-doubling time between 30 and 400 days (47, pg 341)		PET-CT, surgery (pneumonectomy, lobectomy, sub-lobar resection, lymph node biopsy, FNA biopsy (47, Table 2, pg 344)		5 rounds of screening, 1 yr apart (baseline, yr 1 to yr 4) (47, pg 341)	
Wilson 2008 (49) (PLuSS)	Patients with previous lung cancer were excluded (pg 957)			High suspicion nodules: thoracoscopy with excisional biopsy or mediastinoscopy; moderate suspicion: thoracic CT, PET, or PET-CT; low suspicion: periodic thoracic CT (pg 958)	Patients were alerted after CT screen of central airway abnormalities, thoracic lymph enlargement, or other incidental findings with physician-directed diagnostic follow-up (pg 958)	2 rounds of screening (baseline, yr 1) (pg 956)	
Menezes 2010 (50)	Patients with previous cancer other than non-melanoma skin cancer were excluded (pg 178)	Growth defined as an interval increase in the diameter of nodules in any direction as	1-mo thin-slice LDCT through the lesion and antibiotics for nodules ≥15 mm; 3-mo thin-slice LDCT through solid nodules ≥5 mm	CT-guided biopsy, follow-up CT with contrast enhancement (pg 179)		6 rounds of screening, 1 yr apart (baseline, yr 1 to yr 5) (pg 178)	

Study	Risk	Defining a positive scan & follow-up actions				Planned screening interval and duration	Smoking-cessation program
	Previous cancer history	Growth	CT follow-up technique (limited scan?)	Other tests	Incidental findings	Interval	
		determined on cross-sectional CT images (pg 178)	(pg 178)				
Sobue 2002 (51) (ALCA)			Thin-section CT if the findings showed a solitary noncalcified nodule >4.9 mm, or an area of localized opacification increasing in size (pg 912)	CT fluoroscopy-guided transbronchial biopsy, CT fluoroscopy-guided percutaneous needle biopsy, VATS, bronchoscopy, thoracotomy (pg 915)		6-monthly screening (pg 913) Patients received LDCT, CXR, and sputum cytology (pg 912)	
Swensen 2003 (52) Swensen 2002 (53)	Previous cancer within the past 5 yr (except for non-melanoma skin cancer, cervical cancer in situ, or localized prostate cancer) were excluded (53, pg 508)		Follow-up CT done at numerous institutions; technique used not dictated by study protocol, but most medical centres used standard-dose chest CT with thin sections for nodule analysis (53, pg 509)	Nodules <4 mm: CT at 6 mo; nodules 4-8 mm: CT at 3 mo; nodules 8-20 mm, CT immediately and consider nodule-enhancement protocol or PET; nodules >20 mm: biopsy (52, pg 757)	Incidental findings on CT were considered clinically significant if they required further evaluation, or had substantive clinical implications (53, pg 510). Other diagnoses recorded in database (52, pg 757, Table 2 pg 759)	5 rounds of screening, 1 yr apart (baseline, yr 1 to yr 4) (53, pg 508)	
Pastorino 2003 (22)	History of malignant disease excluded (pg 593)		Spiral thin-section CT limited to the area of interest and 3-D analysis for noncalcified lesion >5 mm (pg 594)	High-resolution CT for lesions >5 mm, PET for noncalcified lesions ≥7 mm after high-resolution CT (pg 593) Biopsy (pg 594)	Each patient contacted twice yearly to record diagnosis or treatment of any concurrent disease, particularly respiratory disorders and interval cancers (pg 594)	5 rounds of screening, 1 yr apart (baseline, yr 1 to yr 4) (pg 593)	
Henschke2001a	History of	Tumour volume	For newly detected	Biopsy by		3 rounds of	

Study	Risk	Defining a positive scan & follow-up actions				Planned screening interval and duration	Smoking-cessation program
	Previous cancer history	Growth	CT follow-up technique (limited scan?)	Other tests	Incidental findings	Interval	
(54) Henschke 2001b (55) (ELCAP)	malignant disease (except for non-melanoma skin cancer) excluded (54, pg 154)	and time between high-resolution CT screens were used to calculate doubling time of tumour (54, pg 155)	nodules that had grown, further work-up with standard-dose diagnostic CT, including high-resolution CT of the nodules was recommended (54, pg 155)	percutaneous CT-guided transthoracic FNA or by VATS (54, pg 155)		screening, 1 yr apart (baseline, yr 1, yr 2) (54, pg 154)	
Bastarrika 2005 (56)		Growth was defined as an increase of the diameter of the nodule in at least 1 dimension and was assessed visually by the radiologist comparing 2 CTs side by side on the workstation (Suppl, pg 4)		Noncalcified nodules ≥10 mm or nodules >7 mm showing growth were evaluated with PET. Percutaneous FNA biopsy or intraoperative biopsy (pg 1379)		2 rounds of screening (baseline, yr 1) (pg 1379)	
Diederich 2004 (57) Diederich 2000 (58) Diederich 2002 (23)	Patients with known pulmonary metastases excluded (23, pg 774)	Growth was defined as an increase of the nodule's diameter in at least 1 dimension: craniocaudal, ventrodorsal, or mediolateral (positive test result) (23, pg 775)	Immediate thin-section LDCT of noncalcified nodules (57 pg 692) Limited thin-section LDCT covered a maximum of 50 mm in the craniocaudal axis, with maximum dose less than that of CXR in 2 views (23, pg 774)	Bronchoscopic, percutaneous or thoracoscopic biopsy (57, pg 692)		6 rounds of screening, 1 yr apart (baseline, yr 1 to yr 5) (57, pg 692)	
Novello 2005 (59)	Personal history of malignancy excluded (pg 1663)	Growth was defined as an increase of the nodule's diameter in at least 1 dimension (pg 1663)	Within 1 mo, contrast-medium chest CT with enhancement assessment. From 2nd year, standard-dose CT with thin sections to further analyze and follow-up new	Patients with positive enhancement were occasionally considered for PET scan (pg 1663)	All incidental findings had additional imaging investigations to reach a definitive diagnosis unless the abnormalities were already known and diagnosed (pg	5 rounds of screening, 1 yr apart (baseline, yr 1 to yr 4) (pg 1663)	

Study	Risk	Defining a positive scan & follow-up actions				Planned screening interval and duration	Smoking-cessation program
	Previous cancer history	Growth	CT follow-up technique (limited scan?)	Other tests	Incidental findings	Interval	
			nodules or any increase in size of previously detected nodule (pg 1663)		1665)		
Callol 2007 (60)	Neoplastic antecedents or tumour symptoms or cancer of some other location were excluded (pg 218)			Nodules <5 mm had LDCT with annual controls; nodules 5-10 mm had high-resolution CT after 3, 6, 12, 24 mo plus biopsy or resection if growth; nodules >10 mm had PET, angiographic CT, FNA biopsy, VATS, bronchoscopy, or thoracotomy (pg 218)	Any non-nodular image raising diagnostic doubts as to its benignity was studied by applying the same conventional diagnostic protocol (pg 218)	2 rounds of screening, 2 yr apart (baseline, yr 2) (pg 218)	
MacRedmond 2004 (19) MacRedmond 2006 (20) (PALCAD)	Previous history of cancer excluded (19, pg 237)			Noncalcified nodules ≤5 mm in diameter were followed up by high-resolution CT at 6, 12, 24 mo unless growth detected; 6-10 mm were biopsied (VATS or percutaneous) if characteristics highly suspicious of malignancy; nodules ≥11 mm referred for biopsy (19, pg 238)	Other parenchymal, mediastinal, pleural, & extrathoracic abnormalities were recorded (19, pg 238). Incidental findings were evaluated by one of the study physicians, discussed with patient and primary care physician and referred, where appropriate, for specialist evaluation or more diagnostic testing (19, pg 238)	2 rounds of screening, 1 yr apart (baseline, yr 1) (19, pg 238)	Smoking cessation recommended and facilitated for all patients (19, pg 238)
Picozzi 2005 (16)	Personal history of malignancy excluded (pg 18)	Nodule growth was defined as an increase in its	In the case of a positive test on initial LDCT, a targeted	Indeterminate nodules <10 mm had LDCT and high-		3 rounds of screening, 1 yr apart (baseline,	

Study	Risk	Defining a positive scan & follow-up actions				Planned screening interval and duration	Smoking-cessation program
	Previous cancer history	Growth	CT follow-up technique (limited scan?)	Other tests	Incidental findings	Interval	
		diameter of ≥20% or 1 mm or the transformation of a semi-solid nodule into a solid nodule, even with unchanged diameter (pg 19)	spiral acquisition on the nodules with a full dose, 1 mm collimation, pitch 1 and 1 mm reconstruction interval was done (pg 18)	resolution CT at 3, 6, 9, 12 mo when detected at baseline and at 1, 3, 6 mo when detected at 1st or 2nd annual screen; indeterminate nodules ≥10 mm had CT-guided biopsy and cytology. New indeterminate nodules >3 mm detected after baseline CT were assessed with high-resolution CT following antibiotic treatment. In nodules >7 mm, CT-guided biopsy or VAT biopsy were considered. Limited use of PET was made in nodules ≥7 to 8 mm (pg 20-21)		yr 1, yr 2) (pg 19)	

ALCA = Anti-Lung Cancer Association; CT = computed tomography; CXR = chest x-ray; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST = Danish Lung Cancer Screening Trial; ELCAP = Early Lung Cancer Action Project; FNA = fine-needle aspiration; LDCT = low-dose computed tomography; mo = month; MRI = magnetic resonance imaging; NELSON = Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST = National Lung Screening Trial; PET = positron emission tomography; pg = page; Suppl = supplement; US = ultrasound; VATS = video-assisted thoracoscopic surgery; yr = year.
Empty cells indicate the study did not provide information on that topic.

Appendix 5. UK National Screening Committee Criteria for Appraising the Viability, Effectiveness, and Appropriateness of a Screening Program
(http://www.screening.nhs.uk/criteria)

The Condition
1. The condition should be an important health problem. 2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood, and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage. 3. All the cost-effective primary prevention interventions should have been implemented as far as practicable. 4. If the carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood, including the psychological implications.
The Test
5. There should be a simple, safe, precise and validated screening test. 6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed. 7. The test should be acceptable to the population. 8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals. 9. If the test is for mutations, the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.
The Treatment
10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than for late treatment. 11. There should be agreed evidence-based policies covering which individuals should be offered treatment, and the appropriate treatment to be offered. 12. Clinical management of the condition and patient outcomes should be optimized in all health care providers prior to participation in a screening program.
The Screening Program
13. There should be evidence from high-quality RCTs that the screening program is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an “informed choice” (e.g., Down’s syndrome, cystic fibrosis carrier screening), there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened. 14. There should be evidence that the complete screening program (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public. 15. The benefit from the screening program should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment). 16. The opportunity cost of the screening program (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e., value for money). Assessment against these criteria should have regard to evidence from cost-benefit and/or cost-effectiveness analyses and have regard to the effective use of available resource. 17. All other options for managing the condition should have been considered (e.g., improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available. 18. There should be a plan for managing and monitoring the screening program and an agreed

set of quality assurance standards.
19. Adequate staffing and facilities for testing, diagnosis, treatment and program management should be available prior to the commencement of the screening program.
20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.
21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.
22. If screening is for a mutation, the program should be acceptable to people identified as carriers and to other family members.

Evidence-Based Series #15-10: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Screening High-Risk Populations for Lung Cancer: Development Methods, Recommendations Development and External Review Process

H. Roberts, C. Walker-Dilks, K. Sivjee, Y. Ung, K. Yasufuku, A. Hey, N. Lewis, and the Lung Cancer Screening Guideline Development Group

Report Date: April 18, 2013

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC produces evidence-based and evidence-informed guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

This EBS is comprised of the following sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.

- *Section 3: Development Methods, Recommendations Development, and External Review Process*. Summarizes the EBS development process, the recommendations development process and the results of the formal external review of the draft version of the EBS.

FORMATION OF GUIDELINE DEVELOPMENT/WORKING GROUP

CCO Prevention and Cancer Control asked the PEBC to develop a guideline on LDCT screening for lung cancer. In consultation with Prevention and Cancer Control a Working Group was identified from the memberships of the Lung Cancer DSG, the Cancer Imaging Program, and Provincial Primary Care and Cancer Network. This Working Group consisted of a radiologist, a radiation oncologist, a respirologist, a thoracic surgeon, a primary care physician, and a methodologist. The Working Group and Prevention and Cancer Control also formed the Lung Cancer Screening Guideline Development Group. This group would take responsibility for providing feedback on the guideline as it was being developed and acted as Expert Panel for the document at Internal Review, reviewing the document and requiring changes as necessary before approving it.

OBJECTIVES

This Working Group developed the following objective for this guideline in consultation with Prevention and Cancer Control:

To determine the appropriate use, if any, of low-dose computed tomography (LDCT) in the screening of high-risk populations for lung cancer, including:

- Patient characteristics that define a high-risk population
- The necessary elements involved in defining a positive result on LDCT and follow-up of a positive result
- The appropriate screening interval
- Organized versus opportunistic screening

EVIDENTIARY BASE DEVELOPMENT

An existing systematic review on CT screening for lung cancer provided the evidentiary base for this guideline (3), as described in Section 2 of this EBS. The literature search from the systematic review was run again in May 2012 to retrieve any relevant studies published since the systematic review was completed.

INITIAL RECOMMENDATIONS

Using the evidentiary base in Section 2, the Working Group developed a set of initial recommendations. These initial recommendations were developed through a consideration of the aggregate evidence quality and the potential for bias in the evidence, and the likely benefits and harms of LDCT screening. The Working Group considered the values they used in weighing benefits compared to harms, and then made a considered judgement.

Main Recommendation

Key Evidence for Benefits and Harms

- High-quality evidence from one RCT shows a statistically significant mortality benefit for screening under strict parameters in a controlled health care environment (4).
- The number needed to screen (NNS) of 320 to prevent one lung cancer death should be considered in the context of other screening programs: for mammography, an NNS of

1339 women aged 50 to 60 years to prevent one breast cancer death (5), for flexible sigmoidoscopy an NNS of 489 to prevent one colorectal cancer death (6), and for PSA screening an NNS of 100 to prevent zero to one prostate cancer deaths (7).

- The RCT also showed a benefit for all-cause mortality (RR 0.93, 95% CI 0.86 to 0.99, p=0.02).
- LDCT screening is associated with a high rate of noncancerous nodule detection (false-positive results) (90% to 97%).
- Repeat diagnostic imaging ranges from 2% to 58% and invasive procedures from 1.3% to 8% per screened individual.
- LDCT exposes patients to a small amount of radiation. NLST participants received about 8 mSv over 3 years, including screening and diagnostic examinations.
- Screening does not appear to influence smoking continuation, re-initiation, or cessation among participants.
- The ages of participants for enrolment in the studies in the systematic review varied from 40 to 60 for the lower age limit and from 69 to 85 years for the upper age limit. The NLST recruited participants between 55 and 74 years of age.
- Participant eligibility with respect to smoking history ranged from ≥10 to ≥30 pack-years, and the number of years since quitting among former smokers ranged from ≤0.5 to ≤15. Participation in the NLST required a smoking history of ≥30 pack-years, and former smokers had to have quit within the past 15 years.

Aggregate Evidence Quality and Potential for Bias

Two RCTs (NLST and DLCST) had a low risk of bias. The other RCTs had a variable risk of bias because of smaller sample sizes and mostly preliminary results. The results for lung cancer-specific mortality favoured LDCT in the two trials with low risk of bias, and were statistically significant in one of the trials.

Values of the Working Group

The decrease in lung cancer mortality outweighs the increased risk of false positives. Detecting lung cancer early is a priority. An entry age for screening of 50 years was initially favoured in the interest of not missing any cancers. But it was estimated that an additional 100,000 persons would need to be screened to include age 50 to 55. This would increase the false-positive rate.

Smoking history is crucial to determining who is at high risk for lung cancer, but it is a subjective risk factor, and we acknowledge that it cannot be precisely measured. The NLST used ≥30 pack-years as a criterion for screening (4). Although it was the only trial to show a reduction in mortality, the lung cancer detection rate was 4.0%. Similar detection rates were observed in other studies (8-11). These studies had lower smoking history thresholds for enrolment of ≥10 to ≥20 pack-years. The Working Group considered the rate of lung cancer detection as indirect evidence likely to lead to a mortality reduction and considered whether a ≥20 pack-year smoking history was a reasonable eligibility criterion for screening.

Considered Judgement

The Working Group agrees with the age parameters in the NLST and advocates for lung cancer screening to begin in persons ≥55 years of age and to stop at age 74. Using data from the Ontario population projections update (12) and the Canadian Tobacco Use Monitoring Survey (13), and a screening compliance rate of 25%, we estimated that in the age group of 55 to 74 years of age, 285,000 people would need to be screened. Screening would cease at 74 years of age unless the physician and patient agreed on its continuation.

The Working Group recommends lung cancer screening for persons with a 30 pack-year history, and suggests that screening for persons with a shorter smoking history should be optional. This recommendation will be revisited when the results of the NELSON trial (with a 15 pack-year requirement) are published.

The Working Group advocates a recruitment strategy for screening based on age and smoking history. A previous cancer diagnosis should not exclude persons from being screened unless active disease is still present. Occupational exposure (e.g., asbestos or radon) or passive smoking should similarly not be considered as exclusion criteria, but should be recorded during data collection.

Initial (DRAFT) Recommendation 1 Screening for lung cancer with LDCT is recommended in high-risk populations defined as persons 55 to 74 years of age with a minimum smoking history of ≥30 pack-years* who currently smoke or have quit within the past 15 years and are disease-free at the time of screening.

*Pack-years = number of cigarette packs smoked per day x the number of years smoked.

Defining a Positive Result on LDCT and Follow-up of a Positive Result

Key Evidence for Benefits and Harms

- In most studies, follow-up was triggered by the size of a detected nodule. Nodule sizes warranting further follow-up ranged from any size to ≥5 mm. The average nodule detection rate per screening round was about 20%, but in the RCTs, it ranged from 3% in the RCT by Garg et al, which used a nodule size cut-off of any size (14), to 30% in the ITALUNG trial (15), which used a cut-off of ≥5 mm. The NLST classified noncalcified nodules ≥4 mm in diameter as positive and had a positive rate of 27.3%.
- The type of follow-up investigations also varied across studies, and several studies, including the NLST, did not follow a diagnostic protocol for evaluation of nodules. Two ongoing studies, the Pan-Canadian Early Detection of Lung Cancer study and the I-ELCAP both have protocols for LDCT scan and follow-up. The protocols are based on the nodule size and/or consistency and the growth rate of the nodules in determining the follow-up investigations.

Aggregate Evidence Quality and Potential for Bias

Variation exists among the studies in terms of defining a positive test result (size of nodule) and follow-up. Detected nodules in general prompted further imaging, and management protocols were inconsistently reported.

Values of the Working Group

The working group values high accuracy in identifying lung cancer nodules and a low false-positive rate. Radiation exposure as low as can reasonably be achieved with LDCT scans is necessary for the safety of the patient, particularly in the setting of ongoing screening. Judicious use of imaging resources and follow-up investigations is required.

Considered Judgement

With respect to nodule size warranting further investigation, the recommendation deviates from the parameters of the NLST. In general, the smaller the nodule defining a positive scan, the larger the number of positive scans, and the larger the number of false-positive results and unnecessary investigations for benign nodules. Based on a 4-mm threshold, 7191 of 26,309 (27.3%) scans in the NLST were positive; 6921 (96%) of the positive results were false positive. A 5-mm threshold will lower the false-positive rate, and if nodules

between 4 and 5 mm are assessed on an annual scan, it is unlikely a significant finding will be missed.

Initial (DRAFT) Recommendation 2: Positive Result and Follow-up

- **Screening modality: Screening for lung cancer should be done using an LDCT multi-detector scanner with the following parameters: 120 to 140 peak kilovoltage (kVp), 20 to 60 milliampere seconds (mAs), with an average effective dose ≤1.5 millisieverts (mSv).**
- **Collimation should be ≤3mm.**
- **Definition of a positive result: A nodule size of ≥5 mm found on LDCT indicates a positive result and warrants a 3-month follow-up CT. Nodules ≥15 mm should undergo immediate further diagnostic procedures to rule out definitive malignancy. In addition, volume-doubling time between 30 and 400 days suggests malignant growth. Growth outside of these parameters is usually benign, but can be malignant.**
- **Appropriate follow-up of a positive result: Follow-up CT of a nodule should be done at 3 months as a limited LDCT scan (i.e., only a slab covering the nodule will be scanned, not the entire chest). Depending on the location of a nodule and the overall clinical situation, a PET/CT or bronchoscopy could be performed. Growth of an existing nodule, development of a solid component in GGO, or a new nodule detected on an annual or any repeat LDCT scan should prompt an additional limited scan in 3 months, and successive scans or biopsy should be determined by the physician and radiologist. Any non-lung-related abnormalities identified on LDCT should be followed up as directed by the medical team for the individual undergoing screening.**

LDCT Screening Interval:

Key Evidence for Benefits and Harms

- Seven of eight RCTs conducted screening on an annual basis, and 11 of the 13 cohort studies screened annually. Several studies are ongoing, but have not completed follow-up.
- The NLST had a significant mortality benefit with screening annually, but had only one initial LDCT scan followed by two annual screens.
- The MILD trial, retrieved in the update search from May 2012, included a randomization component comparing LDCT screening every year (annual) with every 2 years (biennial) (16). Of the 49 lung cancers detected by LDCT screening, 29 were in the annual group and 20 in the biennial group. Sixty-two percent of the cancers in the annual and 70% in the biennial group were stage I, and the proportion of advanced disease (stage III to IV) was 31% in the annual and 25% in the biennial group. Thus, biennial screening did not result in a shift to higher stage disease.

Aggregate Evidence Quality and Potential for Bias

The NLST study had a low risk of bias.

The MILD trial was initially designed with a planned sample size of 10,000 participants, a 10-year screening period, and a 100,000 person-year follow-up, and powered to detect a 30% difference in lung cancer mortality between LDCT and usual care groups. Recruitment was slow as volunteers were reluctant to be assigned to the usual care group, leading to an underpowered trial, unable to detect differences of 10%.

Values of the Working Group

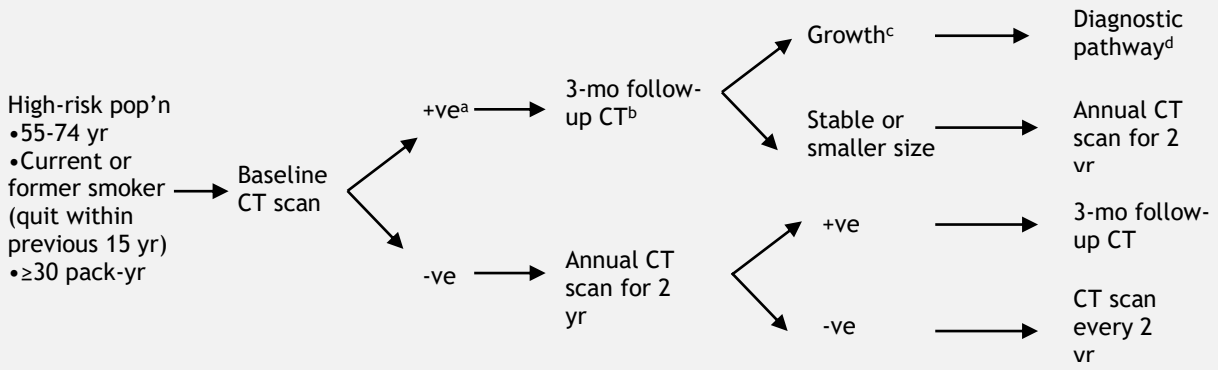
Determining the appropriate frequency of screening is challenging because population screening involves an ongoing intervention over several years, while clinical trials have a defined beginning and end. The NLST had planned three annual LDCT examinations, at which time the endpoint of mortality was to be assessed. This guideline is concerned with the implementation of screening in an at-risk population. As with other screening programs, lung cancer screening needs to go on as long as the risk persists.

The Working Group acknowledges that the current evidence does not support a specific screening interval. The Working Group acknowledges the risks of accumulated radiation exposure to the individual and the accumulated costs to the health care environment with more frequent scans, and the risks of missing early, curable lung cancer nodules with less frequent scans.

Considered Judgement

There is a paucity of long-term or comparison data on screening frequency. Most studies follow an annual screening interval, but yearly screening indefinitely may not be necessary or practical. The Working Group proposes following the interval of the NLST (initial baseline screen followed by two annual screens), then stratifying screening according to the CT findings with screening once every two years following each negative scan result. Persons with no abnormalities detected on the baseline scan should have a repeat LDCT scan in 12 months. Persons in whom the largest solid nodule identified on baseline scan is <5 mm in diameter (or a part-solid nodule <8 mm) should also receive a repeat LDCT scan in 12 months.

Initial (DRAFT) Recommendation 3: Screening Interval
Persons at high risk for lung cancer should commence screening with an LDCT scan once per year for 3 years, then once every 2 years after each negative scan.



[a]A positive test is defined as a solid nodule ≥5 mm or a non-solid nodule (part solid or ground glass nodules) ≥8 mm.
[b]If the nodule appearance dictates a different approach (e.g., bronchoscopy or PET), this can be chosen at the discretion of the reading physician.
[c]Volume-doubling time of between 30 and 400 days.
[d]https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=124606.

Organized Versus Opportunistic Screening
Key Evidence for Benefits and Harms

- There is RCT evidence that LDCT screening reduces mortality in high-risk persons when performed in specialized centres with multidisciplinary care teams and expertise in screening, diagnosis, management of findings, and treatment of lung cancer.
- The 33 study sites of the NLST were all academic medical centres, most with >400 beds and were designated cancer centres. Several had subspecialty training programs in thoracic surgery.
- Participants in two RCTs had access to a smoking-cessation program and in one single-arm study, smoking cessation was recommended and facilitated.

Aggregate Evidence Quality and Potential for Bias

There is no direct evidence that compares opportunistic with organized screening. All RCTs of screening to date have been conducted in an organized setting because they were controlled clinical trials, and not studies of population-based interventions (e.g., entire cities, counties, etc). Therefore, the benefit of screening in persons at risk for lung cancer has been measured only in an organized setting, and its benefit in an opportunistic setting is unknown.

Values of the Working Group

Screening for lung cancer with LDCT is inevitable and already occurring. There are substantial harms associated with opportunistic screening in this population, including a high risk for false positives and ensuing unnecessary treatment, and uneven coverage of persons at risk. A programmatic approach will ensure that standardized procedures regarding participant recruitment, equipment, staffing, training, communication, and quality assurance are followed. It would also provide the opportunity to collect data in a consistent manner and support a database of information that can be used for evaluation and planning.

Considered Judgement

In consideration of the potential harms of screening in an opportunistic fashion, and the fact that, to date, the benefit of screening has only been demonstrated in an organized setting, the Working Group proposes that LDCT screening for lung cancer should only be undertaken within the parameters of an organized screening program.

Initial (DRAFT) Recommendation
Lung cancer screening with LDCT should be provided through an organized program and administered by specialized centres with multidisciplinary care teams and expertise in screening, diagnosis, management of findings, evaluation, and treatment of lung cancer. Smoking cessation interventions should be an integral part of the program.

INTERNAL REVIEW

Almost all PEBC documents undergo internal review. This review is conducted by the Expert Panel of the Lung Cancer Screening Guideline Development Group and the Report Approval Panel. The Working Group was responsible for incorporating the feedback and required changes of both of these panels, and both panels had to approve the document before it could be sent to External Review.

Expert Panel Review and Approval

The Expert Panel for this document was comprised of members of the Lung Cancer DSG and experts in the field of screening and population (Appendix 1). The members of this group were required to submit conflict-of-interest declarations prior to reviewing the document. These declarations are described at the end of Section 2. The document must be approved by formal vote. In order to be approved, 75% of the Expert Panel membership must cast a vote or abstain, and of those that voted, 75% must approve the document. At the time of the voting, the Expert Panel members could suggest changes to the document, and possibly make their approval conditional on those changes. In those cases, the Working Group was responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

A complete draft of the document was sent to the Expert Panel (11 members of the Lung Cancer DSG and three experts in screening or population health) on 3 August 2012 by email with instructions to review it and provide feedback.
The vote results were as follows:
Do not approve = 3
Approve with conditions = 5
Approve = 6
The Expert Panel provided the following feedback:

One Panel member withheld approval of the document for two main reasons:

1. The guideline development group lacked expertise in population health, public health, chronic disease epidemiology, and health economics and health policy. The intervention uses some clinical processes, but is fundamentally not a clinical activity.
2. Release of this guideline should wait until the publication of several trials that are currently in progress.

A second Panel member withheld approval of the document for the following reasons:

1. The document provided inadequate evaluation of the harms associated with LDCT. There was no description of safety criteria or appraisal of safety issues.
2. The claim that an organized screening program is necessary to avoid ad hoc adoption of lung screening is not valid. The same could be said for PSA screening or ovarian cancer screening.
3. The body of evidence supporting the guideline rests completely on the NLST. What about the generalizability of the findings? What if the findings of this single trial are not confirmed? Where do we stand with other (ongoing) trials?

A third Panel member withheld approval of the document because of recommendations that deviated from the available data:

1. With respect to the duration of screening, the guideline proposed that after age 75, screening decisions should be based on discussion between patients and health care providers. The justification for a cut-off age based on discussion is not precise enough for a screening program. Once parameters based on discussion become part of the guideline, other criteria are susceptible to change, such as a lower age, or a few less cigarettes. Changing age, pack-years, and other eligibility criteria will have a substantial effect on sensitivity, specificity, and cost-effectiveness, thus strict criteria are urged.

2. With respect to the definition of a positive result, the guideline defined a positive result on a CT scan as a lung nodule with a diameter of at least 5 mm, whereas the NLST stipulated ≥4 mm. A change from 4 to 5 mm could have a profound effect on the survival benefit.
3. The screening interval proposed by the guideline involved an initial LDCT scan followed by annual screen for 2 consecutive years, and then once every 2 years after each negative scan. Participants in the NLST had a baseline scan and two annual scans only. Without more data can biennial scans be recommended with any authority?

Feedback from the other Expert Panel members, apart from requesting more discussion or clarification of certain points, mainly focused on the justification for recommendations that diverged from the parameters of the NLST and echoed the queries mentioned above including the change from a 4-mm nodule to a 5-mm nodule, a biennial screening interval, and the duration of screening.

A few Panel members held contrasting views:

1. One Panel member stated that moving to biennial screening seemed reasonable given the feasibility challenges to continuing annual screening, and another Panel member indicated that data from the Canadian study supported biennial screening from the outset.
2. One Panel member suggested that high risk be expanded to include asbestos and occupational exposure in combination with a smoking history lower than 30 pack-years. Given that the NLST began 10 years ago, its eligibility criteria may not be current, and a broader baseline risk could be warranted. This panel member also questioned the NLST criterion of quitting smoking within 15 years. Is there a significant drop in smoking-related lung cancer at the 15 year abstinence point? Does the 15-year mark pertain to stopping screening as well? If a person becomes abstinent for 15 years during the screening period, does screening stop? Since it would be hoped that most people who are screened are also quitting if they have not already, the question of when to stop screening is relevant.

In response to this feedback, the Working Group made the following changes.

- The mandate of the Working Group was to review the clinical evidence for lung cancer screening and to make recommendations based on this evidence. Members of the Working Group were selected and invited for their expertise and knowledge about the clinical aspects of lung cancer screening. The Expert Panel is an approval-granting body and is part of the guideline development group for this document. Population and public health experts were among the members of the Expert Panel and their feedback is taken into consideration in amending the recommendations. This is done with the goal of achieving consensus among the Expert Panel members in approving the guideline.
- More emphasis on the benefits and harms of LDCT screening was added to Section 1 in response to the observation that the safety of LDCT was not adequately described.
- In the opinion of the Working Group, the results of the NLST carry the greatest weight in informing the recommendations. The smaller ongoing trials are unlikely to influence the impact of the NLST to any large extent. A statement to this effect was added to Section 1 in response to the observation that the recommendations should wait for the results of the ongoing studies.
- The main recommendation and justifications were tightened to be precise about duration and inclusive ages in response to the observation that any vagueness in the

recommendations will affect the clinical and cost effectiveness of screening. Furthermore, unambiguous justification was added to recommendations that included any deviations from the parameters of the NLST.

- The recommendation urging the creation of an organized screening program was replaced with a proposal that a lung cancer screening program be considered.

Report Approval Panel Review and Approval

The purpose of the Report Approval Panel (RAP) review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of nine clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. For each document, three RAP members review the document: the Director and two others. RAP members must not have had any involvement in the development of the guideline prior to Internal Review. All three RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made, with the Assistant Director of Quality and Methods, PEBC, making a final determination that the RAP's concerns have been addressed.

In November 2012 the RAP reviewed this document. The RAP approved the document. Key issues raised by the RAP included the following:
No key issues were raised by the RAP.
General suggestions included:

1. Add a table to Section 1 including some of the outcomes that appear in various areas in Section 2 (e.g., incidence of lung cancer in the general population and high-risk population, all cause and lung cancer-specific mortality; number needed to screen; incidence of repeat diagnostic imaging and invasive procedures; and rates of smoking continuation, re-initiation, and cessation).
2. The description of the guideline development process in Section 3 is rather confusing: the presentation of the initial recommendations, key evidence, etc., in Section 3 in its entirety, while documenting the development process and how the final recommendations were arrived at in a transparent fashion, is confusing for the reader, especially when some data are in the initial draft recommendations, but do not appear in the final recommendations in Section 1. If it is important to include what was initially drafted to place into context the views of the expert panel, then perhaps only the initial draft recommendations should be presented.
3. The key evidence that describes the definition of tumour growth does not relate to any of the recommendations.
4. While it is not within the scope of the guideline to provide risk-of-cancer induction in relation to radiation exposure, estimates based on radiation-exposure literature can be provided to complement the discussion.

The Working Group made the following changes in response to the RAP review:

1. The outcomes that are integral to the recommendations appear in Section 1.
2. The 3-part guideline template was recently redesigned so that Sections 1 and 3 would be more obviously linked together. The recommendations in Section 1 are accompanied by justifications that are summaries of the values of the working group and considered judgement pieces in Section 3. The documentation of the development process is more clearly laid out and more detailed in Section 3.
3. Tumour growth is the most important independent factor to assess the nature of a lung nodule found on LDCT. Tumour growth is one of the factors considered in the follow-up of a positive result on LDCT screening and invokes the lung cancer diagnostic pathway. This

is discussed in the recommendations pertaining to defining a positive result and follow-up, and the LDCT screening interval.
4. Estimates of cancer risk from radiation exposure were added to Section 1.

EXTERNAL REVIEW BY ONTARIO CLINICIANS AND OTHER EXPERTS

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the Lung Cancer Screening Guideline Development Group circulated the draft document with recommendations modified as noted under Internal Review, above, to external review participants for review and feedback.

Methods

Targeted Peer Review

During the guideline development process, two targeted peer reviewers from Canada considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Two reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations, and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on January 31, 2013. Follow-up reminders were sent at 2 weeks (email) and at 4 weeks (telephone call). The Lung Cancer Screening Guideline Development Group reviewed the results of the survey.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. By searching the terms *screening, primary care, lung, thoracic, or imaging* in the PEBC database, clinicians likely to be interested in the guideline were identified and contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on February 13, 2013. The consultation period ended on March 19, 2013. The Lung Cancer Screening Guideline Development Group reviewed the results of the survey.

Results

Targeted Peer Review

Two targeted peer reviewers provided responses. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.			1		1
2. Rate the guideline presentation.				2	
3. Rate the guideline recommendations.				2	
4. Rate the completeness of reporting.			1	1	
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	
6. Rate the overall quality of the guideline report.			1	1	
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			1	1	
8. I would recommend this guideline for use in practice.			1	1	

9. What are the barriers or enablers to the implementation of this guideline report?

The main barriers mentioned by reviewers concerned funding and the availability of resources and expertise.

Summary of Written Comments

The main points contained in the written comments were:

1. There is little discussion of the studies in the systematic review other than the NLST. How were they considered in crafting the recommendations?
2. The false-positive rate is not presented in a consistent fashion throughout the document.
3. Clarification is needed around the distinction between additional testing and diagnostic imaging.
4. The definition of opportunistic screening requires a better explanation.
5. Recommend a lower collimation for the LDCT scan.
6. The definition of a positive scan is based on expert opinion.
7. The estimate that there would be one death per 2500 people screened needs explanation about what this was based on (modelling or actual data).
8. Justify the comment that concern exists about a tendency for smokers with negative screening results to continue smoking.
9. The information on risk/benefit is not explicitly addressed so that it is clear that the benefit outweighs the risk.
10. Tighten up language around mortality vs. survival rate.

Modifications/Actions

1. The recommendations mainly reflect the parameters of the NLST. The conclusions of the systematic review in Section 2 also summarize the issues with the other studies compared with the NLST.

2. The reporting of false-positive rates varied across the studies included in the systematic review. The NLST uses the proportion of noncancerous nodules of all nodules over the study threshold (≥4 mm) (b/a+b) as the definition of false positive, while other studies (DLCST, LSS) used the proportion of noncancerous nodules among all patients tested (b/a+b+c+d). Ultimately, the false-positive rate is the proportion of noncancerous nodules above a certain threshold. The threshold could be 0 mm, 4 mm (as in the NLST), 5 mm (as in ELCAP), etc. There is currently research suggesting an increase of the threshold to a larger nodule diameter (17).
3. The text describing a positive result and follow-up was amended to be clearer. It now indicates that nodule size warranting additional imaging means additional CT and/or PET scans; nodule size warranting diagnostic testing means more invasive testing such as biopsy, bronchoscopy, or thoracoscopy.
4. The Working Group uses opportunistic screening to refer to the application of the test to individuals who are asymptomatic and may not qualify for the test, and also to those referred on an ad hoc basis without a programmatic structure. This was conveyed more clearly in the text.
5. Given the variation in collimation among the studies, the Working Group believed that collimation ≤3 mm was reasonable. As there is no compelling evidence to deviate from that used in the NLST, the Working Group is revising the recommendation for collimation to align with that of the NLST, ≤2.5 mm.
6. The Working Group is aware of recent studies suggesting increasing the threshold for determining a positive result (see 2 above).
7. The estimate that one cancer death may be caused by radiation from imaging per 2500 persons screened was done by modelling, as described in the collaborative review (3). This has been noted in the text.
8. The Working Group found evidence based on expert opinion that concern exists around smokers continuing to smoke after a negative CT scan. More discussion has been added to the text in the section on smoking, one of the outcomes of the collaborative systematic review.
9. The Working Group is aware there is substantial risk associated with LDCT screening for lung cancer: false-positive results, radiation exposure and ad hoc screening. The risks are addressed in detail in the document, and methods are proposed to keep them as low as possible so that they are outweighed by the benefits.
10. The text referring to survival has been amended.

Professional Consultation

Seventy-six responses were received. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	1	2	8	34	31
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	2	3	10	31	30

3. I would recommend this guideline for use in practice.	6	6	14	22	28

4. What are the barriers or enablers to the implementation of this guideline report?
The main barriers mentioned by the respondents were:

- Concern about accessibility to and availability of LDCT scans (patients in rural areas, availability of personnel, availability of diagnostic services for follow-up of positive results, state-of-the-art scanners, wait times)
- Logistical implications of implementing a screening program (infrastructure, call-back systems, education of primary care practitioners/general population, training, capital equipment, identification of appropriate centres, resource utilization, risk of inequitable application, increased burden on radiologists/thoracic surgeons)
- Cost to the healthcare system and the individual patient (cost of CT scans, follow-up imaging, biopsy, equipment, personnel and individual patient costs of travel, parking, time off work)
- Adverse effects and risk with respect to screening (radiation exposure, potential to continue smoking after a negative scan)
- How to deal with patients who fall outside of the parameters of the screening program.

Summary of Written Comments

The main points contained in the written comments were fairly evenly split between negative and positive reaction to the guideline. Some of the respondents expressed reservations about the implementation of lung cancer screening guidelines, citing the reasons expressed above as barriers, mainly safety, cost, and resources, while others applauded the effort to highlight current best evidence for lung cancer screening and to propose recommendations about how this could be achieved in Ontario.

Modifications/Actions

No modifications were made to the guideline in response to the Professional Consultation feedback.

UPDATE SEARCH

In keeping with the PEBC guideline development process, the literature search was updated on April 9, 2013 because the last search was done more than 9 months previously. The search was done in the MEDLINE and EMBASE databases using the identical search strategy of the previous search and covered the period from May 2012 to April 2013. No evidence was found that would alter the current recommendations.

CONCLUSION

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Lung Cancer Screening Guideline Development Group and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol.

REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12. Comment in: Ann Oncol. 2002;13(9):1507-9; author reply: 1509.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.
3. Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA. 2012;307(22):2418-29.
4. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409.
5. US Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;151(10):716-26, W-236.
6. Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, et al; UK Flexible Sigmoidoscopy Trial Investigators. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375:1624-33.
7. Moyer VA; on behalf of the U.S. Preventive Services Task Force. Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2012;157(2):120-34.
8. Infante M, Cavuto S, Lutman FR, Brambilla G, Chiesa G, Ceresoli G, et al; DANTE Study Group. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med. 2009;180(5):445-53.
9. Swensen SJ, Jett JR, Sloan JA, Midthun DE, Hartman TE, Sykes AM, et al. Screening for lung cancer with low-dose spiral computed tomography. Am J Respir Crit Care Med. 2002;165(4):508-13.
10. Henschke CI, Naidich DP, Yankelevitz DF, McGuinness G, McCauley DI, Smith JP, et al. Early lung cancer action project: initial findings on repeat screenings. Cancer. 2001;92(1):153-9.
11. Picozzi G, Paci E, Lopez Pegna A, Bartolucci M, Roselli G, De Francisci A, et al. Screening of lung cancer with low dose spiral CT: results of a three year pilot study and design of the randomised controlled trial "Italung-CT". Radiol Med. 2005;109(1-2):17-26.
12. Ontario Ministry of Finance. Ontario population by five-year age group and gender, selected years (reference, low and high scenarios) [cited July 2012]. Available from: http://www.fin.gov.on.ca/en/economy/demographics/projections/table4.html
13. Health Canada. Canadian Tobacco Use Monitoring Survey (CTUMS) 2010 [cited July 2012]. Available from: http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/ctums-esutc_2010_graph-eng.php
14. Garg K, Keith RL, Byers T, Kelly K, Kerzner AL, Lynch DA, et al. Randomized controlled trial with low-dose spiral CT for lung cancer screening: feasibility study and preliminary results. Radiology. 2002;225(2):506-10.
15. Lopes Pegna A, Picozzi G, Mascalchi M, Maria Carozzi F, Carrozzi L, Comin C, et al; ITALUNG Study Research Group. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. Lung Cancer. 2009;64(1):34-40.
16. Pastorino U, Rossi M, Rosato V, Marchianò A, Sverzellati N, Morosi C, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. Eur J Cancer Prev. 2012;21(3):308-15.

17. Henschke CI, Yip R, Yankelevitz DF, Smith JP; International Early Lung Cancer Action Program Investigators. Definition of a positive test result in computed tomography screening for lung cancer: a cohort study. Ann Intern Med. 2013 Feb19;158(4):246-52.