10-year and beyond results in the NELSON Trial

(Dutch-Belgian Lung-Cancer Screening Trial)

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- The step-wise decision-making concerning **potential new cancer screening programmes** include the establishment of evidence of effectiveness, benefits that outweigh the harms, and cost-effectiveness.

In: European Guide on Quality Improvement in Comprehensive Cancer Control (2017) by Tit Albreht, R. Kiasuwa & M. van den Bulcke

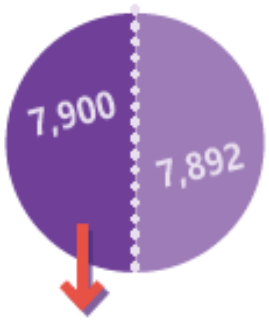
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial

H.J. de Koning, C.M. van der Aalst, P.A. de Jong, E.T. Scholten, K. Nackaerts, M.A. Heuvelmans, J.-W.J. Lammers, C. Weenink, U. Yousaf-Khan, N. Horeweg, S. van 't Westeinde, M. Prokop, W.P. Mali, F.A.A. Mohamed Hoesein, P.M.A. van Ooijen, J.G.J.V. Aerts, M.A. den Bakker, E. Thunnissen, J. Verschakelen, R. Vliegenthart, J.E. Walter, K. ten Haaf, H.J.M. Groen, and M. Oudkerk

NELSON trial



15,792 people voluntarily participated in the study. 85% of these participants are male.
The study was designed to include mainly male volunteers because of the difference in smoking behaviour in the past, but there is also relevance for women. The results that we present here are only about men. Those of the women follow in more detail.

The participants were randomly assigned to one of the study groups:
- Screening group: 7,900 participants receive a series of CT scans
- Control group: 7,892 participants do not receive a CT scan (usual care)

Lung cancer screening
Participants in the screening group received four CT scans, with increasing intervals.

De Koning et al., NEJM 2020

NELSON - trial *NL580*

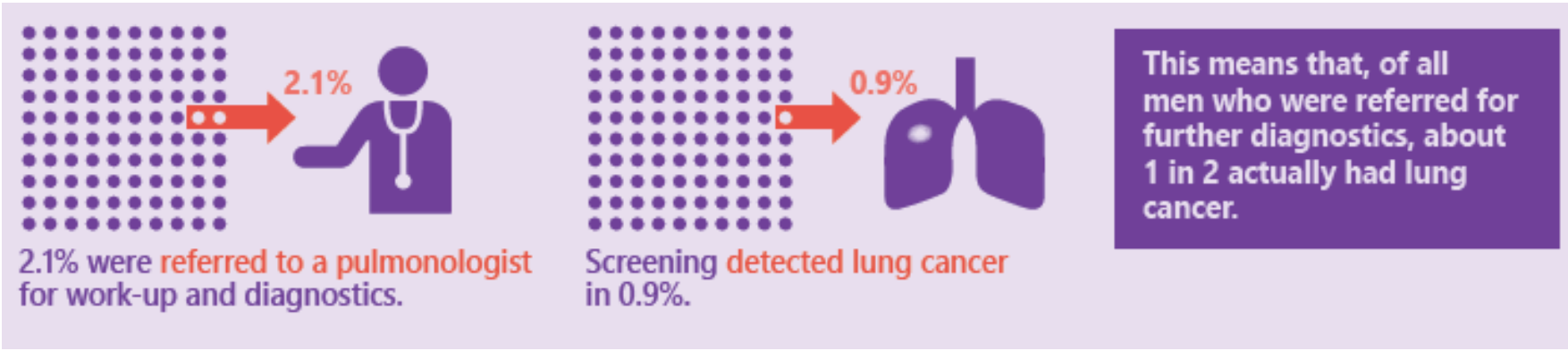
- ***Randomized Controlled Trial***
- ***Recruitment through population-based registries***
- ***CT screening vs. no screening***
- ***Different screening intervals***
- ***<u>Volume & Volume Doubling Time of nodules</u>***
- ***Central reading of CT images***
- ***Expert causes of death committee &***
- ***Follow up through national registries***

*Trial, initially powered (80%) for high risk **males**, to detect a lung cancer mortality reduction of ≥ 25% at 10 years after randomization (individual FU) in ages 50-74*

And includes a small subgroup of women (16%)

De Koning et al., NEJM 2020

NELSON trial (males)



De Koning et al. NEJM. 2020

Screening Test Results in Male Participants

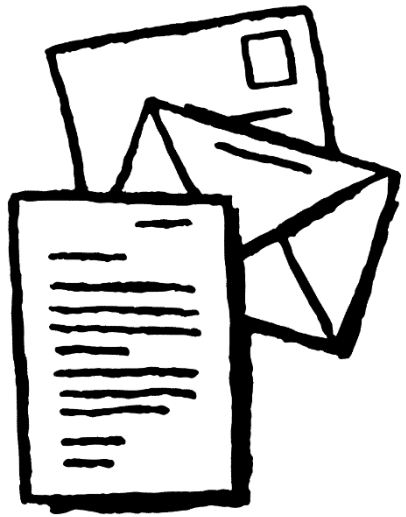
Table 2. Screening-Test Results in Each Screening Round for Male Participants in the Screening Group.

Screening	Screening Uptake		Indeterminate Test	Positive Test	Detection of Lung Cancer	Positive Predictive Value
	Men Eligible for Screening	Men Undergoing Randomization				
	number/total number (percent)					*percent*
Round 1	6309/6583 (95.8)	6309/6583 (95.8)	1241/6309 (19.7)	147/6309 (2.3)	56/6309 (0.9)	38.1
Round 2	6086/6459 (94.2)	6086/6583 (92.5)	357/6086 (5.9)	95/6086 (1.6)	45/6086 (0.7)	47.4
Round 3	5768/6285 (91.8)	5768/6583 (87.6)	385/5768 (6.7)	136/5768 (2.4)	65/5758 (1.1)	47.8
Round 4	4437/5771 (76.9)	4437/6583 (67.4)	86/4437 (1.9)	89/4437 (2.0)	37/4437 (0.8)	41.6
Total	22,600/25,098 (90.0)	22,600/26,332 (85.8)	2069/22,600 (9.2)	467/22,600 (2.1)	203/22,600 (0.9)	43.5

De Koning et al. NEJM. 2020

Message indeterminate screening test result

“We have observed a very small abnormality in your lung (5–10 mm long). Such a small abnormality is often detected in many persons and it usually represents a small scar or a minor inflammation. Therefore, at this moment there is no need for any further investigations. However, in order to see whether there has been any change in this abnormality, a new CT scan of the lungs will be made after 3 to 4 months.”



Lancet Oncol 2014; 15: 1332–41

Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening

Nanda Horeweg*, Joost van Rosmalen*, Marjolein A Heuvelmans, Carlijn M van der Aalst, Rozemarijn Vliegenthart, Ernst Th Scholten, Kevin ten Haaf, Kristiaan Nackaerts, Jan-Willem J Lammers, Carla Weenink, Harry J Groen, Peter van Ooijen, Pim A de Jong, Geertruida H de Bock, Willem Mali, Harry J de Koning*, Matthijs Oudkerk*

Lancet Oncol 2016; 17: 907–16

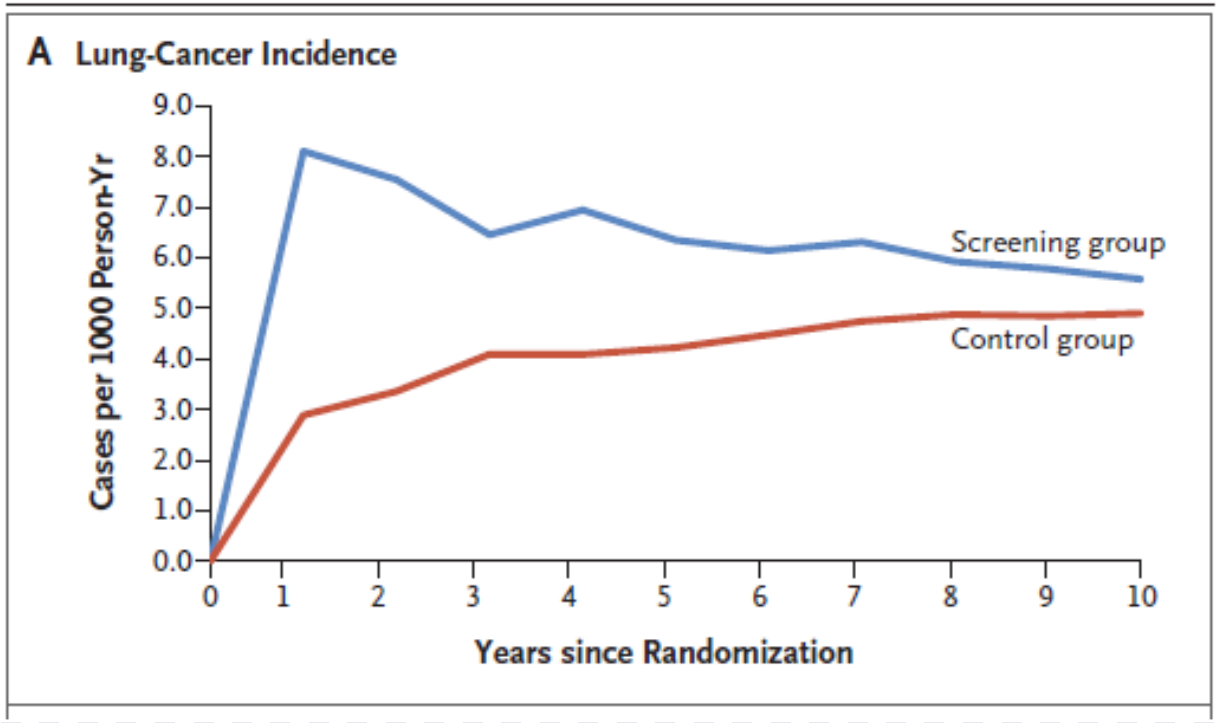
Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial

Joan E Walter, Marjolein A Heuvelmans, Pim A de Jong, Rozemarijn Vliegenthart, Peter M A van Ooijen, Robin B Peters, Kevin ten Haaf, Uraujh Yousaf-Khan, Carlijn M van der Aalst, Geertruida H de Bock, Willem Mali, Harry J M Groen, Harry J de Koning, Matthijs Oudkerk

Lung-Cancer Incidence in Male Participants

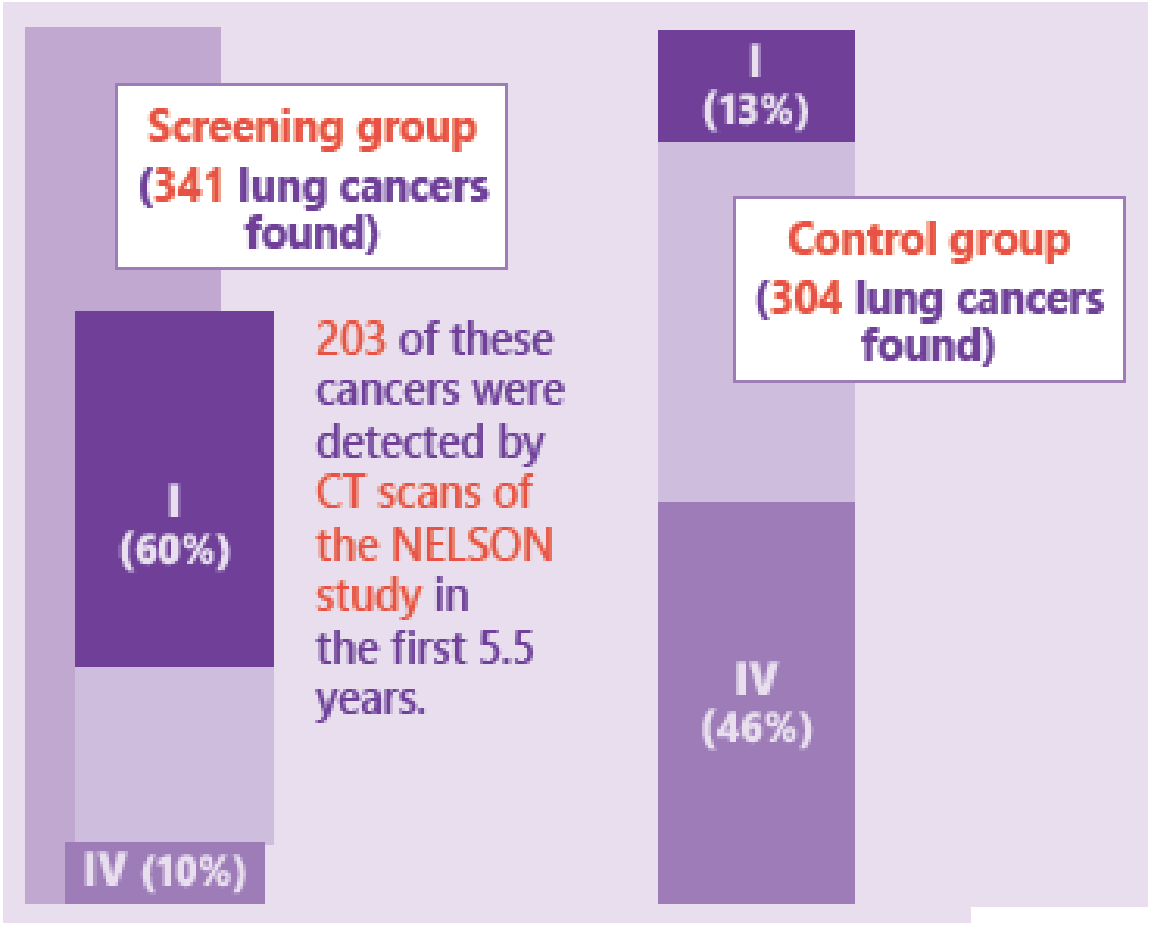
Lung-Cancer Incidence at 10 years of follow-up

- *5.58 cases per 1000 person- years in the **screening group***
- *4.91 cases per 1000 person-years in the **control group***



De Koning et al. NEJM. 2020

Stage Shift NELSON males

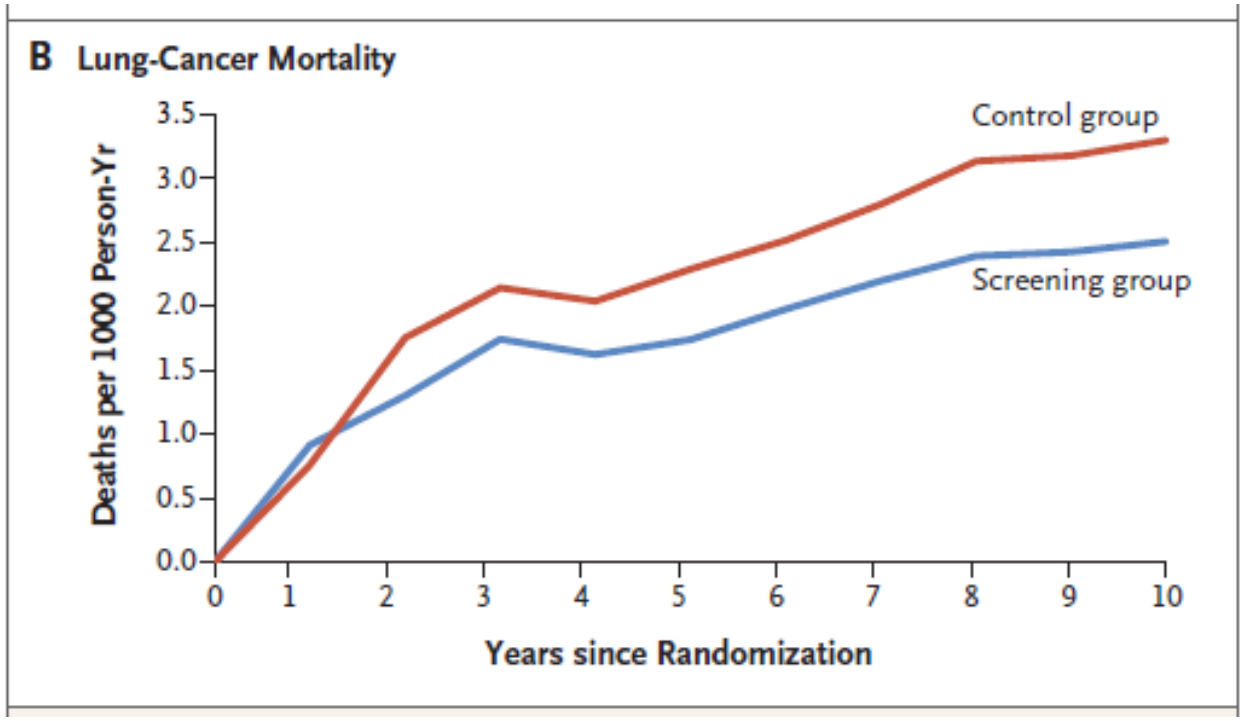


De Koning et al. NEJM. 2020

Lung-Cancer Mortality in Male Participants

Lung-Cancer Mortality at 10 years of follow-up (known incidence date)

- *2.50 deaths per 1000 person-years in the **screening group***
- *3.30 deaths per 1000 person-years in the **control group***



Cumulative RR:

0.76 (95%-CI: 0.61-0.94)

De Koning et al. NEJM. 2020

Lung cancer mortality rate ratio (95% CI)	Year 8	Year 9	Year 10
MALES	**0.76** (0.60-0.97)	**0.76** (0.61-0.96)	**0.76** (0.61-0.94)

De Koning et al. NEJM. 2020

Lung cancer mortality rate ratio (95% CI)	Year 8	Year 9	Year 10		Year 11
MALES	**0.76** (0.60-0.97)	**0.76** (0.61-0.96)	**0.76** (0.61-0.94)		**0.78** (0.63-0.95)

De Koning et al. NEJM. 2020

Subgroup analysis: per age group

in male NELSON participants

Table S2. Analyses amongst NELSON male participants by age group.

Age at randomization	Screen arm			Control arm			Rate ratio (CI)
	Lung cancer deaths	Person-years	Lung cancer mortality rate*	Lung cancer deaths	Person-years	Lung cancer mortality rate*	
50-54	25	15,739	1.59	31	16,681	1.86	0.85 (0.48-1.50)
55-59	35	21,376	1.64	50	21,543	2.32	0.71 (0.44-1.11)
60-64	49	14,631	3.35	56	13,897	4.03	0.83 (0.55-1.24)
65-69	26	7,270	3.58	43	7,107	6.05	0.59 (0.35-0.98)
70-74	19	2,876	6.61	24	2,808	8.55	0.77 (0.40-1.47)

* Per 1,000 person-years
CI: confidence interval

De Koning et al. NEJM. 2020

Cause of Death in Male Participants NELSON

Table 4. Cause of Death of Deceased Male Participants at 10 Years of Follow-up or until the Data-Cutoff Date of December 31, 2015.*

Variable	Screening Group (N=868)	Control Group (N=860)	Total (N=1728)	Rate Ratio (95% CI)
		number (percent)		
Cause of death — no. (%)				
Lung cancer	160 (18.4)	210 (24.4)	370 (21.4)	0.76 (0.62–0.94)
No lung cancer after cause-of-death review, no other specification	6 (0.7)	11 (1.3)	17 (1.0)	0.55 (0.17–1.61)
Other neoplasm	318 (36.6)	289 (33.6)	607 (35.1)	1.10 (0.94–1.30)
Cardiovascular disease	189 (21.8)	181 (21.0)	370 (21.4)	1.05 (0.85–1.29)
Respiratory disease	42 (4.8)	43 (5.0)	85 (4.9)	0.98 (0.62–1.53)
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	37 (4.3)	20 (2.3)	57 (3.3)	1.86 (1.05–3.37)
Diseases of the digestive system	30 (3.5)	21 (2.4)	51 (3.0)	1.43 (0.79–2.63)
External causes of illness and death	24 (2.8)	19 (2.2)	43 (2.5)	1.27 (0.67–2.45)
Endocrine, nutritional, and metabolic diseases	21 (2.4)	9 (1.0)	30 (1.7)	2.34 (1.03–5.80)
Diseases of the nervous system	9 (1.0)	19 (2.2)	28 (1.6)	0.48 (0.19–1.10)
Other cause of death	26 (3.0)	28 (3.3)	54 (3.1)	0.93 (0.52–1.65)
Unknown	6 (0.7)	10 (1.2)	16 (0.9)	0.60 (0.18–1.83)
Total person-yr at risk	62,298	62,484	124,782	
All-cause mortality — deaths per 1000 person-yr	13.93	13.76	13.85	1.01 (0.92–1.11)

* Percentages may not total 100 because of rounding.

De Koning et al. NEJM. 2020

Small subgroups with statistical differences

- Symptoms, signs, and abnormal clinical findings, otherwise not specified (n=57)
- Endocrine, nutritional and metabolic diseases (n=30)

- ONLY one lung cancer confirmed: reviewed by expert committee (NOT LC)
- ONLY 3 with a (false positive) CT scan result: death at least 16 months later

De Koning, Aalst CM van der, Oudkerk M. authors reply. NEJM 382;22;2164-66 2020

Lung cancer mortality rate ratio (95% CI)	Year 8	Year 9	Year 10
MALES	**0.76** (0.60-0.97)	**0.76** (0.61-0.96)	**0.76** (0.61-0.94)
FEMALES	**0.41** (0.19-0.84)	**0.52** (0.28-0.94)	**0.67** (0.38-1.14)

Rand: 23-12-2003 – 06-07-2006

FU: 23-12-2003 – 31-12-2015

De Koning et al. NEJM. 2020

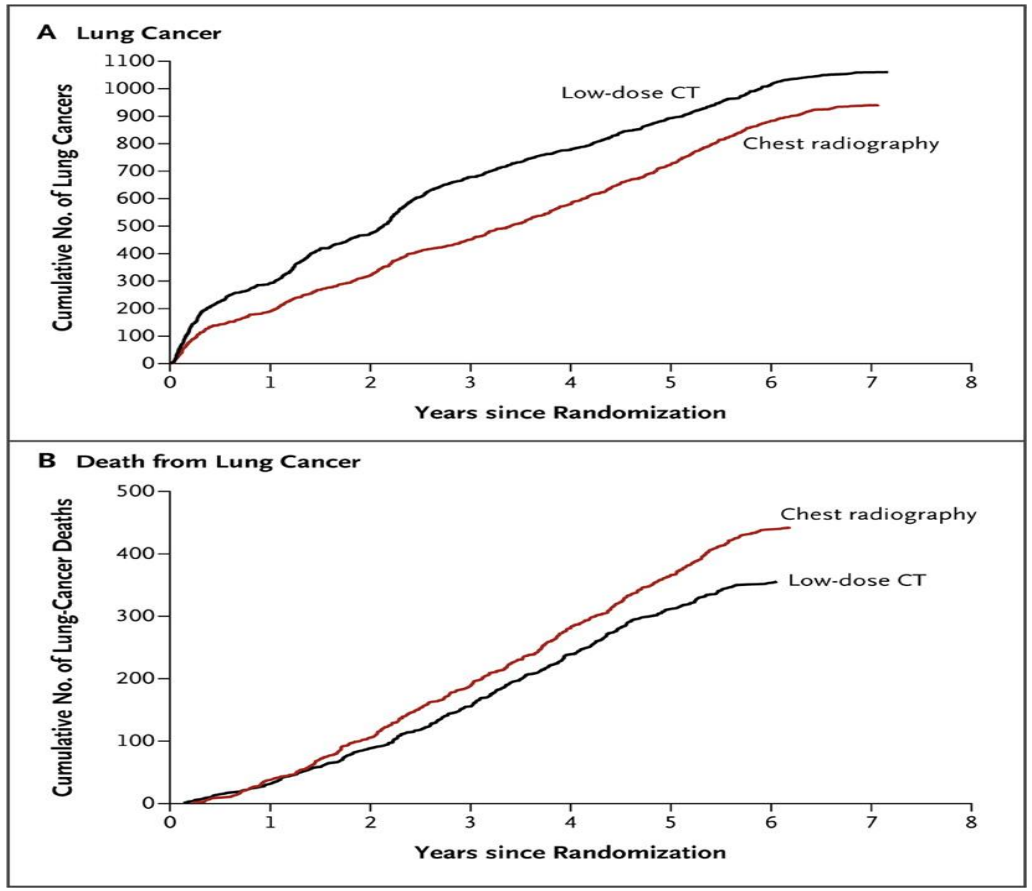
Lung cancer mortality rate ratio (95% CI)	Year 7	Year 8	Year 9	Year 10
MALES		**0.76** (0.60-0.97)	**0.76** (0.61-0.96)	**0.76** (0.61-0.94)
FEMALES	**0.46** (0.21-0.96)	**0.41** (0.19-0.84)	**0.52** (0.28-0.94)	**0.67** (0.38-1.14)

Rand: 23-12-2003 – 06-07-2006

FU: 23-12-2003 – 31-12-2015

De Koning et al. NEJM. 2020

Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer NLST



Lung cancer mortality rate ratio (95% CI)	Year 8 NELSON	Year 8 NLST	Year 8 NLST-eligible in NELSON
MALES	**0.76**	**0.92**	**0.78** (0.59-1.04)
FEMALES	**0.41**	**0.73**	**0.37** (0.14-0.87)

Rand: 23-12-2003 – 06-07-2006

FU: 23-12-2003 – 31-12-2015

De Koning et al. NEJM. 2020
Pinsky et al. Cancer 2013

MISCAN-Lung preclinical durations

Table 2. MPST estimates (in years) of preclinical stages by gender[a]

	AD	SQ	SM	OTH
Men				
IA	1.82	2.16	1.25	1.96
IB	0.64	0.76	0.44	0.69
II	0.46	0.55	0.32	0.50
IIIA	0.46	0.55	0.32	0.50
IIIB	0.36	0.42	0.25	0.39
IV	0.74	0.88	0.51	0.80
Total mean preclinical duration[b]	4.48	5.32	3.09	4.84
Women				
IA	2.44	2.15	1.36	2.31
IB	0.86	0.76	0.48	0.81
II	0.62	0.55	0.34	0.59
IIIA	0.62	0.55	0.35	0.59
IIIB	0.48	0.42	0.27	0.45
IV	0.99	0.88	0.55	0.94
Total mean preclinical duration[b]	6.01	5.31	3.35	5.69

All-Cause Mortality NELSON males

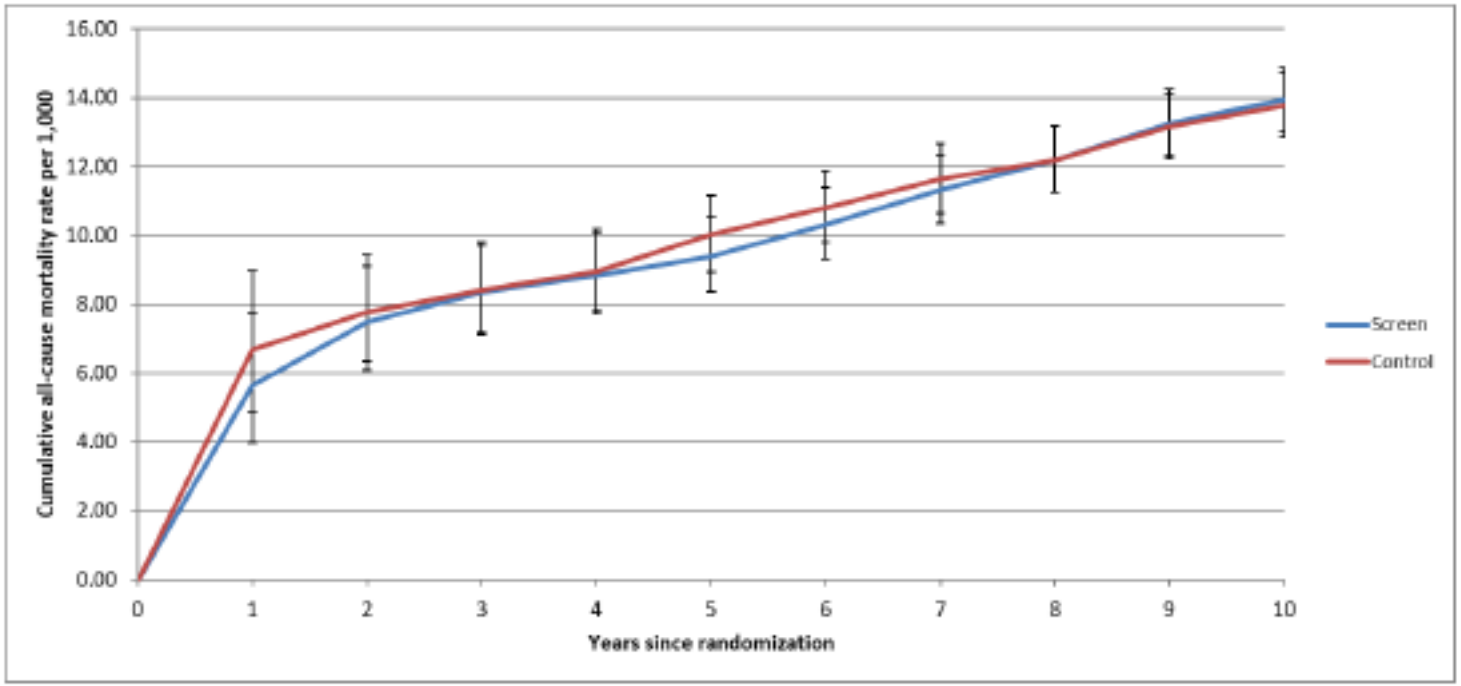
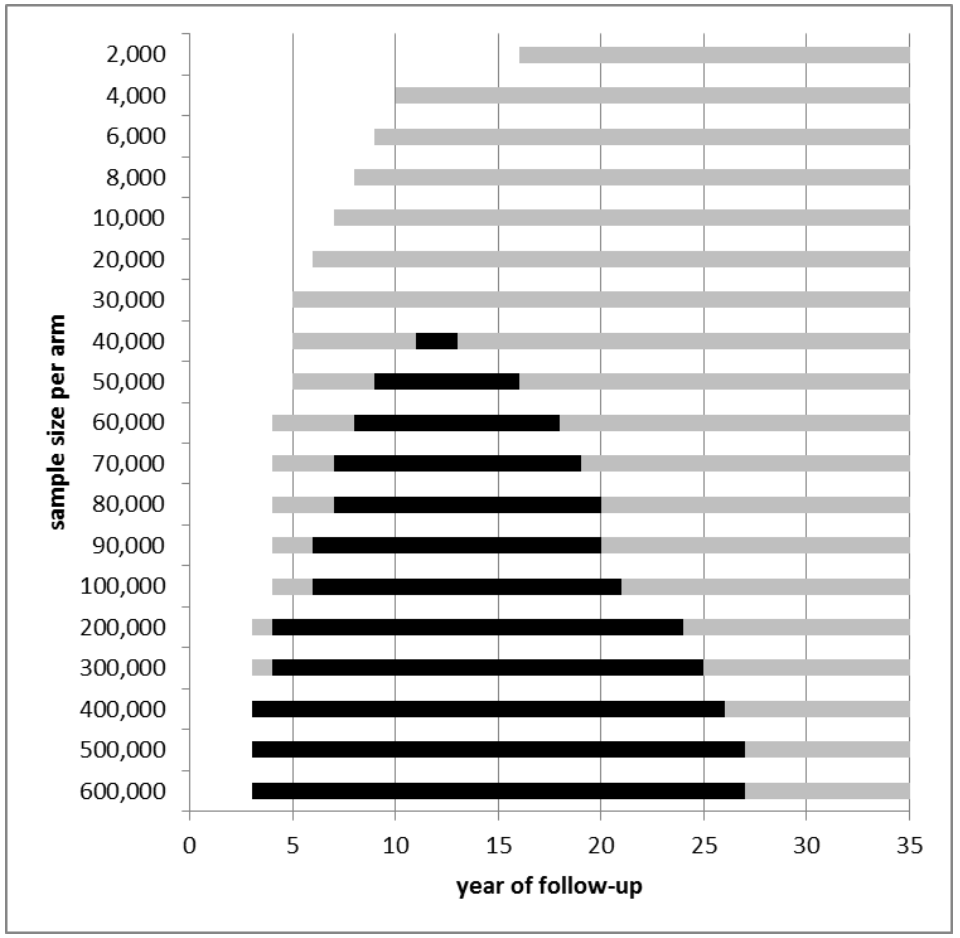


Figure S4a-b. The cumulative all-cause mortality rate (per 1,000) per year since randomization,

De Koning et al. NEJM. 2020

All-cause mortality, and needed minimum trial sample size



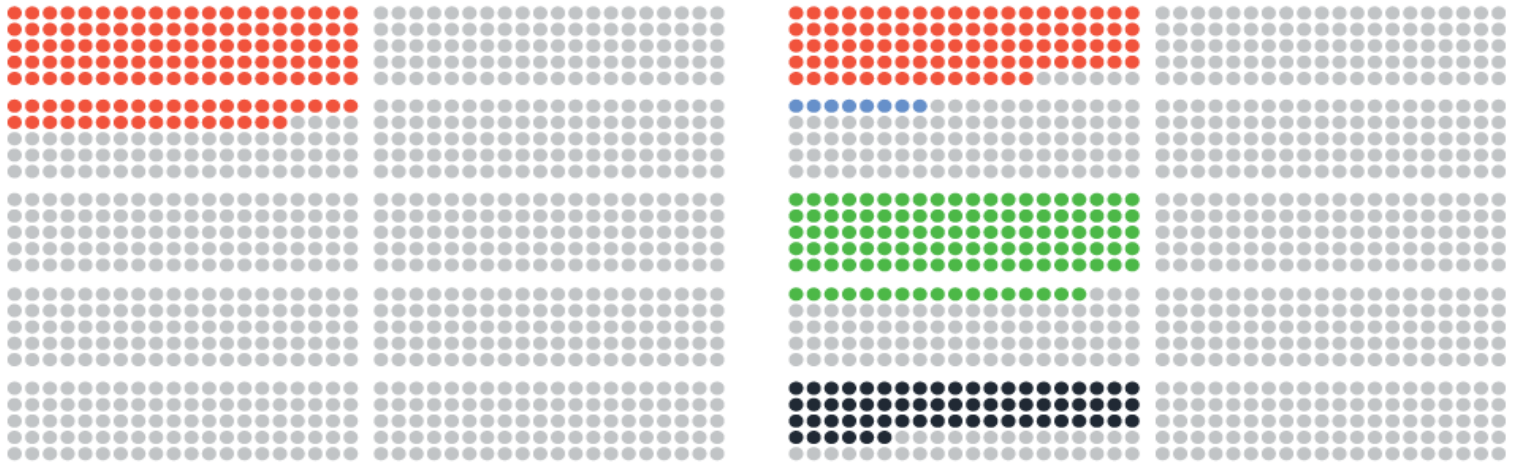
Heijnsdijk et al., Cancer Med 2019

Benefits and harms of lung cancer screening

This graphic represents 1000 persons that would be eligible for lung cancer screening at any point in their life. The left panel shows how many of these 1000 persons are expected to die of lung cancer when they are not screened. The right panel shows the lifetime benefits and harms when these 1000 individuals would undergo lung cancer screening using annual low-dose computed tomography scans.

1000 ever-eligible persons without screening

1000 ever-eligible persons with screening



	Without screening	With screening
Persons dying of lung cancer	136	94
Persons with lung cancer that would never cause symptoms *	-	8
False positive scan results (per 1000 scans) **	-	117
Persons undergoing surgery or biopsy for benign lesion ***	Unknown	66
Other persons	864	715

WHAT NEXT

- For lung cancer screening, the evidence on effectiveness, benefits that outweigh the harms, and cost-effectiveness, is now firm.

- Once evidence exists to support these criteria, implementation research in each country is needed to assess the feasibility of fulfilling the national requirements in practice.

Comparison of screening programmes

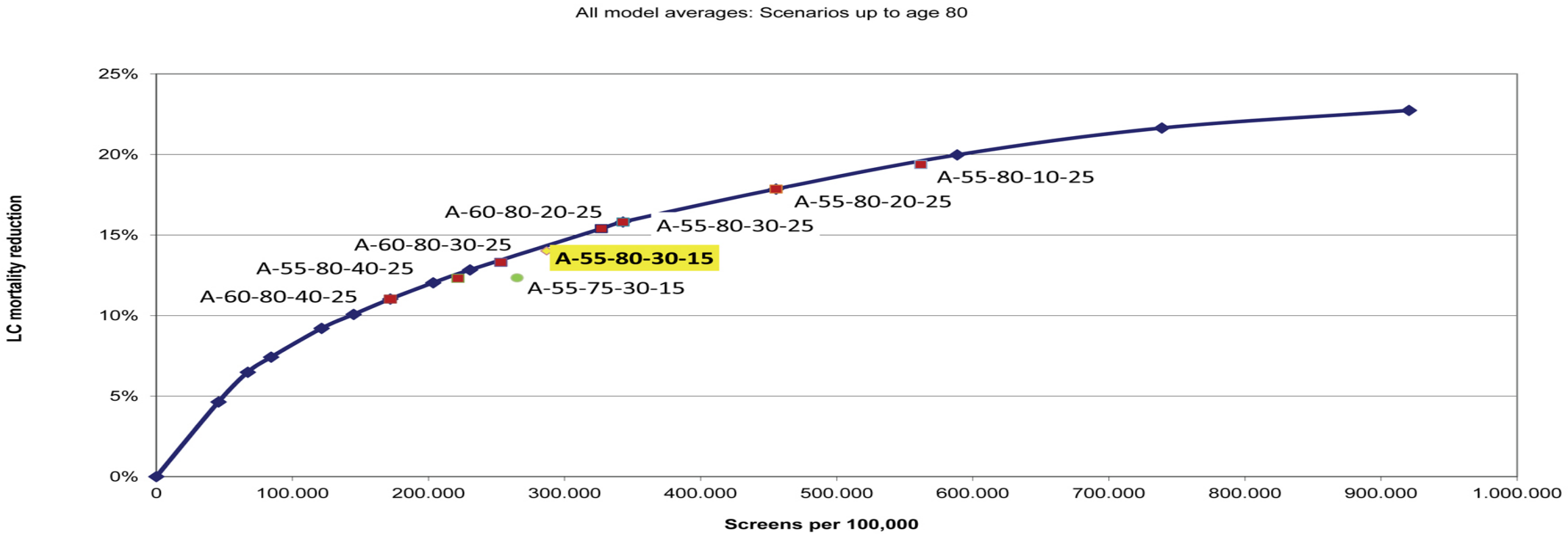
	Colorect FIT	LUNG CT	Breast mmg	Prostate PSA	Cervical HPV
Deaths target group without screening	6,200	10,000	2,100	2,750	450
Cancer mort reduction	30%	35%	40%	27.5%	50%
Number deaths prevented	2,250	**1,600-2,600**	1,000	650	250
Life-years gained/death	11	**11**	16	10	22
Screens NL*	1.6 million	**300,000**	1.1 million	215,000	450,000
Cost	20 million	60 million	68 million	7 million	29 million
Ages	55-75	55-80	50-75	55-64	30-60
Interval	2	1	2	3	5-10

Annals of Internal Medicine | ORIGINAL RESEARCH

Benefits and Harms of Computed Tomography Lung Cancer Screening Strategies: A Comparative Modeling Study for the U.S. Preventive Services Task Force

Harry J. de Koning, MD; Rafael Meza, PhD; Sylvia K. Plevritis, PhD; Kevin ten Haaf, MSc; Vidit N. Munshi, MS; Jihyoun Jeon, PhD; Saadet Ayca Erdogan, PhD; Chung Yin Kong, PhD; Summer S. Han, PhD; Joost van Rosmalen, PhD; Sung Eun Choi, SM; Paul F. Pinsky, PhD; Amy Berrington de Gonzalez, PhD; Christine D. Berg, MD; William C. Black, MD; Martin C. Tammemägi, PhD; William D. Hazelton, PhD; Eric J. Feuer, PhD*; and Pamela M. McMahon, PhD*

Erasmus MC



Costs

- Program related costs
  - Costs for inviting individuals
  - Costs for risk assessment(s)
  - Costs of the screening test and follow-up examinations
  - Costs for maintaining the program (IT infrastructure etc.)

- Treatment related costs:
  - Shift in treatment (costs) from advanced cancers to less advanced cancers
  - Long-term care costs for persons that now survive cancer
  - Cancer care costs that would not have occured without screening (due to overdiagnosis)

Some reported CE-analyses including the issues

Country	Screening starting age	Screening stopping age	Screening interval	Eligibility criteria	Cost-effectiveness ratio (per lide-year gained)	Reference
Canada	**55**	**74**	**Annual**	**40 pack-years,** **Current smoker or quit <10 years**	**CAD $ 40,000**	ten Haaf et al., PLOS Medicine, 2017
Switzerland	**60**	**80**	**Annual**	**40 pack-years,** **Current smoker or quit <10 years**	**EUR 39,500**	Tomonaga et al., Lung Cancer, 2018
U.S.	**55**	**75** **77** **80**	**Annual**	**30 pack-years,** **Current smoker or quit <15 years**	**US $ 49,200** **US $ 68,600** **US $ 96,700**	Criss et al., Annals of Internal Medicine, 2019

Discussion & conclusion

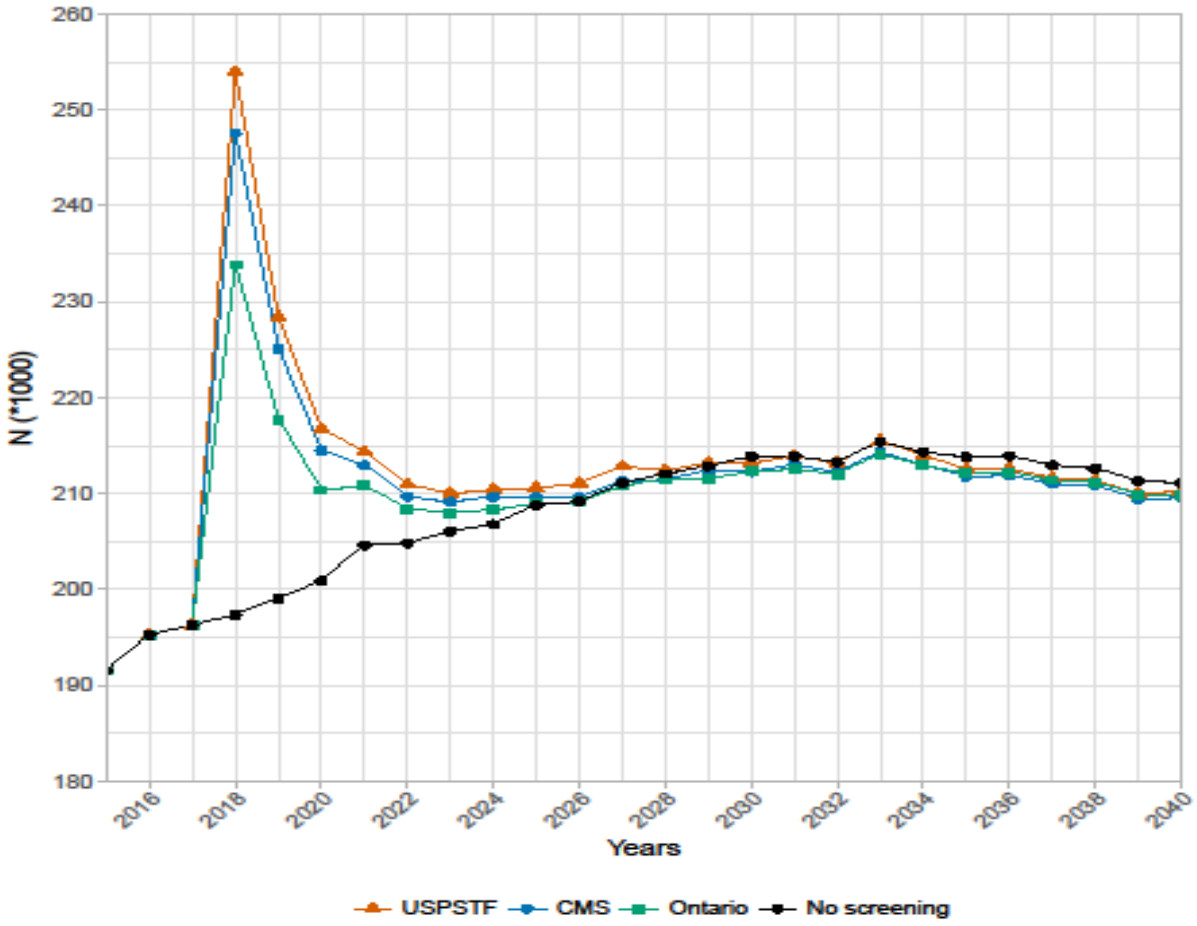
- Newest more favorable results NELSON not yet incorporated
- Conservative estimates cost of screening (unit cost 250+)
- Cost (savings) immunotherapies not yet included
- Cost savings after negative baseline CT possible? (4-ITLRun trial)

- Absolute benefits can be substantially higher than present other cancer screening programmes

- **We have to be selective in eligibility, but CT lung cancer screening can be a cost-effective preventive health care scenario**

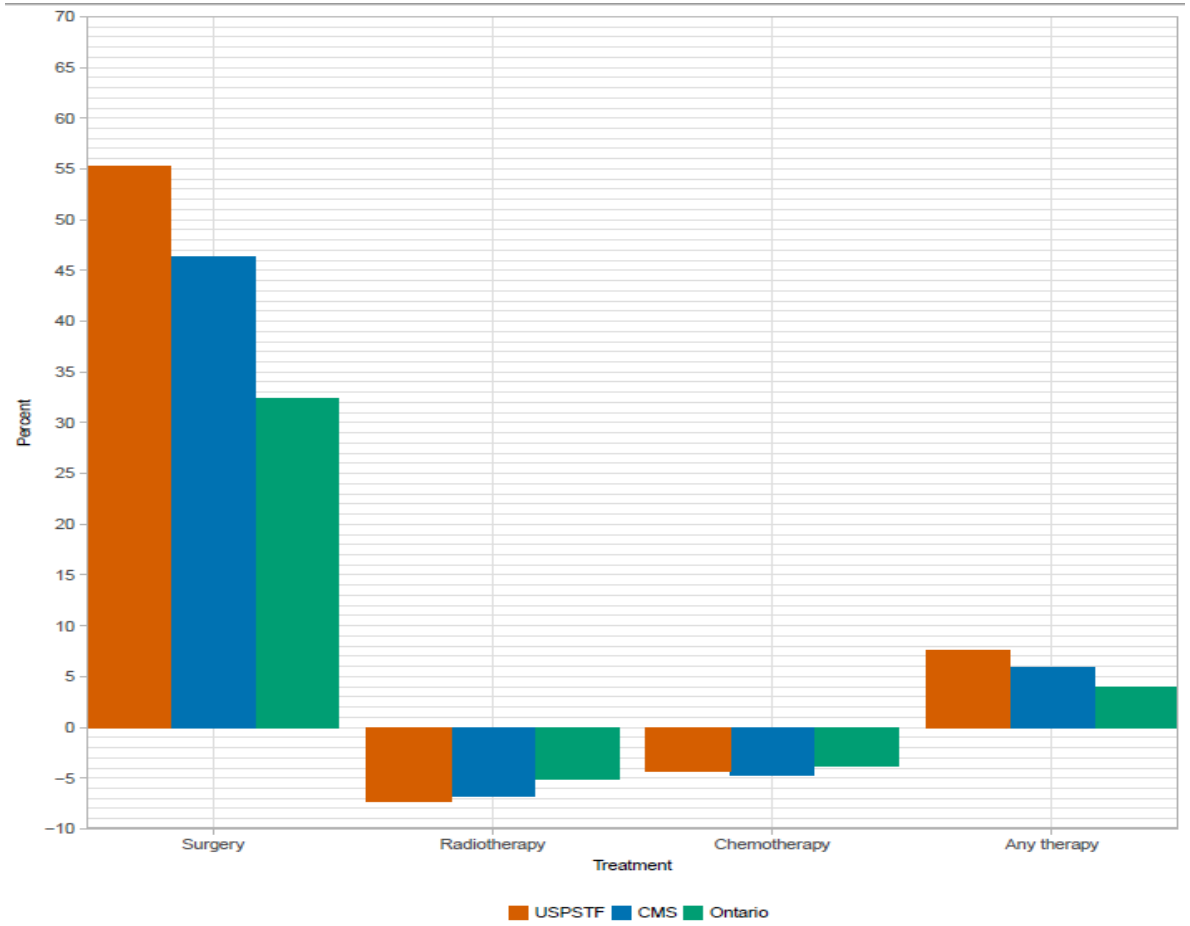
Capacity challenge

(Blom et al., Cancer 2019)



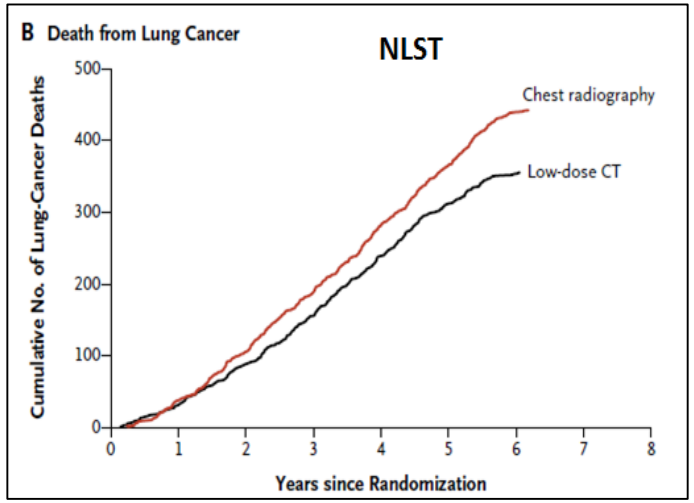
Capacity challenge

Blom et al., Cancer 2019

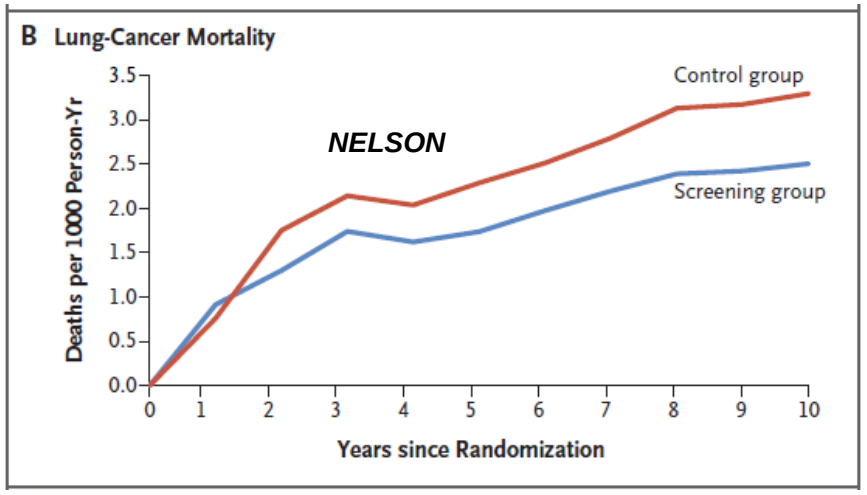


Home messages

- Lung cancer is the leading cause of cancer-related mortality
- RCT's have confirmed substantial reductions in lung cancer mortality with low-dose computed tomography (LDCT) screening in high-risk populations
  - The National Lung Screening Trial (NLST; n=53,454) and Dutch-Belgian Lung Cancer Screening trial (NELSON; n=15,792): 8-24% (men) and 26-61% (women)



NLST team. NEJM. 2011

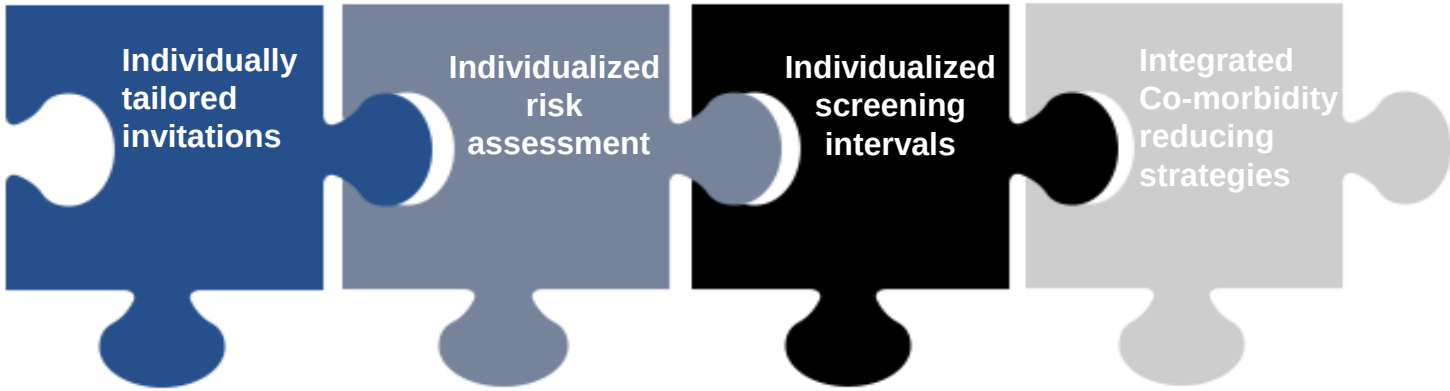


De Koning et al. NEJM. 2020

Missing Pieces of Information

- Lung cancer screening means personalised, risk-based approaches
- Health care systems' implementation of personalised screening and prevention is still sparse, and likely to be of variable quality

→ Important issues have to be addressed to ensure effective and high quality implementation, such as:



Tailored Recruitment

- **Recruitment Challenge**
  - Need for adequate (self-) selection based on risk assessment
  - Low participation rates among individuals in the more deprived socioeconomic groups (SES), although lung cancer risk is elevated in these groups.
  - Factors relating to eligibility for lung cancer screening differ greatly from the factors associated with (intended) lung cancer screening uptake
  - No one-size-fits-all approach

- **Need more evidence about:**
  (1) the information needs per subcategory of the general (high-risk) population (how to tailor)
  (2) the potential teachable moments to contact/invite potential eligibles
  (3) preferences regarding the media of recruitment materials (i.e. letter, brochure, online information, interactive website, call centre, health care provider)

Risk-Based Eligibility

- Prevent screening of the low-risk (but anxiety?) population
  - Example: $PLCO_{m2012}$ 1.5% vs 1.83%

    ↓ risk threshold yields a similar number of LYG as the USPSTF criteria, but requires 6% less CT screens
- Risk-based strategies more likely to recruit older individuals and groups with diminished life-expectancies

  → More research needed to identify the optimal thresholds for risk-based selection
- How do we communicate lung cancer risk and screening eligibility to low- and high-risk individuals?
- Role of risk prediction models in risk-based selection

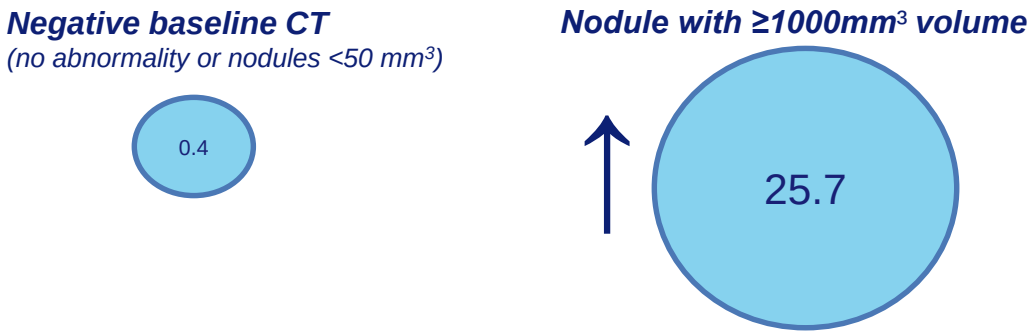
Potential variables for risk-based selection
Age
Gender
Level of education
(Race/ Ethnicity?)
Smoking status, intensity, duration
Time since quitting
Lung cancer history
COPD
Family history of lung cancer
BMI

Tammemagi, 2014, PloS Med

Risk-Based Screening Intervals

- Current trial results and modelling favour annual screening
- But risk-stratification by CT result can substantially reduce the screens needed:
  - ↓ harms (e.g. false positives, anxiety, overdiagnosis, radiation)
  - ↓ costs

- E.g. results NELSON: probability of a lung cancer diagnosis in the two years following



- → Biennial screening for participants with negative baseline results? Need hard trial evidence

European Lung Cancer Screening Implementation Trial

4-IN-THE-LUNG-RUN

(accronym: TOWARDS INDIVIDUALLY TAILORED INVITATIONS, SCREENING INTERVALS, AND INTEGRATED CO-MORBIDITY REDUCING STRATEGIES IN LUNG CANCER SCREENING)

- the first large-scale multi-centered implementation trial on Volume CT lung cancer screening across 5 European countries

- to develop and implement the optimal personalized CT lung cancer screening programme for high-risk populations.

Study Ob

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4 IN THE LUNG RUN

Erasmus MC

- To assess the relative safety (i.e., comparable detection of favourable lung cancer stages I-II) of a personalised risk-based (often) less intensive screening regimen on the basis of a combination of (a) health risk factors, (b) baseline CT scan result and possibly ultimately (c) biomarker outcomes amongst individuals aged 60-79 years at high risk for developing lung cancer.

  24,000 individuals with a baseline negative screening test result, who have given consent, will be randomised (1:1) to personalised screening (initially biennially) or standard screening (annually).

- # men and women, aged 60-70 years, with a $PLCO_{m2012}$ 6-year risk for developing lung cancer of ≥3.25% or a smoking history of ≥40 pack-years, being a current smoker or former smoker who quit smoking ≤10 years ago.