Memorial Sloan Kettering Cancer Center

The USPSTF Prostate Cancer Screening Recommendation

A Swinging Pendulum

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How will we explain this to our future colleagues???

1987-1991: PSA test

Volume 317 OCTOBER 8, 1987 Number 15

PROSTATE-SPECIFIC ANTIGEN AS A SERUM MARKER FOR ADENOCARCINOMA OF THE PROSTATE

Thomas A. Stamey, M.D., Norman Yang, Ph.D., Alan R. Hay, M.D., John E. McNeal, M.D., Fuad S. Freiha, M.D., and Elise Redwine, B.A.

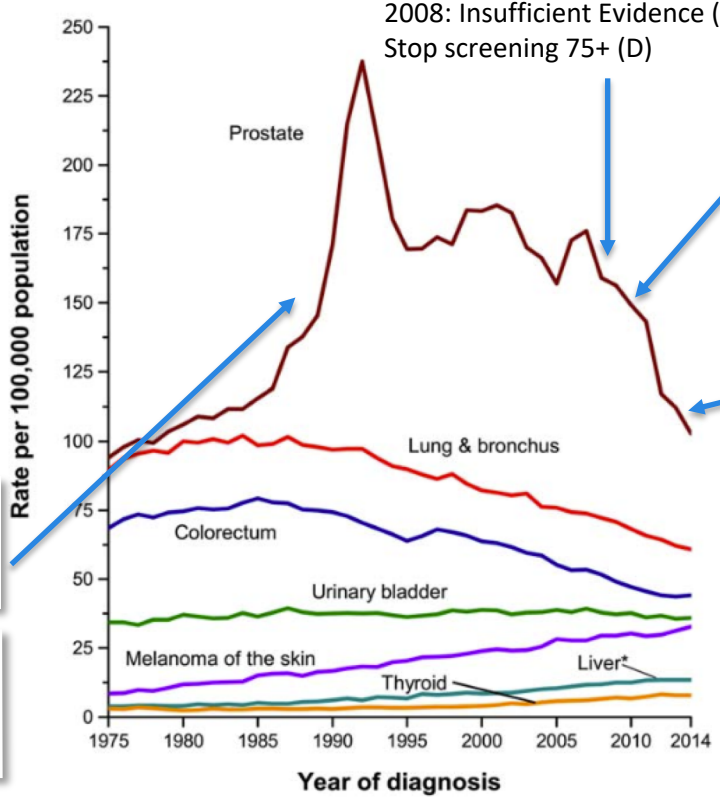
1156 THE NEW ENGLAND JOURNAL OF MEDICINE April 25, 1991

MEASUREMENT OF PROSTATE-SPECIFIC ANTIGEN IN SERUM AS A SCREENING TEST FOR PROSTATE CANCER

William J. Catalona, M.D., Deborah S. Smith, Ph.D., Timothy L. Ratliff, Ph.D., Kathy M. Dodds, R.N., Douglas E. Coplen, M.D., Jerry J.J. Yuan, M.D., John A. Petros, M.D., and Gerald L. Andriole, M.D.

U.S. Preventive Services TASK FORCE

2008: Insufficient Evidence (I)
Stop screening 75+ (D)



2009: 2 conflicting RCTs

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D.,

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D.,

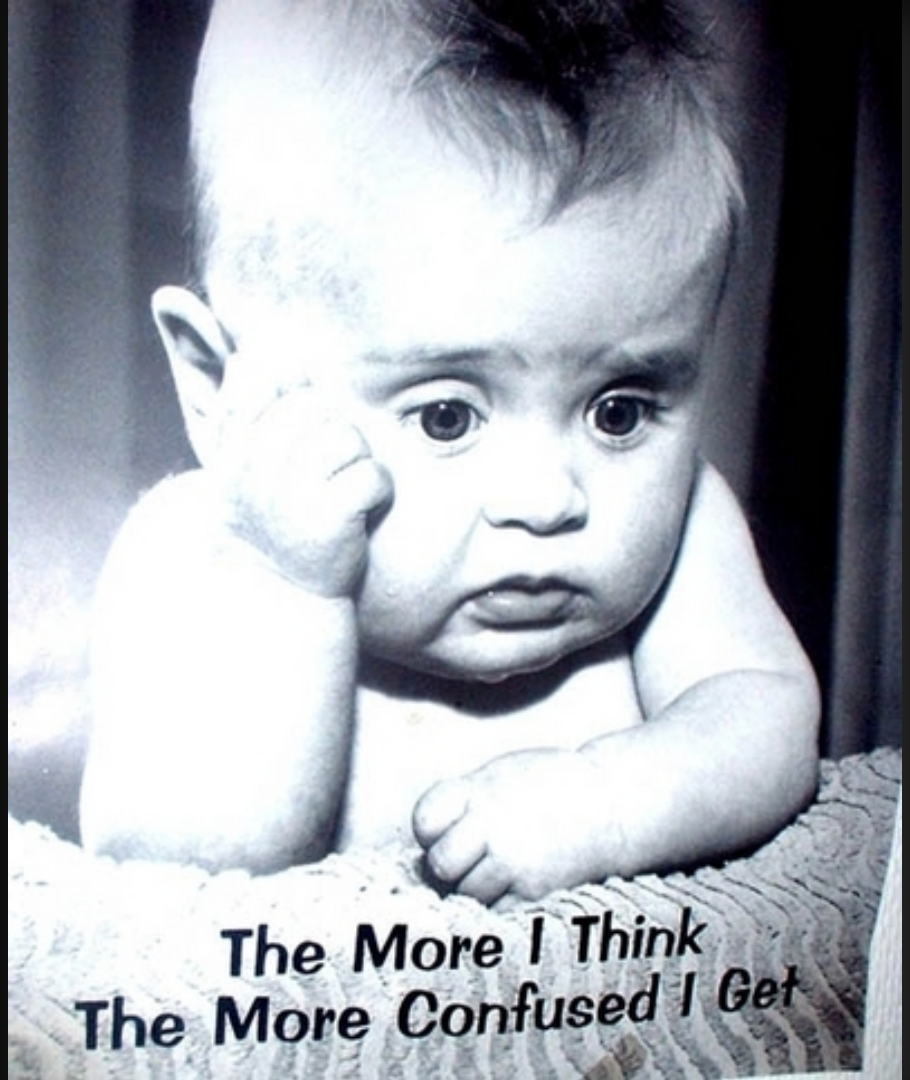
U.S. Preventive Services TASK FORCE

2012: Screen none (D)

U.S. Preventive Services TASK FORCE

2018: Screen some (C)

Siegel R, et al. *CA Cancer J Clin*. 2018;68(1):7-30. Stamey TA et al, *N Engl J Med* 1987;317. Catalona WJ et al, *N Engl J Med* 1991;324. Schröder F, *N Engl J Med* 2009. Andriole G, *N Engl J Med* 2009.


The More I Think
The More Confused I Get

USPSTF consists of an independent panel of experts and is the most influential of guideline groups in the US

- Makes evidence-based recommendations about clinical preventive services in the primary care setting
  - Screening
  - Counseling
  - Preventive medications
- Volunteer experts from primary care disciplines
  - Family medicine, internal medicine, nursing, obstetrics/gynecology, pediatrics, behavioral medicine

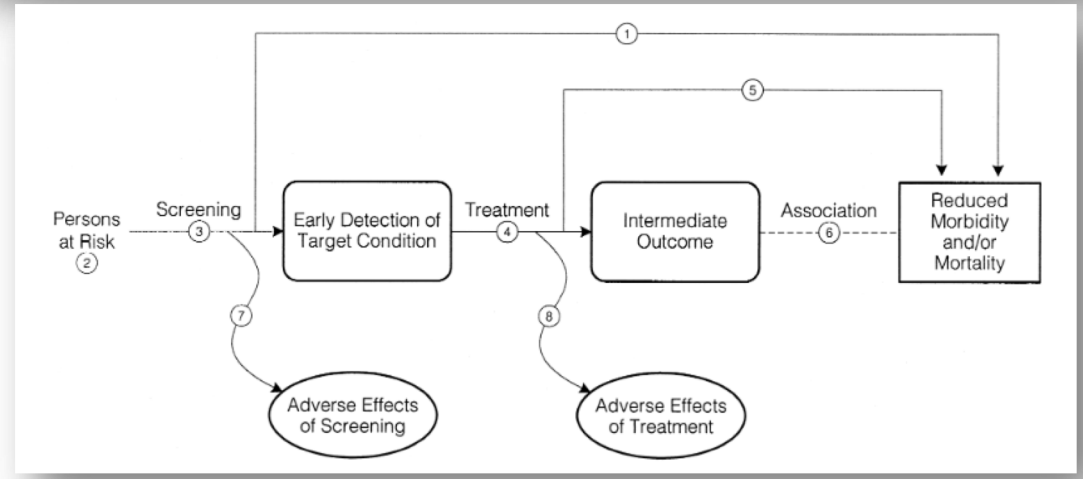
https://www.uspreventiveservicestaskforce.org/Page/Name/understanding-how-the-uspstf-works

Behind every USPSTF recommendation is a thorough systematic review of the evidence

REVIEW | Annals of Internal Medicine

Screening for Prostate Cancer: A Review of the Evidence for the U.S. Preventive Services Task Force

Roger Chou, MD; Jennifer M. Croswell, MD, MPH; Tracy Dana, MLS; Christina Bougatsos, BS; Ian Blazina, MPH; Rongwei Fu, PhD; Ken Gleitsmann, MD, MPH; Helen C. Koenig, MD, MPH; Clarence Lam, MD, MPH; Ashley Maltz, MD, MPH; J. Bruin Rugge, MD, MPH; and Kenneth Lin, MD



Chou R et al. *Ann Intern Med*. 2011;155(11):762-71. Harris et al. *Am J Prev Med*. 2001;20(3 Suppl):21-35.

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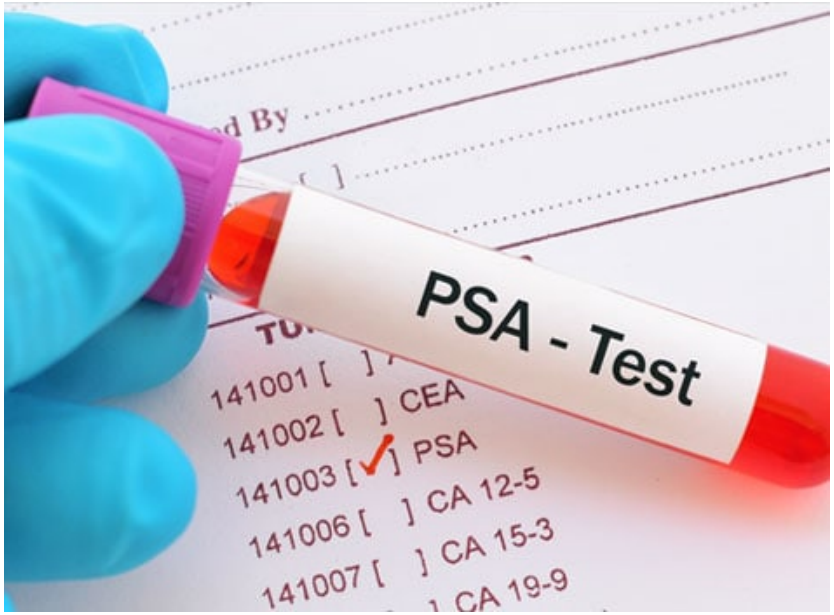
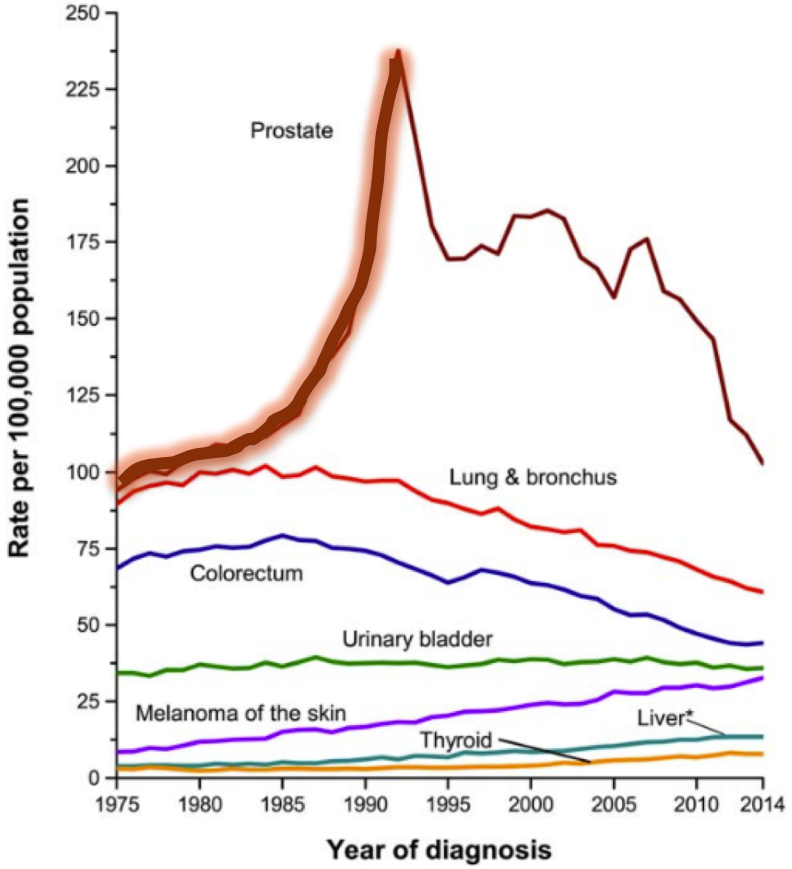
U.S. Preventive Services TASK FORCE

Grade	Definition
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

The test used to screen for prostate cancer is a simple blood draw that measures the Prostate-Specific Antigen (PSA) level



The discovery of the PSA-test led to a dramatic surge in prostate cancer incidence in the late 80s-early 90s



Siegel R, et al. *CA Cancer J Clin*. 2018;68(1):7-30.

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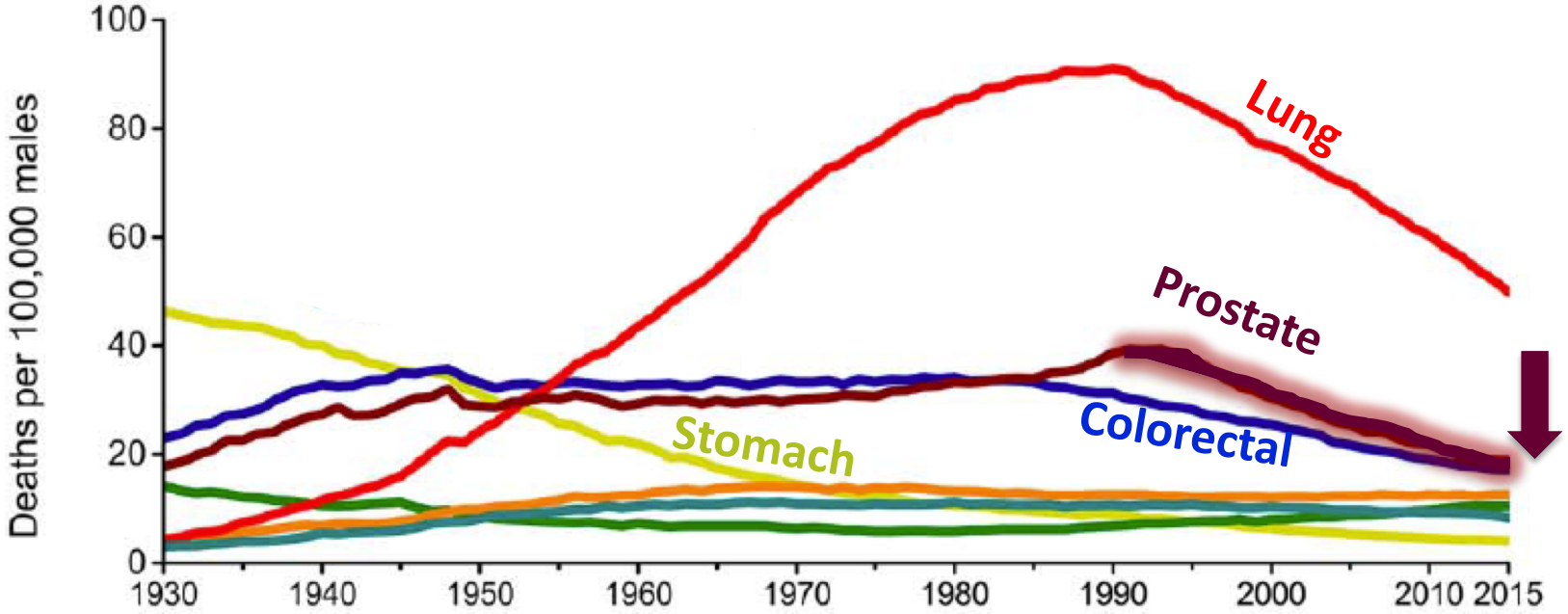
The age-adjusted death rate from prostate cancer in the US is down by 51% from peak rates



Siegel R, et al.
CA Cancer J Clin.
2018;68(1):7-30.

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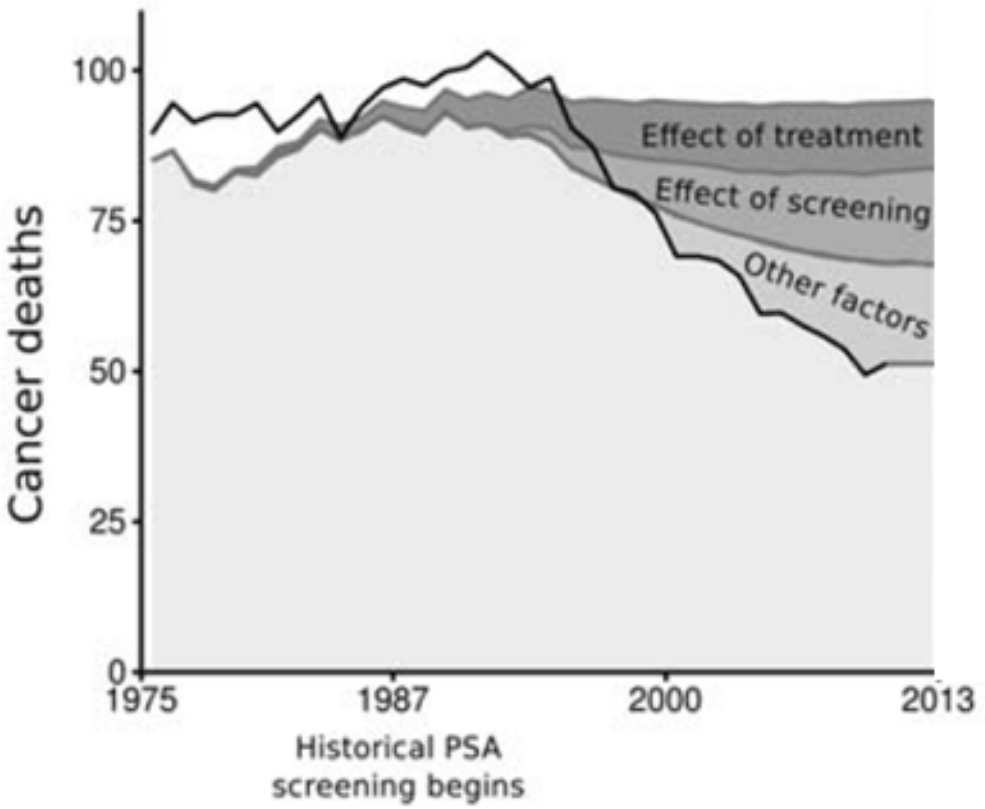
…mainly explained by screening



Gulati R, et al. *Cancer.* 2014;120:3519-26.

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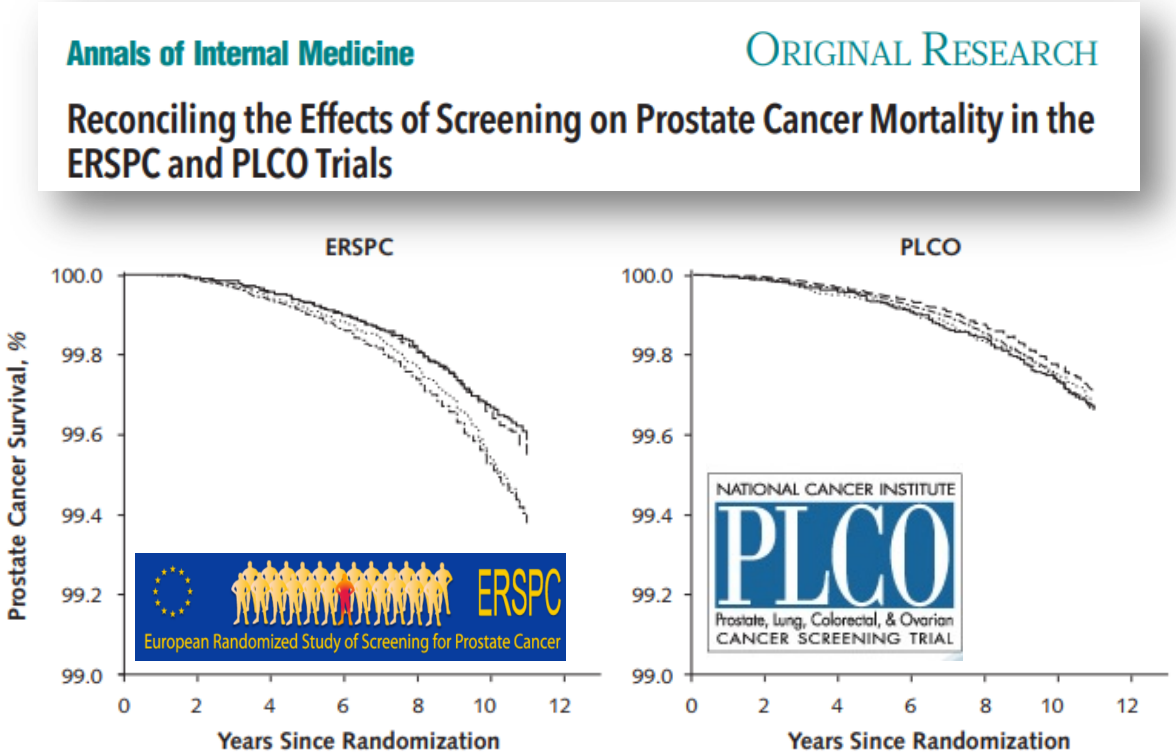
Both the European and US trials now provide compatible evidence that screening reduces prostate cancer mortality



Tsodikov A, et al. *Ann Intern Med*. 2017.

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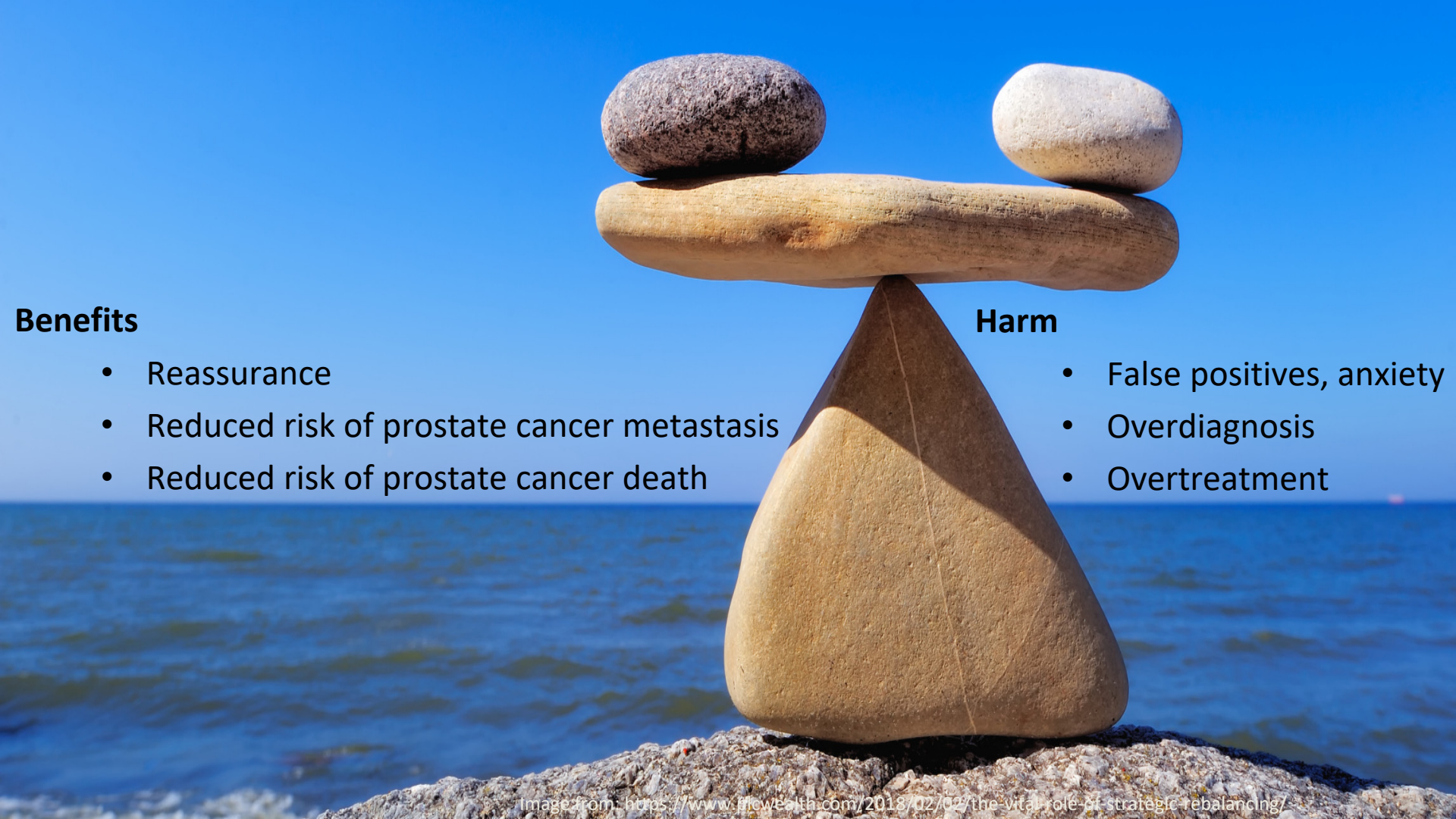


Benefits

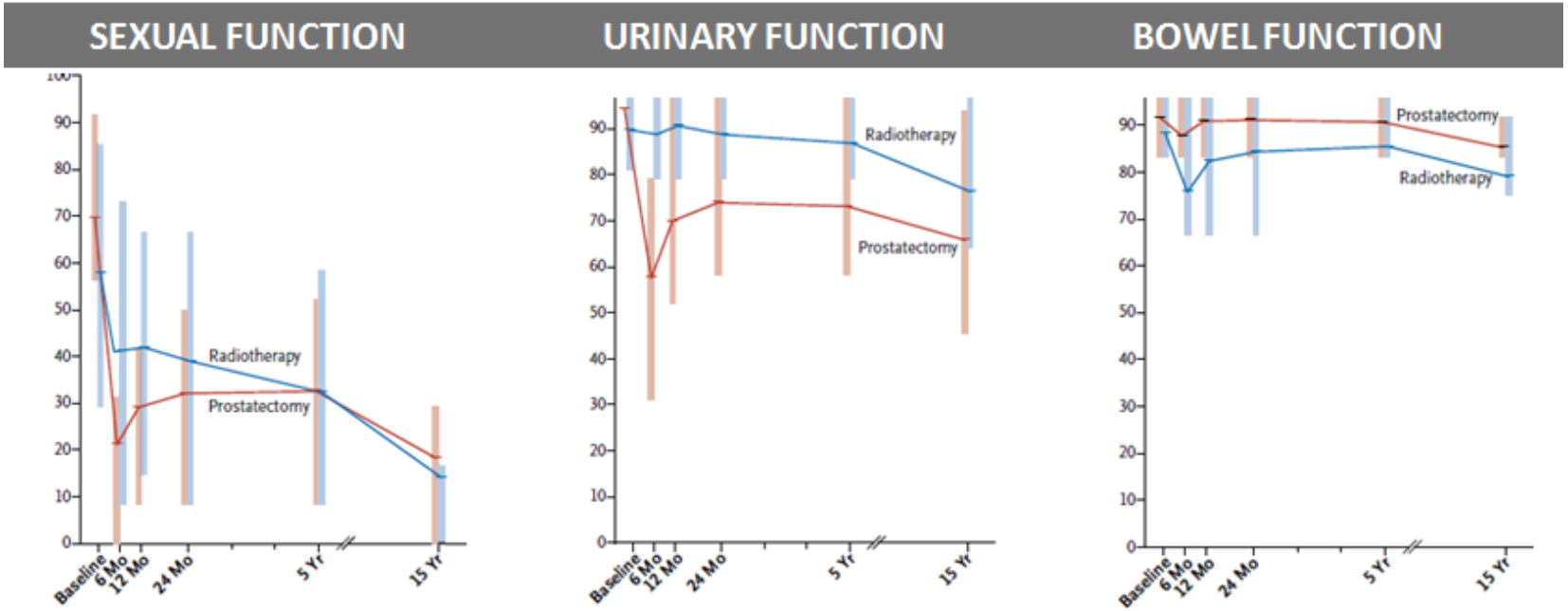
- Reassurance
- Reduced risk of prostate cancer metastasis
- Reduced risk of prostate cancer death

Harm

- False positives, anxiety
- Overdiagnosis
- Overtreatment

Image from: https://www.fnewealth.com/2018/02/02/the-vital-role-of-strategic-rebalancing/

Side-effects from treatment have a substantial impact on men's quality-of-life



Sanda et al. *NEJM,* 2008. Resnick et al. *NEJM,* 2013. Heinsdijk et al. *NEJM,* 2012.

U.S. Preventive Services TASK FORCE

Archived: Prostate Cancer: Screening, 2008

Original Release Date: August 2008

This version of this topic is currently archived and inactive. It should be used for historical purposes

Archived: Recommendation Summary

Population	Recommendation	Grade (What's This?)
Men younger than age 75 years	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of prostate cancer screening.	I
Men age 75 years or older	The USPSTF recommends against screening for prostate cancer.	D

https://www.uspreventiveservicestaskforce.org/

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U.S. Preventive Services TASK FORCE

Prostate Cancer: Screening

Release Date: May 2012

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Men	The U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA)–based screening for prostate cancer.	D

"The USPSTF concludes that there is moderate certainty that the benefits of PSA-based screening for prostate cancer do not outweigh the harms."

https://www.uspreventiveservicestaskforce.org/

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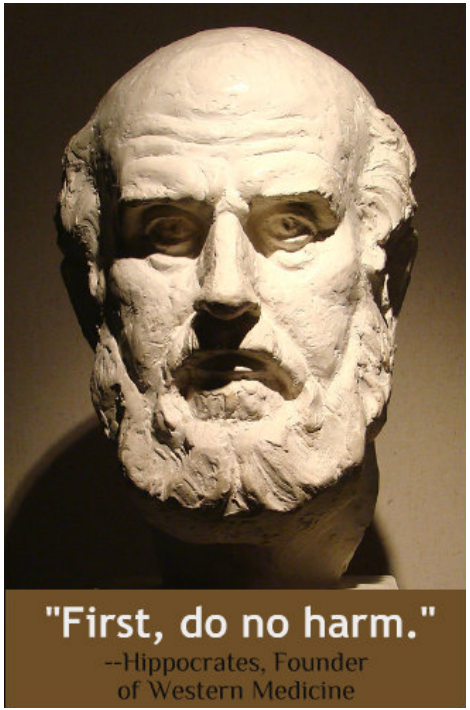
PSA-screening for prostate cancer
has been a public health disaster!

What has been wrong with PSA screening and treatment practices in the US?

1. One in four primary care physicians order the PSA test without discussing it with the patient



Volk RJ, et al. *Ann Fam Med*. 2013;11:67–74.

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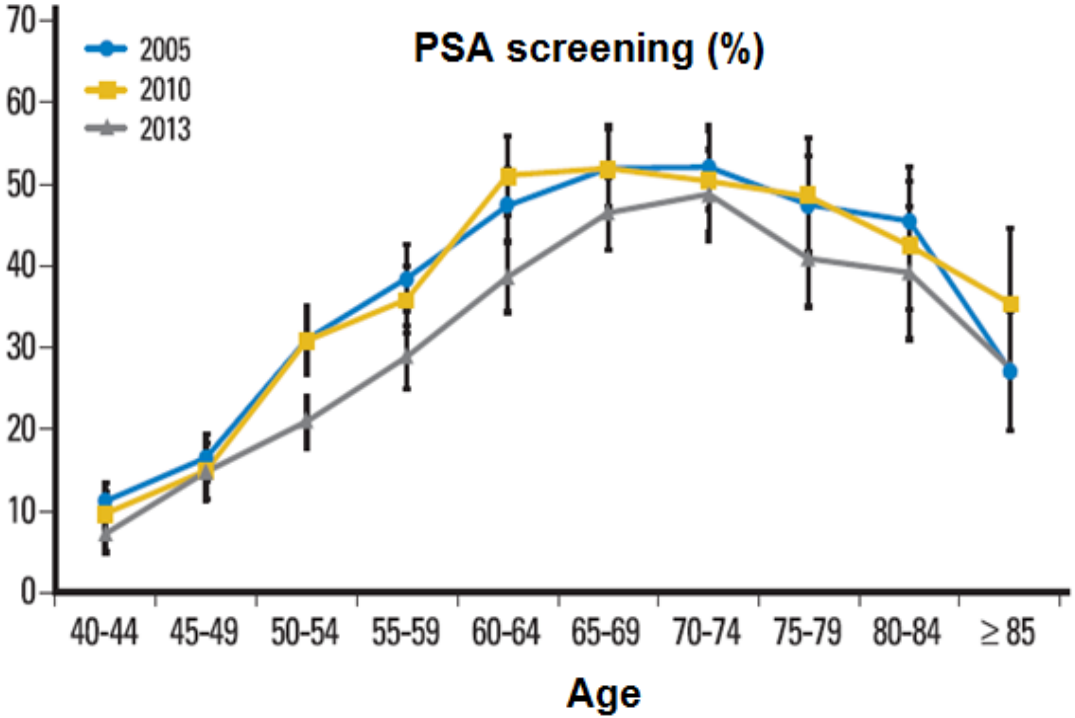
2. There is excessive PSA-screening of elderly men with multiple co-morbidities



Drazer, et al. *J Clin Oncol*. 2015;33:2416-23.

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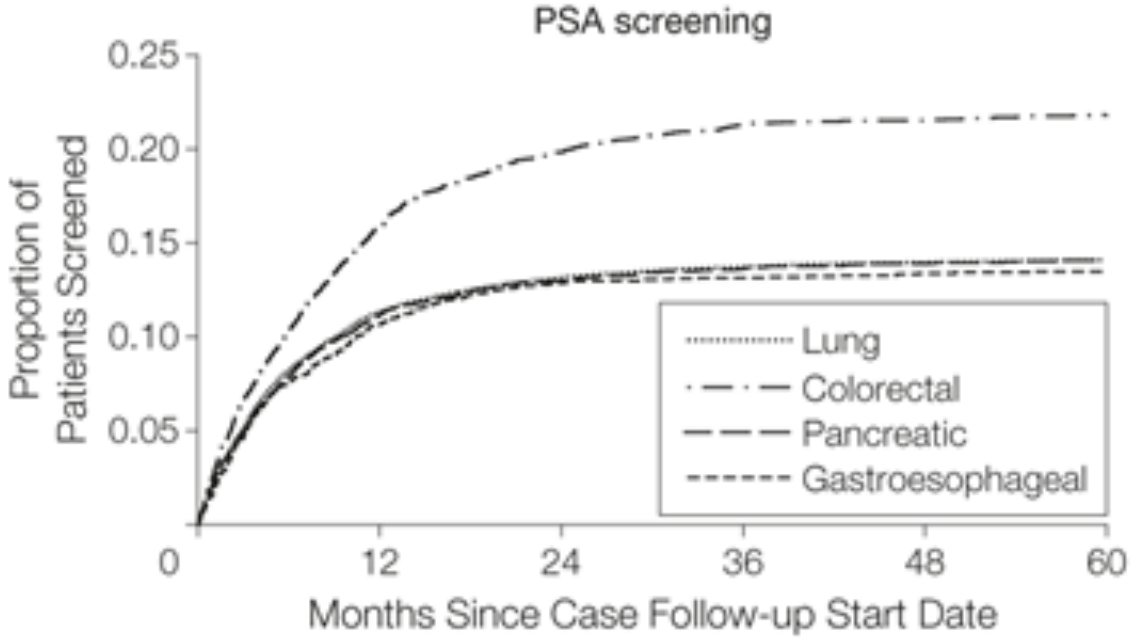
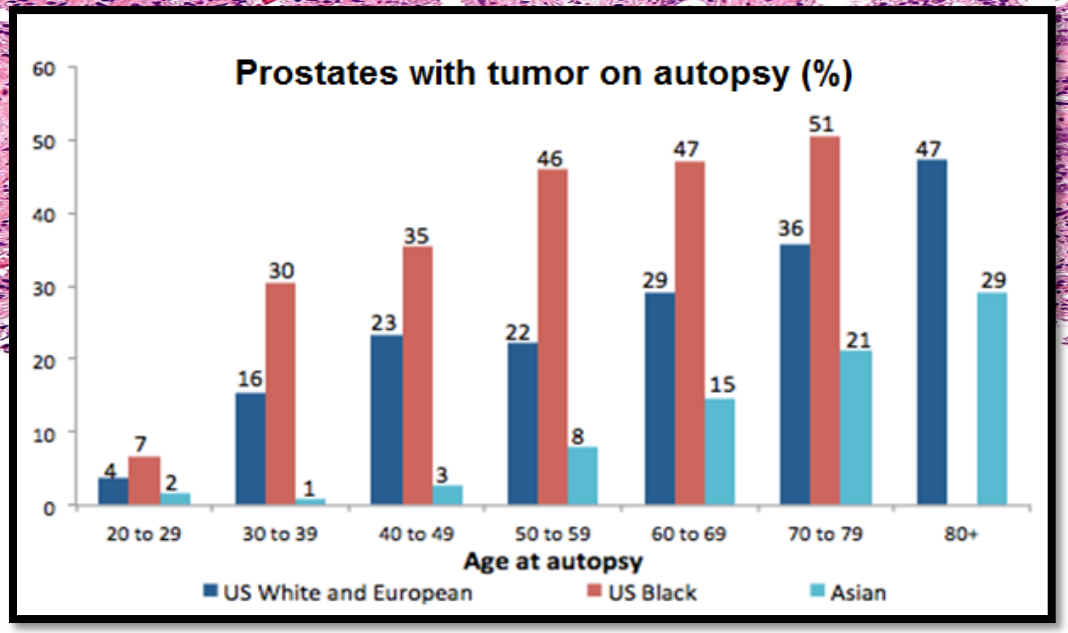
Men are being screened who are dying from other cancers



Sima CS et al. *JAMA*. 2010;304:1584-91.

Most men will develop prostate cancer if they live long enough



Jahn, JL & Stampfer, MJ. *Int J Cancer.* 2015. Haas GP, et al. *J Natl Cancer Inst*. 2007;99:1484-9.

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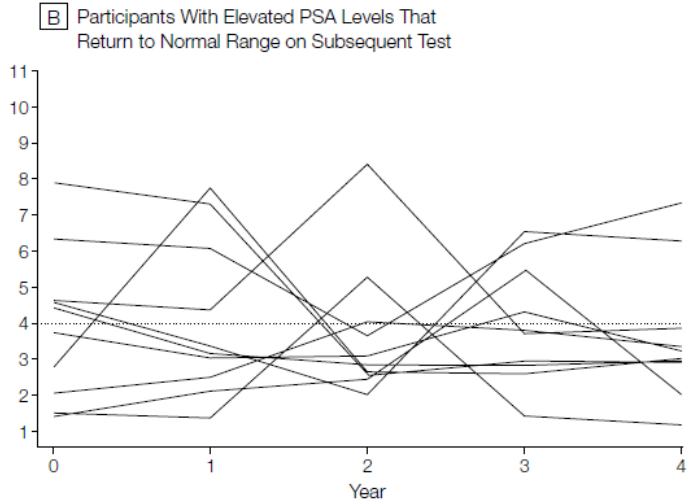
3. We have had too liberal criteria for prostate biopsy

- PSA has low specificity
  - Most men with modestly elevated PSA (3-10 ng/mL) do not have cancer on biopsy
- PSA has a tendency to fluctuate

Vickers AJ, et al. *BMJ*. 2010;341:c4521.
Thompson IM, et al. *NEJM*. 2004;350:2239–46.
Eastham JA, et al. *JAMA*. 2003;289:2695–700.

The probability that PSA would return to normal and remain normal during a 5-year period was high in a dietary study for colon polyps

Definition of abnormal PSA	% ever abnormal	Probability that PSA would return to normal	Probability that PSA would remain normal
> 4.0 ng/mL	21%	44%	80%
> 2.5 ng/mL	37%	40%	65%



Eastham JA, et al. *JAMA.* 2003;289:2695–700.

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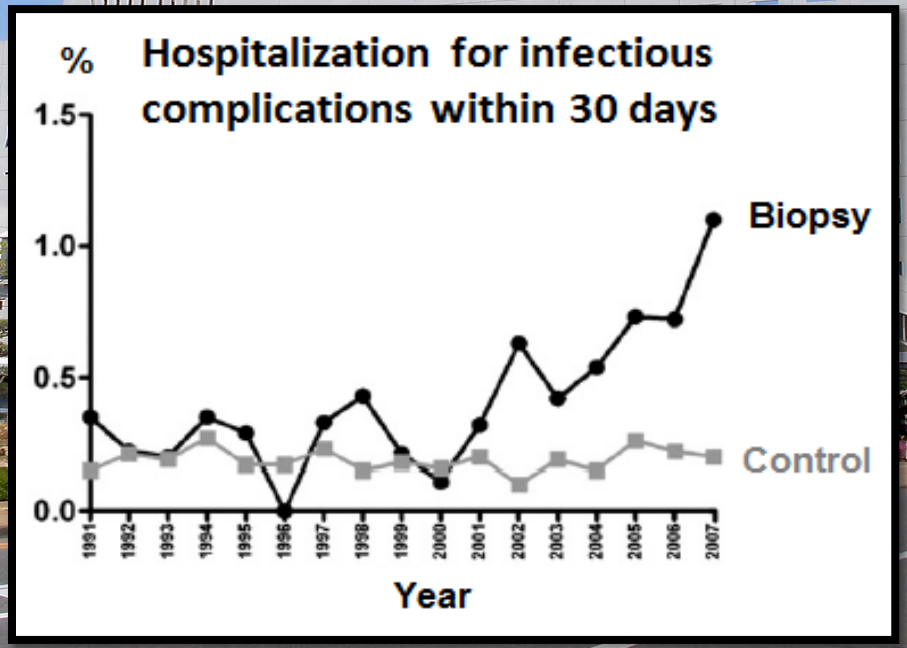
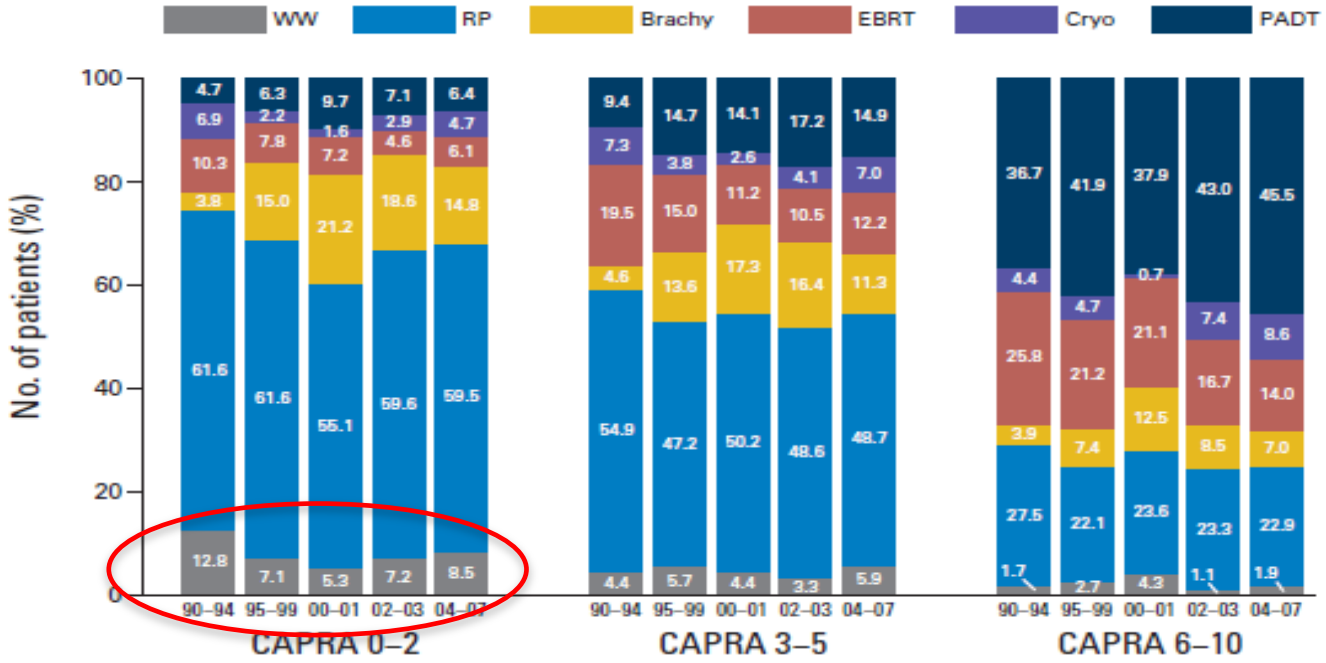
Men are being biopsied <u>without compelling reasons</u>



Nam R, et al. *J Urol.* 2013;189: S12-S18. Loeb S, et al. *Eur Urol.* 2013;64:876-892.

4. We have been treating low-risk cancer too aggressively



Use of expectant management among U.S. patients with localized prostate cancer by risk category (1990-2006)

Cooperberg MR et al. *J Clin Oncol.* 2010;28:1117-1123.

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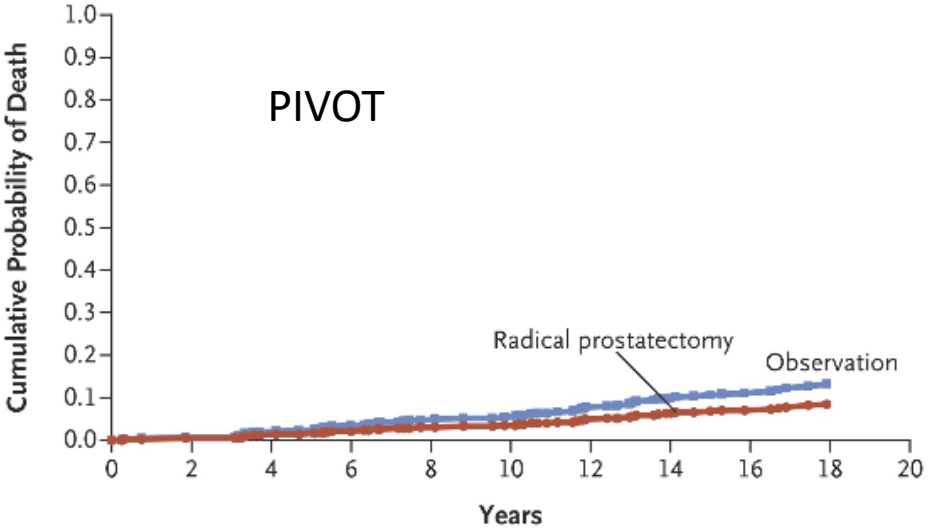
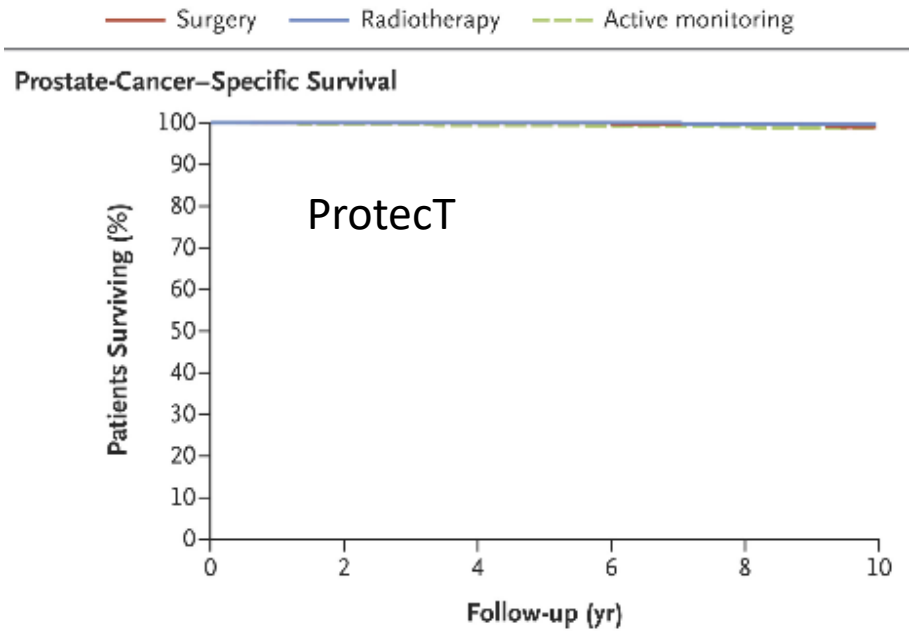
Risk of death from localized prostate cancer is low

PIVOT



ProtecT



Wilt TJ et al. *NEJM.* 2017;377:132-142. Hamdy F, et al. *NEJM*. 2016;375:1415-1424.

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5. Treatment has largely been administered by low-volume providers

Typical annual radical prostatectomy caseload of a U.S. surgeon in 2005:

3

Savage CJ, Vickers AJ. *J Urol.* 2009;182:2677–9.

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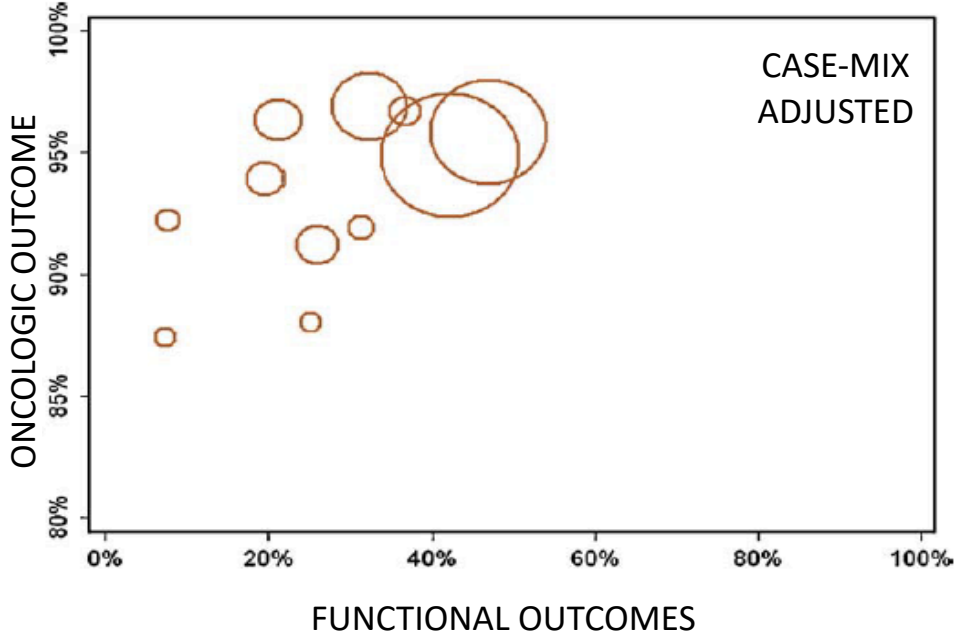
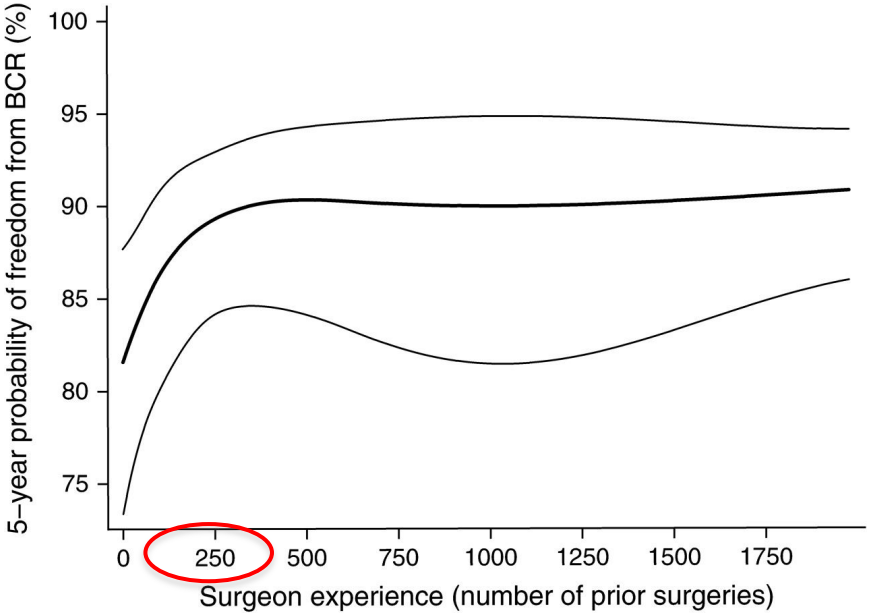
Whose hands perform the radical prostatectomy can have a significant impact on oncologic and functional outcomes





Eastham JA. *Urol Oncol.* 2009;27:417–21.
Savage CJ, Vickers AJ. *J Urol.* 2009;182:2677–9. Vickers AJ, et al. *JNCI.* 2007;99(15):1171-7.

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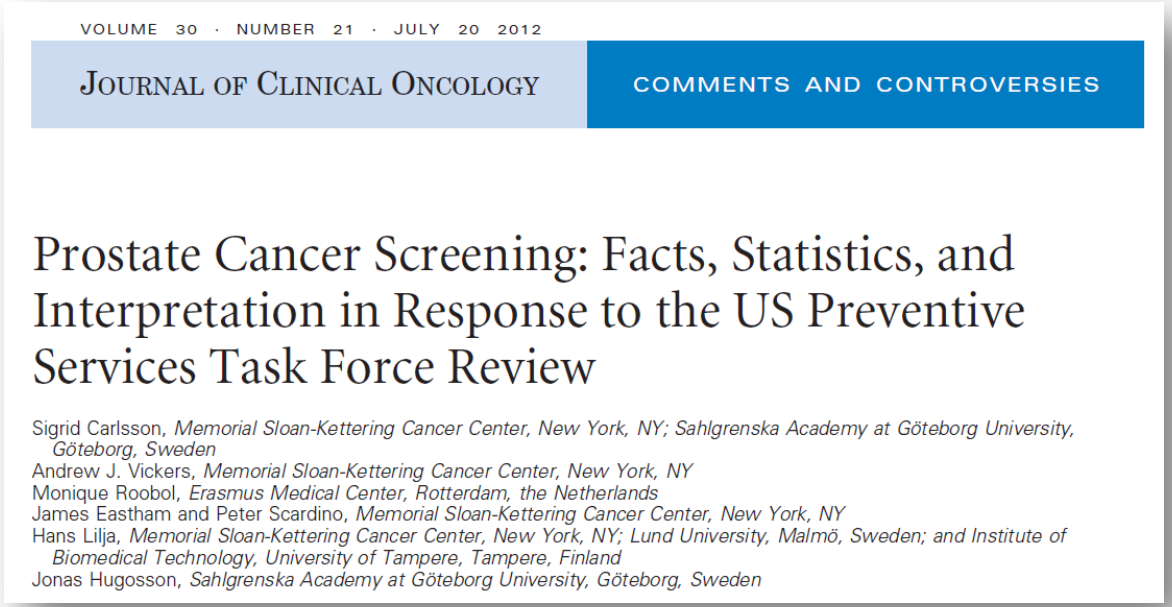
We can understand why a guideline group might recommend against PSA screening, particularly the way in which it has been practiced



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JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Prostate Cancer Screening: Facts, Statistics, and Interpretation in Response to the US Preventive Services Task Force Review

Sigrid Carlsson, *Memorial Sloan-Kettering Cancer Center, New York, NY; Sahlgrenska Academy at Göteborg University, Göteborg, Sweden*
Andrew J. Vickers, *Memorial Sloan-Kettering Cancer Center, New York, NY*
Monique Roobol, *Erasmus Medical Center, Rotterdam, the Netherlands*
James Eastham and Peter Scardino, *Memorial Sloan-Kettering Cancer Center, New York, NY*
Hans Lilja, *Memorial Sloan-Kettering Cancer Center, New York, NY; Lund University, Malmö, Sweden; and Institute of Biomedical Technology, University of Tampere, Tampere, Finland*
Jonas Hugosson, *Sahlgrenska Academy at Göteborg University, Göteborg, Sweden*

Carlsson S, et al. *J Clin Oncol*. 2012.

Critical misinterpretations of the evidence by USPSTF in 2012

- Definitive conclusions based on **incomplete data**
- Failure to address the **time-to-event** nature of the data of ERSPC

Years of monitoring	Number needed to screen to avoid		Number needed to diagnose to avoid	
	1 cancer-specific death	1 incidence of metastatic disease	1 cancer-specific death	1 incidence of metastatic disease
9	1,410	736	48	25
11	979	393	35	14
13	781	333*	27	14*

- Using **overall mortality** as an endpoint
  - much lower power than cancer-specific mortality because of the statistical noise of deaths from other causes
- Combining data from **incompatible trials**

Carlsson S, et al. *J Clin Oncol*. 2012;30(21):2581-4. van der Kwast, Roobol MJ. *Nat Rev Urol.* 2017.

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The AUA's response to USPSTF 2012:

American Urological Association

Sushil S. Lacy, MD

AUA President

2011 – 2012

"The USPSTF is doing a great disservice to the men worldwide who may benefit from the PSA test."

http://auanet.mediaroom.com/2011-10-07-AUA-RESPONDS-TO-NEW-RECOMMENDATIONS-ON-PROSTATE-CANCER-SCREENING?articleNo=262

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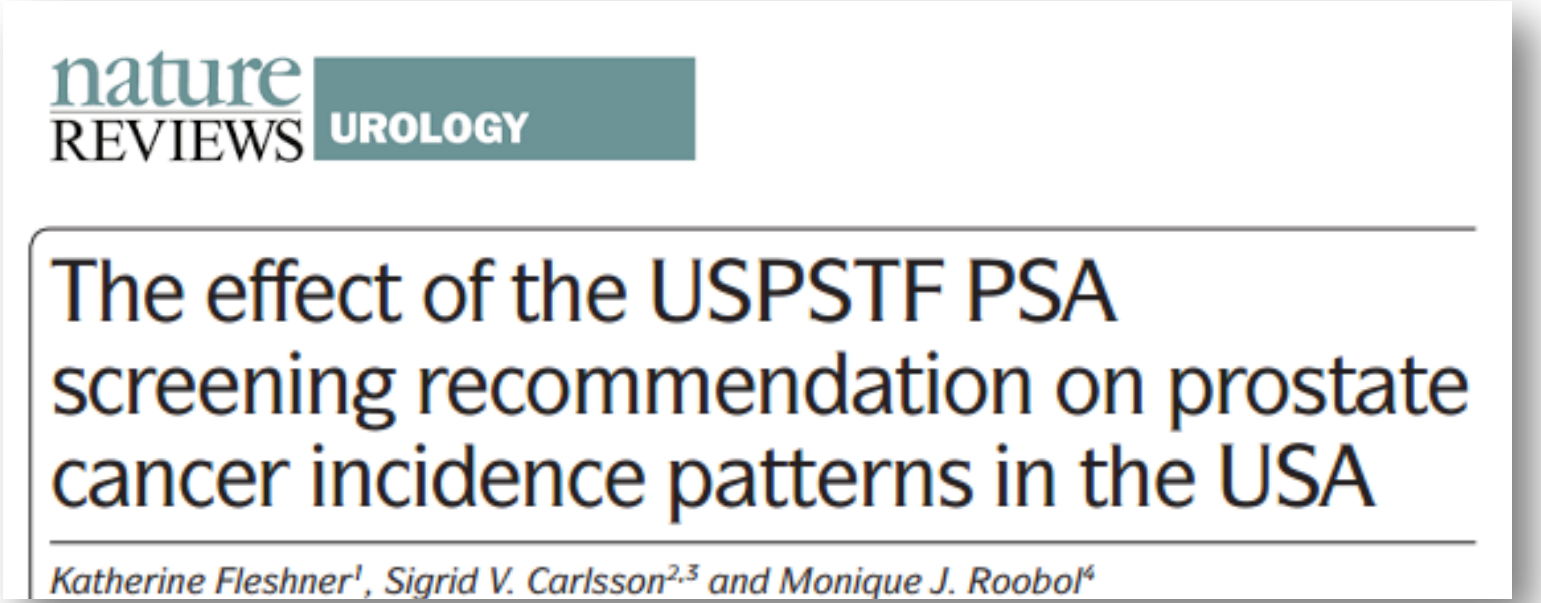
The impact of the 2012 USPSTF recommendation has been documented in multiple studies



Fleshner K, Carlsson SV, Roobol MJ. *Nat Rev Urol*. 2017;14:26-37. Eapen RS, et al. *Curr Opin Urol*. 2017.

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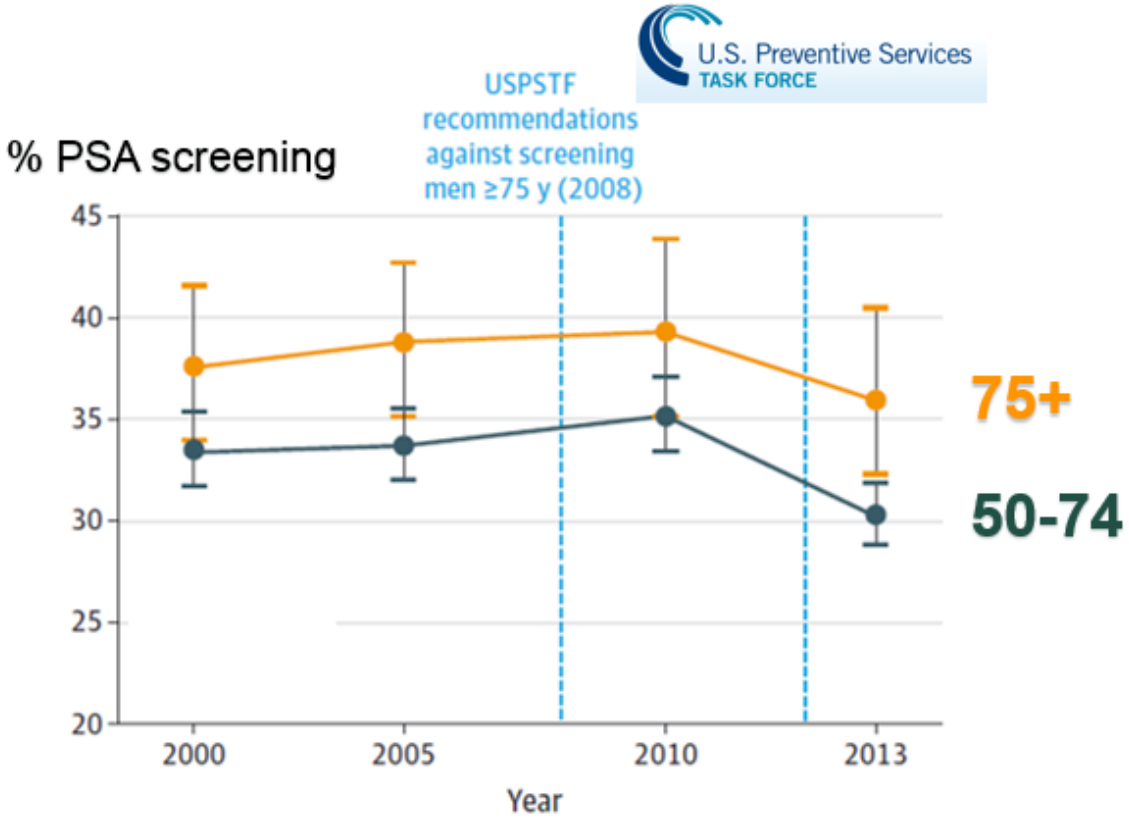
PSA-testing rates have declined in all age groups



Sammon, et al. *JAMA*. 2015;19:2077-9. Jemal A, et al. *JAMA*. 2015;314:2054-61.
Fleshner K, Carlsson SV, Roobol MJ. *Nat Rev Urol*. 2017;14(1):26-37.

Prostate cancer incidence has declined in all ages and is now down to pre-PSA era levels

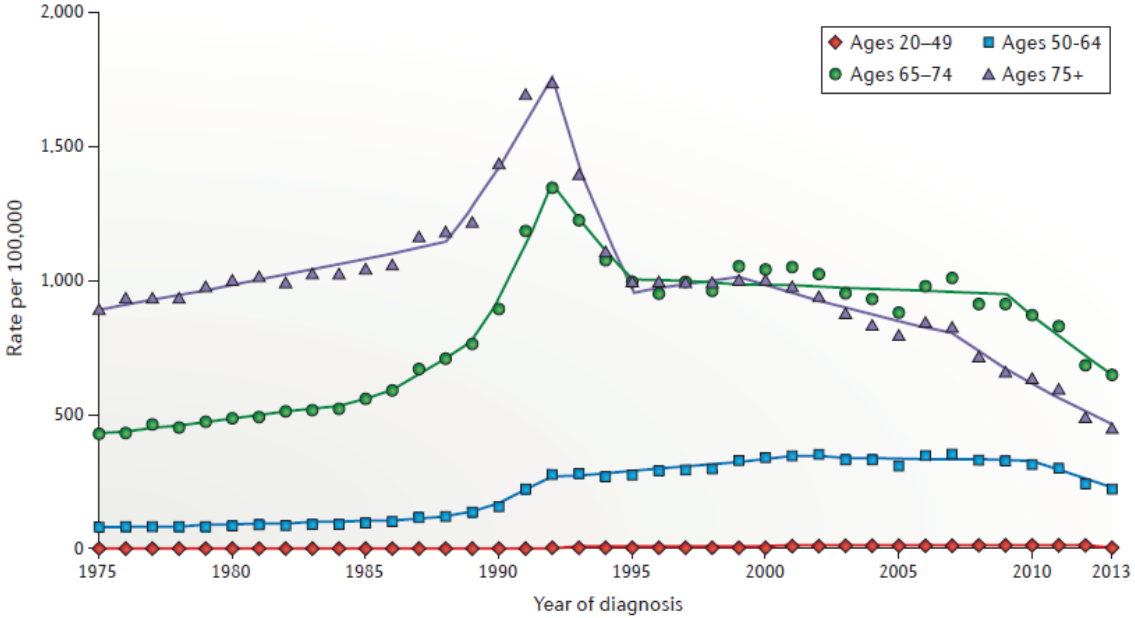


Figure 2 | **Age-adjusted prostate cancer incidence rates in the Surveillance, Epidemiology and End Results (SEER) database by age at diagnosis from 1975 to 2013 in the USA.** Trends in the graph are similar to those depicted in FIG. 1, but the effect of the use of the PSA test is most noticeable in men aged >65 years from the SEER 9 Database. Rates are per 100,000 and age-adjusted to the 2000 US standard population. The figure is extracted with permission from the SEER Database.

Siegel R, et al. *CA Cancer J Clin*. 2018;68(1):7-30.
Fleshner K, Carlsson SV, Roobol MJ. *Nat Rev Urol*. 2017;14(1):26-37.

…and races

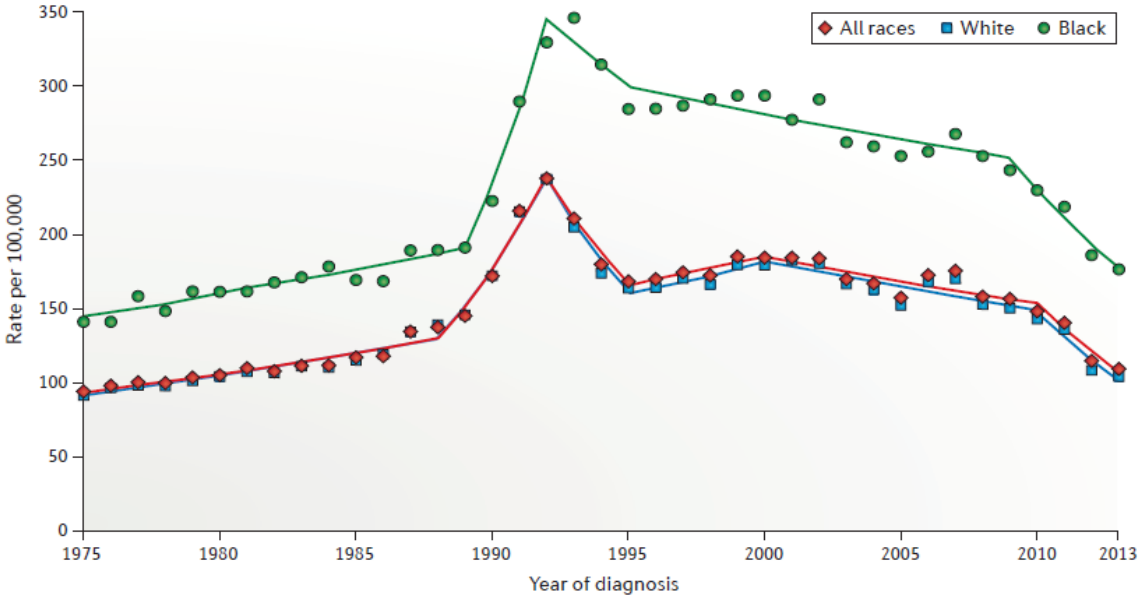


Figure 3 | **Age-adjusted prostate cancer incidence rates in the Surveillance, Epidemiology and End Results (SEER) database in men of all ages by race/ethnicity, from 1975 to 2013 in the USA.** The temporal trends in prostate cancer incidence, which are reflective of changes in PSA testing over time, are seen in all ethnicities in the SEER 9 Rates are per 100,000 and age-adjusted to the 2000 US standard population. The figure is extracted with permission from the SEER Database.

Rates of prostate biopsy have declined in unison, with a shift towards tumors being of higher grade and stage upon detection

Siegel R, et al. *CA Cancer J Clin*. 2018;68(1):7-30.
Fleshner K, Carlsson SV, Roobol MJ. *Nat Rev Urol*. 2017;14(1):26-37.

Don't throw the baby out with the bathwater!

Do we want to go back to seeing these scenarios as the first presentation of prostate cancer?

- Local growth

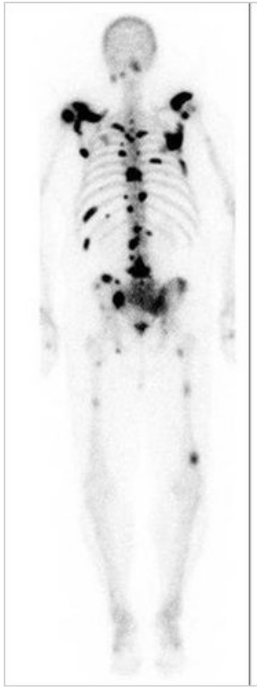
  → Urinary retention → kidney failure

- Skeletal metastases

  → Unrelenting bone pain and malaise

- Spinal cord compression

  → Paralysis of the legs and urinary bladder



Screening decreases the risk of metastatic disease

12 years

- M+ at diagnosis — 50% risk reduction
  (HR 0.50; 95% CI 0.41-0.62; *p<0.001*)
- M+ during follow-up — 30% risk reduction
  (HR 0.70; 95% CI 0.60-0.82; *p=0.001*)

Schröder et al. *Eur Urol.* 2012;62:745-52.

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The number of men presenting with metastatic prostate cancer would be 3 times greater without PSA screening

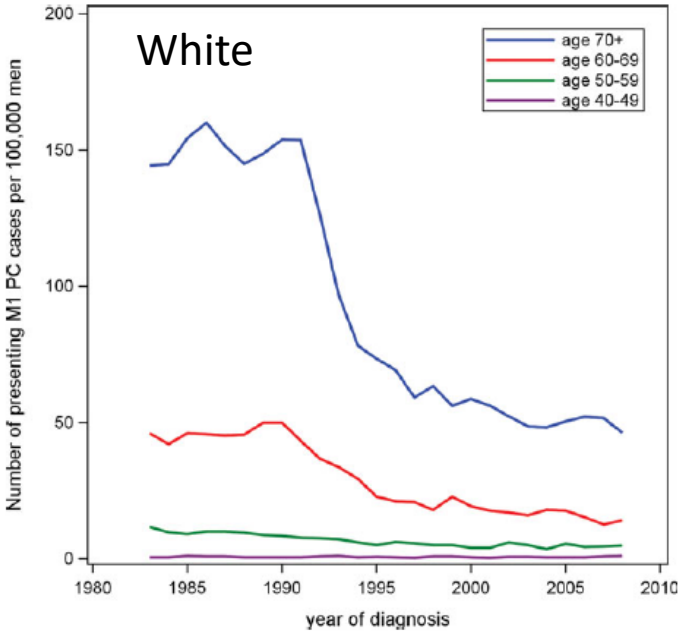

Figure 1. Annual incidence rates of presenting with metastatic prostate cancer (M1 PC) are illustrated according to age among white men.

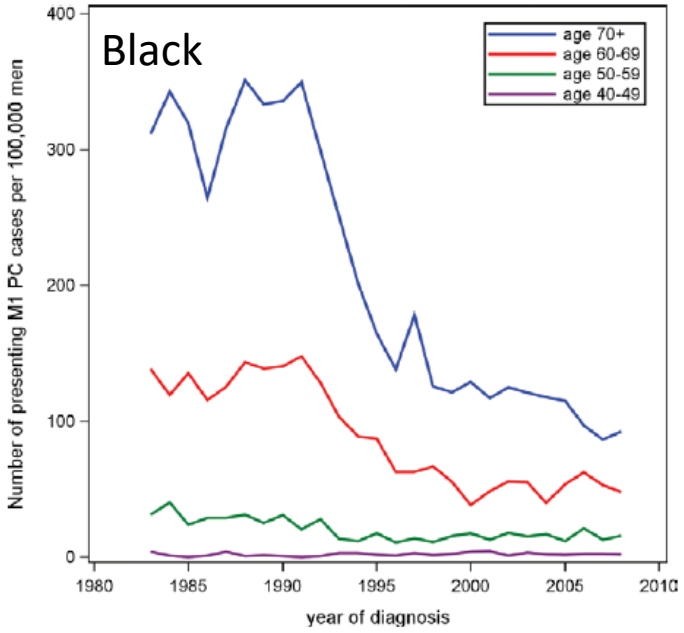

Figure 2. Annual incidence rates of presenting with metastatic prostate cancer (M1 PC) are illustrated according to age among black men.

Scosyrev et al. *Cancer.* 2012;118:5768-76.

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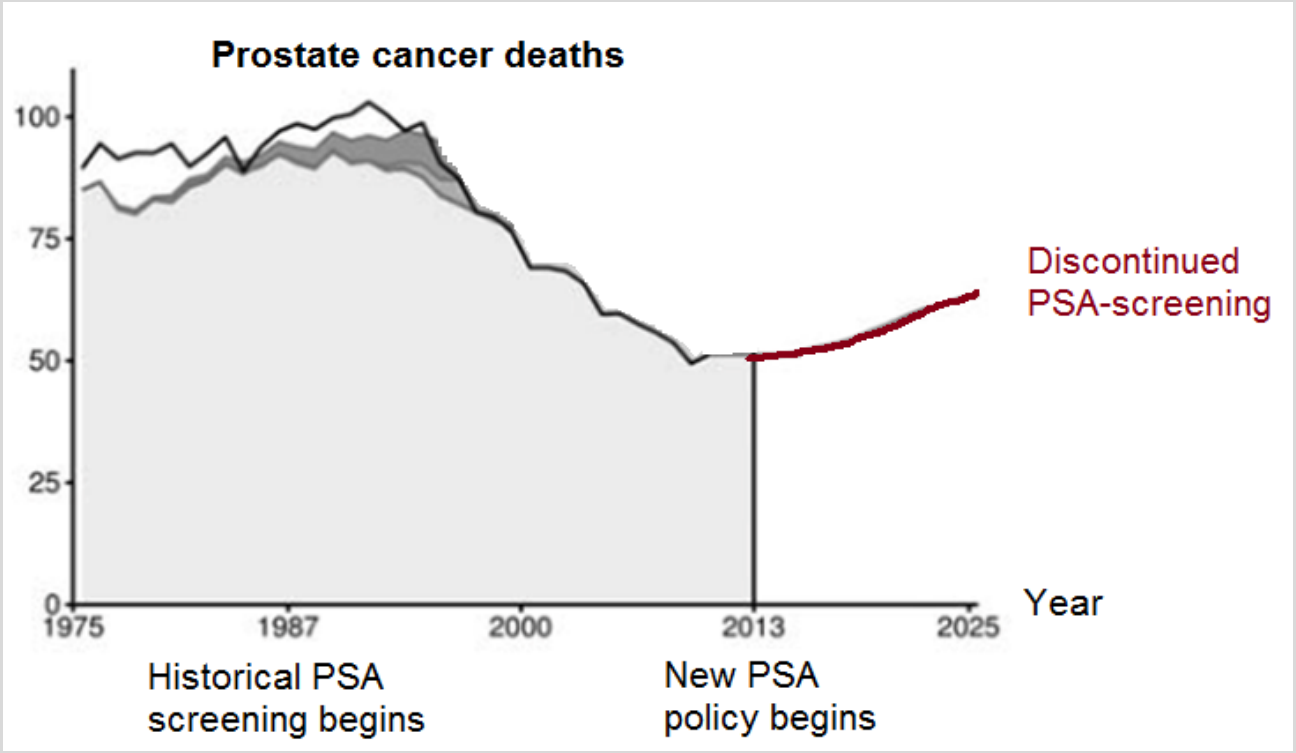
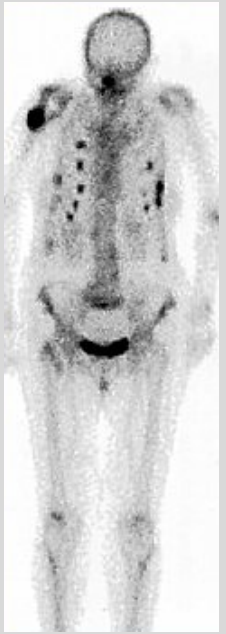
Discontinuation of screening could lead to a failure to prevent 36,000 – 57,000 prostate cancer deaths (2013-2025)





Gulati R, et al. *Cancer*. 2014;120:3519-3526.

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U.S. Preventive Services TASK FORCE

2018

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Men aged 55 to 69 years	For men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)–based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and erectile dysfunction. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. Clinicians should not screen men who do not express a preference for screening.	C
Men 70 years and older	The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older.	D

https://www.uspreventiveservicestaskforce.org/

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The 2018 recommendation is a sea-change that puts USPSTF into mainstream academic thought

National Comprehensive Cancer Network®

American Society of Clinical Oncology

European Association of Urology

The Melbourne Consensus Statement

Memorial Sloan Kettering Cancer Center

American Cancer Society®

U.S. Preventive Services TASK FORCE

ACP American College of Physicians

American Urological Association

Age to start	40-45	45	50	55
Age to stop	70-75	70 75 if healthy 60 if PSA < 1	70 or 10-15 year life expectancy	70

Carlsson SV, Roobol MJ. *Curr Opin Urol.* 2016:26;447–458.

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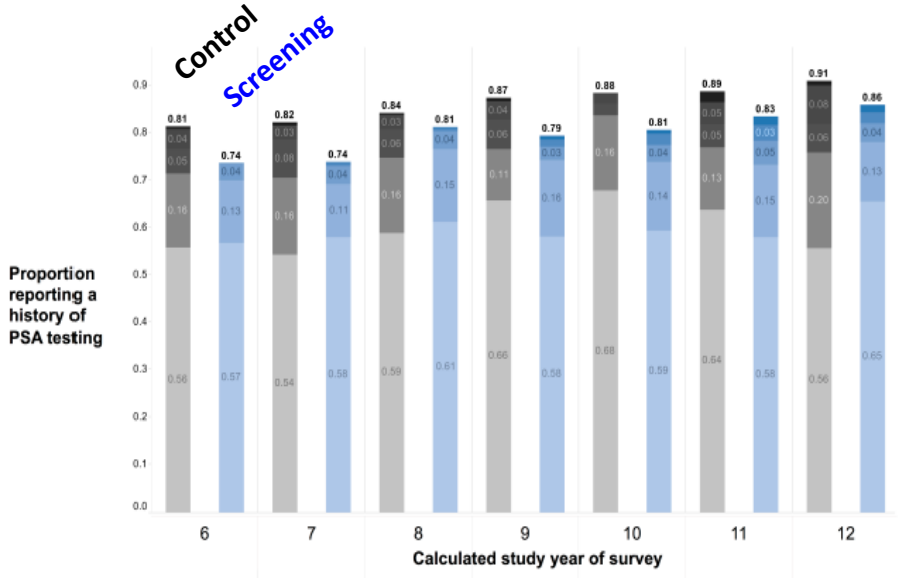
What tipped the scale from a D to a C?

- Critique
- Solicited input from urologists
- Longer follow-up from RCTs
  - ERSPC
  - PIVOT
- Increased uptake of active surveillance

The 2018 USPSTF update does not attempt to adjust down the mortality benefit based on the PLCO

99% of the men in the screening arm: **systematic** screening

86% of the men in the control arm: **opportunistic** screening



Shoag J et al. *N Engl J Med.* 2016:374;18. Pinsky P et al. *Clin Trials.* 2010;7:303.
Andriole GL, et al. *JNCI*. 2012;104(2):125-32. Pinsky P, et al. *Cancer*. 2016.

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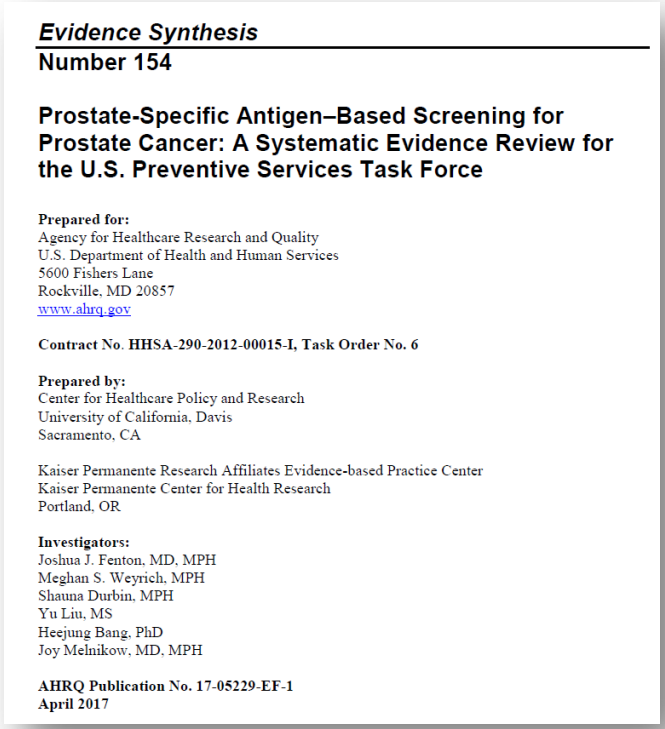
We applaud the new position of USPSTF 2018, but...

- Rigid age range (55-69)
  - Still excludes the Göteborg trial (RCT)
  - Ignores level 1 evidence for screening benefit 50-55
  - Ignores evidence for screening benefit 45-50
- Benefits: Excludes observational studies
  - Baseline PSA
- Harms: Includes both RCTs and cohort studies
  - Outdated studies → overestimation of harms
  - Misses important studies
- Time horizon still short (13 years)
- Excludes modeling studies (lifetime)
- "One investigator abstracted study data"
  - Massive volume of prostate cancer research published between 2012-2017
  - Insurmountable challenge
- Will primary care physicians have time to do shared decision-making? What should they say?



Evidence Synthesis
Number 154

Prostate-Specific Antigen–Based Screening for Prostate Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
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AHRQ Publication No. 17-05229-EF-1
April 2017

https://www.uspreventiveservicestaskforce.org/Page/Document/draft-evidence-review/prostate-cancer-screening1 Cooperberg MC. *Eur Urol*. 2017(72):326–328.

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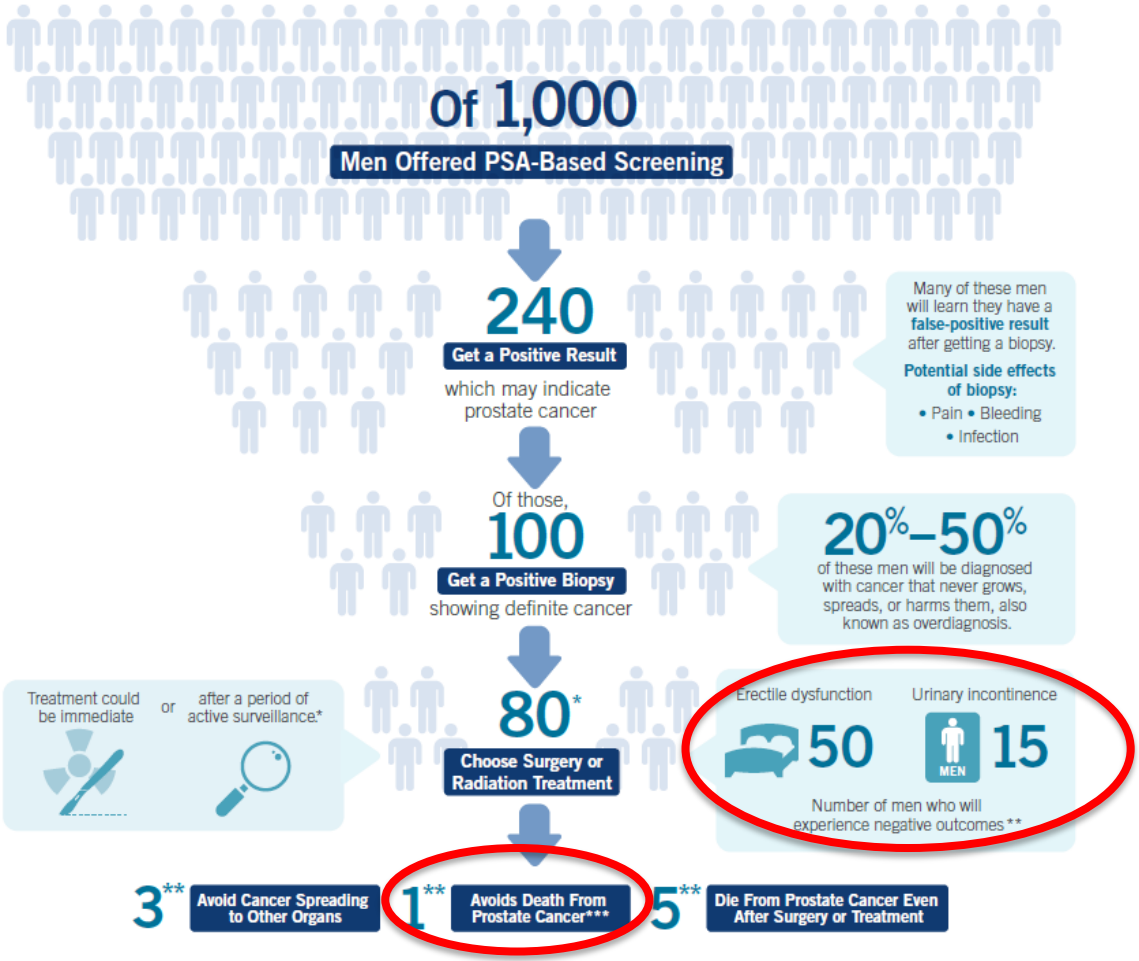

https://screeningforprostatecancer.org/get-the-facts/
Cooperberg MC. *Eur Urol*. 2017(72):326–328.
Heijnsdijk et al *NEJM* 2012.

10-15 years: 1-2/1000
Lifetime: 9/1000

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Organized PSA-screening?

No

Yes

Carry on

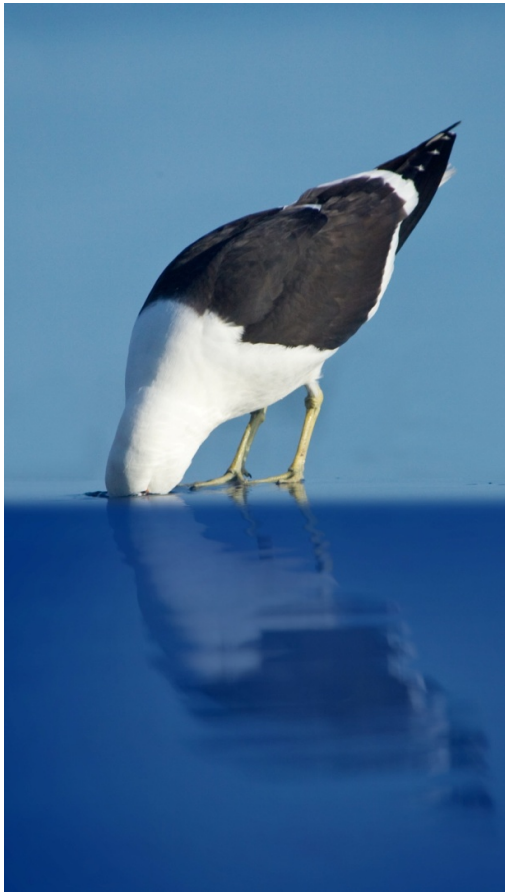
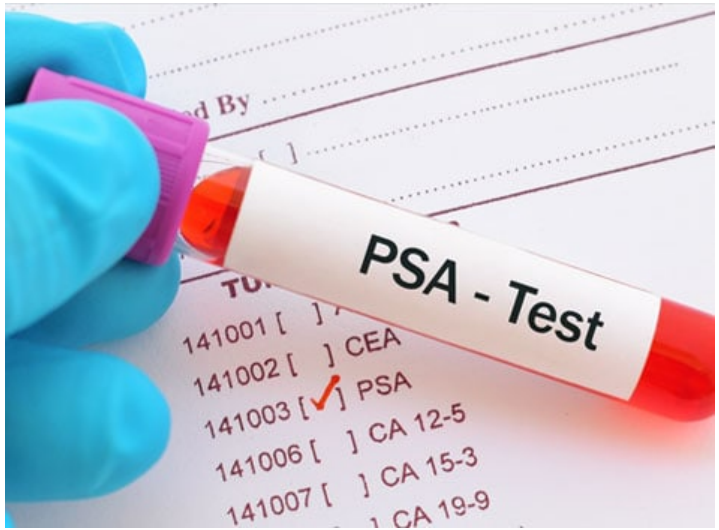
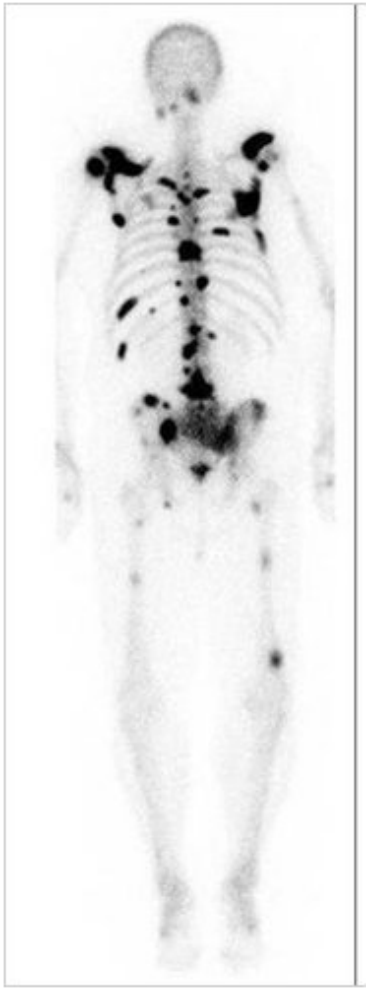


Photo: Gunnar Aus


STOP


PSA - Test
141001 [ ]
141002 [ ] CEA
141003 [ ] PSA
141006 [ ] CA 12-5
141007 [ ] CA 19-9



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5 GOLDEN RULES

#1 Get consent (shared decision making)

#2 Don’t screen men who won’t benefit

#3 Don’t biopsy without a compelling reason

#4 Don’t treat low-risk disease

#5 If you have to treat, refer men to a high-volume provider

Vickers A, Carlsson S, et al. *Eur Urol*. 2014.

TO BE CONTINUED