Memorial Sloan Kettering Cancer Center

The International Academy of Pathology
Hong Kong Division

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Lobular Carcinoma
In situ and invasive

Edi Brogi, MD PhD

Director Breast Pathology - Memorial Sloan Kettering Cancer Center

Professor of Clinical Pathology & Laboratory Medicine - Weill Cornell Medical College

New York City, New York

Overview

- Lobular carcinoma in Situ (LCIS)
  - Classic
  - Florid
  - Pleomorphic

  Atypical lobular hyperplasia (ALH)
- Invasive lobular carcinoma
  - Classic
  - Special forms
  - Grading
- E-cadherin, p120 and Beta-catenin

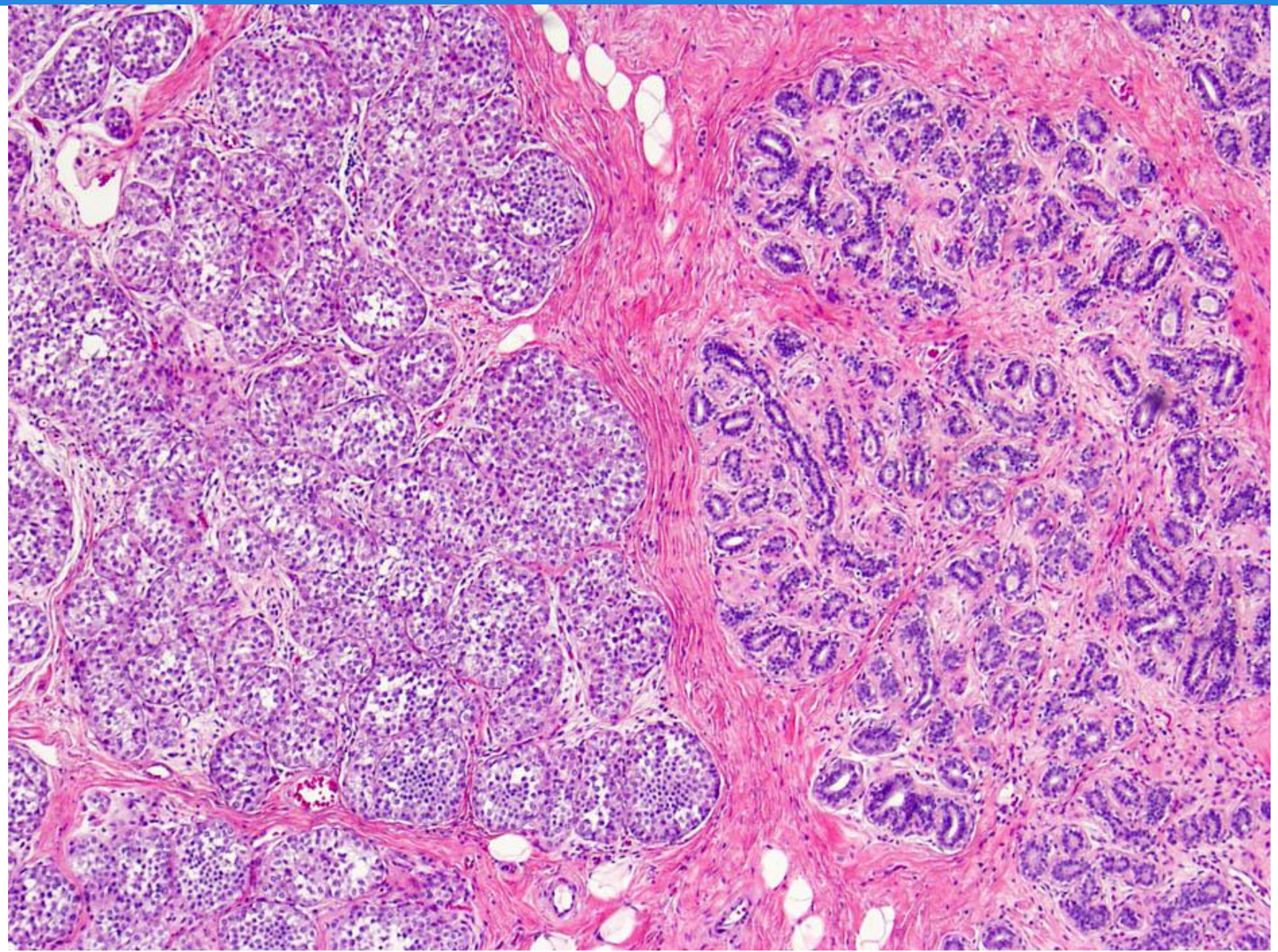
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	2026 WHO 6th ed.	
Classic Lobular Neoplasia (classic LN)	Atypical Lobular Hyperplasia	ALH
	Classic Lobular Carcinoma In Situ	classic LCIS

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Classic LCIS

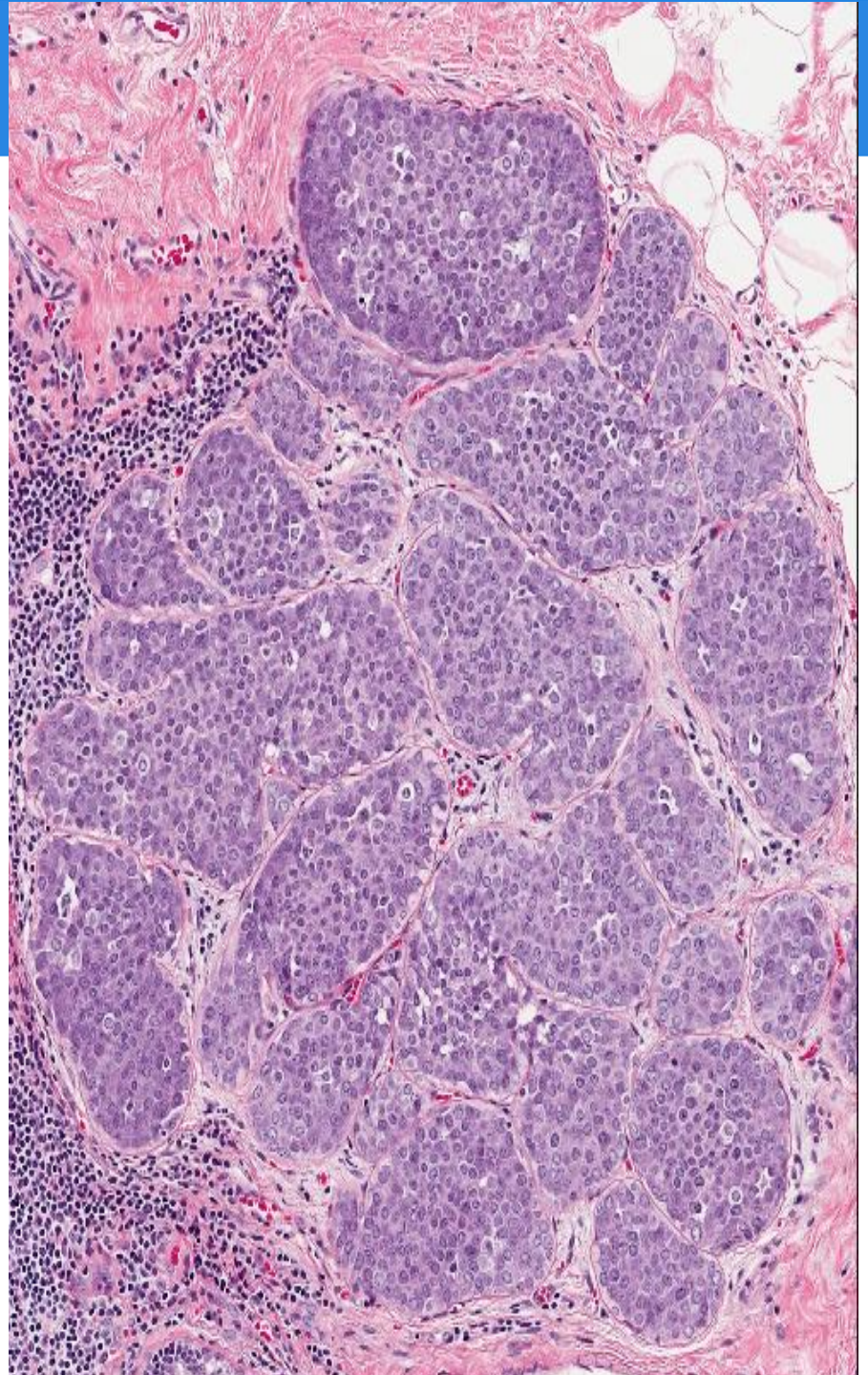
Normal TDLU



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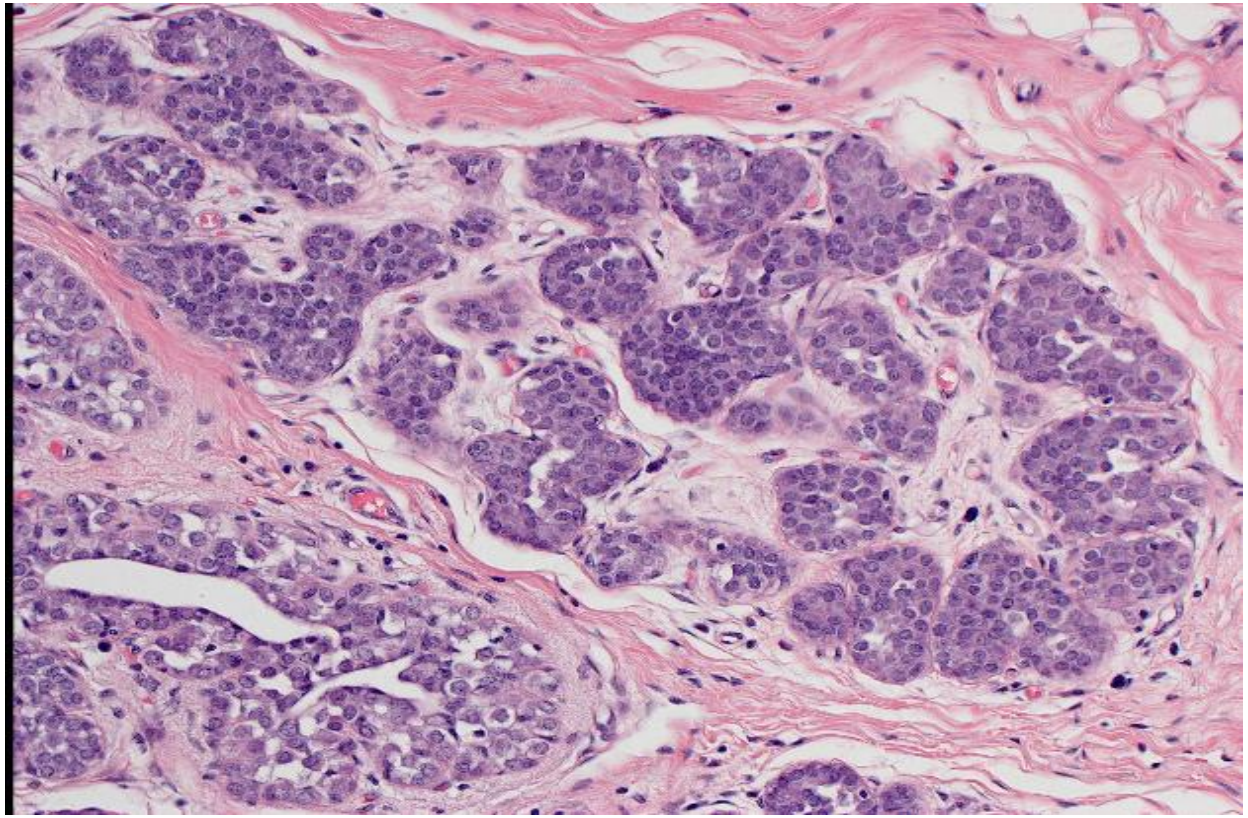
Classic LCIS - WHO 6th definition

- Non-invasive neoplastic proliferation of discohesive cells, originating in the TDLUs, with or without pagetoid involvement of terminal ducts.
- More than half of the acini in a TDLU are filled and expanded by the neoplastic cells.



WHO 6th ed (2026) - Atypical Lobular Hyperplasia (ALH) definition

<50% acini filled and expanded



Non-invasive low-grade neoplastic proliferation of small, discohesive cells, originating in the TDLUs, with or without pagetoid involvement of terminal ducts.

Fewer than half of the acini in a TDLU are filled and expanded by the neoplastic cells.

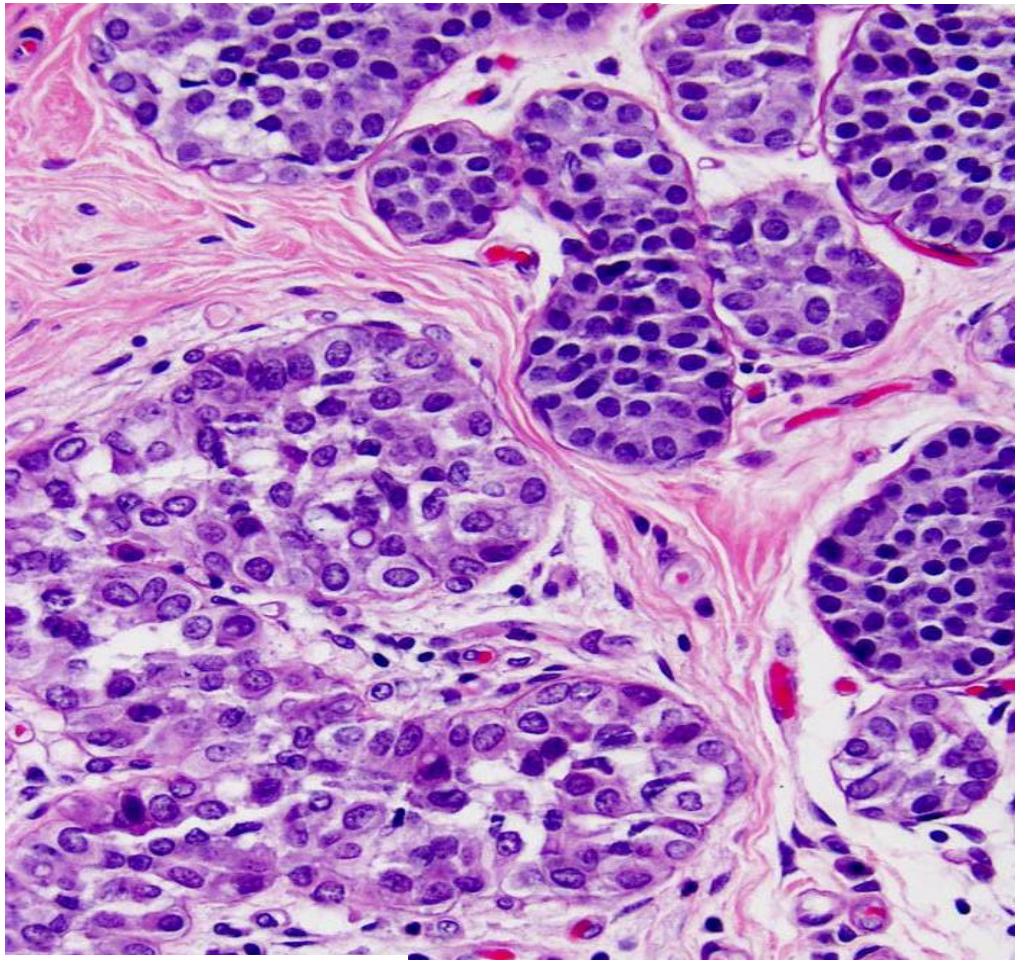
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Classic LCIS - histopathology

- Discohesive proliferation of type A and/or type B epithelial cells.
  - **Type A cells are small cells with uniform hyperchromatic nuclei (1–1.5 times the size of a lymphocyte)**
  - **Type B cells have slightly larger vesicular nuclei (2 times the size of a lymphocyte), with mild variability in size and shape and small nucleoli**
  - **The cell populations may be mixed in individual proliferations.**

Type A and Type B cells: Terminology first introduced by Haagensen CD, Lane N, Lattes R, Bodian C. Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. Cancer. 1978 Aug;42(2):737-69. PMID: 209887.

Type A cells

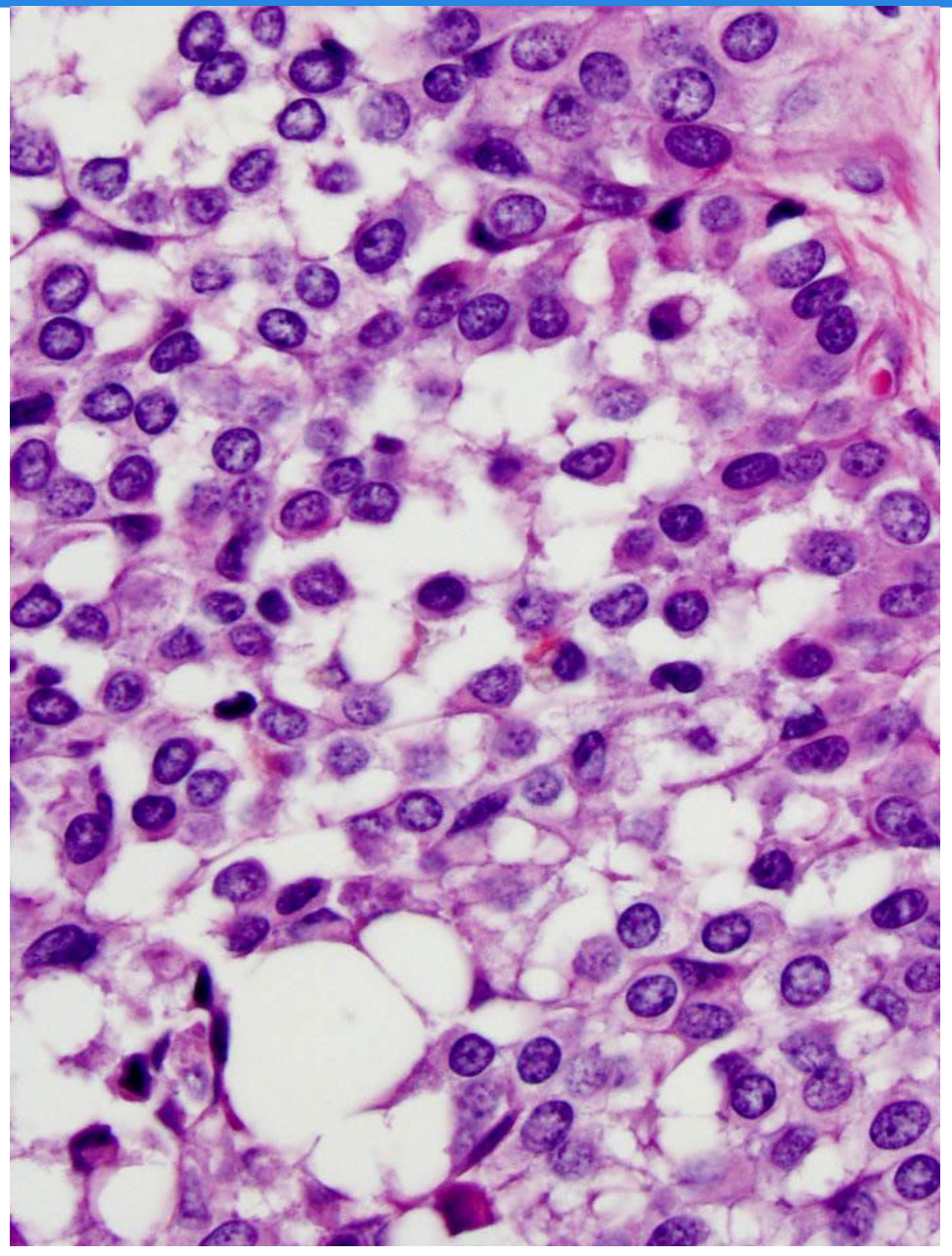


Type B cells

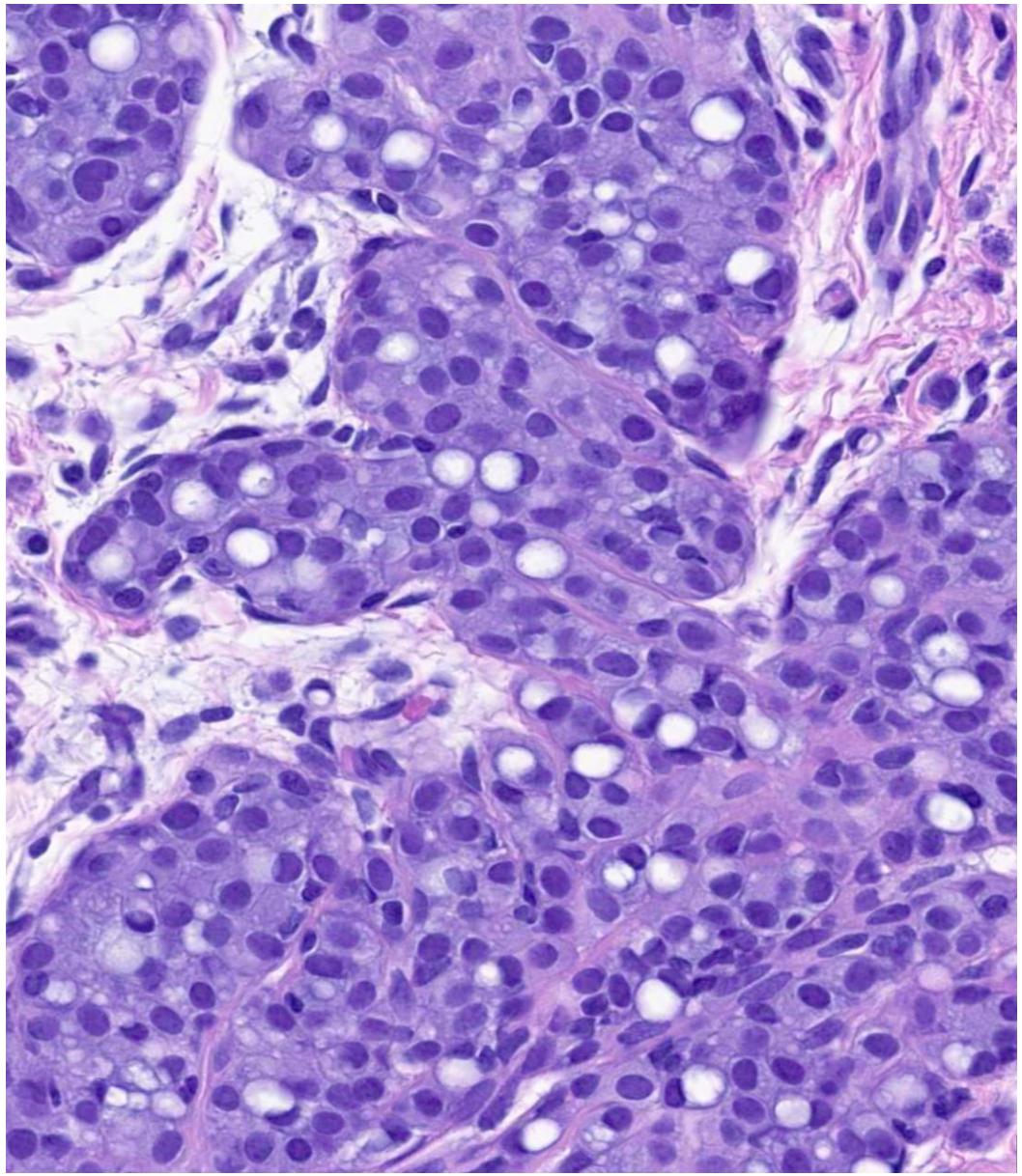
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Classic Lobular Neoplasia - Histopathology

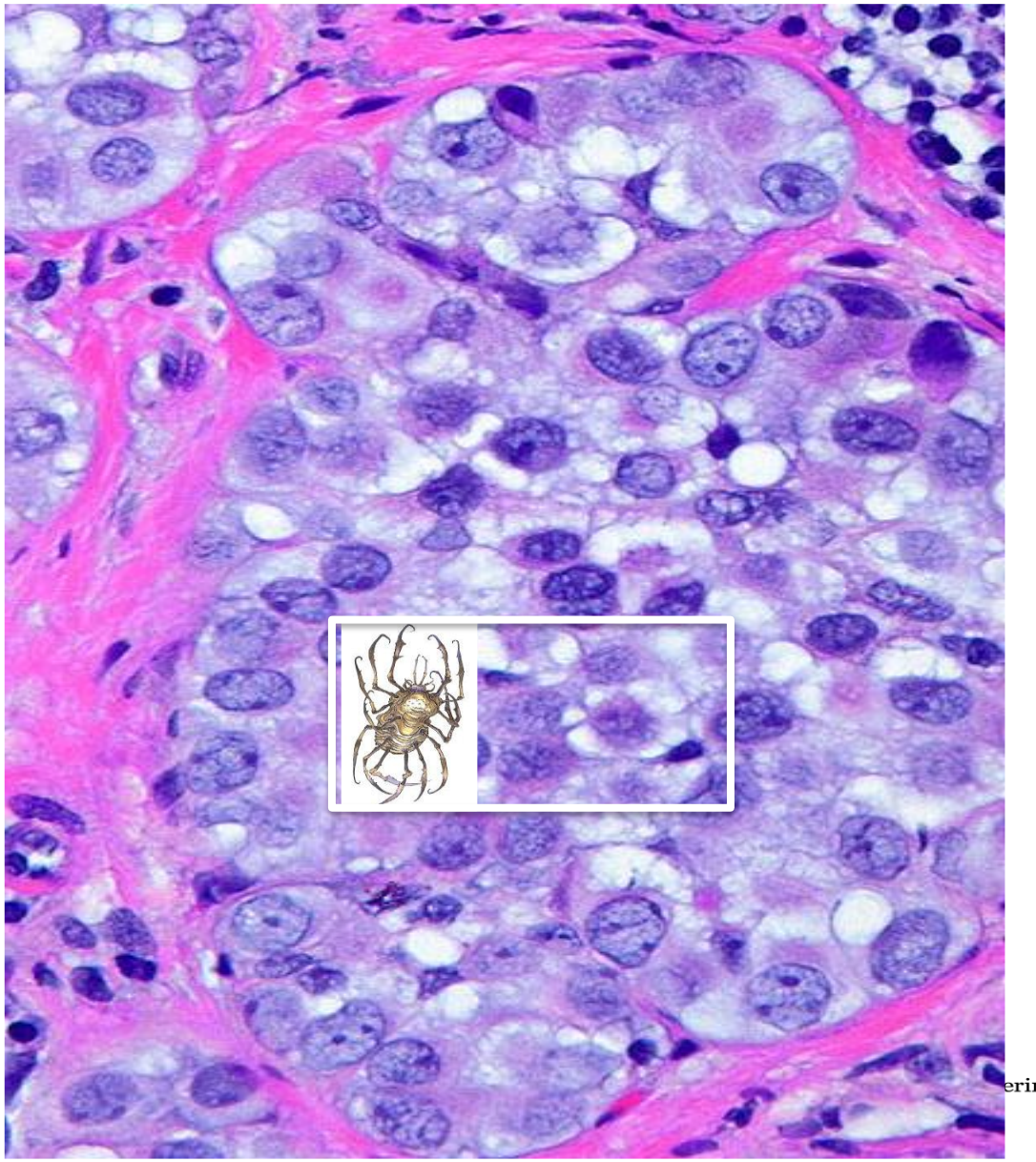
- Lobulocentric +/- Pagetoid spread
- Cell dyshesion
- Cytomorphology
  - **Round-oval cells with central nucleus**
  - **Lack of cell polarization ("fried egg" cells)**
  - Low (to intermediate) nuclear grade
  - Nucleolus absent or inconspicuous
  - Intracytoplasmic vacuoles common
- ***usually no mitotic activity***
- ***Single cell necrosis possible***
- ***Ca^{2+} rare and minute***



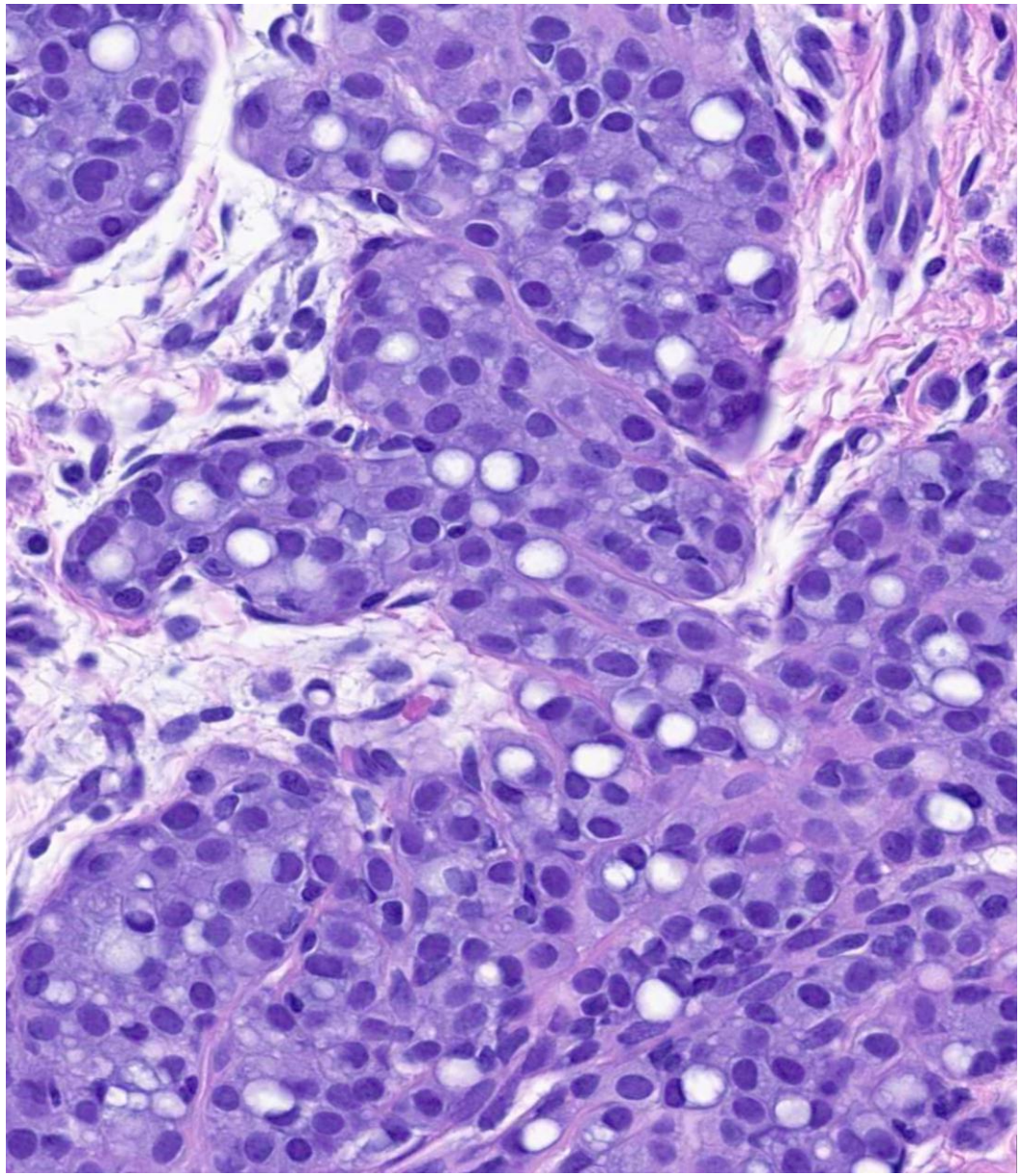
intracytoplasmic vacuoles



“spidery” cells

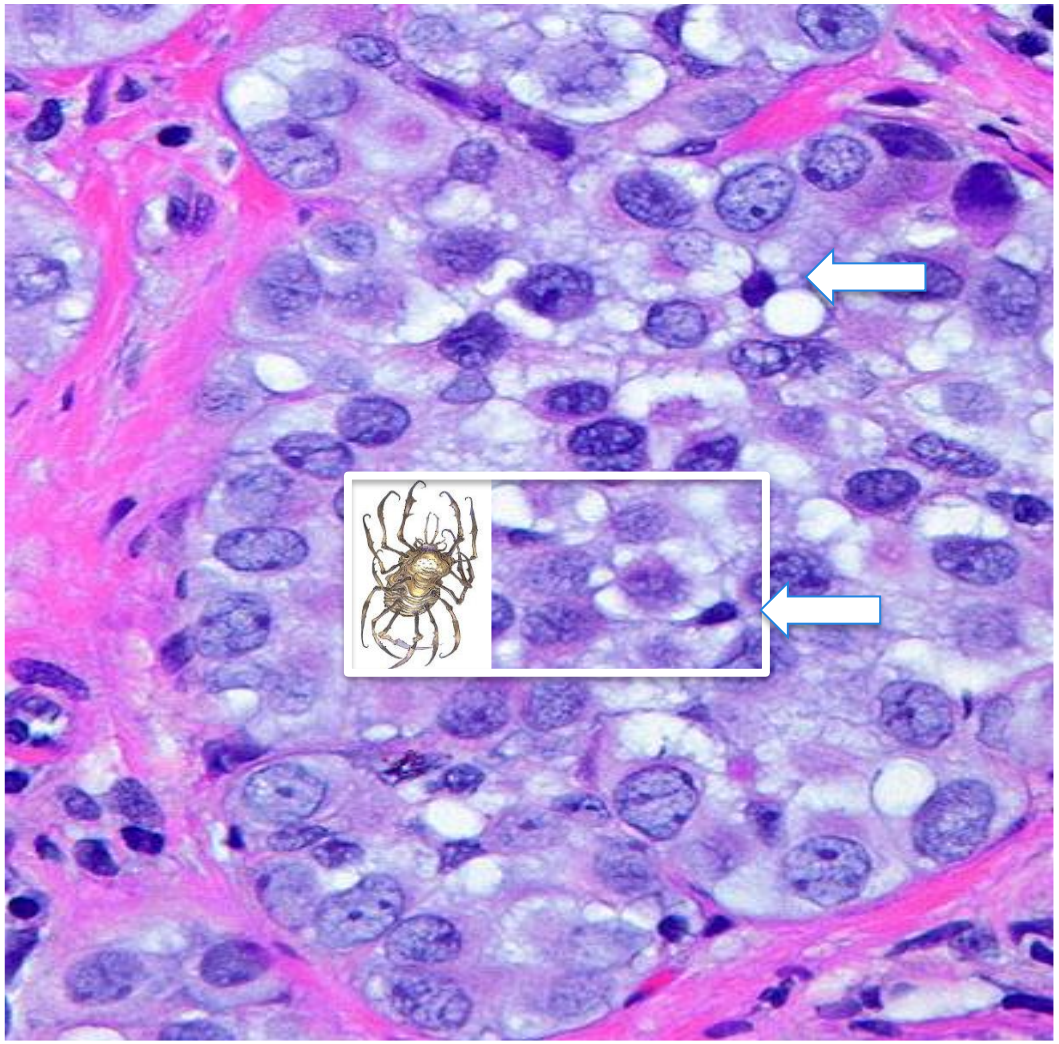


intracytoplasmic vacuoles



“spidery” cells

myoepithelial cell nuclei
admixed with classic LN



Classic LN – incidence and distribution

- **More common in premenopausal women (mean age: ~50 y)**
  - ER-dependent proliferation; regresses to some degree after the menopause
- **Incidental finding in breast biopsies performed for other indications**
  - <2% in biopsies of mammographic Ca^{2+} or MRI non-mass enhancement
    MRI detects LCIS as non-mass enhancement = LCIS is NOT an incidental finding on MRI
  - in 0.5–3.6% of otherwise benign breast biopsies
  - in 0.04–1.2% of reduction mammoplasty specimens
  - Incidence has increased in recent years
    - Possible contributing factors: breast screening; better imaging; more biopsies; hormone replacement therapy; pathology training and use of IHC
- **Multifocal/ multicentric in ~80% cases, bilateral in 40% cases**

Haagensen CD, et al(1978) Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. Cancer. 42(2):737–769

Differential Diagnosis

Morphologic mimics of Classic LN

- Poor tissue preservation
- Secretory change
- Clear cell change
- DCIS with clear cells
- Myoepithelium/ myoepithelial hyperplasia

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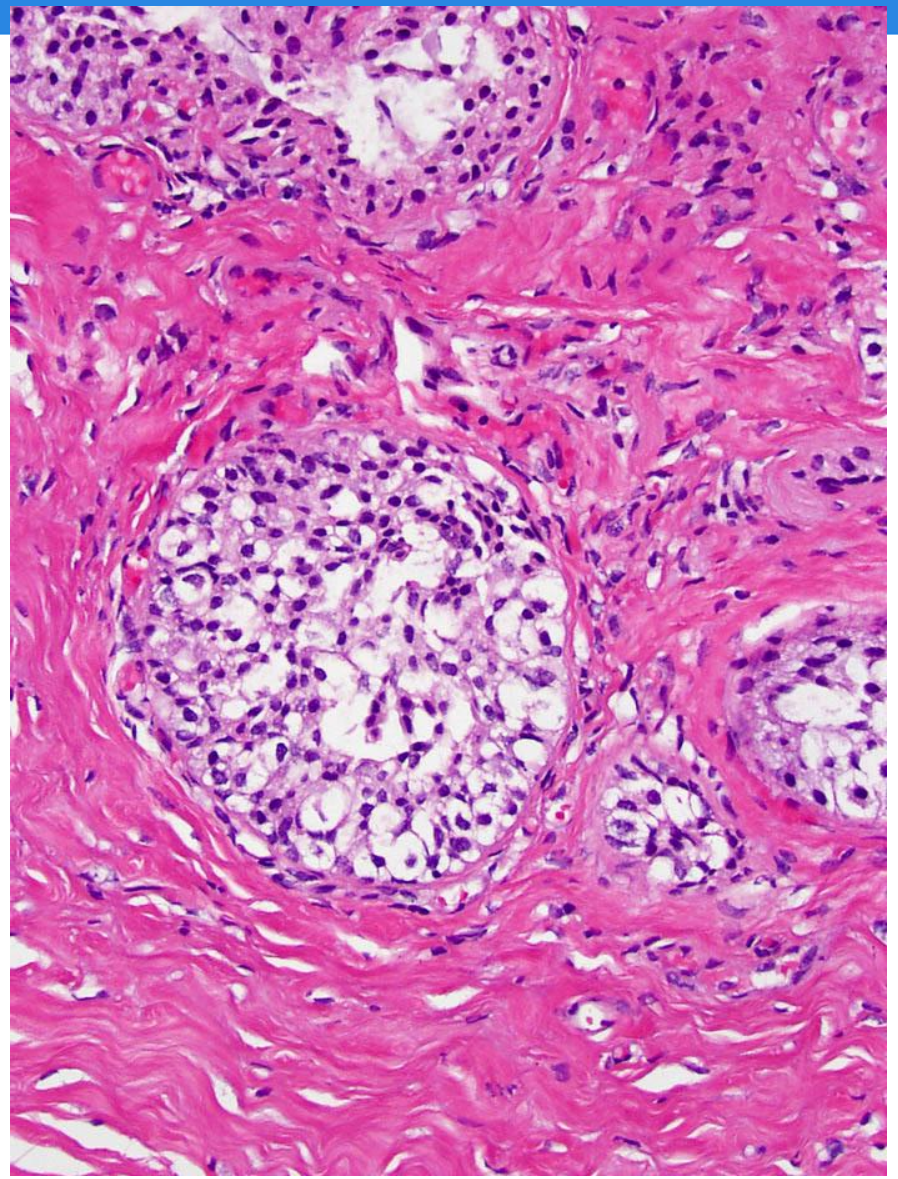
Poor tissue preservation

General rule: cannot render a definitive diagnosis of carcinoma/ high risk lesion if the tissue is poorly preserved

Evaluate adjacent well-preserved tissue

Interpret IHC cautiously

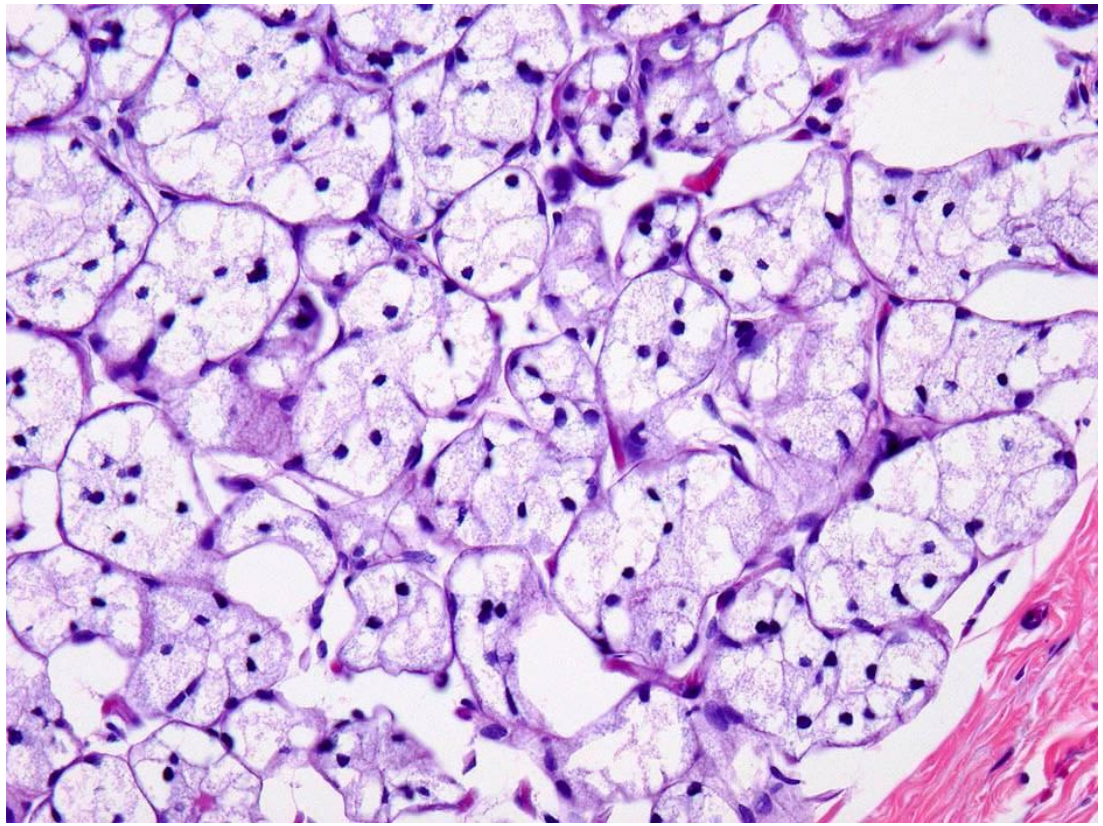
- poorly preserved/ cauterized tissue may not stain at all
- absence of staining is not always diagnostic
- only positive staining that appears to be appropriate for the expected cell type/ lesion can be interpreted with confidence



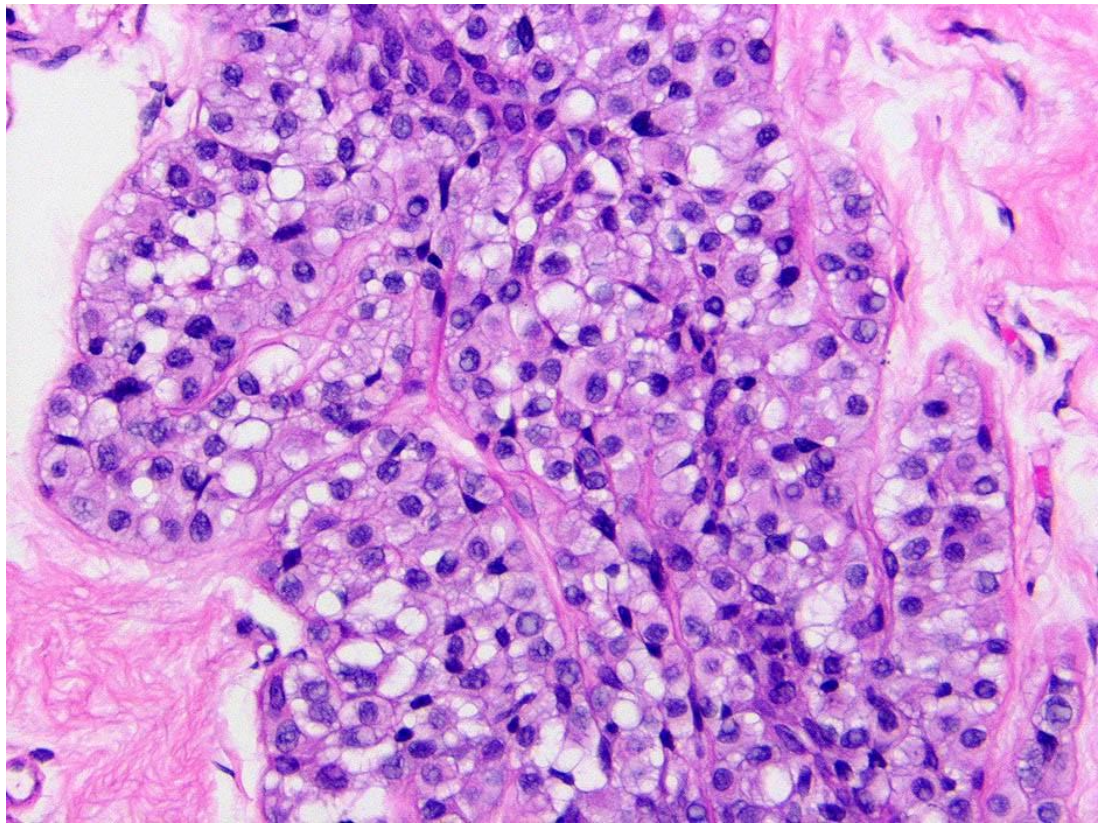
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Common mimics of classic LCIS/ ALH

Clear Cell Change



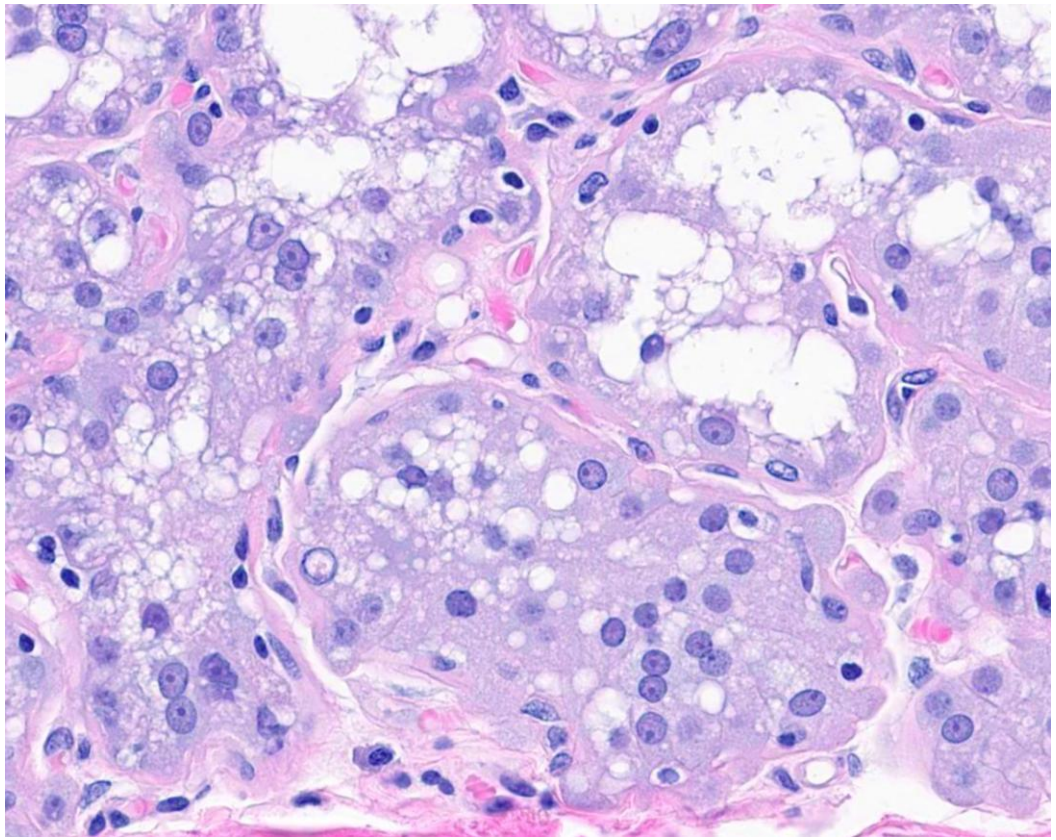
Classic LCIS



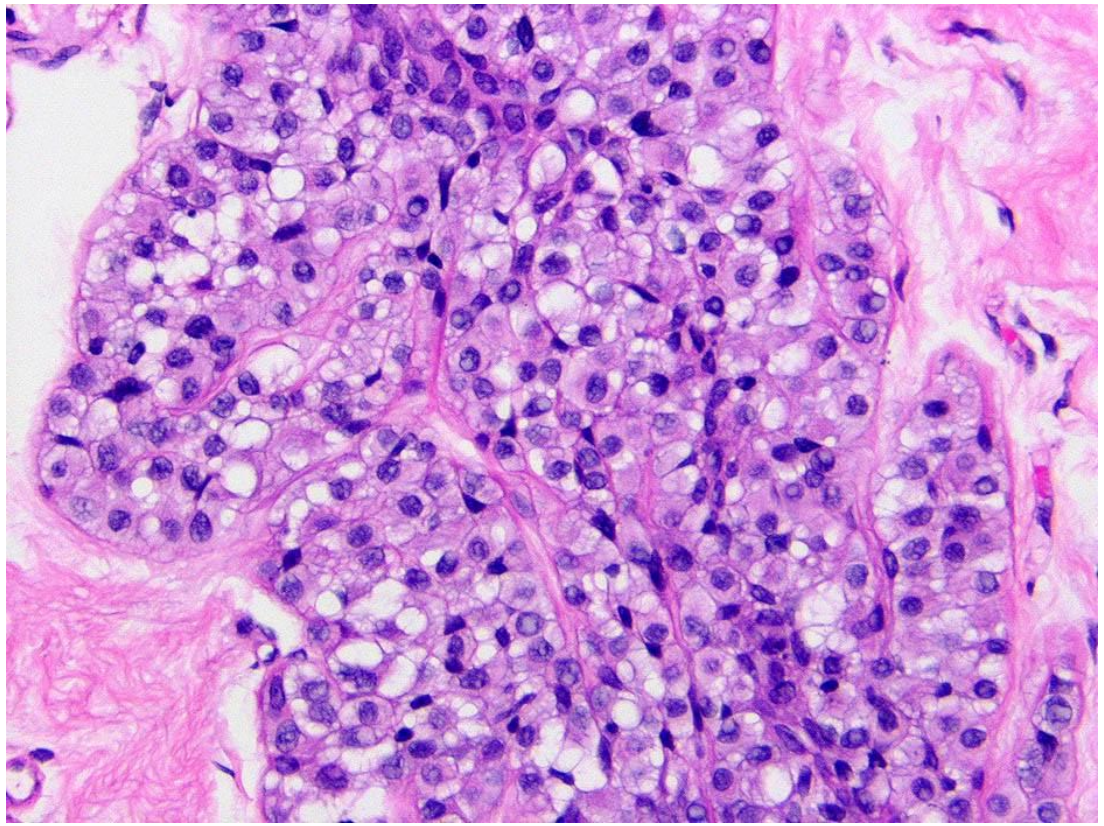
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Common mimics of classic LCIS/ ALH

secretory/ lactation change



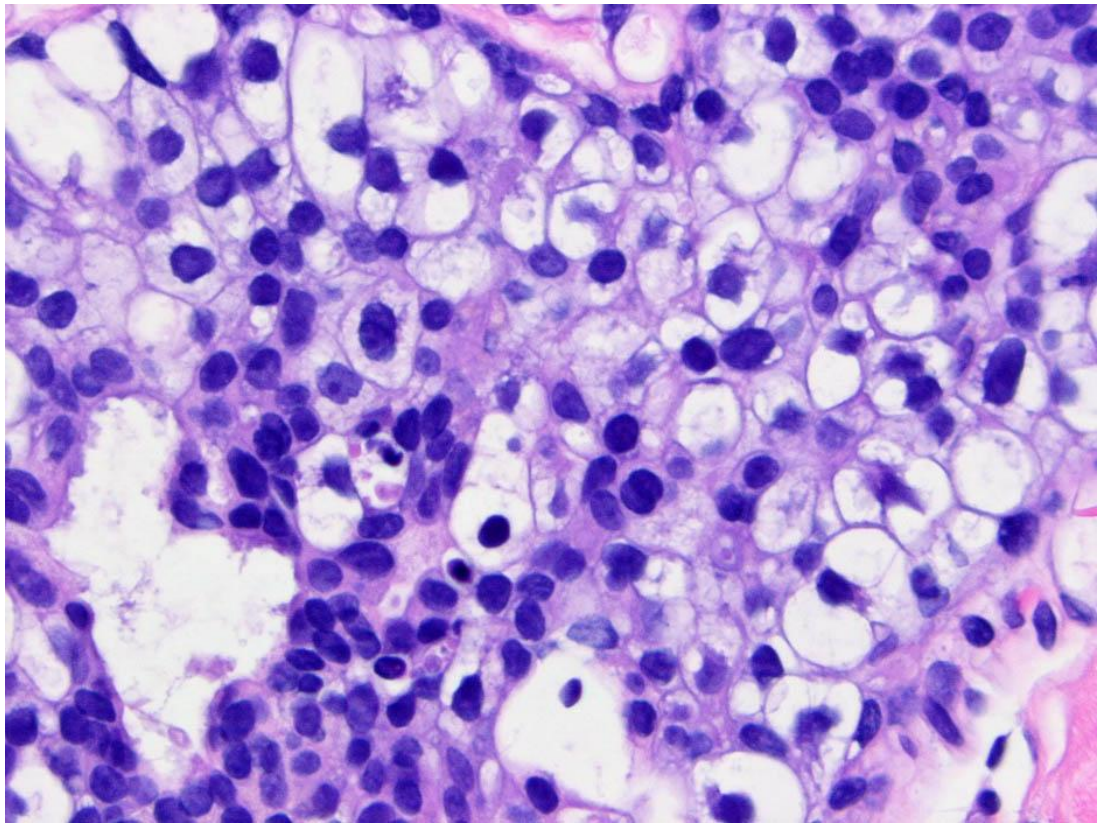
Classic LCIS



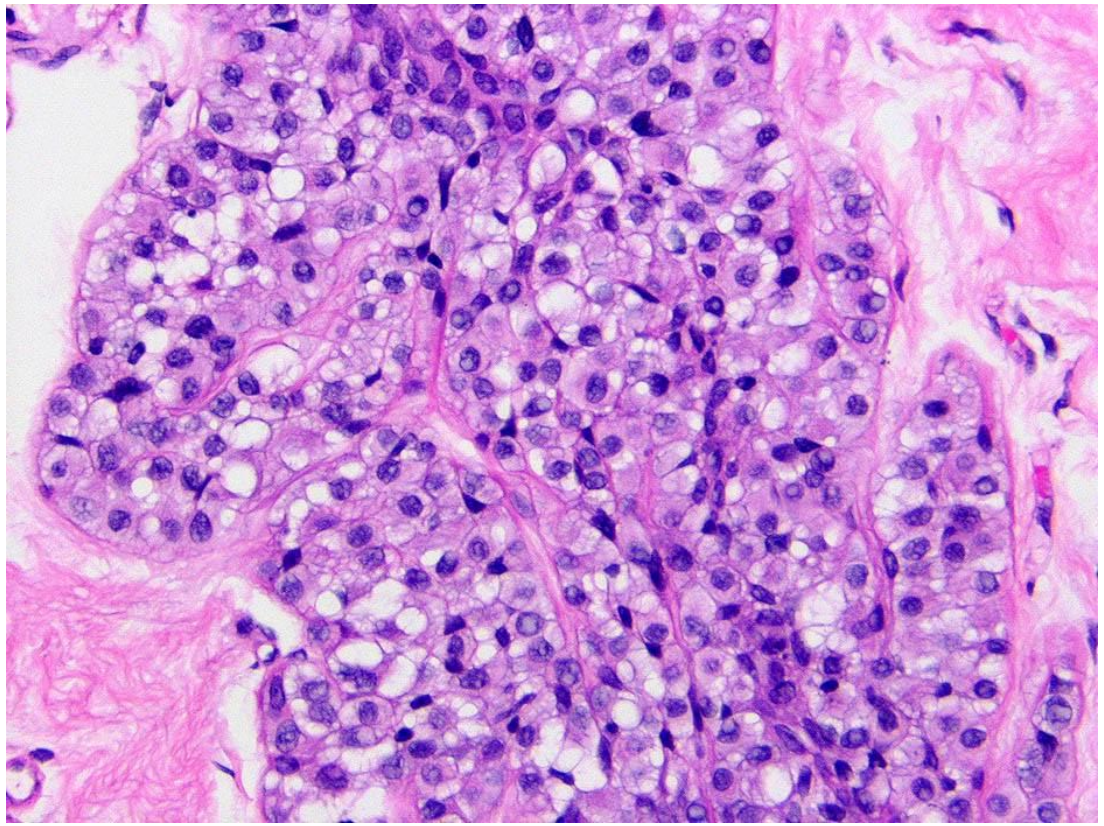
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Common mimics of classic LCIS/ ALH

DCIS with clear cell morphology

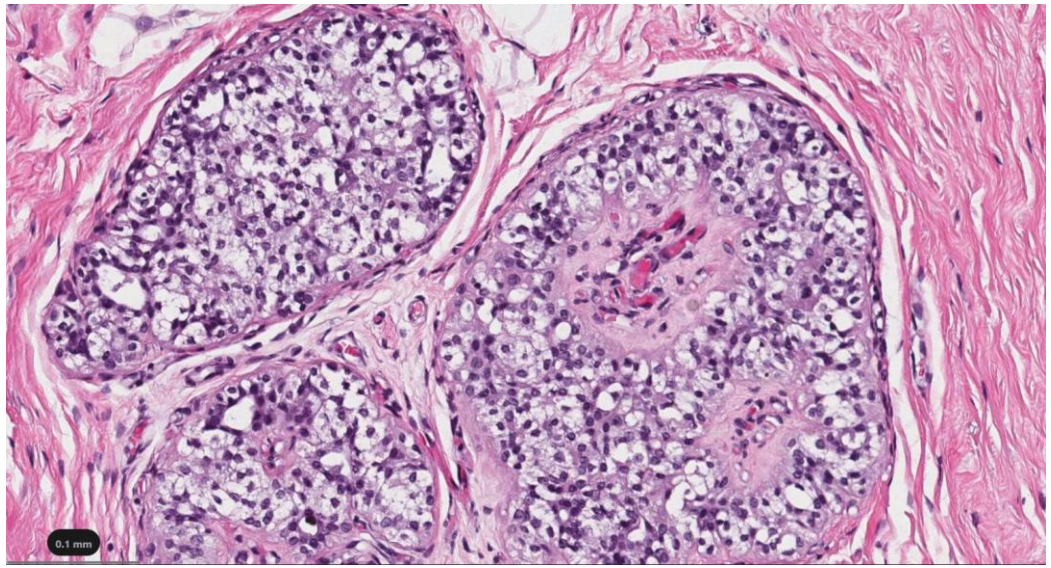


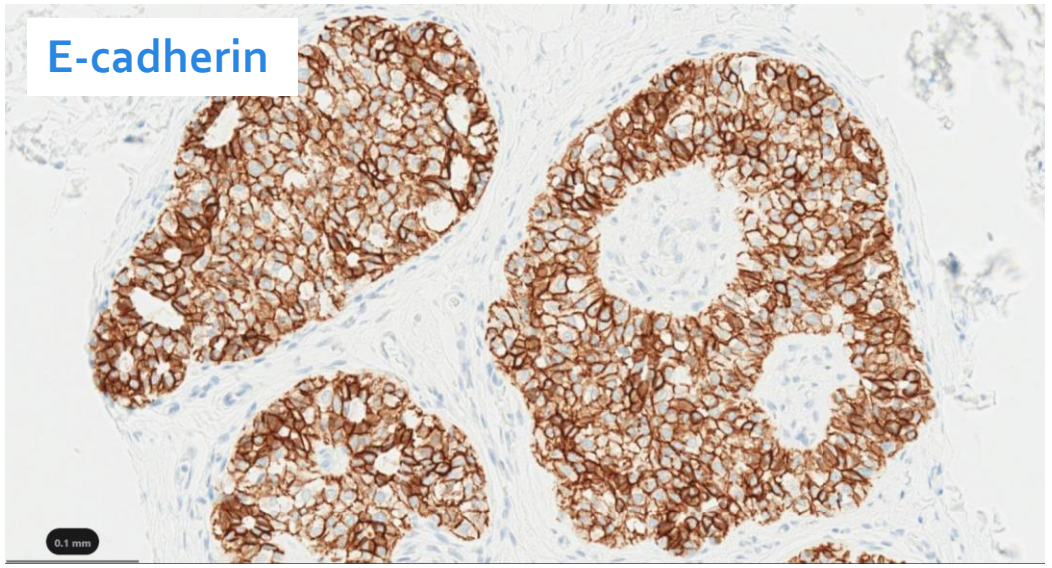
classic LCIS

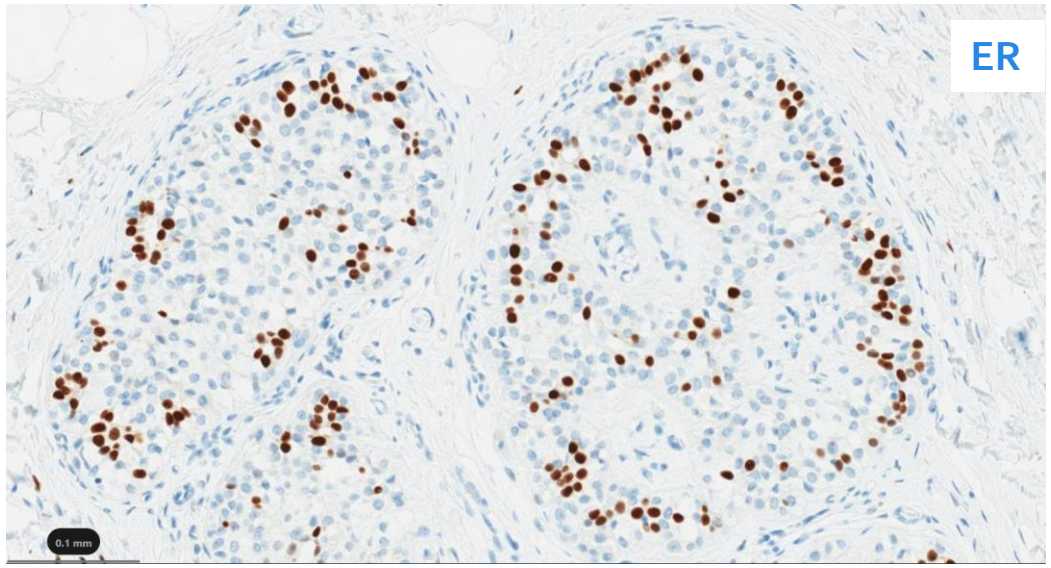


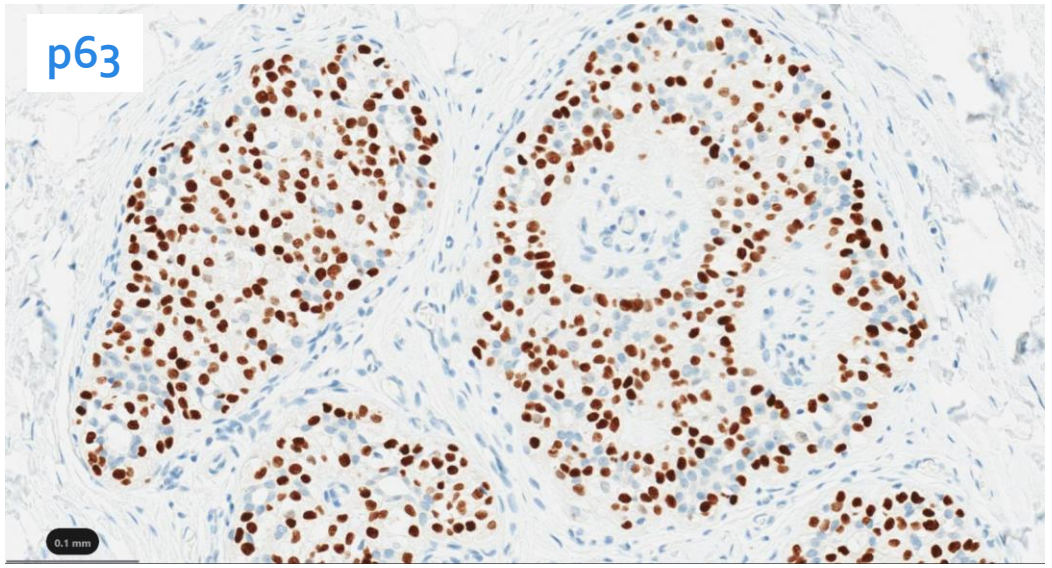
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Myoepithelial cells may mimic Classic Lobular Neoplasia







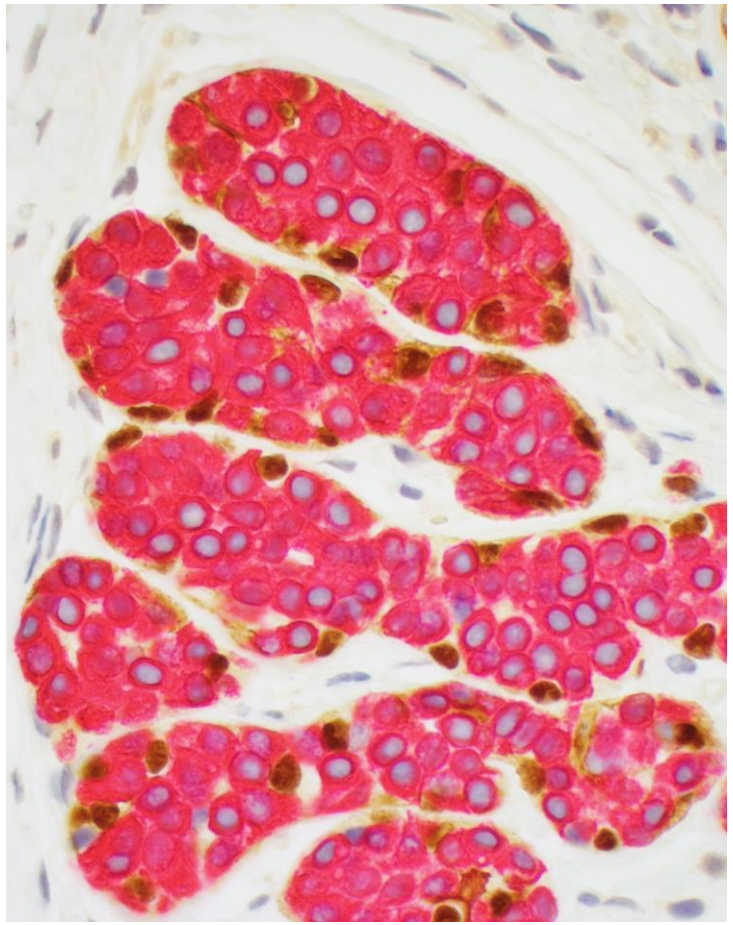


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Myoepithelium and classic LCIS: 3 possible patterns

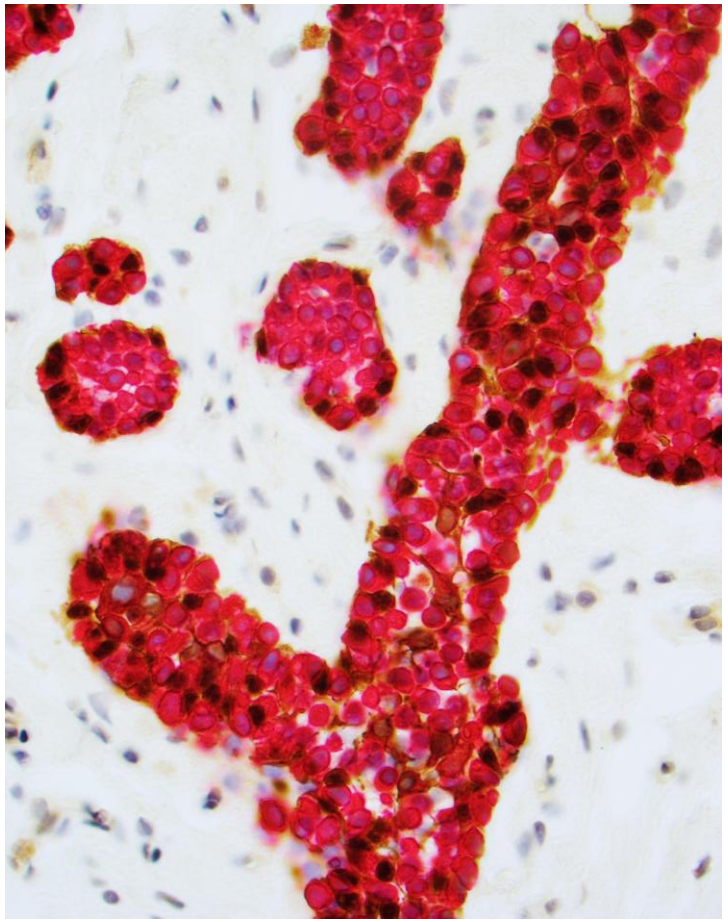
Normal

MECs lie flat on BM



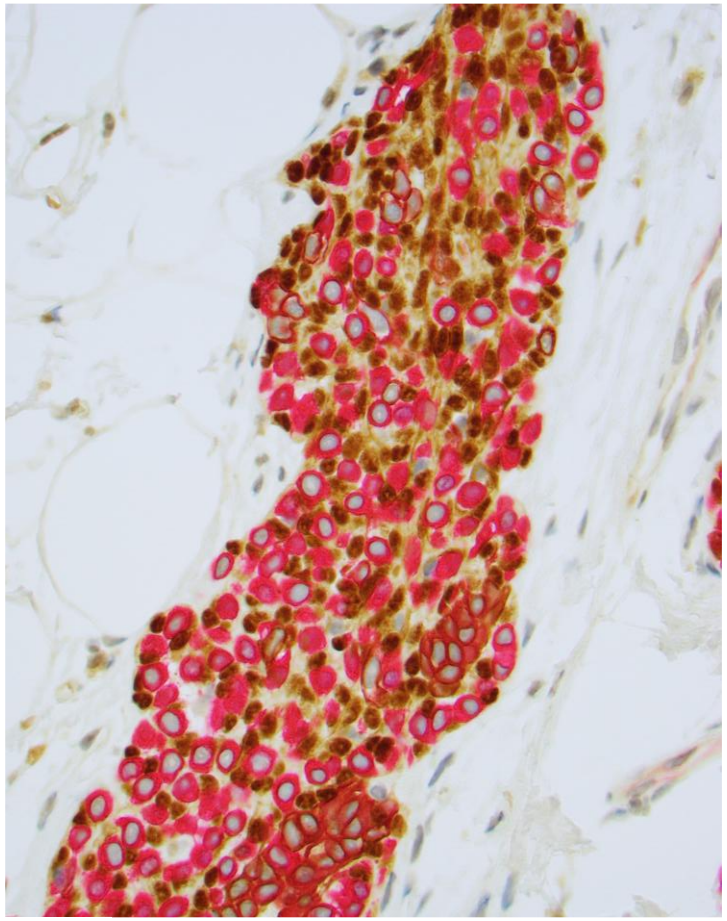
Perpendicular

MECs perpendicular to BM



Central

MECs interdigitate with LCIS



ADH5 IHC: Brown= p63, CK5/14 Red= CK7/18

Wang Y, et al. Myoepithelial cells in lobular carcinoma in situ: distribution and immunophenotype. Hum Pathol. 2016;55:126-34.

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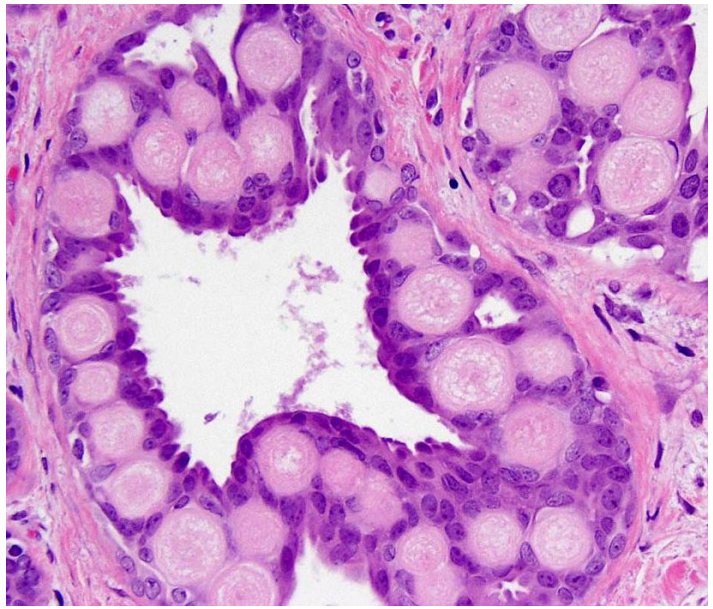
Collagenous Spherulosis (CS)

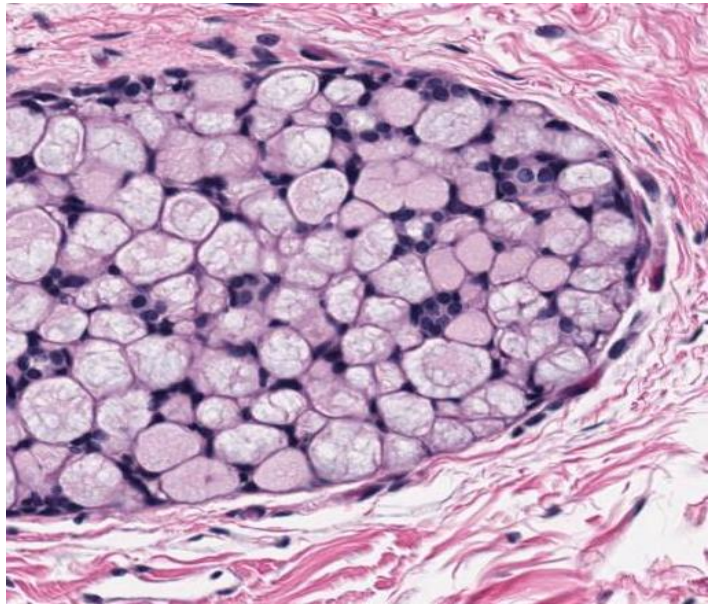
- Globoid deposits of eosinophilic or myxoid extracellular matrix surrounded by basement membrane and myoepithelium

Clement P et al, *AJSP* 1987

- Usually incidental, but may be mass-forming (1-3 mm)
- may harbor Ca^{2+} → mammographic detection

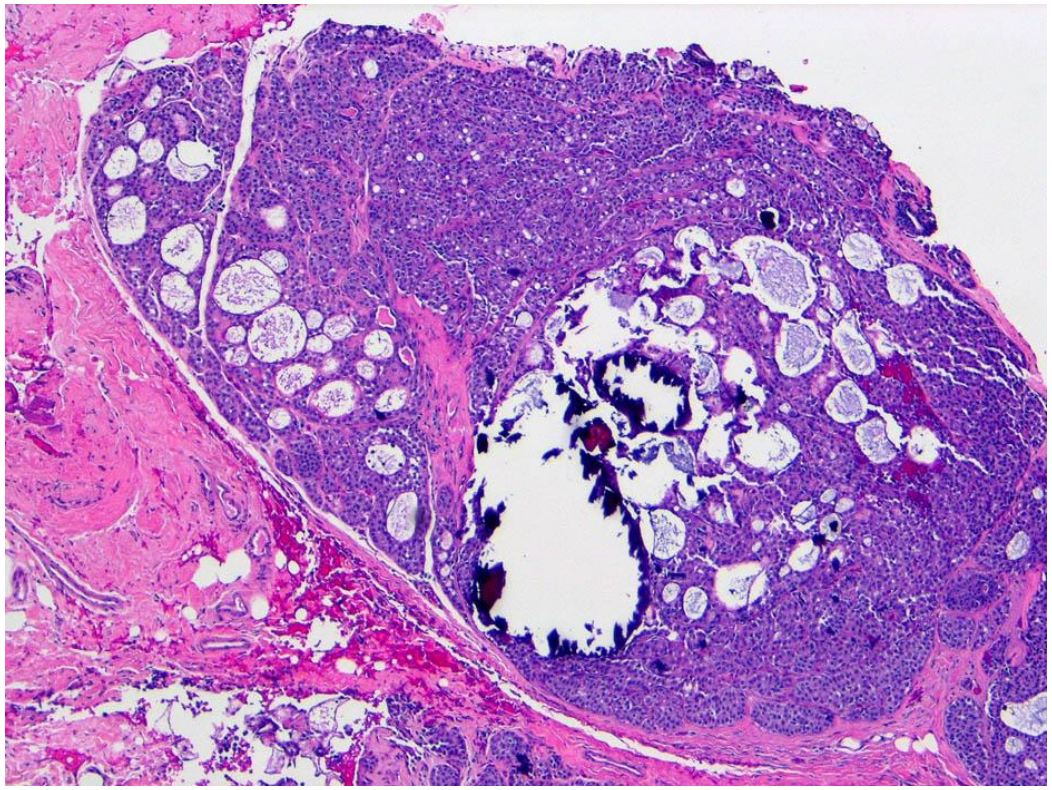
Resetkova E et al, *AJSP* 2006

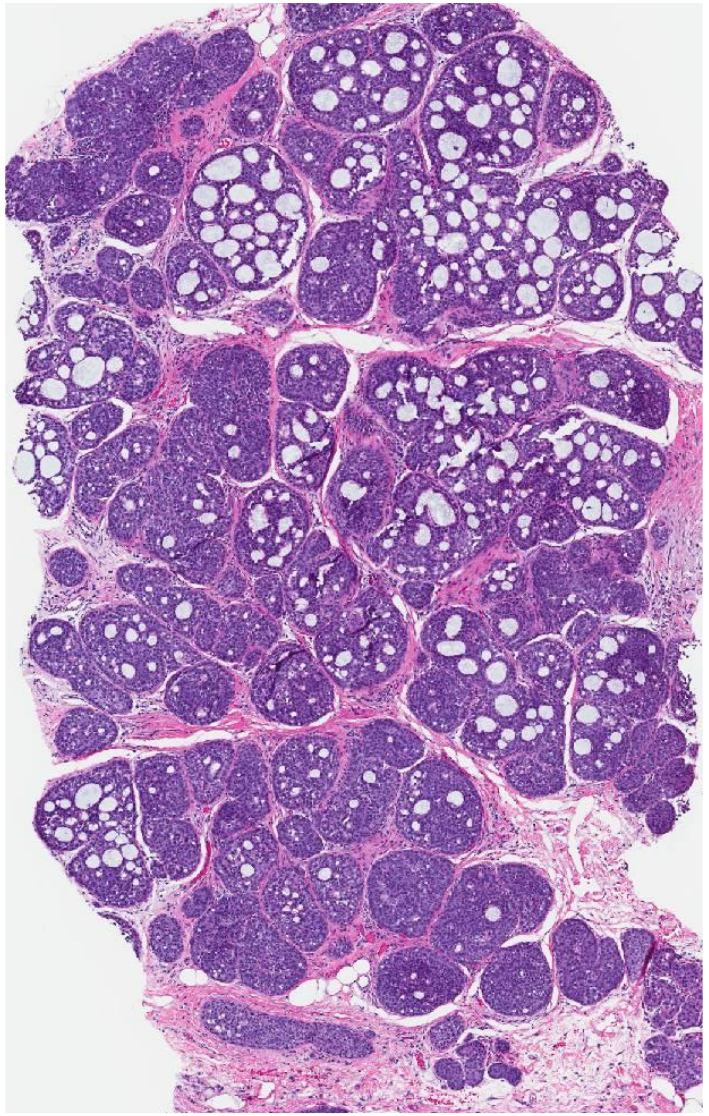


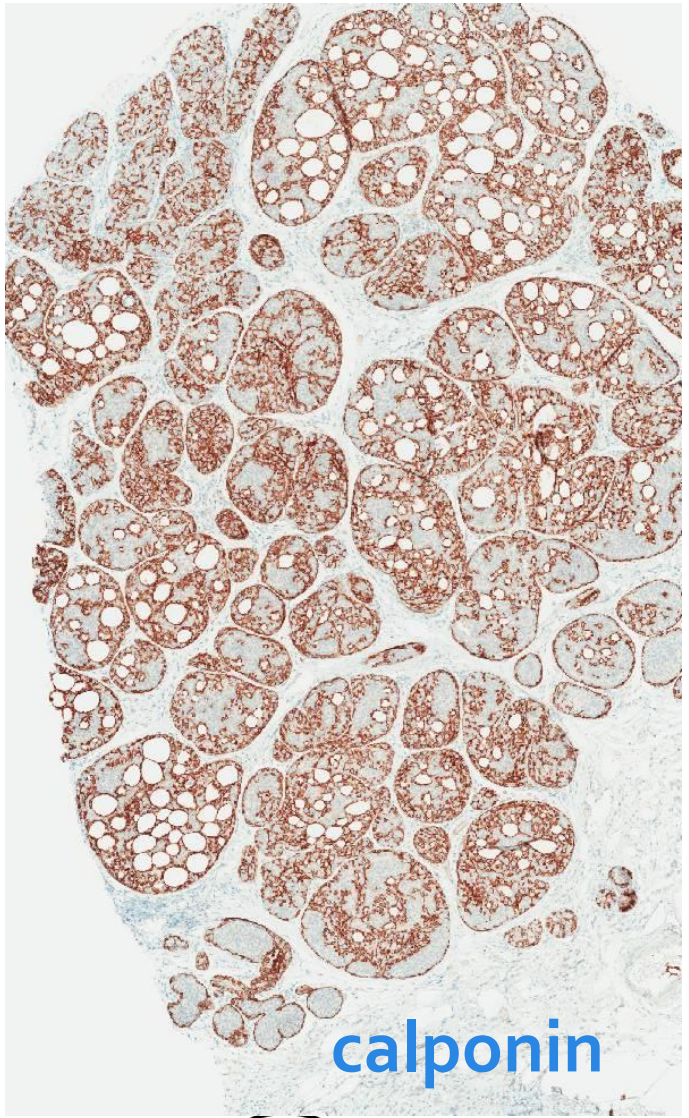




Classic LN in collagenous spherulosis may mimic ADH/ low grade DCIS







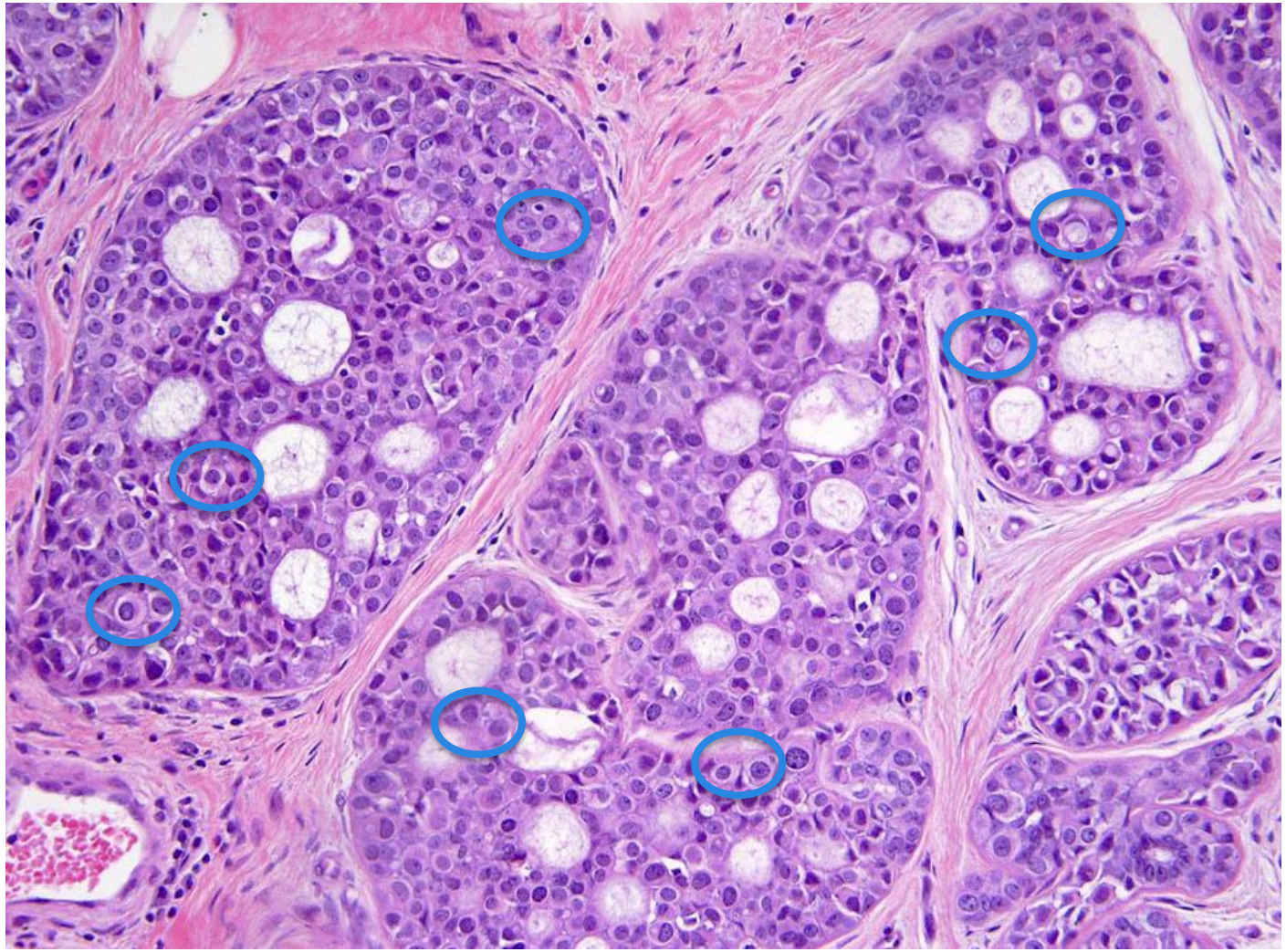
Sgroi D, Koerner FC. Involvement of collagenous spherulosis by lobular carcinoma in situ. Potential confusion with cribriform ductal carcinoma in situ. Am J Surg Pathol. 1995;19(12):1366-70.

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How to recognize CS with Classic Lobular Neoplasia

Atypical cells

- "fried egg" and "signet ring" cells
- no polarized cells present



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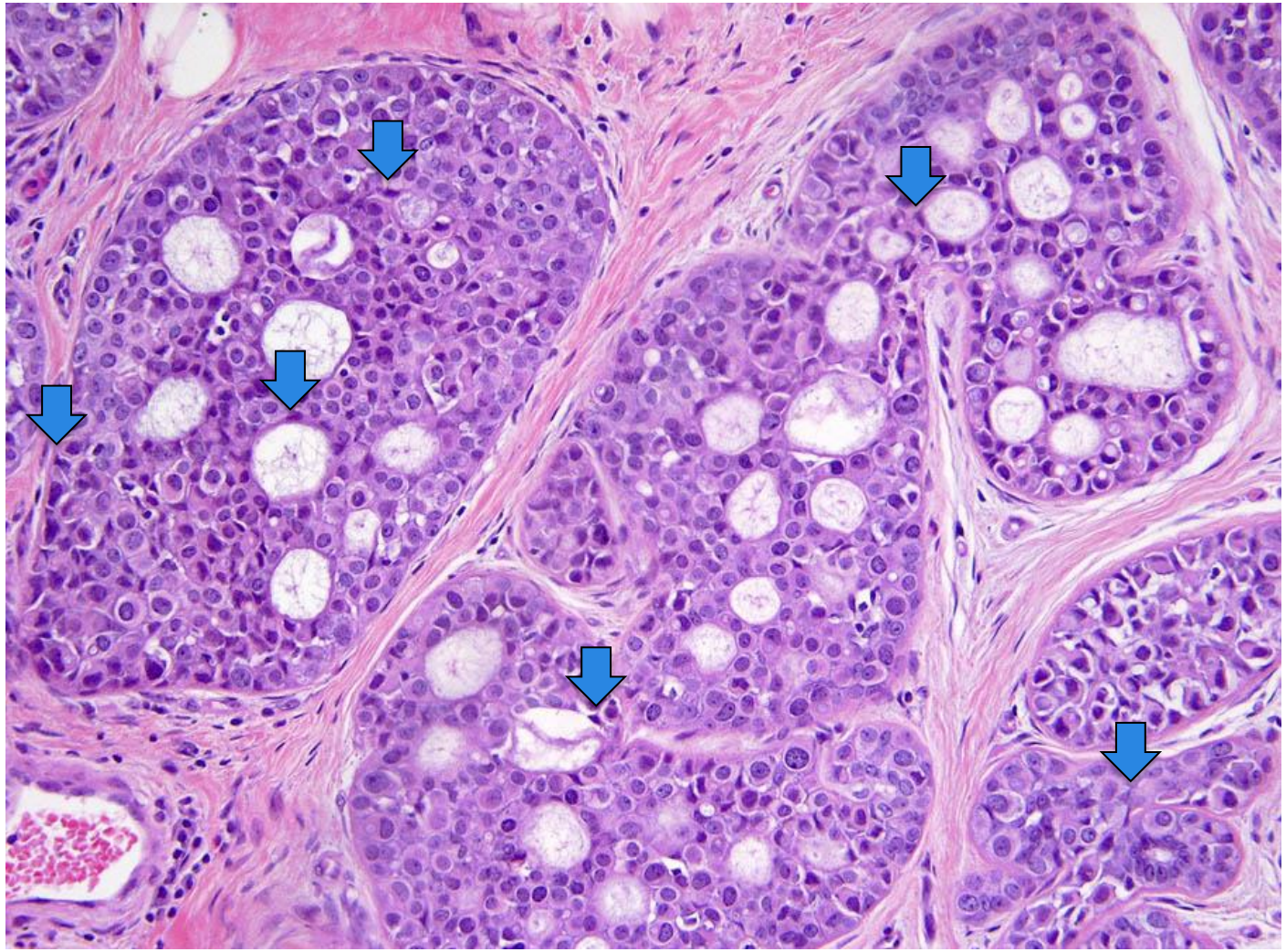
How to recognize Classic Lobular Neoplasia in CS

Atypical cells

- "fried egg" and "signet ring" cells
- no polarized cells present

MEC nuclei

- tangential arrangement in relation to pseudocribriform spaces
- comma- or apostrophe-like shape, dense chromatin, admixed with classic LN



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How to recognize Classic Lobular Neoplasia in CS

Atypical cells

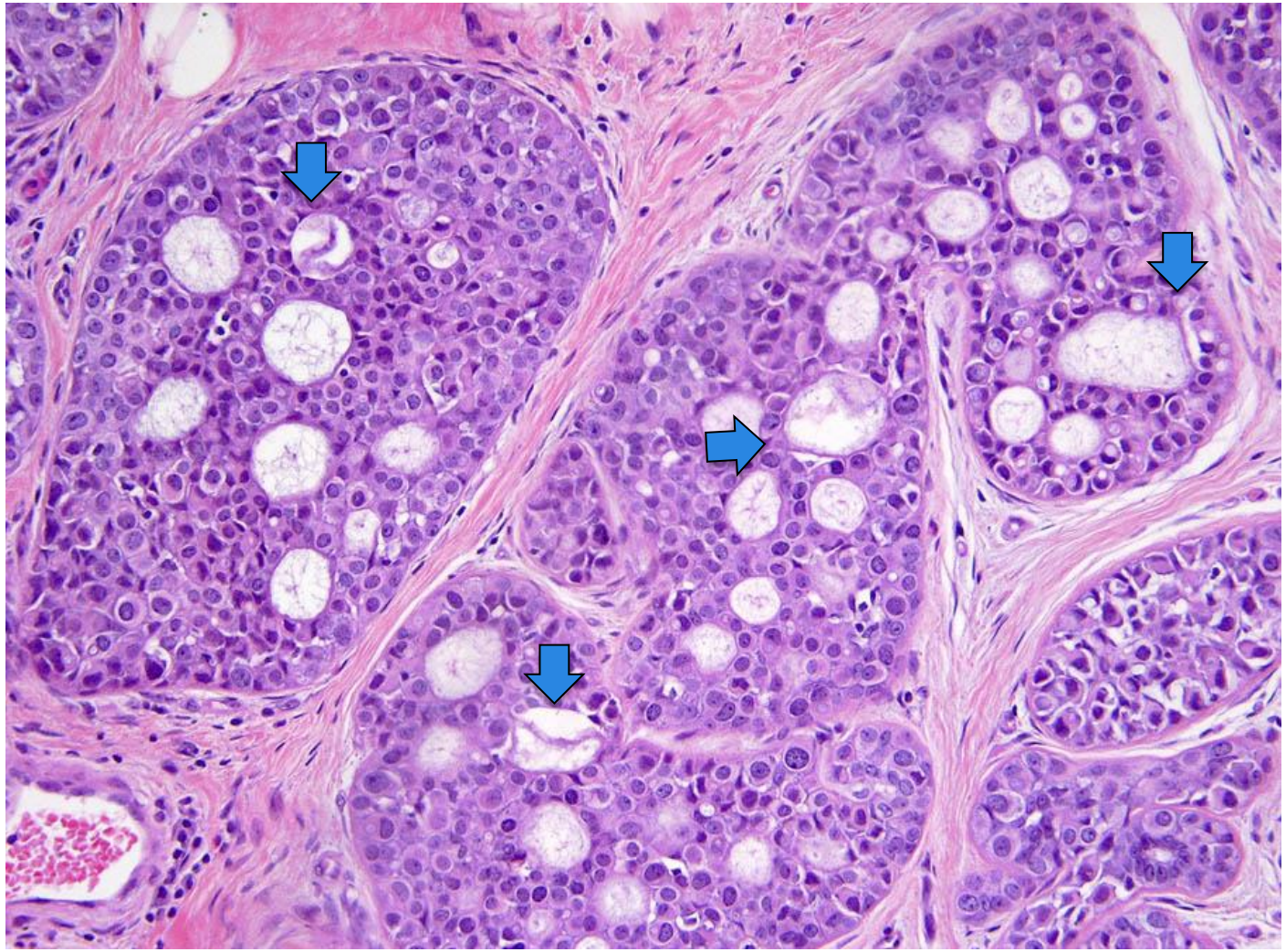
- "fried egg" and "signet ring" cells
- no polarized cells present

MEC nuclei

- tangential arrangement in relation to pseudocribriform spaces
- comma- or apostrophe-like shape, dense chromatin, admixed with classic LN

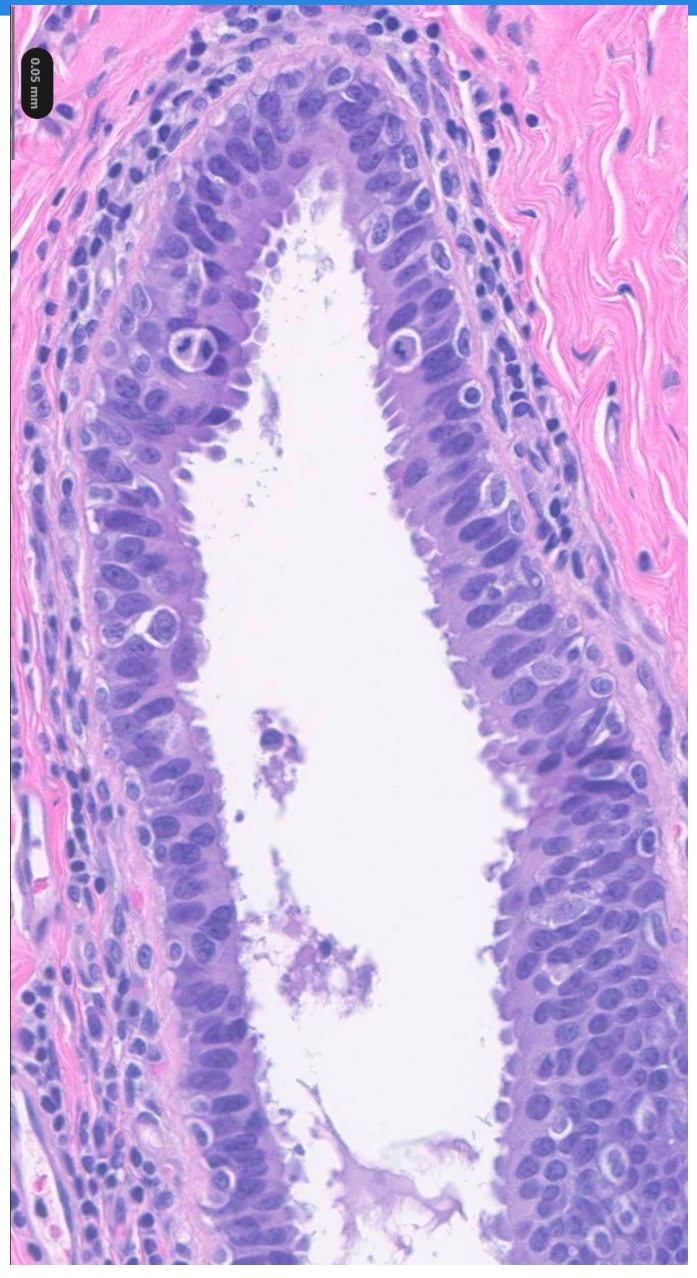
Pseudocribriform spaces

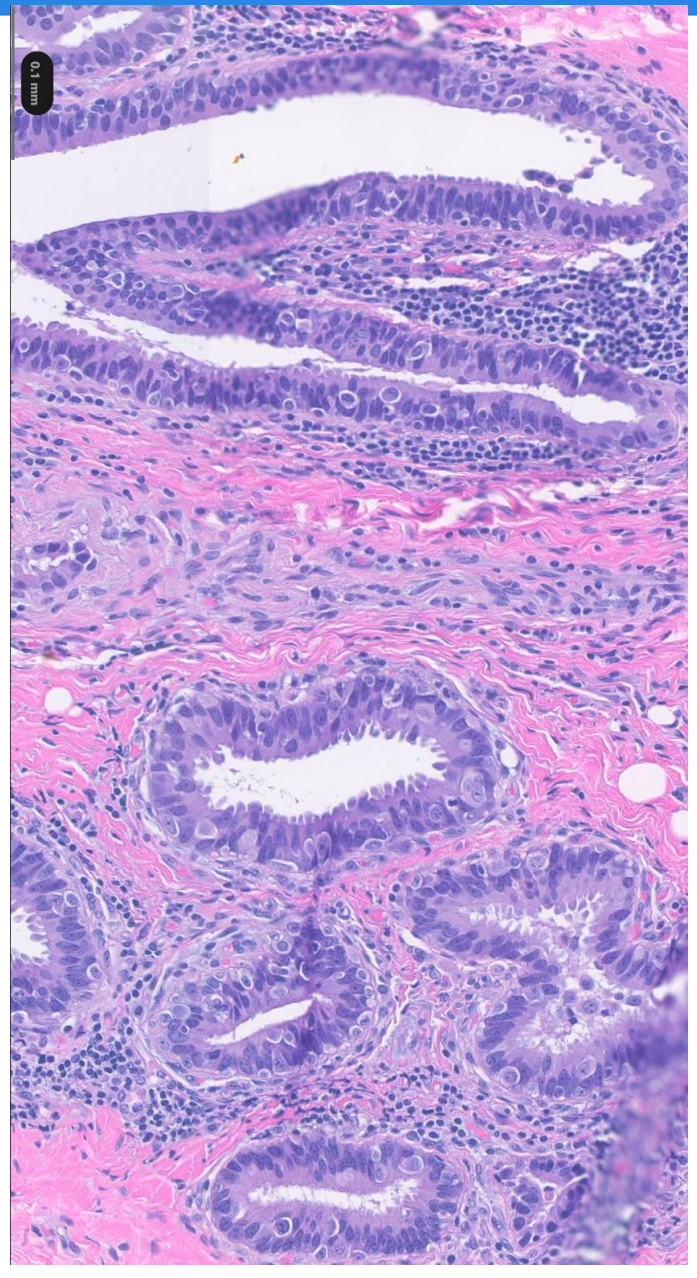
- **contain myxoid fibrillary material**
- **surrounded by cuticle of dense BM**
- **focal collapse of the BM cuticle around CS → cord that transects a pseudo-lumen**

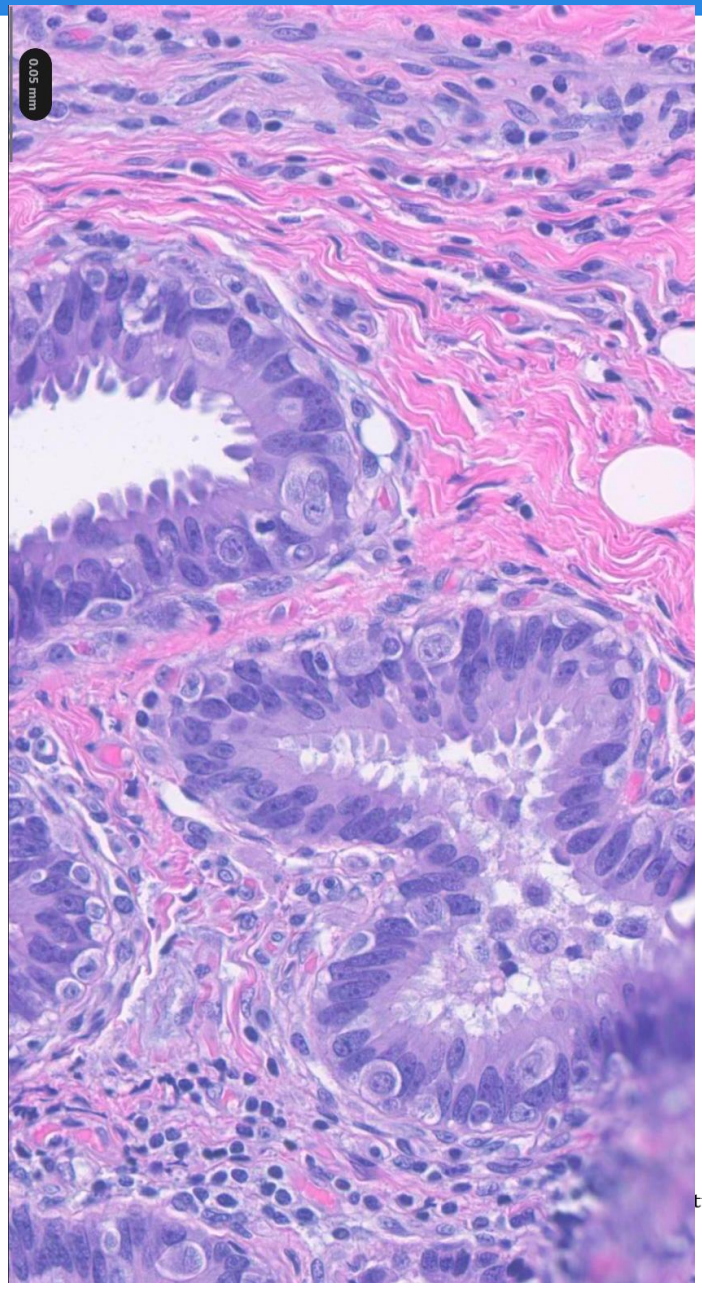


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Another recent case



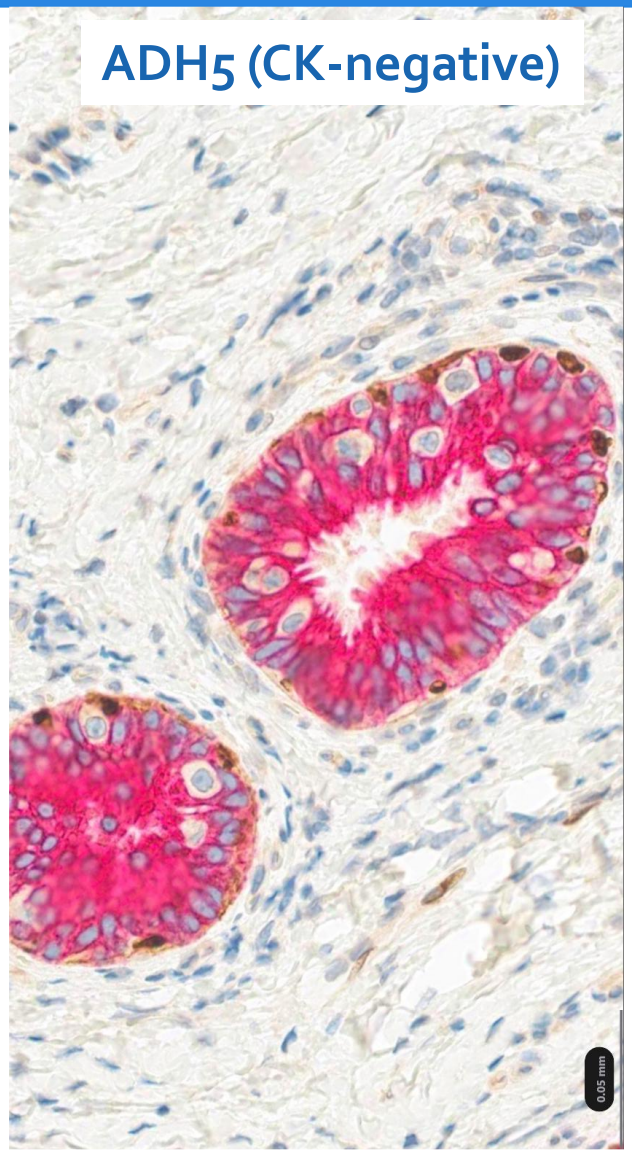




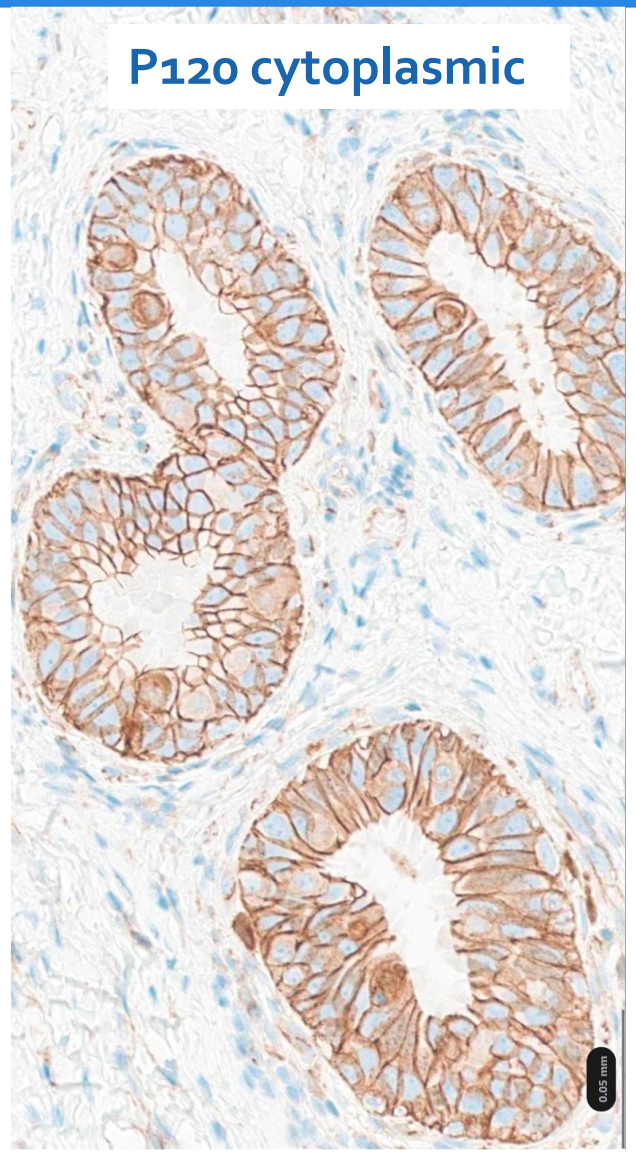
ttering

Another recent case: immunohistochemistry

ADH5 (CK-negative)

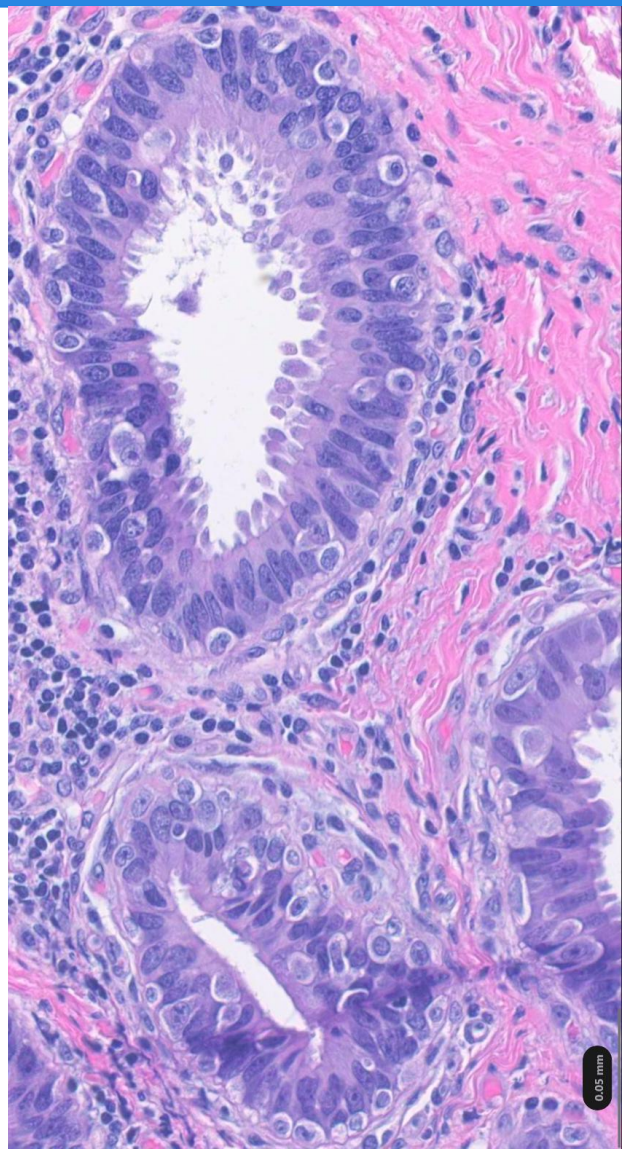


P120 cytoplasmic



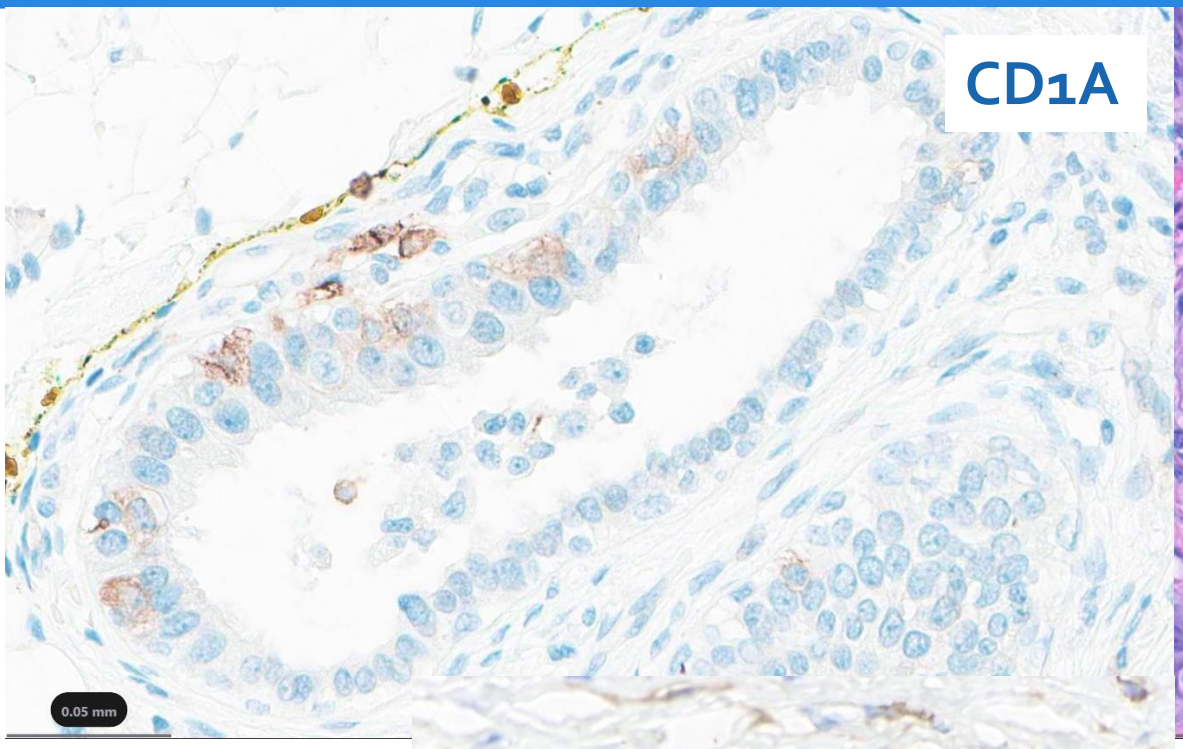
E-cadherin negative

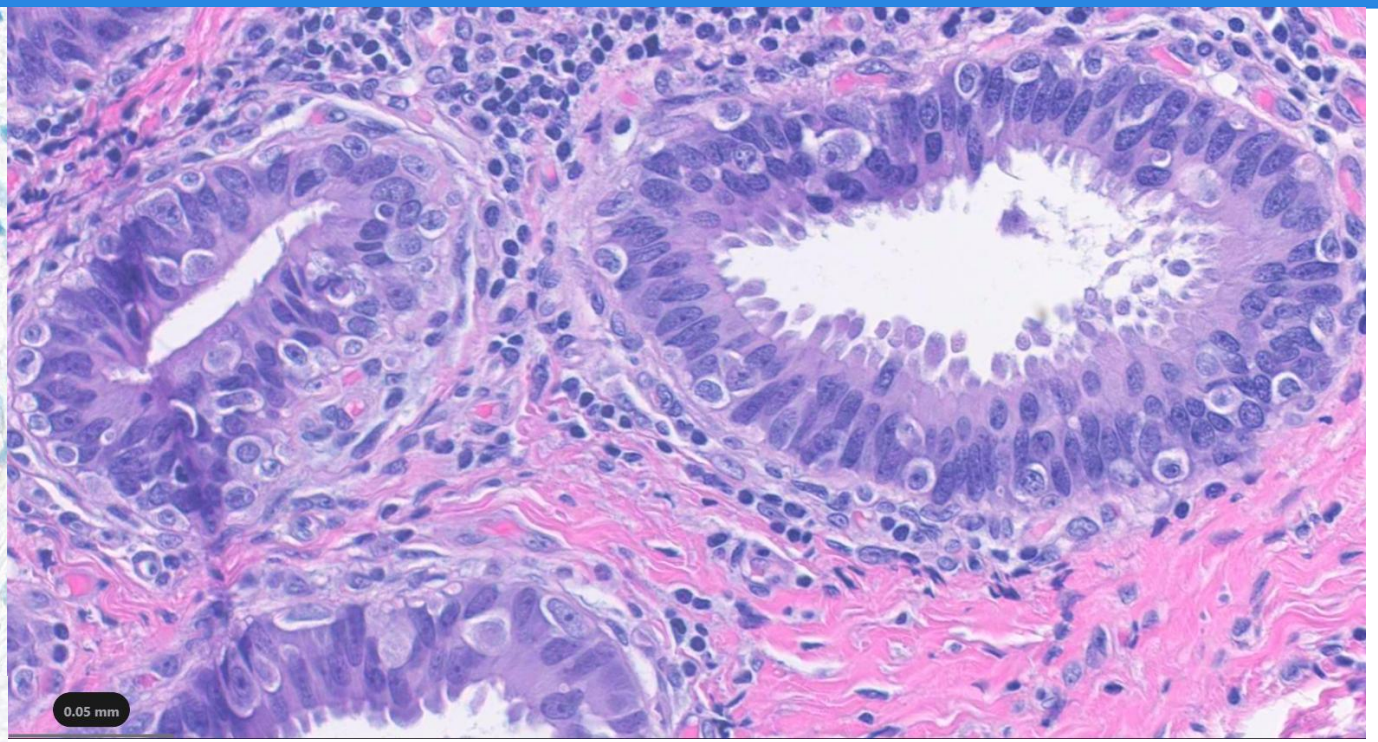


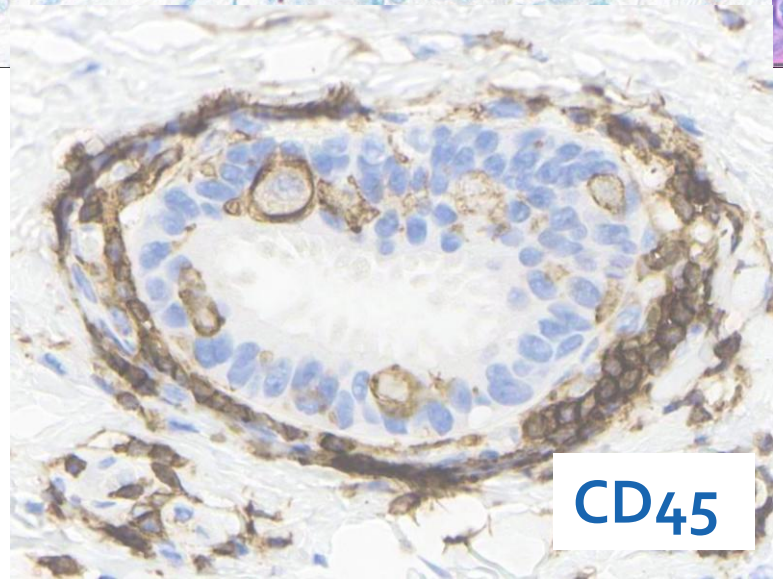


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Intraepithelial Langerhans cells may mimic classic LN







more common scenario

Largerhans cells in the nipple epidermis may mimic Paget disease

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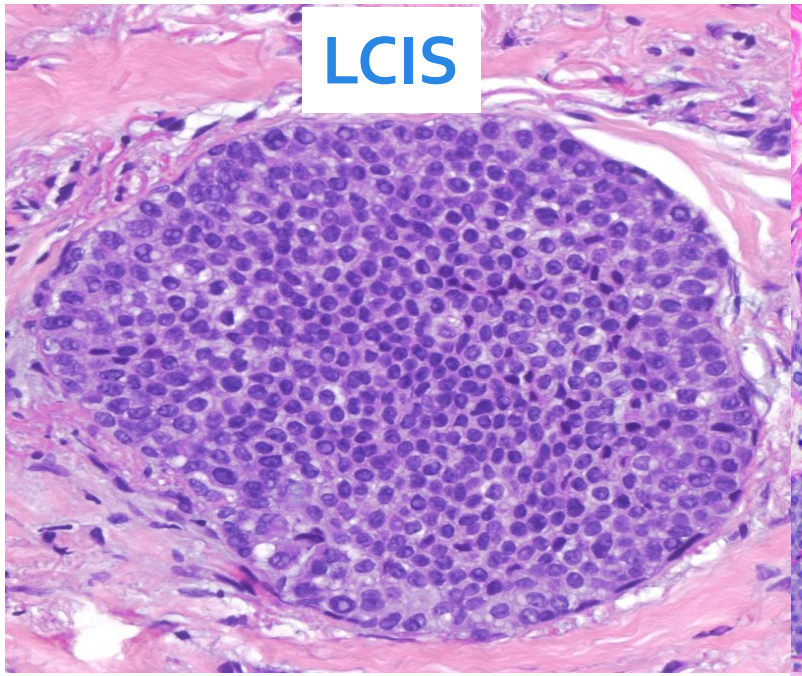
Classic LN may mimic other lesions

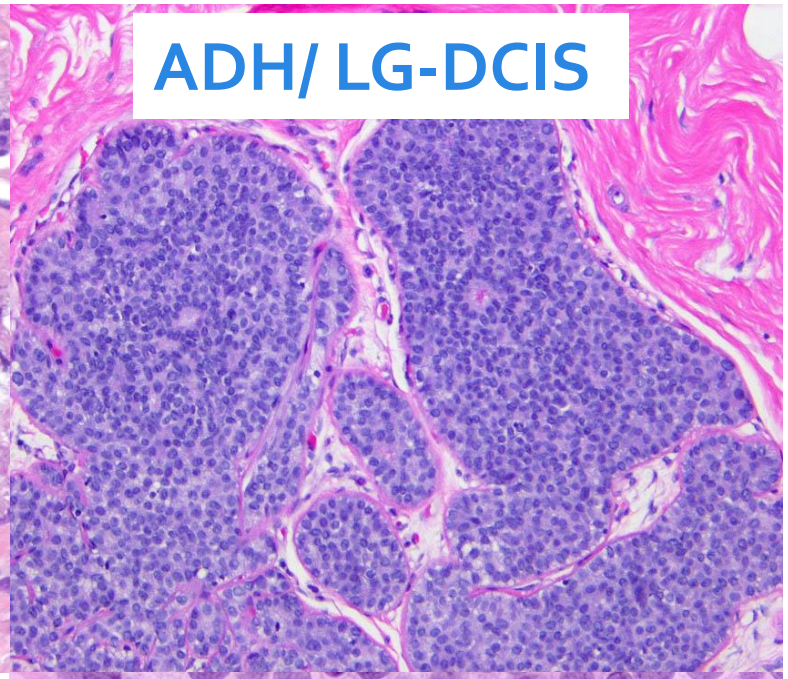
Classic LN of limited extent and/ or involving another lesion	Possible Differential Diagnosis
Partial involvement acini	ADH and UDH
Usual ductal hyperplasia (UDH)	UDH, ADH, Low grade DCIS and "mixed" ductal and lobular CIS
Collagenous spherulosis	ADH and Low grade DCIS
Sclerosing adenosis	Invasive carcinoma
Classic LCIS	Low grade DCIS, solid type

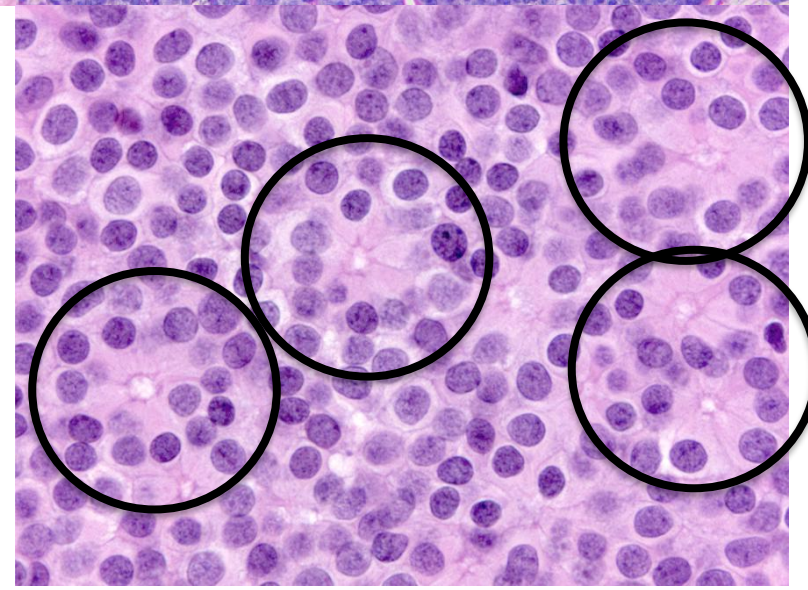
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Focal solid C-LCIS may mimic solid ADH/ Low Grade DCIS

Microacini found only in neoplastic intraductal proliferations

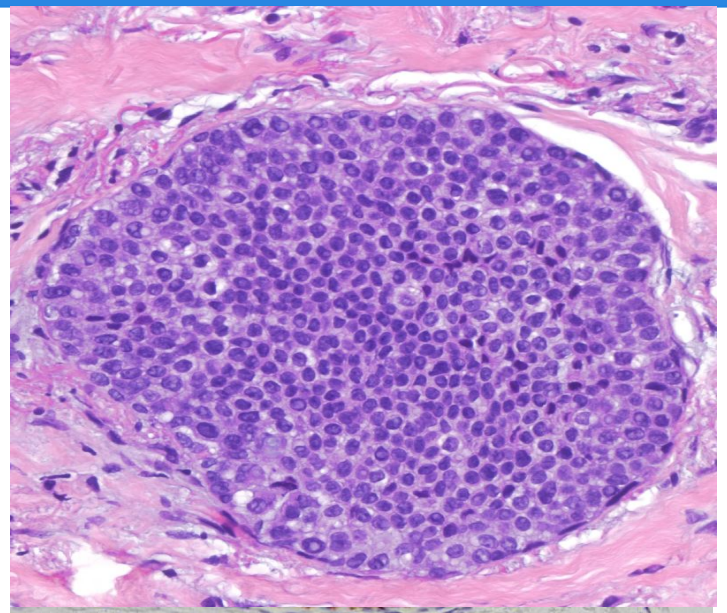


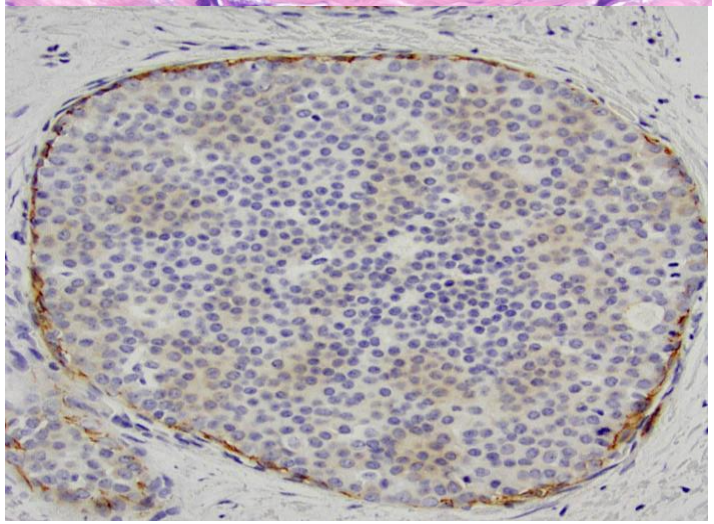




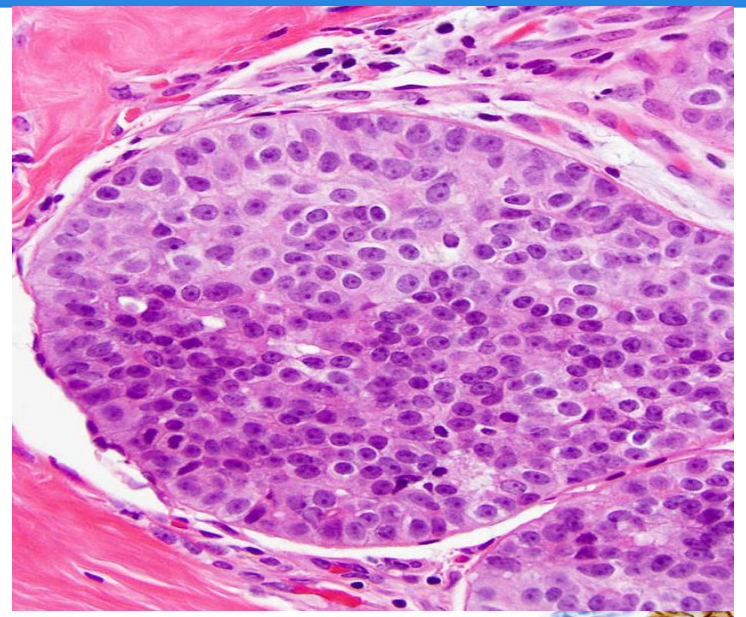
Classic LCIS

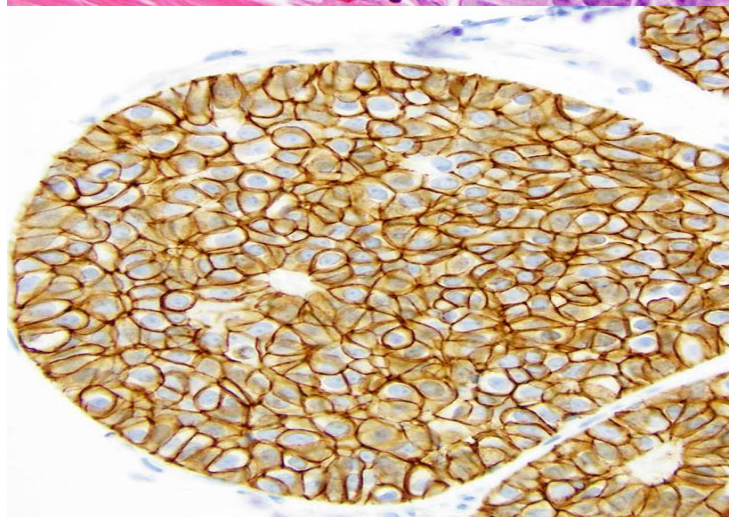
DCIS, low grade, solid





E-Cadherin





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Non-invasive Classic Lobular Neoplasia

Risk of subsequent carcinoma

Margin assessmen

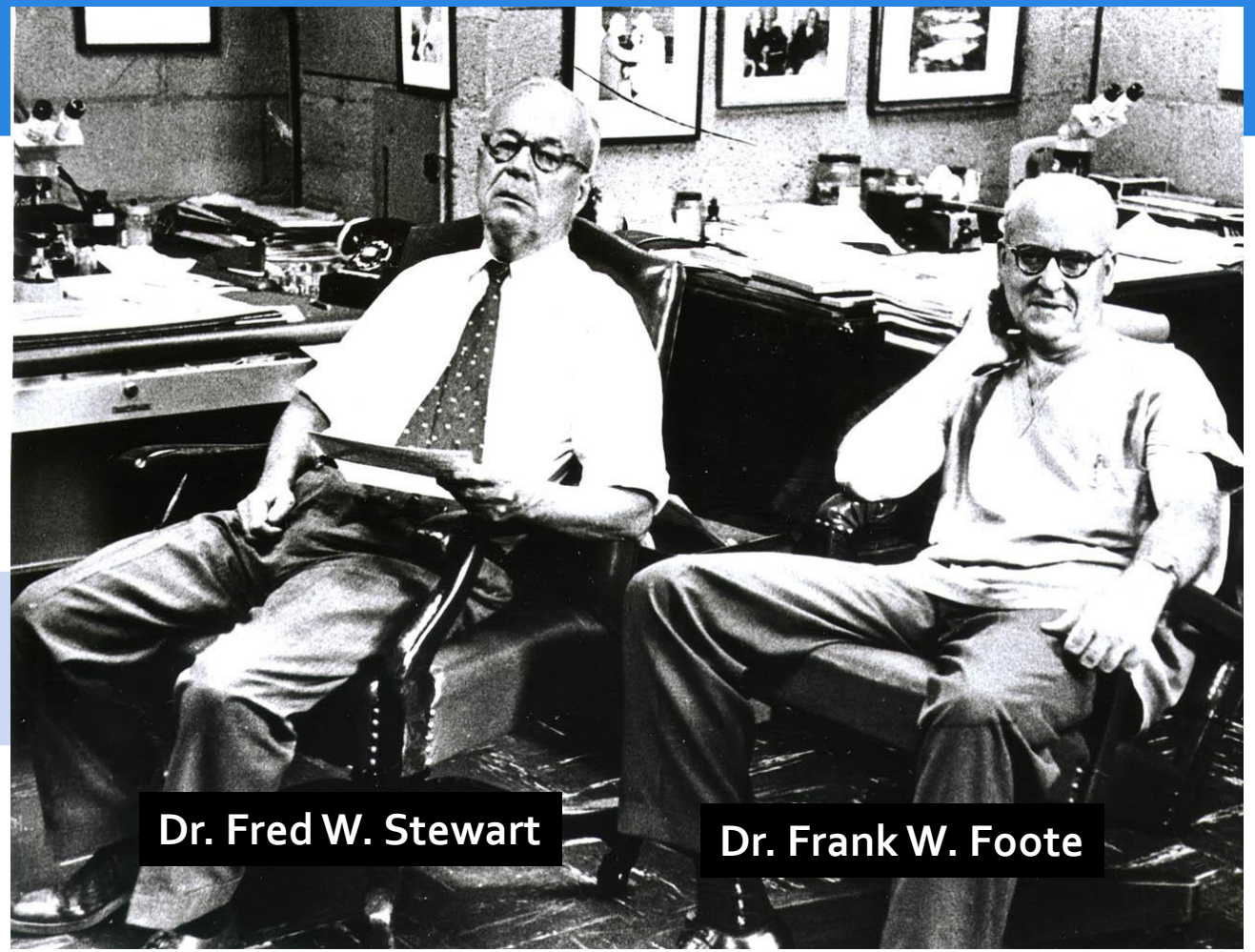
Core needle biopsy

"Classic" LCIS

Precursor lesion

1941

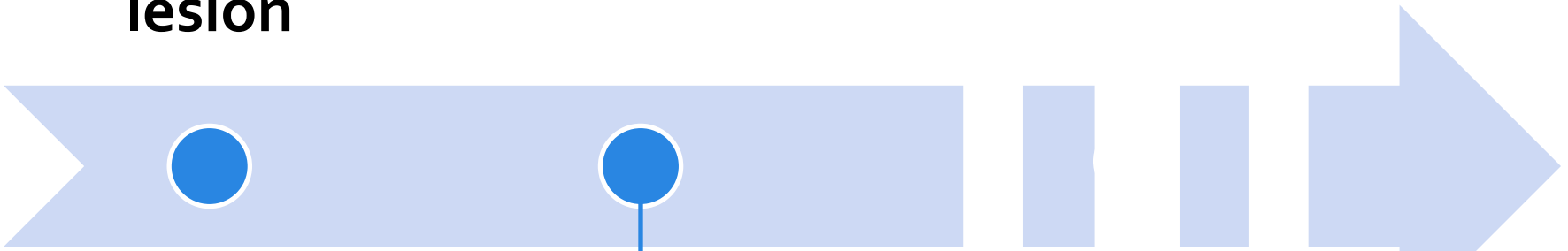
- Morphologically similar to Invasive Lobular Carcinoma (ILC)
- Proximity to ILC



Foote FW, Stewart FW. Lobular carcinoma in situ: A rare form of mammary cancer. Am J Pathol. 1941;17(4):491-496.3.

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Classic LCIS and ALH



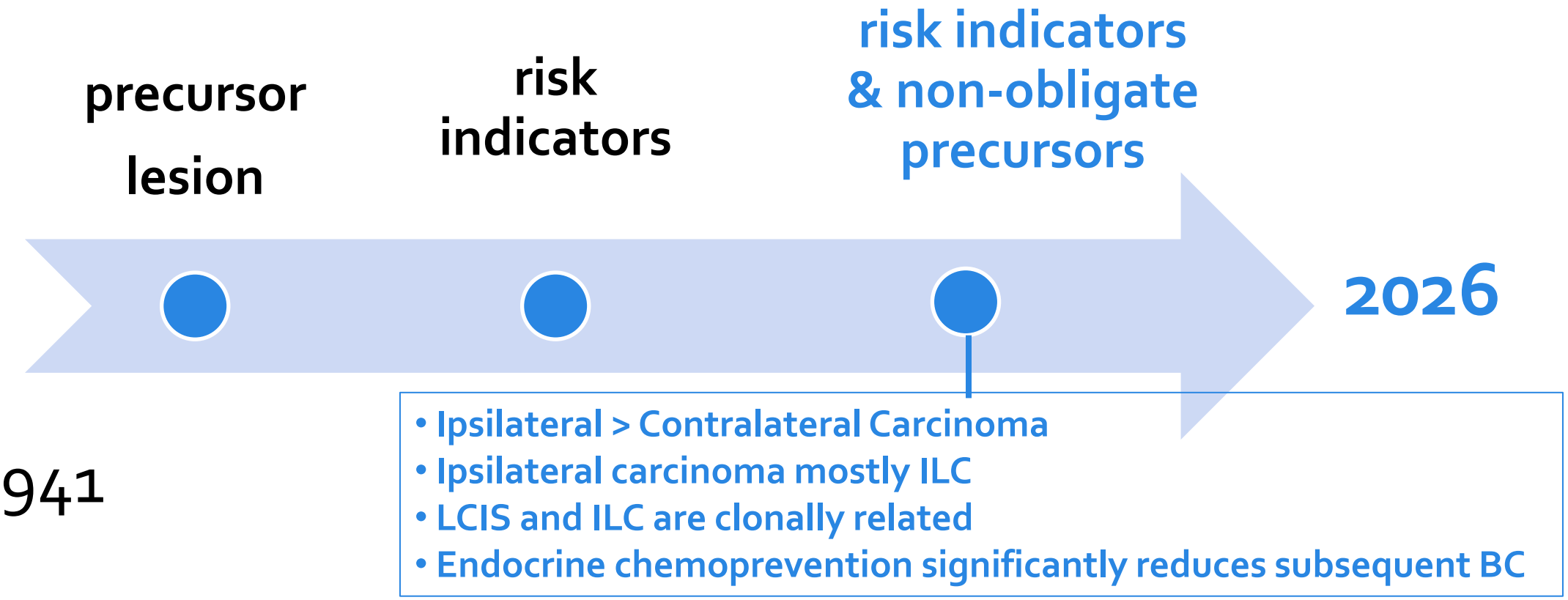
1941

- Risk Bilateral
  - ALH RR 4-5X
  - LCIS RR 8-10X
- F/U: IDC = ILC

1980-90's

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Classic LCIS and ALH



Vos CB, Cleton-Jansen AM, Berx G, de Leeuw WJ, ter Haar NT, van Roy F, Cornelisse CJ, Peterse JL, van de Vijver MJ. E-cadherin inactivation in lobular carcinoma in situ of the breast: an early event in tumorigenesis. Br J Cancer. 1997;76(9):1131-3. PMID: 9365159.

Andrade VP, Ostrovnaya I, Seshan VE, Morrogh M, Giri D, Olvera N, De Brot M, Morrow M, Begg CB, King TA. Clonal relatedness between lobular carcinoma in situ and synchronous malignant lesions. Breast Cancer Res. 2012;14(4):R103. PMID: 22776144.

Begg CB, Ostrovnaya I, Carniello JV, Sakr RA, Giri D, Towers R, Schizas M, De Brot M, Andrade VP, Mauguen A, Seshan VE, King TA. Clonal relationships between lobular carcinoma in situ and other breast malignancies. Breast Cancer Res. 2016;18(1):66. PMID: 27334989.

Sakr RA, Schizas M, Carniello JV, Ng CK, Piscuoglio S, Giri D, Andrade VP, De Brot M, Lim RS, Towers R, Weigelt B, Reis-Filho JS, King TA. Targeted capture massively parallel sequencing analysis of LCIS and invasive lobular cancer: Repertoire of somatic genetic alterations and clonal relationships. Mol Oncol. 2016;10(2):360-70. PMID: 26643573.

Ciriello G, Gatza ML, Beck AH, Wilkerson MD, Rhie SK, Pastore A, Zhang H, McLellan M, Yau C, Kandoth C, Bowlby R, Shen H, Hayat S, Fieldhouse R, Lester SC, Tse GM, Factor RE, Collins LC, Allison KH, Chen YY, Jensen K, Johnson NB, Oesterreich S, Mills GB, Cherniack AD, Robertson G, Benz C, Sander C, Laird PW, Hoadley KA, King TA; TCGA Research Network; Perou CM. Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. Cell. 2015;163(2):506-19.. PMID: 26451490.

King TA, et al. Lobular Carcinoma in Situ: A 29-Year Longitudinal Experience Evaluating Clinicopathologic Features and Breast Cancer Risk. J Clin Oncol. 2015;33(33):3945-52

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Classic LCIS and ALH in surgical specimens

Margin status not reported

- WHO 6th ed. "There is no indication that excision of classic LCIS to negative margins is useful, and it is not necessary to assess or report the status of excision margins for classic LCIS, even in the setting of coexistent pleomorphic LCIS, florid LCIS, and/or ILC.
- NCCN guidelines Version 8.2026

  Pure (classic) LCIS at surgical margin: no margin assessment necessary

  https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Classic LN in surgical specimens with DCIS or Invasive carcinoma does not increase the risk of subsequent recurrence

Ciocca RM, et al. Presence of lobular carcinoma in situ does not increase local recurrence in patients treated with breast-conserving therapy. Ann Surg Oncol. 2008 ;15(8):2263-71.
Sadek BT, et al. Risk of local failure in breast cancer patients with lobular carcinoma in situ at the final surgical margins: is re-excision necessary? Int J Radiat Oncol Biol Phys. 2013;87(4):726-30.

CNB Dx of Classic LN and upgrade rates at excision

- **Meta-analysis of 16 studies**
  - ➢ complete information on rad-path concordance
  - ➢ excluding cases of non-classic LCIS
- **Pooled risk for upgrade to any malignancy**
  - ✓ **3.1% for classic LN**
  - ✓ **2.5% for ALH**

Shehata MN, et al. Risk for Upgrade to Malignancy After Breast Core Needle Biopsy Diagnosis of Lobular Neoplasia: A Systematic Review and Meta-Analysis. J Am Coll Radiol. 2020;17(10):1207-1219

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Classic LN in CNB: classification and management according to different organizations

Organization	How is it classified and reported?	What does that mean for management?
American Society Breast Surgeons (ASBrS) (resource guide 2024)	**"Classic LCIS / ALH" are high-risk lesions** **C-LCIS risk of BC: 1-2% per year**	**Rad-path concordance: No EXC; Clinical and imaging F/U @6, 12, 24 m** **Rad-path discordance or another lesion with potential for upgrade or LN not incidental → EXC** **For ALL pts with C-LN: BC risk assessment + high-risk screening + consider risk-reducing medication as appropriate.**
RCPath / UK (2021) NHS England/ NHS Breast Screening Programme (updated 2026)	**On CNB, classic LN (ALH or LCIS) is a B3 lesion.** **"Classic lobular neoplasia"** **No need to separate classic LCIS from ALH on limited CNB or VAB material**	**MDT discussion is essential.** **VAE recommended, even if classic LN is incidental.** **Women with B3 lesions not upgraded at VAE → routine NHS screening**
EUSOMA/EUSOBI ESP/ESSO European guidelines (2024)	**Classic lobular neoplasia is a B3 lesion.**	**VAE recommended, even if classic LN is incidental.** **After VAB/ VAE:** **1) Rad-path concordance + no residual lesion → surveillance** **2) Rad-path discordance → VAE or surgical excision**

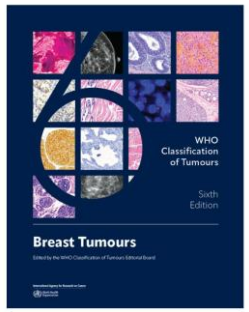
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Non-Classic LCIS

Florid LCIS

Pleomorphic LCIS



Non-classic LCIS (according to WHO 6th ed - 2026)

morphology	terminology
• Cells cytologically similar to those of classic LCIS; • Acini expanded so that little/ no residual intervening intralobular stroma is present; • An expanded acinus or duct spans ~40–50 cells in diameter	Florid LCIS (F-LCIS)
• Pleomorphic nuclei > 4 times the size of a lymphocyte (equivalent to the nuclei of high-grade DCIS) • with or without apocrine features	Pleomorphic LCIS (P-LCIS)

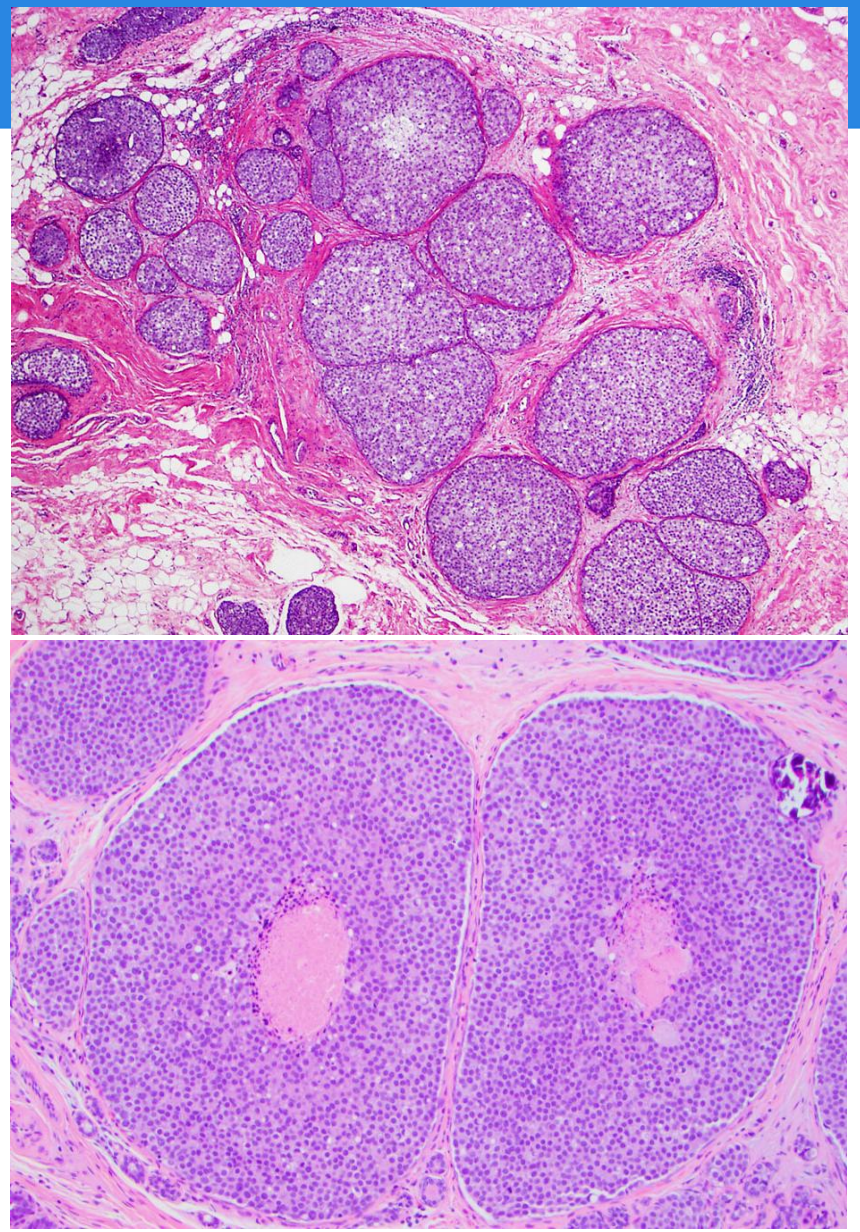
The term "lobular neoplasia" does not include F-LCIS and P-LCIS

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Florid LCIS

- Classic LCIS cytomorphology
  (*type A and/or type B cells)*
- Marked distention of TDLUs or ducts, creating a confluent mass-like architecture
- At least one of two architectural features:
  - little to no intervening stroma between markedly distended acini of involved TDLUs
  - a size cut-off point at which an expanded acinus or duct spans approximately 40-50 cells in diameter.

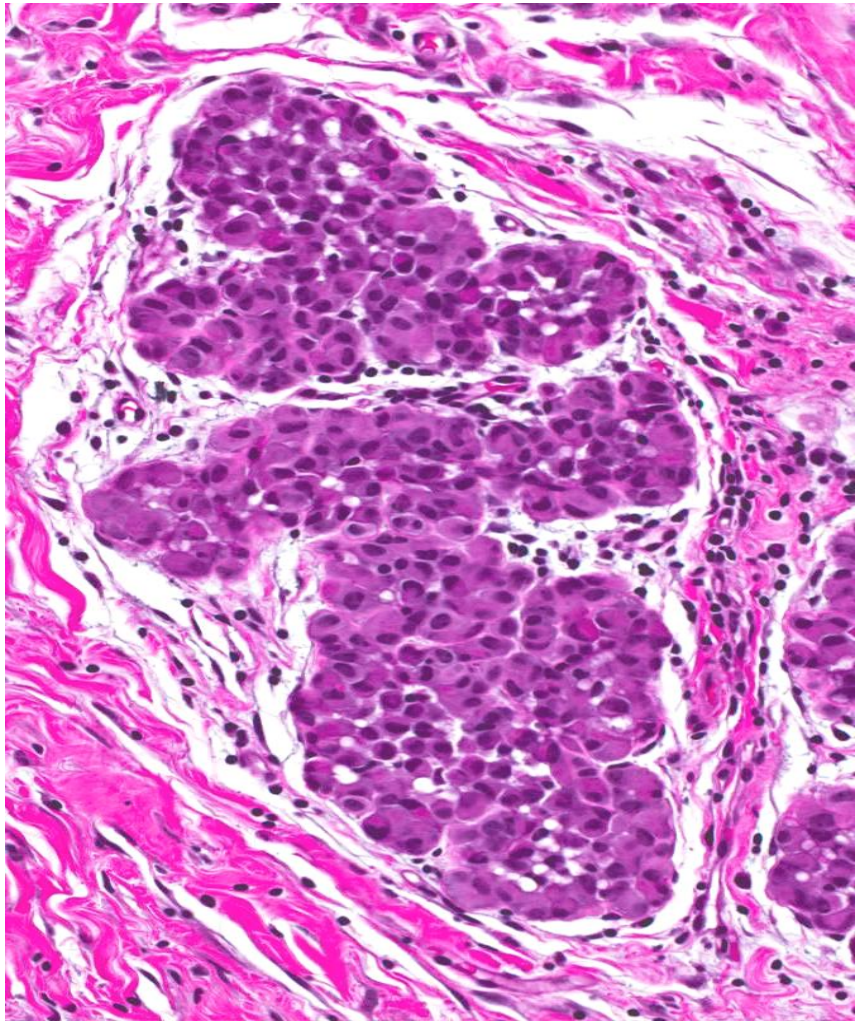
Necrosis and/or Ca^{2+} may be present but are NOT required for diagnosis

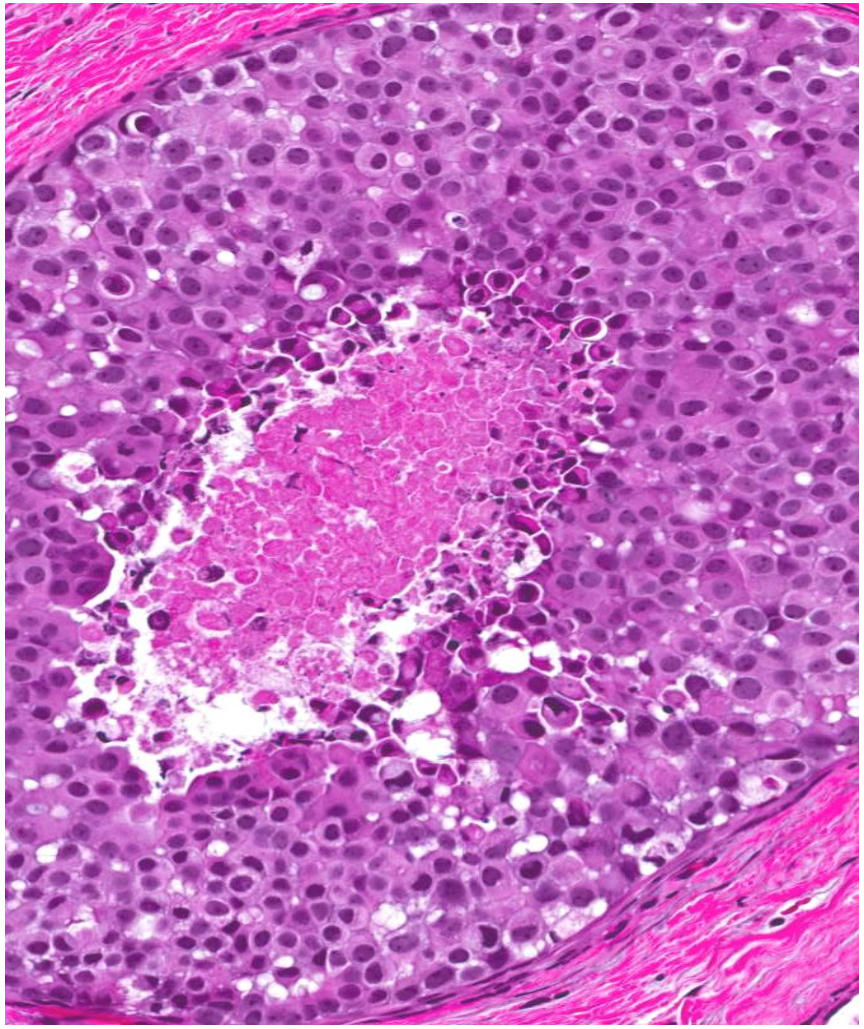


World Health Organization Classification of Tumours of the Breast. 6th ed. 2026.

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F-LCIS *Classic* LCIS cytomorphology with "exaggerated" architecture





classic LCIS

florid LCIS

(images from the same case, same magnification)

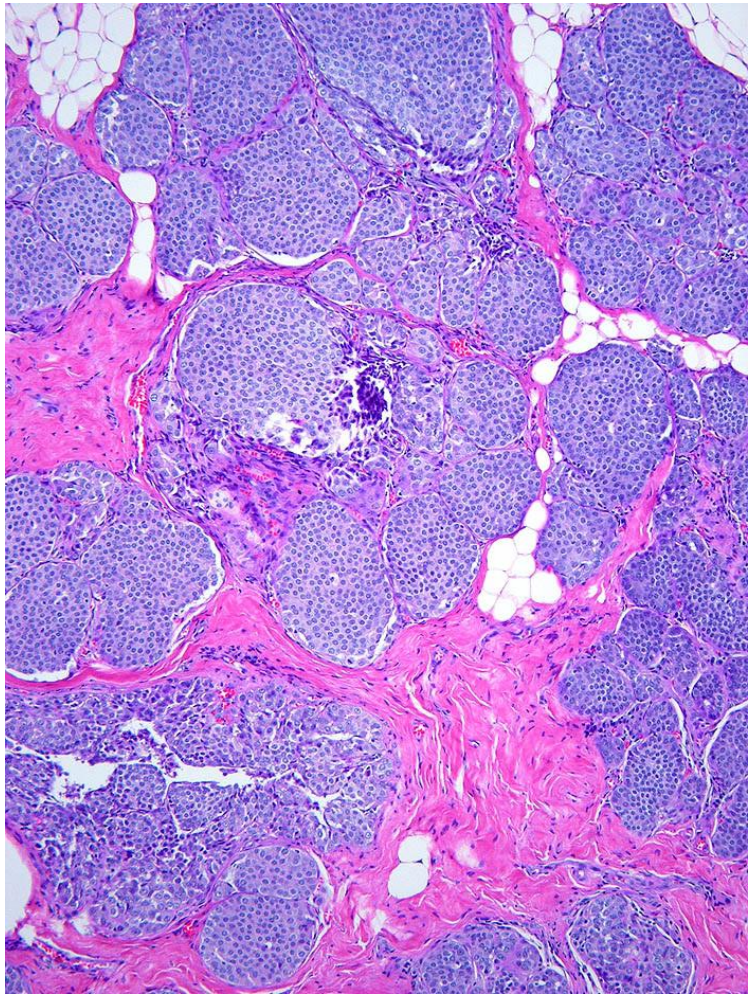
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Is it Florid LCIS or Classic LCIS?

"Lesions with cytological features of classic LCIS that show distension of the acini borderline between classic LCIS and florid LCIS should be designated as classic LCIS, even when LCIS is extensive."

World Health Organization Classification of Tumours of the Breast. 6th ed., 2026.

"Florid" is NOT synonymous with "extensive" or "diffuse"

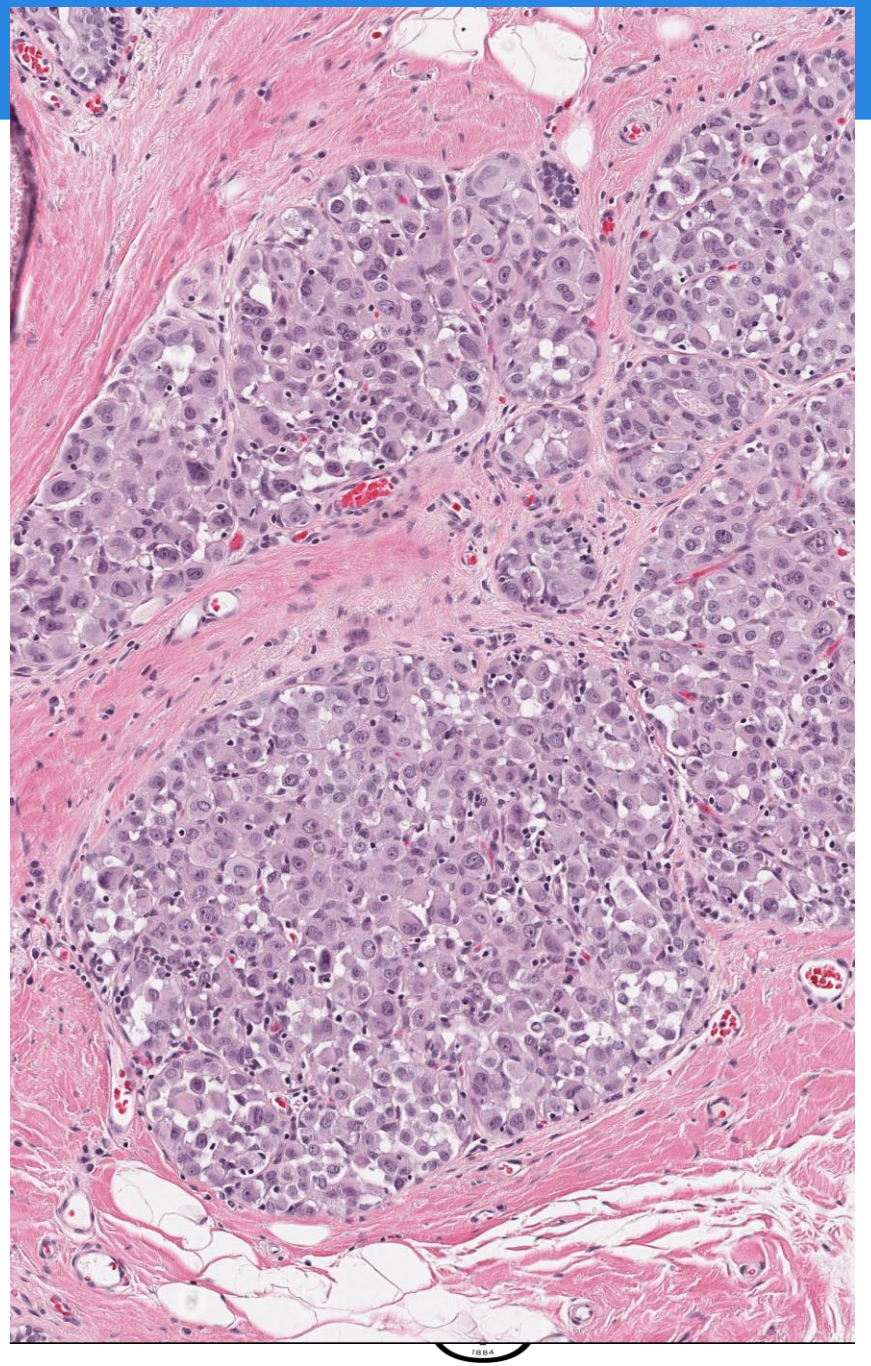


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Pleomorphic LCIS

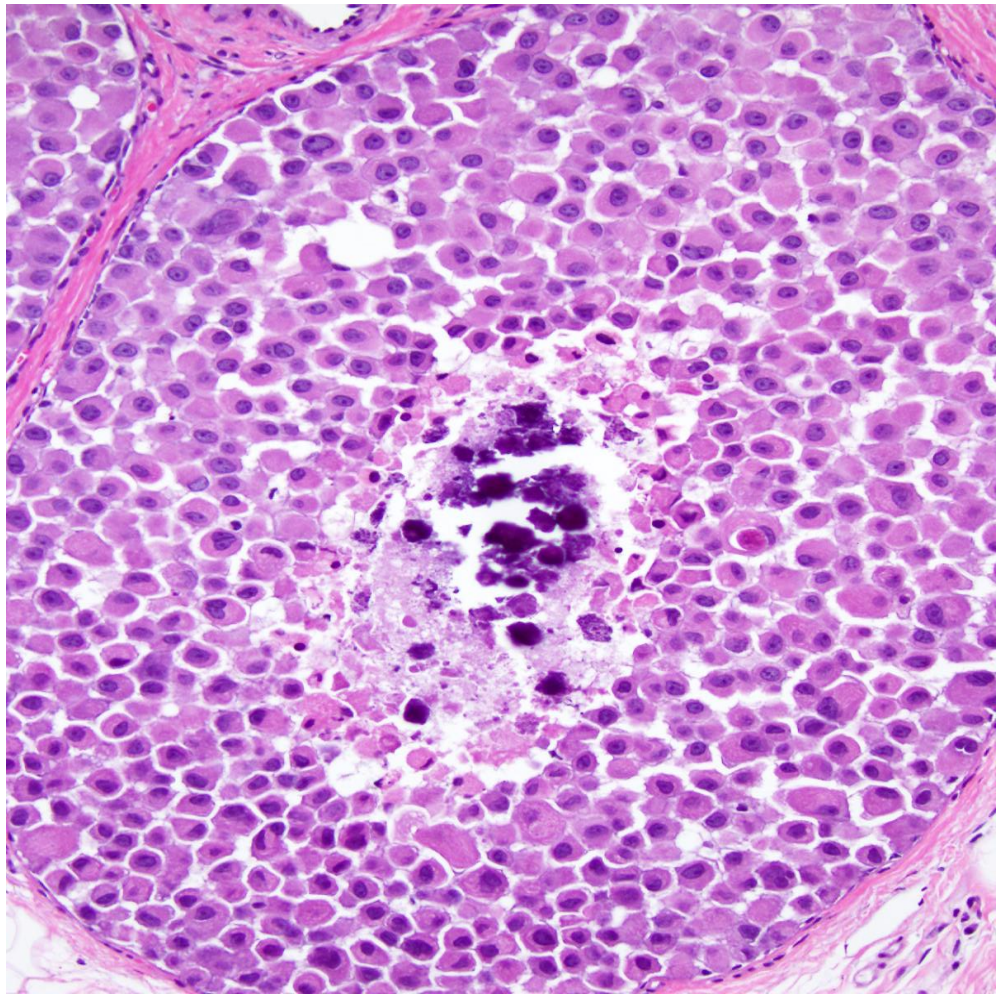
- Large cells with marked nuclear pleomorphism
- Nuclei are >4 times the size of a lymphocyte / equivalent to the nuclei of high-grade DCIS, with or without apocrine features.
- Binucleated or multinucleated cells are more frequent in pleomorphic LCIS as compared with classic LCIS or DCIS.

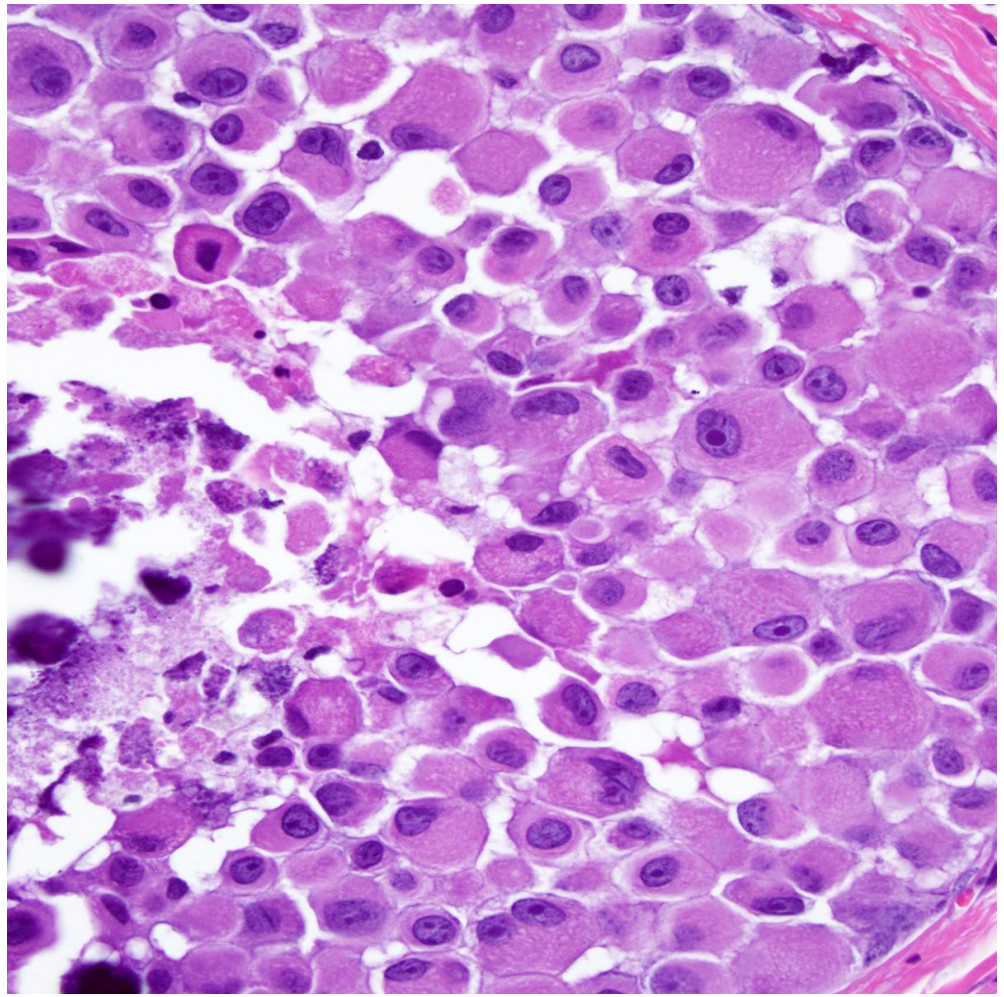
Necrosis and/ or Ca^{2+} may be present but are NOT required for diagnosis



World Health Organization Classification of Tumours of the Breast. 6th ed. 2026.

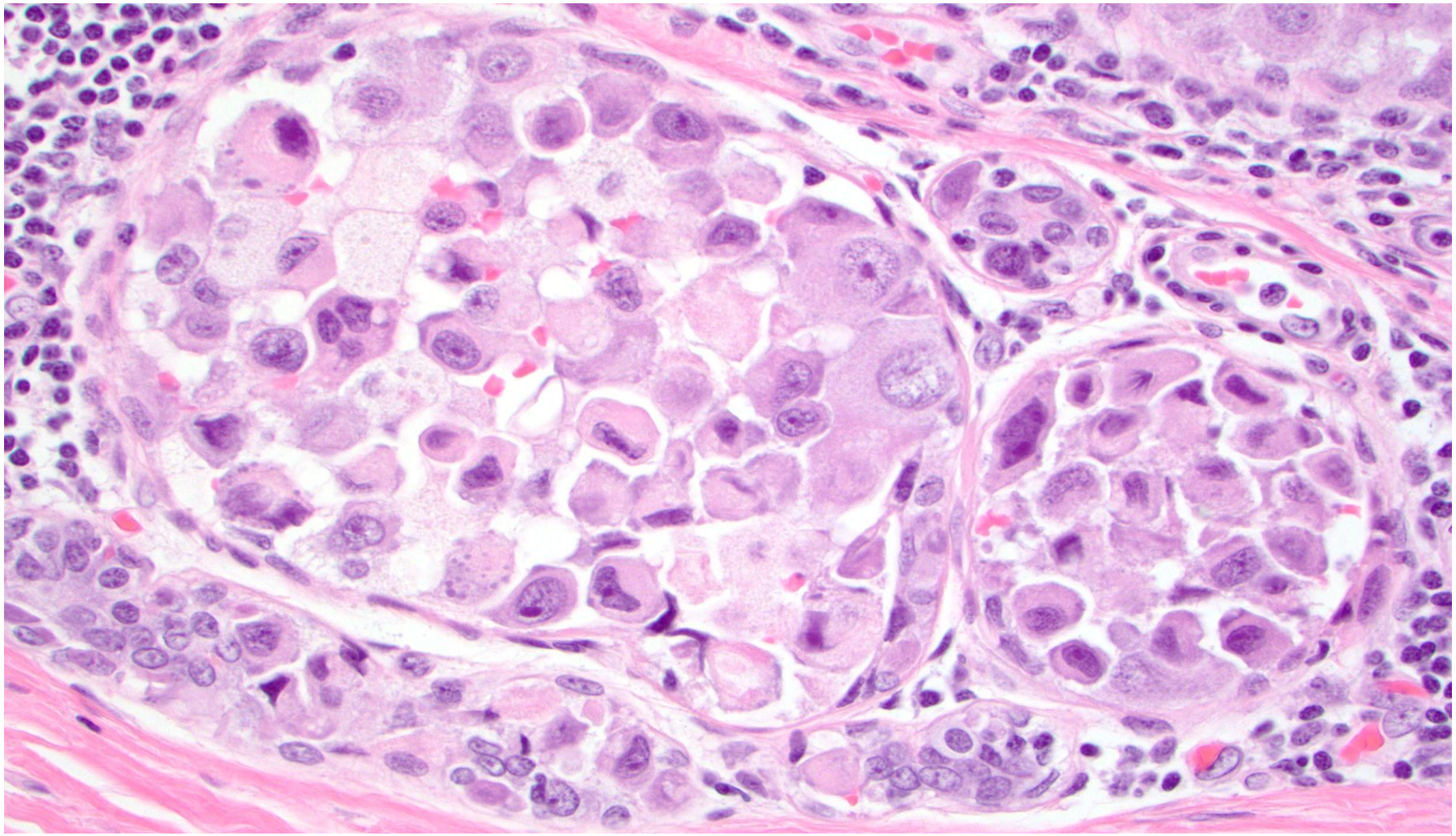
Apocrine Pleomorphic LCIS





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P-LCIS Dyshesive cells with marked nuclear pleomorphism

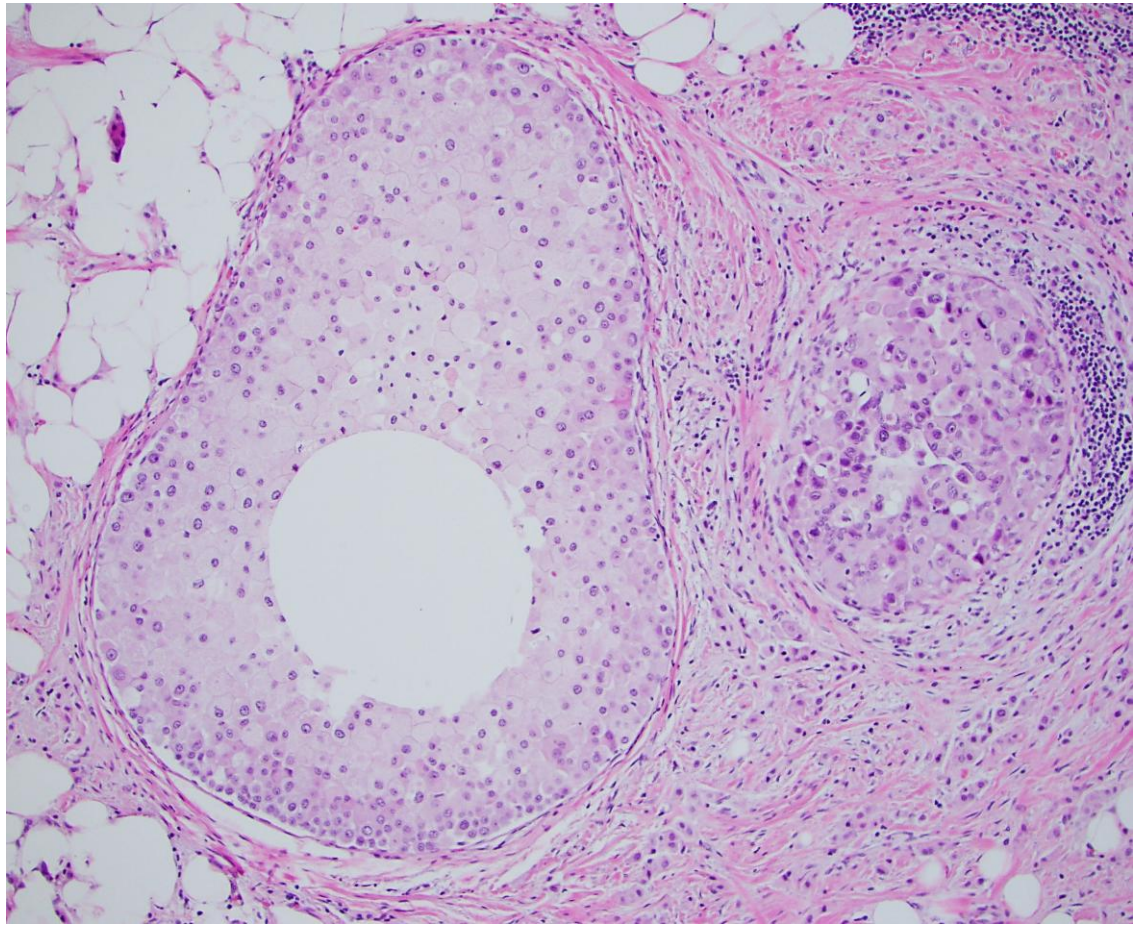


acinar expansion may be less conspicuous than in Florid LCIS

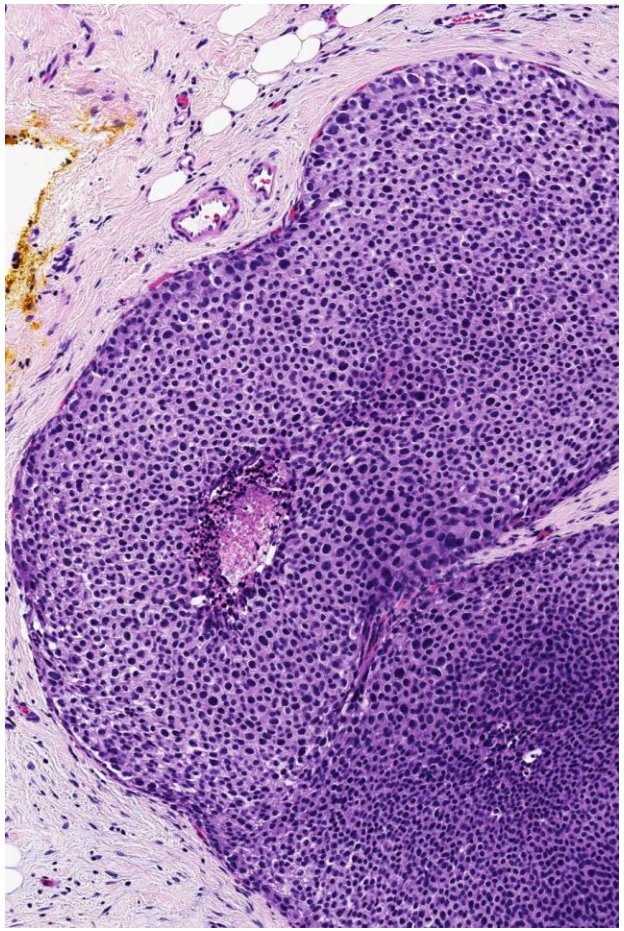
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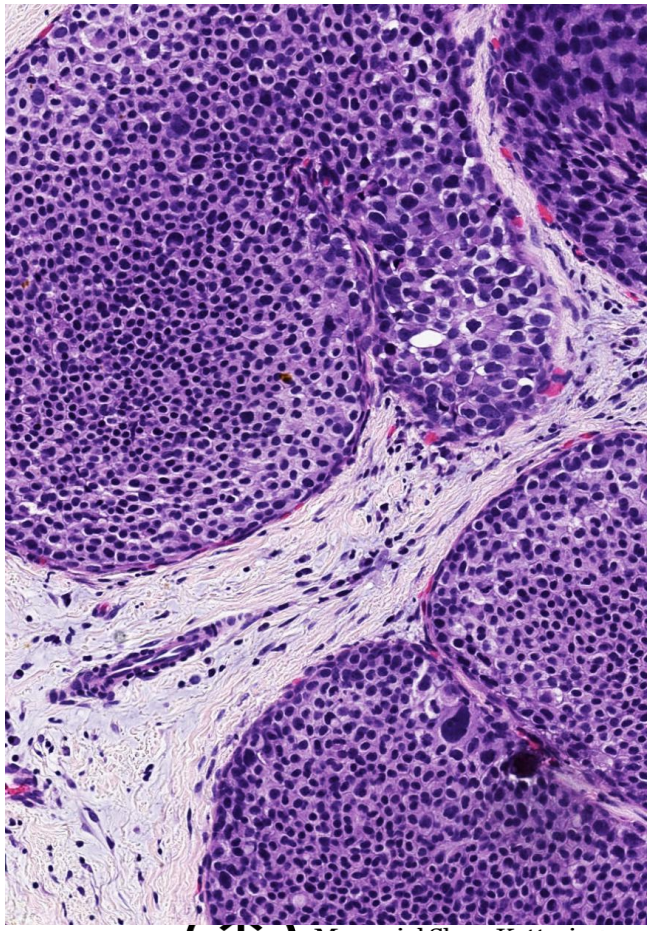
F-LCIS and P-LCIS (and C-LCIS) may coexist

In adjacent ducts/ acini



In the same ducts/ acini

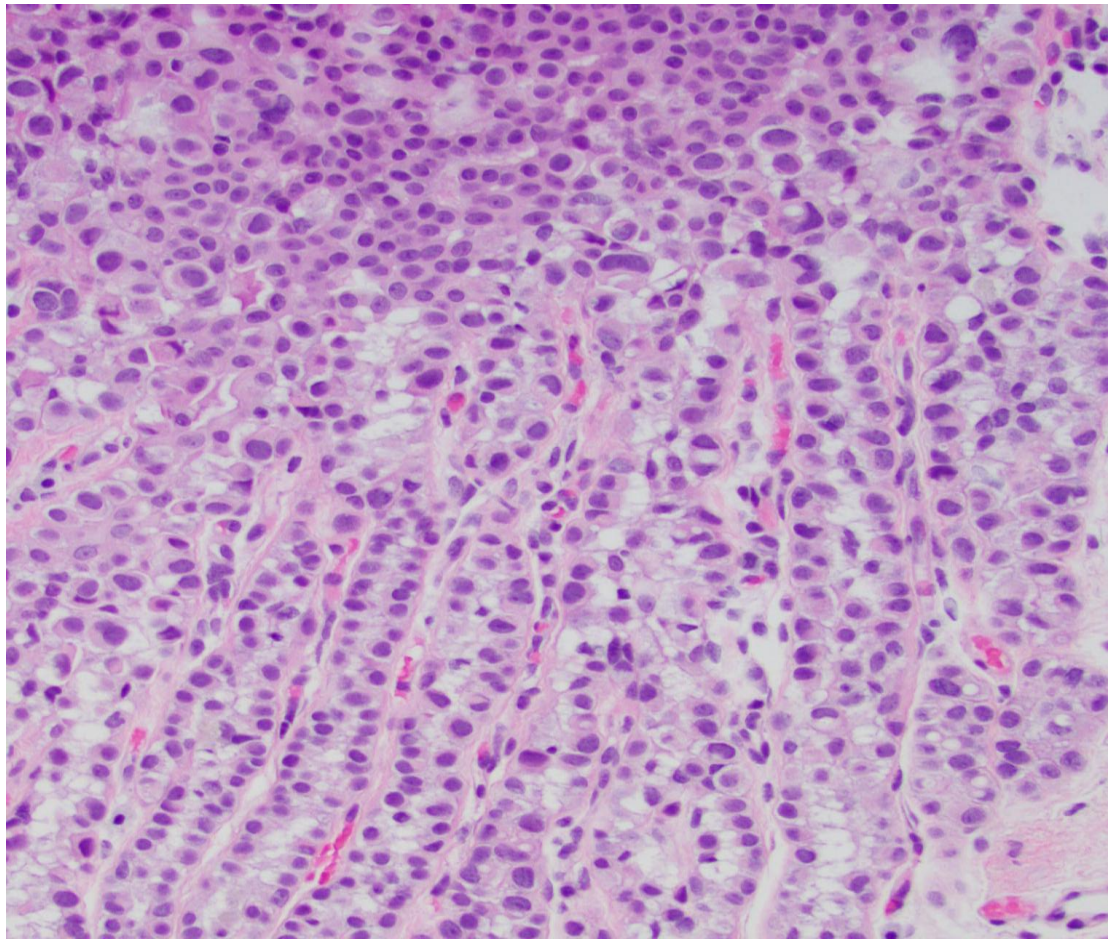




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Mix of type B + pleomorphic cells→ classify as classic LCIS

without massive acinar expansion



"*In surgical specimens*, LCIS lesions that are borderline between classic LCIS composed of type B cells and pleomorphic LCIS should be categorized as classic LCIS composed of type B cells."

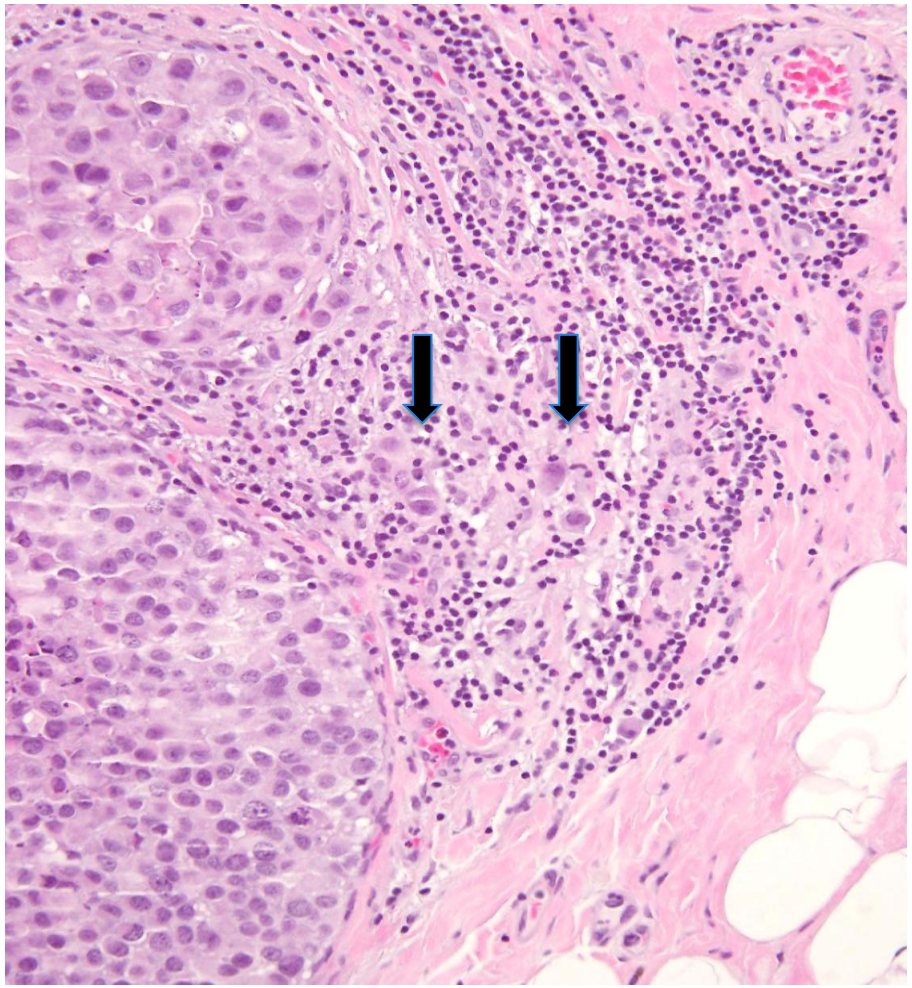
World Health Organization Classification of Tumours of the Breast. 6th ed. 2026.

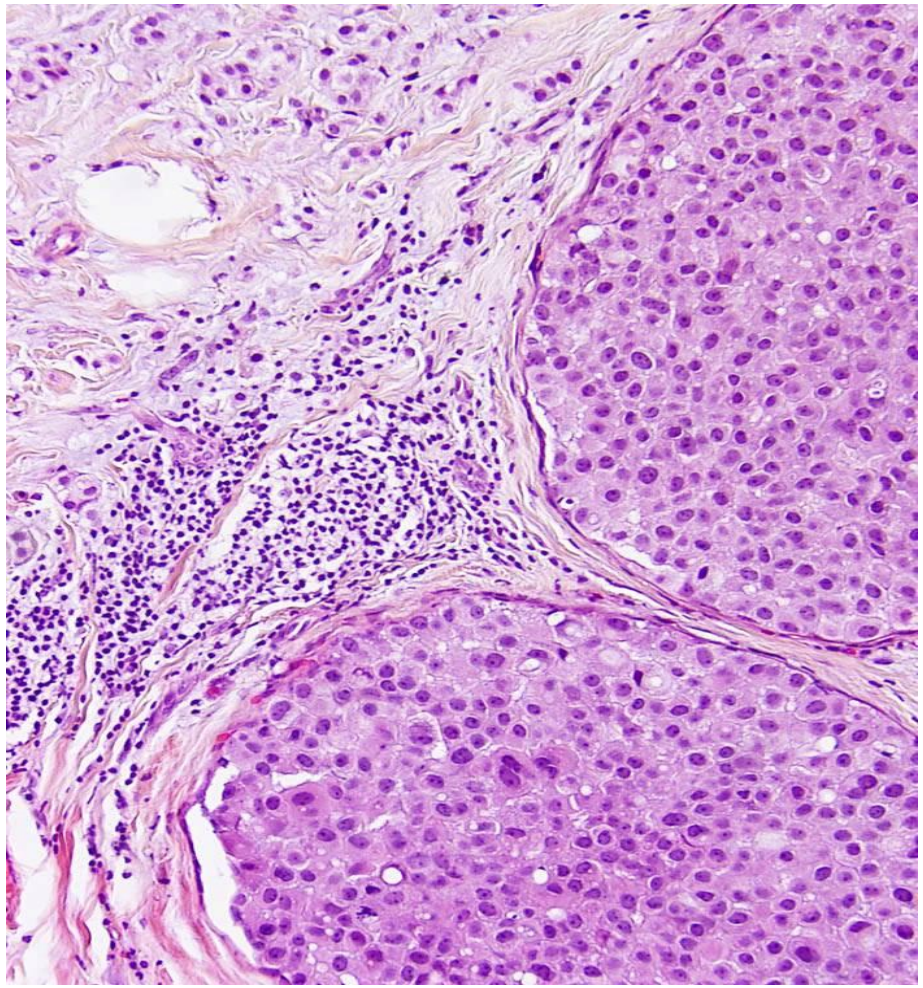
P-LCIS and F-LCIS – clinical features

- More common in postmenopausal women (mean age 60)
- Detected as mammographic Ca^{2+} (~ 80% of cases), or mass lesion +/- Ca^{2+}
- Relative risk of progression to frank invasion is still unclear, but studies show high association with invasive carcinoma (40%-87% cases), usually of lobular morphology

- Sneige N, Wang J, Baker BA, Krishnamurthy S, Middleton LP. Clinical, histopathologic, and biologic features of pleomorphic lobular (ductal-lobular) carcinoma in situ of the breast: a report of 24 cases. Mod Pathol. 2002;15(10):1044-50. PMID: 12379750.
- Fadare O, Dadmanesh F, Alvarado-Cabrero I, Snyder R, Stephen Mitchell J, Tot T, Wang SA, Ghofrani M, Eusebi V, Martel M, Tavassoli FA. Lobular intraepithelial neoplasia [lobular carcinoma in situ] with comedo-type necrosis: A clinicopathologic study of 18 cases. Am J Surg Pathol. 2006;30(11):1445-53. PMID: 17063087.
- Sapino A, Frigerio A, Peterse JL, Arisio R, Coluccia C, Bussolati G. Mammographically detected in situ lobular carcinomas of the breast. Virchows Arch. 2000;436(5):421-30. PMID: 10881735.
- Chen YY, Hwang ES, Roy R, DeVries S, Anderson J, Wa C, Fitzgibbons PL, Jacobs TW, MacGrogan G, Peterse H, Vincent-Salomon A, Tokuyasu T, Schnitt SJ, Waldman FM. Genetic and phenotypic characteristics of pleomorphic lobular carcinoma in situ of the breast. Am J Surg Pathol. 2009;33(11):1683-94. PMID: 19701073.
- Shin SJ, Lal A, De Vries S, Suzuki J, Roy R, Hwang ES, Schnitt SJ, Waldman FM, Chen YY. Florid lobular carcinoma in situ: molecular profiling and comparison to classic lobular carcinoma in situ and pleomorphic lobular carcinoma in situ. Hum Pathol. 2013;44(10):1998-2009. PMID: 23809857.
- Flanagan MR, Rendi MH, Calhoun KE, Anderson BO, Javid SH. Pleomorphic Lobular Carcinoma In Situ: Radiologic-Pathologic Features and Clinical Management. Ann Surg Oncol. 2015;22(13):4263-9. PMID: 25893410.
- Khoury T, Karabakhtsian RG, Mattson D, Yan L, Syriac S, Habib F, Liu S, Desouki MM. Pleomorphic lobular carcinoma in situ of the breast: clinicopathological review of 47 cases. Histopathology. 2014;64(7):981-93. PMID: 24372322.
- Susnik B, Day D, Abeln E, Bowman T, Krueger J, Swenson KK, Tsai ML, Bretzke ML, Lillemoe TJ. Surgical Outcomes of Lobular Neoplasia Diagnosed in Core Biopsy: Prospective Study of 316 Cases. Clin Breast Cancer. 2016;16(6):507-513. PMID: 27425222.
- Fasola CE, Chen JJ, Jensen KC, Allison KH, Horst KC. Characteristics and clinical outcomes of pleomorphic lobular carcinoma in situ of the breast. Breast J. 2018;24(1):66-69. PMID: 28929550.
- De Brot M, Koslow Mautner S, Muhsen S, Andrade VP, Mamtani A, Murray M, Giri D, Sakr RA, Brogi E, King TA. Pleomorphic lobular carcinoma in situ of the breast: a single institution experience with clinical follow-up and centralized pathology review. Breast Cancer Res Treat. 2017;165(2):411-420. PMID: 28612228.
- Foschini MP, Miglio R, Fiore R, Baldovini C, Castellano I, Callagy G, Bianchi S, Kaya H, Amendoeira I, Querzoli P, Poli F, Scatena C, Cordoba A, Pietribiasi F, Kovács A, Faistova H, Cserni G, Quinn C. Pre-operative management of Pleomorphic and florid lobular carcinoma in situ of the breast: Report of a large multi-institutional series and review of the literature. Eur J Surg Oncol. 2019;45(12):2279-2286. PMID: 31301938.
- Harrison BT, Nakhlis F, Dillon DA, Soong TR, Garcia EP, Schnitt SJ, King TA. Genomic profiling of pleomorphic and florid lobular carcinoma in situ reveals highly recurrent ERBB2 and ERRB3 alterations. Mod Pathol. 2020;33(7):1287-1297. PMID: 31932682.
- Shamir ER, Chen YY, Krings G. Genetic analysis of pleomorphic and florid lobular carcinoma in situ variants: frequent ERBB2/ERBB3 alterations and clonal relationship to classic lobular carcinoma in situ and invasive lobular carcinoma. Mod Pathol. 2020;33(6):1078-1091. PMID: 31907376.
- Kuba MG, Murray MP, Coffey K, Calle C, Morrow M, Brogi E. Morphologic subtypes of lobular carcinoma in situ diagnosed on core needle biopsy: clinicopathologic features and findings at follow-up excision. Mod Pathol. 2021;34(8):1495-1506. PMID: 33824462.

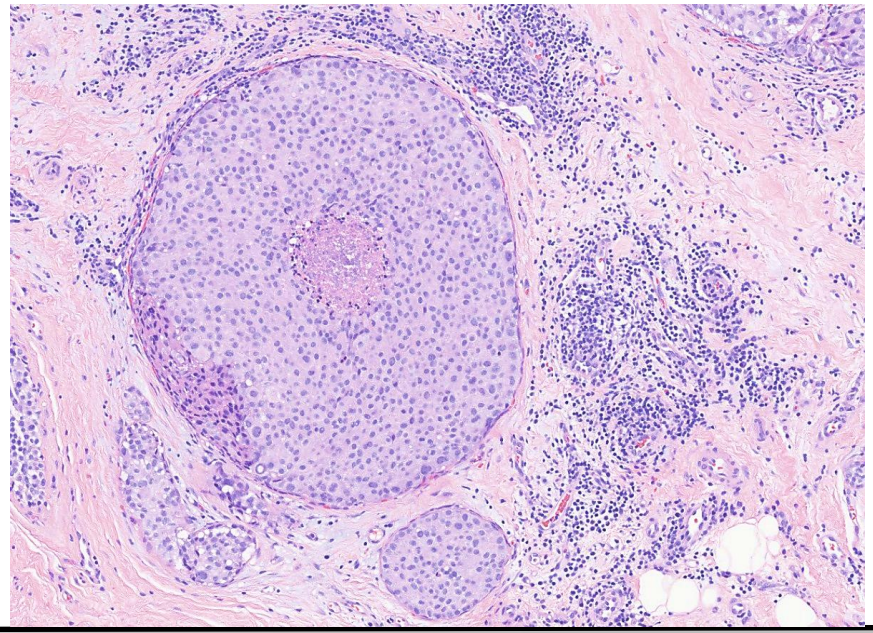
F/ P-LCIS: Rule out (micro)ILC in foci of inflammation or reactive stroma

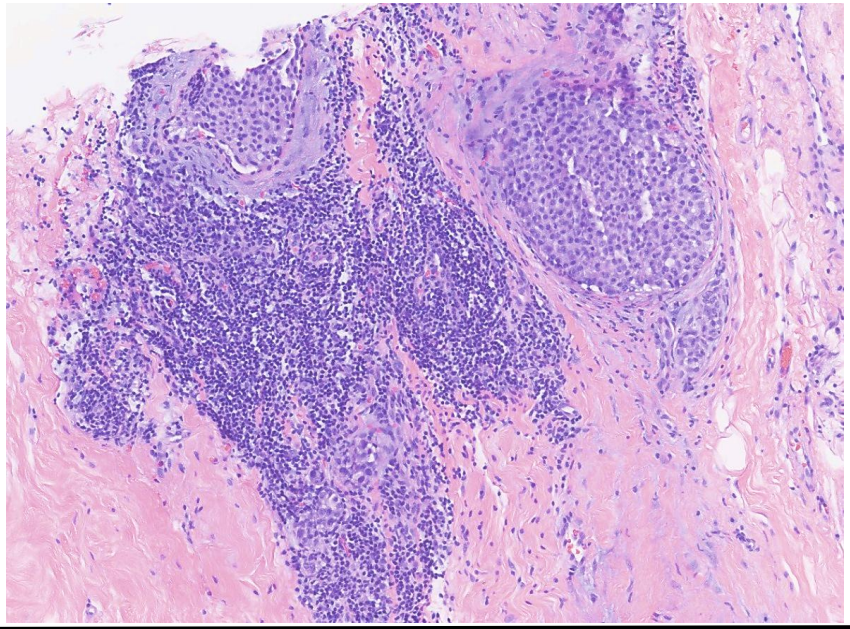


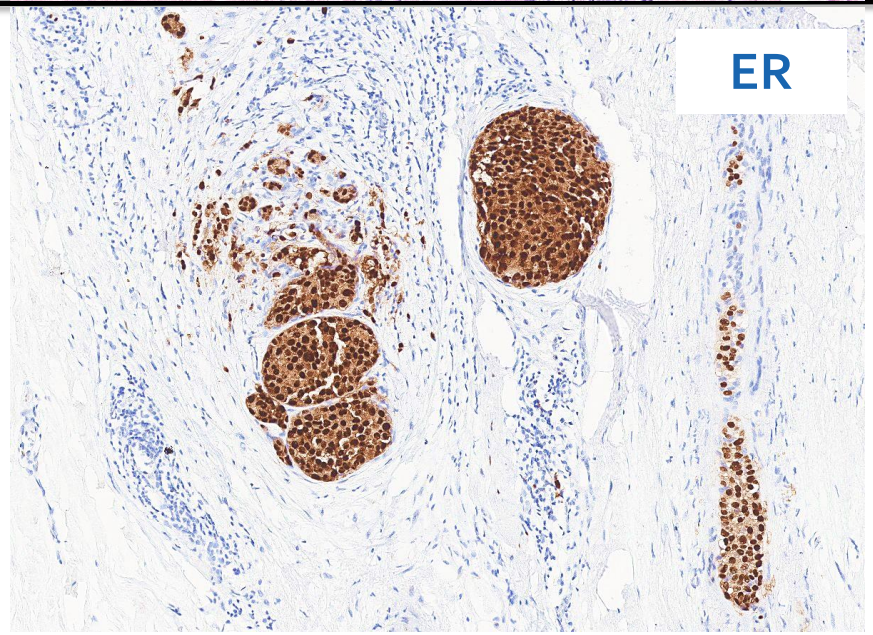


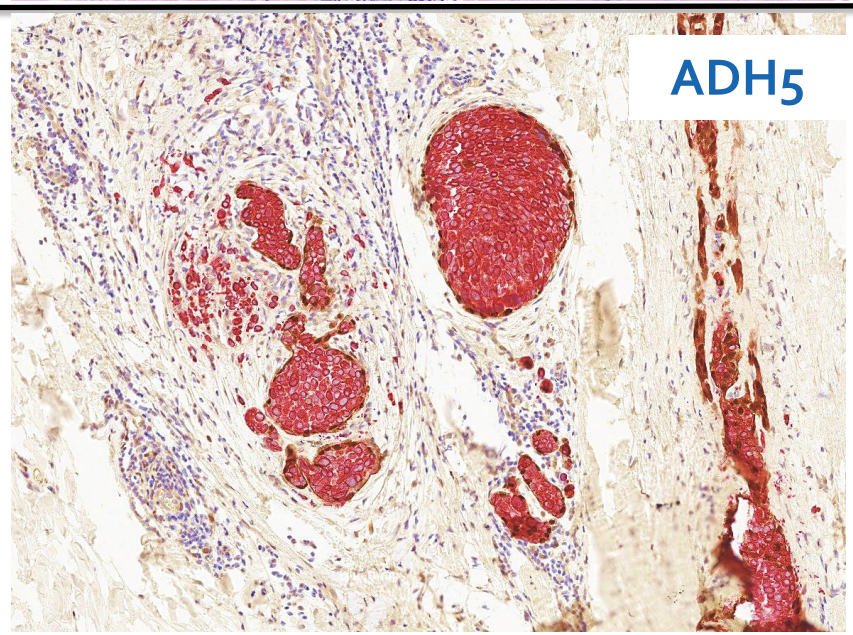
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(Micro)ILC: include IHC of "positive" antigen(s)



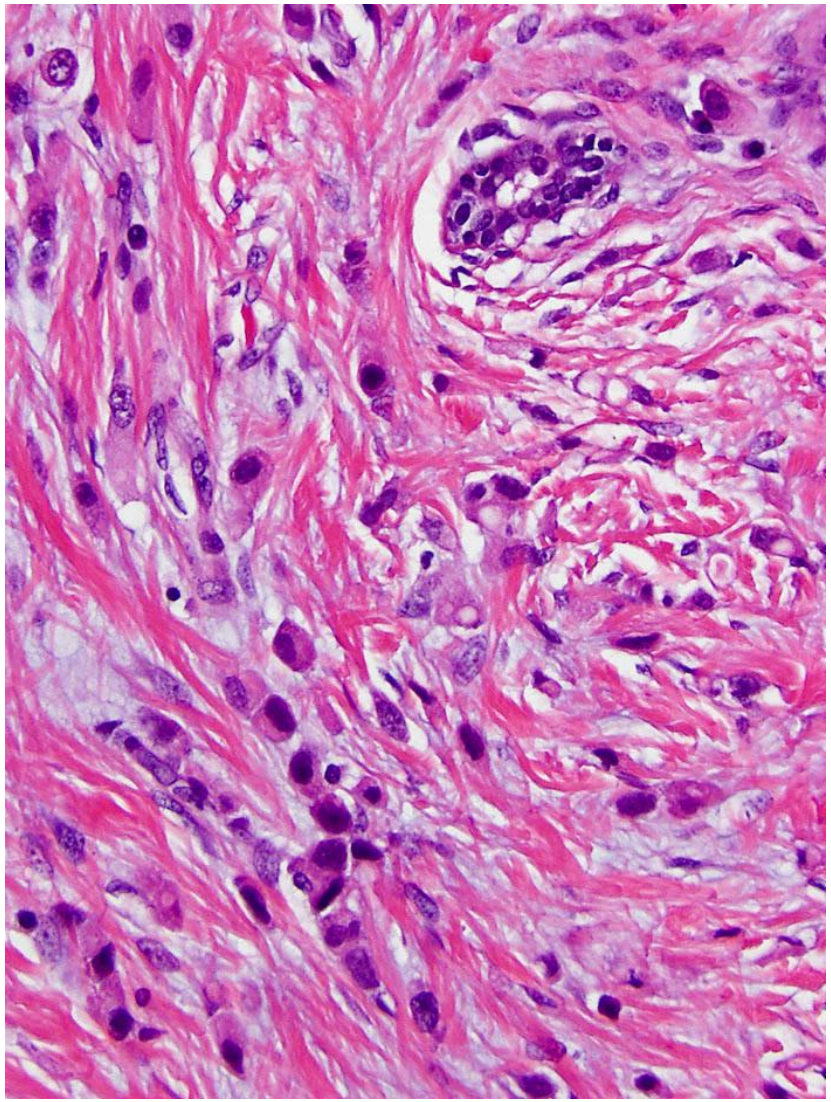


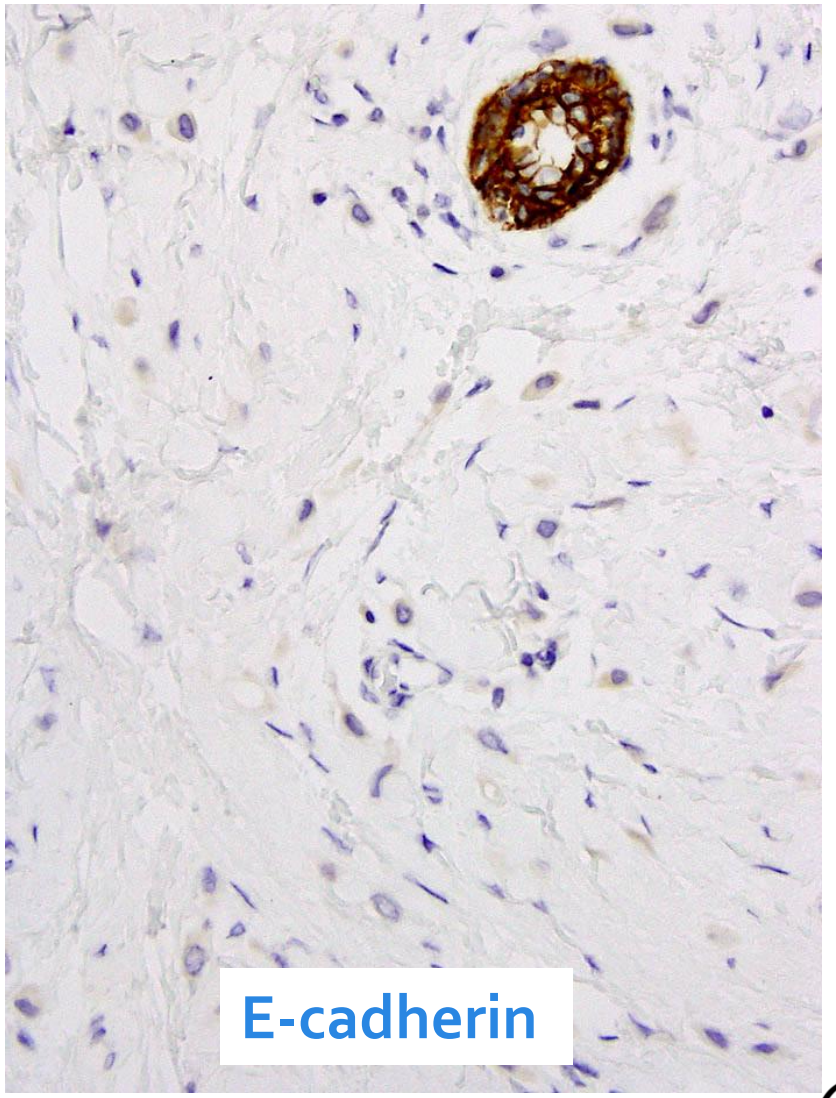




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E-cadherin IHC: useful to subtype a carcinoma, not to assess invasion





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Morphologic clues for the DDx of F-LCIS and P-LCIS versus solid DCIS

	Florid LCIS	Low/ intermediate NG DCIS	Pleomorphic LCIS	High NG DCIS
Dyshesion	Present	Absent (usually)	Present	Absent (usually)
Adjacent Classic LN	Common	May be present	Common	May be present
Pagetoid duct extension	Common	Uncommon	Common	Uncommon
Intracytoplasmic vacuoles	Common	Not very common	Common	Not common
Microacini	Not present	Common	Not present	Possible
Epithelium at the periphery of the ducts/ acini	No polarity	Usually the peripheral cells are columnar, with nuclei located closer to the base of the cells	No polarity or plasmacytoid cells	May be more columnar

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E-CADHERIN

120 kDA transmembrane glycoprotein involved in many cell functions, including cell-to-cell adhesion

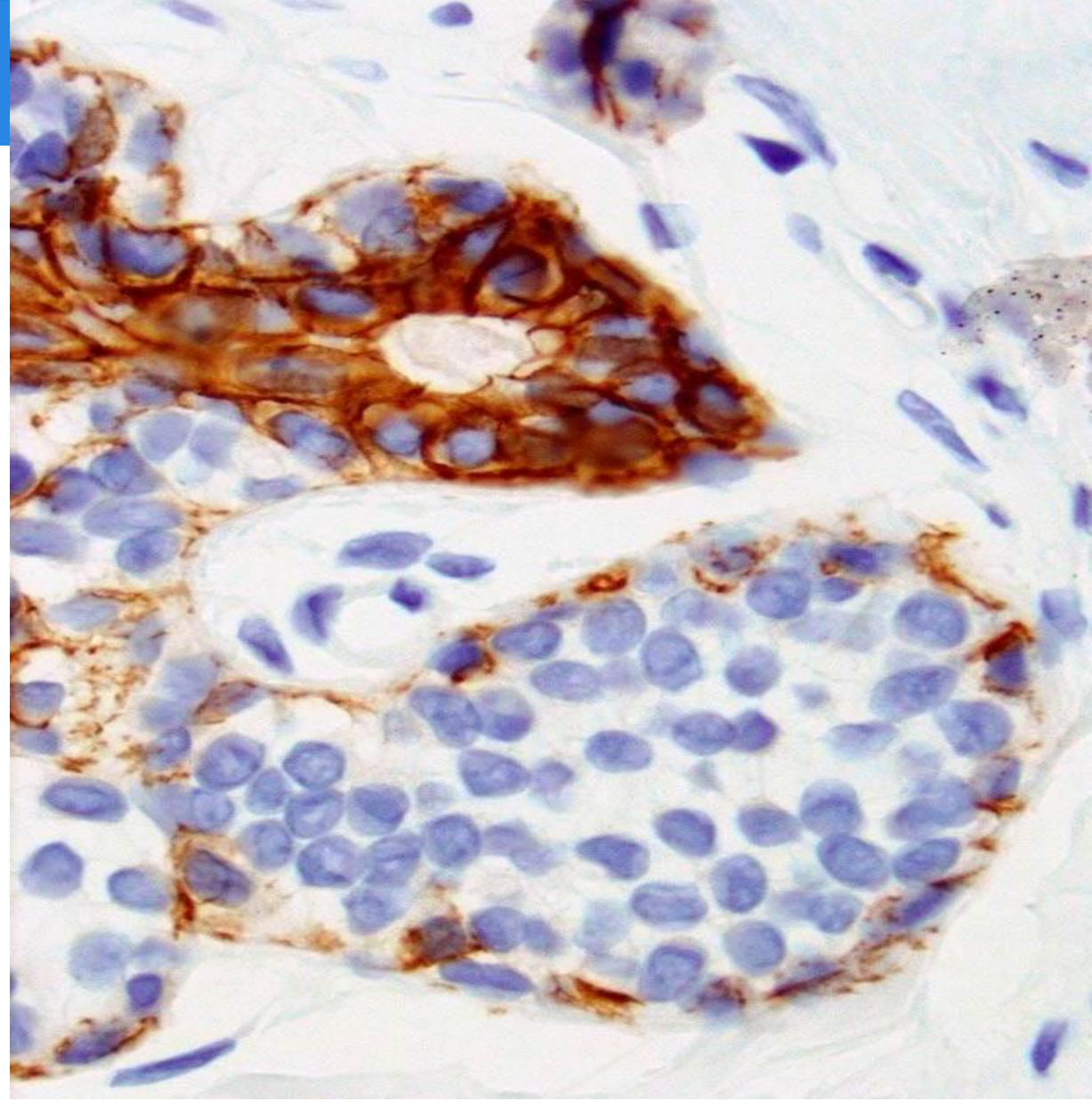
Encoded by CDH1 (chromosome 16q22.1)

Ductal epithelium: (+)cell membrane; continuous linear staining

Myoepithelium: (+)cell membrane facing the epithelium; “dot-like”/granular linear staining

Classic LN, F-LCIS, P-LCIS: all show loss of E-cadherin

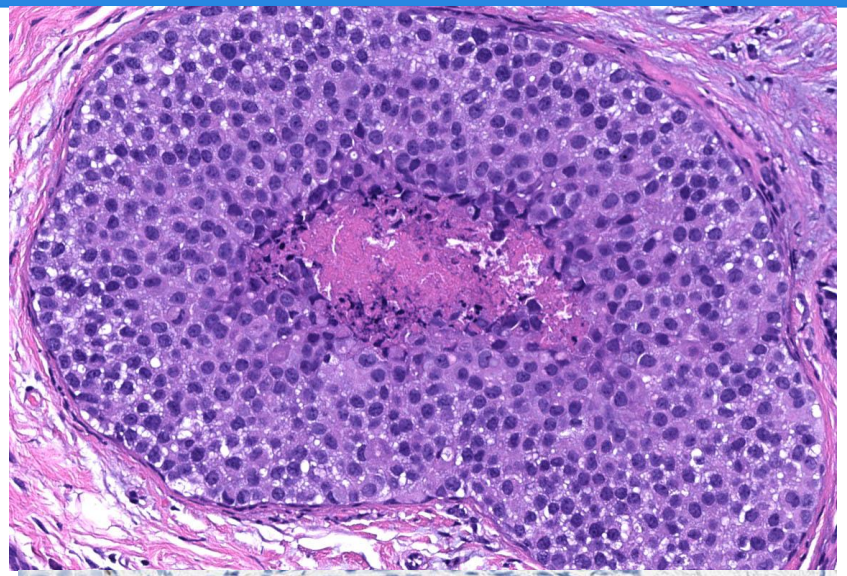
Secondary to CDH1 biallelic homologous inactivation (deletion, inactivating mutation, or epigenetic inactivation)

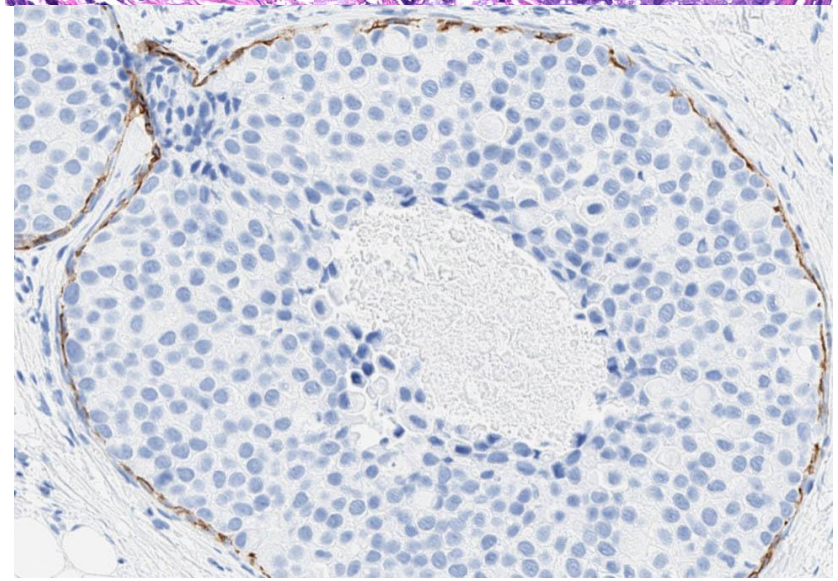


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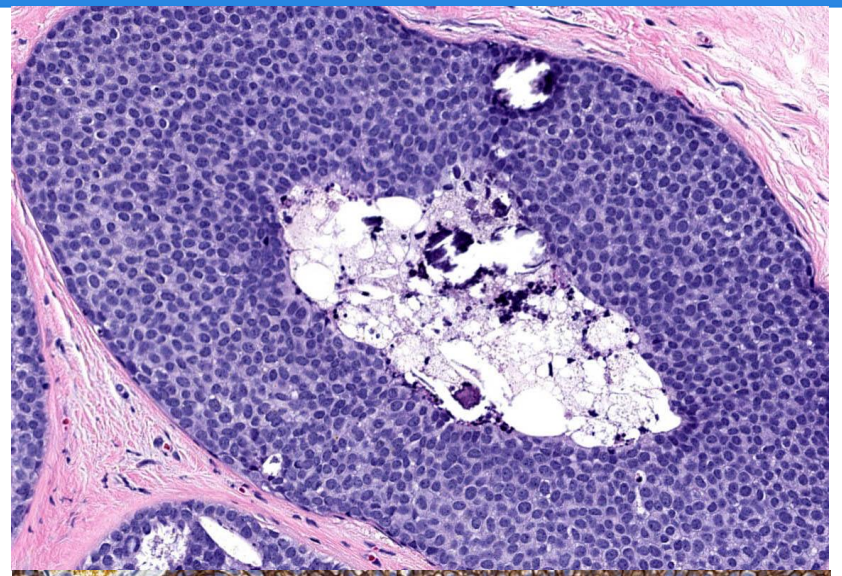
F-LCIS (and P-LCIS)

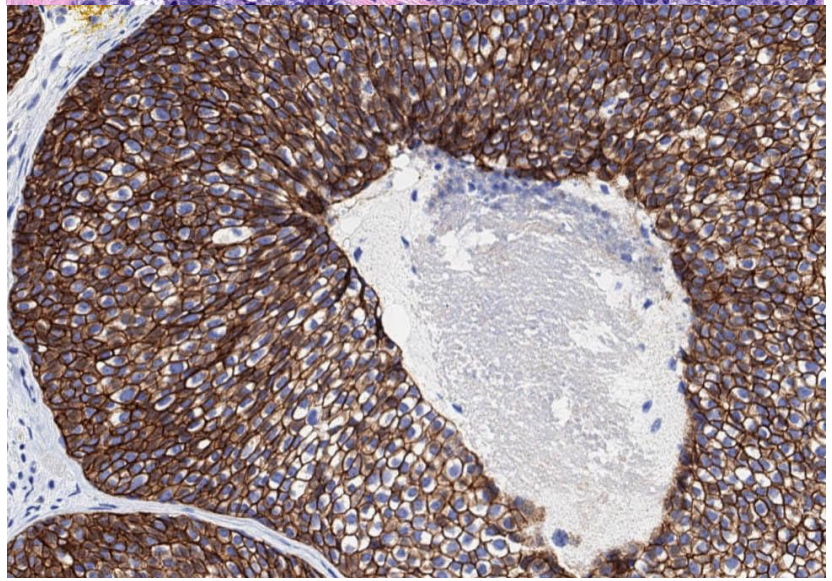
Solid DCIS





E-Cadherin



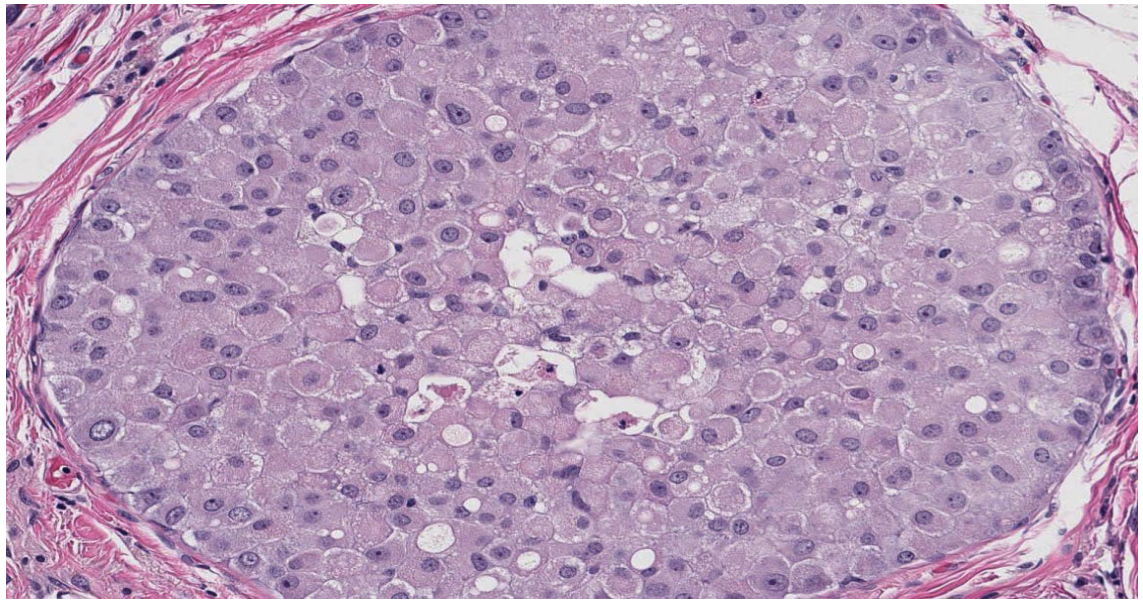


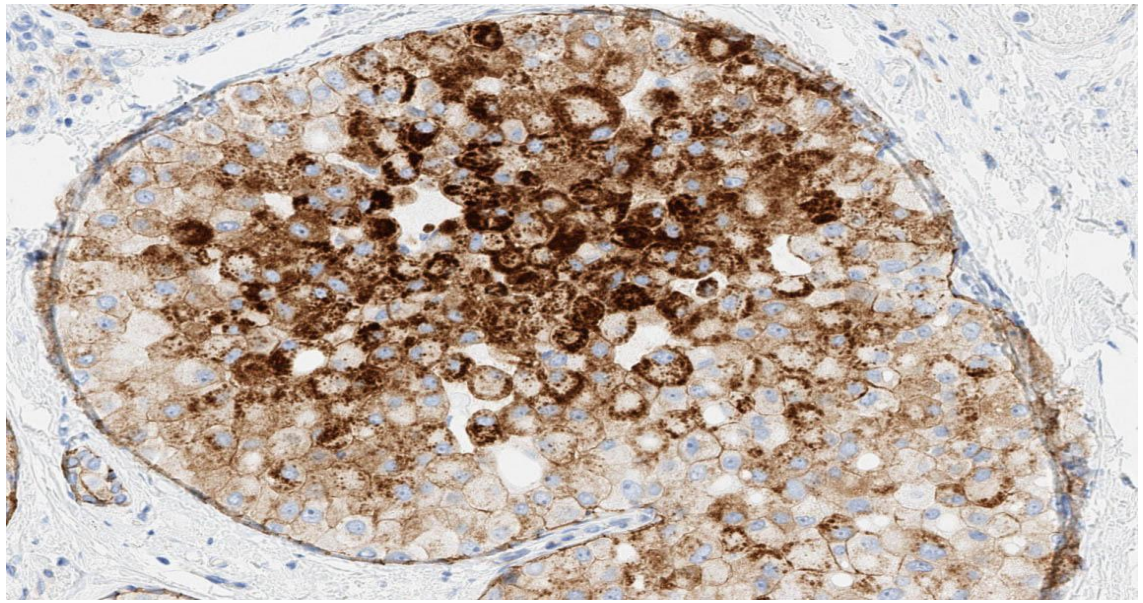
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Aberrant E-cadherin IHC in F-LCIS and P-LCIS

Granular cytoplasmic staining

more common in F/ P-LCIS with apocrine morphology

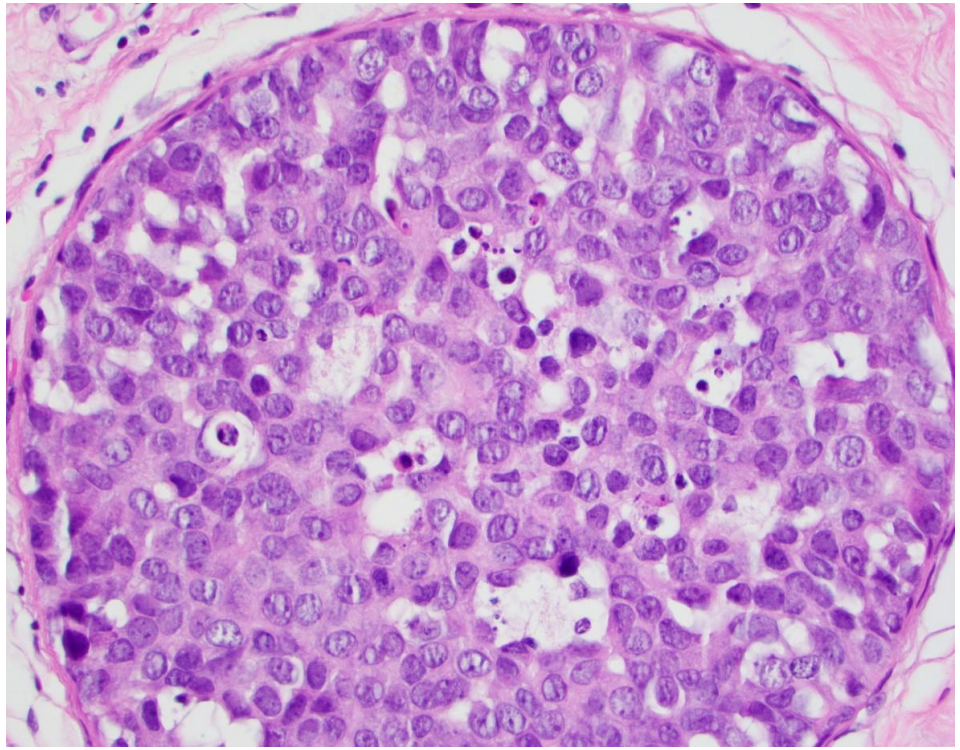


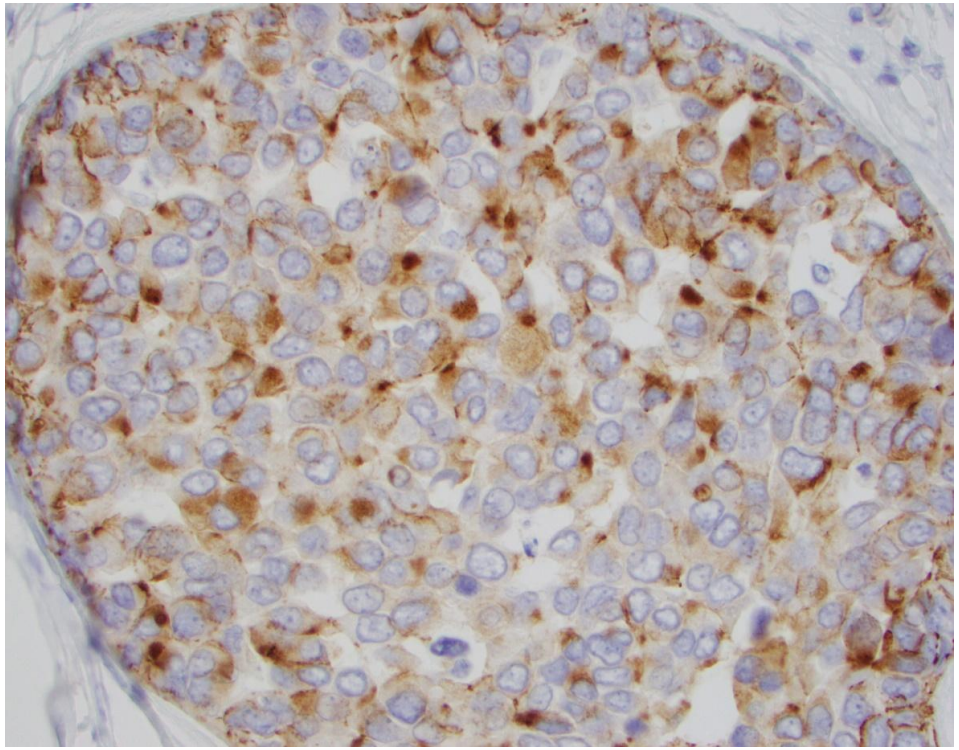


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Aberrant E-cadherin IHC in F-LCIS and P-LCIS

Punctate/ Golgi apparatus distribution

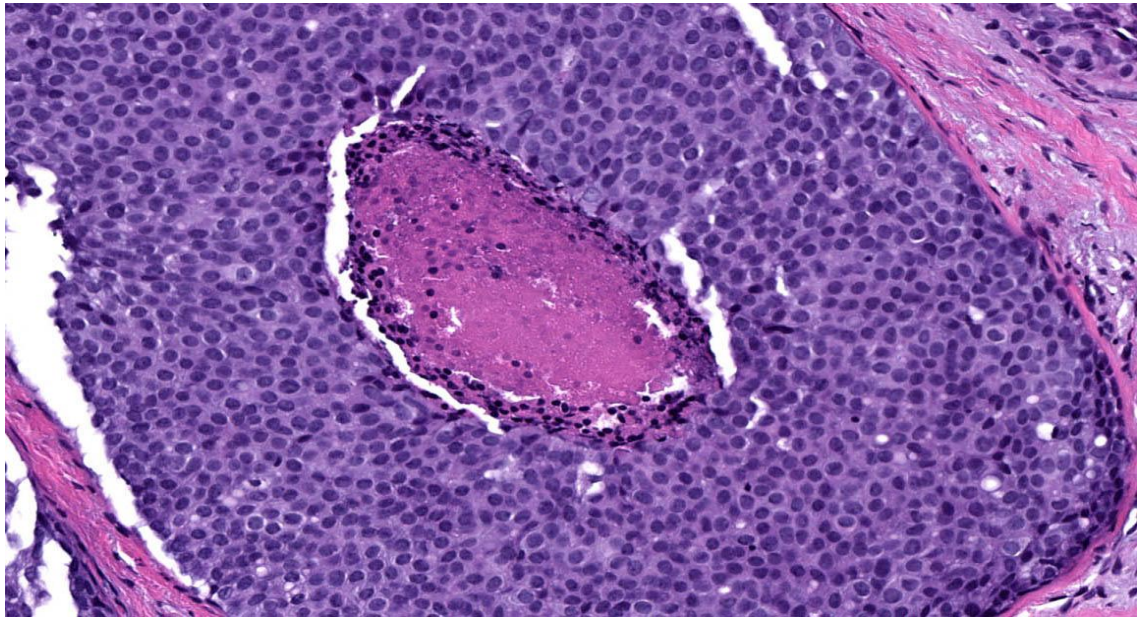


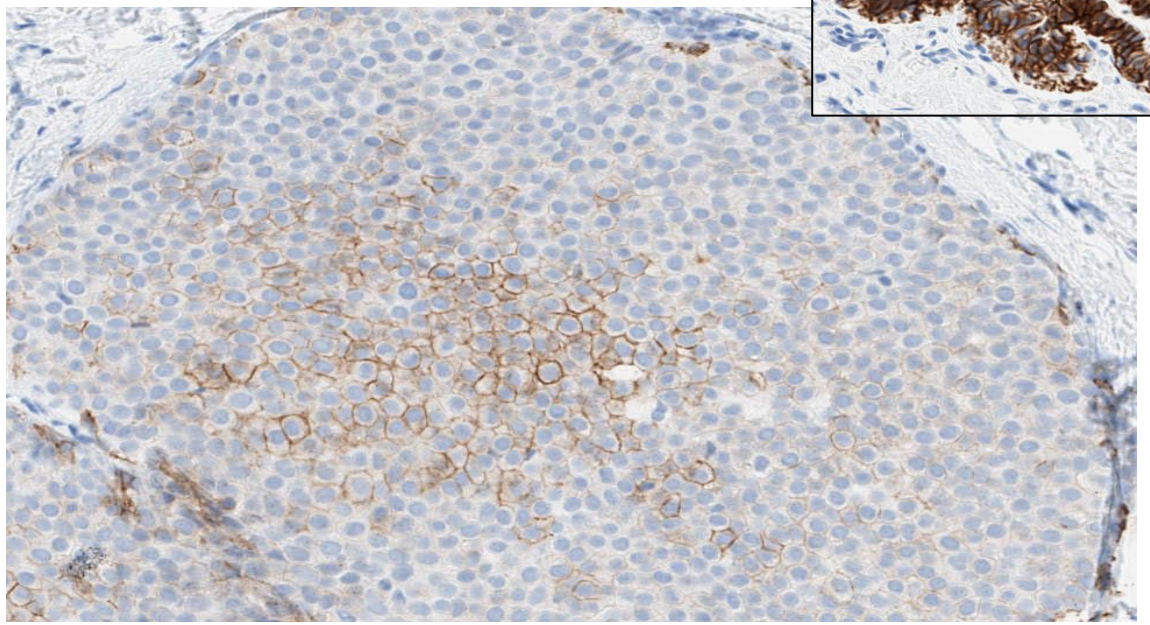


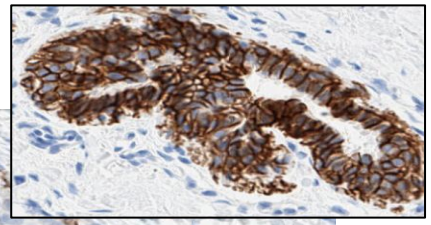
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Aberrant E-cadherin IHC in F-LCIS and P-LCIS

Circumferential membrane staining, especially in the center of the acini, but reduced inteInnsity compared with adjacent ductal cells



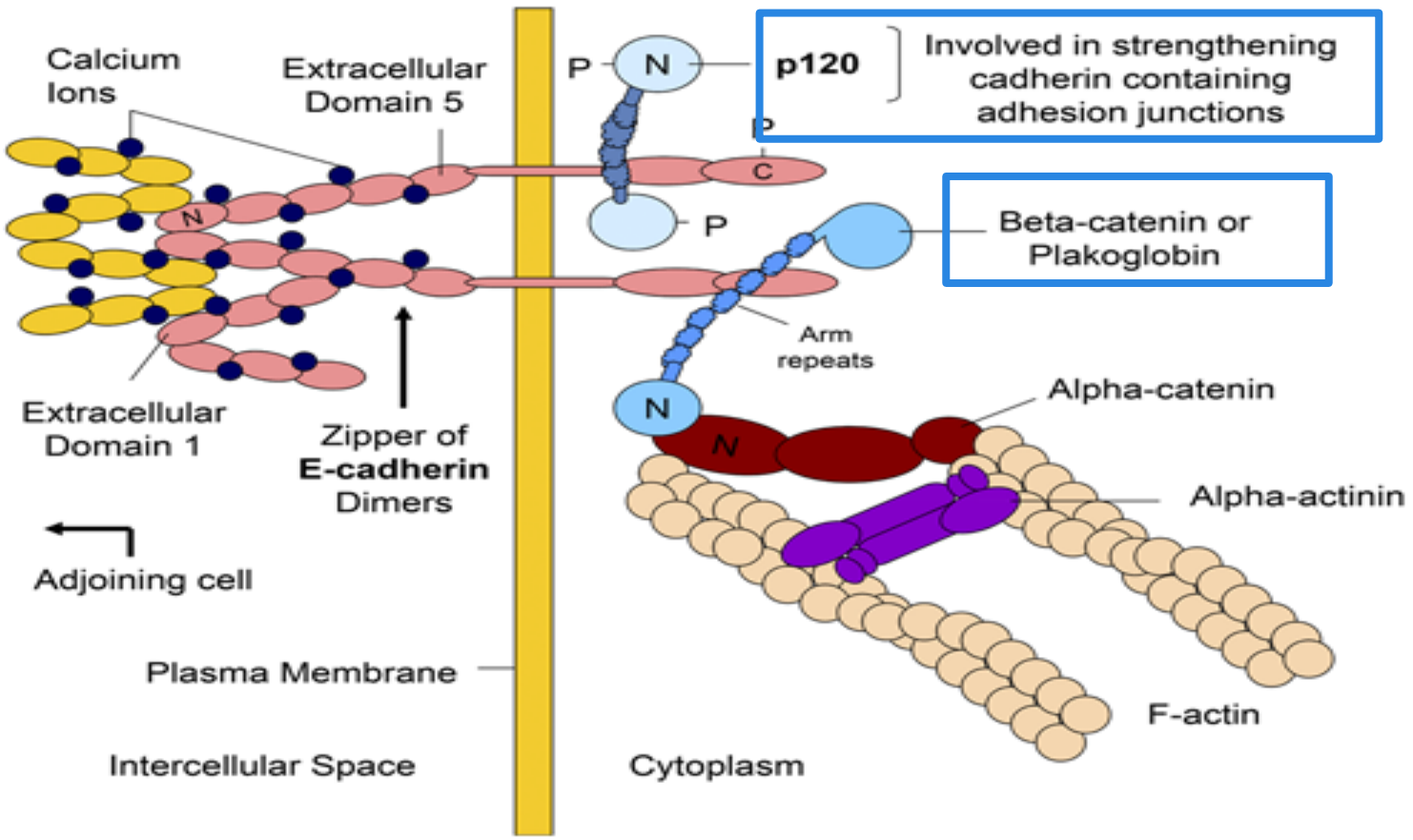




Always compare E-cadherin IHC intensity and pattern in the cells of interest to E-cadherin staining of the internal positive control ductal epithelium (benign, atypical or neoplastic)

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E-cadherin and *wnt*-related proteins



E-cadherin intracellular domain *bound to* α, β and p120 (δ catenin) *bound to* actin cytoskeleton

Dabbs DJ, Bhargava R, Chivukula M. Lobular versus ductal breast neoplasms: the diagnostic utility of p120 catenin. Am J Surg Pathol. 2007 Mar;31(3):427-37.

Dabbs DJ, et al. Lobular neoplasia of the breast revisited with emphasis on the role of E-cadherin immunohistochemistry. Am J Surg Pathol. 2013;37(7):e1-11

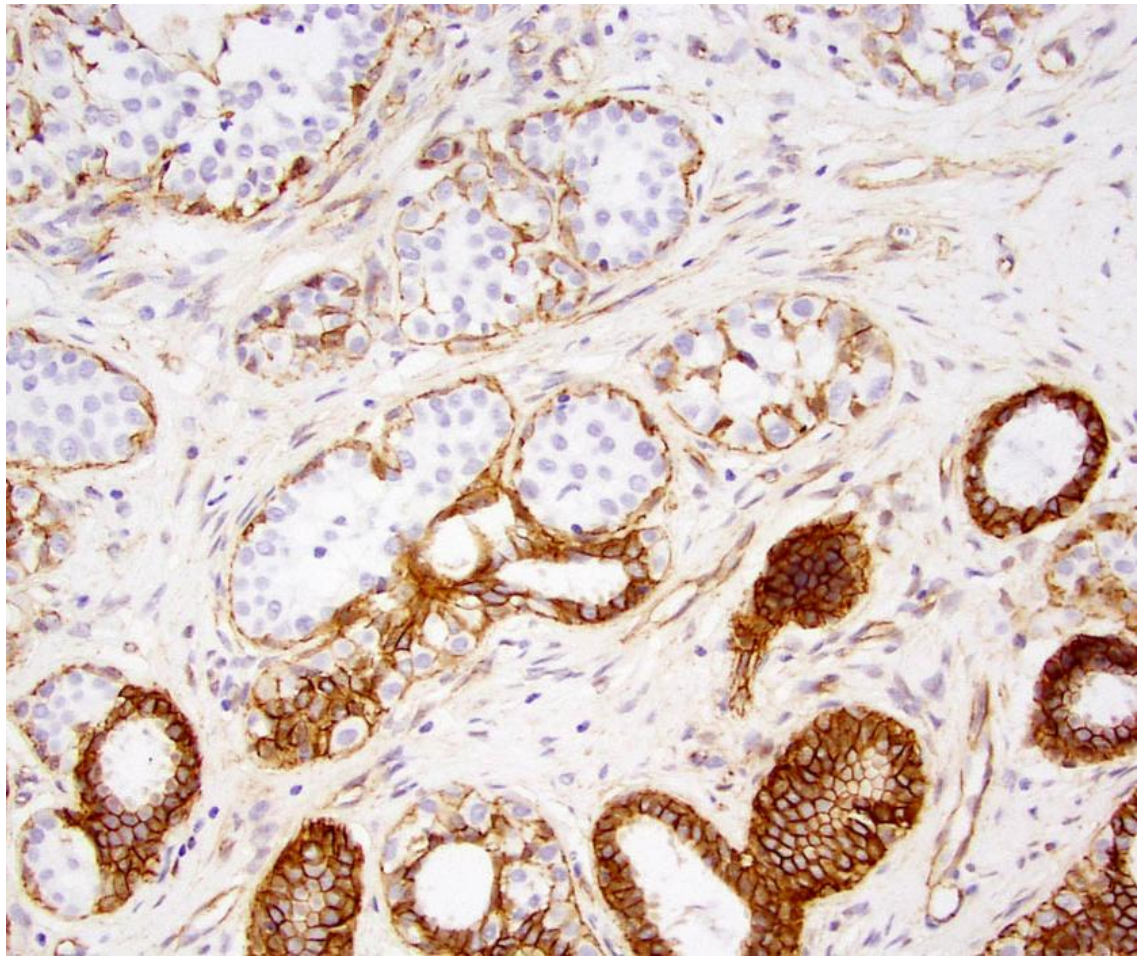
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β-catenin

Staining pattern akin to E-cadherin
Absent in cells of lobular phenotype

Ductal epithelium: (+) cell membrane; continuous linear positivity

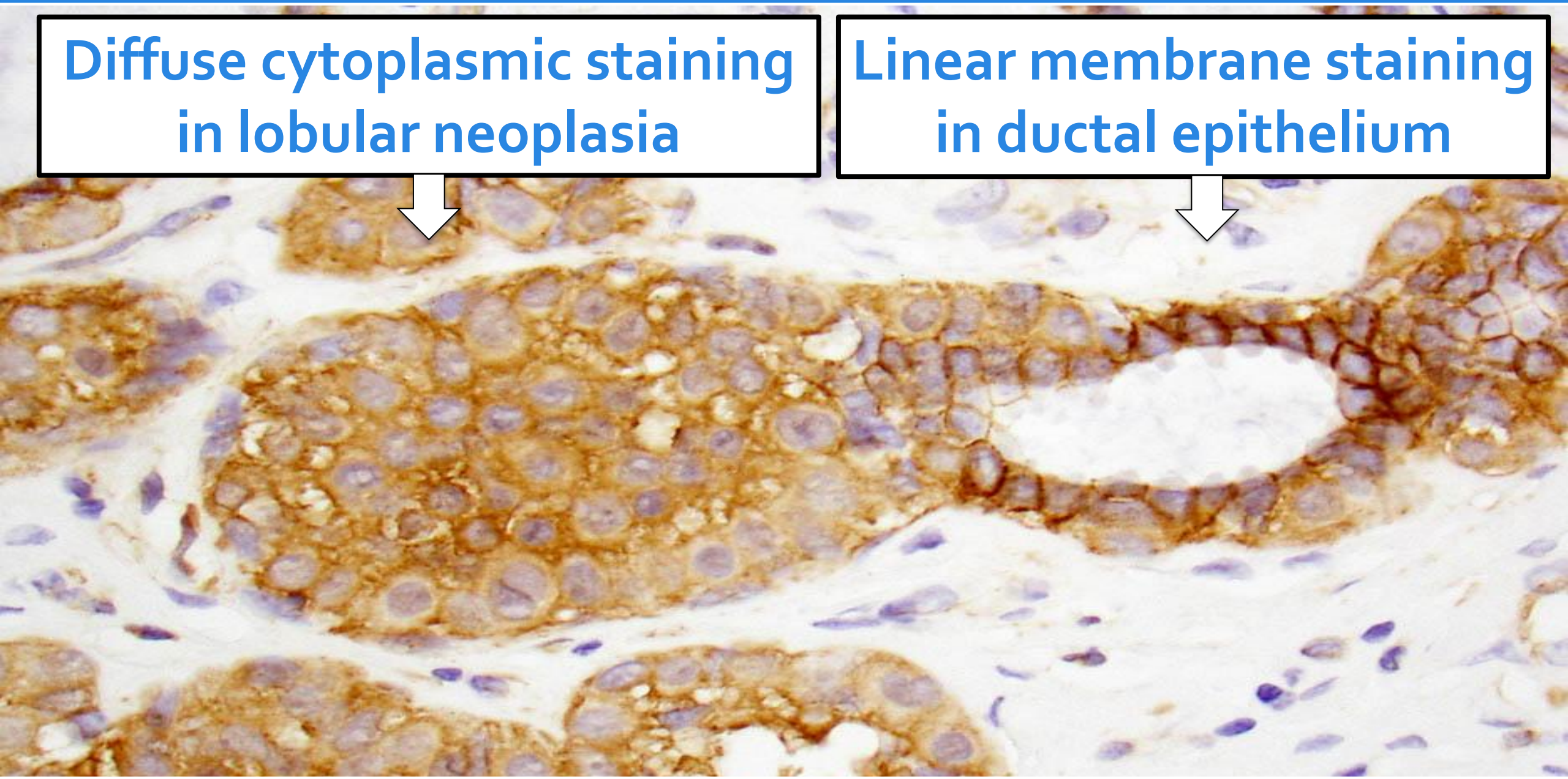
Myoepithelium: (+)cell membrane facing the epithelium; "dot-like"/granular linear positivity



De Leeuw WJ et al. J Pathol. 1997 Dec;183(4):404-11
Dabbs AJ et al. *AJSP* 2013;37:e1-e11

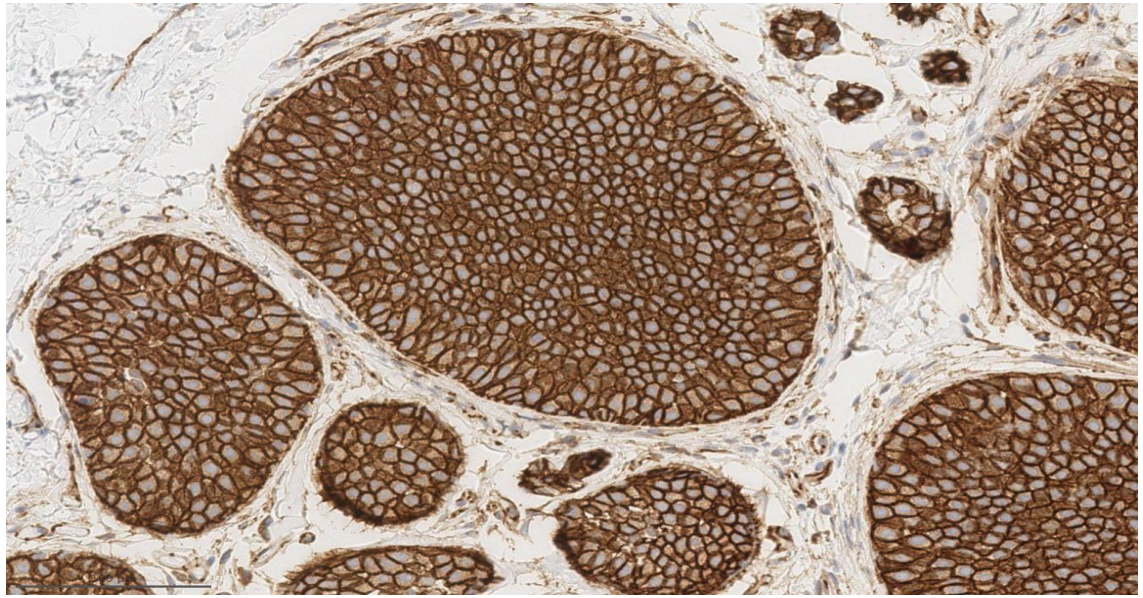
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P120

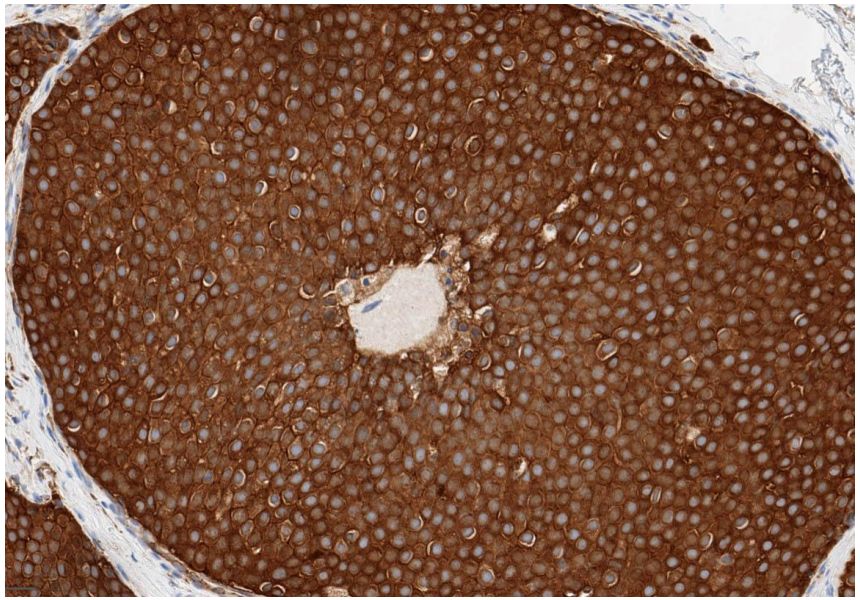

Diffuse cytoplasmic staining in lobular neoplasia
Linear membrane staining in ductal epithelium

Immunohistochemistry for p120

useful to evaluate morphologically ambiguous solid intraductal epithelial proliferations



DCIS: (+) cell membrane



(Florid) LCIS: (+) cytoplasm

Dabbs DJ, Bhargava R, Chivukula M. Lobular versus ductal breast neoplasms: the diagnostic utility of p120 catenin. Am J Surg Pathol. 2007 Mar;31(3):427-37.

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P-LCIS immunoprofile

	ER	PR	AR	HER2
Classic LCIS	**100%**	**100%**	**100%**	**0%**
All P-LCIS	**66%**	**62%**	**100%**	**13%**
Non-apocrine	*100%*	*94%*	*100%*	*0%*
Apocrine	*23%*	*17%*	*100%*	*31%*

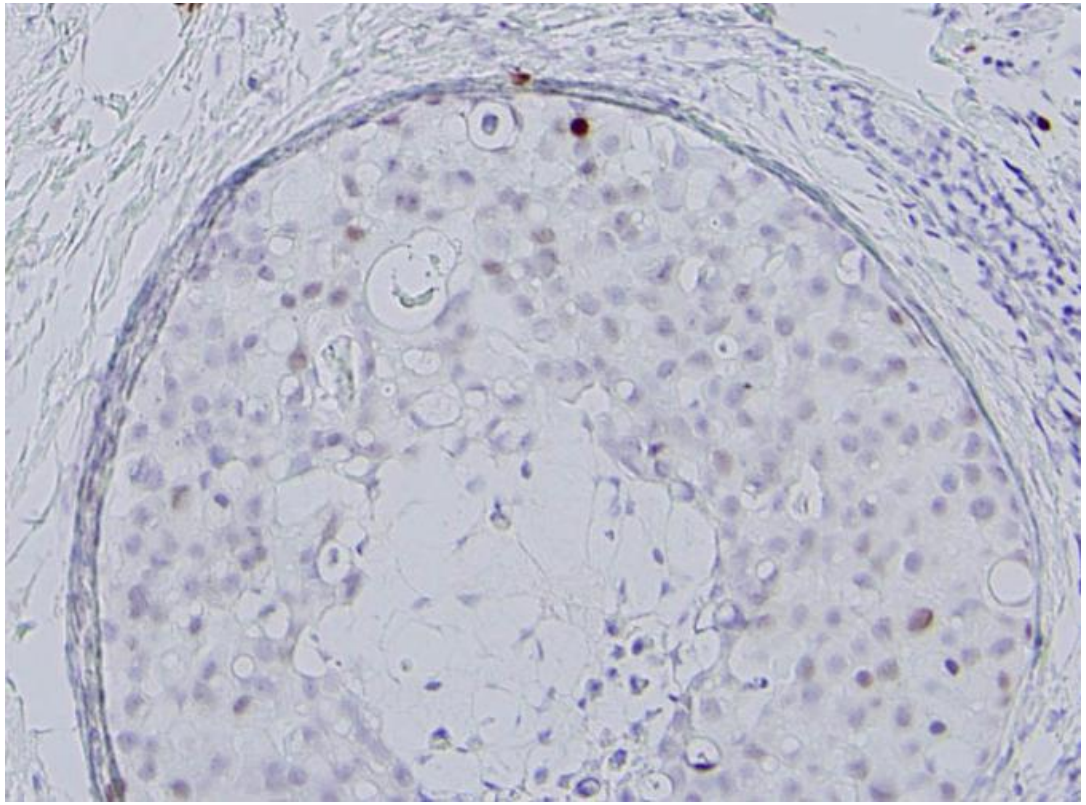
HER2 positivity usually restricted to apocrine P-LCIS
High mitotic rate
No significant expression of CK 5/6

Chen YY et al. AJSP 2009

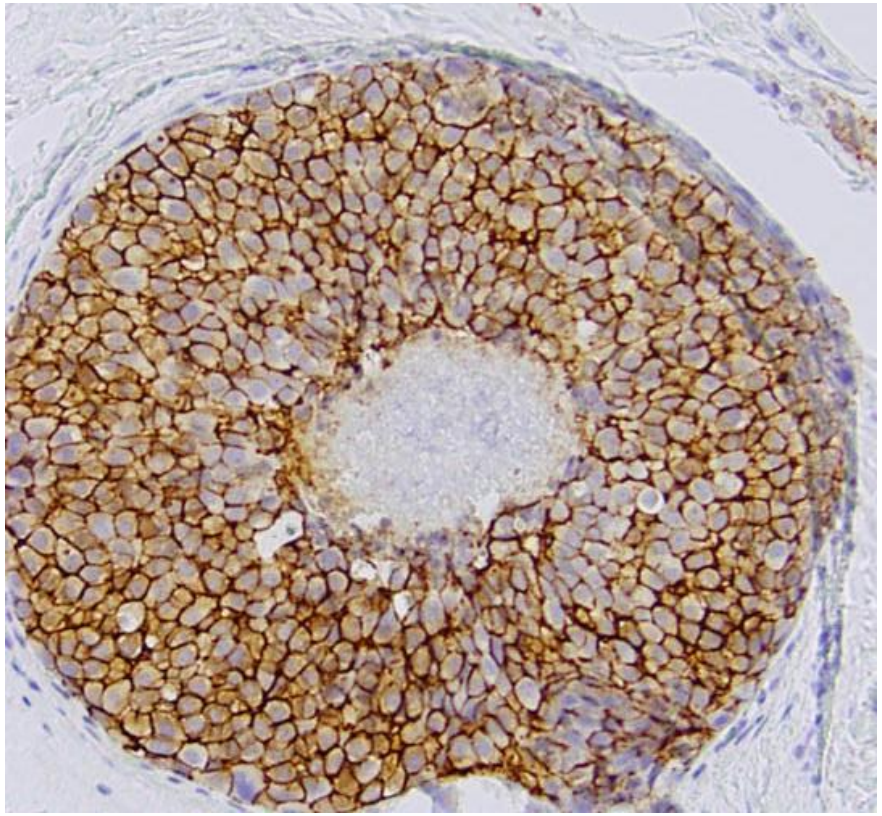
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Any type of LCIS: ER, PR and HER2 assessment is NOT required

ER



HER-2



Management of pure F-LCIS and P-LCIS in CNB

- **Systematic review of 38 studies with primary data on non-classic LCIS**
- **Total 629 cases**
  - 411 P-LCIS, 98 F-LCIS, 120 LCIS with pleomorphic/ non classic features
- **Pooled upgrade rate at excision: 35.3%**
  - Upgrade rate of PLCIS: 35.1%
  - Upgrade rate of FLCIS: 33.3%
  - Most upgrades are ILC (28.8%)

Ferrucci M, et al. Pleomorphic and florid lobular carcinoma in situ of the Breast: A systematic review of current evidence and knowledge gaps. *Breast*. 2026;86:104711

Surgical excision is warranted regardless of radiologic-pathologic concordance practice accepted worldwide

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Florid LCIS and Pleomorphic LCIS

Margin status

Adjuvant treatment

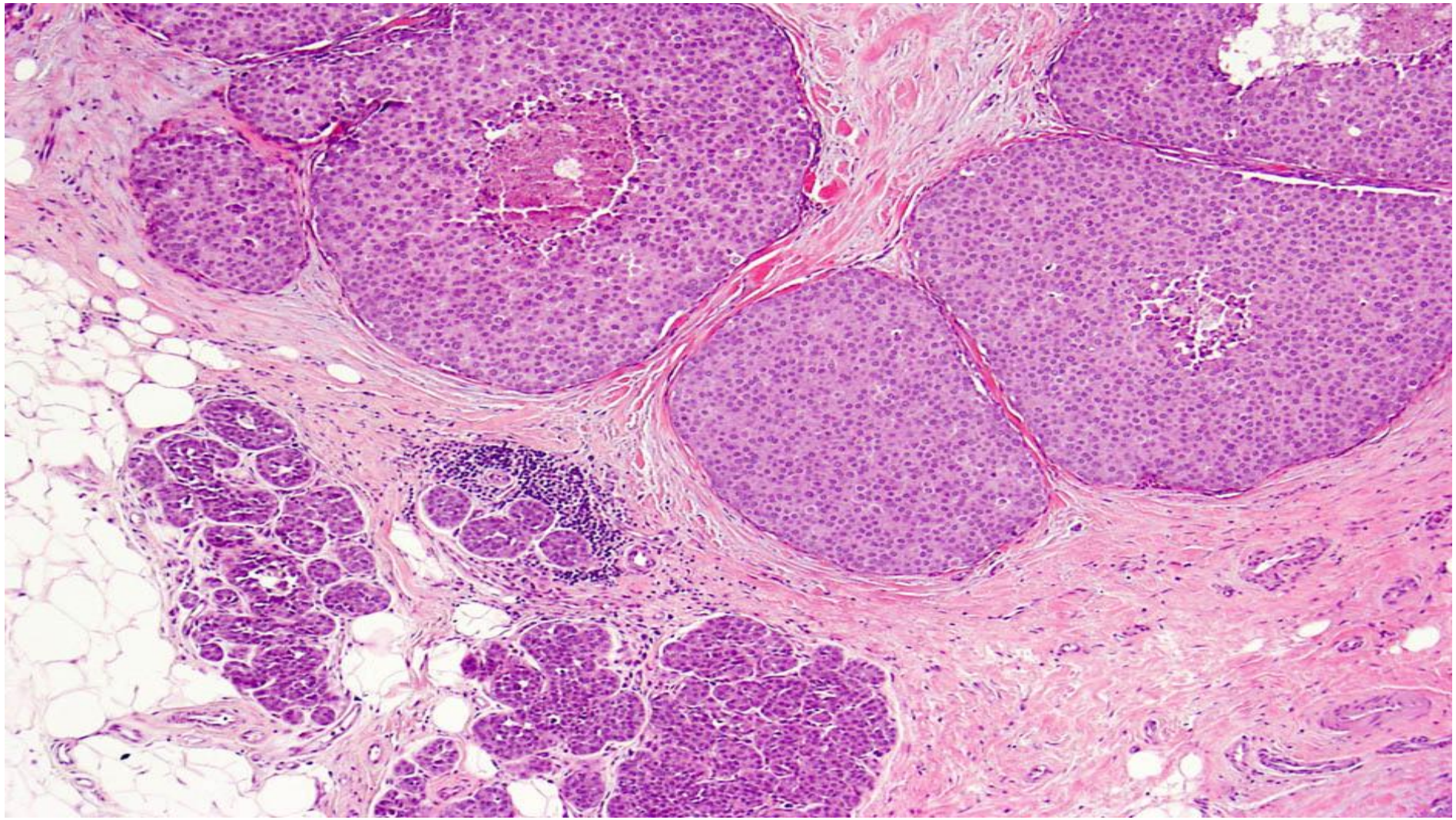
Risk of subsequent carcinoma

P-LCIS: Local Recurrence (LR) according to surgical margin status

author, year	Index Cases	LR of index cases with (+) margin	LR of index cases with <2 mm margin	LR of index cases with ≥2 mm margin
Sneige, 2002	10 PL/DCIS	-	1/1 (100%)	0/6
Downs Kelly, 2011	20 PLCIS 6PLCIS+microILC	1/6 (16.7%)	0/11	0/9
Khoury, 2014	31 PLCIS	4/9 (44.4%)	-	2/21 (9.5%)
Meroni, 2014	2 PLCIS	-	-	1 of 2 (50%)
Flanagan, 2015	12 PLCIS	0/3	0/4	0/5
Fasola, 2018	12 PLCIS	0/2	-	0/10
De Brot, 2017	11 PLCIS	0/2	1/3 (33%)	0/3
Desai, 2018	15 PLCIS	1/1 (100%)	-	1/14 (7.1%)
Savage, 2018	16 PLCIS	0/1	-	0/15
Hoffmann, 2019	11 PLCIS	-	1/3 (33%)	0/8
Ferrucci, 2025	20 PLCIS 6 P/FLCIS	2/3 (66.7%) 1/1 (100%)	1 of 2 (50%) -	0/15 0/5
Middleton, 2025	34 PLCIS	1/6 (16.6%)	2/3 (33%)	0/21
Total	**206**	**10/34 (29.4%)**	**6/27 (22%)**	**4/134 (0.3%)**

modified from Ferrucci M, et al. Pleomorphic and florid lobular carcinoma in situ of the Breast: A systematic review of current evidence and knowledge gaps. Breast. 2026 Apr;86:104711.

Classic LCIS usually found near F/P-LCIS



Classic LCIS→ margin status is not reported

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WHO 6th ed. - Comments on the management of F-LCIS and P-LCIS

Information about the natural history of F-LCIS and P-LCIS is extremely limited.
The recurrent lesions may be P-LCIS, DCIS, ILC, or invasive carcinoma NST.

Optimal treatment of patients without invasive carcinoma after excision remains unclear.

It is recommended that margin status be reported to help inform further management decisions.

The use of radiotherapy is debated, and data are limited to very small retrospective series.

Some guidelines recommend treating PLCIS akin to DCIS, after multidisciplinary discussion.
There are no recommendations for the treatment of florid LCIS.

The presence of F/P-LCIS at the margin of breast conserving surgery specimens performed for DCIS or invasive carcinoma does not appear to influence the patient outcomes.

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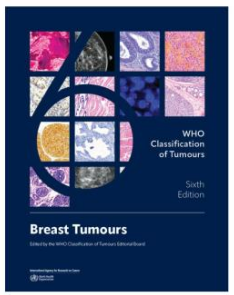
F-LCIS/ P-LCIS: classification and management according to different organizations

Organization	How is it classified and reported?	What does it mean for management?	Staging
NCCN Breast Cancer Screening and Diagnosis v1.2026	In CNB, F/P-LCIS grouped as "non-classic LCIS"	Complete excision with negative margins No invasion on EXC → routine screening and risk-reduction counseling.	F/P-LCIS not included in AJCC staging guidelines
American Society of Breast Surgeons (ASBrS) Resource Guide	In CNB, F/P-LCIS grouped as "non-classic LCIS" Represent distinct forms of LCIS	Surgical excision; 2 mm margin clearance recommended	
RCPath guidance	In CNB: F-LCIS : B4 lesion P-LCIS : B5a lesion	Wide local excision aiming for clear margins, akin to DCIS	P-LCIS staged as pTis *F-LCIS?*
European B3 Guidelines (EUSOMA/EUSOBI/ESP/ESSO, 2024) ESMO	In CNB: F-LCIS : B4 lesion P-LCIS : B5a lesion	Surgical excision	P-LCIS staged as pTis F-LCIS - no specific staging
ICCR dataset for DCIS, P-LCIS and F-LCIS, and low-grade lesions	Features overlapping with DCIS *F- LCIS: Low/ intermediate NG DCIS* *P-LCIS: High NG DCIS*	F-LCIS and P-LCIS to be managed as DCIS Excision to negative margins; report size and margins status.	P-LCIS and F-LCIS staged as pTis

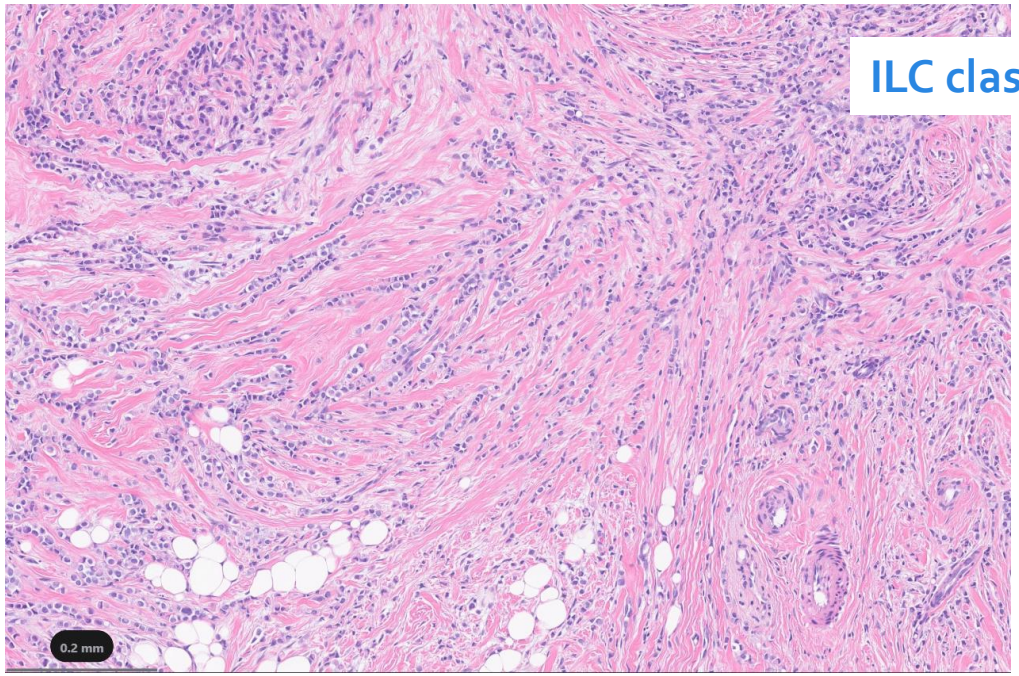
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Invasive lobular carcinoma

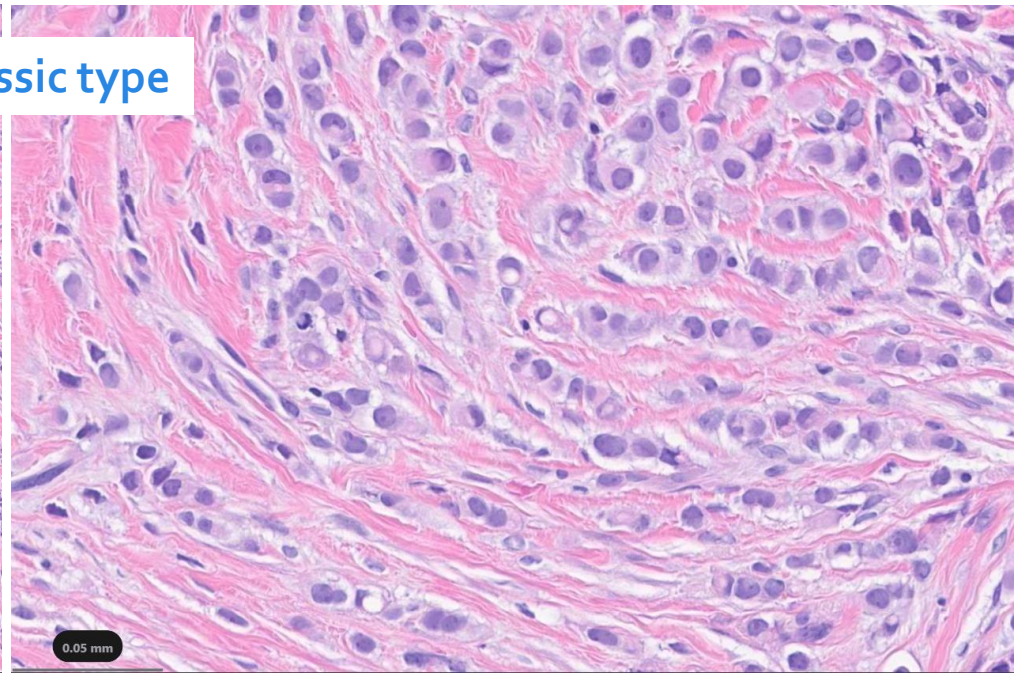
Invasive lobular carcinoma (ILC)



- Most often composed of dyscohesive monotonous cells … dispersed or arranged in single-file linear cords with minimal or no stromal reaction.
- Most common special type of Invasive Breast Carcinoma (IBC) (10–15% of all IBCs)
- Uncommon in males



ILC classic type



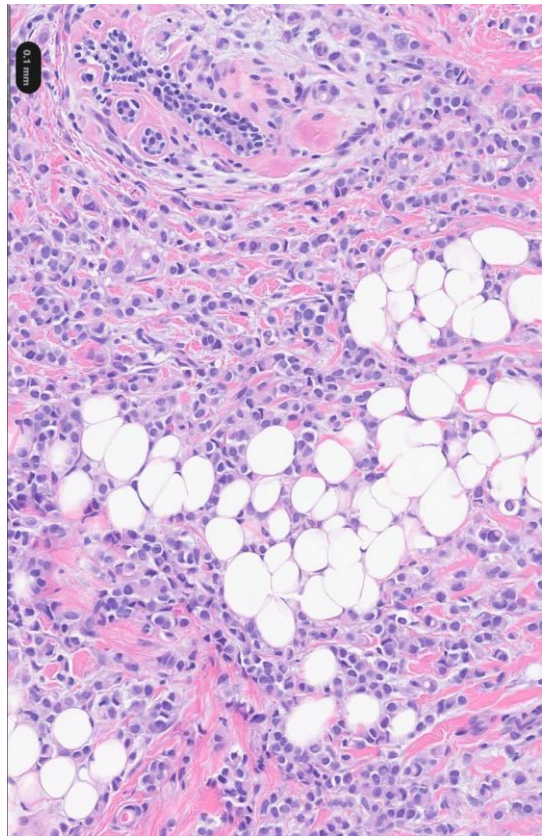
Memorial Sloan Kettering Cancer Center

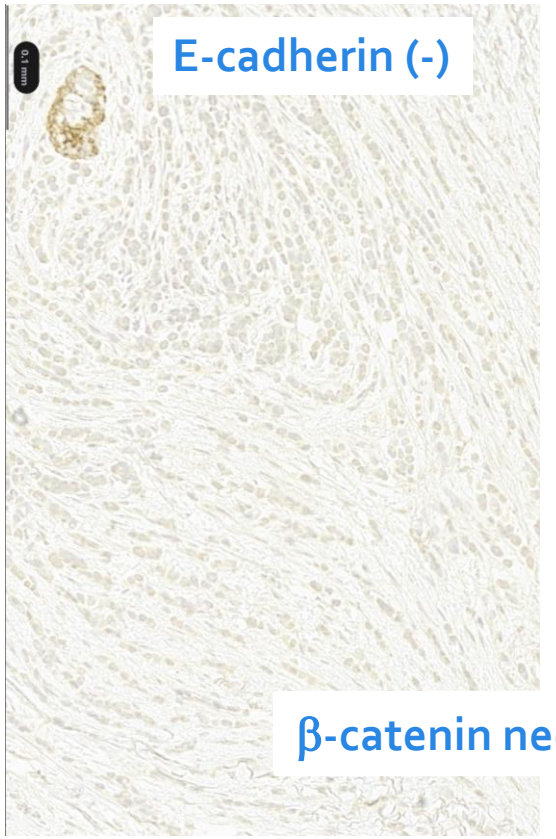
Invasive lobular carcinoma – molecular underpinnings

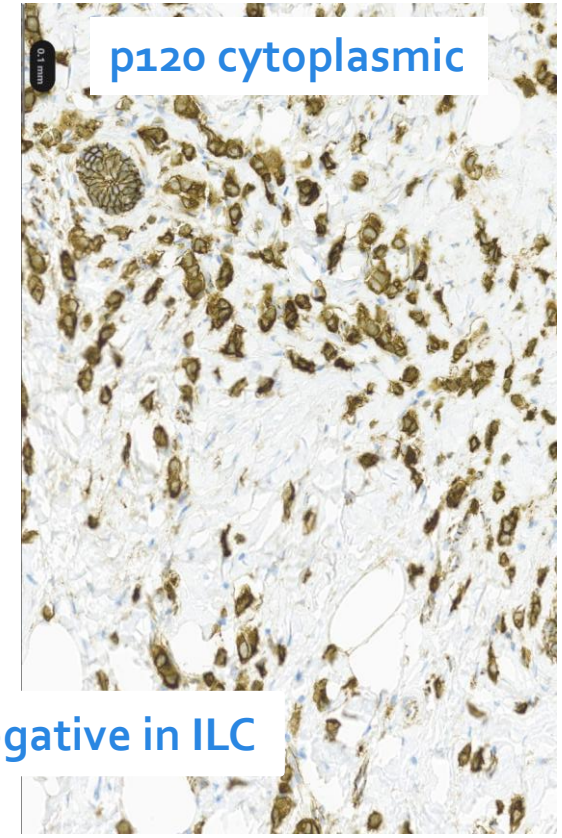


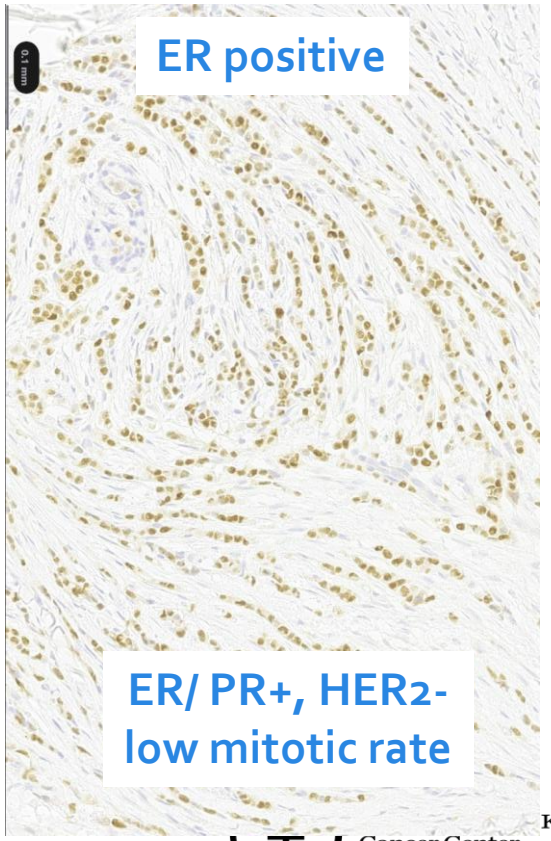
Lack of cohesiveness …due to loss of function of the E-cadherin protein. Most ILCs display loss of heterozygosity of chromosome 16q (*CDH1* gene locus at 16q22.1). Approximately 71% of ILCs harbour deleterious *CDH1* mutations. *CDH1* inactivation may also result from fusion genes, deletions, and non-coding variants.

Loss of *CDH1* function causes cytosolic translocation of p120 catenin (p120).







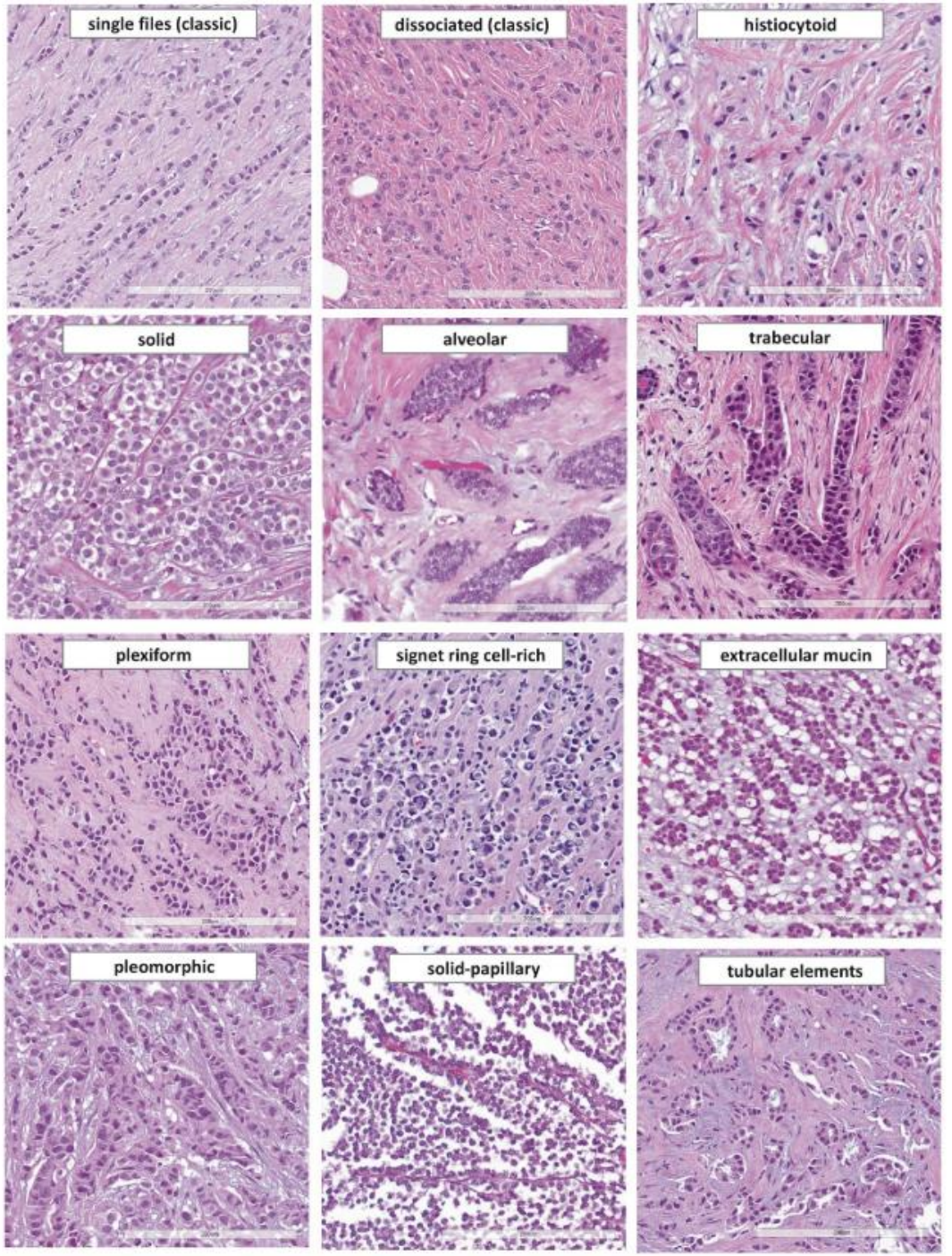


β-catenin negative in ILC

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Invasive lobular carcinoma

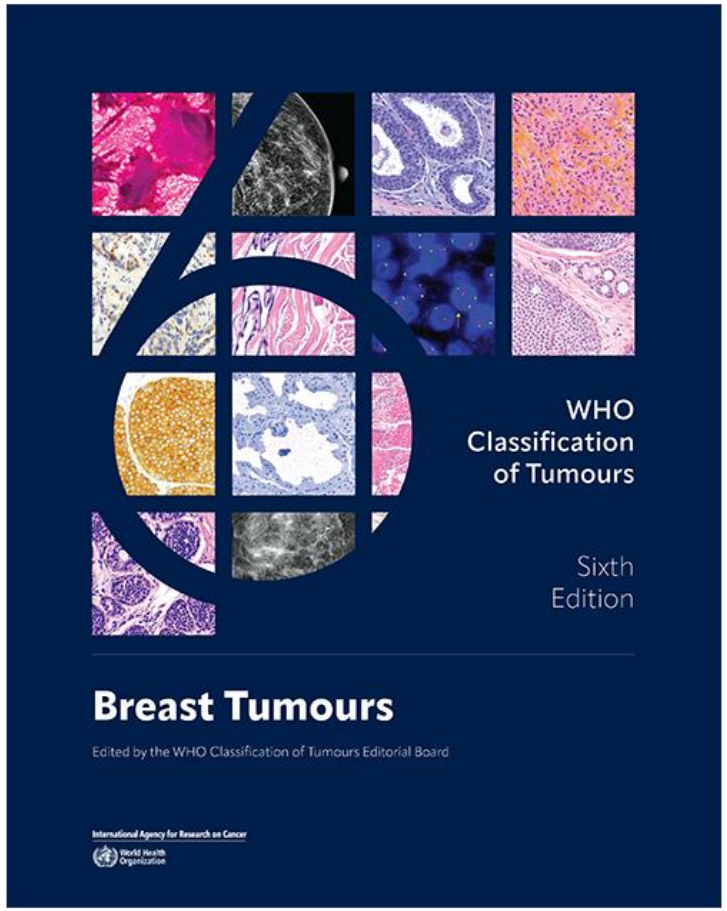
- Many morphologic patterns reported in the literature
- Reportedly some of ILC patterns are associated with worse prognosis compared to classic ILC
- Criteria for the diagnosis of ILC morphologic patterns are not well defined



Christgen M, Cserni G, Floris G, Marchio C, Djerroudi L, Kreipe H, Derksen PWB, Vincent-Salomon A. Lobular Breast Cancer: Histomorphology and Different Concepts of a Special Spectrum of Tumors. Cancers (Basel). 2021 Jul 22;13(15):3695.

10 ILC patterns (according to WHO 6th ed)

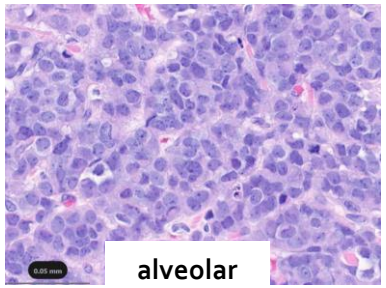
- Solid pattern
- Alveolar pattern
- Solid papillary
- Trabecular
- Signet ring–cell features
- Histiocytoid
- Apocrine
- Pleomorphic ILC
- Tubulolobular / ILC with tubular elements
- ILC with extracellular mucin

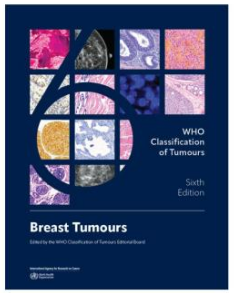


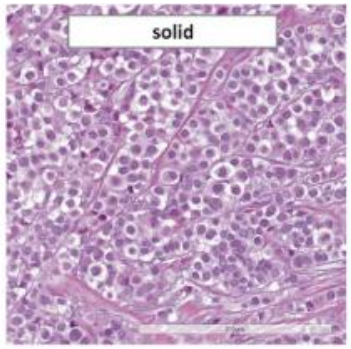
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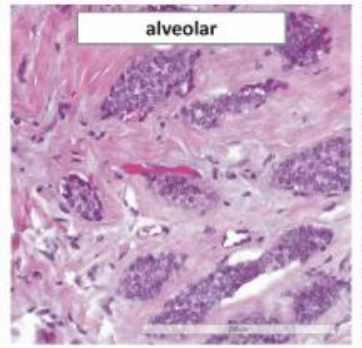
ILC morphology/ growth patterns

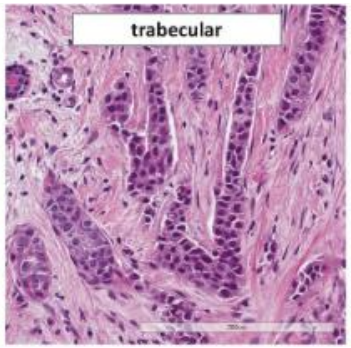
- Trabecular = discohesive trabeculae 2-3 cell thick
- Signet ring-cell rich
- Alveolar = globular aggregates of ≥20 cells separated by thin bands of collagenous stroma
- Solid = solid growth of discohesive cells with little to no intervening stroma

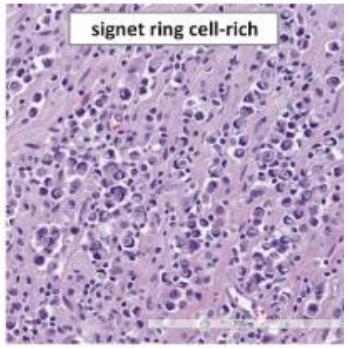












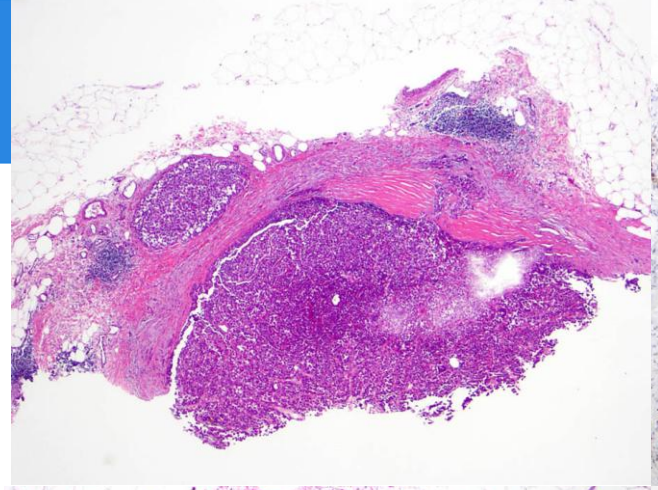
ILC of solid papillary pattern

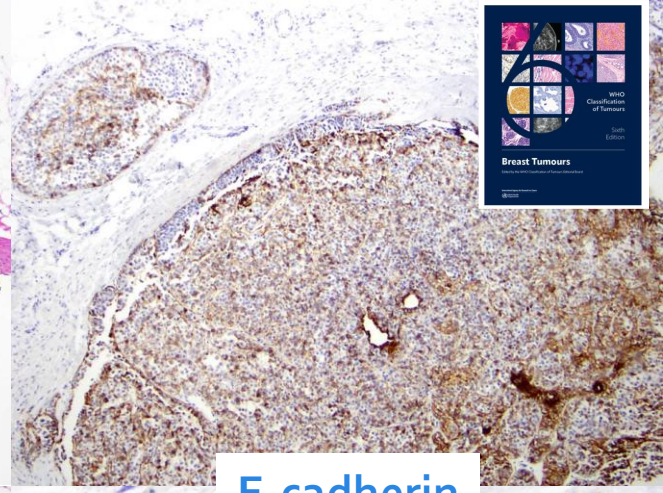
"A variation of the solid pattern with solid papillary architecture

- well delimited peripherally with a pseudocapsule
- often associated with peripheral satellite foci of ILC. "

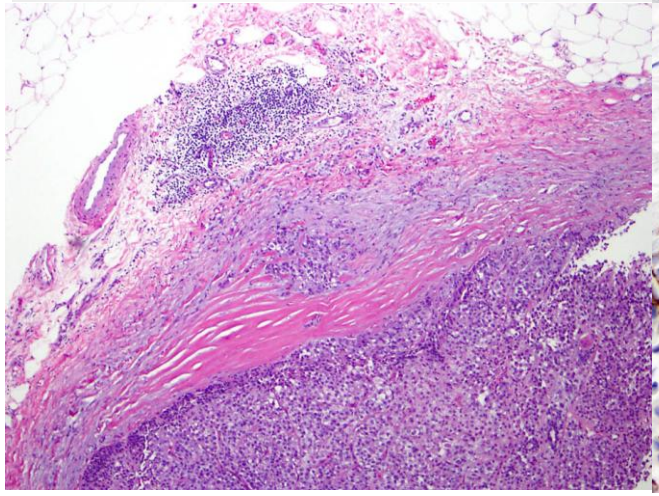
Differential Diagnosis

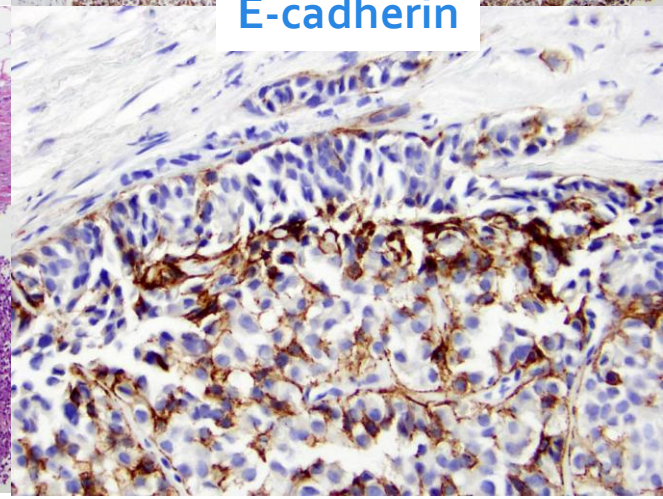
- Solid papillary carcinoma (E-cadherin positive)
- Other papillary lesions





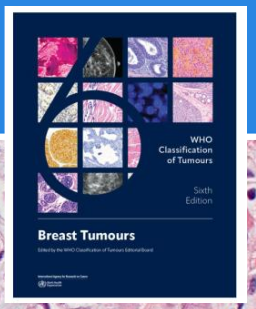
E-cadherin





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Pleomorphic Invasive lobular carcinoma



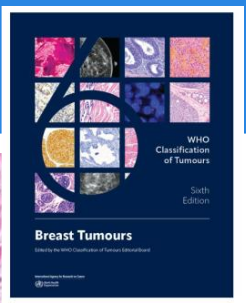
- Grade 3 nuclear pleomorphism = P-LCIS-like nuclei
  - >4 times the size of a lymphocyte
  - equivalent to those of high-grade DCIS
  - +/- binucleated or multinucleated cells
- May display apocrine differentiation
- Frequently associated with P-LCIS
- Higher mitotic rate than classic ILC
- Lower levels of ER and PR, may be HER2+

- "Pleomorphic morphology is unlikely to have prognostic value in itself, with overall histological tumour grade being of superior prognostic relevance."

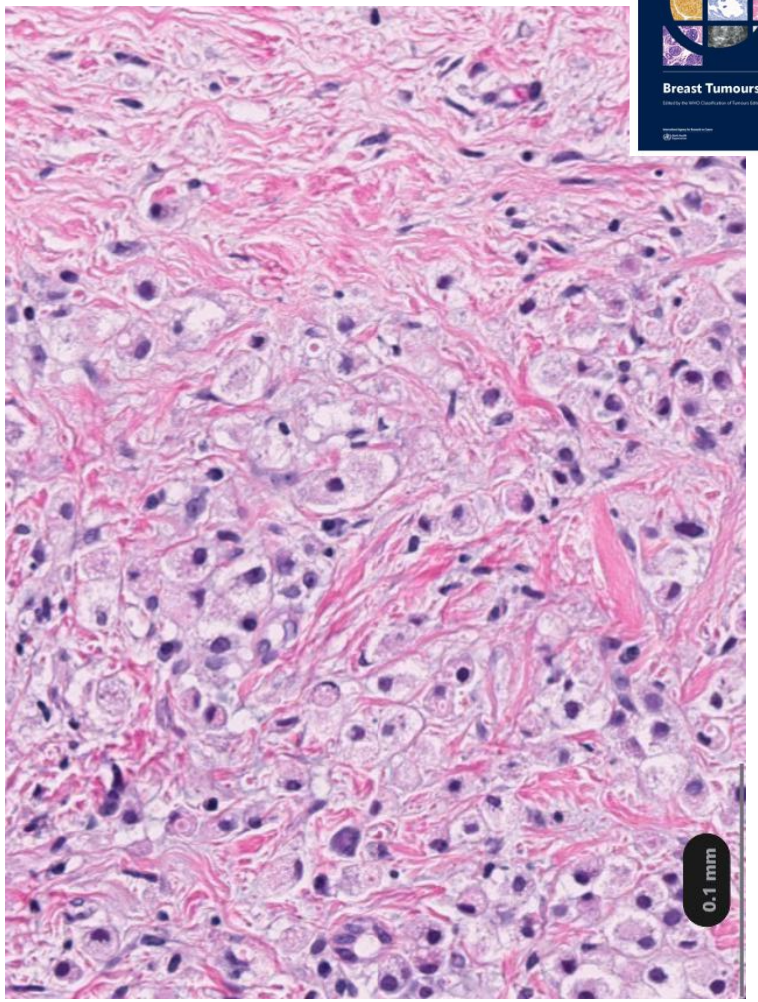
Pleomorphic ILC (WHO 6th ed.)
With apocrine features

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Histiocytoid Invasive lobular carcinoma



- Relatively bland, uniform nuclei, single small eosinophilic nucleoli, and ample granular or foamy cytoplasm.
- WHO 6th ed: "It may be difficult to distinguish histiocytoid from apocrine differentiation, and ILCs with histiocytoid and apocrine features are both typically ER-negative and AR-positive.
- The prognostic relevance of these cytological features … is likely …superseded by histological grade and biomarker profile."



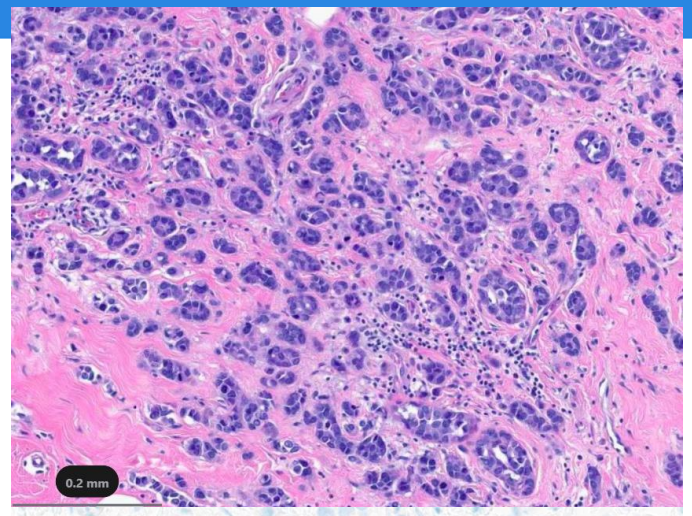
Histiocytoid ILC

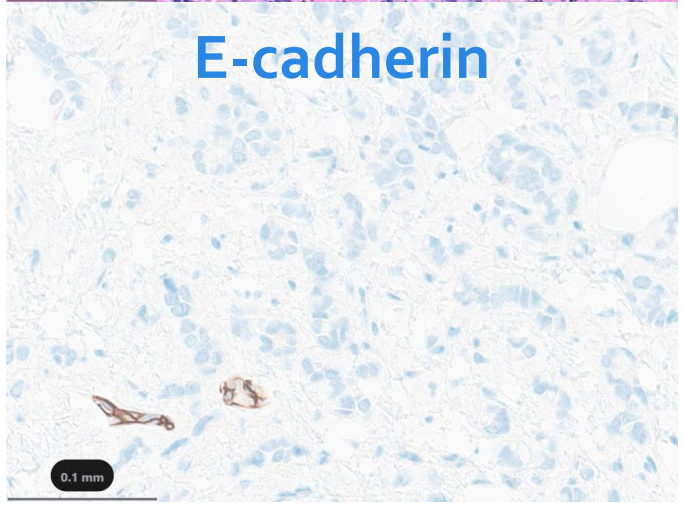
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Tubulolobular carcinoma - terminology

- Some ILCs contain small, well-formed glands or tubules
  - Some are E-cadherin positive
  - Some are E-cadherin–negative but demonstrate a switch to expression of P-cadherin re-establishing adherens junctions.

- It is recommended to diagnose:
  - Tubulolobular carcinoma
    - tubulolobular morphology, negative for E-cadherin
  - Mixed ILC and tubular carcinoma
    - tubulolobular morphology
    - E-cadherin–negative ILC elements
    - E-cadherin–positive tubular elements

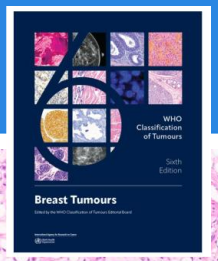




Tubulolobular carcinoma

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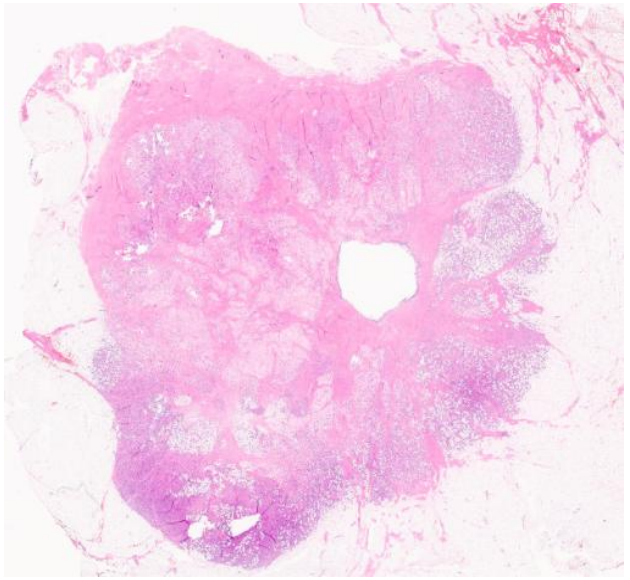
ILC with extracellular mucin

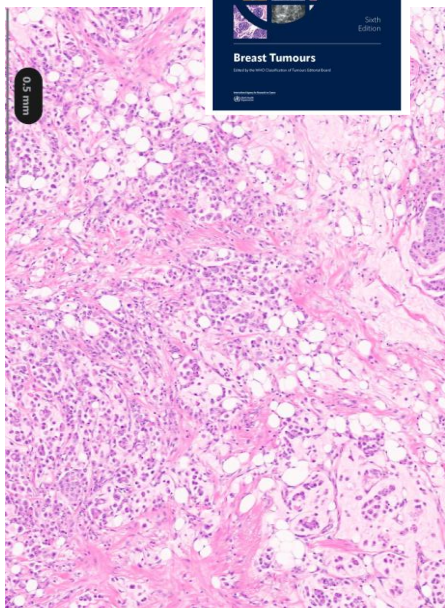


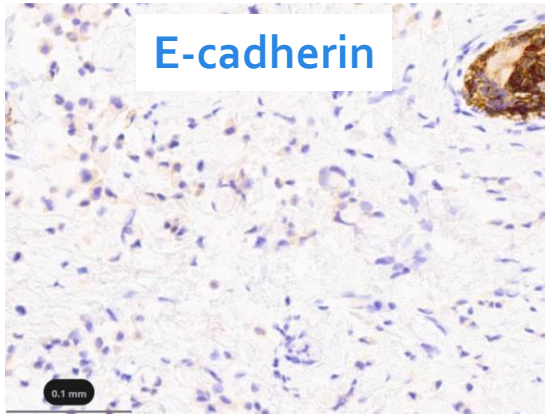
- Usually grade 3 with tumor necrosis
- Predominantly composed of signet ring cells
- Extracellular mucin may be focal (% cutoff not defined)
- May also have solid architecture
- Usually ER(+), may be HER2(+)
- *PIK3CA, POLQ, TP53, ERBB3, ERBB2, RUNX1, GATA3, FOXA1, CCND1* mutations

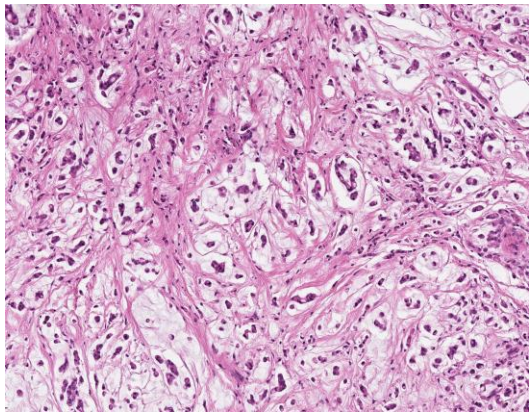
Clinically aggressive

- LN mets in >50% cases
- Distant metastases common





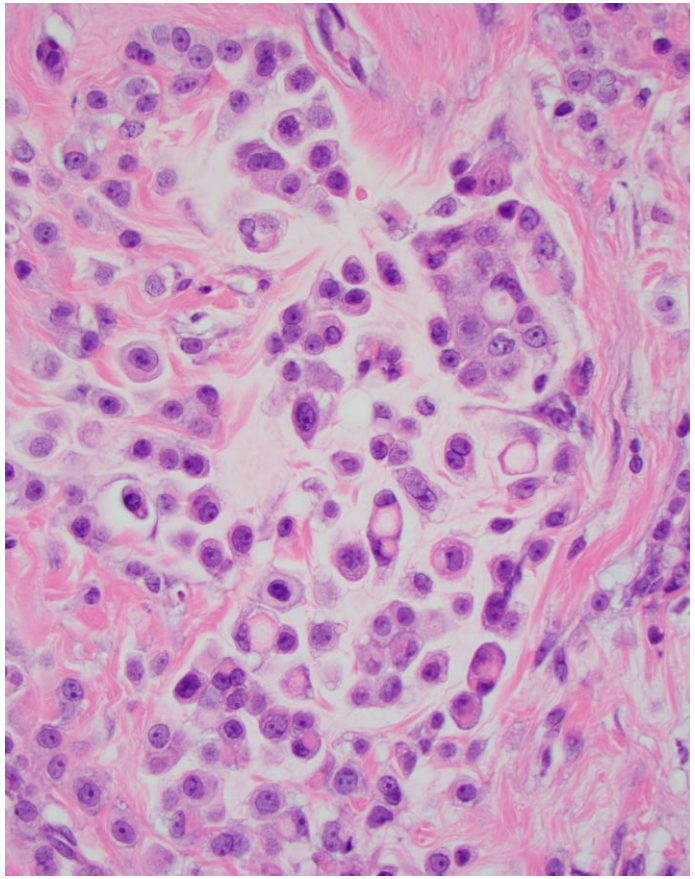




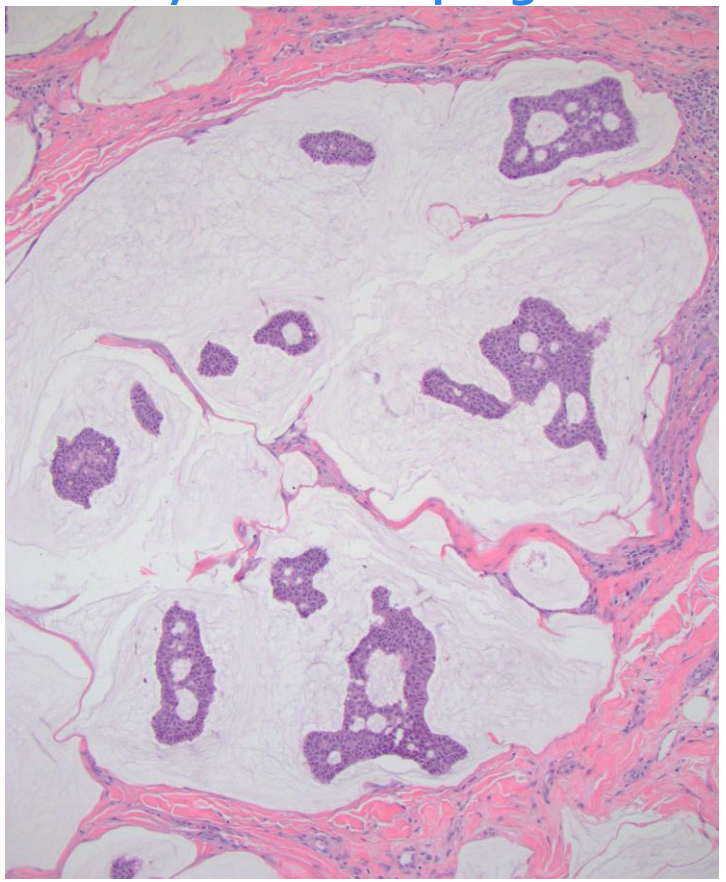
Rosa M, Mohammadi A, Masood S. Lobular carcinoma of the breast with extracellular mucin: new variant of mucin-producing carcinomas? Pathol Int. 2009;59(6):405-9
Cserni G, et al. Invasive lobular carcinoma with extracellular mucin production-a novel pattern of lobular carcinomas of the breast. Virchows Arch. 2017;471(1):3-12.
Soong TR, et al. Invasive lobular carcinoma with extracellular mucin (ILCEM): clinicopathologic and molecular characterization of a rare entity. Mod Pathol. 2022;35(10):1370-1382.

Differential diagnosis

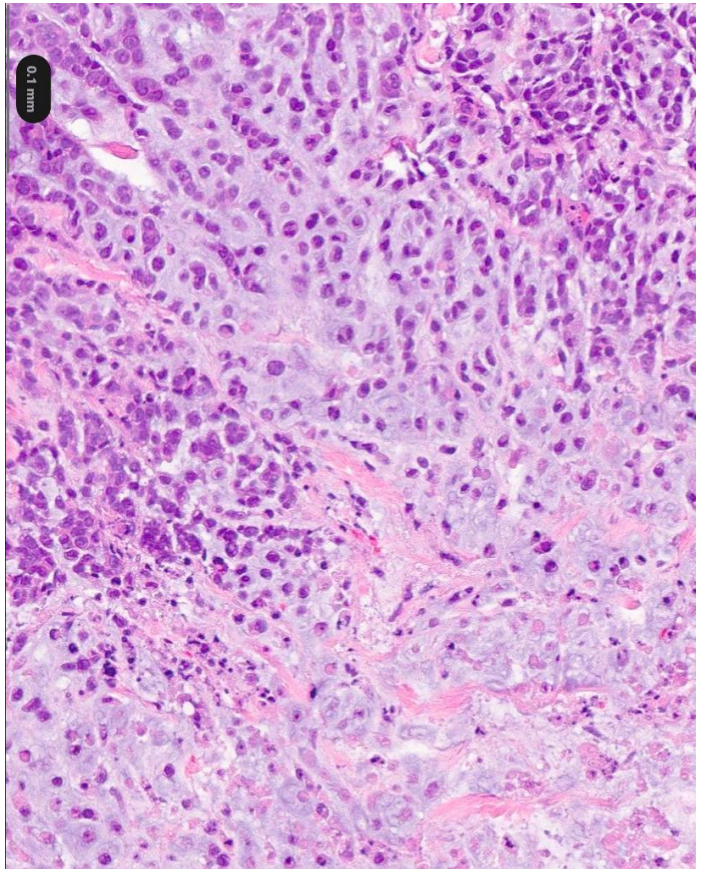
ILC
with extracellular mucin



Mucinous carcinoma
usually favorable prognosis



Metaplastic
matrix-producing
(myxochrondroid)



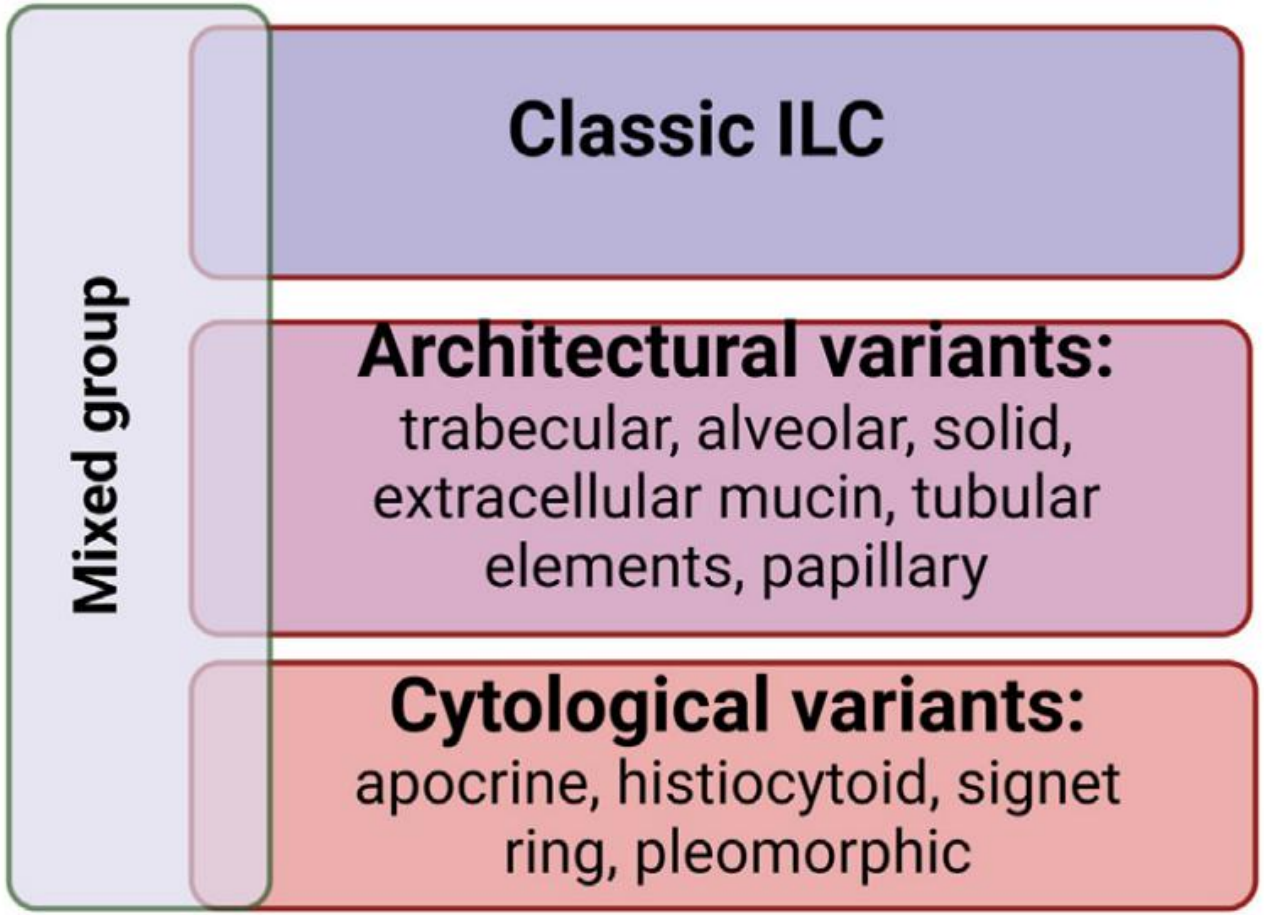
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ILC morphology, receptor profile, behavior

ILC morphology	ER, PR positive	HER2	Triple negative	behavior
classic	>90%	negative	Very uncommon	Less aggressive than IDC
alveolar				
solid				
solid papillary				
pleomorphic	may be negative, often AR-positive	approximately 30-40% positive	rare (10%) but possible	Likely more aggressive than classic ILC
apocrine				
histiocytoid		may be positive	not uncommon	
ILC with extracellular mucin	Usually ER/ PR positive	may be positive	uncommon	aggressive

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ILC- many different morphologies and patterns



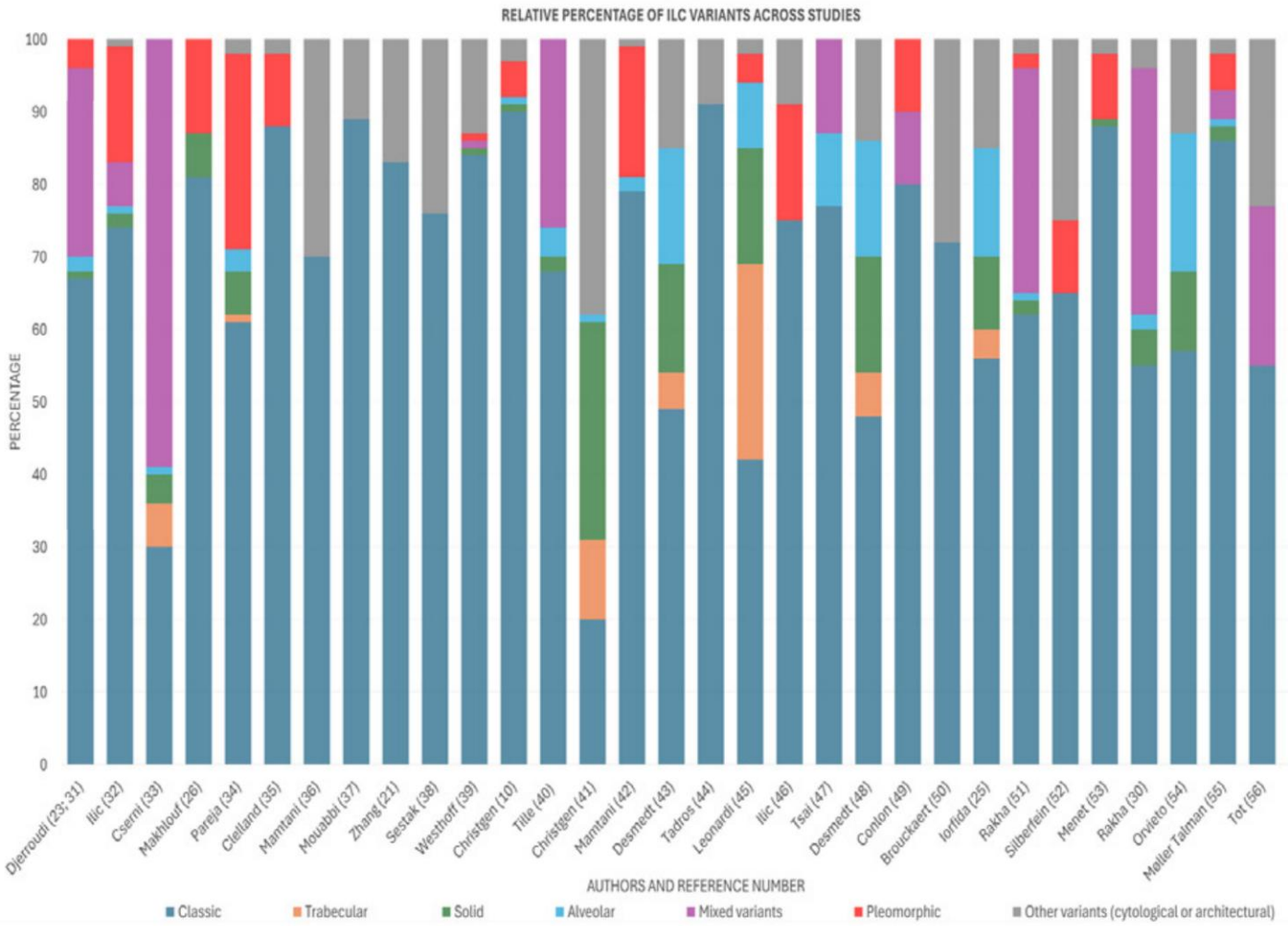
Floris G, Djerroudi L, Zels G, et al. Pitfalls in the Histological Diagnosis of Morphologic Variants of Invasive Lobular Carcinoma of the Breast. Mod Pathol. 2025;38(9):100837.

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ILC morphologic patterns are poorly reproducible

High variability in the relative prevalence undermines credibility and reproducibility of results

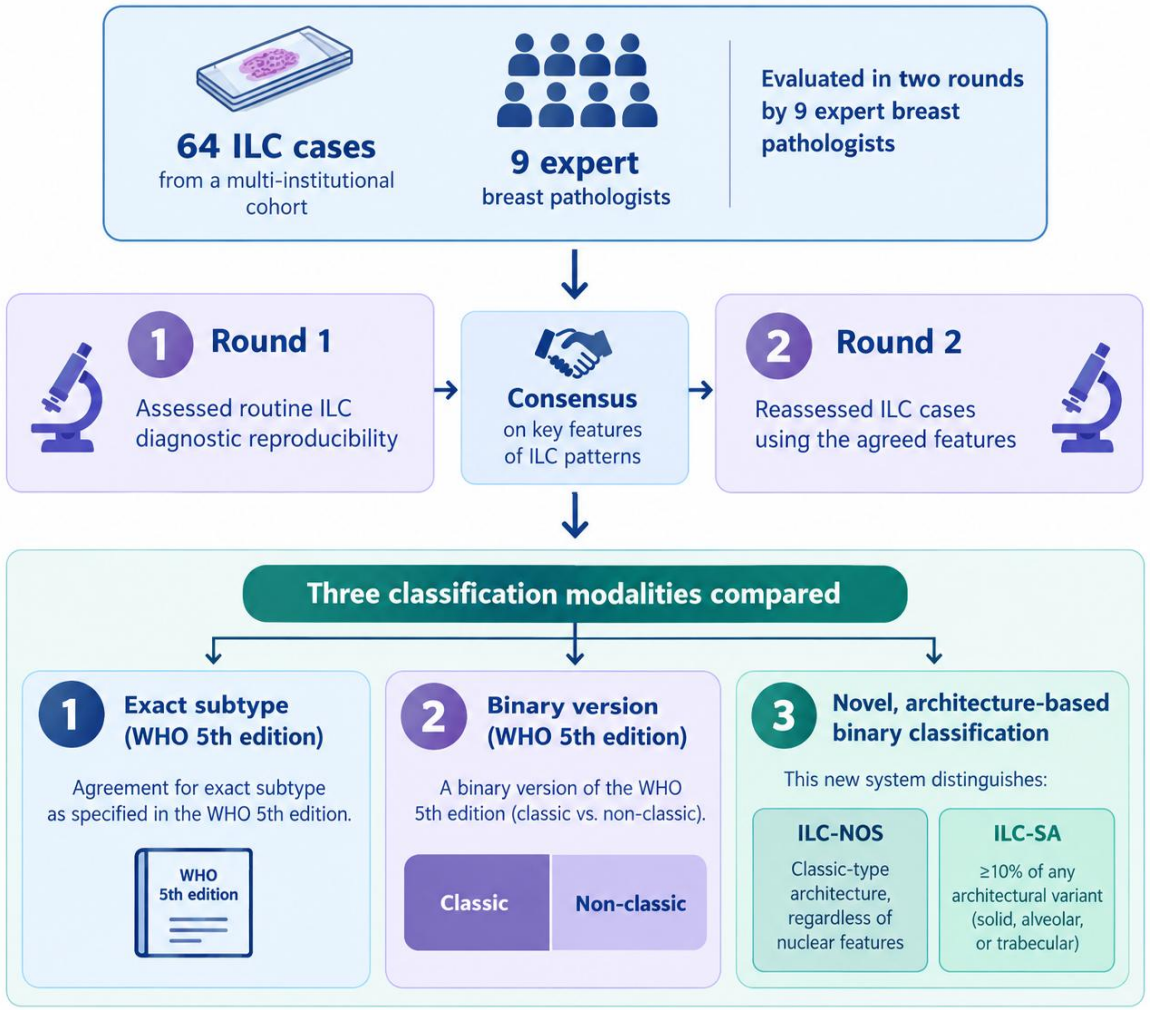
- Highly variable cutoffs and definitions
- ILC subtypes are reported inconsistently



Floris G, Djerroudi L, Zels G, et al. Pitfalls in the Histological Diagnosis of Morphologic Variants of Invasive Lobular Carcinoma of the Breast. Mod Pathol. 2025;38(9):100837.

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Improving Reproducibility of Invasive Lobular Carcinoma Subtypes



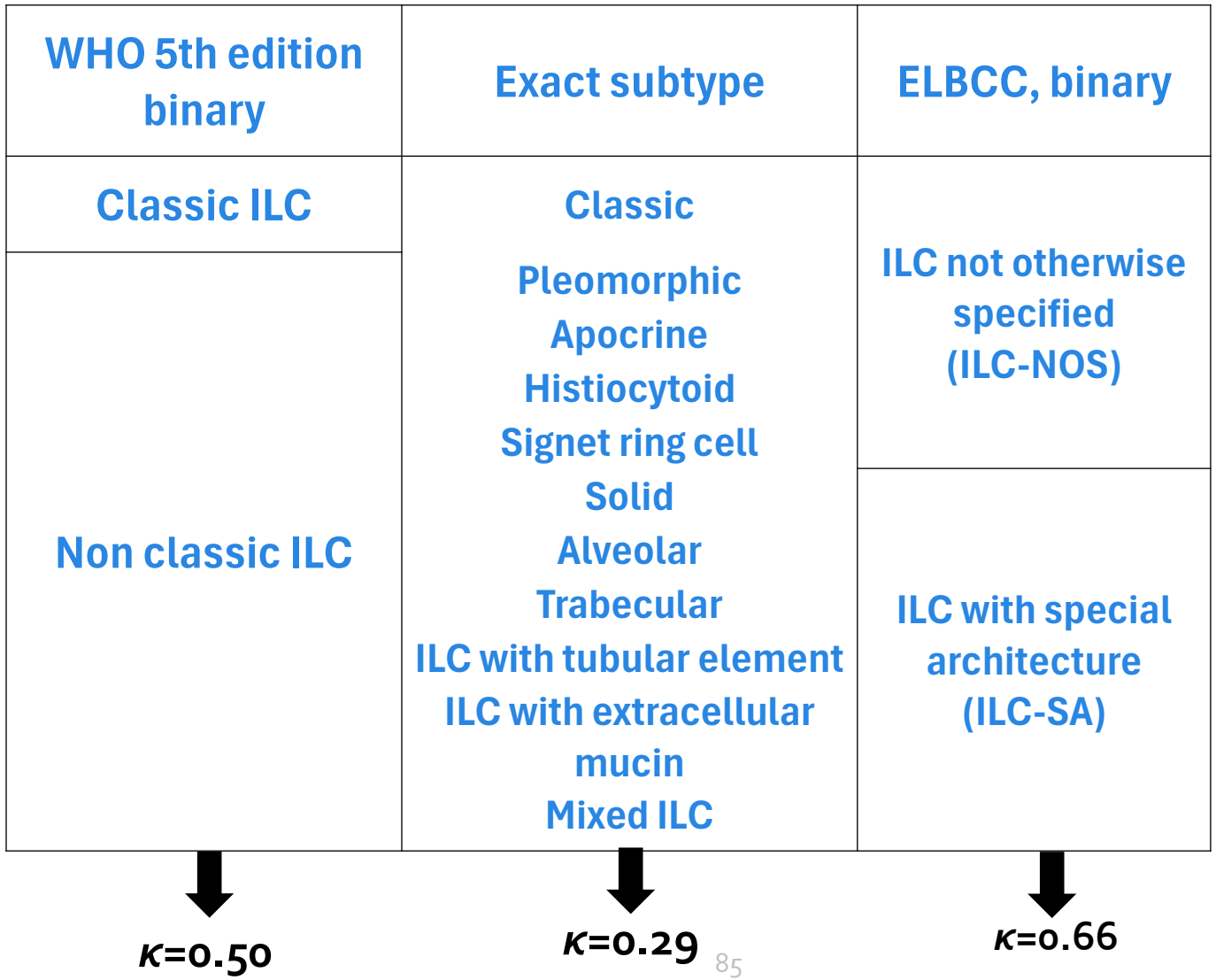
European Lobular Breast Cancer Consortium

Lounes Djerroudi, François Richard, Gitte Zels et al, Improving Reproducibility of Invasive Lobular Carcinoma Subtypes: A Proposal for a New Architecture-Based Classification from the European Lobular Breast Cancer Consortium. Manuscript under review.

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Improving Reproducibility of Invasive Lobular Carcinoma Subtypes



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Invasive lobular carcinoma – Take Home points

- Criteria for Dx of ILC
  - Classic ILC diagnosis rests on morphology
  - Many ILC subtypes, but diagnostic criteria (% cutoffs) not well established
  - WHO 6th recommends grading of ILC according to Nottingham system

- Subclassifying ILC into ILC Not Otherwise Specified (ILC-NST) and ILC of Special Architecture (ILC-SA) may increase interobserver reproducibility

- *Accurate Dx of ILC needed for appropriate patient management and enrollment in clinical trials*

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Thank you for your attention



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