

# Is Gleason 6 Really Prostate Cancer?

## *-YES*

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The logo for Tufts Medical Center, featuring the word "Tufts" in a large, bold, blue serif font, followed by "Medical Center" in a smaller, blue serif font to its right.

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# Outlines:

- **Summary of studies/evidence for Gleason 6 as cancer**
- **New evidence**
- **Shift debate from the label (cancer vs non-cancer) to better risk stratification for Gleason 6 cancer**

# What is “Cancer”

- **Uncontrolled growth of abnormal cells in a part of body**
  - **Local invasive/destructive growth**
  - **Distant metastasis**
  - **Death if not treated**

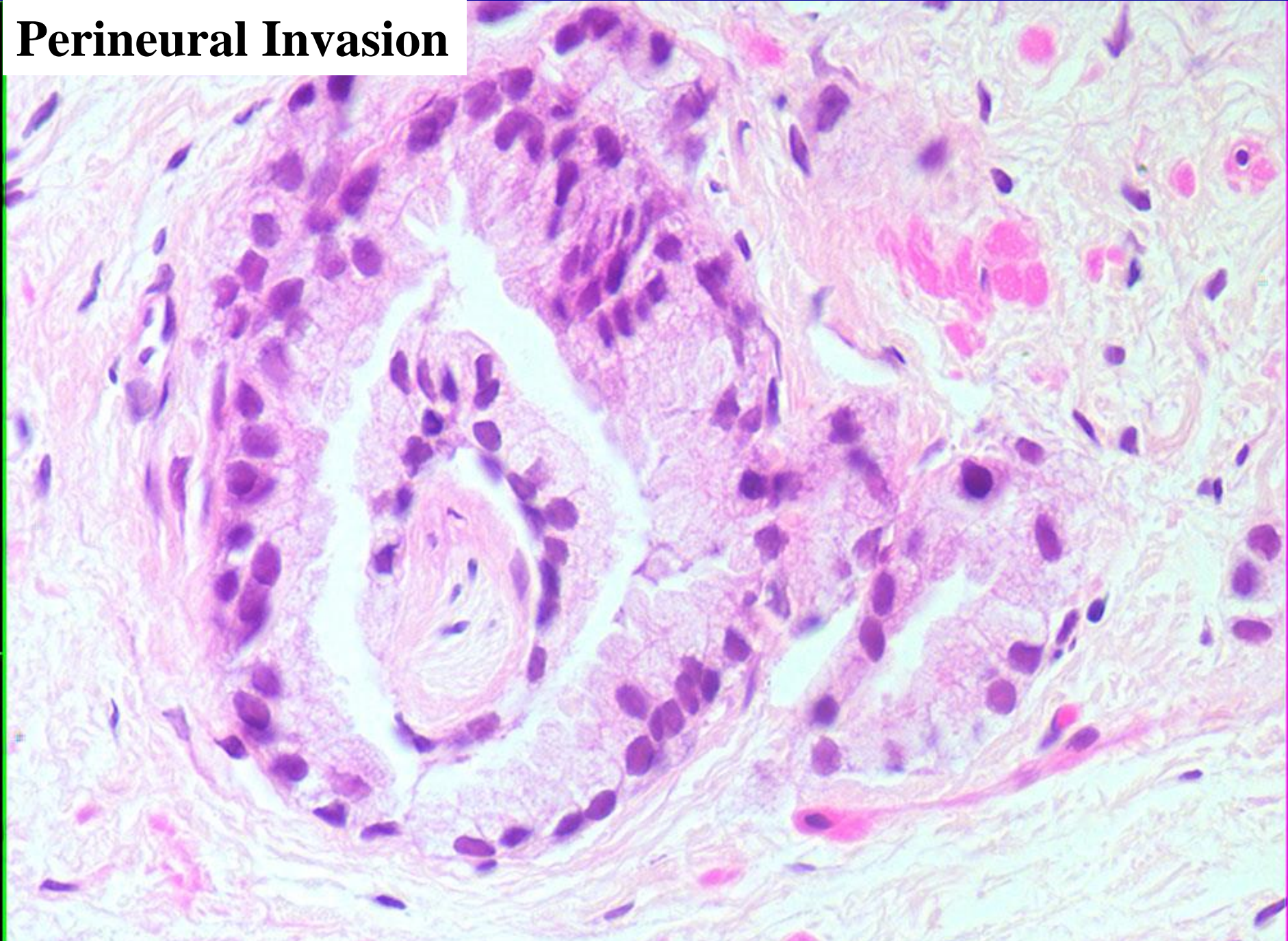
**Does Gleason 6 cancer fit this definition?**

# Pathological Arguments Favoring Calling Gleason 6 Prostate Tumors Cancer

## Morphologically it is Cancer

- **Loss of basal cells**
- **Cytologically (indistinguishable from higher grade cancer)**
- **Architecturally (ie. infiltrative)**
- **Merges in with higher grade cancer**
- **Local invasive growth**
  - **Perineural invasion**
  - **Extra-prostatic extension**

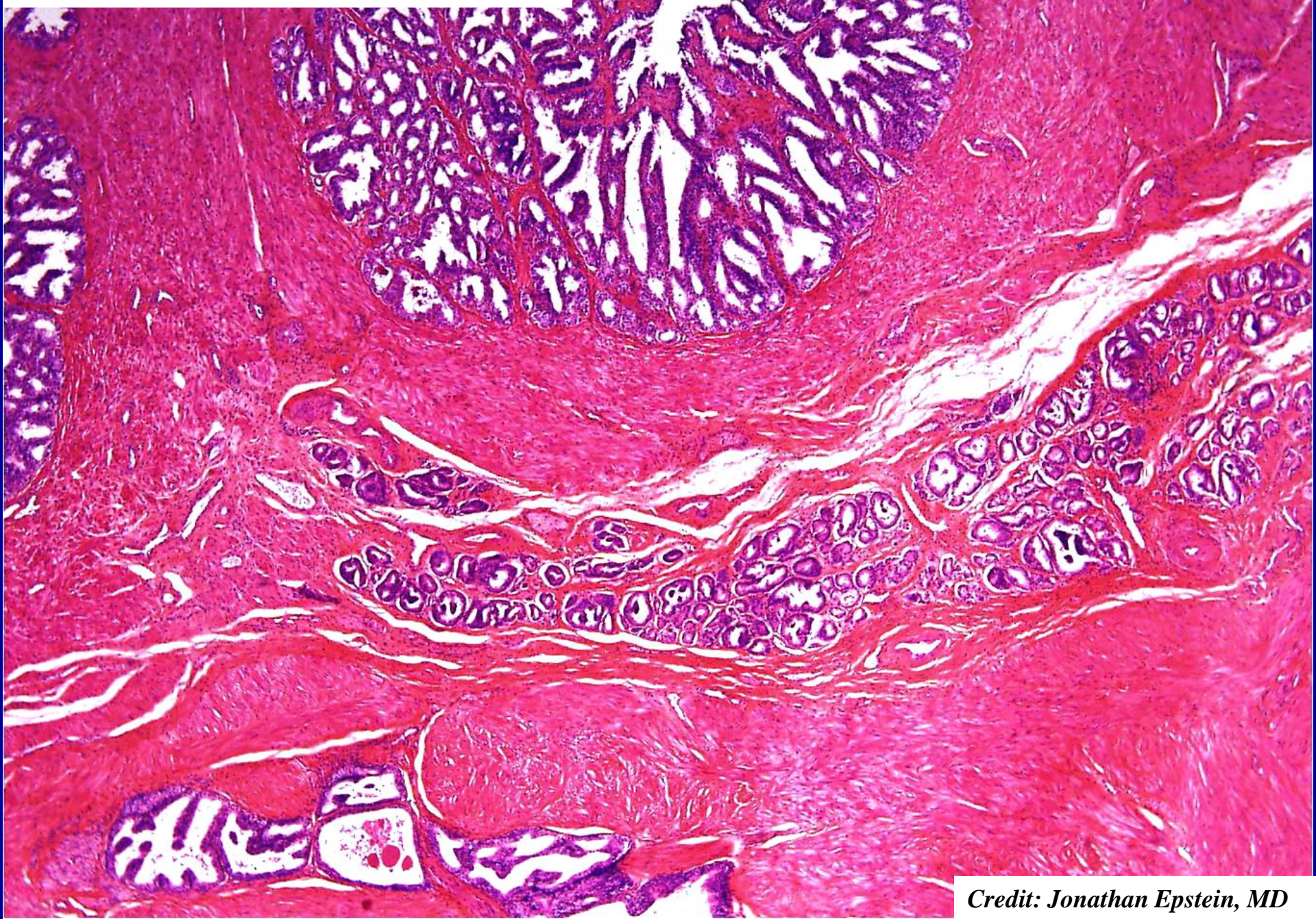
# Perineural Invasion



*Credit: Jonathan Epstein, MD*



# Seminal Vesicle Invasion



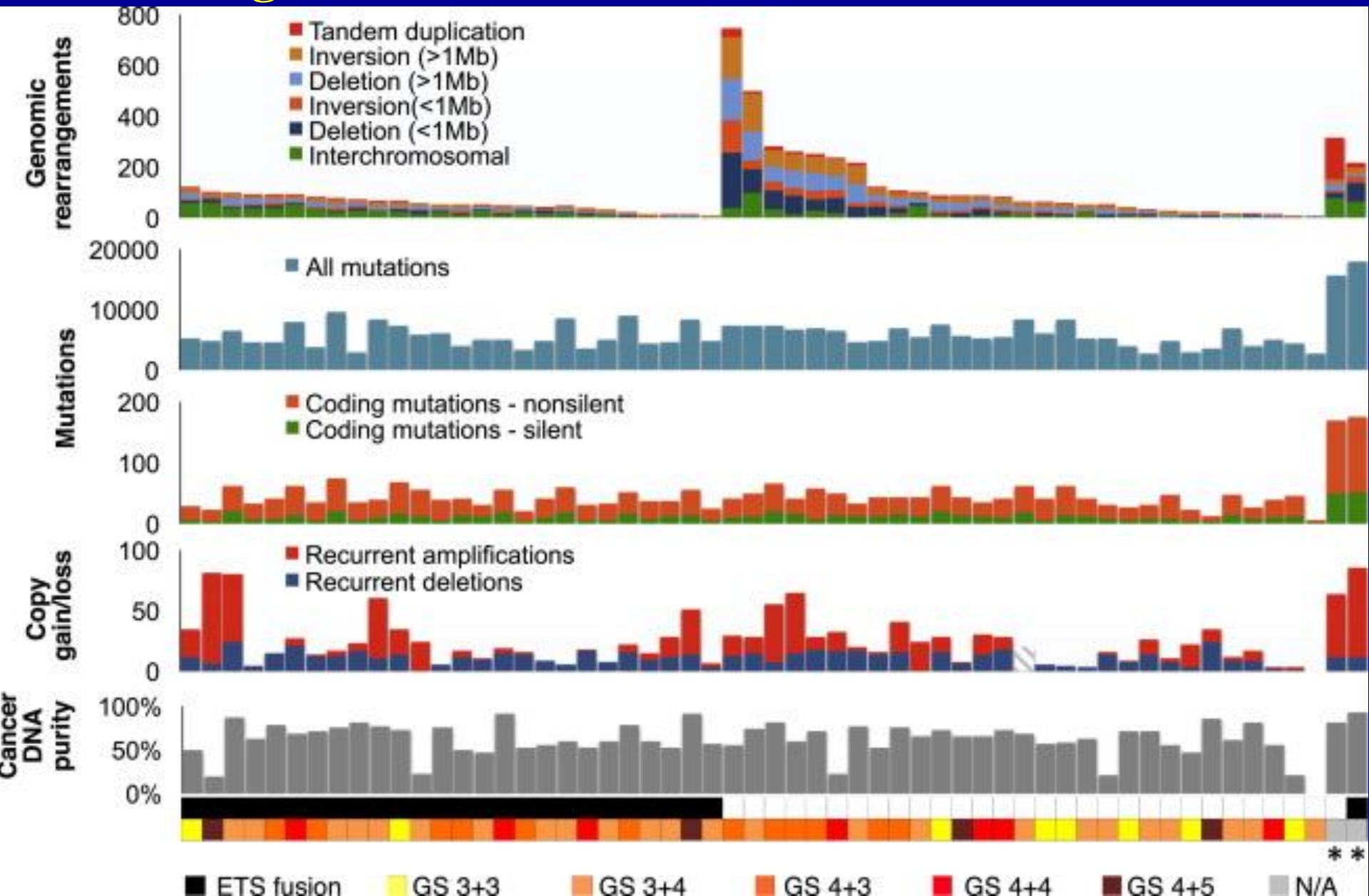
*Credit: Jonathan Epstein, MD*



**Gleason 6 Tumors Exist on a  
Molecular Continuum with  
Higher Gleason cancers**

# 57 prostate tumor genomes show similar extent of somatic genomic alterations

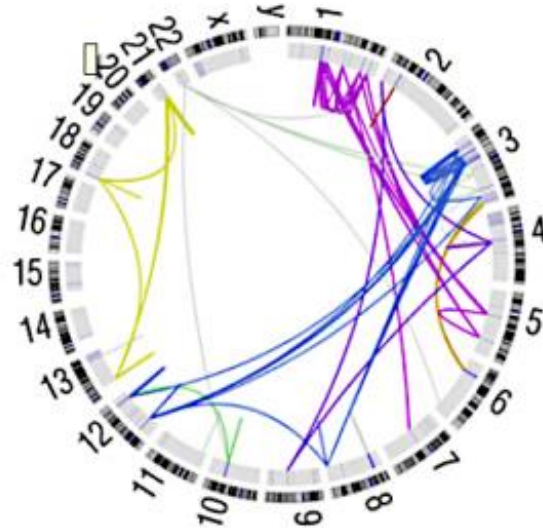
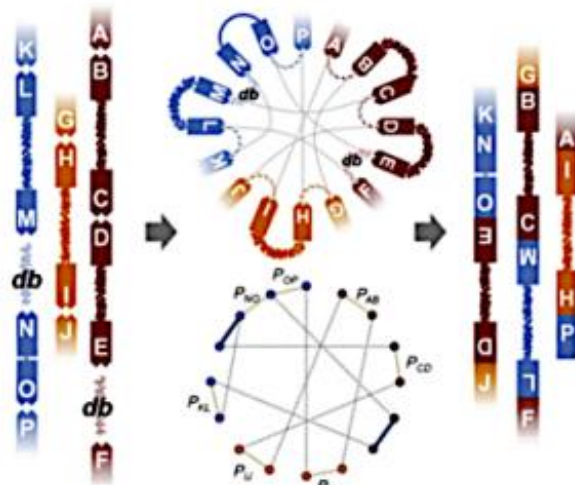
(Baca SC et al, Cell, 2013)



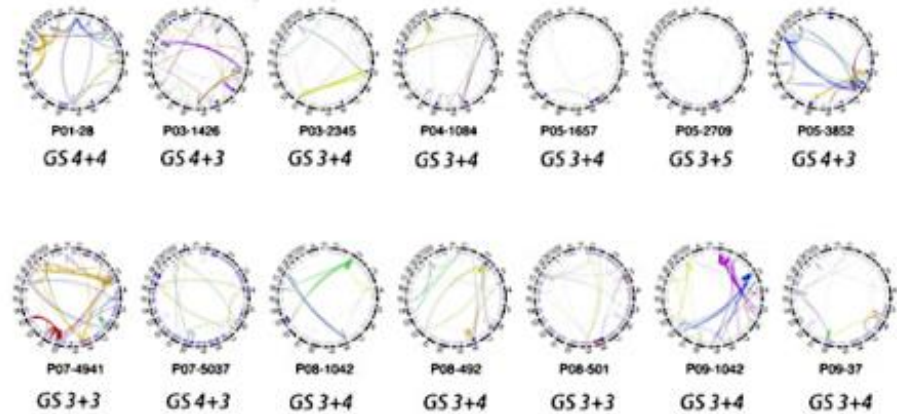


# Chromoplexy in Prostate Tumors by Gleason Scores

(Baca SC et al, Cell, 2013)



C



- **Molecular alterations are shared between Gleason 6 and higher grade tumors**

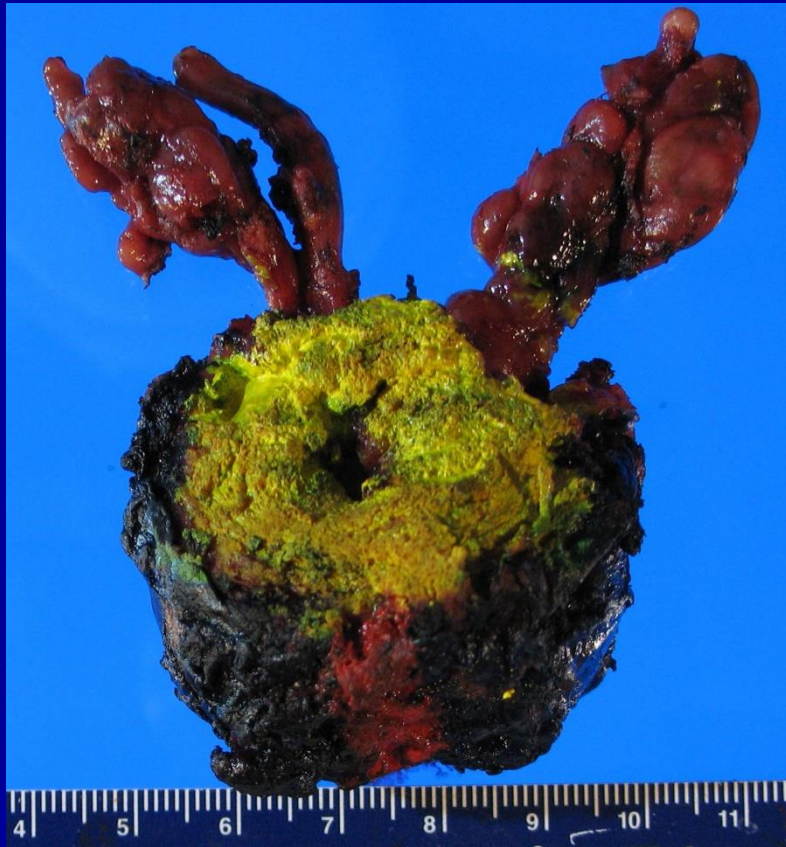
**ETS gene fusions**

**Chromoplexy**

**Hypermethylation of specific genes**

- **Although some of these changes are substantially less common in Gleason 6 tumors, they nevertheless are similar between Gleason 6 and higher grade cancers, and thus support similar pathways of tumor development**

# “Cancer” Has Different Implications in Different Types of Prostate Specimens



**Radical  
Prostatectomy (RP)**



**Transurethral  
resection of  
prostate (TURP)**



**Prostate  
needle  
biopsy (PBx)**



# Gleason 6 prostate cancer in RP can be considered non-cancer

- **Local invasion rare**
  - **Extraprostatic invasion: 0.28-3.9%**
  - **Seminal vesicle invasion: 0.17%**
- **No regional lymph node metastasis**
- **15-year biochemical recurrence for organ-confined <1.5%**
- **Cancer specific death <1% (due to high grade cancer undergraded as Gleason 6)**

**Indolent lesion of epithelial origin (IDLE)**

**IneRRT (Dr. Eggener)**

# **Gleason 6 Prostate Cancer in RP Is Analogous to NIFTP** (Nikiforov YE et al, JAMA Onco 2016)

- **Encapsulated follicular variant of papillary thyroid carcinoma**
  - **Very low risk of adverse outcomes**
  - **“Cancer” was removed and renamed “noninvasive follicular thyroid neoplasm with papillary-like nuclear features” (NIFTP)**
- **Diagnosis made only after tumor entirely removed and carefully examined to look for capsular and vascular invasion and papillary architecture**
- **NIFTP can not be made on small biopsy**

**IDLE/INeRRT should not be made in prostate biopsies!**

# **Gleason 6 Prostate Cancer in RP Is Analogous to PUNLMP**

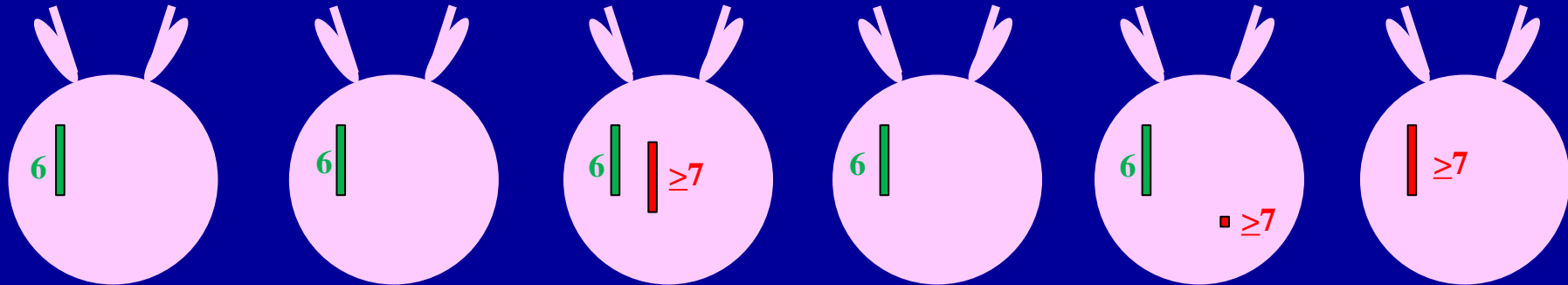
- **Papillary urothelial neoplasm of low malignant potential (PUNLMP)**
  - **A type of non-invasive low grade urothelial tumor with excellent outcomes**
    - **Recurrence: 25-47%; metastasis exceedingly rare**
  - **“Cancer” dropped from the nomenclature, renamed as PUNLMP to alleviate psychological/financial burden** (Epstein JE et al, AJSP 1998)
- **PUNLMP diagnosis does not significantly change the management**
  - **Repeat transurethral resection for visually incompletely resected or high volume tumor**
  - **Assures patient that he does not have “cancer”**



**I agree Gleason 6 prostate tumor  
should be not called cancer in  
radical prostatectomy**

**Should it be labeled as cancer in  
prostate biopsy?**

# Gleason 6 Prostate Cancer Diagnosed in Biopsy Is A Diverse Group of Diseases



*F O L L O W - U P*



Non-progressor

Progressor

Harbinger

Imposter

Non-cancer

Cancer or non-cancer?



# Gleason 6 Prostate Cancer Diagnosed in Biopsy-Imposter

## *Gleason Grading Reproducibility*

General Pathologists	Urological Pathologists
38 cases graded by 41 pathologists	46 cases graded by 10 pathologists
Kappa=0.435 (fair agreement)	Consensus defined as 7/10 agreement
43% Gleason 7, 6% Gleason 8 were mis-graded as Gleason 6	No consensus in 8/46 (17%) 3/46 (7%): graded as Gleason 6 or 7, Gleason 6/7/8-10
Allsbrook WC et al, Hum Pathol 2001	Allsbrook WC et al, Hum Pathol 2001

## Gleason grading reproducibility among general pathologists in India (Singh RV et al, Indian J Cancer 2016)

Consensus Gleason score	No. of readings with							Total no. of readings	
	-3	-2	-1	Exact agreement	+1	+2	+3		
6	0	2	4	30	39	6	3	64%	84
7	0	2	12	41	6	2	0	22%	63
8	0	4	53	72	73	8	0	2%	210
9	0	3	5	30	4	0	0		42
10	1	1	10	9	0	0	0		21
Total	1	12	84	182	122	16	3		420
Percentage	0.2	2.8	20	43.3	29	4	0.7		

- Gleason grading reproducibility continues to be a diagnostic challenge
- Expert consultation may improve grading reproducibility



# Upgrading of Biopsy Gleason 6

- **25-40% of Gleason 6 on biopsy are Gleason 7 or higher in repeat biopsies or radical prostatectomies due to sampling error**
- **MRI imaging and targeted biopsy improves the detection of, but still misses clinically significant cancer**

# MRI Diagnostic Accuracy for Clinically Significant Prostate Cancer

PI-RADS v2	Sensitivity	Specificity
$\geq 3$	89%	39%
$\geq 4$	72%	78%

# **Problems with Labeling Gleason 6 as Non-cancer**

- **If not called cancer, a significant number of men with Gleason 6 cancer will not be followed as closely and potentially progress to incurable cancer; miss the treatment opportunities**

# **Gleason 6 Prostate Cancer Diagnosed in Biopsy**

## *Will It Progress to Higher Grade Cancer?*

- **Grade progression (higher Gleason in repeat biopsies)**
  - ~20%, 30% and 40% at 5-, 10- and 15-year in several large active surveillance cohorts
  - 50-80% occurs within 2-2.5 years, indicative of undersampling by the initial biopsy (“harbinger”)
  - In grade progression after 2-2.5 years, 2/3 in the same areas of the prior positive sites; may be indicative of true tumor progression (Porten SP et al, J Clin Oncol 2011)
- **Molecular evidence** (Salami SS et al Eur Urol 2021)
  - Repeated molecular assessment of 15 Gleason 6 tumors using MRI tracking (to ensure same tumor focus sampled and studied)
  - Shared clonality between the initial Gleason 6 and subsequent higher grade tumors of the same location, supporting the possibility of progression of Gleason 6 cancer to higher grade



# **Will Gleason 6 Cancer Kill Patients When Diagnosed in Prostate Biopsy**

- **European Randomized Study of Screening for Prostate Cancer (ERSPC) Rotterdam part: PSA-based prostate cancer screening for 54-74 years** (Roobol MJ et al, Eur Urol 2013)

- **During follow up of 12.8 years, cancer mortality of 4.3% (151) reported**

- **22/151 (14.6%) in Gleason 6 cancer**

- **15/151 (10%) in low risk (cT1/2), Gleason 6 cancer**

- **Prostate cancer specific mortality in active surveillance is very low (0.1%), but not zero**

- **While very low or low risk cancer is Gleason 6 cancer by definition, the reverse can not be assumed**
- **Gleason 6 cancer can not be assumed to be low risk when diagnosed in biopsy**

# Racial Differences in Prostate Cancer Biology and Outcomes



# Racial Disparities in Prostate Cancer

- **African Americans with very low or low risk cancer are more likely to have adverse pathology at radical prostatectomy** (Sundi et al J Clin Oncol 2013; Maurice et al, J Urol 2017)
- **Prostate cancer deaths with Gleason 6 disease significantly higher than in non-blacks (0.4% vs 0.22%)** (Mahal et al JAMA 2018)
- **Genomic risk scores** (Mahal et al Eur Urol 2019)
  - **Gleason 6 tumors: significantly higher among African-American than among white men**
  - **≥ Gleason 7: not significantly different between African-American and white men**
- **Disparities in Gleason 6 tumors may in part be driven by underlying tumor biology; disparities in high grade tumors may largely be accounted for by social factors and healthcare access;**
- **Data regarding racial differences still emerging**
- **Any conclusions, including labeling Gleason 6 as non-cancer, should be vigorously tested in African Americans and other racial groups**

# Summary

- **Gleason 6 prostate cancer in radical prostatectomy can be considered “non-cancer”**
- **Gleason 6 cancer in prostate biopsies have diverse range of clinical behaviors**
  - **Vast majority have indolent behavior and excellent outcomes**
  - **May progress and cause morbidity and death in some patients**
  - **Should still be called “cancer”**
- **Rather than debating whether Gleason 6 is cancer or non-cancer, we need to change what patients think when they hear they have Gleason 6 cancer**
- **Urologists need to reassure and educate patients**



# Summary

- **Need to further refine the risk stratification to identify patients with Gleason 6 (or any Gleason grade) who may have aggressive disease and need treatment, or patients who may have indolent disease and can be safely followed**

# Personalized Prostate Cancer Diagnosis and Treatment with Multivariate Risk Prediction Tools

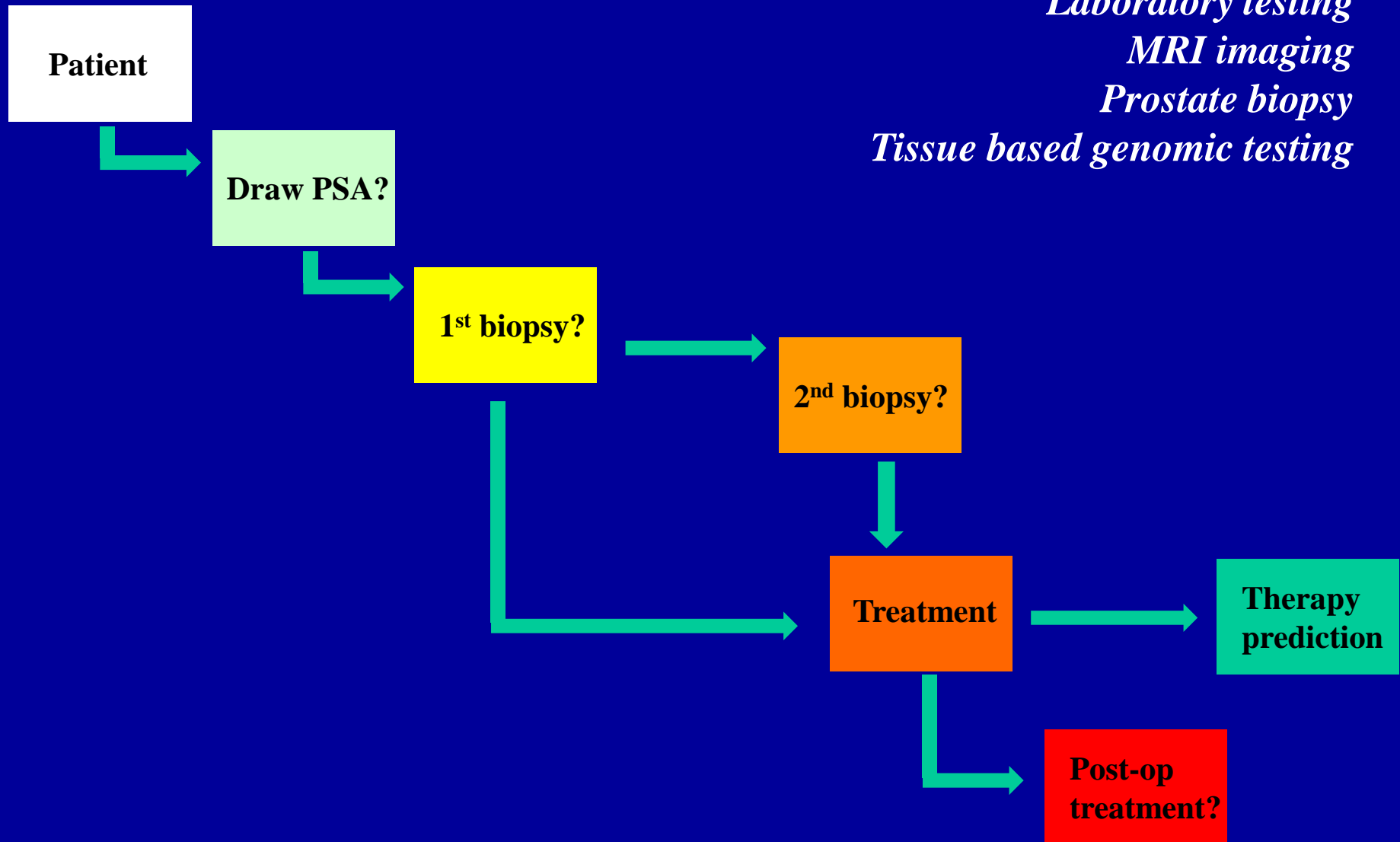
*Clinical characteristics*

*Laboratory testing*

*MRI imaging*

*Prostate biopsy*

*Tissue based genomic testing*



**Lets do not dwell on whether  
Gleason 6 should be called  
cancer, and focus on finding  
better risk stratification for  
Gleason 6 cancer diagnosed in  
prostate biopsies!**

**Thank You!**

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