Lung Cancer Screening: The End of the Beginning

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Exact Sciences

Off Label Usage
None

Learning Objectives
• Understand the results of recent studies of CT screening
• Recognize who is a candidate for lung cancer screening and how this differs from other types of screening
• Recognize the potential harms of lung cancer screening
• Summarize the appropriate follow-up for screen findings
Lung Cancer: The Problem

• 2017 estimated 222,500 new cases
• By 2022 only 40,050 of these will be alive
• Approximately 427 people die of lung cancer every day
• 25% of lung cancer is surgically removable for intended cure at time of diagnosis


Leading Cancers:
5 year Survival: 2006-12

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>18%</td>
</tr>
<tr>
<td>Colon</td>
<td>65%</td>
</tr>
<tr>
<td>Breast</td>
<td>90%</td>
</tr>
<tr>
<td>Prostate</td>
<td>99%</td>
</tr>
</tbody>
</table>


Lung cancer screening is different than other screening

• Selection of candidates is complicated
• Highly modifiable risk
• Can’t screen the lung without looking at lots of other things
• Lungs are internal and come with risk
• Lung cancer screening is more effective
Q1. An effective screening test for lung cancer should demonstrate which of the following in the participants screened for lung cancer?

A) More cancers than in an unscreened group.
B) More stage I cancers than usual practice.
C) Fewer advanced stage cancers than an unscreened group.
D) Marked increase in 5 and 10 year survival.
E) That fewer people die of lung cancer than in an unscreened group.

Q2. Mrs. G is a 65 year old former smoker comes to see you after her first ever colonoscopy showed a 2cm adenomatous polyp. She is happy she finally took your advice and wonders if there is anything else she can do proactively for her health. She has a 30 pack year history and quit 10 years ago. Which of the following would you recommend?

A. Bronchoscopy
B. Chest X-ray
C. Low-dose CT
D. Sputum cytology
E. None of the above

National Lung Screening Trial (NLST)

Mayo Clinic: RST 1183, FL 288

NLST Results

53,454 participants, Median duration F/U 6.5 years

<table>
<thead>
<tr>
<th></th>
<th>Baseline image positive</th>
<th>Screen detected CA</th>
<th>Interval CA</th>
<th>CA post screen</th>
<th>Total Cancers</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>27%</td>
<td>649</td>
<td>44</td>
<td>367</td>
<td>1060</td>
<td>356</td>
</tr>
<tr>
<td>CXR</td>
<td>9%</td>
<td>279</td>
<td>137</td>
<td>525</td>
<td>941</td>
<td>443</td>
</tr>
</tbody>
</table>

- Absolute reduction lung cancer-specific mortality from 1.66 to 1.33%  
  (p=.004)
- 20% relative reduction in mortality
- NNT 320

USPSTF

"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. Grade: B recommendation.

CMS

55 to 77 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years.

I outlived Michael Jackson

Bet you didn’t see that coming
Q3. Mrs. G’s husband accompanied her to the appointment and spoke up after the discussion about LDCT screening. He is a 70 year old former smoker of 30 years who quit 20 years ago. Which of the following would you recommend for him?

A. No LDCT screening.
B. Yes, LDCT screening now.
C. Yes, LDCT, but he needs to resume smoking.
D. You would simply follow the guideline recommendations.
E. Not sure, need more information.

Q4. The recommendation of whether or not to screen Mr. G for lung cancer should be made primarily based on which of the following?

A) Anticipated increase in 5 year survival.
B) Gender.
C) Guideline recommendations.
D) Reimbursement for screening.
E) Risk for lung cancer.
### Who to Screen: Guidelines

<table>
<thead>
<tr>
<th>Author</th>
<th>Age Range</th>
<th>Quit ≤ 15 yrs</th>
<th>Additional criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS¹</td>
<td>55-74, 70 Pk-yr</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ACCP/ASCO²</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>NCCN³</td>
<td>Yes</td>
<td>No</td>
<td>≥50 Years and ≥20 Pk Years and COPD or family history of lung CA</td>
</tr>
<tr>
<td>AATS⁴</td>
<td>55-79</td>
<td>No</td>
<td>≥50 Years and ≥20 Pk Years and 5% risk over 5 years</td>
</tr>
<tr>
<td>USPSTF⁵</td>
<td>55-80</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>AAFP⁶</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CMS⁷</td>
<td>55-77</td>
<td>Yes</td>
<td>Yes - strict site criteria</td>
</tr>
</tbody>
</table>


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### Too few are eligible

The eligible Aren’t being Screened

Lung CA Deaths*  
Est Eligible Deaths Averted**  
Est Actual Deaths Averted***

*Siegel, CA Cancer J Clin 2017; 67;7-30  
**Ma, Cancer 2013;119:1381-5  
***Jemal,JAMA Oncol 2017, on line

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### Lung Cancer Patients Seen at Mayo Clinic

A

Community cohort (n=850)

- 5.5% history of COPD
- 6.0% heavy smoking
- 49.7% other risk factors
- 0.1% lower age adjustment
- 0.0% family lung cancer history
- 0.1% radiation exposure history

B

Hospital cohort (n=5988)

- 12.9% history of COPD
- 11.7% heavy smoking
- 14.7% other risk factors
- 0.2% lower age adjustment
- 0.0% family lung cancer history
- 0.0% radiation exposure history

Targeting Screening Based on Risk of Lung Cancer Death

Who To Screen?

PLCO2012 Risk calculator

Modeled on 80,375 smokes in PLCO

PLCO_M2012 Criteria vs NLST

- Improved sensitivity (83.0% vs. 71.1%, P<0.001)
- Positive predictive value (4.0% vs. 3.4%, P = 0.01)
- Specificity (62.9% and 62.7%, respectively; P = 0.54)
- 41.3% fewer lung cancers were missed.

Tammemagi, NEJM 2013;368:728-36

NNS: 161       171         415        531         5276
Based on PLCO smokers, to sample the same proportion for screening as is selected by USPSTF criteria, a PLCOM$_{2012}$ risk $\geq 0.0134$ threshold is required.

Q5. A 70 year old former smoker comes to see you for a routine check and inquires about CT screening. She has a 30 pack year history but quit 15 years ago. Which of the following best reflects her risk for lung cancer?

A) Her risk is about half compared to 55 when she was smoking
B) Her risk has stayed about the same compared to when she quit smoking as she's aged.
C) Her risk is 1.5 times that of when she quit smoking.
D) Her risk fallen close to that of a never smoker of comparable age.
Smoking and Lung Cancer
Figure 4.1: Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer by age 75 for men

Do USPSTF/CMS Promote Smoking?
55 YO Current 30 pk-yr (risk 1.2%)*
Smoking at age 70: keep screening (risk 5.8%)*
Quit at age 55: stop screening at 70 (risk 1.8%)*

Do USPSTF/CMS Promote Smoking?
50 YO Current 25 pk-yr (risk 0.7%)*
Smoke another 5 years: start screening at 55 (risk 1.2%)*
Quit at 50: lie or never be screened (at age 69, quit 19 yrs risk 1.3%)*
Mayo Clinic Lung Screening Program (MCLSP): Enrollment

Inclusion: one of two ways

• Meet USPSTF criteria: 55-80 30 pk yrs, if quit <15 years
• Or have Tammemagi (PLCO_M2012) risk calculation of 1.34% over the next 6 years

Program Entry

Outside request:

• Phone call (507-538-0340), assess risk
• Schedules shared decision making and schedules the CT for 1 visit (and NDC if smoking)

Inside request:

• Order for ‘Lung Cancer Screen Assessment’
• NP/PA does risk assessment and if a candidate then shared decision making, NDC if smoking
• CT scheduled

Who should not be screened?

Exclusion Criteria:

• Lower Risk
• History of lung cancer within the past 5-years (still in active surveillance; consider screening after 5 years)
• Poor lung function or other serious conditions that would not allow you to be a candidate for surgery if needed
• Need for continuous oxygen supplementation
• An unexplained weight loss of >15 lbs in the 12 mos prior
• Recent hemoptysis
• A chest CT examination in the prior 12 months
• Current symptoms of an acute or resolving respiratory tract infection (best to reschedule at least 1 month after symptom resolution)
CT Screening: Harm

- Benign Nodules
- Over diagnosis
- Radiation
- Cost
- Incidental findings

NLST: Harm

- 16 Deaths within 60 days of an invasive procedure
- 10 had cancer

Q6. After making an estimate of a 1.5% risk for lung cancer, a 65 YO former smoker decides to pursue CT screening. What is the likelihood the scan will show one or more lung nodules?

A) 1%  
B) 5%  
C) 10%  
D) 25%  
E) 50%

CT Screening
Prevalence: Detected Nodules

<table>
<thead>
<tr>
<th>Study</th>
<th># Participants</th>
<th>Non-calcified nodules</th>
<th>CT Collimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaneko</td>
<td>1369</td>
<td>588* (17%)</td>
<td>10 mm</td>
</tr>
<tr>
<td>ELCAP</td>
<td>1000</td>
<td>233 (23%)</td>
<td>10 mm</td>
</tr>
<tr>
<td>Mayo</td>
<td>1520</td>
<td>782 (51%)</td>
<td>5 mm</td>
</tr>
<tr>
<td>Diederich</td>
<td>817</td>
<td>350 (43%)</td>
<td>5 mm</td>
</tr>
<tr>
<td>McWilliams</td>
<td>561</td>
<td>431 (75%)</td>
<td>7 mm</td>
</tr>
<tr>
<td>McWilliams</td>
<td>561</td>
<td>431 (75%)</td>
<td>1.25 mm</td>
</tr>
<tr>
<td>NELSON</td>
<td>7557</td>
<td>3816 (51%)</td>
<td>1 mm</td>
</tr>
<tr>
<td>NLST</td>
<td>26,314</td>
<td>7193 (27.3)</td>
<td>2.5 mm</td>
</tr>
</tbody>
</table>

Definition of a Positive Test
NLST: baseline & 2 annual scans
18,141 (24%) positive (nodule > 4mm)

<table>
<thead>
<tr>
<th>Threshold for positive screen</th>
<th>Cancers (n = 598)</th>
<th>False positive (n = 17543)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnoses delayed, No. (%)</td>
<td>False positive avoided, No. (%)</td>
</tr>
<tr>
<td>&gt;= 4 mm</td>
<td>0 (0.00)</td>
<td>2366 (15.77)</td>
</tr>
<tr>
<td>&gt;= 6 mm</td>
<td>18 (2.01)</td>
<td>9461 (36.90)</td>
</tr>
<tr>
<td>&gt;= 7 mm</td>
<td>26 (2.65)</td>
<td>9470 (36.02)</td>
</tr>
<tr>
<td>&gt;= 8 mm</td>
<td>63 (10.54)</td>
<td>11642 (205.79)</td>
</tr>
<tr>
<td>&gt;= 9 mm</td>
<td>92 (15.96)</td>
<td>12,009 (73.58)</td>
</tr>
<tr>
<td>&gt;= 10 mm</td>
<td>112 (19.73)</td>
<td>13,903 (79.99)</td>
</tr>
</tbody>
</table>

CT Results to Patient and Practitioner

Example

Radiology Dictation for: largest nodule: Solid nodule <6 mm or part-solid nodule <6mm total diameter (Lung RADS category 2)

Impression: Negative for screening purposes. Tiny nodule(s) identified with very low likelihood of malignancy.

Recommendation: Follow-up with next annual low-dose CT in 12 months.

Screening Trials: Benign Nodule Resections

Diederich 22%
Mayo 18%
McWilliams 20%
Nawa 29%
Pastorino 26%
NLST 24%

People don’t die of false positives, but they can die of their evaluation!

Who manages the screen results?

- Colonoscopist doesn’t call
- Mammographer does the biopsy
- Evaluation of LDCT lung findings abnormalities can be difficult
- Screening Program needs to take ownership: multidisciplinary - yes, but this is a pulmonary problem
Q7. Prospective studies of LDCT have shown that the likelihood of a malignancy in a never smoker compared to a current or former smoker was about:

A) 1:1.
B) 1:2.
C) 1:3.
D) 1:5.
E) 1:10.

CT Screening: Non-smokers vs. Smokers
Overdiagnosis

7847 participants

<table>
<thead>
<tr>
<th></th>
<th>NS (4251)</th>
<th>S (3596)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number cancers</td>
<td>45</td>
<td>39</td>
</tr>
<tr>
<td>Detection rate</td>
<td>1.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Well diff ACA</td>
<td>88%</td>
<td>29%</td>
</tr>
<tr>
<td>Path 1A prevalence</td>
<td>92%</td>
<td>58%</td>
</tr>
<tr>
<td>Path 1A incidence</td>
<td>100%</td>
<td>70%</td>
</tr>
<tr>
<td>Size</td>
<td>12.4 mm</td>
<td>18.2 mm</td>
</tr>
<tr>
<td>GGO/Mixed</td>
<td>86%</td>
<td>46%</td>
</tr>
</tbody>
</table>


Growth Rate of Screen Detected Cancers

- 82 lung cancers detected in 3 year CT Screening Trial & 61 cases examined

<table>
<thead>
<tr>
<th>Type GGO</th>
<th>VDT (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS</td>
<td>457 ± 260</td>
</tr>
<tr>
<td>S</td>
<td>149 ± 125</td>
</tr>
</tbody>
</table>

Over Diagnosis in the NLST

1,089 lung cancers in the LDCT arm, 969 in the CXR arm

- Probability of overdiagnosis:
  - 18.5% (95% CI, 5.4-30.6%)
  - 22.5% that an NSCL was overdiagnosis
  - 78.9% that a BAC was overdiagnosis

- More than 18% of the LDCT detected cancers were overdiagnosis

Q8. Estimates of the amount of radiation from LDCT screening suggest that if applied in mass screening the radiation will:

A) Be a smaller effect than ambient radiation.
B) Be comparable to the dose with CXR screening.
C) Be comparable to standard CT.
D) Likely induce a prohibitive # of lung cancers.
E) Surely be a way to get a great tan.
**Adult Effective Doses – CT Procedures**

<table>
<thead>
<tr>
<th>Exam</th>
<th>Average Value (mSv)</th>
<th>Range Reported in Literature (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>2</td>
<td>0.9-4.0</td>
</tr>
<tr>
<td>Chest</td>
<td>7</td>
<td>4.0-18.0</td>
</tr>
<tr>
<td>Abdomen</td>
<td>8</td>
<td>3.5-25</td>
</tr>
<tr>
<td>3-phase Liver</td>
<td>15</td>
<td>---</td>
</tr>
<tr>
<td>Coronary Angio</td>
<td>16</td>
<td>5.0-32</td>
</tr>
<tr>
<td>LDCT Chest</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Background radiation</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

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**Estimated Risk of Radiation to induce 1 cancer**

CT coronary angiography

- Age 40:
  - 1 in 270 women
  - 1 in 600 men

- Age 20: risks were doubled
- Age 60: risk 50% lower.

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**Screening for Lung Cancer: $COST$**

**NLST Calculation:** $67,000/QALY

**Comparisons**

- Colorectal cancer screening: range of $13,000 to $32,000/QALY
- Breast cancer screening: mammography women aged ≥ 40 years $47,700/QALY
**Number Needed to Screen**

*8 years*

- **Fecal occult blood** testing for colorectal cancer: 1250
- **Mammography** for breast cancer: 781  
  Richardson A. J Med Screen 2001; 8:125–127
- **PSA**: NNS 1410, 48 cases cancer would need to be treat to save 1 life (9 years)  

**What about incidental findings?**

*Anxiety & uncertainty; benefit?*

- Prevalence of incidental findings have been reported to be as high as 59 to 73% of those scanned
  

- Clinically significant findings, defined as those requiring additional evaluation, were present on an average of 14% of those scanned
  

**Lung Cancer Screening Program**

*Reducing Harms*

- Must assure high risk
- Must assure low dose
- Linked to smoking cessation
- Expert reading & handling of the findings
- Registry of results
60 yo former smoker, 75 pk-years
Screen detected stage IIA squamous CA

68 YO F current smoker: Interval small cell
9-29-16 dyspnea  LDCT screen 6-2-16

Lung Screening Program
Report Card:
• How many meet criteria
• How many benign biopsies/resections
• Stage I/II cancers
• % VATS resections
• How many met follow-up recs
• How many continued screening
Which is more effective in saving lives
CT Screening or Smoking Cessation?

- The NLST showed that about 1 in 320 participants had a life saved from lung cancer by screening.
- About 1 in 6 life-long smokers will get lung cancer and quitting reduces that risk.
- About 1 in 2 smokers will die from early heart disease and quitting greatly reduces that risk.
- Quitting smoking (and not restarting) is more likely to save a life than is CT screening!

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Summary:
The End of the Beginning

- LDCT screening is appropriate for your high risk patients
- USPSTF: age 55-80, 30 pack years, smokers or quit within 15 years
- Many at high risk don’t meet criteria
- Many at high risk don’t get screened
- Result management is critical
- We have a lot to learn
Lung Cancer Screening at Mayo
Special Thanks

• Robert Fontana, MD
• Stephen Swensen, MD
• Jim Jett, MD

Thank you