Lung Cancer Screening - 2022

Catherine R. Sears, M.D.
Assistant Professor, Indiana University School of Medicine
VA-PALS Director of Lung Cancer Screening, Indianapolis VA Medical Center
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Disclosure Slide

1. Research and Programmatic Funding:
   - American Cancer Society, National Institutes of Health (NIH-NHLBI), Veterans Affairs BLR&D, VA-Office of Rural Health, Biodesix Inc.

2. Research/Scientific Consultant:
   - Bristol Myers Squibb

3. This presentation does not represent the views of the Department of Veterans Affairs of the United States Government.
Background and Overview

- Background
- Rationale for screening
- National Lung Screening Trial
- Lung screening recommendations
- Risks and Benefits
- Special Considerations of a Lung Cancer Screening Program
- Ongoing Questions and Needs
<table>
<thead>
<tr>
<th>Lucas Oil Stadium Capacity</th>
<th>New Lung Cancer Cases</th>
<th>Lung Cancer Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>68,000</td>
<td>236,740</td>
<td>130,180</td>
</tr>
</tbody>
</table>

Siegel et. al. Cancer Statistics, 2022, CA Cancer J Clin
Lung Cancer Stage at Diagnosis

- I (Localized): 7%
- II and III (Regional): 22%
- IV (Distant): 56%
- Unknown/Unstaged: 15%

Significance of Early Diagnosis

Survival by Stage at Diagnosis

History of Lung Cancer Screening

1980-1990s: Failed studies, overdiagnosis:
- Mayo Clinic Project (CXR/sputum cytology)
- Johns Hopkins Lung Project
- Czechoslovakian RCT
- Improved detection, more Stage I, no lung cancer mortality

1990
- PLCO- confirmed no impact yearly CXR on lung CA mortality
- ELCAP (1992, observational)
- Smaller/LDCT screening studies
  - Mayo Clinic
  - DANTE

2000
- NCCN Cat. 1*
- 2002-2004 NLST enrollment
- 2006 ELCAP observations published

2010
- MILD, DLCST, ITALUNG, UKLS
- 2011 NLST published

2012-2013
- LCS Recommended: ACCP*/ASCO/ATS, ALA, AATS

2015
- CMS Coverage Approved

2019
- Revised USPSTF

2020
- NELSON publication
- PanCan
- ELIPSE Abstract IASLC-WCLC

USPSTF “B” recommendation 2013
Nelson publication 2020
NCCN Cat. 1* 2012
NLST (National Lung Screening Trial)

- Enrollment: 53,454 from 8/02-4/04
- Randomized to screening with low dose CT vs CXR
- Three annual screenings
- Median follow-up 6.5 yrs
- Total adherance 91%
# The NEW ENGLAND JOURNAL of MEDICINE

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-74 y/o</td>
<td>Previous lung or other cancer (5 years)</td>
</tr>
<tr>
<td>Tobacco ≥ 30 pack-yrs</td>
<td>CT chest ≤ 18 months</td>
</tr>
<tr>
<td>Quit ≤ 15 yrs</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td></td>
<td>Weight loss &gt; 15 lbs/last yr</td>
</tr>
<tr>
<td></td>
<td>Unable to undergo surgery</td>
</tr>
</tbody>
</table>
Table 5. Stage and Histologic Type of Lung Cancers in the Two Screening Groups, According to the Result of Screening.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Stage and Histologic Type</th>
<th>Low-Dose CT</th>
<th>Chest Radiography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive Screening Test (N=649)</td>
<td>Negative Screening Test (N=44)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>329/635 (51.8)</td>
<td>5/44 (11.4)</td>
</tr>
<tr>
<td>IIA</td>
<td>71/635 (11.2)</td>
<td>2/44 (4.5)</td>
</tr>
<tr>
<td>IIB</td>
<td>26/635 (4.1)</td>
<td>2/44 (4.5)</td>
</tr>
<tr>
<td>IIIA</td>
<td>20/635 (3.1)</td>
<td>3/44 (6.8)</td>
</tr>
<tr>
<td>IIIB</td>
<td>59/635 (9.3)</td>
<td>3/44 (6.8)</td>
</tr>
<tr>
<td>IV</td>
<td>49/635 (7.7)</td>
<td>15/44 (34.1)</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchioloalveolar carcinoma</td>
<td>95/646 (14.7)</td>
<td>1/44 (2.3)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>258/646 (39.9)</td>
<td>8/44 (18.2)</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>136/646 (21.1)</td>
<td>13/44 (29.5)</td>
</tr>
<tr>
<td>Large-cell carcinoma</td>
<td>28/646 (4.3)</td>
<td>3/44 (6.8)</td>
</tr>
<tr>
<td>Non–small-cell carcinoma or other</td>
<td>75/646 (11.6)</td>
<td>4/44 (9.1)</td>
</tr>
<tr>
<td>Small-cell carcinoma</td>
<td>49/646 (7.6)</td>
<td>15/44 (34.1)</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>5/646 (0.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} \text{Aberle DR et al.; National Lung Screening Trial Research Team. New Engl J Med. 2011;365(5):395-409}
Probability of Survival: Participants with Lung Cancer

Years from Diagnosis

0 1 2 3 4 5 6 7

1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0

CT Arm
CXR Arm

20% relative reduction in lung cancer death
3 fewer lung cancer deaths/1000 screened

## Lung Cancer Screening Trials

### TABLE 3: Summary of Design of Included Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Age (y)</th>
<th>Smoking History</th>
<th>Smoking Cessation (Years Since Quit)</th>
<th>Screening Interval and Duration</th>
<th>Follow-up (y)</th>
<th>Definition of Positive Result</th>
<th>% Male</th>
<th>Lung Cancer Mortality (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDCT vs CXR</td>
<td>53,454</td>
<td>55-74</td>
<td>≥ 30 pack-years</td>
<td>≤ 15</td>
<td>3 annual screens</td>
<td>6.5 (median)</td>
<td>≥ 4 mm</td>
<td>59%</td>
<td>0.85</td>
</tr>
<tr>
<td>NLST²,¹³</td>
<td>765</td>
<td>50-75</td>
<td>≥ 15 cigarettes/ d for ≥ 20 y</td>
<td>≤ 15</td>
<td>3 annual screens</td>
<td>NK</td>
<td>&gt; 5 mm</td>
<td>71%</td>
<td>*</td>
</tr>
<tr>
<td>Depscans</td>
<td>2,472 males</td>
<td>60-74</td>
<td>≥ 20 pack-years</td>
<td>&lt; 10</td>
<td>5 annual screens; baseline CXR for both study arms</td>
<td>8</td>
<td>&gt; 5 mm</td>
<td>100%</td>
<td>1.01*</td>
</tr>
<tr>
<td>DANTE¹⁵-¹⁷</td>
<td>4,104</td>
<td>50-70</td>
<td>≥ 20 pack-years</td>
<td>&lt; 10</td>
<td>5 annual screens</td>
<td>10</td>
<td>&gt; 15 mm or rapid growing 5- to 15-mm nodules (&gt;25% increase in volume on 3-mo follow-up CT)</td>
<td>55%</td>
<td>1.03*</td>
</tr>
<tr>
<td>NELSON²²,²³</td>
<td>15,822</td>
<td>50-75</td>
<td>≥ 15 cigarettes/ d for ≥ 25 y or ≥ 15 cigarettes/d for ≥ 30 y</td>
<td>&lt; 10</td>
<td>4 screening rounds; interval after baseline: 1 y, 2 y, and 2.5 y</td>
<td>7</td>
<td>Volume &gt; 500 mm³ or volume 50-500 mm³ with VDT &lt; 400 d on 3-mo repeat CT</td>
<td>84%</td>
<td>0.76</td>
</tr>
<tr>
<td>ITALUNG²⁴,²⁵</td>
<td>3,205</td>
<td>55-69</td>
<td>≥ 20 pack-years</td>
<td>≤ 10</td>
<td>4 annual screens</td>
<td>6</td>
<td>≥ 5 mm solid nodule, a ground-glass nodule = 10 mm, or any part-solid nodule</td>
<td>64%</td>
<td>0.70*</td>
</tr>
<tr>
<td>MILD²⁷-²⁹</td>
<td>4,099</td>
<td>≥ 49</td>
<td>≥ 20 pack-years</td>
<td>&lt; 10</td>
<td>Two study arms: 5 annual screenings; or 3 biennial screens</td>
<td>5</td>
<td>Volume &gt; 250 mm³ or rapid growing 60-250 mm³ (≥25% increase in volume on 3-mo repeat CT)</td>
<td>68,69%</td>
<td>Annual: 2.48* Biennial: 1.24*</td>
</tr>
<tr>
<td>LUST²⁹,³¹</td>
<td>4,052</td>
<td>50-69</td>
<td>≥ 15 cigarettes/ d for ≥ 25 y or ≥ 10 cigarettes/d for ≥ 30 y</td>
<td>&lt; 10</td>
<td>4 annual screens</td>
<td>3</td>
<td>≥ 5 mm</td>
<td>66%</td>
<td>*</td>
</tr>
<tr>
<td>UKLS³²-³⁴</td>
<td>4,055</td>
<td>50-75</td>
<td>LLNv2 risk ≥ 5%</td>
<td></td>
<td>One screening</td>
<td>10</td>
<td>Volume &gt; 500 mm³ or volume 50-500 mm³ with VDT &lt; 400 d on 3-mo repeat CT</td>
<td>75%</td>
<td>*</td>
</tr>
<tr>
<td>LS³⁵,³⁶</td>
<td>3,318</td>
<td>55-74</td>
<td>≥ 30 pack-years</td>
<td>&lt; 10</td>
<td>One screening</td>
<td>1</td>
<td>≥ 4 mm</td>
<td>58%</td>
<td>*</td>
</tr>
</tbody>
</table>
## Current Screening Criteria?

<table>
<thead>
<tr>
<th>Criteria according to:</th>
<th>US Preventative Services Task Force (2021)</th>
<th>Centers for Medicare &amp; Medicaid Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insurance:</td>
<td>Private health insurance</td>
<td>Medicare beneficiaries</td>
</tr>
<tr>
<td>Age (years):</td>
<td>50-80</td>
<td>50-77</td>
</tr>
<tr>
<td>Smoking History:</td>
<td>20 pack-years or more</td>
<td>20 pack-years or more</td>
</tr>
<tr>
<td>Smoking Status:</td>
<td>Current smoker or quit within 15 years</td>
<td></td>
</tr>
<tr>
<td>Health Requirement:</td>
<td>Asymptomatic of lung cancer</td>
<td></td>
</tr>
<tr>
<td>Screening Frequency:</td>
<td>Annually</td>
<td></td>
</tr>
<tr>
<td>When to stop LCS</td>
<td>When any of the below conditions occur:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Exceeds upper age criterion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Has not smoked for &gt; 15 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Comorbidity that substantially limits life expectancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Unable or unwilling to have curative surgery/treatment or follow-up</td>
<td></td>
</tr>
</tbody>
</table>
Components of Lung Cancer Screening

Shared Decision Making Visit

- Review medical history, habits, current health
- Review **personalized** risks and benefits
- Review the program, communications and referrals, yearly screening & answer questions

Tobacco Treatment Counseling

**Benefits**
- 12 in 1000: fewer people like you will die from lung cancer among those who were screened compared to those who were not screened.

**Risks**
- 120 in 1000 people who were screened found a lung nodule that was not cancer.
- 13 in 1000 had an invasive procedure, such as biopsy or surgery, due to a lung nodule that was not cancer.
- Fewer than 1 in 1000 had a major complication from invasive procedures.
- Of the lung cancers found by screening, fewer than 1 in 10 would have harmed you. This may lead to unnecessary treatment and complications.
Benefits vs harms

False positives
False negatives
Overdiagnosis
Psychological harms
Procedure complications
Radiation exposure
Cost

Decreased mortality
20-26% decrease lung cancer death
7% decrease all cause

Teachable moment for cigarette smoking cessation
Causes of Lung Nodules

26-60% LDCTs

- Pneumoconiosis
- Cancer
- Autoimmune disorders
- Enlarged lymph nodes
- Benign tumors
- Lung infections
- Scars from past infection

96% Benign
62 Year Old Male Smoker

54 Year Old Male Smoker

LUNG CANCER

HISTOPLASMOSIS
Minimizing risks of radiation exposure

Avg. NLST participant = 8mSv

~ 1 death per 2500 screened patients

# needed to screen to prevent 1 death:
320 (3 years)
130 (10 years)


Components of Lung Cancer Screening

- Low Dose Computed Tomography of Chest (Low Dose CT Chest)
- Low Radiation Dose
- Quick (~ 3-5 minutes)
- Non-contrasted (no needles!)
- Protocolized Interpretation and Management Plan

Lung cancer survivor Mr. Bobby Richardson receives follow-up care at the Richard L. Roudebush VA Medical Center in Indianapolis. (Photo by Mark Turney, Richard L. Roudebush VA Medical Center.)
Components of Lung Cancer Screening

- Standardized Reporting System
- Review of Imaging/Results ("Nodule" board)
- Protocolized Follow-up
- Streamline Referral and Diagnostic Procedures
- Patient tracking and yearly follow-up
- Management of Incidental Findings
# Lung-RADS™ Version 1.1

**Assessment Categories Release date: 2019**

<table>
<thead>
<tr>
<th>Category/Description</th>
<th>Lung-RADS I-ELCAP LU-RADS Others</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung-RADS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>I-ELCAP</strong></td>
<td></td>
</tr>
<tr>
<td><strong>LU-RADS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Assessment</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Categories</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Incomplete</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Benign Appearance or Behavior</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Probably Benign</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Probably Suspicious</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Suspicious</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Other Clinical Signs of Potential or Clinically Significant Findings (Non Lung cancer)</strong></td>
<td></td>
</tr>
</tbody>
</table>

## Lung-RADS

**Summary**

- **Incomplete**
  - Prior chest CT examination(s) being located for comparison
  - Part or all of lungs cannot be evaluated

- **Negative**
  - No nodules and definitely benign nodules
    - Nodules with specific characteristics: complete, central, popcorn, concerning edge and talc-containing nodules

- **Benign Appearance or Behavior**
  - Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth

- **Probably Benign**
  - Nodules ≥ 6 mm in basal or OR
  - Very low risk of malignancy

- **Probably Suspicious**
  - Findings for which additional diagnostic testing is required

- **Suspicious**
  - Findings for which additional diagnostic testing or tissue sampling is recommended

- **Other**
  - Clinical signs of potential or clinically significant findings (non-lung cancer)

**Lung-RADS**

- **Assessment Criteria**
  - Immediate follow-up suggested
  - Nodules with a low likelihood of becoming a clinically active cancer

**I-ELCAP**

- **Assessment Criteria**
  - Annual screening with nodule diameter,
  - Risk of malignancy,
  - Population characteristics

**LU-RADS**

- **Assessment Criteria**
  - Annual screening with nodule diameter,
  - Risk of malignancy,
  - Population characteristics

**Others**

- **Assessment Criteria**
  - Immediate follow-up suggested
  - Nodules with a low likelihood of becoming a clinically active cancer

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**INDIANA UNIVERSITY MELVIN AND BREN SIMON COMPREHENSIVE CANCER CENTER**
Ongoing Challenges/Needs in Lung Cancer Screening
LCS Uptake is Increasing.. But still Low

Clinformatics Data Mart (CDM) Database (2016-2017)

Okereke et al. J Thorac Dis. 2019
Lung Cancer Screening in Indiana

44th in new lung cancer diagnosis
19% smoking rate in Indiana

22nd in lung cancer screening

Location, location, location…

Pink = Blue

Gray = minimal equipment for LCS
Yearly Compliance

1. Yearly compliance is low: 46% (T1), 38% (T2) and 28% (T3)

2. Compliance with Lung-RADS recommended follow-up increased:
   - Older (65-73 years) compared to younger (50-64 years) patients
   - Concerning Nodule (LungRADS 4 > 3 > 2 compared to LungRADS 1)
   - Hiring a dedicated program coordinator and active reminders
   - Former smokers > Current smokers

3. **System Barriers**: patient communication, failure to order scan or follow-up, misunderstanding (program vs scan), tracking system

4. **Patient Barriers**: transportation, communication, asymptomatic, fear, other medical, financial costs

5. *Highlights the need for systematic dedication to adequate resources and patient tracking.*
   Lin et al. J Thorac Onc. 25 Sept 2021
Disparities and missed high-risk populations

Screening Inclusion/Barriers
- Rural and urban (vs low-resource urban)
- Minority groups
- Social and economically disadvantaged
  Resource-poor environments
- Other high-risk exposures (radon, radiation, coal/tar pitch, 2nd-hand smoke)
- Other high-risk groups (EGFR)

Aldrich et al. JAMA Oncol 2019.
Minimizing Barriers
Risk prediction models
Biomarkers
Radiomics
Outreach/Advocacy
- focused clinical
- diversity research
Resources
Cross-institutional collaborations

Pulmonary oncologist Dr. Catherine R. Sears meets with VALOR clinical trial participant Mr. Bobby Richardson. (Photo by Mark Tumey, Richard L. Roudebush VA Medical Center.)