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Cancer Center™

Prostate Cancer
The Basics

Vincent P. Laudone, M.D.
Chief of Surgery, Josie Robertson Surgery Center
Memorial Sloan Kettering Cancer Center
New York, NY

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Disclosures

- **NO conflicts of interest.**
- Unpaid consultant - *Illuminaire* - fluorescent molecular probe for intraoperative illumination of nerves.

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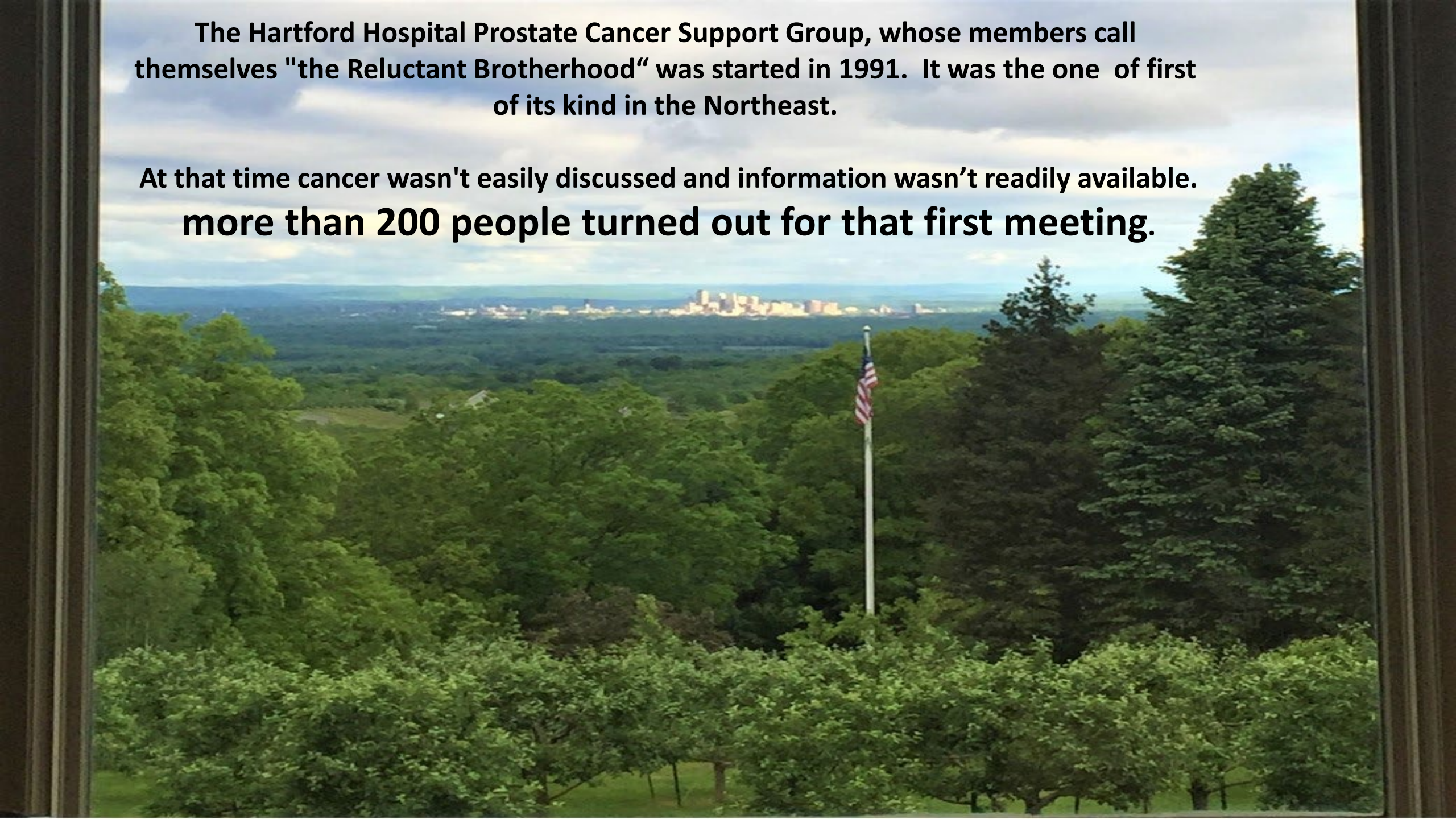
Josie Robertson Surgery Center



The Hartford Hospital Prostate Cancer Support Group, whose members call themselves "the Reluctant Brotherhood“ was started in 1991. It was the one of first of its kind in the Northeast.

At that time cancer wasn't easily discussed and information wasn’t readily available.

more than 200 people turned out for that first meeting.

When individuals come together to support each other:

Questions are answered.
Uncertainty gives way to confidence.
Fear turns into hope.
And compassion heals.

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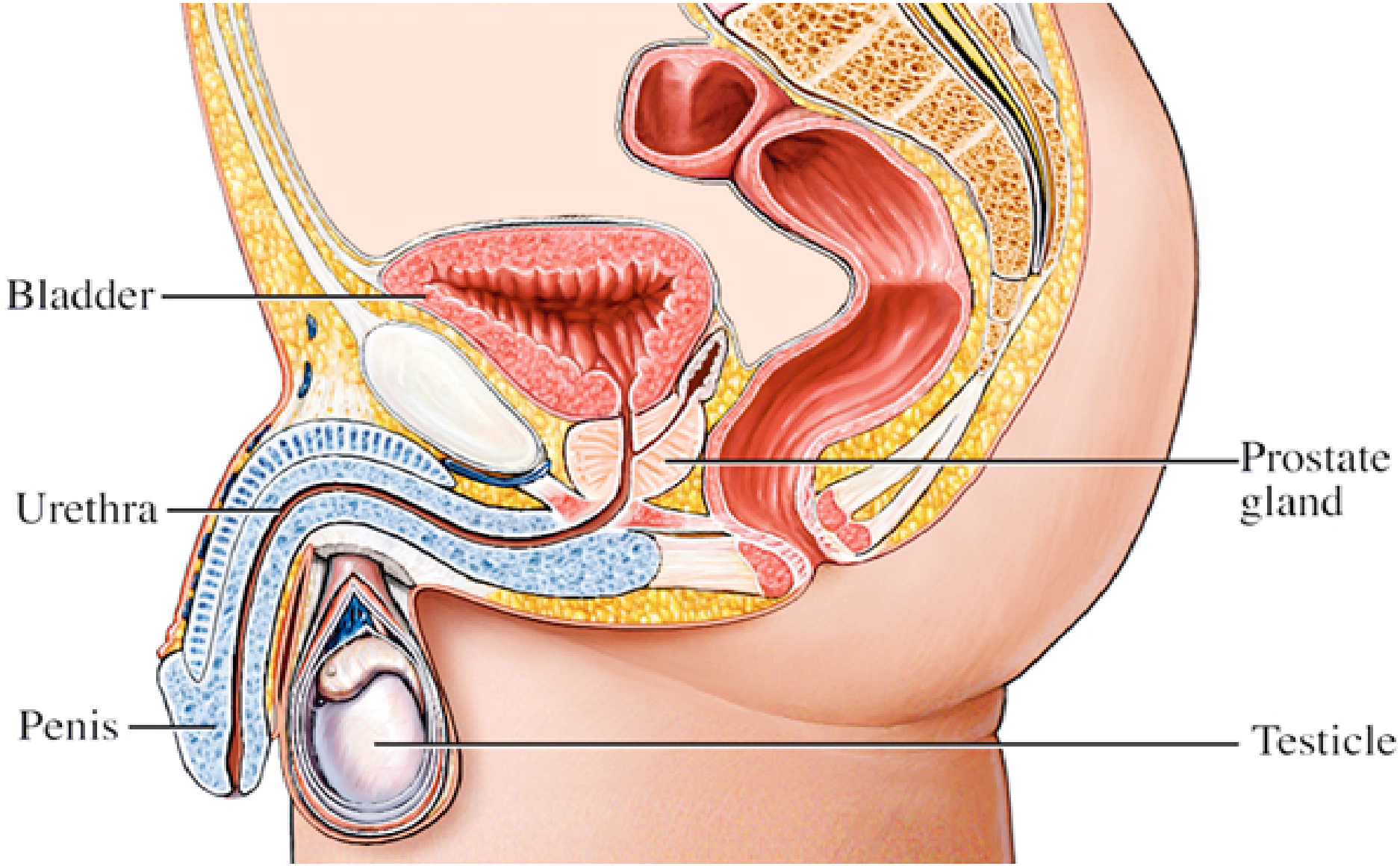
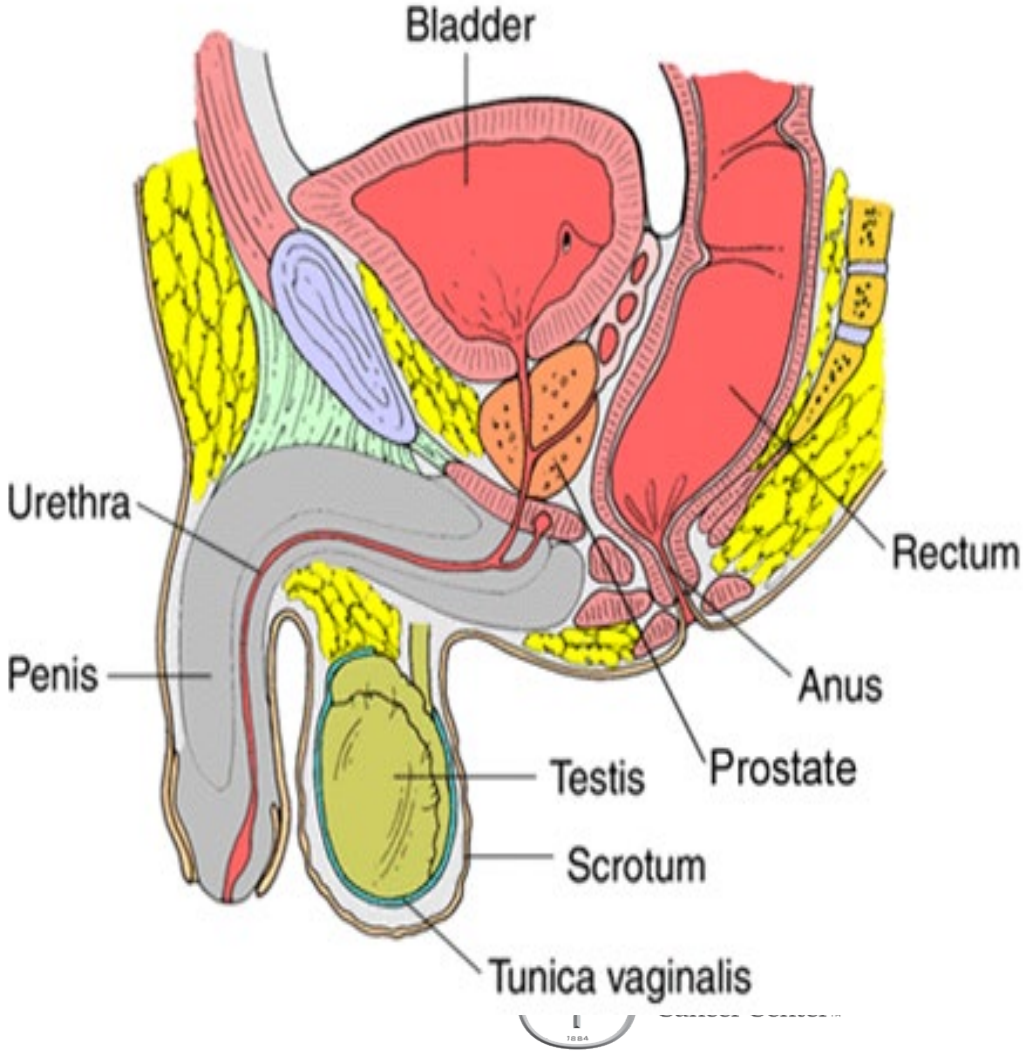


The Prostate

- Male sexual gland
- Adds fluids and nutrients to the ejaculate to aid sperm function.
- Nerves for erection are attached to the outside.
- Urethra (urine channel) runs through the middle of the prostate.



Should a man worry about prostate cancer?

Lifetime risk of:

Being diagnosed with cancer	1 in 3
Being diagnosed with prostate cancer	1 in 6
Dying of cancer	1 in 5
Dying of prostate cancer	1 in 41
Dying in an auto accident	1 in 103
Dying in an airplane accident	1 in 188,364

National Safety Council estimates based on data from
National Center for Health Statistics—Mortality Data for 2017

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Risk Factors for Prostate Cancer

Genetics

- 1st degree relatives – 2.48x (> age under 65, brother >father)
- Ethnicity -
- Genes - BRAC-2 BRAC-1, HOXB13, CHECK2

Environment –

- Cadmium, Ionizing RT, Infection/inflammation

Lifestyle

- Heavy smoking, Increased BMI, diet (red meats, dairy, fat)

Hormones

- Androgens, IGF-1

Age

Lifetime Risk of Developing or Dying of Prostate Cancer for a 50-Year-Old Man in the US

Lifetime Risk of	Risk	Risk Ratio
Developing histologic cancer	42%	11.7
Developing clinical cancer	16%	4.4
Dying of prostate cancer	3.6%	1.0

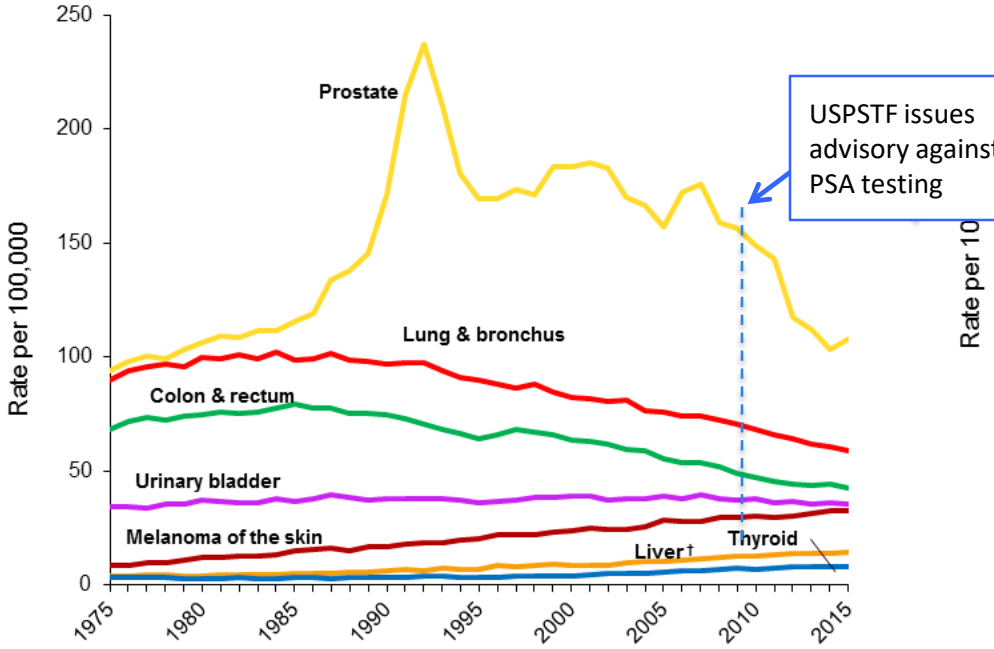
Modified from Scardino PT. Urol Clin N Am 1989,
Hum Path 1992, and from CA Cancer J Clin Jan-Feb, 2000.

Prostate cancer 2019

New cases: 174,650

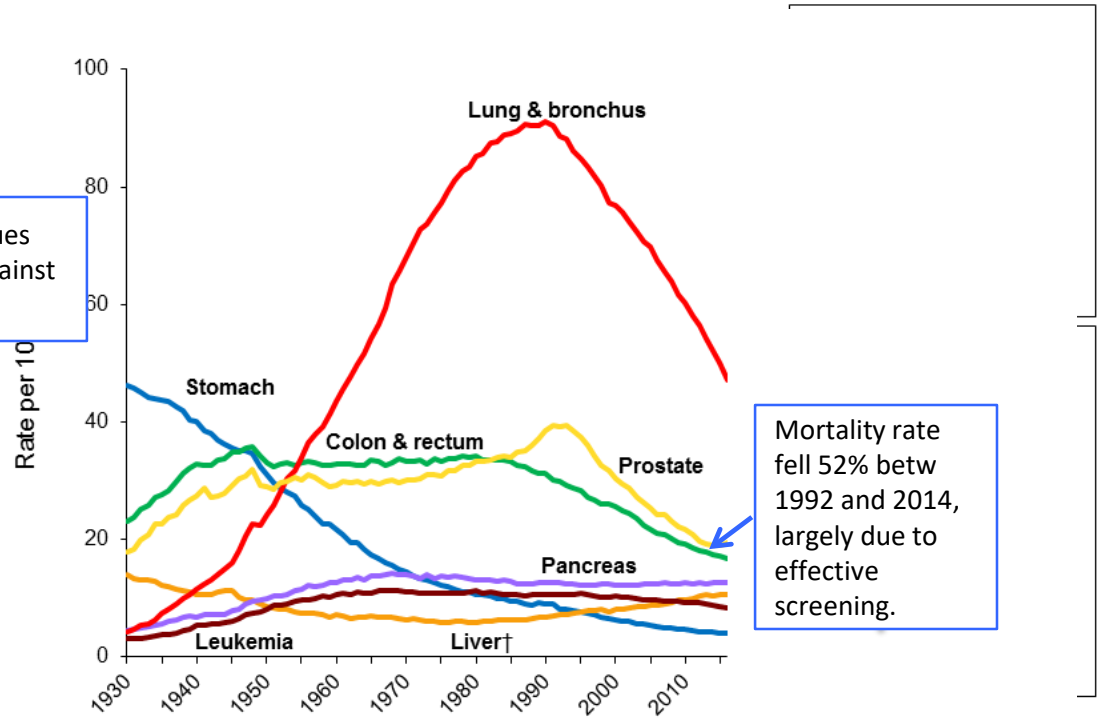
Estimated deaths: 31,620

Trends in Cancer Incidence Rates* Among Males, US, 1975-2015



*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting. †Includes the intrahepatic bile duct.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2018.

Trends in Cancer Death Rates* Among Males, US,1930-2016



*Age-adjusted to the 2000 US standard population. †Includes intrahepatic bile duct, gallbladder, and other bi
NOTE: Due to International Classification of Diseases coding changes, numerator information for colorectal,
Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2018.

https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2019.html and Draisma et al. *J Natl Cancer Inst* 2009;101:374-83

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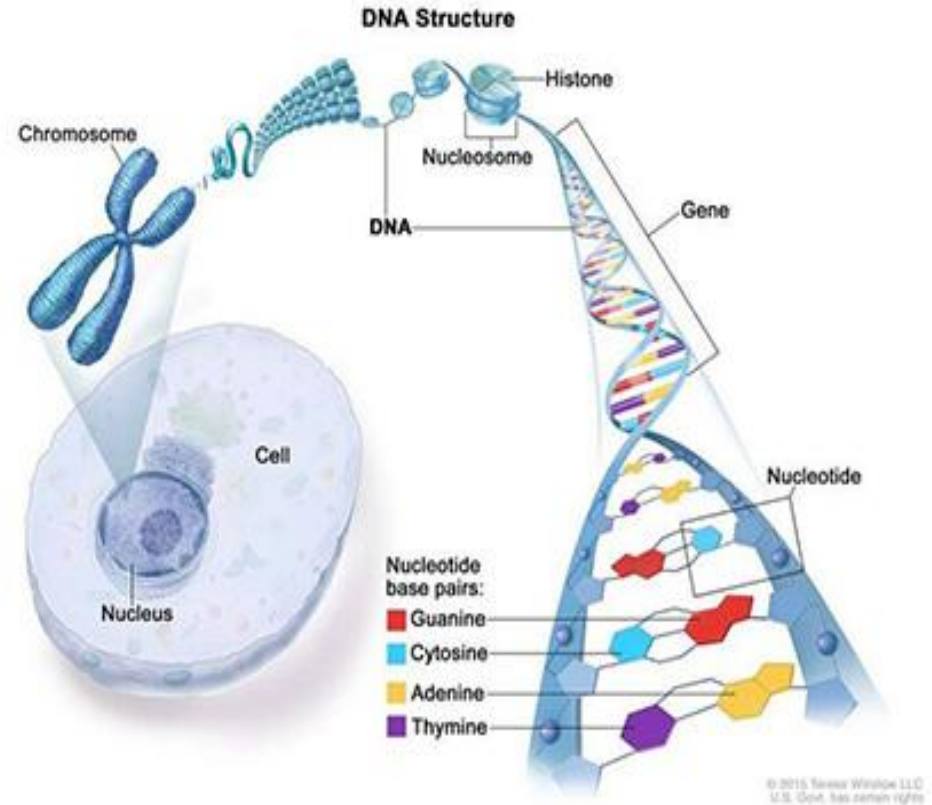
What is Cancer?

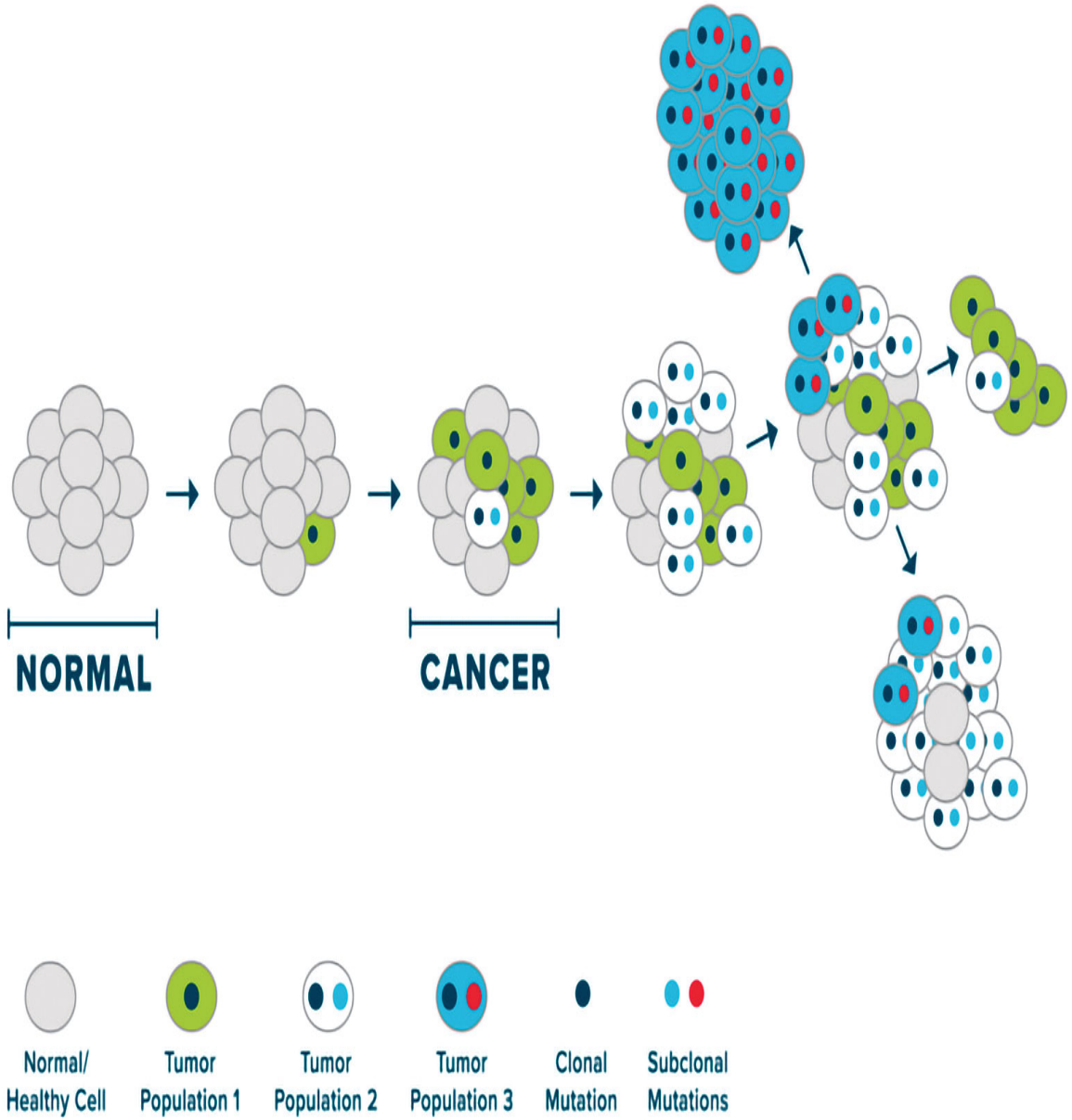
- **Normal** tissue cells that have mutated.



Radiation - sunlight
Chemicals
Viruses
Errors in cell division

What is Cancer?

- These genetically abnormal cells, *in the right environment*, can:
  - grow out of control
  - continue to mutate
  - invade and spread throughout the body.



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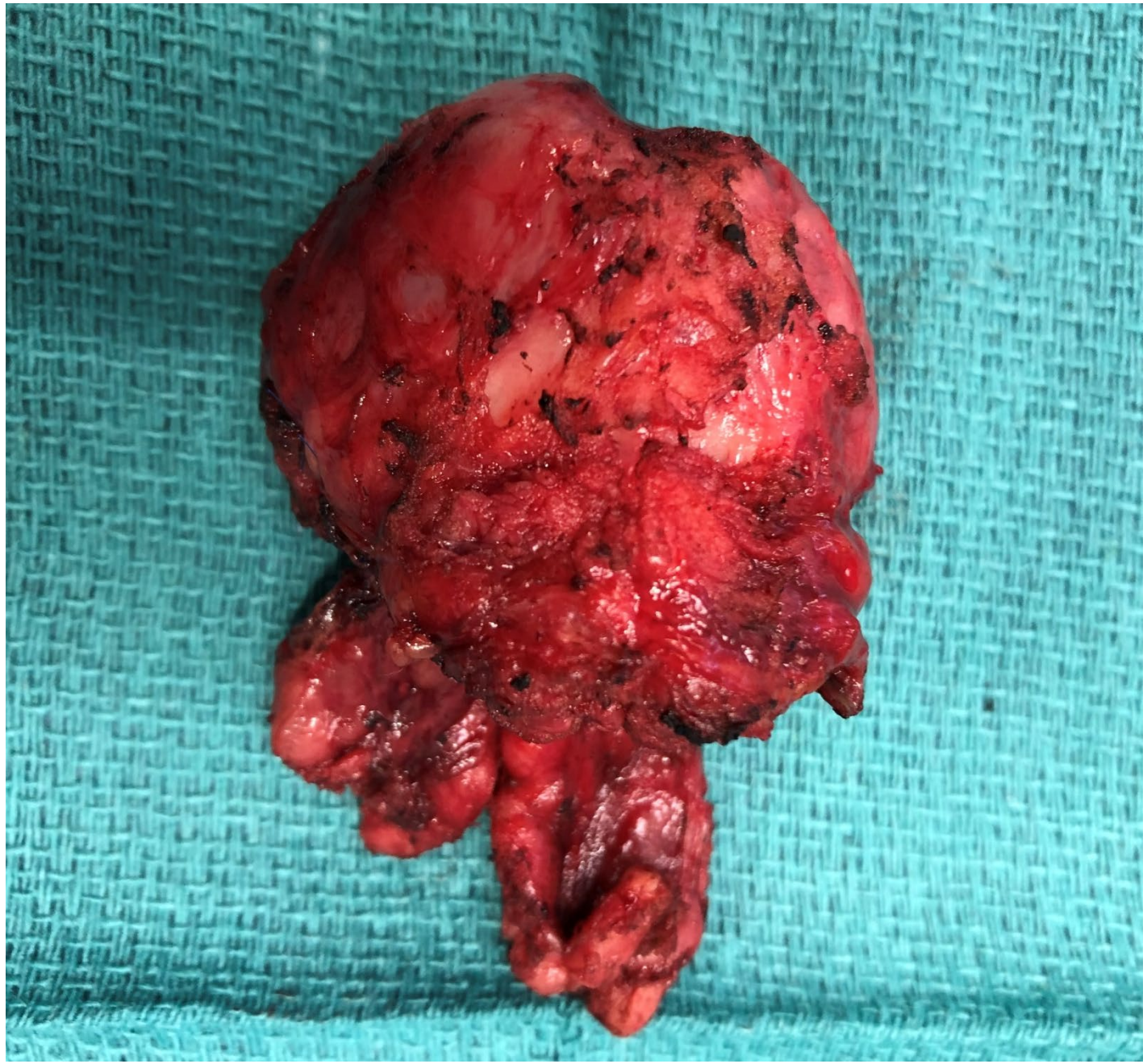
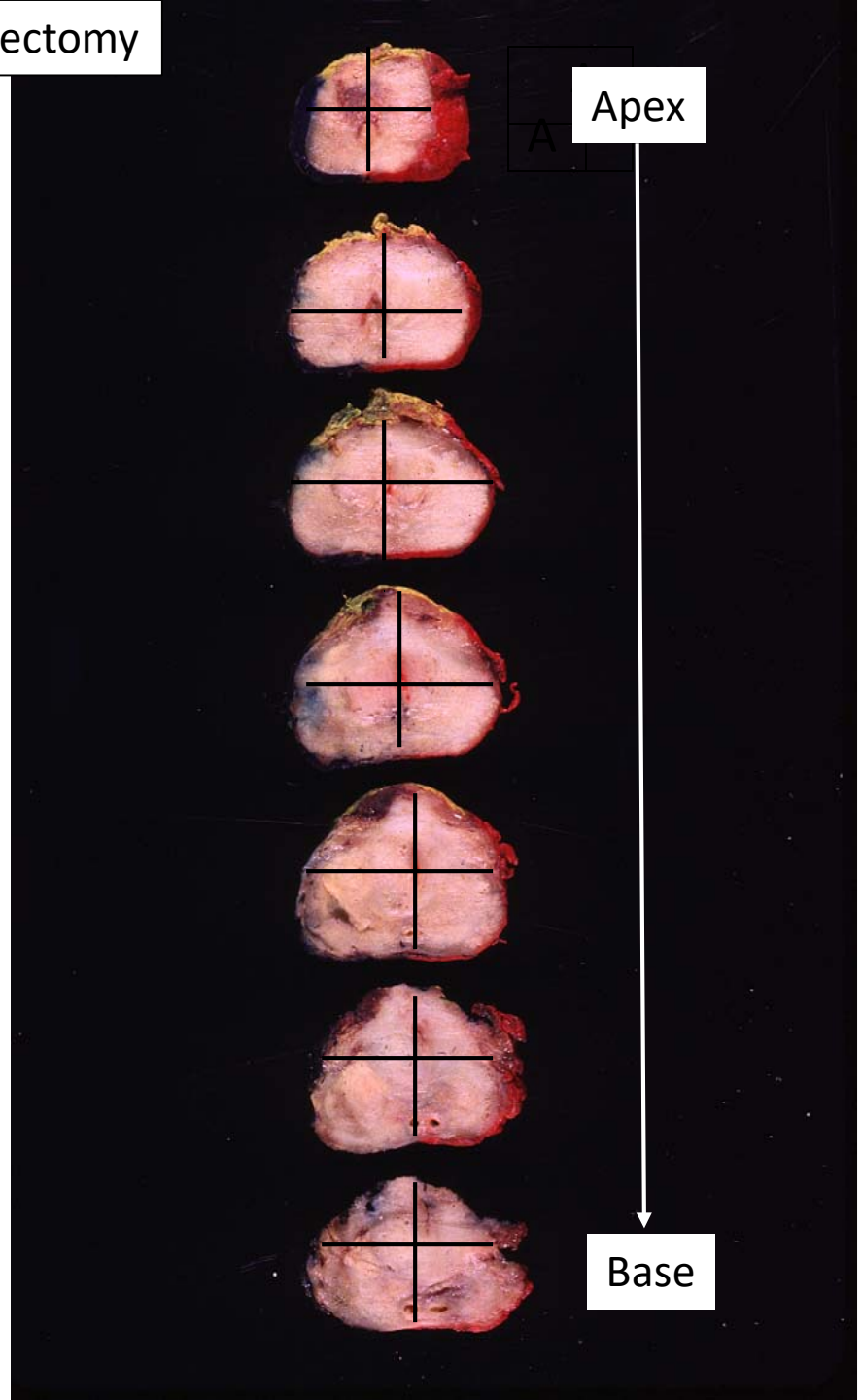
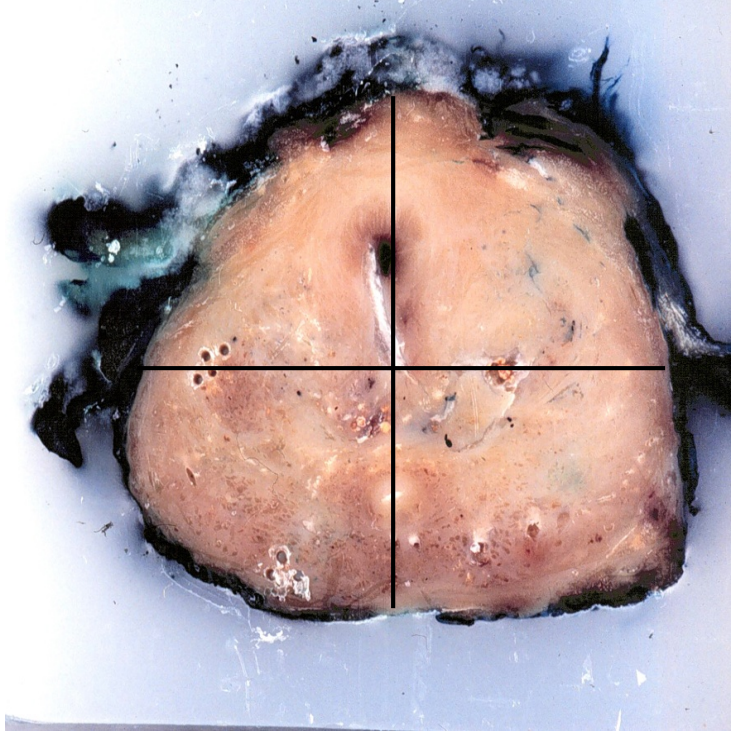
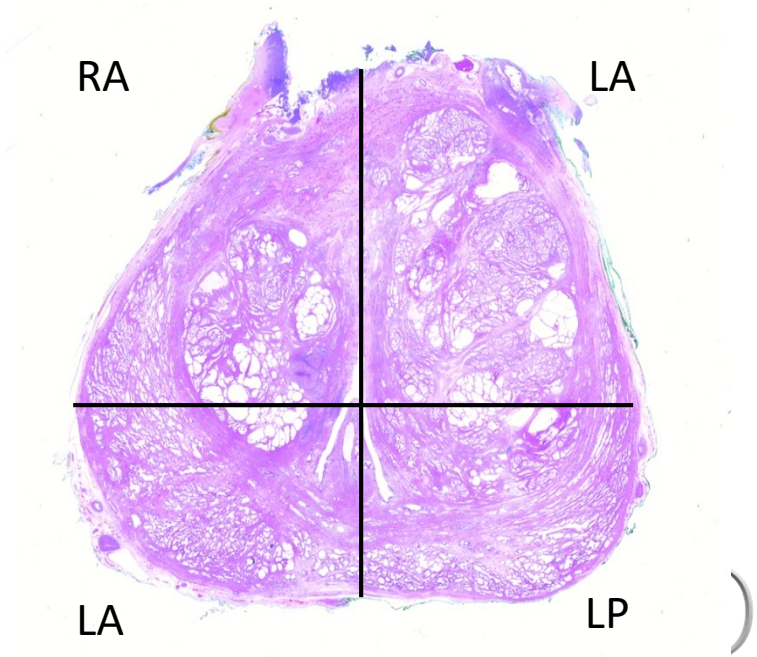


Radical prostatectomy







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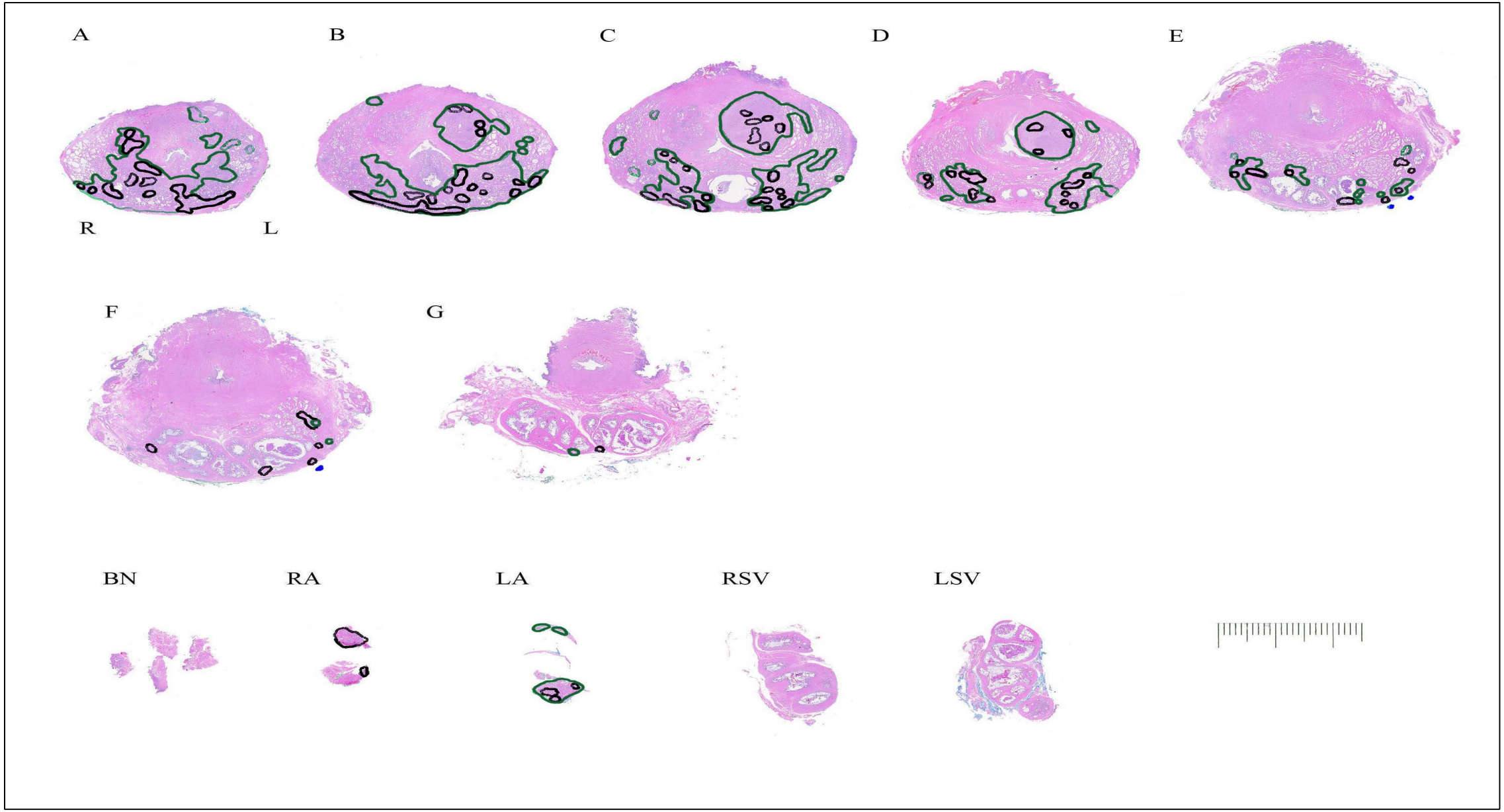
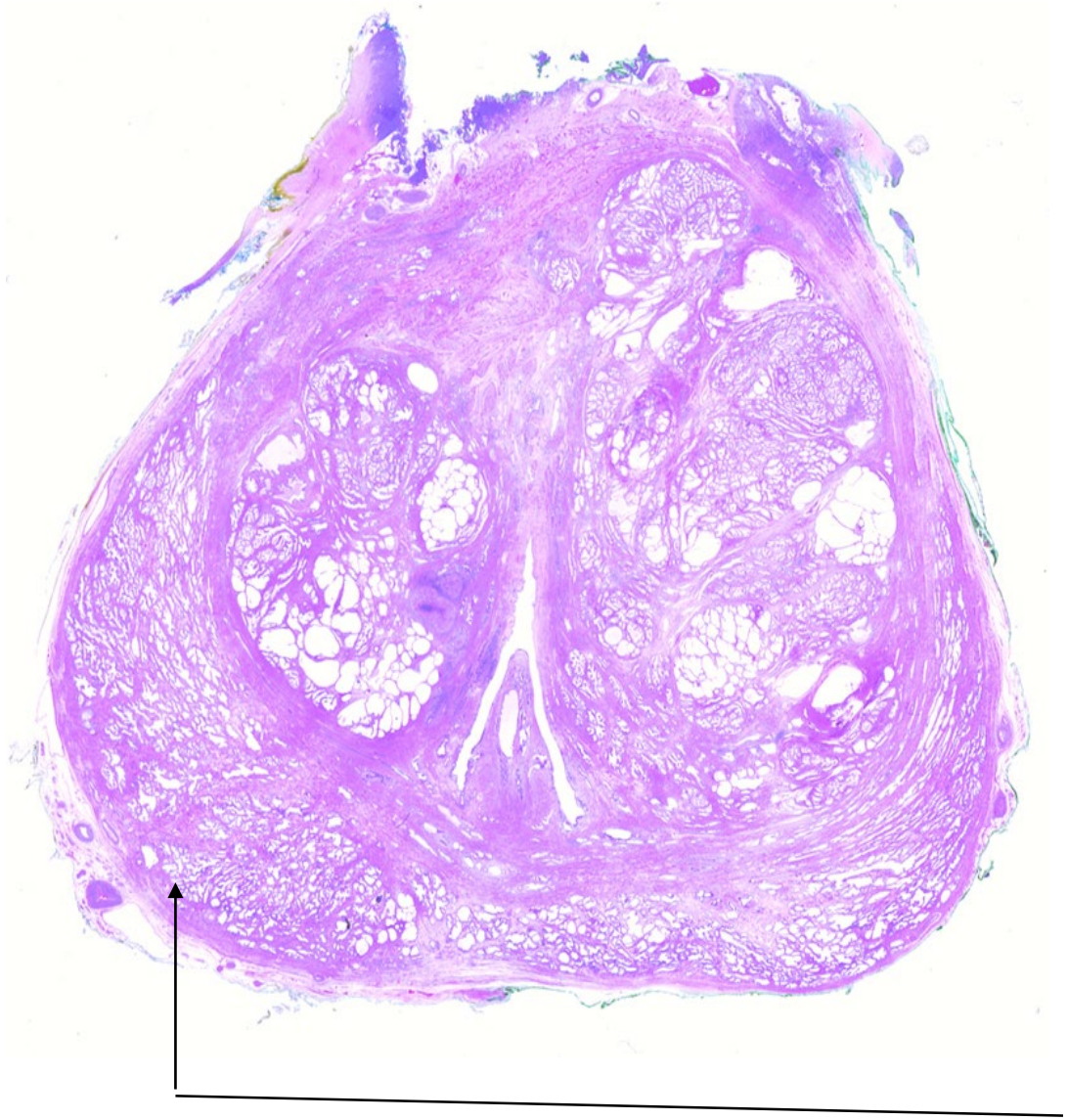
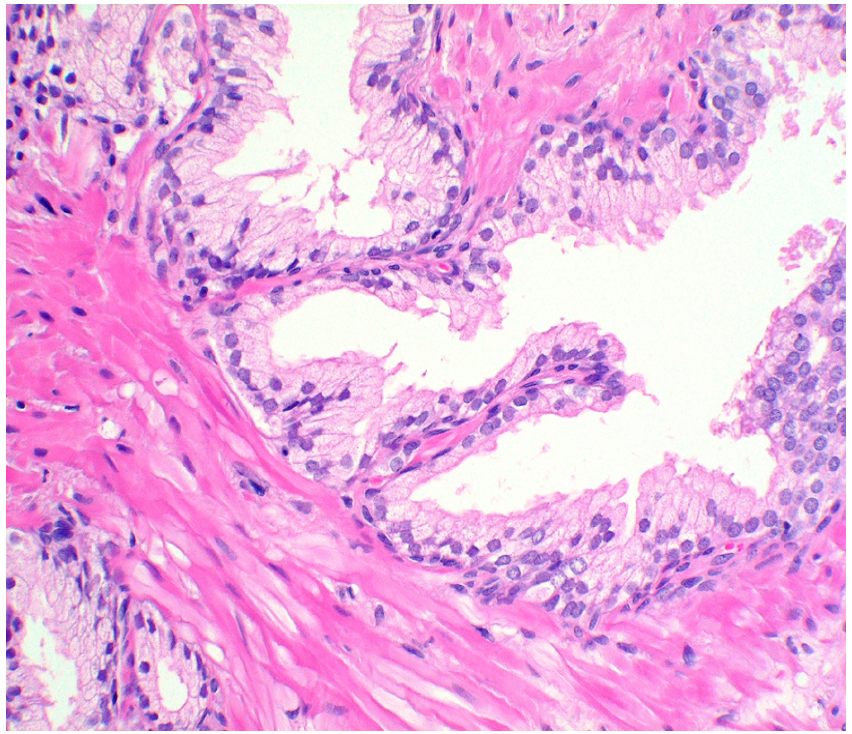
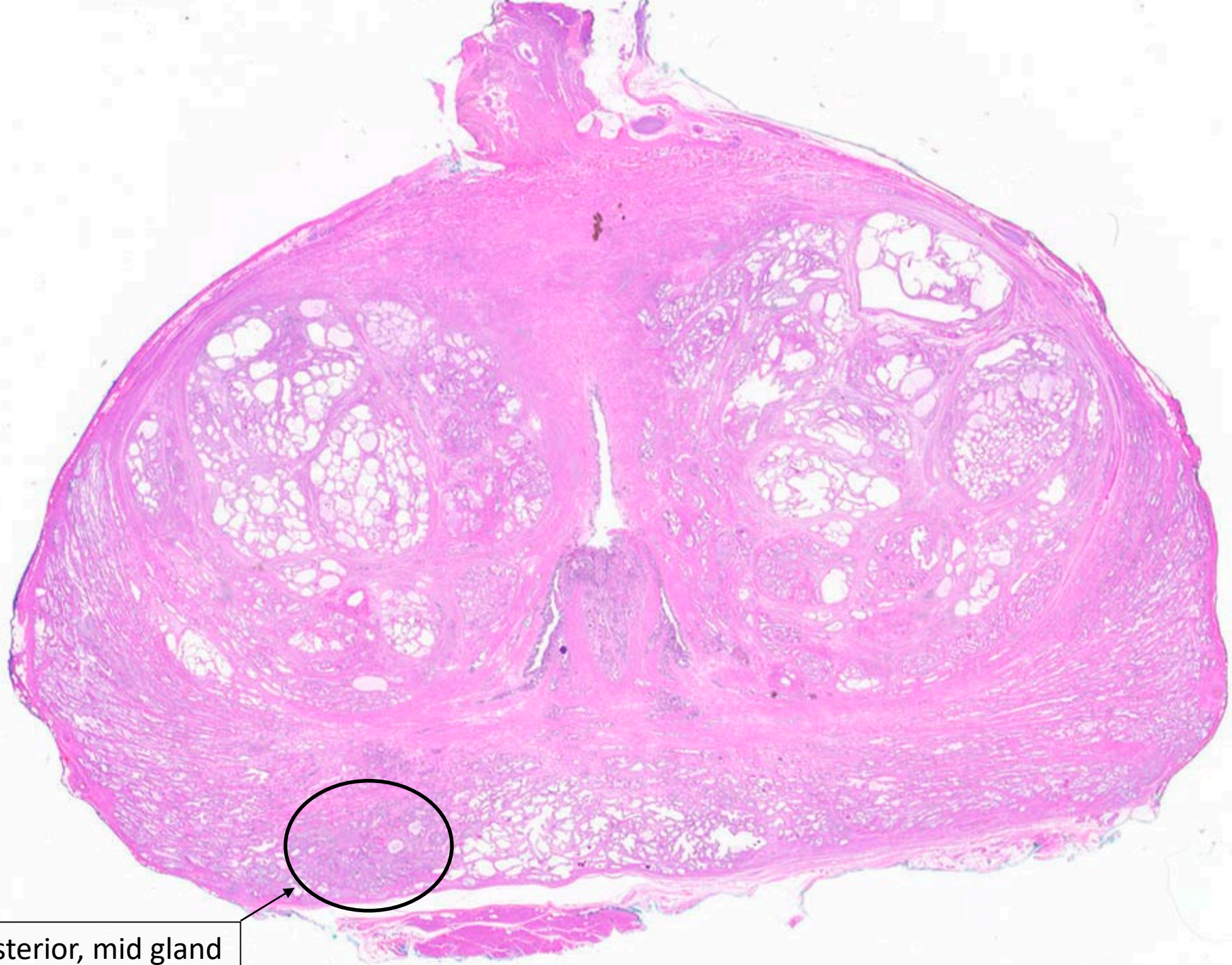


Wholemount of the prostate through the mid-gland

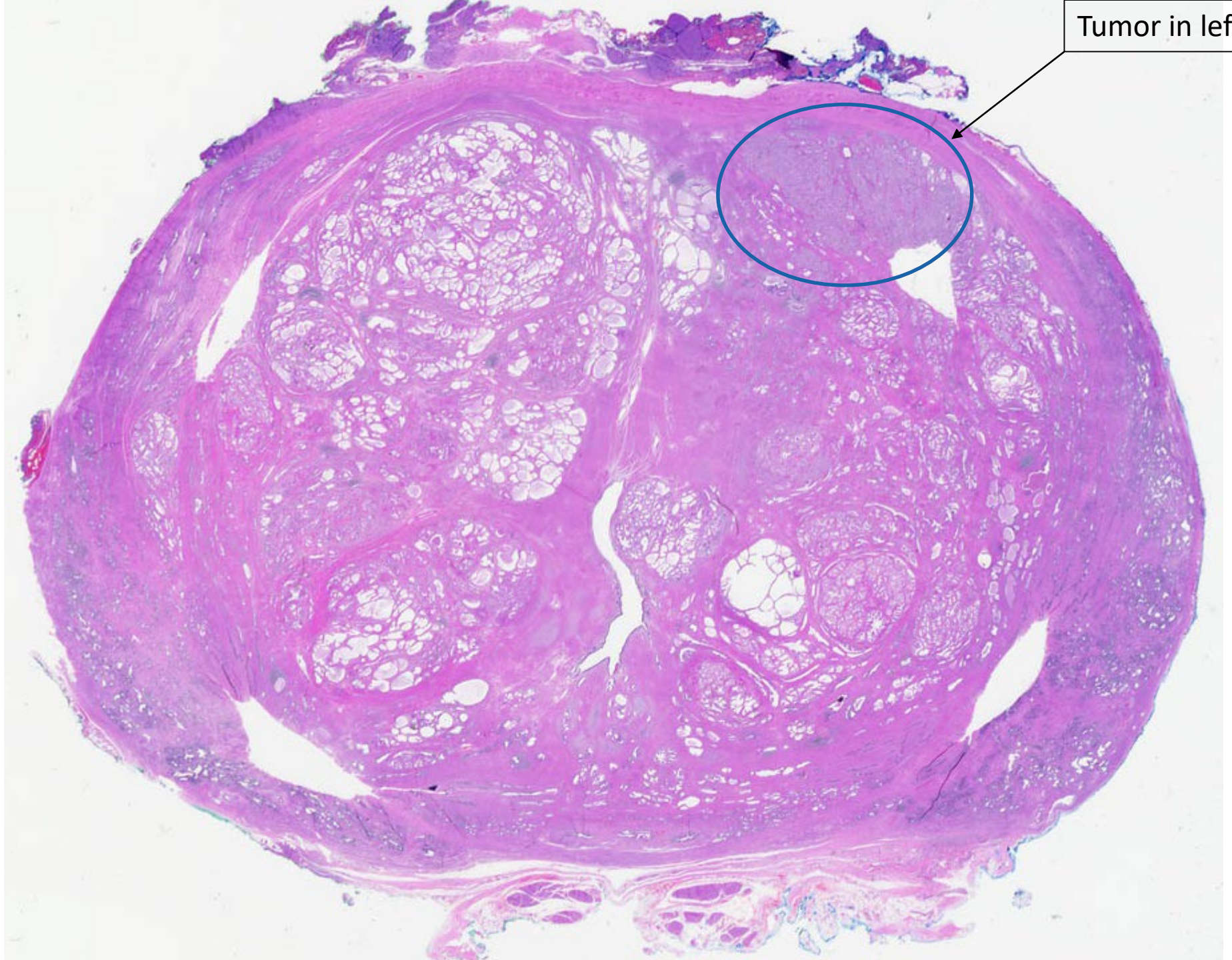


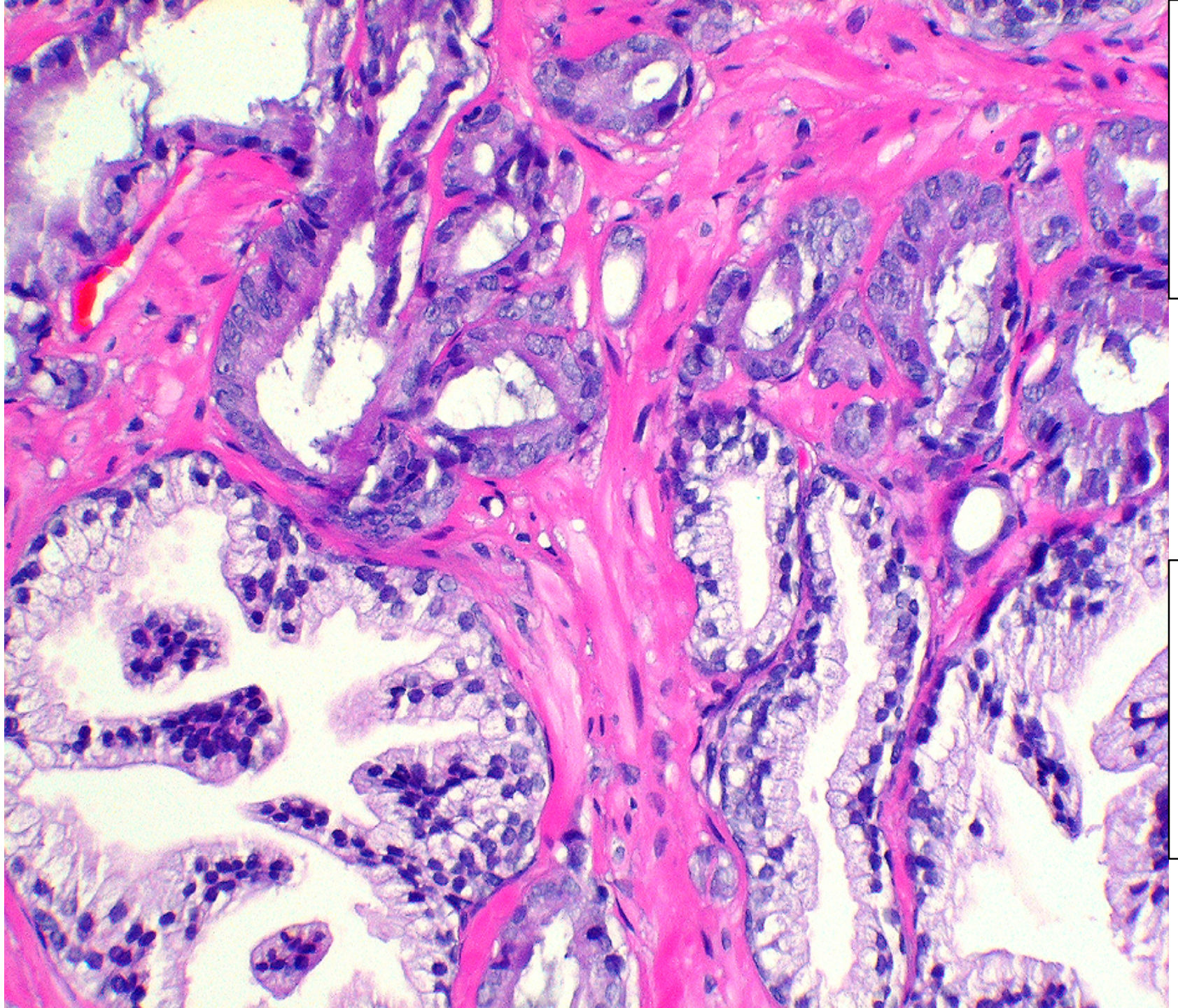


Normal (benign peripheral gland)



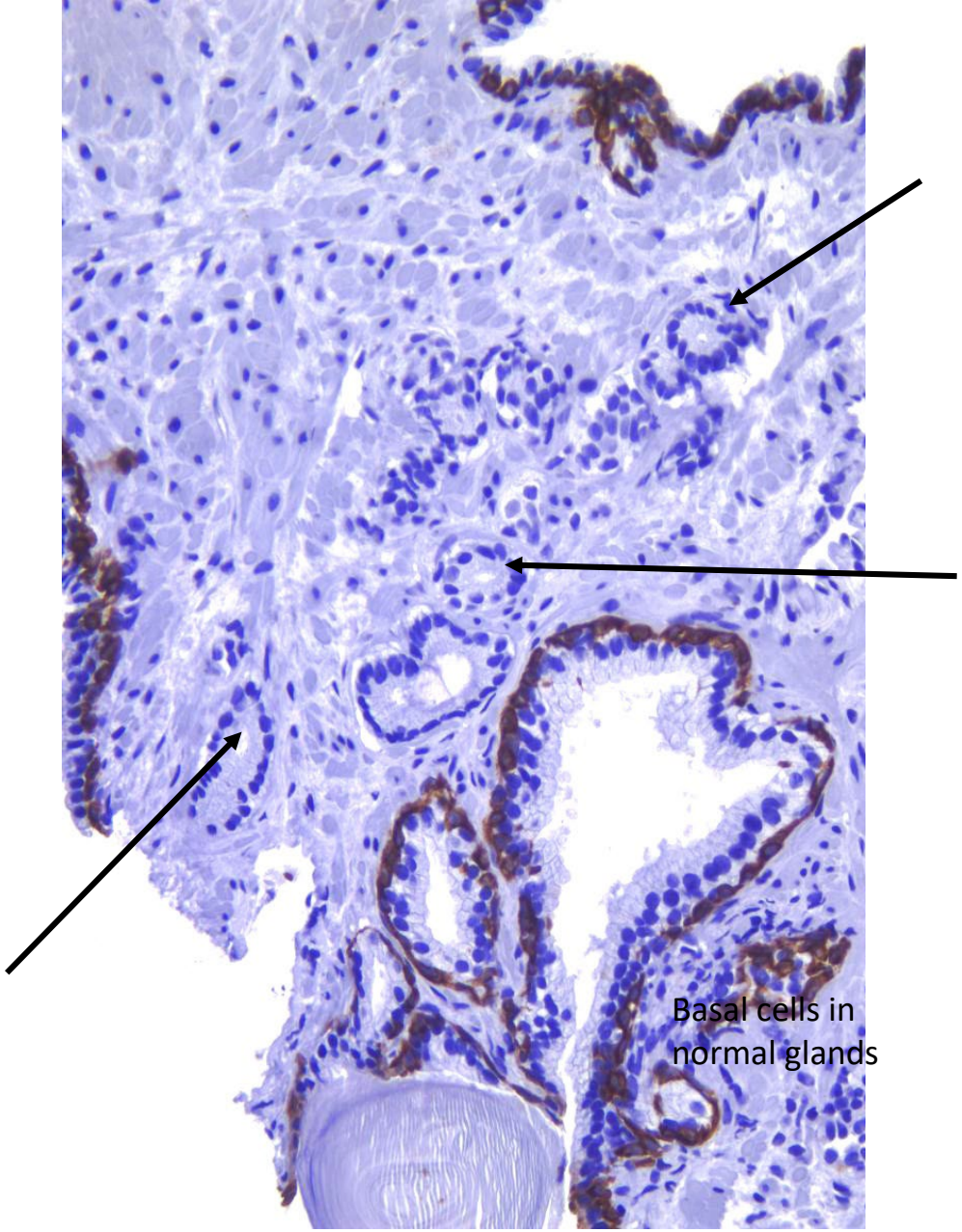
Tumor in right posterior, mid gland


Tumor in left anterior, mid gland

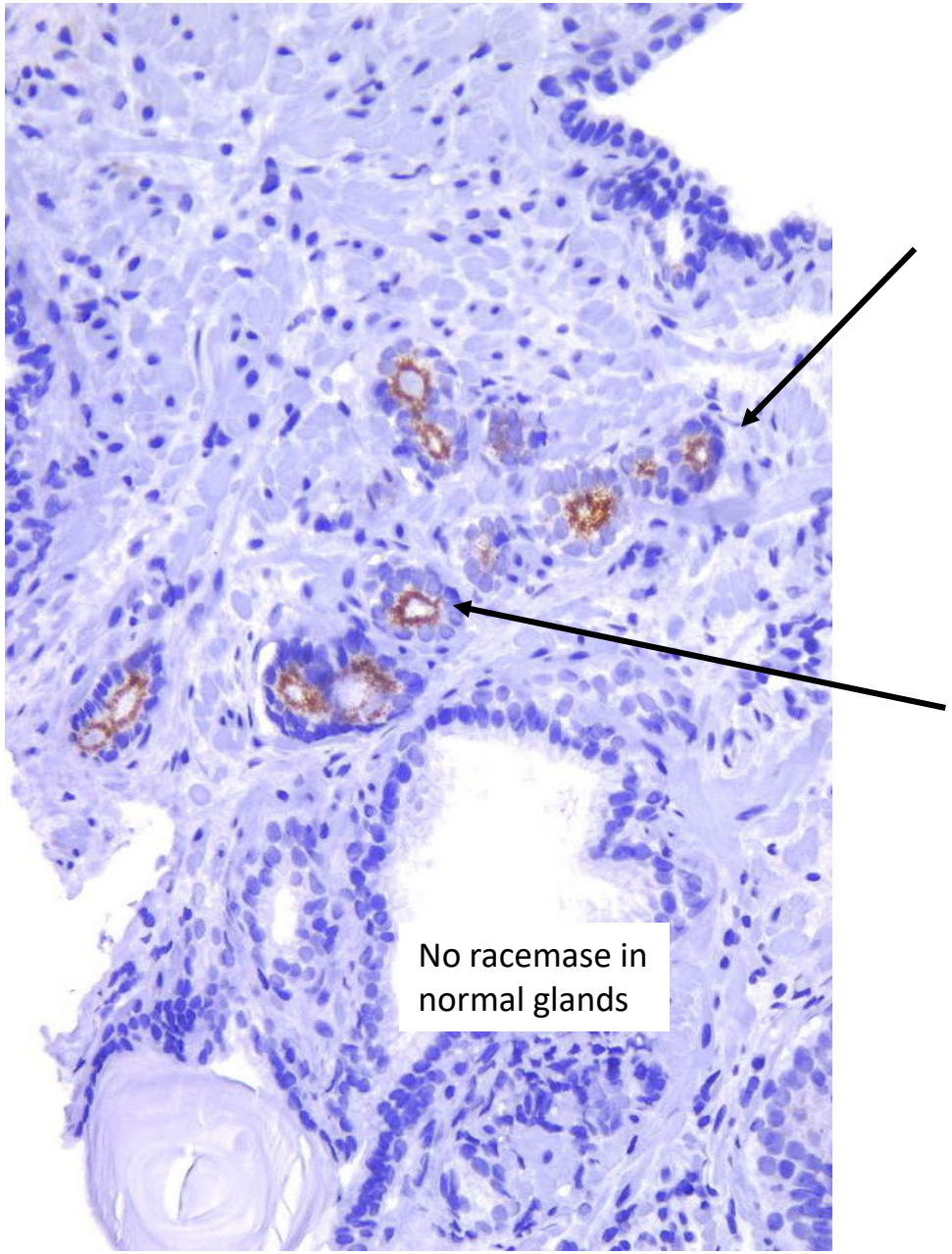


Prostatic adenocarcinoma
- -Acinar pattern
- -Infiltrative
- -No basal cells
- -Enlarged nuclei
- -Prominent nucleoli
- -Cytoplasmic eosinophilia

Benign prostatic glands
- -Two cell layers
  - -Acinar (luminal)
  - -Basal cells
- -Clear cytoplasm
- -Papillary infoldings
- -No nucleoli



Carcinoma lacks basal cells
(IHC marker for 34BE12)



Carcinoma expresses racemase
(IHC marker for AMACR)

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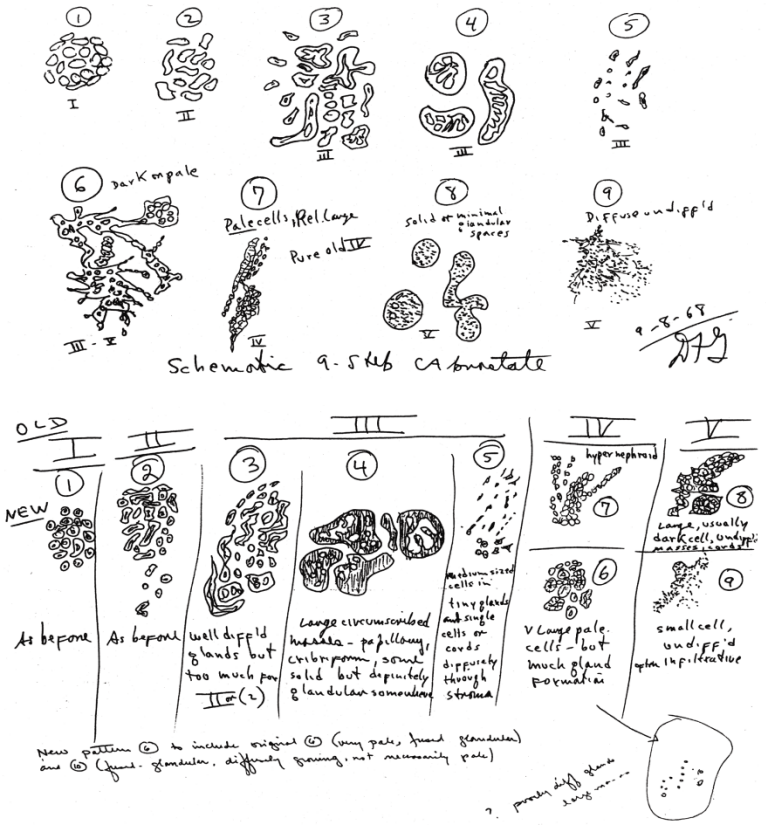
GLEASON GRADING SYSTEM

- Developed from 1960-1975 and based on follow-up of 5,000 prostate cancer patients
- Extent of glandular differentiation and pattern of growth
- Nuclear atypia, not mitoses



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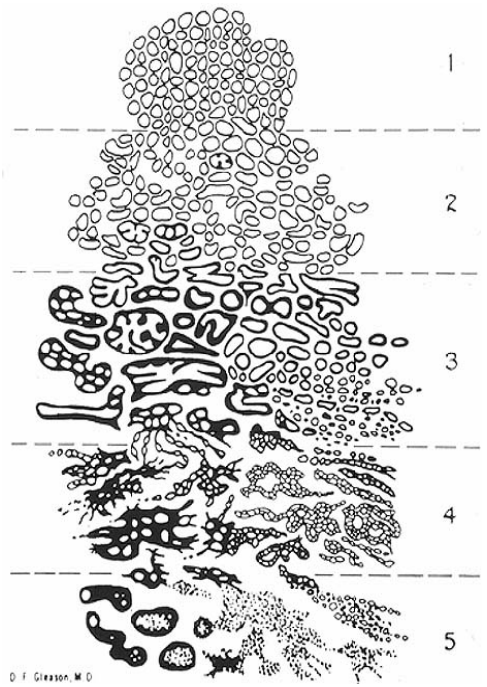
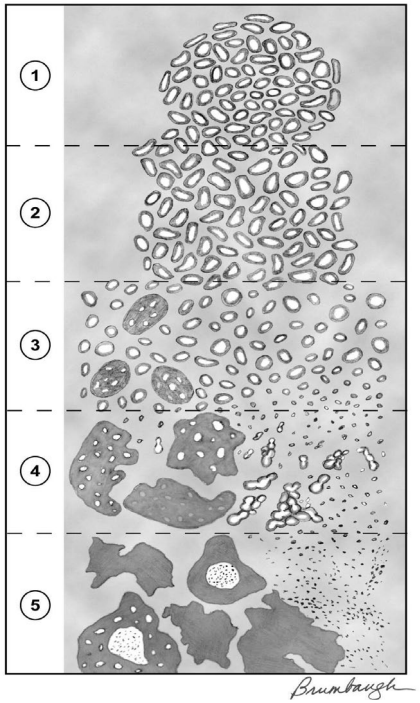
Evolution of the Gleason grade diagram 1968-2016 (WHO, 4th edition)

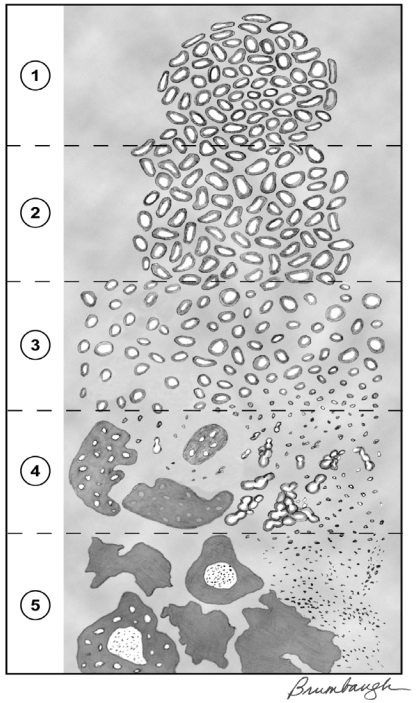
1968



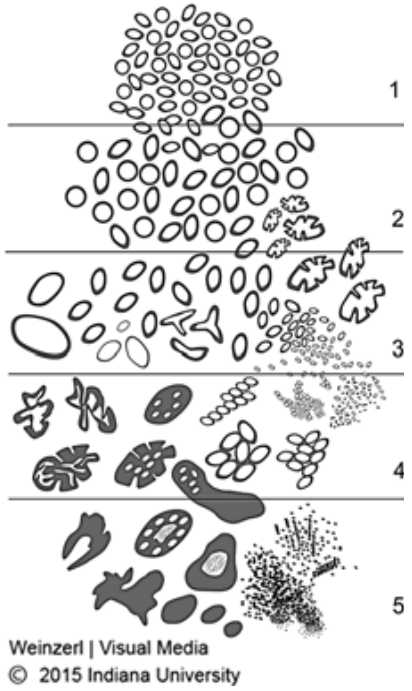
2005



2010



2015



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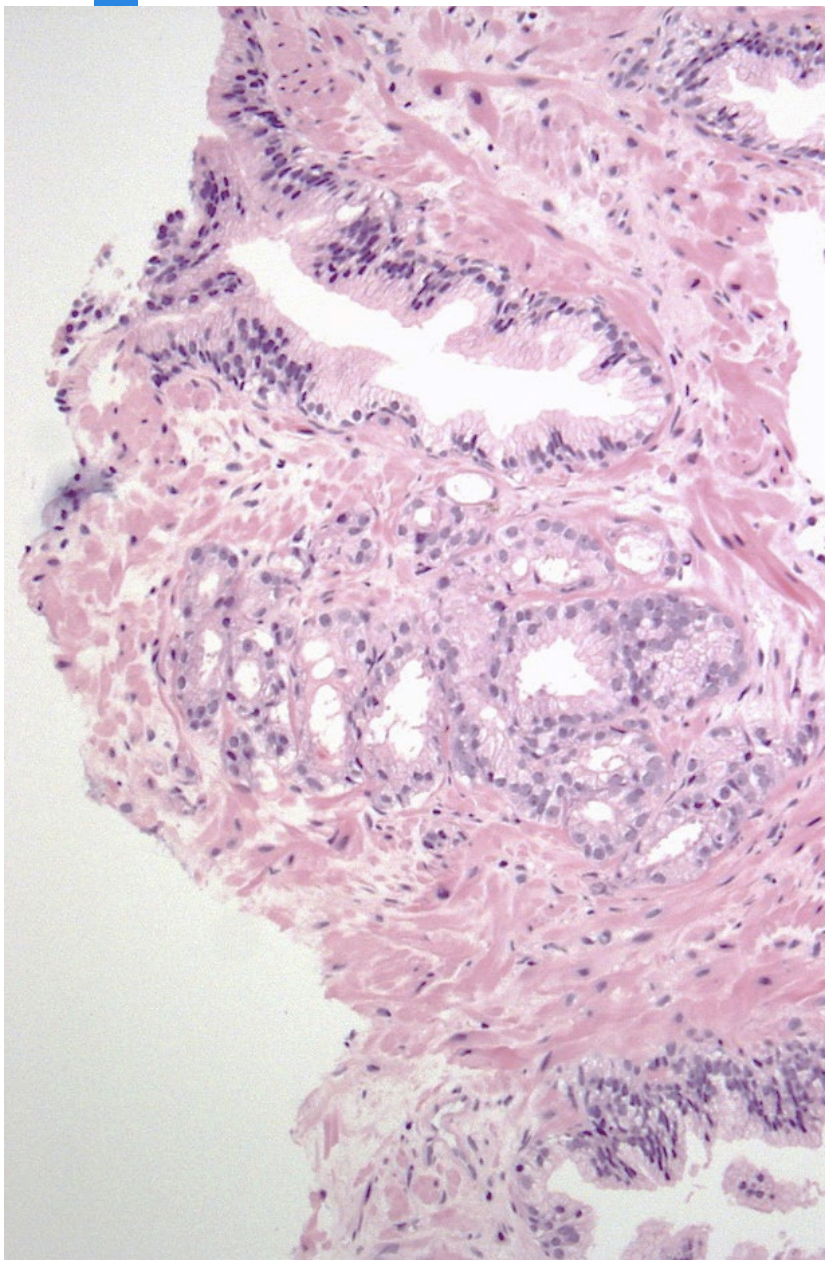
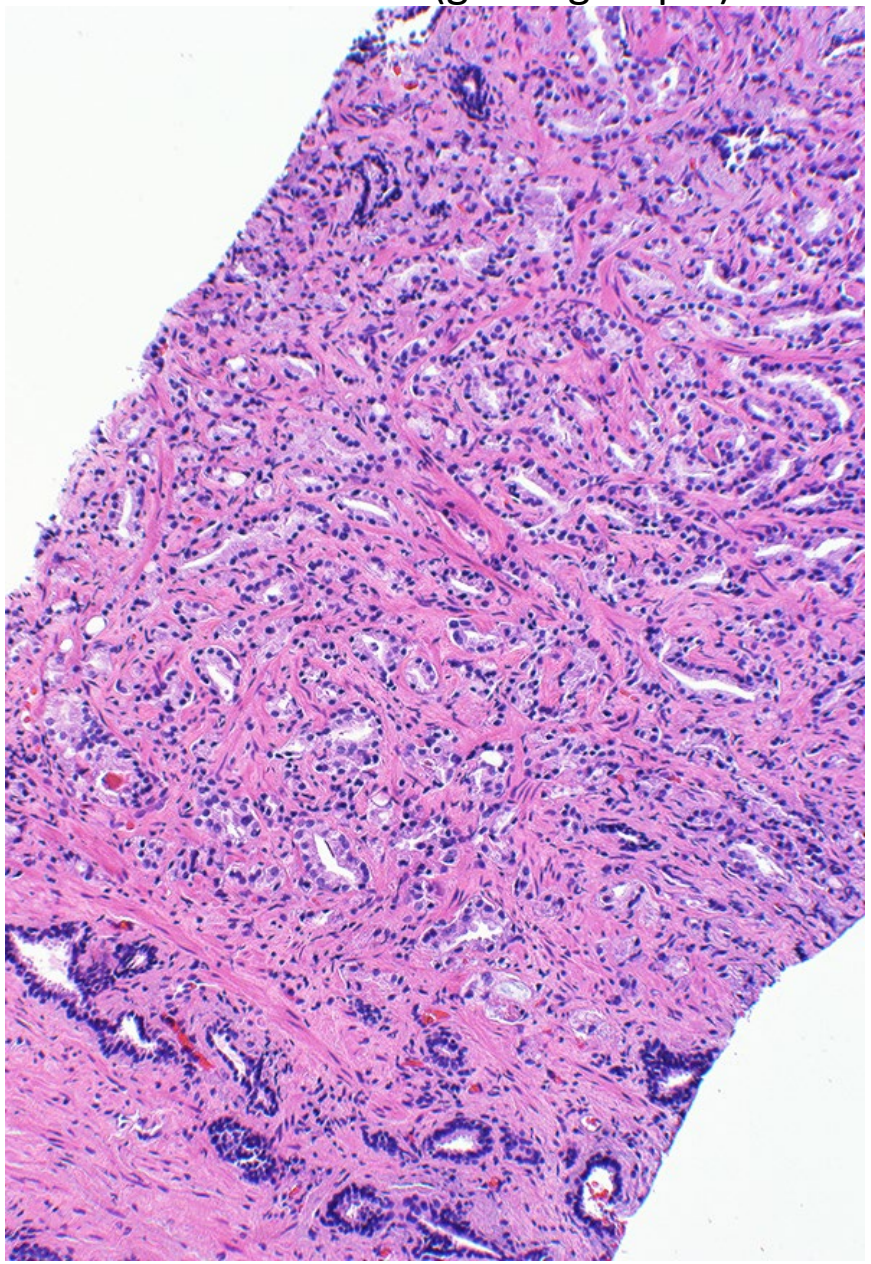
Gleason 3+3=6 (grade group 1)



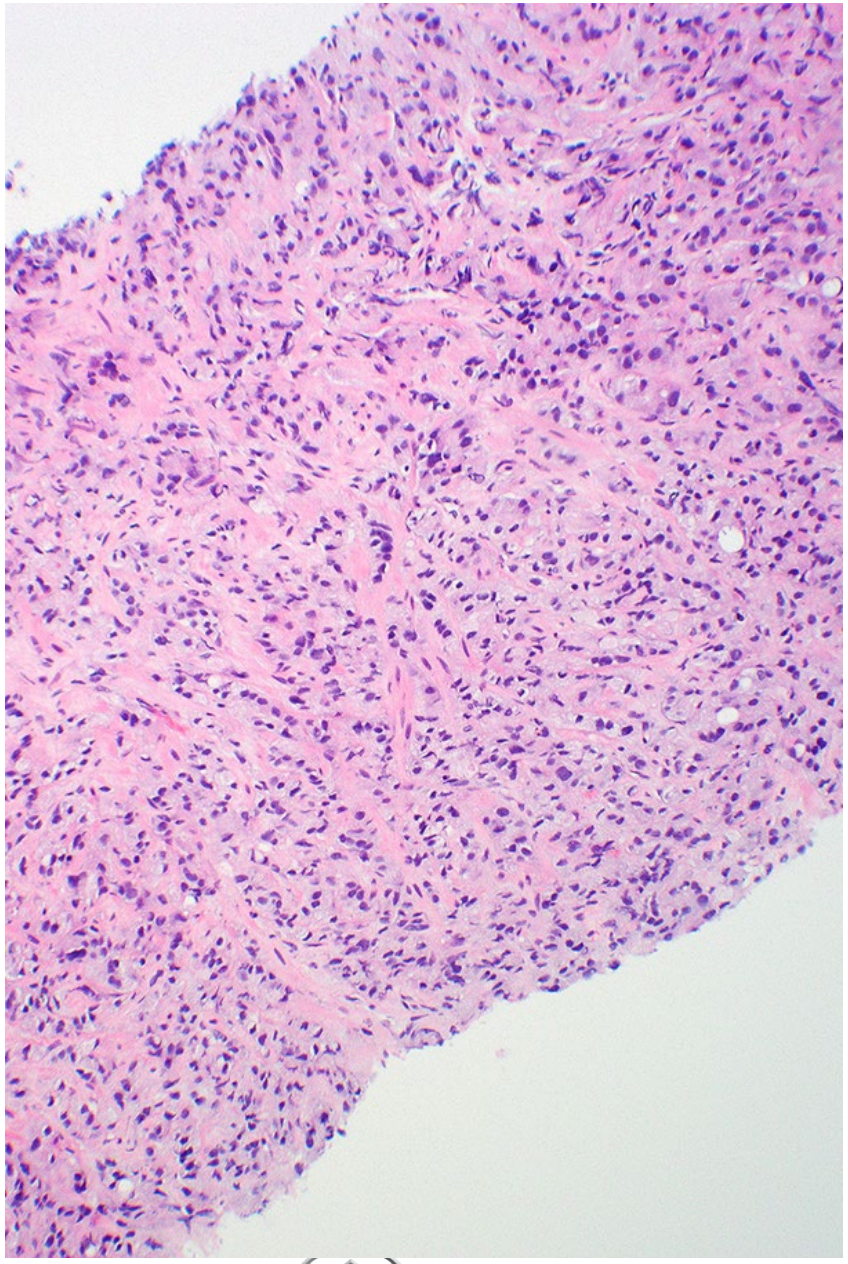
Well formed glands

Gleason 3+4=7 (grade group 2)



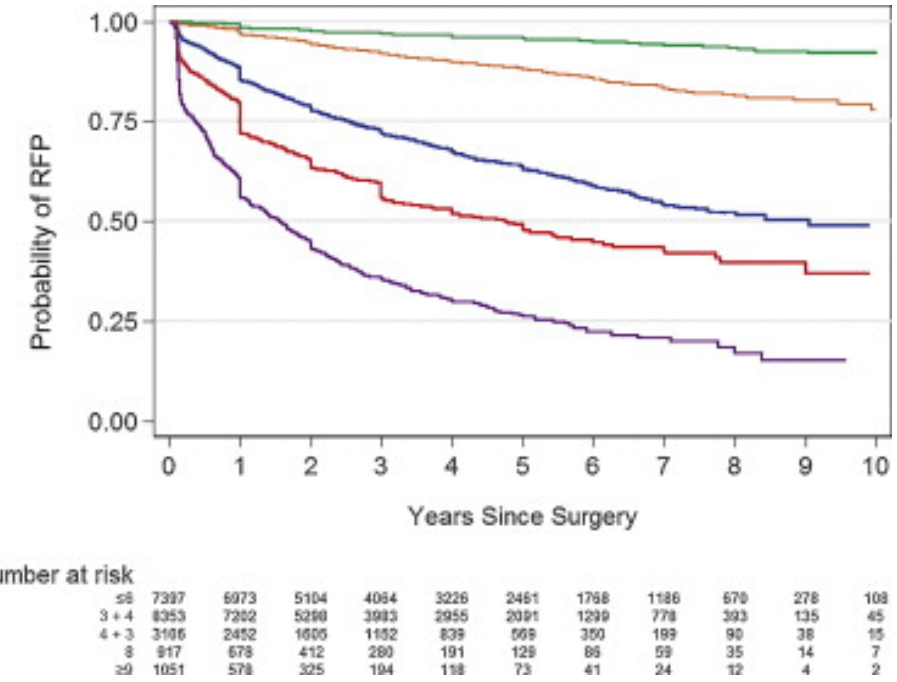
Well formed and poorly formed glands

Gleason 4+5=9 (grade group 5)



Poorly formed glands and solid growth

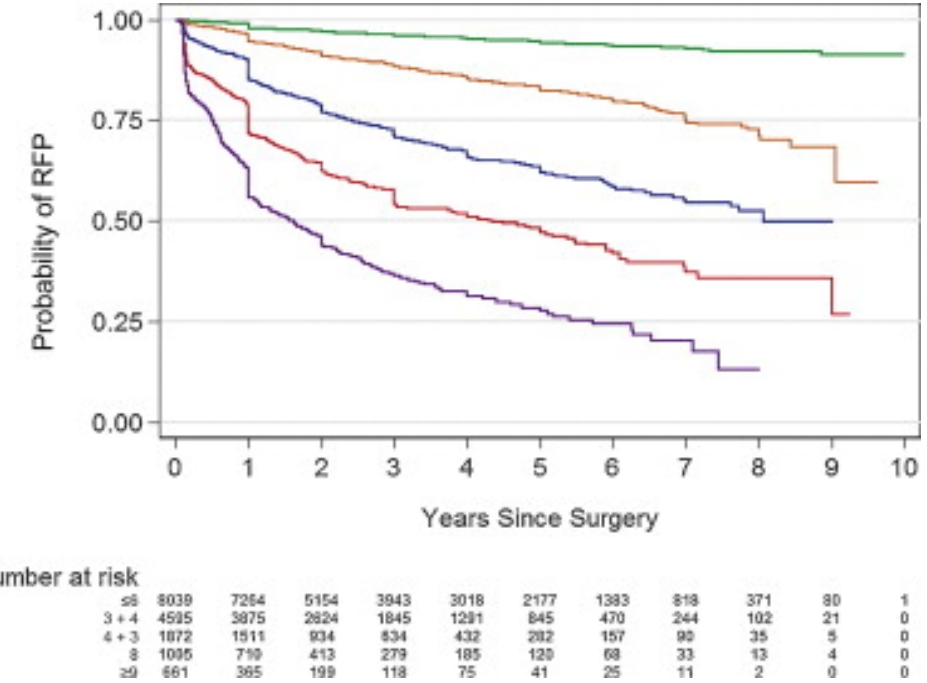
A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score
Epstein JI et al, Eur Urol, *in press*



Number at risk

≤6	7337	6973	5104	4084	3226	2461	1768	1186	670	278	108
3 + 4	8353	7202	5298	3983	2955	2091	1299	778	393	135	45
4 + 3	3106	2452	1605	1152	839	569	350	199	90	38	15
8	917	678	412	280	191	129	86	59	35	14	7
≥9	1051	578	325	194	118	73	41	24	12	4	2

Recurrence-free progression following radical prostatectomy stratified by prostatectomy grad.
Green line: Gleason score ≤6,
grade group 1. Orange line: Gleason score 3 + 4, grade group 2.
Dark blue line: Gleason score 4 + 3, grade group 3.
Red line: Gleason score 8, grade group 4.
Purple line: Gleason score ≥9, grade group 5.



Number at risk

≤6	8039	7254	5154	3943	3018	2177	1383	818	371	80	1
3 + 4	4525	3875	2624	1845	1291	845	470	244	102	21	0
4 + 3	1872	1511	934	634	432	282	157	90	35	5	0
8	1035	719	413	279	185	120	68	33	13	4	0
≥9	661	365	199	118	75	41	25	11	2	0	0

Recurrence-free progression following radical prostatectomy stratified by pre-prostatectomy biopsy grade.
Green line: Gleason score ≤6, grade group 1.
Orange line: Gleason score 3 + 4, grade group 2.
Dark blue line: Gleason score 4 + 3, grade group 3.
Red line: Gleason score 8, grade group 4.
Purple line: Gleason score ≥9, grade group 5

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Genomic Profiles/Signatures

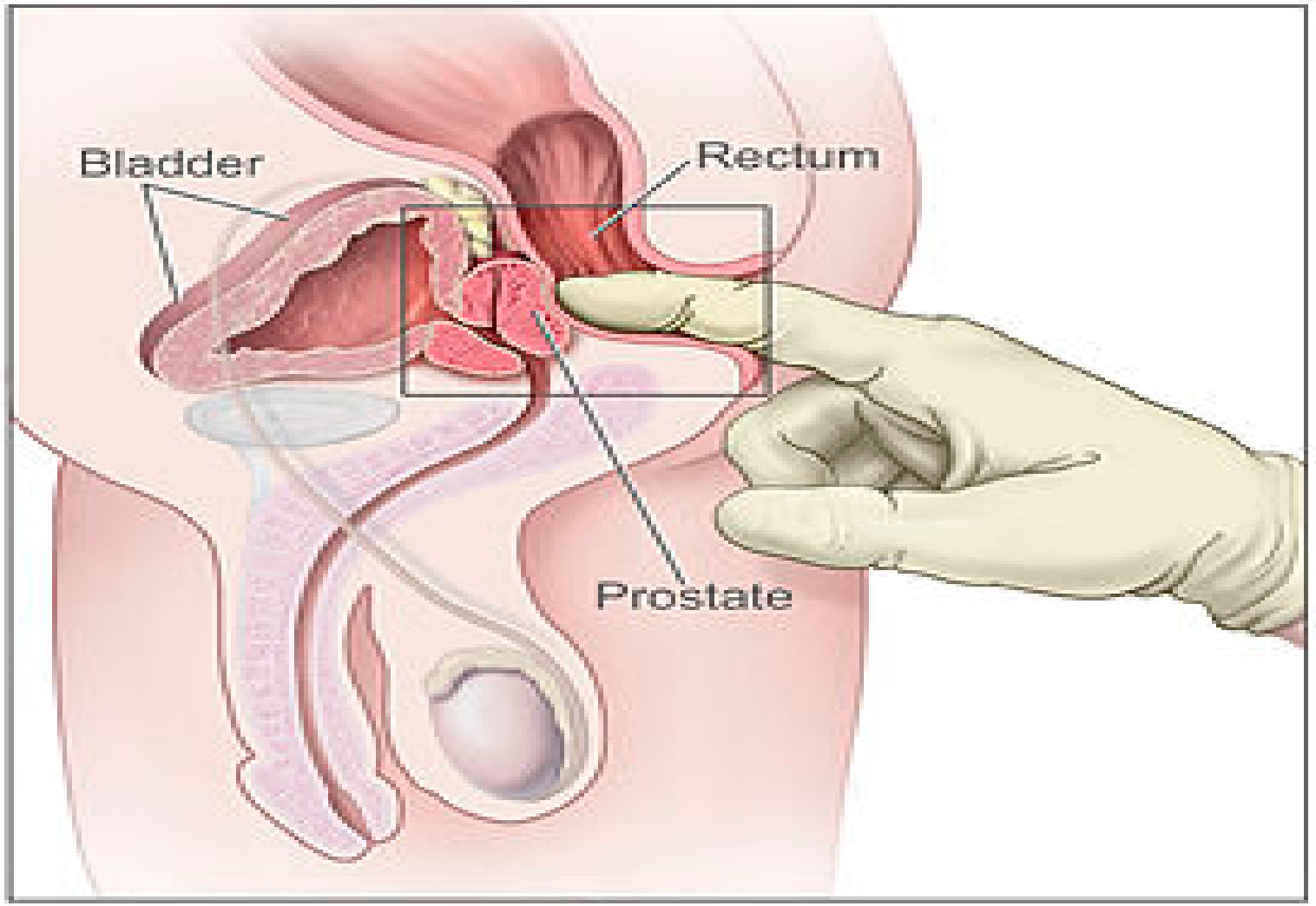
- Copy Number Alterations (CNA)
- *Prolaris* (Myriad)
- *Oncotype-Dx* (Genomic Health)
- Decipher
- ProMark

Diagnosis

- Digital Rectal exam (**DRE**)
- Prostate Specific Antigen blood test (**PSA**)
- **Biopsy**

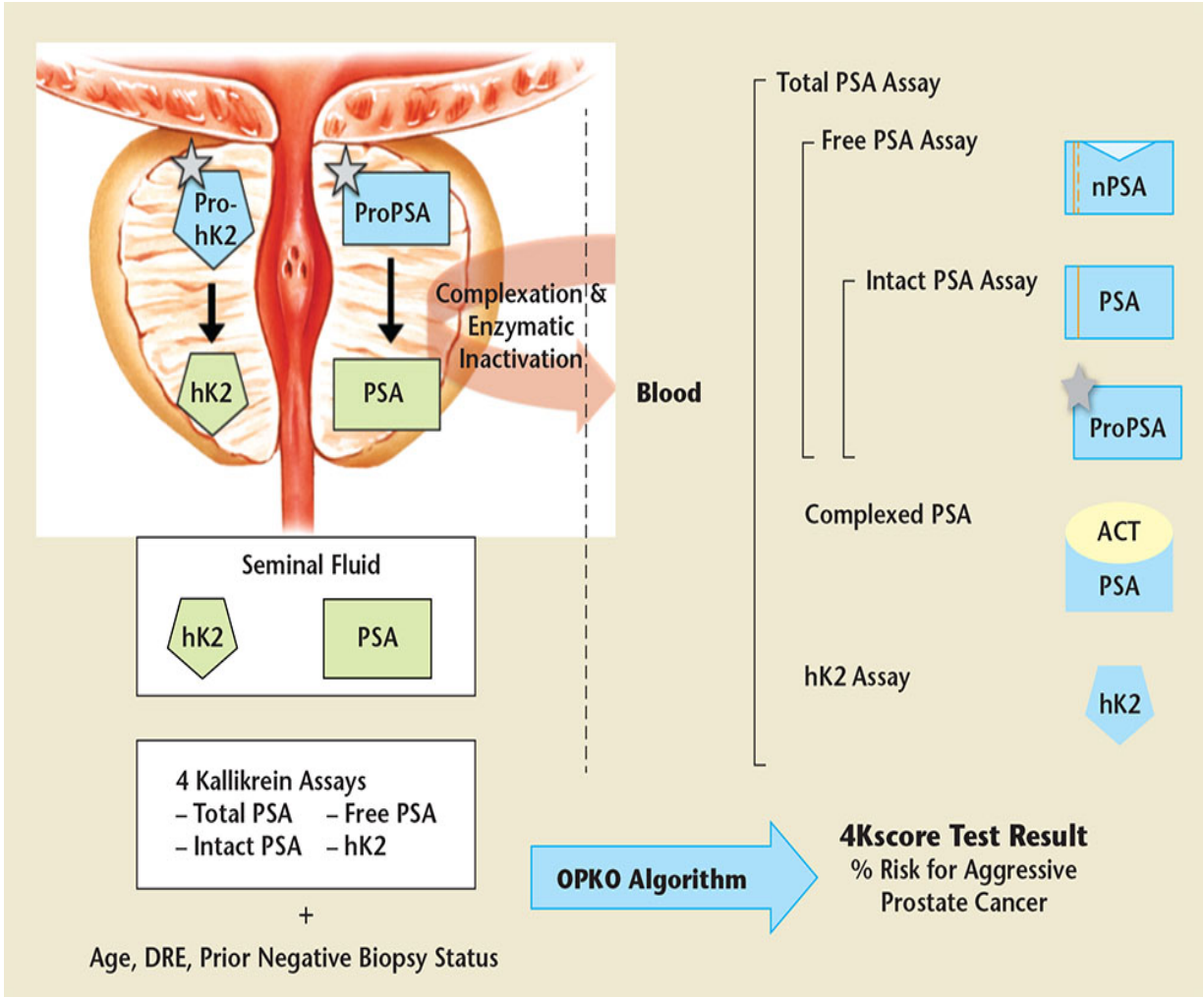
NOT SYMPTOM DRIVEN

Digital Rectal Exam (DRE)




walldesk.net

PSA



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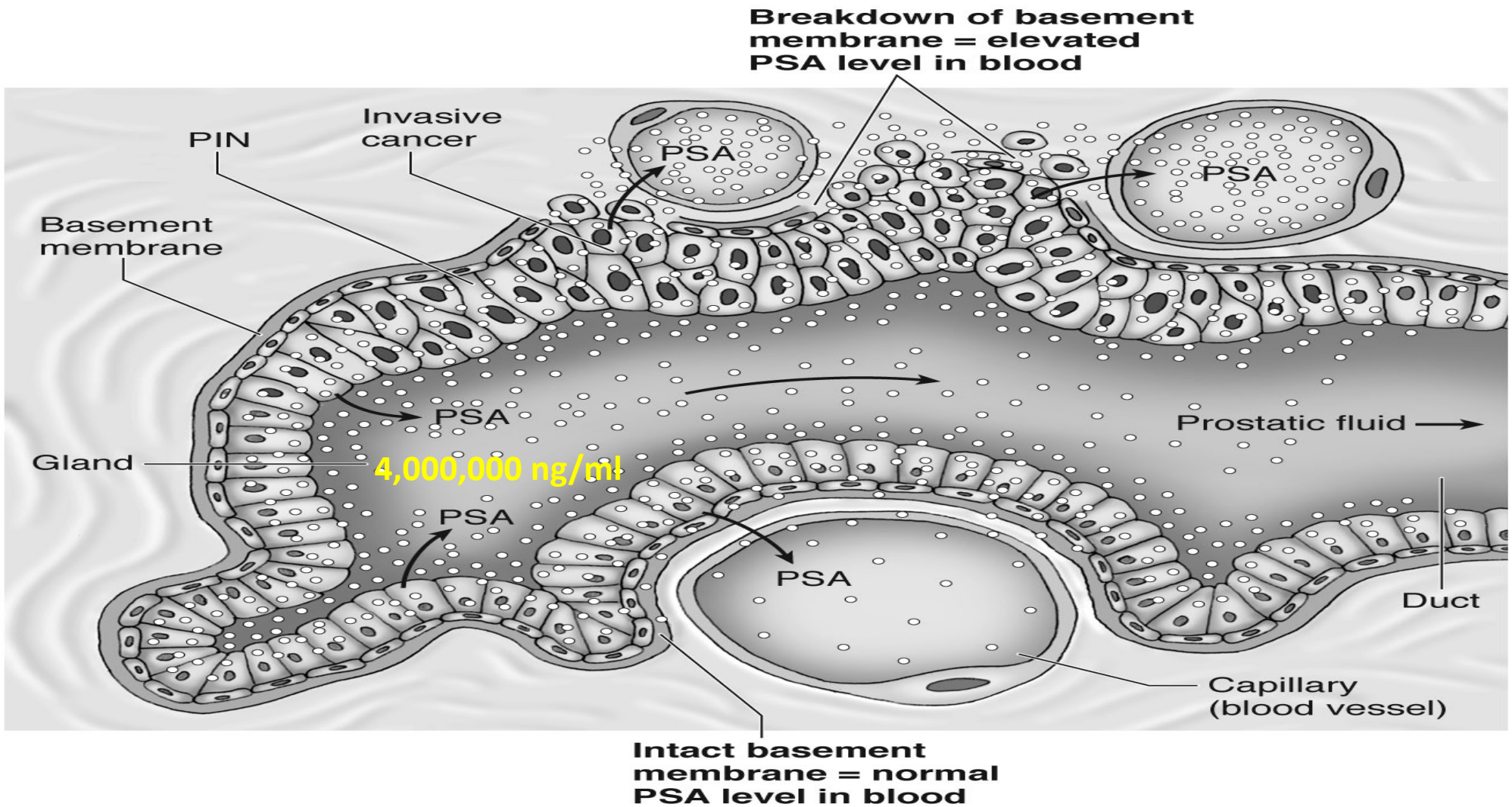

Breakdown of basement membrane = elevated PSA level in blood
PIN
Invasive cancer
Basement membrane
PSA
PSA
PSA
Prostatic fluid
Gland
4,000,000 ng/ml
PSA
PSA
Duct
Capillary (blood vessel)
Intact basement membrane = normal PSA level in blood

Measured Annually, PSA Levels Vary Spontaneously

Percent of 972 healthy men in a dietary trial for colon polyps who had an abnormal PSA during 5-year period - and probability that PSA would later *return to normal* then *remain normal*

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 %
Age-specific	20%	55 %	83 %
%FPSA (PSA 4-10)	15%	53 %	74 %

The high degree of PSA variability leads to false positive elevations, reducing specificity of PSA for cancer.

Modified from Eastham J, et al. *JAMA* 2003;289:2695.

U. S. Preventive Services Task Force (USPSTF) 2010 - 2012
Screening for Prostate Cancer

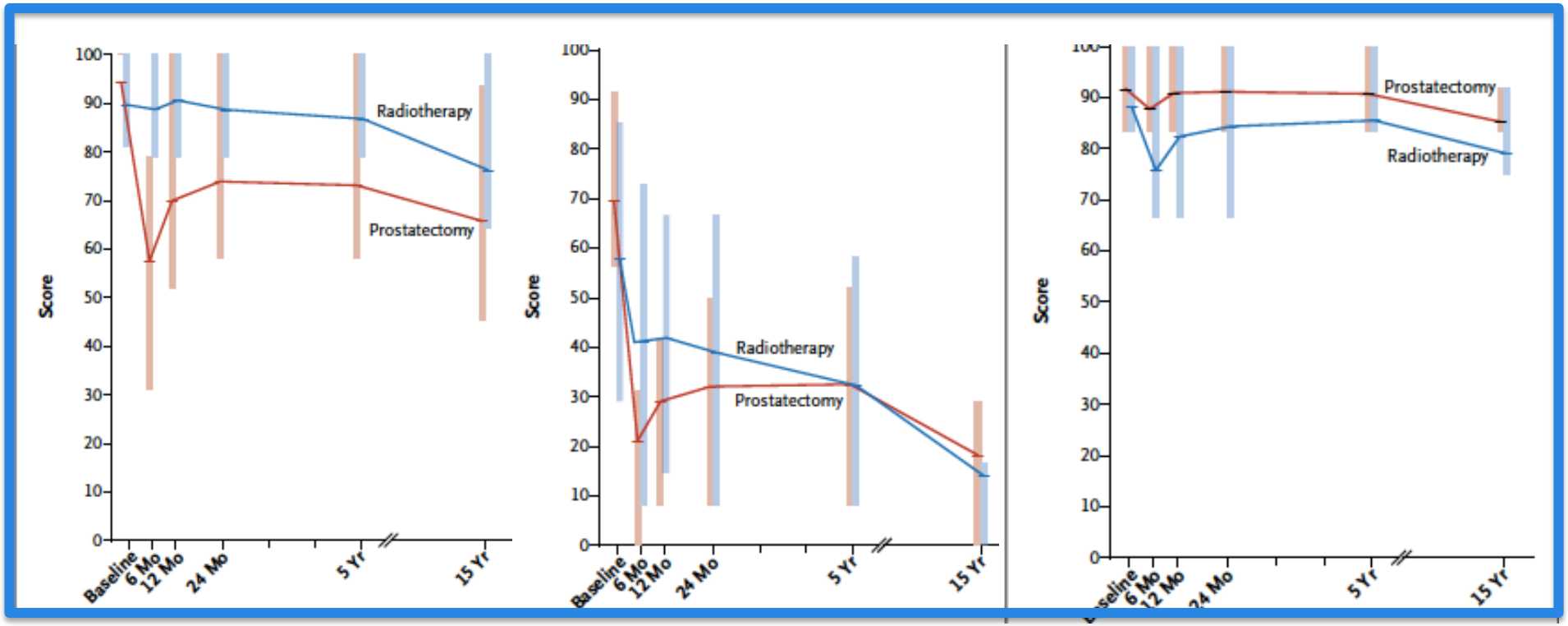
Grade: D

Definition: The USPSTF recommends against screening for prostate cancer with PSA. There is moderate or high certainty that there is no net benefit or that the harms outweigh the benefits.

Suggestions for practice: Discourage the use of PSA screening.

Declines in self-reported urinary, sexual or bowel function are common after surgery or radiation therapy

Urinary Sexual Bowel



Resnick M, et al. *N Engl J Med.* 2013;368:436-45.

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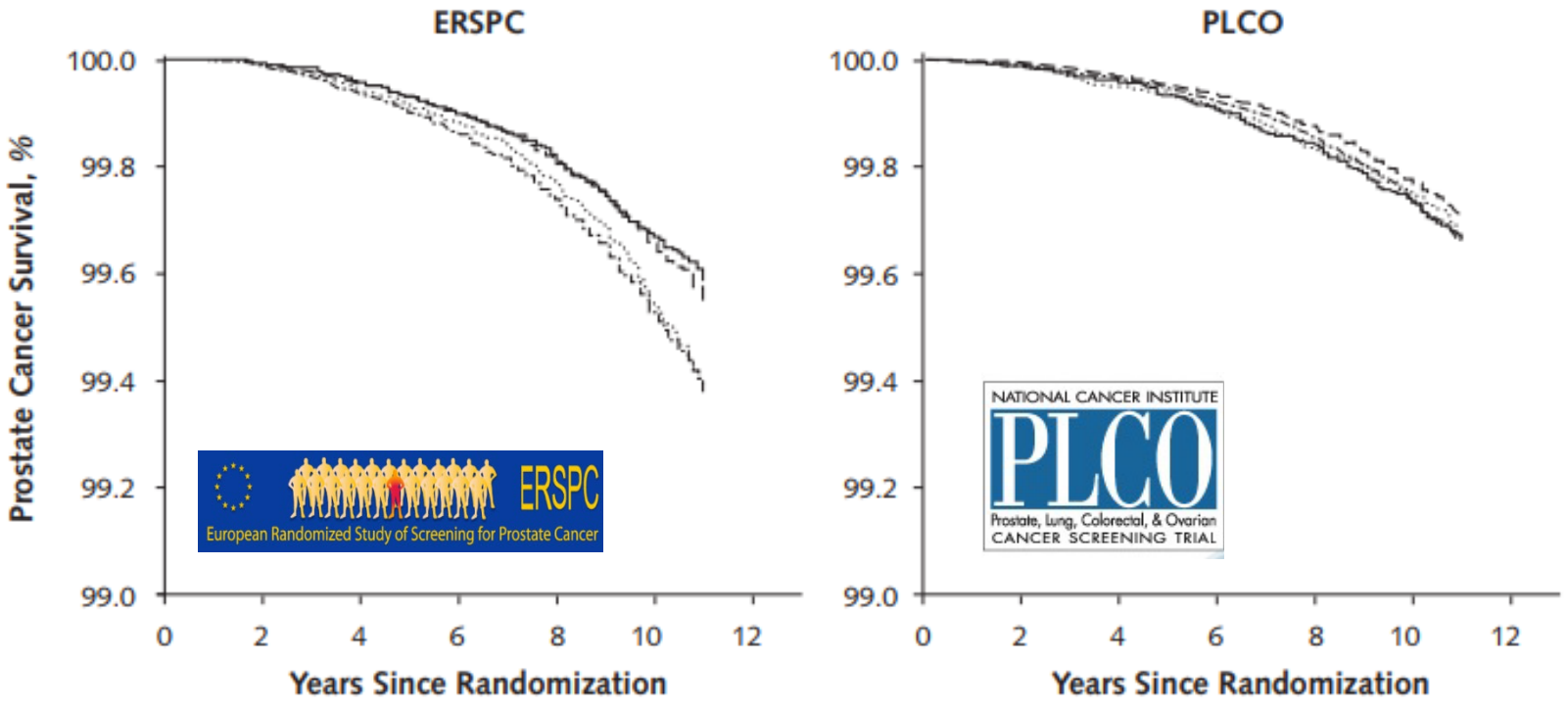
Annals of Internal Medicine ORIGINAL RESEARCH

Reconciling the Effects of Screening on Prostate Cancer Mortality in the ERSPC and PLCO Trials

Both ERSPC and PLCO now provide comparable evidence that screening reduces prostate cancer mortality by 30%



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

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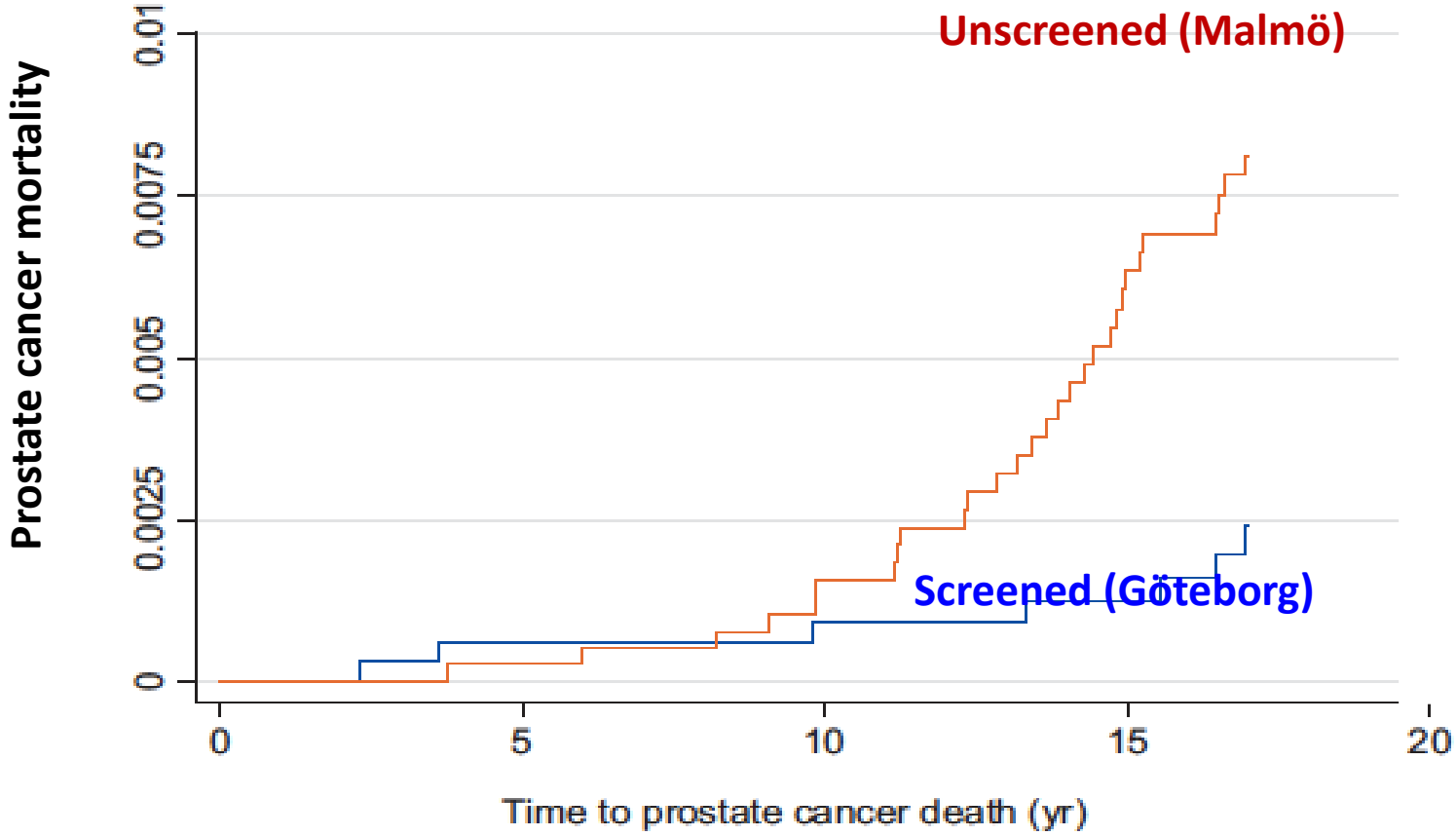
Starting screening at ages 50-54 reduced pros ca mortality by 71% at 17 yrs compared to no screening (comparative effectiveness trials) while cancer diagnosis was increased 2-fold



To prevent 1 prostate cancer death at 17 years

- 176 men needed to be screened
- 16 men needed to be diagnosed

Carlsson S, Vickers A, Lilja H et al. *Eur Urol*. 2017;71:46-52.

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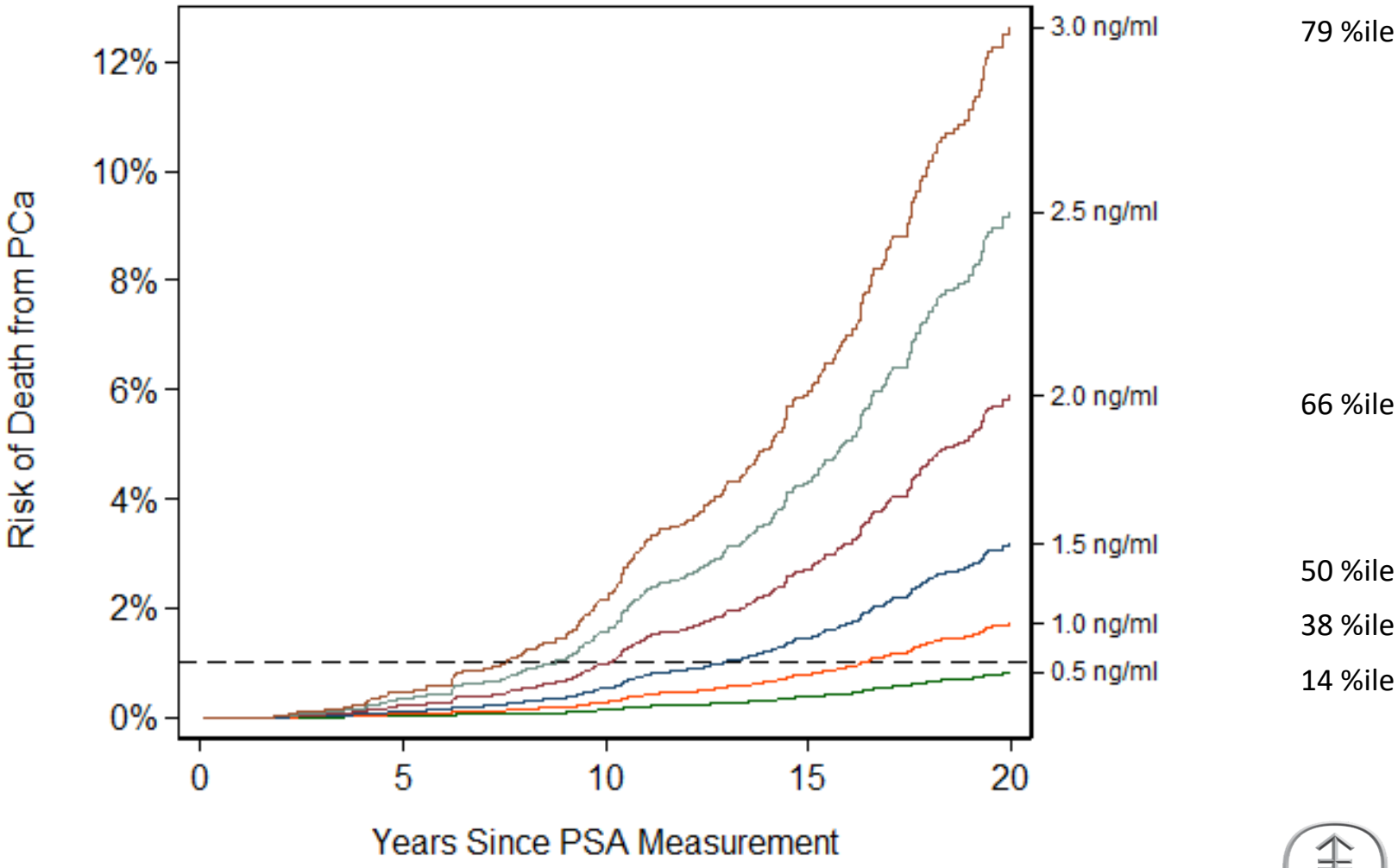
PSA at mid-life is the most powerful predictor of the risk that a man will eventually die of prostate cancer (>FHx, ethnicity).

Risk of death from prostate cancer by PSA levels in healthy men age 60



Sjoberg D, Vickers A, Lilja H et al. *Eur Urol* 2018; 73:941; *Vertosick E, et al. *J Urol*. 2014;192(3):724-8.

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How to increase the benefits and reduce the risks of screening for prostate cancer

Recognize that PSA is highly sensitive to the presence of cancer but not very specific. However, when properly performed:

- PSA screening substantially reduces mortality from cancer
- PSA at midlife strongly predicts lifetime risk of dying of cancer
- PSA testing begining early - at age 45-50 - reduces mortality even more than screening begining after age 60 - *screen early but screen intelligently*!

Vickers AJ, Lilja H. Time for another rethink on prostate cancer screening. *Nat Rev Clin Oncol* 2011;9:7-8.
Carlsson S, Vickers AJ, Roobol M et al. Prostate cancer screening. *J Clin Oncol* 2012;30:2581-4.
Vickers A, Roobol M, Lilja H. *Annu Rev Med* 2012; 63:161-70.

NCCN Guidelines Version 1.2019
Prostate Cancer Early Detection

NCCN Guidelines Index
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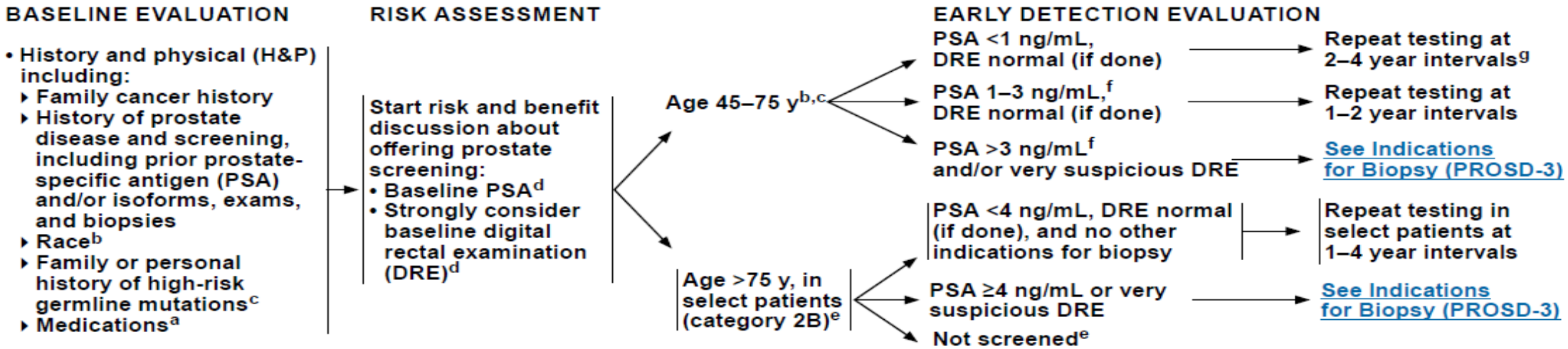
Discussion



[a] Medications such as 5α-reductase inhibitors (finasteride and dutasteride) are known to decrease PSA by approximately 50%. PSA values in these men should be corrected accordingly.

[b] African-American men have a higher incidence of prostate cancer, increased prostate-cancer mortality, and earlier age of diagnosis compared to Caucasian-American men. This is attributable to a greater risk of developing preclinical prostate cancer and a higher likelihood that a preclinical tumor will spread. Consequently, it is reasonable for African-American men to consider beginning shared decision-making about PSA screening at age 40 and to consider screening at annual intervals rather than every other year. Tsodikov A, Gulati R, de Carvalho TM, et al. Is prostate cancer different in black men? Answers from 3 natural history models. Cancer 2017;123:2312-2319.

[c] If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional is recommended. *BRCA1/2* pathogenic mutation carriers have an increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline *BRCA2* mutations occurs earlier and is more likely to be associated with prostate cancer mortality. Consequently, it is reasonable for men with germline *BRCA1/2* mutations to consider beginning shared decision-making about PSA screening at age 40 and to consider screening at annual intervals rather than every other year.

[d] The best evidence supports the use of serum PSA for the early detection of prostate cancer. DRE should not be used as a stand-alone test, but should be performed in those with an elevated serum PSA. DRE may be considered as a baseline test in all patients as it may identify high-grade cancers associated with "normal" serum PSA values. Consider referral for biopsy if DRE is very suspicious. Halpern JA, Shoag JE, Mittal S, et al. Prognostic significance of digital rectal examination and prostate specific antigen in the prostate, lung, colorectal and ovarian (PLCO) cancer screening arm. J Urol 2017;197:363-368.

[e] Testing after 75 years of age should be done only in very healthy men with little or no comorbidity (especially if they have never undergone PSA testing) to detect the small number of aggressive cancers that pose a significant risk if left undetected until signs or symptoms develop. Widespread screening in this population would substantially increase rates of overdetection and is not recommended.

[f] The median PSA values for men aged 40–49 years range from 0.5–0.7 ng/mL, and the 75th percentile values range from 0.7–0.9 ng/mL. Men who have a PSA above the median for their age group are at a higher risk for prostate cancer and aggressive prostate cancer. The higher above the median, the greater the risk.

[g] Men ≥60 years with PSA <1.0 ng/mL and men >75 years of age with a PSA <3.0 ng/mL have a very low risk of prostate cancer metastases or death and may be counseled to consider stopping PSA testing. This low risk is especially true for those in the latter category.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Newer PSA marker panels increase specificity, reduce false positives and help to identify high-grade cancers

<u>New marker panels</u>

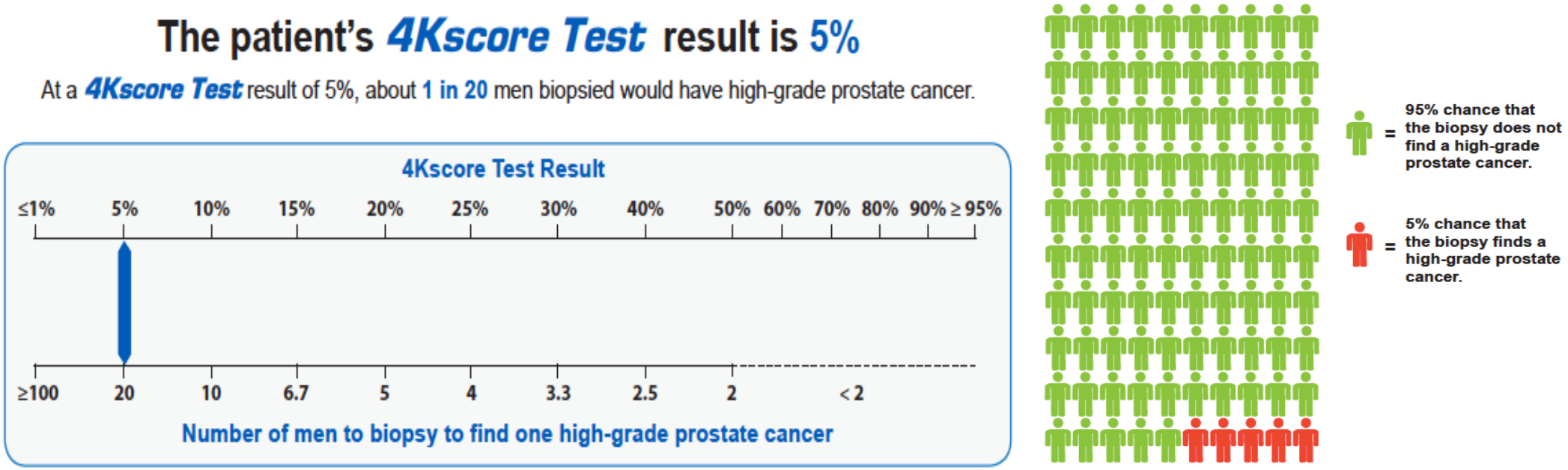
4K panel = tPSA, fPSA, iPSA, hK2*

phi* = ([-2] proPSA/fPSA x √tPSA)*

Urinary PCA3

*OPKO Diagnostics, Inc.
** Beckman Coulter, Inc.
***GenProbe

The 4Kscore presents to the clinician the patient's individual risk of biopsy-detectable high-grade prostate cancer (GS7 or greater)



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U. S. Preventive Services Task Force (USPSTF)

Revised Recommendations for Screening for Prostate Cancer, 2018

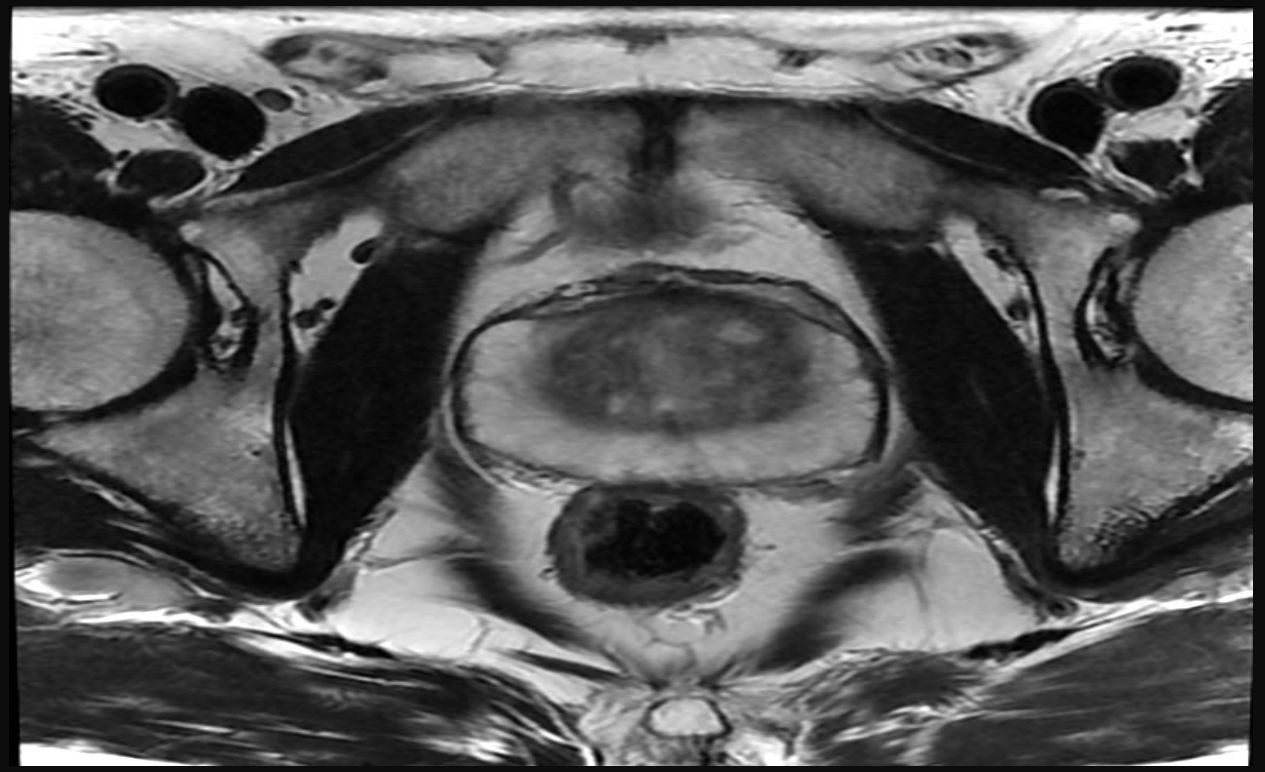
Grade: C (D for men >70)

Definition: For men ages 55-69, the decision for screening should be an individual one. Clinicians should inform men about the small potential benefits and the risks of harm to many men, including false-positive tests, unnecessary work-ups, overdiagnosis and overtreatment, and treatment-related complications. For men age 70+, the USPSTF recommends against screening.

Suggestions for practice: Individualized decision making after discussion with a clinician.

US Preventive Services Task Force, et al. JAMA 2018; 319:1901.

PROSTATE MRI
A valuable tool in the diagnosis of prostate cancer



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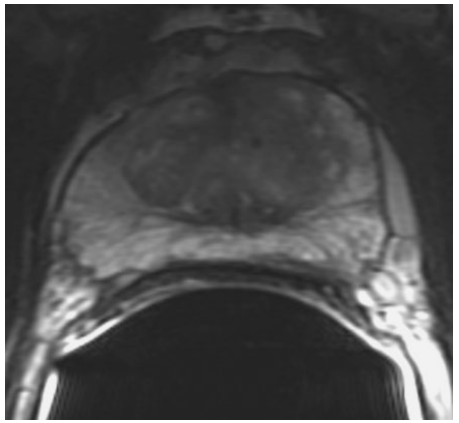
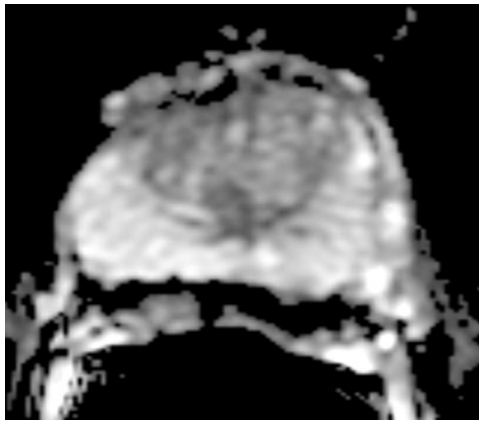
Multiparametric MRI of the prostate

Identifies impalpable cancers sometimes missed by systematic biopsies

Normal (no tumor)

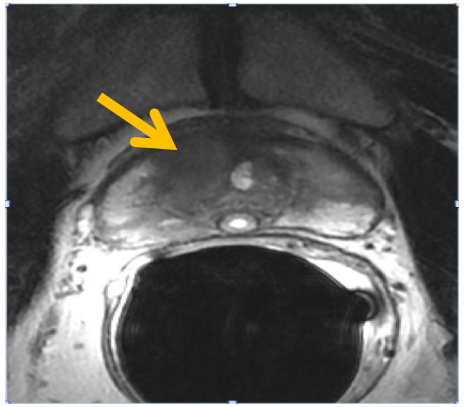


T2-weighted image

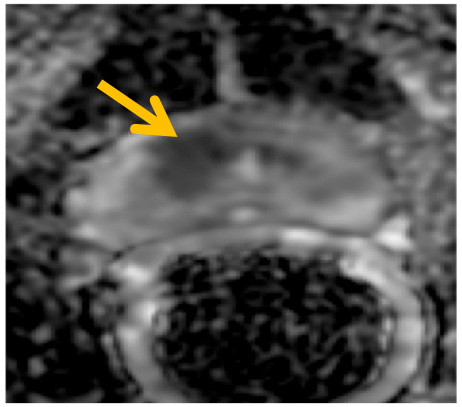


ADC map from DWI

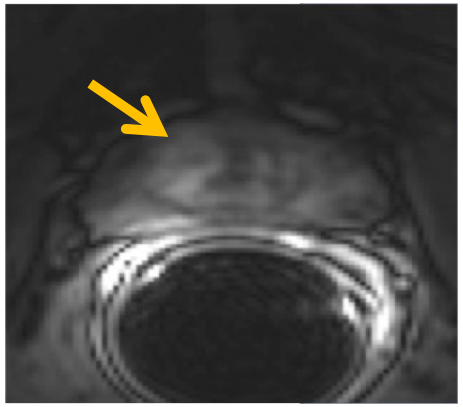
TZ cancer



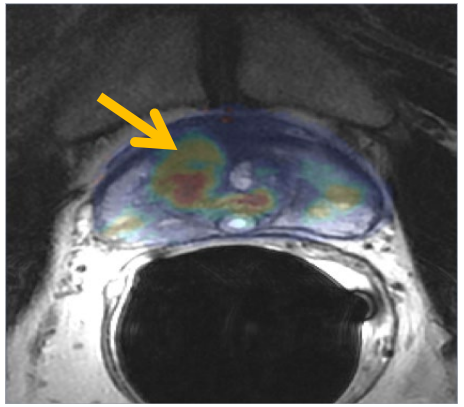
T2-weighted image



ADC map from DWI



DCE-MRI



K-trans map from DCE-MRI fused with T2-weighted image

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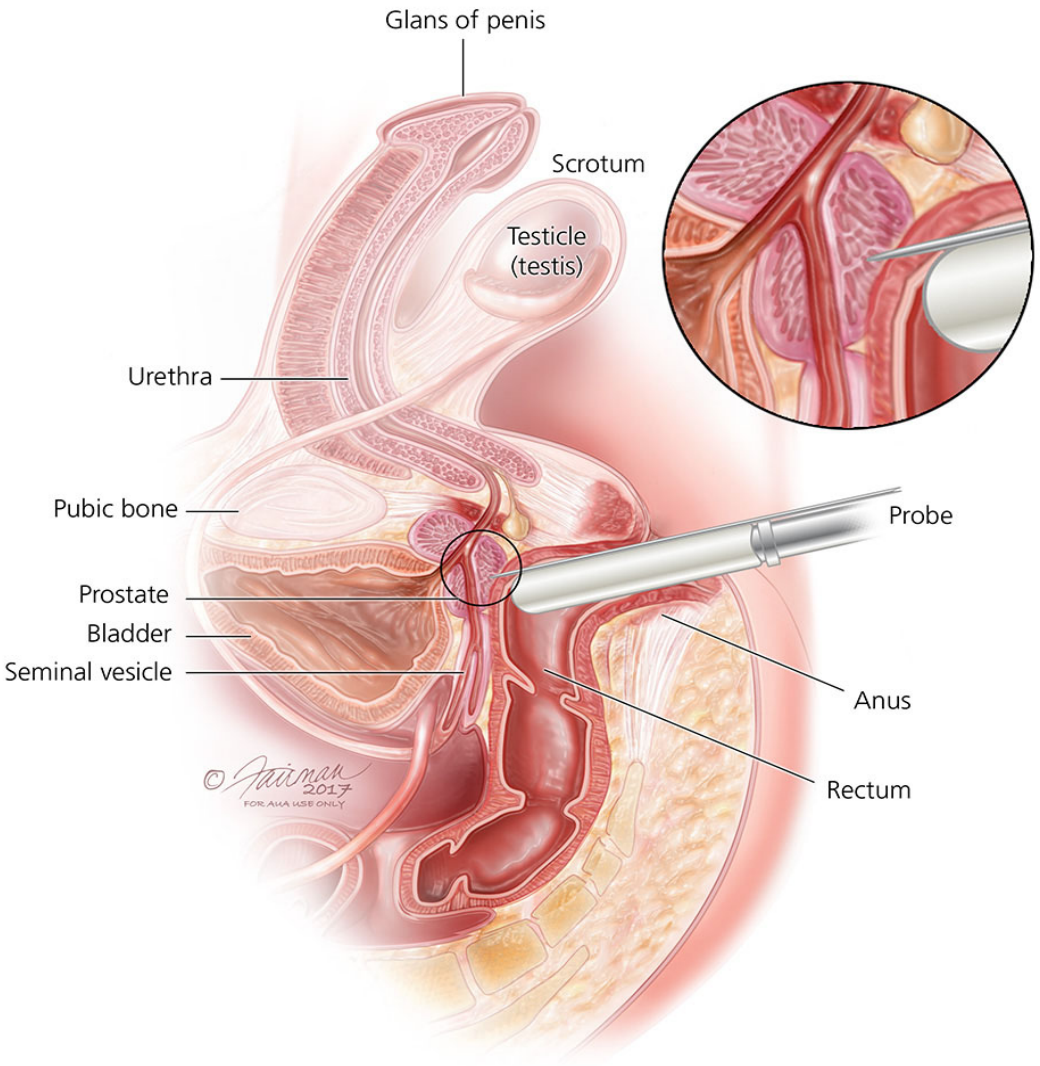
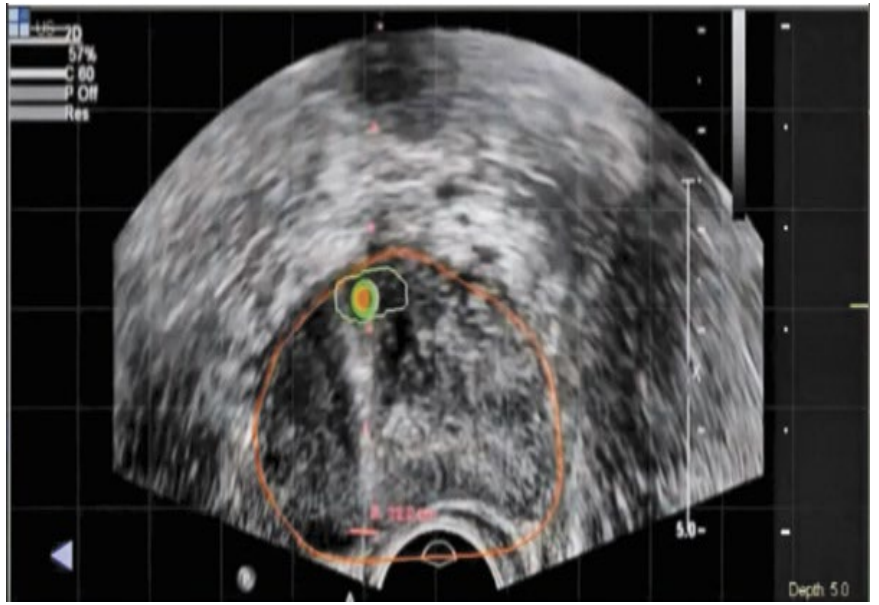
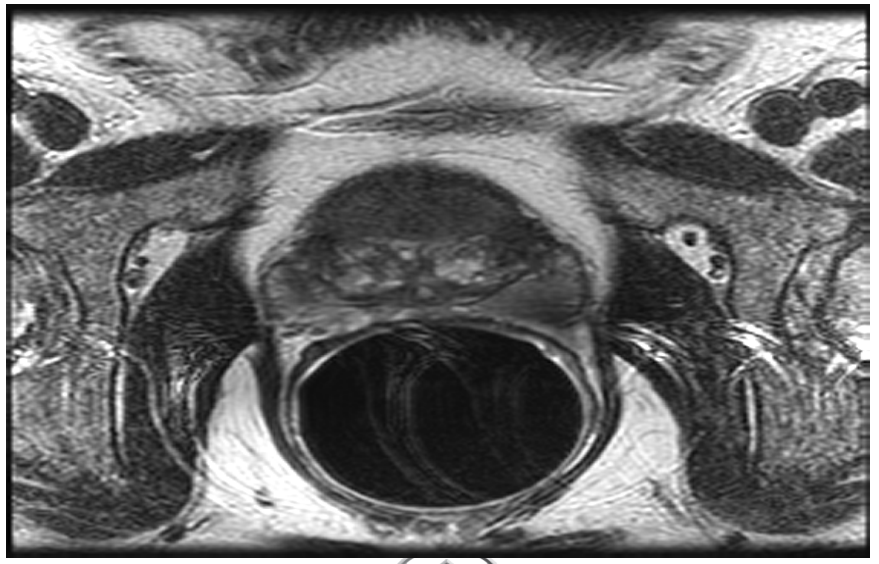
BIOPSY

PROSTATE BIOPSY: TRANSRECTAL ULTRASOUND







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Risk Diagnosis Screening Grading **Staging**

Stage is the determination of the extent of the cancer.

STAGE AND GRADE

DETERMINE

TREATMENT

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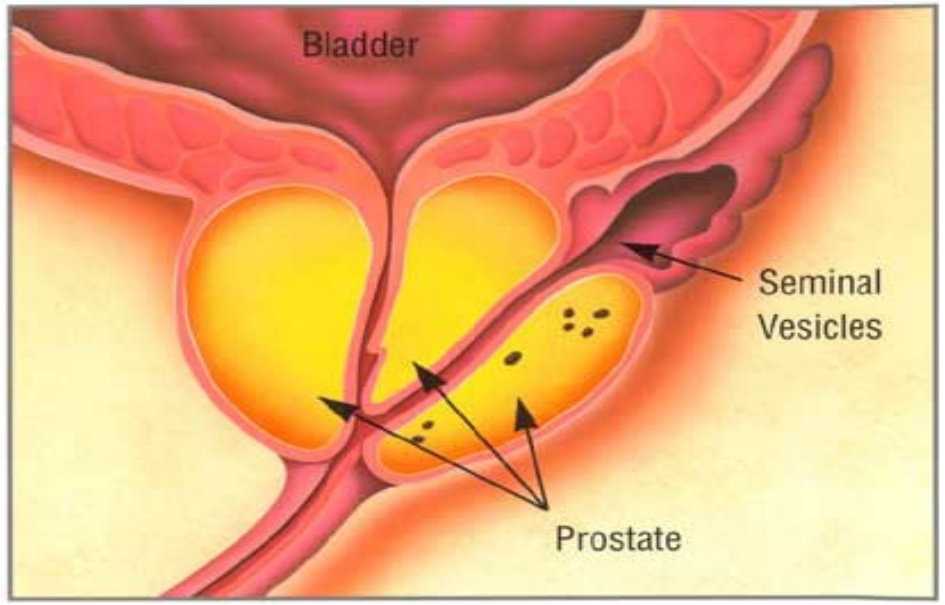
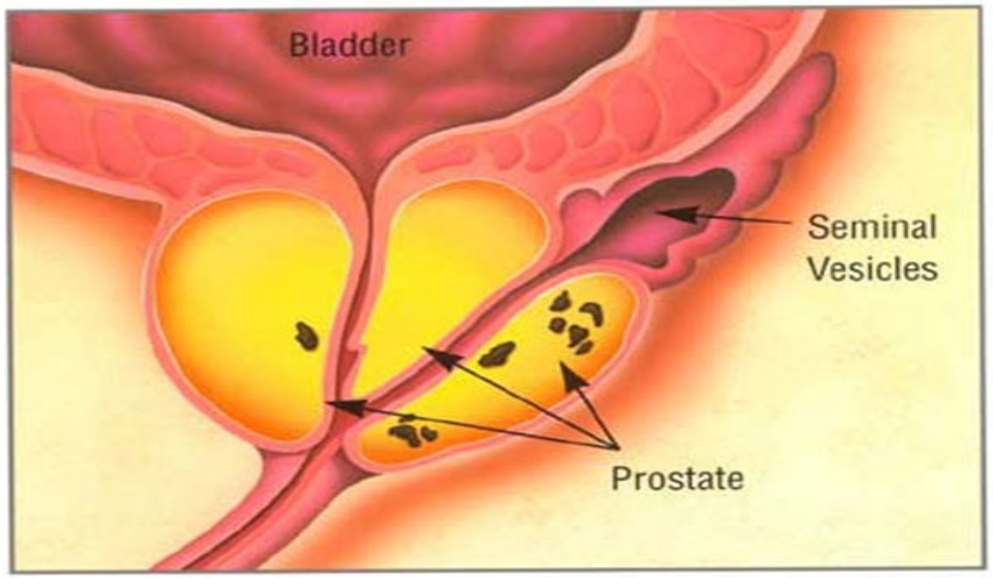
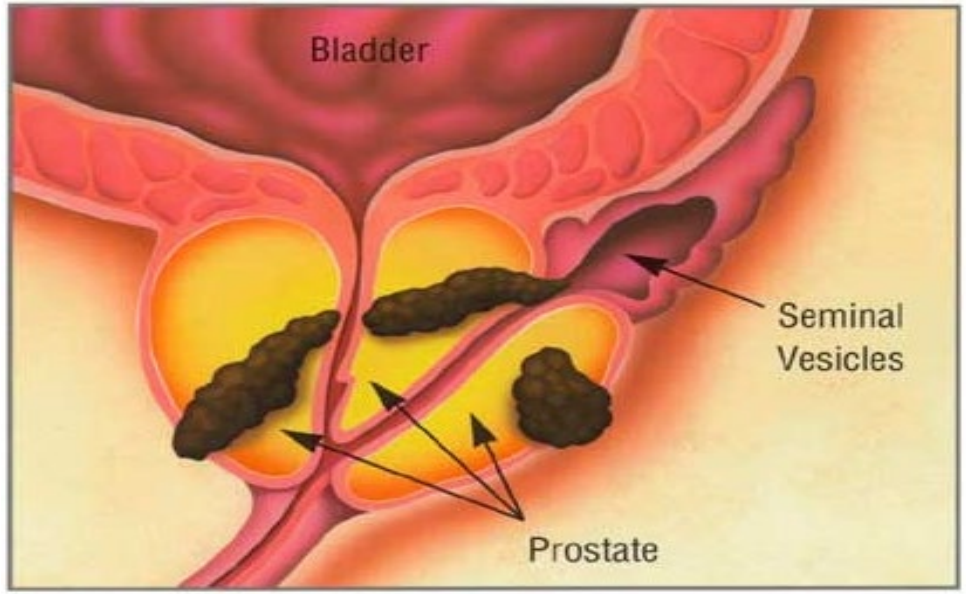
STAGE I



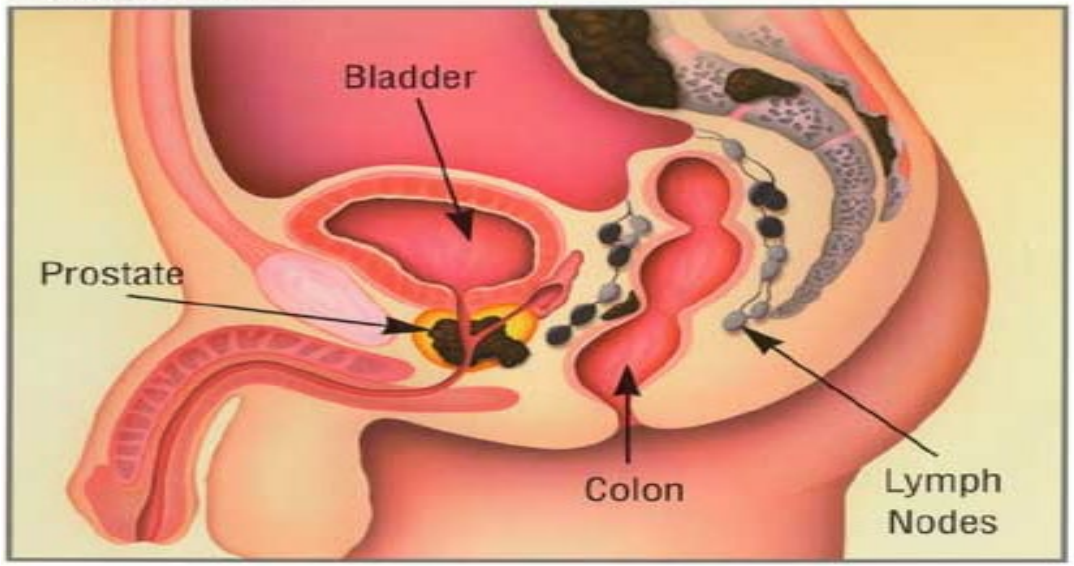
STAGE II



STAGE III



STAGE IV



American Joint Committee on Cancer (AJCC)
TNM Staging System For Prostate Cancer (8th ed., 2017)
***Table 1.* Definitions for T, N, M**
Clinical T (cT)

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.

Pathological T (pT)

T	Primary Tumor
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Note: There is no pathological T1 classification.
Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Note: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.

Treatment options - 1988

- Surgery: Open radical prostatectomy
- Radiation: Cobalt or brachytherapy
- Hormone therapy: Castration, estrogen

Treatment Options Today

- Surgery – Open, Laparoscopic , or **Robotic** RP
- Radiation – External beam: Conformal, IGRT, IMRT, Proton beam, Gamma knife, **CyberKnife**, Brachytherapy with gold, iodine or palladium seeds – permanent or high dose removable.
- Hormone Therapy – Orchiectomy, GnRH (**Lupron**, Zoladex, Valstar, …..) Anti androgens (flutamide, Casodex). **abiraterone**, enzalutamide, apalutatmide – Neo-adjuvant, adjuvant, intermittent or continuous.
- Chemotherapy – mitoxantrone (Novantrone) ,estramustine phosphate (Emcyt), etoposide (Vepsid), paclitaxel (Taxol), **docetaxel** (Taxotere), doxorubicin (Adriamycin), vinblastine (Velban)
- Targeted Therapies – Dasatinib (Sprycel), Nilotinib (Tasigna), Trastuzumab (Herceptin), Gefitinib (Iressa), Erlotinib (Tarceva), Cetuximab (Erbitux) Lapatinib (Tykerb), Temsirolimus (Torisel),Bevacizumab (Avastin), Srafenib (Nexavar), Suitinib (Sutent), Rituximab (Rituxan), Alemtuxumab (Campath), Gemtuzmab (Mylotarg), Tostumomab (Bexxar), Ibritumomab (Zevalin)
- Vaccine Therapy – **Provenge**
- Cryotherapy – focal or whole gland
- Interstitial Laser Treatments
- Photodynamic Therapy
- **HIFU** – high intensity focused ultrasound
- Irreversible Electroporation
- **Active Surveillance**

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