Hyperplasia, FEA, ADH, and Lobular neoplasia

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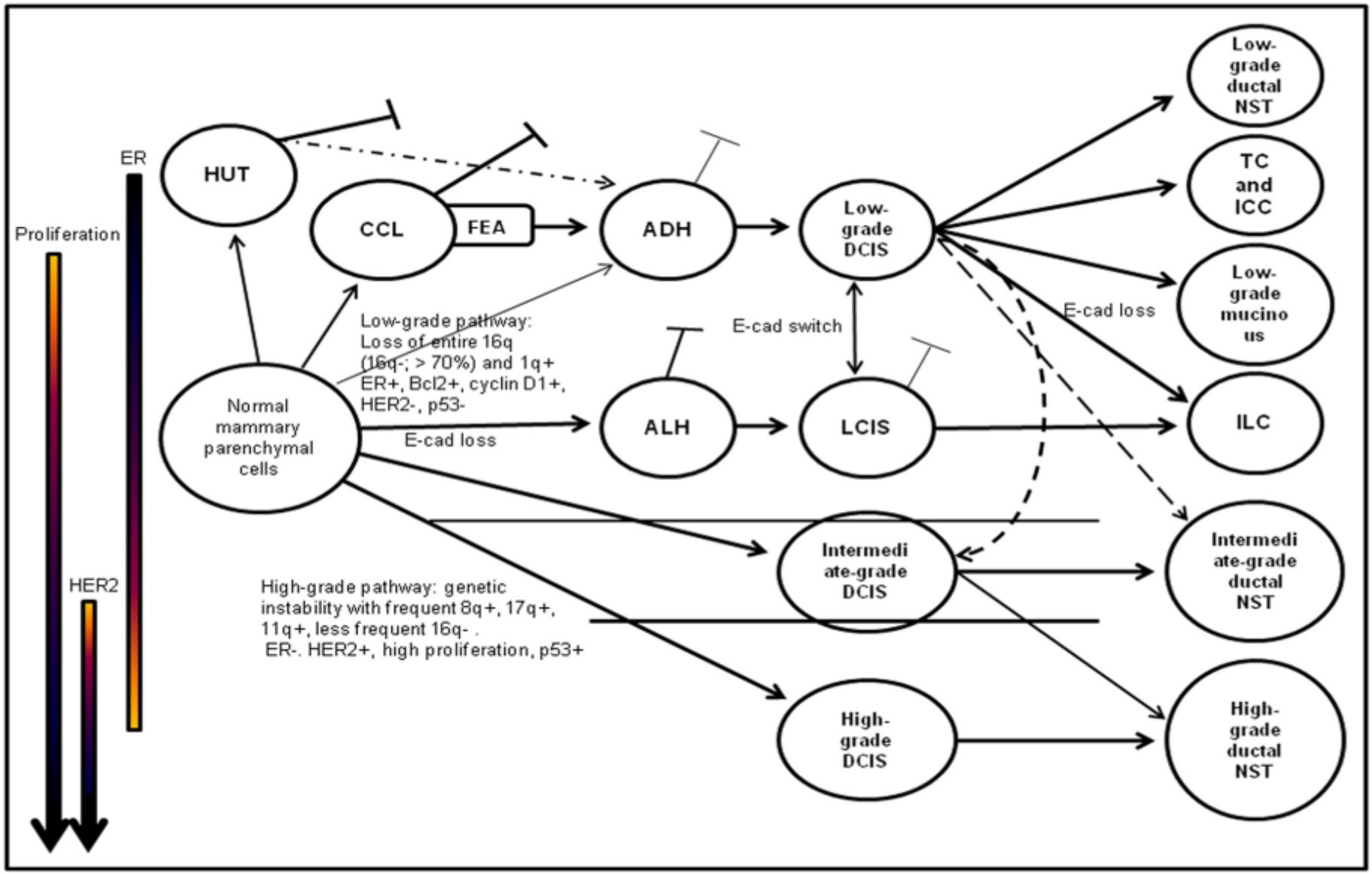
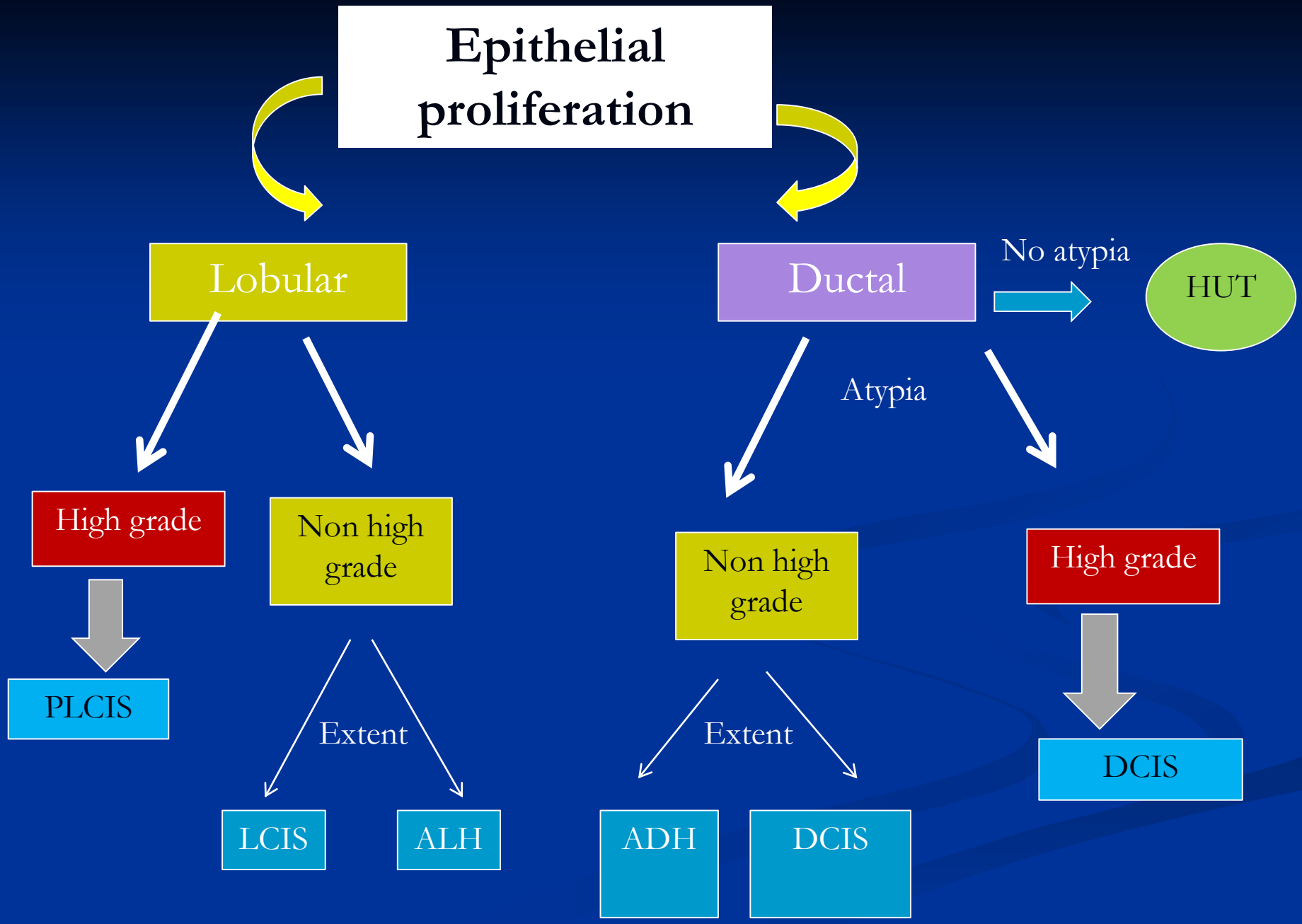


Rakha E, Diagnostic Histopathology 2012

Intraductal Epithelial proliferation

- Ductal or lobular
- Atypical or not
- Extent of atypia

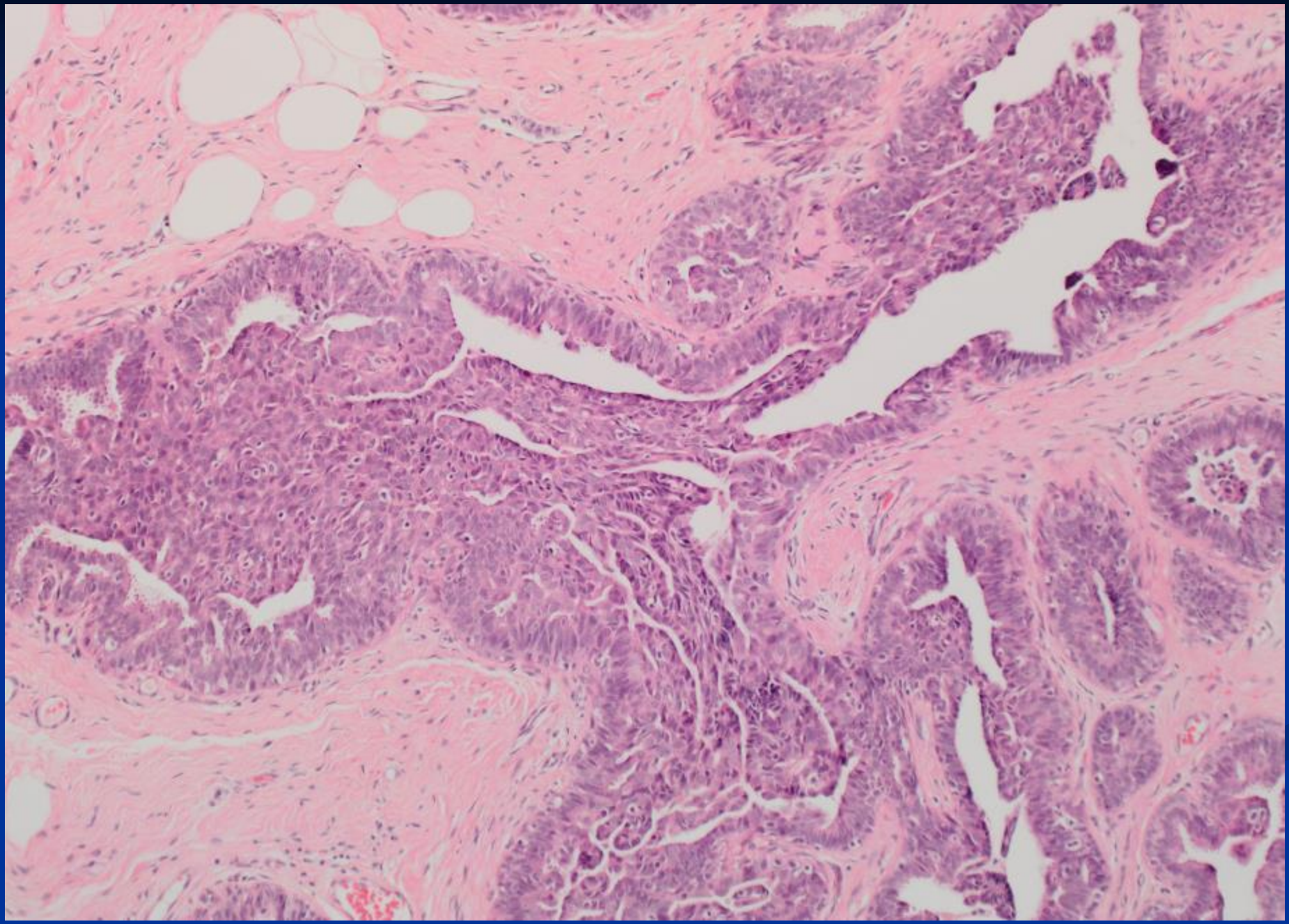

Epithelial proliferation
Lobular
Ductal
No atypia
HUT
Atypia
High grade
Non high grade
Non high grade
High grade
PLCIS
Extent
Extent
DCIS
LCIS
ALH
ADH
DCIS

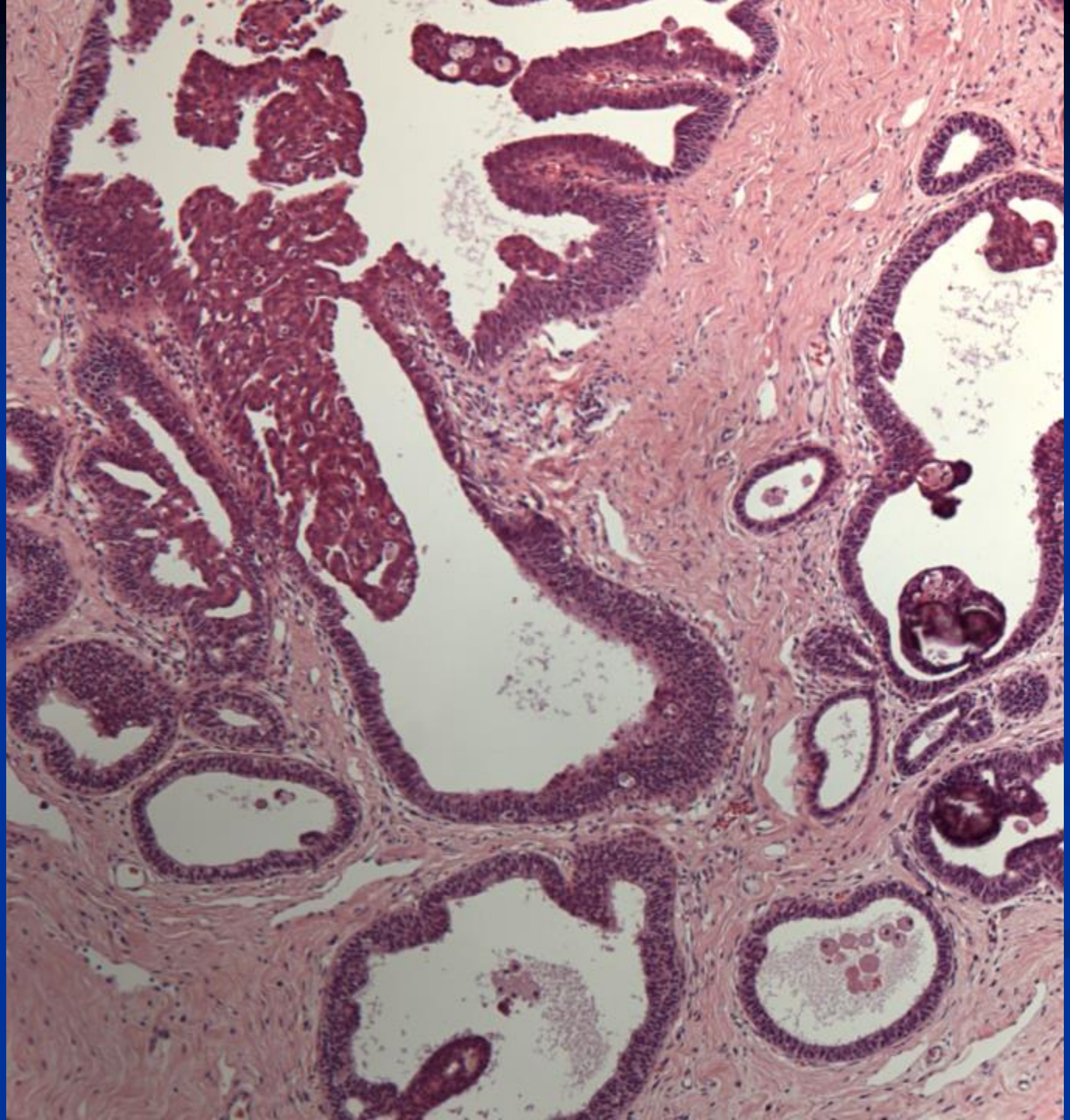
Non atypical ductal hyperplasia

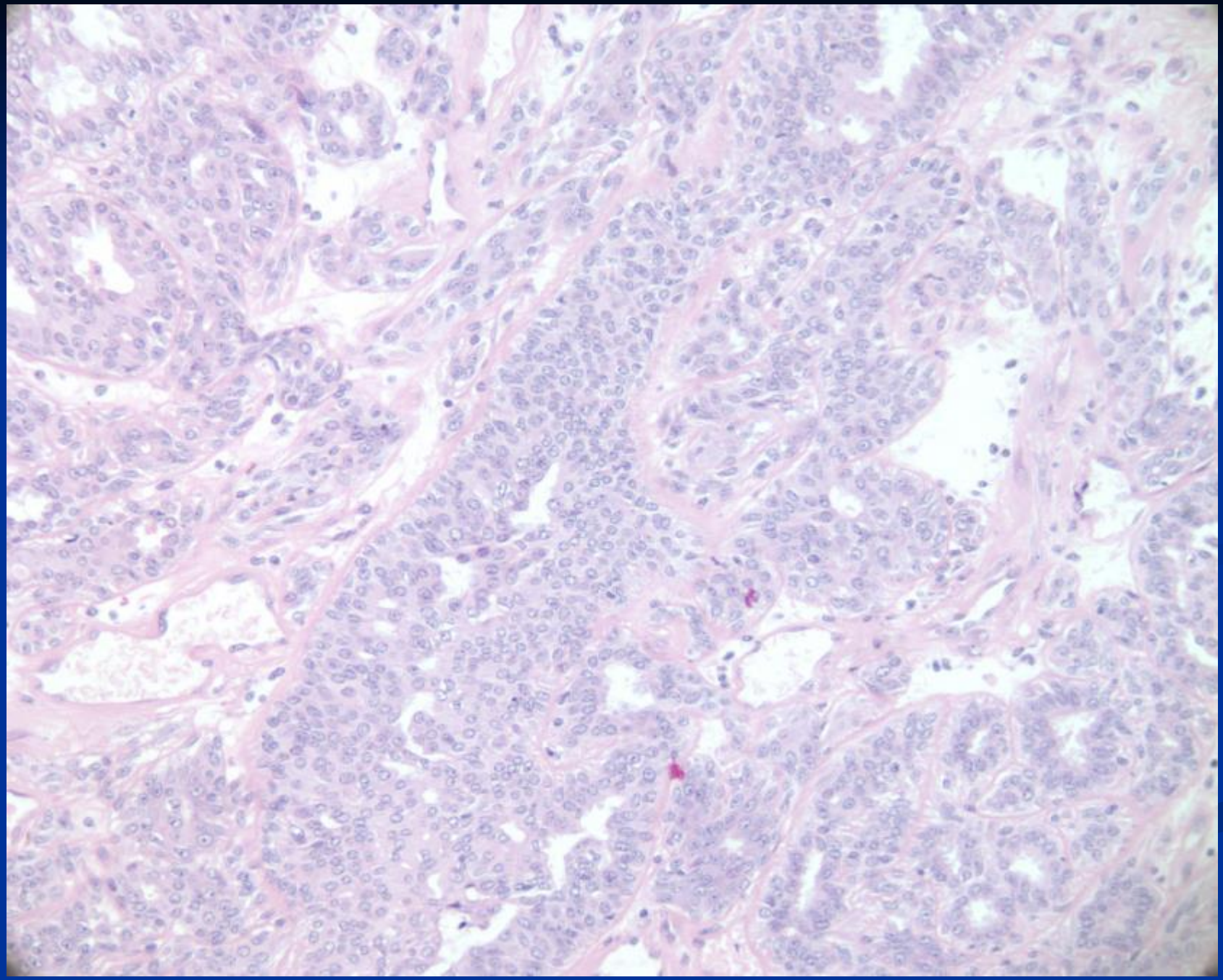
(Epithelial hyperplasia of usual type, Usual ductal hyperplasia)

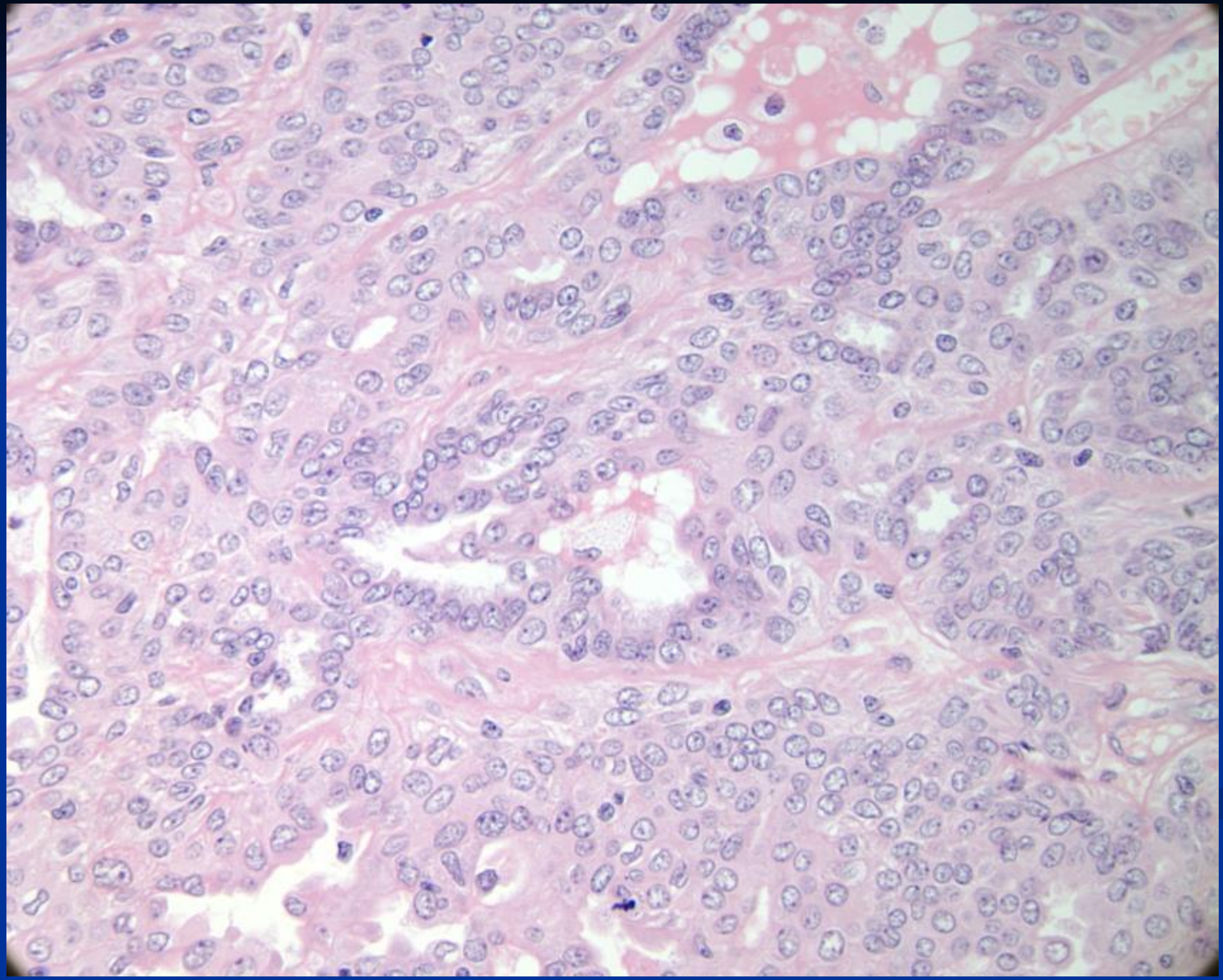
- Architecture: solid with peripheral slit like spaces, streaming of nuclei.

- Cytological: mixed population
  - Rounded and ovoid cells
  - Variation in size and shape



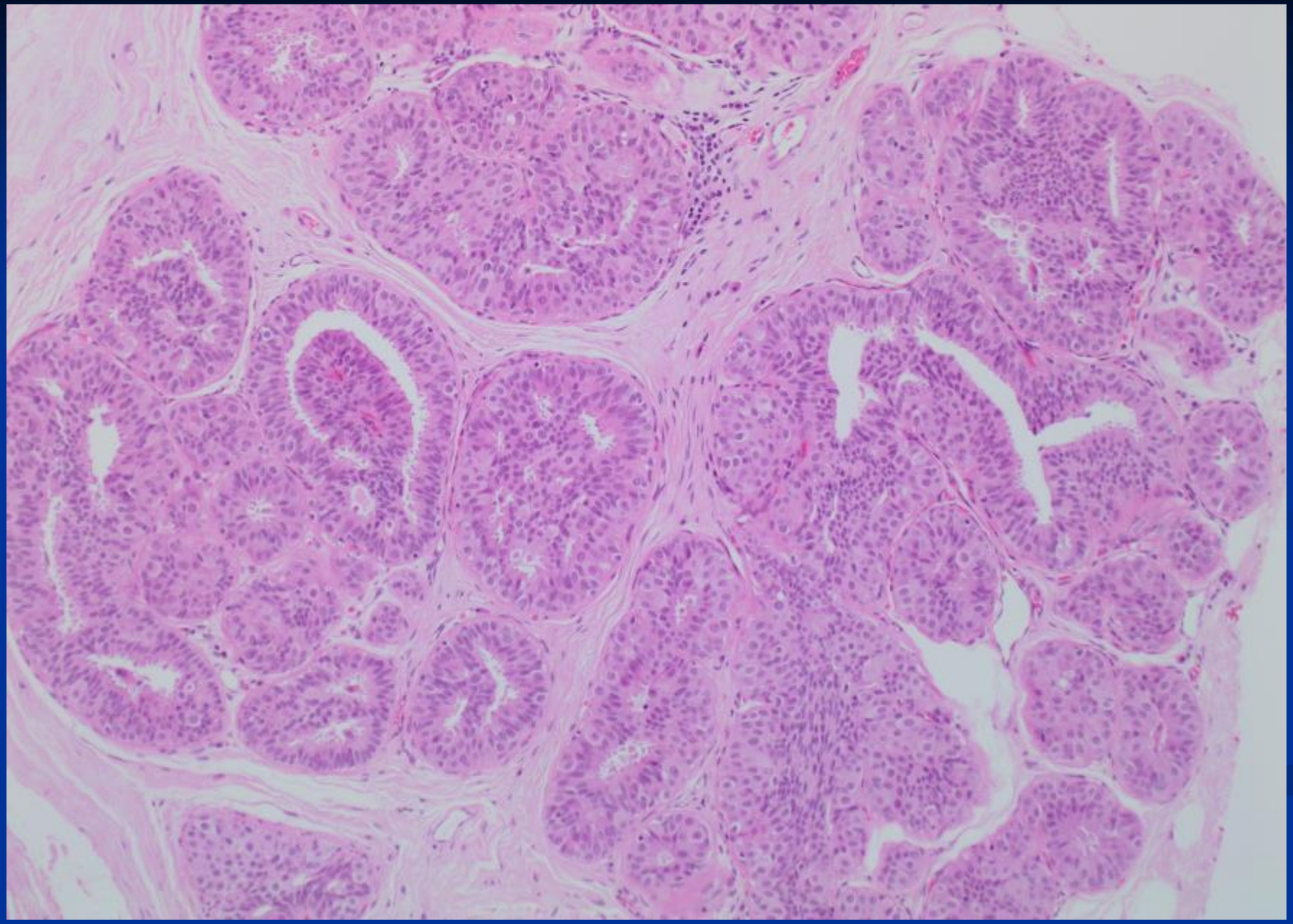






Epithelial hyperplasia

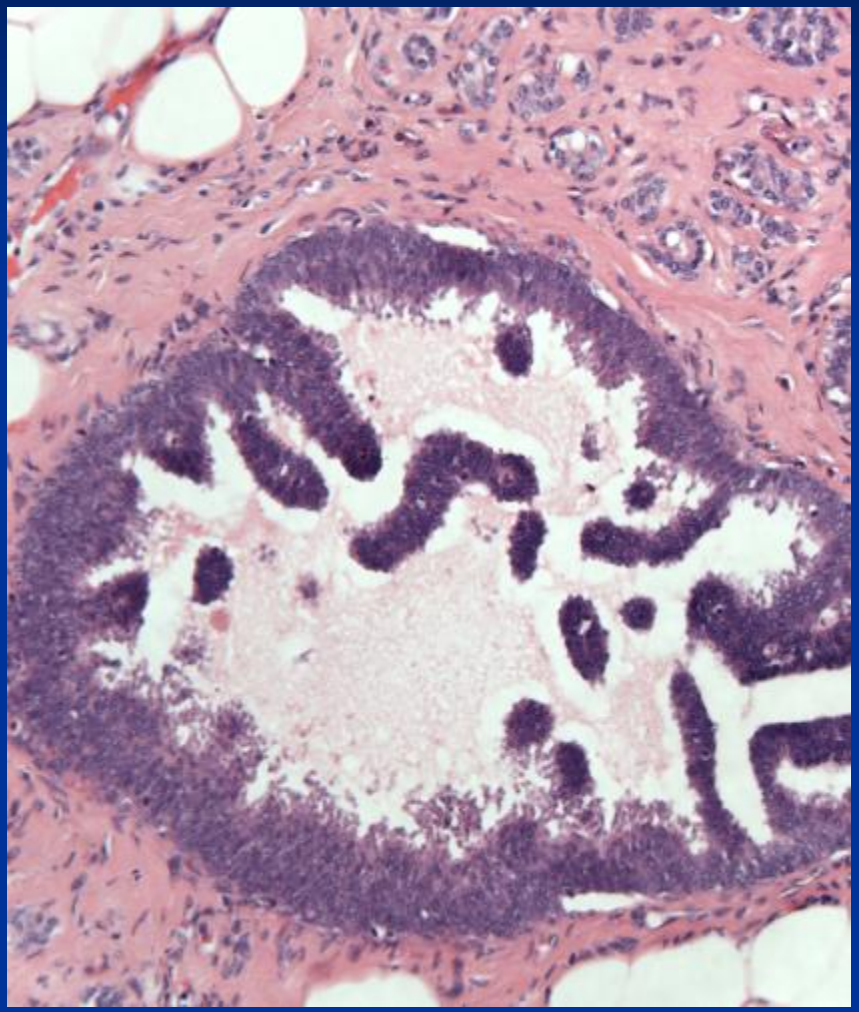
- Papilloma
- Columnar cell change
- Radial scar
- Fibroadenoma
- Apocrine metaplasia
- Nipple adenoma
- Gynaecomastia

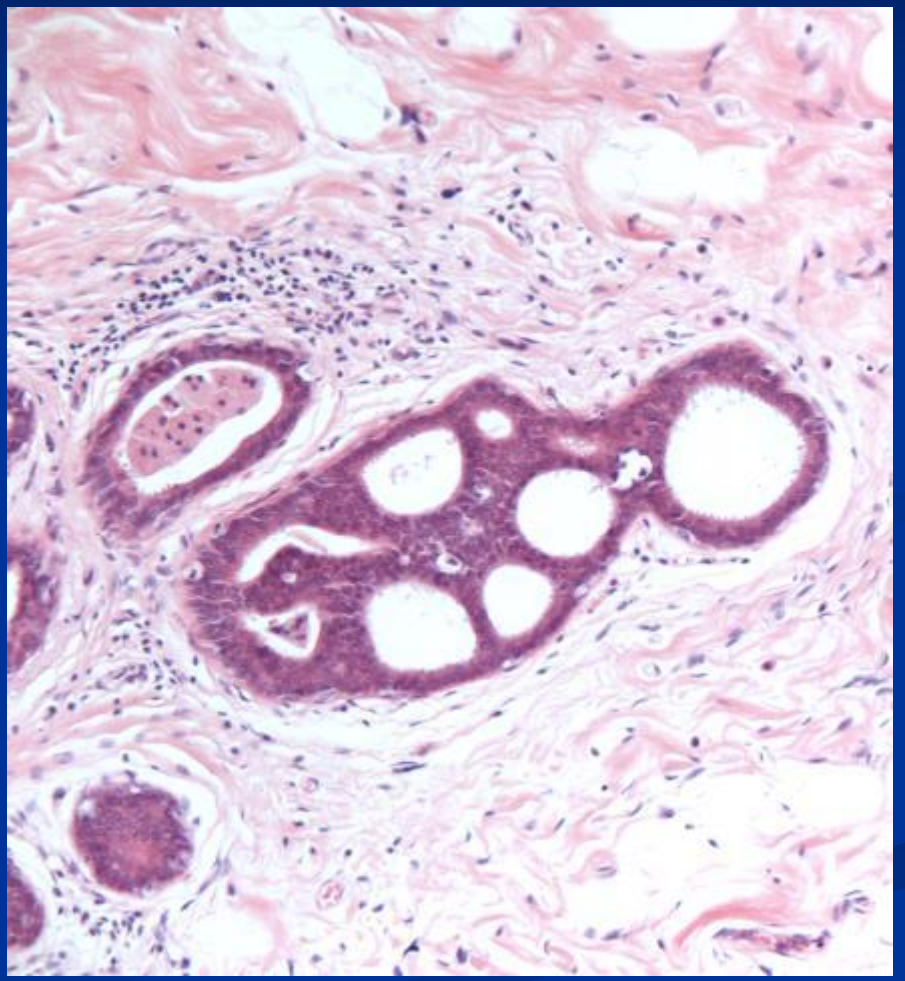


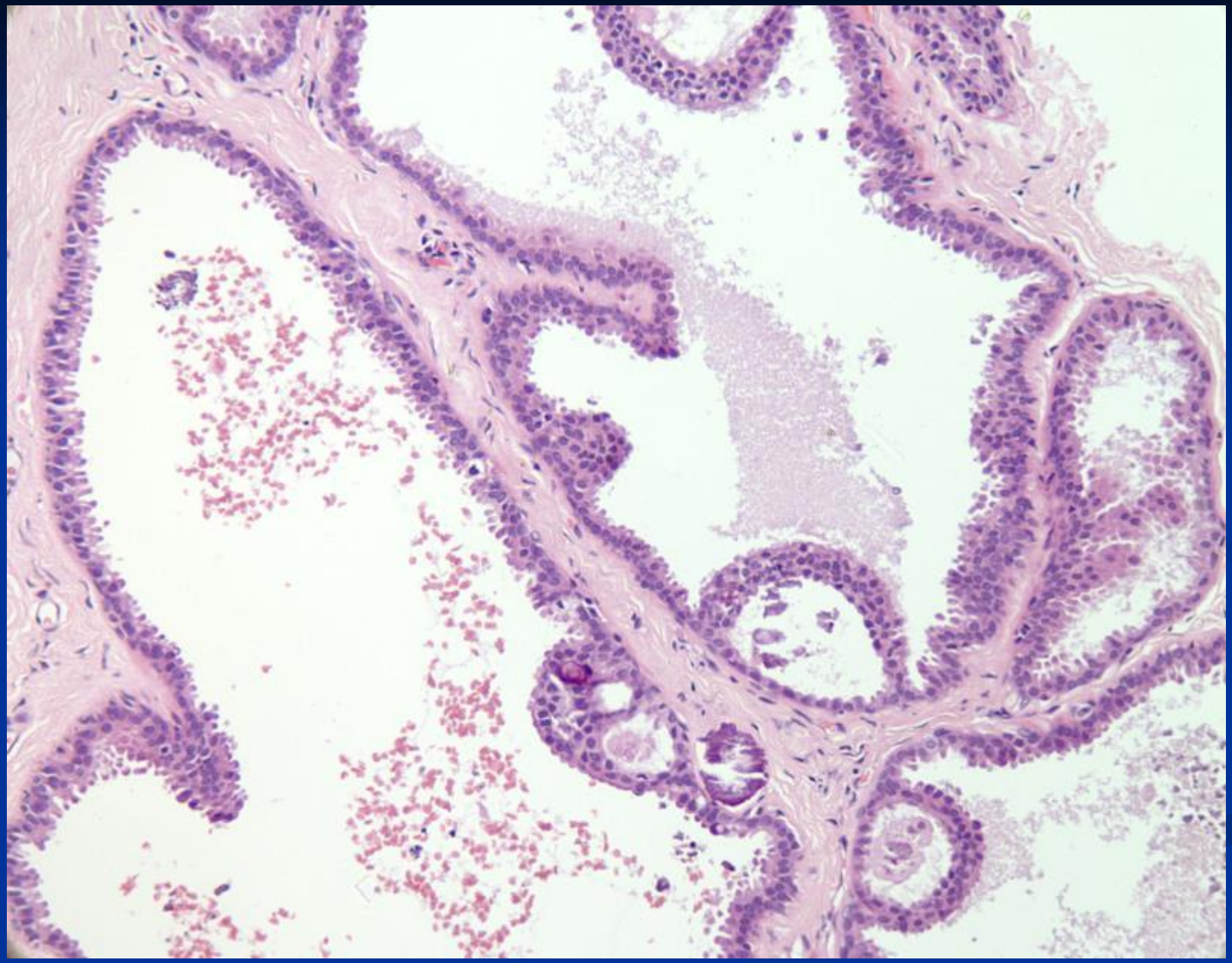
ADH

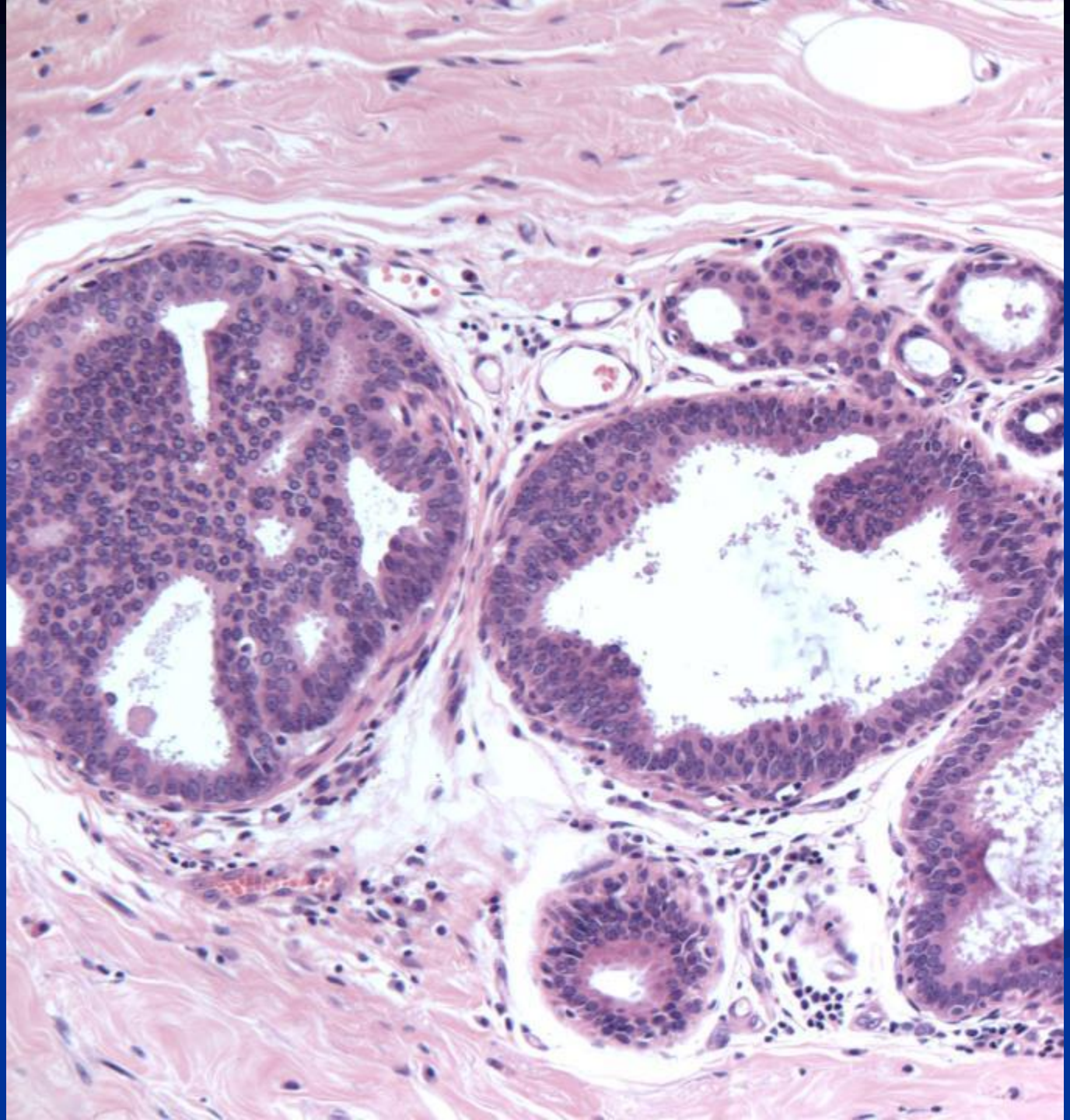
- Quantitative diagnosis
- **Not high grade**
- If on core biopsy: designate as AIDEP
- B-coding B3

Architectural atypia



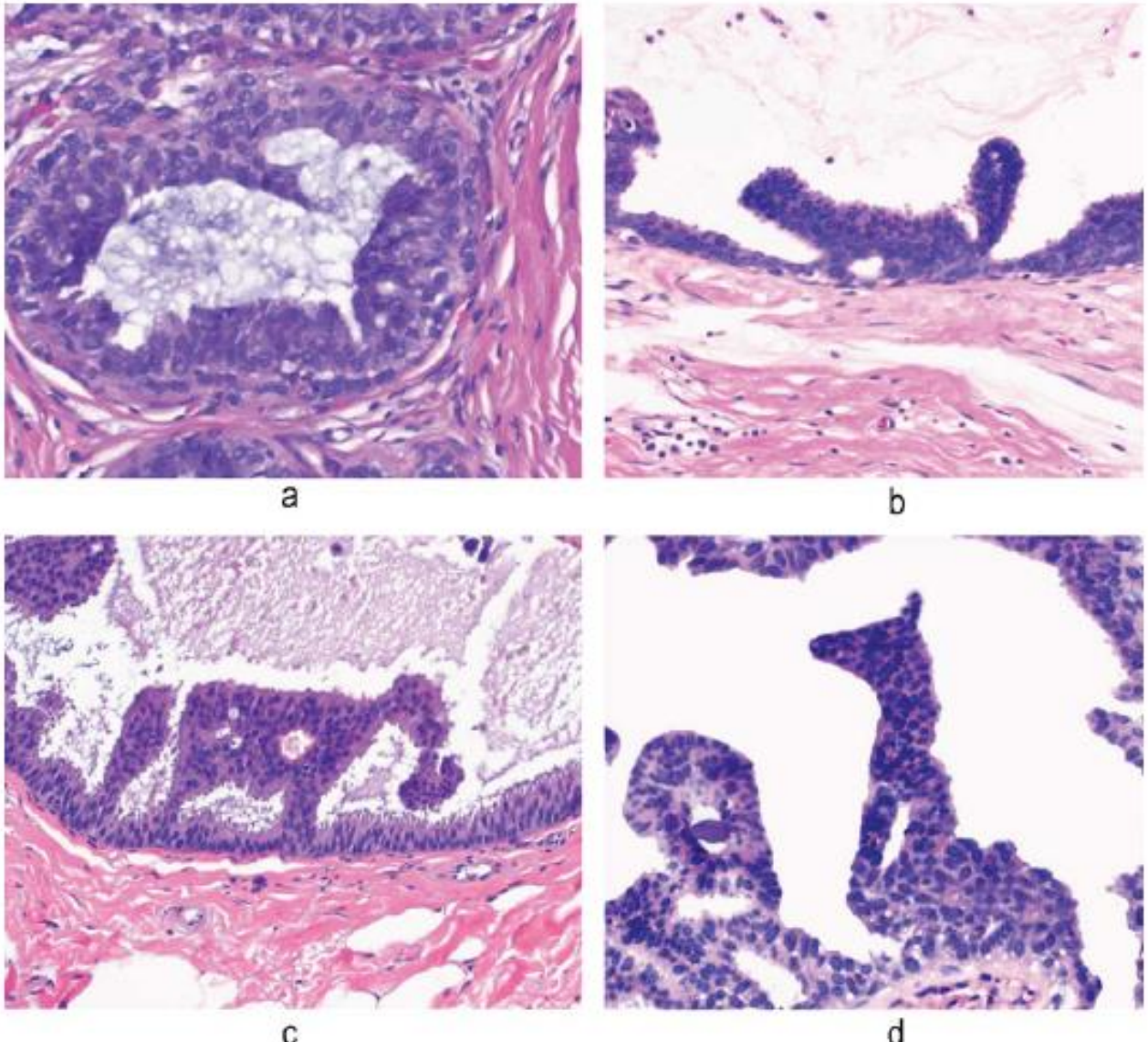






Fauna-form changes in the breast

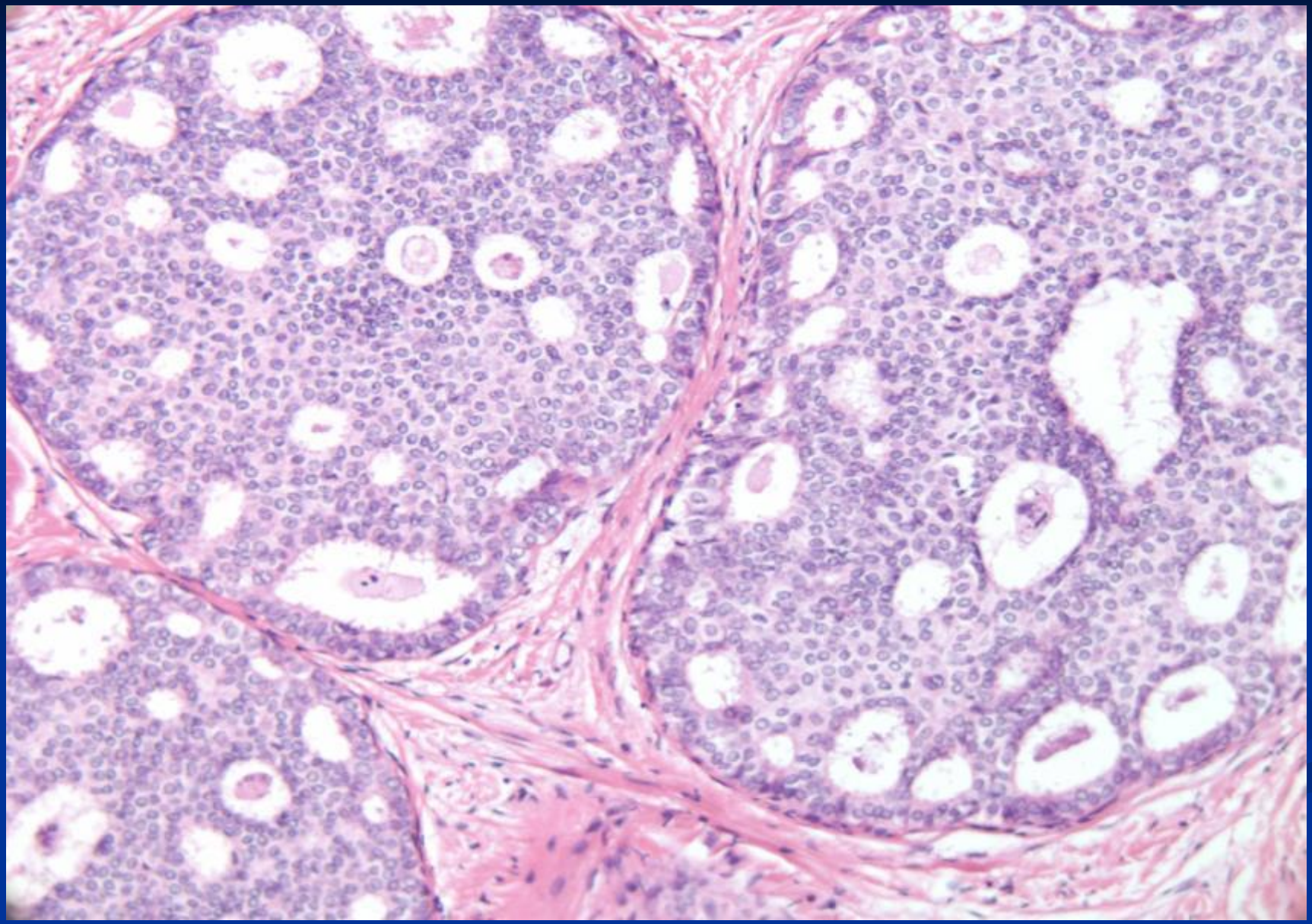
Shamonki et al Am J Surg Pathol 2006



ADH vs DCIS

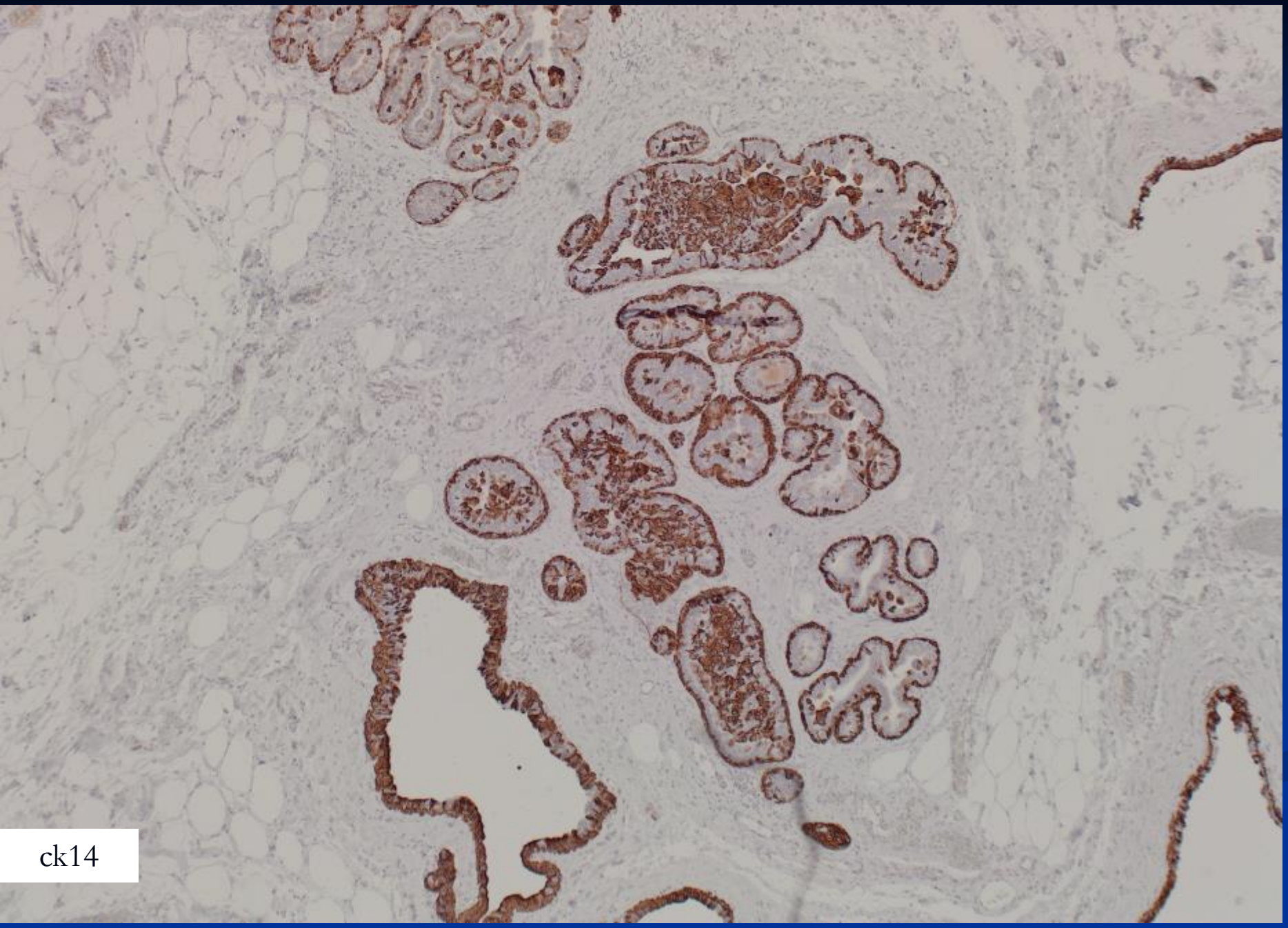
- Extent of atypia: 2mm or 2 fully involved ductal spaces = DCIS (NOT FOR HIGH GRADE LESIONS)

- Atypia in papillomas: 3mm

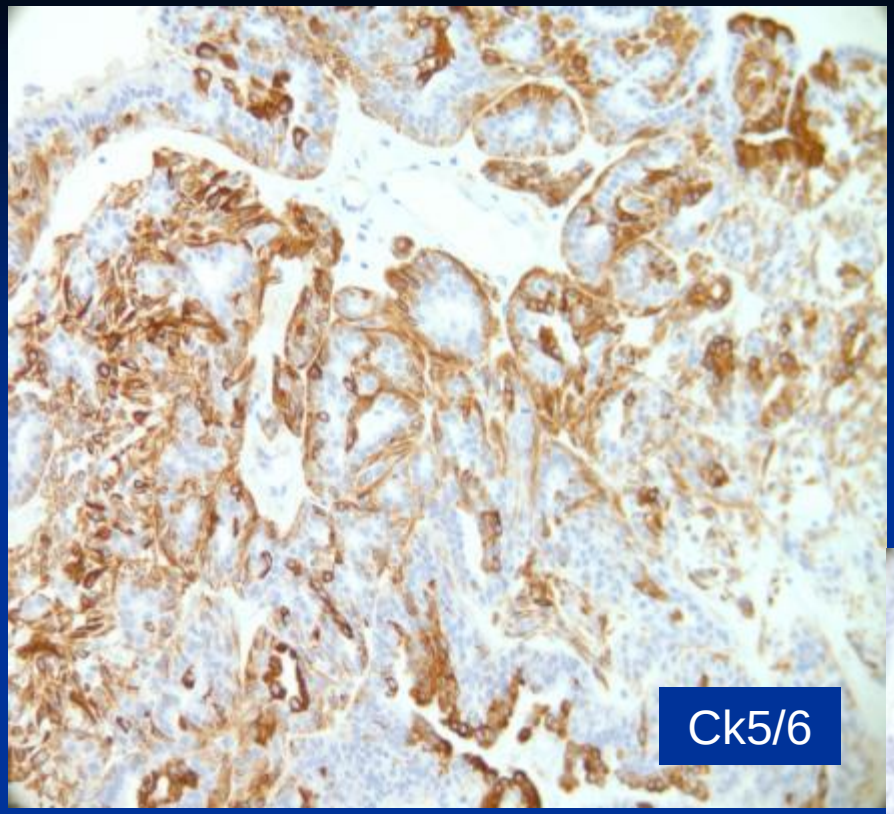


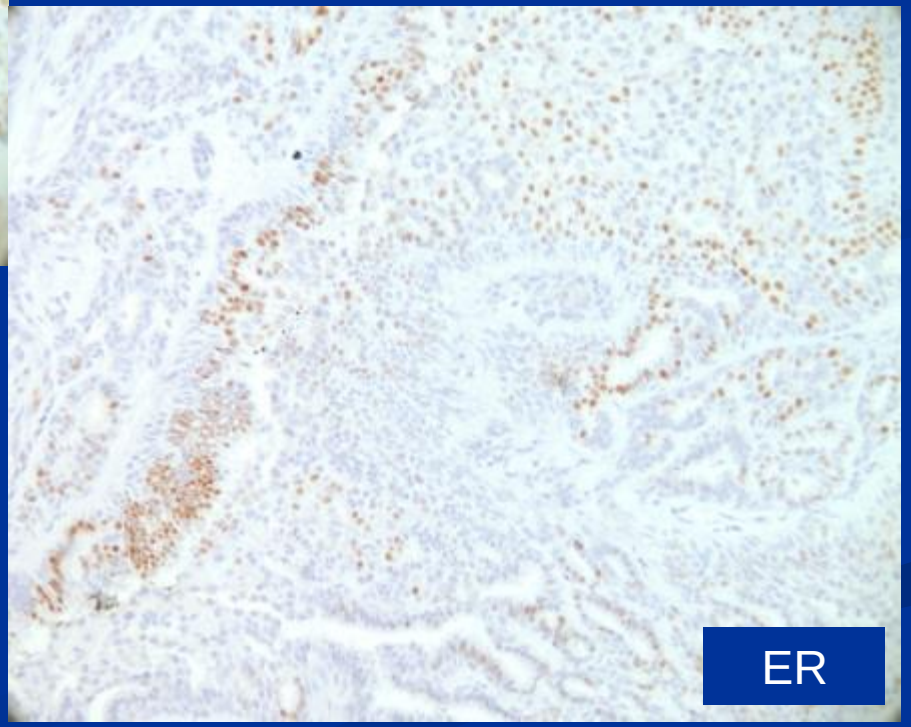
Useful Immunohistochemistry

	Hyperplasia	ADH/DCIS
CK5	mixed	Negative
ER	Patchy positive	Uniformly positive

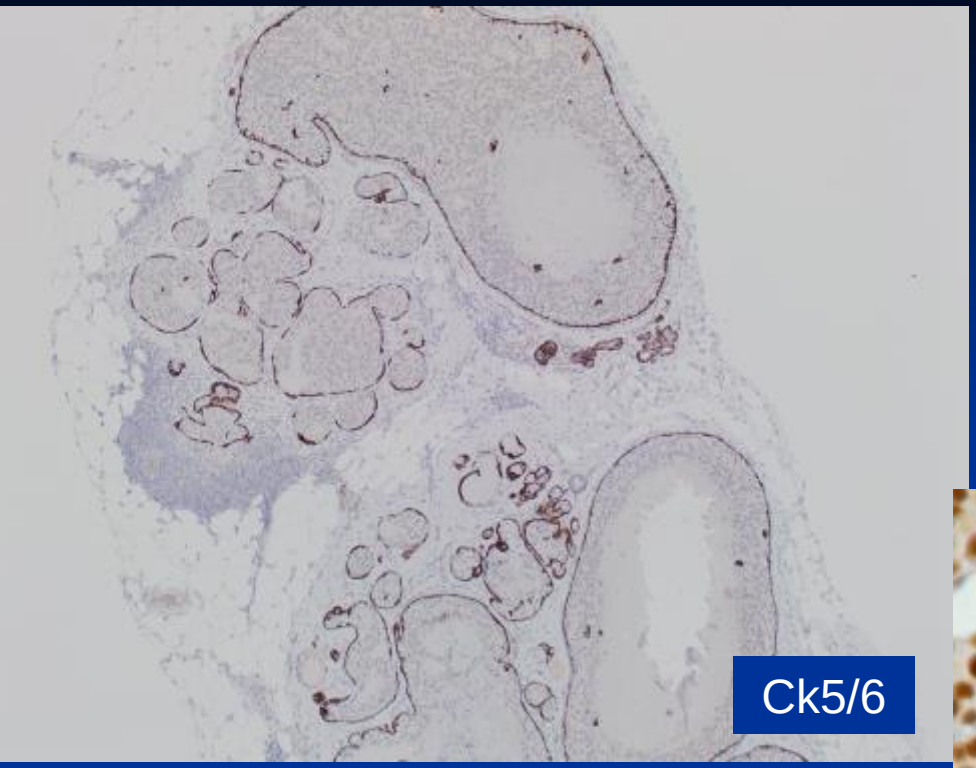


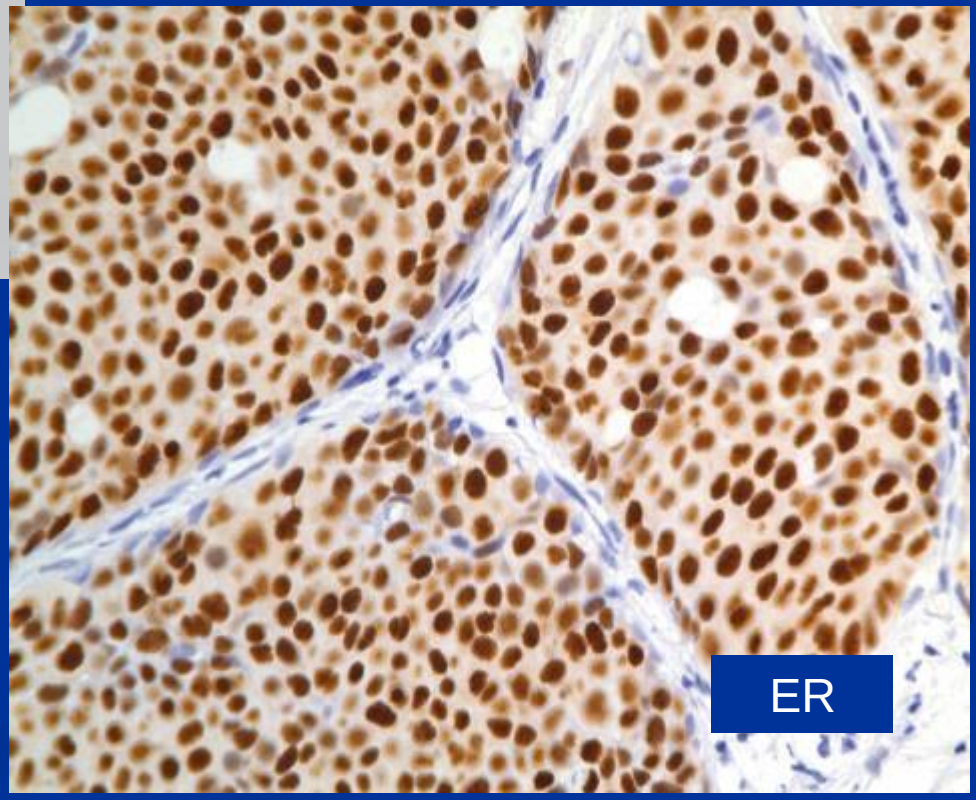
ck14

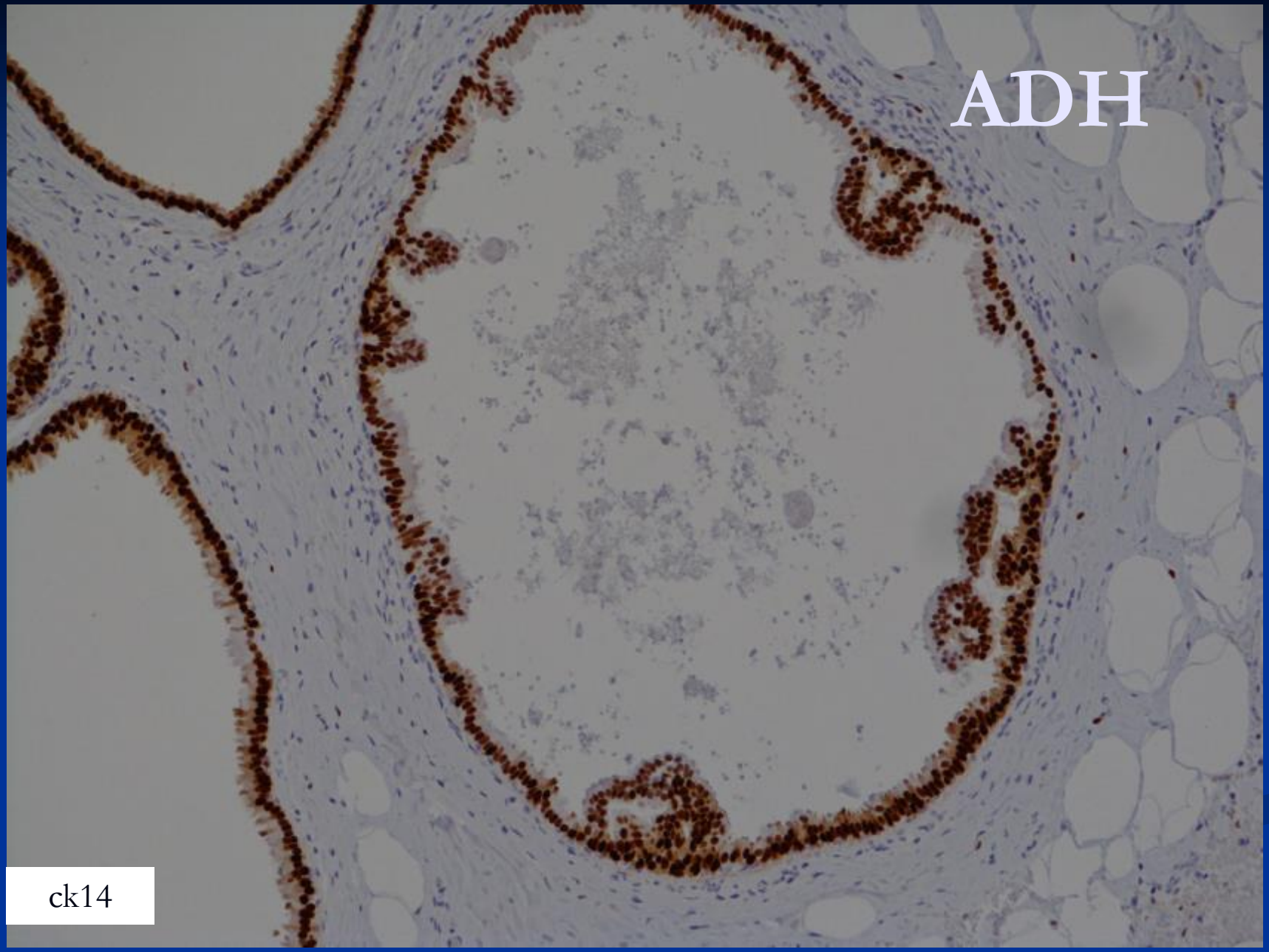

Ck5/6

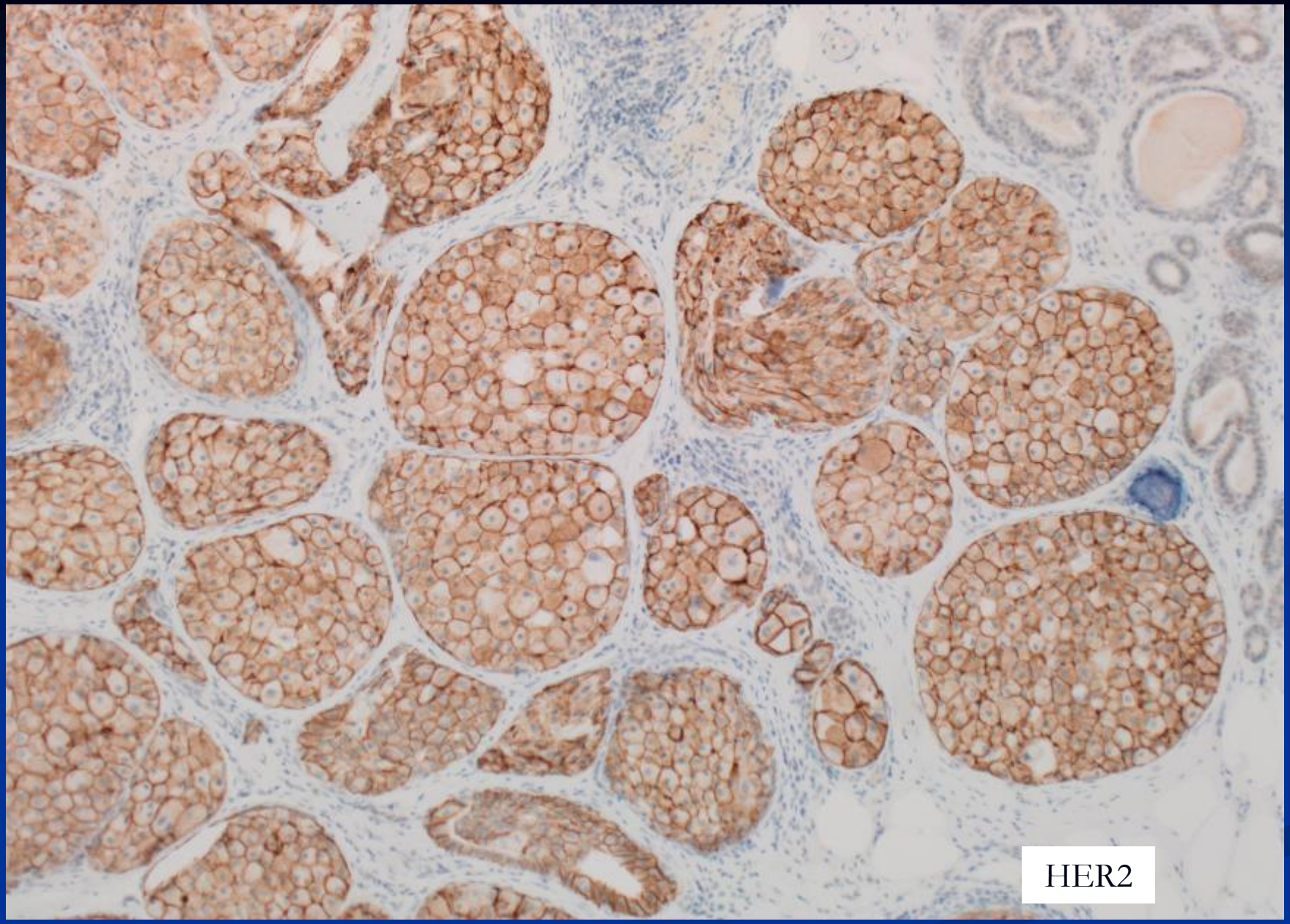

ER

DCIS






ADH
ck14

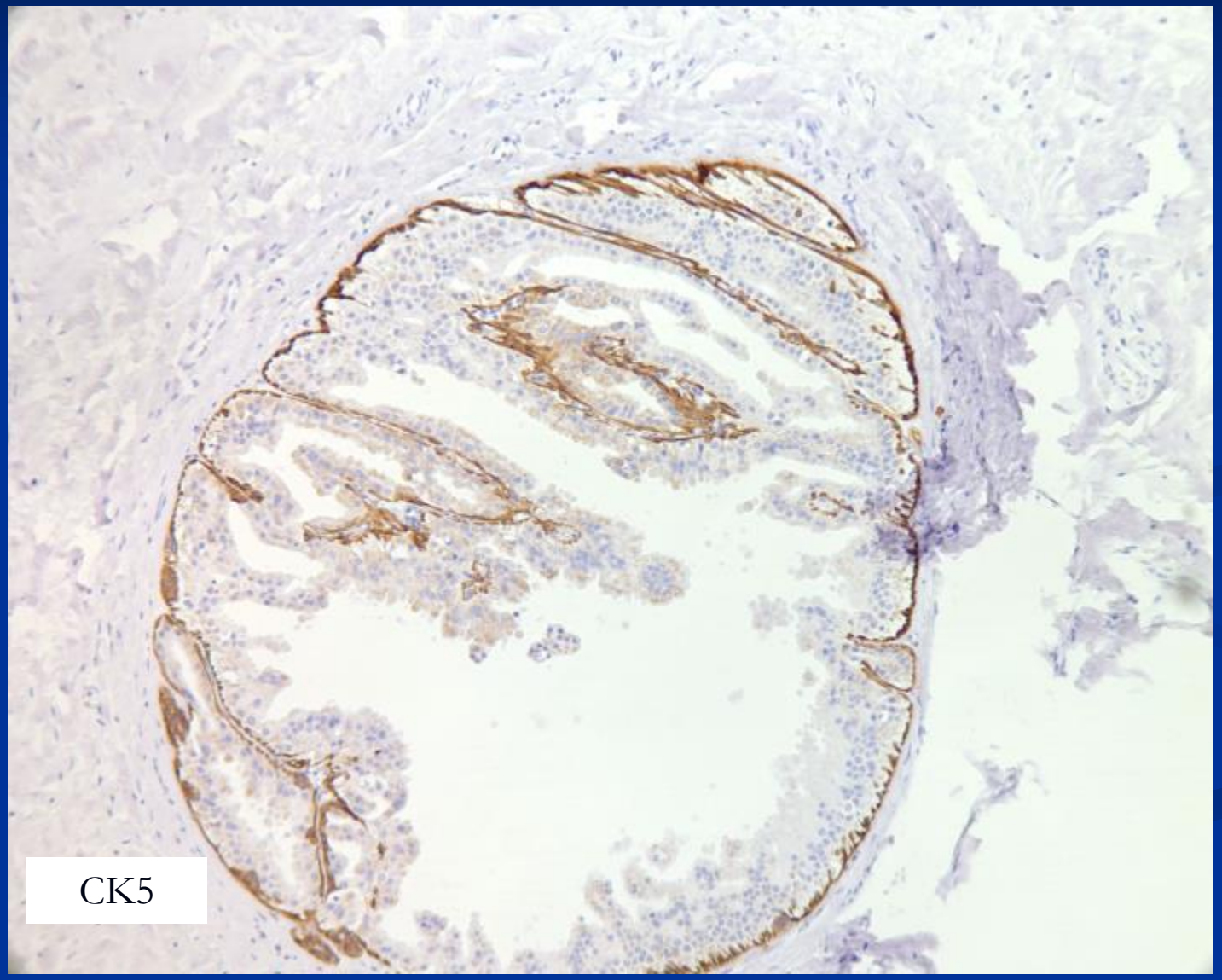


HER2 IHC can be helpful in confirming the diagnosis of DCIS

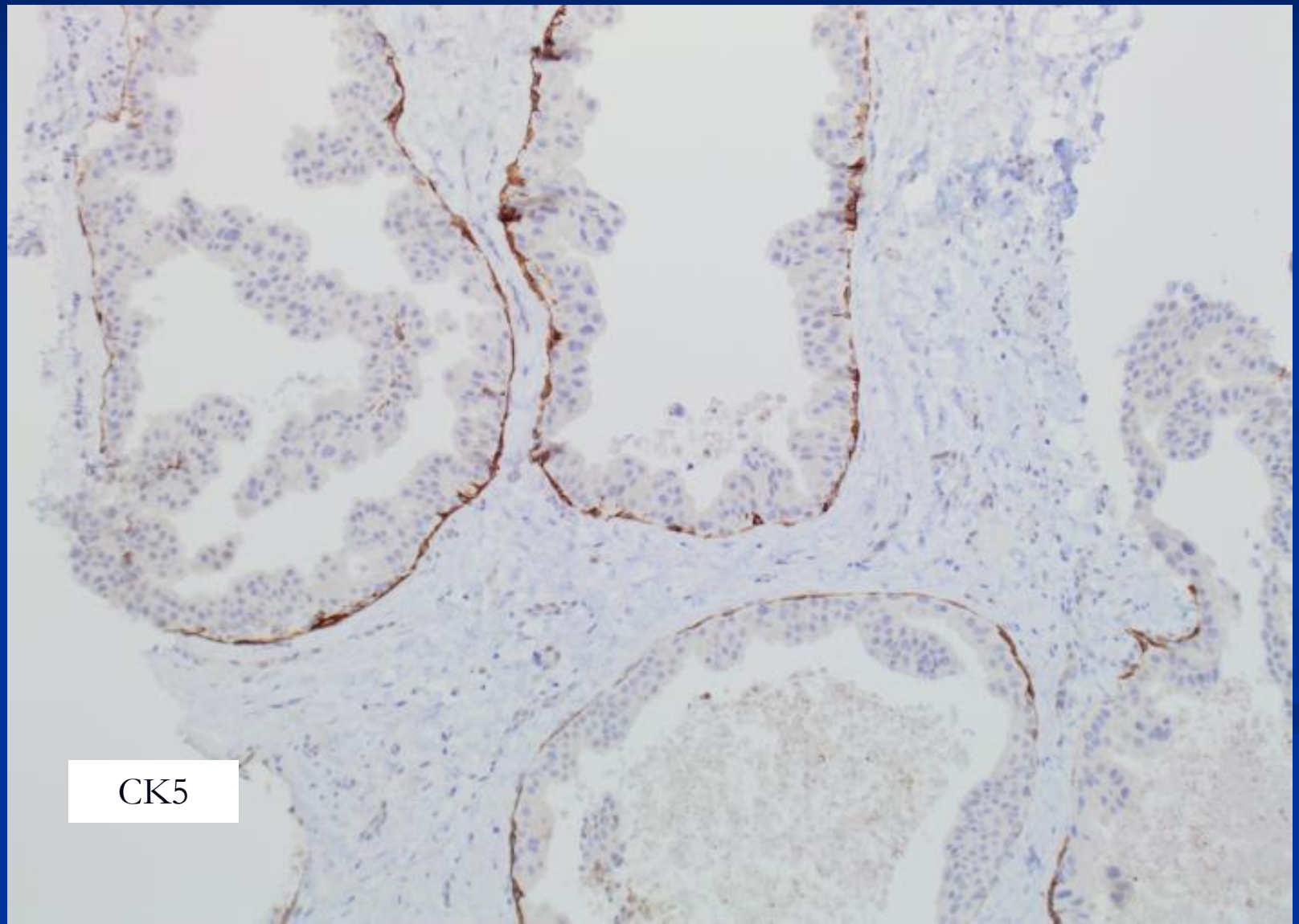
IHC Pitfalls

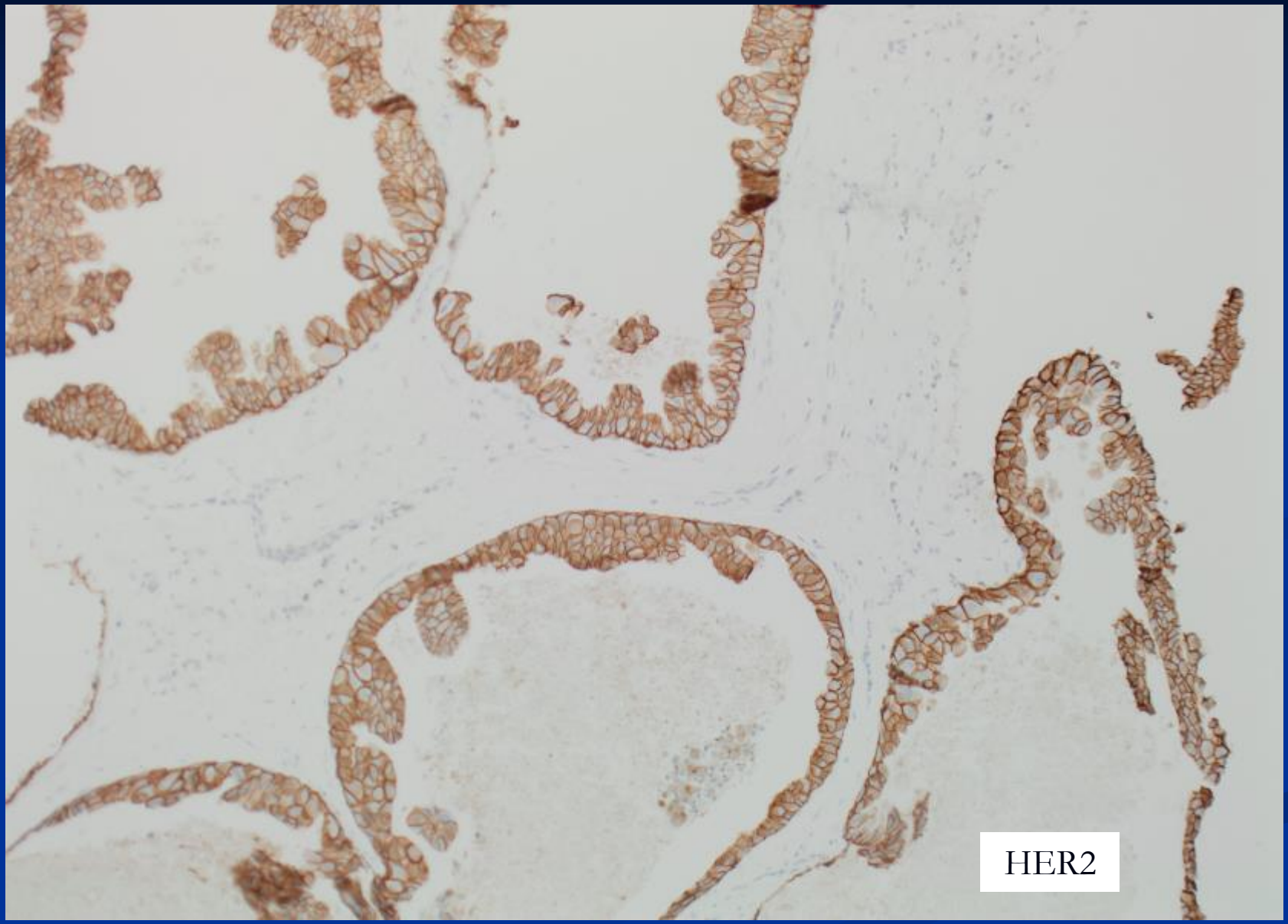
1. Apocrine lesions

Apocrine metaplasia

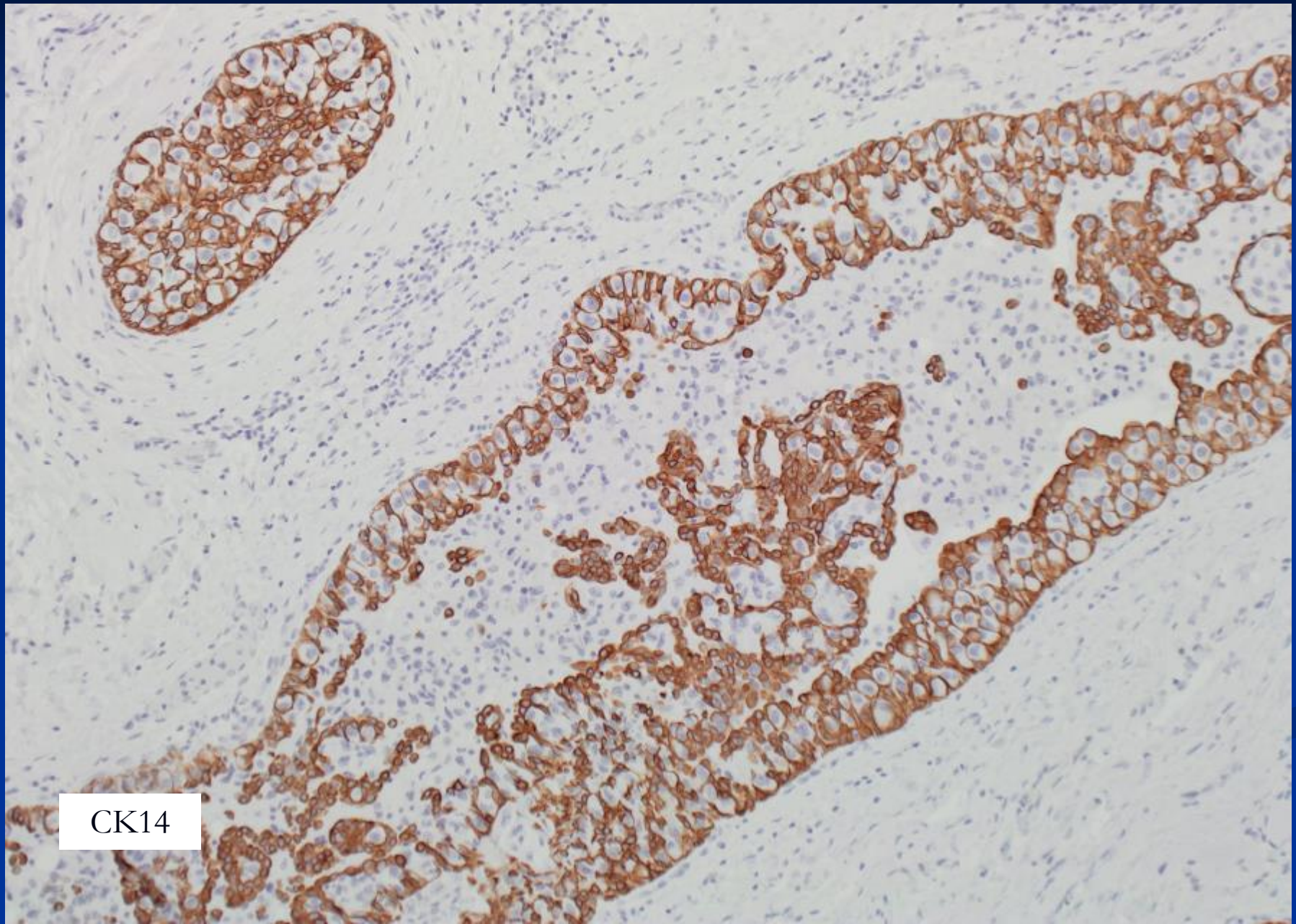


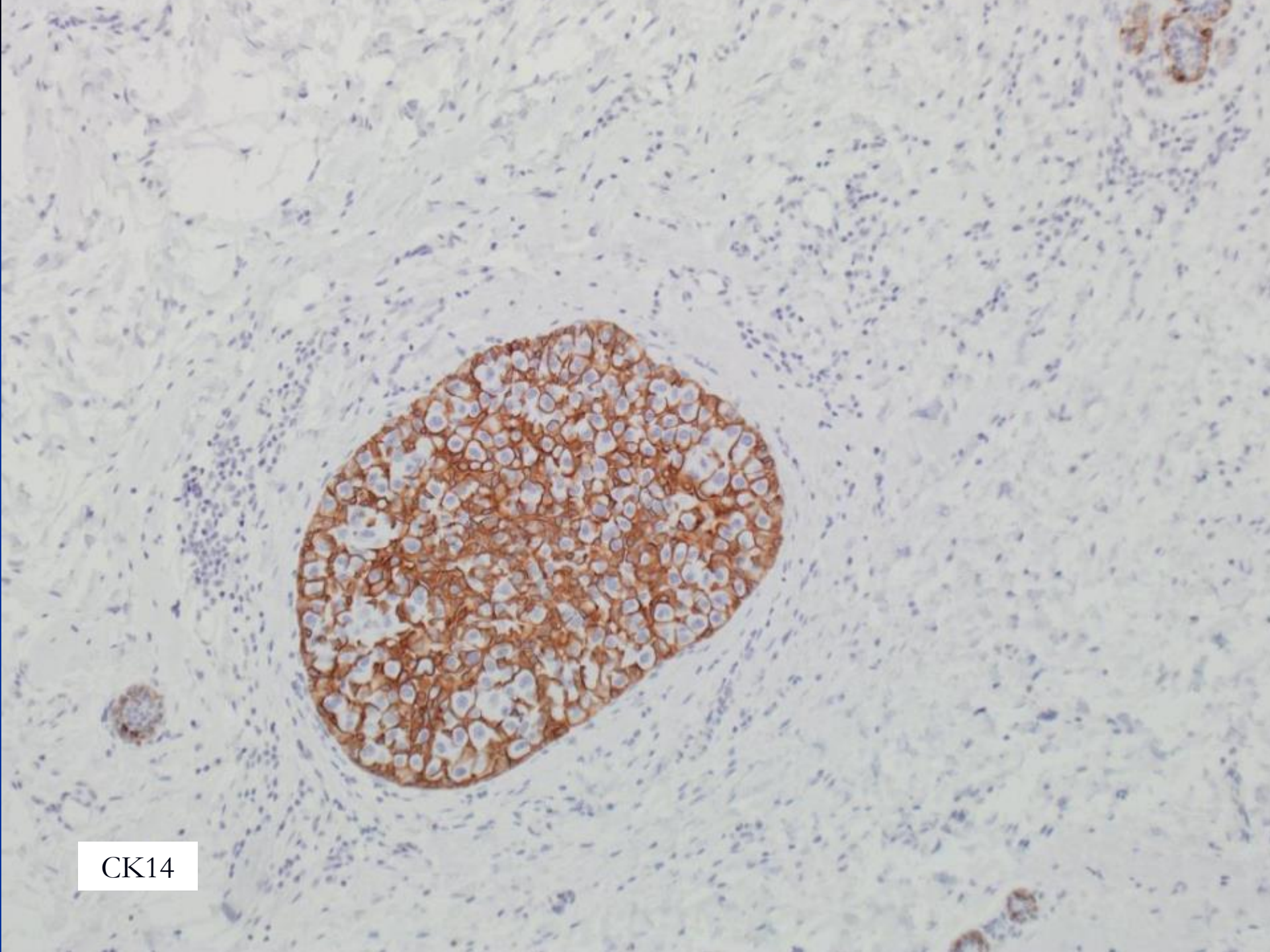
Atypical apocrine proliferation



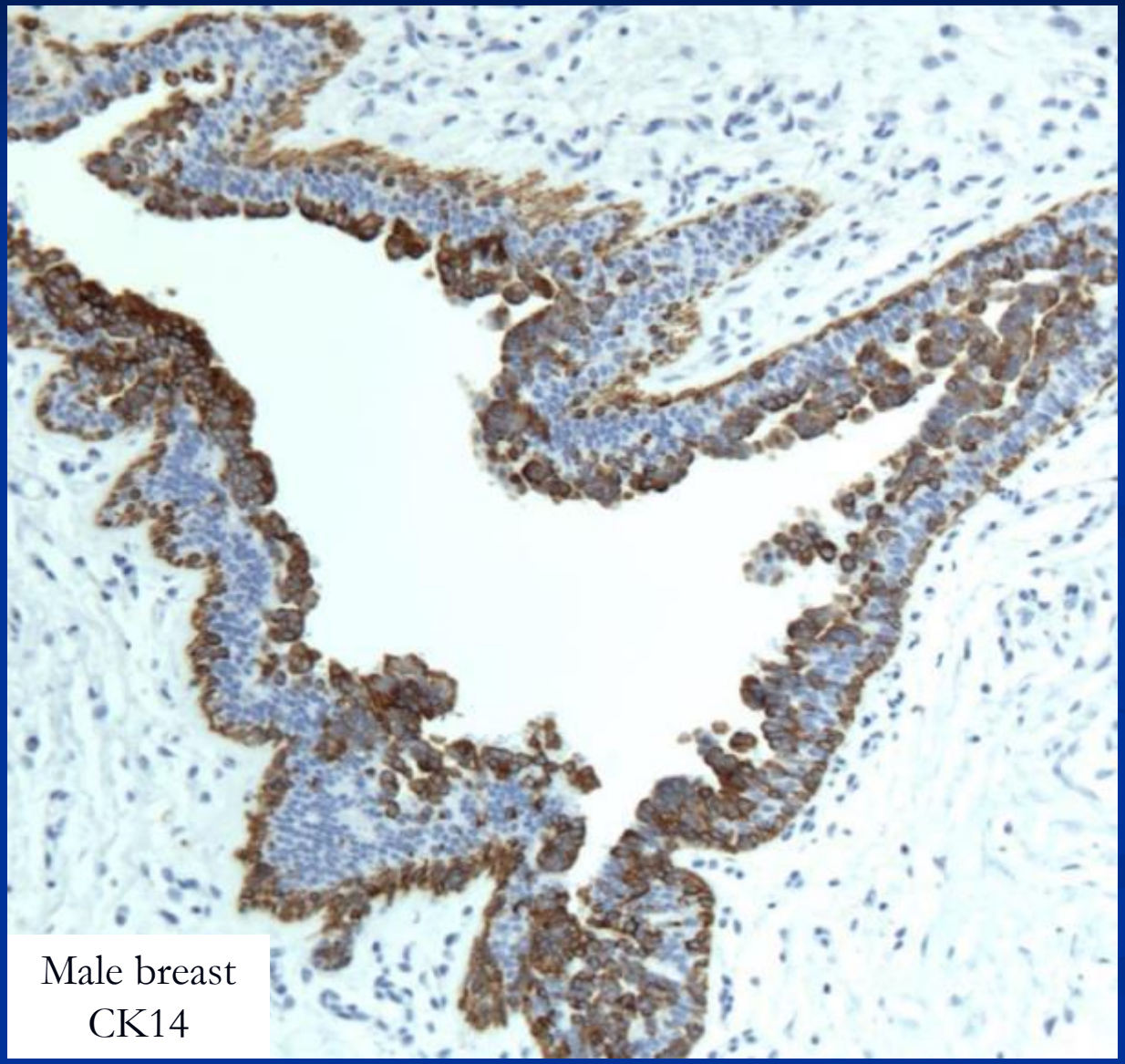

HER2

2. Basal phenotype DCIS




CK14

3. Hyperplasia in the male breast



Male breast
CK14

Kornegoor et al Am J Surg Pathol 2012

Table 1 κ Values for overall diagnosis (all participants)

Circulation group	Benign	Atypical hyperplasia	In situ/micro-invasive	Invasive
No of cases				
19 902–20 002	60	5	62	125
20 011–20 141	112	6	36	170
Total	172	11	98	295
Circulations				
19 902–20 002	0.79	0.18	0.76	0.88
20 011–20 021	0.83	0.15	0.83	0.96
20 022–20 032	0.79	0.18	0.75	0.90
20 041–20 051	0.70	0.20	0.65	0.90
20 052–200 62	0.87	0.19	0.78	0.96
20 071–20 081	0.82	0.10	0.70	0.92
20 082–20 092	0.76	0.17	0.23	0.89
20 101–20 111	0.83	0.14	0.44	0.92
20 112–20 122	0.79	0.18	0.75	0.90
20 131–20 141	0.81	0.13	0.83	0.95
20 011–20 141	0.81	0.17	0.72	0.92
Overall				
19 902–20 141	0.80	0.17*	0.75	0.91

Rakha et al 2016

Flat epithelial atypia

Columnar cell lesions

- *Columnar cell change (without atypia):* columnar cell change/columnar cell hyperplasia
- ***Flat epithelial atypia***

If high grade nuclei = flat DCIS

FEA: WHO 2012 Definition

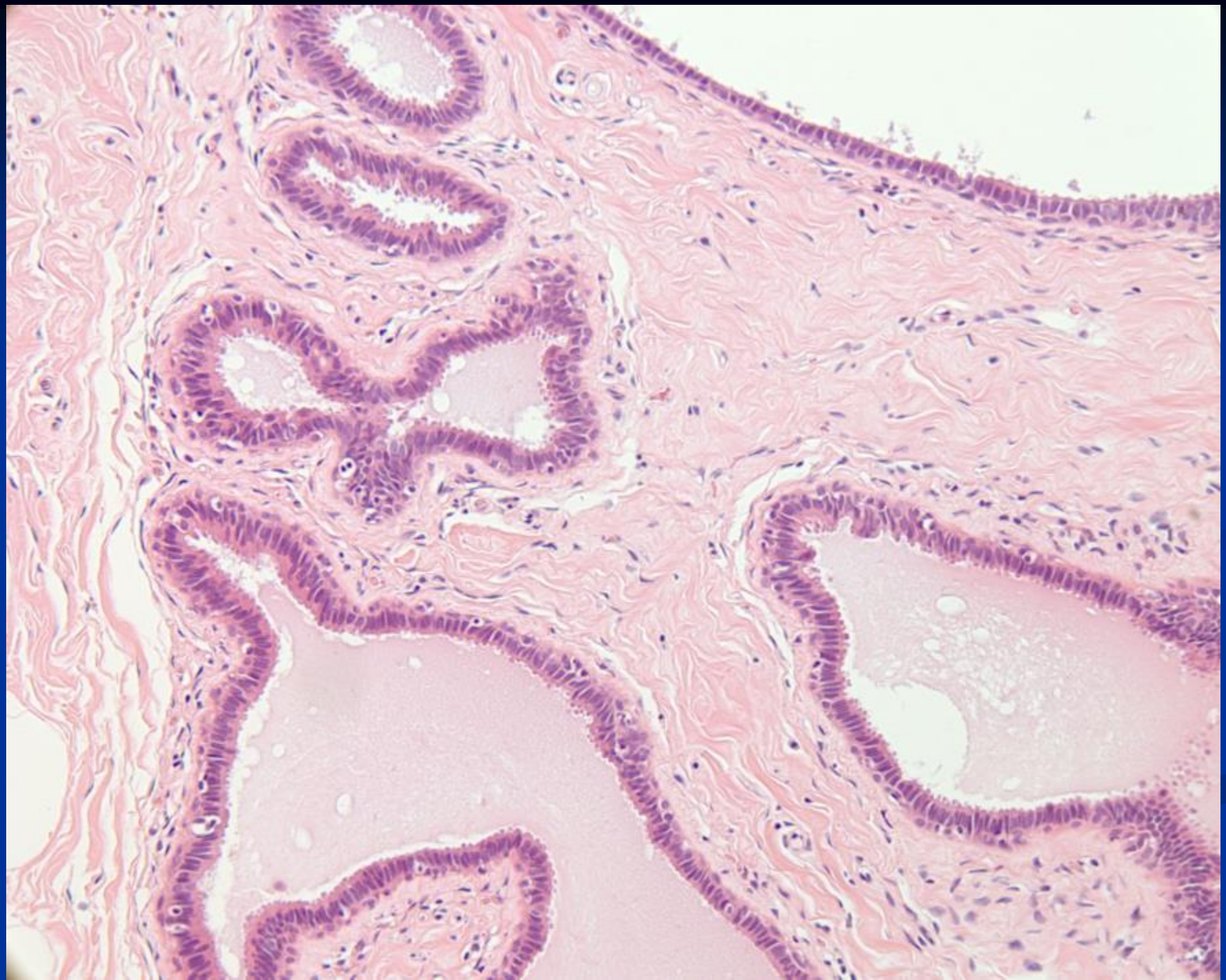
A neoplastic proliferation of TDLUs characterised by replacement of the native epithelial cells by one to several layers of a single epithelial cell type showing low grade (monomorphic) cytological atypia

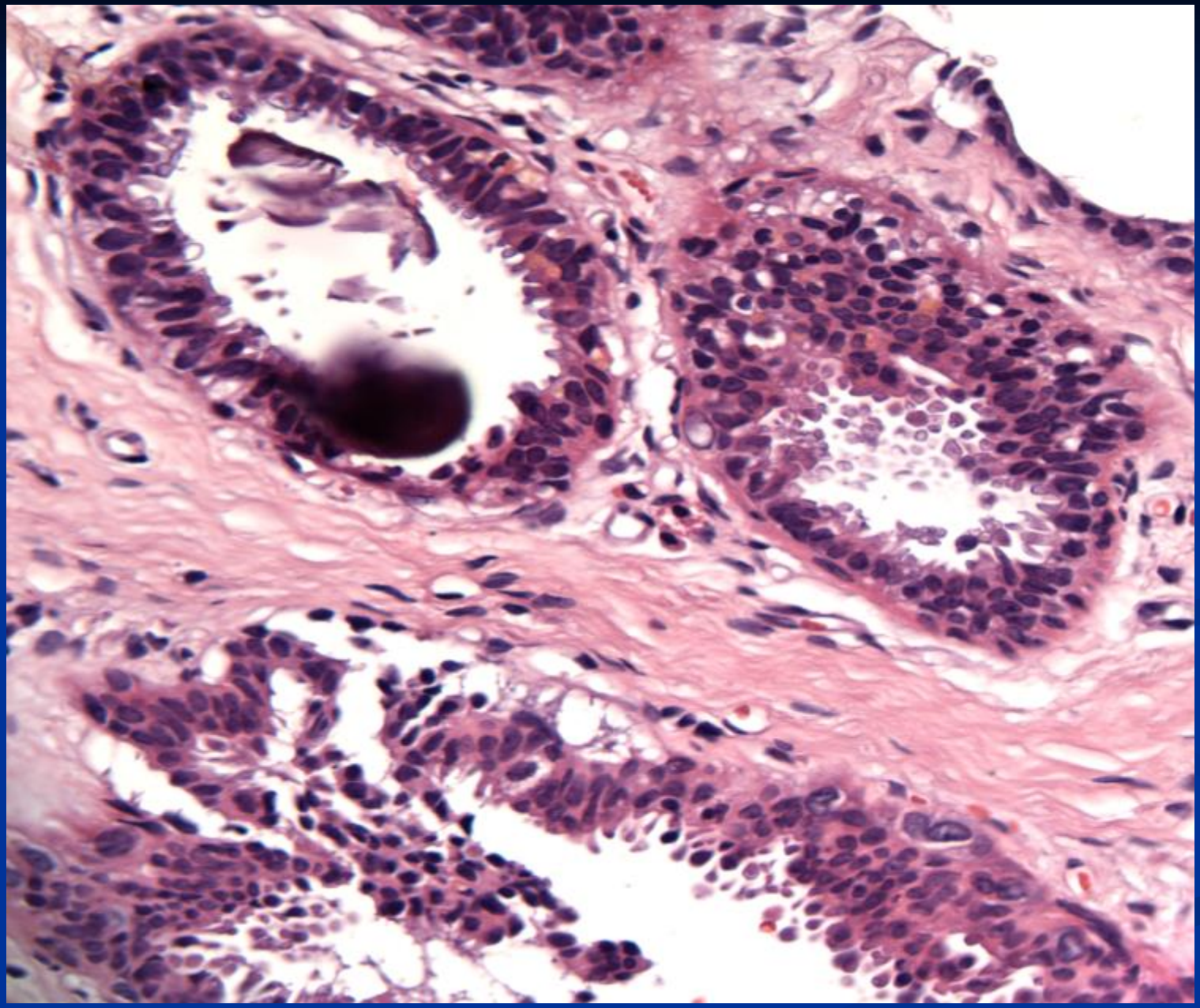
Previous terminology of FEA

- Atypical lobule type A
- Atypical columnar cell metaplasia
- Atypical cystic lobules
- Atypical cystic duct
- Hypersecretory hyperplasia with atypia
- Columnar cell change with atypia
- DIN (DIN1a = FEA)
- Clinging carcinoma (monomorphic type)
- Monomorphic epithelial proliferation

Columnar cell change

- Dilated TDLU (oval/branching)
- Columnar cells with polarity
- Apical snouts
- ±Calcification
- ER positive, CK5 negative

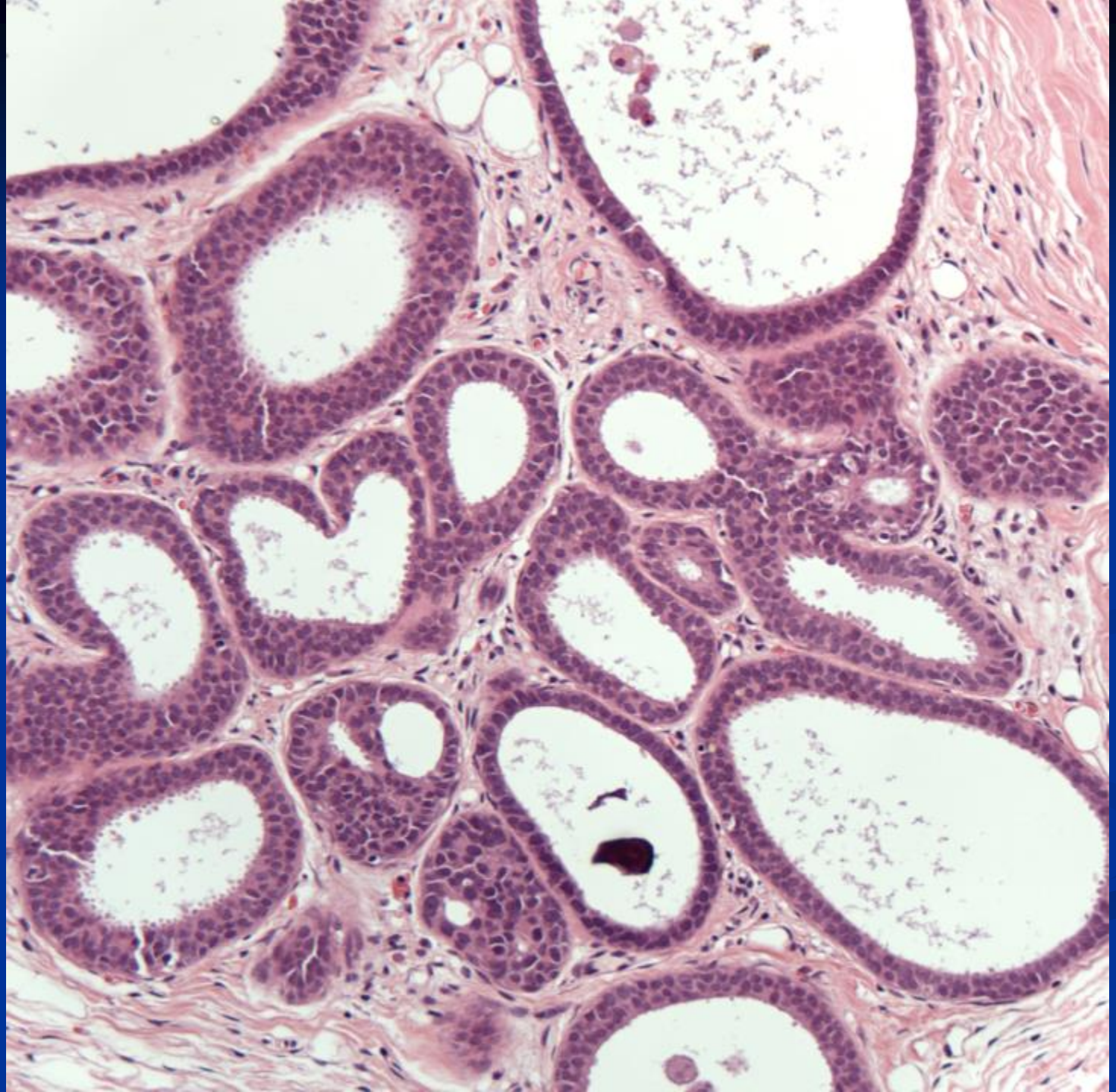


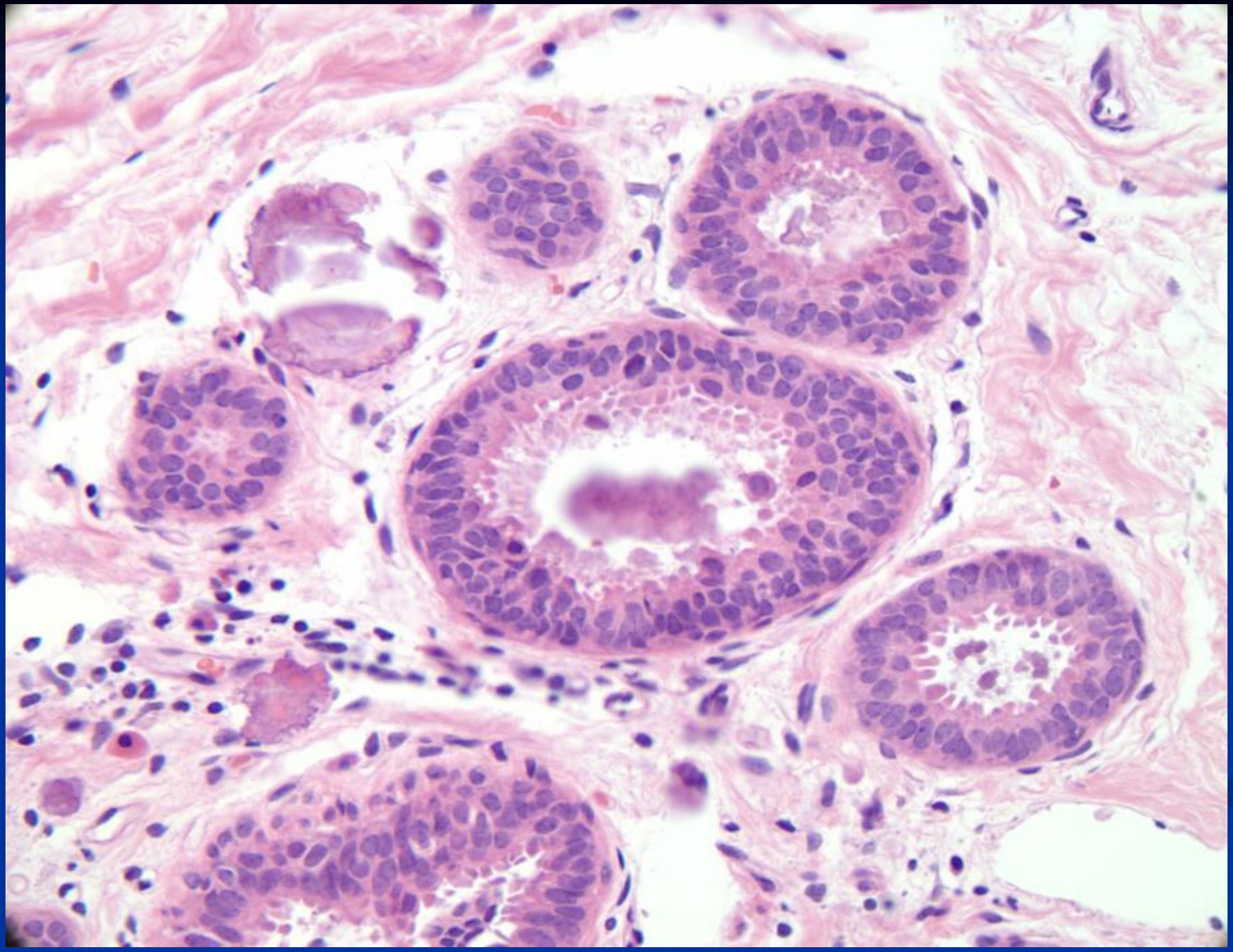


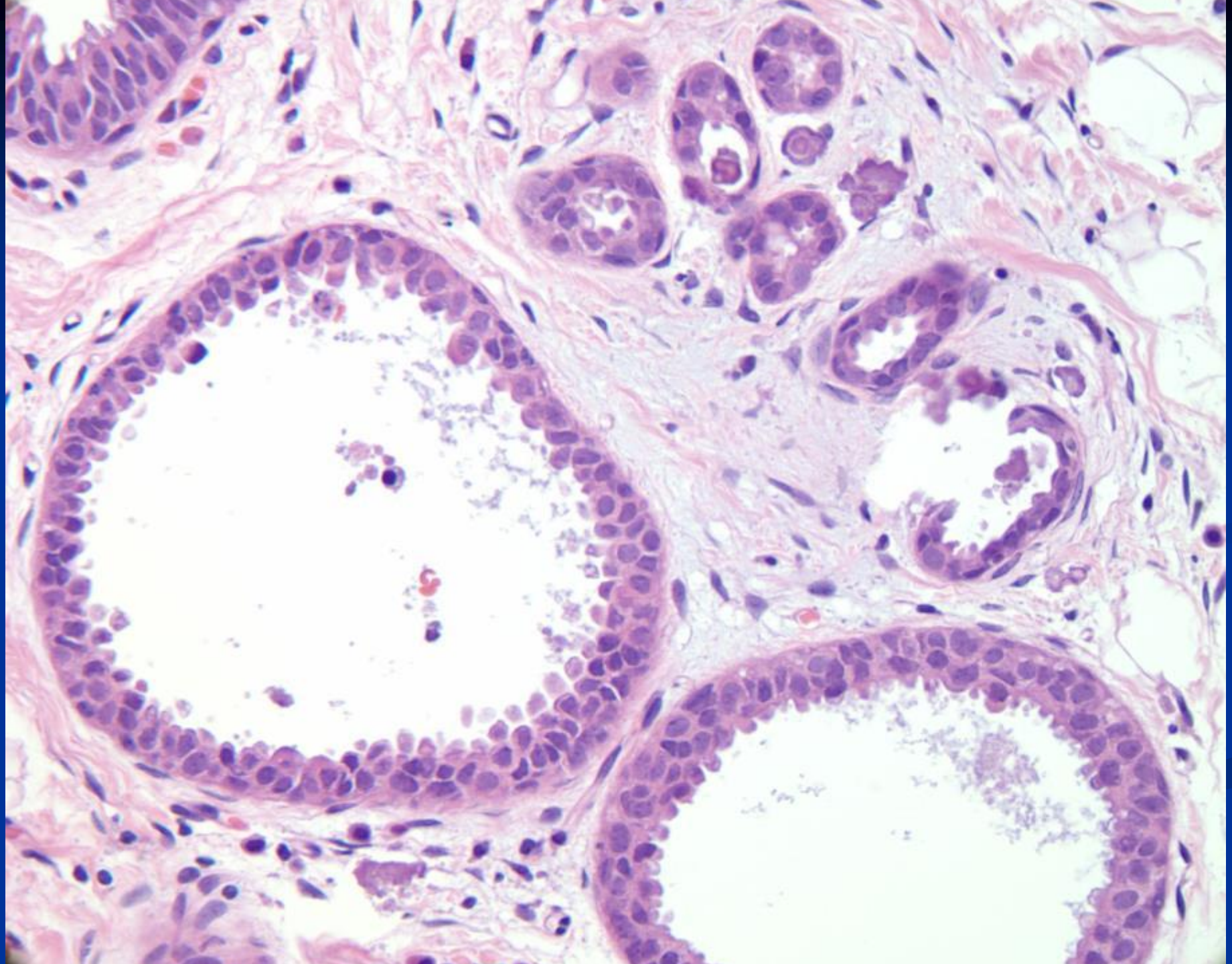
FEA

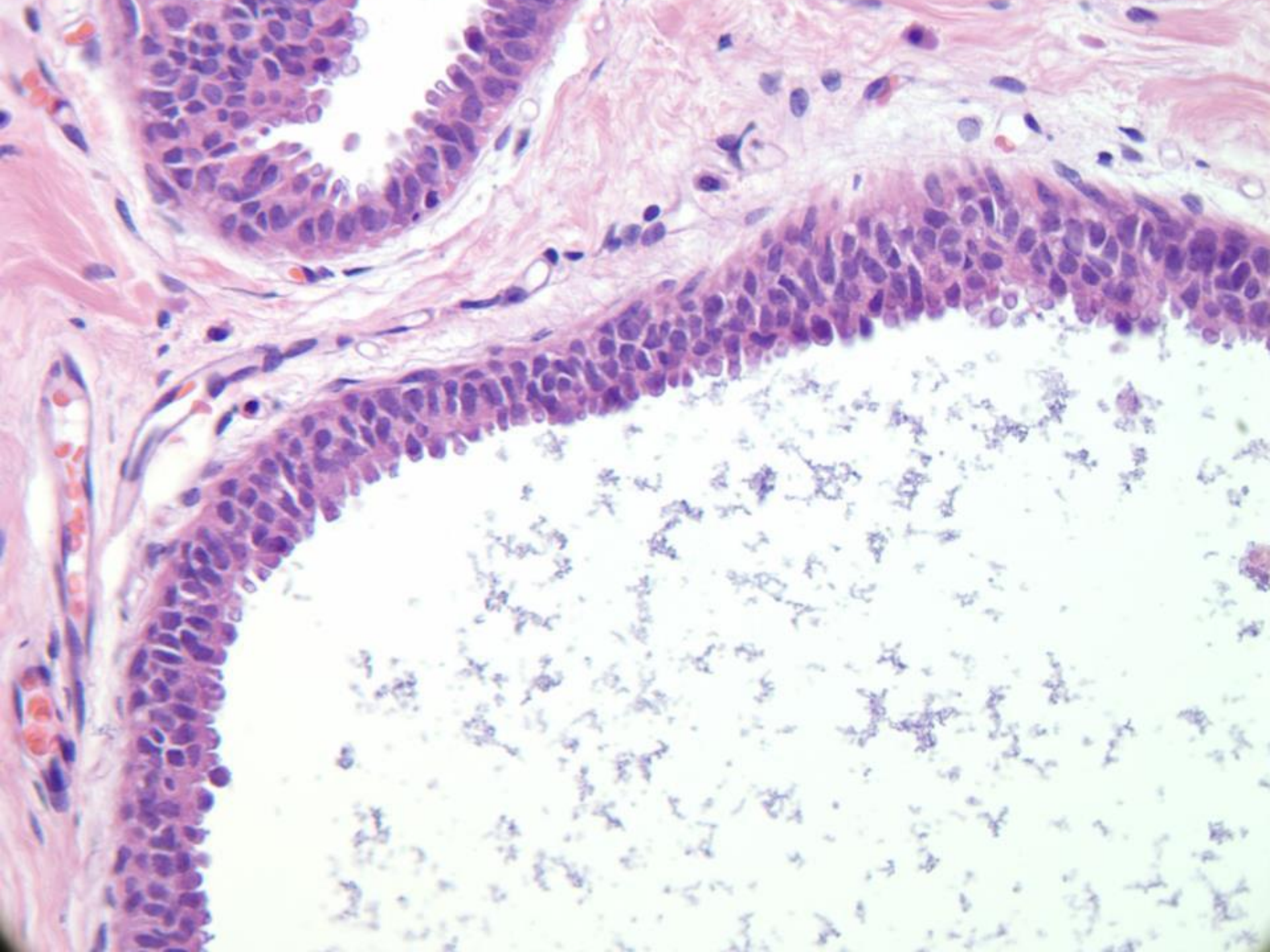
- Dilated TDLU, regular/rounded acini
- Round/oval nuclei
- Monotonous nuclei with loss of polarity
- Cytological atypia, often hyperchromasia
- Usually with apical snouts
- May have small nucleoli
- ER positive, CK5 negative

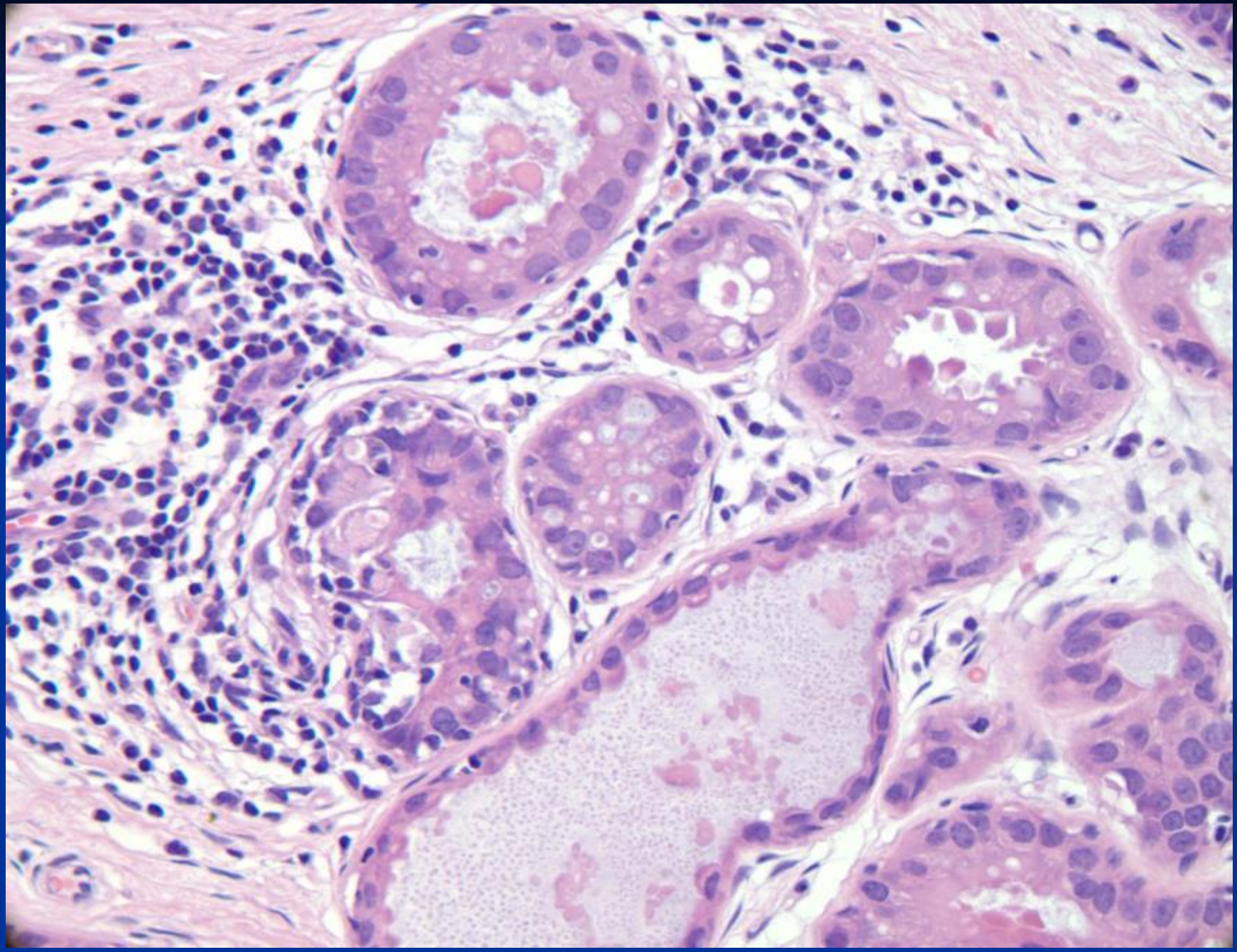
- **No high grade atypia** or complex architecture

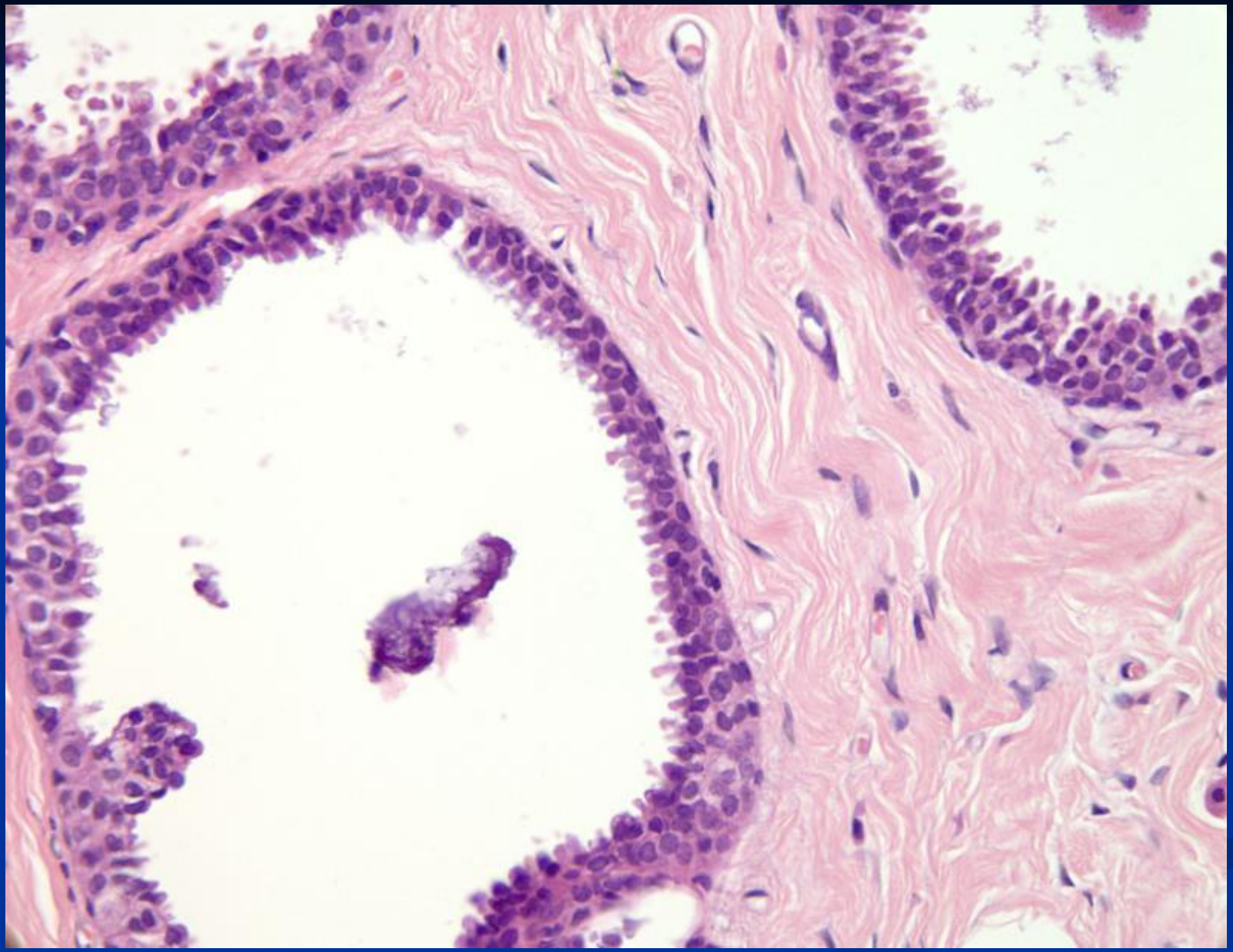


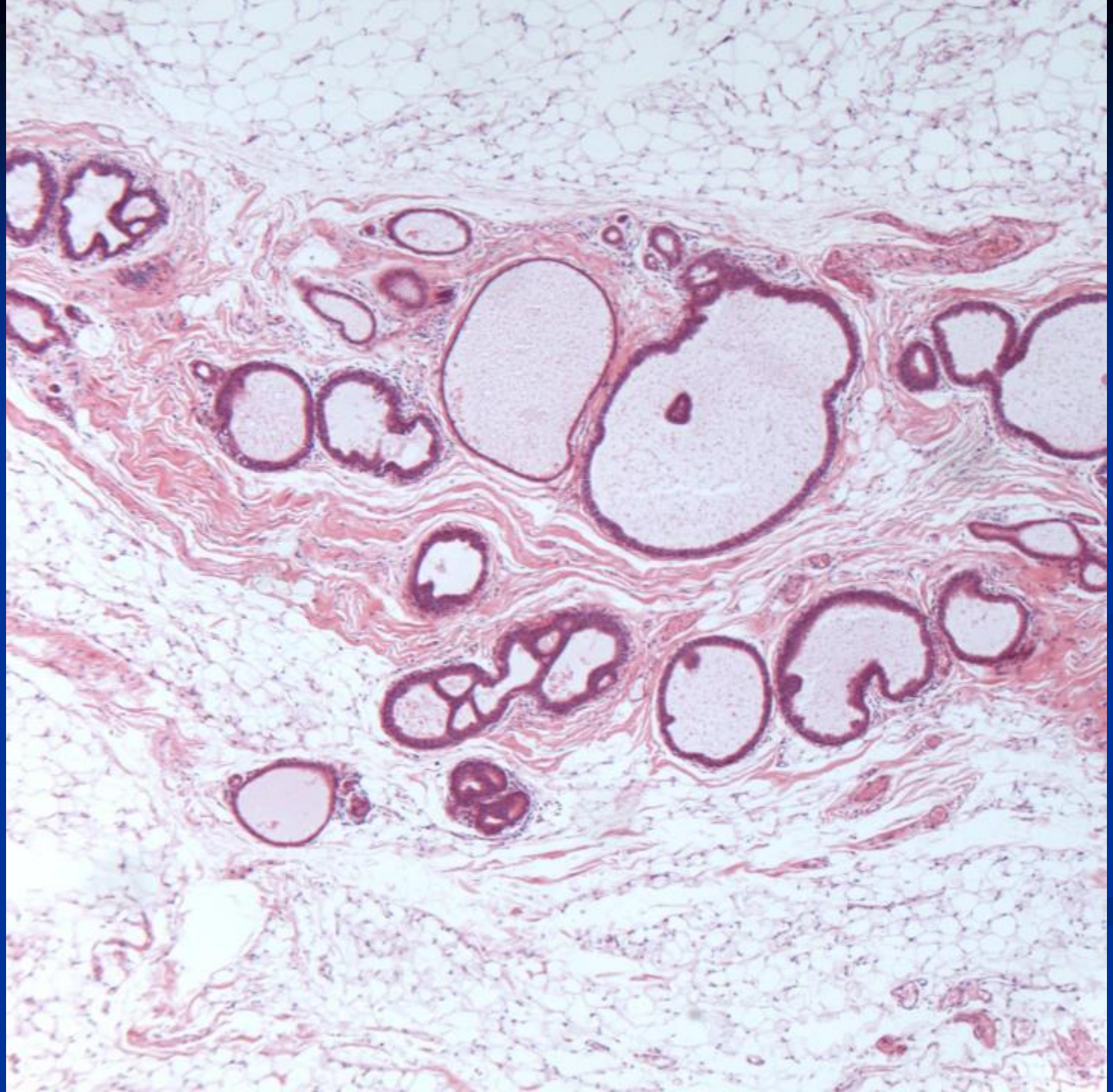


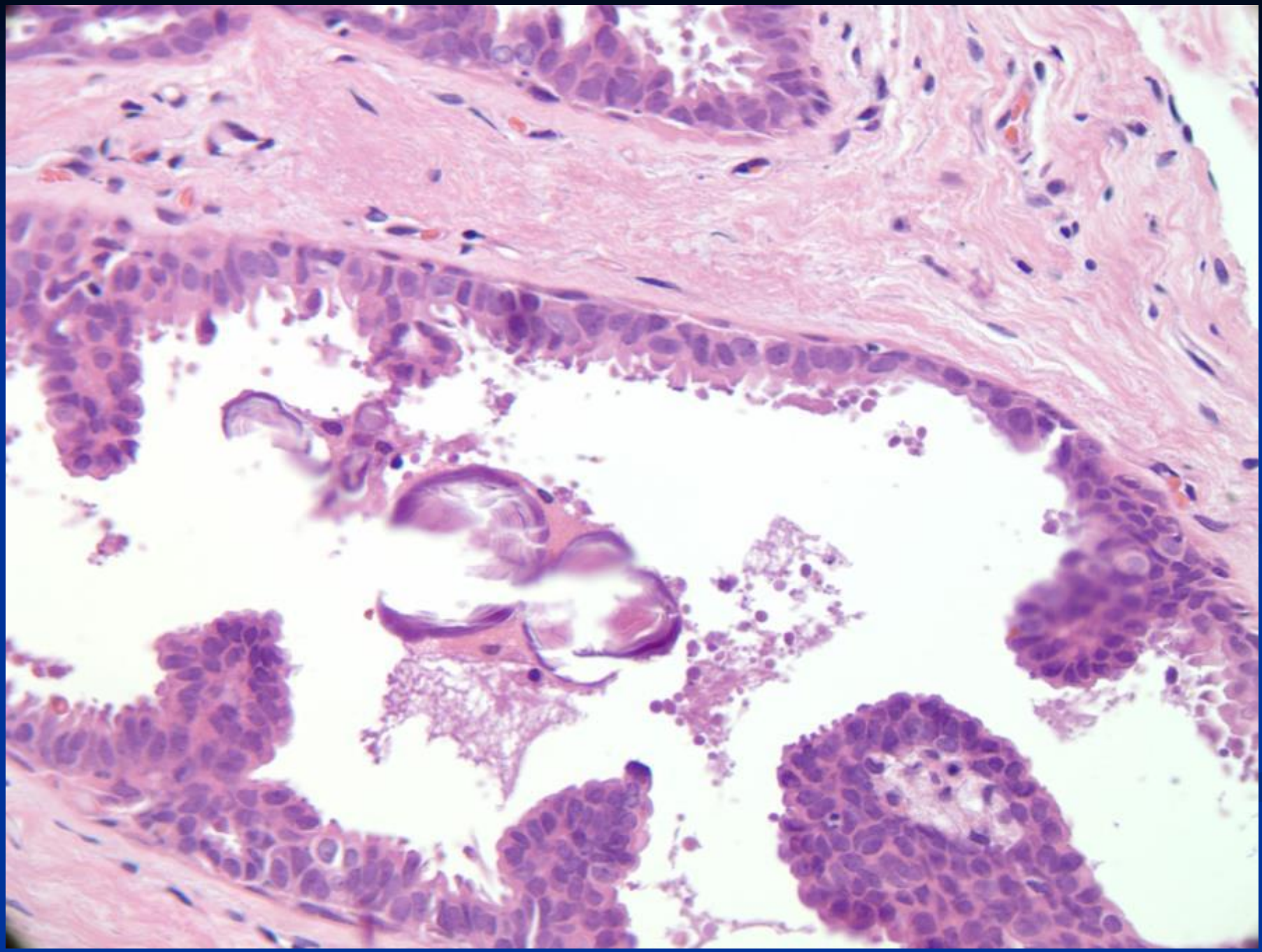


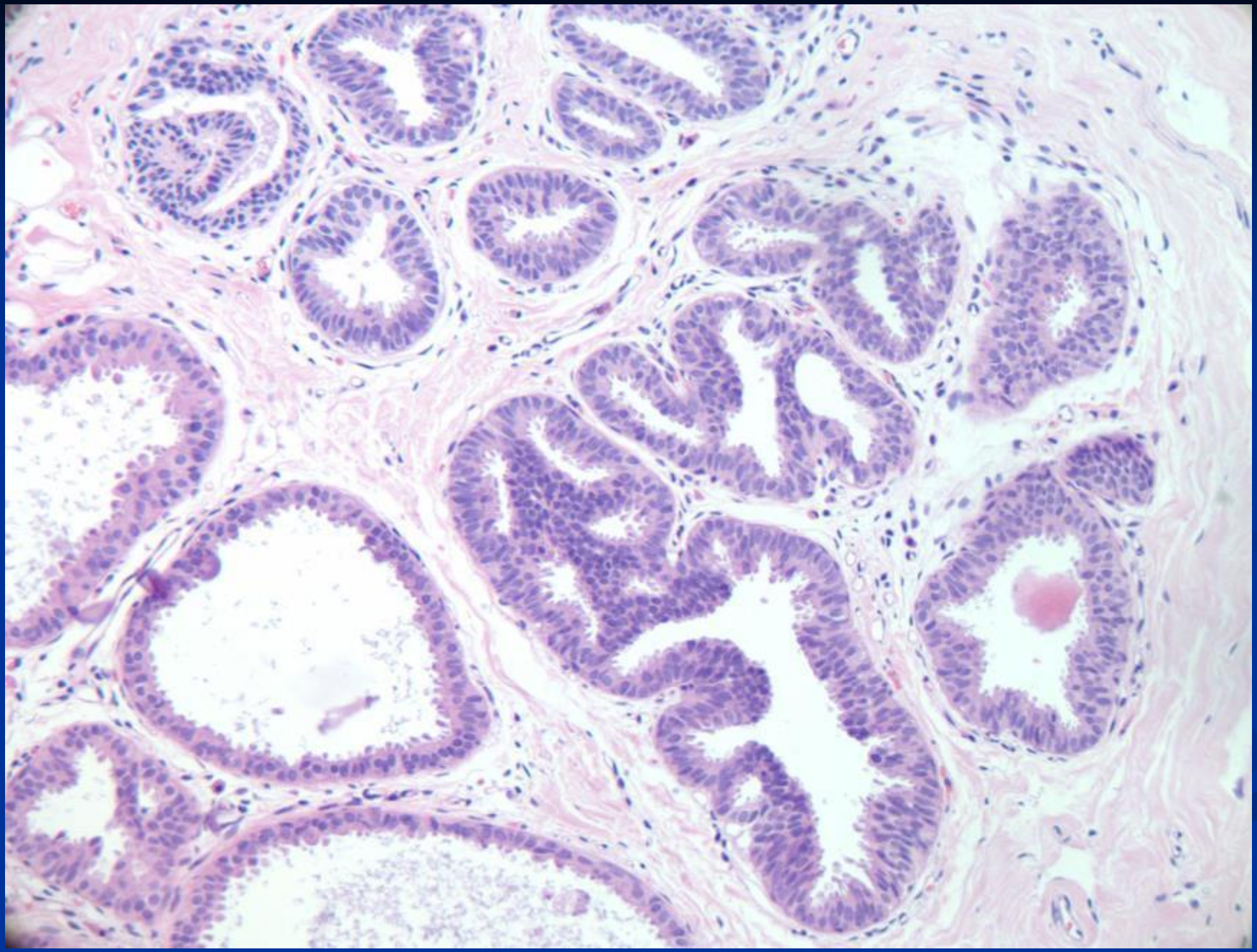










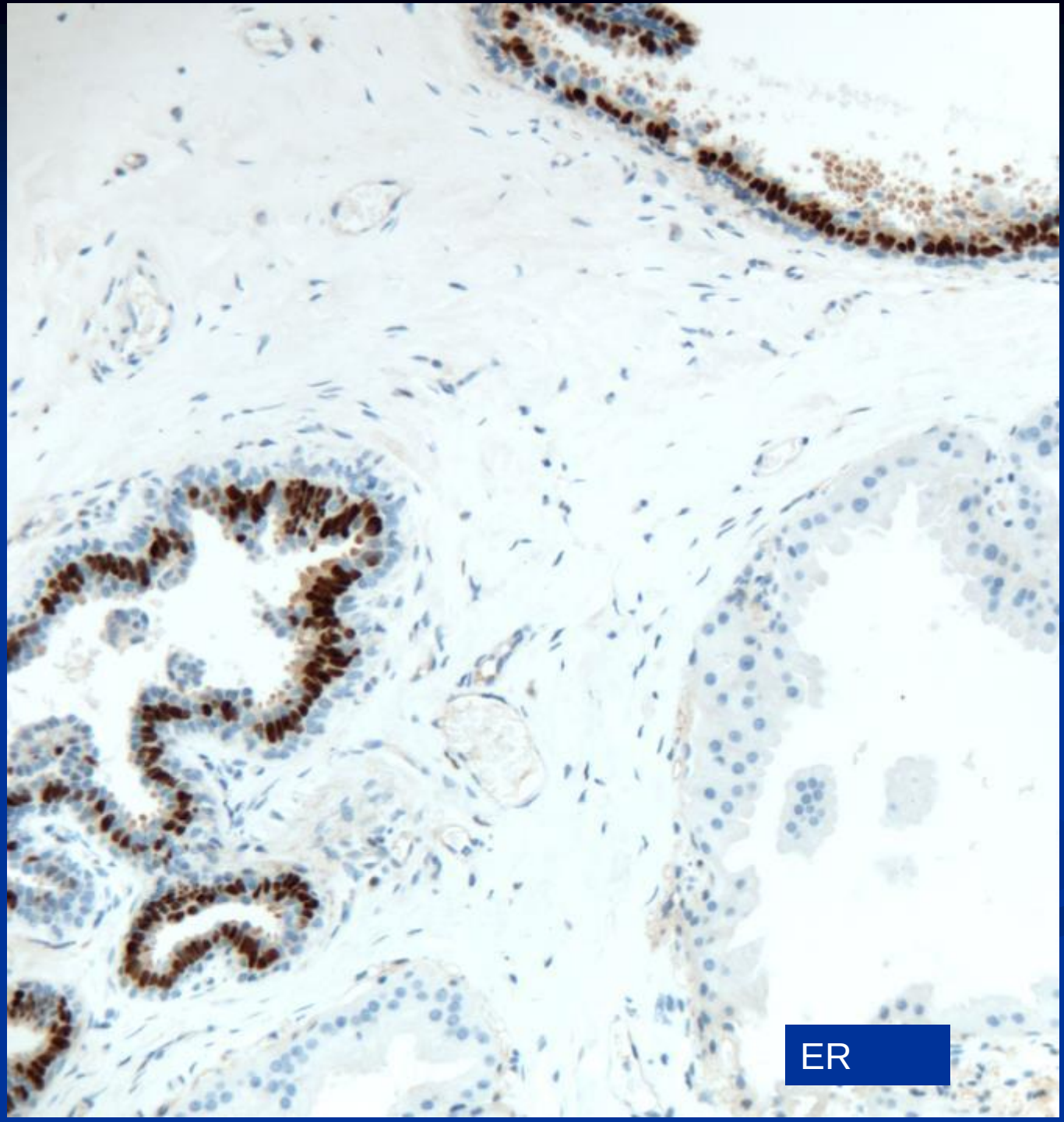


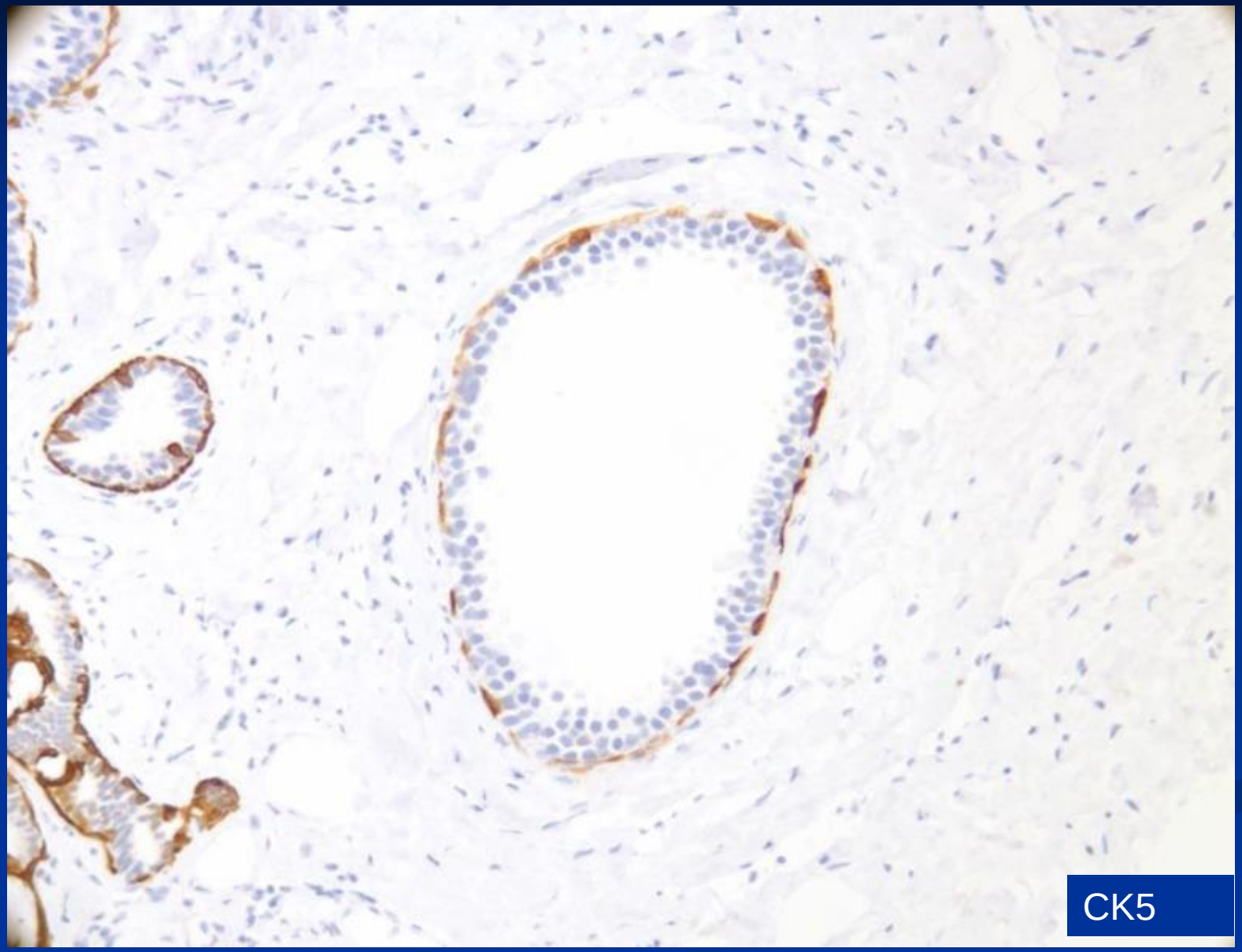
FEA Immunohistochemical profile

- ER, PR +, Bcl2+
- CK5 –
- Her 2 negative

Similar to ADH and low grade DCIS

FEA diagnosis is morphological


ER


CK5

FEA Reproducibility of Diagnosis

- Poor agreement on assessment of images by a mixed group of pathologists

  Tan et al., . Pathological diagnosis of columnar cell lesions of the breast: are there issues of reproducibility? J Clin Pathol 2005;58(7):705-9.

- Excellent agreement among breast pathologists after PowerPoint training session (better for exclusion of atypia)

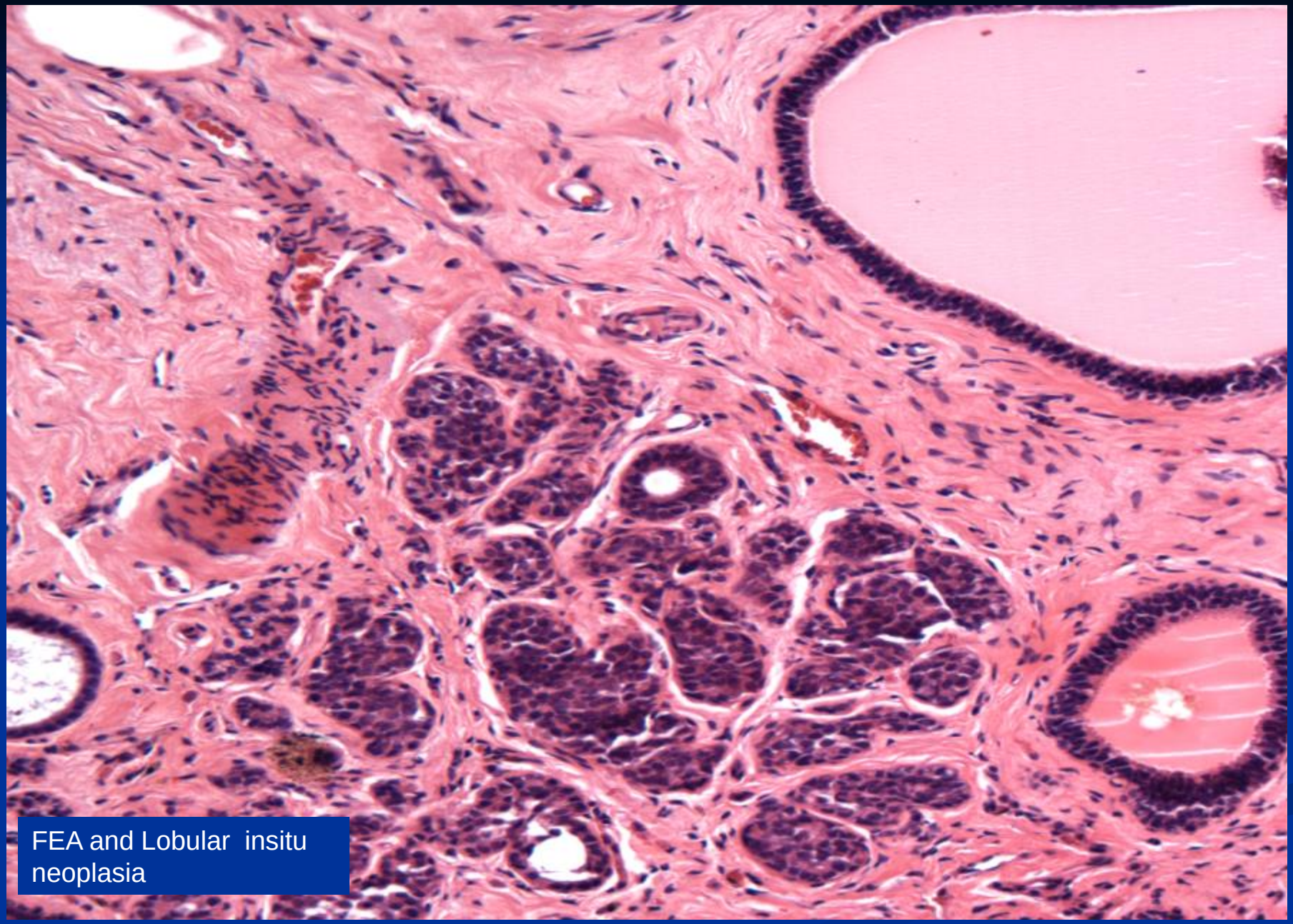
  O'Malley et al. Interobserver reproducibility in the diagnosis of flat epithelial atypia of the breast. Mod Pathol 2006;19(2):172-9

Tips

- Do not over-diagnose atypia
- Discuss with colleagues!

Rosen's triad

Columnar cell lesions, lobular neoplasia, tubular carcinoma


FEA and Lobular insitu neoplasia

Associated lesions

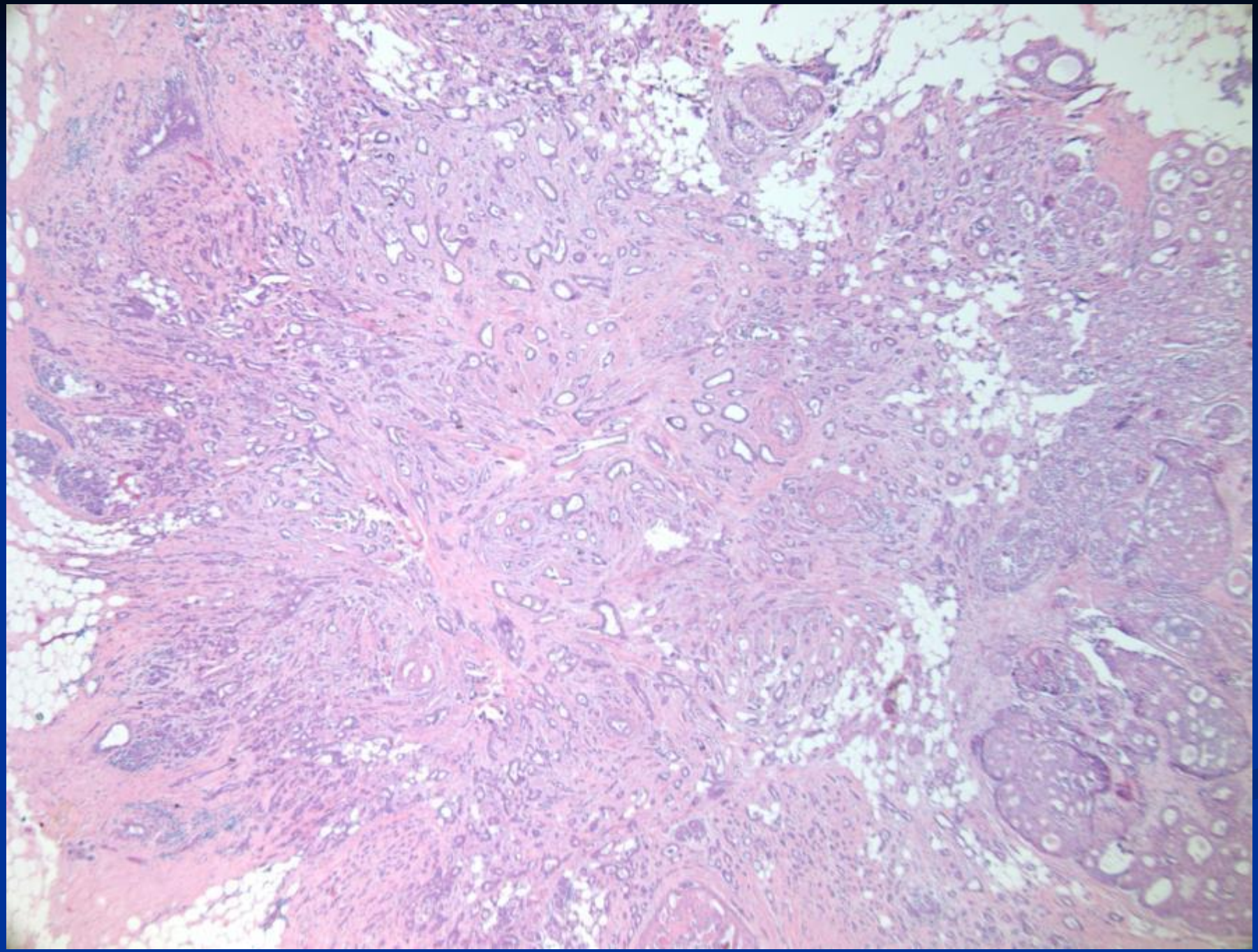
Low nuclear grade neoplasia family

-Tubular, cribriform, grade 1 ductal NST, lobular, tubulo-lobular carcinoma

-CCC, FEA, ADH, low grade DCIS, lobular in situ neoplasia

-ER, bcl2, CK8, 18, 19 positive. CK5, 14, p53, HER2 neg

Abdel-Fatah et al, Am J Surg Pathol 2008



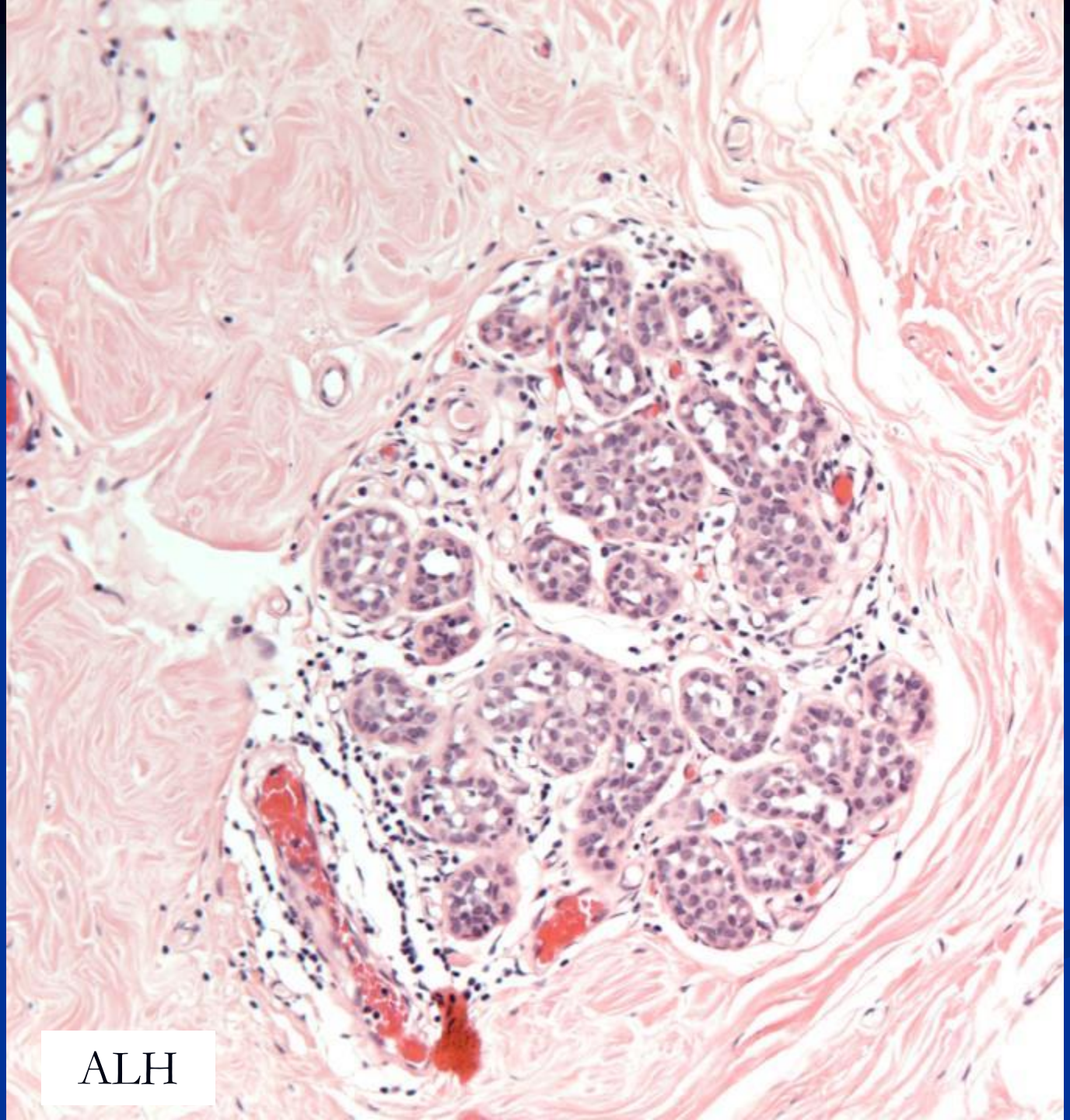
Lobular neoplasia

- Encompasses atypical lobular hyperplasia (ALH) and lobular in situ carcinoma (LCIS).

- LCIS: classical and variants

ALH vs LCIS

- Depends on extent of lesion
- LCIS: more than half of the acini are filled, distended and distorted by the dyscohesive lobular cells.

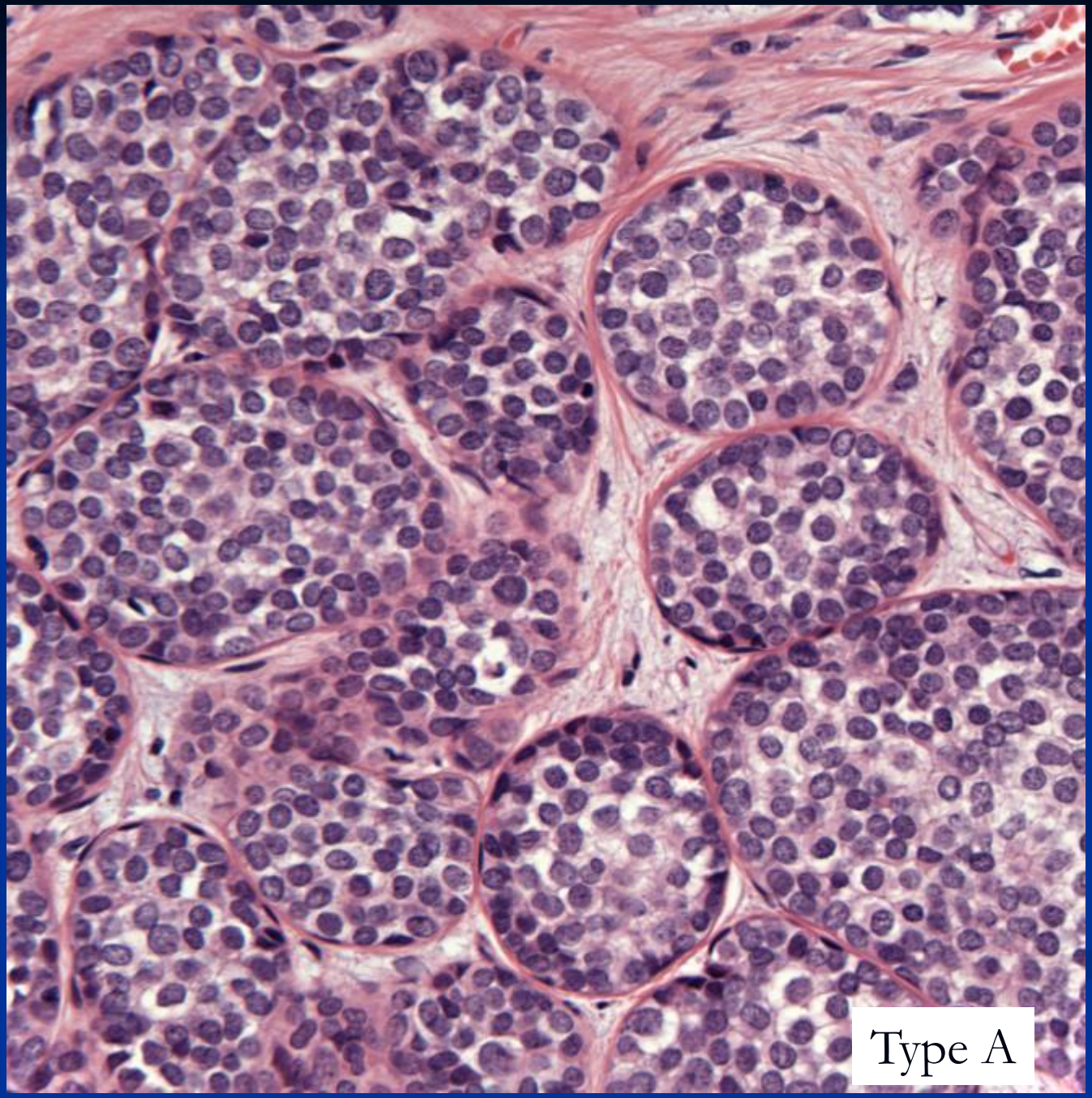

ALH

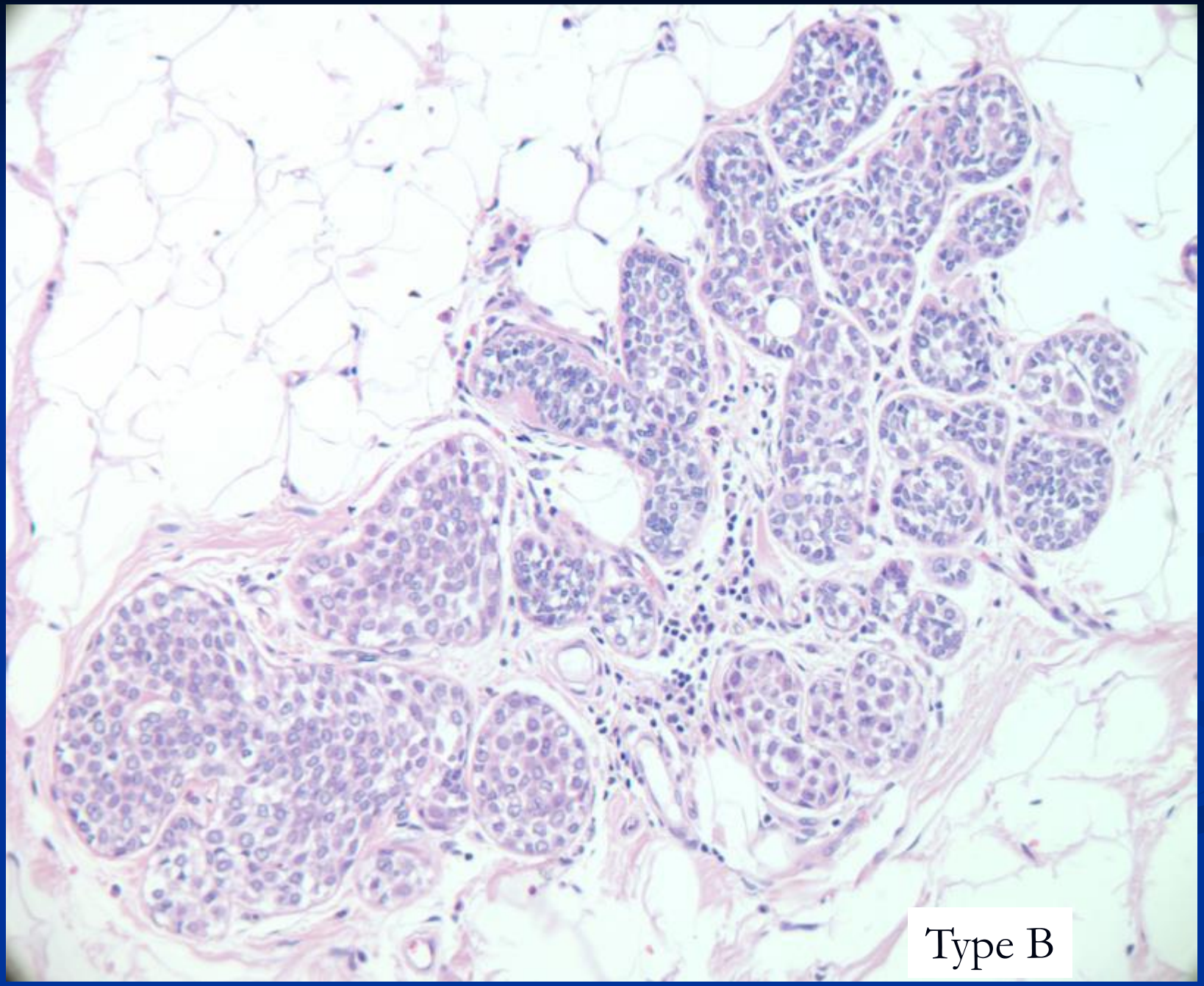
Histologically

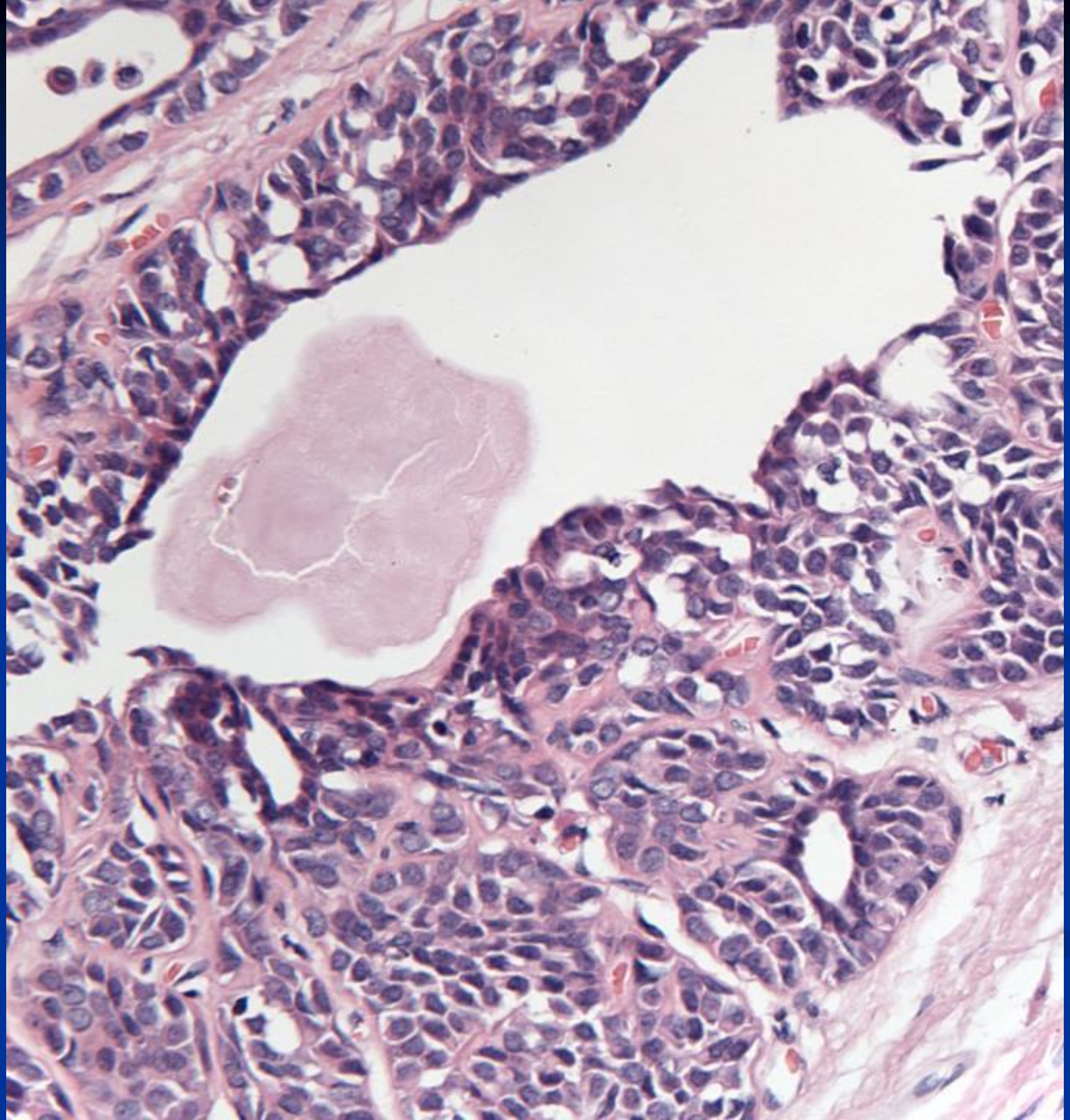
- A monomorphic proliferation within TDLU of dyscohesive cells with uniform round nuclei, indistinct nucleoli and scant cytoplasm.
- Intracytoplasmic lumina are often present
- Pagetoid spread can be seen.

- **Type A cells:** small uniform cells with bland nuclei and scant cytoplasm

- **Type B cells:** cells are larger, with more cytoplasm and mild to moderate atypia

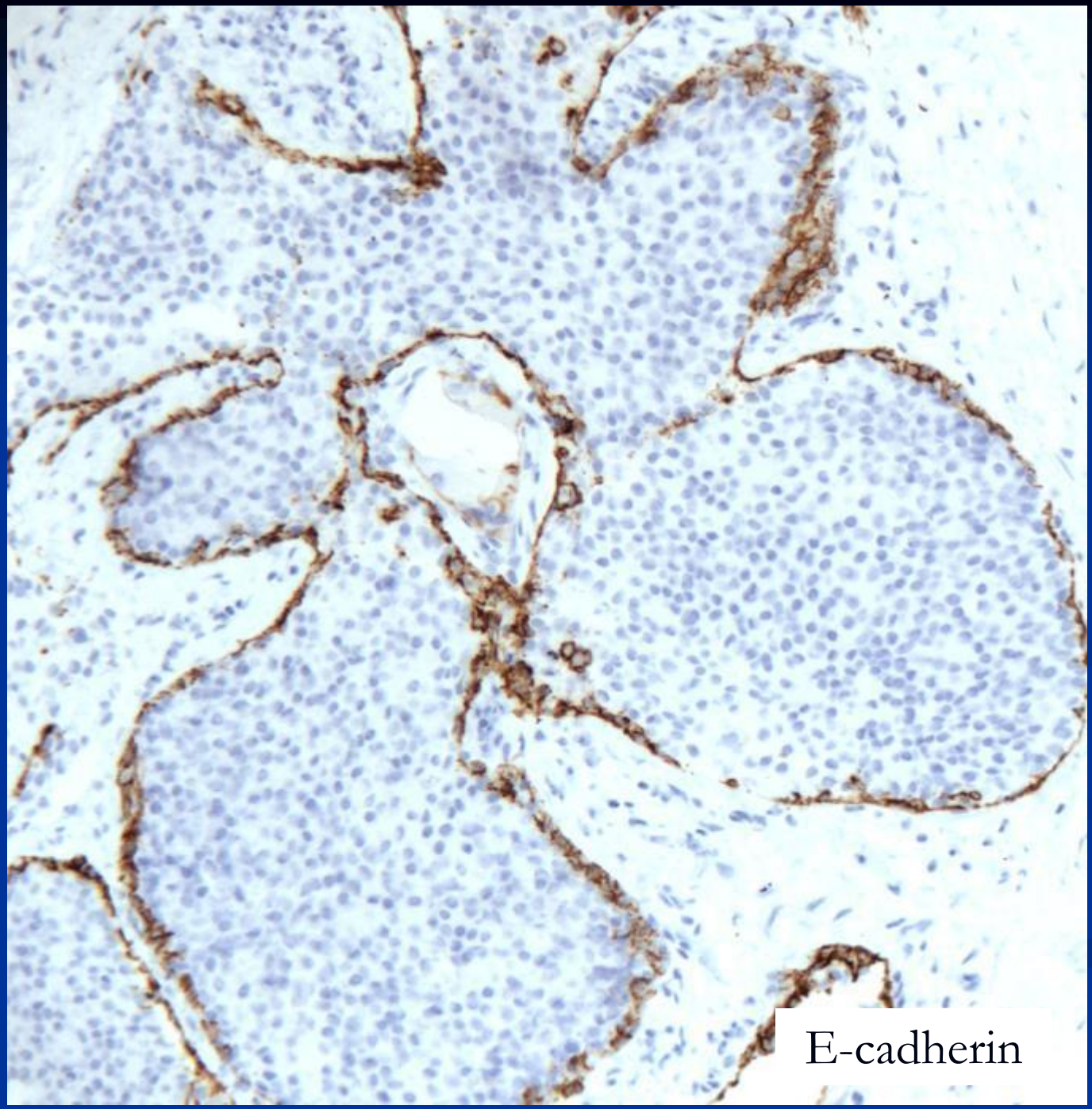

Type A

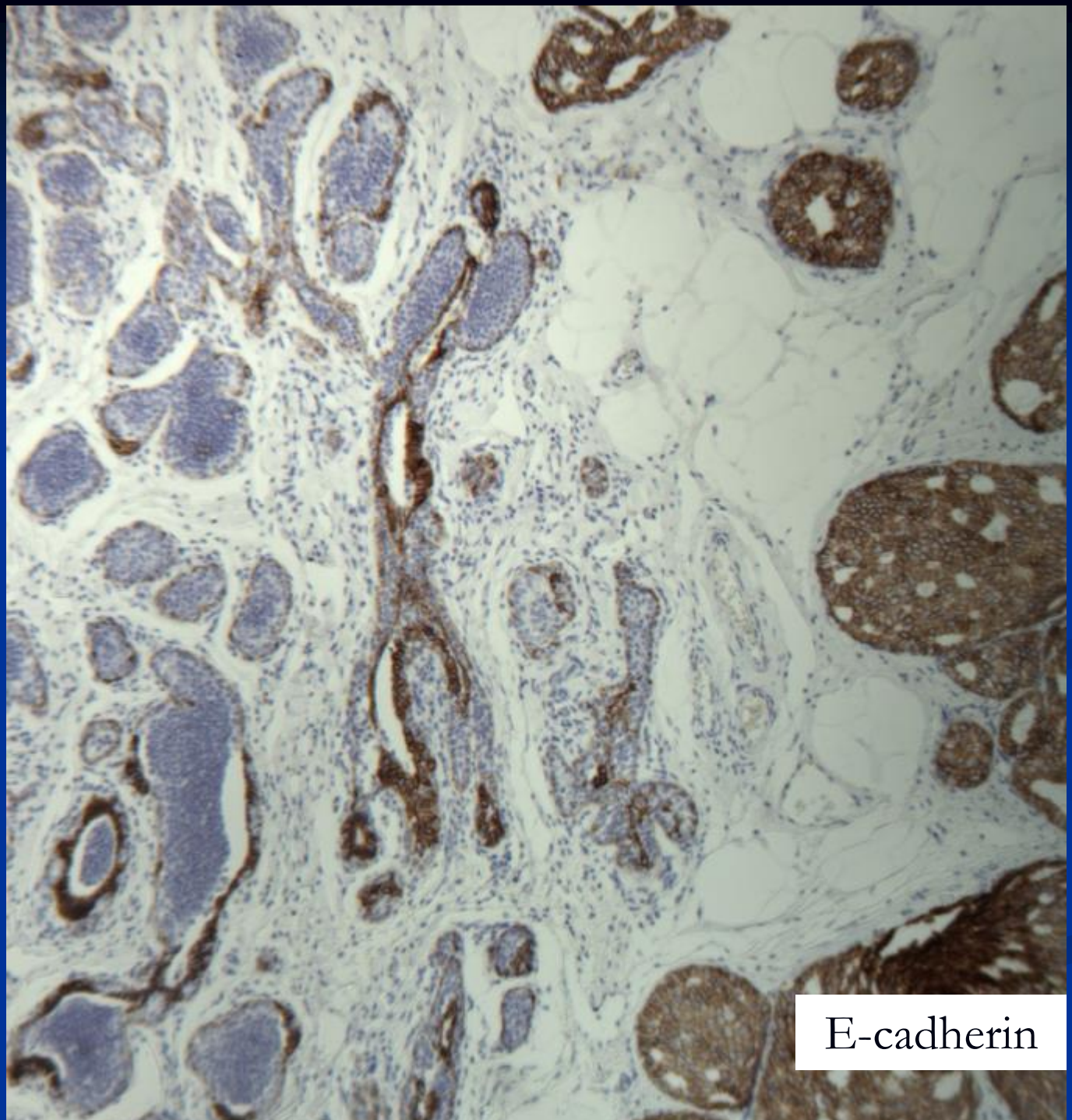

Type B



Immunohistochemistry

- E-cadherin: negative (but not always)
- CK5, CK14: negative
- ER: positive
- Her2: negative
- Loss of β-catenin
- Cytoplasmic catenin p120: indicates e-cadherin complex is dysfunctional


E-cadherin


E-cadherin


E-cadherin

- The diagnosis of lobular neoplasia is morphological.
- E-cadherin is often negative (but not always) in invasive lobular carcinoma.
- Expression may be diminished, aberrant or heterogeneous.
- Bcatenin (neg)and p120 (cytoplasmic) may be helpful in difficult cases

Histopathology

Histopathology 2016, 68, 57–69. DOI: 10.1111/his.12869

REVIEW

E-cadherin immunohistochemistry in breast pathology: uses and pitfalls

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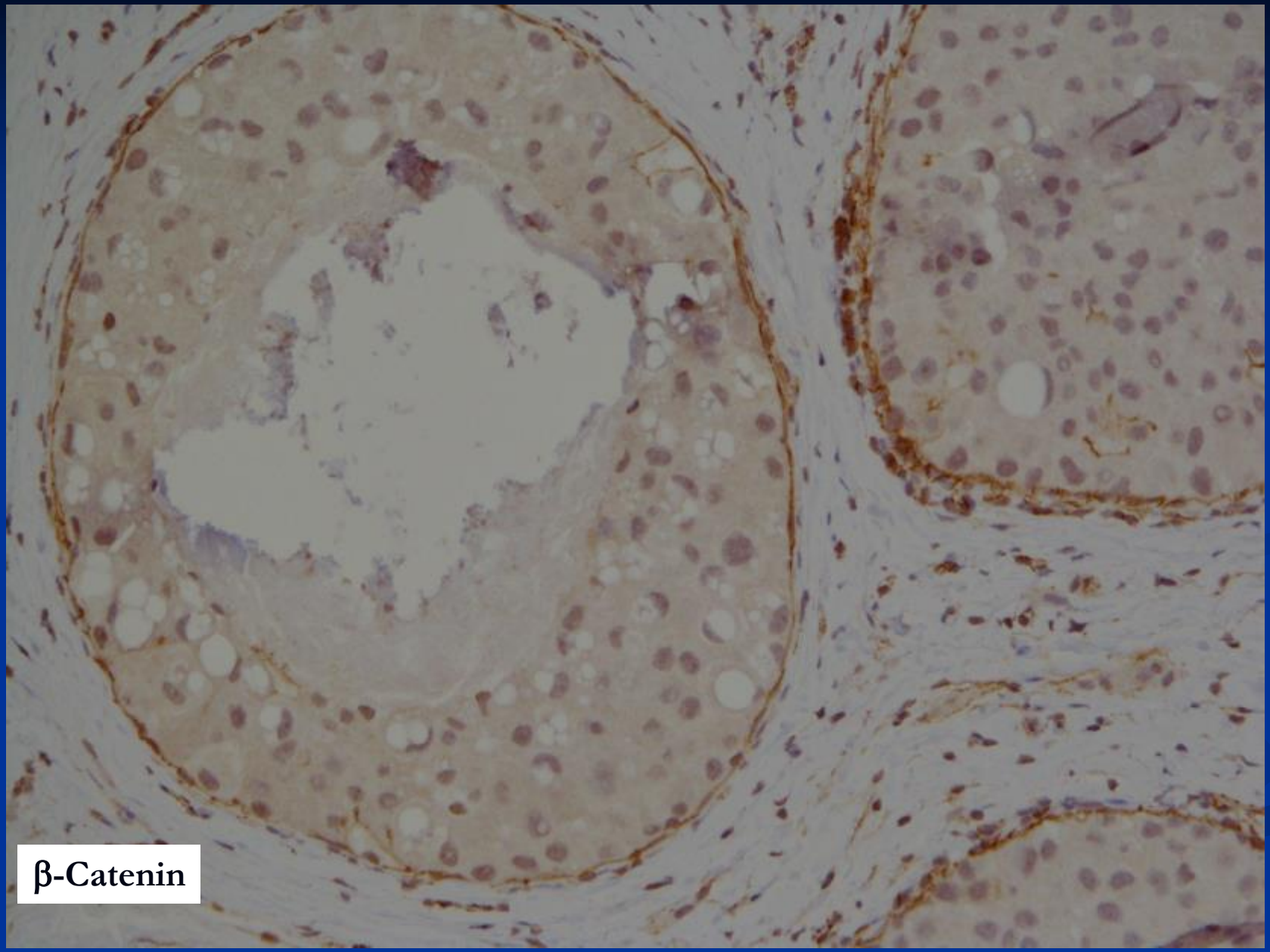
Table 2. Frequency of aberrant E-cadherin expression in invasive lobular carinomas in series with at least 20 cases

First author	No. (%) E-cadherin-positive
Kuroda[19]	0 of 20 (0%)
Sivonen[20]	0 of 55 (0%)
Acs[21]	1 of 42 (2.4%)
Goldstein[22]	5 of 143 (3.5%)
Qureshi[23]	5 of 44 (11.4%)
Da Silva[17]	4 of 25 (16%)
Rakha[18]	38 of 239 (15.9%)
Sarmo[24]	12 of 51 (23.5%)
Total	65 of 619 (10.5%)


β-Catenin

Variants of LCIS

Pleomorphic LCIS (PLCIS)

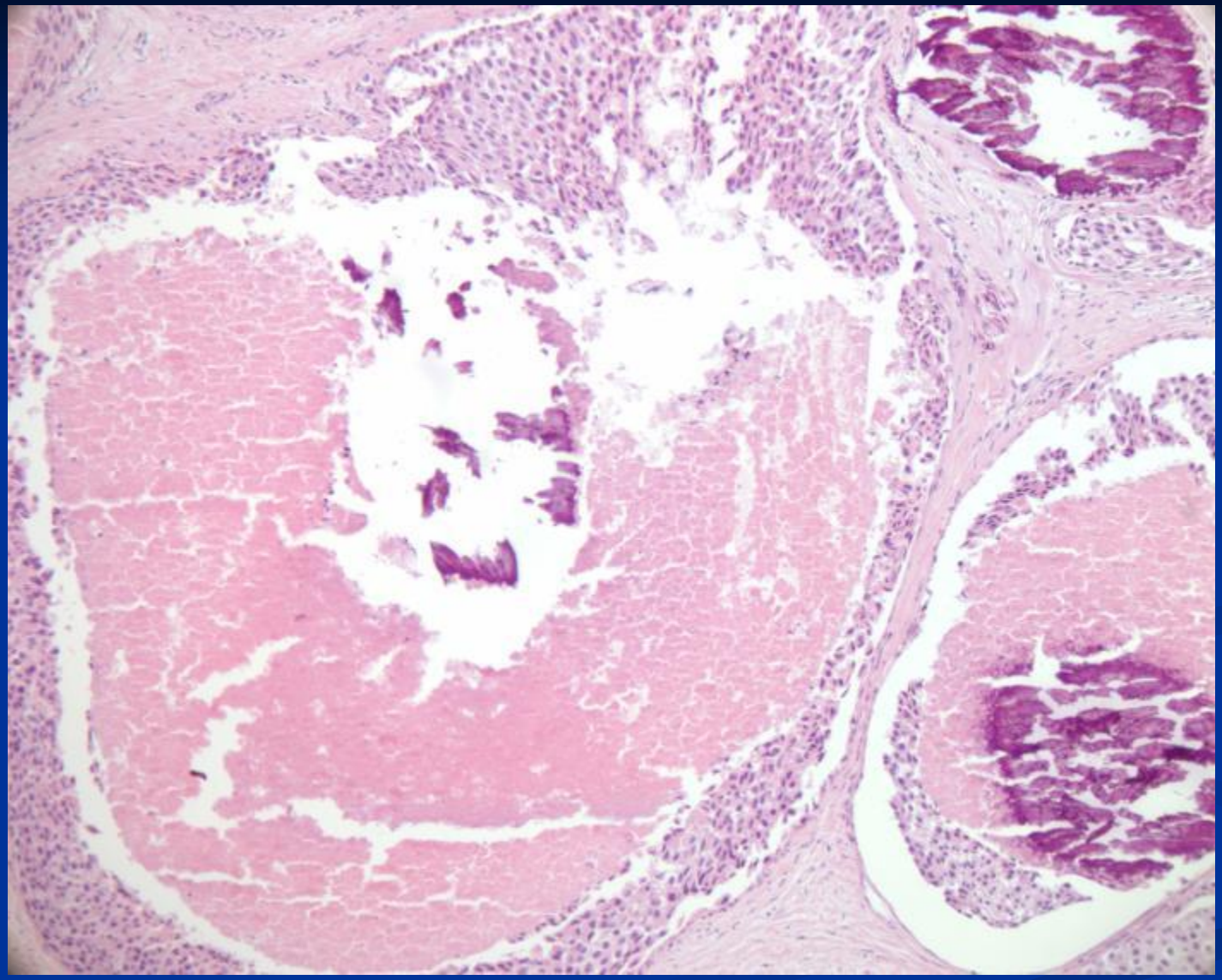
PLCIS
Definition

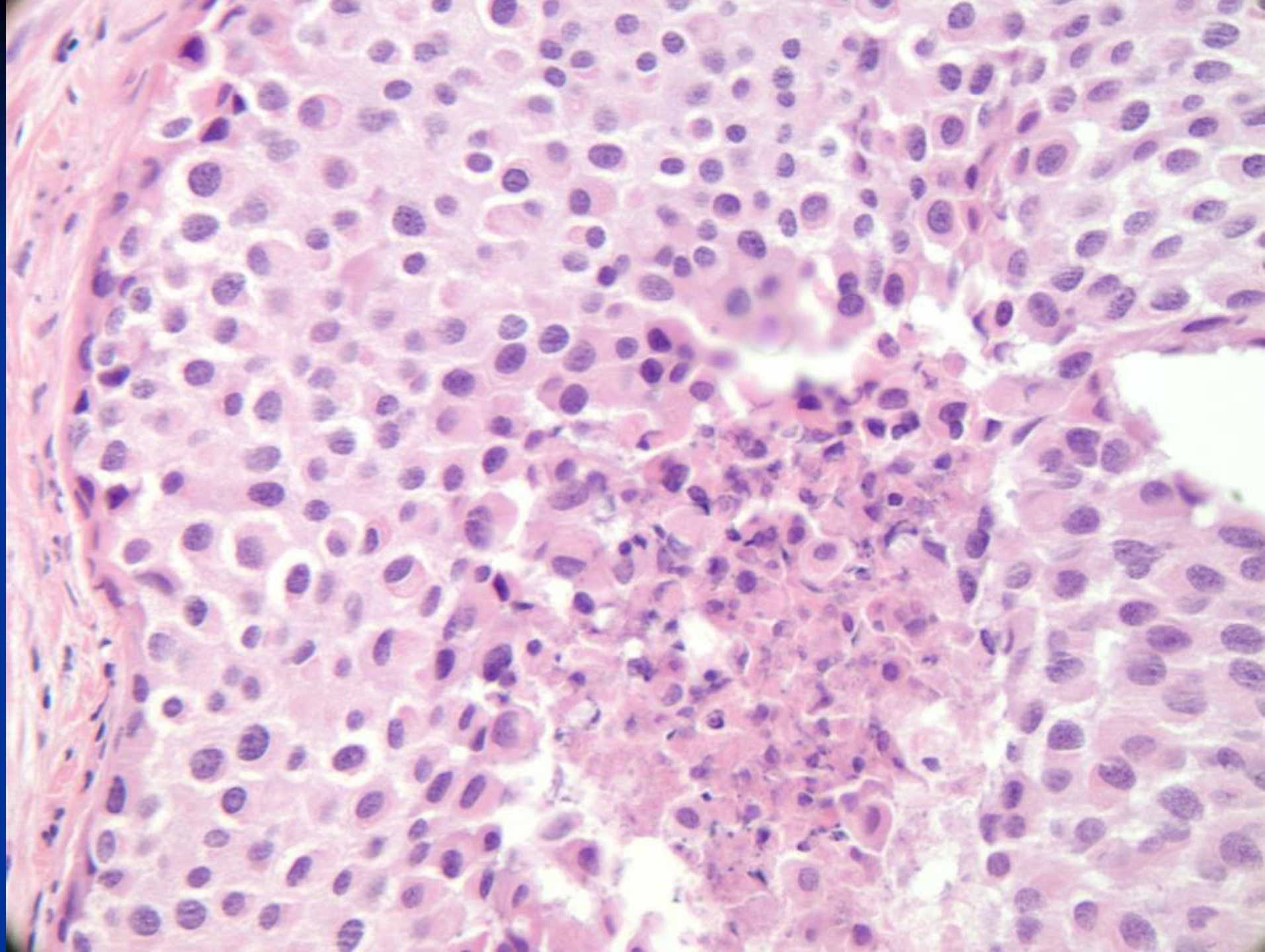
Similar to Rosen's criteria for classic LCIS:

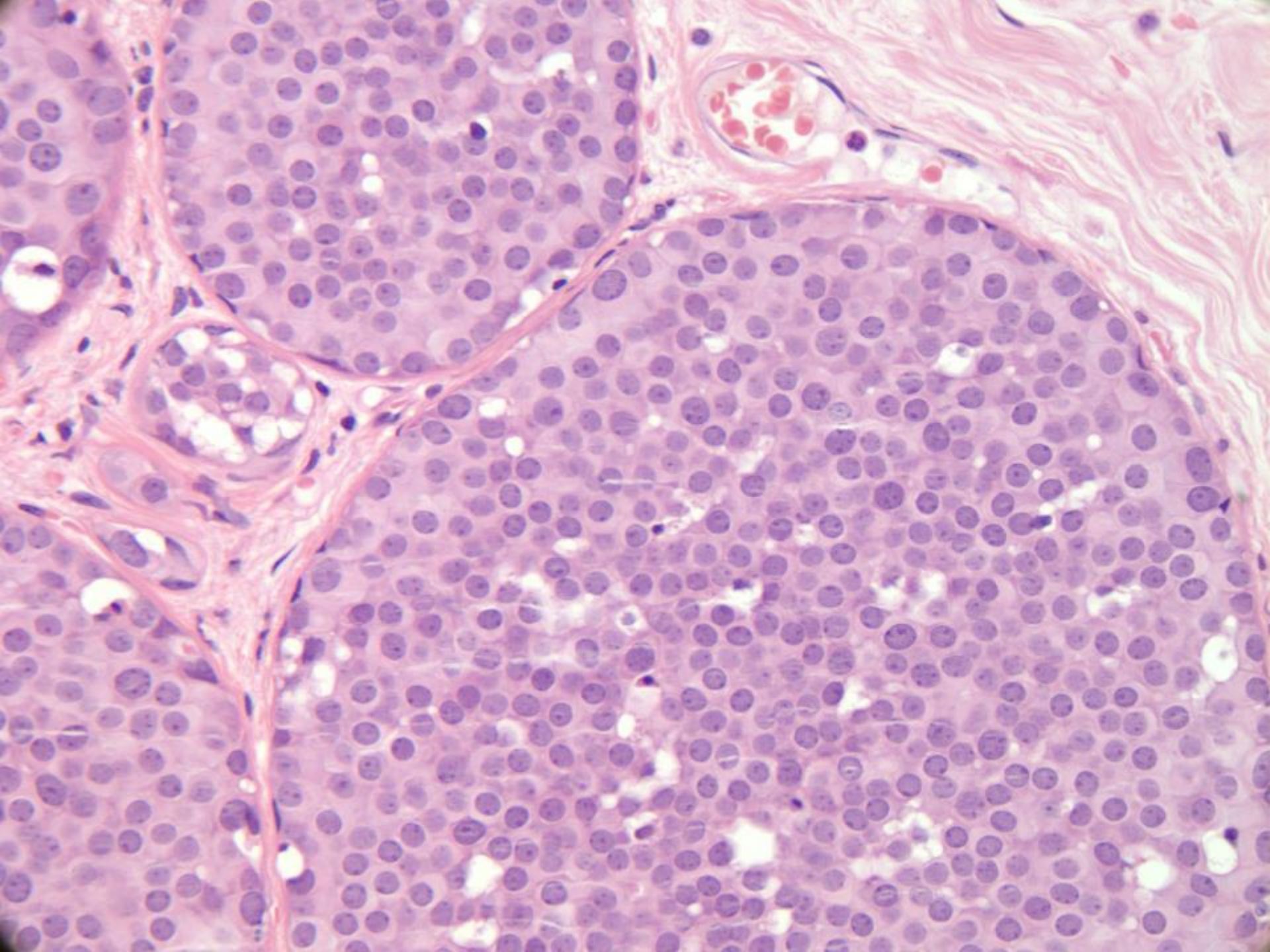
lobular units expanded by dyscohesive, pleomorphic cells with abundant eosinophilic cytoplasm, grade 3 nuclei, and prominent nucleoli (Chivukula et al 2008)

PLCIS

- Recently recognized variant of Lobular Carcinoma In Situ (LCIS)
- May calcify hence present through breast screening
- Biology and natural history uncertain
- Histologically: mimics high grade DCIS

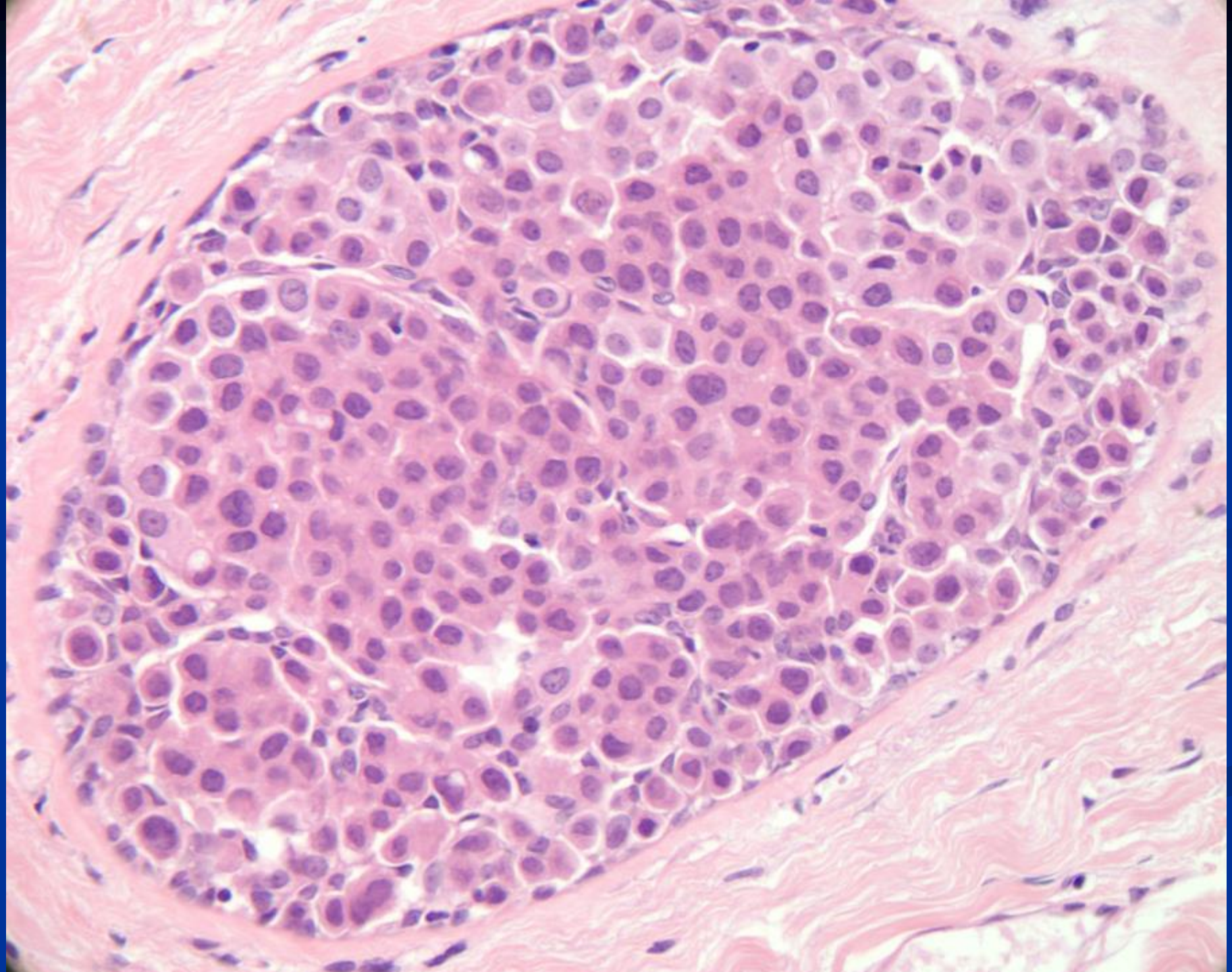






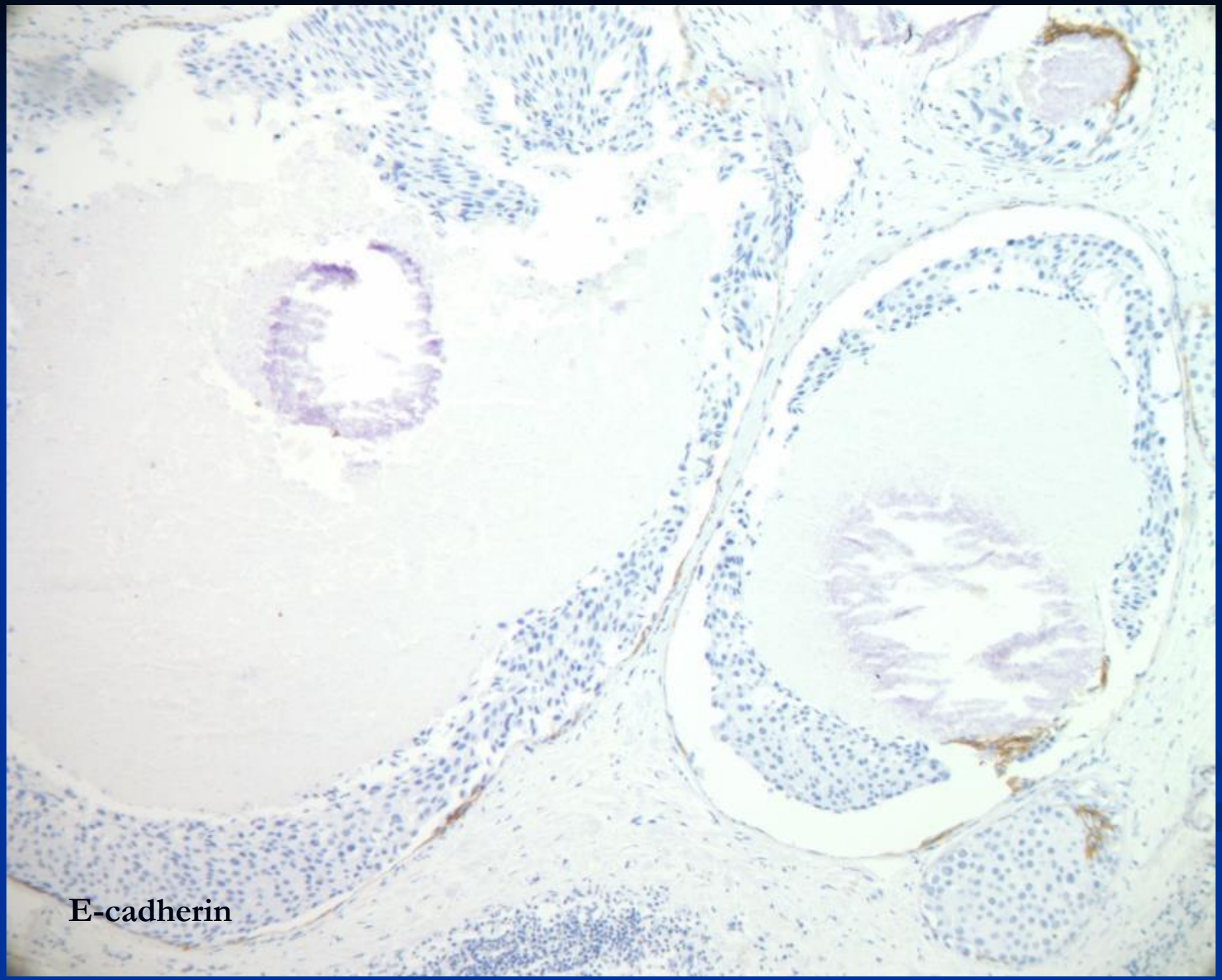
Pleomorphic apocrine LCIS PAL-CIS

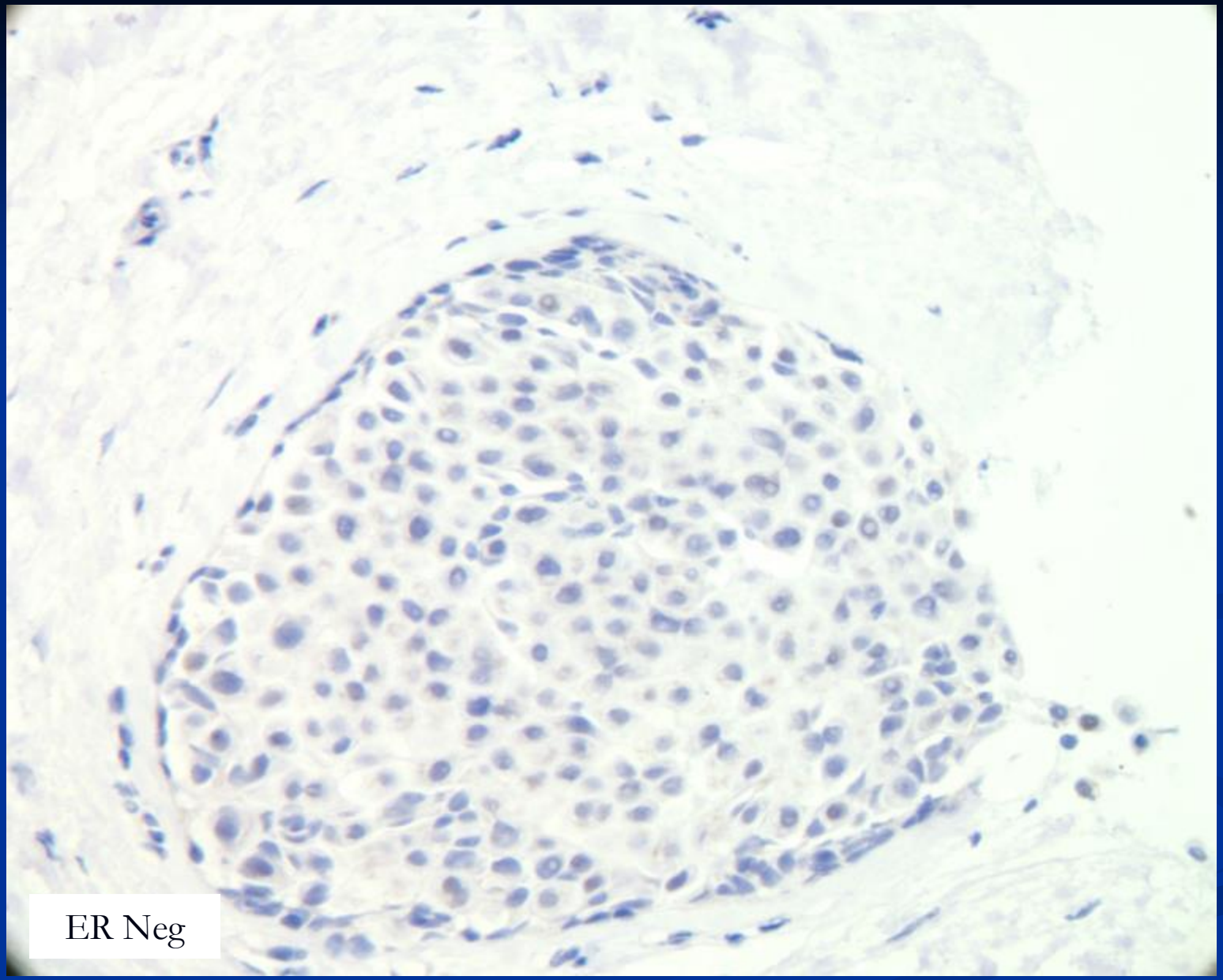
- Chen et al 2005 (suppl) described 10 cases
- Pleomorphic apocrine LCIS: LCIS with myxoid, apocrine and pleomorphic cytology
- CGH: Loss of 16Q, gain at 1Q
- DD apocrine DCIS with involvement of lobules

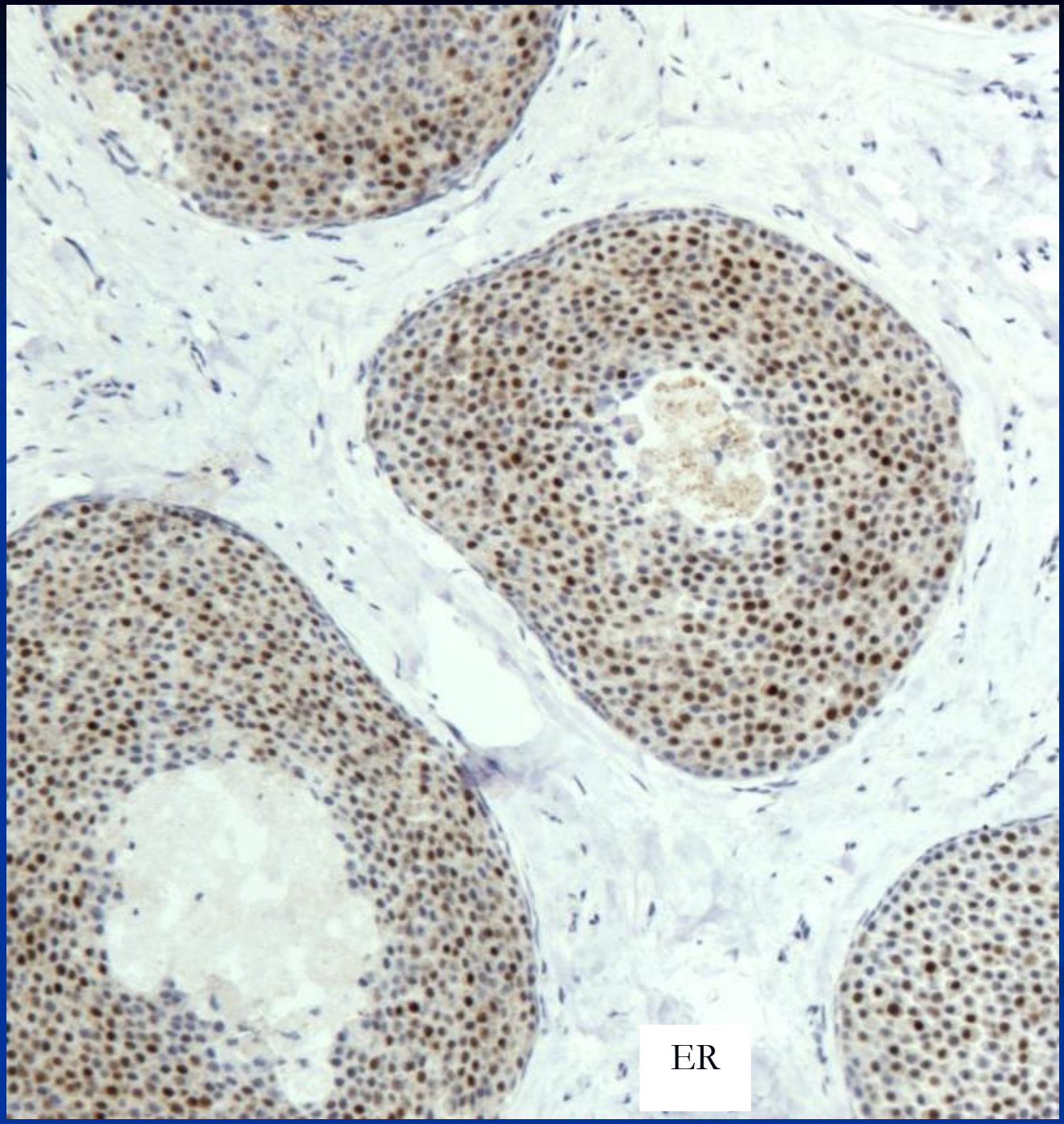


Immunohistochemistry of PLCIS

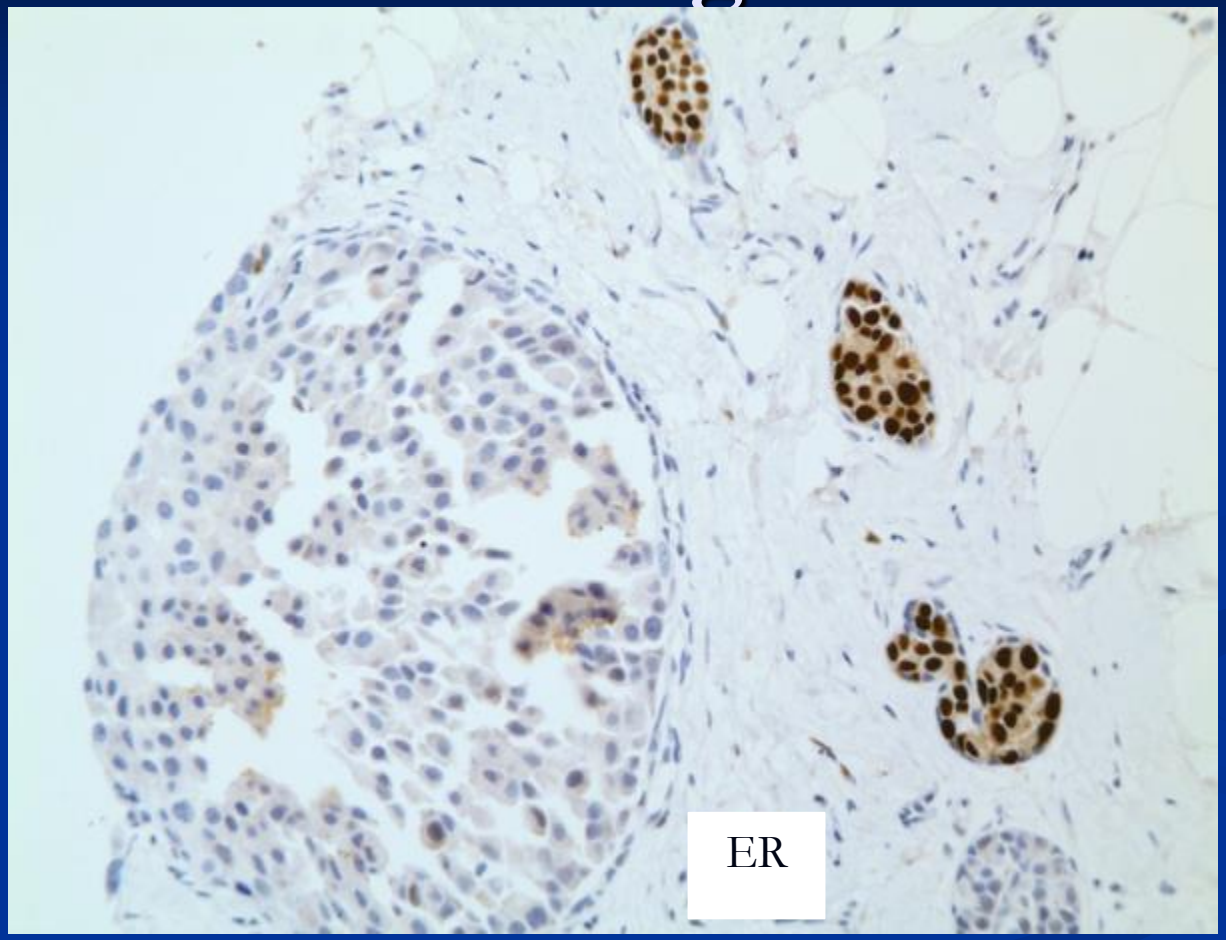
- E-CADHERIN NEGATIVE
- OESTROGEN RECEPTOR may be POSITIVE OR NEGATIVE
- GCDFP-15 OFTEN POSITIVE– may be helpful in histological diagnosis
- HER-2 may be POSITIVE
- P120 catenin: cytoplasmic staining in LCIS, membranous in ductal


E-cadherin


ER Neg

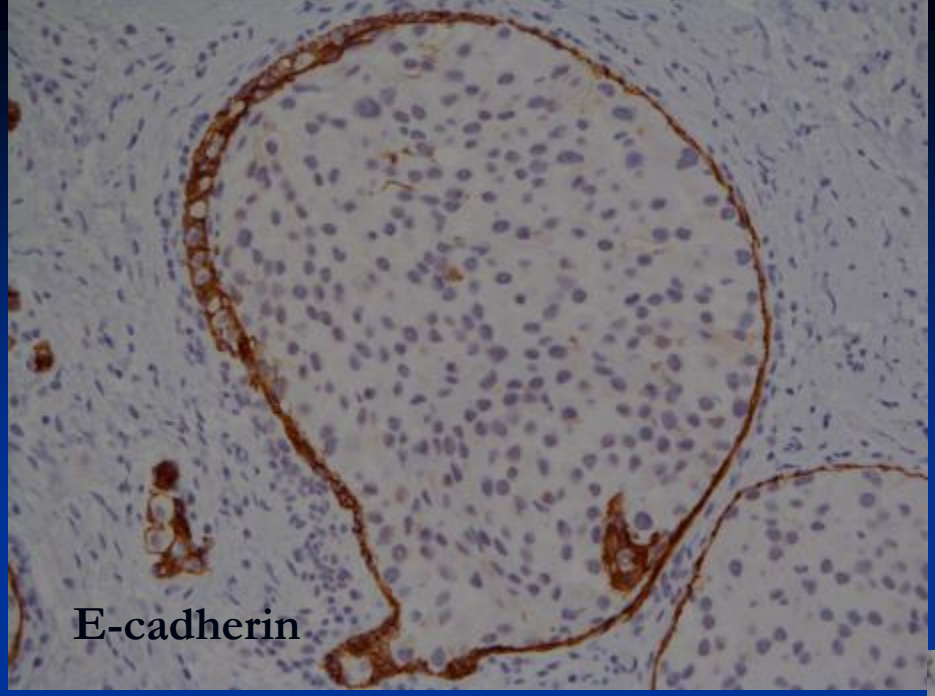

ER

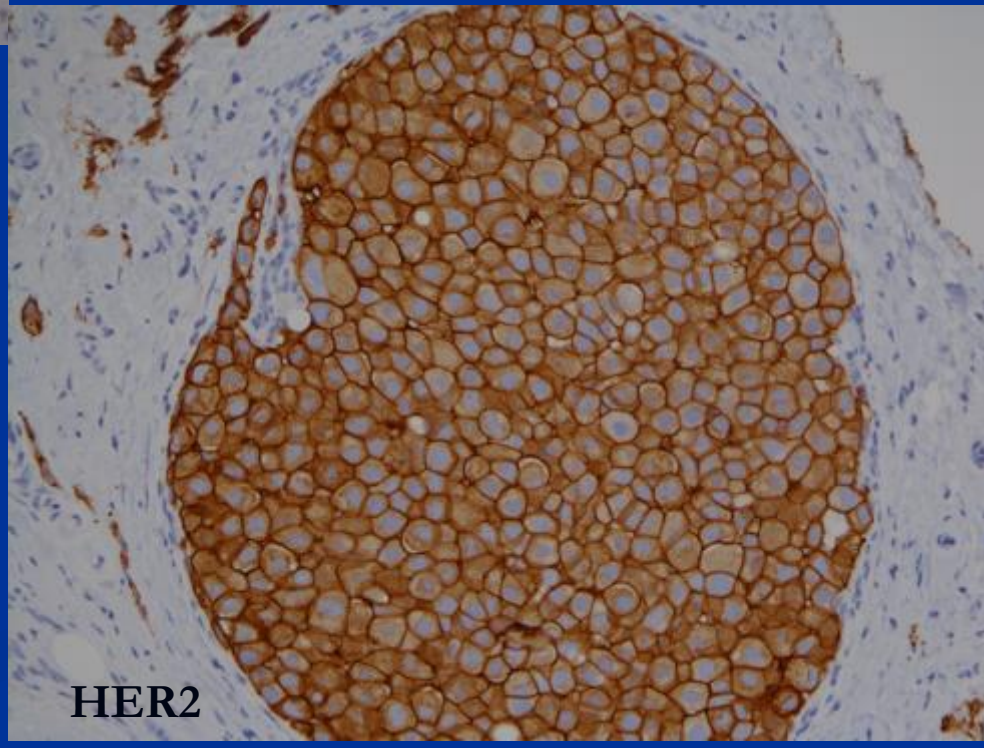
PLCIS within background of LCIS



PLCIS (ER neg) with conventional LCIS (ER pos)

Carder et al 2010

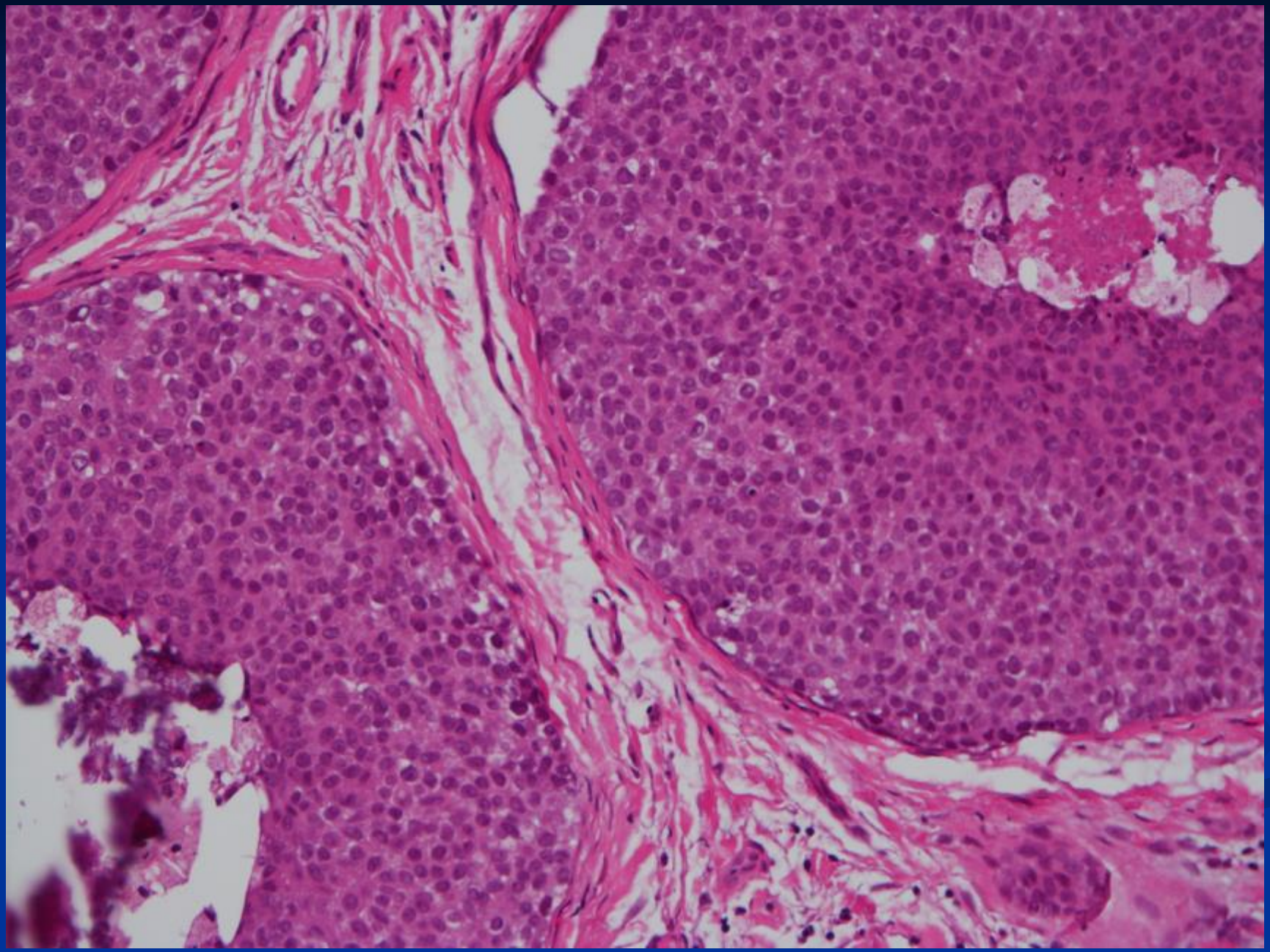

E-cadherin

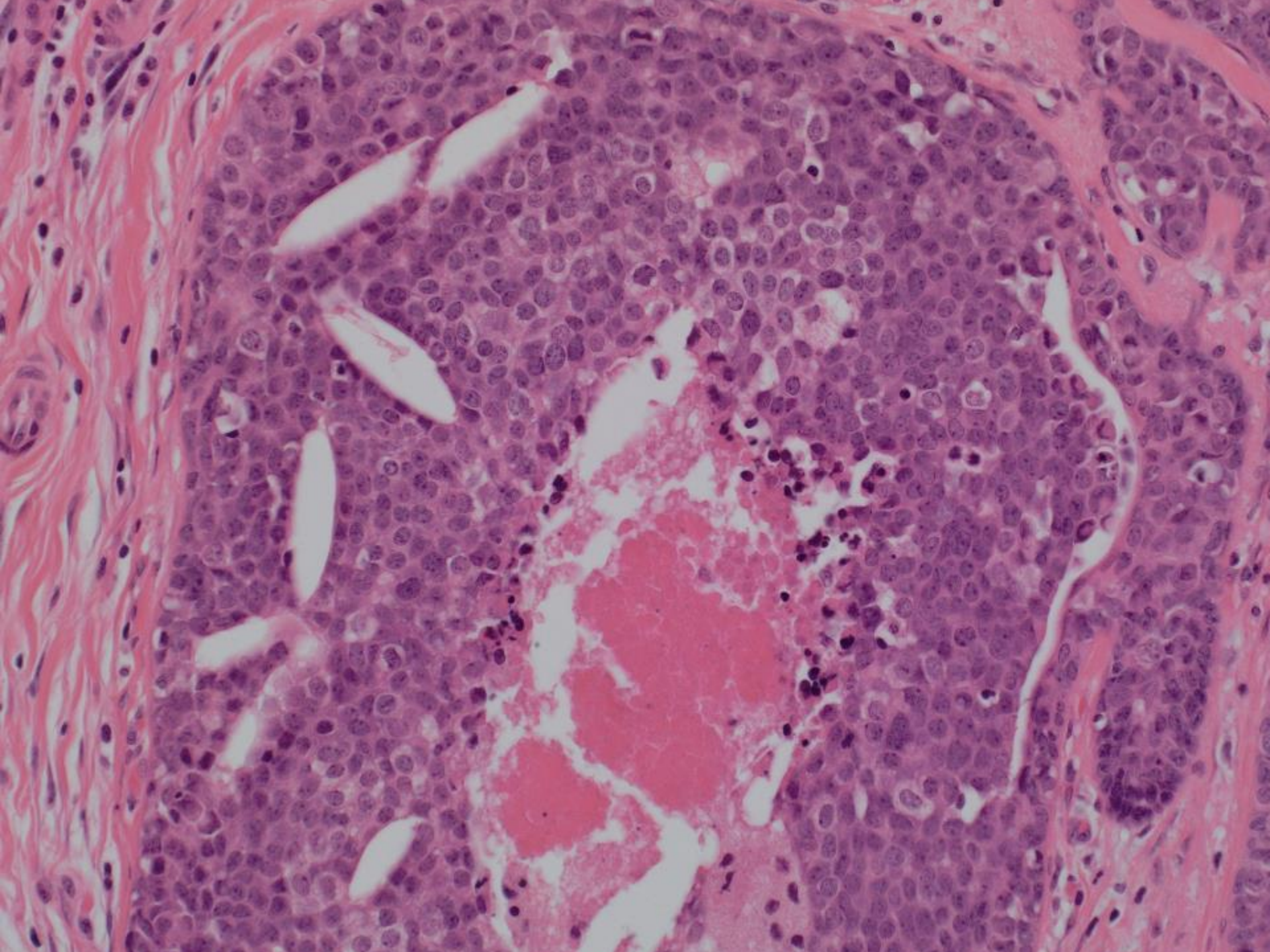

HER2

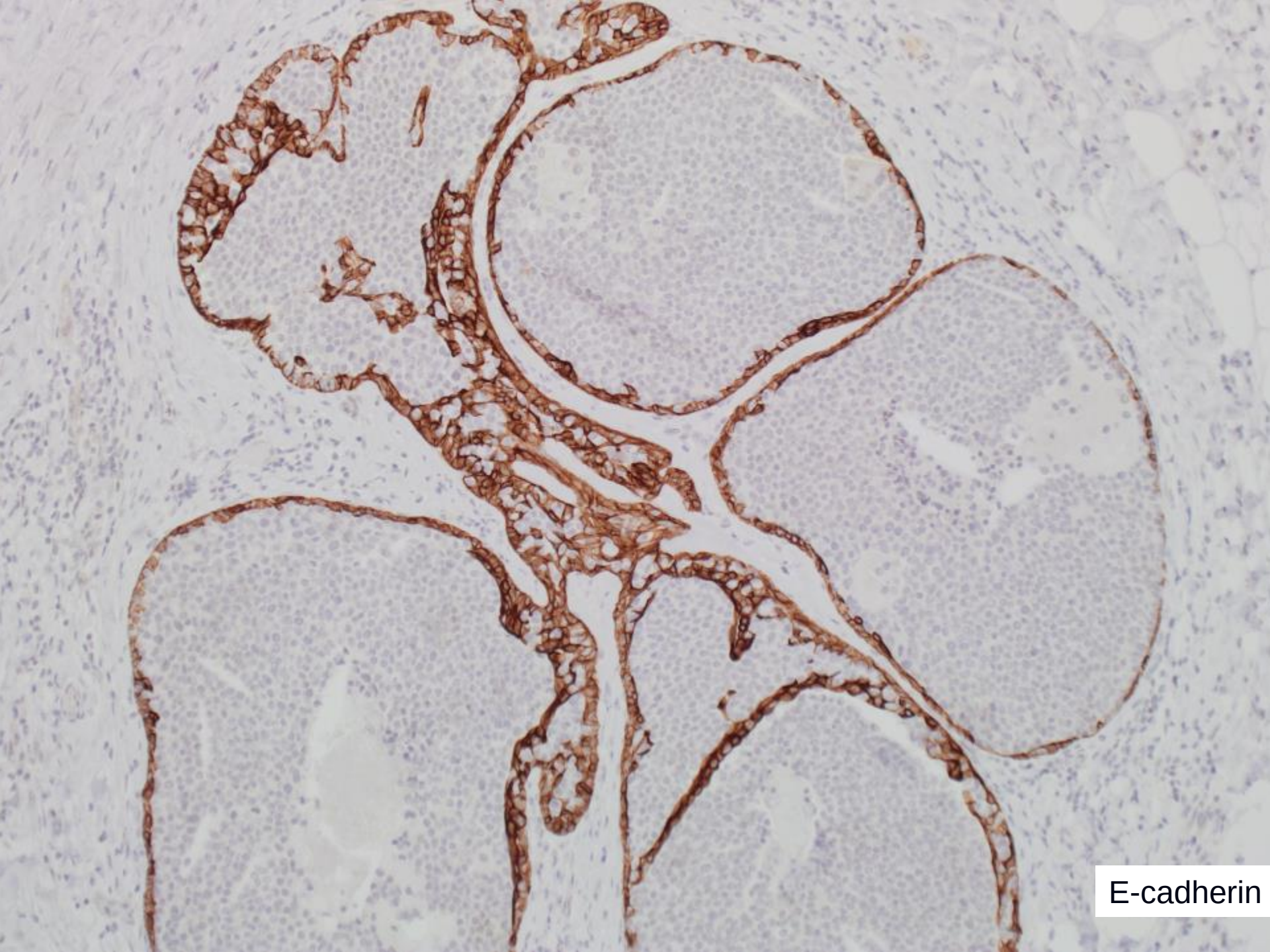
Rare variant of LCIS

Classical LCIS with comedo necrosis

(Mass forming LCIS, Florid LCIS






E-cadherin

- Sapino et al 2000 described 10 cases of LCIS with necrosis, 4 of which associated with invasive carcinoma

- A study of 18 cases reported a strong association with invasive cancer (67% of cases) Fadare et al Am J Surg Pathol 2006 30:1445–1453

- Chin et al 2013 examined the genetic profile of 20 cases of "Florid LCIS". Lesions showed loss of 16q (all cases) and 1q gain (80%)

UK multicentre series

- 28 cases
- Association with malignancy 53.6%
- Upgrade following core biopsy diagnosis: 35.7%
- Associated invasive: predominantly lobular

Shaaban et al., manuscript in preparation

Diagnostic challenges

Is the proliferation ductal or lobular?

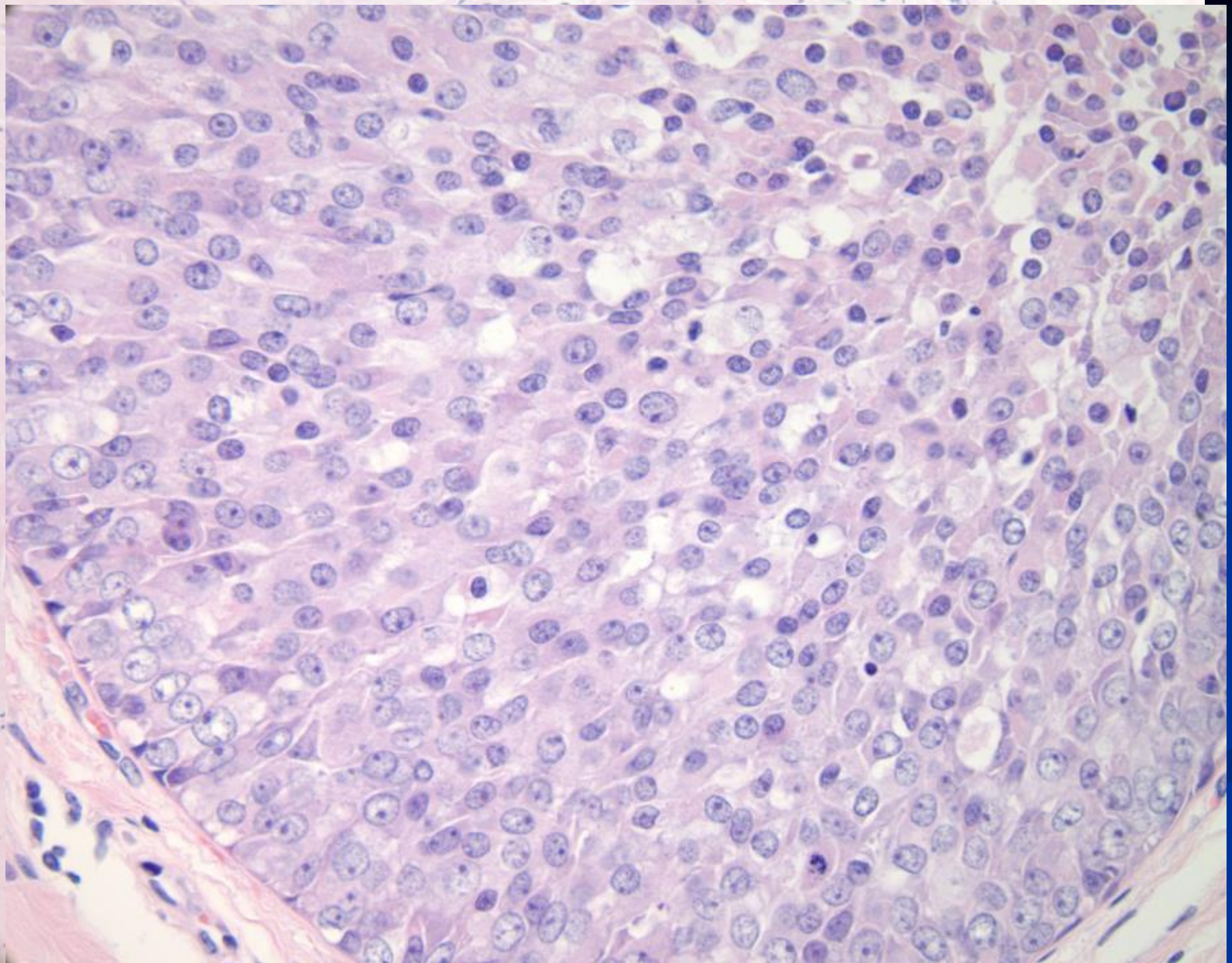
(Low/intermediate grade DCS VS LCIS)
(High grade DCIS VS PLCIS)

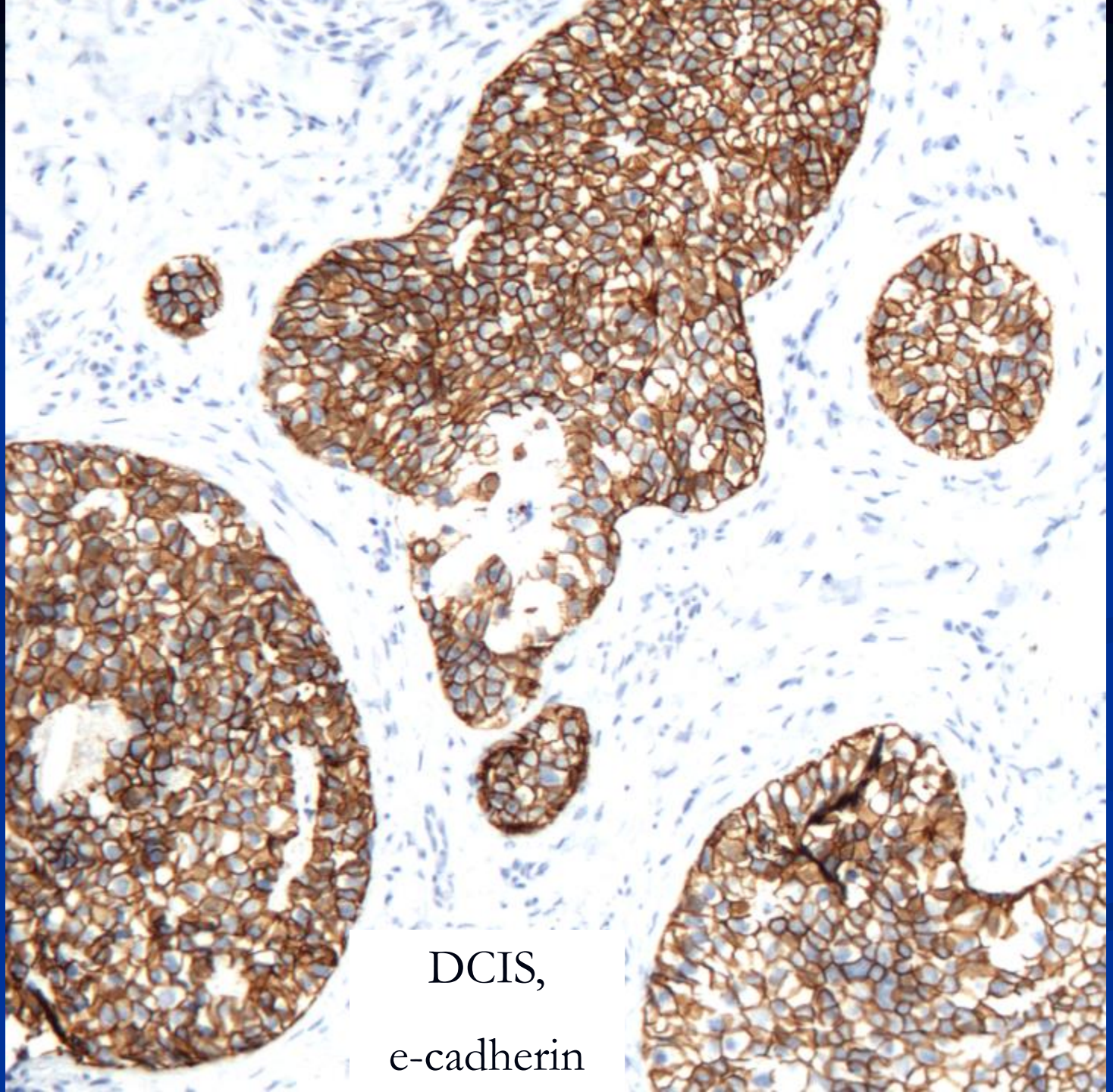
Look for:

- Cellular cohesion
- Architectural pattern of DCIS
- E-cadherin IHC can help

Are the nuclei pleomorphic enough to designate as PLCIS?

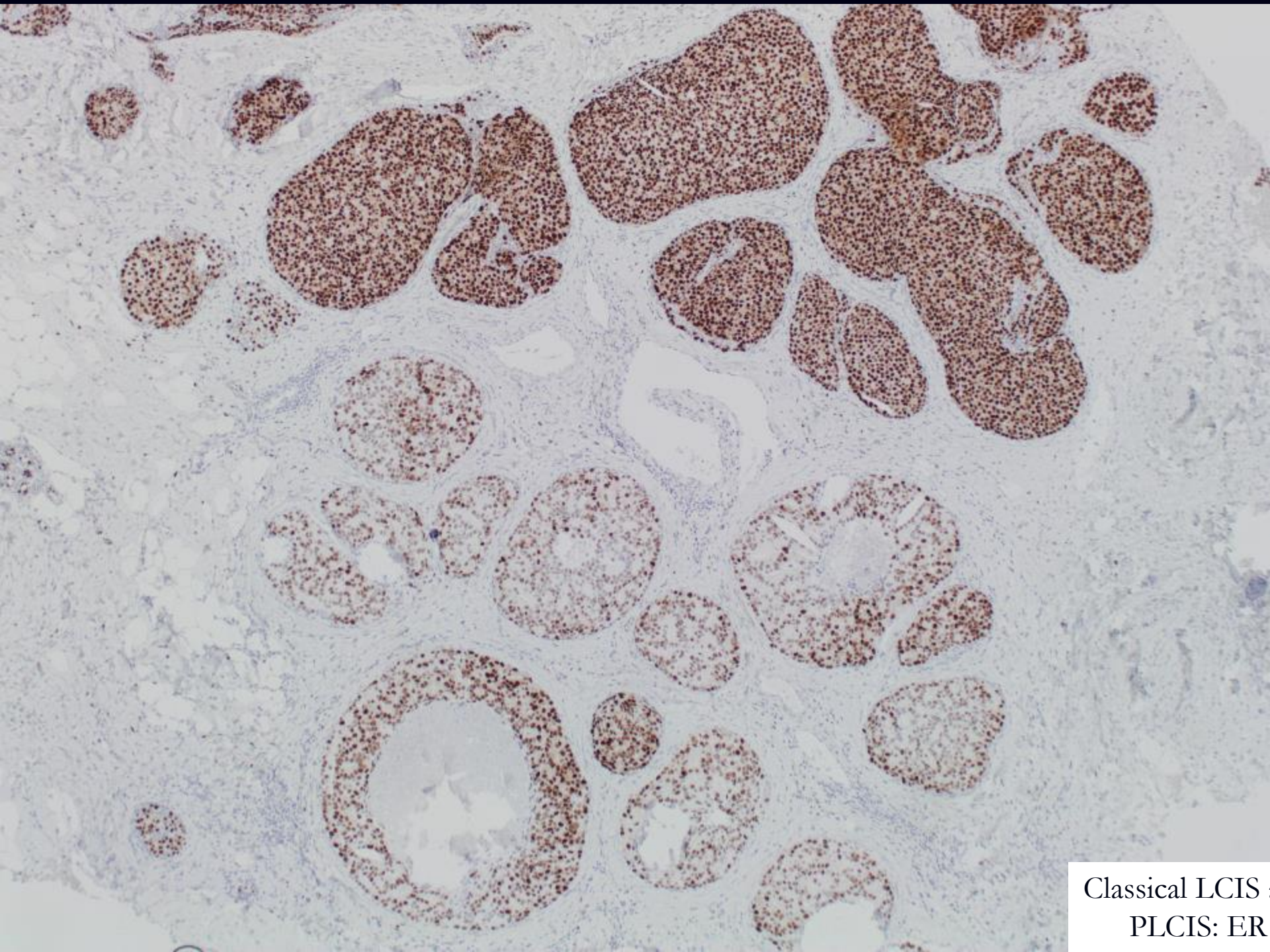
- Compare size with normal ductal epithelial cell.
- IHC: ER, GCDFP-15, HER2 may help





DCIS,

e-cadherin



Classical LCIS
PLCIS: ER

Breast Cancer Res Treat
DOI 10.1007/s10549 017 4334 1

EPIDEMIOLOGY

Pleomorphic lobular carcinoma in situ of the breast: a single institution experience with clinical follow-up and centralized pathology review

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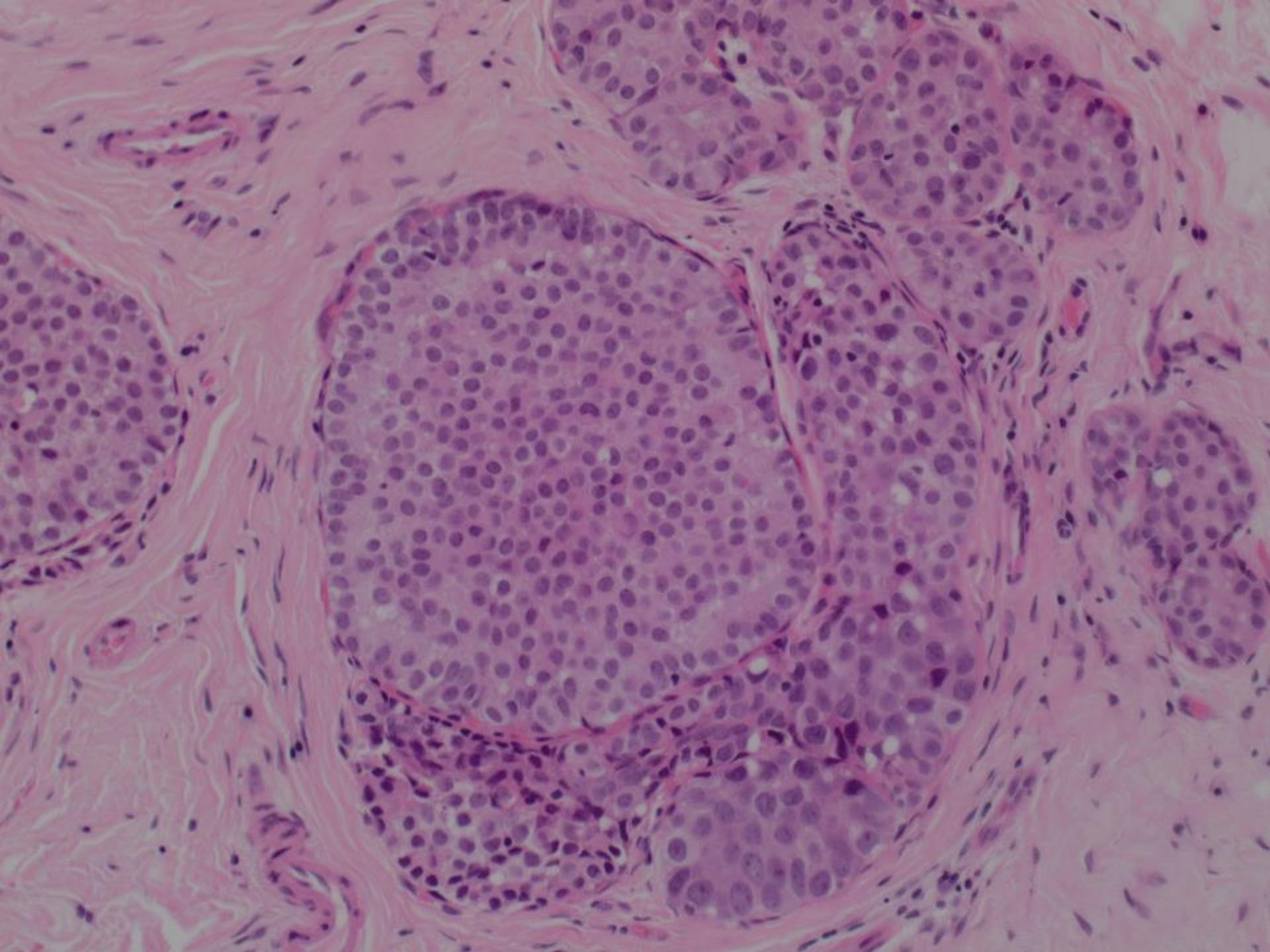
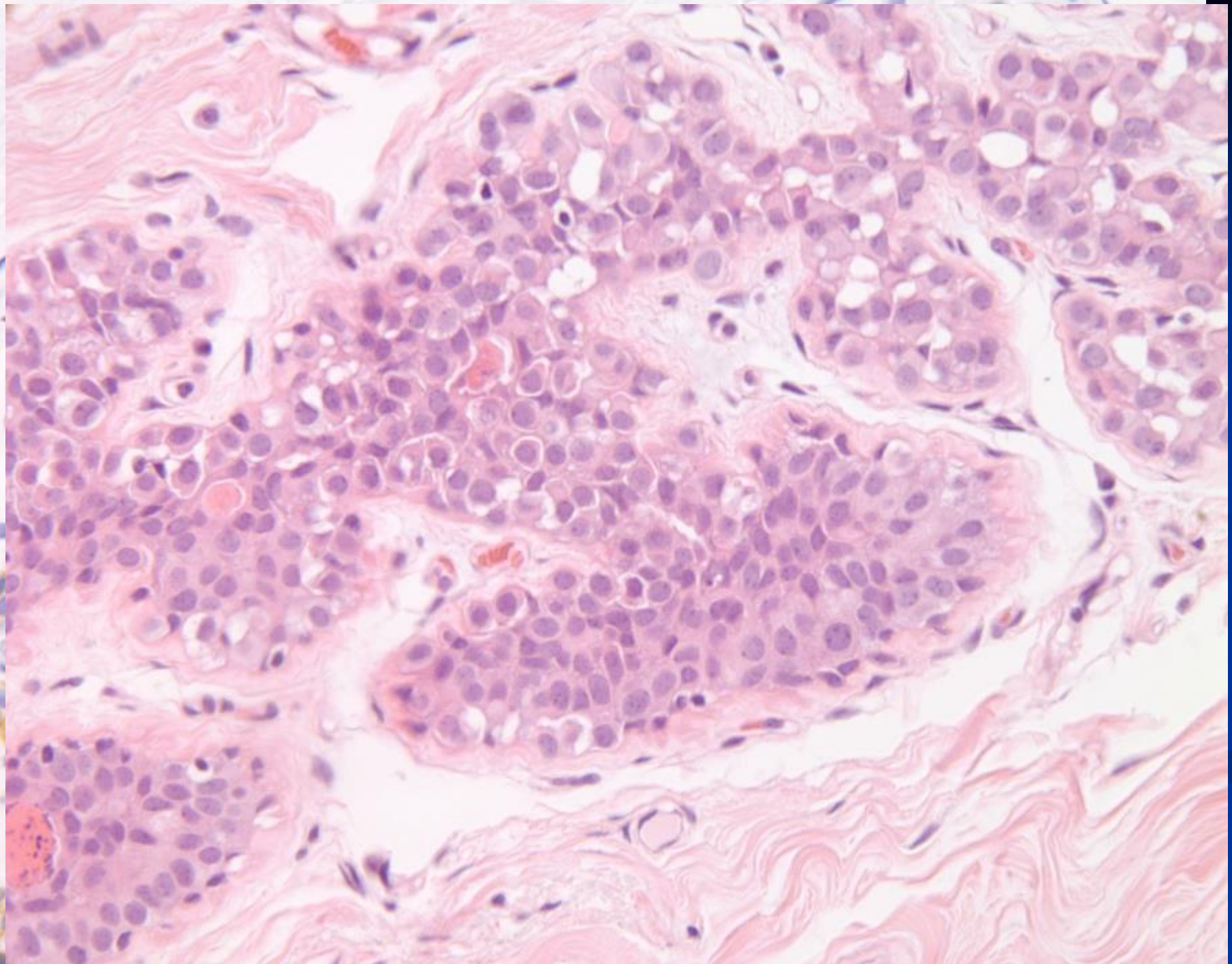
- New terminology from MSKCC
- LCIS-PF: LCIS with pleomorphic features

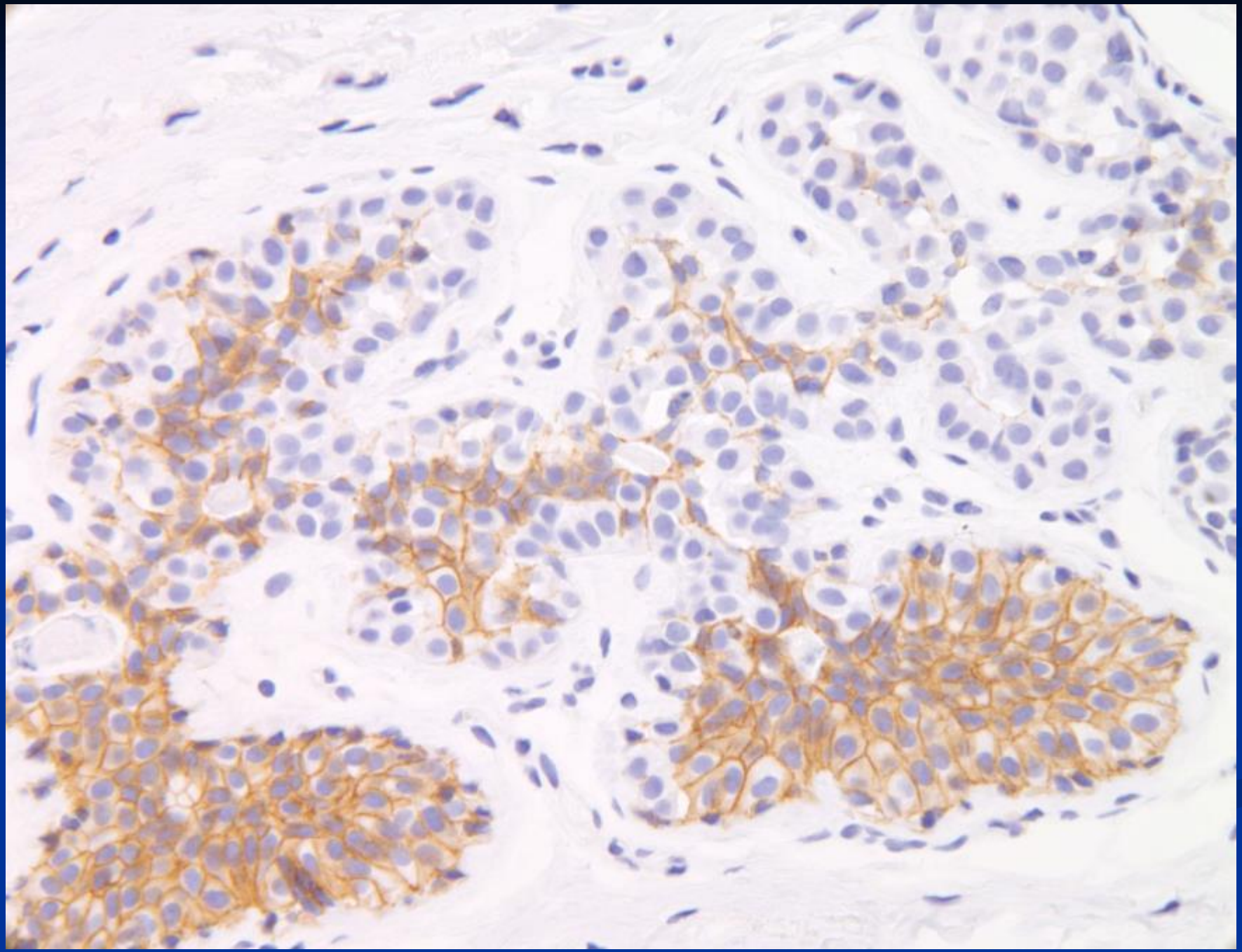


In situ carcinoma with mixed ductal and lobular features

- E cadherin IHC may show heterogeneous staining (DD positive residual cells)

Schnitt group: Jacobs et al Carcinomas in situ of the breast with indeterminate features: role of Ecadherin staining in categorization. Am J Surg Pathol 2001;25:229–236.





Clinical relevance

Lesion	Relative risk	Upgrade risk
FEA	X2	13-21%, average 15% (in pure form); if co-existent with AIDEP then higher risk: pooled 29%
AIDEP	x4.4-5 x8 if FH	37-53 %, pooled value 21% after VAB
ALH	x4-5	0-43%, pooled data 19%
LCIS	x8-10	0-60, pooled value 27%

Pinder and Shaaban, book chapter 2017

B - Categorisation

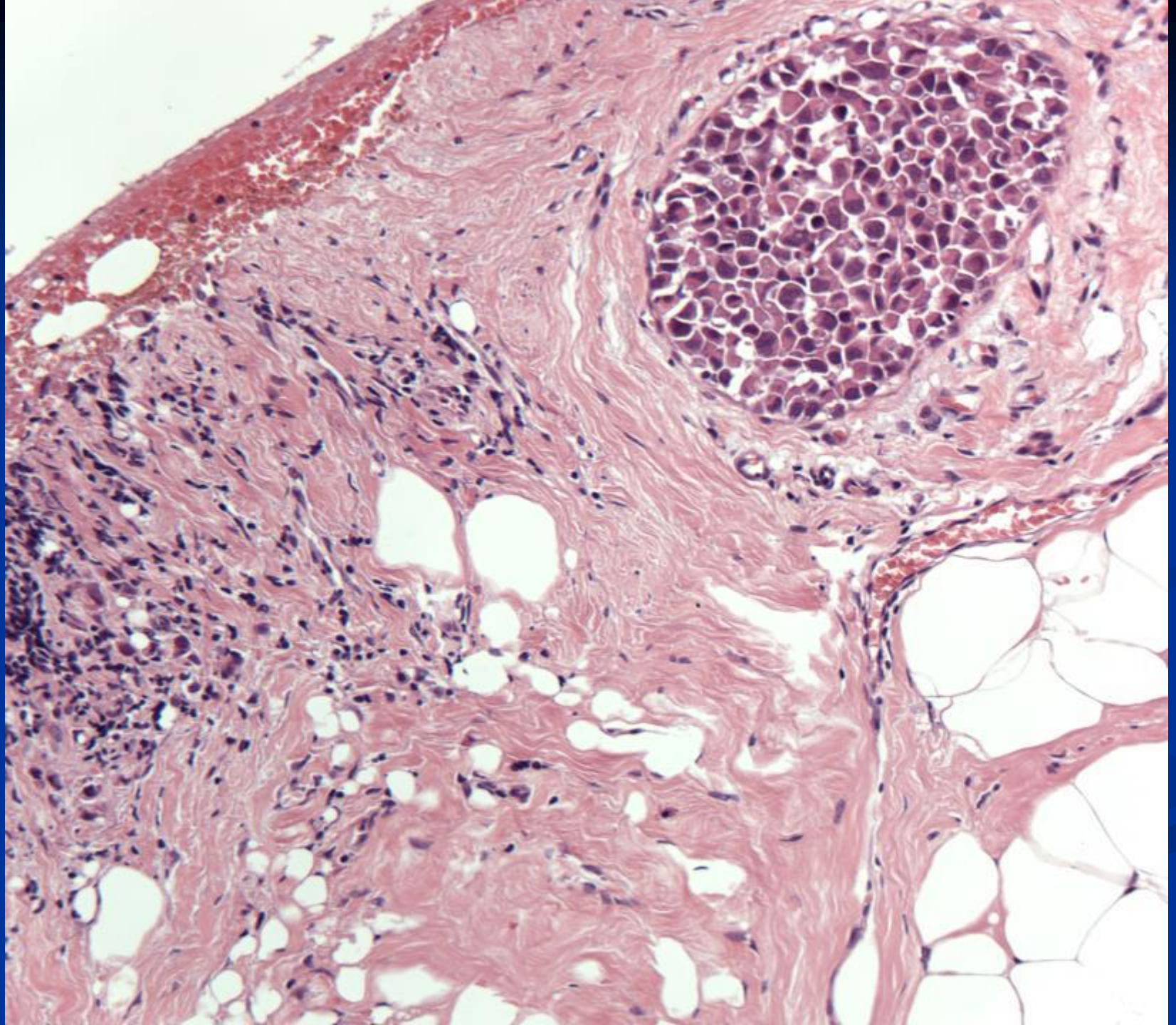
- Epithelial hyperplasia, no atypia: B2
- FEA, AIDEP, Lobular neoplasia: B3
- DCIS/PLCIS: B5a
- LCIS with necrosis: best coded as B4

Lobular neoplasia on core biopsy

- ALH/Classical LCIS: code as B3 and recommend second line VAB
- PLCIS: code as B5a and manage as DCIS
- Classical LCIS with necrosis: rare, best coded as B4, recommend surgical excision.

PLCIS on excision

- Sample well to exclude invasion
- Assess lesion size, relation to margin
- If associated with invasion: include size in whole tumour size
- If at margin: re-excision



THANK YOU