Cribriform lesions of the prostate

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIPS:

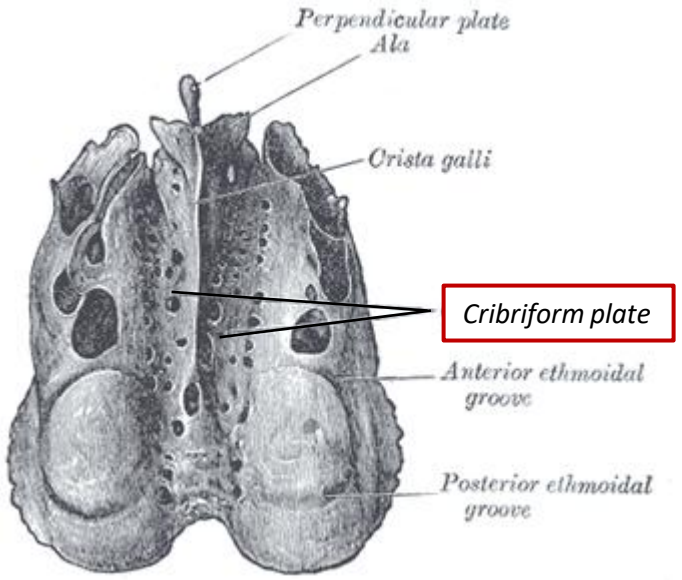
Cristina Magi-Galluzzi reported no relevant financial relationships

LEARNING OBJECTIVES

- Accurately characterize prostatic lesions with cribriform architecture
- Distinguish cribriform changes in benign prostatic glands from premalignant and malignant lesions
- Recognize unfavorable pathologic features as important predictors of clinical outcome in prostate cancer patients

Crib·ri·form

- Denotes a structure pierced by numerous small holes, in particular the ethmoid bone plate



Origin:

LATIN

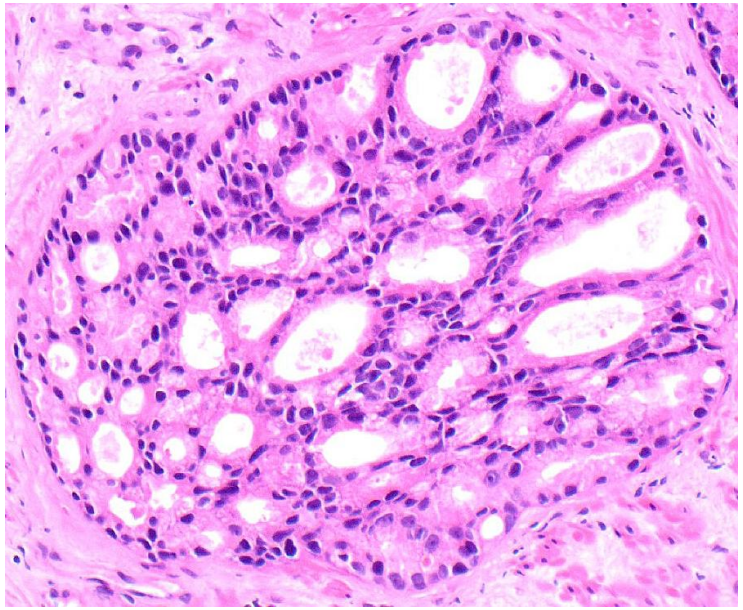
Cribrum (sieve)

ENGLISH

Form

Cribriform

mid 18th century



- Used to describe glands composed of cells forming cohesive rounded or irregularly shaped trabeculae with perforations or multiple “punched out” lumina

COMMON AND UNCOMMON CRIBRIFORM LESIONS OF THE PROSTATE

Benign	Premalignant	Malignant

COMMON AND UNCOMMON CRIBRIFORM LESIONS OF THE PROSTATE

Benign	Premalignant	Malignant
Central zone histology		
Clear cell cribriform hyperplasia		
Basal cell hyperplasia		

COMMON AND UNCOMMON CRIBRIFORM LESIONS OF THE PROSTATE

Benign	Premalignant	Malignant
Central zone histology	Cribriform high-grade prostatic intraepithelial neoplasia (HGPIN)	
Clear cell cribriform hyperplasia	Atypical intraductal proliferation (AIP)	
Basal cell hyperplasia		

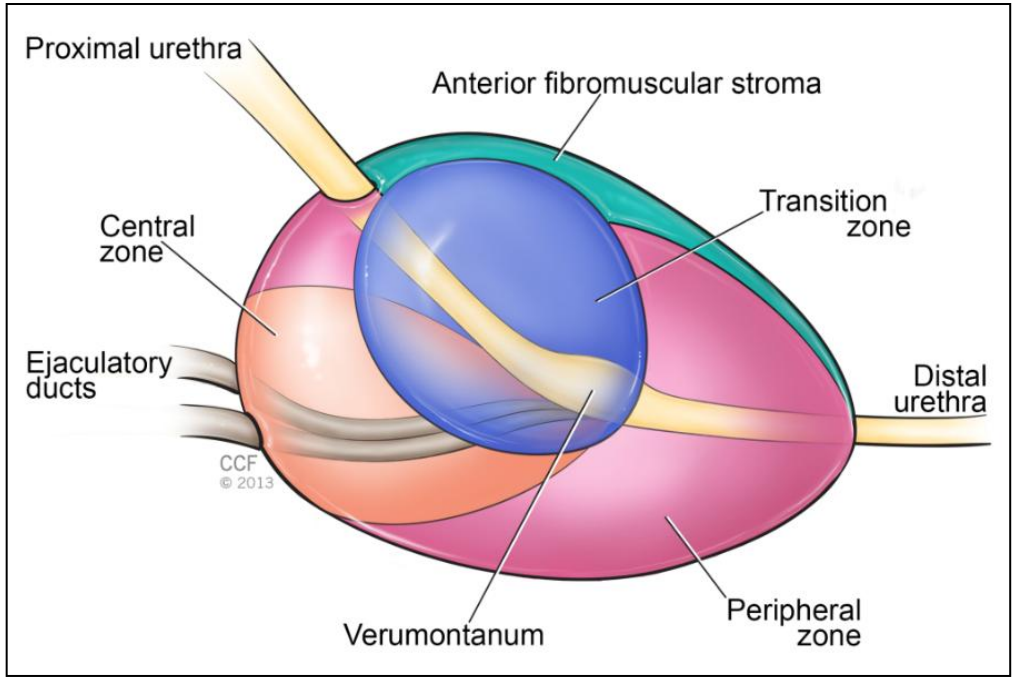
COMMON AND UNCOMMON CRIBRIFORM LESIONS OF THE PROSTATE

Benign	Premalignant	Malignant
Central zone histology	Cribriform high-grade prostatic intraepithelial neoplasia (HGPIN)	Intraductal carcinoma of prostate (IDC-P)
Clear cell cribriform hyperplasia	Atypical intraductal proliferation (AIP)	Intraductal urothelial carcinoma
Basal cell hyperplasia		Cribriform acinar prostate cancer
		Cribriform ductal adenocarcinoma

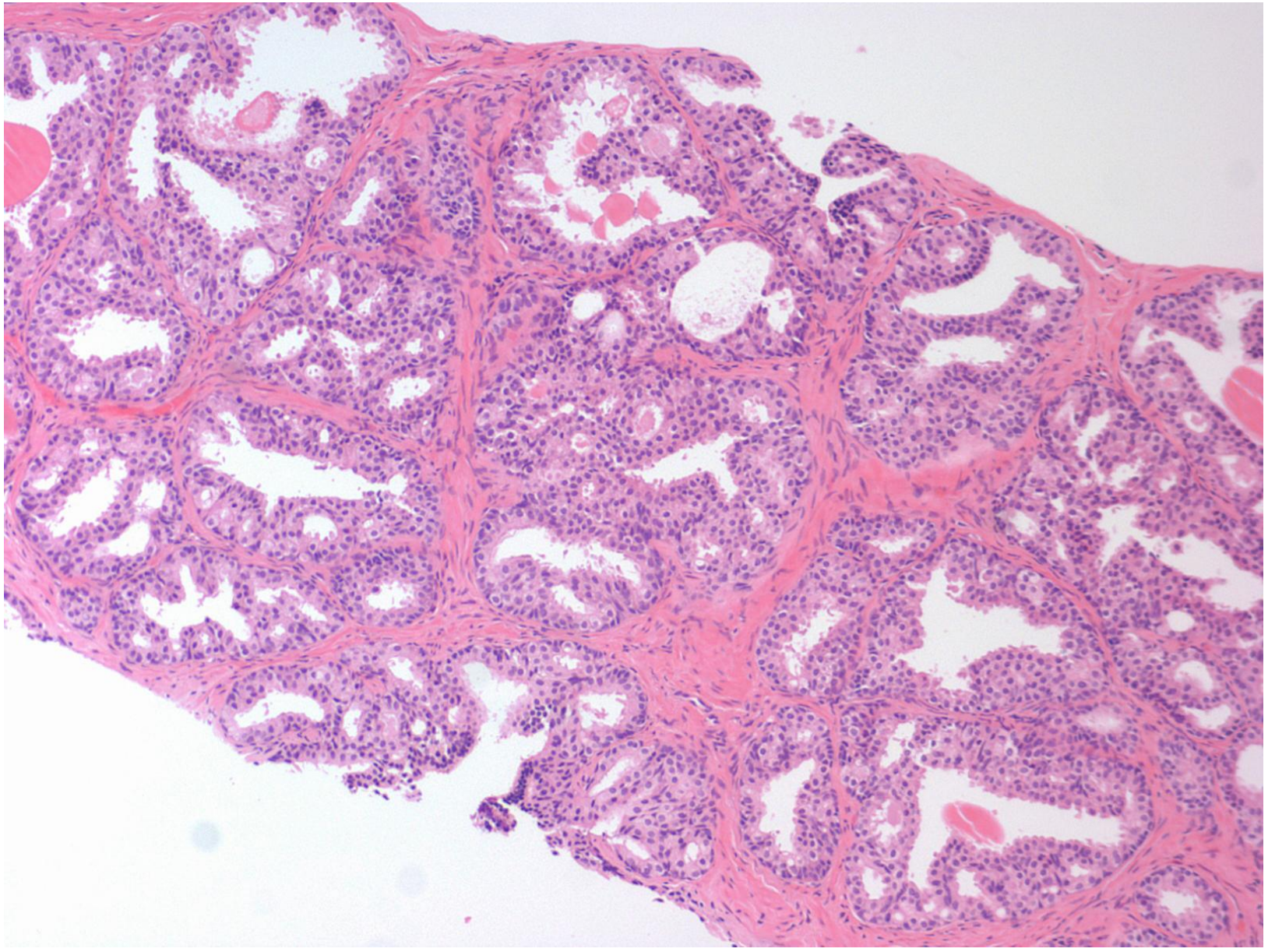
BENIGN CRIBRIFORM LESIONS

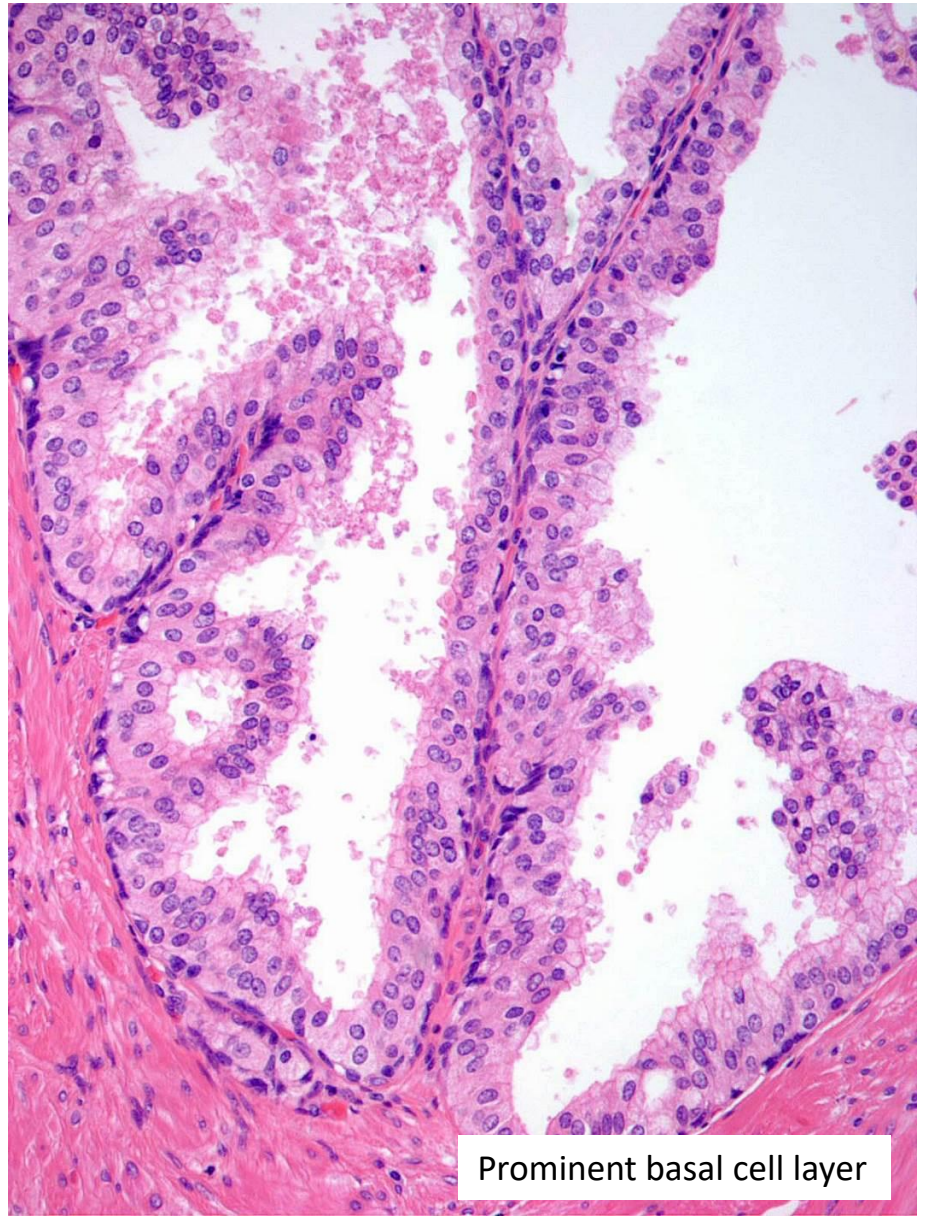
CENTRAL ZONE HISTOLOGY

- Located at base of prostate, adjacent to seminal vesicles and ejaculatory ducts
- Most common distinctive histologic features:
  - Complex architecture with cribriform formation & roman bridges
  - Tall cells with eosinophilic cytoplasm
  - Prominent basal cell layer
  - No nuclear atypia



CENTRAL ZONE HISTOLOGY





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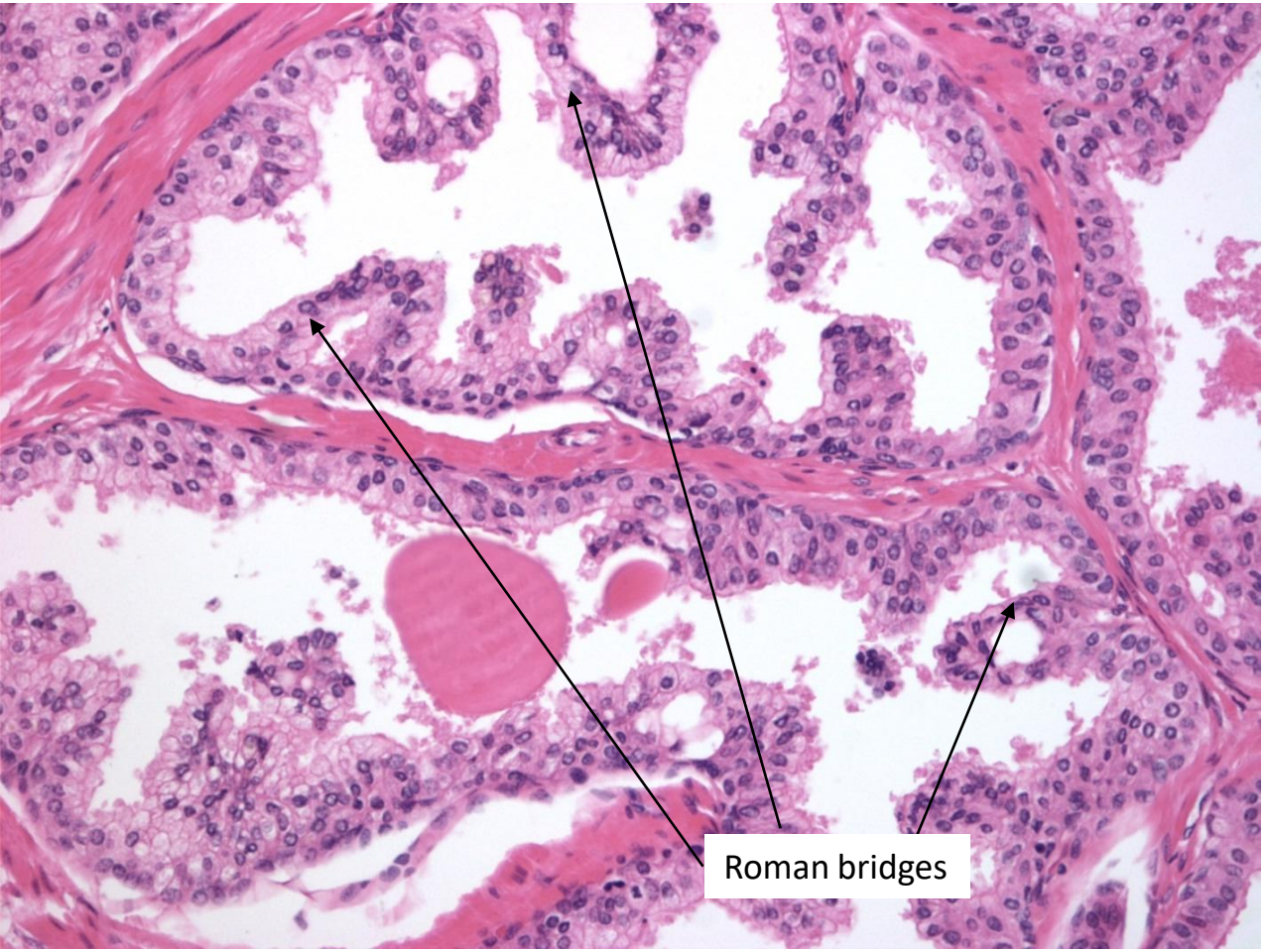

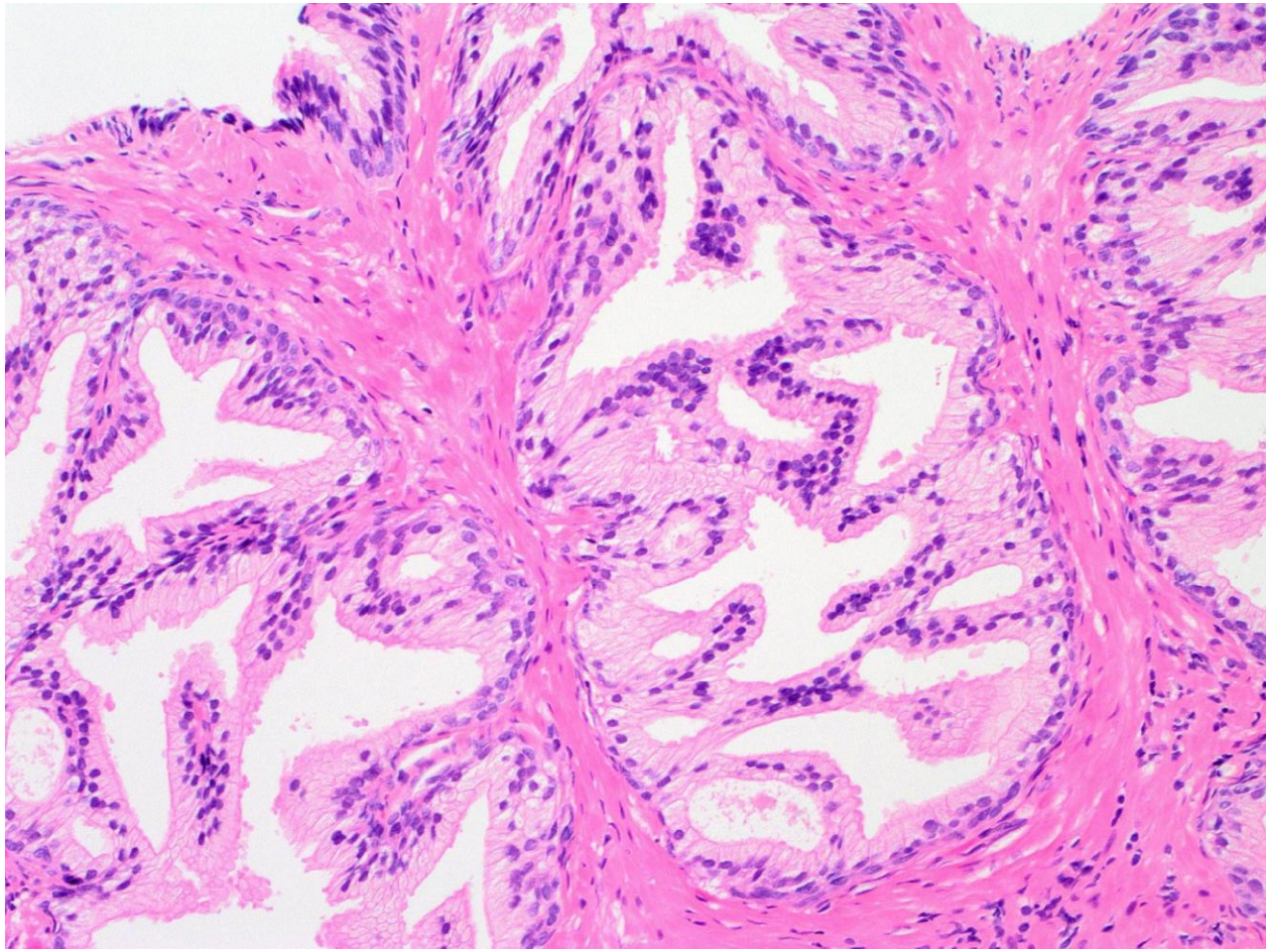

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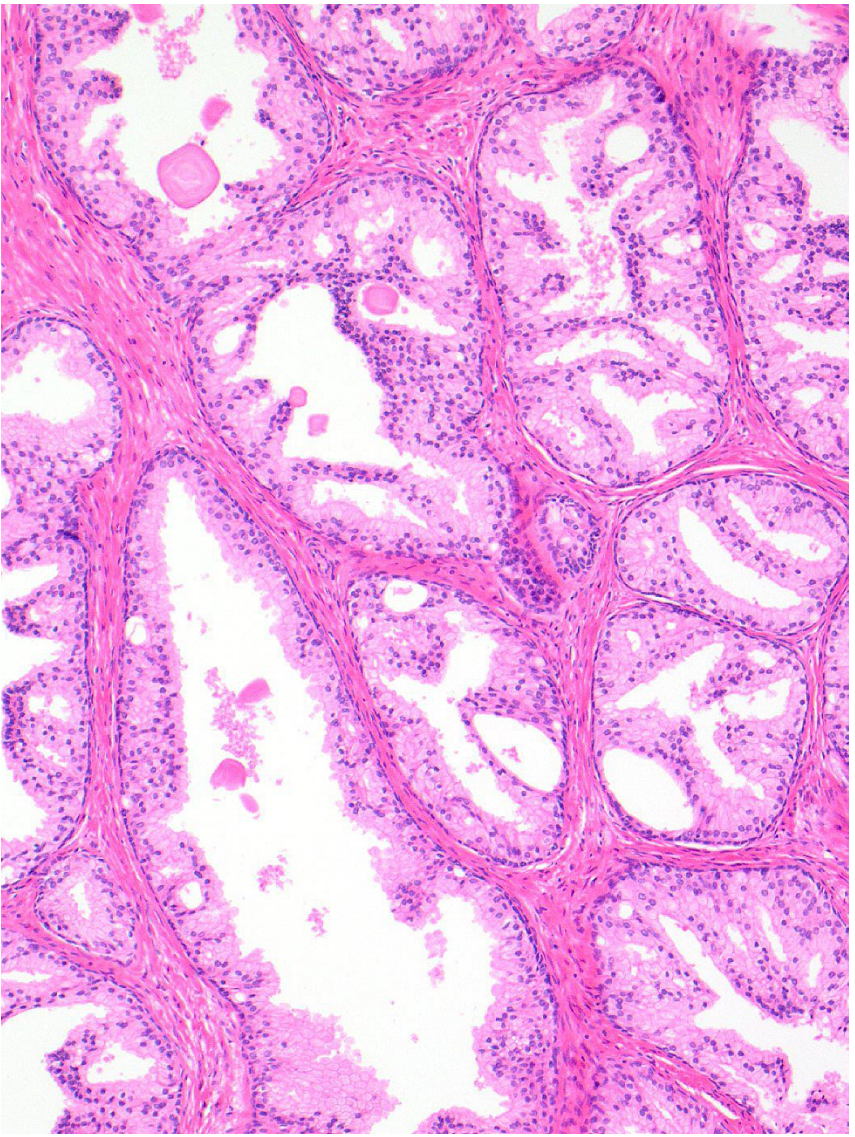

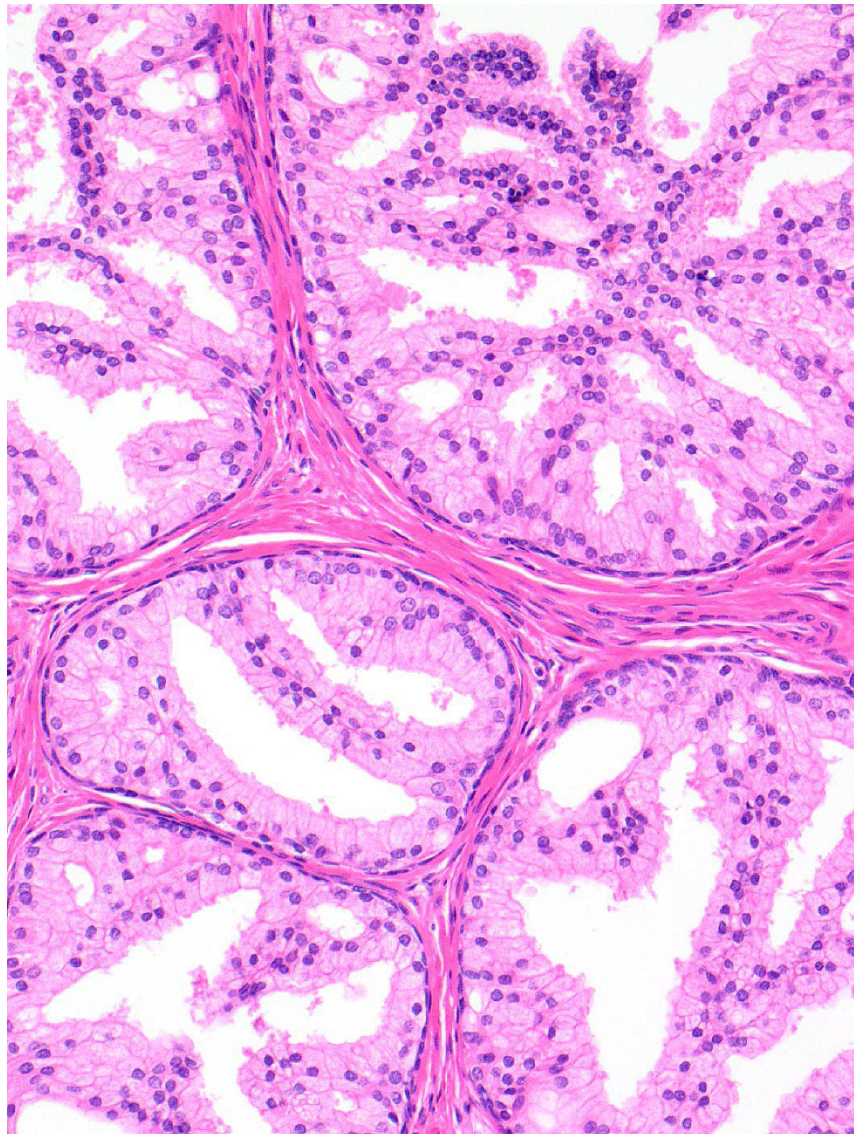

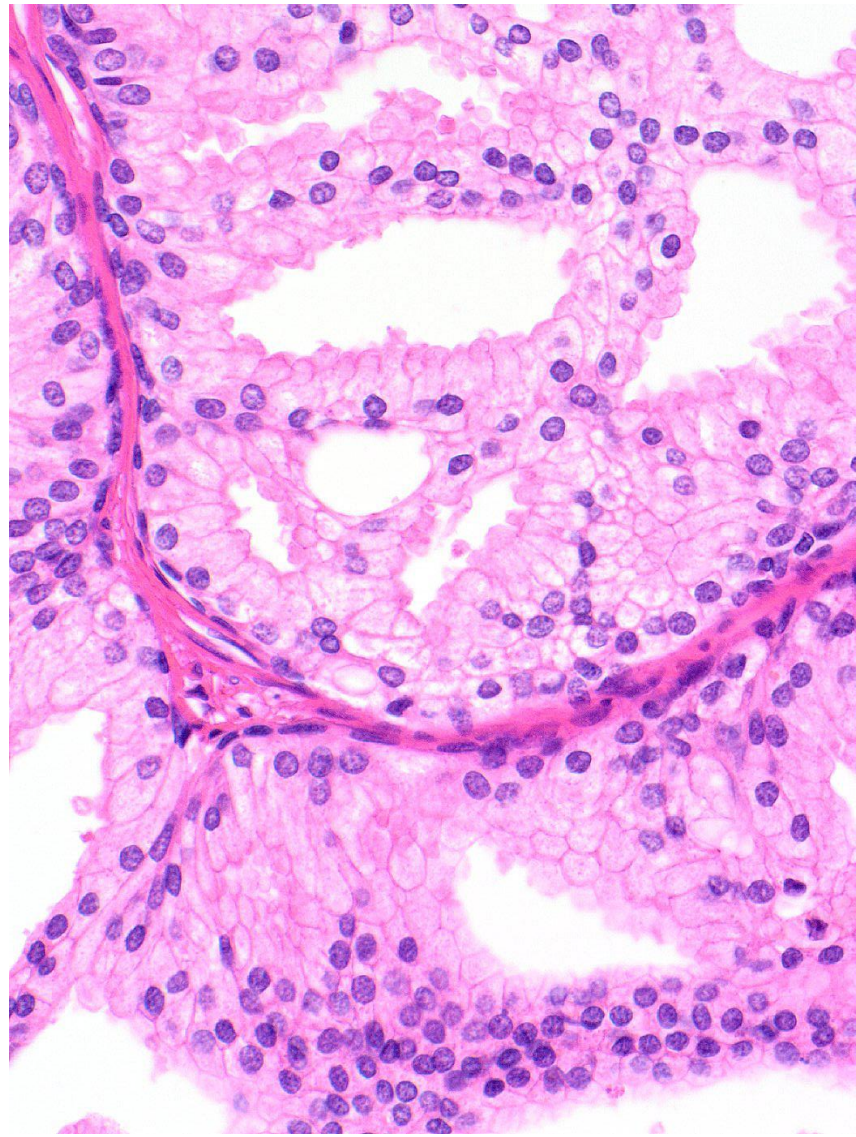

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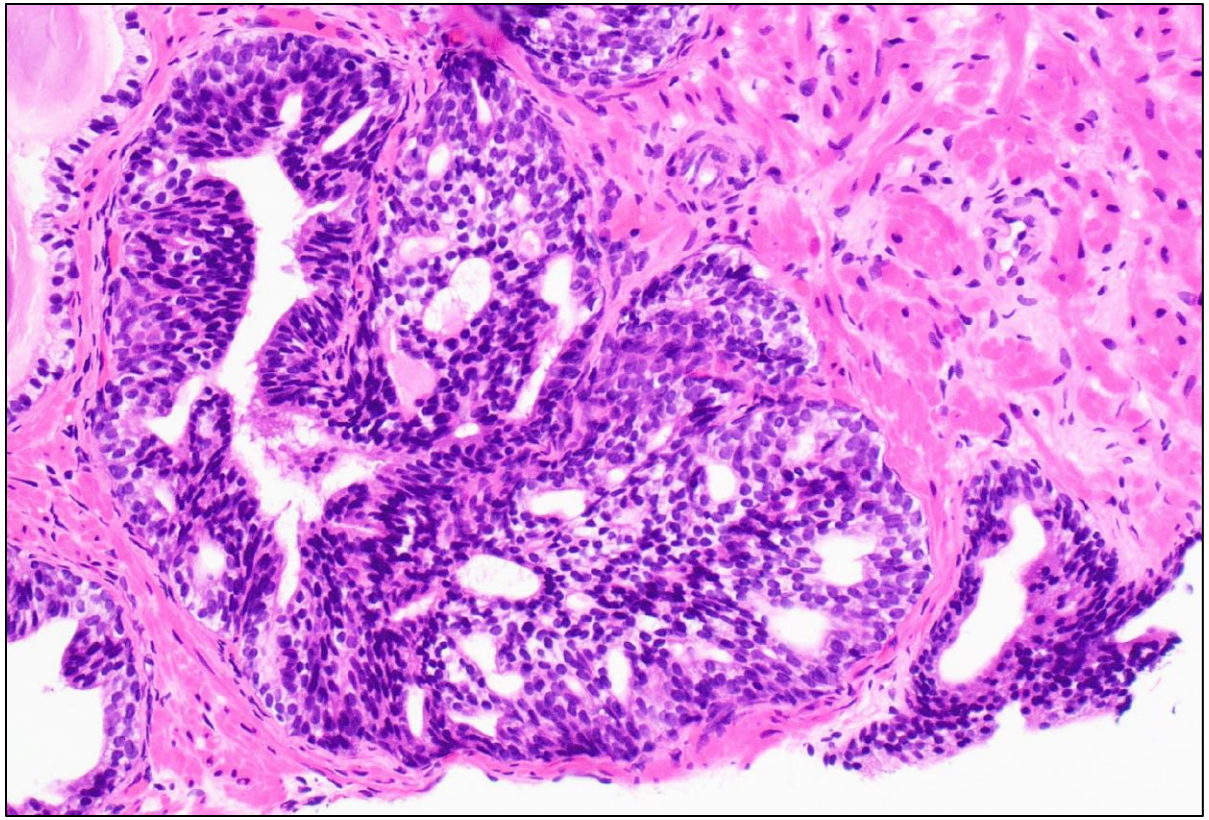
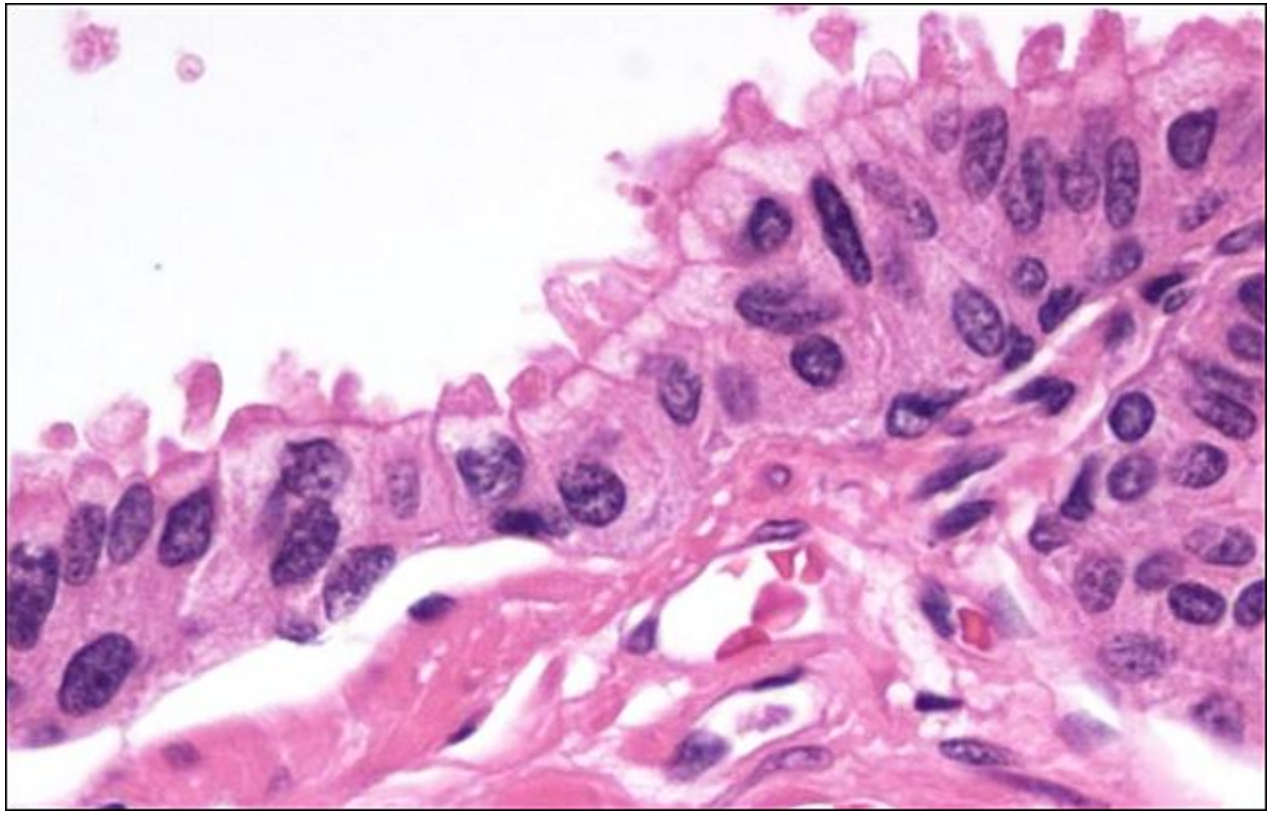
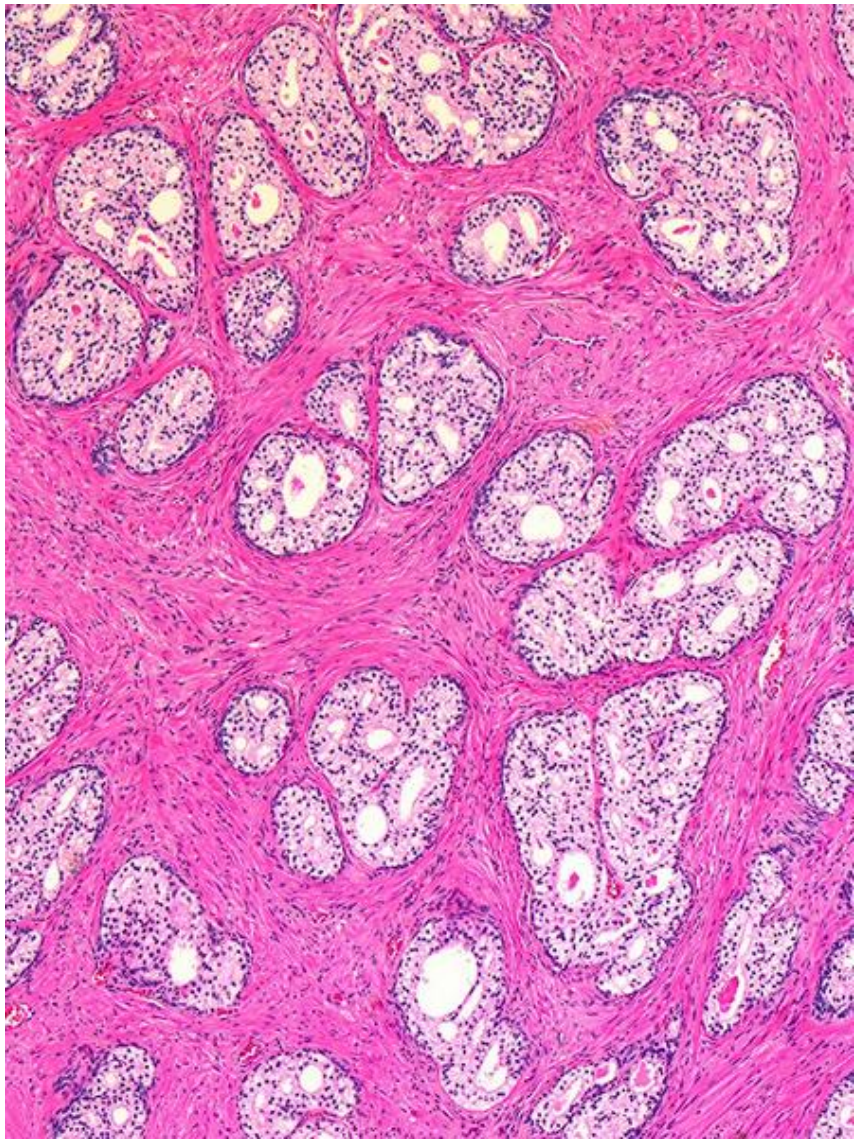




CLEAR CELL CRIBRIFORM HYPERPLASIA

- Unusual form of BPH; nodular at low power
- Predominantly involves CZ and TZ
- Glands with cribriform and complex papillary proliferation of cells
- Clear cytoplasm and uniform, round lumina



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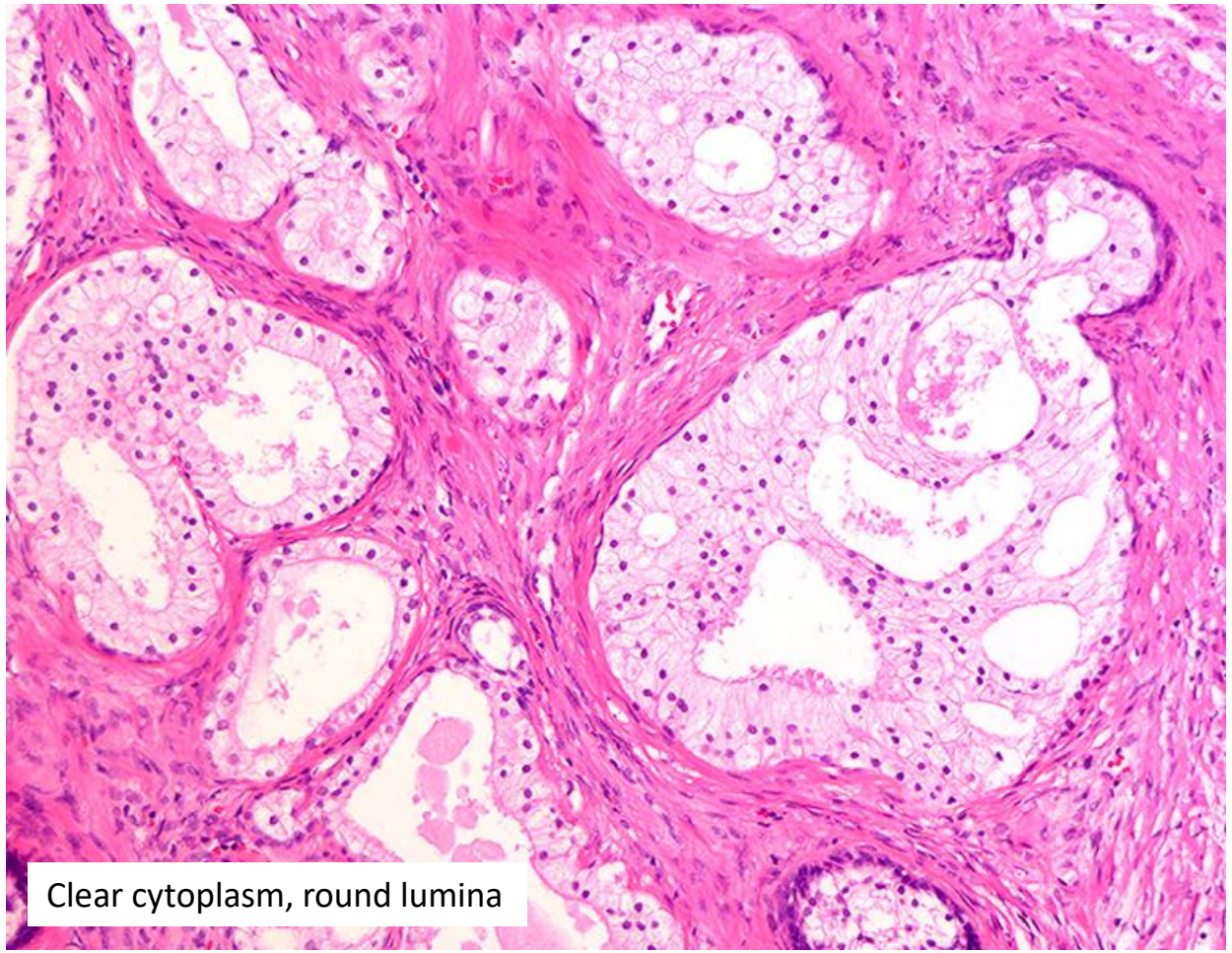
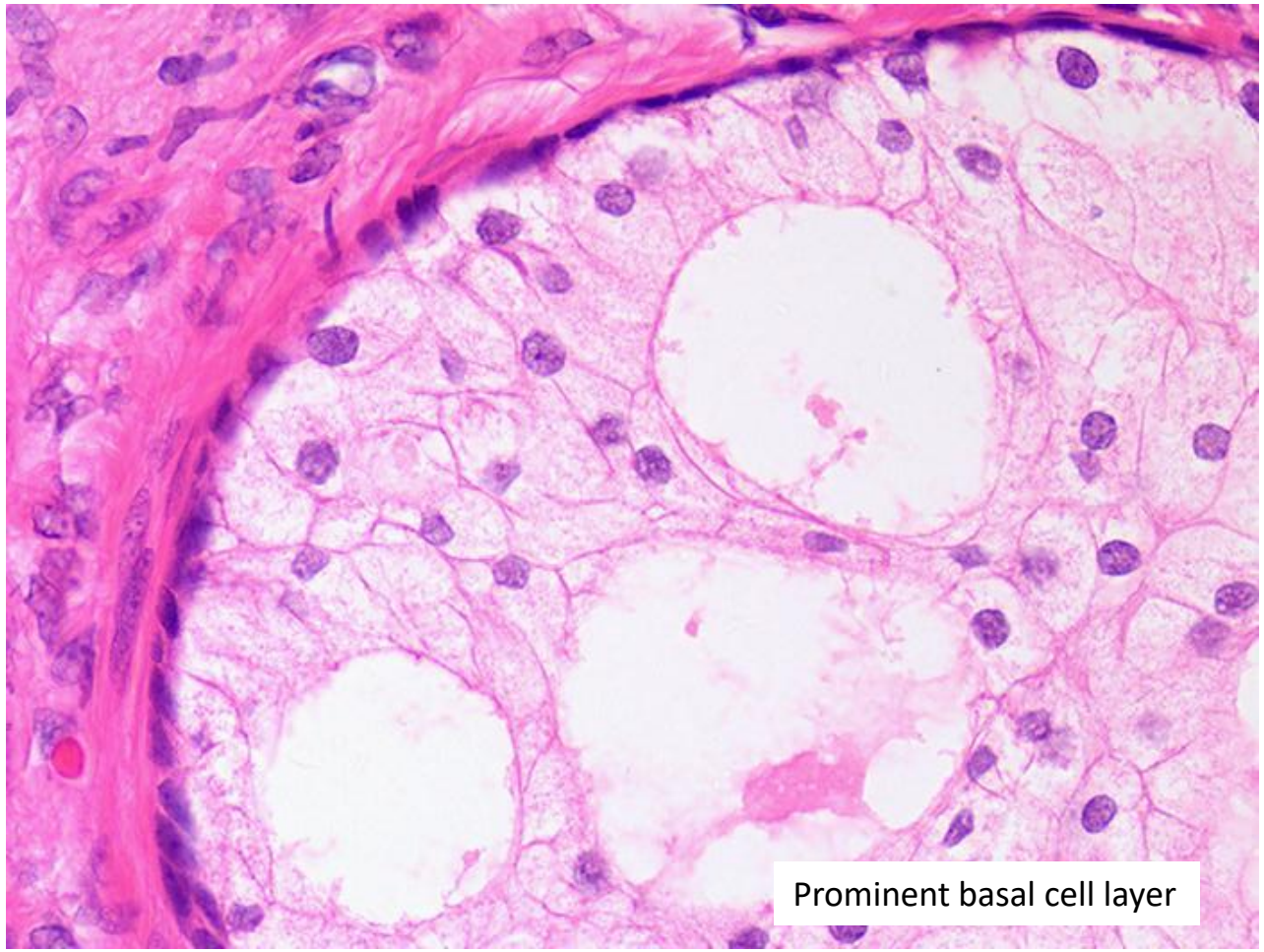
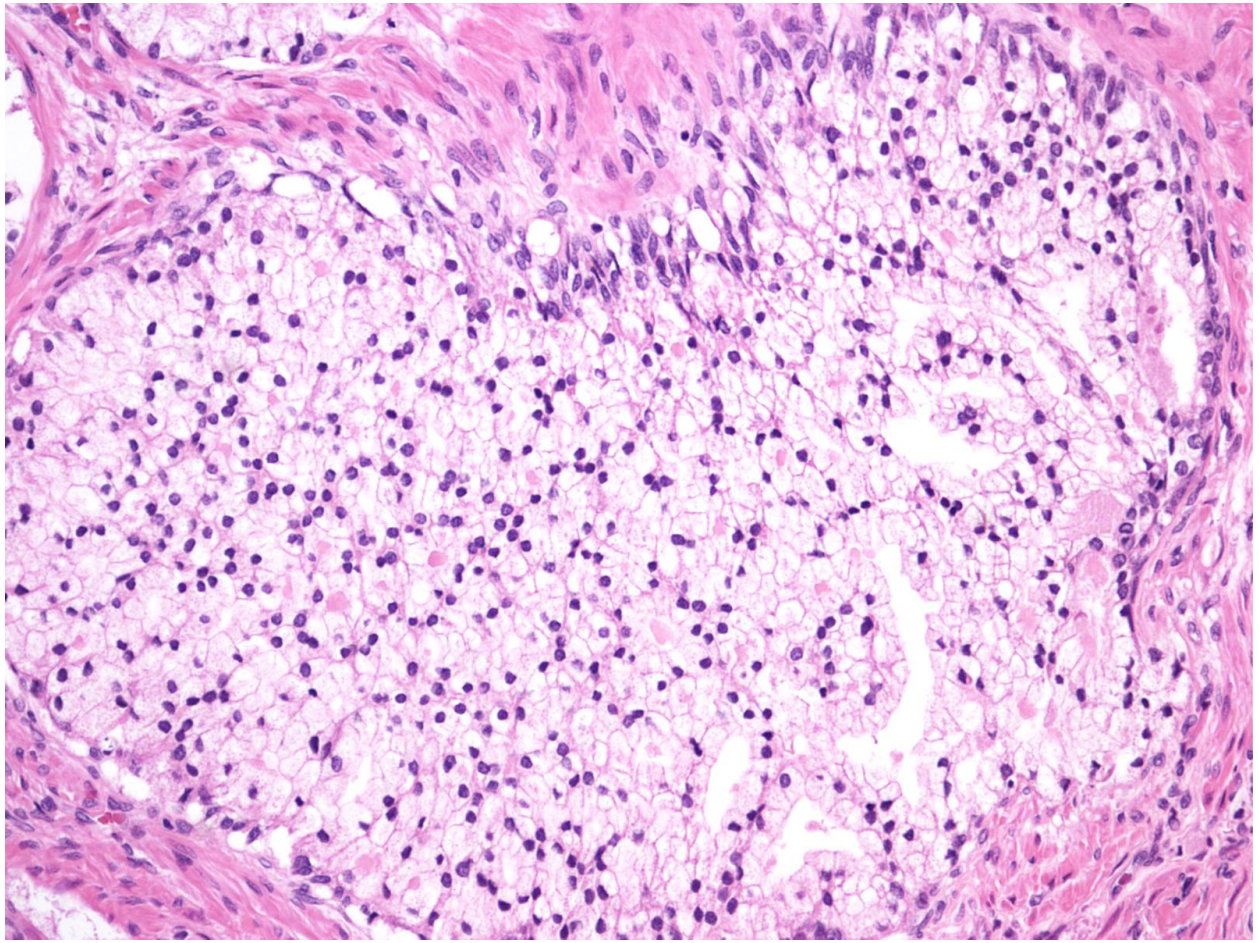


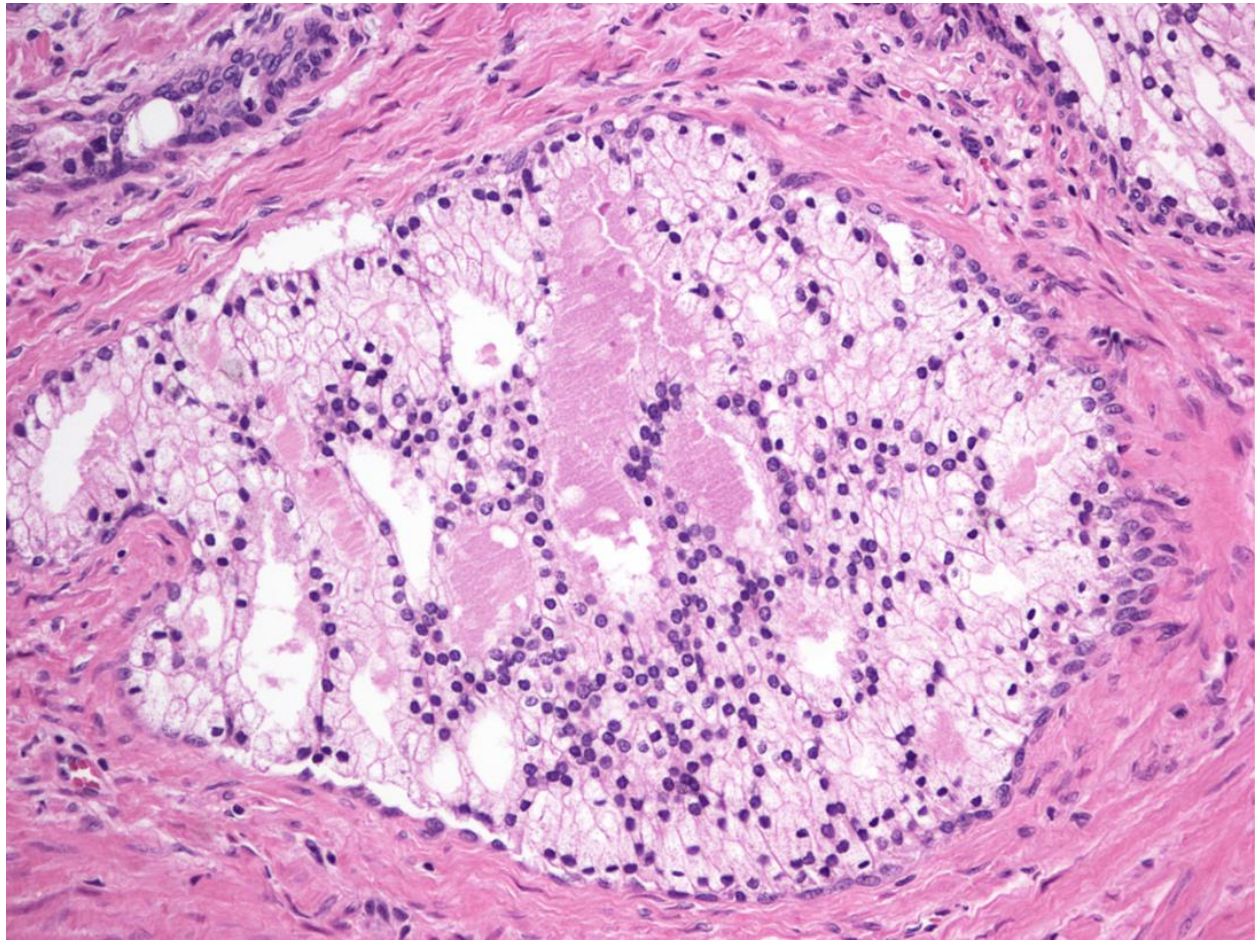
Clear cytoplasm, round lumina



Prominent basal cell layer

CLEAR CELL CRIBRIFORM HYPERPLASIA





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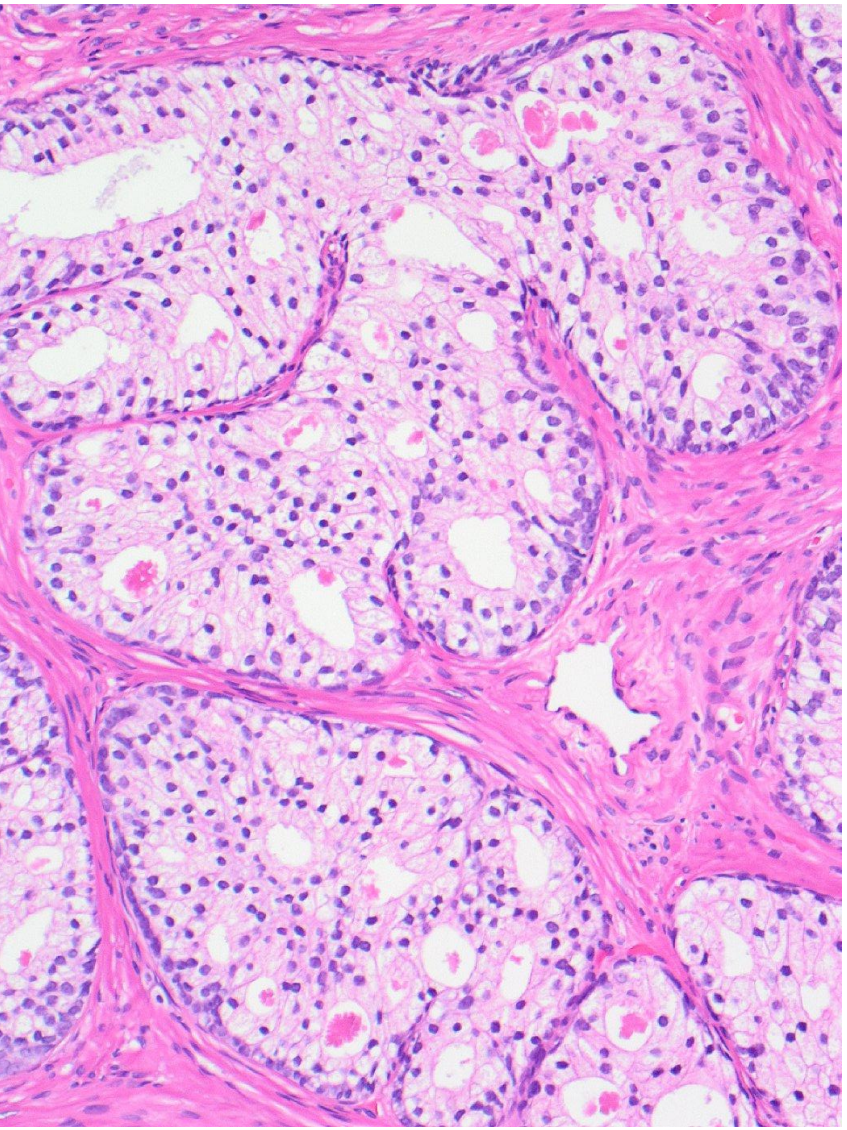
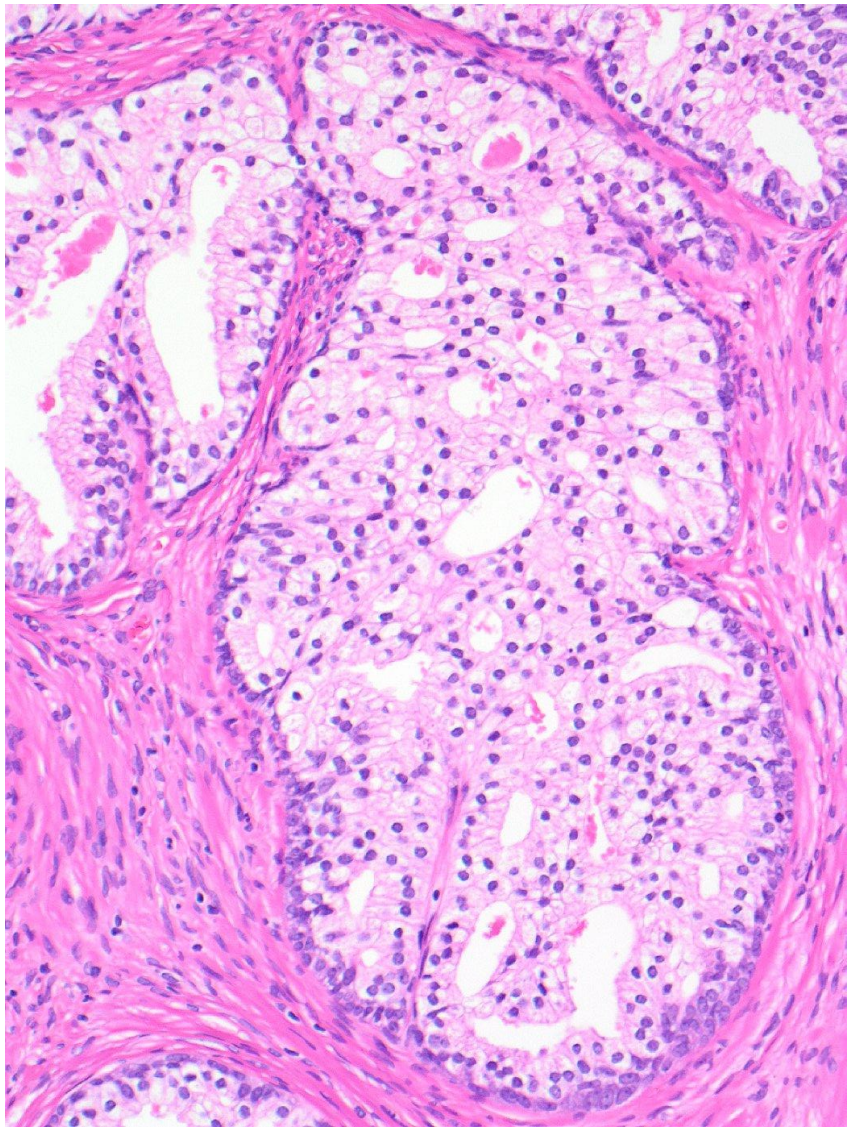
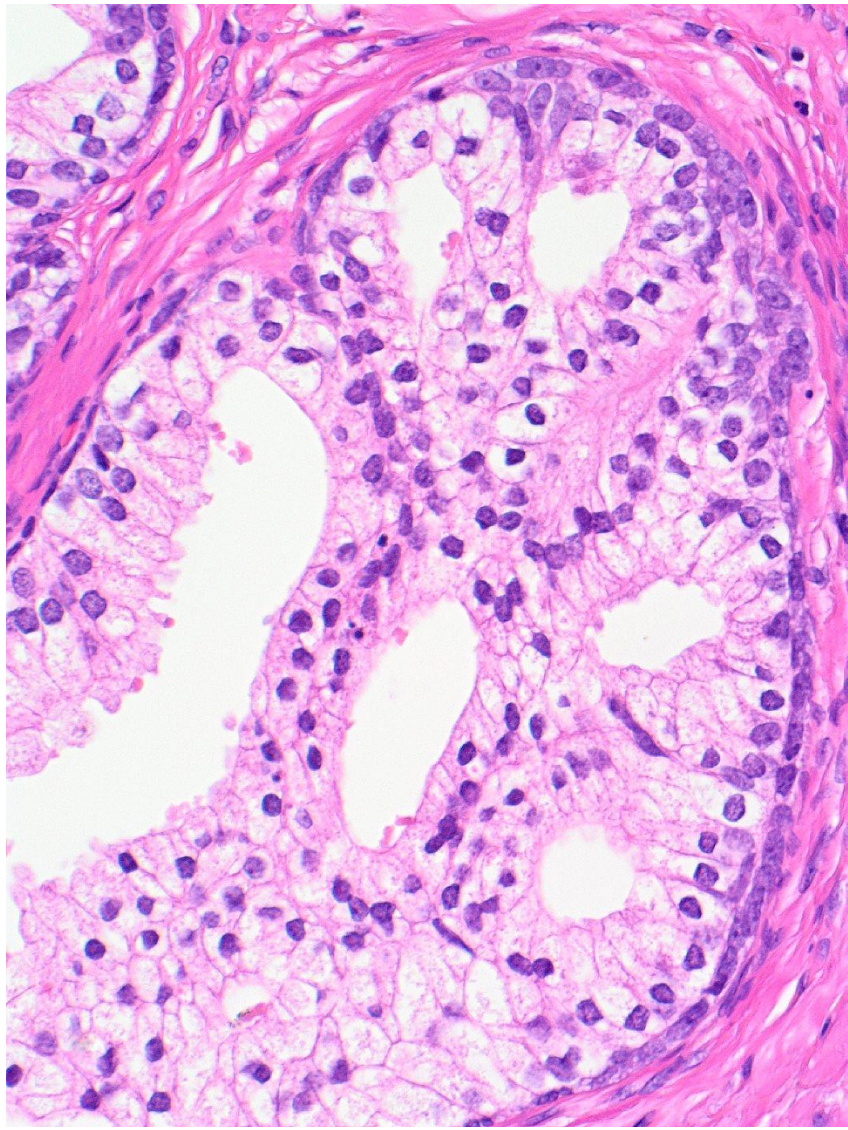




BASAL CELL HYPERPLASIA

- Nodular or diffuse proliferation of round or occasional cribriform glands associated with acellular stroma (BPH-like)
- Most common in TZ, it can be found in PZ

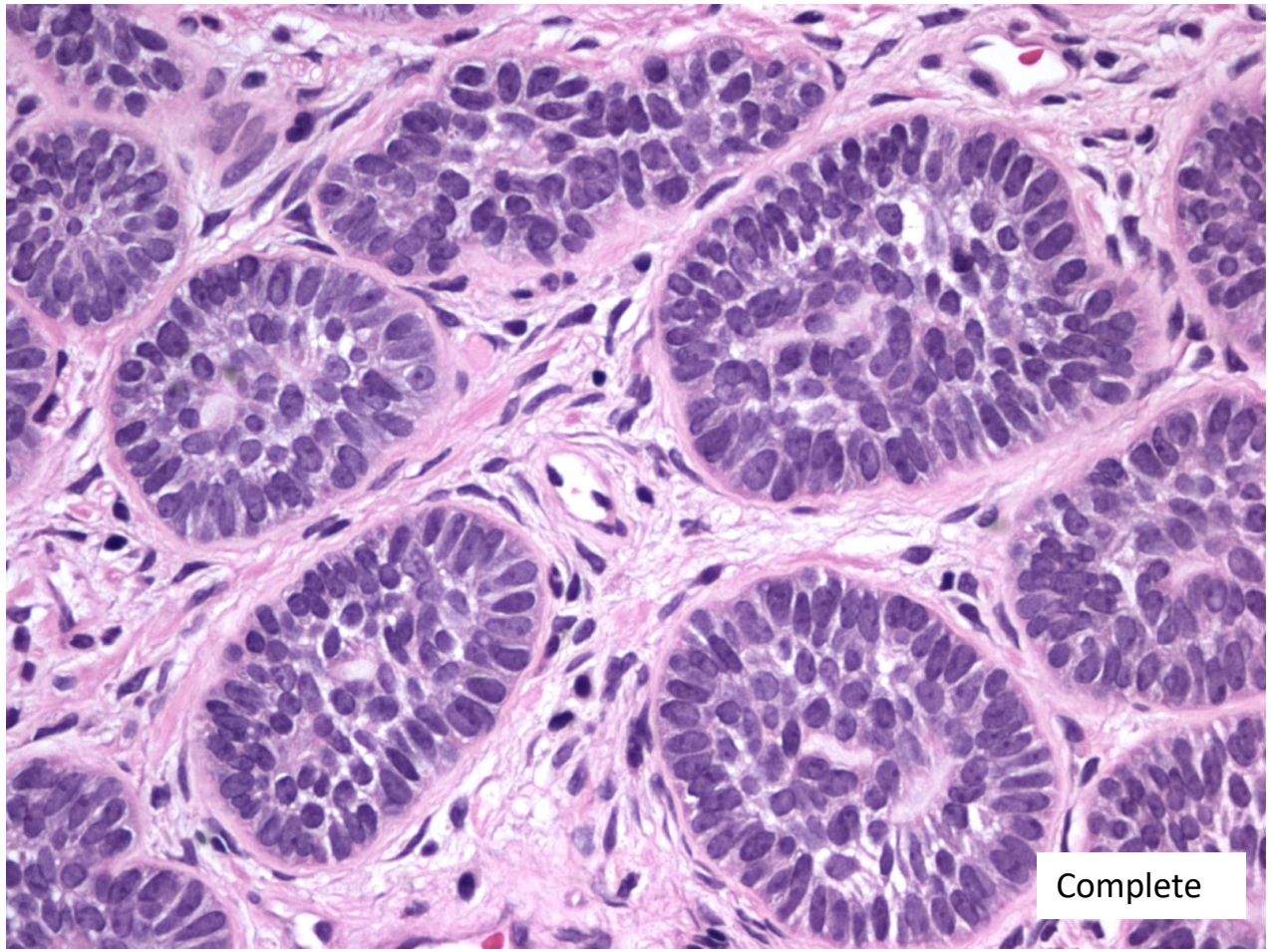
Complete:

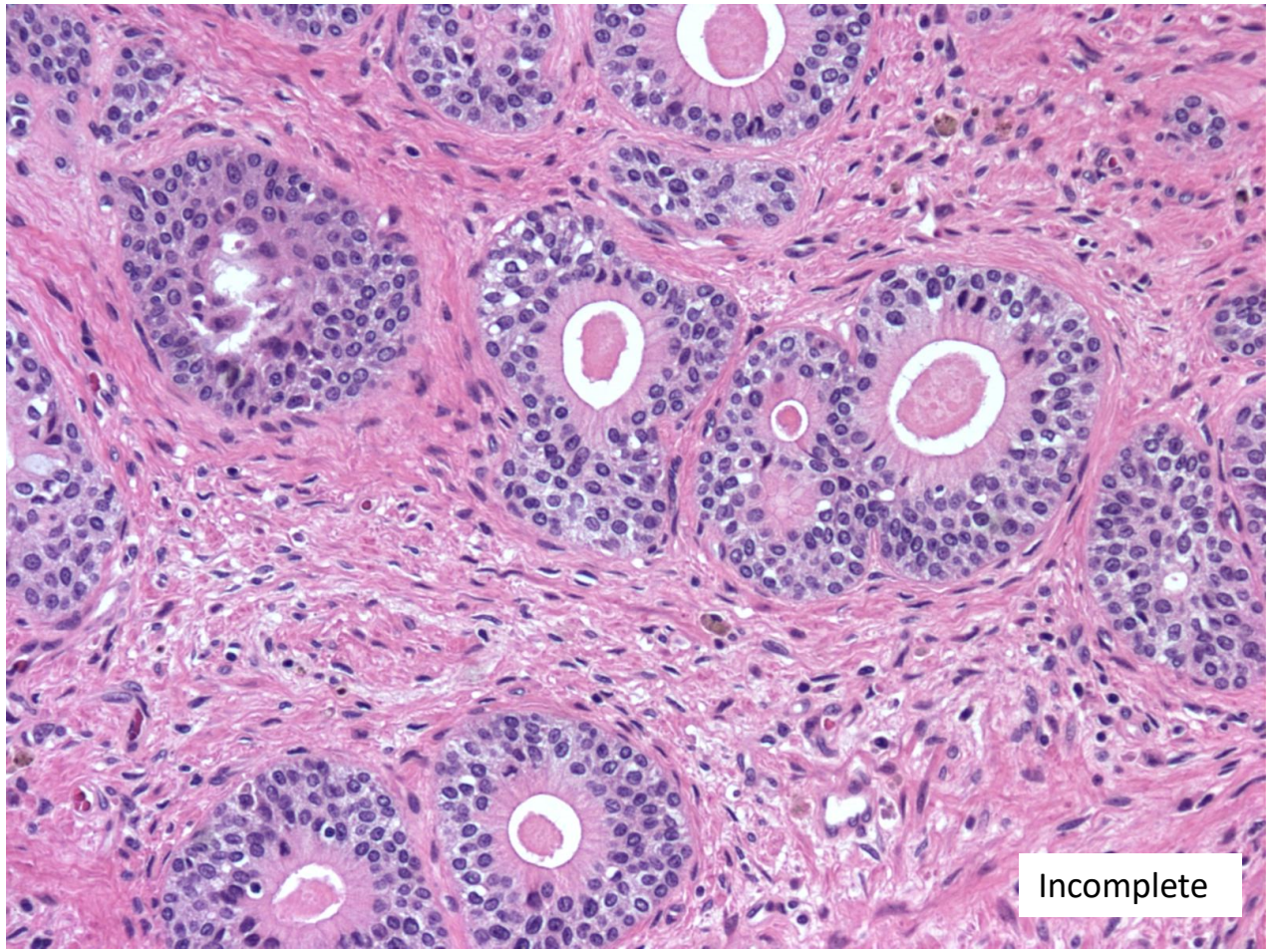
- solid nests of dark cells
- lack of luminal cell differentiation

Incomplete:

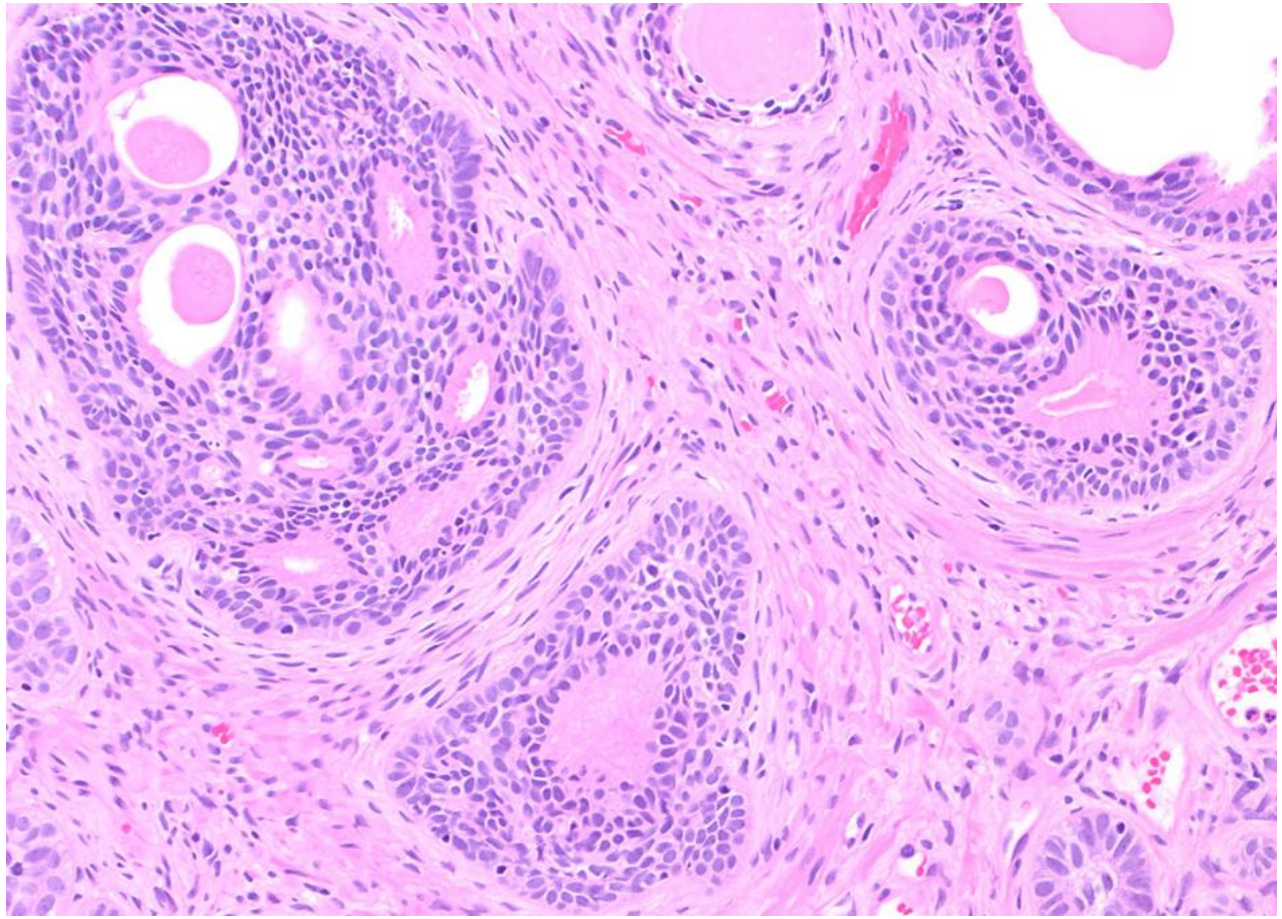
- residual small lumina lined by cells with clear cytoplasm
- multiple layers of basal cells with scant cytoplasm and round or spindled hyperchromatic nuclei

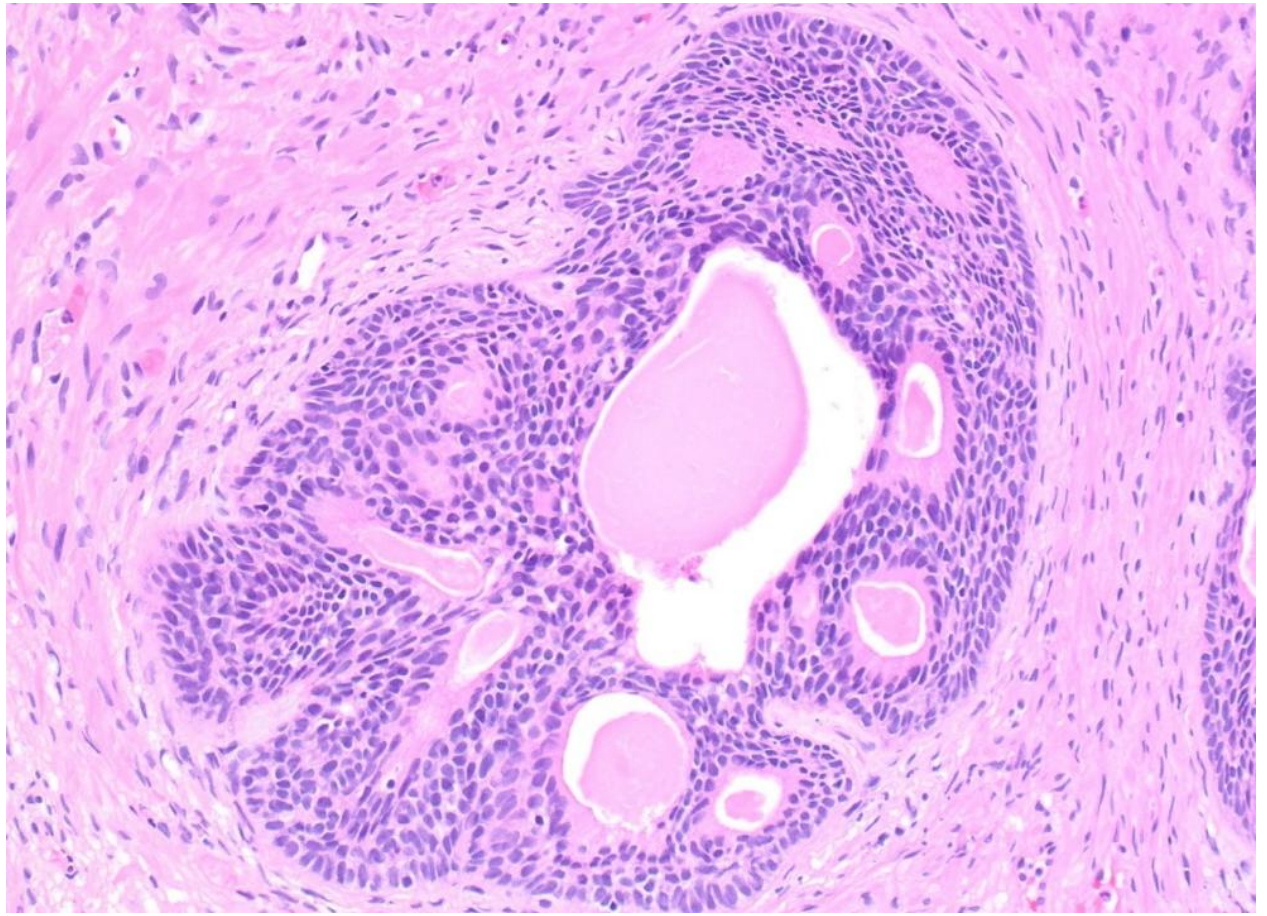
BASAL CELL HYPERPLASIA



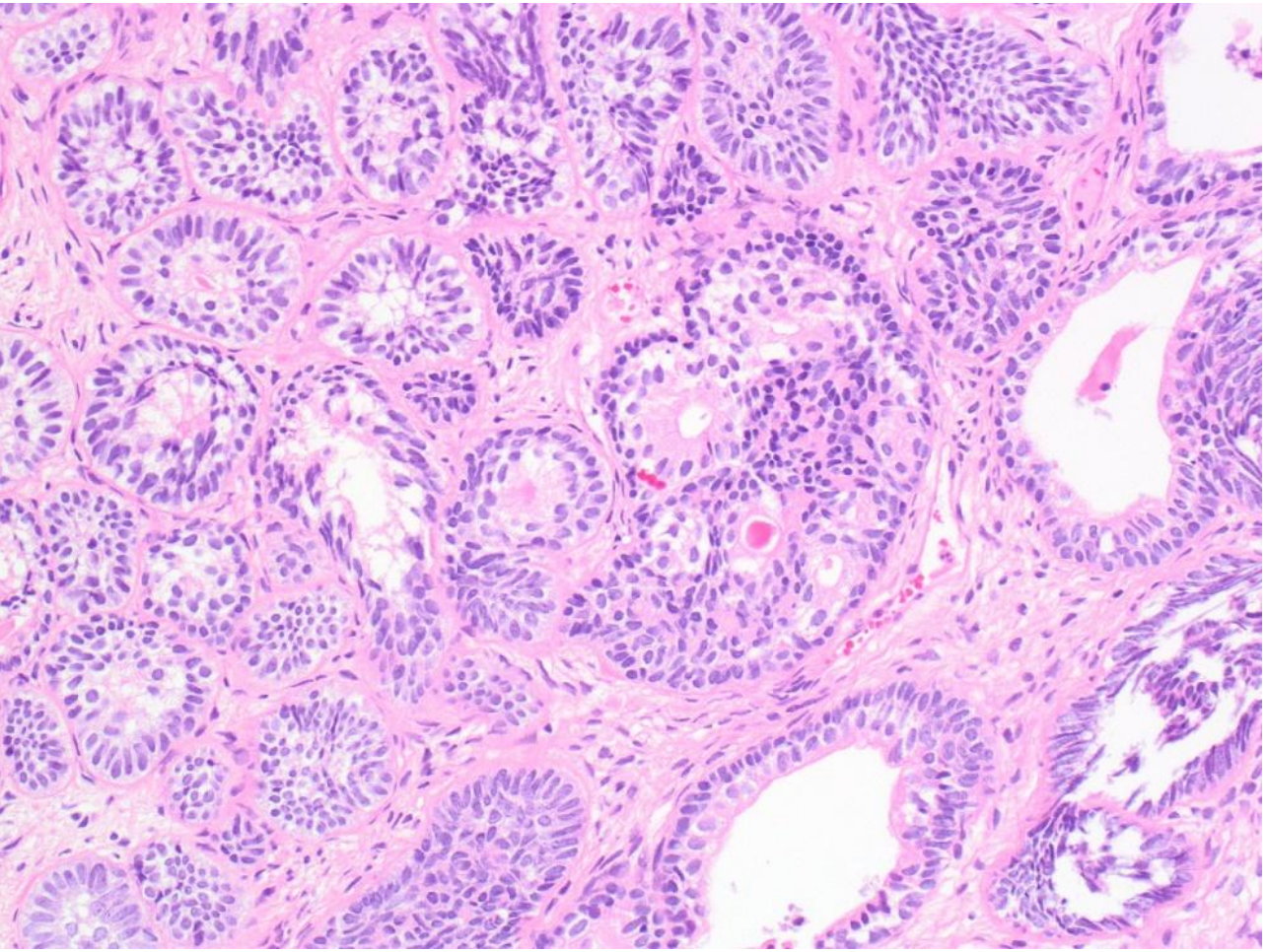


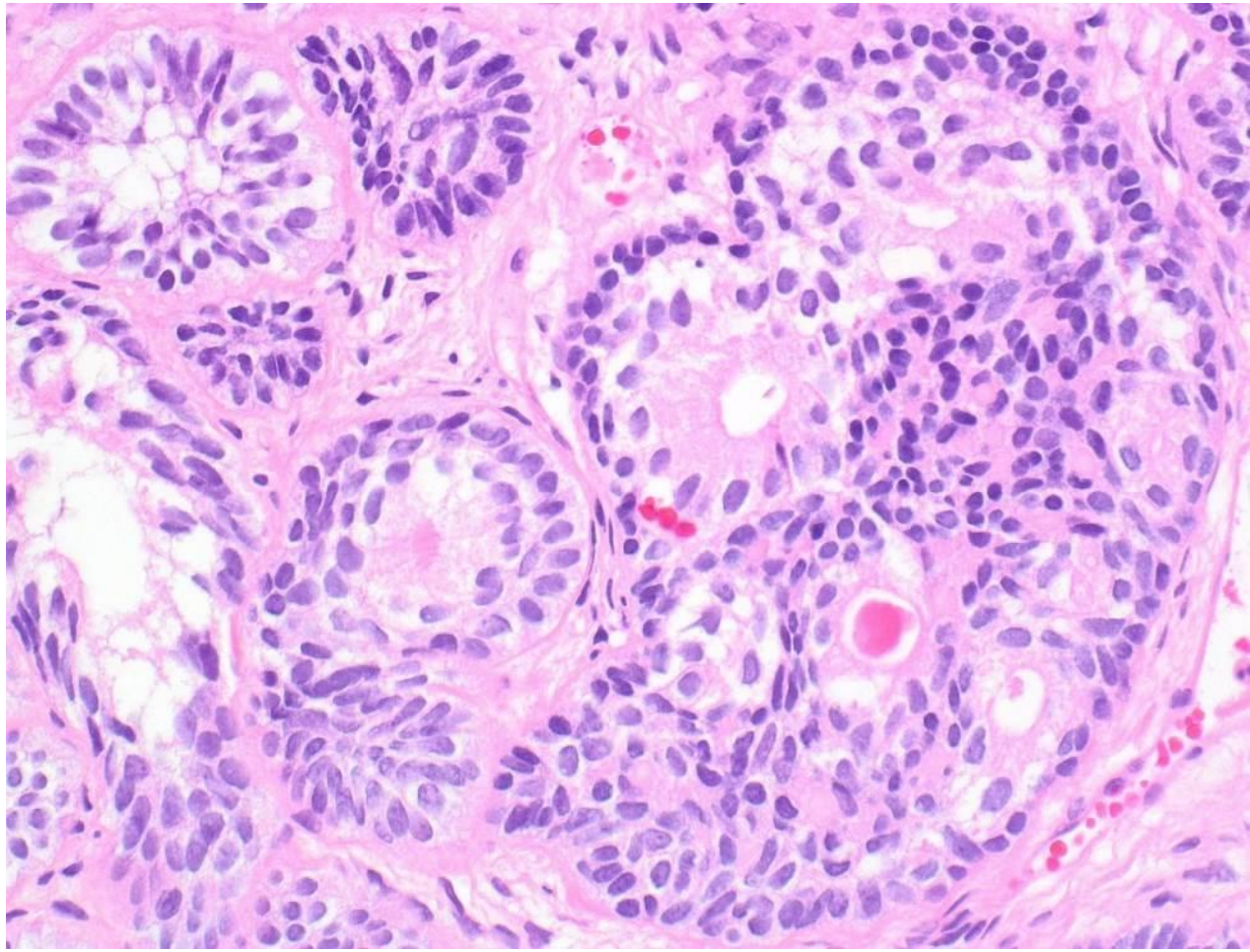
BASAL CELL HYPERPLASIA





BASAL CELL HYPERPLASIA





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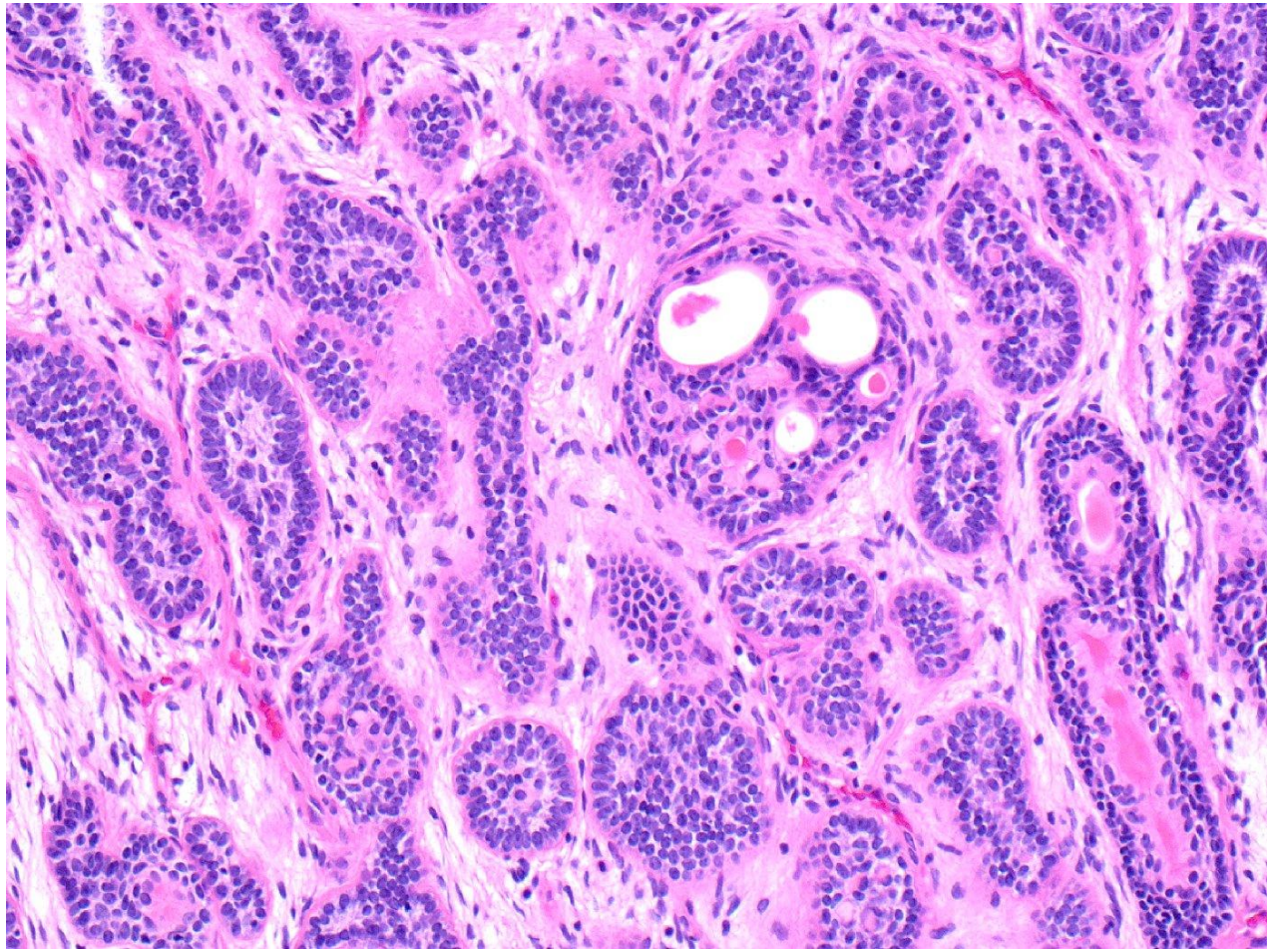
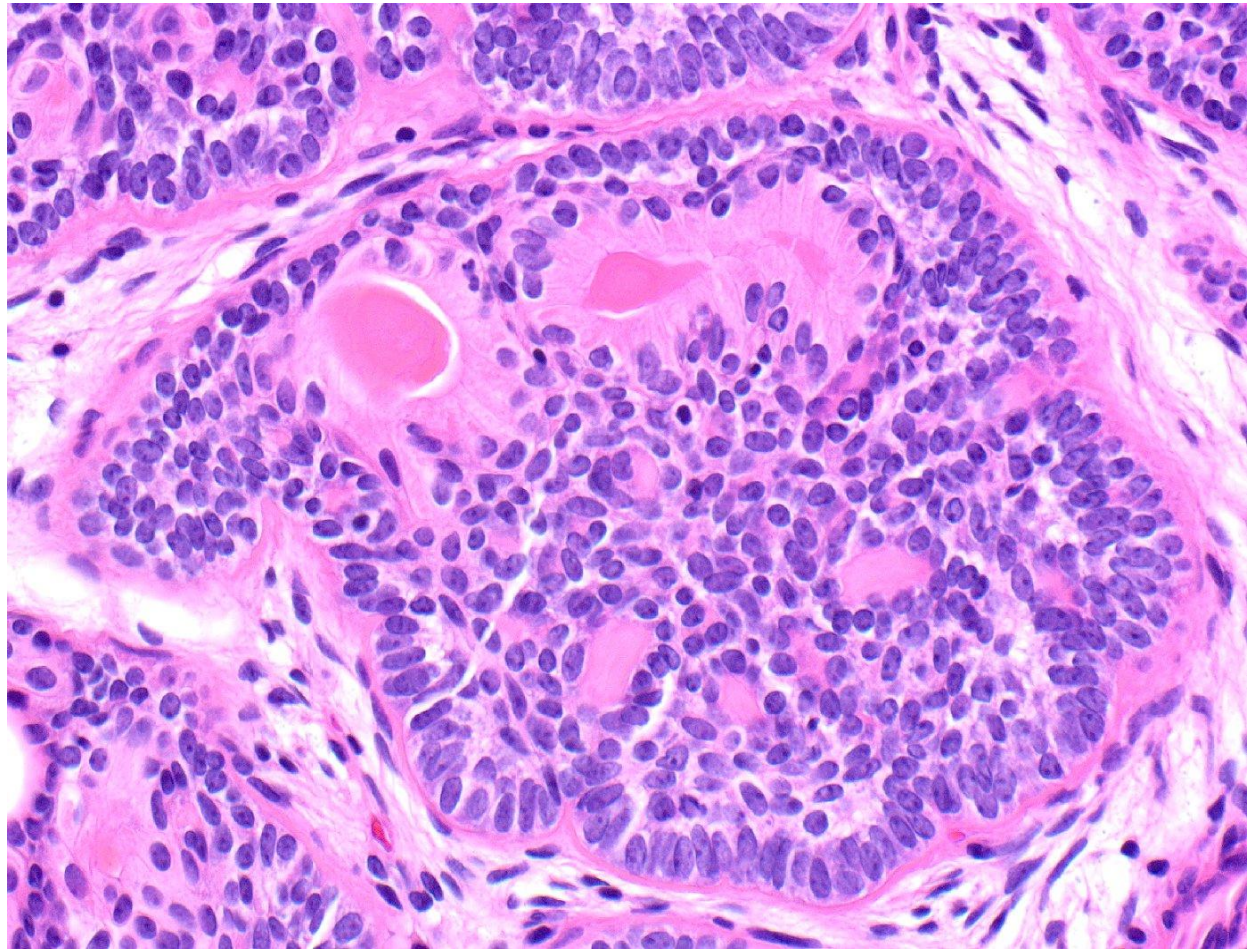
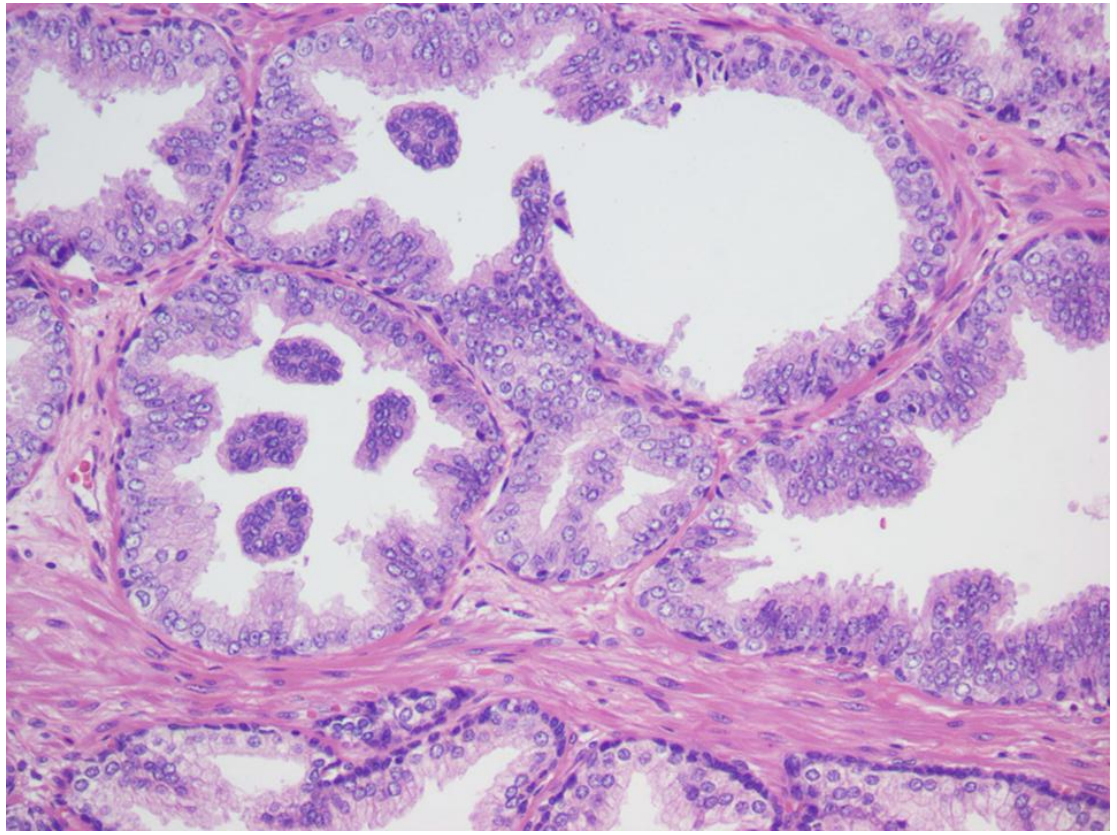




PREMALIGNANT CRIBRIFORM LESIONS

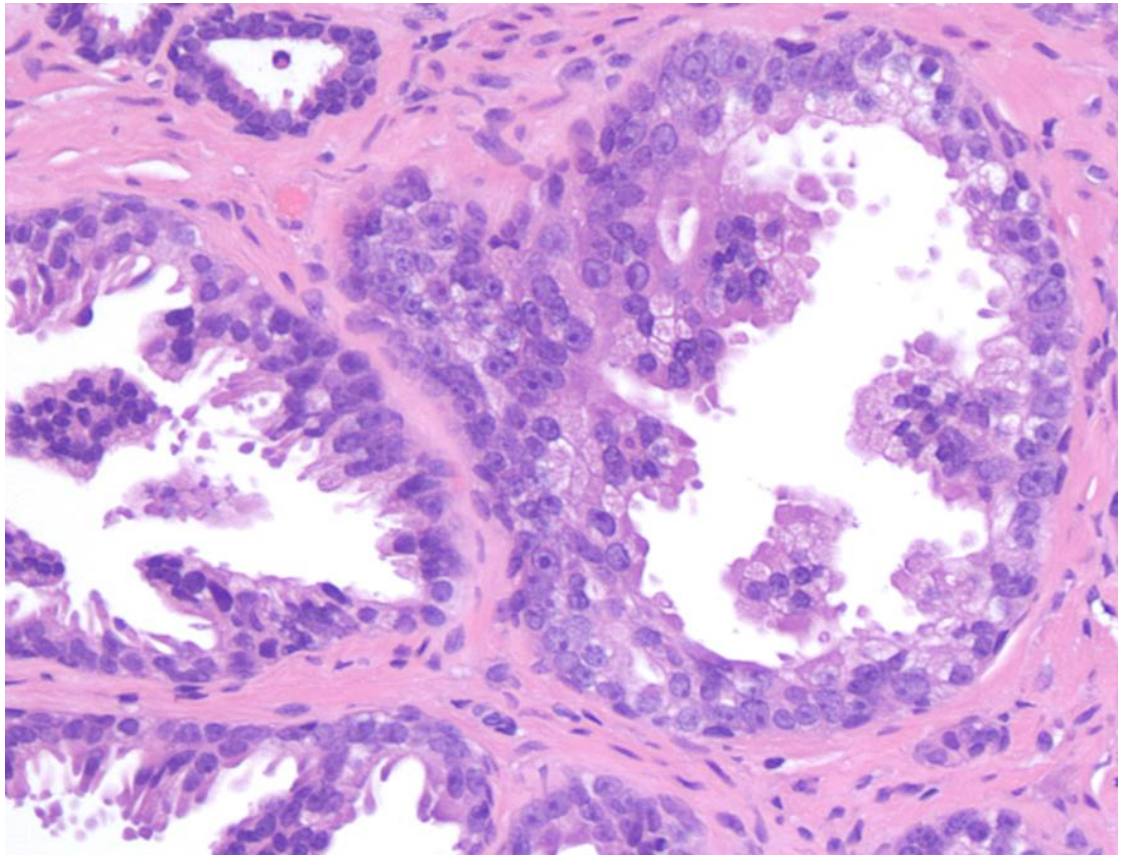
PROSTATIC INTRAEPITHELIAL NEOPLASIA

- Earliest putative precursor of prostate cancer
- Proliferation of secretory cells displaying cytologic atypia within architecturally benign pre-existing ducts/acini
- Prevalence increases with age

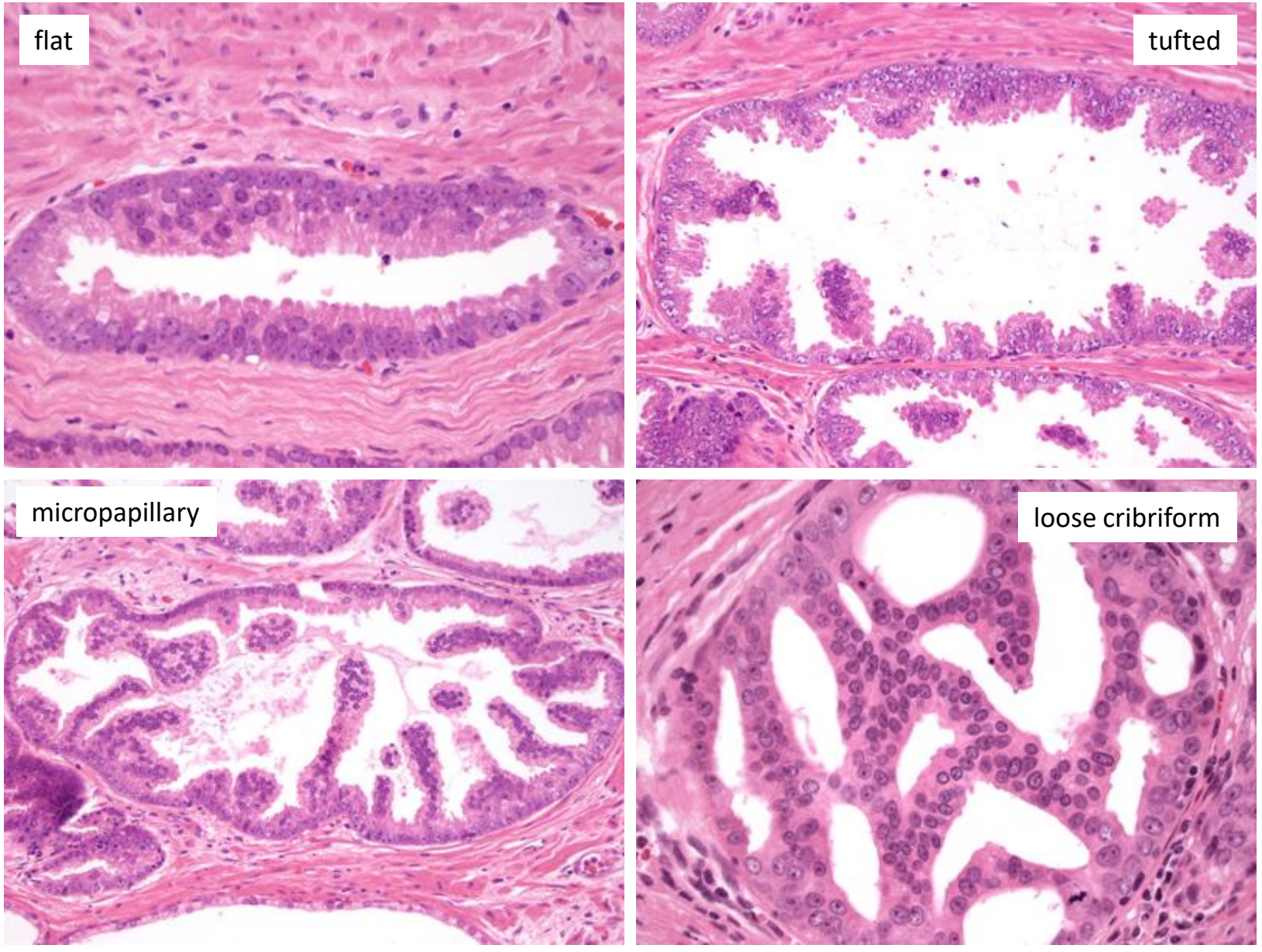


HIGH-GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA

- Stratified, enlarged nuclei
- Coarse and clumpy chromatin
- Conspicuous nucleoli visible at 20x
- Hyperchromasia
- Mitotic figures



HIGH-GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA

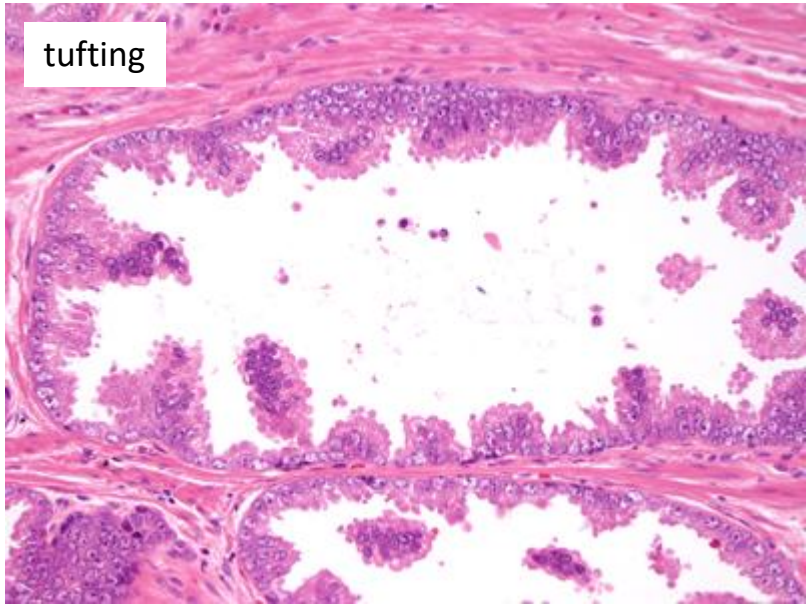


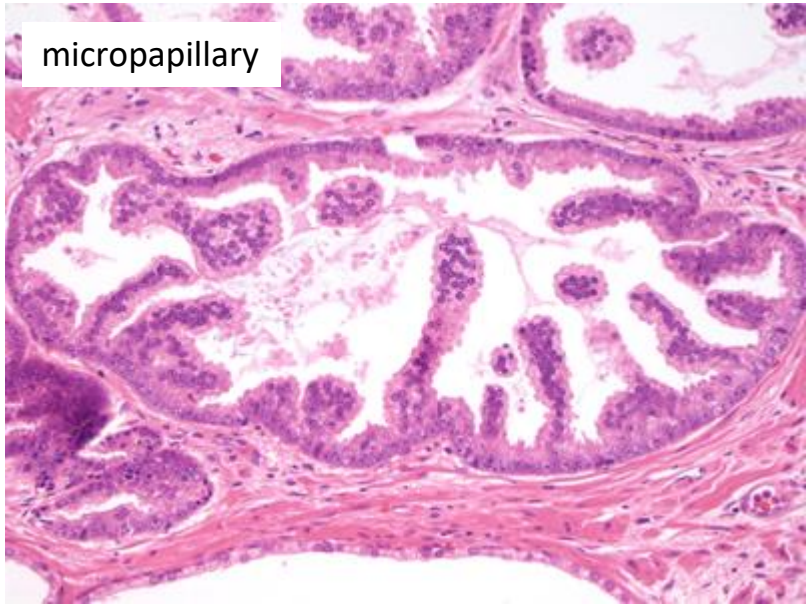
Bostwick et al. Hum Pathol 1993

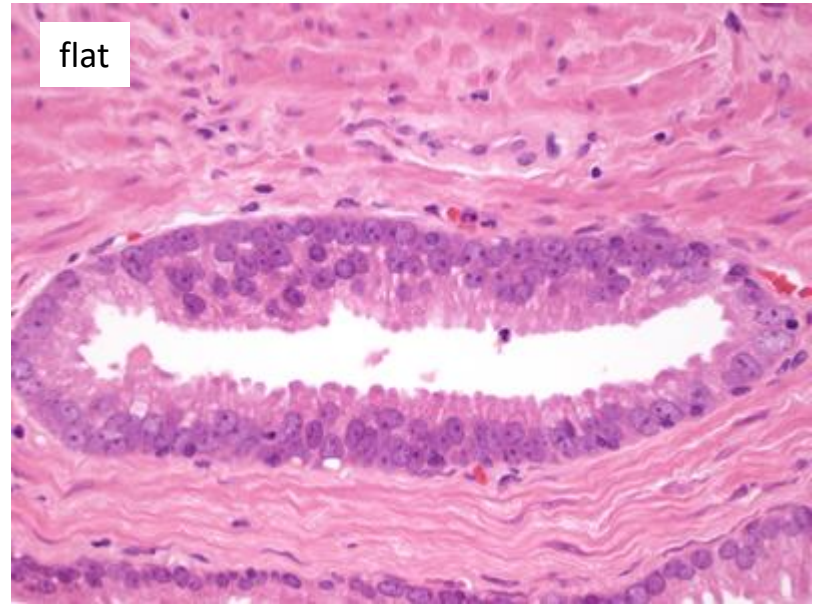
HIGH-GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA

WHO 5th edition (2022):

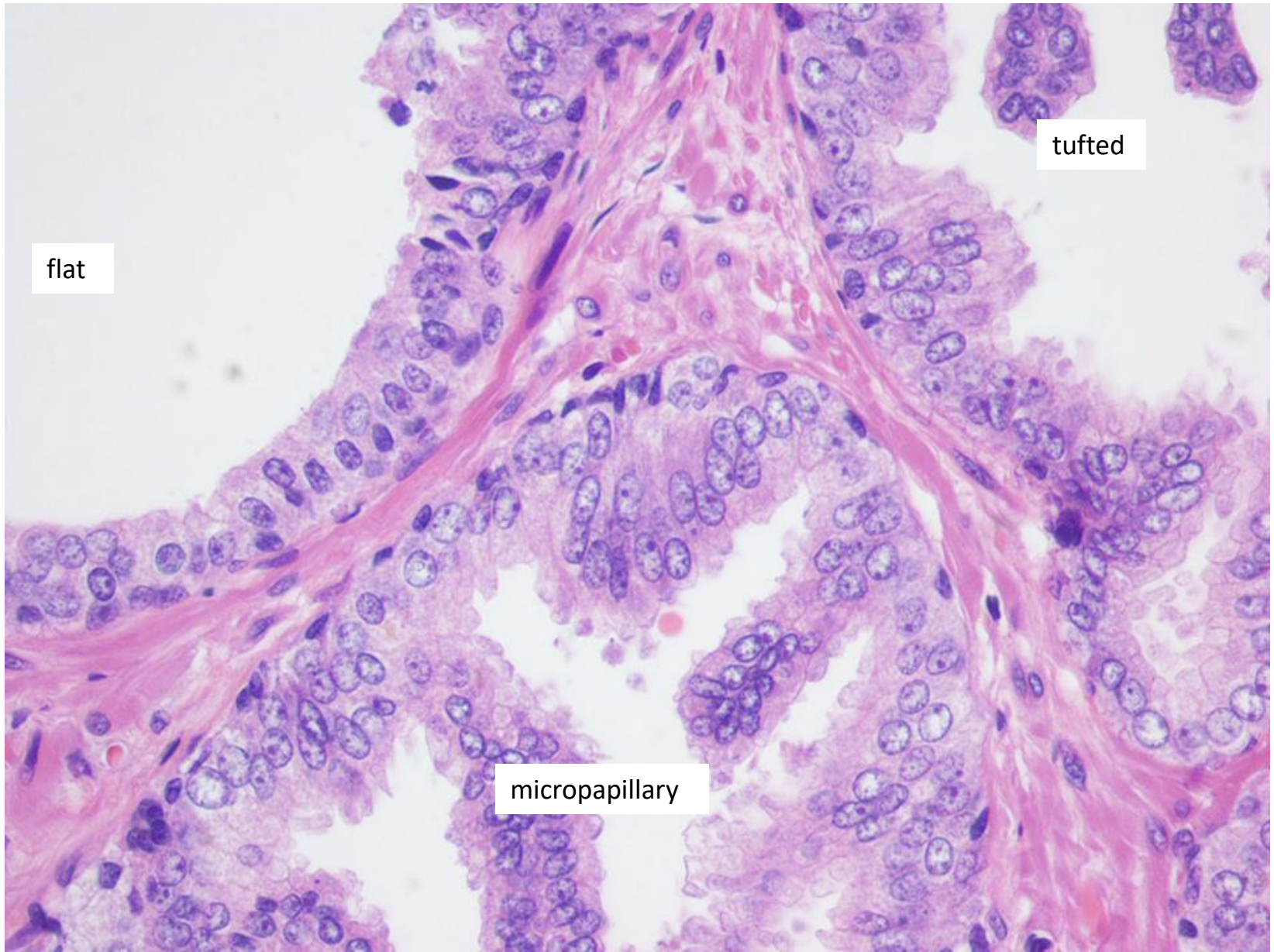
- Low grade PIN (LGPIN) and cribriform HGPIN are no longer regarded as distinct entities
- 3 main histologic patterns of HGPIN are recognized:





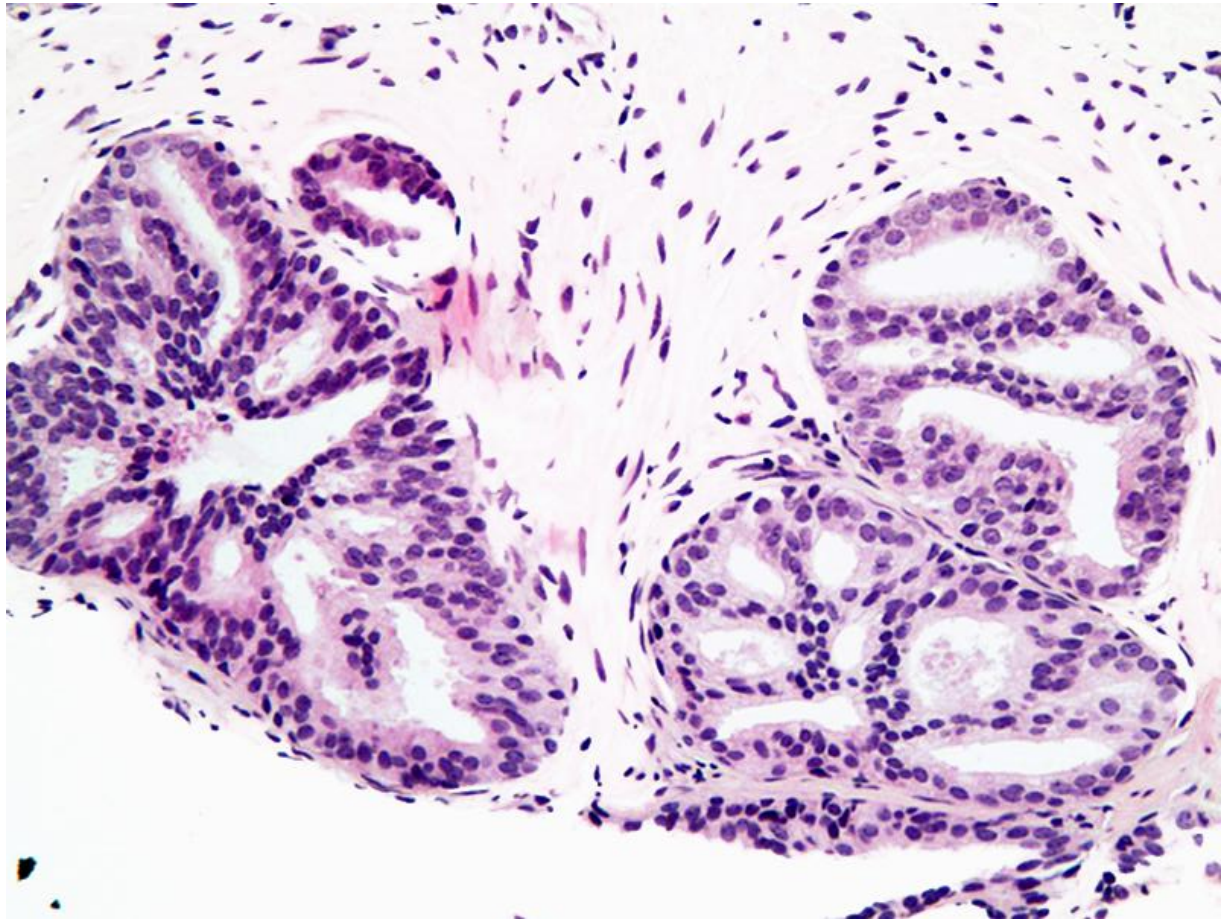


HIGH-GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA



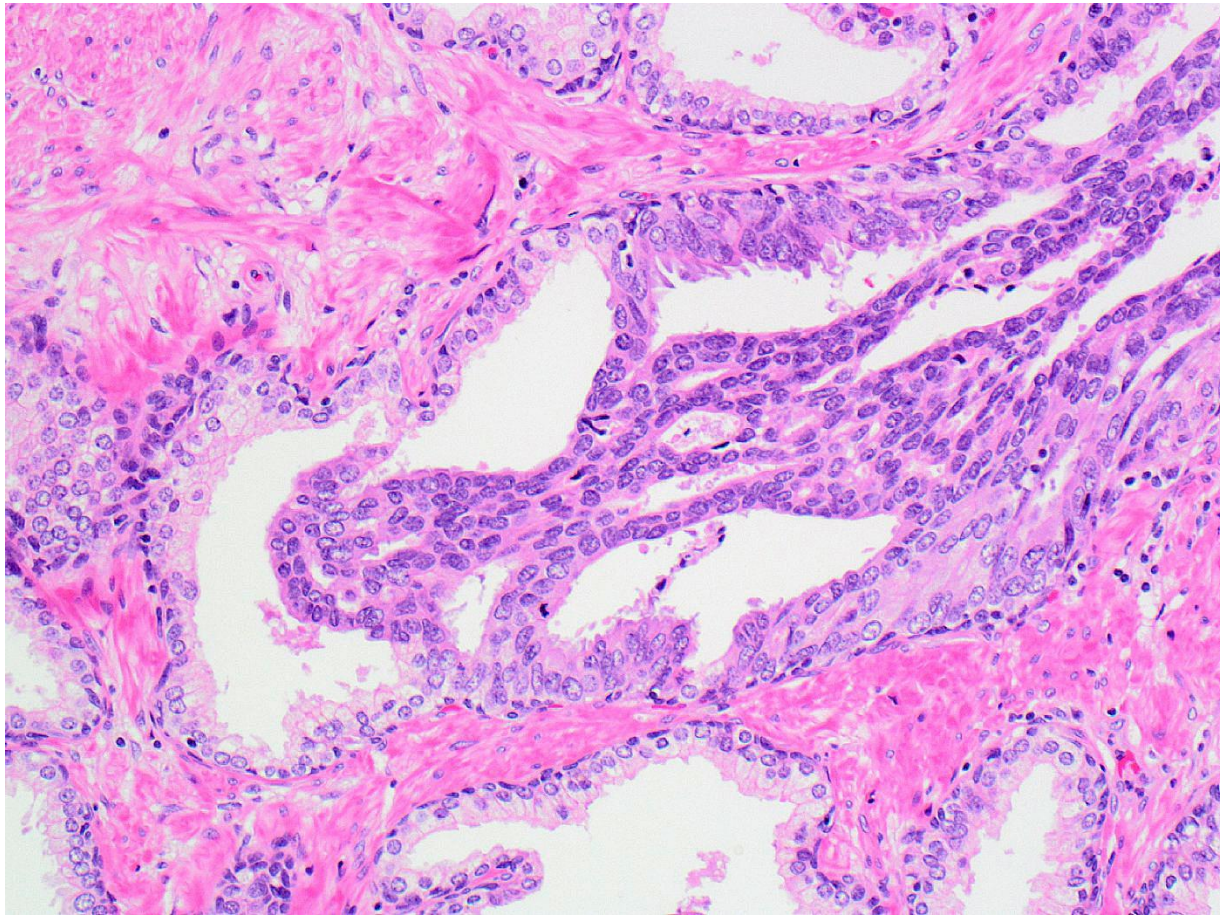
ATYPICAL INTRADUCTAL PROLIFERATION (AIP)

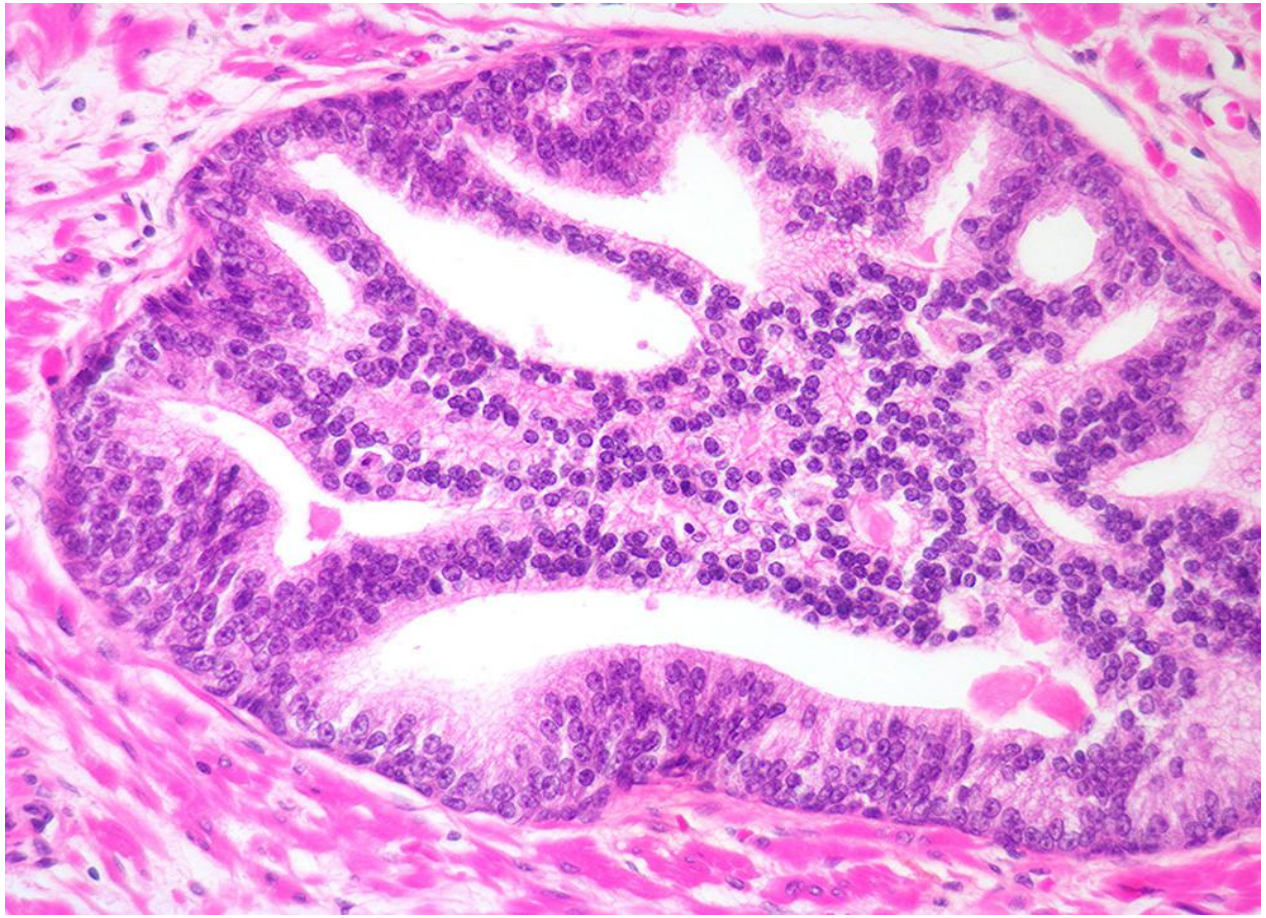
- Intraductal proliferation of secretory cells architecturally and/or cytologically more complex than HGPIN, but short of intraductal carcinoma (IDC-P)
- Atypical cribriform proliferation; atypical intraductal proliferation, suspicious for IDC-P
- Cribriform HGPIN is now referred to as AIP



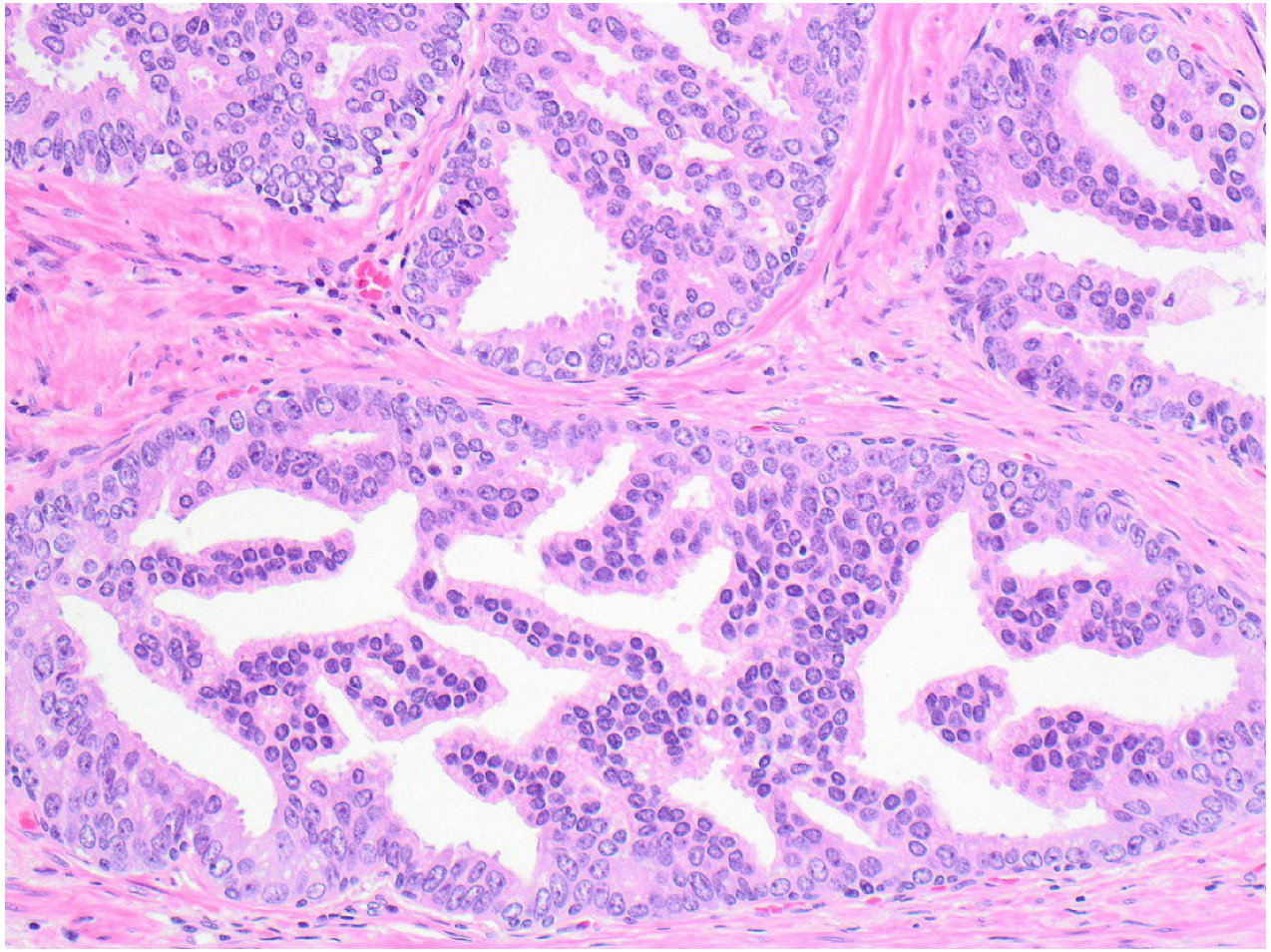
Shah et al. AJSP 2010; Shah & Zhou Adv Anat Pathol 2012; Shah et al. Histopathology 2019; Epstein et al. Arch Pathol Lab Med 2021

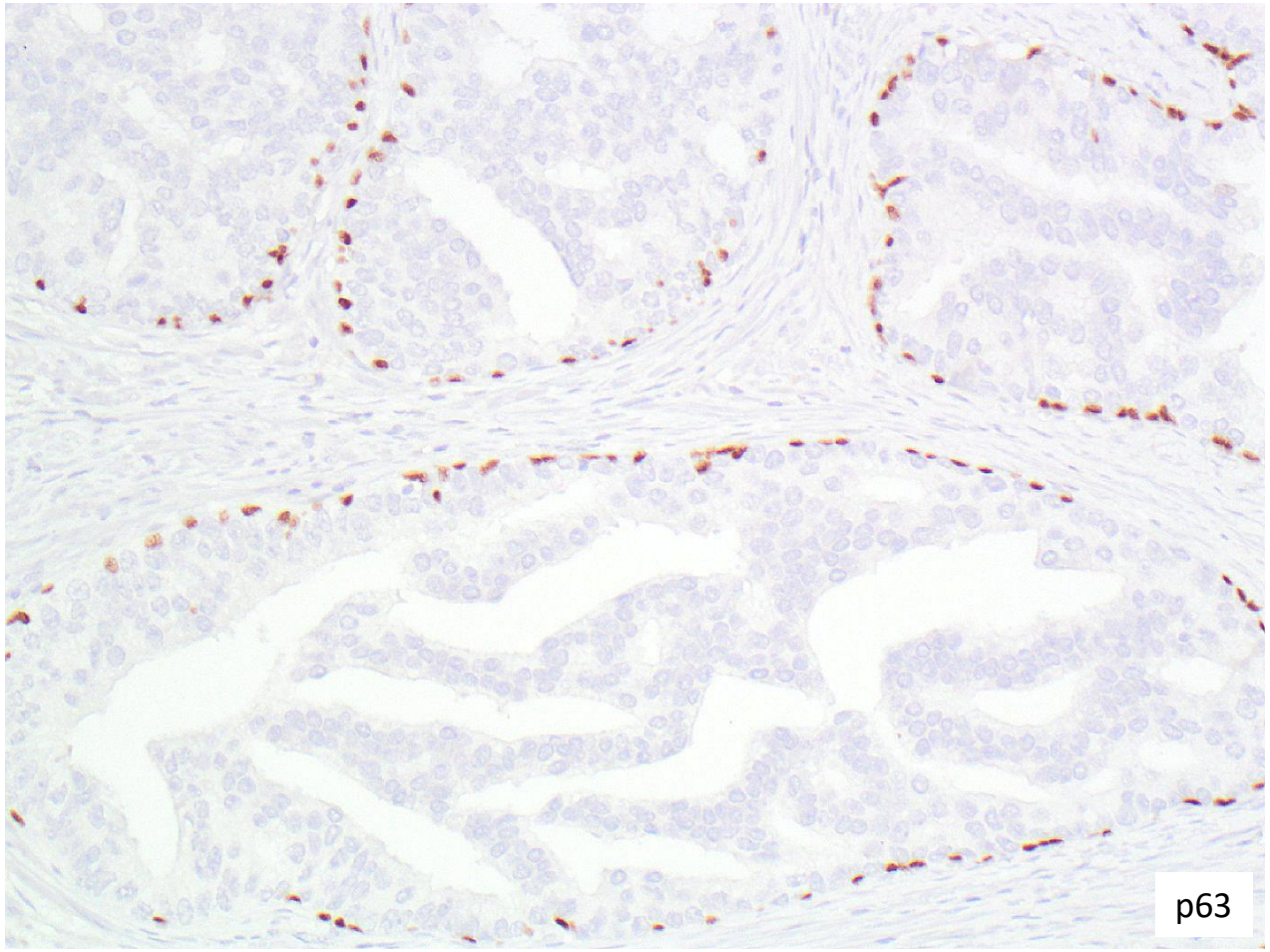
ATYPICAL INTRADUCTAL PROLIFERATION (AIP)





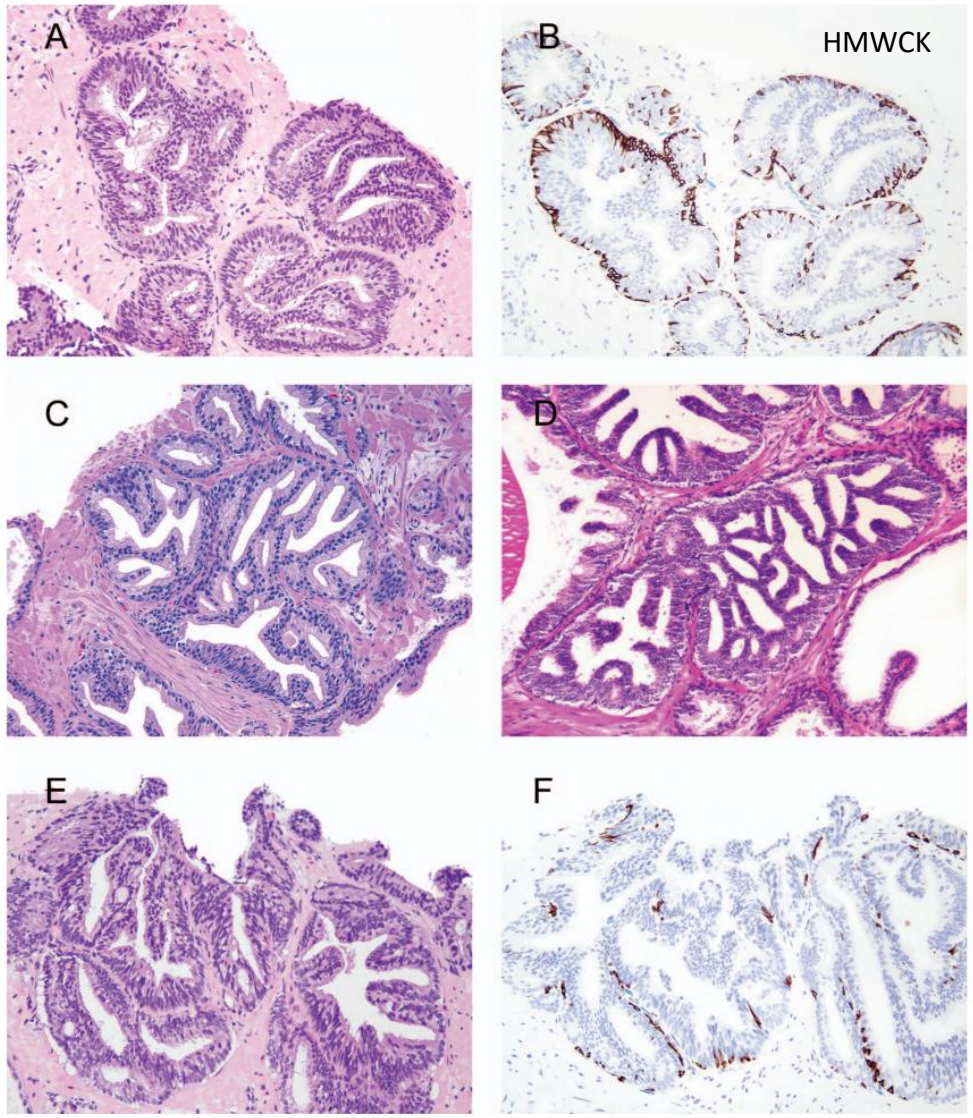
ATYPICAL INTRADUCTAL PROLIFERATION (AIP)





Cribriform HGPIN is now referred to as Atypical Intraductal Proliferation

ATYPICAL INTRADUCTAL PROLIFERATION (AIP)



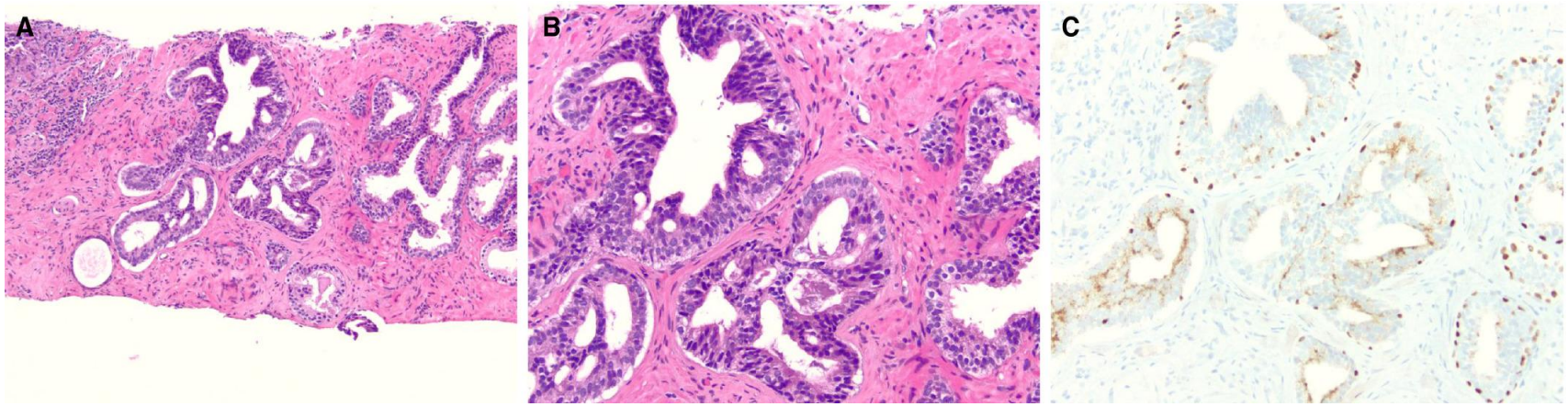
Loose cytologically atypical cribriform glands

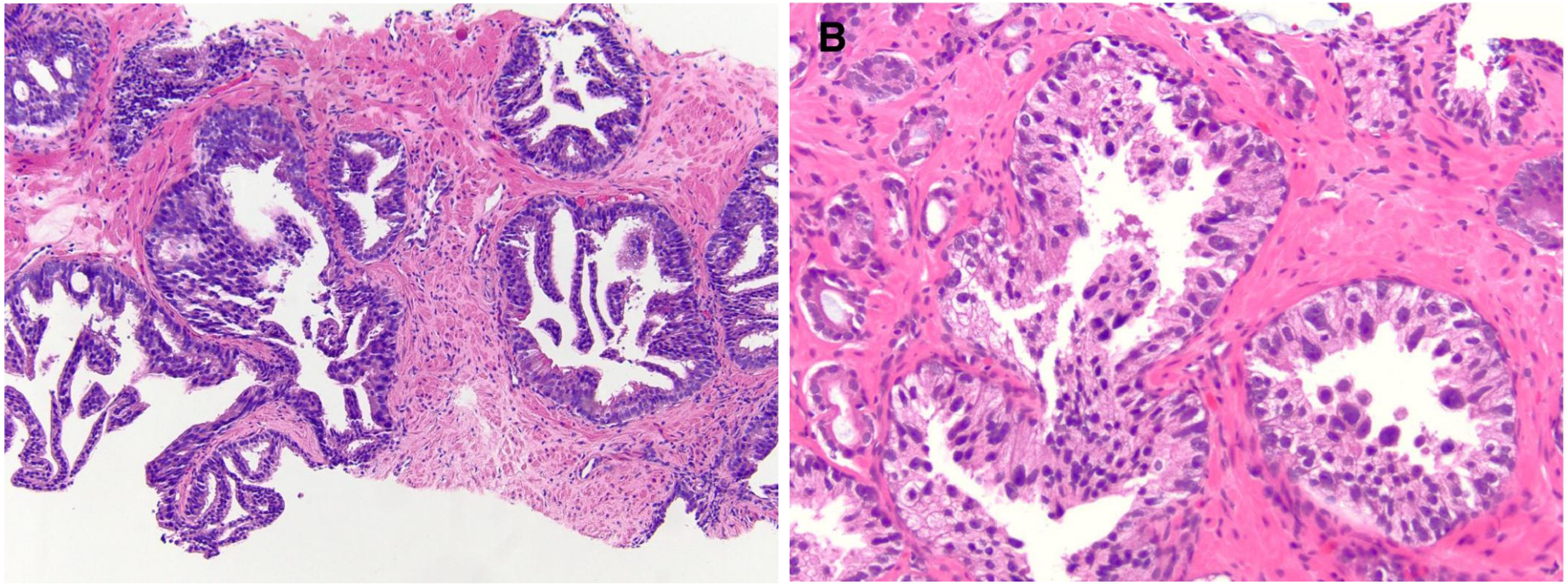
Loose cytologically bland cribriform glands

Loose cytologically atypical cribriform glands

GUPS Grading of Prostate Cancer. Epstein et al. Arch Pathol Lab Med 2020

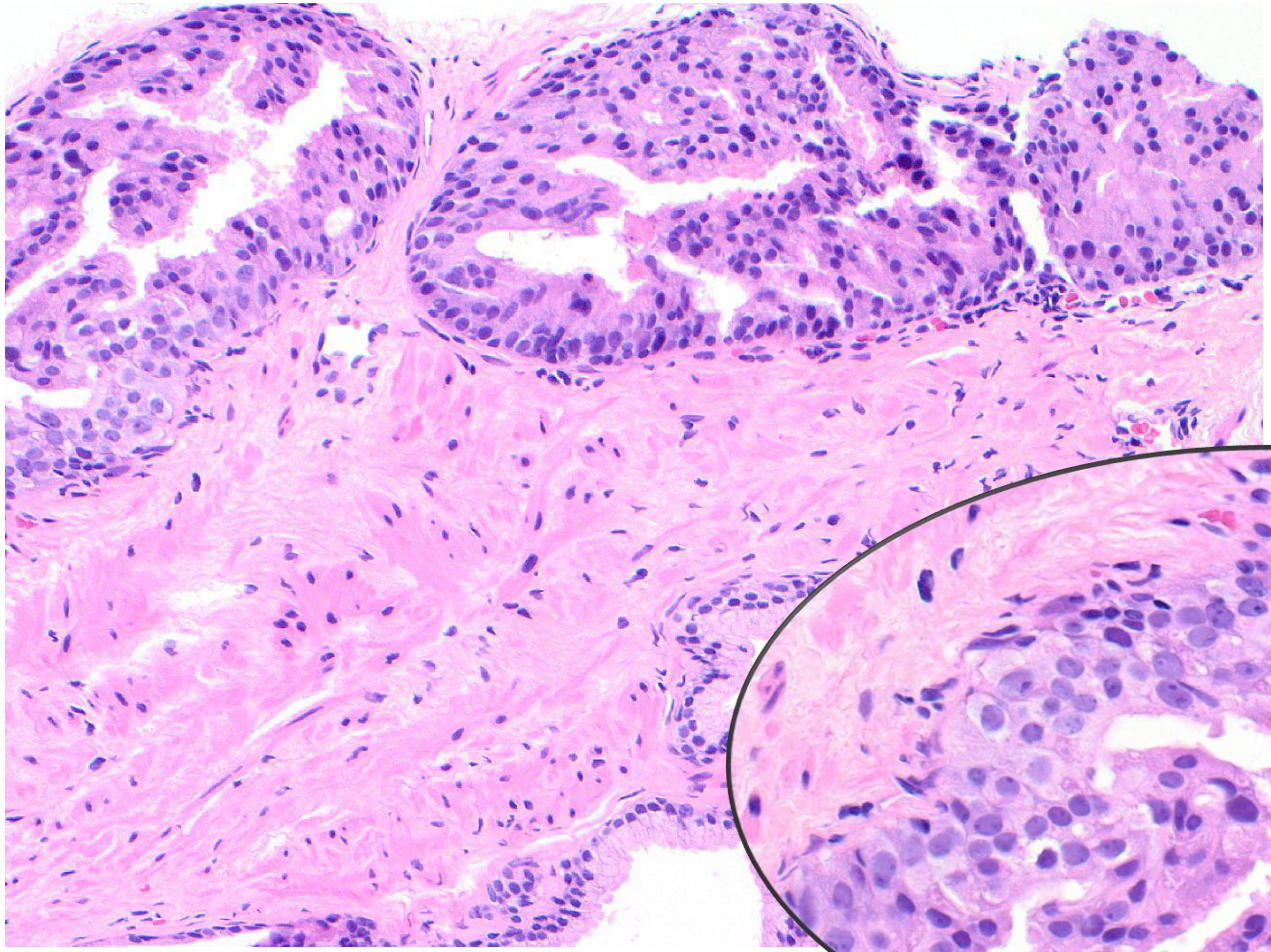
ATYPICAL INTRADUCTAL PROLIFERATION (AIP)

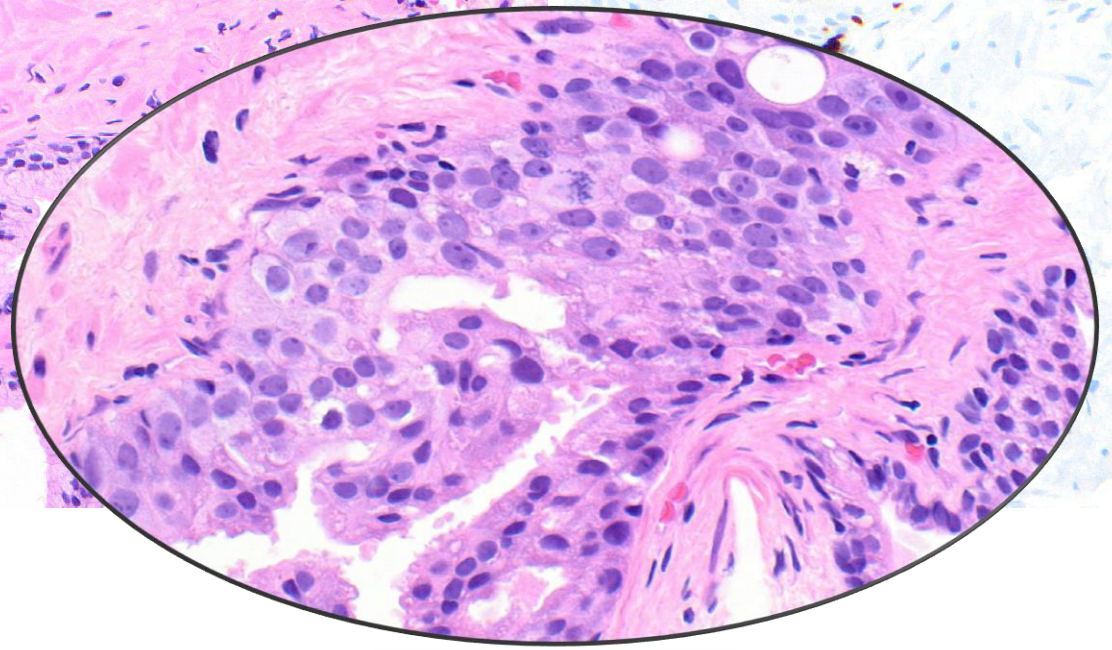


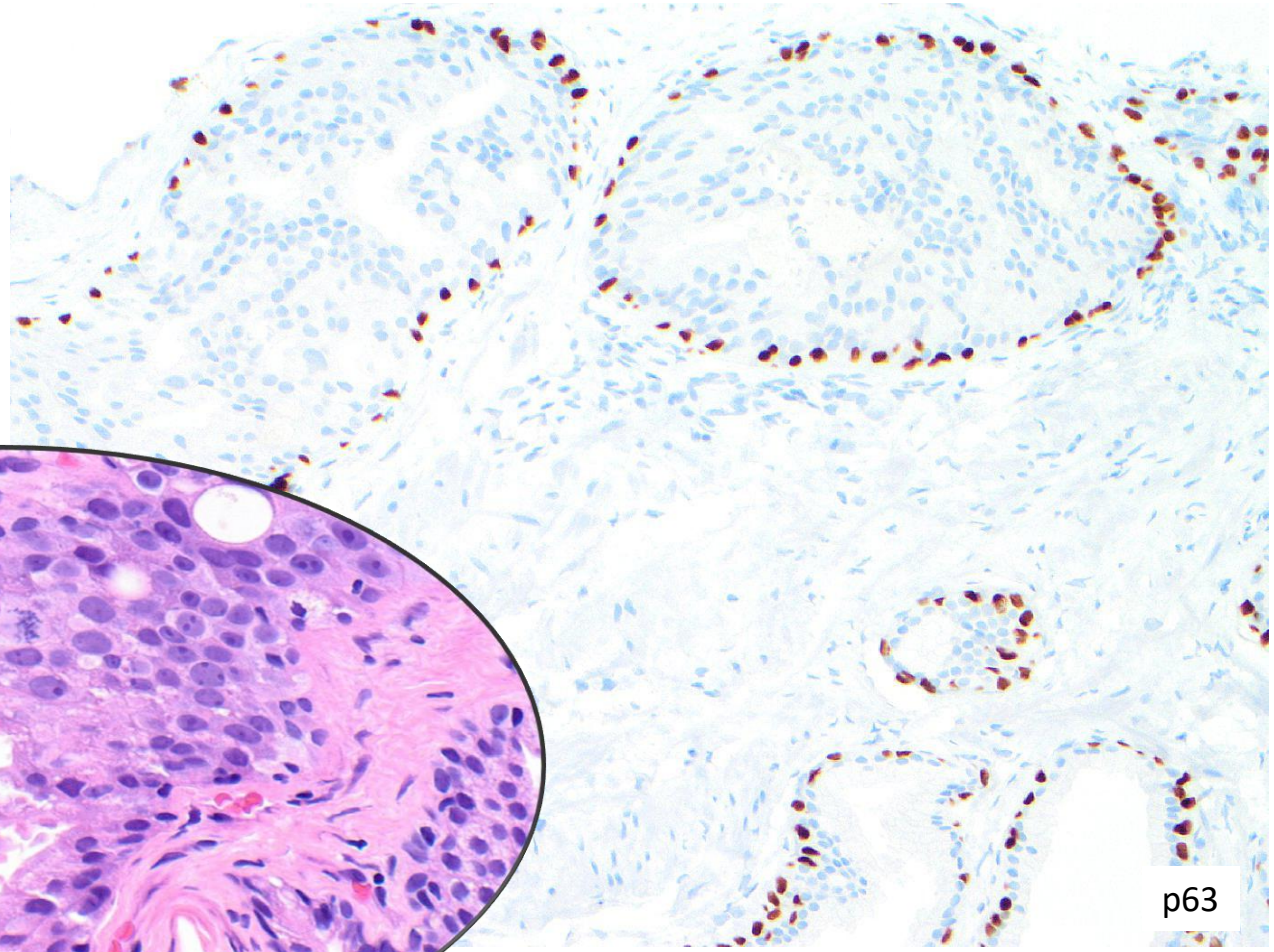


Shah et al.
Histopathology
2019

ATYPICAL INTRADUCTAL PROLIFERATION (AIP)



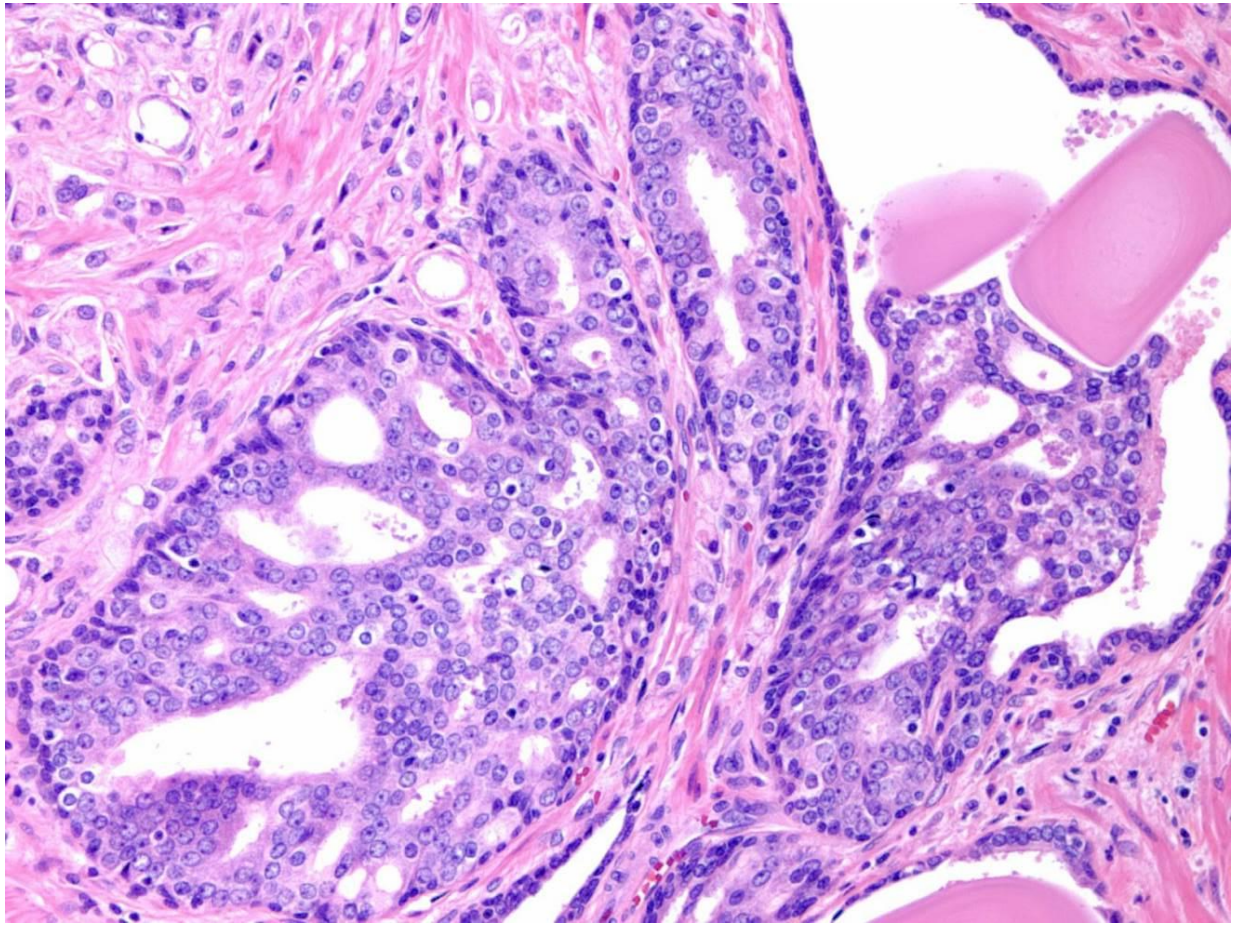




MALIGNANT CRIBRIFORM LESIONS

INTRADUCTAL CARCINOMA OF THE PROSTATE (IDC-P)

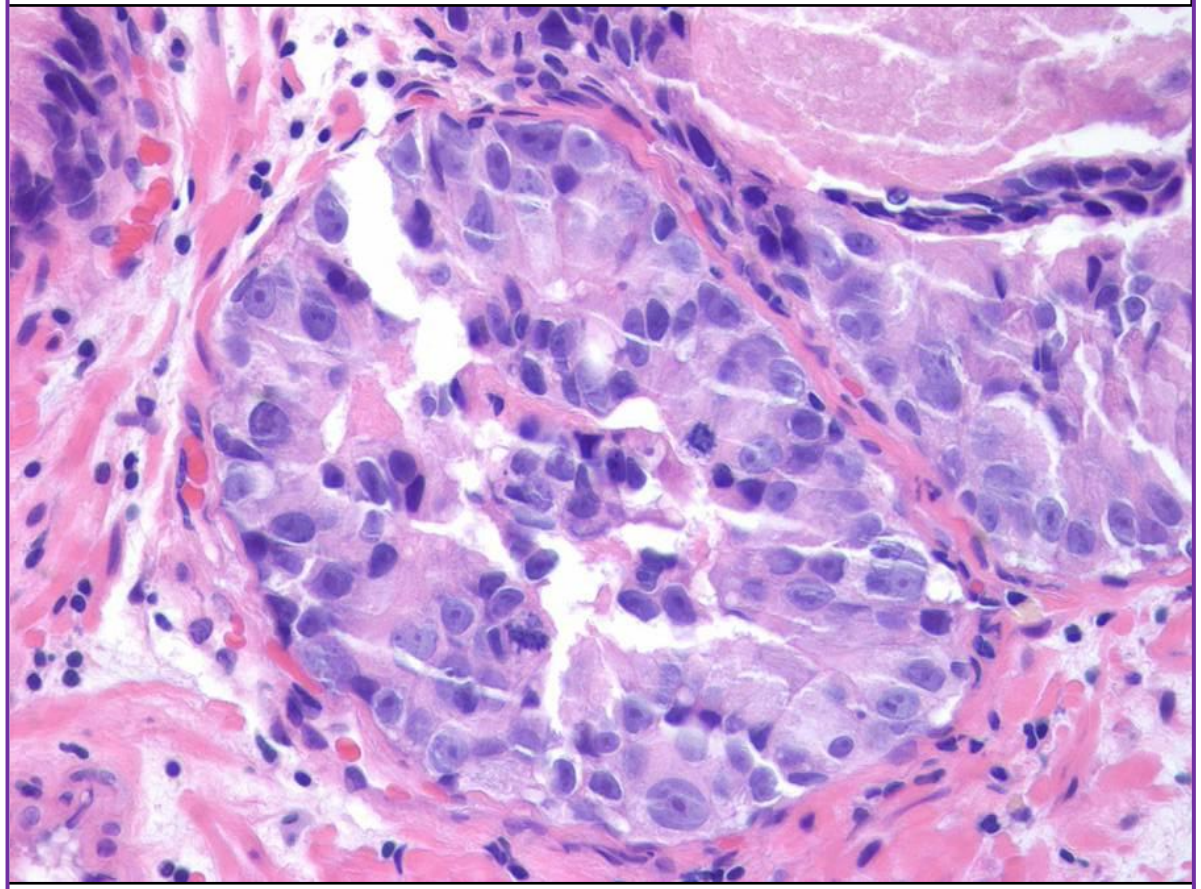
- Distinct entity since WHO 4th edition (2016)
- Malignant secretory cells growing within and expanding prostatic ducts/acini
- Associated with adverse prognostic features at RP
- Independent predictor of clinical outcome



INTRADUCTAL CARCINOMA OF THE PROSTATE (IDC-P)

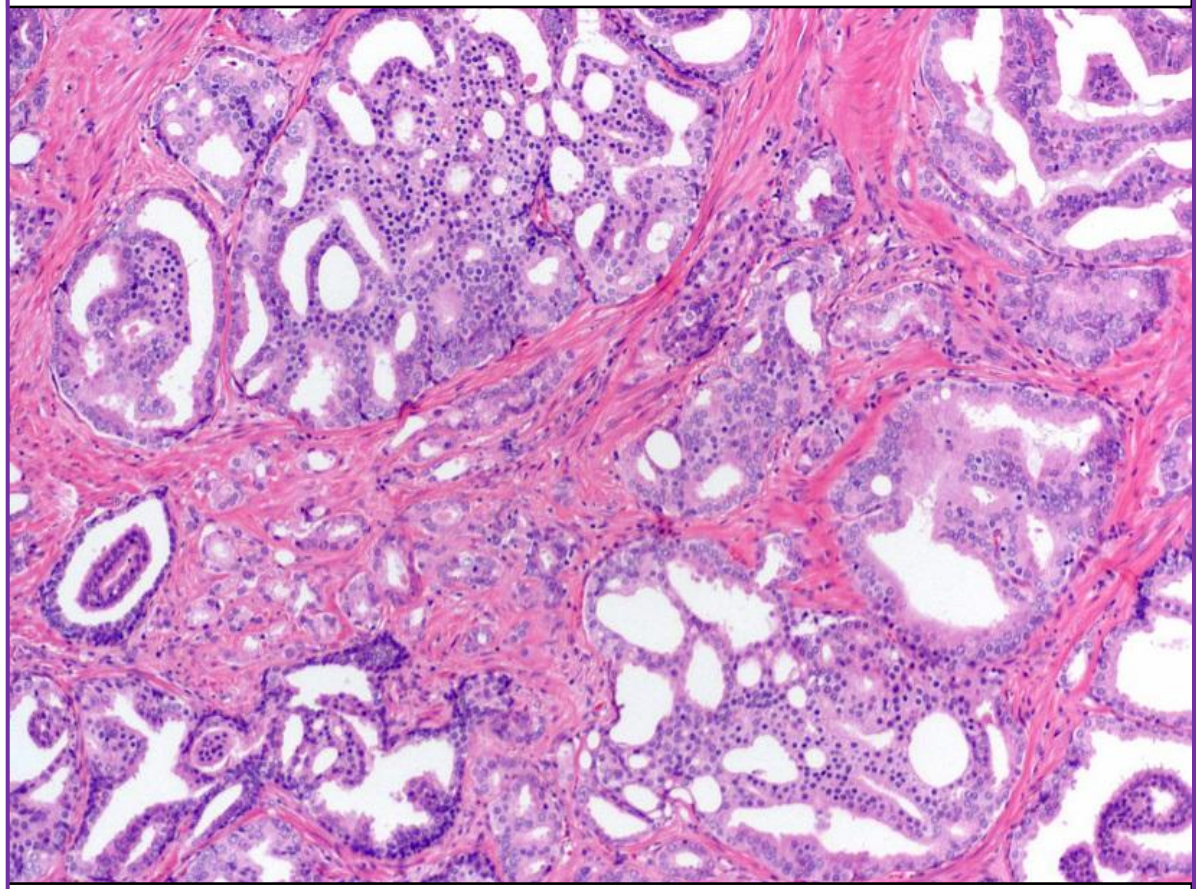
Two distinct entities:

Isolated IDC-P (in situ) – small minority



Progression from HGPIN precursor

Invasive spreads into benign ducts/acini



Late event in tumor progression

IDC-P: Diagnostic Criteria

Spanning of large acini/ducts by malignant epithelial cells with **preservation of basal cells**

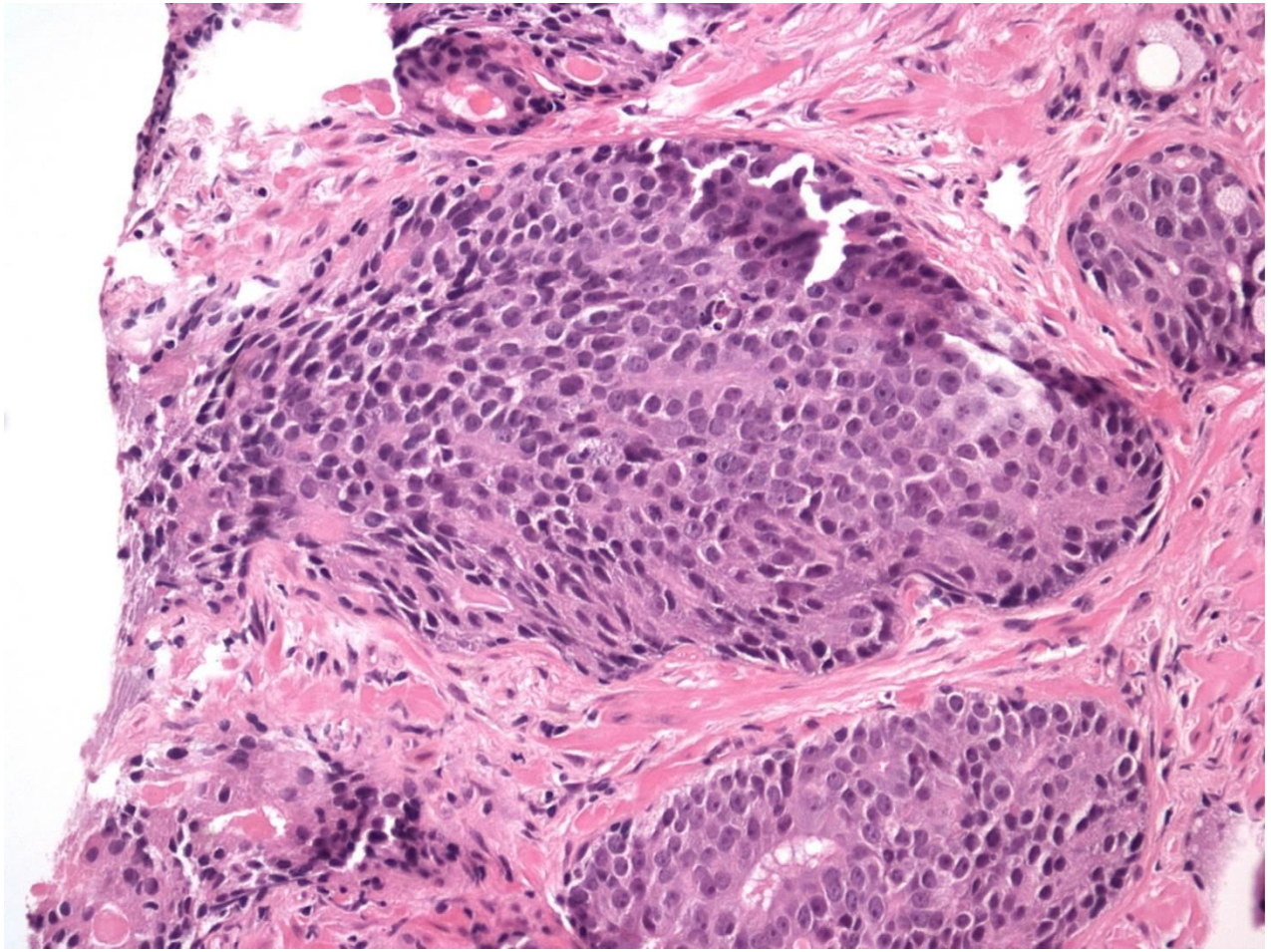
- **Solid** or **dense cribriform** (>50% epithelium)

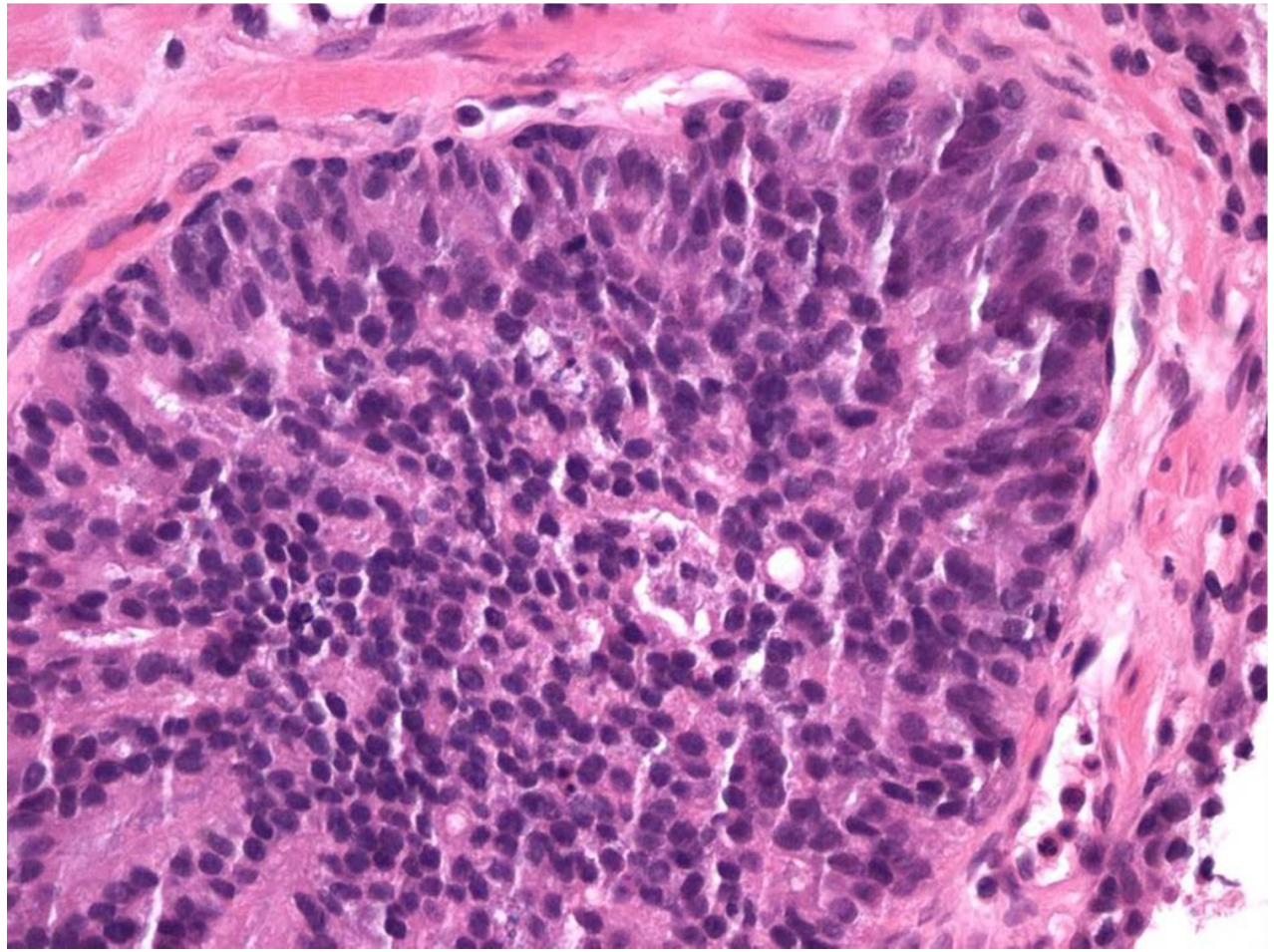
  or

- **Loose cribriform** (<50%) or **micropapillary** with:
  - Comedonecrosis (non-focal)
  - Marked nuclear atypia (nuclear size ≥6x normal)

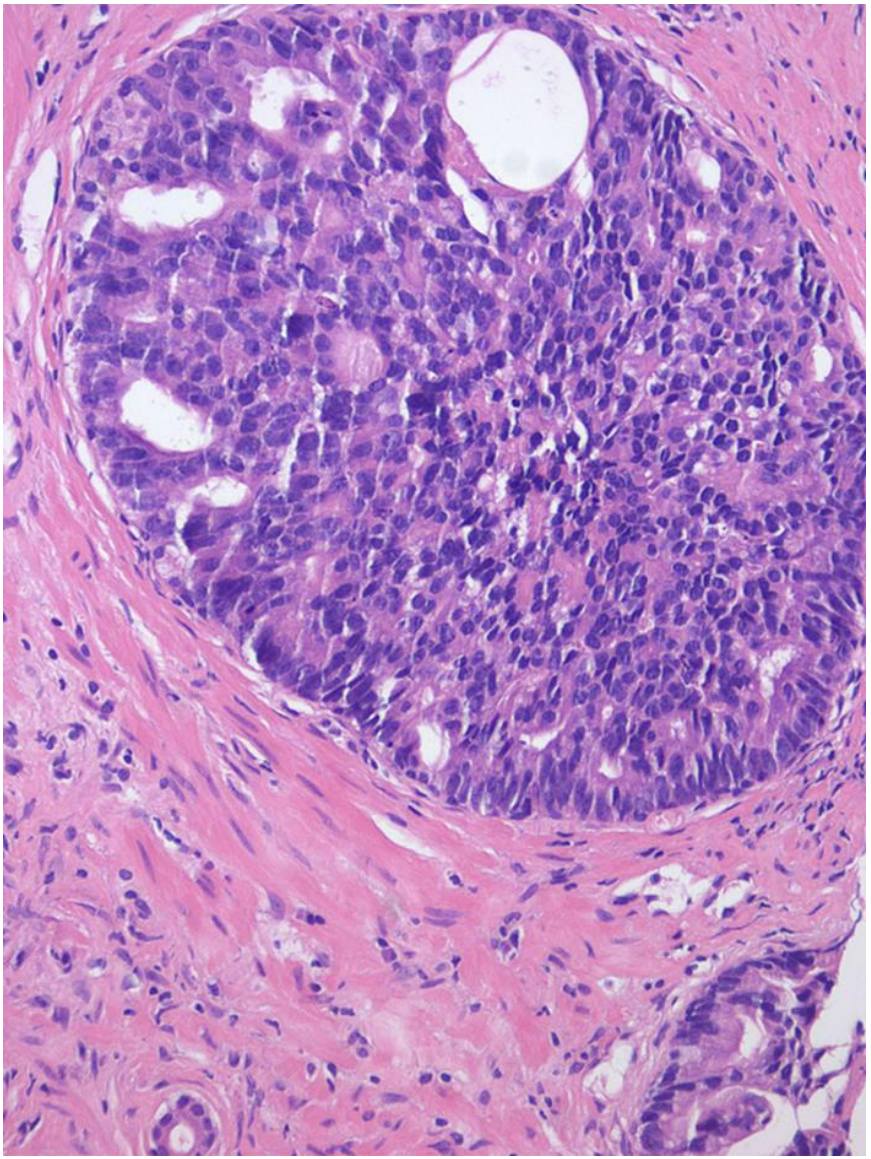
Guo & Epstein. Mod Pathol 2006

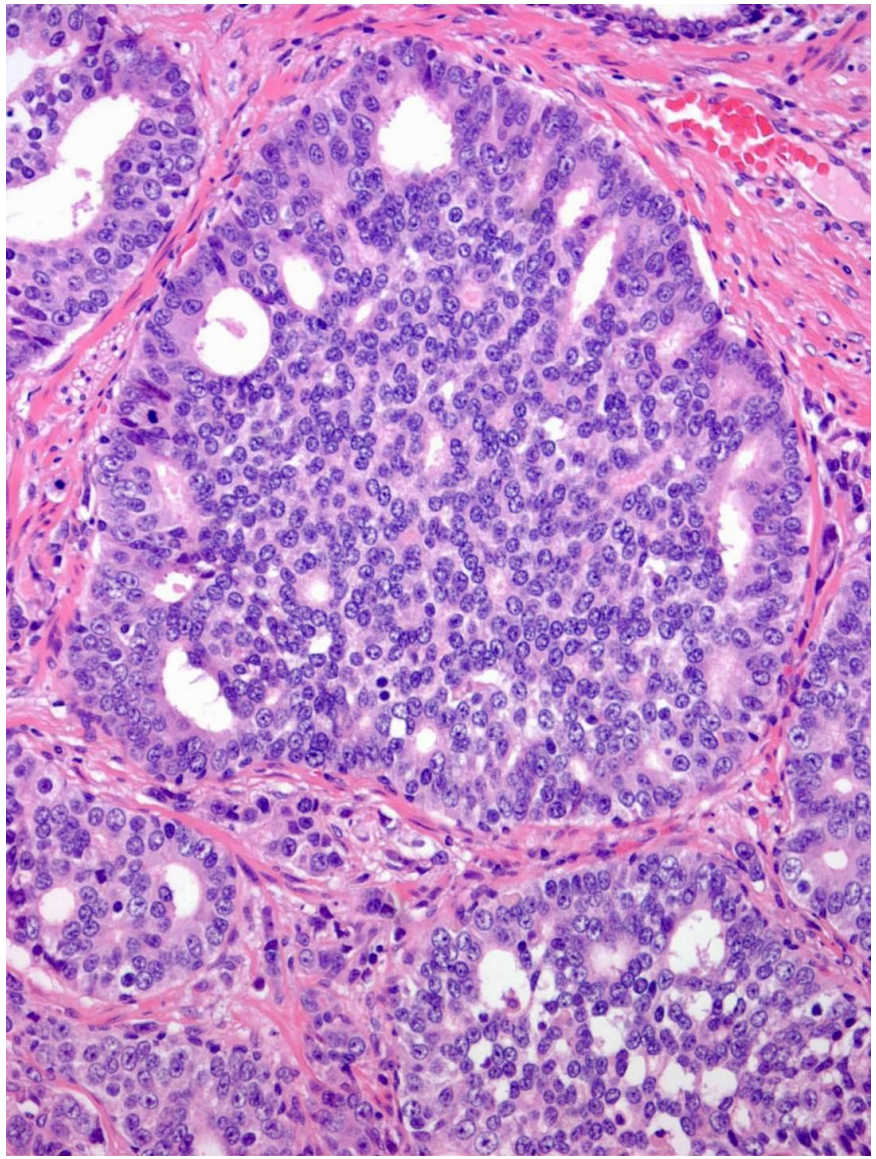
IDC-P: SOLID

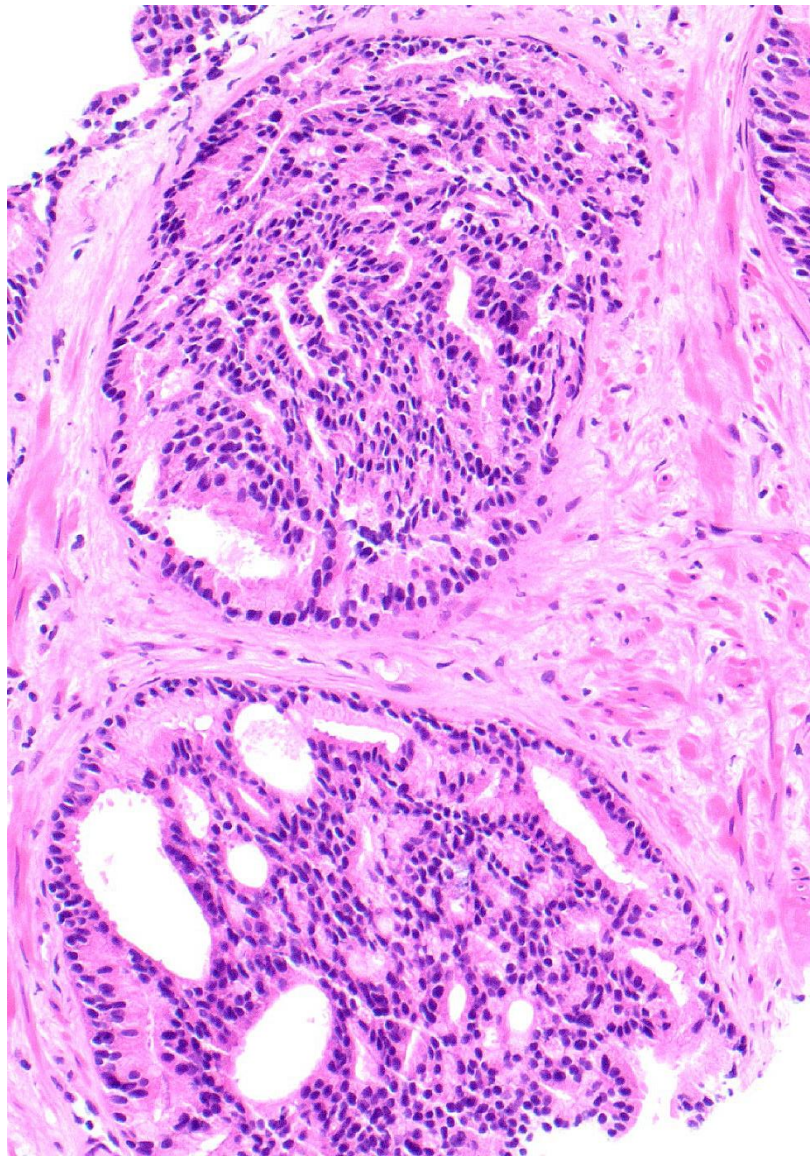




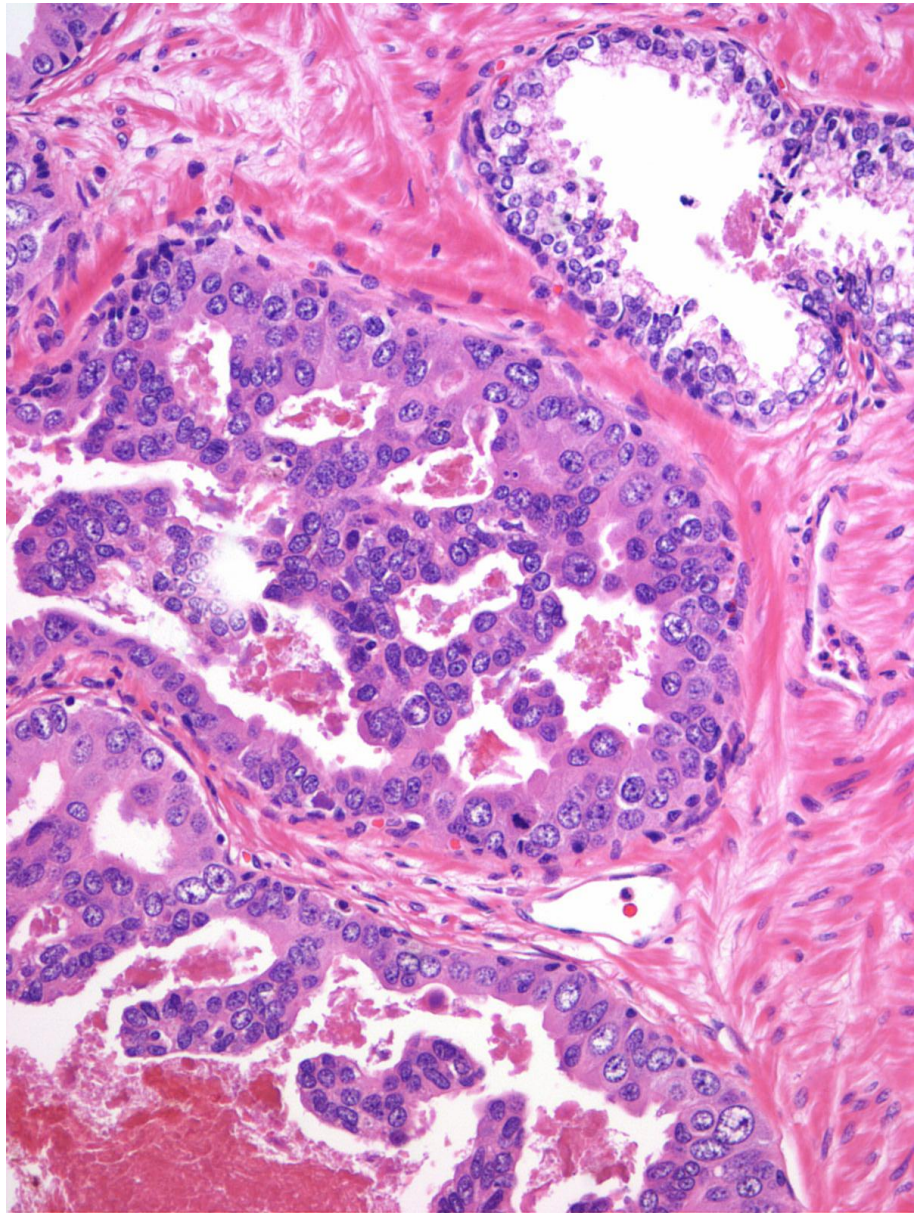
IDC-P: DENSE CRIBRIFORM

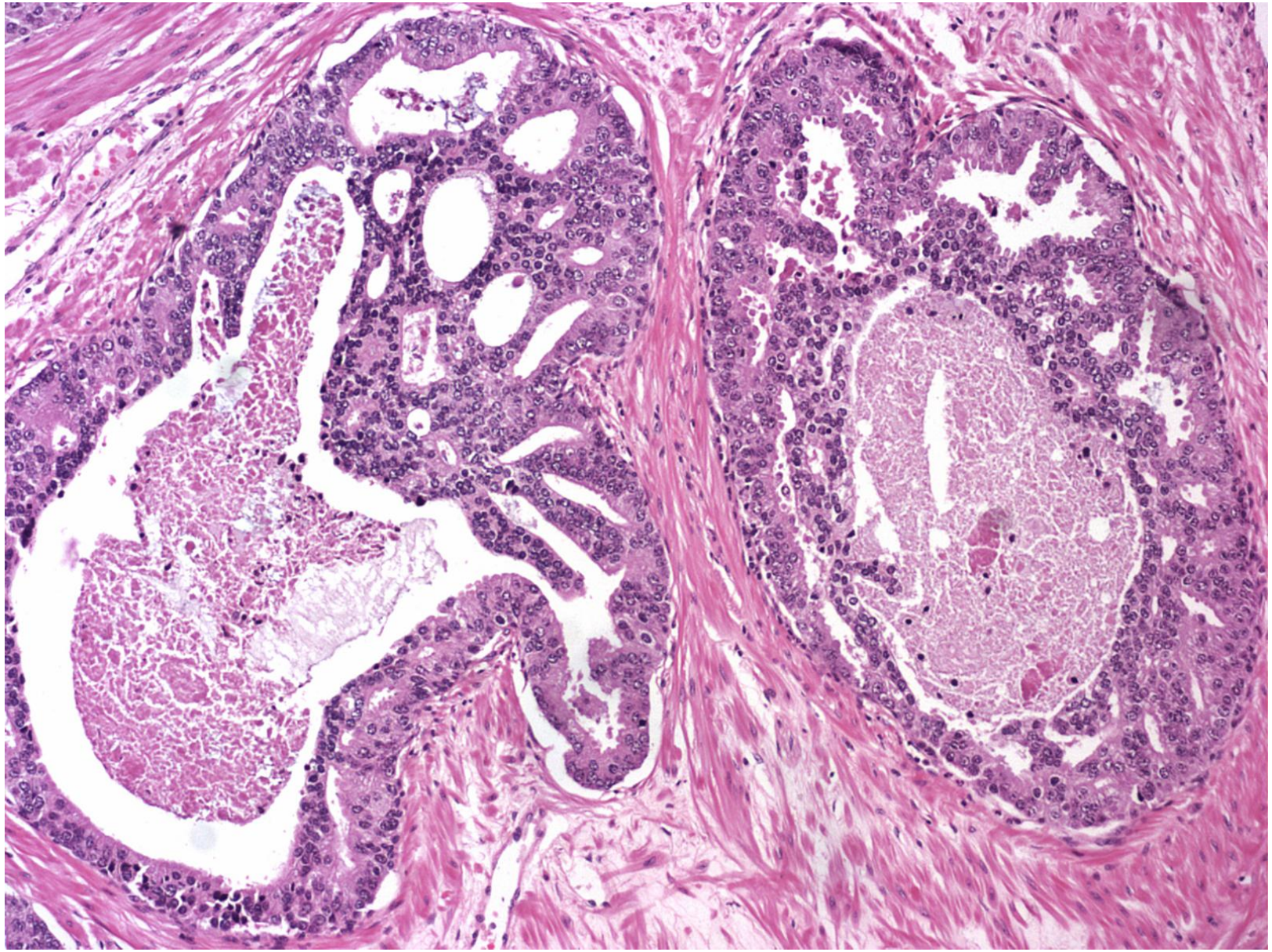




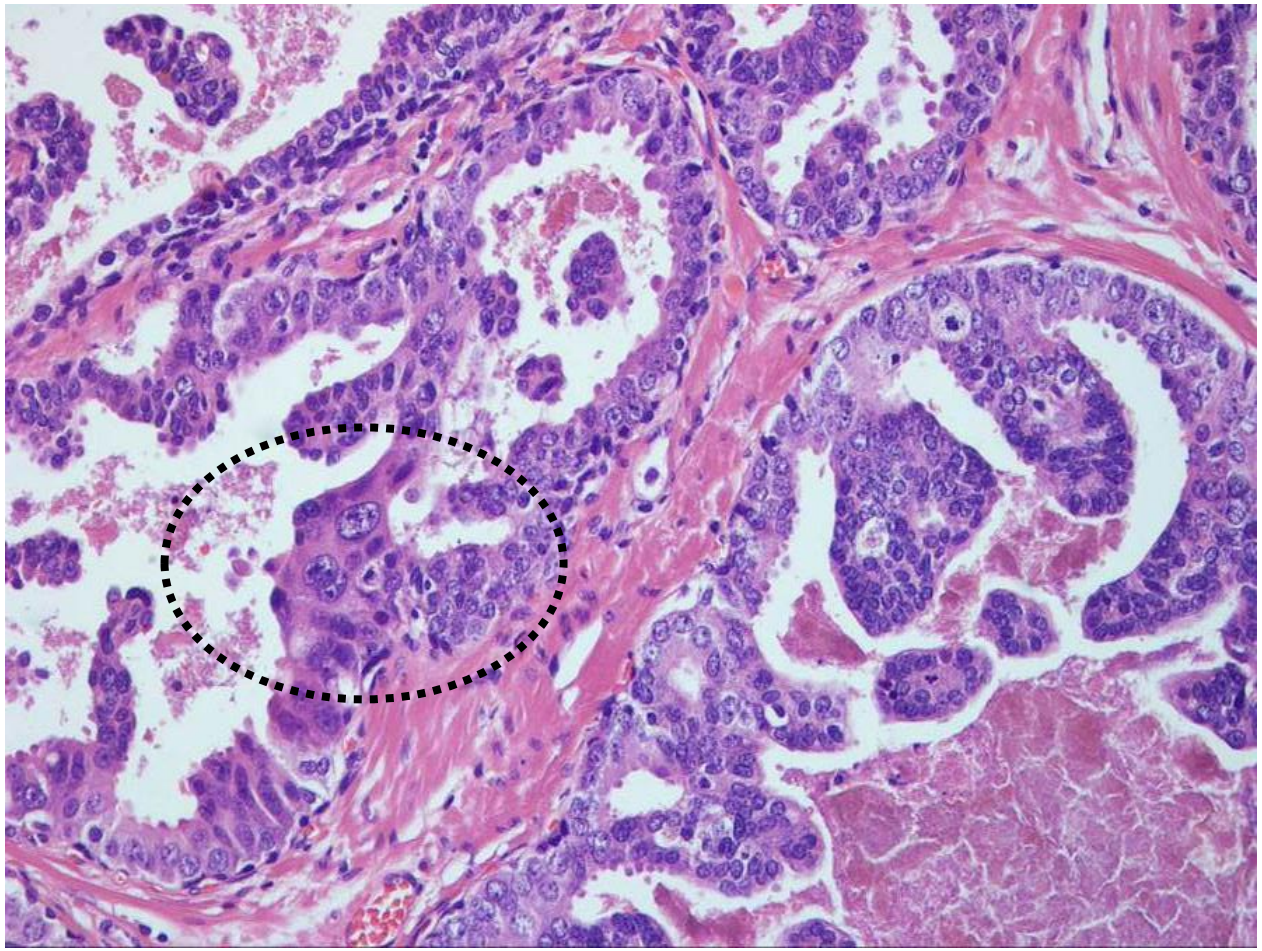


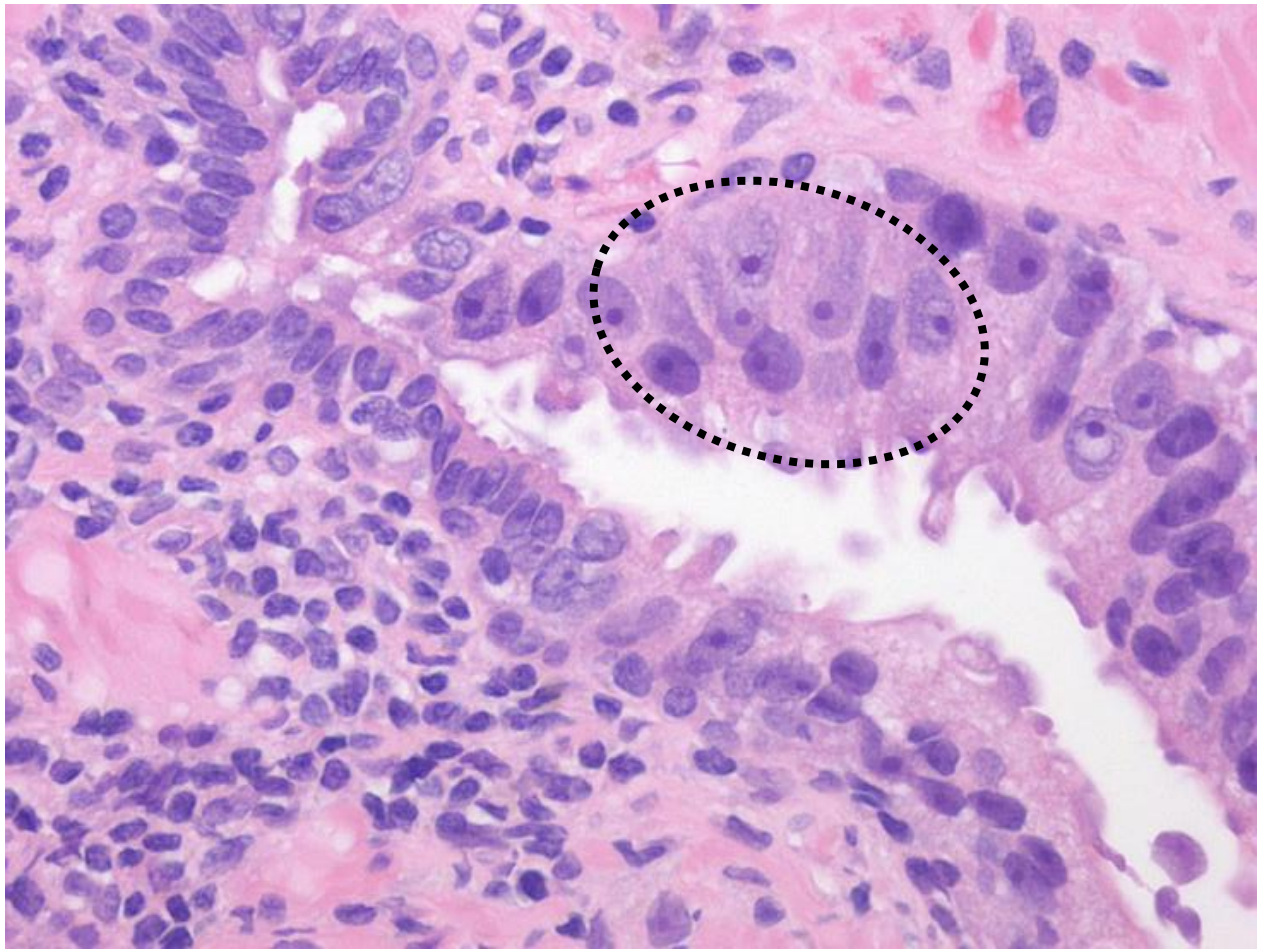
IDC-P: LOOSE CRIBRIFORM WITH COMEDONECROSIS



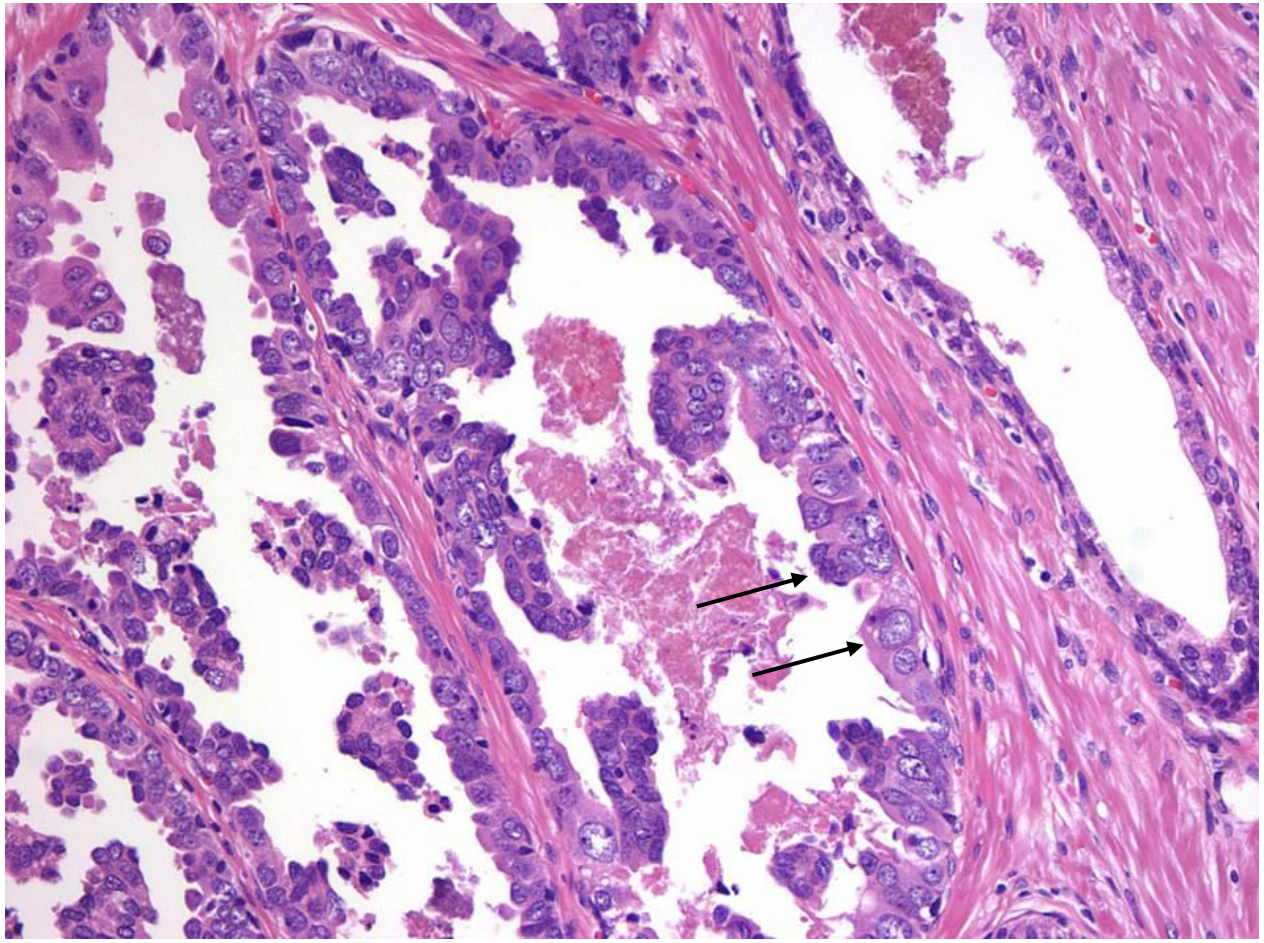


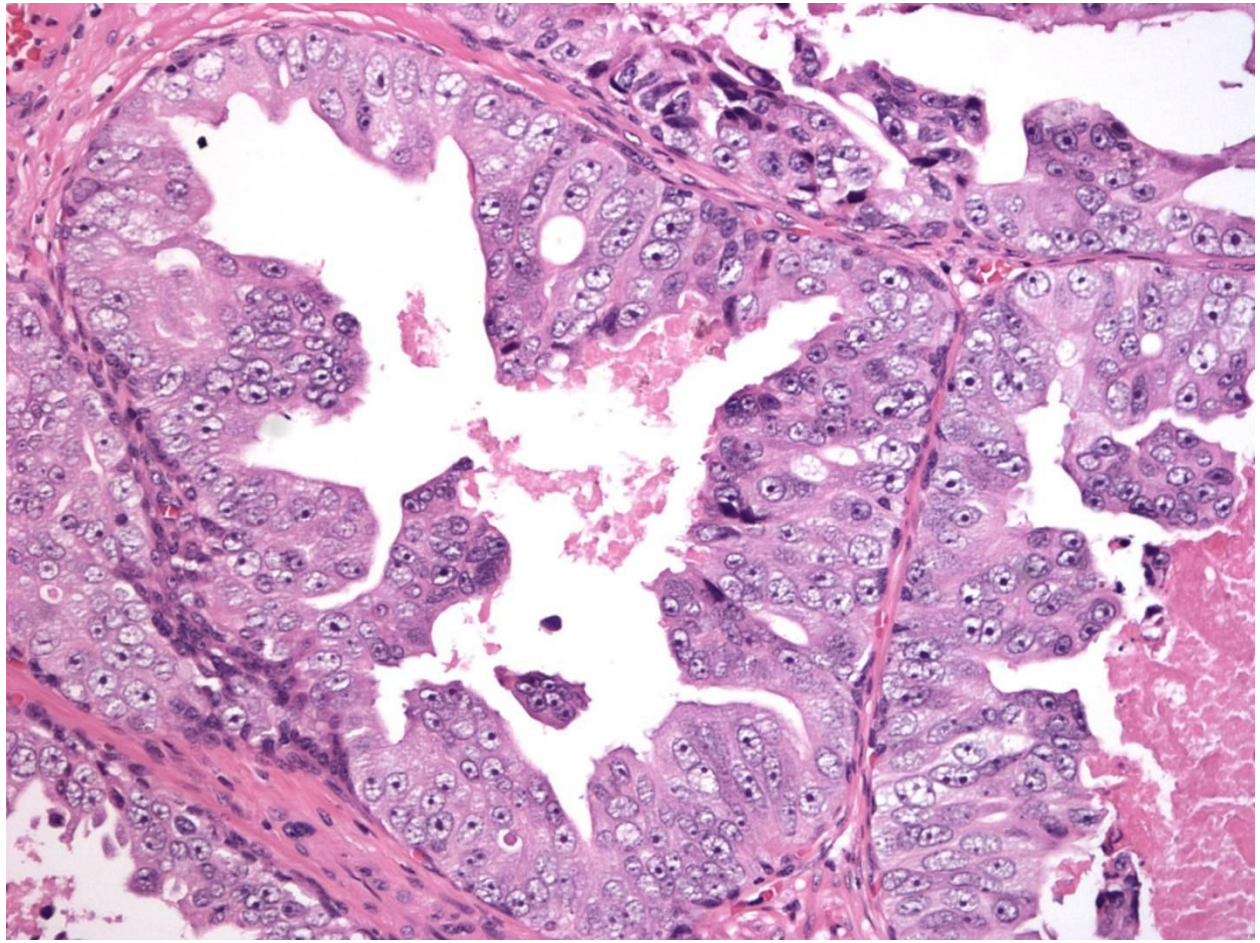
IDC-P: MICROPAPILLARY WITH MARKED NUCLEAR ATYPIA





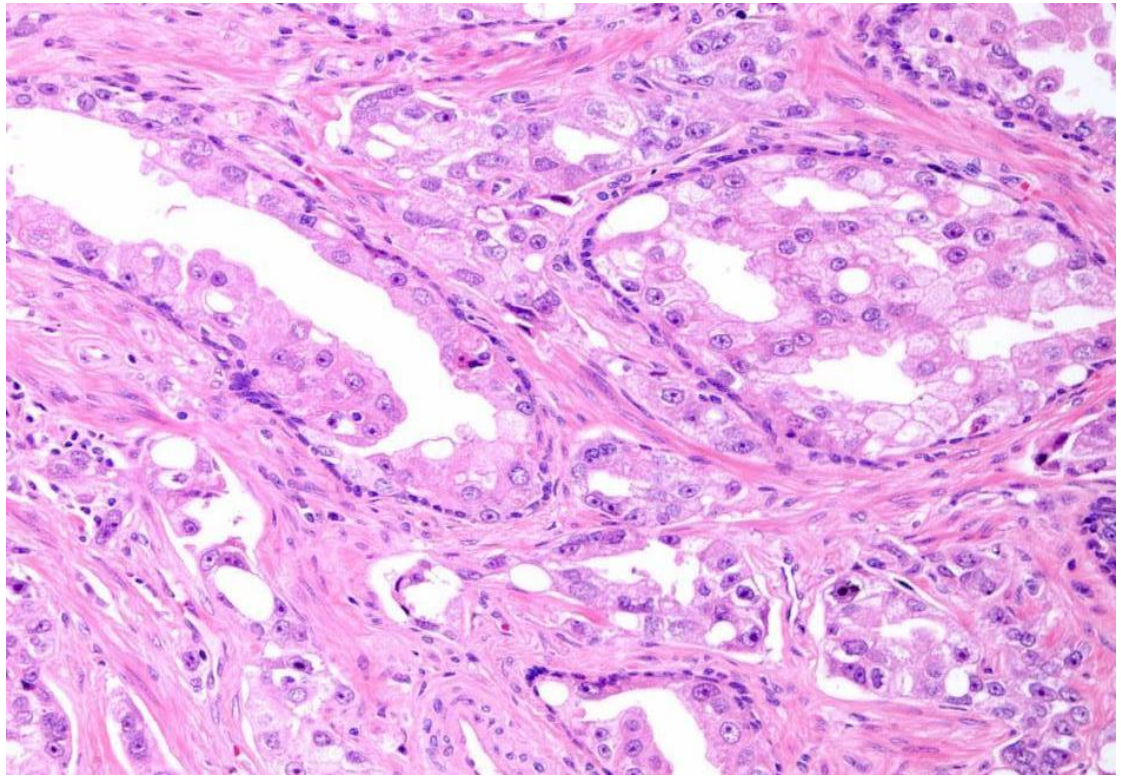
IDC-P: NUCLEAR PLEOMORPHISM

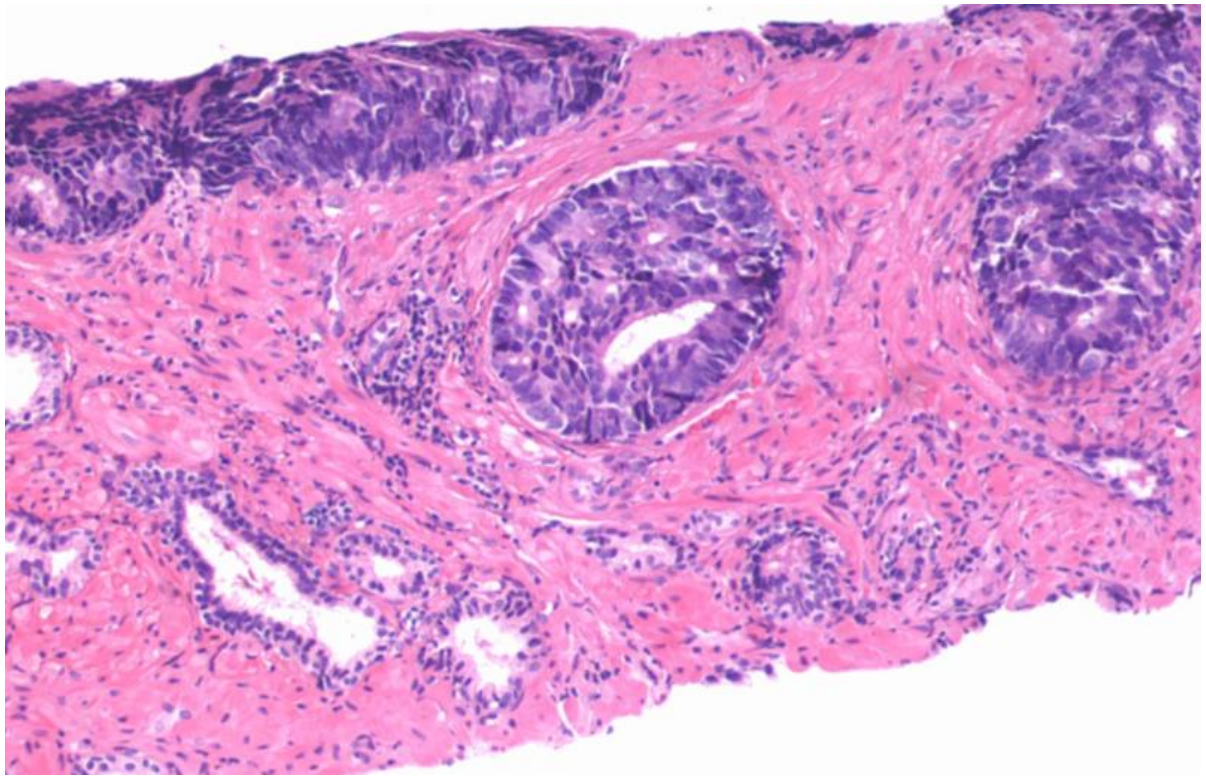




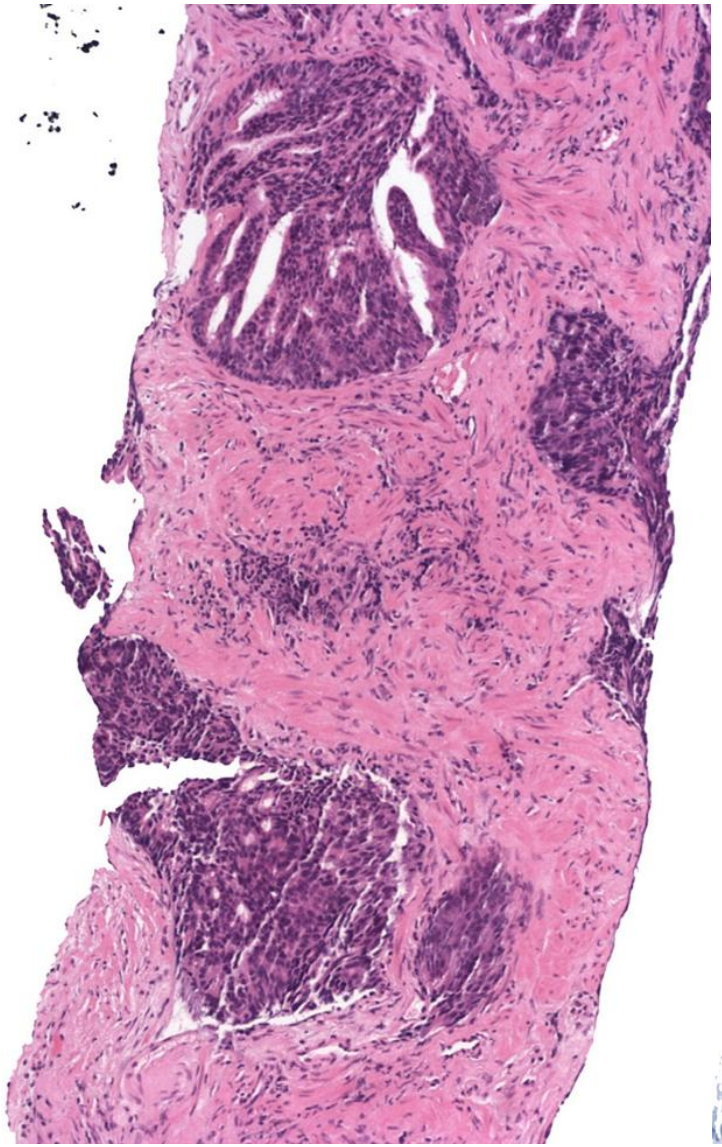
IDC-P

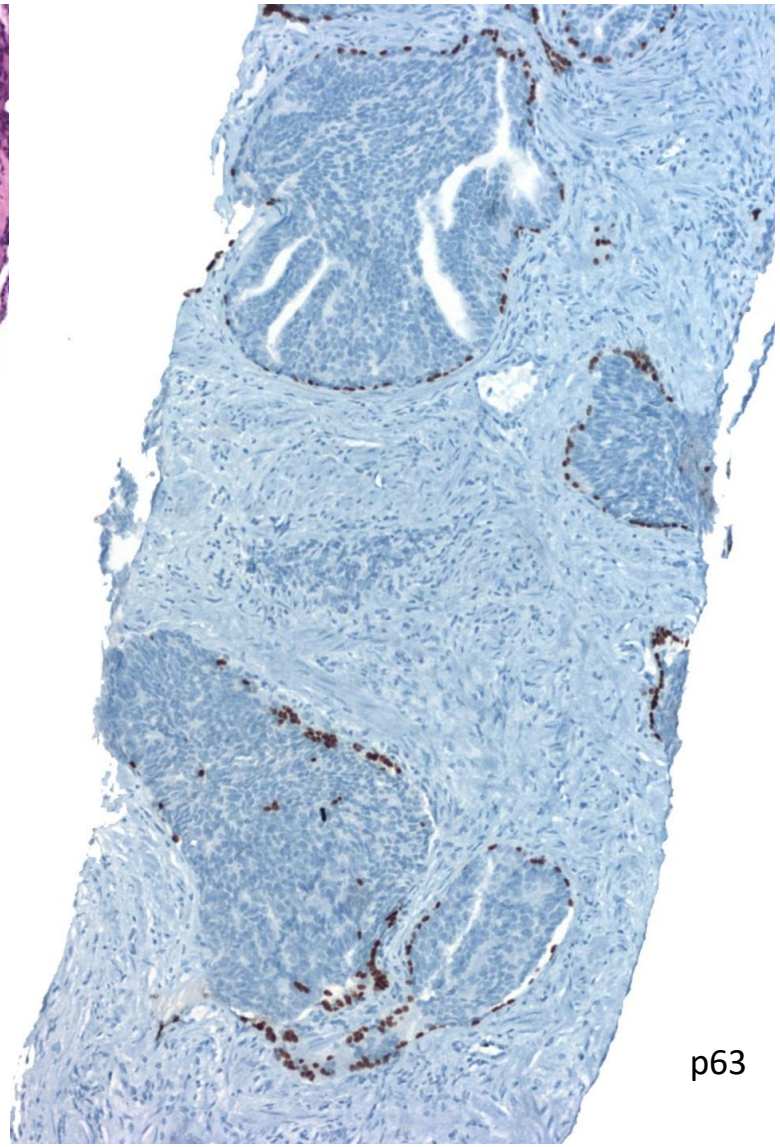
- 17% of RP cases
- 2.8% of Bx with high-grade PCA (mean GS 8)
- 0.1-0.3% of Bx without invasive PCA (isolated IDC-P)



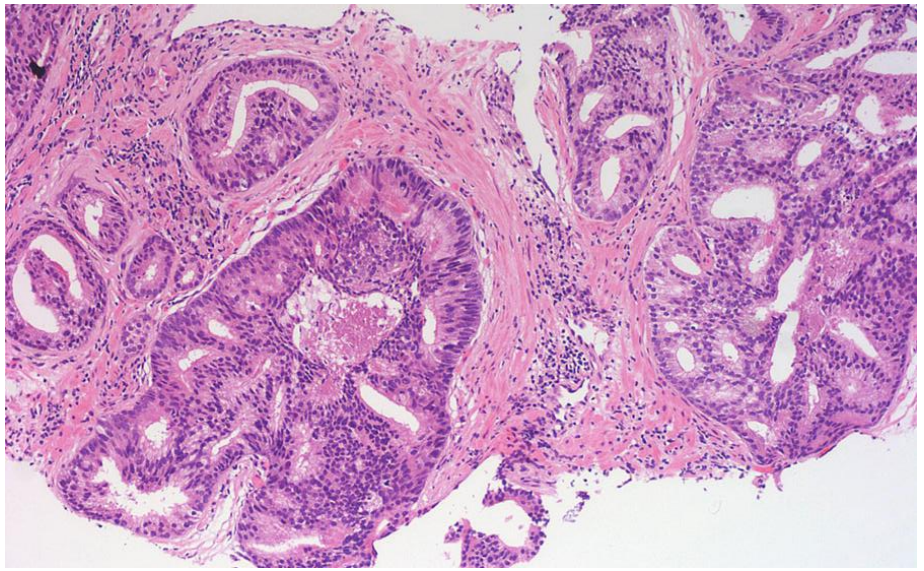


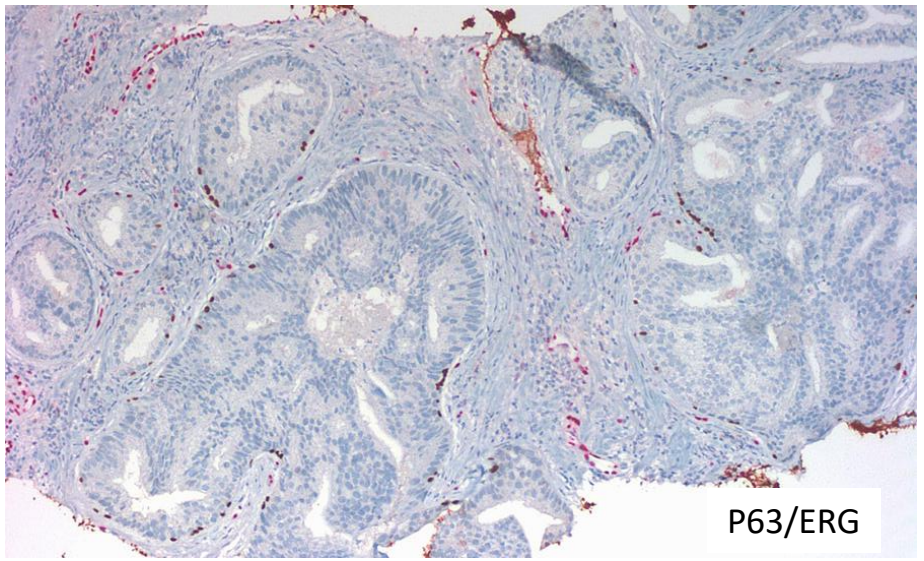
ISOLATED IDC-P





p63





P63/ERG

IDC-P: DIFFERENTIAL DIAGNOSIS

	IDC-P	AIP (*cribriform HGPIN*)	Intraductal Urothelial CA	Cribriform Invasive PCA
Architecture				
- Duct	Expanded	Preserved	Preserved	Distorted
- Duct/gland size	Increased (2x)	Normal	Increased	Distorted
- Lumen spanning cells	Present	Absent	Present	Present

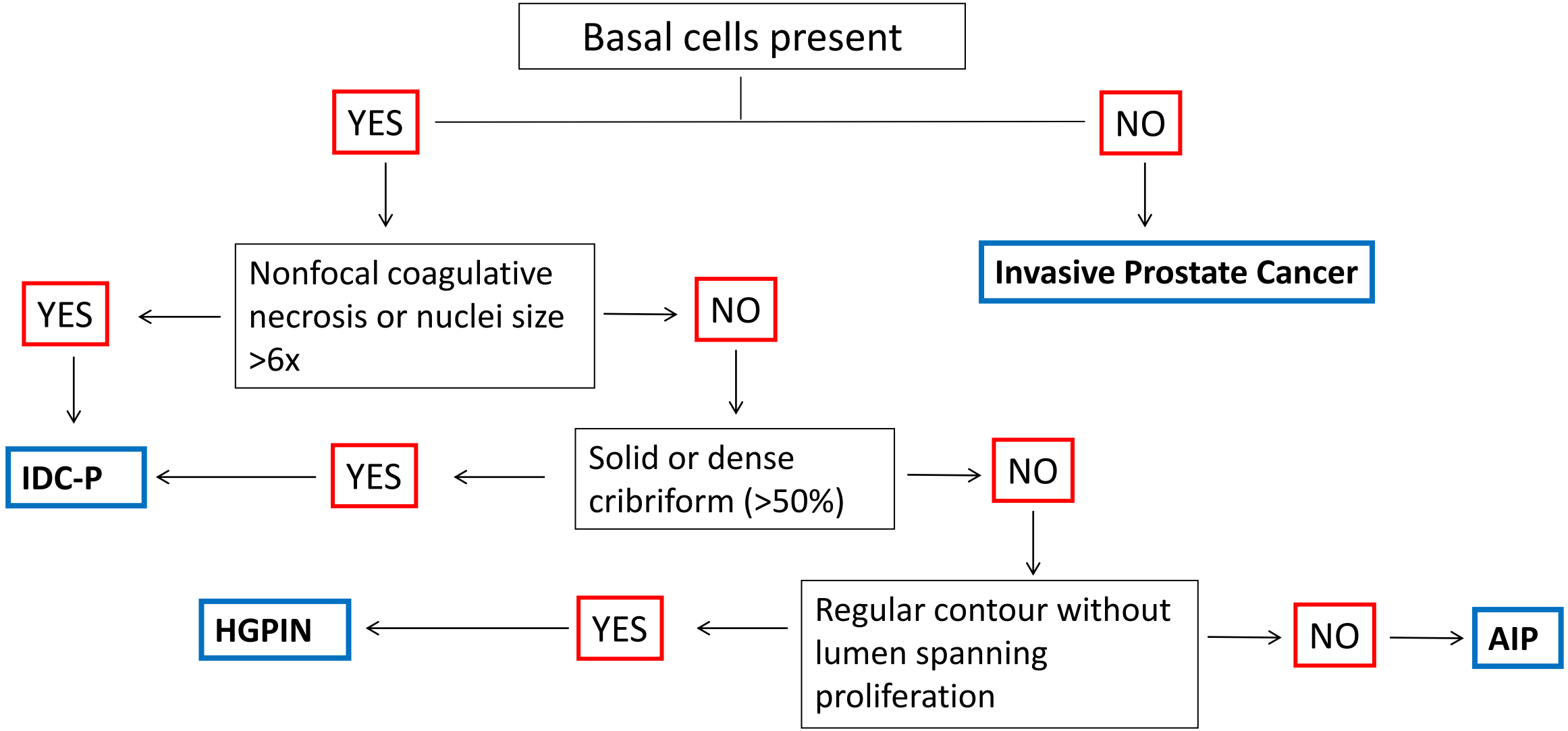
Adapted from Henry & Evans. J Clin Pathol 2009

IDC-P: DIFFERENTIAL DIAGNOSIS

	IDC-P	AIP (*cribriform HGPIN*)	Intraductal Urothelial CA	Cribriform Invasive PCA
Architecture				
- Duct	Expanded	Preserved	Preserved	Distorted
- Duct/gland size	Increased (2x)	Normal	Increased	Distorted
- Lumen spanning cells	Present	Absent	Present	Present
IHC				
- Basal cells	HMWCK/p63 +	HMWCK/p63 +	HMWCK/p63 +	Absent
- Neoplastic cells	HMWCK/p63 -	HMWCK/p63 -	HMWCK/p63 +	HMWCK/p63 -
	PSA + (central)	PSA +	PSA -	PSA +
	NKX3.1 +	NKX3.1 +	NKX3.1 -	NKX3.1 +
	GATA3 -	GATA3 -	GATA3 +	GATA3 -
	ERG +/-	ERG -/+	ERG -	ERG +/-
	PTEN loss	PTEN +	n/a	PTEN loss

Adapted from Henry & Evans. J Clin Pathol 2009

Atypical Cell Proliferation in Large Glands (>1 mm)



ATYPICAL INTRADUCTAL PROLIFERATION

HGPIN

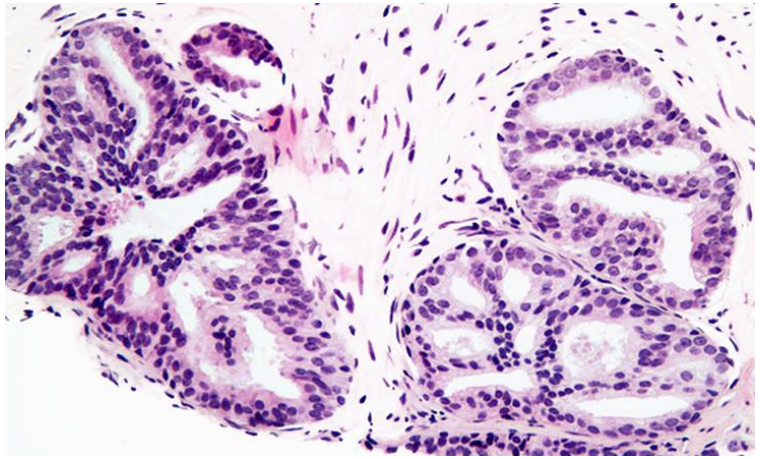
1. Normal duct/acinus size
2. Architectural patterns
   - flat
   - tufted
   - micropapillary
3. Increased nuclear size (x2-3)
4. Uniform atypia
5. No comedonecrosis

AIP

IDC-P

1. Increased duct/acinus size
2. Architectural patterns
   - dense cribriform
   - solid
3. Markedly increased nuclear size (x6)
4. Frequent pleomorphism/mitoses
5. Comedonecrosis

Loose cribriform architecture



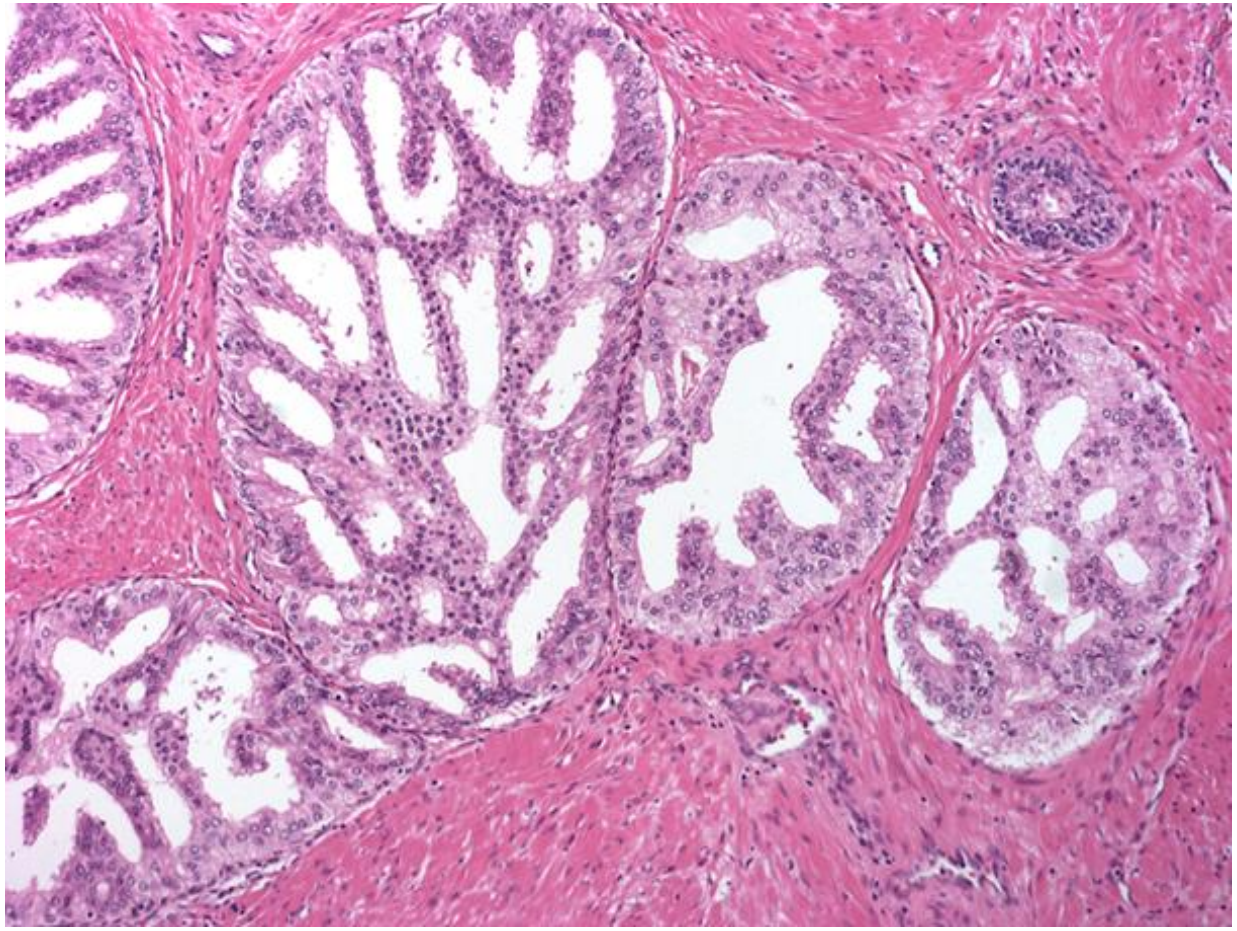
Mild to moderate cytological atypia

MANAGEMENT OF BIOPSY RESULTS

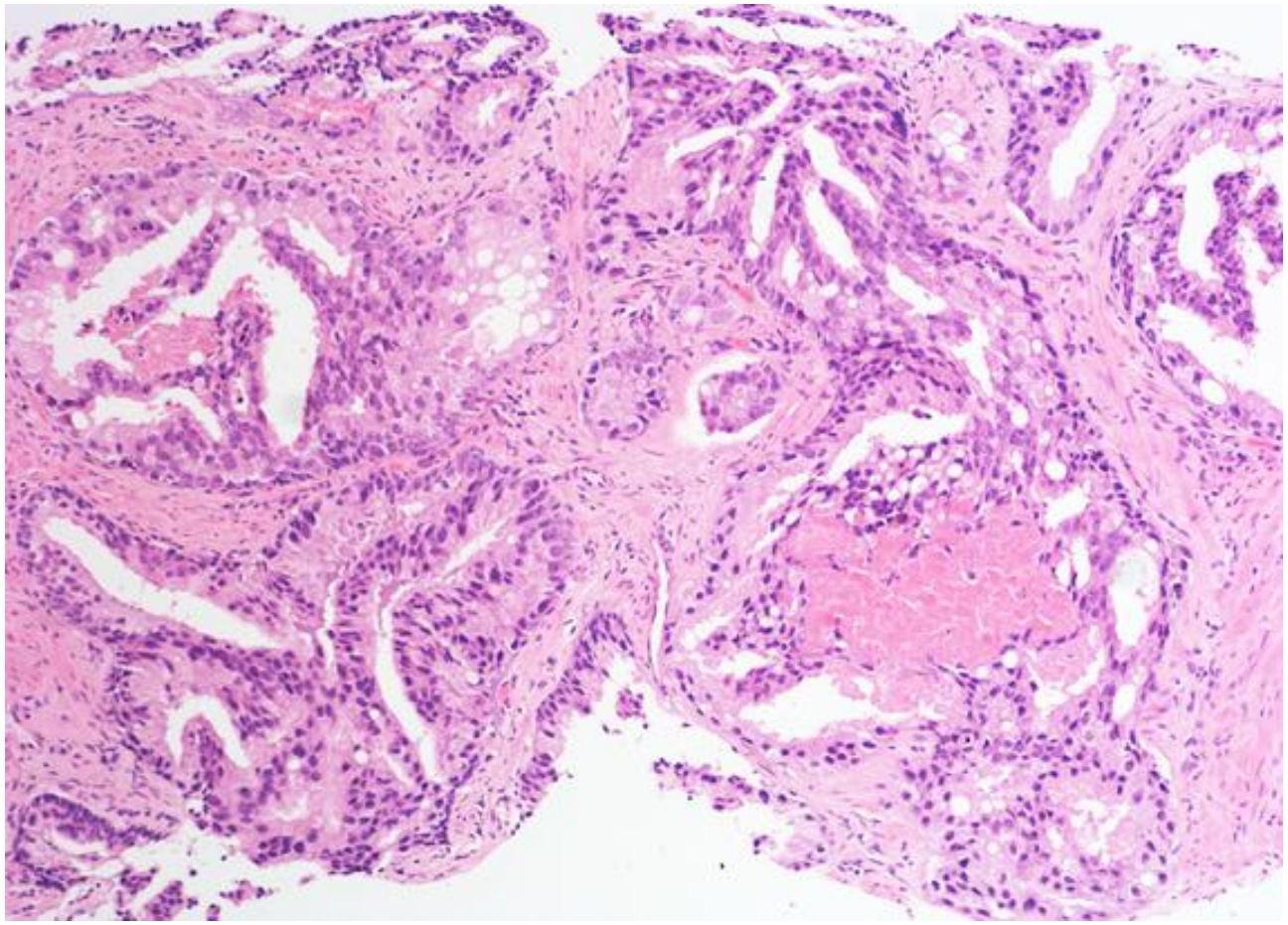
Cancer	See NCCN Guidelines for Prostate Cancer
Intraductal carcinoma (IDC) without invasive carcinoma[o]	See NCCN Guidelines for Prostate Cancer or Repeat biopsy using MRI targeting and systematic biopsy to look for invasive carcinoma
Atypical intraductal proliferation (AIP) without invasive carcinoma[p]	Repeat biopsy using MRI targeting and systematic biopsy to look for invasive carcinoma
Atypia, suspicious for cancer	Follow-up: • Consider biomarkers that improve the specificity of screening[s] and/or multiparametric MRI[t] • Consider repeated biopsy with relative increased sampling of the atypical site
High-grade prostatic intraepithelial neoplasia (PIN)[q,r]	Follow-up: • PSA and DRE at 6- to 24-month intervals and • Consider biomarkers that improve the specificity of screening[s] and/or multiparametric MRI[t]
Benign[q,r,s,t]	Repeat prostate biopsy with refined biopsy techniques, based on risk[t]

IDC-P: DIFFERENTIAL DIAGNOSIS

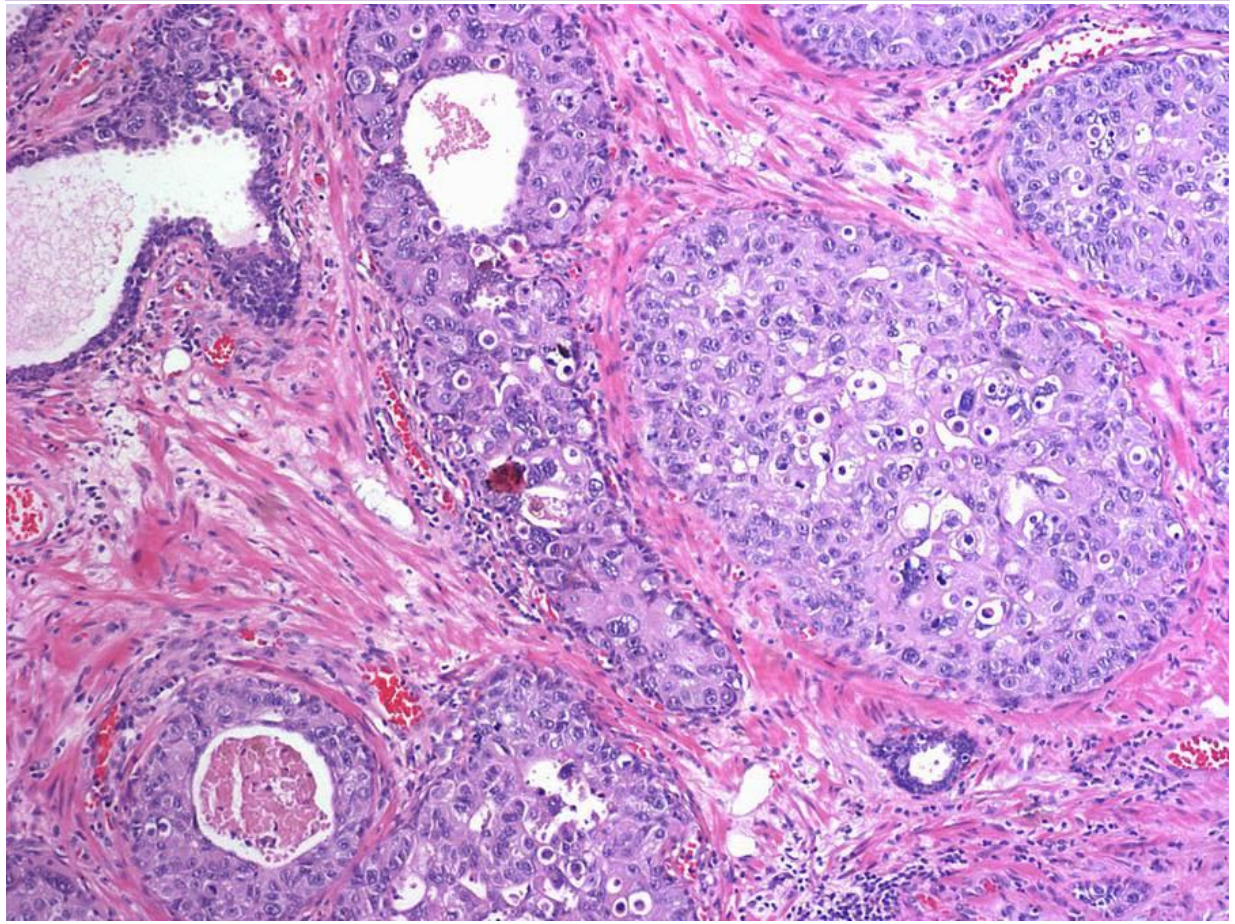
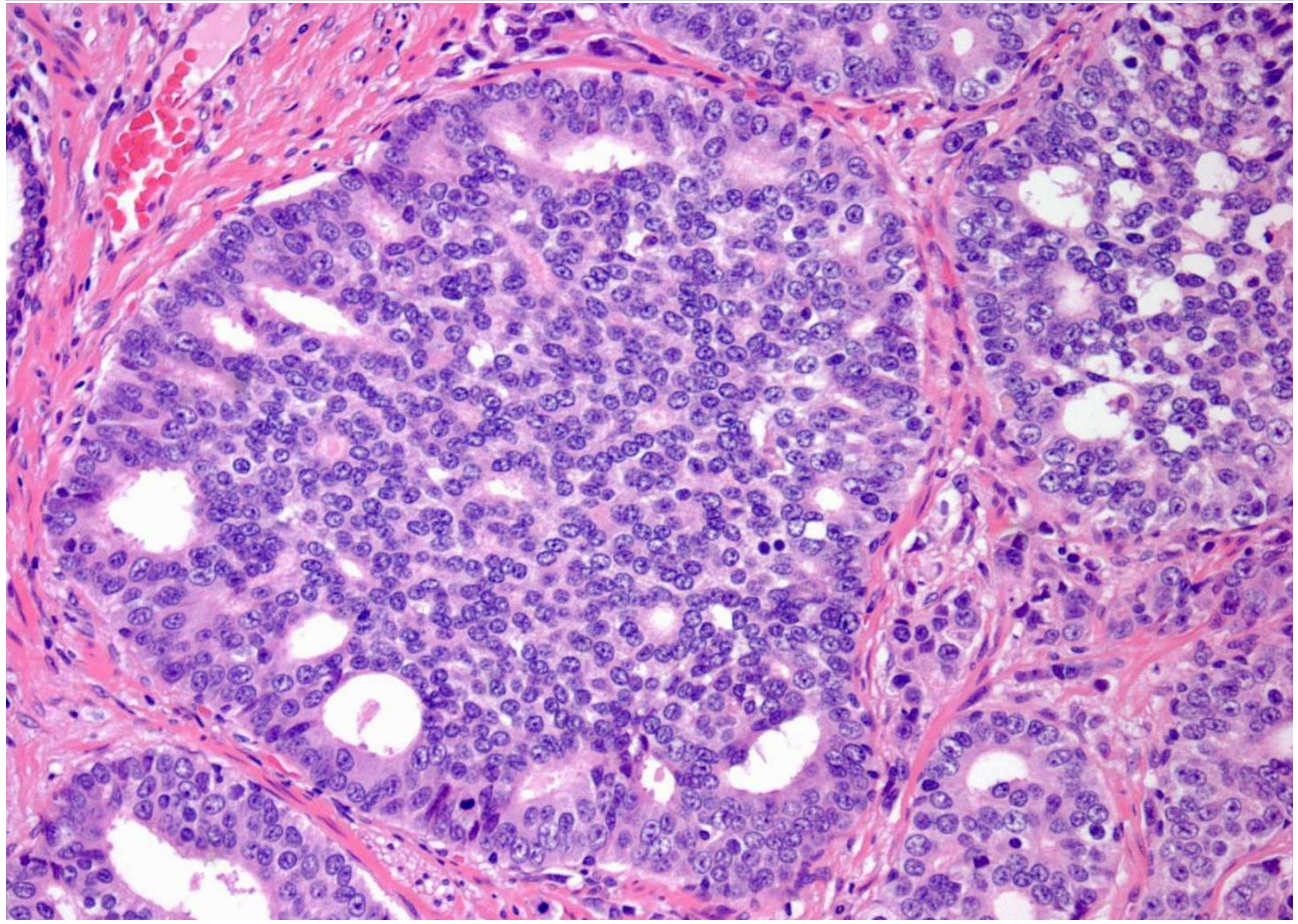
AIP*/cribriform HGPIN*



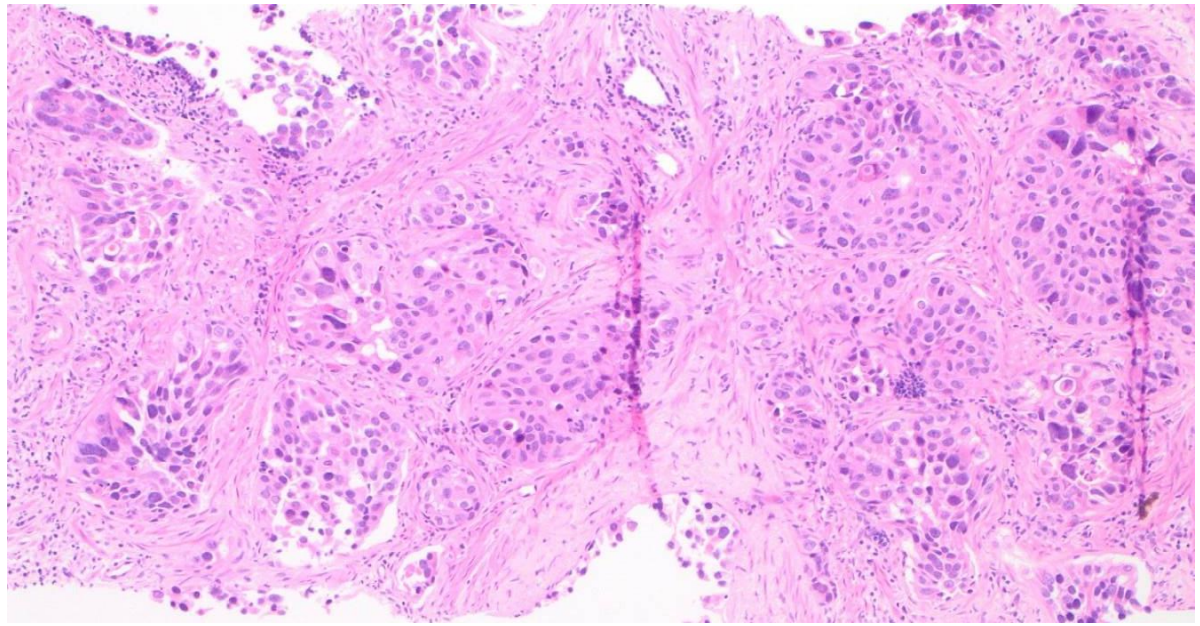
IDC-P loose cribriform with comedonecrosis

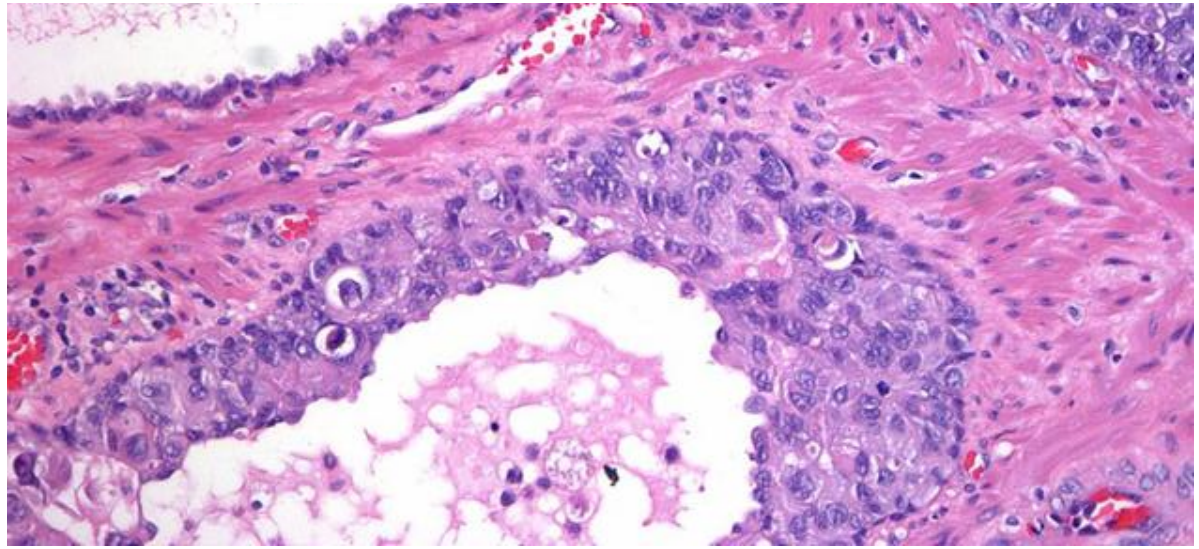


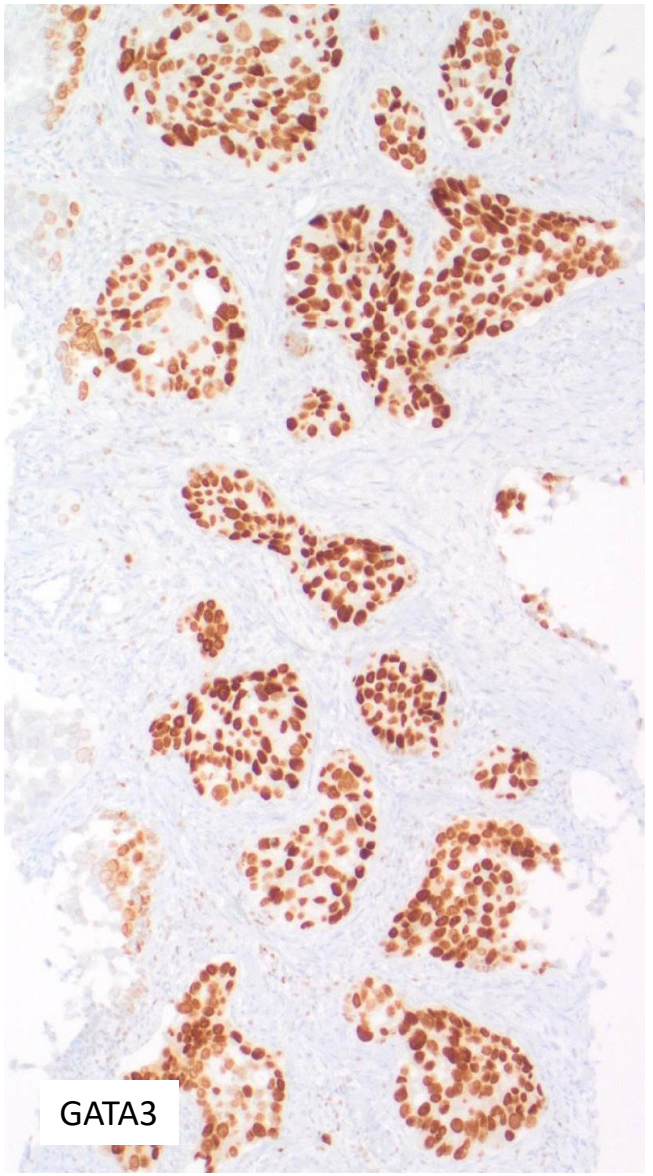
IDC-P: DIFFERENTIAL DIAGNOSIS

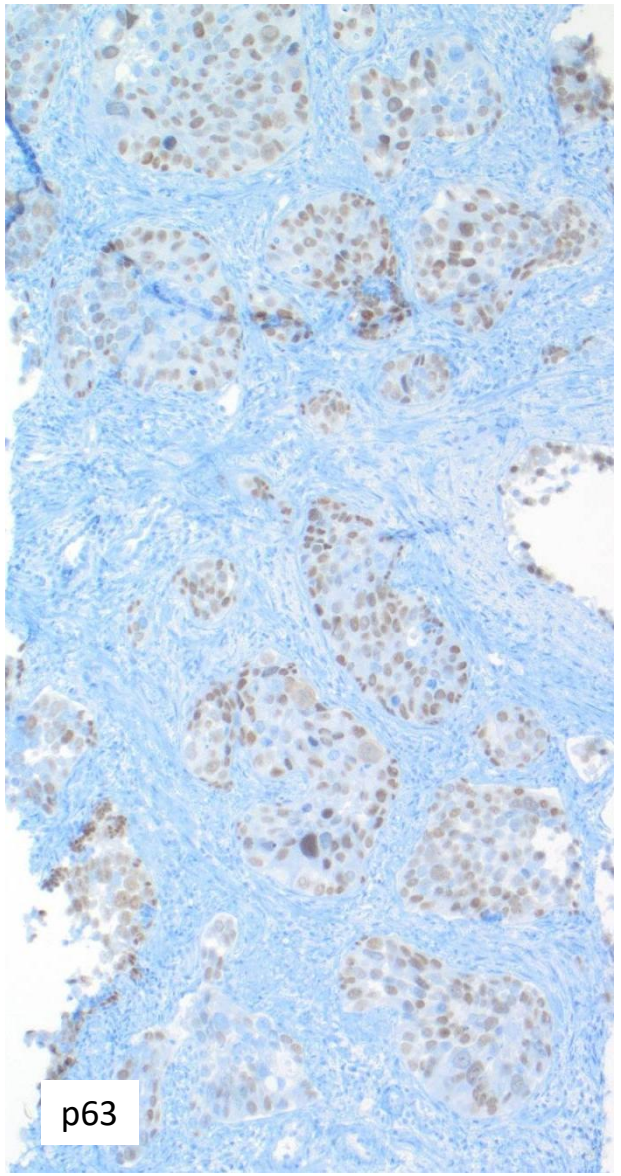
Intraductal Urothelial Carcinoma	IDC-P dense cribriform
	

Intraductal Urothelia Carcinoma

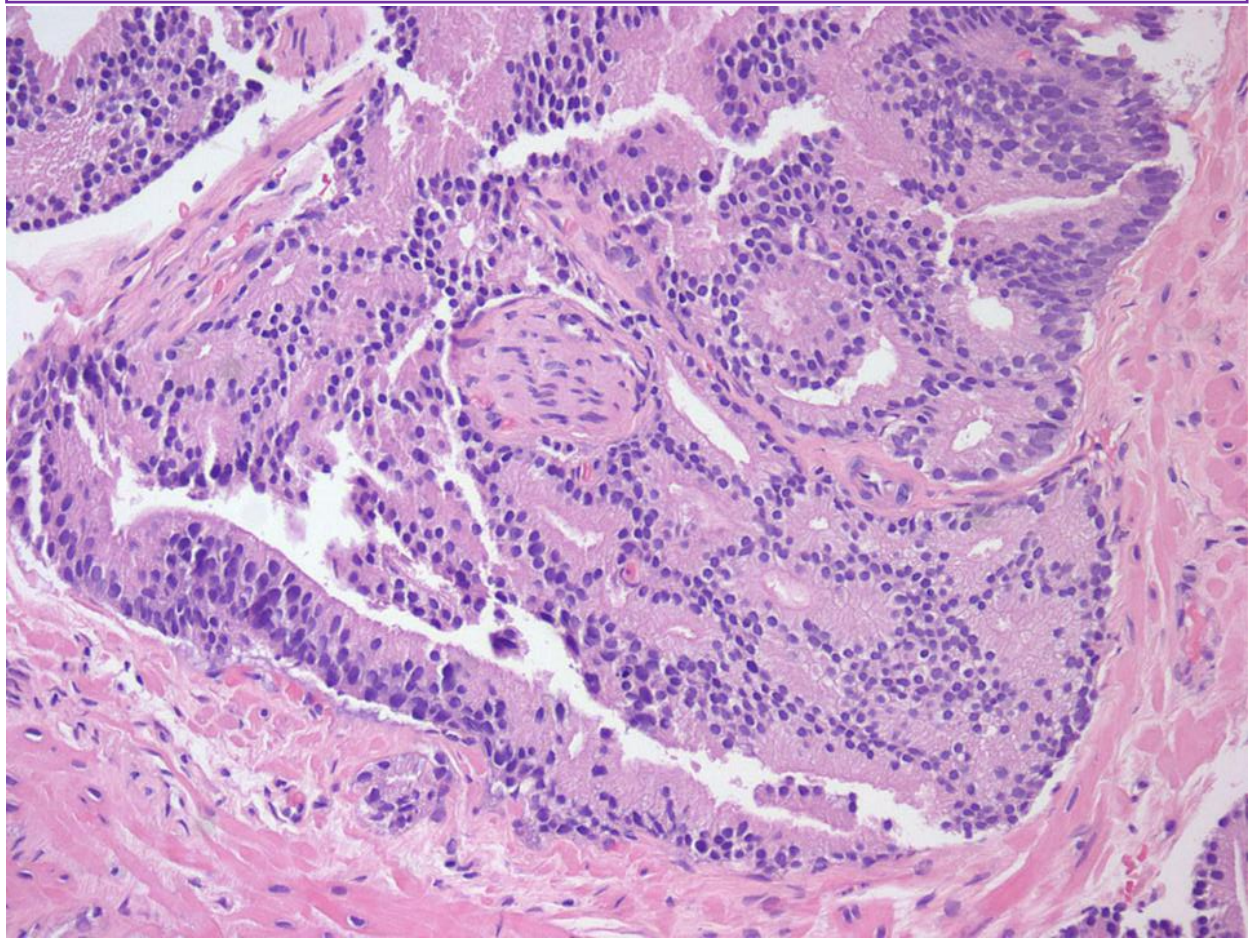
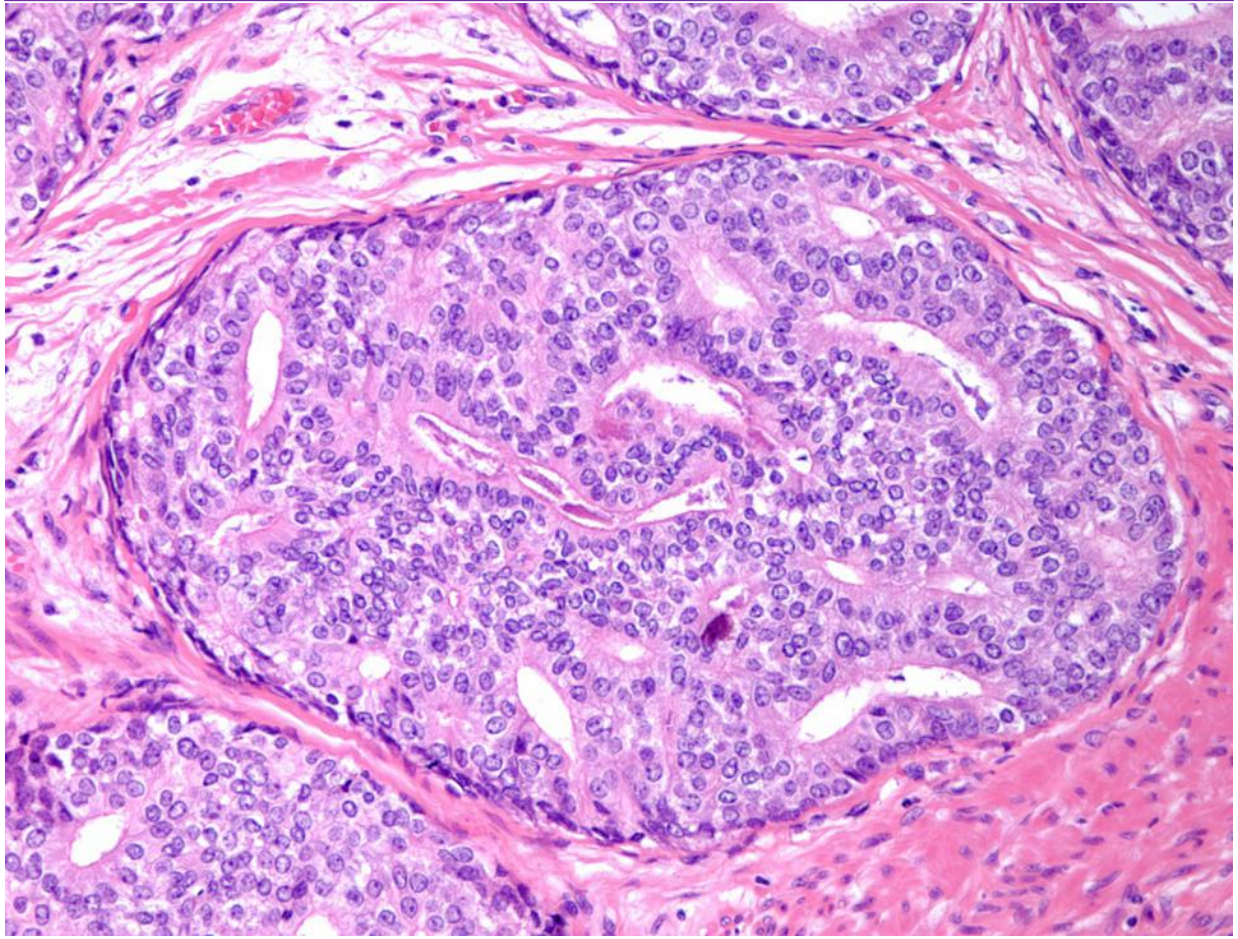






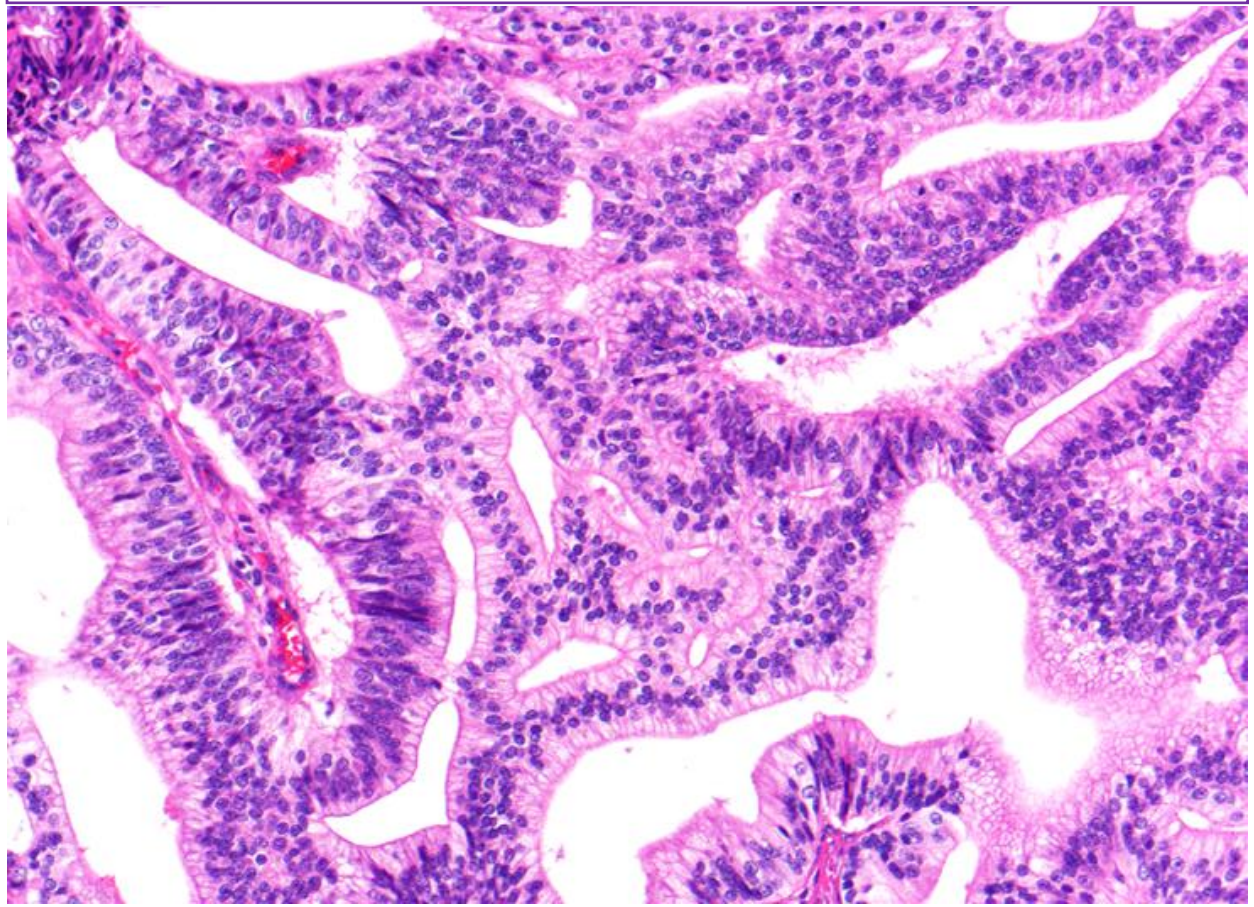


IDC-P: DIFFERENTIAL DIAGNOSIS

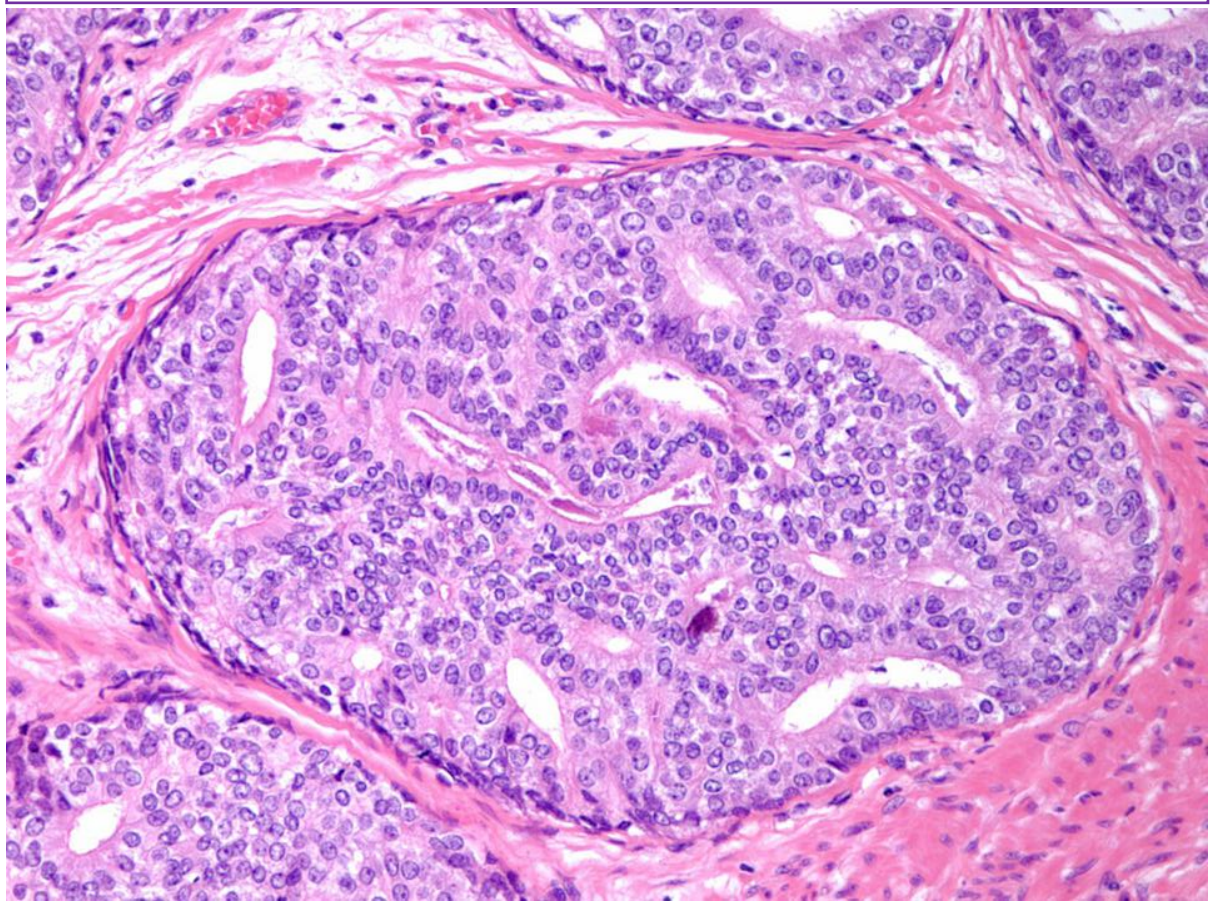
Cribriform Acinar Adenocarcinoma	IDC-P dense cribriform
	

IDC-P: DIFFERENTIAL DIAGNOSIS

Cribriform Ductal Adenocarcinoma

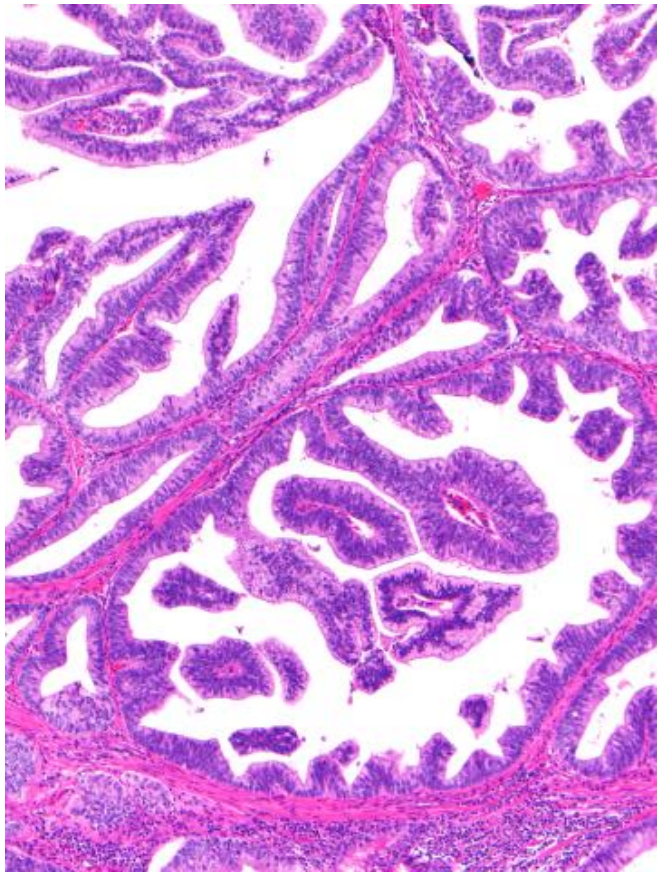


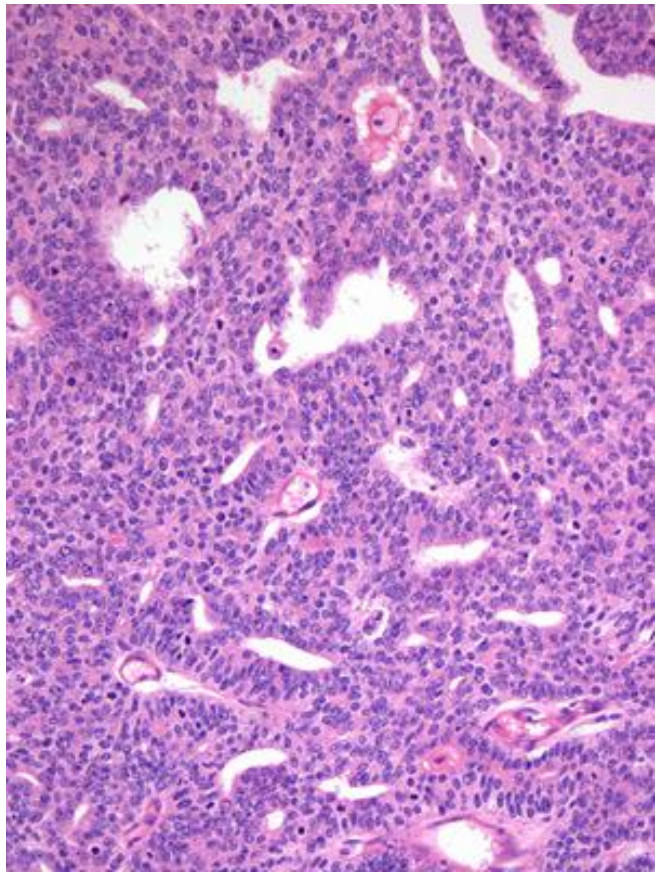
IDC-P dense cribriform



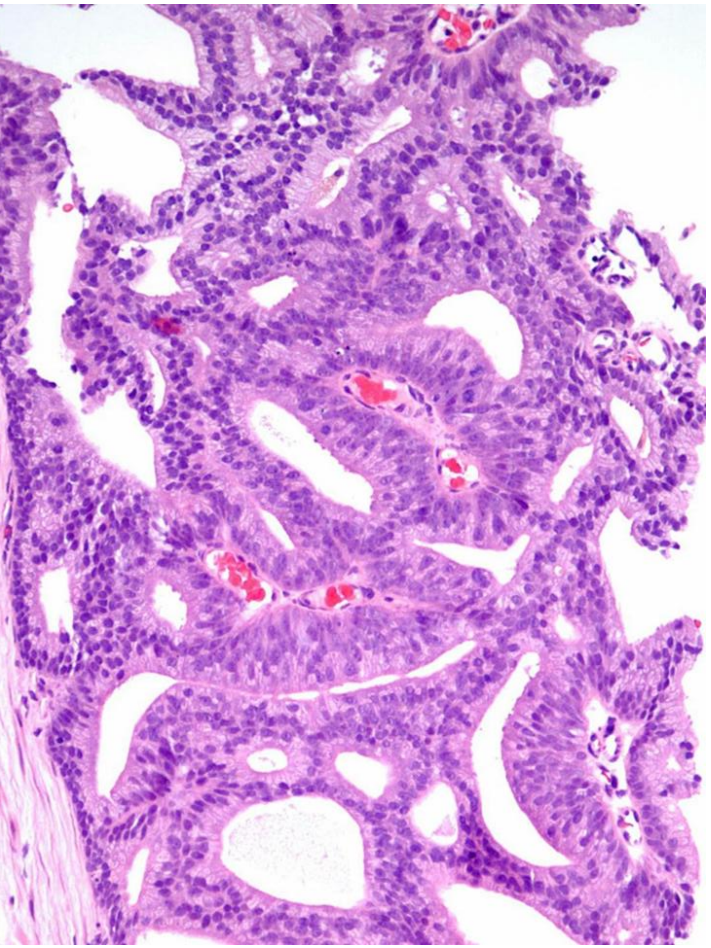
PROSTATIC DUCTAL ADENOCARCINOMA

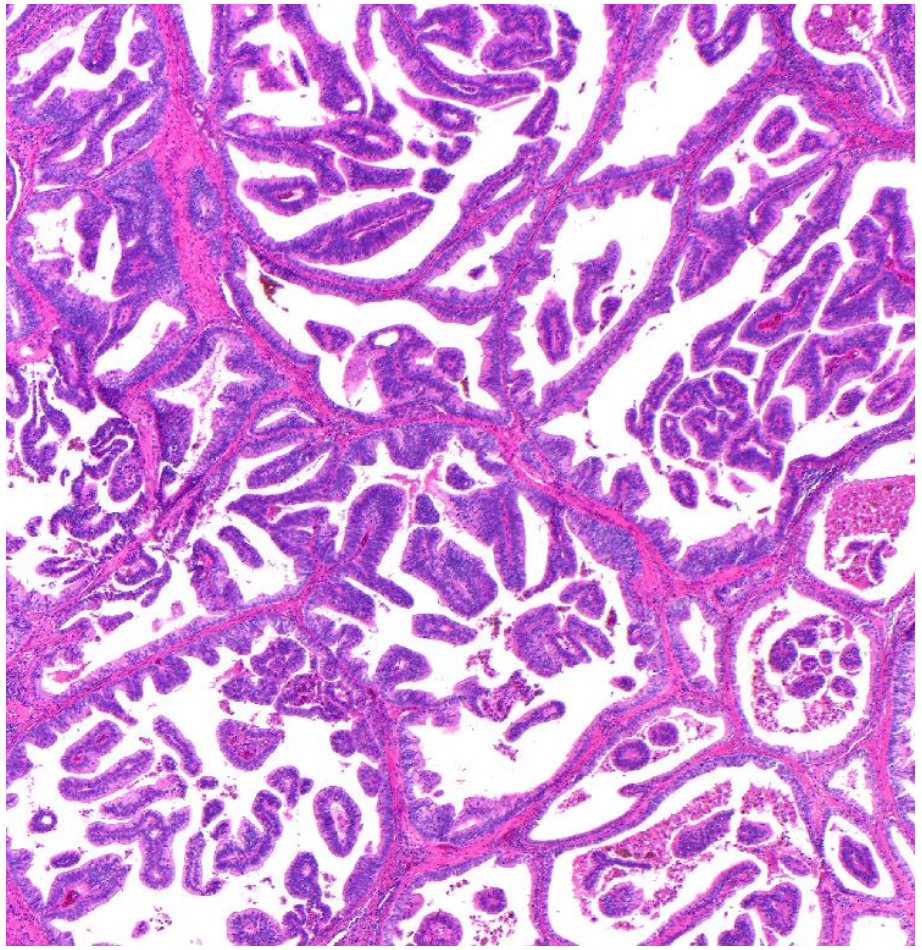
- Uncommon (~3%) variant derived from prostatic glandular cells
- Clonally similar to acinar
- 2 major architectural patterns:
  - **Papillary**: true fibrovascular cores lined by stratified columnar cells
  - **Cribriform**: complex glandular arrangements with acini showing slit-like lumina and multilayered nuclei

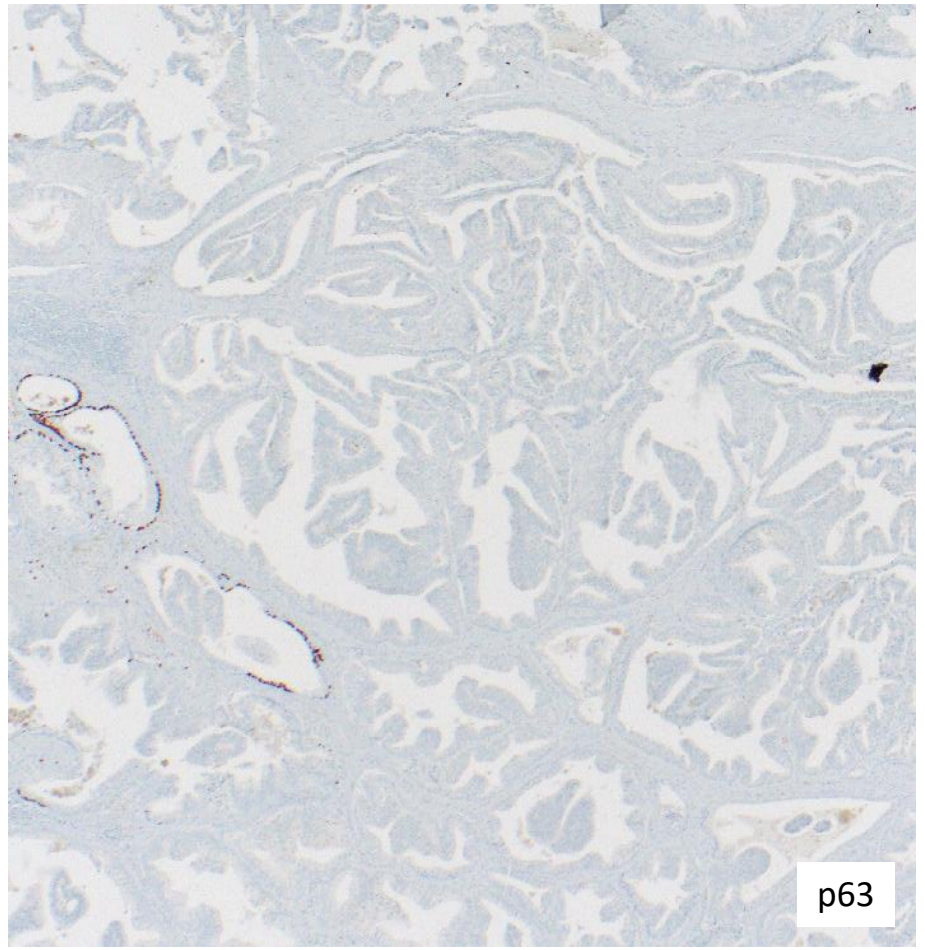




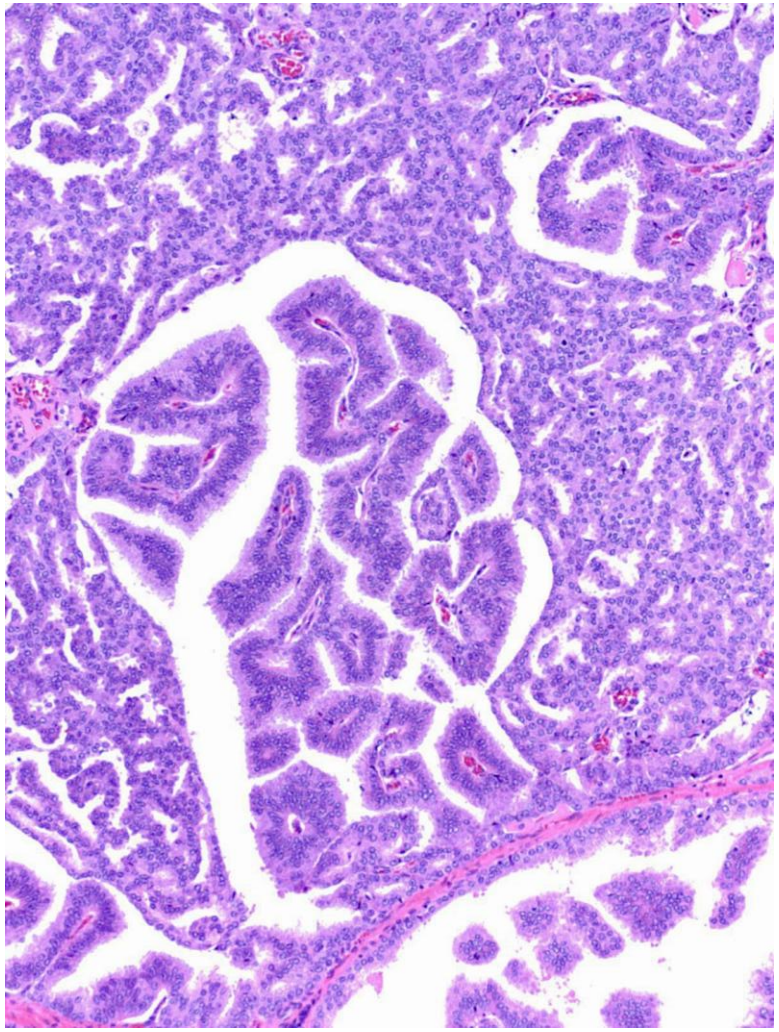
PROSTATIC DUCTAL ADENOCARCINOMA





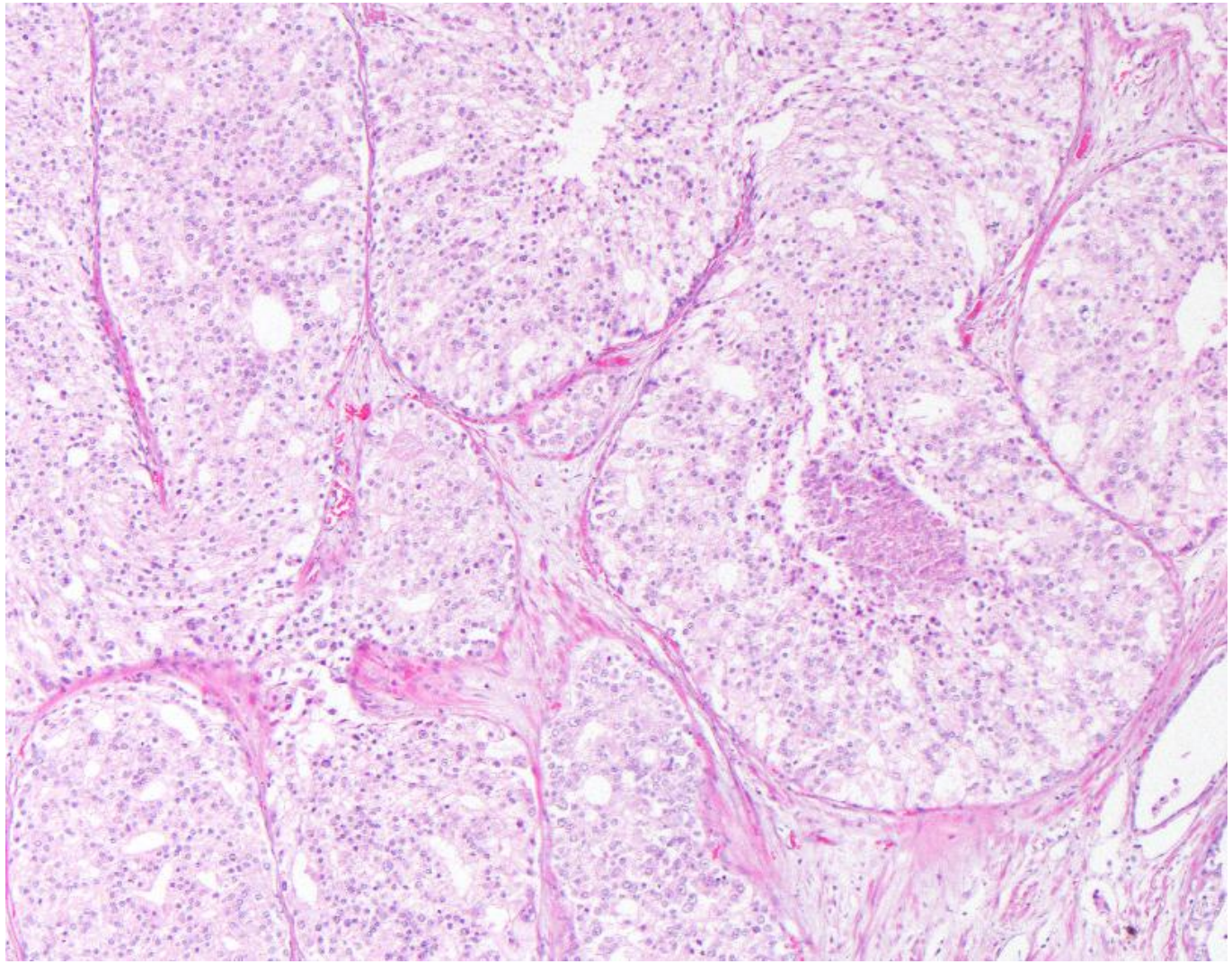


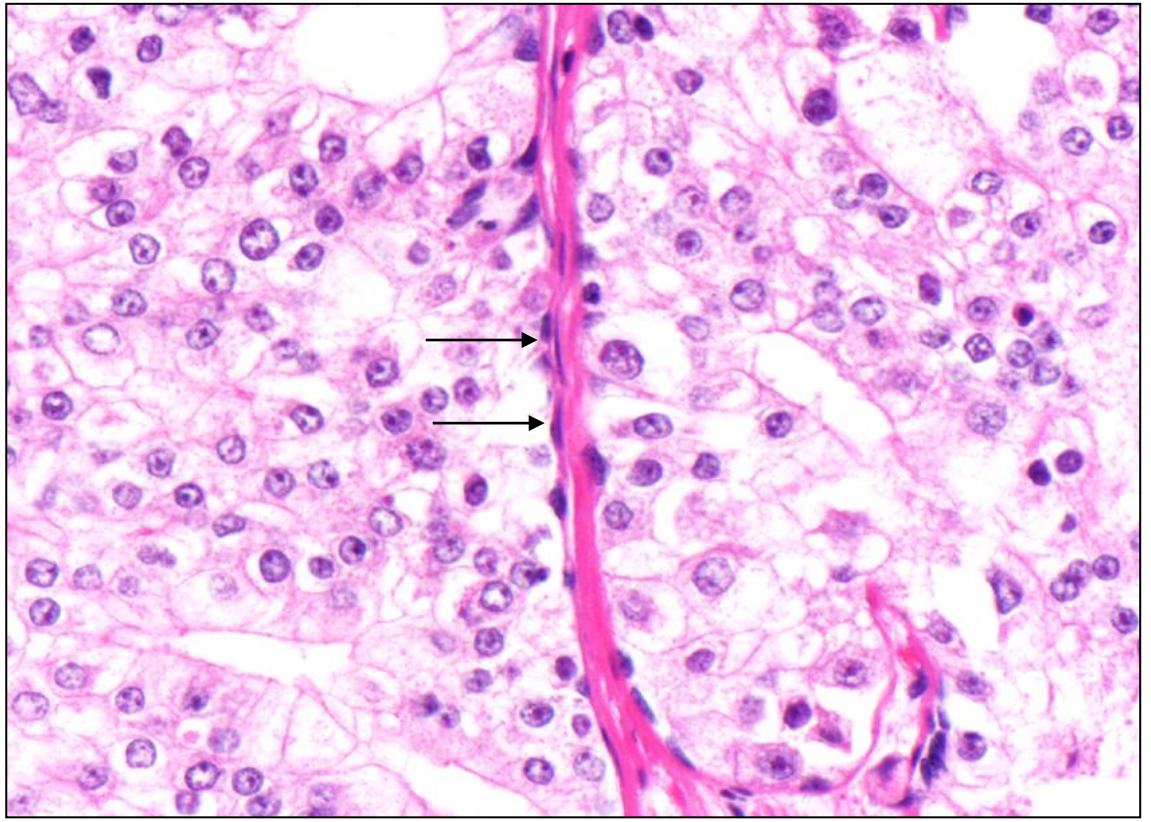
PROSTATIC DUCTAL ADENOCARCINOMA



- On RP, ductal is reserved for >50% ductal morphology
- On Bx, adenocarcinoma with ductal features is recommended
- Any proportion of ductal carries increased risk of BCF and metastatic disease
- Less responsive to ADT compared to acinar
- Higher propensity for visceral metastasis (lungs, liver, testis) than acinar PCA
- Equivalent to GP4 or 5 (comedonecrosis)

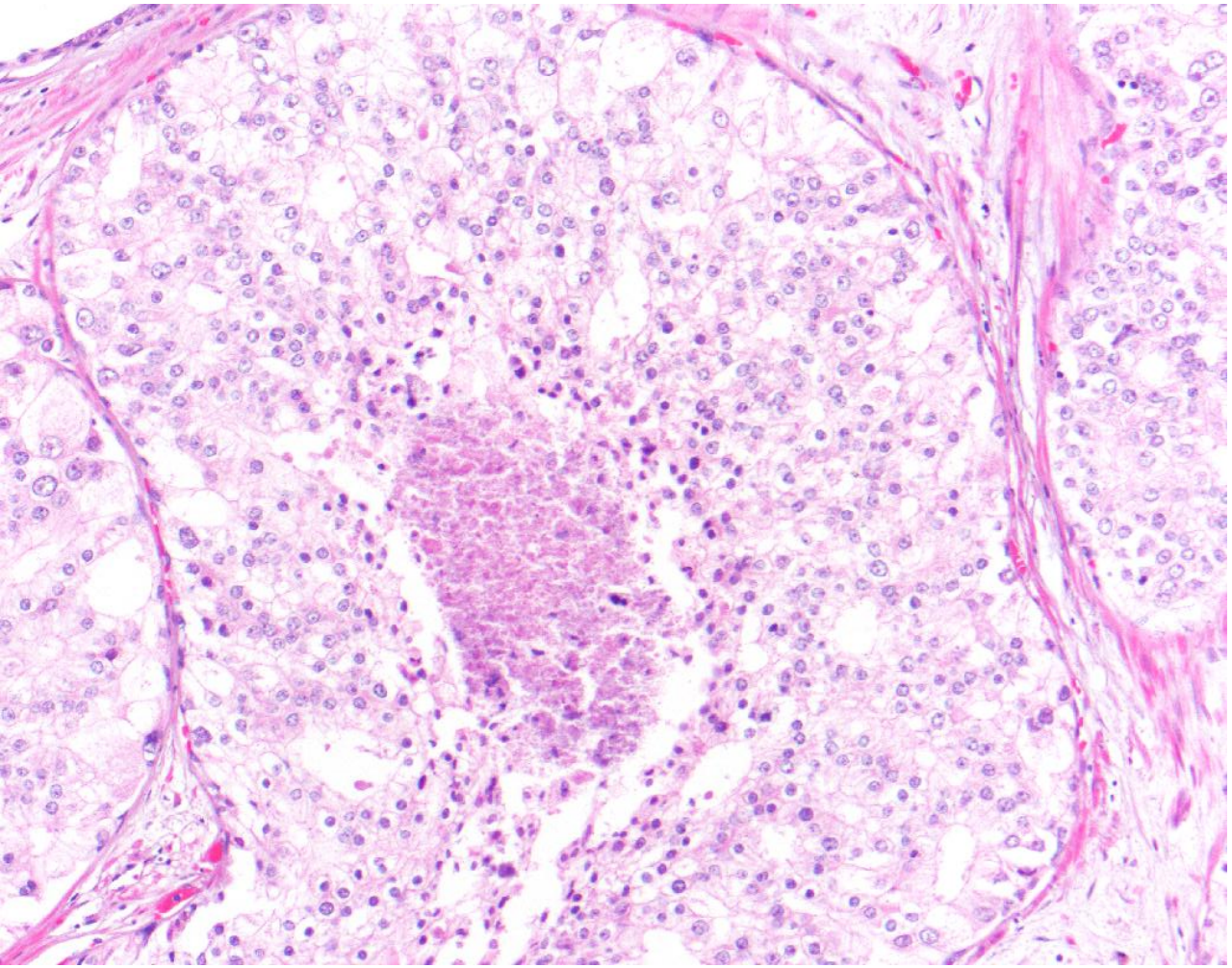
IDC-P WITH COMEDONECROSIS VS. GLEASON PATTERN 5

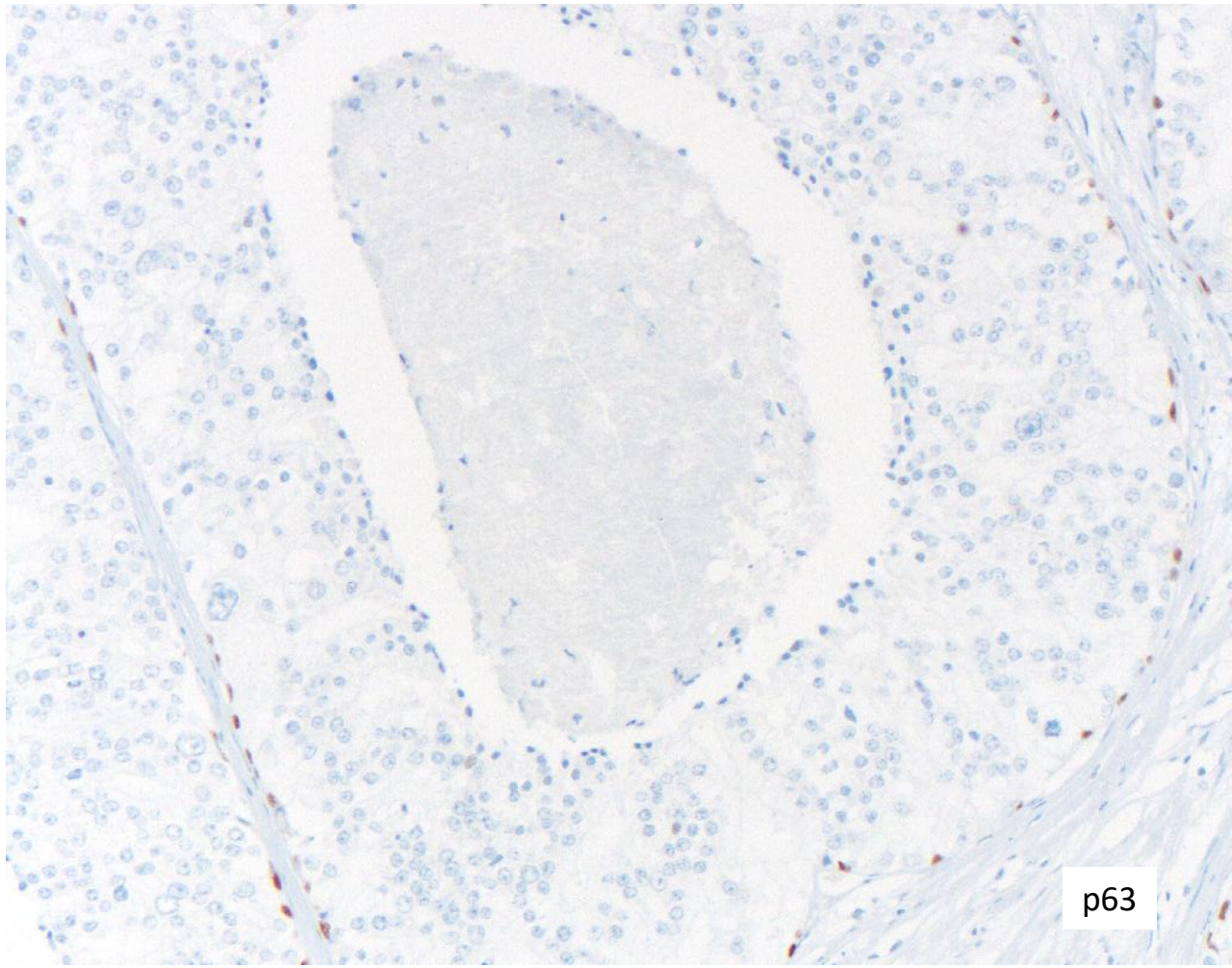




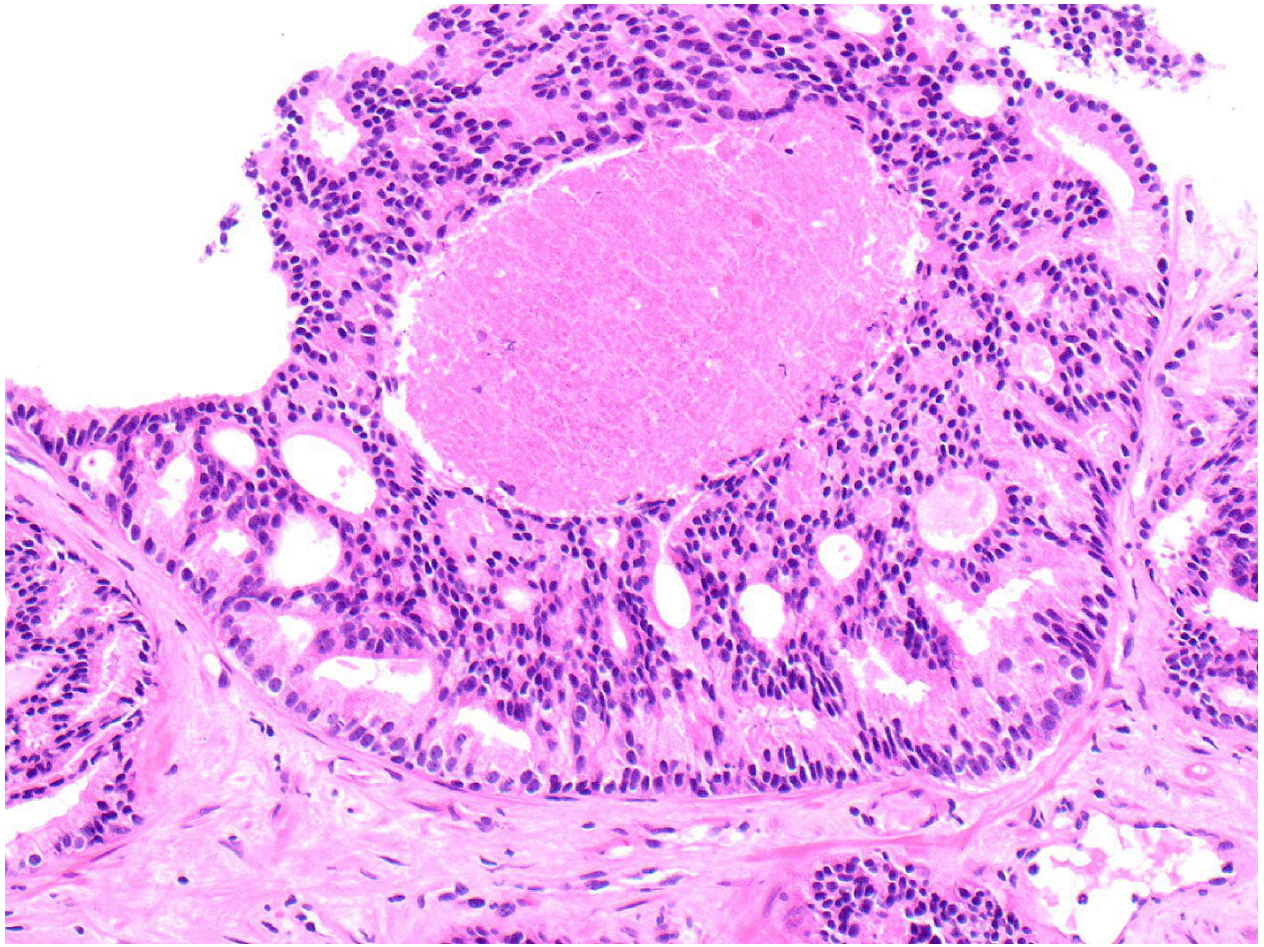
Fine et al. Am J Surg Pathol 2018

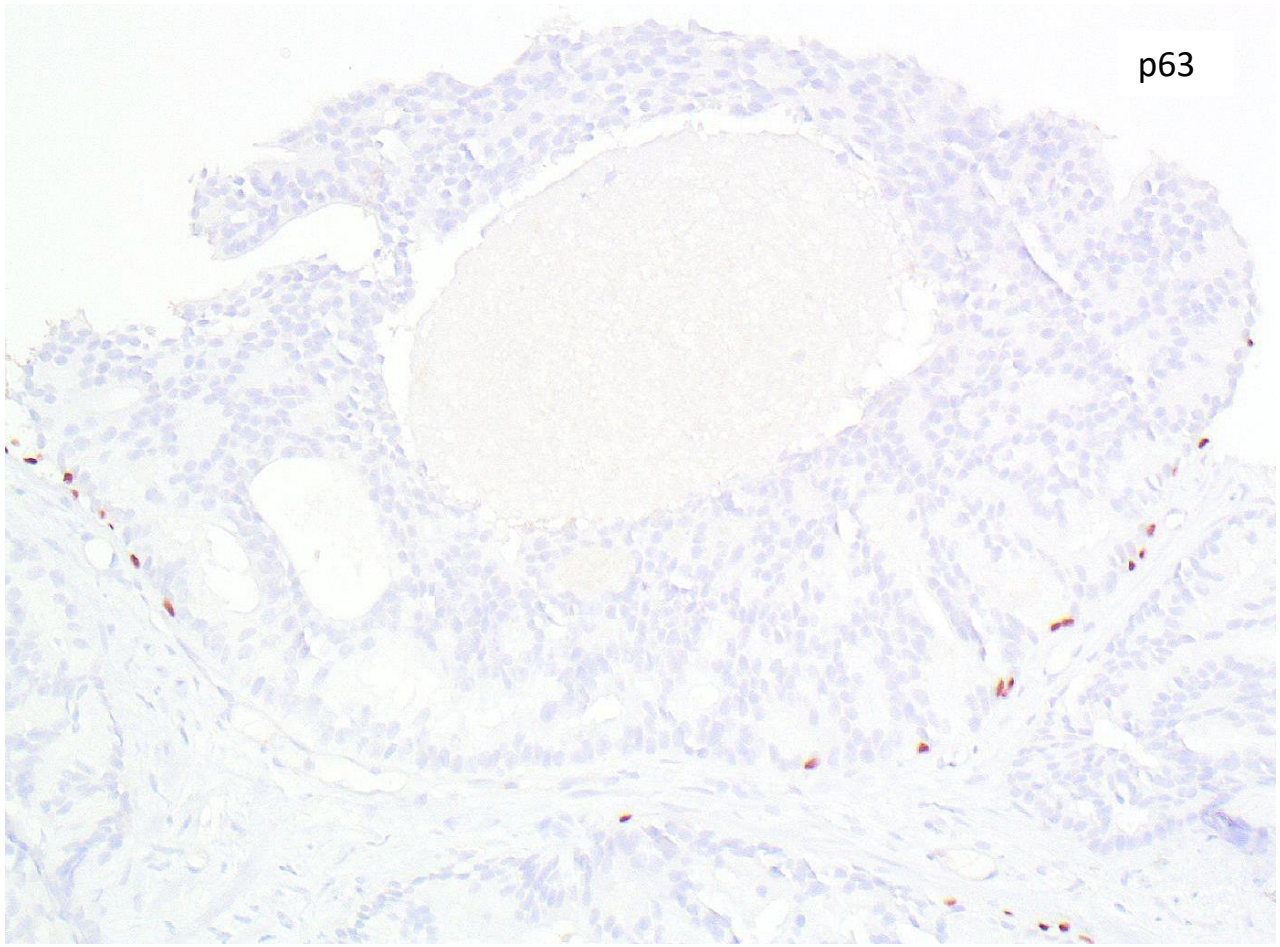
IDC-P WITH COMEDONECROSIS VS. GLEASON PATTERN 5



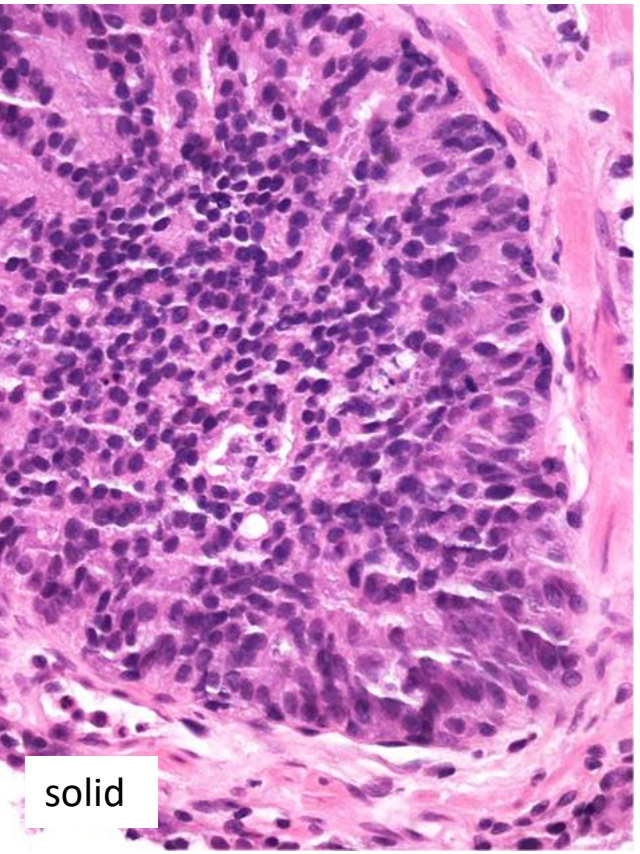


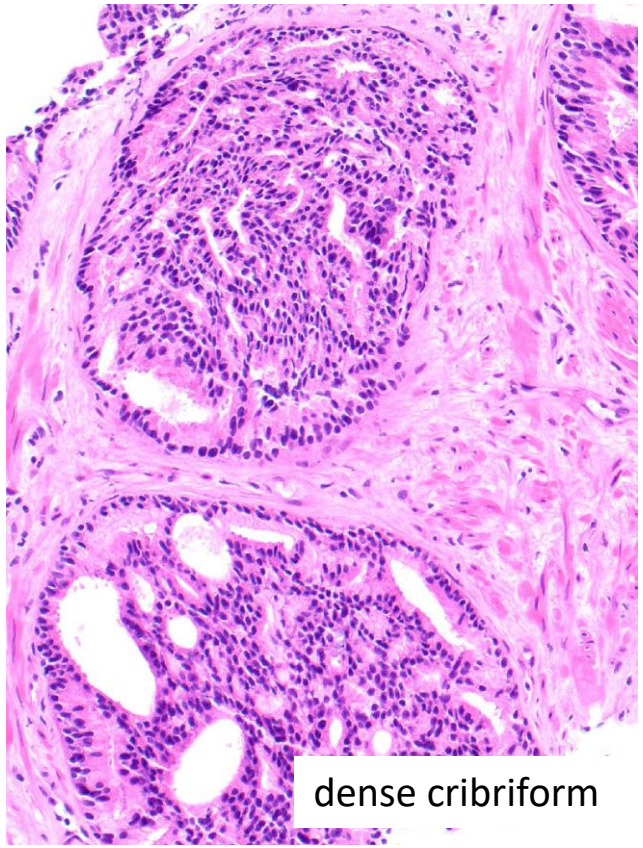
IDC-P WITH COMEDONECROSIS VS. GLEASON PATTERN 5



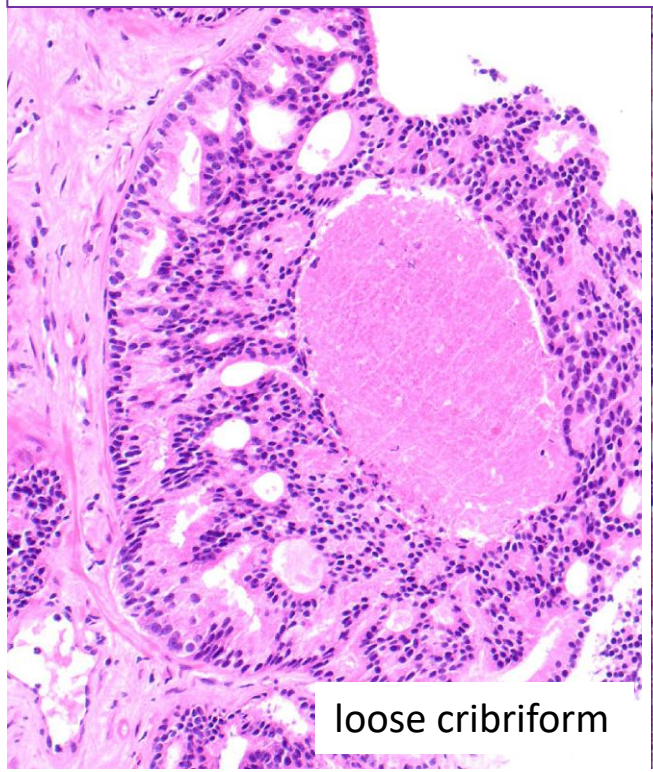


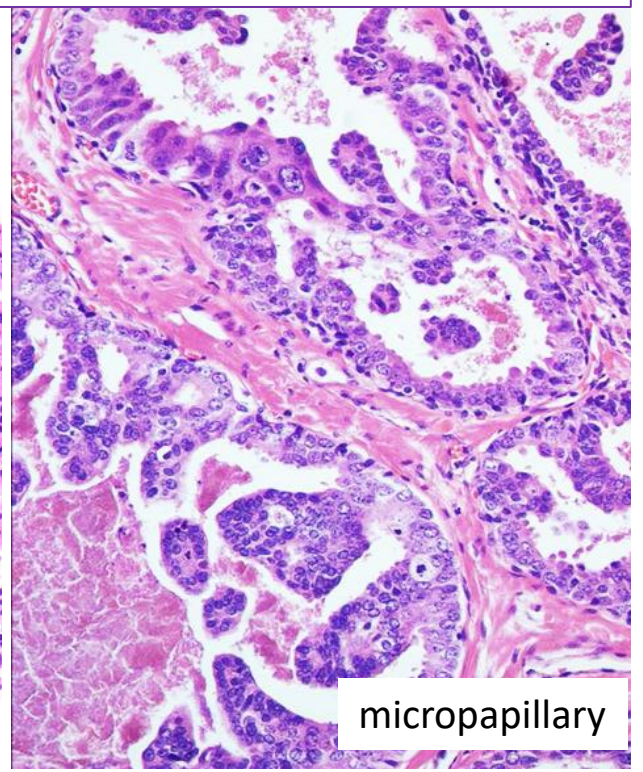
INTRADUCTAL CARCINOMA OF THE PROSTATE (IDC-P)





Marked cytologic atypia +/- comedonecrosis





- Presence of IDC-P associated with invasive PCA **should be noted**
- Isolated IDC-P on PBx (<1%) should **NOT** be **graded**
- Still controversial whether IDC-P should be incorporated into PCA grading

IDC-P

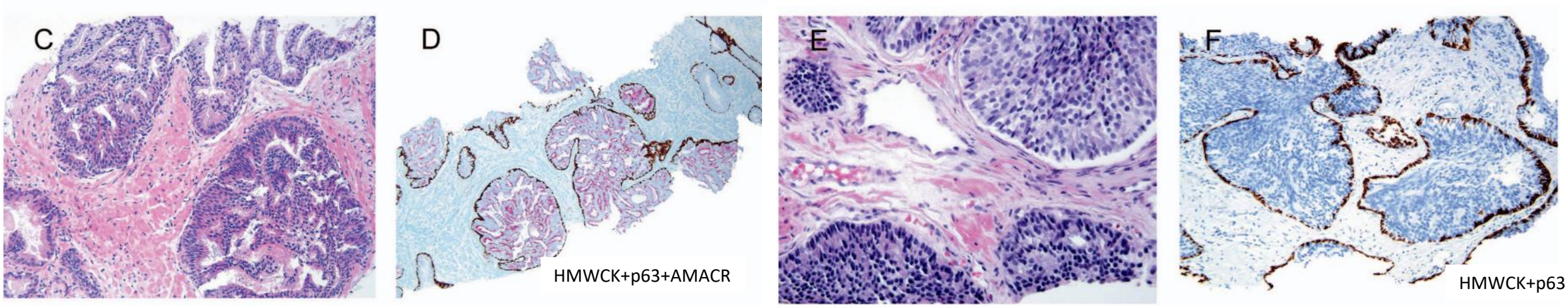


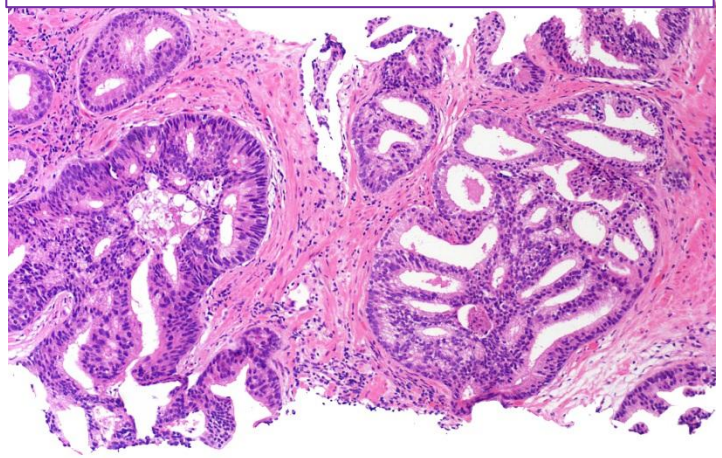
Table 8. Summary of Recommendations on Intraductal Carcinoma (IDC-P)

1	Report the presence of IDC-P in biopsy and radical prostatectomy specimens
2	Use criteria based on dense cribriform glands and/or solid nests and/or marked pleomorphism/necrosis. Dense cribriform glands are defined >50% of the gland composed of epithelium relative to luminal spaces; where the ratio is approximately equal, it is prudent to be conservative and diagnose the lesion as not meeting full criteria for IDC-P
3	When IDC-P is identified on prostate biopsy without concomitant invasive adenocarcinoma, add a comment stating that IDC-P is usually associated with high-grade prostate cancer
4	**Perform IHC for basal cell markers when the biopsy shows Gleason score 6 cancer and cribriform glands that include a differential diagnosis of IDC-P versus Gleason pattern 4 cancer**
5	**It is not necessary to perform basal cell IHC on needle biopsy and radical prostatectomy to identify IDC-P if the results of the stains would not change the overall highest Gleason score/Grade Group for the case**
6	**Do not include IDC-P in determining the final Gleason score on biopsy and/or radical prostatectomy**

GUPS Grading of Prostate Cancer. Epstein et al Arch Pathol Lab Med 2020

IDC-P: clinical significance

Isolated IDC-P

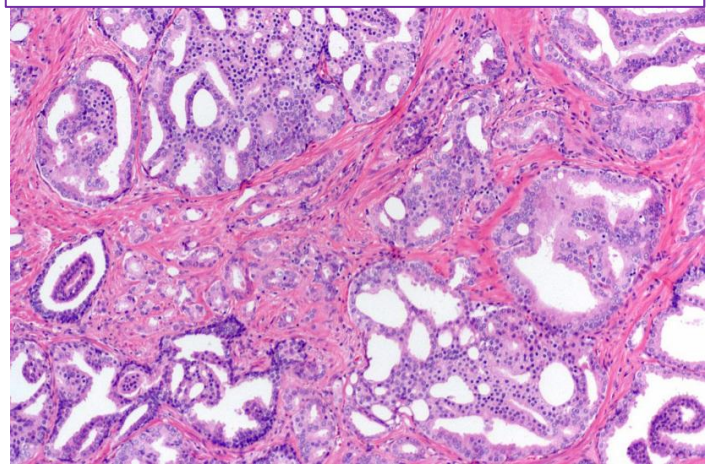


Impact decision for therapy

Definitive therapy or repeat Bx

In preop. models improves prediction of stage on RP

IDC-P + PCA

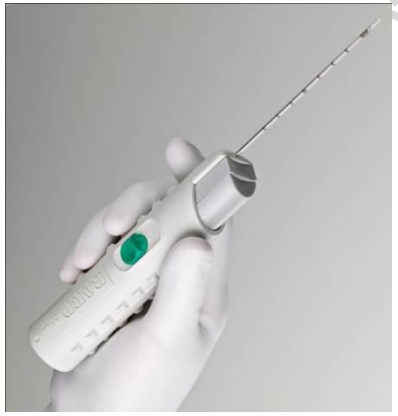


Prognostic factor to predict outcome

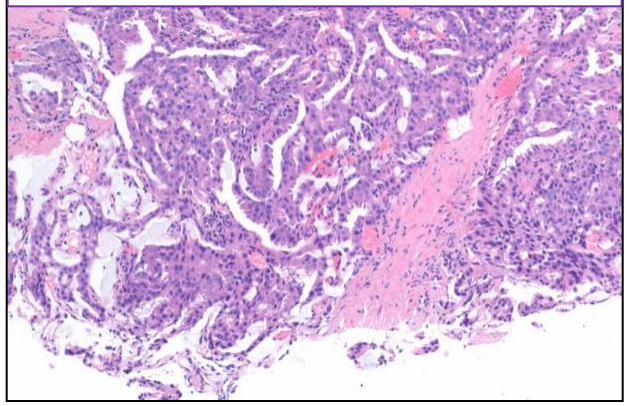
Reduced PFS
Increased BCF
Early metastatic disease
Hormonal resistance

Kimura et al. Prostate 2014; Saeter et al. Prostate 2017; Porter et al. BJU Int 2018; Gandhi et al. Am J Surg Pathol 2020

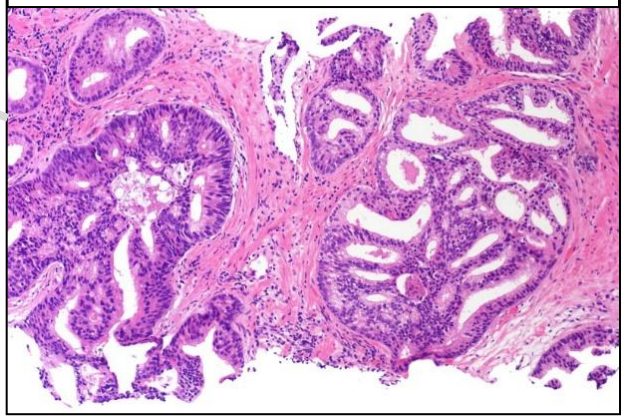
Unfavorable Pathology with Clinical Implications



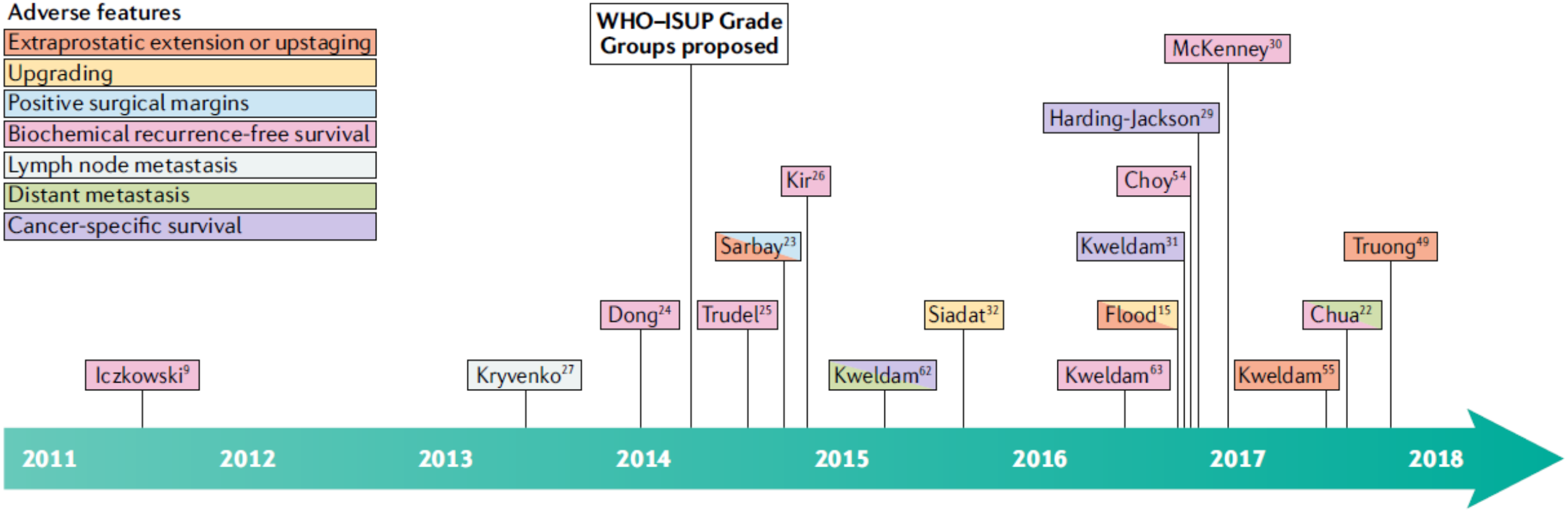
Cribriform architecture



Intraductal carcinoma



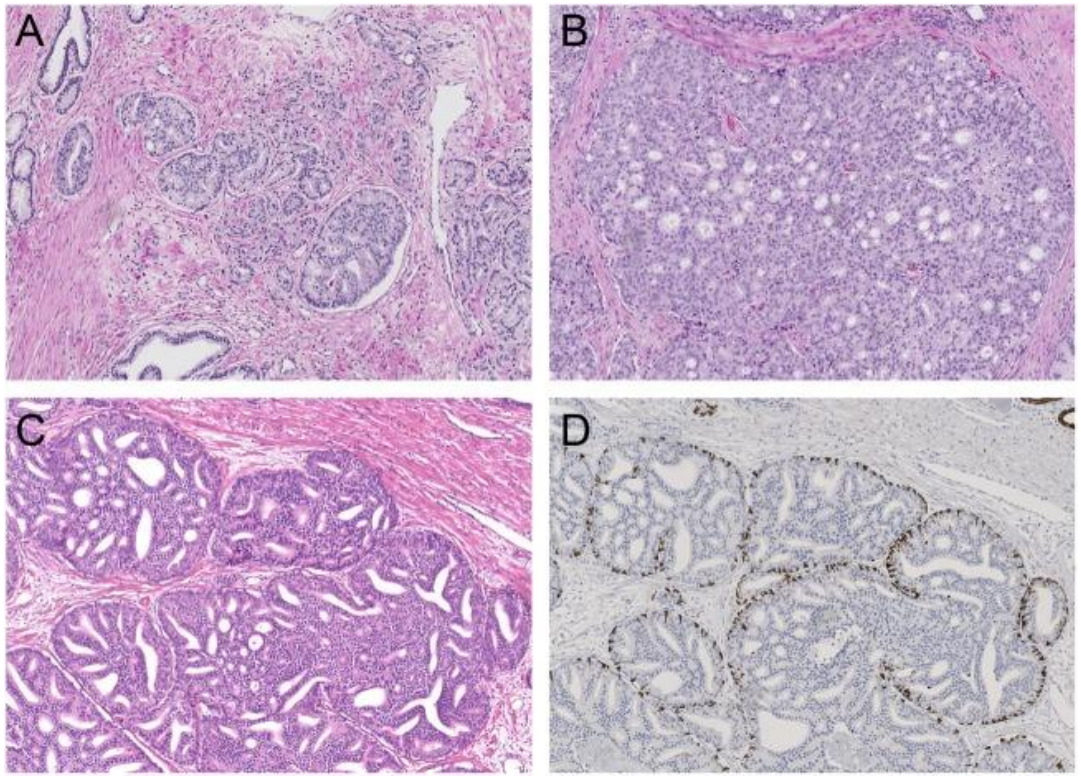
Cribriform morphology



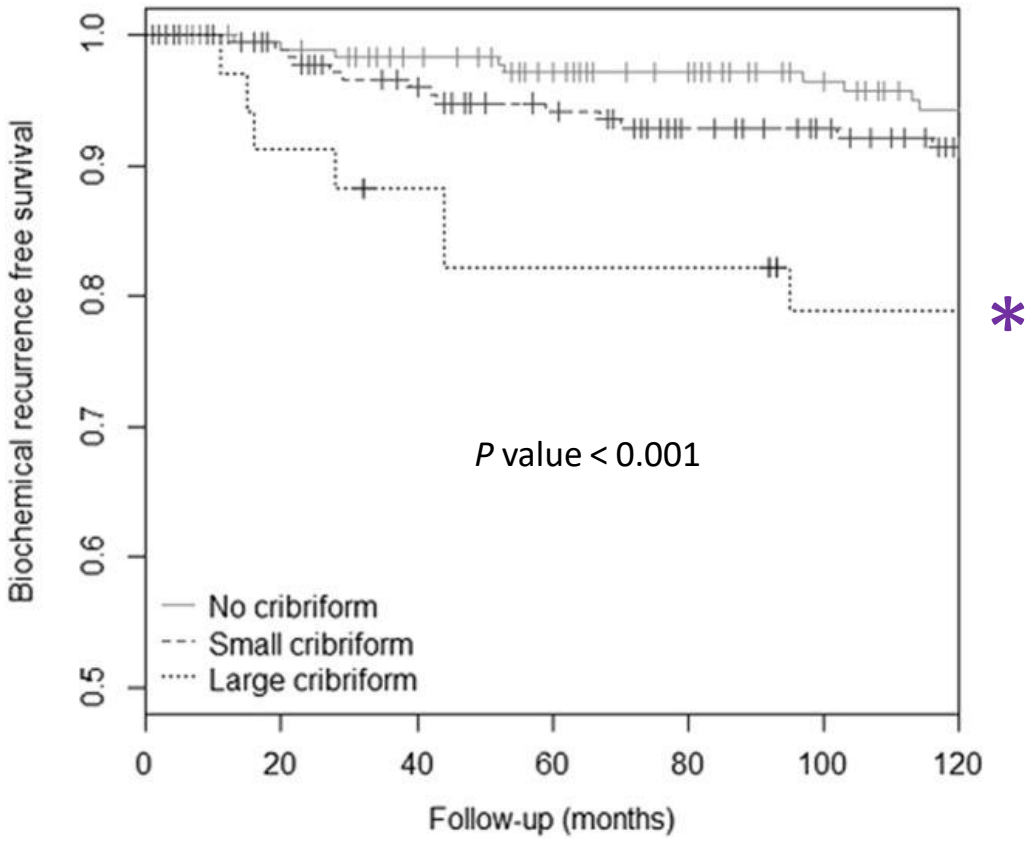
- Cribriform morphology is recognized as most aggressive GP4 subtype & associated with adverse outcome
- Routine reporting of cribriform morphology on Bx should be encouraged

Truong et al. Nature Reviews. Urology 2018

Large cribriform growth pattern identifies ISUP grade 2 prostate cancer at high risk for recurrence and metastasis

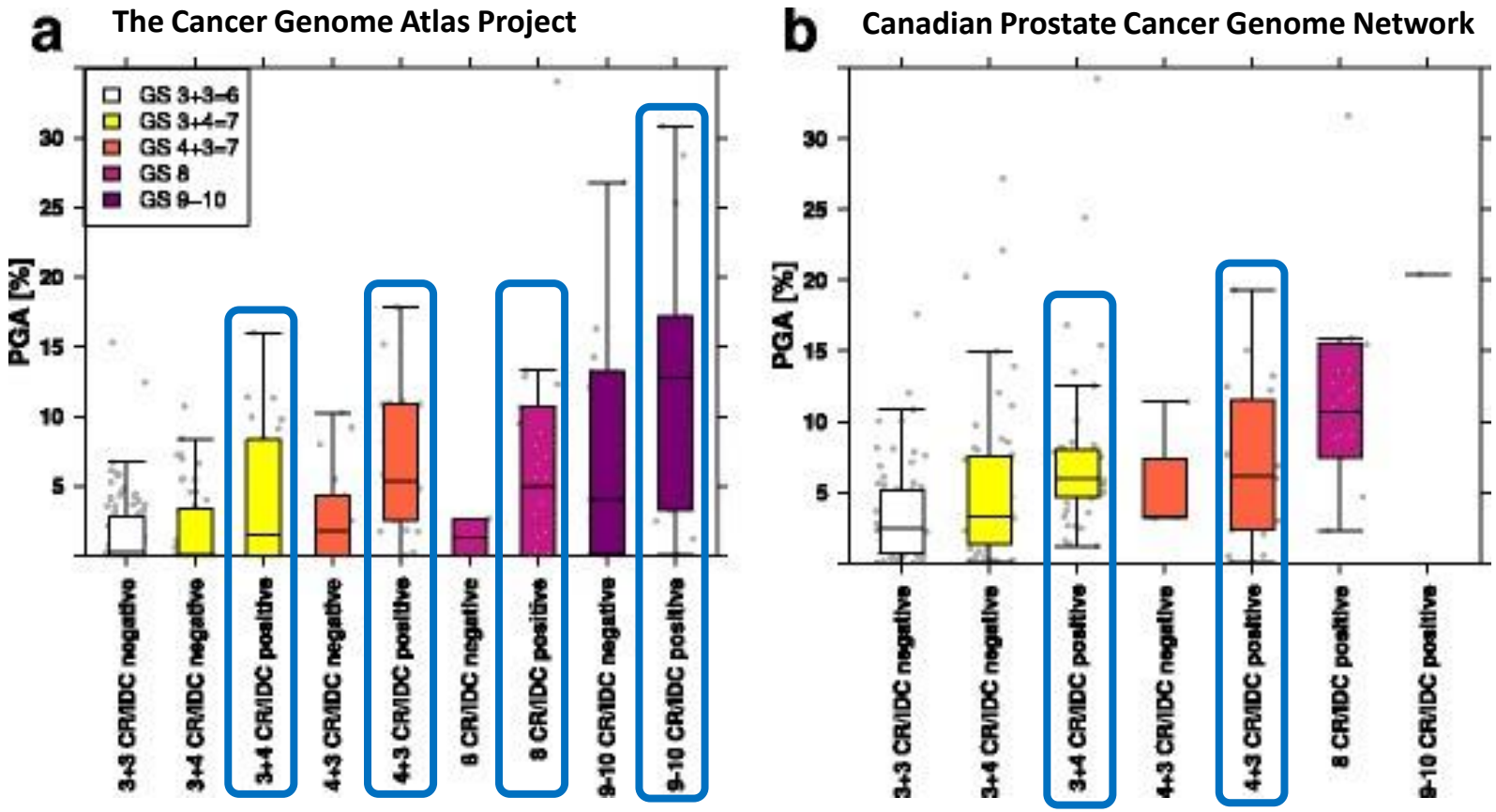


Large cribriform glands: diameter of at least **2X** size of adjacent benign glands



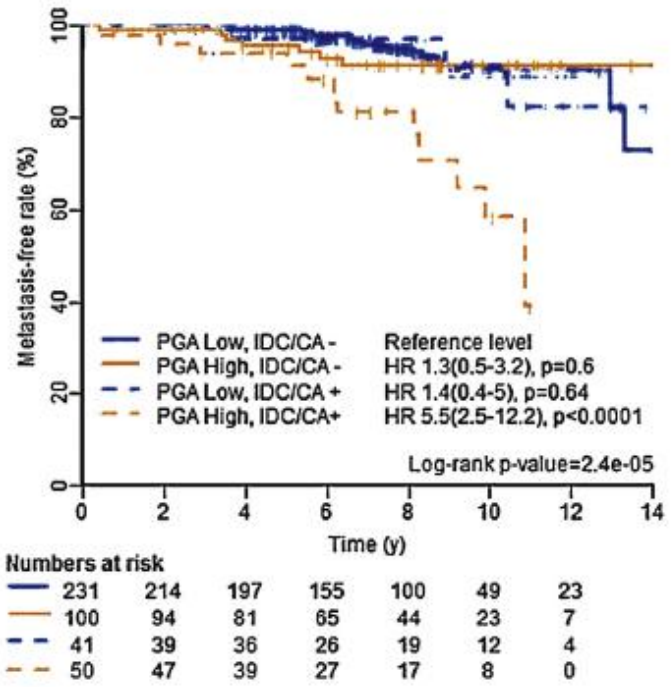
Hollemans et al. Mod Pathol 2019

Cribriform and IDC-P are associated with increased genomic instability and distinct genomic alterations

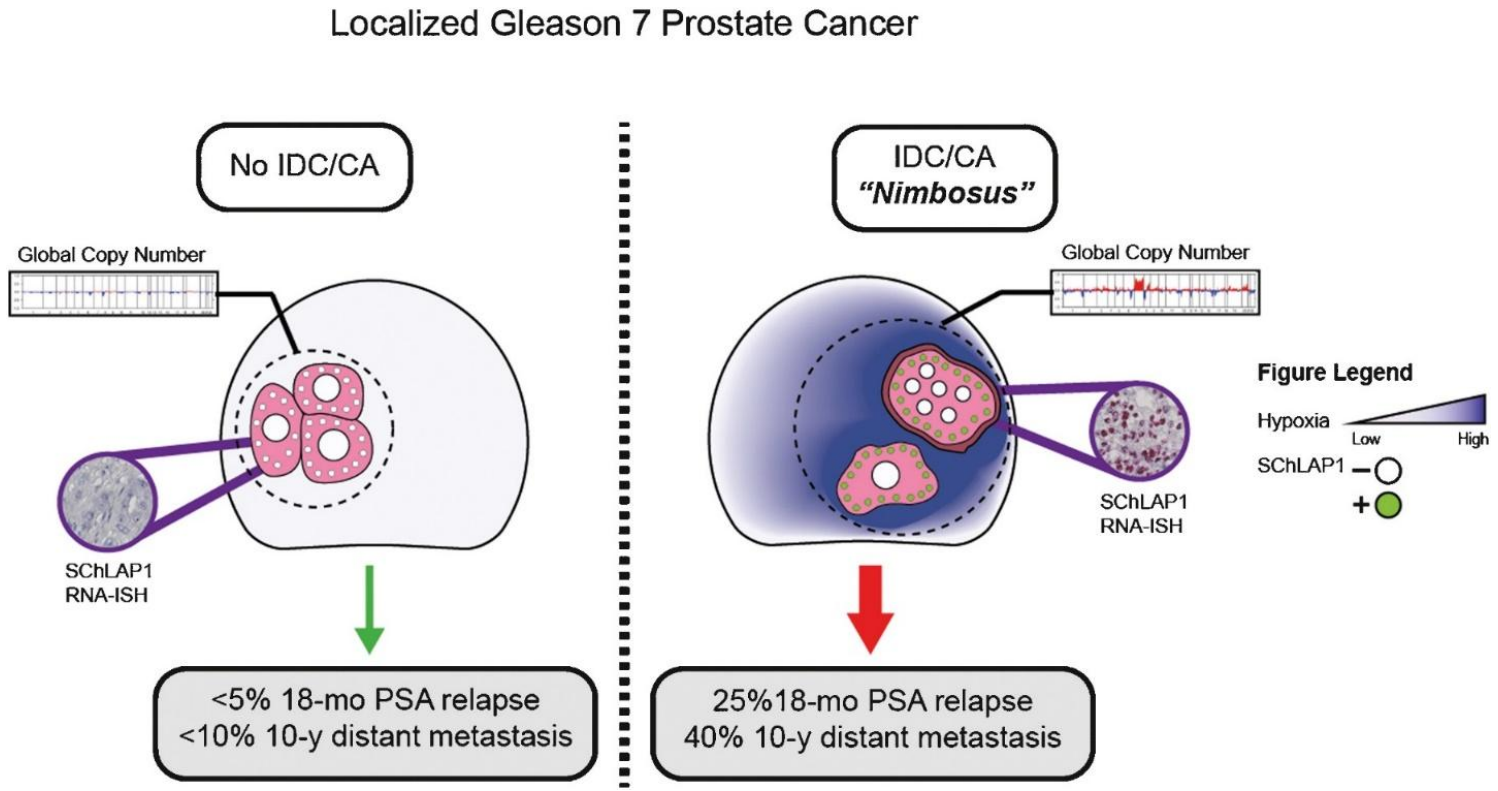


Bottcher et al. BMC Cancer 2018

"Nimbosus": A constellation of unfavorable molecular characteristics co-occur with intraductal and cribriform subpathologies in PCA



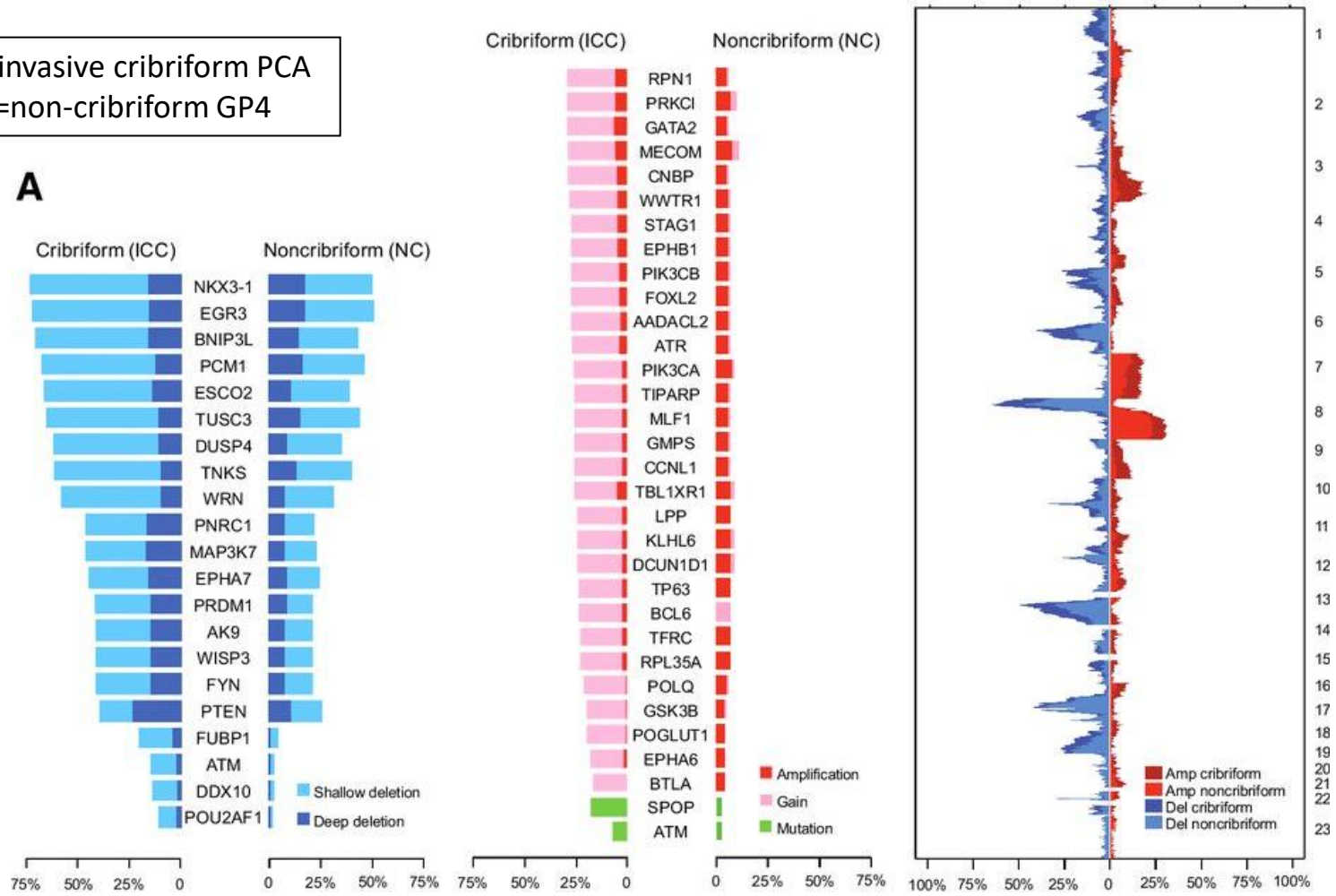
1325 men with NCCN low to high risk PCA treated with RP or radiotherapy



Chua et al. Eur Urol. 2017;72:665-674

Genetic and epigenetic determinants of aggressiveness in cribriform PCA

ICC=invasive cribriform PCA
NC4=non-cribriform GP4



ICC and NC4 have distinctive molecular features:

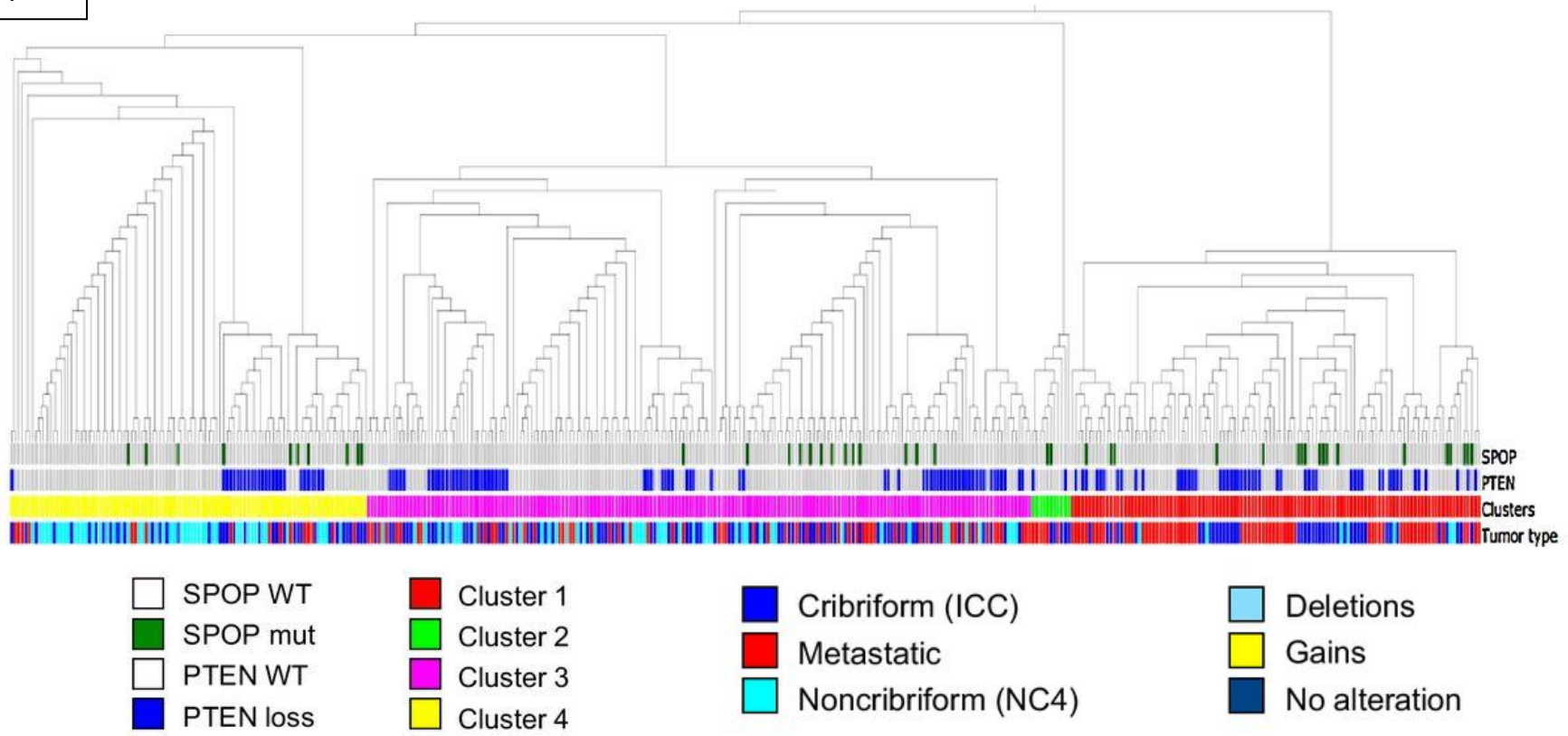
- increased SCNV
- increased *SPOP*^{mut} and *ATM*^{mut}
- enrichment for *mTORC1* and *MYC* pathways
- increased methylation of selected genes

Elfandy et al. Mol Cancer Res 2019

Unsupervised clustering analysis of ICC, NC4 and metastatic PCA

ICC=invasive cribriform PCA
NC4=non-cribriform GP4

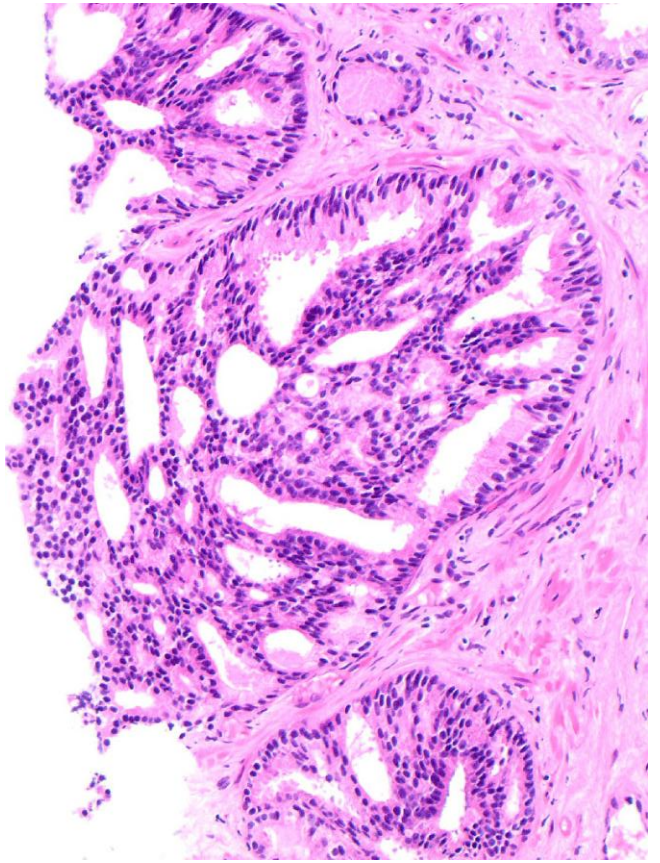
- **ICC** clustered more closely to **metastatic PCA** than NC4
- ICC more likely to develop **lethal cancer, independent from GS**



Elfandy et al. Mol Cancer Res 2019

HEREDITARY TUMORS SYNDROMES

- Germline (or somatic) alterations in DNA repair genes are present in 20% of aggressive primary and metastatic PCA
- **IDC-P** and **cribriform histology** are more likely to harbor DNA repair genetic defect
- Germline genetic testing, with or without pretest genetic counseling, is recommended for patients with IDC-P



TAKE HOME MESSAGE

- Familiarity with prostatic lesion with “cribriform” architecture will assist pathologists to accurately classify benign and malignant lesions
- Recognition of IDC-P is critical, particularly on needle Bx as it carries significant implications for management
- IDC-P and cribriform GP4 represent unfavorable pathology with clinical implications and should be reported in Bx and RP specimens

THANK YOU!

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SCHOOL OF MEDICINE