UCSF
University of California
San Francisco

PSA-based Early Detection in the US:

What Went Wrong, and How to Screen Smarter

Matthew R. Cooperberg, MD, MPH
Departments of Urology and
Epidemiology & Biostatistics

@dr_coops

PAHO/WHO Consultation on Prostate Cancer Screening and
Early Detection in Latin America and the Caribbean
Mexico City, Mexico

September 12, 2017

Prostate cancer 2017

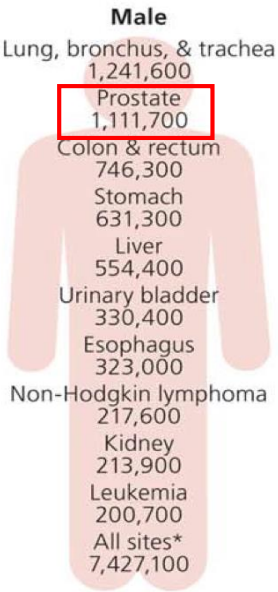
Incidence

Prostate	161,360	19%
Lung & bronchus	116,990	14%
Colon & rectum	71,420	9%
Urinary bladder	60,490	7%
Melanoma of the skin	52,170	6%
Kidney & renal pelvis	40,610	5%
Non-Hodgkin lymphoma	40,080	5%
Leukemia	36,290	4%
Oral cavity & pharynx	35,720	4%
Liver & intrahepatic bile duct	29,200	3%
All Sites	**836,150**	**100%**

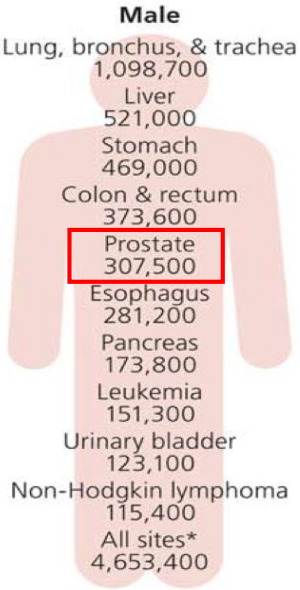
Mortality

Lung & bronchus	84,590	27%
Colon & rectum	27,150	9%
Prostate	26,730	8%
Pancreas	22,300	7%
Liver & intrahepatic bile duct	19,610	6%
Leukemia	14,300	4%
Esophagus	12,720	4%
Urinary bladder	12,240	4%
Non-Hodgkin lymphoma	11,450	4%
Brain & other nervous system	9,620	3%
All Sites	**318,420**	**100%**

Prostate cancer is still a global killer



Incidence

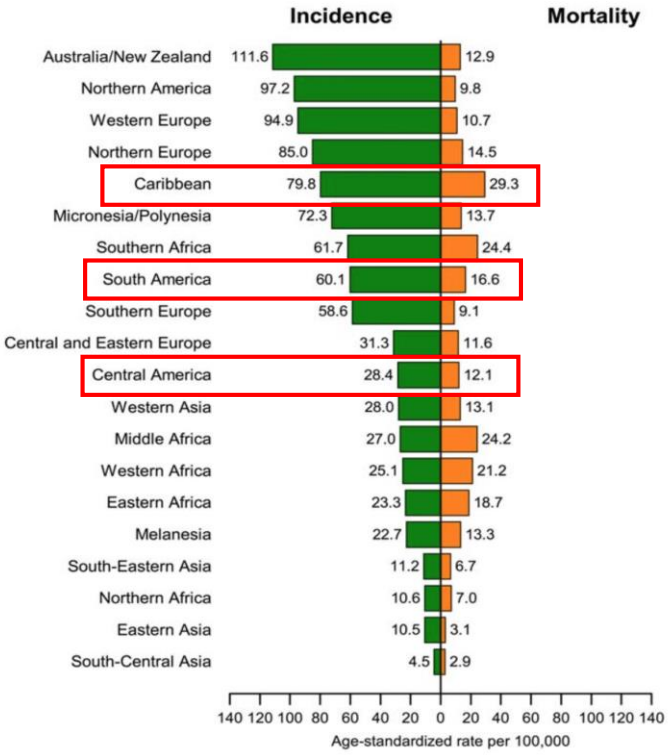


Mortality

Since 2008, up from 258,000

Now passed esophageal

Disease burden varies greatly by region



Torre et al. CA Cancer J Clin 65:87, 2015; https://www.moh.gov.sg/

Major variation even within regions

North America: 113.7 / 100K (15.3% lifetime)

- Regional / ethnic variation: 30.9 (Korean in LA) to 216.0 (African-American in Detroit)

Latin America: 36.4 (Argentina) to 153 (Martinique)

Europe: 17.1 (Bulgaria) to 117.3 (Tyrol, Austria)

Asia: 1.4 (Jiashan, China) to 50.2 (Israel)

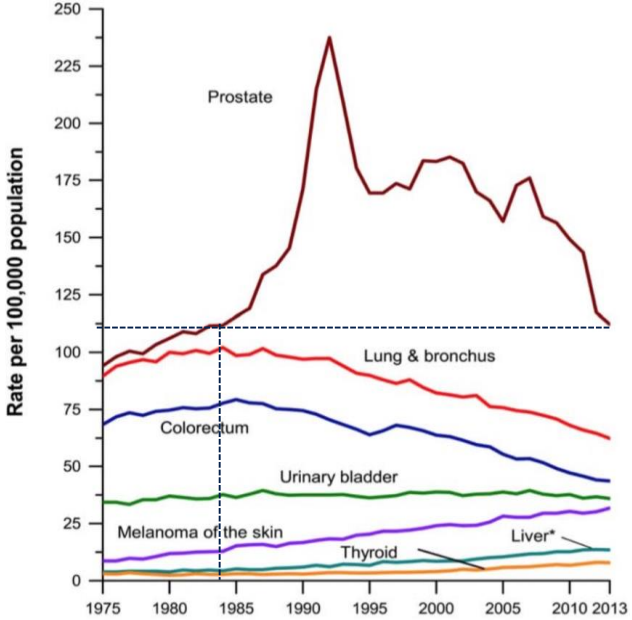
- Asians in U.S.: 58.0

Oceania: 61.7 (Northern Ter) to 104.4 (NZ)

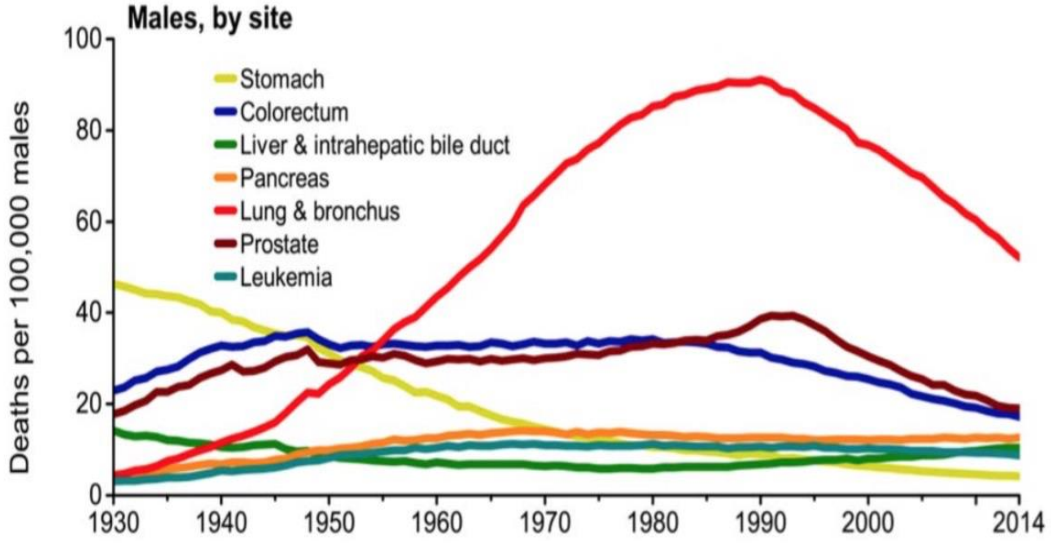
Africa: 7.5 (Algeria) to 38.1 (Zimbabwe)

Trends over time in the U.S.

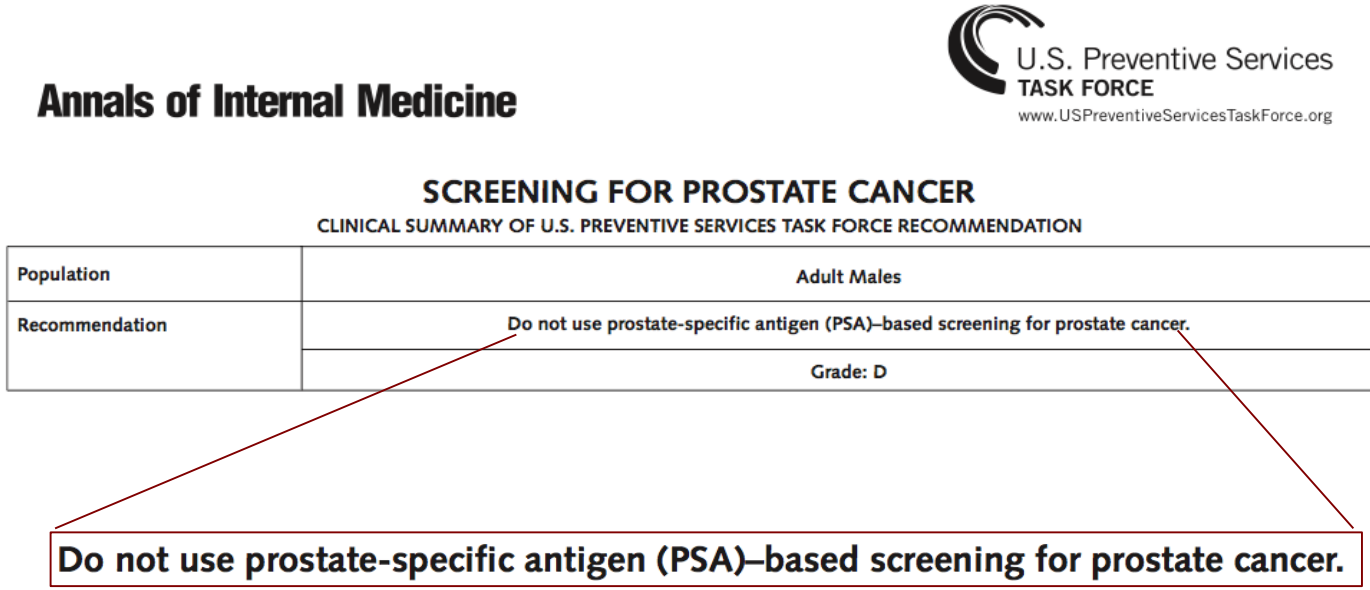
Incidence



Mortality



So how did this happen?



Annals of Internal Medicine

U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

SCREENING FOR PROSTATE CANCER

CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

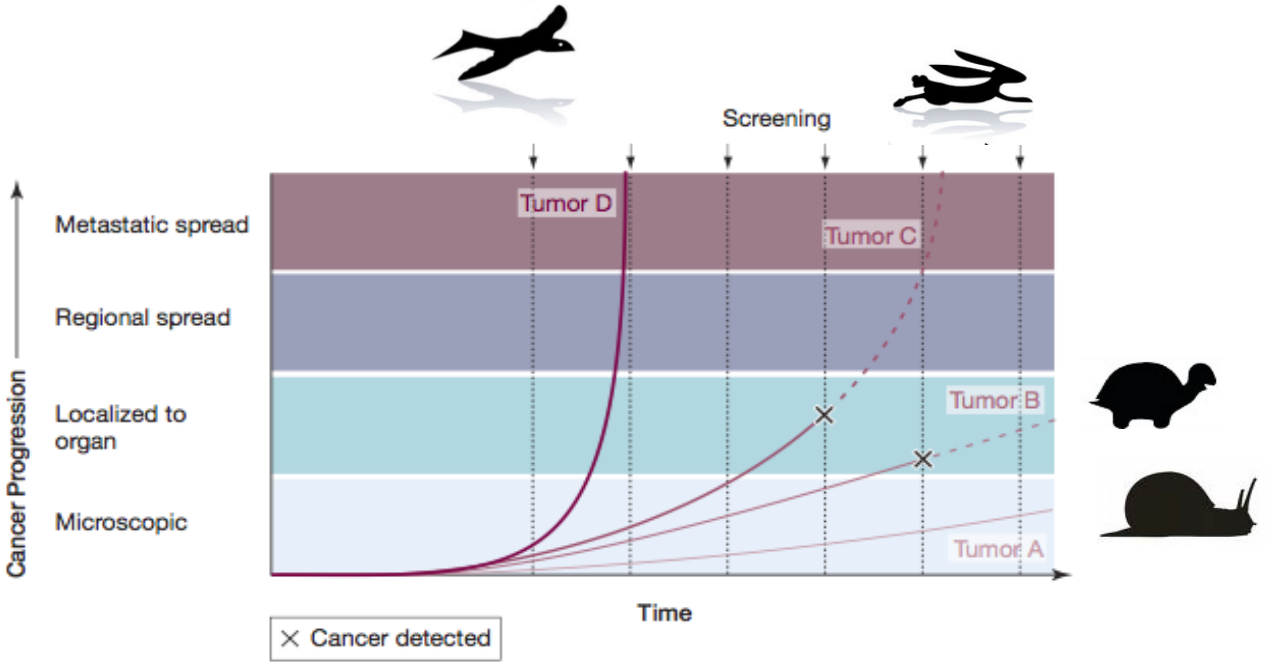
Population	Adult Males
Recommendation	Do not use prostate-specific antigen (PSA)–based screening for prostate cancer.
	Grade: D

Do not use prostate-specific antigen (PSA)–based screening for prostate cancer.

Moyer et al. Ann Intern Med 157:120, 2012.

This is (mostly) our fault.

“Prostate cancer” is highly heterogeneous

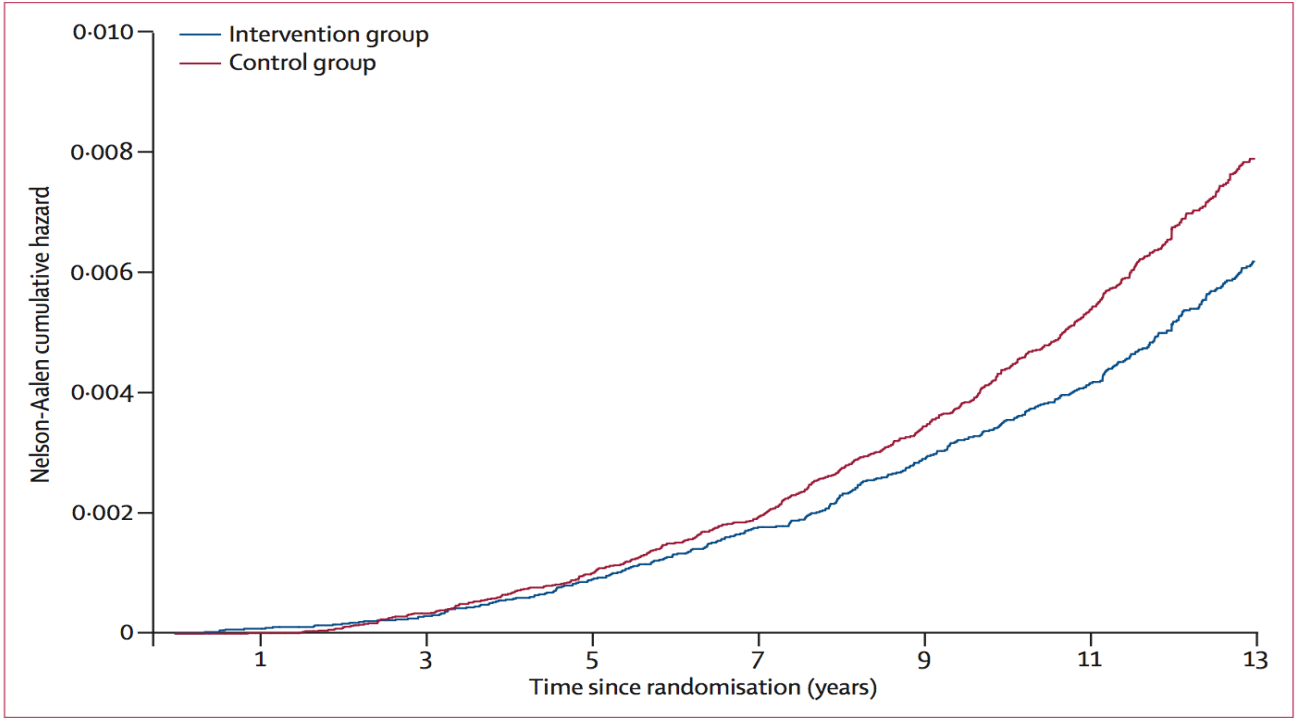


Esserman et al. JAMA 2009; 302:1685

Here's what we know:

- ERSPC: 21-29% relative reduction in prostate cancer mortality (Schröder et al. Lancet 2014)
- Göteborg: 42% relative reduction in prostate cancer mortality (Arnsrud Godtman R et al Eur Urol 2014)
- PLCO: Non-informative with respect to the question of screening vs. no screening (Pinsky et al, Cancer 2017)

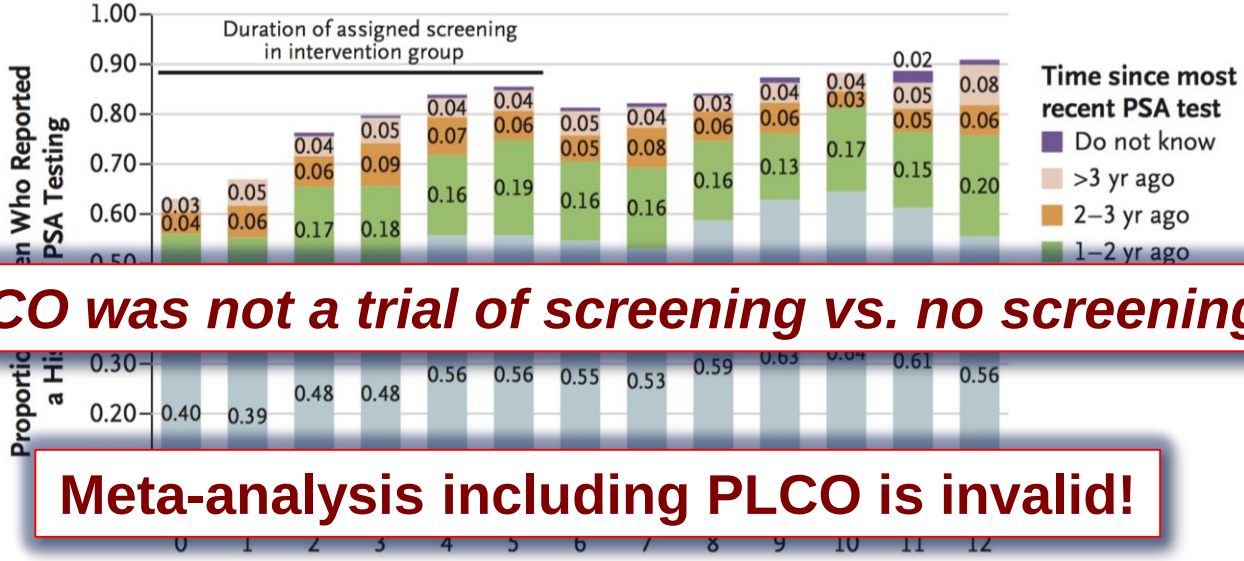
ERSPC: update



Rate ratio 0.73-0.79 for prostate cancer mortality, NND 27

Schröder et al. Lancet 2014; 384:2027

PSA testing in the PLCO “control” arm



PLCO was not a trial of screening vs. no screening

Meta-analysis including PLCO is invalid!

	Calculated Study Year of Survey													Total
Unknown if tested (no.)	14	38	35	46	41	33	24	17	19	15	13	16	7	318
Not tested (no.)	68	144	96	88	71	60	54	47	40	35	25	24	9	761
Tested (no.)	116	292	309	346	370	354	235	217	212	242	189	188	90	3160
Proportion tested														
Main analysis	0.63	0.67	0.76	0.80	0.84	0.86	0.81	0.82	0.84	0.87	0.88	0.89	0.91	0.81
Sensitivity analysis	0.59	0.62	0.70	0.72	0.77	0.79	0.75	0.77	0.78	0.83	0.83	0.82	0.85	0.75

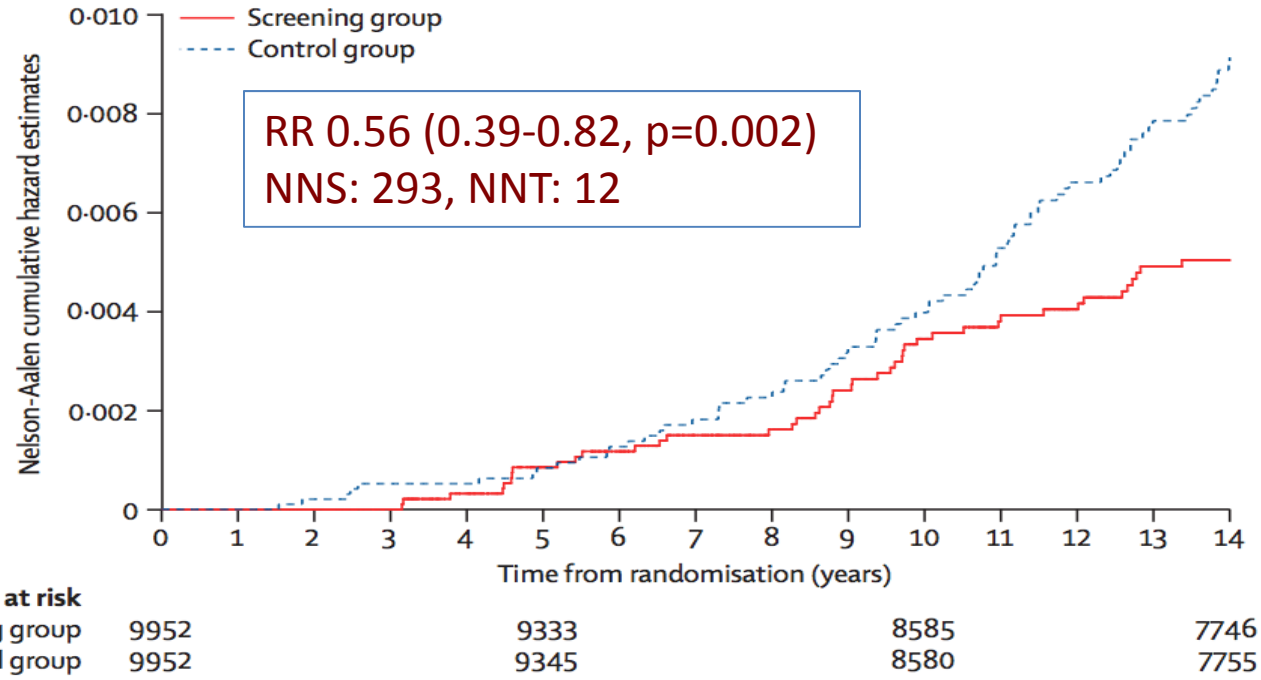
Reconciling PLCO and ERSPC

Table 2. Results of Traditional and Extended Cox Regression Analyses of Death From Prostate Cancer and Estimated Mortality Reductions in the ERSPC and PLCO Intervention Groups Relative to No Screening

Covariate	Cox Regression Analysis		Estimated Mortality Reduction Relative to No Screening			
	Hazard Ratio (95% CI)	*P* Value	ERSPC Intervention Group		PLCO Intervention Group	
			MLT, *y*	Reduction (95% CI), %	MLT, *y*	Reduction (95% CI), %
Traditional analysis						
PLCO setting*	0.53 (0.45–0.62)	<0.001	–	–	–	–
Participant age at randomization†	1.13 (1.11–1.14)	<0.001	–	–	–	–
Randomization to intervention group	0.84 (0.73–0.96)	0.0099	NA	16 (4–27)	NA	16 (4–27)
Extended analyses						
Empirical						
PLCO setting*	0.57 (0.48–0.67)	<0.001	–	–	–	–
Participant age at randomization†	1.13 (1.11–1.14)	<0.001	–	–	–	–
MLT†	0.92 (0.87–0.97)	0.0027	3.96	29 (11–43)	4.02	29 (11–44)
FHCRC						
PLCO setting*	0.58 (0.49–0.69)	<0.001	–	–	–	–
Participant age at randomization†	1.13 (1.11–1.14)	<0.001	–	–	–	–
MLT†	0.93 (0.88–0.97)	0.0029	4.00	27 (10–40)	4.10	27 (10–41)
MISCAN						
PLCO setting*	0.63 (0.51–0.77)	<0.001	–	–	–	–
Participant age at randomization†	1.13 (1.11–1.14)	<0.001	–	–	–	–
MLT†	0.92 (0.87–0.97)	0.0032	3.49	25 (9–38)	4.62	32 (12–47)
UMICH						
PLCO setting*	0.57 (0.48–0.68)	<0.001	–	–	–	–
Participant age at randomization†	1.13 (1.11–1.14)	<0.001	–	–	–	–
MLT†	0.91 (0.85–0.97)	0.0029	3.83	31 (12–45)	4.01	32 (12–47)

Tsodikov et al, Ann Intern Med 2017

The Göteborg randomized trial



Hugosson J. Lancet Oncol 2010; 11:725

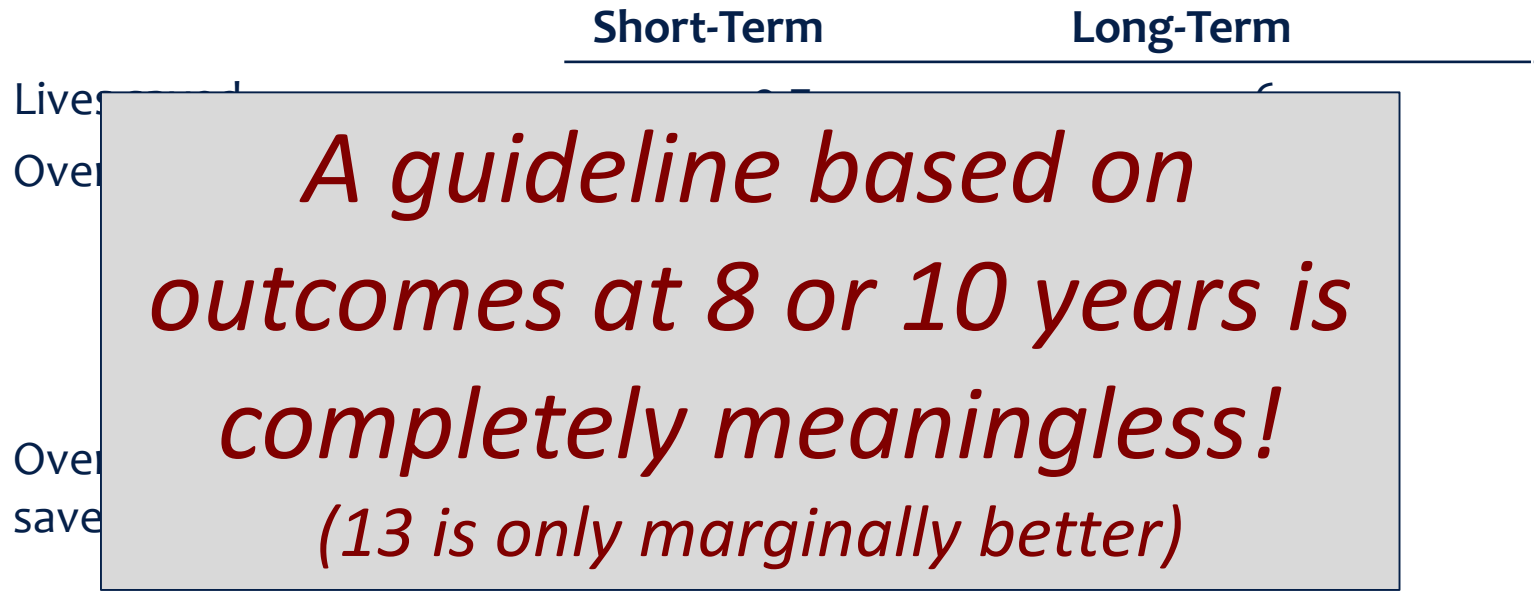
Benefits of screening: bottom line 2017

Screening q1-4 years starting age 55-70 results in a at least 30% relative reduction in prostate cancer mortality

(But this approach is suboptimal)

Absolute mortality reduction depends on followup

Taking the long view on screening



Assessing harms: details matter!

"Adequate evidence shows that up to 5 in 1000 men will die within 1 month of prostate cancer surgery and between 10 and 70 men will have serious complications but survive. Radiotherapy and surgery result in long-term adverse effects, including urinary incontinence and erectile dysfunction in at least 200 to 300 of 1000 men treated with these therapies. Radiotherapy is also associated with bowel dysfunction"

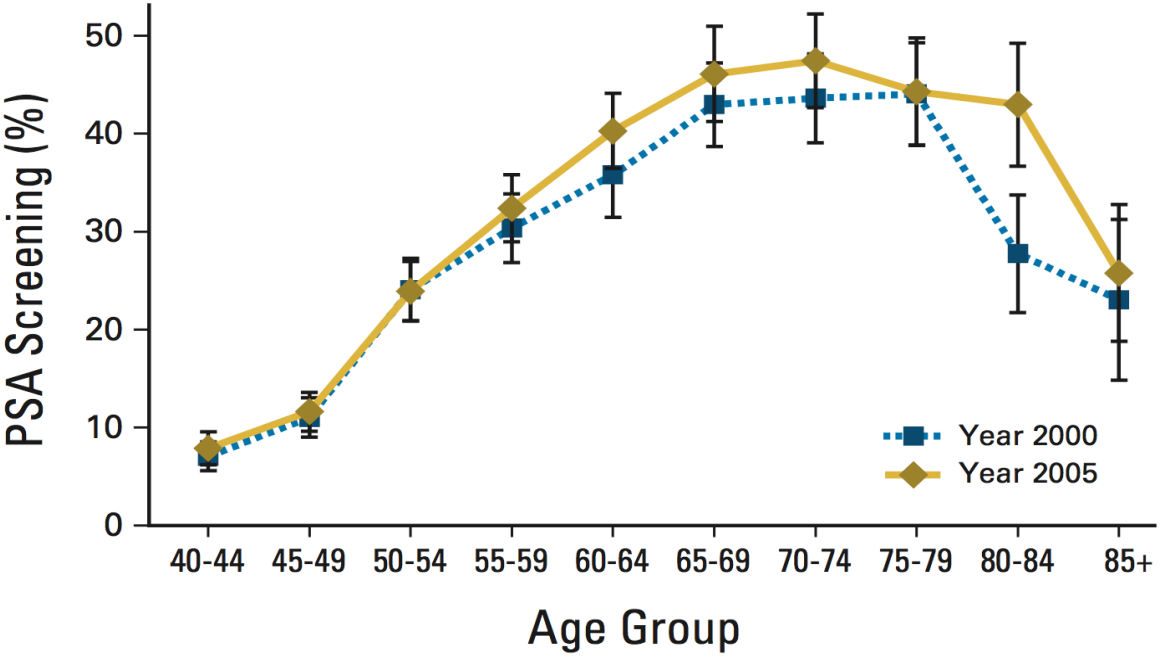
Moyer et al. Ann Intern Med 157:120, 2012

The real problems?

Over- and under-screening,

Over- and under-treatment

What do PCPs in the U.S. do?



Drazer et al. J Clin Oncol 2011; 29:1736

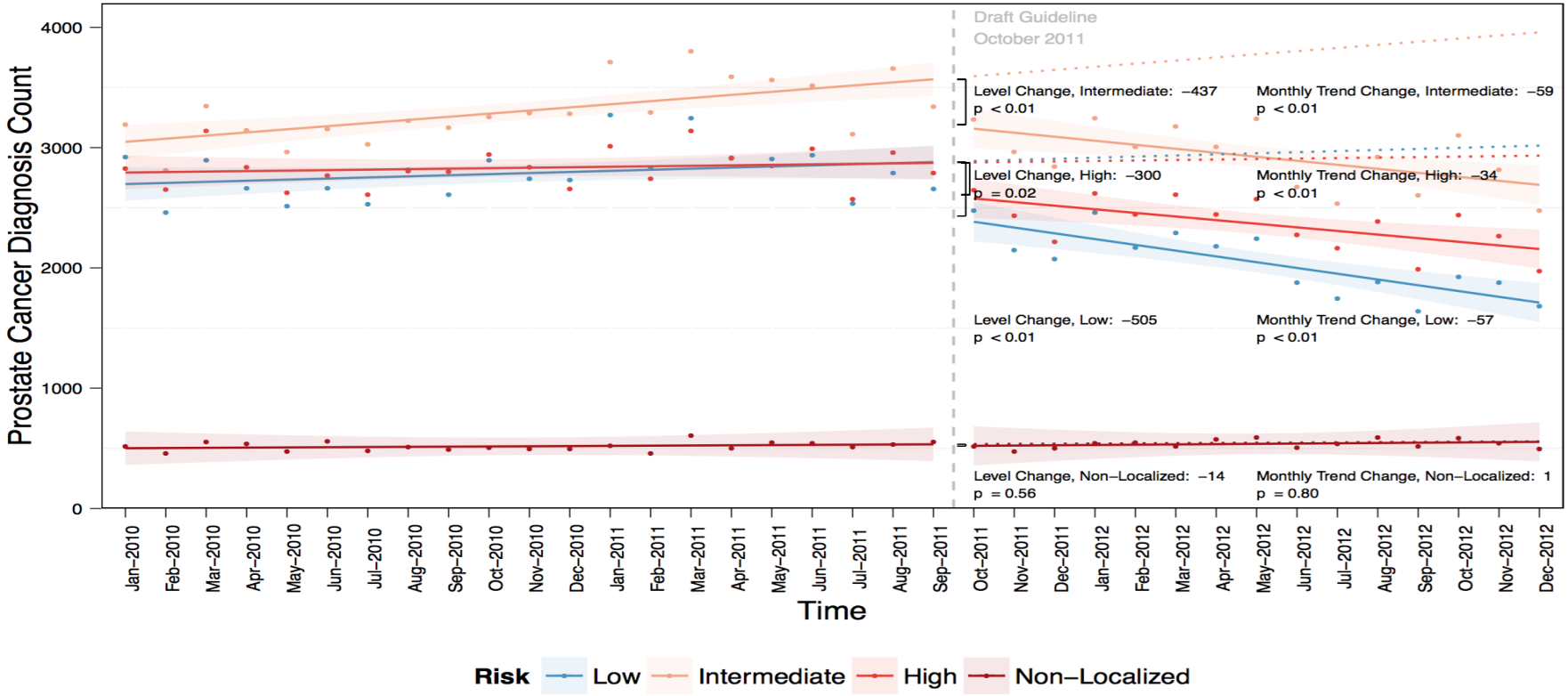
The Impact of the USPSTF in 2012

Table. Adjusted Screening Rate and Rate Ratios of PSA Testing in the Past Year for Screening Reasons Among Men 50 Years and Older[a]

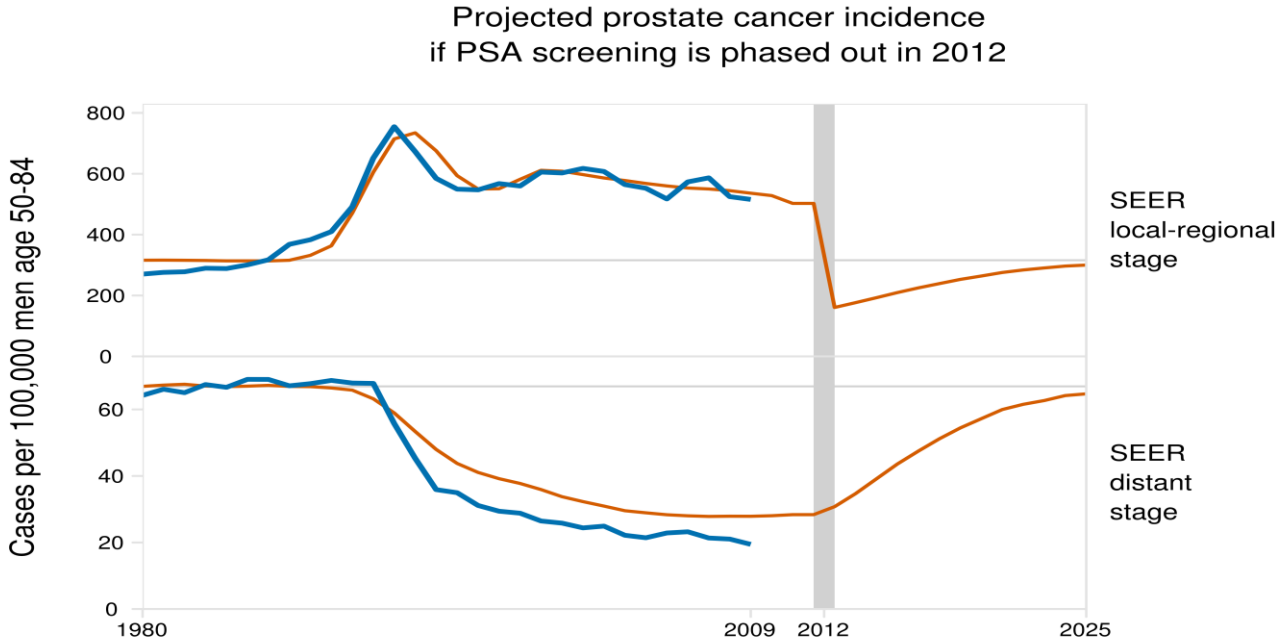
	National Health Interview Survey Year			
	2005	2008	2010	2013
No. of men				
≥50 y	4580	3476	4157	6172
50-74 y	3854	2900	3540	5221
≥75 y	726	576	617	951
No. of men with PSA test in past year				
≥50 y	1633	1345	1457	1771
50-74 y	1332	1079	1220	1464
≥75 y	301	266	237	307
Adjusted screening rate (99% CI)[b]				
≥50 y	36.9 (34.5-39.1)	40.6 (37.9-43.3)	37.8 (35.3-40.2)	30.8 (29.0-32.7)
50-74 y	35.8 (33.4-38.3)	39.1 (36.2-42.0)	36.8 (34.3-39.4)	29.9 (28.0-32.0)
≥75 y	42.6 (37.6-47.9)	50.1 (43.7-56.4)	43.1 (37.1-49.2)	36.3 (31.1-41.9)
Adjusted SRR (99% CI)[c]				
≥50 y		1.10 (1.01-1.21)	0.93 (0.84-1.02)	0.82 (0.75-0.89)
50-74 y		1.09 (0.99-1.21)	0.94 (0.85-1.05)	0.81 (0.74-0.89)
≥75 y		1.18 (0.99-1.40)	0.86 (0.71-1.04)	0.84 (0.68-1.05)

Jemal et al. JAMA 2015; 314:2054

The Impact of the USPSTF in 2012



Rise in metastatic disease *will* follow



~60,000 avoidable deaths 2013-2025

Can we do it all better?

Guidelines 2017

“Simple schema” for SDM

Key take-home messages

The goal of screening is to find aggressive prostate cancer early and cure it before it spreads beyond the prostate.

Most cancer cases found by screening do not need to be treated and can be safely managed by a program of careful monitoring known as “active surveillance.”

If you choose to be screened, there is a good chance that you will be diagnosed with low-risk cancer and you may face pressure from your physicians or family to treat it.

Discrete decision

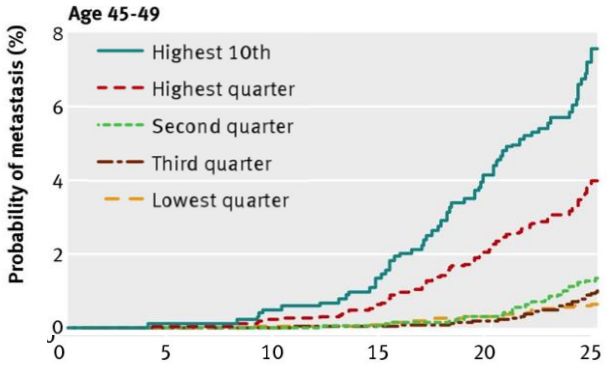
If you are concerned that you would be uncomfortable knowing that you have cancer and not treating it, screening may not be for you.

If you are confident that you would only accept treatment for aggressive cancer and would not be unduly worried about living with a diagnosis of low-risk disease, you are probably a good candidate for screening.

The value of establishing an early baseline

- If PSA … eath <0.3%
- 90% … PSA >2.0 (

Age 45-49 at baseline screen				
Highest 10th	≥1.60	0.74 (0.31 to 1.57)	2.42 (1.48 to 3.75)	5.14 (3.63 to 7.04)
Highest quarter	≥1.10	0.31 (0.13 to 0.66)	1.18 (0.75 to 1.77)	2.67 (1.97 to 3.54)
Second quarter	0.68-1.10	<0.01 (<0.01 to 0.07)	0.24 (0.09 to 0.56)	0.72 (0.40 to 1.21)
Third quarter	0.44-0.68	0 (NA)	0.09 (0.02 to 0.34)	0.54 (0.28 to 0.96)
Lowest quarter	≤0.44	0.08 (0.01 to 0.30)	0.24 (0.09 to 0.54)	0.52 (0.26 to 0.96)
Below median	≤0.68	0.04 (0.01 to 0.16)	0.17 (0.08 to 0.34)	0.55 (0.35 to 0.83)
≤66th centile	≤0.90	0.03 (0.01 to 0.12)	0.14 (0.07 to 0.28)	0.51 (0.34 to 0.74)
≤73rd centile	≤1.00	0.03 (0.01 to 0.11)	0.17 (0.09 to 0.30)	0.56 (0.39 to 0.79)



Vickers et al. BMJ 341:c4521, 2010; Vickers et al BMJ 346:f2023, 2013

The value of establishing an early baseline

Table 4. Cumulative Incidence (%) and 95% CI of Prostate Cancer Death or Development of Distant Metastases, Stratified by Categories of Imputed PSA Levels and Age at Blood Draw

Stratification	PSA Concentration (ng/mL)	Cumulative Risk of Lethal Prostate Cancer Within			
		15 Years	20 Years	25 Years	30 Years
Age 40 to 44 years at blood draw					
Screening cut point	> 4	0 (NE)	2.3 (0.2 to 10.4)	3.5 (0.3 to 14.5)	9.4 (< 0.01 to 59.2)
Top 10th percentile	≥ 1.70	0 (NE)	0.6 (0.1 to 2.6)	1.24 (0.3 to 3.5)	3.4 (1.1 to 8.0)
Quartile 4	≥ 1.15	0 (NE)	0.2 (0.03 to 0.1)	0.5 (0.1 to 1.3)	1.4 (0.4 to 3.7)
Quartile 3	0.72-1.14	0 (NE)	0 (NE)	0.1 (0.01 to 0.7)	0.1 (0.01 to 0.7)
Above median	≥ 0.72	0 (NE)	0.1 (0.01 to 0.5)	0.2 (0.07 to 0.7)	0.6 (0.2 to 1.4)
Below median	< 0.72	0 (NE)	0.03 (NE)	0.09 (0.01 to 0.5)	0.2 (0.02 to 0.9)
Quartile 2	0.53-0.71	0 (NE)	0 (NE)	0 (NE)	0 (NE)
Quartile 1	< 0.53	0 (NE)	0.06 (NE)	0.18 (0.02 to 0.9)	0.4 (0.05 to 1.7)
Age 45 to 49 years at blood draw					
Screening cut point	> 4	4.6 (0.9 to 13.8)	8.5 (2.5 to 19.1)	9.6 (2.8 to 21.4)	15.7 (0.2 to 56.8)
Top 10th percentile	≥ 1.70	0.9 (0.2 to 2.9)	2.5 (0.9 to 5.4)	3.3 (1.4 to 6.6)	4.5 (1.6 to 9.6)
Quartile 4	≥ 1.23	0.7 (0.2 to 1.6)	1.3 (0.6 to 2.6)	1.7 (0.8 to 3.1)	2.3 (0.9 to 4.7)
Quartile 3	0.72-1.22	0.06 (NE)	0.3 (0.03 to 1.1)	0.3 (0.04 to 1.2)	0.4 (0.04 to 1.8)
Above median	≥ 0.72	0.4 (0.1 to 0.8)	0.8 (0.4 to 1.4)	0.9 (0.5 to 1.7)	1.2 (0.6 to 2.1)
Below median	< 0.72	0.07 (NE)	0.3 (0.1 to 1.0)	0.5 (0.2 to 1.2)	0.5 (0.2 to 1.3)
Quartile 2	0.53-0.71	0 (NE)	0 (NE)	0 (NE)	0 (NE)
Quartile 1	< 0.53	0.15 (NE)	0.6 (0.2 to 1.8)	0.9 (0.3 to 2.2)	0.1 (0.3 to 2.5)
Age 50 to 54 years at blood draw					
Screening cut point	> 4	11.4 (3.3 to 25.2)	13.4 (4.6 to 26.9)	18.6 (7.6 to 33.4)	18.6 (7.6 to 33.4)
Top 10th percentile	≥ 2.10	2.4 (0.9 to 5.0)	3.7 (1.8 to 6.9)	5.1 (2.6 to 8.6)	8.4 (3.4 to 16.2)
Quartile 4	≥ 1.43	1.2 (0.5 to 2.4)	1.7 (0.9 to 3.1)	2.2 (1.2 to 3.7)	3.4 (1.7 to 6.0)
Quartile 3	0.89-1.42	0.2 (0.02 to 1.0)	0.2 (0.02 to 1.0)	0.2 (0.02 to 1.0)	0.2 (0.02 to 1.0)
Above median	≥ 0.89	0.7 (0.3 to 1.3)	0.9 (0.5 to 1.6)	1.2 (0.7 to 1.9)	1.6 (0.9 to 2.7)
Below median	< 0.89	0.3 (0.06 to 0.8)	0.3 (0.08 to 0.9)	0.8 (0.4 to 1.4)	1.6 (0.8 to 3.1)
Quartile 2	0.59-0.88	0 (NE)	0 (NE)	0 (NE)	0 (NE)
Quartile 1	< 0.59	0.5 (0.1 to 1.6)	0.6 (0.2 to 1.8)	1.6 (0.8 to 3.0)	2.3 (1.6 to 6.9)

Preston et al. J Clin Oncol 2016; 34:2705

PSA should not be interpreted in a vacuum

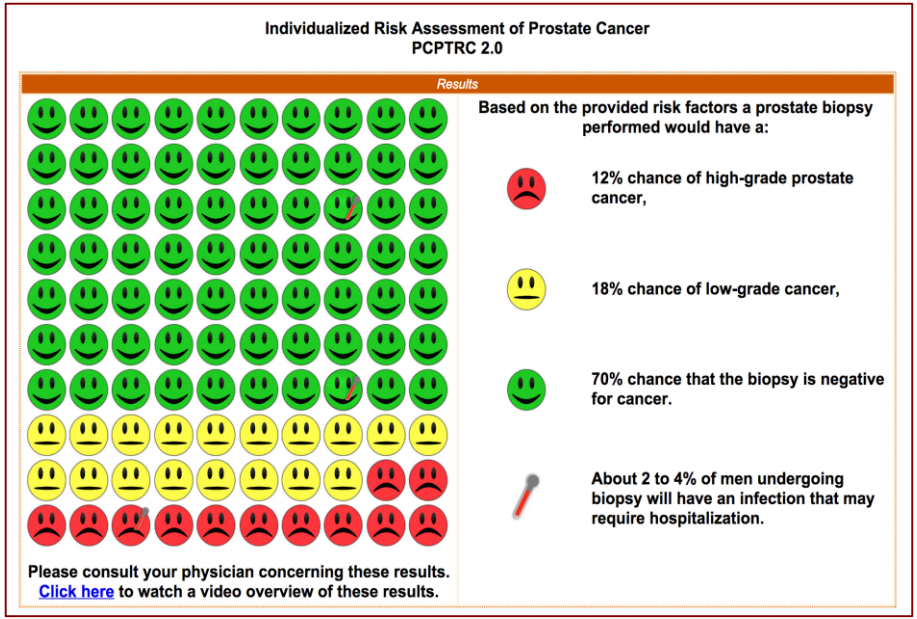
Risk of Biopsy-Detectable Prostate Cancer

Fields marked with asterisks (*) are required.

Enter Your Information	
* Race	
* Age	
* PSA Level ?	ng/ml
* Family History of Prostate Cancer ?	
* Digital Rectal Examination ?	
* Prior Prostate Biopsy ?	
* Is the patient taking finasteride?	

Calculate Cancer Risk

Figures Disclaimer



Consider secondary (reflex?) testing

Urine

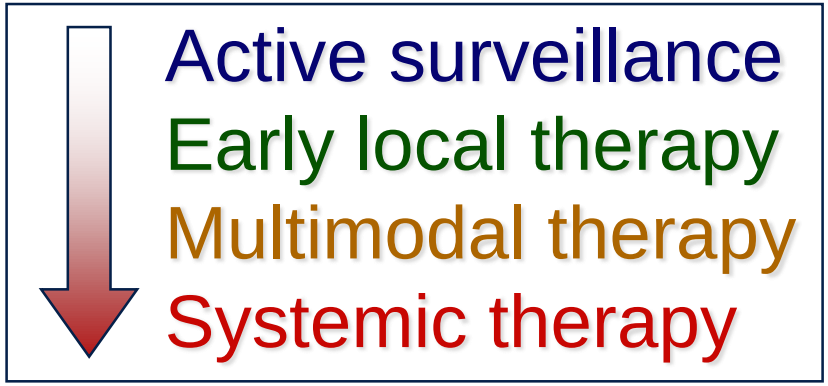
- PCA3
- SelectMDx (HOXC6, DLX1)

Blood

- phi (PSA, fPSA, -2proPSA)
- 4K (PSA, fPSA, iPSA, HK2)

Risk stratify before treatment

Goal: inform physician-patient decisions about optimal initial treatment approach and timing



Risk stratification works!

The UCSF-CAPRA score

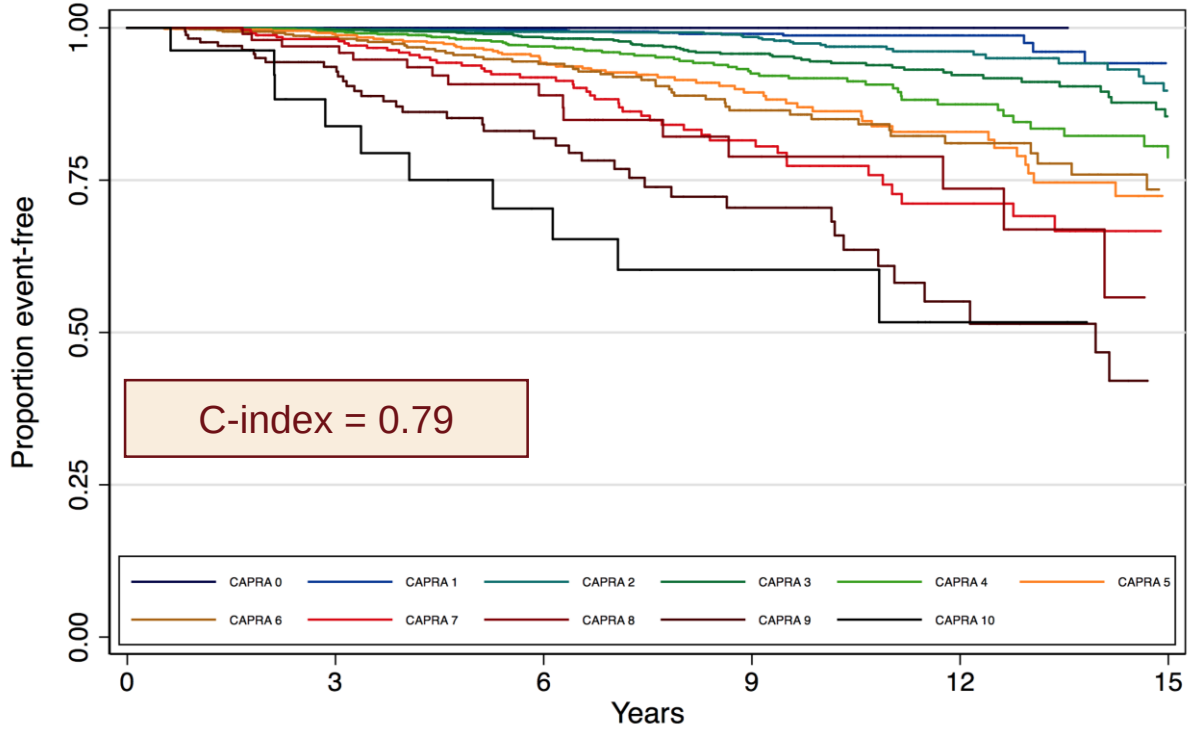
Variable	Level	Points	Variable	Level	Points
PSA	2.0-6	0	**T-stage**	T1/T2	0
	6.1-10	1		T3a	1
	10.1-20	2			
	20.1-30	3	**% pos bx**	<34%	0
	>30	4		≥34%	1
Gleason	1-3/1-3	0			
	1-3/4-5	1	**Age**	<50	0
	4-5/1-5	3		≥50	1

Sum of points from each variable for 0-10 score

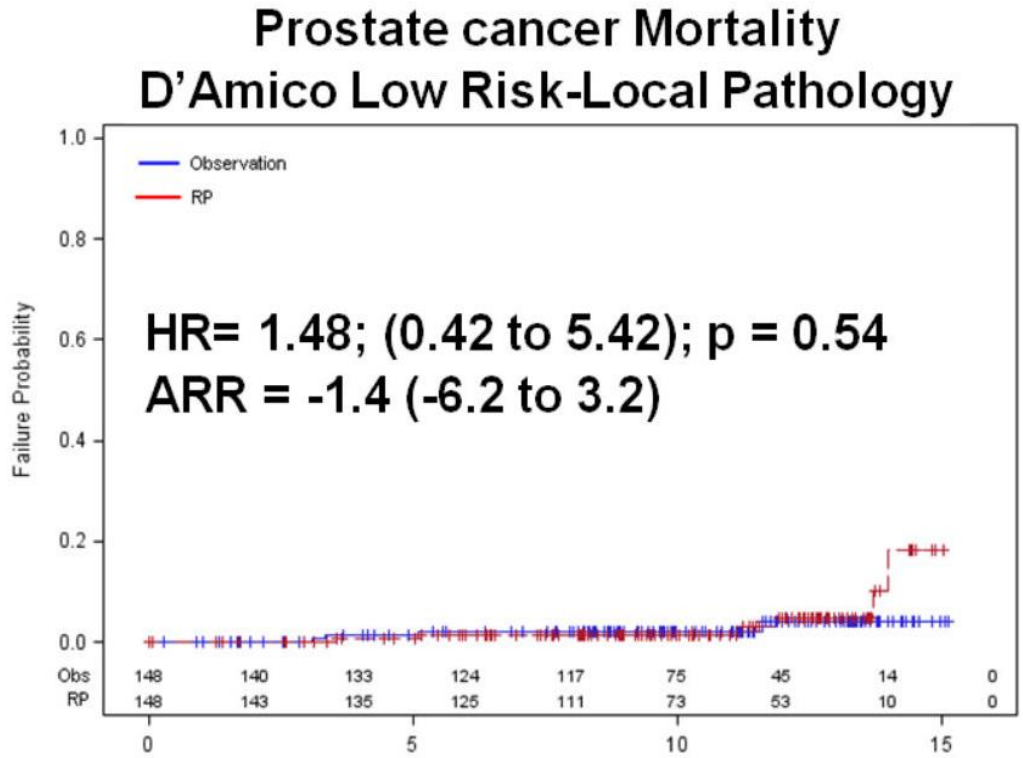
Validated in 14 studies on 4 continents, N>20,000

http://urology.ucsf.edu/capra.html

We *can* tell the rabbits from the turtles

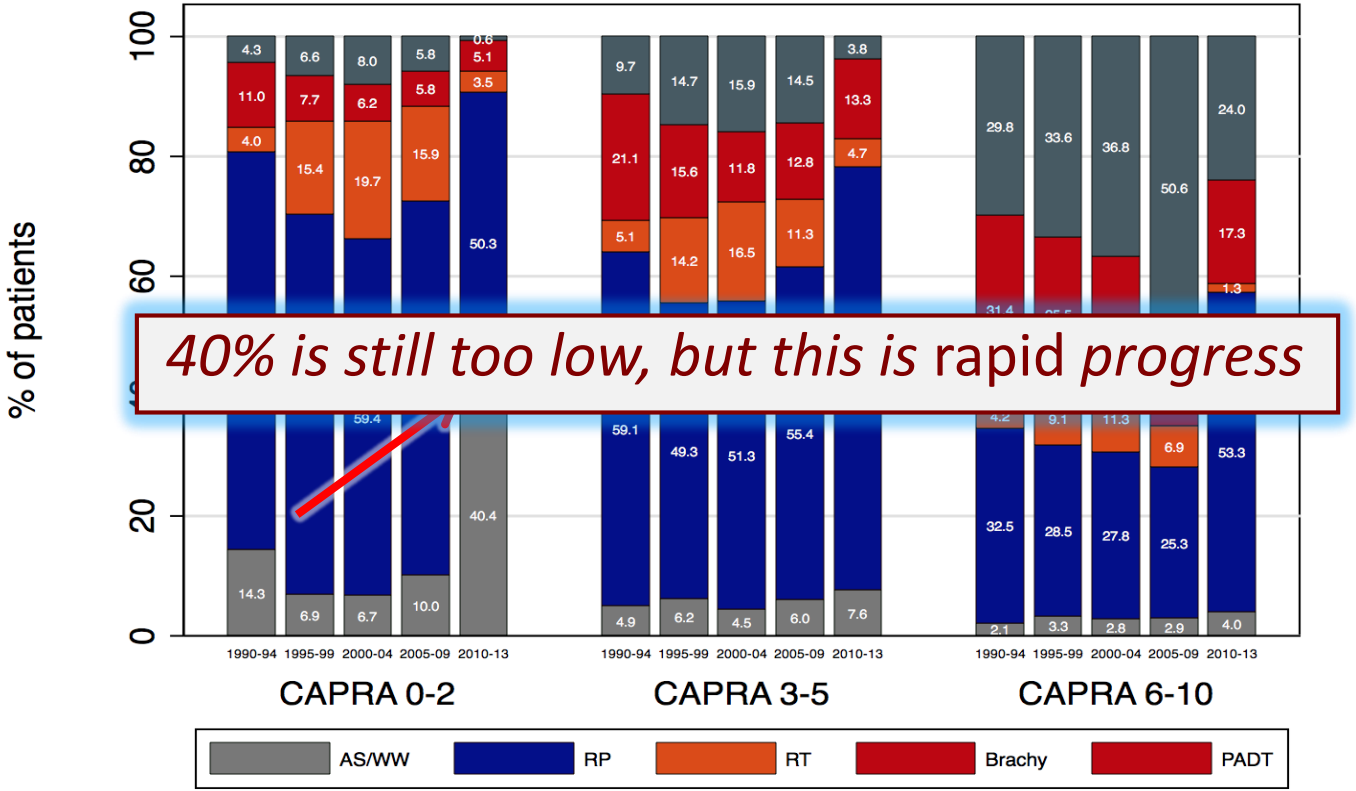


Don’t treat most low-risk disease



Wilt T et al. NEJM 2012; 367:203

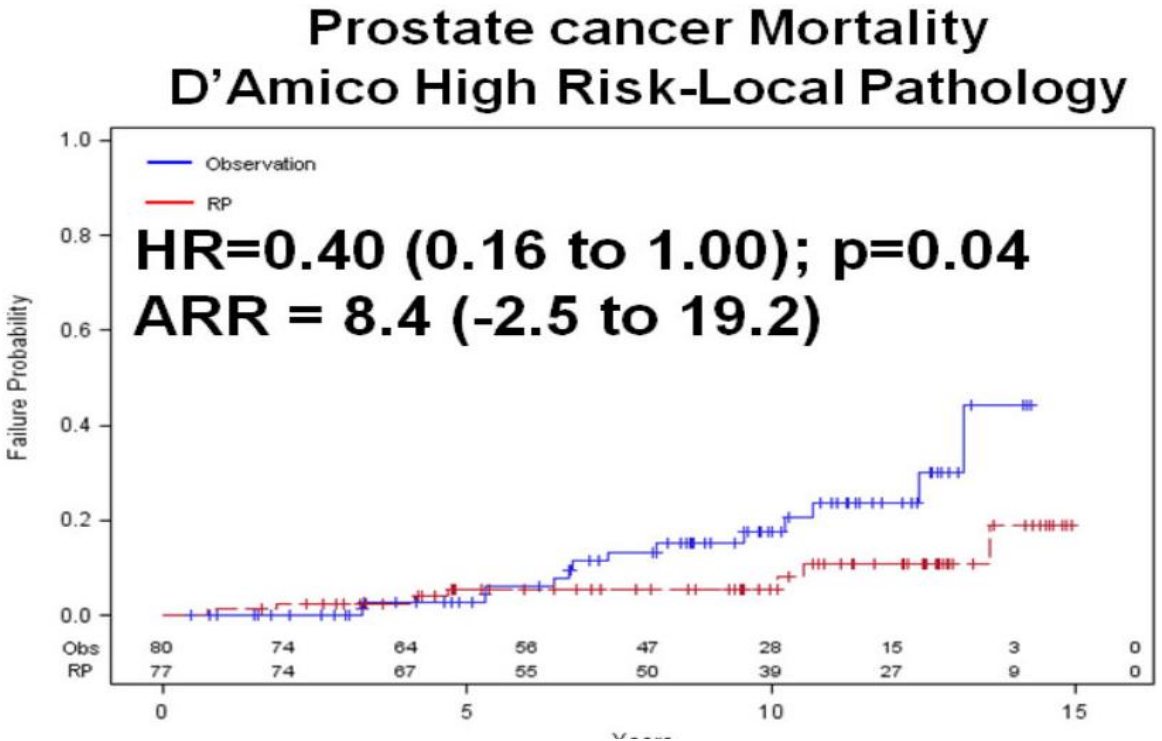
Surveillance is gaining in the real world



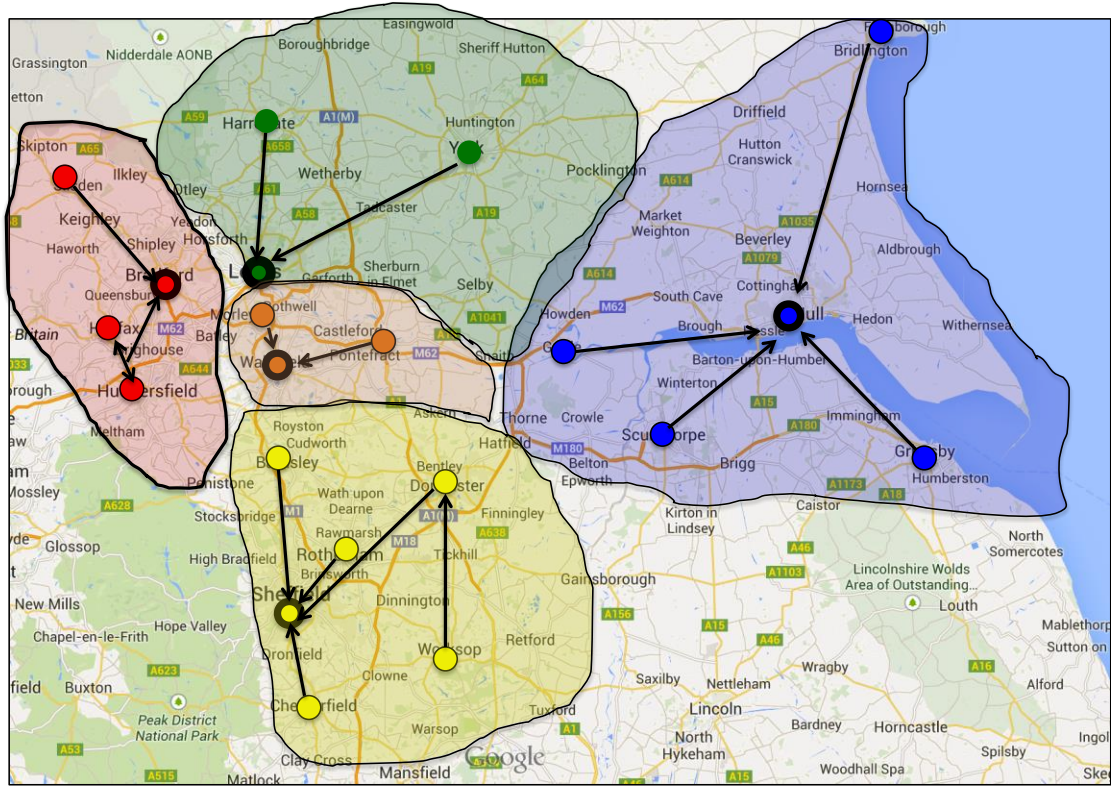
40% is still too low, but this is rapid *progress*

Cooperberg and Carroll. JAMA 2015 314:80

Do treat most high-risk disease



Care should be regionalized



Track practices and outcomes systematically

AQUA
AUA Quality Registry

The British Association of Urological Surgeons

Optimal screening (one opinion)

- Offer screening to most men in good health with baseline around age 45-50 (earlier for strong FHx or other risk factors)
- Purpose of screening is early identification of *potentially lethal* disease
- If baseline is low (<0.7-1) defer next check for *at least* 5 years
- PSA is not a binary test. Forget about 4.0 ng/ml as a threshold!
- Consider secondary testing, and refer early for more complex decision making
- Don’t treat most low-risk disease; treat aggressive disease aggressively (often with multimodal approach)—*in high-quality centers*

UCSF
University of California
San Francisco

Thank you!