CURRENT STATUS OF LUNG CANCER SCREENING

Ugo Pastorino
Thoracic Surgery, Istituto Nazionale Tumori, Milan
DISCLOSURE SLIDE

Nothing to disclose
### 15 Years of LDCT Screening: Consistent Detection Rates

**High Frequency of Stage I Minimally Invasive Approach**

<table>
<thead>
<tr>
<th></th>
<th>screened</th>
<th>positive CT</th>
<th>LC</th>
<th>stage I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>non RCT</strong></td>
<td>16</td>
<td>71,935</td>
<td>21%</td>
<td>1.0%</td>
</tr>
<tr>
<td><strong>all RCTs</strong></td>
<td>8</td>
<td>44,629</td>
<td>23%</td>
<td>1.1%</td>
</tr>
<tr>
<td><strong>NLST alone</strong></td>
<td>26,309</td>
<td>25%</td>
<td>1%</td>
<td>63%</td>
</tr>
</tbody>
</table>
Definition of a Positive Test Result in Computed Tomography Screening for Lung Cancer

A Cohort Study

Claudia I. Henschke, PhD, MD; Rowena Yip, MPH; David F. Yankelevitz, MD; and James P. Smith, MD, for the International Early Lung Cancer Action Program Investigators*

Conclusion: These findings suggest that using a threshold of 7 or 8 mm to define positive results in the baseline round of computed tomography screening for lung cancer should be prospectively evaluated to determine whether the benefits of decreasing further work-up outweigh the consequent delay in diagnosis in some patients.
Optimisation of volume-doubling time cutoff for fast-growing lung nodules in CT lung cancer screening reduces false-positive referrals

Marjolein A. Heuvelmans · Matthijs Oudkerk · Geertruida H. de Bock · Harry J. de Koning · Xueqian Xie · Peter M. A. van Ooijen · Marcel J. W. Greuter · Pim A. de Jong · Harry J. M. Groen · Rozemarijn Vliegenthart

**Conclusion** All malignant fast-growing lung nodules referred after the 3-month follow-up CT in the baseline lung cancer screening round had VDT ≤232 days. Lowering the VDT cutoff may reduce false-positive referrals.

Eur Radiol 2013; 23:1836–1845
DIFFERENTIAL DIAGNOSIS: IS PET SCAN USEFUL?

Surgery for benign disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCST 2012</td>
<td>32%</td>
</tr>
<tr>
<td>LUSI 2012</td>
<td>29%</td>
</tr>
<tr>
<td>NELSON 2009</td>
<td>27%</td>
</tr>
<tr>
<td>DANTE 2009</td>
<td>24%</td>
</tr>
<tr>
<td>NLST 2011</td>
<td>24%</td>
</tr>
<tr>
<td>MILD 2012</td>
<td>8%</td>
</tr>
</tbody>
</table>
Low-dose computed tomography for lung cancer screening: comparison of performance between annual and biennial screen

Nicola Sverzellati¹ · M. Silva¹ · G. Calareso² · C. Galeone³ · A. Marchianò² · S. Sestini⁴ · G. Sozzi⁵ · U. Pastorino⁴

6893 LDCTs in 1152 annual, and 4715 in 1151 biennial participants

• Biennial LDCT screening may be as efficient as the annual screening.
• Annual and biennial LDCT screening have similar frequency of interval lung cancers.
• Biennial screening may save about one third of LDCT scans.
EUROPEAN LUNG CANCER CONFERENCE 2016

LDCT INTENSITY: IS ONE SHOT ENOUGH?

ORIGINAL ARTICLE

UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening

Conclusions The UKLS pilot trial demonstrated that it is possible to detect lung cancer at an early stage and deliver potentially curative treatment in over 80% of cases. Health economic analysis suggests that the intervention would be cost effective—this needs to be confirmed using data on observed lung cancer mortality reduction.

250,000 individuals approached aged 50 – 75 years
LC risk ≥5% over 5 years
>3 mm (or 15 mm$^3$) LDCT at 1 yr
>5 mm (or 50 mm$^3$) LDCT at 3 mos
VDT cut-off 400 days

2,000 LDCT screened
2.1% LC detection rate


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NLST OUTCOME: SIGNIFICANT MORTALITY REDUCTION

53,454 persons: 3 rounds of LDCT screening vs CXR

- 20% reduction of lung cancer mortality
- 7% reduction all cause mortality

- 24.2% positive subjects
- 96.4% false positive = PPV 3.6%

- overdiagnosis by LDCT: > 18% overall up to 79% for indolent cancers

- 1% / year mortality

Patz EF., JAMA 2013

EUROPEAN LUNG CANCER CONFERENCE 2016
Results of the randomized Danish Lung Cancer Screening Trial with focus on high-risk profiling

Authors
Mathilde MW Wille, PhD1,2; Asger Dirksen, DMSc1; Haseem Asraf, PhD3,1; Zaigham Saghir, PhD4; Karen S Bach, M.D.5; John Brodersen, PhD6; Paul F Clementsen, DMSc1,7; Hanne Hansen, M.D.8; Klaus R Larsen, PhD4; Jann Mortensen, DMSc9; Jakob F Rasmussen, PhD6; Niels Seersholm, DMSc1; Birgit G Skov, DMSc10; Laura H Thomsen, PhD1; Philip Tønnesen, DMSc11; Jesper H Pedersen, DMSc12

Long-term follow-up results of the DANTE trial, a randomized study of lung cancer screening with spiral computed tomography

Maurizio Infante, MD1, Silvio Cavuto, DSc2, Fabio Romano Lutman, MD3, Eliseo Passera, MD4, Maurizio Chiarenza, MD5, Giuseppe Chiesa, MD4, Giorgio Brambilla, MD3, Enzo Angeli, MD6, Giuseppe Aranzulla, MD7, Arturo Chiti, MD8, Marta Scorsetti, MD9, Pierina Navarria, MD9, Raffaele Cavina, MD10, Michele Ciccarelli, MD11, Massimo Roncalli, MD, PhD12, Anna Destro, PhD12, Edoardo Bottoni, MD1, Emanuele Voulaz, MD1, Valentina Errico, MD1, Giorgio Ferraroli, MD1, Giovanna Finocchiaro, MD10, Luca Toschi MD10, Armando Santoro, MD10, Marco Alloisio, MD1. For the DANTE Study Group.
Screening with Low-Dose Computed Tomography Does Not Improve Survival of Small Cell Lung Cancer

Mario Silva, MD, a,d,* Carlotta Galeone, PhD, b
Alfonso Marchionè, MD, c Giuseppina Calareso
Carlo La Vecchia, MD, b Gabriella Sozzi, PhD, e
Ugo Pastorino, MD d

Figure 3. Overall survival curve shows no survivors at 3 years after diagnosis of SCLC.
### OVERDIAGNOSIS: HOW BIG IS THE PROBLEM?

<table>
<thead>
<tr>
<th>Method</th>
<th>LC Incidence /10,000 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLST</td>
<td>65</td>
</tr>
<tr>
<td>LDCT</td>
<td>57</td>
</tr>
<tr>
<td>CR</td>
<td>+14%</td>
</tr>
</tbody>
</table>

OVERDIAGNOSIS: **HOW BIG IS THE PROBLEM?**

<table>
<thead>
<tr>
<th></th>
<th>LC incidence</th>
<th>LC mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NLST</strong></td>
<td>65</td>
<td>25</td>
</tr>
<tr>
<td><strong>LDCT</strong></td>
<td></td>
<td>+ 160%</td>
</tr>
</tbody>
</table>

## OVERDIAGNOSIS: HOW BIG IS THE PROBLEM?

<table>
<thead>
<tr>
<th></th>
<th>LC incidence</th>
<th>LC mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NLST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDCT</td>
<td>65</td>
<td>25</td>
</tr>
<tr>
<td>CR</td>
<td>57 + 84%</td>
<td>31</td>
</tr>
<tr>
<td><strong>PLCO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>61</td>
<td>36</td>
</tr>
<tr>
<td>Observation</td>
<td>61 + 60%</td>
<td>38</td>
</tr>
</tbody>
</table>

* subset of 30,321 participants eligible for NLST trial

JAMA 2011, 306:1865
Long-Term Surveillance of Ground-Glass Nodules

Evidence from the MILD Trial

*Silva Mario, MD, *Sverzellati Nicola, MD, PhD, *Manna Carmelinda, MD, *Negrini Giulio, MD, *Marchianò Alfonso, MD, †Zompatori Maurizio, MD, ‡Rossi Cristina, MD, *and Pastorino Ugo, MD

76 ground-glass nodules (GGNs) detected in 56 patients at baseline CT followed for 5 years by CT:
only one (1.3%) progressed (stage Ia ADC)
3 developed LC in other sites

J Thor Oncol 7:1541, 2012
**LARGE SCALE SCREENING: WHICH IS THE BEST DESIGN?**

**POOLED ANALYSIS ESSENTIAL**

Lung cancer screening: European randomised LDCT trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Year started</th>
<th>Subjects enrolled</th>
<th>Recruitment</th>
<th>Age</th>
<th># CT</th>
<th>Years screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>DANTE</td>
<td>IT</td>
<td>2001</td>
<td>2,811</td>
<td>volunteers</td>
<td>60-74</td>
<td>5</td>
<td>5</td>
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<tr>
<td>NELSON</td>
<td>NL–B</td>
<td>2003</td>
<td>15,822</td>
<td>registry</td>
<td>50-74</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>ITALUNG</td>
<td>IT</td>
<td>2004</td>
<td>3,206</td>
<td>GPs</td>
<td>55-69</td>
<td>4</td>
<td>4</td>
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<tr>
<td>DLCST</td>
<td>DK</td>
<td>2004</td>
<td>4,104</td>
<td>volunteers</td>
<td>50-70</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>MILD</td>
<td>IT</td>
<td>2005</td>
<td>4,099</td>
<td>volunteers</td>
<td>49-75</td>
<td>4-8</td>
<td>8</td>
</tr>
<tr>
<td>LUSI</td>
<td>D</td>
<td>2007</td>
<td>4,052</td>
<td>population</td>
<td>50-69</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>UKLS</td>
<td>UK</td>
<td>2011</td>
<td>4,055</td>
<td>registry</td>
<td>50-75</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total** 38,149
<table>
<thead>
<tr>
<th>Year</th>
<th>Study Description</th>
<th>Participants</th>
<th>PY</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>INT-IEO pilot trial</td>
<td>1,035</td>
<td>14,000</td>
</tr>
<tr>
<td>2005</td>
<td>MILD randomized</td>
<td>2,376</td>
<td>20,000</td>
</tr>
<tr>
<td>2013</td>
<td>bioMILD miRNA + LDCT</td>
<td>4,100</td>
<td>6,000</td>
</tr>
</tbody>
</table>

Total LDCT participants: 7,500, 40,000 PY

# blood & tissue samples frozen - 80° > 100,000
Clinical Utility of a Plasma-Based miRNA Signature Classifier Within Computed Tomography Lung Cancer Screening: A Correlative MILD Trial Study

false positive rate = 4% vs. 96.4% in NLST

J Clin Oncol 10;32:768
LC BIOLOGY: CAN BIOMARKERS IMPROVE SCREENING?

Clinical Utility of a Plasma-Based miRNA Signature Classifier Within Computed Tomography Lung Cancer Screening: A Correlative MILDS Trial Study

MSC predicted cohort survival of 1,000 high risk LDCT participants

\[ \chi^2 = 12.57 \]
\[ P = .0004 \]

Survival Distribution Function

Follow-Up Duration (years)

J Clin Oncol 10;32:768
MIRNA + LDCT: BIOMILD TRIAL ON 4,000 SUBJECTS

MSC and LDCT

LDCT positive >260 mm³

• LDCT at 3 months
• PET
• Surgery?

1 year

MSC and LDCT

LDCT negative <113 mm³

Low Risk MSC

LDCT positive >260 mm³

Intermediate Risk MSC

LDCT negative <113 mm³

1 year

Exit screening (3 yrs)

Intermediate Risk MSC

LDCT indeterminate 113-260 mm³

High Risk MSC

LDCT indeterminate 113-260 mm³

LDCT negative <113 mm³
WHY SO LITTLE EFFECT: **LC IS A MINOR CAUSE OF DEATH**

50-Year Trends in Smoking-Related Mortality in the United States


<table>
<thead>
<tr>
<th></th>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURRENT</td>
<td>21%</td>
<td>20%</td>
</tr>
<tr>
<td>FORMER</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>NLST</td>
<td>23%</td>
<td></td>
</tr>
</tbody>
</table>

956,761 COHORT, AGE 55-85, 56% EVER SMOKERS
NEW EVIDENCE: DRUG INTERVENTION WORKS

A combined smoking cessation intervention within a lung cancer screening trial: a pilot observational study

Paolo Pozzi¹, Elena Munarini¹, Francesca Bravi², Marta Rossi²³, Carlo La Vecchia²³, Roberto Boffi¹, Ugo Pastorino⁴

quit rate after one varenicline treatment:

<table>
<thead>
<tr>
<th>Duration</th>
<th>Quitting Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mos</td>
<td>49%</td>
</tr>
<tr>
<td>12 mos</td>
<td>20%</td>
</tr>
</tbody>
</table>

efficacy of varenicline
187 MILD subjects, on LDCT screening > 5 yrs
NEW EVIDENCE: QUITTING IN LDCT IS EFFECTIVE

Stopping Smoking Reduces Mortality in Low-Dose Computed Tomography Screening Participants

3,381 LDCT screened, 32,858 PY

Cumulative mortality at 9 years

J Thor Oncol 2016, epub
NEW EVIDENCE: QUITTING MORE EFFECTIVE THAN LDCT

Stopping Smoking Reduces Mortality in Low-Dose Computed Tomography Screening Participants

Figure 3. Effect of smoking cessation on overall mortality. Hazard ratios (Cox model) and corresponding 95% confidence intervals estimating the effect of smoking cessation on mortality. Estimates are adjusted for covariates measured at baseline (sex, age, predicted forced expiratory volume in the first second of expiration, and average number of pack-years) and during follow-up (lungs cancer detection and smoking status).
LOST OPPORTUNITY: SMOKING ASSESSMENT IN NLST

The Association between Smoking Abstinence and Mortality in the National Lung Screening Trial

Nichole T. Tanner¹,², Neeti M. Kanodra¹, Mulugeta Gebregziabher²,³, Elizabeth Payne³, Chanita Hughes Halbert²,⁴, Graham W. Warren⁵,⁶, Leonard E. Egede²,⁷, and Gerard A. Silvestri¹

¹Division of Pulmonary, Critical Care and Sleep Medicine, ³Department of Public Health Sciences, ⁴Department of Psychiatry and Behavioral Sciences, Hollings Cancer Center, ⁵Department of Radiation Oncology, ⁶Department of Cell and Molecular Pharmacology, and ⁷Department of Medicine, Medical University of South Carolina, Charleston, South Carolina; and ²Health Equity and Rural Outreach Innovation Center, Ralph H. Johnson Veterans Affairs Hospital, Charleston, South Carolina

Current smokers had an increased lung cancer-specific (HR range 2.14-2.29) and all-cause mortality (HR range 1.79-1.85) compared to former smokers.

Seven years of smoking abstinence reduced lung cancer-specific mortality at a magnitude comparable to LDCT screening.

No information on quitting rate during LDCT screening and its impact on mortality.

OPEN QUESTIONS: POOLED ANALYSIS OF DANTE & MILD

6,549 PARTICIPANTS, 52,637 PY, 520 DEATHS

non-significant 11% reduction of overall mortality in LDCT arm as compared to control arm, HR = 0.89 (95% CI: 0.74-1.06)

EUR J CAN PREV, IN PRESS
OPEN QUESTIONS: POOLED ANALYSIS OF DANTE & MILD

6,549 PARTICIPANTS, 52,637 PY, 520 DEATHS

No reduction of overall mortality in former smokers at baseline?

**FORMER**

**CURRENT**

EUR J CAN PREV, IN PRESS

EUROPEAN LUNG CANCER CONFERENCE 2016
OPEN QUESTIONS: SUSTAINABLE HEALTH CARE

- targeted therapy of all metastatic LC ???
- QUALY > 150,000 €
- similar prospect for BPCO & HD
- better treatment of tobacco addiction
- aging requires preventive strategies
LDCT SCREENING IN 2016: SUMMARY

- good prospects for targeted screening
- results of European RCTs are crucial
- optimize individual selection (biologic)
- improve diagnostic algorithm
- validate biomarkers
- combine with primary prevention
**SCREENING + PREVENTION: THE SMILE TRIAL**

pilot study on the feasibility of integrated prevention in high risk individuals

**Population:**
55-75 yrs-old current smokers ≥ 30 pack / years

**Behavioural counselling (Eurocode)**
+ annual or biennial LDCT

**Behavioural counselling (Eurocode)**
+ annual or biennial LDCT

+ **Integrated prevention:**
  - Pharmacological approach (varenicline, ASA)
  - Balanced diet
  - Physical exercise