PSA Screening in 2025

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American Cancer Society

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Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Disclosure & Disclaimer

William K. Oh, MD

Consulting:

- Abbott
- Pfizer
- GSK
- Sumitomo
- Astra Zeneca
- Cytogen
- VieCure
- Novartis

Equity:

- GeneDx
- NTx
- Archetype Therapeutics
- Previvor Care

Case

- 52 yo white M with family history of breast cancer in mother (47) and sister (44)
- Hypertension, smoker
- No urinary symptoms
- Baseline PSA two years ago was 1.2 ng/mL
- Current PSA: 4.1 ng/mL

Epidemiology

The Burden of Prostate Cancer

In 2025, prostate cancer remains the **leading** cancer diagnosis in men and the **2nd leading** cause of cancer death (and rising!)

Estimated New Cases

Male

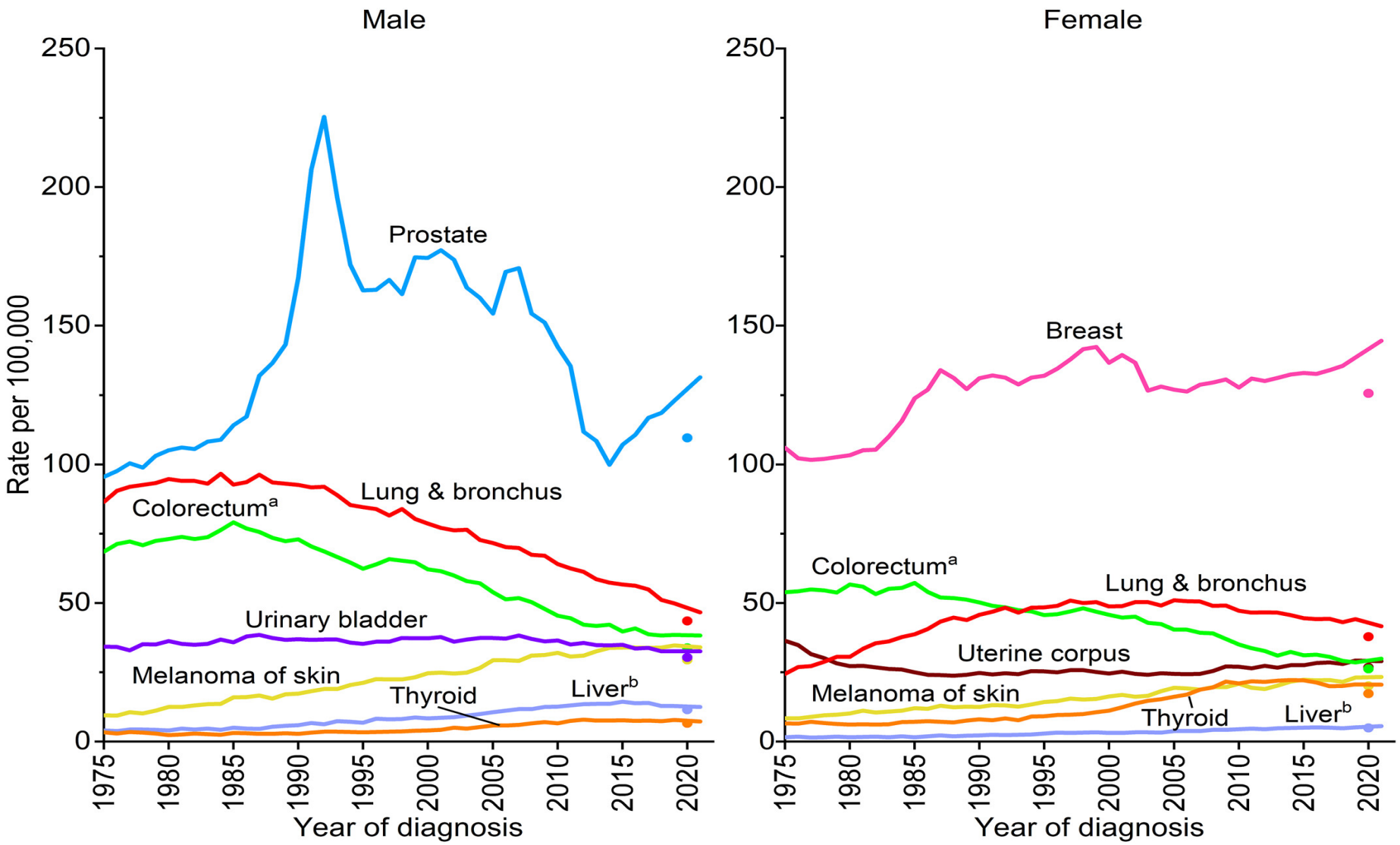
Prostate	313,780	30%
Lung & bronchus	110,680	11%
Colon & rectum	82,460	8%
Urinary bladder	65,080	6%
Melanoma of the skin	60,550	6%
Kidney & renal pelvis	52,410	5%
Non-Hodgkin lymphoma	45,140	4%
Oral cavity & pharynx	42,500	4%
Leukemia	38,720	4%
Pancreas	34,950	3%
All sites	**1,053,250**	

Male

Lung & bronchus	64,190	20%
Prostate	35,770	11%
Colon & rectum	28,900	9%
Pancreas	27,050	8%
Liver & intrahepatic bile duct	19,250	6%
Leukemia	13,500	4%
Esophagus	12,940	4%
Urinary bladder	12,640	4%
Non-Hodgkin lymphoma	11,060	3%
Brain & other nervous system	10,170	3%
All sites	**323,900**	

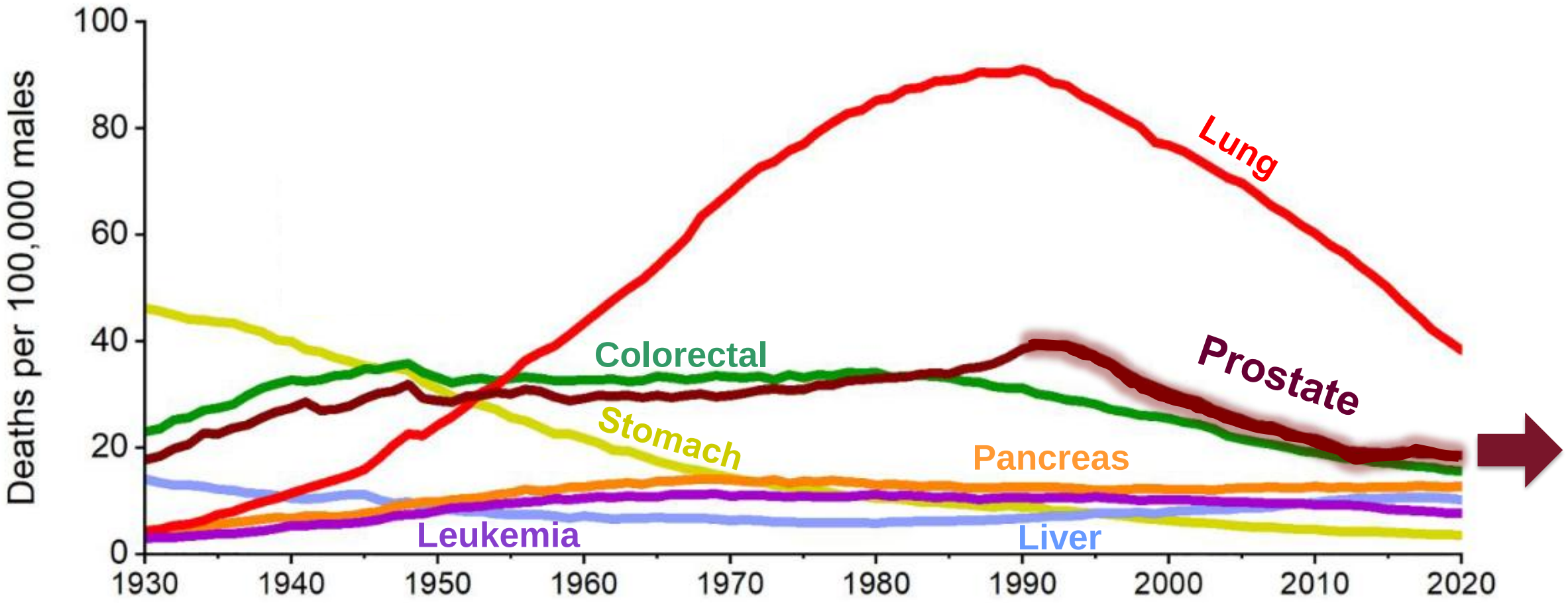
American Cancer Society 2025 Cancer Facts and Figures

Prostate Cancer Incidence Rising Sharply Since 2014



American Cancer Society 2025 Cancer Facts and Figures

US Death Rate for Prostate Cancer has Plateaued → Due to Decreased PSA Screening?



Siegel R, *CA Cancer J Clin* 2023

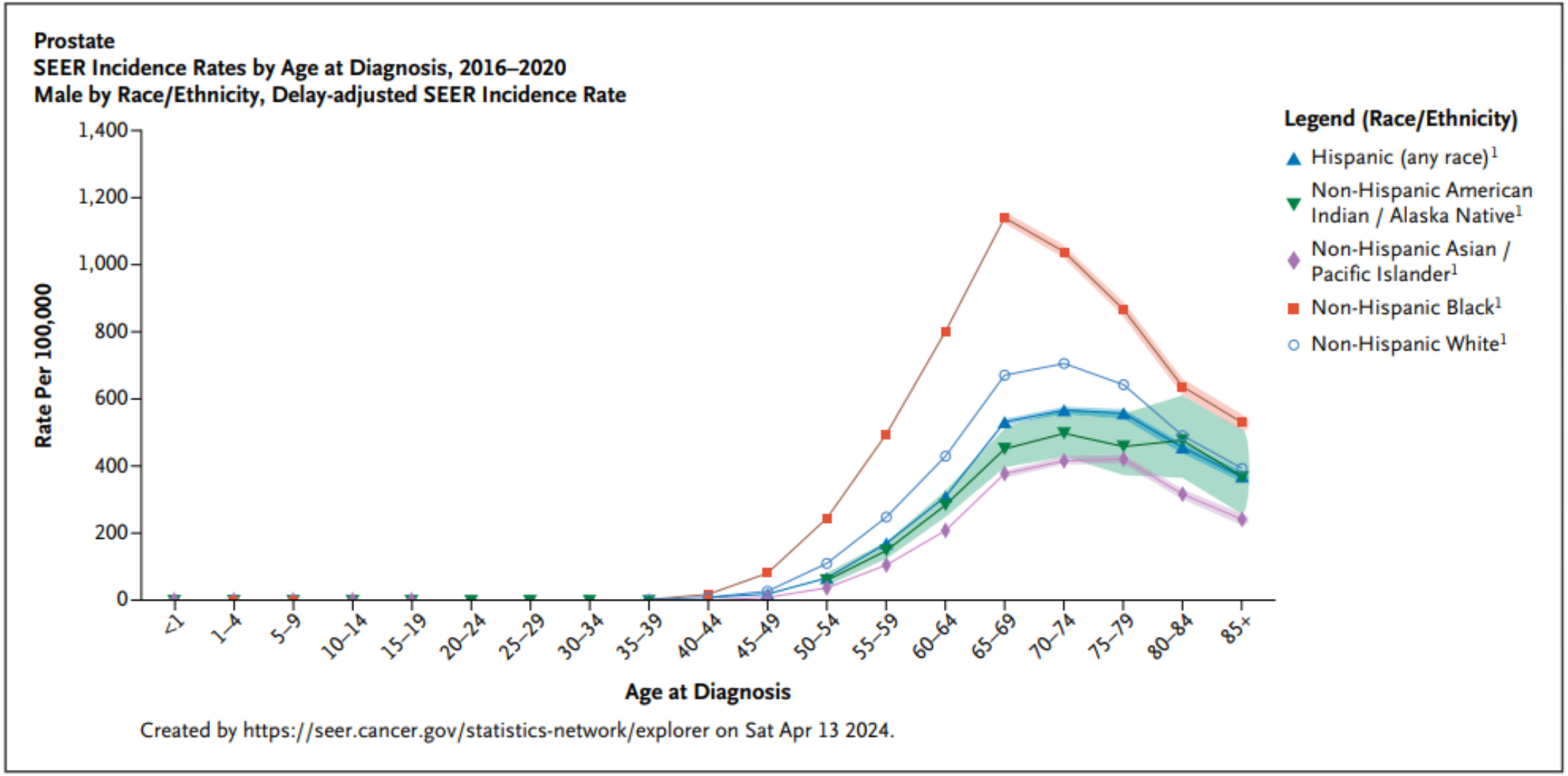
Common Risk Factors for Prostate Cancer

Age: PC is frequently diagnosed in elderly men, with 60% of cases diagnosed in men older than 65 years

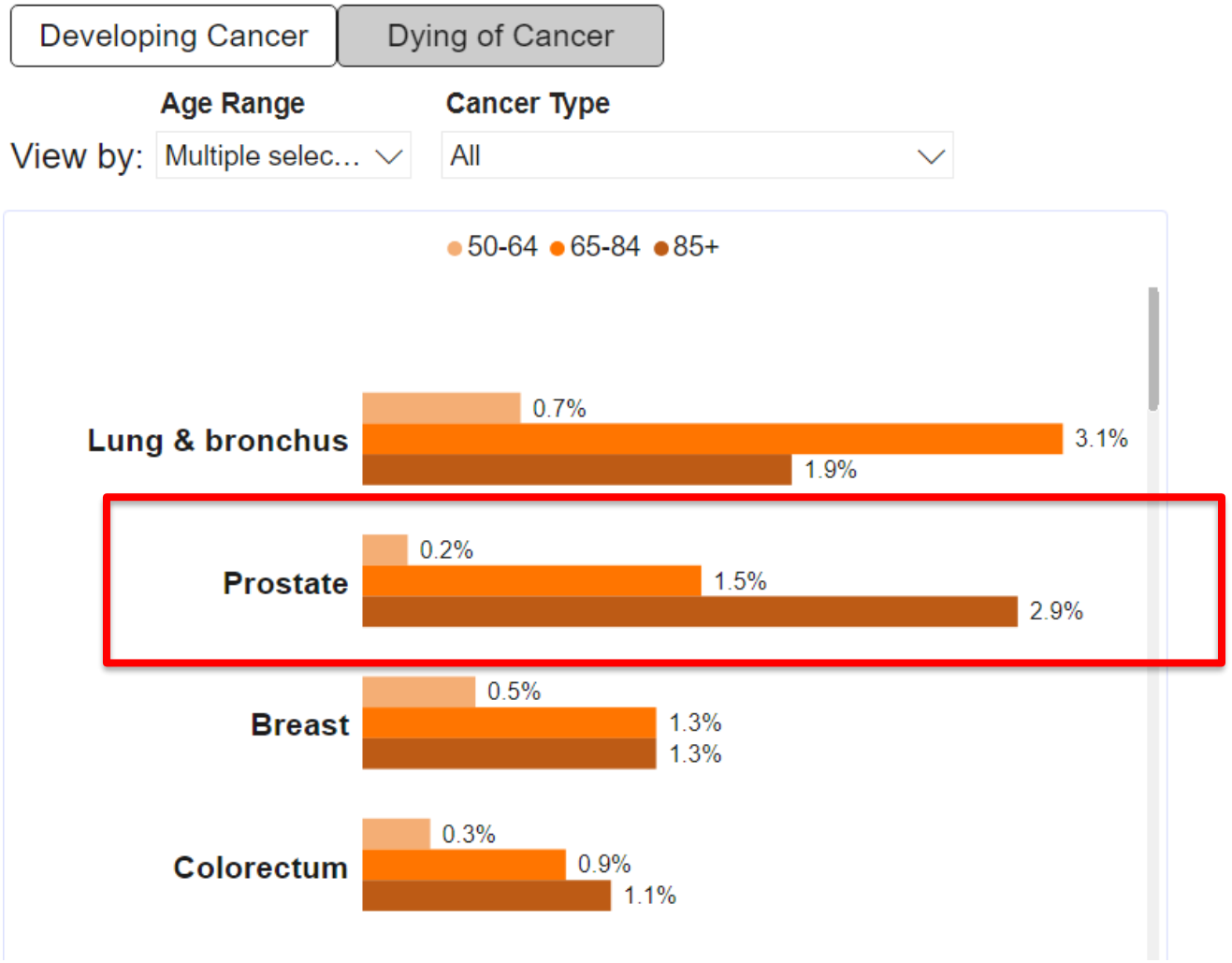
Ethnicity: African ancestry is a strong risk factor for PCa development, with up to a 70% higher incidence rate observed in Black men compared with white men

Family History: Genetics and shared environmental exposures can drive PCa development in families

Prostate Cancer Incidence is Driven by Older Age and Race/Ethnicity

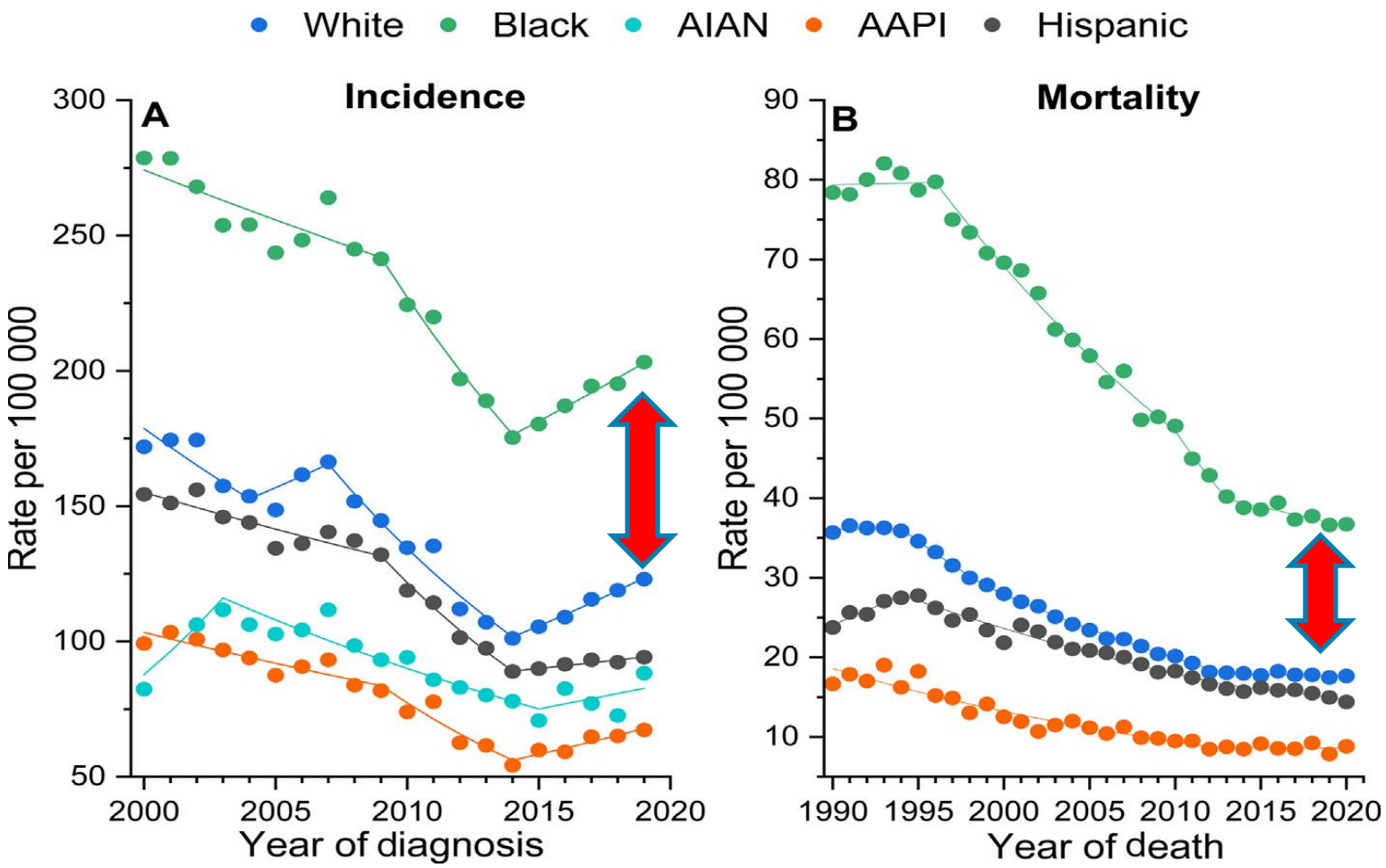


Older Age Does NOT EQUAL Indolent Disease!



American Cancer Society 2024 Cancer Facts and Figures

Prostate Cancer Incidence Rising Faster and Mortality Much Higher in Black Men



Schafer. Eur Urol. 2022. https://doi.org/10.1016/j.eururo.2022.11.023

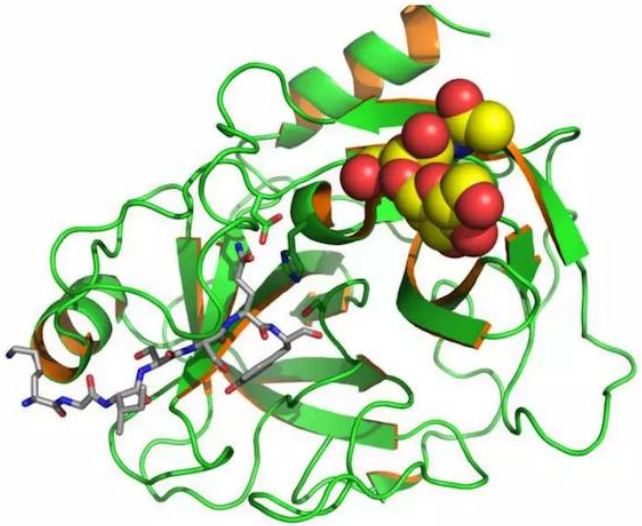
Family History And Risk Of Prostate Cancer

# of Affected First-Degree Relatives	Odds Ratio (95% CI)
1	2.2 (1.4-3.5)
2	4.9 (2.0-12.3)
3	10.9 (2.7-43.1)

Prostate Specific Antigen (PSA)

PSA

- Human kallikrein (hk3)
- Secreted by epithelial cells of the acini and ducts of the prostate gland
- Glycoprotein enzyme liquefies semen → fertility?
- Present in low levels in blood normally



Identification of PSA as a Biomarker

PURIFICATION OF A HUMAN PROSTATE SPECIFIC ANTIGEN[1]

M. C. WANG, L. A. VALENZUELA, G. P. MURPHY, AND T. M. CHU[2]

Department of Diagnostic Immunology Research and Biochemistry, Roswell Park Memorial Institute, Buffalo, New York

(Reprinted with permission from Invest. Urol, 17: 159–163, 1979)

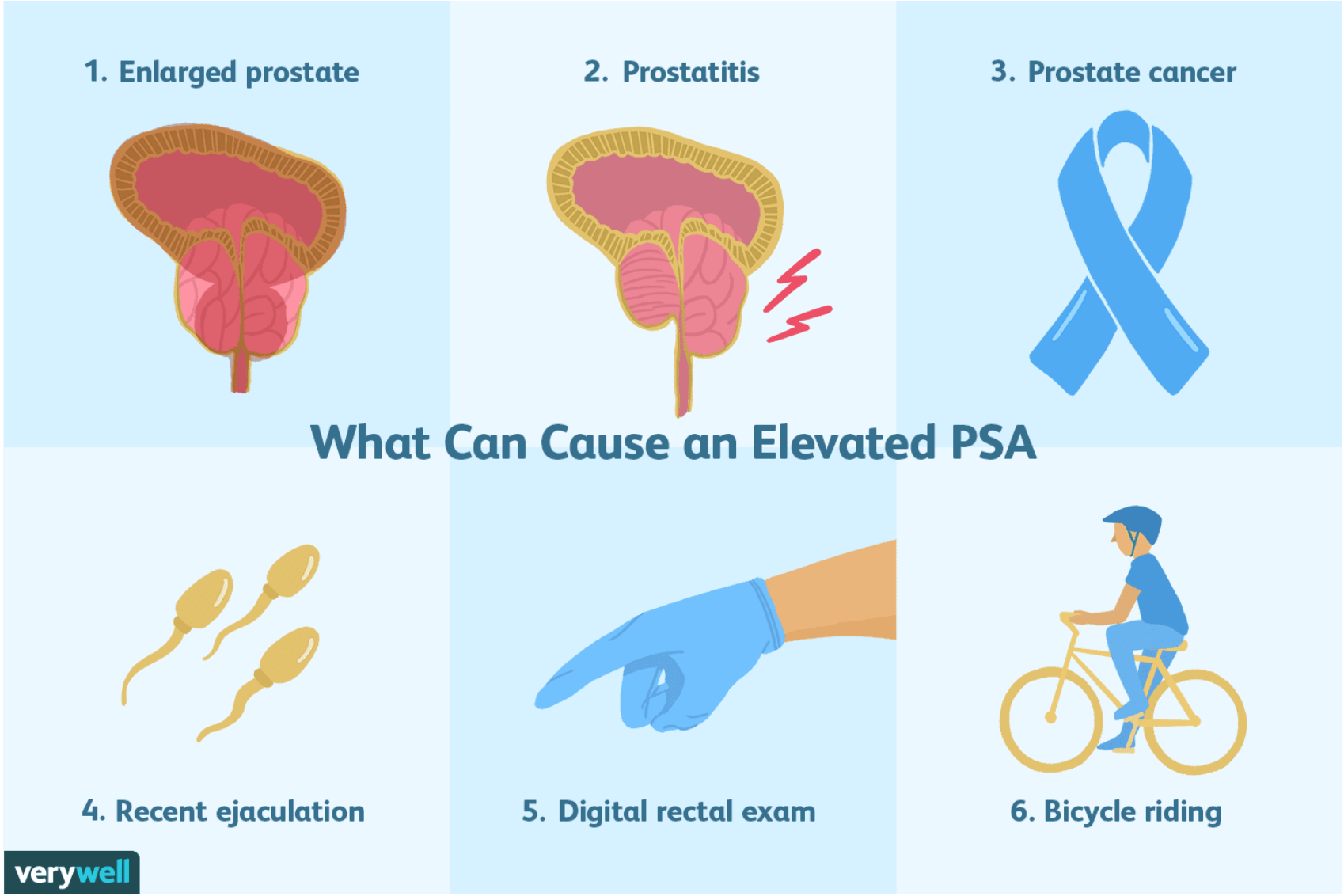
The New England
Journal of Medicine

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.

What Causes Elevations in Serum PSA?



Is There a "Normal" Cutoff for PSA?

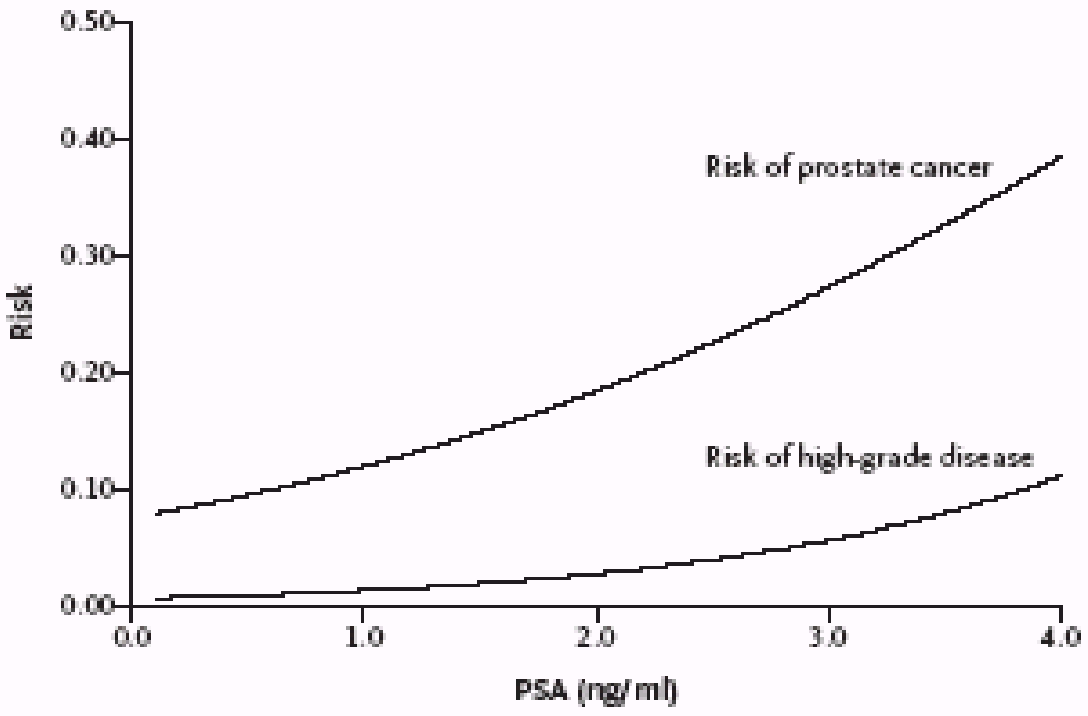


Figure 2. Estimated Risk of Prostate Cancer and High-Grade Disease as a Function of the Prostate-Specific Antigen (PSA) Level.
High-grade disease was defined by a Gleason score of 7 or greater.

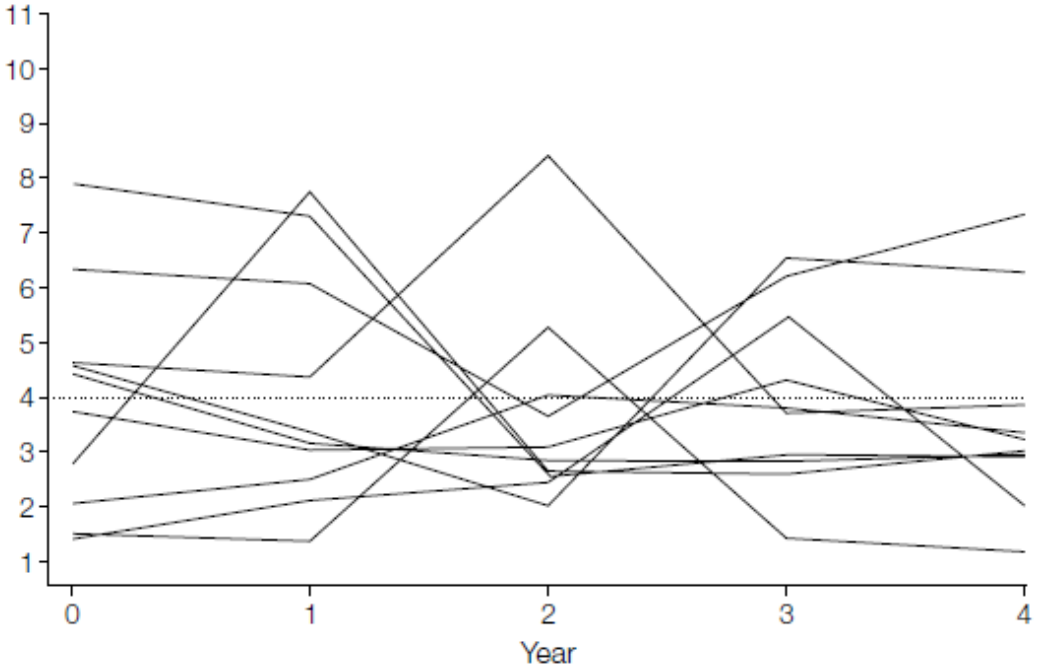
Thompson NEJM 2004

Variation of Serum Prostate-Specific Antigen Levels

An Evaluation of Year-to-Year Fluctuations

Repeat the PSA!

James A. Eastham, MD
Elyn Riedel, MA
Peter T. Scardino, MD
Moshe Shike, MD
Martin Fleisher, PhD
Arthur Schatzkin, MD, DrPh
Elaine Lanza, PhD
Lianne Latkany, MS
Colin B. Begg, PhD
for the Polyp Prevention Trial Study Group



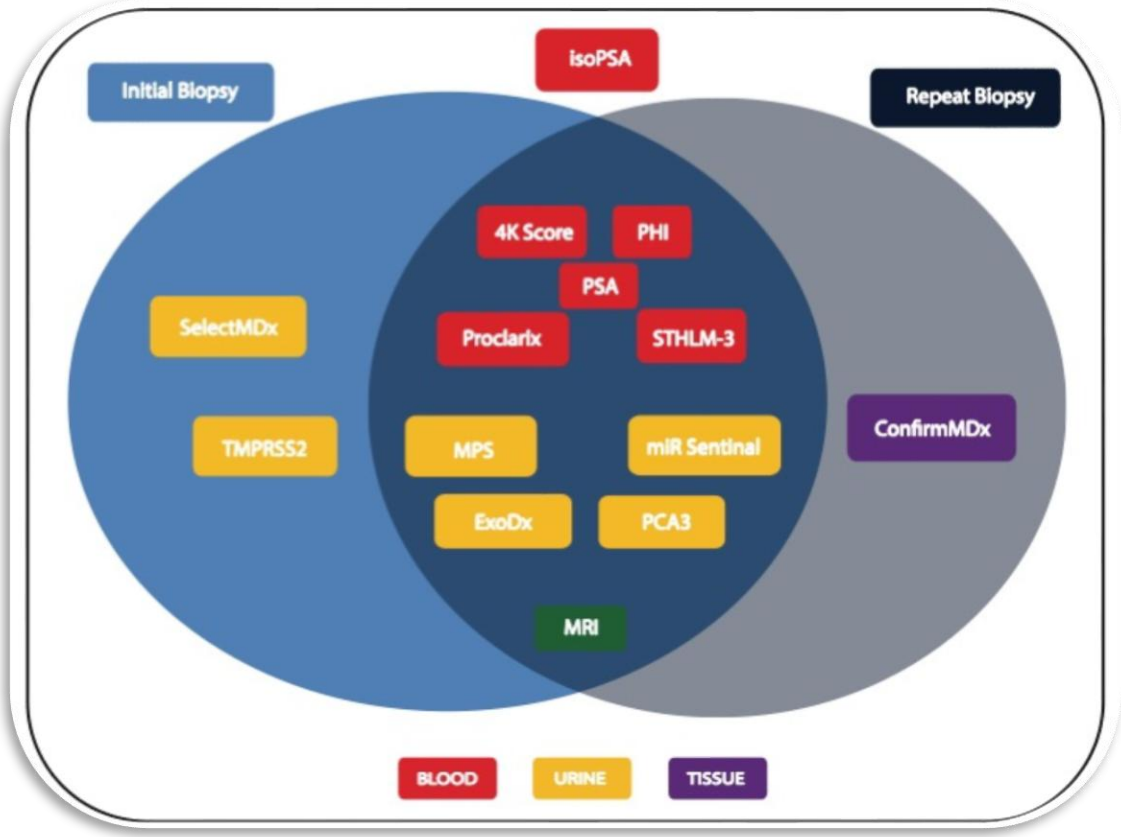
Definition of abnormal PSA	Probability that PSA would return to normal
> 2.5 ng/mL	40%
> 4.0 ng/mL	44%

Eastham J, *JAMA* 2003

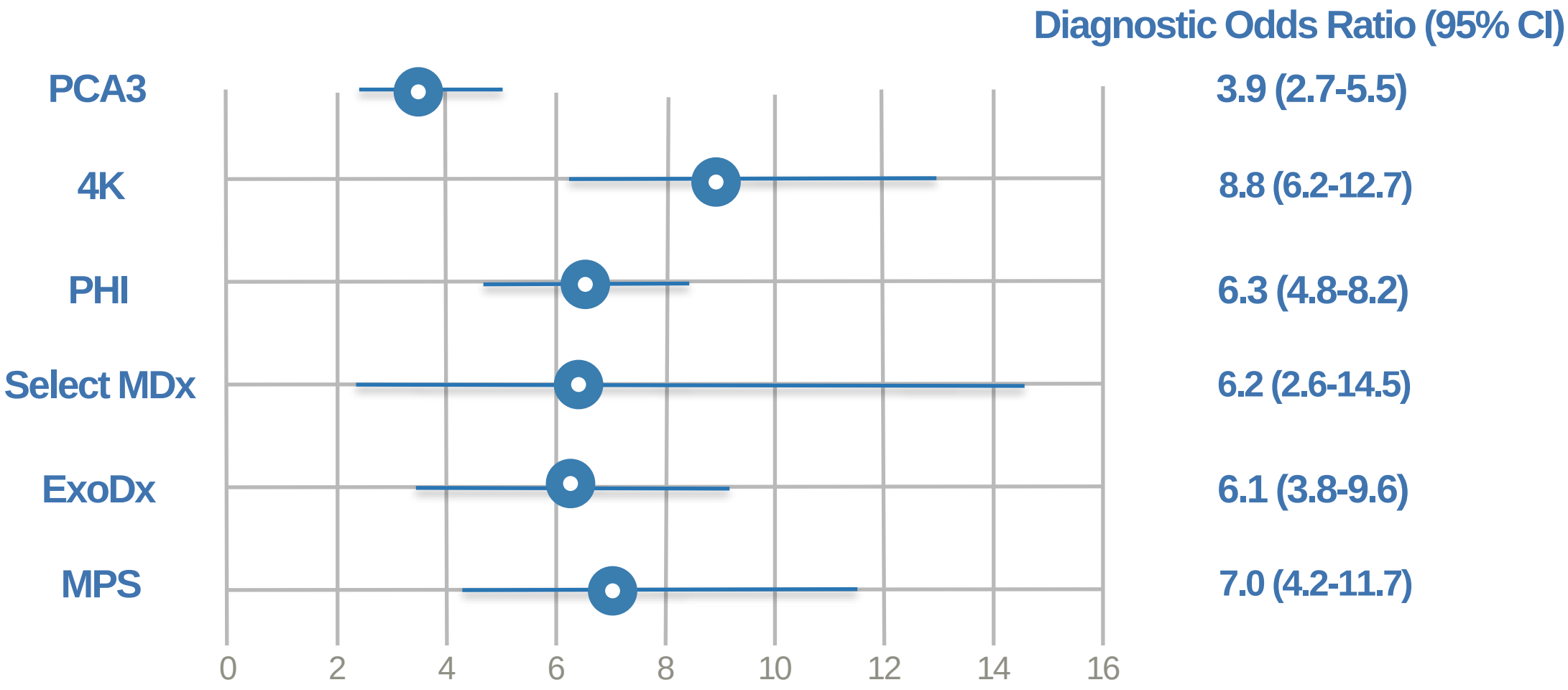
Median age 62

Markers To Improve Accuracy

- Age-Specific PSA
- PSA Density
- % Free PSA
- PSA Doubling Time (Velocity)



Systematic review of 49 studies on liquid biomarkers demonstrate their clinical utility in detecting clinically significant prostate cancer and avoiding unnecessary biopsy



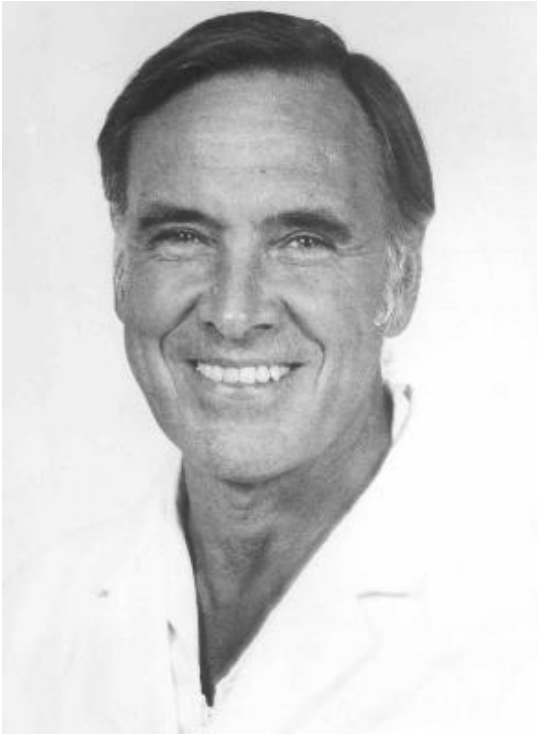
Kawada T, *Eur Urol Oncol* 2023

Screening for Prostate Cancer

The Quandary Of Prostate Cancer

"Growing old is invariably fatal; prostate cancer is less so."

"Is cure possible in those for whom it is necessary, and is cure necessary for those in whom it is possible?"



Willet Whitmore, MD
MSKCC

Digital Rectal Exam (DRE) has little diagnostic value as an independent screening test or supplement to PSA

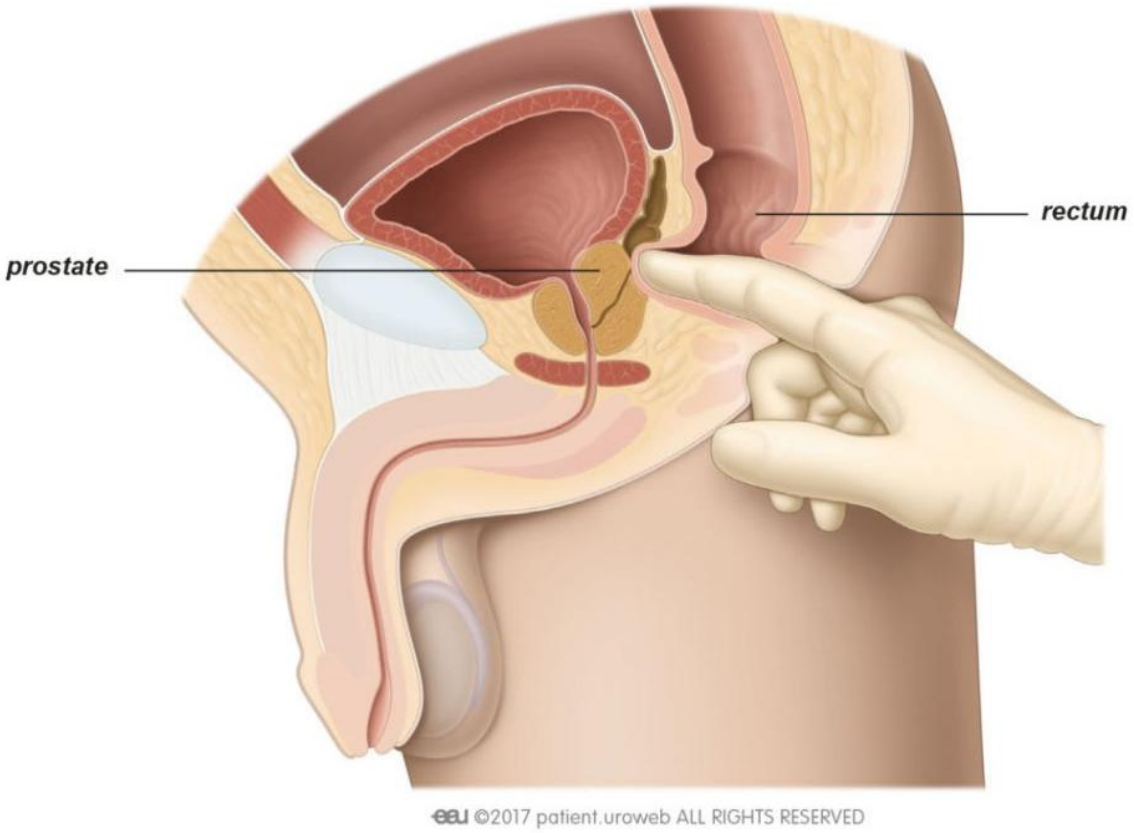
Systematic review
PPV: 21%
Prostate cancer detection rate: **1%**

PROBASE
DRE acceptance 37% at age 45

Suspicious DRE: 1%

Cancer detection rate = **0.05%**
3 prostate cancers found (2 GG1, 1 GG2)

What about DRE as part of clinical work-up of an elevated PSA? **YES!**



Matsukawa A, *Eur Urol Oncol* 2024

Arsov C, *Int J Cancer* 2022
Krilaviciute A, *Eur Urol Oncol* 2023

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., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D.,

N ENGL J MED 360;13 NEJM.ORG MARCH 26, 2009

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., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D., Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D., Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D., Barbara O'Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S., Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D., Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D., Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., and Christine D. Berg, M.D.,

N ENGL J MED 360;13 NEJM.ORG MARCH 26, 2009

	ERSPC	PLCO
N	182,000	76,693
Age	50-74 yrs	55-74 yrs
Sites	Europe	USA
% Screened	**82%**	**85%** **(52% controls)**
Screening interval	Every 2-4 yrs	Annual (stopped after 6 rounds)
PSA for bx	3 ng/ml	4 ng/ml

Both ERSPC and PLCO confirm that PSA-screening reduces prostate cancer mortality by 30% after >11 years of follow-up

ERSPC

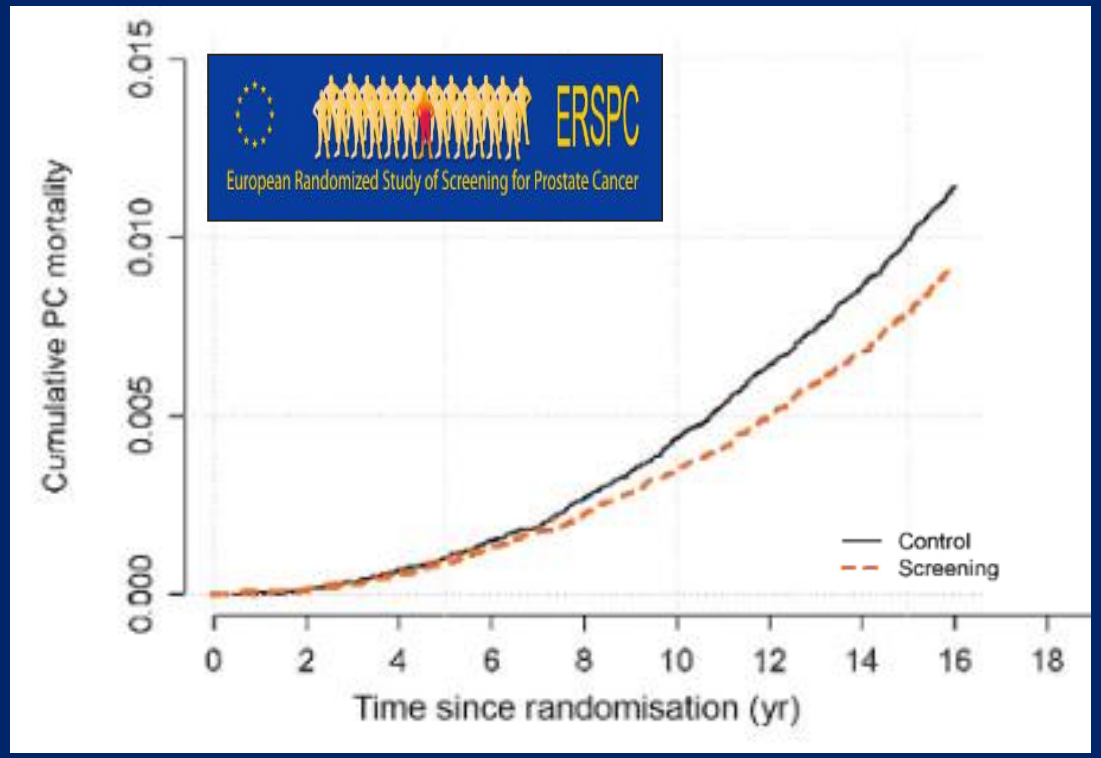
Hugosson J, *Eur Urol* 2019

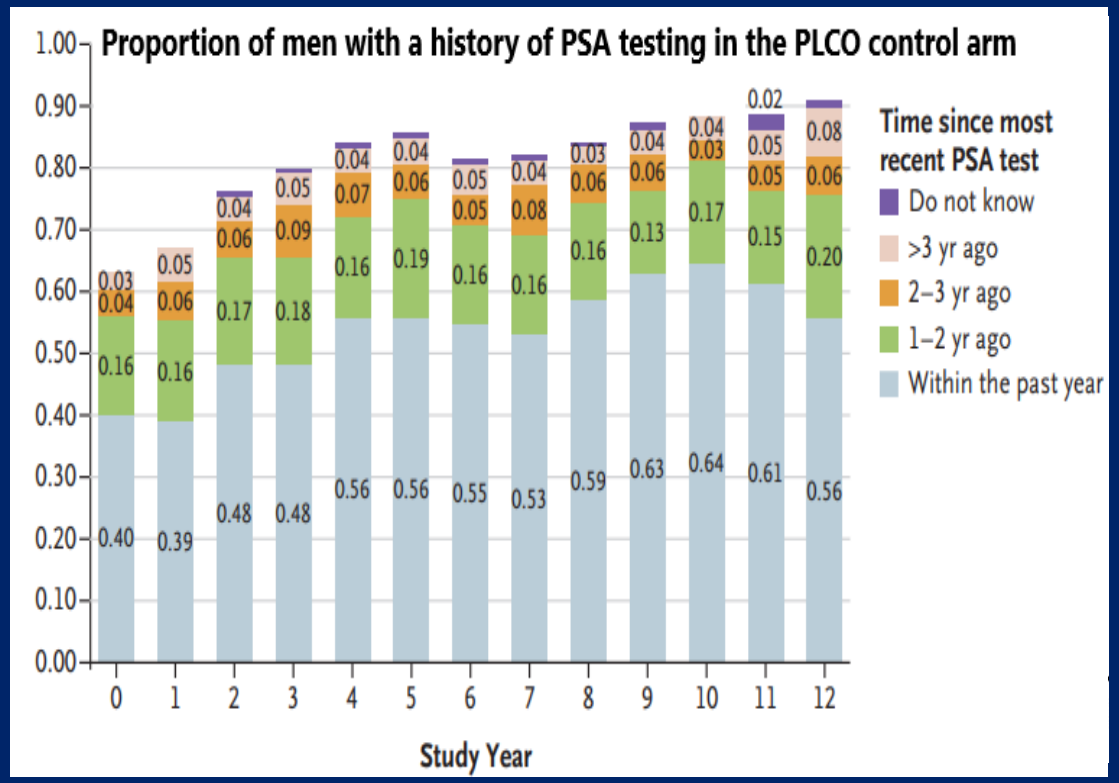
PLCO

Pinsky P, *BJUI* 2018

PLCO

Shoag J, *NEJM* 2016





European Randomized Screening for Prostate Cancer (ERSPC)

Benefit of screening appears to improve over time

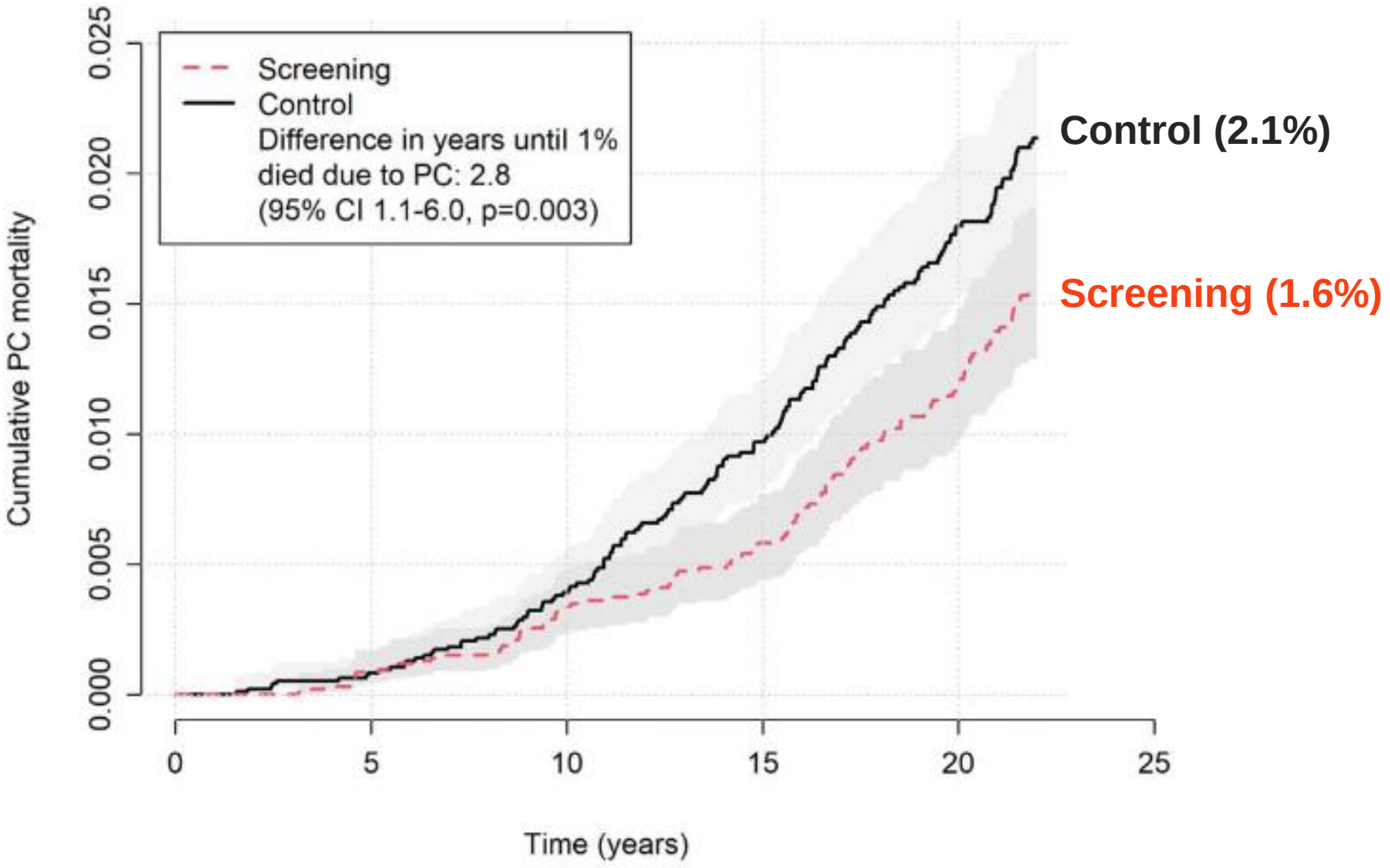
	Years 1–9	Years 1–11	Years 1–13	Years 1–16
Rate ratio (95% CI)	0.84 (0.70–1.00)	0.78 (0.67–0.91)	0.79 (0.69–0.90)	0.80 (0.72–0.89)
p value	0.053	0.001	<0.001	<0.001
NNI (95% CI)	1947 (963–inf)	962 (598–2463)	742 (478–1650)	570 (380–1137)
NND	76	34	26	18

NNI = Number Needed to Invite for Screening to Prevent 1 Death

NND = Number Needed to Diagnose to Prevent 1 Death

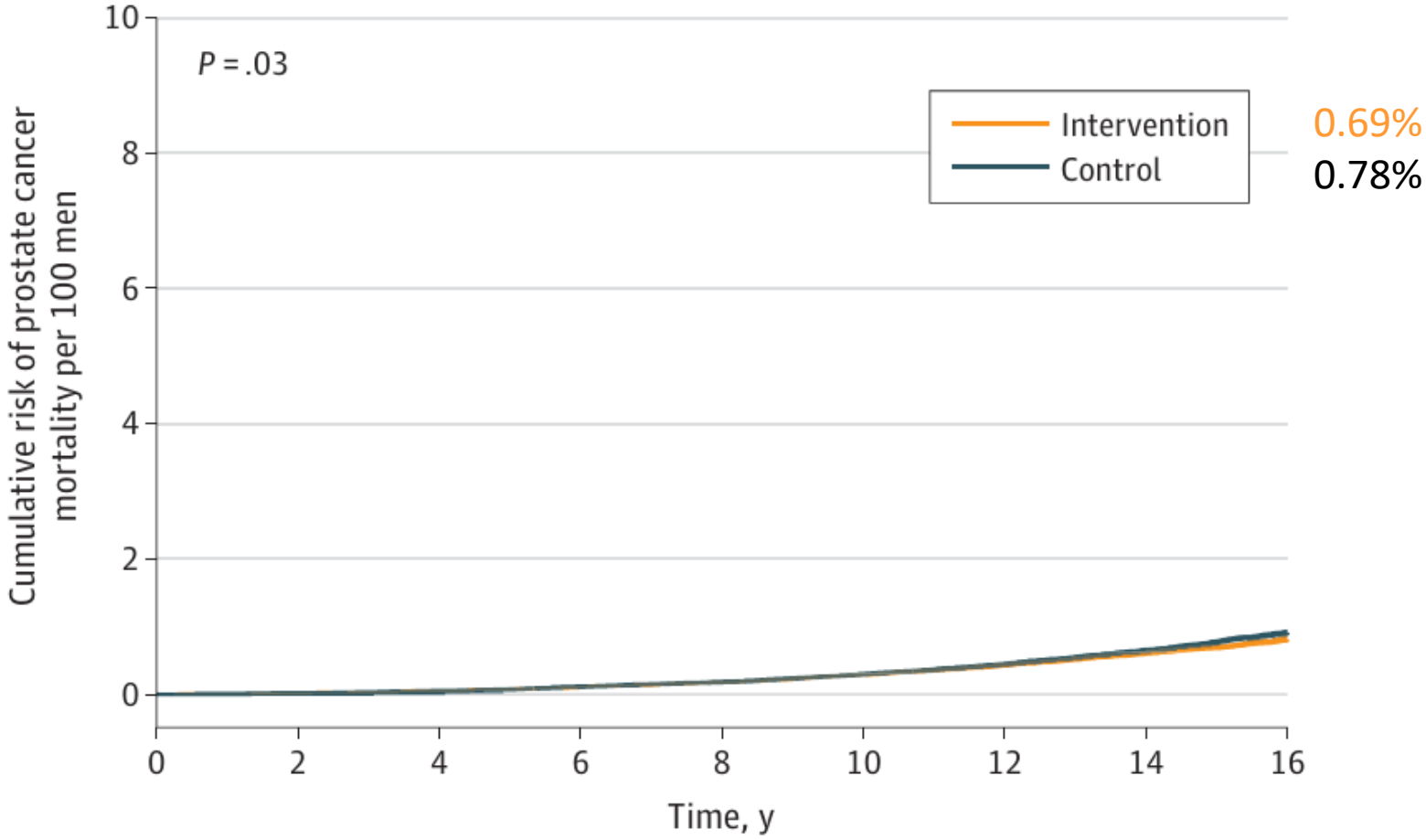
Hugosson Eur Urol 2019

Swedish Goteborg-1 Trial: Regular PSA Screening Reduces Prostate Cancer Mortality by 29% at 22 years



Frånlund M, *J Urol* 2022

UK CAP Trial: Single Invitation for PSA Screening Reduced Prostate Cancer Deaths by 8% at 15 years



Martin R, *JAMA* 2024

Conclusions of Randomized Screening Studies

- Several randomized trials with long follow up demonstrate survival benefit to PSA screening
- Significant contamination in PLCO trial (US)
- Survival benefit to screening may increase with time
- Need to consider patient age, relative risks and benefits of screening
- *Consider active surveillance more often once diagnosis is made

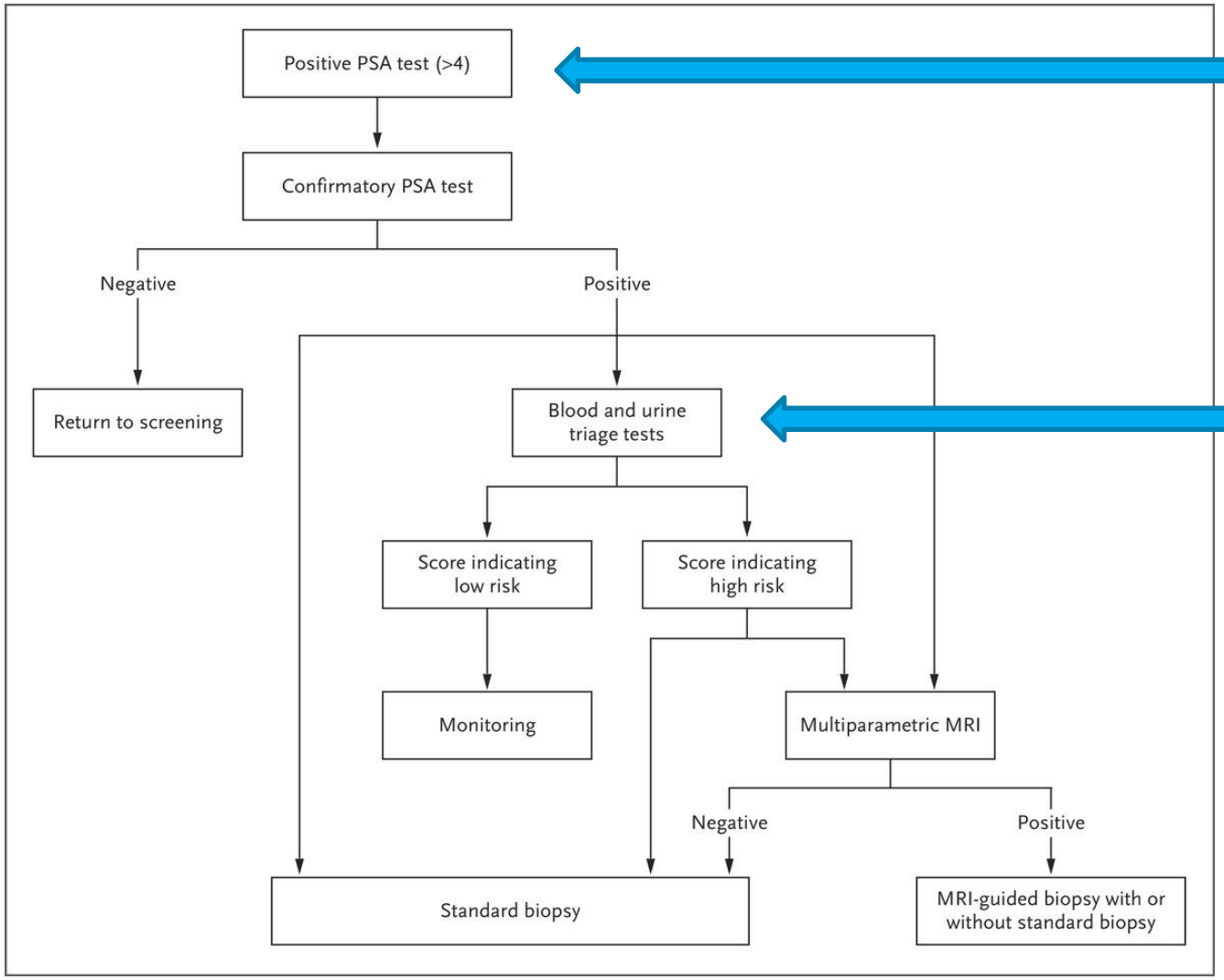
USPSTF Screening Recommendation (2018)

To Be Updated Soon

Recommendation Summary

Population	Recommendation	Grade
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

PSA Screening Algorithm



Positive PSA value threshold varies based upon:

- Age at PSA test
- Prostate size
- Use of medications that affect PSA levels
- Other health factors

- Prostate Health Index (PHI)
- 4K Score
- PCA-3

PF Pinsky, H Parnes. N Engl J Med 2023;388:1405-1414.

Defining of High Risk Individuals for Prostate Cancer Screening

- Almost every authoritative guideline recommends earlier and regular screening among high risk individuals
- Definition of high-risk was classically defined based upon either RACE or FAMILY HISTORY
  - Problem:
    - Many patients of mixed race and difficult to categorize or fully assess
    - Family history information is often incomplete, unknown and can change as family members diagnosed

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Prostate Cancer Early Detection

- History and physical (H&P) including:
  - Family cancer history[a,b,c]
  - Family or personal history of high-risk germline mutations[a,b,c]
  - History of prostate disease and cancer early detection, including prior prostate-specific antigen (PSA) and/or isoforms, exams, and biopsies
  - Black/African American identity[d]
  - Medications[e]
  - Environmental exposure[f]

→ Start risk and benefit discussion about offering prostate cancer early detection:
- Baseline PSA[g]
- Consider baseline digital rectal examination (DRE)[g]

AUA Guidelines 2023: Who is at Increased Risk of Prostate Cancer?

Clinicians should offer prostate cancer screening beginning at age 40 to 45 years for people at increased risk of developing prostate cancer based on the following factors: Black ancestry, germline mutations, strong family history of prostate cancer. (*Strong Recommendation; Evidence Level: Grade B*)

Black ancestry

BRCA 1/2, ATM, MLH1, MSH2, MSH6, PMS2, HOXB13, NBS1, CHEK2

Although there is no standard definition of strong family history, several guidelines and consensus statements propose common criteria that include: 1) people with one brother or father or two or more male relatives with one of the following: a) diagnosed with prostate cancer at age < 60 years; b) any of whom died of prostate cancer; c) any of whom had metastatic prostate cancer. 2) family history of other cancers with two or more cancers in hereditary breast and ovarian cancer syndrome or Lynch syndrome spectrum.[47, 48]

Wei J, Carlsson S et al J Urol 2023

PROSTATE CANCER FOUNDATION

PCF

CURING TOGETHER

PCF Screening Guidelines for Prostate Cancer in Black men in US: Baseline PSA at 40-45 and Annual Screening

NEJM Evidence

Published April 23, 2024
NEJM Evid 2024; 3 (5)
DOI: 10.1056/EVIDoa2300289

ORIGINAL ARTICLE | CLINICAL GUIDELINES DEVELOPMENT

Prostate Cancer Foundation Screening Guidelines for Black Men in the United States

Isla P. Garraway, M.D., Ph.D.,[1] Sigrid V. Carlsson, M.D., Ph.D., M.P.H.,[2,3] Yaw A. Nyame, M.D., M.S., M.B.A.,[4,5] Jason L. Vassy, M.D., M.P.H., M.S.,[6,7] Marina Chilov, M.L.S.,[8] Mark Fleming, M.D.,[9] Stanley K. Frencher Jr., M.D., M.P.H.,[10] Daniel J. George, M.D.,[11] Adam S. Kibel, M.D.,[12] Sherita A. King, M.D.,[13] Rick Kittles, Ph.D.,[14] Brandon A. Mahal, M.D.,[15,16] Curtis A. Pettaway, M.D.,[17] Timothy Rebbeck, Ph.D.,[18,19] Brent Rose, M.D.,[20,21] Randy Vince, M.D.,[22] Robert A. Winn, M.D.,[23,24] Kosj Yamoah, M.D., Ph.D.,[25,26] and William K. Oh, M.D.[27,28]

PROSTATE CANCER FOUNDATION

PCF

CURING TOGETHER

PCF Screening Guidelines for Prostate Cancer in Black men in US: Baseline PSA at 40-45 and Annual Screening

Table 1. Prostate Cancer Foundation 2023 Guideline Statements for Prostate Cancer Screening in Black Men in the United States.*

No.	Key Questions	Prostate Cancer Foundation Recommendations
1	Should Black men be screened for prostate cancer?	Yes. Since Black men are at high risk for prostate cancer, the benefits of screening generally outweigh the risks.
2	What should Black men know about how screening for prostate cancer is conducted?	Prostate-specific antigen (PSA) is a blood test that should be considered first-line for prostate cancer screening. Some providers may recommend an optional digital rectal exam (DRE) in addition to the PSA test.
3	What information should Black men obtain to make an informed decision about PSA screening and early detection of prostate cancer?	Decisions about PSA testing depend on individual preferences. Black men should engage in shared decision-making with their health care providers and other trusted sources of information to learn about the pros and cons of screening.
4	At what age should Black men obtain their first PSA test and how often should they be screened for prostate cancer?	For Black men who elect screening, a baseline PSA test should be done between ages 40–45. Depending on the PSA value and the individual's health status, annual PSA screening should be strongly considered.
5	At what age should Black men consider stopping PSA screening?	Black men over age 70 who have been undergoing prostate cancer screening should talk with their health care provider about whether to continue PSA testing and make an informed decision based on their age, life expectancy, health status, family history, and prior PSA levels.
6	How should family history and genetic risk be taken into consideration when screening Black men for prostate cancer?	Black men with an even higher risk of prostate cancer due to a strong family history and/or known carriers of high-risk genetic variants should consider initiating annual PSA screening as early as age 40.

Garraway I, Carlsson S, Oh W, et al. NEJM Evidence 2024

Image-based Screening Next?

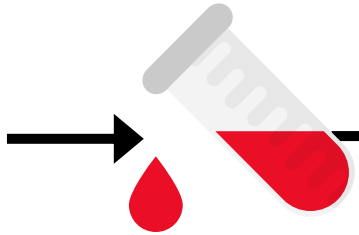
Mammography for breast cancer

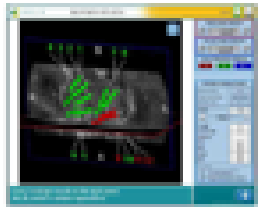
Low-dose CT for lung cancer

MRI for prostate cancer?

We can keep the benefits of PSA screening and reduce the harms through risk-stratified screening

Historic pathway	MRI only pathway	Modern pathway	Combined pathway	Exploratory pathway
• PSA & DRE • PSA > 3 • Systematic TRUS biopsy	• MRI • Targeted biopsy	• Risk stratification • PSA • mpMRI • Targeted biopsy	• PSA • Biomarker • mpMRI • Targeted biopsy	• PSA • Polygenic Risk Score • mpMRI • Targeted biopsy





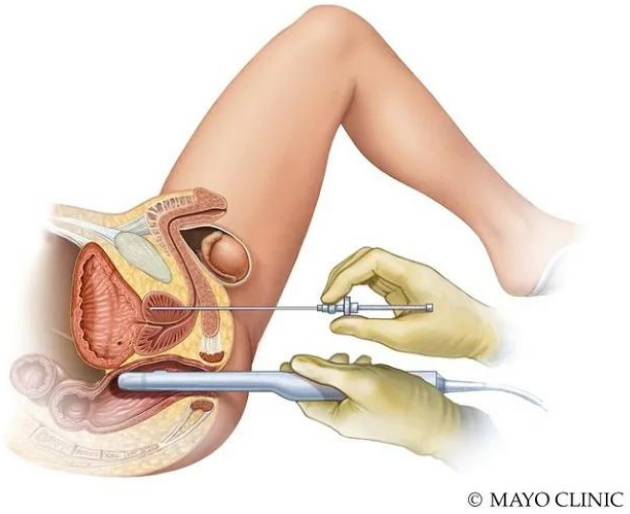
Diagnosis

Diagnosis Suspected

- Abnormal PSA (typical)
- Abnormal MRI (increasingly common)
- Abnormal DRE (uncommon)
- Symptoms (uncommon)
- Cancer detected on TURP (rare)

Prostate Cancer Diagnosis

- Biopsy
  - TRUS guidance, now transperineal
  - Fusion biopsy: MRI-guided to target lesion in addition to template
- Pathology
  - Gleason score of 2-10 is grouped into 5 ISUP categories of risk (group grade)



Treatment Options for Localized Prostate Cancer

- Active surveillance (“Watchful waiting”)
- Radical prostatectomy
  - Robot-assisted laparoscopic (RALP)
  - Open
- External beam radiotherapy +/- ADT
  - SBRT
  - IMRT
  - Proton beam
- Seed implants (brachytherapy)
- Cryosurgery
- High frequency ultrasound (“HiFU”, focal therapy)

Summary: PSA Screening

- PSA screening remains controversial but is an option for men 55-69 yrs old
- Randomized trials suggest a survival benefit that increases with time
- Men with genetic risk, strong family history and/or African ancestry have higher risk and should be offered screening earlier and more frequently
- Men with life expectancy <10 years should stop screening

Case

- 52 yo white M with family history of breast cancer in mother (47) and sister (44)
- Hypertension, smoker
- No urinary symptoms
- Baseline PSA two years ago was 1.2 ng/mL
- Current PSA: 4.1 ng/mL

What Happens Next?

- Free PSA performed: 12%
- DRE large prostate, no nodules

Referred to Urology

- Prostate MRI shows 1 cm suspicious lesion on L side
- Fusion biopsy demonstrates Gleason 3+4=7 cancer in 3/12 cores
- Germline genetic testing confirms BRCA2 pathogenic mutation
- Undergoes robot-assisted laparoscopic prostatectomy

Thank you!

William K. Oh, MD

Director, Precision Medicine
Yale Cancer Center and Smilow Cancer Hospital

Service Line Medical Director
Smilow Cancer Hospital at Greenwich Hospital

Chair, National Prostate Cancer Roundtable
American Cancer Society

YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

PSA Testing in the Clinic

Engaging Patients and Physicians in Shared Decision Making

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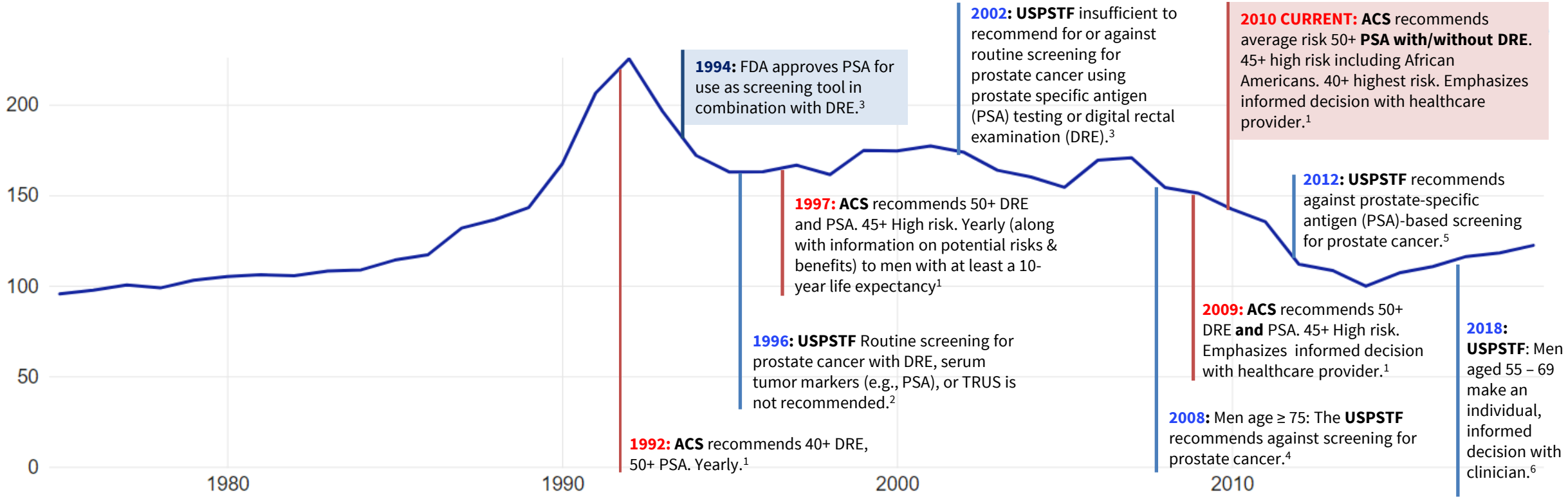
Incidence Rates for Prostate Cancer Over Time With ACS & USPSTF Screening Guideline Changes



Data Sources: Surveillance, Epidemiology, and End Results 8 registries, National Cancer Institute, 2022

Average annual rate per 100,000, age-adjusted to the 2000 US standard population. Incidence is adjusted for delays when possible.

Incidence trend data for 2020 is not shown (See Resources).

SOURCE: American Cancer Society. Cancer Statistics Center. https://cancerstatisticscenter.cancer.org/ | Accessed 2/5/2024. *Citations in notes section.*