CURRENT STATUS OF LUNG CANCER SCREENING

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elcc2016.org

DISCLOSURE SLIDE

Nothing to disclose

15 YEARS OF LDCT SCREENING:

CONSISTENT DETECTION RATES HIGH FREQUENCY OF STAGE I MINIMALLY INVASIVE APPROCH

		screened	positive CT	LC	stage I
non RCT	16	71,935	21%	1.0%	78%
all RCTs	8	44,629	23%	1.1%	62%
NLST alone		26,309	25%	1%	63%

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BEST PERFORMANCE: WHAT IS A POSITIVE LDCT ?

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.
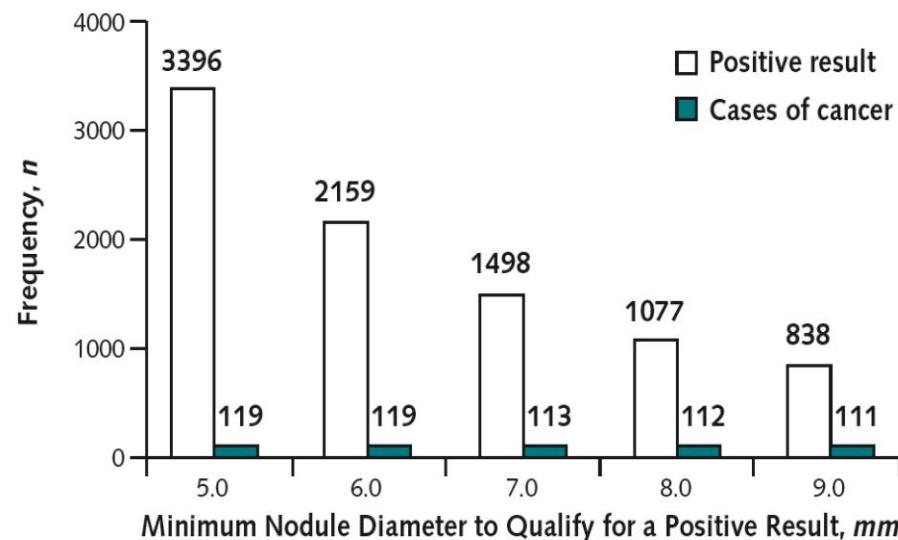
BEST PERFORMANCE: HOW TO ASSESS GROWTH ?

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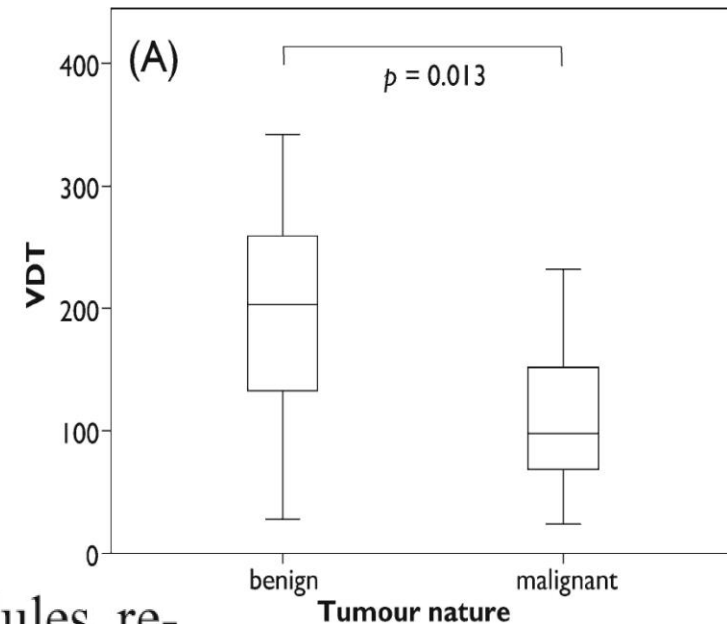
Conclusion All malignant fast-growing lung nodules referred after the 3-month follow-up CT in the baseline lung cancer screening round had VDT ≤232 days. Lowering the VDT cutoff may reduce false-positive referrals.

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DIFFERENTIAL DIAGNOSIS: IS PET SCAN USEFUL ?

Surgery for benign disease

DLCST 2012	**32%**
LUSI 2012	**29%**
NELSON 2009	**27%**
DANTE 2009	**24%**
NLST 2011	**24%**
MILD 2012	**8%**

LDCT INTENSITY: HOW OFTEN TO SCREEN ?

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CHEST

Low-dose computed tomography for lung cancer screening: comparison of performance between annual and biennial screen

Nicola Sverzellati[1] · M. Silva[1] · G. Calareso[2] · C. Galeone[3] · A. Marchianò[2] · S. Sestini[4] · G. Sozzi[5] · U. Pastorino[4]

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.*

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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.
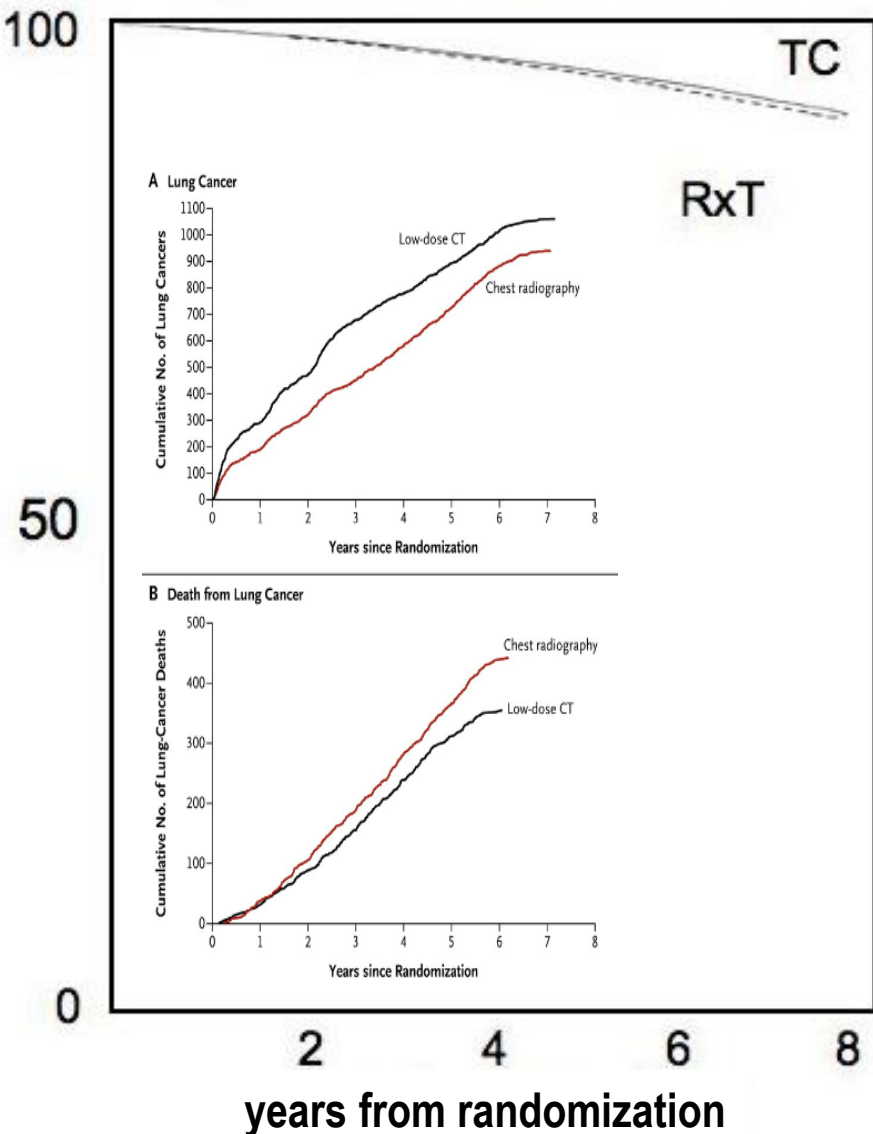
250,000 individuals approached aged 50 – 75 years
LC risk ≥5% over 5 years

>3 mm (or 15 mm^3)	LDCT at 1 yr
>5 mm (or 50 mm^3)	LDCT at 3 mos

VDTcut-off 400 days

2,000 LDCT screened
2.1% LC detection rate

Field JK, *et al*. *Thorax* 2016;**71**:161–170.

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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

Aberle DR,. N Engl J Med 2011
Patz EF., JAMA 2013

EUROPEAN RCTs: NO EVIDENCE OF MORTALITY REDUCTION

Results of the randomized Danish Lung Cancer Screening Trial with focus on high-risk profiling

Running head: Results of the Danish Lung Cancer Screening Trial

Authors
Mathilde MW Wille, PhD[1,2]; Asger Dirksen, DMSc[1]; Haseem Asraf, PhD[3,1]; Zaigham Saghir, PhD[4]; Karen S Bach, M.D.[5]; John Brodersen, PhD[6]; Paul F Clementsen, DMSc[1,7]; Hanne Hansen, M.D.[8]; Klaus R Larsen, PhD[4]; Jann Mortensen, DMSc[9]; Jakob F Rasmussen, PhD[6]; Niels Seersholm, DMSc[1]; Birgit G Skov, DMSc[10]; Laura H Thomsen, PhD[1]; Philip Tønnesen, DMSc[11]; Jesper H Pedersen, DMSc[12]

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

Maurizio Infante, MD[1], Silvio Cavuto, DSc[2], Fabio Romano Lutman, MD[3], Eliseo Passera, MD[4], Maurizio Chiarenza, MD[5], Giuseppe Chiesa, MD[4], Giorgio Brambilla, MD[3,] Enzo Angeli, MD[6], Giuseppe Aranzulla, MD[7], Arturo Chiti, MD[8], Marta Scorsetti, MD[9], Pierina Navarria, MD[9], Raffaele Cavina, MD[10], Michele Ciccarelli, MD[11], Massimo Roncalli, MD, PhD[12], Anna Destro, PhD[12], Edoardo Bottoni, MD[1,] Emanuele Voulaz, MD[1], Valentina Errico, MD[1], Giorgio Ferraroli, MD[1], Giovanna Finocchiaro, MD[10], Luca Toschi MD[10], Armando Santoro, MD[10], Marco Alloisio, MD[1]. For the DANTE Study Group.

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IASLC

ORIGINAL ARTICLE

Screening with Low-Dose Computed Tomography Does Not Improve Survival of Small Cell Lung Cancer

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Mario Silva, MD,[a,d,*] Carlotta Galeone, PhD,[b]
Alfonso Marchianò, MD,[c] Giuseppina Calareso
Carlo La Vecchia, MD,[b] Gabriella Sozzi, PhD,[e]
Ugo Pastorino, MD[d]
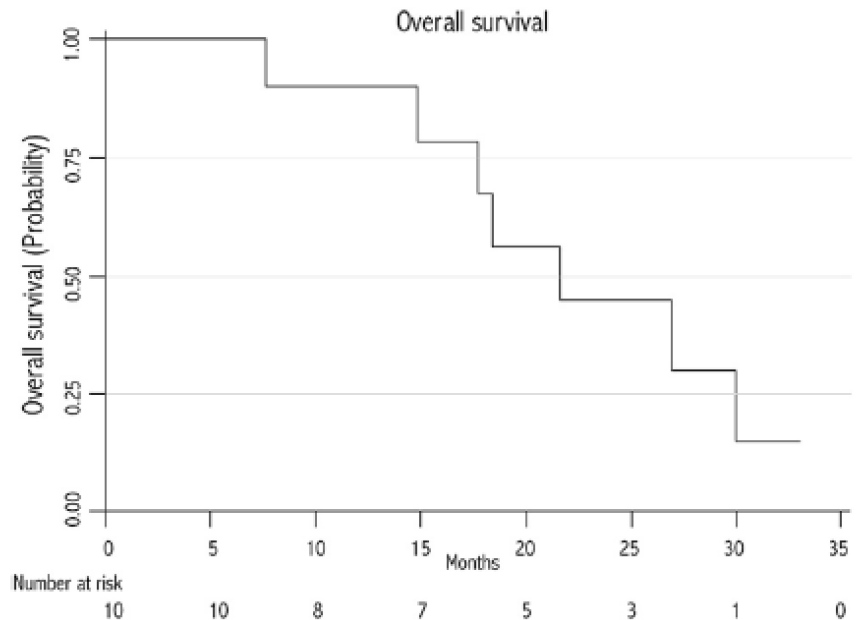
Figure 3. Overall survival curve shows no survivors at 3 years after diagnosis of SCLC.

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OVERDIAGNOSIS: HOW BIG IS THE PROBLEM ?
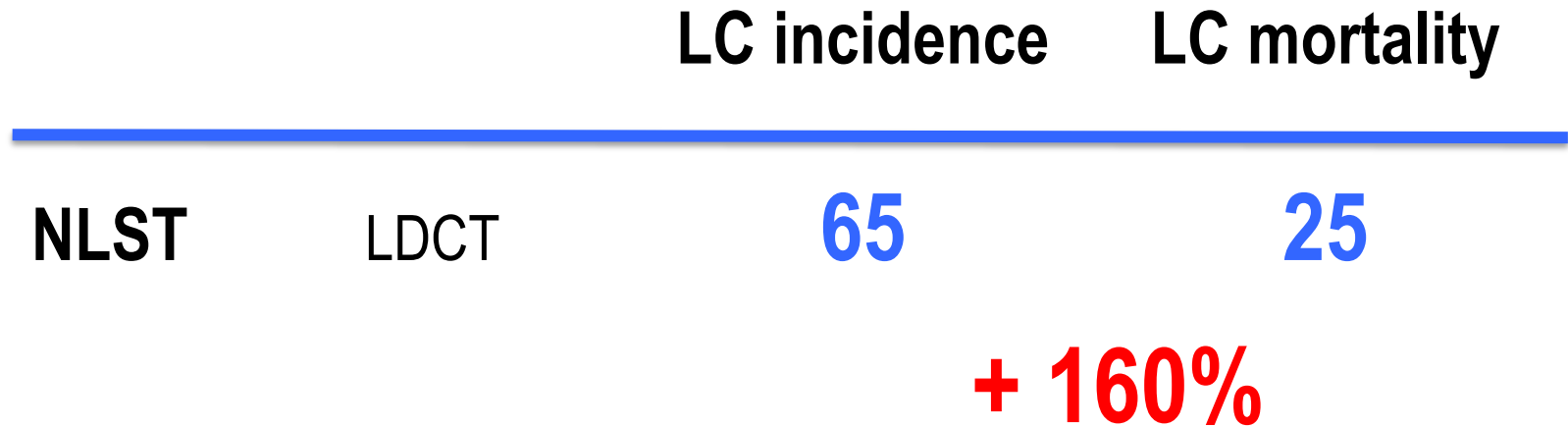
		LC incidence	/10,000 PY
NLST	LDCT	**65**	**+ 14%**
	CR	**57**	

N Engl J Med 2011, 365:395

OVERDIAGNOSIS: HOW BIG IS THE PROBLEM ?

		LC incidence	LC mortality
NLST	LDCT	**65**	**25**

+ 160%

N Engl J Med 2011, 365:395

OVERDIAGNOSIS: HOW BIG IS THE PROBLEM ?

		LC incidence	LC mortality
NLST	LDCT	65	25
	CR	57 **+ 84%**	31
PLCO*	CR	61	36
	Observation	61 **+ 60%**	38

* subset of 30,321 participants eligible for NLST trial

N Engl J Med 2011, 365:395

JAMA 2011, 306:1865

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NON SOLID LESIONS: IS IT WORTH TO RESECT THEM ?

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
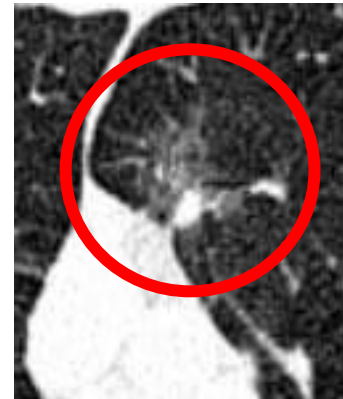
J Thor Oncol 7:1541, 2012

LARGE SCALE SCREENING: WHICH IS THE BEST DESIGN ?

POOLED ANALYSIS ESSENTIAL

Lung cancer screening: European randomised LDCT trials

Study	Country	Year started	Subjects enrolled	Recruitment	Age	# CT	Years screening
DANTE	IT	2001	2,811	volunteers	60-74	5	5
NELSON	NL–B	2003	15,822	registry	50-74	3	4
ITALUNG	IT	2004	3,206	GPs	55-69	4	4
DLCST	DK	2004	4,104	volunteers	50-70	5	5
MILD	IT	2005	4,099	volunteers	49-75	4-8	8
LUSI	D	2007	4,052	population	50-69	5	5
UKLS	UK	2011	4,055	registry	50-75	1	1
Total			**38,149**				

LC BIOLOGY: TRANSLATIONAL RESEARCH IN LDCT

LDCT screeening cohorts at INTM

2000	**INT-IEO** pilot trial:	1,035	14,000 PY
2005	**MILD** randomized:	2,376	20,000 PY
2013	**bioMILD** miRNA + LDCT:	4,100	6,000 PY
	Total LDCT participants	**7,500**	**40,000 PY**

blood & tissue
samples frozen - 80°   > 100,000
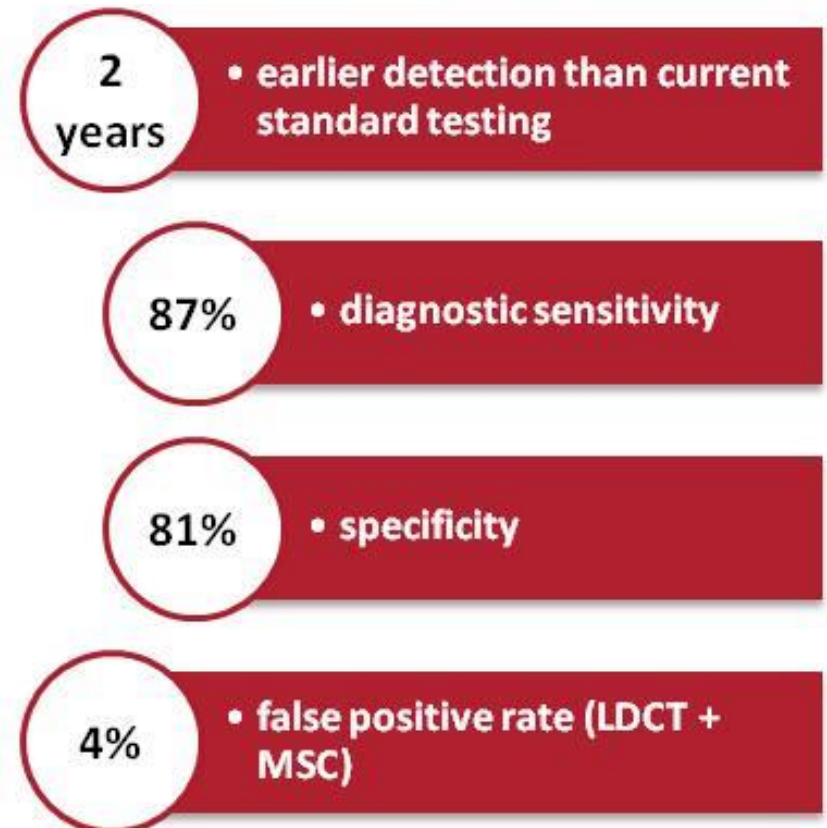
LC BIOLOGY: CAN BIOMARKERS IMPROVE SCREENING ?

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

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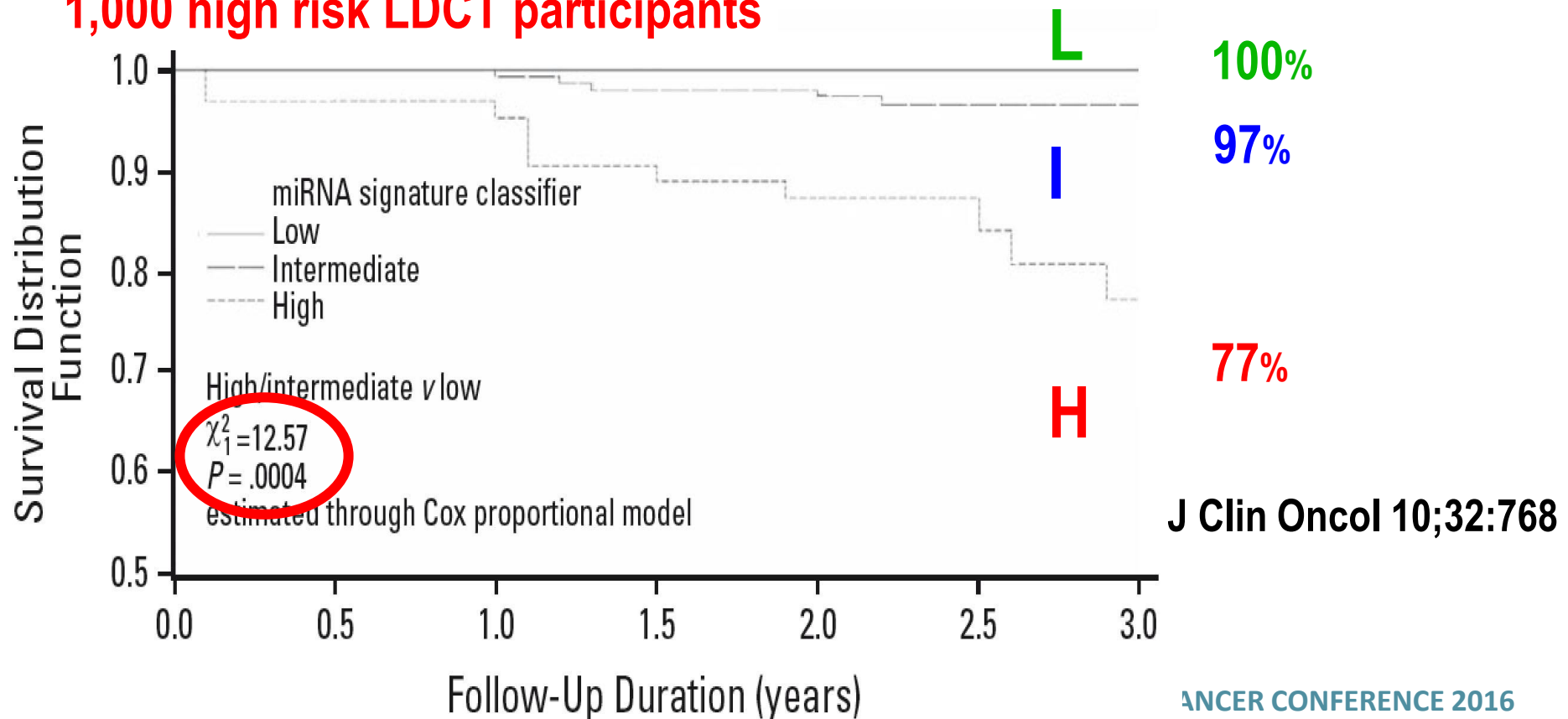vs. 96.4% in NLST**

J Clin Oncol 10;32:768

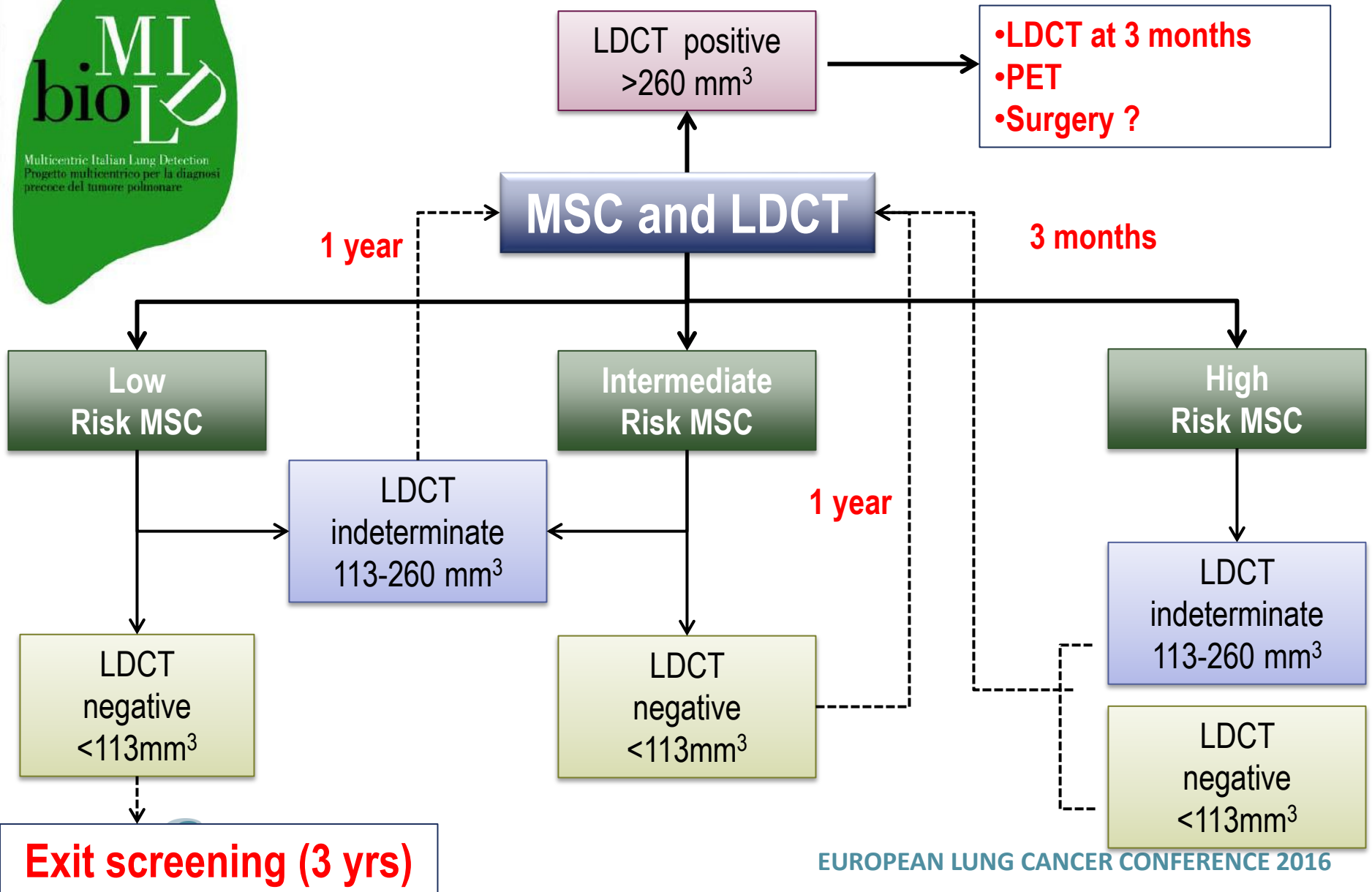|	
2 years	• earlier detection than current standard testing
87%	• diagnostic sensitivity
81%	• specificity
4%	• false positive rate (LDCT + MSC)

LC BIOLOGY: CAN BIOMARKERS IMPROVE SCREENING ?

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

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

L   **100%**

I   **97%**

H   **77%**

miRNA signature classifier
— Low
-- Intermediate
··· High

High/intermediate *v* low
$\chi^2_1 = 12.57$
$P = .0004$
estimated through Cox proportional model

Survival Distribution Function

Follow-Up Duration (years)

J Clin Oncol 10;32:768

MIRNA + LDCT: BIOMILD TRIAL ON 4,000 SUBJECTS

WHY SO LITTLE EFFECT: LC IS A MINOR CAUSE OF DEATH

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

Michael J. Thun, M.D., Brian D. Carter, M.P.H., Diane Feskanich, Sc.D.,
Neal D. Freedman, Ph.D., M.P.H., Ross Prentice, Ph.D., Alan D. Lopez, Ph.D.,
Patricia Hartge, Sc.D., and Susan M. Gapstur, Ph.D., M.P.H.

956,761 COHORT, AGE 55-85, 56% EVER SMOKERS

% DEATHS	MALES	FEMALES
CURRENT	21%	20%
FORMER	10%	9%
NLST	23%	

NEW EVIDENCE: DRUG INTERVENTION WORKS

efficacy of varenicline

187 MILD subjects, on LDCT screening > 5 yrs

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

Paolo Pozzi[1], Elena Munarini[1], Francesca Bravi[2], Marta Rossi[2,3], Carlo La Vecchia[2,3], Roberto Boffi[1], Ugo Pastorino[4]

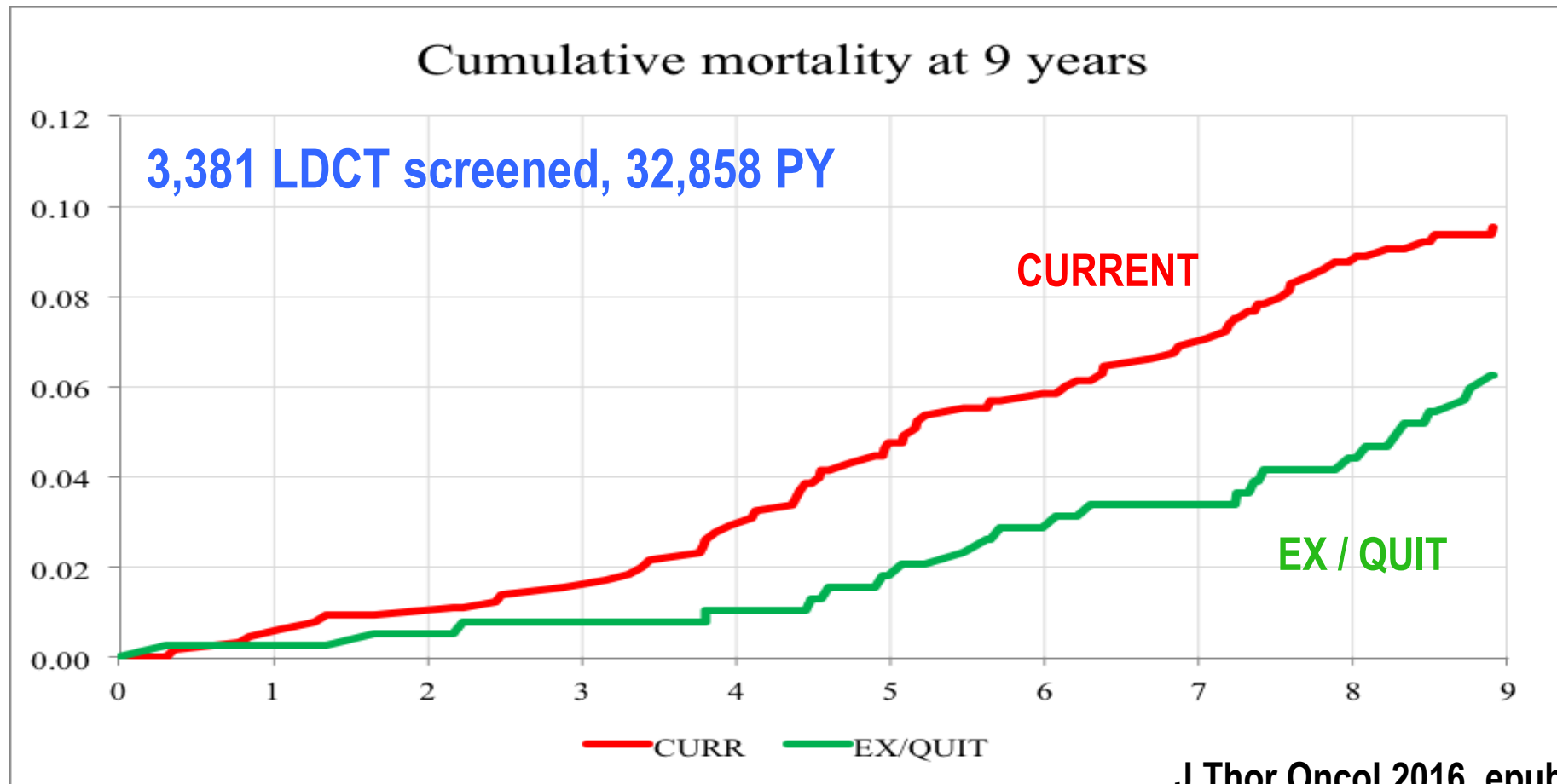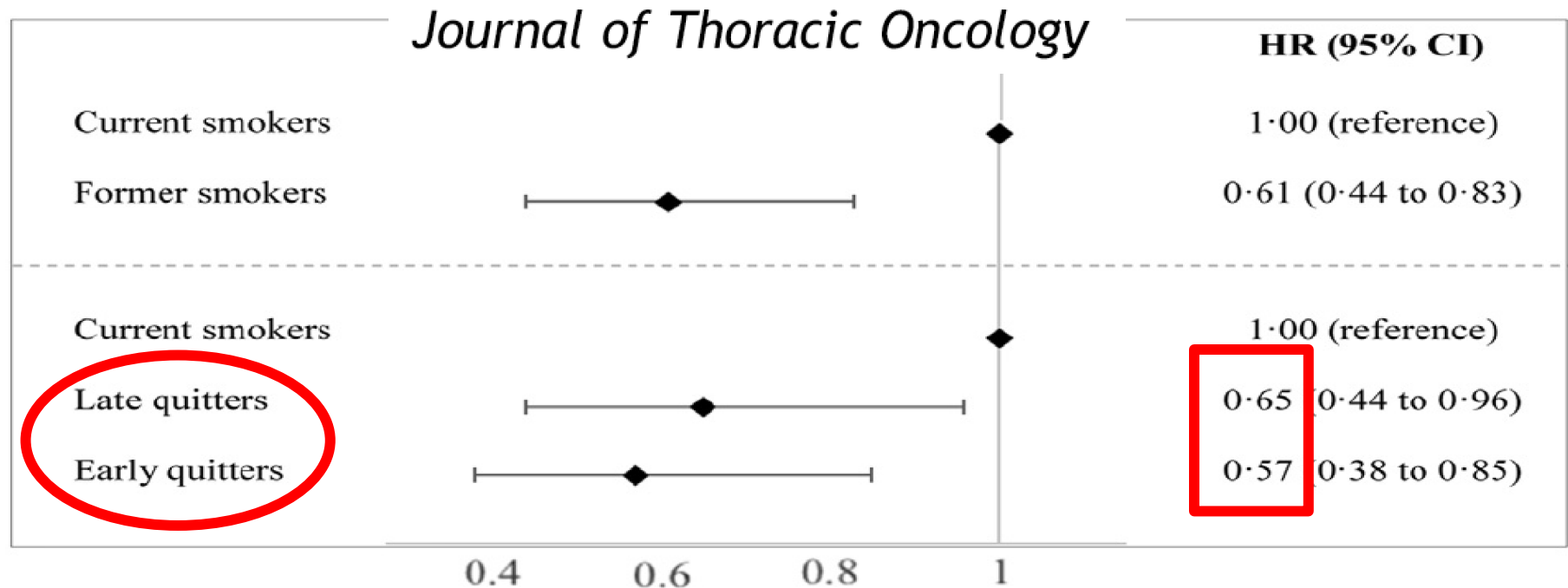| quitting rate after one varenicline treatment:	3 mos	12 mos
	49%	**20%**

NEW EVIDENCE: QUITTING IN LDCT IS EFFECTIVE

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

Cumulative mortality at 9 years

3,381 LDCT screened, 32,858 PY

CURRENT

EX / QUIT

CURR — EX/QUIT

J Thor Oncol 2016, epub

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

Journal of Thoracic Oncology

	HR (95% CI)
Current smokers	1·00 (reference)
Former smokers	0·61 (0·44 to 0·83)
Current smokers	1·00 (reference)
Late quitters	0·65 (0·44 to 0·96)
Early quitters	0·57 (0·38 to 0·85)

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)

ERENCE 2016

LOST OPPORTUNITY: SMOKING ASSESSMENT IN NLST

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

Nichole T. Tanner[1,2], Neeti M. Kanodra[1], Mulugeta Gebregziabher[2,3], Elizabeth Payne[3], Chanita Hughes Halbert[2,4], Graham W. Warren[5,6], Leonard E. Egede[2,7], and Gerard A. Silvestri[1]

[1]Division of Pulmonary, Critical Care and Sleep Medicine, [3]Department of Public Health Sciences, [4]Department of Psychiatry and Behavioral Sciences, Hollings Cancer Center, [5]Department of Radiation Oncology, [6]Department of Cell and Molecular Pharmacology, and [7]Department of Medicine, Medical University of South Carolina, Charleston, South Carolina; and [2]Health 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
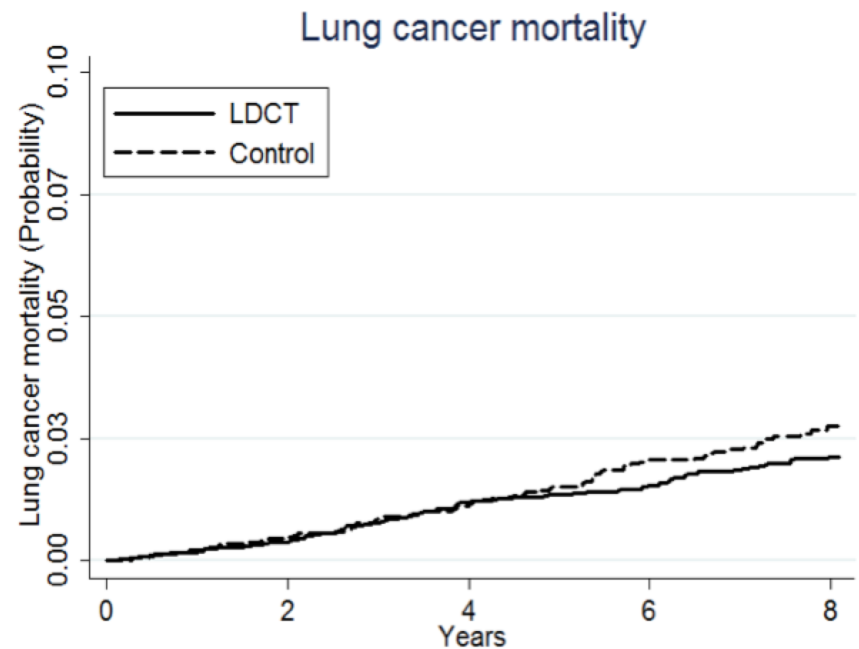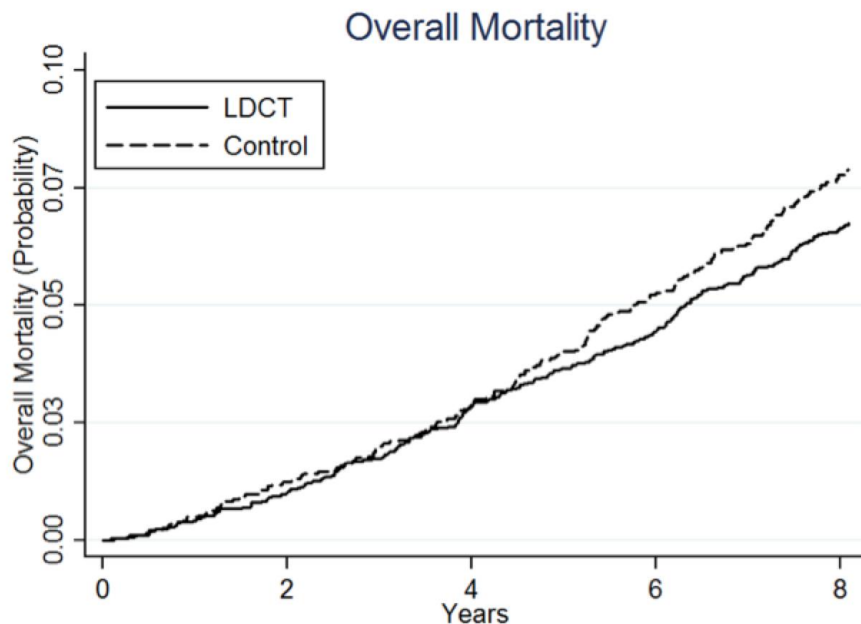
No information on quitting rate during LDCT screening and its impact on mortality

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# 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 ?

Overall Mortality - Former smokers at baseline

FORMER

Overall Mortality - Current smokers at baseline

CURRENT
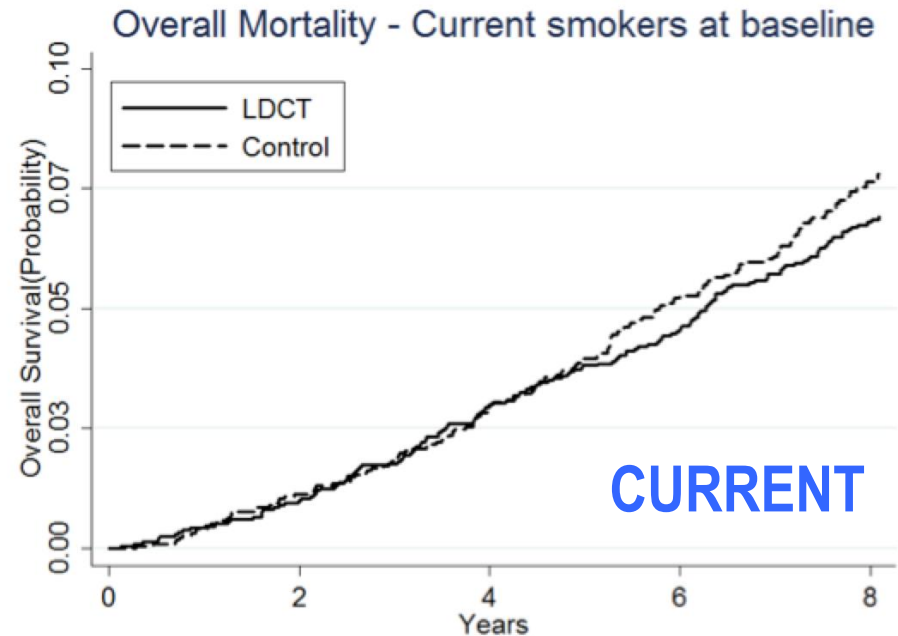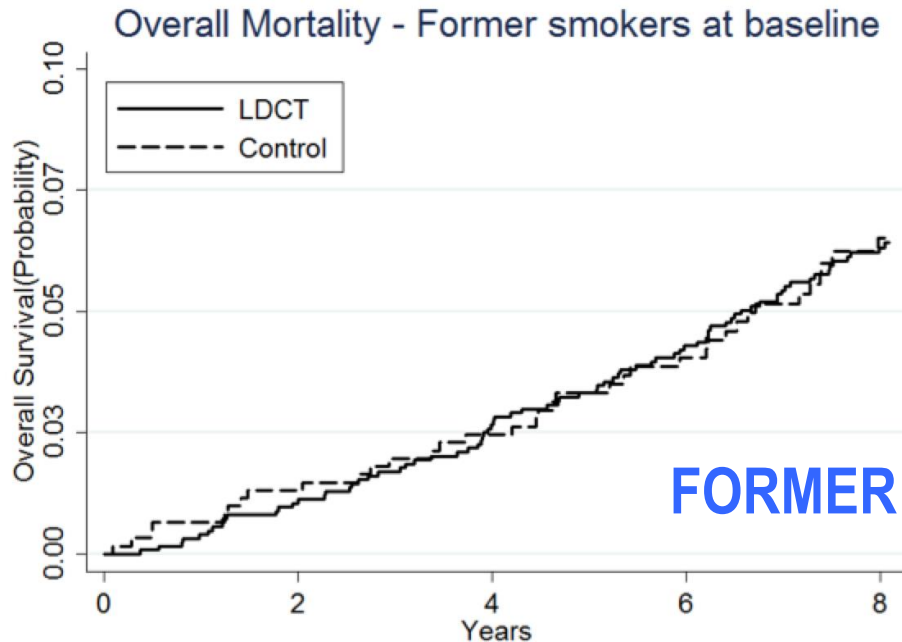
EUR J CAN PREV, IN PRESS

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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**

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SCREENING + PREVENTION: THE SMILE TRIAL
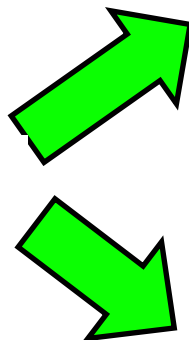

pilot study on the feasibility of integrated prevention in high risk individuals

Population:

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

1:1

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

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

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