



JOHNS HOPKINS
M E D I C I N E

Prostate Cancer Grading A Decade After the 2005 Modified System

Jonathan I. Epstein

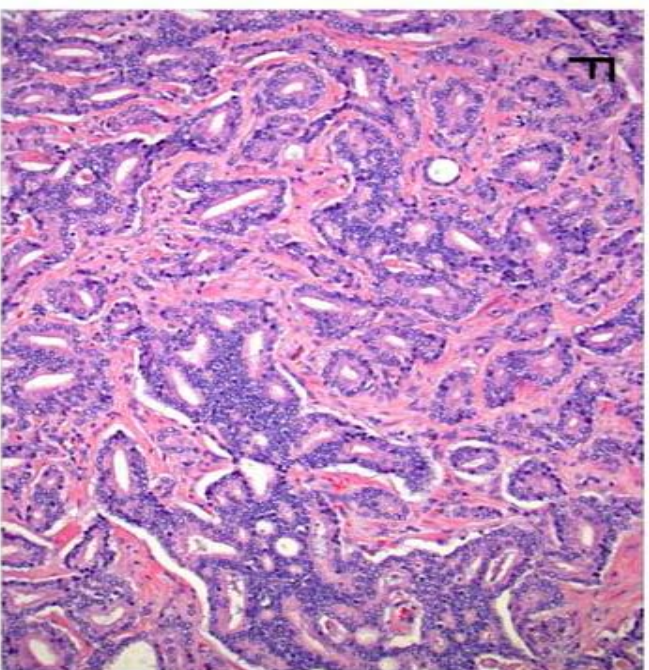
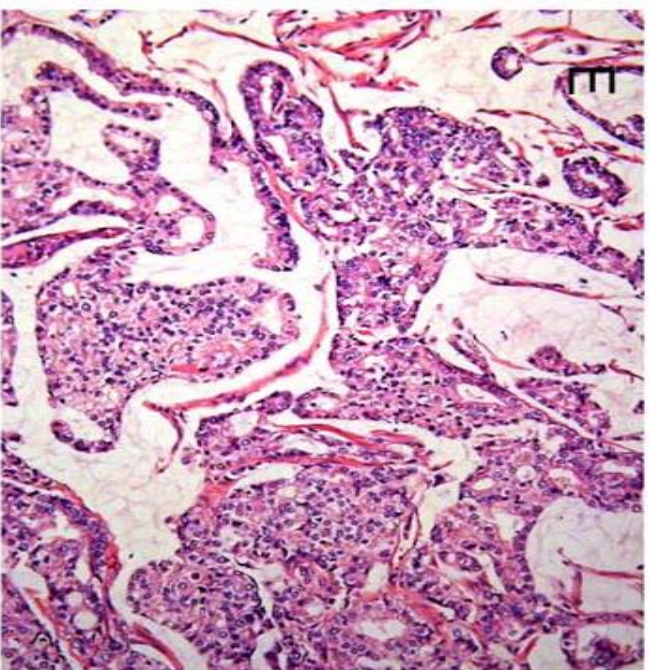
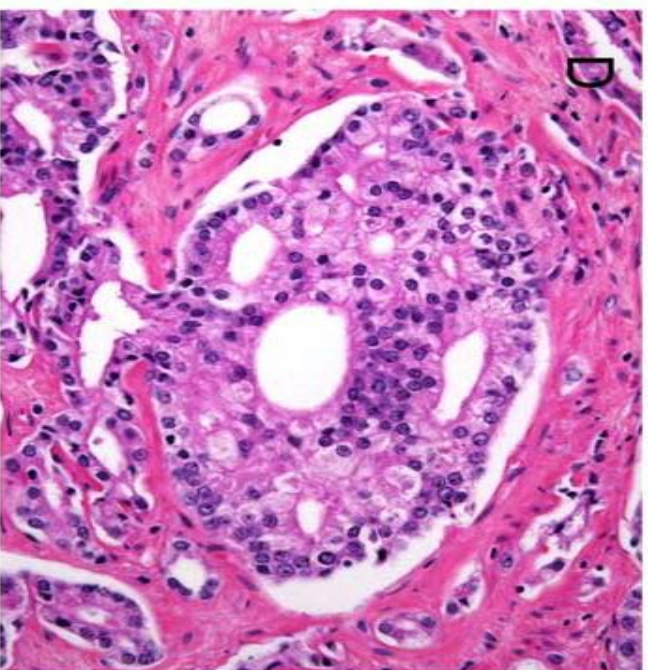
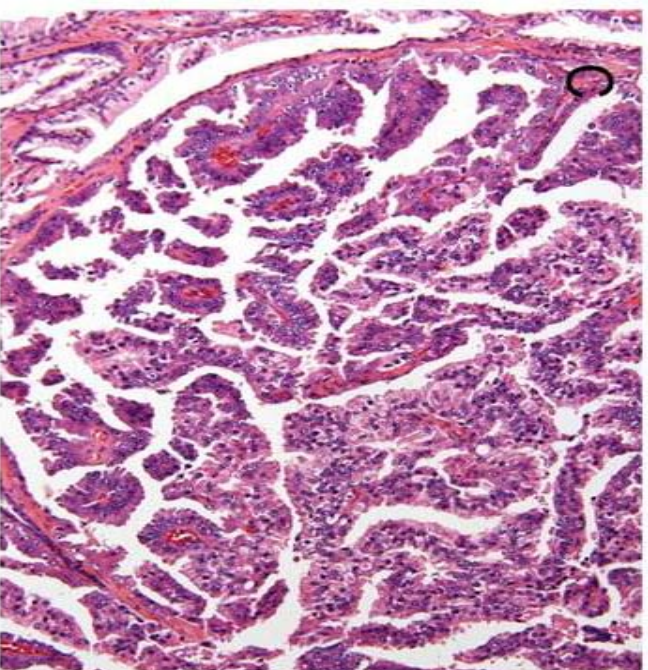
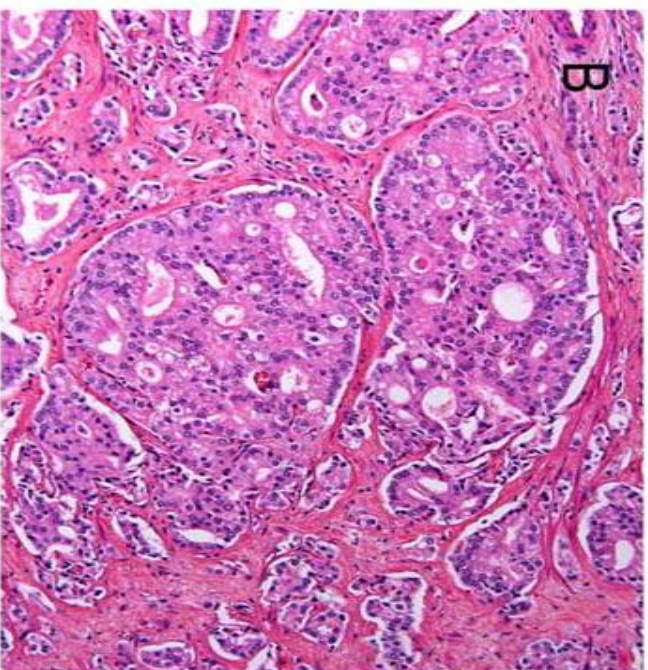
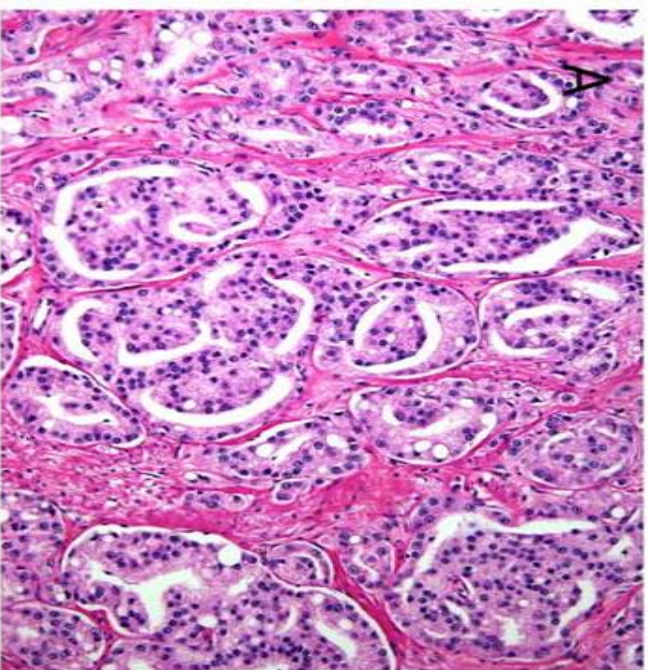


Breakdown of Gleason Patterns

2,911 cases (percentages added up to approximately 150% since 50% of the tumors showed at least two different patterns).

- Pattern 1 - 3.5%
- Pattern 2 - 24.4%
- Pattern 3 - 87.7%
- Pattern 4 - 12.1%
- Pattern 5 - 22.6%.

Cribriform Pattern 3 Prior to 2005



Gleason Score 2-4 on Needle Should Not Be Made

Editorial AJSP (Epstein), 2000

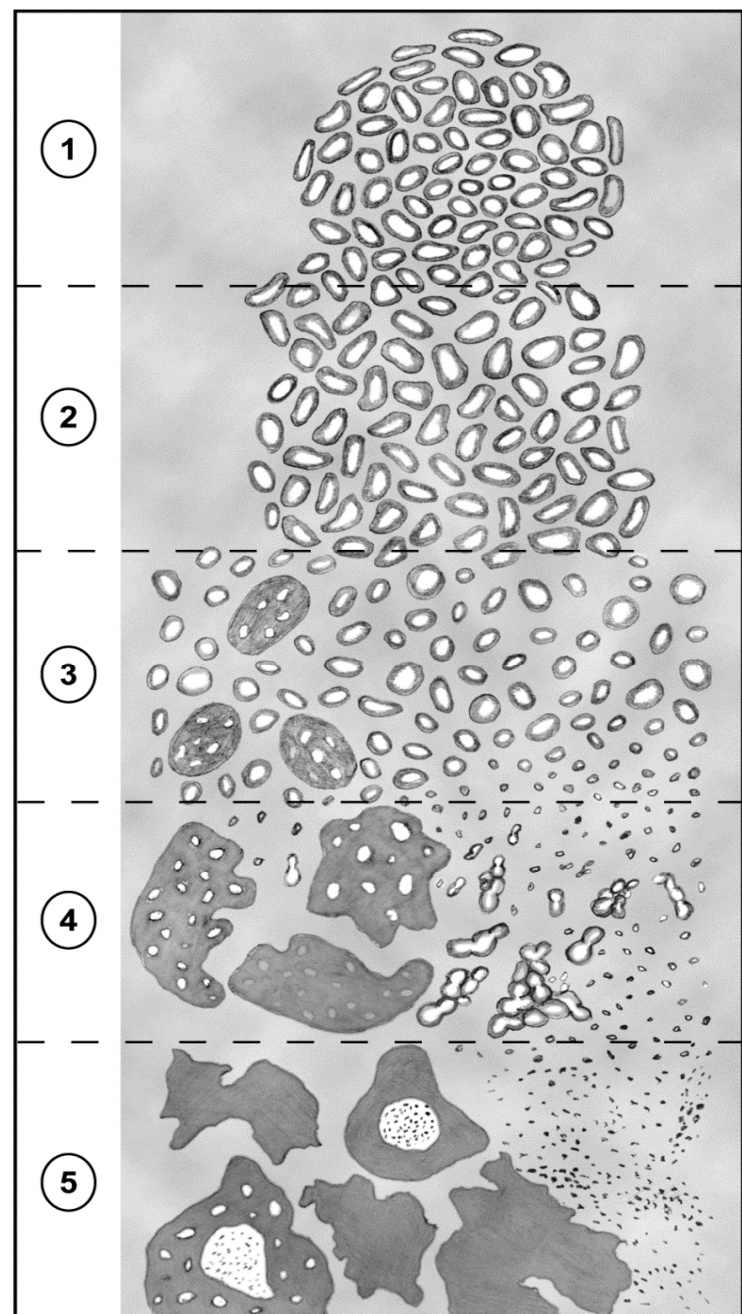
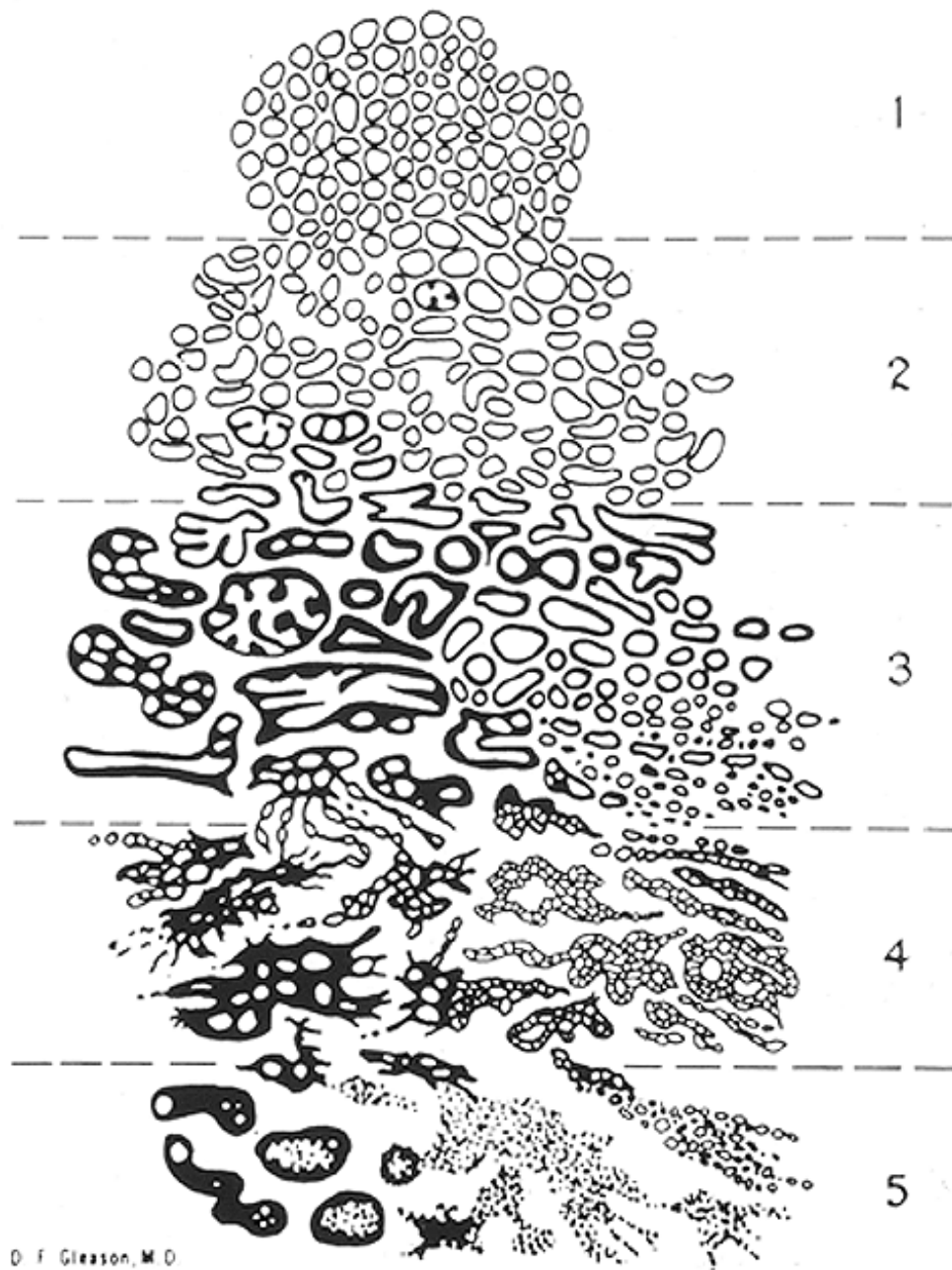
- **1) Poor reproducibility among experts for lower grade tumors.**
- **2) Correlation with the prostatectomy score for Gleason 2-4 tumors is poor and up to 50% of the corresponding prostatectomies may have extraprostatic extension.**
- **3) Gleason 2-4 may misguide clinicians and patients into believing that there is an indolent tumor.**

The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

**The American Journal of Surgical Pathology: Volume 29.
September 2005 pp 1228-1242**

**Epstein, Jonathan I ; Allsbrook, William C Jr; Amin,
Mahul B; Egevad, Lars L and the ISUP Grading
Committee**

PROSTATIC ADENOCARCINOMA (Histological Patterns)



Brunnbaugh

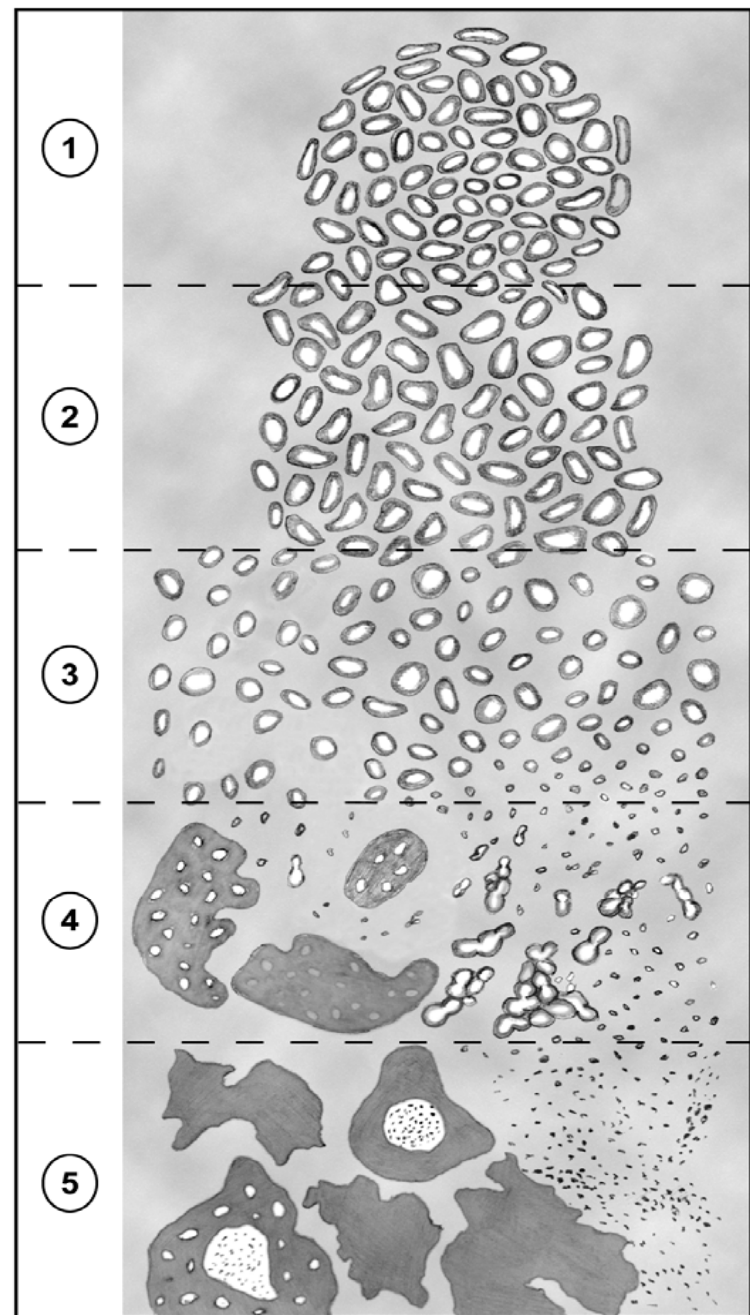
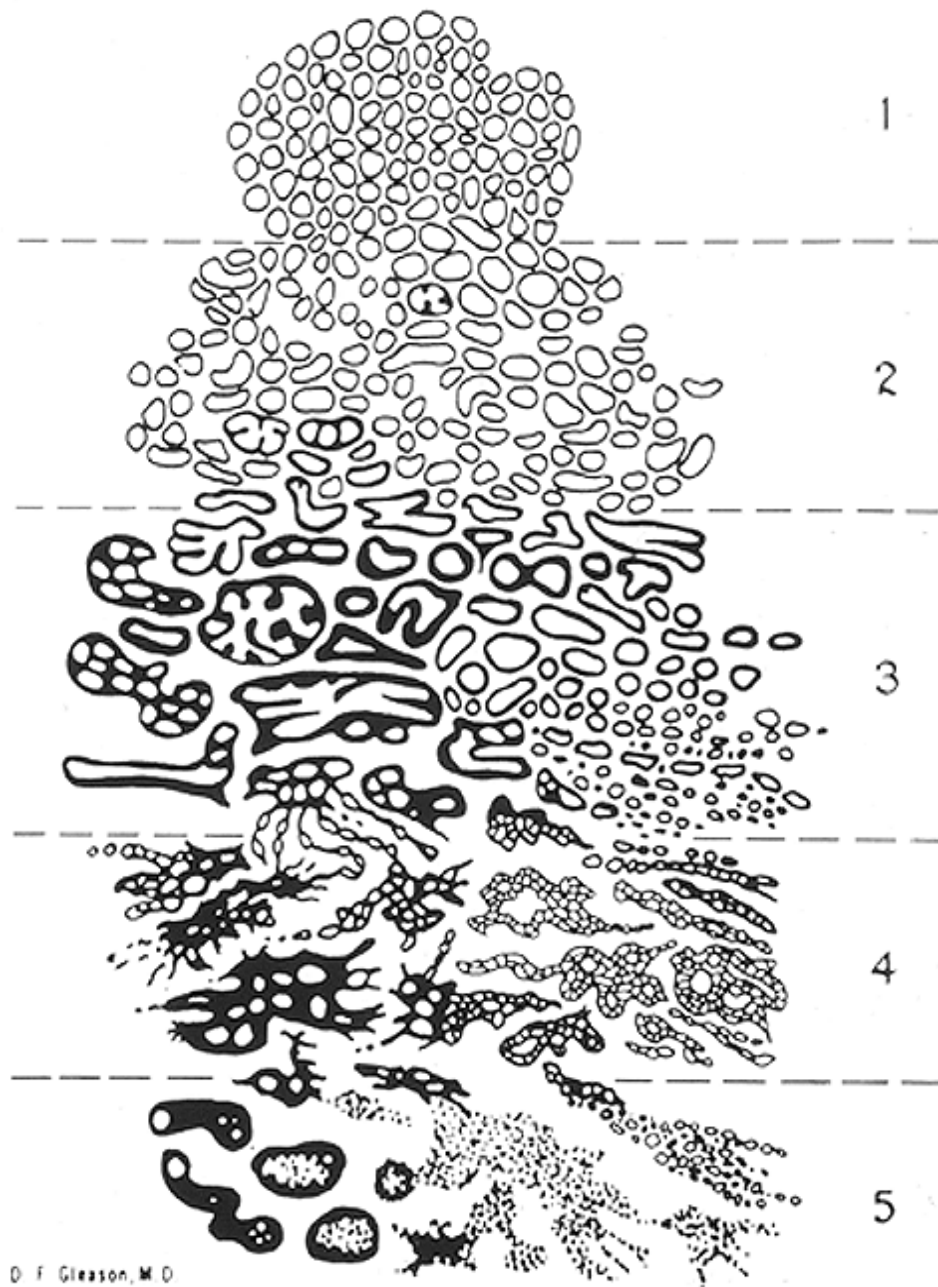
The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Definition of Grading Patterns and Proposal for a New Grading System

Jonathan I. Epstein, MD, Lars Egevad, MD, PhD,† Mahul B. Amin, MD,‡ Brett Delahunt, MD,§
John R. Srigley, MD,|| Peter A. Humphrey, MD, PhD,¶ and the Grading Committee*

**The American Journal of Surgical Pathology: Volume 40.
February 2016, p 244-52**

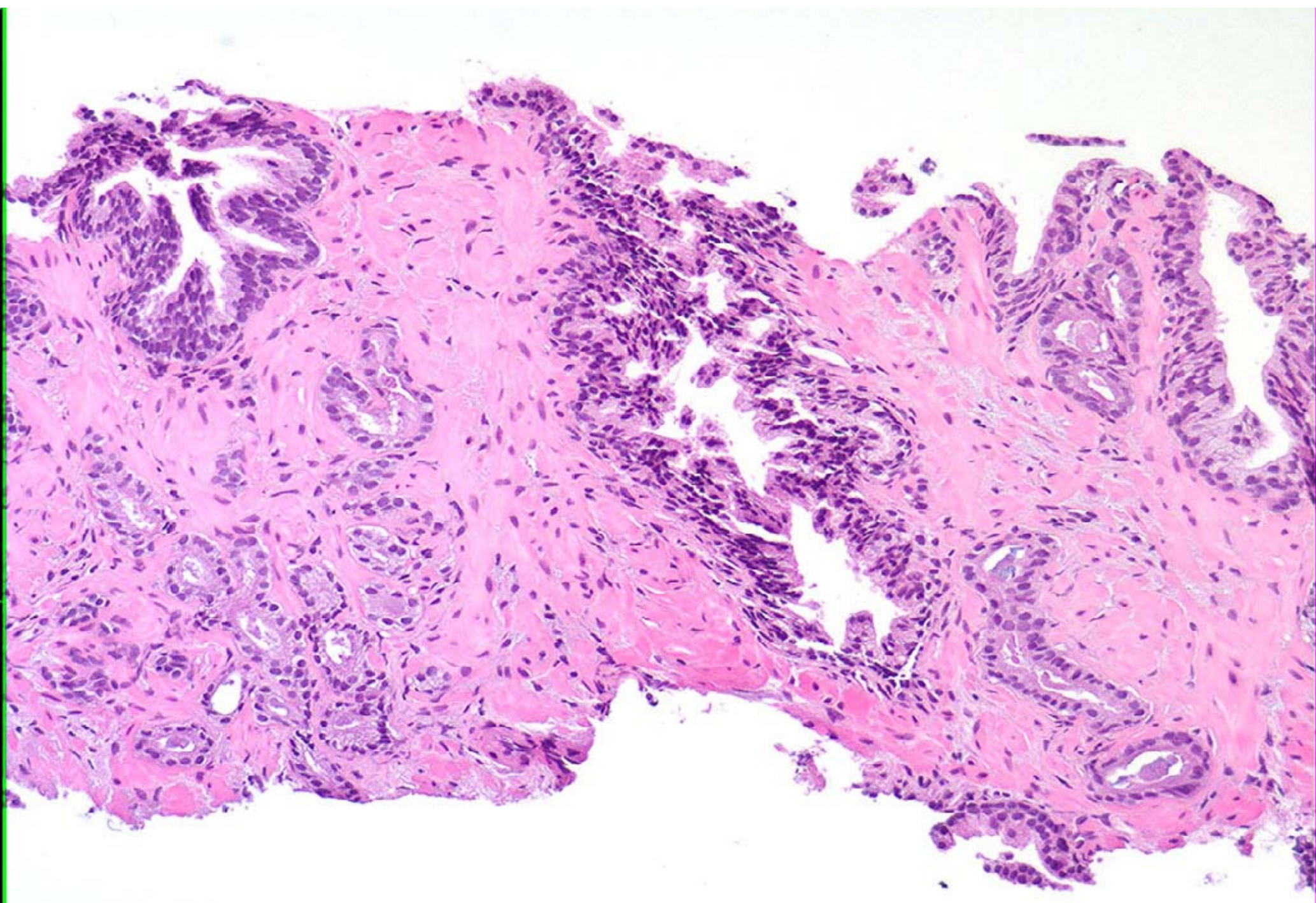
PROSTATIC ADENOCARCINOMA (Histological Patterns)

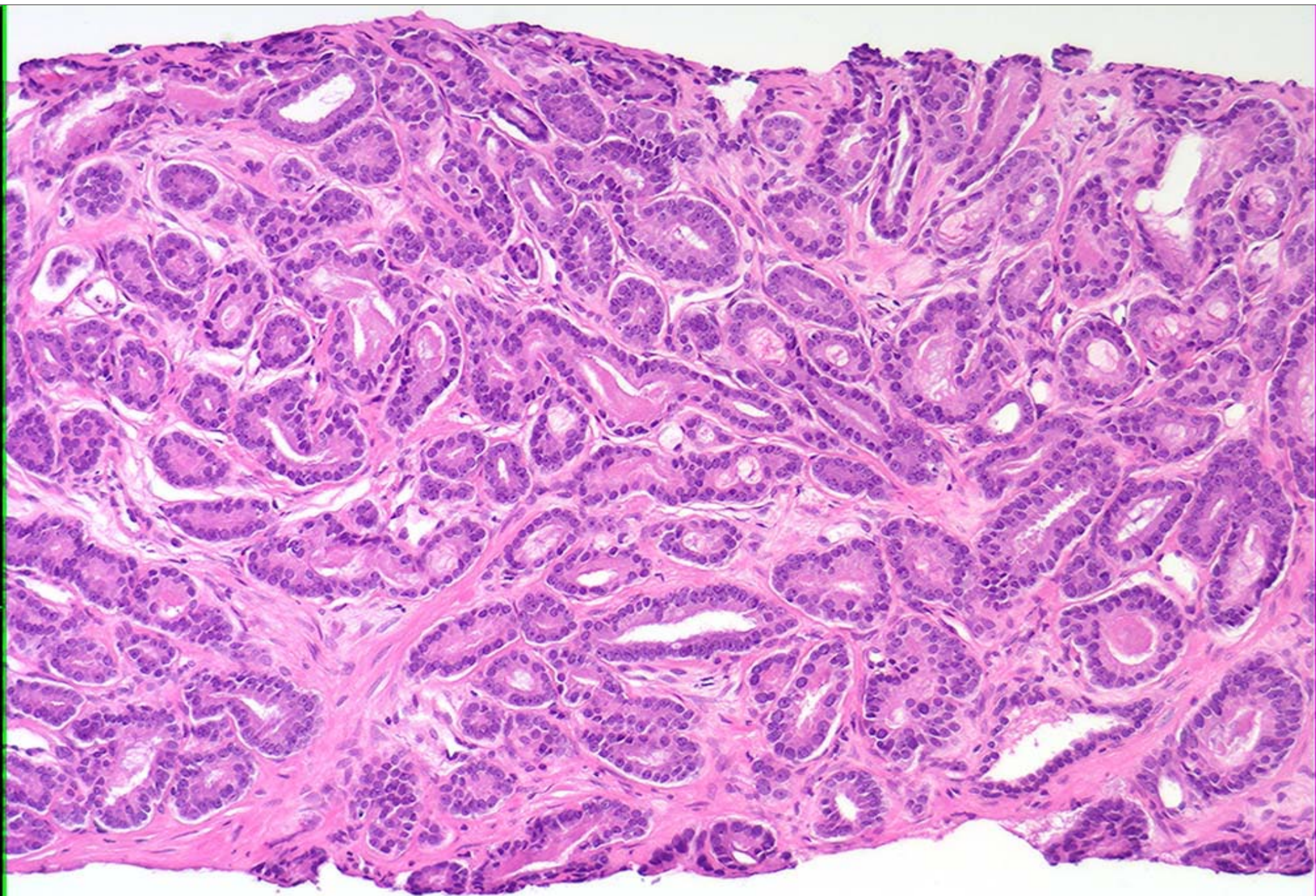


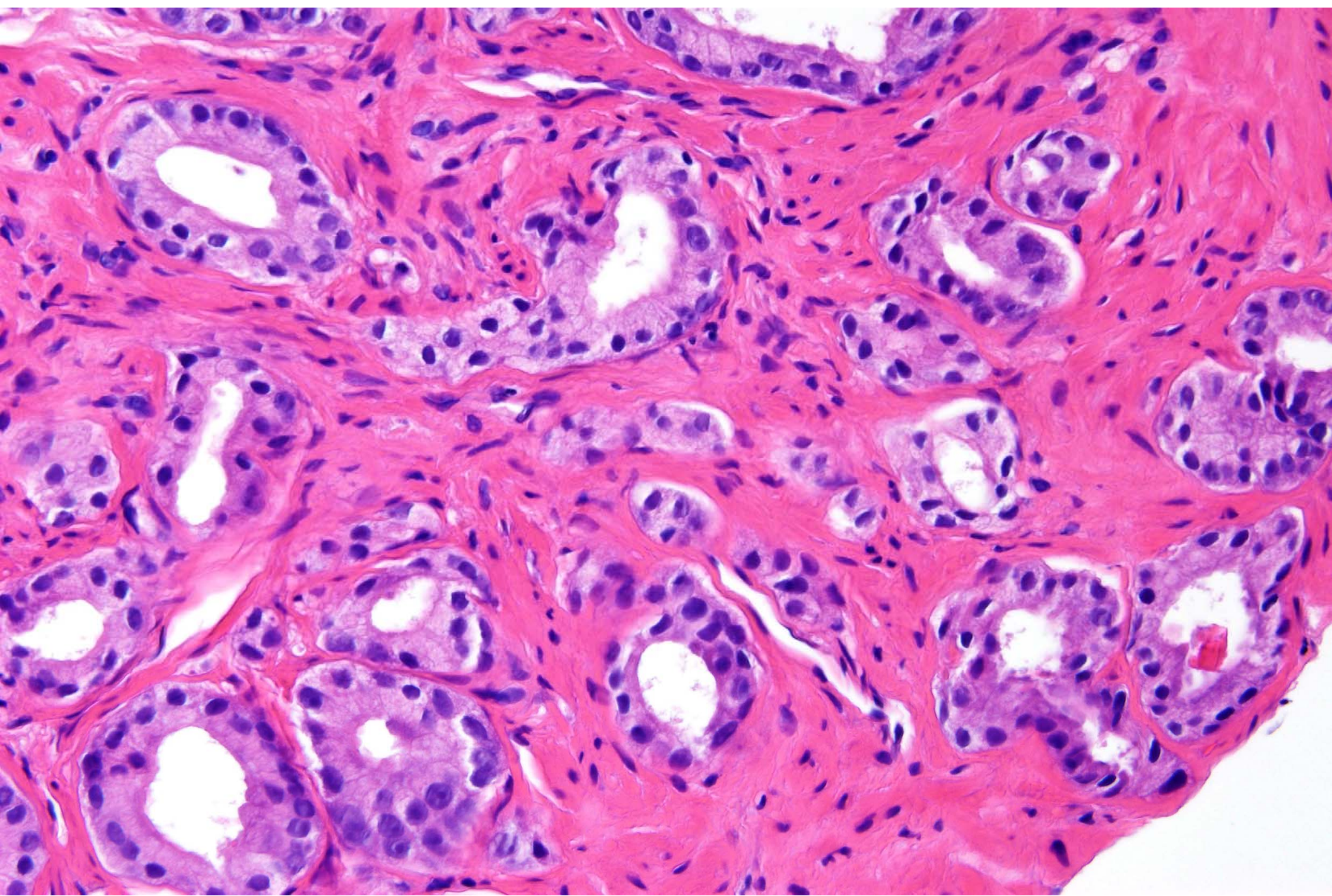
Brumbaugh

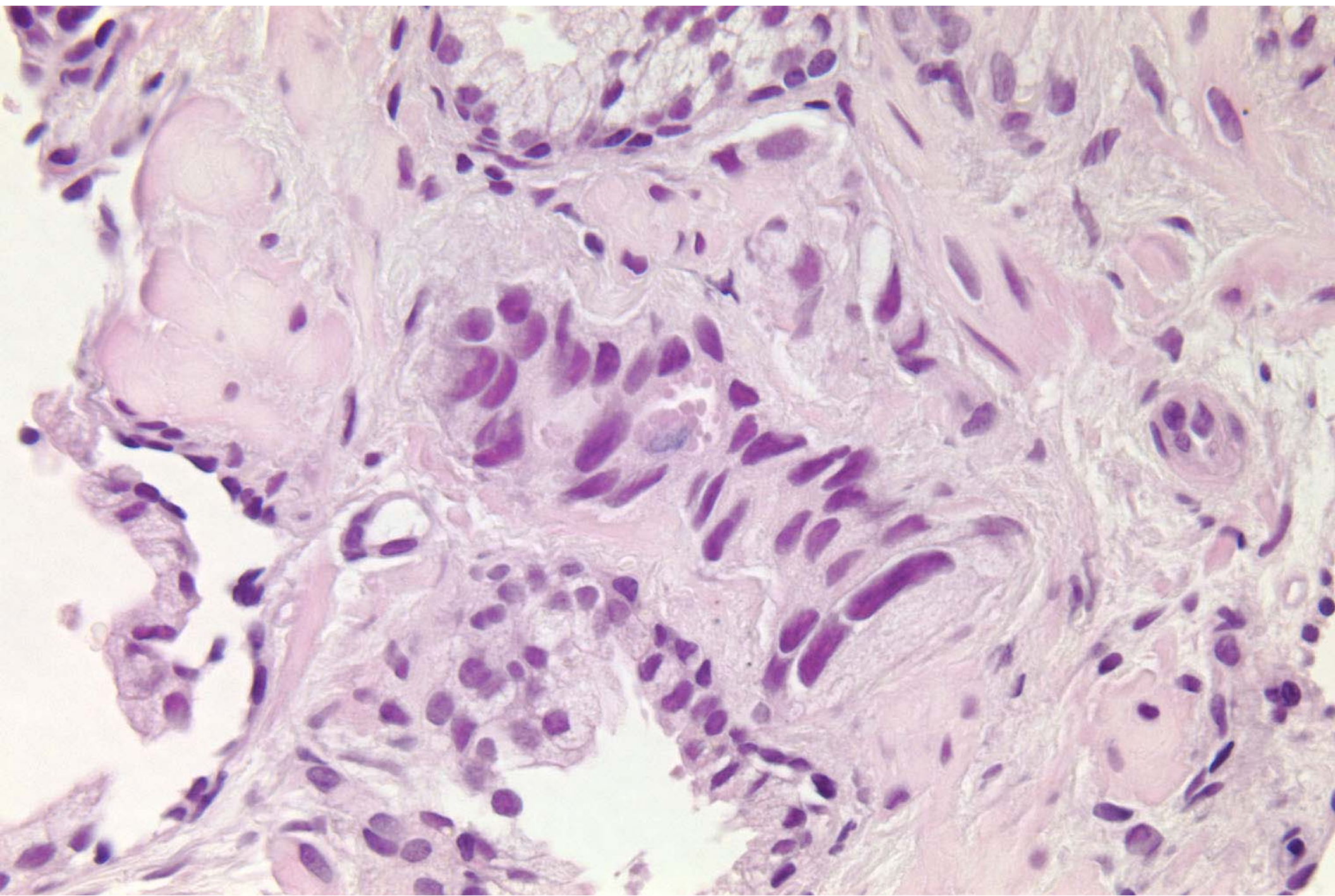
Gleason Pattern 3

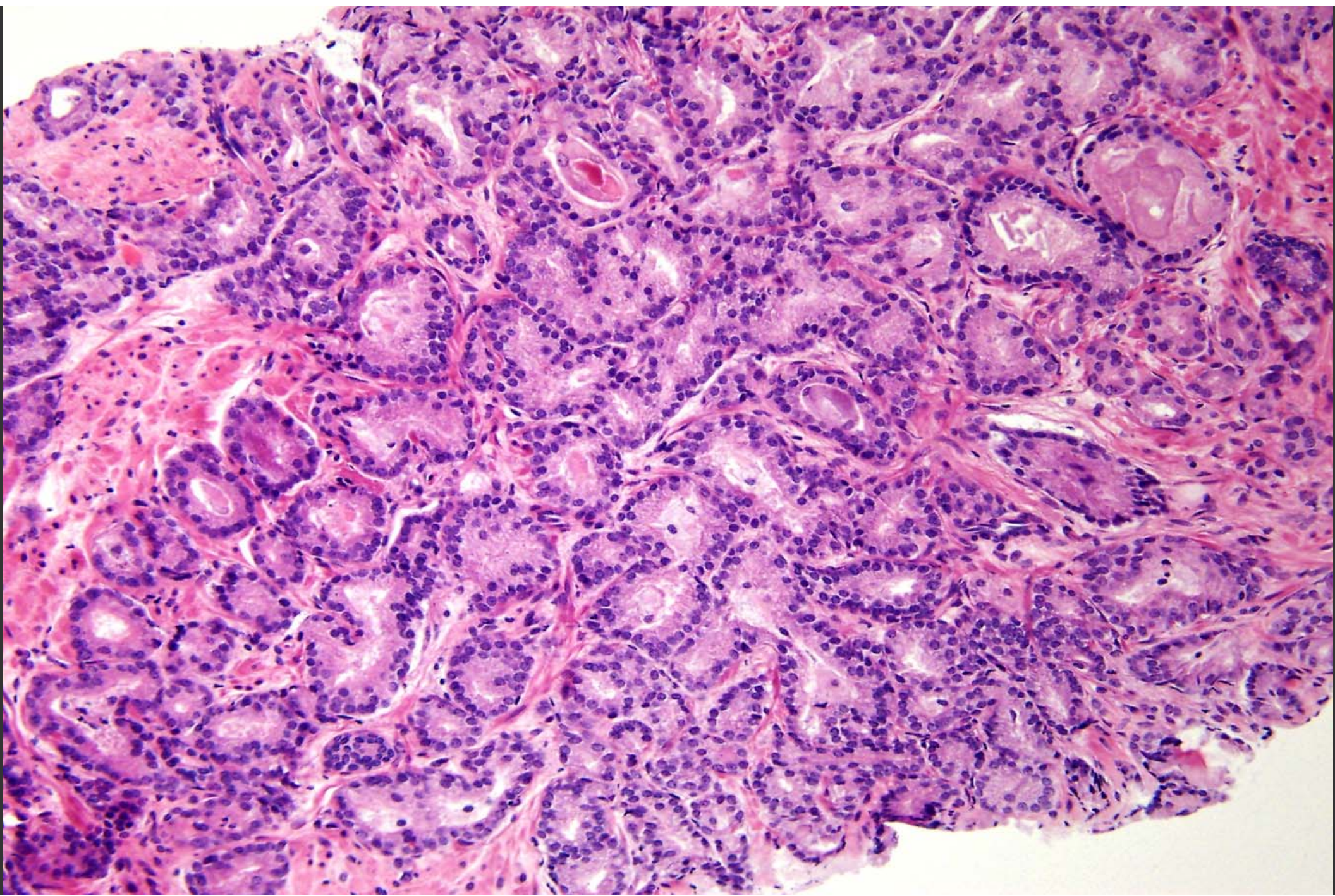
- **Individual well-formed discrete glands**

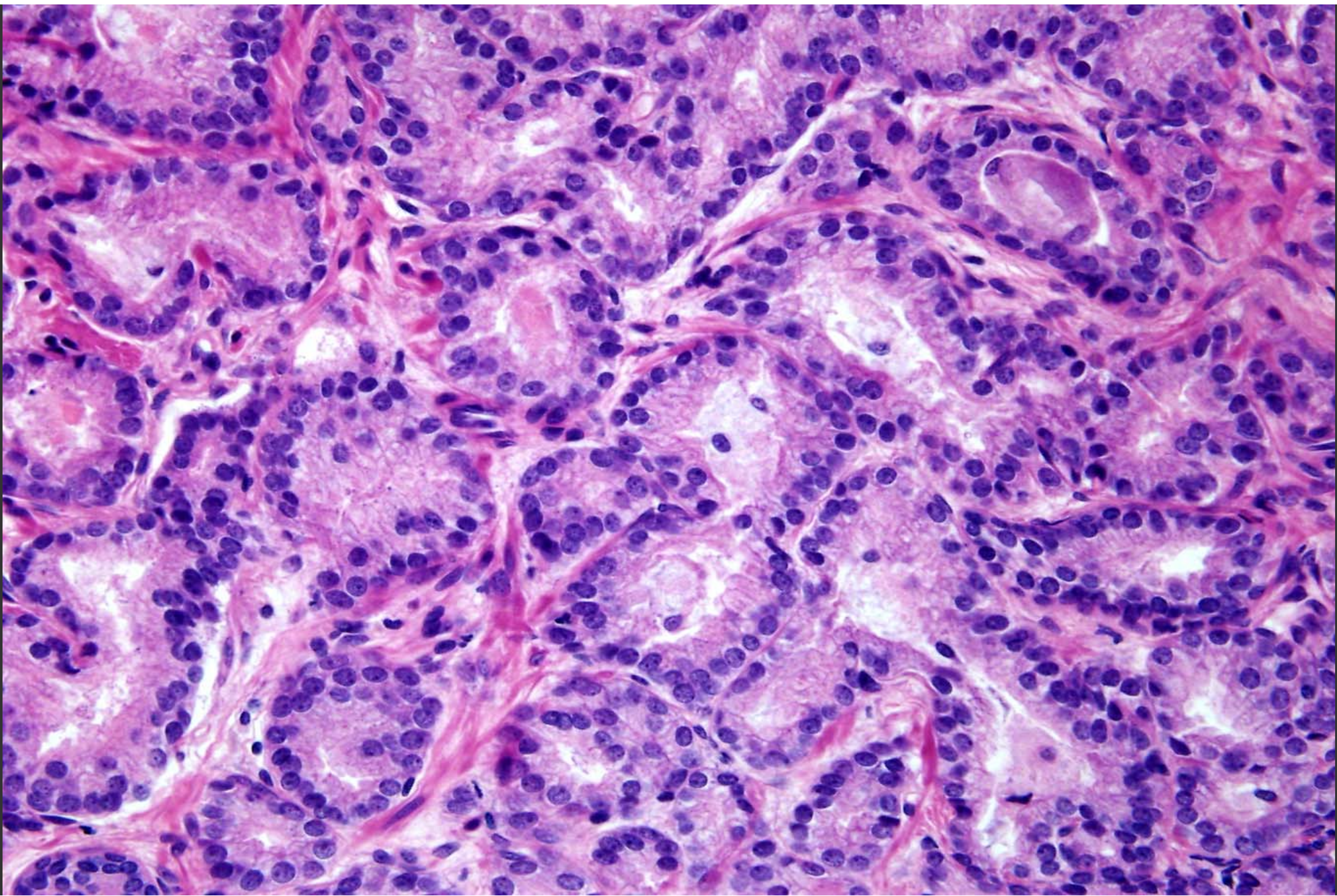




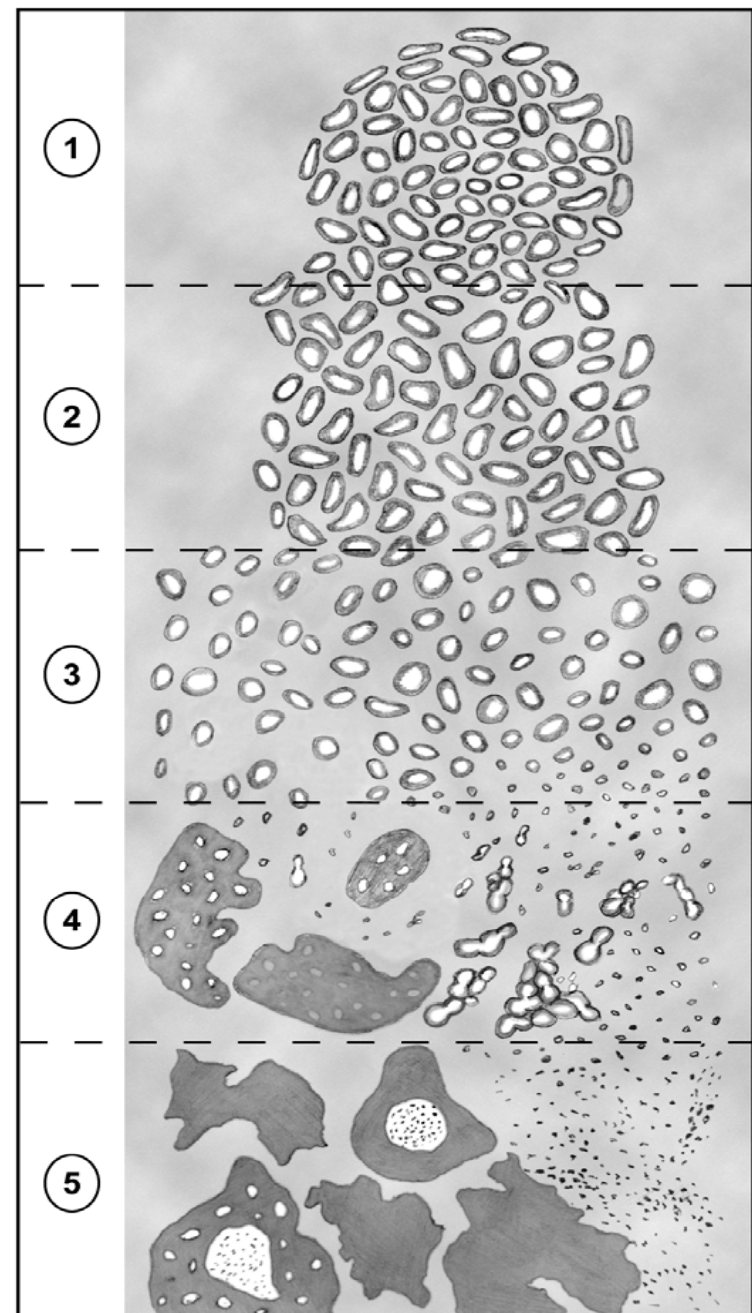
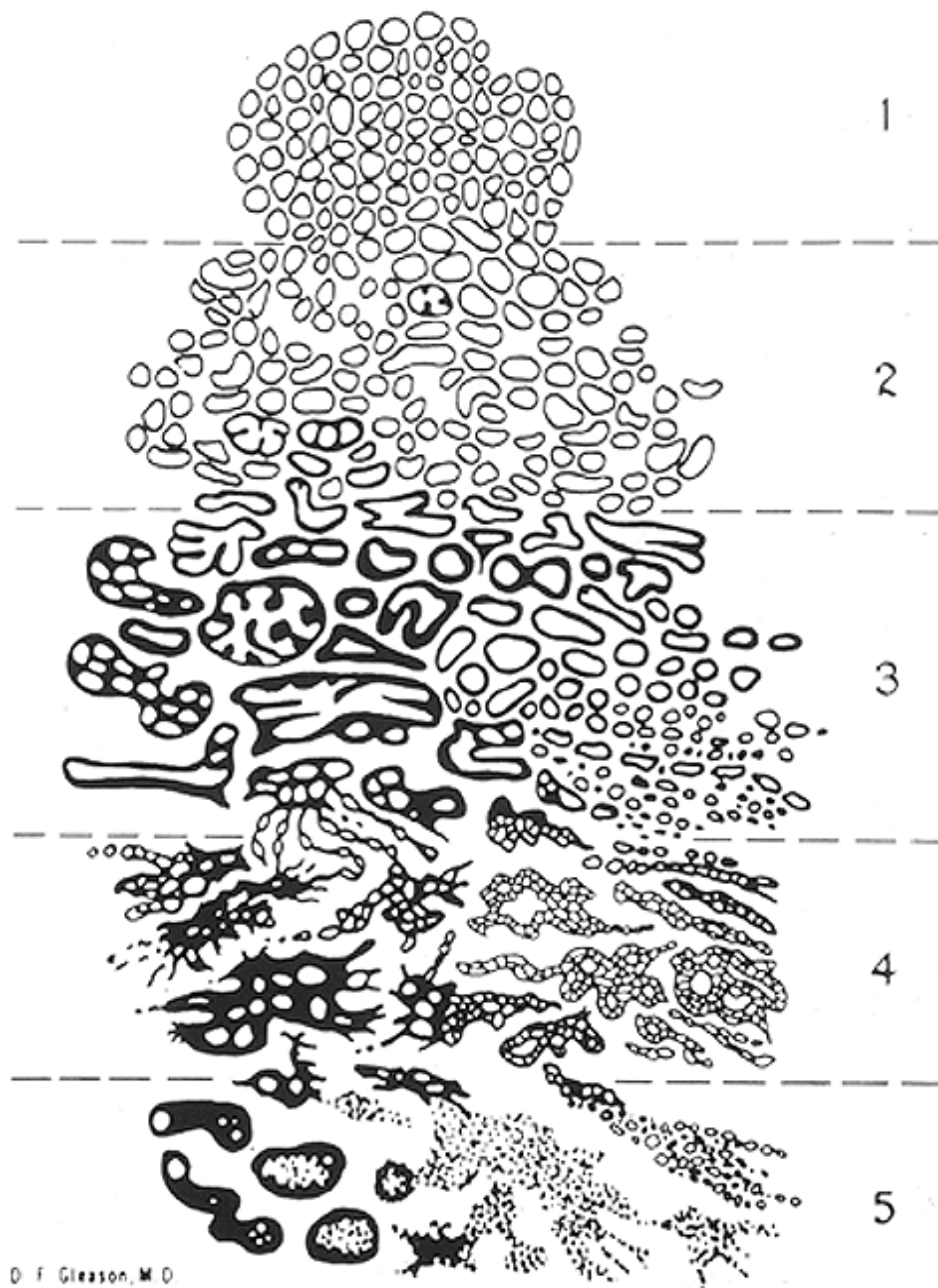






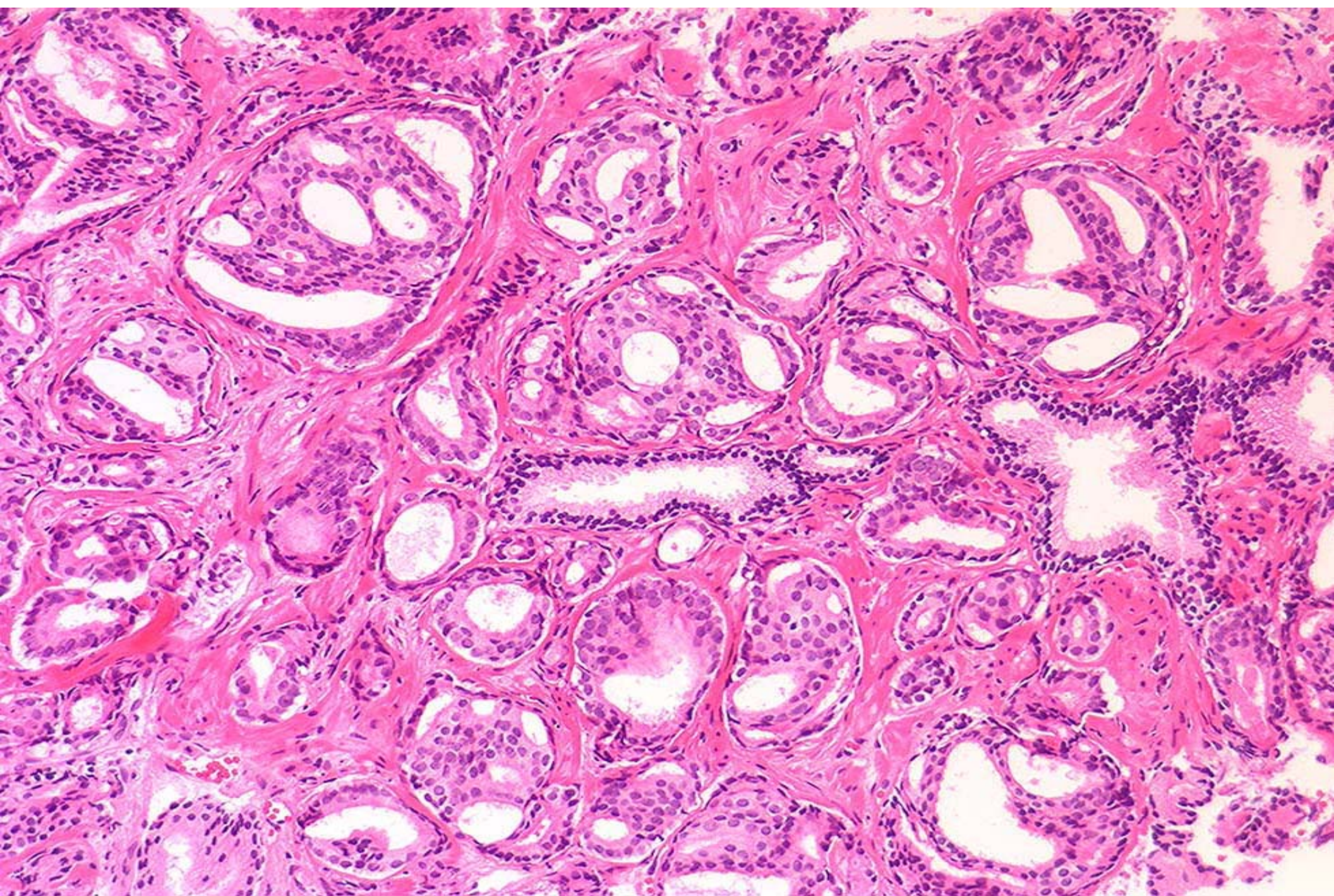


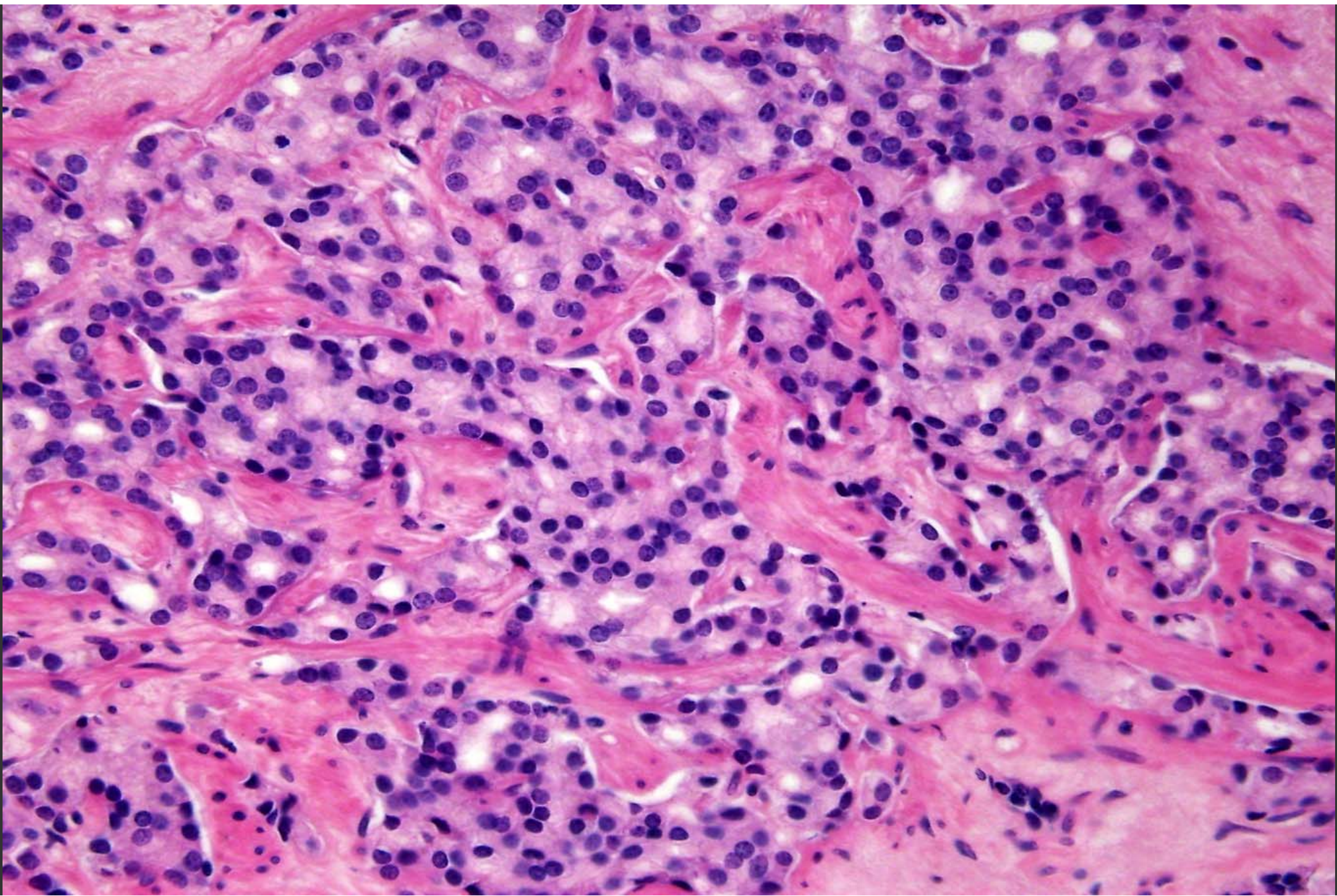
PROSTATIC ADENOCARCINOMA (Histological Patterns)



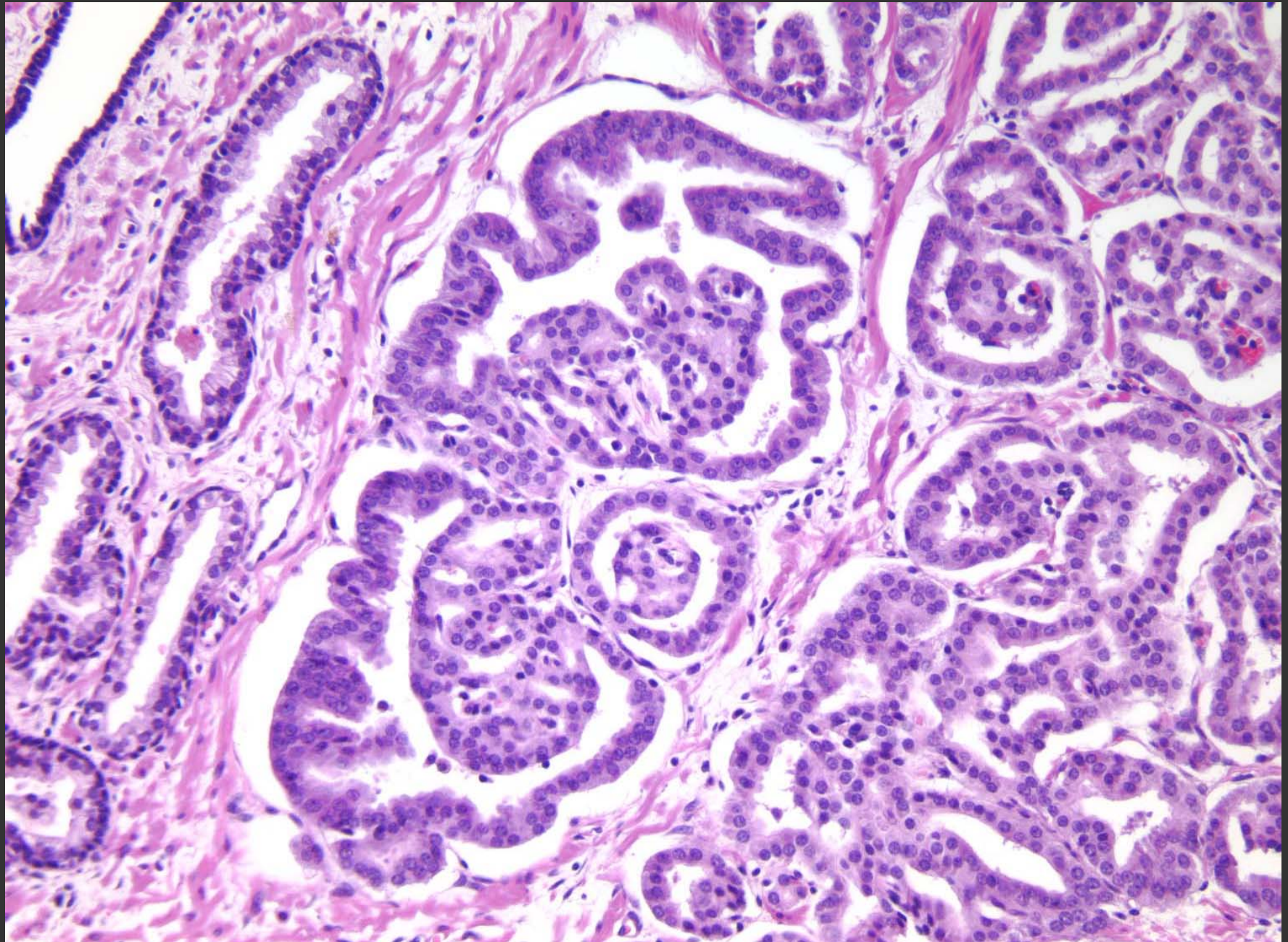
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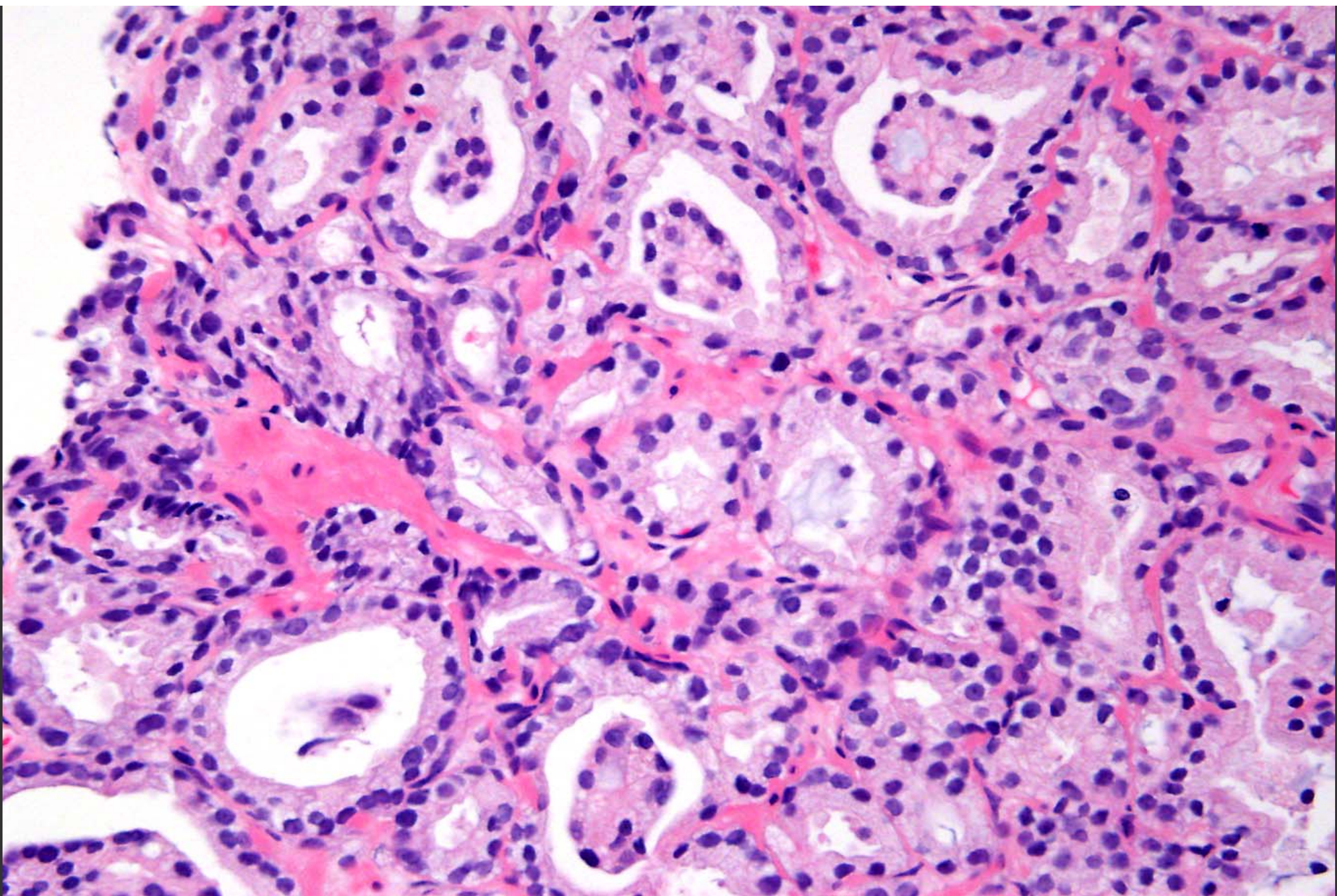
**All Cribriform Cancer Glands are
Graded as Gleason Pattern 4**

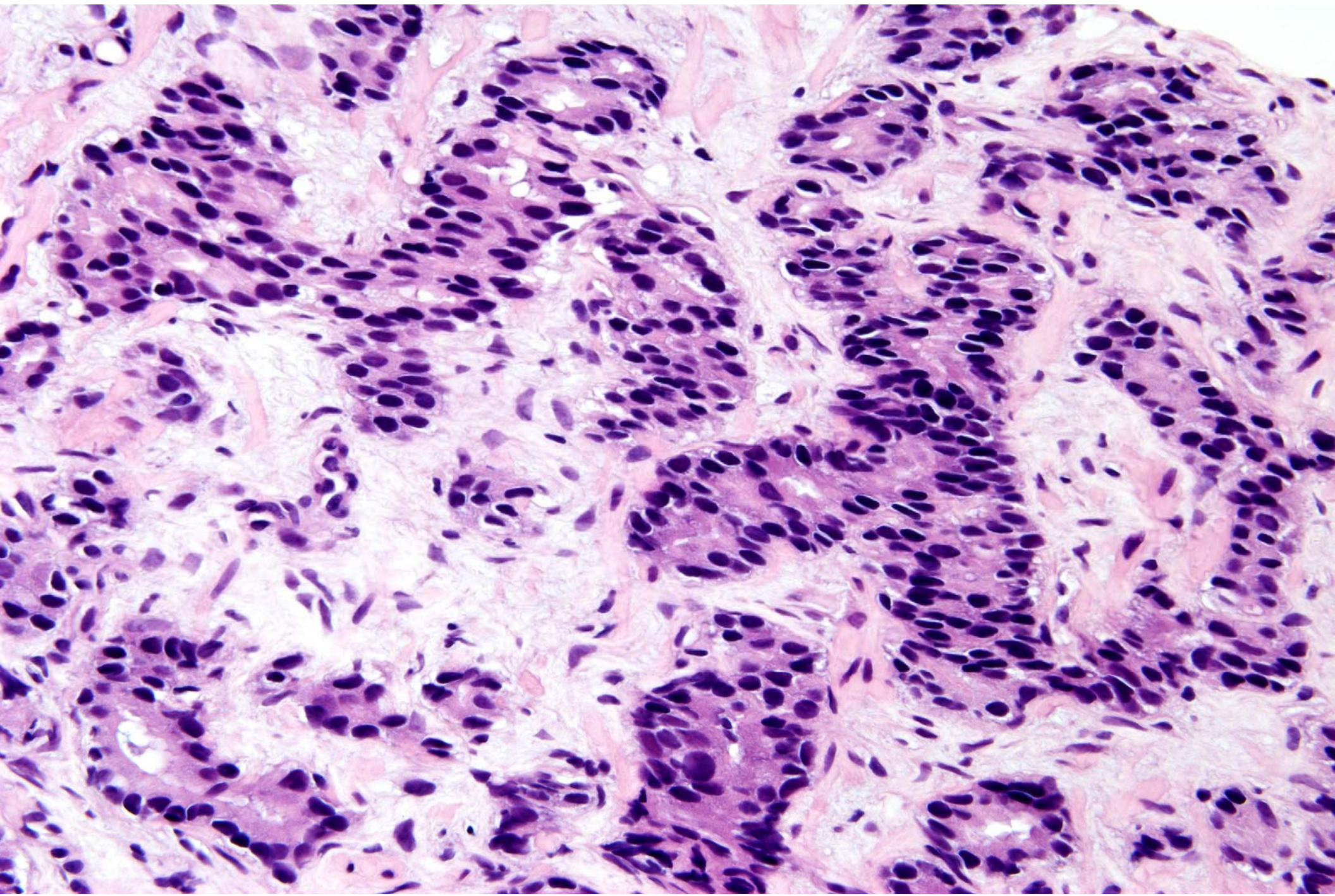


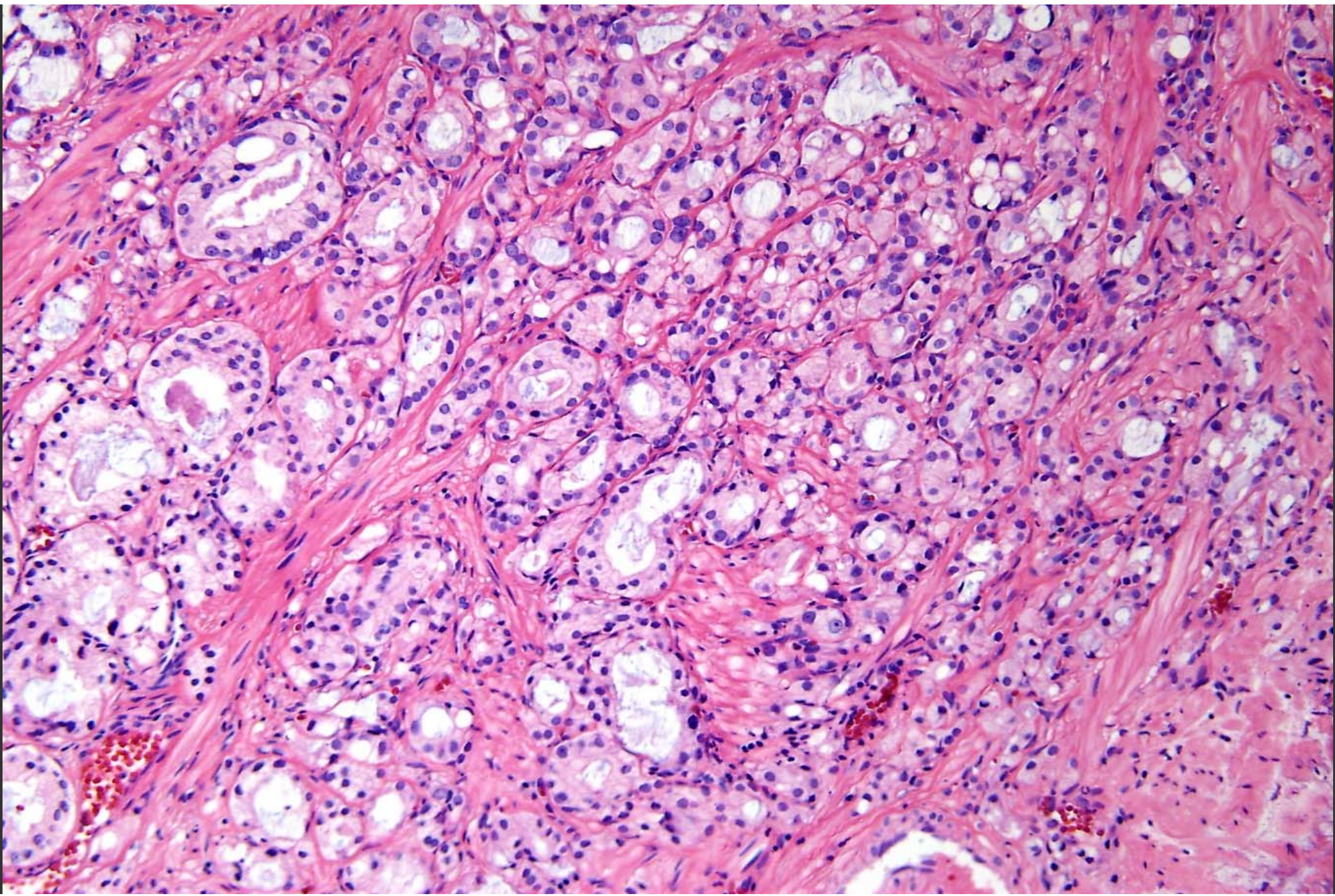


Glomeruloid Glands: Pattern 4

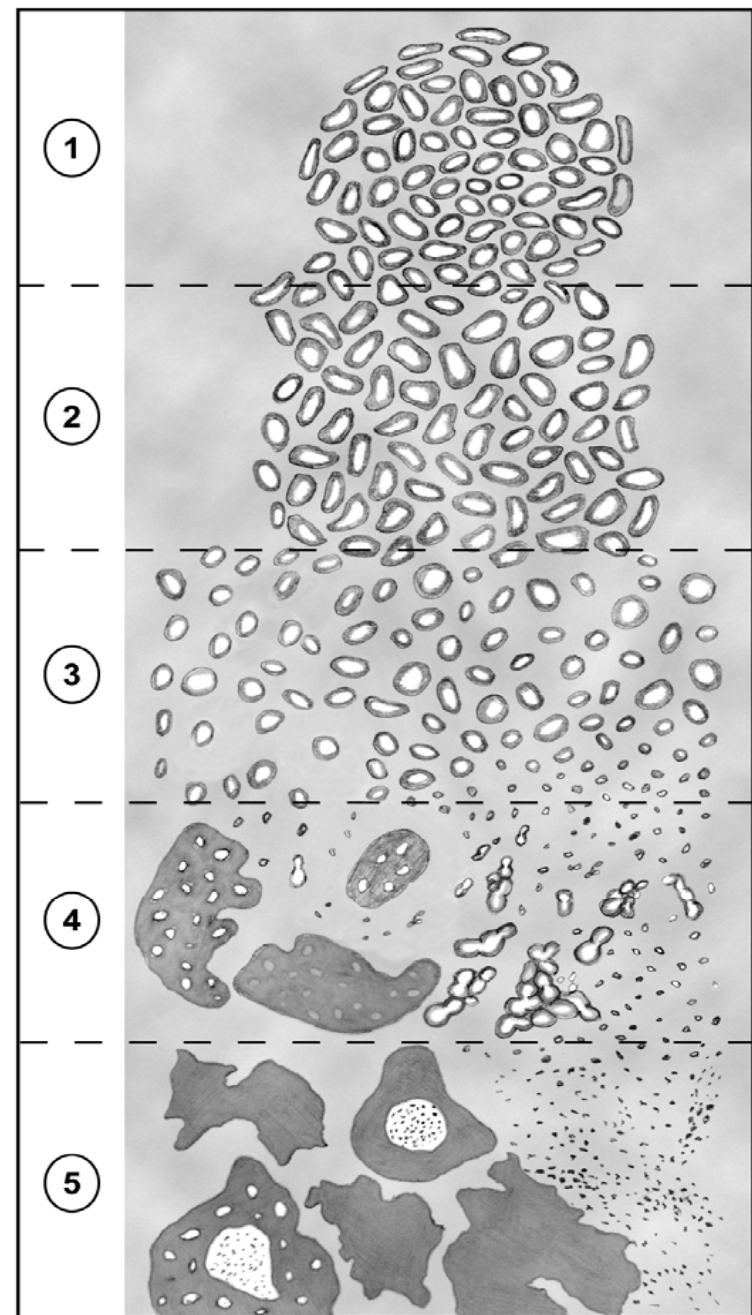
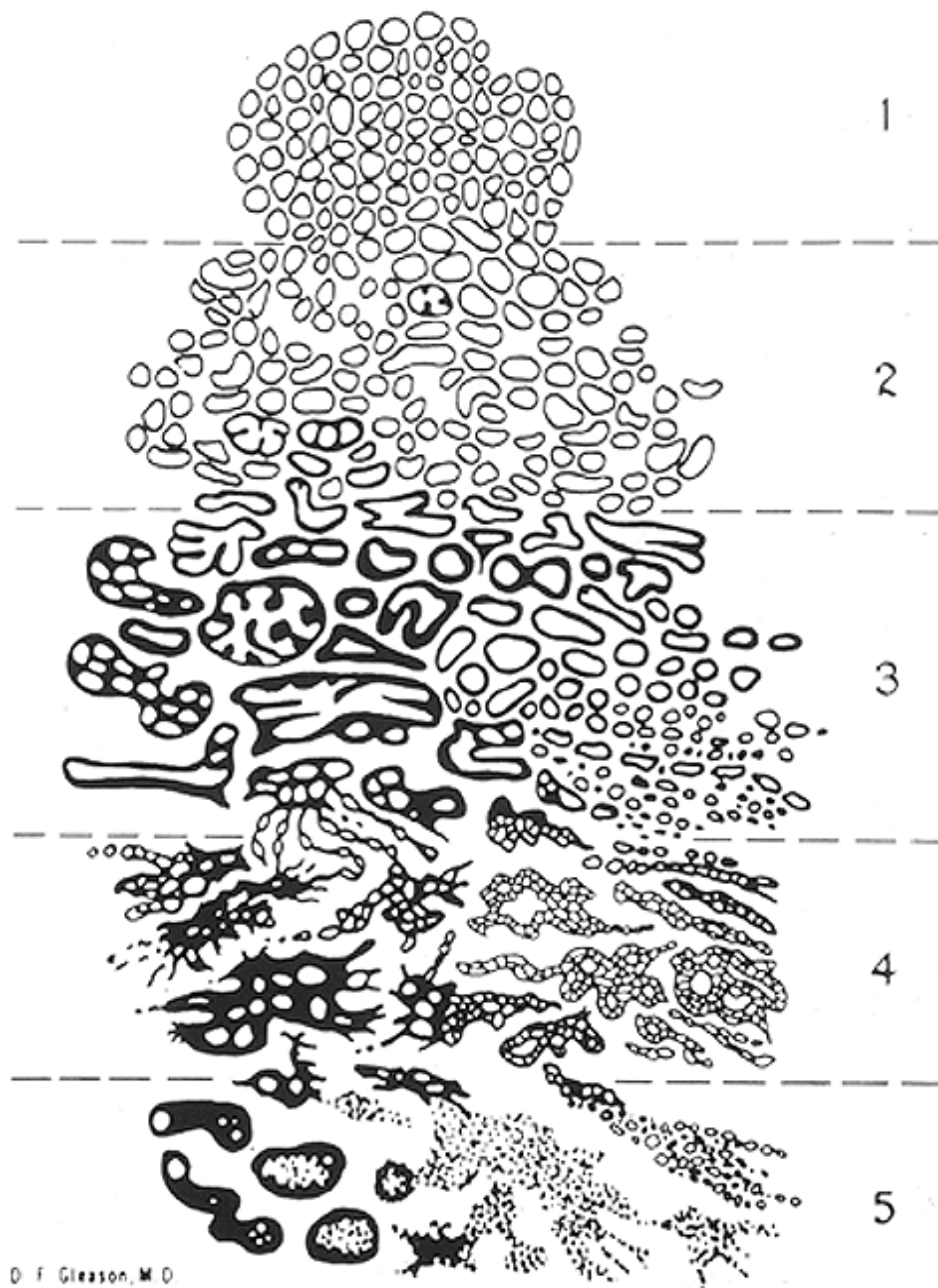




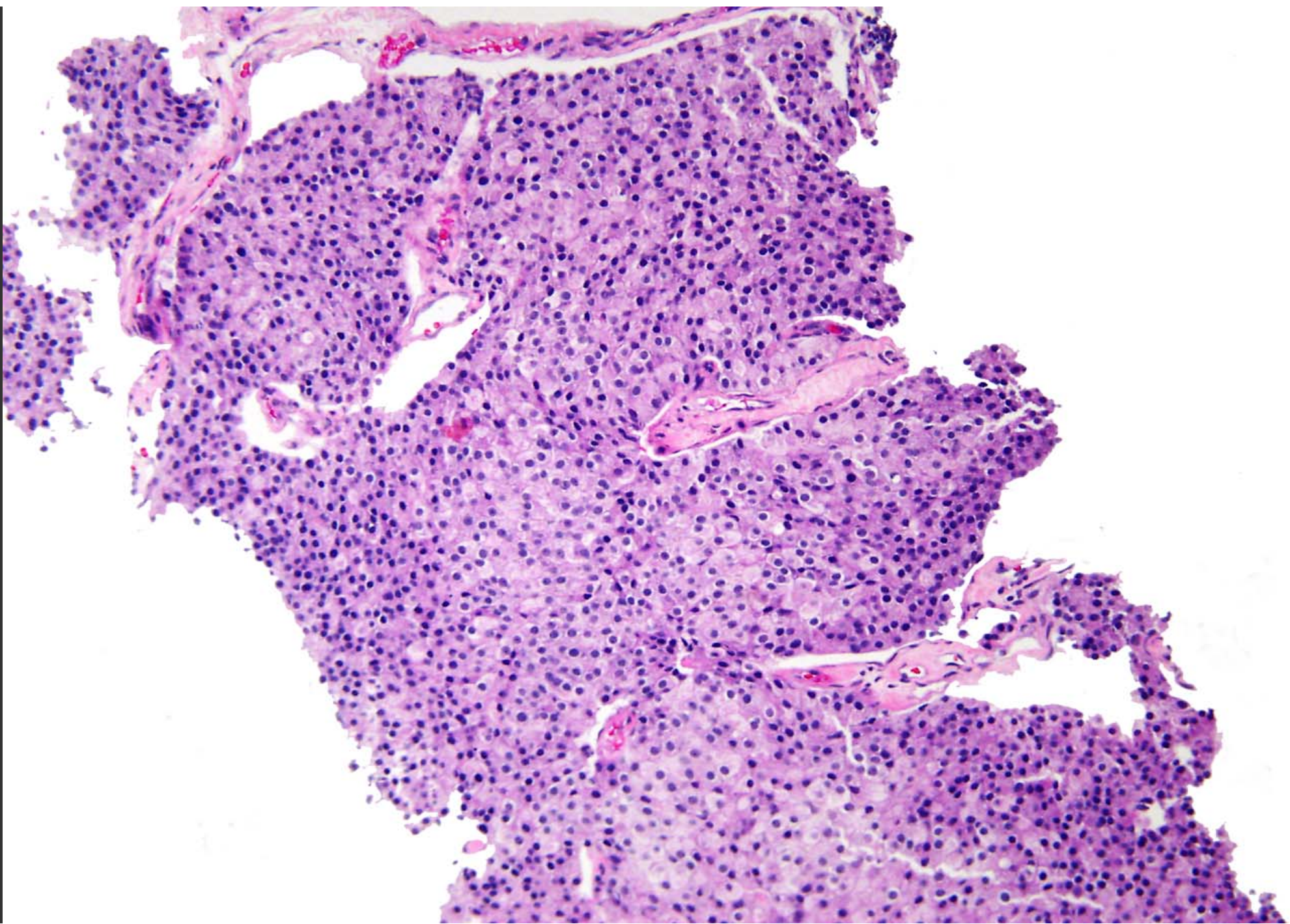


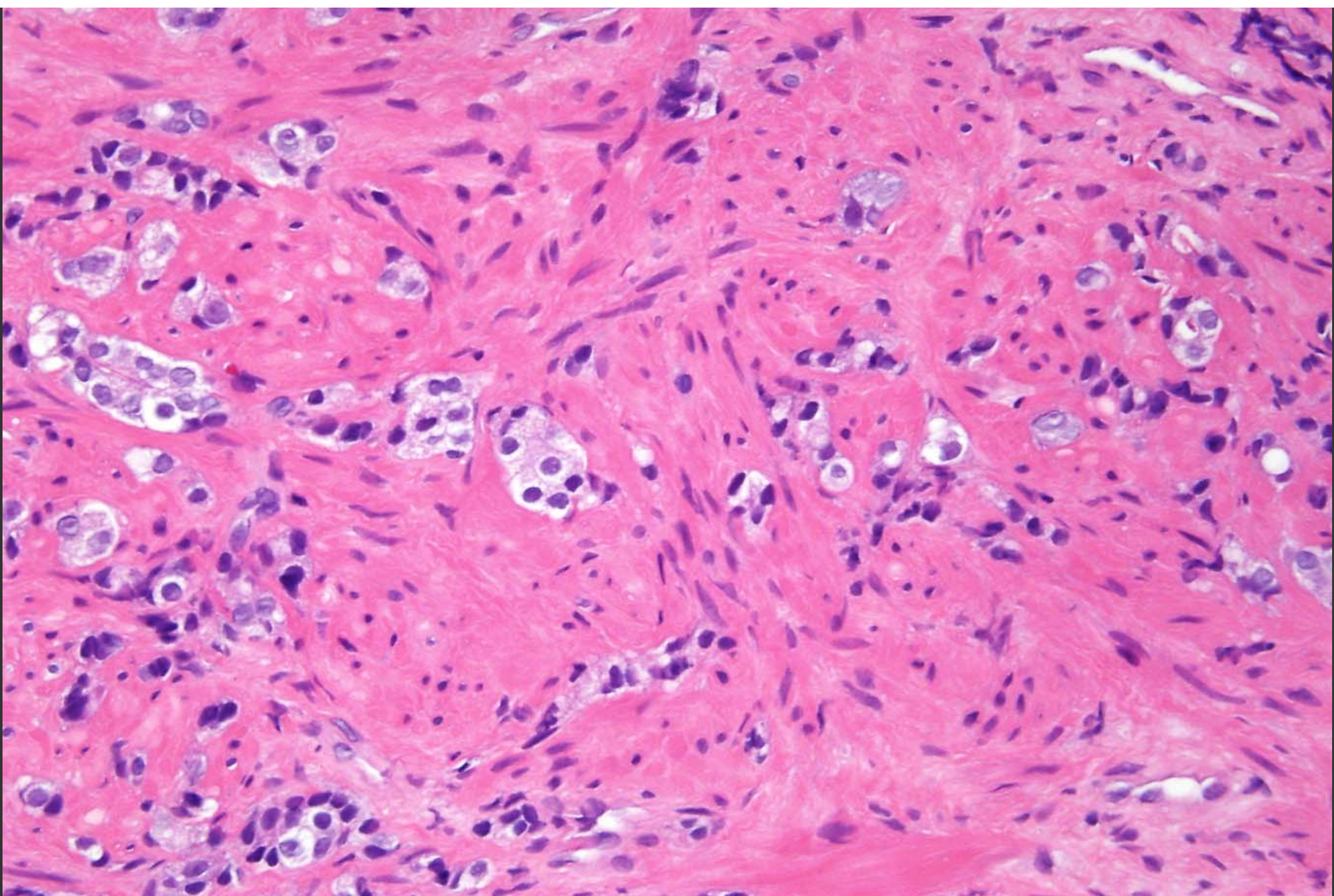


PROSTATIC ADENOCARCINOMA (Histological Patterns)

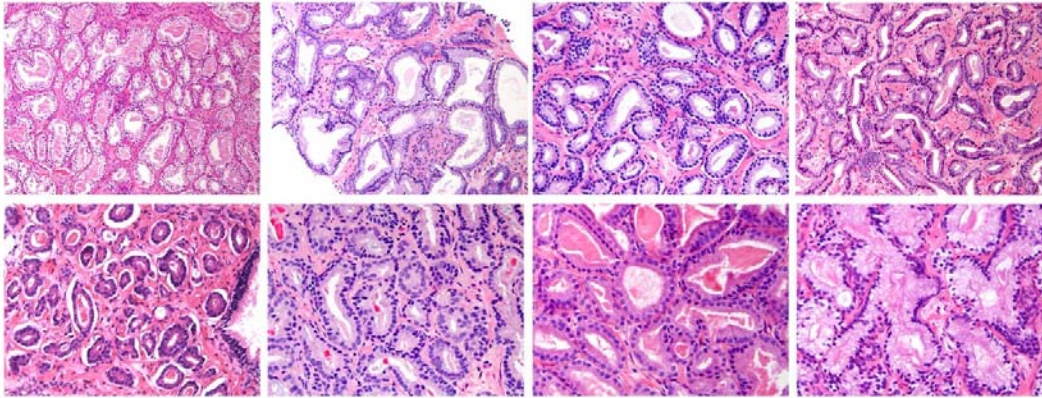


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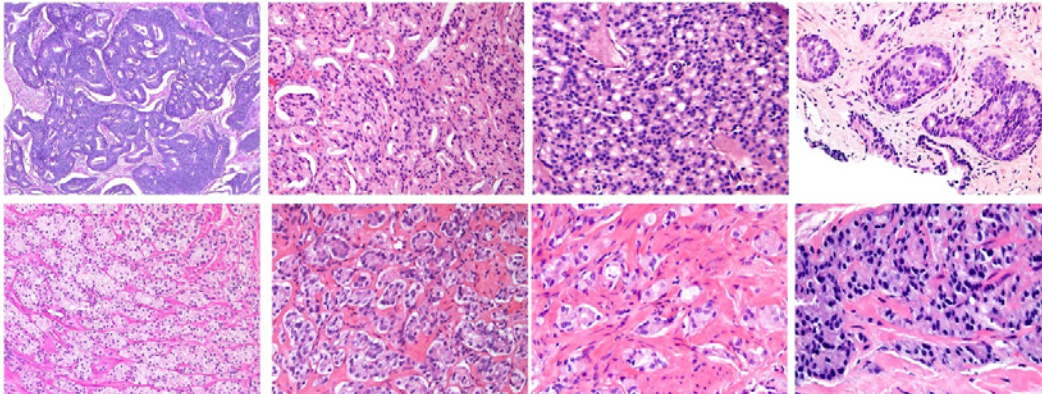




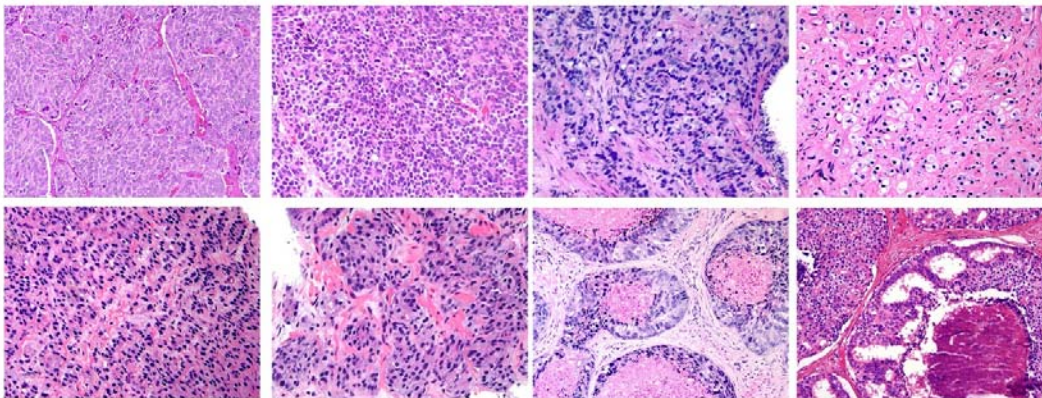
Discrete Well-formed Glands (Gleason Patterns 1-3)



Cribriform/Poorly-formed/Fused Glands (Gleason Pattern 4)



Sheets/Cords/Single Cells/Solid Nests/Necrosis (Gleason Pattern 5)



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Jonathan Epstein

CONTEMPORARY PROSTATE CANCER GRADING IMAGES

Grading diagram that
uses photomicrographs
instead of line drawings
to show the various
patterns within each
grade.

Sent to Pathologists
in >40 Countries

jepstein@jhmi.edu

VARIANTS of ADENOCARCINOMA

Grading Variants of Prostate Adenocarcinoma

Same rule as grading usual prostate adenocarcinoma based on underlying grade pattern, except small cell carcinoma.

- Individual well-formed glands – pattern 3**
- Cribriform – pattern 4**
- Individual cells or necrosis – pattern 5**

Foamy Gland Cancer

Pseudohyperplastic Cancer

Colloid Carcinoma

Signet Ring Cell-Like Adenocarcinoma

Ductal Adenocarcinoma

Ductal Adenocarcinoma

- Cribriform/papillary ductal adenocarcinomas should be graded as Gleason score $4+4=8$
- PIN-Like ductal adenocarcinoma graded $3+3=6$.
- Duct adenocarcinoma with necrosis grades as Gleason pattern 5.

Small Cell Carcinoma

Small cell carcinoma of the prostate has unique histological, immunohistochemical, and clinical features, which differ from those associated with Gleason pattern 5 prostatic acinar carcinoma, such that small cell carcinoma should not be assigned a Gleason grade.

Post-RT or HT Cancer

If histologically, ordinary prostate cancer is seen following hormone or radiation therapy, which resembles non-treated cancer – “Cancer without significant treatment affect” and Gleason grade.

Histologically cancer is seen, yet shows treatment effect – “Cancer with significant treatment affect” and do not Gleason grade.

Post Cryo or HIFU

- **Following cryotherapy or HIFU, benign prostate tissue and prostate cancer undergoes infarction.**
- **Successful therapy eventually shows scarring, hemosiderin deposition, and maybe necrotic tumor.**
- **If non-necrotic tumor is seen, looks like non-treated cancer and can be graded and indicates viable active tumor that needs further treatment.**

Intraductal Carcinoma

- Do not grade intraductal carcinoma (IDC)
- Only do IHC if the overall highest grade per part in the case would change depending on whether IDC or infiltrating high grade carcinoma

Reporting Rules for Gleason Grading

Rationale for Reporting Percent Pattern 4 for Gleason Score 7

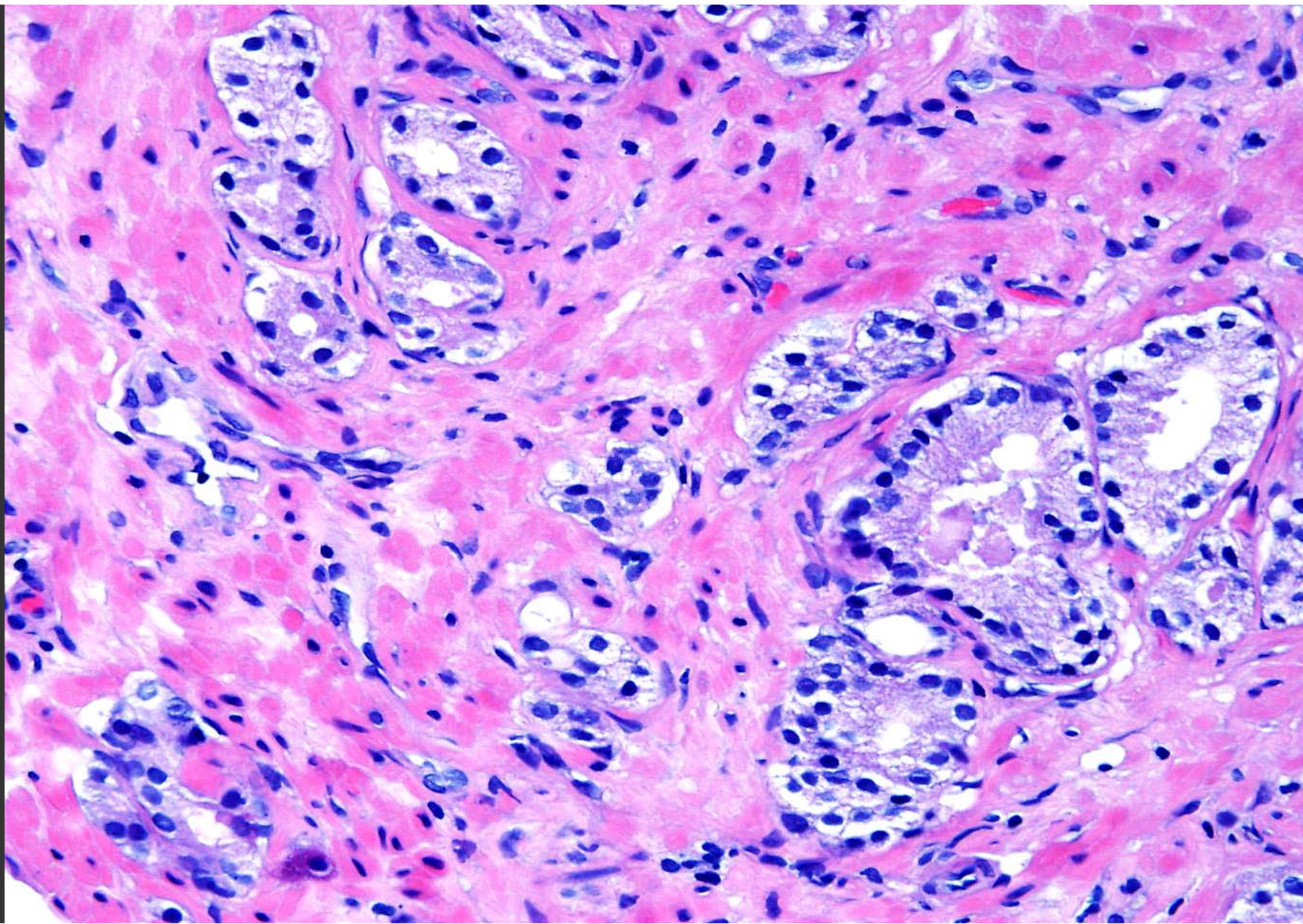
IMPROVED PATIENT CARE

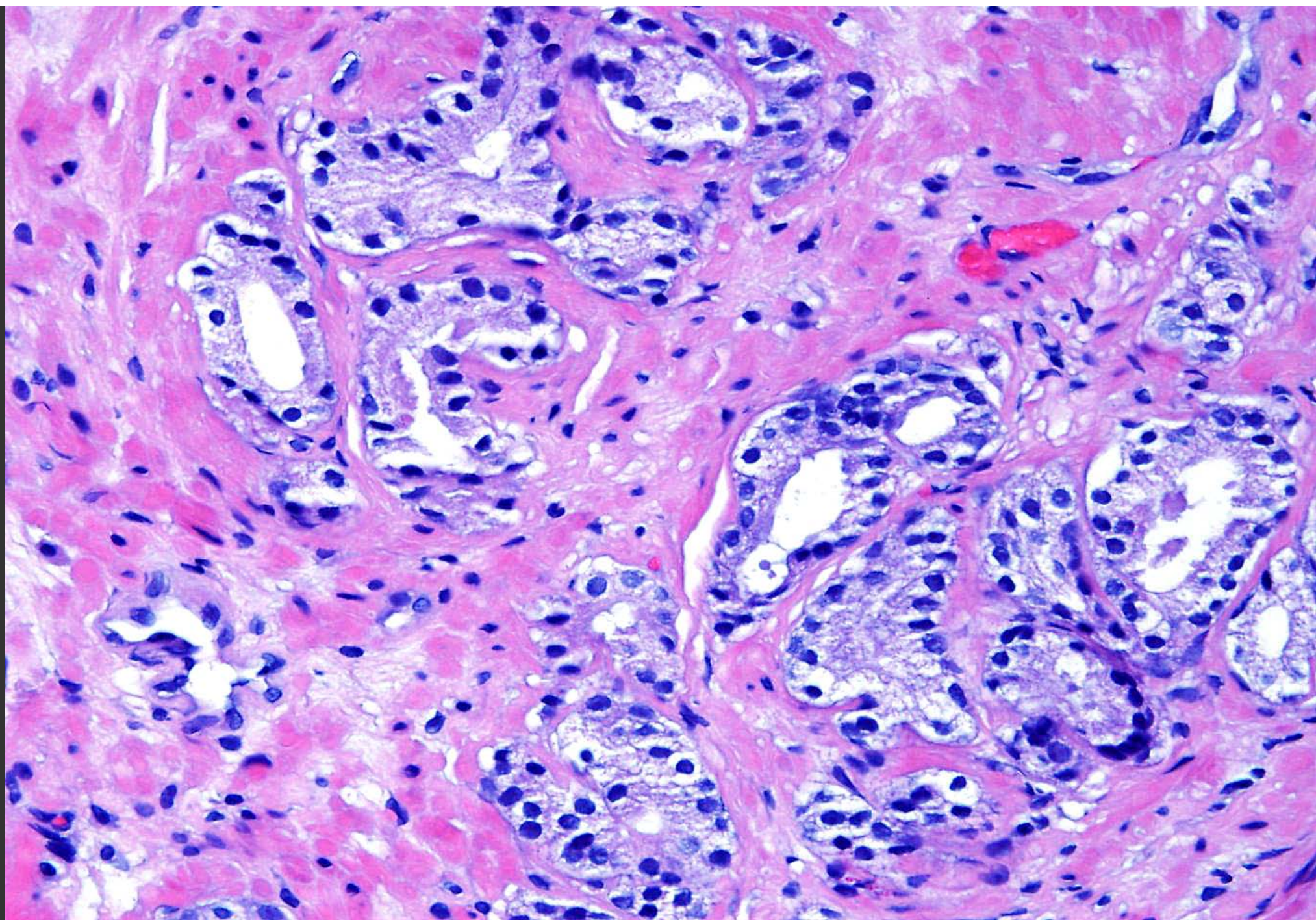
1. The major advantage for patient care to record the percent pattern 4 on needle for Gleason $3+4=7$ would be for active surveillance (AS). For the appropriate patient, Gleason $3+3=6$ is accepted for men to undergo AS. However, there may be some men, depending on age, co-morbidity, extent of cancer, MRI findings, patient desire, etc, that could be a candidate for AS with $3+4=7$ if the pattern 4 is limited. Currently, this information is not apparent in pathology reports.

2. The amount of pattern 4 is not only used for active surveillance but could be used for radiation therapy as well. Currently, there is different radiation therapy for 3+4 vs 4+3. In a case with borderline 3+4 vs 4+3, one pathologist could call it 3+4 and the other 4+3. Depending on whether 3+4 or 4+3 the percent pattern 4 could range from <5% to 90% and would not be evident in a report. By reporting the case as 3+4=7 (approaching 50% pattern 4) or 4+3=7 (60% pattern 4) the borderline nature of the case would be evident and clinicians could use other factors (PSA, number of cores positive, imaging, etc.) for therapy.

Personal Preferences in My Practice

- I do not record percent pattern 4 in small foci of $3+4=7$ or $4+3=7$.
- I record: <5%, 10%, 20%, 30%, 40%, approaching 50%, 60%, 70%, 80%, 90%
- I do not record percent pattern 4 if any other core has Gleason score 9 or 10.
- If borderline between lower and higher grade cancer, I assign the lower grade and do levels to clarify.





Minor Pattern of Lower Grade

- On RP or needle do not mention if the lower grade component is $<5\%$.
- Core or RP nodule with 98% pattern 4 and 2% pattern 3 is graded as $4+4=8$.

Tertiary Patterns

Three Patterns With Very Minor Component of Higher Grade

- On RP if pattern 5 is $<5\%$ and 3rd most common pattern then report 3+4=7 with tertiary pattern 5. If $>5\%$ then is the secondary pattern (ie. 3+5=8).
- On needle bx. if pattern 5 is 3rd most common pattern, regardless of percentage, then include in score (ie. 3+5=8) (most common + highest grade).
- Only use “tertiary” for 3+4=7 with $<5\%$ (tertiary) pattern 5 or 4+3=7 with $<5\%$ (tertiary) pattern 5 on RP

NEEDLE BIOPSY WITH DIFFERENT CORES SHOWING DIFFERENT GRADES

One should assign individual Gleason scores to separate cores as long as the cores were submitted in separate containers or the cores were in the same container yet specified by the urologist as to their location (ie. by different color inks).

Assigning a global (composite) score is optional.

Reporting of Gleason Grade in RPs

- Each major tumor focus should be graded separately. For example: 2 tumor nodules – One left PZ 4+4=8 with larger right PZ 3+3=6. Give two scores and not call 3+4=7.
- Typically only the largest tumor foci are graded. Not necessary to report small multifocal lower grade cancer.
- Exception when there is a smaller tumor focus of higher grade, report this Gleason score.

Problems with Gleason System: Scale

- **6 is the lowest grade reported although the scale goes from 2-10**
- **Patients are told they have a Gleason score of 6 out of 10 and logically but incorrectly think that they have a tumor in the middle of the grade spectrum, contributing to the fear of cancer**

Problems with Gleason System Grouping

- Gleason 7 is not homogeneous: $4+3=7$ has a much worse prognosis than $3+4=7$
- Gleason 8-10 is often considered as one group - high grade disease

Problems with Gleason Grading

Too Many Grades with Similar Prognoses

- 1+1; 1+2; 1+3; 1+4; 1+5; 2+1; 2+2; 2+3; 2+4; 2+5;
3+1; 3+2; 3+3; 3+4; 3+5; 4+1; 4+2; 4+3; 4+4; 4+5;
5+1; 5+2; 5+3; 5+4; 5+5
- 25 potential grades!
- What are the least number of grades with a similar prognosis?

Prognostic Gleason grade grouping: data based on the modified Gleason scoring system

Phillip M. Pierorazio*, Patrick C. Walsh*, Alan W. Partin* and Jonathan I. Epstein*†‡

BJU International 2013; 111:753-60

New 5 Grade System

- **Grade Group 1 (≤ 6)**

Only individual discrete well-formed glands

- **Grade Group 2 (3+4)**

Predominantly well-formed glands with a lesser component of poorly- formed/fused/cribriform glands

- **Grade Group 3 (4+3)**

Predominantly poorly formed/fused/cribriform glands with a lesser component of well-formed glands

- **Grade Group 4 (4+4/3+5/5+3)**

Only poorly-formed/fused/cribriform glands or

Predominantly mix of well-formed and lack of glands

- **Grade Group 5 (4+5/5+4/5+5)**

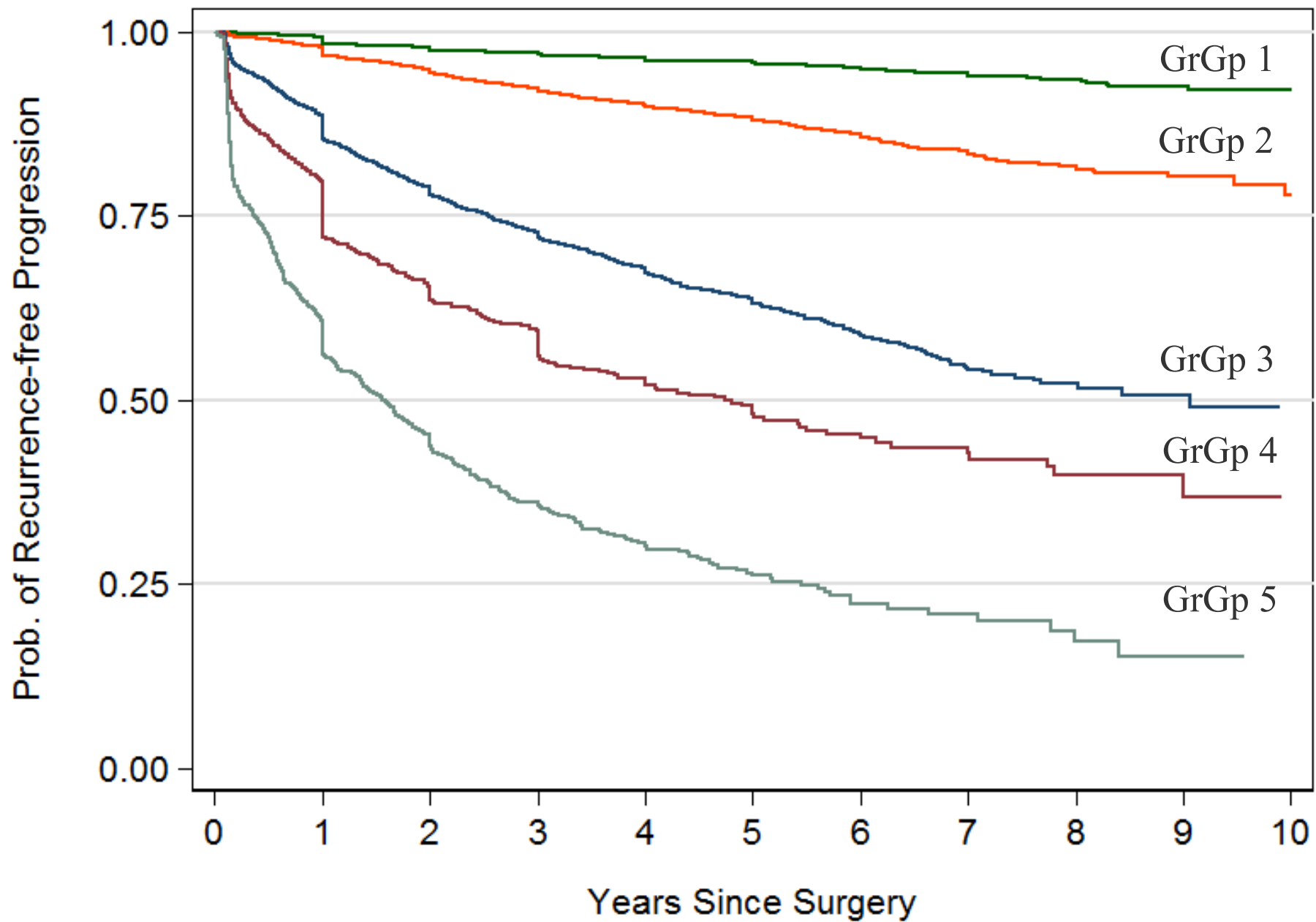
Lack gland formation (or with necrosis) with or w/o
poorly formed/fused/cribriform glands

2014 - RP Data From 5 Institutions

- Since 2005 – Modified Gleason grades
- **University of Pittsburgh** – J. Nelson, A. Parwani
- **MSKCC** – V. Reuter, S. Fine, A. Vickers, J. Eastham,
D. Sjoberg
- **CCF** – C. Magi-Galluzzi, E. Klein, J. Ciezki, C. Reddy
- **Karolinska** – L. Egevad, P. Wiklund, T. Nyberg
- **Johns Hopkins** – J. Epstein, M. Han

RP Grade Meta-Analysis

Hosp	Freq.
-----+-----	
Pittsburgh	2,102
Karolinska	3,763
Hopkins	6,137
Memorial	6,673
CCF	2,170
-----+-----	
Total	20,845



RP Grade

5 Year Biochemical Risk Free Survival

Grade	Gleason	BRFS	95% Confidence Intervals
1	3+3=6	96%	94%-95%
2	3+4=7	88%	87%-89%
3	4+3=7	63%	61%-65%
4	4+4=8	48%	44%-52%
5	9-10	26%	23%-30%

Multiple Additional Studies Validating New Grading System

**Correlating with BCR, distant metastases, mortality following RT
and radical prostatectomy**

2016-2017 Review of the Literature

How Grades Listed

From Ideal to Least Ideal

Order to Ideal	2016 (n=601)	2017 (n=541)	
≤ 6 , 3+4=7, 4+3=7, 8, 9-10	71 (11.8%)	132 (34.4%)	<0.001
≤ 6 , 3+4=7, 4+3=7, 8-10	108 (18.0%)	79 (14.6%)	
≤ 6 , 7, 8, 9, 10	44 (7.3%)	38 (7.0%)	
≤ 6 , 7, 8-10	219 (36.4%)	161 (29.8%)	
≤ 7 , 8-10 OR <6 , 7-10	159 (26.5%)	131 (24.2%)	

More Accurately Reflects Biology of Disease than Current System

Grade Group 1 (as opposed to 6/10): Excellent prognosis – no metastases. Avoids issues of GS<6

Grade Group 2 (as opposed to 7/10): Very good prognosis – rare metastases

Grade Group 3 (4+3 and 3+4 both = GS7 – D'Amico): Greater distinction from Grade Group 2

More Accurately Reflects Biology of Disease than Current System

Grade Group 4 (as opposed to combined 8-10): Better prognosis than 9-10.

Grade Group 5: No need to distinguish 9 vs 10.

The new grading system was recently accepted

2016 World Health Organization (WHO)

Pathology & Genetics:

Tumours of the Urinary System and Male Genital System

College of American Pathologists (CAP)

AJCC Cancer Staging Manual –TNM System (8th Edition)

Needle Biopsy: Adenocarcinoma of the prostate Gleason score $3+4=7$ (Grade Group 2) with 20% pattern 4 involving 80% of 1 core.

Radical Prostatectomy: Adenocarcinoma of the prostate Gleason score $3+4=7$ (Grade Group 2) with tertiary (<5%) pattern 5.



Controversy Gleason Score 3+5 & 5+3

- **Conflicting studies on whether $3+5=8$ & $5+3=8$ should be in Grade Group 4 (along with Gleason score $4+4=8$) or Grade Group 5 (along with Gleason Score 9-10)**
- **Needle Bx: Separate cores with $3+3=6$ and $5+5=10$. If average could be $3+5=8$ or $5+3=8$. If highest grade core would be $5+5=10$.**
- **RP: Separate nodules with $3+3=6$ and $5+5=10$. If average or not process to determine if separate, then could be $3+5=8$ or $5+3=8$. If highest grade nodule would be $5+5=10$.**

How Common is 5+3=8?

- Our prior multi-institutional study of over 20,000 men using highest grade core or highest grade nodule
- Only 4/20,824 (0.02%) radical prostatectomies and 6/16,172 (0.04%) needle biopsies were Gleason score 5+3=8