Methodologic Overview of Screening Studies

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With thanks to Diana Miglioretti

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Financial Disclosure

- Research grant: GE Healthcare

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Learning Objectives

- Understand the difference between screening and diagnostic tests.
- Appreciate the balance between the harms and benefits of screening.
- Understand when and how lead time bias, length bias, and overdiagnosis can influence screening studies.
- Compare and contrast potential endpoints in screening trials.

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What is Screening?

- ACR Task Force on Screening Technologies:

  "Systematic testing of asymptomatic individuals for some target disease."

Purpose:

- Prevent, interrupt, or delay the development of advanced disease in individuals with preclinical disease through early detection (or prevention).
- Reduce morbidity &/or mortality due to the target disease.

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Summary

- Screening differs from diagnostic testing
- Potential effectiveness depends on the natural history of disease and treatment effectiveness
- RCT is most valid design, but has limitations
- Survival statistics are inappropriate and biased
- Once a test is shown to reduce mortality, important to measure and weigh benefits vs. harms
- Decision modeling can be used to extrapolate study results to help inform public policy

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Screening vs. Diagnosis

Screening	Diagnosis
• Healthy individuals	• Patients, ill individuals
• Asymptomatic	• Symptomatic
• Low prevalence of disease, many people tested	• High prevalence of disease, few people tested
• Test non-diagnostic: separates groups into high/low risk of disease	• Test diagnostic
• Test is noninvasive, low risk, not time consuming, inexpensive	• Test may be invasive, higher risk, time less of a consideration, costly

Burden of proof for effectiveness is higher for screening interventions than for diagnostic & treatment interventions

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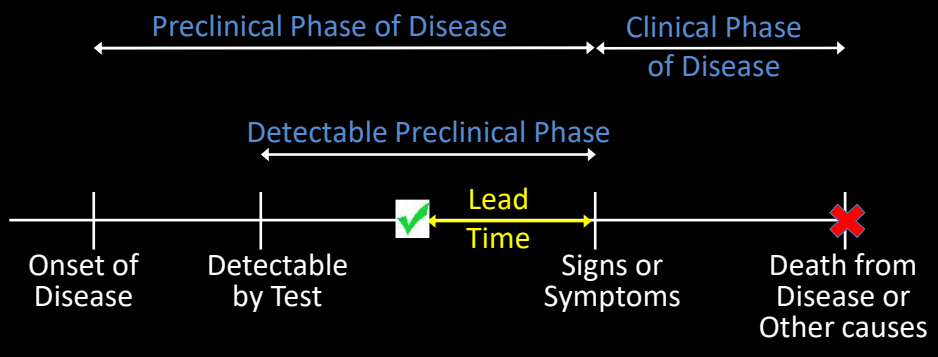
Natural History of Disease



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Critical Point

The point in the natural history of disease before which therapy is more effective.

For screening to be effective, the critical point must occur within the detectable preclinical phase.

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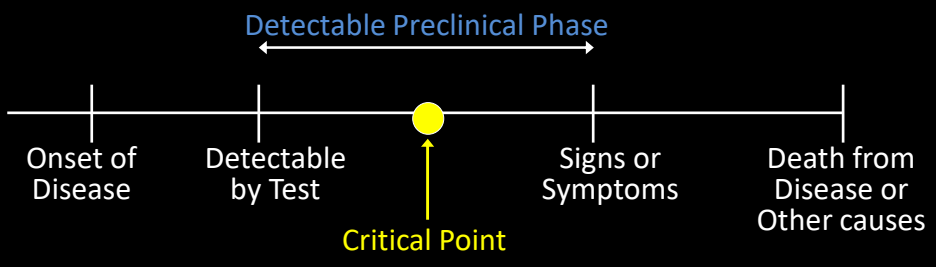
Natural History of Disease



Screening may be effective

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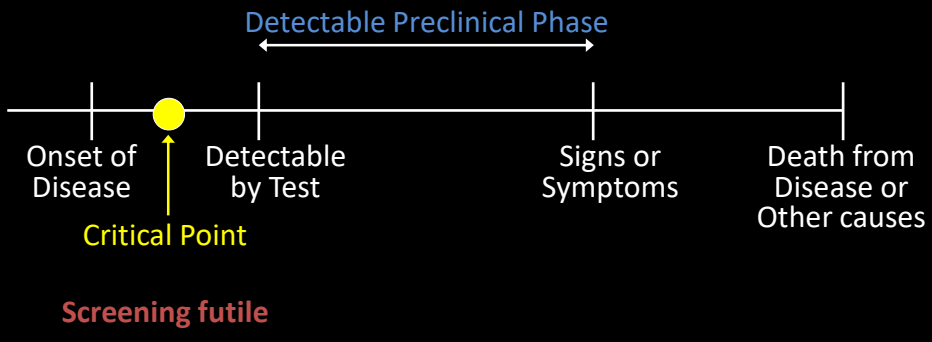
Natural History of Disease



Screening futile

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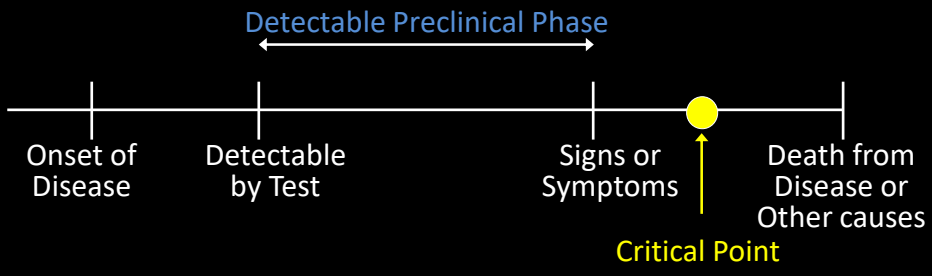
Natural History of Disease



Screening unnecessary

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Potential Biases in Screening Studies

- Lead time bias
  - Survival time increased by lead time, even if screening ineffective
- Length bias
  - Less aggressive tumors more likely to be screen detected
- Overdiagnosis bias
  - Diagnosis of disease that would never harm an individual

All favor screening!

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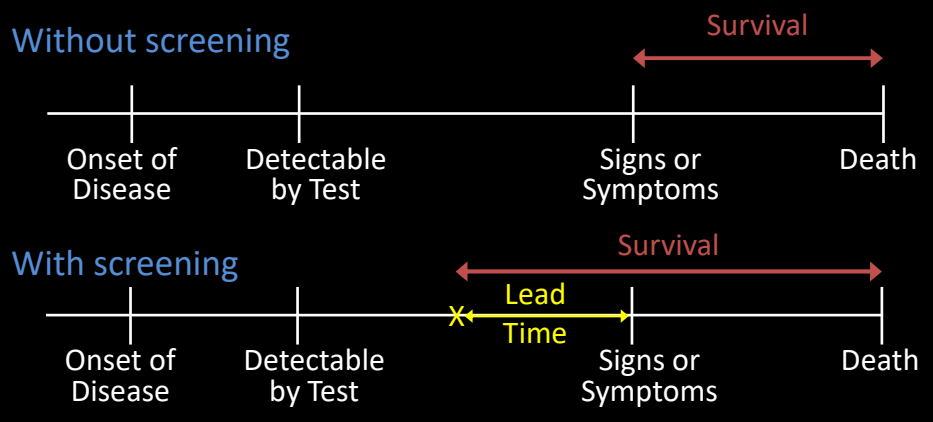
Lead Time Bias – Effect on Survival



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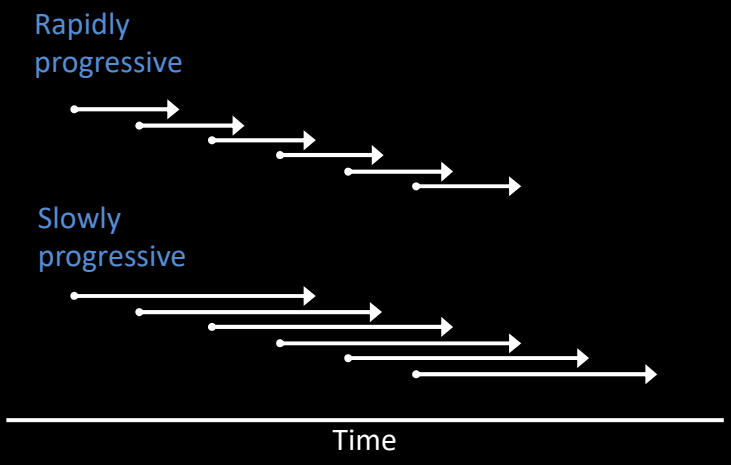
Length Bias



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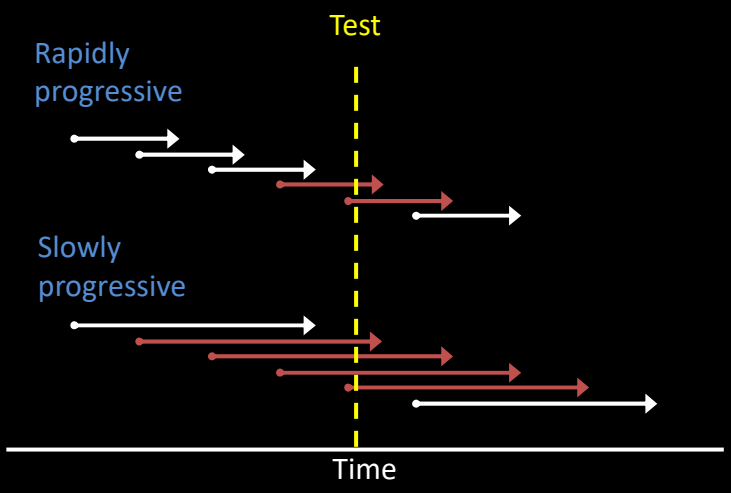
Length Bias



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Overdiagnosis

- The diagnosis of disease that will never cause symptoms or death during the person's lifetime
- A harm of screening
  - Leads to treatments that don't benefit the person and may do harm → "Overtreatment"
  - Once a disease is screen-detected, it is typically impossible to know if it was "overdiagnosed"

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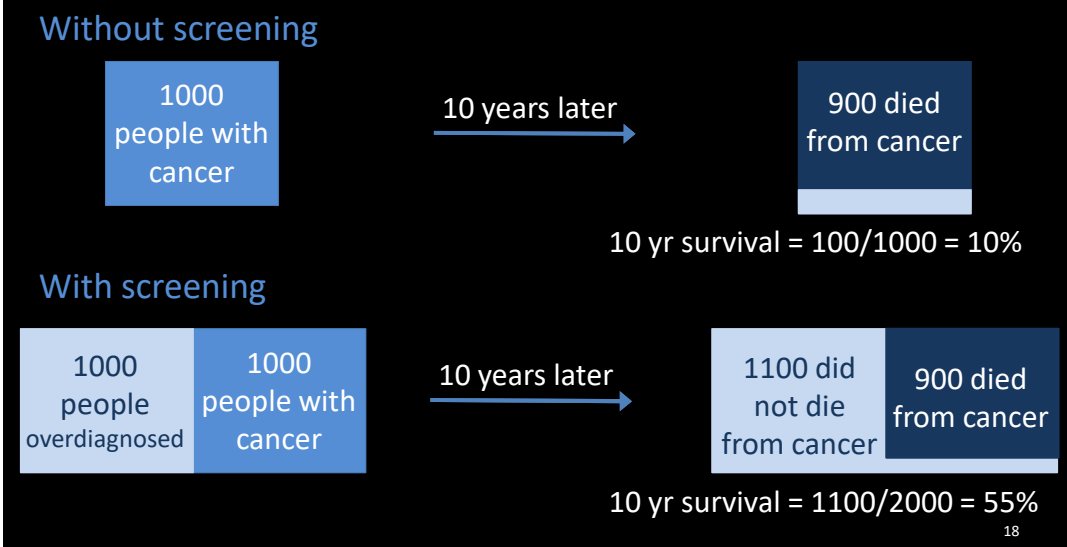
Effect of Overdiagnosis on Case Survival



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Effects of Overdiagnosis on Screening Performance

Underlying Truth

Test Result	Disease	No Disease
Test +	True Positive (TP)	False Positive (FP)
Test -	False Negative (FN)	True Negative (TN)

Detection rate = (TP+O)/N
Sensitivity = (TP+O)/(TP+O+FN)
PPV = (TP+O)/(TP+FP-O)
Specificity = TN/(TN+FP-O)
NPV = TN/(TN+FN)

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Effects of Overdiagnosis on Screening Performance

Underlying Truth (no overdx)

Test Result	Disease	No Disease	
Test +	90	180	270
Test -	10	720	730
	100	900	1000

Detection rate = 90/1000
Sensitivity = 90/100 = 90%
PPV = 90/270 = 33%
Specificity = 720/900 = 80%
NPV = 720/730 = 97%

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Effects of Overdiagnosis on Screening Performance

Underlying Truth (50 cases overdx)

Test Result	Disease	No Disease	
Test +	90	50 + 130	270
Test -	10	720	730
	100	900	1000

Detection rate =

Sensitivity =

PPV =

Specificity =

NPV =

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Effects of Overdiagnosis on Screening Performance

Underlying Truth (50 cases overdx)

Test Result	Disease	No Disease	
Test +	140	130	270
Test -	10	720	730
	150	850	1000

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Effects of Overdiagnosis on Screening Performance

Underlying Truth (50 cases overdx)

Test Result	Disease	No Disease	
Test +	140	130	270
Test -	10	720	730
	150	850	1000

↑Detection rate = 140/1000

↑Sensitivity = 140/150 = 93%

↑PPV = 140/270 = 52%

↑Specificity = 720/850 = 85%

NPV = 720/730 = 97%

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Effects of Overdiagnosis on Outcomes

- ↑detection rate and incidence
- ↑sensitivity of test
- ↑specificity of test
- ↑PPV of test

- Improves stage distribution (as a percentage)
  - Also related to length bias
- Improves case survival
  - Also related to length bias
- Does not decrease population (all cause) mortality

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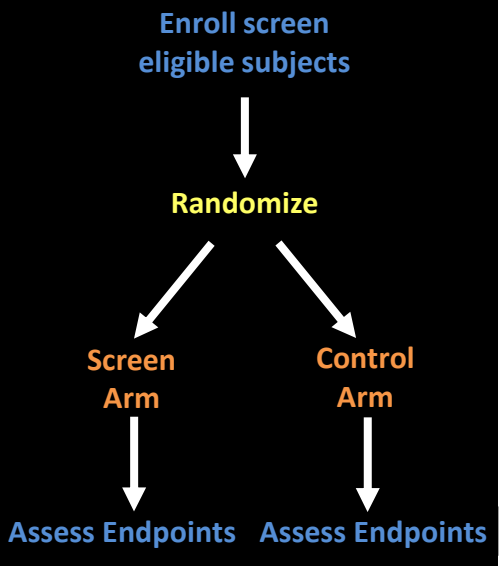
Randomized Controlled Trial

- Strongest study design
- Randomization evenly distributes the known and unknown confounders
- Groups similar except for screening test under study
- Controls for most selection bias



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Potential limitations

- No clinical signs or symptoms of disease
  - May need large sample sizes
  - Higher risk or symptomatic individuals may differentially volunteer
- Screen individuals at higher risk for disease?
  - Screening higher risk population reduces RCT sample size
  - Limits generalizability to average-risk individuals
- Willing and able to:
  - Accept randomization, for all rounds in full study
  - Undergo workup and treatment per protocol
  - Be followed for outcomes

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Endpoints/Outcomes

- Comparisons of **survival** are invalid and biased!
  - Lead time bias, length bias, overdiagnosis bias
- Disease-specific mortality
  - Most widely used & accepted
  - Assumes cause of death can be determined accurately and screening doesn't increase risk of dying from other causes
- All cause mortality =>

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All Cause Mortality

- Not affected by cause-of-death misclassification
- Insensitive measure of efficacy
  - Breast cancer screening: sample size 25–60 times larger (1.2-1.5 million per arm) if overall vs. disease specific mortality
- Still useful to measure along with Disease Specific Mortality
  - May reveal deficiencies in randomization
  - Puts screening in perspective
    - Annual FOBT: 33% ↓ DSM $\Rightarrow$ 1% ↓ overall mortality
  - Helps ensure a major harm (or benefit) is not being missed. Important if test or treatment causes mortality.

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Other Endpoints/Outcomes

- Absolute risk reduction or number needed to screen to prevent one death (reciprocal)
- Stage of target disease at diagnosis (rates, not percentages)
  - Include both screen-detected and interval cancers
- Adverse events
  - Morbidity caused or prevented by screening
- Quality of life
- Resource utilization and costs
  - Medical and nonmedical/opportunity costs

Covered in other CTMW presentations

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Example: National Lung Screening Trial

- Enrolled 53,454 persons 55-74 years at high risk (30 pack years) from 8/2002 to 4/2004
  - 33 medical centers
- Randomly assigned to three annual screens with either
  - Low-dose CT
  - Single view chest x-ray
- Followed through 2009
- Power: 90% to detect 21% decrease in lung cancer mortality

N Engl J Med 2011; 365:395-409

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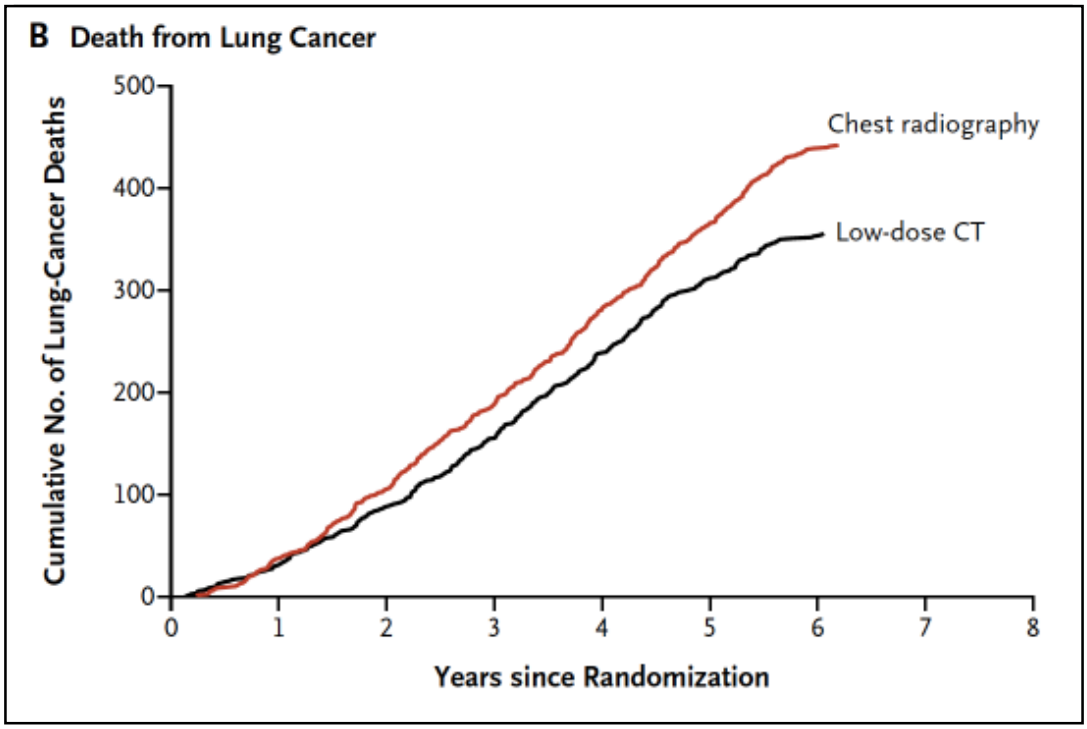
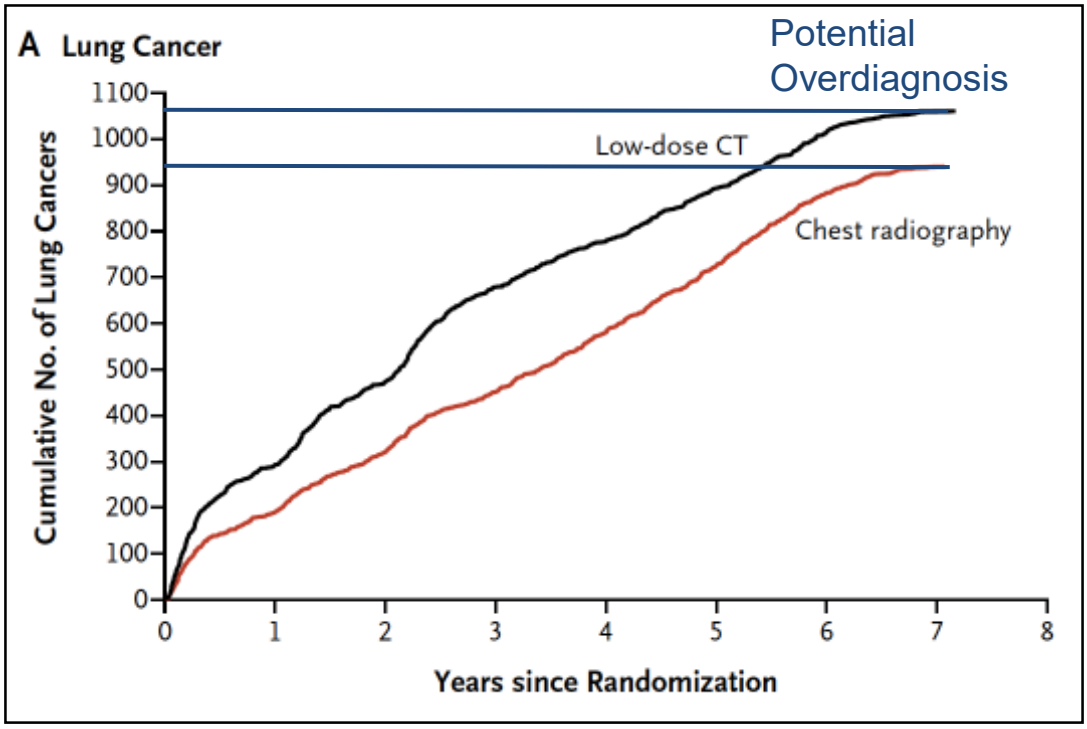

B Death from Lung Cancer
Cumulative No. of Lung-Cancer Deaths
500
400
300
200
100
0
Chest radiography
Low-dose CT
0
1
2
3
4
5
6
7
8
Years since Randomization

33


A Lung Cancer
Potential Overdiagnosis
Cumulative No. of Lung Cancers
1100
1000
900
800
700
600
500
400
300
200
100
0
Low-dose CT
Chest radiography
0
1
2
3
4
5
6
7
8
Years since Randomization

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Results: National Lung Screening Trial

Adherence >90%

	Low Dose CT	X-Ray
Recall rate	24.2%	6.9%
False-positive rate	23.3%	6.5%
Cancer rate (per 100,000 PY)	645	572
Lung cancer deaths (per 100,000 PY)	247	309
Risk reduction	20% (95% CI 6.8% to 26.7%, p=0.004)	
All cause mortality risk reduction	6.7% (95% CI 1.2% to 13.6%, p=0.02)	
Other cause mortality risk reduction	3.2% (p=0.28)	

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Observational Studies vs RCT

- Both compare groups receiving different interventions
  - In observational studies, group assignment may be due to
    - Patient or provider factors, or policy changes
  - May be prospective or retrospective
- Strengths
  - Increased generalizability
    - Ability to enroll more diverse populations
    - Larger sample sizes potentially
    - Community and academic settings
- Multiple designs
  - Correlation/Ecological, Case-control, or Cohort

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Bias Limits Observational Studies

- Observer and recall bias due to retrospective data collection
- Selection bias: Screened individuals at different risk than unscreened individuals
- Confounding: known or unknown differences b/w screened and unscreened groups also related to outcomes
  - Can only adjust for known confounders

Can bias results in either direction!

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JAMA Internal Medicine | Original Investigation

Performance of Screening Ultrasonography as an Adjunct to Screening Mammography in Women Across the Spectrum of Breast Cancer Risk

Janie M. Lee, MD, MSc; Robert F. Arao, MPH; Brian L. Sprague, PhD; Karla Kerlikowske, MD; Constance D. Lehman, MD, PhD; Robert A. Smith, PhD; Louise M. Henderson, PhD; Garth H. Rauscher, PhD; Diana L. Miglioretti, PhD

- Observational cohort study
- 6,081 Screening mammography + same day US exams compared with screening mammography alone
- But women receiving mammo + US were
  - Younger, white non-Hispanic
  - Have dense breasts, family history, higher 5-yr risk

JAMA Intern Med. 2019;179(5):658-667

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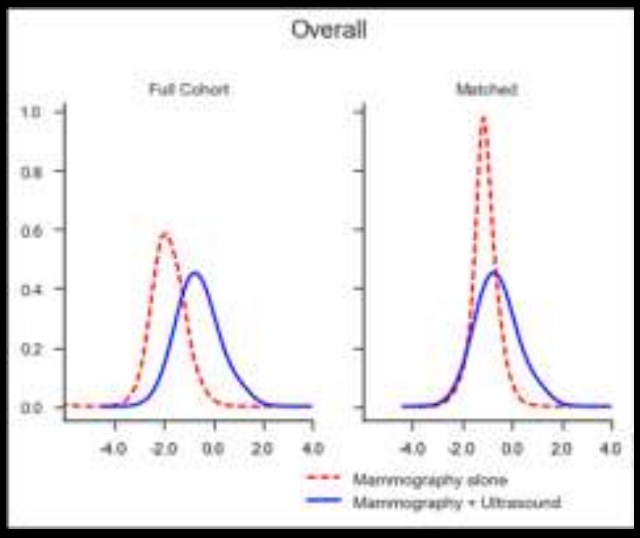

- Used propensity scores to match Mammo+US exams to Mammo alone exams 1:5
- Kernel density plots provide a visual summary of propensity score distributions

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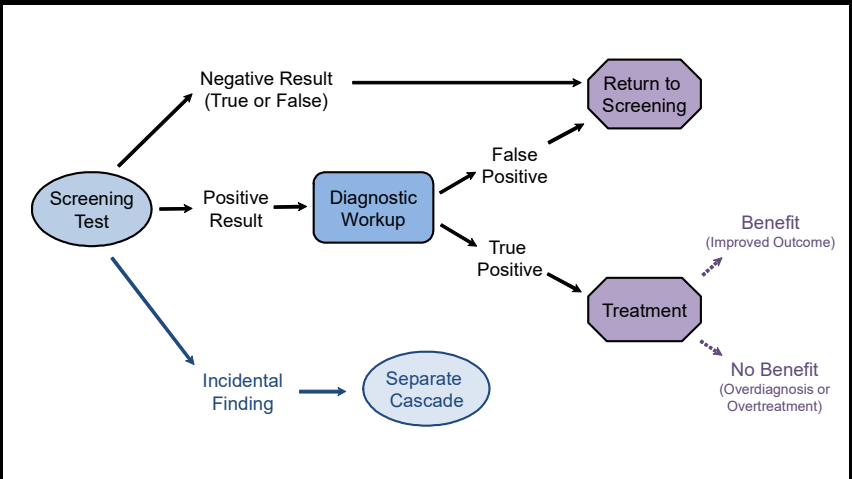
Screening Cascade



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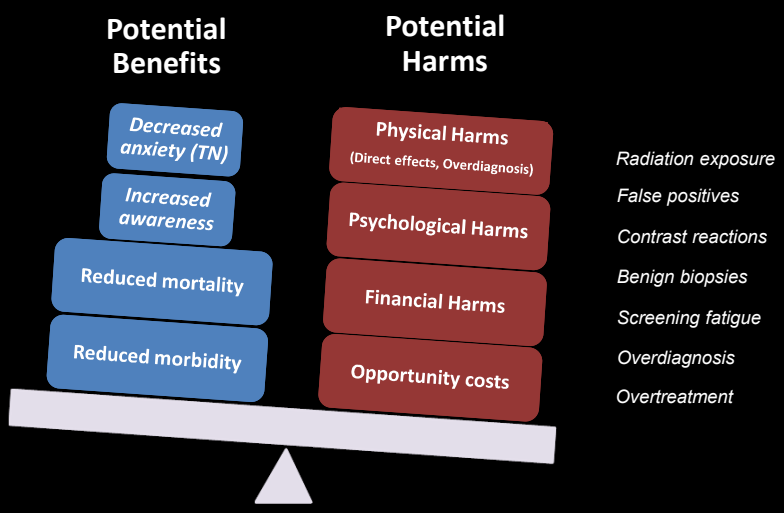
Benefit-Harm Balance of Screening



**"All screening programs do harm;
some also do good, and of these, some do more good than harm."**

Gray et al. BMJ 2008. 336(7642) 480-483

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Thank you!

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