Pathology of Lobular and Ductal Intraepithelial Neoplasia

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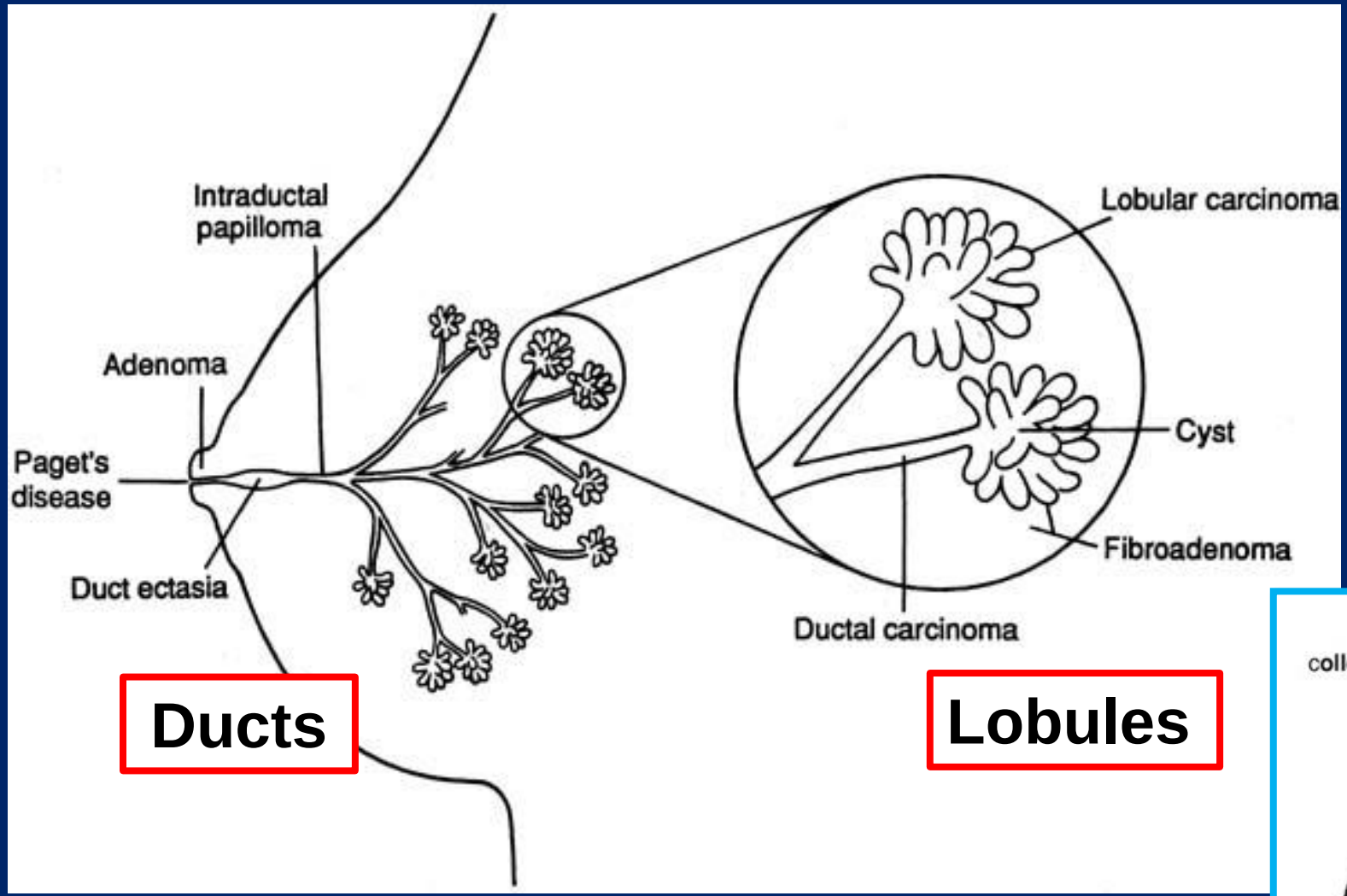
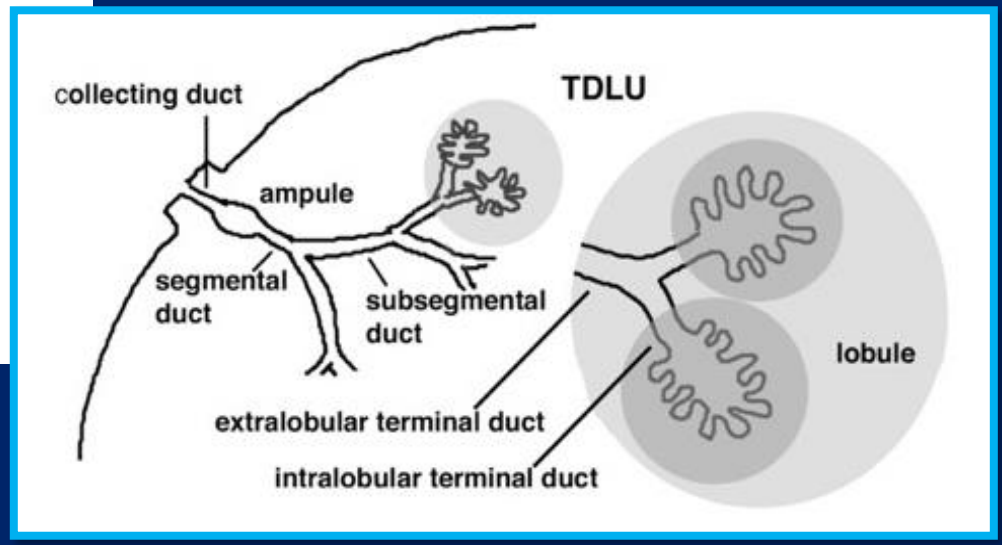
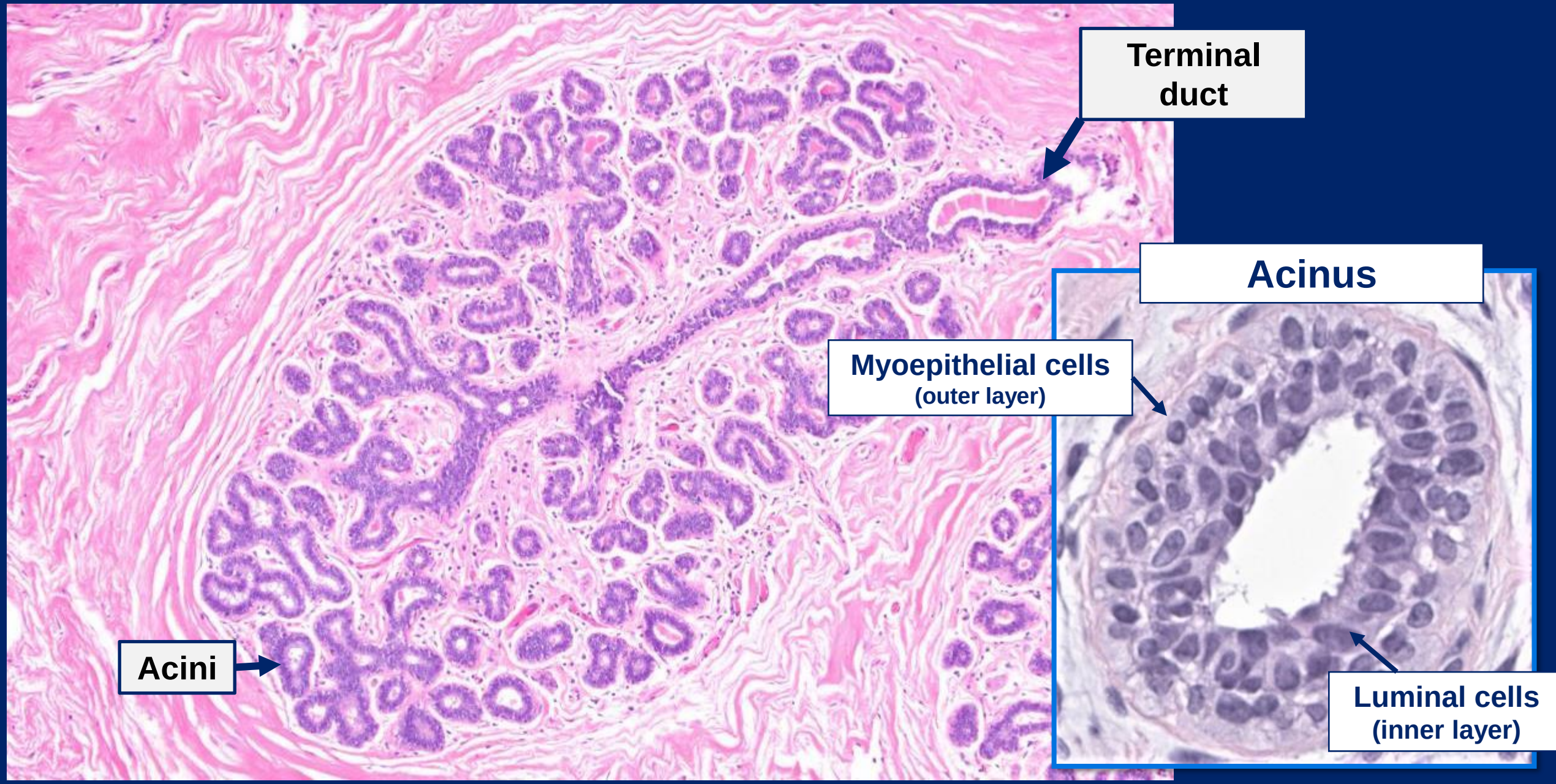
I have nothing to disclose related to the content of this presentation

Normal Breast Histology





Terminal Duct Lobular Unit (TDLU)



Intraductal proliferative lesions

- Usual ductal hyperplasia (UDH)
- Columnar cell lesions
- Atypical ductal hyperplasia (ADH)
- Ductal carcinoma in situ (DCIS)

- Classic lobular neoplasia
- Non-classic lobular carcinoma in situ (LCIS)

Usual ductal hyperplasia (UDH)

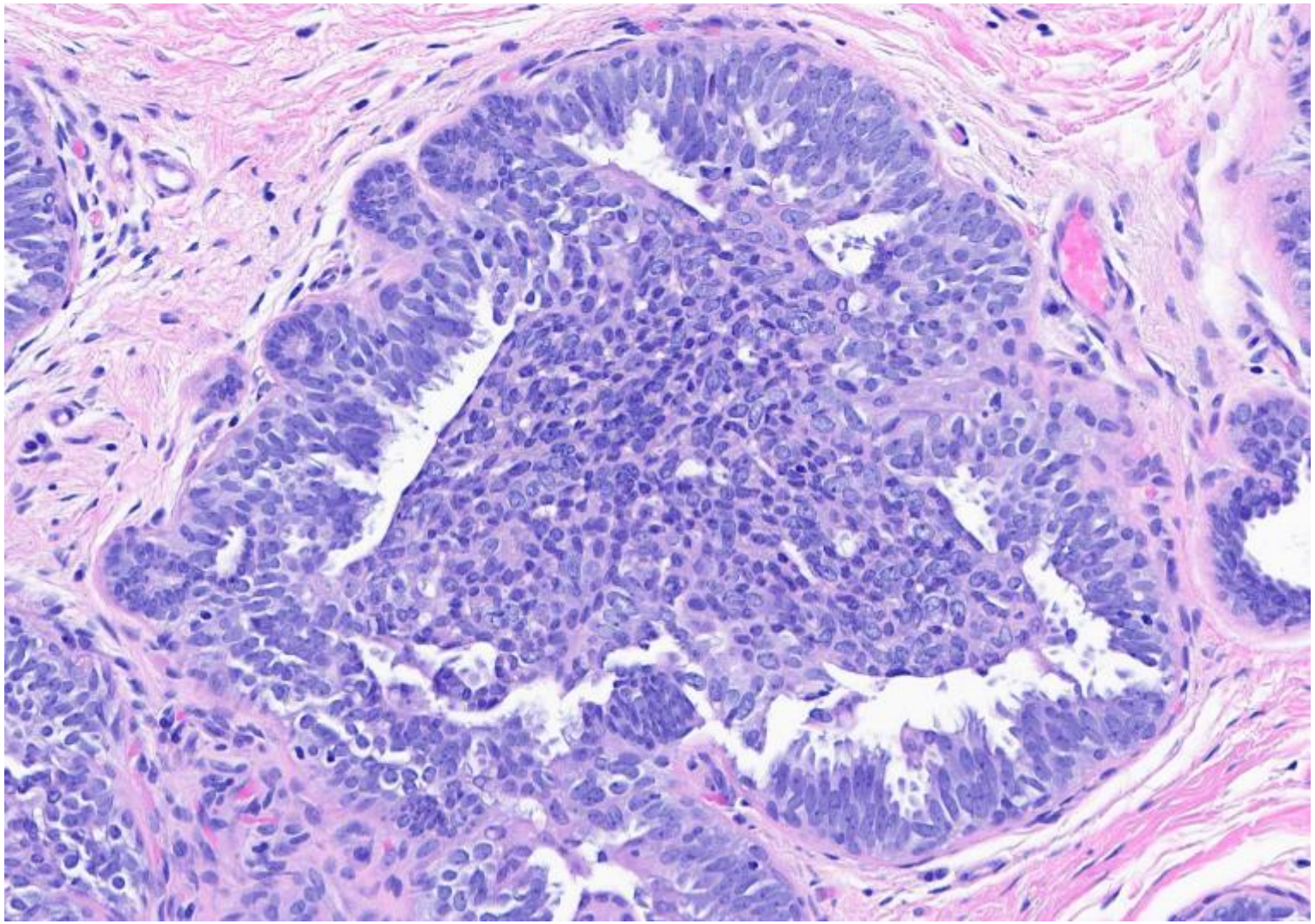
Key Features of UDH

Cytologic Features

- Heterogeneous cell population
- Variation in cell size, shape and orientation
- Areas of overlapping, nuclear grooves and intranuclear inclusions

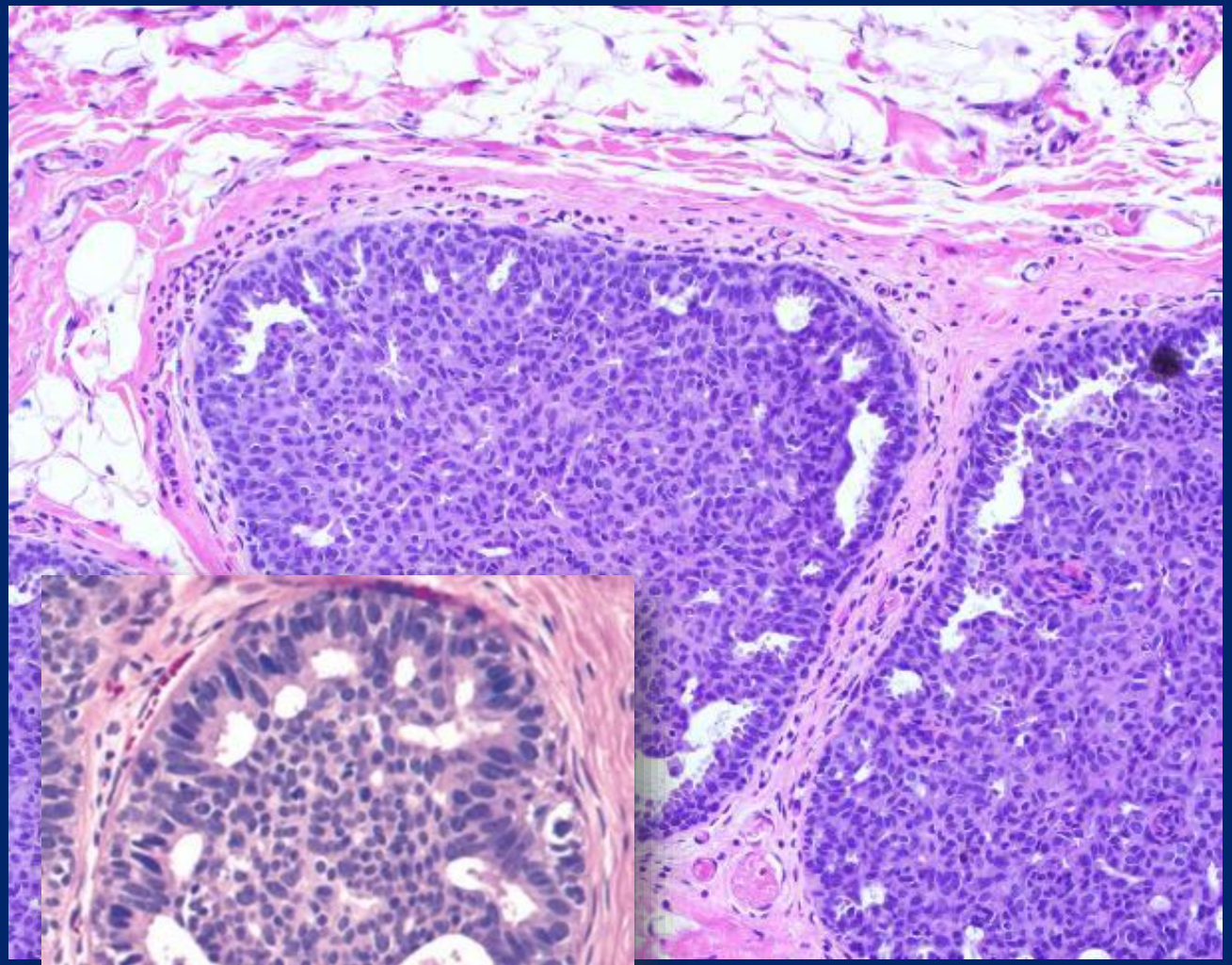
Architectural Features

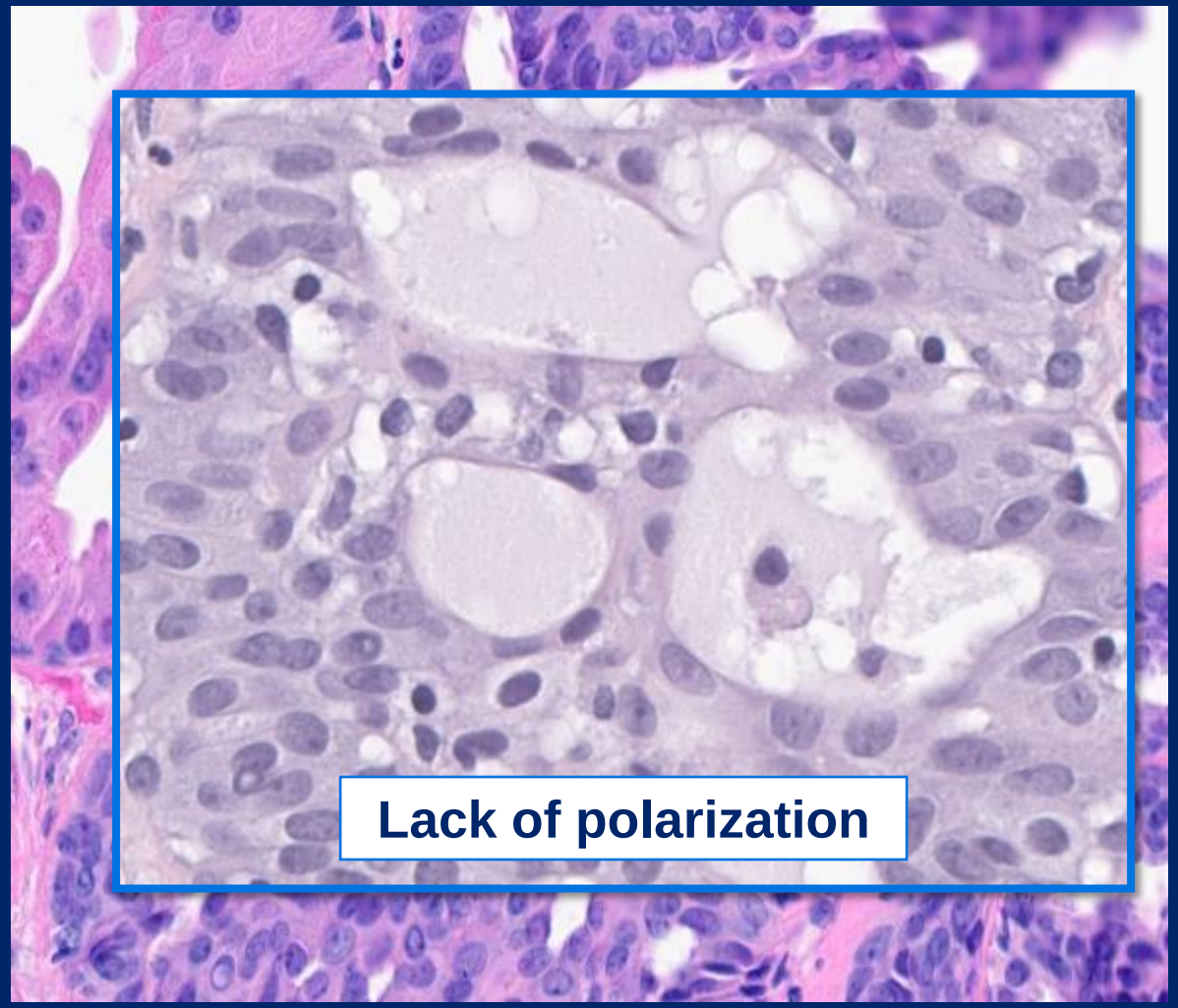
- Lumens: irregular, variable in size and shape, often slit-like and displaced to periphery
- No polarization of cells around lumens
- Bridges stretched or twisted



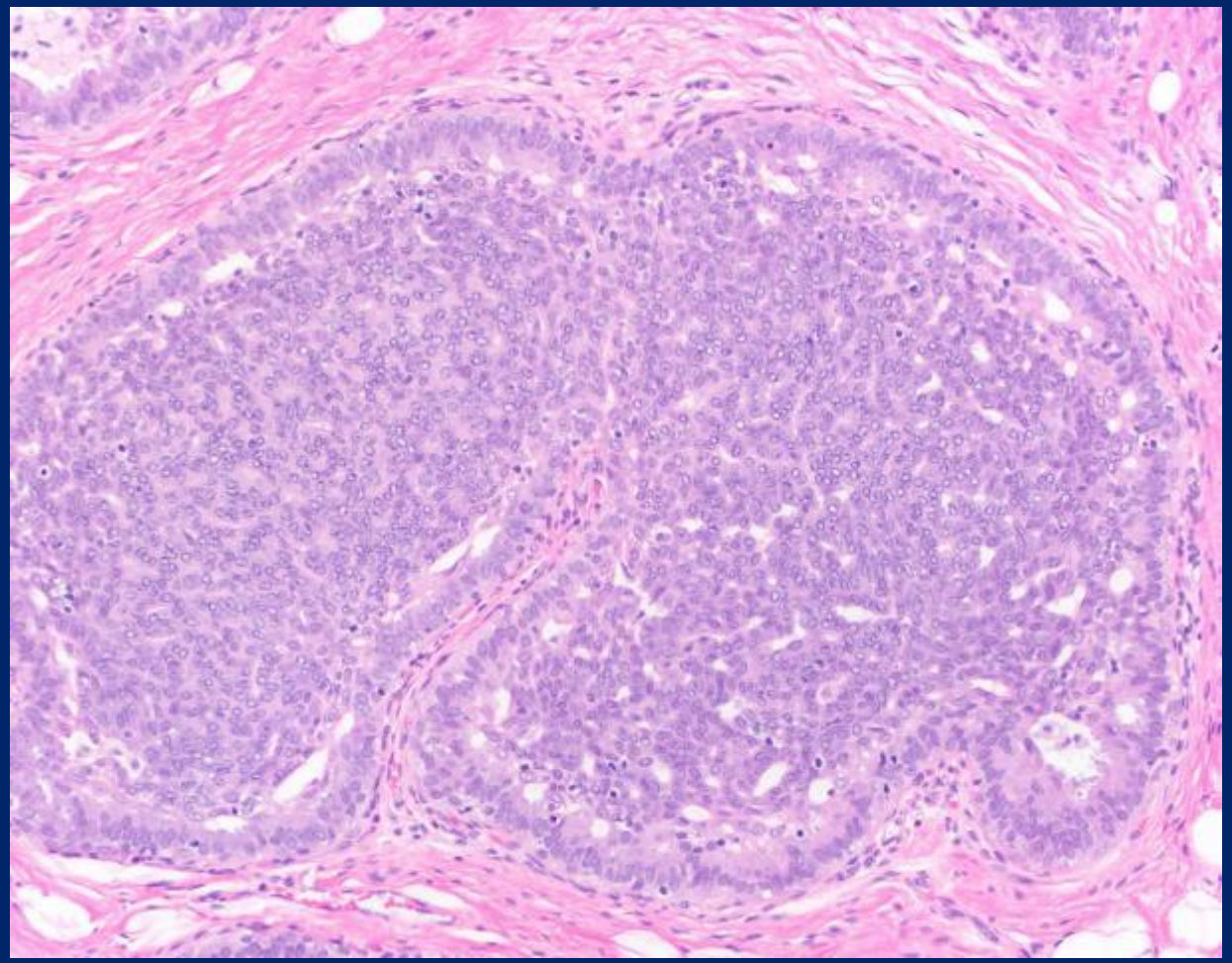
Koerner FC. *Semin Diagn Pathol*. 2004;21(1):10-7.

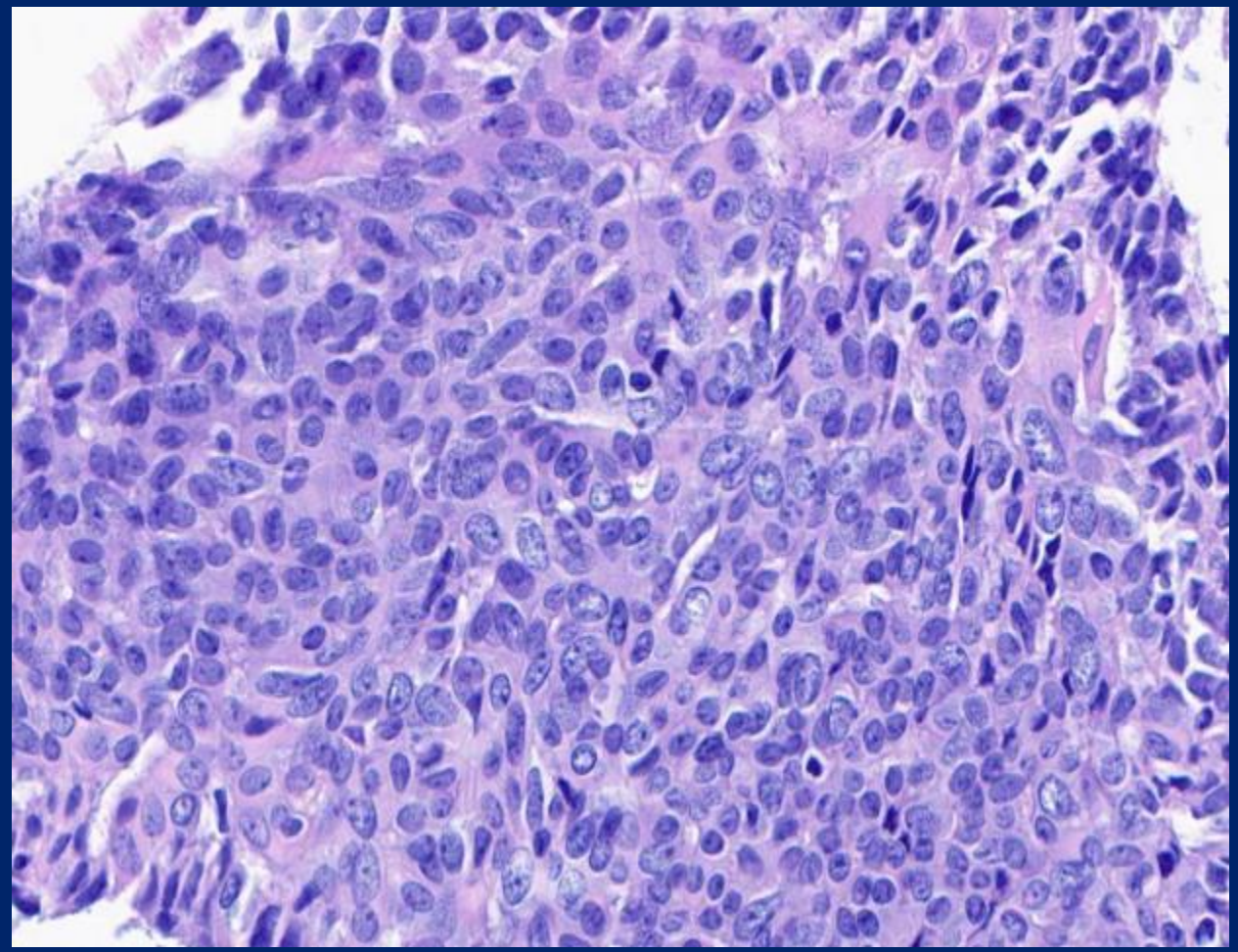
UDH: Irregular spaces at periphery





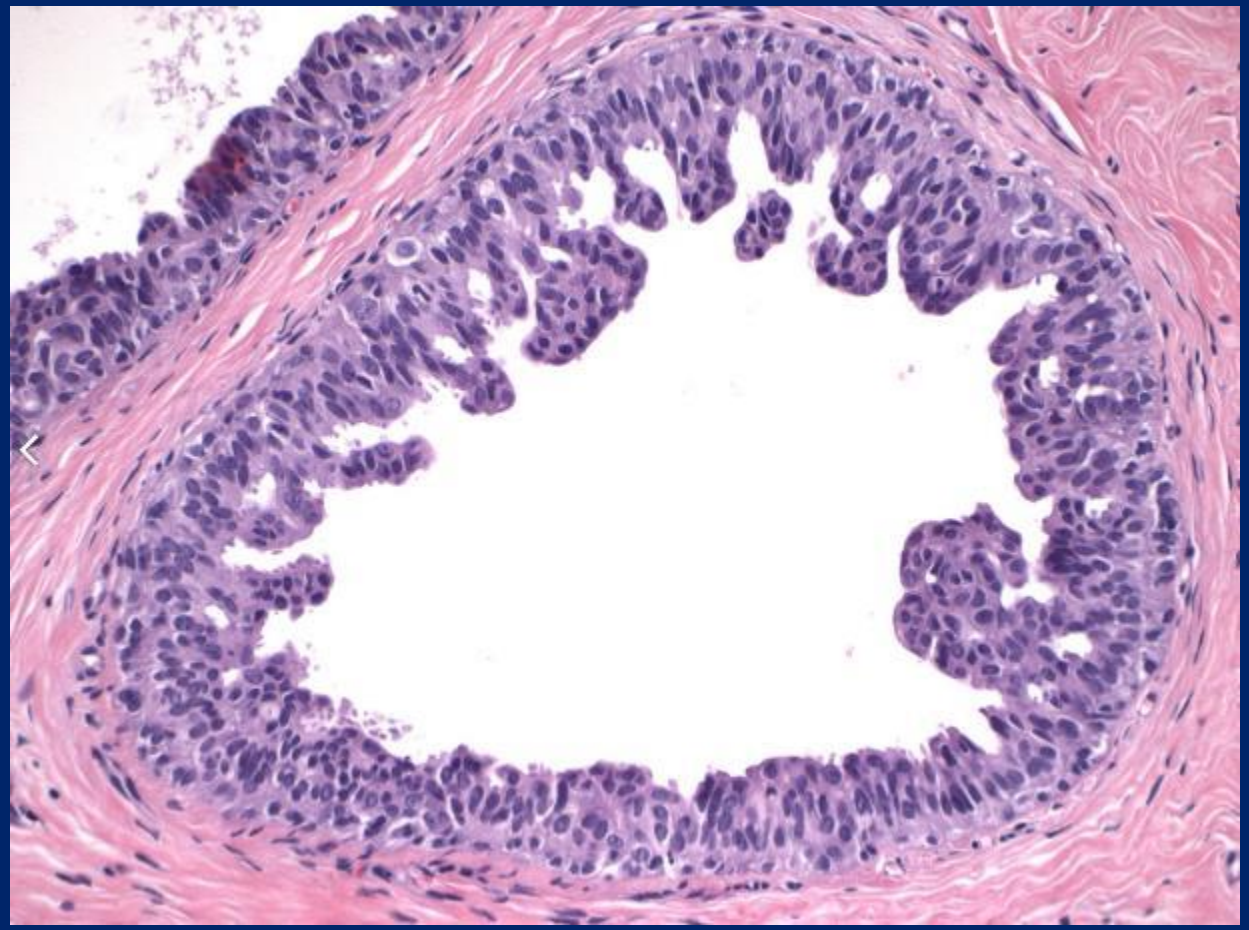
UDH: Streaming of cells



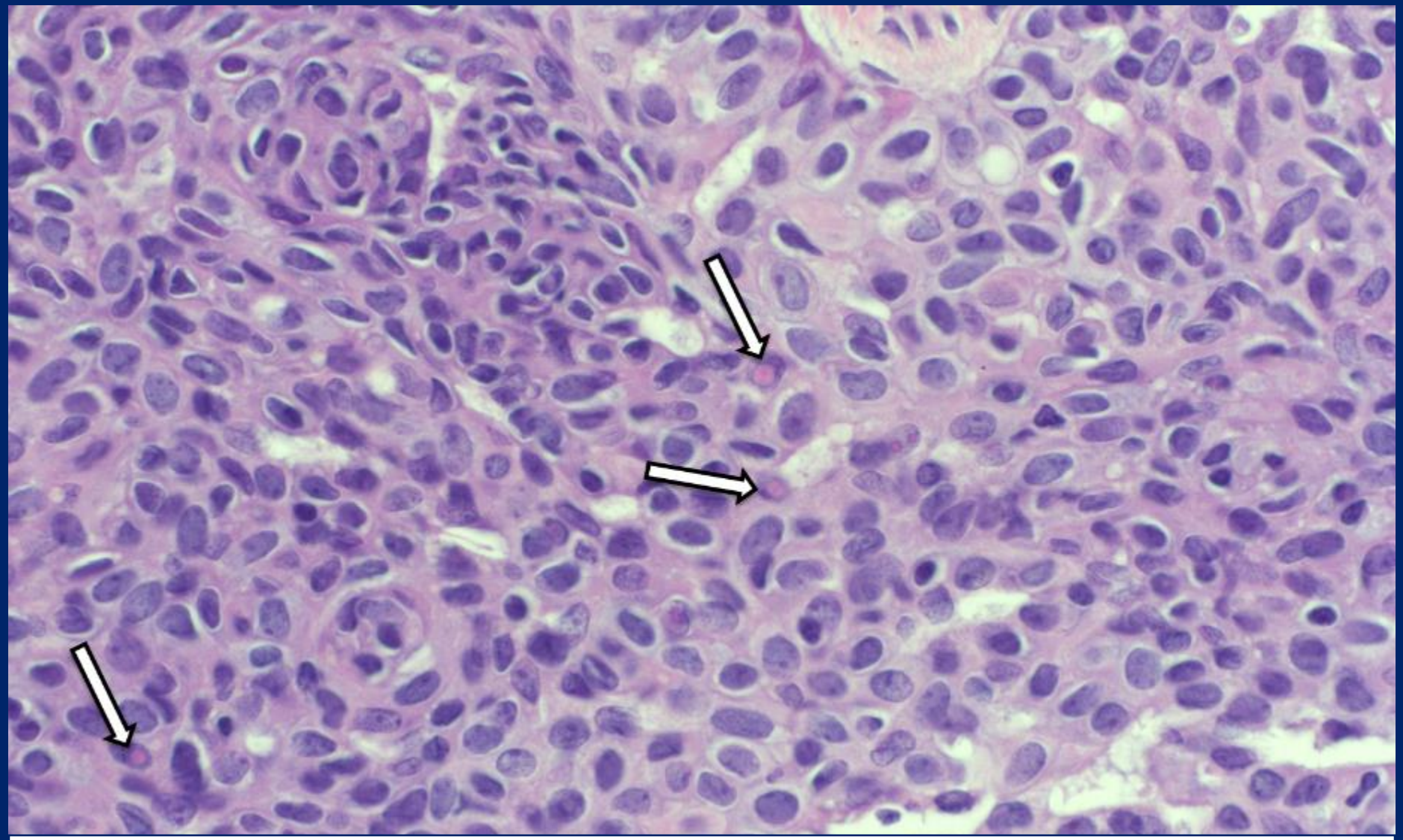


UDH: Micropapillary proliferations

- Micropapillae have similar shape and height
- Lumens generally empty
- Maturation of cells

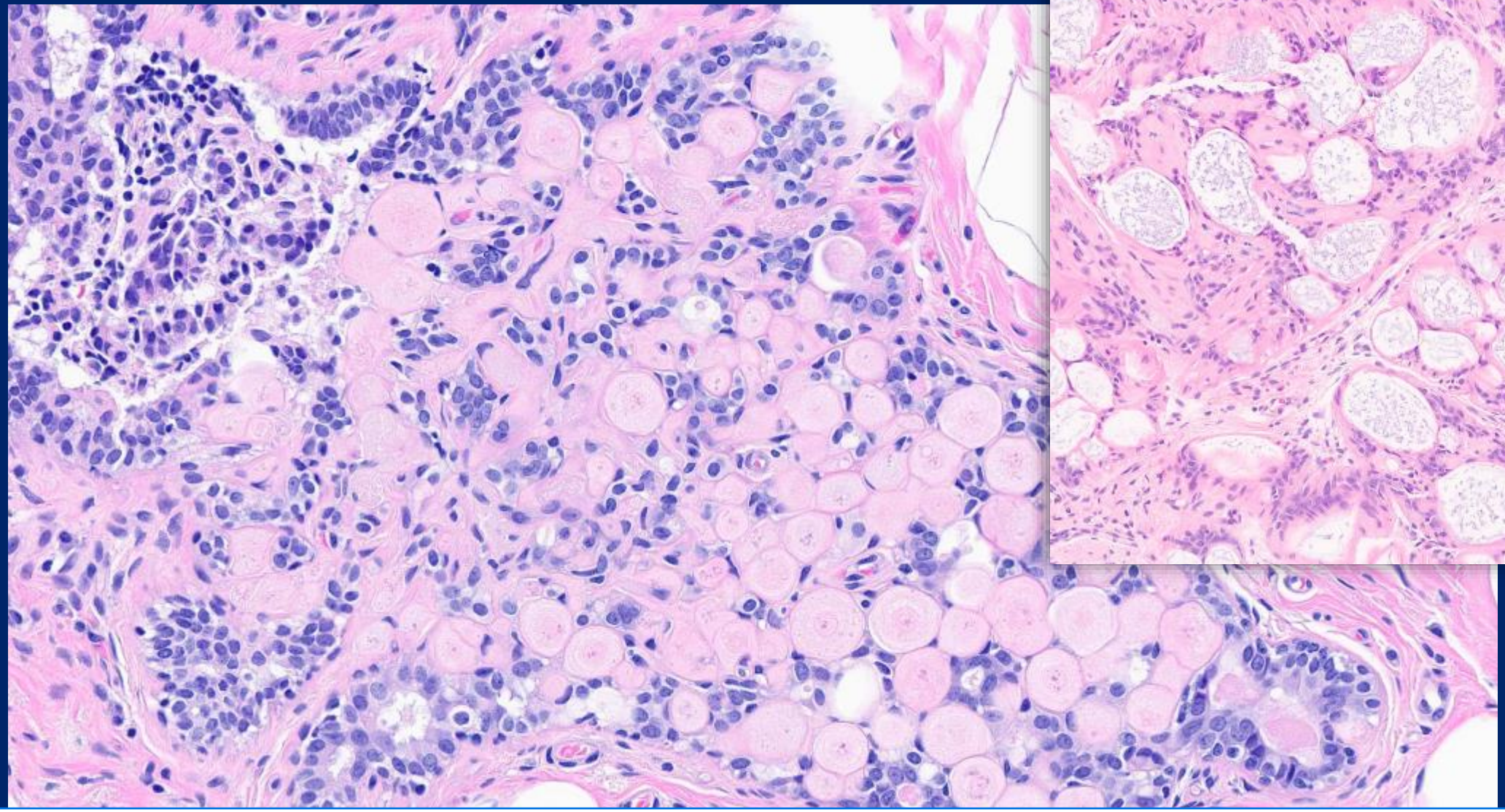


Acidophilic nuclear inclusions



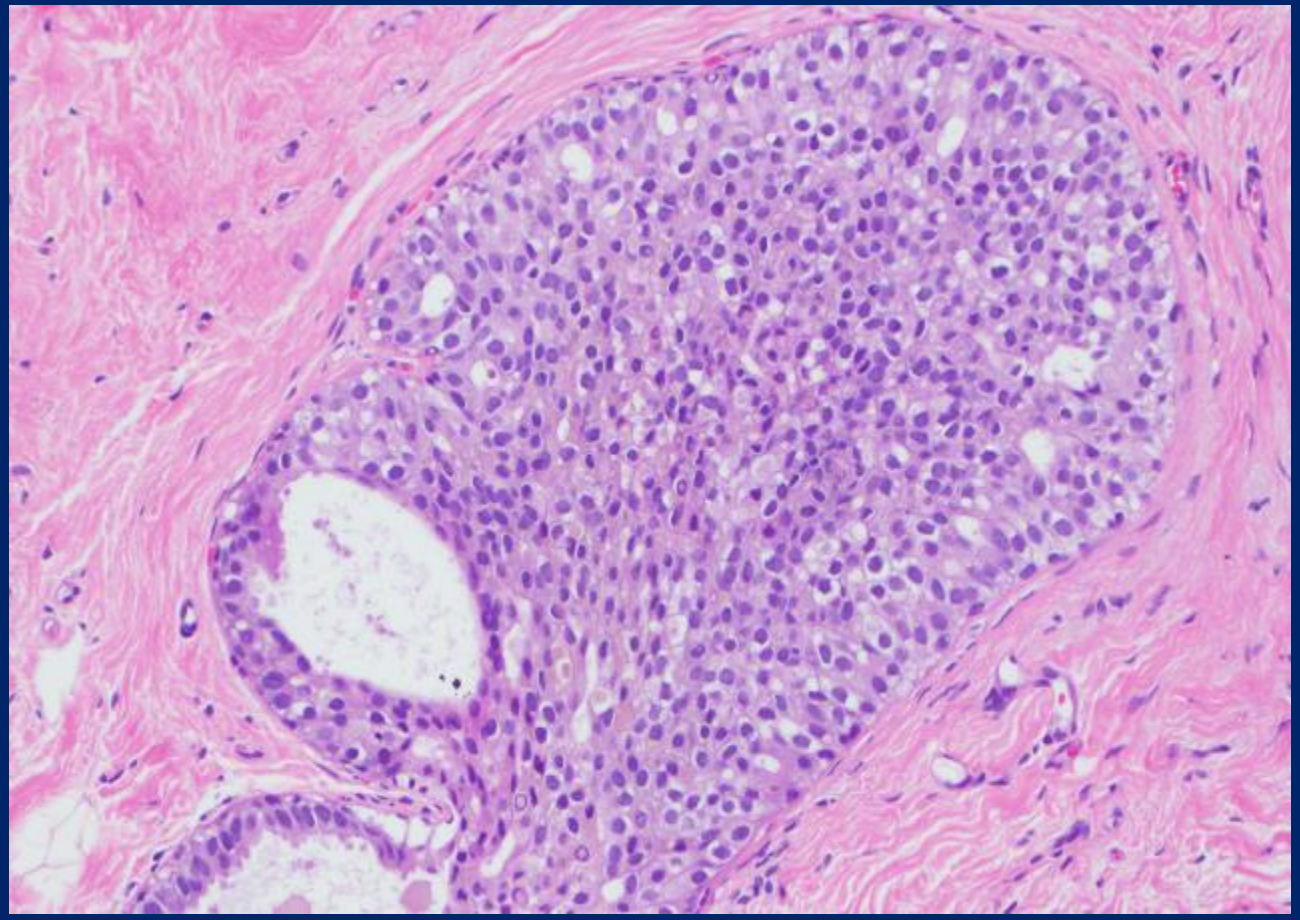
Soft sign for usual ductal hyperplasia

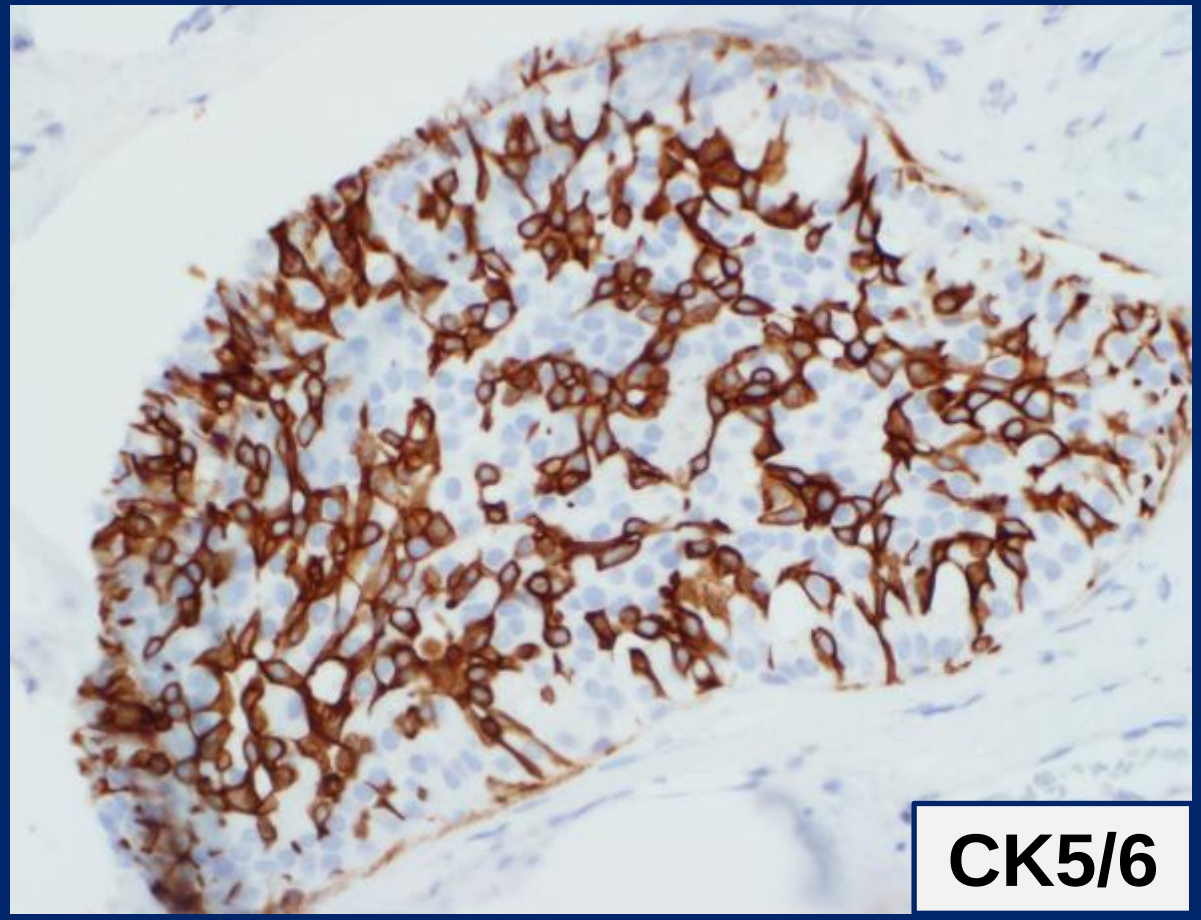
Collagenous spherulosis



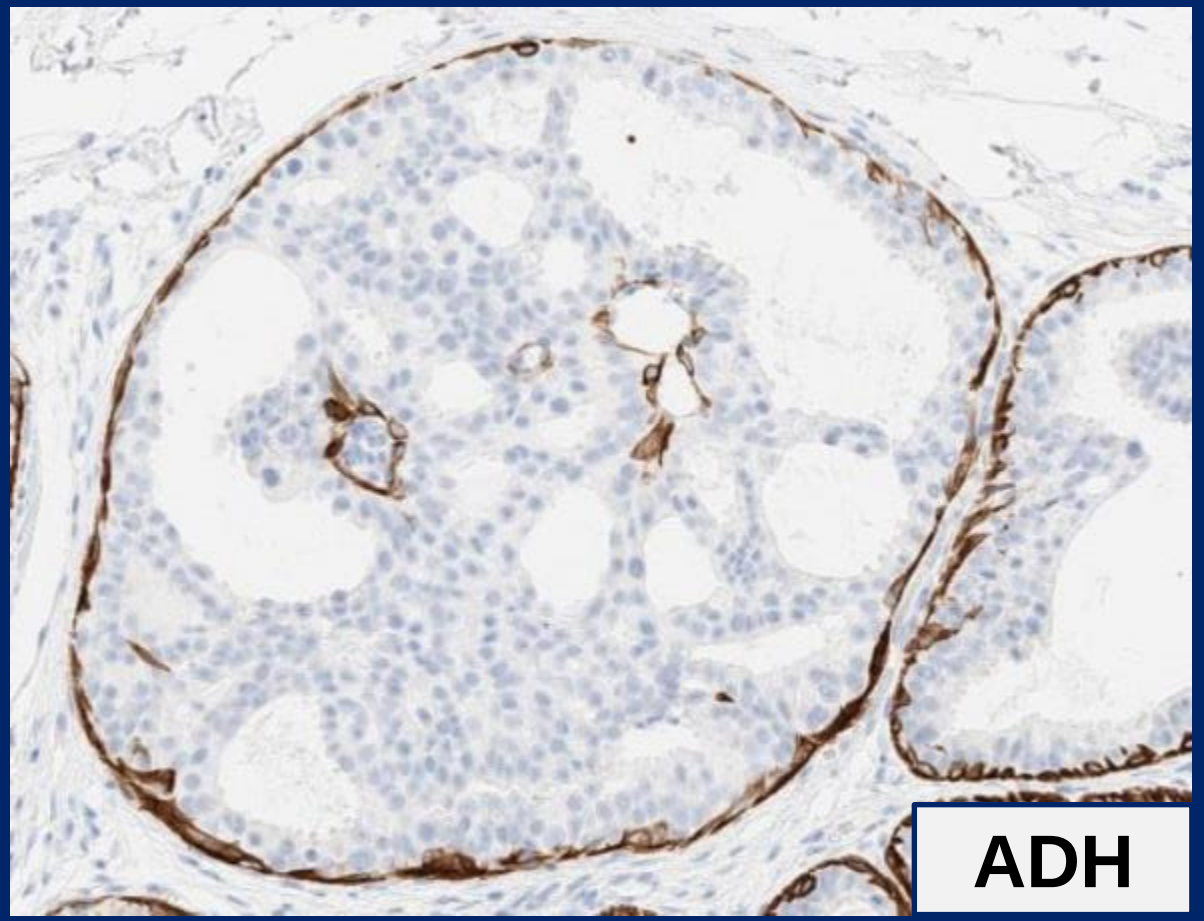
Collagenous spherulosis is only important due to its mimicry of DCIS and adenoid cystic carcinoma. It is important to be aware of features of collagenous spherulosis to avoid misdiagnosis of cancer.

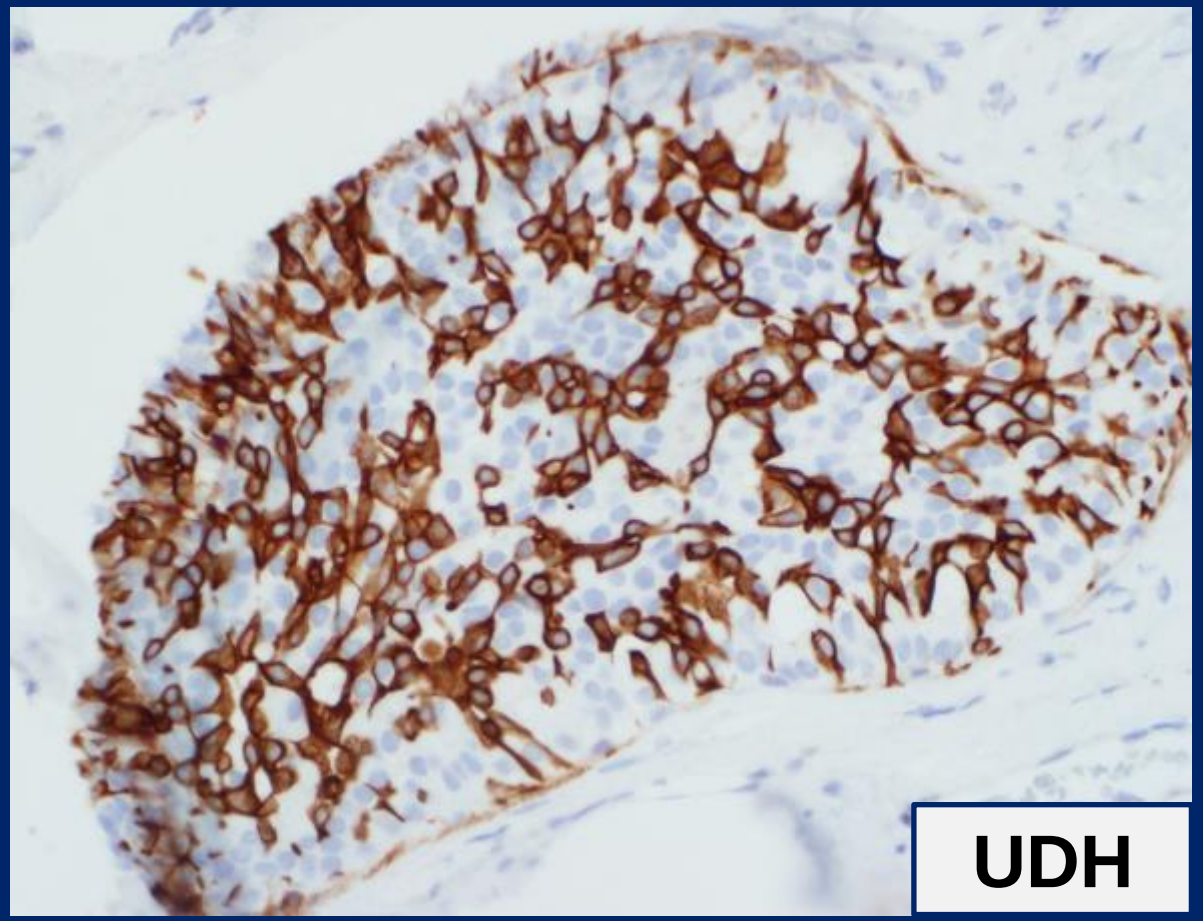
UDH: heterogenous “mosaic” staining pattern with CK5/6 and other high-molecular weight cytokeratins



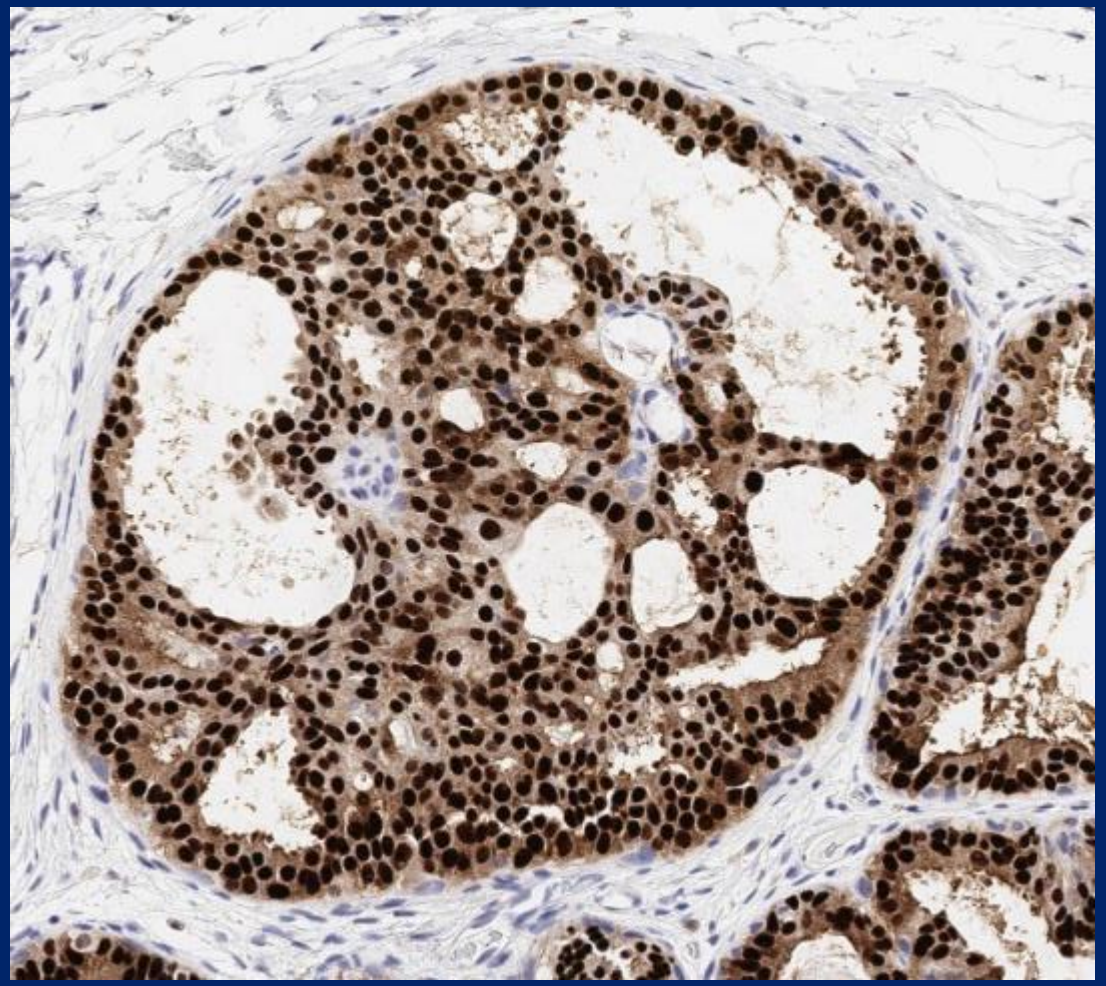


UDH: heterogenous “mosaic” staining with CK5/6
ADH/DCIS: absence of staining with CK5/6

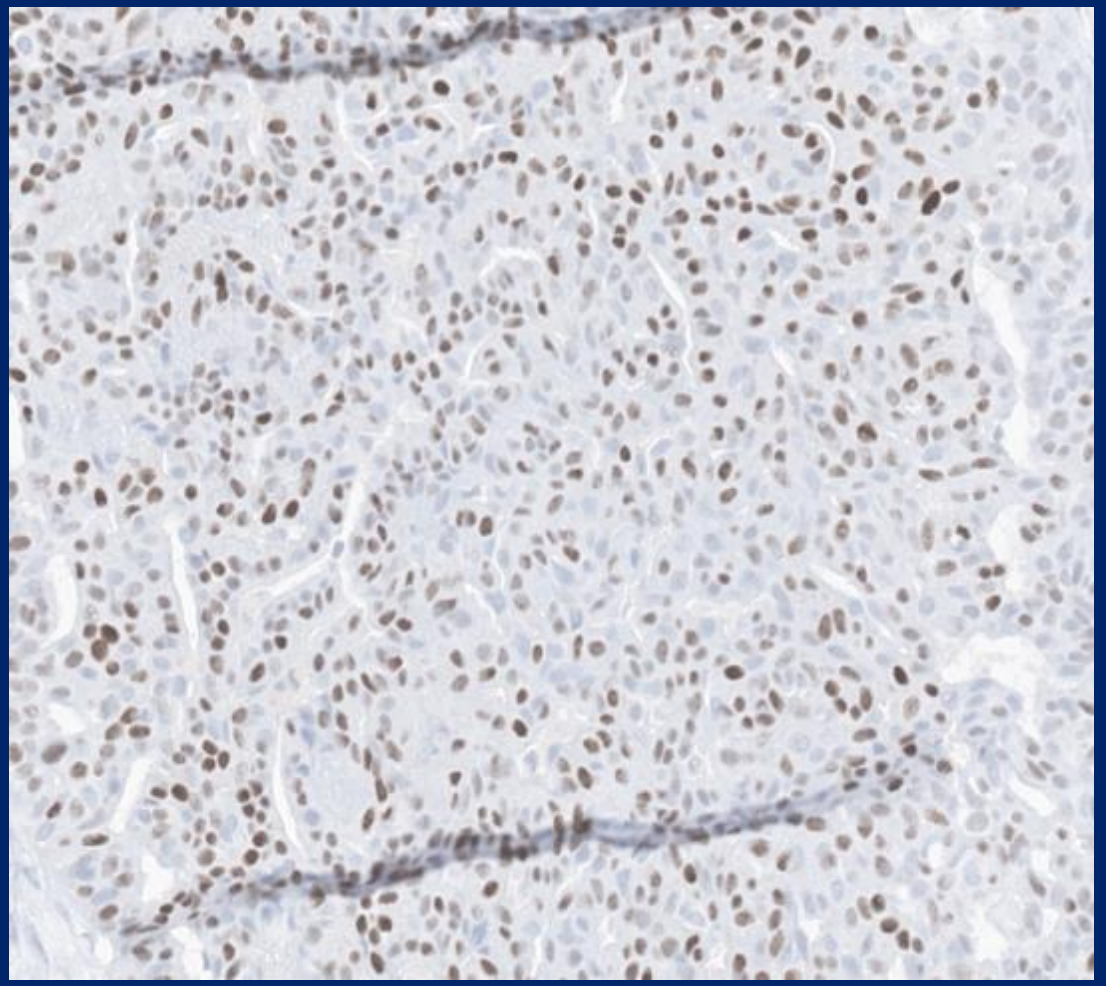




UDH: heterogeneous expression of ER
ADH/LG-DCIS: strong and diffuse expression of ER

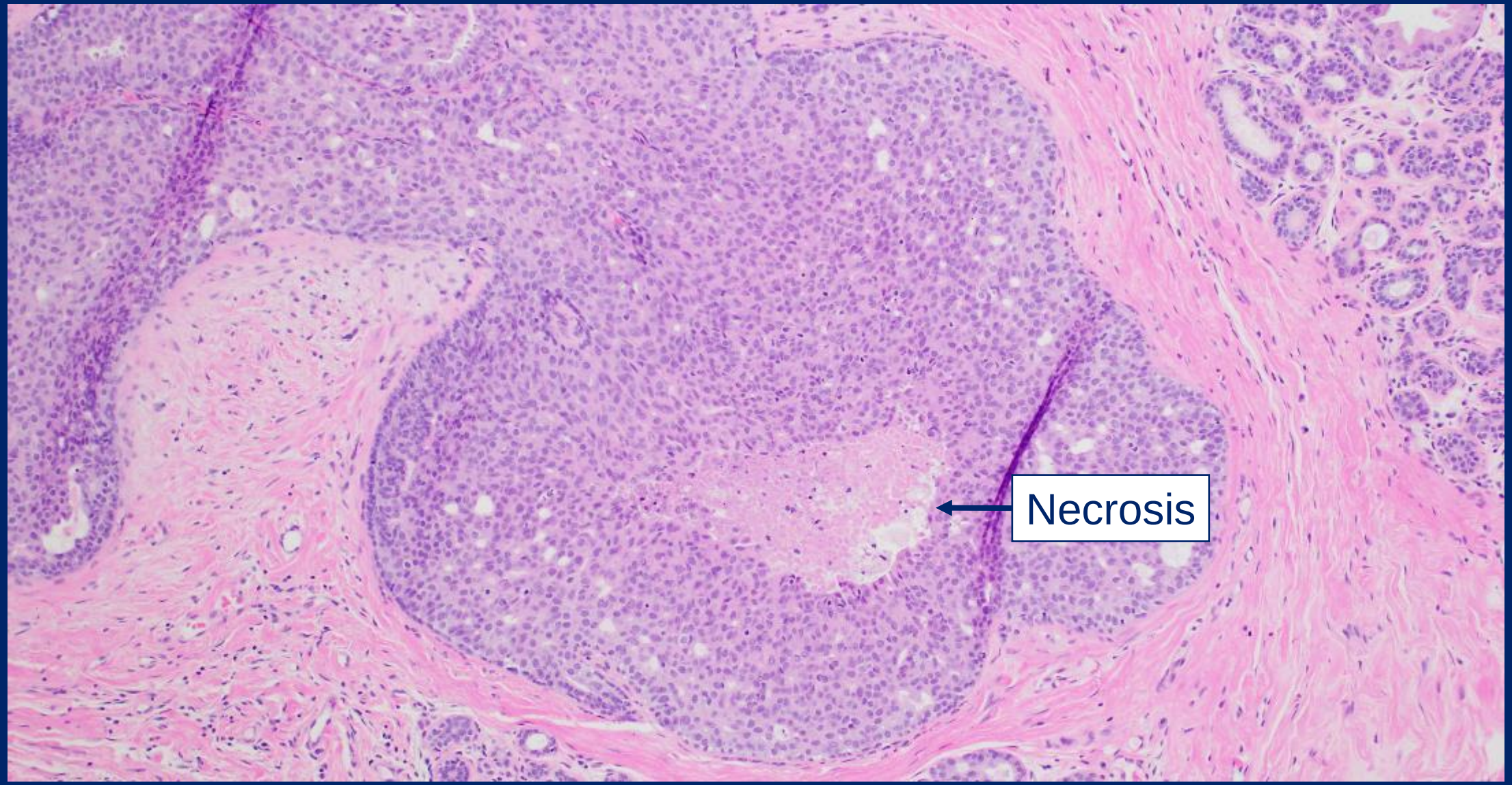


ADH



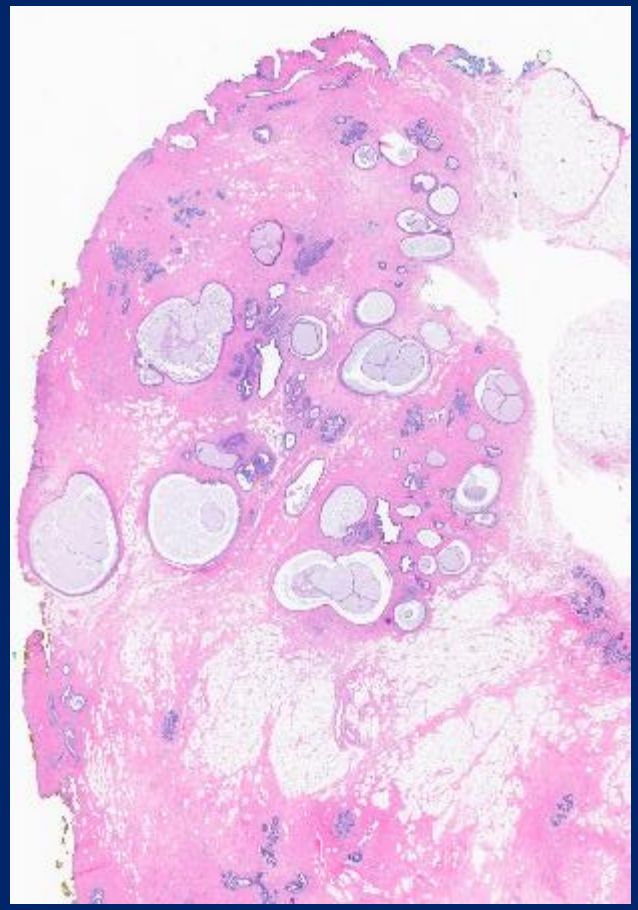
UDH

UDH with necrosis



Juvenile Papillomatosis (JP)

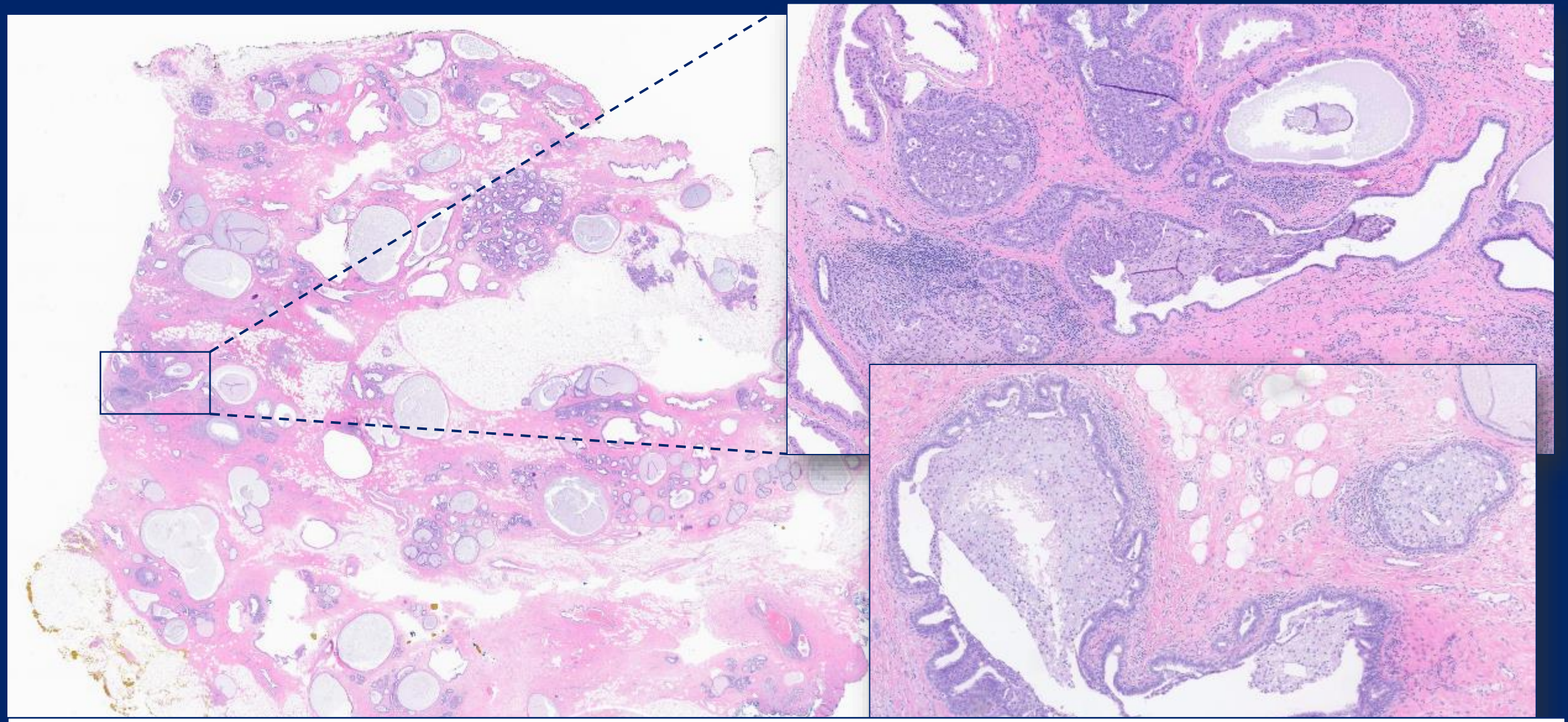
- Rare: <1% of all excised breast masses
- Mean age: 23 (range: 12-48 years)
  - 1/3 to 2/3 of women report family history of breast cancer
  - ½ of male infants have neurofibromatosis 1
- Presents as palpable, circumscribed, mobile mass
  - Often prebiopsy diagnosis is fibroadenoma
- Can be multiple and bilateral



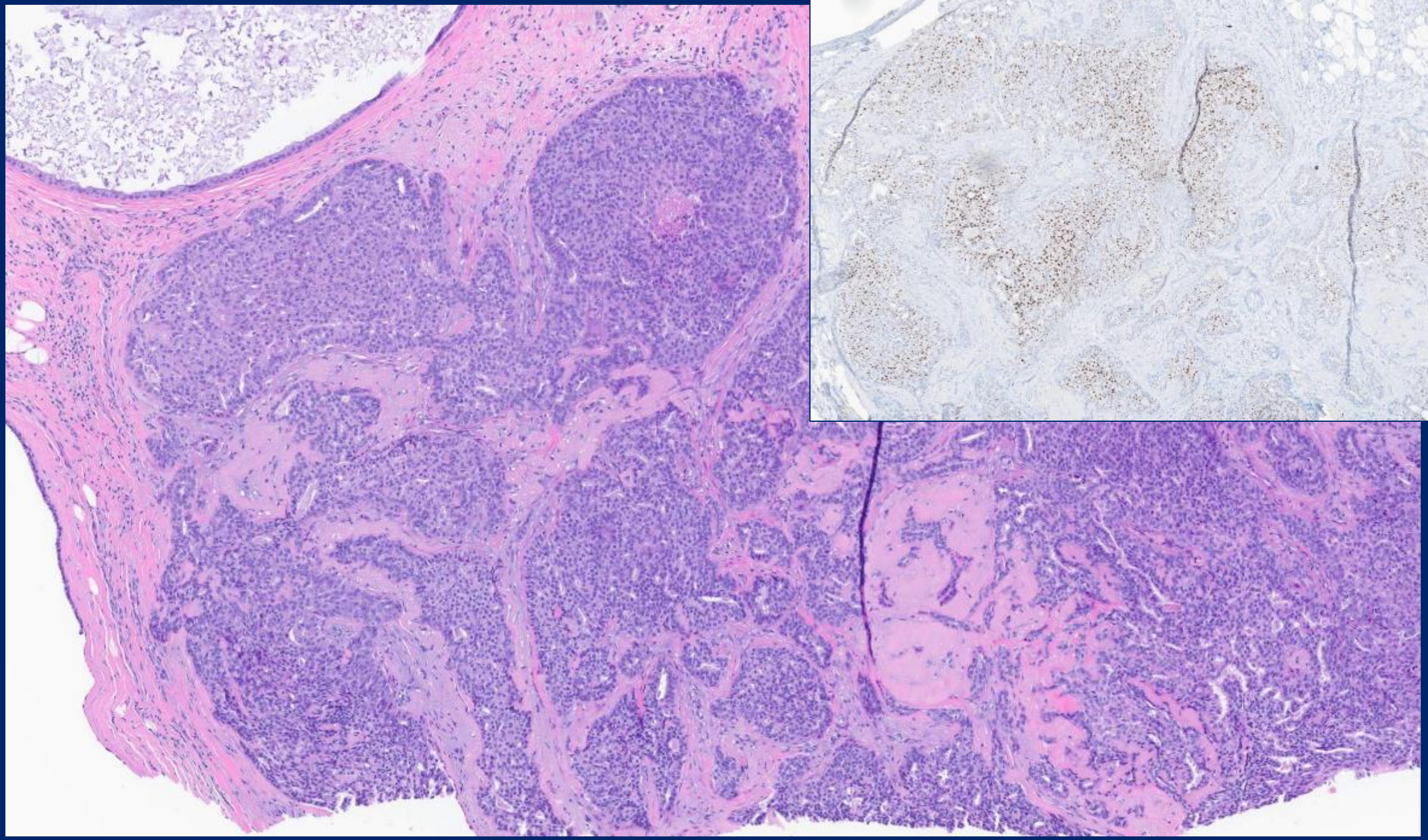
- Can recur if not completely excised
  - 10-15% of patients have concurrent cancer
    - DCIS, LCIS, invasive ductal, invasive lobular, invasive secretory carcinoma
  - 10% may subsequently develop cancer

Hoda SA, Brogi E, Koerner FS, Rosen PP. *Rosen's Breast Pathology*. LWW, Philadelphia 2014.

Juvenile Papillomatosis



Any findings of JP can be present as multiple small lesions in the breast. However, essential diagnostic criteria for JP is presence of changes within grossly defined palpable mass in a young person.


ER

Follow-up of UDH

- Slight increase in subsequent breast cancer risk: 1.5-2x
  - Slightly higher among patients with a strong family history of breast cancer
- Magnitude of risk is similar to that associated with certain reproductive factors (early menarche and late menopause) – should not alter frequency of mammographic screening

Hartmann et al. *N Engl J Med*. 2005;353(3):229-37.

Columnar cell lesions

Terminology

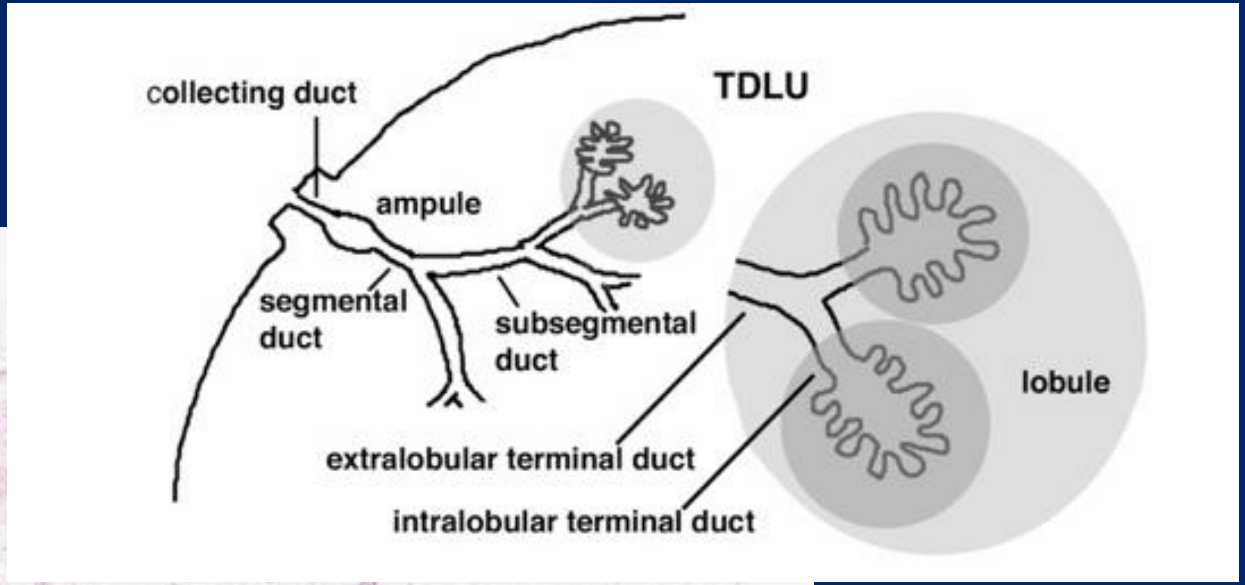
Columnar cell lesions

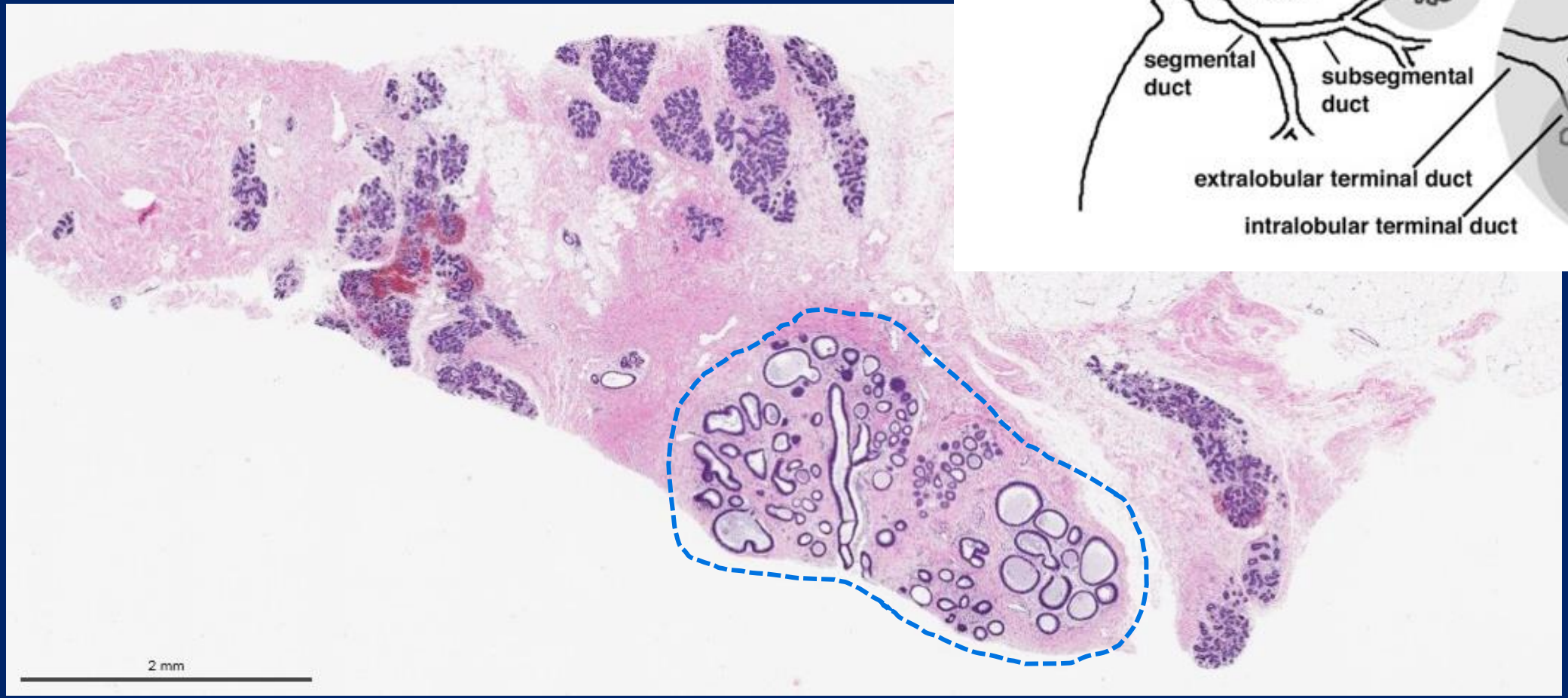
- Columnar cell change
- Columnar cell hyperplasia

Flat epithelial atypia

- Columnar cell change with atypia
- Columnar cell hyperplasia with atypia

Terminal duct lobular unit (TDLU)





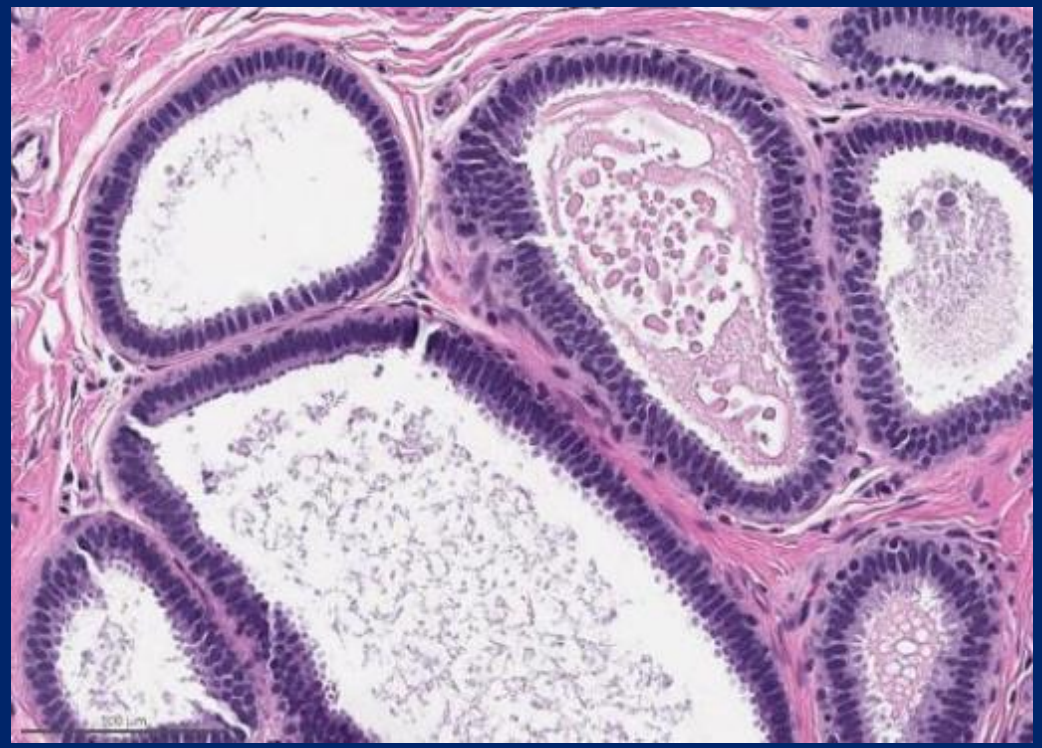
Key Features of Columnar Cell Change

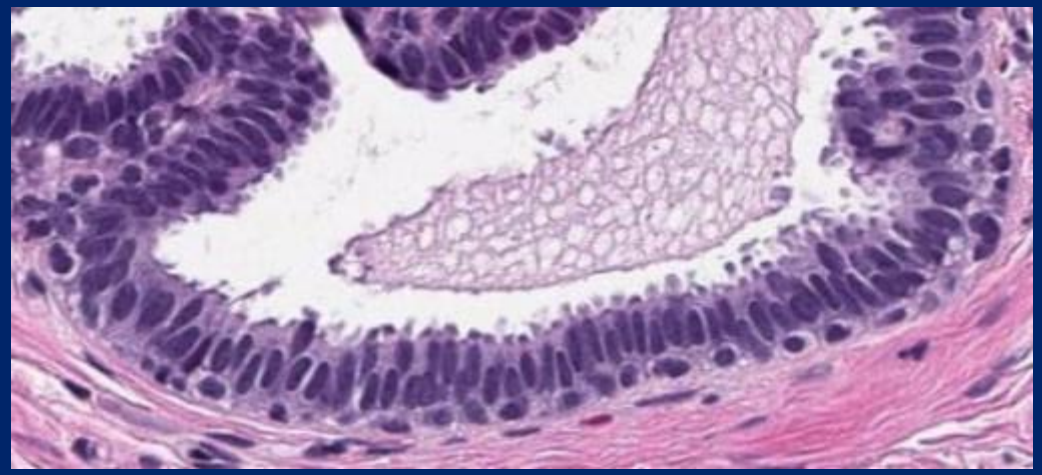
Cytologic Features

- Columnar epithelial cells
- Ovoid nuclei
- Apical cytoplasmic snouts
- NO atypia

Architectural Features

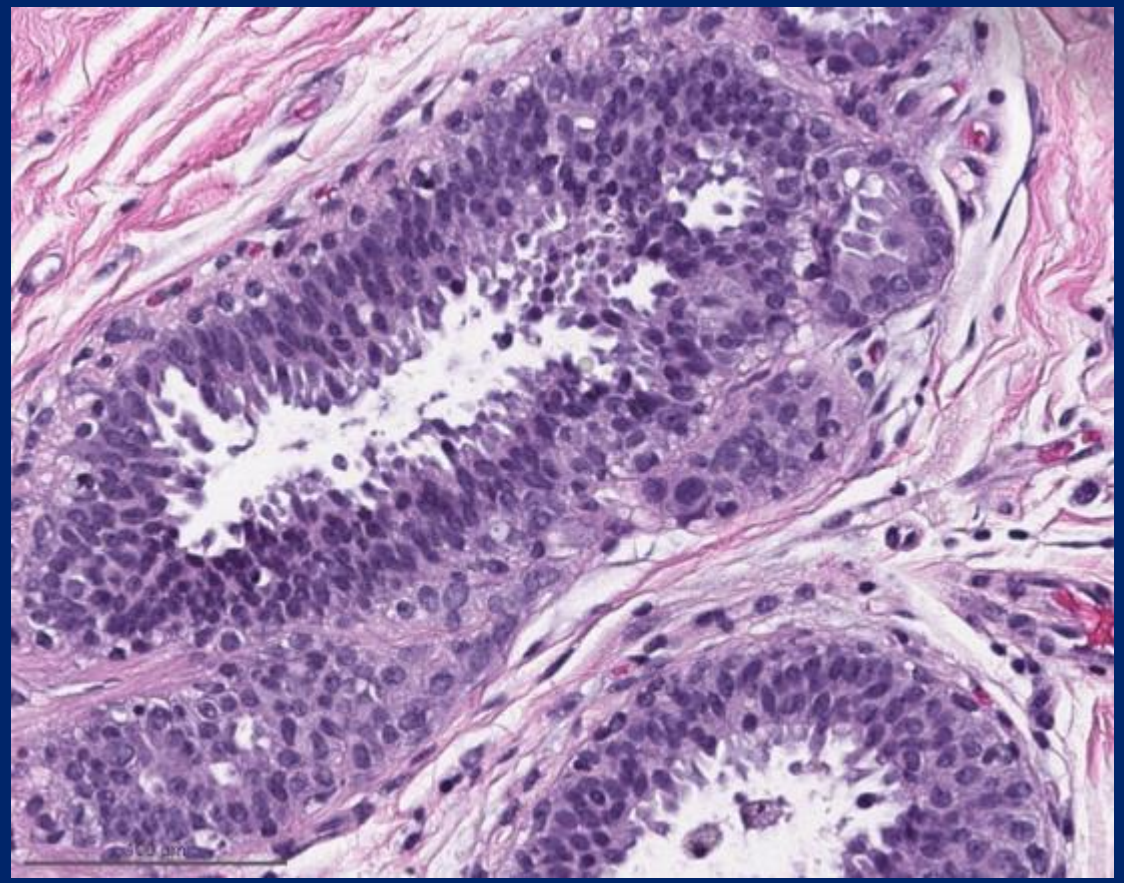
- 1-2 cell layers
- Variably enlarged and dilated acini
- Secretions and calcifications often present



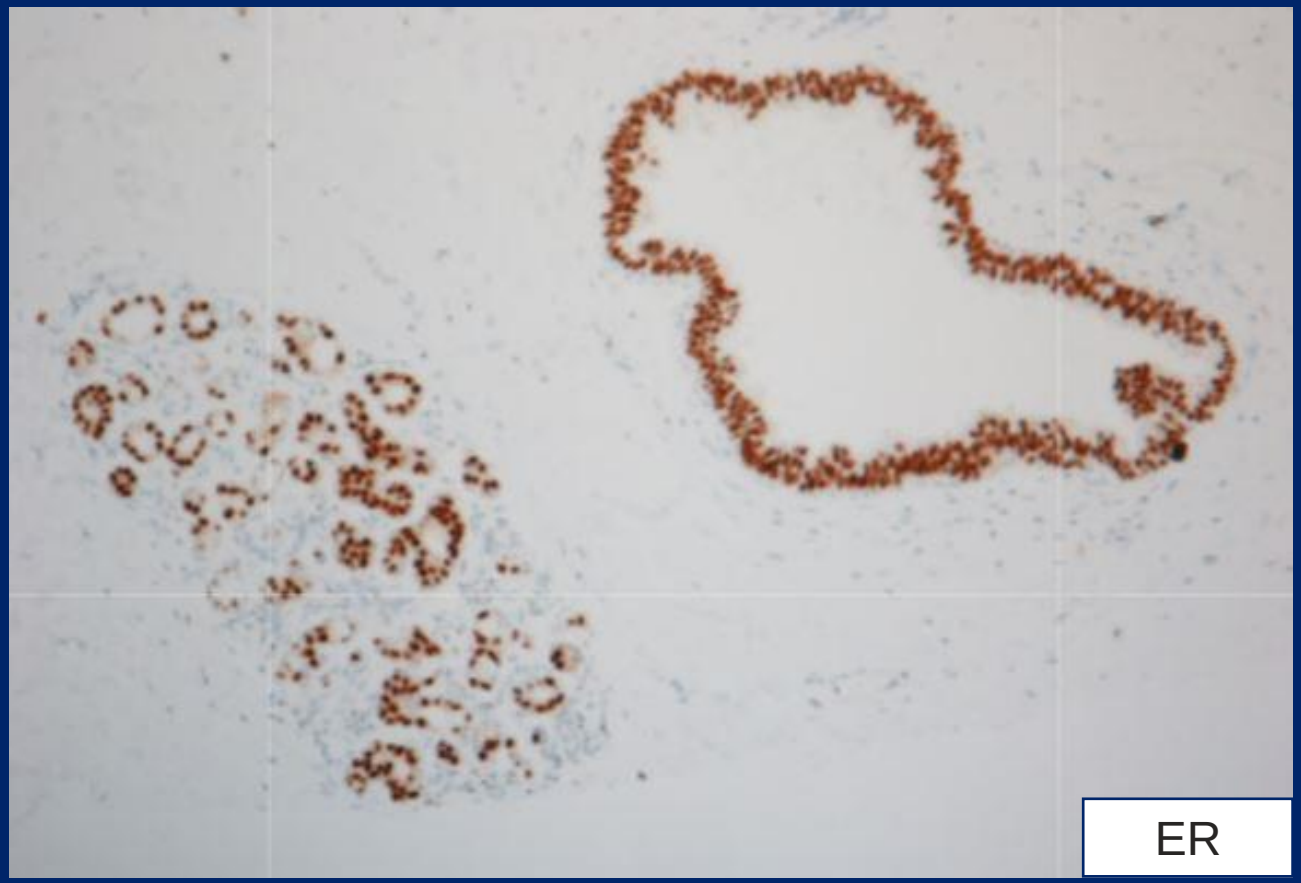


Columnar cell hyperplasia

Cellular stratification or tufting >2 cell layers



CCL with ***and*** without atypia stain the same: ER positive and CK5/6 negative



Flat epithelial atypia (FEA)

(columnar cell change with atypia)

Terminology

Prior to adoption of term flat epithelial atypia (FEA) by WHO in 2003 the lesion was referred to as:

- Columnar alteration with prominent apical snouts and secretions (CAPSS)[1]
- Atypical ductal cells with apocrine snouts involving small ectatic ducts[2]
- Atypical cystic lobules[3]
- Columnar cell changes with atypia[4]

[1]Fraser et al. *Am J Surg Pathol*. 1998; 22(12): 1521-1527.
[2]Goldstein et al. *Am J Clin Pathol*. 1997; 107(5): 561-566.
[3]Brogi et al. *Int J Surg Pathol*. 2001; 9(3): 201-206.
[4]Schnitt et al. *Adv Anat Pathol*. 2003; 10(3): 113-124.

FEA: Imaging and Gross Findings

No radiologic features diagnostic of FEA

- Vast majority of cases of CCL/FEA have Ca^{++} on mammogram
  - May appear rounded, branching, amorphous, indistinct or pleomorphic
  - Usually interpreted as suspicious
- CCL ranks 5th among common findings associated with Ca^{++}
  - FCC, FA, DCIS, sclerosing adenosis

Sonographic features are ambiguous

- May resemble those associated with DCIS/ADH – irregular masses

No specific gross findings

Lokuhetty D, White VA, Watanabe R, Cree IA. *WHO Classification of Tumours Editorial Board. Breast tumors.* IARC, Lyon; 2019.

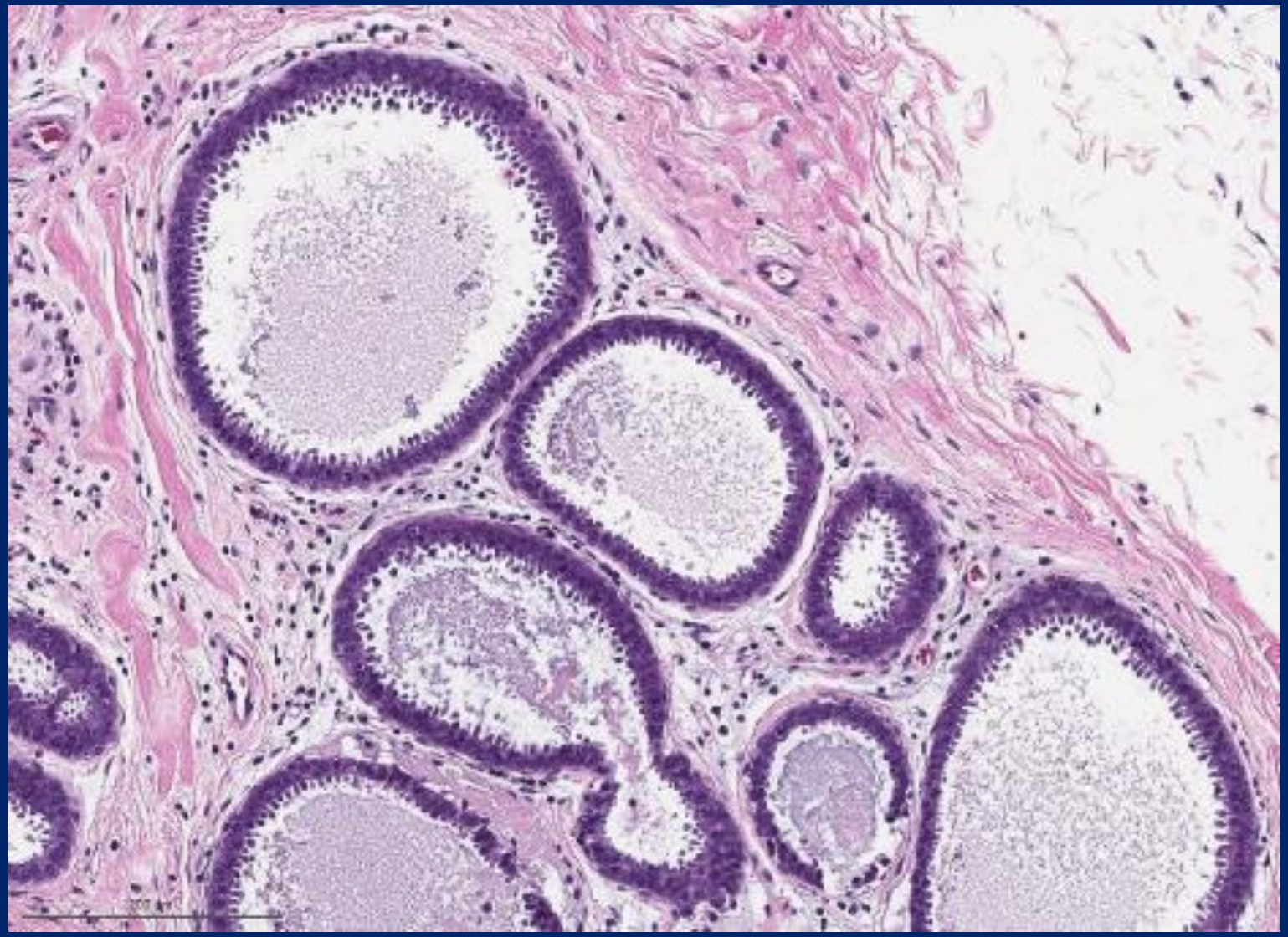
Key Features of FEA

Cytologic Features

- Low grade cytologic atypia
- Cuboidal to columnar
- Frequent apical snouts

Architectural Features

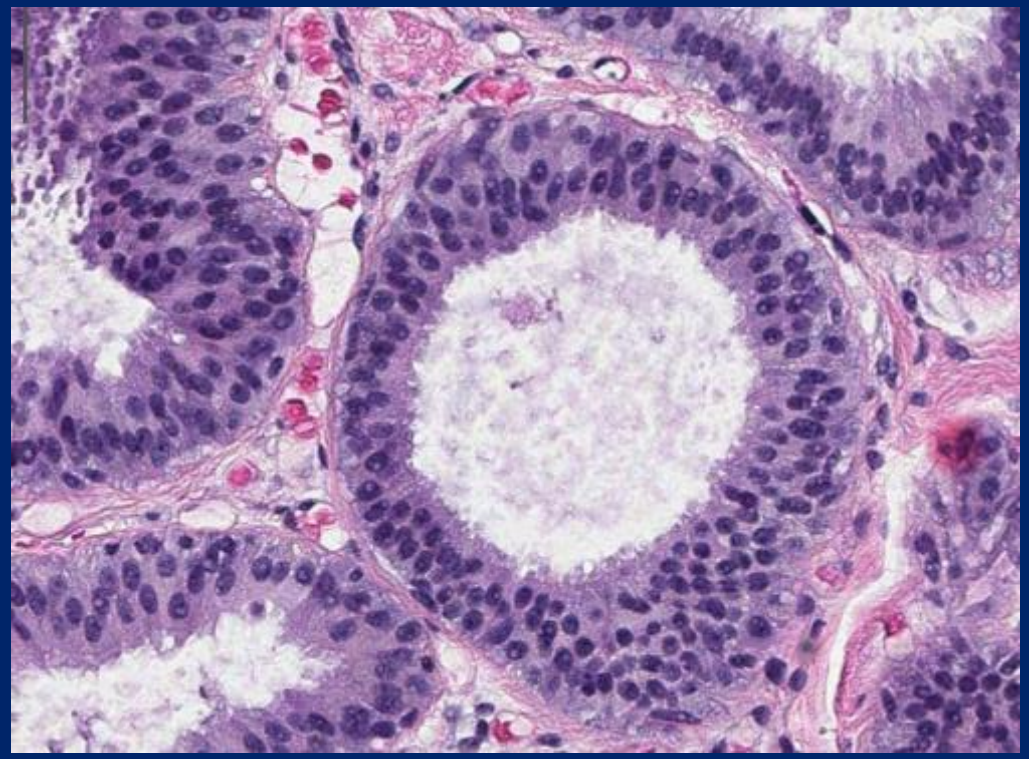
- Flat proliferation (1-several layers)
- Variably distended TDLUs
- Intraluminal secretions and calcifications may be present
- No architectural atypia



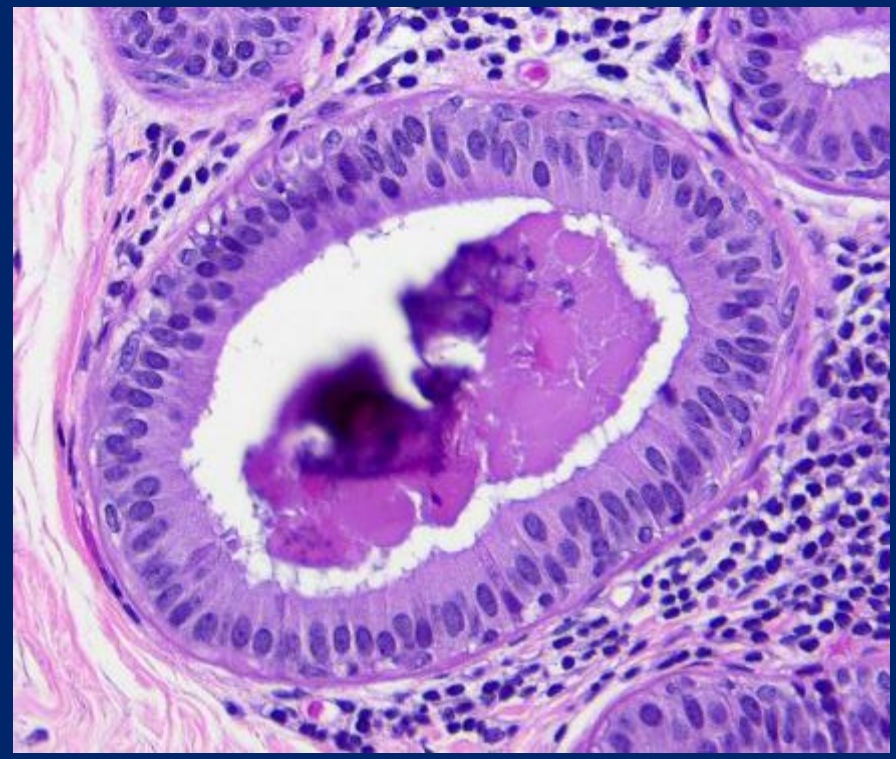
Grabenstetter A et al. *Am J Surg Pathol*. 2020;44(2):182-190.

FEA diagnosis according to WHO vs MSK

Flat proliferation of at least 2 layers of ductal cells with low grade atypia

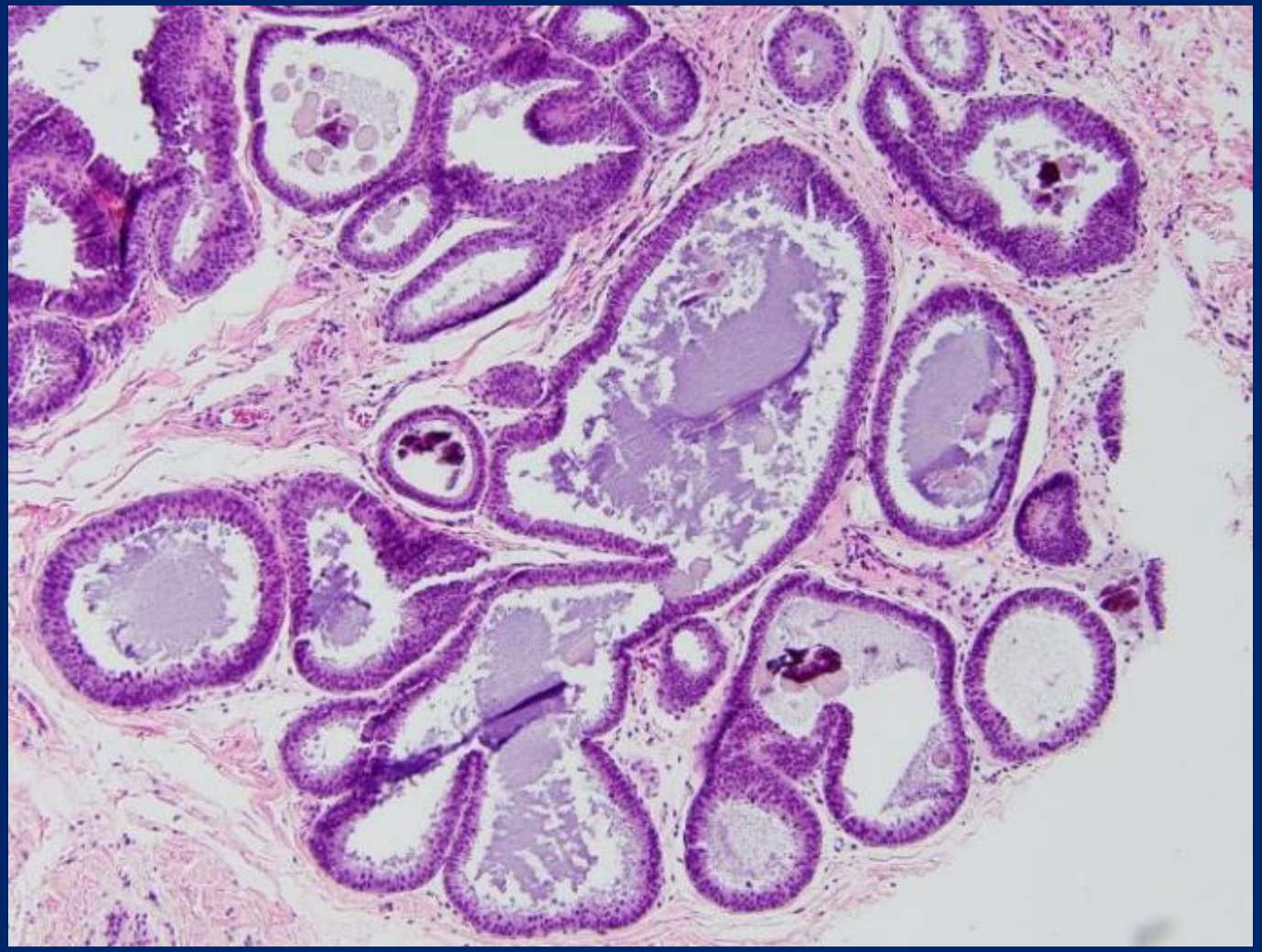


At least 2 cell layers = FEA



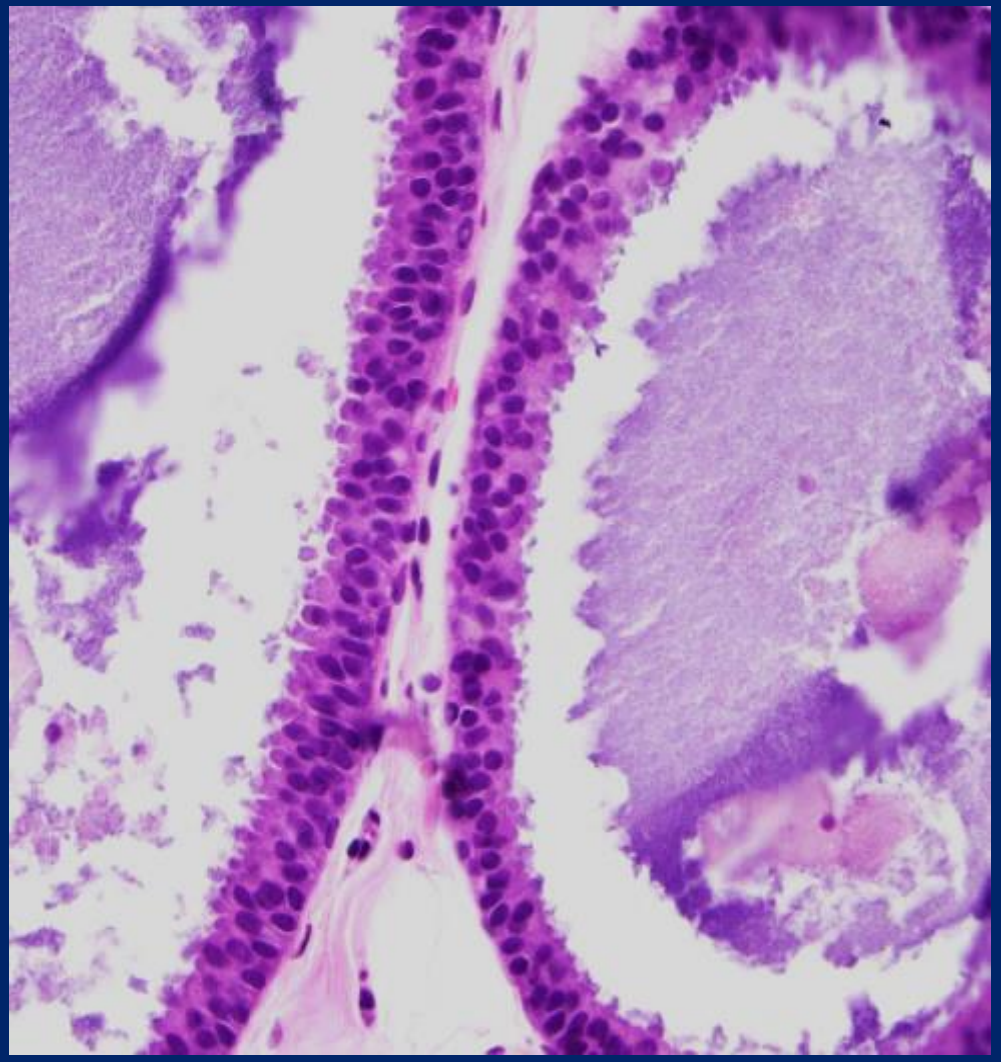
1 cell layer = benign CCC

FEA: Variably distended TDLUs

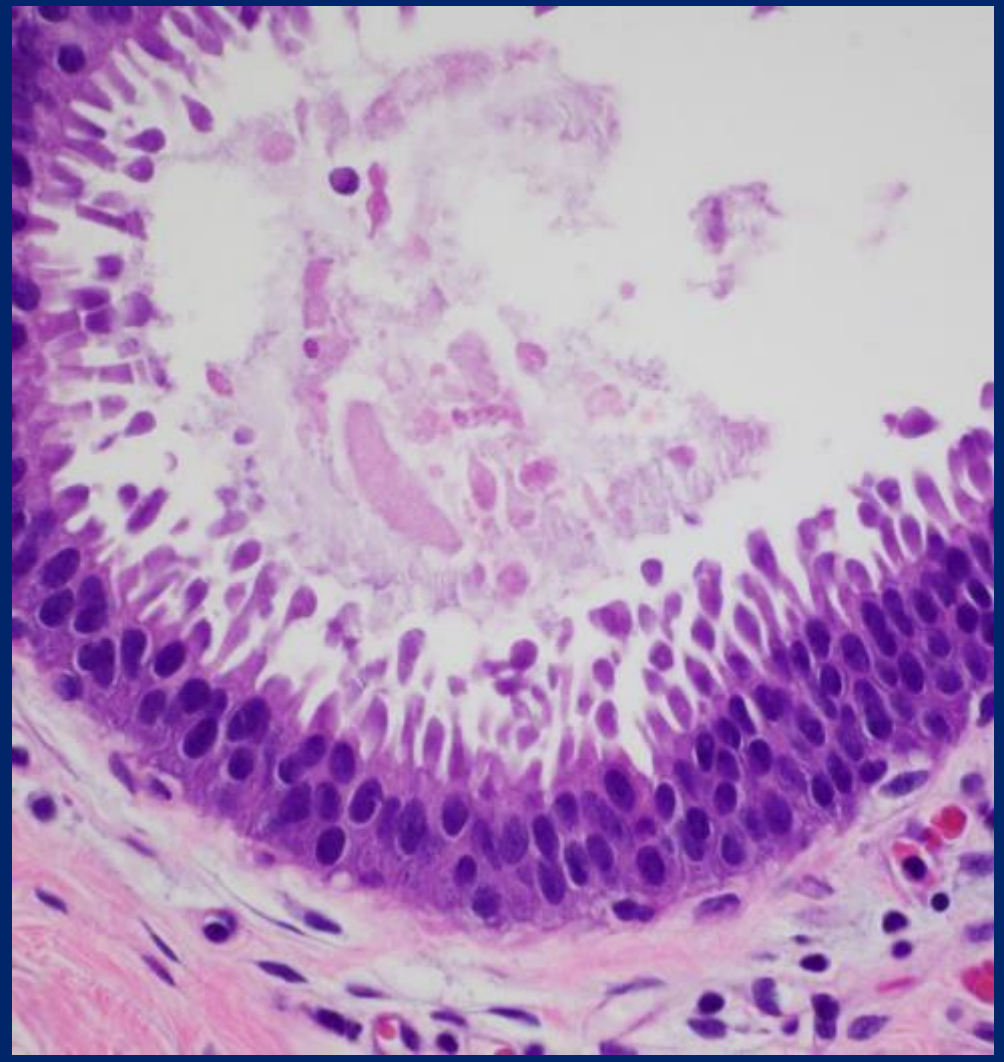


Intraluminal secretions and calcifications

FEA: Low grade cytologic atypia

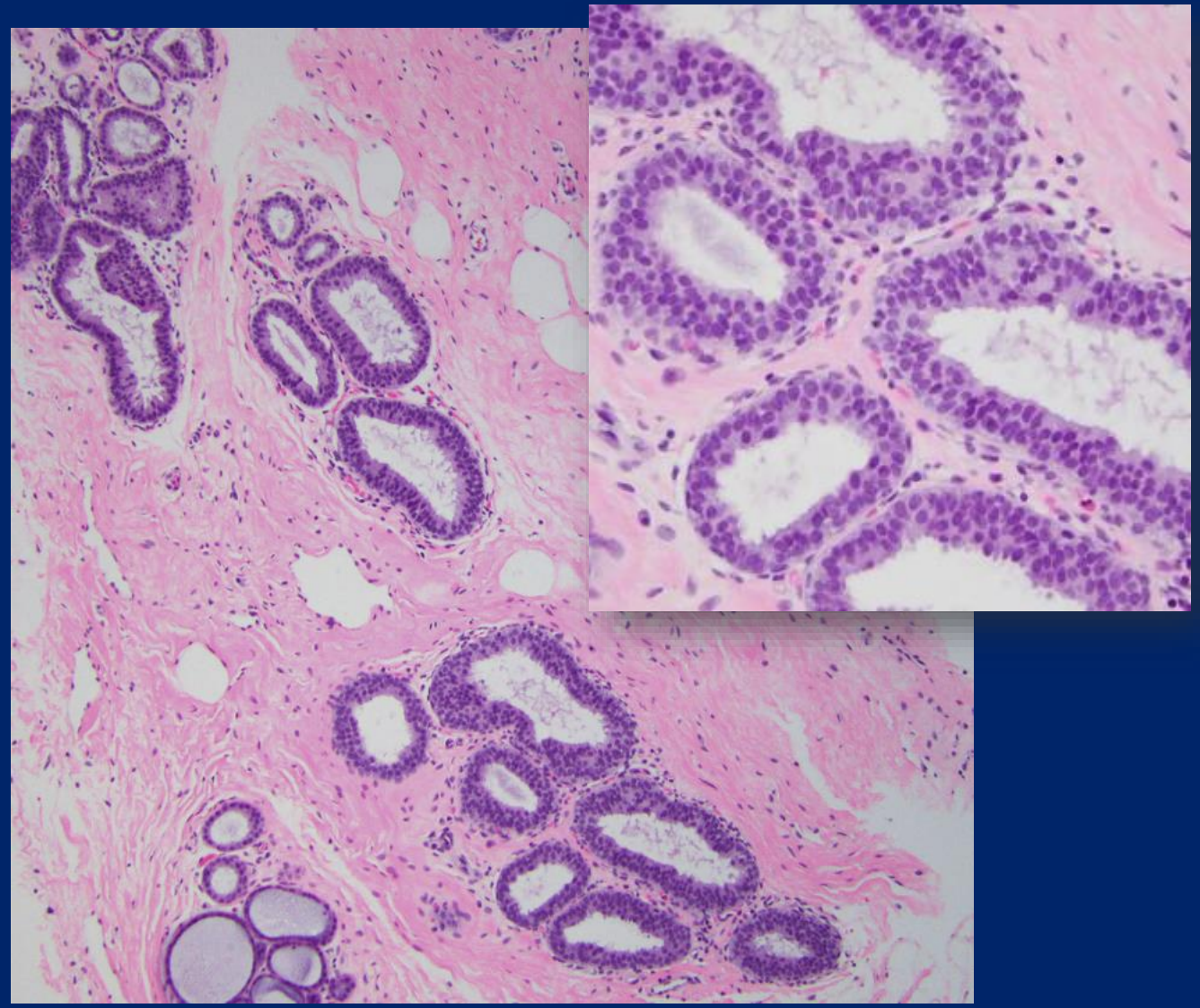


Cuboidal, monomorphic cells

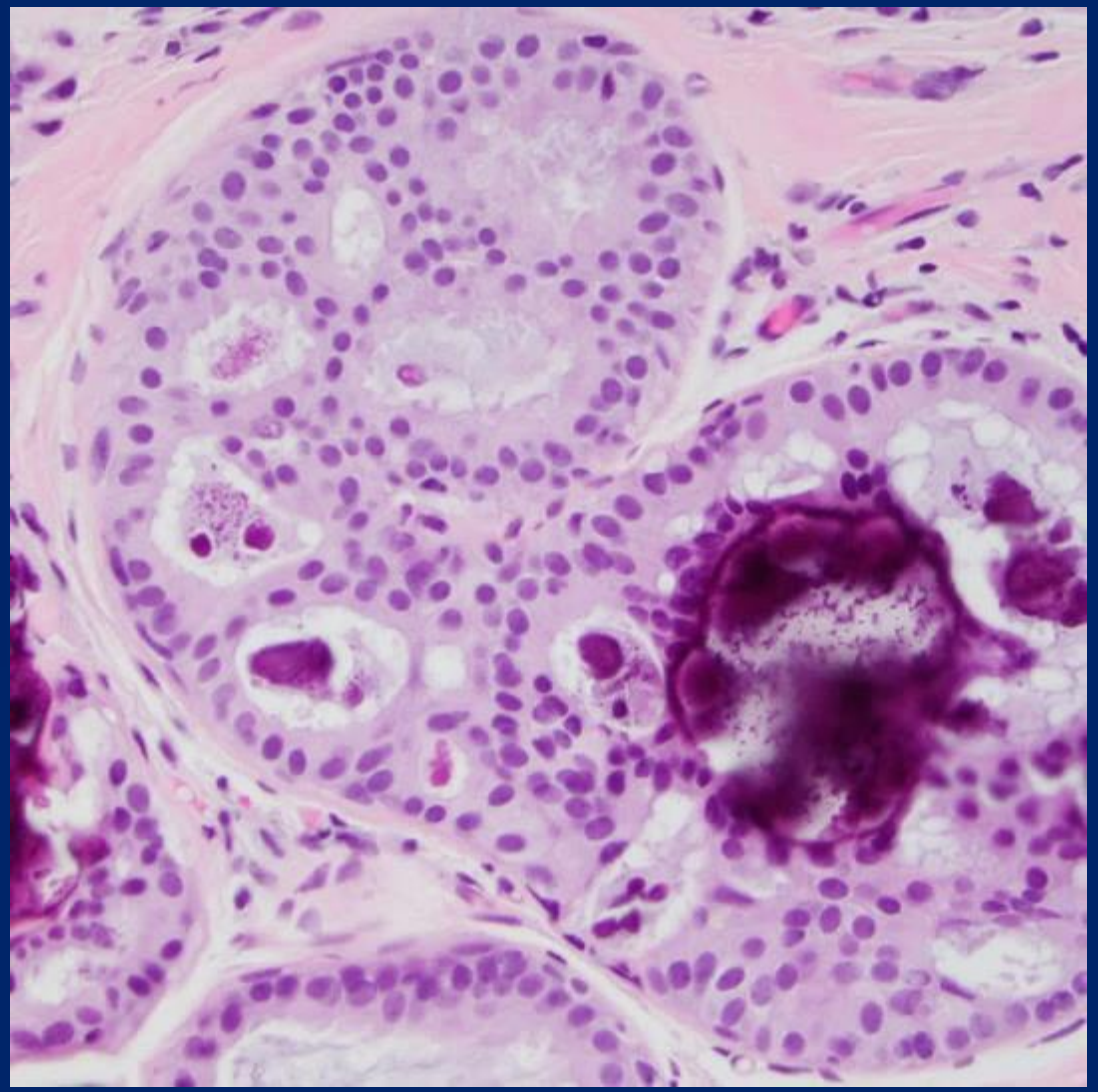


Apical snouts

FEA: No architectural atypia



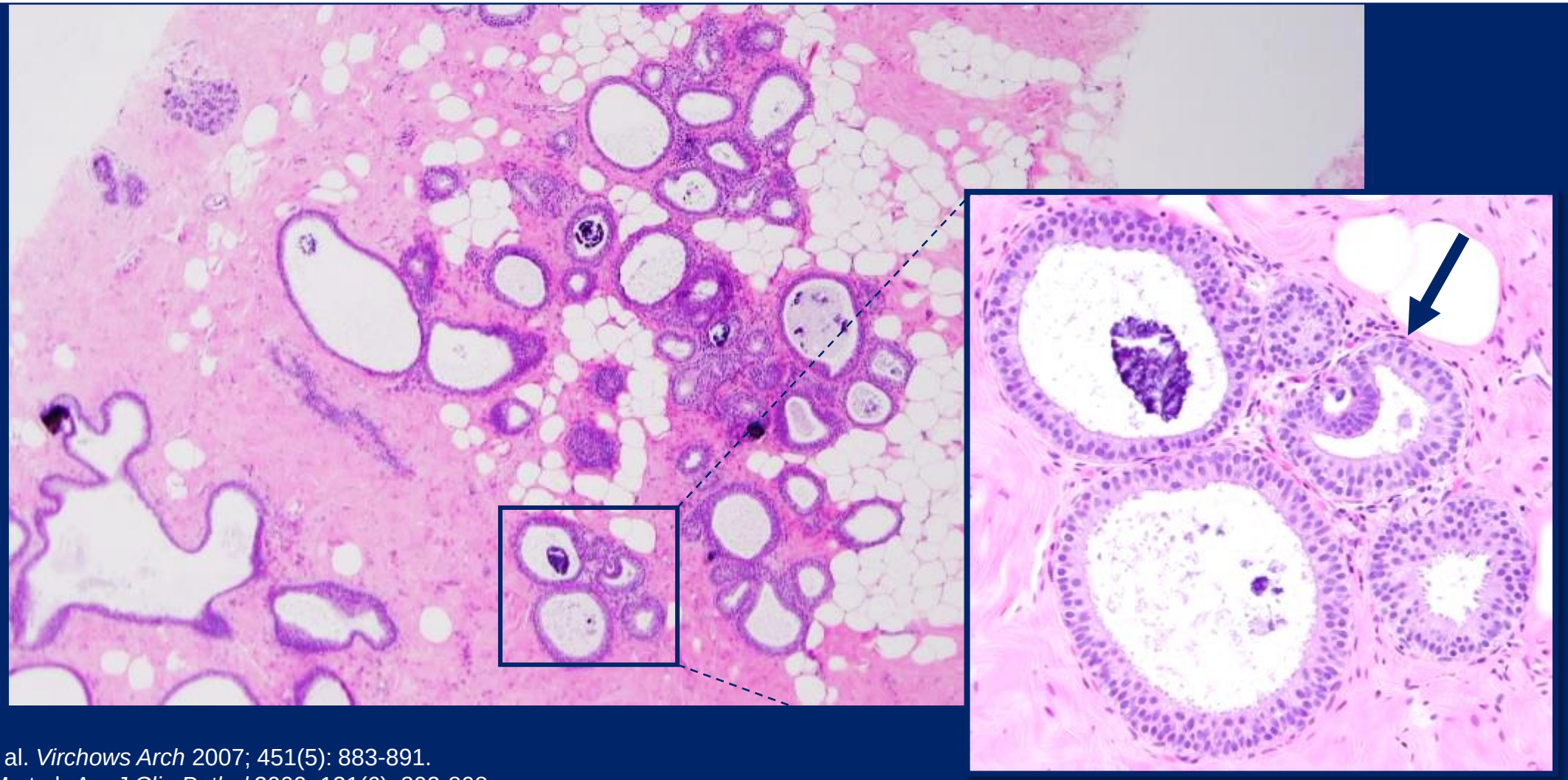
FEA



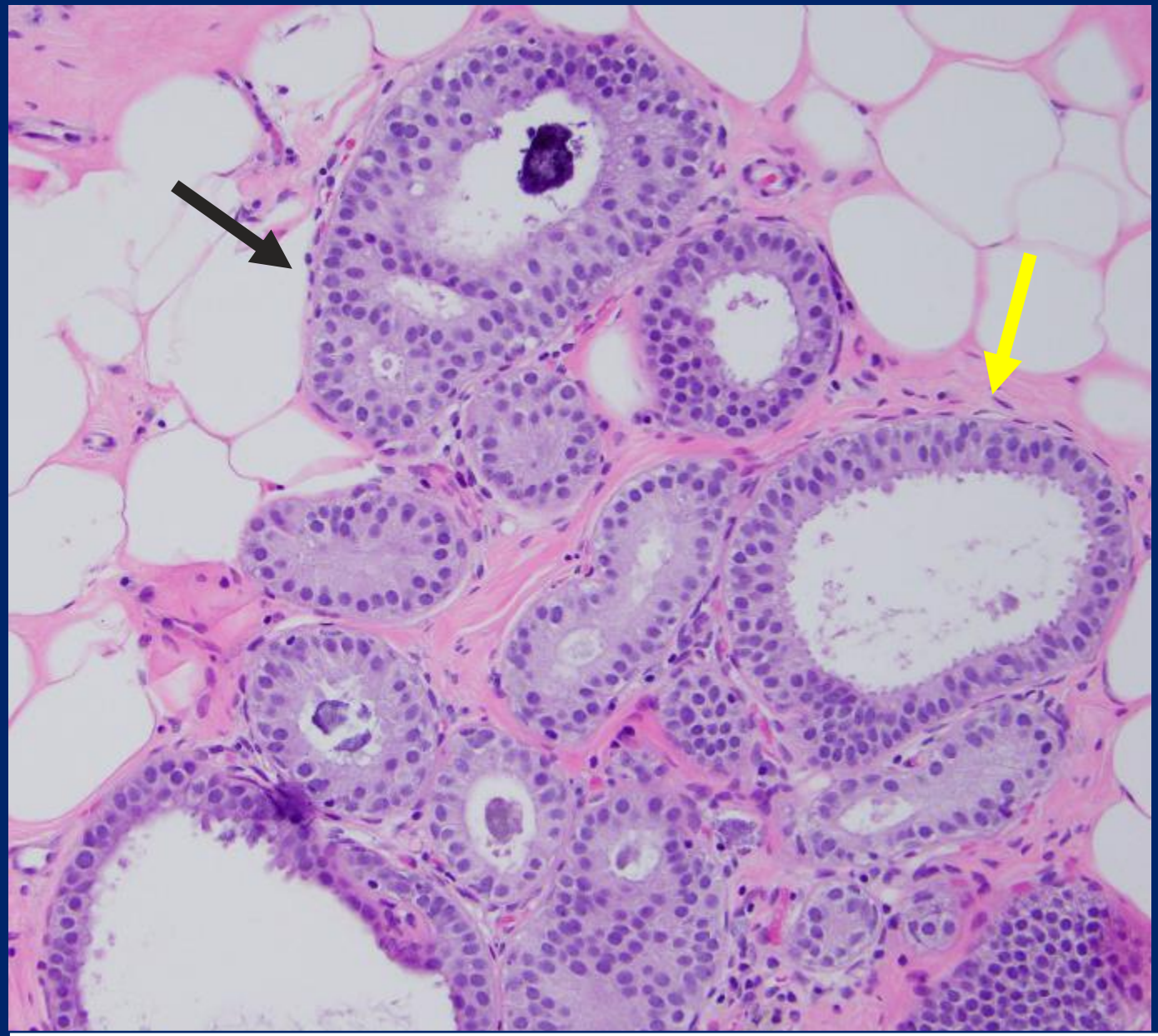
ADH

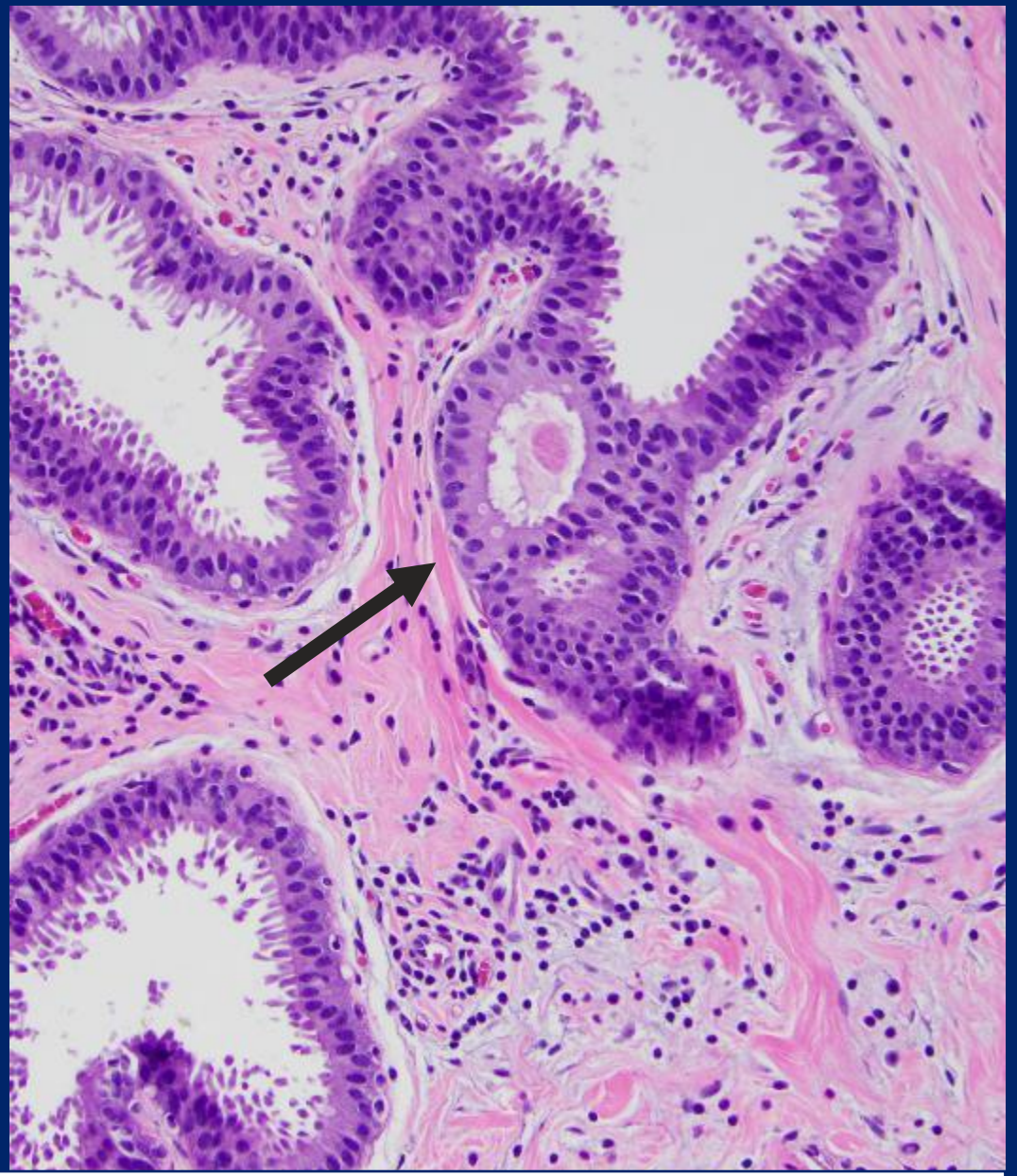
Any architectural complexity → focal ADH

FEA evolves into ADH at same site in 3-4 tissue levels in up to 17% of cases.
Recommend getting deeper level histologic sections to rule out a higher risk lesion.



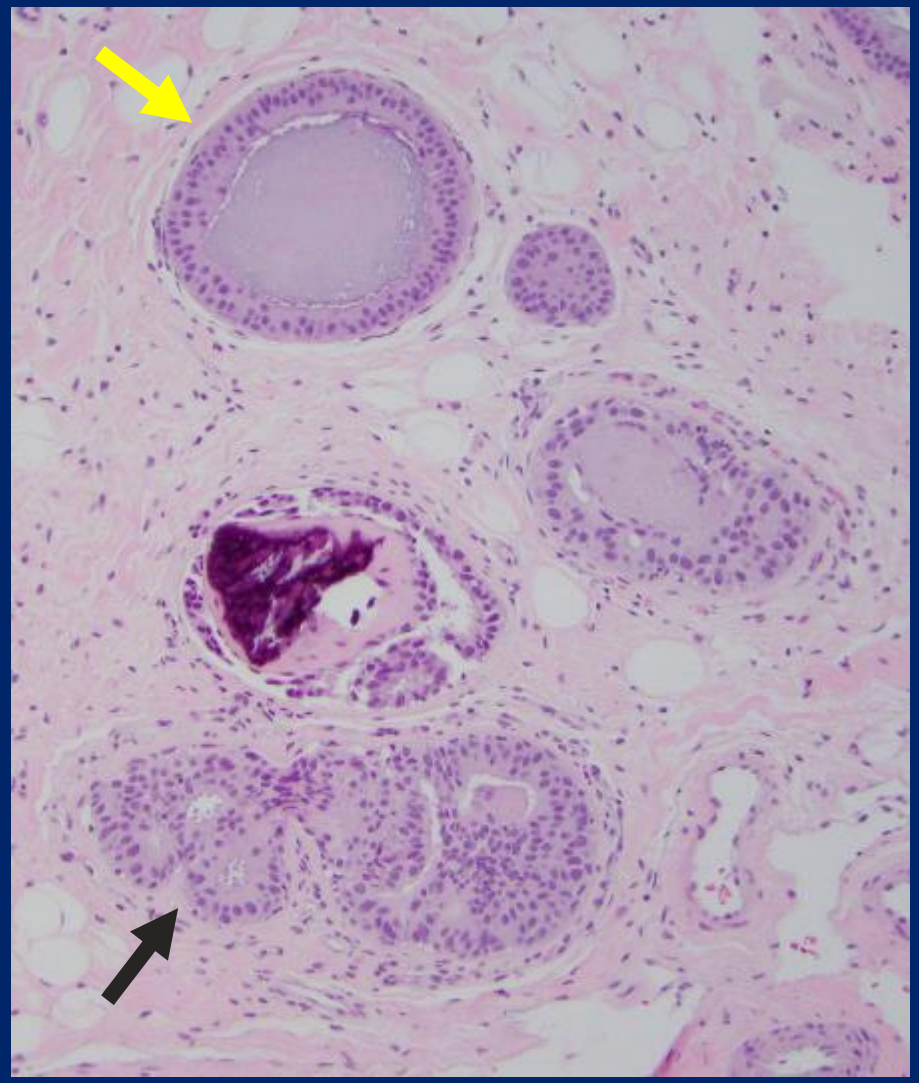
Martel M et al. *Virchows Arch* 2007; 451(5): 883-891.
Chivukula M et al. *Am J Clin Pathol* 2009; 131(6): 802-808.



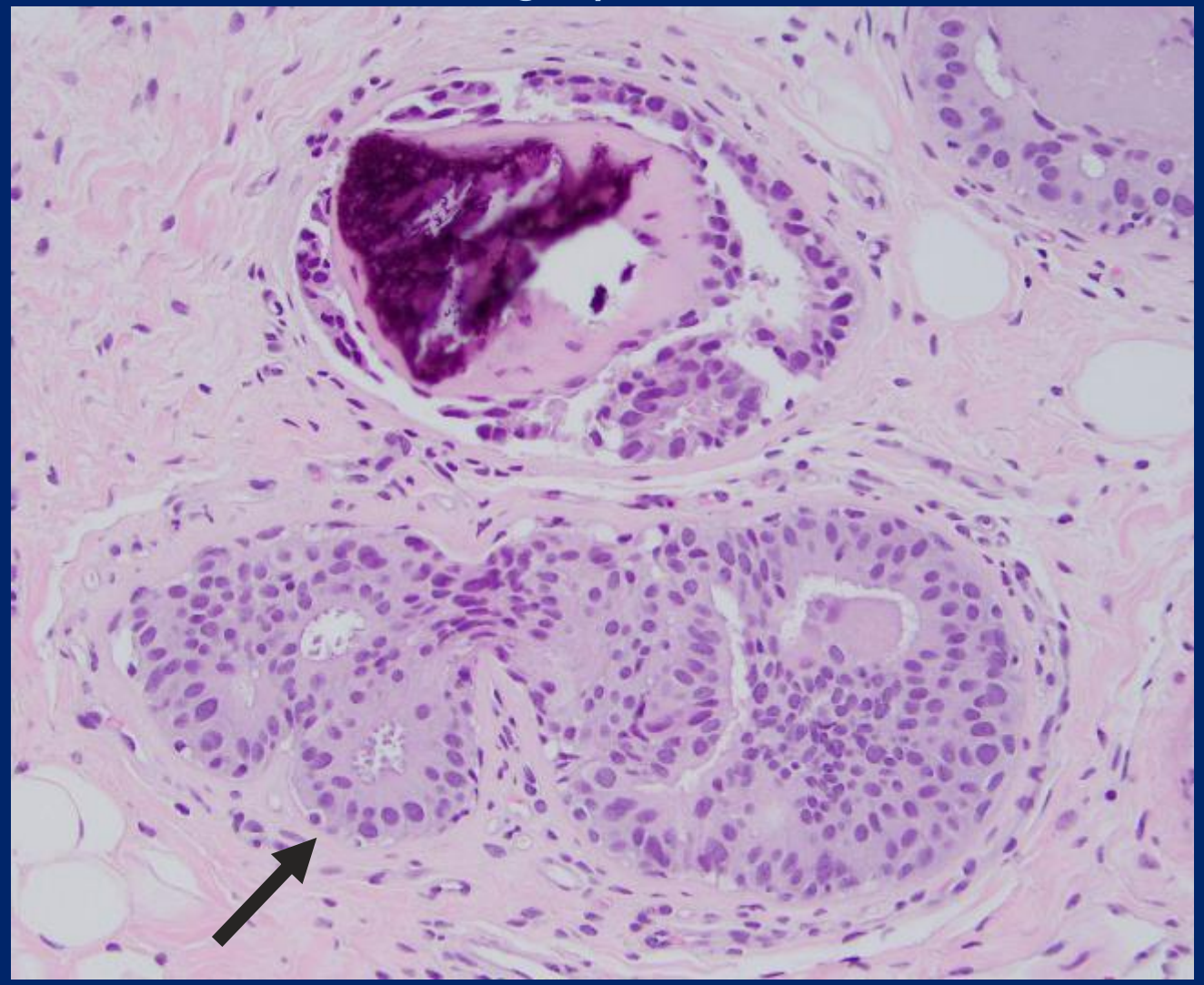


Black arrow: ADH Yellow arrow: FEA

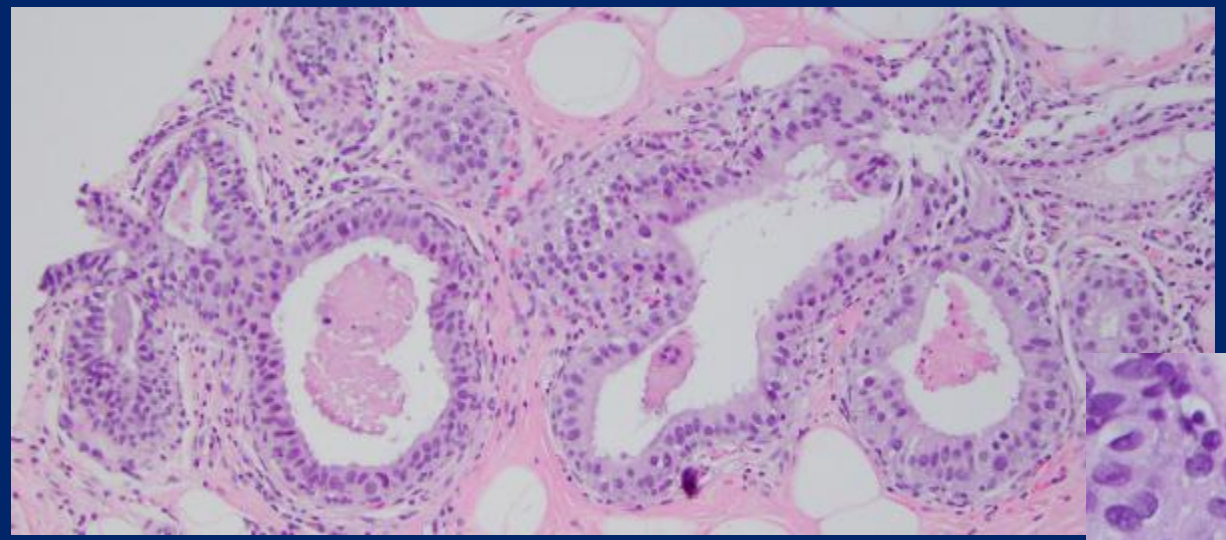
Low power



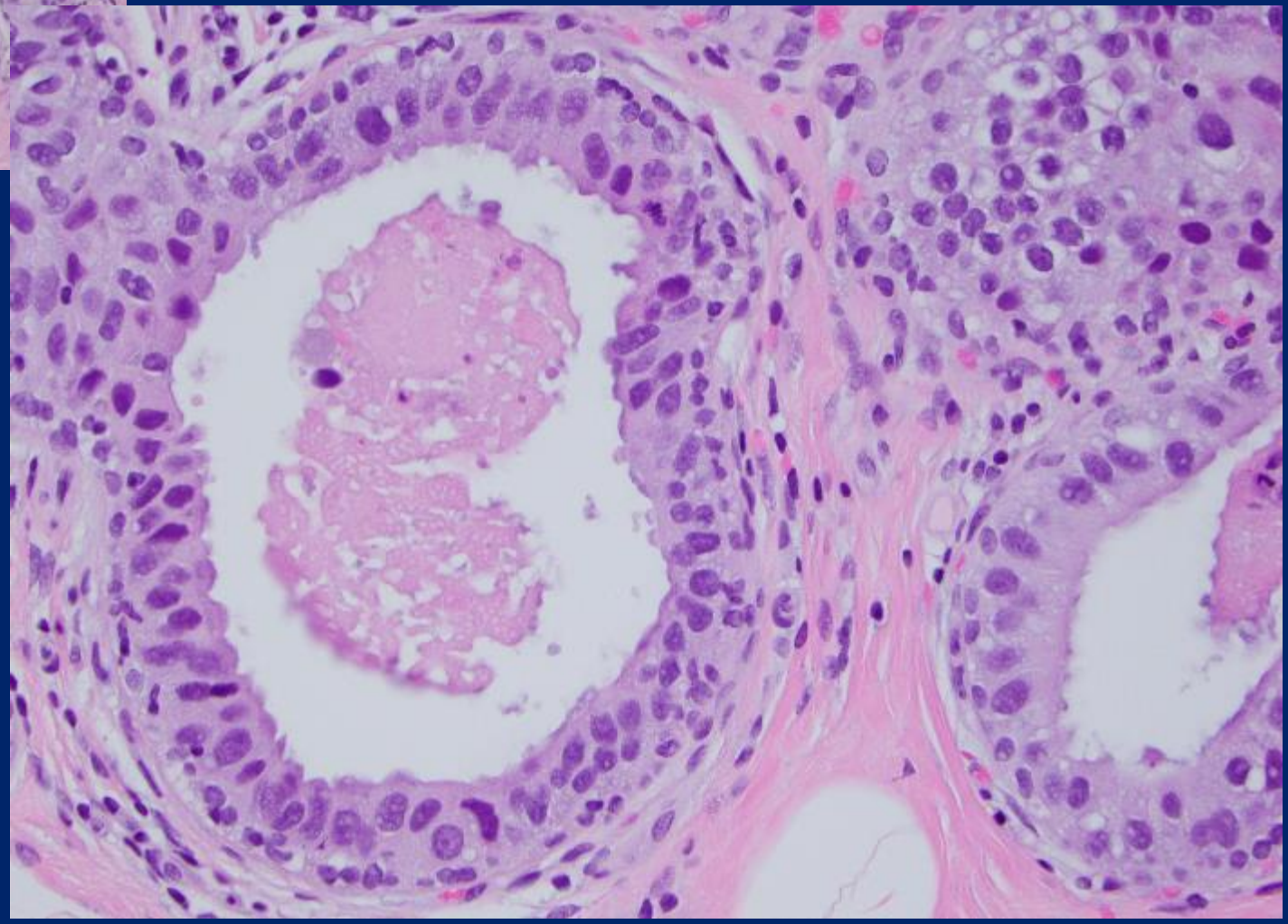
High power



Black arrow: ADH Yellow arrow: FEA



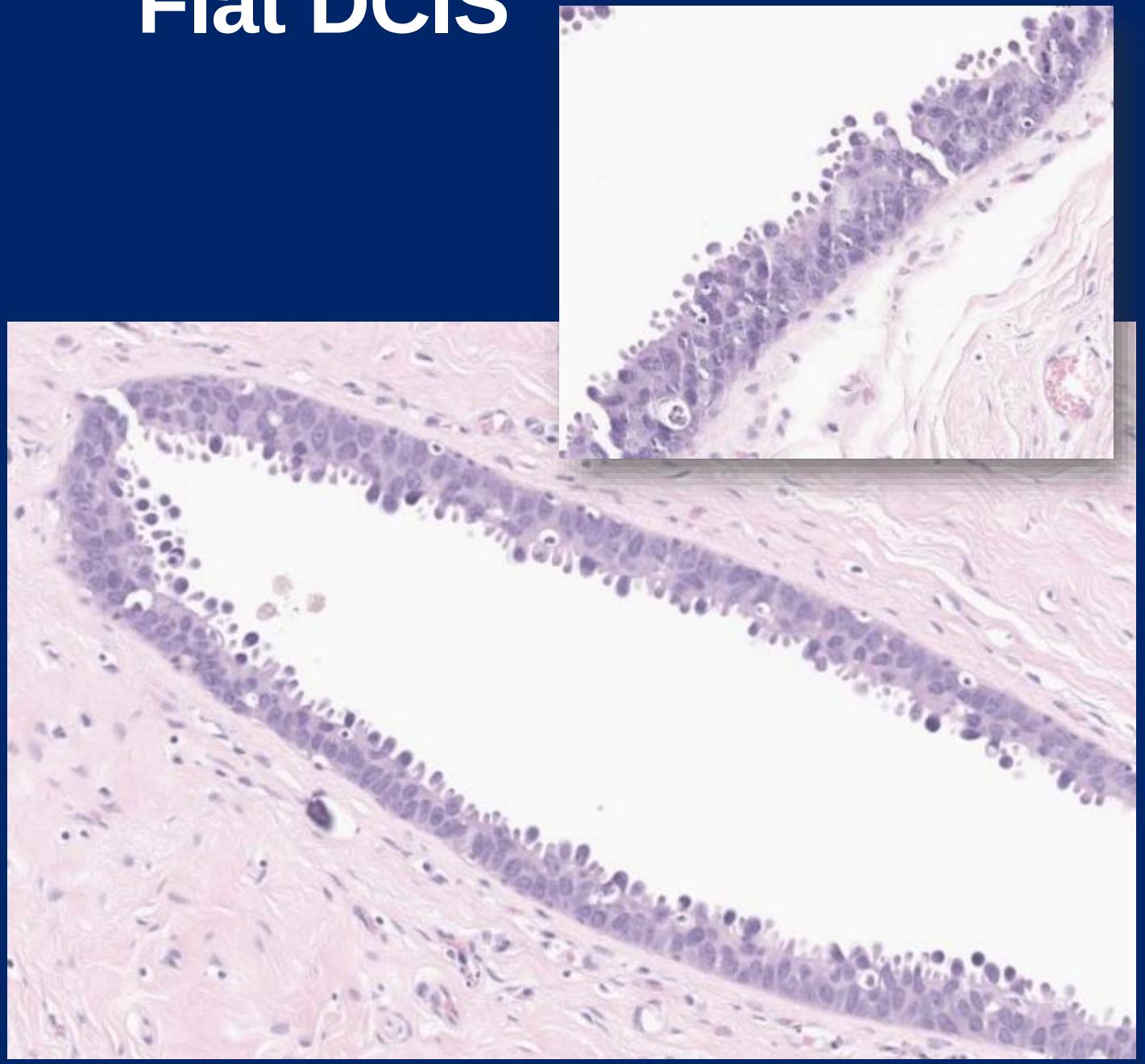
At least ADH

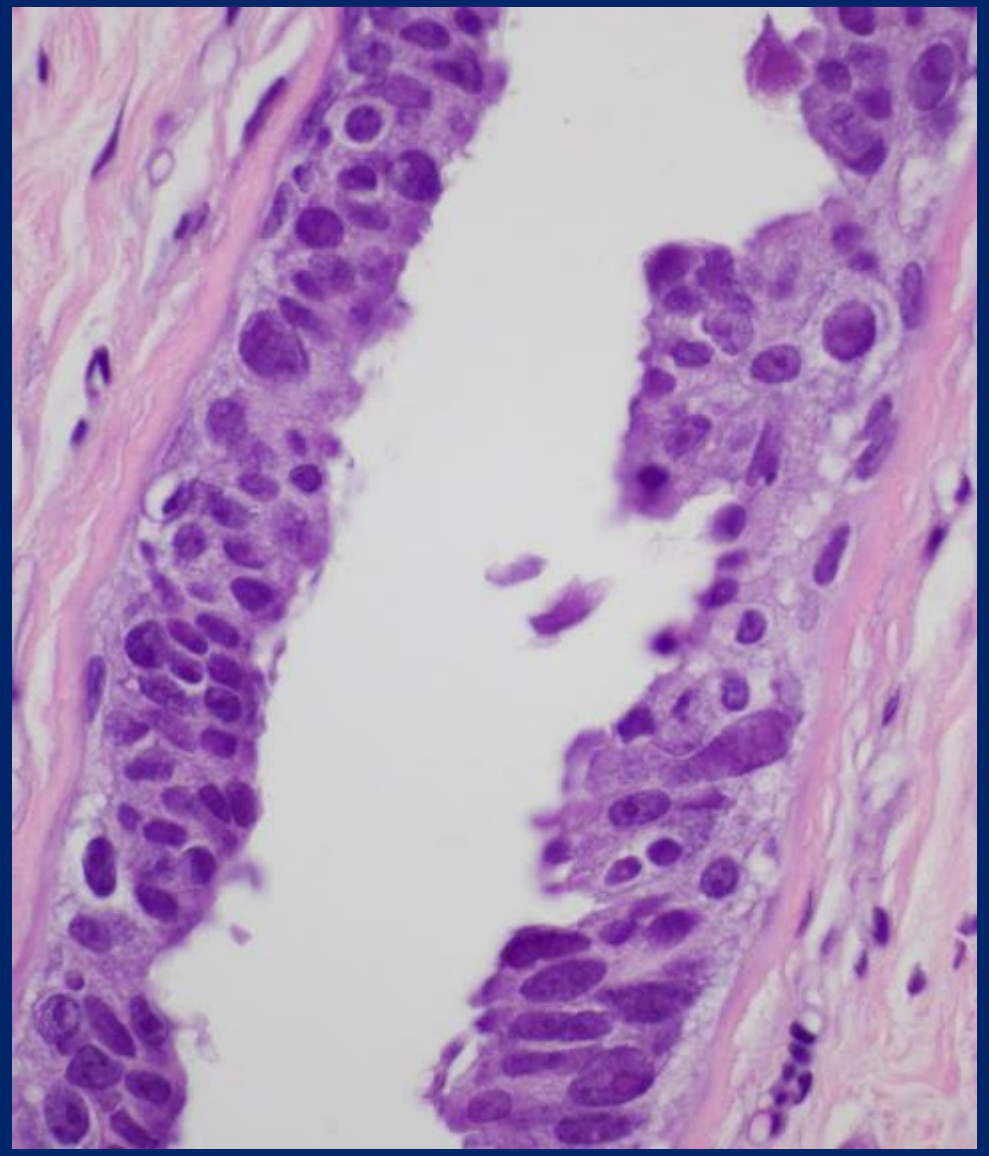


FEA should have only low grade atypia.

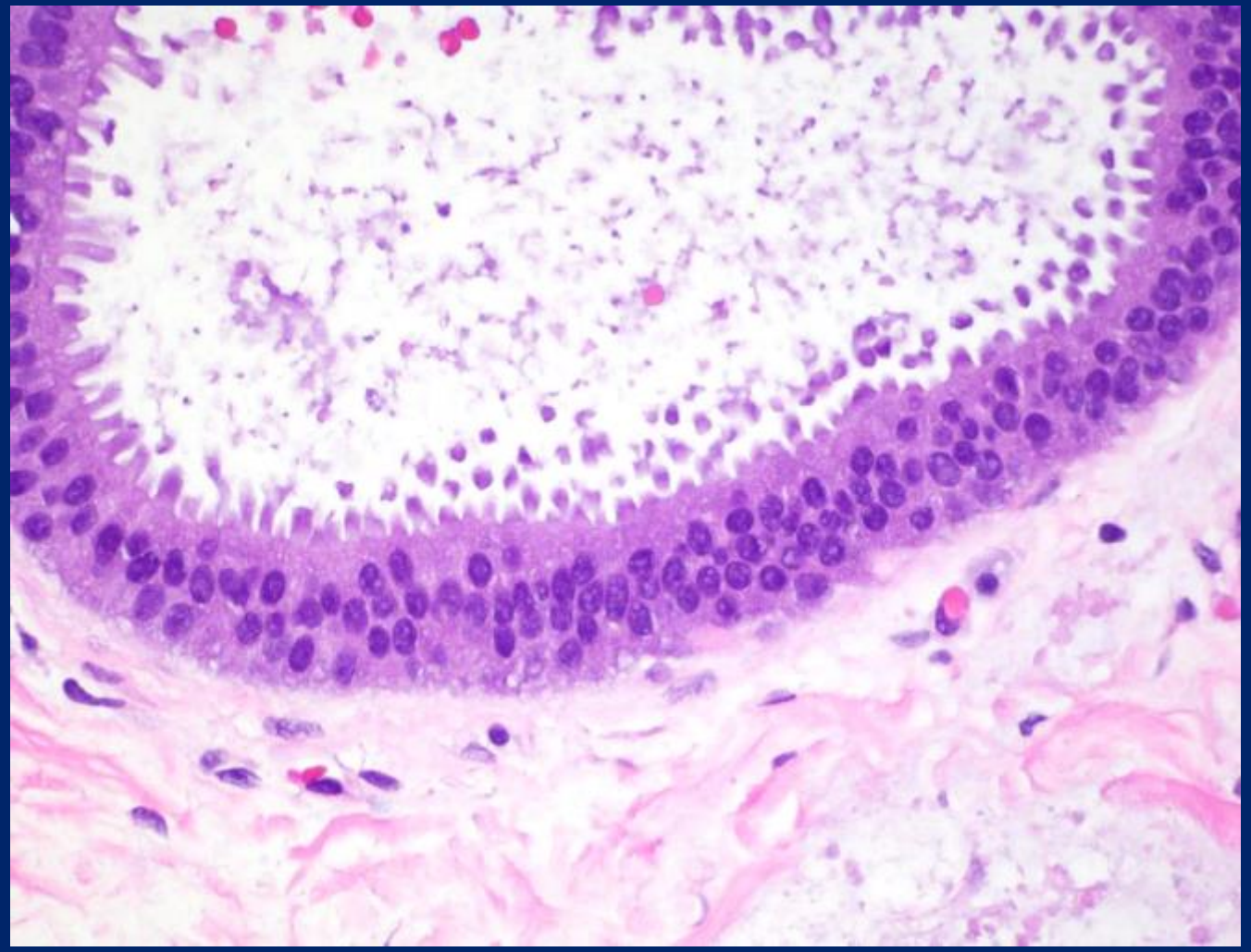
High grade cytologic atypia is not a feature of FEA. The presence of marked atypia should be classified as at least ADH (with marked atypia) or flat DCIS.

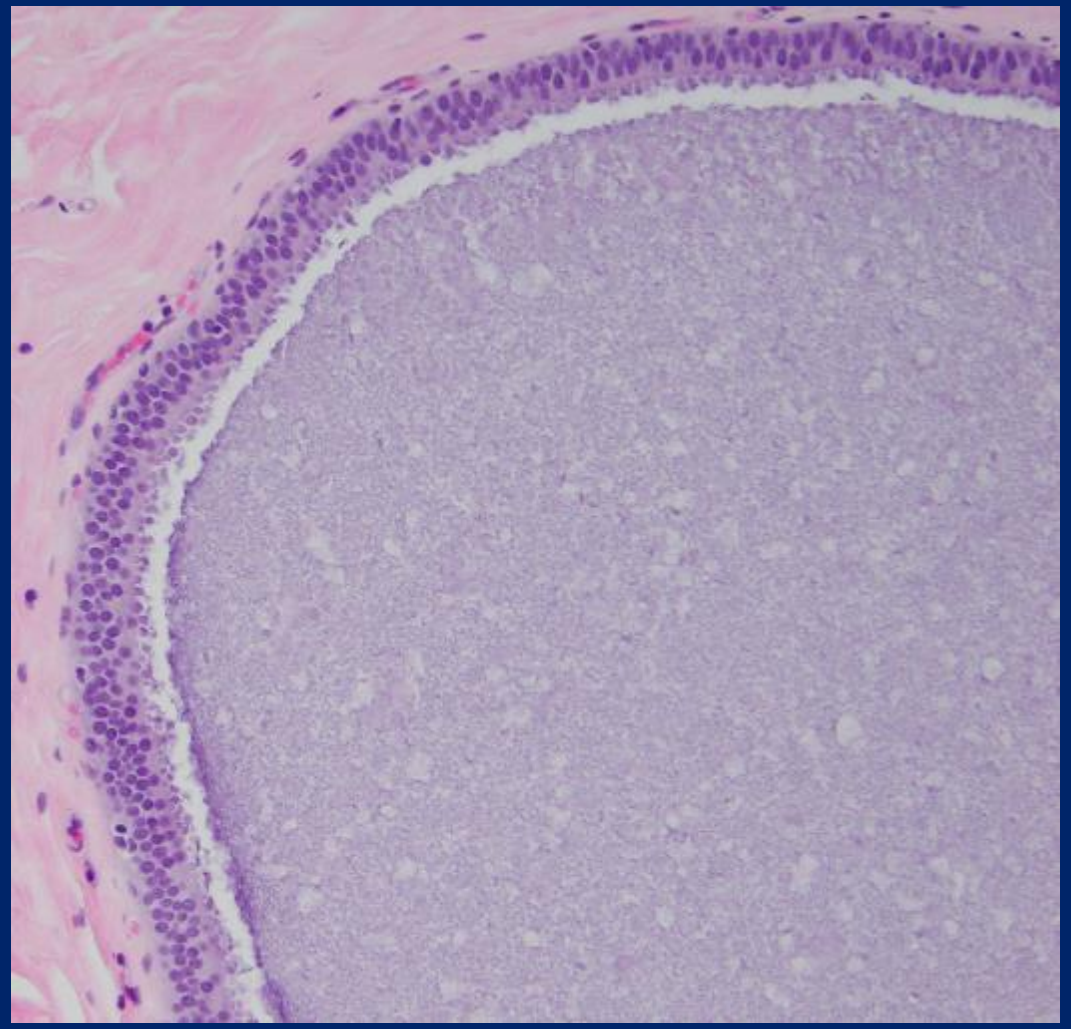
Flat DCIS



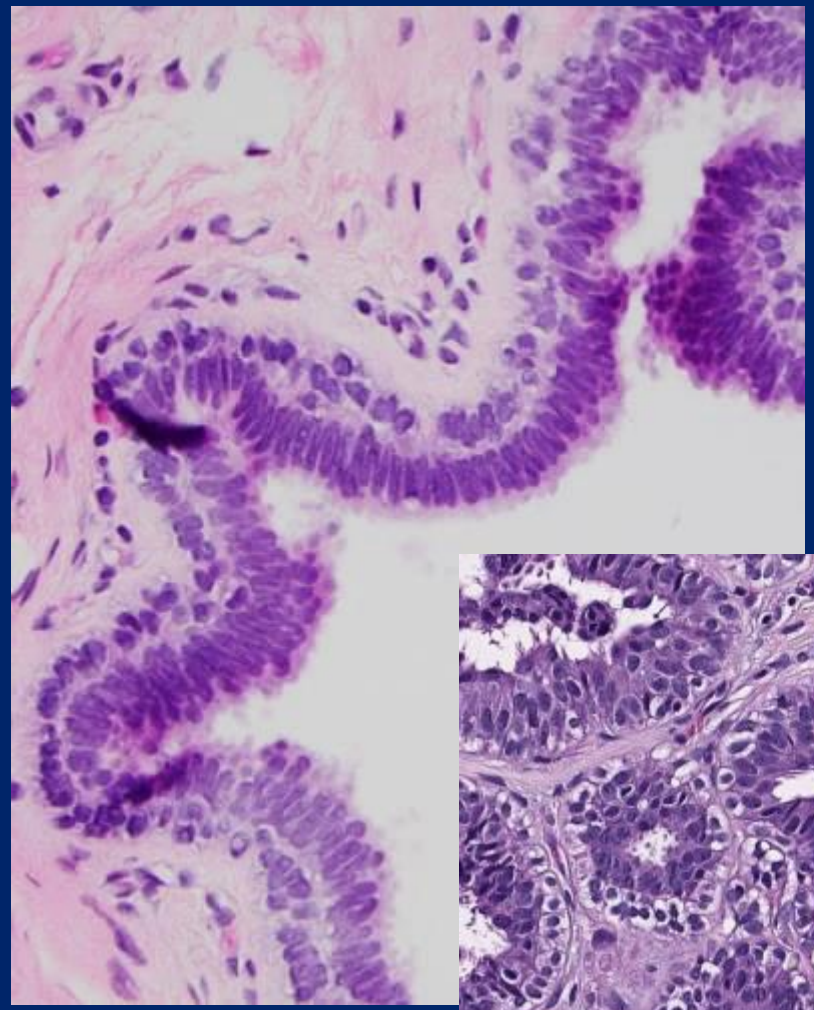


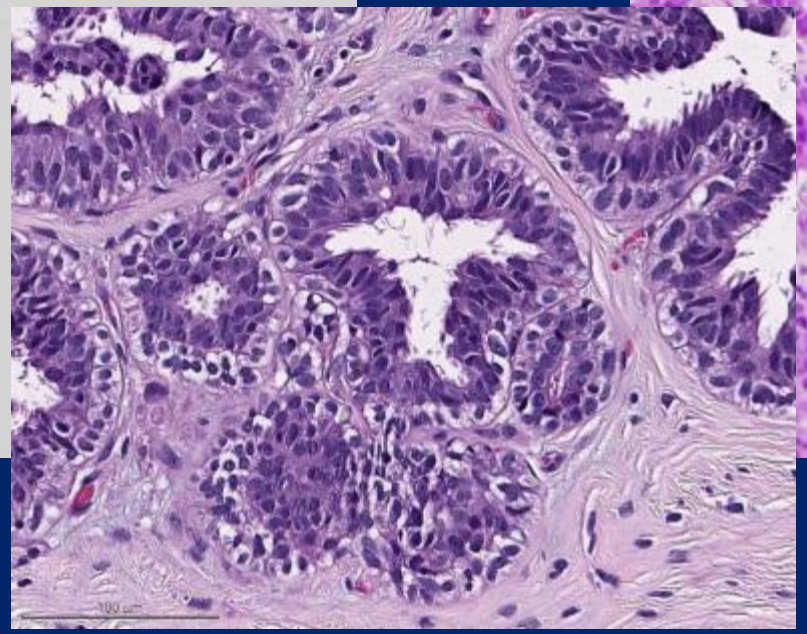
FEA: Attenuated myoepithelial cell layer

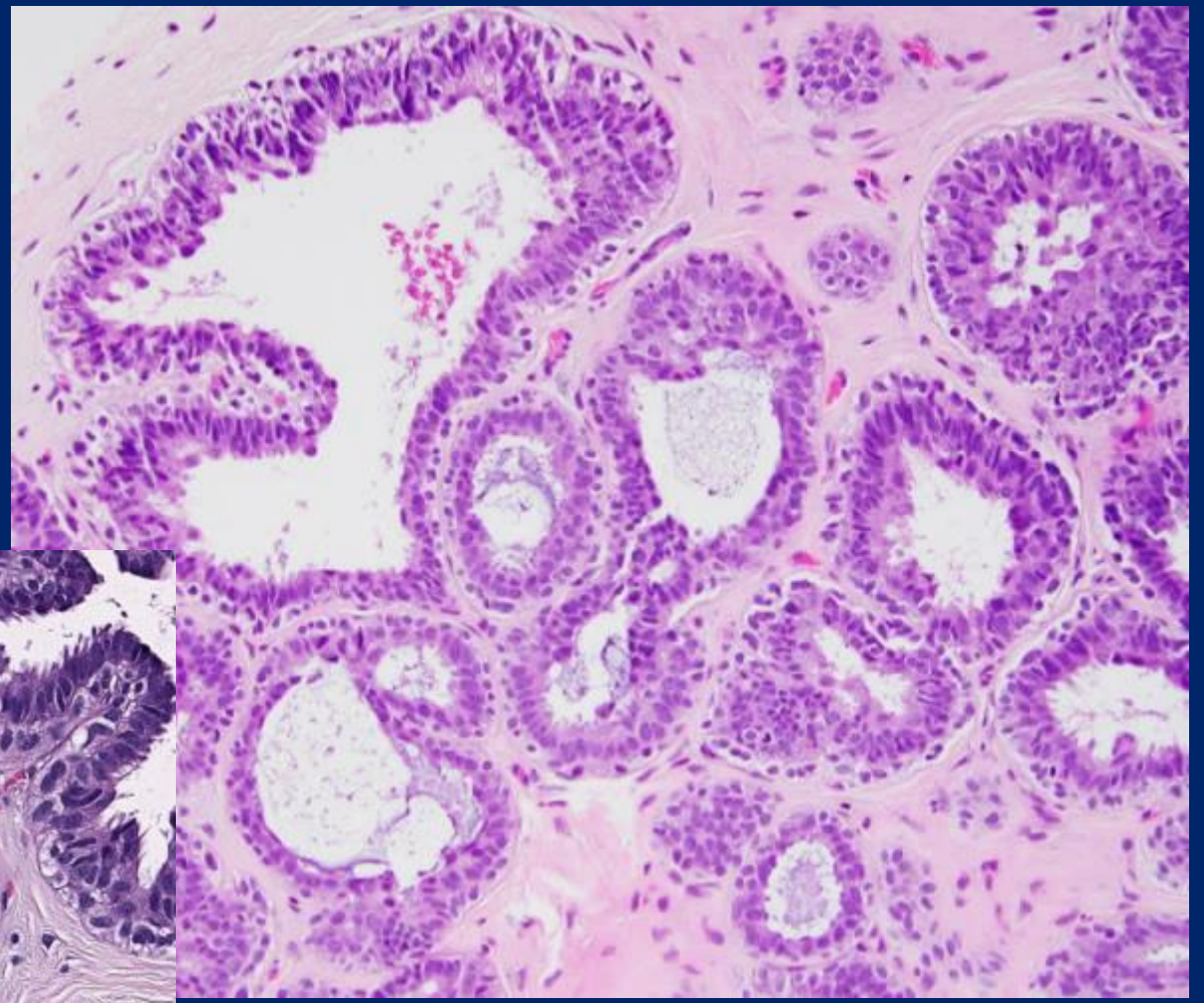




Benign epithelial proliferations







Atypical ductal hyperplasia (ADH)

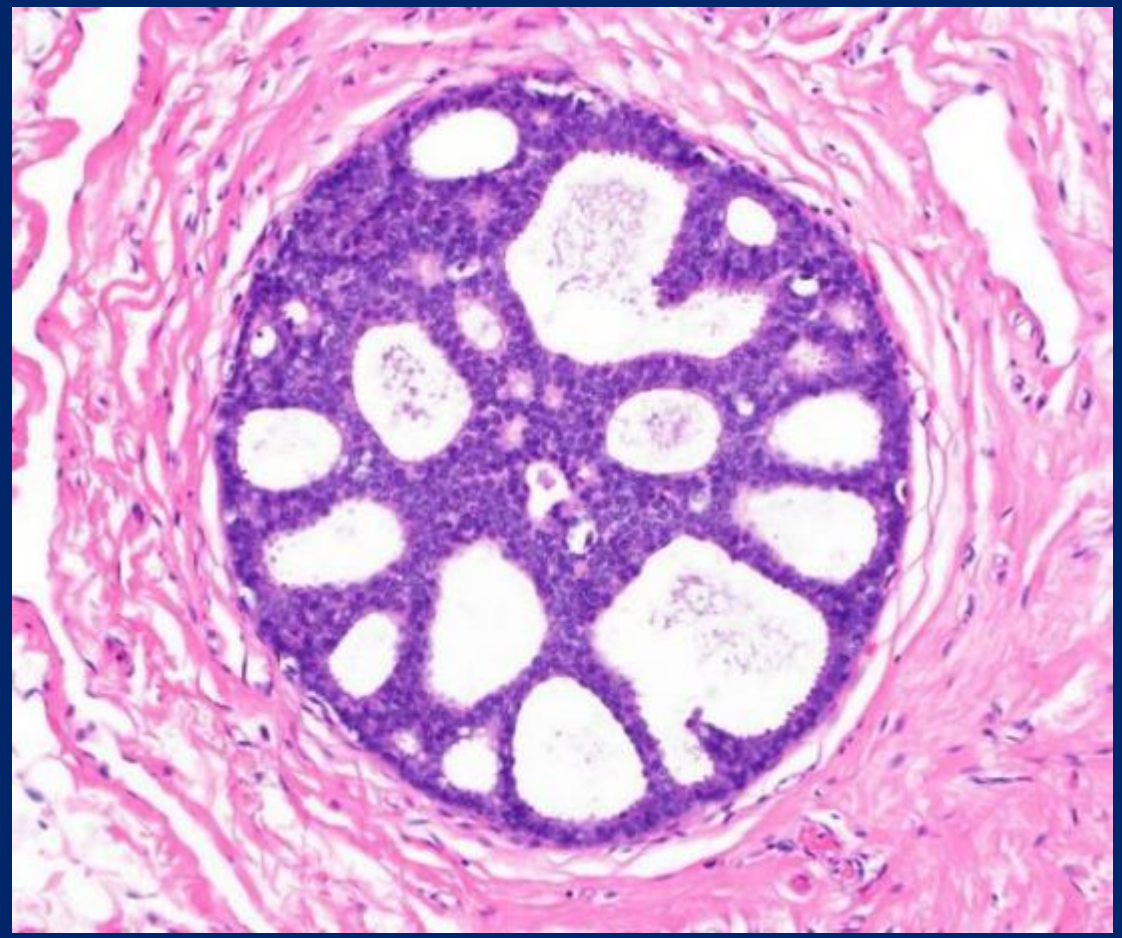
Key Features of ADH

Cytologic Features

- Atypical cells – similar to those seen in low grade DCIS
- Small uniform cells with well defined borders and generally rounded, evenly spaced nuclei

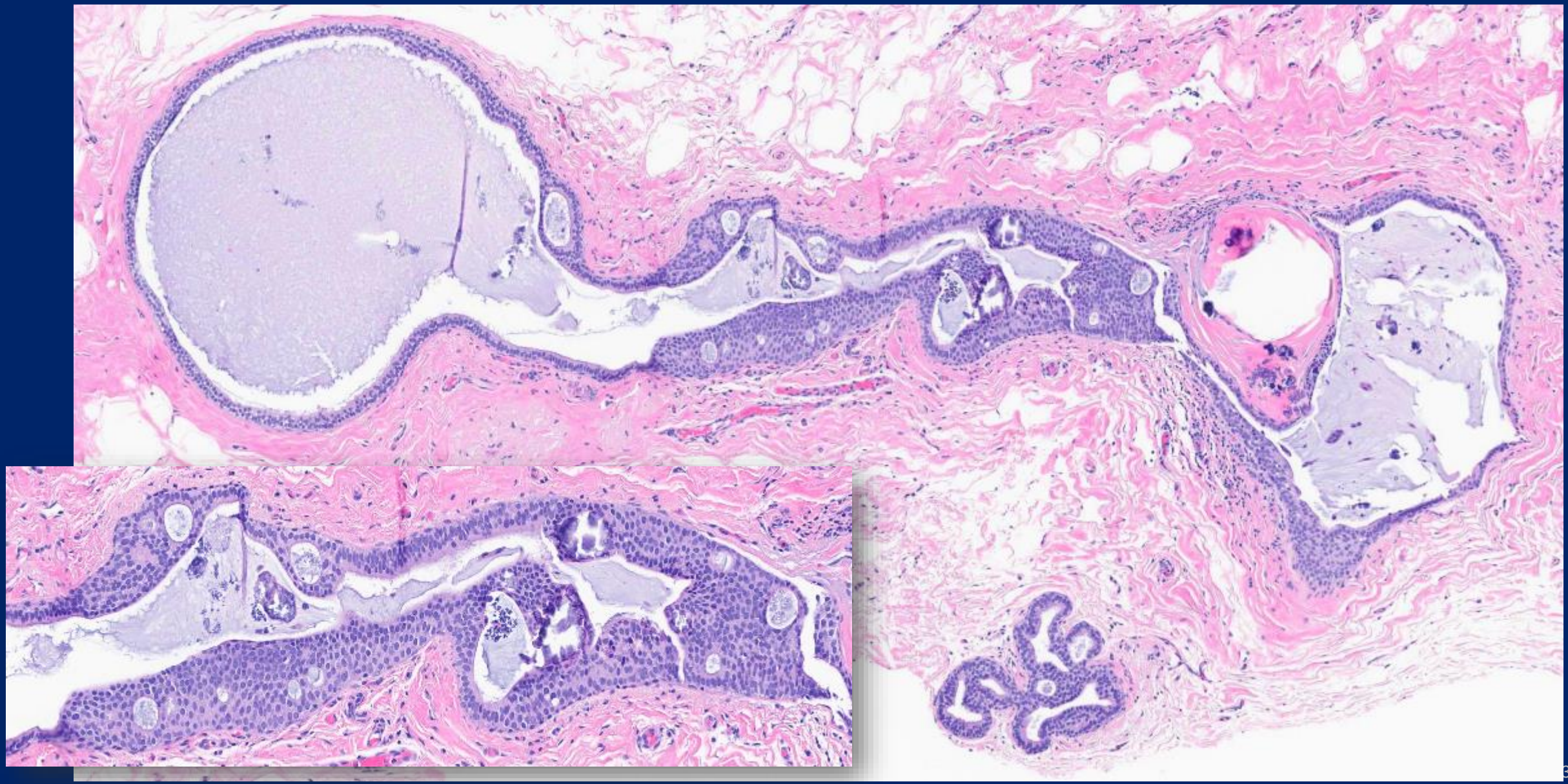
Architectural Features

- Rigid bridges and arcades of uniform thickness
- Cribriform pattern with polarization of cells around lumens
- Solid pattern
- Micropapillations with bulbous tips

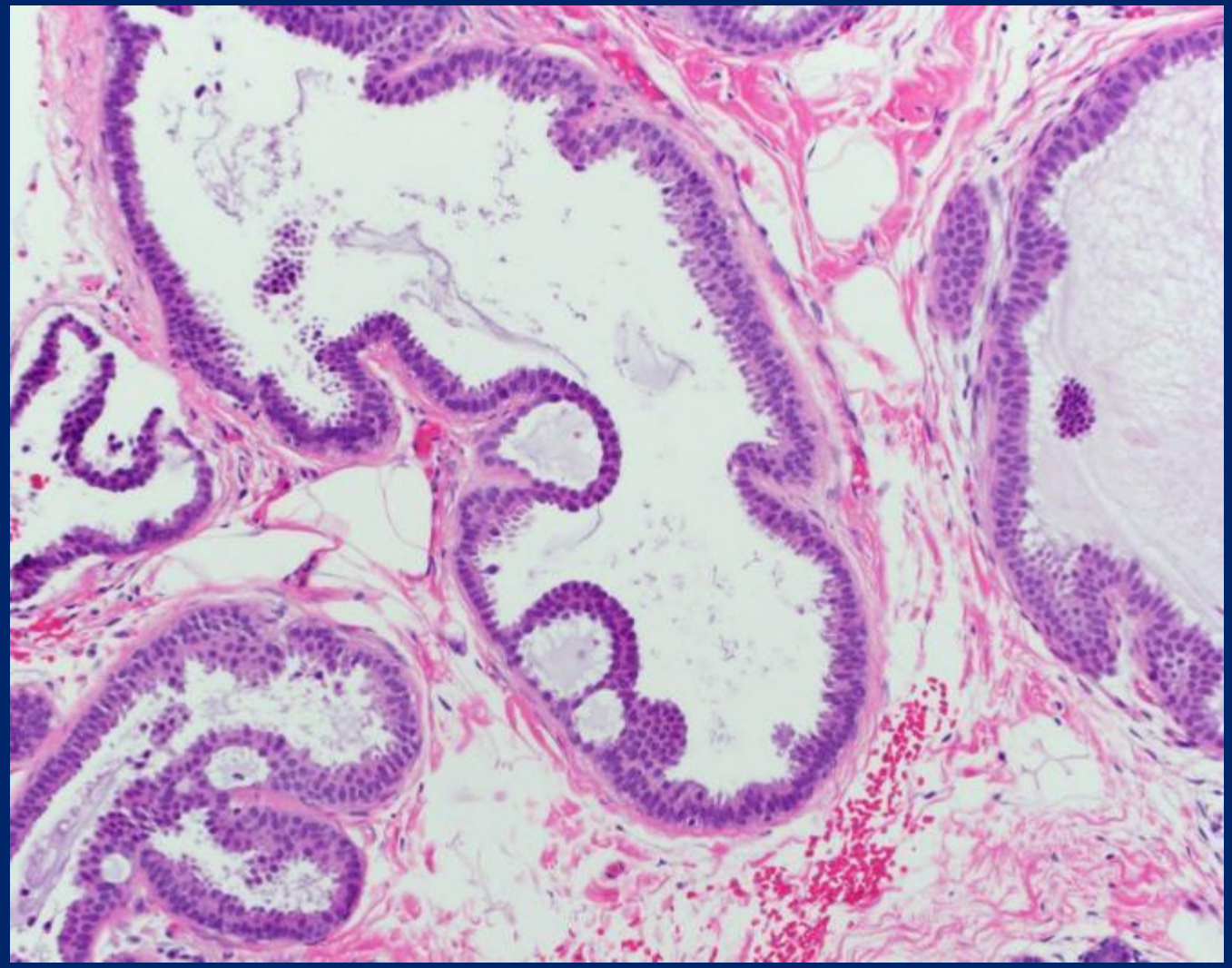


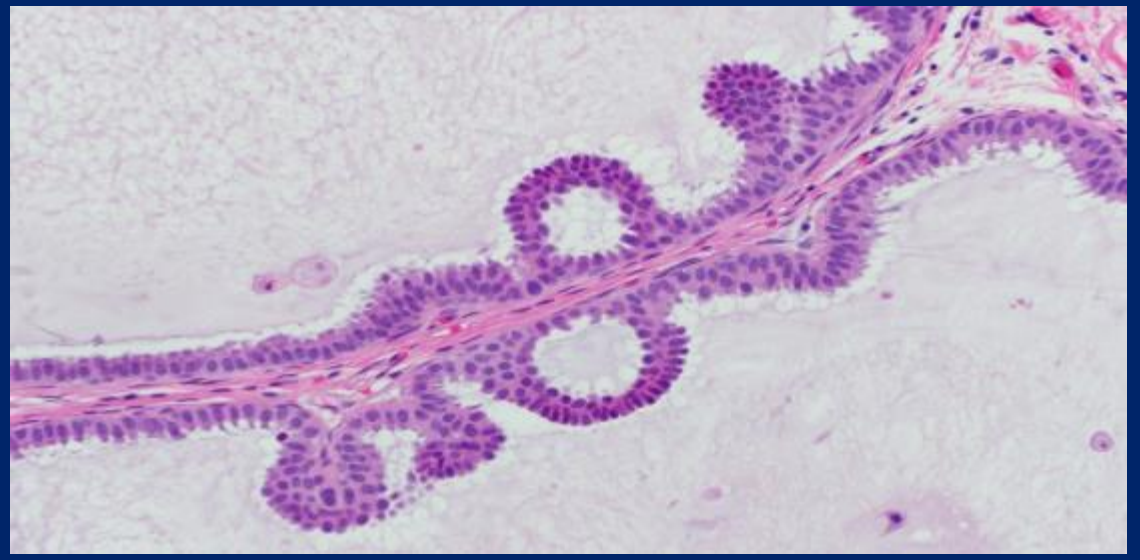
Sapino A, Kulka J, eds. *Breast Pathology*. 1st ed. Springer; 2020.

ADH: Low grade atypia



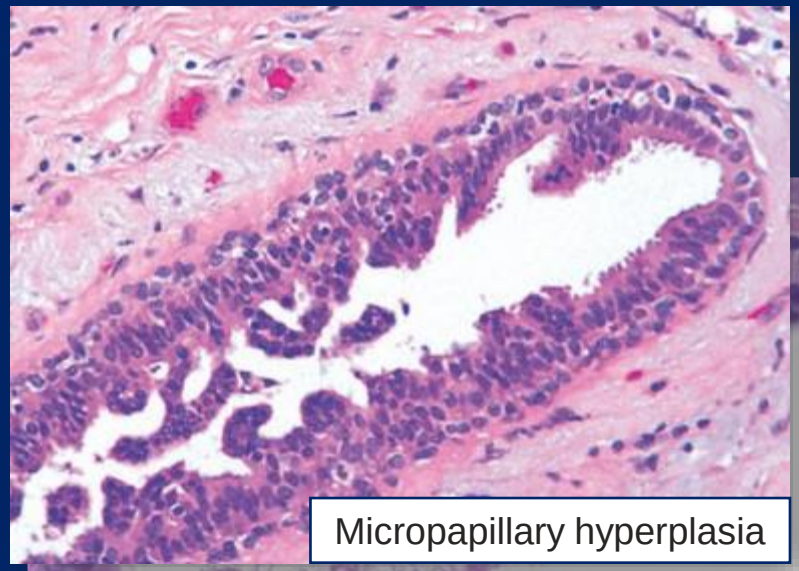
ADH: Rigid arches and bridges



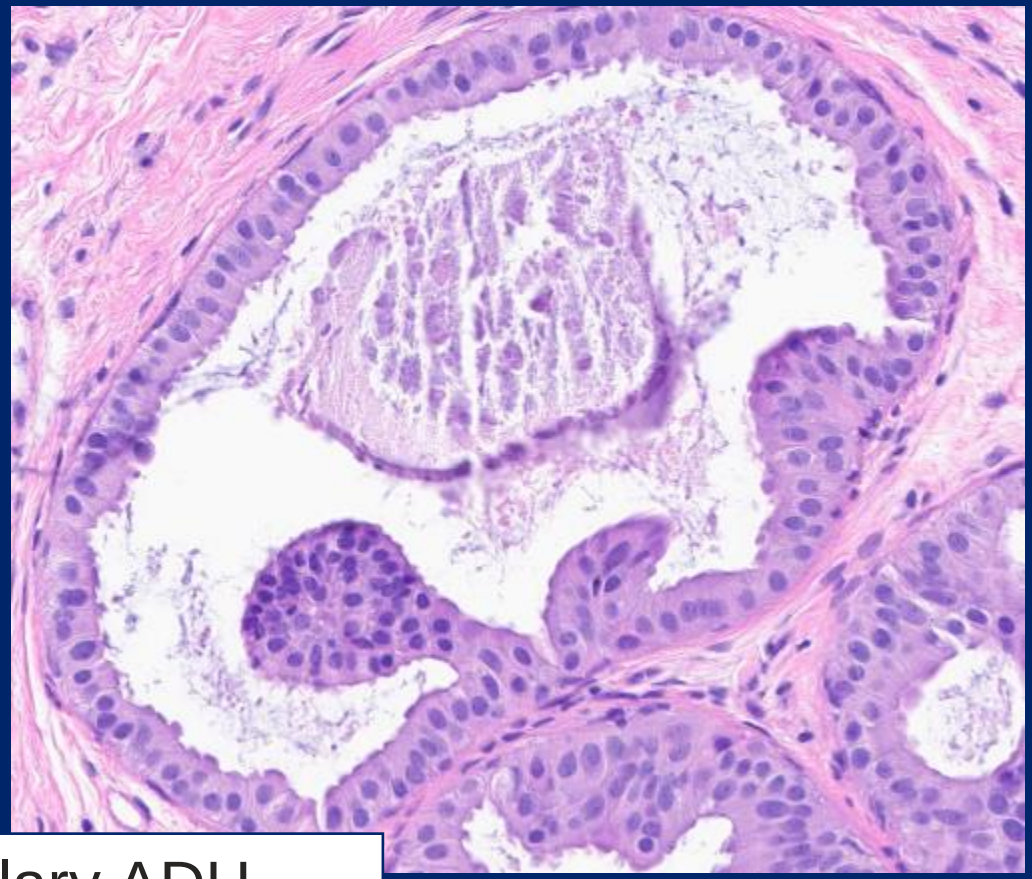


“Roman bridges”

ADH: Micropapillary projections

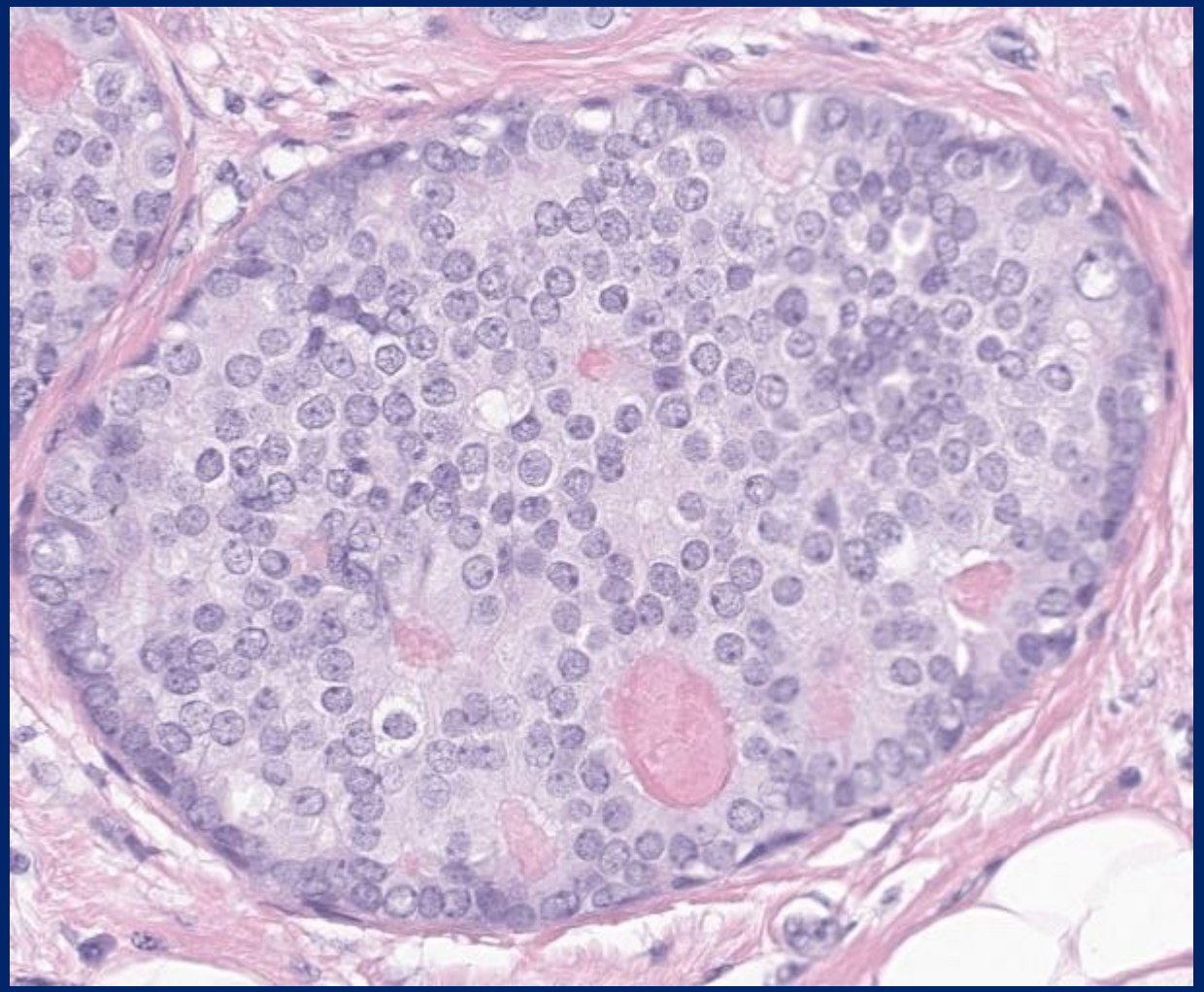


Micropapillary hyperplasia

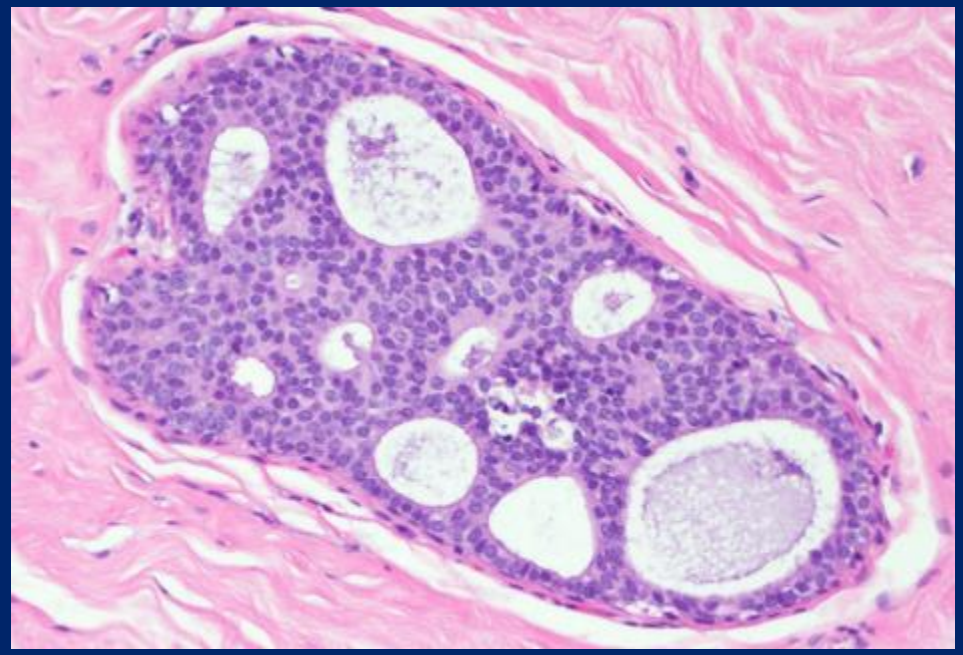


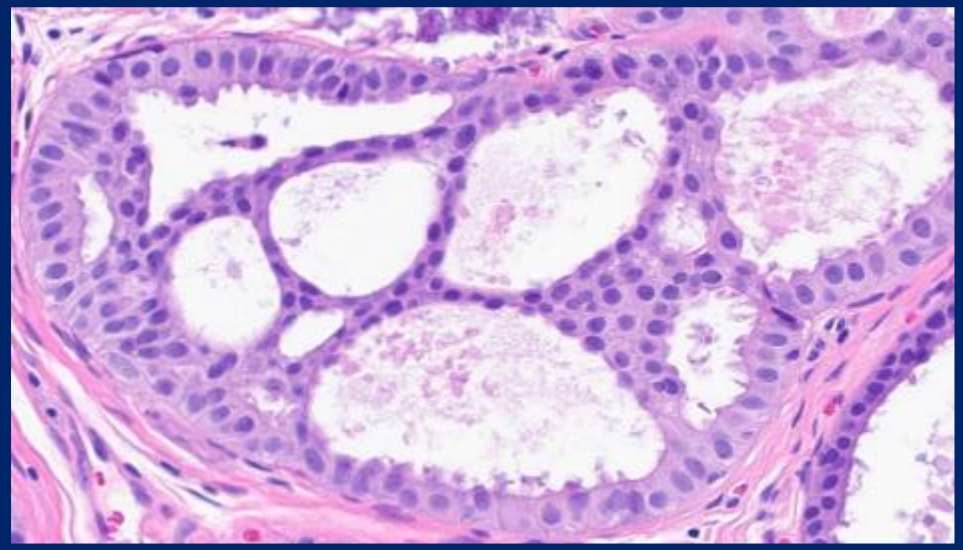
Micropapillary ADH

ADH: Cribriform pattern

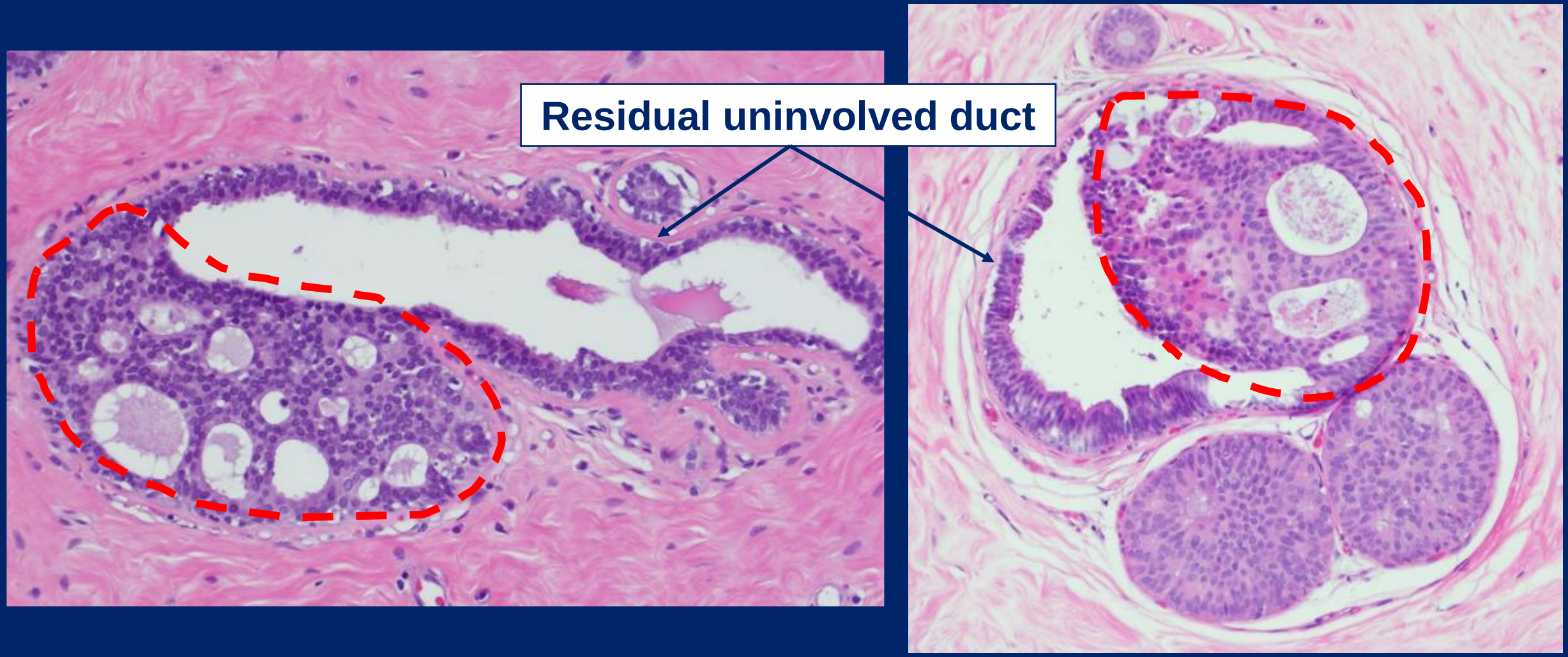


Polarization of cells around lumen

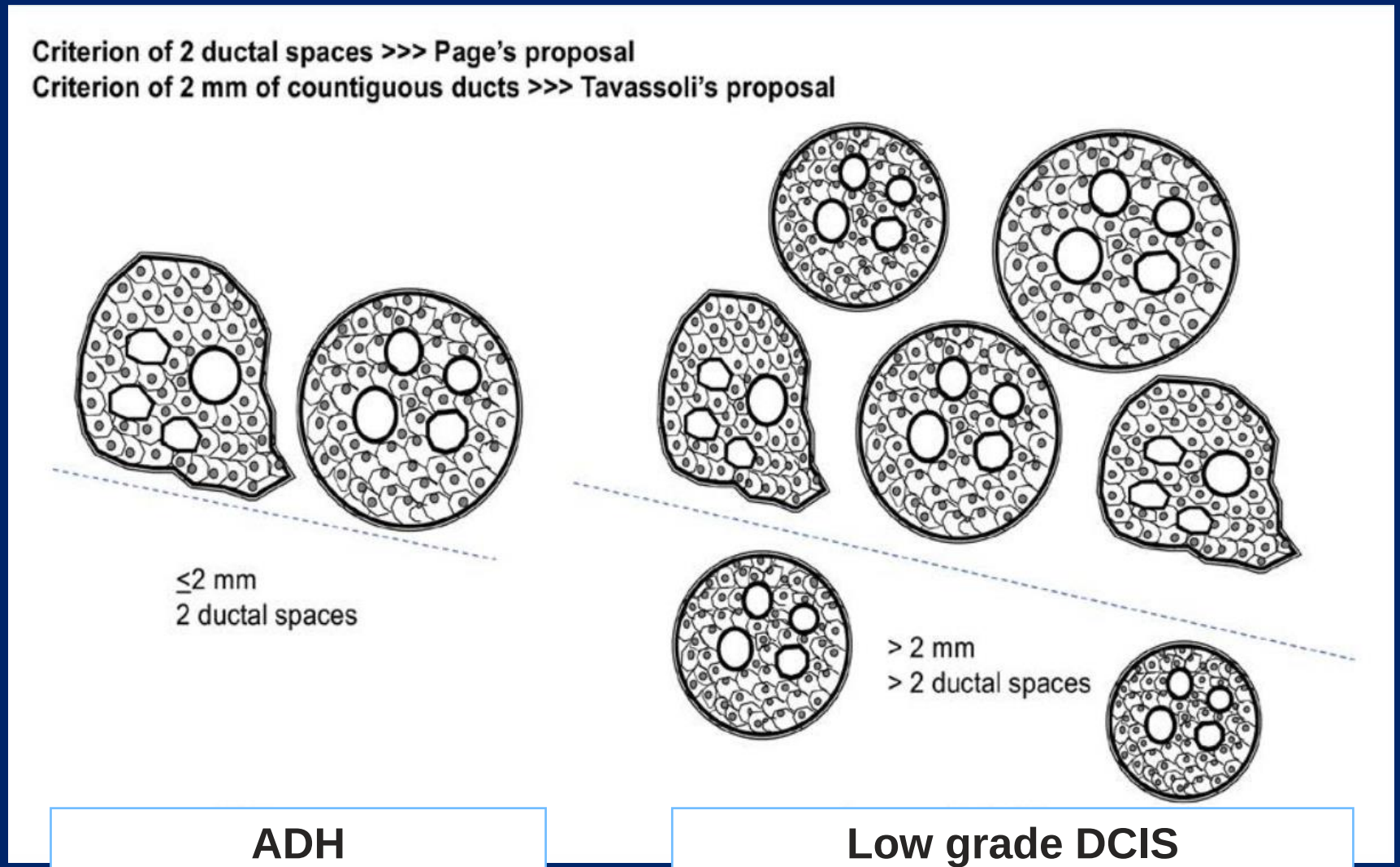




ADH: Partial involvement of ducts by architectural atypia



ADH: Quantitative criteria



Size/Extent: complete involvement of <2 spaces or ≤2 mm in size

Sapino A et al. *Pathologica*, 2021. 113(5): p. 354-359.

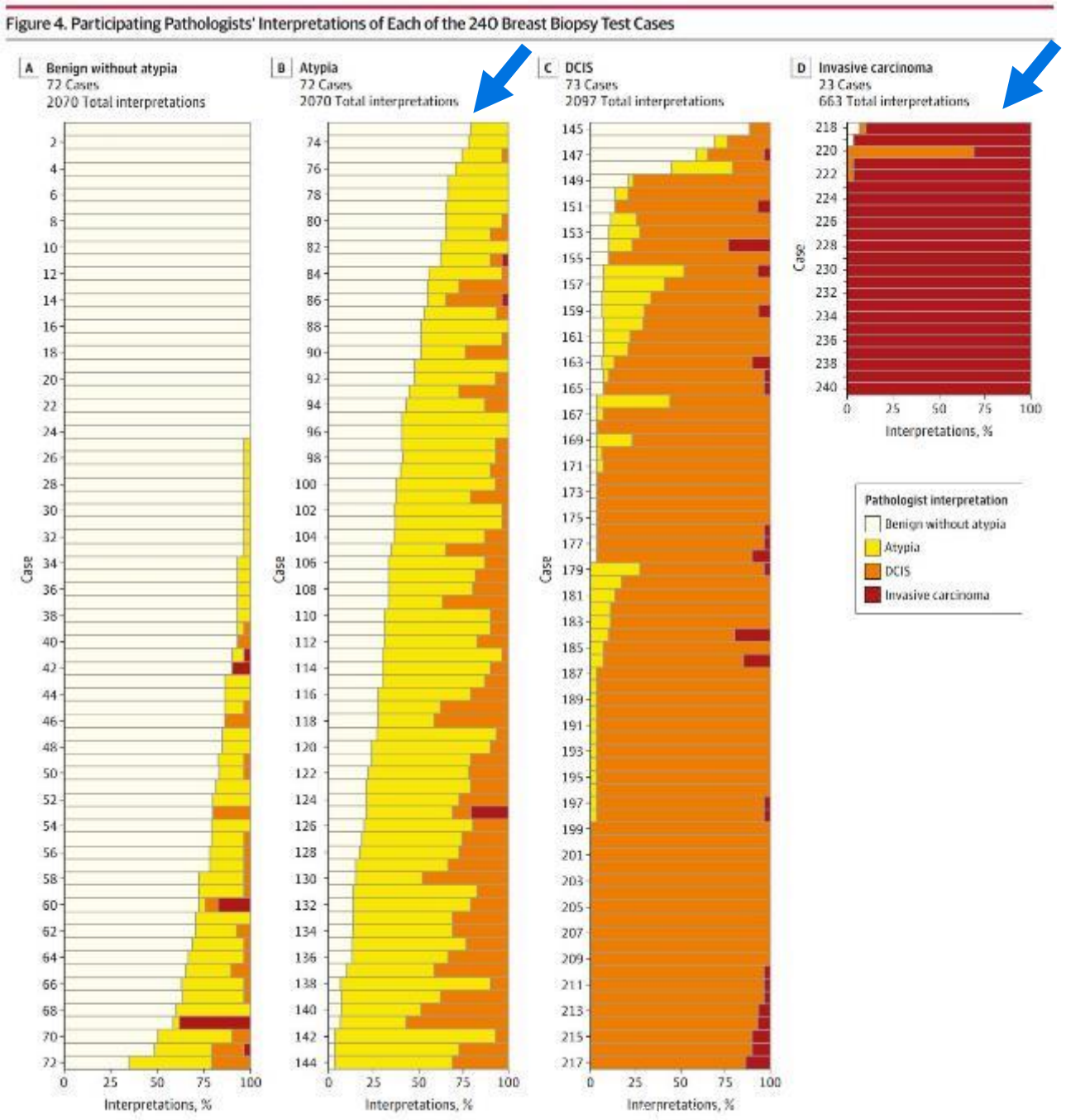
Original Investigation

Diagnostic Concordance Among Pathologists Interpreting Breast Biopsy Specimens

Joann G. Elmore, MD, MPH; Gary M. Longton, MS; Patricia A. Carney, PhD; Berta M. Geller, EdD; Tracy Onega, PhD; Anna N. A. Tosteson, ScD; Heidi D. Nelson, MD, MPH; Margaret S. Pepe, PhD; Kimberly H. Allison, MD; Stuart J. Schnitt, MD; Frances P. O'Malley, MB; Donald L. Weaver, MD

JAMA. 2015;313(11):1122-32.

- 115 participants each interpreted 60 cases
- Participants agreed with the consensus diagnosis in 75.3% of total cases
- Overinterpretation and under-interpretation was not limited to a few cases or a few practicing pathologists but was widely distributed among pathologists and cases
- Pathologists were significantly less likely to agree with the consensus diagnosis if they were from nonacademic settings, those with lower weekly volumes of breast cases and those from small sized practices



ADH vs low grade DCIS: Diagnostic Issues

Consensus Reference Diagnosis	Total, No.	Rate of Overinterpretation or Underinterpretation vs Consensus Diagnosis		Overall Concordance Rate vs Consensus Diagnosis
		Overinterpretation	Underinterpretation	Concordance
Benign without atypia	72	9 (3-13)		91 (87-97)
Atypia	72	12 (7-17)	8 (1-15)	80 (75-87)
DCIS	73	1 (0-1)	2 (0-4)	97 (95-100)
Invasive carcinoma	23		3 (0-4)	97 (96-100)

- Interobserver variability (agreement rates 40-60%)
- Special studies (IHC, molecular) not helpful in distinction
- Criteria variably used by pathologists
  - Involvement of two duct spaces or 2 mm (developed on excisional biopsy)
  - Practical guidelines
  - Combination of criteria often used

Elmore JG et al. *JAMA*. 2015;313(11):1122-32.

WHO Guide to Evaluation of Atypia in Intraductal Proliferations

STEP 1: Evaluate the cytology

Is a population present with low grade monotony?

STEP 2: Evaluate the architecture

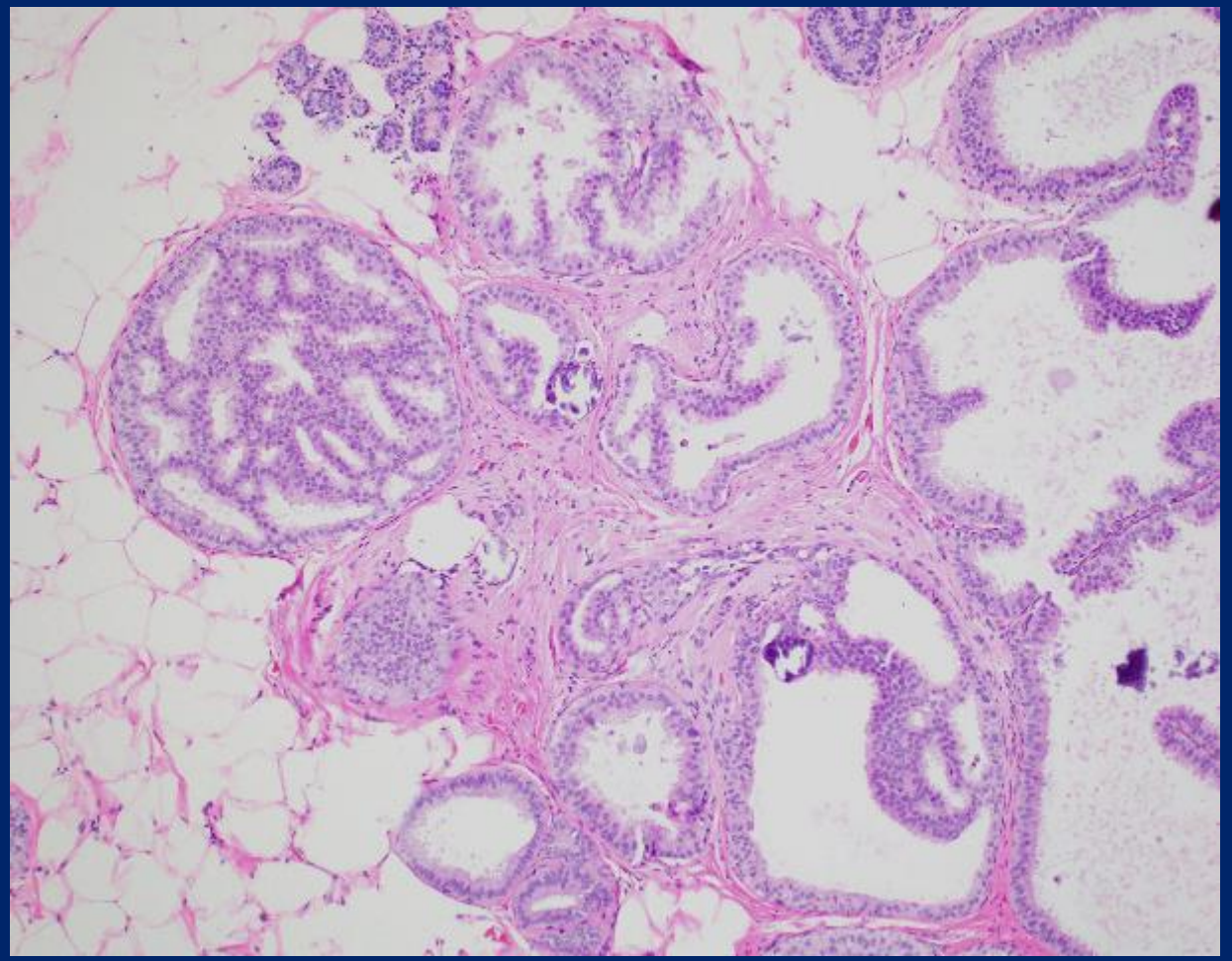
Are there neoplastic architectural features present?

- ❑ Rigid bridges, arches
- ❑ Bulbous micropapillae
- ❑ Polarized spaces or microacini
- ❑ Solid (but E-cadherin positive)

STEP 3: Evaluate extent

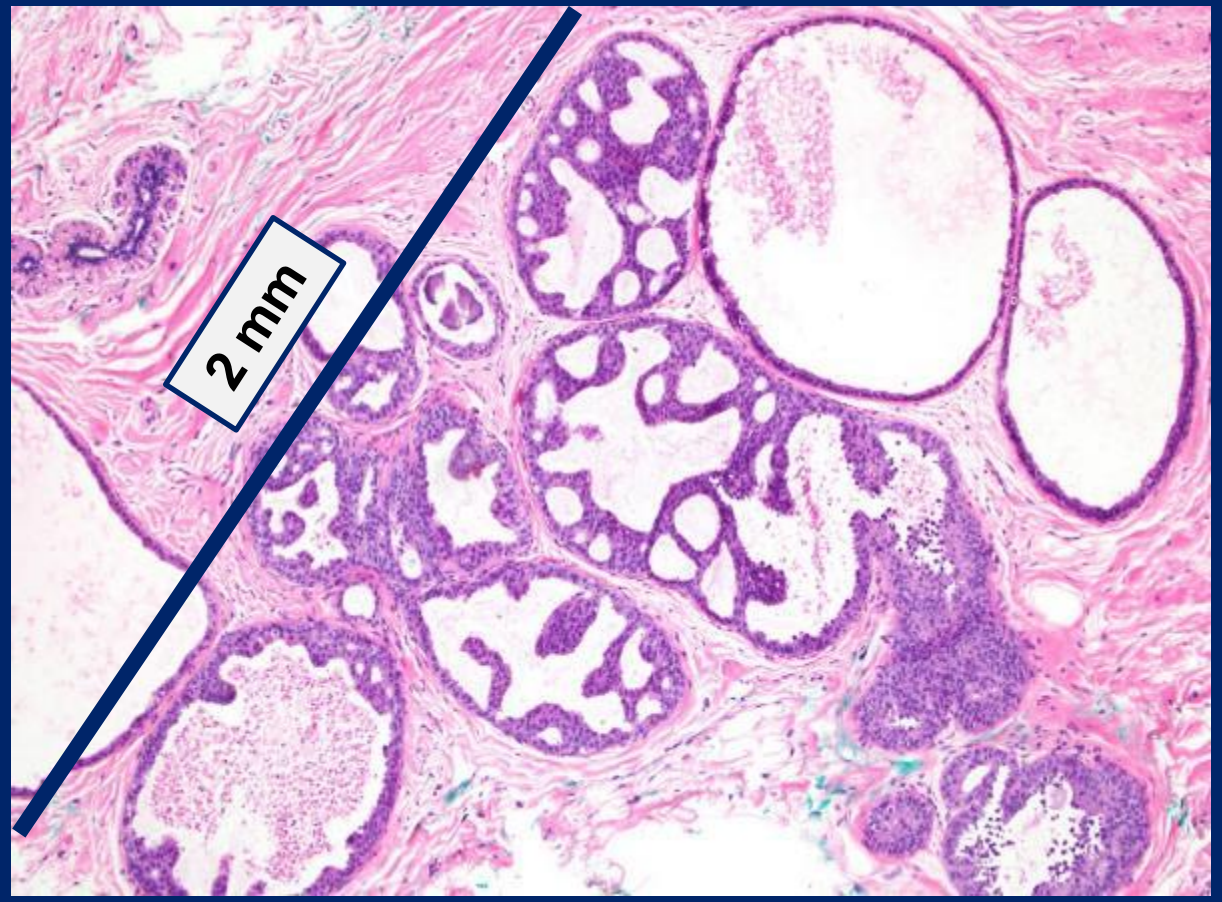
Either of the following true:

- ❑ Non-uniform involvement of duct spaces
- ❑ Uniform involvement of duct spaces but $\leq$ 2 mm

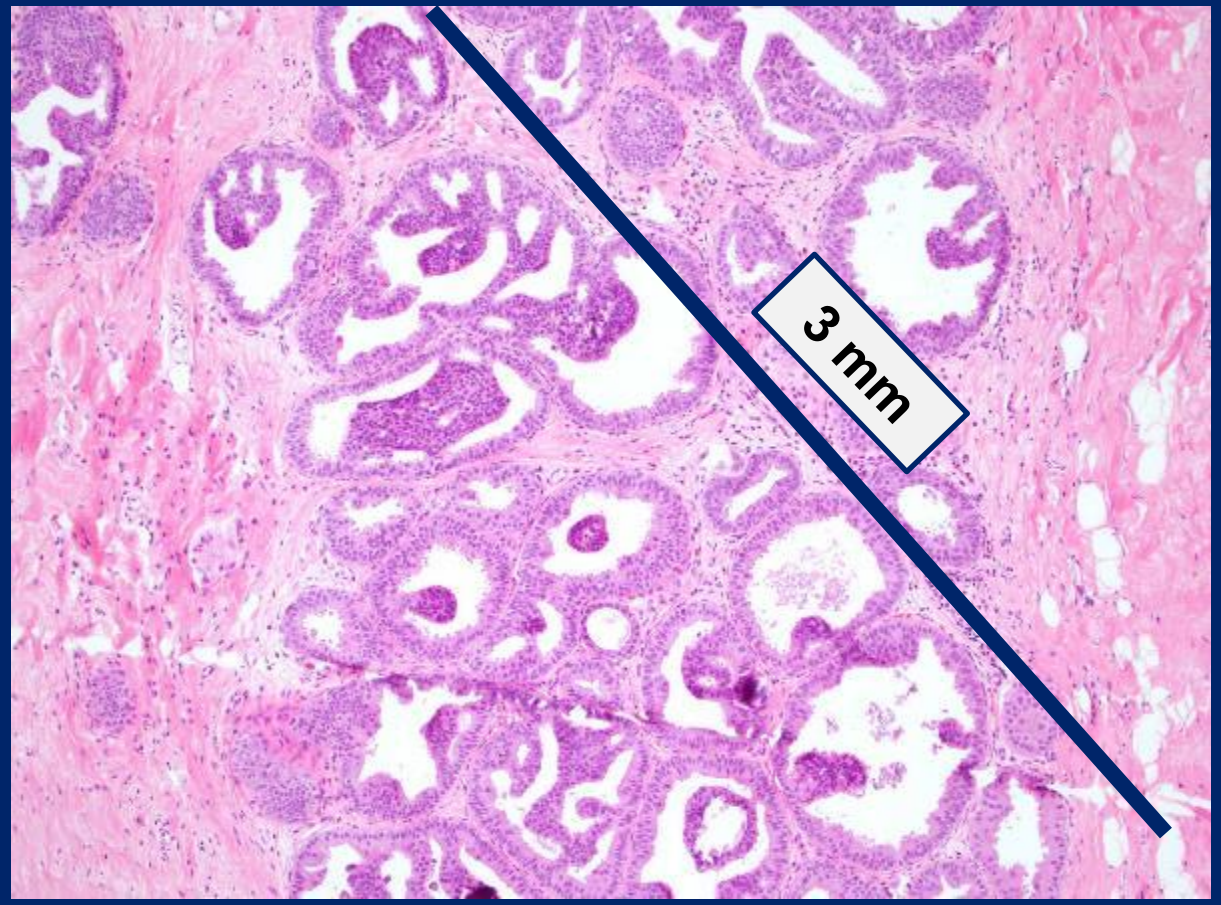


Lokuhetty D, White VA, Watanabe R, Cree IA. *WHO Classification of Tumours Editorial Board. Breast tumors.* IARC, Lyon; 2019.

ADH: Diagnostic Dilemmas



“Borderline lesion”



ADH spanning 3 mm

ADH v DCIS: Clinical Management

ADH bordering on DCIS

?

High risk lesion: ADH

Excision to rule out underlying malignancy
+
Endocrine therapy for risk reduction

Cancerous lesion: DCIS

Excision to negative margins
+
Endocrine therapy if ER+
+/-
Radiotherapy

Subtle pathologic differences → major treatment differences

Original Article

Atypical Ductal Hyperplasia Bordering on Ductal Carcinoma In Situ: Interobserver Variability and Outcomes in 105 Cases

International Journal of Surgical Pathology
2017, Vol. 25(2) 100–107

DOI: 10.1177/1066896916662154
journals.sagepub.com/home/ijs
SAGE

Gary Tozbikian, MD[1], Edi Brogi, MD, PhD[1], Christina E. Vallejo, MD[1], Dilip Giri, MD, FCAP[1], Melissa Murray, DO[1], Jeffrey Catalano, BA[1], Cristina Olcese, BS[1], Kimberly J. Van Zee, MS, MD, FACS[1], and Hannah Yong Wen, MD, PhD[1]

- 5 specialized breast pathologists reviewed 105 “borderline” cases and reclassified each as either: benign, ADH or DCIS
- Majority diagnosis (MajDx) for each case reflects agreement by ≥3 pathologists
  - ADH: 80% (84/105)
  - DCIS: 17% (18/105)
  - 3% (3/105) – no majority diagnosis
- Diagnostic agreement among all 5 pathologists in 30% of cases

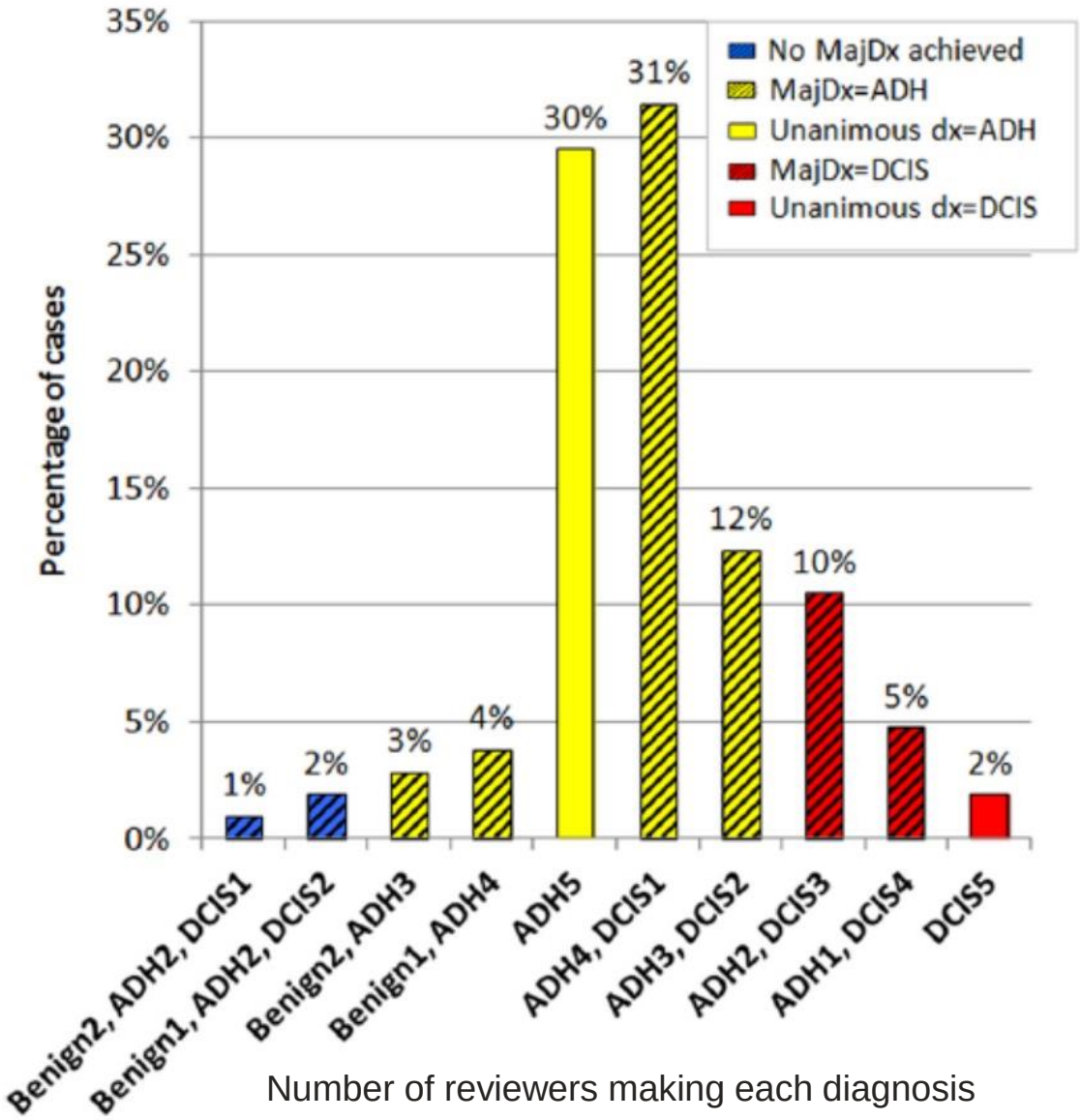
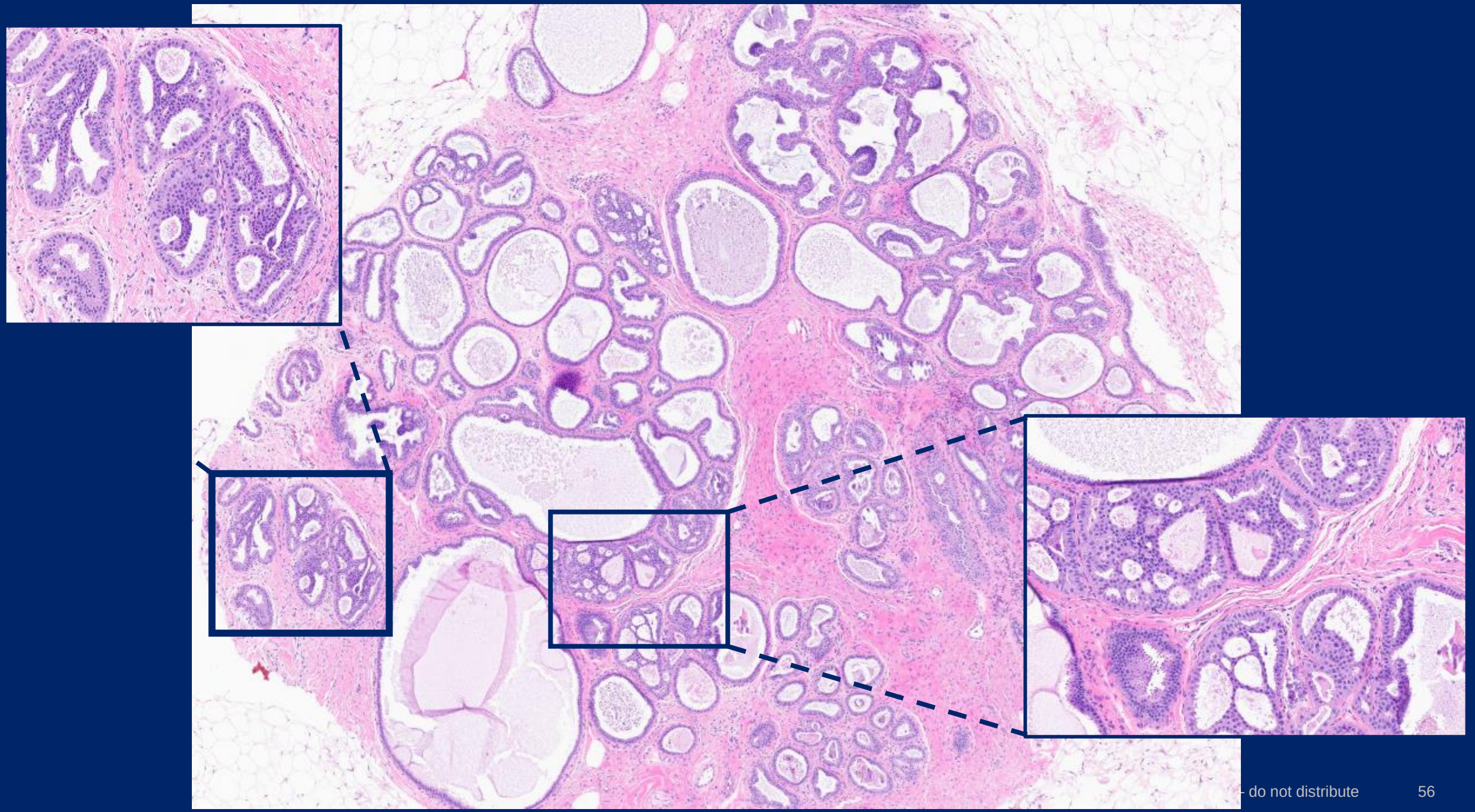


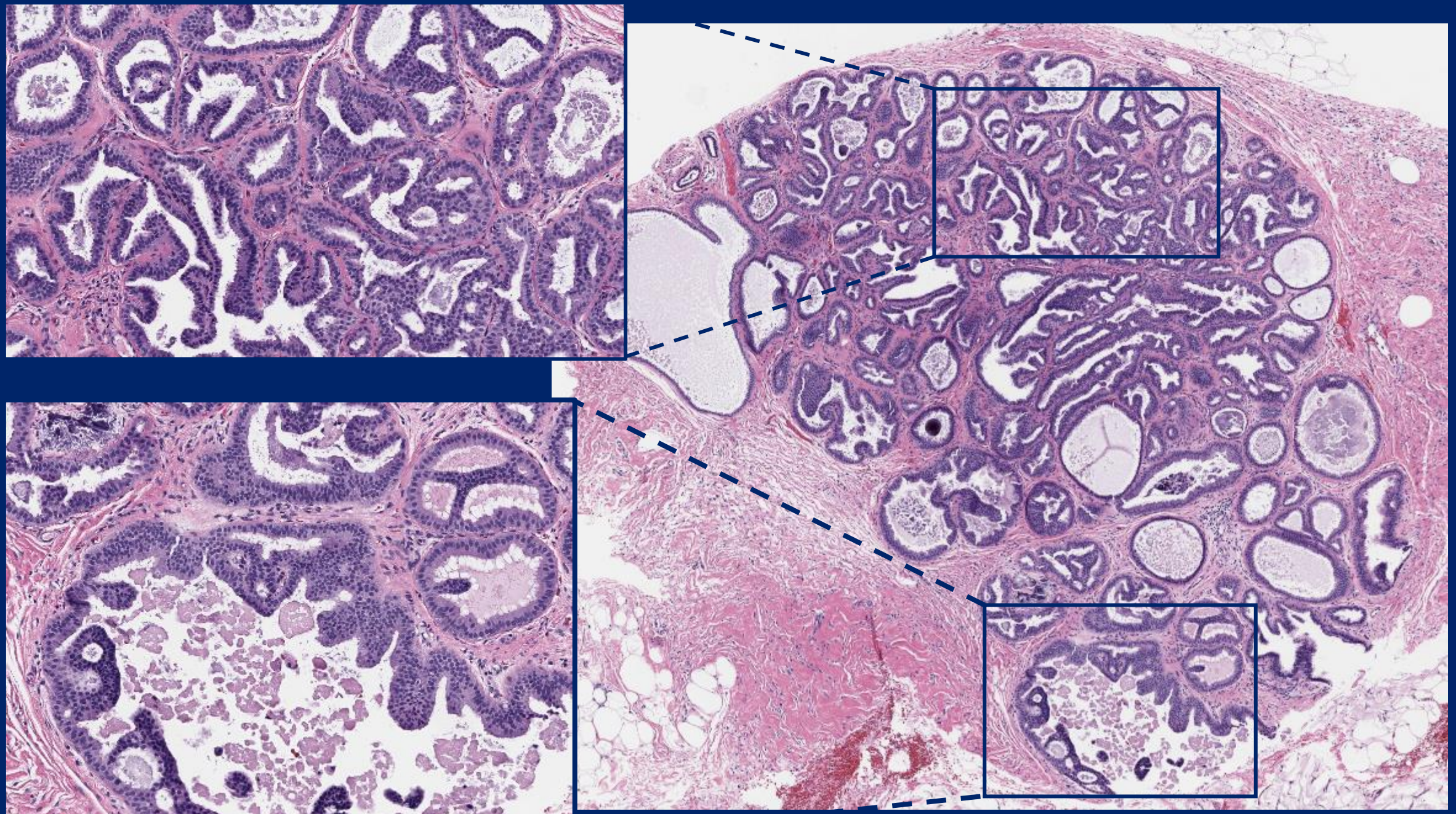
Table 2. Pathologic Features of Cases in Entire Population and Comparison Between Cases With MajDx of ADH and DCIS.

	Entire population (n = 105),[a] n (%)	MajDx ADH (n = 84), n (%)	MajDx DCIS (n = 18), n (%)	*P*
Size, mm, mean (95% CI)	2.48 (2.13-2.83)	2.30 (1.94-2.66)	3.26 (2.12-4.40)	.04
Size, mm				.03
≤2	67 (64)	58 (69)	7 (39)	
>2	38 (36)	26 (31)	11 (61)	
No. of involved ducts				.12
1	15 (14)	14 (17)	0 (0)	
2	8 (8)	7 (8)	1 (6)	
>2	82 (78)	63 (75)	17 (94)	
Nuclear grade				.03
1	89 (85)	74 (88)	12 (67)	
1-2	16 (15)	10 (12)	6 (33)	
Calcifications in lesion	61 (58)	51 (61)	9 (50)	.44
Classic LCIS or ALH	35 (33)	25 (30)	10 (56)	.05

At median follow up of 37 months, 4 patients developed ipsilateral carcinoma (2 invasive, 2 DCIS).
All 4 had majority diagnosis of ADH.

Categorization of challenging borderline ductal lesions remains variable.
No histologic feature can predict the risk of breast carcinoma among these patients



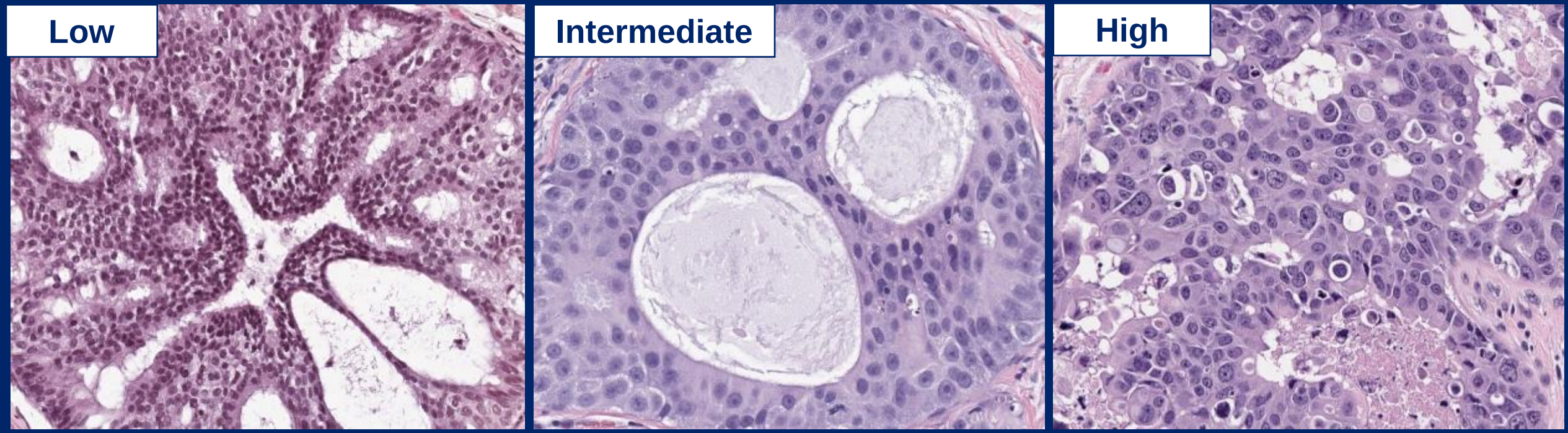


ADH: Diagnostic Workup

- ADH can be diagnosed in those cases in which the diagnosis of low grade DCIS is being seriously considered
  - But architectural, cytologic and quantitative features do not support a confident diagnosis of DCIS
- Helpful to prepare multiple H&E sections (recuts/levels/deepers) from areas which contain a “borderline” focus
  - DCIS usually persists and may enlarge
  - ADH more likely if the lesion decreases in size or is essentially unchanged
- Reviewing previous material can also be helpful
- **On core biopsy, a diagnosis of LG-DCIS should NOT be rendered unless unequivocal**
  - Diagnosis of “atypical intraductal proliferative lesion” is sufficient to prompt surgical excision

Ductal carcinoma in situ (DCIS)

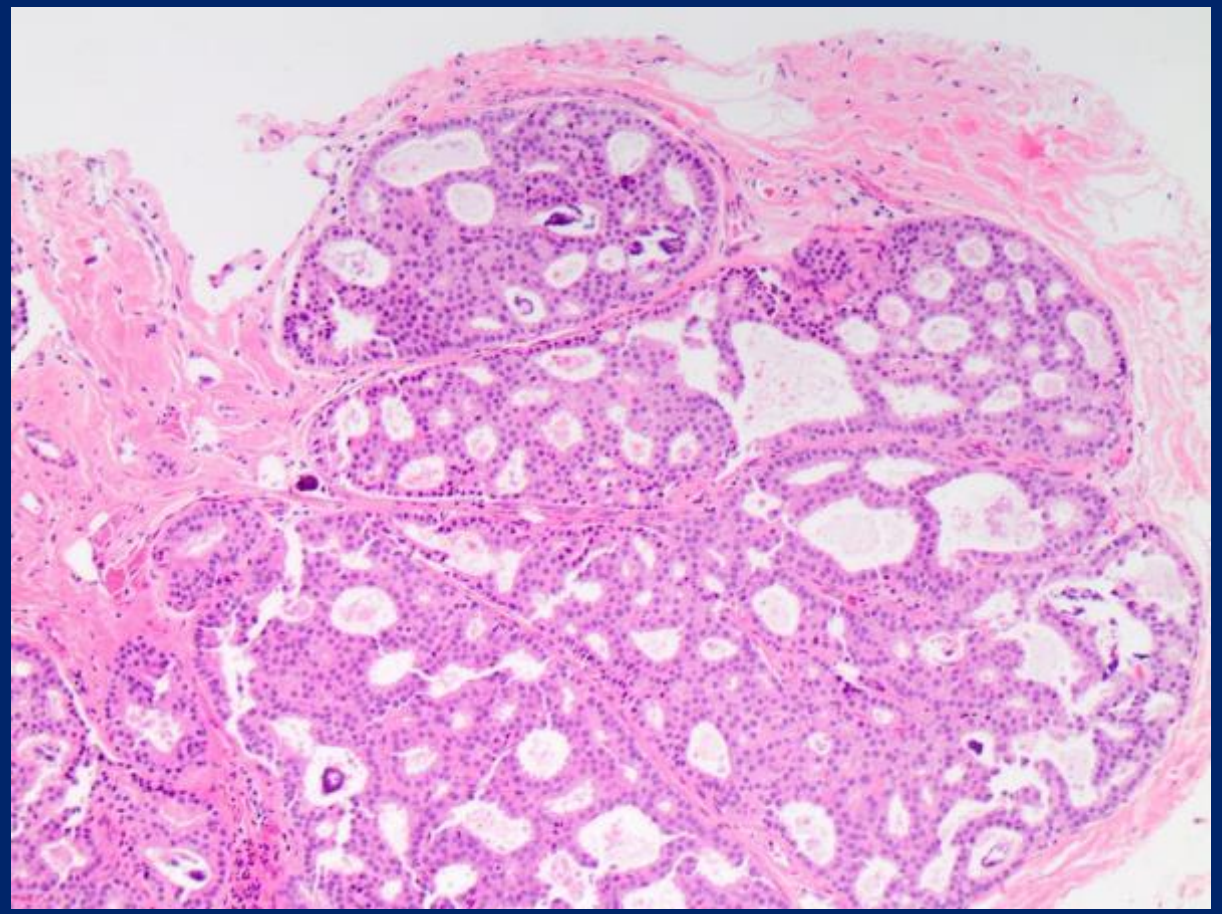
Classification of DCIS



DCIS is classified according to nuclear grade

Architectural pattern and presence of absence of necrosis also noted

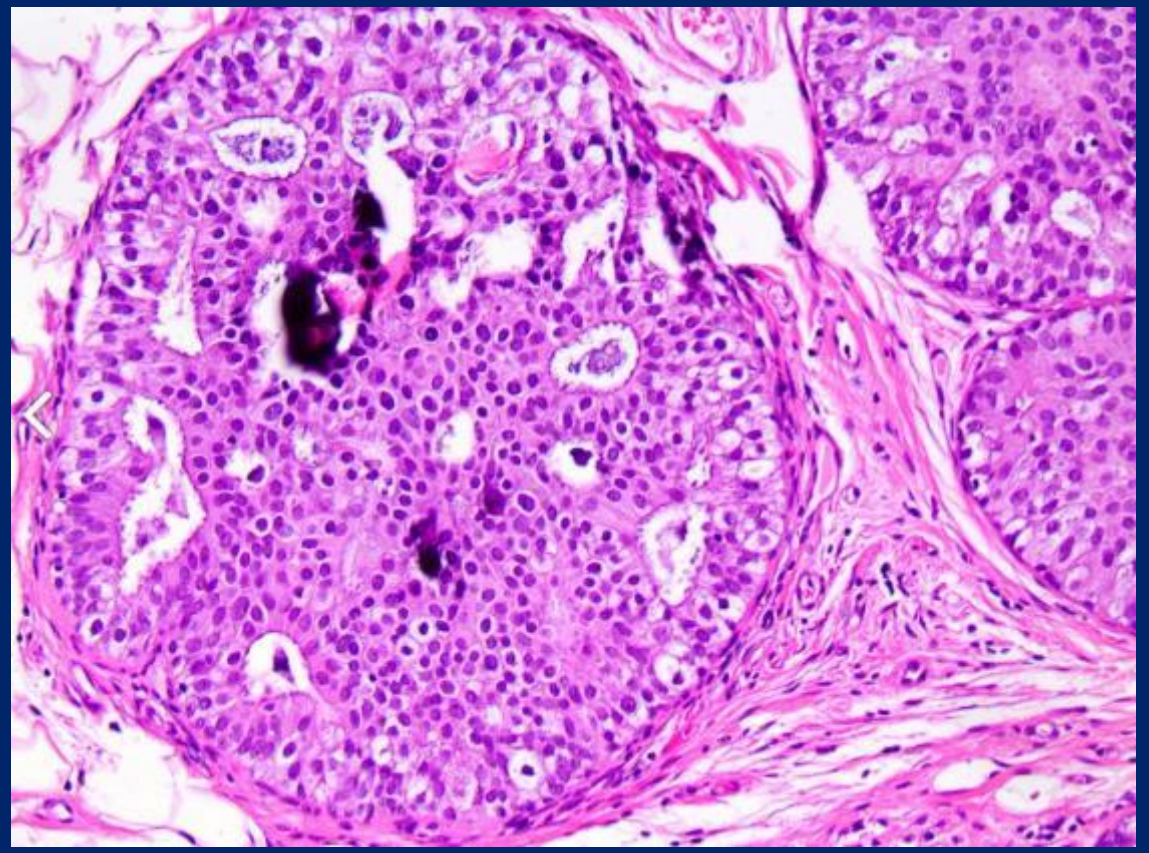
Low Grade DCIS



- Small, monomorphic cells
  - Typically in cribriform, micropapillary or (less often) solid pattern
- Nuclei uniform in size and shape
- Mitotic figures are rare
- Necrosis is uncommon

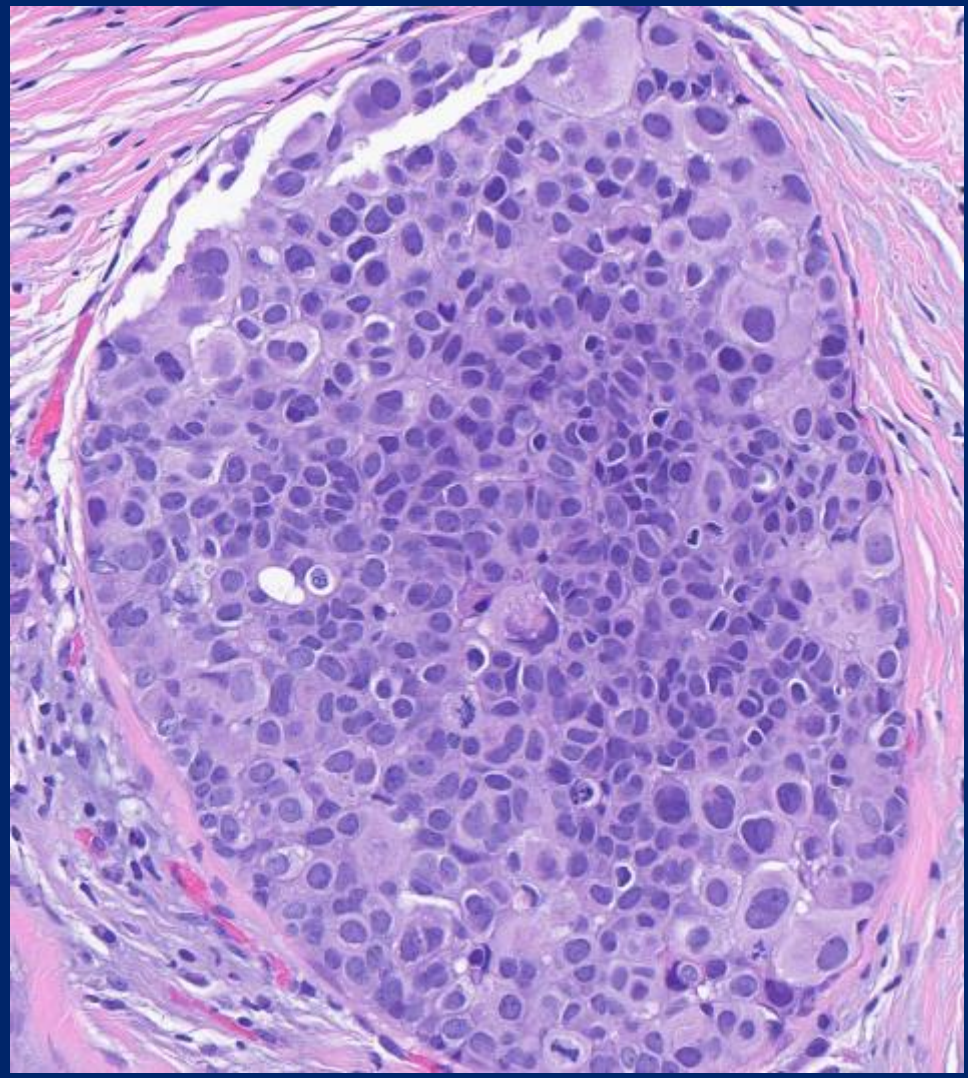
Intermediate Grade DCIS

- Cells show moderate variability in size and shape
- Nuclei variably coarse chromatin, sometimes prominent nucleoli
- Necrosis and mitoses may be seen



High Grade DCIS

- Large, atypical cells
  - Nuclei large and pleomorphic
  - Nuclei >2.5x size of RBC
- Most commonly shows solid architecture
- Can be single layer in flat DCIS (formerly clinging type)
- Mitoses frequent
- Central necrosis often present (not required for dx)



ADH vs DCIS in a papilloma

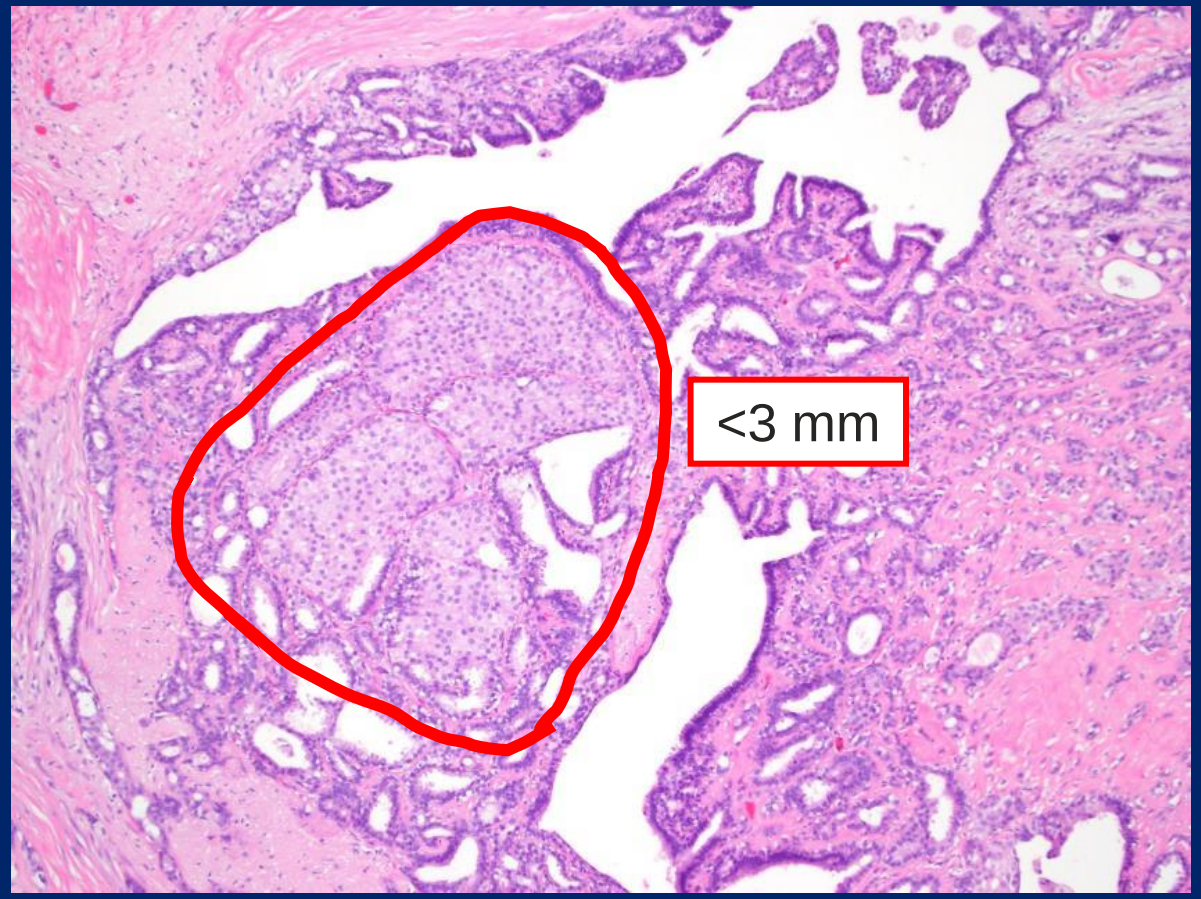
- Intraductal papillomas may contain areas that would be diagnostic of ADH or DCIS elsewhere in the breast
  - Lesion has focal population of monotonous cells with cytologic and architectural features of low grade neoplasia
  - Myoepithelial cells typically scant or absent in area of atypia
  - Foci lack staining for HMWCK (CK5/6) and show uniform staining with ER

- **For low grade atypia WHO recommends relying on size as criterion (cut off 3 mm)**
  - Intermediate or high grade cytology should be classified as papilloma with DCIS, regardless of size

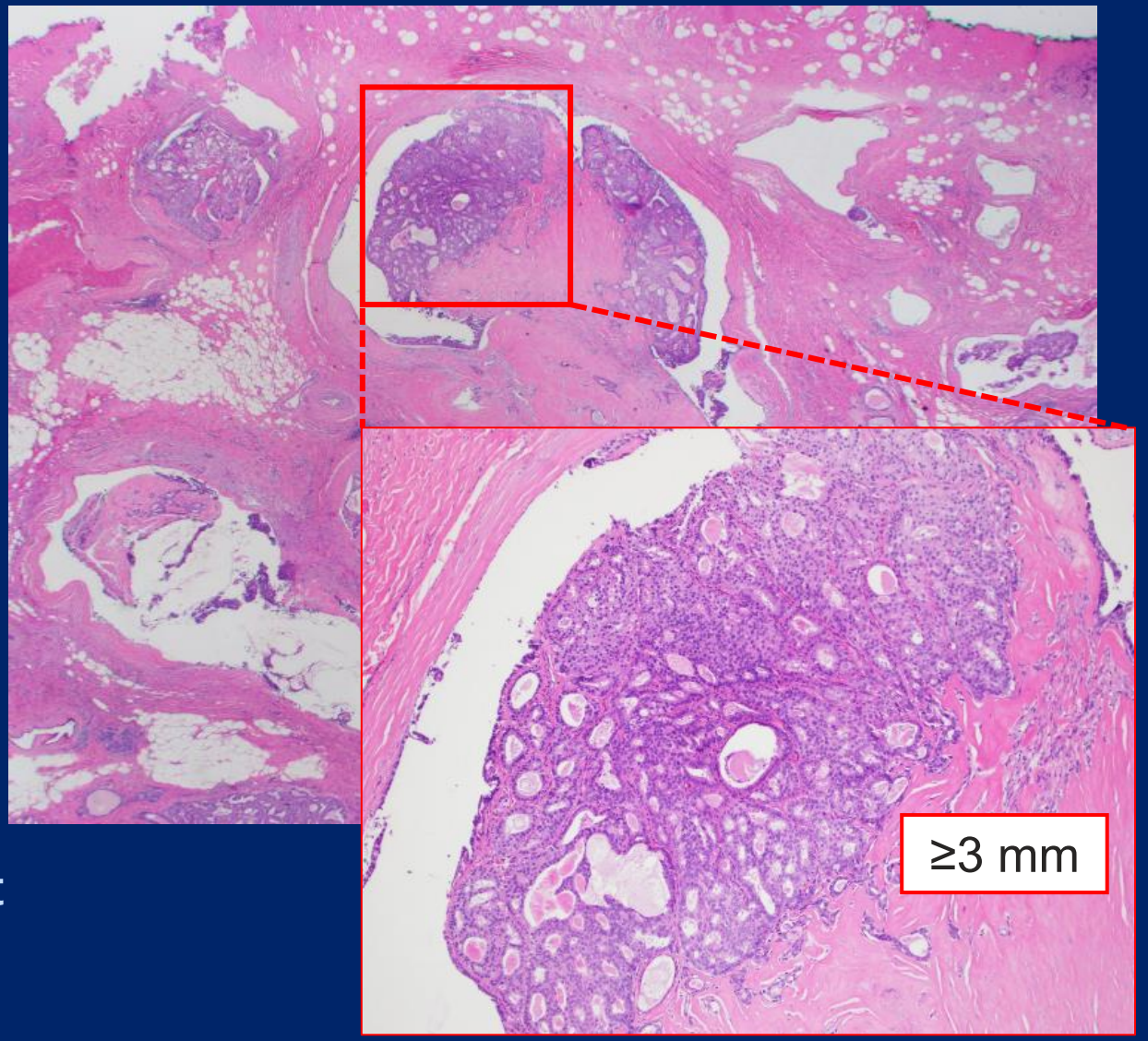
Lokuhetty D, White VA, Watanabe R, Cree IA. *WHO Classification of Tumours Editorial Board. Breast tumors.* IARC, Lyon; 2019.

Atypical Papillomas

Papilloma with ADH

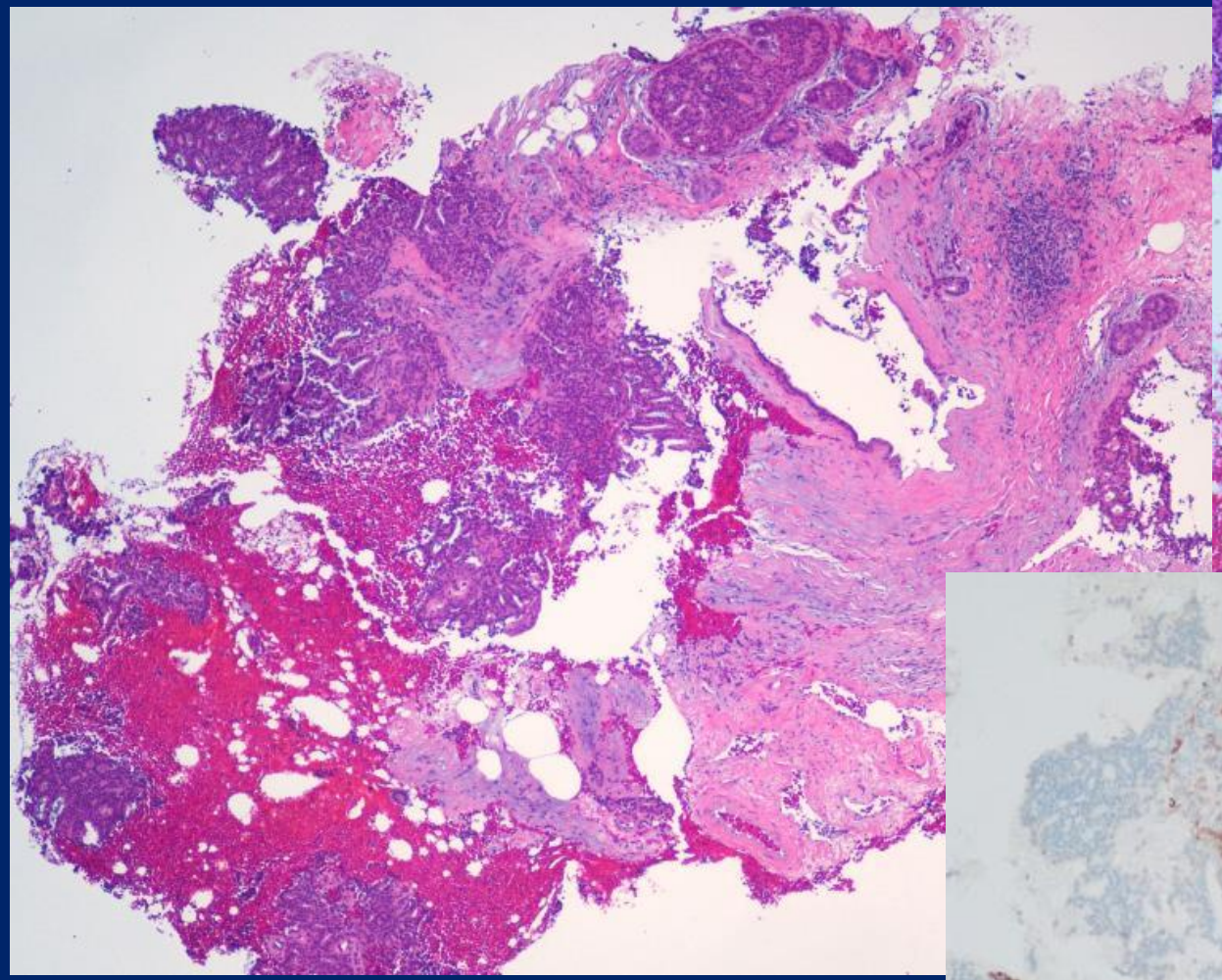


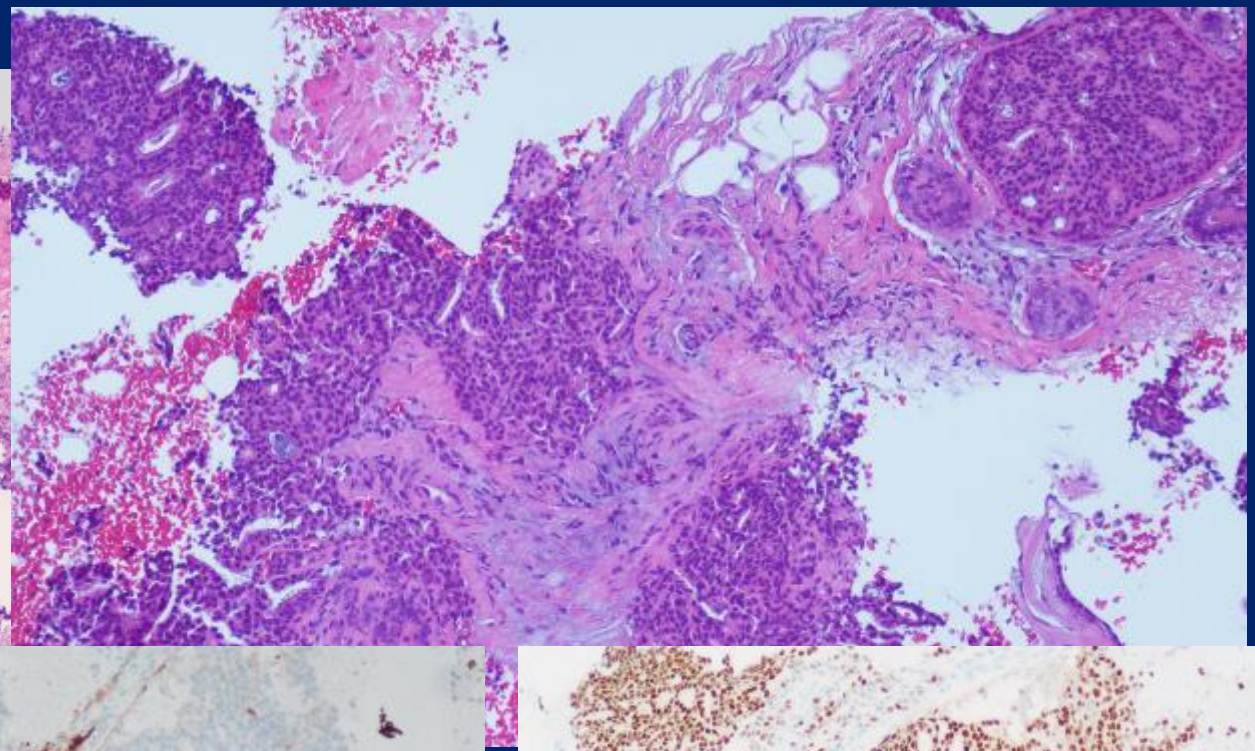
Papilloma with DCIS

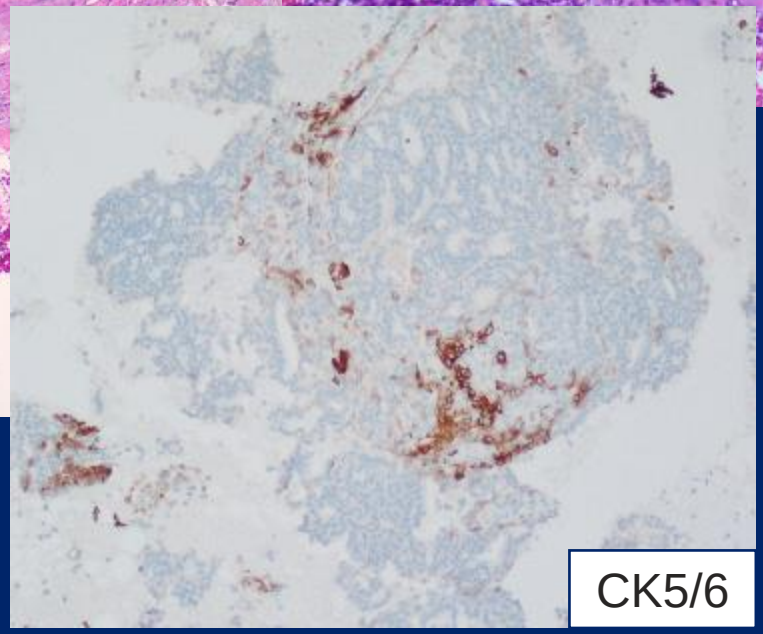


WHO: 3 mm is practical cutoff point
< 3 mm: papilloma with ADH
≥ 3 mm: papilloma with DCIS

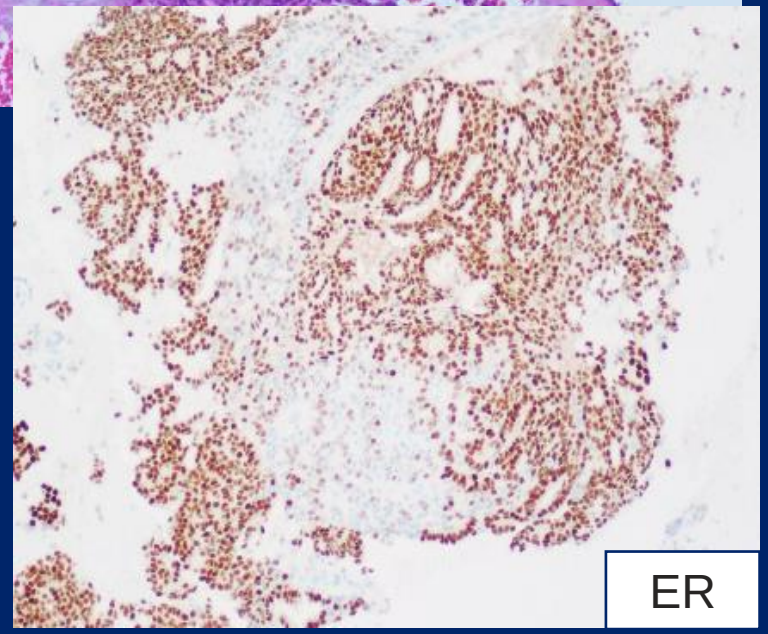
ADH in a papilloma





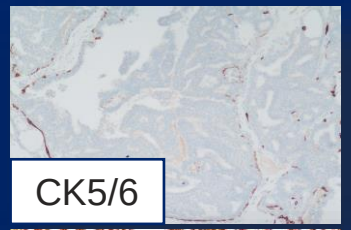


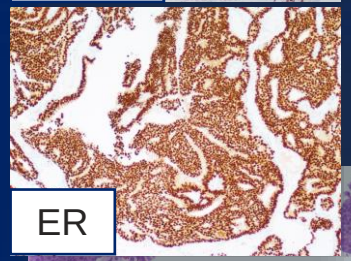
CK5/6

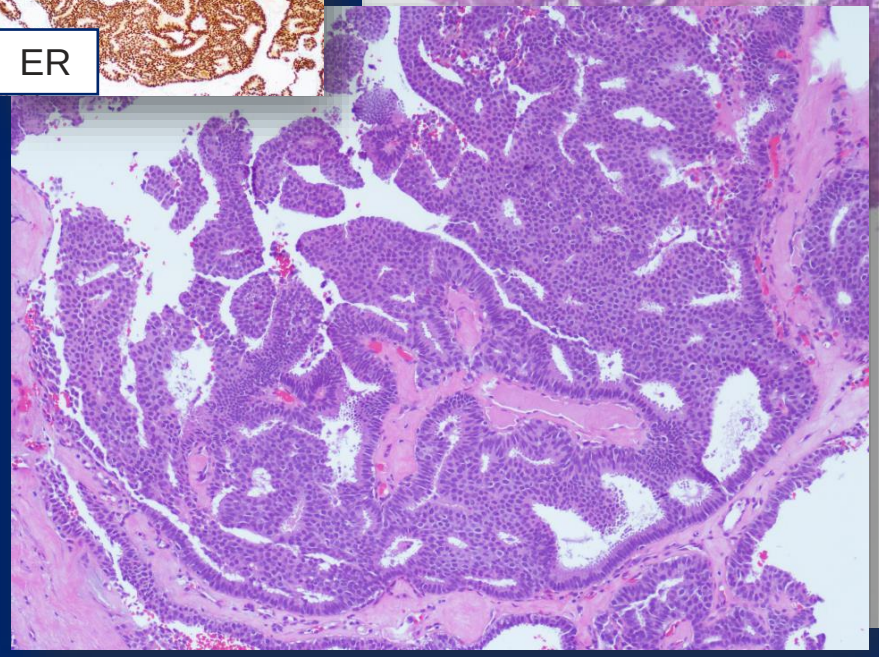


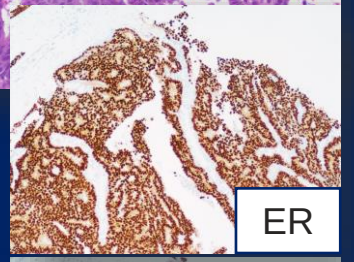
ER

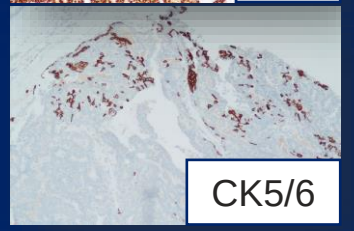
DCIS in a papilloma











DCIS-associated myoepithelial cells

- Myoepithelial cells that surround DCIS are phenotypically abnormal and differ from normal myoepithelial cells
  - Show up regulation of genes that enhance epithelial cell proliferation, migration, invasion and stromal angiogenesis
  - Have higher levels of enzymes that degrade extracellular matrix
  - Show epigenetic changes
    - May influence the progression of DCIS to invasive carcinoma

CAUTION: Some myoepithelial cell markers show reduced sensitivity for DCIS-associated myoepithelial cells (when compared to their sensitivity for normal myoepithelial cells).

Hilson JB et al. *Am J Surg Pathol* 2009; 33(2): 227-232.
Rohilla M et al. *Clinical Breast Cancer* 2015; 15(5): 335-342.
Allinen M et al. *Cancer Cell* 2004; 6: 17-32.

Number of cases with reduced staining intensity in DCIS associated myoepithelial cells for each marker

TABLE 3. Staining Intensity for 7 Myoepithelial Markers in DCIS-associated Myoepithelial Cells Compared With Staining Intensity of Myoepithelial Cells in Adjacent Normal Ducts and Lobules

	Staining Intensity of DCIS-associated Myoepithelial Cells				
Antibody (No. Evaluable)	**3**	**2**	**1**	**0**	**No. (%) Cases With Decreased or no Expression in DCIS-associated Myoepithelial Cells (%)**
SMA (100)	99	1	0	0	1/100 (1.0)
Calponin (98)	81	15	2	0	17/98 (17.4)
CD10 (88)	58	19	10	1	30/66 (34.0)
CK5/6 (96)	67	20	7	2	29/96 (30.2)
p63 (95)	83	8	3	1	12/95 (12.6)
SMMHC (98)	23	34	29	12	75/98 (76.5)
p75 (96)	92	4	0	0	4/96 (4.2)

3: staining intensity of DCIS-associated myoepithelial cells similar to that of myoepithelial cells surrounding normal ducts and lobules; 2: staining intensity of DCIS-associated myoepithelial cells slightly reduced compared with that of myoepithelial cells surrounding normal ducts and lobules; 1 staining intensity of DCIS-associated myoepithelial cells markedly reduced compared with that of myoepithelial cells surrounding normal ducts and lobules; 0: complete absence of staining of DCIS-associated myoepithelial cells.

CK indicates cytokeratin; DCIS, ductal carcinoma in situ; SMA, smooth muscle actin; SMMHC, smooth muscle myosin heavy chain.

Hilson JB et al. *Am J Surg Pathol* 2009; 33(2): 227-232.

SMMHC significantly reduced in High-grade DCIS

TABLE 4. Proportion of Cases Showing Reduced Staining of DCIS-associated MEC According to DCIS Nuclear Grade

	Non–high-grade DCIS (%)	High-grade DCIS (%)	*P*
SMA	0/40 (0)	1/60 (2.0)	0.32
Calponin	6/40 (15.0)	11/58 (19.0)	0.61
CD 10	10/35 (28.6)	20/53 (37.7)	0.34
CK 5/6	14/37 (37.8)	16/59 (27.1)	0.27
p63	5/39 (12.8)	7/56 (12.5)	0.96
SMMHC	24/39 (61.5)	50/59 (84.8)	**0.01**
p75	2/36 (5.6)	2/60 (3.3)	0.60

CK indicates cytokeratin; DCIS, ductal carcinoma in situ; MEC, myoepithelial cell; SMA, smooth muscle actin; SMMHC, smooth muscle myosin heavy chain.

Hilson JB et al. *Am J Surg Pathol* 2009; 33(2): 227-232.

DCIS associated myoepithelial cells have immunophenotypic differences from normal myoepithelial cells

- At least 1 common myoepithelial cell maker is reduced in DCIS associated myoepithelial cells in >80% of cases
  - Intensity of 2 or more markers reduced in ~66%
- Markers expressed most similar to those in normal myoepithelial cells: SMA, p75, p63 and calponin
- Markers most frequently reduced in DCIS associated myoepithelial cells: SMMHC, CD10 and CK5/6

Two or more markers, preferably p63 and calponin, should be used to distinguish in situ from invasive carcinoma.

In cases in which demonstration of myoepithelial cells is of diagnostic importance: SMMHC, CD10, CK5/6 should not be only antibodies used.

Hilson JB et al. *Am J Surg Pathol* 2009; 33(2): 227-232.
Rohilla M et al. *Clinical Breast Cancer* 2015; 15(5): 335-342.
Chivukula M et al. *Appl Immunohistochem Mol Morphol* 2009; 17(6): 495-499.

Lobular Proliferative Lesions

Lobular Proliferative Lesions

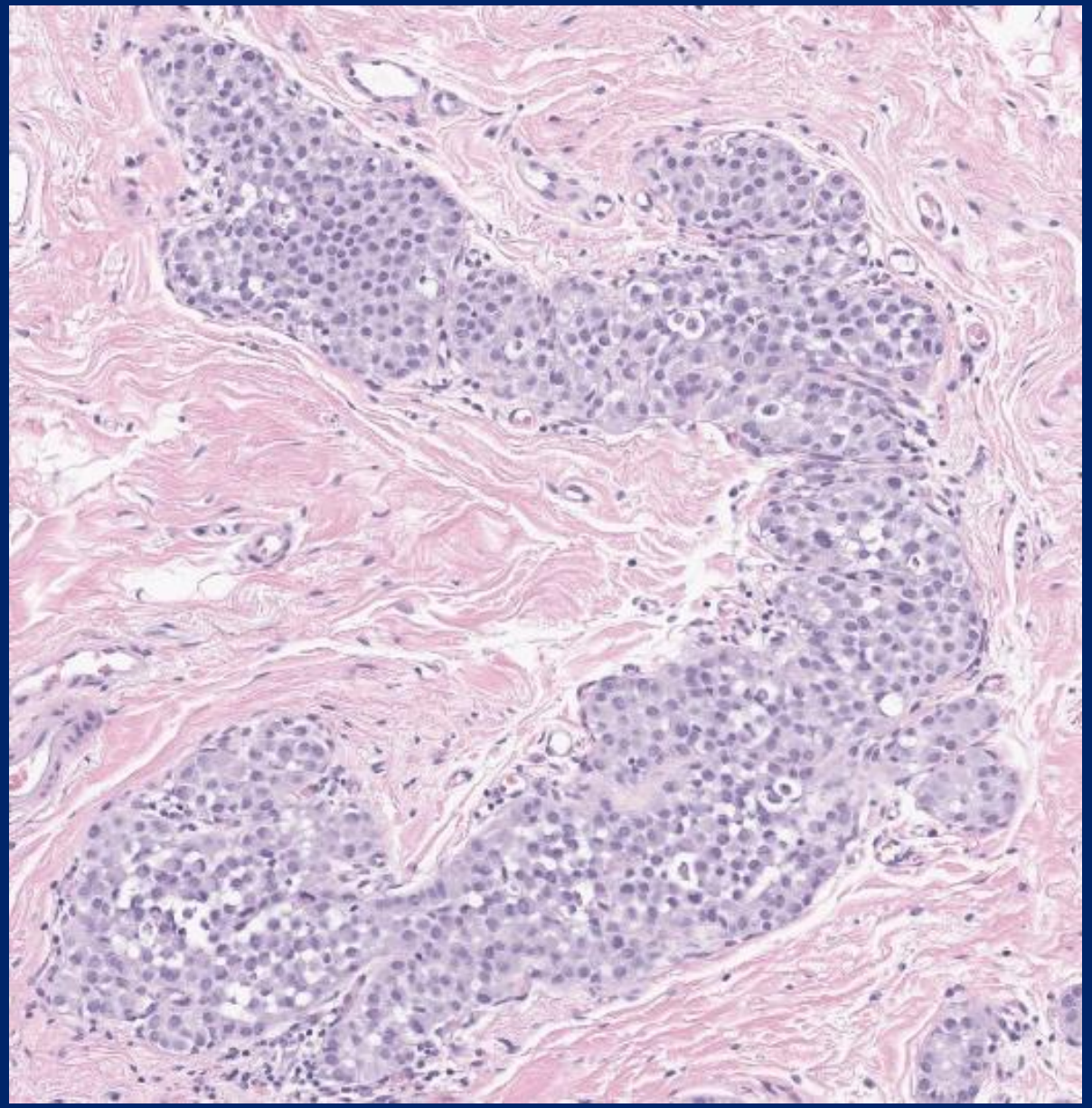
Classic Lobular Neoplasia

- Atypical lobular hyperplasia (ALH)
- Lobular carcinoma in situ (LCIS), classic type

Non-classic lobular neoplasia

- Pleomorphic lobular carcinoma in situ (P-LCIS)
- Florid lobular carcinoma in situ (F-LCIS)

Key Features of Classic Lobular Neoplasia



Cytologic Features

- Uniform, loosely cohesive and evenly spaced cells
- Cells slightly larger than normal
- Small uniform nuclei, evenly distributed chromatin and inconspicuous nucleoli

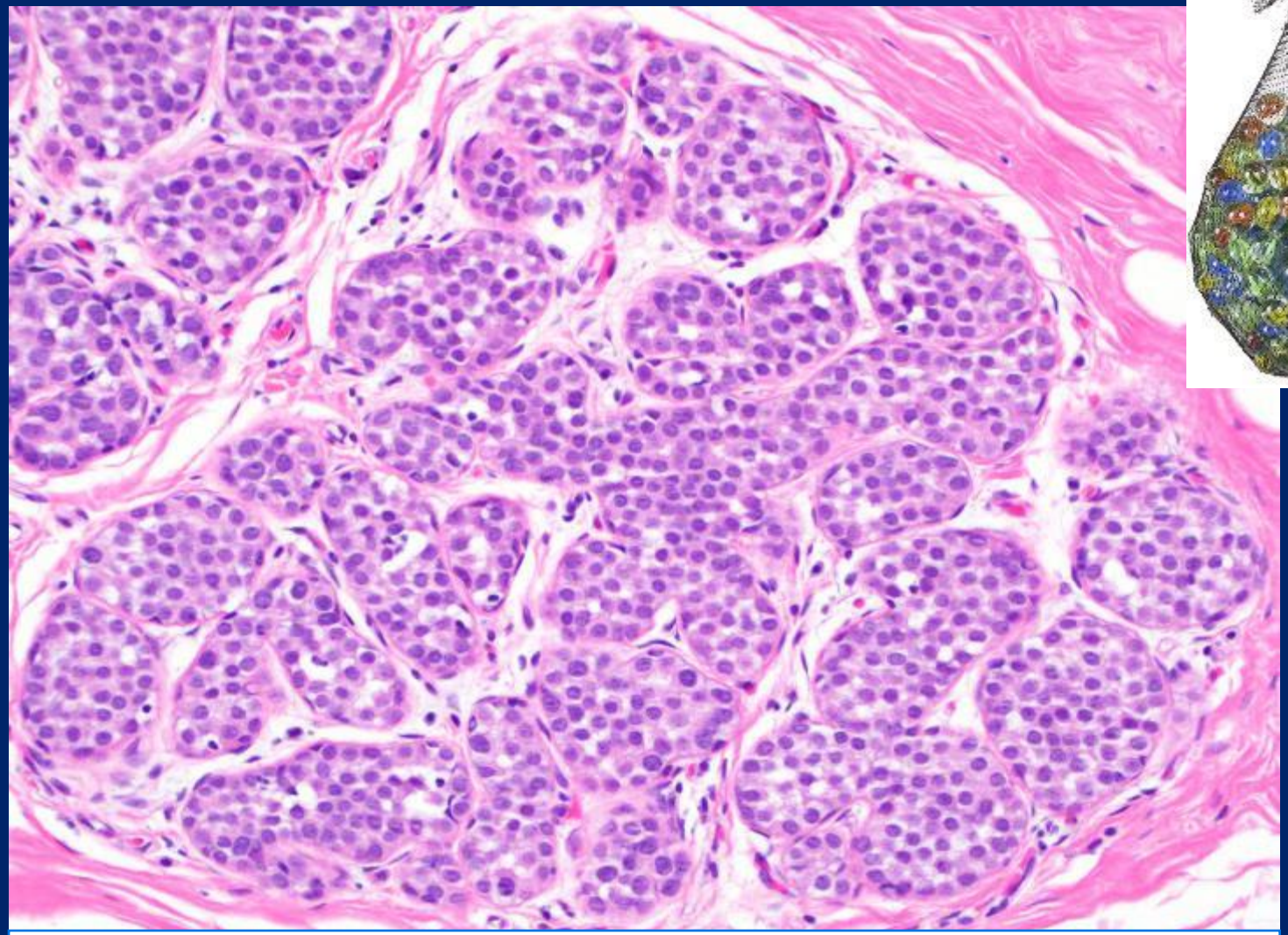
Architectural Features

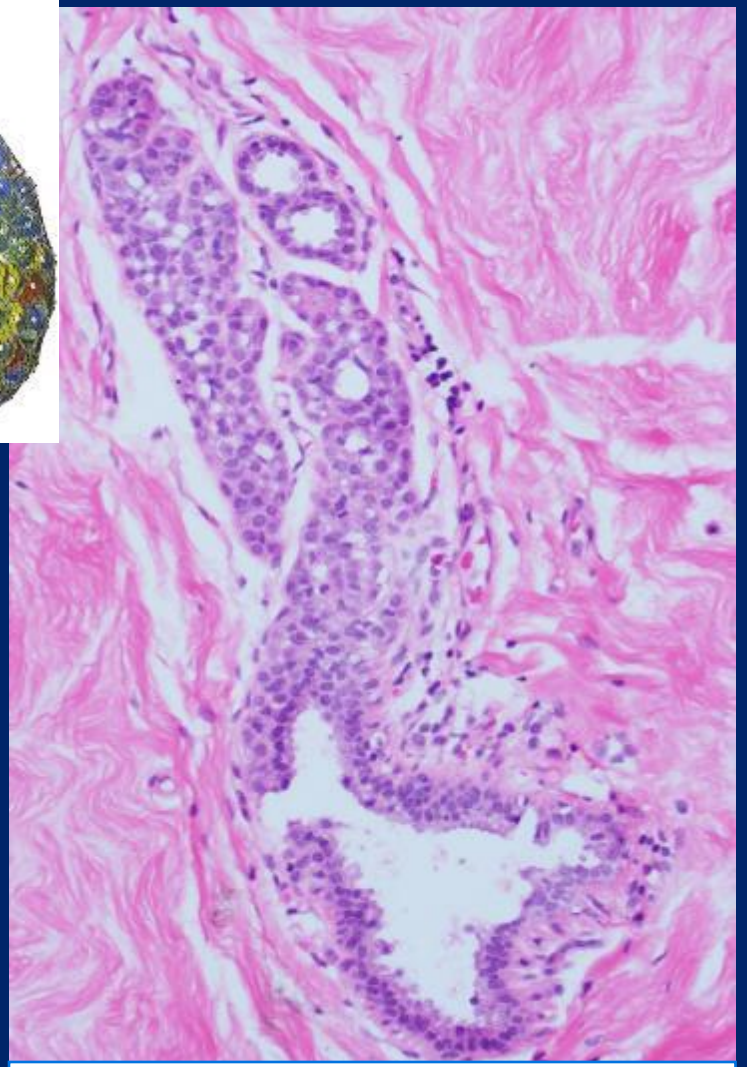
- Lobulocentric proliferation, expands lobular unit
- +/- pagetoid involvement of terminal ducts
- Distinction of ALH and LCIS: percentage of TDLU involved

Calle C et al. *Breast J*. 2020;26(5):1148-1155.

Classic LCIS

ALH

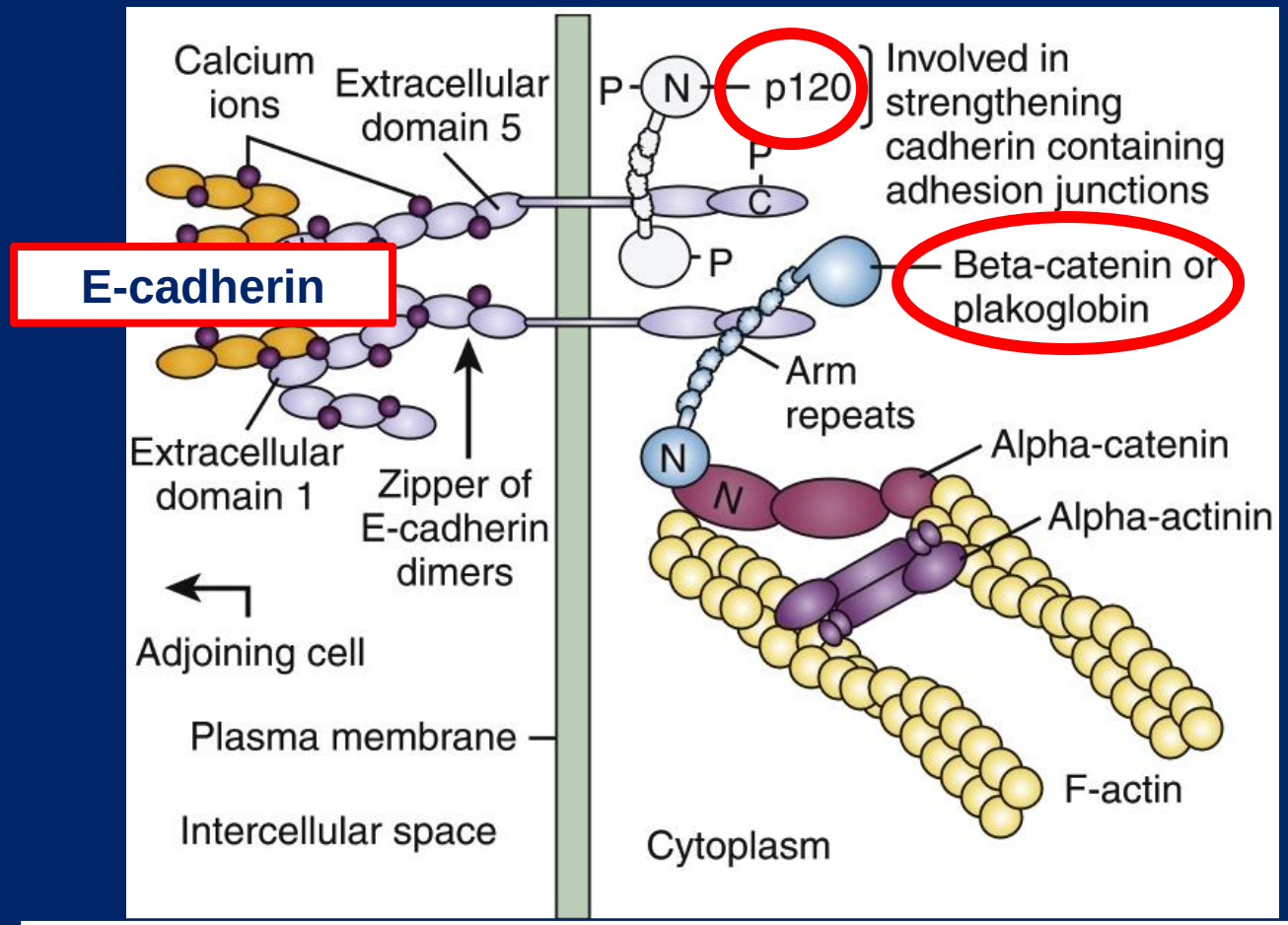




Uniform, discohesive, evenly spaced cells
Distention of >50% of acini of TDLU

<50% acini in TDLU
Minimal expansion

Hallmark Feature of Lobular Neoplasia: Loss of cellular cohesion due to dysfunctional cadherin-catenin complex



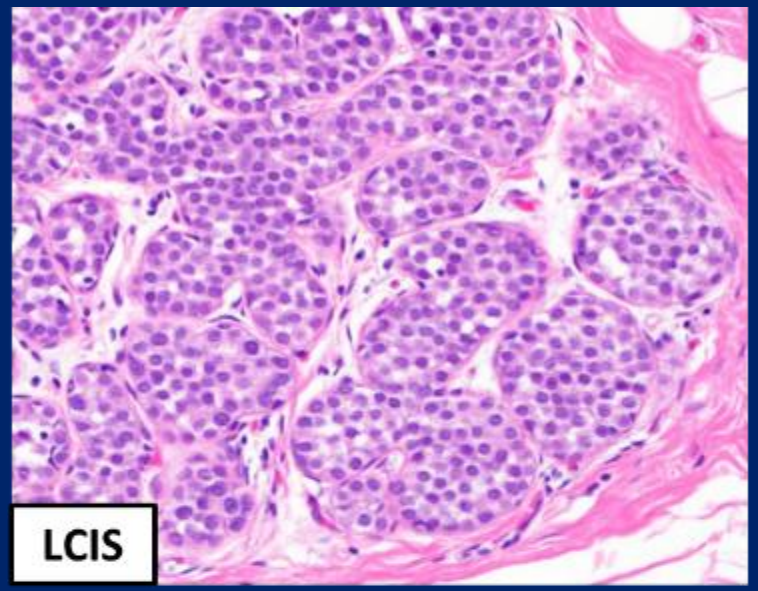
Inactivation of E-cadherin driven by genomic alterations targeting *CDH1* gene
(on chromosome 16q22.1)

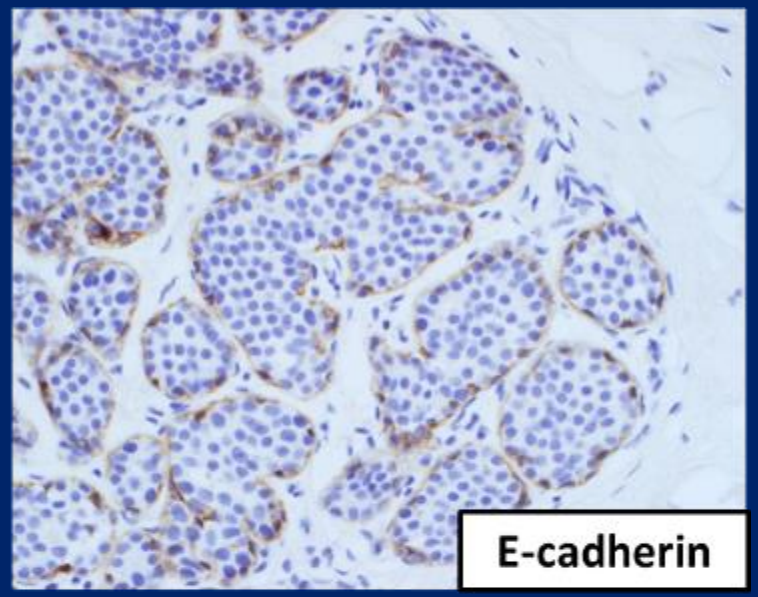
IHC for lobular lesions:

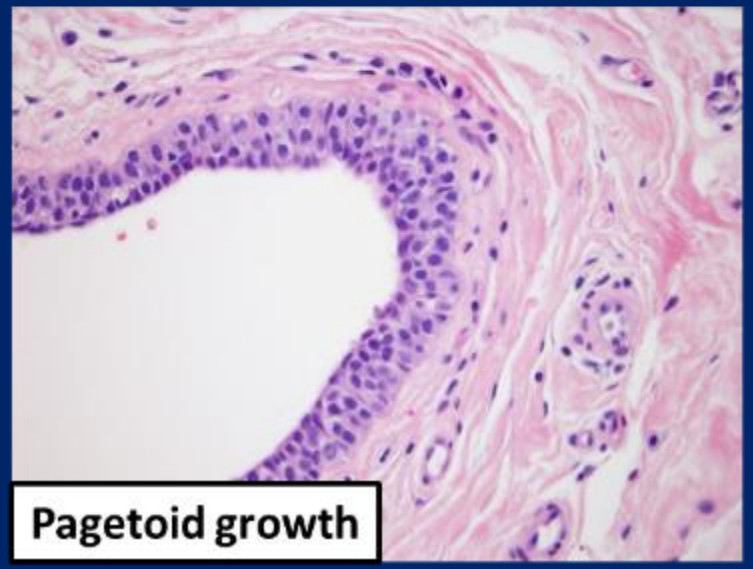
- **E-cadherin**
  - Absence of membranous expression
- **p120**
  - Cytoplasmic expression
- **Beta-catenin**
  - Absence of membranous expression

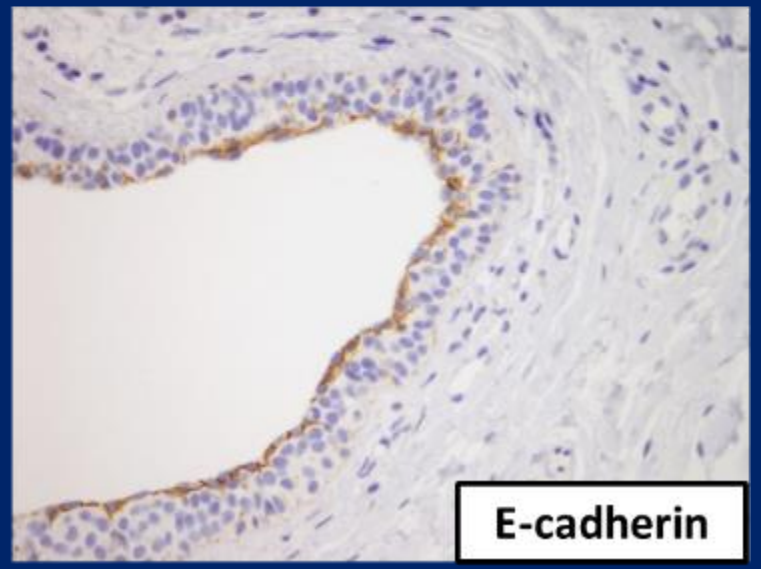
Dabbs DJ, ed. *Breast Pathology.* 2nd ed. Elsevier; 2017.

E-cadherin IHC: loss of membranous staining





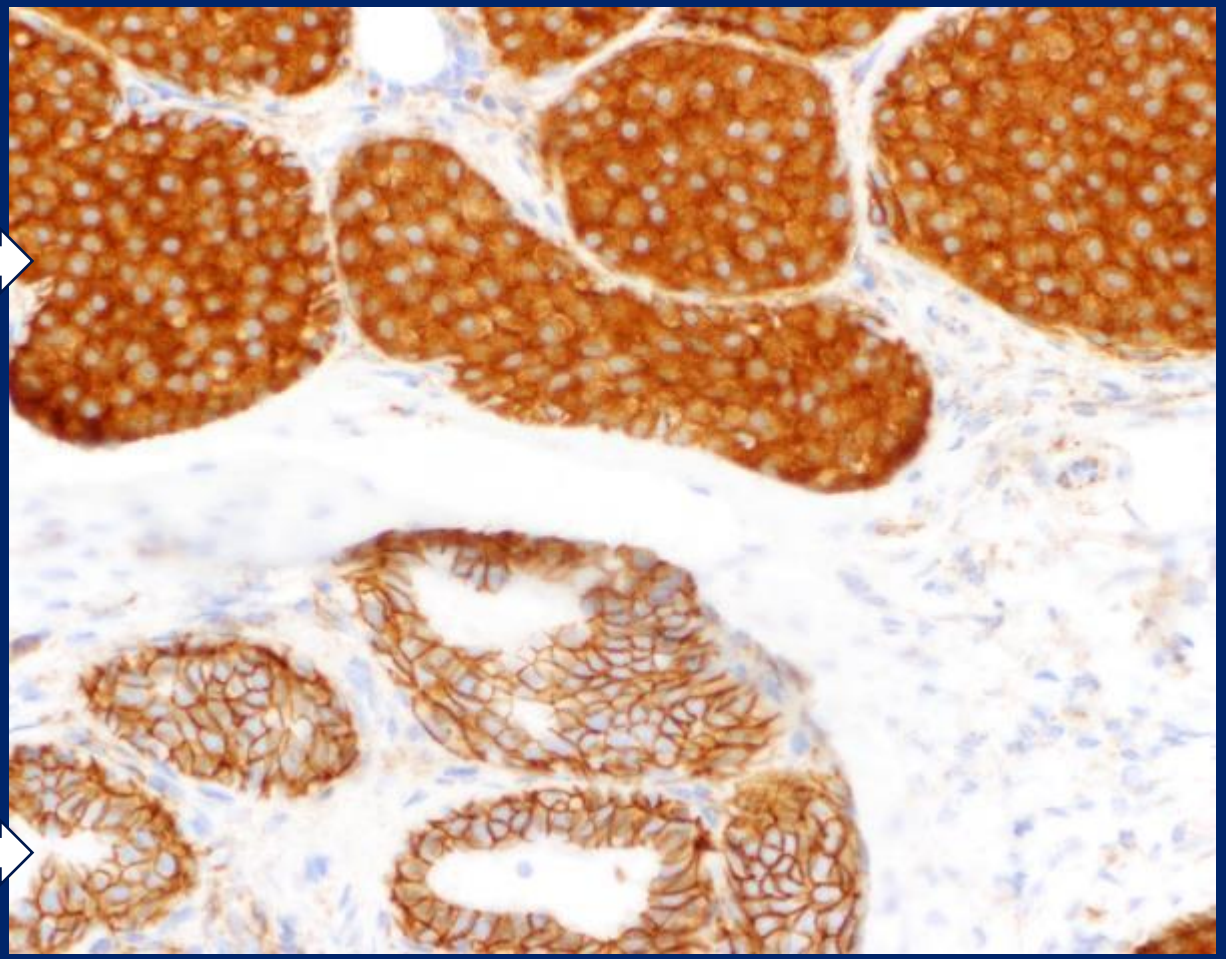




Inactivation of E-cadherin results in accumulation of p120 in the cytoplasm

LCIS – cytoplasmic staining with p120

Benign glands – membranous staining with p120



Why do we care if a tumor is lobular vs ductal?

Differentiation of invasive carcinoma:

- Little clinical impact, but still routinely used

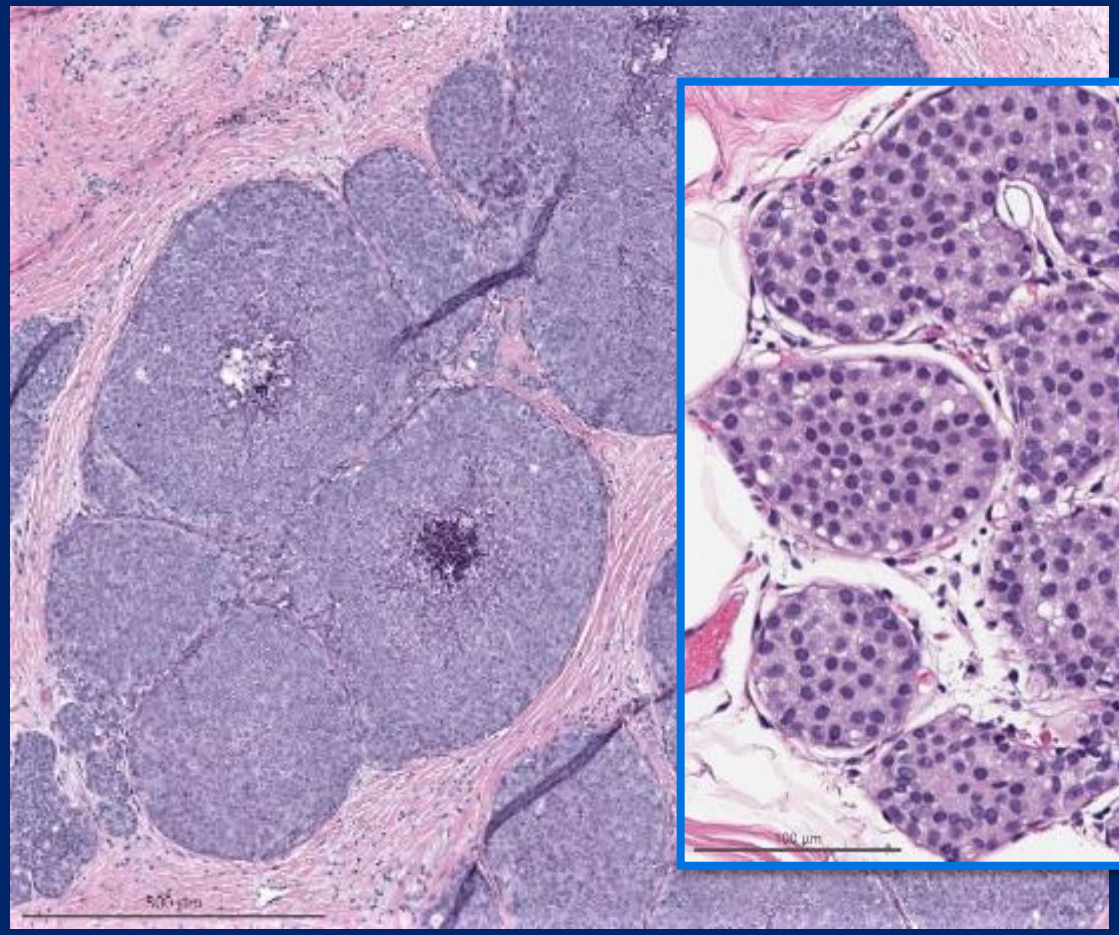
Distinguishing DCIS vs Classic LCIS

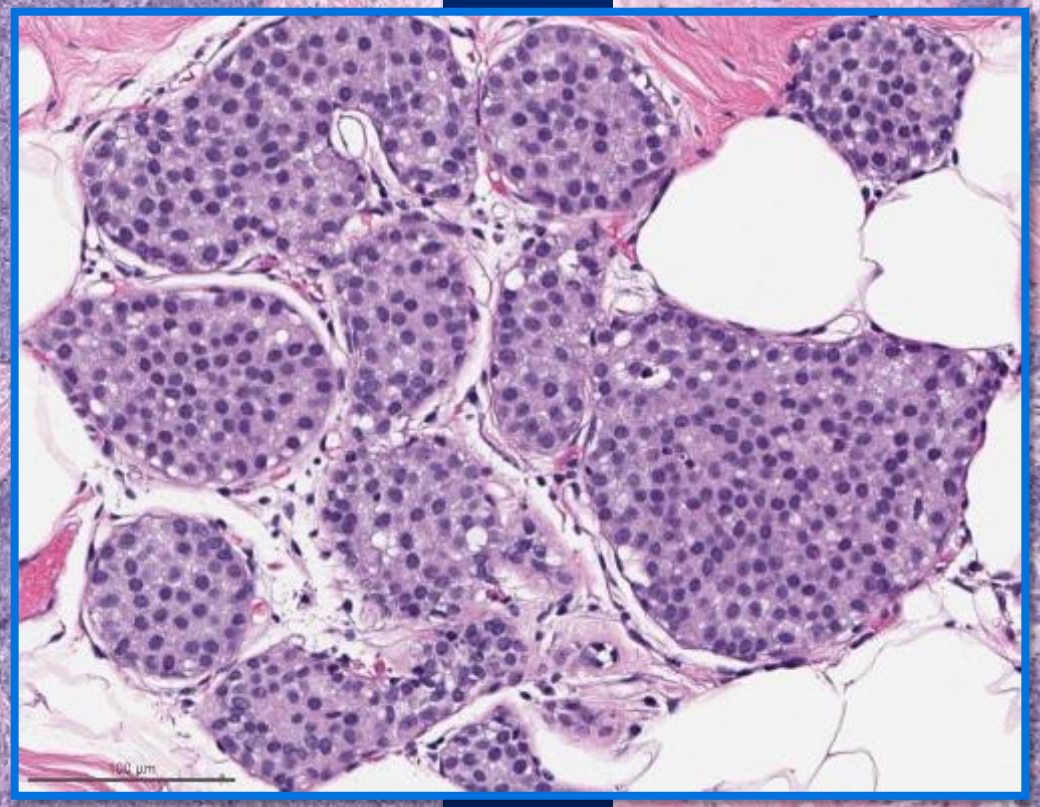
- DCIS: local eradication, XRT
- LCIS: follow up, chemoprevention

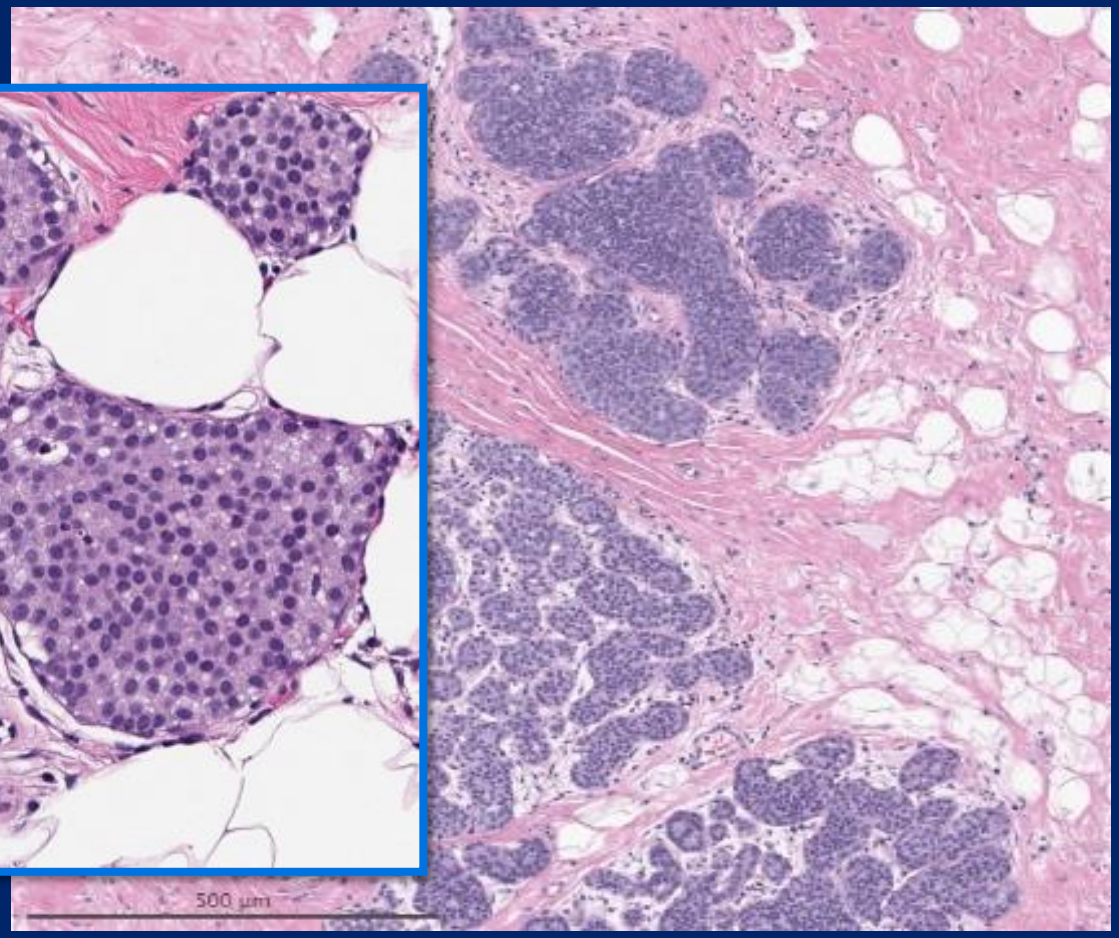
Non-classic LCIS: Pleomorphic and Florid

Florid LCIS

Classic LCIS





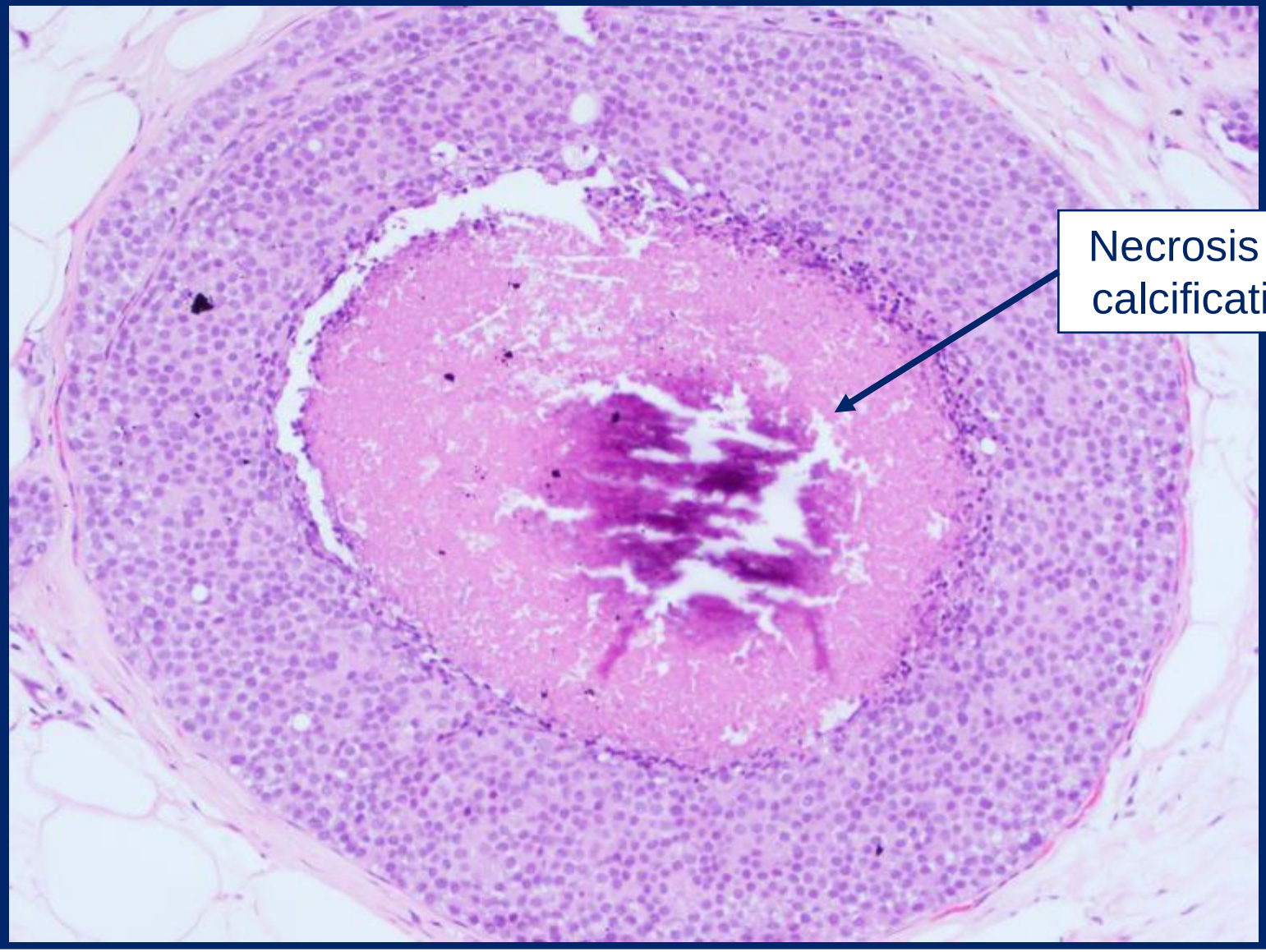


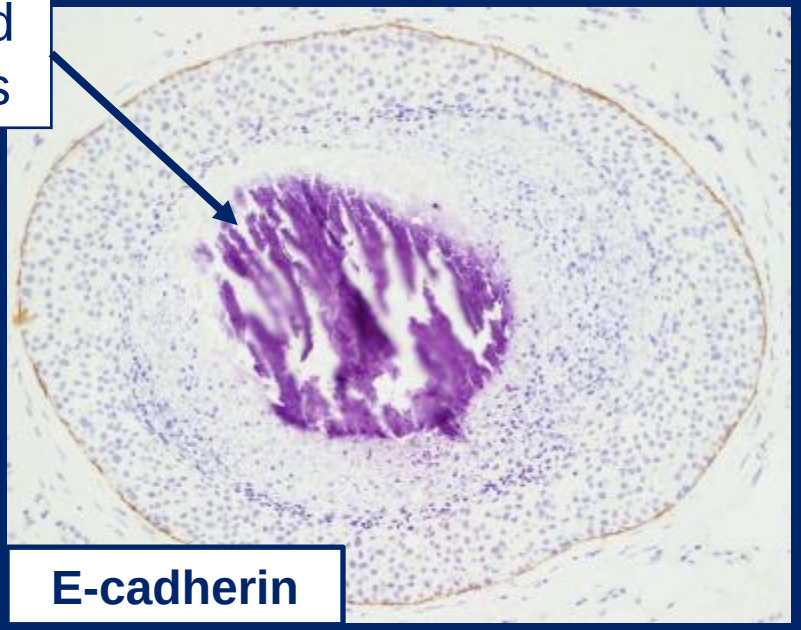
Need at least 1 of 2 architectural features:

- Little to no intervening stroma between distended acini
- Minimum diameter of ~40-50 cells

Schnitt SJ et al. *Ann Diagn Pathol*. 2020;45:151481.

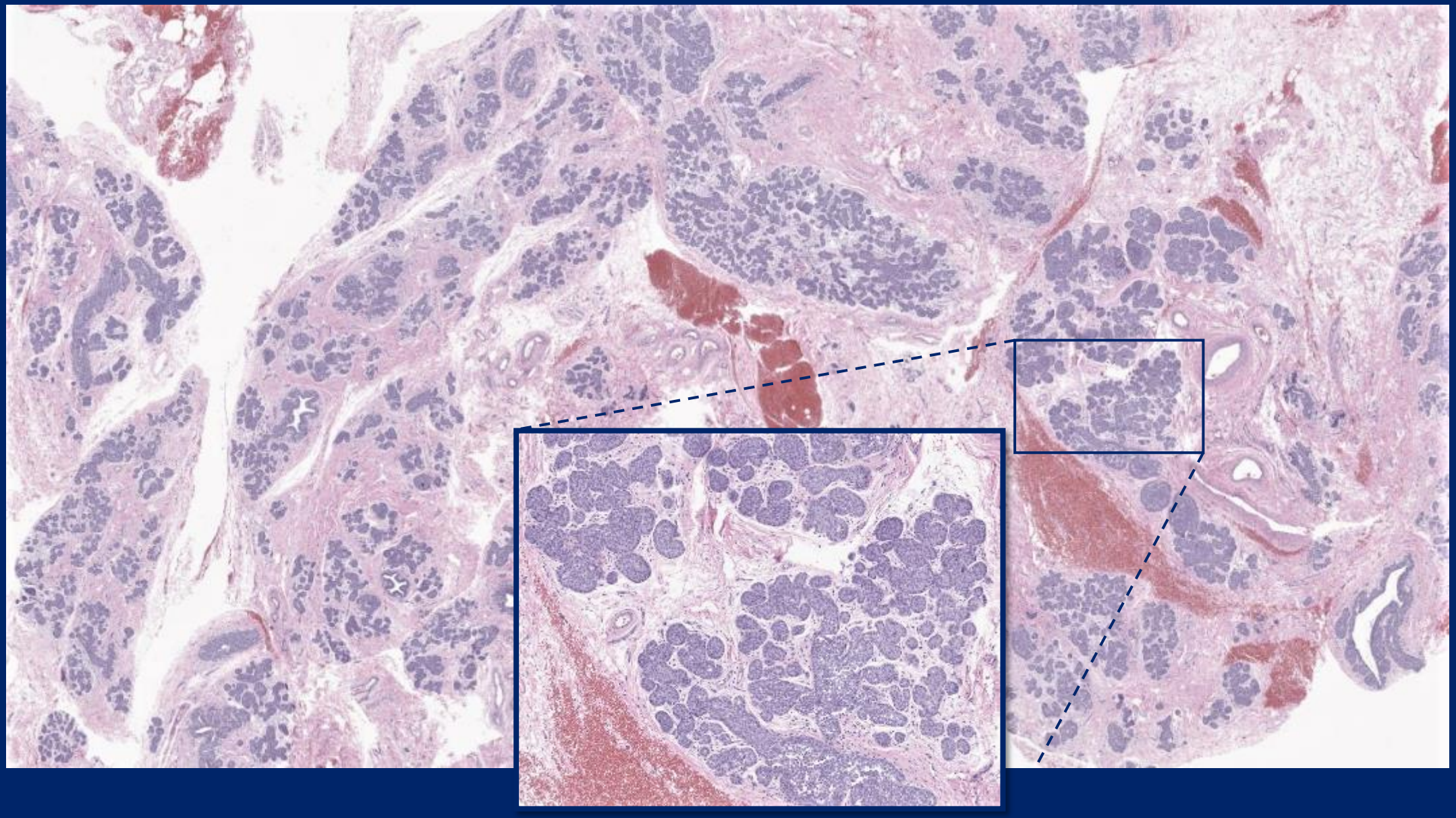
Florid LCIS



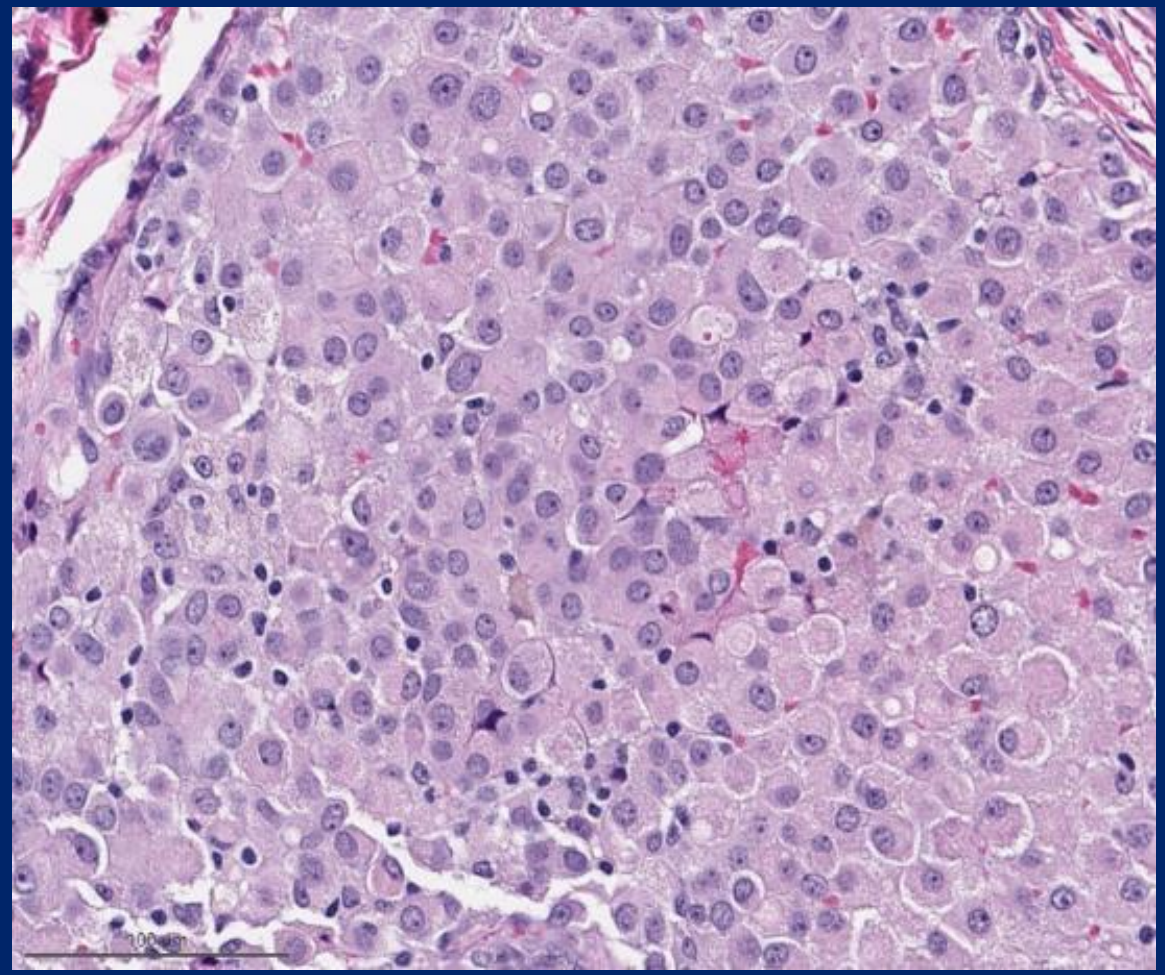


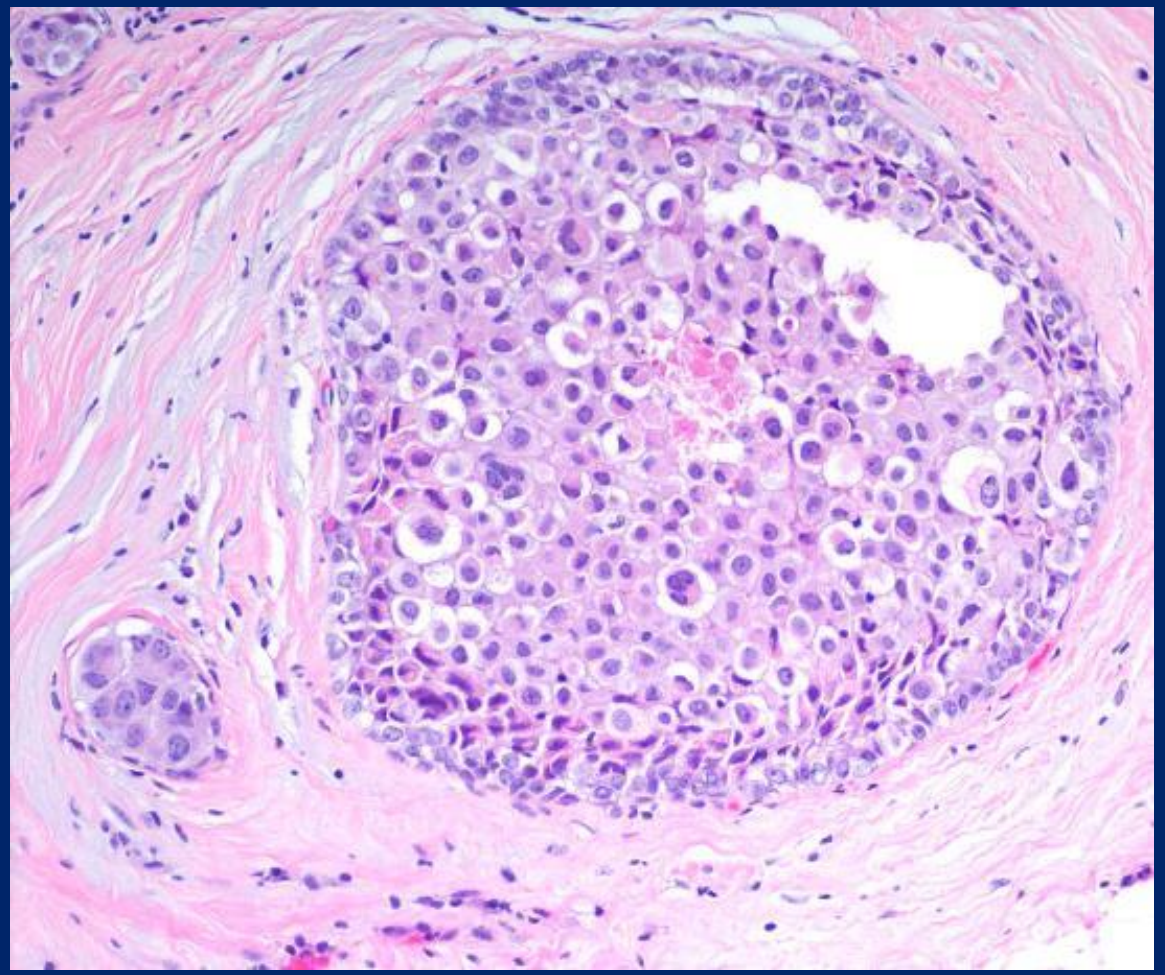
Expansion of ducts with low to intermediate grade LCIS cells

Extensive classic LCIS ≠ Florid LCIS



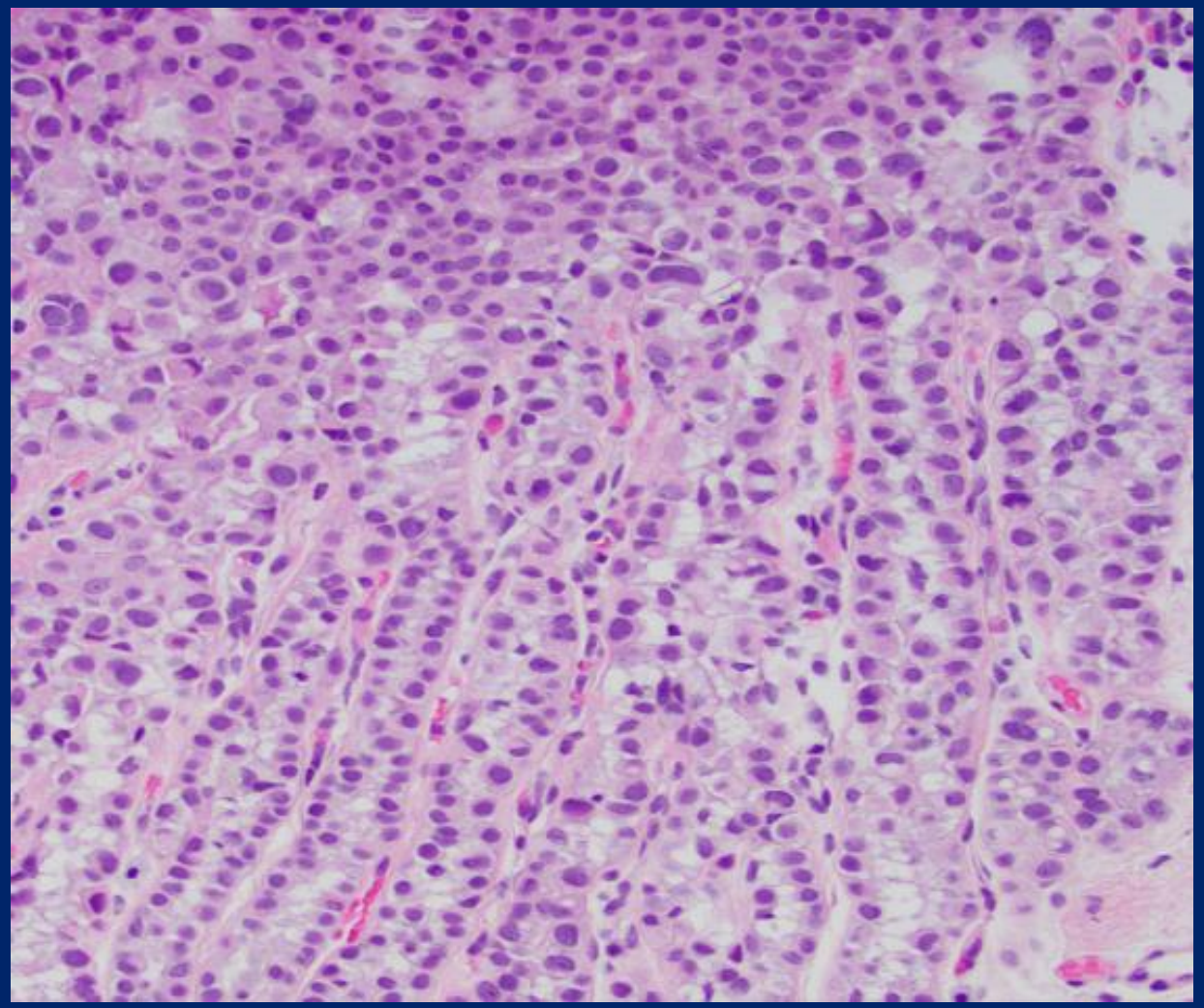
Pleomorphic LCIS





Solid proliferation of discohesive cells with marked nuclear pleomorphism equivalent to high grade DCIS

LCIS with pleomorphic features



- WHO 5th Edition: LCIS lesions that are borderline between classic and pleomorphic should be categorized as classic LCIS in excision specimens
- Clinical significance in core biopsy is unknown

Lokuhetty D, White VA, Watanabe R, Cree IA. *WHO Classification of Tumours Editorial Board. Breast tumors.* IARC, Lyon; 2019.

LCIS Clinical Presentation

Classic LCIS

- Premenopausal, mean ~45 years
- Incidental
  - Less commonly biopsied due to calcifications
- Multifocal, multicentric

- Virtually all ER positive, HER2 negative

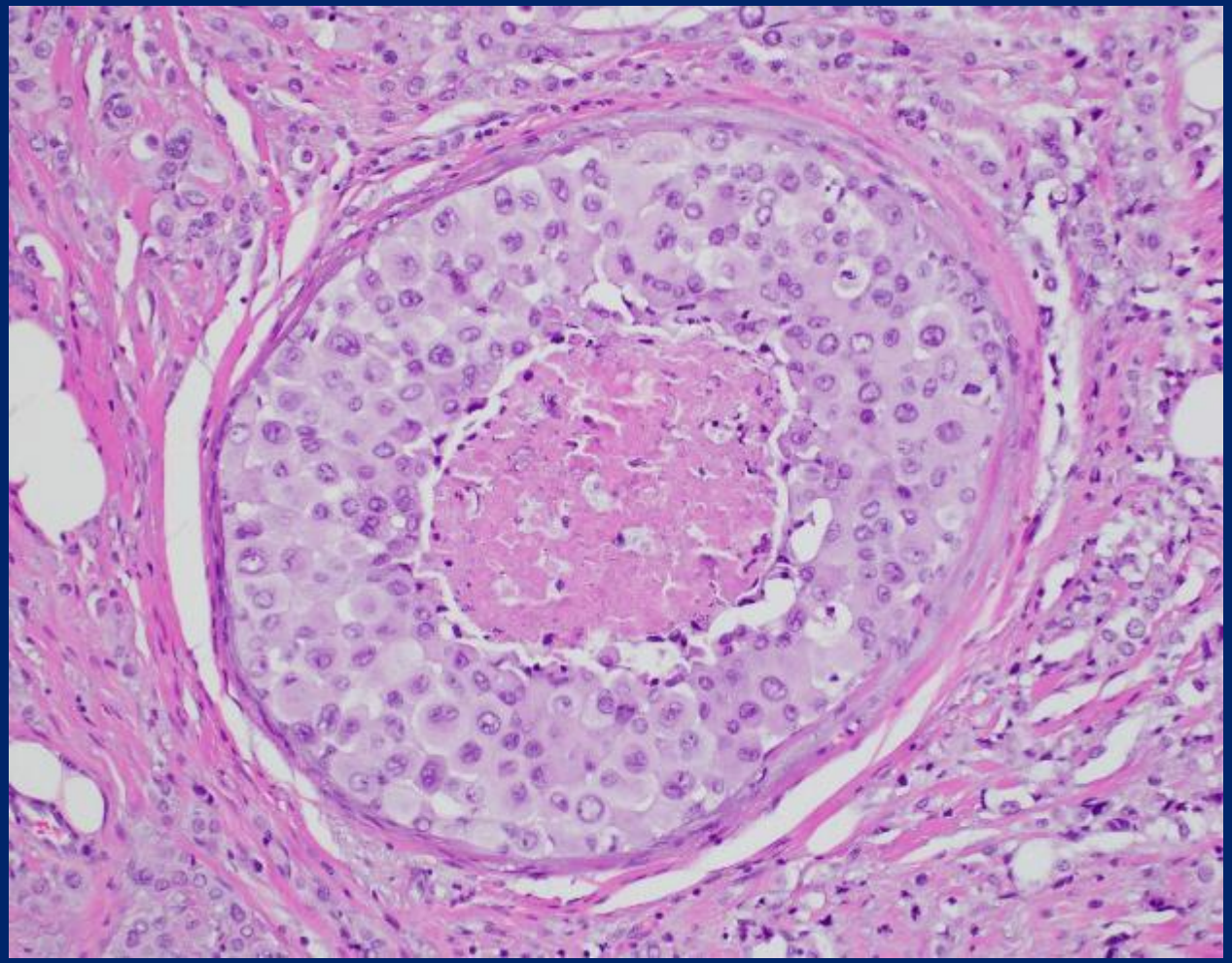
Florid and Pleomorphic LCIS

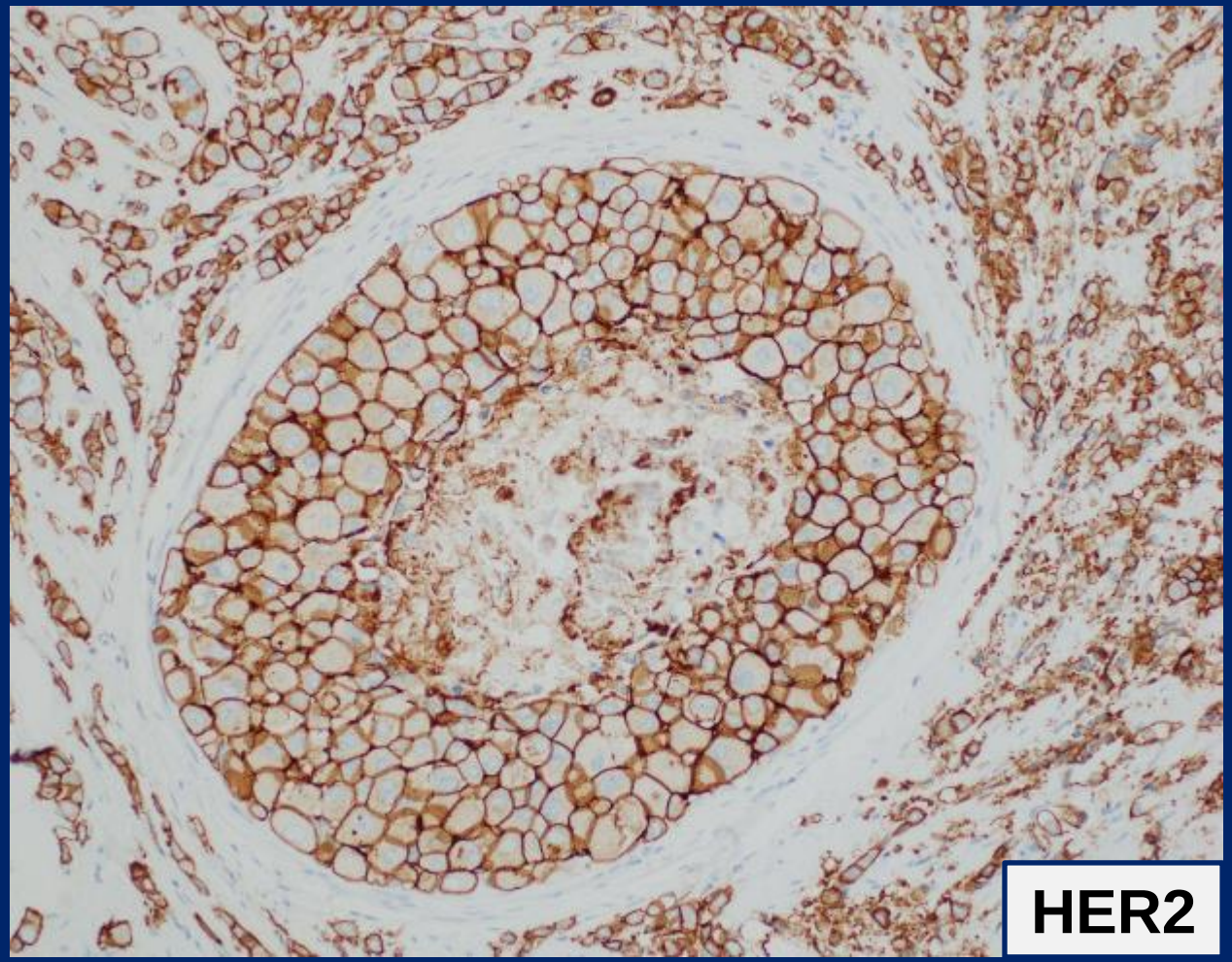
- Postmenopausal, mean ~60 years
- Imaging target: calcifications or mass
- Unifocal
- Commonly seen in association with classic LCIS

- Majority ER positive, HER2 negative
  - **Pleomorphic: HER2 overexpression in ~20% (particularly apocrine type)**

Lokuhetty D, White VA, Watanabe R, Cree IA. *WHO Classification of Tumours Editorial Board. Breast tumors.* IARC, Lyon; 2019.

Pleomorphic invasive lobular carcinoma and LCIS with apocrine differentiation





Molecular Features of LCIS

Classic LCIS

- 16q loss, gain of 1q
- *CDH1* alteration
  - Up to 81%
- *PIK3CA* mutation (41%)

Florid LCIS

- 16q loss, gain of 1q
- Greater genomic instability
- Increased copy number alterations

Pleomorphic LCIS

- 16q loss, gain of 1q
- Greater genomic instability
- Increased copy number alterations
- **HER2 amplification**

Sakr RA et al. *Mol Oncol.* 2016;10(2):360-70.
Shin SJ et al. *Hum Pathol.* 2013;44(10):1998-2009.
Shah V et al. *Breast Cancer Res.* 2017;19(1):7.
Harrison BT et al. *Mod Pathol.* 2020;33(7):1287-1297.

Summary

- Diagnosis of intraductal proliferative lesions is based predominantly on H&E findings
- Risk is dependent on the degree of atypia (and possibly extent)
- Recommend additional deeper histologic sections and/or immunohistochemical work up for challenging cases
  - Consultation with colleagues is advised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