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MEDICINE & BIOLOGICAL SCIENCES

Prostate Cancer: Screening, Diagnosis, and Surveillance

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Optimal Care Grand Rounds, Optum
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Disclosures

Insightec (advisory)

Francis Medical (advisory)

Profound Medical (investigator; advisory)

Candel Therapeutics (investigator)

CellVax (advisory)

MetasTx (advisory)

Janssen (speaker)

AstraZeneca (advisory)

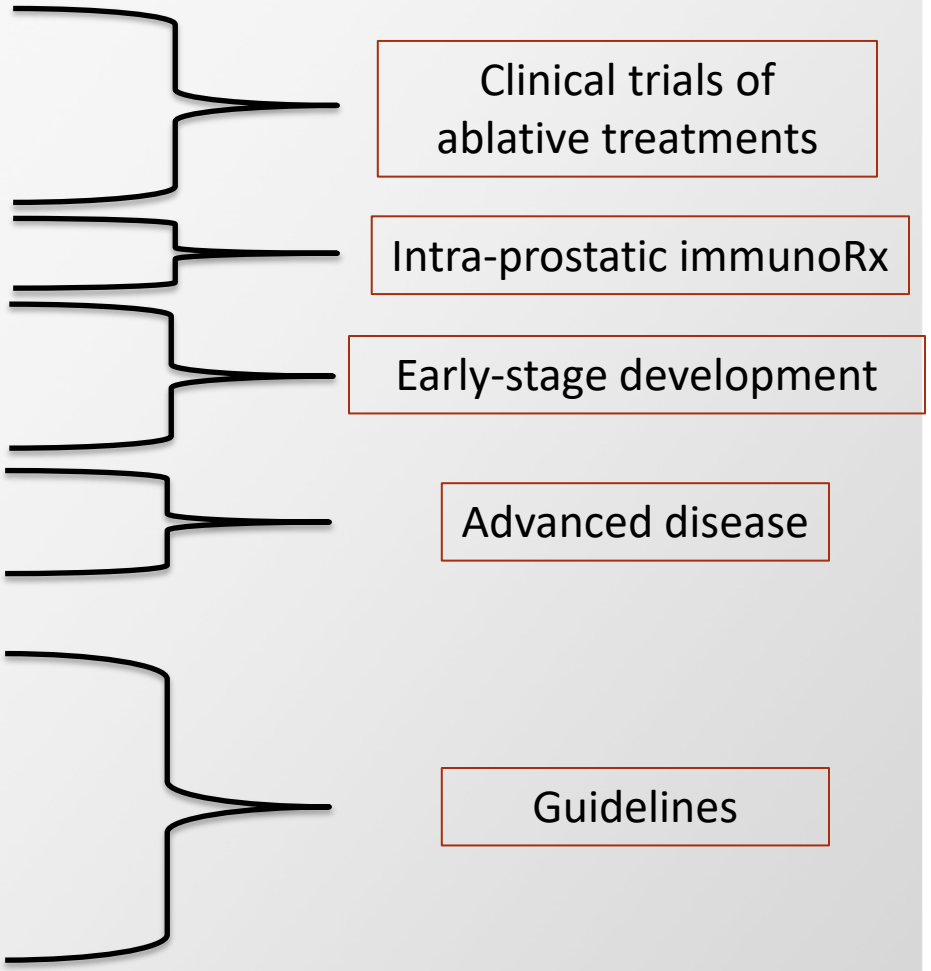
Early Detection of Prostate Cancer - AUA

Management of Localized Prostate Cancer - AUA

Genomic/Molecular Markers (Localized) –ASCO

Germline/Somatic Testing (Metastatic)– ASCO

Optum Healthcare



PSA and Prostate Cancer in 2023: The Good, The Bad, and The Ugly

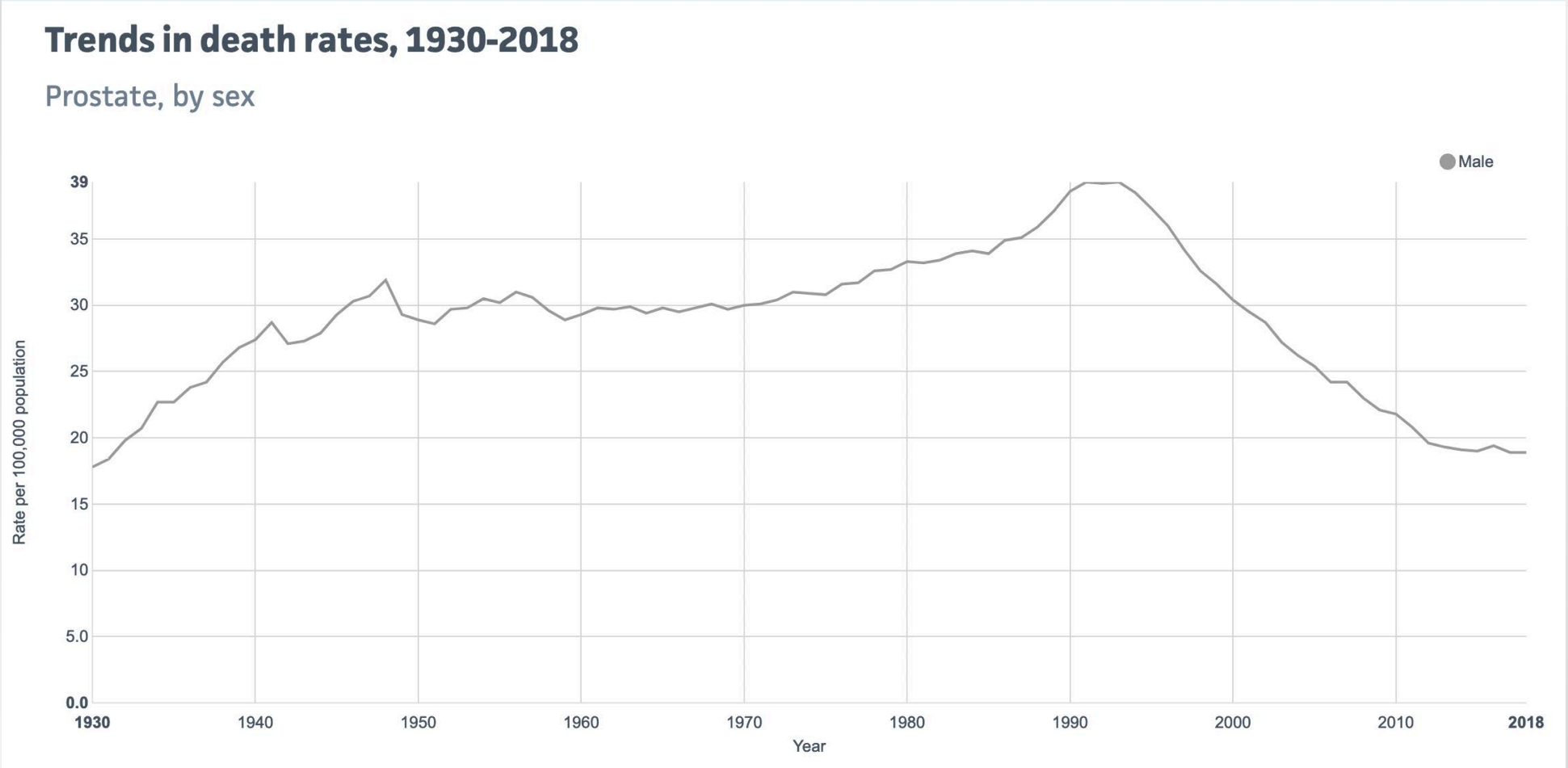
- The Good
  - Lower Cancer-Specific Mortality (50%)
  - Data from Randomized Studies
- The Bad
  - Indiscriminate screening
  - Underscreening
  - Overdiagnosis and overtreatment
- The Ugly
  - Screening and treatment patterns
  - $$$

Outline

- Epidemiology and Screening Trials
- 7 Tips on How to Optimize Screening (if you choose to screen)
- Beyond PSA: Basics of Secondary Biomarkers and MRI
- Options Following a Diagnosis of Prostate Cancer
- Rationale, Outcomes, and Details of Active Surveillance

Epidemiology and Screening Trials

Prostate Cancer Mortality in U.S. Through 2019



Reference: National Center Health Statistics, CDC

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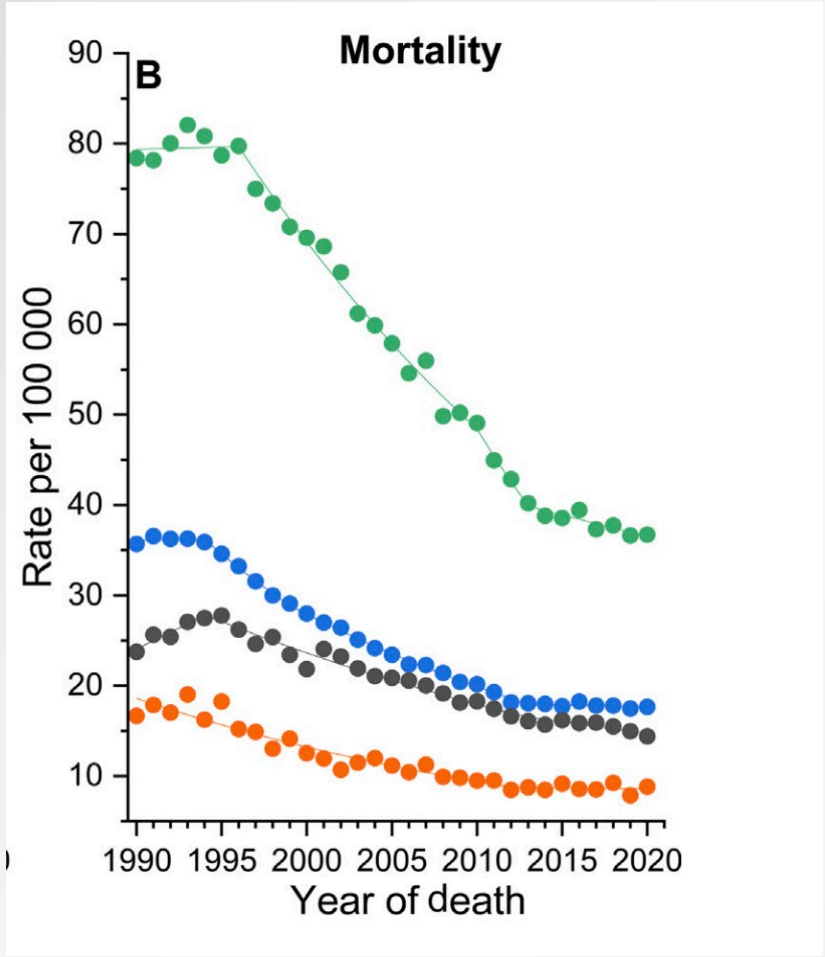
Prostate Cancer Mortality Through 2020 by Race



White Black AIAN AAPI Hispanic

Reference: Shafer, Eur Urol, 2023

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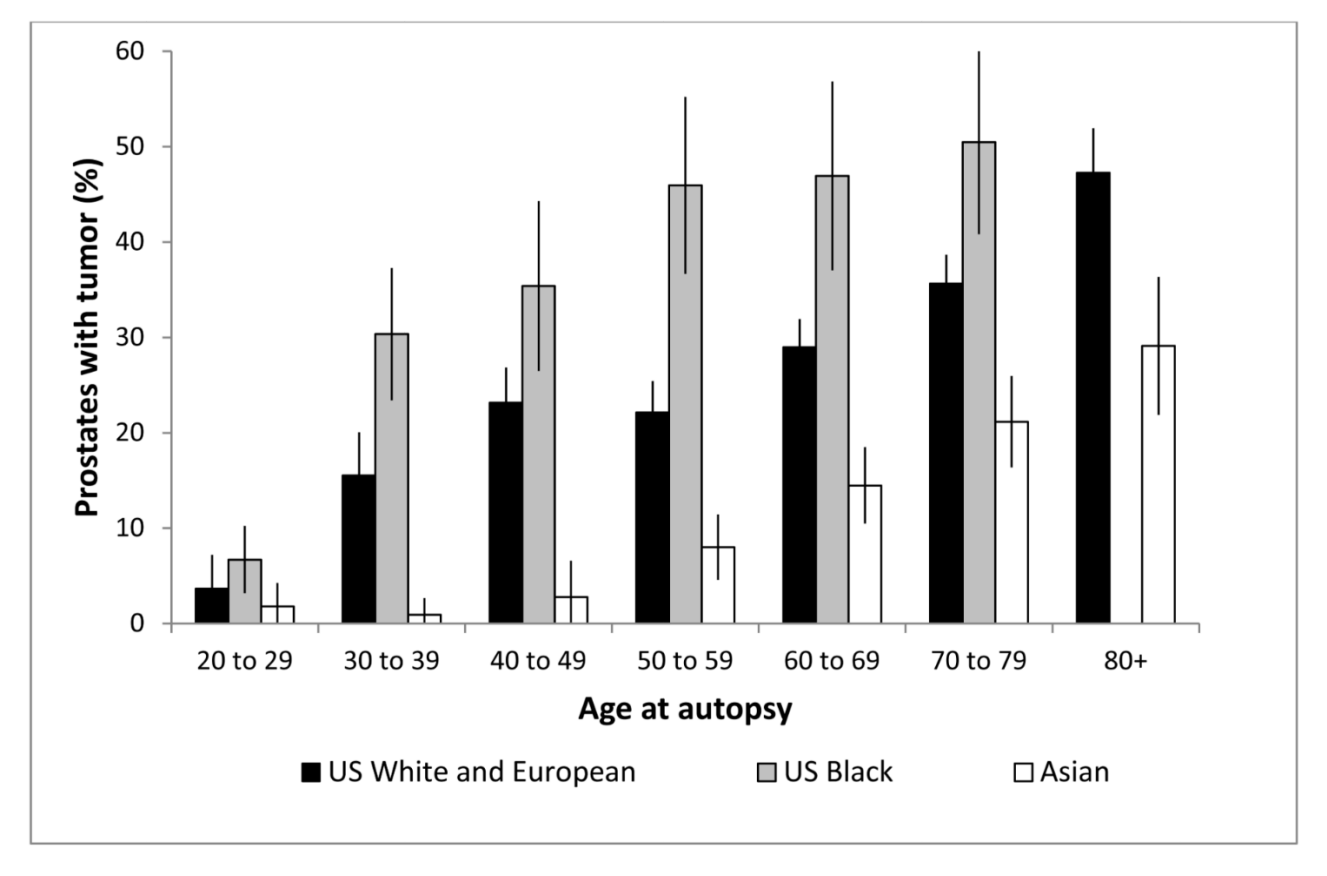
Prostate Cancer Screening Saves Lives But…..

Need to minimize overdetection and overtreatment

Prostate Cancer Is Common Among Men Dying of Other Causes



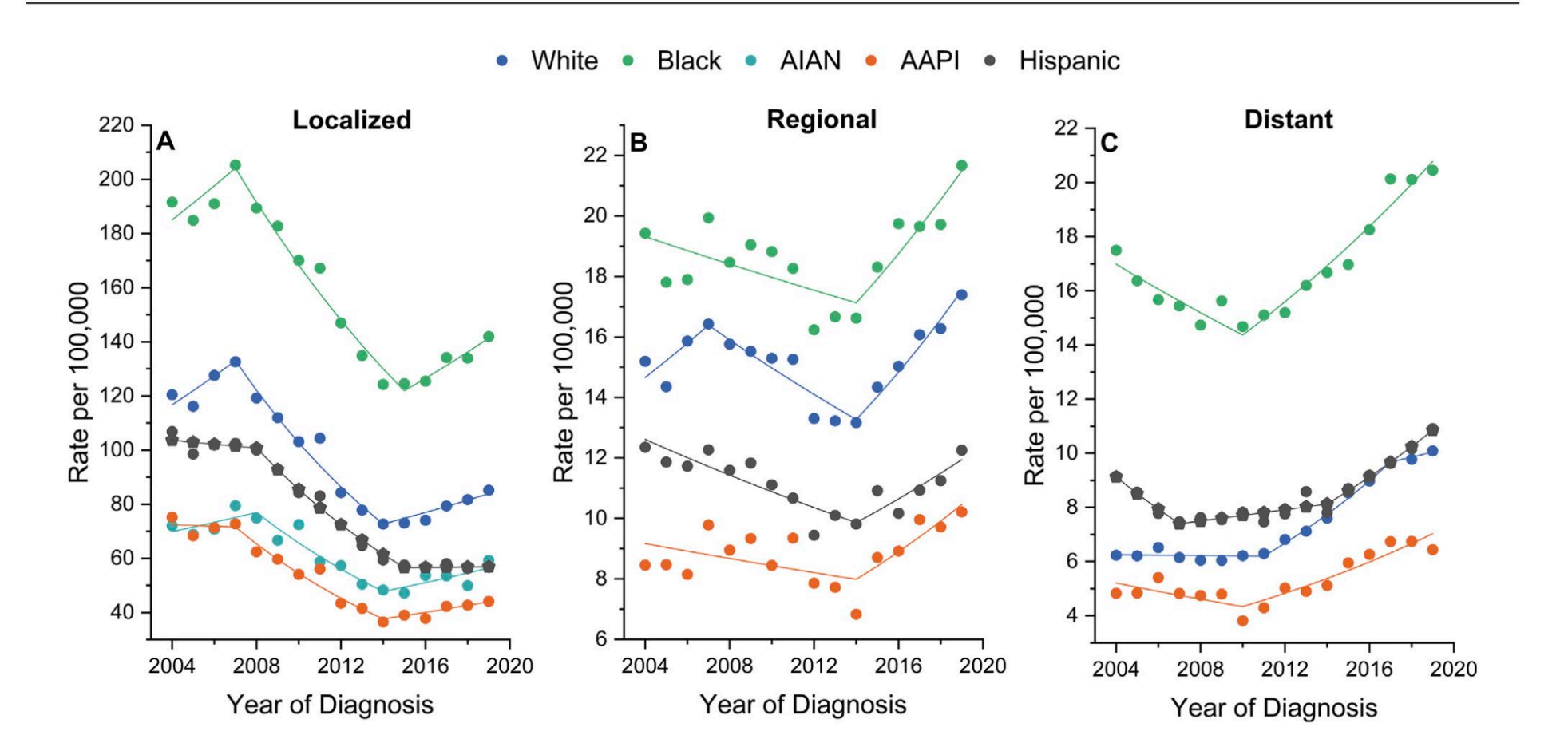
19 autopsy studies including 6,000 men

Reference: Jahn et al, Int J Cancer Vivo, 2015

How to Minimize Overdetection and Overtreatment

2012 USPSTF: Grade D – Discourage Screening

Only 35% of US Men > 50 yo Get Screened



Reference: Shafer, Eur Urol, 2023

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2018 USPSTF: Grade C
May offer to men age 55 – 69 based on individual circumstances (SDM)

Population	Men aged 55 to 69 y	Men 70 y and older
Recommendation	The decision to be screened for prostate cancer should be an individual one.	Do not screen for prostate cancer. Grade: D

Brief Overview of the Most Notable Screening Trials (From Best to Worst)

#1) Swedish Randomized Study

- In 1994, 20,000 Swedish men were randomized to:
  1) PSA testing every 2 years
  2) not invited for PSA testing

- PSA threshold to recommend biopsy varied from 2.5 – 3.0 ng/ml

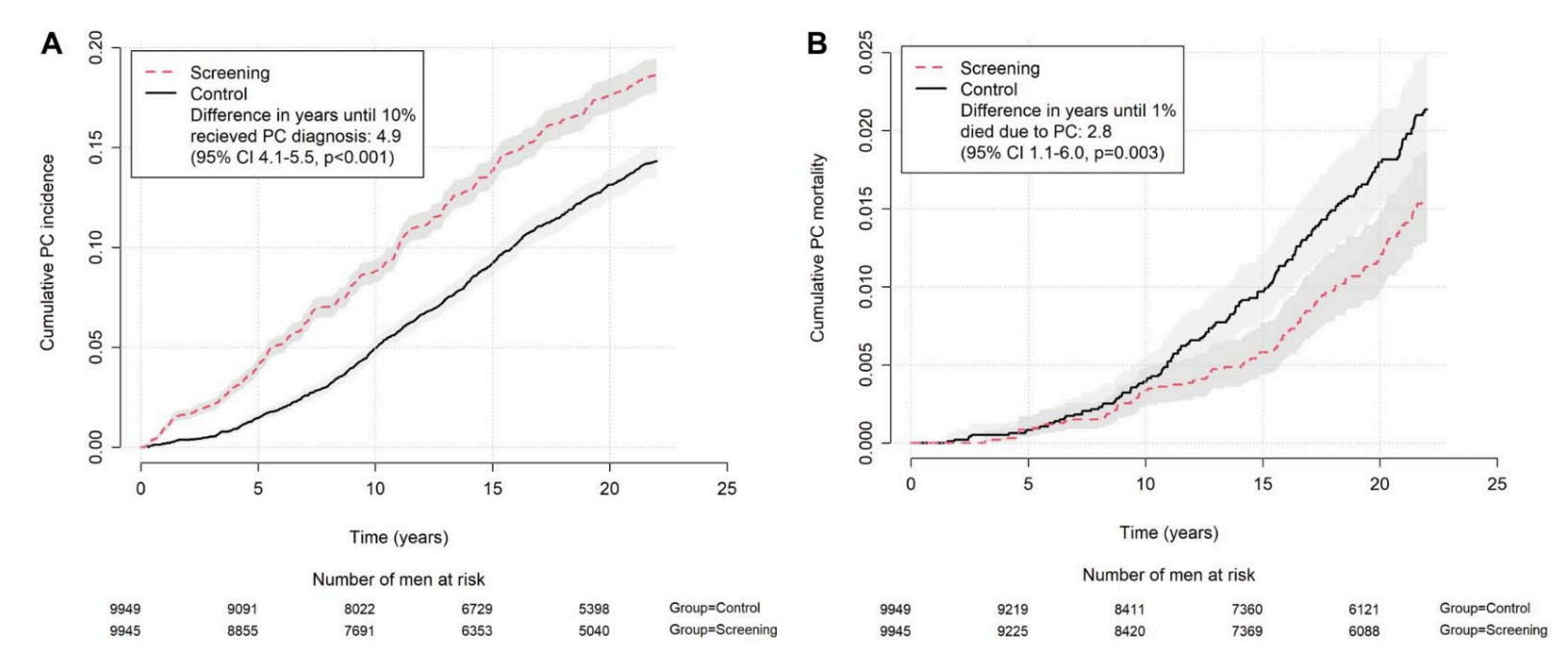
- Median follow-up: 22 years

- Best study for three reasons:
  - control group had relatively low rates of contamination
  - longest follow-up
  - PSA threshold lowest

Reference: Franlund, J Urol, 2022

#1) Swedish Randomized Study

- Screened men: 40% lower risk of death from prostate cancer

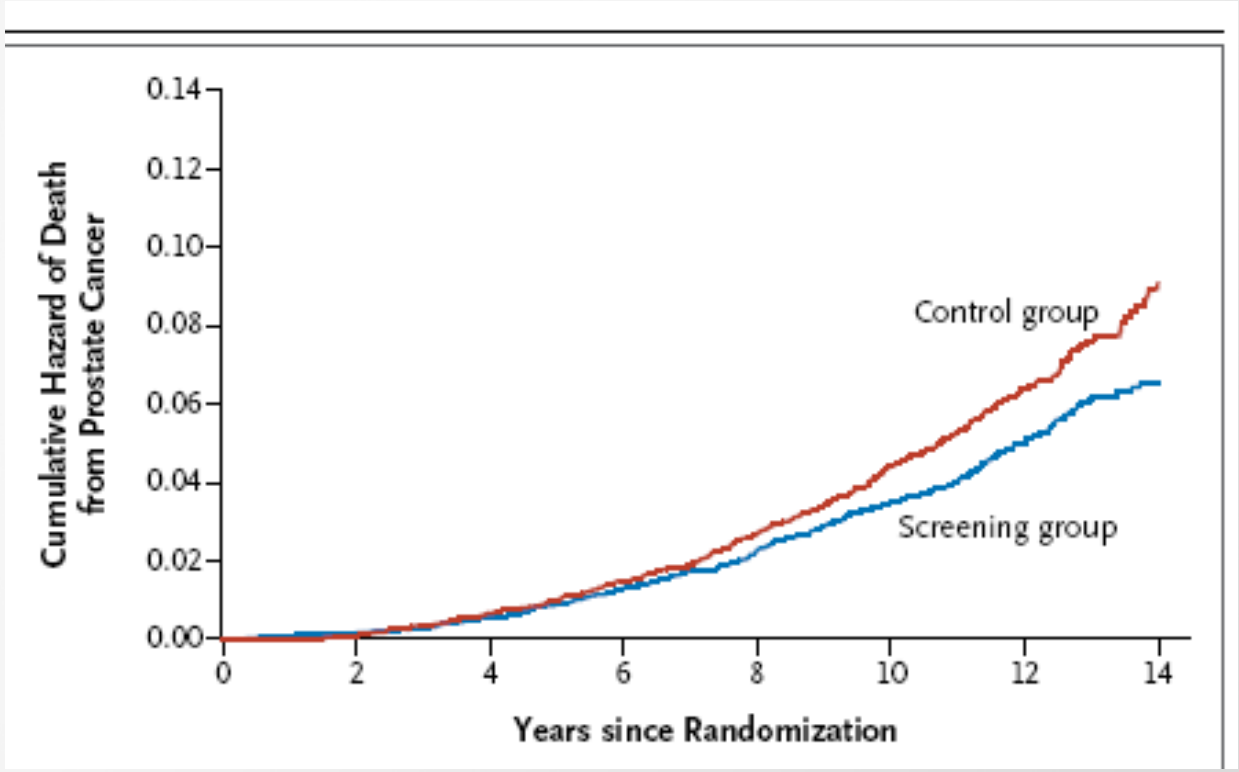


- ****Surveillance chosen by 42% of patients****
- Number to screen (221) and diagnose (9) to save a life

Reference: Franlund, J Urol, 2022

#2) European Screening Study: ERSPC

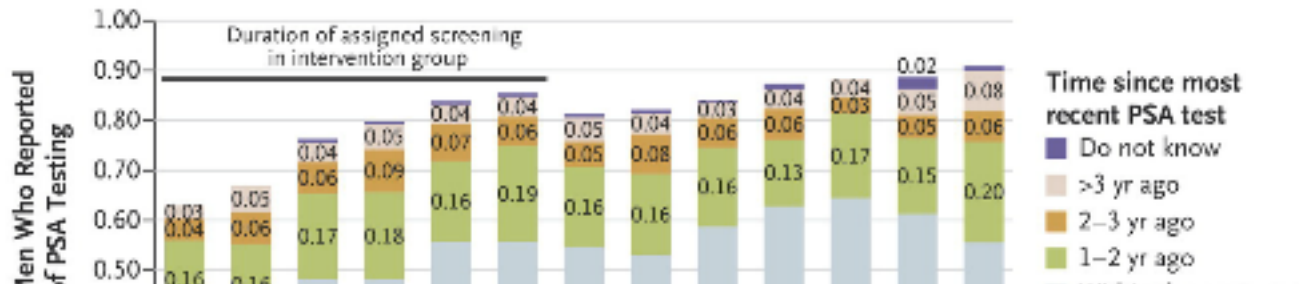
- 182,000 patients screened every 4 years at most sites with median follow-up of 13 years
- Relative decreased risk of death from prostate cancer: 21% (when adjusting for non-participation: 27%)
- Number of men needed to invite (NNS) to prevent one prostate cancer death: 570
- **Number of men needed to diagnose (NND) to prevent one prostate cancer death: 18**



Reference: Hugosson et al. Eur Urol, 2019

#3) PLCO Screening Trial: Garbage In, Garbage Out

- **~90% of men in the CONTROL group got a PSA before or during the trial**
- **Cumulatively, more PSA's in the control group vs screened group**

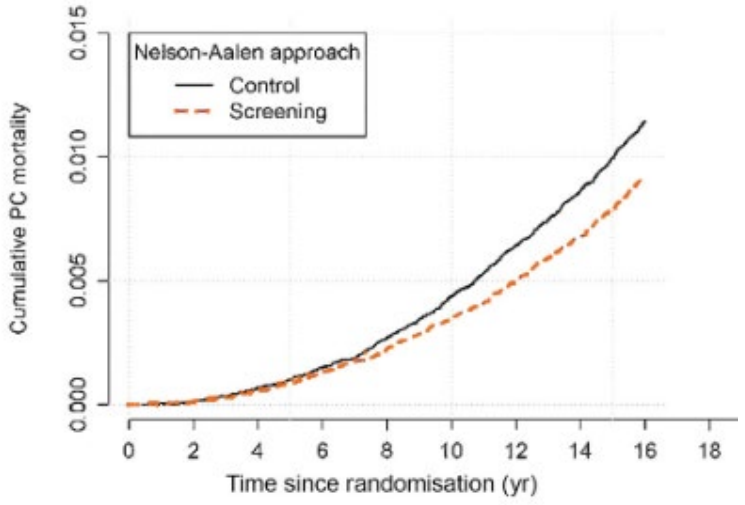


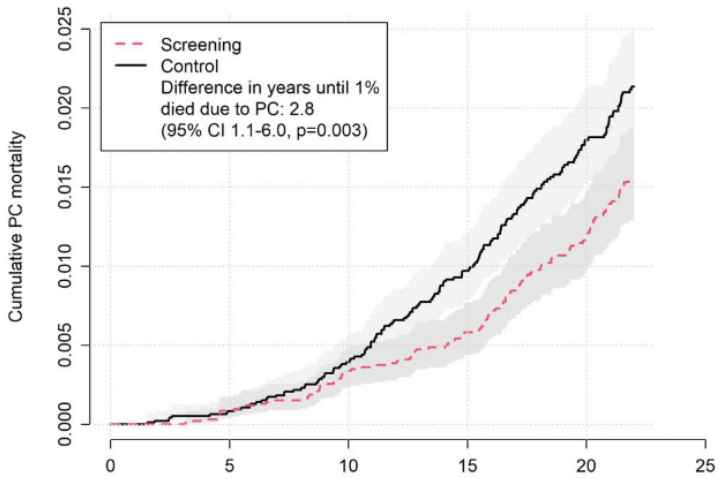
	0	1	2	3	4	5	6	7	8	9	10	11	12	Total
Unknown if tested (no.)	14	38	35	46	41	33	24	17	19	15	13	16	7	318
Not tested (no.)	68	144	96	88	71	60	54	47	40	35	25	24	9	761
Tested (no.)	116	292	309	346	370	354	235	217	212	242	189	188	90	3160
Proportion tested														
Main analysis	0.63	0.67	0.76	0.80	0.84	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

Reference: Shoag et al, NEJM, 2016

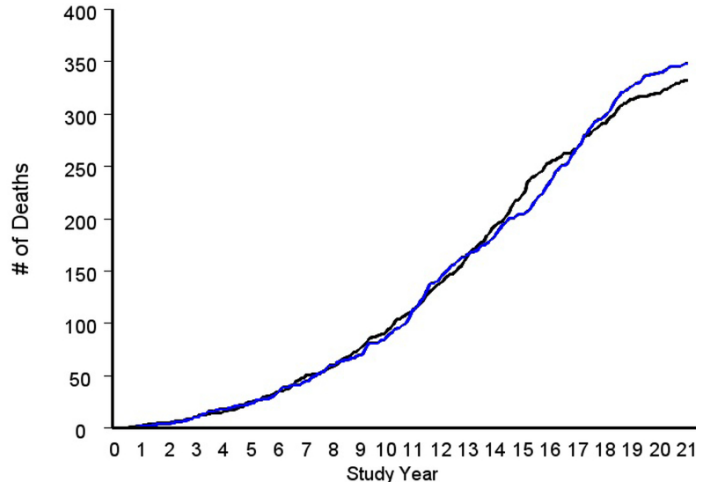
Randomized trials have demonstrated that regular PSA screening reduces the risks of prostate cancer metastasis and mortality

ERSPC
European Randomized Study of Screening for Prostate Cancer





NATIONAL CANCER INSTITUTE
PLCO
Prostate, Lung, Colorectal, & Ovarian
CANCER SCREENING TRIAL



	# men	Screening	MedianF/U	Results	Limits
U.S.	76,000	Annually 6 years	13 years	negative	contamination
European	182,000	Every 4 years	13 years	NNS=570 NNT=18	relaxed screening
Sweden	20,000	Every 2 years	22 years	NNS=221 NNT=9	overdiagnosis

Comparing Screening Tools:
Number needed to screen (NNS) and number need to diagnosis (NND) to save a life

- PSA testing:
  - NNS: 221
  - NND: 9
- Mammography:
  - NNS: 377 (age 60-69)
  - NNS: 1,339 (age 50-59)
  - NND at 10 years: 10
- Colorectal cancer:
  - NNS: 1173 (fecal blood)
  - NNS: 489 (flex sig)
- Hyperlipidemia
  - NNS: ~400
- Hypertension
  - NNS: ~300-1300

7 Tips on How To Optimize Screening

aka Saving Lives While Minimizing Overdetection

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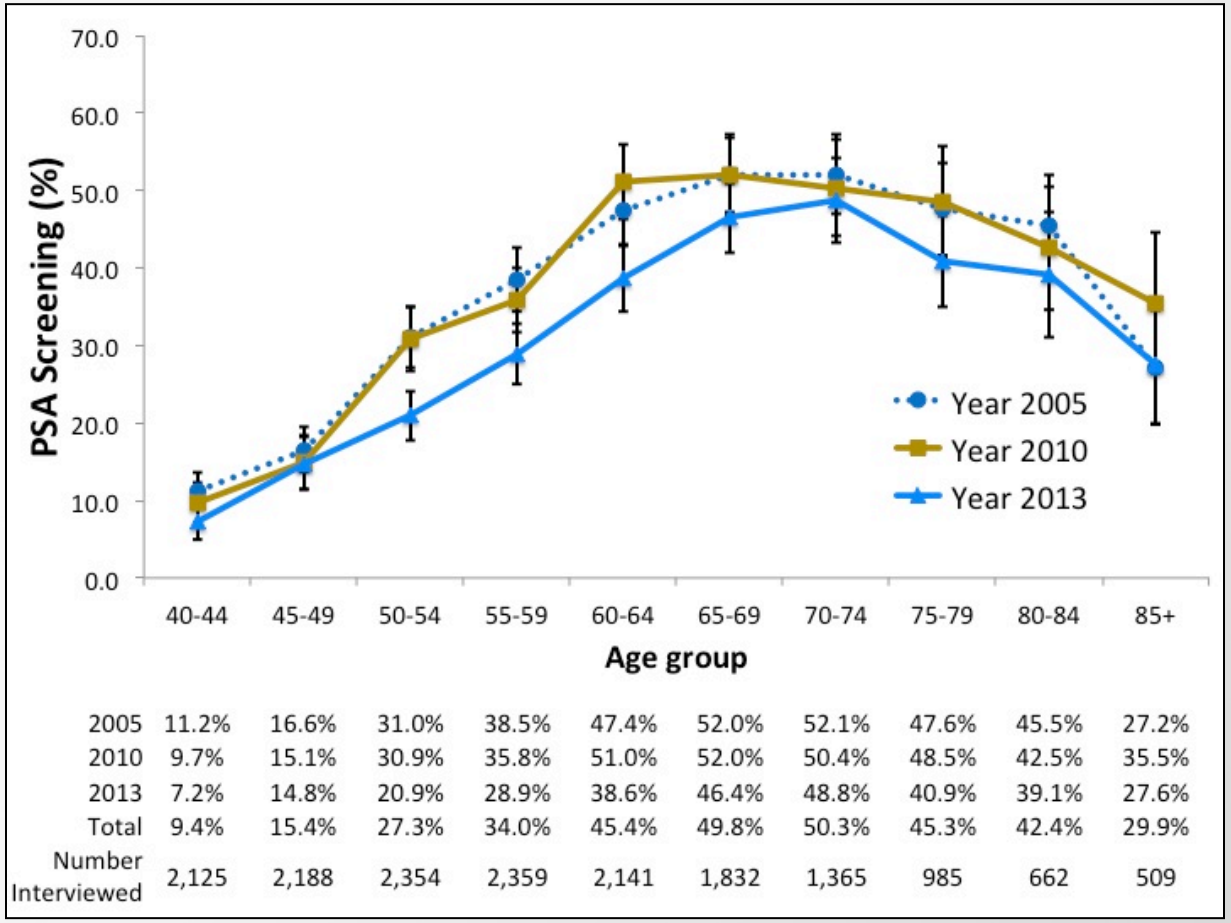
1) Stop Screening Old/Sick Men

Way (Way Way) Too Many Old Men Being Screened

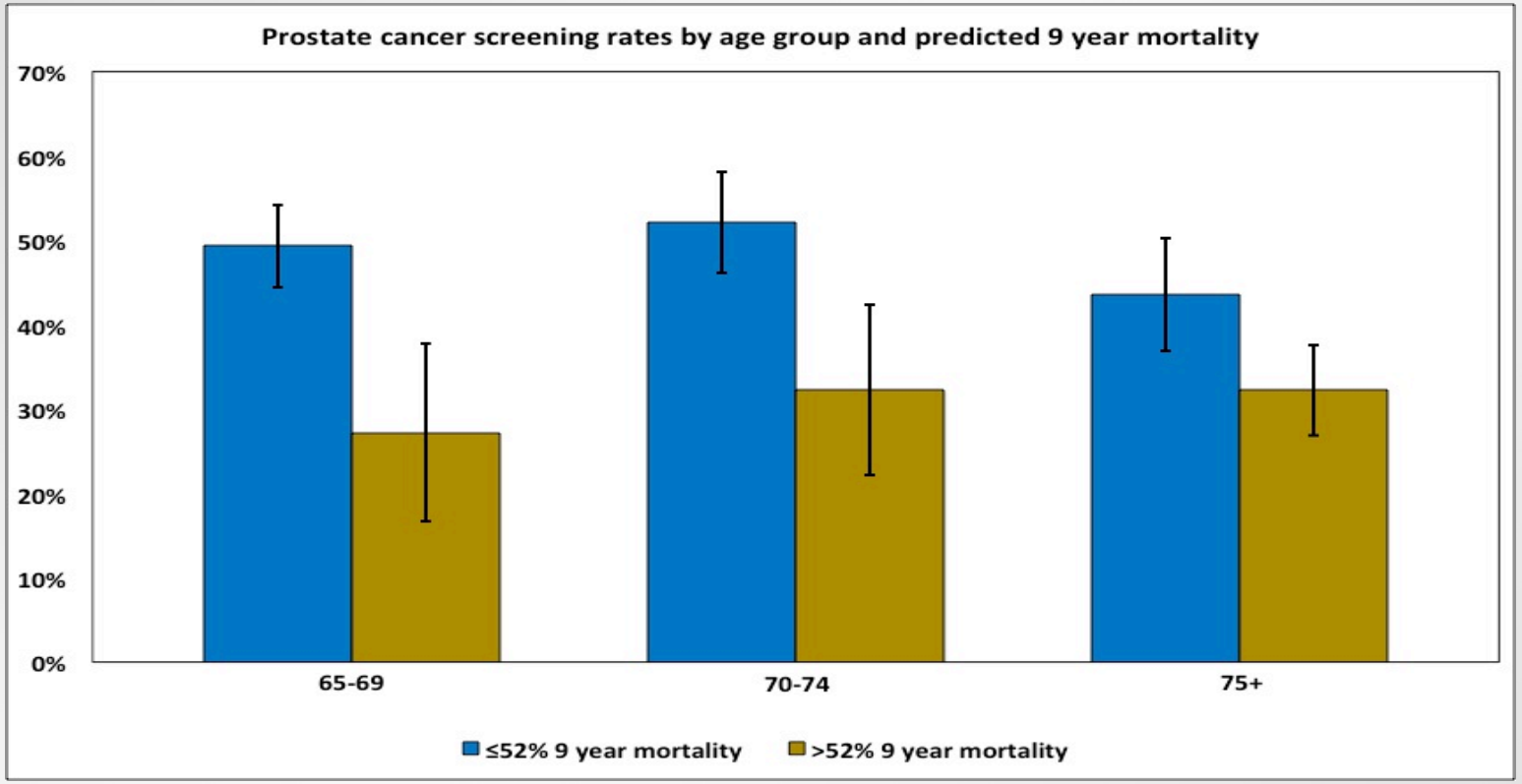
- Population-based survey (NHIS) from 2005, 2010, and 2013
- Excessive PSA screening in elderly and men with limited life expectancies
- Under-screening in younger men is a problem of similar magnitude



	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2005	11.2%	16.6%	31.0%	38.5%	47.4%	52.0%	52.1%	47.6%	45.5%	27.2%
2010	9.7%	15.1%	30.9%	35.8%	51.0%	52.0%	50.4%	48.5%	42.5%	35.5%
2013	7.2%	14.8%	20.9%	28.9%	38.6%	46.4%	48.8%	40.9%	39.1%	27.6%
Total	9.4%	15.4%	27.3%	34.0%	45.4%	49.8%	50.3%	45.3%	42.4%	29.9%
Number Interviewed	2,125	2,188	2,354	2,359	2,141	1,832	1,365	985	662	509

Reference: Drazer, J Clin Oncol, 2015

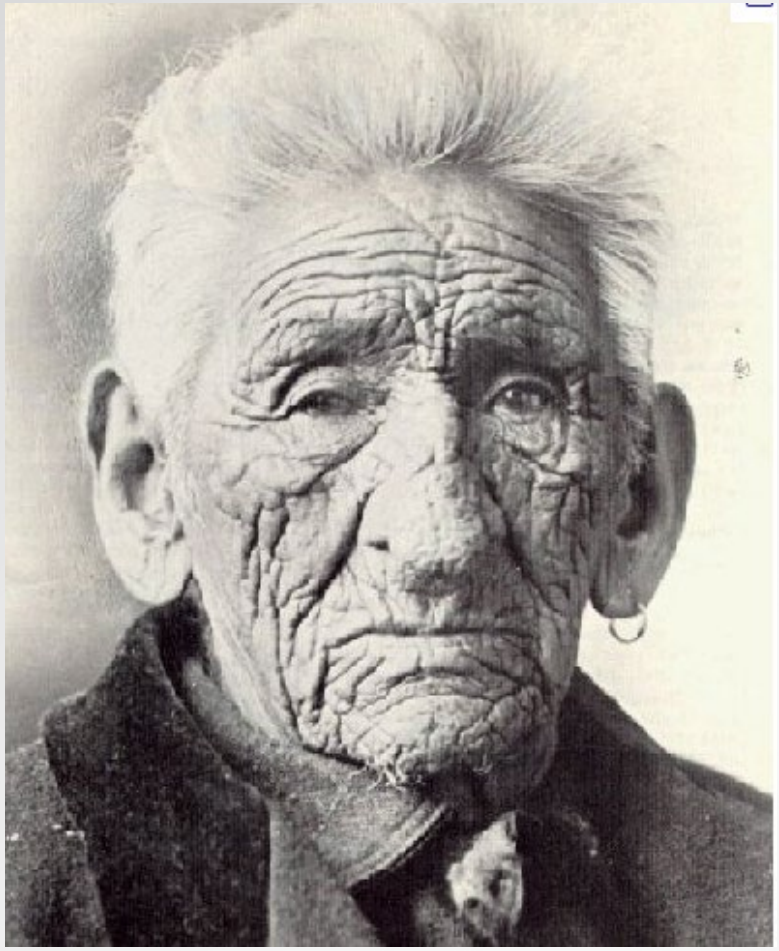
Patterns of PSA Screening in Sick Men

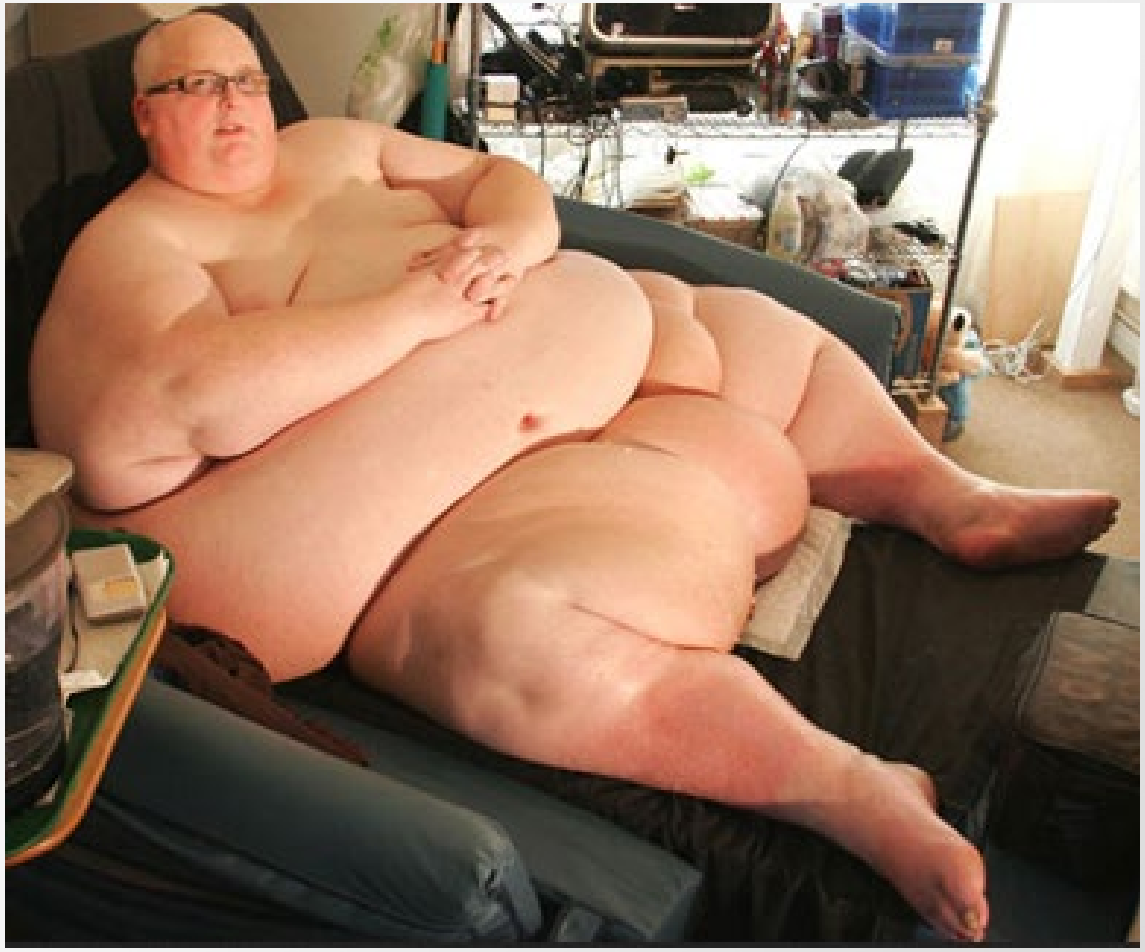


1.4 million men age > 65 or older with a high risk (52%) of 9-year mortality underwent screening

Reference: Drazer, JCO, 2015

Fifty-Year-Old Men NOT to Check a PSA





Very reasonable to screen certain older men…

All these men are in their 80s

What is the Life Expectancy of Older Men in the US?

For the ***average health man***:

- 65-year-old US male will live to be 83 years old
- life expectancy drops below 10 years at age 78

Exact age	Death probability [a]	Number of lives [b]	Life expectancy
70	0.022364	72,924	14.60
71	0.024169	71,293	13.92
72	0.026249	69,570	13.25
73	0.028642	67,744	12.59
74	0.031380	65,804	11.95
75	0.034593	63,739	11.32
76	0.038235	61,534	10.71
77	0.042159	59,181	10.12
78	0.046336	56,686	9.54
79	0.050917	54,059	8.98

Reference: Social Security Data, 2019 (latest available)

2) Be Fair When Explaining Risks/Benefits of Screening

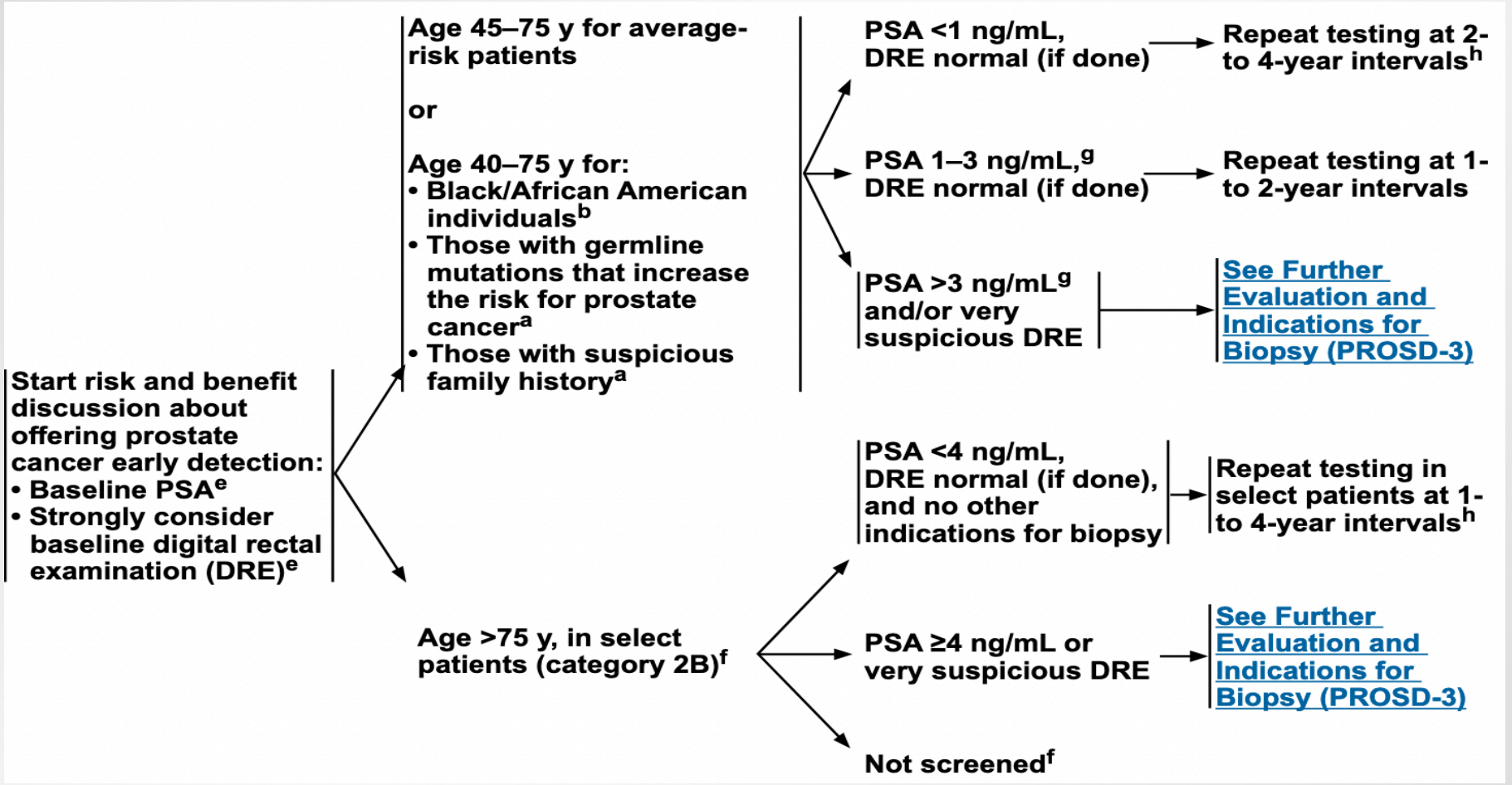
Shared Decision Making Among Screened Men 75 Years & Older

9 Year Mortality Probability	Physician Recommended PSA	Physician Discussed Advantages	Physician Discussed Disadvantages	Physician Discussed Controversy
Healthy (<53%)	96.3%	54.1%	21.8%	18.3%
Less Healthy (≥53%)	94.2%	55.0%	24.7%	23.1%

Ref: Drazer et al, Cancer, 2014

3) Be Familiar with Modified Guideline Recommendations

NCCN Guidelines 2022: Screen at 1– 4 Year Intervals



4) Always Repeat A Newly Elevated PSA

Repeat a Newly Elevated PSA (Year Over Year)

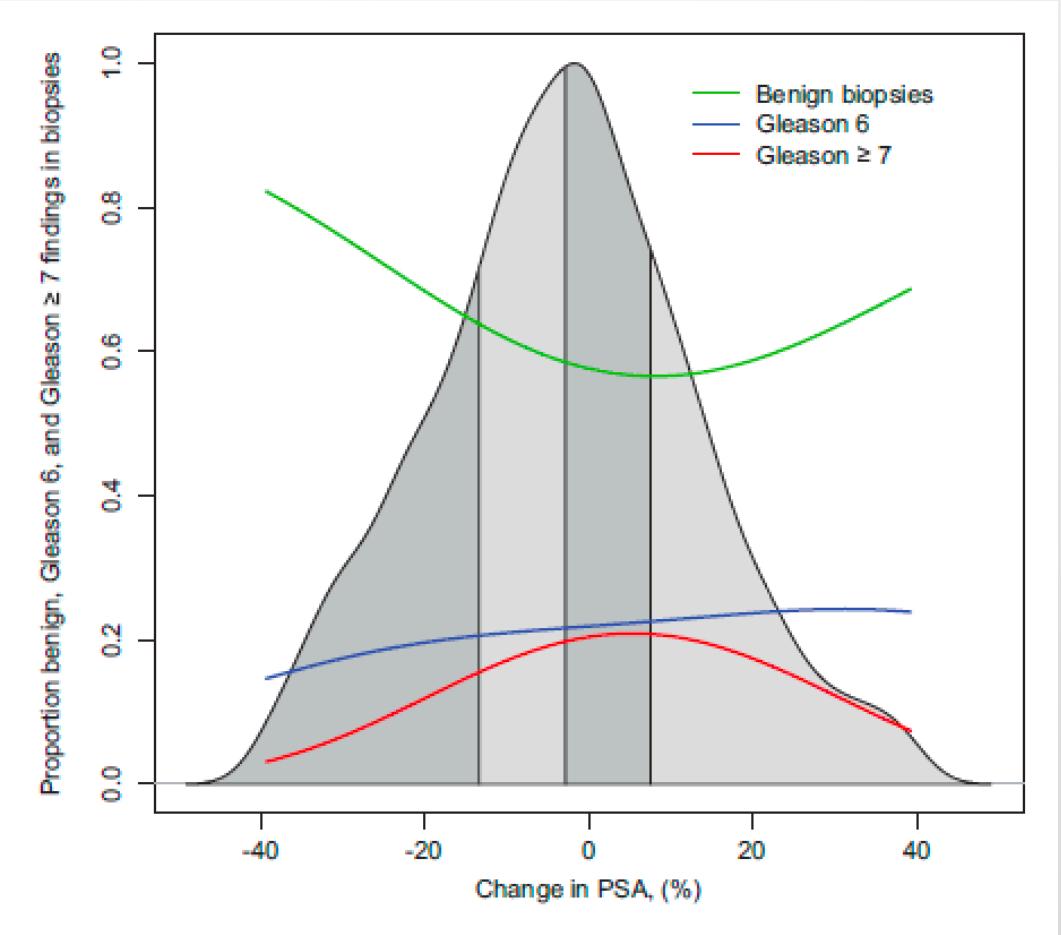
- 972 men from colon polyp prevention trial with 5 annual blood draws
- Median age: 62
- **If 'abnormal' PSA, 40-55% were 'normal' at subsequent visit**

Criterion	No. of Participants		No. (%) of Participants With Normal Level at Any Subsequent Visit
	Abnormal PSA Level*	Returned for Subsequent Visit	
PSA level, ng/mL			
>4.0	172	154	68 (44)
>2.5	319	291	116 (40)
Age-specific PSA level	139	117	64 (55)
Free PSA ratio	156	143	76 (53)

Reference: Eastham et al, JAMA, 2003

Value of Repeating PSA (Within 8 Weeks)

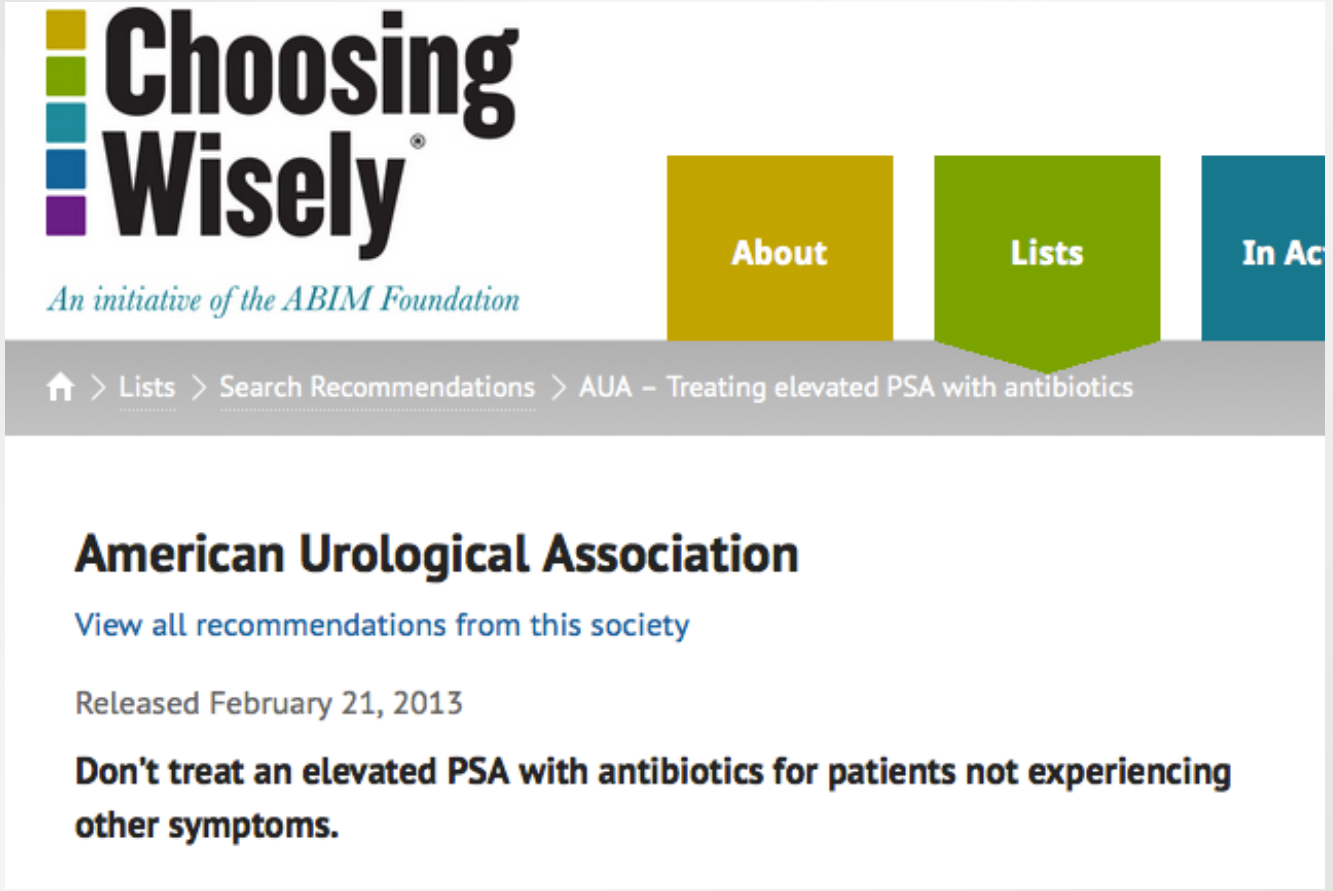
- STHLM3 study:
  - 1,686 men with PSA 3-10 ng/ml
  - all had repeat PSA within 8 weeks
  - all had biopsy



Reference: Nordstrom et al, JNCI, 2016

5) Don’t Give Empiric Antibiotics for an Elevated PSA

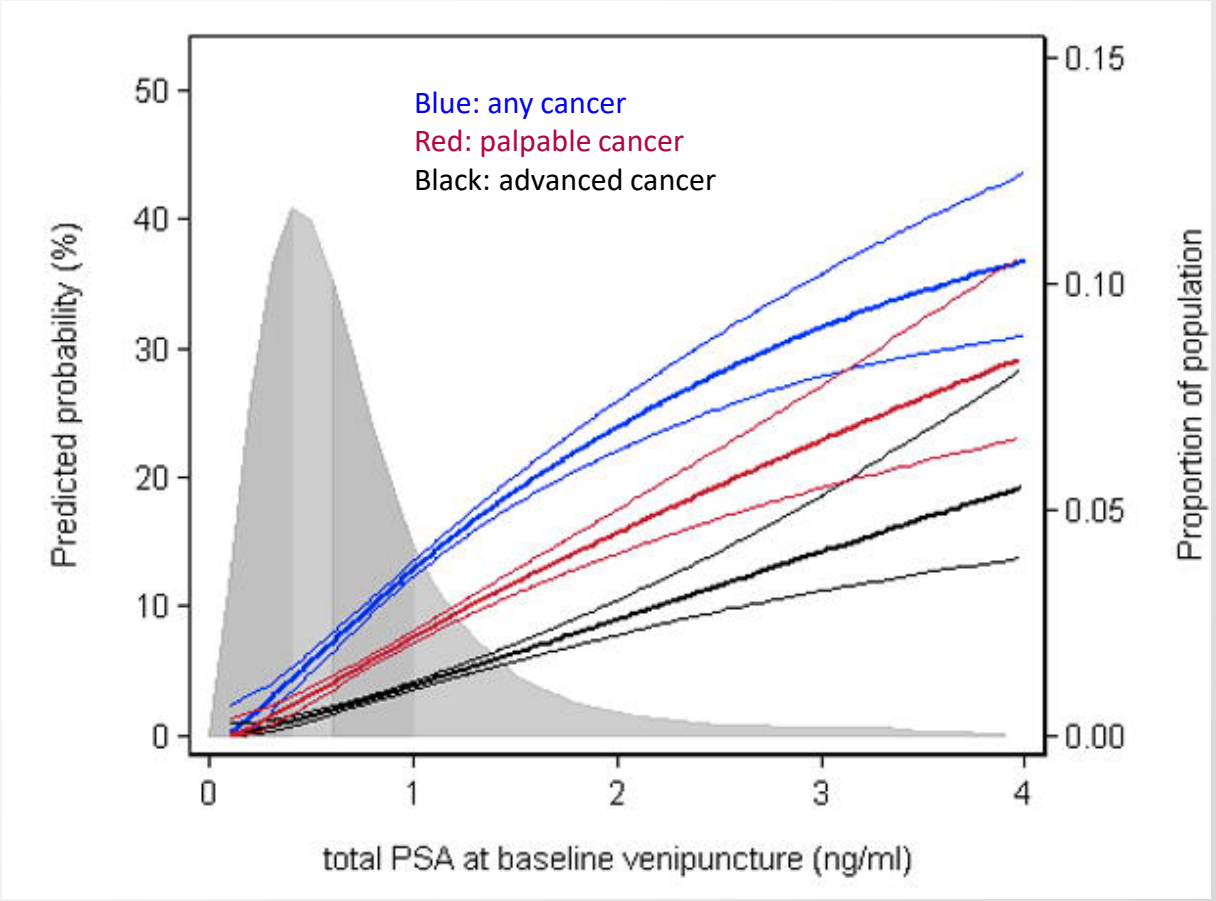
No Empiric Antibiotics For Elevated PSA



6) Risk-Stratify Based on Baseline PSA

PSA at Age 44-50 is a Very Useful Clinical Tool

- Blood from 21,277 Swedish men during 1974-1986
- Median follow-up: 23 years
- Figure: age 44 - 50



Reference: Lilja et al, Cancer, 2011

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Baseline PSA is Valuable, Even When 'Normal'

- Physician's Health Study, 22,000 men age 40-59
- Median PSA
  - Age 40-49: 0.68 ng/ml
  - Age 50-54: 0.88 ng/ml
  - Age 55-59: 0.96 ng/ml
- Of men age 55-59:
  - 86% of all prostate cancer deaths had PSA > median
  - **If PSA < median, risk of lethal PrCa over 30 years: 0.59%**

Reference: Preston et al, JCO, 2016

Utility of PSA at Age 60

- Gothenburg, Sweden (screened)
  - 1,756 men in randomized study with PSA between age 57-62
- Malmo, Sweden (unscreened)
  - 1,162 men age 60 gave blood in 1981

- **PSA < 2 at age 60: ↑incidence (7 per 100), no change mets or mortality**
- PSA > 2 at age 60: ↓mortality (4 per 100), NND to save life @15 yrs = 6

Reference: Carlsson et al, BMJ, 2014

7) Know When to Stop Screening

When to Stop Checking PSA

- Sweden (Malmo Prevention Project)
  - 1,167 men age 60 gave blood in 1981
  - Median PSA = 1 ng/ml
  - Men with PSA < 1 ng/ml at age 60 had 0.5% risk of metastases and 0.2% risk of dying from prostate cancer by age 85

Consider stopping (or relaxing) screening if:

****PSA < 1 ng/ml at age 60****

Reference: Vickers and Lilja, BMJ, 2010

Summary of 7 **Cheap (or Free)** Ways to Minimize Overdetection

- Stop screening old/sick men
- Explain risks/benefits of screening (not every man needs a PSA)
- Know the modified screening guidelines
- Always repeat an elevated PSA
- Never give empiric antibiotics
- Use baseline PSA to risk-stratify screening plan
- When to stop screening (e.g. PSA < 1 [or 2 ng/ml] @ age 60)

Beyond PSA:
Basics of Secondary Biomarkers and MRI

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Two (Nearly Free) Serum Screening Biomarkers

1) Power of Free PSA

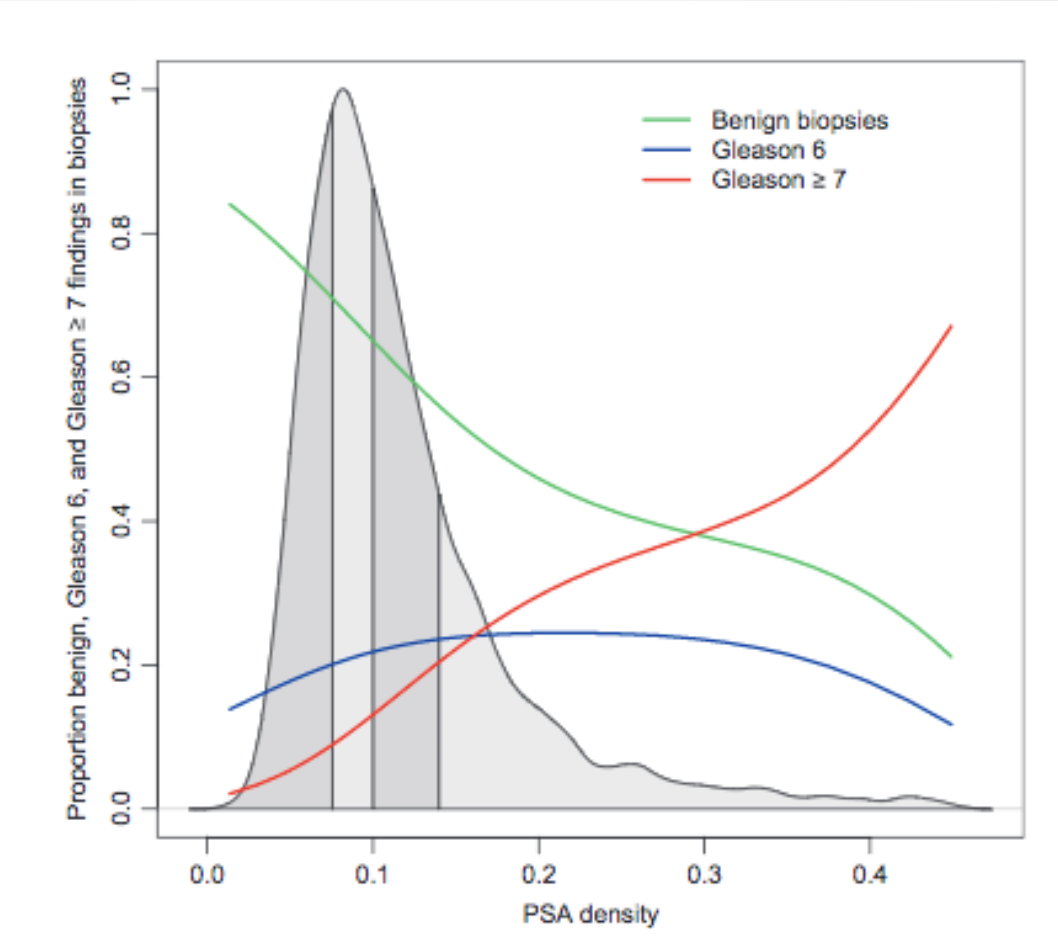
PCPT Risk Calculator (available online) based on 6,600 biopsies

- For a 65-year-old Black man with PSA=4 ng/ml, normal DRE, no family history, and no previous biopsy:
  - 8% free PSA: 47% rate of Gleason 7 (GG2) or higher on biopsy
  - 20% free PSA: 13% rate of Gleason 7 (GG2) or higher
  - 40% free PSA: 8% rate of Gleason 7 (GG2) or higher

When screening patients, I order free and total PSA every time

2) PSA Density: Importance of Prostate Size

- PSA density is PSA ÷ estimated prostate volume
- Swedish men age 50-69
- 5,291 men had 10-12 core biopsy
- Median
  - PSA = 4.2 ng/ml
  - Prostate volume = 43 cm^3
  - PSA density = 0.10 $ng/ml/cm^3$



Ref: Nordstrom, Prostate Cancer and Prostatic Diseases, 2018

What to do in a man with an elevated age-specific PSA (repeated), concerning free PSA, or meaningful FH?

- **Refer to a urologist you trust (who doesn't biopsy everyone nor treat everyone who is diagnosed)**
  - Secondary screening biomarker
  - MRI
  - Biopsy

Gleason grading system

Risk Group*	Grade Group	Gleason Score
Low/Very Low	Grade Group 1	Gleason Score ≤ 6
Intermediate (Favorable/Unfavorable)	Grade Group 2	Gleason Score 7 (3 + 4)
	Grade Group 3	Gleason Score 7 (4 + 3)
High/Very High	Grade Group 4	Gleason Score 8
	Grade Group 5	Gleason Score 9-10

Intent of Screening: Evolution to Trying **NOT** to Diagnose Gleason 6 (GG1)

- Most experts agree the goal of screening is to identify Gleason ≥7 (GG2)
- Secondary biomarkers (PHI, 4K, Select MDx, etc) appropriately marketed as:
  - fewer men requiring a biopsy
  - diagnose fewer men with Gleason 6 (GG1)
  - identify nearly all the men with Gleason ≥7 (GG2) (compared to biopsy for all)
- Favorable attributes of MRI:
  - doesn't routinely visualize Gleason 6 (GG1)
  - intends to visualize Gleason ≥7 (GG2)

10 Commercially Available Screening Biomarkers: "Show me the Gleason ≥ 7 (GG2)"

Prostate Cancer Biomarkers (Serum, Urine, Tissue)

SERUM
4K
PHI
isoPSA
STHLM3

URINE
PCA3
Select MDx
MyProstateScore
ExoDx
miRNA (Sentinel)

TISSUE
Confirm MDx (only if previously negative bx)

- General characteristics:
  - decreases number of men needing a biopsy (20-30% less)
  - minimizes number of men being diagnosed with Gleason 6 (Grade Group 1)
  - captures nearly all men with Gleason 7 (Grade Group 2) or higher

Legend: Serum, Urine, Tissue

Multi-parametric Prostate MRI

- Main sequences are:
  - T2 weighted
  - diffusion weighted imaging (DWI) leading to an ADC map
  - dynamic contrast-enhanced (DCE)

- PIRADS system correlates to likelihood of clinically significant cancer:
  - PIRADS 3: ~15%
  - PIRADS 4: ~40%
  - PIRADS 5: ~70%

MRI is a Valuable Screening Biomarker and Improves Quality of the Biopsy (if needed)

- 500 men with elevated PSA, no previous biopsy, **randomized** to:
  - 12 core ultrasound-guided biopsy (standard)
  - MRI of the prostate with biopsy, if needed

- In MRI arm, 28% didn't need biopsy ('negative' MRI)
- Clinically significant cancer: 38% (MRI arm) vs 26% (standard)
- Clinically insignificant cancer: 9% (MRI arm) vs 22% (standard)

Reference: Kasivisnathan, NEJM, 2018

Why (Most of Us) Don't Want To Find Gleason 6 (Grade Group 1)

1) 0.28% extend beyond prostate capsule at surgery (Anderson, Eur Urol, 2017)
2) Never invade seminal vesicles at surgery (Anderson, Eur Urol 2017)
3) Never metastasize to lymph nodes (Ross, Am J Surg Path, 2014)
4) Following surgery, 15-yr cancer-related mortality < 1% (Eggener, J Urol, 2011)
5) Not aware of anyone ever having a met/dying from pure Gleason 6 (GG1)

Is Gleason 6 (GG1) Cancer?

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Gleason Score 6 Adenocarcinoma: Should It Be Labeled As Cancer?

H. Ballentine Carter, Alan W. Partin, Patrick C. Walsh, Bruce J. Trock, Robert W. Veltri, William G. Nelson, and Donald S. Coffey, *The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, MD*
Eric A. Singer, *National Cancer Institute, National Institutes of Health, Bethesda, MD*
Jonathan I. Epstein, *The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, MD*

Do low-grade and low-volume prostate cancers bear the hallmarks of malignancy?

Hashim Uddin Ahmed, Manit Arya, Alex Freeman, Mark Emberton

Low-Grade Prostate Cancer: Time to Stop Calling It Cancer

Scott E. Eggener, MD[1]; Alejandro Berlin, MD[2]; Andrew J. Vickers, PhD[3]; Gladell P. Paner, MD[4]; Howard Wolinsky[5]; and Matthew R. Cooperberg, MD[6]

Reference: Carter, JCO, 2012; Ahmed, Lancet Oncology, 2012; Eggener, JCO, 2022

Merriam-Webster Dictionary

Benign: of a mild type or character that does not threaten health or life

Cancer: a malignant tumor of potentially unlimited growth that expands locally by invasion and systemically by metastasis

Following the Diagnosis of Prostate Cancer: To Treat or Not?

Management Menu for Localized Prostate Cancer

- Active surveillance
- Radical prostatectomy
  - open
  - robotic
- Radiation therapy
  - brachytherapy (seeds)
  - external beam (IMRT)
  - proton beam
  - hypofractionated
- Ablation
  - cryotherapy
  - HIFU
  - electroporation
  - laser
  - transurethral US ablation
  - injectable cytotoxin
  - water vaporization
  - local immunotherapy
  - focal brachytherapy

Not All Men With Prostate Cancer Require Treatment

Guidelines for Low-Risk Prostate Cancer: Active Surveillance

European Association Urology (2022): "offer to all patients"

NCCN (2023): "preferred management strategy"

American Urological Association (2022): "clinicians should recommend active surveillance as the preferred management option"

Exceptions: When Treatment is an Option for Low-Risk

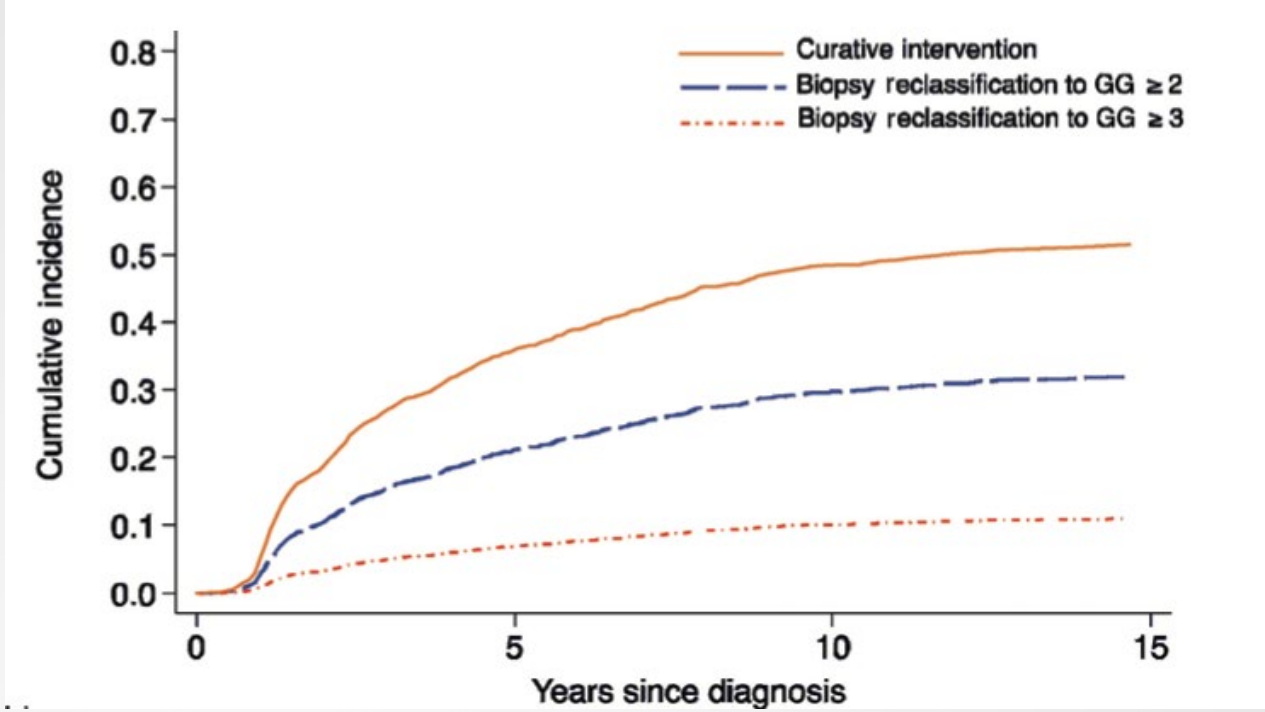
- Very high volume cancer
- Very high PSA density

No magic cutpoints

- PIRADS 5
- Compelling family history of lethal prostate cancer
- Specific germline mutations (e.g. BRCA2, ATM, CHEK2)
- Extreme anxiety, despite thoughtful discussion/explanation
- Concerns about compliance

Johns Hopkins Active Surveillance (Strict)

1800 men with very-low and low-risk prostate cancer



15-year likelihood of metastases/death: 0.1%

Reference: Tosoian, Eur Urol, 2020

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University of Toronto (Loose)

- 993 men with median age of 67
- Inclusion criteria:
  - clinical stage T1-T2c with occasional T3
  - PSA< 10 ng/ml (up to 15 ng/ml until 2000)
  - Gleason 6 (up to Gleason 7 until 2000)
- Method of surveillance:
  - PSA every 3 months for 2 years, then every 6 months
  - Re-biopsy (8-14 core) at 6-12 months, then every 3-4 years
- Metastasis-free survival at 10 and 15 years: 95% and 91%
- **Metastasis-free survival among Gleason 6: 98%**

Reference: Klotz, J Clin Oncol, 2015

ProtecT: Prostatectomy vs Radiotherapy vs Active Monitoring

- 1,643 men
  - 77% were Gleason 6 (GG1)
  - 21% were Gleason 7 (GG2-3)
  - 2% were Gleason 8-10 (GG4-5)

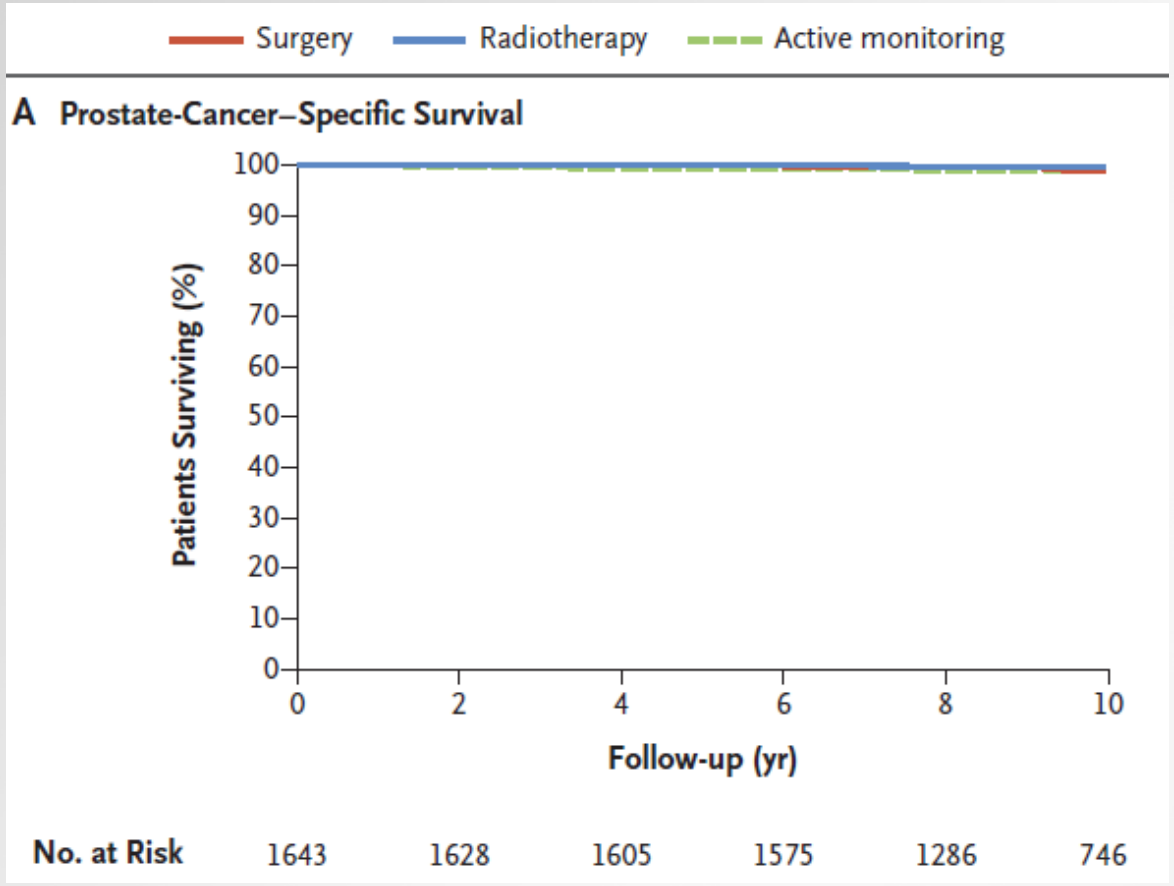
- Active monitoring:
  - PSA every 3 months x 1 year
  - Then PSA every 6-12 months
  - If PSA increase > 50% in 1 year, then further tests or continued monitoring

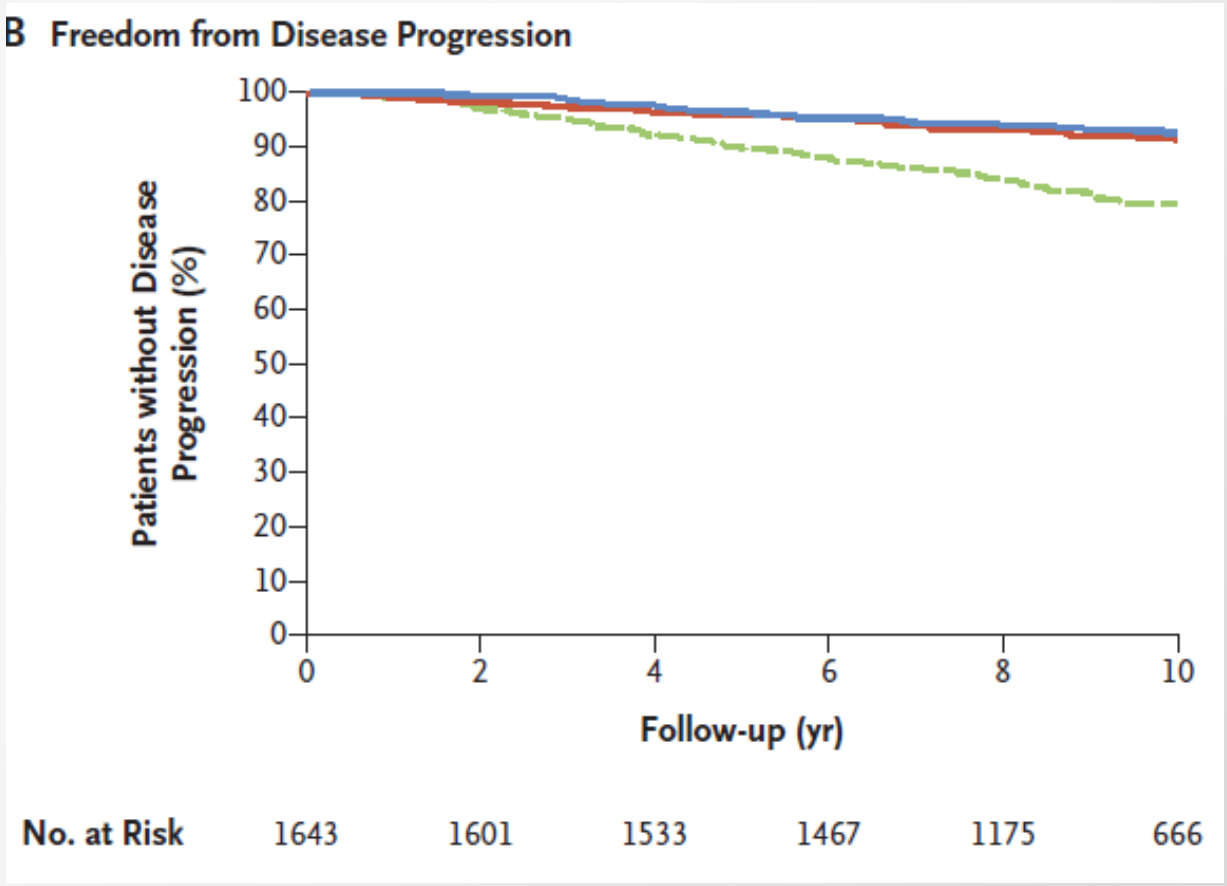
Table 2. Deaths from Prostate Cancer, According to Subgroup.*

Variable	No. of Deaths Due to Prostate Cancer†			P Value‡
	Active Monitoring (N=545)	Surgery (N=553)	Radiotherapy (N=545)	
Age at randomization				0.09
<65 yr	1	3	1	
≥65 yr	7	2	3	
PSA level at diagnosis				0.72
<6 ng/ml	5	3	4	
≥6 ng/ml	3	2	0	
Gleason score at diagnosis§				0.69
6	3	3	2	
≥7	5	2	2	
Clinical stage at diagnosis¶				0.95
T1c	5	3	3	
T2	3	2	1	

Reference: Hamdy, NEJM, 2016

ProtecT: Prostatectomy vs Radiotherapy vs Active Monitoring





Reference: Hamdy, NEJM, 2016

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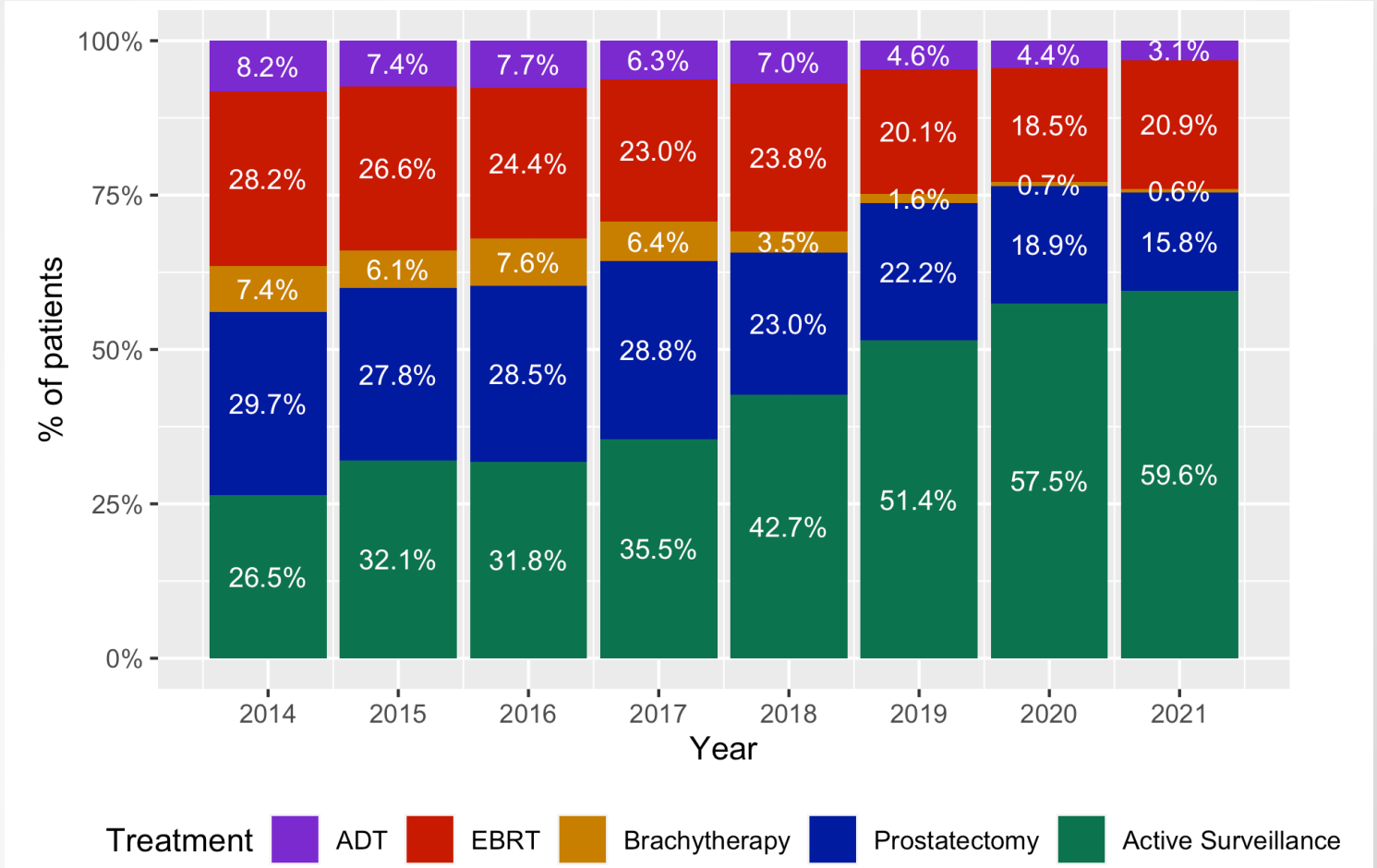
Management of Low-Risk Prostate Cancer in the US

- 40% of men with low-risk prostate cancer in the US undergo immediate treatment
- “We’ve come a long way, we’ve got a long way to go”



REF: Cooperberg et al, JAMA Network Open, 2023

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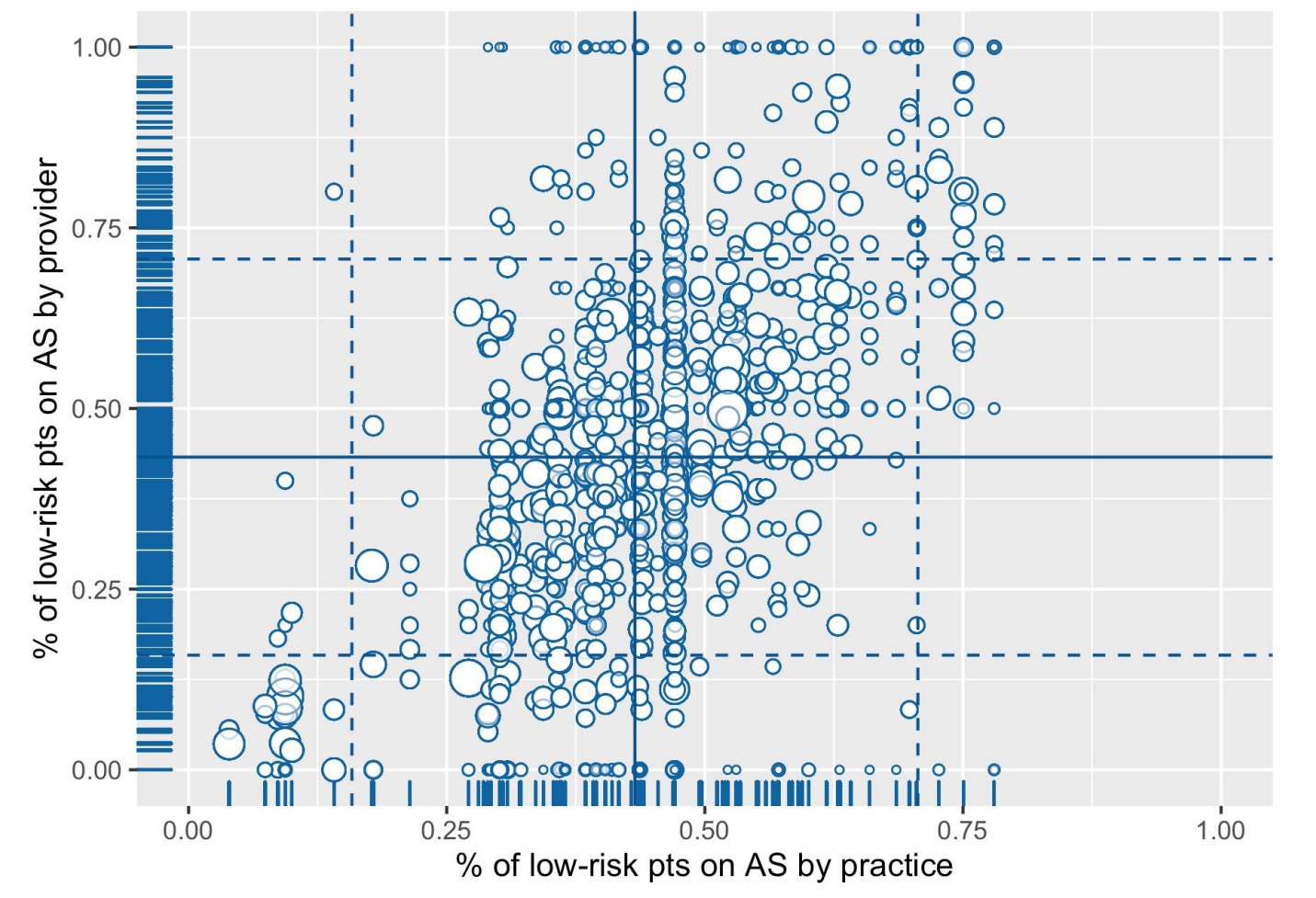
Massive Variation Depending on Urologist and Practice



Each circle represents a urologist, organized in columns by practice.

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Cooperberg et al, AUA, 2022

Global Benchmarks

- For men with low-risk prostate cancer, rates of surveillance are >90% in:

England

Sweden

Australia

Points of General Consensus Amongst Prostate Cancer Specialists

- For men with low-risk prostate cancer:
  - surveillance should be recommended to the vast majority
  - there are some patients where treatment should be discussed as an option

- If your urologist recommends treatment for most or nearly all low-risk patients:
  - unlikely anything I'm gonna say or show will change their mind
  - at best: impressively stubborn and inflexible in their interpretation of data
  - at worst: highly unethical

Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline

- Tissue-based molecular biomarkers (Prolaris, Oncotype Dx, Decipher) may improve risk stratification when added to standard clinical parameters
- The Expert Panel endorses their use only in situations in which the assay results, when considered as a whole with routine clinical factors, are likely to affect a clinical decision.
- These assays are **not recommended for routine use**

Reference: Eggener and Beltran, JCO, 2019

How I (Typically) Do Surveillance

- **Discuss with everyone with Gleason 6 or 7 (Grade Group 1 - 3) and estimate likelihood of metastases/death over 10-15 years while on surveillance**
- **MRI (if not already done) with fusion re-staging biopsy, typically within 6-12 months**
- **PSA every 6 months (no need for 3 months); DRE every 1-2 years**
- **Always repeat a new significant rise in PSA prior to changing plan**
- **Surveillance biopsy (+/- MRI) every 1–4 years (risk-stratify) based on age, health, total millimeters of cancer, PSA density, previously negative biopsy (and other factors)**

Conclusions

- Thoughtful prostate cancer screening in men who choose to be screened is possible and leads to significant decreases in mortality
- There are many clinical opportunities to optimize screening, diagnosis, and management but they are not used as frequently as they should
- Active surveillance is a standard of care and should be discussed with every man diagnosed with early-stage prostate prostate cancer