

Prostate Cancer: Diagnostic Criteria and Ancillary Testing

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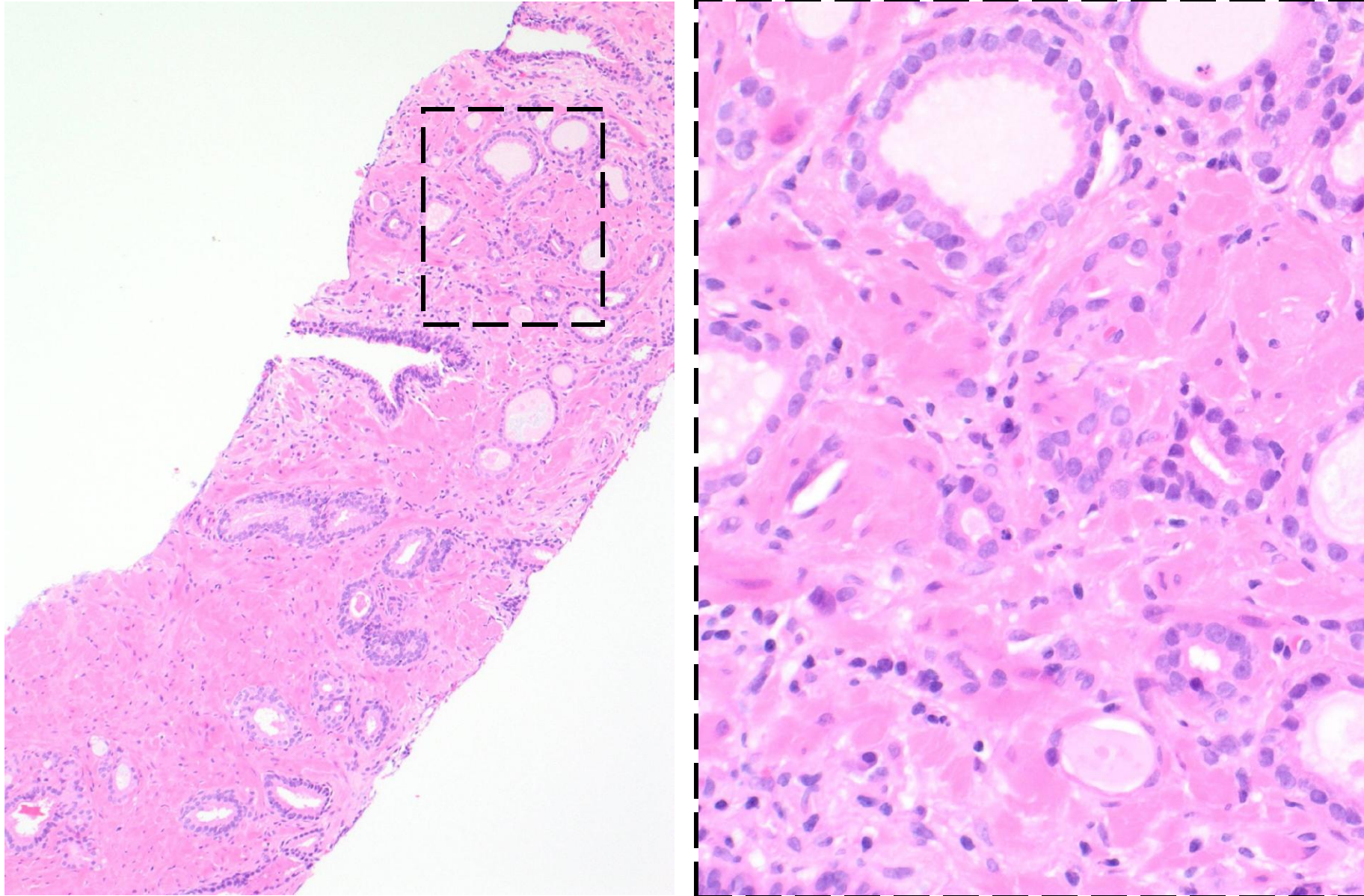
The C. Bruce Alexander Endowed Professorship in Pathology

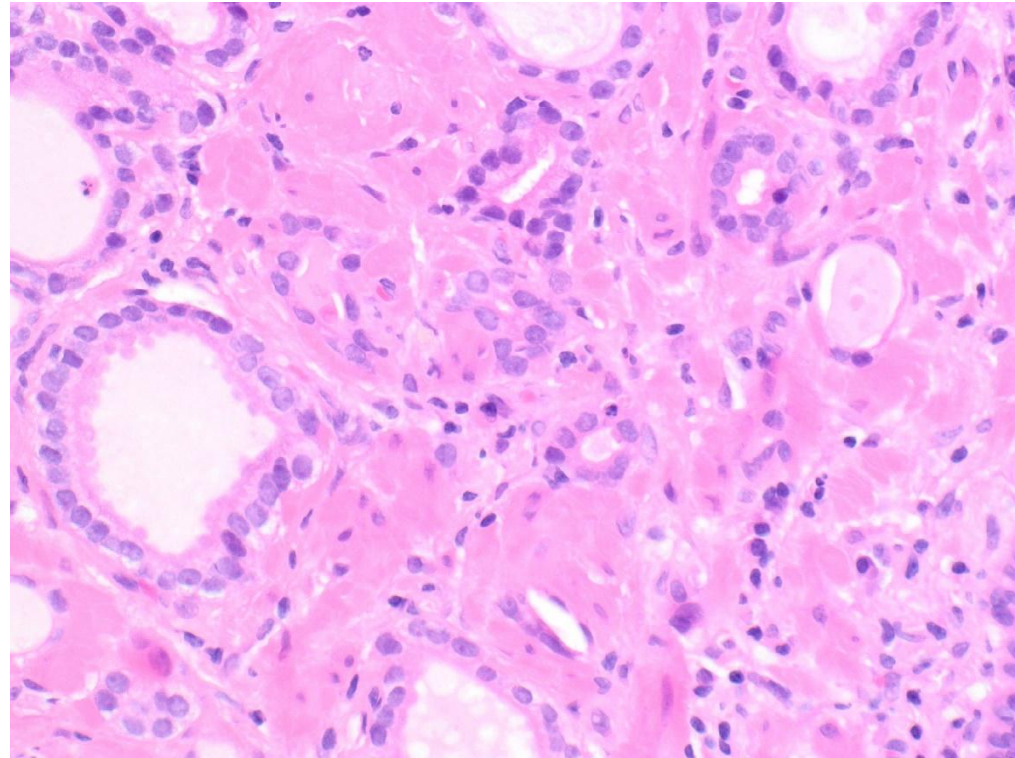
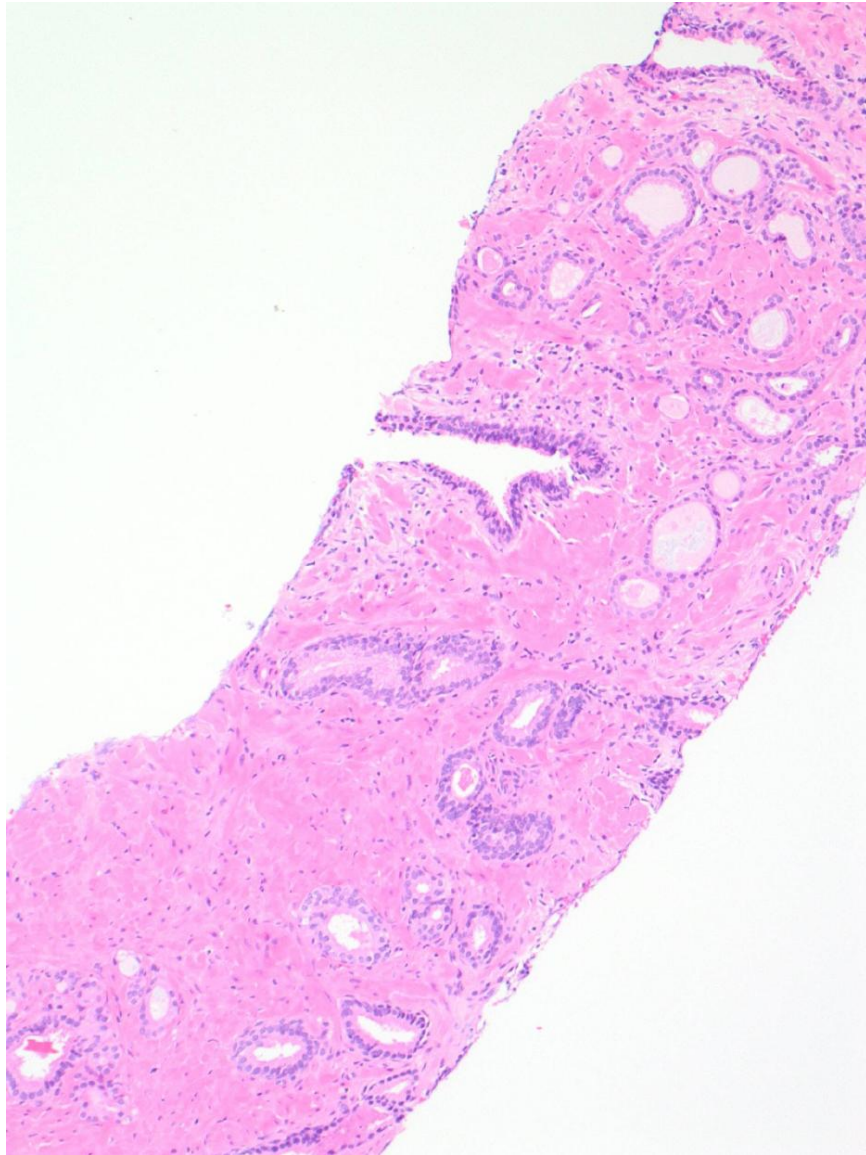


OBJECTIVES

- Review histologic criteria for diagnosing PCA
- Discuss diagnostic features of PCA
- Review use of IHC stains

- 56 year-old man with elevated PSA

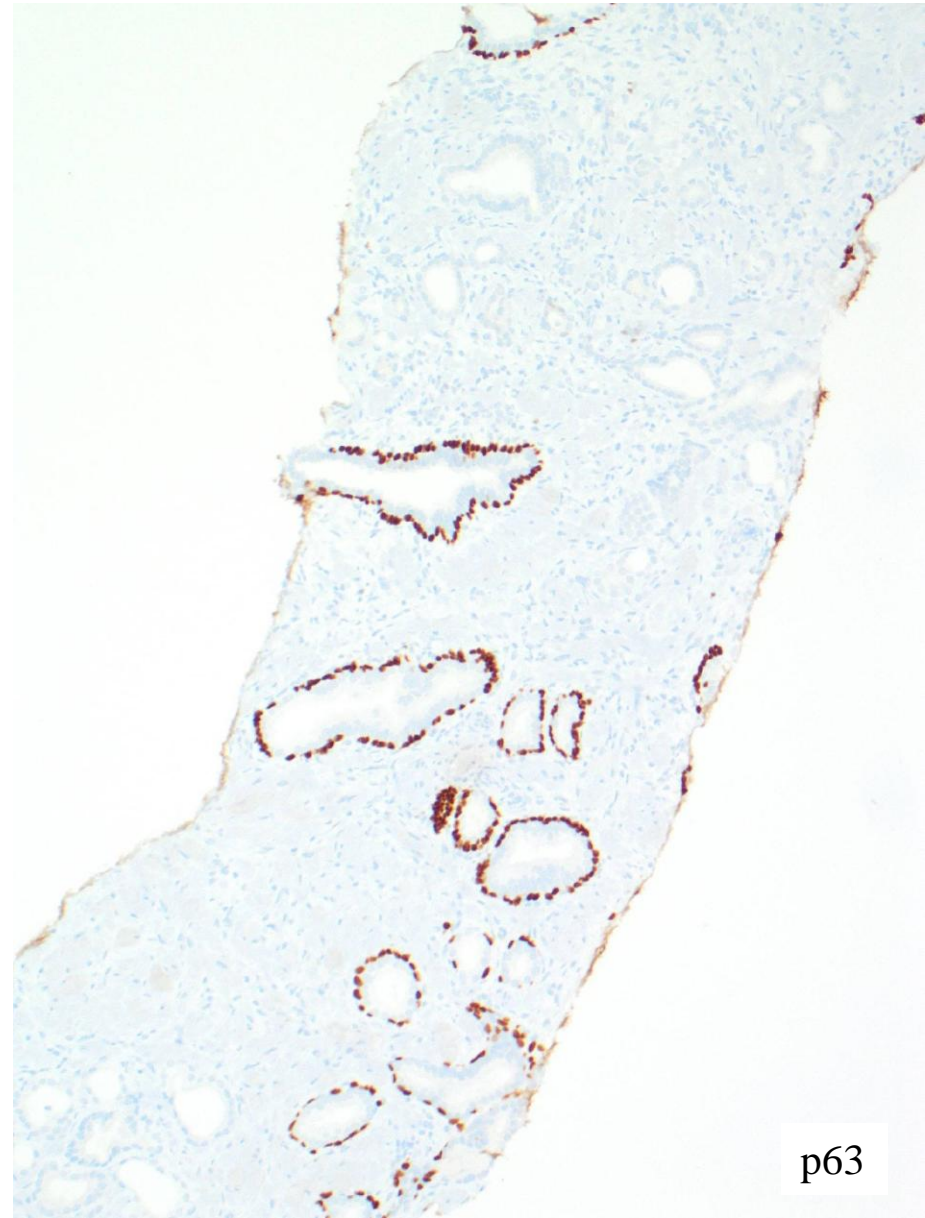
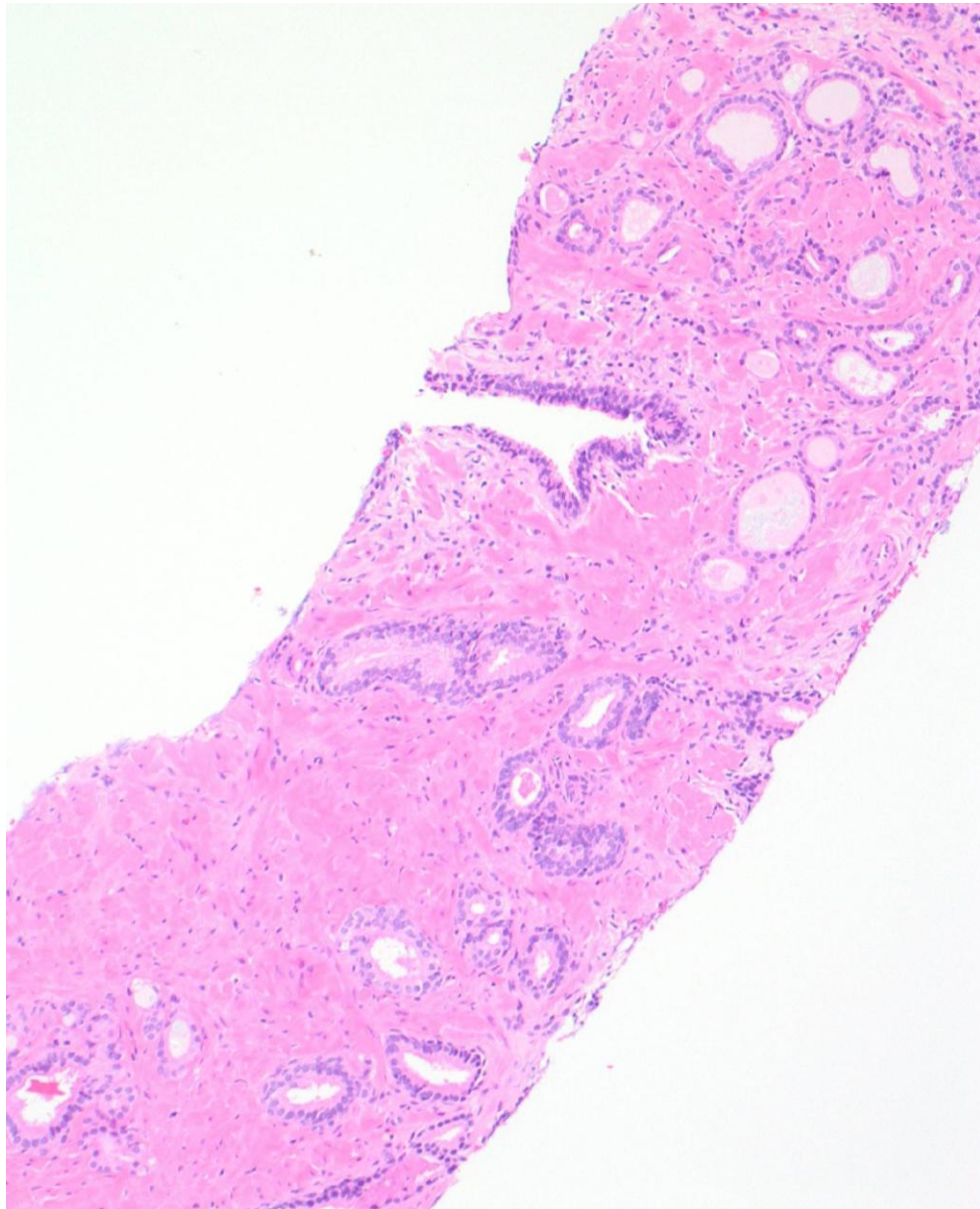




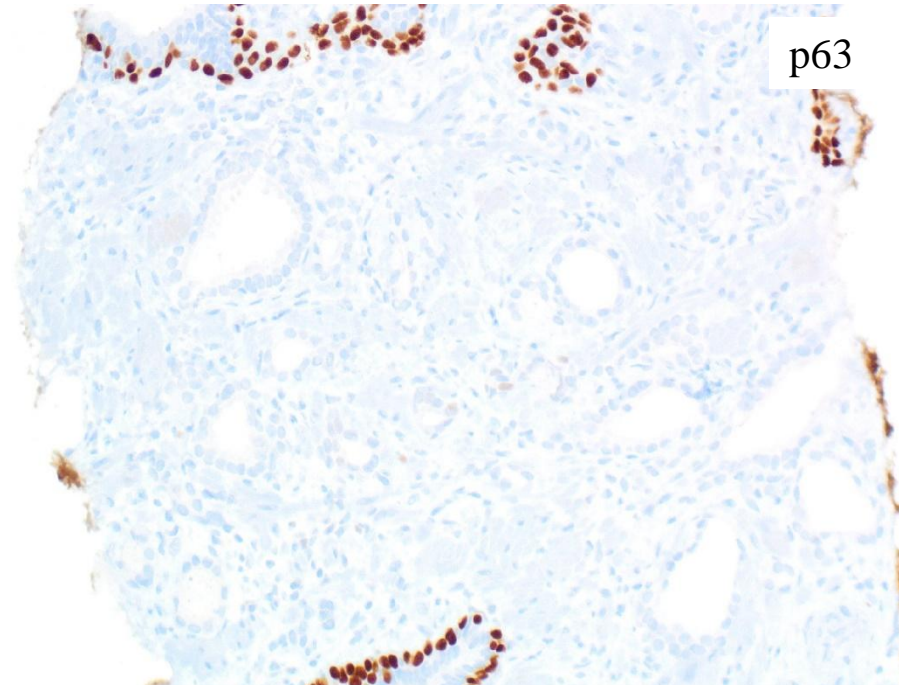
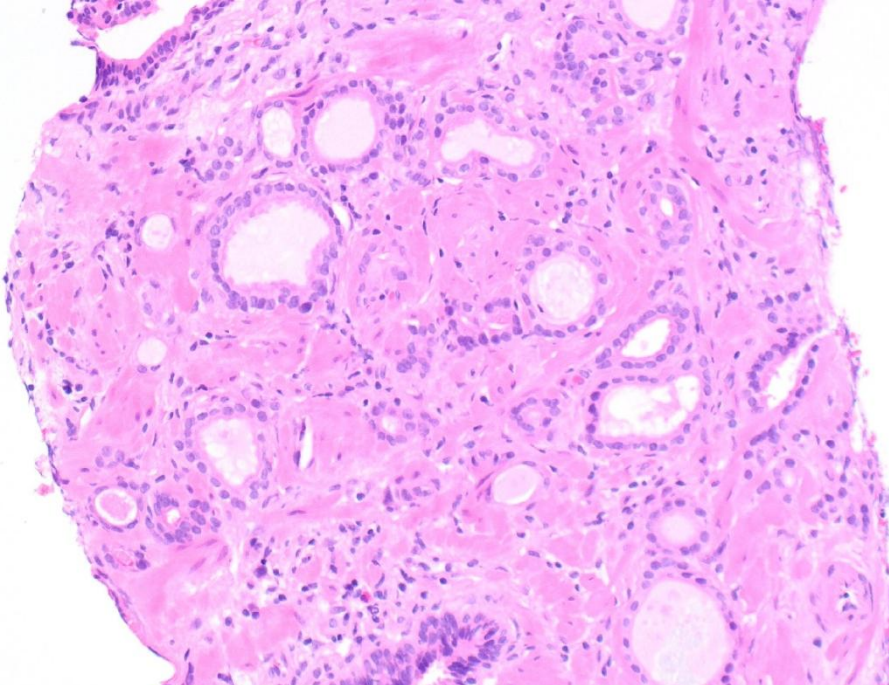
How would you best classify this lesion?

- A. Adenosis
- B. Prostate cancer with atrophic features
- C. Partial atrophy

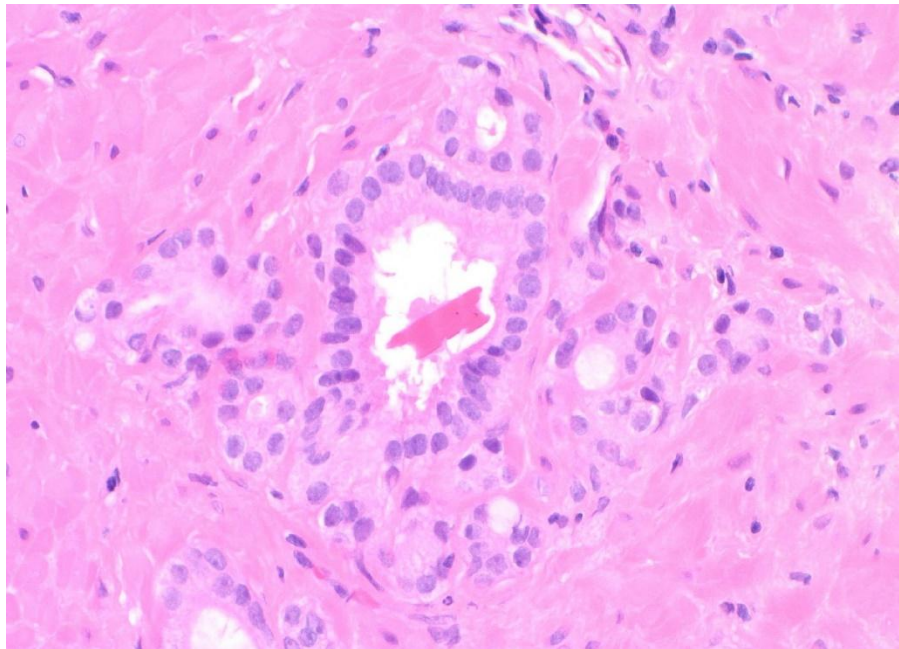
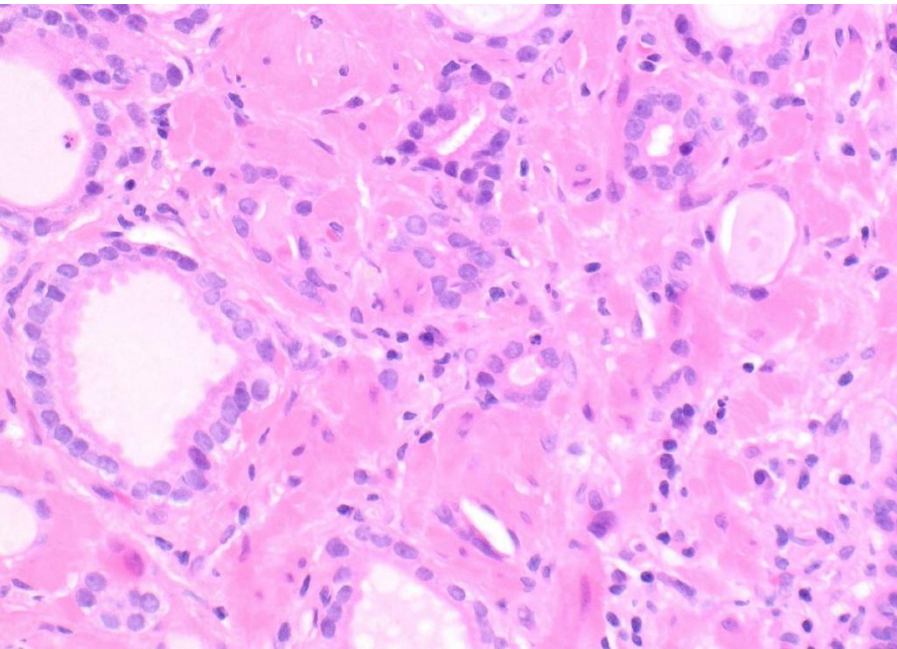
Prostate cancer with atrophic features



p63



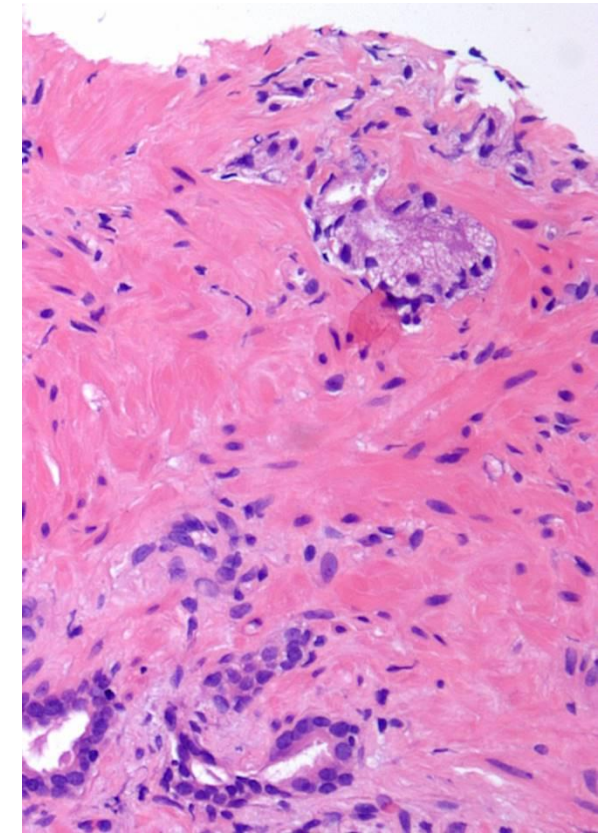
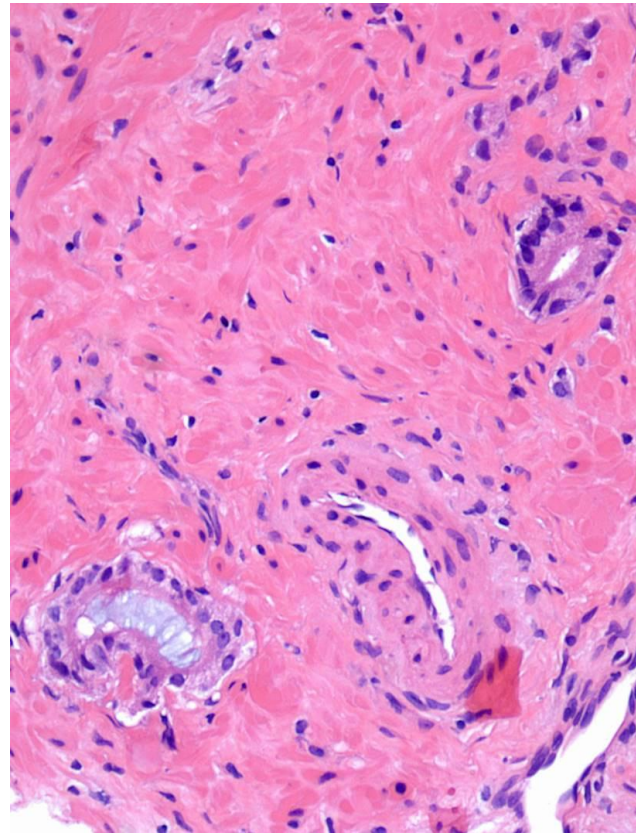
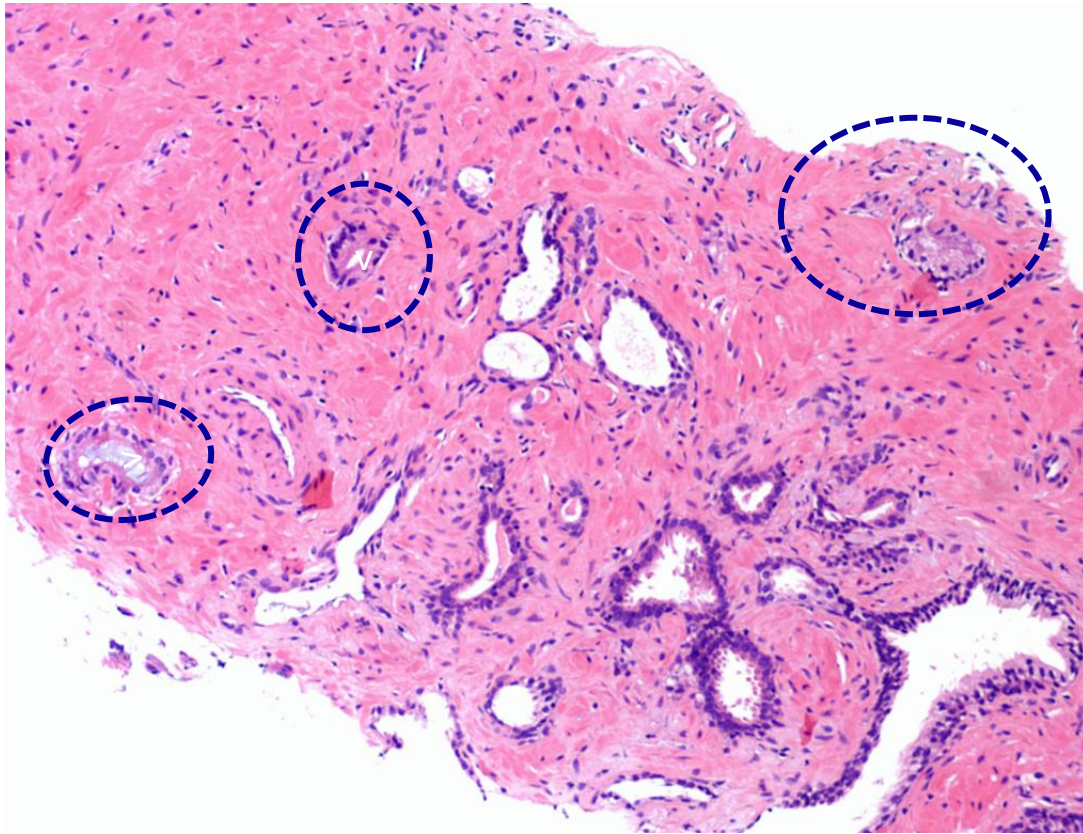
Prostate cancer with atrophic features



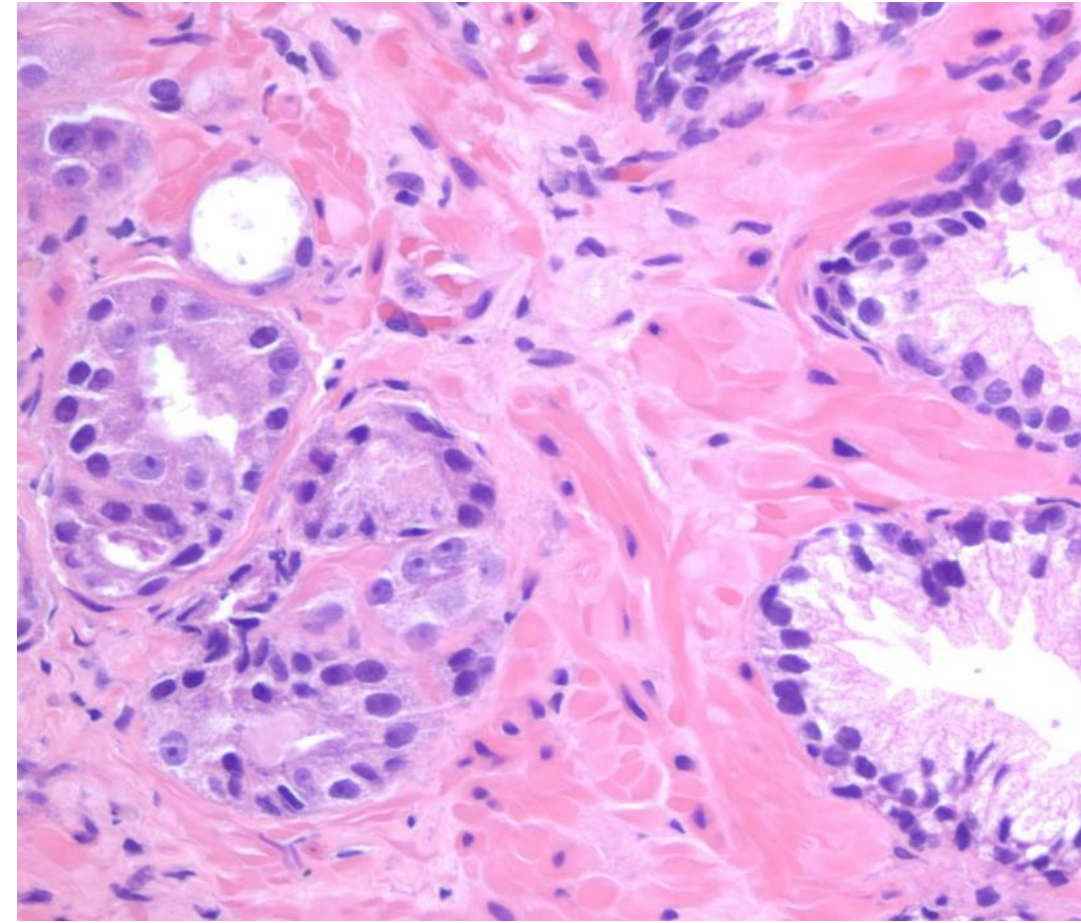
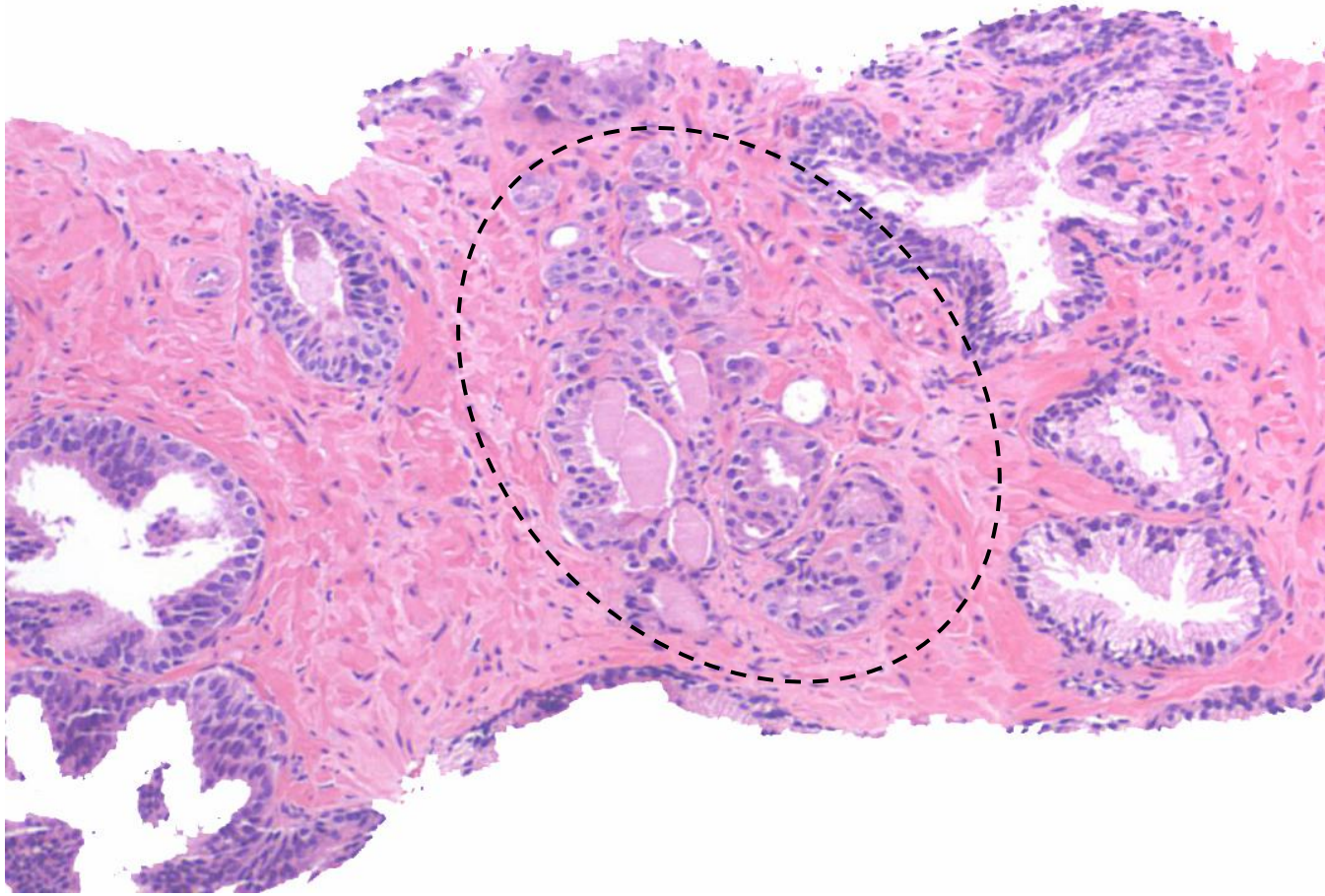
Diagnosis of Prostatic Adenocarcinoma in Needle Core Biopsy

- PSA screening has resulted in prostate needle core biopsy specimens with decreasing volume of prostate cancer
- Infiltrative architectural pattern of growth can be difficult to appreciate on narrow (18-gauge) needle biopsy specimen
- Minimal or limited PCA is defined as involving <5% of biopsy tissue or measuring <1 mm

Limited Prostate Cancer (PCA) on needle biopsy



Scan biopsy at low- and high-power magnification



Limited Prostate Cancer (PCA) vs. Atypical Small Acinar Proliferation (ASAP/ATYP)

In assessing small foci of atypical glands on NBx, one looks for differences between benign glands and atypical glands in terms of:

- Nuclear features
- Cytoplasmic features
- Intraluminal content

Histological Criteria for Diagnosis of Limited PCA

	ASAP/ATYP (n=56)	PCA (n=100)	P value
Linear extent (mm)	0.4	0.8	<0.0001
# of acini	11 ± 10	17 ± 14	<0.0001
Infiltrative growth	75%	100%	<0.0001
Mitotic figures	0%	10%	<0.01
Prominent nucleoli in ≥10% of cells	55%	100%	<0.0001
Nuclear hyperchromasia	44%	9%	<0.0001
Nuclear enlargement	1.2	1.8	0.0002
Luminal blue mucin	6%	33%	<0.0001
Concomitant HGPIN	23%	57%	<0.0001
Moderate-to-severe atrophy	59%	35%	0.003

Histological Criteria for Diagnosis of PCA

	Benign glands (n=100)	PCA (n=150)	P value
Prominent nucleoli	25%	94%	<0.001
Marginated nucleoli	7%	88%	<0.001
Multiple nucleoli	0%	64%	<0.001
Blue-tinged mucinous secretions	0%	52%	<0.001
Intraluminal crystalloids	1%	41%	<0.001
Intraluminal amorphous eosinophilic material	2%	87%	<0.001
Glomerulations	0%	15%	<0.001
Perineural invasion	0%	22%	<0.001
Retraction clefting	7%	39%	<0.001
Invasion of adipose tissue	0%	1%	>0.99

Histologic Criteria for Diagnosis of Limited PCA

Major criteria

Architectural:

- Infiltrative growth pattern*
- Small crowded glands
- Confluent/irregular cribriform glands
- Single cells

Loss of basal cells*

Nuclear atypia:

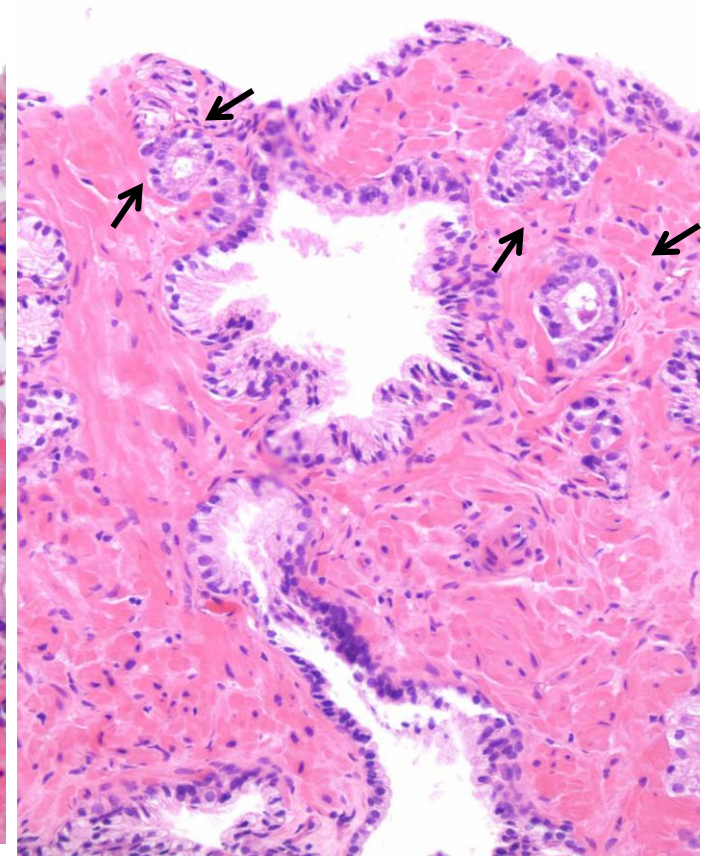
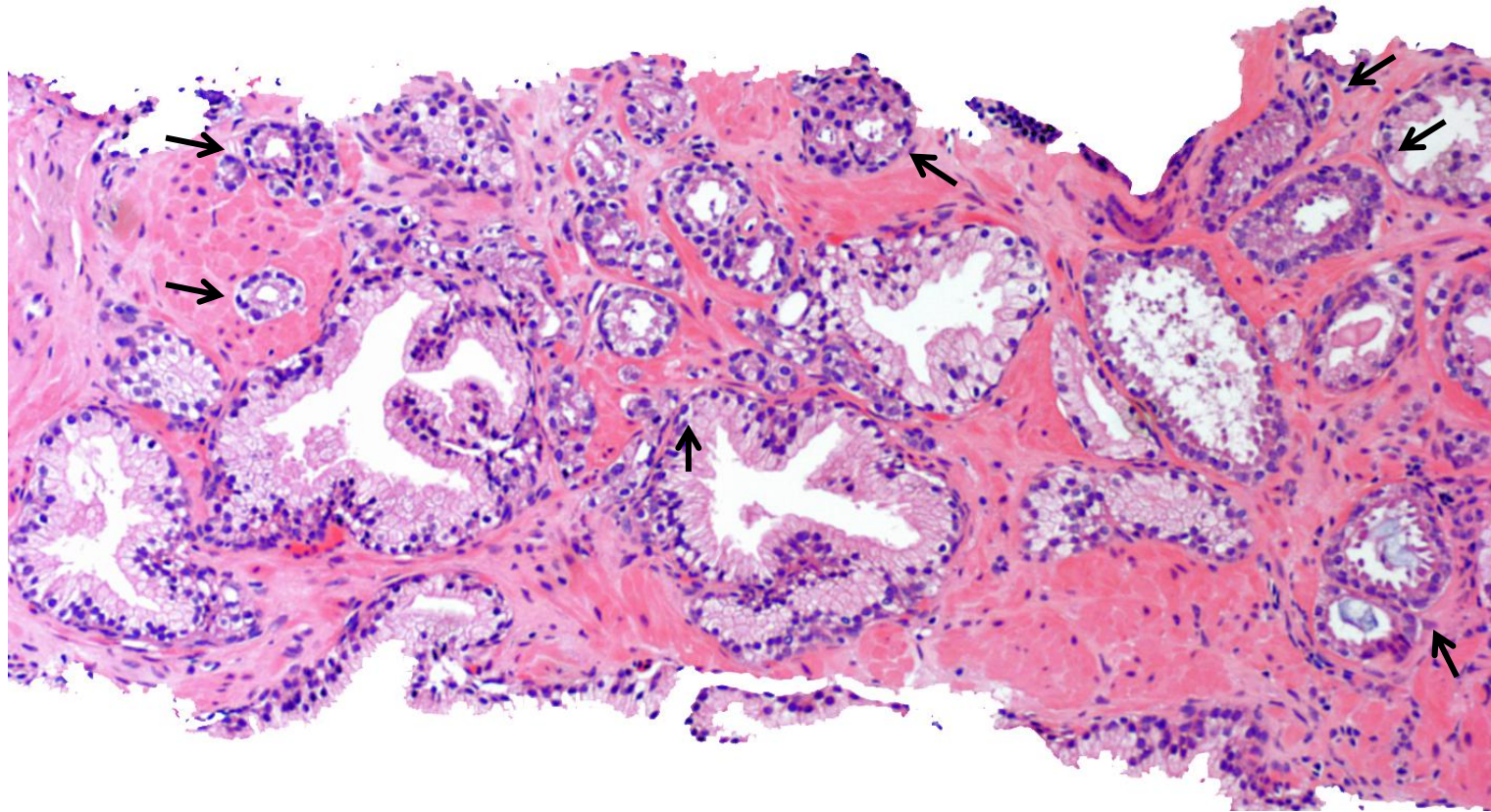
- Nuclear enlargement
- Prominent nucleoli*

Minor criteria

- Amphophilic cytoplasm
- Straight luminal borders
- Pink amorphous secretions
- Intraluminal blue mucin
- Intraluminal crystalloids
- Adjacent HGPIN
- Mitotic figures
- Nuclear hyperchromasia

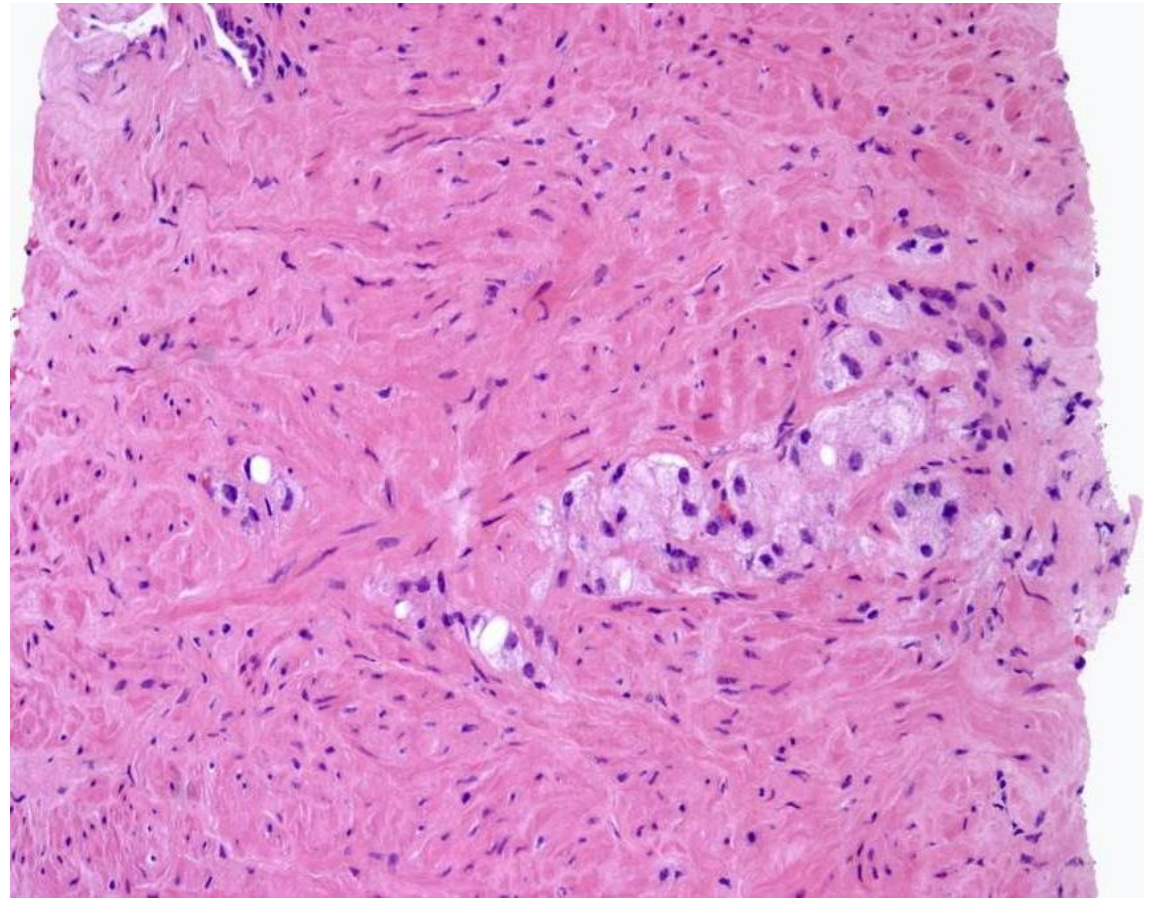
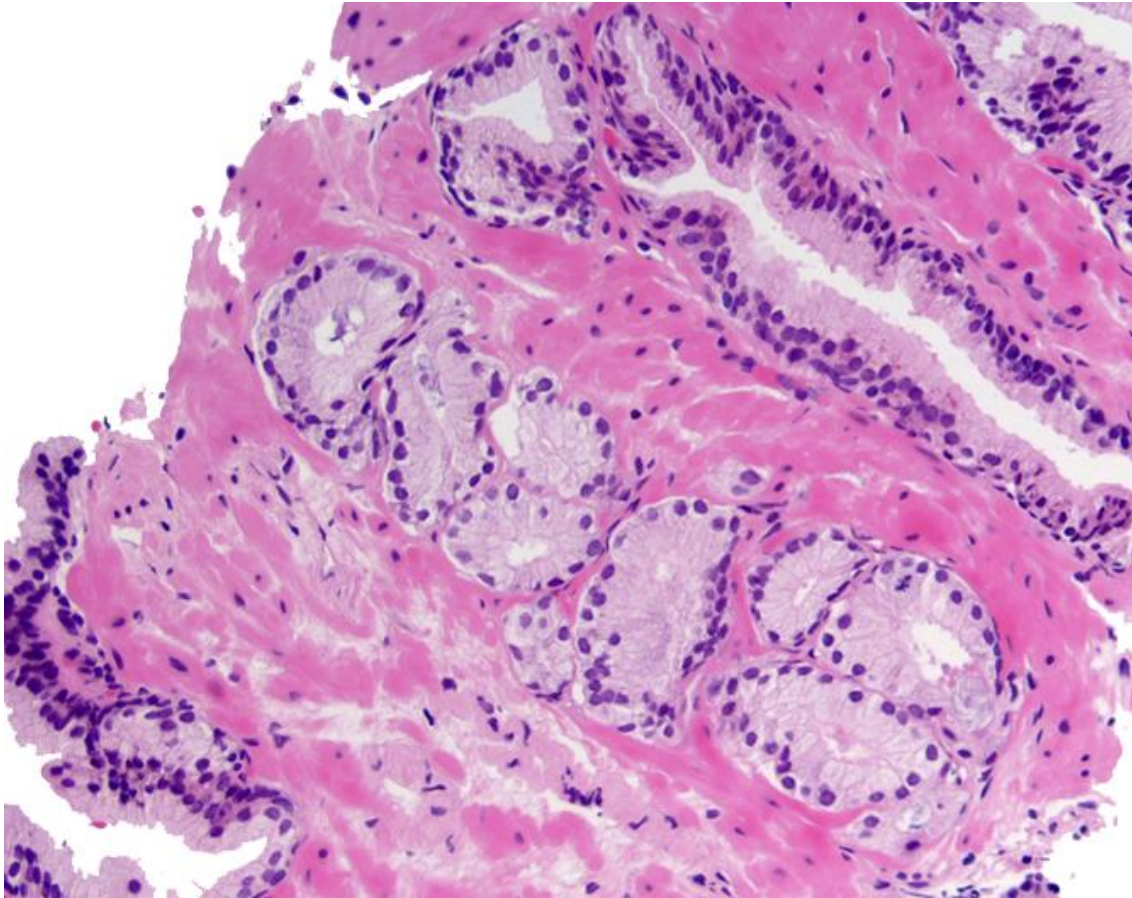
Abnormal Architecture

Infiltrative Growth Pattern



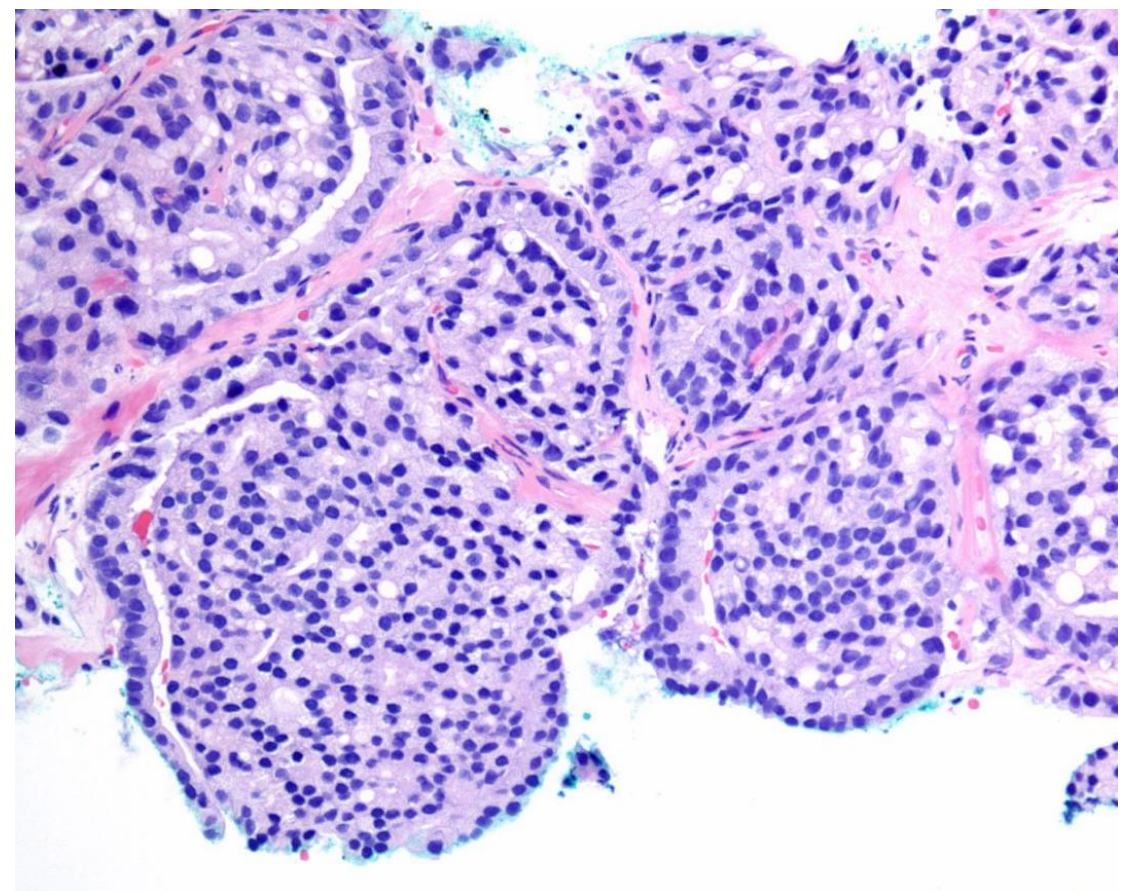
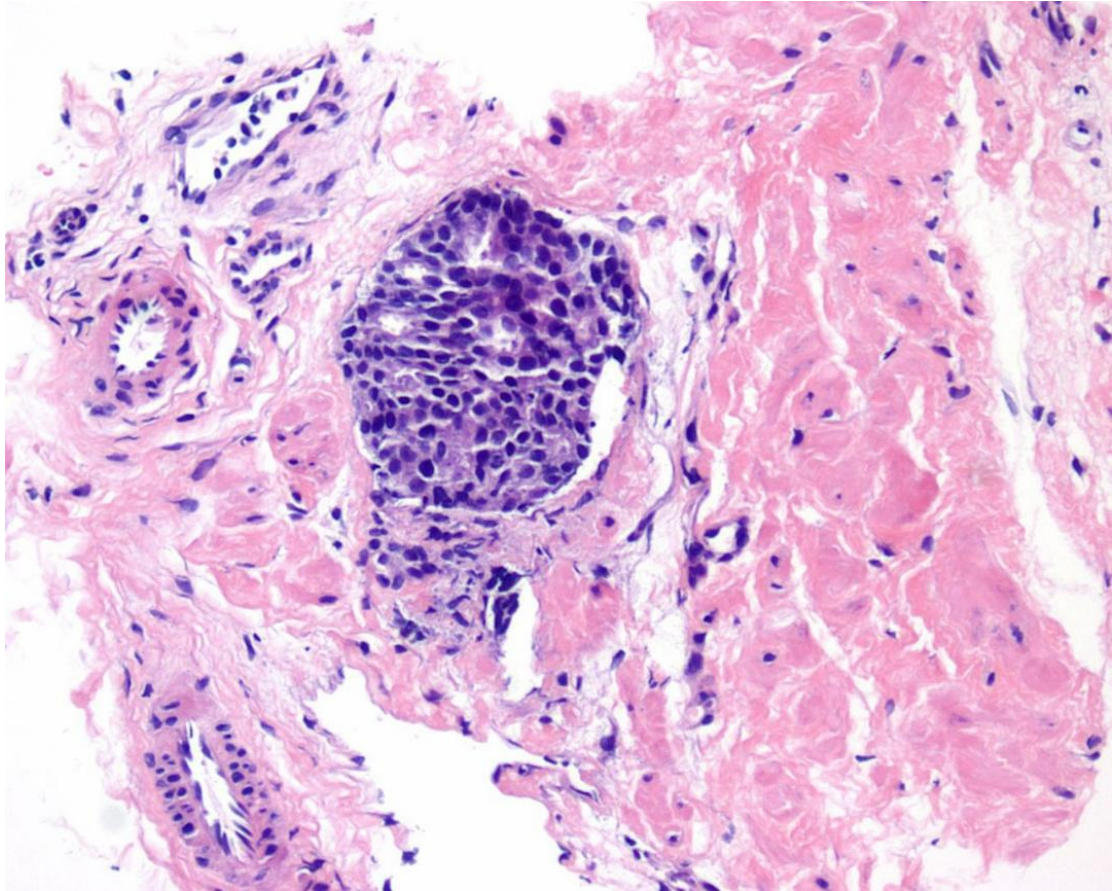
Abnormal Architecture

Crowded Glands



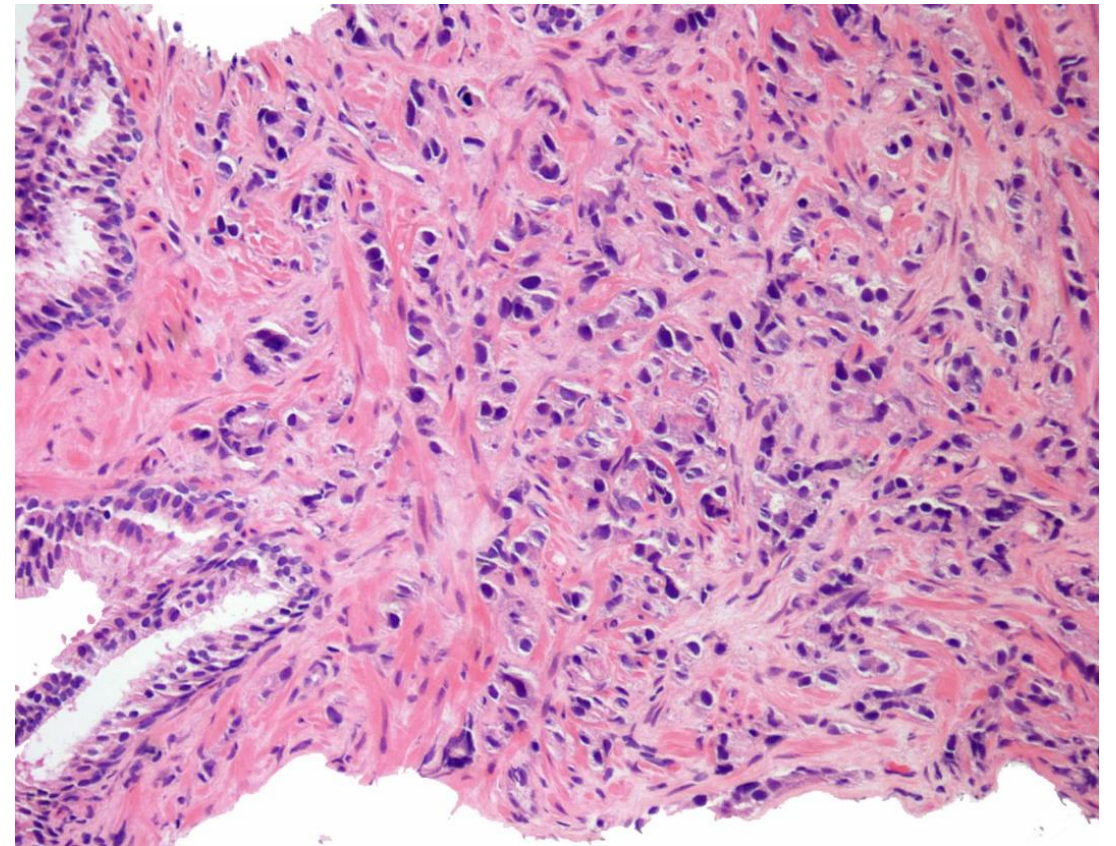
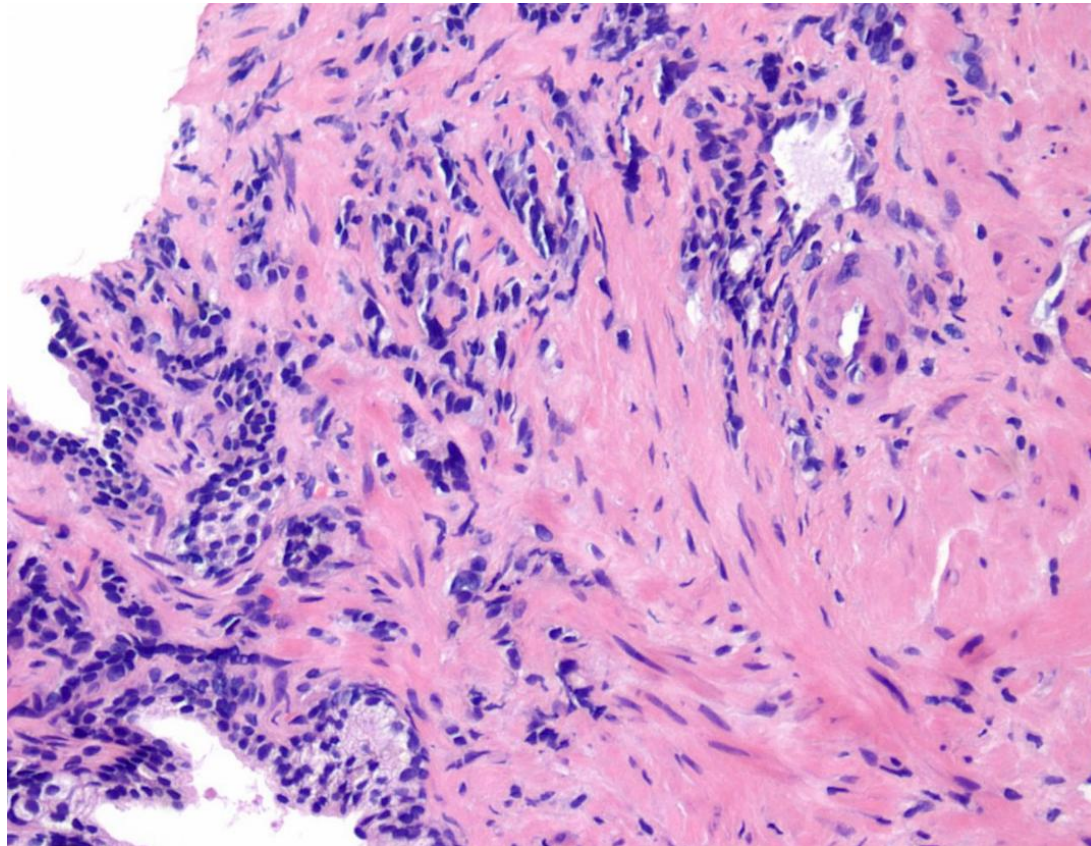
Abnormal Architecture

Cribriform Glands



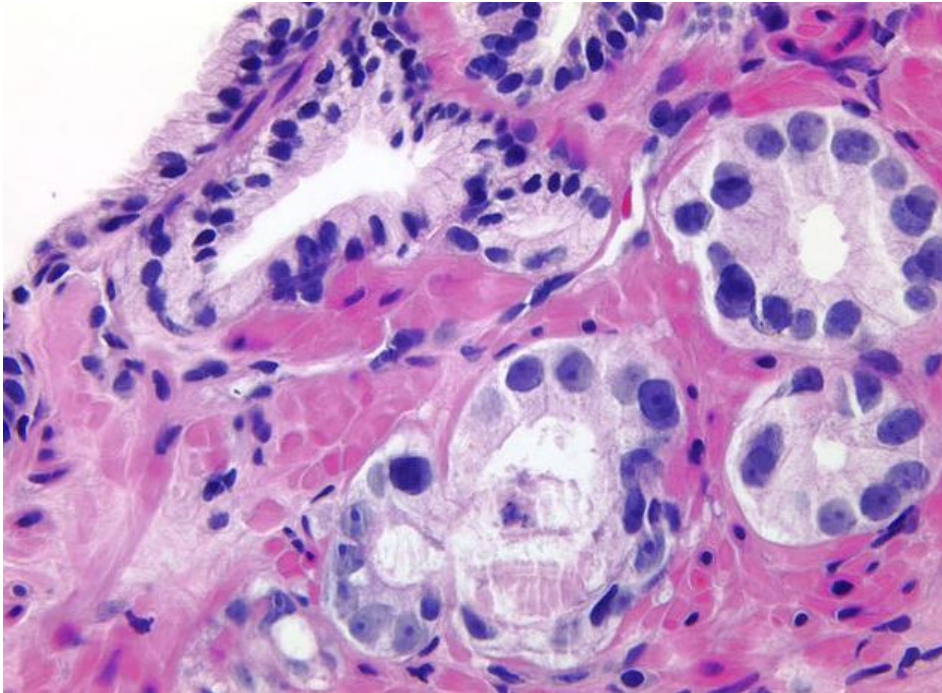
Abnormal Architecture

Single Cells

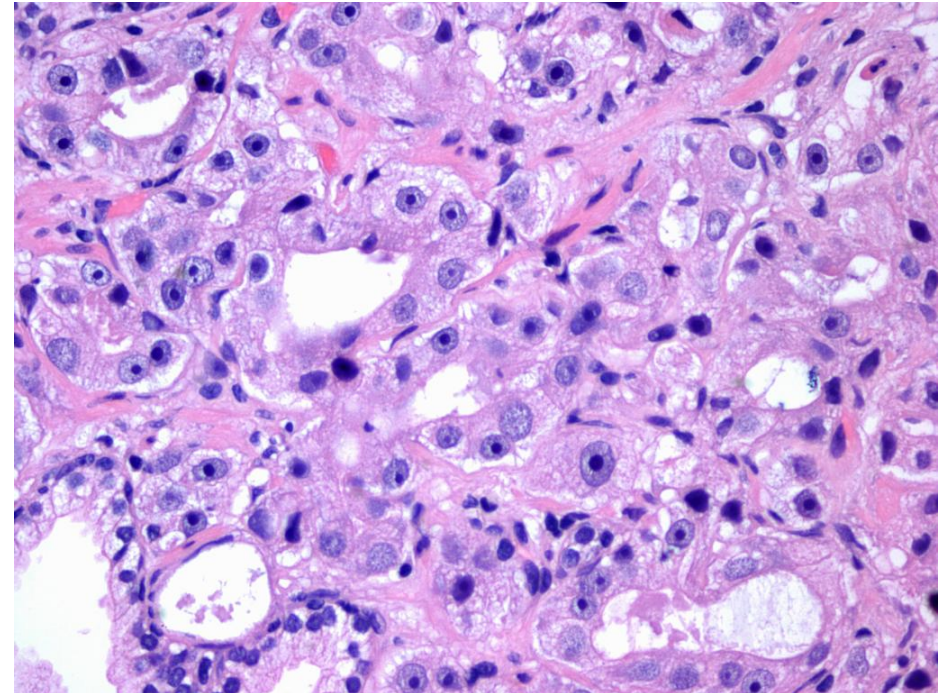


Nuclear Atypia

Nuclear Enlargement

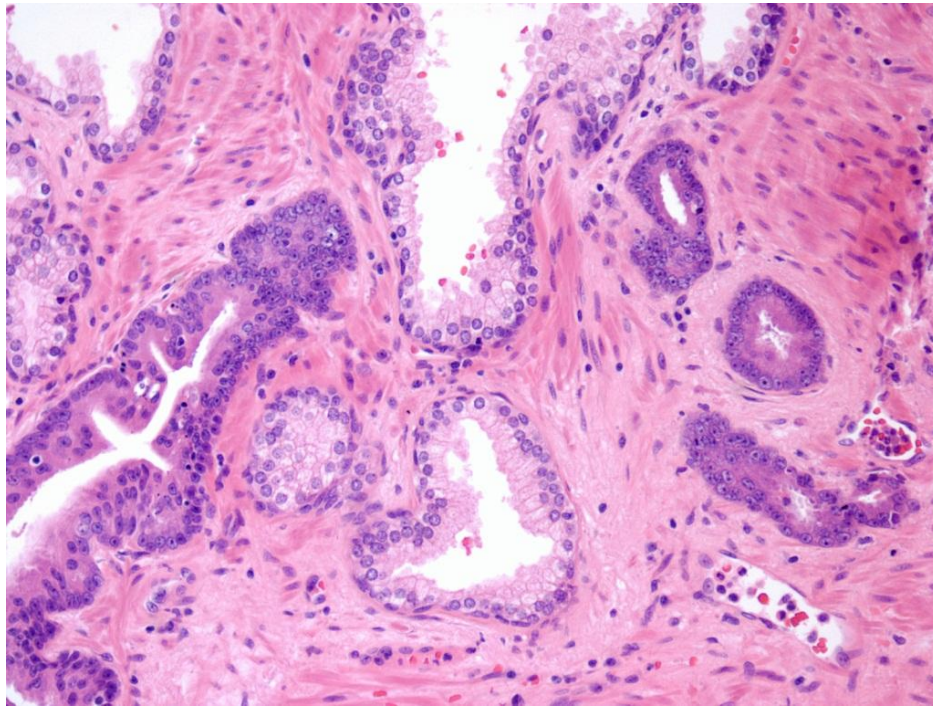


Prominent Nucleoli

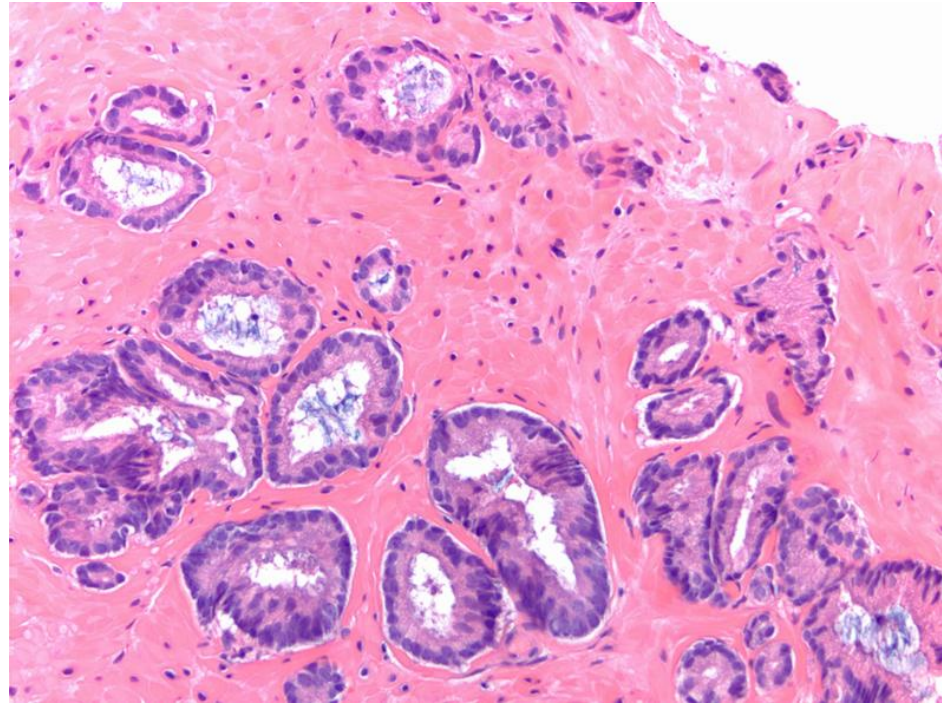


Cytoplasmic Features/Intraluminal Content

Amphophilic Cytoplasm

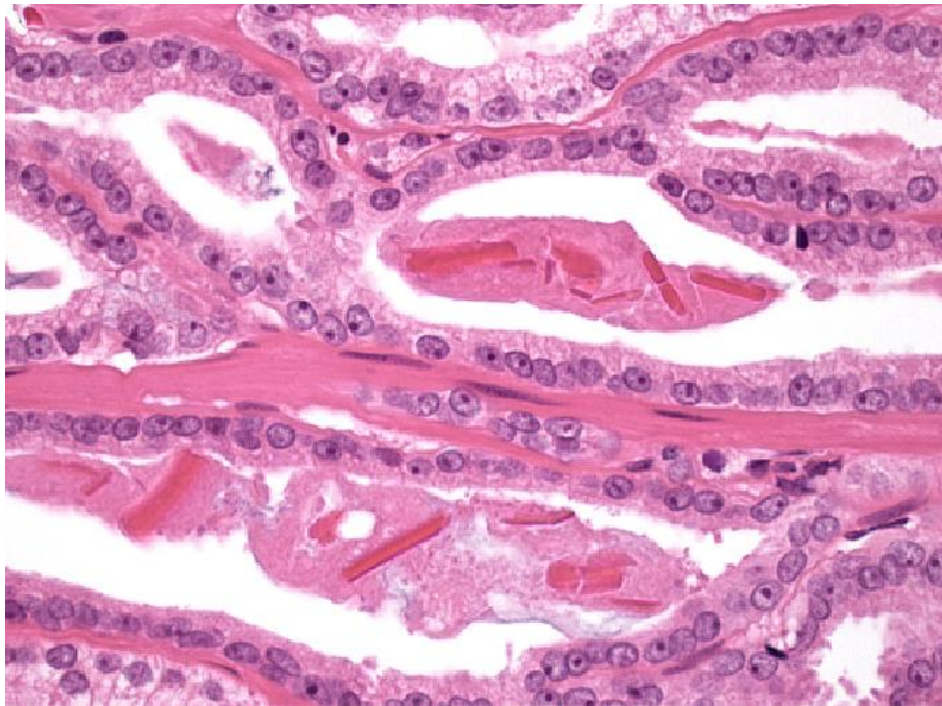


Blue Mucin

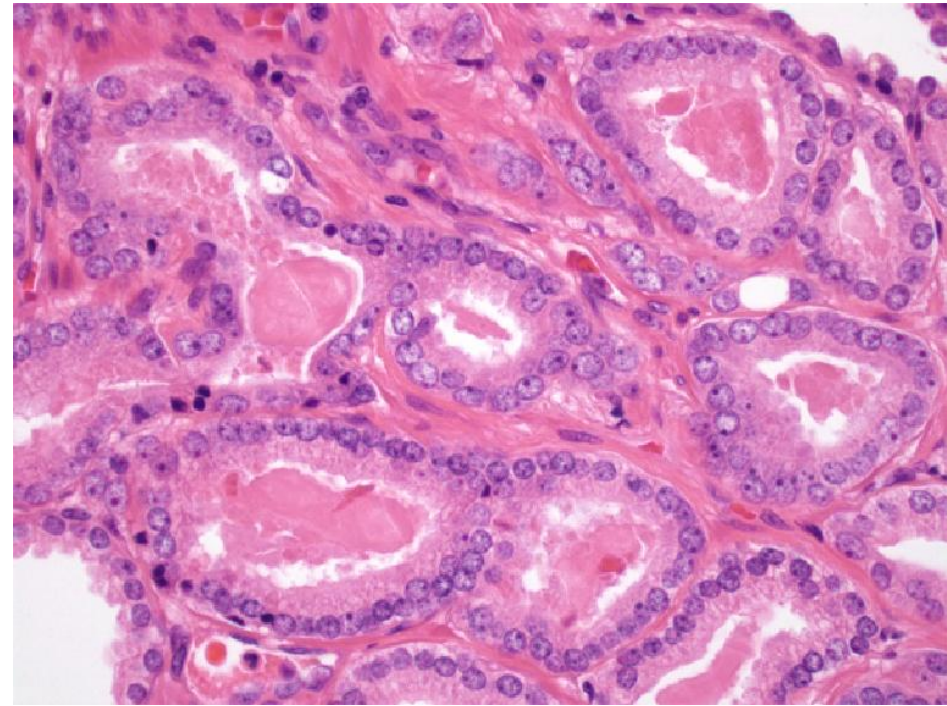


Intraluminal Content

Crystalloids

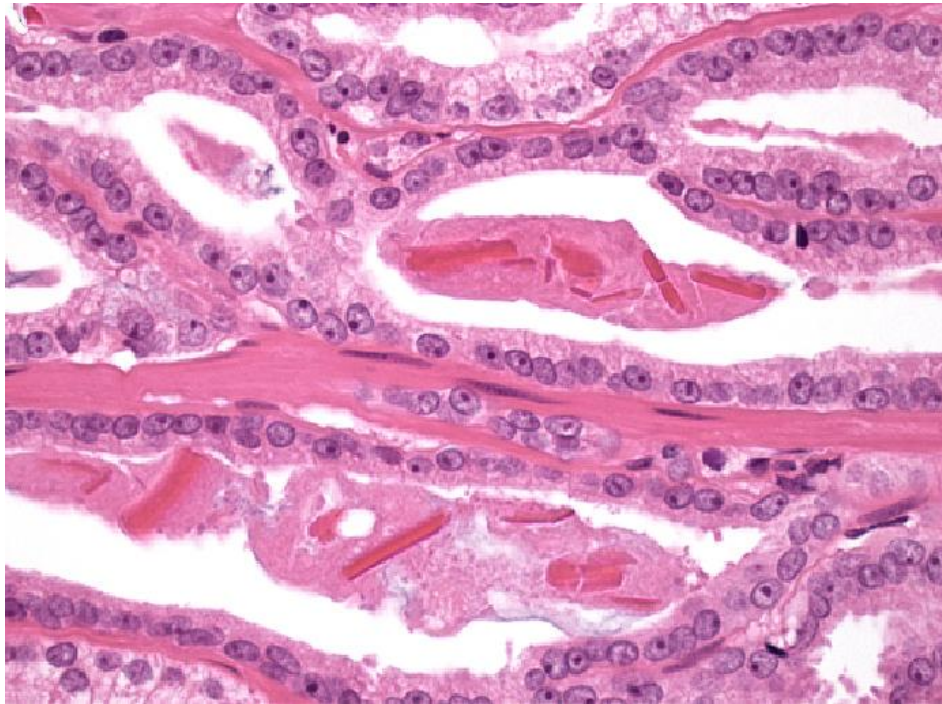


Amorphous Secretions

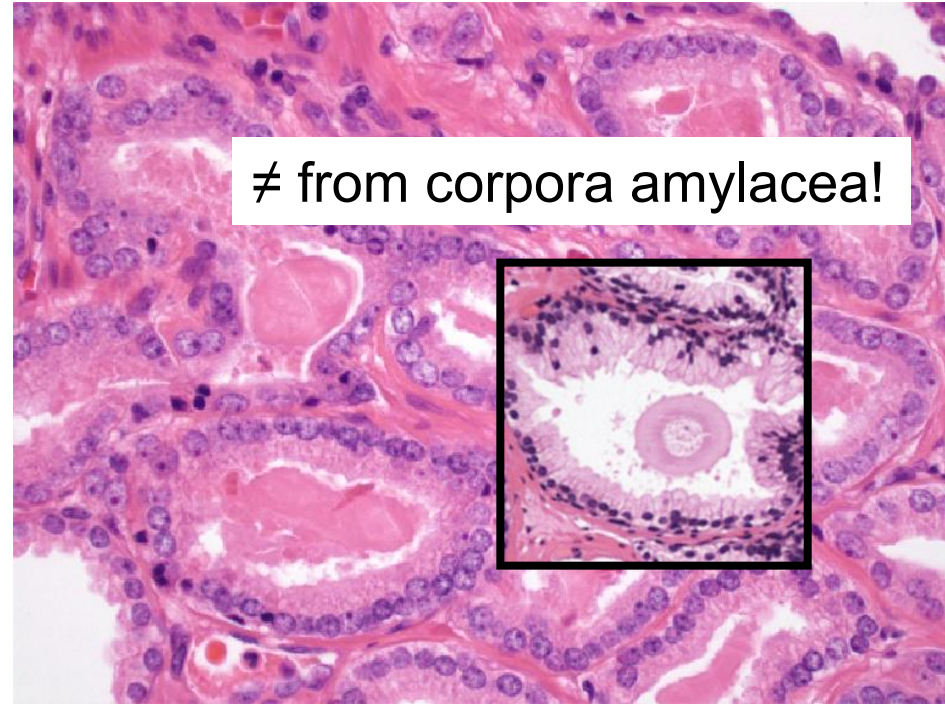


Intraluminal Content

Crystalloids

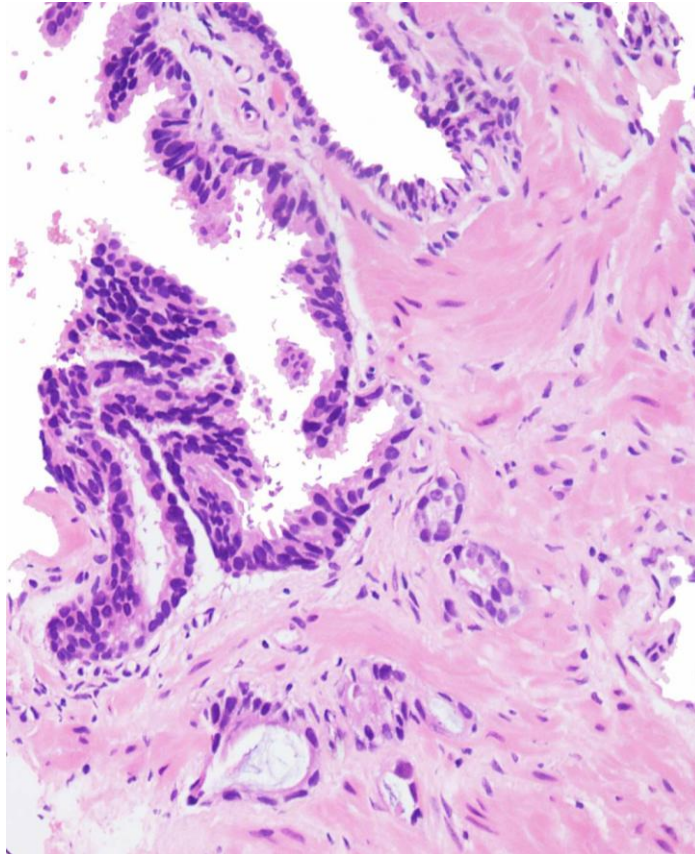


Amorphous Secretions

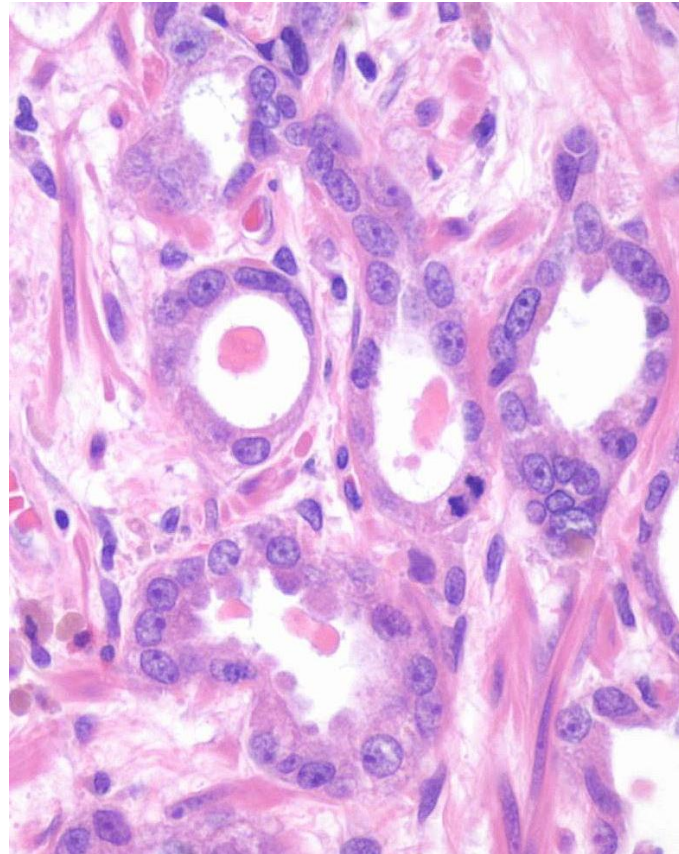


Minor Criteria

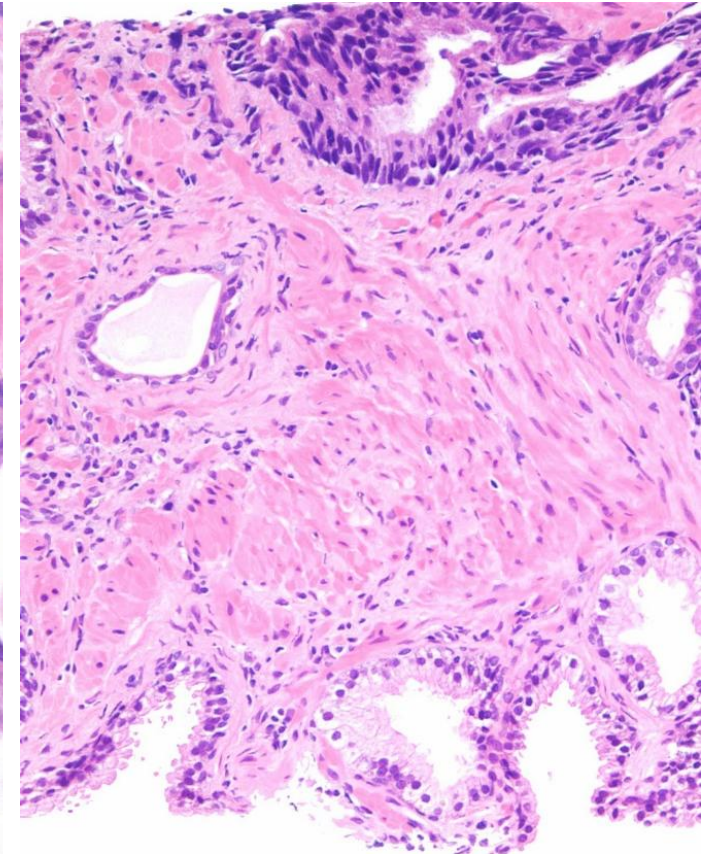
Adjacent HGPIN



Mitotic figures

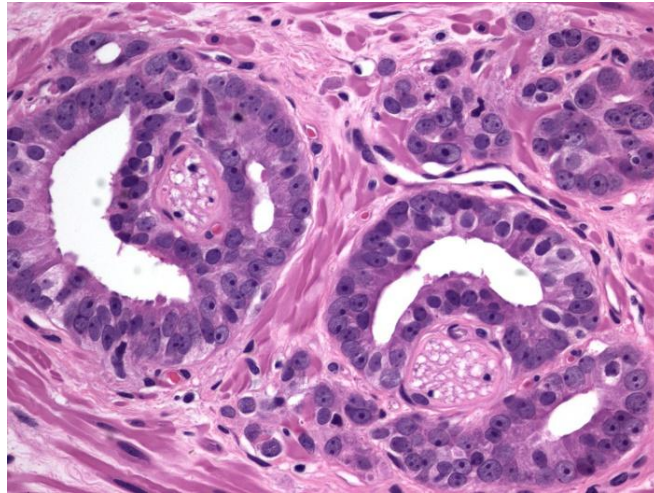


Hyperchromasia



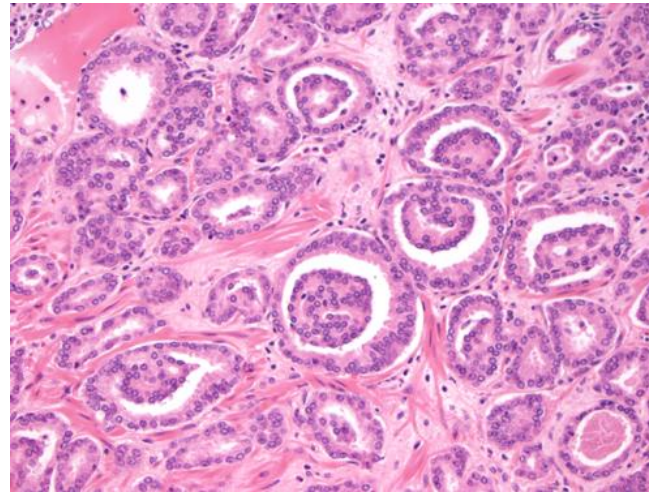
Diagnostic Features of Prostate Cancer

Perineural Invasion



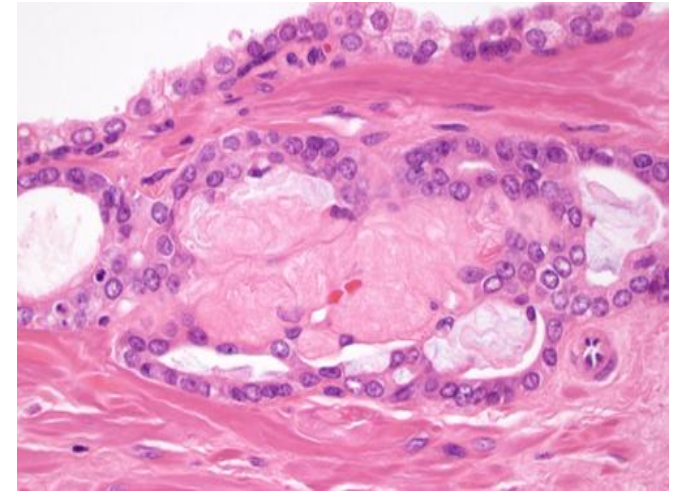
11-37% of PCA on Bx
0-3% of minimal PCA

Glomerulations



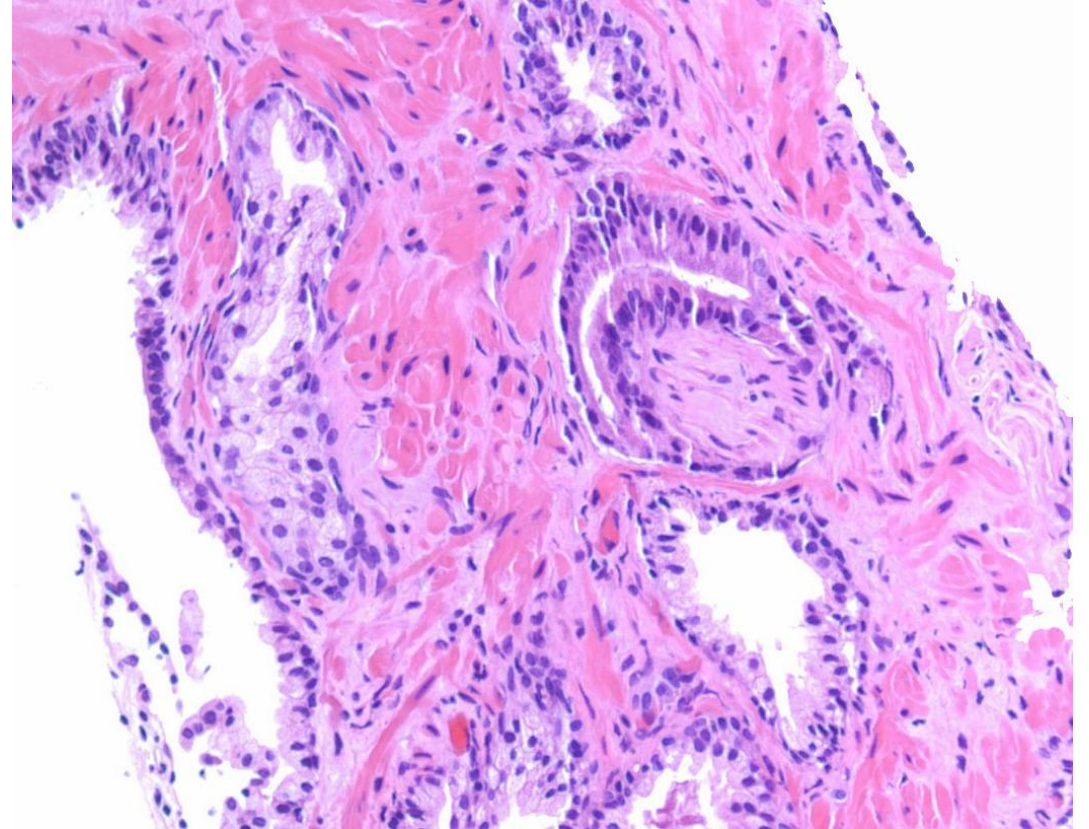
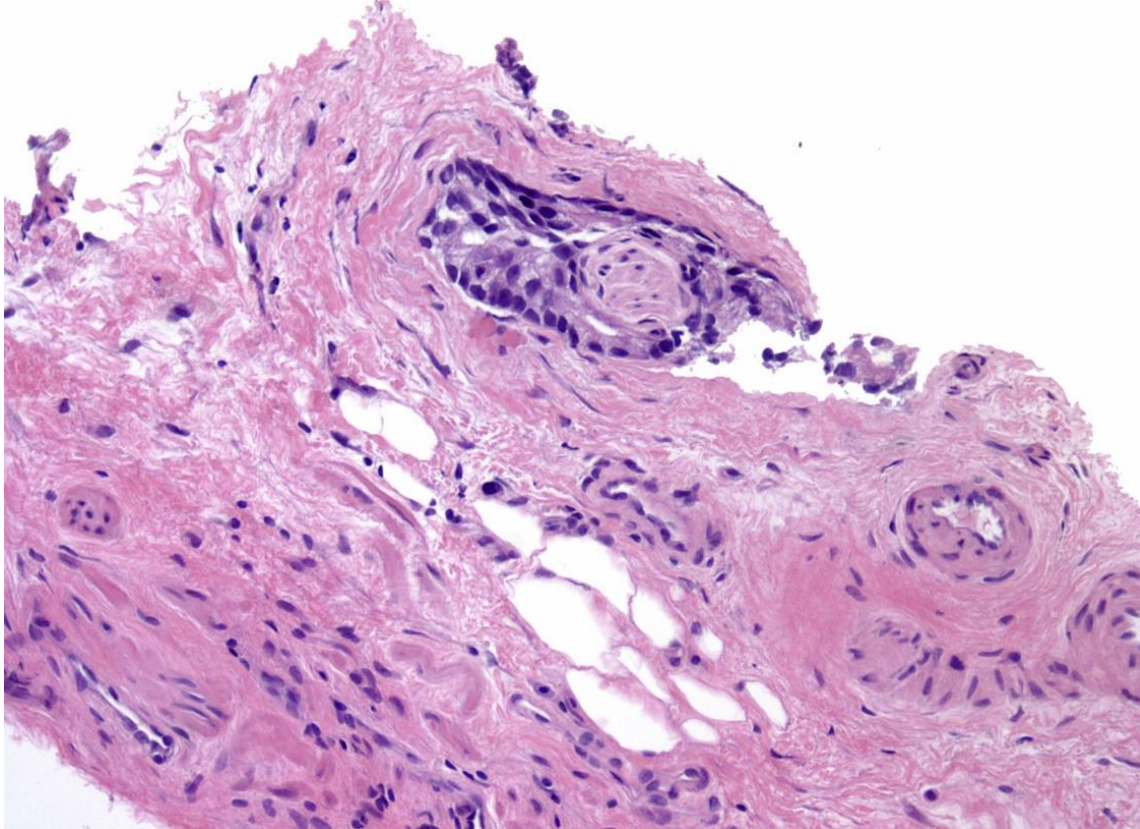
3-15% of PCA on Bx
very rare in minimal PCA

Mucinous Fibroplasia

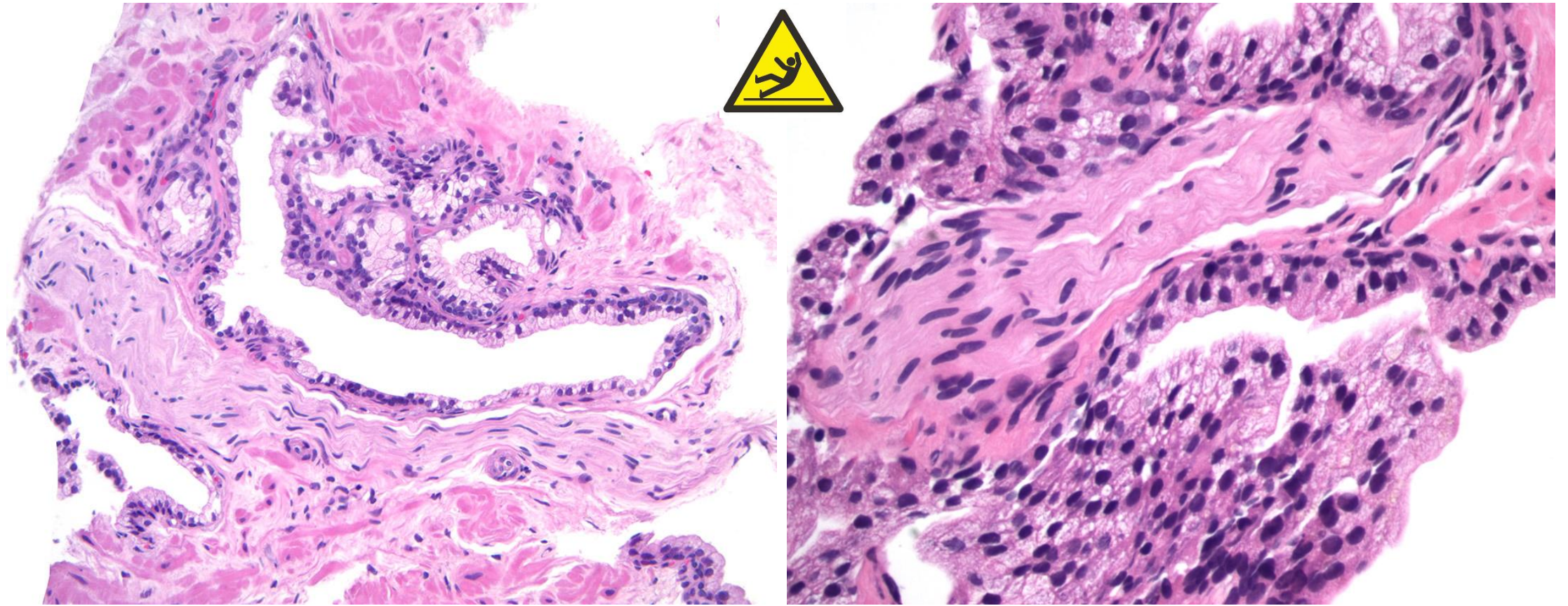


1-5% of PCA on Bx
0.1% of minimal PCA

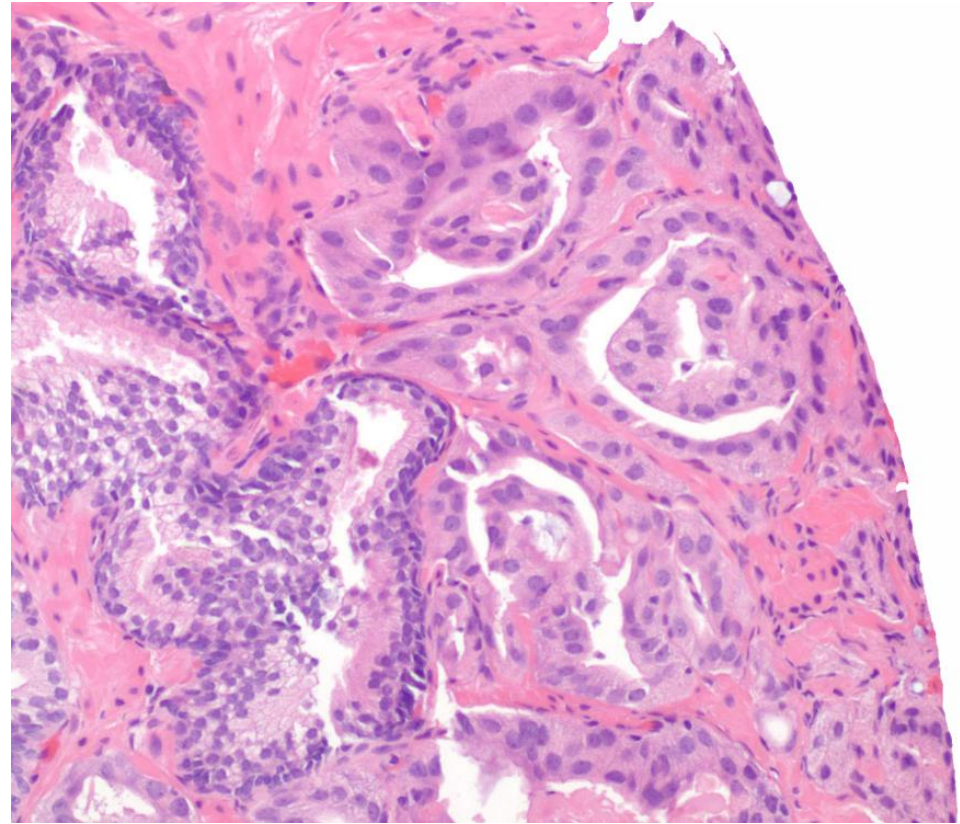
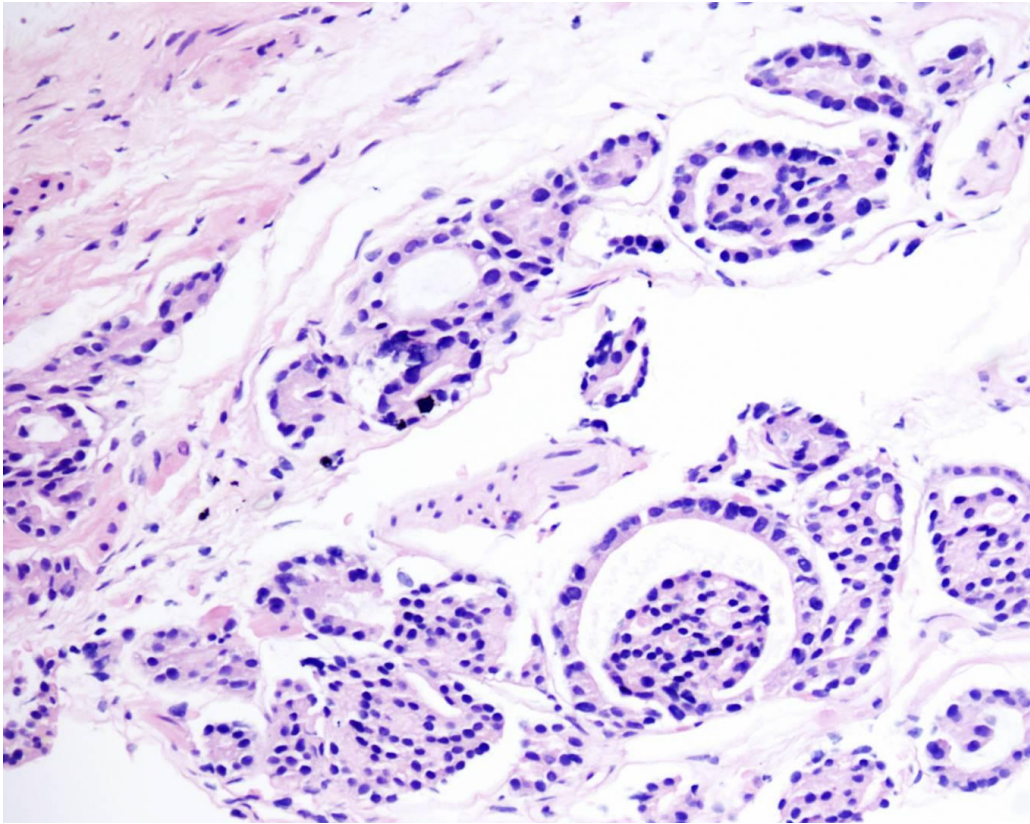
Perineural Invasion



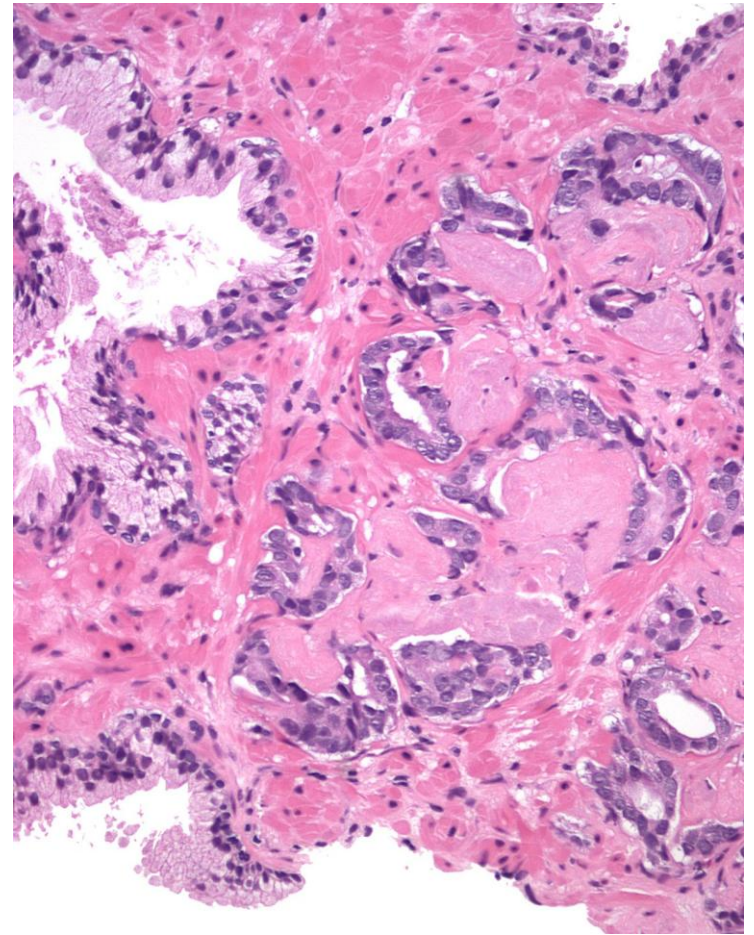
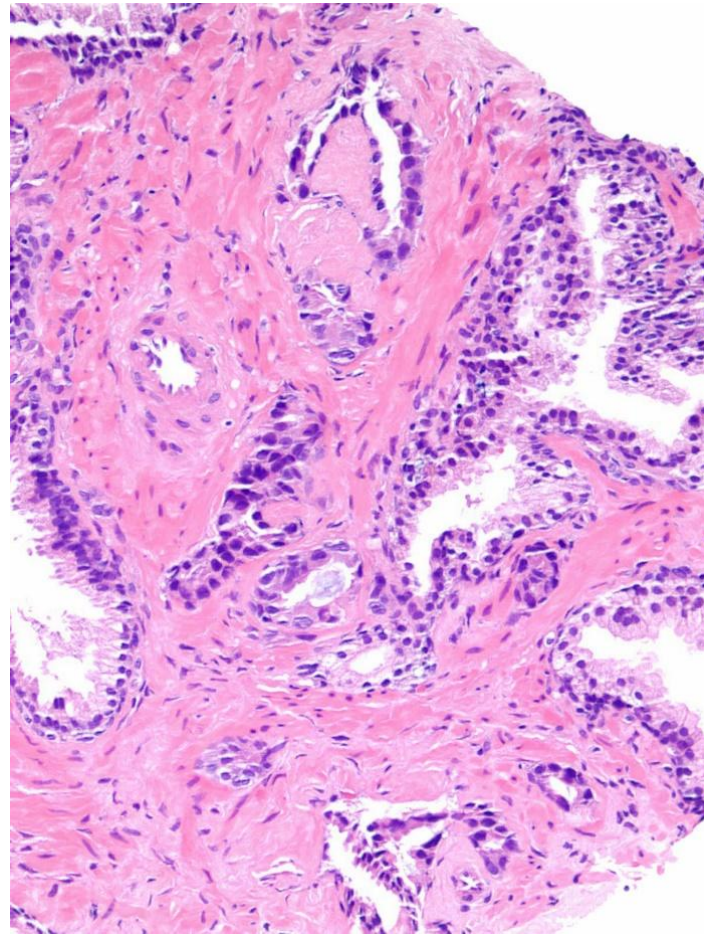
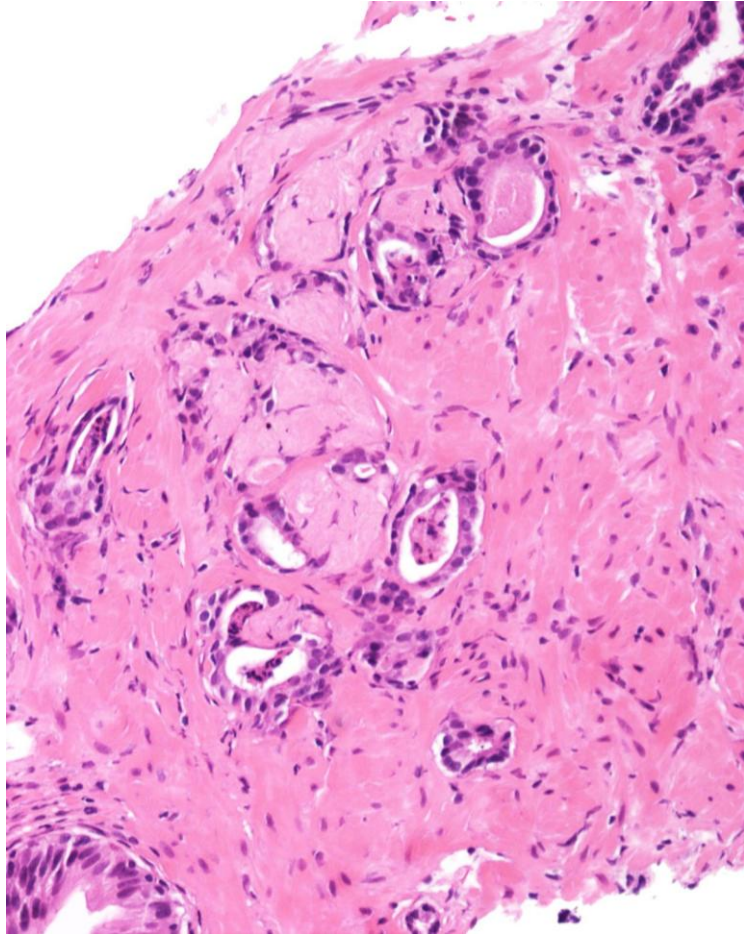
Perineural Indentation is \neq from Perineural Invasion!



Glomerulations

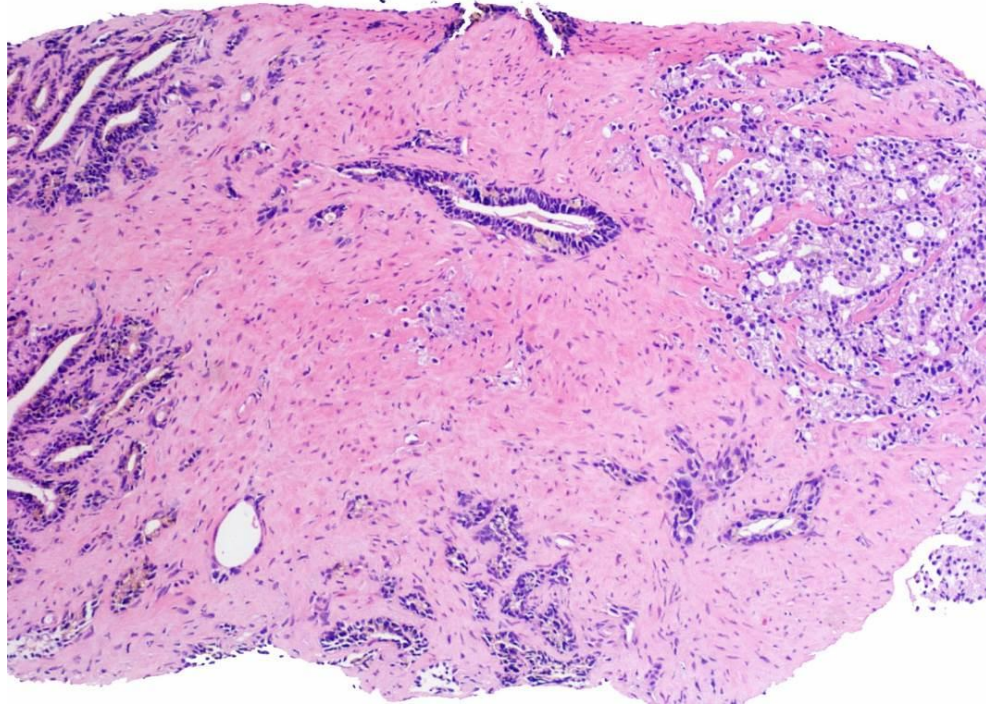


Mucinous Fibroplasia

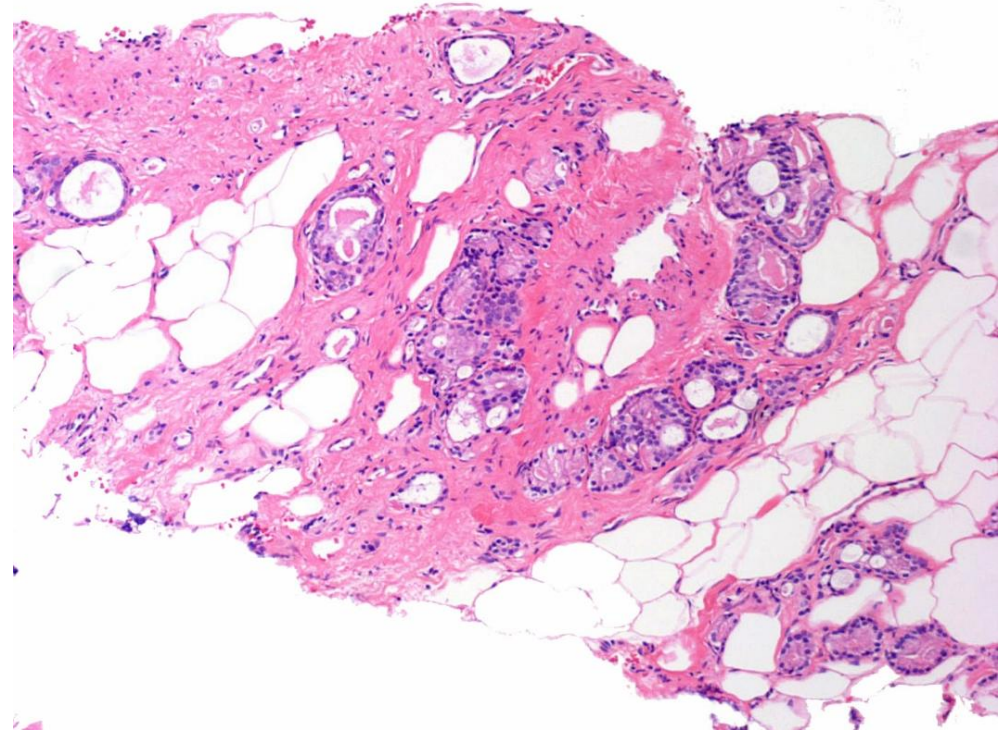


Diagnostic Features of Prostate Cancer

Seminal Vesicle Invasion

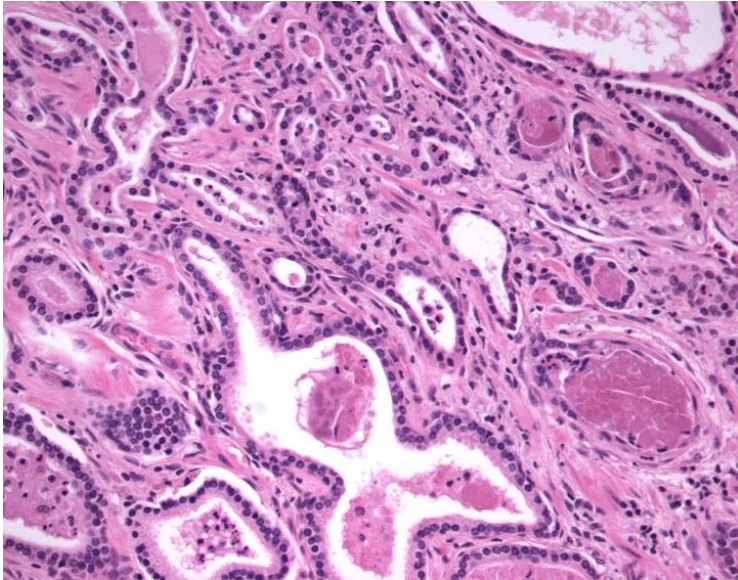


Extraprostatic Extension



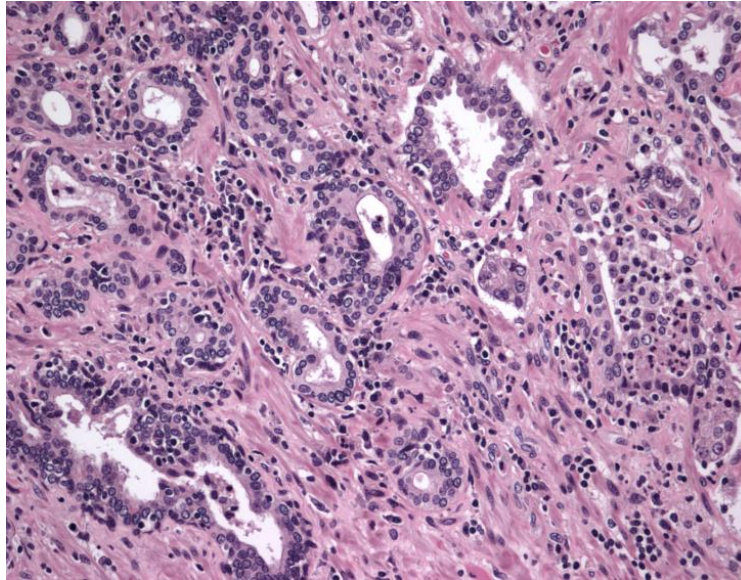
Features Against Diagnosis of Limited PCA

Atrophic cytoplasm



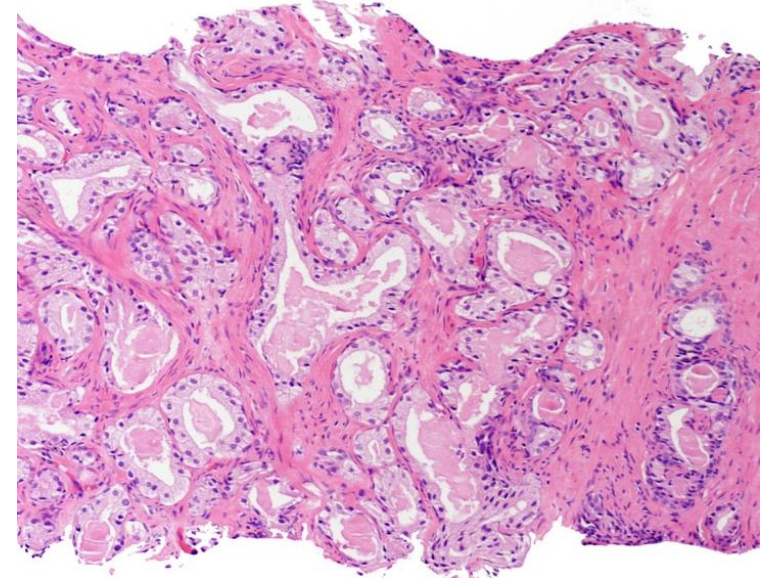
Atrophy

Inflammation



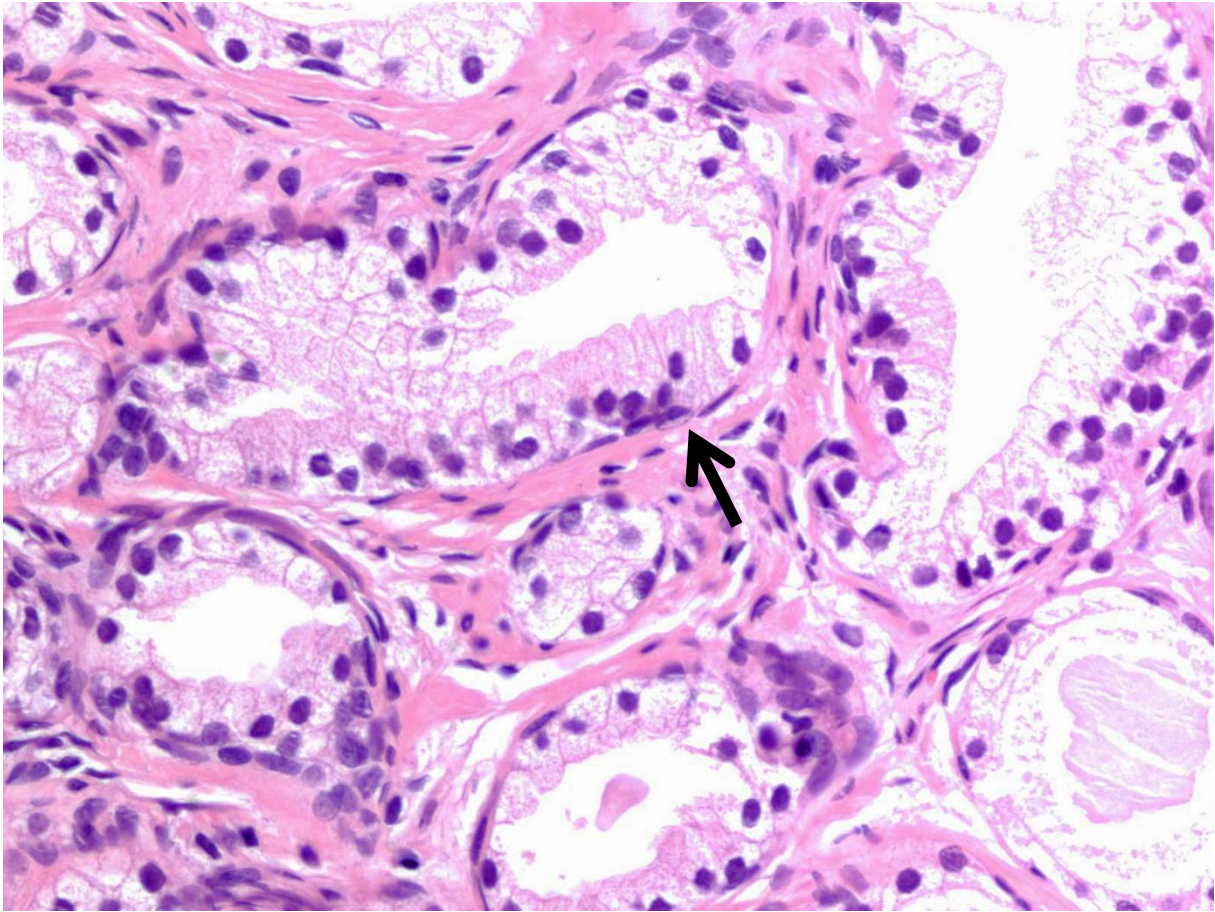
Inflammatory atypia

Merging with benign

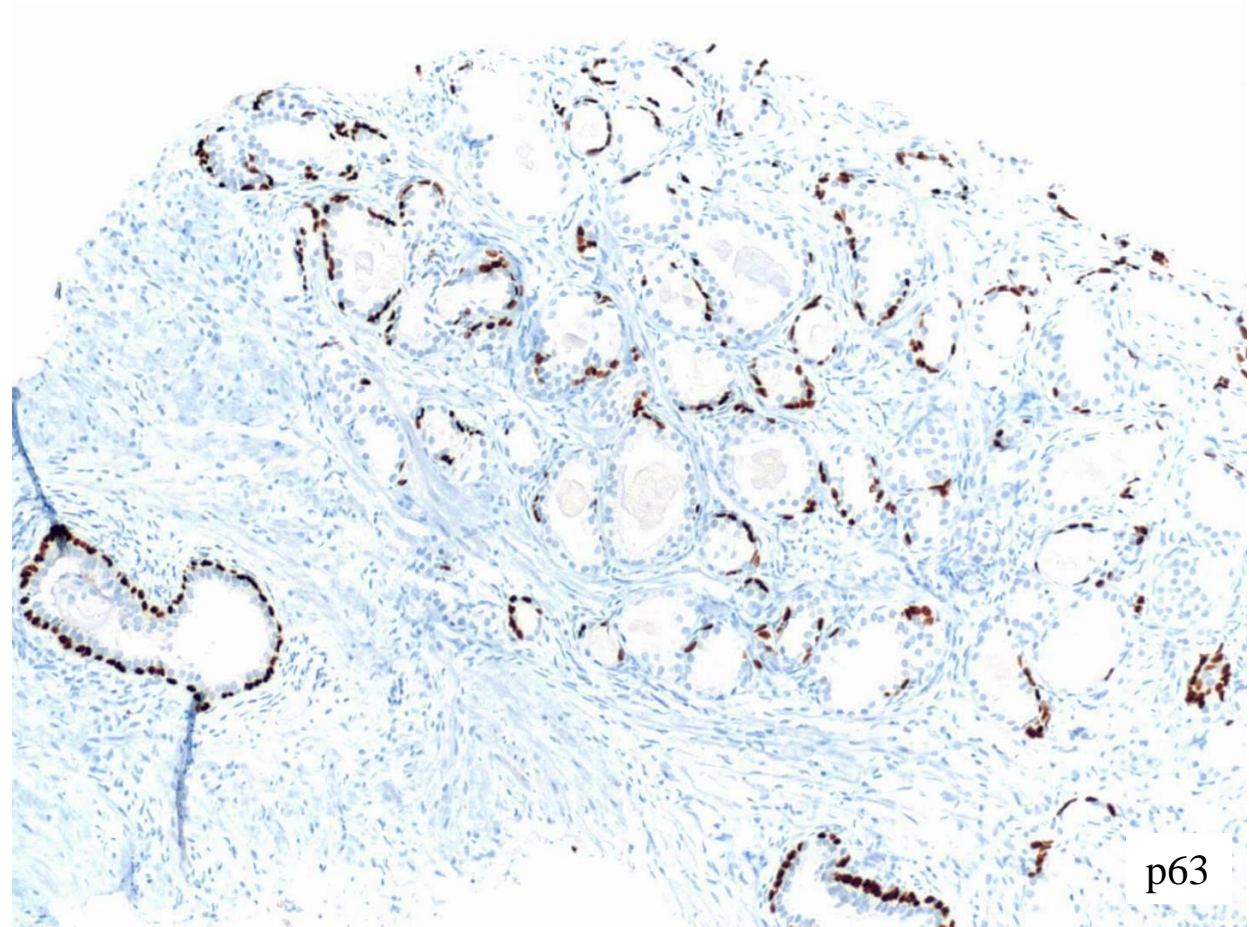
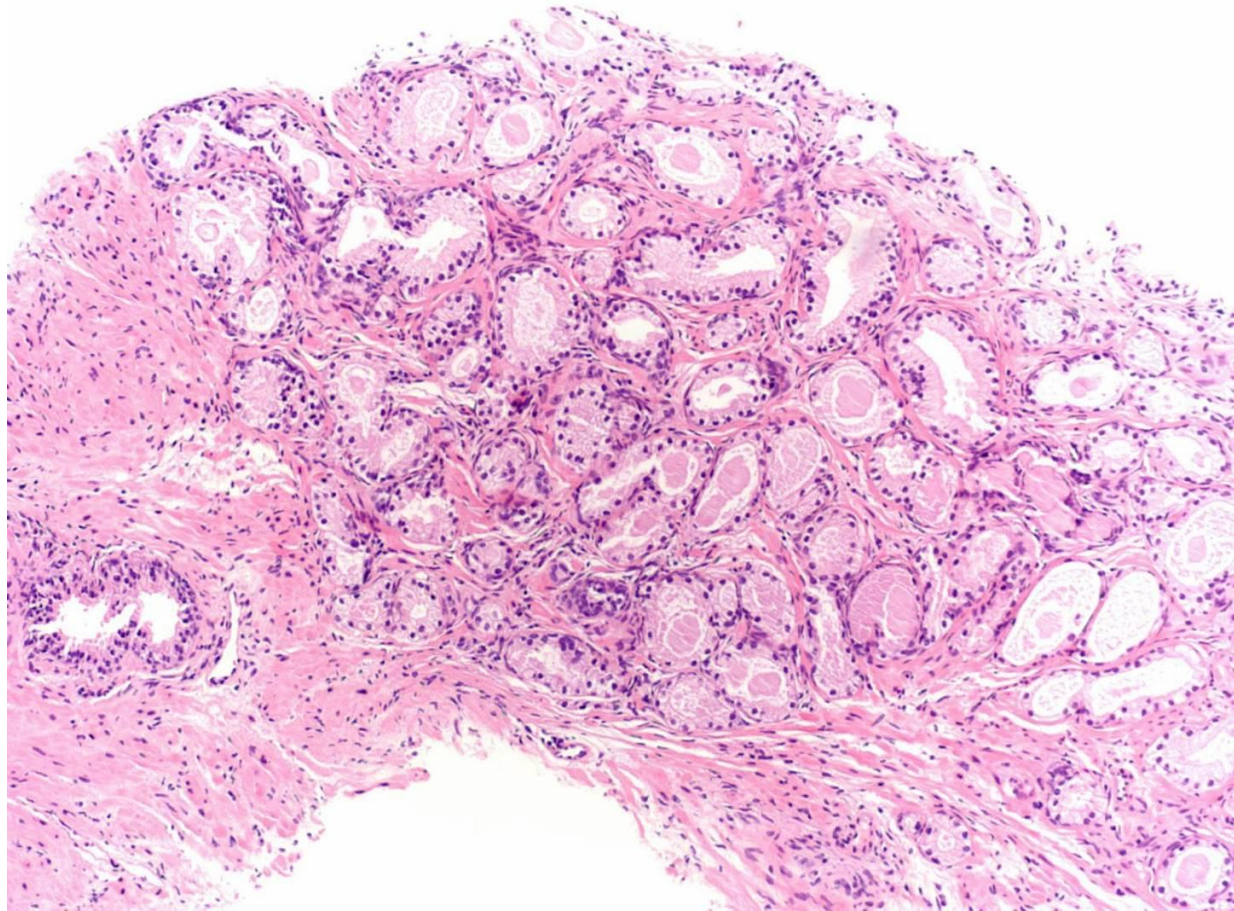


Adenosis

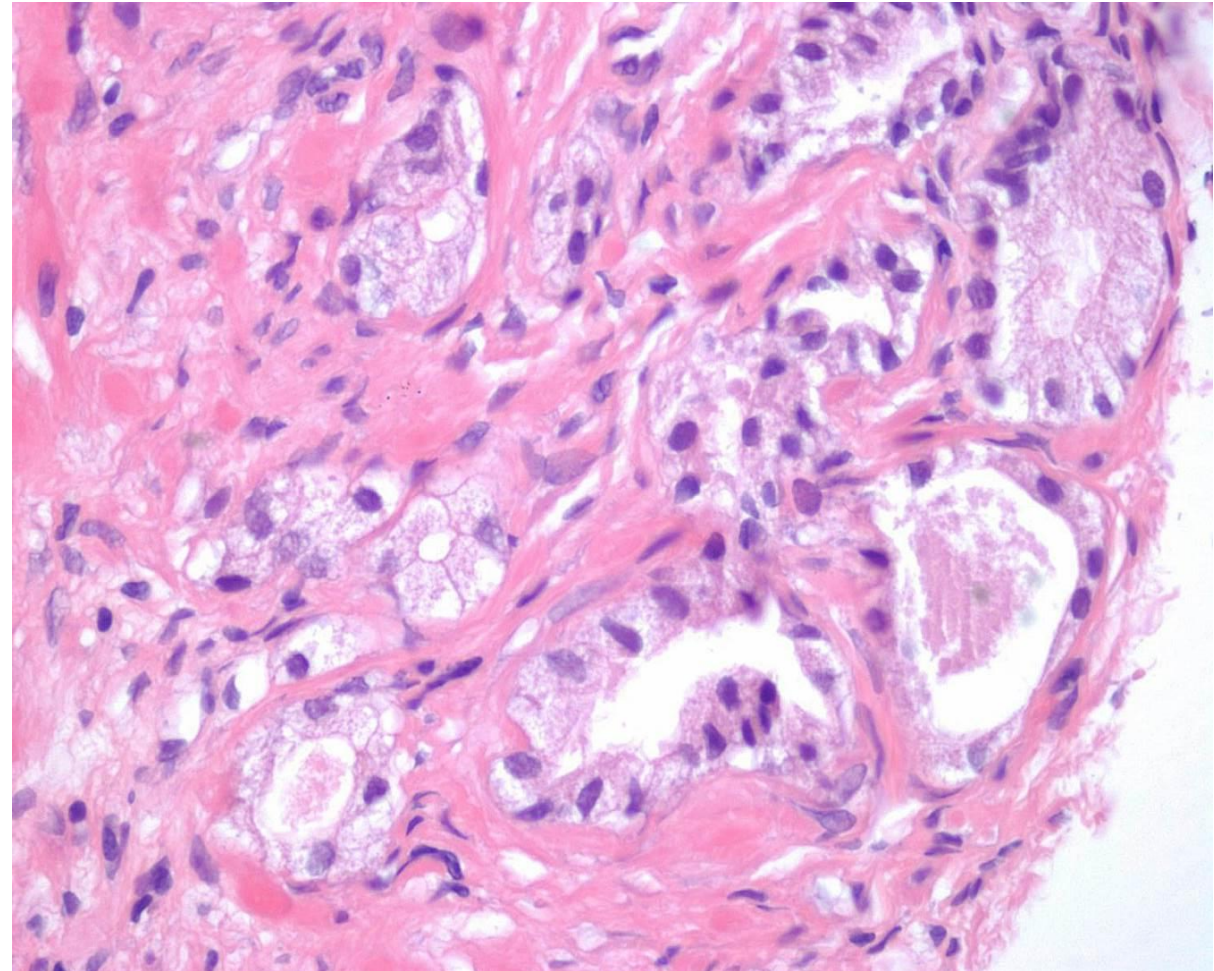
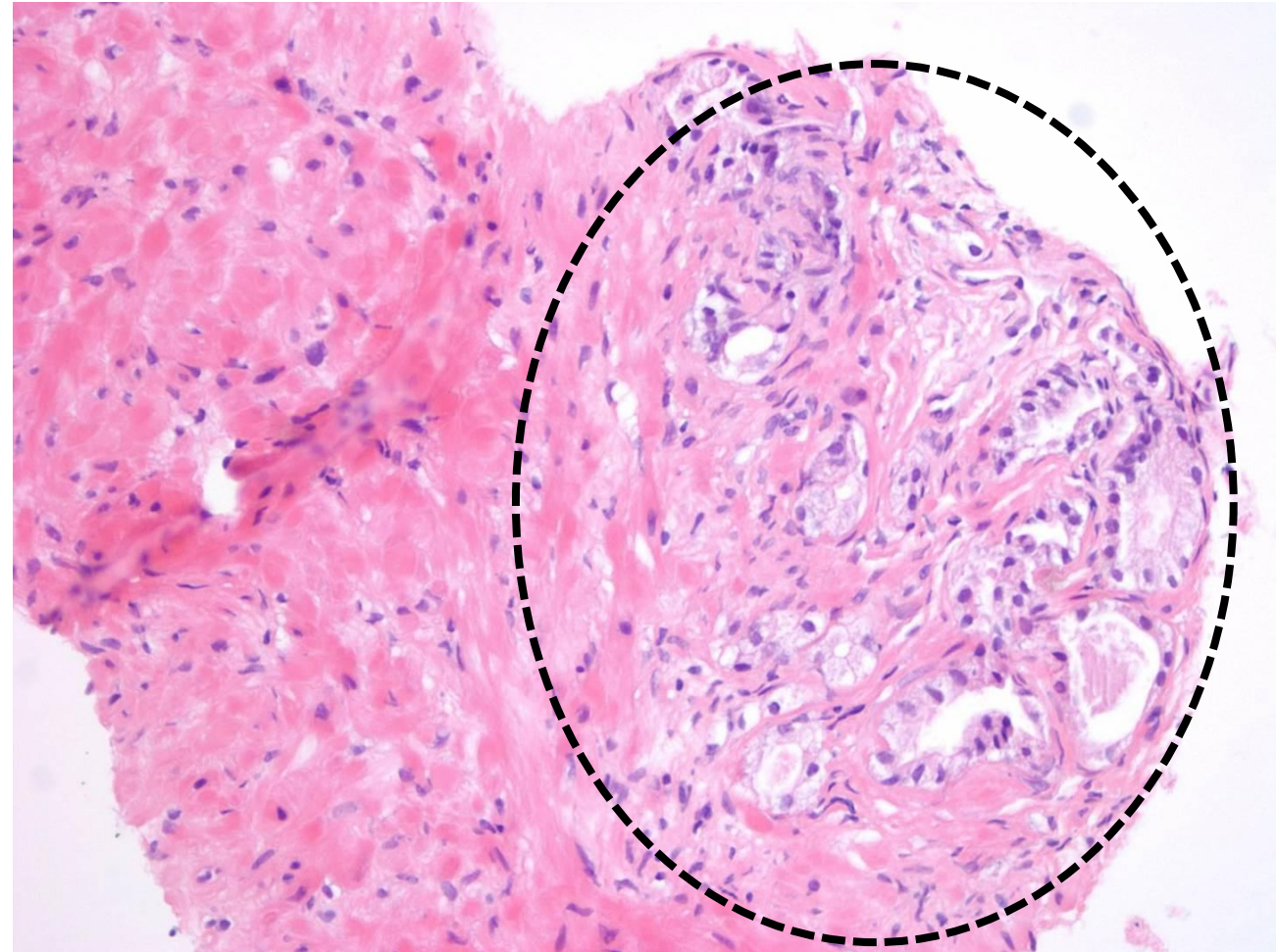
Adenosis



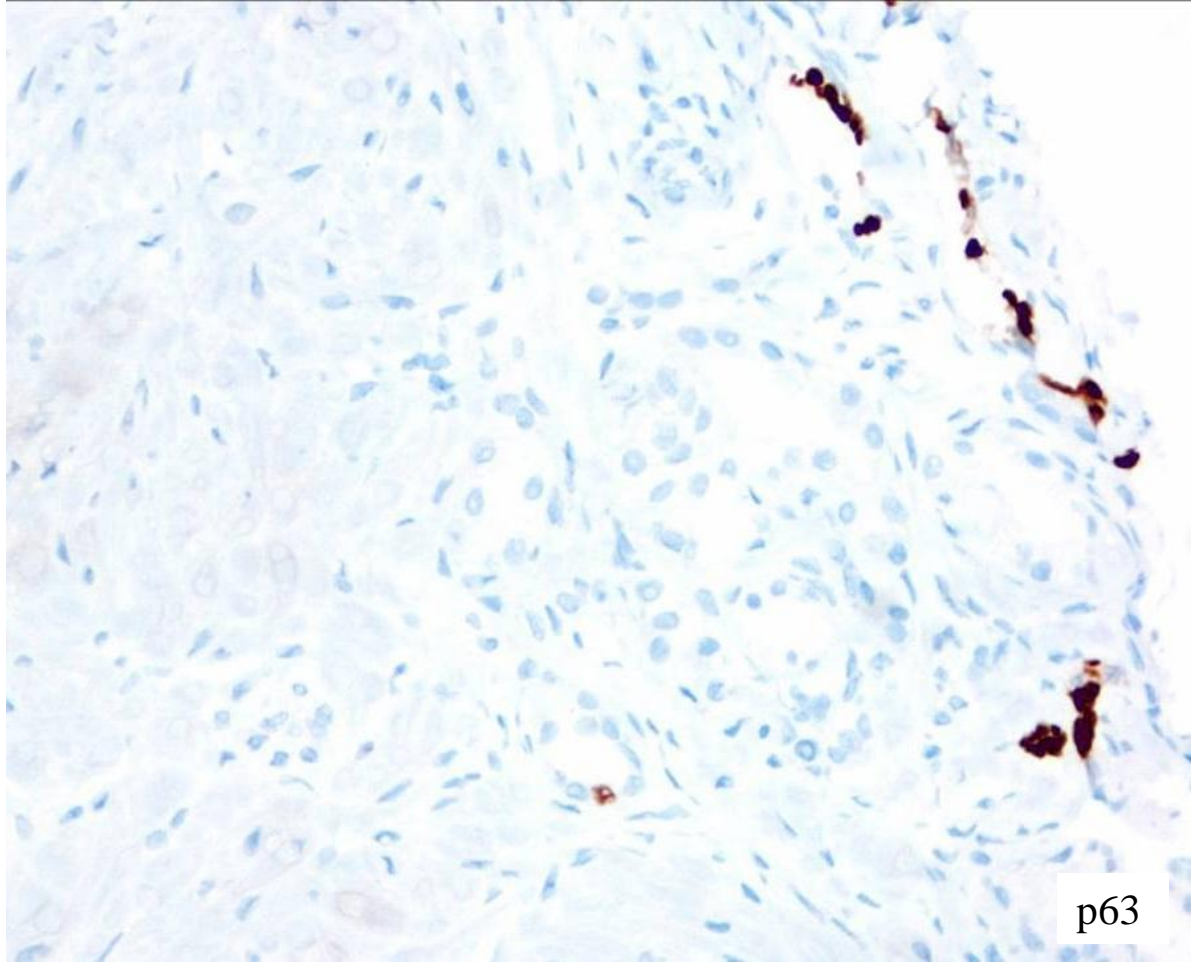
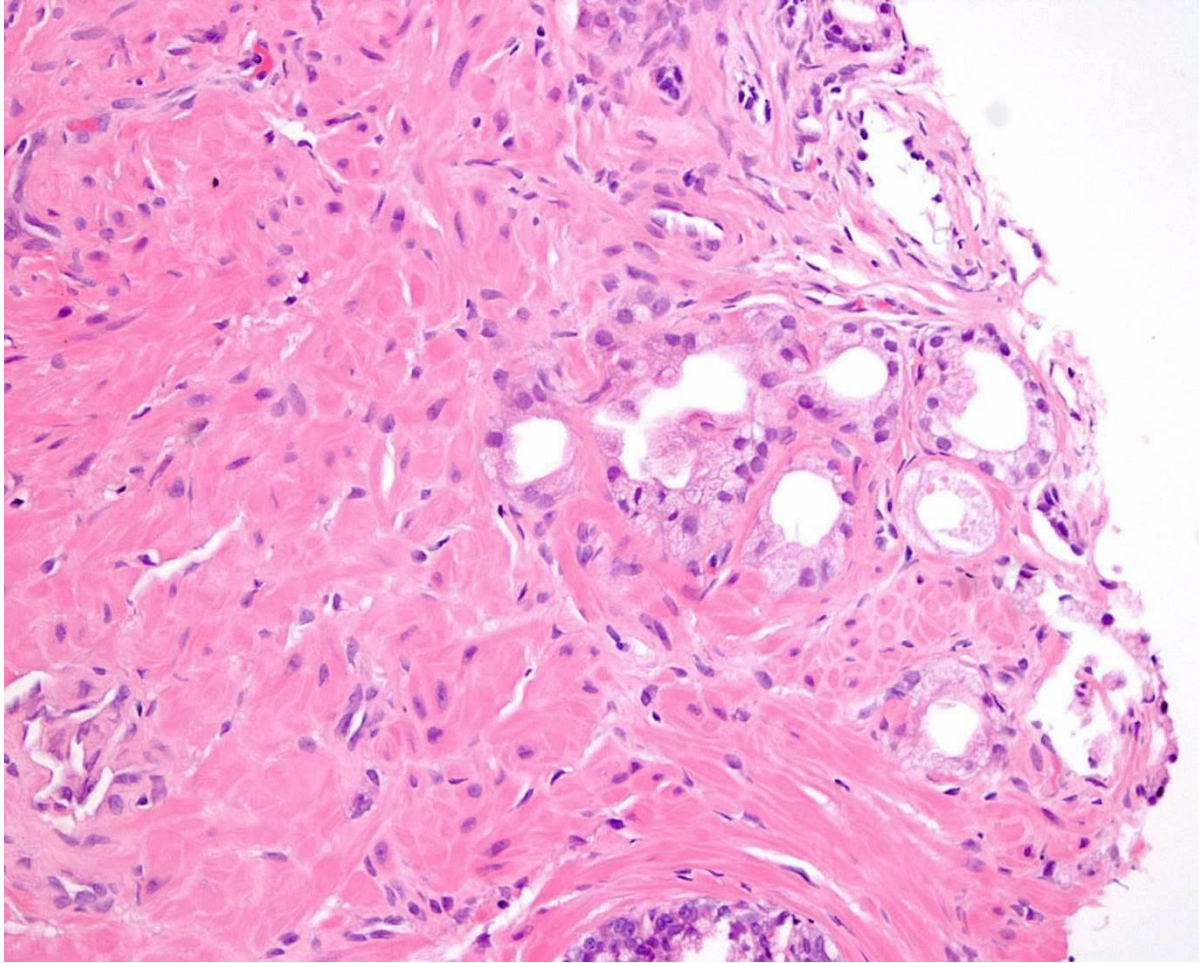
Adenosis



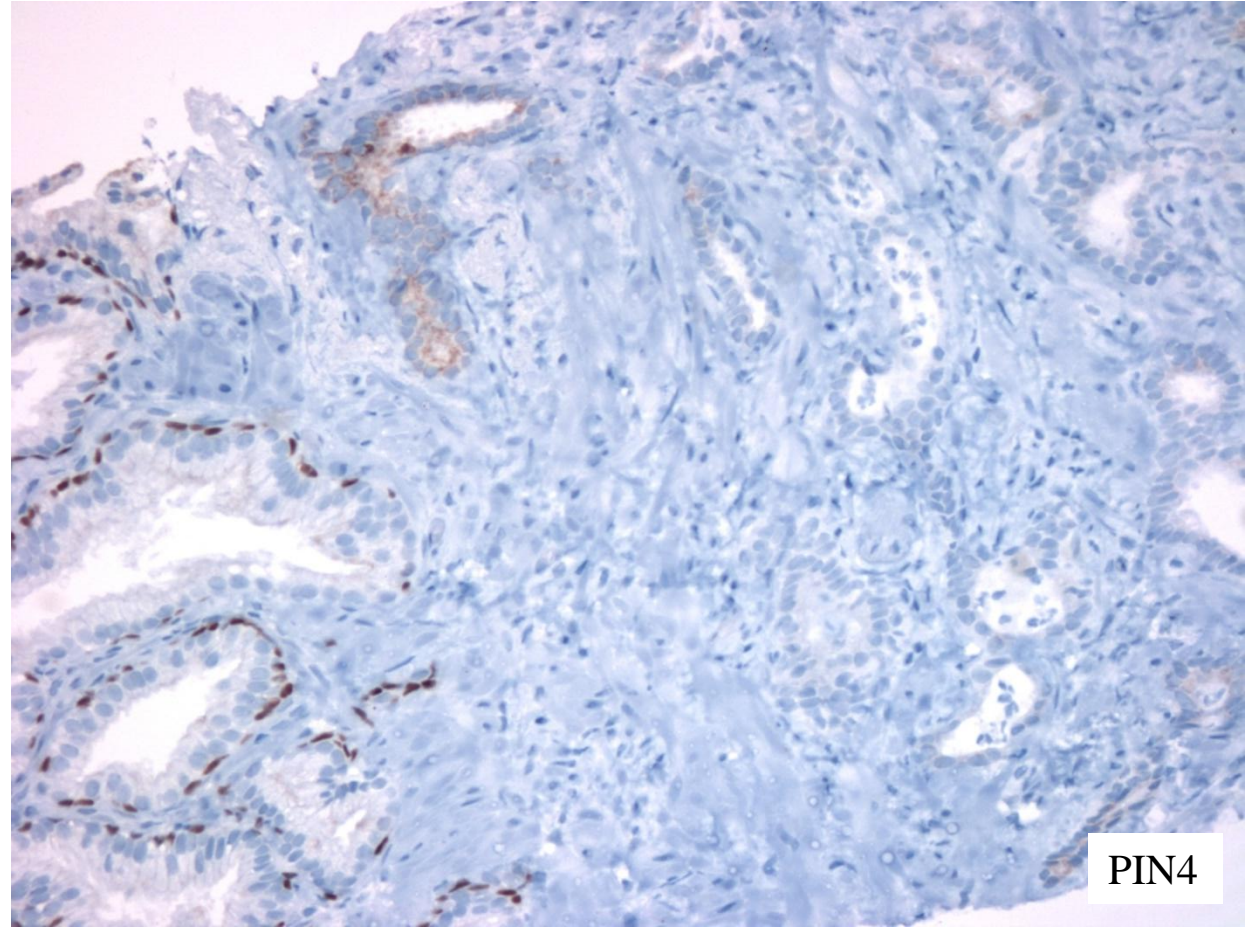
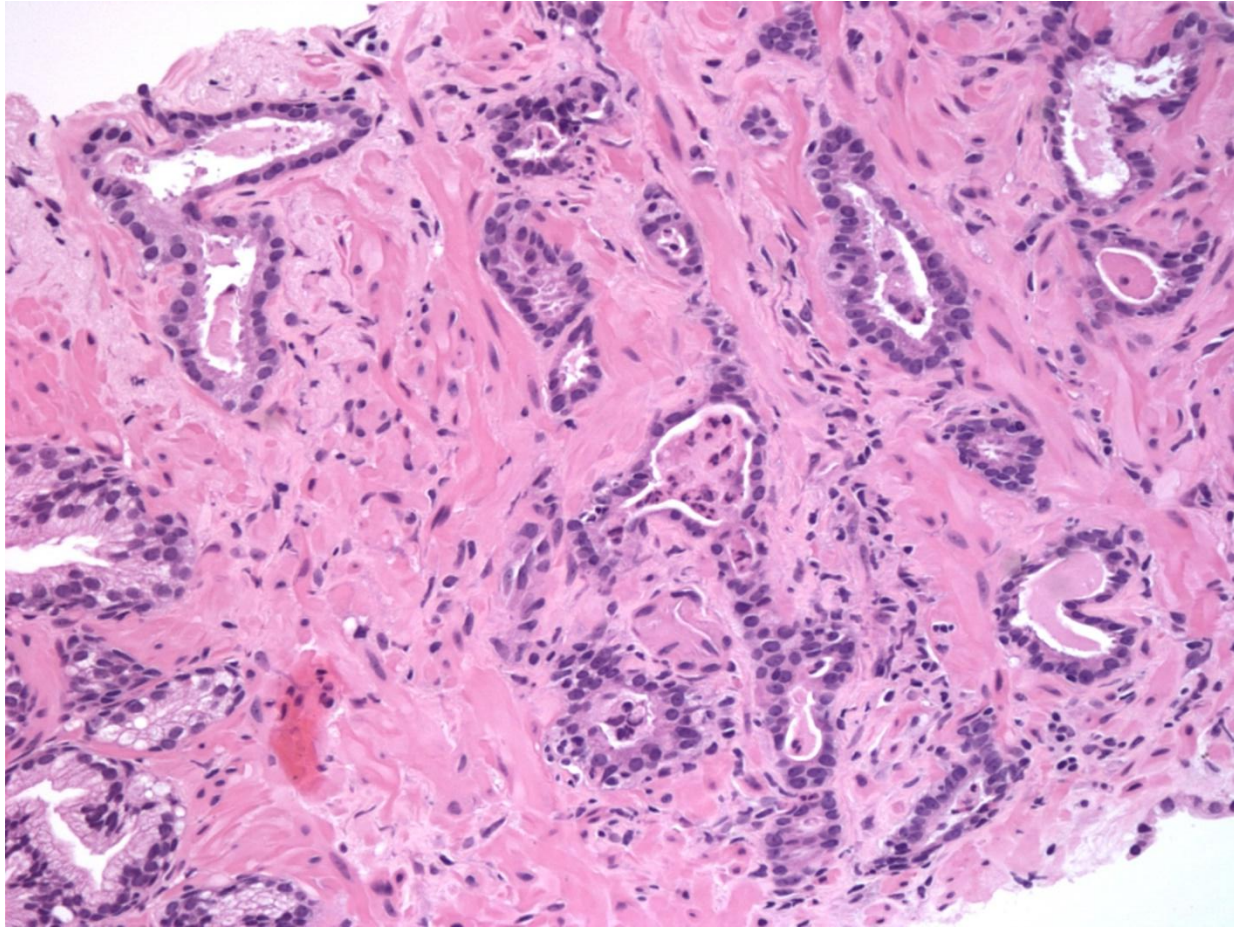
Partial Atrophy



Partial Atrophy

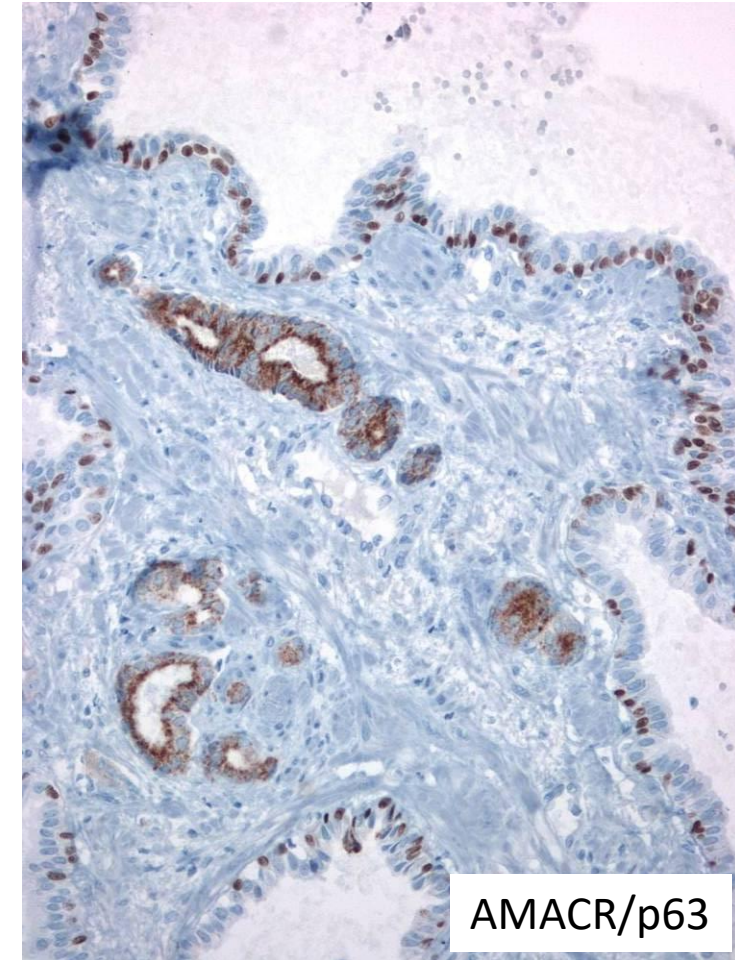
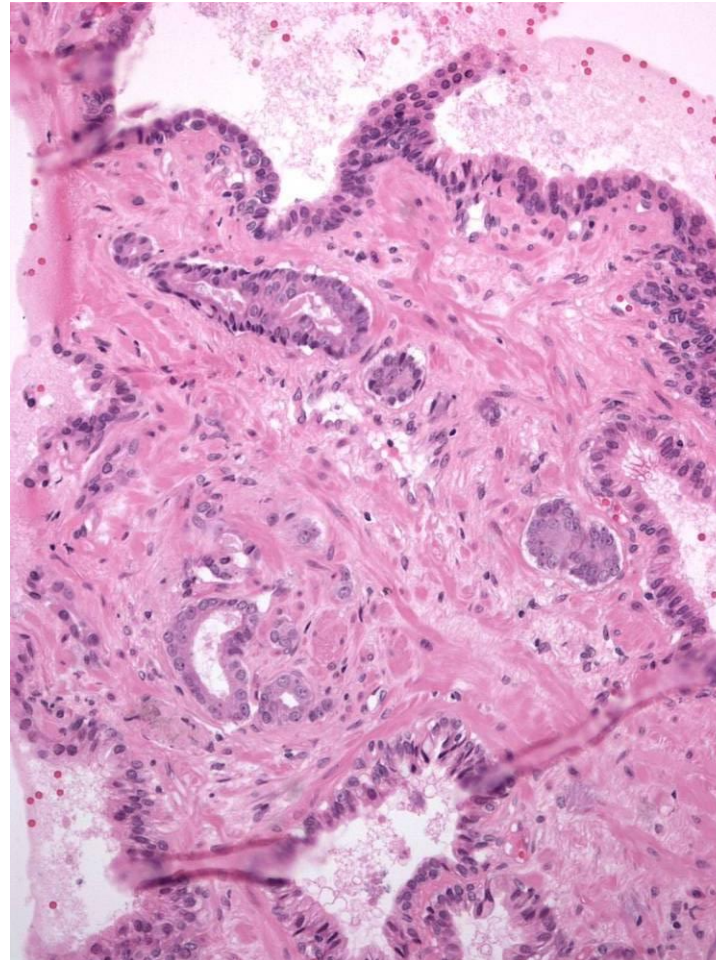


Atrophic Prostate Cancer



DIAGNOSIS OF LIMITED PROSTATE CANCER

- Relies on a constellation of architectural and cytological features
- Absence of basal cells may be confirmed by IHC
- AMACR is commonly used in conjunction with morphology and basal cell markers to help establish a PCA diagnosis

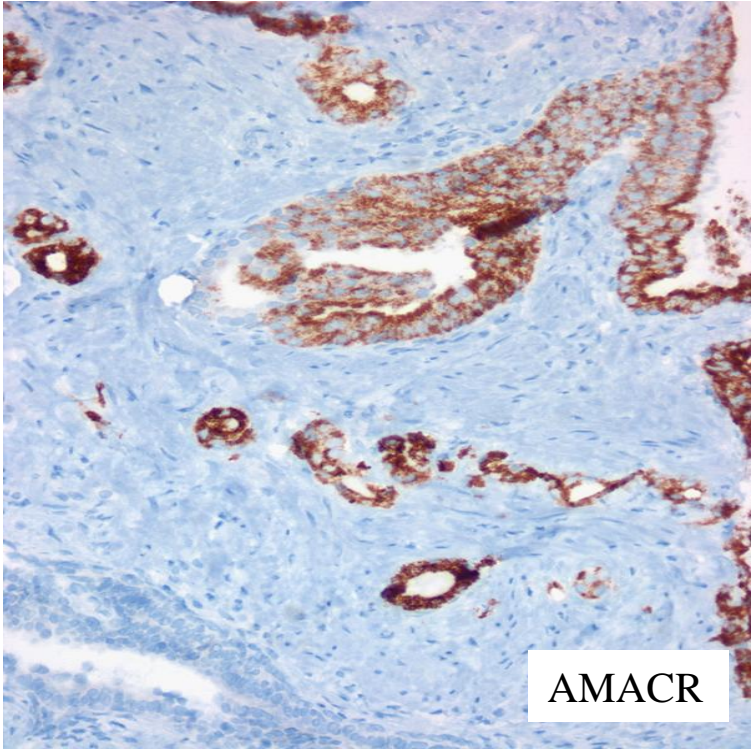
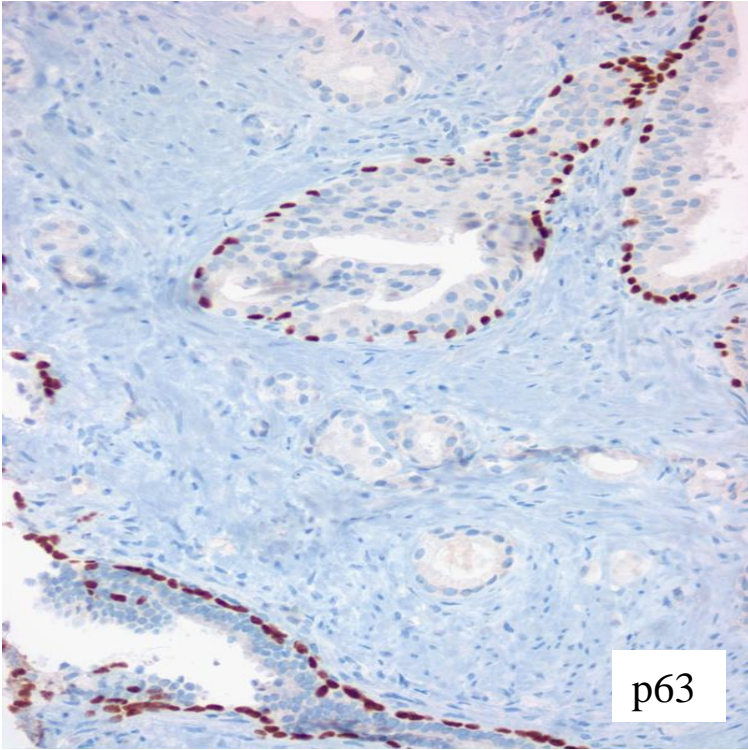
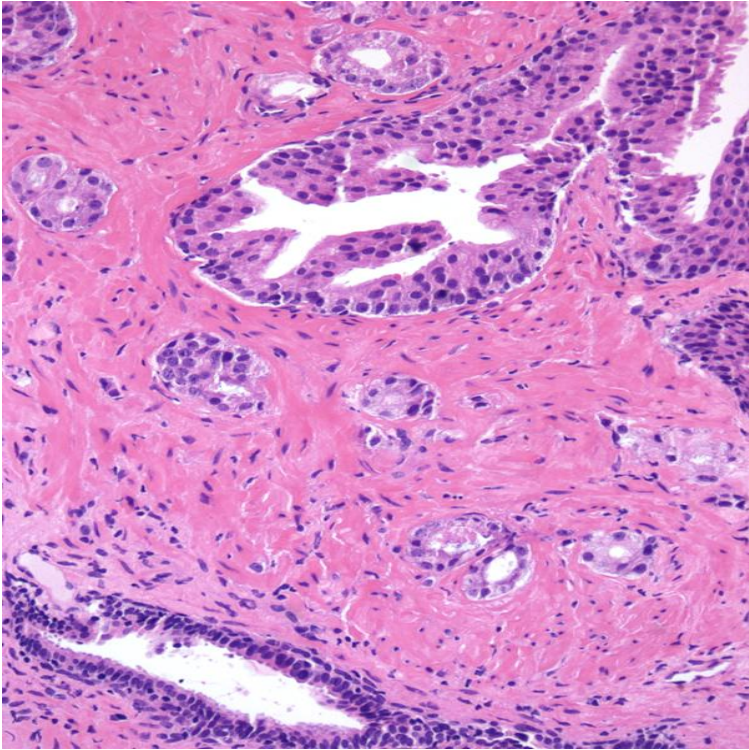


Diagnosis of Limited PCA: Role of IHC

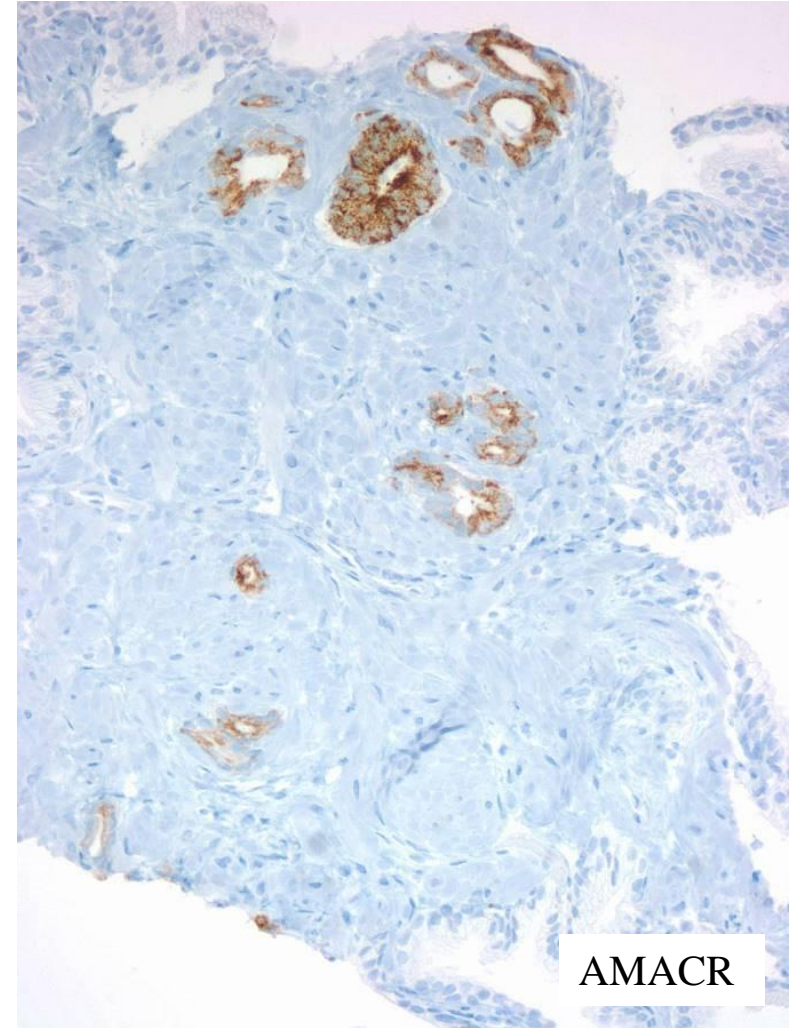
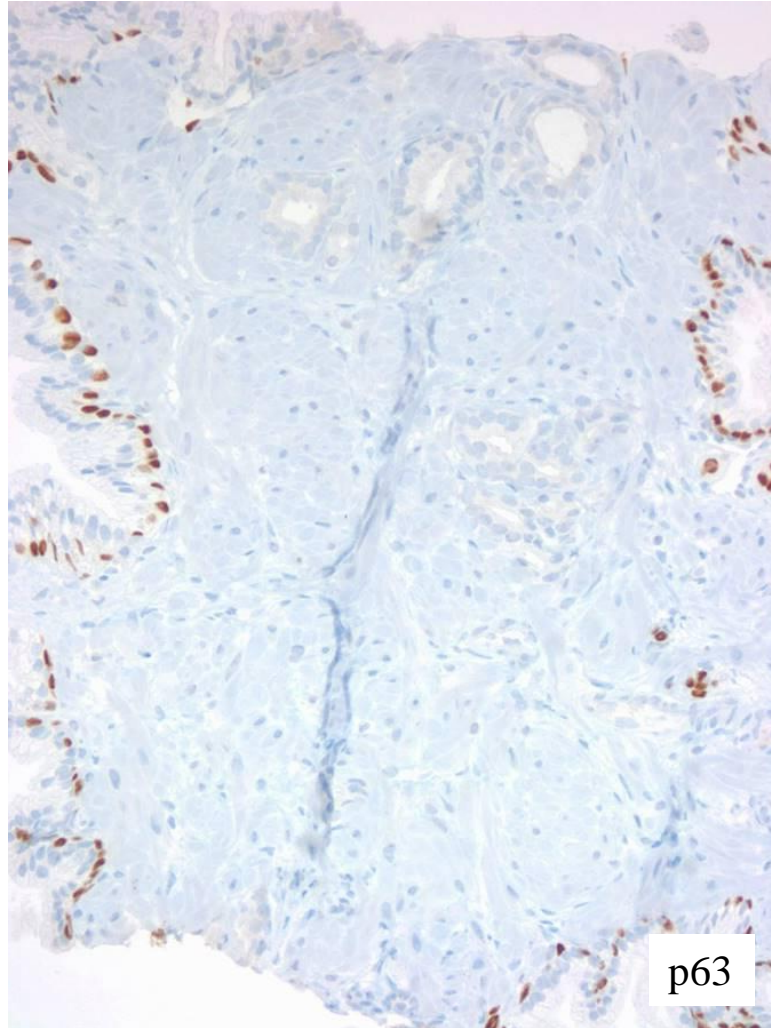
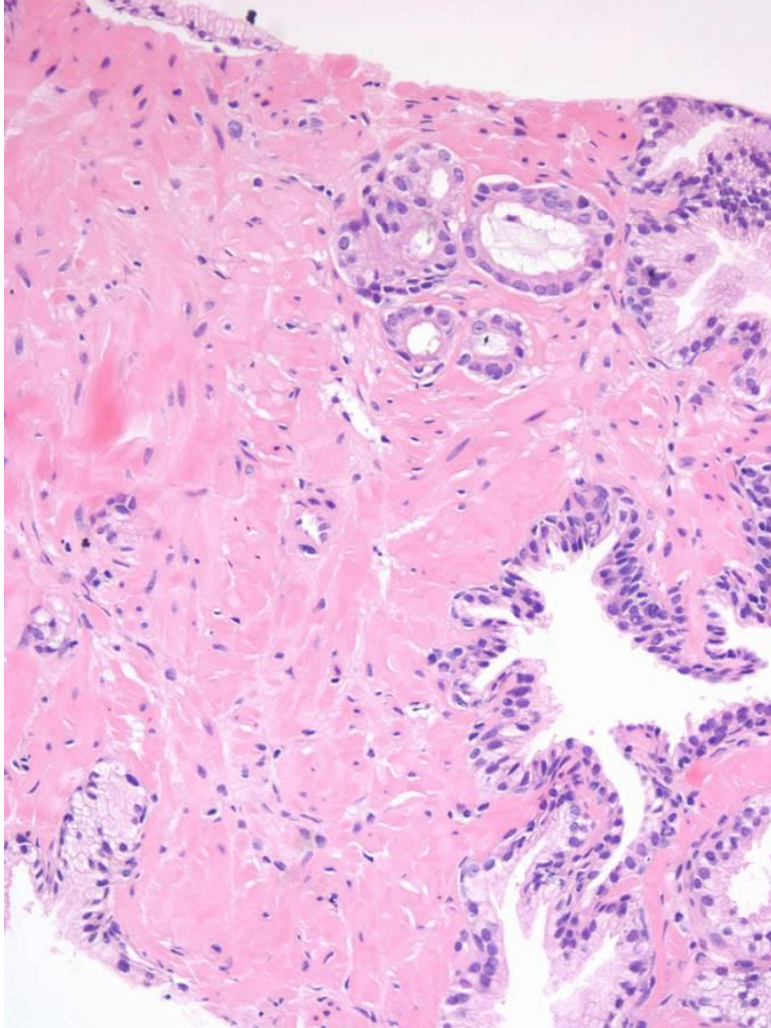
Stain	Advantages	Disadvantages
p63	More specific	p63+ aberrant PCA; false – in mimics
HMWCK (34BE12)	No aberrant HMWCK+ PCA	Increased non-specificity False – in mimics
HMWCK/p63	Conserves tissue	May not recognize p63+PCA
AMACR (P504s)	+ in 80-90% PCA	False + in mimics
AMACR/p63	Conserves tissue	Difficult to see rare p63+ basal cells if using same chromogen
p63/AMACR/HMWCK (PIN4)	Conserves tissue	Dual color May not recognize p63+PCA
ERG	Highly specific for PCA	+ in 40-60% PCA and ~20% HGPIN adjacent to PCA

Best practice recommendations in application of IHC in prostate: Epstein et al. Am J Surg Pathol 2014

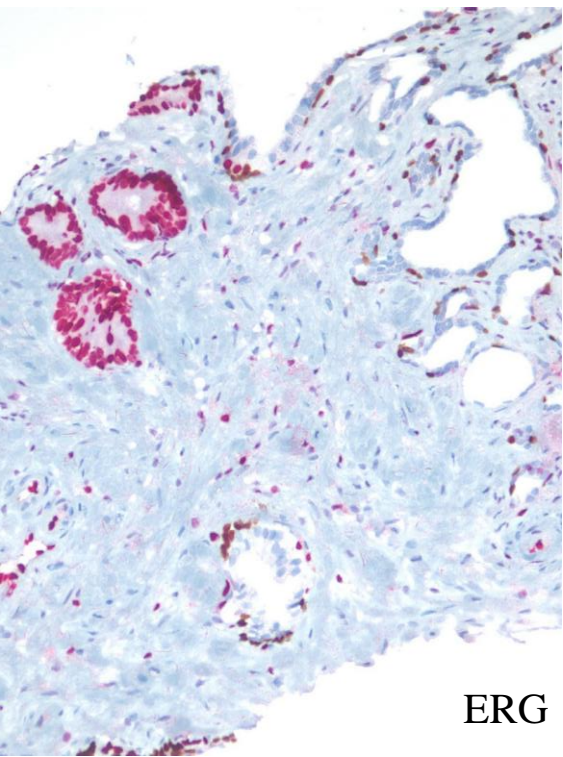
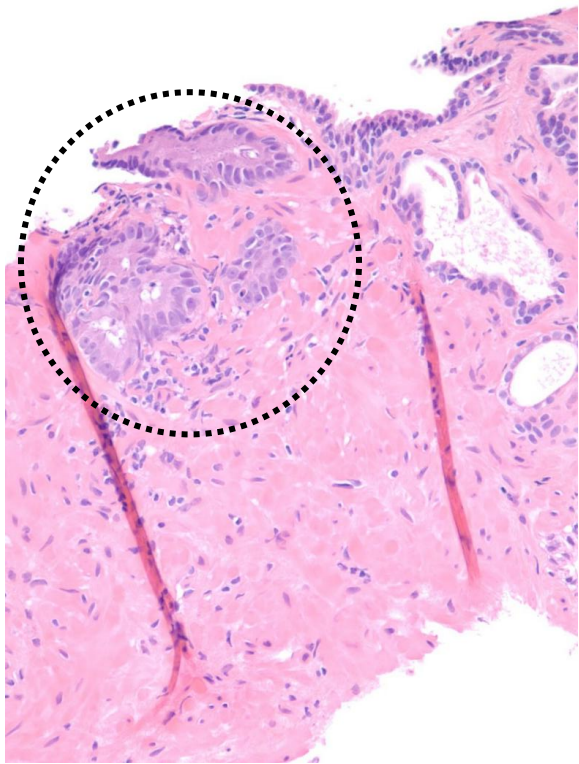
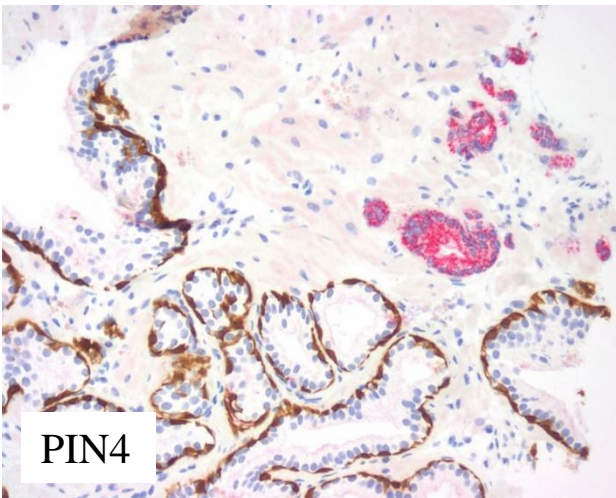
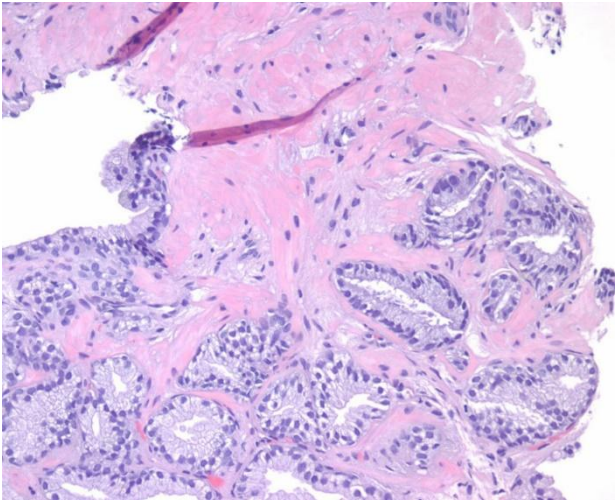
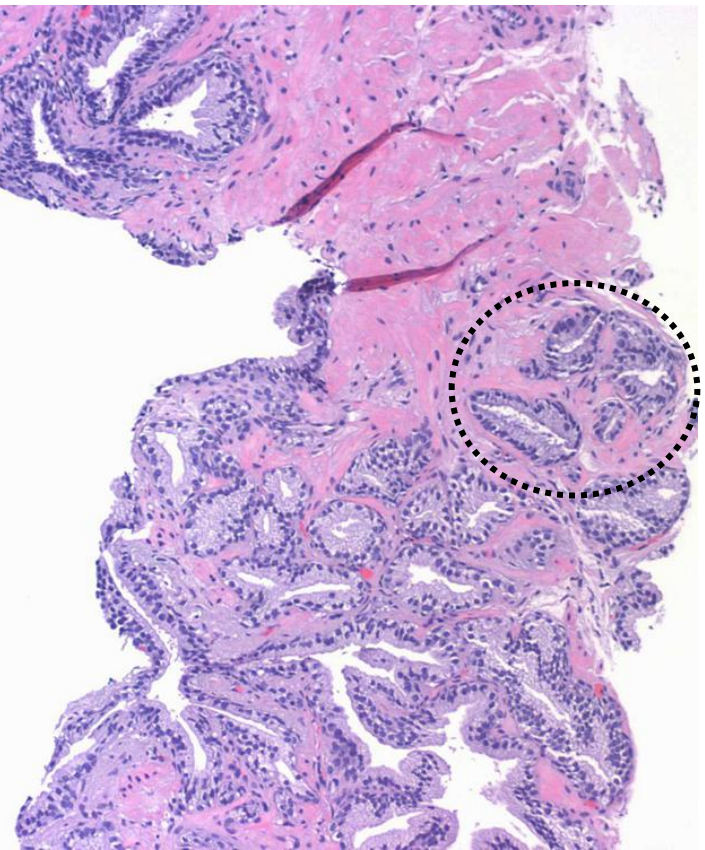
Diagnostic Utility of IHC Stains in Limited Prostate Cancer



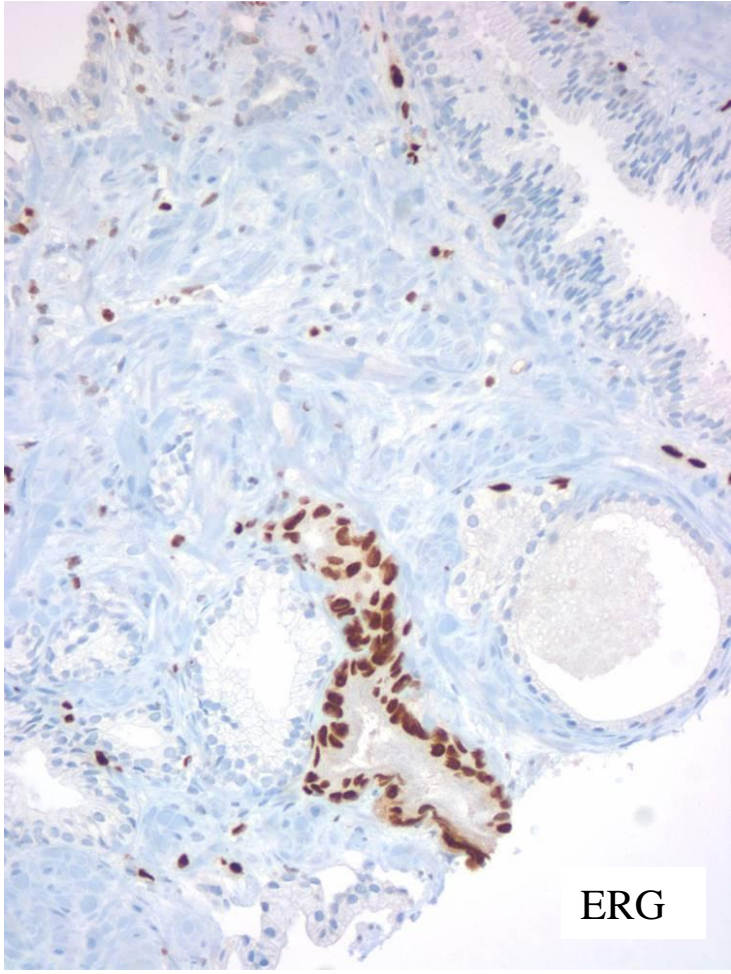
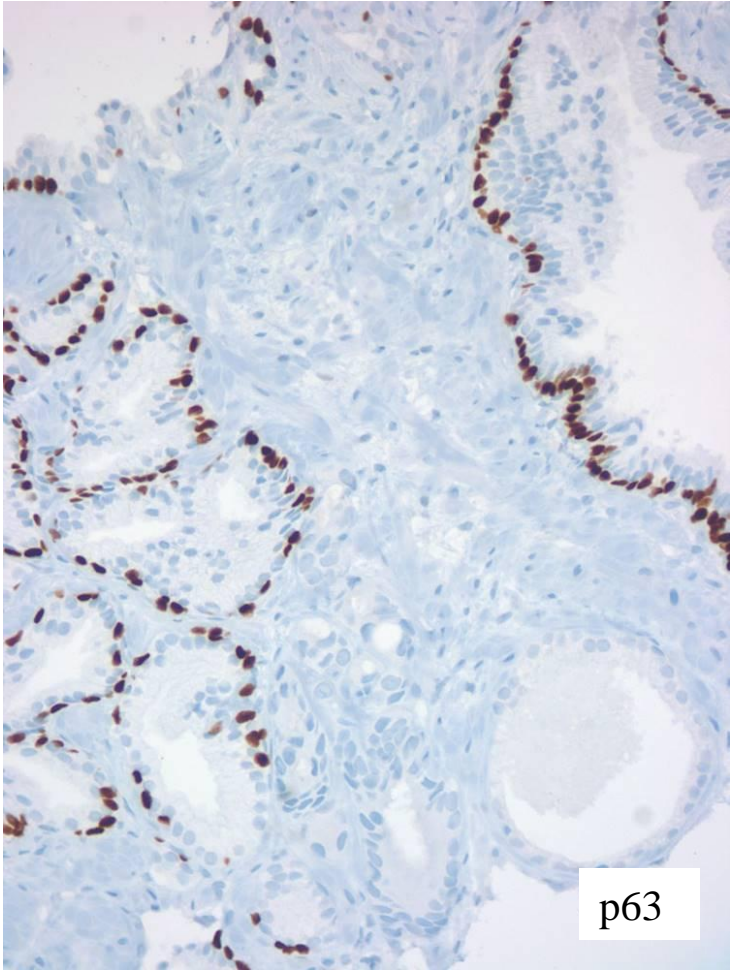
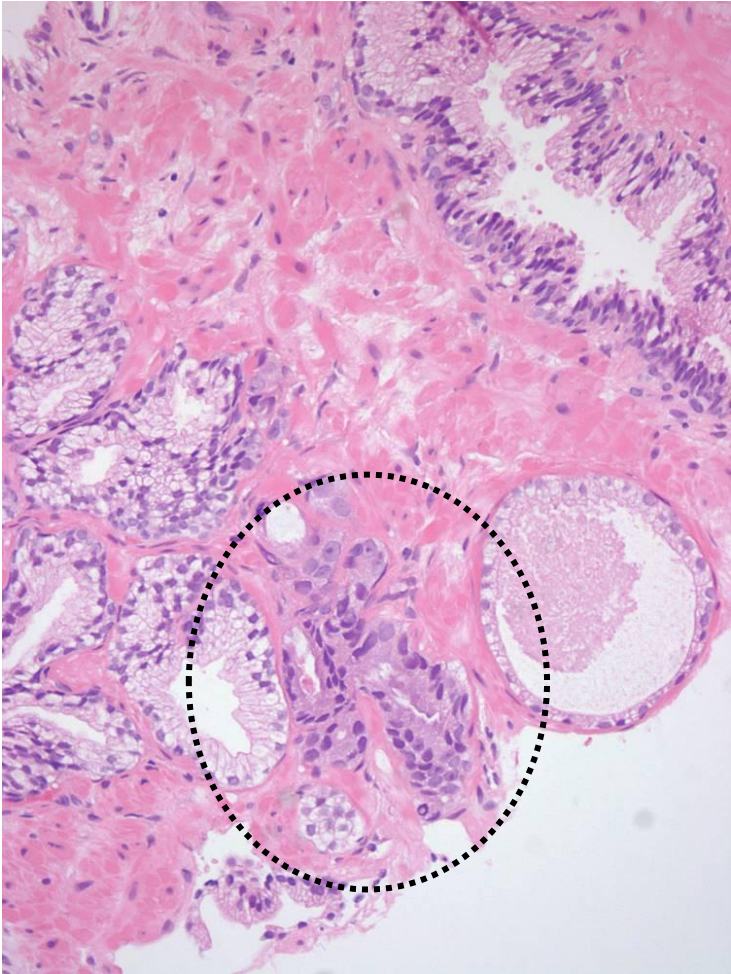
Diagnostic Utility of IHC Stains in Limited Prostate Cancer



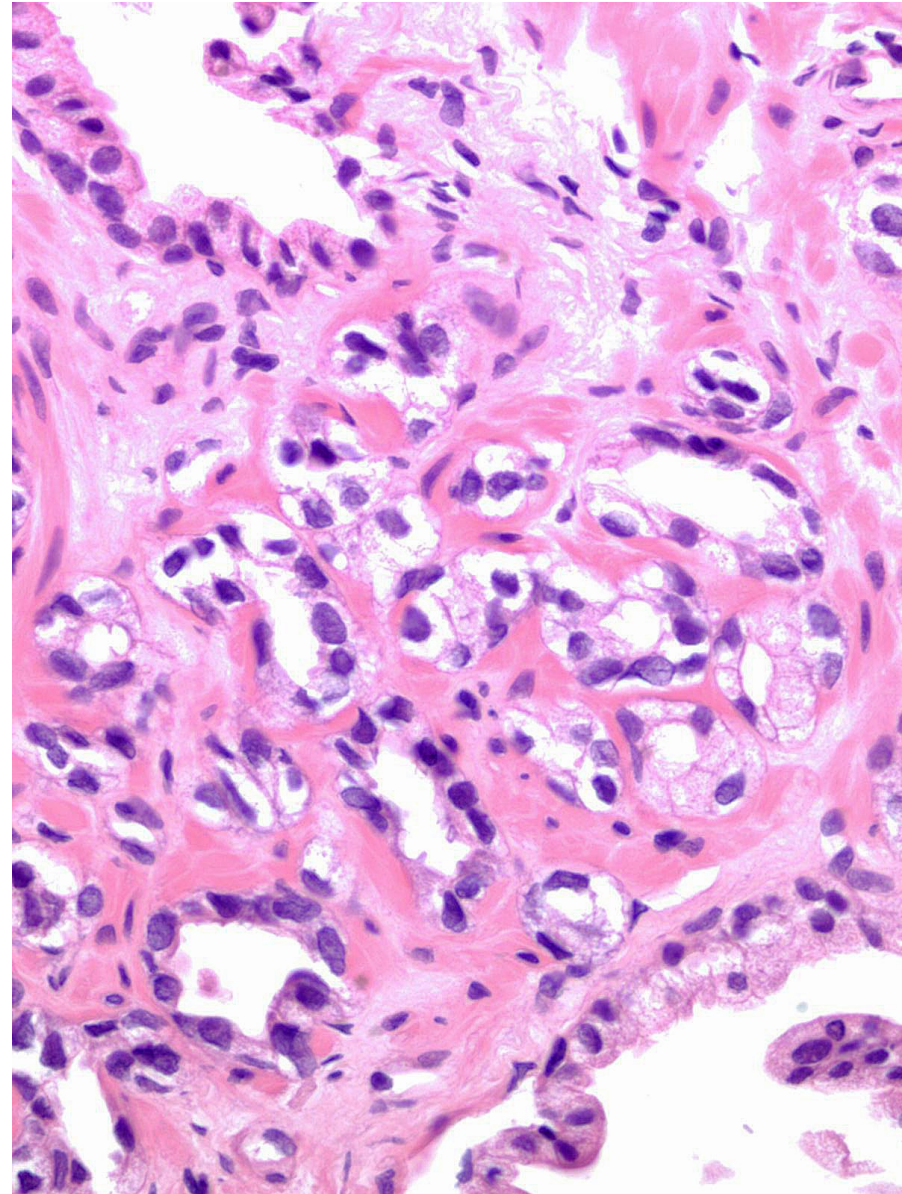
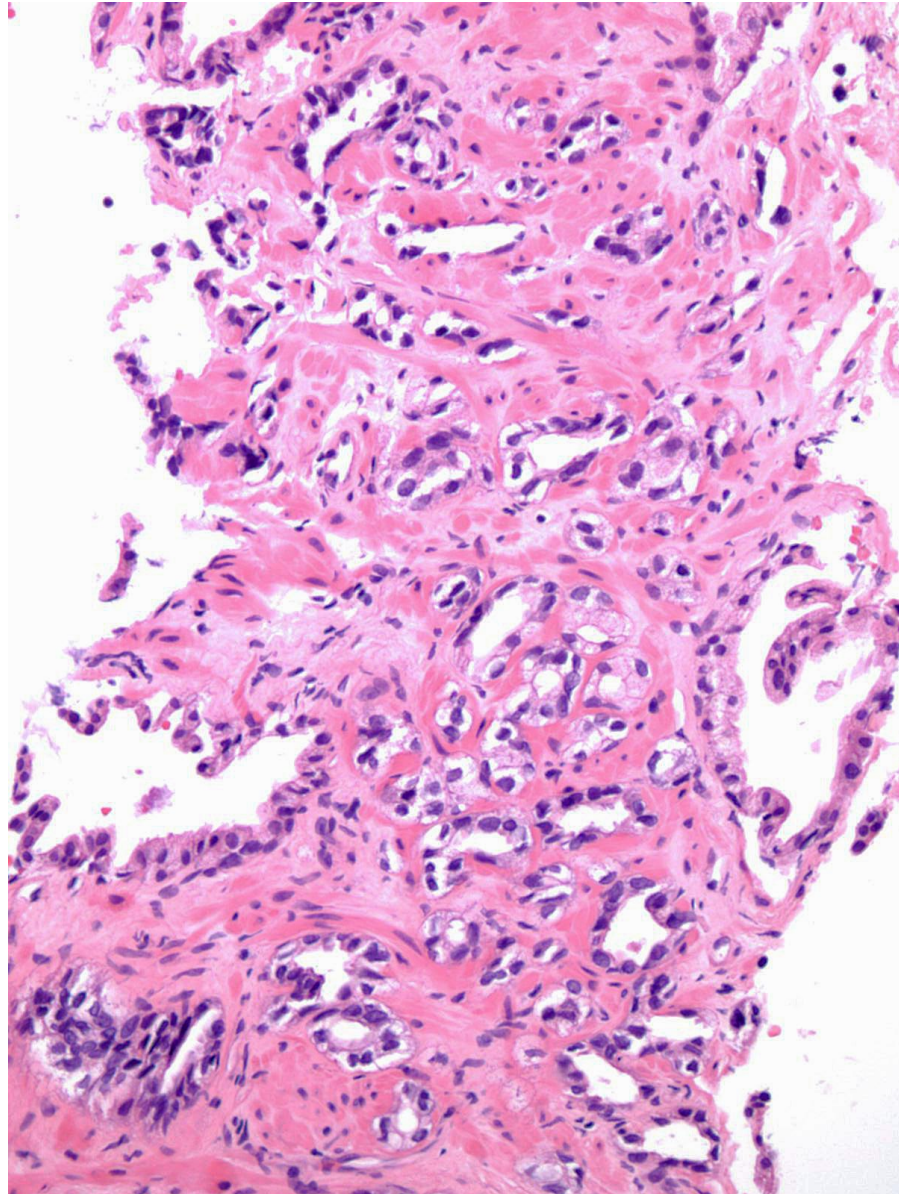
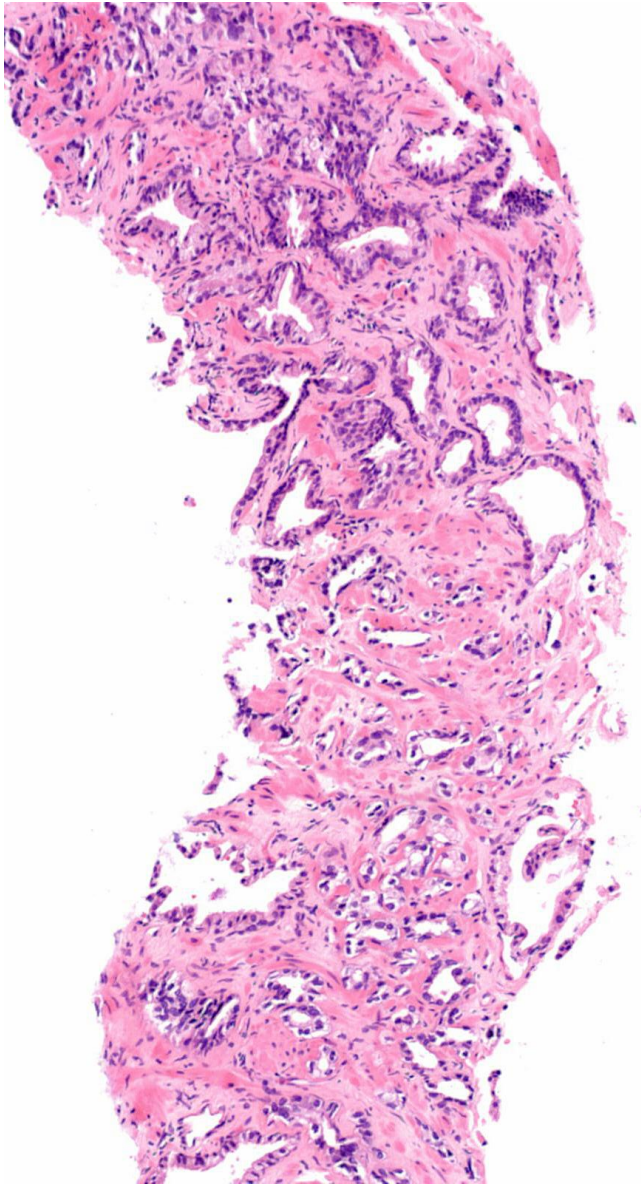
Diagnostic Utility of IHC Stains in Limited Prostate Cancer



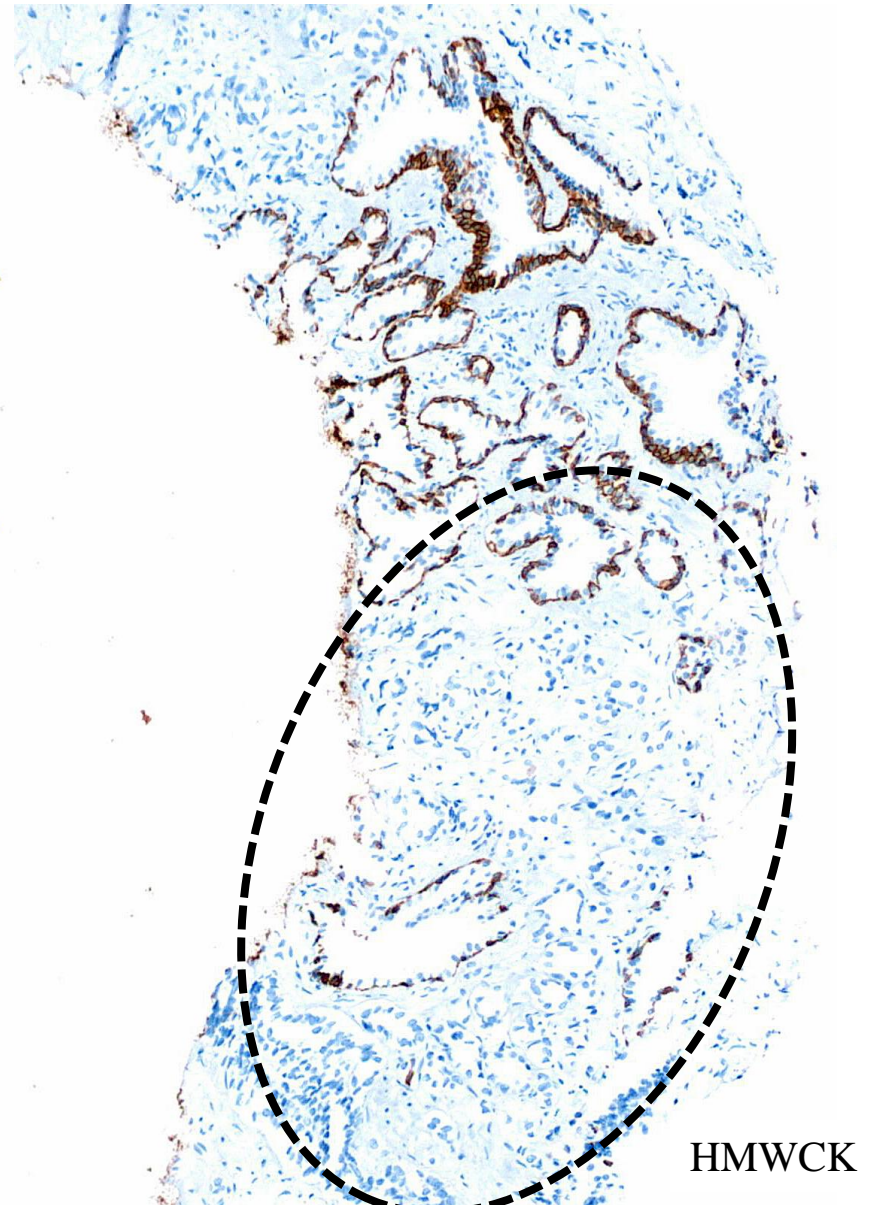
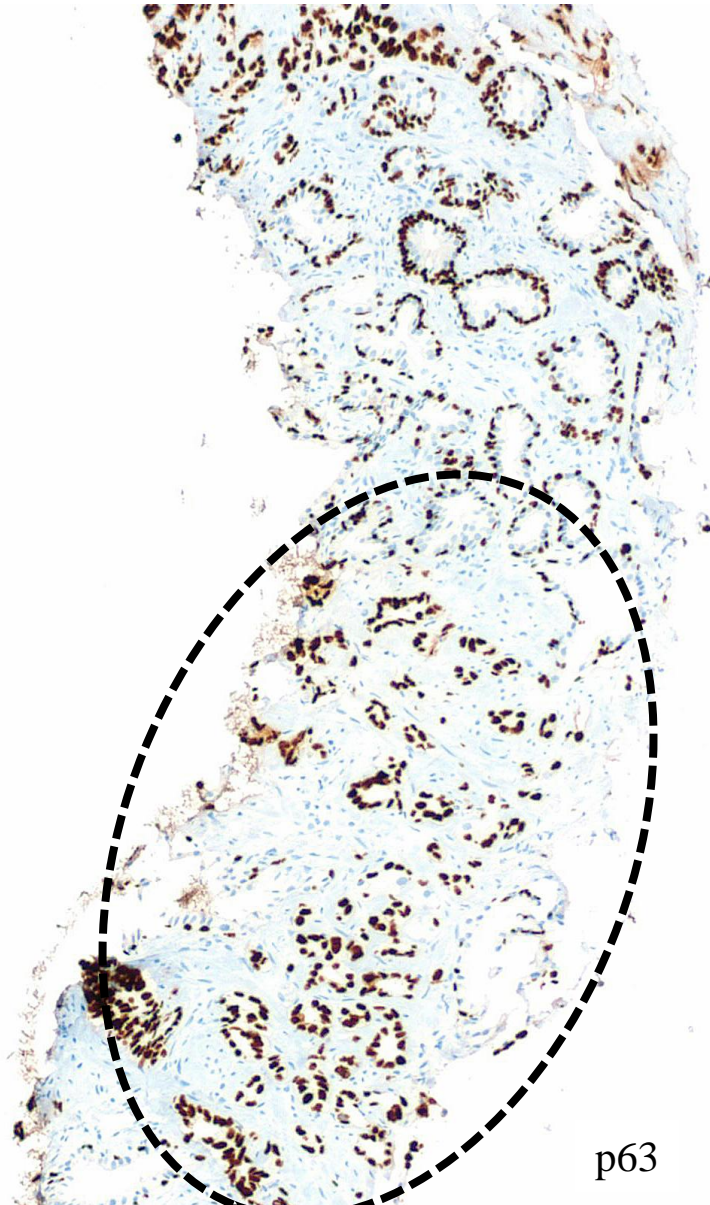
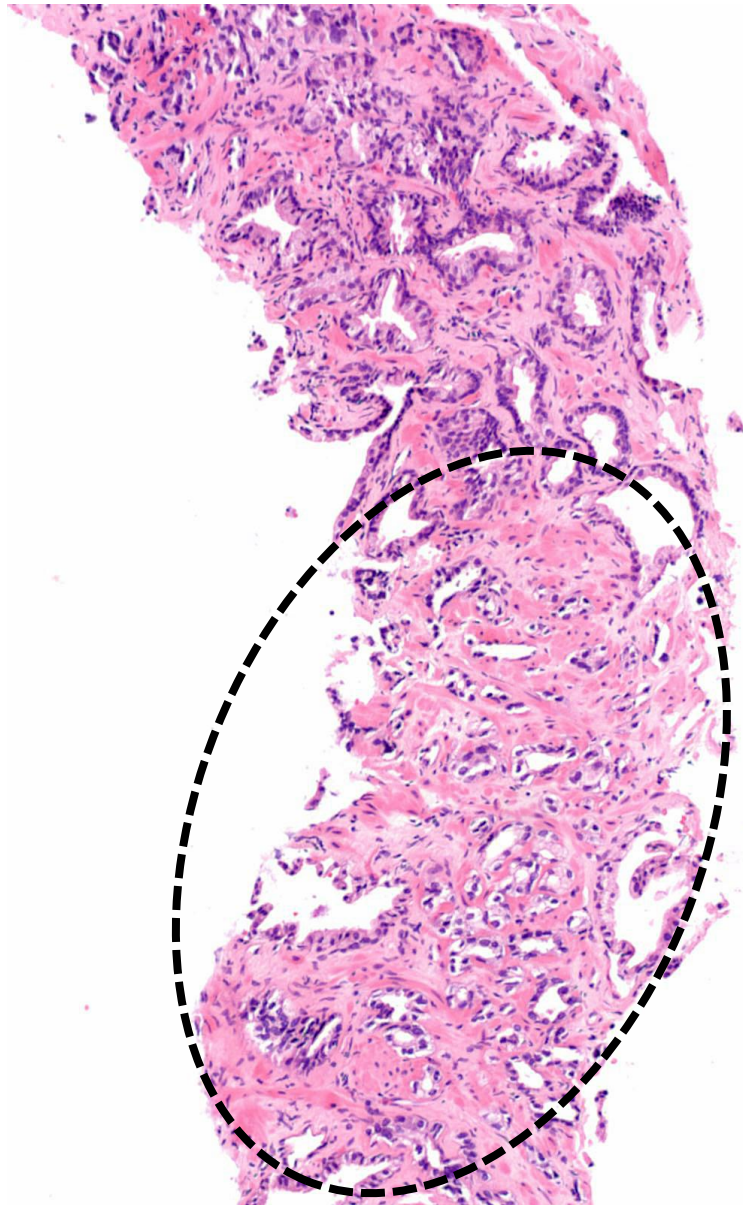
Diagnostic Utility of IHC Stains in Limited Prostate Cancer



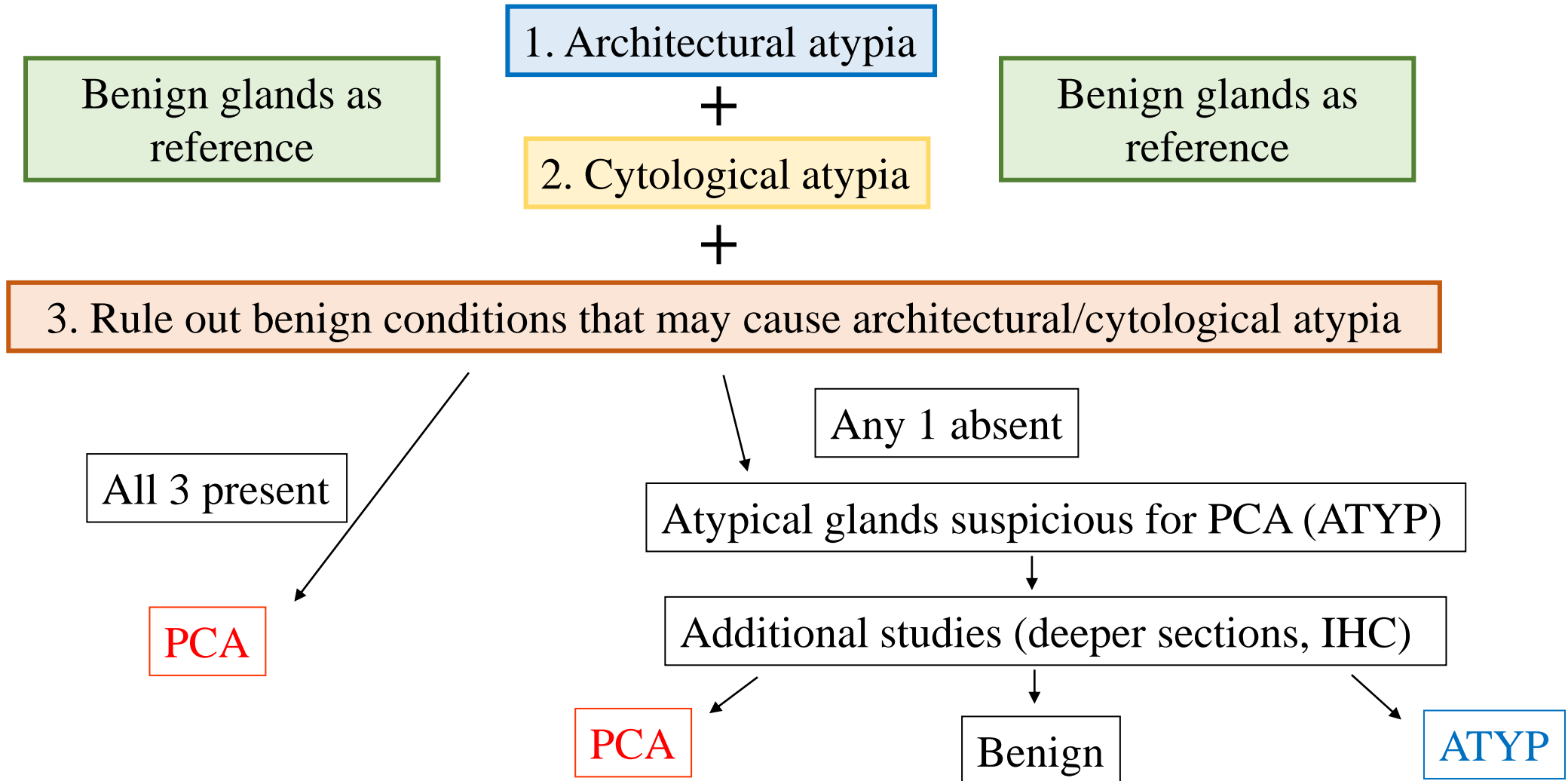
DIAGNOSTIC UTILITY OF IHC STAINS IN PROSTATE CANCER

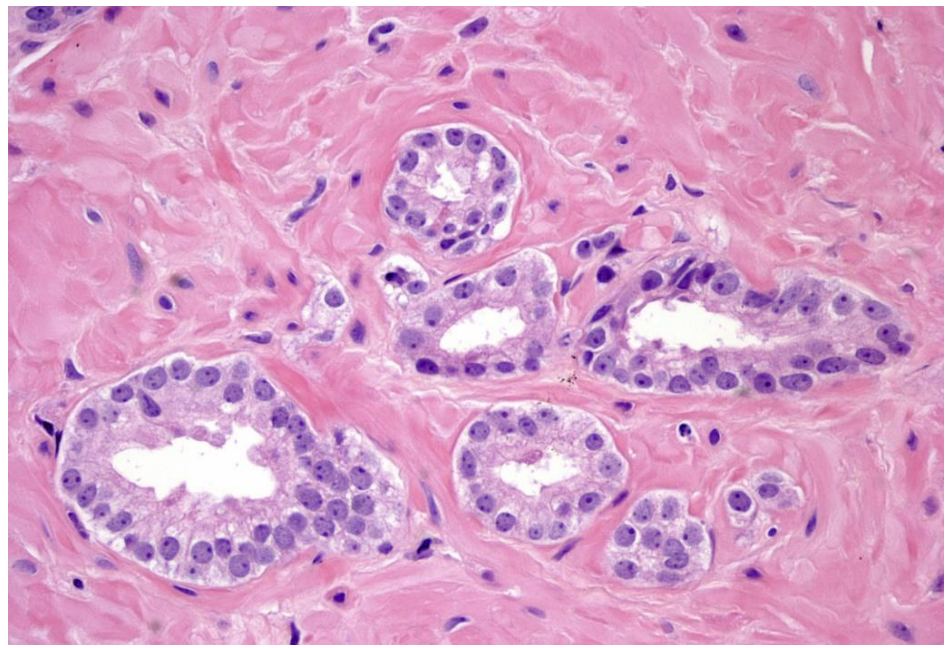
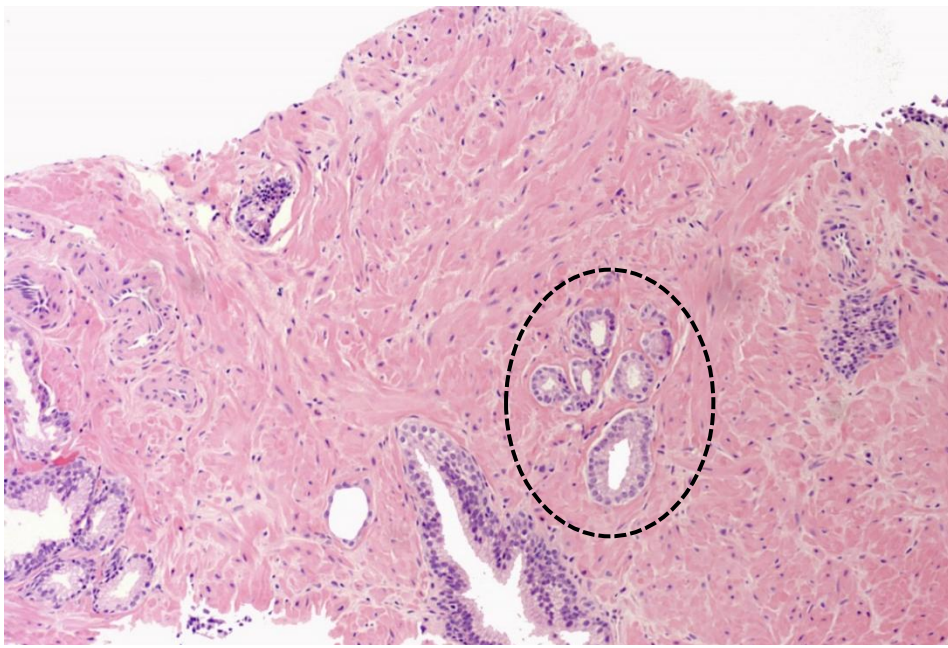


ABERRANT P63 EXPRESSION IN PROSTATE CANCER

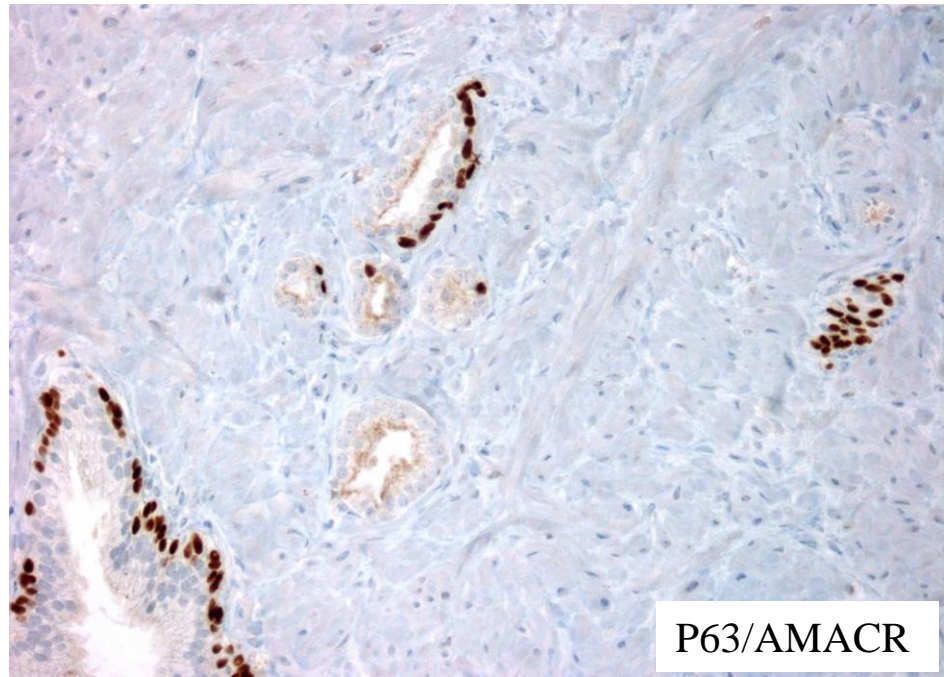
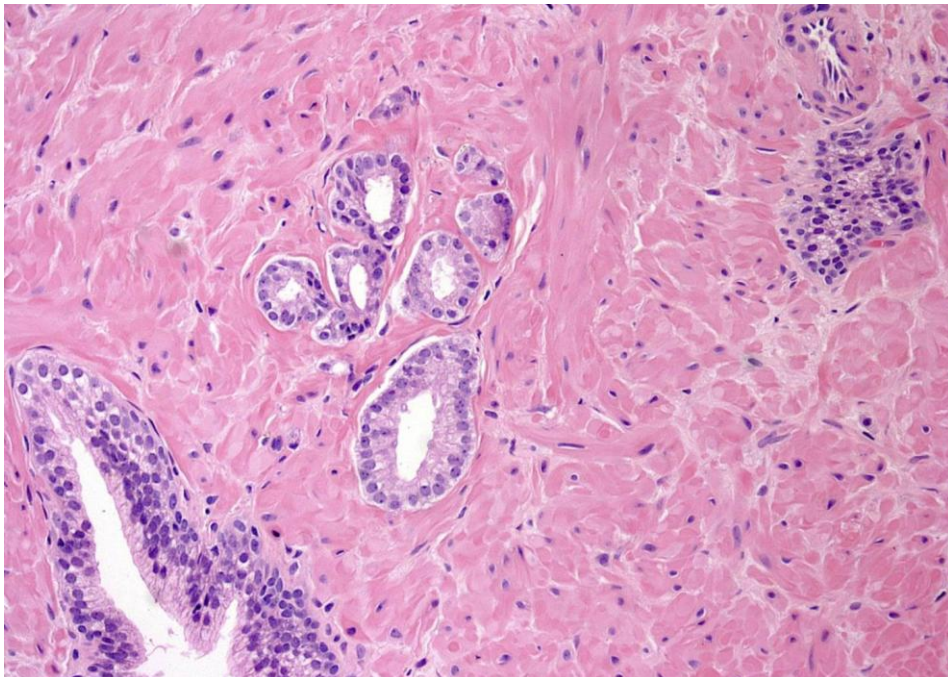


DIAGNOSTIC APPROACH TO LIMITED ATYPICAL GLANDS





Atypical Glands Suspicious for PCA (ATYP/ASAP)



Atypical glands suspicious for cancer (ATYP) or Atypical Small Acinar Proliferation (ASAP)

- Small focus of atypical glands suspicious for PCA, but with insufficient cytologic and/or architectural atypia to establish a definitive diagnosis of cancer
- NOT a distinct biological entity, but rather comprehends a range of different lesions
- Incidence on Bx ranges from ~1% to 23% (median 4.4)
- Likelihood of finding PCA on repeat Bx is 40-50%, compared to 20-25% risk associated with HGPIN
- Patients with ATYP/ASAP on initial biopsy are recommended to undergo repeat biopsies within 3-6 months

Histologic Features Resulting in ATYP/ASAP

Limited number of atypical glands (minimally sampled lesion)

Biopsy and tissue processing artifact

- Crush artifact obscuring morphology
- Poorly fixed or stained tissue sections
- Atypical glands at the edge of the core

Atypical morphology seen in both malignant and benign lesions

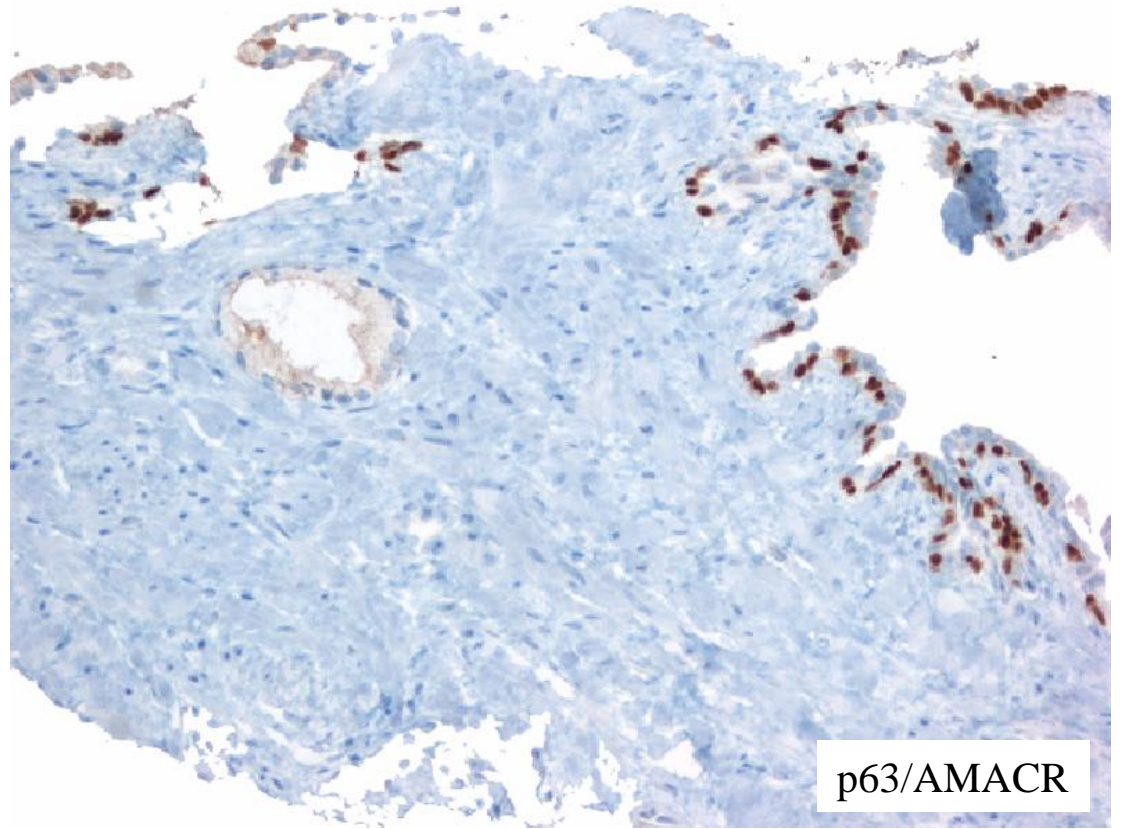
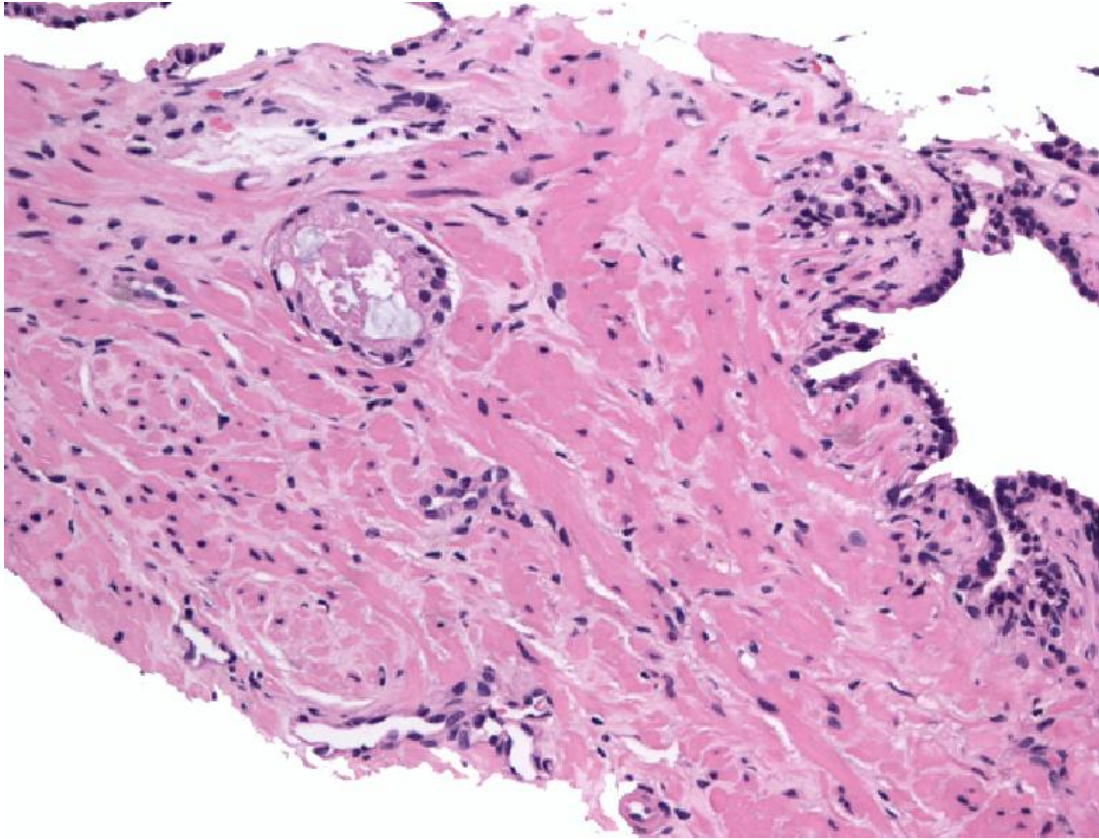
- Crowded glands with minimal cytologic atypia (cancer vs. adenosis)
- Poorly formed glands (cancer vs. partial atrophy)
- Atypia in atrophic glands (atrophic cancer vs. benign atrophy)
- HGPIN with adjacent small focus of atypical glands (PINATYP) (microinvasive cancer vs. outpouching or tangential sectioning of HGPIN)
- Atypia associated with inflammation (inflamed cancer glands vs. reactive atypia)

Confusing IHC stains

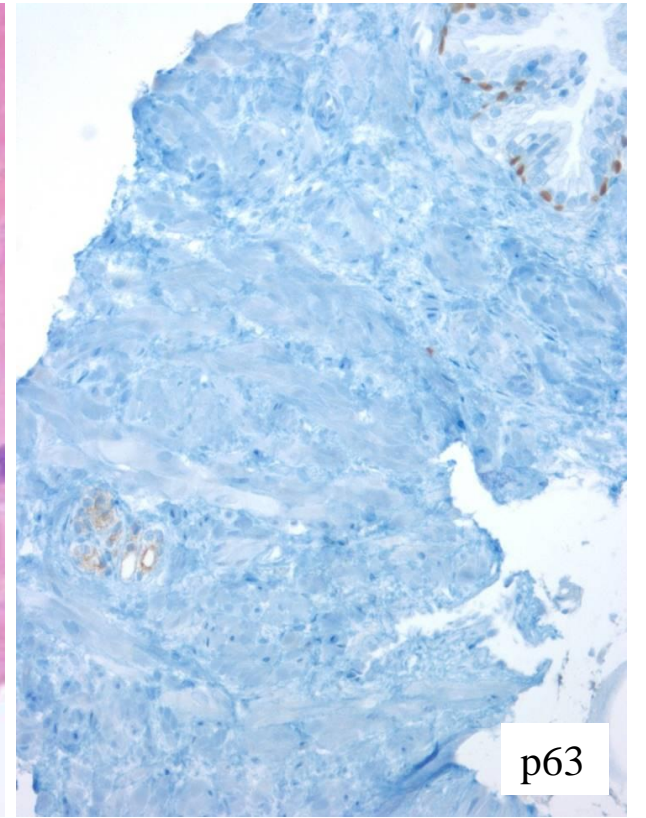
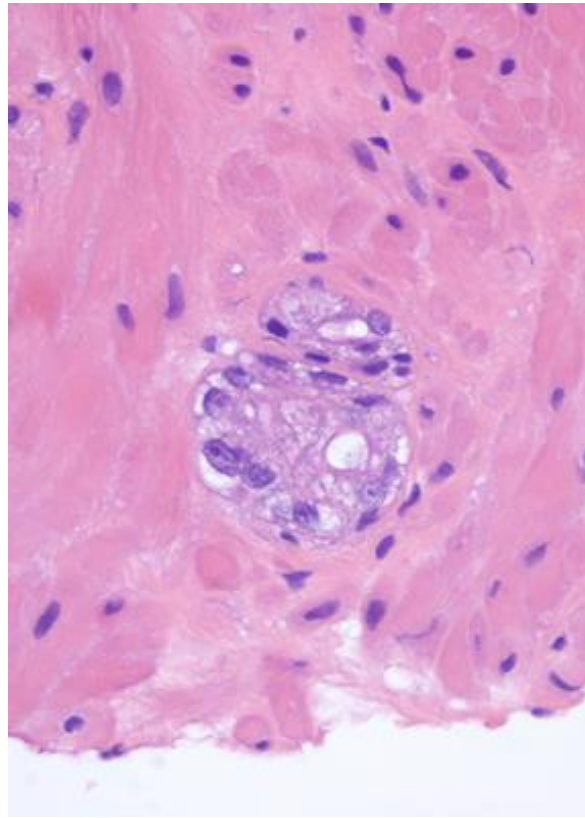
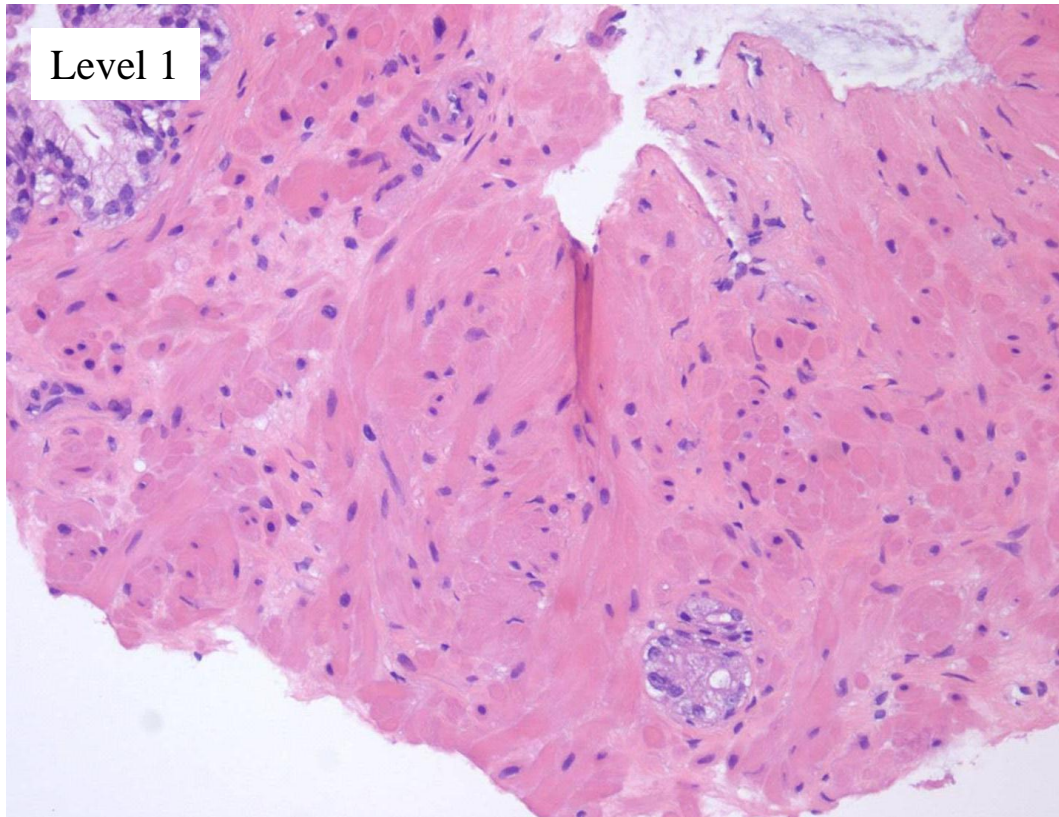
- Negative basal cell markers in a benign-looking lesion
- Positive AMACR in a benign-looking lesion
- Focal positive basal cell marker in cancer-looking glands

Adapted from Prostate
Biopsy Interpretation:
An Illustrated Guide, by
RB Shah & M Zhou

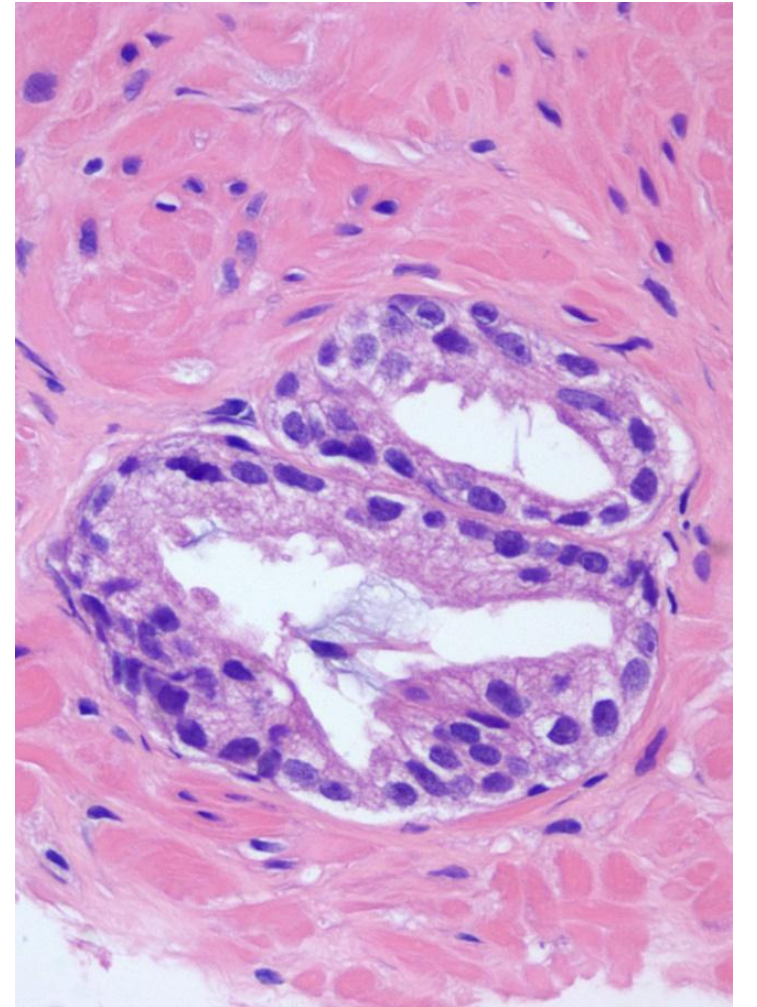
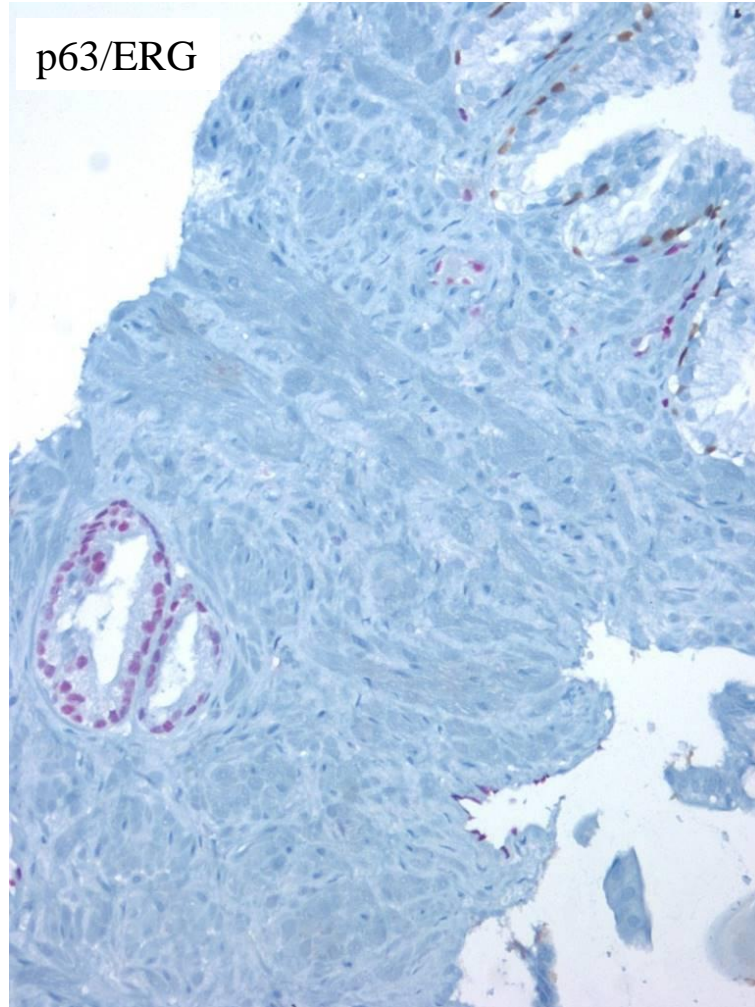
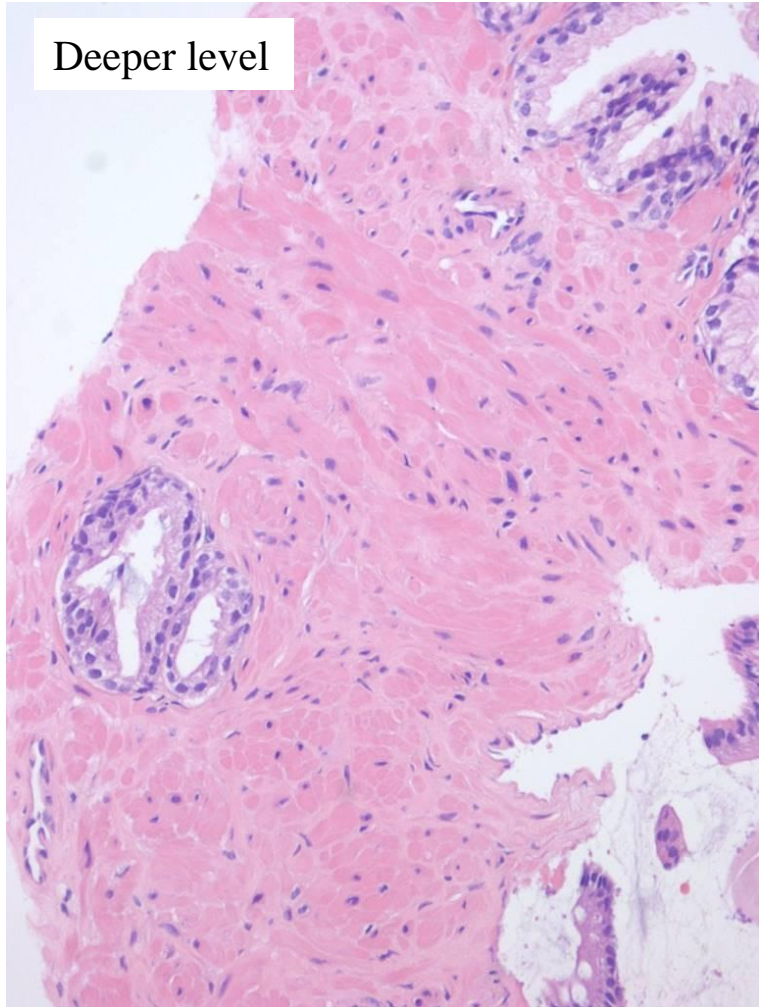
ATYP/ASAP - Limited Number of Atypical Glands



ATYP/ASAP - Limited Number of Atypical Glands

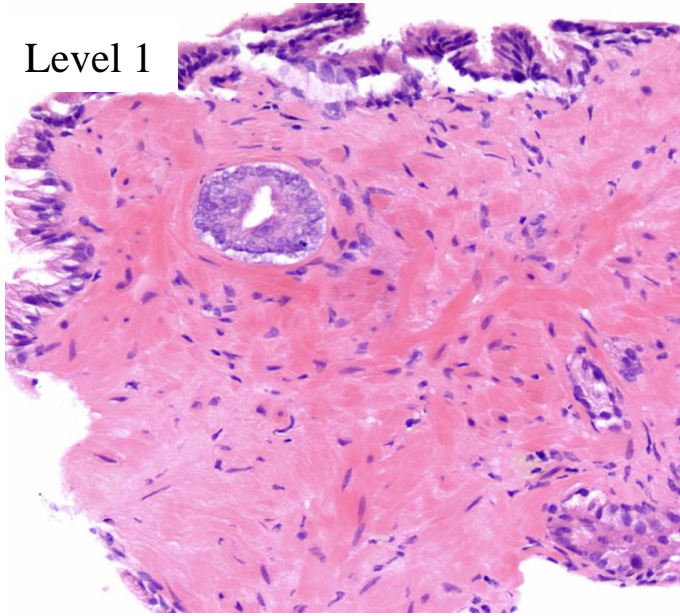


ATYP/ASAP - Limited Number of Atypical Glands

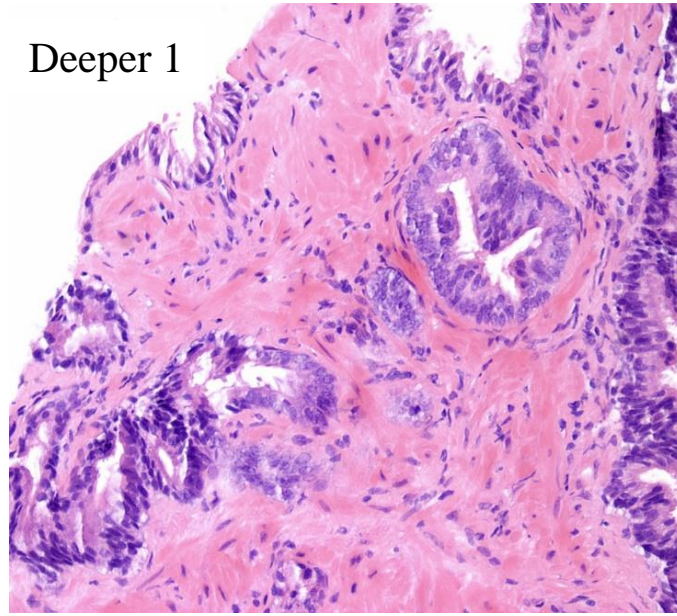


ATYP/ASAP - Limited Number of Atypical Glands

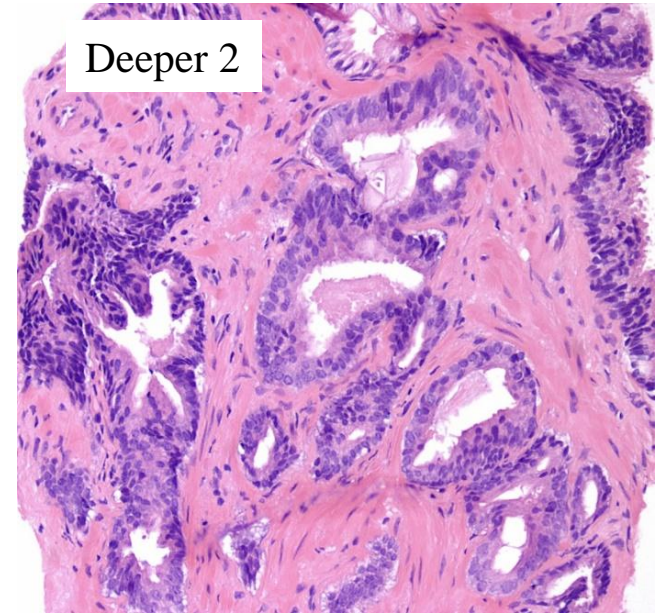
Level 1



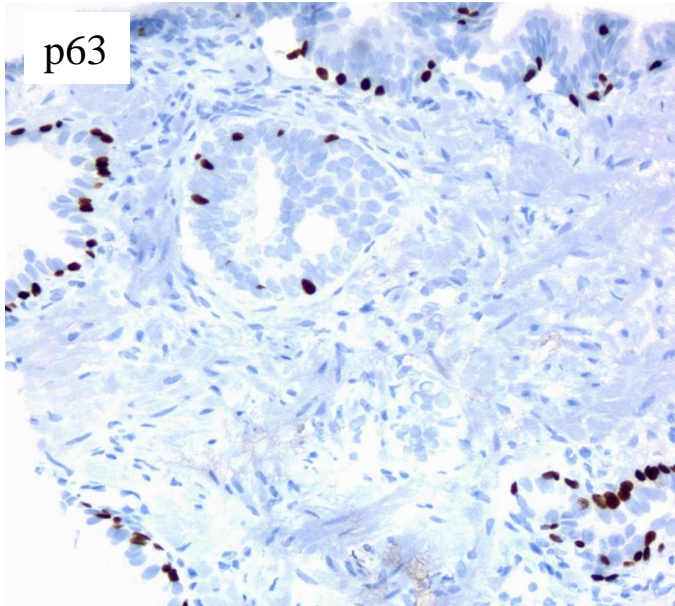
Deeper 1



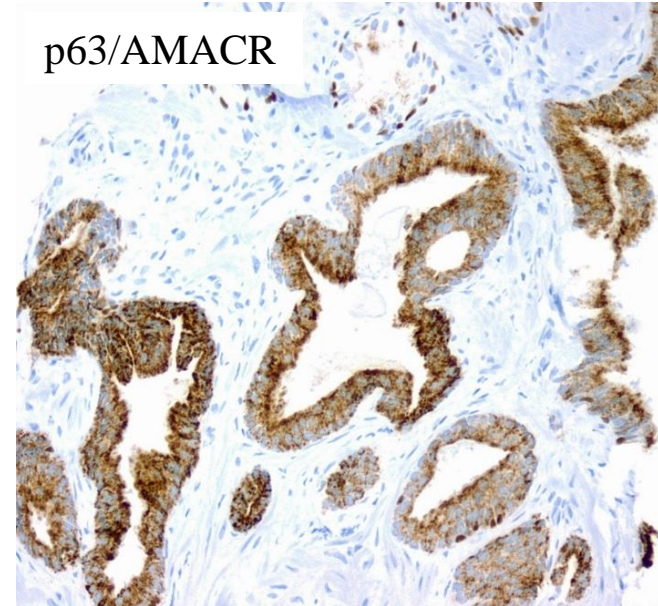
Deeper 2



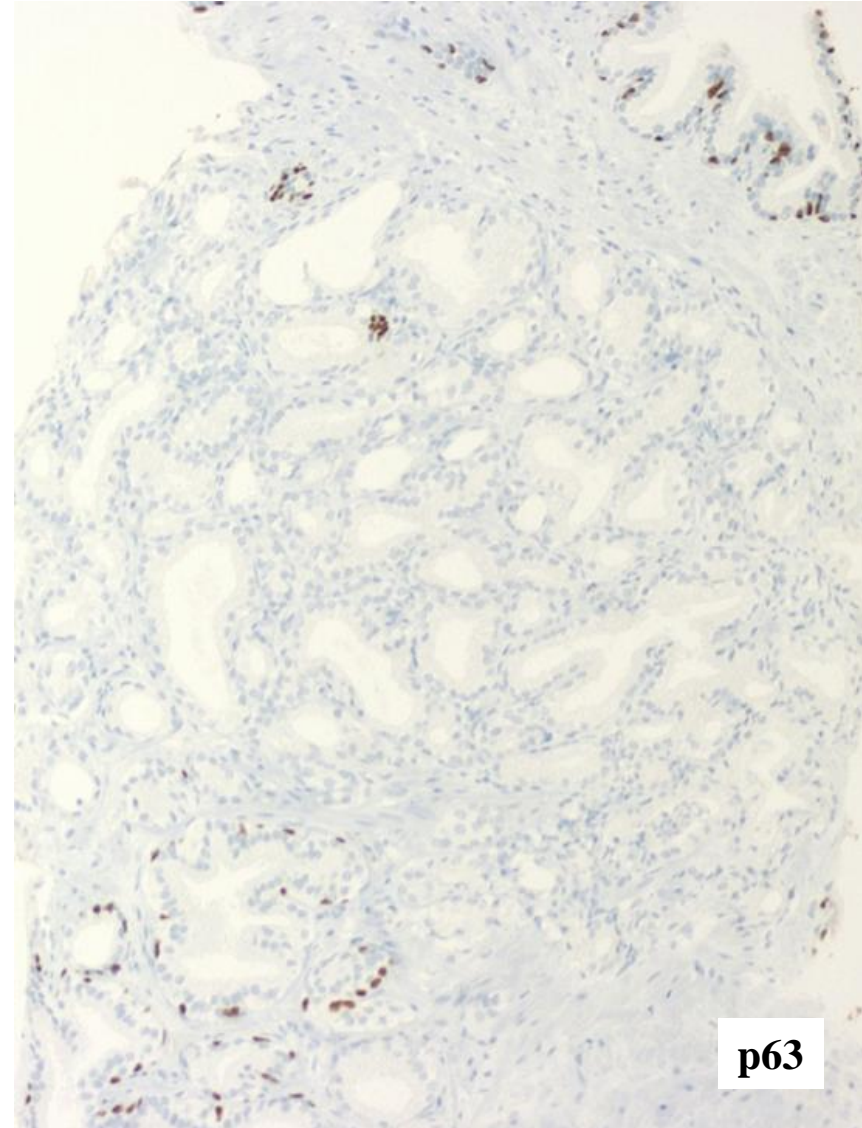
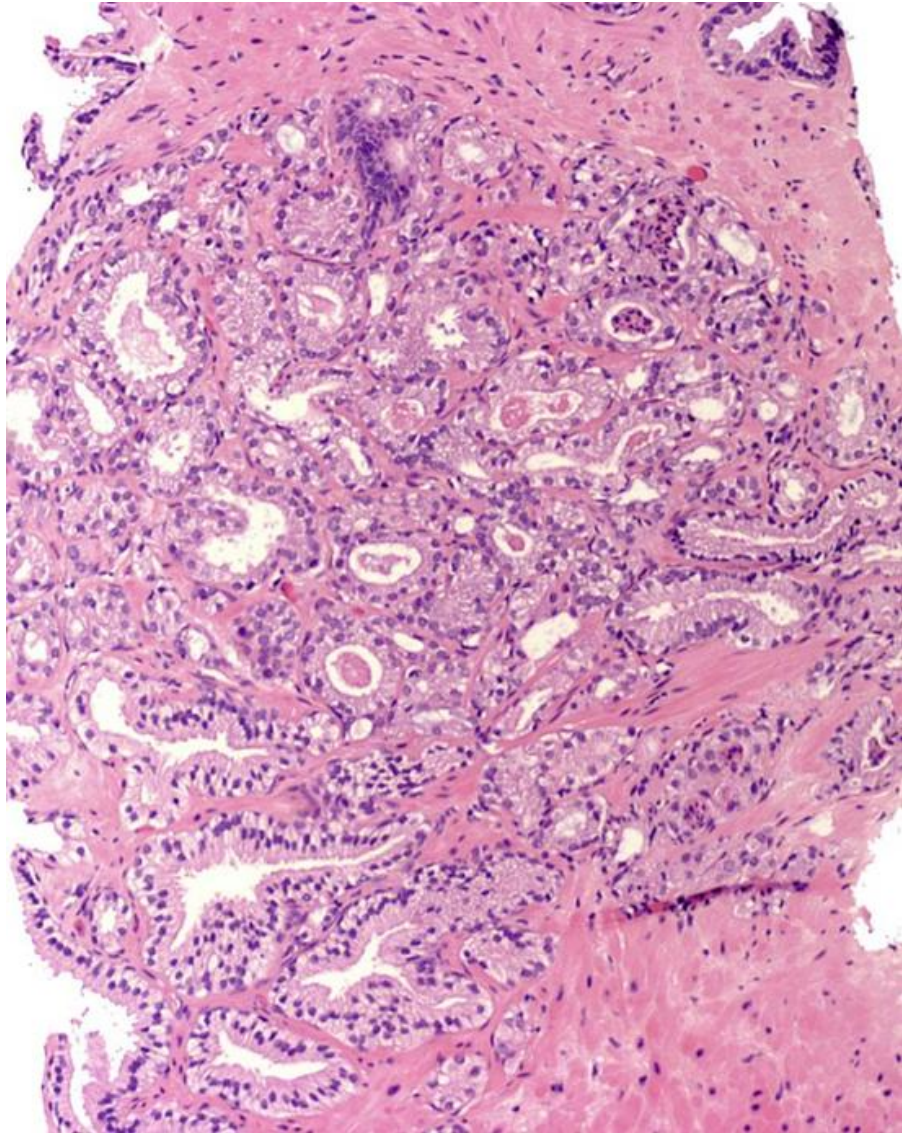
p63



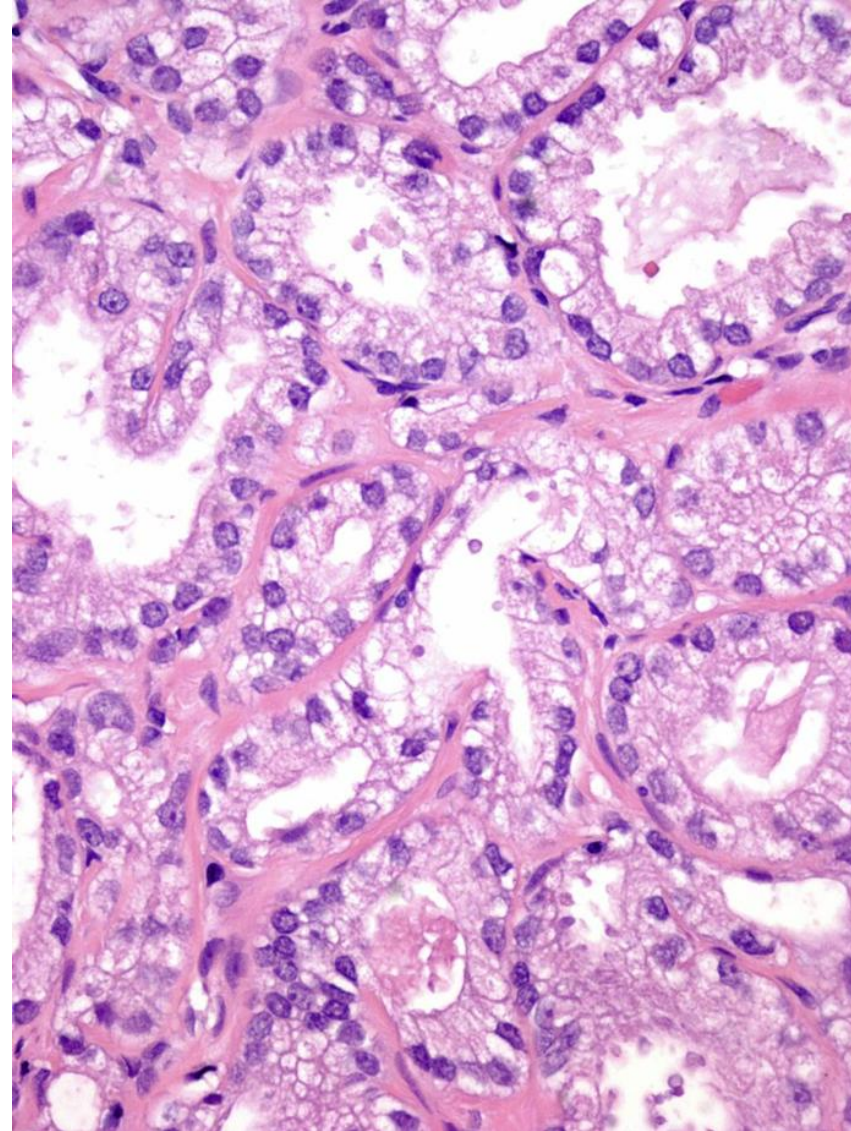
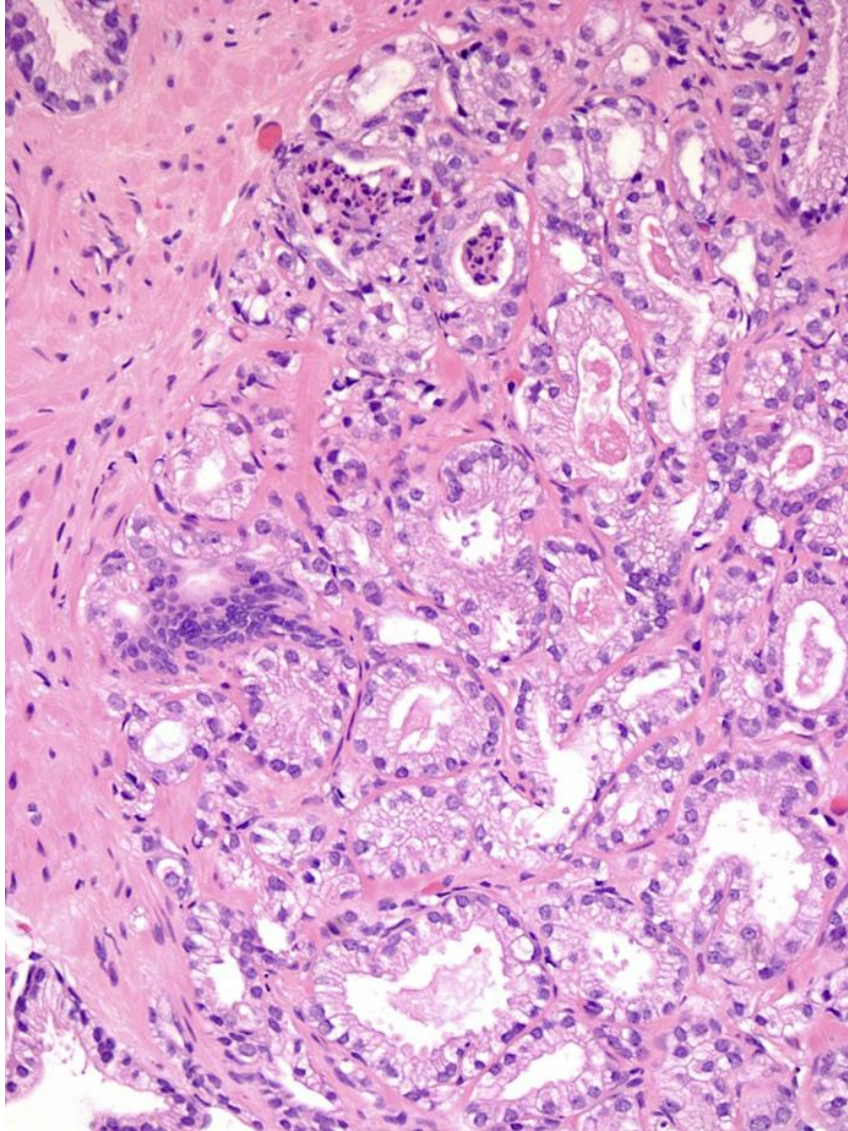
p63/AMACR



Crowded glands with minimal cytologic atypia: cancer vs. adenosis



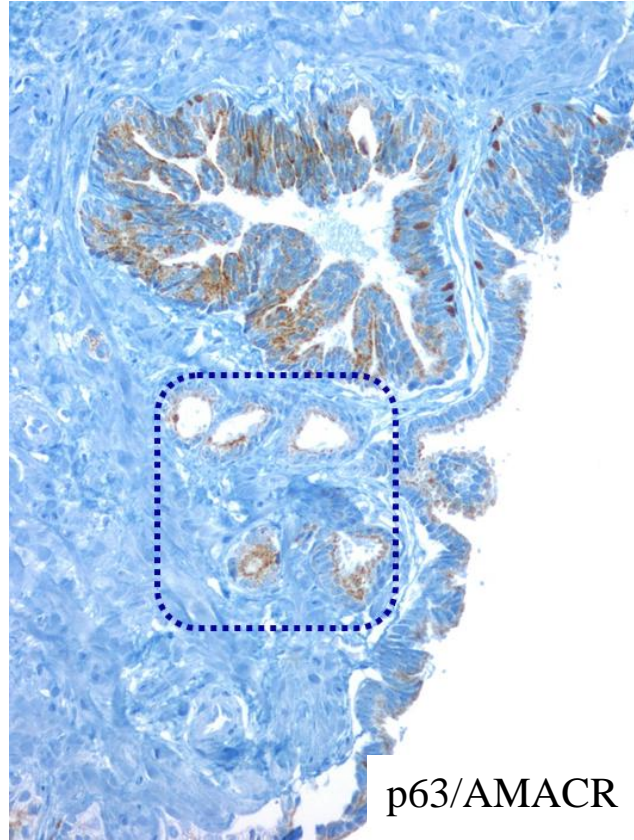
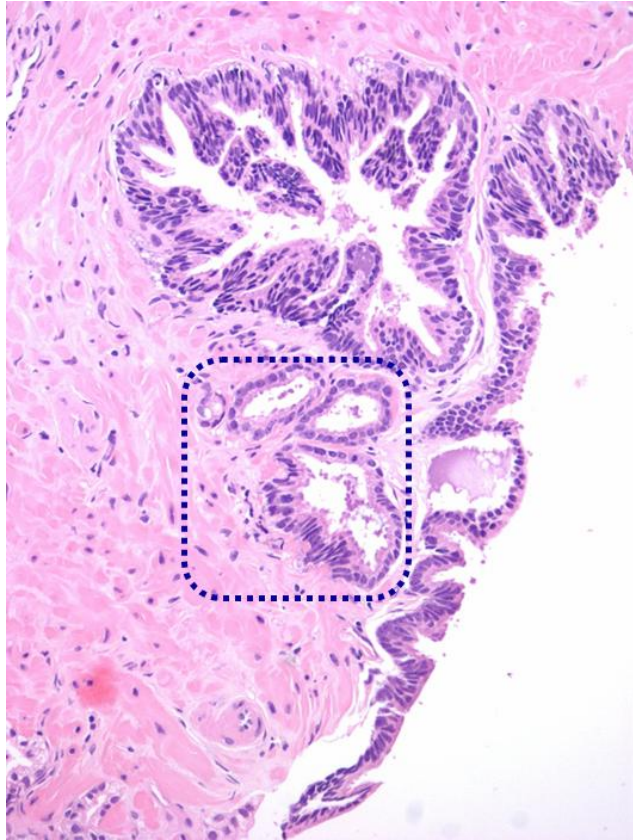
Crowded glands with minimal cytologic atypia: cancer vs. adenosis



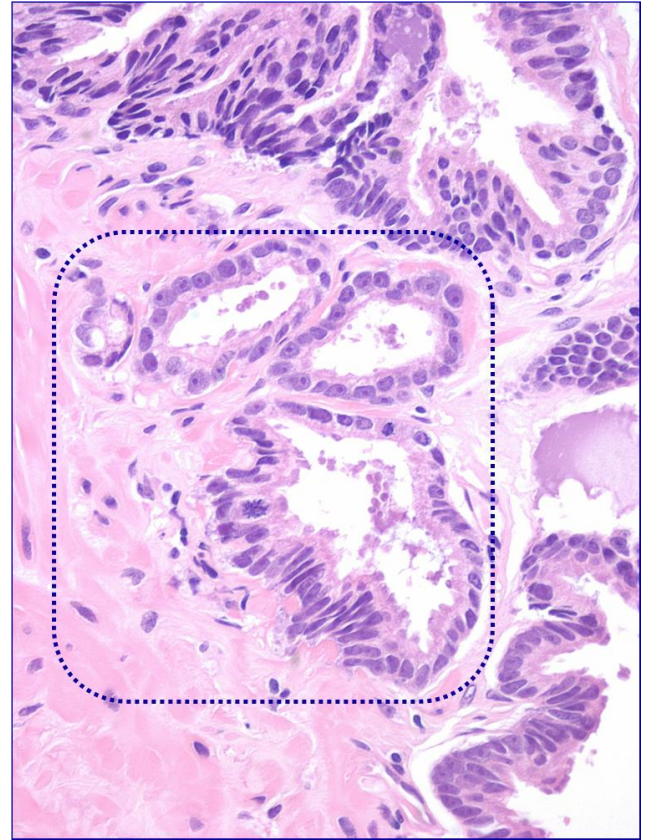
Atypical Glands Adjacent to HGPIN: PINATYP

- Small atypical glands closely associated with (or adjacent to) HGPIN glands
- While these small glands may represent a microscopic focus of infiltrating cancer, tangential section or outpouching of adjacent HGPIN glands cannot be excluded
- Frequently HGPIN glands and adjacent small atypical glands share common nuclear/nucleolar features and have similar darker amphophilic cytoplasm

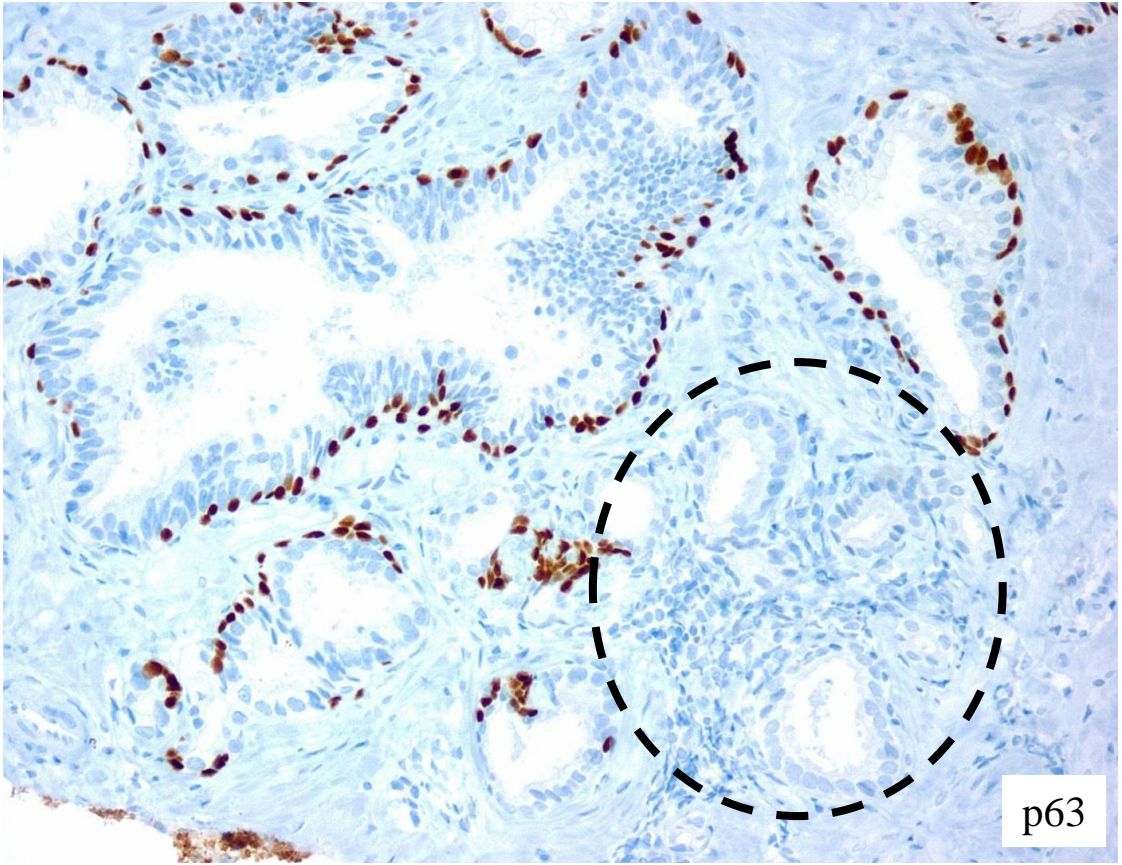
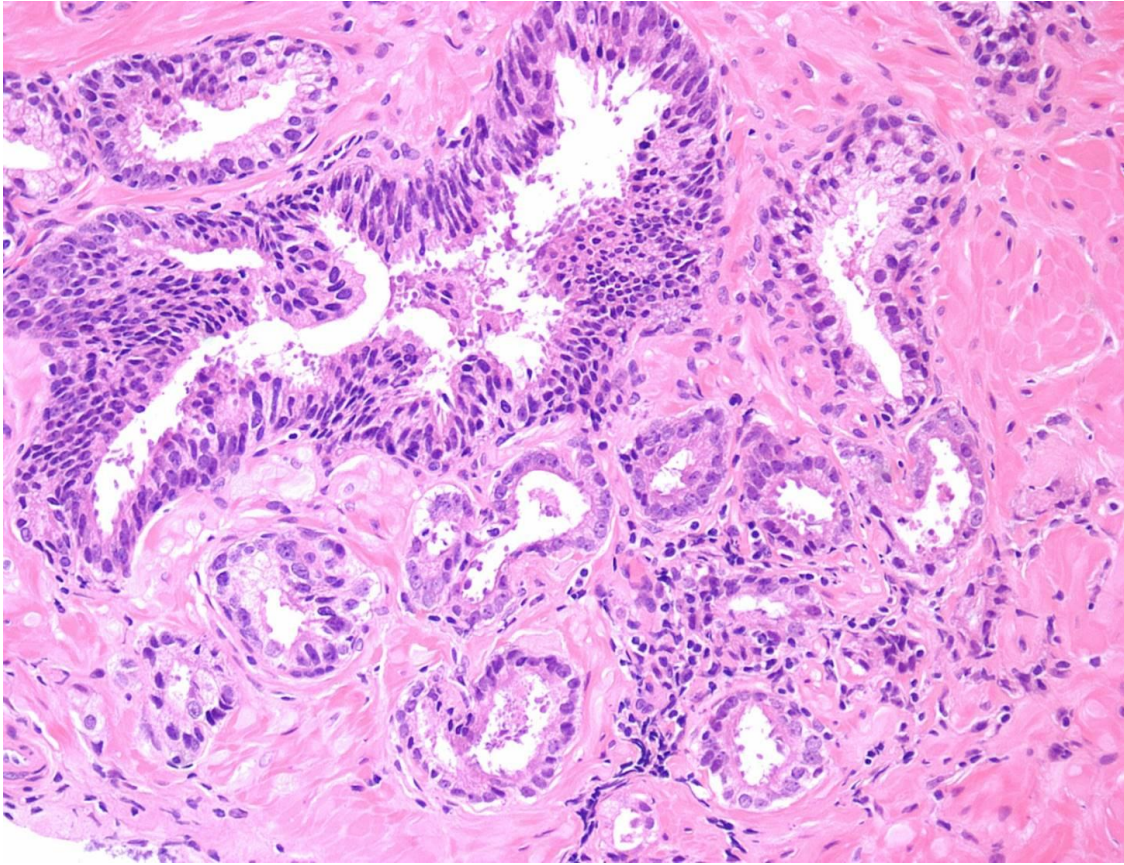
PINATYP



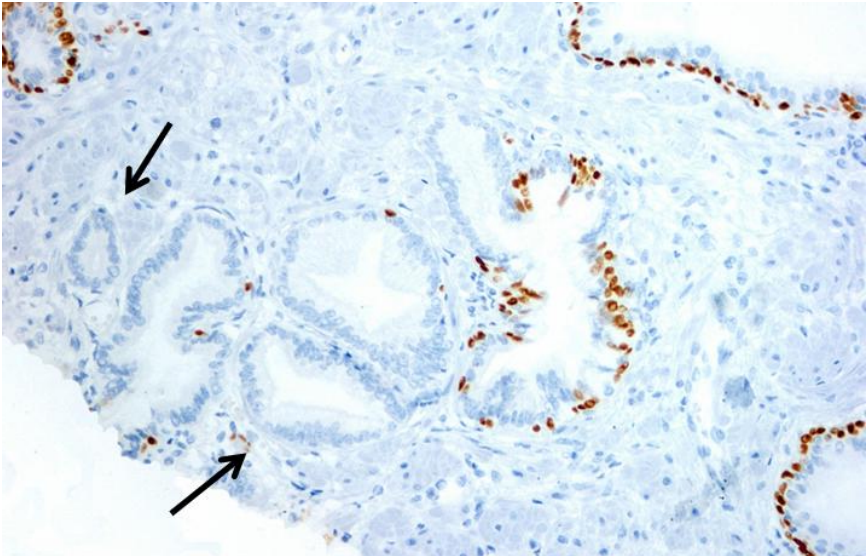
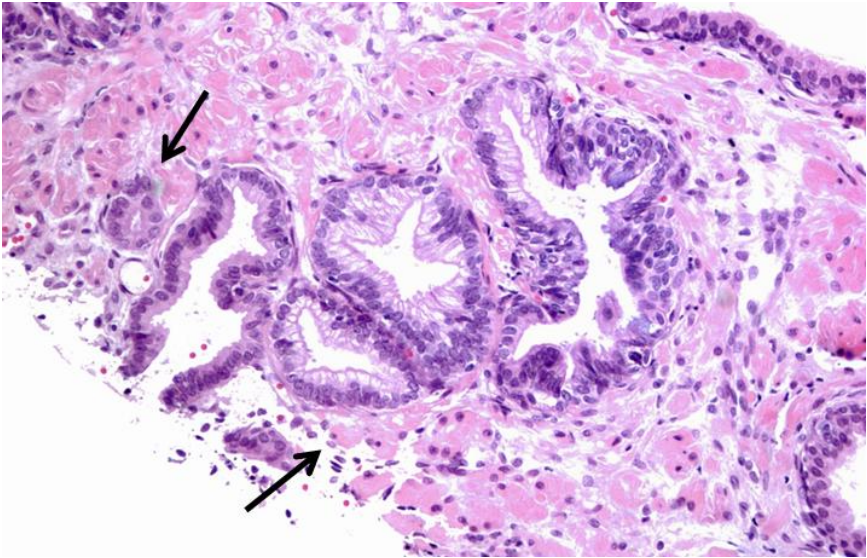
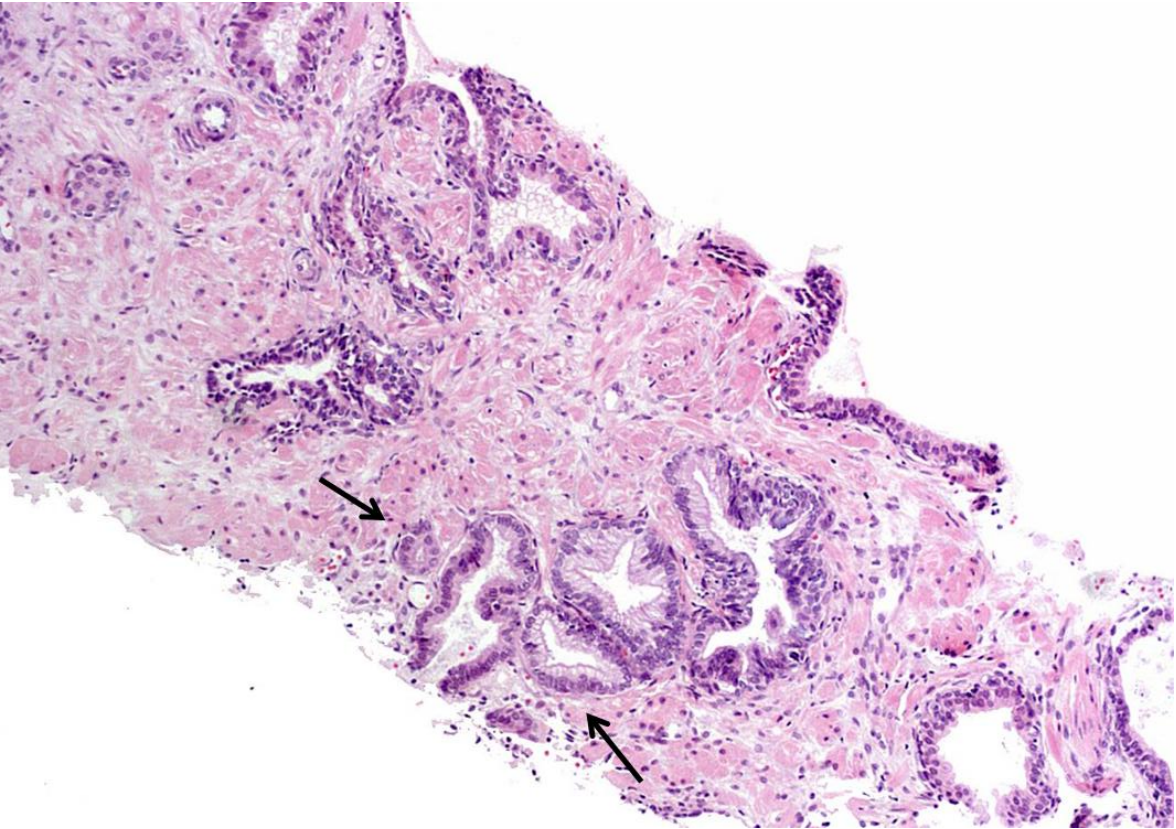
p63/AMACR



PINATYP

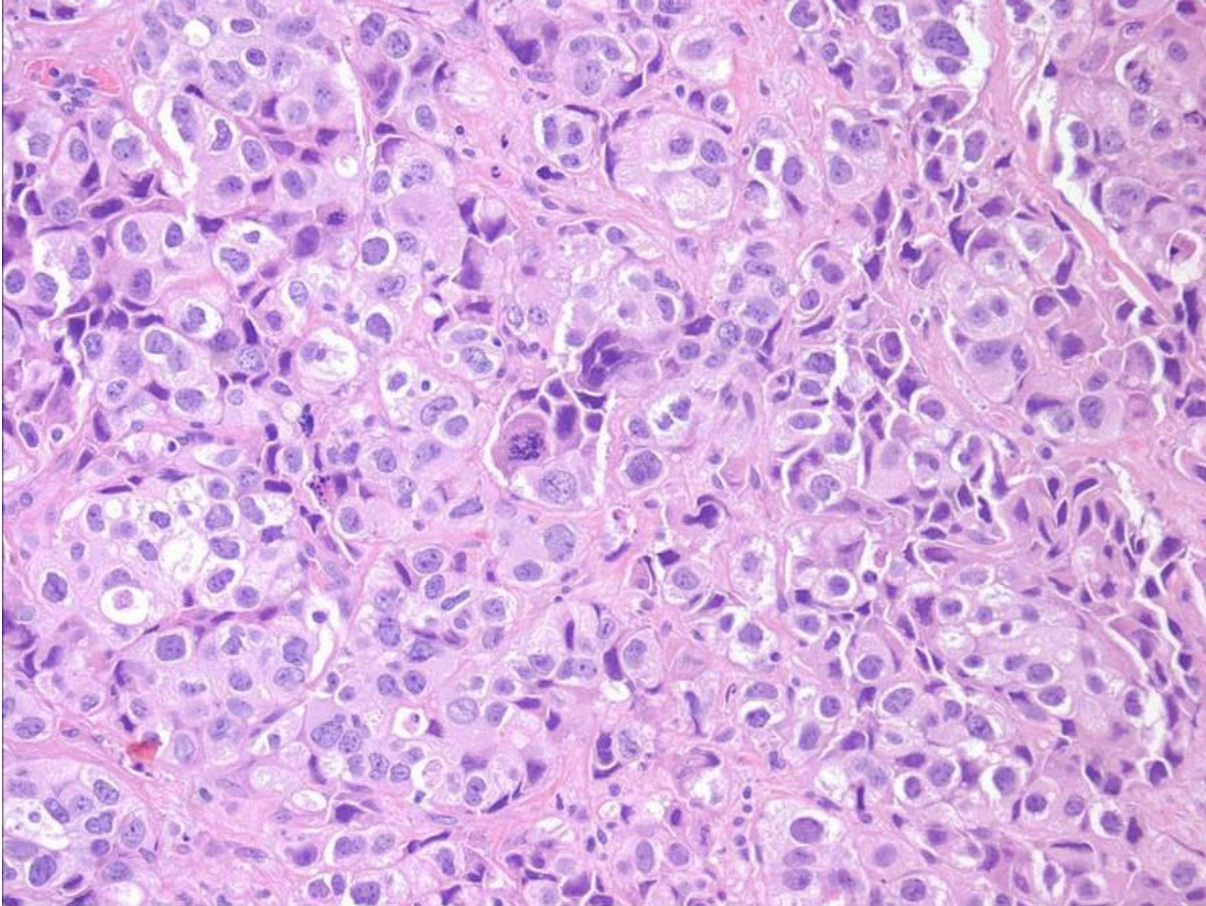


PINATYP

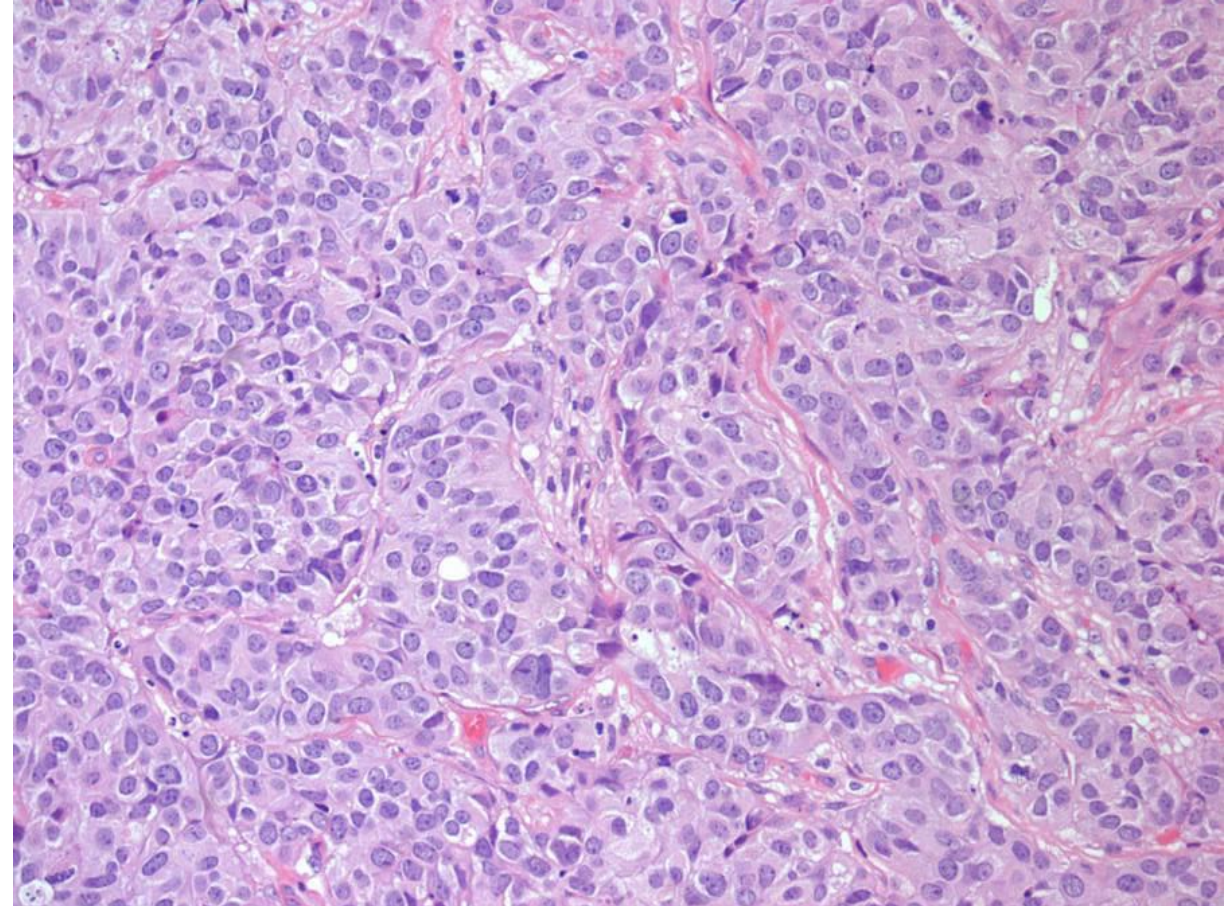


POORLY DIFFERENTIATED BLADDER NECK CARCINOMA

#1 - 70 y/o men; bladder neck tumor

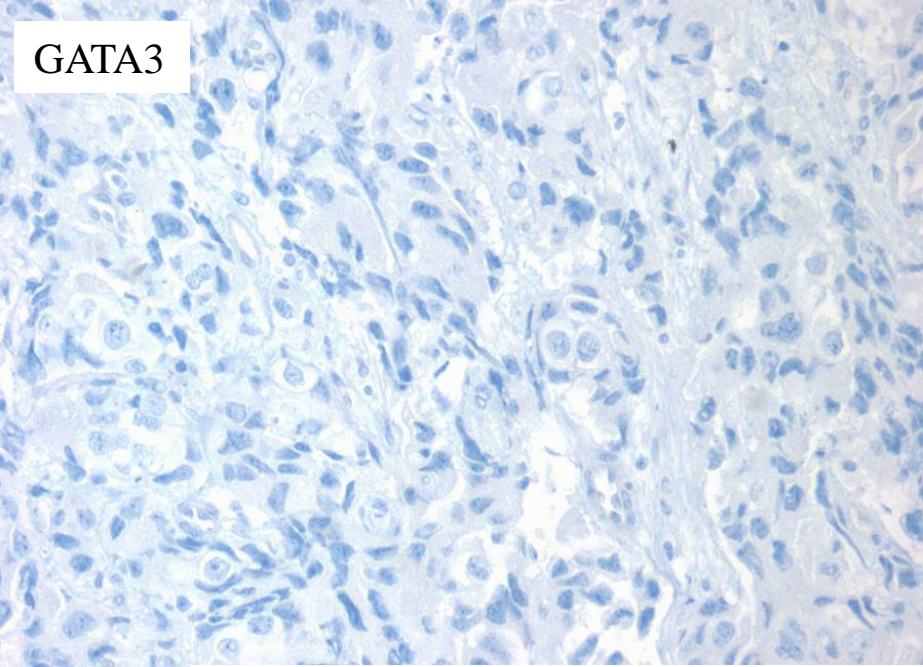
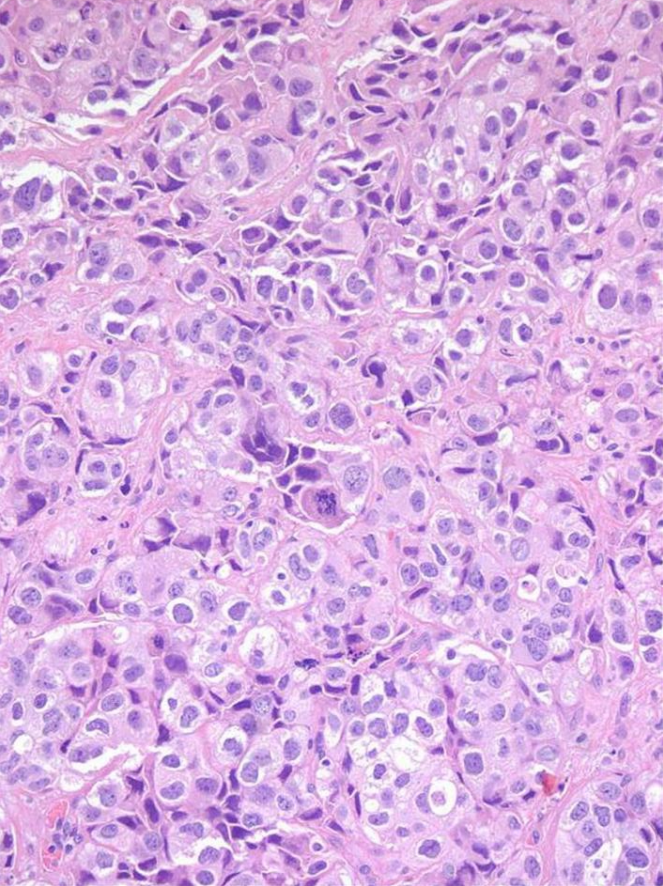


#2 - 67 y/o men; bladder mass

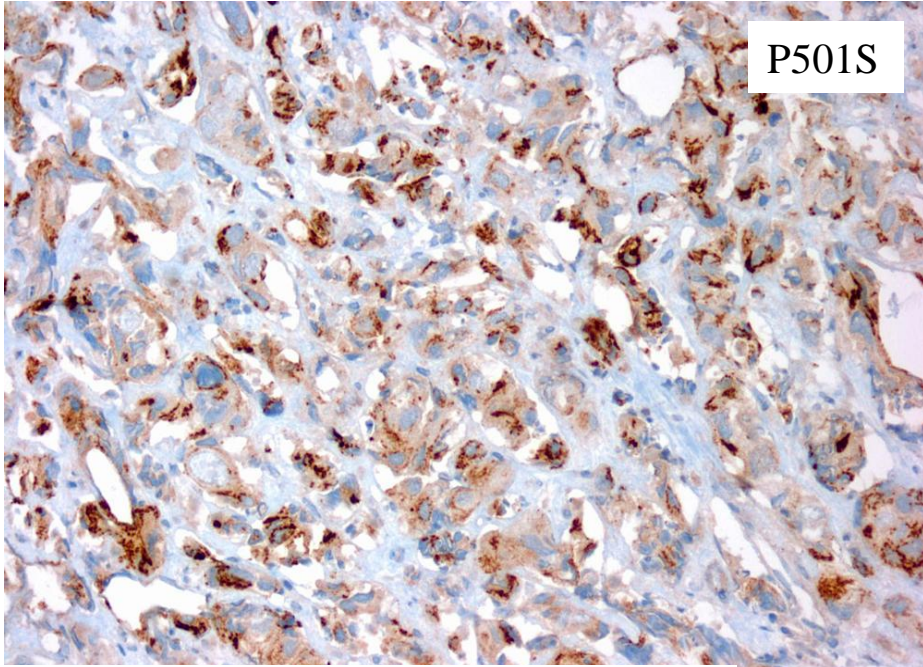


Urine cytology + for malignant cells: Urothelial cell carcinoma

Case #1

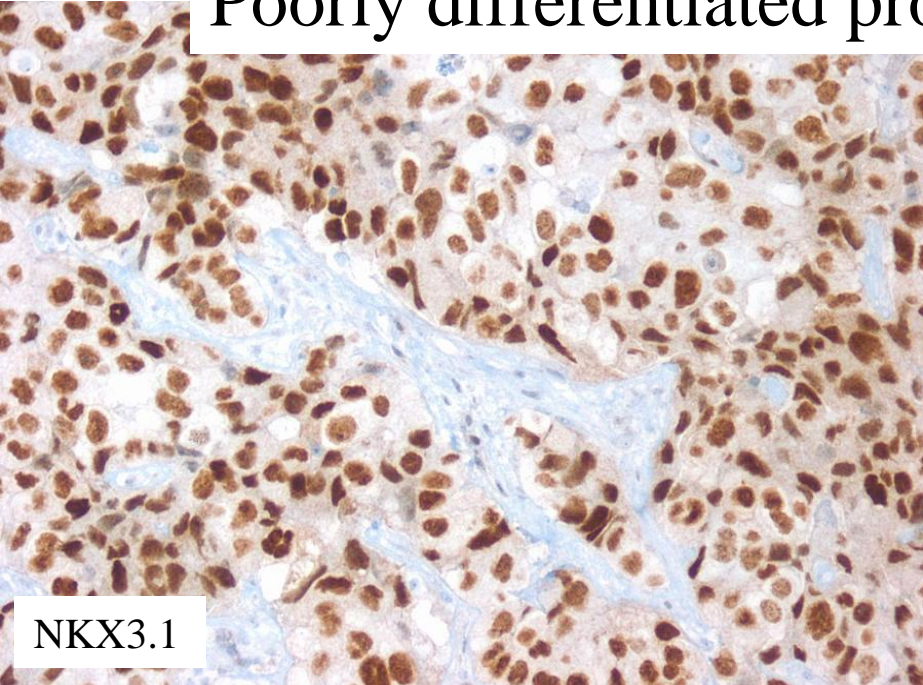


GATA3

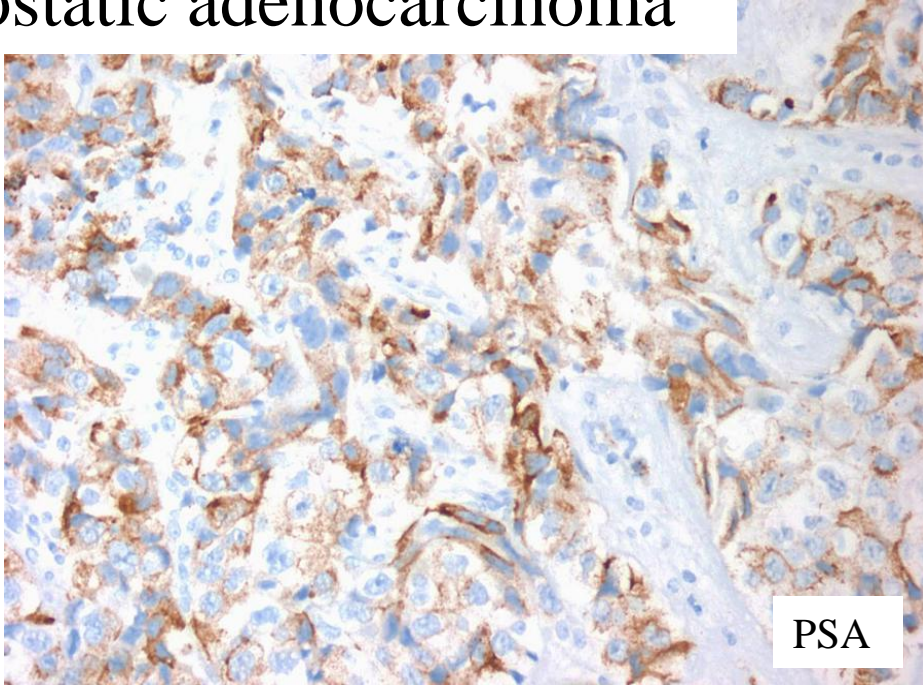


P501S

Poorly differentiated prostatic adenocarcinoma

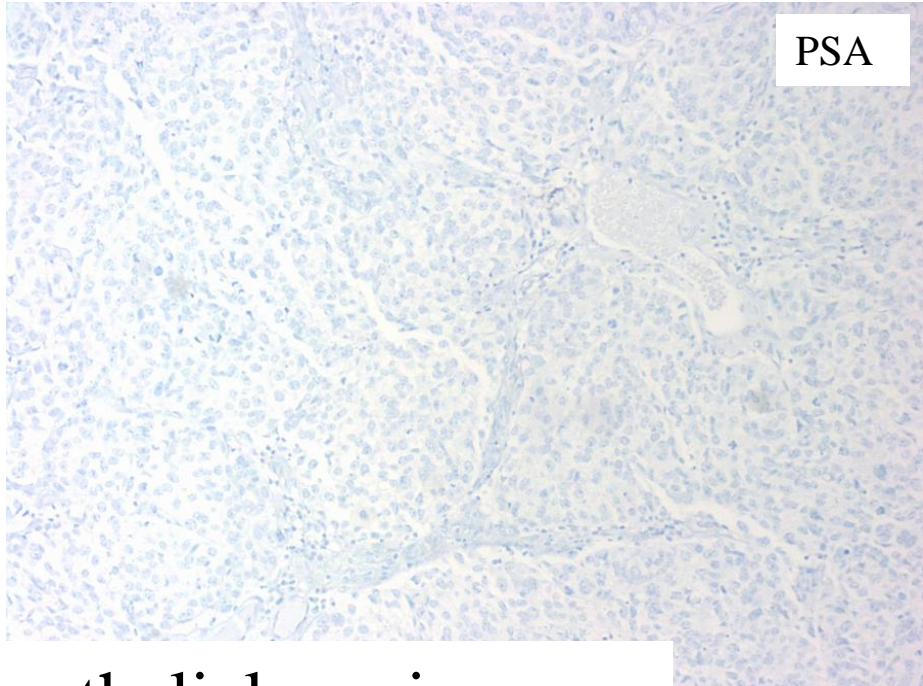
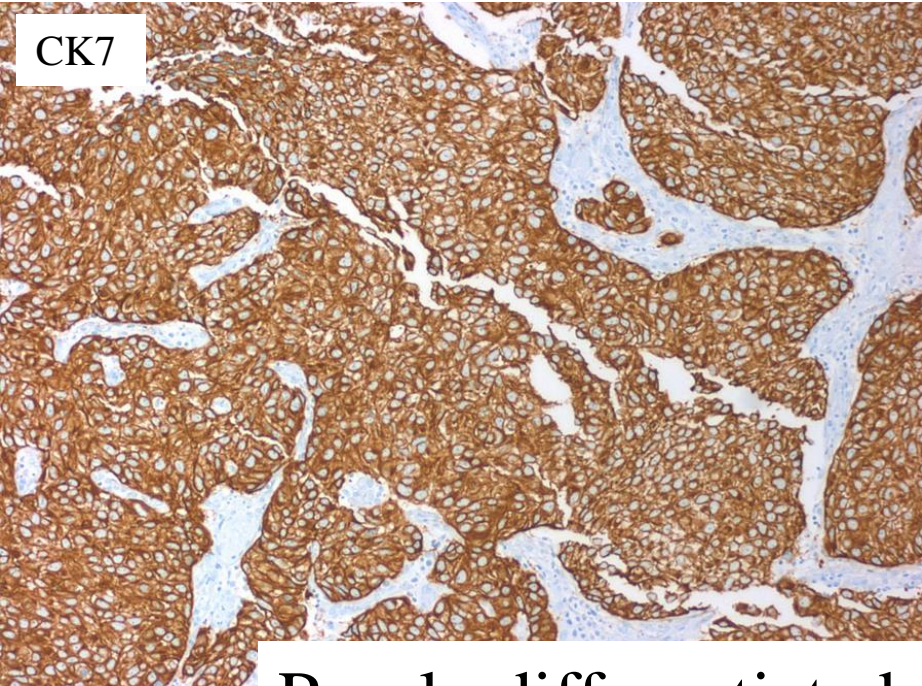
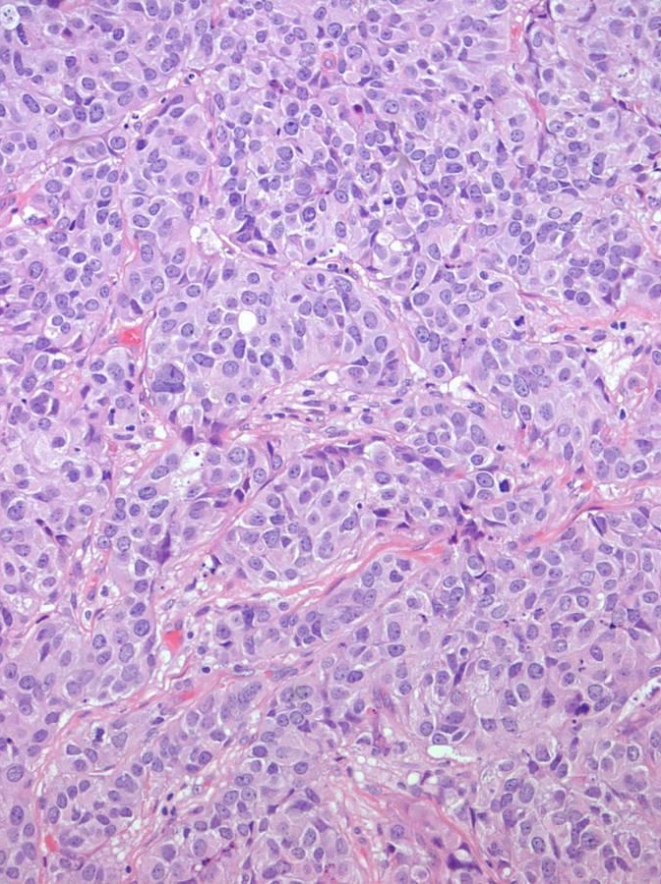


NKX3.1

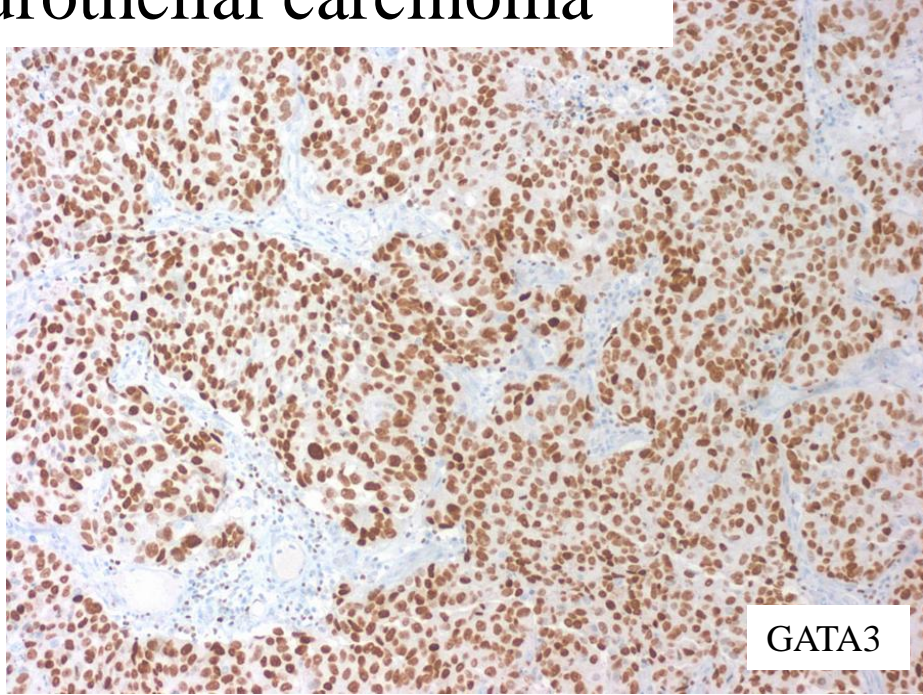
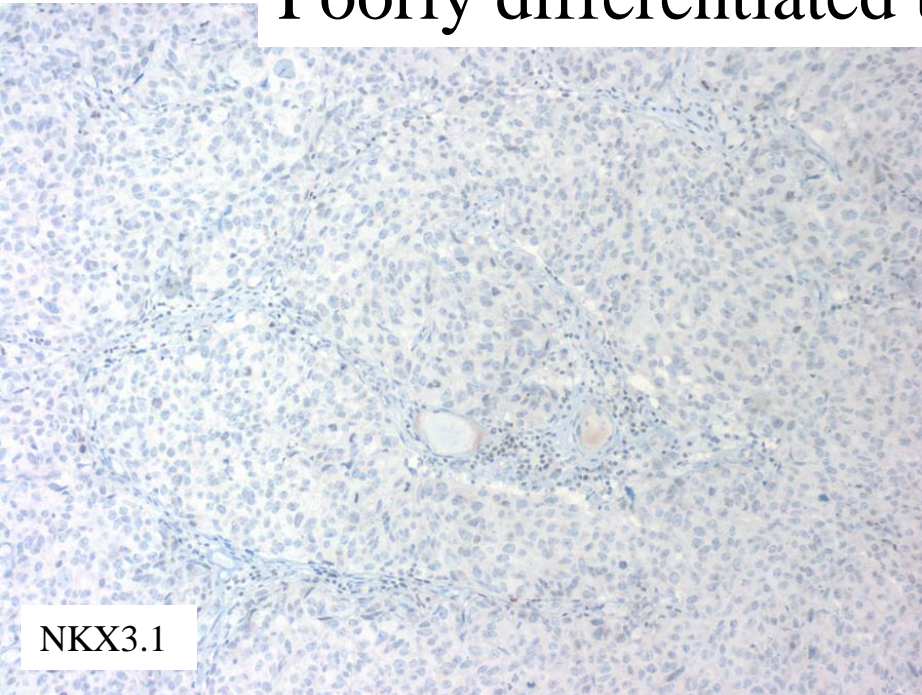


PSA

Case #2



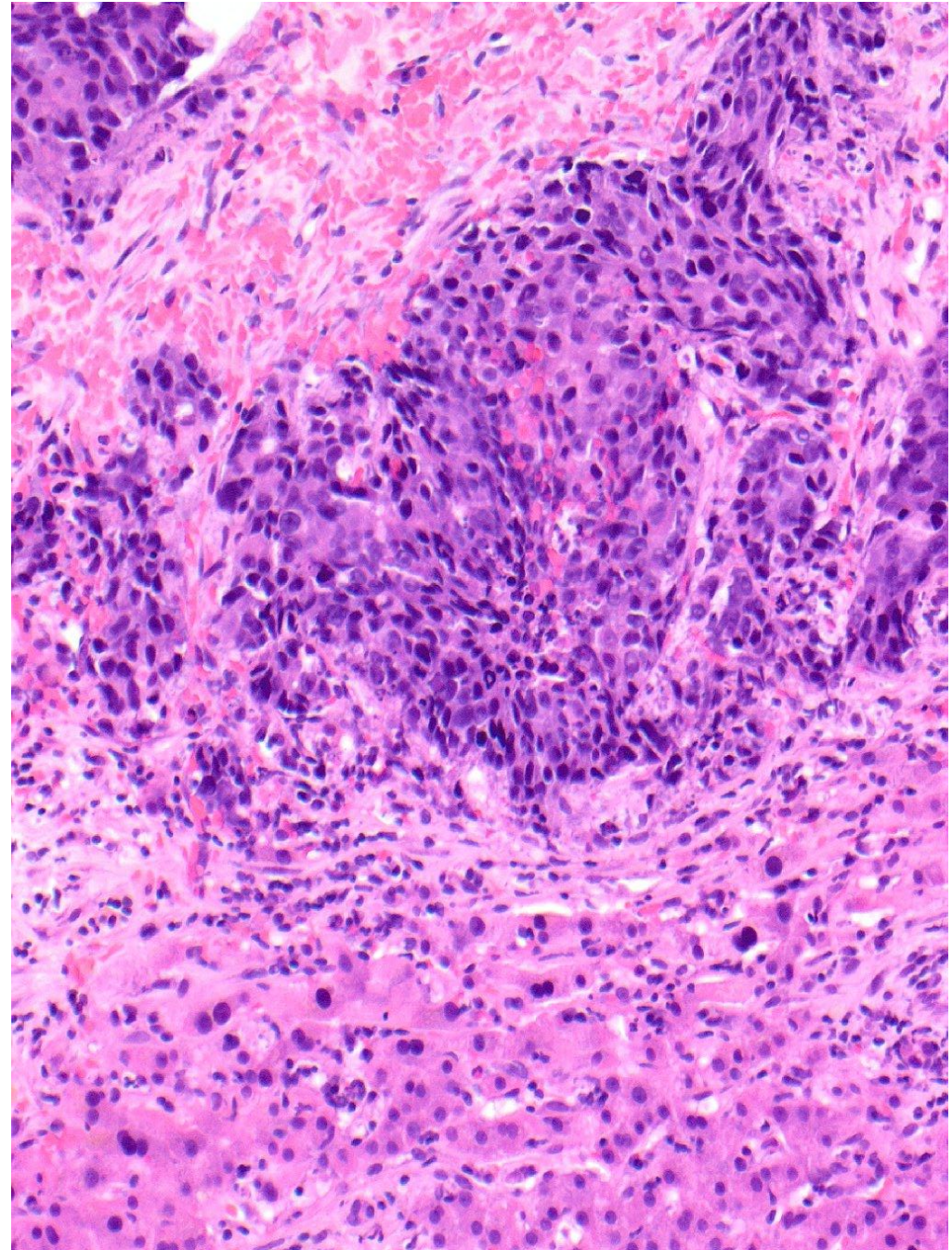
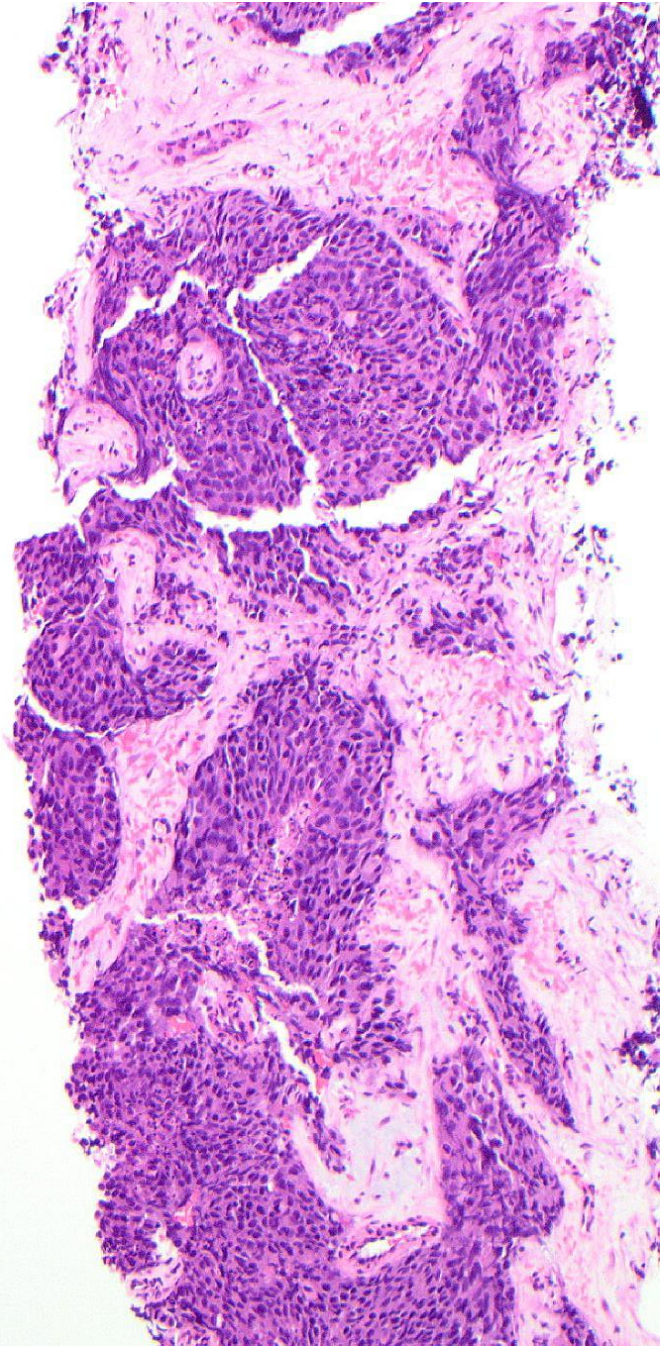
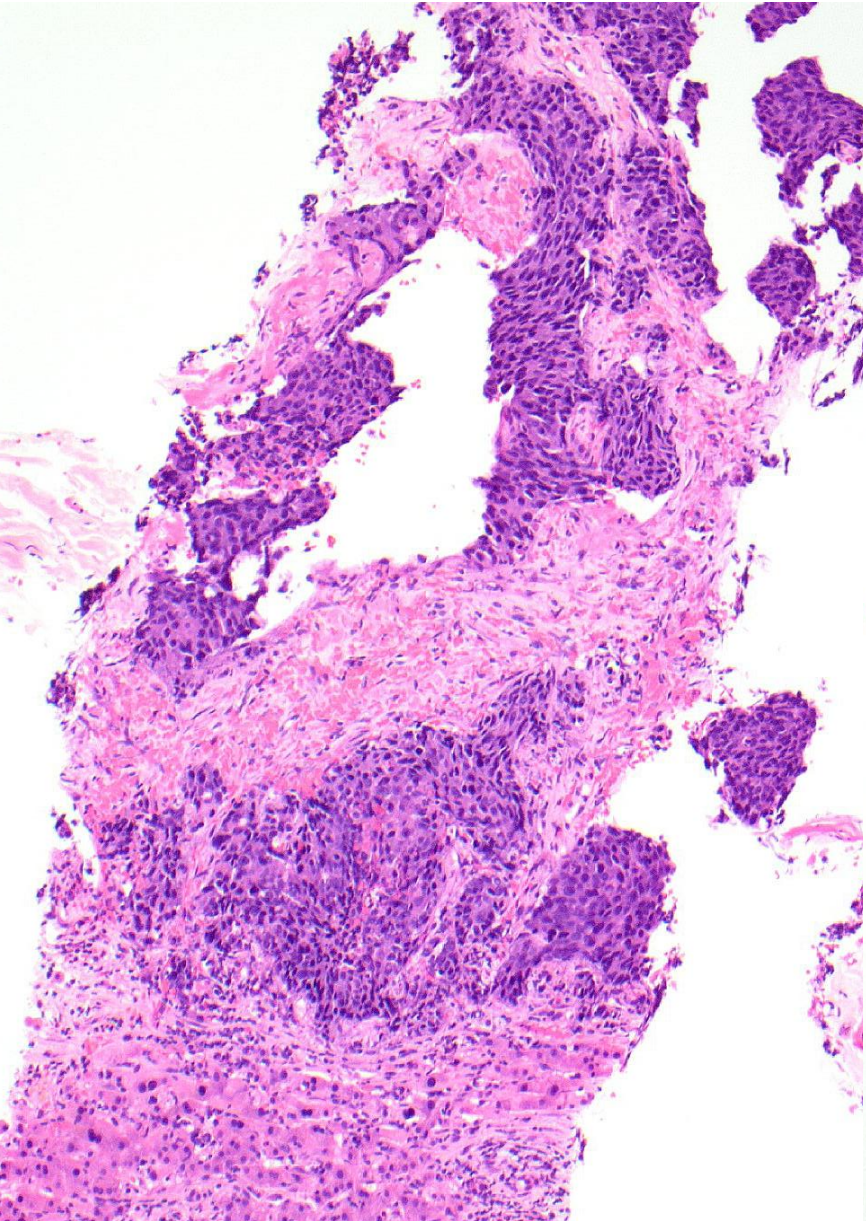
Poorly differentiated urothelial carcinoma



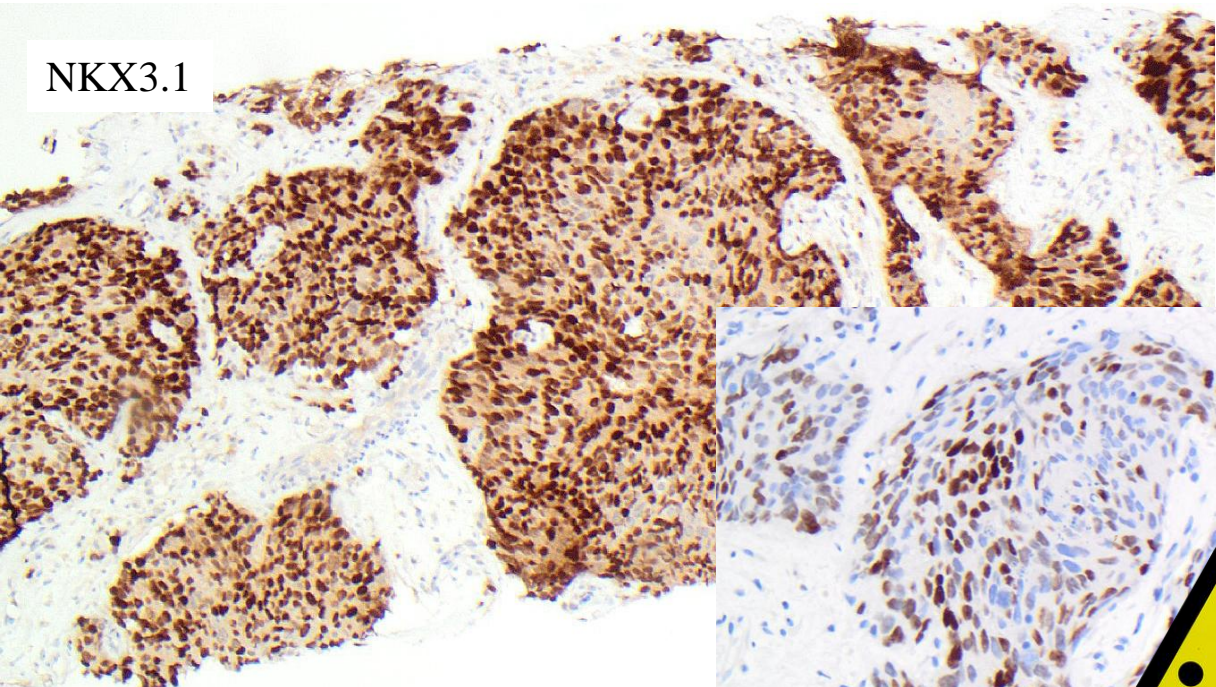
Diagnosis of Poorly Differentiated PCA vs. Urothelial Carcinoma

Stain	Advantages	Disadvantages
PSA	+ in 85-90% GS10, - in UC	Negative in some PCA; weak NS +
PSAP (polyclonal)	+ in 85-90% GS10; - in UC	Monoclonal has lower sensitivity
P501S	+ in many PSA- PCA, - in UC	Weak stain, not widely used
NKX3.1	+ in many PSA- PCA; - in UC	Not widely used
GATA3	Negative in most PCA; + in 80% UC	+ in some high-grade PCA
AMACR	High sensitivity for PCA	+ in some UC
PSMA	High sensitivity for PCA	+ in 14% of UC
CK7/CK20	Negative CK7 favors PCA	Non specific; both can be + in PCA
p63 HMWCK	p63 < false + in PCA than HWMCK; diffuse + r/o PCA	+ in only 2/3 of UC; occasional false + in PCA
Thrombomodulin	Widely used	+ in 63% of UC, false + in 5% PCA
Uroplakin	- in PCA	+ in 60% of UC

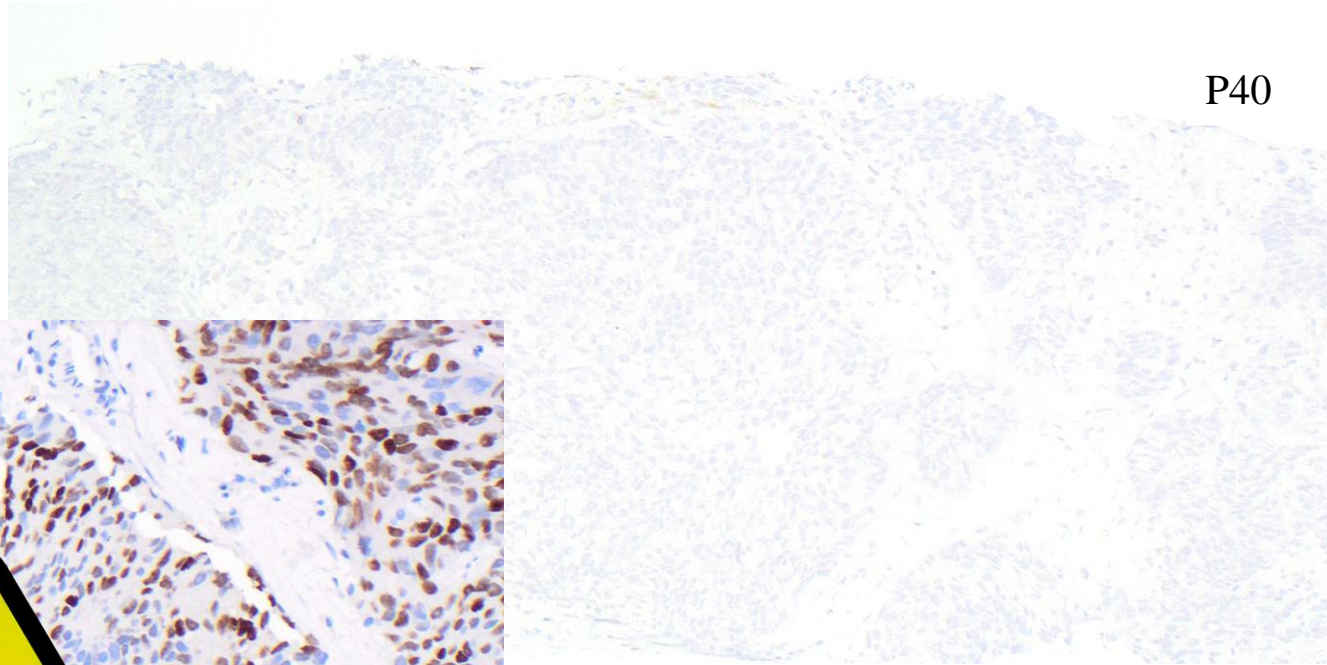
Liver lesion



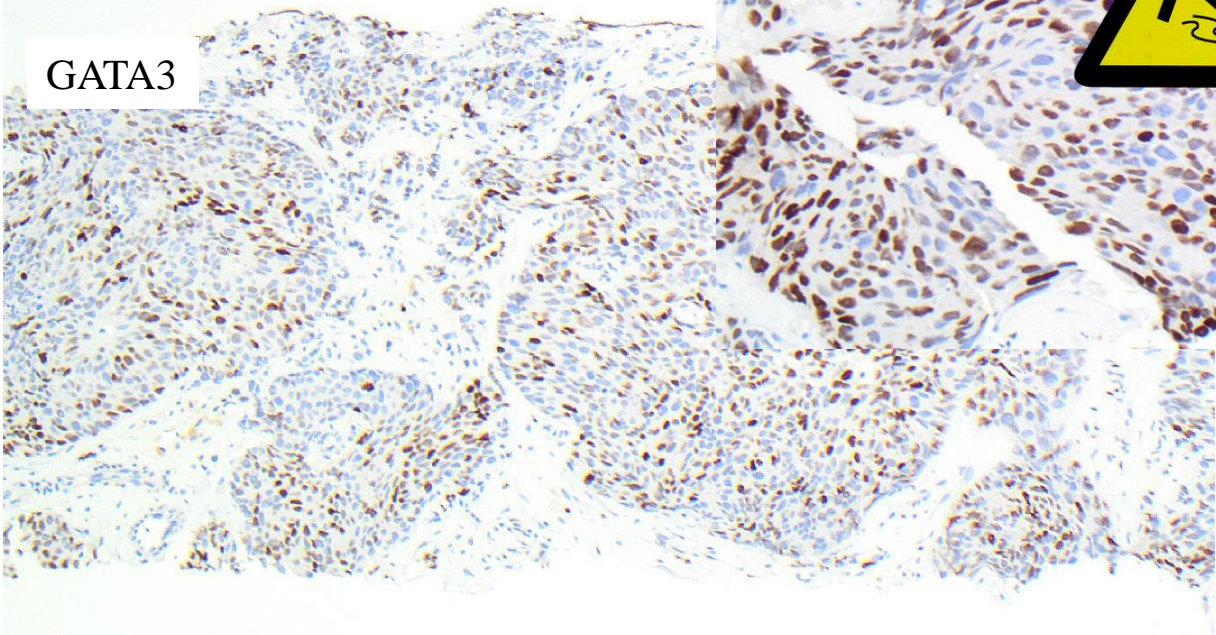
NKX3.1



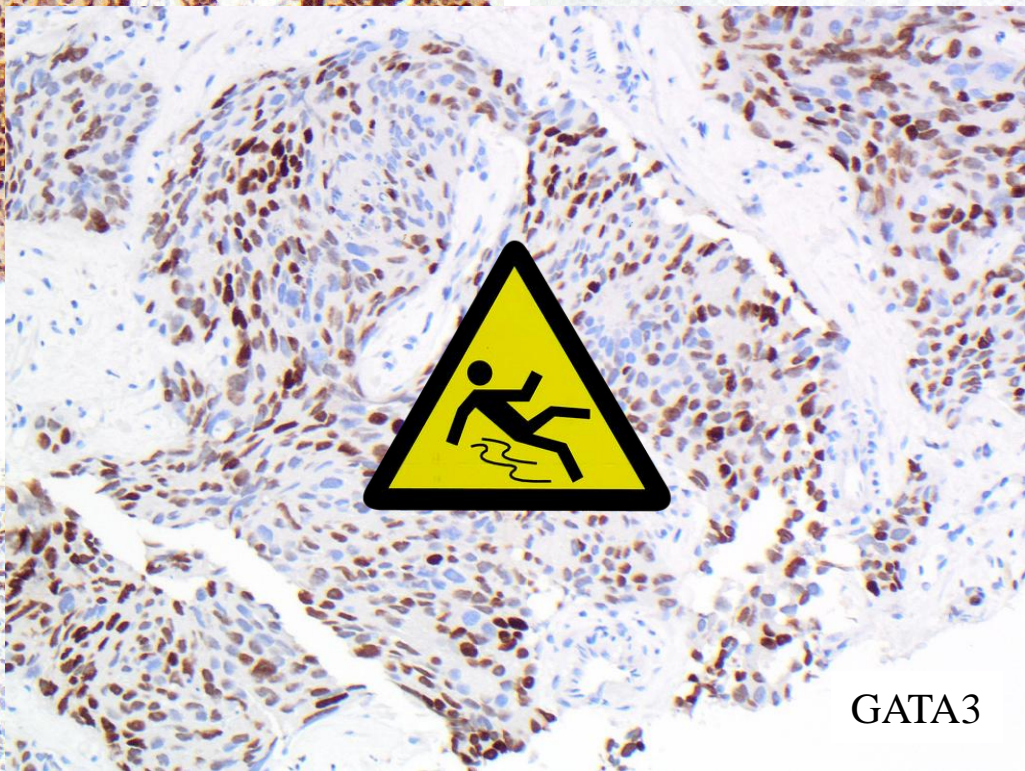
P40



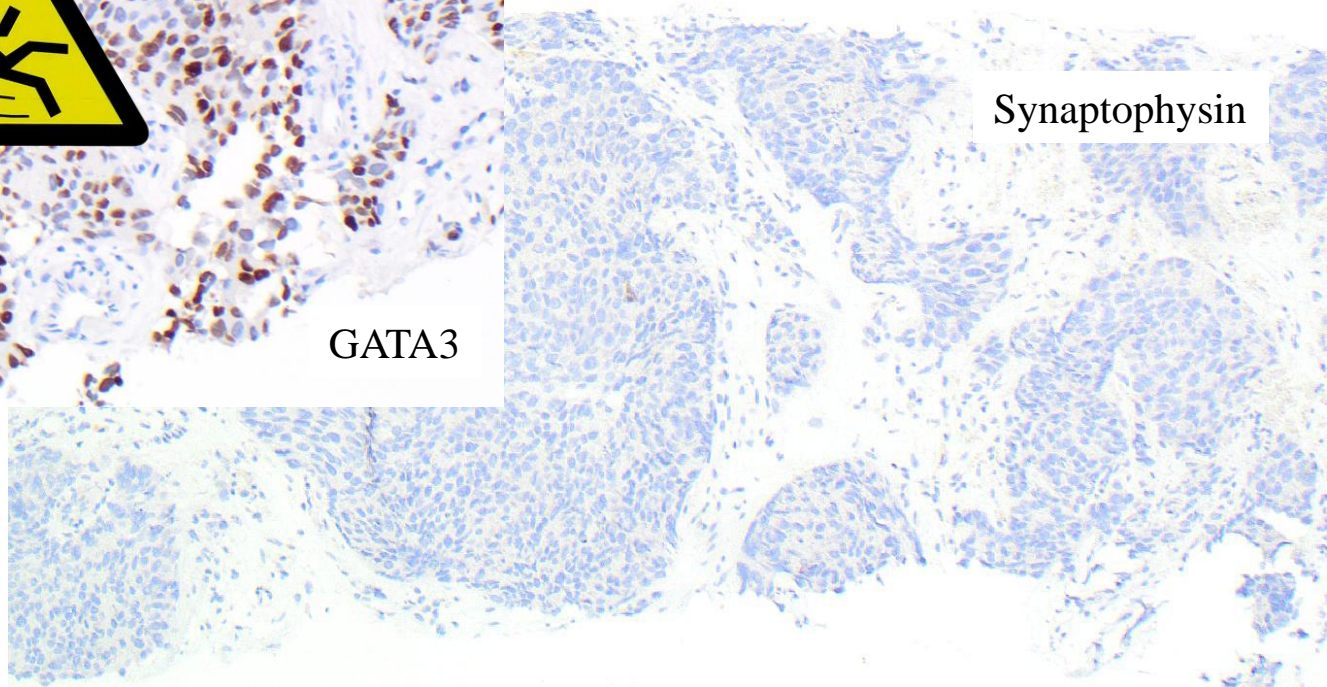
GATA3



GATA3



Synaptophysin



Aberrant GATA3 Staining in Prostatic Adenocarcinoma

A Potential Diagnostic Pitfall

Timothy M. McDonald, MD and Jonathan I. Epstein, MD

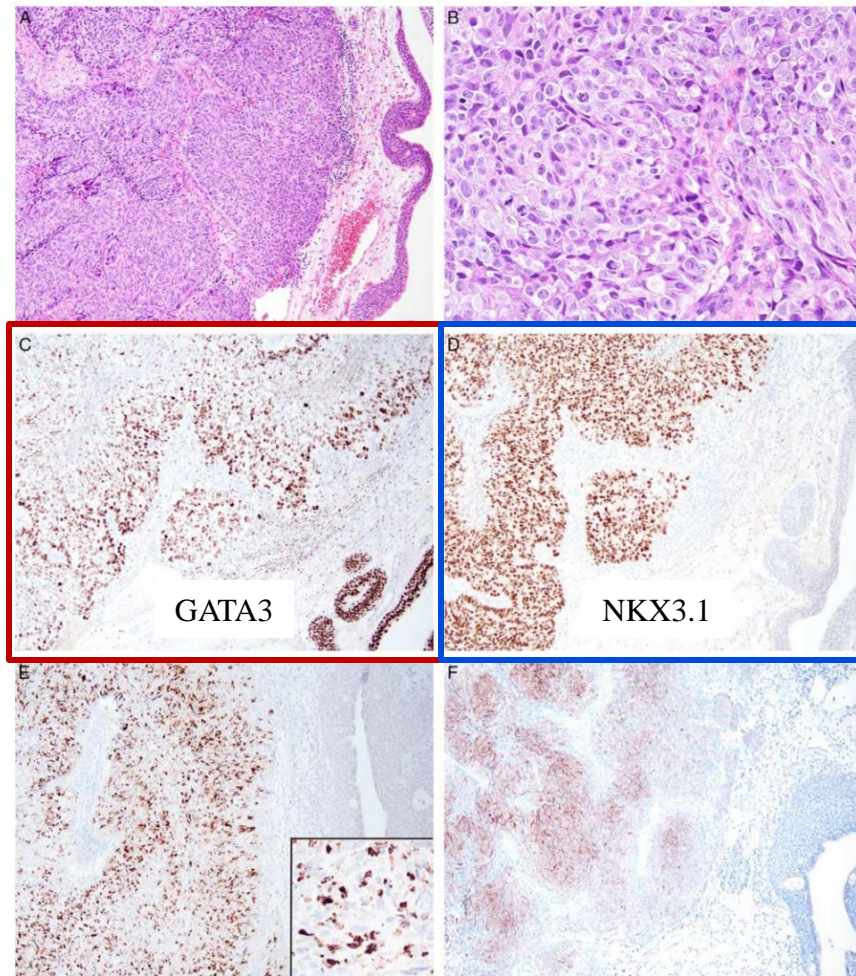


FIGURE 1. Case of poorly differentiated adenocarcinoma of the prostate invading the bladder. A, Solid sheets of carcinoma undermine normal urothelium (right). B, Higher magnification with relatively uniform nuclei containing prominent nucleoli and numerous mitotic figures. C, GATA3 labels carcinoma with a range from strong to moderate to weak intensity. Normal urothelium (lower right) stains intensely. D, NKX3.1 stains carcinoma diffusely and intensely. Normal urothelium (lower right) is negative. E, P5015 labels carcinoma diffusely and intensely. Inset show characteristic clumpy granular juxtannuclear labeling. Normal urothelium (upper right) is negative. F, PSA stains carcinoma with diffuse strong staining. Normal urothelium (right) is negative.

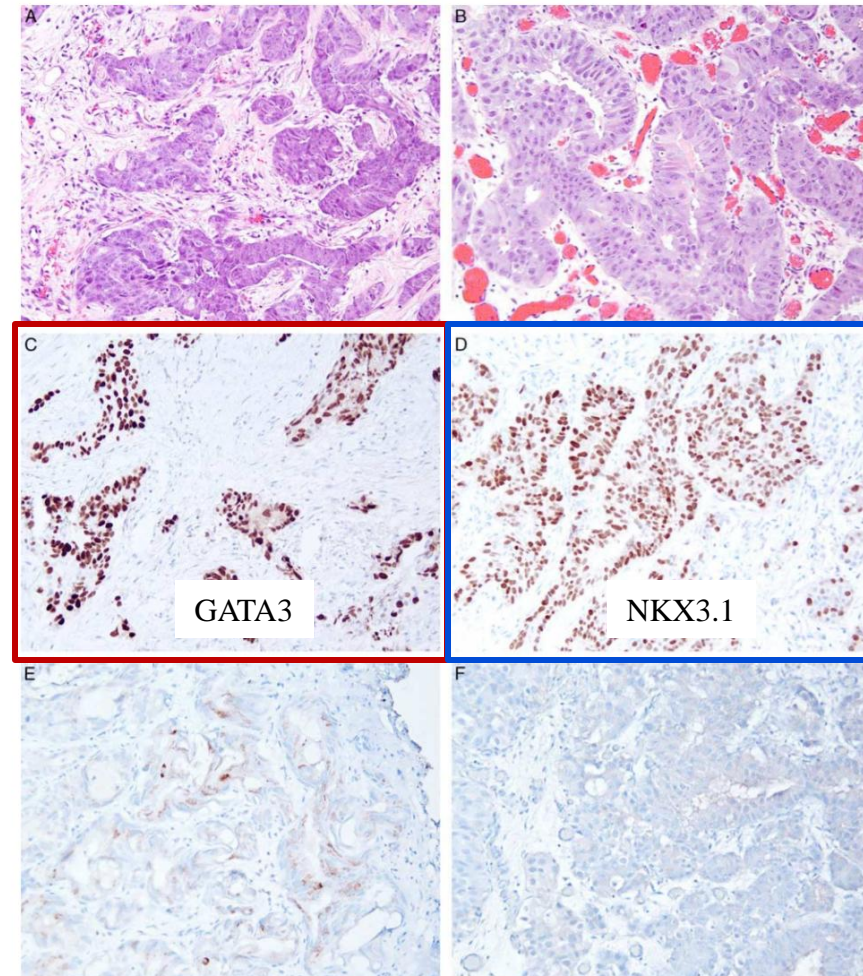
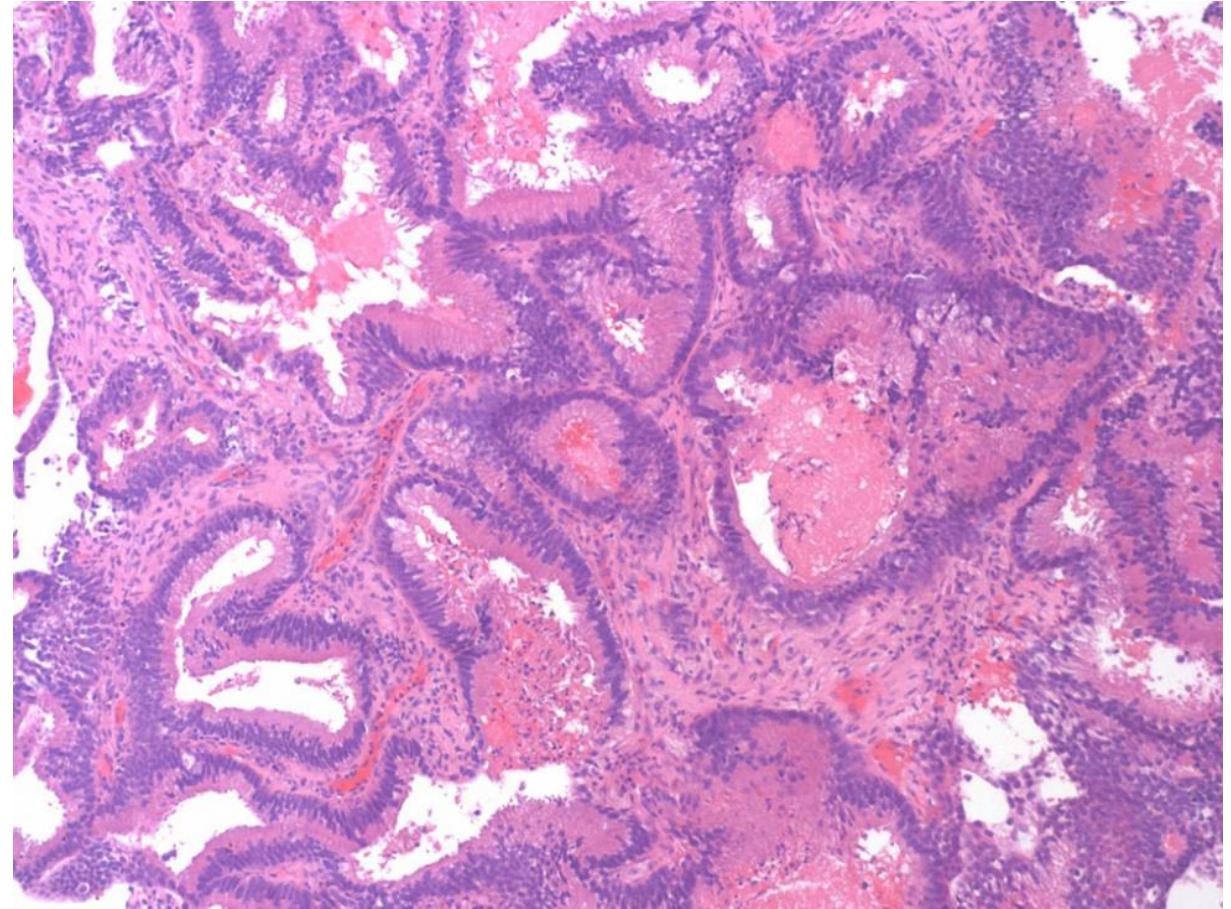
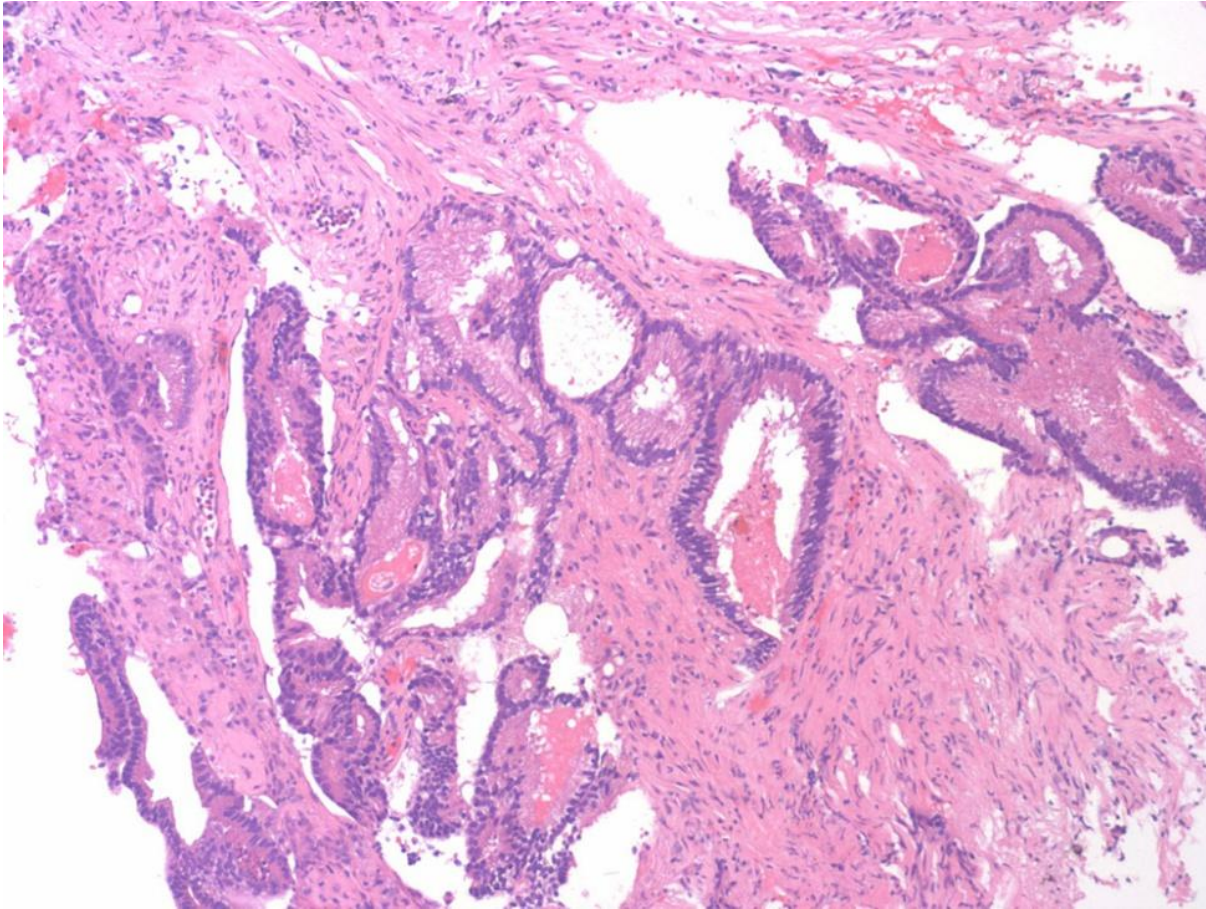
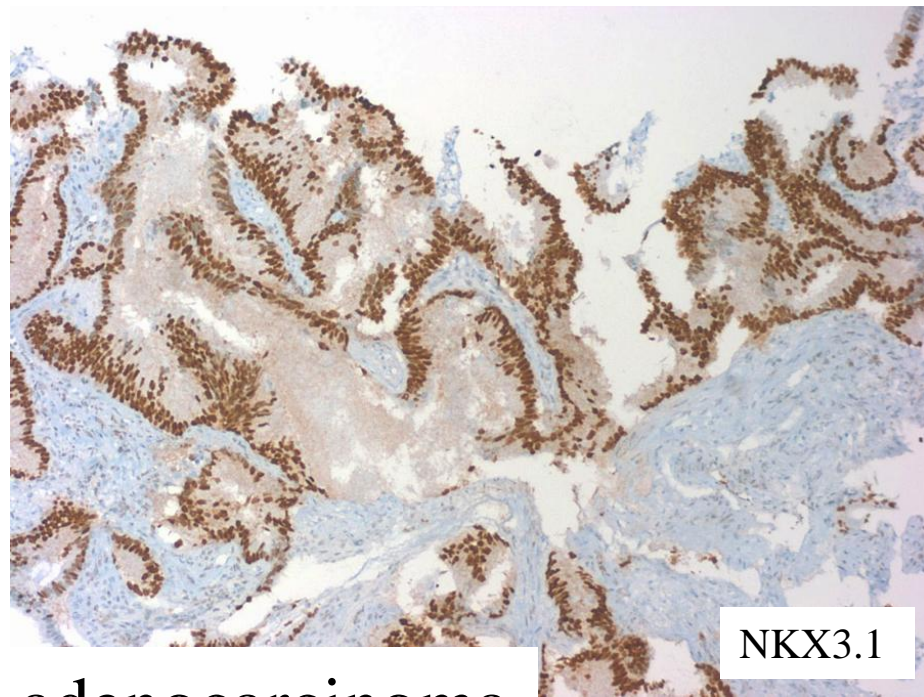
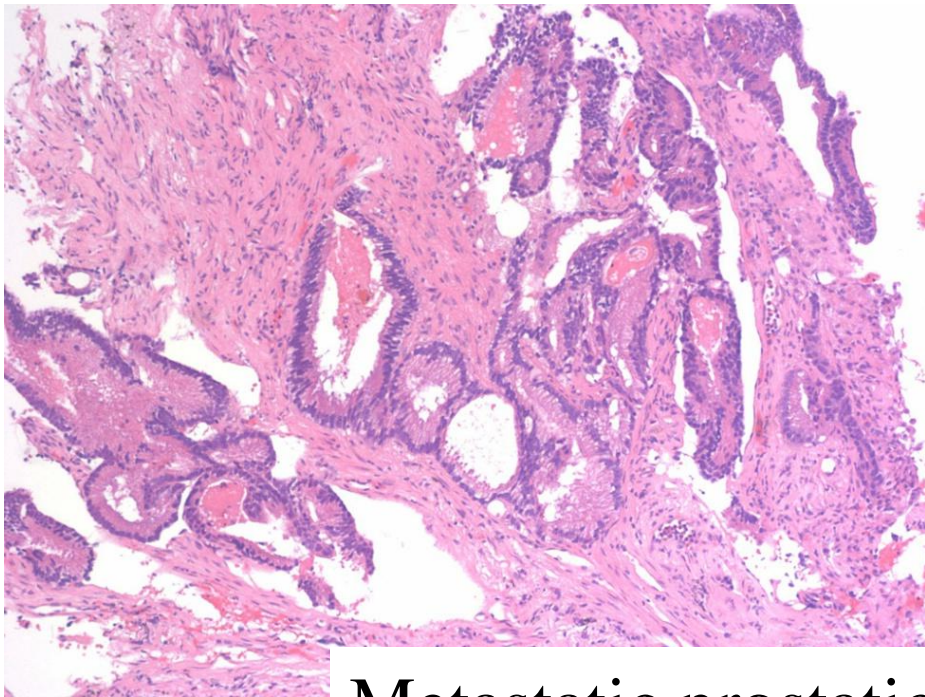


FIGURE 2. Poorly differentiated adenocarcinoma of the prostate. A, Solid nests of cells mimicking urothelial carcinoma. B, Areas of the tumor showed glandular differentiation more typical of prostate adenocarcinoma. C, GATA3 was focal but strong and intense. D, NKX3.1 with diffuse staining. E, Positive P5015 immunoreactivity. F, PSA was negative with only a diffuse weak blush of nonspecific staining.

DIAGNOSIS OF METASTATIC CARCINOMA

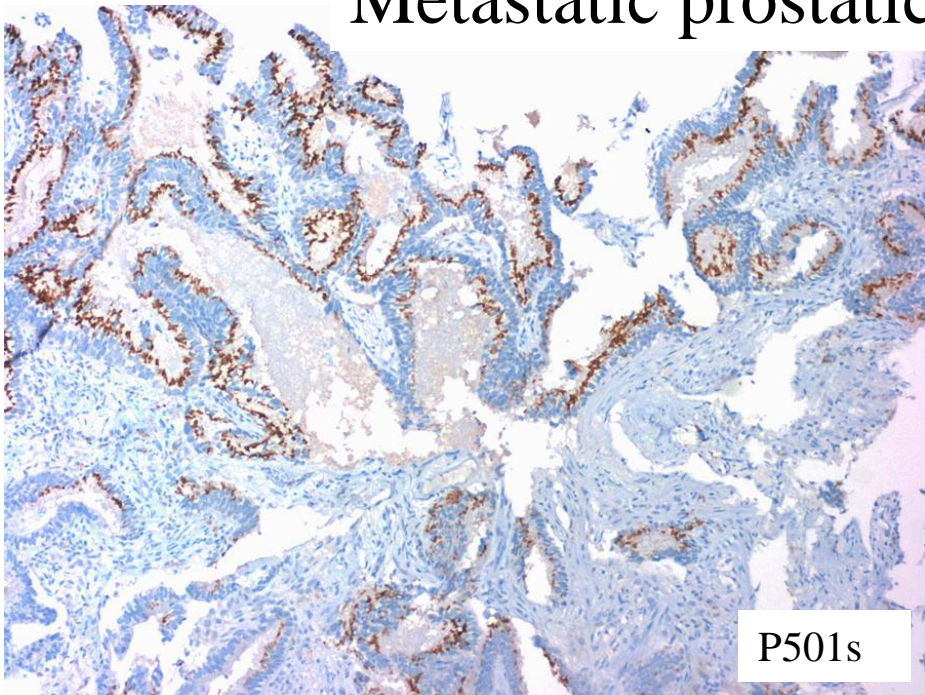
75 y/o men, R lung, upper lobe biopsy



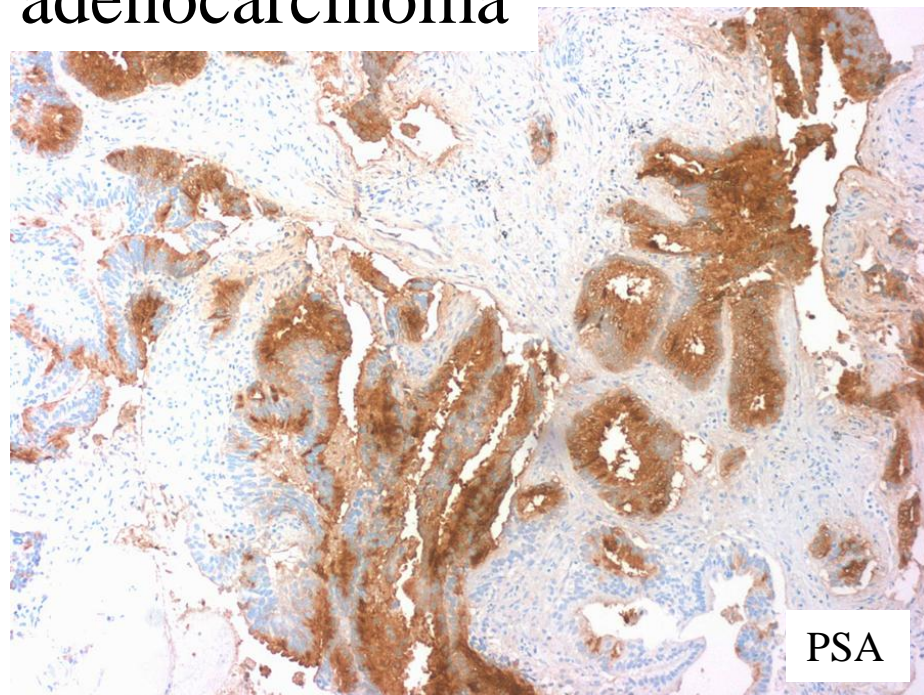


NKX3.1

Metastatic prostatic adenocarcinoma

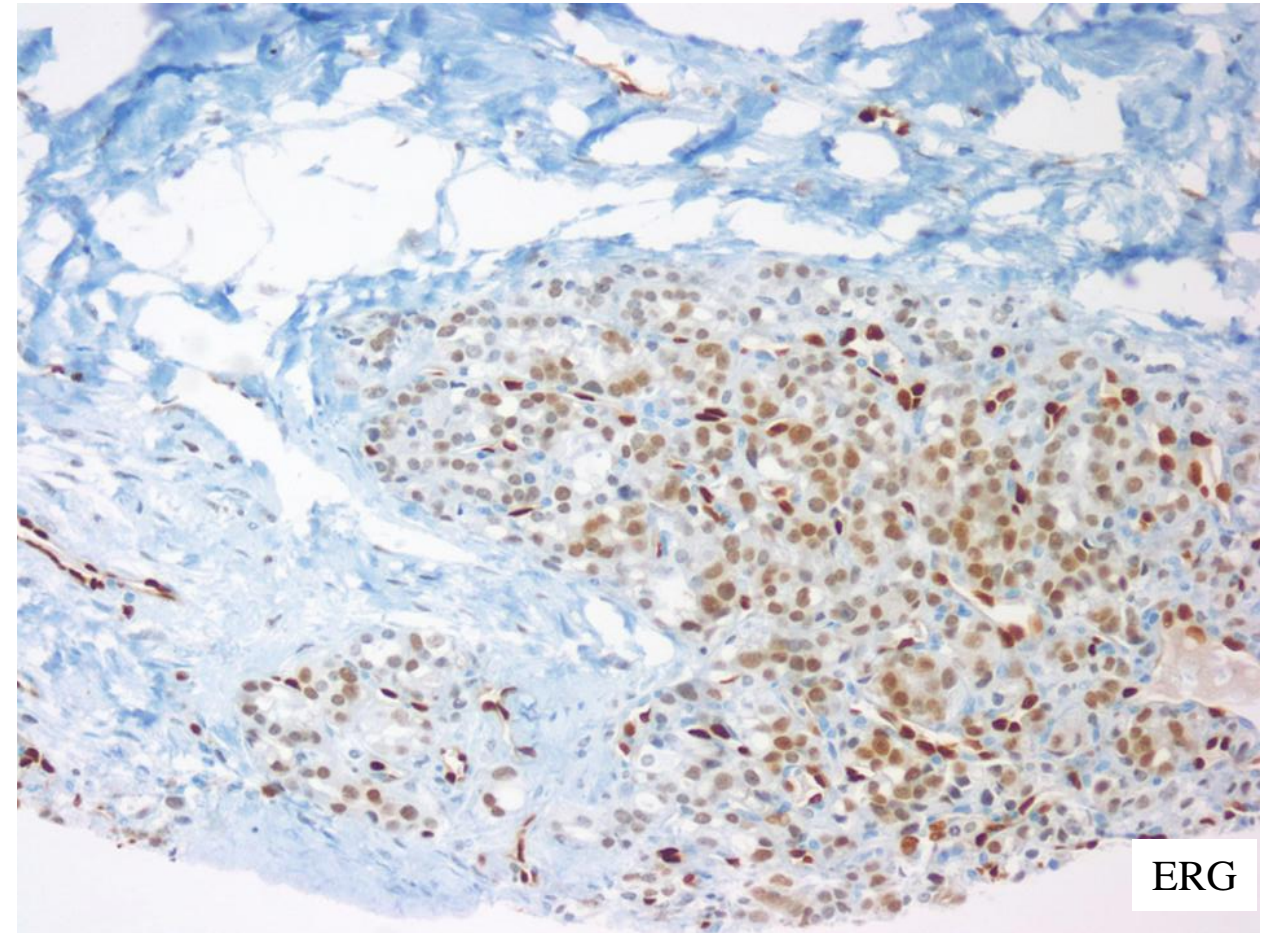
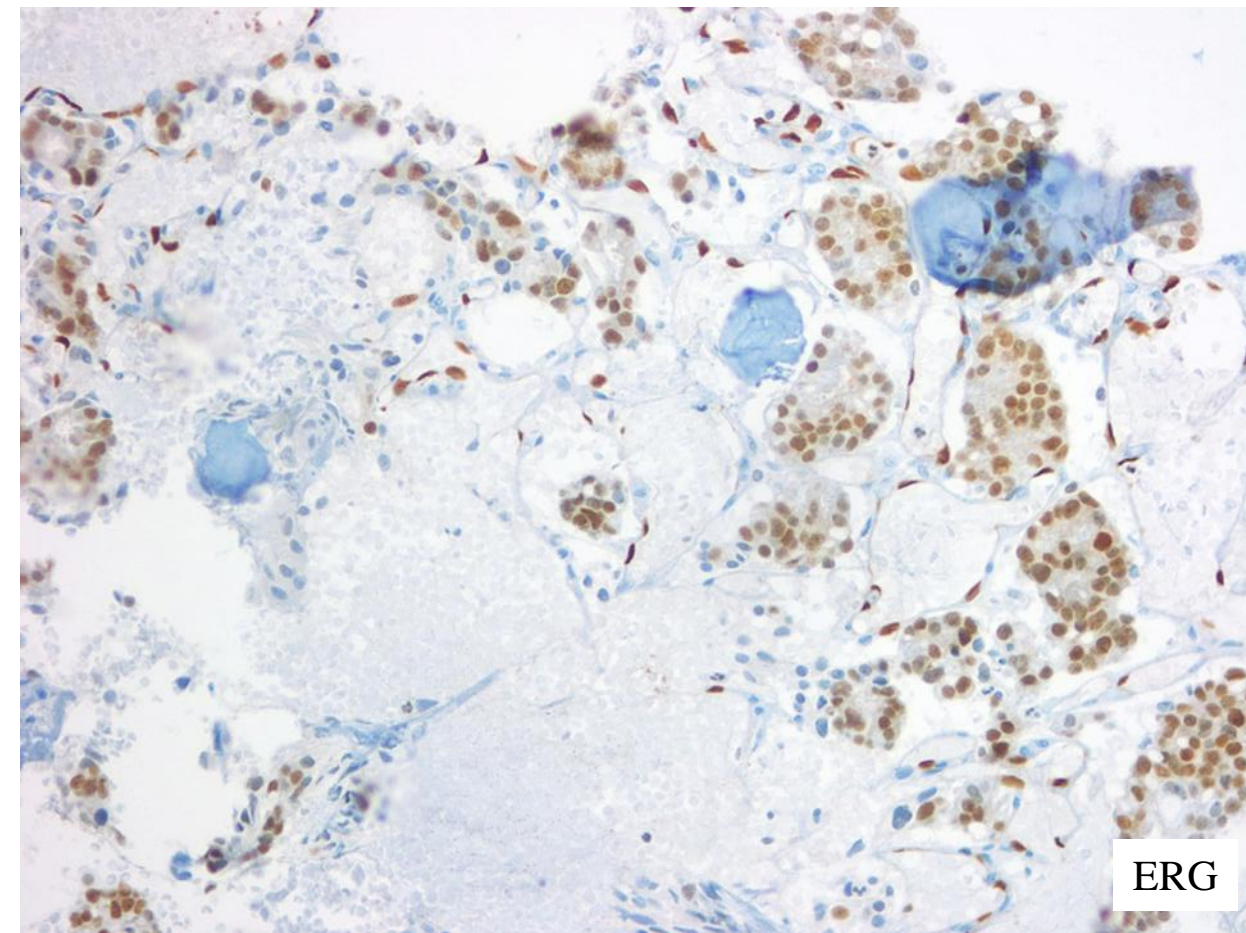


P501s



PSA

Thoracic vertebral lesion



Diagnosis of Metastatic Prostatic Adenocarcinoma

Stain	Advantages	Disadvantages
PSA	97% sensitive in metastasis High specificity	Rare + cells in GS9-10 Decreased with hormone therapy Salivary, bladder adeno, melanoma may be +
PSAP	99% sensitive in metastasis	Less specific than PSA; + in NE tumors, decreased with hormone therapy
P501S	99% sensitive in metastasis No decreased with hormone therapy	Limited studies
NKX3.1	94% sensitive in metastasis	<i>Lobular breast cancer may be +</i>
PSMA	88-100% sensitive in metastasis	Not specific
AMACR	81-93 sensitive in metastasis	Not specific
ERG	Fairly specific, + in vascular tumors	50% sensitivity

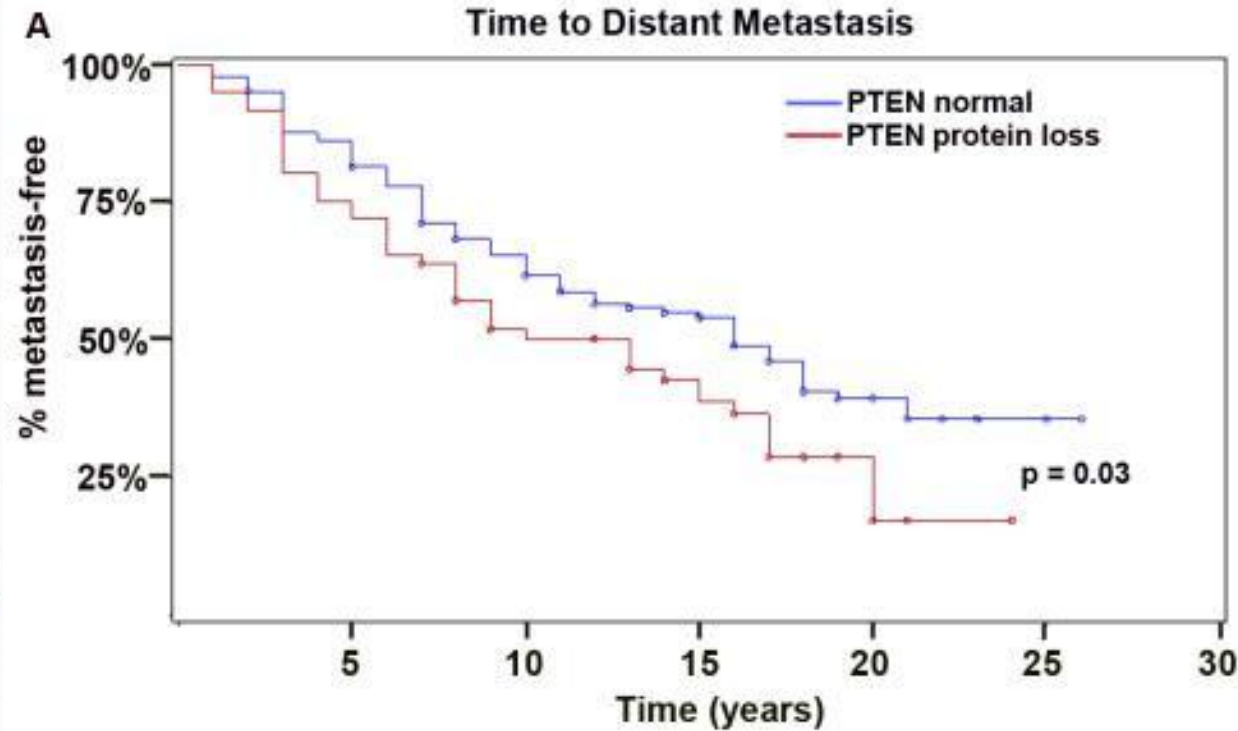
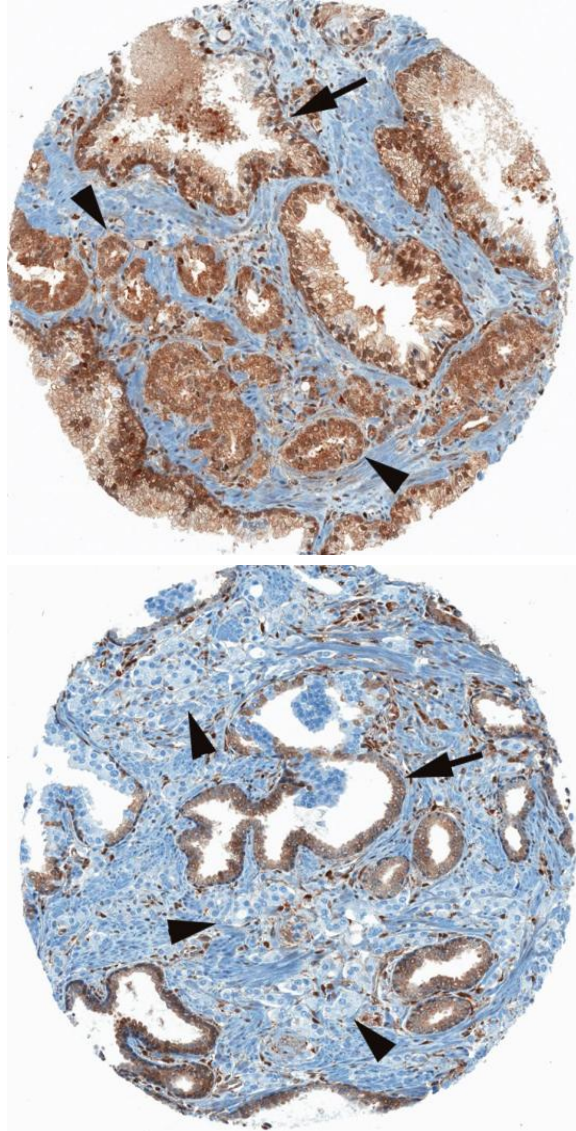
Best practice recommendations in application of IHC in prostate: Epstein et al. Am J Surg Pathol 2014

Prognostic/Predictive Markers in Prostatic Adenocarcinoma

Stain	Advantages	Disadvantages
Ki67	Readily available; most widely studied	Not prospectively validated
p53	Association with aggressive disease	Not prospectively validated
PTEN loss	Association with aggressive disease	Not prospectively validated; rarely loss in GS6
NKX3.1 loss	Evidence of association with aggressive disease; common alteration	Not prospectively validated
MYC	Evidence of association with aggressive disease; common alteration	Not prospectively validated
ERG	Common alteration	Most studies show no correlation with prognosis
SPINK1	Correlated with aggressive disease	Not prospectively validated
EZH2	Predictive of disease progression, poor prognosis, outcome	Not prospectively validated

Currently, no prognostic IHC/molecular studies are routinely performed on Bx or resection specimens

PTEN



- PTEN is downregulated in 20% primary PCA and 50% CRPC
- 84-100% IDC-P show PTEN loss
- PTEN loss is strongly associated with poor outcomes and CRPC

Take Home Messages

- PCA diagnosis relies on a constellation of features
- Awareness of mimickers' histologic features prevents over-diagnosing PCA
- Correlation of morphological features with adjunctive IHC stains may be necessary to make correct diagnosis
- Accurate diagnosis of tumor type and/or side of origin usually requires more than a single IHC marker
- Accurate validation of biomarkers is critical for appropriate integration into clinical practice
- **Be aware of pitfalls!.....no IHC stain is perfect**

THANK YOU!

cmagigalluzzi@uabmc.edu

SCHOOL OF MEDICINE