LUNG CANCER SCREENING
2012

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Nothing to disclose
Cigarette smoking
How big is the problem?

- 90% of lung cancer is due to smoking

- 46 million U.S. smokers:
  - 30% no high school degree
  - 6% graduate degree
  - 31% U.S. smokers are below poverty line

Lung Cancer Death Rates are Decreasing

- **Men**: dec. by 3% per year (2005-07)
- **Women**: dec. by 0.9% per year (2003-07)
  - 2° a dec. in women smoking in 1980’s

- There would be a 50% dec. in ALL cancer death rates if all tobacco were removed from the population today

CA Cancer J Clin  July / August 2011
Incidence of Lung CA decreasing

CA July 2011

FIGURE 5: Annual Age-adjusted Cancer Incidence Rates* for Selected Cancers by Sex, United States, 1975 to 2017
Lung Cancer Statistics - 2011

- New cases (USA 2011 est.) 221,130
- Deaths - (USA 2011 est.) 156,940
- Worldwide (2002) 1.18 million deaths

- 18 patients die every hour from lung cancer in U.S.A.
- More deaths from lung cancer than colorectal, breast, prostate & pancreas combined
- 5 year survival 15% (Current), 13% (1974), 8% (early 1960’s)

Jemal A. CA Cancer J Clin 2006; 56:106-13
CA Cancer J Clin July / August 2011

History of Lung Cancer Screening

- 1949 Boston First Lung Cancer Survey
  Over 530,000 persons living in Boston
- 1951 Philadelphia Pulmonary Neoplasm Research Project
- 1971 National Cancer Act - Richard Nixon
- Mayo Lung Project
  - Fontana Chest 1975
  - Fontana Am Rev Respir Dis 1984
  - Fontana Cancer 1991 (critique)
Are Serial Chest X-rays good screening tools?  
“NO” from 1975 to 2010

- Mayo Lung Project (1983): 90% (45 of 50) of peripheral carcinomas were visible in retrospect on CXR despite 3 radiologists reading CXR
- MSKCC (1984): 66% lung CA visible in retrospect
- Quekel (1999): 19% CA missed in retrospect, median missed lesion 1.6 cm. (0.6 - 3.8 cm)

Conclusion: These data suggest CXR not a good screening tool (esp. < 2 cm), too much of the lung is hidden by normal structures
Rationale for Lung Cancer screening

- Only 15% of lung cancers are Stage I or II at presentation
- U.S. spends $5 billion / yr taking care of pts. w/ lung CA
- Lung cancer is only 14% of cancers, but represents 26 - 28% of cancer deaths
- Stage I lung cancer, 5-year survival is 70-80%
- Best chance for improved survival is for pts who have resected early stage disease (Stage 1 A/B or II A/B)


What are the criteria of a good screening test so that it will improve survival?

- The tests must detect a disease which is curable and for which there are adequate therapeutic interventions for a cure if the disease is detected early
- Should pick up more cases than you pick up by chance in practice - Dr. Henschke
- Do no harm to subject without cancer
- Do no harm to society

Marcus PM. J Natl Cancer Inst 2006 Jun 7; 98(11):748-56
Options for Lung Cancer Screening

- Chest X-rays
- Low Dose CT screening
- C.T. Individual Nodule Analysis
- Automated Quantitative sputum cytometry
- Biomarkers of blood, lung tissue, BAL, sputum, or oral buccal mucosal cells
- Volatile Organic Compound analysis of exhaled breath
- Autofluorescence bronchoscopy
- PET scanning, PET / CT scanning
Lung Cancer Who's at Risk?

- Tobacco smoking (~90%)
- Asbestos
- Radon, uranium
- Arsenic, Beryllium
- Vinyl Chloride, Nickel
- Chromium, Chromates
- Mustard Gas, Coal products
- Chloromethyl ethers
- Gasoline, Diesel exhaust
- XRT to lung
- XRT to breast in smokers
- Recurrent Inflammation
- Second Hand Smoke (Scar)
- Talc, talc miners, millers
- Silicosis
- Personal or family Hx
- Air pollution (possible)

www.cancer.org (American Cancer Society) 2011

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32,000 never smokers die each year from Lung Cancer

- **HealthDay** December 2, 2011
- **Lung Cancer's Hidden Victims: Those Who Never Smoked**
- More than 32,000 Americans who never lit up will die each year, with women at higher risk, experts say
- By E.J. Mundell
- Reporter
- FRIDAY, Dec. 2 (HealthDay News) -- Opera legend Beverly Sills never smoked. Neither did actress and health advocate Dana Reeve, wife of the late actor Christopher Reeve.
- And yet in 2007 and 2006, respectively, both joined the ranks of about 32,000 Americans each year who never touch a cigarette but die of lung cancer anyway.
- In fact, experts say, one in every five cases of the leading cancer killer occurs in nonsmokers. The annual death toll among this group now approaches that of breast cancer (about 40,000 per year) and is roughly equal to that of prostate cancer (32,000). Many never-smoking women may also be unaware that they are more than twice as likely to die of lung cancer as they are of ovarian cancer (14,000 deaths per year).
- **HealthDay** "much like breast tumors, lung tumor aggressiveness in women appears linked to estrogen"
Computer Tomography Screening for Lung CA

Problems with CT screening for lung cancer:

- Prior to NLST (August 2011), Lack of controlled clinical trials showing lung cancer specific mortality reduction
- Cost of CT Scans and follow-up: $ and Psychological
- Radiation Risk to patients
- Unnecessary Thoracic Surgery for benign disease
- Overdiagnosis bias
- Interval cancers and deaths in screened patients
- Lack of Organizational Support

New Techniques in Cardiothoracic Imaging Boiselle PM, 2007

Lung cancer-specific mortality is defined as:
the number of lung cancer deaths
the total number of individuals screened

An increase in survival is not the same as a
Reduction in Lung cancer specific Mortality

1. Lead Time Bias
CA picked up earlier; no Δ in date of death

2. Length Time Bias
aggressive CA's may escape detection

3. Overdiagnosis Bias
CA, even if not dx'd, will not kill pt.
1-14, 2008

United States Lung Cancer Screening Trials

U.S. trials confined to high risk groups, not screening all individuals

✓ 2. ELCAP (‘93-’00), NYELCAP, IELCAP (NEJM 2006)
ADDITIONAL LUNG CANCER SCREENING TRIALS CURRENTLY ONGOING

NELSON (2016) – Netherlands
DANTE - Italy -no mortality benefit
DEPISCAN - France
DLCST - Denmark: more pts. died in CT group

Computer Tomography Screening for Lung Cancer


Single arm, no control group NEJM 2006

NELSON 2016
DANTE
DEPISCAN

USA 2010 (2014)

(+) Randomized, (+) control groups
Contributions of ELCAP Observational Study to Lung Cancer Screening Trials

1. Significant number of early lung cancers are identified with CT screening

2. How to deal with nodules – algorithms

3. When to screen - ? yearly

4. Treatment – we don’t perform lobectomies on CT detected 5 mm nodules any more
Prior to NLST, there was a lack of Controlled Clinical Trials showing a Lung Cancer specific mortality reduction.
National Lung Screening Trial

- Sponsored by NCI / ACRIN + PLCO
- 53,454 pts, randomized, 30 centers U.S.
- Digital chest radiograph (N=26,732)
- Low dose spiral CT (N=26,722)
- Dr. Denise Aberle (UCLA) P.I.


CRITERIA FOR ENTRY

- Age 55 to 74 yrs, C / F smoker of 30 pk yrs quit within previous 15 years
- No Chest CT w/in 18 mos. of enrollment
- Never have had lung CA or any CA within 5 years of enrollment
- No hemoptysis
- No unexplained weight loss > 15 lb (6.8 kg) past year

**NLST Inclusion Criteria**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td>Age 55–74 years</td>
</tr>
<tr>
<td></td>
<td>30 or more pack-years of cigarette smoking history (pack-years = packs per day × years smoked)</td>
</tr>
<tr>
<td></td>
<td>Former smokers; quit smoking within the previous 15 years</td>
</tr>
<tr>
<td></td>
<td>Ability to lie on the back with arms raised over the head</td>
</tr>
<tr>
<td></td>
<td>Signed informed consent form</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Metallic implants or devices in the chest or back, such as pacemakers or Harrington fixation rods</td>
</tr>
<tr>
<td></td>
<td>Treatment for, or evidence of, any cancer other than nonmelanoma skin cancer or carcinoma in situ (with the exception of transitional cell carcinoma in situ or bladder carcinoma in situ) in the 5 years prior to eligibility assessment</td>
</tr>
<tr>
<td></td>
<td>History of lung cancer</td>
</tr>
<tr>
<td></td>
<td>History of removal of any portion of the lung, excluding needle biopsy</td>
</tr>
<tr>
<td></td>
<td>Requirement for hemoptysis supplementation</td>
</tr>
<tr>
<td></td>
<td>Participation in another cancer screening trial</td>
</tr>
<tr>
<td></td>
<td>Participation in a cancer prevention study, other than a smoking cessation study</td>
</tr>
<tr>
<td></td>
<td>Unexplained weight loss of more than 15 pounds in the 12 months prior to eligibility assessment</td>
</tr>
<tr>
<td></td>
<td>Recent hemoptysis</td>
</tr>
<tr>
<td></td>
<td>Pneumonia or acute respiratory infection treated with antibiotics in the 12 weeks prior to eligibility assessment</td>
</tr>
<tr>
<td></td>
<td>Chest CT examination in the 18 months prior to eligibility assessment</td>
</tr>
</tbody>
</table>

**National Lung Screening Trial**

- Largest (53,454 participants) and Most expensive (> $200 million) randomized trial of a single screening test in the history of U.S. medicine
- “Stringently control trial”
- CT scanners calibrated bi-monthly

*Annals of Internal Medicine*, October 18, 2011
Goals of the trial

1. Lung CA specific mortality
2. Stage distribution at diagnosis
3. Sensitivity & specificity of both screening tests (not yet reported)
1 prevalence, 2 annual incidence studies
Patients via PCP followed until 2009, if necessary – mean 6.5 years
Study has a 90% power to detect a 20% reduction in lung specific mortality

NLST Protocols for Detected nodules

CT Detected

CXR Detected

Proposed guidelines for incidental nodules found on Chest CT scan

<table>
<thead>
<tr>
<th>Mean Soli Nodule Size (mm)</th>
<th>Timing of Followup (Months) Age ≤ 35</th>
<th>Timing of Followup (Months) Age &gt; 35</th>
</tr>
</thead>
<tbody>
<tr>
<td>------------------------------</td>
<td>-------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>up to 3</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3 to 4</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>4 to 6</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>6 to 7</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>7 to 8</td>
<td>Pulm Consult</td>
<td>Pulm Consult</td>
</tr>
<tr>
<td>&gt;8</td>
<td>Pulm Consult</td>
<td>Pulm Consult</td>
</tr>
<tr>
<td>Known Cancer (any stage)</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
RESULTS

✓ Results to be published in 2014, but published early when primary endpoint was reached - 20% reduction of lung cancer specific mortality

✓ ~31% patients had a positive result either group

✓ ~96% were followed with imaging

✓ Only ~1 to 2% had any type lung biopsy - LOW

### National Lung Screening Trial

#### RESULTS

**POSITIVE RESULTS of screening**

<table>
<thead>
<tr>
<th>Test</th>
<th>Low Dose CT Positive Result (%)</th>
<th>Chest X-ray Positive Result (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TO</td>
<td>27.3</td>
<td>9.2</td>
</tr>
<tr>
<td>T1</td>
<td>27.9</td>
<td>6.2</td>
</tr>
<tr>
<td>T2</td>
<td>16.8</td>
<td>5.0</td>
</tr>
</tbody>
</table>

TO to T1, T1 to T2 = 1 year


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#### RESULTS

**Histologic Type of Cancer**

<table>
<thead>
<tr>
<th>Type</th>
<th>Low Dose CT</th>
<th>Chest X-Ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdenoCA</td>
<td>380</td>
<td>328</td>
</tr>
<tr>
<td>Squamous</td>
<td>243</td>
<td>206</td>
</tr>
<tr>
<td>Bronchoalveolar</td>
<td>110</td>
<td>35</td>
</tr>
<tr>
<td>Small cell</td>
<td>137</td>
<td>159</td>
</tr>
<tr>
<td>Non-small cell</td>
<td>131</td>
<td>158</td>
</tr>
<tr>
<td>Large cell</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

Total 1060 941

National Lung Screening Trial

RESULTS

Stage of Cancer
Low Dose CT (N=1060)  Chest X-Ray (N=941)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Low Dose CT</th>
<th>Chest X-Ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>416</td>
<td>196</td>
</tr>
<tr>
<td>IB</td>
<td>104 Operable</td>
<td>93</td>
</tr>
<tr>
<td>IIA</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>IIB</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>IIIA</td>
<td>99</td>
<td>109</td>
</tr>
<tr>
<td>IIIB</td>
<td>122</td>
<td>122</td>
</tr>
<tr>
<td>IV</td>
<td>226</td>
<td>335</td>
</tr>
<tr>
<td>Total</td>
<td>1040</td>
<td>929</td>
</tr>
</tbody>
</table>


National Lung Screening Trial

RESULTS

Number of Lung Cancers
2002-2009

Deaths from Lung Cancer
2002-2009

Mortality LDCT group – 1.3%
Mortality CXR group – 1.7%
20% reduction
87 deaths

### National Lung Screening Trial

**RESULTS  N = 3856**

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>LDCT</th>
<th>CXR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>427</td>
<td>503</td>
<td>(24.1%)</td>
</tr>
<tr>
<td>Other neoplasm</td>
<td>416</td>
<td>442</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>486</td>
<td>470</td>
<td></td>
</tr>
<tr>
<td>Complications of Medical/Surgical Care</td>
<td>12</td>
<td>7</td>
<td>(75.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>349</td>
<td>343</td>
<td></td>
</tr>
</tbody>
</table>


### Computer Tomography Screening for Lung Cancer

**Cost of Screening**

**Financial and Psychological**
Health Affairs
2012

**EXHIBIT 4**

Cost Of Cervical, Colorectal, Breast, And Lung Cancer Screening Per Life-Year Saved

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Screening technique</th>
<th>Cost per life-year saved (dollars, year of original study)</th>
<th>Acceptable range</th>
<th>Cost per life-year saved (2012 dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>Pap smear</td>
<td>33,000</td>
<td>$50,000 - $100,000</td>
<td>50,000 - 75,000</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Colonoscopy</td>
<td>11,900</td>
<td>1999</td>
<td>18,705 - 28,958</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18,800</td>
<td>1997</td>
<td>31,094 - 51,274</td>
</tr>
<tr>
<td>Breast</td>
<td>Mammography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>LDCT (baseline scenario)</td>
<td>18,862</td>
<td>2012</td>
<td>18,862 - 30%</td>
</tr>
<tr>
<td></td>
<td>LDCT (lowest-cost scenario)</td>
<td>11,708</td>
<td>2012</td>
<td>11,708 - 20%</td>
</tr>
<tr>
<td></td>
<td>LDCT (highest-cost scenario)</td>
<td>26,016</td>
<td>2012</td>
<td>26,016 - 40%</td>
</tr>
</tbody>
</table>


**An Actuarial Analysis Shows That Offering Lung Cancer Screening As An Insurance Benefit Would Save Lives At Relatively Low Cost**
*Health Affairs*, 31, no.4 (2012):770-779

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By Bruce S. Pyenson, Mariia S. Sanders, Yiling Song, Howard Kahn, and James L. Mckeehan

**ABSTRACT** Lung cancer screening is not established as a public health practice, yet the results of a recent large randomized controlled trial showed that screening with low-dose spiral computed tomography reduces lung cancer mortality. Using actuarial models, this study estimated the costs and benefits of annual lung cancer screening offered as a commercial insurance benefit in the high-risk US population ages 50-64. Assuming current commercial reimbursement rates for treatment, we found that screening would cost about $1 per insured member per month in 2012 dollars. The cost per life-year saved would be below $10,000, an amount that compares favorably with screening for cervical, breast, and colorectal cancers. Our results suggest that commercial insurers should consider lung cancer screening of high-risk individuals to be high-value coverage and provide it as a benefit to people who are at least fifty years old and have a smoking history of thirty pack-years or more. We also believe that payers and patients should demand screening from high-quality, low-cost providers, thus helping set an example of efficient system innovation.
Computer Tomography Screening for Lung Cancer

**Cost of Screening - 1**

- Each scan costs $300 in NLST
- Cost of work-up for positive scan (PET, Bx)
- Patient or family member taking time off from work for scan and office visit follow-up
- **Psychological cost** being measured by NLST

Mahadevia JAMA 2003
http://www.cancer.gov/cancertopics/factsheet/lung-spiral-CTscan

**Cost of Screening - 2**

- “In the USA, 50 million men & women who are EVER Smokers between the ages of 45 and 75 years.
- If 50% of this group received periodic annual screening = **$115 billion** based on our study estimates (20 years)
- $116,300 per QALY gained

Computer Tomography Screening for Lung Cancer

Radiation Risk to Patients

Approximately

CTA = 100 CXR’s
CT (I +) = 60-80 CXR’s
Low dose = 15-20 CXR’s
### Dose of radiation for common diagnostic radiologic tests

<table>
<thead>
<tr>
<th>Test</th>
<th>mSv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammogram</td>
<td>0.7</td>
</tr>
<tr>
<td>LDCT</td>
<td>1.0</td>
</tr>
<tr>
<td>Diagnostic regular CT</td>
<td>10</td>
</tr>
<tr>
<td>Triphasic CT Abdomen</td>
<td>25</td>
</tr>
<tr>
<td>Background</td>
<td>3 / year</td>
</tr>
<tr>
<td>Colorado</td>
<td>4.5 / year</td>
</tr>
<tr>
<td>Occupational exposure</td>
<td>50 / year</td>
</tr>
<tr>
<td>Trans-Atlantic flight</td>
<td>0.1</td>
</tr>
<tr>
<td>Atomic Bomb Survivors</td>
<td>5 – 100</td>
</tr>
</tbody>
</table>


### CT Lung Cancer Screening Morbidity

**Radiation exposure**
- MDCT resolution allows for dose reduction
- LDCT <1mSv, Mammography 0.7mSv

![1 mSv CT scan](image1.png)  
![10 mSv CT scan](image2.png)
Radiation risk of low dose CT screening for Lung Cancer

✓ Atomic Bomb Survivors Radiation exposure:
  5 – 100 mSv

✓ NLST
  o LDCT  < 2 mSV;( ~ same as mammogram) x 3 = 6 mSv
  o CXR   0.05 mSV x 3 = 0.15 mSv


NLST based Radiation risk of LD CT screening for Lung Cancer

• Estimates in a 55 year old smoker
• 1 to 3 deaths from lung cancer per 10,000 persons screened
• 0.3 new breast cancers per 10,000 persons screened

• Cumulative mortality reduction in NLST
• 30 cases of lung cancer per 10,000 screened
• Lifetime risk for fatal cancer from LDCT “very low” (1 per 10,000 to 1 per 100,000)

Before age 50, the mortality reduction from lung CT screening that is required to outweigh the radiation risk may be substantial, and in some cases unattainable.

**RESULTS**

Operations for suspected lung cancer 907
Operations for benign disease 209 (23%)

<table>
<thead>
<tr>
<th>BENIGN DISEASE</th>
<th>LDCT</th>
<th>CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
<td>26 (15.9%)</td>
<td>7 (15.6%)</td>
</tr>
<tr>
<td>Operative Mortality within 60 days</td>
<td>2 (1.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

4 deaths from bronch


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**The Future**

“We are in our infancy”

- Which smokers should get LD CT screening?
- C.T. Individual Nodule Analysis
- Automated Quantitative sputum cytometry
- Biomarkers of blood, lung tissue, BAL, sputum, or oral buccal mucosal cells
- VOC analysis of exhaled breath
- Need for smoking cessation education (COST EFFECTIVE)
- Autofluorescence bronchoscopy
- PET scanning, PET / CT scanning
National Lung Screening Trial

SUMMARY

✓ Reduced lung CA specific mortality by 20% (Mammography 14-15% reduction)
✓ Mortality CT screened group – 1.3%
✓ Mortality CXR screened group – 1.7%
✓ Mortality “death from any cause” decreased by 7%


National Lung Screening Trial

SUMMARY

✓ 75% of deaths in the study were not from lung CA (CAD, COPD, stroke)
✓ Cost of Low Dose Chest CT ~ $300
✓ 25% of pts. in the study needed follow-up testing – will add to expense
✓ Number to screen to avoid one death= ~ 320
✓ Mammography = 2,000

SUMMARY

- Cost effectiveness ratio
- ~ $26,000 per life saved
- Acceptable range $50,000 - $100,000
- Screening should not replace smoking cessation

Criticisms of NLST

- NLST had a very narrow study group
  - Evaluated a younger, less ethnic, higher educated population
  - Only 8% of the study population was in the oldest age category 70 to 74 years old
  - Average age of dx of Lung Cancer = 70 years
- 96.4% of LDCT in NLST yielded false-positive
- 16 pts. died w/in 60 days of ANY invasive procedure to evaluate abnormal scan
- 6 of those pts. did not have lung cancer
  
  *Annals of Internal Medicine, October 18, 2011*

False Positive Rate vs. False Discovery Rate

- False Discovery Rate (def.) = the false positive rate in a group with a discovered nodule

- False Positive Rate (def.) = the number of false positive tests in the entire screened population
Should we be screening mass populations of smokers in the USA?

- Look to European studies NELSON (Netherlands), DANTE (Italy) on how to possibly better handle nodule analysis to avoid unnecessary surgery.

- Await “cost-effectiveness” and “over-diagnosis bias” analysis of NLST data: May take 15-20 years to see the true over-diagnosis bias in NLST.

- Subgroups of smokers: Do some smokers benefit more from screening than others? 
  *Annals of Internal Medicine, October 18, 2011*

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**Management of Lung Nodules Detected by Volume CT Scanning**

Rob J. van Klaveren, M.D., Ph.D., Matthijs Oudkerk, M.D., Ph.D., Mathias Prokop, M.D., Ph.D., Ernst T. Scholten, M.D.

**NELSON Trial – Netherlands, Belgium (Final results 2016)**


**Conclusions**

Among subjects at high risk for lung cancer who were screened in three rounds of CT scanning and in whom noncalcified pulmonary nodules were evaluated according to volume and volume doubling time, the chances of finding lung cancer 1 and 2 years after a negative first-round test were 1 in 1000 and 3 in 1000, respectively.

(Current Controlled Trials number, ISRCTN63545820.)
A Randomized Study of Lung Cancer Screening with Spiral Computed Tomography
Three-year Results from the DANTE Trial

Maurizio Infante, Silvio Cavuto, Fabio Romano Lutman, Giorgio Brambilla, Giuseppe Chiesa, Giovanni Cerezo, Eliseo Passera, Enzo Angelis, Maurizio Chilenzio, Giuseppe Azzellino, Umberto Cariboni, Valentina Erizzo, Francesco Inzirillo, Edoardo Bottoli, Emanuele Voulaz, Marco Alloisio, Anna Destro, Massimo Roncalli, Armando Santoro, and Gianluigi Ravasi, for the DANTE Study Group

Radioscopy has been the standard method in the early detection of lung cancer since the late 1970s. This intervention has been associated with a relative reduction of lung cancer mortality of 20% (1). The American Thoracic Society (ATS) (2) and the European Respiratory Society (ERS) (3) have stated that low-dose CT scanning (LDCT) has the potential to reduce lung cancer mortality, but they have also highlighted the need for randomized controlled trials (RCTs) to confirm these findings. The DANTE Lung Cancer Screening Trial was a multicenter, randomized controlled trial designed to evaluate the effectiveness of LDCT in reducing lung cancer mortality among high-risk individuals.

**Objective:** To determine the effectiveness of LDCT in reducing lung cancer mortality among high-risk individuals.

**Methods:**
- **Participants:** Male smokers aged 50 to 74 years who had smoked ≥20 pack-years (≥150 pack-years for period 1 smokers) were enrolled.
- **Randomization:** Participants were randomized to the LDCT or control group.
- **Follow-up:** Participants were followed for up to 10 years after randomization.

**Results:**
- **Mortality Reduction:** There was no statistically significant difference in lung cancer mortality between the LDCT and control groups (9.2% vs. 9.7%, respectively; P = 0.8).
- **Cost-Effectiveness:** At the time of publication, the cost-effectiveness analysis indicated that LDCT was cost-effective compared to conventional screening.

**Conclusion:** The DANTE trial did not demonstrate a statistically significant reduction in lung cancer mortality with LDCT. Further research is needed to determine the role of LDCT in lung cancer screening.

**References:**
1. Limited data available.
2. ATS Statement on the Use of CT Scanning for the Early Detection of Lung Cancer.
3. ERS Statement on the Use of CT Scanning for the Early Detection of Lung Cancer.

Bepler G. Am J Respir Crit Care Med 2009; 180:384-385

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**DANTE Lung Cancer Screening Trial**
Italy - March 2001 to February 2006

- **N = 2811 randomized; N = 2,472 enrolled**
- **20 pack years tobacco**
- **Baseline CXR x 1, CT scan and sputum Q year for 4 years vs. Control (medical exam only)**
- **Time frame reported 34 months**
- **NO MORTALITY REDUCTION**
- **Awaiting 6 year (72 month) data**

Bepler G. Am J Respir Crit Care Med 2009; 180:384-385
PLCO Cancer Screening Trial
Entry & random 1993 - 2001

☑ Began 1992; 154,942 patients, 13 years follow-up
☑ 77,747 (Control) , 77,465 (Intervention) 55-74 y.o.
☑ Men (38,350) and Women (39,115)
☑ Baseline CXR + annually (Smokers x 3), (Non- x 2)
☑ Control: No baseline + CXR’s outside of study OK
☑ Compliance for first CXR  86.5%
☑ Caucasian 88.5%, AA 5.1%, Other minorities 6.4%
☑ Current or Former smokers 64% men, 45% women,
☑ 29% 20 pack years (range < 15 to ≥ 30 pack years)


Screening with CXR’s showed No reduction in lung cancer specific mortality
JAMA 2011
Benefits and Harms of CT Screening for Lung Cancer
A Systematic Review

Context: Lung cancer is the leading cause of cancer death. Most patients are diagnosed with advanced disease, resulting in a very low 5-year survival. Screening may reduce the risk of death from lung cancer.

Objective: To conduct a systematic review of the evidence regarding the benefits and harms of lung cancer screening using low-dose computed tomography (LDCT). A multisociety collaborative initiative involving the American Cancer Society, American College of Chest Physicians, American Society of Clinical Oncology, and National Comprehensive Cancer Network was undertaken to create the foundation for development of an evidence-based clinical guideline.

Data Sources: MEDLINE (Ovid: January 1966 to April 2012), EMBASE (Ovid: January 1980 to April 2012), and the Cochrane Library (April 2012).

Study Selection: Of 291 citations identified and reviewed, 8 randomized trials and 12 cohort studies, of LDCT screening methods for individuals at increased risk from lung cancer mortality and all-cause mortality, and secondary outcomes included nodule detection, invasive procedures, follow-up tests, and smoking cessation.

Conclusion: Low-dose computed tomography screening may benefit individuals at an increased risk for lung cancer, but uncertainty exists about the potential harms of screening and the generalizability of results.
Should we be screening mass populations of smokers in the USA?

- Generalizing the results of NLST to community practices may be problematic
  - LDCT in NLST were interpreted by dedicated chest radiologists
  - Few pts. required invasive testing
  - Community radiologists without expertise in evaluating lung nodules may feel compelled to advise invasive testing for a screen-detected nodule

Annals of Internal Medicine, October 18, 2011

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**Box: Role of Computed Tomography Screening for Lung Cancer Recommendations From the American College of Chest Physicians and the American Society of Clinical Oncology**

**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 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 in the National Lung Screening Trial (NLST) participants. (Grade of recommendation: 2B.)

**Remark 1**
Consulting should include a complete description of potential benefits and harms (as outlined in the full guideline text) so the individual can decide whether to undergo LDCT screening.

**Remark 2**
Screening should be conducted in a center similar to those where the NLST was conducted, with multidisciplinary coordinated care and a comprehensive process for screening, image interpretation, management of findings, and evaluation and treatment of potential cancers.

**Remark 3**
A number of important questions about screening could be addressed if individuals who are screened for lung cancer are entered into a registry that captures data on follow-up testing, radiation exposure, patient experience, and smoking behavior.

**Remark 4**
Quality metrics should be developed such as those in use for mammography screening, which could help enhance the benefits and minimize the harms for individuals who undergo screening.

**Remark 5**
Screening for lung cancer is not a substitute for stopping smoking. The most important thing patients can do to prevent lung cancer is not smoke.

**Remark 6**
The most effective duration or frequency of screening is not known.

**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.)

Full text of the American College of Chest Physicians and the American Society of Clinical Oncology evidence-based practice guideline on the role of CT screening for lung cancer is available in Appendix 4.

Box. Role of Computed Tomography Screening for Lung Cancer: Recommendations From College of Chest Physicians and the American Society of Clinical Oncology

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Lung Cancer Screening
How should I advise my patients in 2012?

Low Risk: Do not screen

High Risk: (NLST criteria)

90 million smokers/former smokers in USA

7-8% meet NLST criteria

1. Review the available data from NLST w/ patient

2. Discuss initial & follow-up costs ($300-400/scan); not covered by Medicare and insurance

Lung Cancer Screening
How should I advise my patients in 2011?

High Risk:

3. Inform them of risks and benefits (false positives with lengthy follow-up (2 to 5 years); possible unnecessary surgery, psychological stress of follow-up)
Lung Cancer Screening
How should I advise my patients in 2011?

High Risk:

4. Smoking Cessation – one year quit rate in screening trials 12-20%

5. Screen if they desire to proceed; if currently smoking – concurrent smoking cessation

6. If IM, refer to Pulmonary (Local or Lahey) if positive CT scan

7. Your institution should have a follow-up system (like mammography) with algorithm (NLST) to handle abnormal scans; not shopping mall or medical facility w/o expertise in follow-up & referral

8. NLST data support annual screening LDCT for 3 to 5 years and maybe lifelong: new information on length and frequency of screening may be available when future data from NLST is published.
Lung Cancer Screening Volume for a typical Internal Medicine PCP

- Total # of patients = 2500
- 75 pts. (3%) screened per year
- ~20 pts./total pts. will have a lung finding
- ~5 pts./total pts. will have findings not related to the lung
- 1 pt. in ~320 screened with a LDCT will have died from lung CA if they were not screened

Based on NLST data

Proposed algorithm for lung cancer screening

Dear Fellow Physician:

FREE Lung Cancer CT Screening

The National Lung Screening Trial (NLST), a large, National Cancer Institute (NCI)-sponsored, randomized controlled trial, recently confirmed that screening individuals at high risk for lung cancer with an annual low-dose CT (LDCT) of the chest saves lives. In the NLST:

- One in 70 high-risk persons enrolled in the study were found to have lung cancer on the first screening exam.
- One life was saved for every 320 high-risk persons screened with LDCT over two years, resulting in a 20 percent lung cancer-specific mortality benefit versus annual chest radiography.

As a result of the high-risk individual cancer, which inch
Currently, most pay for LDCT lung scan accessibility of individuals who
To Order a Screening
We strongly believe primary care physicians for LDCT.

Rescue Lung Rescue Life at Lahey Clinic

To Schedule a Screening

Thank you,

The Sophia Gordon Cancer Center and the Department of Radiology
Lahey Clinic Medical Center
Lung Screening Questionnaire

Patient Name:  
LC #:  
Date:  

<table>
<thead>
<tr>
<th>#</th>
<th>QUESTION</th>
<th>PATIENT RESPONSE</th>
<th>GUIDELINE</th>
<th>RESULT</th>
<th>why step</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>How old are you? (Date of birth)</td>
<td>Age 50-74 y</td>
<td>YES</td>
<td>Go to Question 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO</td>
<td>GROUP 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Do you have a family history of lung cancer?</td>
<td>Using calculator determine family history and order risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pack Years (PY) = ___</td>
<td>Age 55-74 &amp; PY &gt; 30</td>
<td>Go to Question 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Everyone Else</td>
<td>GROUP 3</td>
<td>GROUP 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Are you currently smoking? If not, have you quit less than 15 years ago?</td>
<td>Currently smoking or quit less than 15 years ago</td>
<td>YES</td>
<td>GROUP 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>GROUP 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GROUP 1: Meets Criteria for Free Screening
1. Schedule appointment, including patient's name, Lahey Clinic.
2. Record contact information and preferred method of communication.
3. Inform patient they may receive an order from their PCP to perform the exam. PCPs can fax the order to (781) 744-3284 otherwise the patient must bring the order with them at the time of their appointment. The patient will receive a letter to give to their PCP explaining the program and ordering process.
4. If the patient does not have a PCP, please instruct patient to call (781) 744-3281 to obtain a PCP.

GROUP 2: May Meet Criteria for Free Screening
Complete the contact information and inform the patient that a member of the screening team will contact them within one week to determine their eligibility.

GROUP 3: Does Not Meet Criteria for Free Screening
While patient does not meet criteria for free screening they should be encouraged to discuss the role of CT screening for lung cancer for their situation with their primary care physician.

Please ask all callers, “How did you hear about our program?”

Patient Response:

Contact Information:
- Cell: ____________________________
- Home: ____________________________
- Work: ____________________________
- Email: ____________________________
- Other: ____________________________
- Preferred Contact Method (circle one):
  - Email
  - Home Phone
  - Cell Phone
  - Work Phone
  - Other
  - Mail at Home

A pitch for lifetime screening?

Adeno CA, BAC

Actual NLST subject who developed lung cancer after the completion of the NLST trial
WellPoint to Cover Lung CT Scans for Heavy Smokers

This summer, the New England Journal of Medicine published the results of a government-funded trial that found screening current and former heavy smokers with low-dose CT scans was tied to a 20% reduction in lung-cancer deaths.

Now, the study is starting to have a concrete impact. Insurer WellPoint, with around 34 million members, says it will start covering the tests based on its findings. It's the latest twist in a long debate about using the scans to detect lung cancer, an idea that has been the subject of clashing research findings over the years.

Under WellPoint's new policy, CT scans for lung-cancer screening will be covered for people who match the characteristics of those involved in the National Lung Screening Trial.

LUNG CANCER SCREENING
2012
ANY QUESTIONS?
Hey Chief,

Here's the MRN of that guy who was in the NLST study, but subsequently developed lung CA.

#2674962, Frank Judge.

He saw Williamson on December 1st, and he is going to the OR on the 16th for VATS and lobectomy. All of his CT scans from the trial are loaded in our system. I am going to follow up his pathology.

Caleb