Columnar Cell Lesions, Flat Epitheial Atypia, Atypical Ductal Hyperplasia

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Objectives/Summary

- Columnar Cell Change
- Columnar Cell Hyperplasia
- Flat Epithelial Atypia (FEA)
- FEA and Outcomes Management
- Atypical Ductal Hyperplasia
- Low and High Grade Pathways

Columnar Cell Alterations

BACKGROUND
Columnar Cell Lesions

- Distinct epithelial change in the TDLU.
- 80% microcalcifications-rounded.
- Most patients are >35 years of age

Background

- Schimmelbusch (1892)
- Sasse (1897)
- Warren (1905)-”abnormal involution”
- Bloodgood(1906)-”adenoidcystic stage of senile parenchymatous hypertrophy”

Background

- Wellings-1975: “hyperplastic unfolded lobules”-subgross examination of whole mount breasts.
- Sarnelli- 1980-”atypical lobules”-subgross whole mounts.
- Columnar Alteration with Prominent Apical Snouts (CAPSS) (Fraser, 1998)
- Atypical Cystic Lobules (Oyama, 1999)

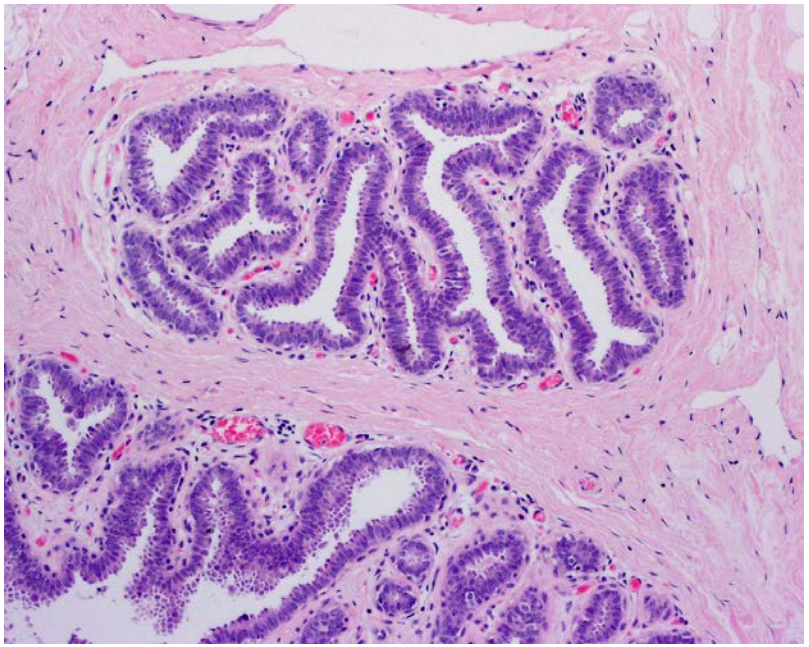
- Enlarged Lobular Units Columnar Alteration “ELUCA” (Page)
- Hyperplastic Enalrged Lobular Units “HELU” (Allred)

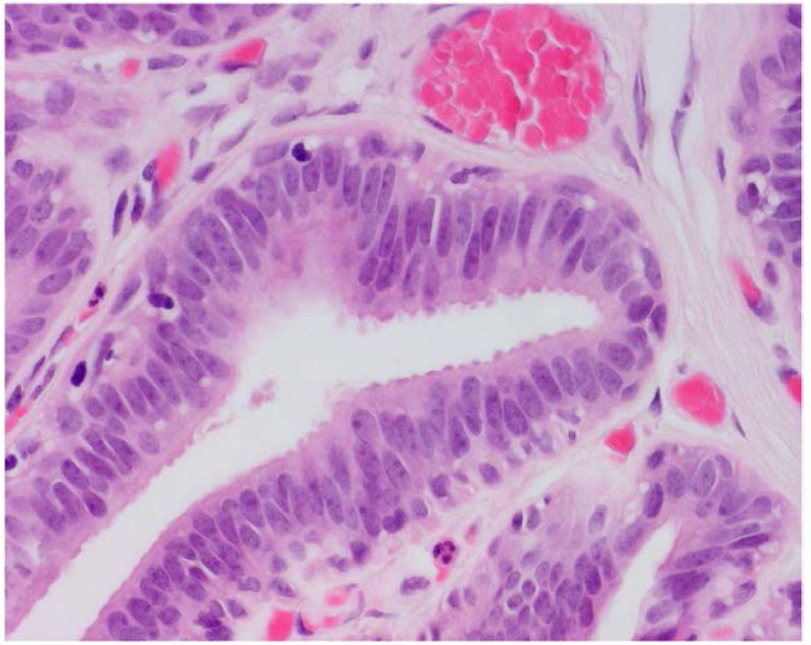
Terminology

- Columnar Cell Change
- Columnar Cell Hyperplasia-CCH->2 cells
- Columnar Cell Change with atypia "flat epithelial atypia"
- Azzopardi "clinging carcinoma"

Columnar cell lesions

- Spectrum of lesions characterised by
  - Enlargement of TDLUs
  - Columnar epithelial cells
  - Monomorphic nuclei
  - Varying degrees of atypia
    - Unremarkable
    - ADH-like nuclei
- ER +, PgR +
- HER2-
- Basal-keratins -
- Luminal A phenotype





Modern Pathology (2006) 19, 344–349

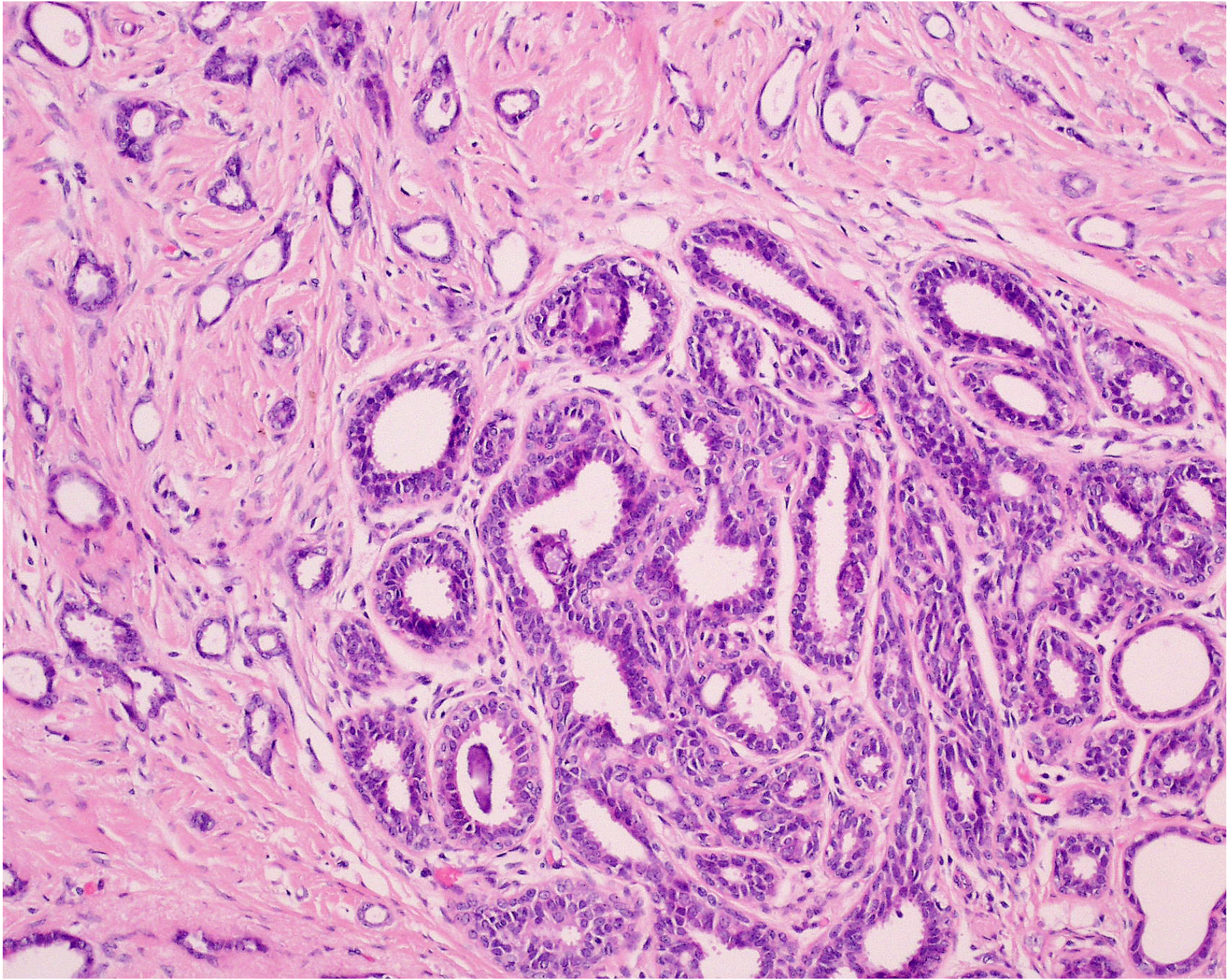
www.modernpathology.org

Molecular alterations in columnar cell lesions of the breast

David J Dabbs, Gloria Carter, Mary Fudge, Yan Peng, Pat Swalsky and Sidney Finkelstein

- 10 microsatellite markers

	Normal	CCC	CCH	ACCH	DCIS	IC
Fractional mutation %	0%	0%	0-15%	0-20%	0-36%	0-40%
LOH at least 1 locus	0/10 (0%)	0/3 (0%)	2/3 (66%)	10/15 (66%)	10/10 (100%)	8/8 (100%)



Columnar Cell Lesions of the Breast: The Missing Link in Breast Cancer Progression?

A Morphological and Molecular Analysis

Peter T. Simpson, PhD, Theo Gale, BSc,* Jorge S. Reis-Filho, MD,* Chris Jones, PhD,† Suzanne Parry, MSc,* John P. Sloane, FRCPath,‡ Andrew Hanby, FRCPath,§ Sarah E. Pinder, FRCPath,‖ Andrew H. S. Lee, MRCPath,‖ Steve Humphreys, FRCPath,¶ Ian O. Ellis, FRCPath,‖ and Sunil R. Lakhani, FRCPath*#***

Genetic Abnormalities in Mammary Ductal Intraepithelial Neoplasia-Flat Type ("Clinging Ductal Carcinoma In Situ")

A Simulator of Normal Mammary Epithelium

Farid Moinfar, M.D.[1]
Yan-Gao Man, M.D., Ph.D.[1]
Gary L. Bratthauer, M.S., MT (ASCP)[1]
Manfred Ratschek, M.D.[2]
Fattaneh A. Tavassoli, M.D.[1]

BACKGROUND. Mammary ductal intraepithelial neoplasia (DIN)-flat type ("clinging ductal carcinoma in situ [DCIS]") generally is a subtle epithelial alteration characterized by one or a few layer(s) of atypical cells replacing the native epithelium. The "low power" appearance of DIN-flat type can be misinterpreted easily as "normal" because of the frequent absence of multilayered proliferation and often subtle

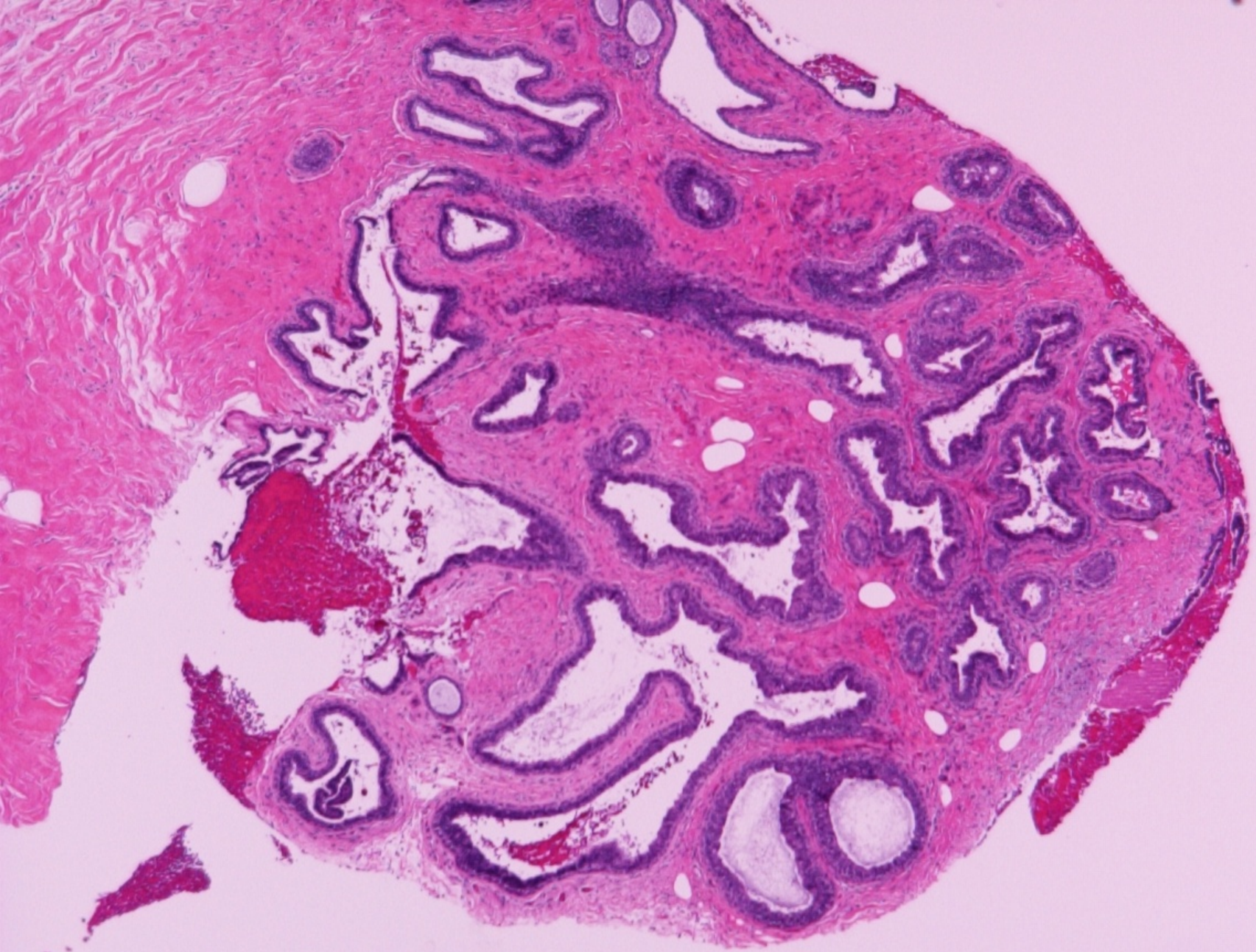
Significant associations with CCC, FEA, LGDCIS, LN

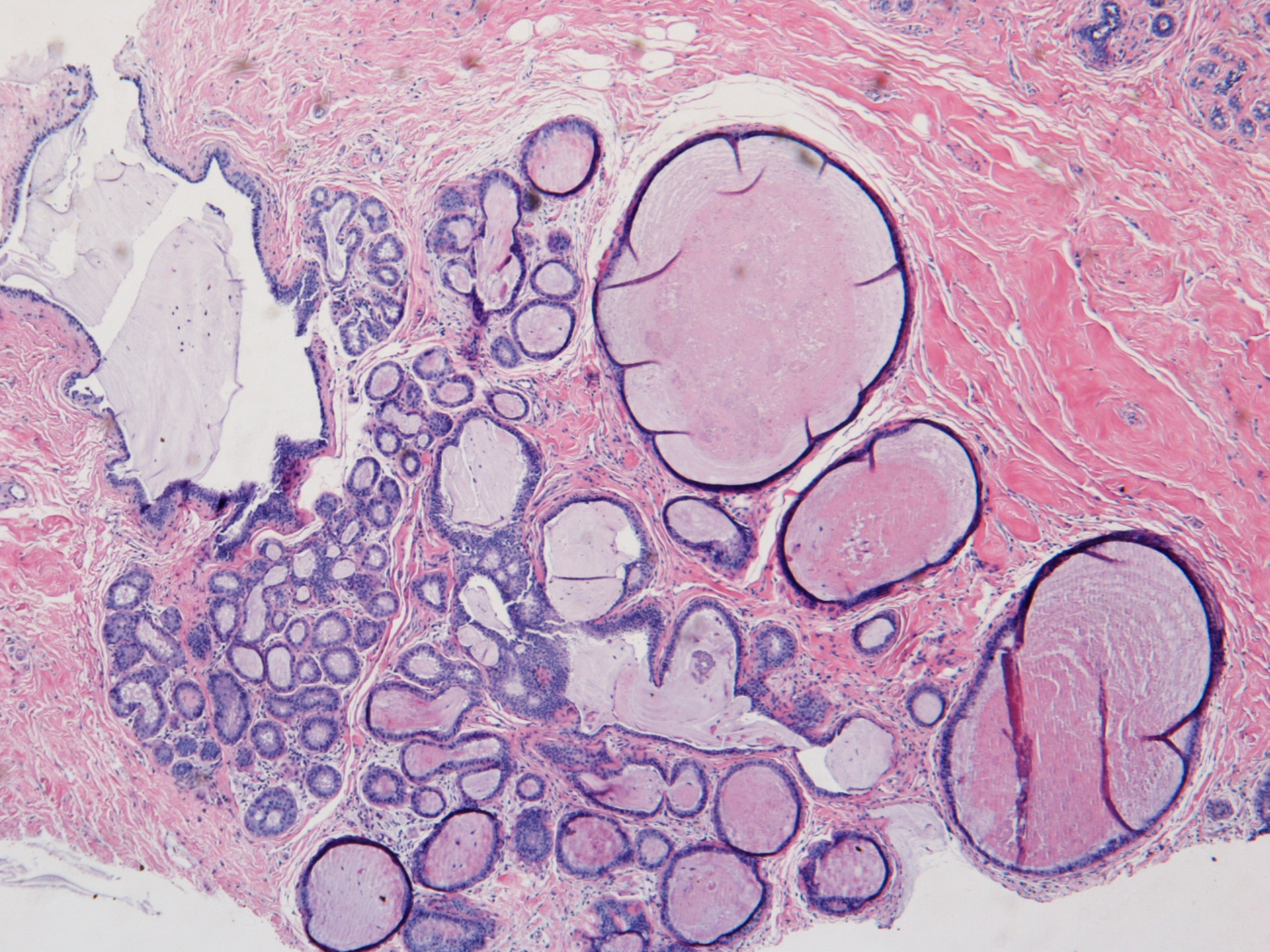
Modern Pathology (2007) 20, 1149–1155

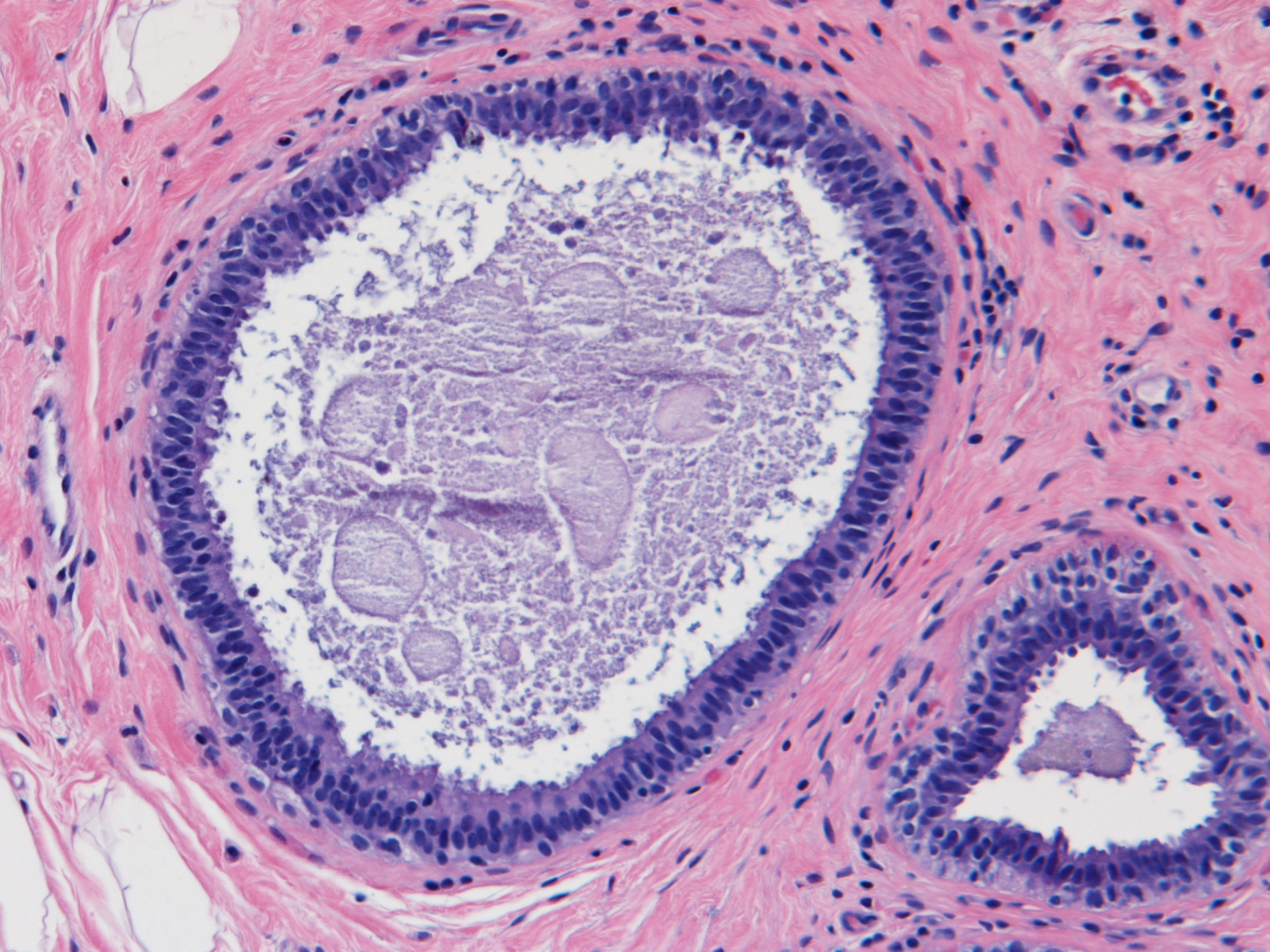
www.modernpathology.org

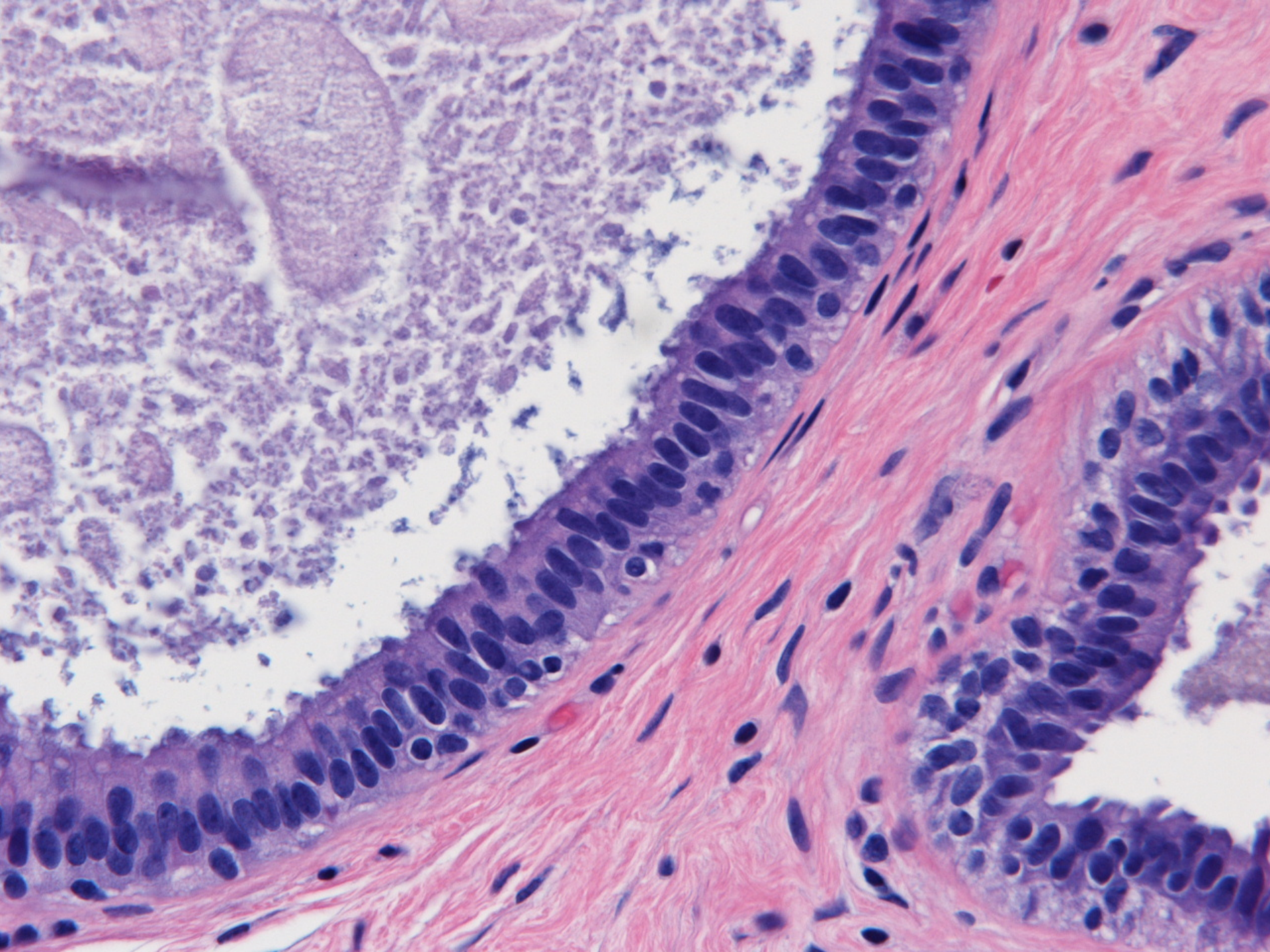
Clinical and pathologic features of ductal carcinoma *in situ* associated with the presence of flat epithelial atypia: an analysis of 543 patients

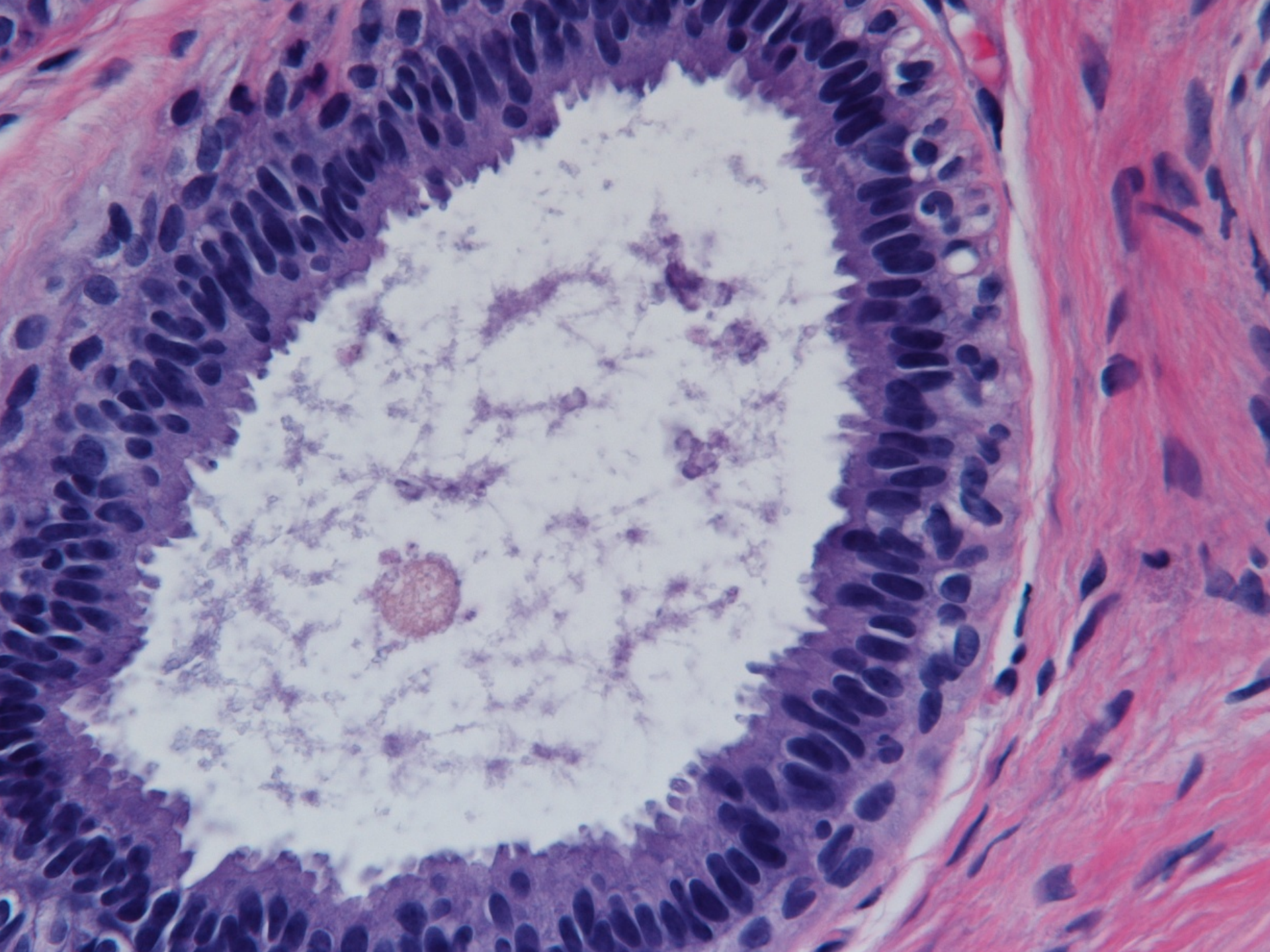
Laura C Collins[1], Ninah A Achacoso[2], Larissa Nekhlyudov[3], Suzanne W Fletcher[3], Reina Haque[4], Charles P Quesenberry Jr[2], Najeeb S Alshak[5], Balaram Puligandla[6,7], Gilbert L Brodsky[8], Stuart J Schnitt[1] and Laurel A Habel[2,9]



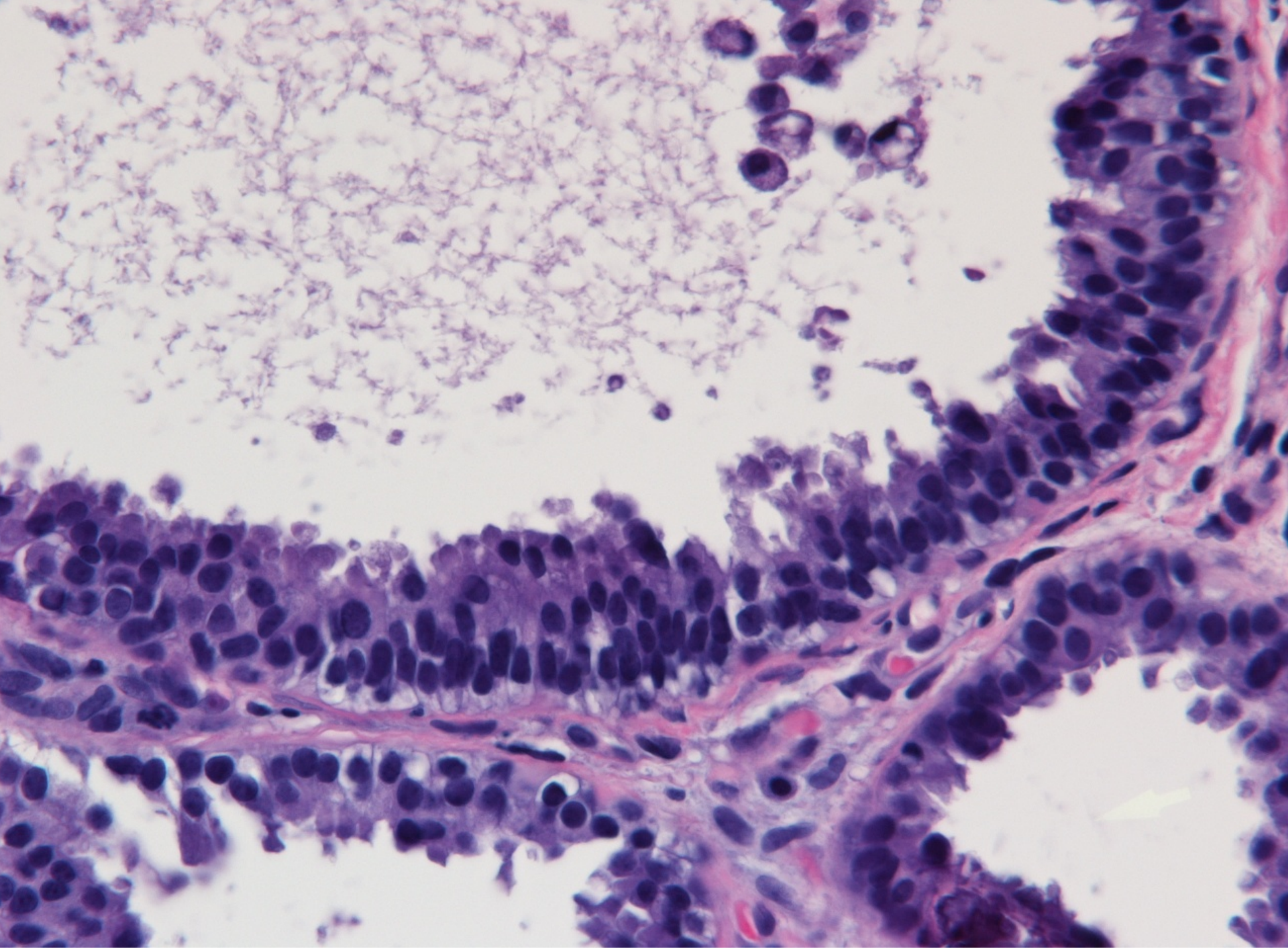


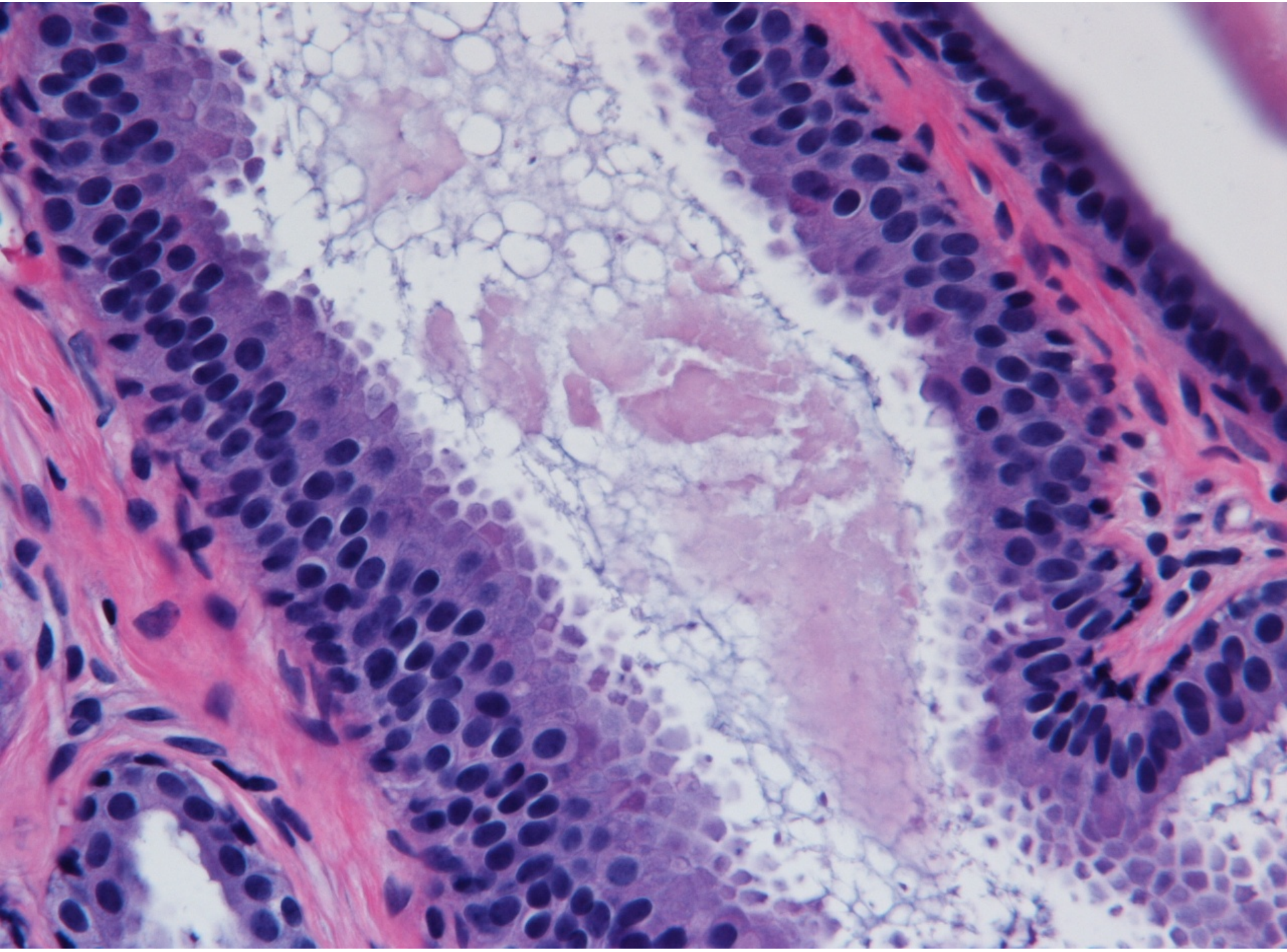


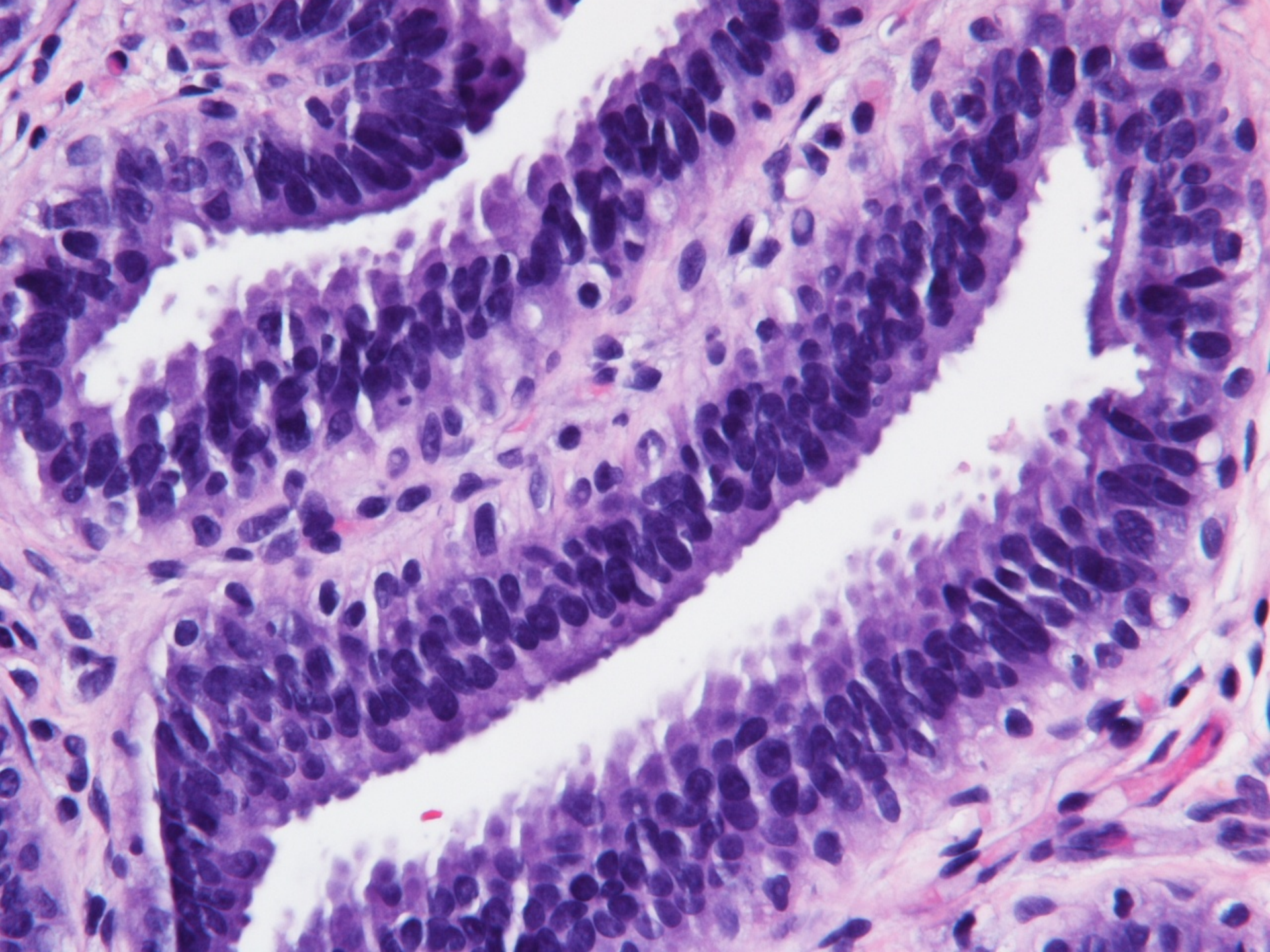




Columnar Cell Hyperplasia







Columnar Cell Hyperplasia with Atypia
Flat Epithelial Atypia (FEA)

Background

Columnar cell Alterations with apical Snouts and Secretions (CAPSS) with atypia", "atypical cystic lobules", "ductal intraepithelial neoplasia, flat type" or "clinging carcinoma"

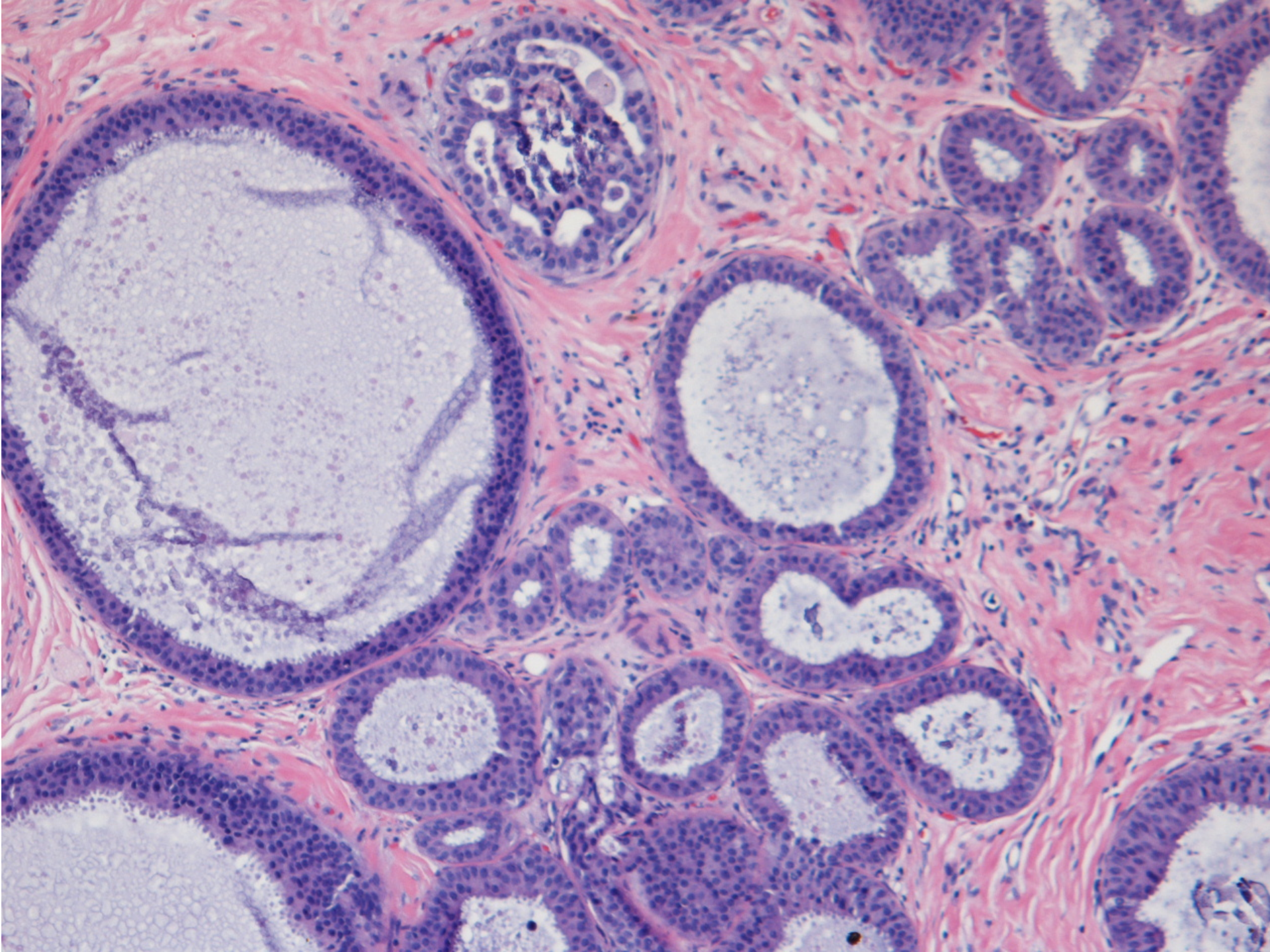
- Flat epithelial atypia (FEA) introduced by WHO in 2003
- Current WHO (2014): columnar cell change, columnar cell hyperplasia, flat epithelial atypia.

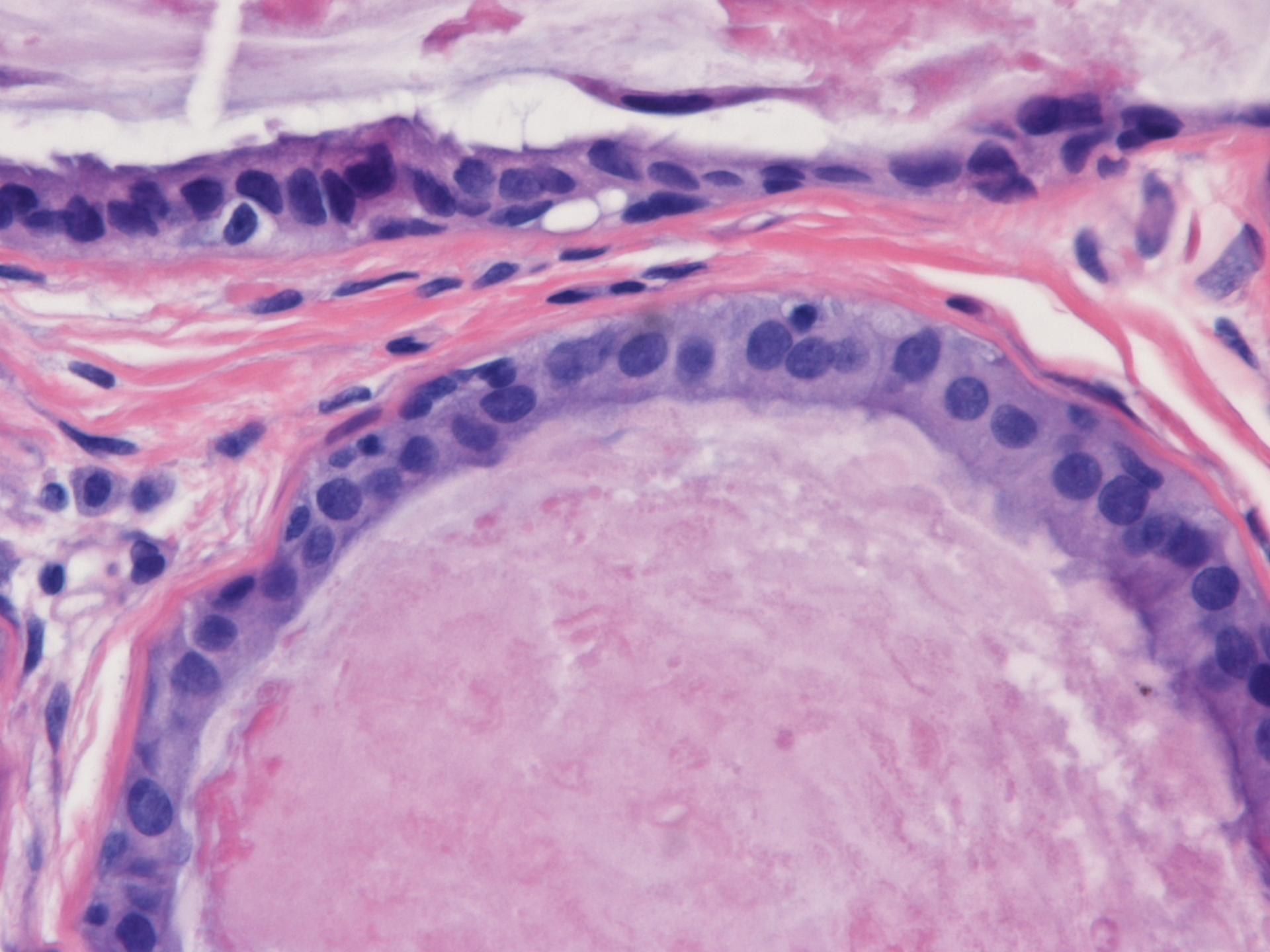
Flat Epithelial Atypia

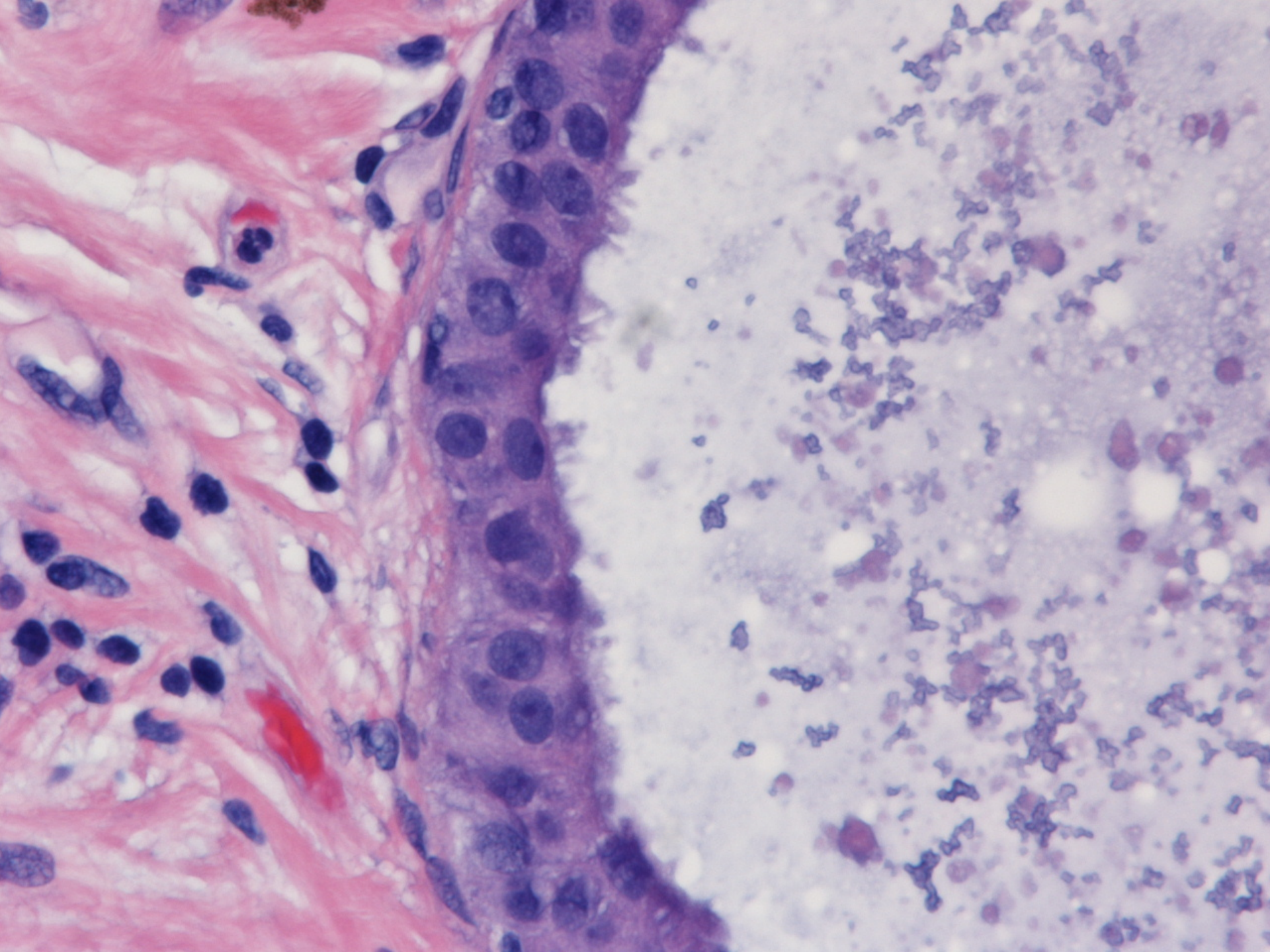
- "dilated acini lined by a single layer of evenly spaced monomorphic cells with apical snouts and containing flocculent material containing calcifications"
- the cells may be stratified, with loss of polarity but lack complex architectural patterns (as seen in ADEH)
- low grade cytologic atypia with enlarged round /ovoid nuclei, inconspicuous nucleoli and +/- abundant eosinophilic cytoplasm

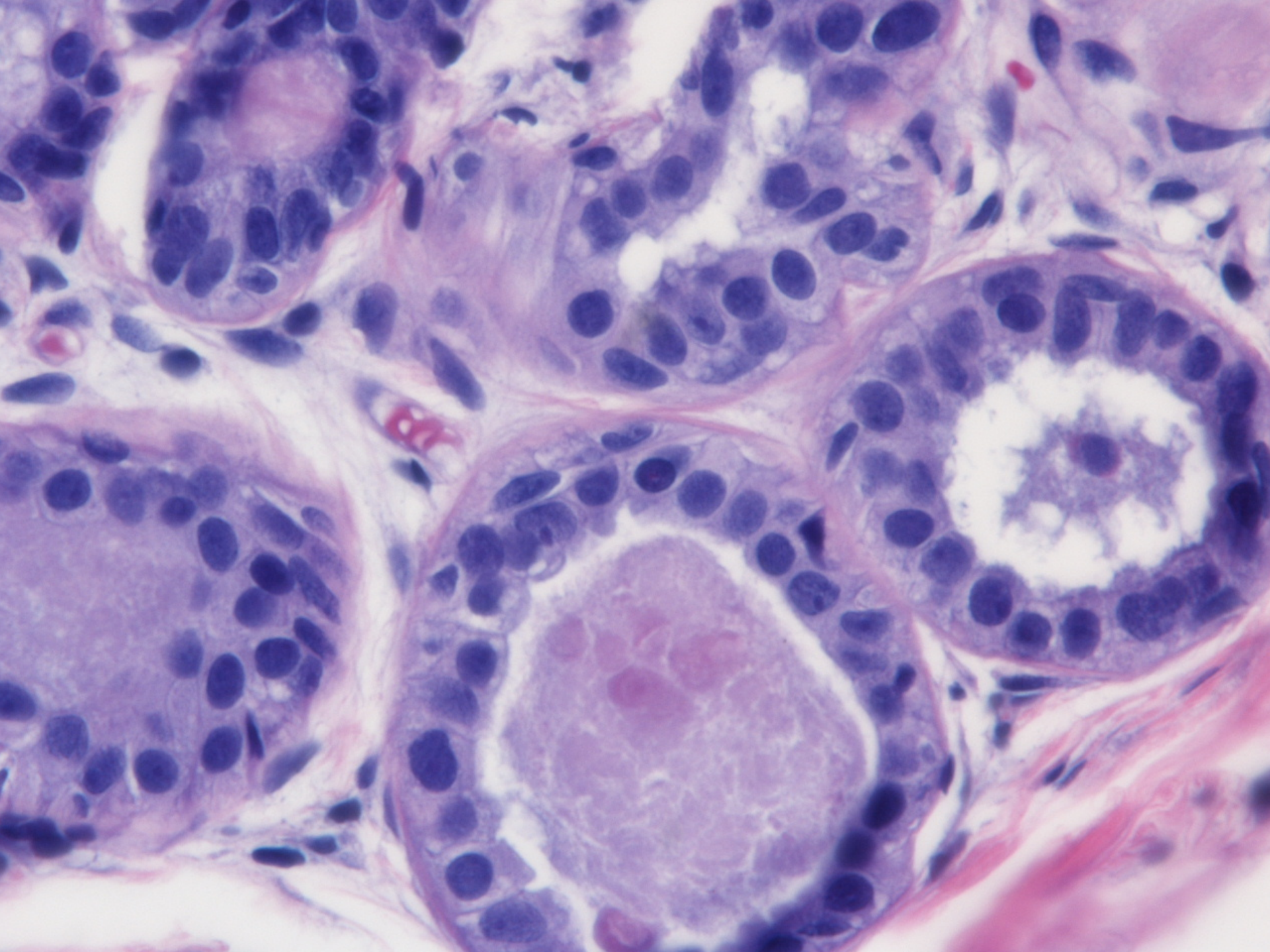
Kinships?

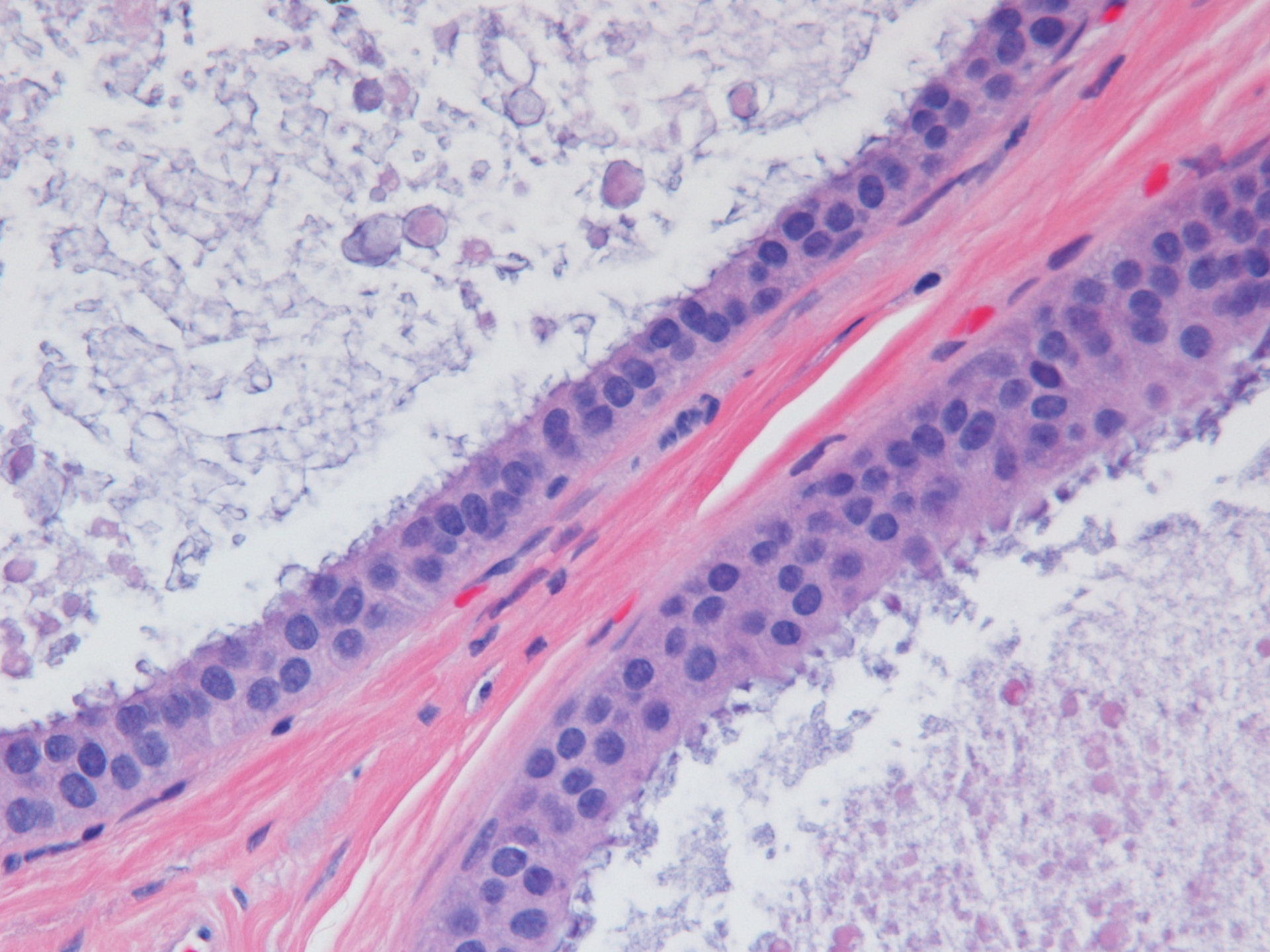
- Flat epithelial atypia, atypical duct hyperplasia (ADH) and lobular neoplasia are frequently seen on the same tissue slide.
- Frequently (~20% of the time), deeper levels of FEA may reveal areas of ADH (Am J Clin Pathol 2009;131:802–808.)
- Similar molecular alterations are seen in CCC, FEA, DCIS on the same slide (***Dabbs et al, 2006 Mod Pathol 2006 Mar;19(3):344-9***; ***Aulmann S et al 2012 Am J Surg Path 36: 1247***)
- Commonality: “Low Grade Pathway” with loss of 16q, gain of 1q (***Stacher E et al 2011 Histopathol 59: 549-55***)

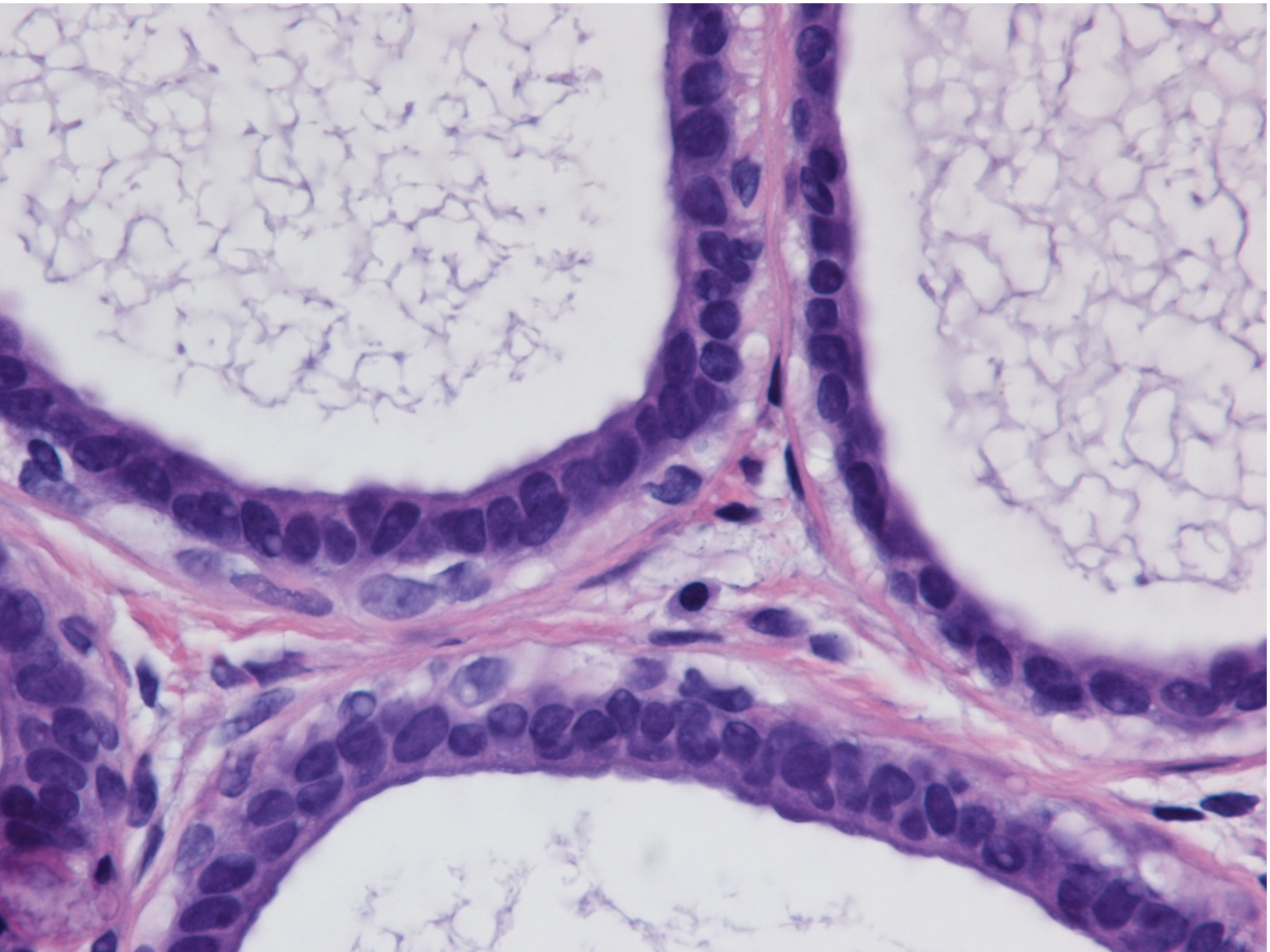


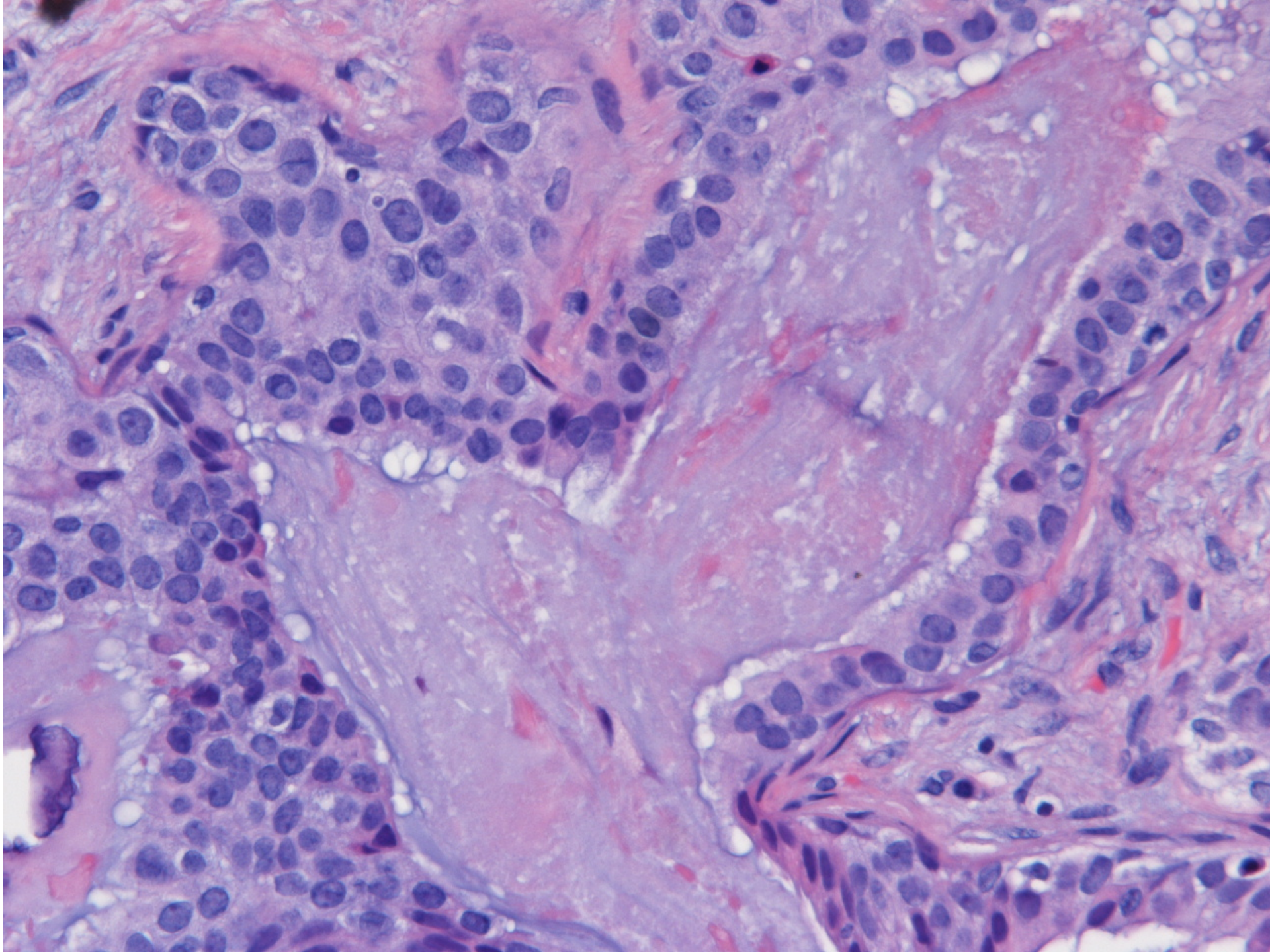


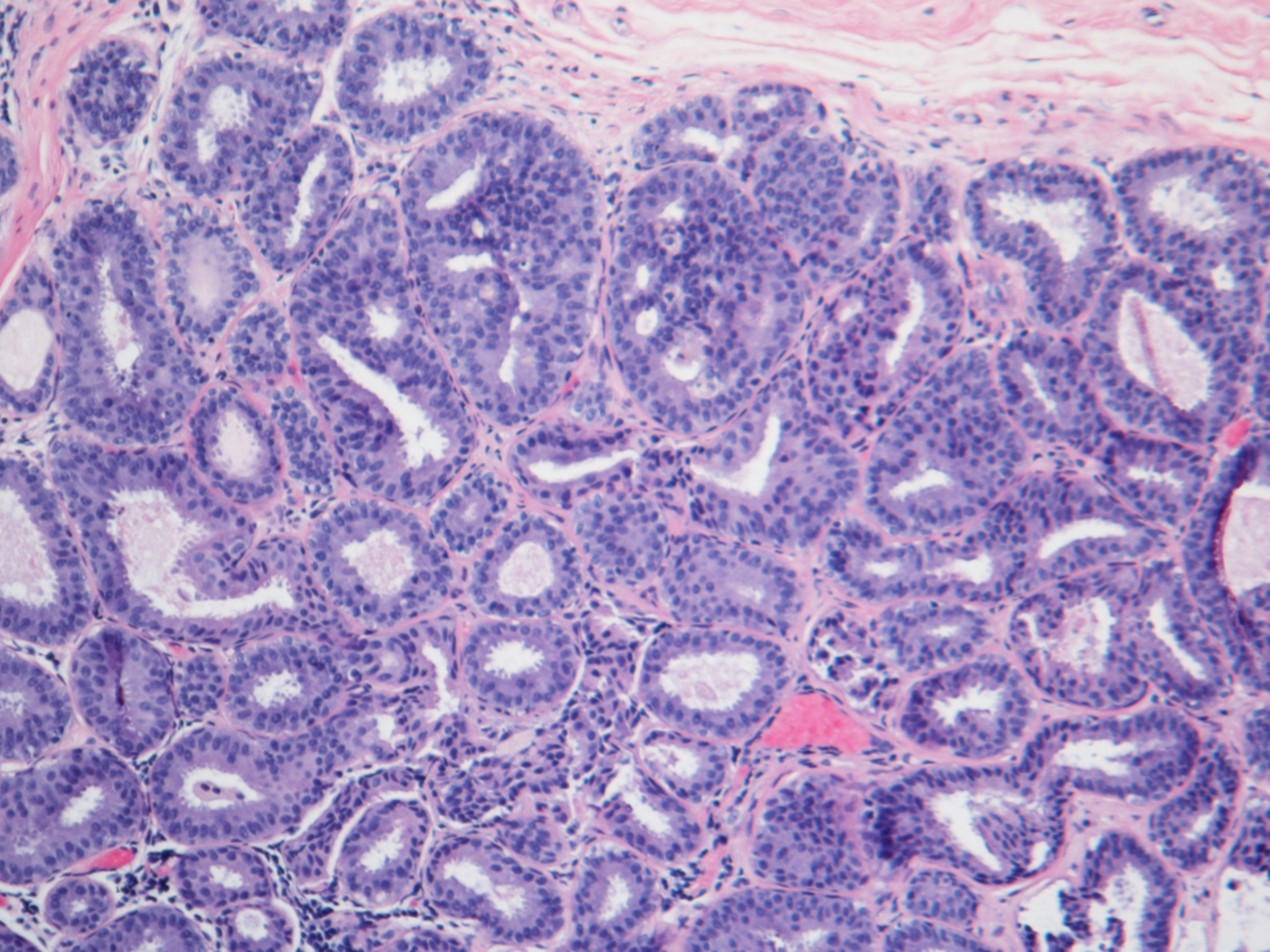


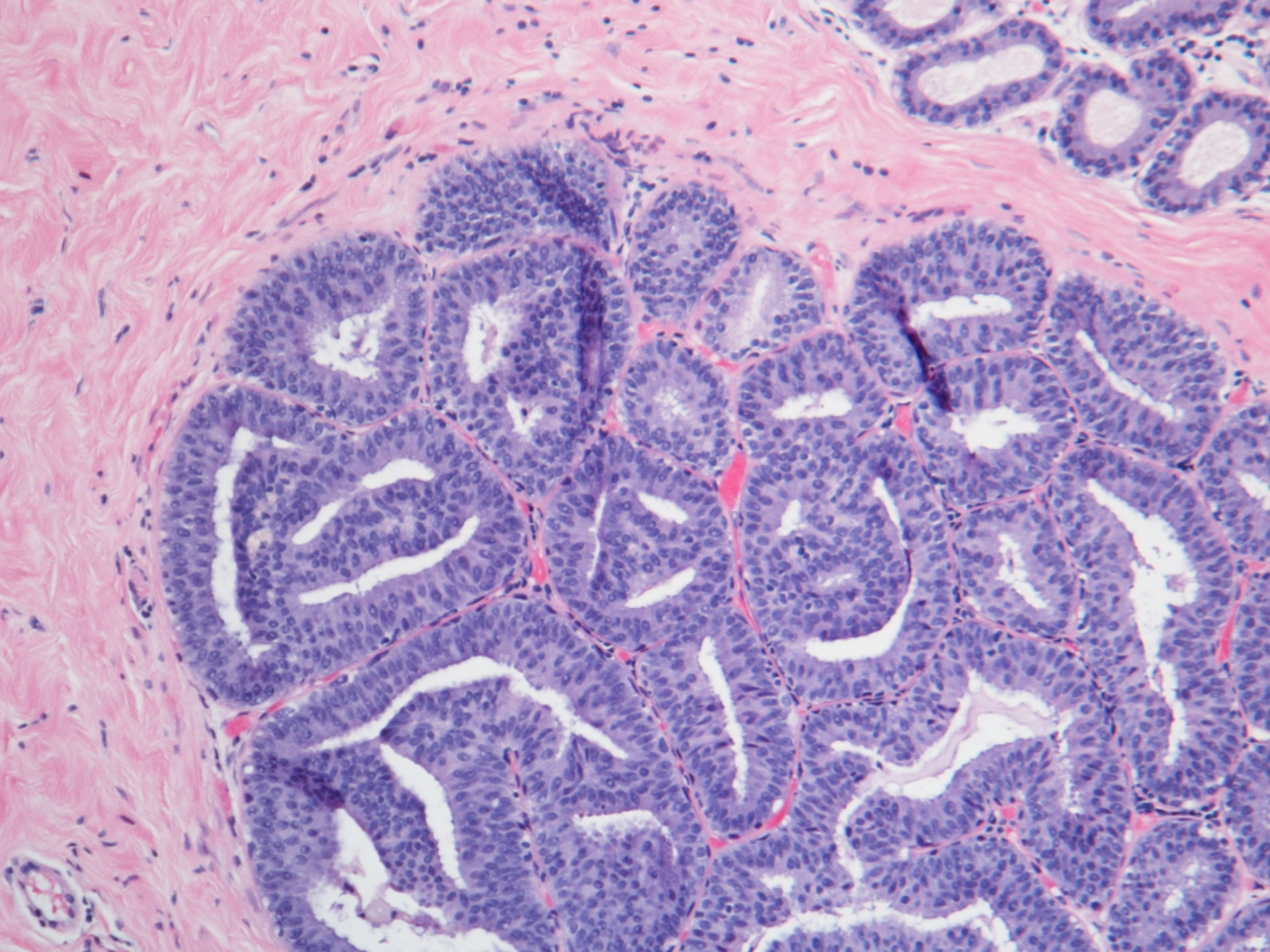


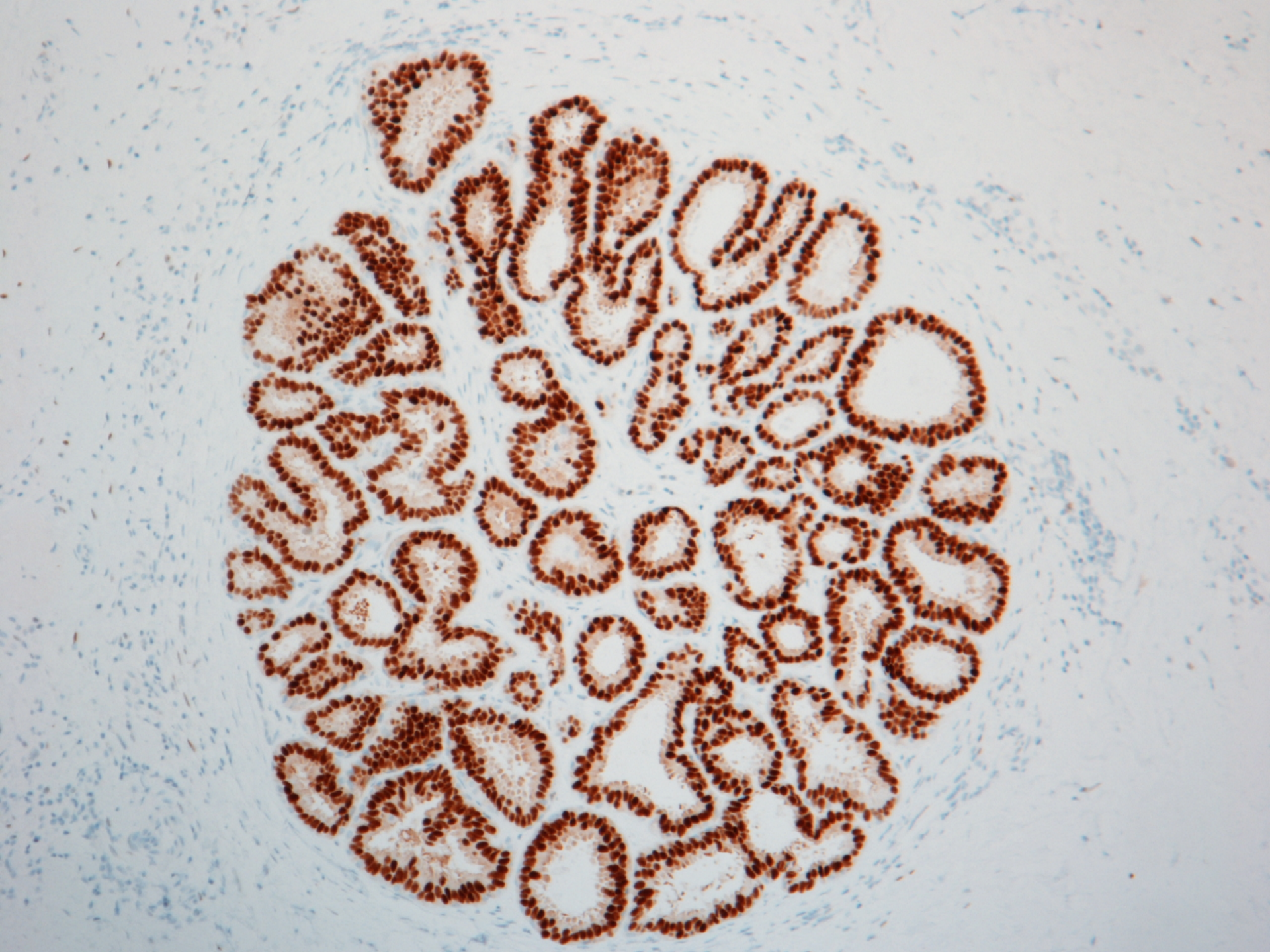


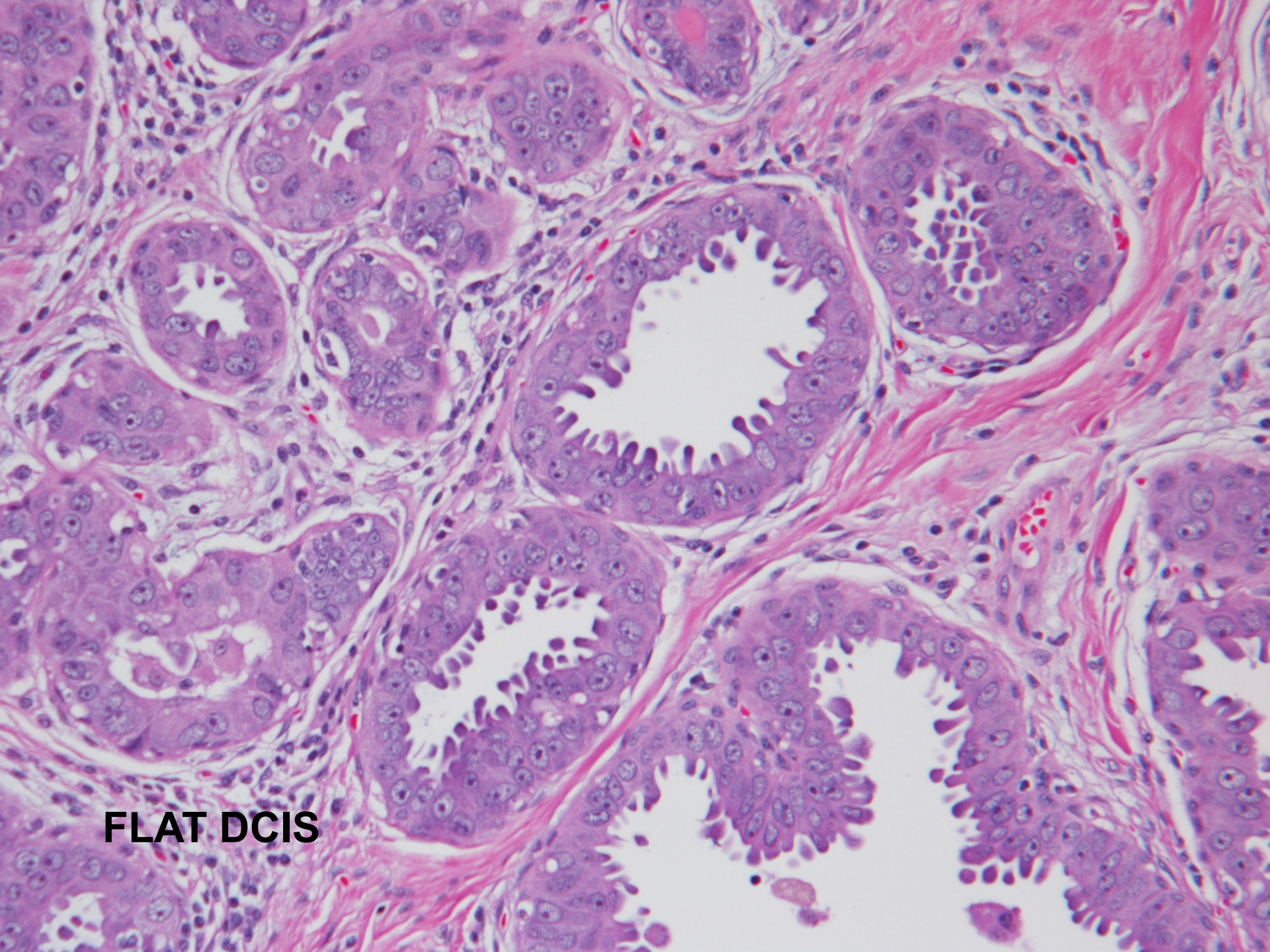


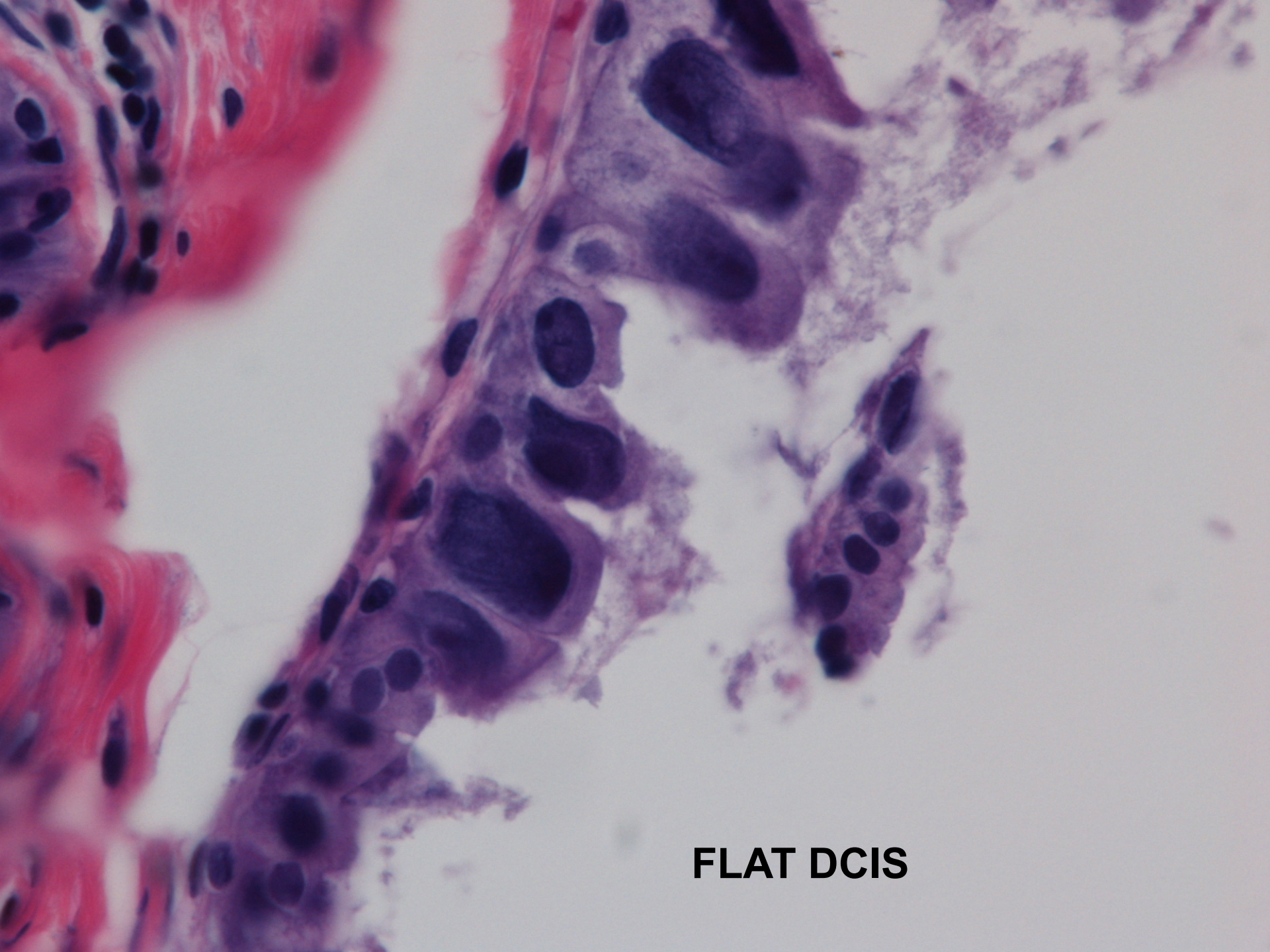


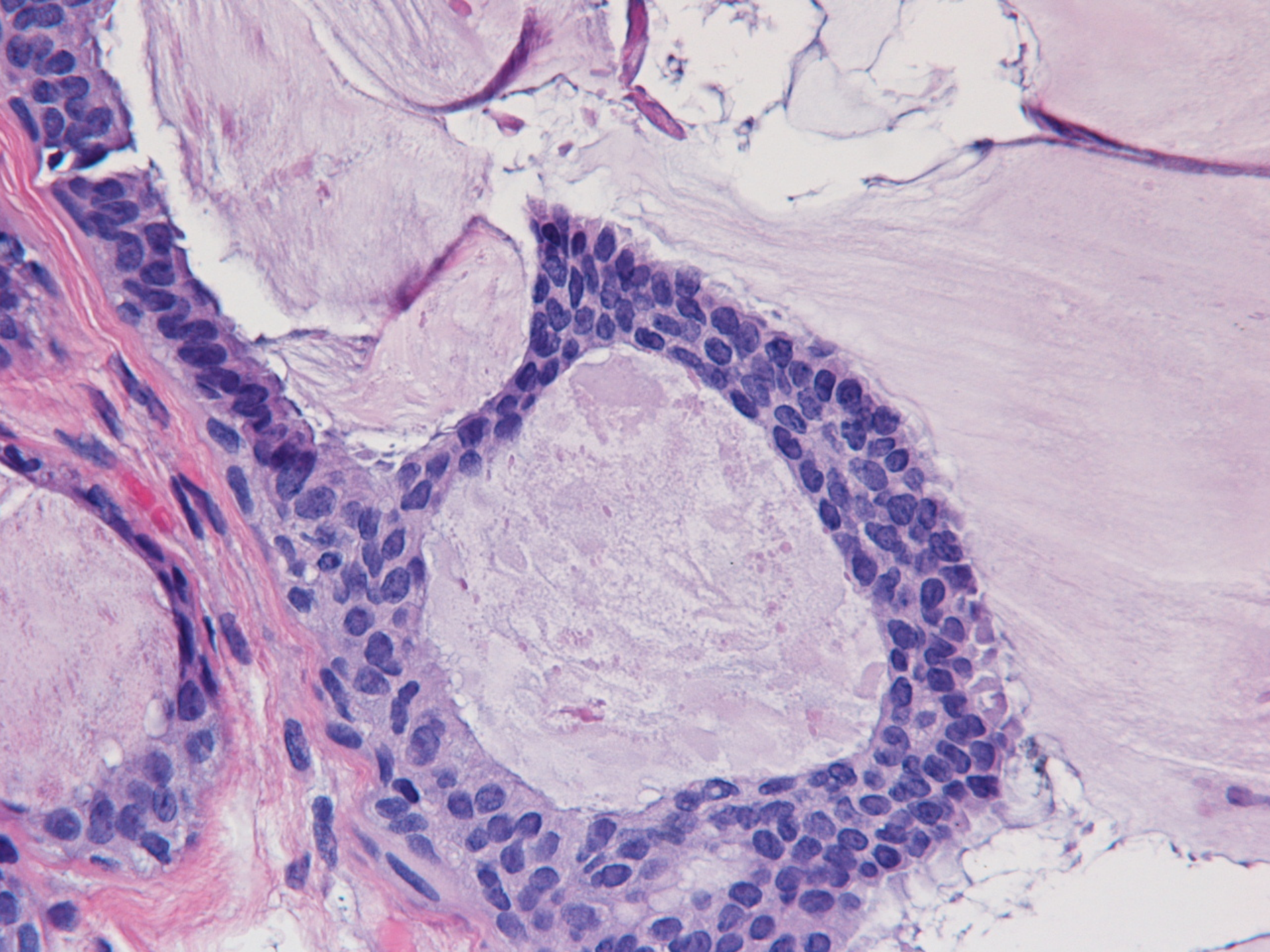







FLAT DCIS


FLAT DCIS



Senetta et Mod Pathol 2009 22:762-9

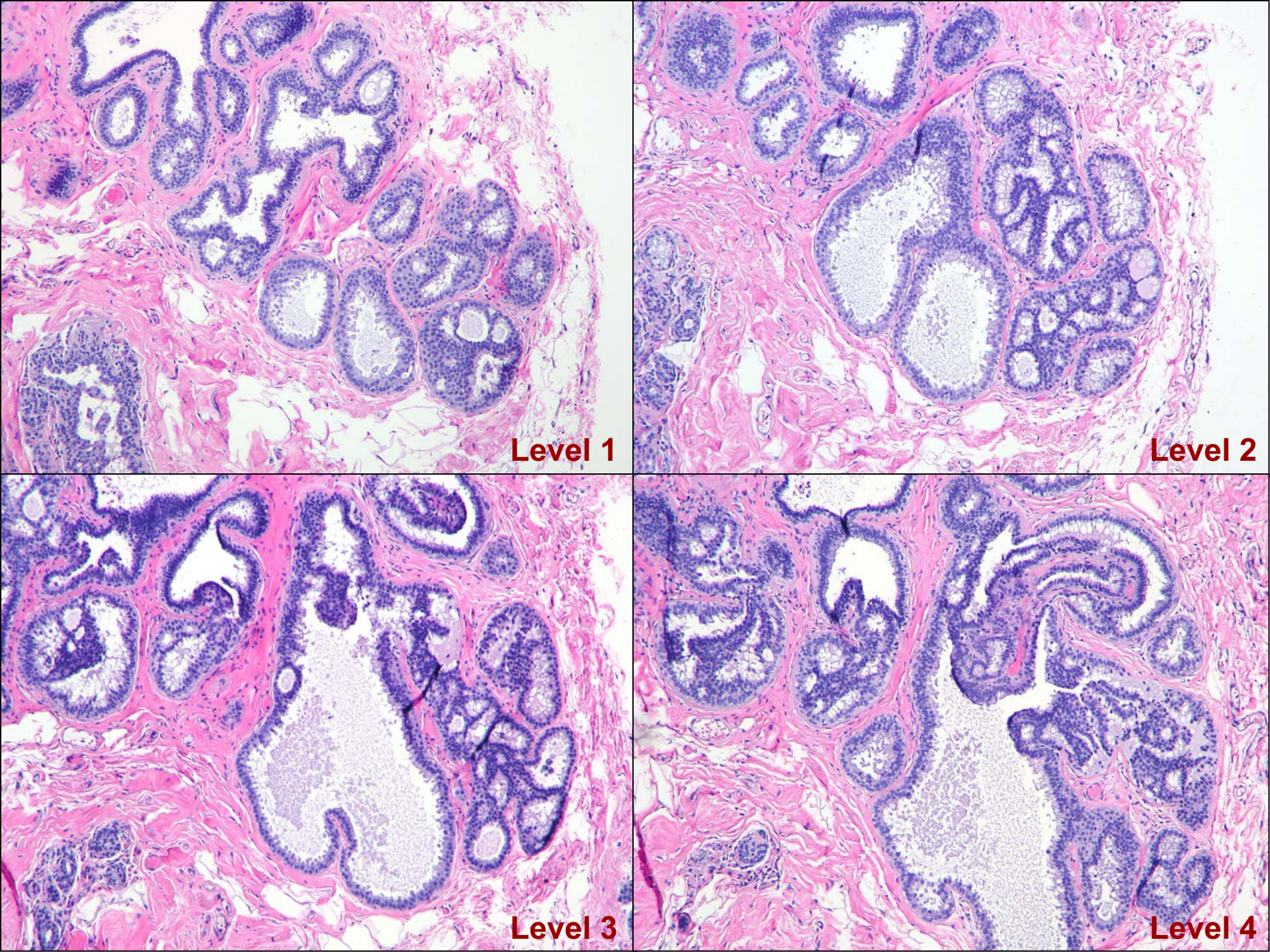
- 41 pure FEA, 38 BIRADS **3**, 3 BIRADS **4**
- Calcifications were all determinate for FEA
- 36/41 (88%) pure FEA had surgery FUE
- 53% with atypia/ADH, LN,FEA on excision
- No upstage to DCIS or IDC on FUE
- Conclusion: Low risk 11g, VACB (BIRADS 3) calcifications likely do not require FUE, especially if most or all of lesion removed

Piubello Q et al. FEA on CNB: Which is the right management? Am J Surg Pathol 2009;33:1078-84

- 33 pure FEA, 11G VACB
- 20 with FUE (61%)
- BIRADS 3 for 18/20 cases (90%)
- No upstage to DCIS/IDC
- 30% upstage in ADH cases (2 DCIS, 1 IDC)
- 90% of lesions removed by VACB

Chivukula et al (Am J Clin Pathol 2009; 131:802-8)

- 39 pure FEA cases for indeterminate calcifications. All biopsies were BIRADS 4.
- **Most 9g or 11g vacuum assisted biopsies**
- 35/39 (90%) with FUE
- 3 LGDCIS, 2 LGIDC = 5/35 (14% upstage).
- The upstaging in the follow-up resections for pure FEA in comparison to ADH+FEA was 16% and for pure ADH is 14%. These differences are not statistically different (p=0.8728)


Level 1
Level 2
Level 3
Level 4

Chivukula et al.

- FEA and ADH often present together (71%).
- "Pure" FEA "evolves" into ADH in 17 % of FEA cases at an average of 3-4 tissue levels.
- Conclusion: BIRADS 4 images more likely to contain serious lesions (DCIS, IDC), in association with FEA.

Importantly……

- The size of the lesional area, BIRADS category, biopsy method and whether the lesion is completely removed or almost completely removed, will have impact on patient management.

LN with CCLs~54%

- Frequency and clinical significance of simultaneous association of lobular neoplasia and columnar cell alterations in breast tissue specimens.

Carley AM, **Chivukula M**, Carter GJ, Karabakhtsian RG, Dabbs DJ.

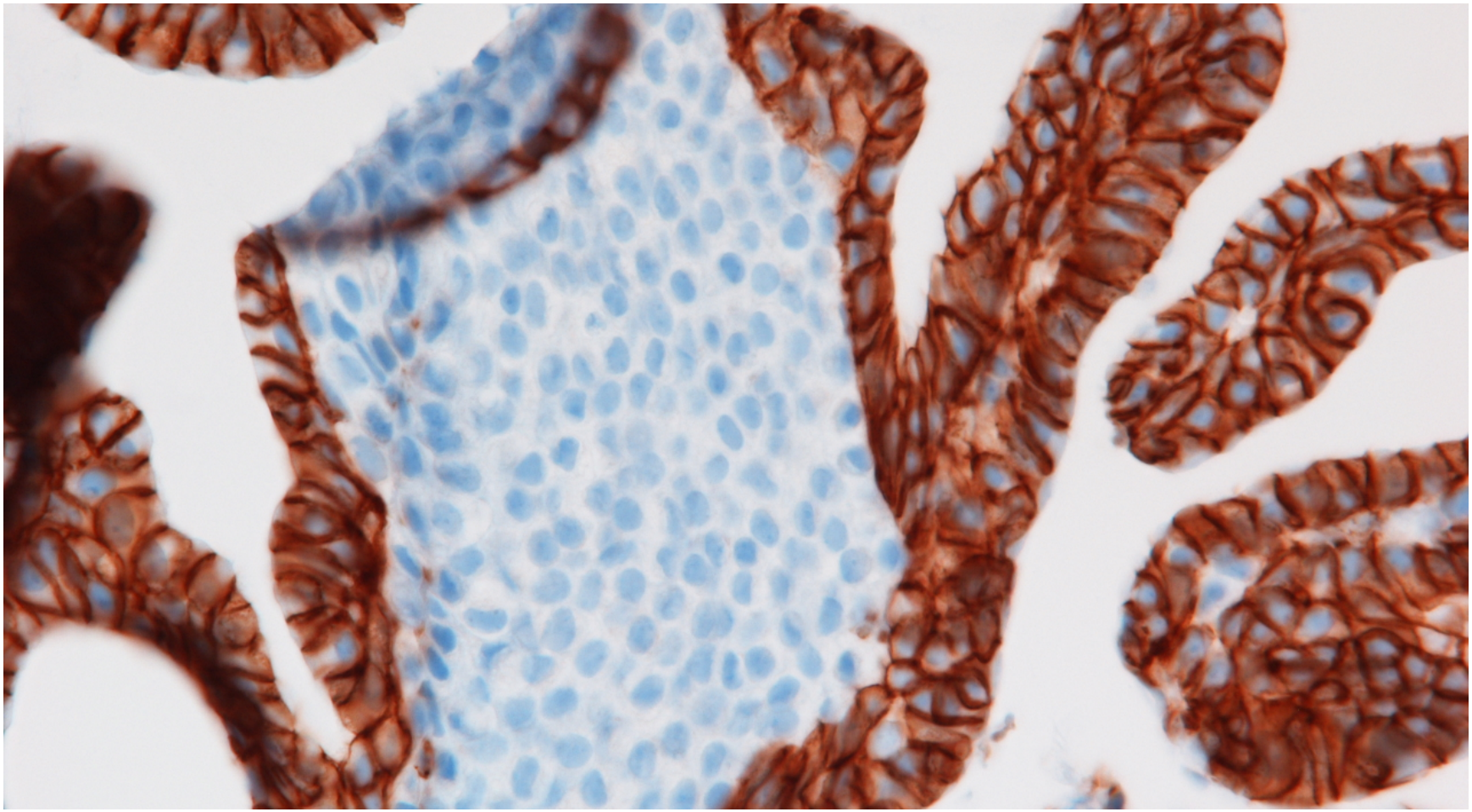
Am J Clin Pathol. 2008 Aug;130(2):254-8.

- **Flat epithelial atypia** (DIN 1a, atypical columnar change): an underdiagnosed entity very frequently coexisting with **lobular neoplasia**.

Leibl S, Regitnig P, Moinfar F. Histopathology. 2007 Jun;50(7):859-65.

- High frequency of coexistence of columnar cell lesions, **lobular neoplasia**, and low grade ductal carcinoma in situ with invasive tubular carcinoma and invasive **lobular** carcinoma.

Abdel-Fatah TM, Powe DG, Hodi Z, Lee AH, Reis-Filho JS, Ellis IO. Am J Surg Pathol. 2007 Mar;31(3):417-26.



FLAT EPITHELIAL ATYPIA
EXCISE OR NOT?

- Most studies carried out are retrospective, and do not specify radiographic imaging findings.
- Other risk entities (ADH, papillomas, etc) are sometimes included.
- The types of lesions counted as “upstaged” are not well defined.
- Unexcised lesions-unknown findings!
- Other lesions found on excision are not well documented.

FEA: EXCISE?

- Verschuur-Maes et al (Ann Sug 2012;255:259) performed a systematic review of literature: 13-67% “upstaging” reported.
- Risk of subsequent cancer with columnar lesions and FEA is very low (***Cancer 2008;113:2415–2421; Breast Cancer Res 2010;12:R61; Said S et al. 2015 Cancer 121:1548***)

Pure FEA on Core Biopsy-Excisonal Biopsy Findings *(Calhoun BC et al. 2015 Mod Pathol 28: 670-6.)*

total	No atypia	FEA	ADH	ALH	DCIS	INVASIVE	
73	20 (27%)	31 (42%)	14 (19%)	3 (4%)	3 (4%)	2 (3%)	

All 73 patients had a surgical excision.

Pure FEA on Core/Carcinoma on Excision

(Calhoun BC et al. 2015 Mod Pathol 28: 670-6.)

DX	Size mm	Grade	ER	BIRADS	Calcs	Calc removed
IDC NST	3	1	+	4	10 mm	<25%
TUBULAR	3	1	+	4	6mm	>75%
DCIS	8	2	+	4	12mm	>75%
DCIS	52	2	ND	4	43mm	<25%
DCIS	38	2	+	4	23 density	NA

5/73 (6.8%) were upstaged.

All cases where calcification removal was complete had no upstaged lesion.

Complete Removal of Calcifications with Pure FEA-No Excision Necessary

- Yu CC et al. Breast J 2015 21: 224
- ***Dialani V et al. 2014 Breast J 20:606***
- ***Calhoun BC et al. 2015 Mod Pathol 28: 670***

SUMMARY: Microcalcs only; Pure FEA on core biopsy; series with nearly all cases excised

Author	"Upstaged"	Percent Upstaged	#Excised
Calhoun	5/73	6.8	100%
Villa	7/121	5.7	100%
Bianchi	18/190	9.5	100%
Solorzano	2/28	7%	85%
Prowler	0/24	0%	100%
Lavoue'	7/60	11.6	100%
Rajan	6/36	16.6	100%

Series Average Upstage: 8%

Clinical factors associated with excisional biopsy upstaging with pure FEA on core biopsy.

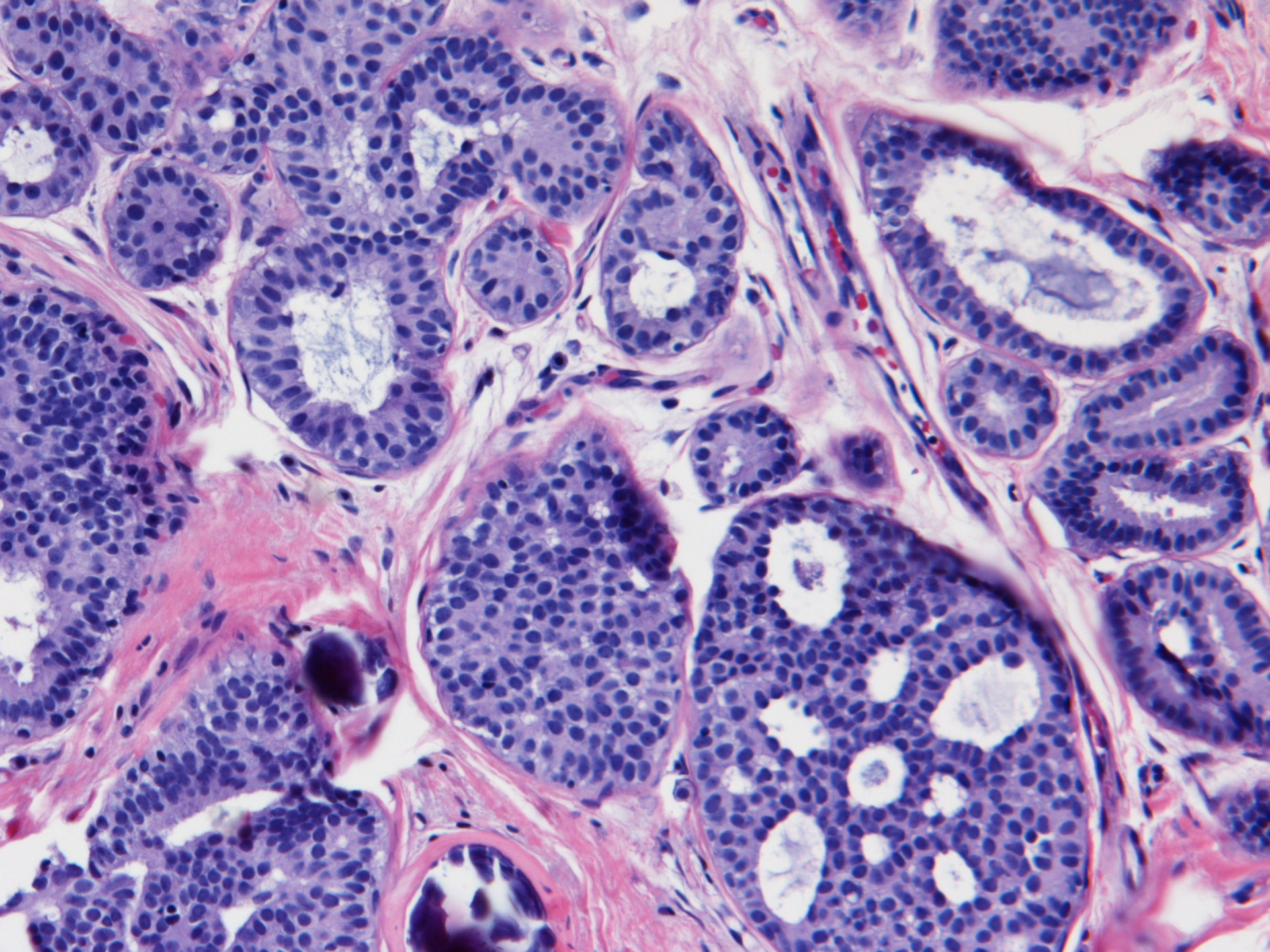
- Family history of cancer
- Lesion size (calcifications)
- BIRADS 4 (vs lower BIRADS)
- Age
- Best managed conservatively…desirable to remove all calcium, and follow the patient.

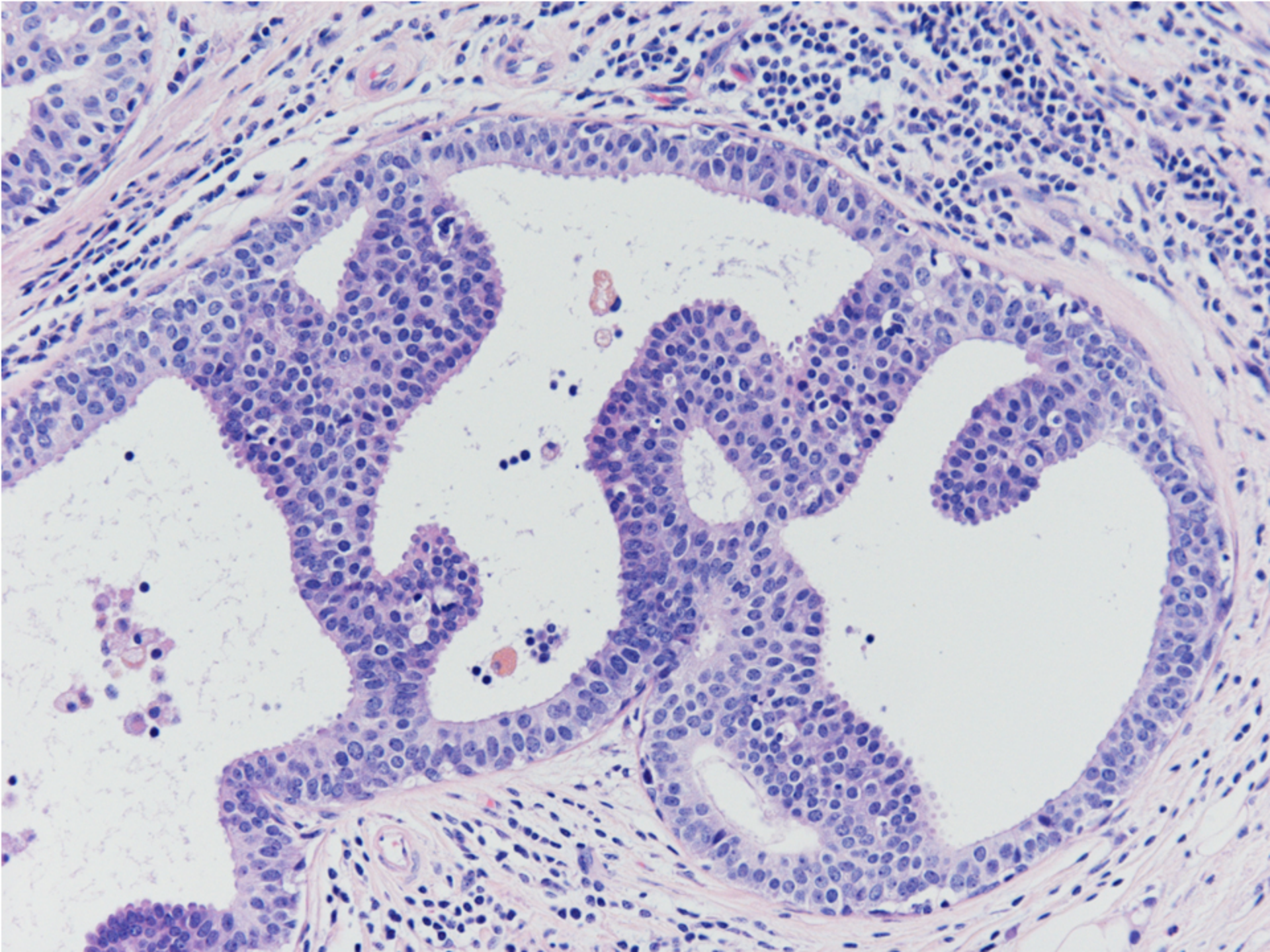
Is the diagnosis of FEA reproducible among pathologists?

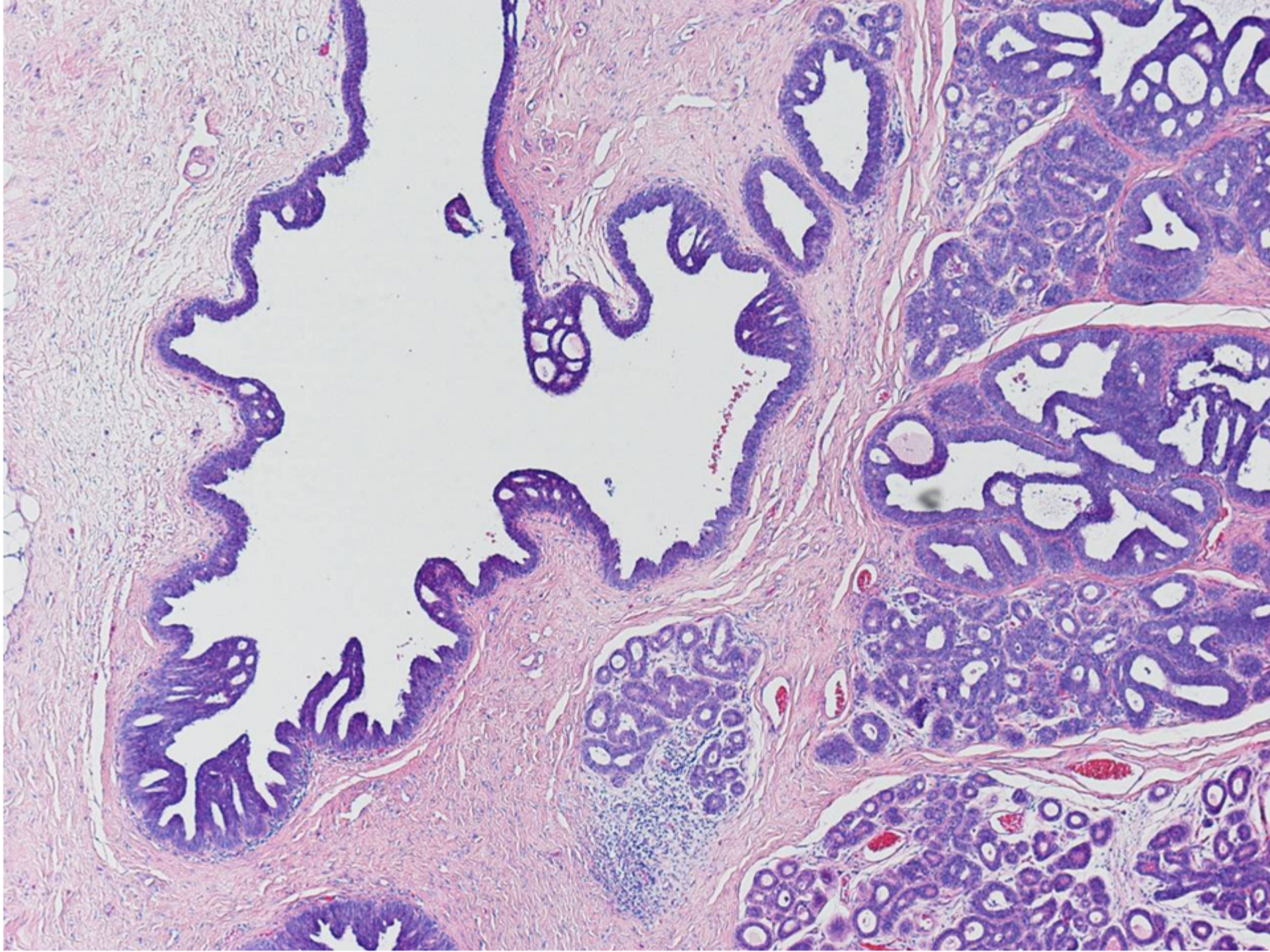
- 8 pathologists with subspecialty interest or expertise in breast pathology examined 30 columnar cell lesions and categorized them as CCC, CCH and FEA.
- All studied a Powerpoint tutorial with written instructions prior to examination.
- Overall agreement was 91.8% (Kappa value .83= excellent agreement).
- ***O'Malley et al 2006 Mod Pathol 19:172-9.***

Atypical Ductal Hyperplasia

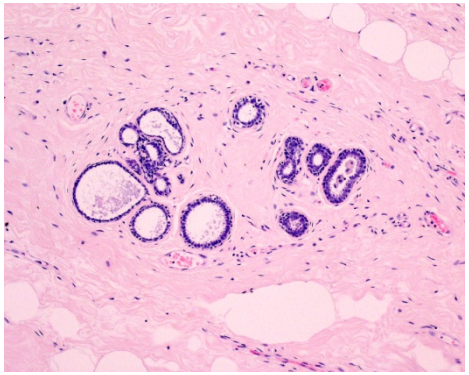
- “Atypical ductal hyperplasia is diagnosed if criteria for DCIS are present, but not involving at least two spaces” (Page & Rogers)-no scientific or biologic basis for this arbitrary defintion.
- Cytologic atypia and/or cribriform, micropapillary clubbing.



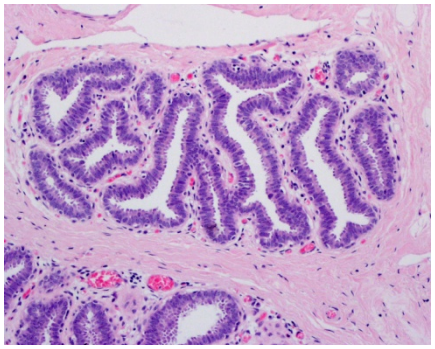




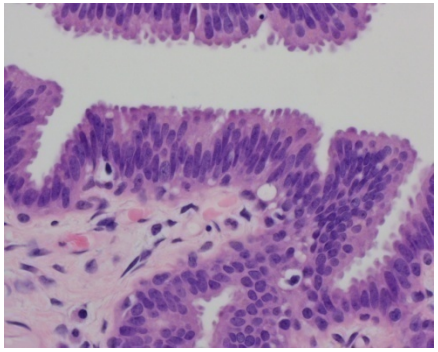
Spectrum of lesions



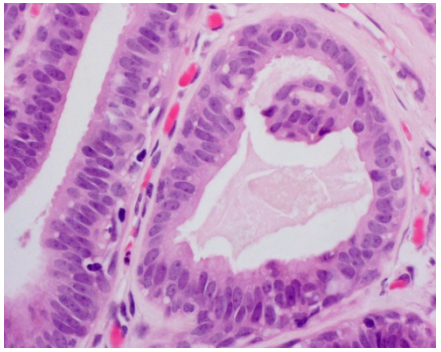
CCC



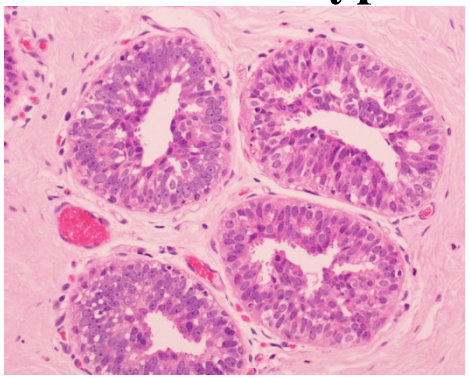
CCH

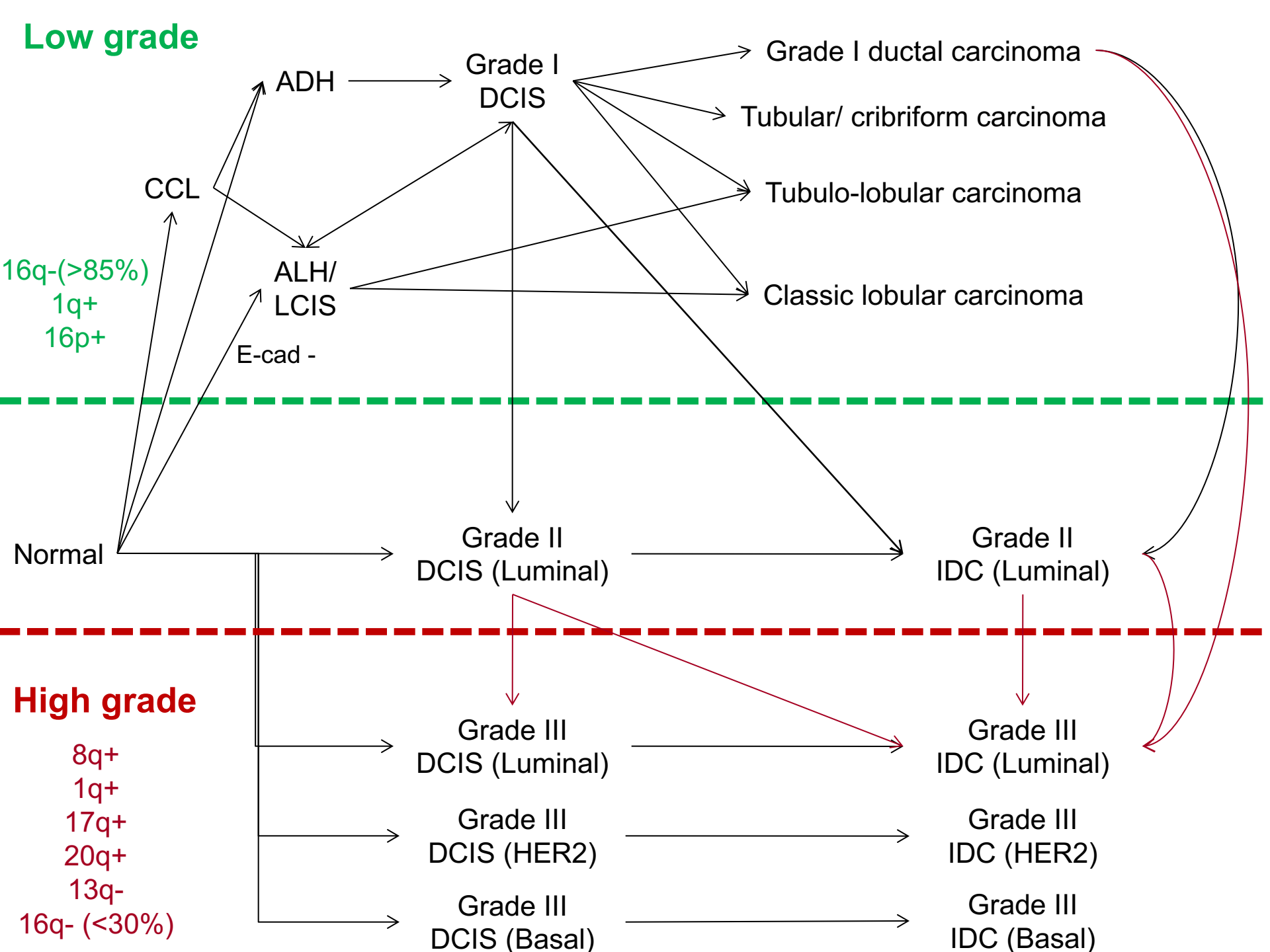


CCC with atypia

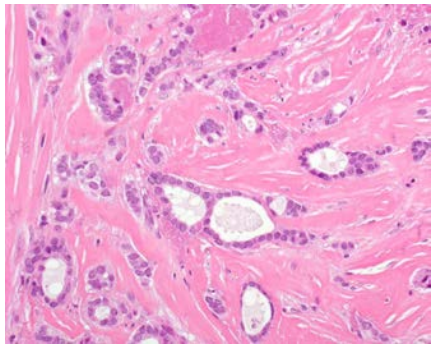
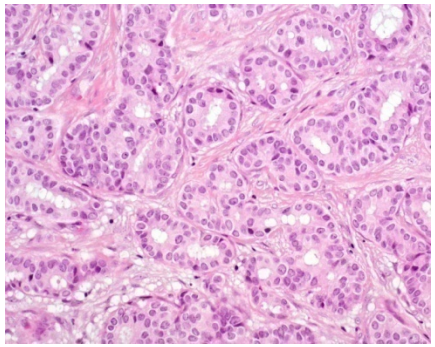
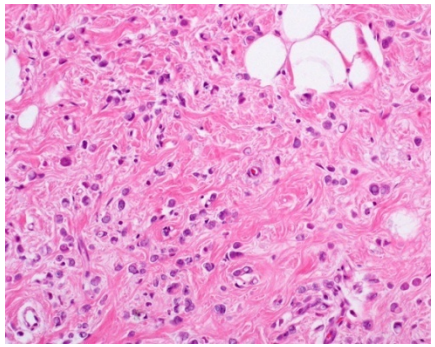


CCH with atypia




Low grade
ADH
Grade I
DCIS
Grade I ductal carcinoma
Tubular/ cribriform carcinoma
Tubulo-lobular carcinoma
Classic lobular carcinoma
CCL
16q-(>85%)
1q+
16p+
ALH/
LCIS
E-cad -
Normal
Grade II
DCIS (Luminal)
Grade II
IDC (Luminal)
High grade
8q+
1q+
17q+
20q+
13q-
16q- (<30%)
Grade III
DCIS (Luminal)
Grade III
IDC (Luminal)
Grade III
DCIS (HER2)
Grade III
IDC (HER2)
Grade III
DCIS (Basal)
Grade III
IDC (Basal)

Low grade ductal and lobular neoplasia

	Tubular	GI IDC	Lobular carcinoma
			
ER	+	+	+
PgR	+	+	+
Her2/neu	-	-	-
p53	-	-	-
Cyclin D1	+	+	+
E-cadherin	+	+	-
Number of changes	low	low	low
Ploidy	diploid/ near diploid	near diploid	diploid/ near diploid
Recurrent changes	1q+, 16q-	1q+, 16q-	1q+, 16q-
Amplifications	8p11, 11q13 (rare)	8p11, 11q13 (rare)	8p11, 11q13 (rare)
Subtype	Luminal A	Luminal A > B	Luminal A > B

Objectives/Summary

- Columnar Cell Change
- Columnar Cell Hyperplasia
- Flat Epithelial Atypia (FEA)
- FEA and Outcomes Management
- Atypical Ductal Hyperplasia
- Low and High Grade Pathways