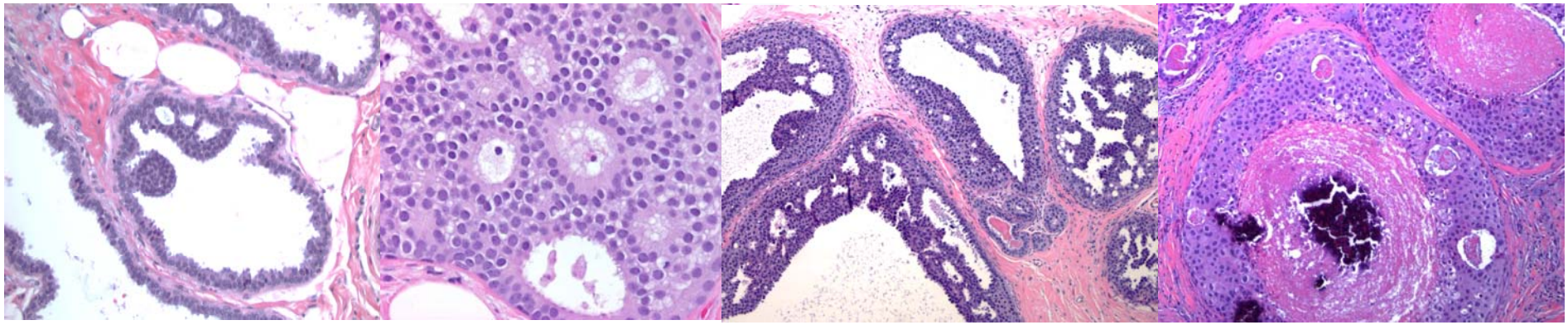

Workshop on Intraductal Proliferations of the Breast

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Goals and Objectives

- Review diagnostic criteria for intraductal lesions (UDH, ADH, DCIS, FEA)
- Understand the biology and clinical implications of these diagnoses
- Review challenging cases/borderline lesions
- Develop practical approaches to cases that take into account clinical considerations

Interobserver Reproducibility in the Diagnosis of Ductal Proliferative Breast Lesions Using Standardized Criteria

Stuart J. Schnitt, M.D., James L. Connolly, M.D., Fattaneh A. Tavassoli, M.D., Robert E. Fechner, M.D., Richard L. Kempson, M.D., Rebecca Gelman, Ph.D., and David L. Page, M.D.

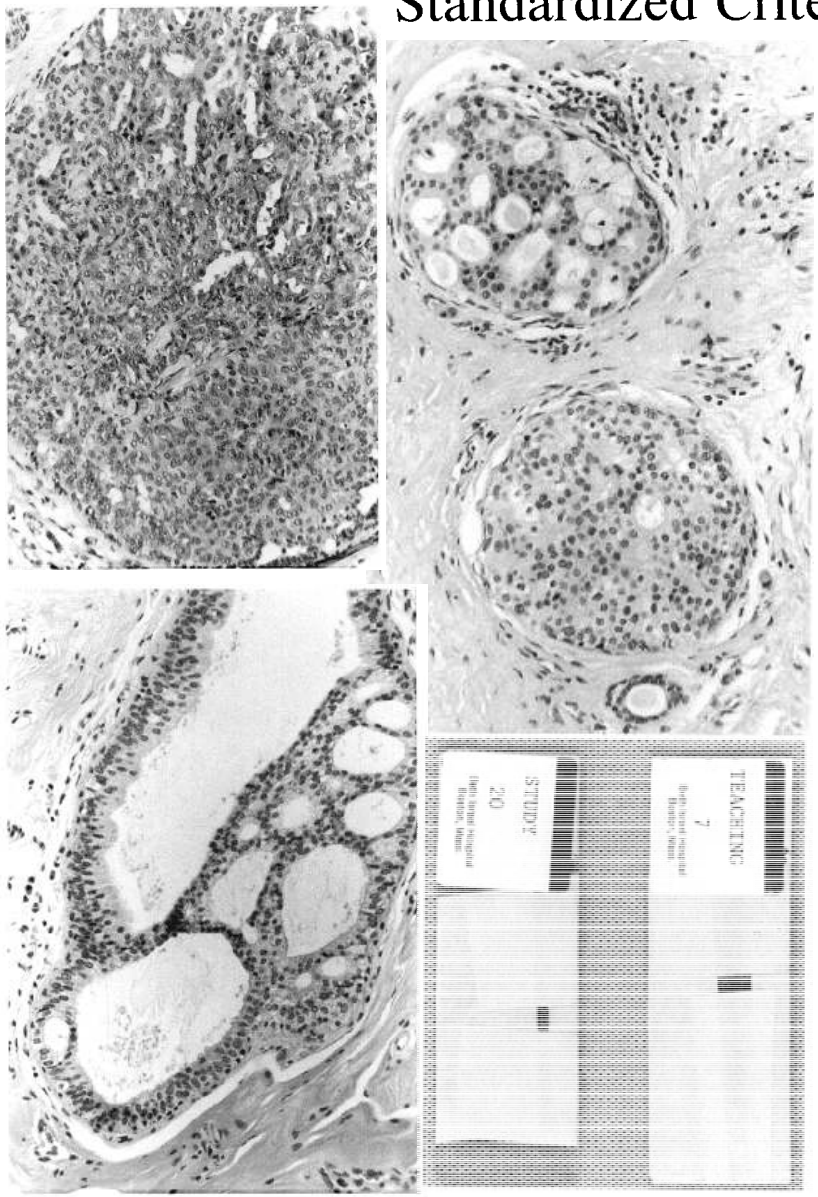


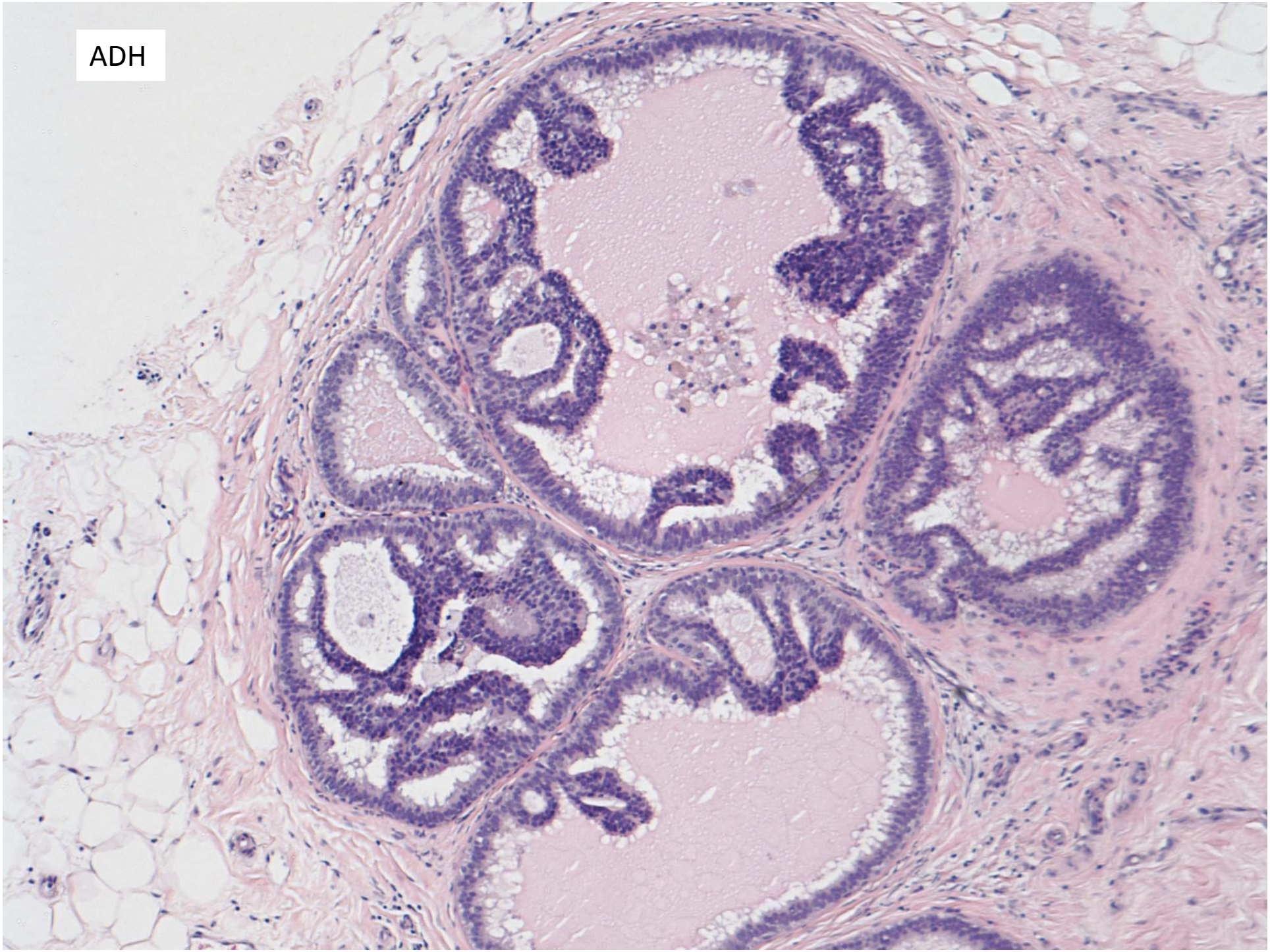
TABLE 1. *Guidelines for evaluation of proliferative ductal breast lesions as provided by Dr. Page*

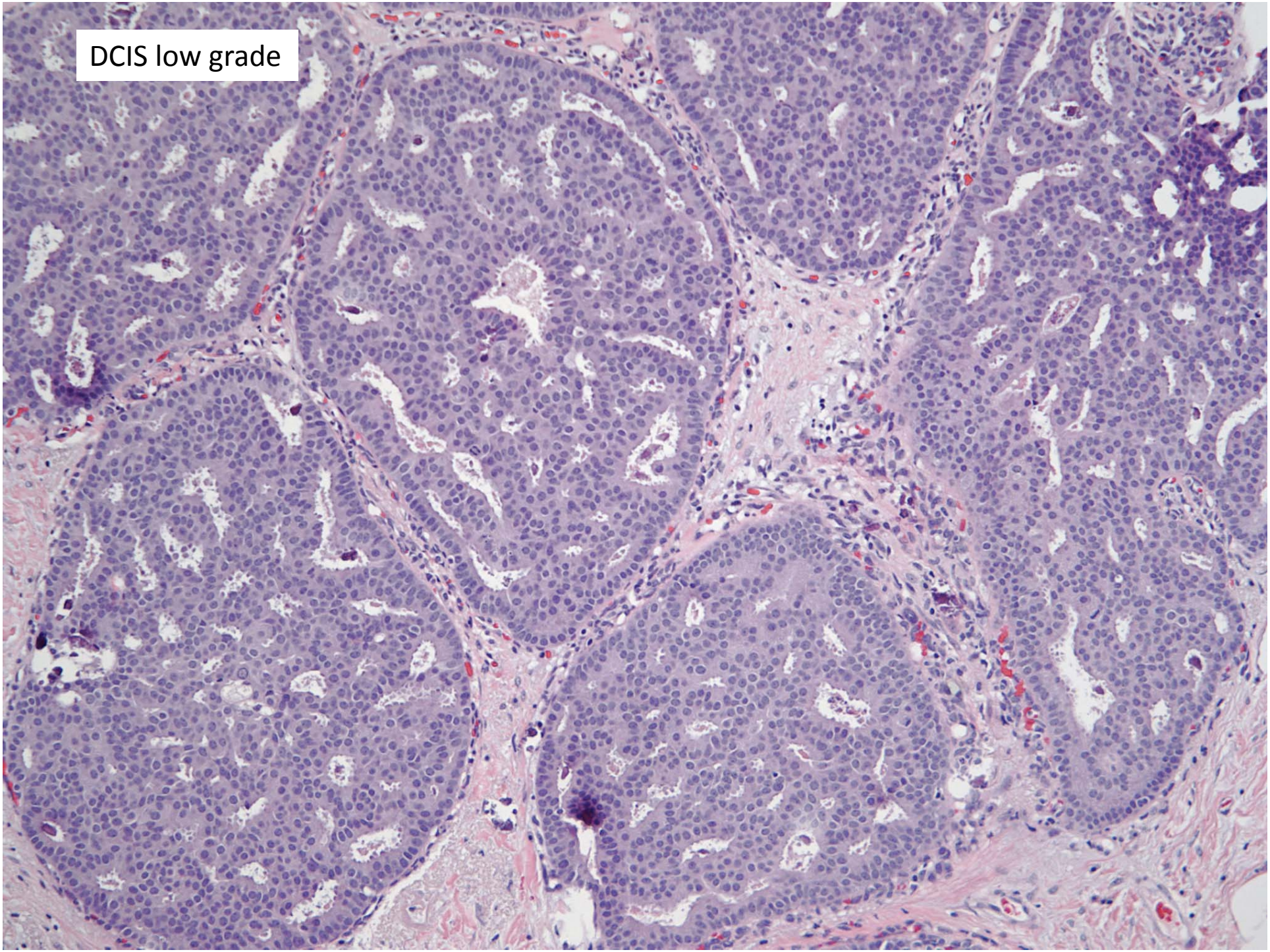
1. Florid hyperplasia without atypia has swirling of cells, variable nuclear shape and placement, and irregular intercellular spaces that are most marked centrally.
2. Ductal carcinoma in situ (noncomedo type) has a population of evenly spaced, uniform cells with uniform nuclear features, comprising without doubt the entire population of cells throughout two membrane-bound spaces.
3. Atypical ductal hyperplasia has the presence of the cell population defined above for noncomedo ductal carcinoma in situ present in part of the space. Usually the second cell population consists of polarized cells as seen in the breast in the luminal position immediately above the basement membrane.
4. When in doubt between atypical ductal hyperplasia and ductal carcinoma in situ, use the more benign designation.
5. To qualify as atypical ductal hyperplasia (as opposed to florid hyperplasia without atypia), the bothersome cell population usually, but not always, has hyperchromatic nuclei.
6. To qualify as atypical ductal hyperplasia (as opposed to florid hyperplasia without atypia), the bothersome cells need to constitute an entire bar crossing a space or at least a cell population of six or seven cells across so as to avoid calling atypical ductal hyperplasia when there is a population of cells less than the numbers indicated. This is an indication of the lower level of definition for atypical ductal hyperplasia.

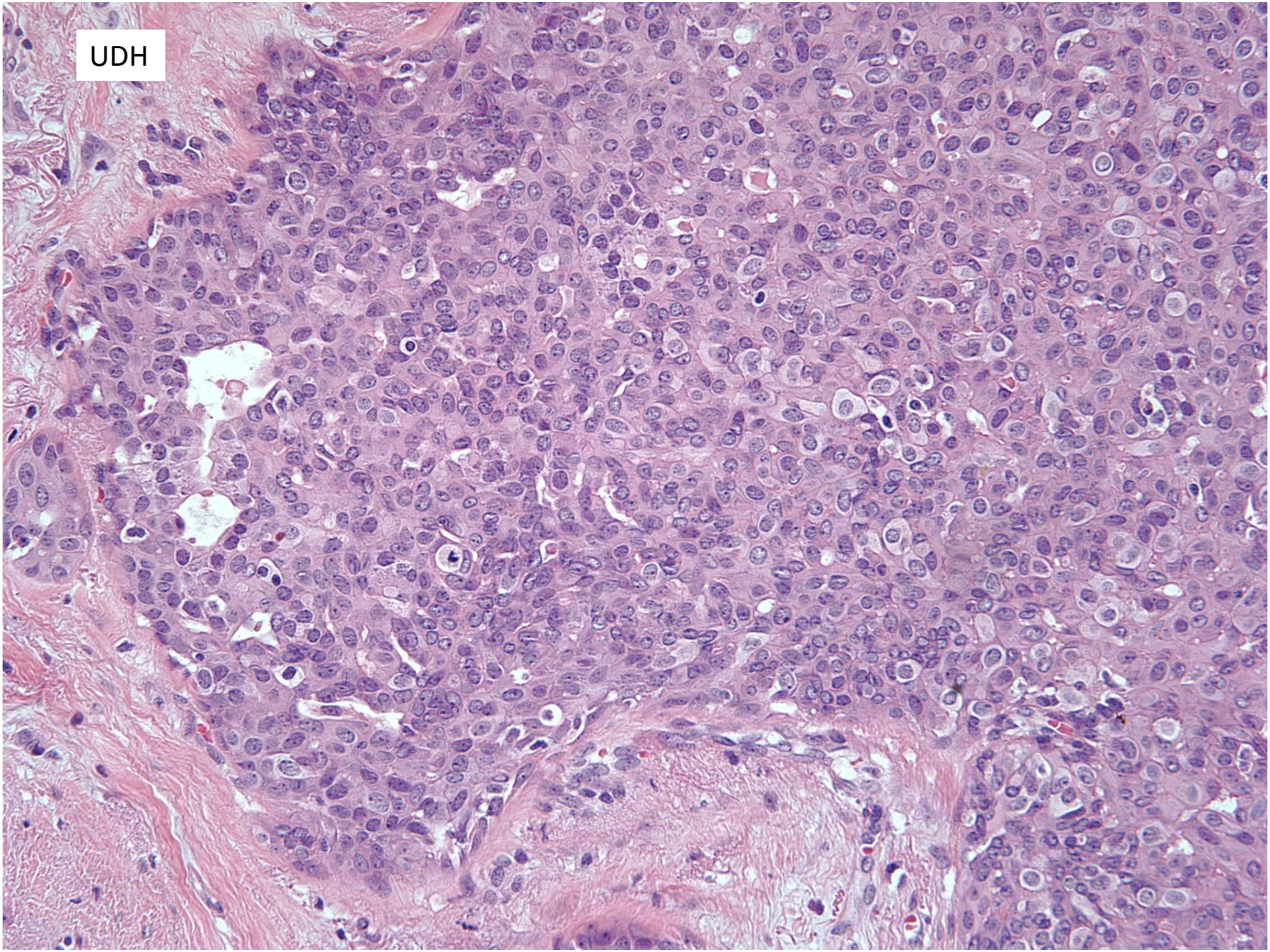
The American Journal of Surgical Pathology *16(12): 1133–1143, 1992*

Definition of ADH

- Some but not all of the features of LG DCIS:
  - Cytology: Low grade monotonous cells
  - Architecture: Bridging, polarized spaces, micropapillae
- Size criteria:
  - Developed for use in excisions only
  - Two duct spaces or 2.0 mm

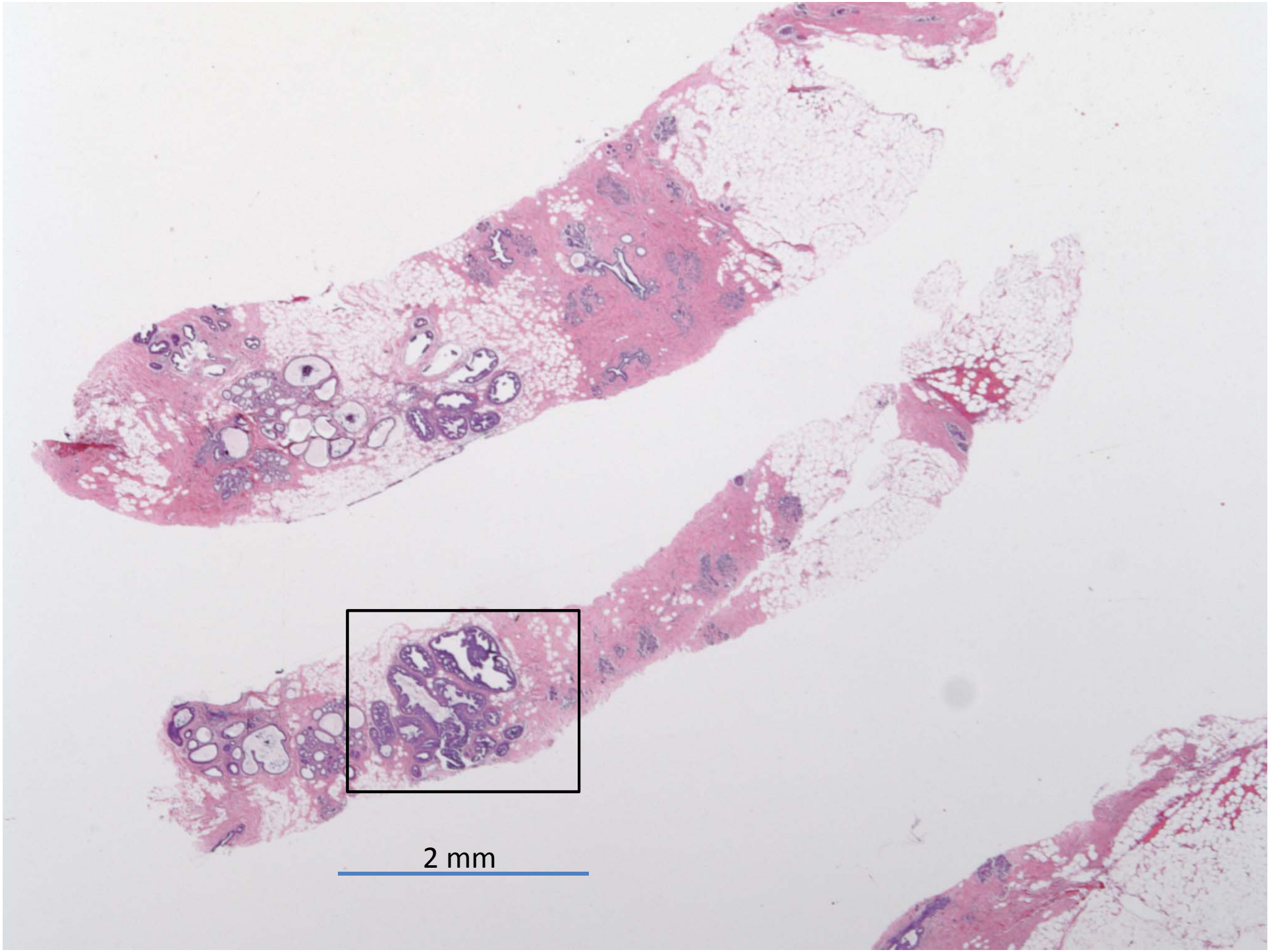

ADH

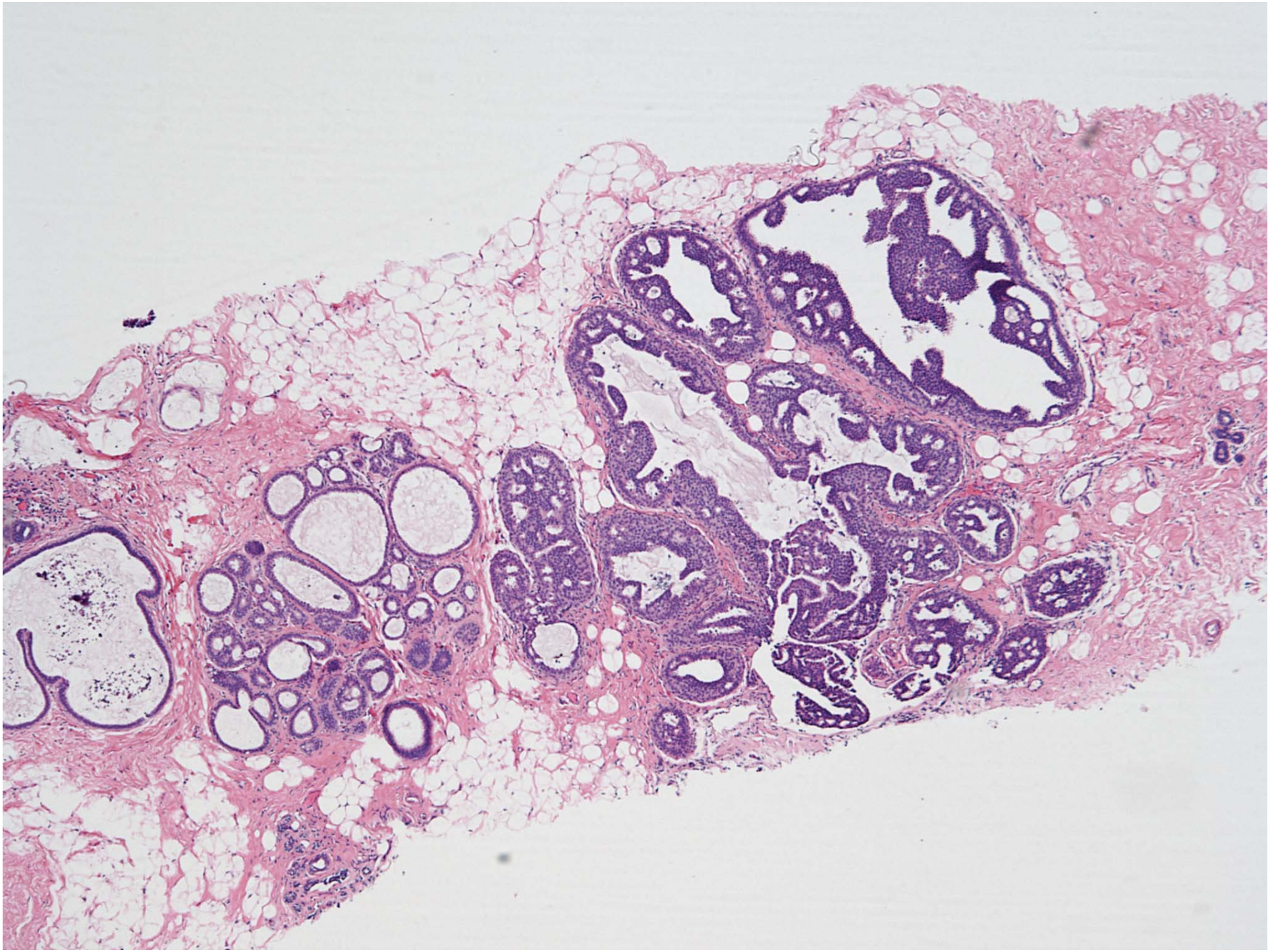

DCIS low grade

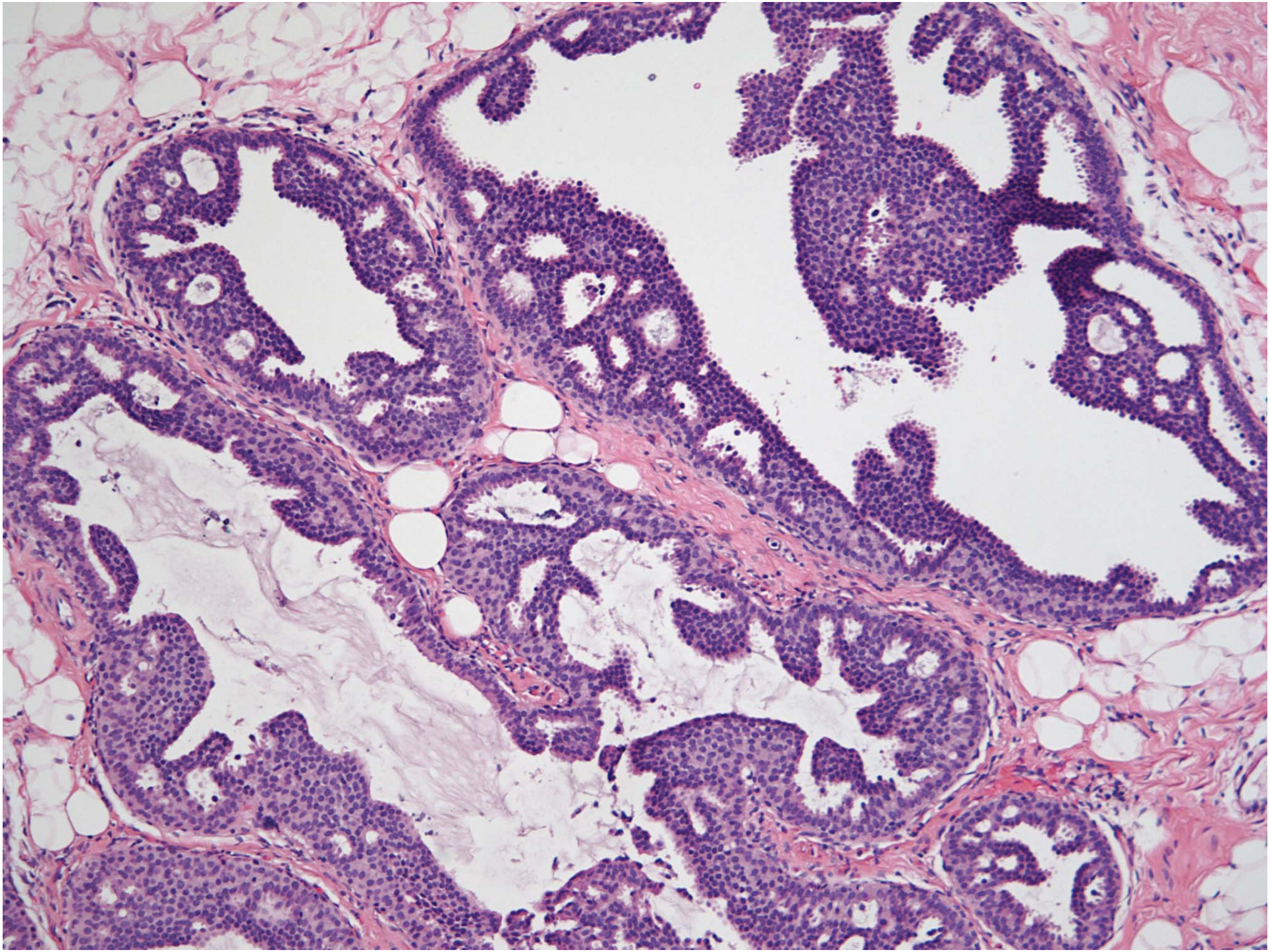

UDH

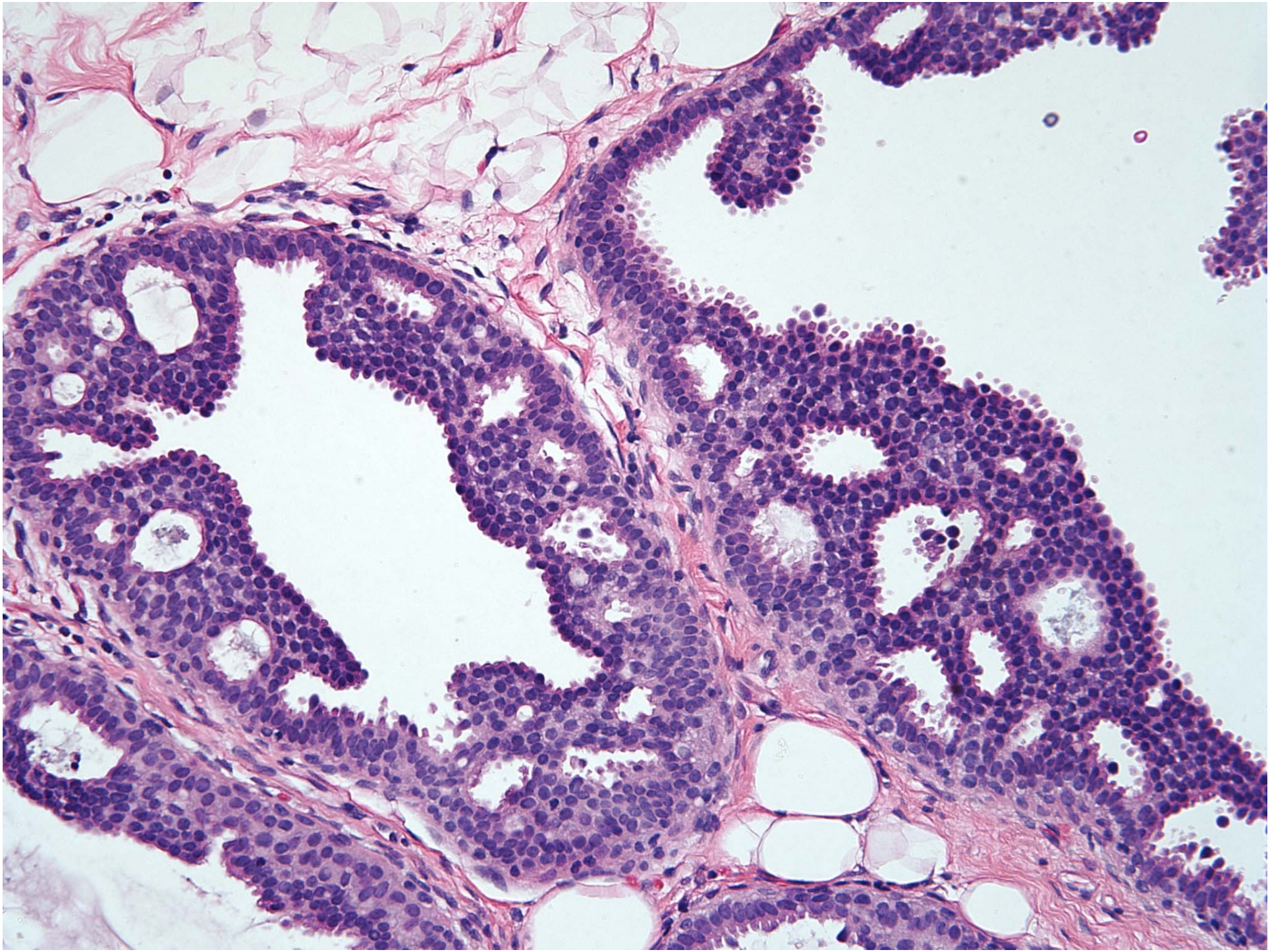
Case #1

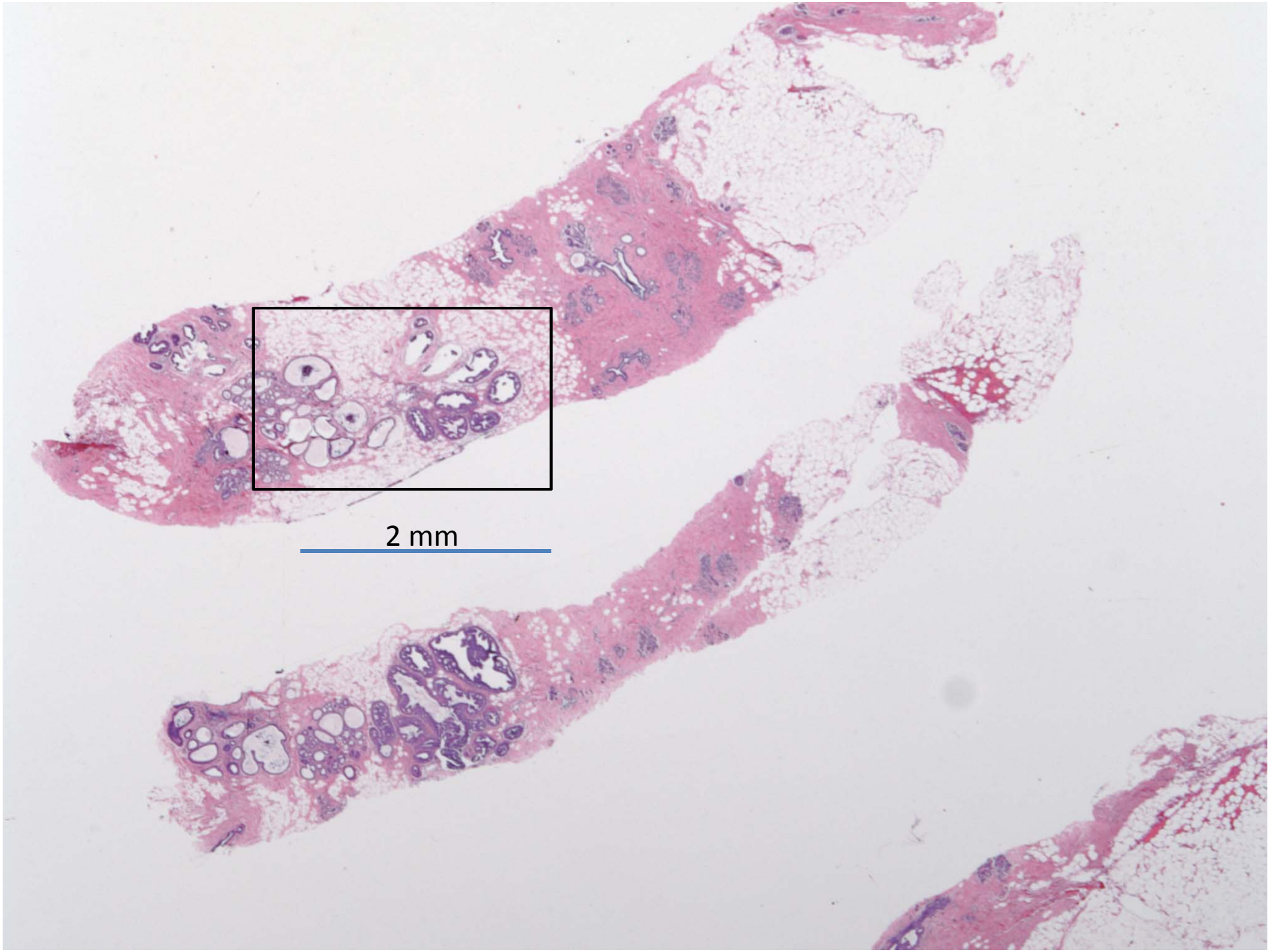
- 65 year old with 1.5 cm of suspicious calcifications


2 mm





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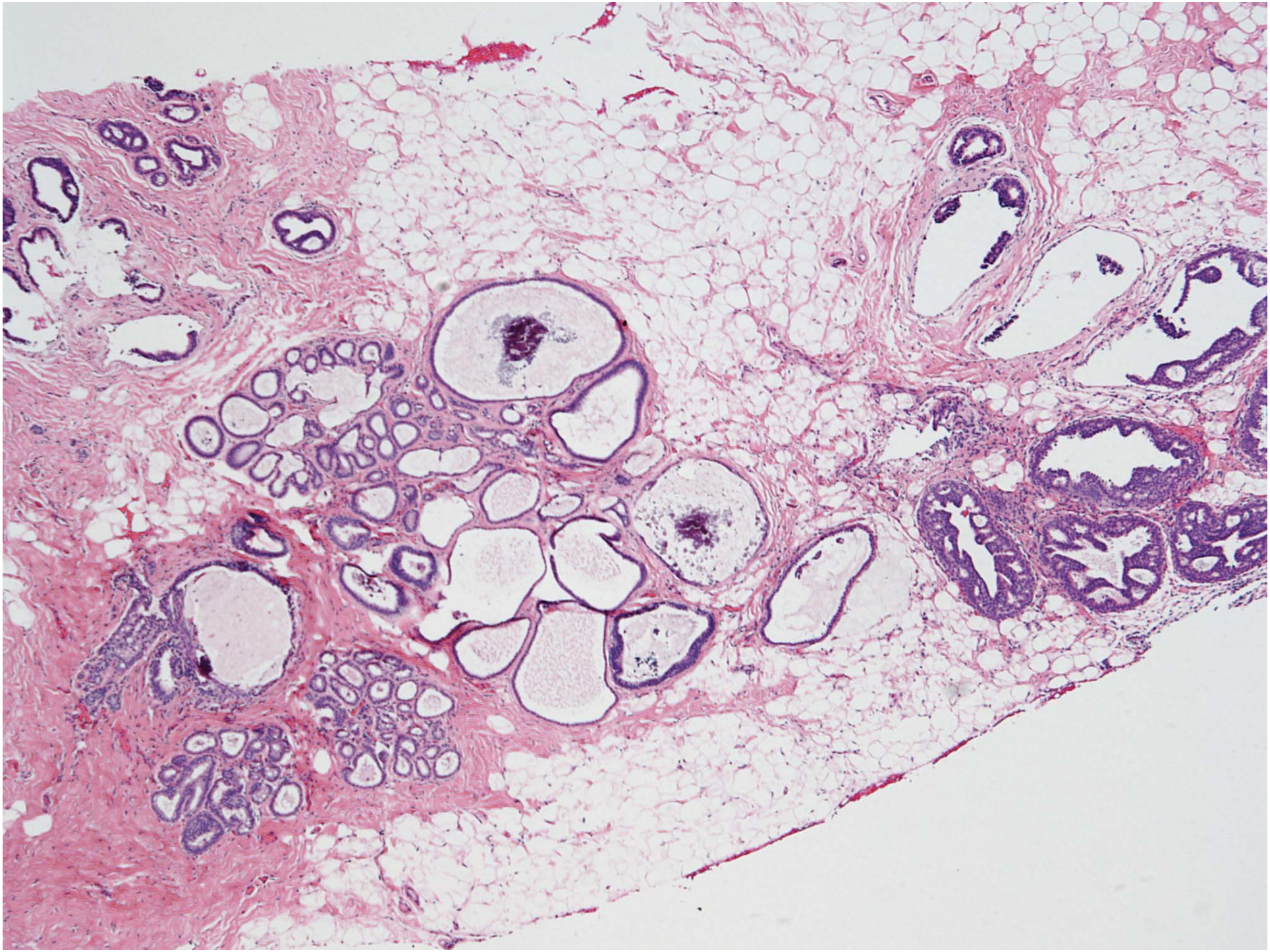
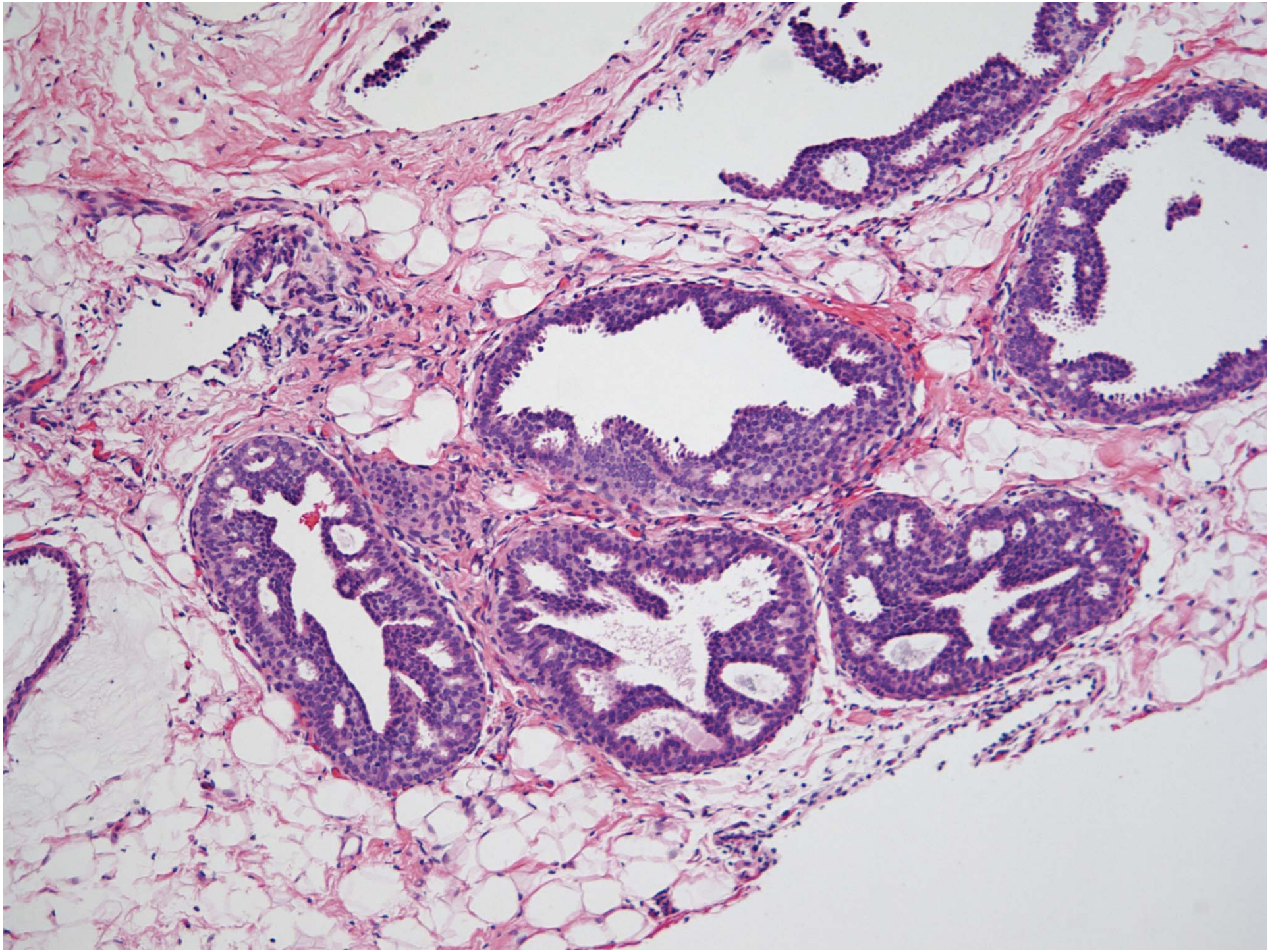




Clinical Impact of Core Biopsy Diagnosis

- UDH → No further management

- ADH → Surgical consultation with excisional biopsy to rule out adjacent DCIS or invasion

Borderline lesion not definite DCIS – get more tissue!

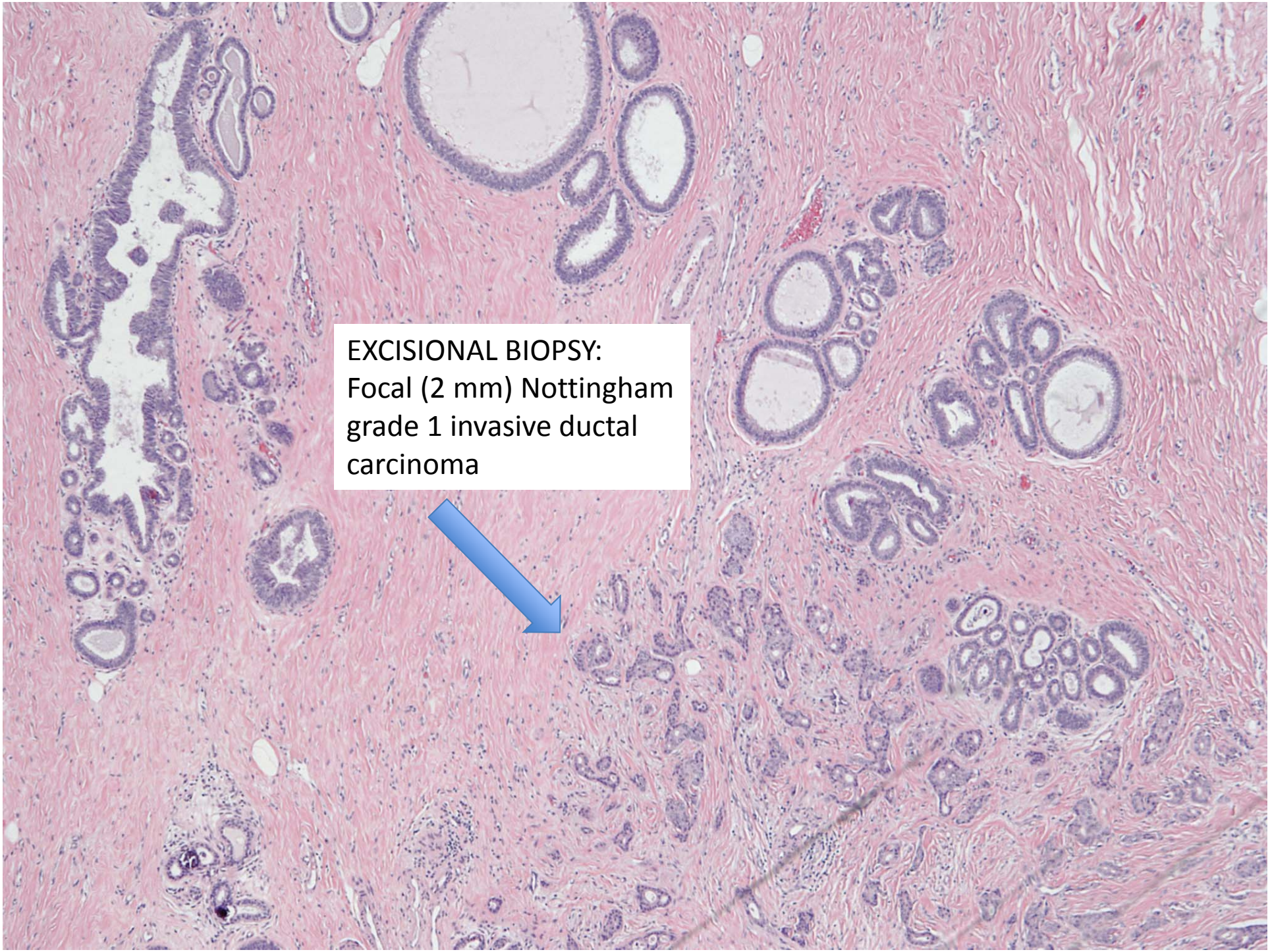
- DCIS → Surgical excision to negative margins (lumpectomy+XRT or mastectomy) +/- hormonal therapy if ER+

Need to be 100% certain = a “cancer” diagnosis with major treatment implications!

Diagnosis:

- Left breast calcifications at 2:00, stereotactic core needle biopsy:
  - Atypical ductal hyperplasia
  - Calcifications present, associated with atypical and non-atypical ducts

Sent for excisional biopsy

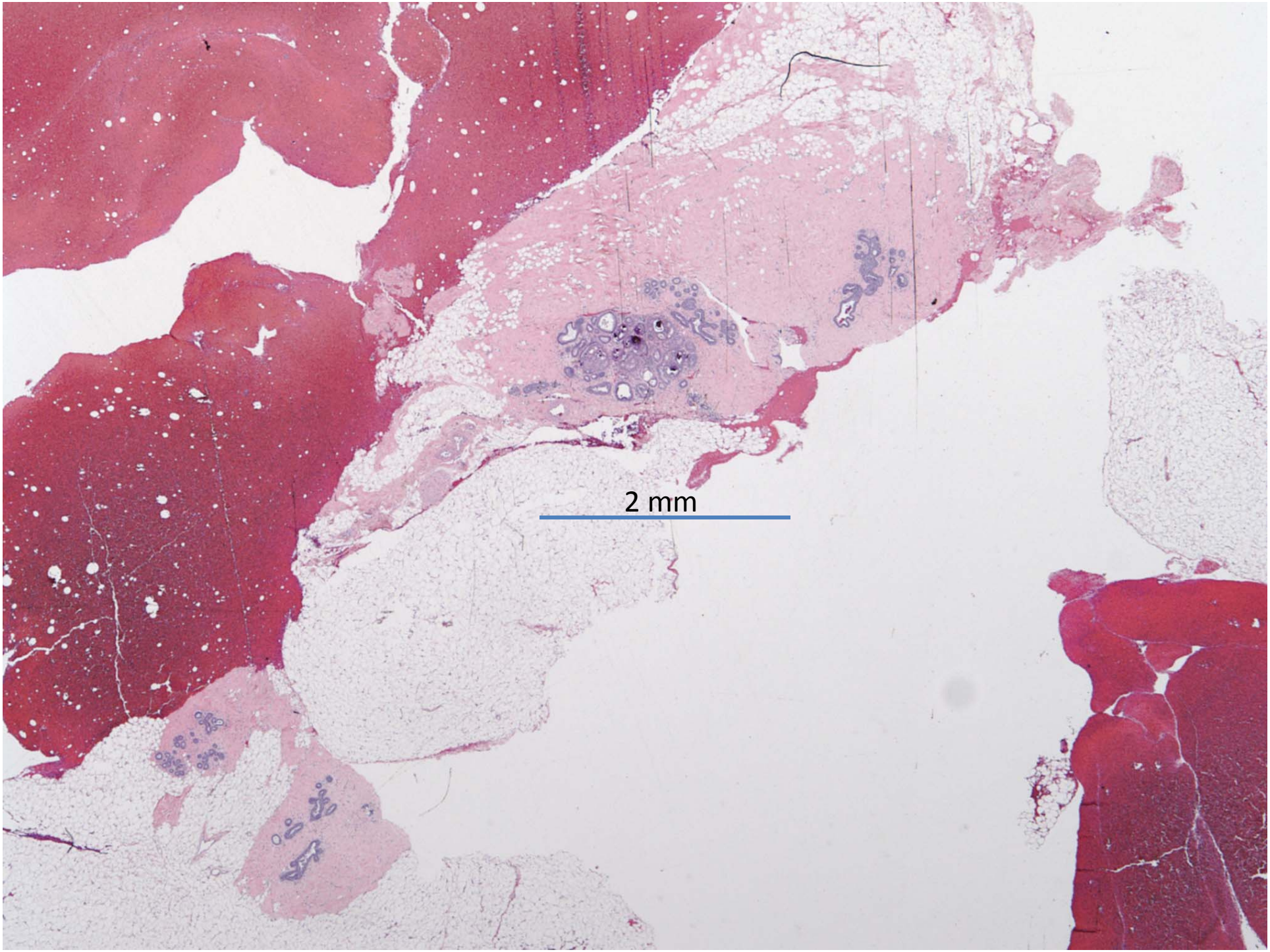

EXCISIONAL BIOPSY:
Focal (2 mm) Nottingham grade 1 invasive ductal carcinoma

Upgrade Rates of ADH on Core

- Wide range depending on study 3-60% (most between 10-20%) – will depend on study population used
- At Stanford:
  - ADH in 9% of breast cores
  - Upgrade rate of 13% to DCIS or invasion
- What does it upgrade to?
  - Low-intermediate grade DCIS
  - Low grade invasive carcinomas

CASE #2:

- 45 year old with 0.2 cm focus of clustered calcifications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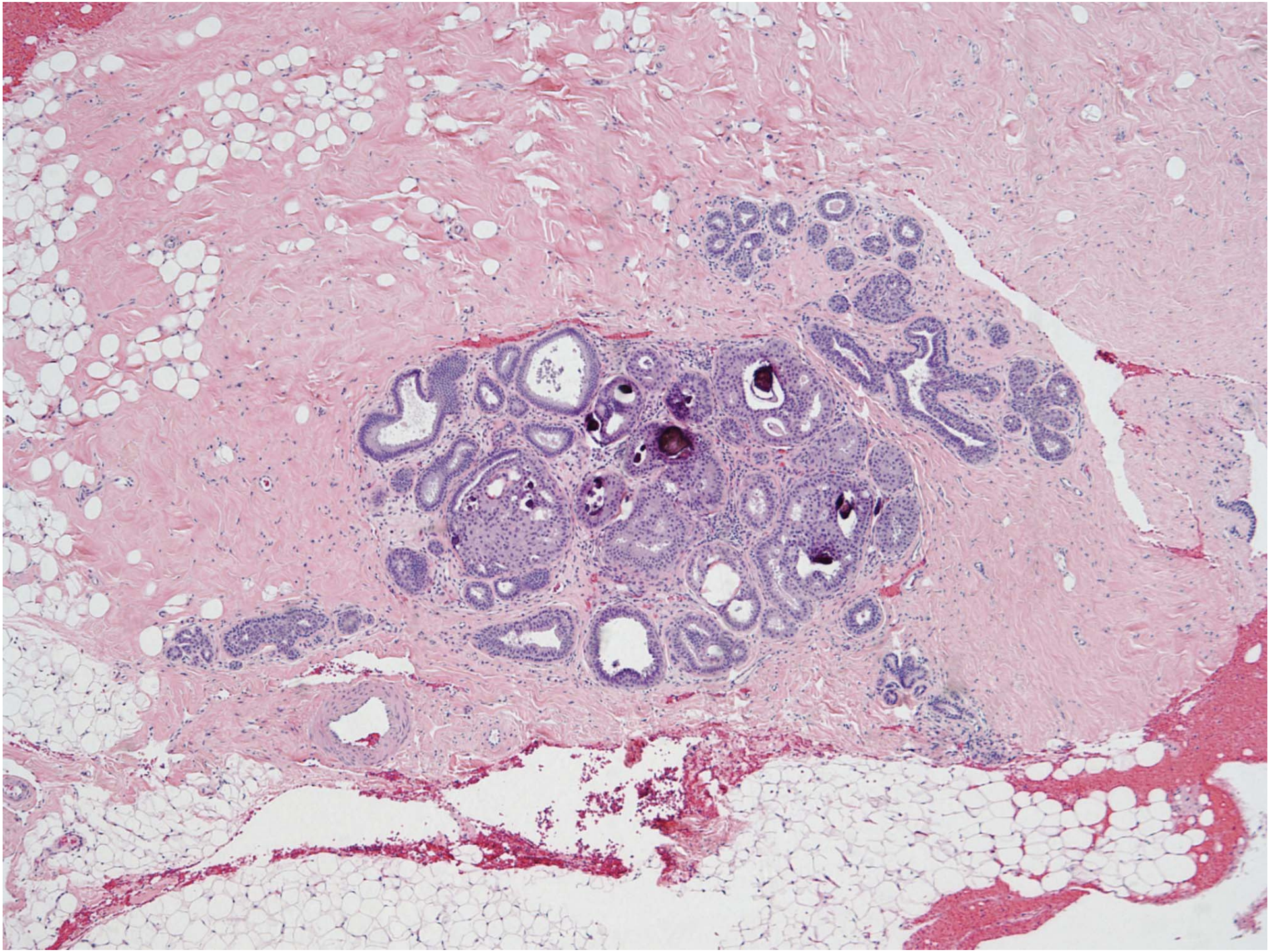
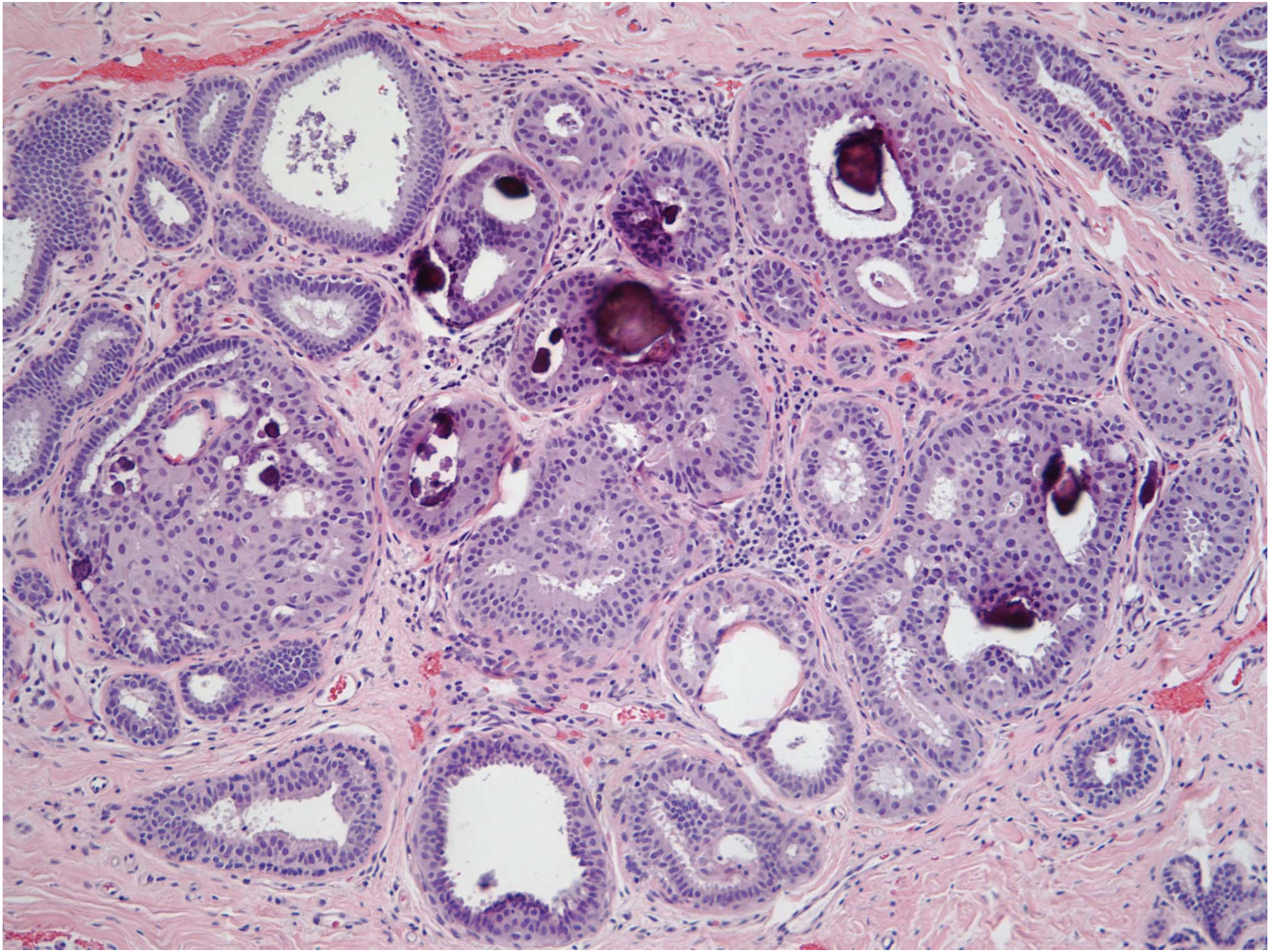




Diagnosis:

- Right breast calcifications at 10:00, stereotactic core needle biopsy:
  - Minimal atypical ductal hyperplasia with associated calcifications

COMMENT: There is a single (< 1 mm) focus of atypical ductal hyperplasia present. Dr Atypia has reviewed selected slides form this case and agrees. Levels were performed in the evaluation of this case.

Minimal ADH

- Studies on # of foci of ADH = can stratify risk some
- What upgrade rate is considered acceptable?
- Agreement is worse with focal lesions
- Correlation with radiology findings

- GET A SECOND REVIEW

Atypical ductal hyperplasia on vacuum-assisted breast biopsy: suspicion for ductal carcinoma in situ can stratify patients at high risk for upgrade☆

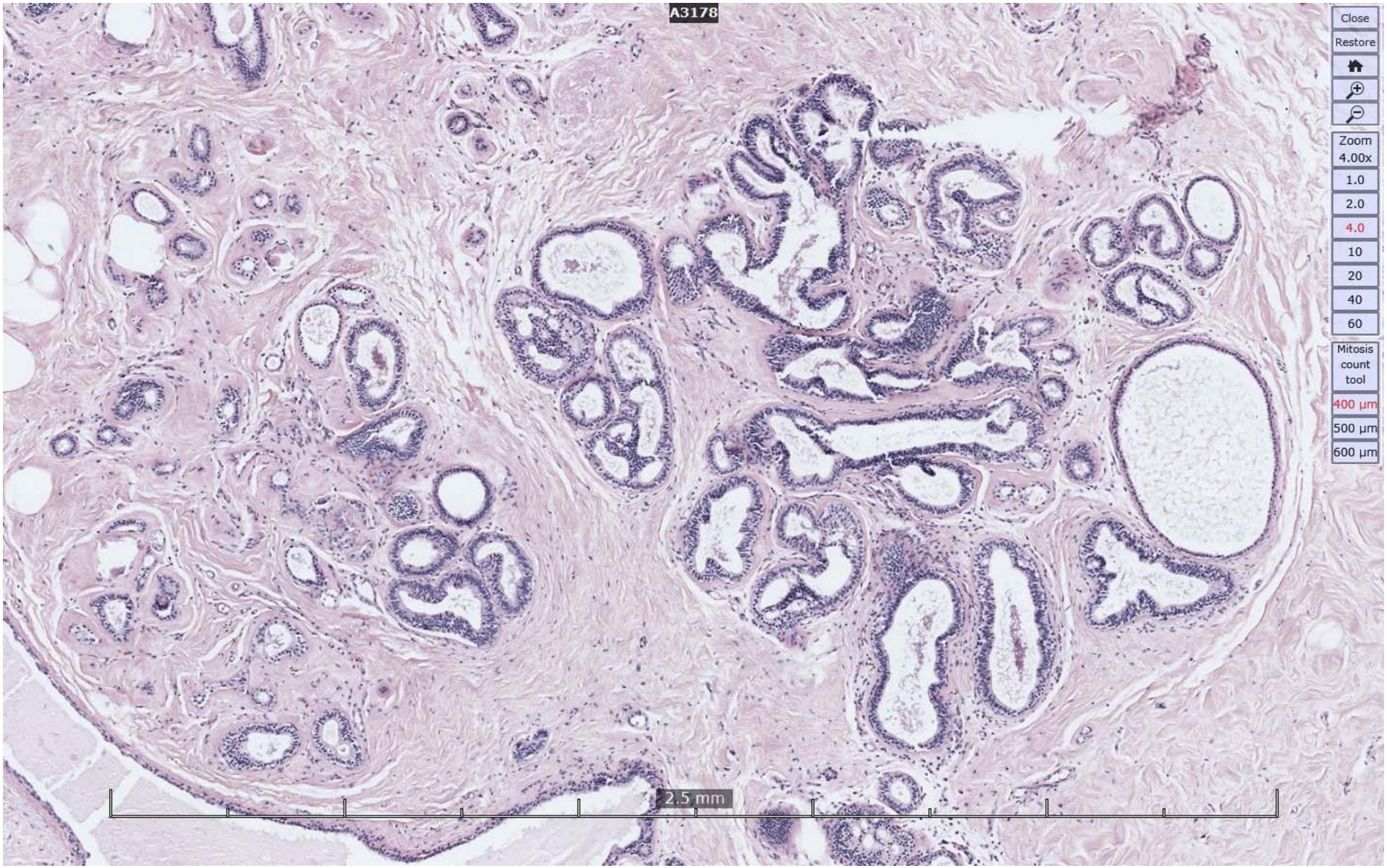
Kimberly H. Allison MD[a,*], Peter R. Eby MD[b], Jennifer Kohr MD[b], Wendy B. DeMartini MD[b], Constance D. Lehman PhD[b]

Table 2 Upgrade rates for ADH using combined features of number of foci and if suspicious

Combined features	Upgrade rate
≥3 foci and suspicious	10/19 (53%)
<3 foci and NOT suspicious	3/38 (8%)
≥3 foci and NOT suspicious	/34 (15%)
<3 foci and suspicious	/6 (33%)
$P = .0003$ value for both *vs* neither	

Human Pathology (2011) **42**, 41–50

All 3 upgraded to 1-3 mm foci of Grade 1 IDC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60
Mitosis
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tool
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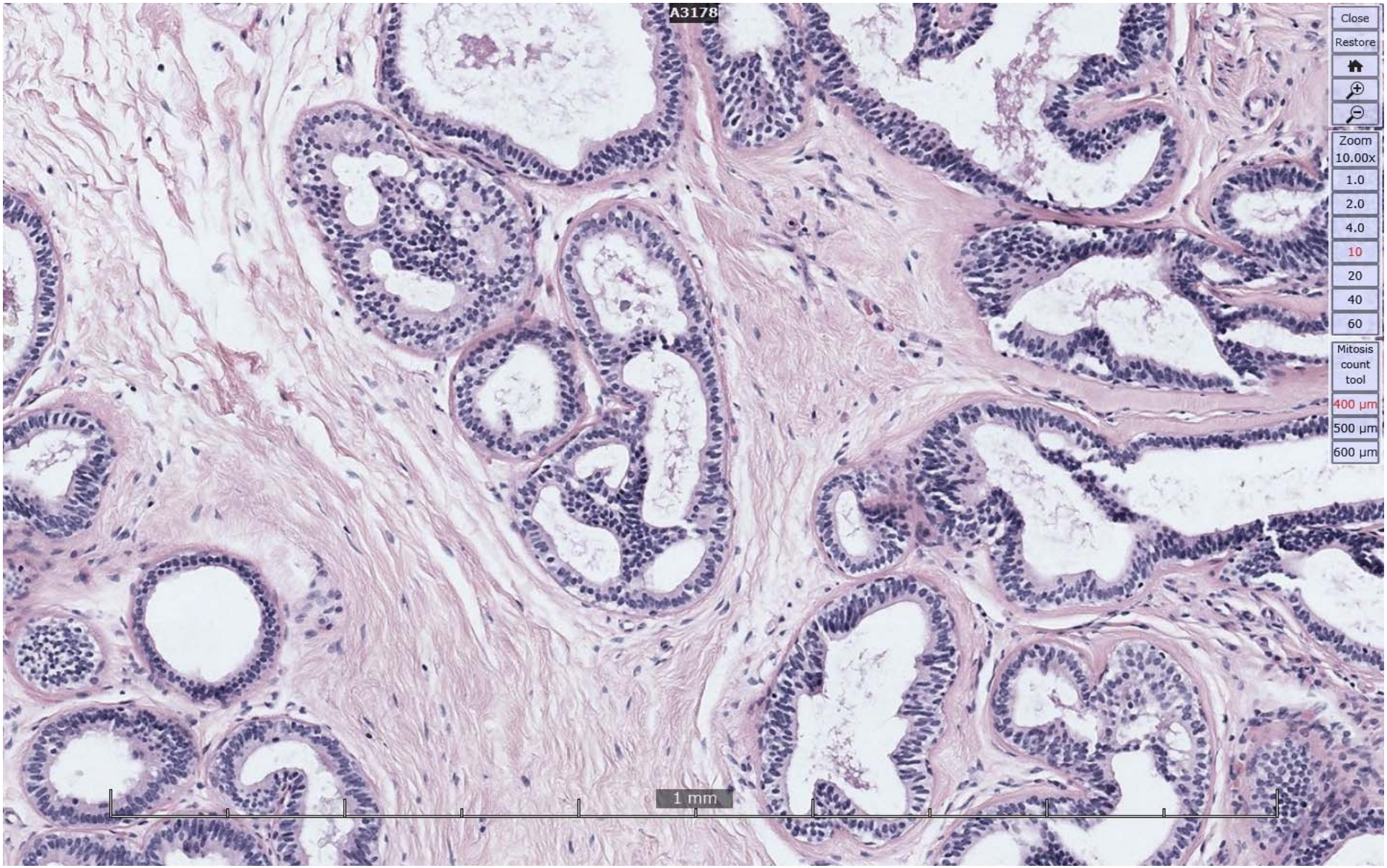
500 µm
600 µm
2.5 mm

BPATH study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40
60
Mitosis
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tool
400 µm
500 µm
600 µm
1 mm

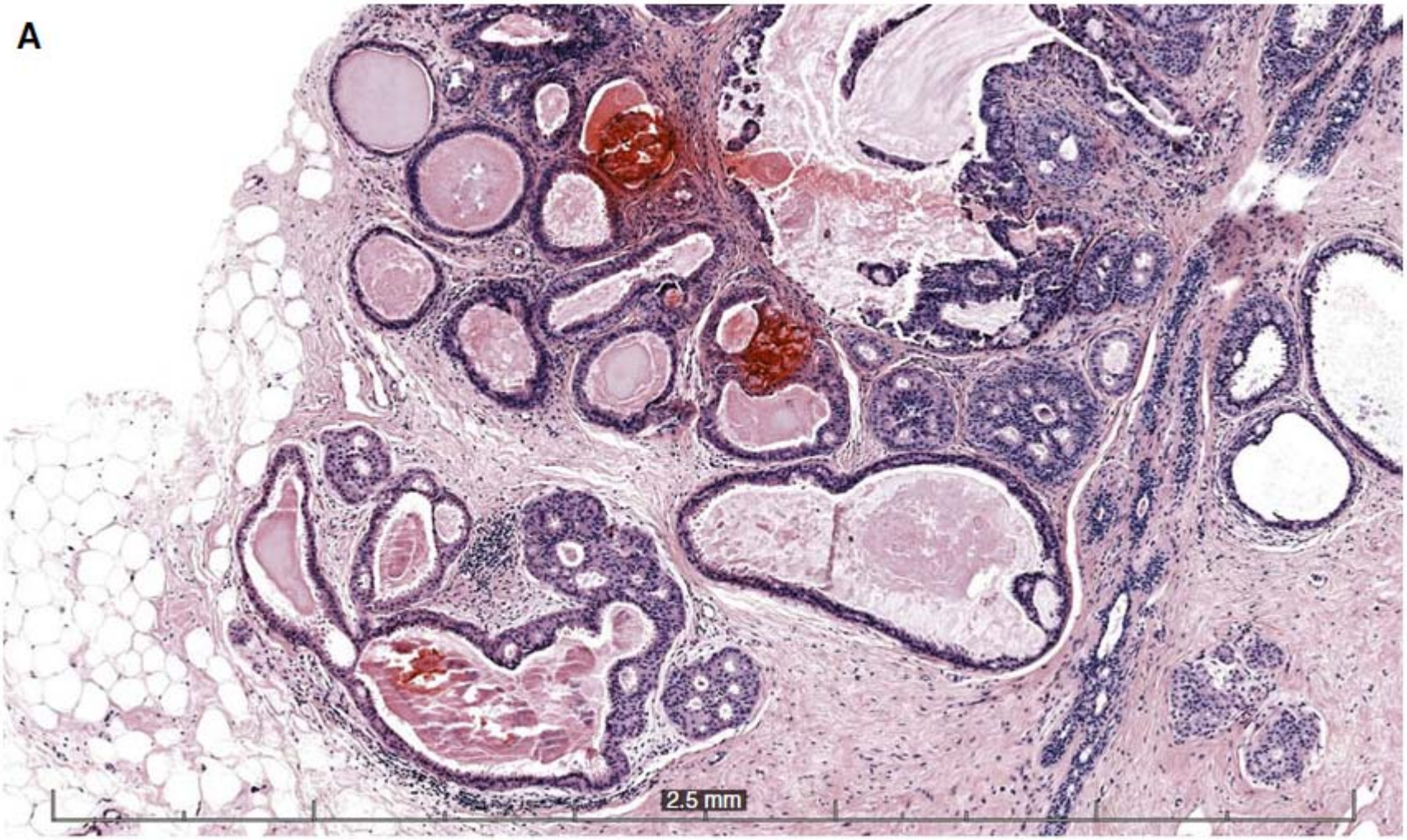
Why do we disagree?

Understanding diagnostic variability in breast pathology: lessons learned from an expert consensus review panel

Kimberly H Allison, Lisa M Reisch,[1] Patricia A Carney,[2] Donald L Weaver,[3] Stuart J Schnitt,[4] Frances P O'Malley,[5] Berta M Geller[6] & Joann G Elmore[1]

Histopathology 2014, **65**, 240–251. DOI: 10.1111/his.12387

Pathologist-related		
Professional differences of opinion on features meeting diagnostic criteria	Discussion focused on subtle differences of professional opinion about whether the features present met the criteria for a specific diagnosis	1st
Not noting a focal diagnostic finding	Pathologist verbally acknowledged not noting the diagnostic area of the slide (all of these were focal findings)	2nd
Different diagnostic philosophy (clinical impact versus morphology)	Discussion focused on differences in taking into account the potential clinical relevance of a diagnosis versus utilizing strictly morphological features	3rd
Different diagnostic criteria	Discussion focused on pathologists' use of different diagnostic criteria for a specific diagnosis in a given case	4th
Different diagnostic features noted	Discussion focused on disagreement about the specific morphological features present	4th



Histopathology 2014, **65**, 240–251. DOI: 10.1111/his.12387

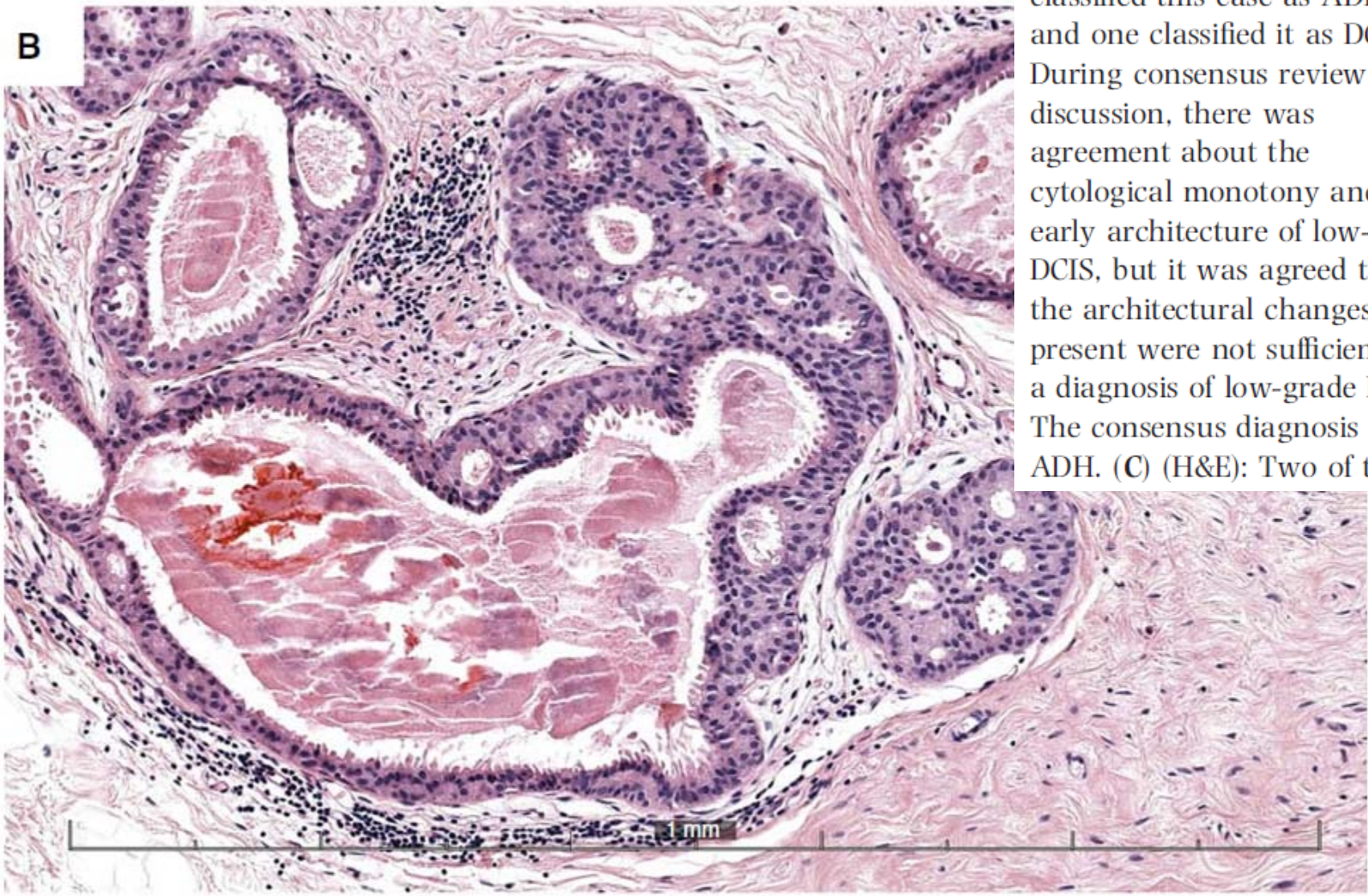
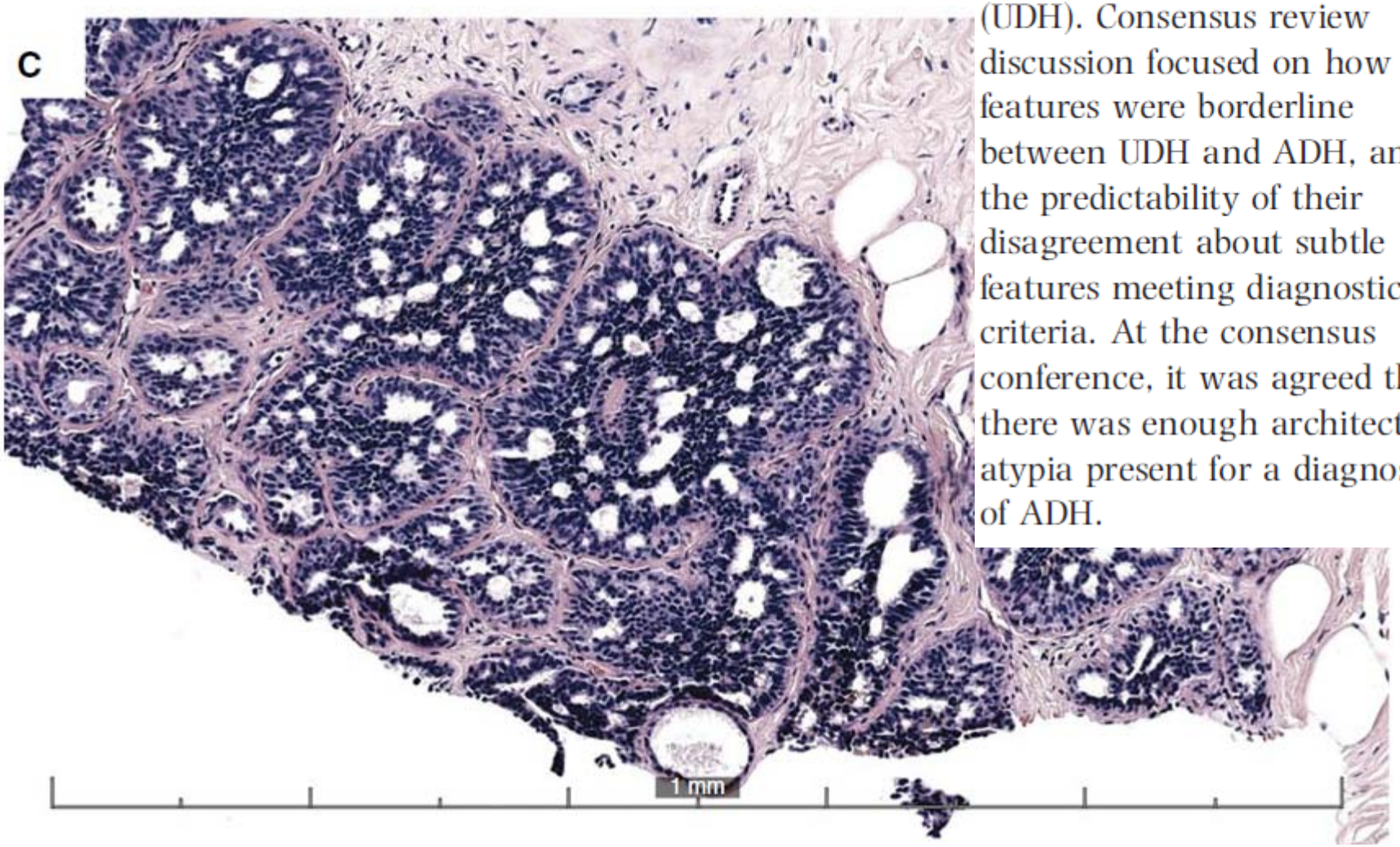


Figure 2. (**A**,**B**) (H&E): Two of the three expert breast pathologists independently classified this case as ADH, and one classified it as DCIS. During consensus review discussion, there was agreement about the cytological monotony and early architecture of low-grade DCIS, but it was agreed that the architectural changes present were not sufficient for a diagnosis of low-grade DCIS. The consensus diagnosis was ADH. (**C**) (H&E): Two of three

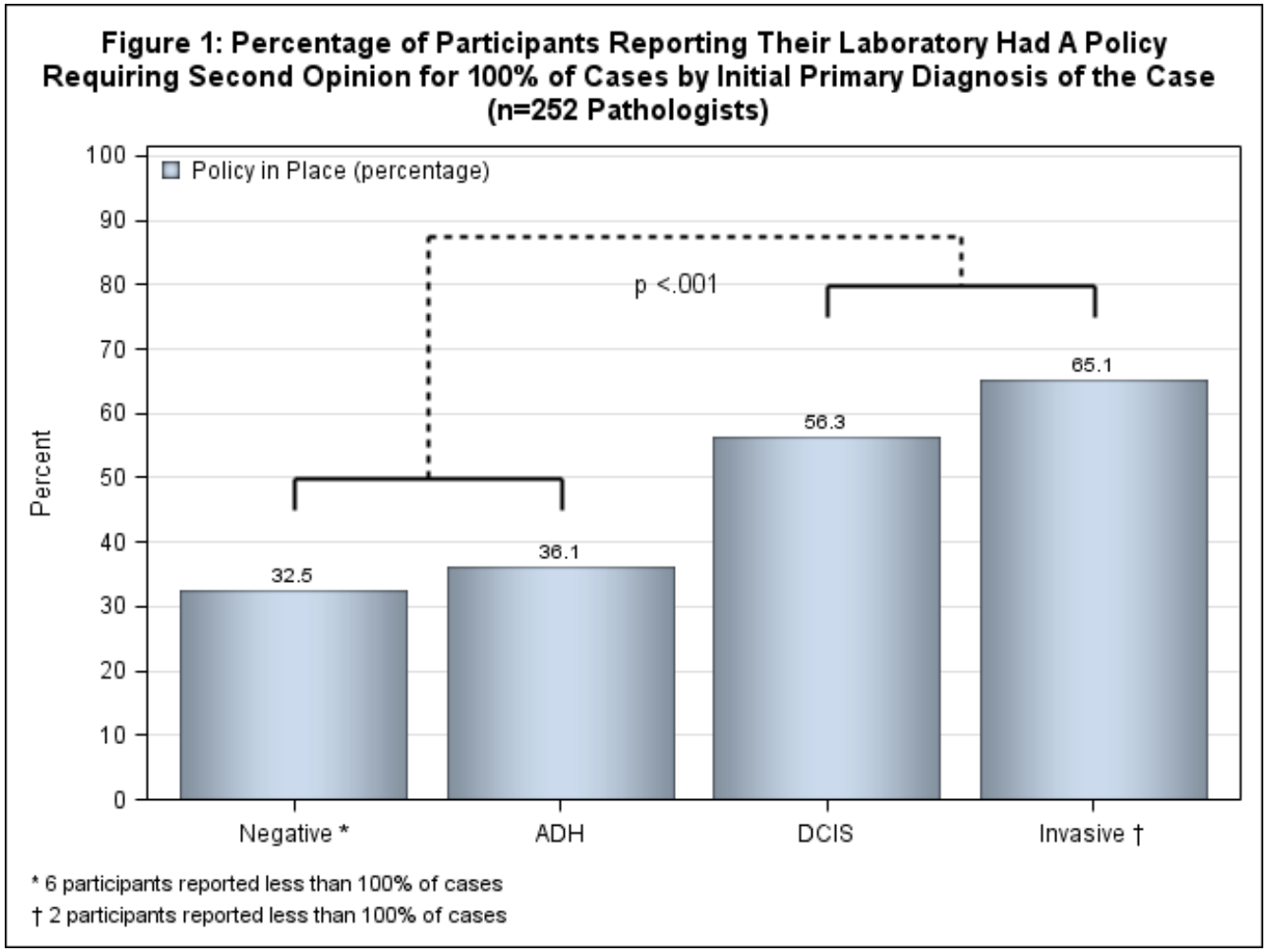
(**C**) (H&E): Two of three expert breast pathologists independently classified this case as ADH, and one classified it as usual ductal hyperplasia (UDH). Consensus review discussion focused on how the features were borderline between UDH and ADH, and the predictability of their disagreement about subtle features meeting diagnostic criteria. At the consensus conference, it was agreed that there was enough architectural atypia present for a diagnosis of ADH.



Reality Check on Intraductal Proliferative Lesions

- It’s a spectrum and there are grey zones
- Specialists and non-specialists both have poor agreement on atypia
- Clinical context matters
- Second reviews!!

Second Review Policies



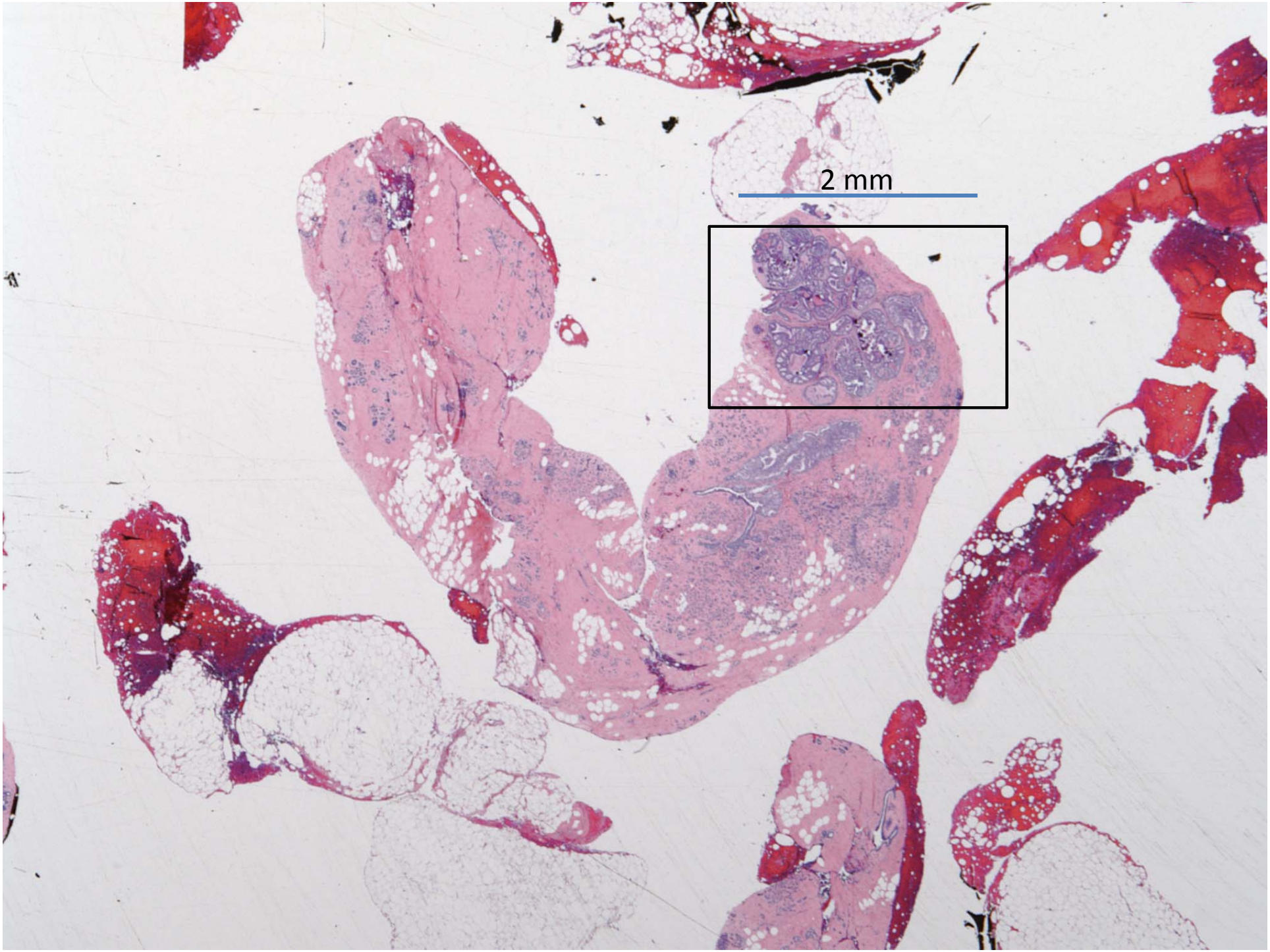
Of participants reporting no second opinion policy for ADH:

- 83.9% obtained second opinions in at least some
- 28.0% in all cases

Gellar BM, et al. Second opinion in breast pathology: Policy, practice and perception. Archives of Pathology, *IN PRESS*

Case #3

- 85 year old with poor performance status found to have a 0.3 cm cluster of suspicious calcifications on screening mammogram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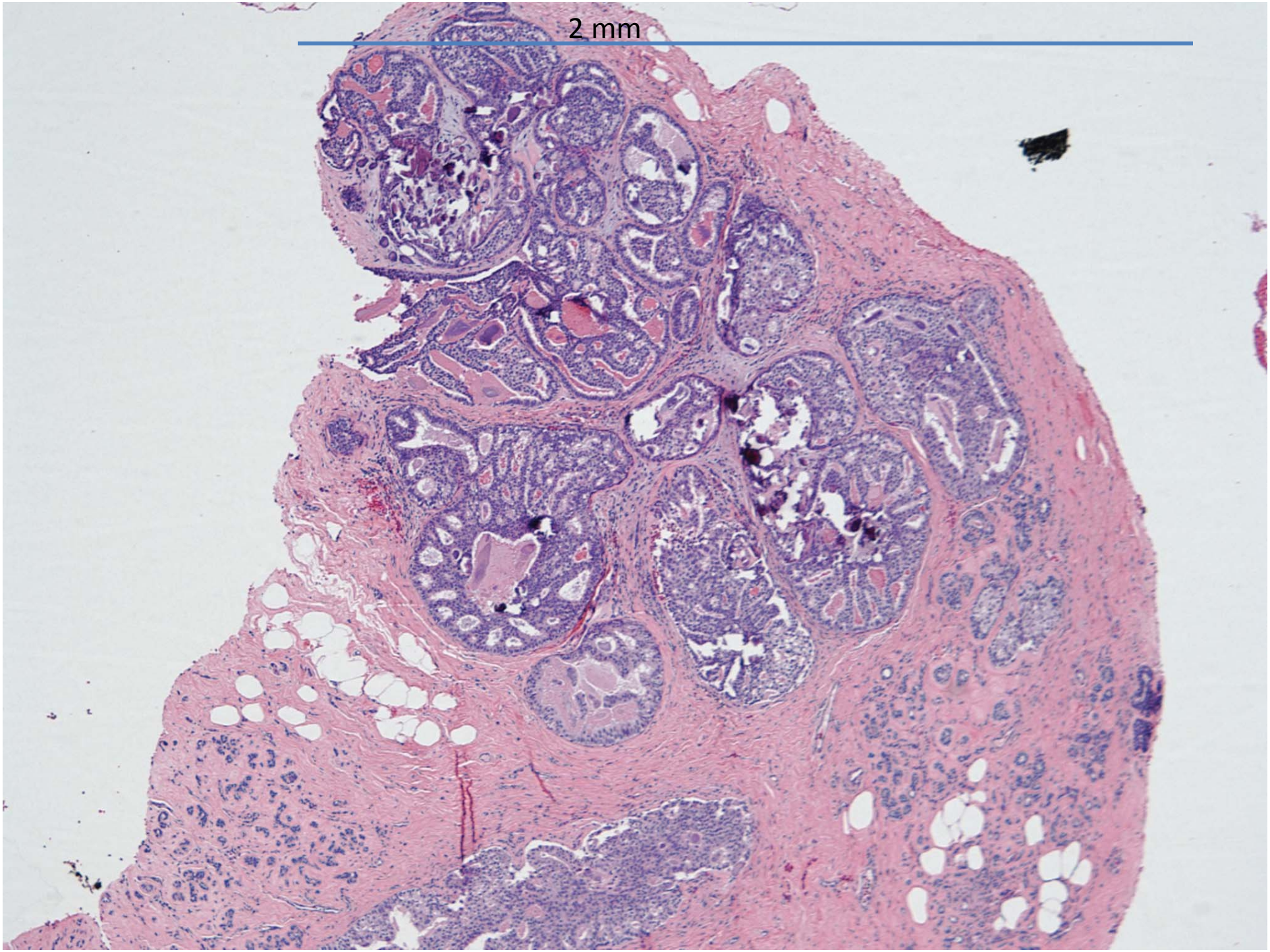
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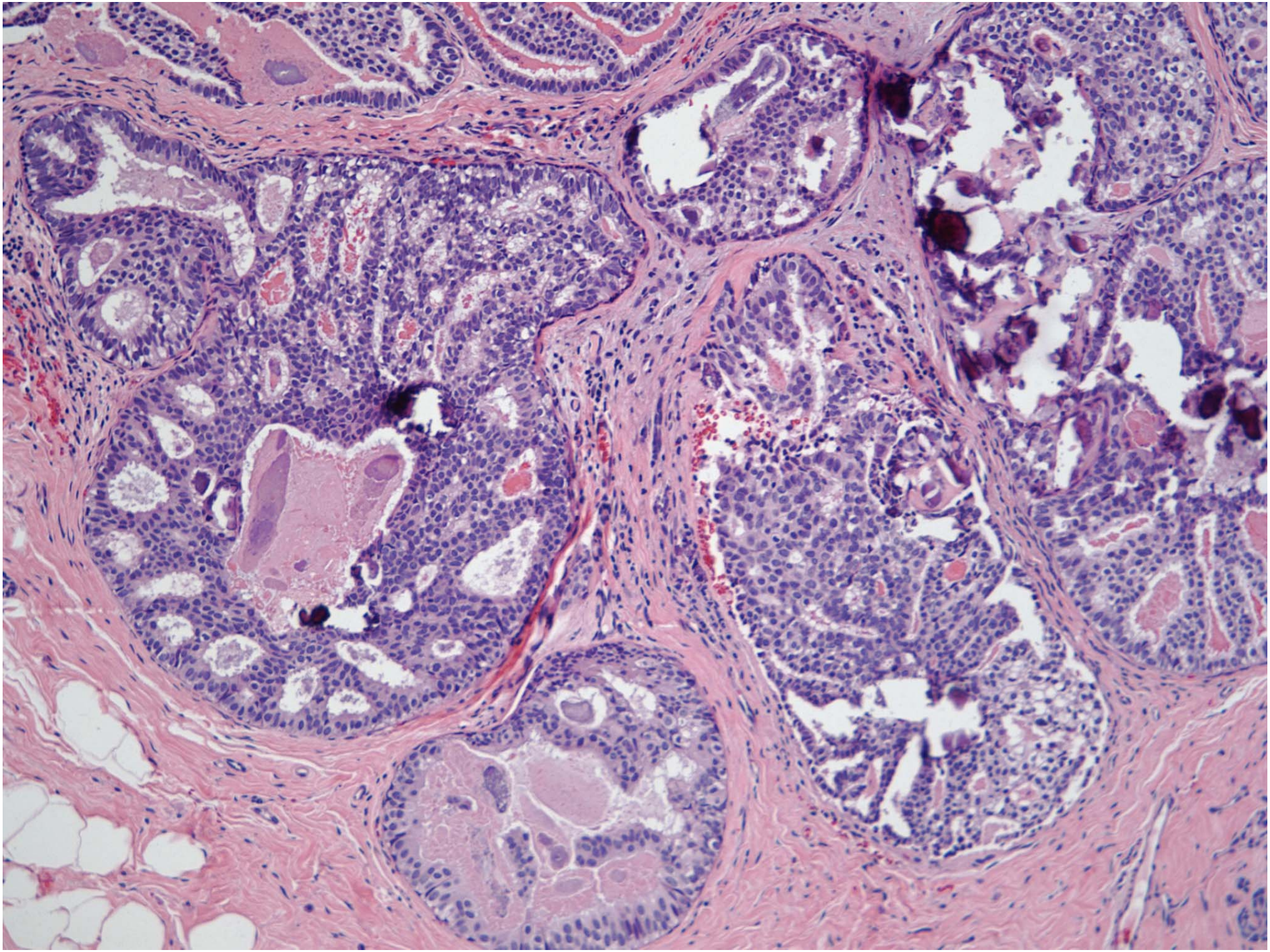


Diagnosis?

A. Atypical ductal hyperplasia
B. At least ADH, bordering on low grade DCIS
C. Severely atypical intraductal proliferation, suspicious for DCIS
D. Low grade DCIS

Excision

- Biopsy site changes only
- Review original biopsy knowing it is the entire extent of disease (< 2 mm lesion)
- Great case for a second review or specialist opinion!
- Clinical context discussion as well! (85 y/o with co-morbidities)

Excision Diagnosis Report:

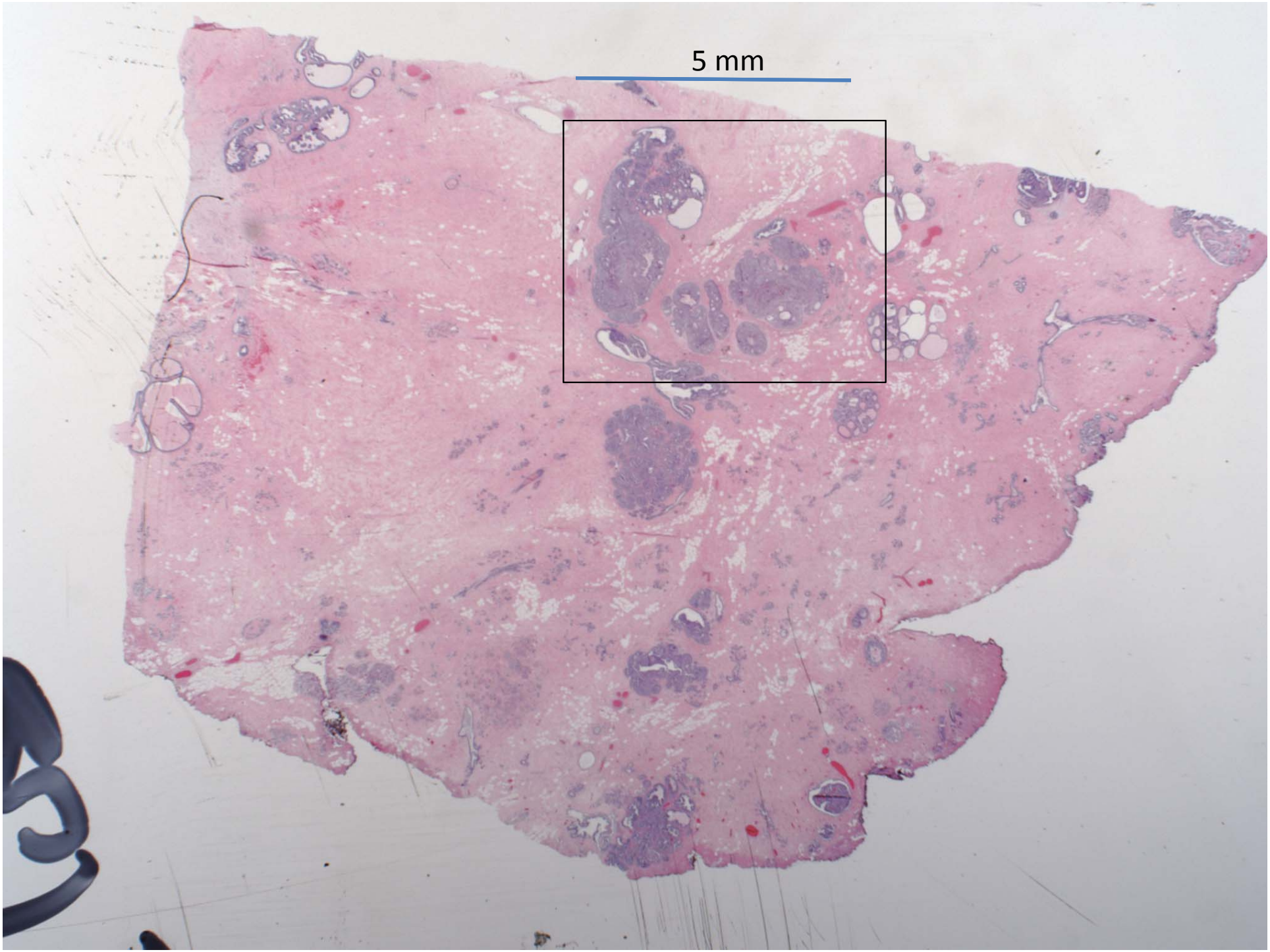
- Left breast, excisional biopsy:
  - Biopsy site changes with no residual atypia or calcifications, see comment

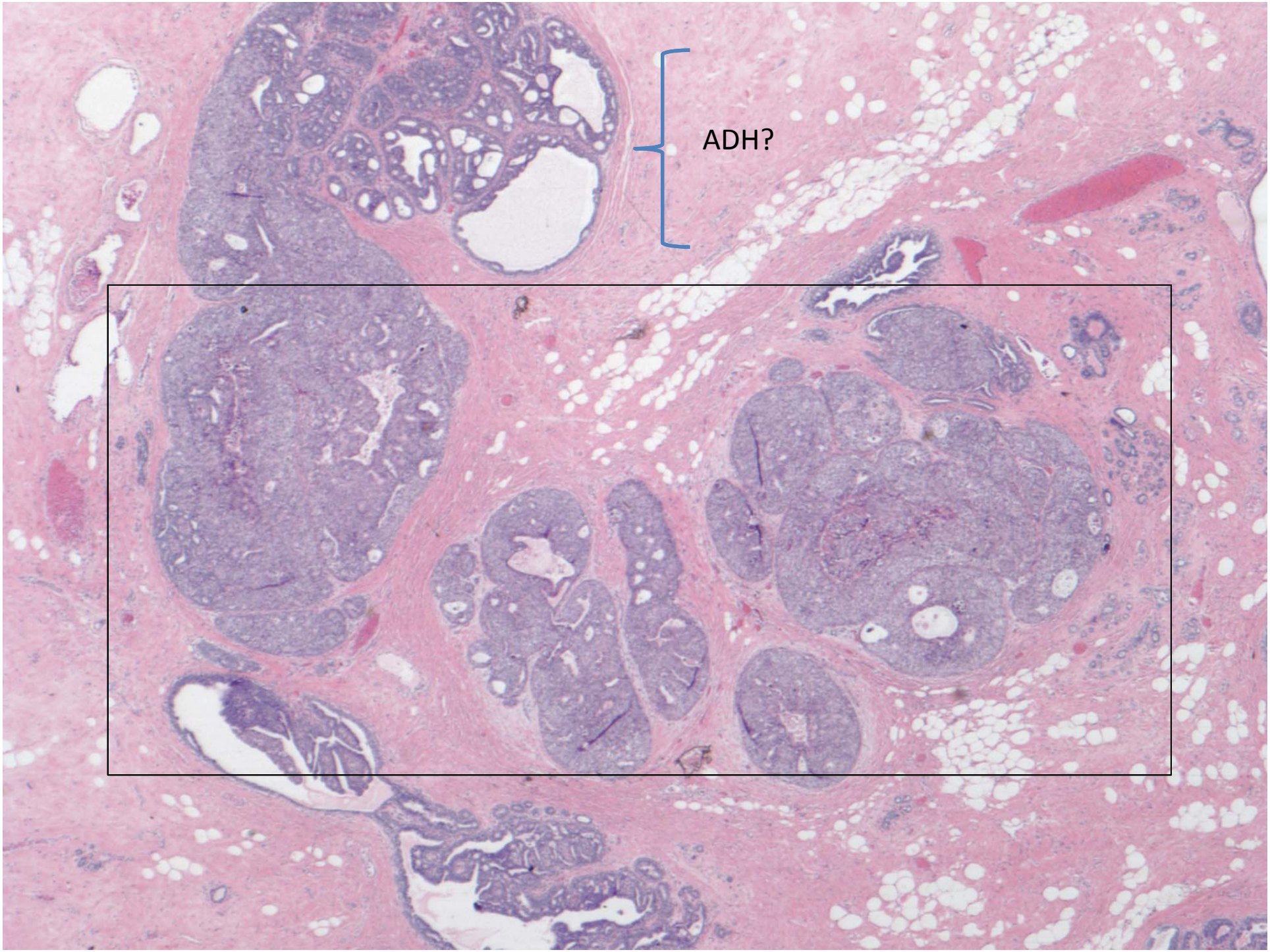
COMMENT:

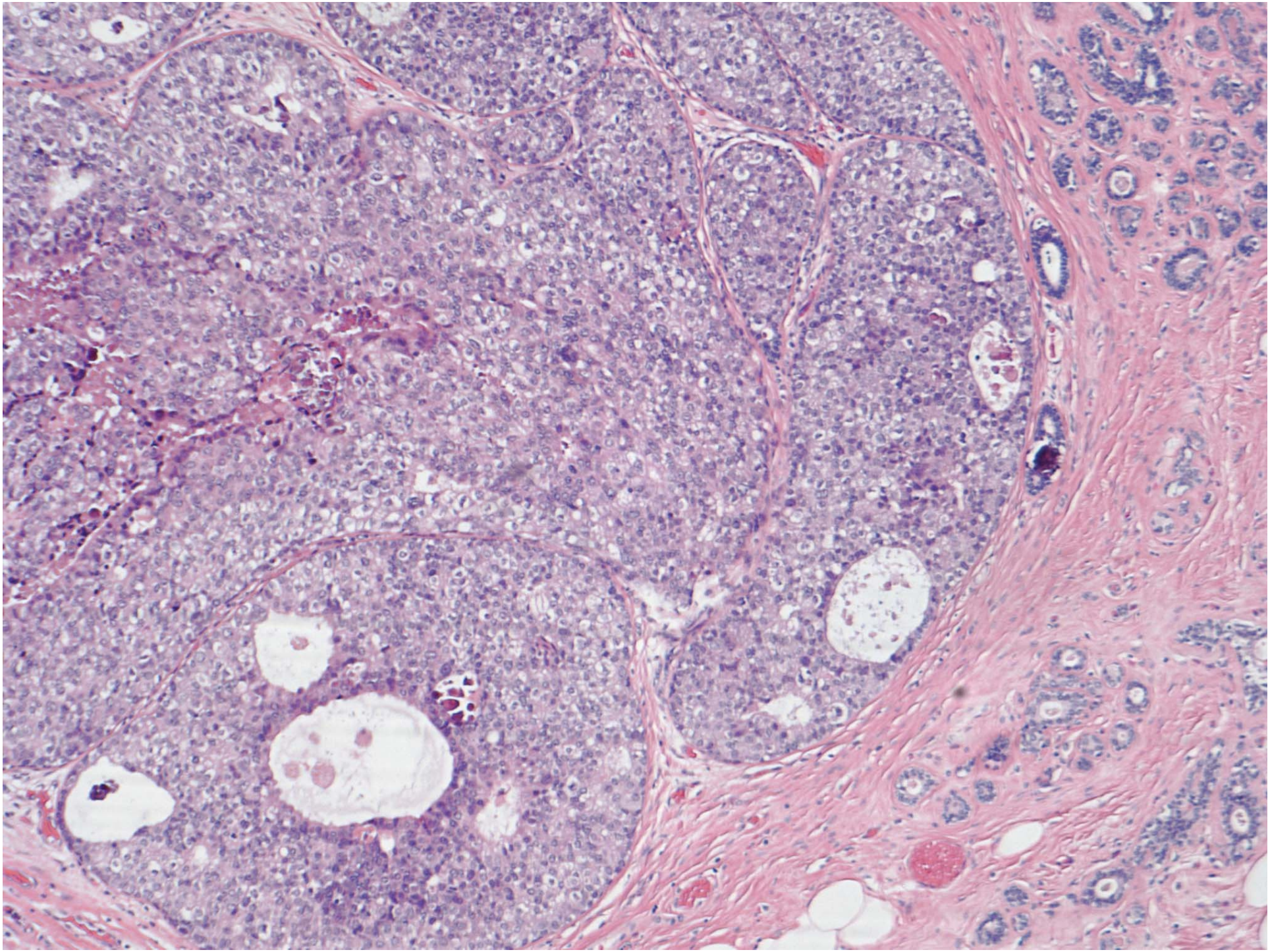
We have reviewed the prior needle core biopsy and agree that there is a 2 mm focus in that sample that borders on a diagnosis of low grade ductal carcinoma in situ. This lesion appears to have been entirely removed with core biopsy sampling. Given the limited extent and borderline histologic findings we favor classification and treatment as atypical ductal hyperplasia. Drs X and Y have also reviewed these findings and agree. The case was discussed with Dr C on 7-14-14 at 3pm.

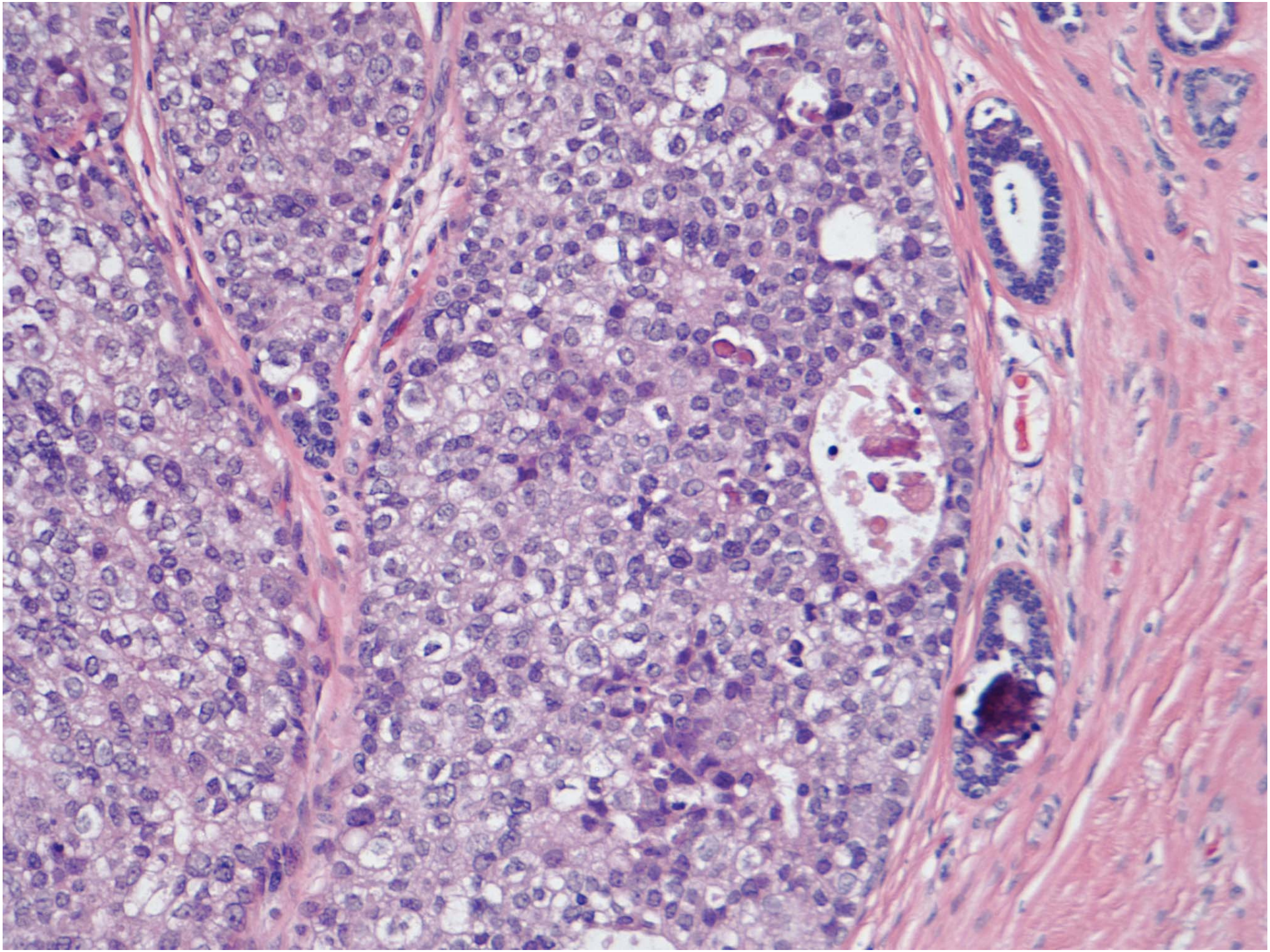
Case #4

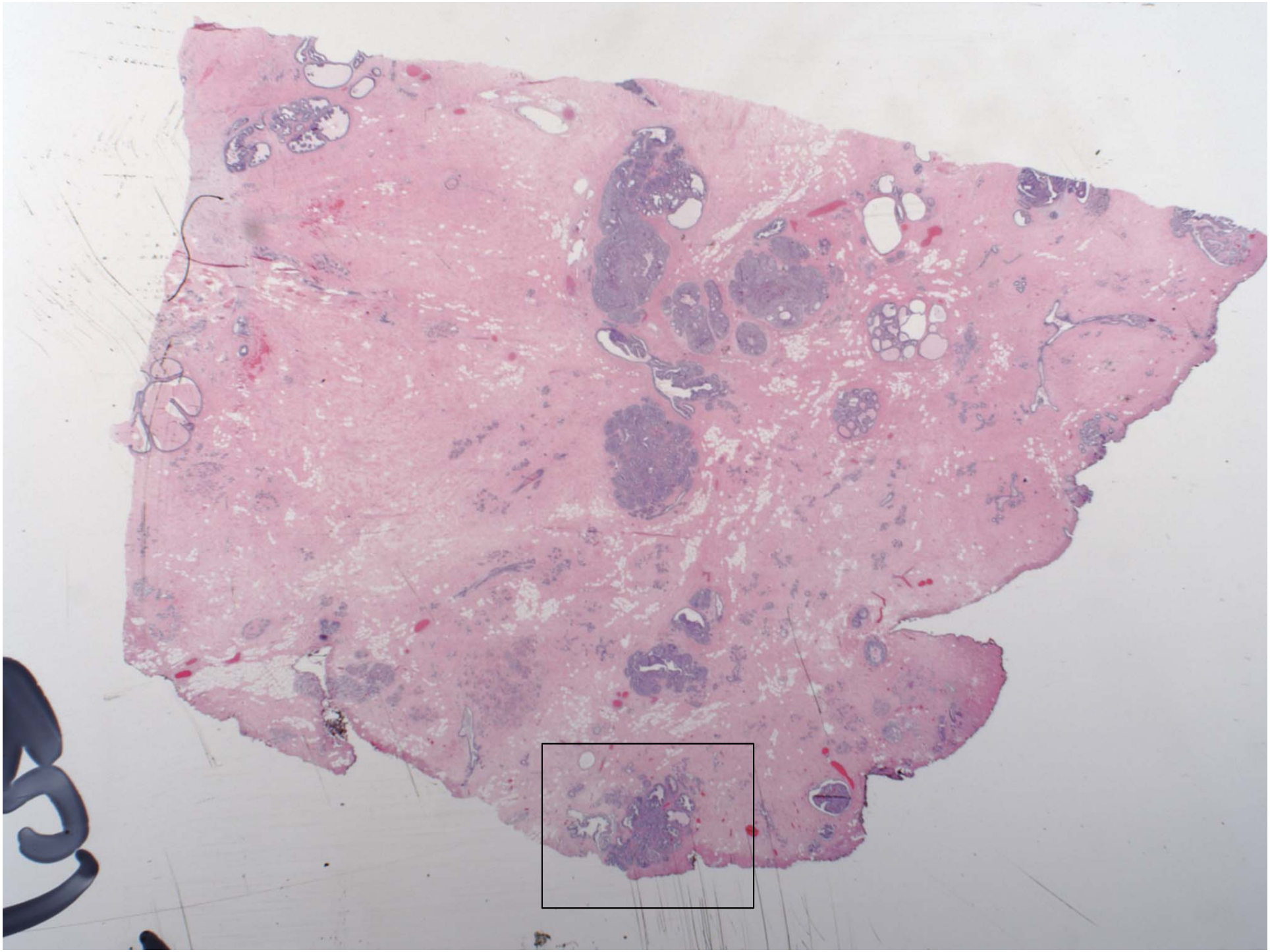
- 67 year old with prior core biopsy diagnosis of atypical ductal hyperplasia and a 2.5 cm area of calcifications

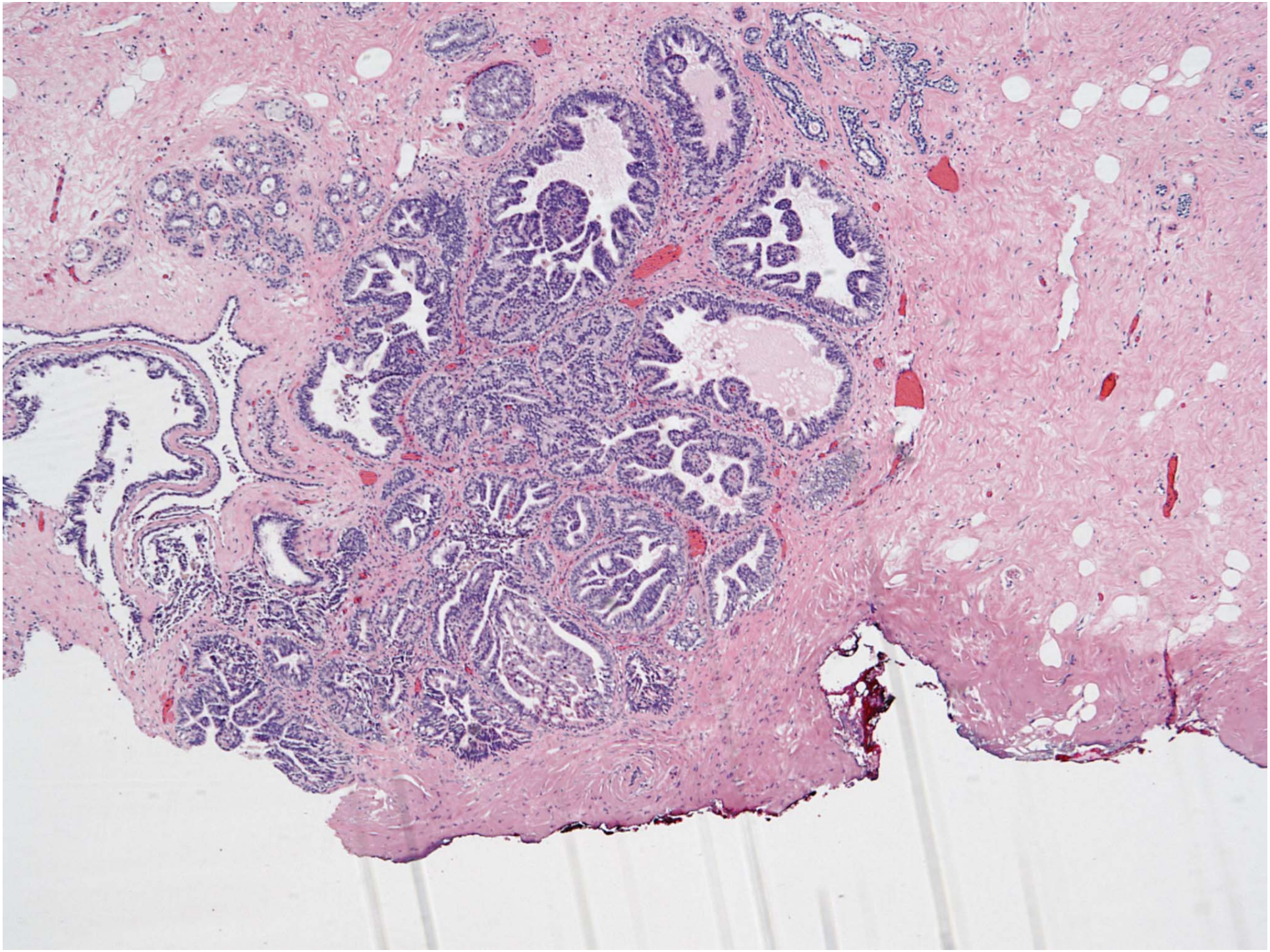

5 mm


ADH?









Diagnosis:

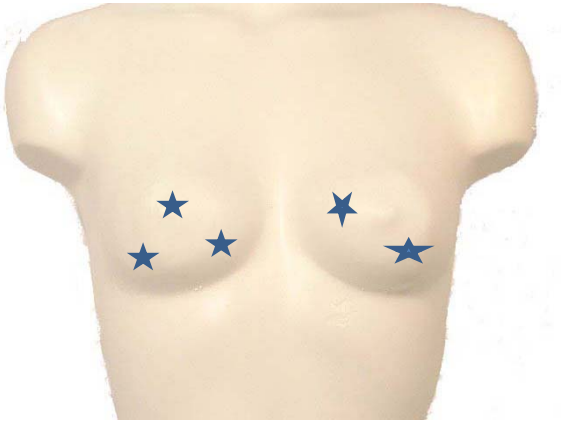
- Spectrum of low grade intraductal neoplasia including the following:
  - 0.5 cm focus of low-intermediate grade DCIS
  - Background atypical ductal hyperplasia over a 2.5 cm area
  - Calcifications present associated with DCIS and ADH
  - Prior biopsy site present
  - Margins:
    - DCIS is greater than 0.5 cm to margin

Risk vs Precursor Breast Lesions: Traditional Thinking

	Relative Risk of Invasive Cancer	Location of Risk
Atypical Ductal Hyperplasia (ADH)	4-5 x	Bilateral
Atypical Lobular Hyperplasia (ALH)	4-5x	Bilateral
Lobular Carcinoma in Situ (LCIS)	8-10 x	Bilateral
Ductal Carcinoma in Situ (DCIS)	8-10 x	Unilateral

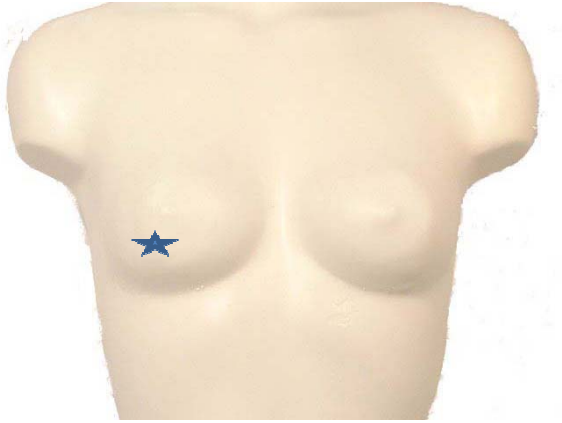
Anatomic Distribution: Traditional Thinking

Risk Lesion



Non-surgical

Precursor Lesion



Remove Surgically

Biology of ADH

Analysis of the progression of intraductal proliferative lesions in the breast by PCR-based clonal assay

- PCR-based clonality assay

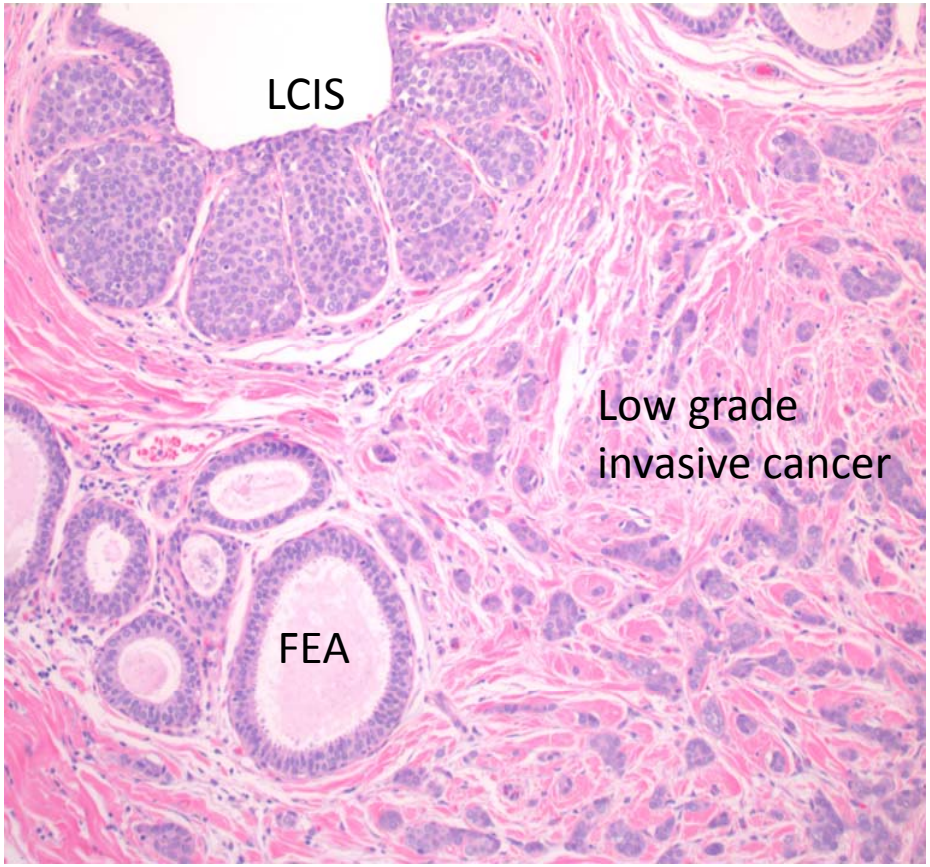
Breast Cancer Res Treat (2009) 114:433–440

Qi Yu · Yun Niu · Yong Yu · XiuMin Ding · YuRong Shi

Sample types (cases no.)	Monoclonal (%)
Normal breast tissue (30)	0
UDH (40)	2.9
FEA (29)	23.1
ADH (40)	51.3
DCIS (40)	100

Risk Lesions Can Also Be Neoplastic!

- Newer molecular evidence indicates that risk lesions ADH, ALH and LCIS are:
  - Clonal proliferations (neoplastic)
  - Very similar alterations to low grade DCIS
  - Frequent molecular alterations shared with invasive disease



→ ADH, ALH/LCIS are Non-Obligate Precursors with a distribution pattern that warrants treatment as Risk Lesions

Natural History of DCIS: Traditional Thinking

Table 1. Natural history of untreated DCIS

Reference	*n* of patients	Patients developing IBC (%)	Follow-up (years)	Relative risk
Rosen et al. (1980) [15]	15	53	1–24	NC
Page et al. (1982) [69]	28	32	3–31	9.1
Eusebi et al. (1994) [70]	80	14	1–14	NC
Collins et al. (2005) [16]	13	46	4–18	13.5

Abbreviations: DCIS, ductal carcinoma in situ; IBC, invasive breast cancer; NC, not calculated.

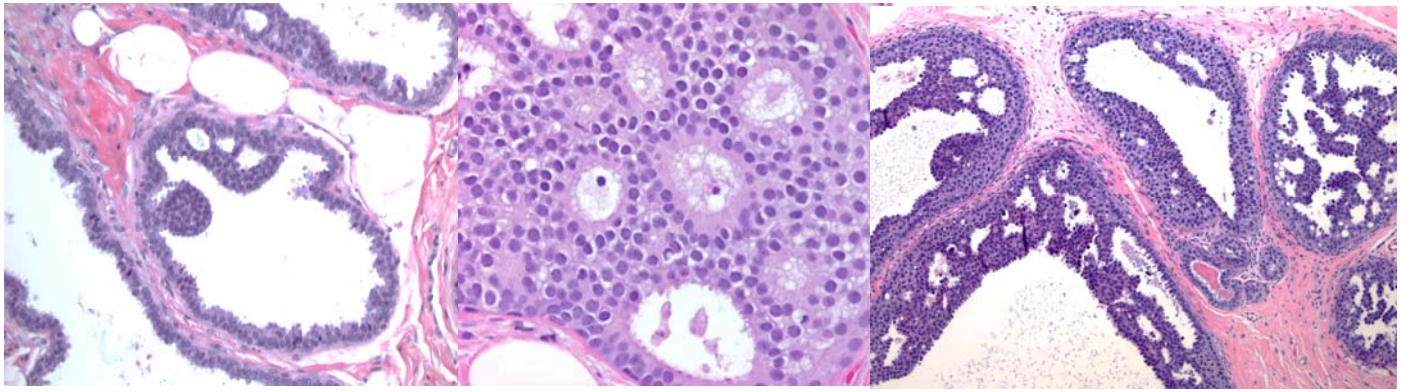
The Oncologist 2007;12:1276–1287

Sounds Bad! Treat aggressively!?

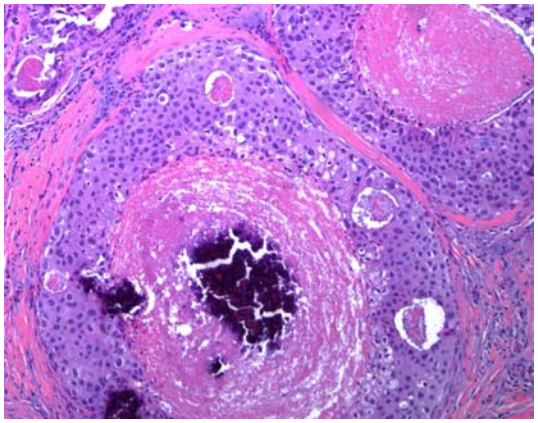
Problem: Mixing biologically different High Grade/Comedo DCIS with Low Grade DCIS

Question: Does all DCIS behave the same?

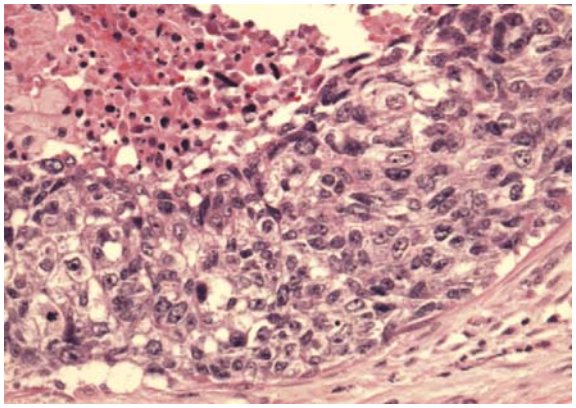
DCIS is not one disease



Luminal (ER positive)



HER2

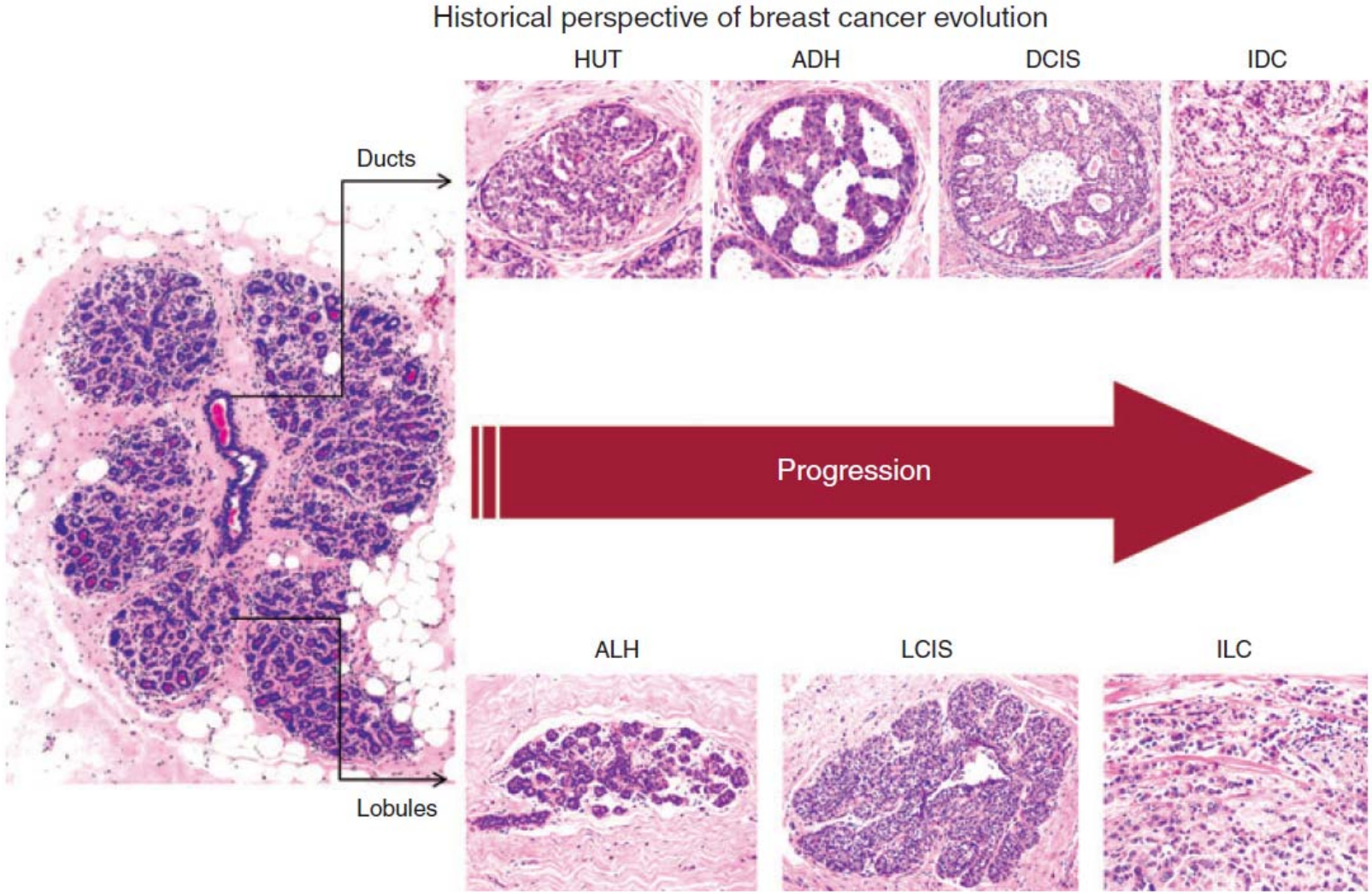


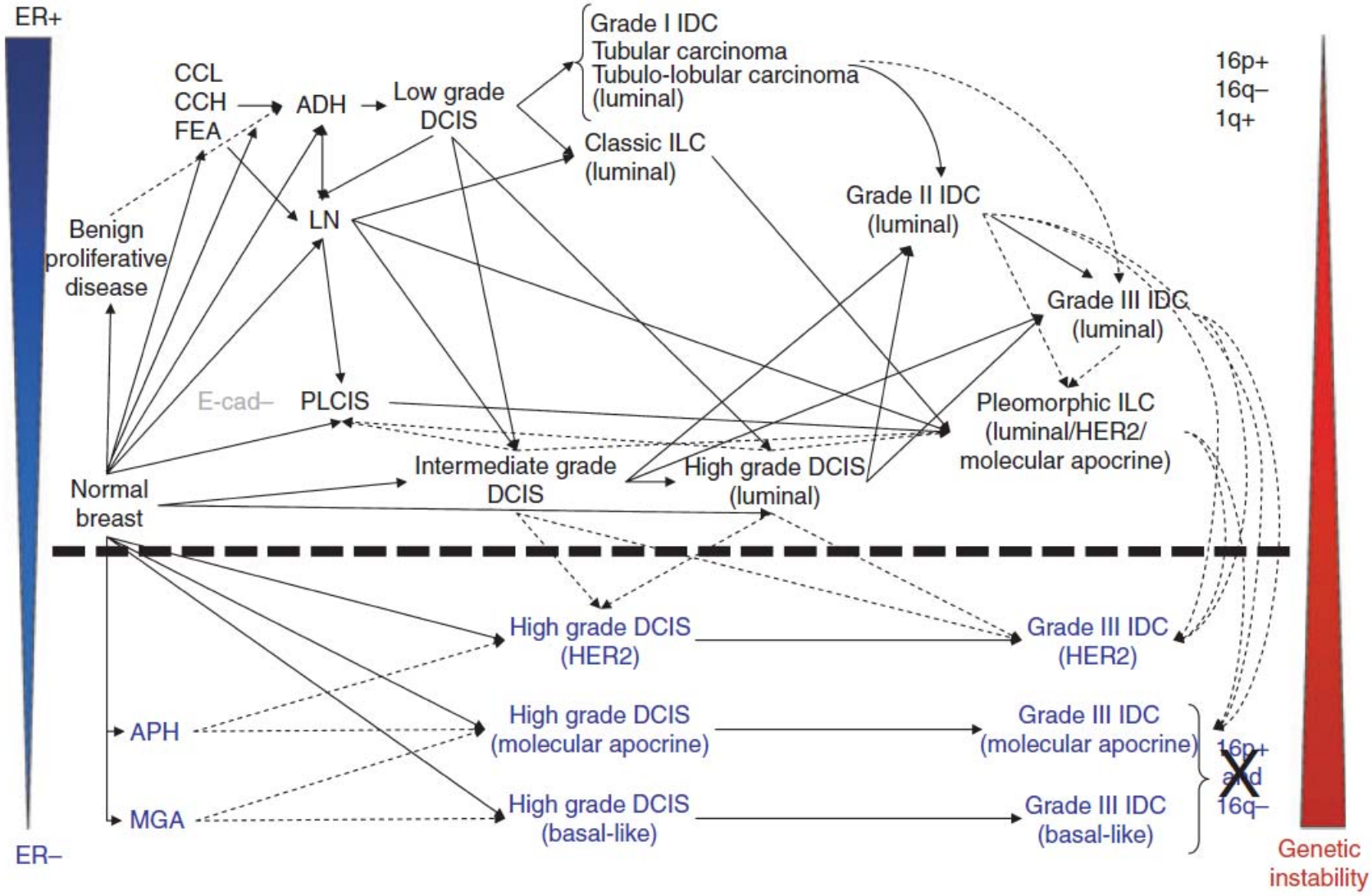
Basal (Triple Negative)

REVIEW *Histopathology* 2010, **57**, 171–192. DOI: 10.1111/j.1365-2559.2010.03568.x

Breast cancer precursors revisited: molecular features and progression pathways

Maria A Lopez-Garcia,[1,2] Felipe C Geyer,[1] Magali Lacroix-Triki,[1,3] Caterina Marchió[4] & Jorge S Reis-Filho[1]





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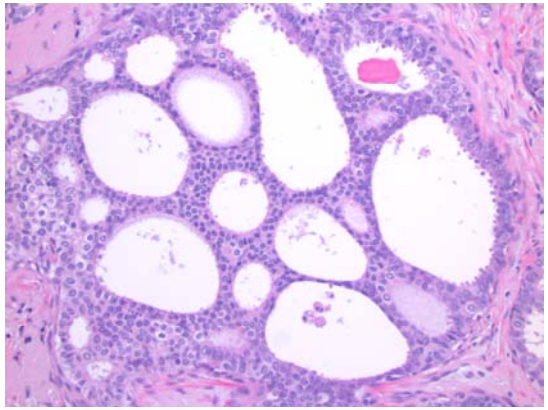
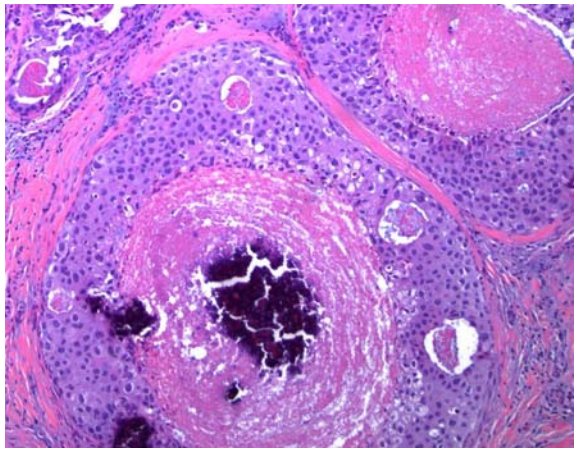
Biology of DCIS: Current Thinking Simplified



Low-Intermediate Grade DCIS:

- ER positive
- Frequent 16q and 1q abnormalities
- Detection: Screening mammography
- Risk of invasion: Extends over decades
- Type of invasion: Low –intermediate grade, ER positive

Lower Risk Precursor



High Grade DCIS:

- More frequently ER negative
- Frequent HER2 amplification, p53 mutations
- Detection: Mass or screening mammography
- Risk of invasion: Typically within a decade
- Type of invasion: High grade, HER2 positive

Higher Risk Precursor

The Natural History of Low-Grade Ductal Carcinoma in Situ of the Breast in Women Treated by Biopsy Only Revealed Over 30 Years of Long-Term Follow-Up

Melinda E. Sanders, M.D.[1]
Peggy A. Schuyler, R.N.[2]
William D. Dupont, Ph.D.[2]
David L. Page, M.D.[1]

Cancer 2005;103:2481–4.

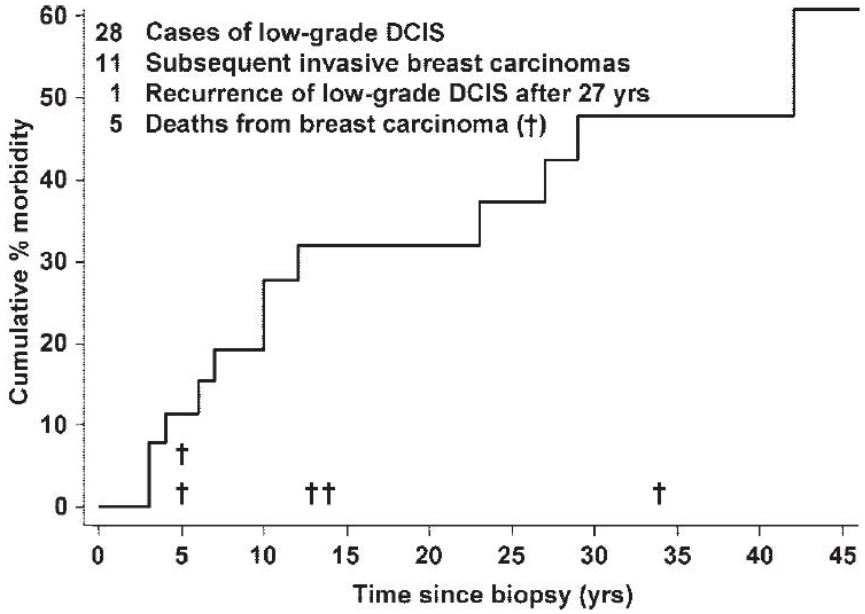
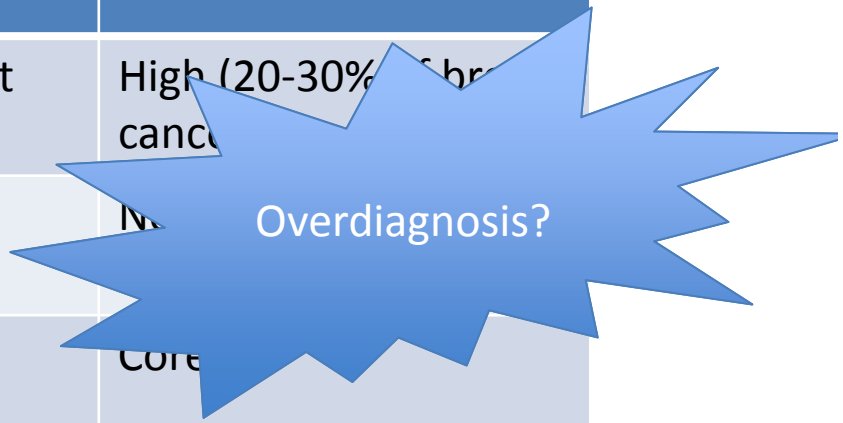


FIGURE 1. This chart illustrates the cumulative incidence of invasive breast carcinoma (using the Kaplan–Meier method) for women with small, noncomedo ductal carcinoma in situ (DCIS) at biopsy who were followed without further therapy. Deaths from breast carcinoma are noted by crosses.

- 28 women with low grade DCIS treated with excisional biopsy alone
- 57% with no additional events
- 3.5% with DCIS recurrence at 27 years
- 39% developed invasion
  - 7 within 5-10 years, 3 > 15
  - 5 with distant mets and died 1-7 years after invasive diagnosis

DCIS has changed with screening

	Pre-Screening Era	Screening Era
Incidence	Low (1-2% of breast cancers)	High (20-30% of br… canc…
Presentation	Palpable Mass	N…
Biopsy sampling	Excision	Core…
Treatment	Mastectomy	Lumpectomy, XRT, HRT



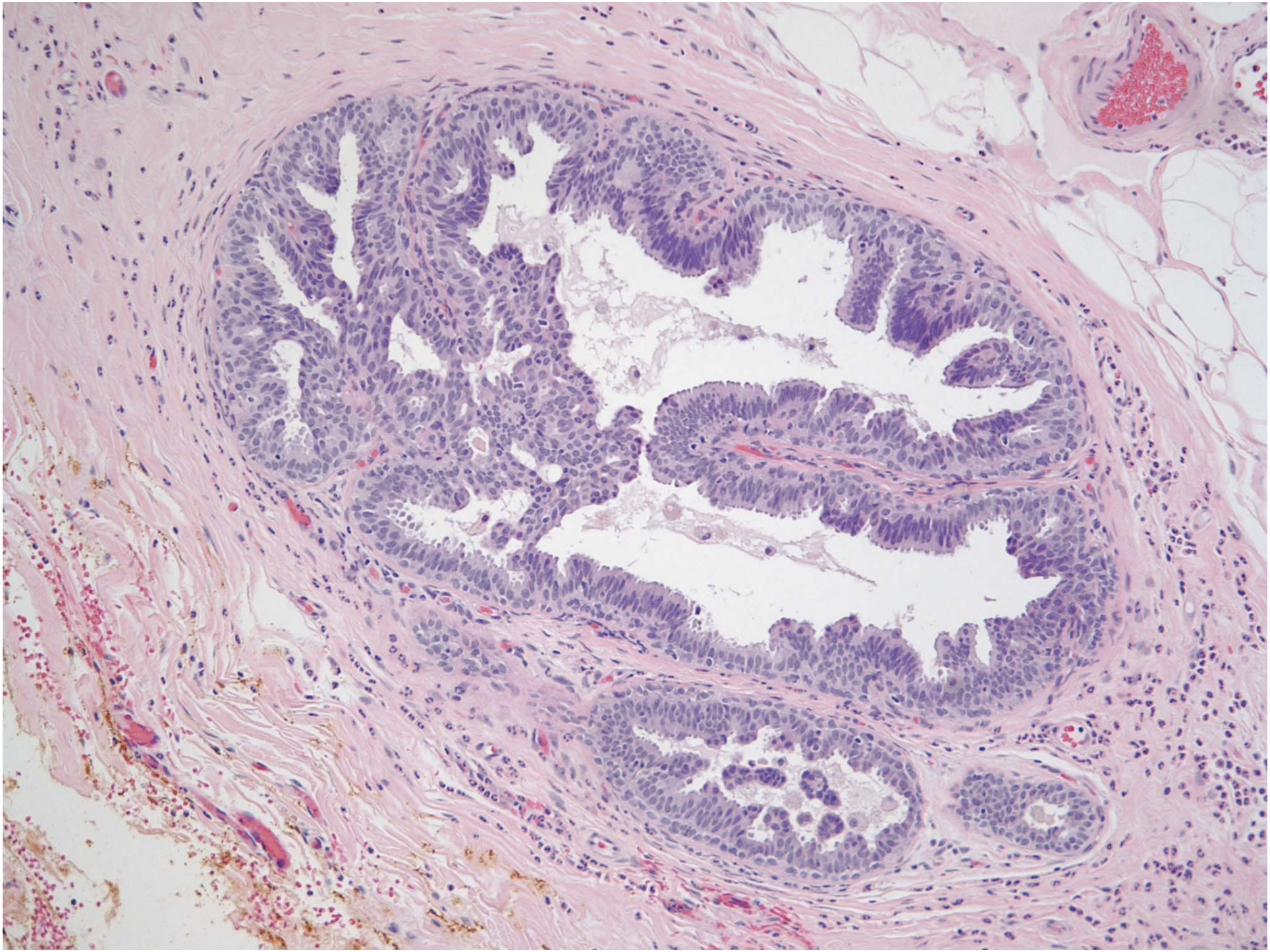
Getting more of the low end of the spectrum!
Most “natural history” studies were done on samples from the pre-screening era.

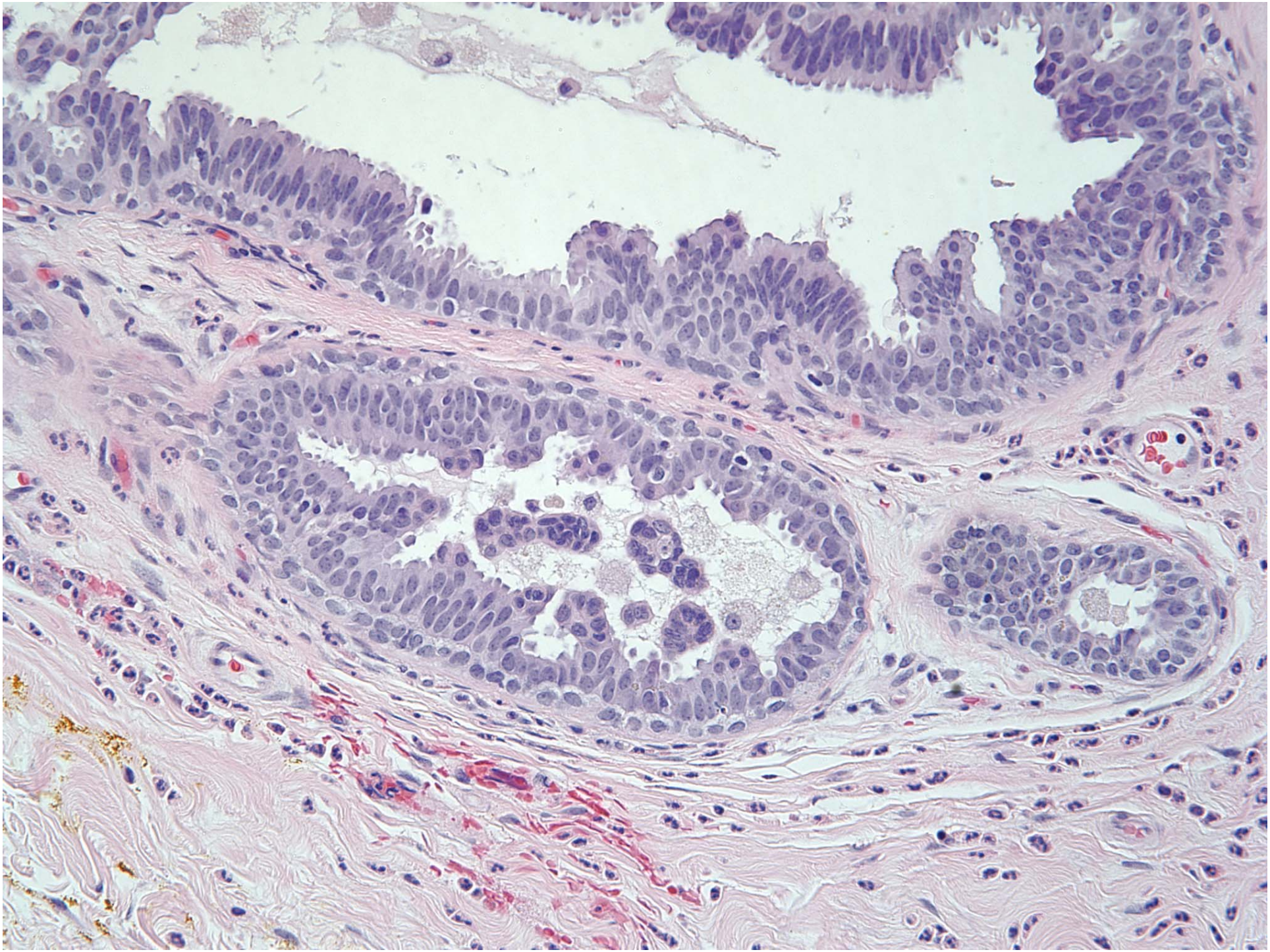
ADH vs DCIS Biology Summary

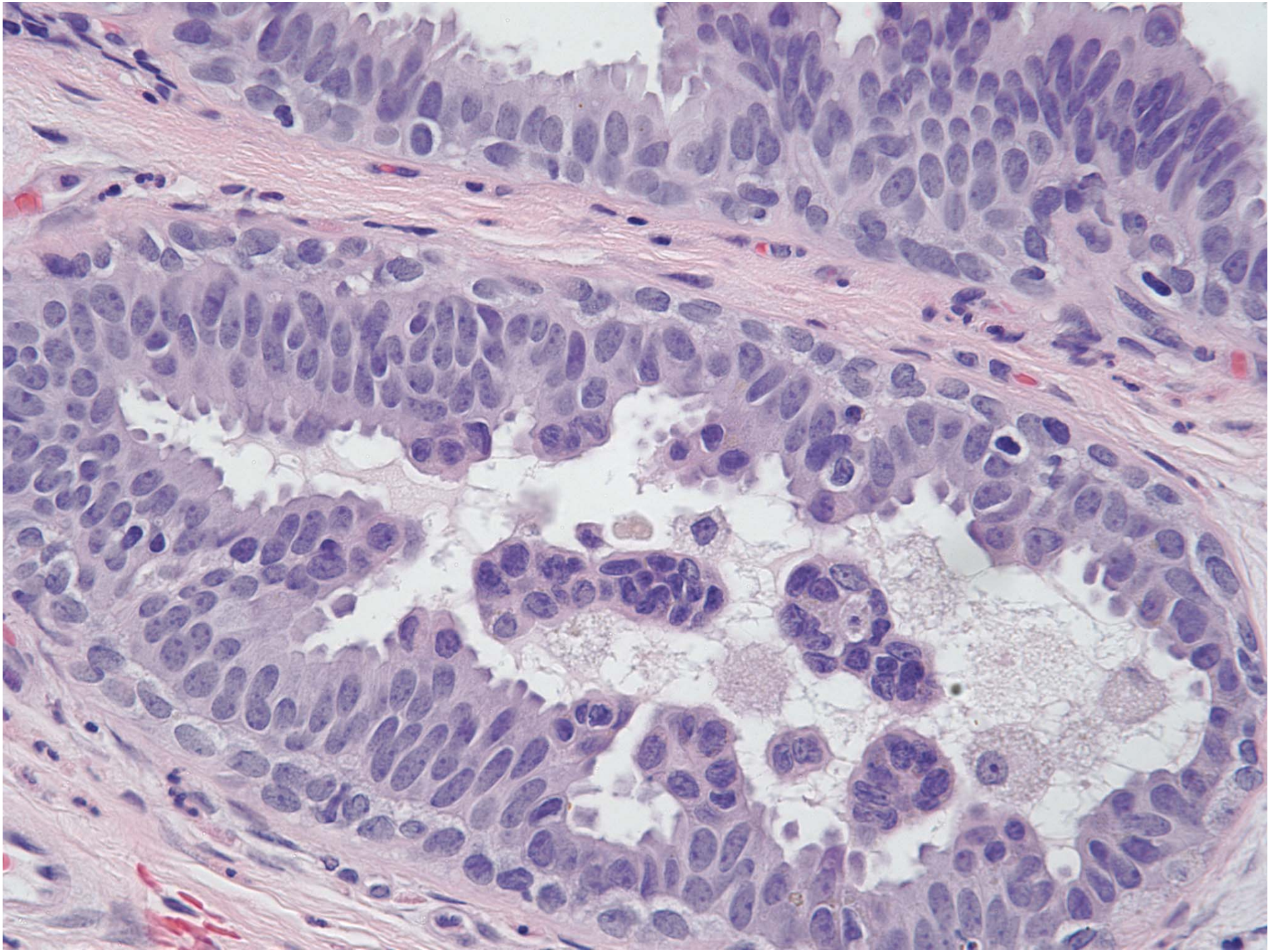
- ADH is often neoplastic and can result in invasion
  - Non-obligate precursor biologically
- ADH has a scattered rather than locally "excisable" growth pattern
  - Treated as a risk lesion clinically (role for hormonal therapies in some cases)
- DCIS is a surgical disease with a risk of local invasion over time (risk is much higher for HG DCIS)

Case #5

- 39 year old with strong family history of breast cancer undergoing MRI screening with 1.5 cm area of NMLE

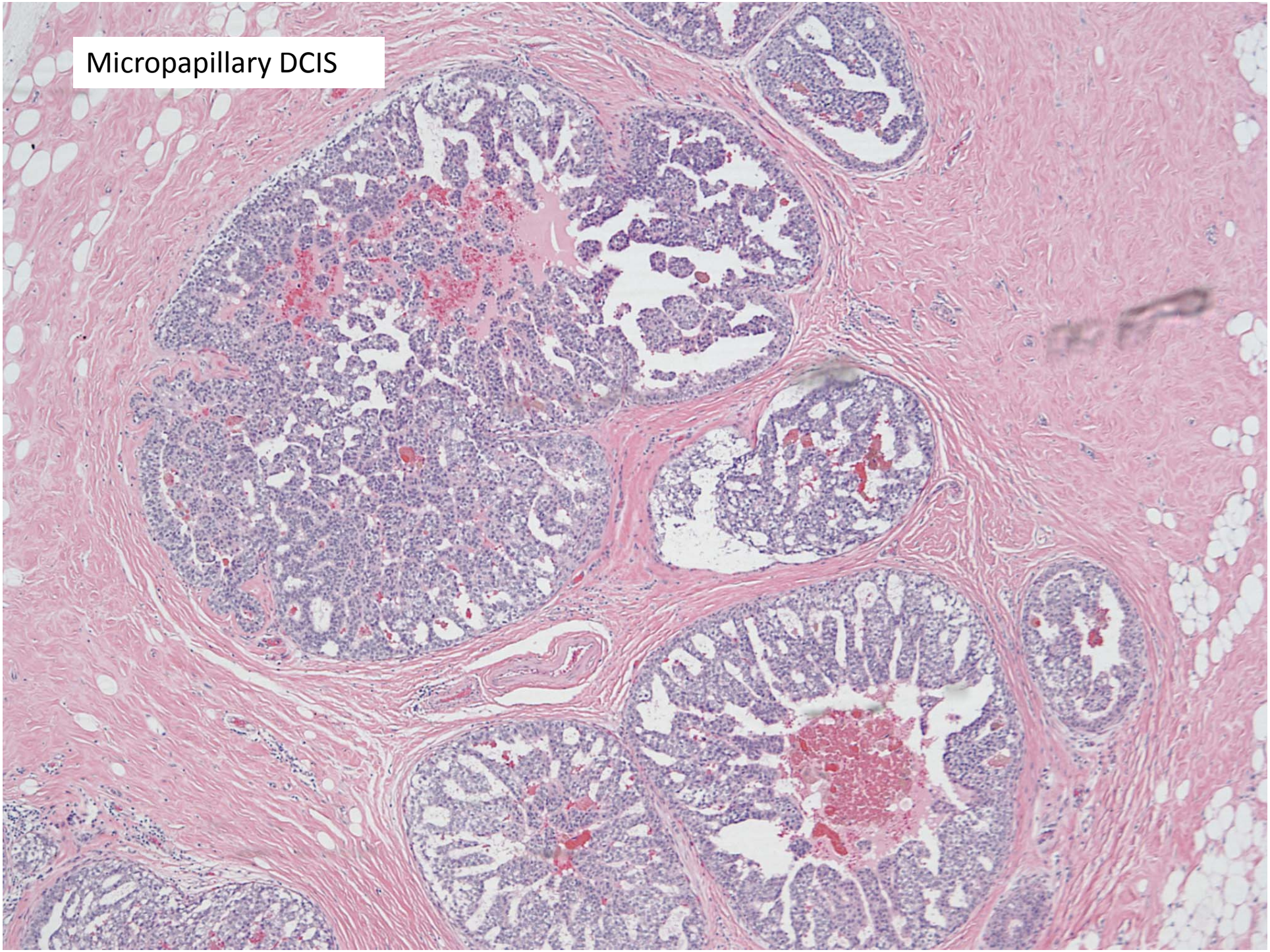


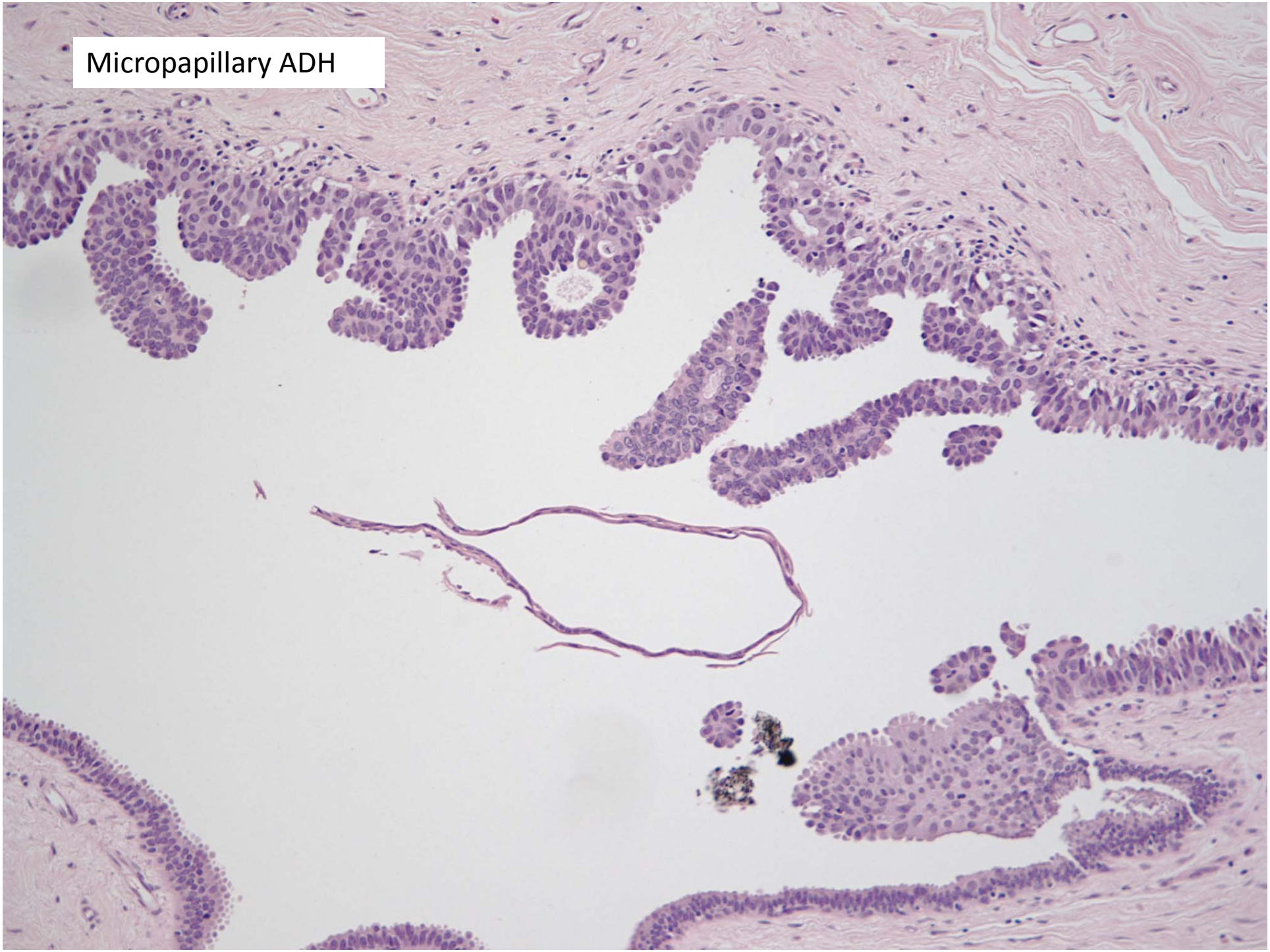


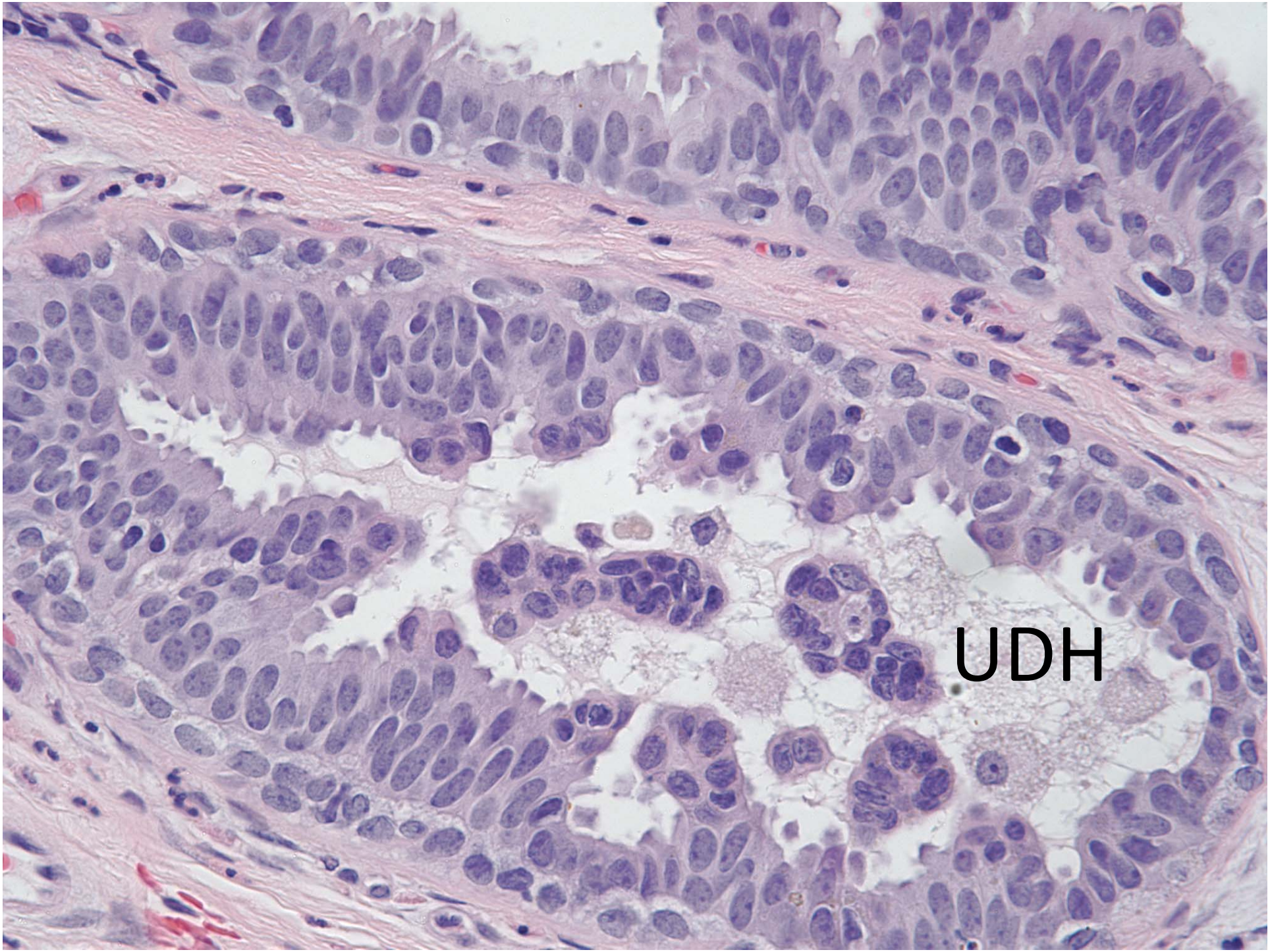


Diagnosis?

A. Micropapillary usual ductal hyperplasia
B. Micropapillary atypical ductal hyperplasia
C. Micropapillary DCIS

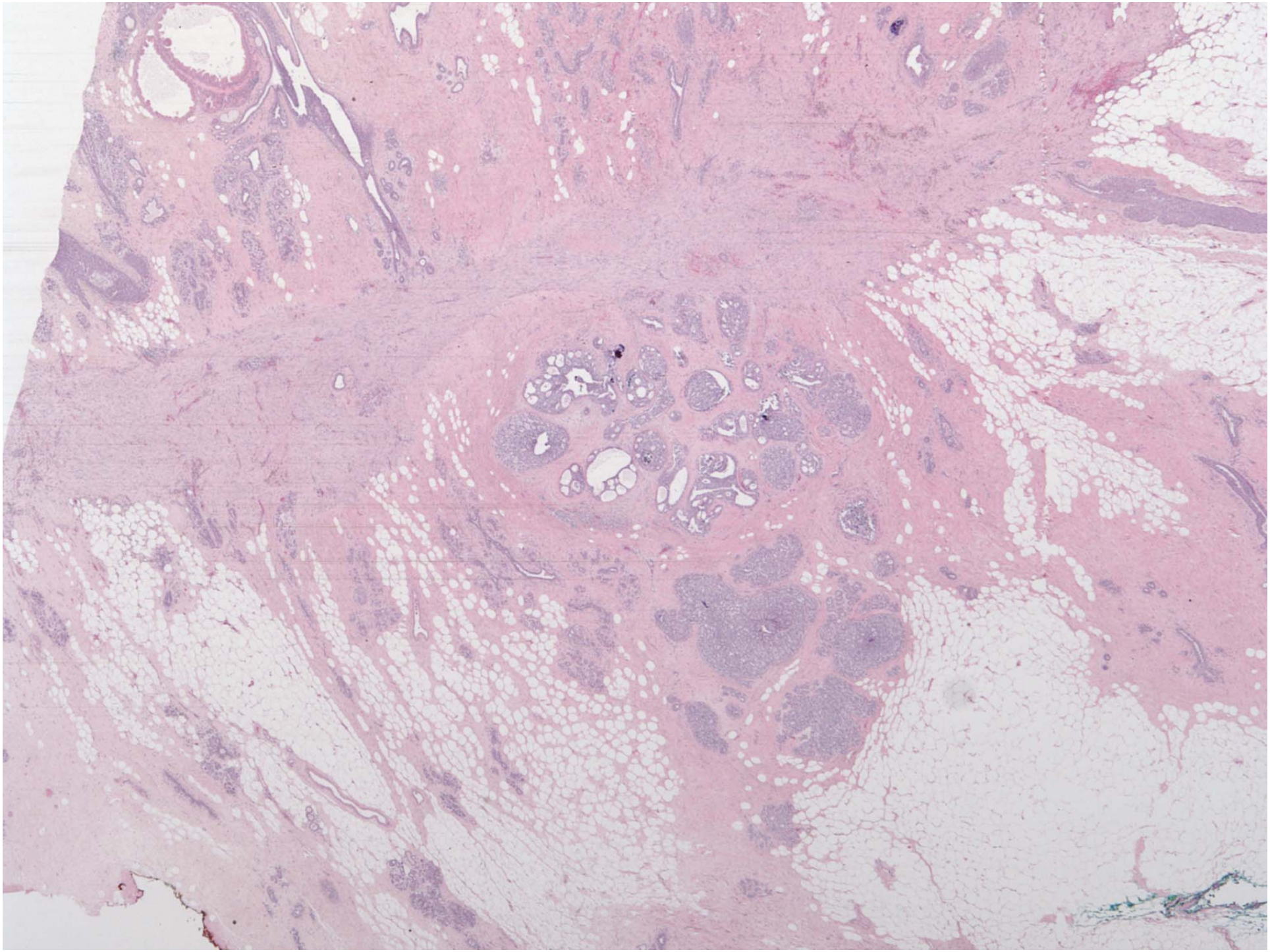

Micropapillary DCIS

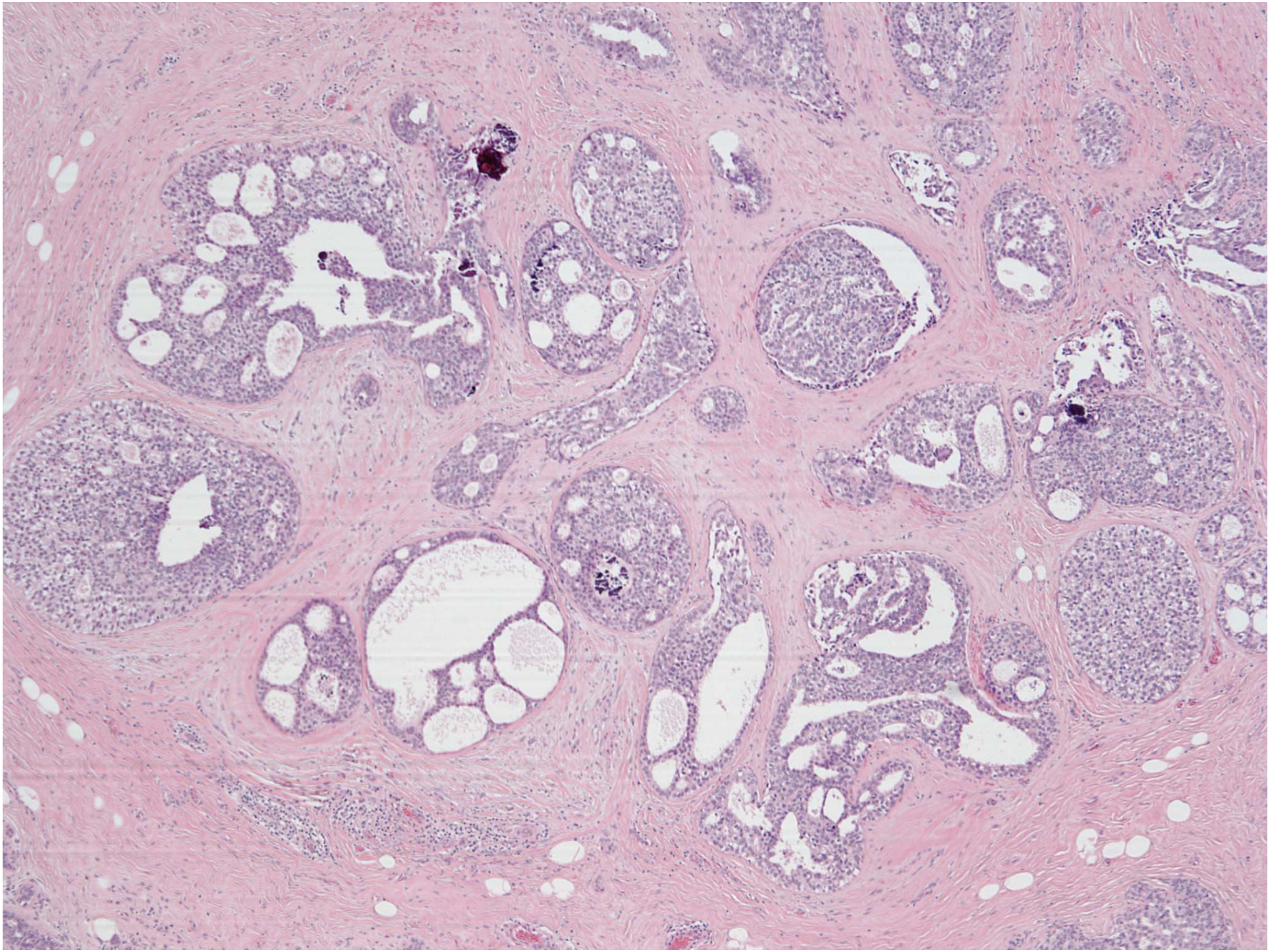

Micropapillary ADH

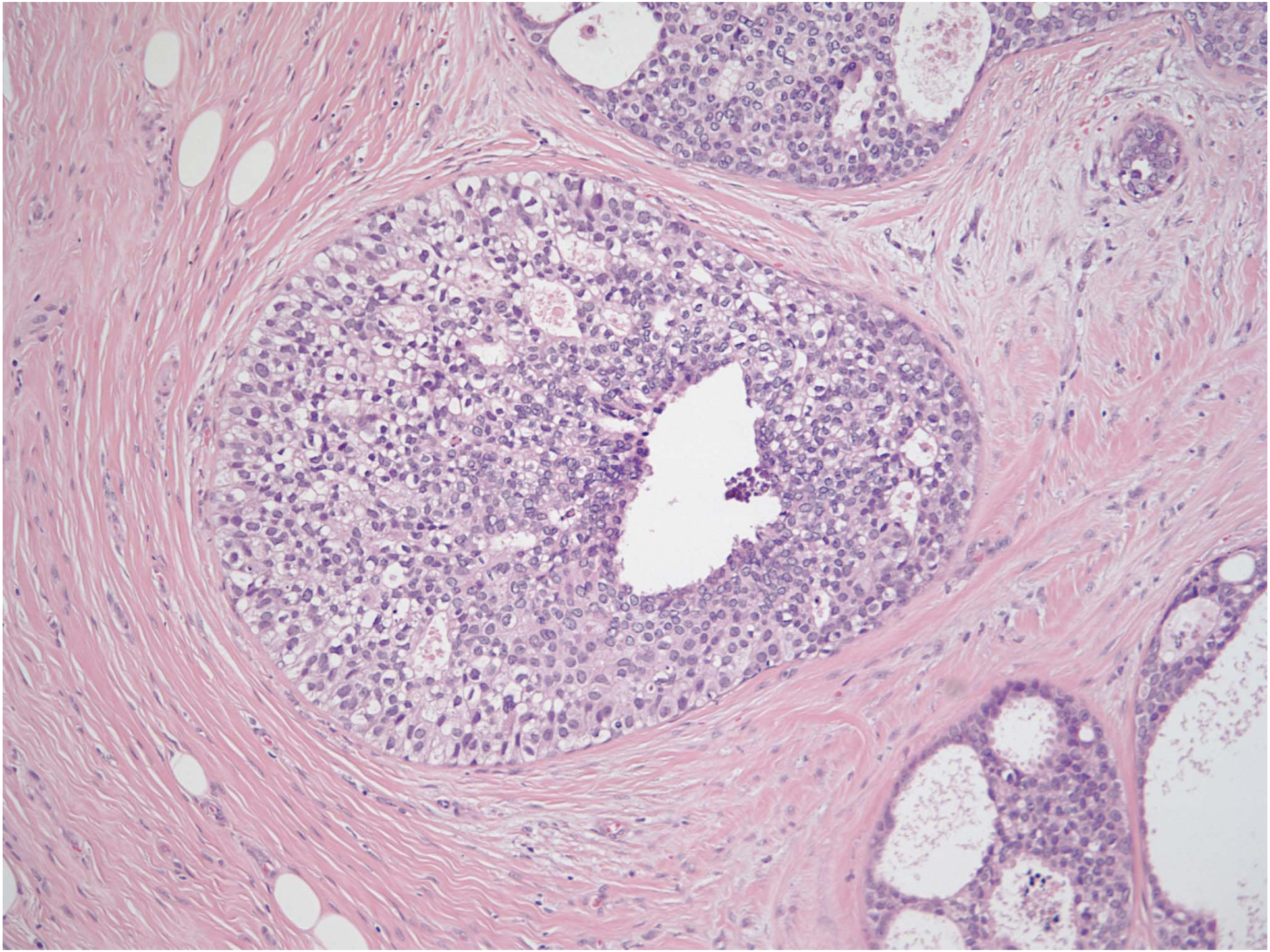

UDH

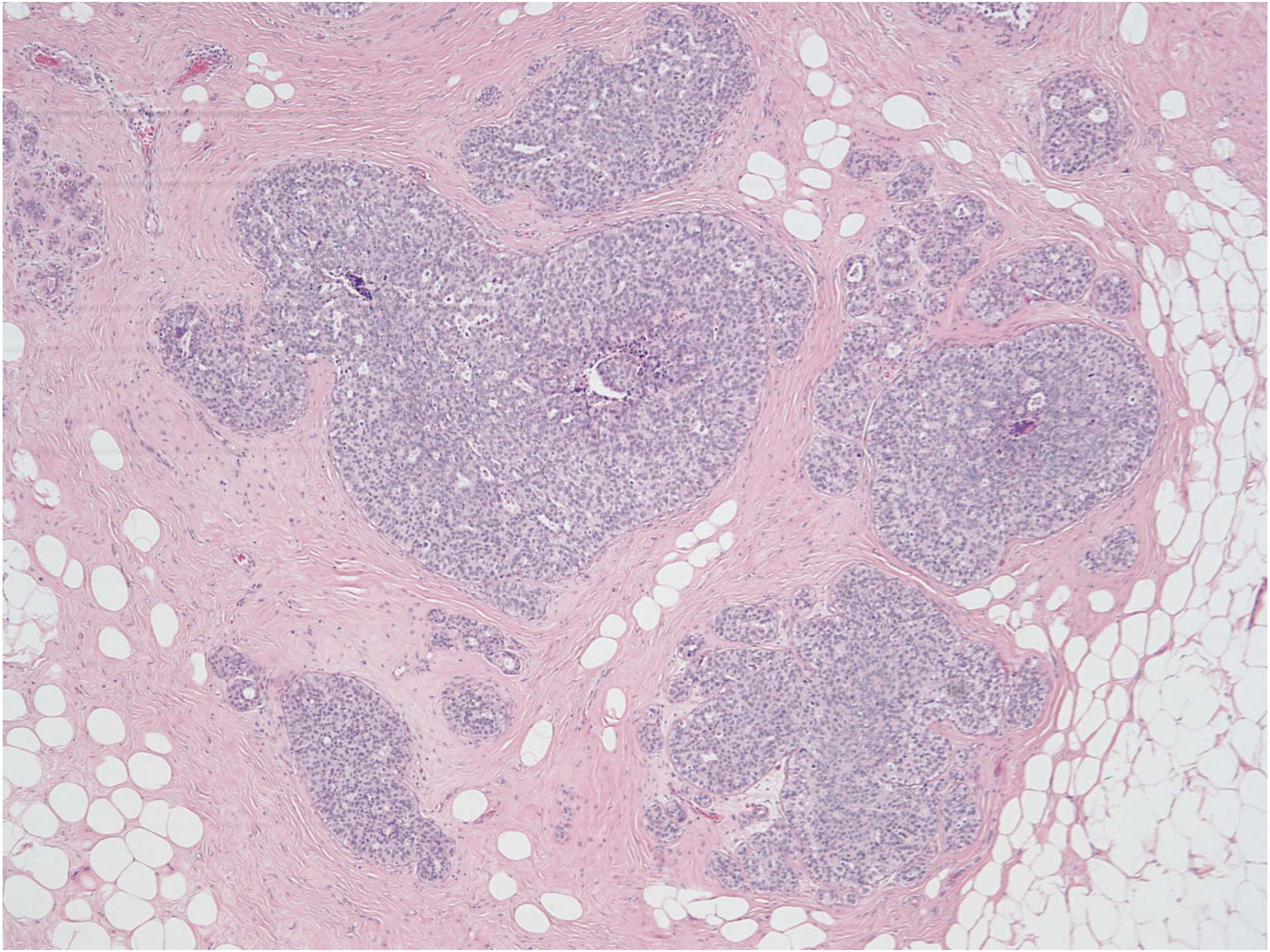
Case #6

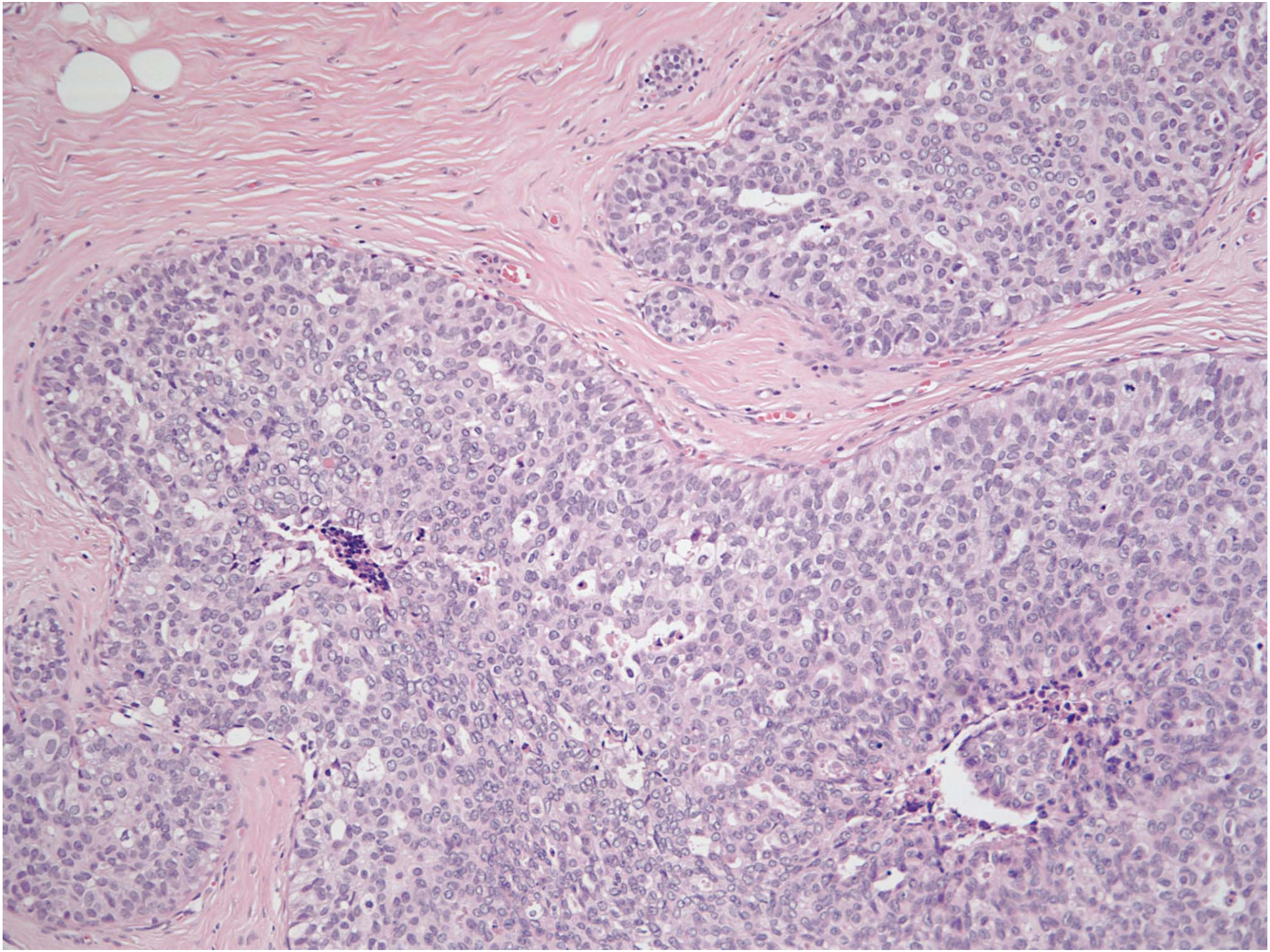
- 55 year old with 2.0 cm of clustered calcifications on screening mammogram and prior core biopsy of ADH

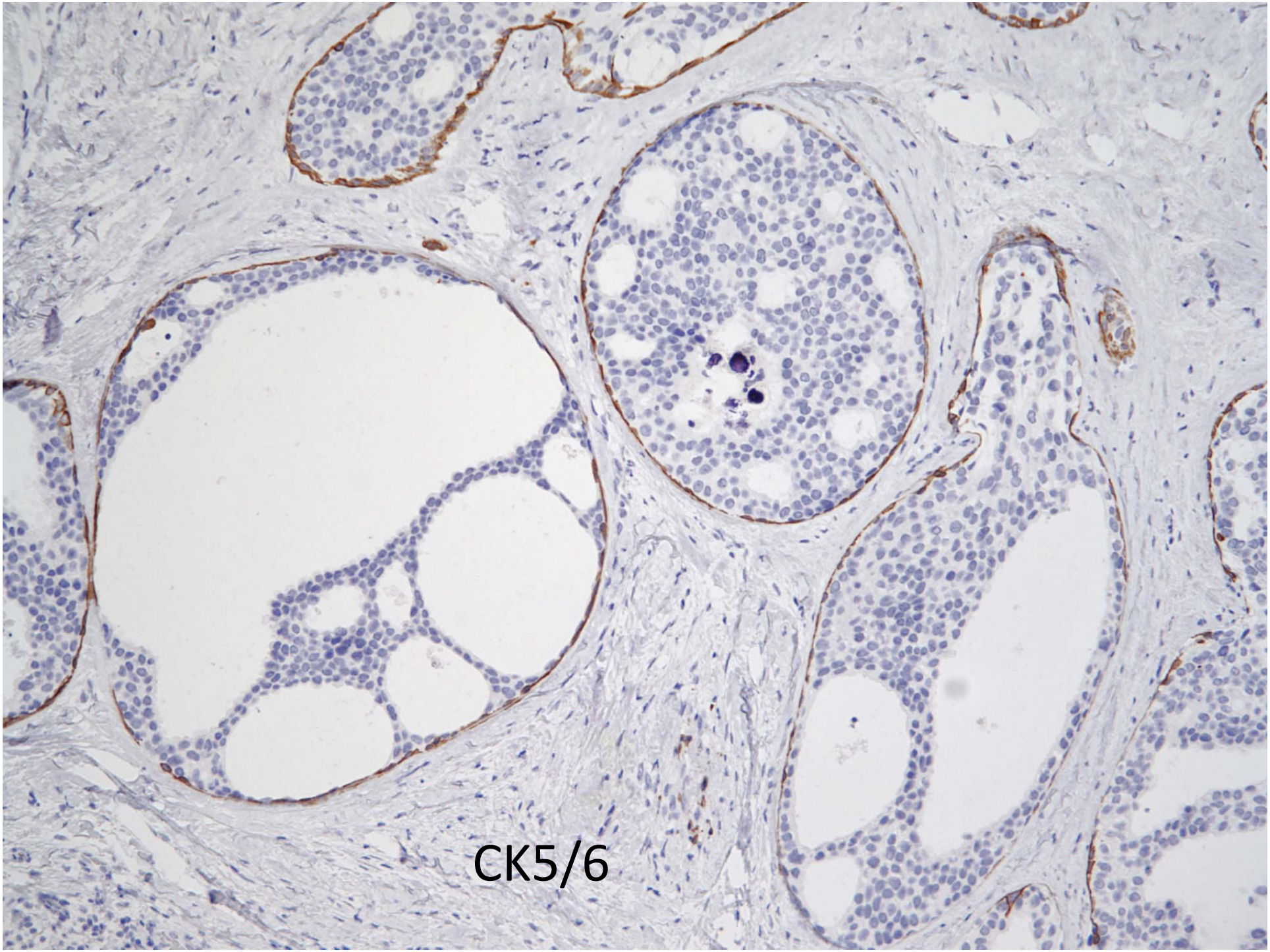


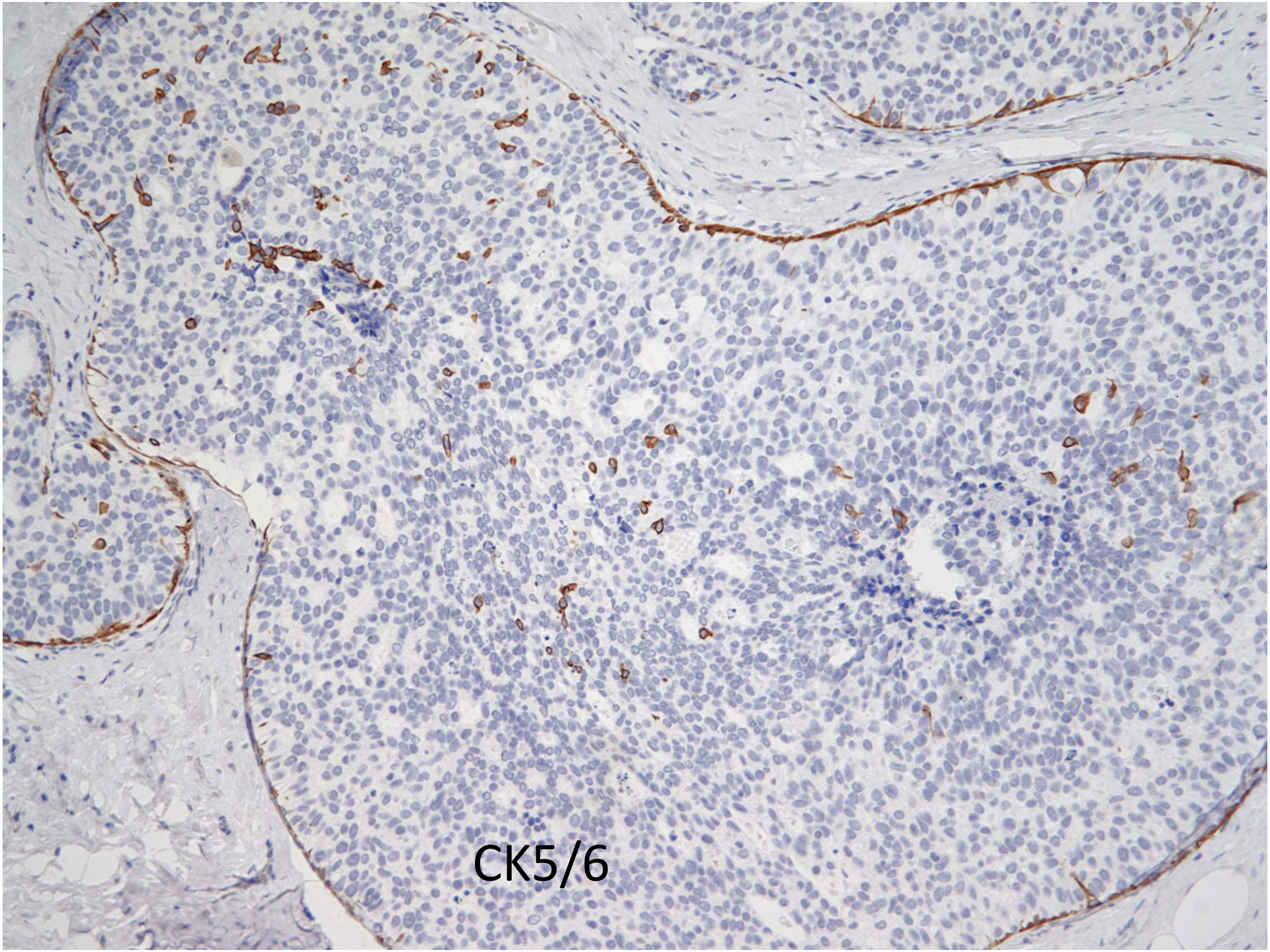









CK5/6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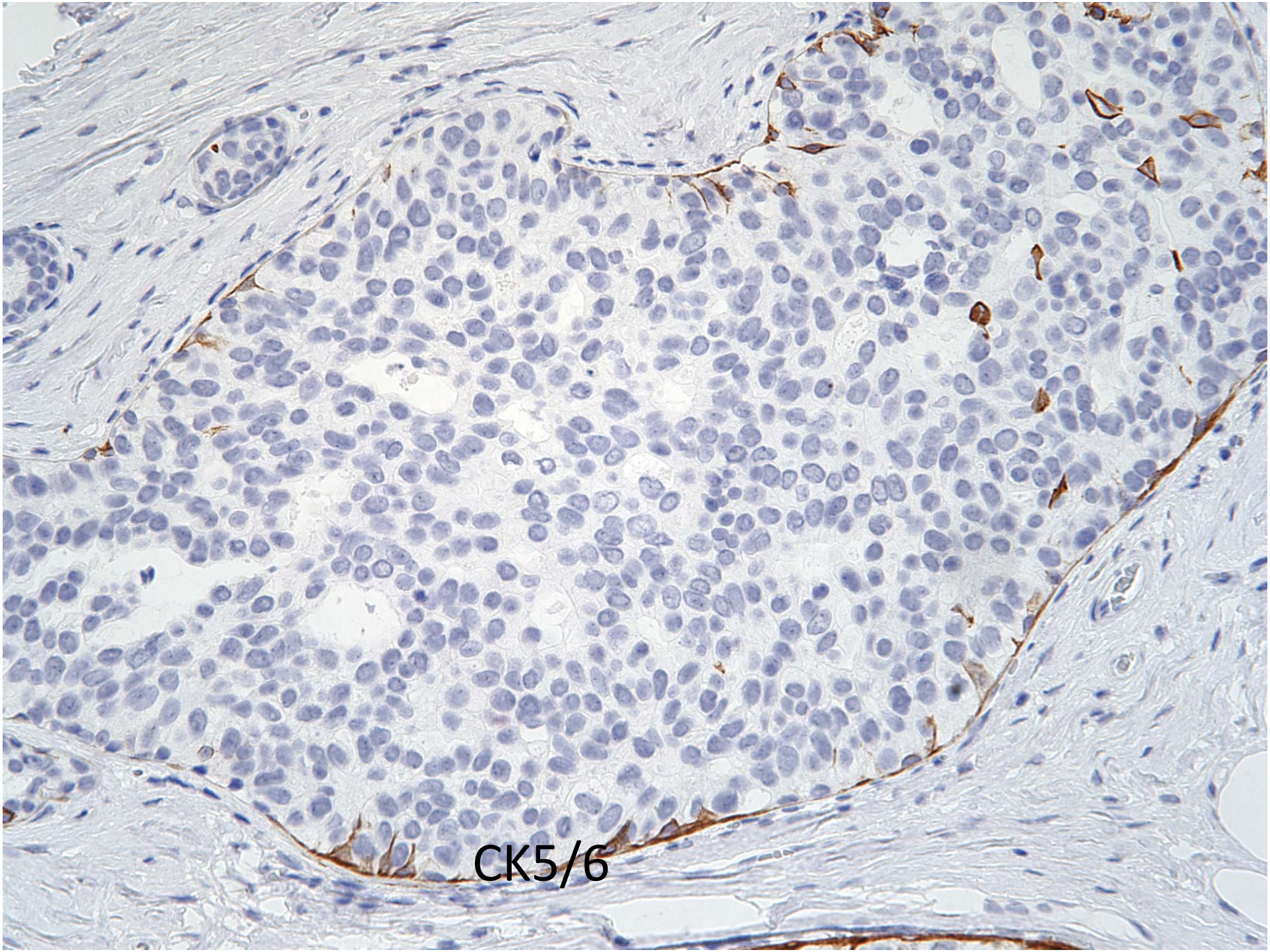
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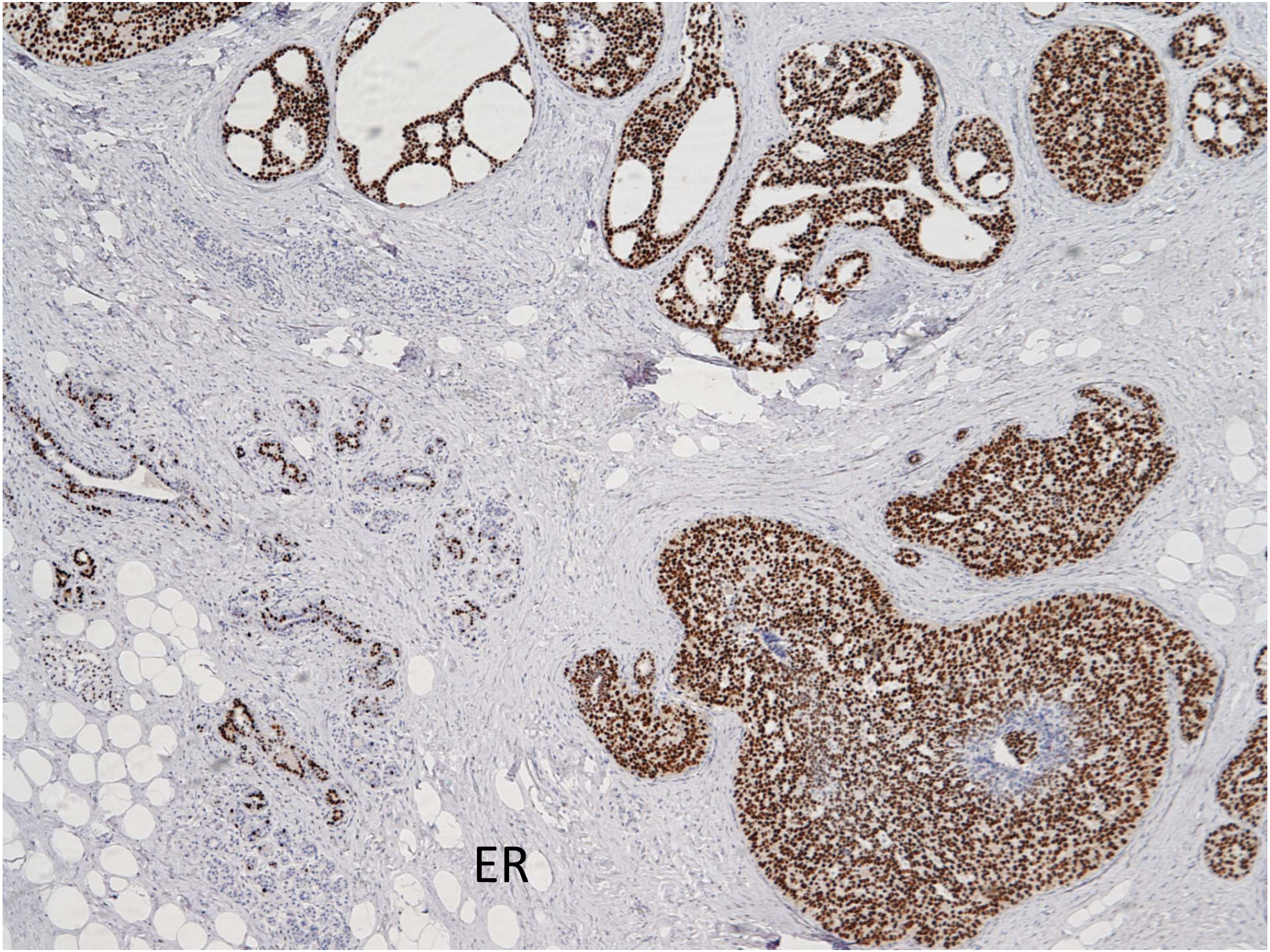
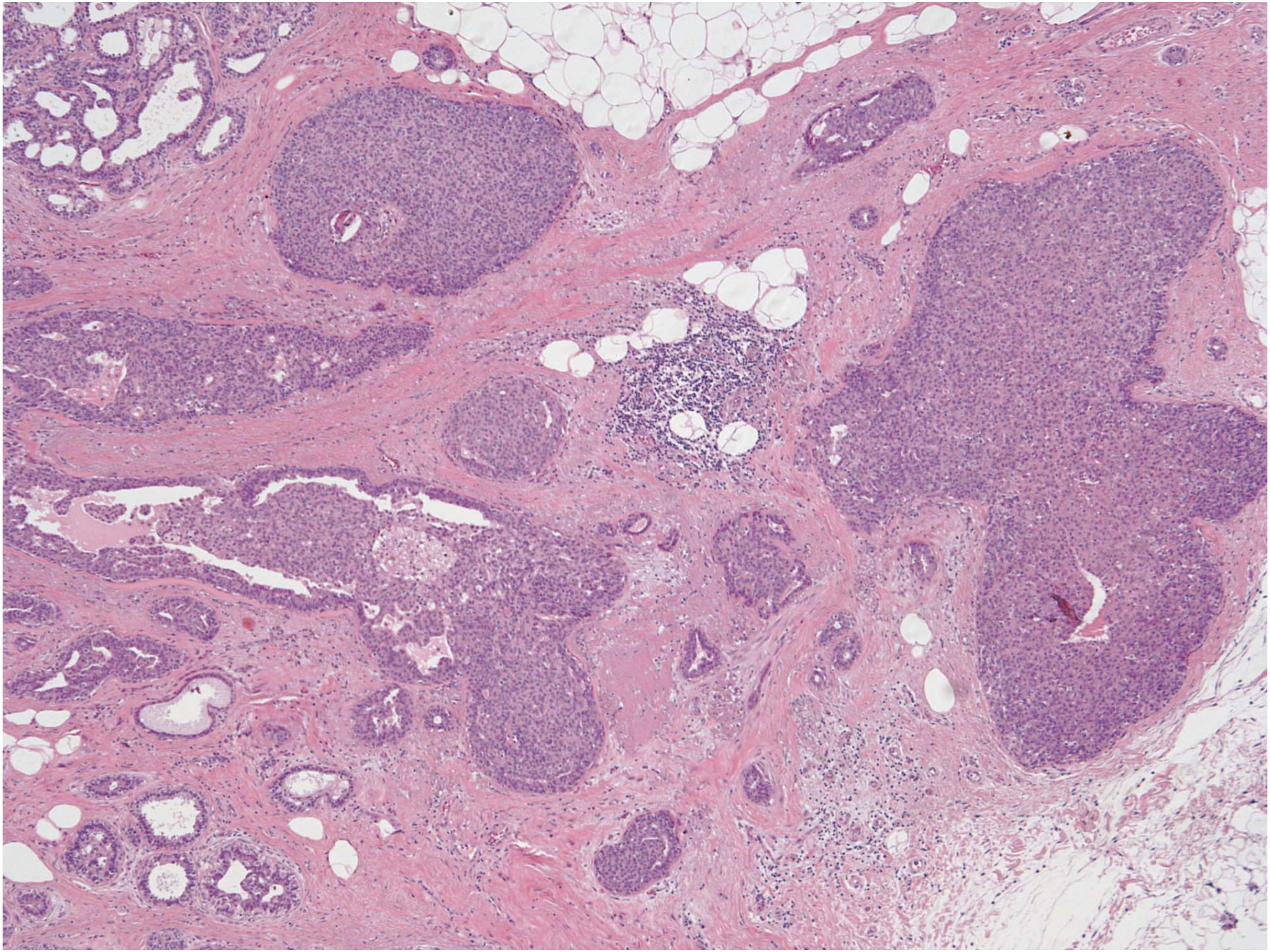
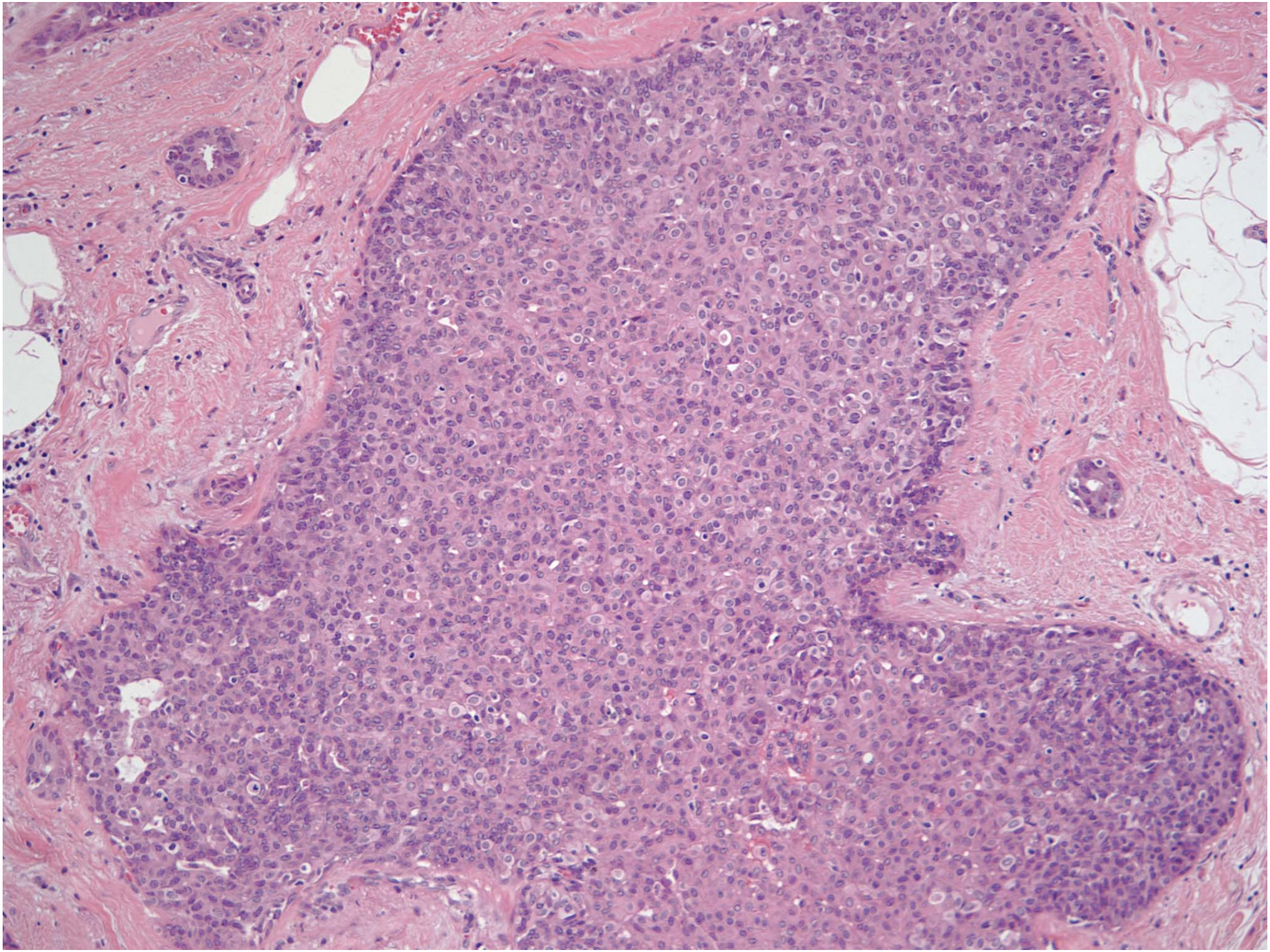
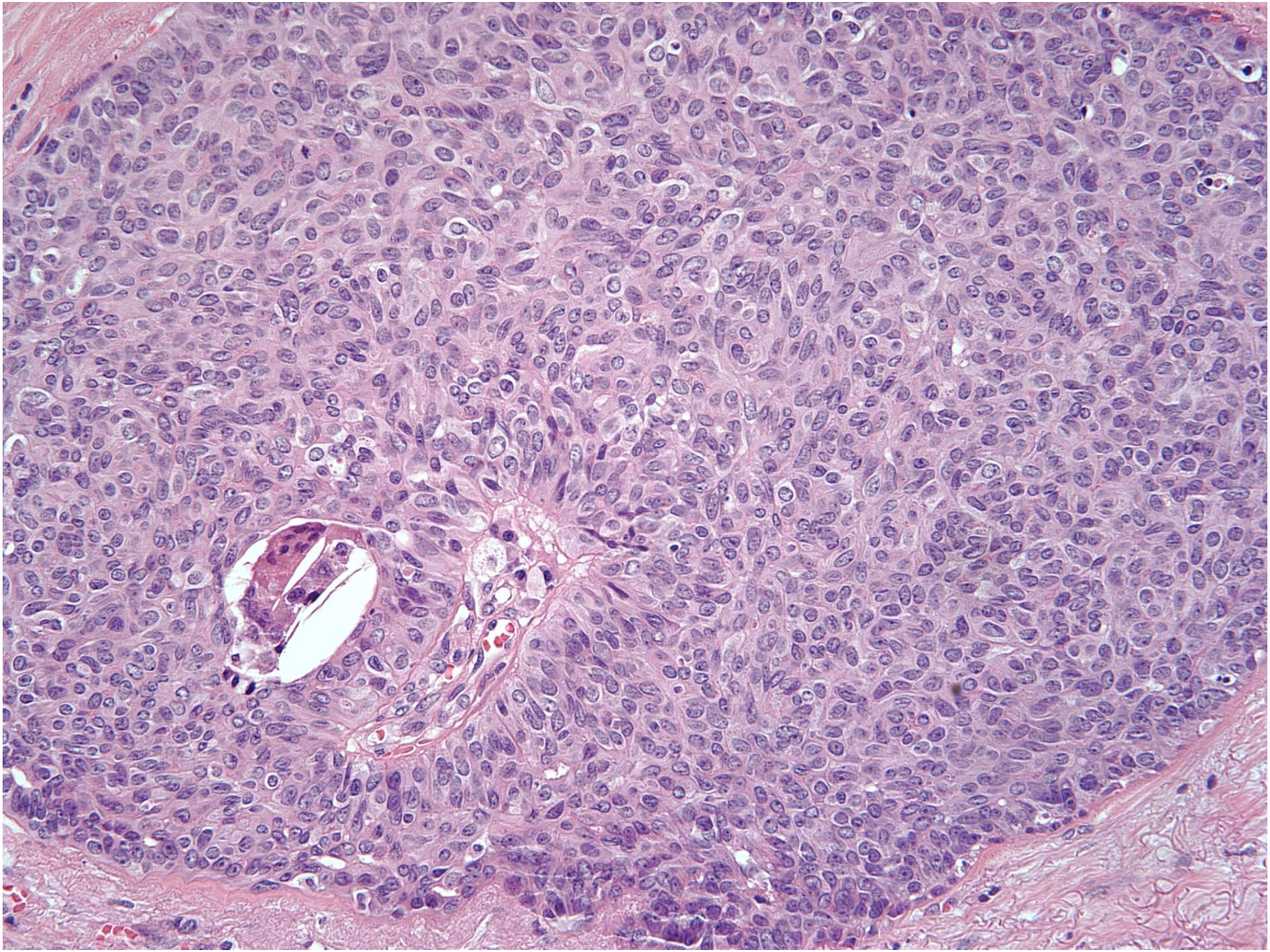
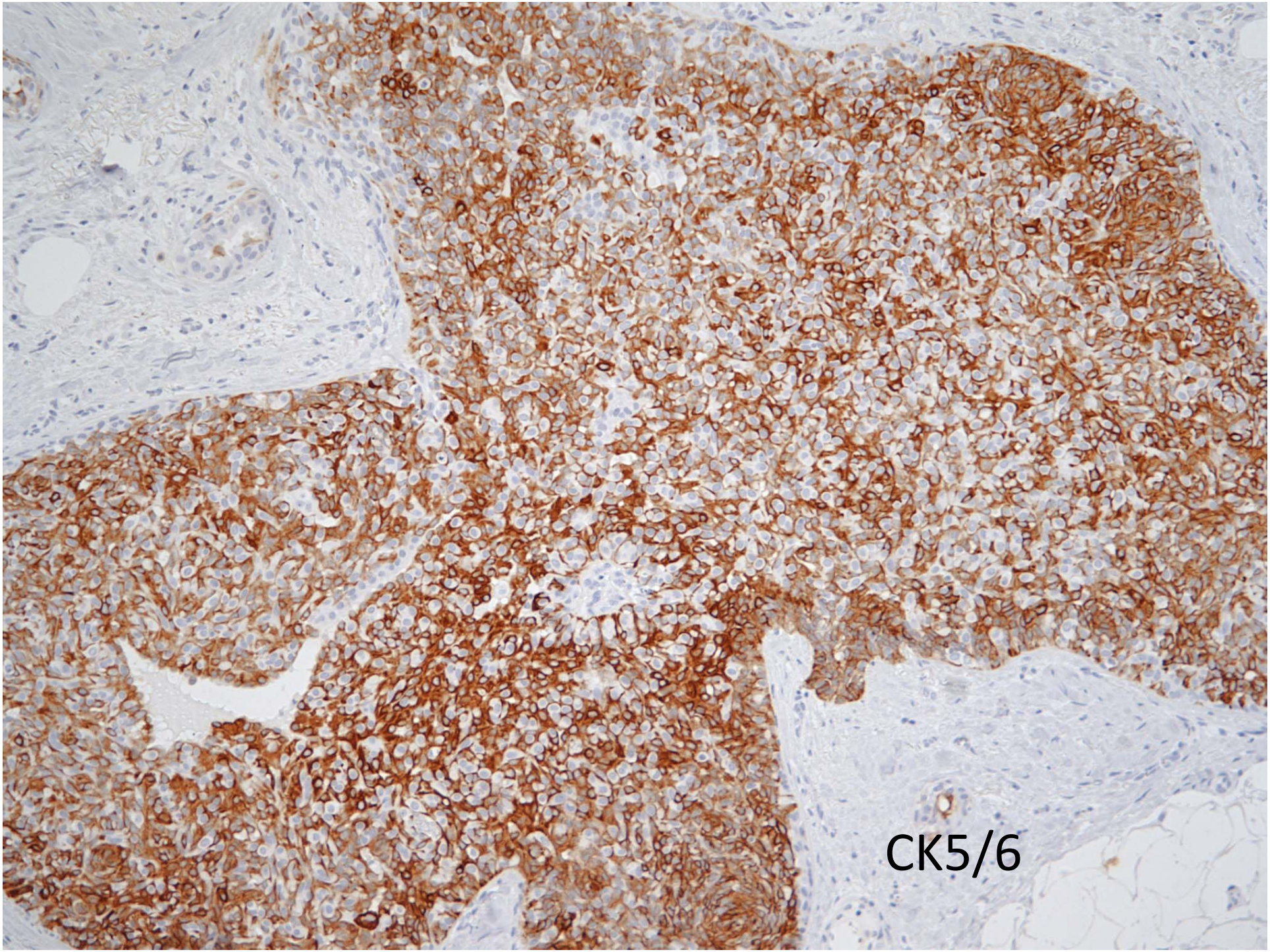

ER





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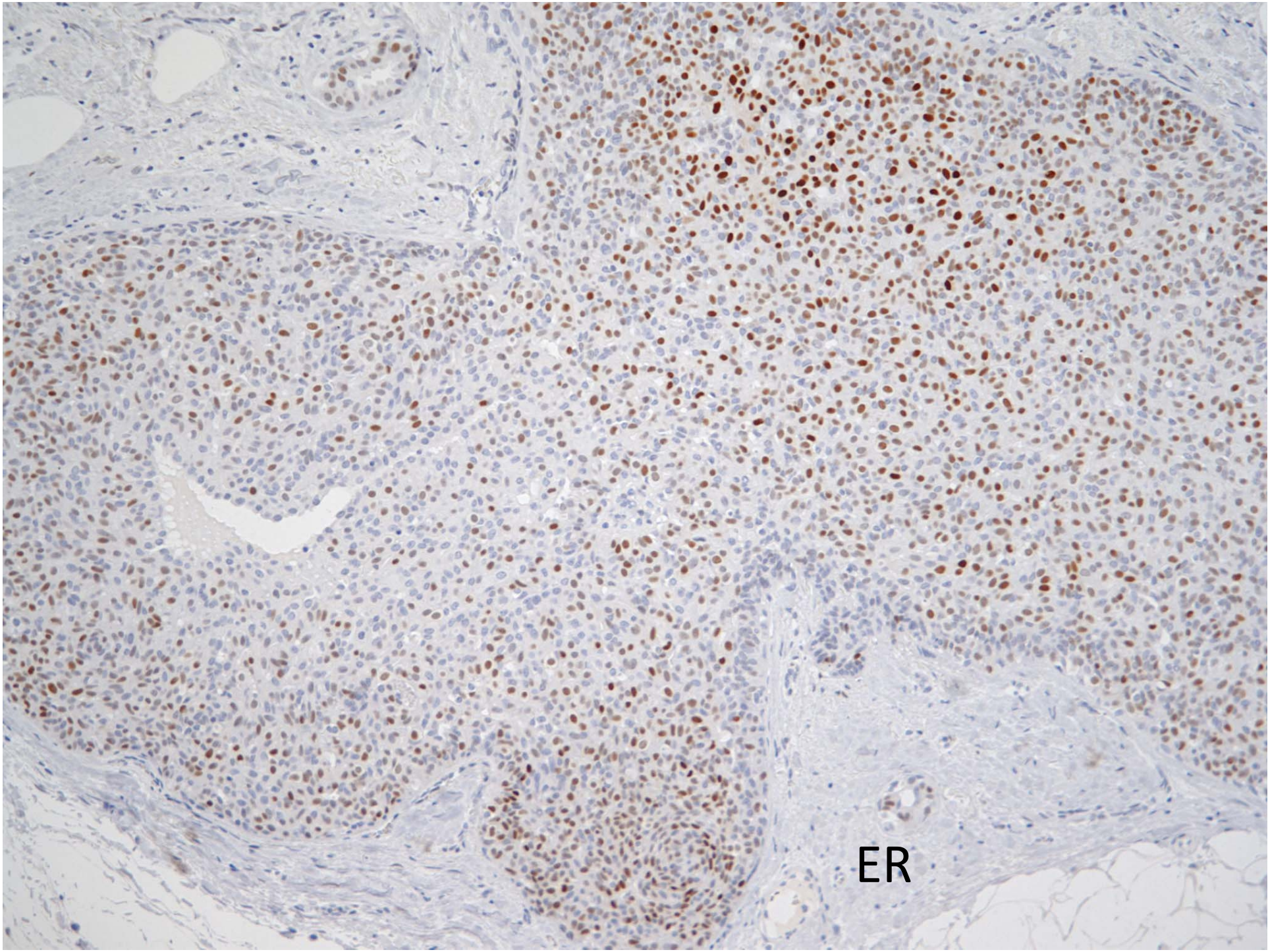
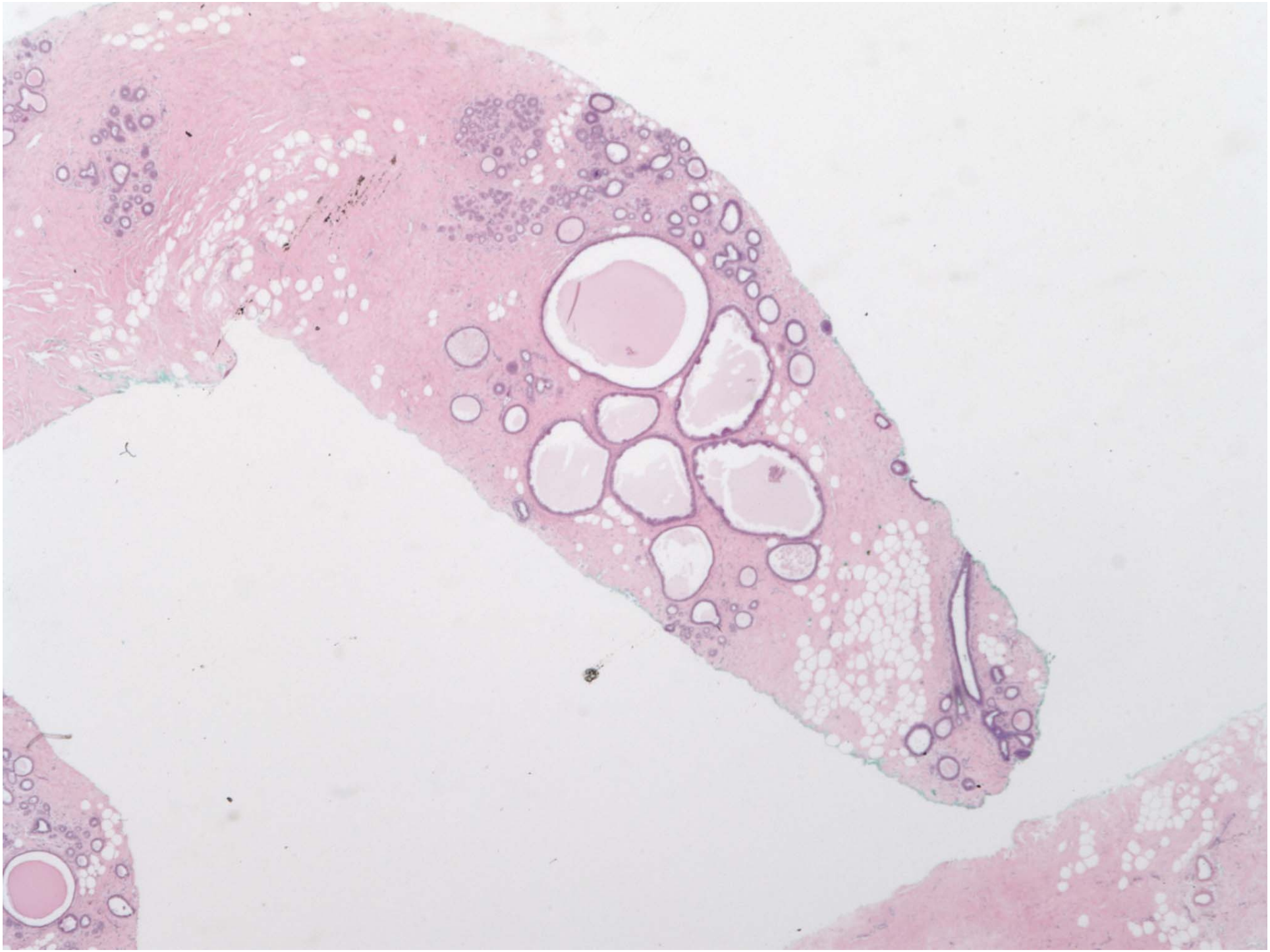
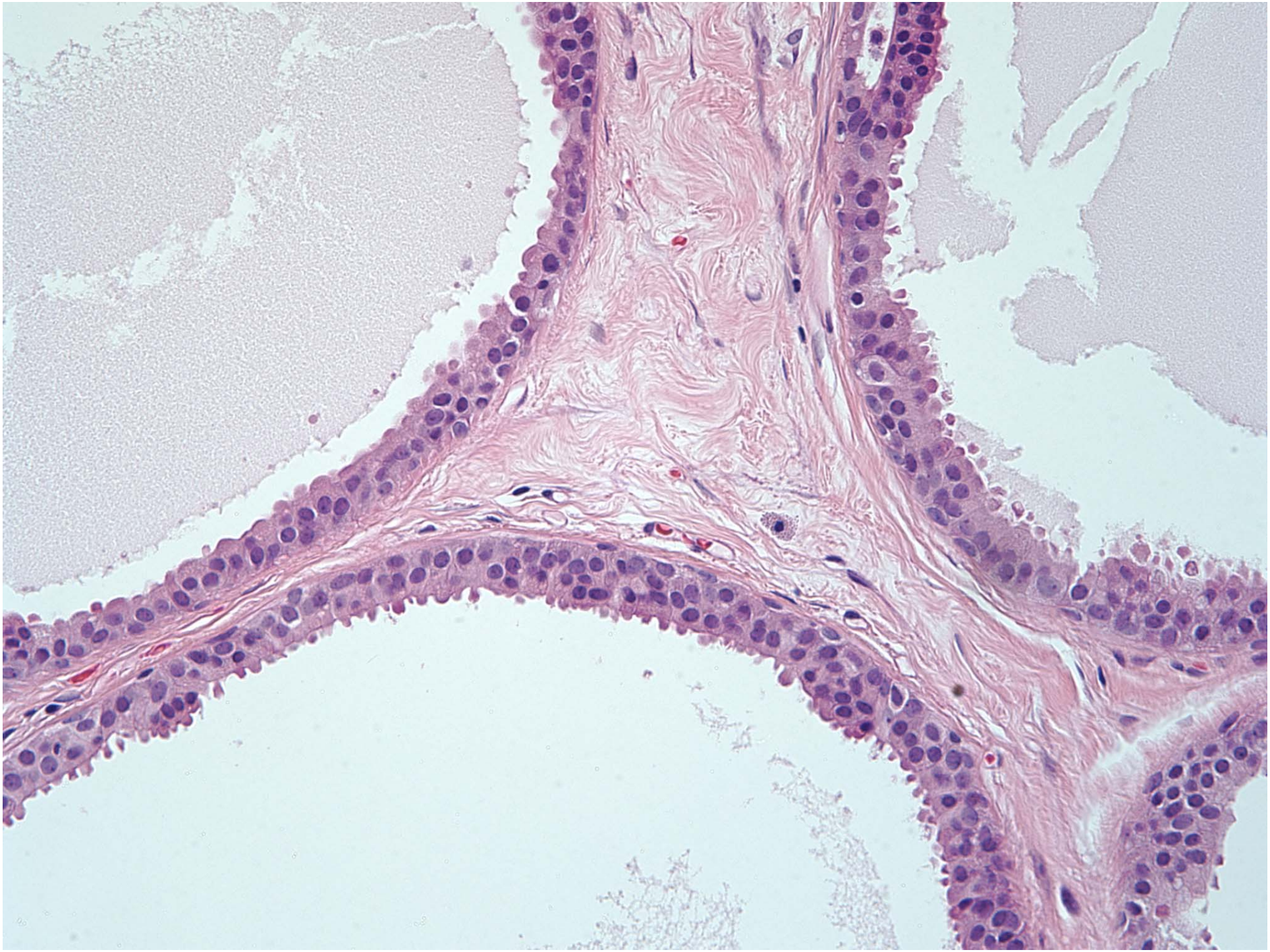

ER

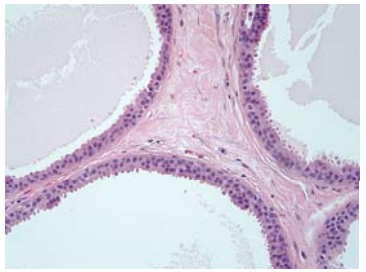
Case #7

- 43 year old with 0.6 cm of clustered calcifications on screening mammogram



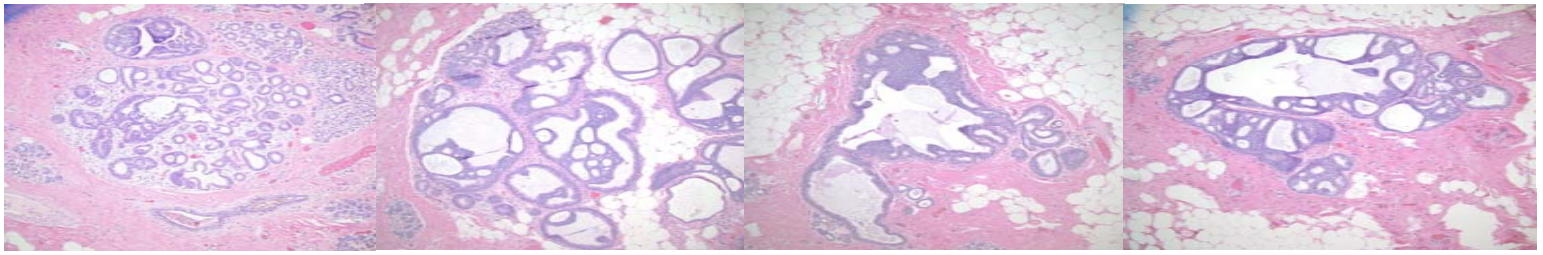


FEA



- Diagnostic agreement issues similar to ADH
- Present most often in association with other risk lesions (ADH, ALH, LCIS) DO LEVELS!!
- Associated with similar molecular abnormalities as concurrent ADH, low grade DCIS and invasion (very early step in neoplastic progression) LOOK NEXT TO ADH AND LG DCIS TO RECOGNIZE FEA
- Upgrade rates on excision 5-20% with most recent studies suggesting 0-3% for pure FEA

Summary of Intraductal Proliferative Lesions



- Minimal LG DCIS vs ADH:
  - Poor diagnostic agreement
  - Not biologically distinct (spectrum) but have different growth patterns, risks and treatments (currently)
  - Often occur intermixed together (estimation of size and margin status a challenge)
  - Remember core biopsy samples are just initial sampling (don’t overcall)

What to do?

- Need for practice policies to address issues
  - Second reviews (within practice or from specialist)
  - Consensus conferences
  - Test set/consensus set circulation
  - Commenting on specific extent/limitations of sample
  - Radiology and clinical correlation
  - How to treat may be what needs to change

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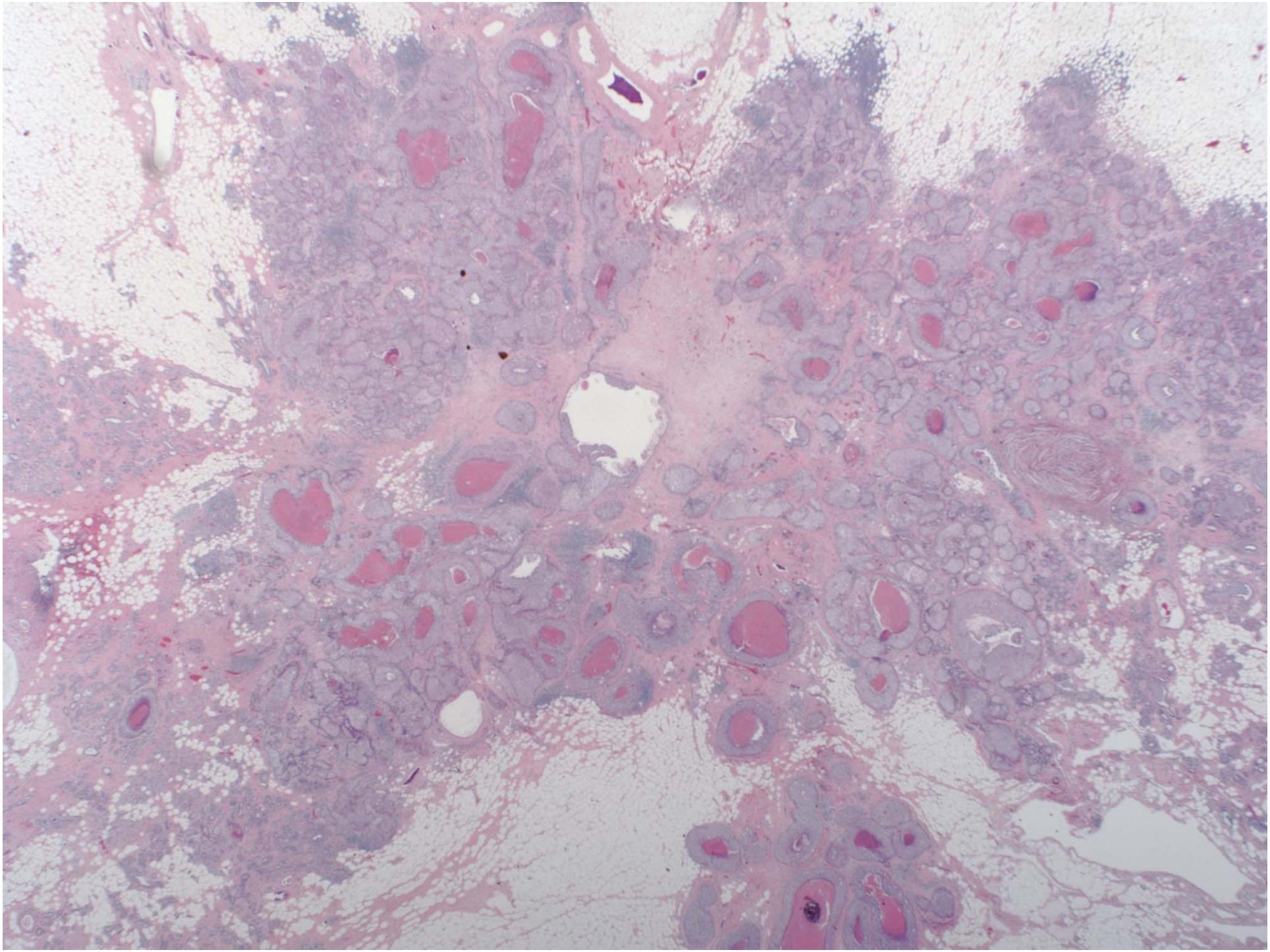
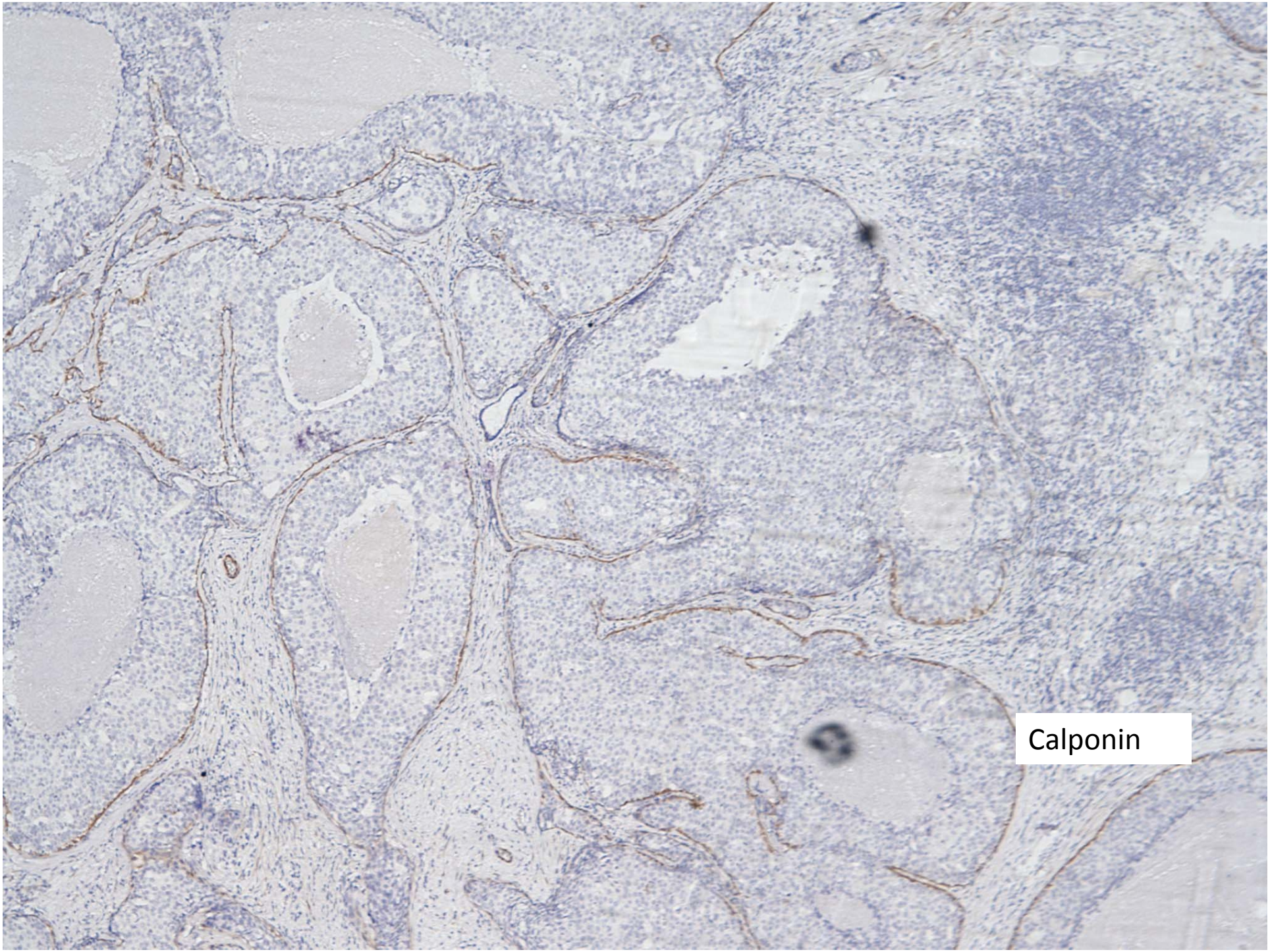
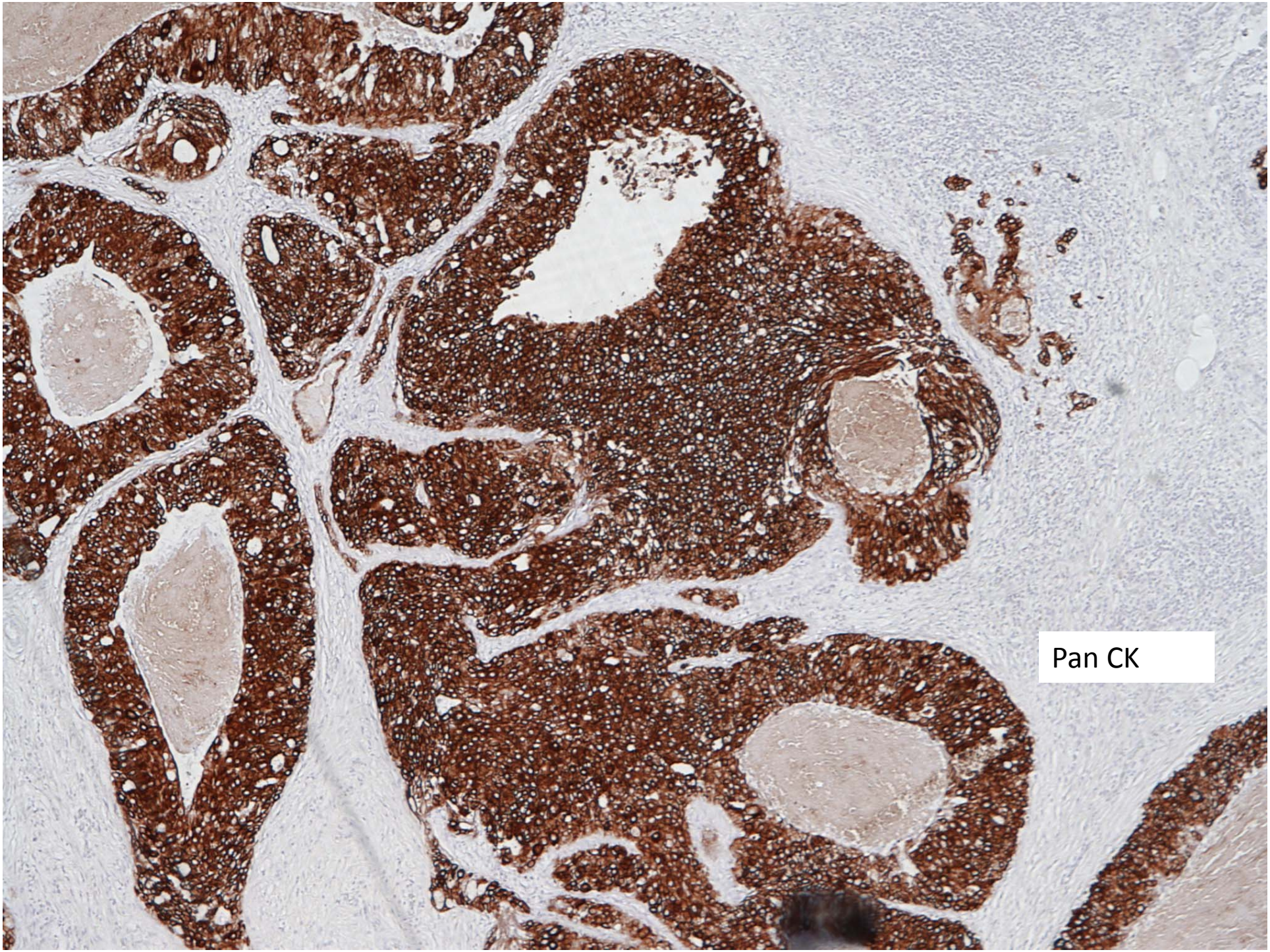
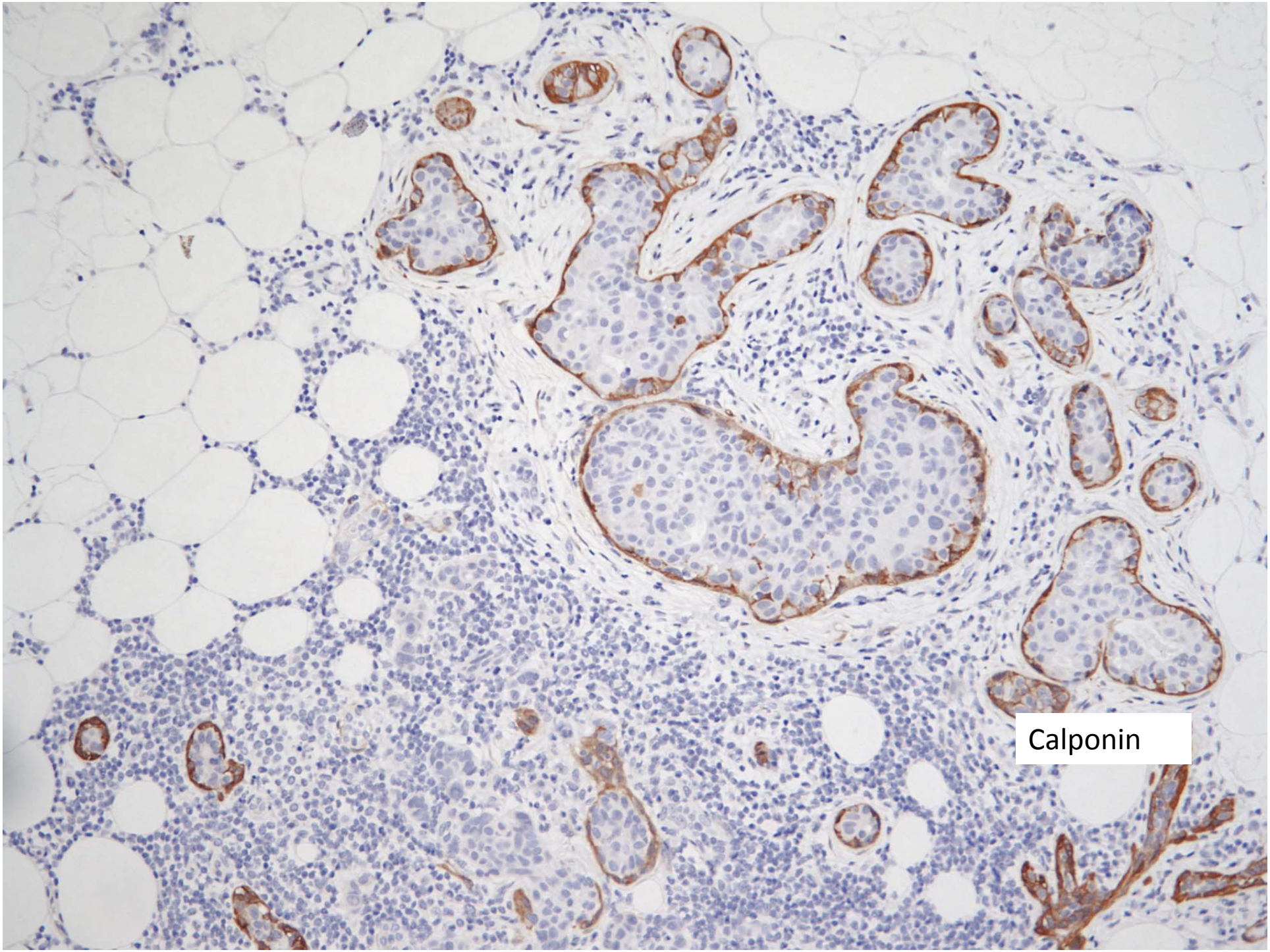
Case #8

- 37 year old with a 6 cm area of abnormal enhancement on MRI with lumpectomy




Calponin


Pan CK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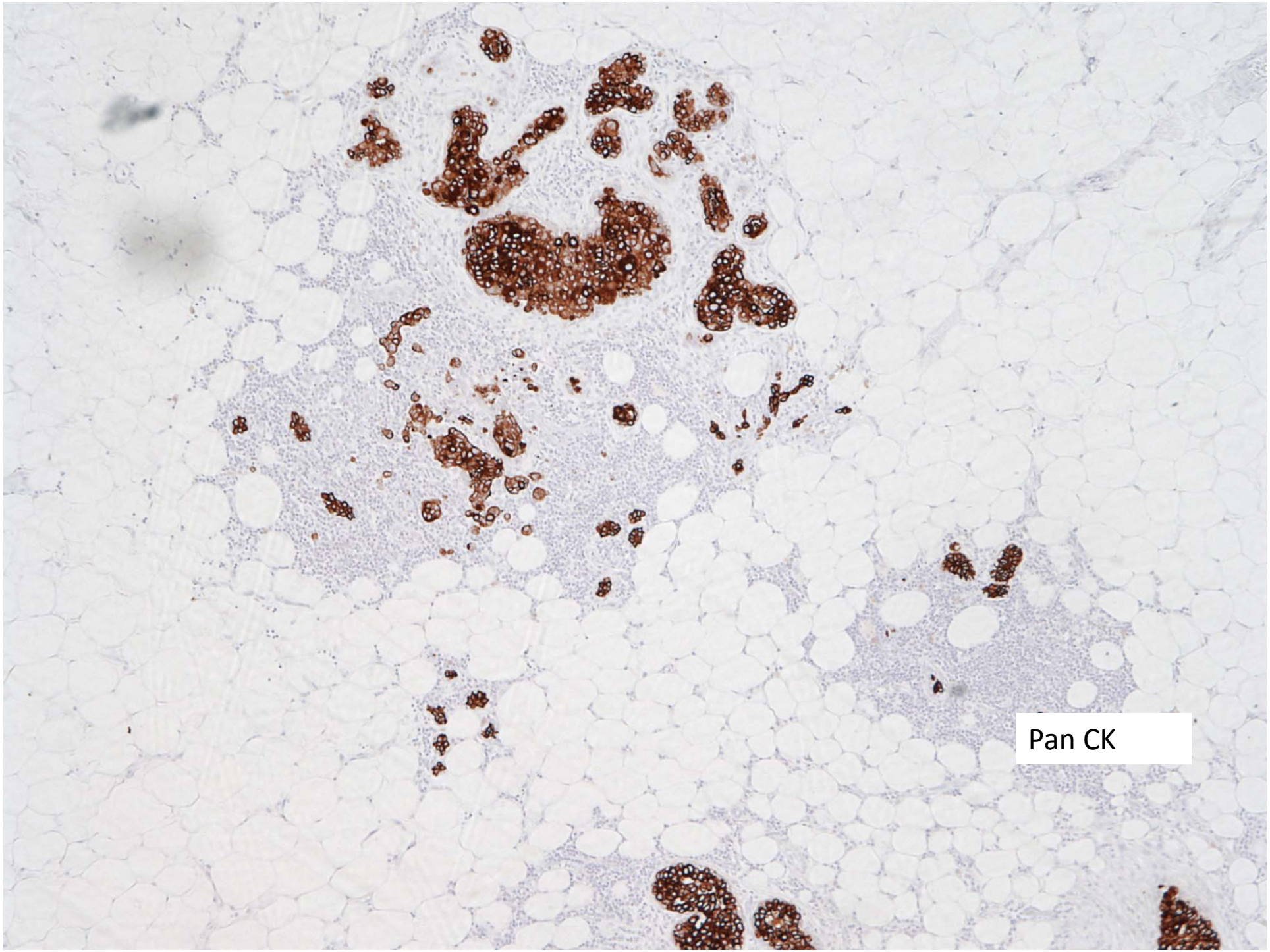
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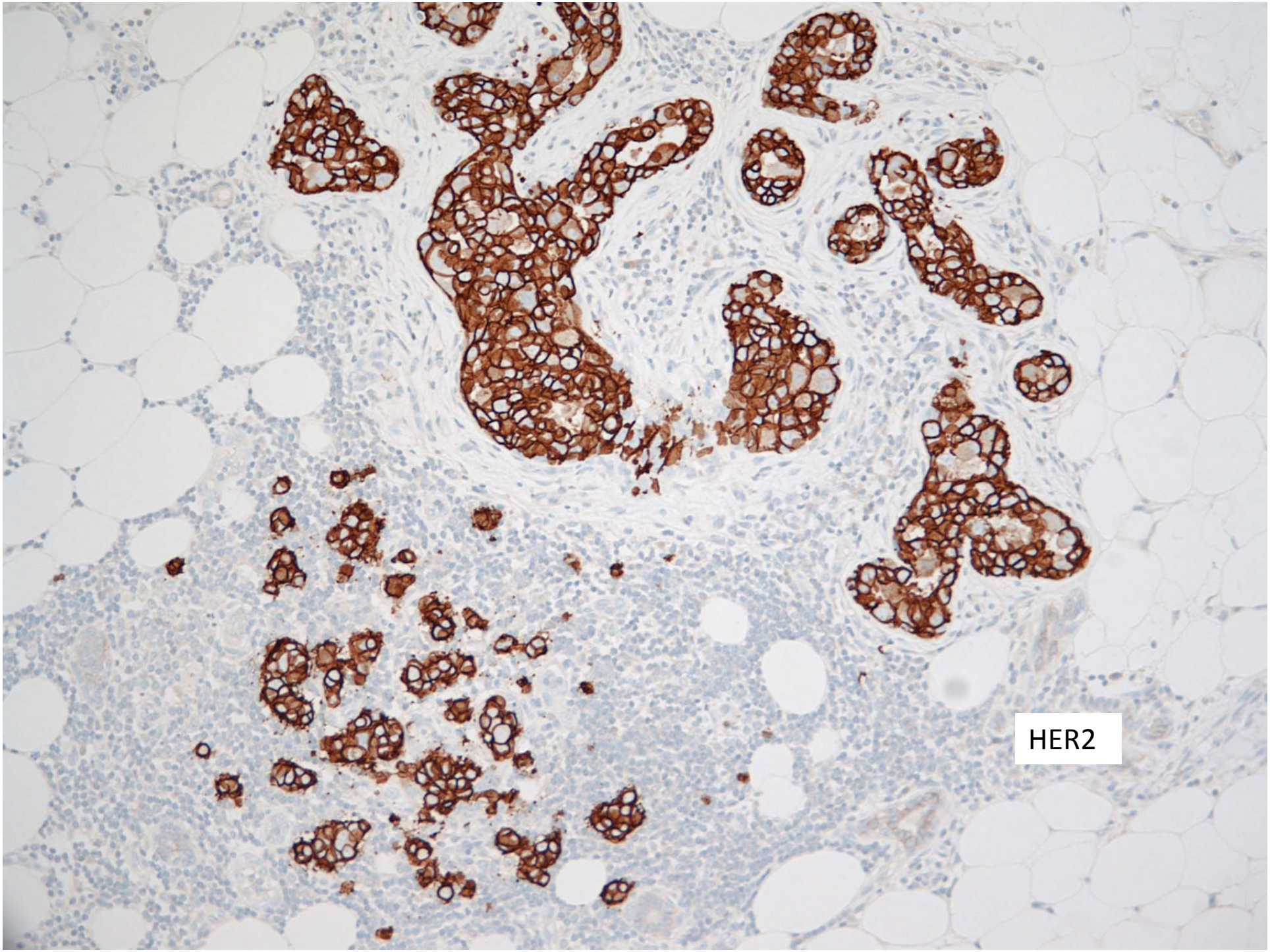
HER2

Tips in DCIS Grossing, Examination and Reporting

- Correct estimation of size requires adequate grossing
- Not missing invasion (esp in HG DCIS)- using panCK in addition to myoepithelial markers
- Margin inking and reporting

THANK YOU