

Lesions with atypical proliferation: the responsibility of the pathologist



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Reporting categories on minimally invasive breast biopsies (so called B-classification)

B1 Normal tissue/uninterpretable

B2 Benign lesion

B3 Lesion of uncertain malignant potential

B4 Suspicious of malignancy

B5 Malignant

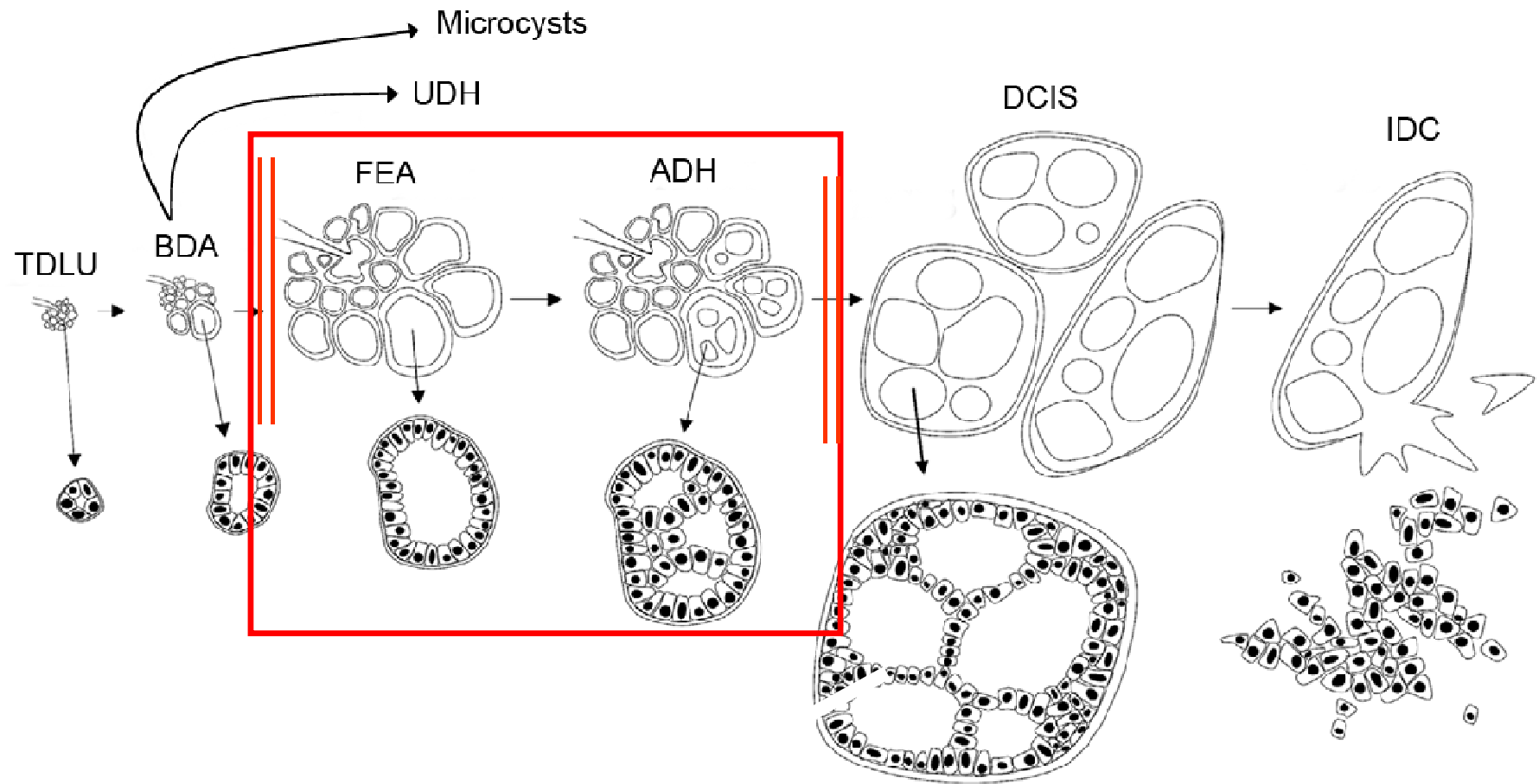
1. High grade LIN

2. Ductal carcinoma in situ

3. Invasive carcinoma

- **Lesions with increased risk of associated malignancy.:**
 - ADH
 - FEA
 - ALH, LN
- **Lesons known to show heterogeneity:**
 - Papilloma
 - Radial Scar
 - Cellular fibroepithelial lesion

Low-grade pathway of breast cancer



Precancerous changes in the breast: A morphologic continuum?



~~Simple Hyperplasia~~

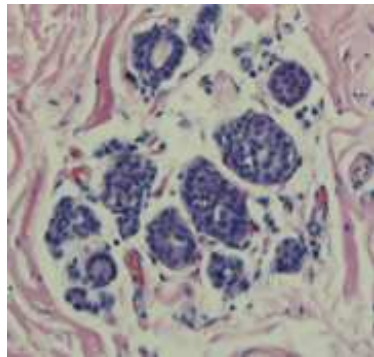
Atypical Hyperplasia

DCIS

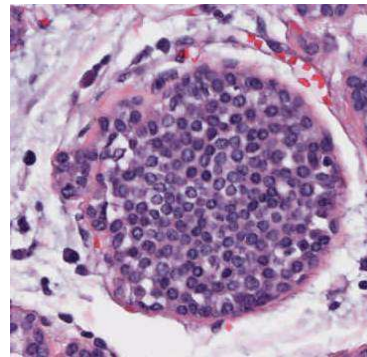
Invasive
Carcinoma

Formal pathogenesis and classification of precursor lesions in the low-grade-pathway

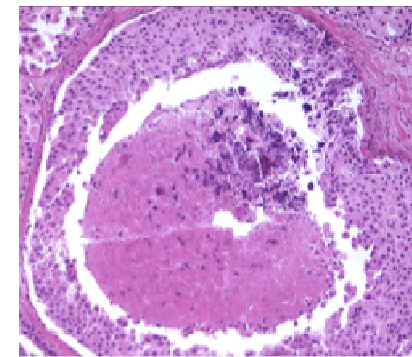
lobular



LIN 1/ALH

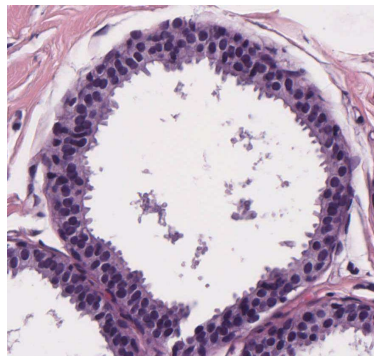


LIN 2

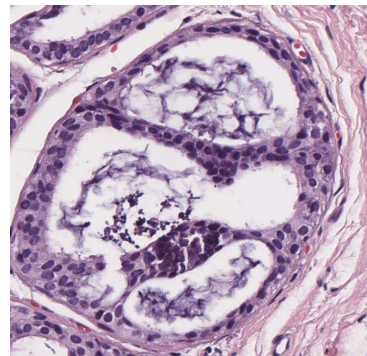


LIN 3

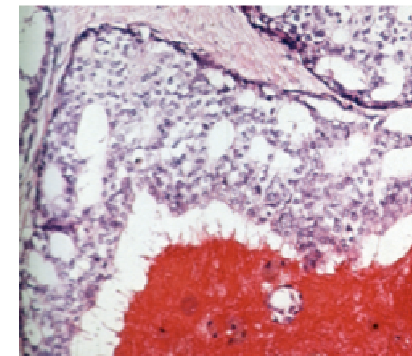
ductal



FEA



ADH

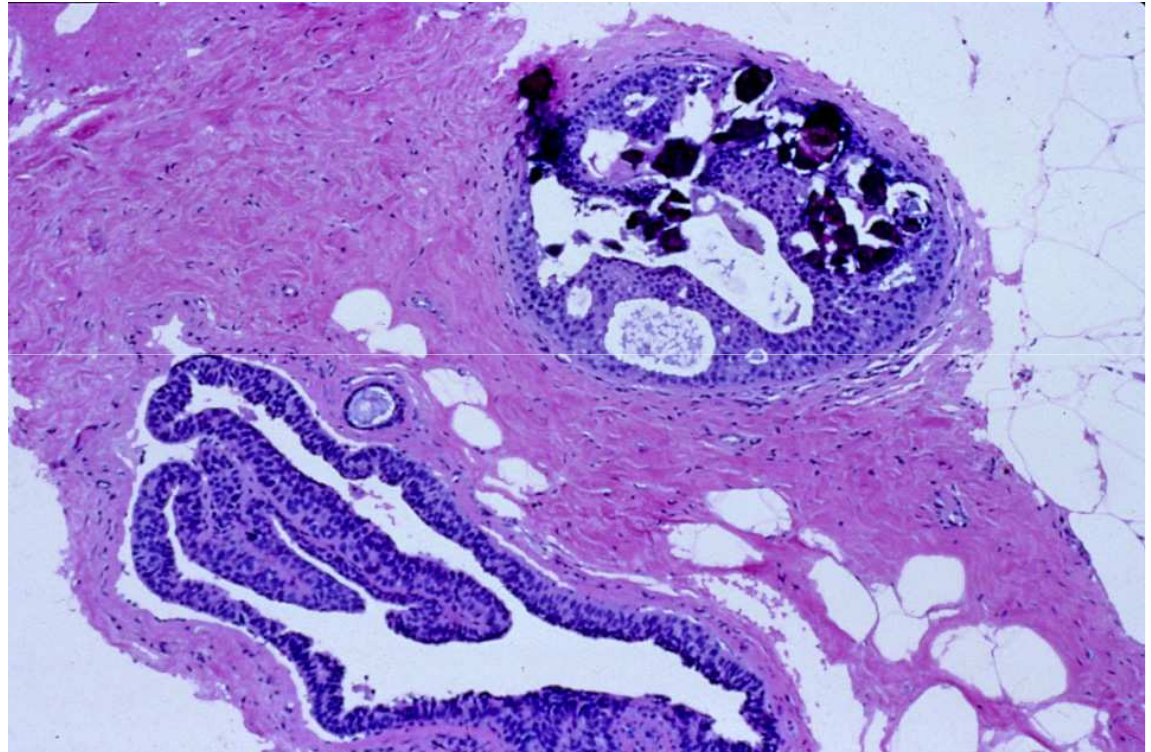


Ig-DCIS

Atypical ductal hyperplasia (ADH)

Atypical ductal epithelial proliferation (ADEP)

- Partial involvement of duct space
- Cell population same as non comedo DCIS
- Second population of polarised basal cells
- At least one non tapering bar (>6 cells across)



Page + Rogers Human Path 1992, 23, 1095

ADH on CNB

Results on excision specimen

141 ADH in CNB
21 invasive Ca
42 DCIS

44.7% upgrade rate

Houssami, Br J Cancer (2007) 96, 1253-57

Issues with the assessment of atypia in minimally invasive breast biopsy

Individual risk assessment

- Flat epithelial atypia (FEA)
- Lobular intraepithelial neoplasia (LN)

Avoidance of overdiagnosis

- Usual ductal hyperplasia
- Adenosis and sclerosing lesions
- Papilloma

Issues with the assessment of atypia in minimally invasive breast biopsy

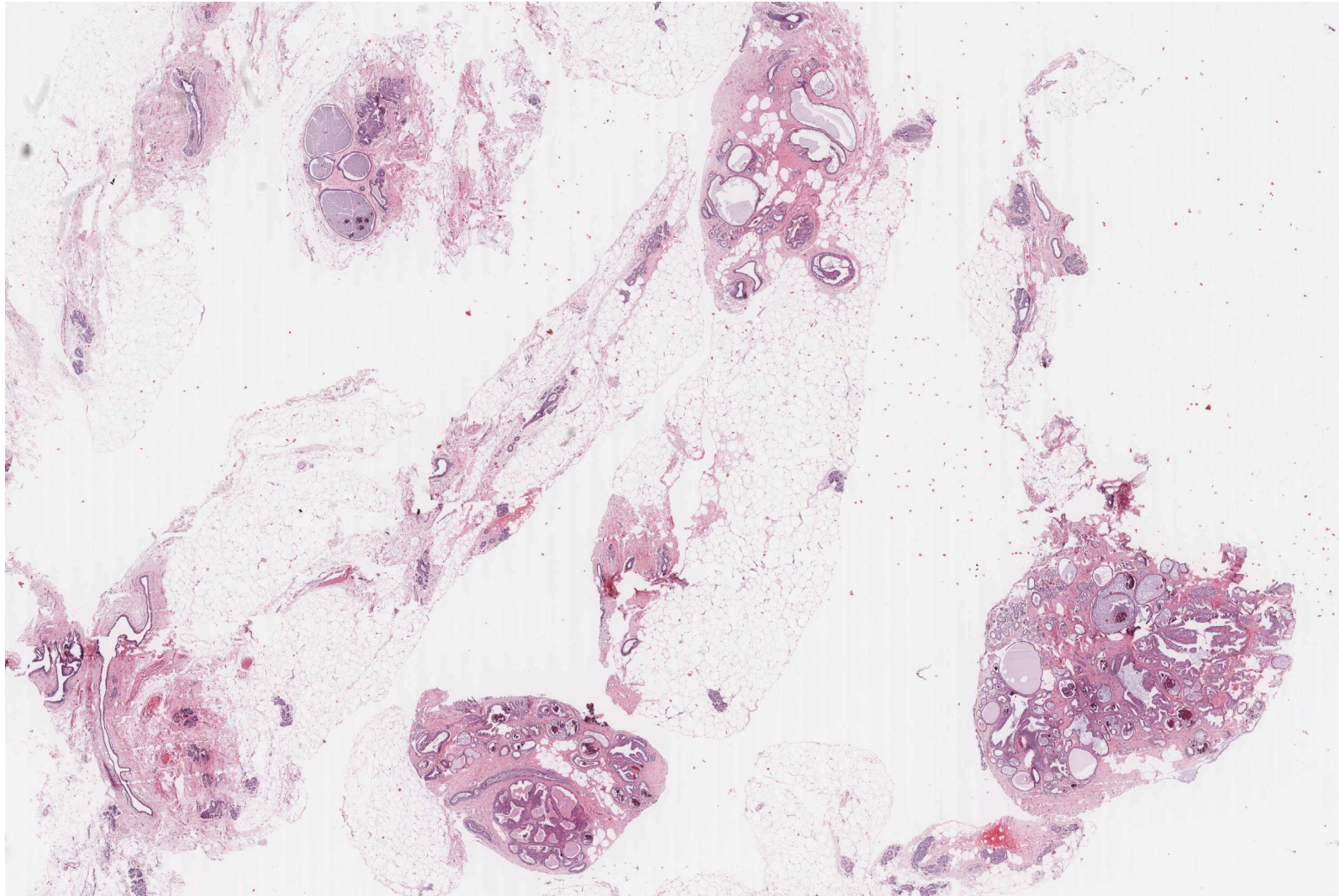
Individual risk assessment

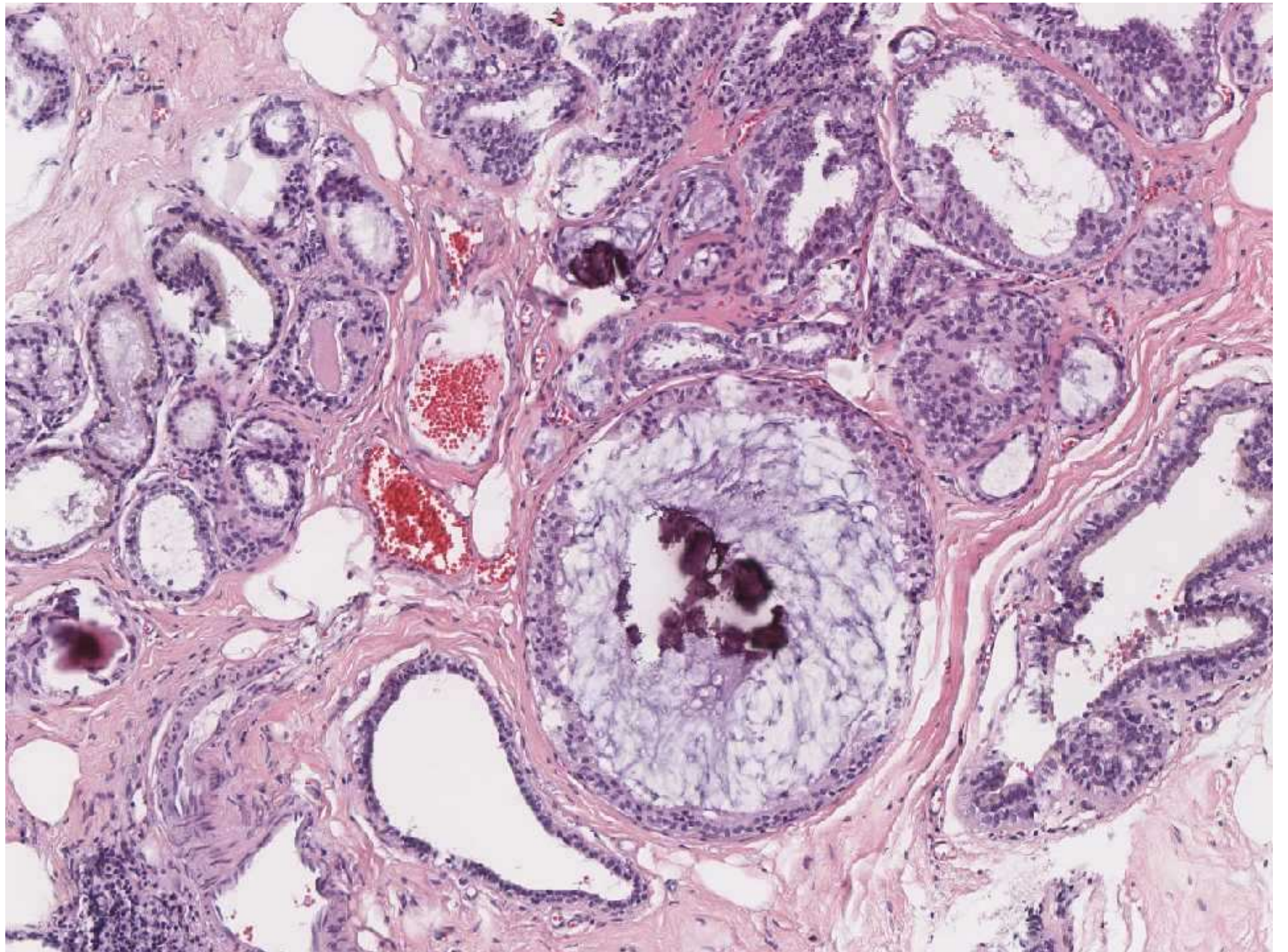
- Flat epithelial atypia (FEA)
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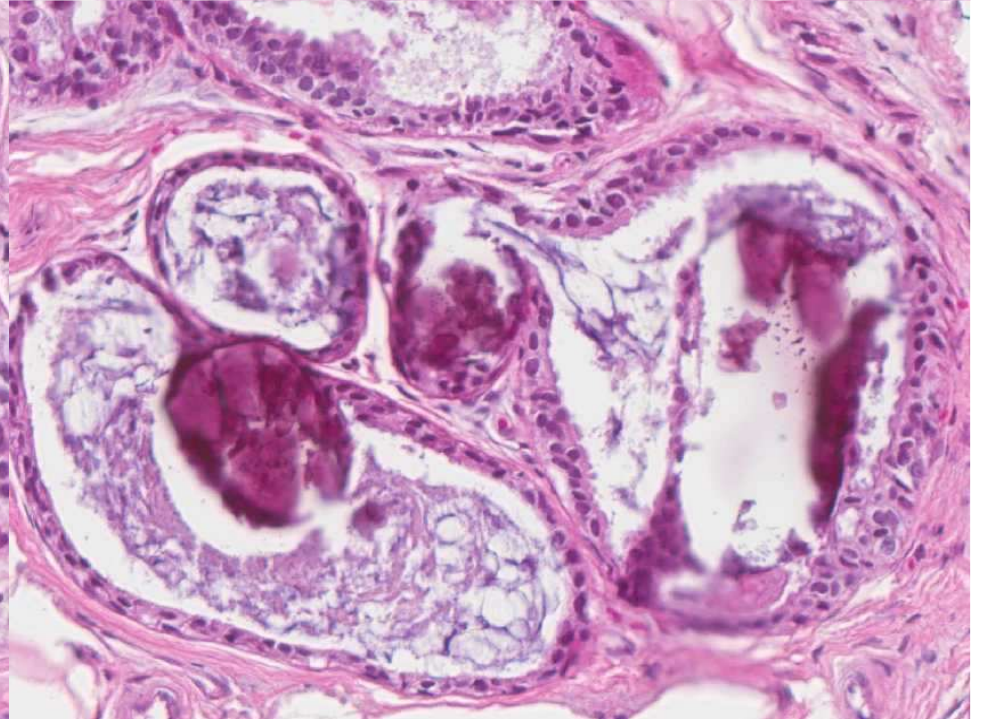
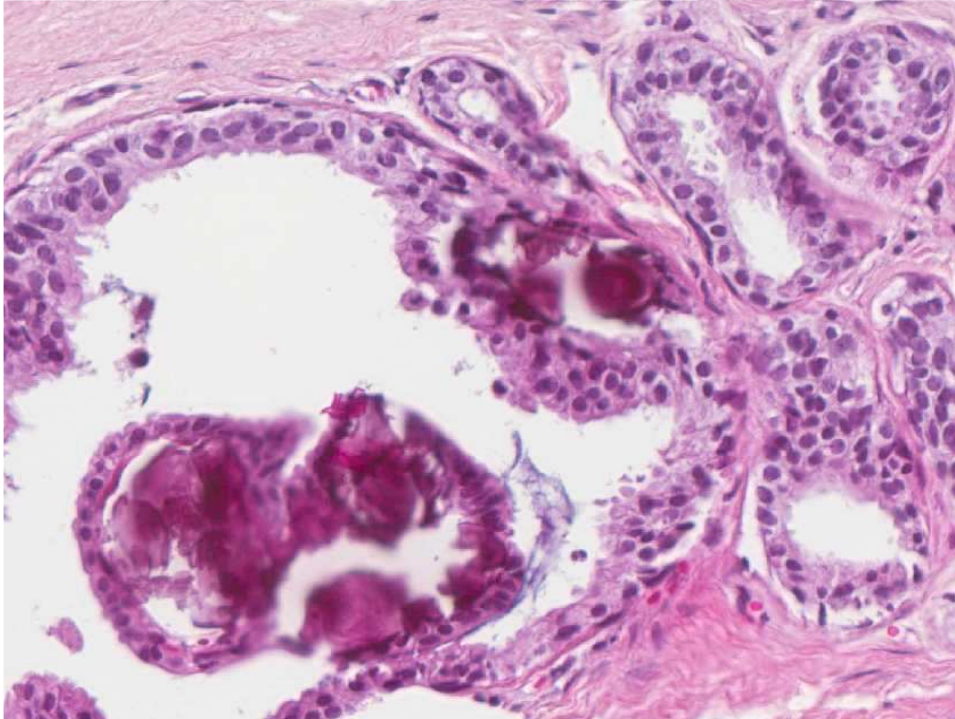
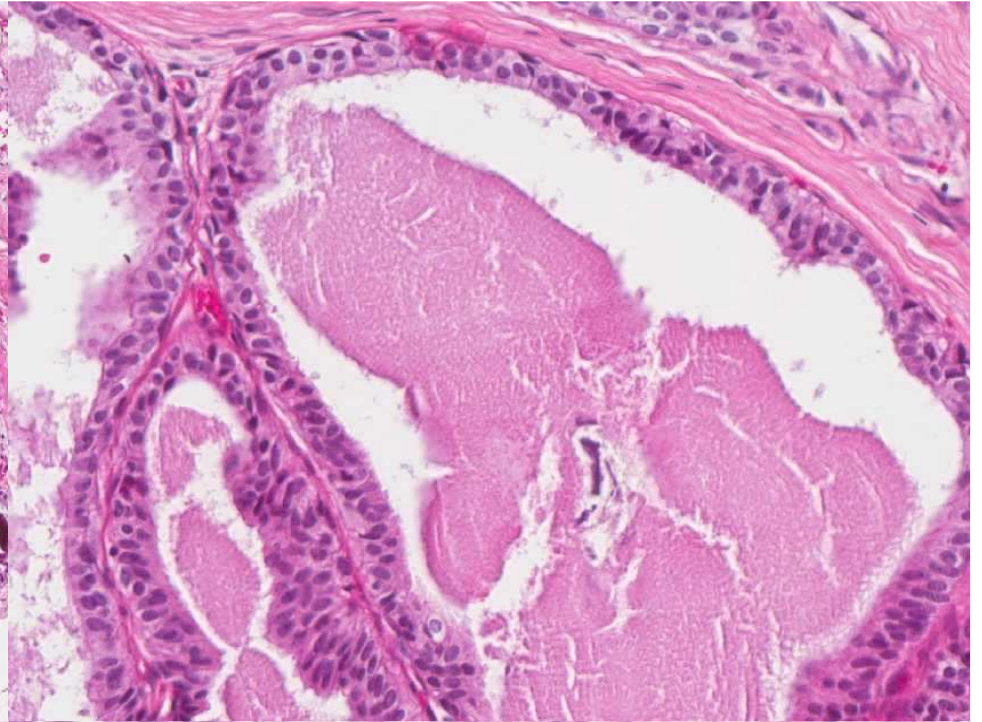
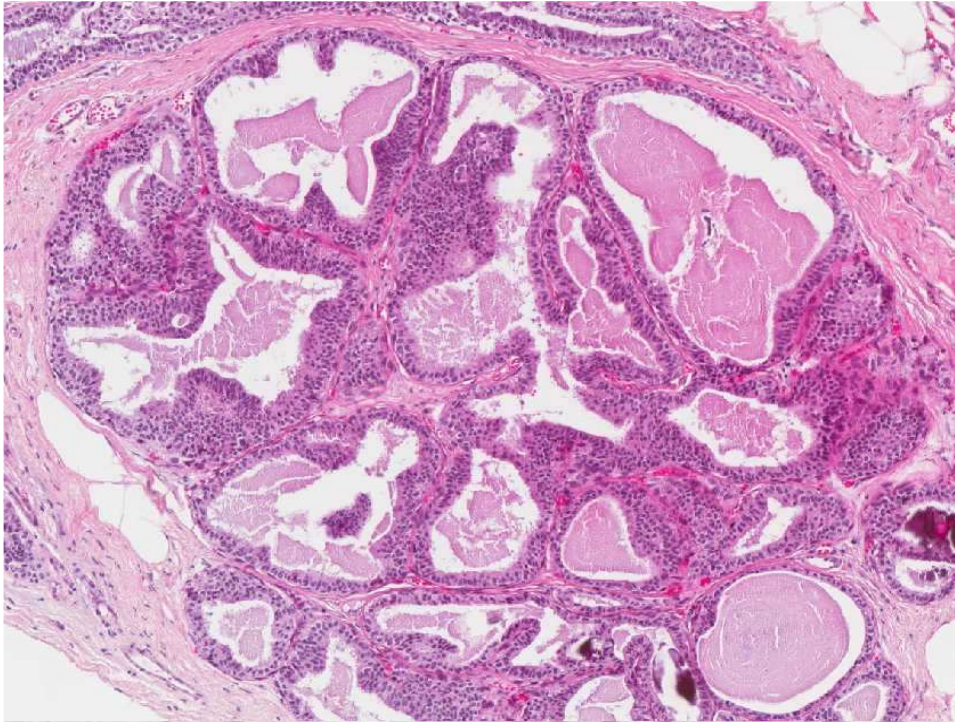
Avoidance of overdiagnosis

- Usual ductal hyperplasia
- Adenosis and sclerosing lesions
- Papilloma

67 yo patient with increasing microcalcifications on mammography



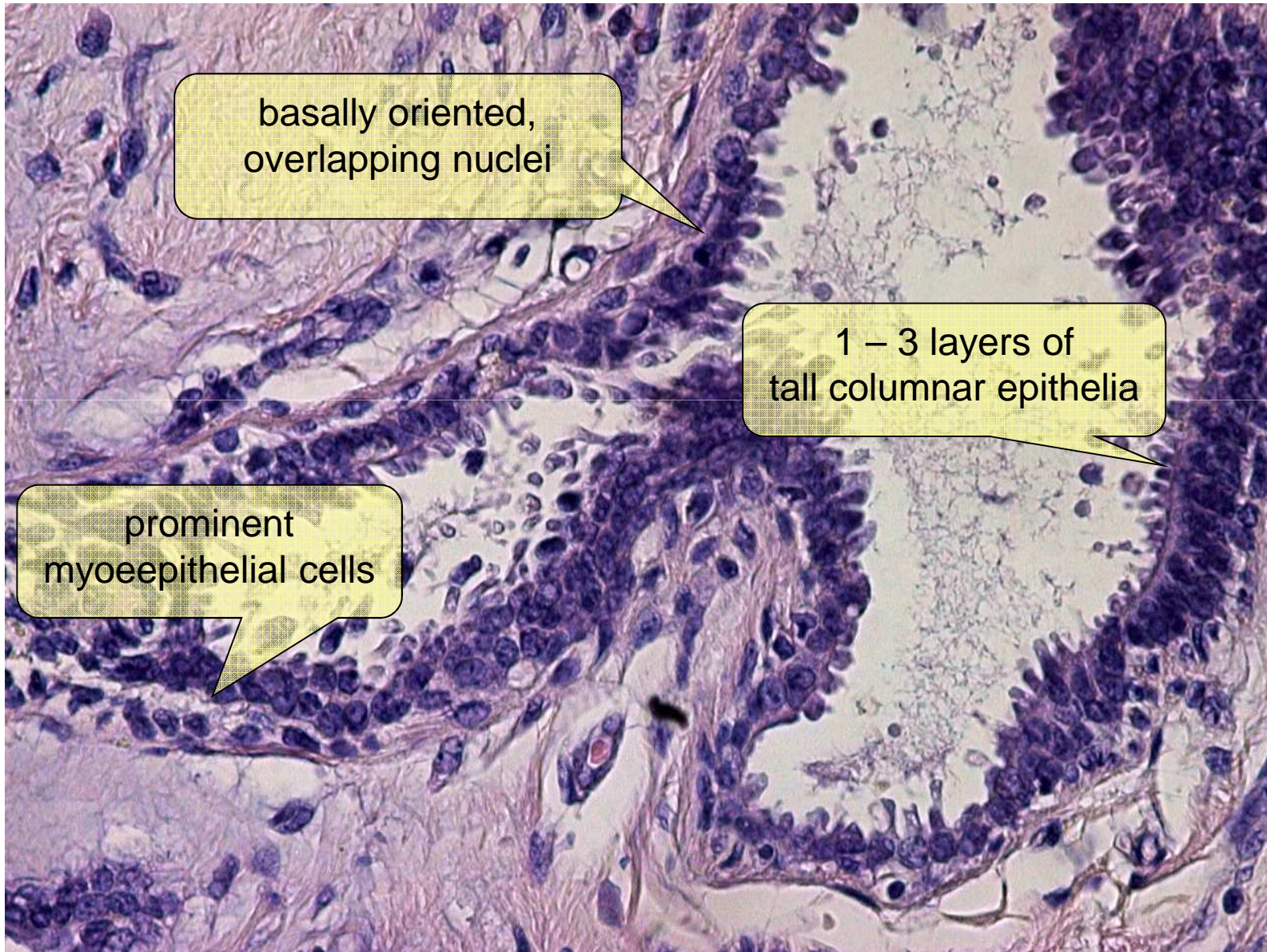




Flat epithelial atypia (FEA) – B3

- Diagnostic criteria
 - single or 3-5 layers of mildly atypical cells
 - monotonous atypical cell proliferation
 - arcadas and micropapillary formations absent or rare
 - TDLUs are variably distended
- Case presented at diagnostic slide seminar
 - B2: 6 votes
 - B3: 17 votes (53%)
 - B4: 3 votes
 - B5a: 6 votes

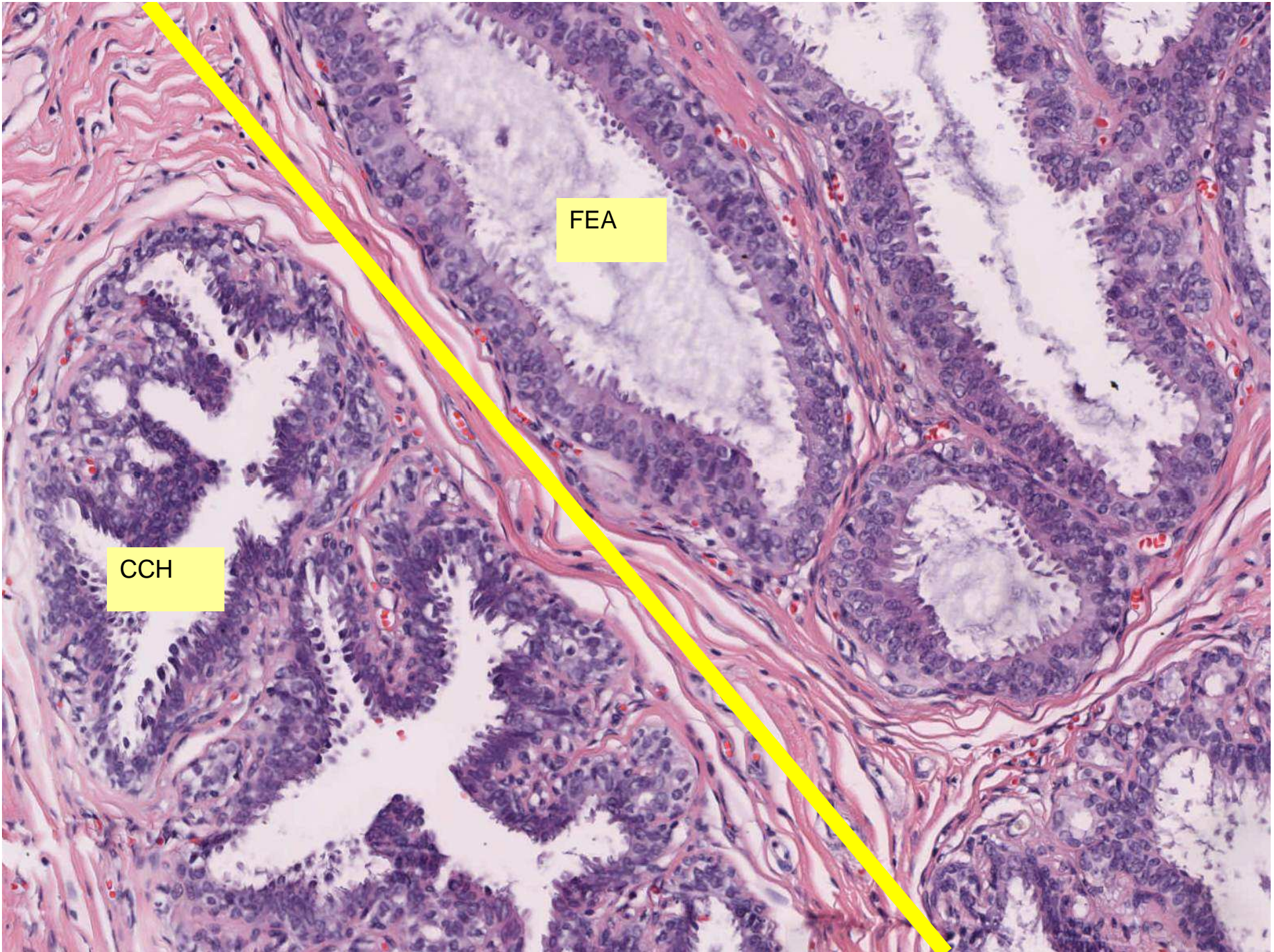
Simple columnar cell change (CCC)



basally oriented,
overlapping nuclei

1 – 3 layers of
tall columnar epithelia

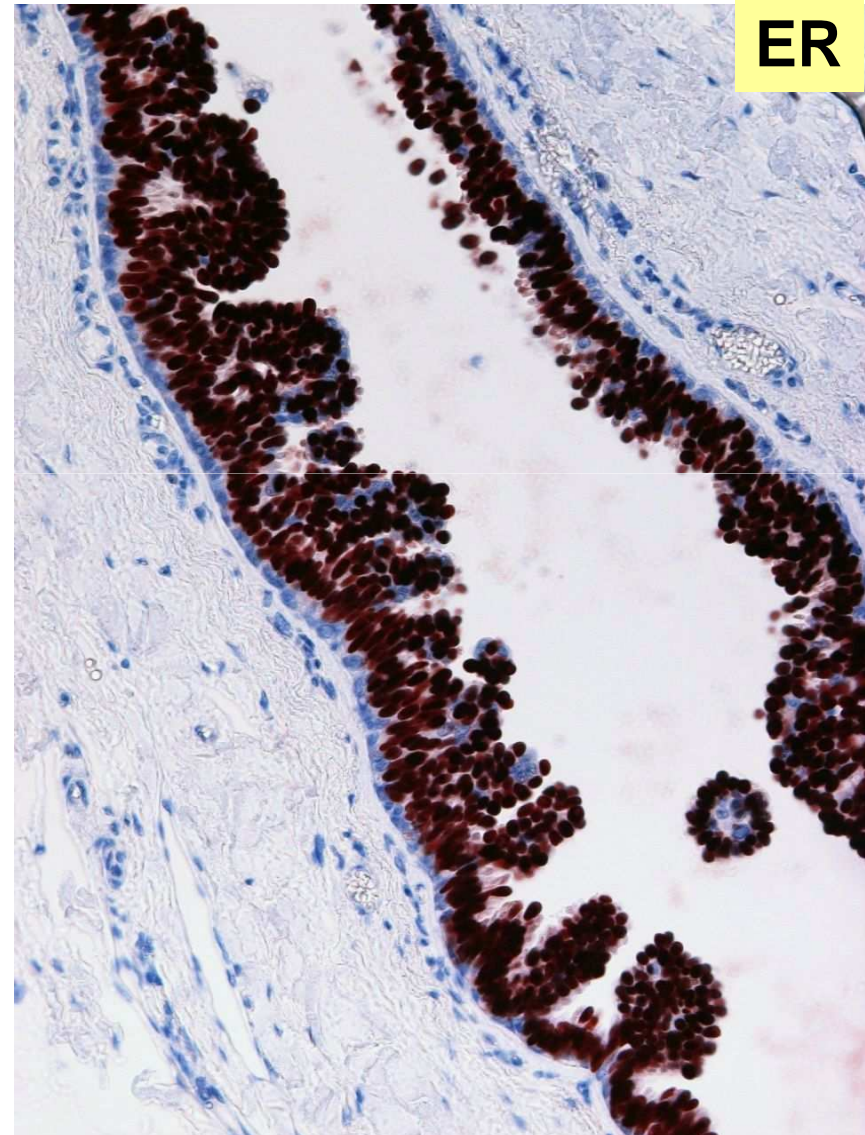
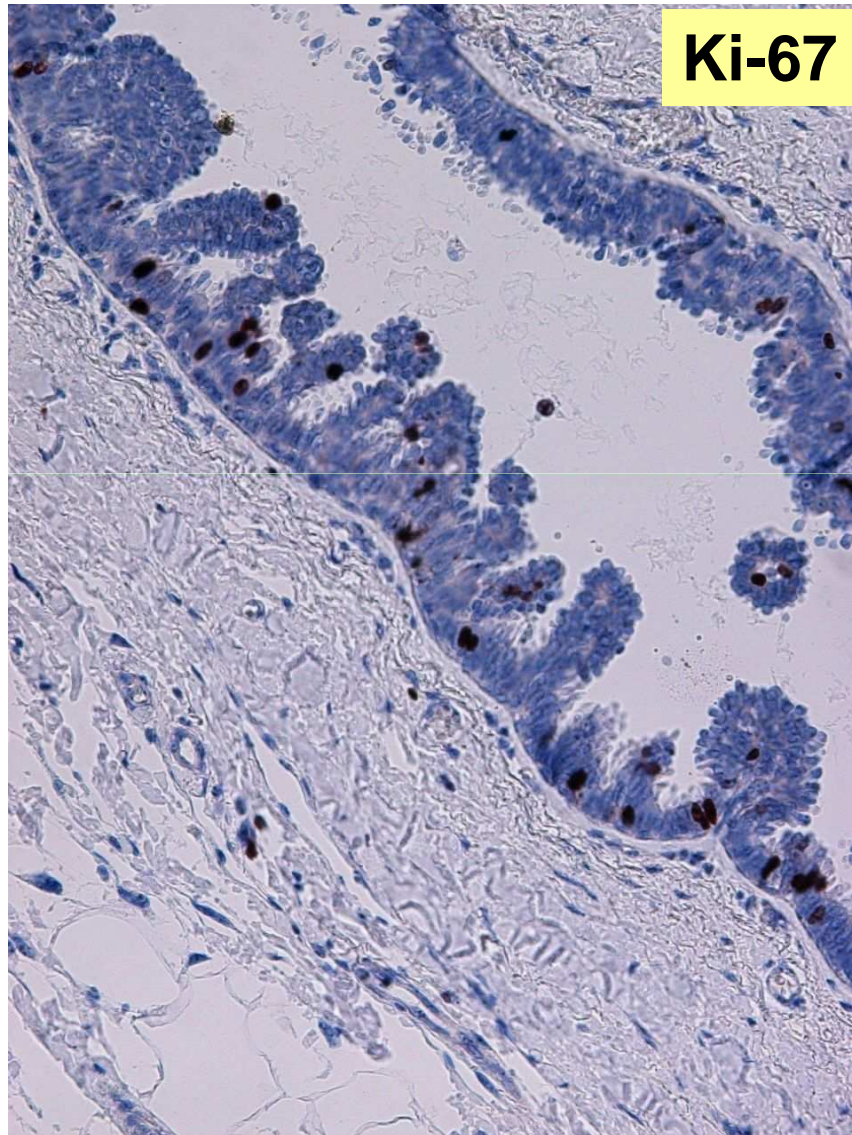
prominent
myoepithelial cells



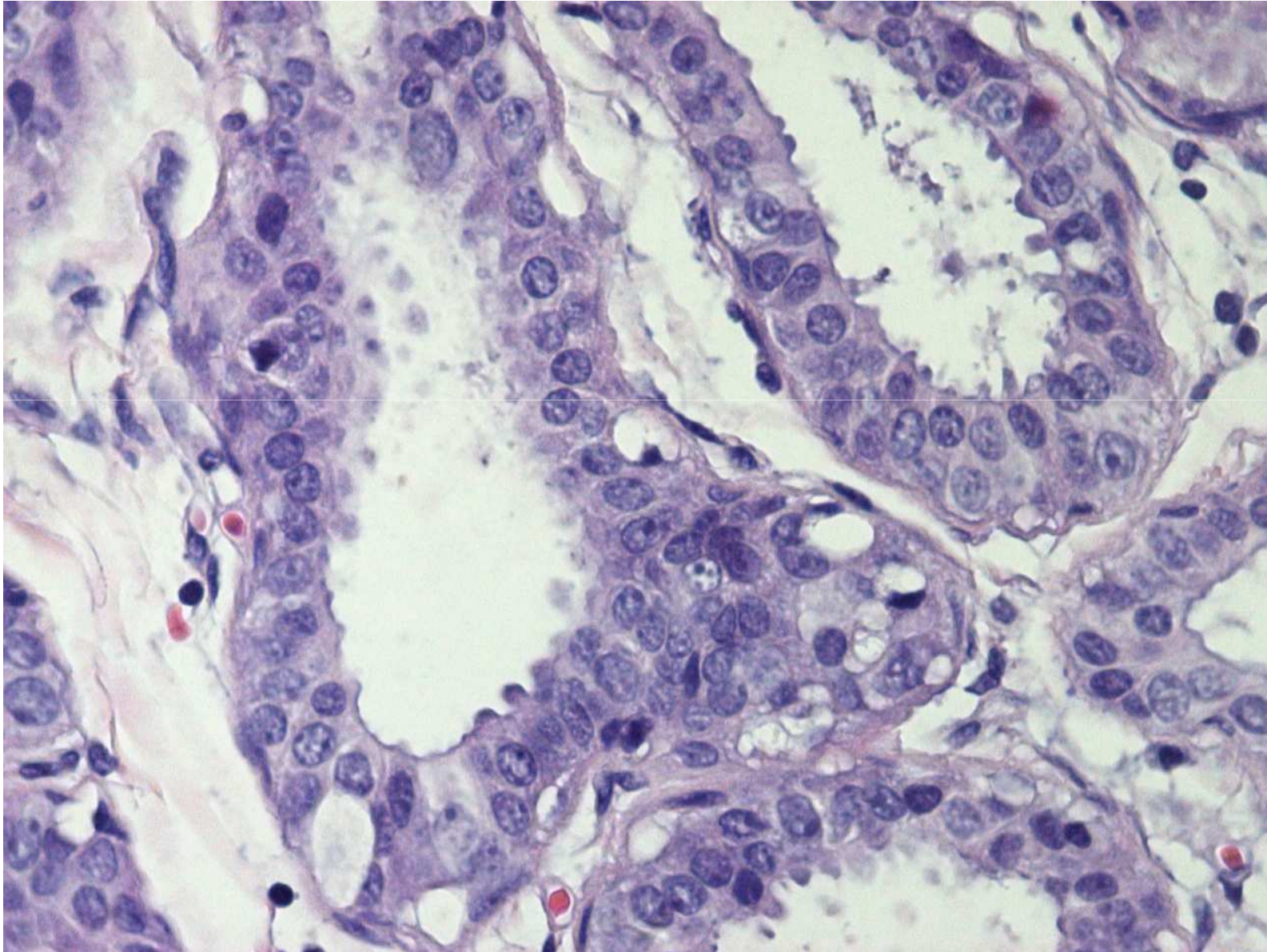
CCH

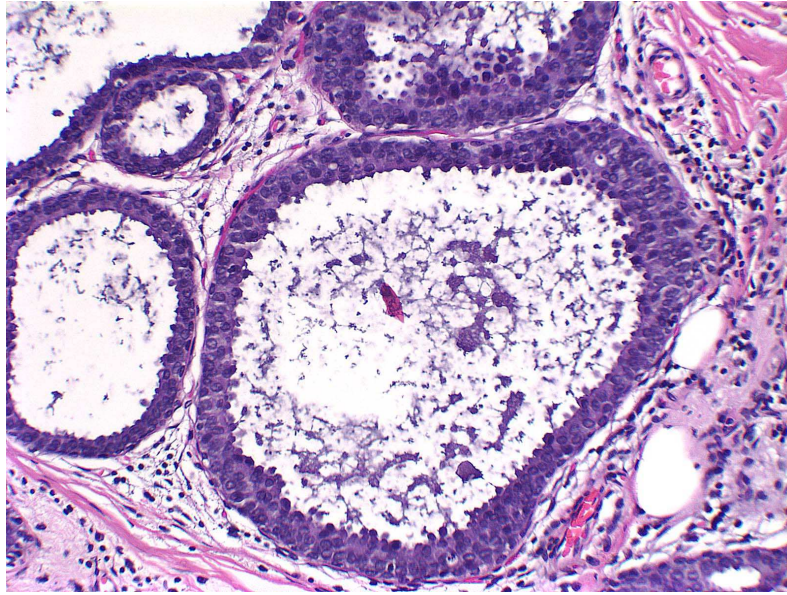
FEA

FEA: low proliferative activity and ER expression

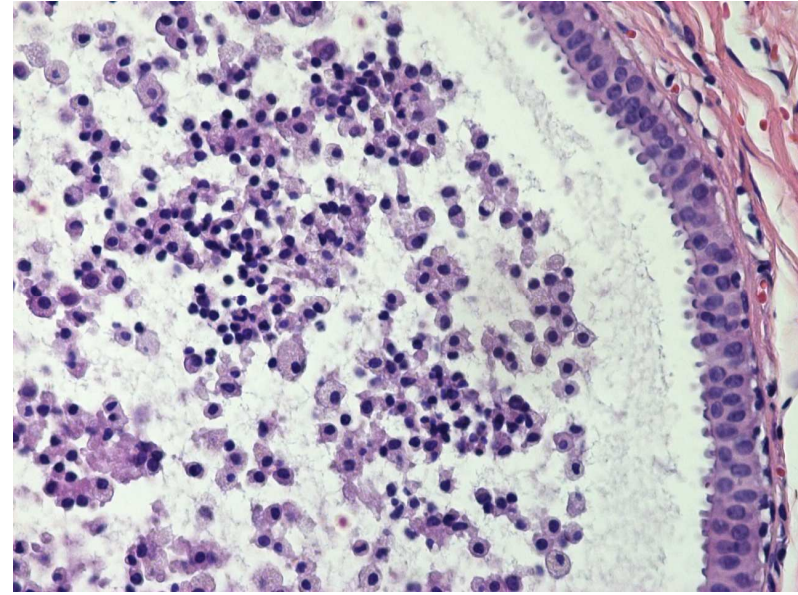


FEA: low grade nuclear atypia

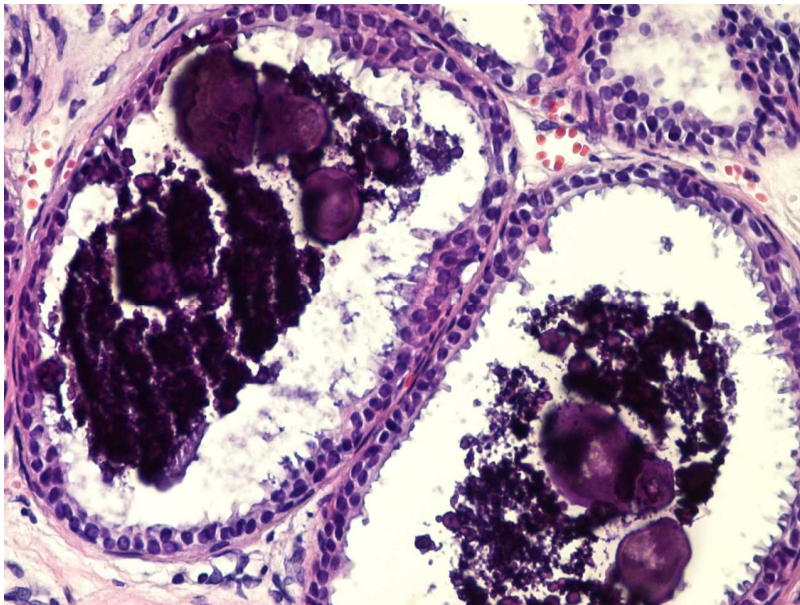




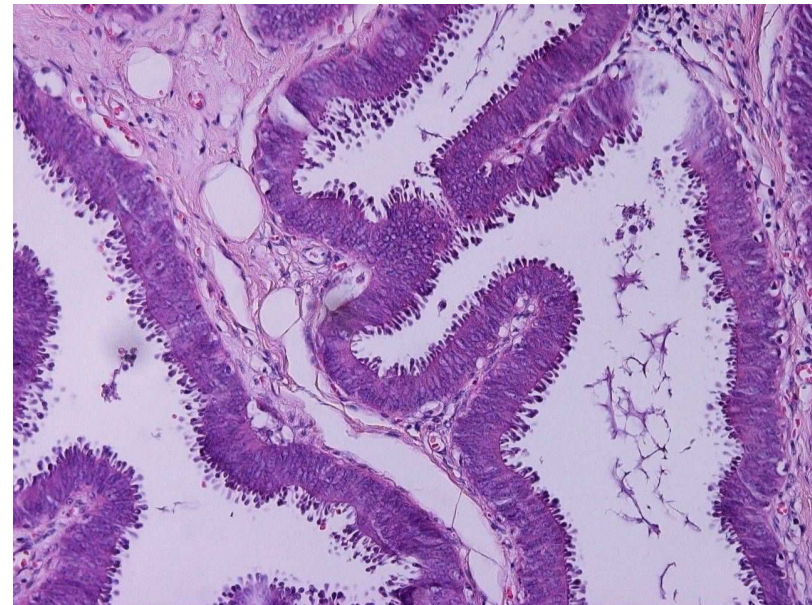
hyperplastic



monomorphic



single cell layer



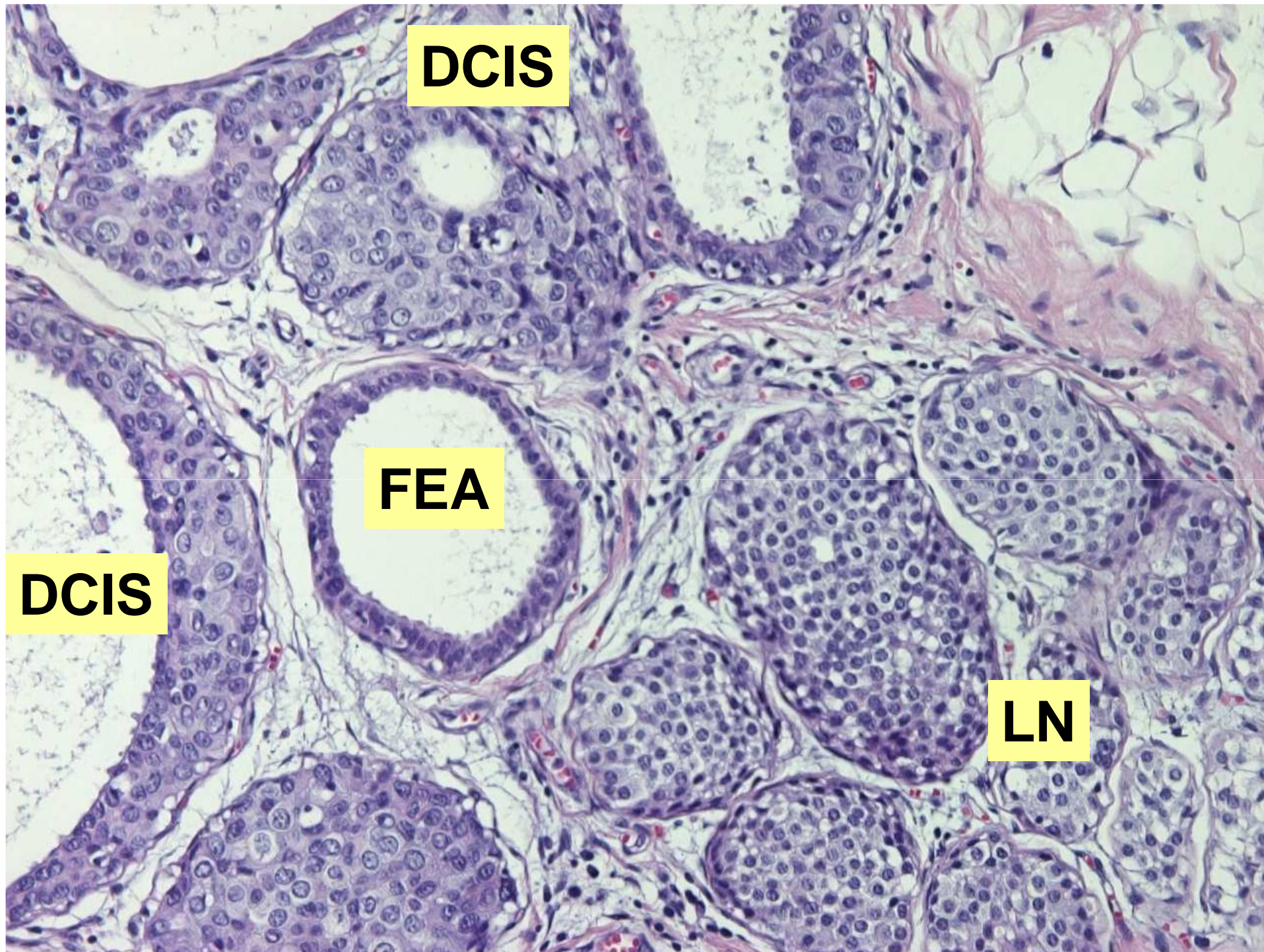
hypersecretory



A histological section of breast tissue stained with hematoxylin and eosin (H&E). The image shows a transition from normal ductal structures to a more cellular, proliferative area. A prominent yellow diagonal line runs from the top-left to the bottom-right, separating the two regions. The upper region, labeled 'CCH', shows a dense population of cells with hyperchromatic nuclei and some architectural disorganization. The lower region, labeled 'FEA', shows more organized ductal structures with a clear luminal space and a surrounding layer of cells. The overall appearance is consistent with a transition from normal ductal hyperplasia to a more advanced proliferative lesion.

CCH

FEA

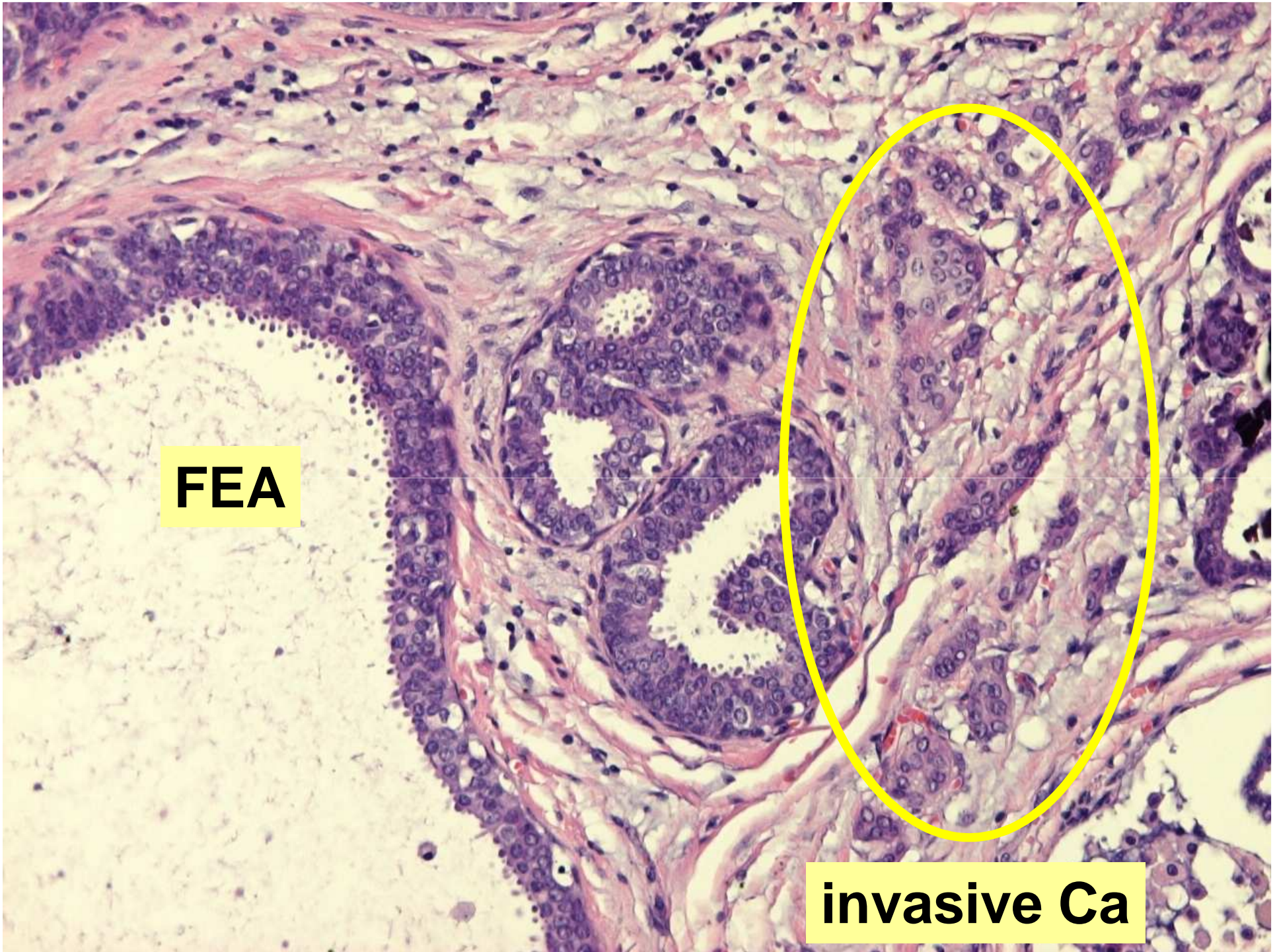


DCIS

FEA

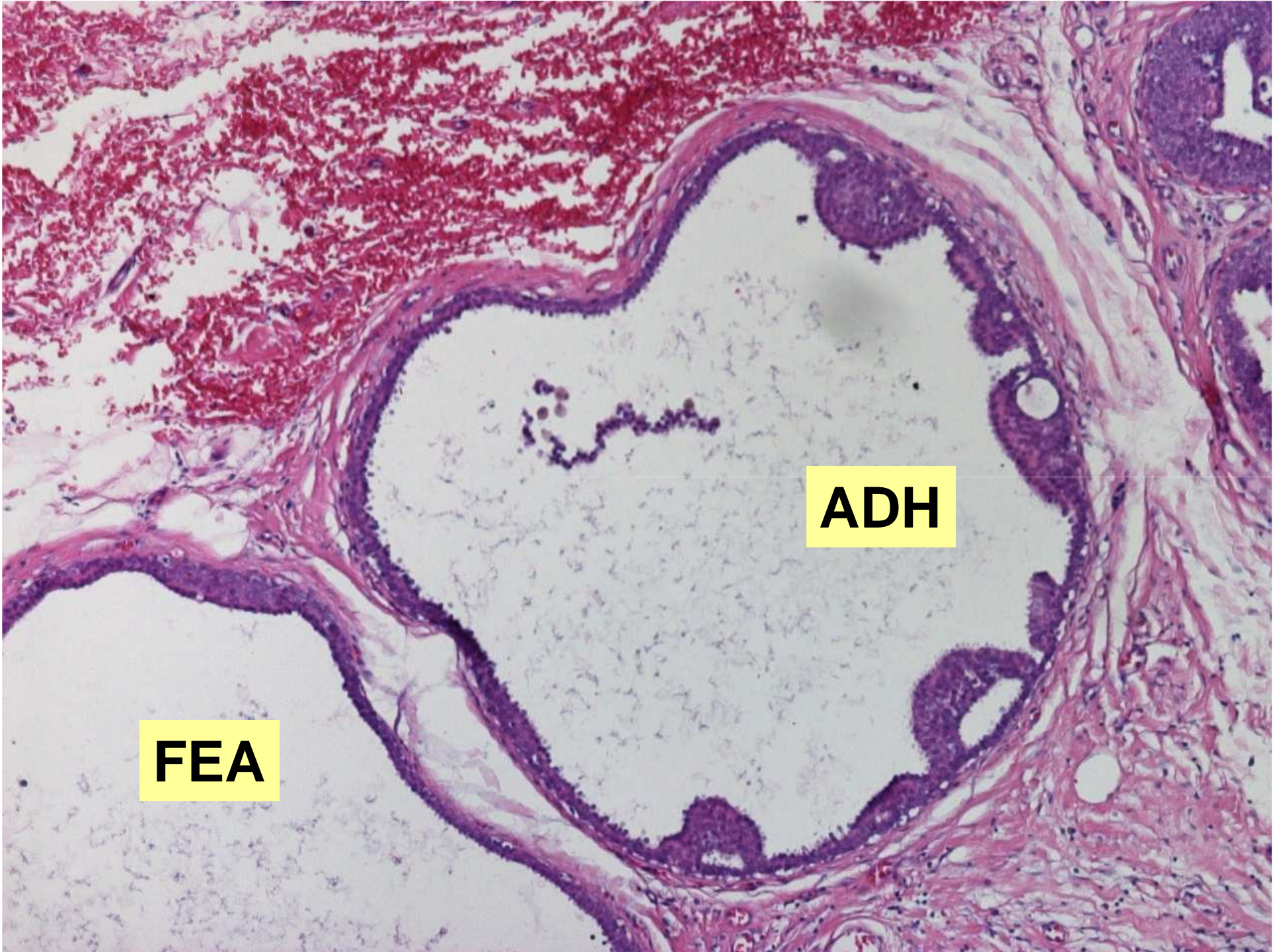
DCIS

LN



FEA

invasive Ca



FEA

ADH

European Guidelines 4th ed. Columnar cell changes (CCC)

- **B2:** Columnar cell change or hyperplasia without atypia (no atypical cells, no cellular tufting),
- **B3:** Columnar cell change or hyperplasia with atypia
 - atypical cells with some cellular tufting and
 - multiple cell layers
- **B5a:** Low grade ductal in situ carcinomas that encompass forms of cribriform to micropapillary in situ (clinging) carcinomas.

Issues with the assessment of atypia in minimally invasive breast biopsy

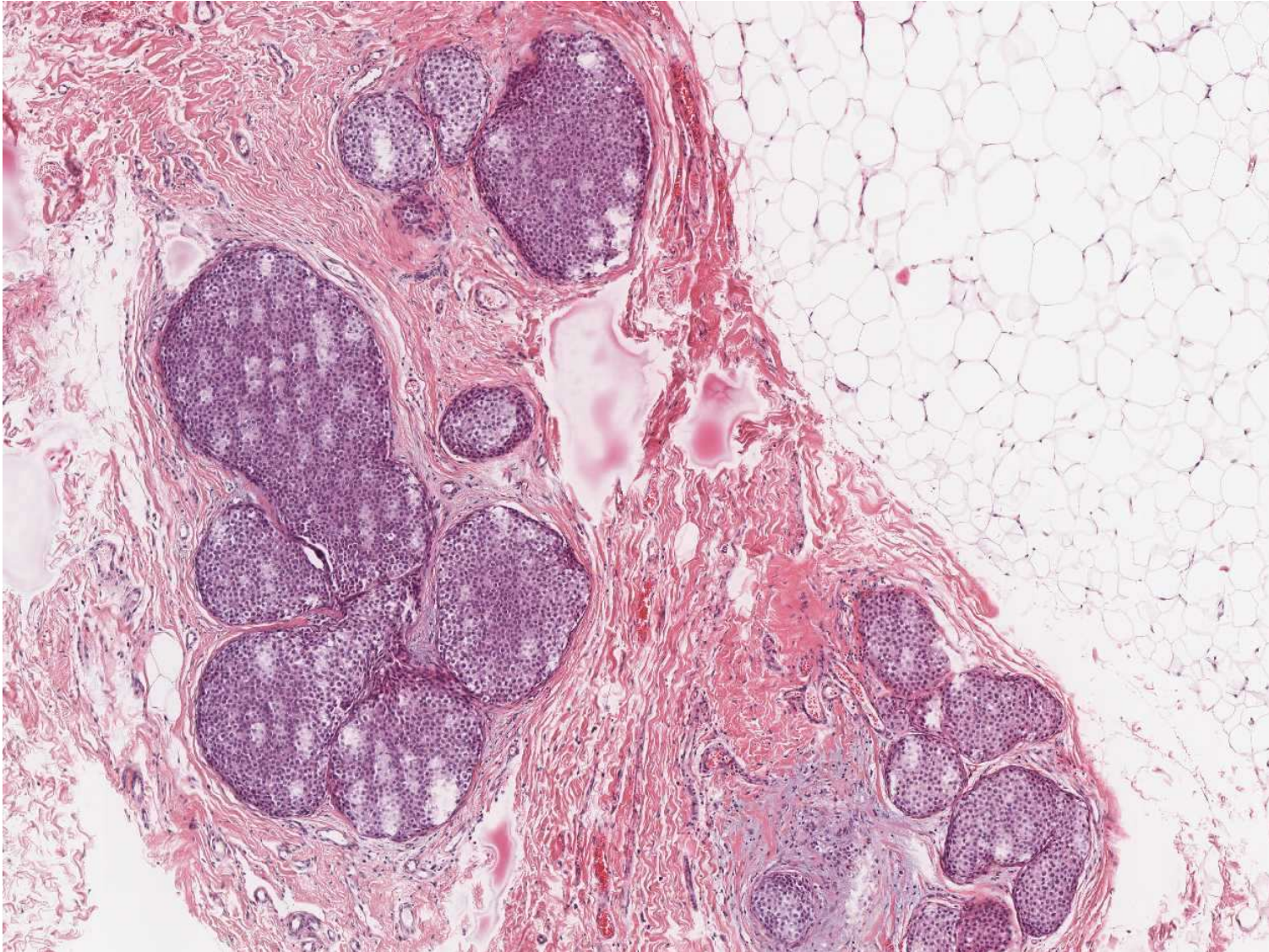
Individual risk assessment

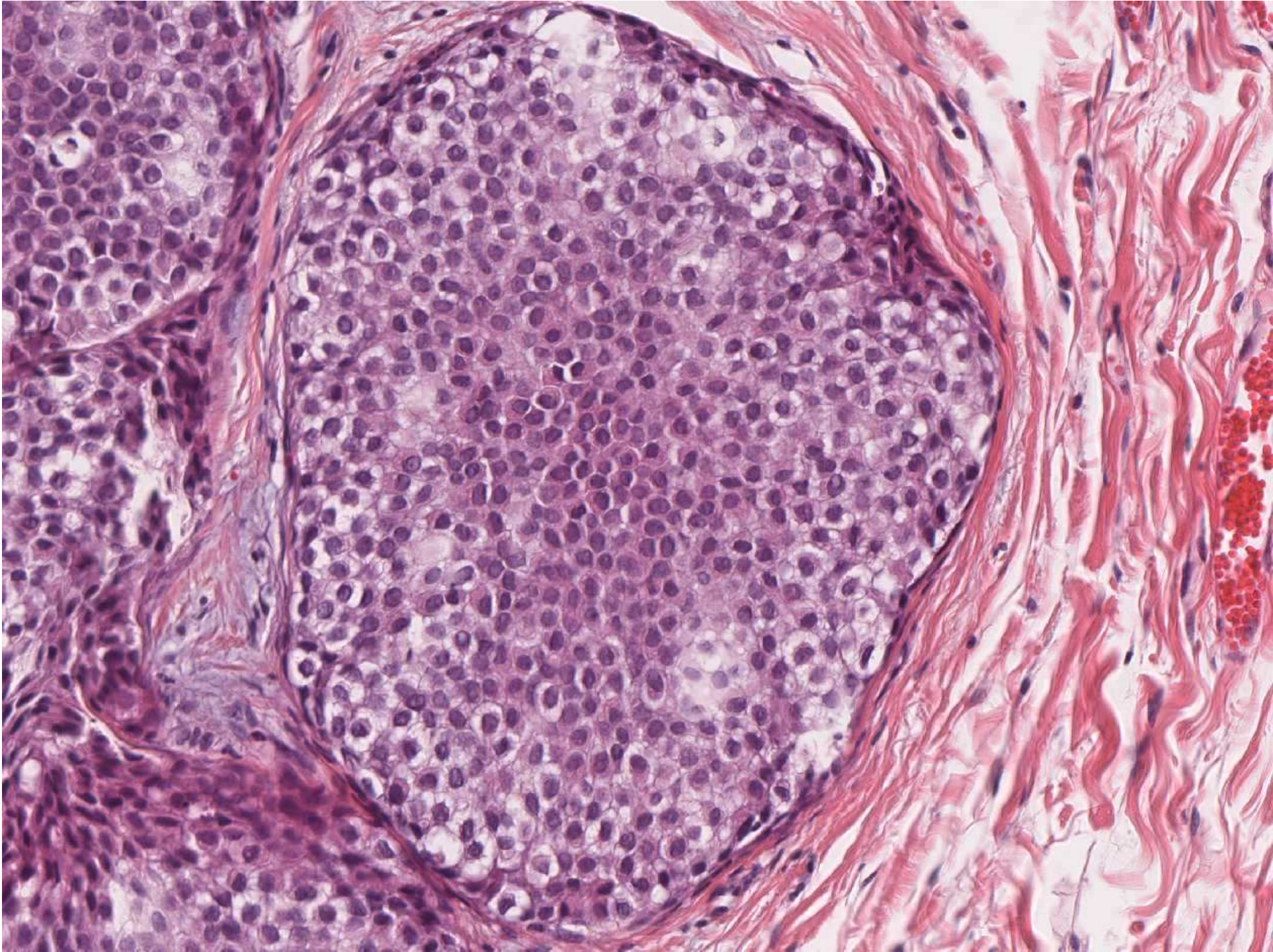
- Flat epithelial atypia (FEA)
- Lobular intraepithelial neoplasia (LN)

Avoidance of overdiagnosis

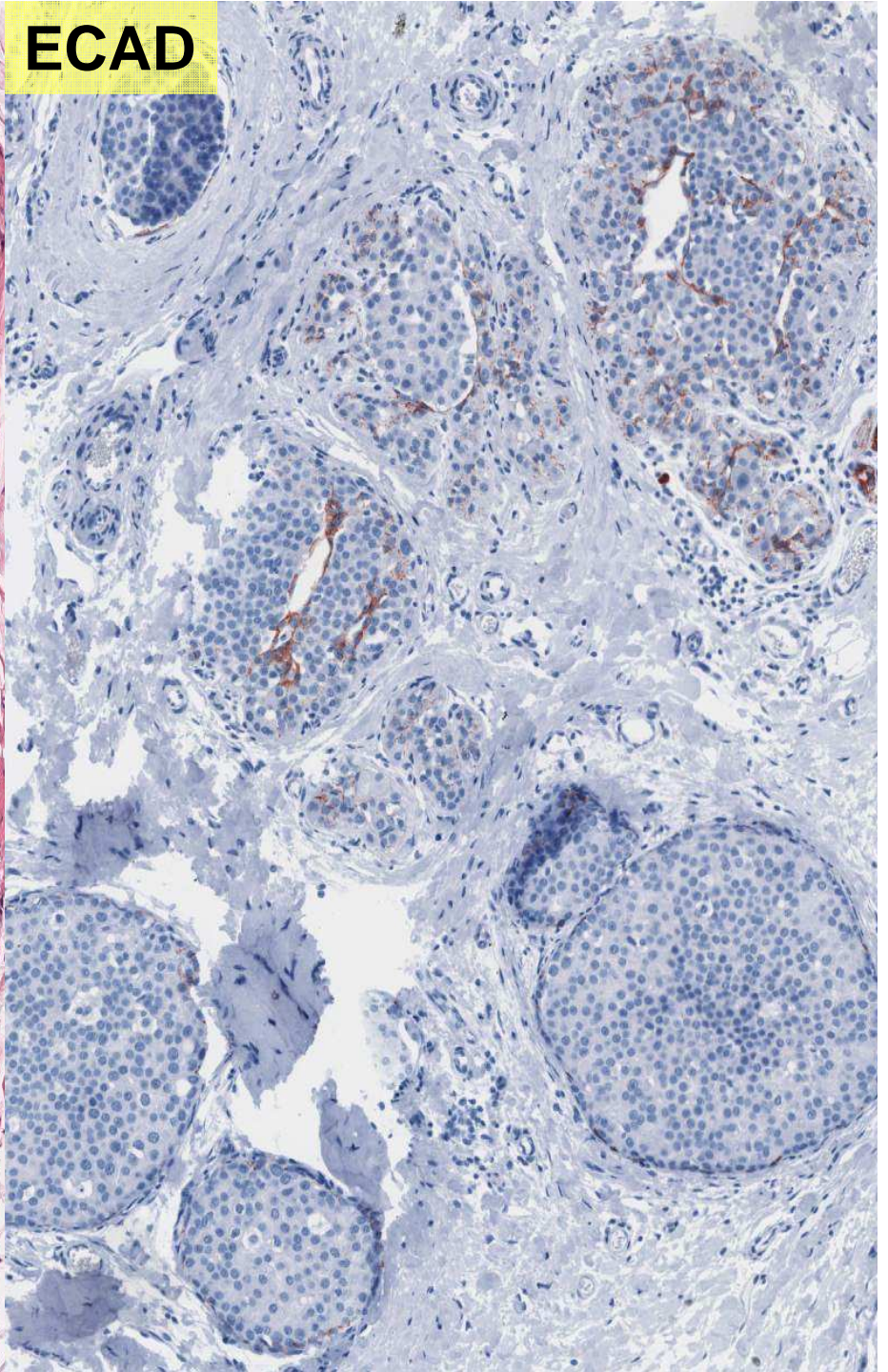
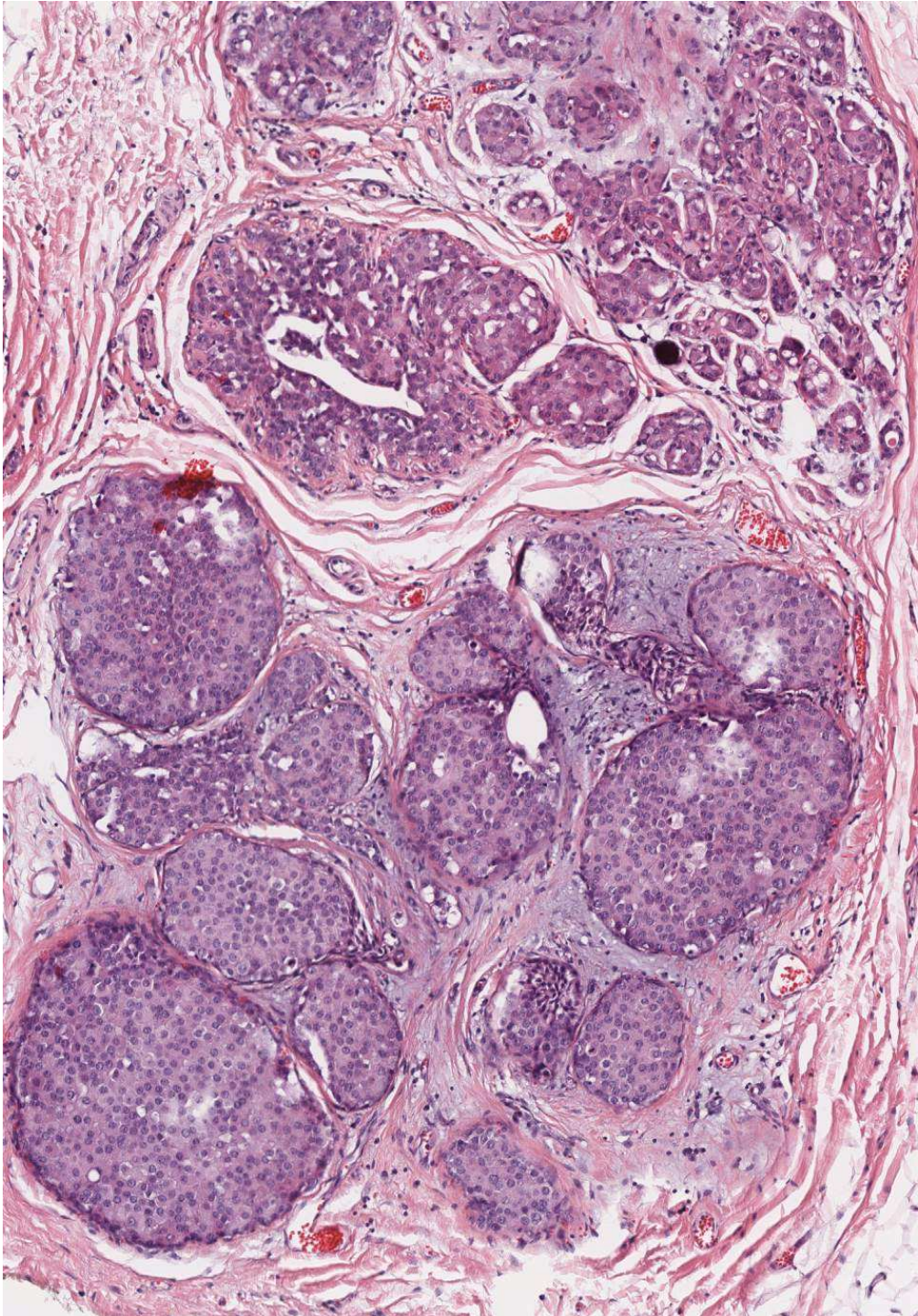
- Usual ductal hyperplasia
- Adenosis and sclerosing lesions
- Papilloma

**Lobular intraepithelial neoplasia, high grade
(LIN 3), reporting category: B5a**



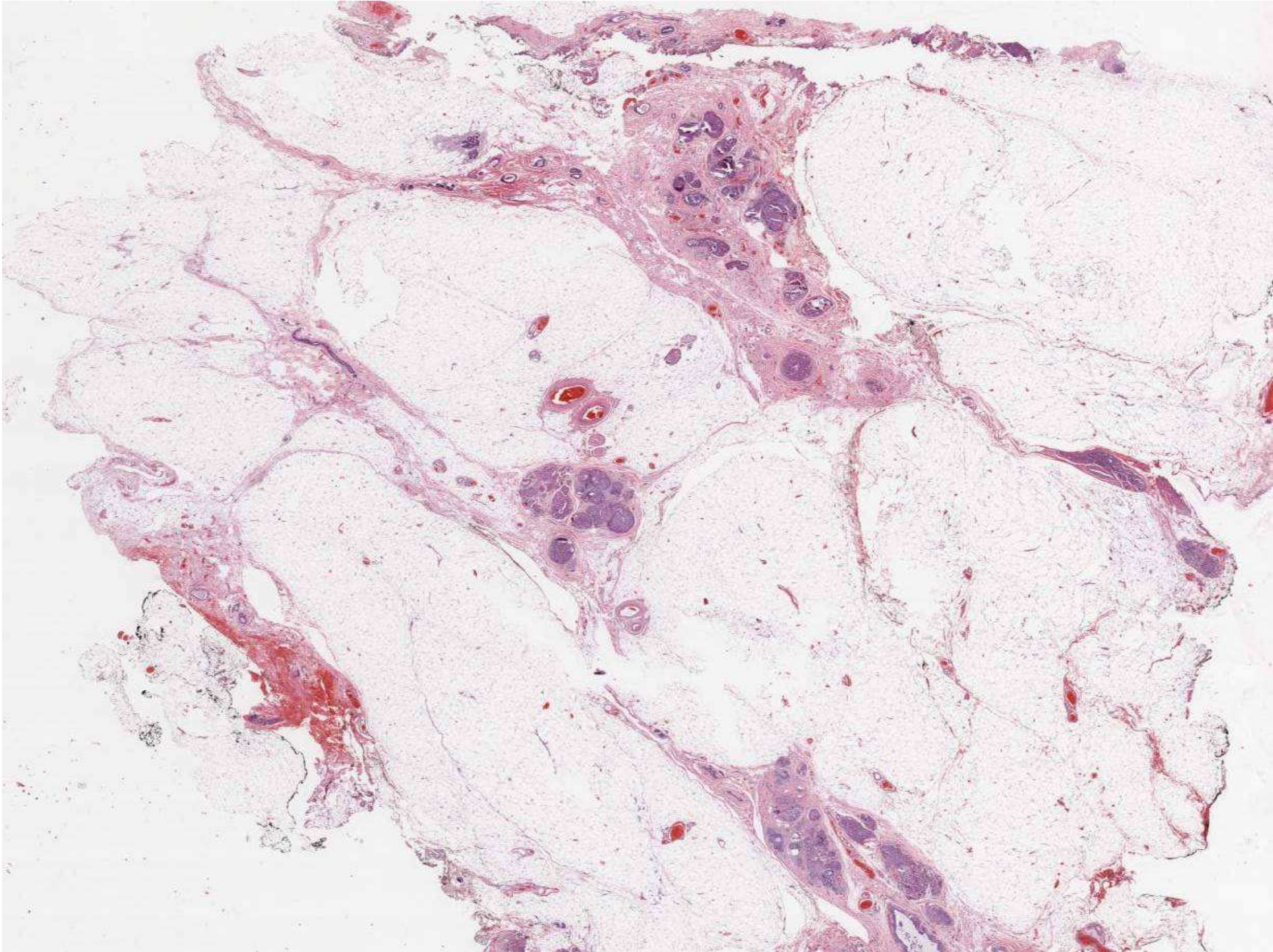


ECAD

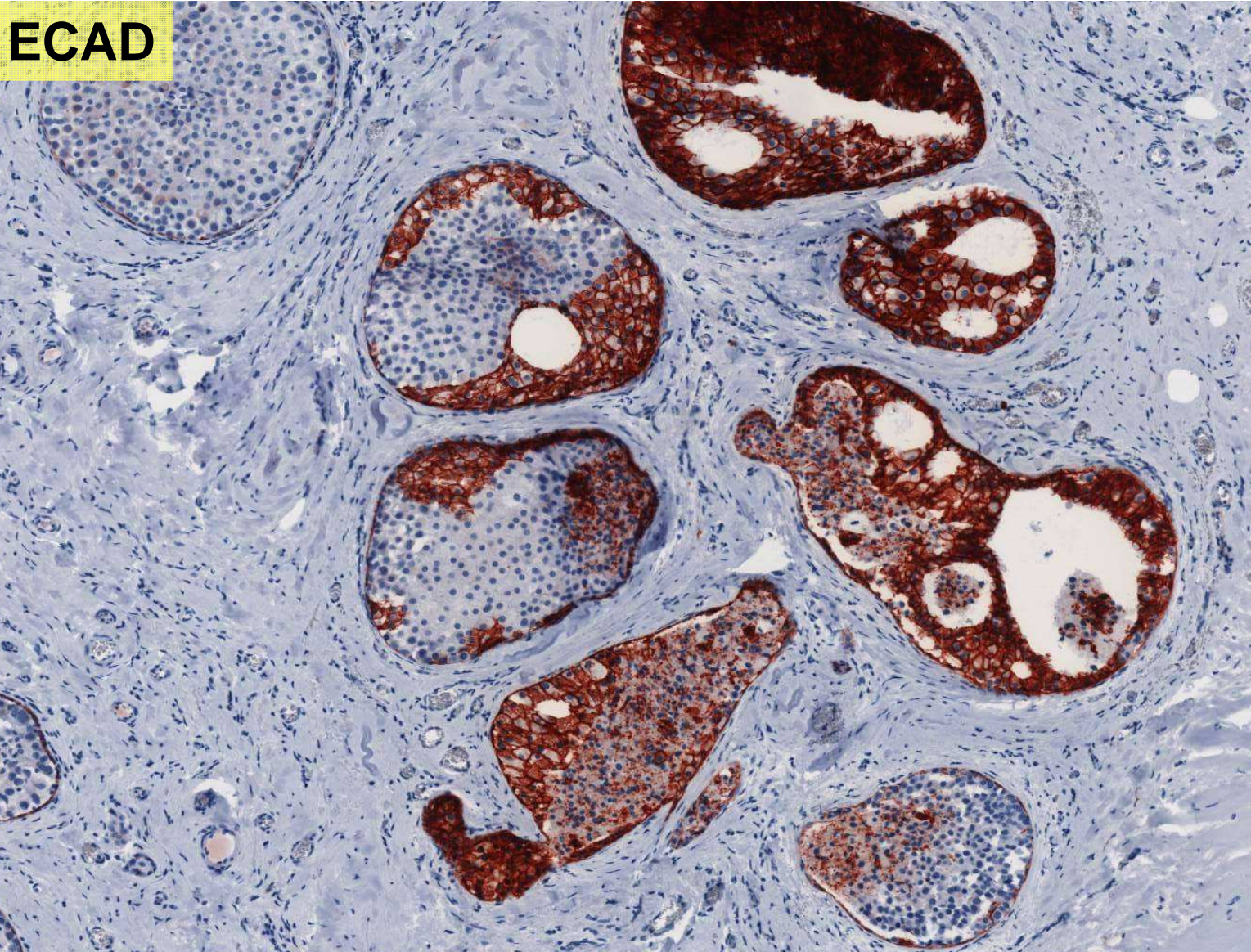


Lobular intraepithelial neoplasia, high grade (LIN 3), reporting category: B5a

- Diagnostic criteria
 - distended, and often confluent acini
 - extension into the ductal system
 - comedo-type necrosis may be present
 - loss of E-Catherin expression
- Case presented at diagnostic slide seminar
 - B3: 4 votes
 - B5a: 26 votes (72%)
 - B5a: 6 votes



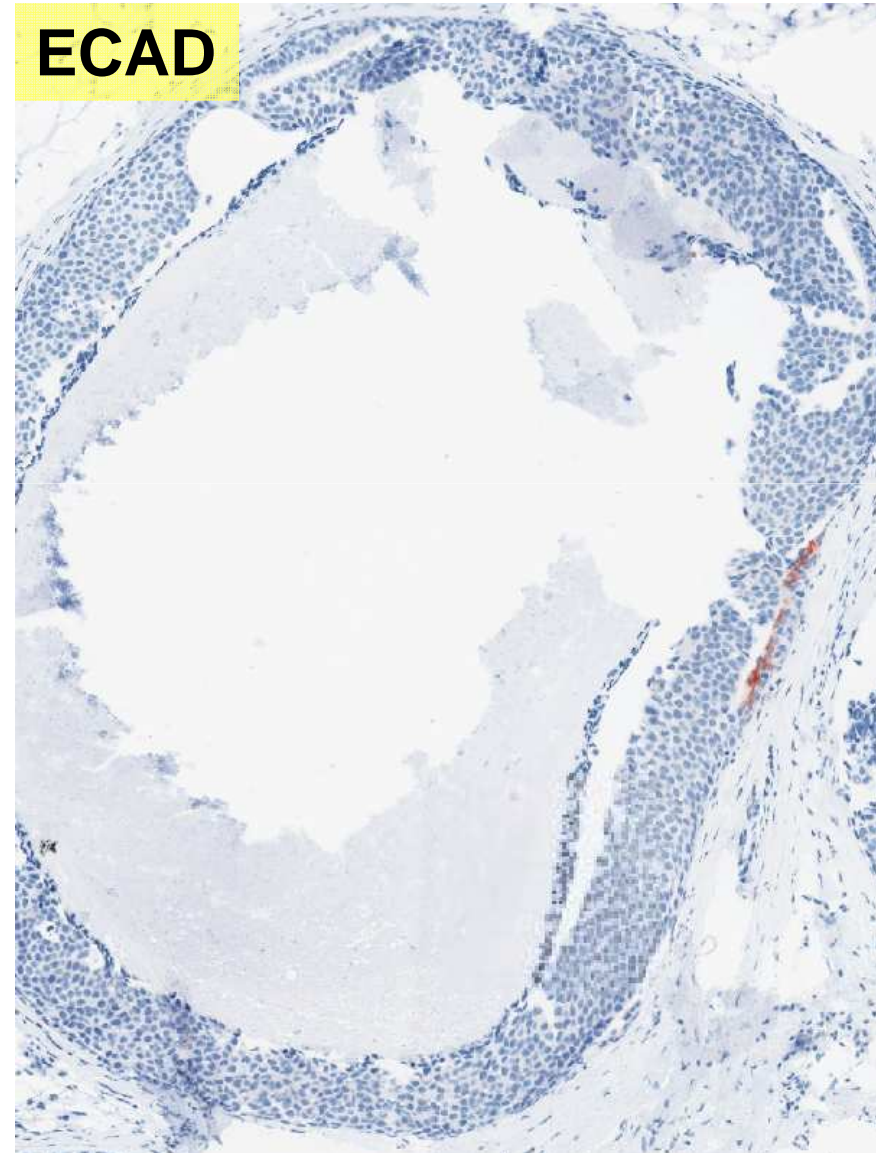
Intraductal neoplasia of mixed ductal and lobular phenotype



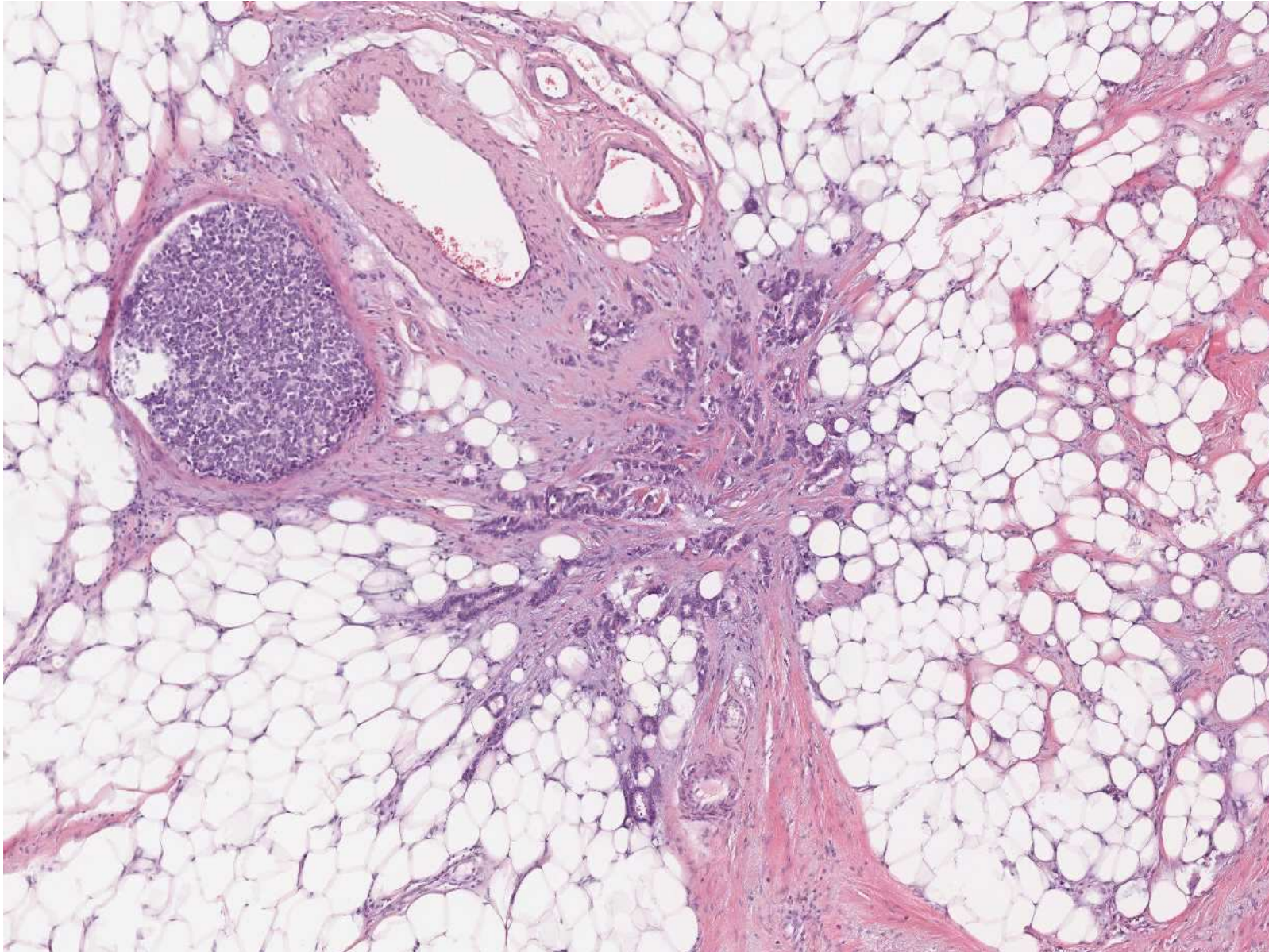
Intraductal neoplasia of mixed ductal and lobular phenotype



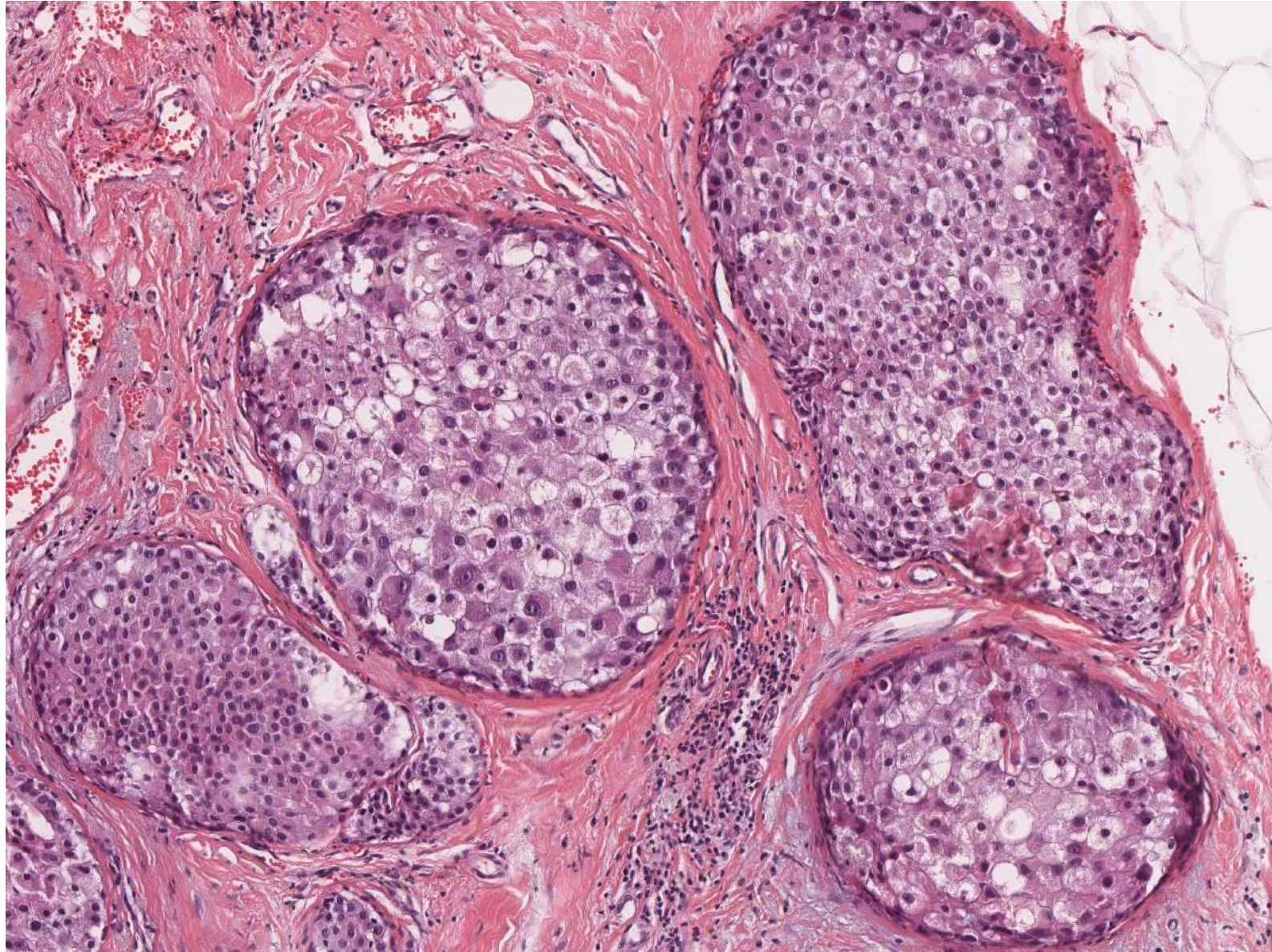
Lobular intraepithelial neoplasia, high grade with comedo-type necrosis (LIN 3) – B5a



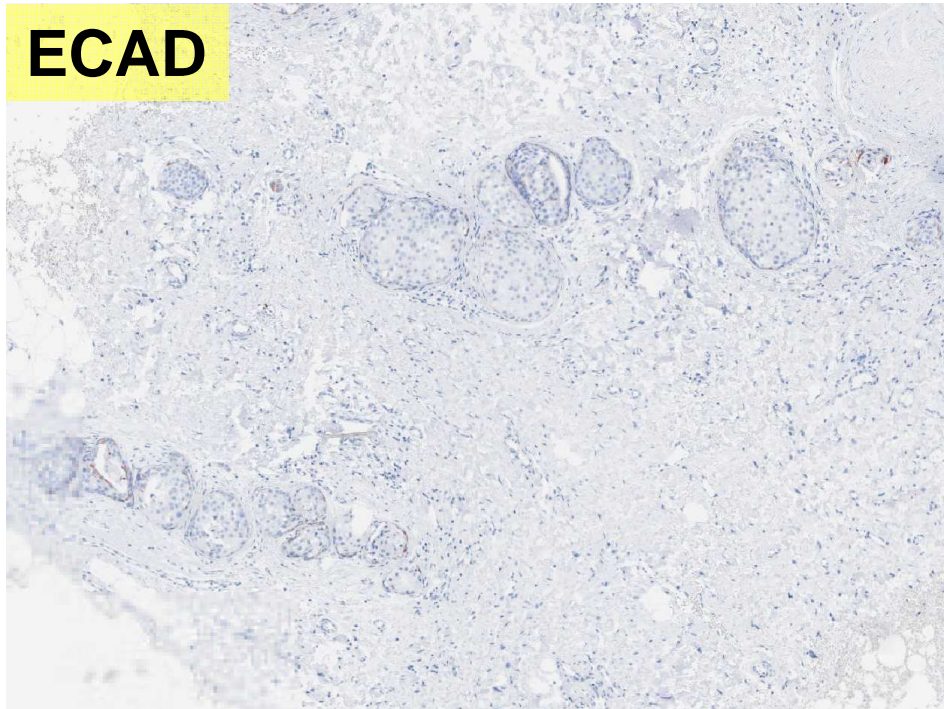
**Lobular intraepithelial neoplasia, high grade, with
invasive lobular carcinoma in resection specimen**



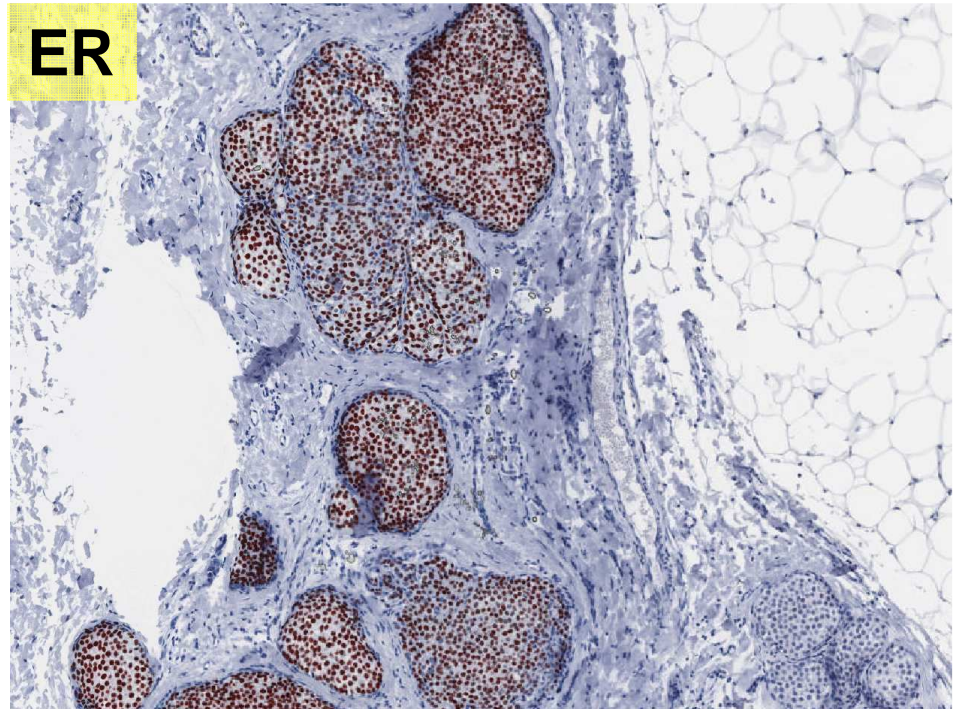
LN, high grade, pleomorphic-apocrine type (LIN 3)



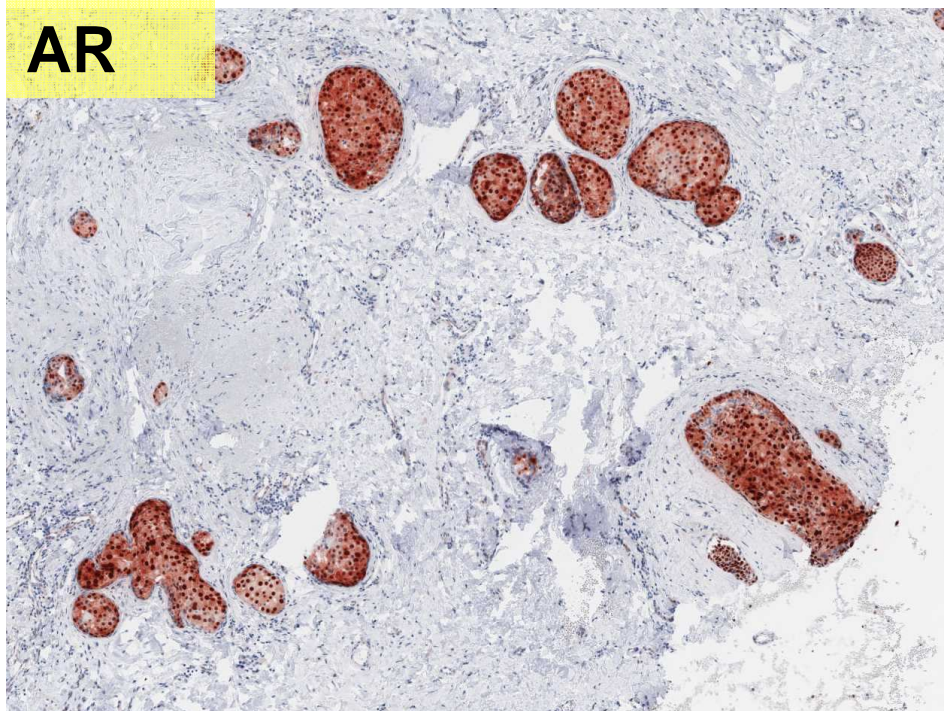
ECAD



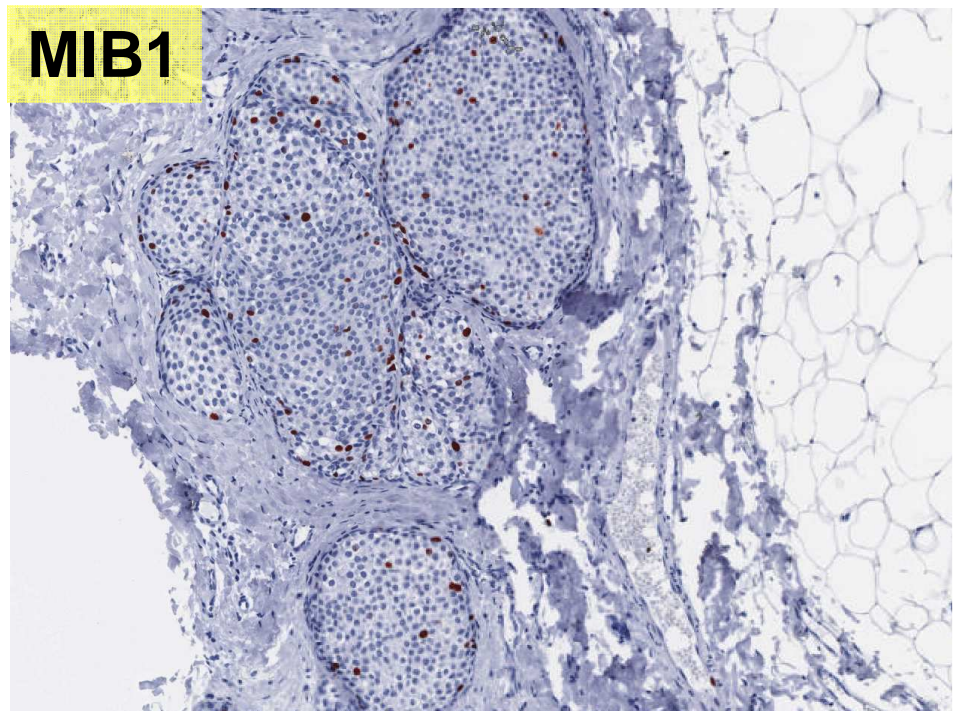
ER



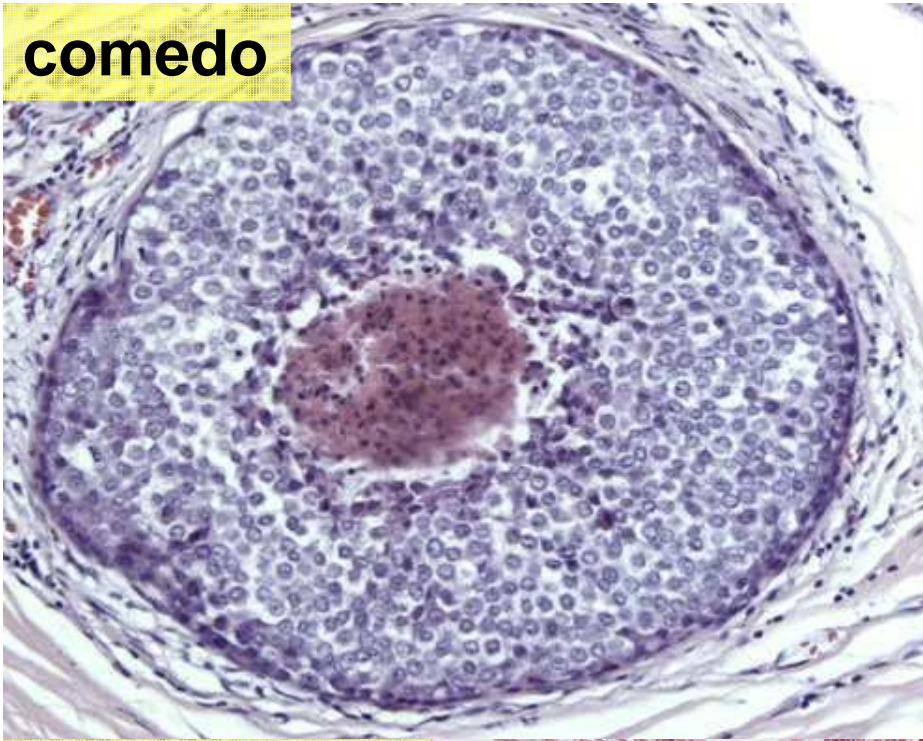
AR



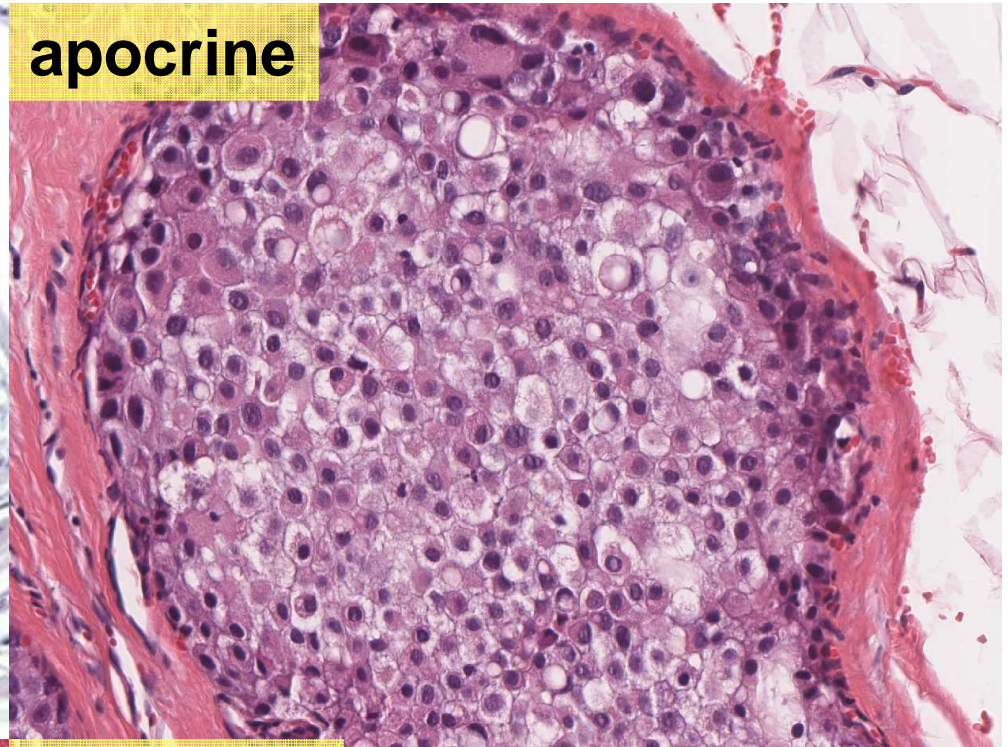
MIB1



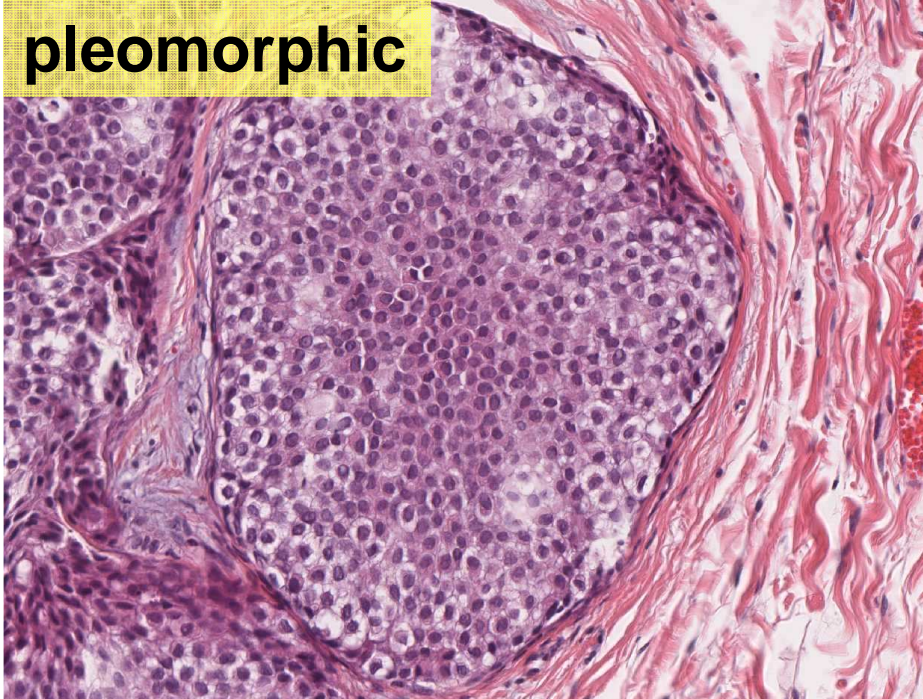
comedo



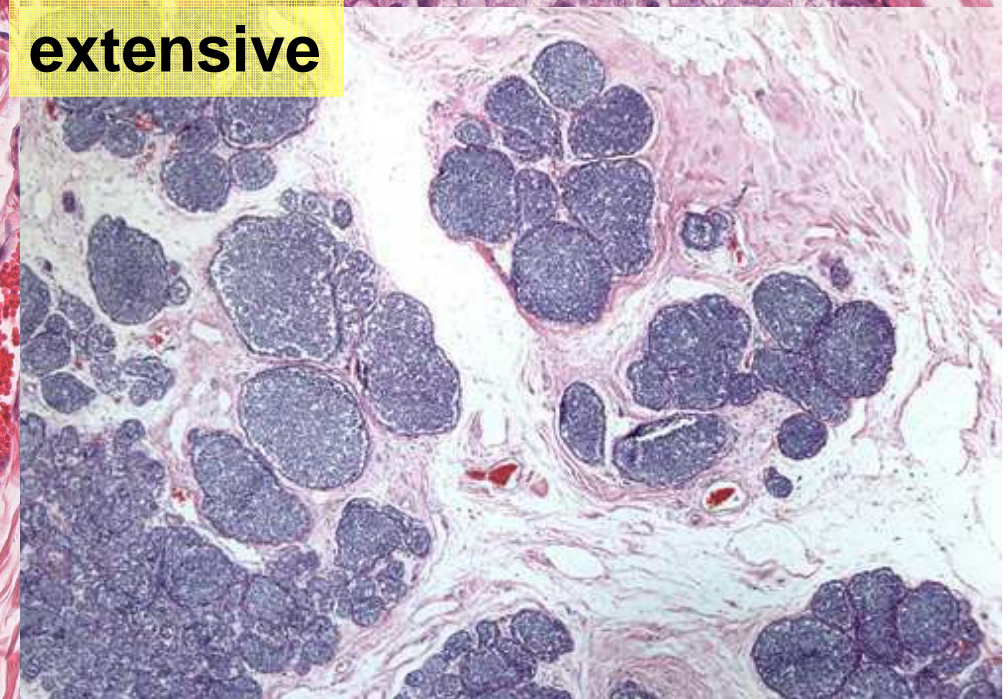
apocrine



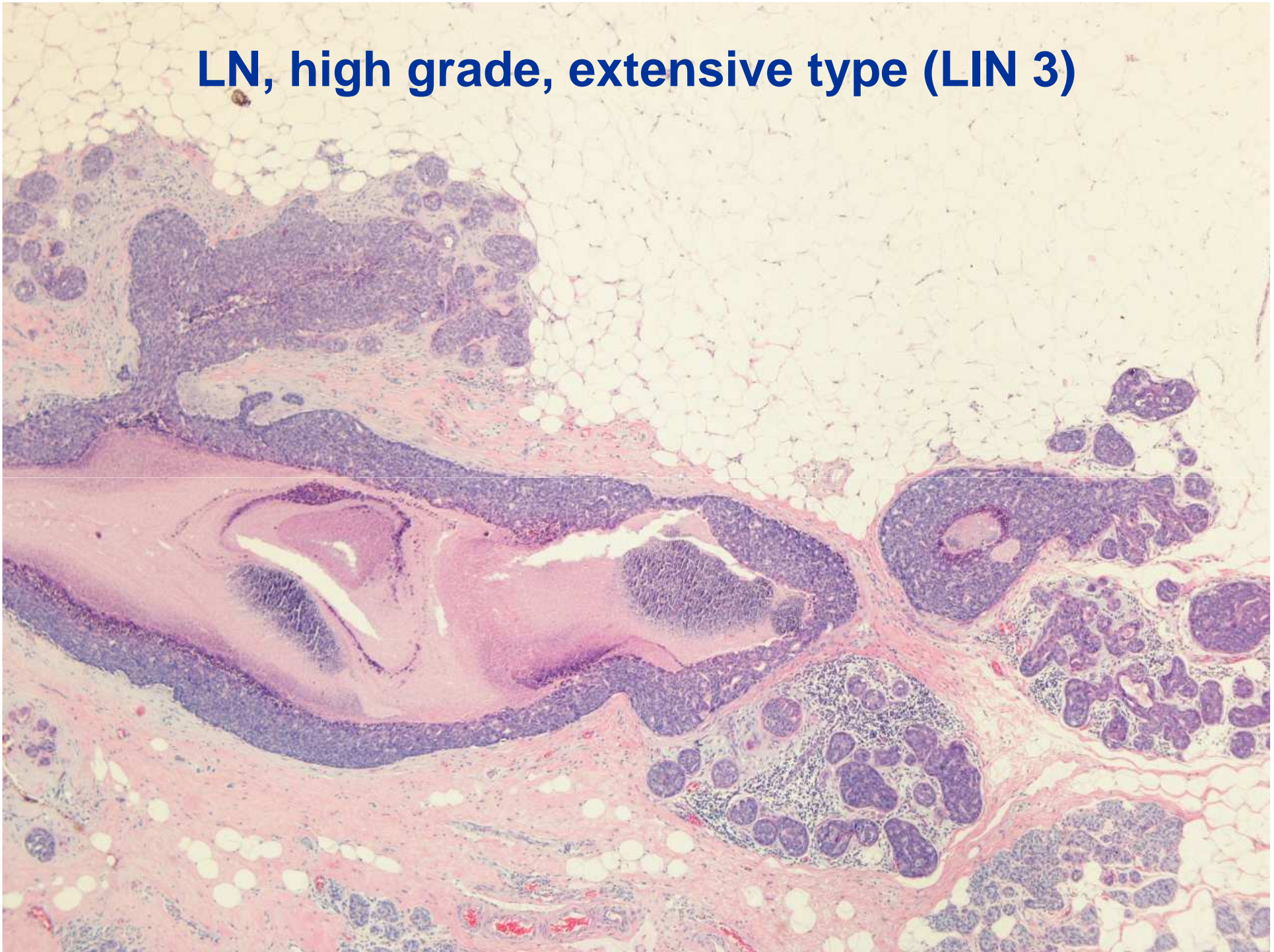
pleomorphic



extensive



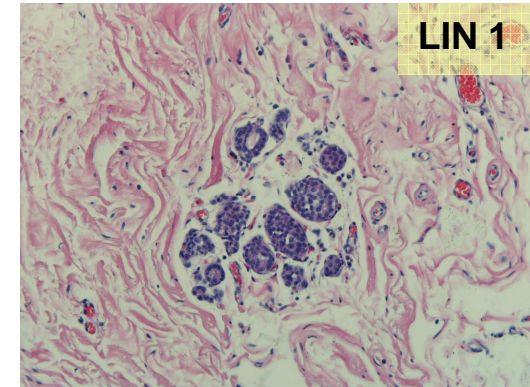
LN, high grade, extensive type (LIN 3)



LIN 1-3 and associated invasive carcinomas

(Brattheuer & Tavassoli 2002)

- LIN 1
 - DCIS/IDC: 16,2%
 - ILC: 1,5%
- LIN 2
 - DCIS/IDC: 24,1%
 - ILC: 8,2%
- LIN 3
 - DCIS/IDC: 31,5%
 - ILC: 19,6%



Heterogeneity of lobular neoplasia

- Clinical and radiologic findings
 - LCIS may be manifest as symptomatic, non-incidental finding
 - LCIS may be tumor forming
 - LCIS can have comedo-type necrosis
- Tumor biology
 - LCIS can have properties of a precursor lesion
- Molecular biology
 - LCIS can have similar alterations like ILC

Issues with the assessment of atypia in minimally invasive breast biopsy

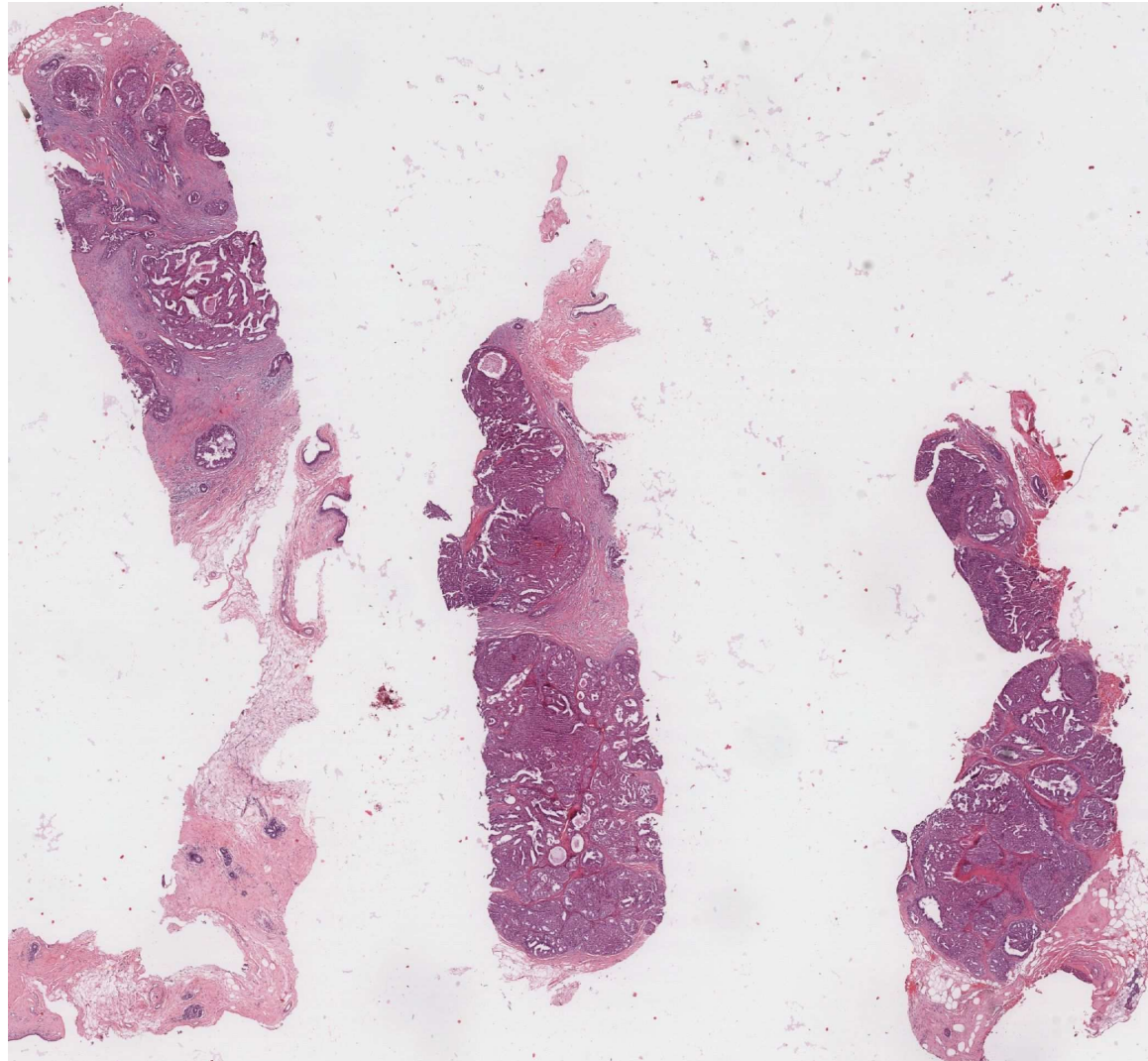
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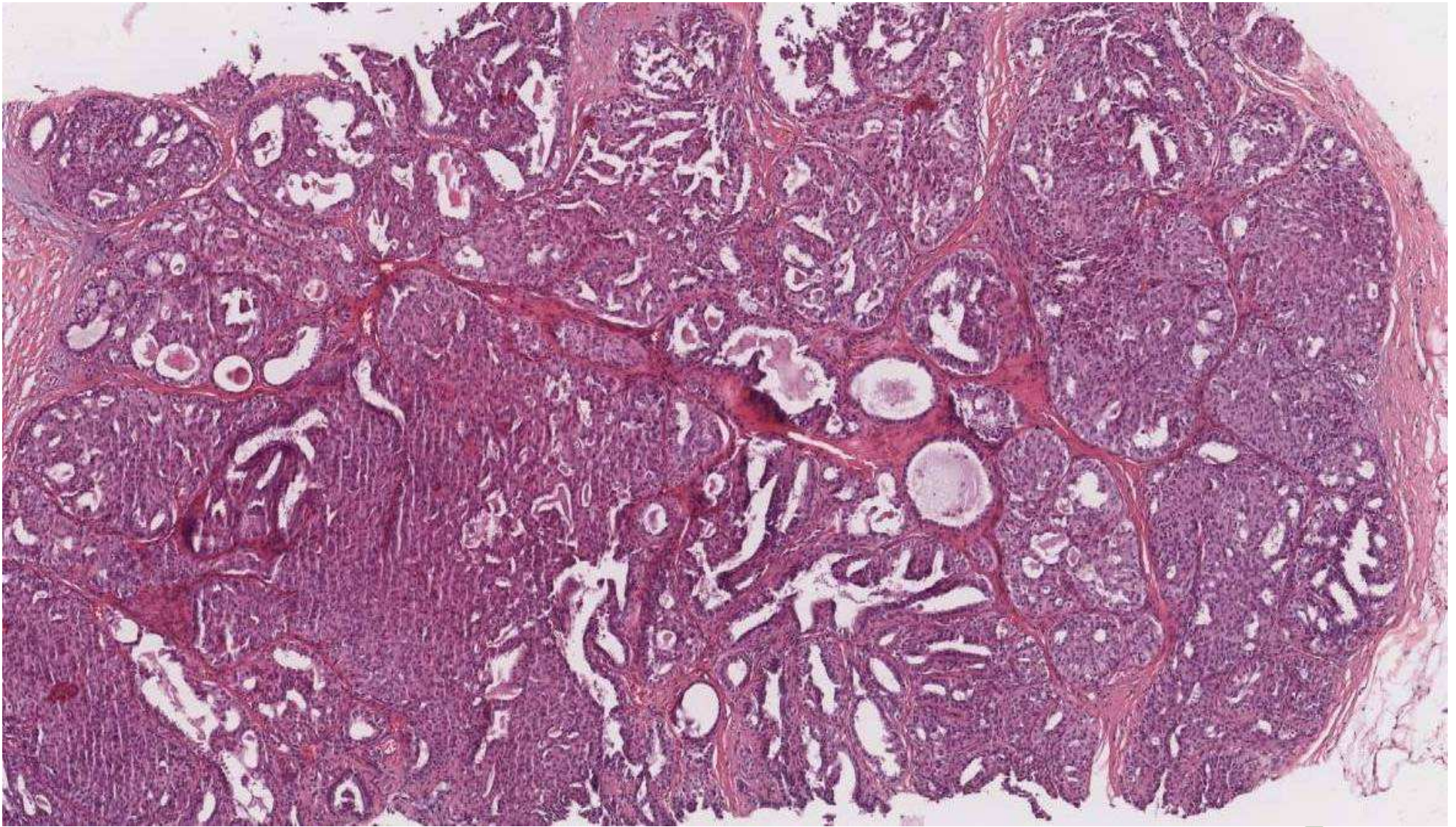
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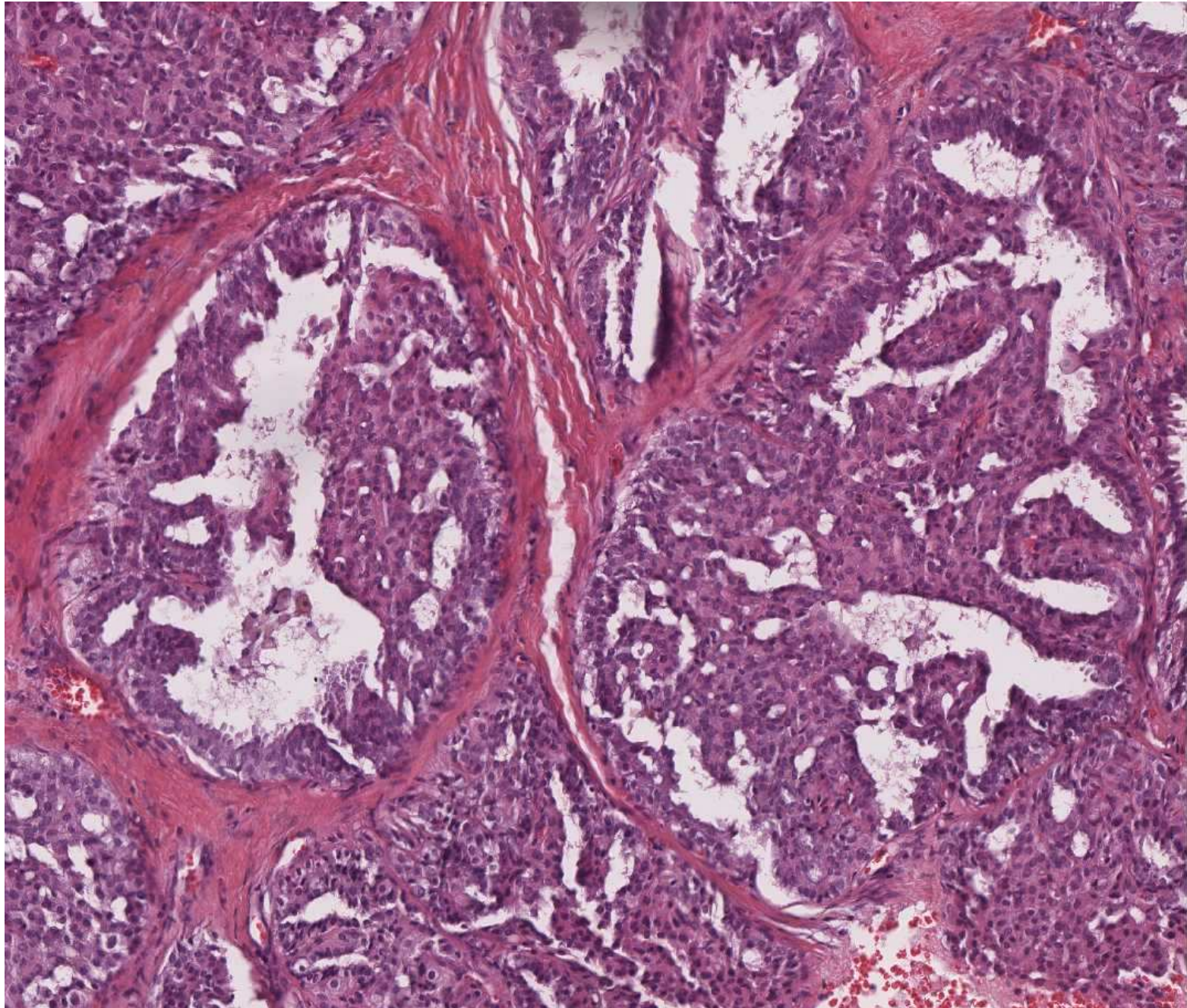
Avoidance of overdiagnosis

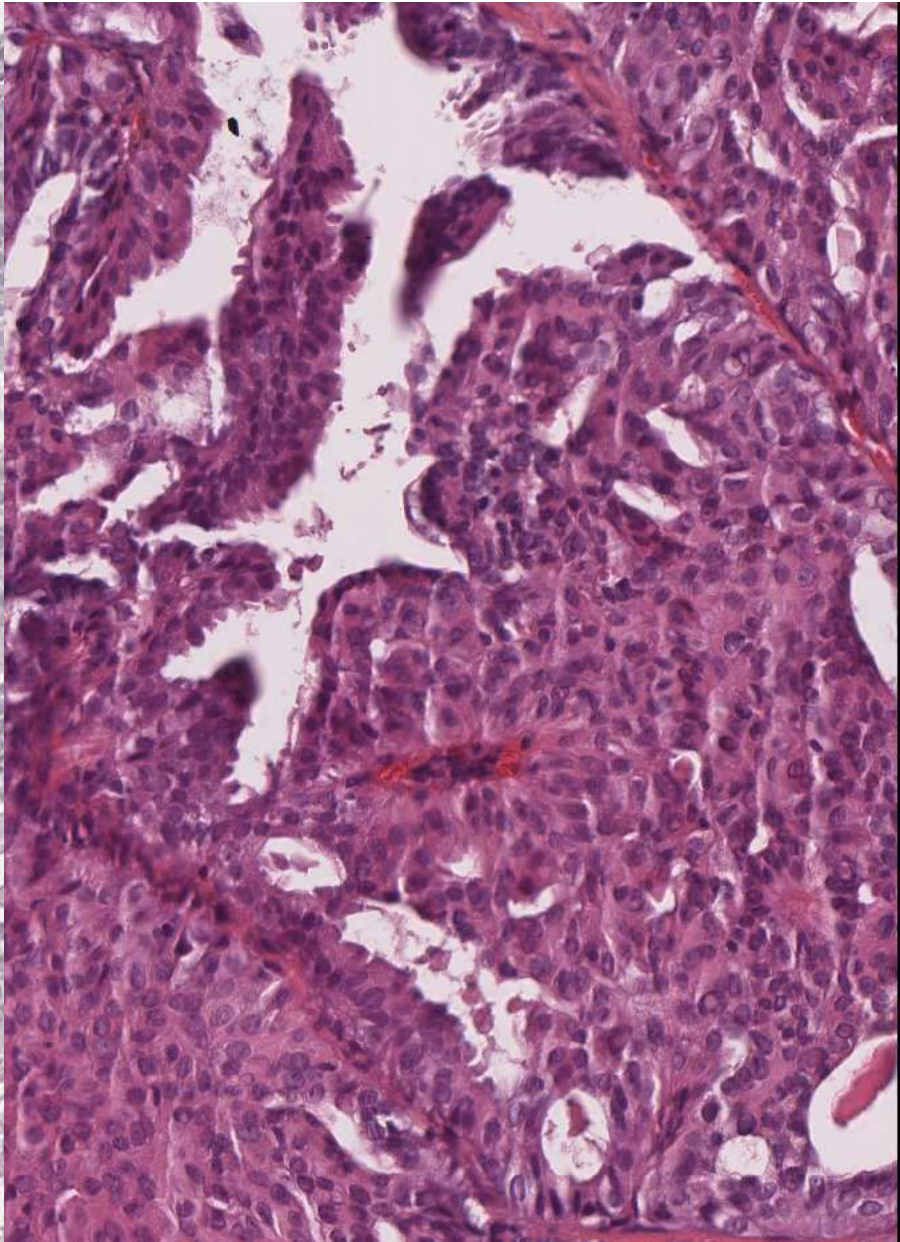
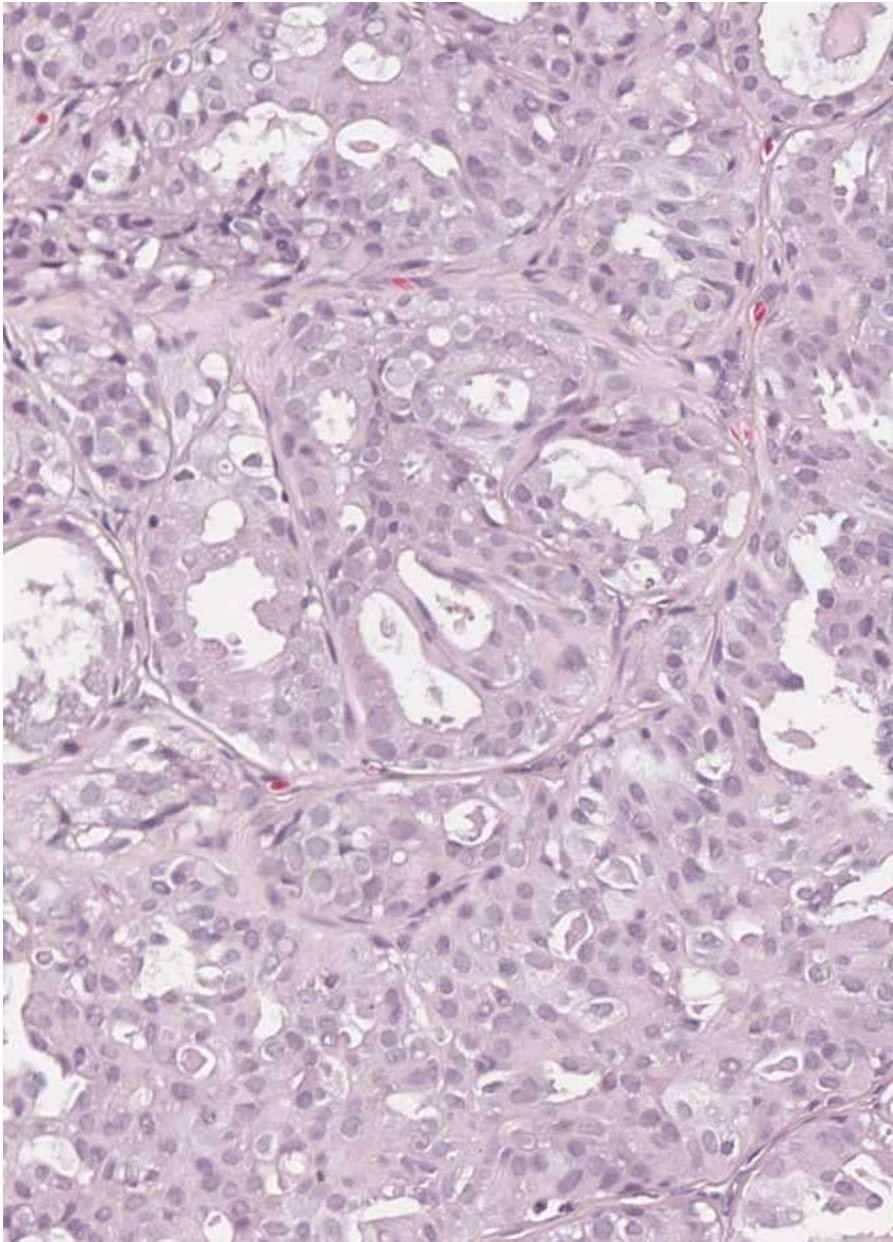
- Usual ductal hyperplasia
- Adenosis and sclerosing lesions
- Papilloma

**74 yo Patient. Unknown lesions bilaterally.
Ultrasound guided biopsy**







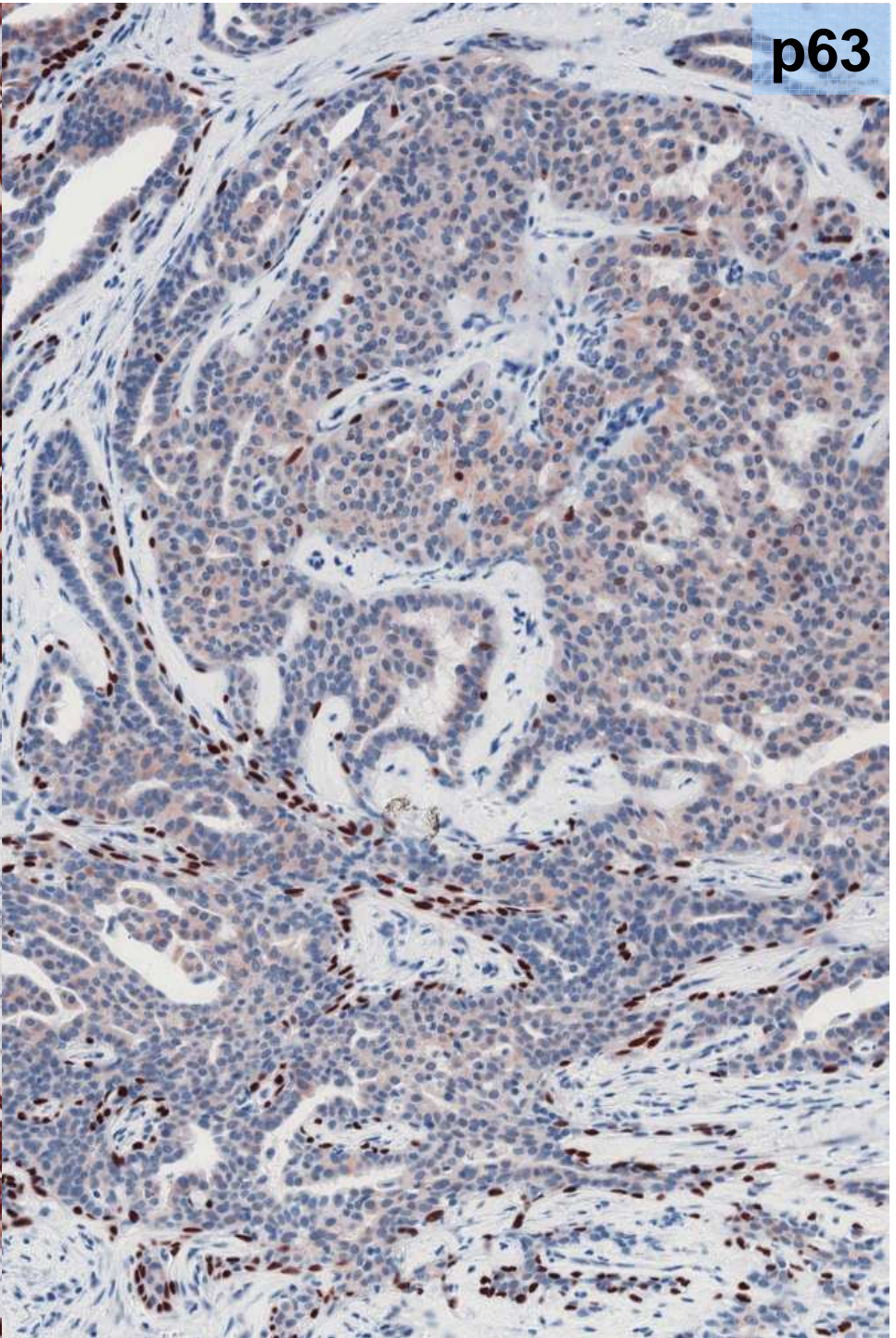
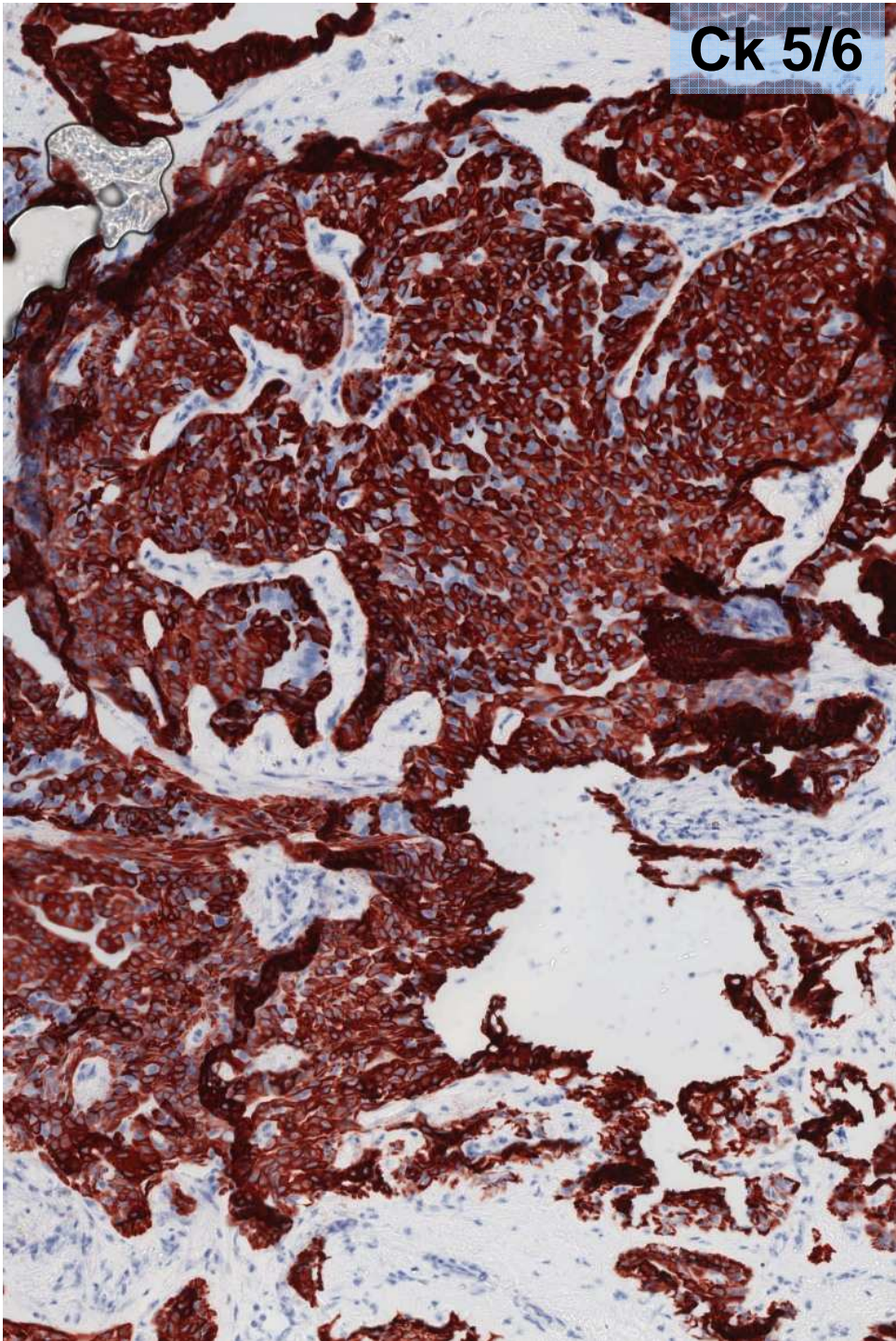


Usual ductal hyperplasia (UDH) – B2

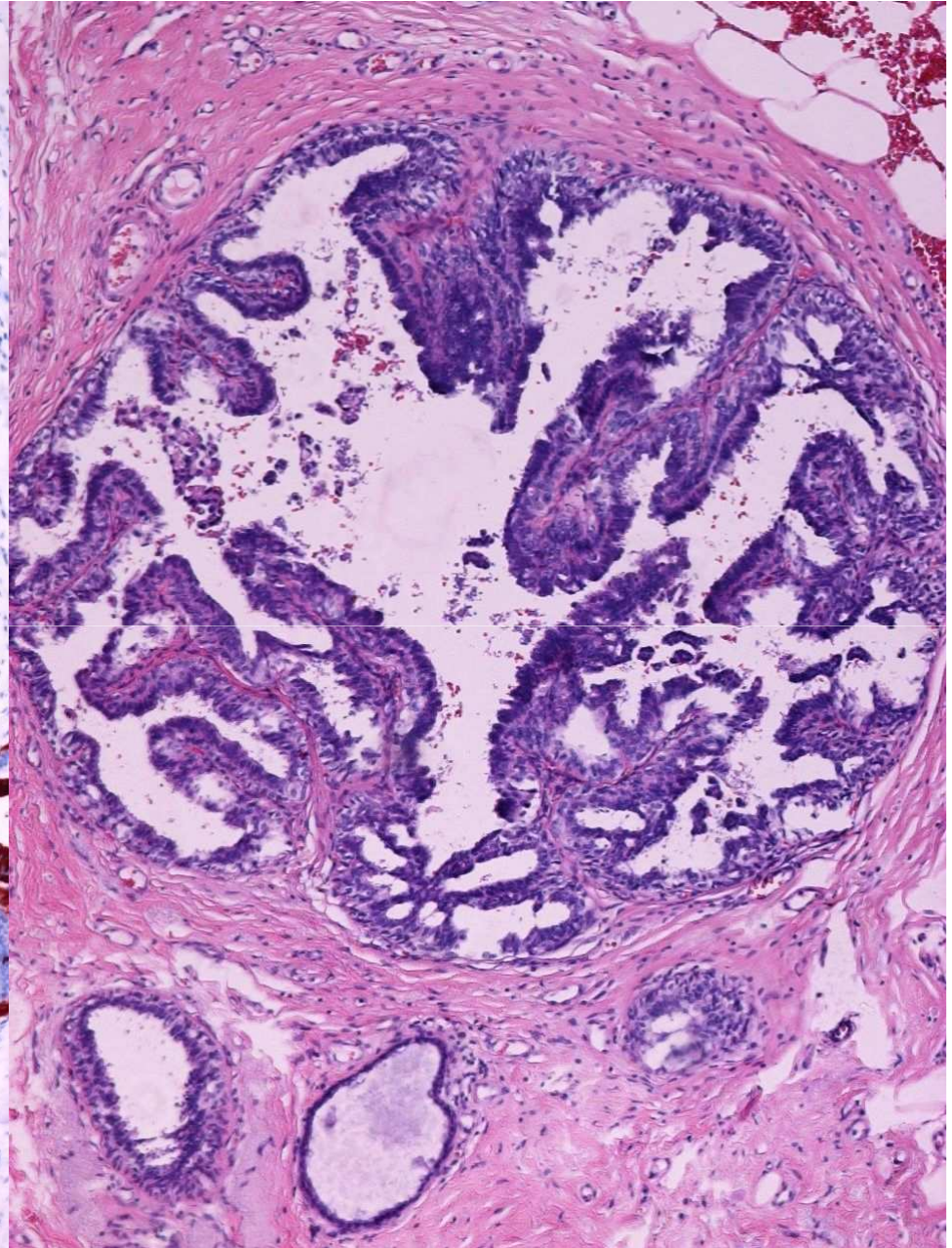
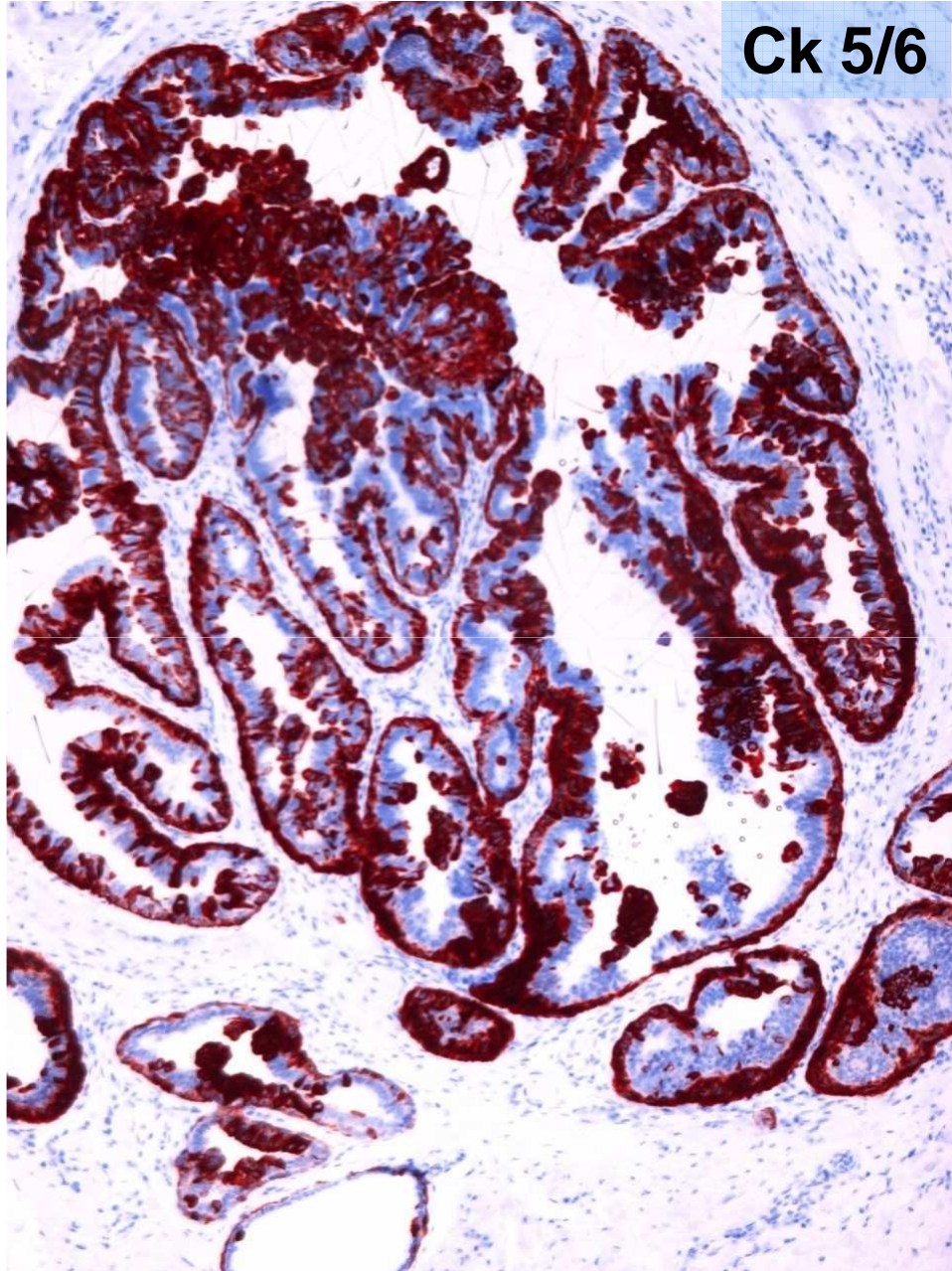
- Diagnostic criteria
 - Heterogeneous cellularity
 - Floating pattern, irregular, peripherally oriented lumina
 - Ck5/6 positivity
- Case presented at pathology slide seminar
 - B2: 9 votes (27%)
 - B3: 18 votes
 - B5a: 6 votes

Ck 5/6

p63

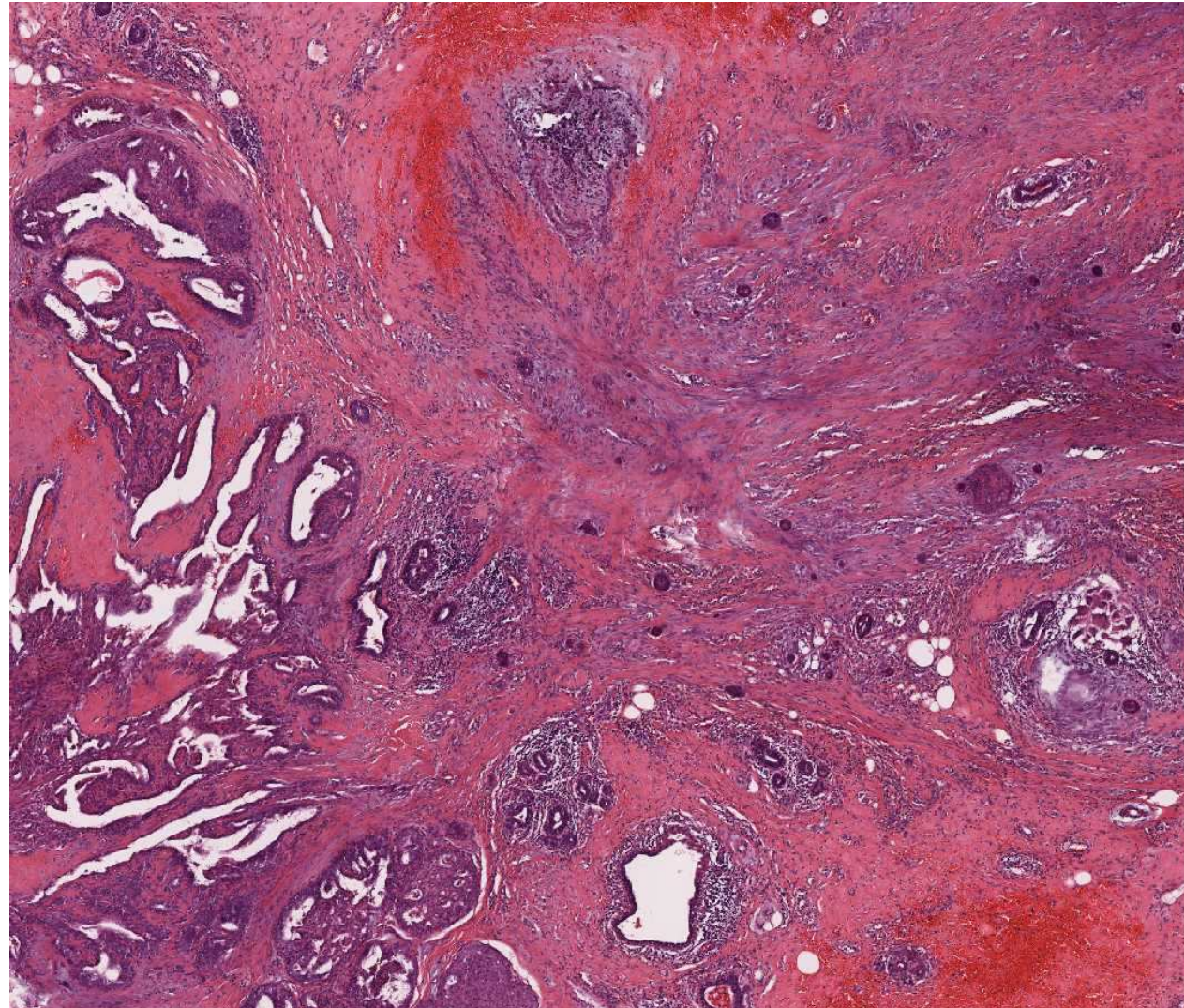


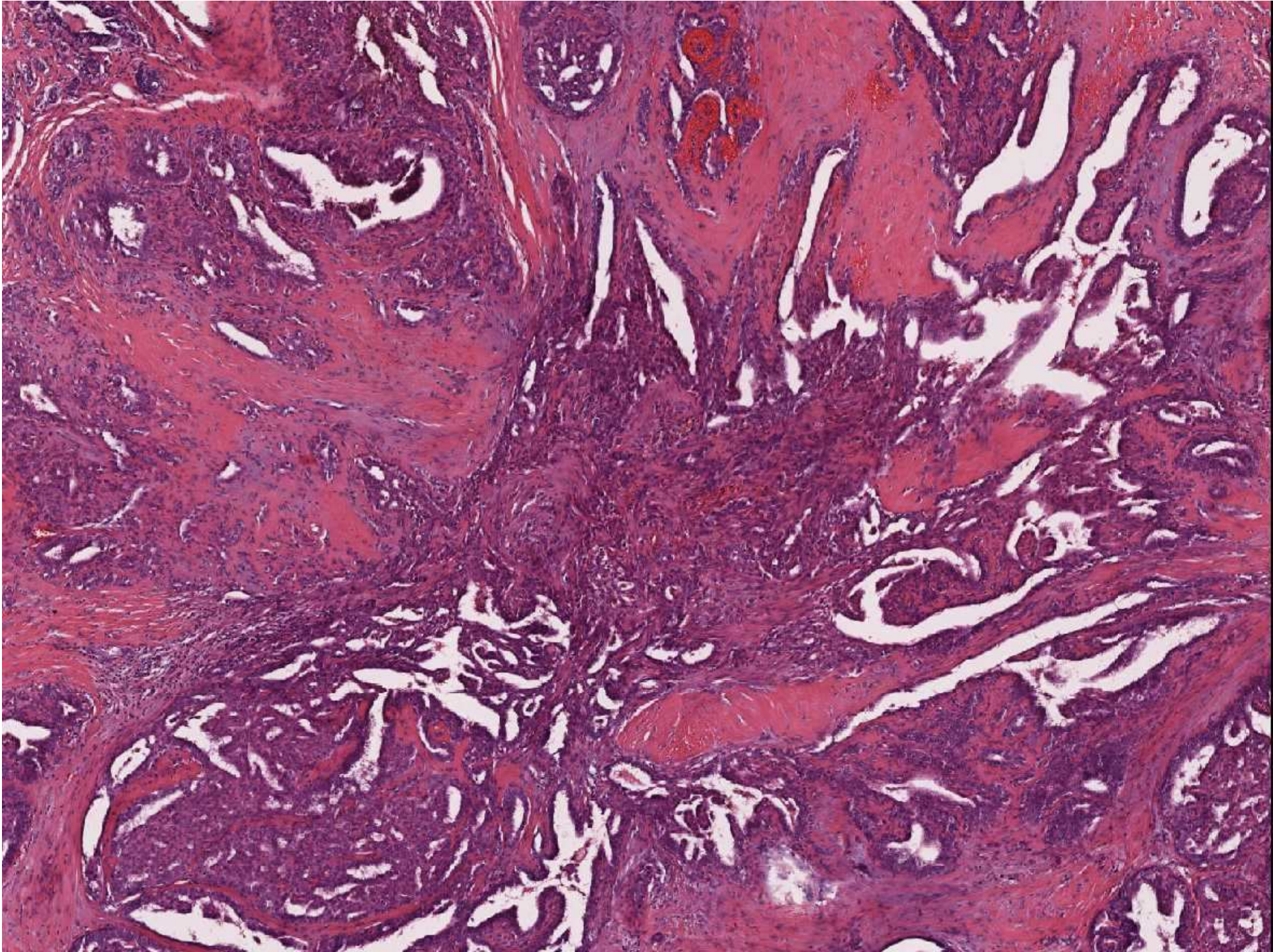
Ck 5/6

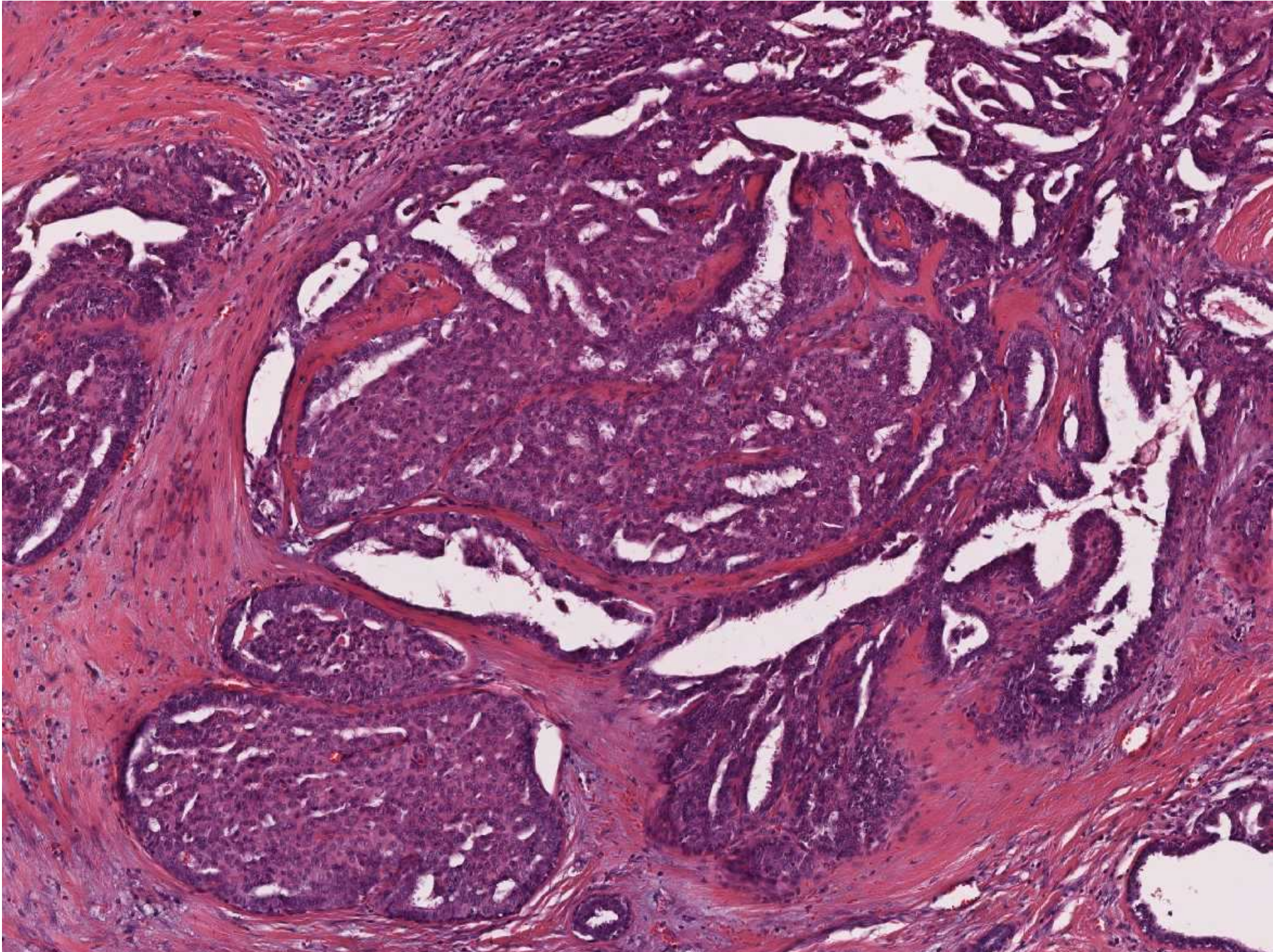


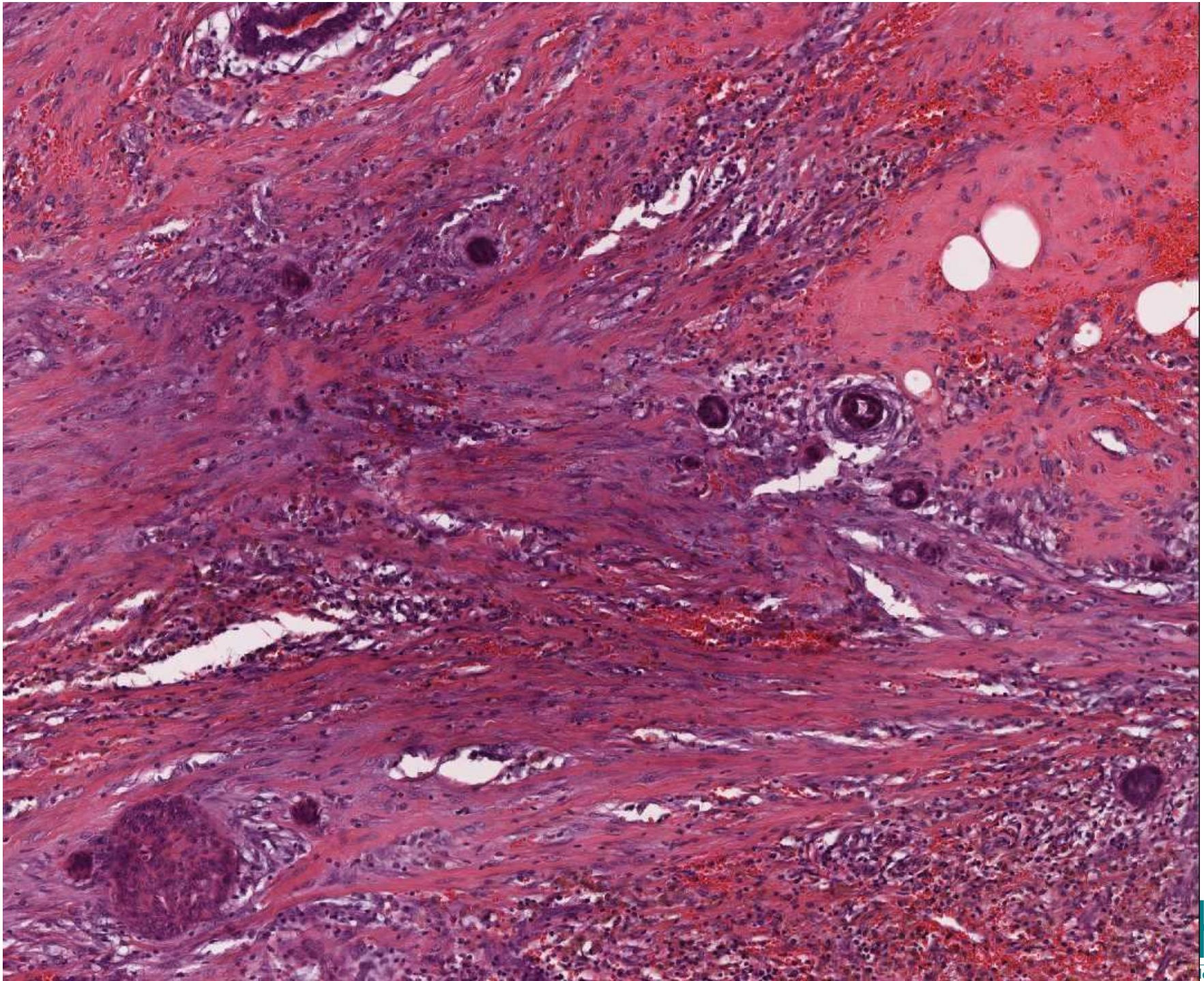
Resection specimen

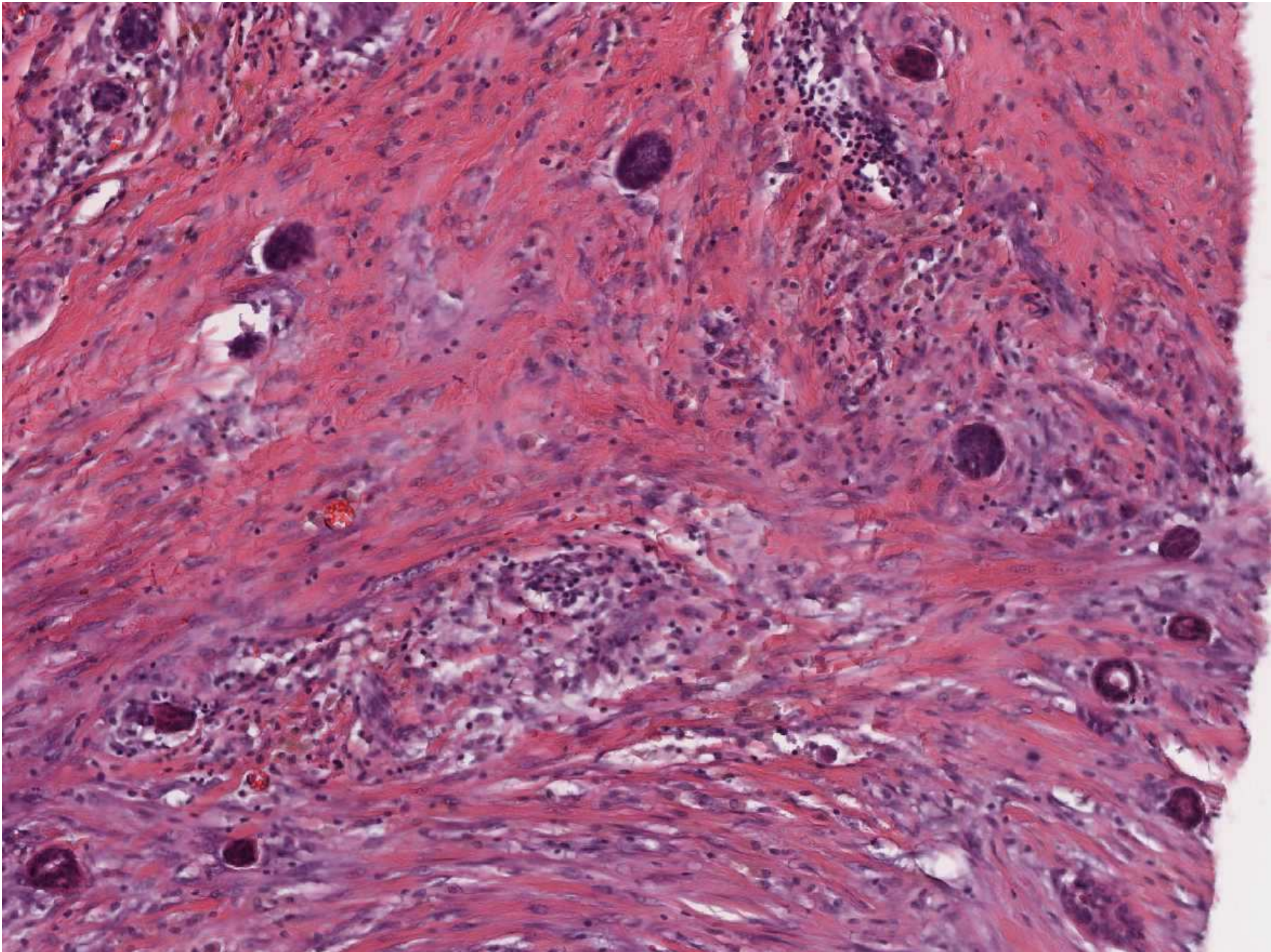
Hyperplastic lesion, sclerosiis, displaced epithelial elements











Issues with the assessment of atypia in minimally invasive breast biopsy

Individual risk assessment

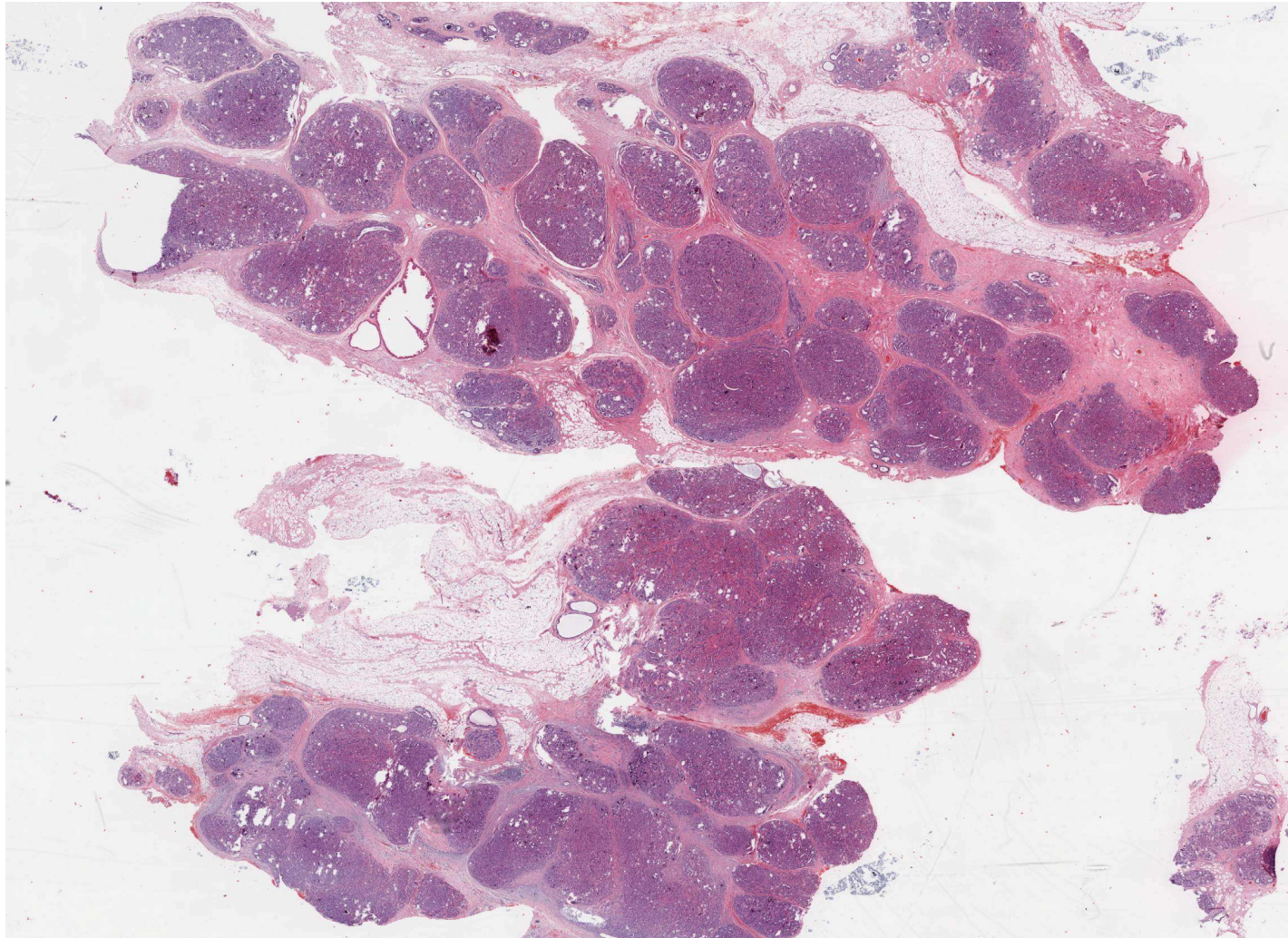
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Avoidance of overdiagnosis

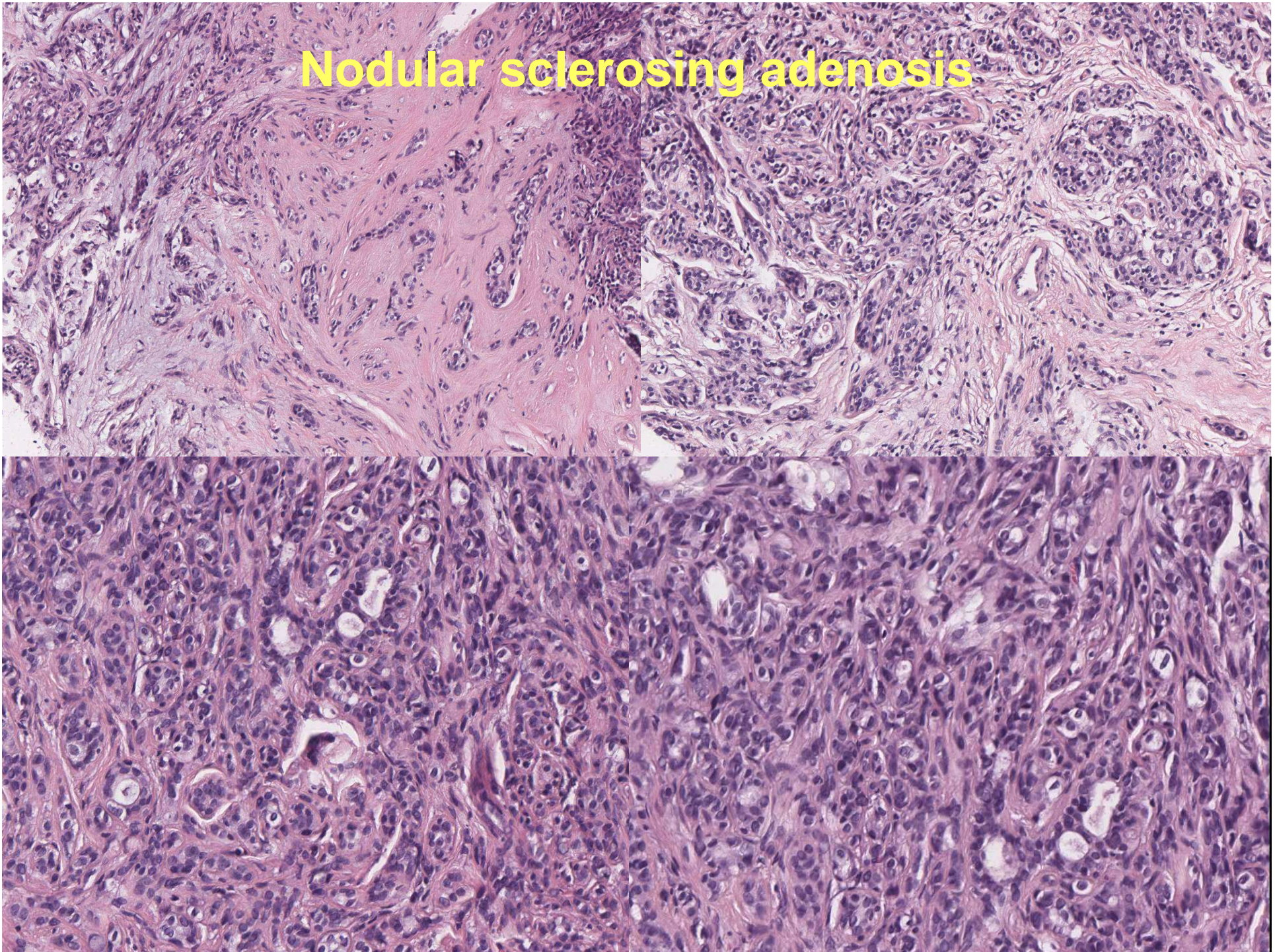
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- Papilloma

Nodular adenosis

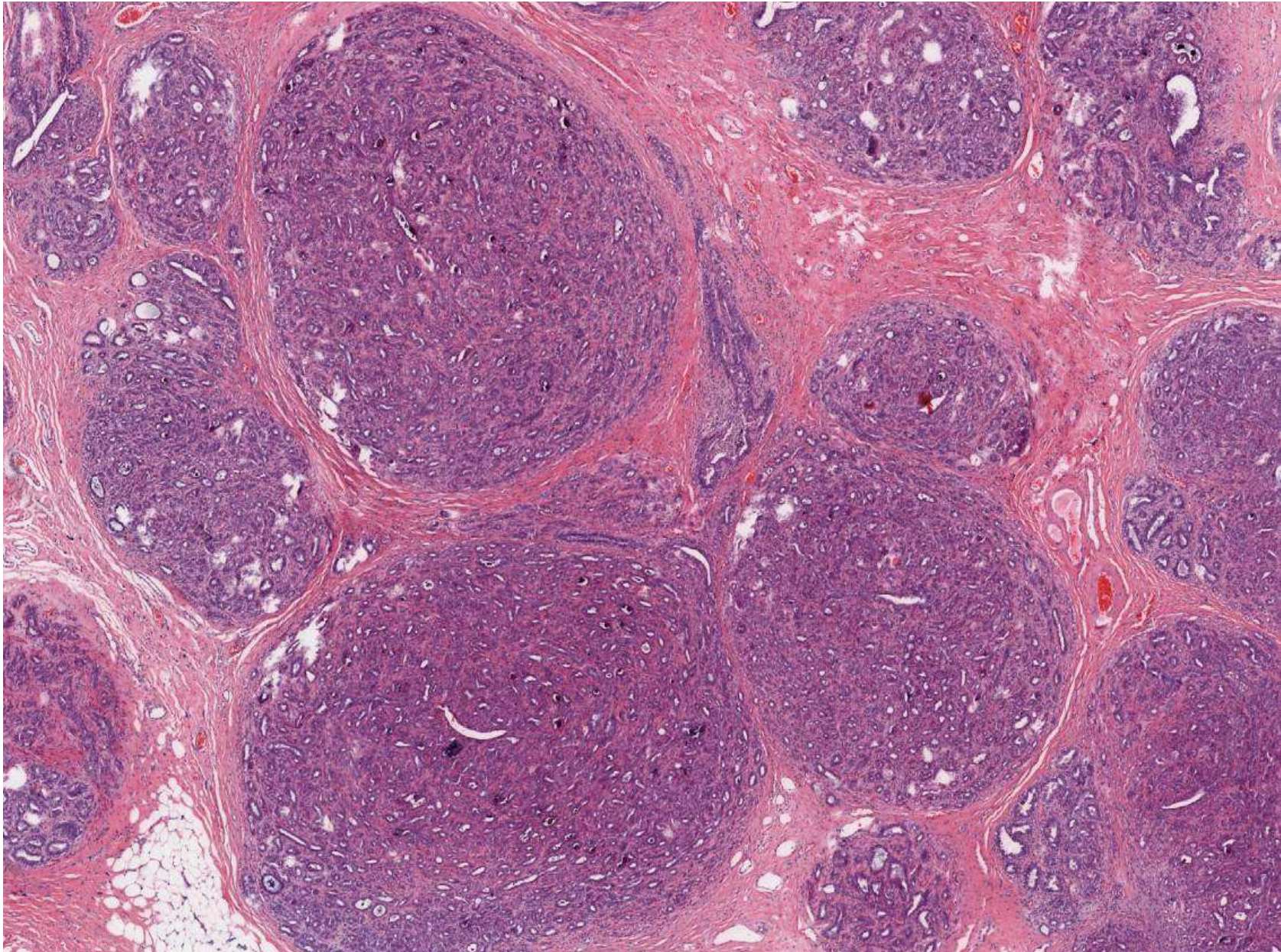
Reporting category: B2



Nodular sclerosing adenosis

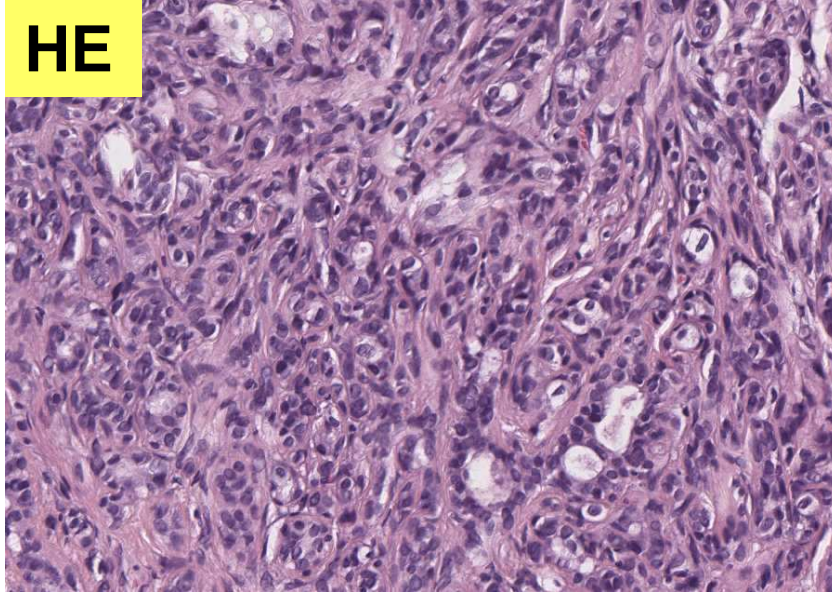


Nodular Adenosis

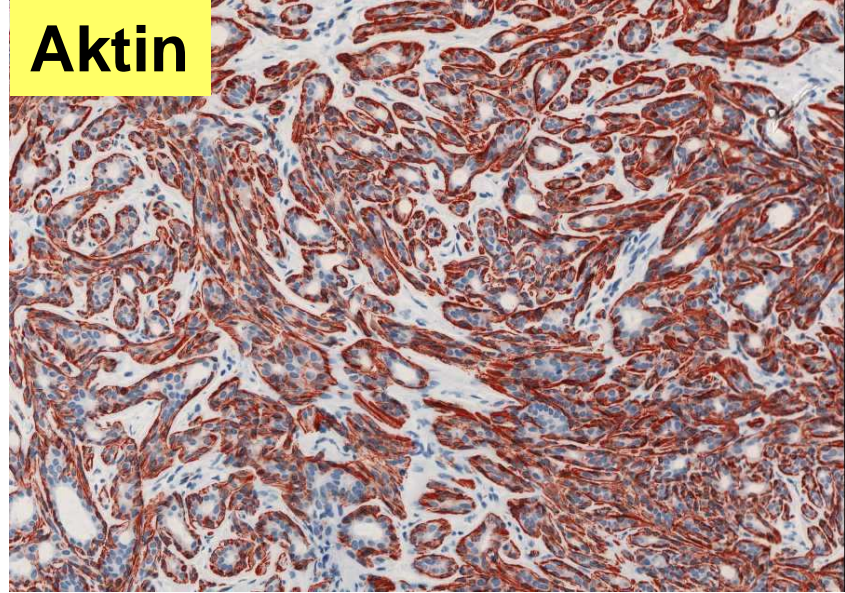


Nodular Adenosis

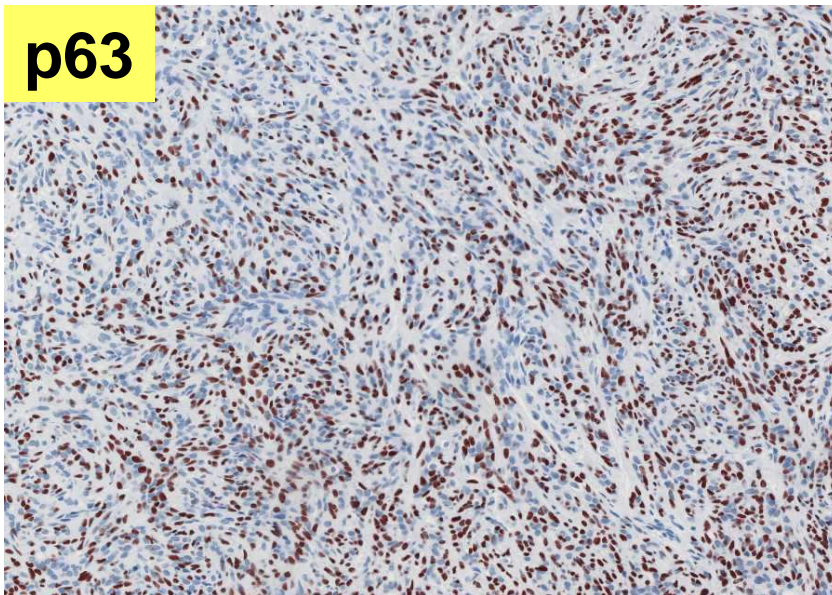
HE



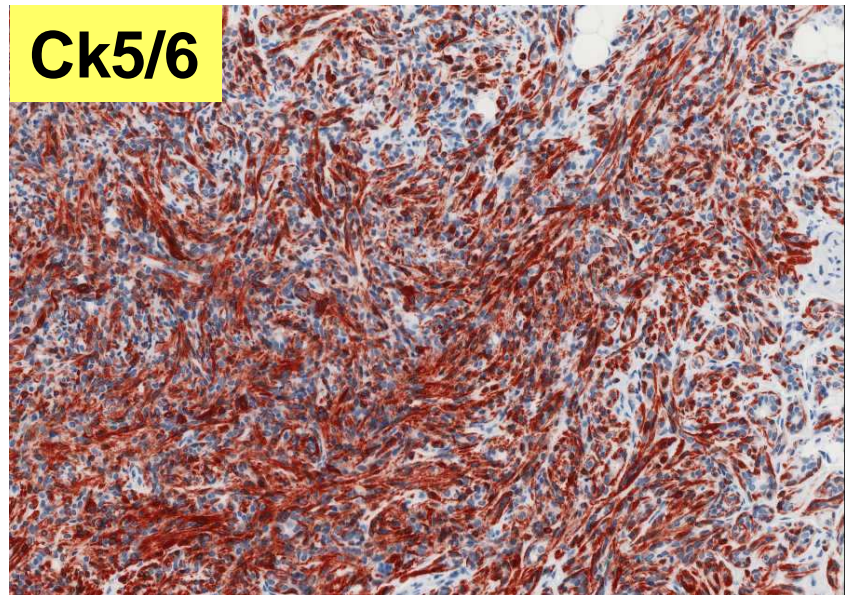
Aktin



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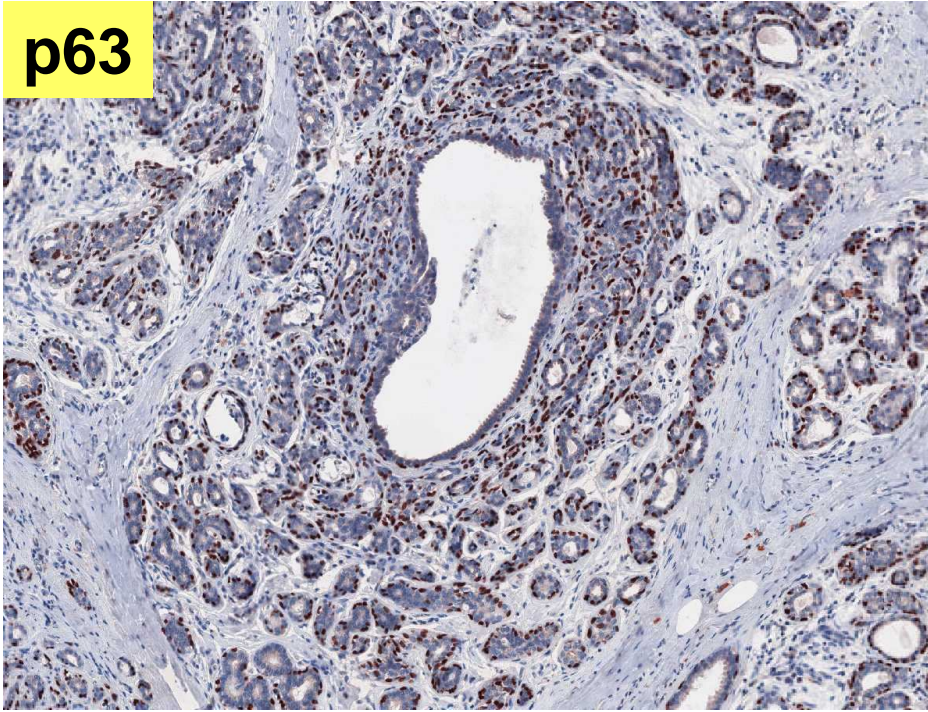
Ck5/6



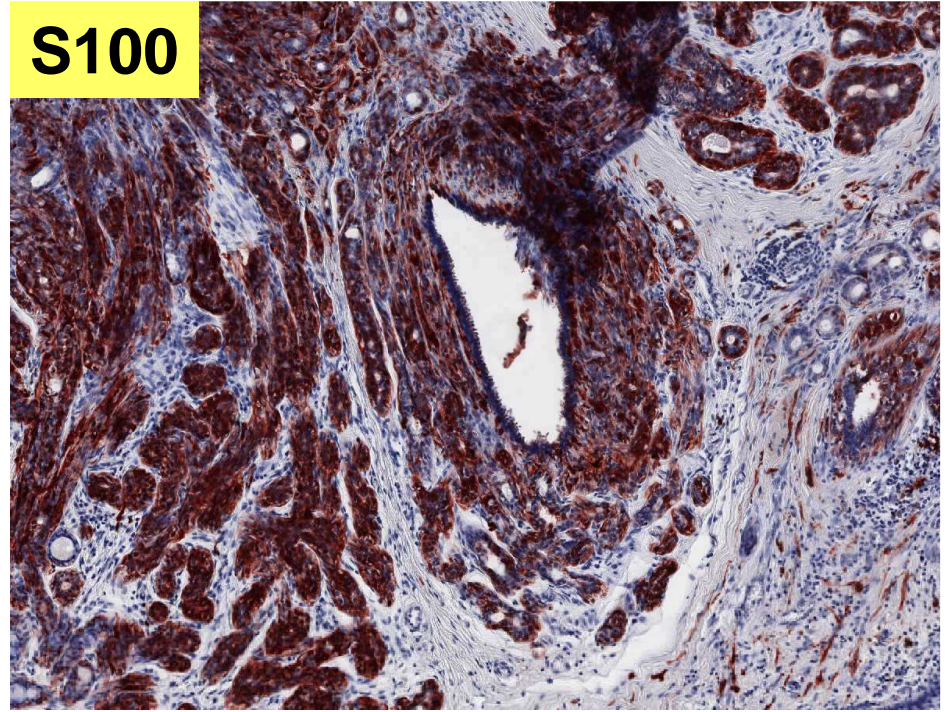
Nodular Adenosis – B2

- Diagnostic criteria
 - organoid, lobulocentric pattern
 - distorted architecture
 - myoglandular differentiation
- Case presented at pathology slide seminar
 - B2: 17 votes (50%)
 - B3: 8 votes
 - B4: 2 votes
 - B5a: 7 votes

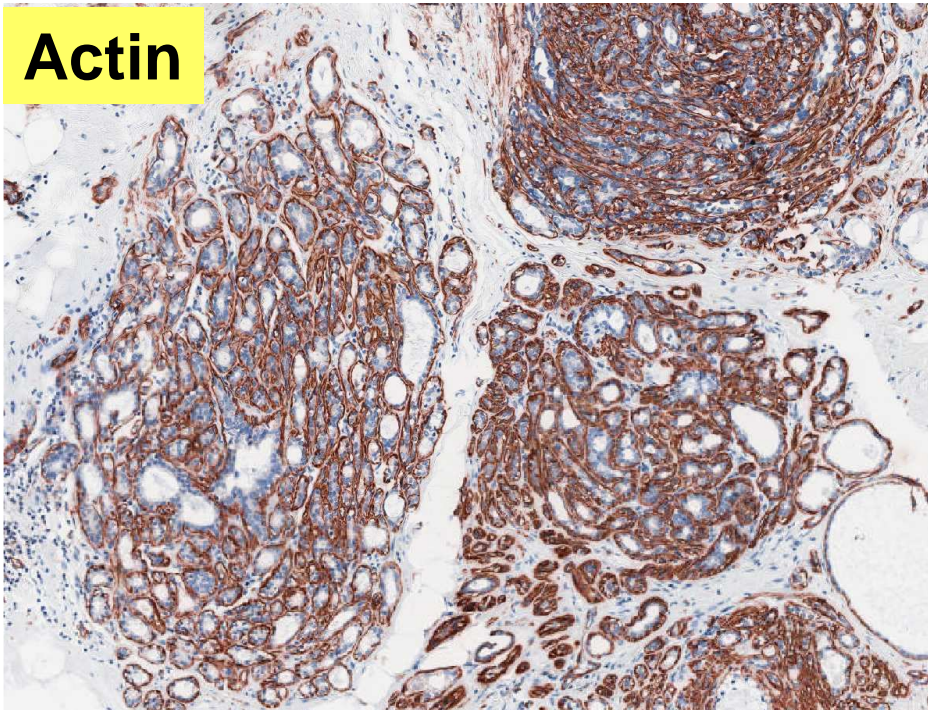
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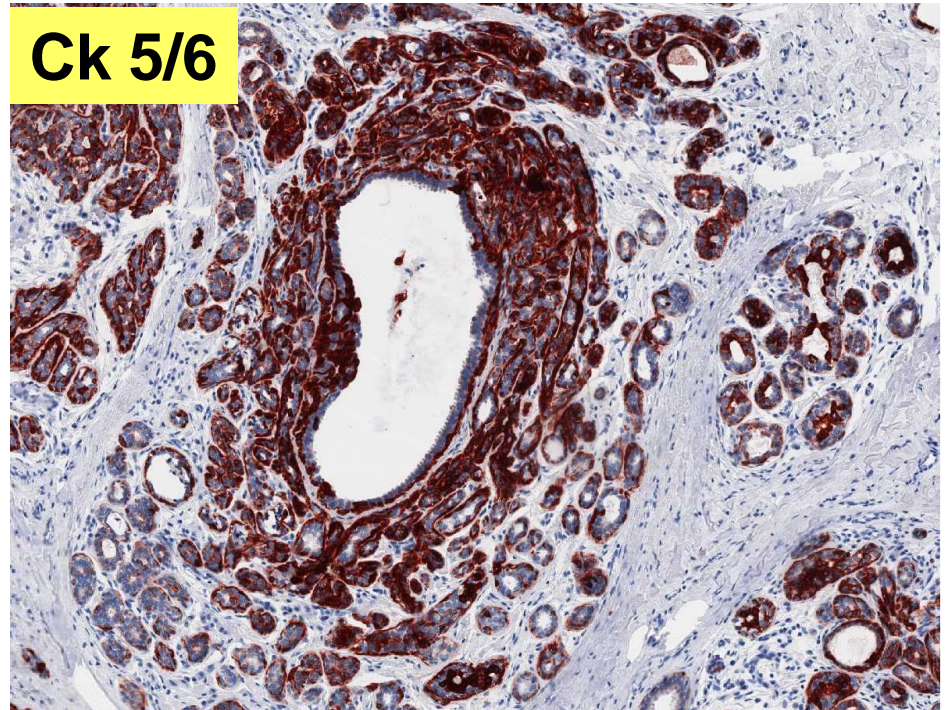
S100



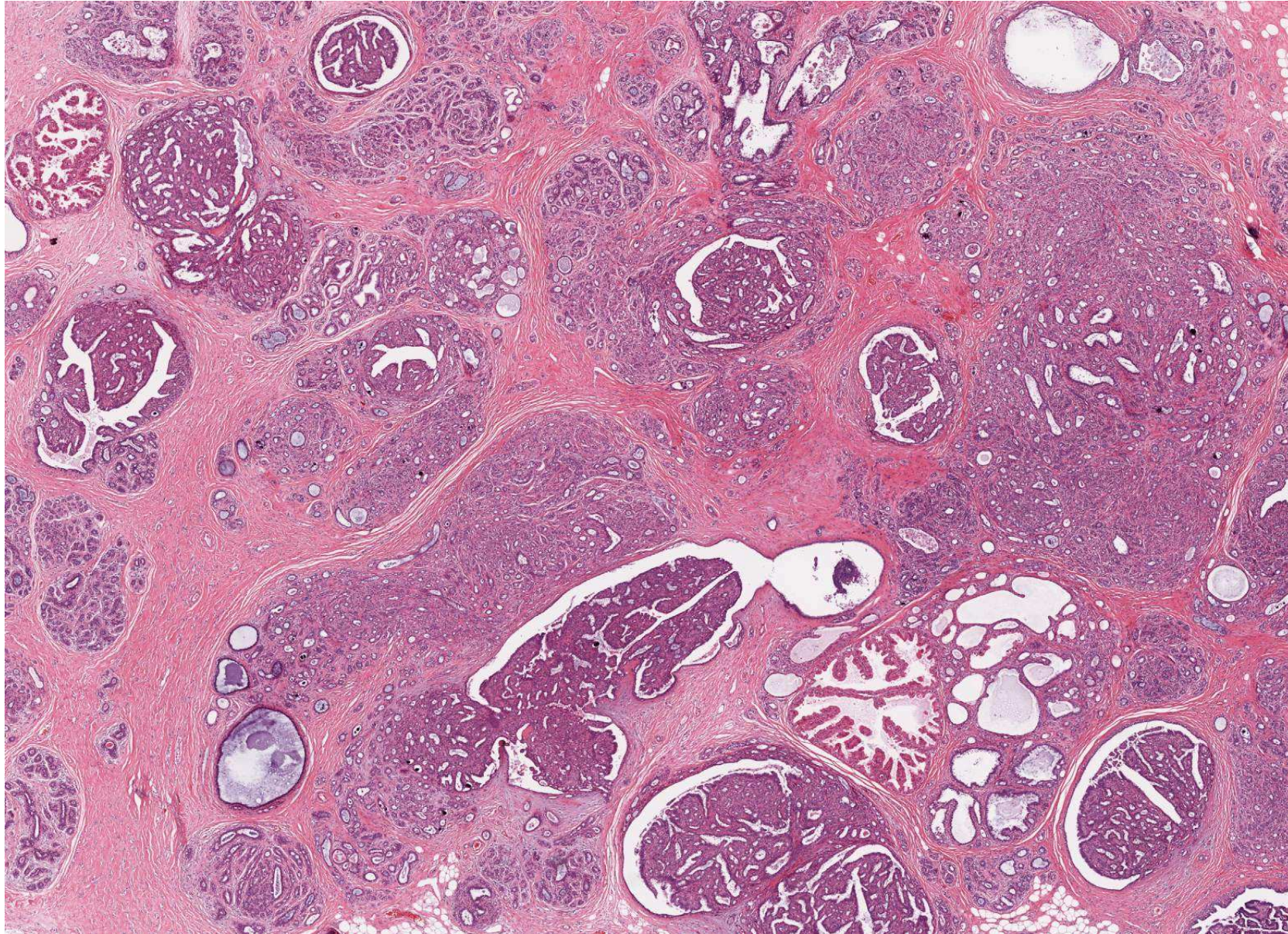
Actin



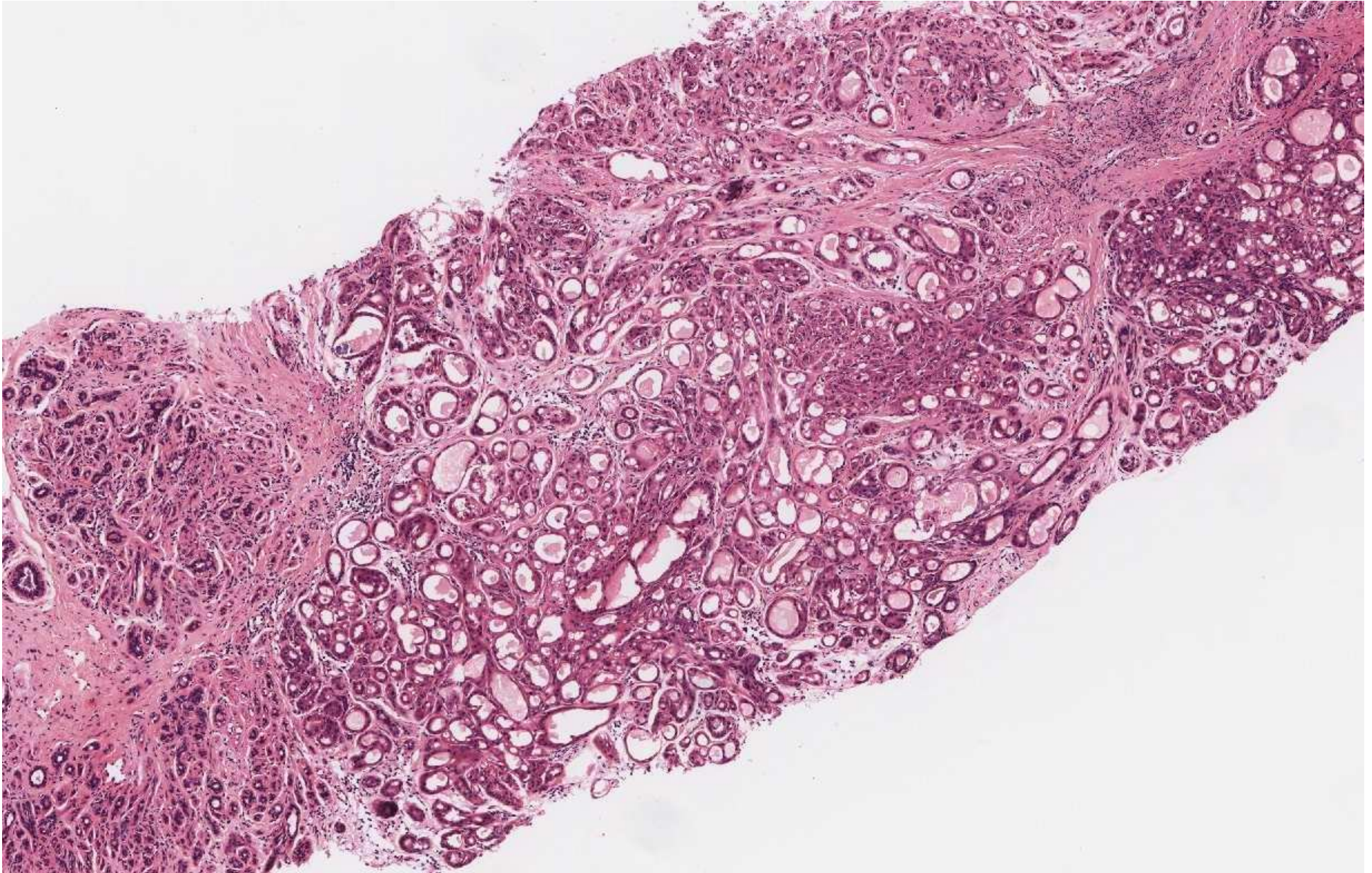
Ck 5/6



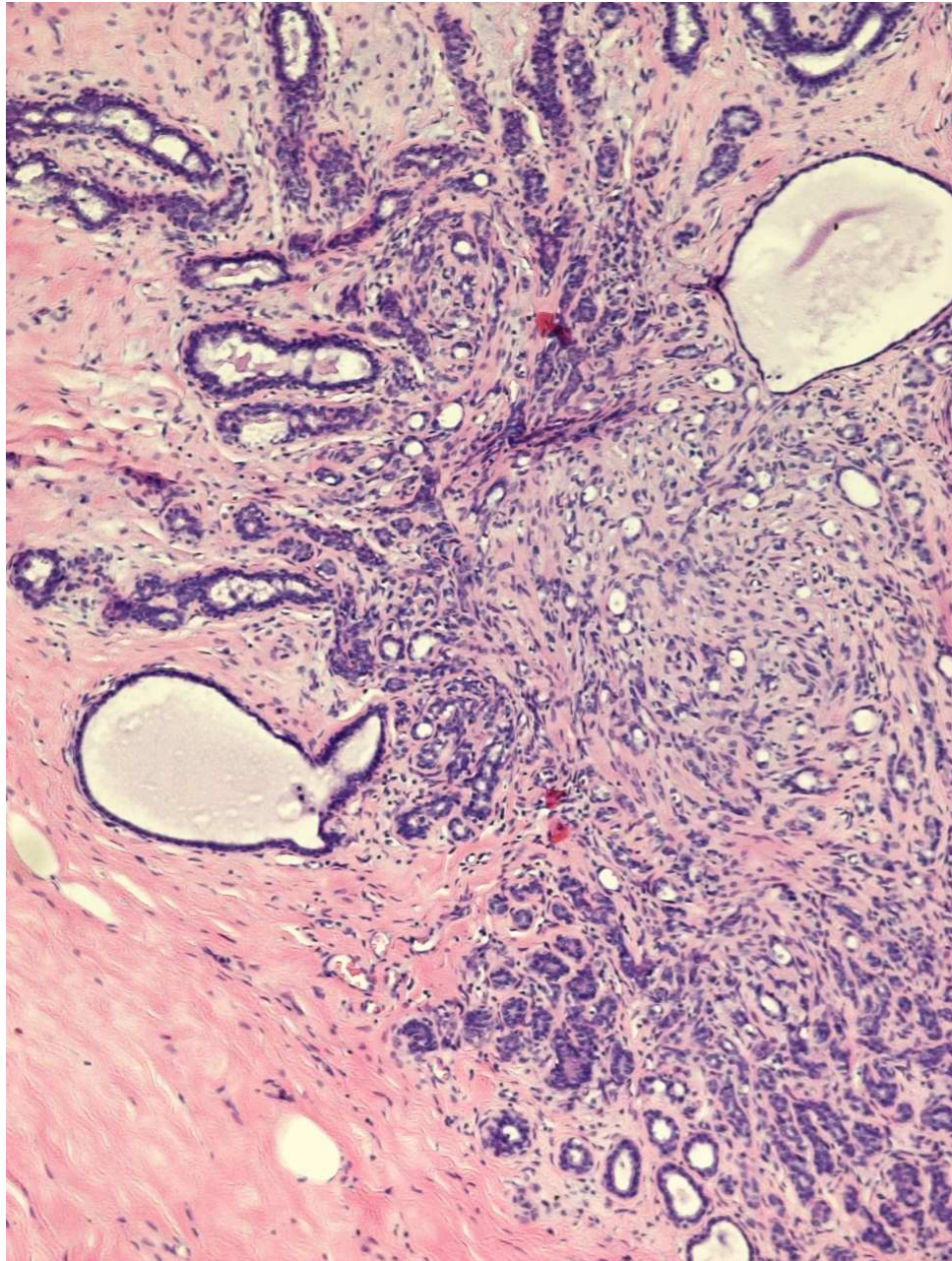
Nodular adenosis and papillomatosis



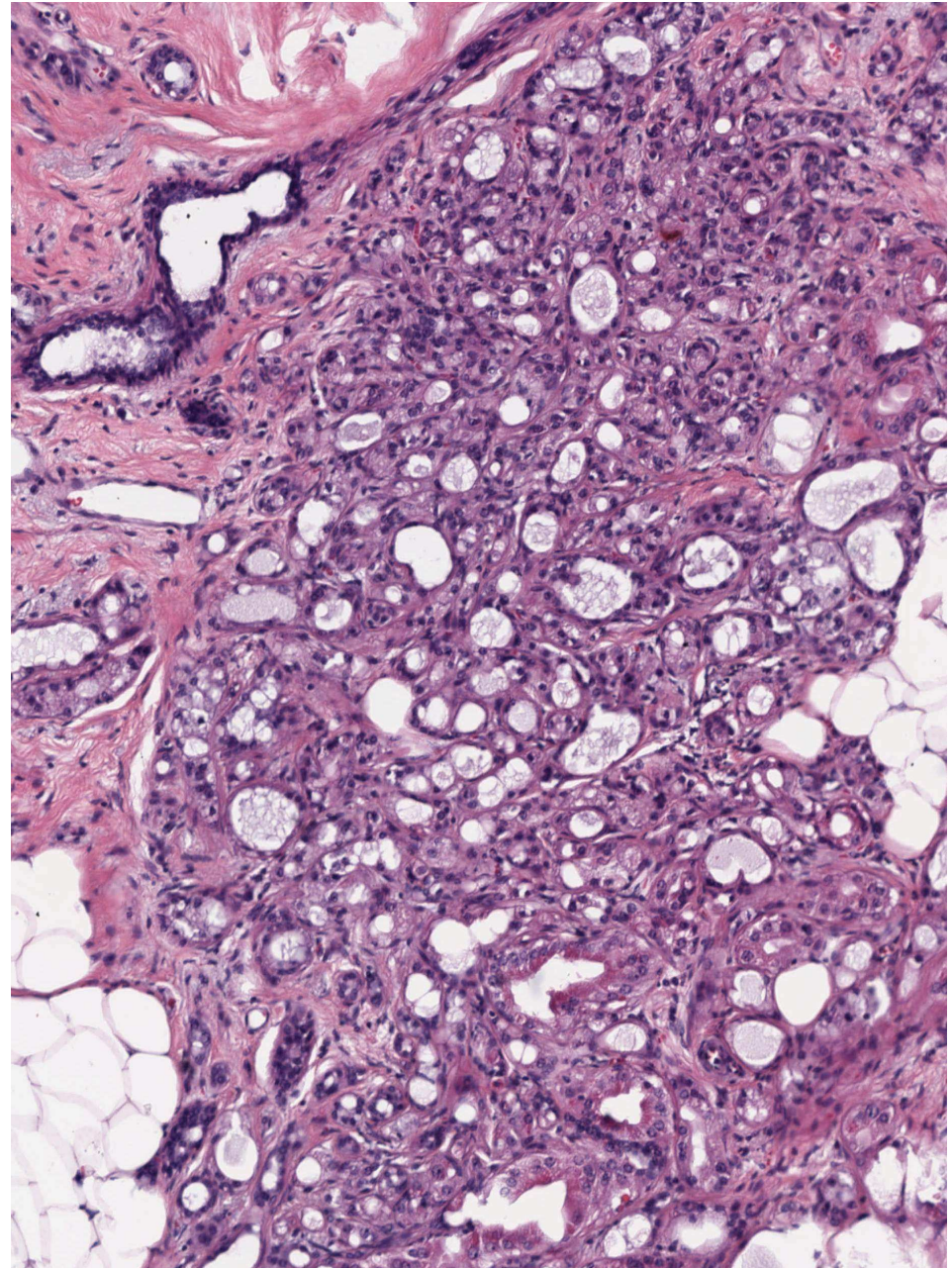
Tumor-like sclerosing and apocrine adenosis



Sclerosing adenosis



Apocrine adenosis



Issues with the assessment of atypia in minimally invasive breast biopsy

Individual risk assessment

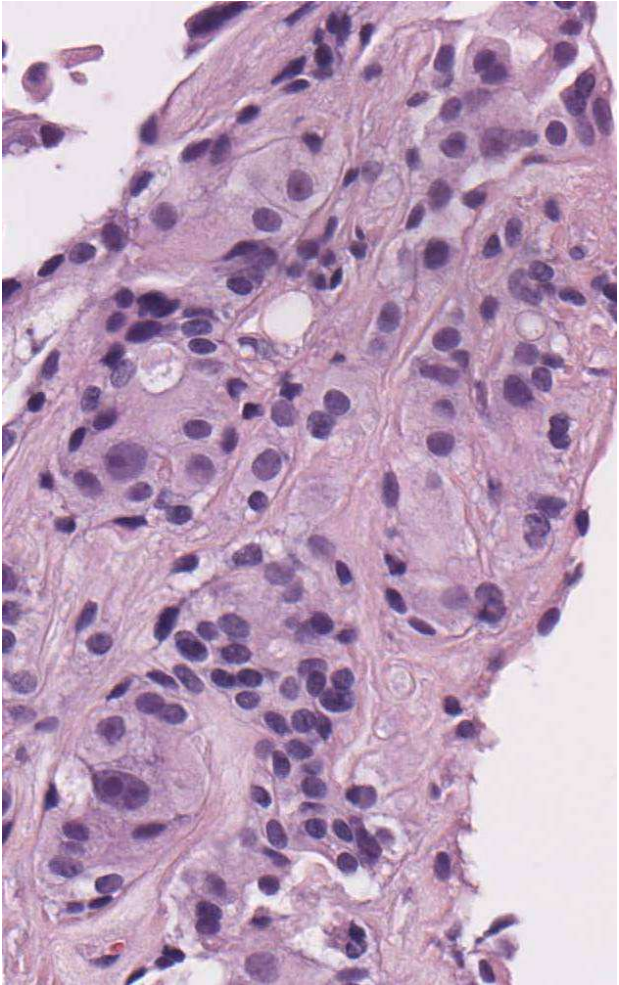
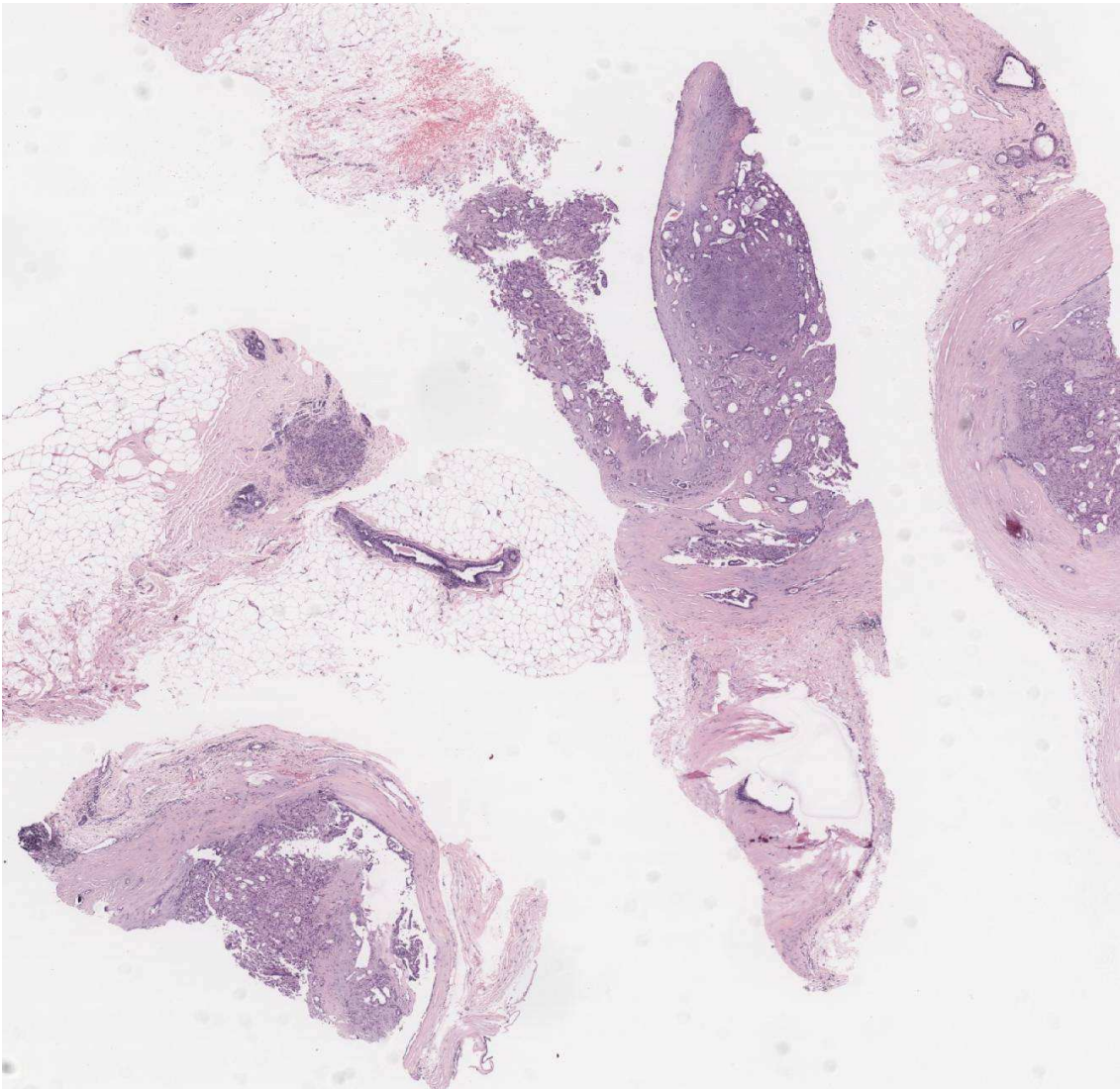
- Flat epithelial atypia (FEA)
- Lobular intraepithelial neoplasia (LN)

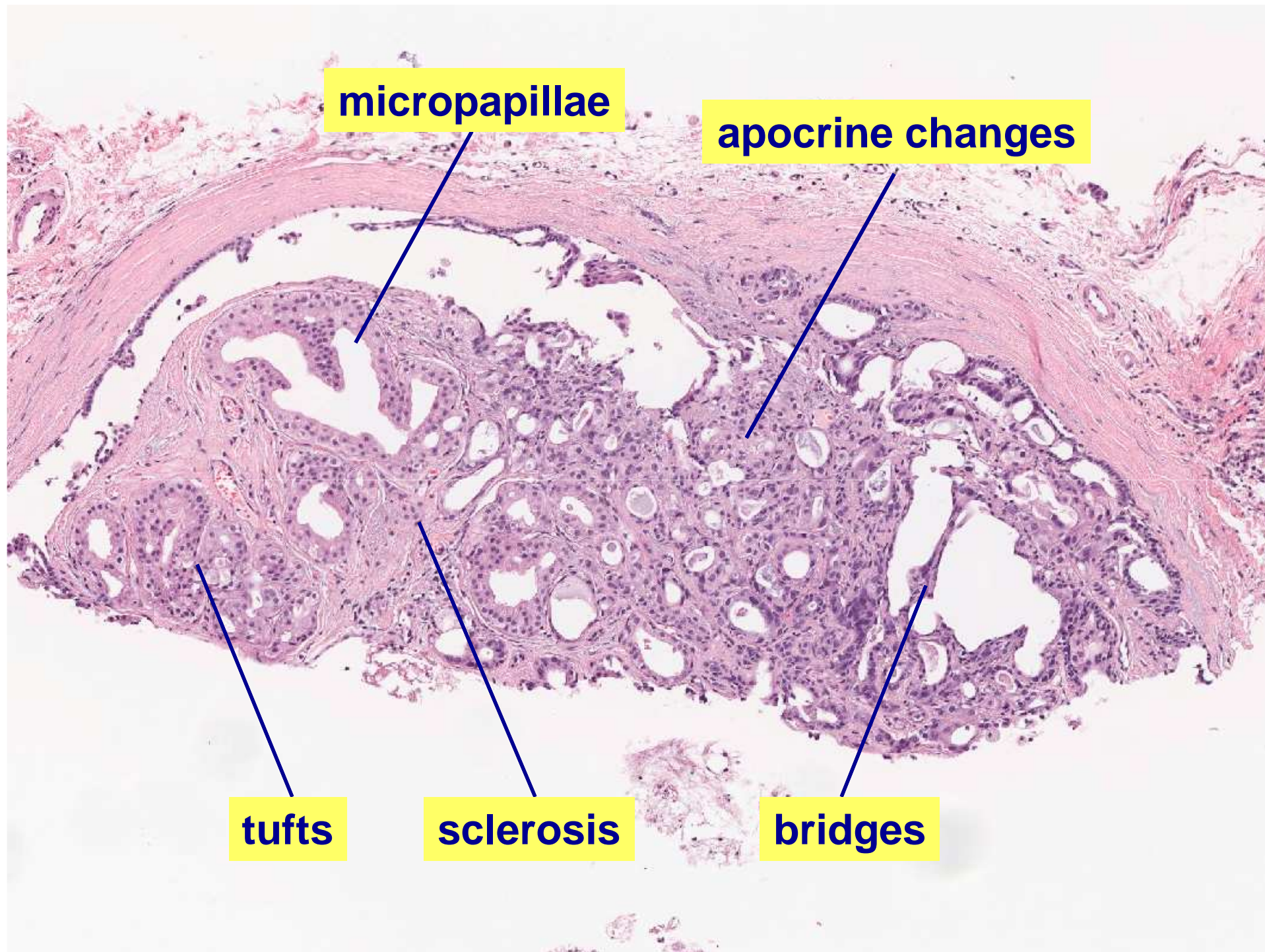
Avoidance of overdiagnosis

- Usual ductal hyperplasia
- Adenosis and sclerosing lesions
- **Papilloma**

Sclerosing papilloma

Reporting category: B3





micropapillae

apocrine changes

tufts

sclerosis

bridges



gland formation

This histological image shows a section of prostate tissue stained with hematoxylin and eosin (H&E). The tissue exhibits numerous glandular units, which are the primary structures of the prostate. These glands are characterized by their circular or oval shape and the presence of a central lumen. The glandular architecture is significantly distorted, with glands appearing crowded and irregular in shape, a hallmark of prostatic adenocarcinoma. The surrounding stroma is dense and fibrous, and the overall tissue organization is disrupted compared to normal prostate tissue.

architectural distortion



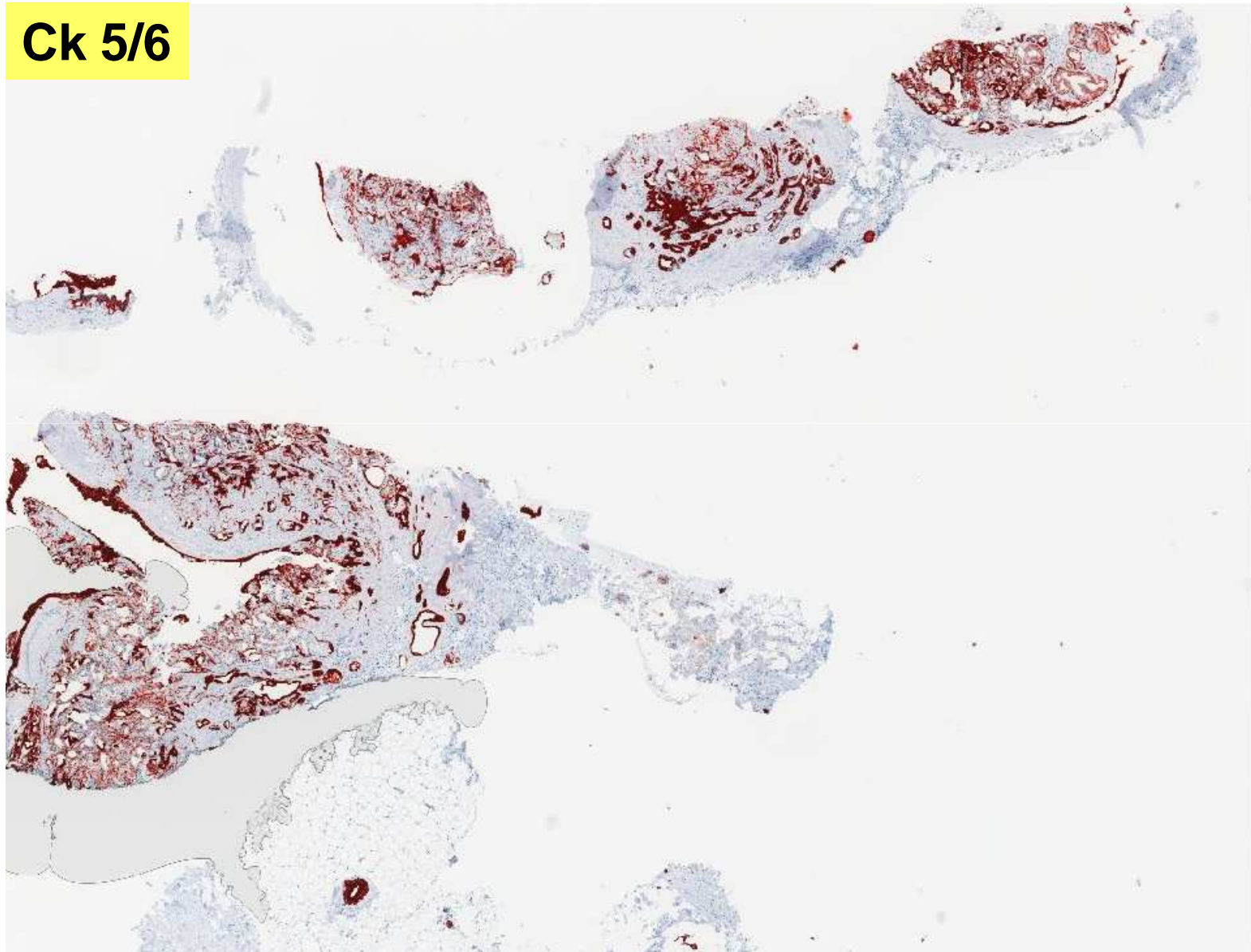
sclerosis

This histological image shows a section of breast tissue stained with hematoxylin and eosin (H&E). The tissue exhibits a dense, fibrous stroma, characteristic of sclerotic changes. The glandular structures are irregular and compressed, with some showing apocrine changes, which are characterized by the presence of large, foamy or vacuolated cells. The overall architecture is disrupted, and the glandular lumens are often filled with secretory material. The stroma is composed of thickened collagen bundles and a high density of spindle-shaped fibroblasts, indicating a reactive or desmoplastic process.

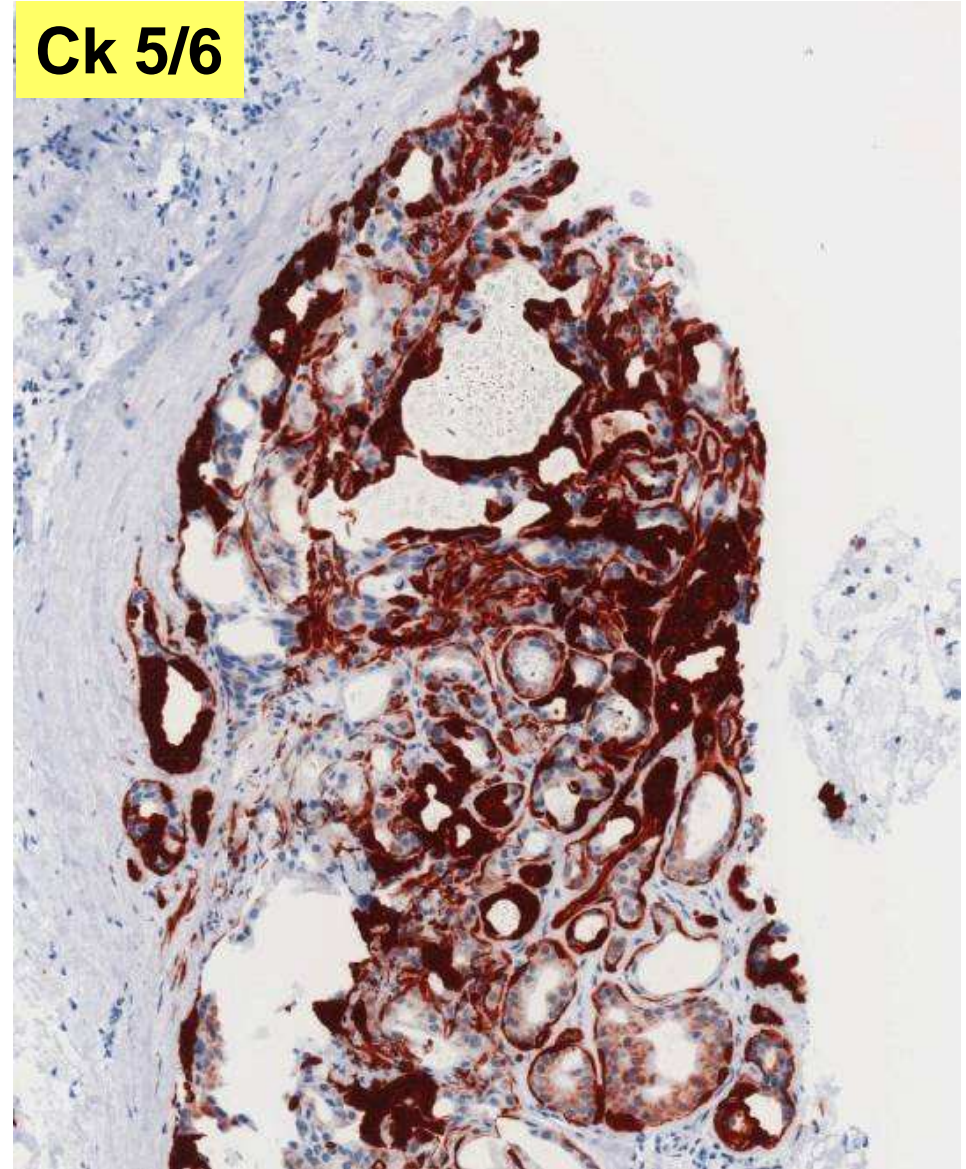
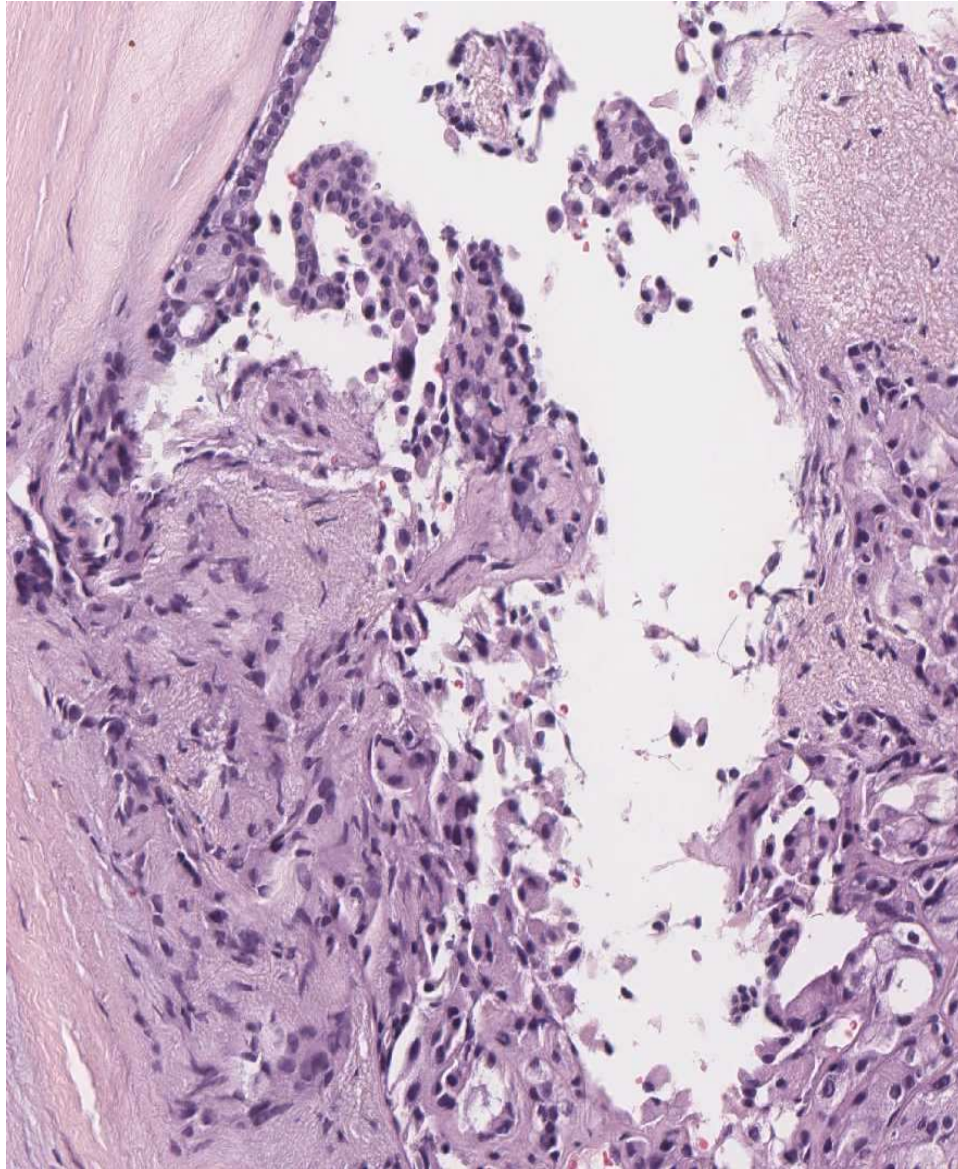
apocrine changes

Heterogenous cell population

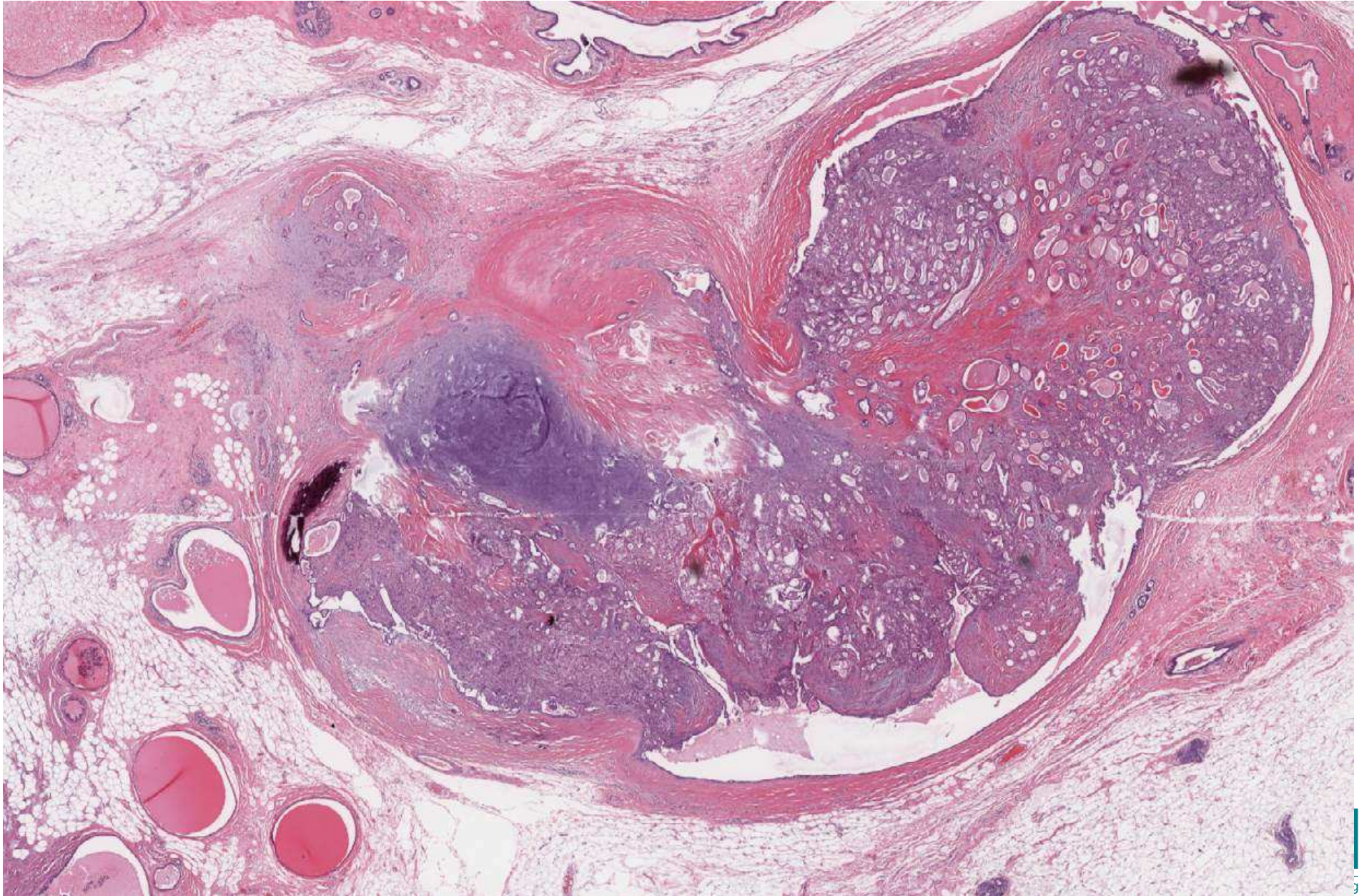
Ck 5/6



Sclerosing papilloma



Resection specimen: Sclerosing papilloma



Sclerosing papilloma – B3

- Diagnostic criteria
 - distorted architecture w/ sclerosis
 - heterogeneous cellularity
 - apocrine changes
- Case presented at seminar for pathologists
 - B2: 4 votes
 - B3: 11 votes (28%)
 - B4: 2 votes
 - B5a: 8 votes
 - B5b: 6 votes

Papillome

- Intraduktale Papillome
 - meist solide, zentral gelegen
 - in 5.-6- Lebensdekade
 - z.T. Mamillensekretion
- Multiple periphere Papillome
 - seltener
 - eher jüngere Patientinnen
 - häufig klinisch okkult, selten Mamillensekretion
 - mammographisch: Herdbefund oder selten mit Mikroverkalkungen

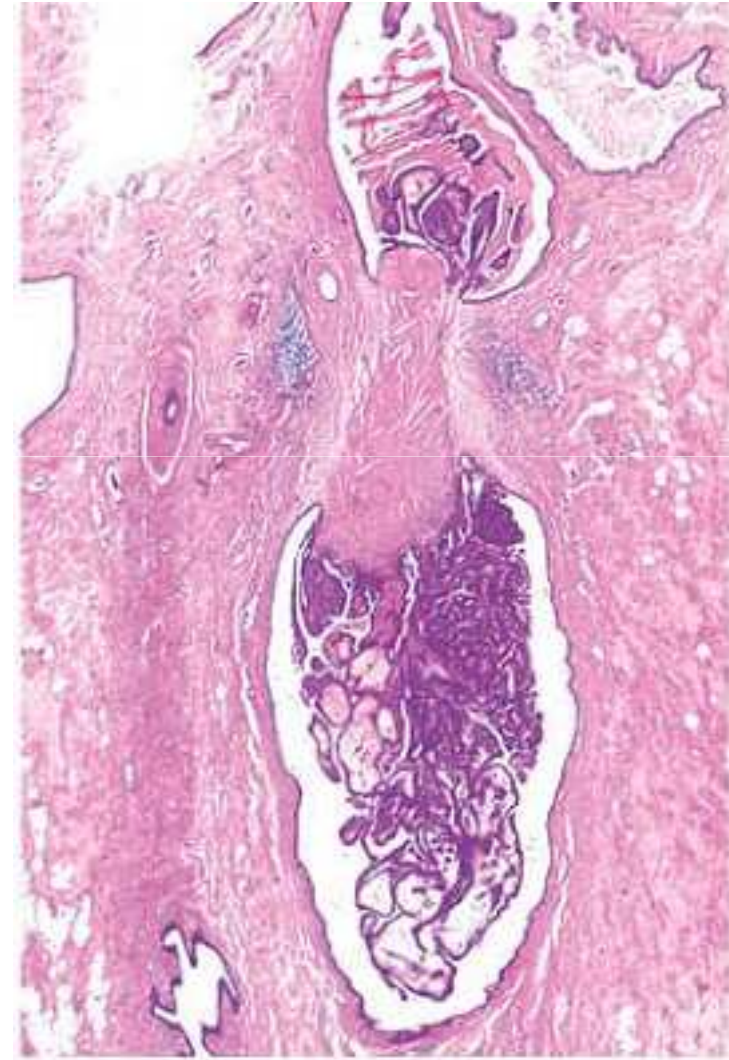
Secondary changes in papilloma

Frequent:

- Sclerosis, calcification
- Apocrine metaplasia
- Usual hyperplasia (UDH)

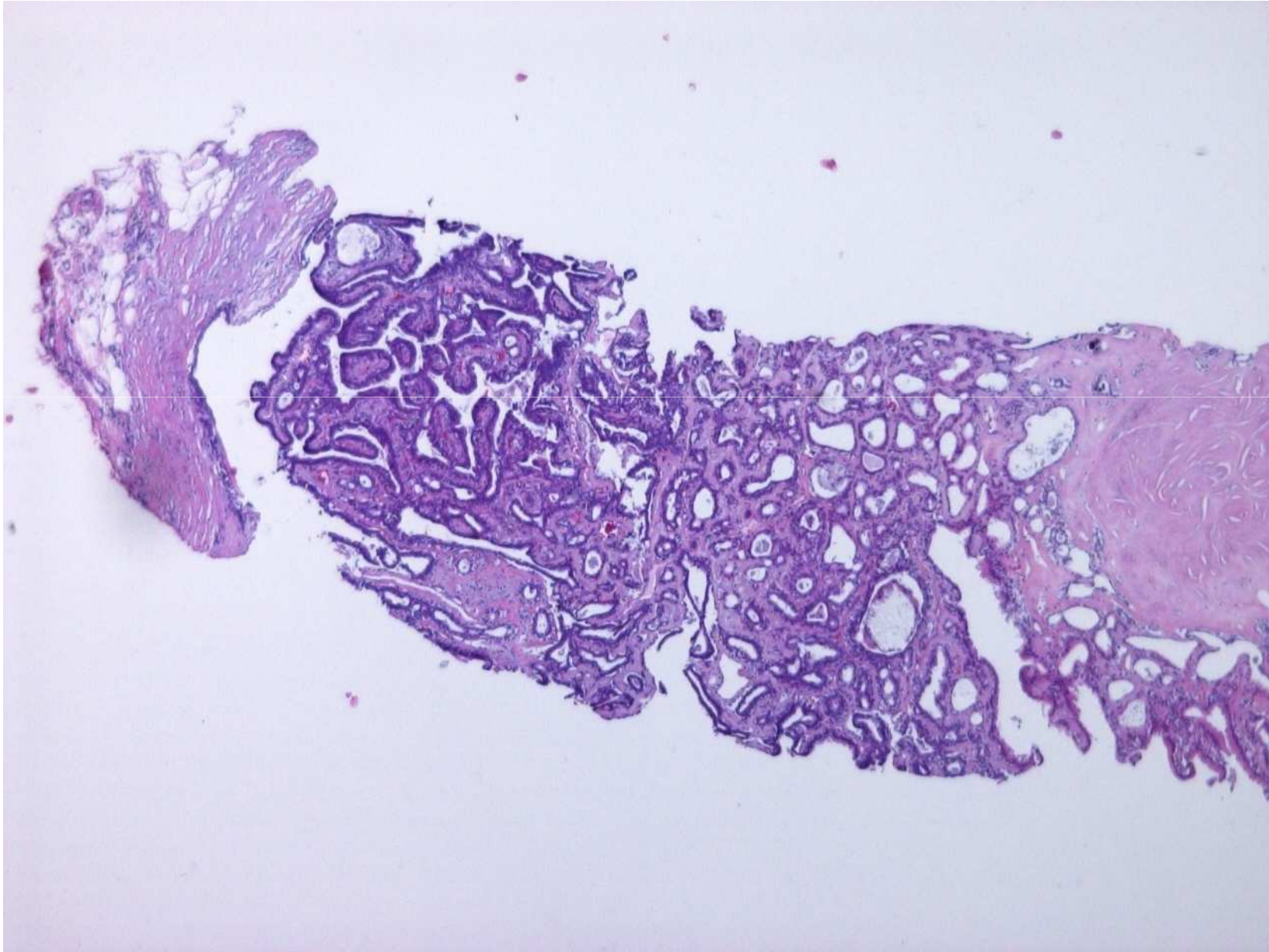
Rare:

- Infarction
- Squamous cell metaplasia

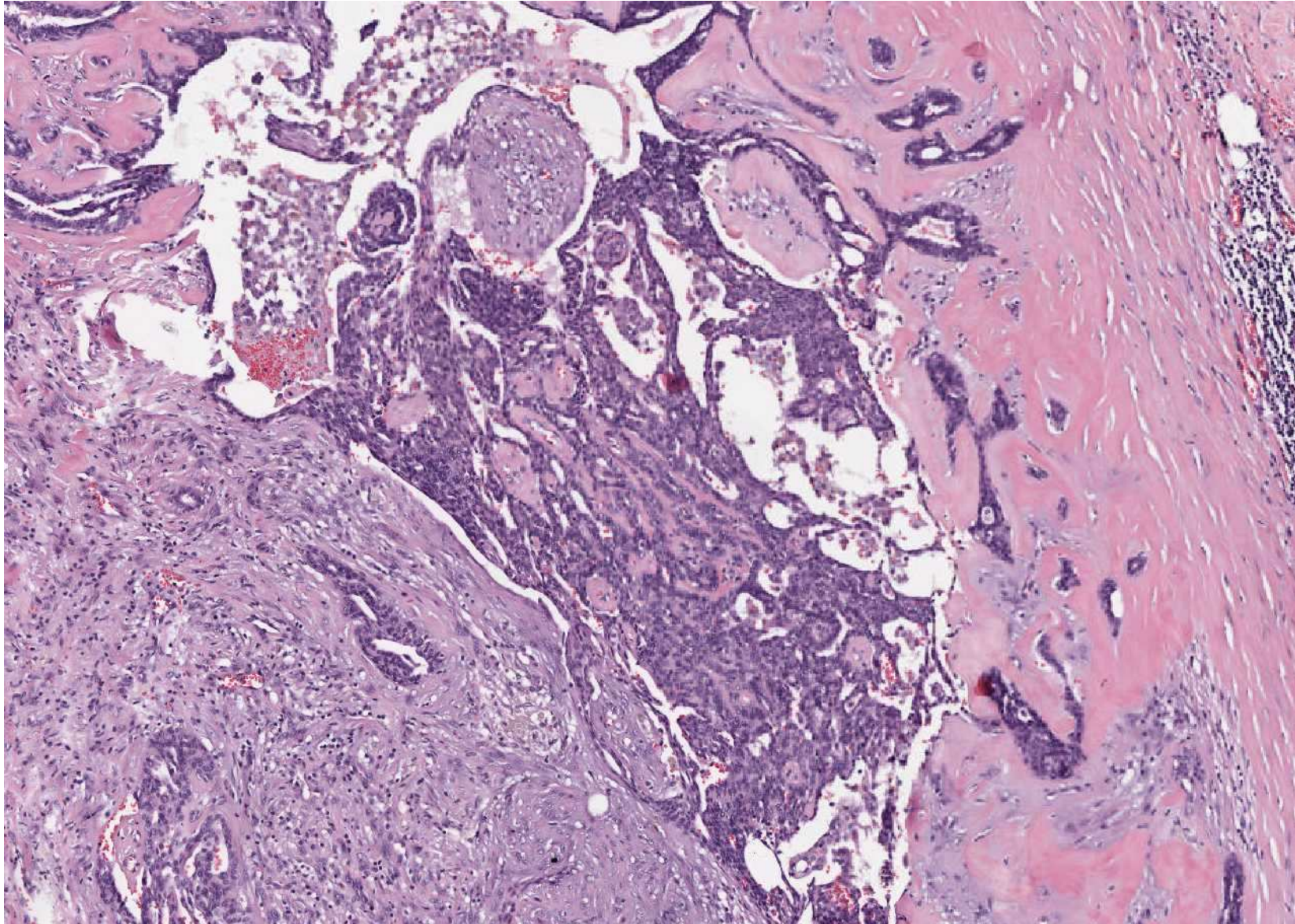


Trommelschlägelartiges Papillom
(Rosen, 2001)

Glandular papilloma

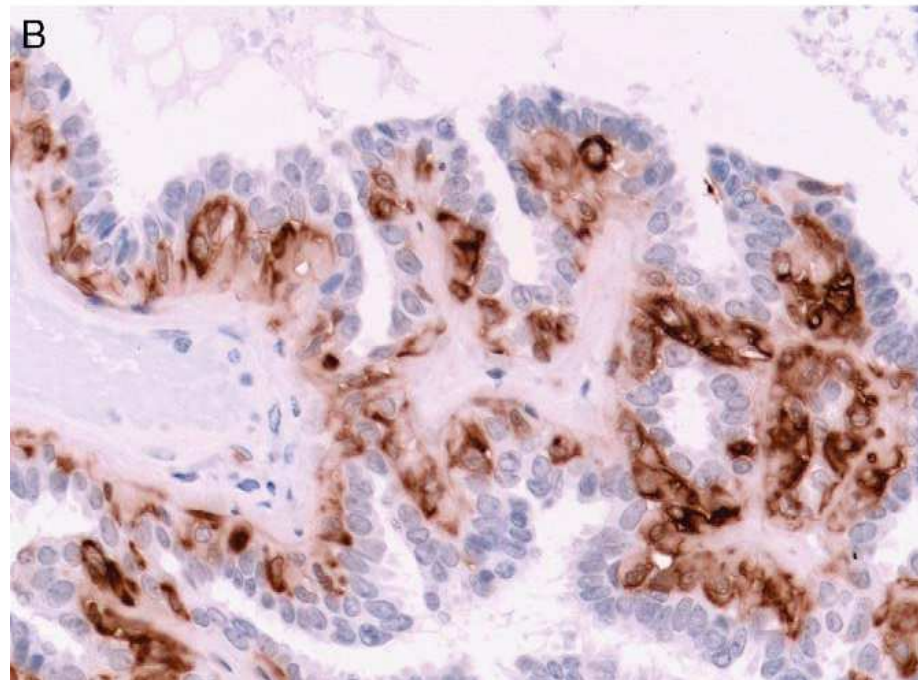
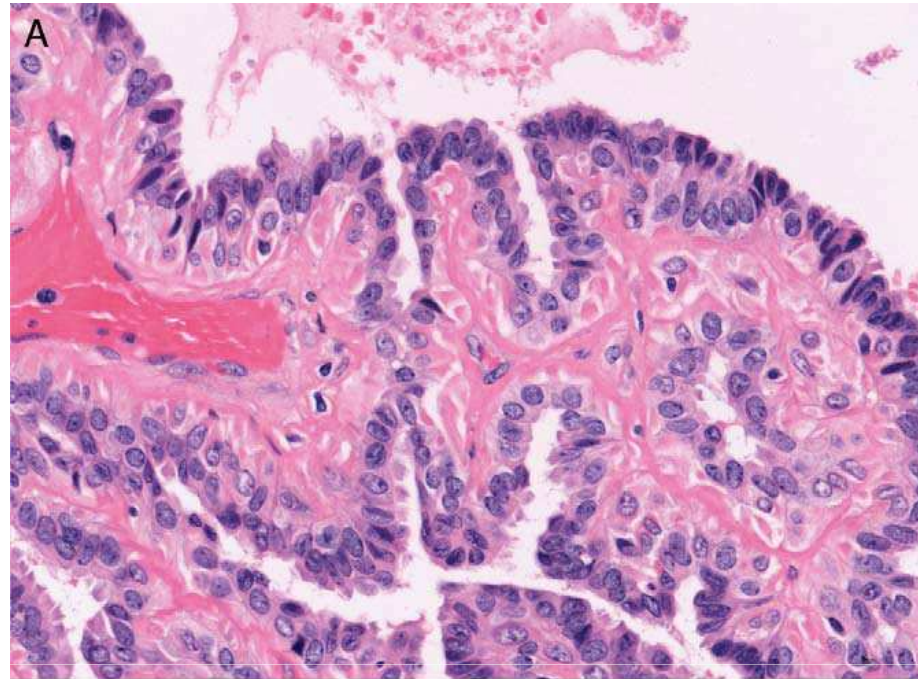


Papilloma with sclerosis and pseudoinvasion



Myoepithelial Markers

- smooth muscle actin (SMA)
- p63
- S100
- CD10
- Ck5/6



Core biopsy in papillomas

- Excision recommended for central intraductal papillomas
- Upgrade risk for papilloma on core biopsy → 0,73-4%
(Rhenshaw et al 2004, Rubin et al 1995)
- Upgrade risk for atypical papilloma → 75% DCIS on resection (Mercado et al 2006; Liberman et al 1999; Ivan et al 2004, Agoff et Lawton 2004, Saddik et al 1999)
- Increased risk with multiple peripheral papillomas on follow up than with solitary central papilloma

Summary

- The interpretation of breast specimens requires special expertise in breast pathology, and should be conducted by a specialized breast pathologist.