Prostate Cancer-

Screening and beyond: disparities, therapy, medical malpractice avoidance and advances

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Core Updates and Essentials in Primary Care

9 November 2024

Learning Objectives

- Review national recommendations on PSA based screening for prostate cancer and changing strategies for screening
- Discuss the expanding biomarkers (including MRI) landscape
- Review strategies to avoid being named in a PSA-based malpractice suit
- Discuss racial disparities in Black men with prostate cancer
- Appreciate the differing states of prostate cancer and how that affects overall management of prostate cancer- directly related to your practice

Prostate Cancer Factoids

(by the numbers)

- 13% – lifetime risk of being diagnosed
- 2.5% - lifetime risk of prostate cancer death
- 80 – median age of death from prostate cancer

► For the same patient with prostate cancer, the options range from

Radical Treatment_____No Treatment

so how can we decide?

▼

Now– Should testing that led to the prostate cancer Dx even be offered?

Framing the Problem

- We screen **older men** who are **unlikely to die** from a screen detected cancer
- We practice **widespread overtreatment** of low risk disease
- **Surgical complications** are proportional to skill and volume of surgeon, yet most surgeons perform three or fewer prostatectomies per year. (Vickers cancer letter interview 10/10/14
- **Cost to prevent one death** from prostate cancer with PSA screening=$5.2 million

The Gleason Score – Grade Groups

- Two Numbers, each 1 to 5 (most and second most common)
- Based upon Biopsy
  - Gleason 1 = looks like normal prostate tissue
  - Gleason 5 = aggressive looking cancer
- Most cancers are 3+3 **(GG1)** or 3+4 **(GG2)**
- More aggressive cancers are 4+3 **(GG3);** 4+4 **(GG4);** 4+5 or 5+5 **(GG5)**

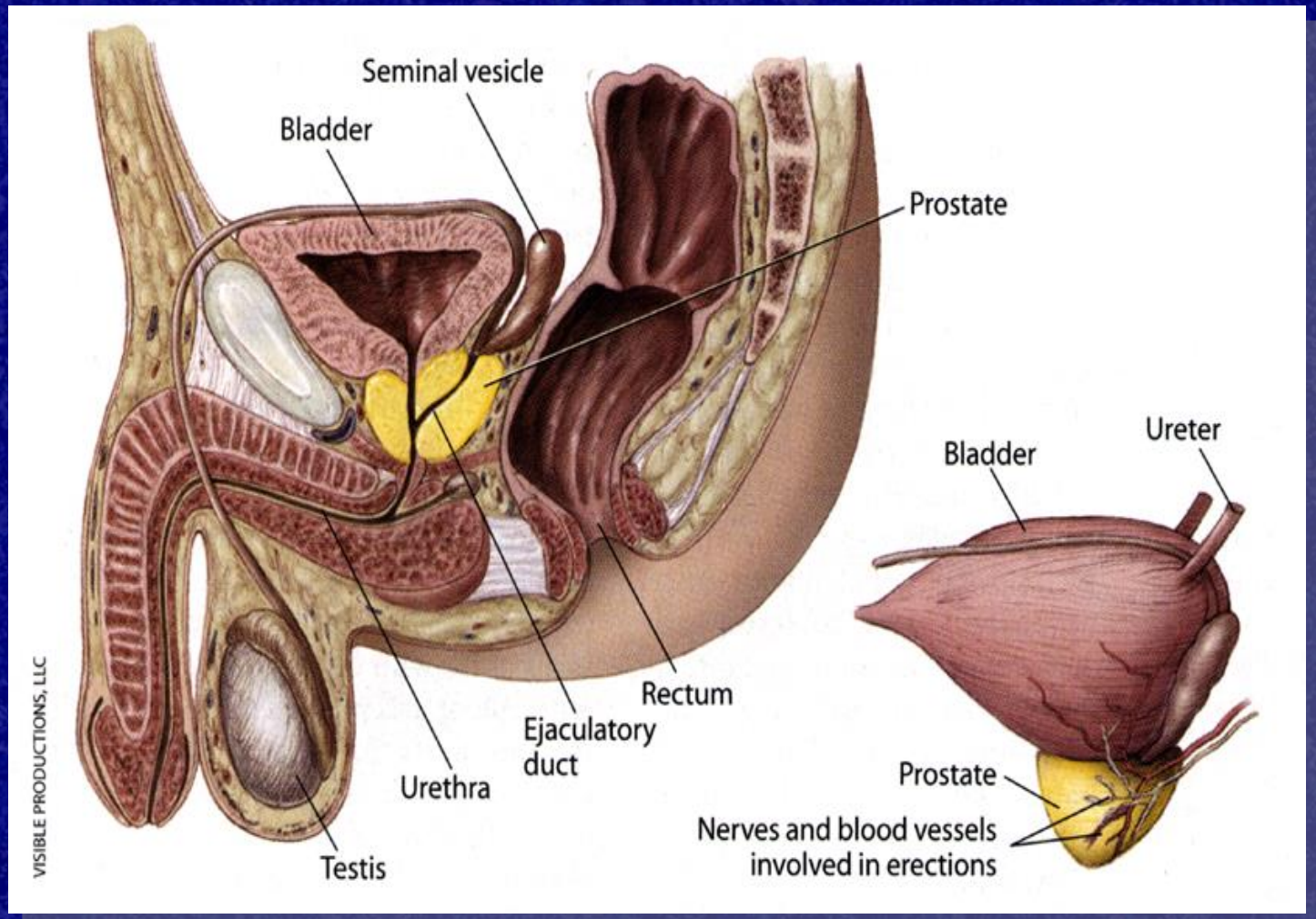
To DRE or not to DRE?

- ► Most controversial topic I face in this lecture with primary clinicians
- DRE also assesses rectal wall and anal area
- Can't assess prostate cT stage without it
- Only study that showed survival advantage for RP used DRE for clinical diagnosis
- There is no "textbook" unambiguous answer

▶ The cT Stage (clinical)

- T 1 cancers – non palpable – elevated PSA – most common T1c
- T2a – nodule in ½ of one lobe
- T2b – nodule in > ½ of one lobe
- T2c – abnormality in both R and L lobes
- T3 – disease clinically o/s capsule or in Seminal Vesicle

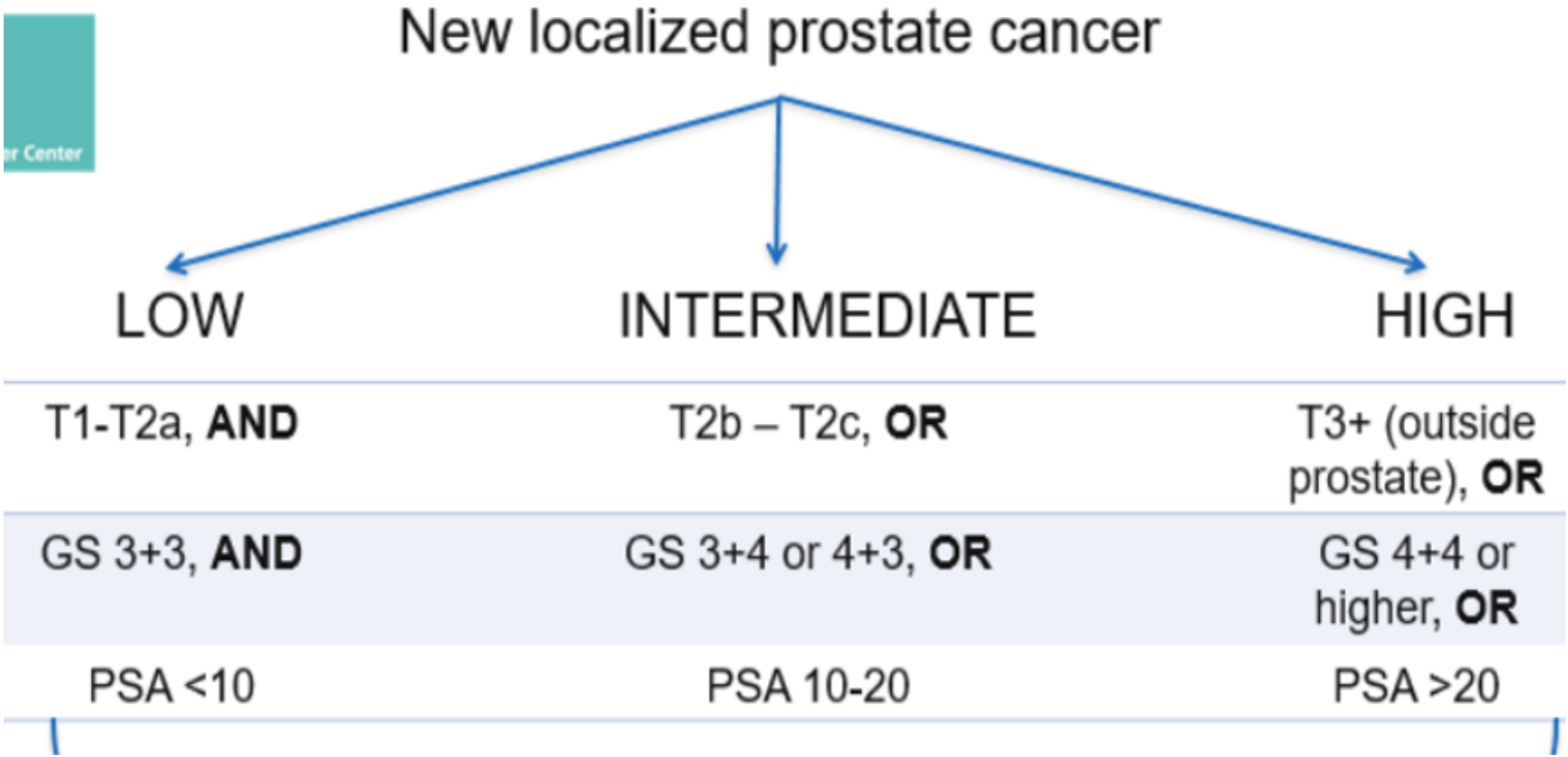
Prostate Anatomy - Understanding Complications



Scientific American 279: 74 '98

Localized Prostate Cancer Risk Categorization

(Necessary for doing a DRE)



► The Screening Controversies

What is your role

in primary care? (especially now with new guidelines)

Know five key studies * (now with 15 year updates)

- ERSPC: no survival benefit (OS); small ca specific survival advantage(CSS)
- PLCO: no OS or CSS benefit
- PIVOT: overall, no survival benefit but possible advantage for higher risk subset; low grade did worse
- ProtecT*: screen, randomize: RP,RT,AM no differences in OS CSS; mets differed
- UK CAP*: one time PSA screen: negative

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

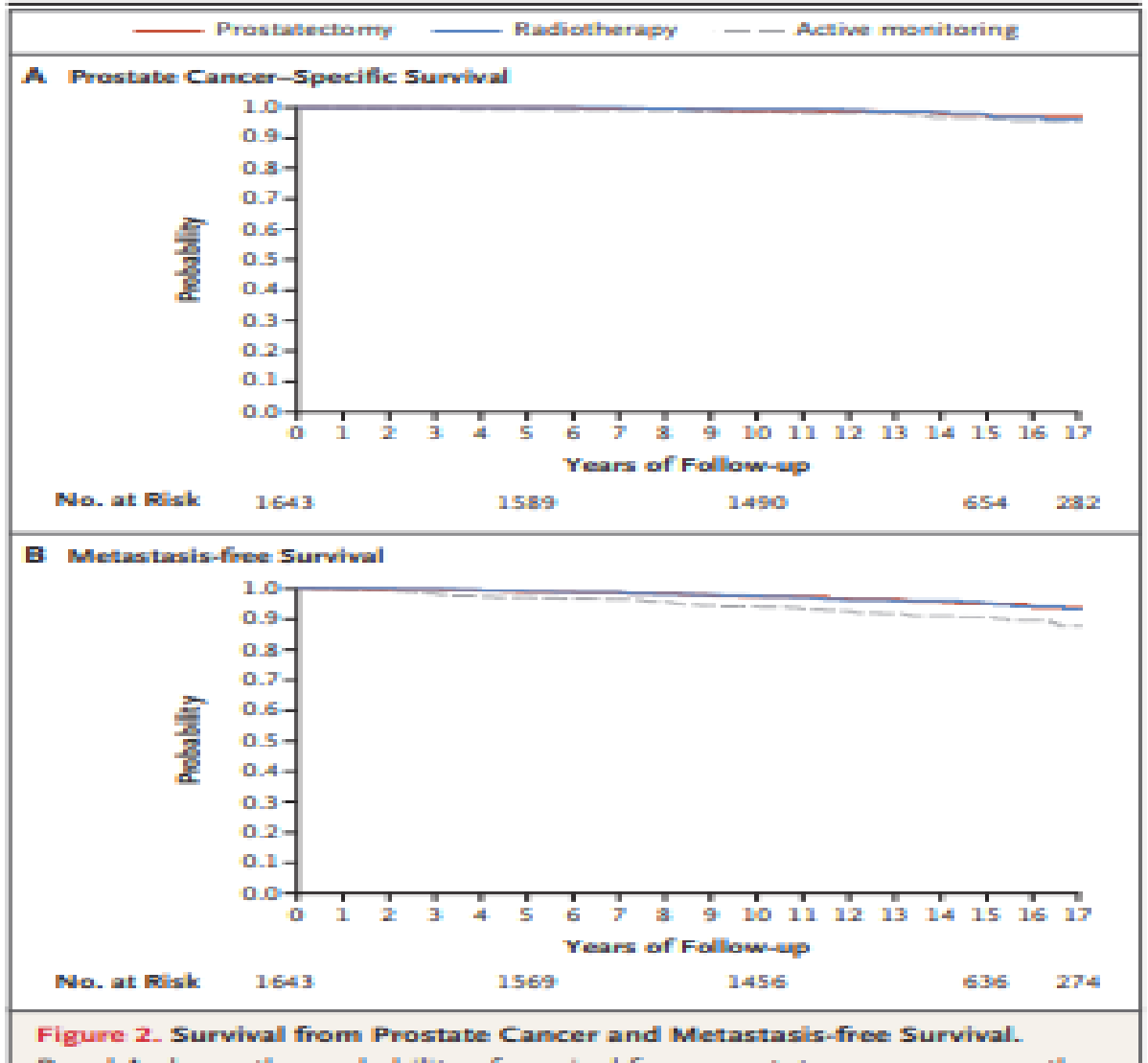


Figure 2. Survival from Prostate Cancer and Metastasis-free Survival.

- Exploratory Analyses The higher incidence of metastatic disease in the active-monitoring group at 10 years was anticipated to have an effect on prostate cancer–specific mortality at 15 years, but this was not the case. Among the 40 men in whom metastatic disease had been diagnosed at 10 years, the risk of death from prostate cancer was lower among those in the active monitoring group (3 of 22 [13.6%]) than in either the prostatectomy group (2 of 8 [25.0%]) or the radiotherapy group (7 of 10 [70.0%])

Concept of Active Surveillance- *Important for Clinicians*

- Diagnosis of prostate cancer made
- Risk stratification for TREATMENT DECISION
- Periodic biopsies/ **Multiparametric MRI**
- Treat if certain characteristics evolve
- Change in Gleason, extent of cancer, PSA doubling time, physical exam or symptoms, others
- A main reason for a change in USPSTF recommendation

Summary of Recommendations and Evidence – finalized *JAMA*. 2018;319(18):1901-1913.

…The **USPSTF** recommends that clinicians inform **men ages 55 to 69** years about the **potential benefits and harms**

The **USPSTF** recommends individualized decision making **after discussion** **with a clinician**, so that each man has an opportunity to understand the potential benefits and harms of screening and to incorporate **his values and preferences into his decision.**

►►”C” recommendation 55-69

►►”D” recommendation ≥ 70

What are the benefits?

In men aged 55 to 69 years, may prevent approximately 1.3 deaths from prostate cancer over approximately 13 years per 1000 men screened.

Screening may prevent approximately 3 cases of metastatic prostate cancer per 1000 men screened.

What are the harms?

- Harms include erectile dysfunction, urinary incontinence, and bowel symptoms.
- About 1 in 5 men who undergo radical prostatectomy develop long-term urinary incontinence
- 2 in 3 men will experience long-term erectile dysfunction.
- Harms of screening in men > 70 are at least moderate and greater than in younger men

Know other guidelines

- *Canadian Task Force on Preventive Health Care, AAFP – NO*
- *ACP, AUA shared with patient preference; 10-15 yr life expectancy*
- *ACS* - shared decision, discussion at age 50 years and earlier for AA men and men with a father or brother with a history of prostate cancer before age 65 years.

- **Every two or more years ****

►What to do in practice 2024

- **Document** **your discussion points (harms and benefits)**
- **Shared Decision with patient choice**
- **??Shared Decision with your recommendation**
- Clinicians should not screen men who do not express a preference for screening.

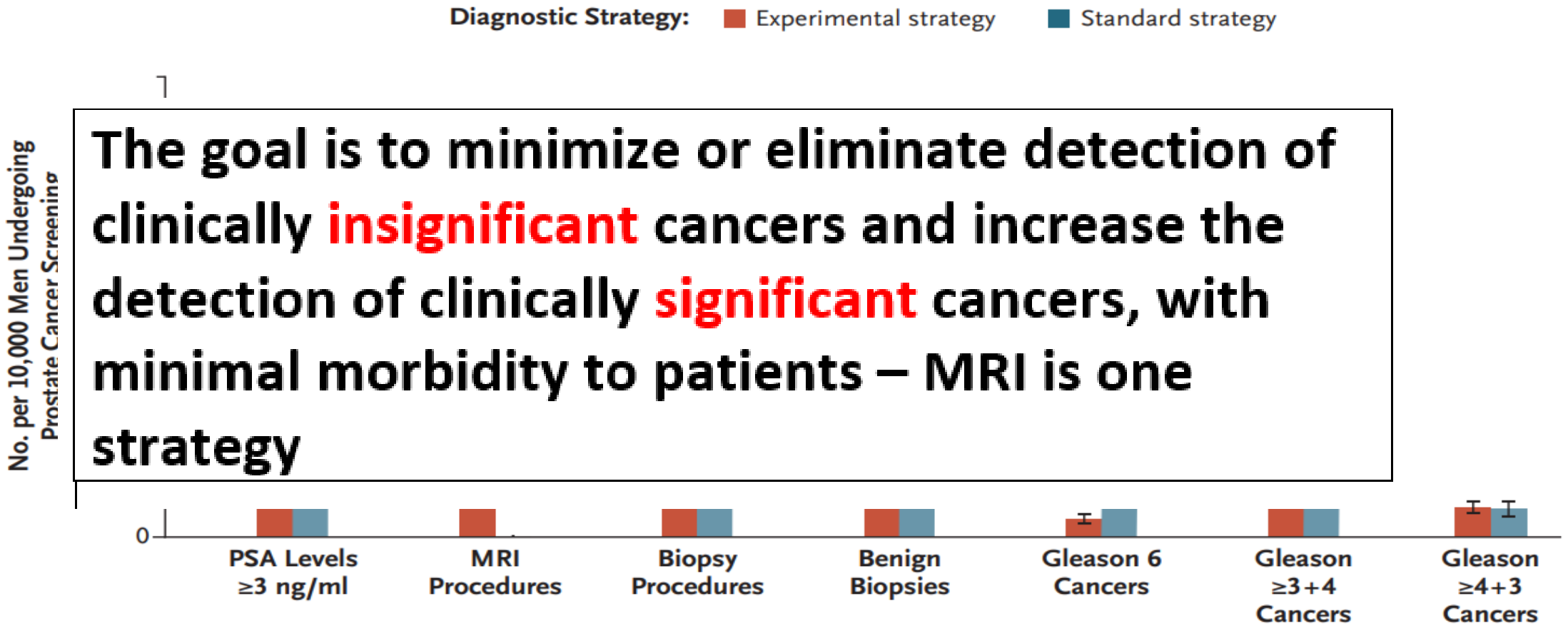
Prostate Cancer: Screening

An Update for This Topic is In Progress

LAST UPDATED: Dec 21, 2023

Optimal use of MRI for screening (Eklund

neim. DOI: 1056:2100852)



The goal is to minimize or eliminate detection of clinically insignificant cancers and increase the detection of clinically significant cancers, with minimal morbidity to patients – MRI is one strategy

	PSA Levels ≥3 ng/ml	MRI Procedures	Biopsy Procedures	Benign Biopsies	Gleason 6 Cancers	Gleason ≥3+4 Cancers	Gleason ≥4+3 Cancers
Experimental Strategy — no.	1221	1112	444	138	54	252	88
Standard Strategy — no.	1175	2	853	504	142	206	84
Absolute Difference	0.5	—	−4.1	−3.7	−0.9	0.5	0.0

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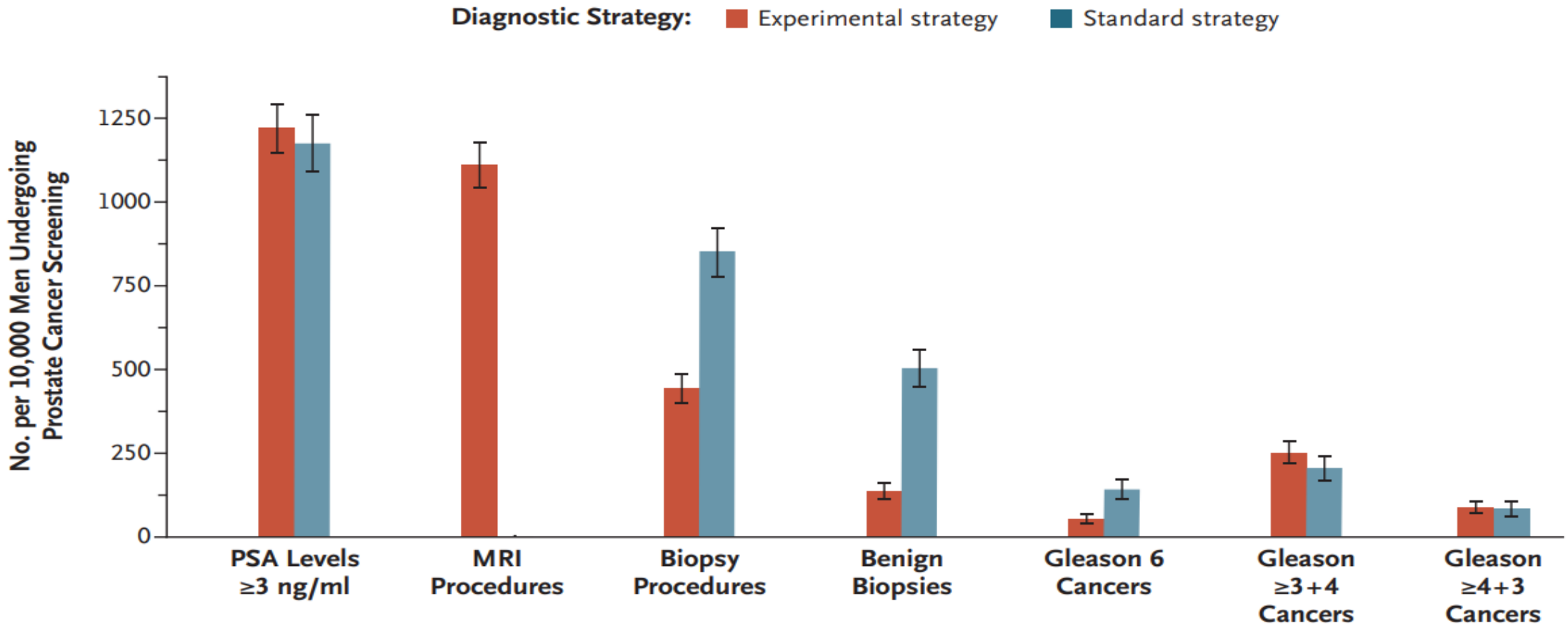

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Follow Up- Optimal use of MRI for screening

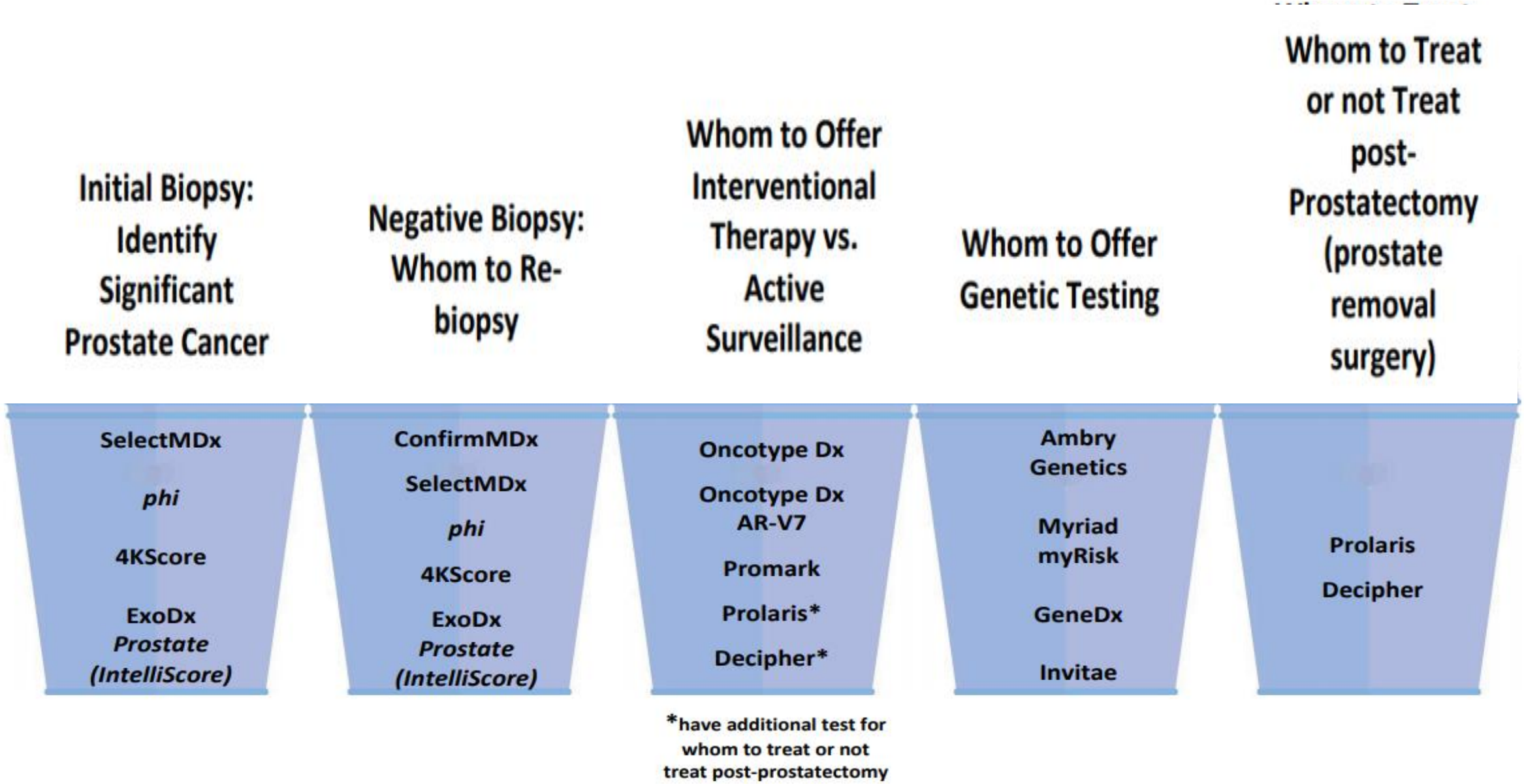
(Hugosson J etal: NEJM 2024:391:1083-95)

- Strategy: MRI negative- no biopsy, now with 4 years of f/u
- 59% less need for PNBx; increased to 75% with >1 screening
- 51% decrease in clinically insignificant cancers
- Low likelihood of missing incurable cancer with this strategy
- ►*"…firm support for changing the current algorithm to perform biopsy only when suspicious lesions are seen on MRI…"*

What to do in practice – emerging strategies

- Shared decision – decision made about PSA test
  - Yes - if elevated, general referral to urology
  - *No – Undecided – may need some expanded information*
    - If elevated, may not necessarily require biopsy
    - Expanding role of MRI and then biopsy decision
    - Expanding role of transperineal vs transrectal biopsy techniques and ID results
    - Goal - identify clinically significant cancers and not the clinically insignificant ones

PCMs


Initial Biopsy: Identify Significant Prostate Cancer
Negative Biopsy: Whom to Re-biopsy
Whom to Offer Interventional Therapy vs. Active Surveillance
Whom to Offer Genetic Testing
Whom to Treat or not Treat post-Prostatectomy (prostate removal surgery)
SelectMDx
phi
4KScore
ExoDx Prostate (IntelliScore)
ConfirmMDx
SelectMDx
phi
4KScore
ExoDx Prostate (IntelliScore)
Oncotype Dx
Oncotype Dx AR-V7
Promark
Prolaris*
Decipher*
Ambry Genetics
Myriad myRisk
GeneDx
Invitae
Prolaris
Decipher
*have additional test for whom to treat or not treat post-prostatectomy

Considerations for Primary Care

minimizing risks in primary practice

Considerations for primary care

- Prostate on PE
  - Normal
  - Symmetrically enlarged
  - Abnormal (asymmetry) > REFER
- Know about changes in PSA on 5ARIs (incl 1mg Propecia dose)
- Do not recommend empiric ABx
- Establish plan of follow up, including those with negative biopsies
- Be cognizant about recommendations for Testosterone Replacement Rx

► Liability Issues

- PSA issues are a leading cause of cancer malpractice claims … and getting worse
- **PSA velocity and PSA post RP** becoming a common malpractice issue
- Physicians, NPs and Institutions all named as defendants
- **Prostate 18***>lung 9>breast 6>colo-rectal 5
- **(#cases over past 7 years)*

Categories of PSA allegations >> Med Mal

Issue leading to allegation	Allegation of harm
Not getting a PSA or not having a discussion when patient turned 50	Prostate cancer worse as a result of not having baseline PSA; initial PSA elevated
Not getting a PSA after USPSTF Guidelines in 2012	Physician was monitoring PSA; why was it stopped?
PSA Velocity	Referral to urologist should have been made even though PSA was “normal”
“Mistaken” PSA elevation attributed to BPH	Elevated PSA was misdiagnosed and convincing evidence of BPH not in medical record
PSA level “normal” after radical prostatectomy	Any detectable PSA value post RP needs evaluation and not timely doing so led to harm
Delay in fully evaluating back pain or other symptomatology	Symptoms eventually found secondary to Pr Ca worsened during delay
Not getting free PSA % when PSA is 4-10	Free PSA (free/total) ≤ 15% more suggestive of cancer

More Vulnerabilities on the way

- NEJM Guideline Watch for Prostate Cancer Screenings in Black Men **Key Recommendations after shared decision**

- **Prostate-specific antigen (PSA) testing is considered the front-line screening method; some clinicians**
  - **may opt to add a digital rectal exam.**
- **Screening should begin with a baseline PSA test between ages 40 and 45. Depending on health status,**
- **yearly PSA testing should be considered.**
- **• Individuals who have a family history of prostate cancer or high-risk genetic variants should consider**
- **starting screening at age 40.**

Minority population considerations

Screening considerations in African American men –*will address momentarily*

European Association of Urology

Review – Prostate Cancer – Editor's Choice

Prostate-Specific Antigen Screening in Transgender Patients

Conclusions: We are in the infancy of our understanding of PSA screening in TW. Important avenues for future research include understanding the risks/benefits of PSA screening in TW, how best to mitigate potential negative psychological effects of PSA screening in TW, establishing baseline PSA values for those on GAHT (and determining what values should be considered "elevated"), establishing when to initiate PSA screening for those on GAHT, and establishing the accuracy of biomarkers for those undergoing GAHT.

Transgender Females (JAMA:2023:329:1877-1879- VA data, n=155)

Castration resistant disease at outset/ (estrogen importance and High Gleason)

PSA >1

More ADT and Radiation Resistant

Mediators of Racial Disparities in Prostate Cancer

Topic	Citations
Black patients less likely to get prostate MRI (6.3 v 9.9%)	**JAMA Oncology**
Bla	
Inst	
Cult professional evaluations	
Prostate cancer basic knowledge is low among Black patients in terms of signs of disease, PSA testing, screening knowledge, and may misperceive severity of disease leading to decisions to not pursue treatment	
Multiple others	

Review Article

Racial disparities in Black men with prostate cancer: A literature review

James W. Lillard, Jr, PhD, MBA[1]; Kelvin A. Moses, MD, PhD [2]; Brandon A. Mahal, MD[3]; and Daniel J. George, MD [4]

Mediators of Racial Disparities in Prostate Cancer

Topic

Black patients less likely to get prostate MRI (6.3 v 9.9%)
Black patients are underrepresented in clinical trials
Institutional Racism accounts for these multifaceted disparities
Cultural Mistrust of healthcare leads to lesser likelihood to seek professional evaluations
Prostate cancer basic knowledge is low among Black patients in terms of signs of disease, PSA testing, screening knowledge, and may misperceive severity of disease leading to decisions to not pursue treatment
Multiple others

A few comments about 5 ARIs

(inhibit conversion of T >> DHT)

(and other common components of your practice)

finasteride [bph (5mg) and hair restoration(1mg)] & dutasteride

5-ARI and PSA Considerations – double the PSA

- **High concern for having prostate cancer if PSA does not decrease by 50% on 5 ARIs**
  - (any ↑on F: 3x risk; 6x HG PrCa)
- Sexual Dysfunction on 5 ARIs
- How to advise patients on 5 ARIs for BPH?
- ►►Need to weigh benefits of 5 ARIs on acute urinary retention and surgical interventions to side effect risk and changes in prostate cancer

Changing nomenclature for advanced prostate cancer

State / Stage
Localized and **regionally advanced**
Metastatic prostate cancer
Oligometastatic disease
►*The continuum between local/regional and metastatic*

Why is Oligometastatic Prostate Cancer so Important?

Enabled by newer diagnostic PSMA scans (F 18-Pylarify and others)

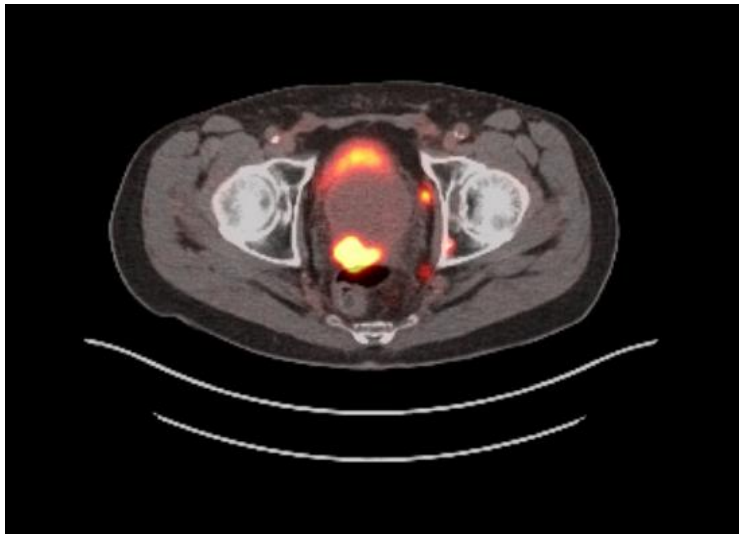
Conventional staging understages many patients (small deposits of metastases are not picked up) leading to misaligned treatments --- "oligometastasis"

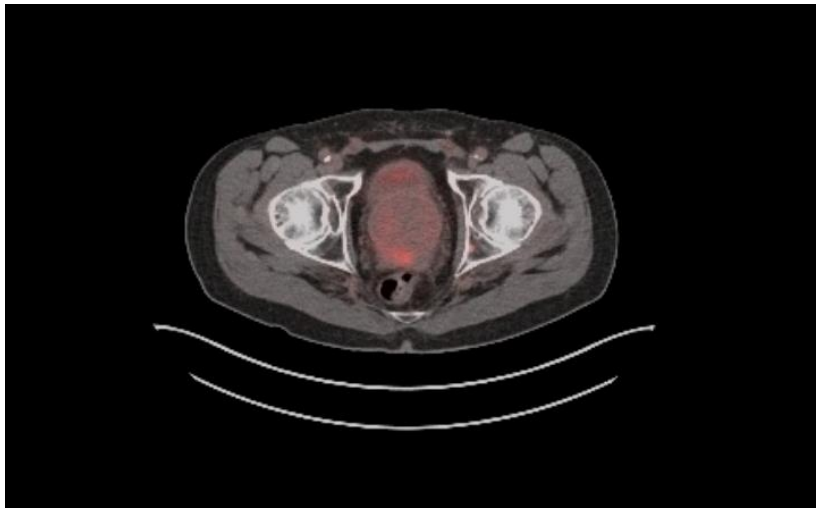
More accurate staging of oligomets can completely alter treatment strategies – can possibly be cured!!

Use of multimodalilty treatments (RT-site directed (MDT)+/- systemic therapies

>>PSMA + scan authorizes use of Lutetium 177 in advanced disease

PSMA PET-CT





6/4/24 PSMA PET:
1. Similar marked prostatomegaly with increasing PSMA uptake in the peripheral zone compatible with disease progression.
2. Worsening size and PSMA avidity of retroperitoneal and pelvic lymphadenopathy.
3. Increased size and FDG avidity of sclerotic lesion involving the left acetabulum.
4. No evidence of abnormal PSMA uptake in the chest.

ABDOMEN/PELVIS: Prostatomegaly with decreased avidity along its posterior aspect, **SUV max 6 (previously 76)** (PET 264)
Decreased size and avidity of previously described bulky retroperitoneal and bilateral pelvic lymphadenopathy, representative nodes including:
*Left para-aortic, SUV max 1.5 (previously 21) (PET 211)
*Left iliac bifurcation, SUV max 3.4 (previously 22) (PET 246)
*Right iliac bifurcation, SUV max 1.8 (previously 3.8) (PET 250)
MUSCULOSKELETAL: **Decreased avidity of a posterior left acetabular sclerotic metastasis**, SUV max 3.1 (previously 13) (PET 264).

Pharmacology of Novel Agents of Importance for Primary Clinicians

- Focus on Abiraterone

Part of intensified androgen deprivation treatments

Adrenal Steroid Synthesis Pathways

Abi inhibits 17αOH and 17,20 lyase

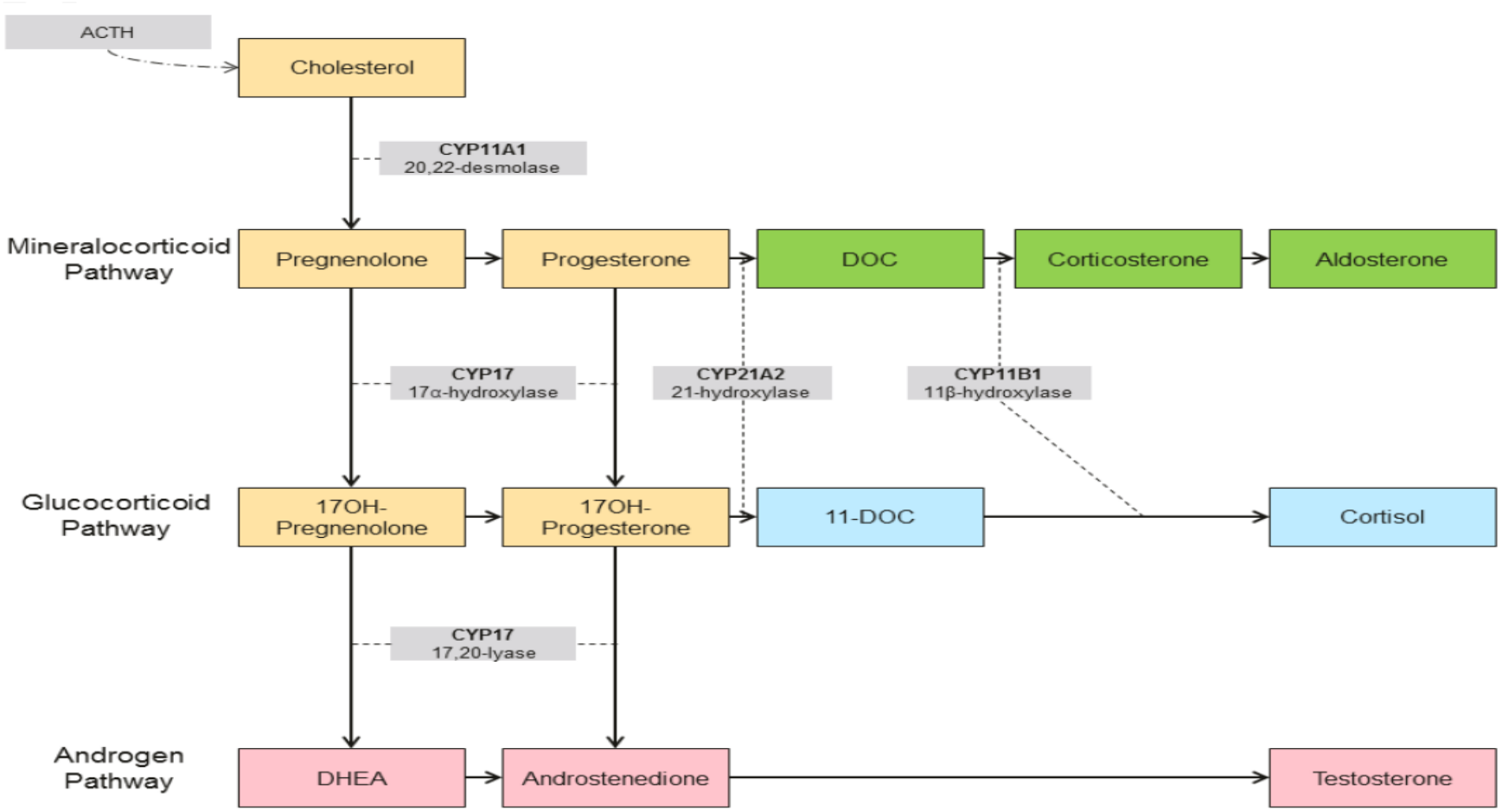


Figure A: The Three Major Pathways of Adrenal Steroid Production

Metabolic consequences of Abiraterone + prednisone/steroid *are all physicians adhering to these guidelines???*

- Fluid retention – already adds to weight gain of ADT
  - Do you weigh patients in your practice?
- Hypertension – sometimes severe requiring change in bp meds
  - Do you routinely check blood pressure in your practice?
- Hypokalemia - can be severe and pro-arrhythmic
  - Do you routinely check electrolytes and potassium levels in your practice?
- Stress- remember to increase steroid doses when stressful situations intervene

Next Steps

- Consider having simple sheet outlining benefits and harms of PSA testing – consider expansion of information transferred
- Understand that more patients pursue active surveillance
- Appreciate the significant disparities in prostate cancer care
- Avoid pitfalls that can lead to a malpractice claim
- Become knowledgeable about the many different prostate cancer “states” and potential new diagnostic scans your patients will be receiving
- Appreciate pharmacologic effects of novel androgen targeting agents and targeted therapies

A Sobering Final Word

JAMA Internal Medicine | Original Investigation

Estimated Lifetime Gained With Cancer Screening Tests
A Meta-Analysis of Randomized Clinical Trials

Michael Bretthauer, MD, PhD; Paulina Wieszczy, MSc, PhD; Magnus Løberg, MD, PhD; Michal F. Kaminski, MD, PhD; Tarjei Fiskergård Werner, MSc; Lise M. Helsingen, MD, PhD; Yuichi Mori, MD, PhD; Øyvind Holme, MD, PhD; Hans-Olov Adami, MD, PhD; Mette Kalager, MD, PhD

RESULTS In total, 2 111 958 individuals enrolled in randomized clinical trials comparing screening with no screening using 6 different tests were eligible. Median follow-up was 10

CONCLUSIONS AND RELEVANCE The findings of this meta-analysis suggest that current evidence does not substantiate the claim that common cancer screening tests save lives by extending lifetime, except possibly for colorectal cancer screening with sigmoidoscopy.

JAMA Intern Med. doi:10.1001/jamainternmed.2023.3798
Published online August 28, 2023.

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