SH02 – HIGHLIGHTS SCREENING

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DISCLOSURES

I do not have any financial relationships to disclose
• PL02.02 - Lung Cancer Screenee Selection by USPSTF Versus PLCOm2012 Criteria – Interim ILST Findings
  • Presenting Author(s): Stephen Lam

• PL02.03 - Early Detection of Cancer of the Lung Scotland (ECLS): Trial Results
  • Presenting Author(s): Frank Sullivan

• PL02.04 - Blood MicroRNA and LDCT Reduce Unnecessary LDCT Repeats in Lung Cancer Screening: Results of Prospective BioMILD Trial
  • Presenting Author(s): Ugo Pastorino

- PL02.05 - Discussant - PL02.02, PL02.03, PL02.04
  08:45 - 08:55  |  Presenting Author(s): Harry J. de Koning
• OA06.02 - The Role of Simulation Modeling in Shaping Lung Cancer Screening Policies in the US and Elsewhere  
  Presenting Author(s): Rafael Meza

• OA06.03 - An Open Source Lung Screening Management System  
  Presenting Author(s): Claudia I Henschke

• MS10 - Lung Cancer Screening, Opportunistic Evaluation of Findings  
  MS10.01 - COPD/Emphysema  Presenting Author(s): Javier Zulueta

P2.11-08 - CT Screening of Never Smokers  Presenting Author(s): Claudia I Henschke

The Greatest Lung Cancer Breakthrough of Our Time  Presenting Author: Raja Fores
Lung Cancer Screenee Selection By USPSTF versus PLCO_{m2012} Criteria: Interim ILST Findings


Canada, Australia, UK, Hong Kong, USA
Lung Cancer Screening

- Screening eligibility based on risk assessment, so that not everyone in a certain age group is offered screening

- Two main selection methods:
  - USPSTF (Age 55-80, ≥30 pack-years, smoked within 15 years)
  - Risk prediction tools such as PLCO_{m2012} (7 non-smoking and 4 smoking predictors)
<table>
<thead>
<tr>
<th>USPSTF – like Model Criteria</th>
<th>PLCO&lt;sub&gt;m2012&lt;/sub&gt; Model Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current Age</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
</tr>
<tr>
<td>Age of smoking initiation</td>
<td></td>
</tr>
<tr>
<td># of years elapsed since quitting</td>
<td>Years Smoked</td>
</tr>
<tr>
<td>Length of in-between quit periods</td>
<td></td>
</tr>
<tr>
<td>Average # of cigarettes smoked daily</td>
<td></td>
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<tr>
<td></td>
<td>Height</td>
</tr>
<tr>
<td></td>
<td>Weight</td>
</tr>
<tr>
<td></td>
<td>Level of education (socio-economic status)</td>
</tr>
<tr>
<td></td>
<td>Personal history of chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>Personal history of cancer</td>
</tr>
<tr>
<td></td>
<td>Family history of lung cancer</td>
</tr>
<tr>
<td></td>
<td>Race/Ethnicity</td>
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Key Issue in LDCT Screening: Define optimal selection criteria

- **USPSTF**: Age 55-80, ≥30 pack-years, smoking within 15 years
- **Risk Prediction Tool –** PLCO$_{m2012}$
- PLCO$_{m2012}$ has superior performance and validation in retrospective studies in US, Canada, UK, Germany & Australia
International Lung Screen Trial

- Prospective multi-center, multi-country study comparing lung cancer screening enrollment using PLCO$^{m2012}$ versus USPSTF criteria
- Started in July 2016
- 9 centers in Canada, Australia, UK, Hong Kong
- Target enrollment 4,500
- 2 rounds of LDCT, minimum 5 years follow-up
### ILST Interim Results

<table>
<thead>
<tr>
<th>Enrolled</th>
<th>5,013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>64 (55-80)</td>
</tr>
<tr>
<td>Sex</td>
<td>54% Male / 46% Female</td>
</tr>
<tr>
<td>Smoking Status</td>
<td>49% Former / 51% Current</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>89% Caucasian / 11% non-Caucasian</td>
</tr>
<tr>
<td>Follow-up (years) (median, range)</td>
<td>2.3 (0.3 - 3.7)</td>
</tr>
<tr>
<td>PLCO&lt;sub&gt;m2012&lt;/sub&gt; risk score (%)</td>
<td>2.9 (0 - 47)</td>
</tr>
<tr>
<td>Pack years (median, range)</td>
<td>41 (7 - 244)</td>
</tr>
<tr>
<td>Smoking Cessation Duration (EX)</td>
<td>10 (1 – 46) years</td>
</tr>
</tbody>
</table>
ILST Interim Results (N= 4985; LC 110)

- PLCO\textsubscript{m2012} Alone
  - N=1079
  - Cancer =25
  - (PLCO\textsubscript{m2012} Alone)

- Both USPSTF & PLCO\textsubscript{m2012}
  - N = 3212
  - Cancer =84
  - (Both Criteria)

- USPSTF Alone
  - N = 694
  - Cancer =1
  - (USPSTF Alone)

- 24 more cancers (21.8\% [95\% CI 14.5\%-30.7\%]) detected by PLCO\textsubscript{m2012}
- 385 more individuals (7.7\%, [95\% CI 6.1\%-9.4\%]) sampled
- Positive Predictive Value: PLCO\textsubscript{m2012} = 2.54\%; USPSTF = 2.17\% (p=0.10)
- USPSTF +ve/PLCO\textsubscript{m2012} –ve Cancer Risk 0.9\% [95\% CI 0.06\%-0.10\%]
Take Home Message (1)

Prospective evaluation of the enrolment criteria in multiple global settings shows

1. $\text{PLCO}_{m2012}$ selects significantly more individuals with lung cancer (22.5% more) than USPSTF - likely beneficial

2. USPSTF positive and $\text{PLCO}_{m2012}$ negative individuals (0.9%) are unlikely to benefit from screening.
Take Home Message (2)

3. Majority (80%) of lung cancers PLCO$_{m2012}$ positive but USPSTF negative are early stage and potentially curable

4. A PLCO$_{m2012}$ threshold of 1.7% appears optimal (number screened ~ USPSTF, but significantly higher sensitivity)

Important prospective study showing that slightly more detailed risk calculators may detect significantly more lung cancers than the present USPSTF-criteria (pack-years) (Harry J de Koning)
The EarlyCDT-Lung Test is a novel Autoantibody (AAB) diagnostic test for the early detection of lung cancer allowing stratification of individuals according to their risk of developing lung cancer.

Research question

Does using the EarlyCDT Lung test, followed by X-ray and CT scanning reduce the incidence of patients with late-stage lung cancer (III & IV/or unclassified), compared to standard clinical practice?

Method: An RCT in 12,210 participants

N= 12,210 - Ages 50-75
Current or ex-smoker with 20+ pack-years
Less pack-years but with positive family history
Biomarker-positive persons got imaging
Biomarker-negative persons got CT every 6 months (protocol)
Results

127 lung cancers were diagnosed in the study period (56 in the intervention group and 71 in the control arm). 9.8% of the intervention group had a positive EarlyCDT-Lung test and 3.4% (n: 18) of these were diagnosed with Lung cancer in the study period.

The number of early stage (I-II) lung cancers diagnosed in the intervention group was higher than in the control group (23 vs 19). The EarlyCDT-Lung test was positive for 12 of the 23 early cancers (sensitivity 52%) and for 6 of the 33 late stage cancers (sensitivity 18%).

Fewer participants in the intervention group were diagnosed at a late stage (III-IV) compared with the control group (33 -58.9% vs 52 -73.2%).
Primary analysis: diagnosis of stage 3/4 and unspecified lung cancers 2 years after randomisation

Hazard ratio 0.64
95% CI 0.41-0.99
The study was not powered to detect a difference in mortality, however there was a non significant trend suggesting fewer deaths in the intervention arm compared to the control (87 vs 108 respectively).

Similar results were noted relating to lung cancer specific mortality (17 vs 24).
Conclusions

The results show that the combination of the EarlyCDT-Lung followed by CT imaging in those with a positive blood test, results in a significant decrease in late stage diagnosis of lung cancer and may decrease all cause and lung cancer specific mortality.

Blood Based biomarker panels such as the Early CDT Lung test may have an important role in future lung cancer screening programme.

Large community based studies required to determine role of a high specificity biomarker & low dose CT scans
- **Tumour markers (TM).** We have published:
  - the use of a combined panel of six circulating TM (CYFRA 21-1, SCC, CA 15.3, CEA, ProGRP, NSE) improves significantly the diagnostic performance of a traditional clinical model that includes tumor size, age and cumulative smoking.

Blood microRNA assay and LDCT reduce unnecessary LDCT repeats in lung cancer screening: results of bioMILD trial

Ugo Pastorino, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
BioMILD trial: AIMS

- evaluate the utility of blood microRNA and LDCT for prediction of individual LC risk
- assess the feasibility and safety of longer screening intervals in subjects with double negative baseline LDCT and microRNA
- reveal potential damage of 3-year LDCT interval: stage I LC, resection rates, interval cancer
Method
At baseline “LDCT and miRNA were tested independently with blind evaluation” choosing a 3-year interval for the next repeat in participants with double negative LDCT and miRNA.

Results
From 01/2013 to 03/2016, bioMILD prospectively enrolled 4,119 volunteers. Median age 60 years, median pack-years 42” current smokers 79% and females 39%
Step 1 General socio-demographic and health questionnaire

Volunteers registered
N = 9735

Eligible
N = 4909

Enrolled
N = 4119

Inclusion Criteria:
• Aged 50-75 years
• Smoking stop ≤ 10 years
• ≥30 pack-years

Exclusion Criteria:
• Cancer diagnosis <5 years ago
• Lung nodules under surveillance
• CT examination <1 year ago

Not recruited:
• No consent
• Personal and health problems
• Inclusion criteria violated

• spirometry (FEV1)
• monoxide (CO)
Risk outcome

<table>
<thead>
<tr>
<th>LDCT INTERVAL</th>
<th>2neg</th>
<th>1pos</th>
<th>2pos</th>
</tr>
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<tbody>
<tr>
<td>0-112 mm³</td>
<td>2384</td>
<td>1526</td>
<td>209</td>
</tr>
<tr>
<td>3Y</td>
<td>58%</td>
<td>37%</td>
<td>5%</td>
</tr>
<tr>
<td>1Y</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3-6M</td>
<td></td>
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**LDCT**

**miRNA**

**LDCT INTERVAL**

**miRNA**

**Risk outcome**

- **2neg**: 0-112 mm³ negative
- **1pos**: ≥ 113 mm³ Ind / pos
- **2pos**: ≥ 260 mm³ Ind / pos

**AND**

**OR**

**AND**

*Ugo Pastorino, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
Results

After four screening runs (LDCT 0/1/2/3) a total of 115 LCs were diagnosed (2,8%).

Cumulative LC incidence was significantly different in the three groups:
0,6% for 2neg subjects;
3,8% for 1pos and
20,1% for 2pos (p<00001).

LC mortality was 0,1%, 0,6% and 3,8% respectively (p<0.0001).
<table>
<thead>
<tr>
<th></th>
<th>Lung Cancer incidence HR* (95%CI)</th>
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<tbody>
<tr>
<td>2neg</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>1pos</td>
<td>5.96 (3.38-10.52)</td>
</tr>
<tr>
<td>2pos</td>
<td>36.64 (20.31-66.11)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex and pack-years.

Log-rank test 2neg vs. 1pos <0.0001
Log-rank test 1pos vs. 2pos <0.0001
Lung Cancer mortality
HR* (95%CI)

<p>| | |</p>
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</thead>
<tbody>
<tr>
<td>2neg</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>1pos</td>
<td>4.67 (1.26-17.24)</td>
</tr>
<tr>
<td>2pos</td>
<td>32.24 (8.55-121.60)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex and pack-years.

Log-rank test 2neg vs. 1pos 0.0103
Log-rank test 1pos vs. 2pos <0.0001

Ugo Pastorino, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
TAKE HOME MESSAGE

No detrimental effect was observed on the proportion of stage I LC, resection rates, or interval cancers in double negatives subjects sent to a 3-year repeat CT scan (FU 4.2 years), so the combination of blood microRNA assay and baseline LDCT is a valuable and safe way to define screening intensity and reduce unnecessary LDCT repeats (Harry J de Koning)

Knowledge of individual biologic risk by microRNA and LDCT improves the efficacy of screening, and should guide future preventive strategies

Personalized prevention is now a real option
Under a 40% lung screening coverage/update, lung screening would prevent ~320 per 100K lung cancer deaths and lead to ~4,860 life-years gained (LYG) per 100K for the US 1950 birth cohort.

Adding a cessation intervention at the time of first screen with a 10% success probability, would increase these gains (~18% increase in lung cancer deaths and ~84% increase in LYG)

Modeling suggests that risk based screening programs lead in general to higher mortality reductions than pack-year based strategies, although with comparable Life-years gained

Simulation modeling continues to play a key role in shaping lung screening interventions in the US and elsewhere
Conclusions – Take home messages

- Modeling has played a key role in the adoption/implementation of lung cancer screening in the US
  + Canada, Netherlands, UK, etc

- Multiple areas:
  + Projection of burden, eligibility, impact
  + Extrapolation of trial results to the whole population
  + Interaction with cessation interventions
  + Cost-effectiveness (e.g. Kong et al, Annals Intern Med, in press)

- Need for country-specific analyses to translate impact to the local context
OPEN SOURCE ERA

• I-ELCAP anticipated the “open science” era:
  
  — Provided the ELCAP Management System free of charge to all participating institutions
  
  — Helped implement screening at 80 institutions around the world
  
  — Provided conferences every 6 months for all I-ELCAP investigators and others around the world

• ELCAP Management System has transitioned to an “open source” system

doi: https://doi.org/10.17226/25116

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VAPALS-ELCAP Management System

• Incorporates the knowledge gained in the past 20 years of screening practice
• Has been tested in many institutions
• “open-source” VAPALS-ELCAP Mgt. System has received the highest OSHERA certification
• Will now be tested at the alpha site in Phoenix AZ
• Then beta-tested at several other sites

Provides a common set of data elements and common terminology
• Allows for routine quality assurance reporting for all participating VA sites
• Will provide data for updating of the enrollment and workup requirements in the context of the VA services to Veterans
• Will SAVE LIVES
Among 14,018 never smokers: 6,733 women and 7,276 men
Noncalcified Nodules of any size were seen in 37.4%; >6.0 mm seen in 6.9%

Lung cancer was diagnosed in 55 (0.4%), 85.5% clinical stage I
Adenocarcinoma in 44, squamous in 7, small-cell in 1, other in 3
Prevalence of lung cancer was significantly associated with:
Extent of secondhand smoke exposure
Coronary artery calcifications (p<0.001),
Emphysema on CT (P=0.03)
Abnormal pulmonary function tests (p=0.04)
Increased main pulmonary artery to aortic ratio (p=0.009)

**Conclusion**

These results suggest that LDCT screening is of benefit for never smokers exposed to smoke exposure for identification of early lung cancer, cardiovascular disease and emphysema.
Take home message

• COPD and emphysema are highly prevalent in smokers undergoing LC screening
• Emphysema is a strong biomarker for LC risk prediction
• Centrilobular – not paraseptal – emphysema is associated with a 2-3 fold increased risk for LC
• Emphysema on baseline LDCT can help select individuals who should continue with annual screenings
The Greatest Lung Cancer Breakthrough of Our Time

Raja M Flores, MD
Professor and Chairman
Department of Thoracic Surgery
Icahn School of Medicine at Mount Sinai
New York, New York, USA
Big Business
Cancer Drugs $$$ /yr

$100 billion
% OF CANCERS DIAGNOSED BEFORE THEY HAVE SPREAD
We have a cure for cancer: Surgery

R. Flores, New York, USA
Screening Evidence

NLST, I-ELCAP, NELSON...
Final Thought

Early 1900’s - Cervical cancer #1 cancer killer of women
PAP screening

Early 2000’s – Lung cancer #1 Killer
CT screening
Our Mission

CT Screening to do for Lung Cancer what Pap Smear Screening did for Cervical Cancer
THANK YOU VERY MUCH FOR YOUR ATTENTION!!