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With appreciation

53,454 trial participants

without whom these studies would not have been possible

Results from the National Lung Screening Trial

- Trial Design and Initial Trial Results
- False-positive Rates and Evaluation of a Positive Screen
- Radiation Dose with Low-Dose Chest CT in the NLST

NLST design

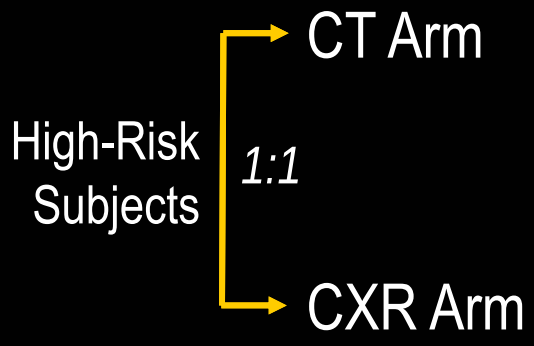
Prospective, randomized trial comparing low-dose helical CT screening to chest x-ray screening with the endpoint of lung cancer specific mortality in high risk participants

Eligibility

- Age 55-74
- Asymptomatic current or former smoker; 30 pack year smoking history
- Former smokers: quit within preceding 15 years
- No prior lung cancer diagnosis
- No evidence of other cancer within preceding 5 years

http://radiology.rsna.org/content/early/2010/10/28/radiol.10091808.full

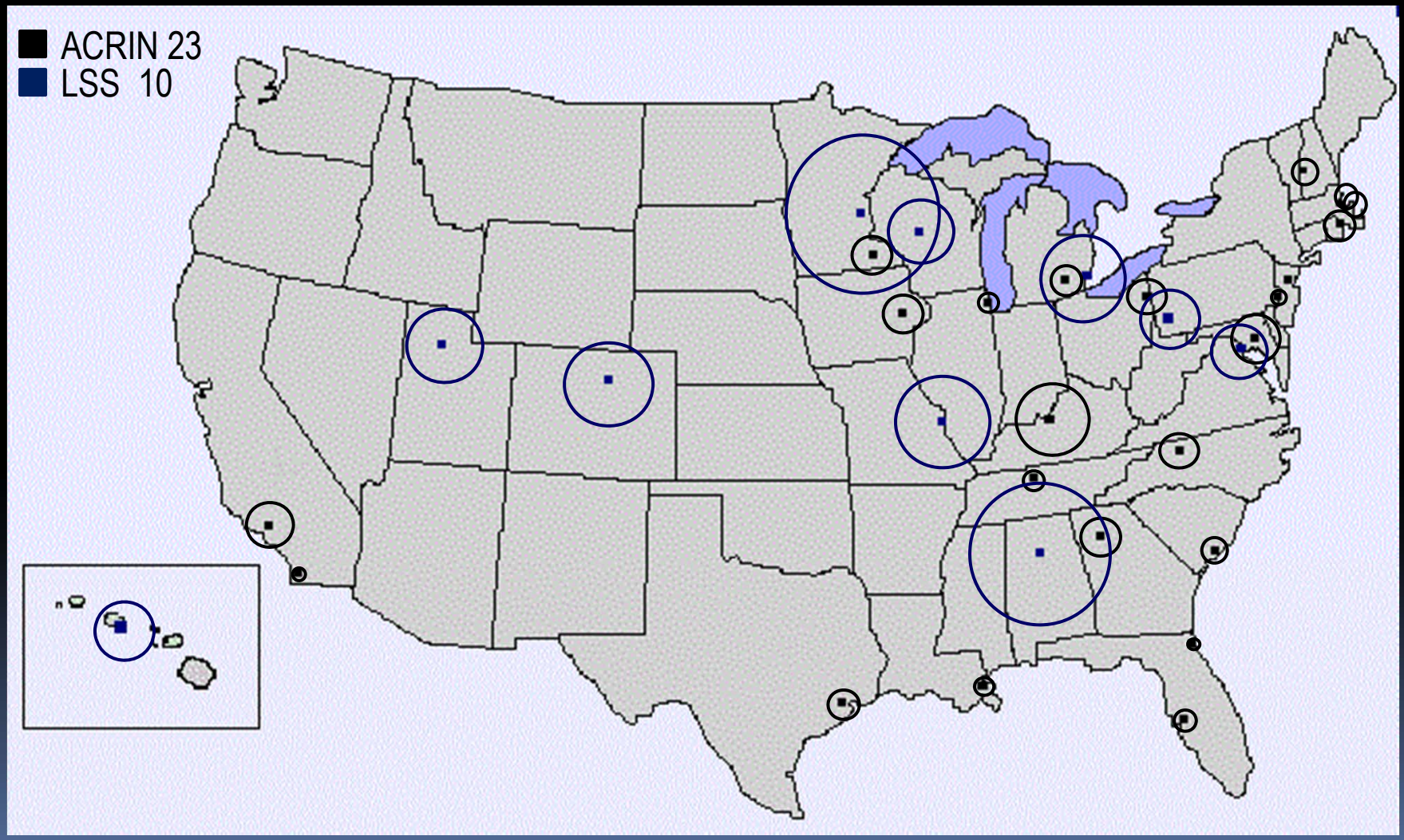
NLST design and projected timeline



Annual Interim Analyses : 4/2006 - 4/2010
Final: October 2010

http://radiology.rsna.org/content/early/2010/10/28/radiol.10091808.full

Participating sites



NLST primary endpoint

	Helical CT vs. CXR
Lung cancer-specific mortality	20% difference
α	5%
Power	90%
Compliance	85% CT | 80% CXR
Contamination	5% CT | 10% CXR
Size	25,000 / arm

http://radiology.rsna.org/content/early/2010/10/28/radiol.10091808.full

NLST secondary endpoints

- Secondary endpoints
  - All cause mortality
  - Lung cancer: prevalence | incidence | interval cancers
  - Stage distribution
  - Screening test performance
  - Medical resource utilization for [+] screen

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NLST cumulative accrual – 33 sites

Comparison to US census data

- United States Census Dept Tobacco Use Supplement of Continuing Population Survey for 2002-2004
- Contains information on 240,000 respondents
- Subset of respondents aged 55-74, with 30+ pack year smoking, either current smoker or former smoker who quit within the past 15 years
- Identified smoking status, age, sex, race, ethnicity, marital status, and education

Comparing NLST with eligible US census population

53,454 participants	NLST	US Census
Male (%)	59.0	58.5
Age		
55-59 (%)	42.8	35.2
60-64 (%)	30.6	29.3
65-69 (%)	17.8	20.8
70-74 (%)	8.8	14.7
Race | Ethnicity		
Black (%)	4.4	5.5
Hispanic (%)	1.7	2.4

JNCI J Natl Cancer Inst (2010) 102 (23): 1771-1779.

Comparing NLST with US census population

	NLST	US Census
Married	66.6	60.9
Education		
< HS	6.1	21.3
≥ College	31.5	14.4
Current smoker	48.2	57.1
Median pack yrs	48.0	47.0

JNCI J Natl Cancer Inst (2010) 102 (23): 1771-1779.

Comparing NLST with US census population

- Compared with similar US population, NLST cohort has similar gender distribution and smoking exposure
- However, NLST participants
  - Younger
  - Better educated
  - Less likely to be current smokers

JNCI J Natl Cancer Inst (2010) 102 (23): 1771-1779.

Participant history of lung disease

Disease [1]	Helical CT %	X-Ray %	Total %
Asbestosis	1.0	1.0	1.0
Bronchiectasis	3.2	3.4	3.3
Emphysema	7.7	7.6	7.7
Chronic bronchitis, emphysema or COPD	17.5	17.4	17.4
Lung fibrosis	0.3	0.2	0.2
Sarcoidosis	0.2	0.2	0.2
Silicosis	0.1	0.1	0.1

1 Lung disease based on participant self-report at baseline.
Does not include sub-study analyses of NLST imaging exams.

Family history of lung cancer across NLST

	Helical CT %	X-Ray %	Total %
Any first degree relative	21.8	21.7	21.7
≥ 2 first degree relatives	3.3	3.2	3.3

Analyses of family history and lung cancer risk ongoing

Screening exam compliance

Study Year	Helical CT		Chest X-ray		Total	
	Expected	Screened	Expected	Screened	Expected	Screened
T0	26,713	98.5%	26,722	97.5%	53,435	98.0%
T1	26,282	94.0%	26,398	91.3%	52,680	92.6%
T2	25,935	92.9%	26,097	89.5%	52,032	91.2%

Screen positivity rate by screening round & arm

	Low-dose helical CT			CXR		
	Number screened	Number positive	% Positive	Number screened	Number positive	% Positive
Screen 1	26,314	7,193	27.3	26,049	2,387	9.2
Screen 2	24,718	6,902	27.9	24,097	1,482	6.2
Screen 3	24,104	4,054	16.8**	23,353	1,175	5.0**
All screens	75,136	18,149	24.2	73,499	5,044	6.9

* Positive screen: nodule ≥ 4 mm *or* other findings potentially related to lung cancer.

** Abnormality stable for 3 rounds *could* be called negative by protocol.

True and false positive screens

Screening Result	Low-dose Helical CT			CXR		
	Screen 1 N (%)	Round 2 N (%)	Round 3 N (%)	Round 1 N (%)	Round 2 N (%)	Round 3 N (%)
Total Positives	**7,193 (100)**	**6,902 (100)**	**4,054 (100)**	**2,387 (100)**	**1,482 (100)**	**1,175 (100)**
Lung cancer	**270 (4)**	**168 (2)**	**211 (5)**	**136 (6)**	**65 (4)**	**78 (7)**
No lung cancer	**6,923 (96)**	**6,734 (98)**	**3,843 (95)**	**2,251 (94)**	**1,417 (96)**	**1,097 (93)**

Data reflect the final interpretation, including benefit of historical comparison exams.

Interim analysis: lung cancer mortality 10-20-2010

Arm	Person Years (py)	Lung cancer deaths	Lung cancer mortality per 100,000 py	Reduction in lung cancer mortality (%)	Value of test statistic	Efficacy boundary
LDCT	144,102.6	356	247	20.0	–3.2	–2.033
CXR	143,367.5	443	309			

p = 0.0041

Deficit of lung cancer deaths in CT arm exceeds that expected by chance, even allowing for multiple looks at the data.

CXR arm compared with matched 30,000 cohort in PLCO, no benefit of CXR seen.

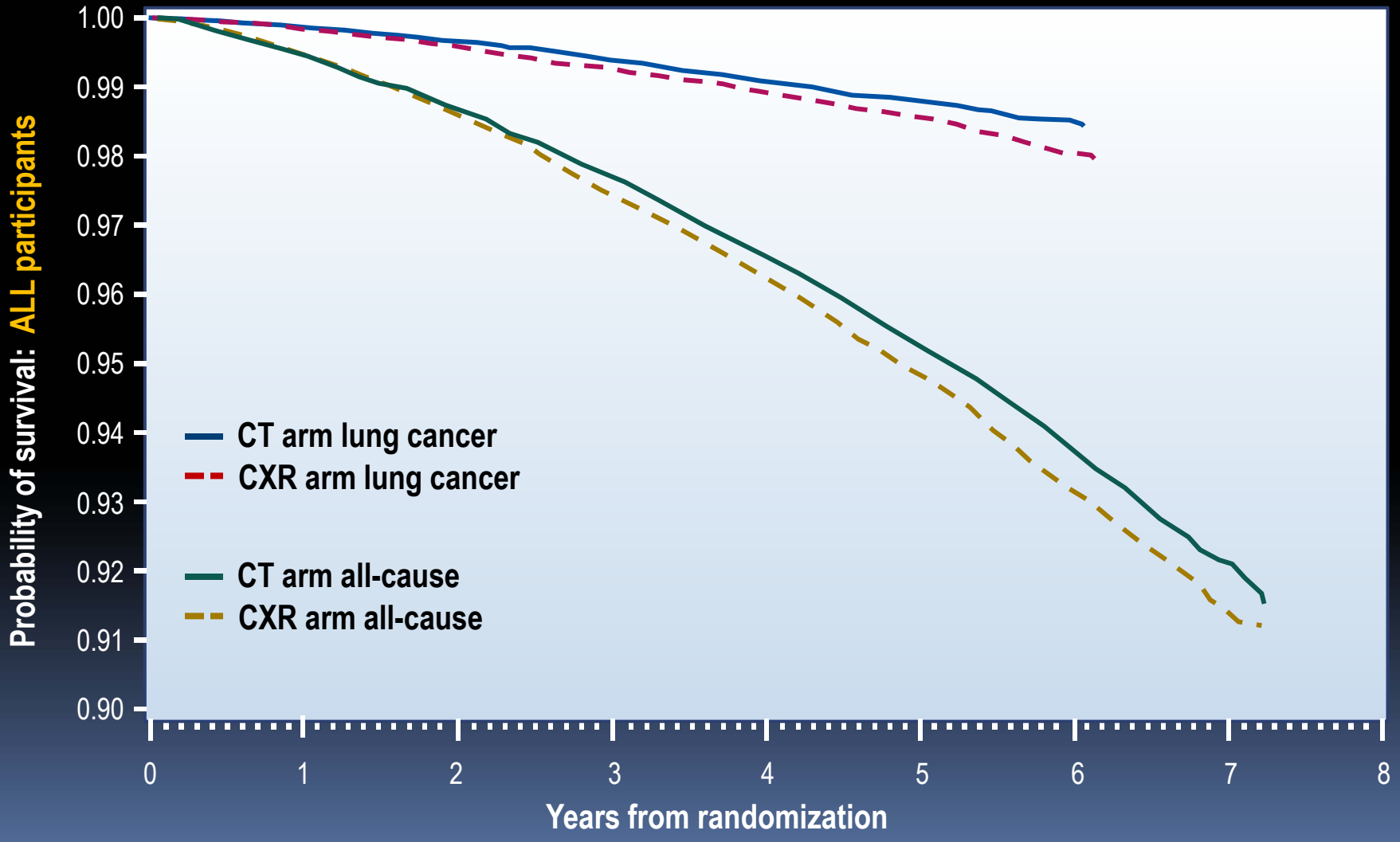
Interim analysis: all-cause mortality 10-20-2010

Arm	Person Years (py)	Deaths	All-cause mortality per 100,000 py	Reduction in all cause mortality (%)	Value of test statistic	Value for significance
CT	167,394.9	1877	1121	6.7	–2.31	–1.96
CXR	166,332.2	2000	1202			

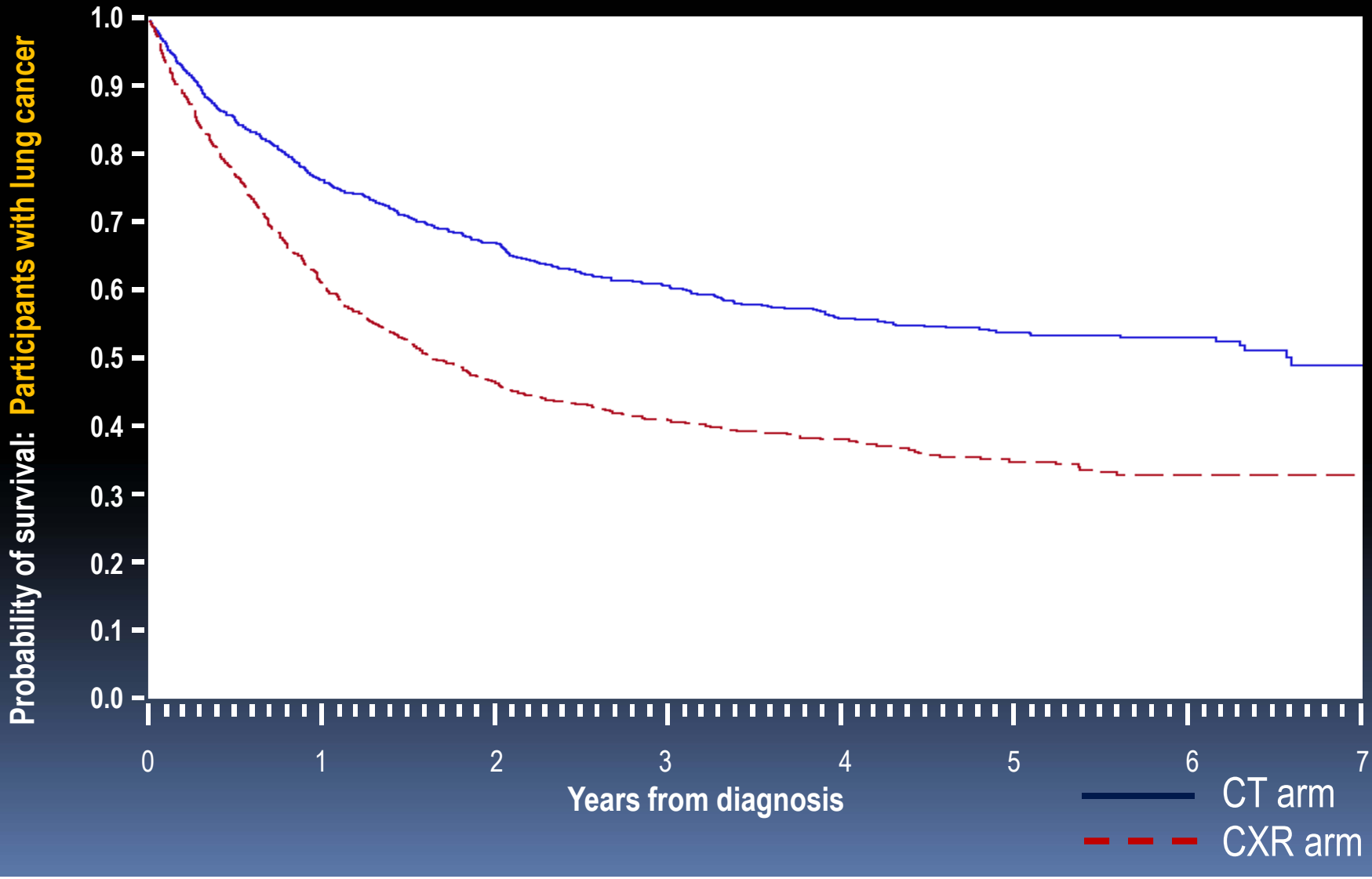
p = 0.021

- Lung cancer: 25% of all deaths in NLST
- Lung cancer: 56% of 123 excess deaths in CXR arm

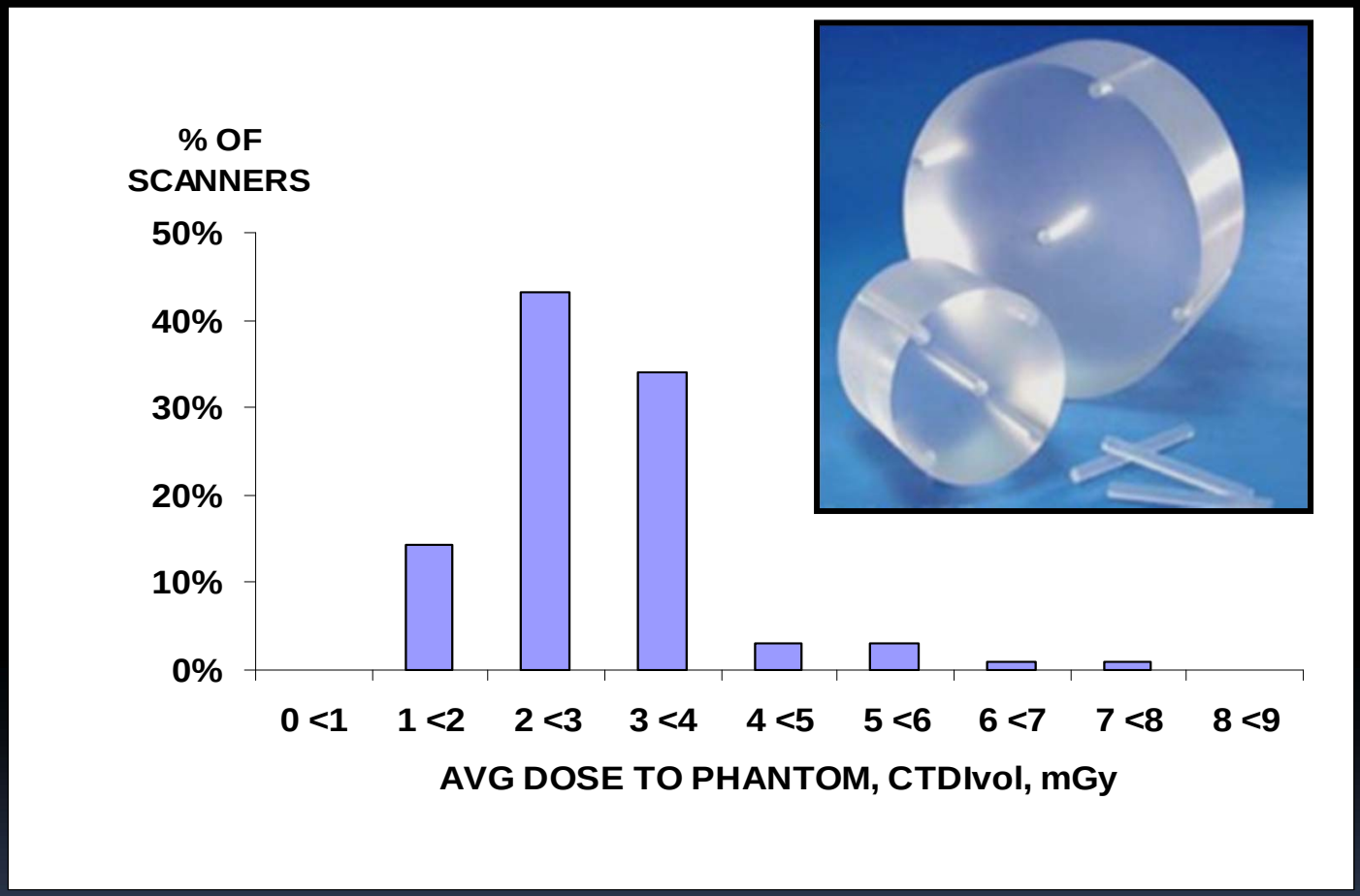
Kaplan-Meier curves for *all-cause mortality*



Lung cancer case survival Kaplan Meier curve



NLST $CTDI_{vol}$ - Estimated Dose to the Phantom

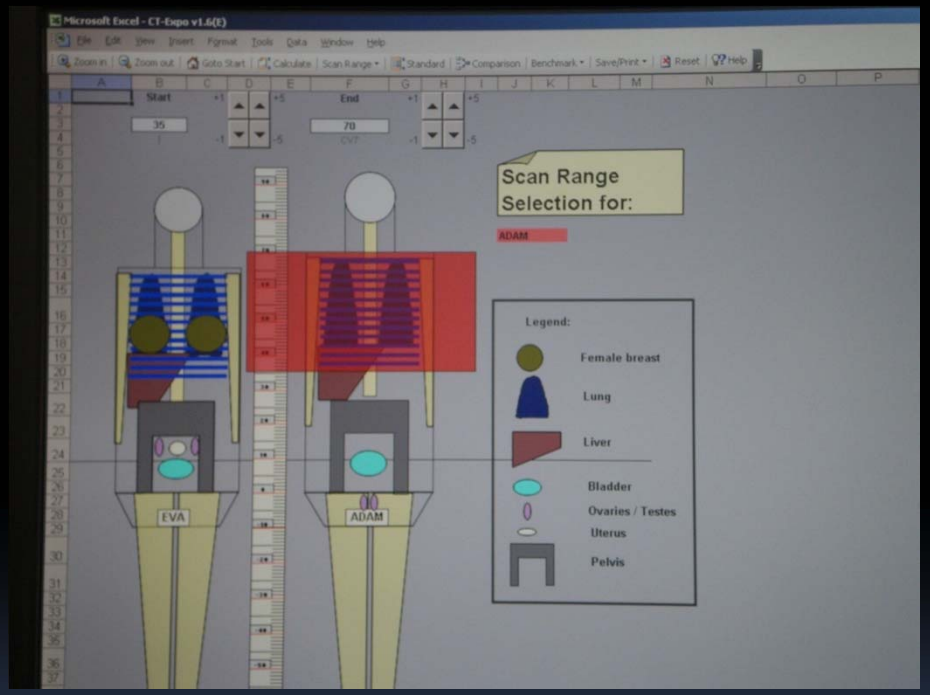


Average $CTDI_{vol}$ = 2.9 mGy (std dev = 1.0 mGy)

(results time averaged by CT scanner over trial period)

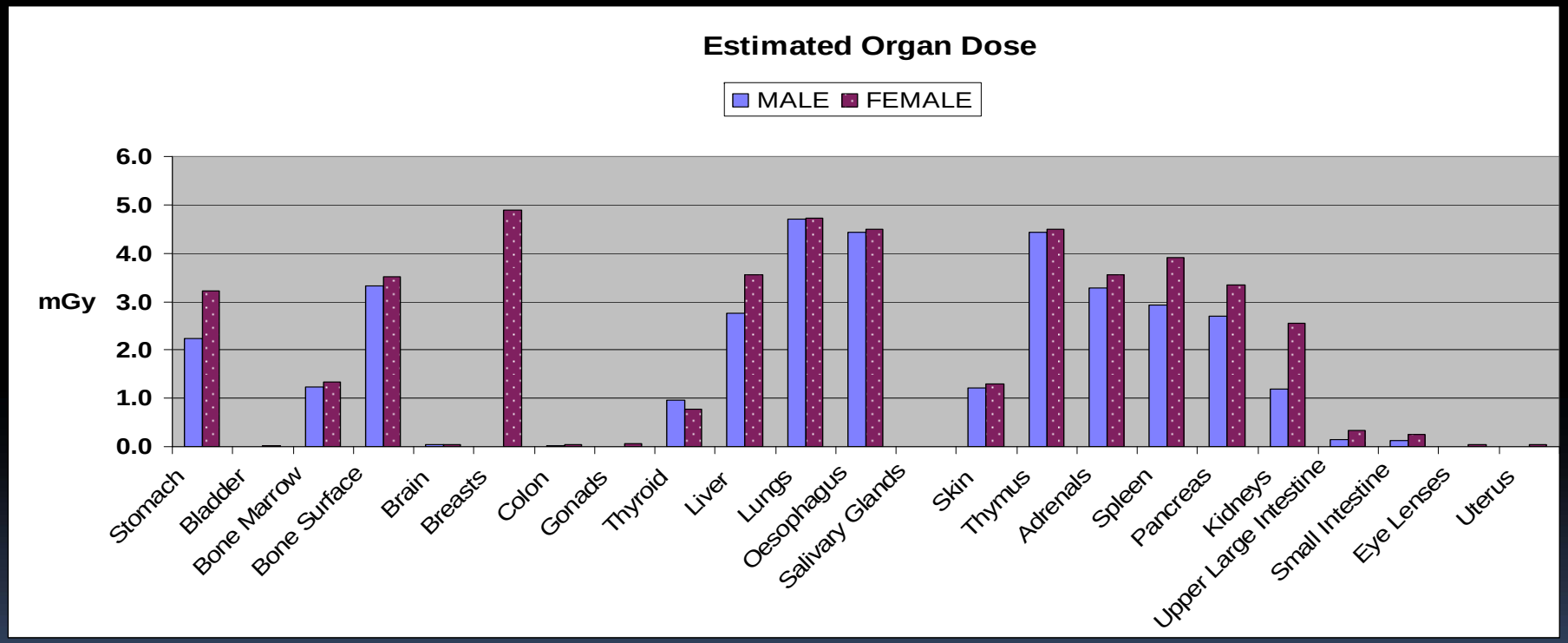
Estimated Organ Doses – Male / Female

- *CT-Expo* Software
- 35 cm thorax scan length
- NLST average $CTDI_{vol}$ of 2.9 mGy used as input to *CT-Expo*

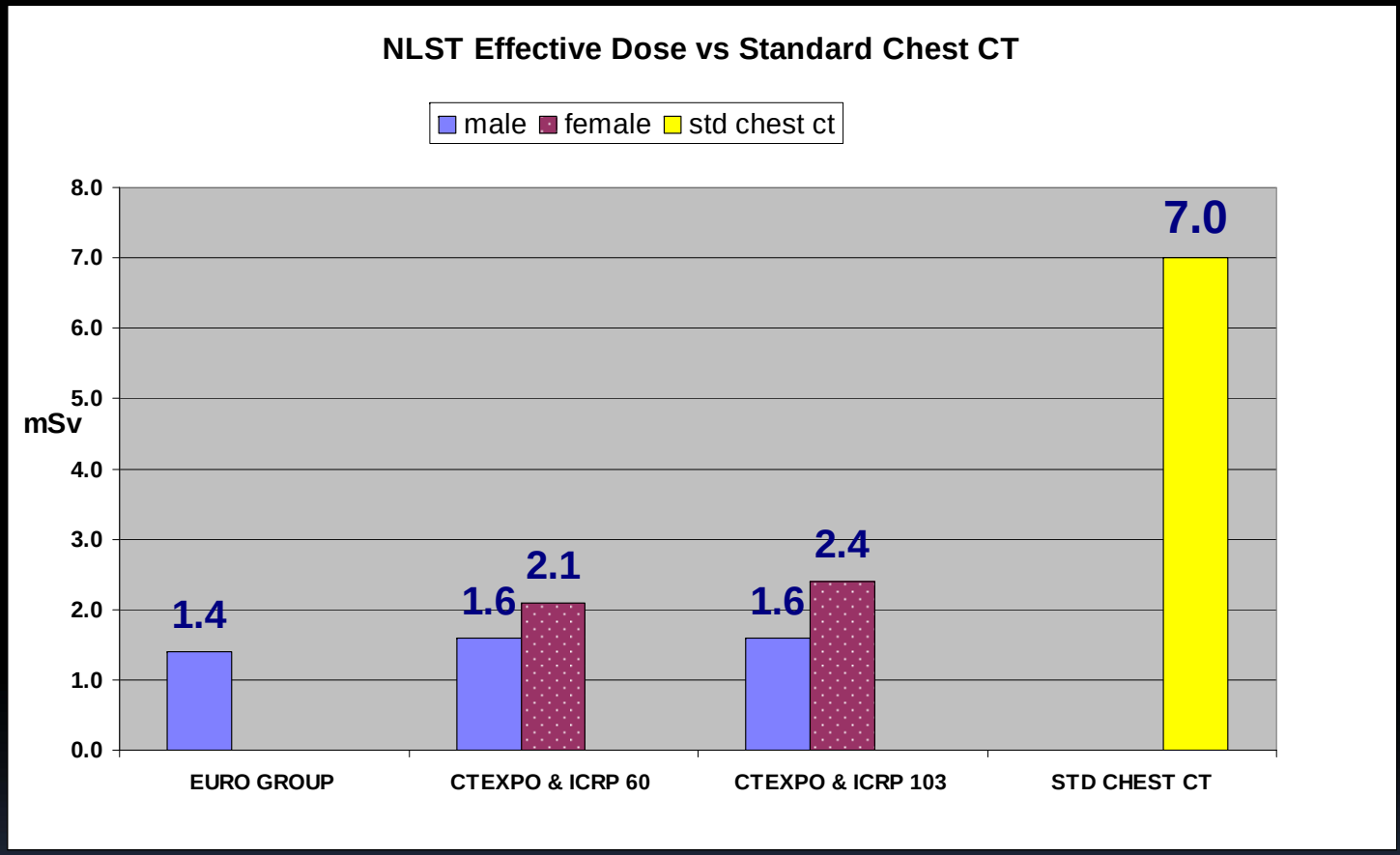


Estimated Organ Doses
Male & Female

(using NLST average $CTDI_{vol}$ of 2.9 mGy, 35 cm scan, and *CT-Expo* Software)



Comparison to Standard Chest CT



- Acceptable chest CT screening can be accomplished at a small fraction of the dose of a standard chest CT

radiation dose

- Whole body effective dose (weighted average dose to each organ)
  - Low dose helical CT: 1.5mSv
  - Mammogram: 0.7mSv
  - CXR: 0.01 mSv
- Low dose helical CT: estimates of organ specific dose
  - Lung: 4 mGy,
  - Breast: 4 mGy for females
  - Red bone marrow, stomach, liver and pancreas: each ~1 mGy
- Screening mammogram organ specific dose:
  - Breast : 4mGy
  - Other organs: < 0.1mGy

Radiation Risks vs Benefits

- 3 screens Smokers Age 55
- Radiation risk from screens
  - 1-3 lung cancer deaths per 10,000 screened
  - 0.3 breast cancers per 10,000 females screened
- Radiation risk from follow-up CT scans
  - Low-dose or thin-section chest CT x 25%
  - Diagnostic chest CT x 100%
- Cumulative mortality reduction NLST
  - 30 lung cancer deaths per 10,000 screened

Collaborative Investigations Initiated

- Lam Canadian study of LDCT with fluorescent bronchoscopy using Tammemagi risk model
- Radiation risk assessment with medical physicists and REB
- Planned individual level meta-analysis with ongoing European studies: NELSON, Danish CT study, etc
- Modeling effort with CISNET lung teams
- CAD and CADx for nodule evaluation
- Two planned and one proposed lung cancer early detection marker validation in PLCO with study in ACRIN biospecimen repository of successful markers

Acknowledgements

NLST Executive Committee

- Denise R. Aberle, MD
- Christine D. Berg, MD
- William C. Black, MD
- Timothy R. Church, PhD, MS
- Richard M. Fagerstrom, PhD
- Barbara Galen, MSN, CRNP, CNMT
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	Fred Larke, PhD	University of Colorado
	Randell Kruger, PhD	Marshfield Clinic
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	Chris Cagnon, PhD	UCLA
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	Randell Kruger, PhD	Marshfield Clinic
	Mike Flynn, PhD	Henry Ford Hospital

NLST Committees

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*** Deceased**

Additional Partners

National Cancer Institute: Cancer Imaging Program, DCTD
Early Detection Research Group, DCP

ACRIN | Westat | IMS | *CARE* Communications

Our many, many site investigators and research staff

Colleagues
- NLST ACRIN Tissue Bank & Biomarker Oversight Committee
- NLST ACRIN Research Evaluation Panel
- ACRIN Specimen Biorepository at University of Colorado
- UCLA Tissue Microarray Laboratory

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With appreciation

53,454 trial participants

without whom these studies would not have been possible