



# Rise and Fall of PSA: and other pearls and pitfalls

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# Overview

**01** Epidemiology

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**02** Anatomy and Physiology

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**03** Screening

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**04** Staging

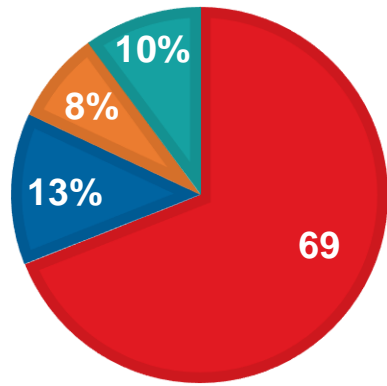
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# Epidemiology

## Incidence and Survival Data, All Ages, SEER 22 Data, 2013-2019

### Stage Distribution

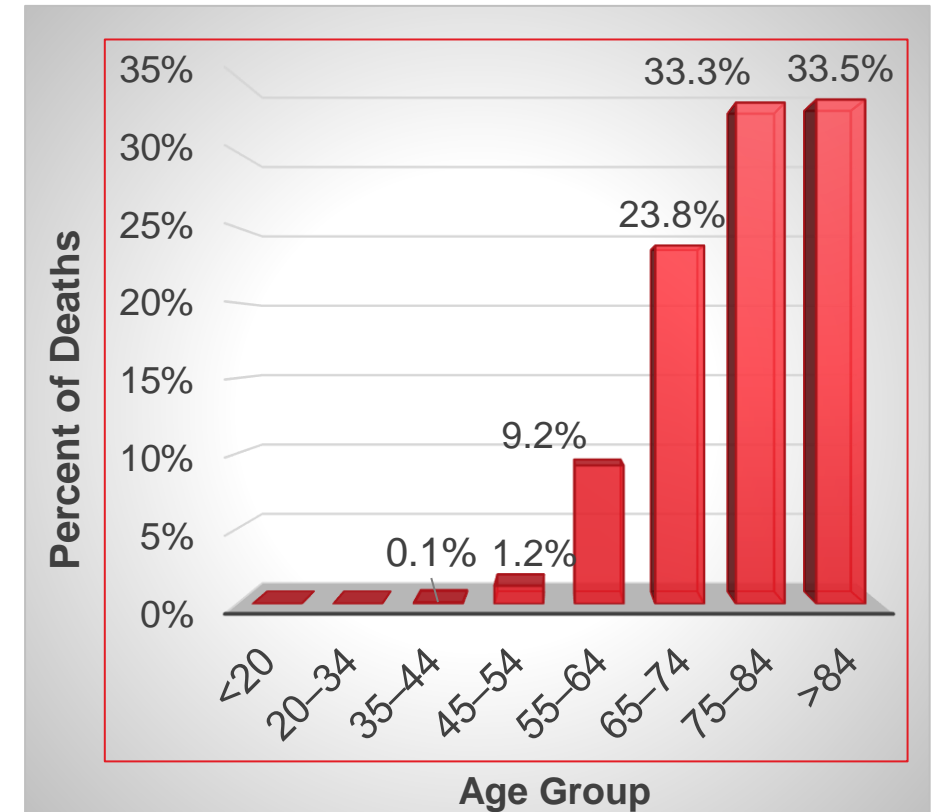


- Localized
- Regional
- Distant
- Unstaged

### 5-year relative survival

SEER Stage	5-year Relative Survival
Combined	97.1%
Localized	100%
Regional	100%
Distant	34.1%

### Percent of Death by Age Group



<https://seer.cancer.gov/statfacts/html/prost.html>

# Risk Factors

## Nonmodifiable

- Age
- Family History RR 2
  - Brother stronger risk than father
- Race
  - African Americans increased incidence and mortality compared to European Americans
- Geographic location
- BRCA 2 mutations
- Hereditary non–polyposis cancer syndrome

## Modifiable

- Smoking: increase risk of death

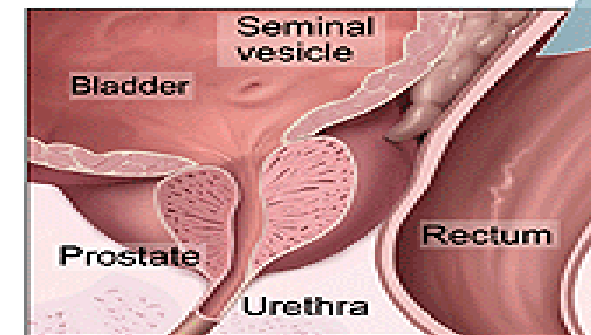
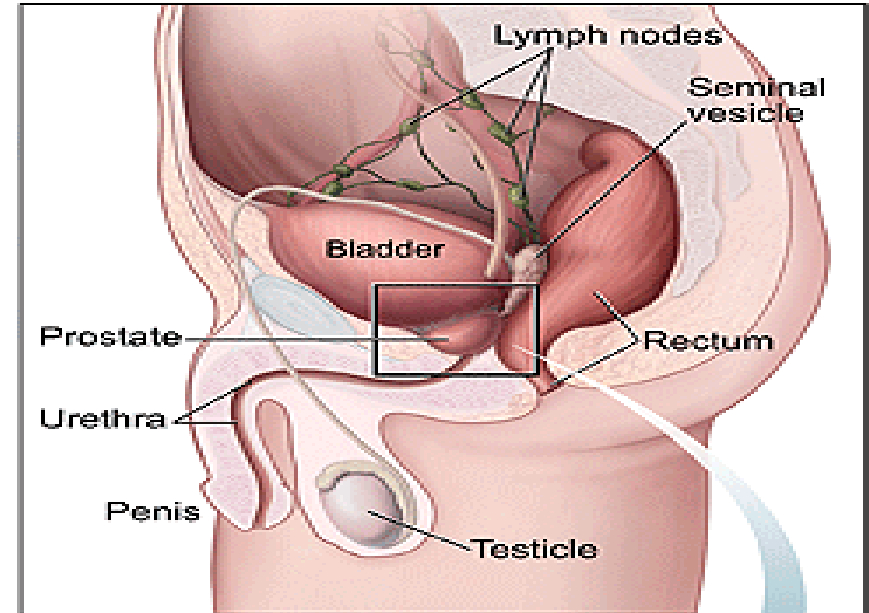
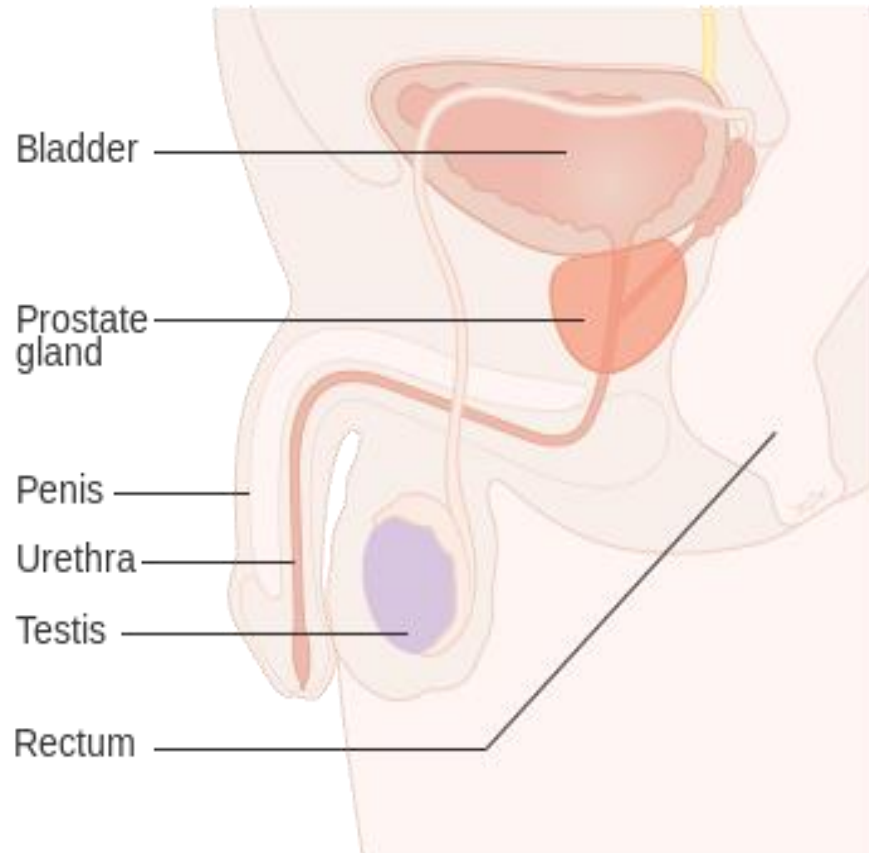
PSA Cancer Screening: A Case for Shared Decision-Making.” *MDedge Family Medicine* 69, no. 1 (January 1, 2020). <https://www.mdedge.com/familymedicine/article/216302/oncology/psa-cancer-screening-case-shared-decision-making>  
Gansler, Ted, Roma Shah, Ying Wang, Victoria L. Stevens, Baiyu Yang, Christina C. Newton, Susan M. Gapstur, and Eric J. Jacobs. “Smoking and Prostate Cancer-Specific Mortality after Diagnosis in a Large Prospective Cohort.” *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 27, no. 6 (2018): 665–72. <https://doi.org/10.1158/1055-9965.EPI-17-0890>.



# Anatomy and Physiology

**RGA**

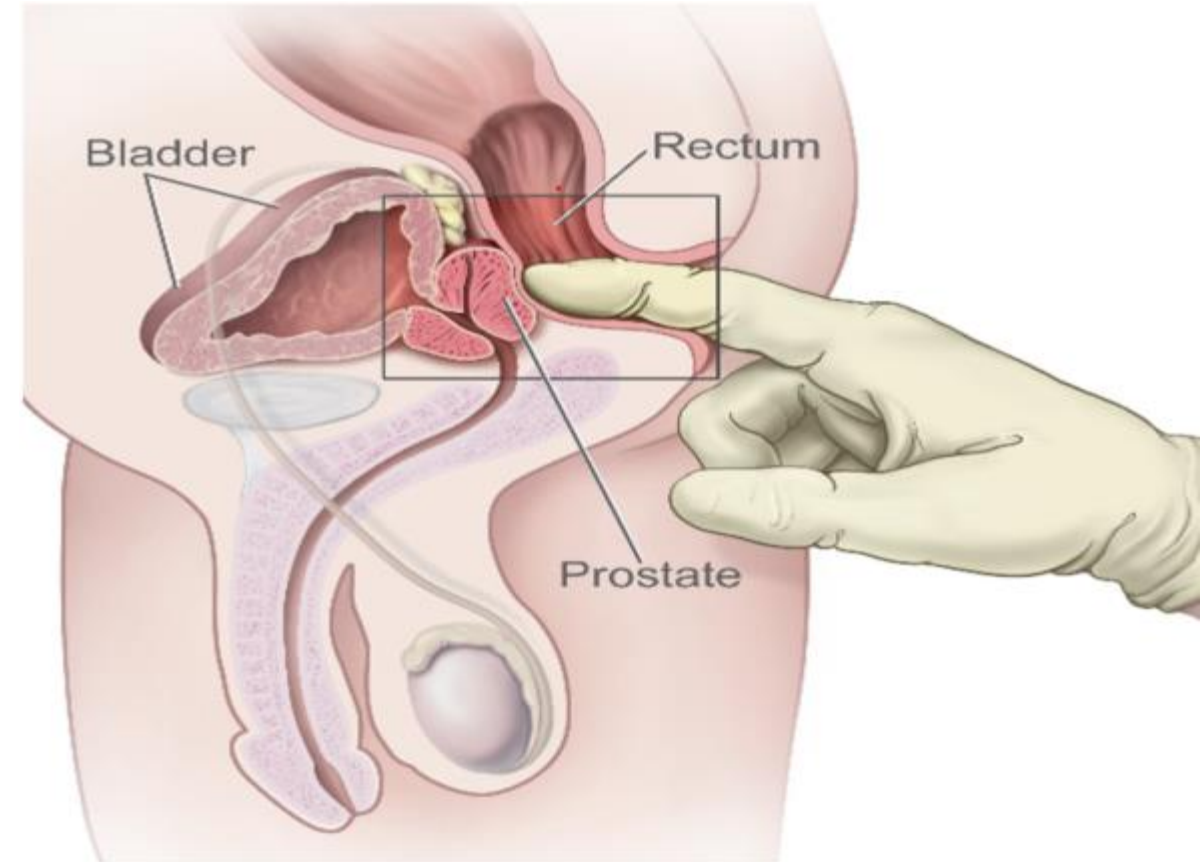
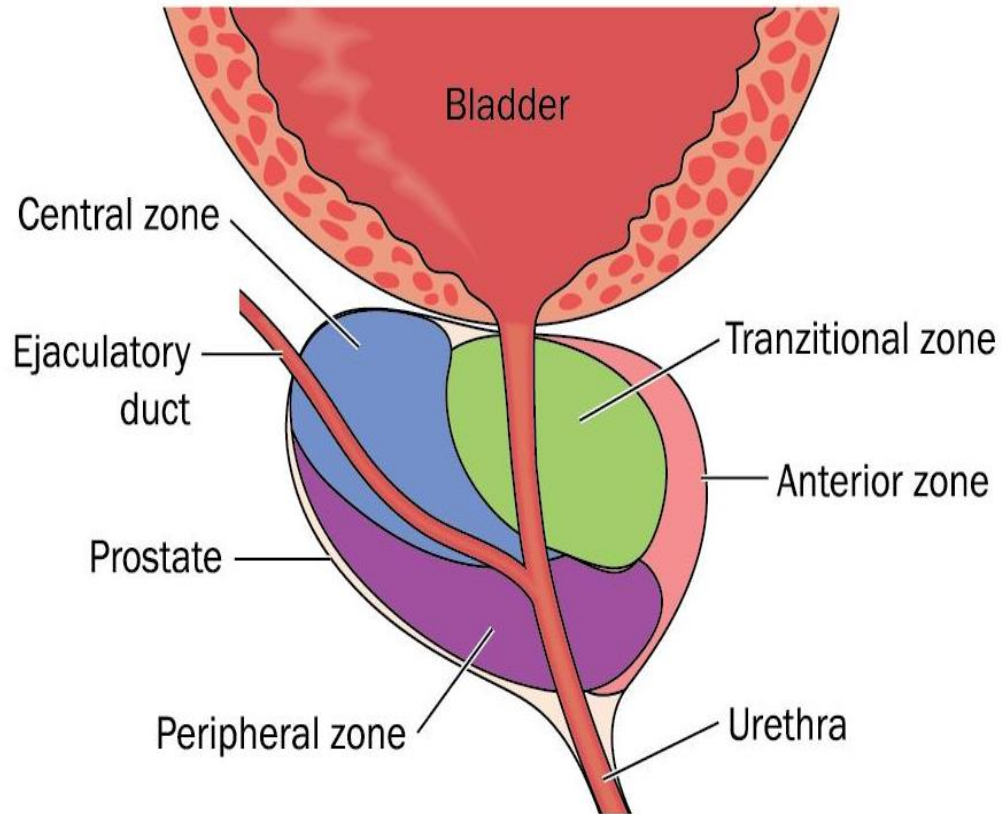
# Prostate Anatomy and Physiology



National Cancer Institute

[https://commons.wikimedia.org/wiki/File:Diagram\\_showing\\_the\\_position\\_of\\_the\\_prostate\\_and\\_rectum\\_CRUK\\_358.svg](https://commons.wikimedia.org/wiki/File:Diagram_showing_the_position_of_the_prostate_and_rectum_CRUK_358.svg)  
<https://visualsonline.cancer.gov/details.cfm?imageid=4280>

# Anatomy and the Digital Rectal Examination (DRE)



[https://commons.wikimedia.org/wiki/File:Digital\\_rectal\\_exam\\_\(male\).jpg](https://commons.wikimedia.org/wiki/File:Digital_rectal_exam_(male).jpg)

<https://mdedge-files-live.s3.us-east-2.amazonaws.com/files/s3fs-public/Document/September-2018/CR02810024.PDF>

Image from Shutterstock



# Screening

**RGA**



# Case 1

- 63-year-old, male, NS, 500K
- PCP visit for insurance: DRE hard nodule left lobe noted, prostate not enlarged
- Fhx: Father – prostate cancer in 60s
- PSA 3.4

# Prostate Screening and Testing

- Screening
  - Prostate-specific antigen (PSA ) test
  - Digital rectal exam (DRE)
  - Transrectal ultrasound (TRUS)
  - MRI
- Biopsy
  - Transrectal ultrasound (TRUS) biopsy
  - MRI guided biopsy
  - Fusion biopsy

# PSA: Primary Screening Test

## Increase PSA

- Benign Prostatic Hypertrophy (BPH)
- Prostatitis with or without active infection
- Perineal trauma (DRE/prostatic massage/bicycling)
- Sexual activity

## Decrease PSA

- Obesity (diluent)
- Medications
  - 5-alpha reductase inhibitors
  - NSAIDS
  - Statins
  - Thiazides
  - Metformin

# PSA as a Screen

Conventional ranges used to help determine need for biopsy

<4.0 ng/mL

**Most men without prostate cancer will have PSA levels under this level.**

- Not a guarantee that a man doesn't have cancer

4.0 to 10.0 ng/mL

**Gray/borderline zone.**

- 1 in 3 chances of prostate cancer

>10.0 ng/mL

**Chance of prostate cancer is over 50%**

**Pearl: Trends are important. No absolute cutoffs.**

# Age adjusted PSA values

Improves sensitivity in younger men and specificity in older men

- Age 40-49 = 2.5
- Age 50-59 = 3.5
- Age 60-69 = 4.5
- Age 70-79 = 6.5

# Secondary Tests: PSA Kinetics

Improve upon low operating characteristics of total PSA

## PSA Density

- Bigger the volume of tissue, the more PSA you would produce
- Normal prostate volume is 20 – 30 mL
- Take the **PSA/prostate volume via US or MRI**
- **>0.15 ng/mL/cc** would be more PSA than expected for the tissue volume

## PSA Velocity

- Subtract the two values and divide by the timeframe
- how quick the rise of PSA level is  
**>0.75 ng/mL/year**

## Free/total PSA ratio (useful in grey range)

- Percentage free PSA is lower in serum of men with prostate cancer
- Clinically <10% more likely to be prostate cancer and less likely at >25%

"PSA Velocity and Doubling Time in Diagnosis and Prognosis of Prostate Cancer." Accessed August 30, 2020. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3375697/>.; Javaeed, Arslaan, Sanniya Khan Ghauri, Abdellatif Ibrahim, and Mohamed Fahmy Doheim. "Prostate-Specific Antigen Velocity in Diagnosis and Prognosis of Prostate Cancer - a Systematic Review." *Oncology Reviews* 14, no. 1 (April 30, 2020). <https://doi.org/10.4081/oncol.2020.449>.

# Digital Rectal Exam

Where does this fit in?

- Peripheral zone closest to the rectum
- “Nodule, lump, asymmetry”
- AUA acknowledges that DRE *alone* as a screening test is not the best
- Adjunct to PSA (and used in staging)
- BPH: enlarged or firmness on DRE



- **“One touch, one dribble”**
- **“Rectal touch”**
- **Brazil public health campaign!**

Image from PublicDomainPictures.net

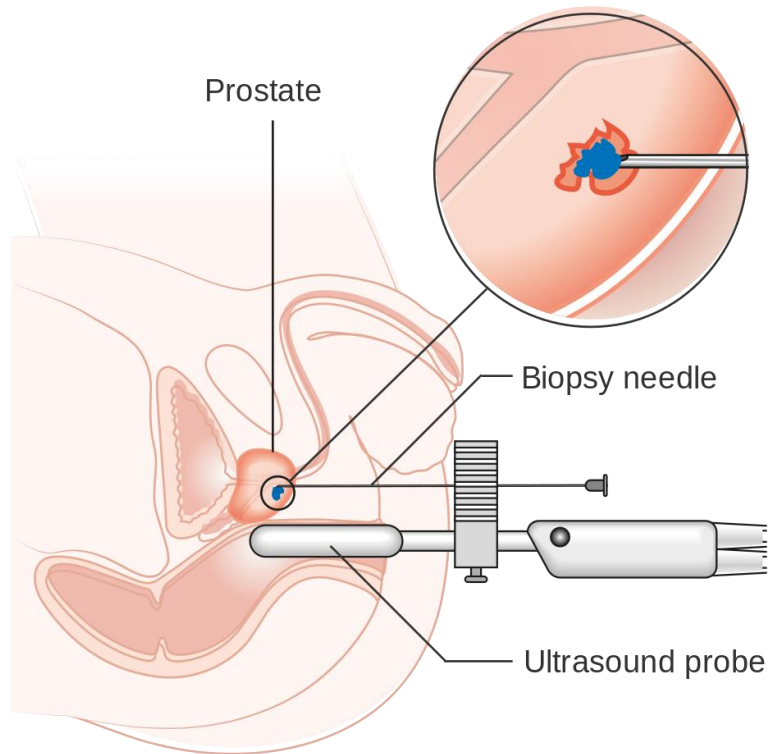
# Case 1

- 63-year-old, male, NS, 500K
- PCP visit for insurance: DRE hard nodule left lobe noted, prostate not enlarged
- Fhx: Father – prostate cancer in 60s
- PSA 3.4
- “Given normal PSA less likely to be malignant”
- No referral to urology

**Pitfall: Do not ignore an abnormal DRE just because the PSA level < 4.0.**



# Transrectal Ultrasound Biopsy (TRUS)



## TRUS

- Relatively blind
- Systematic approach
- Sampling error false negative in 20-50% for csPca in a first biopsy

**Pitfall: TRUS has a false negative rate. Correlate with the rest of the clinical picture.**

Cancer Research UK: [https://commons.wikimedia.org/wiki/File:Diagram\\_showing\\_a\\_transperineal\\_prostate\\_biopsy\\_CRUK\\_473.svg](https://commons.wikimedia.org/wiki/File:Diagram_showing_a_transperineal_prostate_biopsy_CRUK_473.svg)

Wu RC, Lebastchi AH, Hadaschik BA, Emberton M, Moore C, Laguna P, Fütterer JJ, George AK. Role of MRI for the detection of prostate cancer. World J Urol. 2021 Mar;39(3):637-649. doi: 10.1007/s00345-020-03530-3. Epub 2021 Jan 4. PMID: 33394091



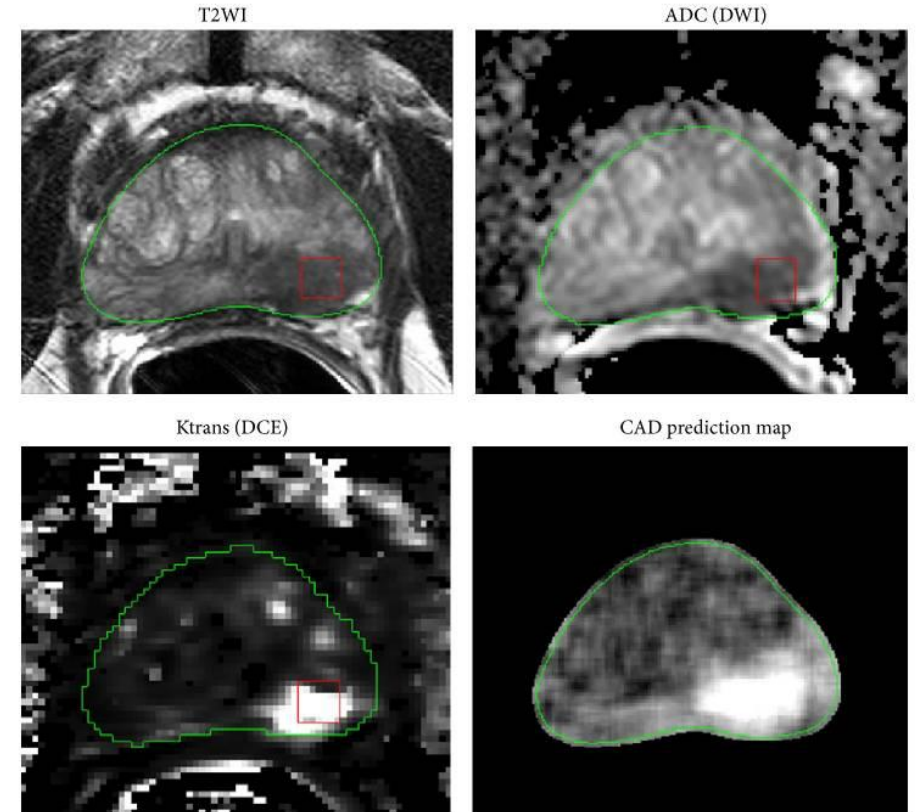
# Mp MRI for Screening

**RGA**

# Multiparametric MRI for screening

What is it?

- Combining MRI techniques for imaging of prostate
- Multiple uses: diagnosis, help with prostate cancer treatment decisions, active surveillance
- Specifically, GG  $\geq 2$
- To increase aggressive tumor detection while limiting ones that won't cause death



[https://upload.wikimedia.org/wikipedia/commons/c/c4/Prostata\\_RM\\_multiparametrica.jpg](https://upload.wikimedia.org/wikipedia/commons/c/c4/Prostata_RM_multiparametrica.jpg)

# Multiparametric MRI

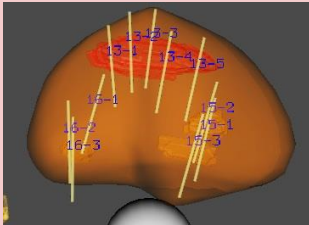
## MpMRI prostate GG $\geq$ 2

PI-RADS	Likelihood of Cancer
PI-RADS 1	Very low: clinically significant cancer is highly unlikely
PI-RADS 2	Low: clinically significant cancer is unlikely
PI-RADS 3	Intermediate: clinically significant cancer is equivocal
PI-RADS 4	High: clinically significant cancer is likely
PI-RADS 5	Very high: clinically significant cancer is highly likely

## Test Characteristics

- Pooled Sensitivity (91%) and Specificity (37%) for GG $\geq$ 2
- Average PPV:
  - PI-RADS 3 12%
  - PI-RADS 4 48%
  - PI-RADS 5 72%

# Two Main Groups

	MpMRI recommended by AUA	Type of biopsy, if needed	Concurrent clinical indicators	Extra caution
<b>Biopsy naive</b>	Not yet	Targeted and systematic 	Yes	Low PI-RADS score: unclear whether can forego biopsy altogether
<b>Prior biopsy</b>	Yes	Targeted	Yes	Low PI-RADS score: if biopsy deferred, continued clinical and laboratory follow-up

# mpMRI

## Limitations

- Radiologist reading failure/standardization
- Lesions missed in targeted biopsy
- Invisibility of lesion

## Additional Factors

- Concurrent clinical factors
- PSA density  $<0.15$  ng/mL/cc improves negative predictive value

## Case 2

60-year-old for FA of 2 million

- Hx of BPH
- Father with prostate cancer
- Hx of a negative TRUS biopsy 3 years ago
- PSA Trend
  - 3 years prior: 5.3
  - 2 years prior: 5.5
  - Most recent: 6.3
- Most recent mpMRI:
  - PIRADS 2
  - Prostate volume 89ml
  
  - PSAD:  $6.3/89\text{ml} = 0.07$
  - PSAD < 0.15 more favorable



# Prostate Cancer Staging

**RGA**



# Case 3

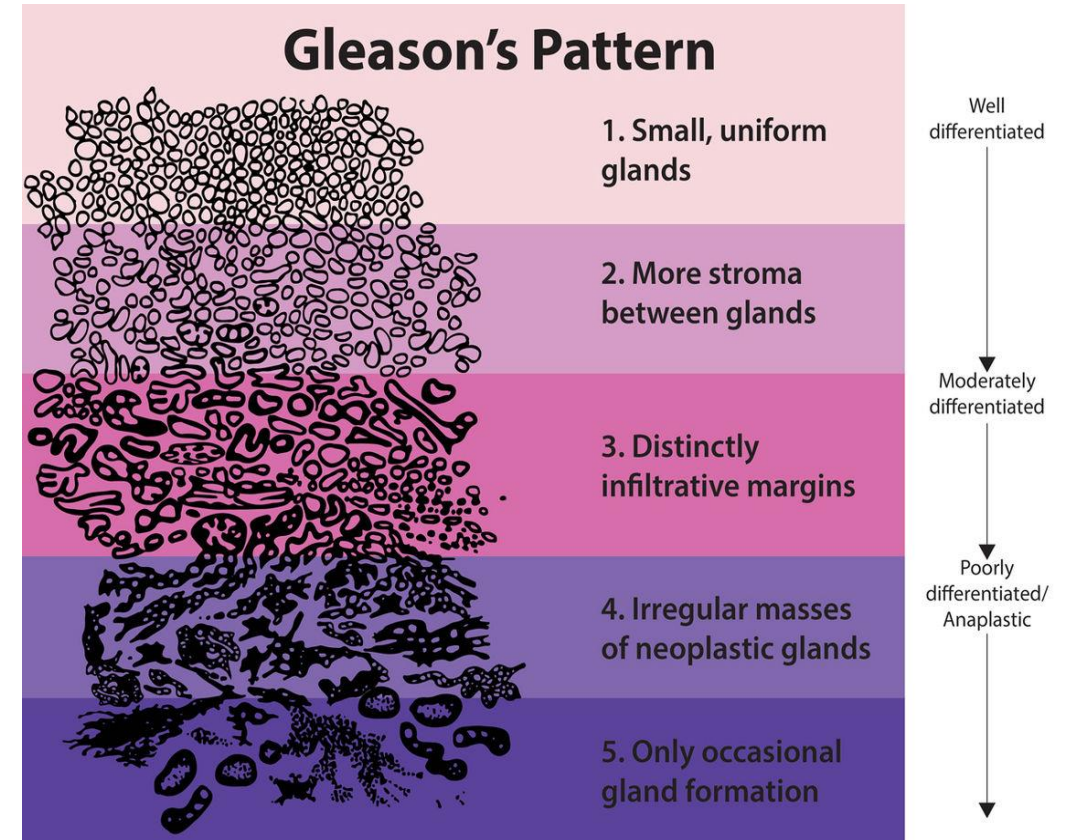
69 yo M 150K

- No concerning FhX
- NMED- prostate cancer s/p prostatectomy 5 years prior to App
- APS: pretreatment PSA is 8.26
  - Biopsy:
  - Gleason 7 (3+4)
  - Stage T2cN0M0
  - Current PSA is 0.01

# Prostate Cancer: Histologic Grading

## International Society of Urological Pathology Grade Group Classification System

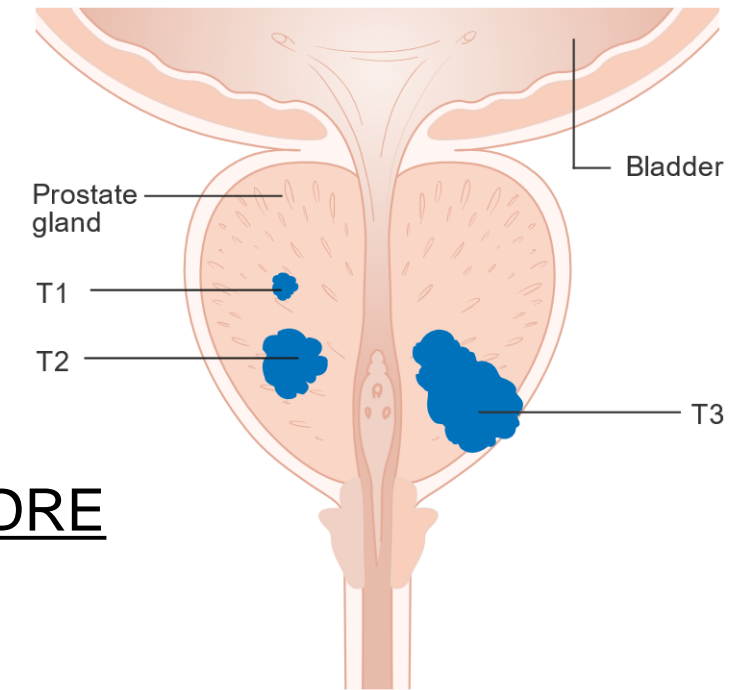
Grade Group	Gleason score and pattern
1	Gleason 6 (3+3)
2	Gleason 7 (3+4)
3	Gleason 7 (4+3)
4	Gleason 8 (4+4, 3+5, 5+3)
5	Gleason 9 or 10 (4+5, 5+4, 5+5)



[https://en.wikipedia.org/wiki/Gleason\\_grading\\_system](https://en.wikipedia.org/wiki/Gleason_grading_system)

# Prostate Cancer Clinical Staging

- T1a: Found incidentally on TURP, <5%, Normal DRE
- T1b: Found incidentally on TURP, >5%, Normal DRE
- T1c: Found on TRUS – NBP for an elevated PSA, Normal DRE
- T2a: Palpable nodule on DRE, < ½ of one lobe
- T2b: Palpable nodule on DRE, > ½ of one lobe
- T2c: Palpable nodule bilaterally on DRE, both lobes
- T3a: Palpable outside the prostate but not seminal vesicles
- T3b: Palpable outside the prostate invading seminal vesicles
- T4: Locally invading the sphincter, rectum, bladder or pelvic wall



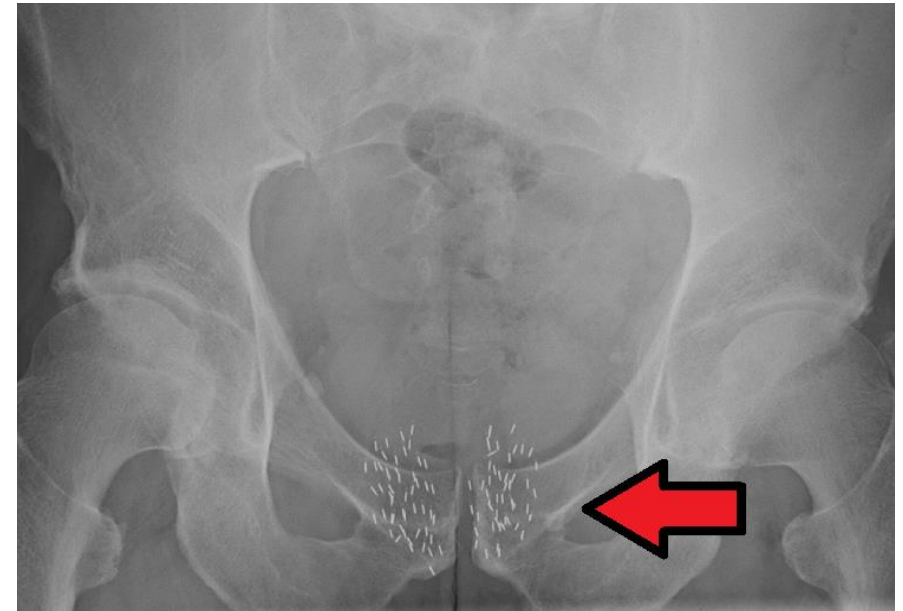
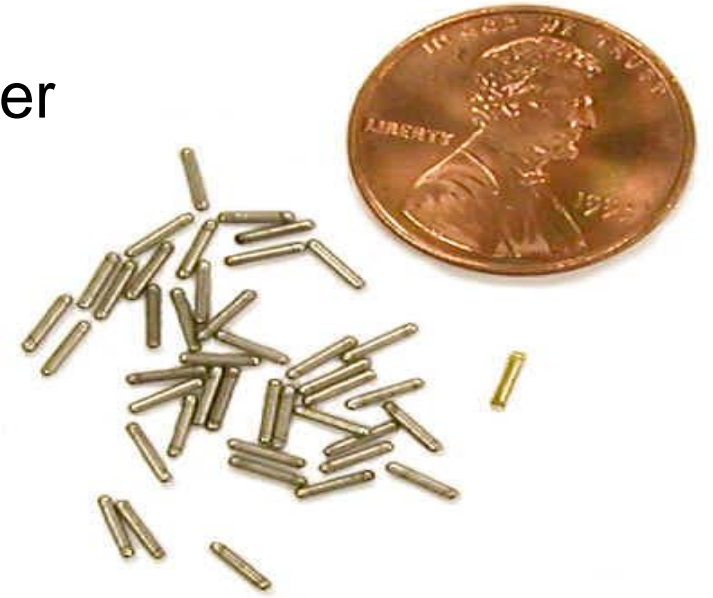
# AJCC 8<sup>th</sup> Edition Prostate Cancer Prognostic Groups

<b>AJCC</b>	<b>T</b>	<b>N</b>	<b>M</b>	<b>PSA</b>	<b>Grade Group</b>	<b>Gleason Score</b>
<b>I</b>	cT1a-c, cT2a	N0	M0	<10	1	≤6
	pT2	N0	M0	<10	1	≤6
<b>IIA</b>	cT1a-c, cT2a	N0	M0	≥10 <20	1	≤6
	cT2b-c	N0	M0	<20	1	≤6
<b>IIB</b>	T1-2	N0	M0	<20	2	7 (3+4)
<b>IIC</b>	T1-2	N0	M0	<20	3	7 (4+3)
	T1-2	N0	M0	<20	4	8
<b>IIIA</b>	T1-2	N0	M0	≥20	1-4	≤8
<b>IIIB</b>	T3-4	N0	M0	Any	1-4	≤8
<b>IIIC</b>	Any T	N0	M0	Any	5	9 or 10
<b>IVA</b>	Any T	N1	M0	Any	Any	Any
<b>IVB</b>	Any T	N0	M1	Any	Any	Any

# Approaches to Prostate Cancer Treatment

## From Indolent Prostate Cancer to Lethal Prostate Cancer

- Immediate Treatment
  - Brachytherapy
  - External beam radiation
  - Radical prostatectomy
  - Hormonal therapy
  
- Active Surveillance



## Case 3

69 yo M 150K

- No concerning FhX
- NMED - prostate cancer s/p prostatectomy 5 years prior to App
- APS: pretreatment PSA is 8.26
  - Biopsy: Gleason 7 (3+4)
  - Stage T2cN0M0
  - Current PSA is 0.01

**Stage 2B. Is this appropriate?**

# Case 3

## Biopsy = Clinical Staging

- Gleason 7 (3+4) in 15% right base, 40% right anterior
- PSA is 8.26
- Volume 24.4
- Evaluation:
  - mpMRI: PIRADS 5 lesion, no lymph node adenopathy

## OR path report = Pathologic Staging

- Prostatectomy:
  - Gleason score 4+4
  - No capsular invasion
  - Margins negative
  - Seminal vesicles negative
  - Lymph nodes negative
  - T2pN0M0
  - **Stage 2C**

**Pearl:** Prostate cancer has a clinical staging and a pathologic staging. Make sure the staging is the appropriate one for the treatment involved.

# Takeaways

- Many things can cause an elevated PSA. Trends are more important, than one clinical cutoff
  - You need to put it into context of the whole case and use secondary tests/adjuncts to help, if available.
- An abnormal DRE warrants investigation, even if the PSA level is below 4.0 ng/ml.
- mpMRI is another tool in the arsenal and can help to risk stratify. Pretest probability is still important. PI-RADS 4-5 should be biopsied.
  - No consensus in biopsy naïve whether a 1 or 2 PI-RADS can forgo biopsy
- Pay attention to the treatment.
  - If the patient had a radical prostatectomy, you need the surgical path report. Clinical staging (biopsy) can underestimate true disease.





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