Lung Cancer Screening:

The Case for Moving Forward

Robert Chapman, M.D.
Josephine Ford Cancer Institute

Disclosure

None

Objectives

- Lung Cancer in Michigan
- Fundamentals of Cancer Screening
- Principles/Biases of Screening
- Background for Lung Cancer Screening
  - ✓ Low dose CT scan trials
- Focus on NLST

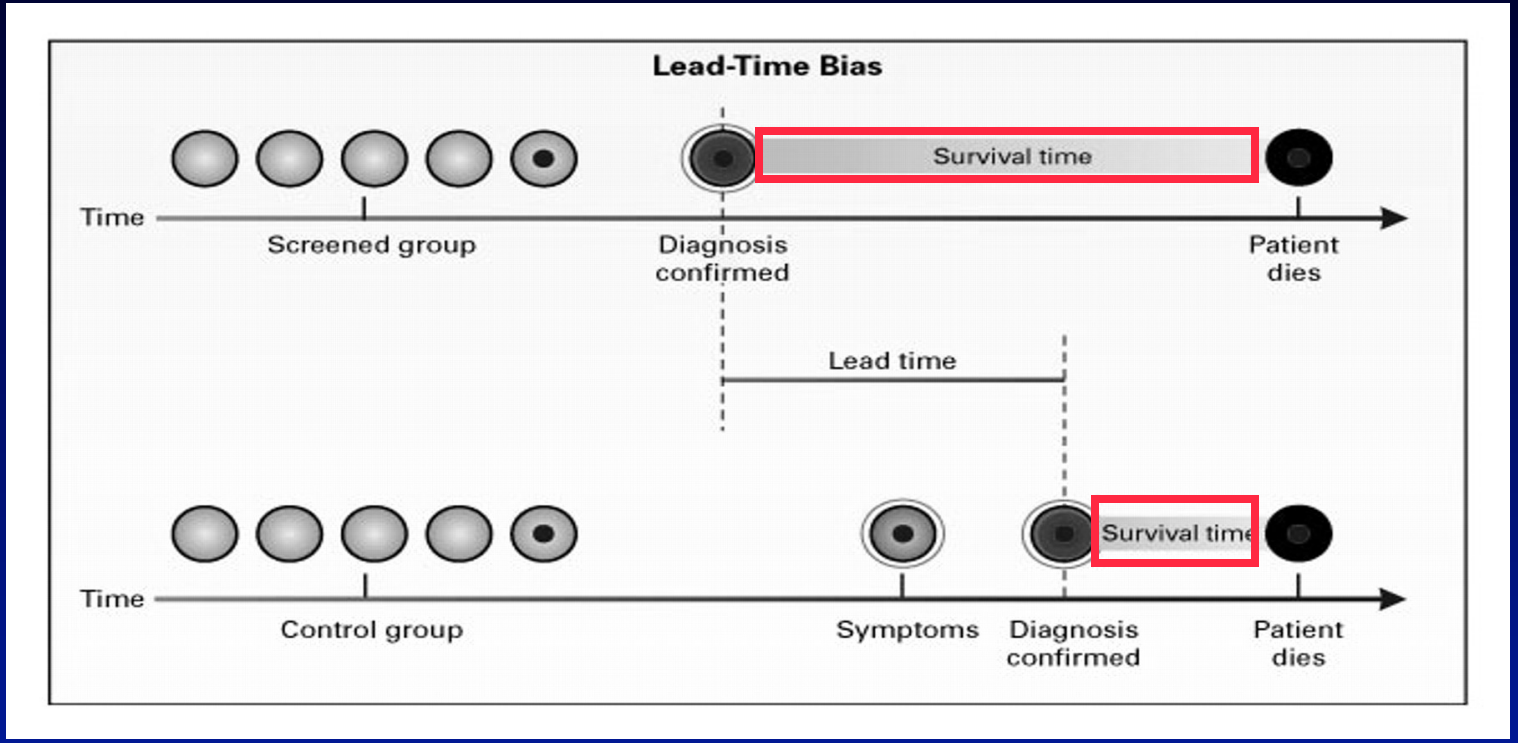
Screening Fundamentals

- Should detect asymptomatic persons at risk
- Effective treatment at the pre-clinical stage
- Early intervention in the pre-clinical stage should decrease ***disease-specific mortality***
- Accessibility, cost and morbidity of the screening test should be reasonable

Screening Fundamentals

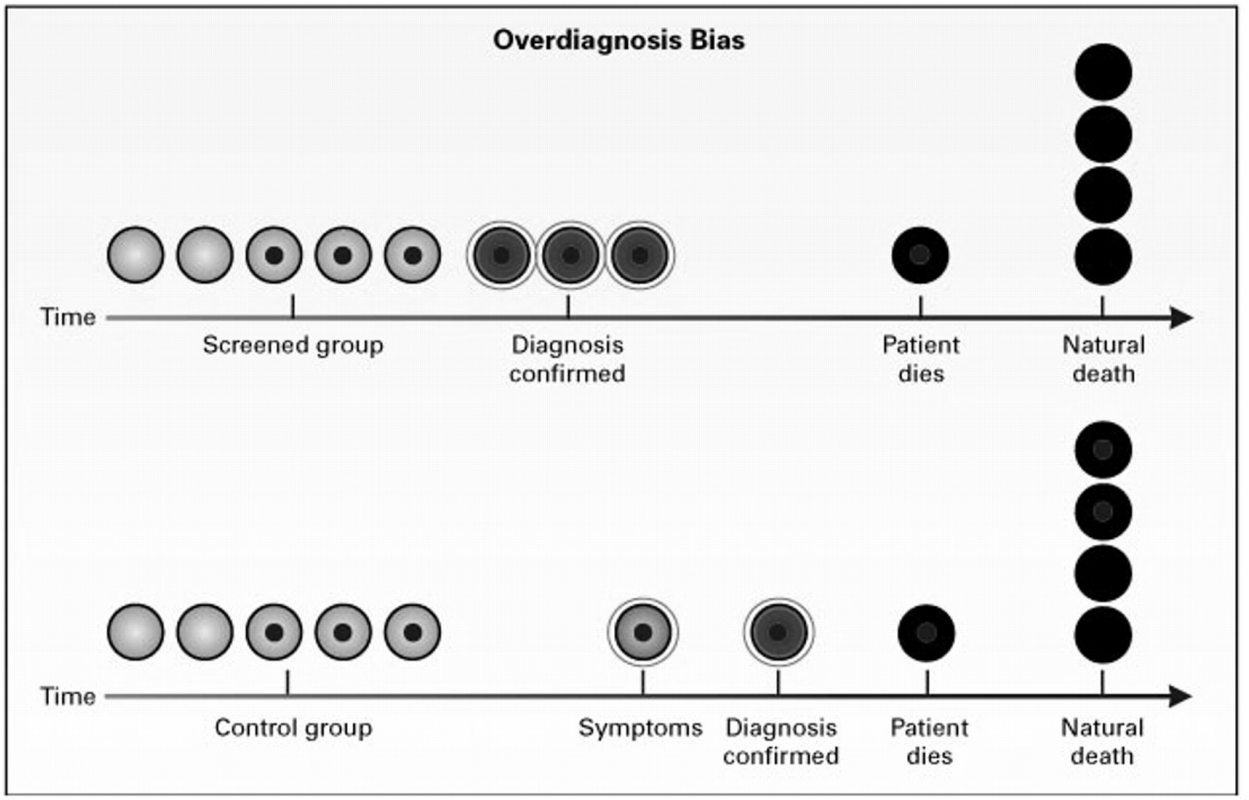
- Effect on mortality rather than survival is required to validate a screening test
- Survival from the time of diagnosis is misleading
  - Lead-time bias
  - Over diagnosis bias

Screening Bias



Lead time bias = time of diagnosis is advanced by screening but the time of death is unchanged

Screening Bias



Overdiagnosis bias = identification of abnormalities that would never cause a problem in a person's lifetime

Background: Lung Cancer Facts

- Most common lethal cancer in the USA
  - 228,190 new cases in 2013
  - Up to 85% will die from their disease
- More deaths from lung cancer than colon, breast and prostate cancers combined
- Often referred to as the “silent” cancer

Lung Cancer in Michigan: 2013

- Estimated new cases: 8,250
- Estimated deaths: 5,940
  - Breast cancer: 1,360
  - Colon and Rectum: 1,700
  - Prostate: 890
  - Pancreas: 1,460

Background: Lung Cancer Screening

- In absence of screening, majority of patients are symptomatic at the time of diagnosis

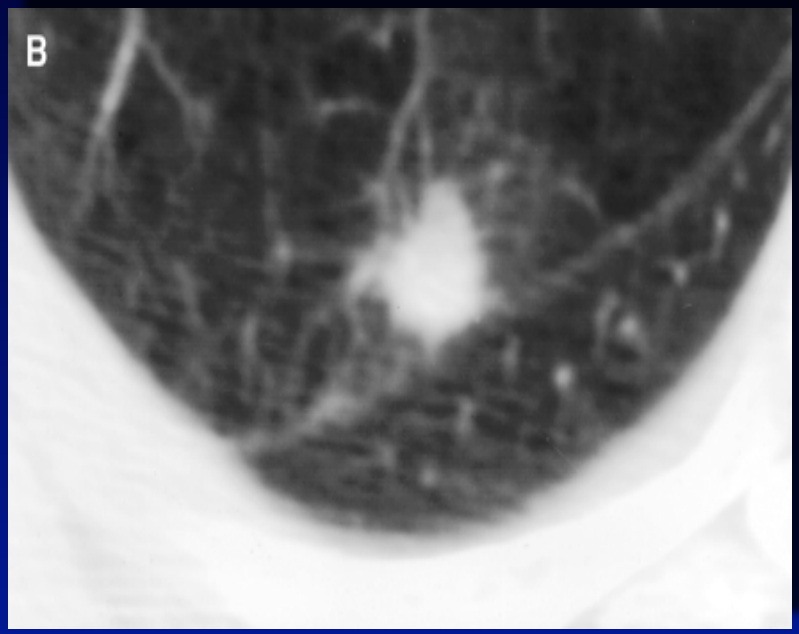
		5-yr survival
Asymptomatic	6%	18%
Symptoms related to 1º tumor	27%	12%
Symptoms of metastatic disease	32%	6%
Systemic symptoms of cancer	34%	0%

Low Dose CT Scan

- Introduction of new technique

- Detect cancer at earlier stage ?
- Cause stage shift ?

Low Dose CT Scan



Low Dose CT Scan - Milestones

- ELCAP
  - 23% NCN on CT vs. 7% on CXR
  - 27 lung ca (85% Stage 1) on LDCT vs. 7 lung ca by CXR
- Mayo LDCT project
  - 51% NCN on initial screen, 74% after 5 screens
  - 68 lung ca (61% Stage 1); 13 pts had surgery for benign NCN

Low Dose CT Scan - Milestones

- **I-ELCAP**
  - 31,567 subjects, 484 lung ca (85% Stage 1)
  - Estimated 10-year *survival rate* = 88 - 92%
- Pittsburgh
  - 3642 subjects, 40.5% NCN
  - 36 noncancer diagnoses who had a major thoracic surgical procedure
  - 28 had thoracotomy or VATS procedures against the investigators' recommendation or without the advice of the investigators

NLST: Trial Design and Initial Results

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

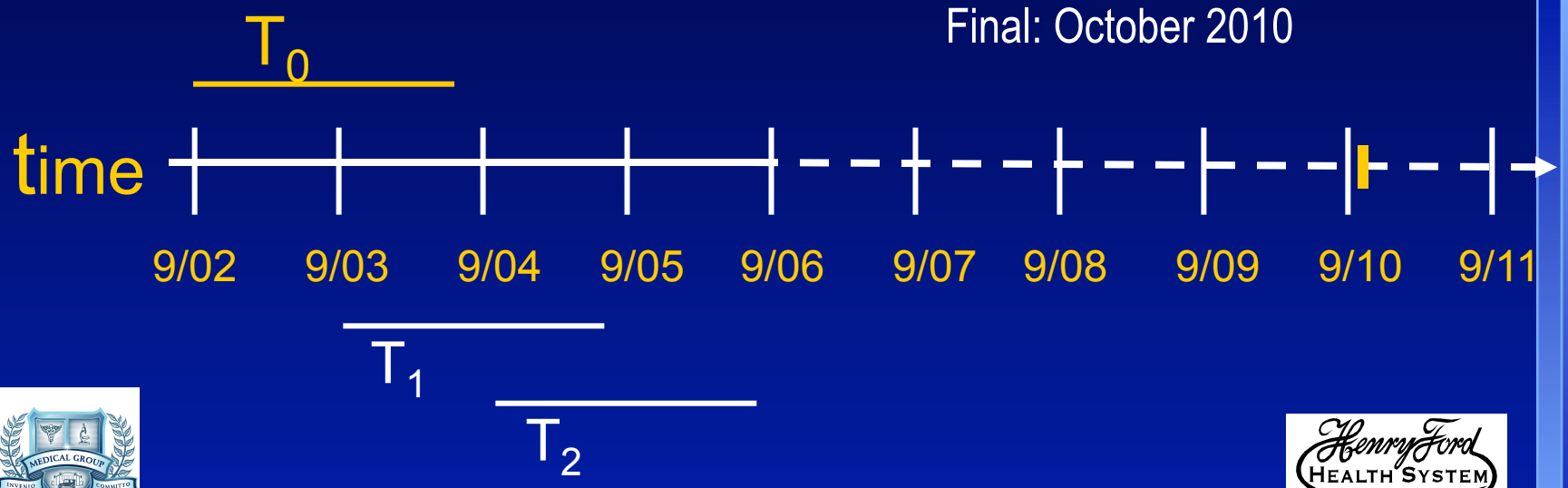
Eligibility

- 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

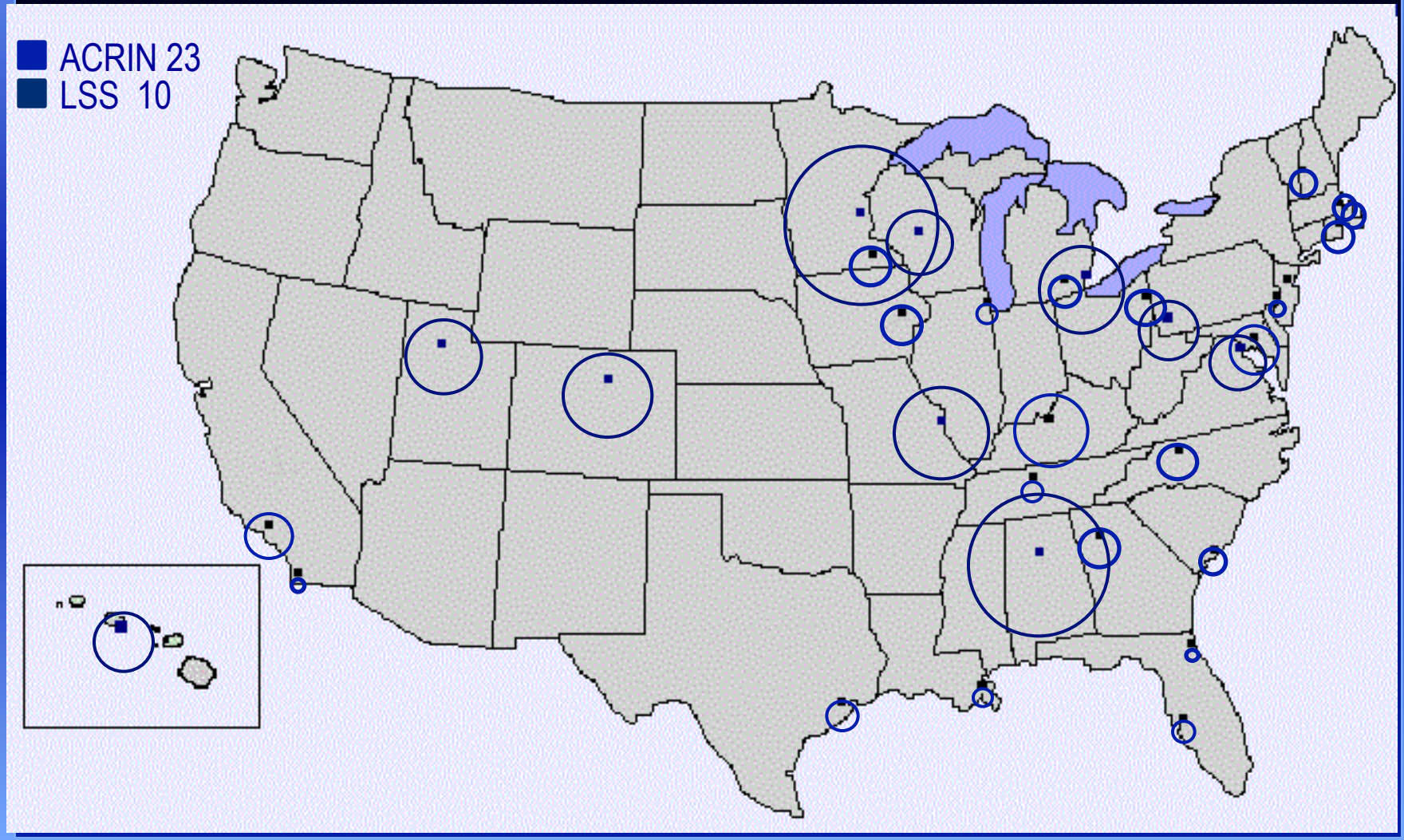
NLST design and projected timeline

High-Risk Subjects — *1:1* — CT Arm / CXR Arm

Annual Interim Analyses : 4/2005 - 4/2010
Final: October 2010



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

NLST secondary endpoints

Secondary endpoints

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

NLST cumulative accrual – 33 sites

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

Lynch DA et al. In press, J Natl Cancer Inst

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

Lynch DA et al. In press, J Natl Cancer Inst

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

Lynch DA et al. In press, J Natl Cancer Inst

NLST Minority Recruitment Efforts

Institution	Location	Population of Interest
Emory University	Atlanta, GA	African American
Jewish Heart and Lung	Louisville, KY	African American
Johns Hopkins University	Baltimore, MD	African American
M.D. Anderson Cancer Center	Houston, TX	Hispanic
St. Elizabeth's Health System [1]	Youngstown, OH	African American
UCLA Jonsson Cancer Center	Los Angeles, CA	African American, Hispanic, Asian
Wake Forest University	Winston-Salem, NC	African American
University of Alabama Birmingham	Birmingham, AL	African American
University of Colorado	Denver, CO	Hispanic
Henry Ford Hospital	Detroit, MI	African American

Duda C et al. NCI-ASCO Cancer Trial Accrual Symposium. April 2010

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
CT	144,097	354	245	20.3	–3.21	–2.02
CXR	143,363	442	308			

p = 0.0041

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

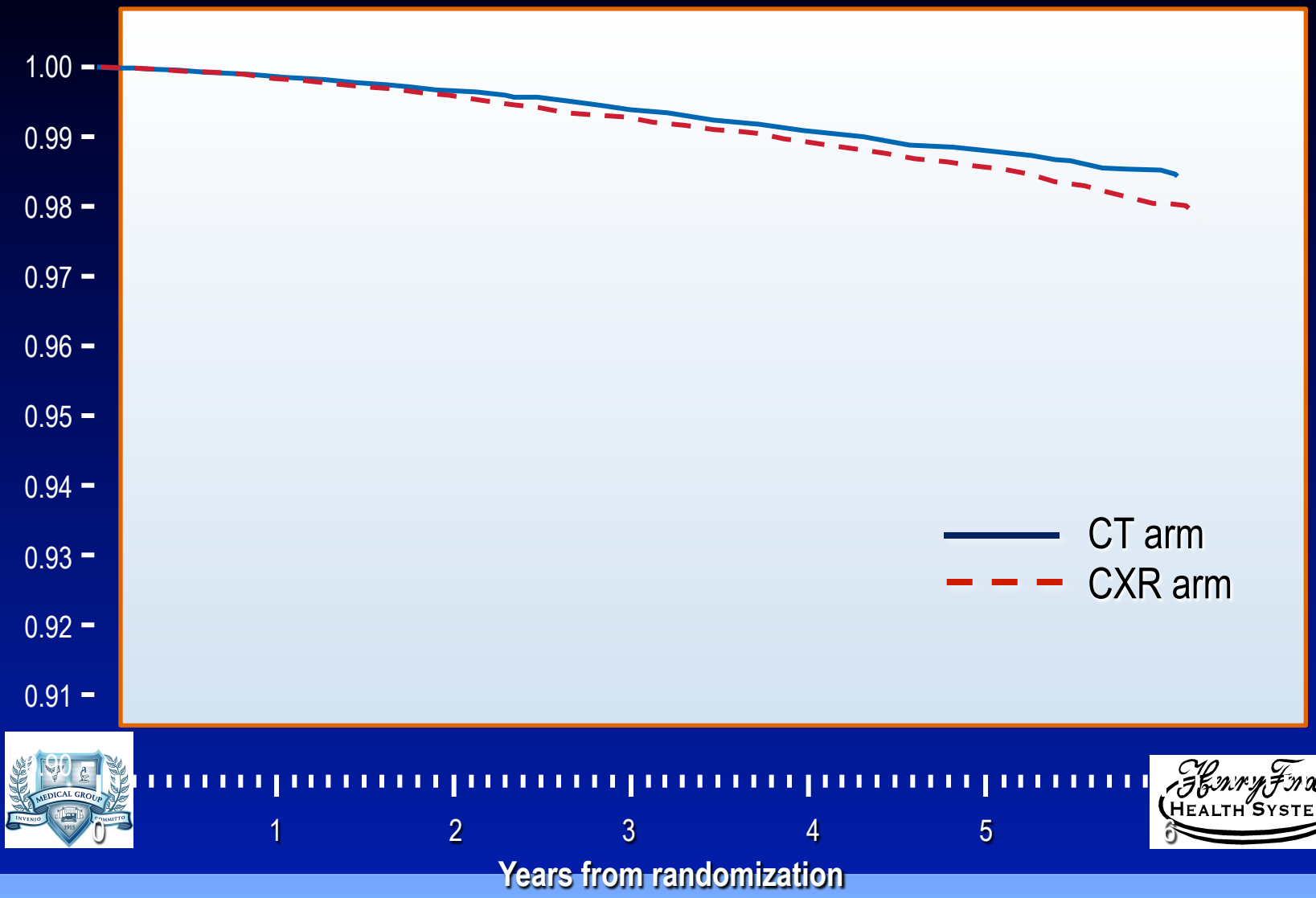
Interim analysis: all-cause mortality 10-20-2010

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	167,390	1870	1117	6.9	–2.27	–1.96
CXR	166,328	1996	1200			

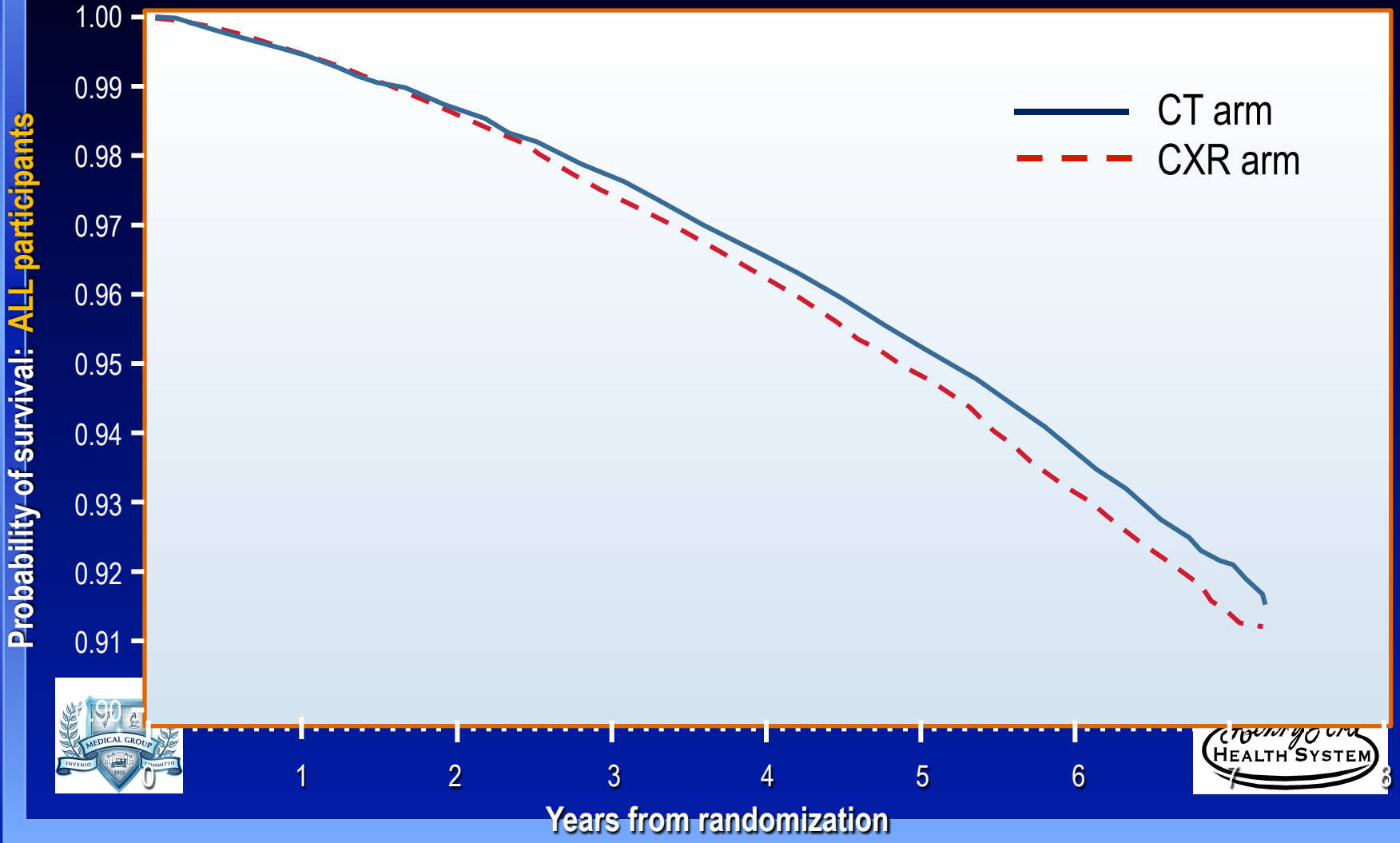
p = 0.023

- Lung cancer: 25% of all deaths in NLST
- Lung cancer: 56% of 126 excess deaths in CXR arm

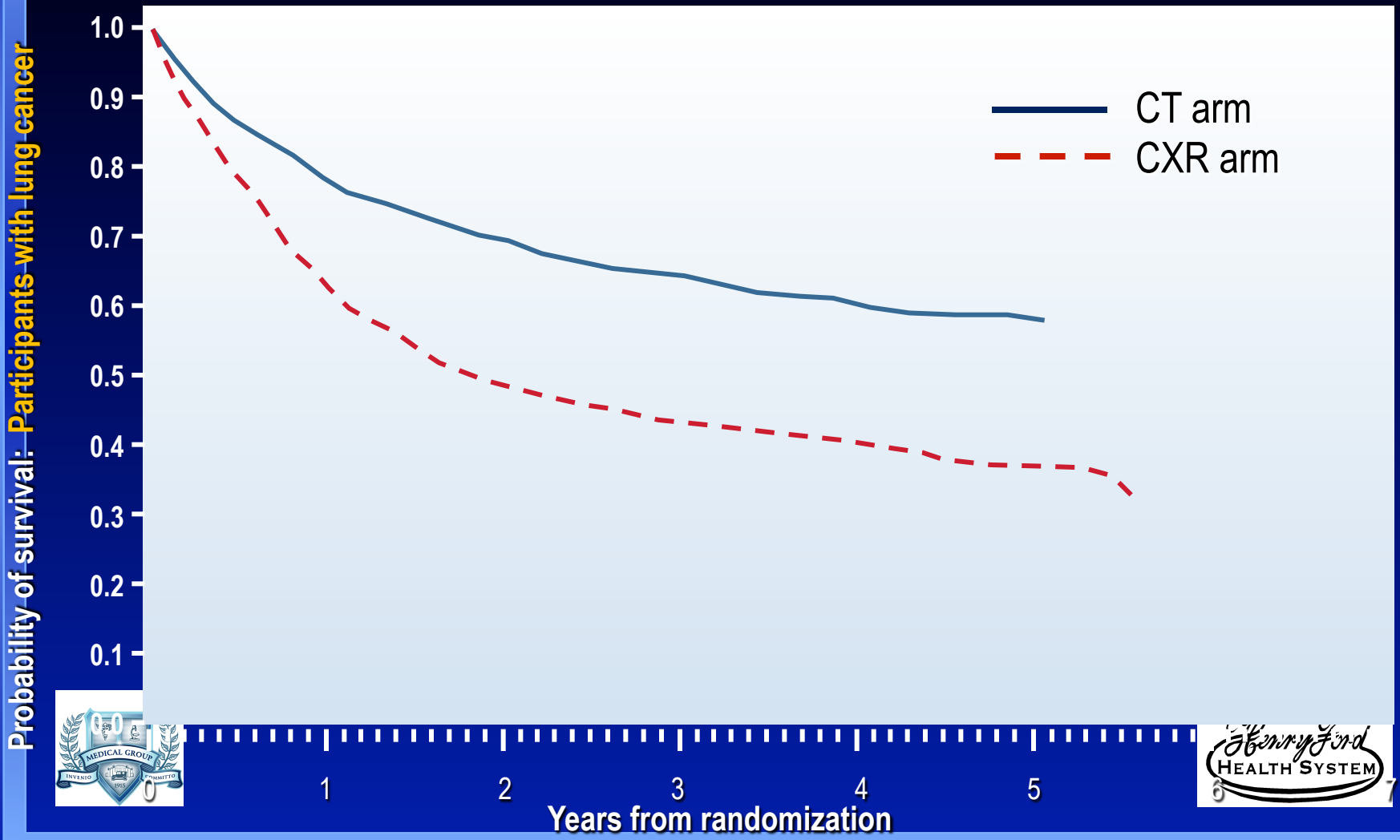
Kaplan-Meier curves for *lung cancer mortality*



Kaplan-Meier curves for *all-cause mortality*



Lung cancer case survival Kaplan Meier curve



Whom should we screen in 2013?

- **Primary target to screen** (based upon the results from the National Lung Screening Trial, patients who meet **all** of the following criteria should have up to 3 annual low-dose chest CT screening examinations):
  - Age = 55 – 74 years
  - Cigarette consumption ≥ 30 pack/years
  - Current smoker, or quit < 15 years ago

Should anybody else be screened in 2013?

- Screening may be considered for the following additional persons:
  - Age ≥ 45 years
  - Cigarette consumption ≥ 20 pack/years
  - Current smoker, or quit < 15 years ago
  - ± family history of lung cancer in 1st generation relative

How long should we continue to screen patients for lung cancer?

- Screening >3 annual LDCTs has not been studied
- Intuitively, continued annual screening through age 74 years seems logical (for patients who continue to meet the primary target criteria), but the cumulative dose of absorbed radiation may create carcinogenic hazards
- Biomarkers may help refine whom to screen

LDCT lung cancer screening is not recommended, and should be discouraged for:

- Age <45 years
- Cigarette consumption <20 pack/years
- Age >74 years
- Patients with only 2nd hand smoke exposure