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STATE OF THE ART REVIEW

Screening for lung cancer using low dose computed tomography

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ABSTRACT

Screening for lung cancer with low dose computed tomography can reduce mortality from the disease by 20% in high risk smokers. This review covers the state of the art knowledge on several aspects of implementing a screening program. The most important are to identify people who are at high enough risk to warrant screening and the appropriate management of lung nodules found at screening. An accurate risk prediction model is more efficient than age and pack years of smoking alone at identifying those who will develop lung cancer and die from the disease. Algorithms are available for assessing people who screen positive to determine who needs additional imaging or invasive investigations. Concerns about low dose computed tomography screening include false positive results, overdiagnosis, radiation exposure, and costs. Further work is needed to define the frequency and duration of screening and to refine risk prediction models so that they can be used to assess the risk of lung cancer in special populations. Another important area is the use of computer vision software tools to facilitate high throughput interpretation of low dose computed tomography images so that costs can be reduced and the consistency of scan interpretation can be improved. Sufficient data are available to support the implementation of screening programs at the population level in stages that can be expanded when found to perform well to improve the outcome of patients with lung cancer.

Introduction

Worldwide, lung cancer is the leading cause of death from cancer, accounting for 1.6 million deaths a year.[1] Over the past four decades, clinical interventions have had only a minimal effect on reducing death from lung cancer.[2] The recent finding that lung cancer screening with low dose computed tomography can reduce death from lung cancer by 20% in high risk smokers provides an alternative strategy to improve outcomes in this group.[3] Many medical institutions and public health agencies worldwide are considering implementation of lung cancer screening.[4]

Effective implementation of lung cancer screening programs is complex and controversial, and it requires input from clinicians, researchers, public health officials, and the public. Major recent developments include lung cancer risk prediction tools to identify people at high risk who should be screened and a cancer risk calculator to guide clinical management of suspicious or indeterminate lung nodules found in a baseline computed tomogram.

This review describes current understanding of low dose computed tomography lung cancer screening, the associated uncertainties, and future advances in the science of lung cancer screening. It also focuses on crucial aspects of screening that are not well covered in other reviews, including who should be screened and what to do when lung nodules are found at screening.

Epidemiology

In 2012, there were 1.8 million cases of lung cancer (13% of all new cases of cancer) and 1.6 million deaths from lung cancer (20% of all cancer deaths) worldwide.[1] It is projected that by 2030, lung cancer will be the third highest cause of death in high income countries and the fifth highest cause in middle income countries.[5] International variation and time trends of the incidence of lung cancer reflect smoking behaviors.[6] The incidence of lung cancer

SOURCES AND SELECTION CRITERIA

We searched PubMed, Medline, and the Cochrane Library from 1 January 1980 to 1 January 2014 using combinations of words or terms that included lung or pulmonary, cancer or neoplasm, epidemiology or risk factors, and screening or early detection. In addition, risk factors were searched individually by names and synonyms. Articles from the reference lists of articles and text chapters were reviewed and relevant articles were identified. Non-English language abstracts and articles were excluded. Weighting of evidence was commensurate with the appropriateness and quality of study design. We regarded randomized controlled trials as being most suitable for interventions; prospective cohort designs as most suitable for potentially injurious exposures and incidence data; and cross sectional population surveys as most suitable for prevalence data. In addition, results from well conducted meta-analyses were considered to provide strong evidence, especially when summarizing randomized controlled trials and cohort studies.

increased throughout most of the 20th century. It then began to decline in American men in the early 1980s and in women around 1999.[6] This pattern is similar in most developed countries, whereas in less developed countries smoking and lung cancer are on the rise.[6]

Most lung cancers are diagnosed at an advanced stage, so survival after lung cancer is generally poor even in developed countries, with five year survival rates of 18% or less.[7] Diagnosis of lung cancer at an early stage is associated with a much higher survival rate of more than 70%.[8] This indicates that early detection with low dose computed tomography could reduce mortality from lung cancer.

Lung cancer screening

Many recent reviews on lung cancer screening exist.[9 10] Only key topics that are not well covered in previous publications are discussed here. Several lung cancer screening studies have been conducted since the 1950s using chest radiography with or without other modalities, such as sputum cytology.[11] Many of these studies were criticized as having methodological weaknesses and none produced encouraging results. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) was the first large well designed and well conducted randomized controlled trial (RCT) to evaluate the effectiveness of annual screening with chest radiography. This trial found that chest radiography screening did not reduce lung cancer mortality.[12]

With rapid advances in imaging technology over the past two decades, it became possible to detect nodules as small as 1 mm by computed tomography using a radiation dose of no more than 1.5 mSv. With this came the hope that low dose computed tomography screening might reduce mortality from lung cancer by detecting early stage cancers while reducing exposure to radiation. Results from the Early Lung Cancer Action Project (ELCAP) suggested that lung cancer could be detected at an earlier stage and survival could be extended.[13] Subsequently, the National Lung Screening Trial (NLST) was the first well powered, designed, and conducted RCT to examine the effectiveness of such screening in reducing death from lung cancer.[10] It found that annual screening reduced death from lung cancer by 20% in high risk people aged 55-74 years who had smoked at least 30 pack years (a pack year is the equivalent of smoking one pack of 20 cigarettes a day for one year) and in former smokers who had quit 15 years ago or less.[3 14] This is the most definite finding regarding screening for lung cancer by low dose computed tomography available to date.

Other smaller RCTs have been conducted or are in progress in Europe:

- Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Assays (DANTE)[15 16]
- Multicentric Italian Lung Detection (MILD) study[17]
- Danish Lung Cancer Screening Trial (DLCST)[18]
- Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial, or Dutch-Belgian Lung Cancer Screening Trial[19]
- Italian Lung Cancer Computed Tomography Screening Trial (ITALUNG)[20 21]
- Depiscan]—a French pilot lung screening RCT[22]
- German lung cancer screening intervention study (LUSI)[23]
- United Kingdom Lung Screening Trial (UKLS).[24]

The study designs of European lung screening trials have been reviewed.[10 25] To date, published interim results from the DANTE trial,[16] MILD trial,[17] and DLCST[18] have not suggested a protective effect for computed tomography screening, possibly because of small sample sizes, inadequate randomization, unclear allocation, differences in baseline demographic characteristics, differential follow-up, or relatively short duration of follow-up.[10]

Results of the NELSON trial, the second largest trial after the NLST, are awaited in 2015. It is hoped that it will more clearly quantify the effects of screening with low dose computed tomography. Lung cancer screening is more effective when enrollment of screenees is based on accurate risk prediction.[26] It is most effective in people with a high risk,[27] and when performed annually.[28] Also, subset analysis of NLST has shown that screening is more effective in women (overall mortality relative risk: 0.92 in men and 0.73 in women; interaction P=0.08).[29] These associations were all unknown when the NELSON trial was designed. The NELSON trial enrolled fewer participants than the NLST (7557 *v* 26 314 in the screening arm) and more men (84% *v* 59%). Participants had also smoked fewer pack years (38 *v* 48 median pack years), and the second to third and third to fourth screenings were spaced 2 and 2.5 years apart, so the study may lack sufficient power and the design may be suboptimal to demonstrate an effect. The European trials, even combined, will probably not have enough statistical power to change the conclusions drawn from the NLST.

As a result of the findings of NLST, several organizations have recommended low dose computed tomography lung cancer screening of high risk people when high quality follow-up and healthcare are available. Recommendations have come from the following organizations:

- American Association of Thoracic Surgery[30 31]
- American College of Chest Physicians, American Society for Clinical Oncology[9]
- American Cancer Society[32]
- American Lung Association[33]
- Cancer Care Ontario[34]
- National Comprehensive Cancer Network[35]
- French Inter-/Oncology Group[36]
- United States Preventive Services Task Force (USPSTF).[37 38]

Most of these recommendations base their definition of high risk on the NLST criteria of age 55-74 years, smoking history of 30 pack years or more (or smokers who had quit no more than 15 years ago), or some variant of the NLST criteria. For the purposes of a screening trial, this definition of risk was practical. However, it is not as useful for selecting people for screening. Because these criteria dichotomize continuous variables, they lose information.[39] Many valuable predictors are omitted, and non-linear effects are ignored.

Recently the USPSTF published recommendations on low dose computed tomography screening for lung cancer.[37 40] It recommended annual screening of people aged 55-80 years who had smoked at least 30 pack years (or smokers who had quit only in the past 15 years). Some USPSTF conclusions were based on microsimulation modeling by the Cancer Intervention and Surveillance Modeling Net-

work (CISNET) Lung Group, which was based on summarizing models prepared by five separate modeling teams.[28] CISNET modeling found that screening was most efficient when conducted every year (versus biennial or triennial screening) and the age range was extended to 80 years.

Over the past few years many institutions have initiated computed tomography lung cancer screening programs and others are planning them. A non-comprehensive list of institutions providing such screening identified by an internet search on 7 February 2014 provides a sense of where screening is being done in the US (box). Variations between selected programs have been documented.[4]

Examples of US institutions providing lung screening

University of Alabama at Birmingham, Columbia University Medical Center, Duke Raleigh Hospital in North Carolina, Oklahoma Heart Hospital, University Hospital Seidman Cancer Center in Cleveland Ohio, University of Kansas Cancer Centre, Virginia Hospital Center, Beverly Hospital in Massachusetts, Huntsman Cancer Institute at University of Utah, University of Illinois, University of Southern California Norris Cancer Hospital, MD Anderson at Orlando, Yale Cancer Center.

Disadvantages of screening

The NLST population was healthier and better educated than expected for the general US population. The quality of medical care and outcomes in the NLST were also better. Consequently, computed tomography screening may not perform as well in the general population as in the NLST.[41] Countering this view is the belief that screening extended beyond three annual rounds may be more efficient than observed in the NLST and may lead to greater than 20% mortality reduction.[28] Several screening guidelines emphasize that screening be undertaken only by centers with multidisciplinary specialized teams capable of providing high quality care and follow-up.[9 34]

False positives

As well as causing psychological distress, false positive results can cause unnecessary expense, exposure to radiation, biopsies, and surgery, which can result in pain, disability, and, rarely, death. It is important to minimize false positive results, which are 20% or more in the baseline screen and 3% or more in subsequent screens,[3 14 19] while still having a high sensitivity for lung cancer.

Psychological stress

Some studies have found that lung cancer screening or false positive results are associated with distress or loss of health related quality of life.[42 43] Others, however, did not detect distress or found that when it was present it was of small magnitude or transient.[44-48]

Overdiagnosis

This refers to cancers that would not have become clinically significant and led to death if left untreated.[49] Such tumors may be relatively common in some cancers that are screened for, such as breast and prostate cancer. Overdiagnosis can result in the same harms as false positive test results. The extent of overdiagnosis in computed tomography lung cancer screening is unknown. A review of the literature found little evidence of substantial numbers of overdiagnosed lung cancers and concluded that overdiagnosis in lung cancer screening is mostly limited to in situ adenocarcinomas (formally called bronchioloalveolar adenocarcinomas), which appear on computed tomograms as non-solid nodules.[50] To reduce overdiagnosis, Grannis suggests "clear evidence of progression in the form of growth or transition from non-solid to part-solid or solid nodules" before recommending a biopsy or surgical resection.[50] Although most pure non-solid nodules seem to be slow growing, a recent study, which retrospectively reviewed resected and pathologically examined non-solid nodules, showed that 12% of pure non-solid nodules were invasive adenocarcinoma and another 16% were minimally invasive adenocarcinoma.[51] The study suggests that the criteria for "evidence of progression" require a clearer definition and further research.

On the basis of CISNET modeling, the USPSTF estimated overdiagnosis to occur in 10-12% of lung cancers.[38] An analysis of overdiagnosis in the NLST estimated an overdiagnosis rate with three annual screens of 19% (95% confidence interval 16% to 23%) versus chest radiography with seven years of follow-up and 9% (5% to 13%) with lifetime follow-up.[52] Another study assessed overdiagnosis using volume doubling time.[53] It found that 25% of the lung cancers detected on screening were slow growing or indolent, and that many of them may have been overdiagnosed. Further research is needed to help understand and estimate the extent of overdiagnosis. For example, we need to understand the differing and interacting roles played by indolence and death not caused by lung cancer in overdiagnosis and how they change with age.

Exposure to excess radiation

It has been estimated that one death from cancer per 2500 people screened may be caused by radiation from three low dose computed tomography screens plus related diagnostic imaging.[9] A contrasting view is presented in the 2011 American Association of Physicists in Medicine policy statement: "Risks of medical imaging at effective doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent."[54] However, this could underestimate the effect of repeated screens, especially in those who are screened annually until 74 or 80 years of age.

The potential for harm is shown by a study in children under the age of 15, which showed a significant excess relative risk of 0.036 per mGy of radiation (95% confidence interval 0.005 to 0.120; P=0.0097) from computed tomography for leukemia and 0·023 per mGy of radiation (0.010 to 0.049; P<0.0001) for brain cancer.[55] Technology is rapidly changing, and lung cancer screening can now be done with as little as 0.1 mSv using the new generation of dual source computed tomography scanners with selective photon shields. However, ongoing research into the harmful effects of radiation is needed, and several large cohort studies of adults exposed to diagnostic imaging are in progress worldwide.

Harris and colleagues reviewed the literature on screening harms and proposed a taxonomy for classifying harms, in particular for lung cancer screening.[56] The review con-

cluded that decisions to screen are more often based on evidence of benefits, and that data on harms are less available and when available are given less weighting.[56]

Cost effectiveness

Cost effectiveness analyses have assessed whether the benefits of computed tomography lung cancer screening outweigh the hazards and whether the costs to society and the medical system are affordable.[57-68] These studies' methods, perspectives, assumptions, data sources, outcomes, subset analyses, and findings differ. Their outcomes have ranged widely, from a low of $2500 (£1500; €1812) for an incremental cost effectiveness ratio per one year of life saved for one baseline screen,[60] to a high of $2 322 700 per one quality adjusted life year saved in former smokers.[59] However, none of these studies was based on real world RCT data. The cost effectiveness analysis based on NLST data estimated $67 000 per quality adjusted life year gained.

Preliminary analysis from the Pan-Canadian Early Detection of Lung Cancer study suggested that the cost of a screening program could be cost neutral to healthcare providers.[69] This is because low dose computed tomography screening led to the detection of mostly early stage (I and II) cancers, which can be treated with surgical resection and cost around half as much to treat as stage III and IV lung cancers.[69] Targeted therapies, such as tyrosine kinase inhibitors, cost much more than chemotherapy.[70] In addition, compared with surgical treatment with curative intent for early stage lung cancer, chemotherapy and targeted therapy for advanced disease are largely palliative.

Several factors influence the cost of a screening program. Costs are highly sensitive to the risk of lung cancer, the number of follow-up computed tomograms and other imaging studies, complications from diagnostic procedures, and treatment.

Smoking cessation rates among current smokers also affect cost effectiveness. In the general population, the annual spontaneous smoking cessation rate is 3-7%.[71] In observational computed tomography studies, cessation rates vary from 7% to 23%. In the Danish Lung Screening Trial, smoking cessation rates in participants with and without positive computed tomography results were 17.7% and 11.9%, respectively.[72] In the Lung Screening Study component of the NLST, the probability of subsequent smoking was inversely associated with the abnormality of the screening result in a dose-response fashion (P<0.001).[73] Other studies have also found higher smoking cessation rates in those who have abnormal results on computed tomography.[74 75] These findings suggest that lung cancer screening may help reduce smoking in current smokers, and hence reduce all cause mortality.

The cost effectiveness of lung cancer screening can be improved by screening high risk people selected by an accurate risk prediction tool, optimization of lung nodule management protocols, and integration of effective smoking cessation programs within screening programs.

Predicting the risk of lung cancer

Lung cancer screening is most effective when applied to people at high risk.[26 27] To identify these people and improve lung cancer risk prediction models, which can be used to select potential screenees, it is useful to understand the risk factors for lung cancer (summarized in web table). The use of an accurate risk prediction model that incorporates risk factors besides age and smoking history is more efficient at identifying people who will develop lung cancer and die from the disease and leads to more efficient screening (lung cancers deaths averted per screen) compared with NLST criteria.[26 27] When the Tammemagi 2012 prediction model[26] used with the same number of smokers from the PLCO trial as the NLST criteria, it had 11.9% (P<0.001) greater sensitivity in identifying those who would be diagnosed with lung cancer in six years of follow-up. It also had a significantly higher positive predictive value (PPV) than the NLST criteria (4.0% *v* 3.4%; P<0.01).

Another prediction model showed that the number of deaths from lung cancer averted per 10 000 person years in the computed tomography screening group, compared with the radiography group, increased with risk (0.2 in the lowest fifth, then 3.5, 5.1, 11.0, and 12.0 in the highest fifth; P=0.01 for trend).[27]

The use of accurate risk prediction models to identify people at high risk should improve cost effectiveness and reduce the numbers of false positive screens. The International Association for the Study of Lung Cancer high risk working group has recommended that lung cancer screening be based on high risk, and that risk prediction models are most useful for this purpose.[76]

To be useful in lung cancer screening, prediction models need to show high predictive performance as measured by discrimination or ability to classify disease status and by calibration—that is, does the model predicted probability match the observed probability. The receiver operator characteristic area under the curve (AUC) or its equivalent, the C-statistic, are often used to evaluate discriminations.

Specific risk prediction models

Currently, at least 15 lung cancer risk prediction models exist. They differ in the populations that they can be used in, requirements for patient contact and clinical information, and study designs used in modeling and evaluating predictive performance. Some models have been developed in special populations and apply only to that population. The Etzel model is for African-Americans, and the Li and Park models apply to Chinese and Korean men, respectively.[77-79] Maisonneuve presented two models. The first is a version of the Bach model recalibrated in an Italian population for identifying those at high risk who would be suitable for screening; the second model uses initial screening results so is not applicable for pre-screening use.[80] The Spitz expanded model, Young, Hippisley-Cox, Li, and Iyen-Omofoman models use biomarker, genetic, or clinical data that require patient contact, biosampling, and testing or they use medical record data.[78 81-84] These models are therefore not useful for population sampling based on self report and non-personal contact. The Kovalchik model is the only one that is primarily modeled on death from lung cancer using NLST data.[27] However, the NLST selected high risk people for screening so the trial's sample was representative of only about 40% of all smokers. In addition, the follow-up periods in many NLST lung cancer cases were not long enough to identify mortality. Hence, this model was based

on less than 50% of the lung cancer deaths expected in a population of smokers.

The Cassidy (Liverpool Lung Projects) and Spitz models are based on matched case-control data so were unable to evaluate important variables including age and some smoking variables.[85 86] They also did not work directly with incidence data, which best estimates risk, so are vulnerable to calibration problems. They show only moderate discrimination when compared with other models that are based on prospective data in smokers. The Bach model was based on a high risk population of smokers or people exposed to asbestos (or both) from the Beta-Carotene and Retinol Efficacy Trial (CARET). The Tammemagi 2011 and 2012 PLCO models and the Hoggart European Prospective Investigation into Cancer and Nutrition (EPIC) model were based on large prospectively followed population based samples not limited to people at high risk of lung cancer,[26 87 88] and they show high discrimination in smokers.

Population and medical system based approaches

Implementation of lung cancer screening may be population based or medical system based, and this will determine how the risk of potential screenees is assessed. Population based approaches can use an existing model and do not require direct contact—risk can be assessed by telephone or online. This approach is relatively simple, has broad coverage, and is less time consuming and costly than the medical system based approach.

The medical system based approach works through direct contact with patients. It can therefore make use of clinical data and data from validated biomarker testing in risk prediction models. Currently, no biomarkers have been shown to help detect early stage lung cancer or select high risk people for screening. However, in the future, validated biomarkers may be measured using assays on airway epithelium, sputum, exhaled breath, and blood.[89] Medical system based enrollment into screening is expected to be more time consuming and costly than the population based approach, but it may be more effective in enrolling some sectors of society. Relevant data from clinical evaluation, medical records, and biomarker assays can be incorporated into novel risk models.

Several problems remain regarding the integration of model based risk prediction into lung screening programs. These include how best to select people for screening to optimize sensitivity, specificity, and cost effectiveness compared with the USPSTF criteria, and whether risk should be revised on the basis of findings in previous screens, increasing age, and duration of smoking cessation. In the next year, ongoing research is likely to provide improvements in the application of risk prediction models to the selection of screenees.

Management of screen detected lung nodules

Other considerations when implementing computed tomography screening at the population level include the definition of a positive screen and the appropriate management of screen detected lung nodules. The first round of screening generates the greatest number of diagnostic investigations because there are no previous imaging studies to help decide whether lung nodules are new or to determine their growth behaviors.[15 19 90-93] To minimize downstream investigations—such as repeat chest imaging, biopsy, or even surgical resection, which can harm the participant and increase costs—RCTs, cohort studies, and

Table 1 | Management thresholds for pulmonary nodules found on first (baseline) low dose computed tomography (LDCT) screen

Guideline or study protocol	Annual or next scheduled scan	Repeat LDCT before next scheduled annual LDCT	Biopsy or surgery with or without prior PET-CT or LDCT in 3 months
Solid nodules			
NCCN[35 94]	<6 mm	6-8 mm	>8 mm, hypermetabolism†, or interval growth
Fleischner Society[95]	≤4 mm	>4 to 8 mm	>8 mm, hypermetabolism, or interval growth
ACCP[96]	≤4 mm	>4-8 mm and pretest probability <5%; nodule >8 mm, pretest probability <30%, and negative PET	Biopsy for nodule >8 mm, pretest probability 5% to 65%, and hypermetabolism or interval growth; surgery for nodule >8 mm and pretest probability >65% or hypermetabolism
NLST (ACRIN)[3 14 97]	<4 mm	4-10 mm	>10 mm
NELSON[19 98]	Benign or nodule <50 mm^3	50-500 mm^3 (diameter 4.6-9.8 mm); pleural based 5-10 mm minimum diameter	>500 mm^3 (diameter >9.8 mm); pleural based >10 mm minimum diameter
I-ELCAP[99 100]	<5 mm	≥5-14 mm	>15 mm
Part solid nodules			
NCCN[35 94]	<6 mm	6-8 mm	>8 mm with interval growth or increased in solid component
Fleischner Society[101]		Solid component <5 mm	Solid component ≥5 mm or nodule >10 mm
ACCP[96]		≤8 mm	>8 mm with interval growth or increase in solid component; nodule >15 mm
NLST (ACRIN)[3 14 97]	<4 mm	4-10 mm	>10 mm
NELSON[19 98]	<8 mm and solid component <50 mm^3	Non-solid component ≥8 mm and solid component 50-500 mm^3	Solid component >500 mm^3
I-ELCAP[99 100]	<5 mm	≥5-14 mm	>15 mm
Non-solid nodules			
NCCN[35 94]	≤5 mm	>5-10 mm	>10 mm with interval growth or increased attenuation
Fleischner Society[101]	None	>5 mm	>10 mm with interval growth or increased attenuation
ACCP[96]	>5 mm		>10 mm and persistent, interval growth, or development of solid component
NLST (ACRIN)[3,14 97]		≤10 mm	
NELSON[19 98]	<8 mm	≥8 mm mean diameter	
I-ELCAP[99 100]	<5 mm	≥8 mm	≥15 mm

*ACCP=American College of Chest Physicians; I-ELCAP=International Early Lung Cancer Action Program; NCCN=National Comprehensive Cancer Network; NELSON=Dutch-Belgium randomized lung screening trial; NLST=National Lung Screening Trial; PET-CT=positron emission tomography-computed tomography.

†Hypermetabolism=increased FDG uptake.

Table 2 | Implication for resource utilization of different clinical follow-up pathways*

Screen	NLST[14 90]	NELSON[19 91]
Baseline screen		
Number screened	26 309	7557
Repeat chest computed tomography	5153 (19.6%)	1438 (19%)
PET-CT	728 (2.8%)	0
Biopsy	461 (1.8%)	162 (2.1%)
Surgery	297 (1.1%)	92 (1.2%)
Lung cancer diagnosed	270 (1%)	70 (0.9%)
Surgery for benign disease	30%	35%
First annual repeat screen		
Number screened	24 715	7289
Repeat chest computed tomography	2046 (8.3%)	275 (3.8%)
PET-CT	350 (1.4%)	0
Biopsy	238 (0.96%)	101 (1.39%)
Surgery	197 (0.8%)	61 (0.8%)
Lung cancer diagnosed	168 (0.7%)	55 (0.8%)
Surgery for benign disease	26%	21%

*NELSON=Dutch-Belgium randomized lung screening trial; NLST=National Lung Screening Trial; PET-CT=positron emission tomography-computed tomography.

practice guidelines use action thresholds based on nodule type and nodule size (table 1).[3 14 35 19 94-101]

Different size cut-offs points (from 4 mm to 15 mm) are used for solid, partly solid, or non-solid nodules. Nodule diameter is used in some protocols, whereas others use volume measurements. Some guidelines use a combination of nodule size, nodule type, and malignancy pre-test probability.[96] Positron emission tomography-computed tomography (PET-CT) is an integral part of the diagnostic algorithm in some guidelines but not in others.

All RCTs defined what a positive screen is. Some trials, such as NELSON, have a formal diagnostic regimen for investigating patients with a positive screen. In NLST, the decision about how to proceed was left to the referring physician owing to variation in clinical practice and local expertise. Nevertheless, resource utilization was similar in NLST and NELSON with regard to repeat imaging studies before the next annual repeat screen, biopsy or surgery rates, and proportion of surgical procedures for benign disease (table 2).[14 19 90 91] After the first annual repeat screen, when the new images could be compared with baseline images to look for new nodules or evidence of growth of pre-existing lung nodules, the proportion of repeat imaging requests was lower in the NELSON study. However, the proportion of lung biopsies was slightly higher in the NELSON study, although a similar proportion of lung cancer cases was diagnosed. Thus, while the volumetric measurement and volume doubling time used in NELSON are theoretically more accurate than two dimensional measurements to monitor growth in subsequent screens, the two methods have similar resource utilization for the first (baseline) scan.

The corresponding data on the I-ELCAP protocol (1.7% biopsy rate, 1.3% surgery rate, and 1.3% lung cancer diagnosed) were similar, although the study does not allow an analysis of frequency of repeat chest computed tomography, the frequency of diagnostic PET-CT, or the proportion of biopsies or surgery performed for benign disease.[102] Depending on the frequency of biopsy to confirm the diagnosis of lung cancer before surgery, 6-43% of surgical procedures were performed for a benign diagnosis.[9]

There is a trade-off between setting a higher nodule size threshold to reduce the proportion of people who need downstream investigation and the risk of missing a cure by delaying investigation until the next scheduled annual screen.[99 103] Although the probability of lung cancer in small nodules is low, it is not trivial: 7% of the lung cancers diagnosed in NLST were 4-6 mm in diameter and 13% were 7-10 mm.[14 90] In subsequent annual repeat screening, 35% of the cancers were 10 mm or smaller.[14]

The premise of screening is to detect and treat lung cancers early, before they metastasize. Raising the threshold size at which a nodule is considered positive would increase specificity for lung cancer but decrease sensitivity.[10] Prospective validation of the relative merits of different size thresholds in the 5-8 mm range would require very large sample sizes because these nodules have a low frequency of cancer.[103] The harm of false reassurance has not been evaluated.[10]

In 20% of patients, the largest lung nodule is not necessarily the one that is malignant.[92] Thus, although nodule size and type are important for determining the probability of malignancy, a risk calculator is needed that integrates individual and nodule characteristics, thereby enabling the risk of lung cancer to be calculated rapidly and easily.

External validation

An externally validated probabilistic approach to guide clinical decisions at the first (baseline) screen without information on growth or density change was recently reported.[92] This Pan Canadian prediction model and calculator (www.brocku.ca/lung-cancer-risk-calculator) simplifies decision management by not having separate models for solid versus non-solid and partly solid nodules.[35 95 96 101] Previous lung nodule prediction models were retrospective in design, hospital or clinic based, and were based on people with a high prevalence of lung cancer (23-54%) compared with the

Table 3 | Accuracy measurements for pulmonary cancer at different risk score thresholds using the Pan Canadian prediction model[92]*

	Risk score (%)								
Measurement	1.5	6	10	20	30	40	50	60	70
Sensitivity (%)	89.1	73.9	60.9	47.83	32.6	23.9	12.0	7.6	2.2
Specificity (%)	88.4	96.4	97.7	98.8	99.3	99.7	99.9	99.9	100.0
Positive predictive value (%)	9.9	22.7	27.1	37.0	40.0	55.0	55.0	63.6	50.0
Negative predictive value (%)	99.8	99.6	99.4	99.3	99.0	98.9	98.8	98.7	98.6
Accuracy (%)	88.4	96.1	97.2	98.1	98.4	98.7	98.6	98.6	98.6
Nodules positive (%)	12.7	4.6	3.2	1.8	1.14	0.61	0.31	0.17	0.06

*Using the parsimonious model without spiculation.

Fig 1 | Probabilistic approach to guide clinical decisions using the Pan Canadian model

Category	Low dose computed tomography finding	Action plan
CAT1	Normal finding, benign calcification, perifissural nodule, hamartoma, nodule risk index <1.5%	Consider biennial screening
CAT2	Low risk of malignancy: Nodule risk index 1.5% to <6%	Schedule annual repeat screening
CAT3	Moderate risk of malignancy: Nodule risk index 6% to <30%	Rescreen in 3 months: • If no growth, annual screening • If interval growth, refer for definitive diagnosis • May consider definitive diagnosis for nodule risk index between 10% and <30% after discussion between the clinician and patient
CAT4	High risk of malignancy: Nodule risk index ≥30%	Refer for definitive diagnosis
CAT5	Suspicious for lung cancer: Mass lesion with a non-infectious cause; mediastinal or hilar lymphadenopathy irrespective of nodule size	Refer for definitive diagnosis

general high risk population screening setting (≤5%).[104-107]

When externally validated, other models have modest accuracy.[107-109] Models based on lung nodules detected by chest radiography may not be applicable to the screening setting,[104-106] where more than half of lung cancers are 2 cm or less and about 25% of lung nodules are non-solid or partly solid and rarely visible on chest radiography.[80 92] When the full Pan Canadian model without spiculation (irregular margins) of the lung nodule was applied to an external validation dataset, the AUC was 0.97 (0.947 to 0.986).[92] Even when the model was limited to nodules 10 mm or less, or to non-solid nodules alone or non-solid plus part solid nodules, the AUC was 0.936 (0.872 to 0.978), 0.918 (0.835 to 0.968), and 0.933 (0.882 to 0.968), respectively.[92 110]

Table 3 shows the Pan Canadian model's prediction accuracies by probability cut-off points. These cut-off points may serve as a framework to guide clinical investigations (fig 1).[92] For example, screenees with no lung nodules or nodules with a risk score of less than 1.5% have a less than 0.7% chance of lung cancer with a median follow-up of 4.7 years (table 4).[92]

In the NELSONa study, the risk of lung cancer was 1% over 5.5 years in people with no nodules or nodules 50 mm^3 or less (table 4).[91] A similarly low risk of lung cancer was found in other studies in people with no nodules or nodules of 3 mm or less.[14 17 111] Annual screening may not be needed in this very low risk group. The thresholds for biopsy or surgery with or without a previous repeat low dose computed tomography scan or PET-CT scan can be determined by the nodule risk score, physician's assessment, and patient preference.

Figure 2 shows the distribution of the risk scores versus tumor stage using the raw data in the Pan Canadian study.[92] Stage IA tumors had a risk score of 10% or more. A risk score of 30% has a PPV of 40% (table 3). Only 1.14% of the nodules have a risk score of 30% or more (table 3).[92] In other studies, the PPV of abnormal screening results using nodule diameter or volume ranges from 2.2% to 36%.[10] In the NLST study, the PPV for nodules larger than 30 mm was 41.3%.[10 90]

A Pan Canadian nodule risk score of 30% or more suggests that a diagnostic biopsy is needed. In people with a Pan Canadian risk score of 6-30%, a repeat scan can be done in three months to look for evidence of interval growth before deciding on a biopsy. This lower limit has a PPV of 22.7 and an NPV of 99.6 for malignancy. Those with risk scores of 1.5% to less than 6% can have their scheduled annual repeat scan. This probabilistic approach (fig 1) can greatly reduce costs and the risk of morbidity and mortality associated with clinical diagnostic investigations. Algorithms like this can be prospectively evaluated by monitoring the frequency of additional imaging studies, non-surgical biopsies, surgical resection, and the outcome of these procedures.

Tumor volume

The management of lung nodules identified after the first screen is simplified by having a previous scan for comparison to determine whether a nodule is new or whether the size or density of a pre-existing nodule have changed. For new nodules detected in the second or subsequent screening rounds, criteria similar to the baseline scan are often used, although some studies use a more aggressive follow-up protocol, with shorter intervals between repeat scans.[100]

For pre-existing nodules, a greater than 25% increase in volume or a tumor volume doubling time of less than 400 days is considered to be a positive test result if volumetric analysis is used. If nodule diameter is used, a minimum of more than 1 mm increase in the maximum diameter or at least a 10% increase is considered positive.[97 112] For non-solid or semi-solid nodules, the development of a solid component or an increase in the size of the solid component, respectively, are suspicious for malignancy (table 1). Positive nodules would then undergo clinical diagnostic investigations.

Although volumetric analysis is theoretically more accurate for measuring growth in non-spherical nodules,[113-116] two dimensional diameter measurement is commonly used because of its simplicity. Semi-automated or fully automated three dimensional volume measurement requires specially provided software and measurement variability is still too high for non-solid and semi-solid nodules,[114 117] although the technology is improving rapidly.[118-120]

Tumor volume doubling time is often misunderstood. Because small nodules are not usually biopsied, it is not possible to tell whether a long volume doubling time reflects the growth behavior of preinvasive lesions (atypical adenomatous hyperplasia or adenocarcinoma in situ) before it becomes invasive versus the true tumor growth rate. In a surgical series, 66% of the pure ground glass nodules suspicious enough to be removed by surgery were

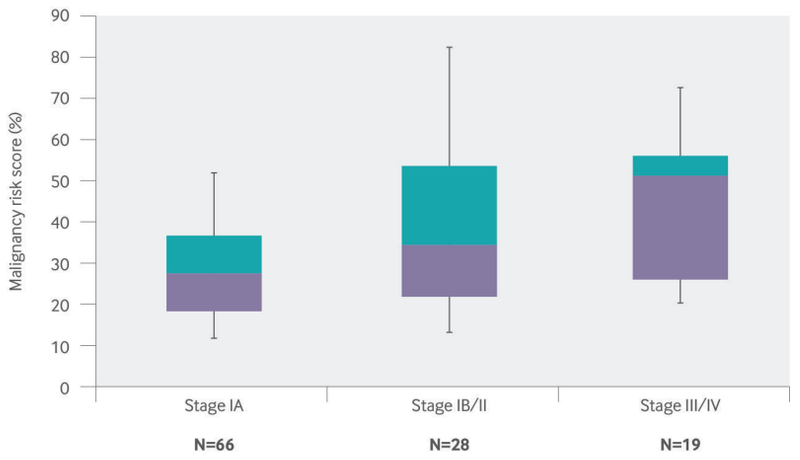

Fig 2 | Box and whisker plot showing the distribution of nodule risk scores according to tumor stage in the Pan Canadian study.[92] The boxes represent the 25th to 75th centiles, with the medians indicated by the horizontal lines. The whiskers represent the 5th to 95th centiles

atypical adenomatous hyperplasia or adenocarcinoma in situ.[51]

Tumor volume doubling time can increase, decrease, or both during the course of disease.[121 122] The fact that a pre-invasive or minimally invasive lesion is growing slowly does not mean that it cannot evolve into a lethal cancer. In addition, it is not possible to determine prospectively, at an individual level, which lung cancers are overdiagnosed because it is not known which patients would have died from lung cancer if they had not been treated.[121] The International Association for the Study of Lung Cancer and other organizations are working to clarify a pathway for the management of lung nodules on the basis of best available evidence.[123]

Frequency of screening

CISNET microsimulation modeling assessed annual, biennial, and triennial screening intervals and concluded that annual screening was most efficient.[28] In contrast, a small Italian pilot RCT comparing annual and biennial CT screening with regular care found no significant difference in lung cancer mortality between annual and biennial screening.[17] However, it also found that screening did not reduce death from lung cancer compared with controls, so the results do not provide strong evidence in favor of biennial screening. The optimum frequency of screening requires further research. In low risk groups, such as those with no nodules on the baseline screen or nodules with a lung cancer risk of 1.5% or less, annual screening may not be needed (table 4).

Duration of screening

The optimum duration of screening is also yet to be defined. The longest duration of screening in an RCT is five years. The benefits of annual screening for up to 25 years are unknown. The potential harm of radiation and the discovery of new nodules that are not malignant should not be underestimated. There are insufficient data to recommend repeat screening annually until age 80 for everyone after participation in the first round of screening. For example, the individual risk of lung cancer may need to be revised downward for those with a negative baseline screen (table 4), those with repeat normal screens, and long term former smokers.[80 91 124] Those at low risk may not benefit from a repeat scan for two or more years. Studying the variability of risk by birth cohorts using pooled data from studies with long term follow-up will shed light on this.

If the duration of smoking cessation is used as an exclusion criterion, a screening program needs to specify that screening would eventually stop in former smokers. However, recent analyses indicate that some increased risks that warranting screening remain long after the 15 years since quitting threshold (MC Tammemagi, unpublished data, 2014).

Evaluation of lung cancer screening programs

It is generally accepted that systematic cancer screening is more effective than ad hoc screening. Quality assurance measures should be in place to evaluate the performance of the program. For lung cancer screening, such measures have not been well defined. However, they may include whether there was a stage shift to earlier stage at detection and a reduction in lung cancer mortality in the screened population compared with the unscreened target population, as well as the proportion of the target population that was contacted and participated.

Future directions

The reading and interpretation of low dose computed tomograms are time consuming because the scans contain 200-400 high resolution sections. Reading involves slowly scrolling through thin slab maximum intensity projections to detect pulmonary nodules. This task requires around 10 minutes per scan, which is substantially more than the amount of time needed to inspect four mammograms in breast cancer screening. Reader variability is substantial.[125]

In the NLST trial, the mean false positive rate for radiologists was estimated at 28.7% (standard deviation 13.7%), with a range of 3.8-69.0%.[126] Quality assurance of the interpretation of diagnostic and screening computed tomograms is a hot topic. Computer vision software tools that interpret such scans to determine whether nodule(s) are present and to identify scans that do not require further formal reading by a chest radiologist are being developed. When they have high accuracy for true negativity, they could be used to process large numbers of lung screening images at reduced costs.

Diagnostic biomarkers using blood or other non-invasively obtained specimens such as exhaled breath may have a role in sub-centimeter nodules or people whose scans are

Table 4 | Lung cancer risk in relation to baseline low dose computed tomography finding

Baseline finding	Participants (%)	Lung cancer risk (%)
NELSON criteria*		
Negative (<50 mm^3)	79.2	1
Indeterminate (50-500 mm^3)	19.2	5.7
Positive (>500 mm^3)	1.6	48.3
Pan Canadian criteria†		
CAT 1: No nodule or nodule risk <1.5%	80	0.7
CAT 2: Nodule risk 1.5% to <6%	12	6
CAT 3: Nodule risk 6% to <30%	6	24
CAT 4: Nodule risk ≥30%	2	57

*Lung cancer risk over 5.5 years.[91]

†From 4360 participants with median follow-up of 4.7 years including those without lung nodules not in reference 92. None of the participants in the CAT 1 group was diagnosed as having lung cancer within 12 months of the baseline scan.

FUTURE RESEARCH AREAS

The accurate measurement of the harmful effects of low dose computed tomography screening radiation

Several problems remain regarding the integration of model based risk prediction into lung screening programs:

- At what model estimated risk should people be selected for screening to optimize sensitivity, specificity, and cost effectiveness compared with the US Preventive Services Task Force criteria?
- For which populations do we need unique risk prediction models? For example, are they needed for those who are exposed to specific occupational lung carcinogens, or populations which may have unique indoor and outdoor environmental exposures and genetic predispositions, such as Asian people? How can this be accomplished in the absence of complete quality data?
- Do repeat normal lung cancer screens revise a person's baseline risk downward?

TRIAL ACRONYMS

CISNET: Cancer Intervention and Surveillance Modeling Network

DANTE: Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Assays

DLCST: Danish Lung Cancer Screening Trial

I-ELCAP: International Early Lung Cancer Action Project

MILD: Multicentric Italian Lung Detection study

NELSON: Nederlands-Leuvens Longkanker Screenings Onderzoek

NLST: National Lung Screening Trial

PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

USPSTF: United States Preventive Services Task Force

negative. A major advance in lung cancer screening would be the ability to identify people who are at risk of developing interval lung cancer that is more likely to be aggressive. Promising predictive biomarkers of the risk of lung cancer, such as spirometry, micro-RNA and pro-surfactant protein B,[127-129] need to be evaluated to determine their incremental value and cost implication versus clinical, demographic, and imaging parameters that are readily obtained without laboratory testing. Quantitative analysis of the nodule and the adjacent lung parenchyma, vessels, and airways may provide valuable information on risk of cancer. The accuracy of an individual's overall risk of lung cancer can also be increased by using information about environmental and occupational exposures as well as validated biomarkers.

Conclusion

Lung cancer screening with low dose computed tomography in high risk smokers can reduce lung cancer mortality by about 20%. Currently, no new treatment modality can reduce death from lung cancer to this extent. The development of lung cancer risk prediction tools to identify people at high risk is a major advance in lung cancer screening. In addition, accurate lung nodule malignancy risk calculators can reduce the number of people who need follow-up scans and other investigations for suspicious or indeterminate lung nodules found in a baseline computed tomogram from over 20% to less than 8%. Sufficient data exist to support implementation of trial screening programs, which if successful and made efficient can be expanded to widespread population based screening programs to improve the outcome of patients with lung cancer. Staged programs will provide the framework to refine the screening parameters to incorporate new data and ideas as they emerge.

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1 Brambilla E, Travis WD, Brennan P, Harris CC, Padilla JRP. Lung cancer. In: Stewart BW, Wild CP, eds. World cancer report 2014. International Agency for Research on Cancer, 2014:350-61.
2 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63:11-30.
3 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;365:395-409.
4 Boiselle PM, White CS, Ravenel JG. Computed tomographic screening for lung cancer: current practice patterns at leading academic medical centers. *JAMA Intern Med* 2014;174:286-7.
5 Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;11:e442.
6 Youlden DR, Cramb SM, Baade PD. The international epidemiology of lung cancer: geographical distribution and secular trends. *J Thorac Oncol* 2008;3:819-31.
7 Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and *the UK*, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet* 2011;377:127-38.
8 Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol* 2007;2:706-14.
9 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 reviewbenefits and harms of ct screening for lung cancer. *JAMA* 2012;307:2418-29.
10 Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive Services Task Force recommendation. *Ann Intern Med* 2013;159:411-20.
11 Manser RL, Irving LB, Byrnes G, Abramson MJ, Stone CA, Campbell DA. Screening for lung cancer: a systematic review and meta-analysis of controlled trials. *Thorax* 2003;58:784-9.
12 Oken MM, Hocking WG, Kvale PA, Andriole GL, Buys SS, Church TR, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. *JAMA* 2011;306:1865-73.
13 Henschke CI. Early lung cancer action project: overall design and findings from baseline screening. *Cancer* 2000;89:2474-82.
14 Aberle DR, DeMello S, Berg CD, Black WC, Brewer B, Church TR, et al. Results of the two incidence screenings in the National Lung Screening Trial. *N Engl J Med* 2013;369:920-31.
15 Infante M, Lutman FR, Cavuto S, Brambilla G, Chiesa G, Passera E, et al. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. *Lung Cancer* 2008;59:355-63.
16 Infante M, Cavuto S, Lutman FR, Brambilla G, Chiesa G, Ceresoli G, et al. 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;180:445-53.
17 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;21:308-15.
18 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;67:296-301.
19 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;361:2221-9.
20 Lopes Pegna A, Picozzi G, Mascalchi M, Maria Carozzi F, Carrozzi L, Comin C, et al. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. *Lung Cancer* 2009;64:34-40.
21 Lopes Pegna A, Picozzi G, Falaschi F, Carrozzi L, Falchini M, Carozzi FM, et al. Four-year results of low-dose CT screening and nodule management in the ITALUNG trial. *J Thorac Oncol* 2013;8:866-75.
22 Blanchon T, Brechot JM, Grenier PA, Ferretti GR, Lemarie E, Milleron B, et al. 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;58:50-8.
23 Becker N, Motsch E, Gross ML, Eigentopf A, Heussel CP, Dienemann H, et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. *J Cancer Res Clin Oncol* 2012;138:1475-86.
24 Baldwin DR, Duffy SW, Wald NJ, Page R, Hansell DM, Field JK. UK Lung Screen (UKLS) nodule management protocol: modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer. *Thorax* 2011;66:308-13.
25 Field JK, van Klaveren R, Pedersen JH, JH, Pastorino U, Paci E, Becker N, et al. European randomized lung cancer screening trials: post NLST. *J Surg Oncol* 2013;108:280-6.

26 Tammemagi MC, Katki HA, Hocking WG, Church T, Caporaso N, Kvale P, et al. Selection criteria for lung-cancer screening. *N Engl J Med* 2013;368:728-36.
27 Kovalchik SA, Tammemagi M, Berg CD, Caporaso NE, Riley TL, Korch M, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med* 2013;369:245-54.
28 De Koning H, Meza R, Plevritis S, ten Haaf K, Munshi VN, Jeon J, et al. Benefits and harms of computed tomography lung cancer screening programs for high-risk populations. Agency for Healthcare Research and Quality, 2013. www.uspreventiveservicestaskforce.org/uspstf13/lungcan/lungcanmodeling.htm.
29 Pinsky PF, Church TR, Izmirlian G, Kramer BS. The national lung screening trial: results stratified by demographics, smoking history, and lung cancer histology. *Cancer* 2013;119:3976-83.
30 Jacobson FL, Austin JH, Field JK, Jett JR, Keshavjee S, Macmahon H, et al. Development of the American Association for Thoracic Surgery guidelines for low-dose computed tomography scans to screen for lung cancer in North America: recommendations of the American Association for Thoracic Surgery task force for lung cancer screening and surveillance. *J Thorac Cardiovasc Surg* 2012;144:25-32.
31 Jaklitsch MT, Jacobson FL, Austin JH, Field JK, Jett JR, Keshavjee S, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. *J Thorac Cardiovasc Surg* 2012;144:33-8.
32 Wender R, Fontham ET, Barrera E Jr, Colditz GA, Church TR, Ettinger DS, et al. American Cancer Society lung cancer screening guidelines. *CA Cancer J Clin* 2013;63:106-17.
33 American Lung Association. American Lung Association provides guidance on lung cancer screening. 2012. www.lung.org/lung-disease/lung-cancer/lung-cancer-screening-guidelines.
34 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;8:1232-7.
35 National Comprehensive Cancer Network clinical practice guidelines for detection, prevention and risk reduction. Version 1.2014. Lung cancer screening. 2014. www.nccn.org/professionals/physician_gls/f_guidelines.asp#lung_screening.
36 Couraud S, Cortot AB, Greillier L, Gounant V, Mennecier B, Girard N, et al. From randomized trials to the clinic: is it time to implement individual lung-cancer screening in clinical practice? A multidisciplinary statement from French experts on behalf of the french intergroup (IFCT) and the groupe d'Oncologie de langue francaise (GOLF). *Ann Oncol* 2013;24:586-97.
37 US Preventive Services Task Force. Screening for lung cancer: US Preventive Services Task Force draft. 2013. www.uspreventiveservicestaskforce.org/draftrec.htm.
38 Moyer VA. Screening for lung cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2013; published online 31 Dec.
39 Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med* 2006;25:127-41.
40 Humphrey L, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, et al. Screening for lung cancer: systematic review to update the US Preventive Services Task Force recommendation. Evidence synthesis no 105. Agency for Healthcare Research and Quality. 2013. www.uspreventiveservicestaskforce.org/uspstf13/lungcan/lungcanes103.pdf.
41 Bach PB. Perilous potential: the chance to save lives, or lose them, through low dose computed tomography screening for lung cancer. *J Surg Oncol* 2013;108:287-8.
42 Bunge EM, van den Bergh KA, Essink-Bot ML, van Klaveren RJ, de Koning HJ. High affective risk perception is associated with more lung cancer-specific distress in CT screening for lung cancer. *Lung Cancer* 2008;62:385-90.
43 Byrne MM, Weissfeld J, Roberts MS. Anxiety, fear of cancer, and perceived risk of cancer following lung cancer screening. *Med Decis Making* 2008;28:917-25.
44 McGovern PM, Gross CR, Krueger RA, Engelhard DA, Cordes JE, Church TR. False-positive cancer screens and health-related quality of life. *Cancer Nurs* 2004;27:347-52.
45 Vierikko T, Kivisto S, Jarvenpaa R, Uitti J, Oksa P, Virtema P, et al. Psychological impact of computed tomography screening for lung cancer and occupational pulmonary disease among asbestos-exposed workers. *Eur J Cancer Prev* 2009;18:203-6.
46 Van den Bergh KA, Essink-Bot ML, Borsboom GJ, Th Scholten E, Prokop M, de Koning HJ, et al. Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). *Br J Cancer* 2010;102:27-34.
47 Van den Bergh KA, Essink-Bot ML, Borsboom GJ, Scholten ET, van Klaveren RJ, de Koning HJ. Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial. *Eur Respir J* 2011;38:154-61.
48 Kaerlev L, Iachina M, Pedersen JH, Green A, Norgard BM. CT-screening for lung cancer does not increase the use of anxiolytic or antidepressant medication. *BMC Cancer* 2012;12:188.
49 Detterbeck FC. Cancer, concepts, cohorts and complexity: avoiding oversimplification of overdiagnosis. *Thorax* 2012;67:842-5.
50 Grannis FW Jr. Minimizing over-diagnosis in lung cancer screening. *J Surg Oncol* 2013;108:289-93.
51 Ichinose J, Kohno T, Fujimori S, Harano T, Suzuki S, Fujii T. Invasiveness and malignant potential of pulmonary lesions presenting as pure ground-glass opacities. *Ann Thorac Cardiovasc Surg* 2013; published online 3 Oct.
52 Patz EF Jr, Pinsky P, Gatsonis C, Sicks JD4, Kramer BS2, Tammemägi MC, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med* 2014;174:269-74.
53 Veronesi G, Maisonneuve P, Bellomi M, Rampinelli C, Durli I, Bertolotti R, et al. Estimating overdiagnosis in low-dose computed tomography screening for lung cancer: a cohort study. *Ann Intern Med* 2012;157:776-84.
54 American Association of Physicists in Medicine. AAPM position statement on radiation risks from medical imaging procedures. 2011. www.aapm.org/org/policies/details.asp?id=318&type=PP&current=true.
55 Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* 2012;380:499-505.
56 Harris RP, Sheridan SL, Lewis CL, Barclay C, Vu MB, Kistler CE, et al. The harms of screening: a proposed taxonomy and application to lung cancer screening. *JAMA Intern Med* 2014;174:281-5.
57 Marshall D, Simpson KN, Earle CC, Chu C. Potential cost-effectiveness of one-time screening for lung cancer (LC) in a high risk cohort. *Lung Cancer* 2001;32:227-36.
58 Chirikos TN, Hazelton T, Tockman M, Clark R. Screening for lung cancer with CT: a preliminary cost-effectiveness analysis. *Chest* 2002;121:1507-14.
59 Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *JAMA* 2003;289:313-22.
60 Wisnivesky JP, Mushlin AI, Sicherman N, Henschke C. The cost-effectiveness of low-dose CT screening for lung cancer: preliminary results of baseline screening. *Chest* 2003;124:614-21.
61 Manser R, Dalton A, Carter R, Byrnes G, Elwood M, Campbell DA. Cost-effectiveness analysis of screening for lung cancer with low dose spiral CT (computed tomography) in the Australian setting. *Lung Cancer* 2005;48:171-85.
62 Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, et al. The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews. *Health Technol Assess* 2006;10:iii-iv, ix-x, 1-90.
63 Castleberry AW, Smith D, Anderson C, Rotter AJ, Grannis FW Jr. Cost of a 5-year lung cancer survivor: symptomatic tumour identification vs proactive computed tomography screening. *Br J Cancer* 2009;101:882-96.
64 Reich JM. Cost-effectiveness of computed tomography lung cancer screening. *Br J Cancer* 2009;101:879-80.
65 McMahon PM, Kong CY, Bouzan C, Weinstein MC, Cipriano LE, Tramontano AC, et al. Cost-effectiveness of computed tomography screening for lung cancer in the United States. *J Thorac Oncol* 2011;6:1841-8.
66 Goulart BH, Bensink ME, Mummy DG, Ramsey SD. Lung cancer screening with low-dose computed tomography: costs, national expenditures, and cost-effectiveness. *J Natl Compr Canc Netw* 2012;10:267-75.
67 Pyenson BS, Sander MS, Jiang Y, Kahn H, Mulshine JL. An actuarial analysis shows that offering lung cancer screening as an insurance benefit would save lives at relatively low cost. *Health Aff (Millwood)* 2012;31:770-9.
68 Shmueli A, Fraifeld S, Peretz T, Gutfeld O, Gips M, Sosna J, et al. Cost-effectiveness of baseline low-dose computed tomography screening for lung cancer: the Israeli experience. *Value Health* 2013;16:922-31.
69 Cressman S, Peacock S, Cromwell I. Resource utilization and costs of screening high-risk individuals for lung cancer in Canada. *J Thorac Oncol* 2013;8 (suppl):S150.
70 Kantarjian HM, Fojo T, Mathisen M, Zwelling LA. Cancer drugs in the United States: Justum Pretium—the just price. *J Clin Oncol* 2013;31:3600-4.
71 Fiore M, Jaen C, Baker T, Bailey W, Benowitz N, Curry S, et al. Treating tobacco use and dependence. Clinical practice guideline: Update 2008. US Department of Health and Human Services. Public Health Service; 2008. www.ncbi.nlm.nih.gov/books/NBK63952/.
72 Ashraf H, Tonnesen P, Holst Pedersen J, Dirksen A, Thorsen H, Dossing M. Effect of CT screening on smoking habits at 1-year follow-up in the Danish Lung Cancer Screening Trial (DLCST). *Thorax* 2009;64:388-92.
73 Tammemagi MC, Berg CD, Riley TL, Cunningham CR, Taylor KL. Impact of lung cancer screening results on smoking cessation. *J Natl Cancer Inst* [forthcoming].
74 Townsend CO, Clark MM, Jett JR, Patten CA, Schroeder DR, Nirelli LM, et al. Relation between smoking cessation and receiving results from three annual spiral chest computed tomography scans for lung carcinoma screening. *Cancer* 2005;103:2154-62.
75 Styn MA, Land SR, Perkins KA, Wilson DO, Romkes M, Weissfeld JL. Smoking behavior 1 year after computed tomography screening for lung cancer: Effect of physician referral for abnormal CT findings. *Cancer Epidemiol Biomarkers Prev* 2009;18:3484-9.
76 International Association for the Study of Lung Cancer (IASLC). Lung Cancer Computed Tomography Screening Workshop 2013 Report. Sydney, Australia, 26-27 October, 2013. *J Thorac Oncol* [forthcoming].
77 Etzel CJ, Kachroo S, Liu M, D'Amelio A, Dong Q, Cote ML, et al. Development and validation of a lung cancer risk prediction model for African-Americans. *Cancer Prev Res (Phila)* 2008;1:255-65.
78 Li H, Yang L, Zhao X, Wang J, Qian J, Chen H, et al. Prediction of lung cancer risk in a Chinese population using a multifactorial genetic model. *BMC Med Genet* 2012;13:118.
79 Park S, Nam BH, Yang HR, Lee JA, Lim H, Han JT, et al. Individualized risk prediction model for lung cancer in Korean men. *PLoS One* 2013;8:e54823.
80 Maisonneuve P, Bagnardi V, Bellomi M, Spaggiari L, Pelosi G, Rampinelli C, et al. Lung cancer risk prediction to select smokers for screening CT—a model based on the Italian COSMOS trial. *Cancer Prev Res (Phila)* 2011;4:1778-89.
81 Spitz MR, Etzel CJ, Dong Q, Amos CI, Wei Q, Wu X, et al. An expanded risk prediction model for lung cancer. *Cancer Prev Res (Phila)* 2008;1:250-4.

82 Young RP, Hopkins RJ, Hay BA, Epton MJ, Mills GD, Black PN, et al. A gene-based risk score for lung cancer susceptibility in smokers and ex-smokers. Postgrad Med J 2009;85:515-24.
83 Hippisley-Cox J, Coupland C. Identifying patients with suspected lung cancer in primary care: derivation and validation of an algorithm. *Br J Gen Pract* 2011;61:e715-23.
84 Iyen-Omofoman B, Tata LJ, Baldwin DR, Smith CJ, Hubbard RB. Using socio-demographic and early clinical features in general practice to identify people with lung cancer earlier. *Thorax* 2013;68:451-9.
85 Spitz MR, Hong WK, Amos CI, Wu X, Schabath MB, Dong Q, et al. A risk model for prediction of lung cancer. *J Natl Cancer Inst* 2007;99:715-26.
86 Cassidy A, Myles JP, van Tongeren M, Page RD, Liloglou T, Duffy SW, et al. The LLP risk model: an individual risk prediction model for lung cancer. *Br J Cancer* 2008;98:270-6.
87 Tammemagi CM, Pinsky PF, Caporaso NE, Kvale PA, Hocking WG, Church TR,et al. Lung cancer risk prediction: prostate, lung, colorectal and ovarian cancer screening trial models and validation. *J Natl Cancer Inst* 2011;103:1058-68.
88 Hoggart C, Brennan P, Tjonneland A, Vogel U, Overvad K, Ostergaard JN, et al. A risk model for lung cancer incidence. *Cancer Prev Res (Phila)* 2012;5:834-46.
89 Hensing TA, Salgia R. Molecular biomarkers for future screening of lung cancer. *J Surg Oncol* 2013;108:327-33.
90 Church TR, Black WC, Aberle DR, Berg CD, Clingan KL, Duan F, et al. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med* 2013;368:1980-91.
91 Horeweg N, van der Aalst CM, Vliegenthart R, Zhao Y, Xie X, Scholten ET, et al. Volumetric computer tomography screening for lung cancer: three rounds of the NELSON trial. *Eur Respir J* 2013;42:1659-67.
92 McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med* 2013;369:910-9.
93 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;4:608-14.
94 Wood DE, Eapen GA, Ettinger DS, Hou L, Jackman D, Kazerooni E, et al. Lung cancer screening. *J Natl Comprehens Cancer Netw* 2012;10:240-65.
95 MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005;237:395-400.
96 Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer. 3rd ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e93S-120S.
97 American College of Radiology Imaging Network. Contemporary screening for the detection of lung cancer. 2013. www.acrin.org/6654_protocol.aspx.
98 Xu DM, Gietema H, de Koning H, Vernhout R, Nackaerts K, Prokop M, et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. *Lung Cancer* 2006;54:177-84.
99 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;158:246-52.
100 Henschke CI, Yip R, Yankelevitz DF, Smith JP. Computed tomography screening for lung cancer. *Ann Intern Med* 2013;159:156-7.
101 Naidich DP, Bankier AA, MacMahon H, Schaefer-Prokop CM, Pistolesi M, Goo JM, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. *Radiology* 2013;266:304-17.
102 International Early Lung Cancer Action Program Investigators; Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;355:1763-71.
103 Lam S, McWilliams A, Mayo J, Tammemagi M. Computed tomography screening for lung cancer: what is a positive screen? *Ann Intern Med* 2013;158:289-90.
104 Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. *Arch Intern Med* 1997;157:849-55.
105 Gurney JW, Lyddon DM, McKay JA. Determining the likelihood of malignancy in solitary pulmonary nodules with Bayesian analysis. Part II. Application. *Radiology* 1993;186:415-22.
106 Gould MK, Ananth L, Barnett PG. A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules. *Chest* 2007;131:383-8.
107 Schultz EM, Sanders GD, Trotter PR, Patz EF, Jr., Silvestri GA, Owens DK, et al. Validation of two models to estimate the probability of malignancy in patients with solitary pulmonary nodules. *Thorax* 2008;63:335-41.
108 Balekian AA, Silvestri GA, Simkovich SM, Mestaz PJ, Sanders GD, Daniel J, et al. Accuracy of clinicians and models for estimating the probability that a pulmonary nodule is malignant. *Ann Am Thorac Soc* 2013;10:629-35.
109 Isbell JM, Deppen S, Putnam JB Jr, Nesbitt JC, Lambright ES, Dawes A, et al. Existing general population models inaccurately predict lung cancer risk in patients referred for surgical evaluation. *Ann Thorac Surg* 2011;91:227-33; discussion 33.
110 Tammemagi M, Mayo J, Lam S. Cancer in pulmonary nodules detected on first screening CT—reply to correspondence to the editor. *N Engl J Med* 2013;369:2061-2.
111 Swensen SJ, Jett JR, Hartman TE, Midthun DE, Mandrekar SJ, Hillman SL, et al. CT screening for lung cancer: five-year prospective experience. *Radiology* 2005;235:259-65.
112 McWilliams AM, Mayo JR, Ahn MI, MacDonald SL, Lam SC. Lung cancer screening using multi-slice thin-section computed tomography and autofluorescence bronchoscopy. *J Thorac Oncol* 2006;1:61-8.
113 Field JK, Oudkerk M, Pedersen JH, Duffy SW. Prospects for population screening and diagnosis of lung cancer. *Lancet* 2013;382:732-41.
114 Heuvelmans MA, Oudkerk M, de Bock GH, de Koning HJ, Xie X, van Ooijen PM, et al. Optimisation of volume-doubling time cutoff for fast-growing lung nodules in CT lung cancer screening reduces false-positive referrals. *Eur Radiol* 2013;23:1836-45.
115 Mehta HJ, Ravenel JG, Shaftman SR, Tanner NT, Paoletti L, Taylor KK, et al. The utility of nodule volume in the context of malignancy prediction for small pulmonary nodules. *Chest* 2014;145:464-72.
116 Xie X, Zhao Y, Snijder RA, van Ooijen PM, de Jong PA, Oudkerk M, et al. Sensitivity and accuracy of volumetry of pulmonary nodules on low-dose 16- and 64-row multi-detector CT: an anthropomorphic phantom study. *Eur Radiol* 2013;23:139-47.
117 Lim HJ, Ahn S, Lee KS, et al. Persistent pure ground-glass opacity lung nodules ≥10 mm in diameter at CT scan: histopathologic comparisons and prognostic implications. *Chest* 2013;144:1291-9.
118 Lassen B, van Rikxoort EM, Schmidt M, Kerkstra S, van Ginneken B, Kuhnigk JM. Automatic segmentation of the pulmonary lobes from chest CT scans based on fissures, vessels, and bronchi. *IEEE Trans Med Imaging* 2013;32:210-22.
119 Jacobs C, Sanchez CI, Saur SC, Twellmann T, de Jong PA, van Ginneken B. Computer-aided detection of ground glass nodules in thoracic CT images using shape, intensity and context features. *Med Image Comput Comput Assist Interv* 2011;14:207-14.
120 Jacobs C, van Rikxoort EM, Twellmann T, Scholtenet ET, et al. Automatic detection of subsolid pulmonary nodules in thoracic computed tomography images. *Med Image Anal* 2014;18:374-84.
121 Horeweg N, de Koning HJ. Reply: Stage distribution of lung cancers detected by computed tomography screening in the NELSON trial. *Am J Respir Crit Care Med* 2013;188:1035-6.
122 Lindell RM, Hartman TE, Swensen SJ, Jett JR, Midthun DE, Mandrekar JN. 5-year lung cancer screening experience: growth curves of 18 lung cancers compared to histologic type, CT attenuation, stage, survival, and size. *Chest* 2009;136:1586-95.
123 Field JK, Smith RA, Aberle DR, Oudkerk M, Baldwin DR, Yankelevitz D, et al. International Association for the Study of Lung Cancer computed tomography screening workshop 2011 report. *J Thorac Oncol* 2012;7:10-9.
124 Veronesi G, Maisonneuve P, Rampinelli C, Bertolotti R, Petrella F, Spaggiari L, et al. Computed tomography screening for lung cancer: results of ten years of annual screening and validation of cosmos prediction model. *Lung Cancer* 2013;82:426-30.
125 Armato SG, 3rd, Roberts RY, Kocherginsky M, Aberle DR, Kazerooni EA, Macmahon H, et al. Assessment of radiologist performance in the detection of lung nodules: dependence on the definition of "truth." *Acad Radiol* 2009;16:28-38.
126 Pinsky PF, Gierada DS, Nath PH, Kazerooni E, Amorosa J. National lung screening trial: variability in nodule detection rates in chest CT studies. *Radiology* 2013;268:865-73.
127 Tammemagi MC, Lam SC, McWilliams AM, Sin DD. Incremental value of pulmonary function and sputum DNA image cytometry in lung cancer risk prediction. *Cancer Prev Res (Phila)* 2011;4:552-61.
128 Sin D, Tammemagi MC, Lam S, Barnett MJ, Duan X, Tam A, et al. Pro-surfactant protein B as a biomarker for lung cancer prediction. *J Clin Oncol* 2013;31:4536-43.
129 Sozzi G, Boeri M, Rossi M, Verri C, Suatoni P, Bravi F, et al. Clinical utility of a plasma-based miRNA signature classifier within computed tomography lung cancer screening: a correlative MILD trial study. *J Clin Oncol* 2014; published online Jan 13.