National Lung Screening Trial

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National PI, ACRIN-NLST

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Division of Cancer Prevention, NCI
Project Officer, LSS-NLST
With appreciation

53,454 trial participants
without whom these studies would not have been possible
Results from the National Lung Screening Trial

- Trial Design and Initial Trial Results
- False-positive Rates and Evaluation of a Positive Screen
- Radiation Dose with Low-Dose Chest CT in the NLST
Prospective, randomized trial comparing low-dose helical CT screening to chest x-ray screening with the endpoint of lung cancer specific mortality in high risk participants

Eligibility
- Age 55-74
- Asymptomatic current or former smoker; 30 pack year smoking history
- Former smokers: quit within preceding 15 years
- No prior lung cancer diagnosis
- No evidence of other cancer within preceding 5 years

http://radiology.rsna.org/content/early/2010/10/28/radiol.10091808.full
NLST design and projected timeline

- **CT Arm**
- **CXR Arm**

**High-Risk Subjects**: 1:1

**Annual Interim Analyses**: 4/2006 - 4/2010

Final: October 2010

- **T0**
- **T1**
- **T2**

[Link](http://radiology.rsna.org/content/early/2010/10/28/radiol.10091808.full)
Participating sites

ACRIN 23
LSS 10
**NLST primary endpoint**

<table>
<thead>
<tr>
<th></th>
<th>Helical CT vs. CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer-specific mortality</td>
<td>20% difference</td>
</tr>
<tr>
<td>α</td>
<td>5%</td>
</tr>
<tr>
<td>Power</td>
<td>90%</td>
</tr>
<tr>
<td>Compliance</td>
<td>85% CT</td>
</tr>
<tr>
<td>Contamination</td>
<td>5% CT</td>
</tr>
<tr>
<td>Size</td>
<td>25,000 / arm</td>
</tr>
</tbody>
</table>

http://radiology.rsna.org/content/early/2010/10/28/radiol.10091808.full
NLST secondary endpoints

- Secondary endpoints
  - All cause mortality
  - Lung cancer: prevalence | incidence | interval cancers
  - Stage distribution
  - Screening test performance
  - Medical resource utilization for [+ ] screen
Secondary endpoints
- All cause mortality
- Lung cancer: prevalence | incidence | interval cancers
- Stage distribution
- Screening test performance
- Medical resource utilization for [+] screen
NLST cumulative accrual – 33 sites

- Total: 53,454
- LSS: 34,614
- ACRIN: 18,840

Participants over time:
- Aug 02: 0
- Nov 02: 0
- Feb 03: 0
- May 03: 0
- Aug 03: 0
- Nov 03: 0
- Feb 04: 0

Month Enrolled
Comparison to US census data

- Contains information on 240,000 respondents
- Subset of respondents aged 55-74, with 30+ pack year smoking, either current smoker or former smoker who quit within the past 15 years
- Identified smoking status, age, sex, race, ethnicity, marital status, and education
53,454 participants

Comparing NLST with eligible US census population

<table>
<thead>
<tr>
<th>53,454 participants</th>
<th>NLST</th>
<th>US Census</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>59.0</td>
<td>58.5</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-59 (%)</td>
<td>42.8</td>
<td>35.2</td>
</tr>
<tr>
<td>60-64 (%)</td>
<td>30.6</td>
<td>29.3</td>
</tr>
<tr>
<td>65-69 (%)</td>
<td>17.8</td>
<td>20.8</td>
</tr>
<tr>
<td>70-74 (%)</td>
<td>8.8</td>
<td>14.7</td>
</tr>
<tr>
<td>Race</td>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Black (%)</td>
<td>4.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>1.7</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Comparing NLST with US census population

<table>
<thead>
<tr>
<th></th>
<th>NLST</th>
<th>US Census</th>
</tr>
</thead>
<tbody>
<tr>
<td>Married</td>
<td>66.6</td>
<td>60.9</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; HS</td>
<td>6.1</td>
<td>21.3</td>
</tr>
<tr>
<td>≥ College</td>
<td>31.5</td>
<td>14.4</td>
</tr>
<tr>
<td>Current smoker</td>
<td>48.2</td>
<td>57.1</td>
</tr>
<tr>
<td>Median pack yrs</td>
<td>48.0</td>
<td>47.0</td>
</tr>
</tbody>
</table>

Compared with similar US population, NLST cohort has similar gender distribution and smoking exposure.

However, NLST participants:
- Younger
- Better educated
- Less likely to be current smokers

### Participant history of lung disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Helical CT %</th>
<th>X-Ray %</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asbestosis</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>3.2</td>
<td>3.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Emphysema</td>
<td>7.7</td>
<td>7.6</td>
<td>7.7</td>
</tr>
<tr>
<td>Chronic bronchitis, emphysema or COPD</td>
<td>17.5</td>
<td>17.4</td>
<td>17.4</td>
</tr>
<tr>
<td>Lung fibrosis</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Silicosis</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

1 Lung disease based on participant self-report at baseline. Does not include sub-study analyses of NLST imaging exams.
Family history of lung cancer across NLST

<table>
<thead>
<tr>
<th></th>
<th>Helical CT %</th>
<th>X-Ray %</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any first degree relative</td>
<td>21.8</td>
<td>21.7</td>
<td>21.7</td>
</tr>
<tr>
<td>≥ 2 first degree relatives</td>
<td>3.3</td>
<td>3.2</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Analyses of family history and lung cancer risk ongoing
## Screening exam compliance

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Helical CT</th>
<th>Chest X-ray</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expected</td>
<td>Screened</td>
<td>Expected</td>
</tr>
<tr>
<td>T0</td>
<td>26,713</td>
<td>98.5%</td>
<td>26,722</td>
</tr>
<tr>
<td>T1</td>
<td>26,282</td>
<td>94.0%</td>
<td>26,398</td>
</tr>
<tr>
<td>T2</td>
<td>25,935</td>
<td>92.9%</td>
<td>26,097</td>
</tr>
</tbody>
</table>
## Screen positivity rate by screening round & arm

<table>
<thead>
<tr>
<th></th>
<th><strong>Low-dose helical CT</strong></th>
<th></th>
<th><strong>CXR</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number screened &amp; Number positive &amp; % Positive</td>
<td>Number screened &amp; Number positive &amp; % Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen 1</td>
<td>26,314 &amp; 7,193 &amp; 27.3</td>
<td>26,049 &amp; 2,387 &amp; 9.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen 2</td>
<td>24,718 &amp; 6,902 &amp; 27.9</td>
<td>24,097 &amp; 1,482 &amp; 6.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen 3</td>
<td>24,104 &amp; 4,054 &amp; 16.8**</td>
<td>23,353 &amp; 1,175 &amp; 5.0**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All screens</td>
<td>75,136 &amp; 18,149 &amp; 24.2</td>
<td>73,499 &amp; 5,044 &amp; 6.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Positive screen: nodule $\geq 4$ mm or other findings potentially related to lung cancer.

** Abnormality stable for 3 rounds could be called negative by protocol.
### True and false positive screens

<table>
<thead>
<tr>
<th>Screening Result</th>
<th>Low-dose Helical CT</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screen 1 N (%)</td>
<td>Round 2 N (%)</td>
<td>Round 3 N (%)</td>
<td>Round 1 N (%)</td>
<td>Round 2 N (%)</td>
<td>Round 3 N (%)</td>
<td></td>
</tr>
<tr>
<td>Total Positives</td>
<td>7,193 (100)</td>
<td>6,902 (100)</td>
<td>4,054 (100)</td>
<td>2,387 (100)</td>
<td>1,482 (100)</td>
<td>1,175 (100)</td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>270 (4)</td>
<td>168 (2)</td>
<td>211 (5)</td>
<td>136 (6)</td>
<td>65 (4)</td>
<td>78 (7)</td>
<td></td>
</tr>
<tr>
<td>No lung cancer</td>
<td>6,923 (96)</td>
<td>6,734 (98)</td>
<td>3,843 (95)</td>
<td>2,251 (94)</td>
<td>1,417 (96)</td>
<td>1,097 (93)</td>
<td></td>
</tr>
</tbody>
</table>

Data reflect the final interpretation, including benefit of historical comparison exams.
Interim analysis: lung cancer mortality 10-20-2010

<table>
<thead>
<tr>
<th>Arm</th>
<th>Person Years (py)</th>
<th>Lung cancer deaths</th>
<th>Lung cancer mortality per 100,000 py</th>
<th>Reduction in lung cancer mortality (%)</th>
<th>Value of test statistic</th>
<th>Efficacy boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDCT</td>
<td>144,102.6</td>
<td>356</td>
<td>247</td>
<td>20.0</td>
<td>–3.2</td>
<td>–2.033</td>
</tr>
<tr>
<td>CXR</td>
<td>143,367.5</td>
<td>443</td>
<td>309</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ p = 0.0041 \]

Deficit of lung cancer deaths in CT arm exceeds that expected by chance, even allowing for multiple looks at the data.

CXR arm compared with matched 30,000 cohort in PLCO, no benefit of CXR seen.
Interim analysis: all-cause mortality 10-20-2010

- Lung cancer: 25% of all deaths in NLST
- Lung cancer: 56% of 123 excess deaths in CXR arm

<table>
<thead>
<tr>
<th>Arm</th>
<th>Person Years (py)</th>
<th>Deaths</th>
<th>All-cause mortality per 100,000 py</th>
<th>Reduction in all cause mortality (%)</th>
<th>Value of test statistic</th>
<th>Value for significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>167,394.9</td>
<td>1877</td>
<td>1121</td>
<td>6.7</td>
<td>–2.31</td>
<td>–1.96</td>
</tr>
<tr>
<td>CXR</td>
<td>166,332.2</td>
<td>2000</td>
<td>1202</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p = 0.021
Kaplan-Meier curves for *all-cause mortality*

- **CT arm lung cancer**
- **CXR arm lung cancer**
- **CT arm all-cause**
- **CXR arm all-cause**

Years from randomization

Probability of survival: ALL participants
Lung cancer case survival Kaplan Meier curve

Probability of survival: Participants with lung cancer

Years from diagnosis

CT arm
CXR arm
Average $\text{CTDI}_{\text{vol}} = 2.9 \text{ mGy}$ (std dev = 1.0 mGy)
(results time averaged by CT scanner over trial period)
Estimated Organ Doses – Male / Female

- **CT-Expo Software**

- **35 cm thorax scan length**

- **NLST average CTDI\textsubscript{vol} of 2.9 mGy used as input to CT-Expo**
Estimated Organ Doses
Male & Female

(Using NLST average CTDI\textsubscript{vol} of 2.9 mGy, 35 cm scan, and CT-Expo Software)
Comparison to Standard Chest CT

- Acceptable chest CT screening can be accomplished at a small fraction of the dose of a standard chest CT
- **Whole body effective dose (weighted average dose to each organ)**
  - Low dose helical CT: 1.5 mSv
  - Mammogram: 0.7 mSv
  - CXR: 0.01 mSv
- **Low dose helical CT: estimates of organ specific dose**
  - Lung: 4 mGy
  - Breast: 4 mGy for females
  - Red bone marrow, stomach, liver and pancreas: each ~1 mGy
- **Screening mammogram organ specific dose:**
  - Breast: 4 mGy
  - Other organs: < 0.1 mGy
Radiation Risks vs Benefits

- 3 screens Smokers Age 55

- Radiation risk from screens
  - 1-3 lung cancer deaths per 10,000 screened
  - 0.3 breast cancers per 10,000 females screened

- Radiation risk from follow-up CT scans
  - Low-dose or thin-section chest CT x 25%
  - Diagnostic chest CT x 100%

- Cumulative mortality reduction NLST
  - 30 lung cancer deaths per 10,000 screened
Collaborative Investigations Initiated

- Lam Canadian study of LDCT with fluorescent bronchoscopy using Tammemagi risk model
- Radiation risk assessment with medical physicists and REB
- Planned individual level meta-analysis with ongoing European studies: NELSON, Danish CT study, etc
- Modeling effort with CISNET lung teams
- CAD and CADx for nodule evaluation
- Two planned and one proposed lung cancer early detection marker validation in PLCO with study in ACRIN biospecimen repository of successful markers
Acknowledgements
NLST Executive Committee

- Denise R. Aberle, MD
- Christine D. Berg, MD
- William C. Black, MD
- Timothy R. Church, PhD, MS
- Richard M. Fagerstrom, PhD
- Barbara Galen, MSN, CRNP, CNMT
- Ilana F. Gareen, PhD
- Constantine Gatsonis, PhD
- Jonathan Goldin, MD, PhD
- Barnett S. Kramer, MD, MPH
- David Lynch, MD
- Irene Mahon, RN, MPH
- Pamela M. Marcus, MS, PhD
- Dorothy Sullivan
- Carl J. Zylak, MD

National Cancer Institute:
DCP, EDRG, Lung Screening Study
DCTD, Cancer Imaging Program, Bethesda, MD
American College of Radiology Imaging Network, Philadelphia, PA
NLST Lead Radiologists

**ACRIN**


**LSS**

Peter Balkin MD, Matthew T. Freedman MD MBA, Kavita Garg MD, David S. Gierada MD, Subbarao Inampudi MD, Howard Mann MB BCh, William Manor DO, Hrudaya Nath MBBS DMR MD, David L. Spizarny MD, Diane C. Strollo MD, John Waltz MD
# NLST Physicists

**CT Physics Committee**

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dianna Cody, PhD</td>
<td>MD Anderson Cancer Center</td>
</tr>
<tr>
<td>Mike McNitt-Gray, Phd</td>
<td>UCLA</td>
</tr>
<tr>
<td>Christopher Cagnon, PhD</td>
<td>UCLA</td>
</tr>
<tr>
<td>Philip Judy, PhD</td>
<td>Brigham and Women’s Hospital</td>
</tr>
<tr>
<td>Fred Larke, PhD</td>
<td>University of Colorado</td>
</tr>
<tr>
<td>Randell Kruger, PhD</td>
<td>Marshfield Clinic</td>
</tr>
<tr>
<td>Mike Flynn, PhD</td>
<td>Henry Ford Hospital</td>
</tr>
<tr>
<td>Xizeng Wu, PhD</td>
<td>University of Alabama</td>
</tr>
</tbody>
</table>

**CXR Physics Committee**

<table>
<thead>
<tr>
<th>Name</th>
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</tr>
</thead>
<tbody>
<tr>
<td>J. Anthony Seibert, PhD</td>
<td>UC Davis</td>
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<td>UCLA</td>
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<td>Henry Ford Hospital</td>
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</tbody>
</table>
NLST Committees

- **Endpoint Verification Team**
  Anthony B. Miller, MB, Chair, Martin J. Edelman, MD, William K. Evans, MD, Robert S. Fontana, MD, Mitchell Machtay, MD

- **Oversight Committee**
  Robert C. Young, MD, Chair, David Alberts, MD, David DeMets, PhD, Peter Greenwald, MD, Dr PH, Paula Jacobs, MD, Theresa C. McLoud, MD, David P. Naidich, MD, James Tatum, MD

- **Data and Safety Monitoring Board**
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* Deceased
Additional Partners

National Cancer Institute: Cancer Imaging Program, DCTD
Early Detection Research Group, DCP

ACRIN | Westat | IMS | CARE Communications

Our many, many site investigators and research staff

Colleagues
- NLST ACRIN Tissue Bank & Biomarker Oversight Committee
- NLST ACRIN Research Evaluation Panel
- ACRIN Specimen Biorepository at University of Colorado
- UCLA Tissue Microarray Laboratory

American Cancer Society: in-kind assistance with recruitment

Advocates & members of lung cancer community who supported NLST
With appreciation

53,454 trial participants

without whom these studies would not have been possible