Lung Cancer Screening: Finally Ready For Prime Time?

October 21, 2016
6th Atlantic Thoracic Oncology Conference
Halifax Nova Scotia

Gordon Buduhan  MD MSc FRCSC
Section of Thoracic Surgery
University of Manitoba, Canada
No conflicts to disclose
Objectives

- Case
- Epidemiology of Lung Cancer
- What Makes an Ideal Screening Test?
- Review of trials
- Lung cancer screening recommendations
- Development of a Lung Cancer Screening Program
Further disclosure...

Who I am...

- Academic thoracic surgeon
- Diagnose & treat lots of lung cancer, all stages
- See firsthand devastating effects of disease
- Want to be at forefront of lung cancer diagnostic / treatment initiatives that may improve survival
- Ensure such initiatives are conducted properly

Who I am NOT...

- Clinical epidemiologist
- Biostatistician
- Economist
- Expert on lung cancer screening
- Politician
- Owner of private radiology clinics!
My first “screened patient”

- 66yr old male accountant
- Smoker: 1 pack/day x 20 yrs
- Mother (smoker) died lung cancer
- Heard on news about lung cancer screening benefits (presently no formal screening program in MB)
- Asked GP for screening CT chest – obliged
- No further discussion on screening details, meaning of results, future tests, smoking cessation counseling...
My first “screened patient”
My first “screened patient”

- Referred to respirologist: flexible bronchoscopy - washings, brushings: (-) cytology, micro

- In my office ++anxious, tearful – “I should have gotten screened earlier...”
Around same time...

- Asked to join CCMB Lung Cancer Screening Working Group
Questions…

- Should we be implementing lung cancer screening?
- Was patient appropriate lung cancer screening candidate?
- Roles & responsibilities of physicians?
- Who should oversee lung cancer screening program?
Lung Cancer Epidemiology

- Most frequent cause of cancer death
- In 2020 = 5\textsuperscript{th} cause of death
- 2015 (Canada) = 10900 deaths in men and 10000 deaths in women (27% of all cancer deaths)
- US – lung ca kills 450 people / day (>daily Boeing747 plane crash)
- Overall 5 yr survival 17%
- 90% of cases attributable to smoking; 50% of new cases in former smokers
Annual Productivity Loss due to Cancer Lung Cancer Leads with $36 Billion

Figure LCOS: Lost productivity due to cancer deaths in the United States among adults aged 20 years and older, 2005.

Lung and bronchus: 36.138
Female breast: 12.096
Colon and rectum: 10.652
Pancreas: 6.610
Brain and ONS: 5.743
Leukemia: 5.722
Non-Hodgkin lymphoma: 5.511
Liver and intrahepatic bile duct: 4.420
Kidney and renal pelvis: 3.424
Head and neck: 3.413
Prostate: 3.301
Stomach: 3.225
Melanoma of the skin: 3.194
Ovary: 2.824
Cervix uteri: 1.627
Urinary bladder: 1.026
Corpus and uterus: 1.041
Hodgkin lymphoma: 0.633
Testis: 0.481
All other sites: 22.547

Present value of lifetime earnings (PVLE) (in billions of dollars)

Screening

- Screen = take asymptomatic people – identify those with disease who would benefit from early intervention
- Goal – reduce morbidity and mortality

**early diagnosis by itself does not justify screening**
Ideal Screening Program

**Disease**
Significant impact on public health
Asymptomatic period during which detection is possible
Outcomes improved by treatment during asymptomatic period

**Test**
Sufficiently sensitive to detect disease during asymptomatic period
Sufficiently specific to minimize false-positive test results
Acceptable to patients, accessible with low cost

**Screened population**
Sufficiently high prevalence of the disease to justify screening
Patients willing to comply with further work-up and treatment
Ideal Screening Program

**Disease**
Significant impact on public health  
Asymptomatic period during which detection is possible  
Outcomes improved by treatment during asymptomatic period

**Test**
Sufficiently sensitive to detect disease during asymptomatic period  
Sufficiently specific to minimize false-positive test results  
Acceptable to patients, accessible with low cost

**Screened population**
Sufficiently high prevalence of the disease to justify screening  
Patients willing to comply with further work-up and treatment
Natural History of Disease

Preclinical Phase

“Critical Point”

Clinical Phase

Intervention more effective
eg. Surgery for localized disease

Intervention less effective
eg. Metastatic disease

-ideally want screening test to detect disease prior to “critical point” !!
NSCLC AJCC Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Deaths</th>
<th>N</th>
<th>MST 5-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>1168/3666</td>
<td>119</td>
<td>73%</td>
</tr>
<tr>
<td>IB</td>
<td>1450/3100</td>
<td>81</td>
<td>58%</td>
</tr>
<tr>
<td>IIA</td>
<td>1485/2579</td>
<td>49</td>
<td>46%</td>
</tr>
<tr>
<td>IIB</td>
<td>1502/2252</td>
<td>31</td>
<td>36%</td>
</tr>
<tr>
<td>IIIA</td>
<td>2896/3792</td>
<td>22</td>
<td>24%</td>
</tr>
<tr>
<td>IIIB</td>
<td>263/297</td>
<td>13</td>
<td>9%</td>
</tr>
<tr>
<td>IV</td>
<td>224/266</td>
<td>17</td>
<td>13%</td>
</tr>
</tbody>
</table>

Survival, Years
Ideal Screening Program

**Disease**
Significant impact on public health
Asymptomatic period during which detection is possible
Outcomes improved by treatment during asymptomatic period

**Test**
Sufficiently sensitive to detect disease during asymptomatic period
Sufficiently specific to minimize false-positive test results
Acceptable to patients, accessible with low cost

**Screened population**
Sufficiently high prevalence of the disease to justify screening
Patients willing to comply with further work-up and treatment
Smoking Dose and Time Since Quit Key Considerations for Screening Program Design

Figure 1. Nonlinear Relationship between Smoking Intensity (Average Number of Cigarettes Smoked per Day) and Lung-Cancer Risk.

Probabilities were calculated on the basis of the following variables: an age of 62 years, white race or ethnic group, some college education, a body-mass index (the weight in kilograms divided by the square of the height in meters) of 27, no chronic obstructive pulmonary disease, no personal history of cancer, no family history of lung cancer, status as a former smoker, smoking history of 27 years, and cessation of smoking 10 years before enrollment.


doi:10.1371/journal.pmed.1001764

doi:10.1371/journal.pmed.1001764


Historical Lung Cancer Screening Trials
1950-1990 – CXR as screening test...

- Randomized and non randomized controlled trials:
  - John Hopkins Lung Project
  - Memorial Sloan Kettering Lung Project
  - Mayo Lung Project
  - Czechoslovakian Study
  - North London Cancer Study
  - Erfurt County Study
  - Kaiser Permanente Study

- Chest radiograph ± sputum cytology every 4 to 12 months compared to less frequent or no screening over 3 to 16 years

- 52000 subjects in intervention groups and 48000 in control groups
1950-1990

- Intervention groups:
  - More lung cancers
  - More early stage lung cancers
  - More resectable lung cancers

- No reduction in lung cancer mortality
Screening by Chest Radiograph and Lung Cancer Mortality
The Prostate, Lung, Colorectal, and Ovarian (PLCO) Randomized Trial

JAMA 2011; 306(17): 1865-73
PLCO Trial

- 154,901 participants aged 55 through 74 years
  - 77,445 assigned to annual CXR screening for 4 years
  - 77,456 assigned to usual care
  - No specific eligibility criteria (45% never smokers)

- 10 US screening centres

- 1993 - 2001

- Management of detected tumors was left to usual practice of screening center

JAMA 2011; 306(17): 1865-73
Incidence RR 1.05; 95%CI 0.98-1.12
### Lung Cancer Mortality by Year

- **Intervention group**
  - Cumulative deaths: 36, 113, 196, 292, 378, 480, 682, 711, 838, 937, 1070, 1150, 1213
  - Cumulative person-years: 77286, 154053, 230270, 305833, 380691, 454773, 527937, 600004, 670274, 735098, 789540, 832441, 864227

- **Usual care group**
  - Cumulative deaths: 30, 111, 198, 301, 426, 527, 639, 761, 884, 987, 1076, 1162, 1230
  - Cumulative person-years: 77286, 154116, 230348, 305902, 380725, 454719, 527804, 599790, 689955, 734523, 788854, 831678, 863330

**mortality RR, 0.99; 95% CI, 0.87-1.22**
Ideal Screening Program

Disease
Significant impact on public health
Asymptomatic period during which detection is possible
Outcomes improved by treatment during asymptomatic period

Test
Sufficiently sensitive to detect disease during asymptomatic period
Sufficiently specific to minimize false-positive test results
Acceptable to patients, accessible with low cost

Screened population
Sufficiently high prevalence of the disease to justify screening
Patients willing to comply with further work-up and treatment
Low-Dose Helical CT

- Allows entire chest to be surveyed in a single breathhold
  - Time: approximately 7 - 15 seconds
  - Reduces motion artifact
  - Eliminates respiratory misregistration

- Narrower slice thickness

- Hourly throughput - 4 patients per hour

- Radiation dose one tenth of diagnostic CT
Survival of Patients with Stage I Lung Cancer Detected on CT Screening

The International Early Lung Cancer Action Program Investigators*
I-ELCAP

- International study - Cornell University lead site (Israel, Japan, Europe, Canada)
- Asymptomatic, ≥ 40yrs, with risk factor of smoking, former smoking, 2nd hand smoke exposure or occupational exposure (specific enrollment criteria up to institutions)
- 31,567 patients between 1993-2004 received a baseline CT and then a screening CT at 12 months, and then annually
- No control arm

Figure 1. Diagnoses of Lung Cancer Resulting from Baseline Screening and Annual Screening with CT.
A description of the I-ELCAP management algorithm for baseline CT and repeated CT screening is available in the study protocol.6

Figure 2. Kaplan–Meier Survival Curves for 484 Participants with Lung Cancer and 302 Participants with Clinical Stage I Cancer Resected within 1 Month after Diagnosis.

The diagnoses were made on the basis of CT screening at baseline combined with cycles of annual CT.
I-ELCAP

- Majority of lung cancers detected were Stage I adenocarcinomas
- Patients undergoing resection had estimated 10-year survival of 94% (347/375)
- “Annual CT screening can detect lung cancer which is curable...80% of lung cancer deaths avoidable with CT screening”
- Single arm study
  - No definite conclusions regarding survival or mortality benefit compared to no screening or CXR screening

“Blood money??”

- NY Times Mar 2008: “Cigarette Company Paid for Lung Cancer Study”
- $3.6 million grants to fund ELCAP – Vector group, parent company of Liggett (tobacco manufacturer) → did not disclose
- Dr. Henschke I-ELCAP lead investigator - 11 patents on CT screening intellectual property: CT software, biopsy needles – 1 patent already licensed by GE → did not disclose
- 90% consent forms “missing”...
1. We do not recommend that low-dose CT be used to screen for lung cancer except in the context of a well-designed clinical trial. Grade of recommendation, 2C

2. We recommend against the use of serial chest X-rays to screen for the presence of lung cancer. Grade of recommendation, 1A

3. We recommend against the use of single or serial sputum cytologic evaluation to screen for the presence of lung cancer. Grade of recommendation, 1A
Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*
National Lung Screening Trial Design Overview

- 53,456 participants
  - LDCT scan
  - CXR
- Enrolled 2002 – 2004
- 3 Annual Screenings

- 55-74 years old
- Are currently a smoker or have quit within the past 15 years
- Have smoked at least a pack of cigarettes a day for 30+ years

Primary endpoint = lung cancer mortality

NLST - Results

- Rate of positive screening tests: 24.2% LDCT and 6.9% with CXR
- 39.1% pts in LDCT grp and 16.0% CXR grp had at least one positive screening result
- 96.4% of the positive screening results in LDCT group and 94.5% in the CXR group were false positive
National Screening Trial Results

More Lung Cancers found in LDCT Arm
- Total Cases
  - LDCT 1060
  - CXR 941
- Cases per 100k person years
  - LDCT 645
  - CXR 572
Difference primarily early stage disease

More Lung Cancer Deaths in CXR Arm
- Total Deaths
  - LDCT 356
  - CXR 443
- Deaths per 100k person years
  - LDCT 247
  - CXR 309
20% Reduction in lung cancer mortality with LDCT
6.7% Reduction in all cause mortality

NLST Low Dose CT (LDCT) Lung Cancer Screening Efficacy

Prevalence = 1 percent (Initial Screen)
Incidence = 0.8 (Following Annual Screens)

For initial screen
  Sensitivity = 93.5 (90.7-96.3)*
  Specificity = 73.4 (72.9-73.9)
  False Positives = 26.60 (26.10-27.10)
  PPV = 3.80 (3.30 – 4.20)
  NPV = 99.90 (99.86-99.94)
  NNS = 320

Incidental Findings not suspicious for lung cancer – 7.5%

* Numbers in parentheses 95% Confidence Intervals
NLST Limitations

- “Healthy volunteer” effect

- NLST was undertaken in quaternary lung cancer centres - ?reproducible “efficacy vs. effectiveness”

- Reduction in mortality if screening continues more than three rounds unknown

NLST Conclusions

- NNS with LDCT to prevent 1 lung cancer death = 320
- (NNS mammography=1000-10000; NNS FOBT=1200)
- 20% reduction in mortality with LDCT compared to CXR

When the Average Applies to No One: Personalized Decision Making About Potential Benefits of Lung Cancer Screening

Peter B. Bach, MD, MAPP, and Michael K. Gould, MD, MS
NSLT concludes screening with LDCT provides a 20% relative risk reduction compared to CXR.

The absolute risk reduction is 1.7% CXR arm → 1.4% LDCT arm = 0.3%.

3 lung cancer deaths averted / 1000 participants screened with LDCT, with 14 deaths not averted.

Statistical modeling to predict benefit of LDCT screening compared to no screening, with estimated NNS for typical risk groups.

Ann Int Med 2012; 157: October
**Table.** Projected Likelihood Over 6 Years of Lung Cancer Death With or Without Screening per 1000 Persons Screened*

<table>
<thead>
<tr>
<th>Participant</th>
<th>Risk Factors</th>
<th>Deaths From Lung Cancer (Without Screening) per 1000 Persons, ( n )</th>
<th>Deaths From Lung Cancer (With Screening) per 1000 Persons, ( n )</th>
<th>Lung Cancer Deaths Averted per 1000 Persons, ( n )</th>
<th>Persons Needed to Be Screened Annually for 3 y to Prevent 1 Death From Lung Cancer Over 6 y, ( n )</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Typical” participant in the NLST</td>
<td>62-year-old male current 1.5-PPD smoker for 35 y</td>
<td>19.5</td>
<td>15.6</td>
<td>3.9</td>
<td>256</td>
</tr>
<tr>
<td>Minimum eligible participant in the NLST</td>
<td>55-year-old female former 1-PPD smoker for 30 y who just quit</td>
<td>4.0</td>
<td>3.2</td>
<td>0.8</td>
<td>1236</td>
</tr>
<tr>
<td>High-risk participant eligible for the NLST</td>
<td>70-year-old current 2-PPD smoker for 55 y</td>
<td>60.9</td>
<td>48.7</td>
<td>12.2</td>
<td>82</td>
</tr>
<tr>
<td>Minimum eligible participant by NCCN guidelines</td>
<td>50-year-old male former 1-PPD smoker for 20 y who quit 10 y ago with an occupational asbestos exposure history</td>
<td>1.6</td>
<td>1.3</td>
<td>0.3</td>
<td>3180</td>
</tr>
<tr>
<td>Low-risk eligible participant for Sequoia Hospital lung screening program</td>
<td>40-year-old female former 1-PPD smoker for 10 y who quit 15 y ago</td>
<td>0.10</td>
<td>0.08</td>
<td>0.02</td>
<td>35 186</td>
</tr>
</tbody>
</table>

NCCN = National Comprehensive Cancer Network; NLST = National Lung Screening Trial; PPD = packs per day.

* Assuming the program includes 3 annual y of screening.
Multi-Society Joint Meta-Analysis and Guidelines

Benefits and Harms of CT Screening for Lung Cancer
A Systematic Review

Written for:
American Cancer Society
American College of Chest Physicians
American Society of Clinical Oncology
National Comprehensive Cancer Network

Pre-publication endorsement:
American Thoracic Society

JAMA 2012; 144:25-32
Multi-Society Joint Meta-Analysis and Guidelines

- Randomized and cohort studies of LDCT screening reviewed
- NLST is the largest study, and the only positive study in favor of screening for lung cancer

JAMA 2012; 144:25-32
# Multi-Society Joint Meta-Analysis and Guidelines

Table 1. Randomized Controlled Trials Identified in the Search of the Literature

<table>
<thead>
<tr>
<th>Source</th>
<th>LDCT</th>
<th>Control</th>
<th>Collimation, mm</th>
<th>Nodule Size Warranting Workup, mm</th>
<th>Years of Accrual</th>
<th>Planned Follow-up From Baseline</th>
<th>No. of Screens, Planned/Completed (at Last Report)</th>
<th>Participant Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>NELSON, 2009</td>
<td>7907 (95)</td>
<td>7915 (100)</td>
<td>0.75</td>
<td>≥4.6, &gt;8.8</td>
<td>2004-NR</td>
<td>10</td>
<td>3/2</td>
<td>84</td>
</tr>
<tr>
<td>DLCST, 2012</td>
<td>2052 (100)</td>
<td>2052 (100)</td>
<td>0.75&lt;sup&gt;1&lt;/sup&gt;</td>
<td>≥5, &gt;15</td>
<td>2004-2006</td>
<td>10</td>
<td>5/5</td>
<td>55</td>
</tr>
<tr>
<td>ITALUNG, 2009</td>
<td>1613 (87)</td>
<td>1593 (100)</td>
<td>1-1.25</td>
<td>≥5, ≥8&lt;sup&gt;h&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>4/1</td>
<td>65</td>
</tr>
<tr>
<td>DANTE, 2009</td>
<td>1276 (91)</td>
<td>1196 (85)</td>
<td>5</td>
<td>Any, ≥6</td>
<td>2001-2006</td>
<td>NR</td>
<td>5/5&lt;sup&gt;l&lt;/sup&gt;</td>
<td>100</td>
</tr>
<tr>
<td>Garg et al, 2002</td>
<td>92 (100)&lt;sup&gt;l&lt;/sup&gt;</td>
<td>98 (100)&lt;sup&gt;l&lt;/sup&gt;</td>
<td>5</td>
<td>Any, &gt;10</td>
<td>2001-NR&lt;sup&gt;l&lt;/sup&gt;</td>
<td>NR</td>
<td>7/1</td>
<td>75</td>
</tr>
<tr>
<td>NLST, 2011</td>
<td>26,722 (98)</td>
<td>26,732 (97)</td>
<td>≤2.5</td>
<td>≤4</td>
<td>2002-2004</td>
<td>&gt;7</td>
<td>3/3</td>
<td>59</td>
</tr>
<tr>
<td>LSS, 2005</td>
<td>1600 (95)</td>
<td>1600 (95)</td>
<td>5</td>
<td>Any&lt;sup&gt;l&lt;/sup&gt;</td>
<td>2000</td>
<td>2</td>
<td>2/2&lt;sup&gt;m&lt;/sup&gt;</td>
<td>59</td>
</tr>
<tr>
<td>Dępska, 2007</td>
<td>385 (86)&lt;sup&gt;n&lt;/sup&gt;</td>
<td>380 (77)</td>
<td>1-1.5</td>
<td>&gt;5, ≥10</td>
<td>2002-2004</td>
<td>NR</td>
<td>3/1</td>
<td>71</td>
</tr>
</tbody>
</table>

JAMA 2012; 144:25-32
## Multi-Society Joint Meta-Analysis and Guidelines

### Table 3. Mortality Due to All Causes, Lung Cancer, and All Causes Other Than Lung Cancer in Randomized Trials: Trial Characteristics and Mortality Events

<table>
<thead>
<tr>
<th>Source</th>
<th>Compared With</th>
<th>No. of Participants Screened or Followed Up</th>
<th>Median Follow-up, mo</th>
<th>P Value on End Point</th>
<th>Mortality Events, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDCT</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DANTE,22 2009</td>
<td>Usual care</td>
<td>1276</td>
<td>1196</td>
<td>34</td>
<td>.84</td>
</tr>
<tr>
<td>NLST,23 2011</td>
<td>Chest radiographs</td>
<td>26,722</td>
<td>26,732</td>
<td>78</td>
<td>.02</td>
</tr>
<tr>
<td>DLCST,10 2012</td>
<td>Usual care</td>
<td>2,052</td>
<td>2,052</td>
<td>58</td>
<td>.43</td>
</tr>
<tr>
<td>Lung Cancer-Specific Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DANTE,22 2009</td>
<td>Usual care</td>
<td>1276</td>
<td>1196</td>
<td>34</td>
<td>.83</td>
</tr>
<tr>
<td>NLST,23 2011</td>
<td>Chest radiographs</td>
<td>26,722</td>
<td>26,732</td>
<td>78</td>
<td>.004</td>
</tr>
<tr>
<td>DLCST,10 2012</td>
<td>Usual care</td>
<td>2,052</td>
<td>2,052</td>
<td>58</td>
<td>.06</td>
</tr>
<tr>
<td>Mortality Not Due to Lung Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DANTE,22 2009</td>
<td>Usual care</td>
<td>1276</td>
<td>1196</td>
<td>34</td>
<td>.93</td>
</tr>
<tr>
<td>NLST,23 2011</td>
<td>Chest radiographs</td>
<td>26,722</td>
<td>26,732</td>
<td>78</td>
<td>.51</td>
</tr>
<tr>
<td>DLCST,10 2012</td>
<td>Usual care</td>
<td>2,052</td>
<td>2,052</td>
<td>58</td>
<td>.08</td>
</tr>
</tbody>
</table>

Abbreviations: DLCST, Danish Lung Cancer Screening Trial; NLST, National Lung Screening Trial; LDCT, low-dose computed tomography.

JAMA 2012; 144:25-32
Recommendation 1

For smokers and former smokers aged 55 to 74 years who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years, we suggest that annual screening with low-dose computed tomography (LDCT) should be offered over both annual screening with chest radiograph or no screening, but only in settings that can deliver the comprehensive care provided to National Lung Screening Trial (NLST) participants. (Grade of recommendation: 2B.)
Recommendation 2
For individuals who have accumulated fewer than 30 pack-years of smoking or are either younger than 55 years or older than 74 years, or individuals who quit smoking more than 15 years ago, and for individuals with severe comorbidities that would preclude potentially curative treatment, limit life expectancy, or both, we suggest that CT screening should not be performed. (Grade of recommendation: 2C.)
Cost Effectiveness of Lung Cancer Screening

- NLST data
- Quality-adjusted life yr (QALY): years of high quality life a person gains from intervention
- Compared with no screening, LDCT cost $81,000 / QALY gained

(US Threshold for “reasonable” cost effectiveness: ≤$100,000/QALY)
Adding Smoking Cessation Estimated to Increase QALY and Lower Cost of Screening by 20 to 45%

Table 2. Projected 15-year costs and quality-adjusted life years saved by lung cancer screening and treatment with and without smoking cessation using stage shifts from the NY-ELCAP and NLST in authors' actuarial model.

<table>
<thead>
<tr>
<th>Screening + light smoking cessation intervention</th>
<th>NY-ELCAP stage shift</th>
<th>NLST stage shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer screening and treatment costs</td>
<td>$27,824,282,242</td>
<td>$34,054,299,361</td>
</tr>
<tr>
<td>QALYs saved by screening and treatment</td>
<td>985,284</td>
<td>722,795</td>
</tr>
<tr>
<td>Cost per QALY saved</td>
<td>$28,240</td>
<td>$47,115</td>
</tr>
<tr>
<td>Screening + intensive smoking cessation intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. NRT generic plus behavioral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional costs for cessation</td>
<td>$3,212,191,737</td>
<td>$3,212,191,737</td>
</tr>
<tr>
<td>Additional QALYs saved by cessation</td>
<td>930,754</td>
<td>930,754</td>
</tr>
<tr>
<td>Cost per QALY saved</td>
<td>$16,198</td>
<td>$22,537</td>
</tr>
<tr>
<td>B. Bupropion generic plus behavioral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional costs for cessation</td>
<td>$4,088,222,965</td>
<td>$4,088,222,965</td>
</tr>
<tr>
<td>Additional QALYs saved by cessation</td>
<td>930,754</td>
<td>930,754</td>
</tr>
<tr>
<td>Cost per QALY saved</td>
<td>$16,556</td>
<td>$23,067</td>
</tr>
<tr>
<td>C. Chantix plus behavioral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional costs for cessation</td>
<td>$5,342,861,783</td>
<td>$5,342,861,783</td>
</tr>
<tr>
<td>Additional QALYs saved by cessation</td>
<td>930,754</td>
<td>930,754</td>
</tr>
<tr>
<td>Cost per QALY saved</td>
<td>$17,310</td>
<td>$23,826</td>
</tr>
</tbody>
</table>

NY-ELCAP, New York Early Lung Cancer Action Project; NLST, National Lung Screening Trial; QALY, quality-adjusted life year.

doi:10.1371/journal.pone.0071379.e002
1% annual reduction in lung cancer mortality would offer the greatest reduction in productivity costs, of approximately $390 million in 2010 and $416 million in 2020.
Recommendations:

Low dose computed tomography (LDCT)
- For adults aged 55-74 years with ≥30 pack-year smoking history who currently smoke or quit less than 15 years ago, we recommend annual screening with LDCT up to three consecutive times. Screening should ONLY be carried out in health care settings with expertise in early diagnosis and treatment of lung cancer. *Weak recommendation; low quality evidence.*
- For all other adults, regardless of age, smoking history or other risk factors, we recommend not screening for lung cancer with LDCT. *Strong recommendation; very low quality evidence.*

Chest x-ray (CXR)
- We recommend that chest x-ray not be used to screen for lung cancer, with or without sputum cytology. *Strong recommendation; low quality evidence*
So what are we waiting for???
HEALTH & SAFETY ANNOUNCEMENT

DO NOT JUMP ON BANDWAGON.

WAIT UNTIL IT HAS COME TO A STOP THEN CLIMB ON WITH CARE.
Pitfalls of Lung Cancer Screening: Radiation Risk

- average Canadian receives approximately 3 mSv of radiation exposure in the home environment each year
- Typical diagnostic CT scan: 7 mSv (range 4-18 mSv) → calculated radiation risk of approximately one fatal cancer in 2,000 exposed individuals*
- LDCT ≤1.4 mSv
- baseline risk of any cancer of approximately 500 fatal cancers per 2000 individuals
- potential imaging benefit for individuals outweighs the small potential radiation risk

Pitfalls of Lung Cancer Screening: Downstream Invasive Testing

- NLST LDCT arm: 1-4% – invasive test
  - 25% of those who had invasive tests - no cancer
  - # deaths occurred within 2 mo of procedure performed for benign disease: 4.1 - 4.5/10,000

- most NLST centres – academic, multidisciplinary case conferences

- **Rate of invasive procedures may be higher** in non-academic centres where comprehensive care not available

- Study of US community pulmonogy practice patterns –n=377 pts with intermediate pulmonary nodule (8-20mm):
  - 33% underwent invasive biopsy
  - 20% underwent surgery: 35% benign
  - rate of surgical resection similar between low, intermediate and high pre-test probability risk pts

Screening Bias

Screening Bias

Pitfalls of Lung Cancer Screening: Overdiagnosis

= detecting cancer that is not lethal, will never cause problems for individual

- Modeling based on NLST data: 18.5% of all cancers detected will be overdiagnoses, or cancers that would never manifest clinically if screening was not performed

- For every 1 lung cancer death prevented, 1.38 clinically unimportant lung cancers would be diagnosed

## Screening Programs

### Organized
- Population based programs target at-risk population
- Mechanisms to encourage participation, follow-up
- Clear guidelines, monitoring outcomes

### Opportunistic
- Testing available, but no specific mechanisms set up to target at-risk group
- No set guidelines or tracking outcomes
- Ad hoc “case finding”
- Helpful if participants in defined high risk grp
- Potential net harm if performed in low risk pts
Lung Cancer Screening in US

- 2014 – US Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) recommended against providing Medicare reimbursement for lung cancer screening – uncertainty over generalizability of NLST results, felt more studies needed

- Center Medicare / Medicaid Services (CMS) currently provides reimbursement for lung cancer screening BUT long list of requirements that need to be met before a healthcare facility can be reimbursed

- CMS also requires data collection for reimbursement...
US CMS Criteria for Lung Cancer Screening Reimbursement

- **Beneficiary eligibility criteria:**
  - Meet NLST criteria for eligibility
  - Receives a written order for LDCT lung cancer screening that meets the following criteria:
    - **Determination of beneficiary eligibility** including age, absence of signs or symptoms of lung cancer, a specific calculation of cigarette smoking pack-years; and if a former smoker, the number of years since quitting;
    - **Shared decision making**, including the use of one or more decision aids, to include benefits and harms of screening, follow-up diagnostic testing, over-diagnosis, false positive rate, and total radiation exposure;
    - Counseling on the importance of adherence to annual lung cancer LDCT screening, impact of comorbidities and ability or willingness to undergo diagnosis and treatment;
    - Counseling on the importance of maintaining cigarette smoking abstinence if former smoker; or the importance of smoking cessation if current smoker and, if appropriate, furnishing of information about tobacco cessation interventions

US CMS Criteria for Lung Cancer Screening Reimbursement

- **Reading radiologist eligibility criteria:**
  - Board certification or board eligibility with the American Board of Radiology or equivalent organization;
  - Documented training in diagnostic radiology and radiation safety;
  - Involvement in the supervision and interpretation of at least 300 chest computed tomography acquisitions in the past 3 years;
  - Documented participation in continuing medical education in accordance with current American College of Radiology standards; and
  - Furnish lung cancer screening with LDCT in a radiology imaging facility that meets the radiology imaging facility eligibility criteria below.

- **Radiology imaging facility eligibility criteria:**
  - Performs LDCT with volumetric CT dose index (CTDInvol) of \( \leq 3.0 \) mGy (milligray) for standard size patients (defined to be 5’7” and approximately 155 pounds) with appropriate reductions in CTDInvol for smaller patients and appropriate increases in CTDInvol for larger patients;
  - Utilizes a standardized lung nodule identification, classification and reporting system;
  - Makes available smoking cessation interventions for current smokers; and
  - Collects and submits data to a CMS-approved registry for each LDCT lung cancer screening performed.

Current State of Canadian Lung Cancer Screening
Are LDCT scans being ordered for lung cancer screening (as opposed to other purposes such as lung cancer diagnosis in individuals with prior x-ray abnormality, follow-up, etc.) in your province / territory?

<table>
<thead>
<tr>
<th>Province/Territory</th>
<th>Yes / No / Don’t Know</th>
<th>If yes, where is this taking place?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yukon</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>NWT</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Nunavut</td>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>BC</td>
<td>Under research protocol and ad hoc screening for COPD pts, smokers with chronic cough</td>
<td>BCCA (research protocol) and outside BCCA (ad hoc)</td>
</tr>
<tr>
<td>Alberta</td>
<td>Yes</td>
<td>Private CT providers</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Manitoba</td>
<td>Don’t know</td>
<td></td>
</tr>
<tr>
<td>Ontario</td>
<td>Yes, however the extent to which opportunistic screening is occurring is unknown</td>
<td>Screening is occurring through hospital based initiatives. Locations and extent of other opportunistic screening is unknown</td>
</tr>
<tr>
<td>Quebec</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>New Brunswick</td>
<td>Don’t know</td>
<td></td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>Yes</td>
<td>On an ad hoc basis</td>
</tr>
<tr>
<td>PEI</td>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>NFLD / Labrador</td>
<td>Anecdotal evidence suggests that opportunistic LDCT testing is occurring</td>
<td>There is currently no mechanism to track or capture the amount of LDCT testing</td>
</tr>
</tbody>
</table>

CPAC July 2015
Development of Lung Cancer Screening Program

Policy guidelines:

▪ potential benefit of screening and for which specific populations;

▪ magnitude of the potential harms – including the likelihood of false positives and subsequent follow-up procedures required

▪ evidence-informed algorithms to manage the different categories of nodules that will be found on LDCT
Development of Lung Cancer Screening Program

Resource issues...

- Diagnostic imaging – can current infrastructure accommodate increased demand? quality assurance?
- Respirology / thoracic surgery
- Pathology
- Medical / radiation oncology – stage shift possible?
- Data collection, national registry?
Development of Lung Cancer Screening Program

Patient Education

- Informed decision making
- Pros and cons
- Counseling on smoking cessation...lung cancer screening not a free pass!
- High risk populations: smokers – lower SES, rural / remote areas
Out of 1,000 people screened with LDCT for lung cancer:

3 lung cancer deaths will be prevented.

18 people will die of lung cancer.

356 people will get a “false alarm.”

18 of the people who get a “false alarm” will have an invasive procedure like a biopsy.

Less than 1 of the 18 people who have an invasive procedure will have a major complication (e.g., infection, bleeding in lung, collapsed lung).

Out of 1,000 people not screened with LDCT for lung cancer:

21 people will die of lung cancer.

* For people screened once a year for 3 years and followed for an average of 6.5 years. This information applies to people who are at high risk of lung cancer because of their smoking history and age.
Development of Lung Cancer Screening Program

Ethical dilemmas...

▪ What level risk should be funded?
  - even within NLST criteria - wide variation of predicted benefit according to risk level

▪ Pan-Cdn study: regression model - probability cancer pulmonary nodules on screening CT
  - older age, female sex, family history lung ca, emphysema, larger nodule size, upper lobe location, lower nodule count, spiculation

McWilliams et al. *NEJM* 2013
### NLST Estimation Canadian Lung Cancer Deaths Preventable by Screening

(Recall: 20,900 lung cancer deaths Canada 2015)

<table>
<thead>
<tr>
<th>Age strata (years)</th>
<th>A: Canadian 2010 population</th>
<th>B: Proportion meeting NLST criteria</th>
<th>C: Number meeting NLST screening criteria (columns B x C)</th>
<th>D: Lung cancer risk per 1 person-year</th>
<th>E: Number of lung cancers in 1 year (columns D x E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55–59</td>
<td>1,128,200</td>
<td>0.2184</td>
<td>246,399</td>
<td>0.0034836</td>
<td>858</td>
</tr>
<tr>
<td>60–64</td>
<td>965,000</td>
<td>0.2310</td>
<td>222,915</td>
<td>0.0065964</td>
<td>1,470</td>
</tr>
<tr>
<td>65–69</td>
<td>712,600</td>
<td>0.2127</td>
<td>151,570</td>
<td>0.0088858</td>
<td>1,347</td>
</tr>
<tr>
<td>70–74</td>
<td>519,500</td>
<td>0.1645</td>
<td>85,458</td>
<td>0.0111079</td>
<td>949</td>
</tr>
</tbody>
</table>

- **Total lung cancers in men**: 4,625
- **5-year mortality if at 83%**: 3,839
- **Mortality reduction in men if at 20%**: 768

**Total lung cancer deaths prevented in 1 year in men and women**: 1,246
“This has the biggest impact on lung cancer that we have ever seen in our lifetime. This will do more to save lives than anything else we have done to date in lung cancer, from a clinical perspective.”

Reginald Munden MD
MD Anderson Cancer Center
Principal Site Investigator NLST
Summary

- Lung cancer remains a significant health burden
- NLST - first RCT to demonstrate cancer specific mortality benefit lung cancer screening
- While most national health organizations recommend lung cancer screening using NLST criteria (including CTFPHC, USPSTF) many questions remain
- Implementation of future Canadian lung cancer screening programs need to be carefully planned, implemented and monitored to maximize potential benefit, minimize harms and costs
Thank you!!