Dr. Tanoue has declared no conflicts of interest related to the content of her presentation.
Lung Cancer 2013

New Developments for Your Practice

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Director, Yale Lung Screening and Nodule Program
Annual Age-adjusted Cancer Death Rates Among Men and Women for Selected Cancers, United States, 1930 to 2007

CA: A Cancer Journal for Clinicians
Volume 61, Issue 4, pages 212-236, 17 JUN 2011 DOI: 10.3322/caac.20121
Lung Cancer Developments 2013

- Screening for lung cancer
- Lung cancer risk assessment
- Nodule evaluation
- Biomarkers for lung cancer evaluation
Case AZ

A 64 year old man presents to you because a family friend who is a nurse told him he should be screened for lung cancer.

The patient is an electrician; his only medical problem is hypertension, well-controlled. He smoked 2 packs of cigarettes per day from age 16 to 42, and quit when his father died of lung cancer at age 75. His local electricians’ union has performed annual chest x-rays on all of its members; the patient states he knows he has pleural plaques, but does not have asbestosis. The patient had a small scalp melanoma resected 9 years ago; it was early stage and the resection had clean margins. His annual skin checks have been negative since. He has never had spirometry and denies any pneumonias; he does cough up a small amount of whitish sputum every morning. BMI is 29. His highest level of education is high school trade work. He currently feels fine and is without physical limitations, but is now worried because of his friend’s concern about lung cancer.
Case AZ: Question 1

Which of the following would you tell this patient?

1. He meets the criteria of the National Lung Screening Trial (NLST), and therefore should be screened with LDCT.
2. He meets the criteria of the National Comprehensive Cancer Network (NCCN) lung cancer screening guidelines, and therefore should be screened with LDCT.
3. He meets the criteria of the American College of Chest Physicians (ACCP) and American Cancer Society (ACS) lung cancer screening guidelines, and therefore should be screened with LDCT.
4. All of the above
Case AZ: Question 2

What is your estimate of AZ’s risk of lung cancer over the next 10 years?

1. <5%
2. 5-10%
3. 10-15%
4. >15%
Case AZ: Question 3

Would you perform lung cancer screening with LDCT in this patient?

1. Yes

2. No
Lung Cancer Screening: PLCO

PLCO (2011): Screening for lung cancer with chest radiograph is no better than no screening (154,901 participants, age 55-74)

Lung Cancer Screening: NLST

- **NLST (2011):** Patients screened with LDCT, as compared to CXR, demonstrated a 20% reduction in relative risk of lung cancer death.

- **NLST criteria:** Ages 55-74, ≥30 pk-yrs smoking, currently smoking or quit within the previous 15 years.

- The majority of screen-detected lung cancers are Stage I.

- LDCT screening saves lives.

Aberle et al. NEJM 2011; 365: 395-409
What are the risks related to screening?

Primum non nocere

- 96% false positive rate – single or multiple pulmonary nodules
  - Further radiographic evaluation
    - Radiation exposure
  - Diagnostic procedures and complications thereof
    - In NLST, 2.7% of patients with abnormalities underwent invasive procedures to prove nonmalignant etiologies
- Overdiagnosis
- Emotional costs
- Economic burden
Screening for Lung Cancer: Costs

*Goulart BHL et al. JNCCN 2012; 10:267*

- 7 million Americans fit NLST criteria
- Assume screening uptake rates of 75%
- 8100 premature lung cancer deaths avoided
- Cost of screening to avoid one lung cancer death = $240,000
- Cost-effectiveness not addressed
- Cost to the nation $1.3 to $2.0 billion
  - Adds 12%-19% to the cost of annual lung cancer care ($12.1 billion)

**ACRIN: Costs of LDCT screening per year**

<table>
<thead>
<tr>
<th>Population</th>
<th>Size</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 55-74, &gt;30 pk-yrs</td>
<td>8 million</td>
<td>$4 billion</td>
</tr>
<tr>
<td>Age 45-64, ever smoker</td>
<td>32 million</td>
<td>$18 billion</td>
</tr>
<tr>
<td>Age &gt;45, ever smoker</td>
<td>47 million</td>
<td>$26 billion</td>
</tr>
<tr>
<td>Age &gt;18, ever smoker</td>
<td>94 million</td>
<td>$53 billion</td>
</tr>
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## Lung Cancer Screening Recommendations

<table>
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  • Individuals age 50 or older with ≥20 pk-yr smoking if additional comorbidities produce a cumulative 5% risk of lung cancer over the following 5 years (FEV1<70%; environmental or occupational exposure, prior cancer/radiation therapy, + fam hx) |
| US Preventive Services Task Force | • Evidence is insufficient to recommend for or against screening asymptomatic persons with any modality                                                                                                                  |
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| US Preventive Services Task Force | • Evidence is insufficient to recommend for or against screening asymptomatic persons with any modality                                                                                                                    |
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 y of annual screening.

Figure Legend:
Projected Likelihood Over 6 Years of Lung Cancer Death With or Without Screening per 1000 Persons Screened
Lung Cancer Risk Assessment Models

## Risk Model Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Bach</th>
<th>PLCO</th>
<th>LLP</th>
<th>Spitz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gender</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prior Hx Asbestos Exposure</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration of Smoking</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Average Amount Smoked/Day</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Duration of Smoking Abstinence</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Educational Level</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>BMI</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>FH of Lung Cancer</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Presence of COPD</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Occurrence of Chest X-ray within 3 years</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Smoking Status (Current, Former, Never)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pack/Years smoked</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prior Diagnosis of Pneumonia</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prior Diagnosis of Malignant Tumor</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prior Diagnosis of Emphysema</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Exposure to Spousal Smoke/Duration Exposed</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Age at Smoking Cessation</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Wood Dust Exposure</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prior Hay Fever</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>FH of Any Cancers</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>FH of Smoking Related Cancers</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Age at Smoking Initiation</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Exposure to Second Hand Smoke</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Exposure to Fumes and Chemicals</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Smoking Quit Time (yrs)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Spitz Model

Estimated Absolute 1 year Risk of Lung Cancer

\[ P(a, r, i, j) = \left( \frac{b_{1ji}r}{b_{1ji}r + b_{2j}} \right) \{1 - \exp[-(b_{1ji}r + b_{2j})]\} \]
PLCO - Nomogram for estimating 9-year probability of lung cancer in former or current smokers

**Nomogram predictors:**

**Education:** 1 = less than eight years, 2 = 8-11 years, 3 = 12 years or completed high school, 4 = after high school training, 5 = some college, 6 = college graduate, and 7 = postgraduate.

**Family history of lung cancer and COPD:** 1 represents that a past history is present.

**BMI** = weight in kg divided by height in meters squared.

**CXR** (in last three years): 0 = none, 1 = once, and 2 = ≥ two

**Current smoker:** 2 = yes, 1 = no.

**Pack-years smoked** = avg number of packages smoked/day times the number of years smoked.

_Tammemagi (PLCO) JNCI, 2011_
Case AZ: What is his lung cancer risk?

- Age 64, history of early stage melanoma resected 9 years ago, and hypertension. BMI = 29
- Smoking history: 52 pack-years, discontinued 22 years ago
- Family history: father died of lung cancer at age 75
- Exposures: asbestos, with pleural plaques
- Education level: high school

Risk predictions using models:
- Spitz: 1-year lung cancer risk = 1.1%
- LLP: 5-year lung cancer risk = 6.5%
- Hoggart: 5-year lung cancer risk = 2.2%
- Bach: 10-year lung cancer risk = 3.3%
Case AZ: Question 4

With this information would you perform lung cancer screening with LDCT in this patient?

1. Yes

2. No
ACCP 2013 Centers of Excellence
Yale Lung Screening Program: ACCP Member Survey

- Indicate level of training
  - Currently in fellowship training
  - Within 5 years of fellowship training
  - 5-10 years post fellowship training
  - 10-20 years post fellowship training
  - >20 years post fellowship training
- Participation in a organized lung cancer screening program (Yes/No)
- Read Case
- Would you screen this patient for lung cancer?   (Yes/No)
- Estimate this patient’s risk for developing lung cancer over the next 5 years (0-100%)
- Estimate this patient’s risk for developing lung cancer over the next 10 years (0-100%)
- Risk model results shown
- Would you still screen this patient knowing now what their estimated lung cancer risk is based on existing predictive models?   (Yes/No)
ACCP Centers of Excellence
Screening Case 4 (non NLST)

<table>
<thead>
<tr>
<th>Question</th>
<th>ACCP MD Avg 5yr Risk</th>
<th>Est. Risk based on LLP Model (5yr)</th>
<th>Est. Risk based on Hoggart Model (5yr)</th>
<th>ACCP MD Avg 10yr Risk</th>
<th>Est. Risk based on Bach Model (10yr)</th>
<th>Est. Risk based on PLCO Model (9yr)</th>
<th>Would you still screen this patient?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Would you screen this patient?</td>
<td>84.31</td>
<td>14.09</td>
<td>6.5</td>
<td>21.59</td>
<td>3.3</td>
<td>N/A*</td>
<td>71.57</td>
</tr>
</tbody>
</table>

A 64 year old man presents to the lung cancer screening program because a family friend who is a doctor told him he is at high risk for lung cancer. The patient has been an electrician for the last 45 years; he recalls that when he was a young man he often worked in a "snowstorm" of asbestos fibers. He smoked 2 packs of cigarettes per day from age 16 to 42, and quit because his father died of lung cancer at age 65. The patient’s local electricians’ union has performed annual chest radiography on all of its members; the patient is aware that he has pleural plaques, but was specifically told that he did not have asbestosis. The patient had a melanoma resected from his scalp 9 years ago; it was an early tumor and the resection demonstrated clean margins. His annual skin checks have been unremarkable since then. He otherwise has no medical problems except for well controlled hypertension. He has never had spirometry performed and denies any recent pneumonias, though he does cough up a small amount of whitish sputum every morning. BMI is 29. His highest level of education is some trade work after high school. He currently is feeling well and without physical limitations, but is now worried because of his friend’s concern about the likelihood that he will get lung cancer.
## Lung Cancer Screening Recommendations

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| US Preventive Services Task Force| • Evidence is insufficient to recommend for or against screening asymptomatic persons with any modality                                                                                                                                                                                                                                                                            |
Lung cancer screening - Issues

- Standardization of low-dose CT
- High false positive rate
- Cumulative radiation exposure
- Potential for unnecessary interventions
  - Diagnostic imaging
  - Invasive procedures
- Persistent smokers
- What to do with non-NLST populations
- Overdiagnosis
Components of a Lung Cancer Screening Program  
*Arenberg et al. Setting Up a Lung Cancer Screening Program.*  *JNCCN* 2012; 10:277

<table>
<thead>
<tr>
<th>Risks/Issues</th>
<th>Specifics</th>
<th>Program approach</th>
</tr>
</thead>
</table>
| High false positive rate            | 20% average nodule detection rate per round of screening, most of which are false positives | • Standardized reading of LDCT, with quality control, by trained and committed radiologists.  
• Nodule program                    |
| Increase in further imaging and radiation exposure | 1%-45% of screened individuals undergo further CT imaging because of abnormal findings | • Standardized and monitored protocol for performance of LDCT.  
• “Nodule Board”: Pulmonary, Thoracic Surgery, Radiology |
| Increase in invasive diagnostic procedures | 1.2%-5.6% of screened individuals undergo surgical biopsy or procedure. Benign results found in 24-32% | • Nodule assessment program with involvement of pertinent disciplines and standardized management algorithm. |
| Ongoing smoking                     | Smoking cessation is more powerful than LDCT in reducing lung cancer mortality | • Smoking cessation program                                                       |
| Screening in non-NLST populations   | Risk prediction in the setting of risk factors other than smoking          | • Research relating to risk prediction  
• Screening registry and biorepository |
After carefully considering AZ’s situation, you decided to get a screening LDCT.
LDCT and pulmonary nodules: too much of a good thing

• Lung cancer screening studies – 20% average annual incidence of small pulmonary nodules:
  – NLST: baseline study 28%; 1\textsuperscript{st} annual repeat 27%; 2\textsuperscript{nd} annual repeat 17%
  – NELSON: baseline study 51%; 1\textsuperscript{st} annual repeat 22%

• >100 million Americans are current or former smokers
• 8 million Americans meet NLST criteria
  – 8 million x .28 = 2.24 million nodules/year
  – 2.24 million nodules/8,000 American pulmonary specialists = 280 nodules/pulmonologist/year
Case AZ

AZ has no prior chest CT scans. The scout films on the current LDCT are identical to the prior CXRs done by his union, ie. the nodule is not seen.

Which of the following would you recommend?

1. Follow up with regular dose chest CT in 3 months
2. PET scan
3. TTNA of LUL nodule
4. Left upper lobectomy
Lung Cancer Risk Prediction for a Pulmonary Nodule

- Patient clinical and demographic factors
  - Age, family history
  - Exposures: Smoking, occupational/environmental
  - Medical history: prior malignancy, COPD, ILD, etc.

- Nodule characteristics
  - size, edge characteristics, calcification pattern, location
  - prior radiograph comparison
Lung Cancer Risk Prediction for a Pulmonary Nodule

*Swensen S et al. Arch Intern Med 1997; 157:849*

Probability of SPN malignancy = \( e^x/(1 + e^x) \)

\[ x = -6.8272 + (0.0391 \times \text{age}) + (0.7917 \times \text{cigarettes}) + (1.3388 \times \text{cancer}) + (0.1274 \times \text{diameter}) + (1.0407 \times \text{spiculation}) + (0.7838 \times \text{location}) \]

AZ: 64 year old male, former 2 pack/day smoker, history of resected melanoma, with an 11 mm spiculated nodule in the left upper lobe.

Probability of AZ’s pulmonary nodule being lung cancer based on the Swensen model = 74%
Screen-detected lung cancers: Overdiagnosis

- Overdiagnosis – the diagnosis of indolent cancers NOT destined to cause death.
- Many cancers diagnosed in screening trials are overdiagnosed.
- How do we distinguish the overdiagnosed cancers from those destined to cause harm?

Bach P et al. JAMA 2007; 297:953-961
Doubling time: the time for a group of cells to double in size.

Lung cancer:
- A 25% increase in diameter corresponds to a doubling of volume
- DT widely variable, from 30 to >400 days.
- 30 doubling times to get to 1 cm diameter
- DT 90 days (parallels the typical 3 month observation period)
  90 days $\times$ 30 DTs = 2700 days = 7 years to get to 1 cm
- Tumors with DT > 400 days likely overdiagnosed (indolent)
  400 days $\times$ 30 DTs = 12,000 days = 34 years to get to 1 cm

Van Klaveren et al. NEJM 2009; 361:2221. (NELSON)
Yankelevitz et al. Cancer 2003; 97:1271 (ELCAP)
Case AZ: Lung nodule volumetric analysis
Lung nodule volume and doubling time issues

• Growth characteristics
  – Exponential vs linear vs asymptotic?
  – Observer variability in measurement

• Nodule characteristics
  – Solid vs partially solid vs ground glass density

• Time and labor
  – Volume measurement is labor intensive for radiologist without increase in compensation

• Patient quality of life
  – Living with the knowledge of an “indolent” cancer
Distribution of incident lung cancer diagnosed over the 5 years of the study, according to VDT and preoperative CT-PET.

64% of cases of cancer had a VDT <400 d. 26% were slow-growing or indolent (VDT ≥400 d). CT-PET was visually assessed as positive or negative. “Missing” indicates that CT-PET was unavailable because it was not done or was done at another hospital. CT = computed tomography; PET = positron emission tomography; VDT = volume-doubling time.
Searching for better lung cancer predictive models

- **Current predictive models: Clinical**
  - Lung cancer risk quantification in an at-risk population
  - Lung cancer risk quantification in solitary pulmonary nodules
    - Components:
      - Demographic factors
      - Clinical variables, including nodule characteristics (diameter)

- **Future predictive models: Clinical-Molecular-Genomic**
  - Lung cancer risk quantification in an at-risk individual
  - Lung cancer risk quantification in an individual SPN
    - Components:
      - Demographic factors
      - Clinical variables, including nodule characteristics (doubling time)
      - Biomarkers reflective of individual-specific risk
Field of Injury (Field Cancerization)

- Cytologically normal bronchial airway epithelial cells may provide a window on the extent of molecular injury
  - Genetic mutations
    - Gene expression profiles - \( p53 \) mutation, allelic loss, SNPs
  - Epigenetic changes
    - promoter methylation, telomerase activity
  - miRNA expression
  - Gene expression quantification
  - Genetic biosignatures

- Lung surrogate tissues
  - Buccal mucosa
  - Exhaled breath

Campbell JD et al. Respirology 2011; 16:407-418
Spira A. Canc Prev Res 2010; 3:255-258*
Exhaled Breath Analysis

Dogs can identify bombs, illicit drugs, people dead and alive, truffles
- Why not lung cancer?


- 110 normal subjects, 84 lung cancer patients, 50 patients with COPD.
- Dog performance: sensitivity 0.72, specificity 0.94, positive predictive value 0.75, negative predictive value 0.93
Exhaled Breath Analysis

- Exhaled breath contains mixtures of hundreds of odorant molecules, typically volatile organic compounds (VOCs).
- "Smellprints" of VOCs are recognizable by gas chromatography, mass spectroscopy, or chemical sensor arrays (electronic nose).
- VOCs present in the exhaled breath of patients with lung cancer:
  - isobutane, methanol, ethanol, acetone, pentane, isoprene, isopropanol, dimethylsulfide, carbon disulfide, benzene, toluene.

Sensitivity 71.4%, Specificity 91.9%

Machado et al. AJRCCM 2005; 171:1286
Future predictive models

• More robust predictive models will incorporate:
  – Patient demographic information
  – Clinical and exposure history
  – Gene expression analysis of respiratory tract epithelium or lung surrogate tissues
  – Breath biosignature analysis
  – Blood biomarkers

• Lung cancer screening
  – Identify individuals who should have imaging studies

• Nodule evaluation
  – Differentiate malignant from benign etiologies
  – Distinguish indolent cancers from those destined to kill
Lung Cancer Guidelines

ACCP Evidence-based Guidelines for the Evaluation and Management of Lung Cancer

CHEST April, 2013
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