“Lung Cancer Screenings: Guidelines, Risks, and Benefits of LDCT”

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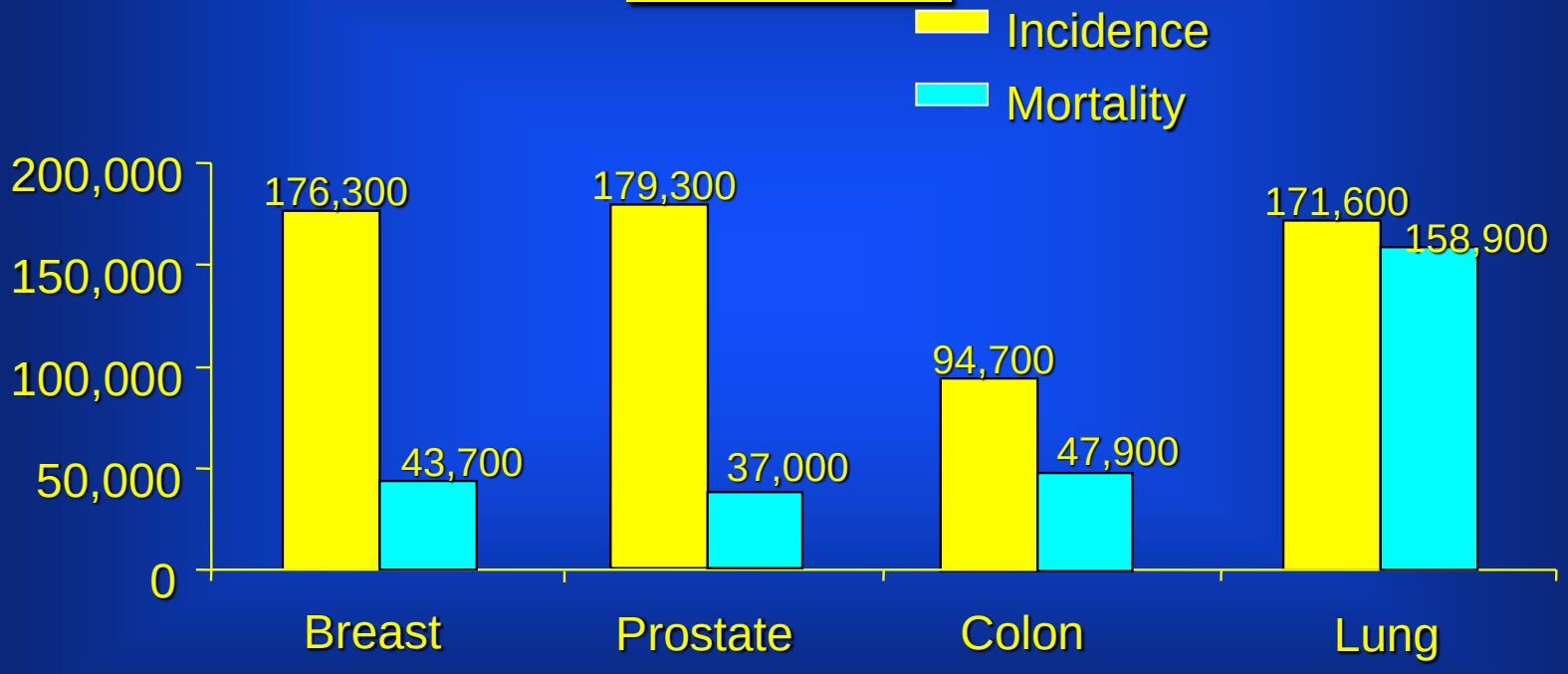
Outline

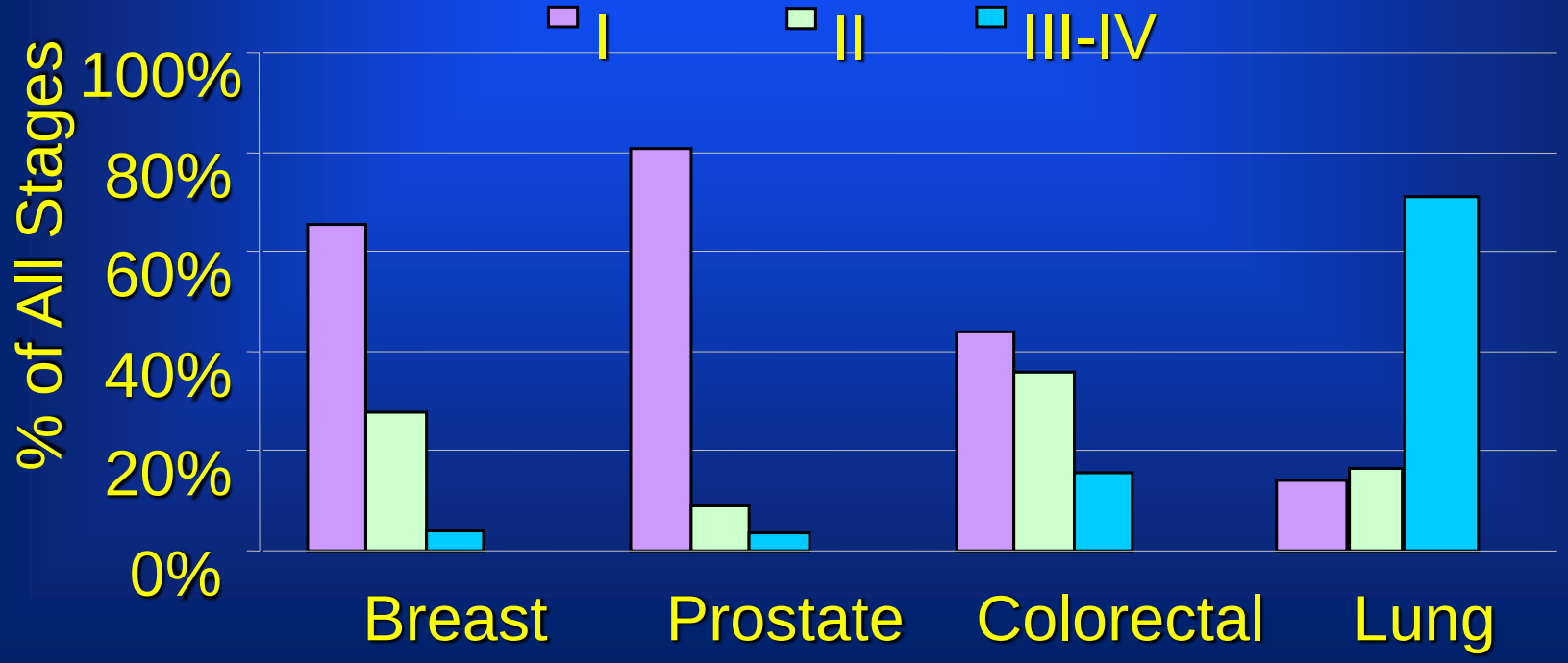
- ***Context***
- ***What are* the benefits?**
- ***What are* the potential pitfalls**
  - **Psychological**
  - **Financial**
  - **Physical/Iatrogenic**
  - ***How do we minimize these?***

One of these things is not like the others



American Cancer Society. *Cancer Facts & Figures–1999.*

Approximate Cancer Stage at Diagnosis



Historical lung cancer screening recommendations

- Pre-1980; Annual CXR for all smokers over 40 years of age was standard of care
- Based upon large NIH sponsored randomized CXR screening trials in 1970's
  - 1980; CXR "…not indicated…people with signs and symptoms of lung cancer should consult their physician

NLST study design

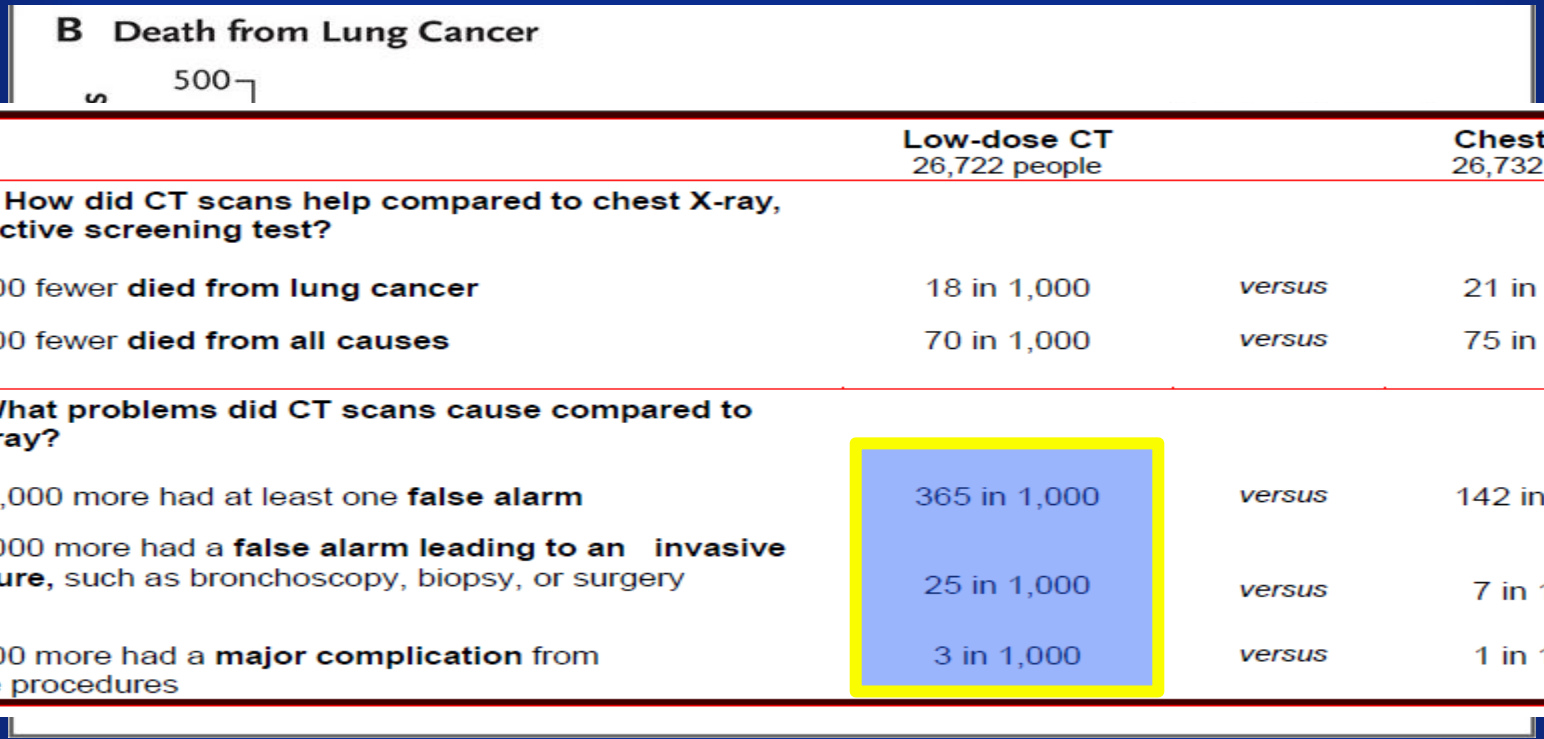
- **Study design**
  - 50,000 ***healthy*** current or former (15 yrs), heavy (30 pk-yr) smokers, age 55-74
  - CXR ***or*** LOW DOSE CT at 0, 1, and 2 years
  - 2002-2008, with follow up through 2011
- **90% power to detect 20% mortality benefit**
  - All cause mortality, Prevalence, incidence, interval cancers, PPV, NPV, Stage distribution
  - HRQOL, and Anxiety instrument
  - Medical resource utilization for positive screen and cost effectiveness

Where we are now

- **USPSTF recommends *annual* screening for lung cancer with low-dose computed tomography (LDCT) in persons at high risk for lung cancer based on age (*55-80*) and smoking history (>30 pk-yrs, within 15 yrs)**
- **Unless we accept that screening results in a "teachable moment" regarding tobacco use, the benefits are truly accrued by only a small minority of those screened, so harms must be minimized**

Ann Intern Med. 2014;160(5):330-338. doi:10.7326/M13-2771

Cumulative Deaths from Lung Cancer.



	Low-dose CT 26,722 people		Chest X-ray 26,732 people
Benefit: How did CT scans help compared to chest X-ray, an ineffective screening test?			
3 in 1,000 fewer **died from lung cancer**	18 in 1,000	*versus*	21 in 1,000
5 in 1,000 fewer **died from all causes**	70 in 1,000	*versus*	75 in 1,000
Harm: What problems did CT scans cause compared to chest X-ray?			
223 in 1,000 more had at least one **false alarm**	365 in 1,000	*versus*	142 in 1,000
18 in 1,000 more had a **false alarm leading to an invasive procedure,** such as bronchoscopy, biopsy, or surgery	25 in 1,000	*versus*	7 in 1,000
2 in 1,000 more had a **major complication** from Invasive procedures	3 in 1,000	*versus*	1 in 1,000

The National Lung Screening Trial Research Team. N Engl J Med 2011. DOI: 10.1056/NEJMoa1102873

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Intervention	Age	Screen frequency	RR of death	Baseline risk of death	NNS	$/QALY
PSA						
ERSPC[1]	55-69	q 2-7 years	0.80 (0.65-0.98)	0.4%	1,400	
PLCO [2]	55-74	Yearly X 6y	1.10 (0.80-1.50)	0.1%	N/A	
Mammography[3,4]						
	39-49[4]	Yearly X 2-9y	0.85 (0.75-0.96)	0.3%	1900	
	50-59	Yearly X 10	0.86 (0.75-0.99)	0.5%	1,300	
	60-69	Yearly X 10	0.68 (0.54-0.87)	0.8%	380	$58,000 [5]
Colon cancer						
Fecal occult blood [3]		~ 9 years	0.77	??	808	
Flex Sig/FOB [6]	50	q 5 years (with FOBT)	0.82	??	361	$92,900
Colonoscopy			(Probably better)	??	??	
Lung cancer						
CXR [7]	55 - 74	Yearly x 4	0.94 (0.81-1.10)	1.6%	NA	
Low-dose CT [8]	55-74	Yearly x 3	0.80 (0.73-0.93)	1.7%	320	$52,000-80,000[9]

1. Chou R, : Ann Int Med 2011; 155(11): 762-771
2. Andriole GL,NEJM 2009; 360(13): 1310-1319
3. Rembold CM. BMJ 1998; 317(7154): 307-312
4. Nelson HD Ann Int Med 2009; 151(10): 727-737
5. Stout JNCI 2006; 98(11): 774-782
6. Elmunzer BJ. PLoS Med 2013; 9(12): e1001352
7. Oken MM JAMA 2011; 306(17): 1865-1873
8. Aberle DR NEJM 2011; 365(5): 395-409
9. Black, W NEJM. 2014; 371 1793-1802

Table 4. Incremental Costs According to Subgroups.

Characteristic	No. of Participants	Incremental Costs	Incremental QALYs	Cost per QALY
		U.S. $	*QALY*	*U.S. $*
Sex				
Male	31,446	1,683	0.0115	147,000
Female	21,856	1,557	0.0340	46,000
Age at entry				
55–59 yr	22,773	1,541	0.0101	152,000
60–64 yr	16,333	1,520	0.0320	48,000
65–69 yr	9,504	1,900	0.0351	54,000
70–74 yr	4,685	1,905	0.0163	117,000
Smoking status				
Former	27,643	1,661	0.0027	615,000
Current	25,659	1,601	0.0369	43,000
Risk of lung cancer				
First quintile	10,660	1,453	0.0086	169,000
Second quintile	10,661	1,454	0.0118	123,000
Third quintile	10,660	1,651	0.0061	269,000
Fourth quintile	10,661	1,672	0.0515	32,000
Fifth quintile	10,660	1,851	0.0354	52,000

- **Incremental Cost Effectiveness of Lung Cancer Screening by Subgroup**
- **Screening more cost effective in women(?)**
- **Mortality benefit was greater *(p=0.07)***

Black WC et al. N Engl J Med 2014;371:1793-1802.

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What are the harms?

False positives….

Harms of screening for Lung Cancer

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“False positives”

- “Positive” was defined as any non calcified nodule > 4 mm
  - 36% screened with LDCT had a positive finding (96% are not cancer)
  - Most are managed by additional follow up CT (Note: Some false positives have been around for decades)
  - A single additional CT at 6 months
    - 0,12 24 months or…
    - 0, 6, 12, and 24 months

How are “positives” managed

- “False positives” is issue not a new problem
  - These have been around since the dawn of radiography
- “Lung nodule problem” predates lung cancer screening by several decades
- Nearly all false positives merely introduce a single additional CT at 6 as opposed to 12 months
  - Minimize biopsies, minimize harm

How is the CT reported?

- LUNGRads is modeled after BiRADS (mammography reporting format)
- A structured reporting system for all findings (lung and non lung-related)
- Minimizes false positives and provides guidance to clinicians on management

Other screening harms?

- Anxiety/QOL
- Invasive procedures
- Overdiagnosis/Overtreatment
- Additional testing and costs

Anxiety/QOL

Impact of Lung Cancer Screening Results on Participant Health-Related Quality of Life and State Anxiety in the National Lung Screening Trial

Ilana F. Gareen, PhD[1,2]; Fenghai Duan, PhD[1,3]; Erin M. Greco, MS[1]; Bradley S. Snyder, MS[1]; Phillip M. Boiselle, MD[4,5]; Elyse R. Park, PhD, MPH[6,7,8]; Dennis Fryback, PhD[9]; and Constantine Gatsonis, PhD[1,3]

CONCLUSIONS: In a large multicenter lung screening trial, participants receiving a false-positive or SIF screen result *experienced no significant difference in HRQoL or state anxiety at 1 or at 6 months after screening* relative to those receiving a negative result.

KEYWORDS: quality of life, anxiety, lung cancer, screening, clinical trials.

Cancer; 25 JUL 2014 DOI: 10.1002/cncr.28833 http://onlinelibrary.wiley.com/doi/10.1002/cncr.28833/full#cncr28833-fig-0002

PATIENT EDUCATION | *INFORMATION SERIES*

What is a Lung Nodule?

Commonly called a "spot on the lung" or a "shadow," a nodule is a round area that is more solid than normal lung tissue. It shows up as a white spot on a CT scan. Lung nodules are usually caused by scar tissue, a healed infection that may never have made you sick, or some irritant in the air. Sometimes, a nodule can be an early lung cancer.

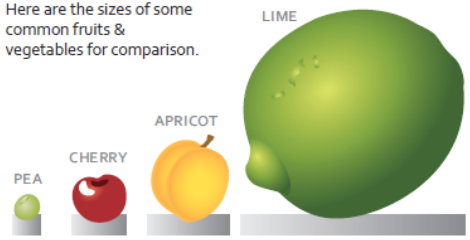
Why have I been given this handout?
One or more lung nodules were seen on your recent chest x-ray or CT ("CAT") scan.

How common are lung nodules?
Nodules are found in up to half of adults who get a chest x-ray or CT scan.

Do nodules cause any symptoms?
In general, small nodules don't cause any noticeable problems. They're too small to cause pain or breathing problems.

How big is the nodule?
Your healthcare team can tell you the exact size of your nodule. Most nodules are less than 10 millimeters (about a ½ inch)

Here are the sizes of some common fruits & vegetables for comparison.



CLIP AND COPY

- are older
- have a larger nodule
- smoked or still smoke cigarettes
- have other cancer risks, such as lung cancer in your family or handling asbestos in the past.

For example, a small nodule in a young person who never smoked is less likely to be cancer than a larger nodule in an older person who recently quit smoking. **However, even in the person with a high risk of lung cancer, most small nodules are not lung cancer.**

Some patients would like an estimate of how likely their nodule is lung cancer. If knowing that number would help you, please contact your provider.

What if my nodule is lung cancer?
Even if a nodule turns out to be lung cancer, it is likely to be an early stage lung cancer. People with early stage lung cancer that is treated are less likely to die of lung cancer than people who are diagnosed at a later stage when the cancer has started to cause symptoms.

Your healthcare team will be with you every step of the way. Please discuss any concerns you have about lung cancer with your healthcare team.

What will happen next?
Your healthcare team will probably recommend getting more CT scans to keep a close eye on the nodule to see if it changes. We call this "active surveillance."

- **ATS has produced a tool that deals with patient anxiety over lung nodules**
- **https://www.thoracic.org/patients/patient-resources/resources/lung-nodules-online.pdf**

Potential harms?

- Anxiety/QOL
- Invasive procedures
- Overdiagnosis/Overtreatment
- Additional testing and costs

Complications after the Most Invasive Screening-Related Diagnostic Evaluation Procedure, According to Lung-Cancer Status.

ble 4. Complications after the Most Invasive Screening

mplication	Lung Cancer Not Confirmed				
	Thoracotomy, Thoracoscopy, or Mediastinoscopy	Bronchoscopy	Needle Biopsy	No Invasive Procedure	Total
			number (percent)		
w-dose CT group					
sitive screening results for which diagnostic informati was complete	164 (100.0)	227 (100.0)	66 (100.0)	16,596 (100.0)	17,053 (100.0)
No complication	138 (84.1)	216 (95.2)	59 (89.4)	16,579 (99.9)	16,992 (99.6)
At least one complication	26 (15.9)	11 (4.8)	7 (10.6)	17 (0.1)	61 (0.4)
Most severe complication classified as major	9 (5.5)	2 (0.9)	0	1 (<0.1)	12 (0.1)
Most severe complication classified as intermedi	13 (7.9)	9 (4.0)	6 (9.1)	16 (0.1)	44 (0.3)
Most severe complica					5 (<0.1)
Death within 60 days afte procedure†					11 (0.1)
diography group					
sitive screening results for was complete					4,674 (100.0)
No complication					4,65 (99.7)
At least one complication					16 (0.3)
Most severe complica					4 (0.1)
Most severe complica					9 (0.2)
Most severe complica					3 (0.1)
Death within 60 days afte procedure†					3 (0.1)

Complications among those without cancer	# (%)
No complication	16, 992 (99.6%)
At least one complication	61 (0.4%)
Major	12 (0.1%)
Intermdiate	44 (0.3%)
Minor	5 (<0.1)
Death within 60 Days	11 (0.1%)

The National Lung Screening Trial Research Team . N Engl J Med 2011;365:395-409.

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Potential harms?

- Anxiety/QOL
- Invasive procedures
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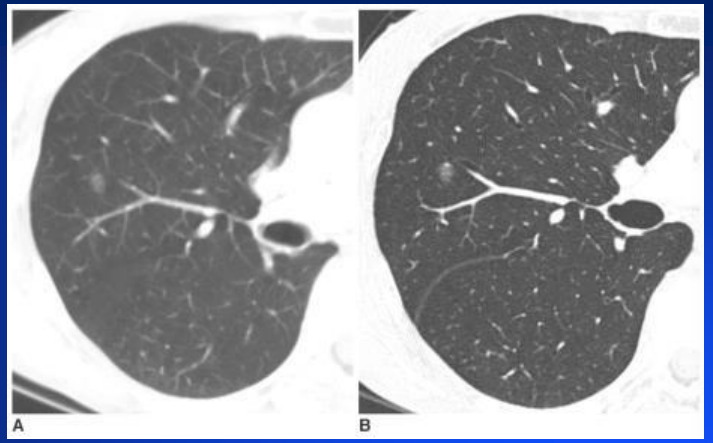
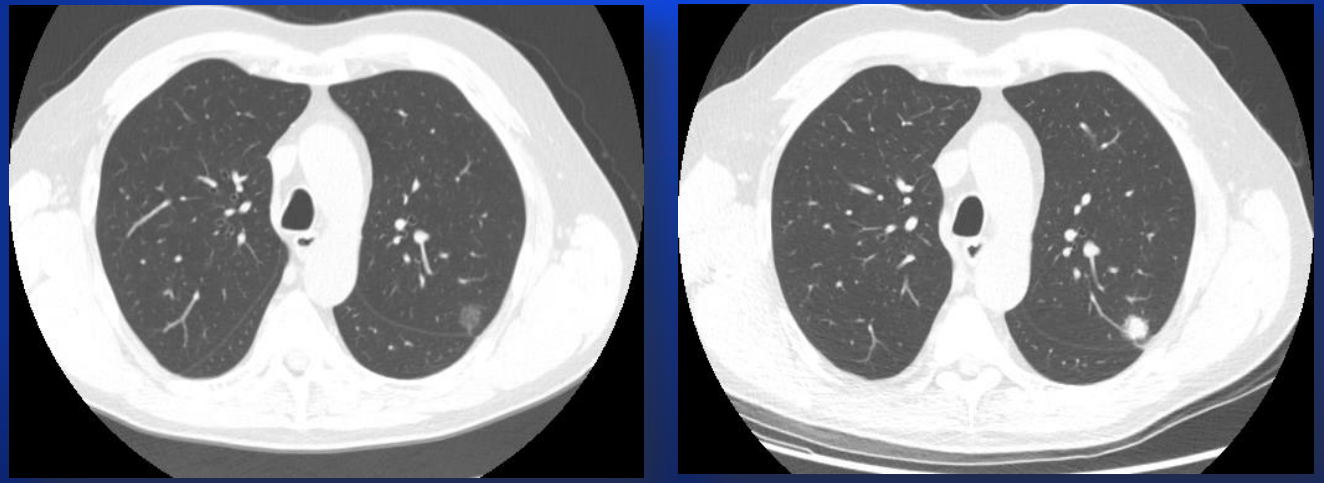


Overdiagnosis or overtreatment of lung cancer almost certainly includes pure ground glass opacities, but where does the line get drawn?

Ground glass nodule

2006 → 2010



Potential harms?

- Overdiagnosis/Overtreatment
  - Studies estimate that this occurs in 9%-18.5% of screen detected lung cancers
  - Estimates of overdiagnosis vary depending on your time horizon
  - Greater co-morbid illness = greater “overdiagnosis” (Competing mortality)

Potential harms?

- Anxiety/QOL
- Invasive procedures
- Overdiagnosis/Overtreatment
- Additional testing for significant incidental findings and costs
  - Thyroid, renal, esophageal and renal and adrenal abnormalities

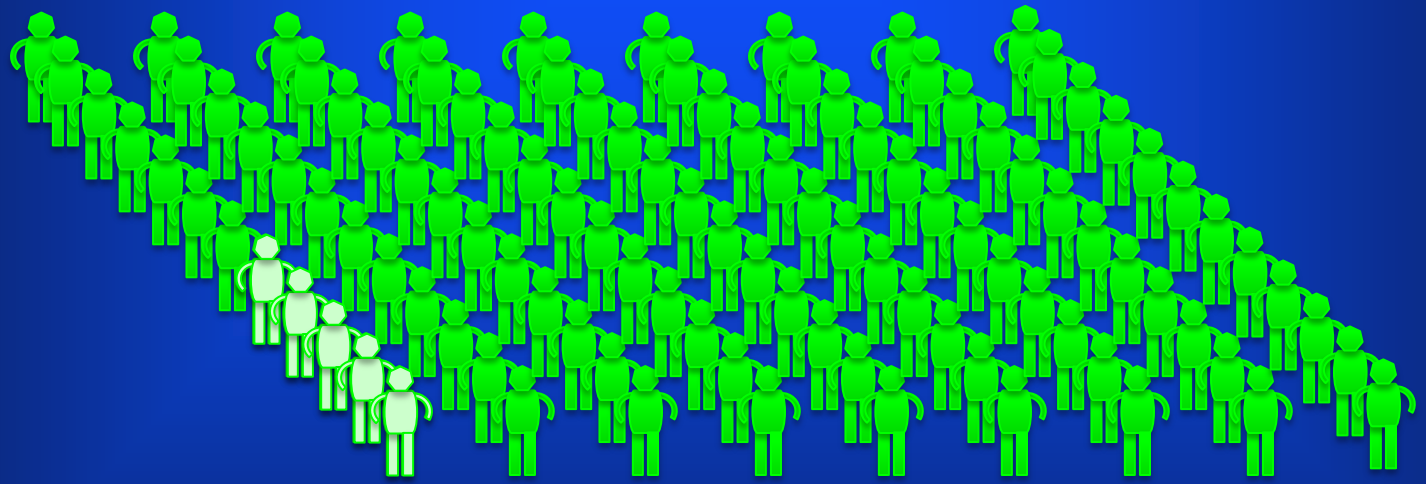
Potential harms?

- "Significant incidental findings"
  - Screening programs and institutions should develop standardized solutions/referral pathways for:
  - Coronary artery calcifications
  - Aortic abnormalities
  - Thyroid nodules
  - Kidney and liver cysts
  - Esophageal abormalities

Potential harms?

- Anxiety/QOL
- Invasive procedures
- Overdiagnosis/Overtreatment
- Additional testing and costs

Variability in risk among smokers



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What if everyone we screened was “High risk”?

$$

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

When the Average Applies to No One: Personalized Decision Making About Potential Benefits of Lung Cancer Screening

Table. **Projected Likelihood Over 6 Years of Lung Cancer Death With or Without Screening per 1000 Persons Screened***

Participant	Risk Factors	Deaths From Lung Cancer (Without Screening) per 1000 Persons, *n*	Deaths From Lung Cancer (With Screening) per 1000 Persons, *n*	Lung Cancer Deaths Averted per 1000 Persons, *n*	Persons Needed to Be Screened Annually for 3 y to Prevent 1 Death From Lung Cancer Over 6 y, *n*
"Typical" participant in the NLST	62-year-old male current 1.5-PPD smoker for 35 y	19.5	15.6	3.9	256
Minimum eligible participant in the NLST	55-year-old female former 1-PPD smoker for 30 y who just quit	4.0	3.2	0.8	1236
High-risk participant eligible for the NLST	70-year-old current 2-PPD smoker for 55 y	60.9	48.7	12.2	82
Minimum eligible participant by NCCN guidelines	50-year-old male former 1-PPD smoker for 20 y who quit 10 y ago with an occupational asbestos exposure history	1.6	1.3	0.3	3180
Low-risk eligible participant for Sequoia Hospital lung screening program	40-year-old female former 1-PPD smoker for 10 y who quit 15 y ago	0.10	0.08	0.02	35 186

NCCN = National Comprehensive Cancer Network; NLST = National Lung Screening Trial; PPD = packs per day.
* Assuming the program includes 3 y of annual screening.

Projected 6 Year Likelihood of Lung Cancer Death With or Without Screening per 1000 Persons Screened

Ann Intern Med. 2013;157(8):571-573

The importance of absolute risk

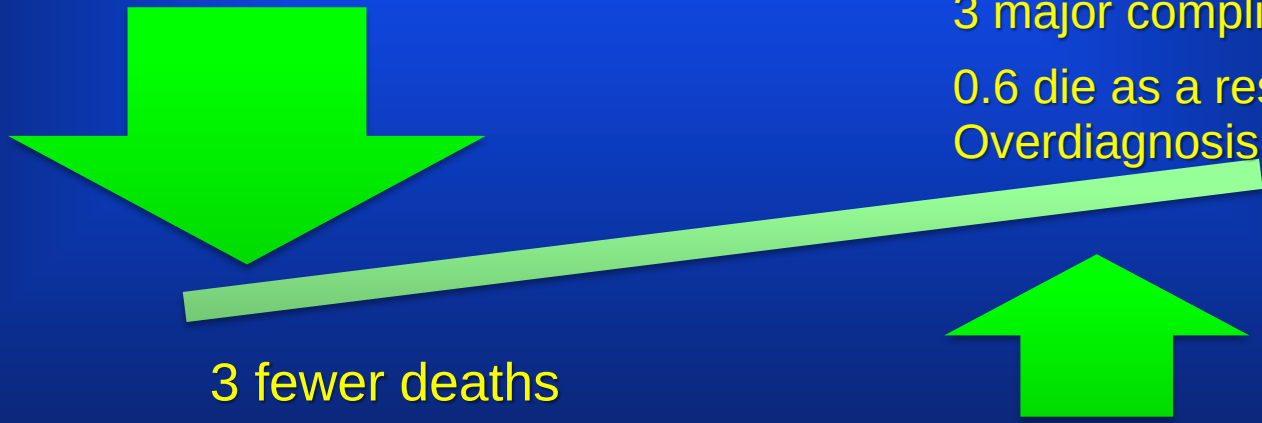
1,000 average risk NLST participants

365 false positives

25 biopsies

3 major complications

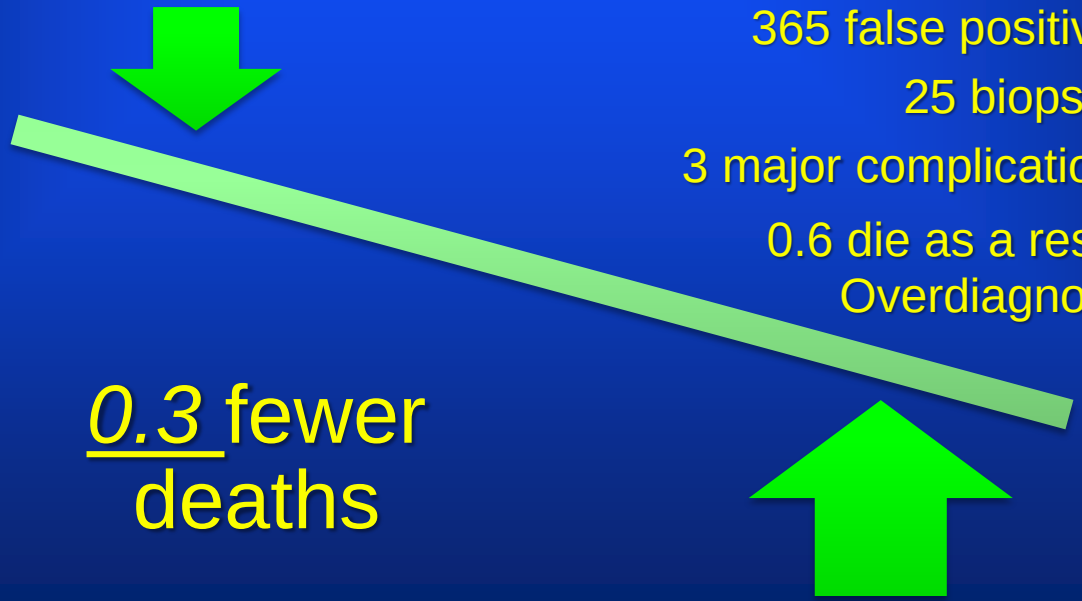
0.6 die as a result Overdiagnosis



3 fewer deaths

The importance of absolute risk

1,000 low risk individuals
("*NCCN group 2*")

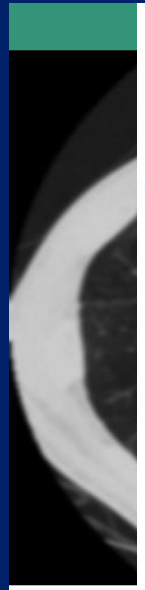


Lung Cancer Risk?

KIRK, SPOCK, MCCOY, AND ENSIGN RICKY ARE BEAMING DOWN TO THE PLANET. GUESS WHO'S NOT COMING BACK.

What tools are out there to help?

- Decision aids (UM, ATS, and AHRQ all developed decision aids)
- "Google" Lung cancer screening decision aids
  - www.shouldIscreen.com
  - https://www.thoracic.org/patients/patient-resources/resources/decision-aid-lcs.pdf
  - http://effectivehealthcare.ahrq.gov/index.cfm/tools-and-resources/patient-decision-aids/lung-cancer-screening/patient/

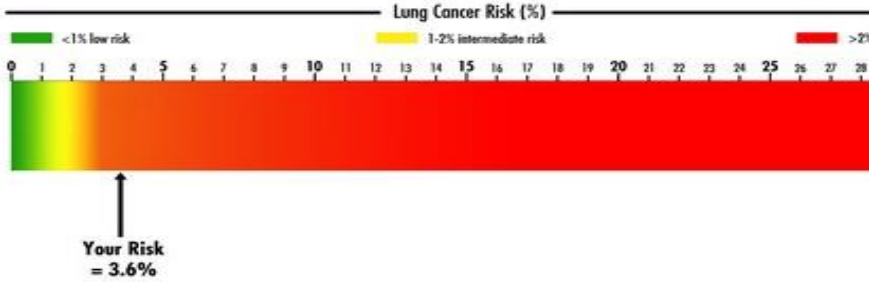


Lung Cancer Screening

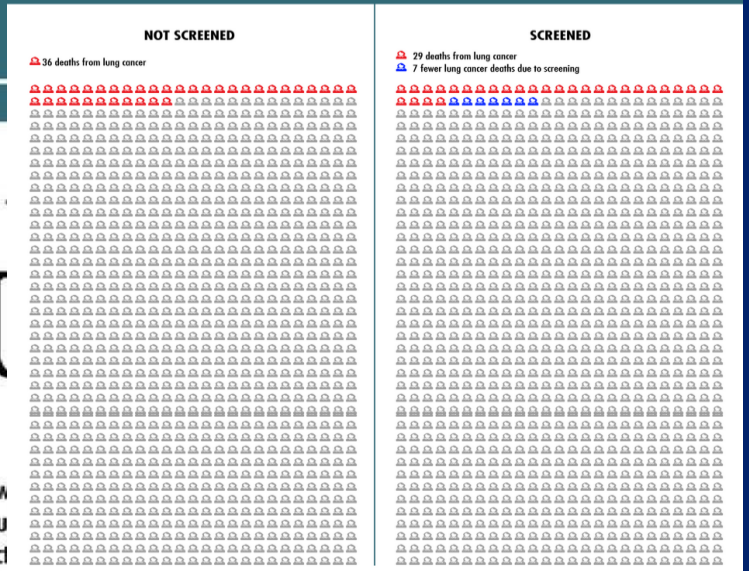
SHOULD I DO IT?

Given your age and smoking history, you are **not eligible*** for screening according to the US Preventive Services Task Force criteria.

*However, the chance of you developing lung cancer in the next 6 years is 3.6%, w
above the threshold where we believe the benefits of screening are large enou
to consider CT screening as an option. You should consider talking to your doct
about whether lung cancer screening might still be a good choice for you.



Compared to other people like you, there will be 7 fewer deaths out of 1000 in the next 6 years if you get screened.



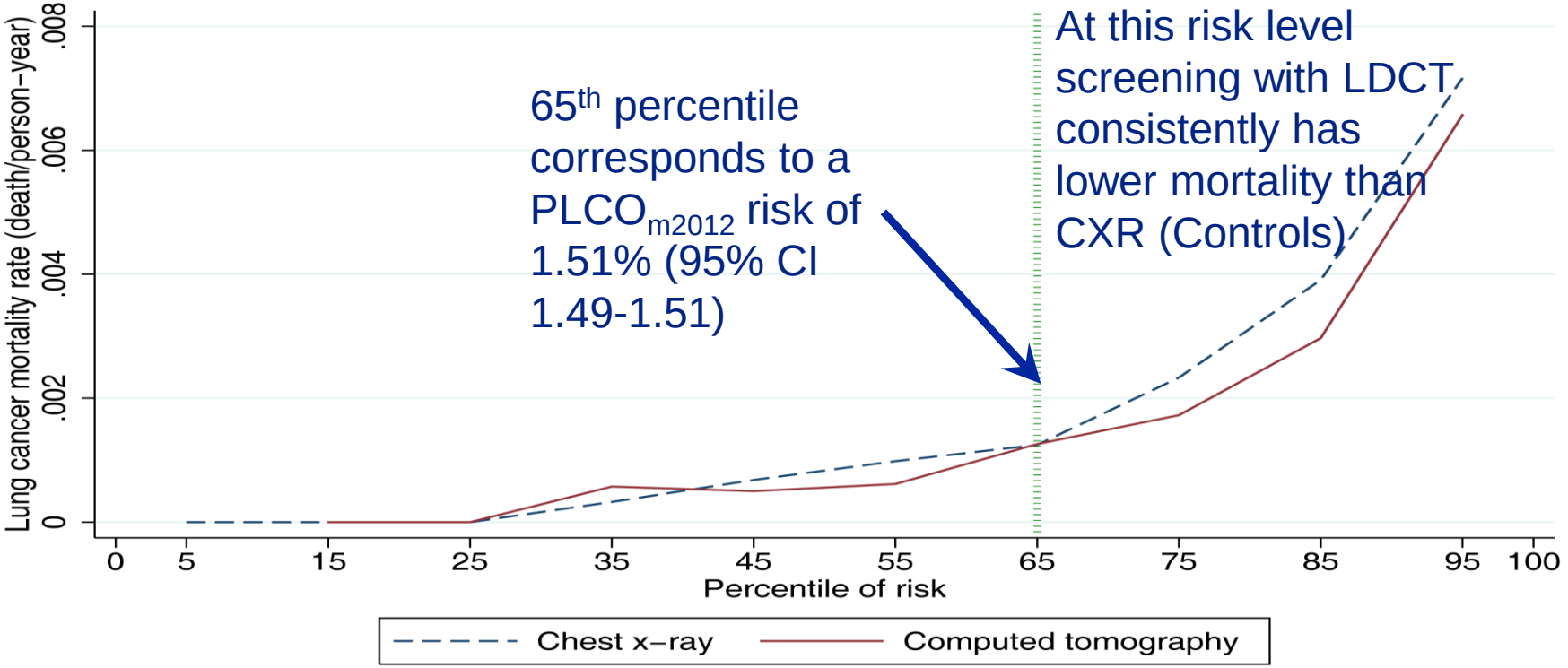
BENEFITS

7 in 1000

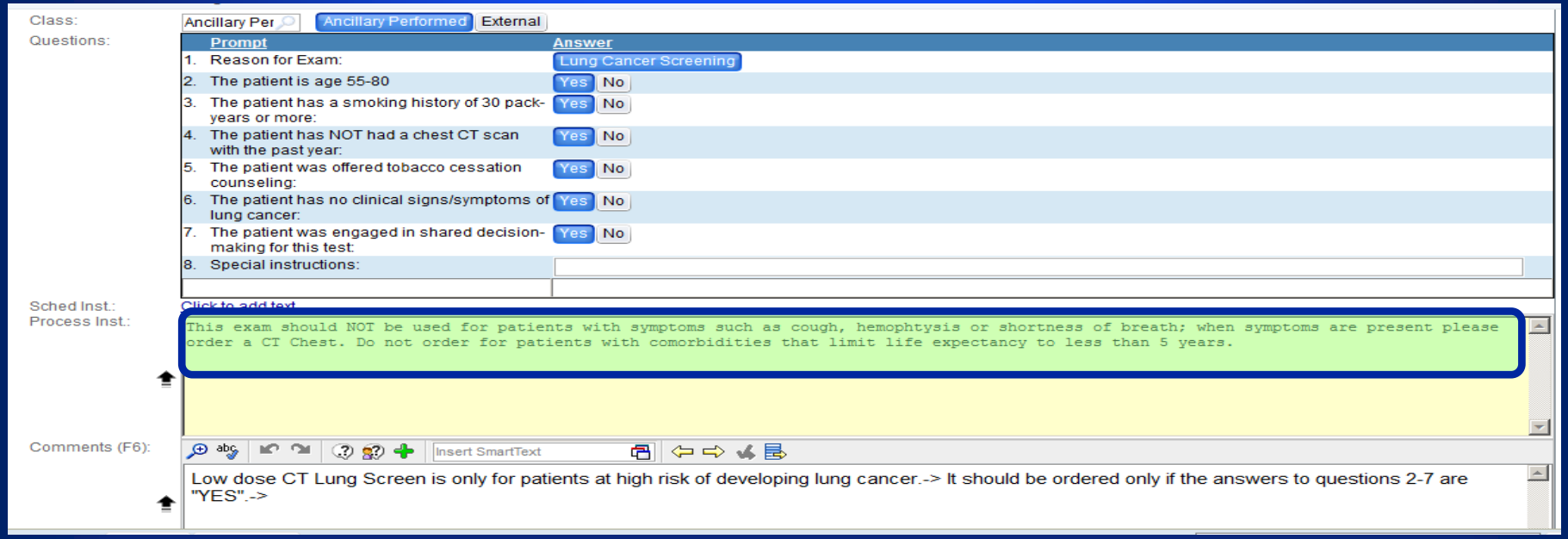
fewer people like you will die from lung cancer among those who were screened compared to those who were not screened.

HARMS

- 365 in 1000 people who were screened found a lung nodule that was not cancer.
- 18 in 1000 had an invasive procedure, such as biopsy or surgery, due to a lung nodule that was not cancer.
- 3 in 1000 had a major complication from invasive procedures.
- Of the lung cancers found by screening, about 1 in 10 would have never harmed you (overdiagnosis). This may lead to unnecessary treatment and complications.


65th percentile corresponds to a PLCOm2012 risk of 1.51% (95% CI 1.49-1.51)
At this risk level screening with LDCT consistently has lower mortality than CXR (Controls)
Lung cancer mortality rate (death/person−year)
0
.002
.004
.006
.008
0
5
15
25
35
45
55
65
75
85
95
100
Percentile of risk
Chest x−ray
Computed tomography

A couple more resources to be aware of



A couple more resources to be aware of

www.xrayrisk.com

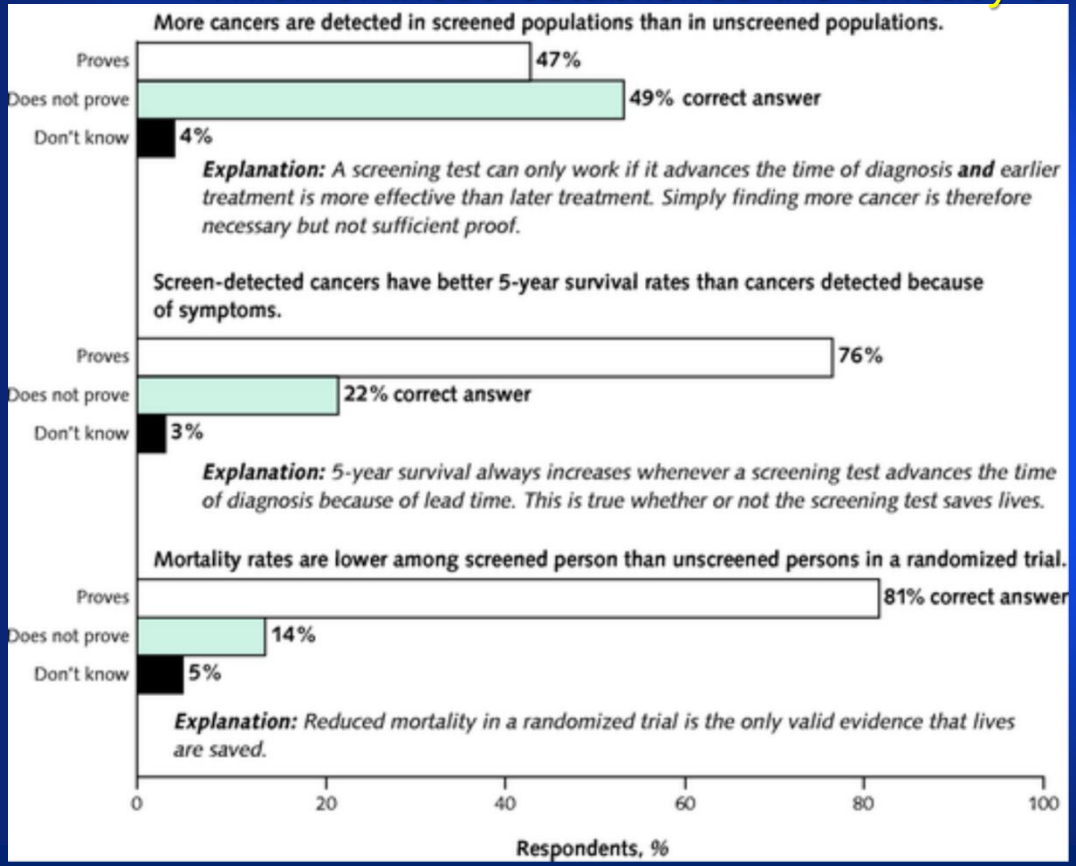
"Shared decision making" recommended by the IOM, and most recently, required by CMS

- How good are we at understanding data from screening studies?
  - Why should we care?
- Patients require a well informed physician to discuss risks and benefits
- How well do we understand screening studies?

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Do Physicians Understand Cancer Screening Statistics? A National Survey of Primary Care Physicians in the United States

Which of these establishes the efficacy of a screening test?



Test detects more cancers than control group

Longer 5 yr survival in test vs. controls

Fewer tested patients die of the disease than controls

Ann Intern Med. 2012;156(5):340-349

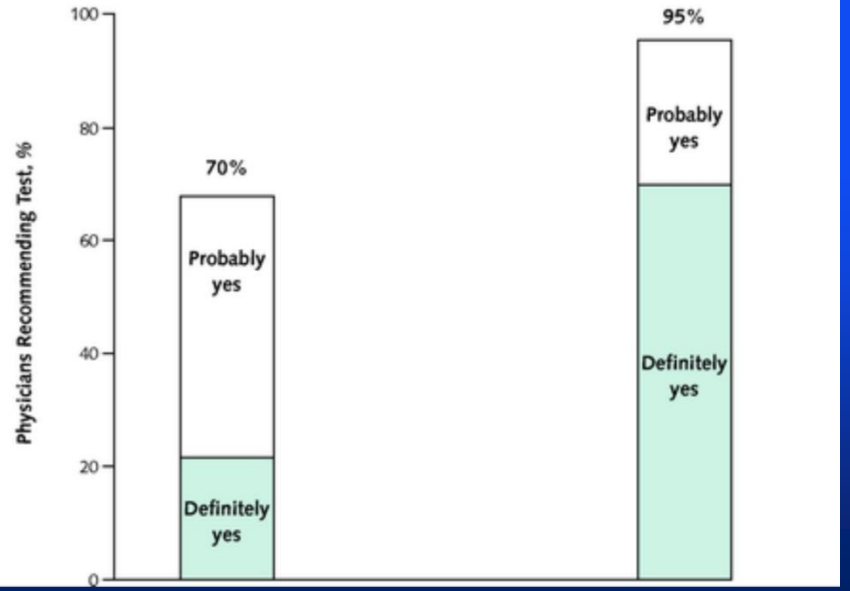
Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Do Physicians Understand Cancer Screening Statistics? A National Survey of Primary Care Physicians in the United States

Ann Intern Med. 2012;156(5):340-349

Would you recommend this test?

Data presented	Case 1: mortality data		Case 2: 5-year survival data	
	No screening	Screening	No screening	Screening
	2 deaths per 1000	1.6 deaths per 1000	68%	99%
Correct answer	Recommend screening because reduced mortality is valid evidence of benefit.		Would not recommend screening because improved survival with screening is not valid evidence of benefit.	

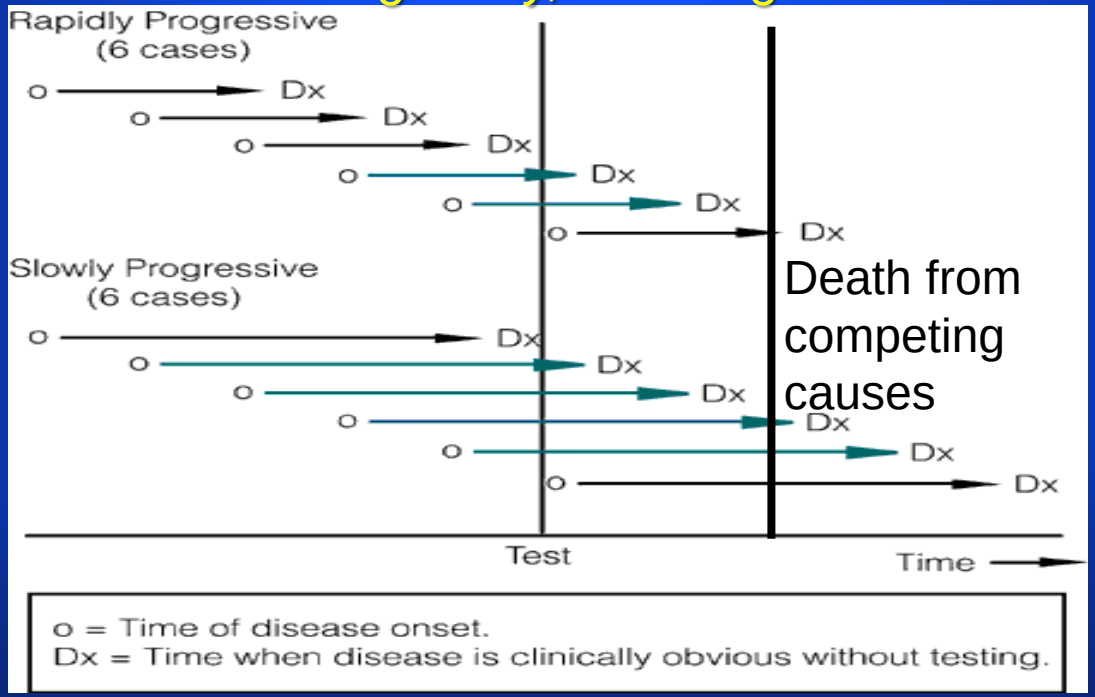


Board certified physicians getting this answer wrong should be a call to action

Screening trials are NOT drug trials!

Length and overdiagnosis bias

Result of disease heterogeneity, overdiagnosis is “infinite lead time”



Adapted from: Finding and Redefining Disease. *Effective Clinical Practice*, March/April 1999. Available at: ACP- Online
http://www.acponline.org/journals/ecp/marapr99/primer.htm

Take a step back: Screening as a concept

Screening is ineffective

Mad cow disease

Screening is effective

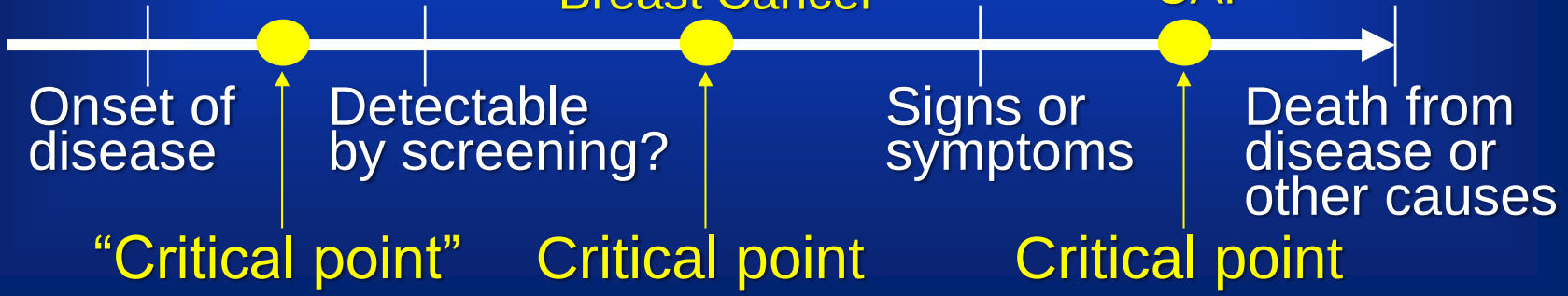
Cervical cancer

Colon cancer

Breast Cancer

Screening is unnecessary

CAP

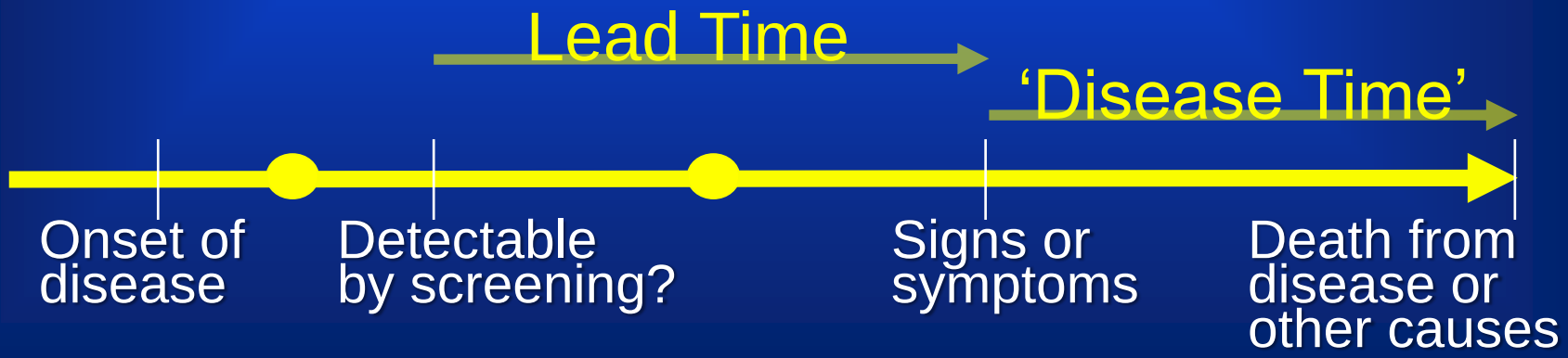


"Critical point"= that time after which treatment no longer alters the outcome

Lead Time vs. Lead Time bias

Lead time is necessary but lead time bias makes survival always look better in screened groups, even if you screen for macd cow disease.

“Screening trials are not drug trials”



Are these biases real or are they just obscure concepts?

- Three NCI CXR screening trials in 1970s
  - > 30,000 subjects
  - CXR detected more cases (Length Bias)
  - More early stage disease (Length and Lead time Bias)
  - Improved survival in the screened group (Length and Lead time bias)
  - *No difference* in mortality (Overdiagnosis?)
  - In short, in the context of CXR screening, Lung Cancer was “Mad Cow Disease”

Take home points

- ***Properly*** **screening** ***high risk*** **people saves lives**
- **Identifying risk is critical to efficient screening**
  - **High risk,** *acceptable burden of co-morbid illness*
- **If you counsel people in shared decision making, YOU must understand biases, risks and benefits**
- **Tobacco cessation increases clinical and cost efficacy of screening**
  - **Do the simple things well**

Some final additional thoughts

Part 1

- Screening has great potential for both harm and good
- Achieving the ideal balance means educating providers and patients about risks/benefits
- Good evidence and anecdote suggests that many front line providers lack (or don't use) tools for
  - Shared decision making
  - Understanding screening biases
  - Proper approach to indeterminate nodules

Tobacco cessation is the most effective means to the end sought through lung cancer screening

Some final additional thoughts

Part 2

- Tobacco cessation best practices should be our primary focus
- ACCP Treating Tobacco Dependence Toolkit
  - http://tobaccodependence.chestnet.org/
- IASLC Tobacco cessation
  - https://www.iaslc.org/patient-resources/tobacco-cessation-0