Lung Cancer Screening:
Evidence and current recommendations

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I have no financial conflicts of interest

I have been a co-investigator on the BCCA & PanCanadian Early Lung Cancer Detection Study

I am a co-investigator on the NHMRC funded ILST study
Lung Cancer

Past

Present
The NLST has definitively shown a reduction in lung cancer mortality in a research setting but effective implementation of a lung cancer screening program needs to be evaluated in different healthcare communities.

- Not an implementation study
- Cost analysis was not endpoint
- Only 3 years of screening- likely underestimation of benefit
Screening for Lung Cancer

This topic page summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on screening for lung cancer.

Current Recommendation

Release Date: December 2013

- The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. Grade: B recommendation.
On the basis of the current evidence and in line with the Population Based Screening Framework, the Standing Committee on Screening does not support an Australian lung cancer screening program, either for the general population or for high risk populations. The Standing Committee on Screening will continue to evaluate and advise on emerging evidence on lung cancer screening.
Position Statement: Lung Cancer Screening using Low-Dose Computed Tomography

There is some evidence to support annual screening for people at high risk of lung cancer using low-dose computed tomography (LDCT). Individuals at high risk are adults aged 55 to 80 years who have a smoking history of at least 30 pack-years\(^1\) and currently smoke or have quit within the past 15 years.\(^6\) However, there are a number of unresolved issues that need further consideration.

Unresolved issues include a high false positive rate of screening with the risk of attendant harms from subsequent investigation; variability in follow up protocols for a positive test; uncertainty regarding the target population and screening interval; uncertainty regarding cost-effectiveness; and the issue of screening versus smoking cessation measures.\(^7,8,9,10\) Further studies are currently underway.
Australian Population Based Screening Framework 2008

Before a national population screening program can be considered there must be clear indications about:

- the cost effectiveness of the program
- who to screen and the screening interval
- the likely uptake of screening
- the most appropriate test, including its sensitivity and specificity
- program organisations, including for registration and recall of people who have been screened for follow-up treatment
- a quality management system supported by the routine collection of data throughout the screening pathway
- availability of treatment and/or management options for people with a screen-detected condition

Australian Health Minister’s Advisory Council
Australian Population Based Screening Framework 2008

- The infrastructure and systems necessary to implement the screening program to achieve outcomes similar to those achieved in the research setting on which the program is based should exist, or be able to be developed in a reasonable time frame.

- An economic evaluation should also be performed to assess whether benefits exceed costs & whether screening is the most cost effective option for achieving the screening programs objectives.

- The program must give more benefit than harm to the target population.
Recommendation to support phased, internationally coordinated “demonstration projects” for different geographic regions and in countries that are not currently undertaking large RCTs. Also smoking cessation programs should be included in a program design.

1. Identification of high-risk individuals for lung cancer CT screening programs.
2. Develop radiological guidelines for use in developing national screening programs.
3. Develop guidelines for the clinical work-up of “indeterminate nodules” resulting from CT screening programmers.
4. Guidelines for pathology reporting of nodules from lung cancer CT screening programs.
5. Recommendations for surgical and therapeutic interventions of suspicious nodules identified through lung cancer CT screening programs.
6. Integration of smoking cessation practices into future national lung cancer CT screening programs.
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Risk Stratification

Screening will be **most effective** in the highest risk population

**How should we select participants for lung cancer screening?**

- National Lung Cancer Screening Trial (NLST)
  - 55-74yo
  - Smoker ≥ 30 pack/years
  - If exsmoker ≤15 years since cessation

- United States Preventive Services Task Force (USPSTF)
  - 55-80yo

- Lung cancer risk prediction model probabilities
PLCO Lung Cancer Prediction Model

Prospective data from 70,962 PLCO participants

- Age
- Smoking history (# cigarettes, yrs smoked, duration of smoking cessation)
- Family history
- Occupational exposures
- Education level
- History of COPD
- Body mass index
- Chest X-ray in previous 3 yrs

Tammemägi et al. J Natl Cancer Inst 2011;103:1–11
Lung cancer mortality rates in NLST by PLCO\textsubscript{M2012} risk model deciles

\begin{itemize}
  \item NNS NA
  \item NNS 963
  \item NNS 255
  \item ≥1.51%
  \item NLST NNS 320
\end{itemize}
## USPSTF vs PLCO\textsubscript{M2012} $\geq$1.5\% risk

<table>
<thead>
<tr>
<th></th>
<th>USPSTF</th>
<th>PLCO\textsubscript{M2012}</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>71.2%</td>
<td>80.1%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Specificity</td>
<td>62.7%</td>
<td>66.2%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>PPV</td>
<td>3.4%</td>
<td>4.2%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

PLCO\textsubscript{M2012} is superior to USPSTF for selection
8.8\% fewer participants would be selected for screening
12.4\% more lung cancers would be detected

Tammemagi PLoS 2014
Distribution of $\text{PLCO}_{M2012}$ risk in NLST or USPSTF criteria positive participants

26% participants had low $\text{PLCO}_{M2012}$ risk
Pan-Canadian Early Detection Study
2537 current/former smokers >50-75yo with PLCO$_{M2009}$ ≥2%

172 lung cancers in 164 people over median 5.5 year FU (6.5%)
77% were Stage I/II

Lancet Oncology November 2017
Selection of high-risk participants for LDCT screening is improved by the use of multivariate risk prediction models.
Large prospective population based “45 and Up” cohort study of 267,019 people ≥ 45yo in NSW

95,882 ever smokers ≥ 45yo with 5 years of followup + 1035 lung cancers

Evaluated the applicability of PLCO_{m2012} in Australian population
“45 and Up” Cohort

- PLCO$_{M2012}$ had high predictive performance (AUC 0.8)
- Performed better than NLST or USPSTF criteria
- ~29% of ever smokers in Australia would be eligible for LDCT screening using PLCO$_{M2012} \geq 1.51\%$
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6. Integration of smoking cessation practices into future national lung cancer CT screening programs.
>50% of screened participants will have a noncalcified nodule
Screen detected pulmonary nodules

- Found in the majority of screened patients
- Need standardised nomenclature + approach
- Need systematic followup for 2-5 years depending on subtype
- Need to avoid unnecessary CT scans, PET, biopsy and surgery
- Surgery for benign disease reported as 10-29% in screening studies
Risk Stratification

*How should we manage all of these pulmonary nodules?*

- Published guidelines or trial algorithms
  - OR
- Nodule risk prediction model probabilities
**Recommendations for the Management of Subsolid Pulmonary Nodules Detected at CT: A Statement from the Fleischner Society**

<table>
<thead>
<tr>
<th>Nodule Type</th>
<th>Management Recommendations</th>
<th>Additional Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary pure GGNs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 mm</td>
<td>No CT follow-up required</td>
<td>Obtain contiguous 1-mm-thick sections to confirm that nodule is truly a pure GGN</td>
</tr>
<tr>
<td>&gt;5 mm</td>
<td>Initial follow-up CT at 3 months to confirm persistence then</td>
<td>FDG PET is of limited value, potentially misleading, and therefore not recommended</td>
</tr>
<tr>
<td></td>
<td>annual surveillance CT for a minimum of 3 years</td>
<td></td>
</tr>
<tr>
<td>Solitary part-solid nodules</td>
<td>Initial follow-up CT at 3 months to confirm persistence. If</td>
<td>Consider PET/CT for part-solid nodules. &gt;10 mm</td>
</tr>
<tr>
<td></td>
<td>persistent and solid component ≤5 mm, then yearly surveillance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT for a minimum of 3 years. If persistent and solid component</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥5 mm then biopsy or surgical resection</td>
<td></td>
</tr>
<tr>
<td>Multiple subsolid nodules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure GGNs 5 mm with a dominant</td>
<td>Obtain follow-up CT at 2 and 4 years</td>
<td>Consider alternate causes for multiple GGNs ≤5 mm</td>
</tr>
<tr>
<td>lesion(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure GGNs &gt;5 mm without a</td>
<td>Initial follow-up CT at 3 months to confirm persistence and</td>
<td>FDG PET is of limited value, potentially misleading, and therefore not recommended</td>
</tr>
<tr>
<td>dominant lesion(s)</td>
<td>annual surveillance CT for a minimum of 3 years</td>
<td></td>
</tr>
<tr>
<td>Dominant nodule(s) with part-solid</td>
<td>Initial follow-up CT at 3 months to confirm persistence. If</td>
<td>Consider lung-sparing surgery for patients with dominant lesion(s) suspicious for</td>
</tr>
<tr>
<td>or solid component</td>
<td>persistent, biopsy or surgical resection is recommended,</td>
<td>lung cancer</td>
</tr>
<tr>
<td></td>
<td>especially for lesions with &gt;5 mm solid component</td>
<td></td>
</tr>
</tbody>
</table>

Note.—These guidelines assume meticulous evaluation, optimally with contiguous thin sections (1 mm) reconstructed with narrow and/or mediastinal windows to evaluate the solid component and wide and/or lung windows to evaluate the nonsolid component of nodules, if indicated. When electronic callipers are used, bidimensional measurements of both the solid and ground-glass components of lesions should be obtained as necessary. The use of a consistent low-dose technique is recommended, especially in cases for which prolonged follow-up is recommended, particularly in younger patients. With serial scans, always compare with the original baseline study to detect subtle indolent growth.
<table>
<thead>
<tr>
<th>Category</th>
<th>Category Descriptor</th>
<th>Findings</th>
<th>Management</th>
<th>Probability of Malignancy</th>
<th>Estimated Population Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete</td>
<td>-</td>
<td>prior chest CT examination(s) being located for comparison part or all of lungs cannot be evaluated</td>
<td>Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed</td>
<td>n/a</td>
<td>1%</td>
</tr>
<tr>
<td>Negative</td>
<td>No nodules and definitely benign nodules</td>
<td>no lung nodules</td>
<td>nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules</td>
<td>&lt; 1%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>No nodules and definitely benign nodules</td>
<td>solid nodule(s):</td>
<td>&lt; 6 mm new &lt; 4 mm</td>
<td></td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth</td>
<td>part solid nodule(s):</td>
<td>&lt; 6 mm total diameter on baseline screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth</td>
<td>non solid nodule(s) (GGN):</td>
<td>&lt; 20 mm OR ≥ 20 mm and unchanged or slowly growing category 3 or 4 nodules uncharged for ≥ 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Probably benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer</td>
<td>solid nodule(s):</td>
<td>≥ 6 to &lt; 8 mm at baseline OR new 4 mm to &lt; 6 mm</td>
<td>1-2%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Possibly benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer</td>
<td>part solid nodule(s):</td>
<td>≥ 6 mm total diameter with solid component &lt; 6 mm OR new &lt; 6 mm total diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>possibly benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer</td>
<td>non solid nodule(s) (GGN):</td>
<td>≥ 20 mm on baseline CT or new</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspicious</td>
<td>Findings for which additional diagnostic testing and/or tissue sampling is recommended</td>
<td>solid nodule(s):</td>
<td>≥ 8 to &lt; 15 mm at baseline OR growing &lt; 8 mm OR new 6 to &lt; 8 mm</td>
<td>5-15%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Findings for which additional diagnostic testing and/or tissue sampling is recommended</td>
<td>part solid nodule(s):</td>
<td>≥ 6 mm with solid component ≥ 6 mm to &lt; 8 mm OR with a new or growing &lt; 4 mm solid component</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Findings for which additional diagnostic testing and/or tissue sampling is recommended</td>
<td>endobronchial nodule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Findings for which additional diagnostic testing and/or tissue sampling is recommended</td>
<td>solid nodule(s)</td>
<td>≥ 15 mm OR new or growing, and ≥ 8 mm</td>
<td>&gt; 15%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Findings for which additional diagnostic testing and/or tissue sampling is recommended</td>
<td>part solid nodule(s) with:</td>
<td>a solid component ≥ 8 mm OR a new or growing ≥ 4 mm solid component</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Clinically Significant or Potentially Clinically Significant Findings (non lung cancer)</td>
<td>solid nodule(s):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>modifier - may add on to category 0-4 coding</td>
<td></td>
<td></td>
<td>n/a</td>
<td>10%</td>
</tr>
<tr>
<td>Prior Lung Cancer</td>
<td>modifier - may add on to category 0-4 coding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IMPORTANT NOTE FOR USE:**
British Thoracic Society guidelines for the investigation and management of pulmonary nodules

PanCan Nodule Risk Calculator

http://www.brocku.ca/lung-cancer-risk-calculator
External validation

Winkler et al: European Radiology 2015
- Danish lung cancer screening trial cohort
- 1152 nodules in 718 people
- AUC 0.83-0.87

Al-Ameri: Lung Cancer 2015
- UK hospital clinical population of 244 patients
- AUC 0.90

SJ Van Riel: WCLC 2015 LungRads vs Brock Nodule Prediction Model in Danish Cohort:
- Evaluated in 60 participants with malignant lesions using baseline CT and 120 participants with benign nodules
- Brock model performs better than LungRADS
## Risk Stratification and effect on nodule management at baseline LDCT

<table>
<thead>
<tr>
<th>% Participants</th>
<th>NLST (axial diameter)</th>
<th>NELSON (volumetric)</th>
<th>PANCAN/BCCA (probabilistic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Positive scan” or action after baseline LDCT</td>
<td>27%</td>
<td>21%</td>
<td>8%</td>
</tr>
<tr>
<td>Short term 3 mth LDCT</td>
<td>19.2%</td>
<td>19.2%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Prospective evaluation of PanCanadian risk stratification underway
Lung cancer screening in Australia: Questions to be answered

- Recruitment strategies for target population
- Establishment of expertise + infrastructure to manage data
- Standardisation of program/QA
- Health economic analysis in Australian healthcare setting
Adhoc/opportunistic Lung Cancer Screening

- Risk of screening low-risk population = risks > benefits
- Incorrect CT techniques = higher radiation dosage
- Incorrect CT follow-up = higher radiation dosage + higher costs
- Unnecessary biopsies, PET, surgery etc
- Lack of integration of smoking cessation
- Lack of infrastructure to manage workload e.g. nodule observation, data collection, tracking participants etc
International LungScreen Trial (ILST)
International LungScreen Trial (ILST)
- Shared centralised database
- Web-based risk assessment tool
- Shared protocol, questionnaire and datapoints
International Lung Screen Trial (ILST)

Collaborative study of 4000 participants between Australia and Canada

- Standardised LDCT technique
- Use of integrated CAD system across all sites
- Standardised LDCT synoptic reporting
- Standardised nodule management
- Incorporation of smoking cessation advice
- Health care cost analysis