EUROPEAN LUNG CANCER CONFERENCE 2016

DOES SCREENING HAVE ANY ROLE IN NSCLC?

No

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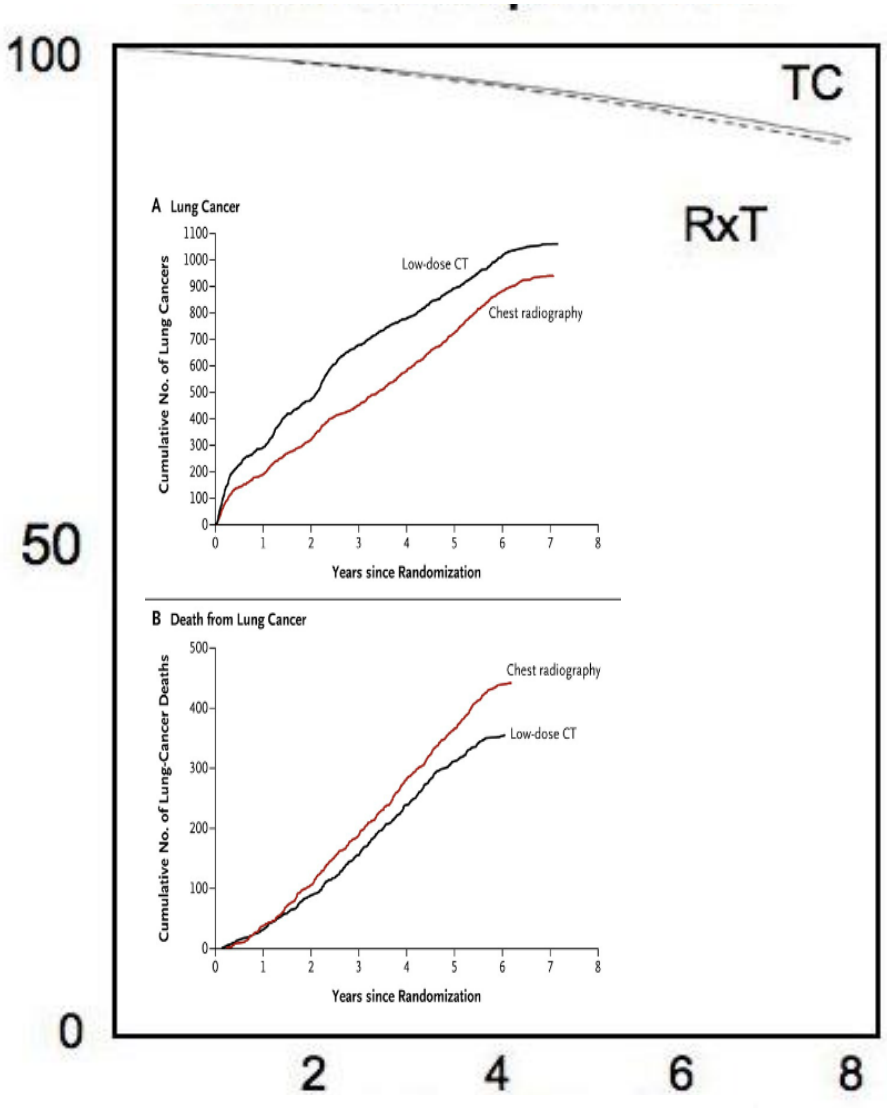
elcc2016.org

DISCLOSURE SLIDE

Nothing to disclose

WHY NOT NOW: LIMITED REDUCTION OF TOTAL MORTALITY



years from randomization

NLST trial

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

WHY NOT NOW: PRESENT RESULTS OF 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.

WHY NOT NOW: NO EFFECT ON AGGRESSIVE DISEASE

ORIGINAL ARTICLE

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 Marchianò, MD,[c] Giuseppina Calareso Carlo La Vecchia, MD,[b] Gabriella Sozzi, PhD,[e] Ugo Pastorino, MD[d]

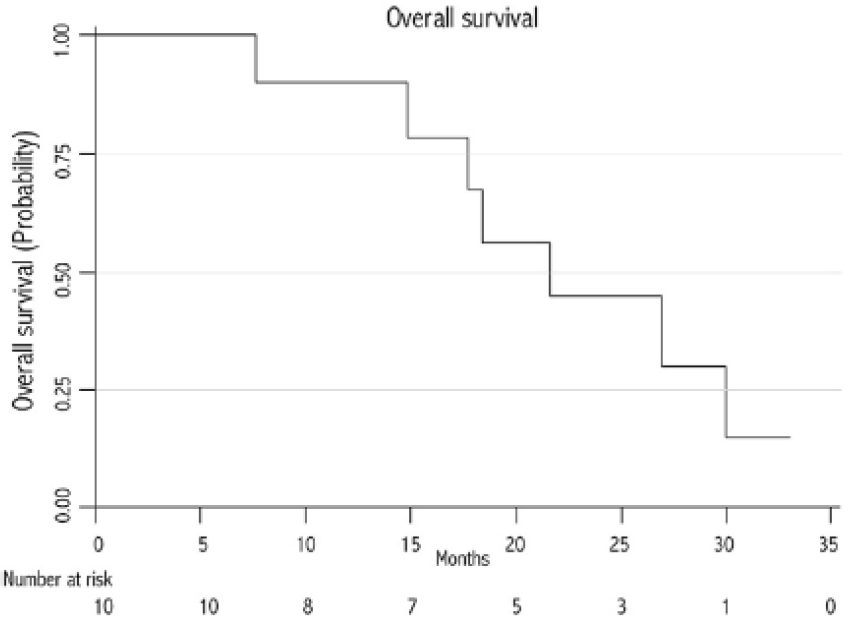


Figure 3. Overall survival curve shows no survivors at 3 years after diagnosis of SCLC.

Journal of Thoracic Oncology *Vol. 11 No. 2: 187-193*

WHY NOT NOW: 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**				

WHY NOT NOW: WHAT IS A POSITIVE LDCT ?

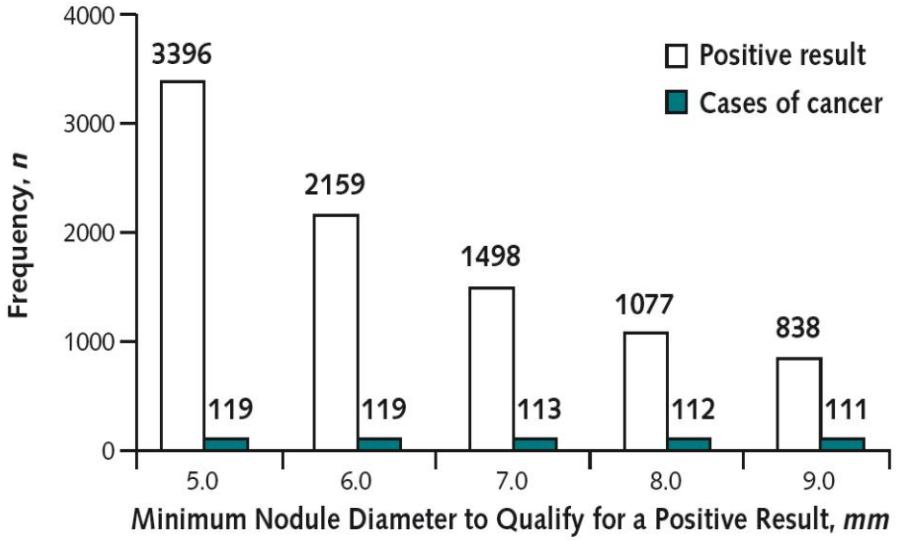
ORIGINAL RESEARCH | Annals of Internal Medicine
2013;158:246-252

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*

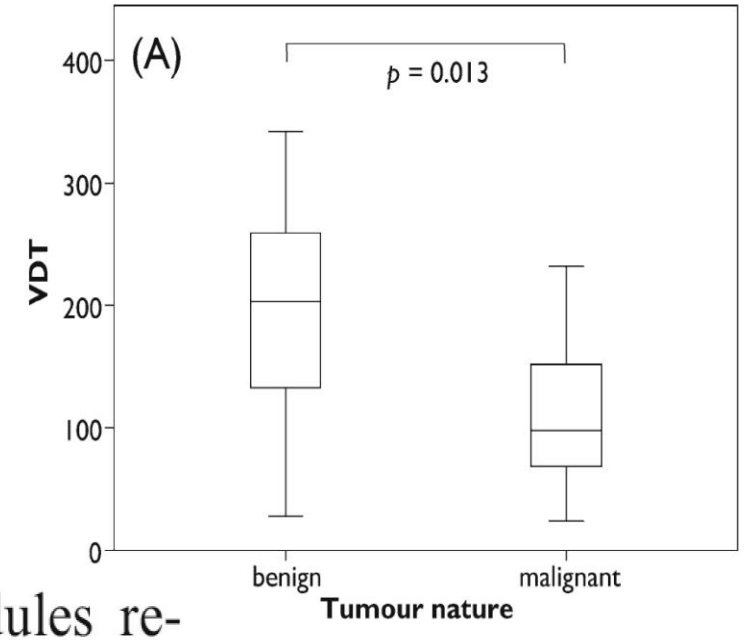
Conclusion: These findings suggest that using a threshold of 7 or 8 mm to define positive results in the baseline round of computed tomography screening for lung cancer should be prospectively evaluated to determine whether the benefits of decreasing further work-up outweigh the consequent delay in diagnosis in some patients.



WHY NOT NOW: HOW SHOULD WE 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.

Eur Radiol 2013; 23:1836–1845

WHY NOT NOW: HOW OFTEN TO SCREEN ?

Eur Radiol
DOI 10.1007/s00330-016-4228-3

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.*

Published online: 11 February 2016

WHY NOT NOW: 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.

WHY NOT NOW: 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%

WHY NOT NOW: HOW BIG IS OVERDIAGNOSIS ?

		LC incidence /10,000 PY	
NLST	LDCT	65	+ 14%
	CR	57	

N Engl J Med 2011, 365:395

WHY NOT NOW: HOW BIG IS OVERDIAGNOSIS ?

		LC incidence	LC mortality
NLST	LDCT	65	25
		+ 160%	

N Engl J Med 2011, 365:395

WHY NOT NOW: HOW BIG IS OVERDIAGNOSIS ?

		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

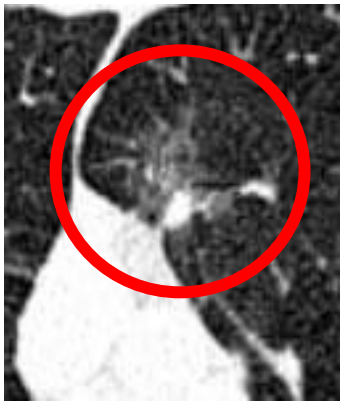
N Engl J Med 2011, 365:395
JAMA 2011, 306:1865

WHY NOT NOW: IS IT WORTH TO RESECT GGOs ?

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

WHY NOT NOW: TRANSLATIONAL RESEARCH IN LDCT

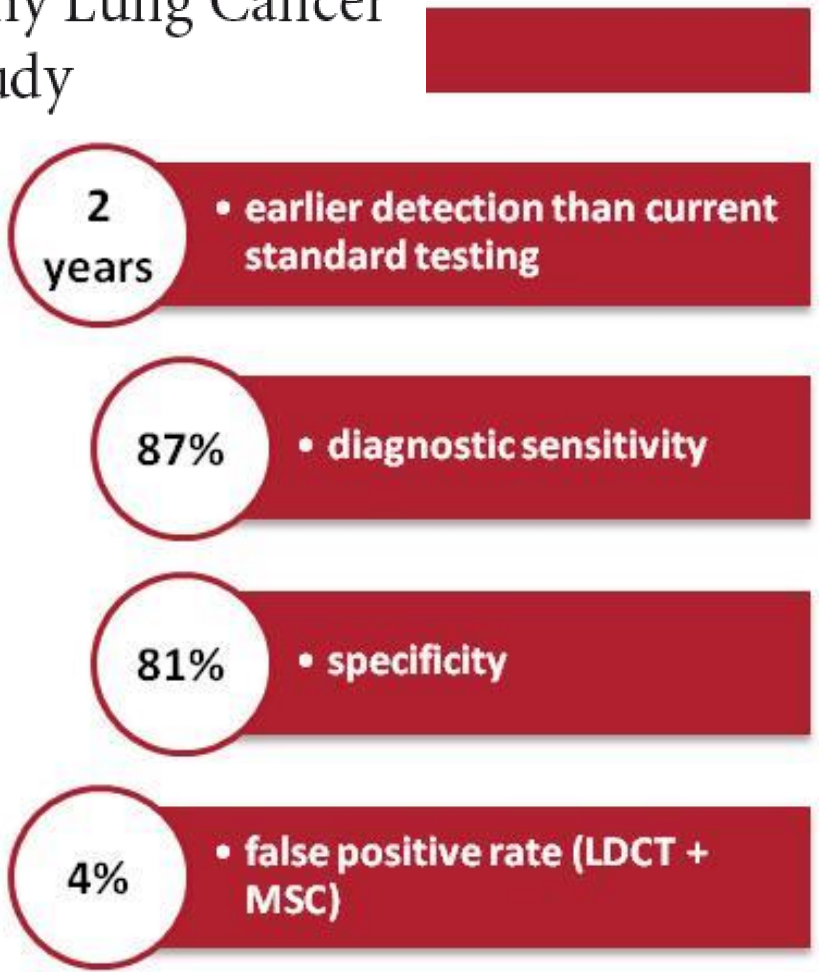
LDCT screeening cohorts at INTM

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**

WHY NOT NOW: CAN BIOMARKERS IMPROVE SCREENING ?

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



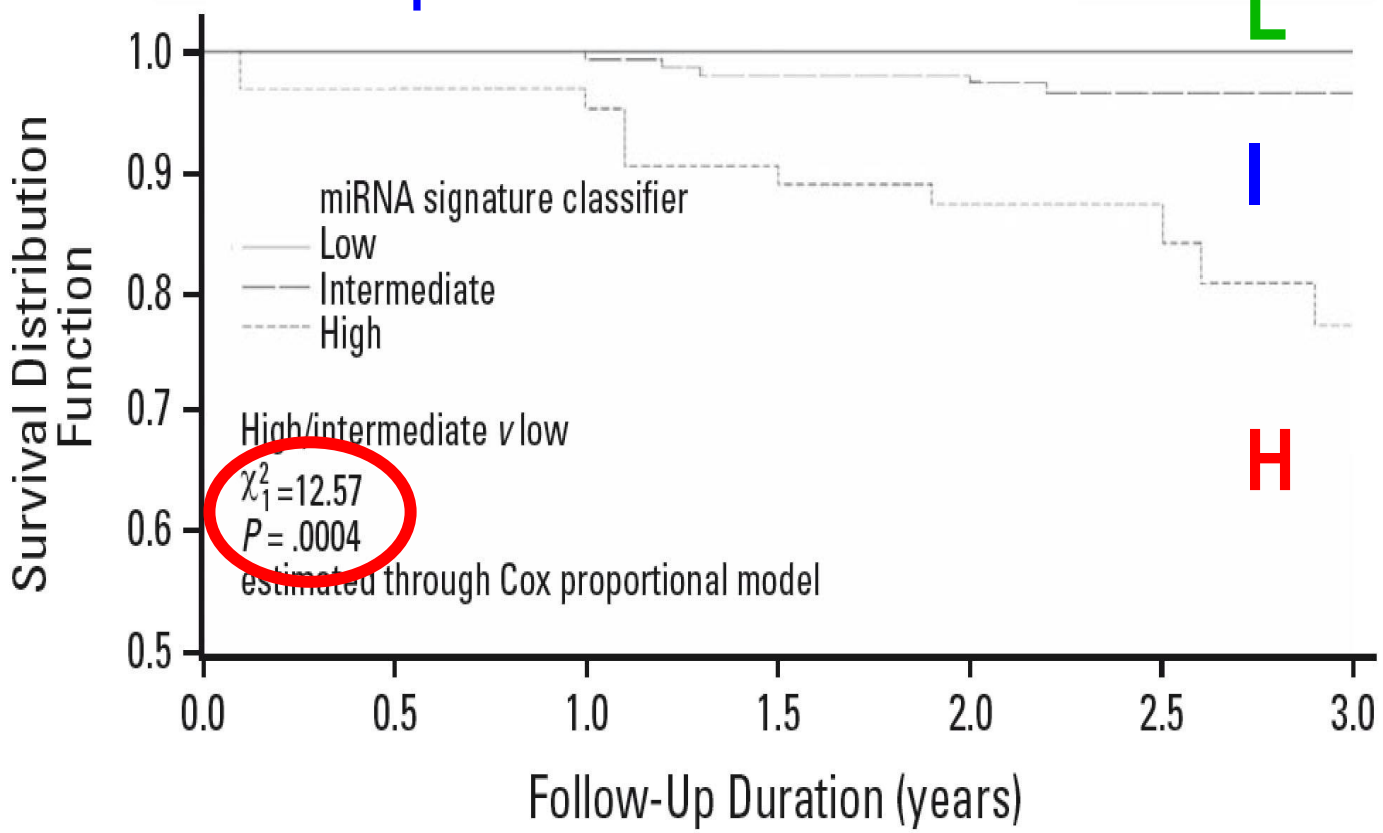
false positive rate = 4%
vs. 96.4% in NLST

J Clin Oncol 10;32:768

WHY NOT NOW: 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 predicts cohort survival



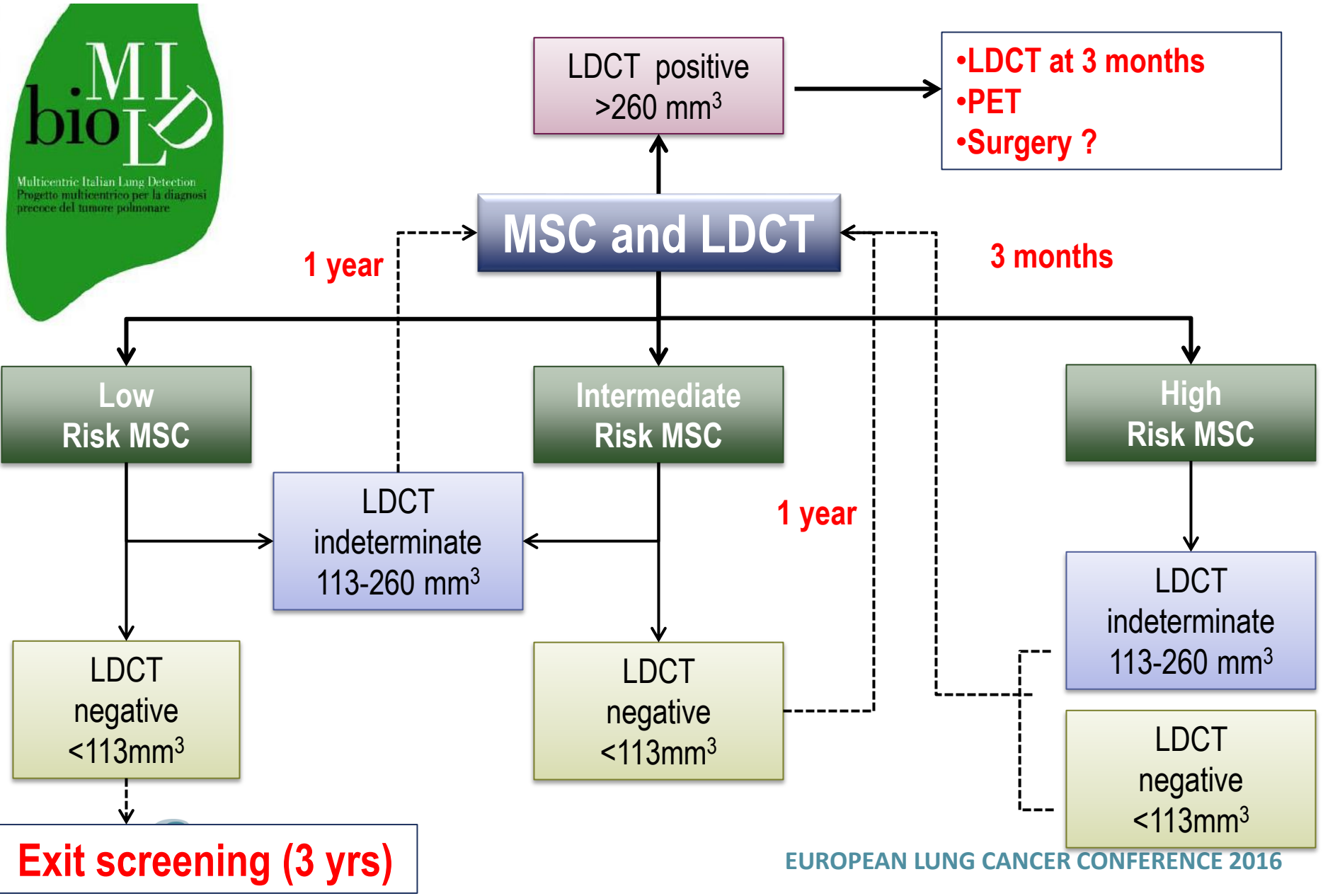
L 100%

I 97%

H 77%

J Clin Oncol 10;32:768

WHY NOT NOW: CAN BIOMARKERS IMPROVE SCREENING ?



WHY NOT NOW: LC IS NOT THE MAJOR 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%**

N Engl J Med 2013;368:351-64

WHY NOT NOW: DRUG INTERVENTION WORKS

TJ
ISSN 0300-8916

Tumori 2015; 101(3): 306-311
DOI: 10.5301/tj.5000282

ORIGINAL ARTICLE

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	3 mos	12 mos
varenicline treatment:	49%	20%

WHY NOT NOW: QUITTING MORE EFFECTIVE THAN LDCT

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

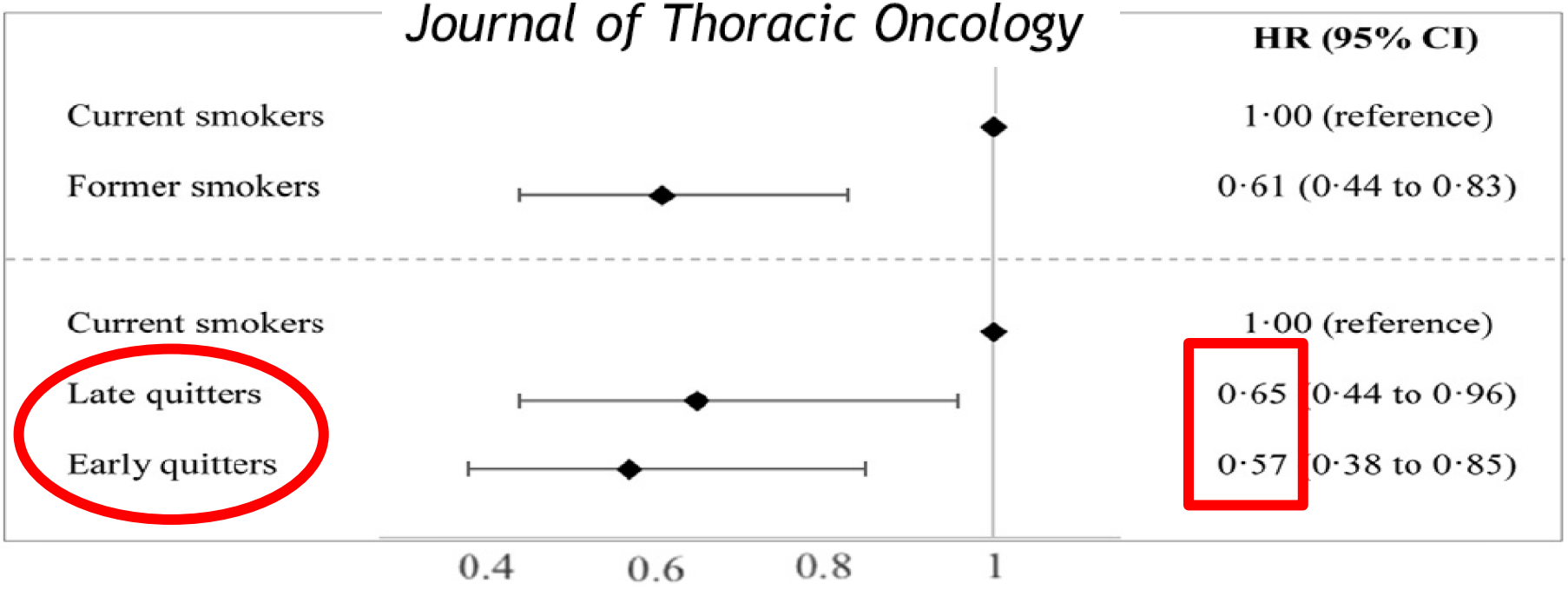


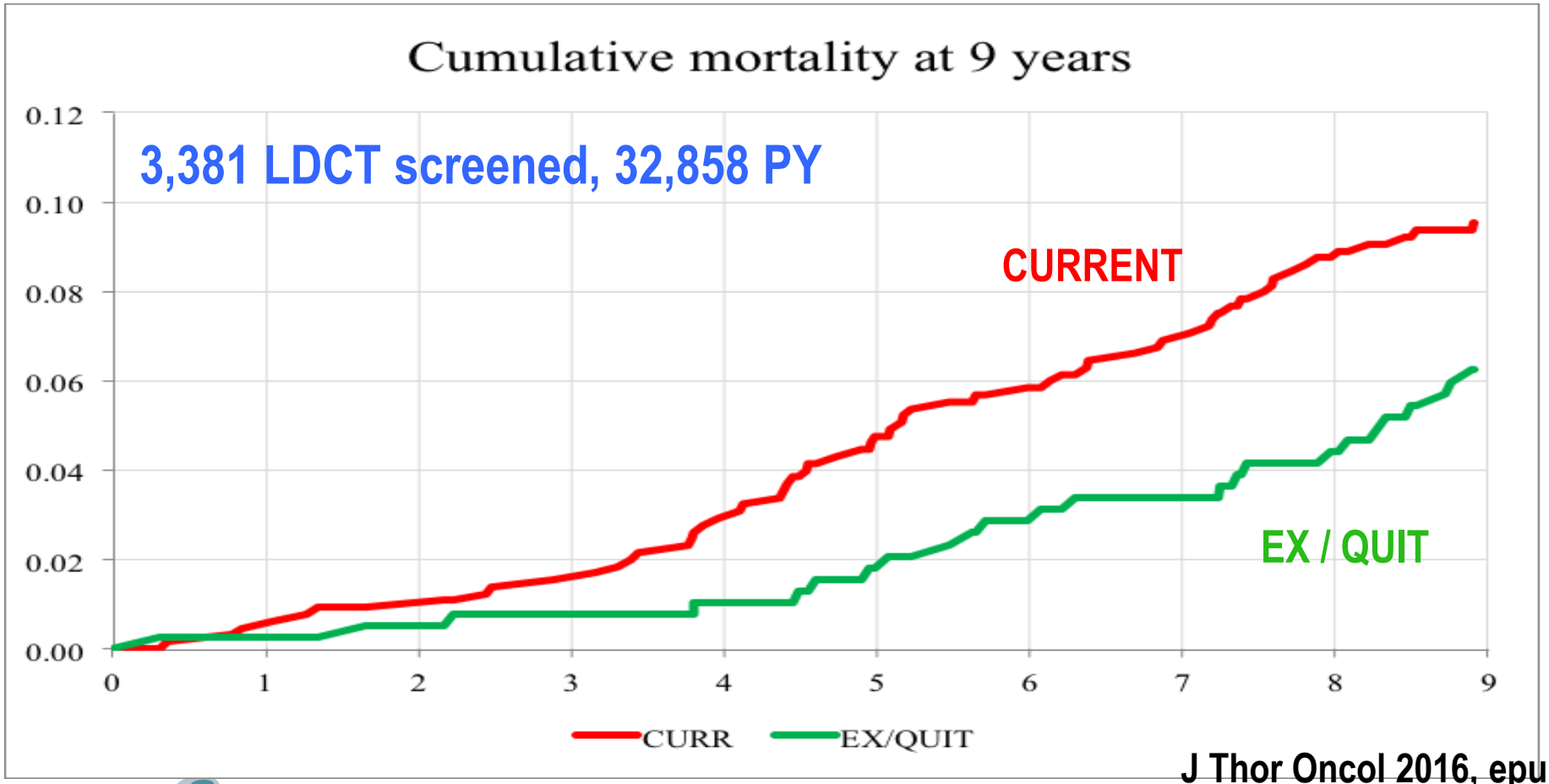
Figure 3. Effect of smoking cessation on overall mortality. Hazard ratios (Cox model) and corresponding 95% confidence intervals estimating the effect of smoking cessation on mortality. Estimates are adjusted for covariates measured at baseline (sex, age, predicted forced expiratory volume in the first second of expiration, and average number of pack-years)

elcc

ERENCE 2016

WHY NOT NOW: QUITTING IN LDCT IS EFFECTIVE

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



J Thor Oncol 2016, epub

WHY NOT NOW: QUITTING MORE EFFECTIVE THAN LDCT ?

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

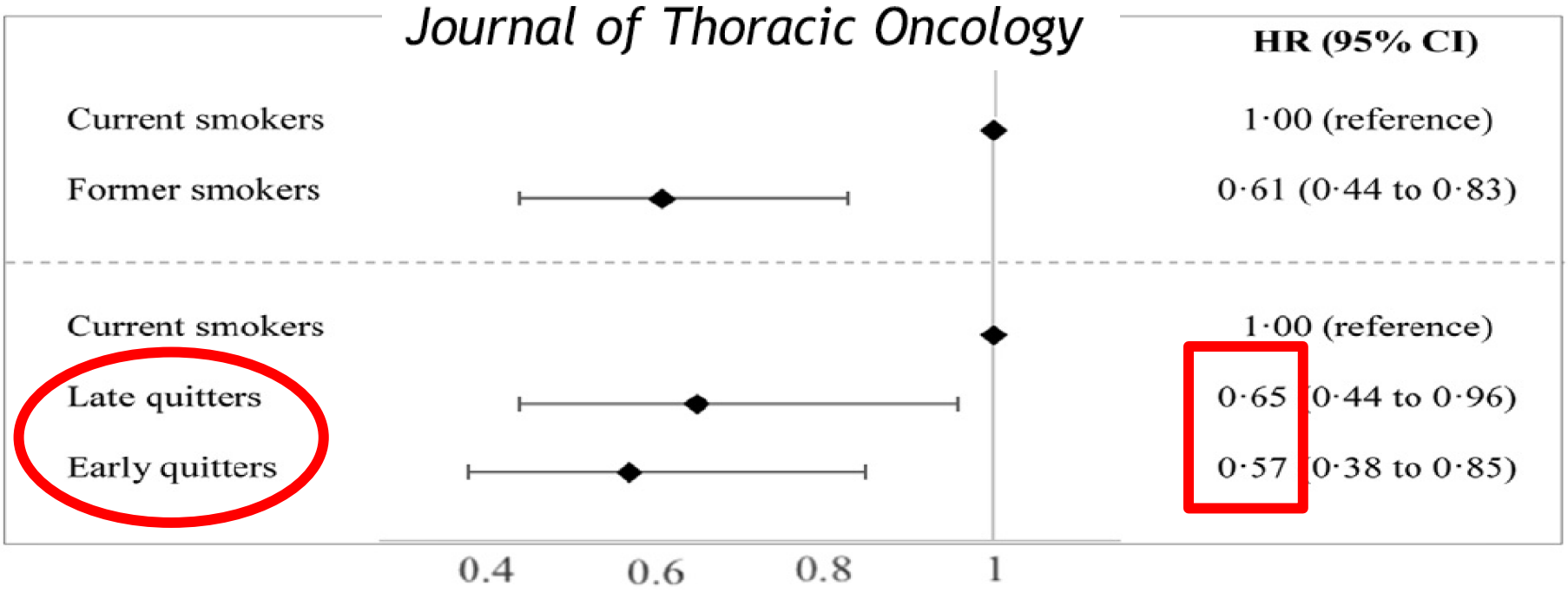


Figure 3. Effect of smoking cessation on overall mortality. Hazard ratios (Cox model) and corresponding 95% confidence intervals estimating the effect of smoking cessation on mortality. Estimates are adjusted for covariates measured at baseline (sex, age, predicted forced expiratory volume in the first second of expiration, and average number of pack-years)

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ERENCE 2016

WHY NOT NOW: SMOKING ASSESSMENT IN NLST

The association between smoking abstinence and mortality in the National Lung Screening Trial

Nichole T. Tanner

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

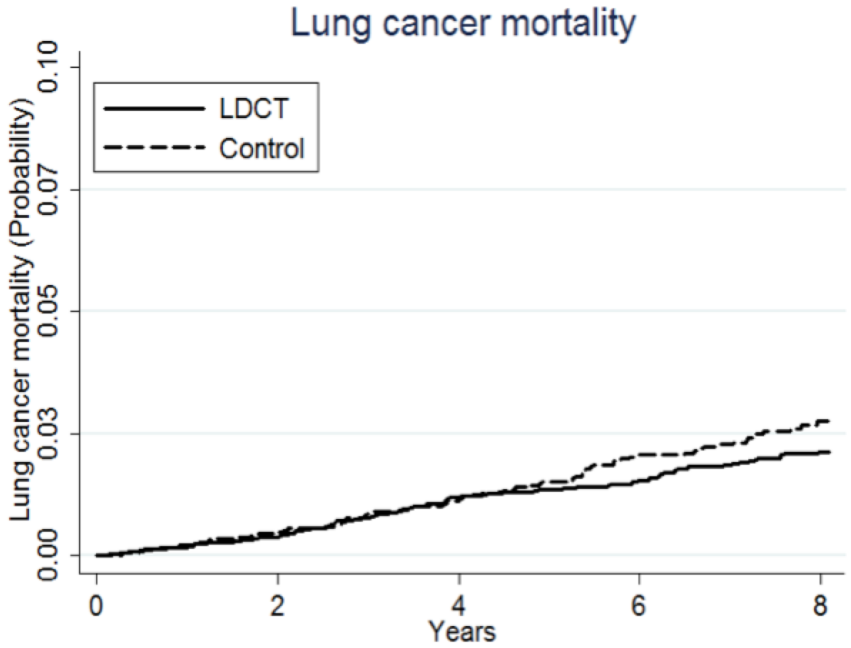
No information on quitting rate during LDCT screening and its impact on mortality

Am J Resp Crit Care Med 2016, 193: 534-541

WHY NOT NOW: 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)



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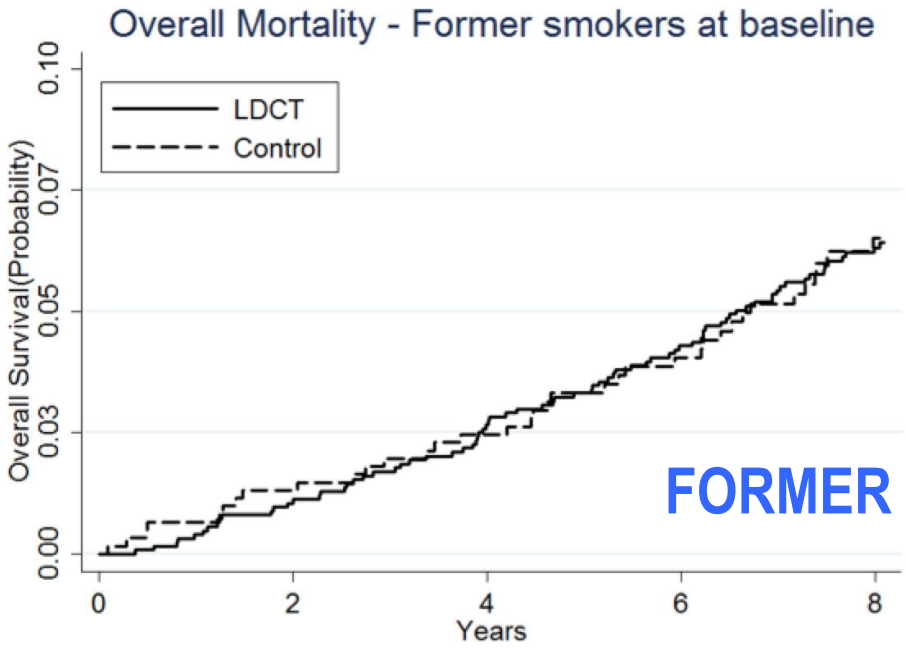
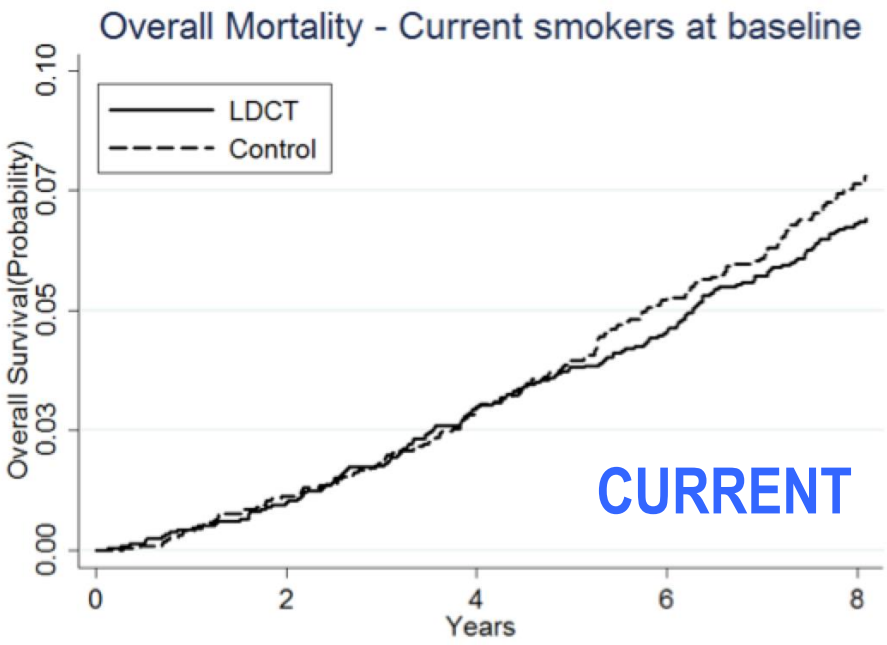
WHY NOT NOW: POOLED ANALYSIS OF DANTE & MILD

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

No reduction of overall mortality in former smokers at baseline





EUR J CAN PREV, IN PRESS

WHY NOT NOW: SUMMARY

- good prospects for targeted screening
- results of European RCTs are crucial
- optimize individual selection
- improve diagnostic algorithm
- validate biomarkers
- combine with primary prevention

WHY NOT NOW: LDCT + PREVENTION

SMILE TRIAL DESIGN

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