Prepared by Dr. Kurt Schaberg

In Situ Lesions of the Breast

In Situ Lesions

These are a collection of **non-invasive** proliferations, with intact surrounding myoepithelial cells. While these lesions are themselves benign, they are associated with a **variable risk of subsequent breast cancer**. This includes non-obligate and obligate precursor lesions. There is a morphologic continuum of intraductal proliferations, with progressively increasing risk of breast cancer.

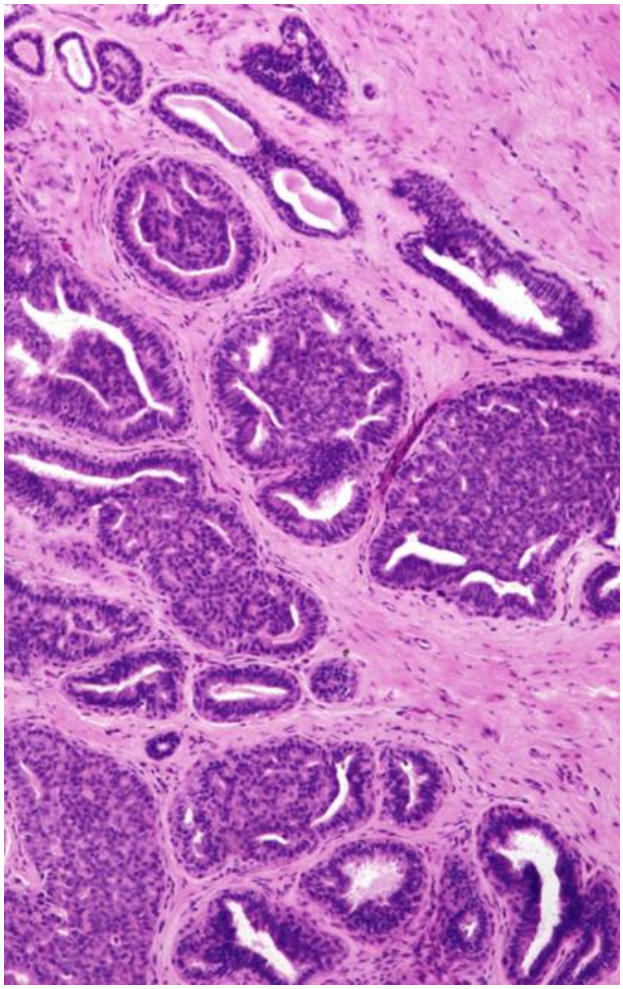
Non-proliferative Fibrocystic change *(no increased risk)*	Proliferative Fibrocystic change *(~2x risk)*	ADH *(~4x risk)*	Low-grade DCIS *(~8x risk)*

Precursor lesions:

ER(+) cancers→ FEA, ADH, Low-grade DCIS are non-obligate precursors

ER(-) cancers→ Microglandular adenosis and High-grade DCIS are non-obligate precursors

Usual Ductal Hyperplasia (UDH)



Benign epithelial proliferation that is architecturally, cytologically, and molecularly heterogeneous.

Think: "*Polyclonal*"

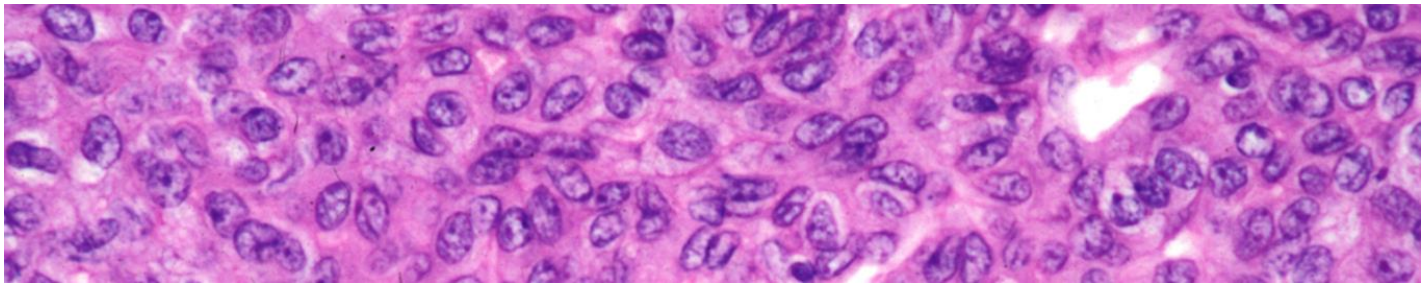
Architectural features:
Cohesive proliferation with **haphazard** architecture
Irregular, slit-like lumina, often peripherally located
No polarization.
Any bridges are thin and stretched
Any micropapillae have broad bases and narrow tips with small pyknotic nuclei.

Cytological patterns:
Heterogeneous population→ lots of variation in size, shape, and orientation.
Poorly-defined cell borders.
Streaming, syncytial pattern.
Overlapping nuclei.
Frequent nuclear grooves, some pseudoinclusions.

Virtual Slide

IHC: Cells stain with a mixture of low-molecular weight cytokeratins (e.g., CK7) and high-molecular with CKs (e.g., CK5/6). Heterogeneous ER staining.

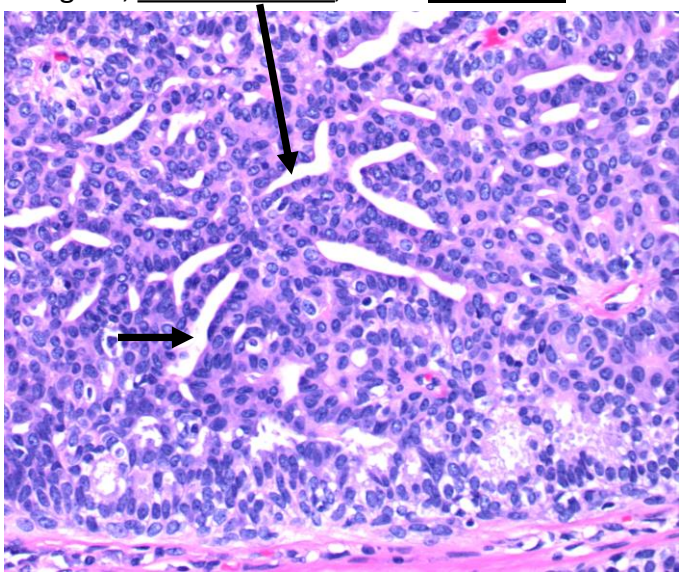
~2x Relative Risk of Developing Cancer → **No treatment**

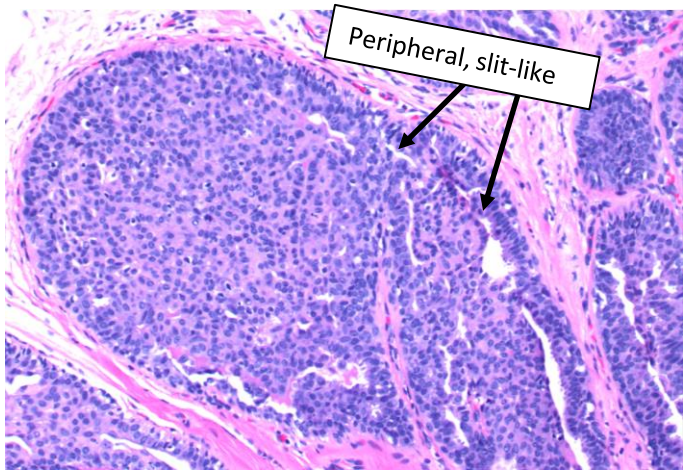


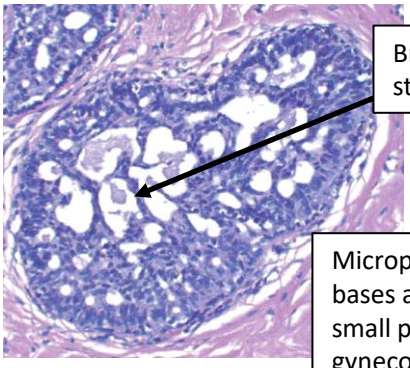
UDH

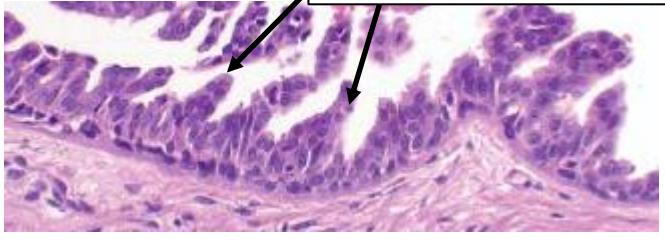
*Think: "**Polyclonal**"*

Irregular, **Slit-like lumina**, often **peripheral**





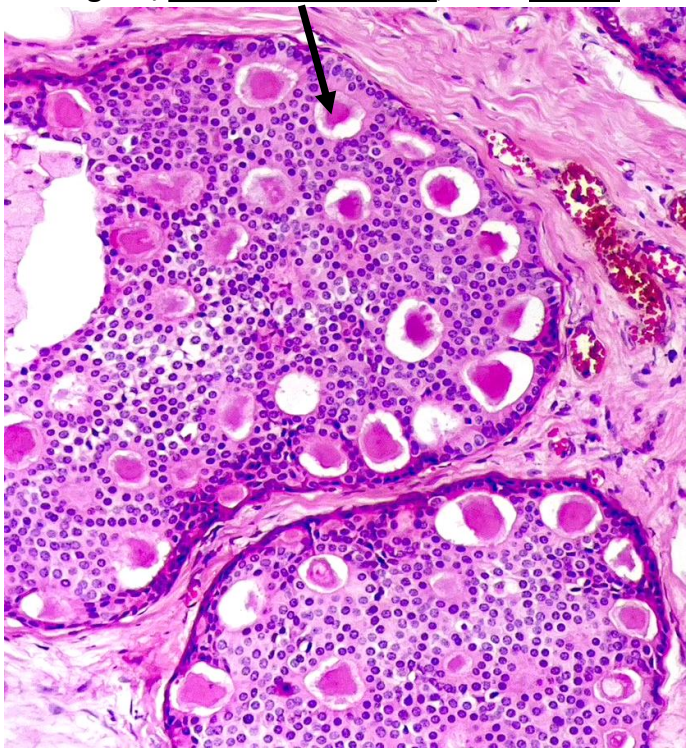


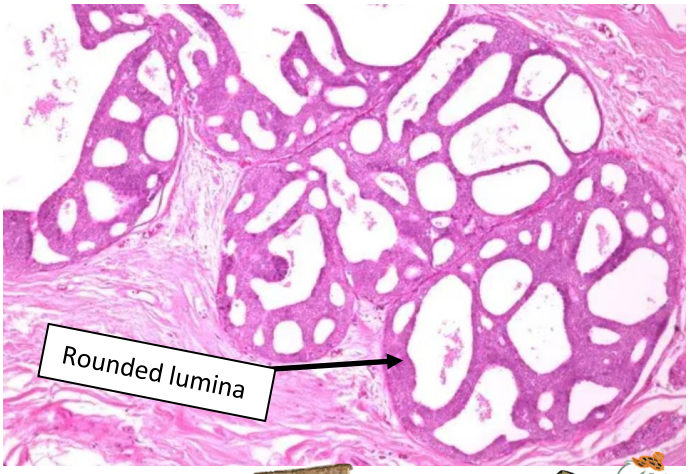


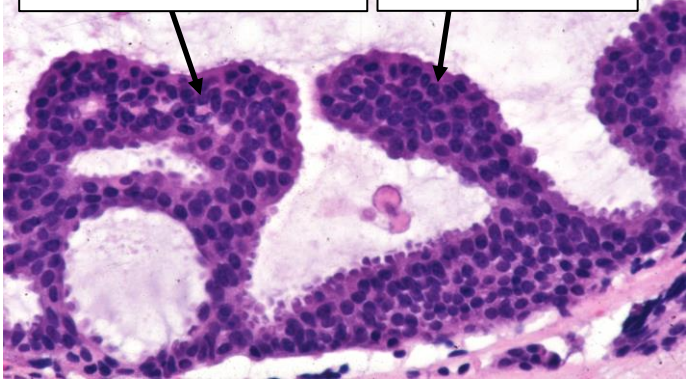
ADH/Low-grade DCIS

*Think: "**Monoclonal**"*

Regular, punched out lumina, often central



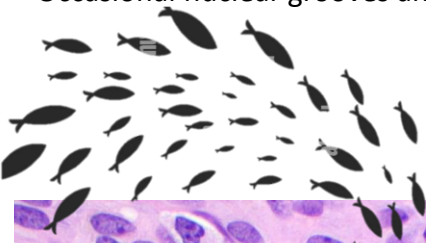


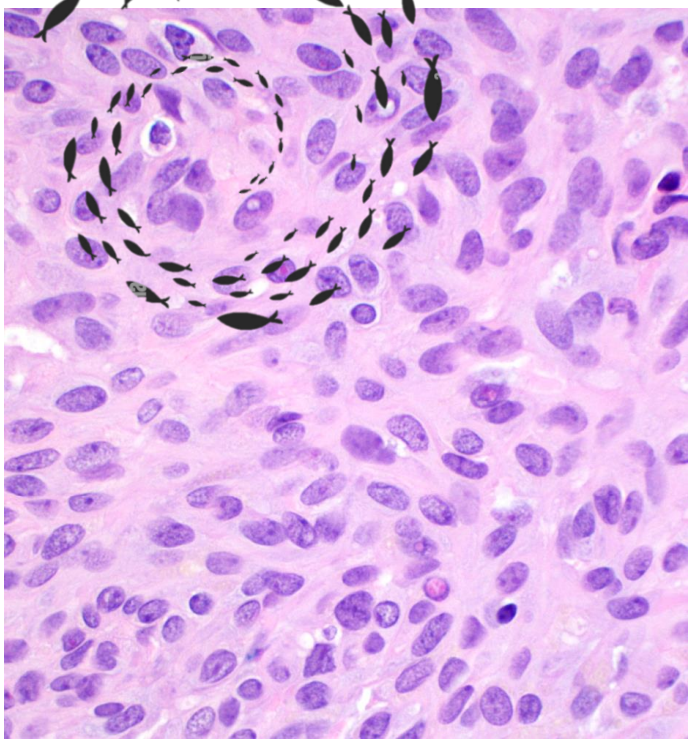


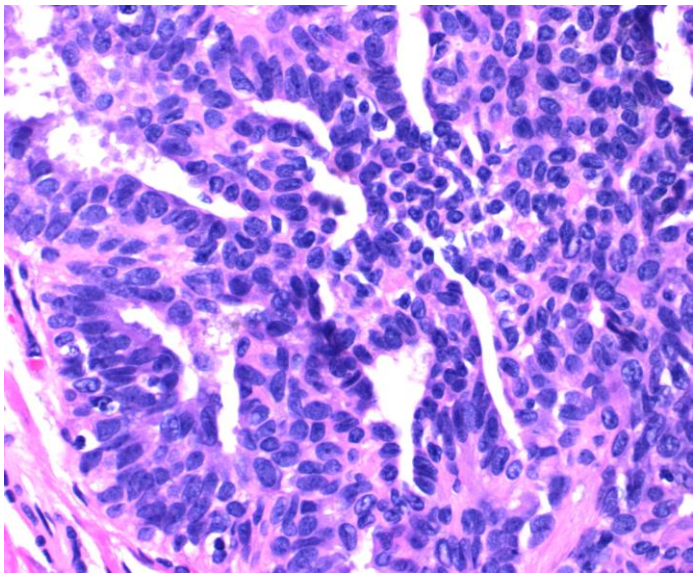
UDH

*Think: "**Polyclonal**"*

Variation in cell size/shape
Streaming architecture, minimal polarization
Indistinct cell margins
Occasional nuclear grooves and inclusions.



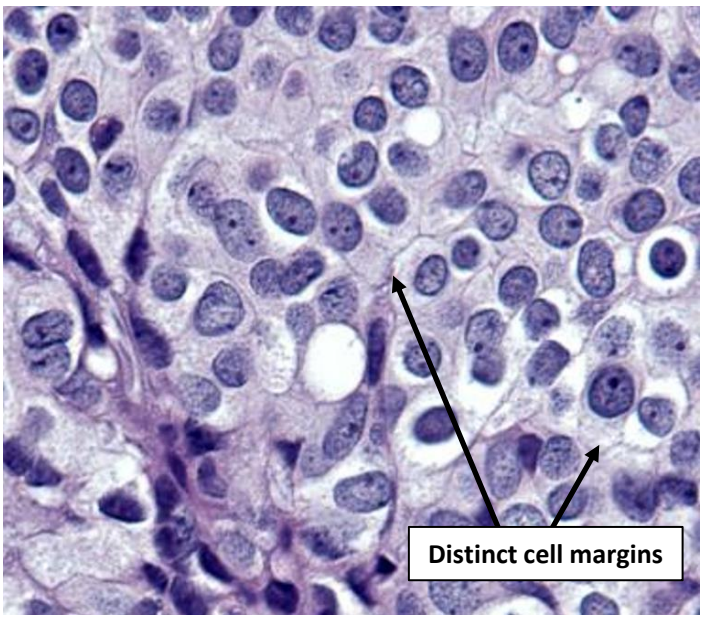


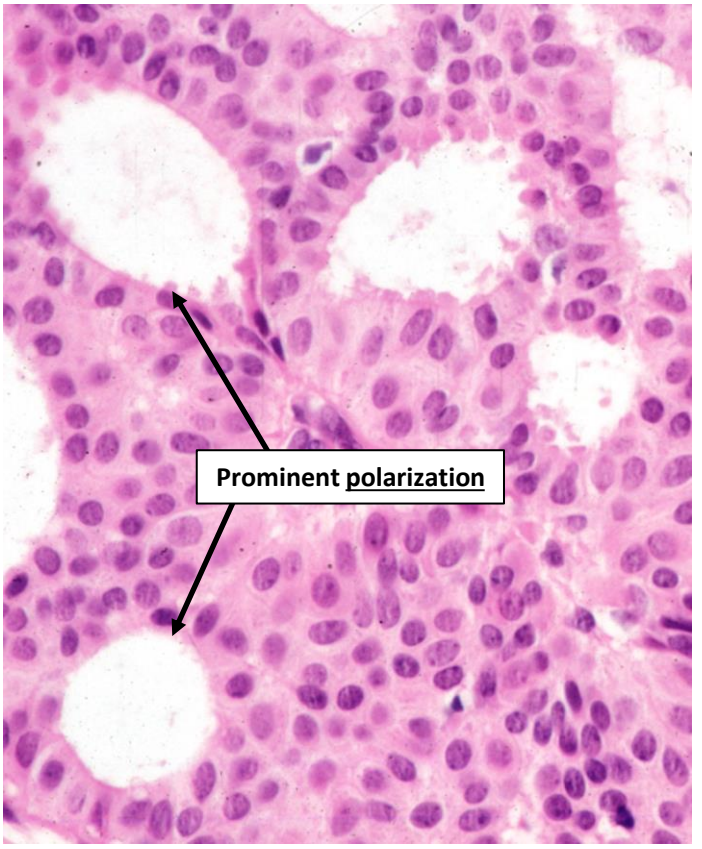


ADH/low-grade DCIS

*Think: "**Monoclonal**"*

Monomorphic cells/shape

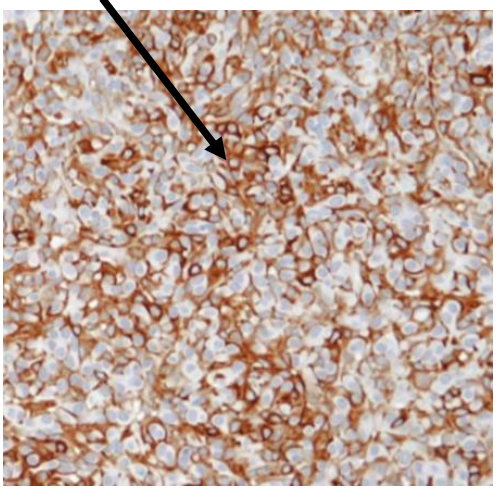




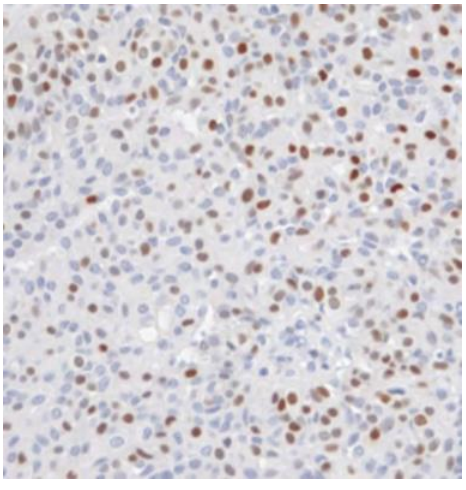
UDH

*Think: "**Polyclonal**"*

CK5/6: Admixture of cell types (epithelial, myoepithelial and/or apocrine)→ *heterogenous* staining with CK5/6 throughout the proliferation



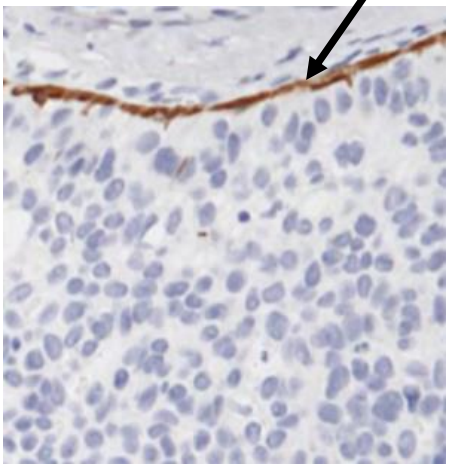
ER: Admixture of cells → *Heterogeneous* ER staining



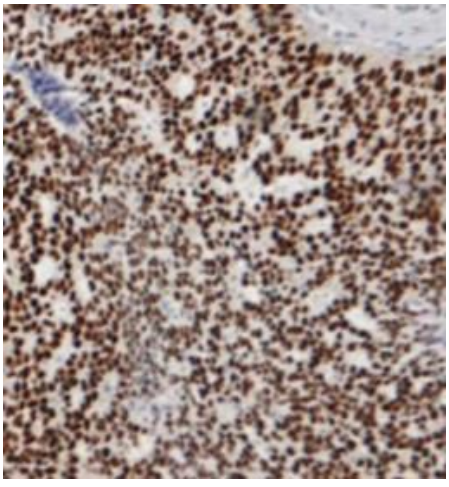
ADH/Low-grade DCIS

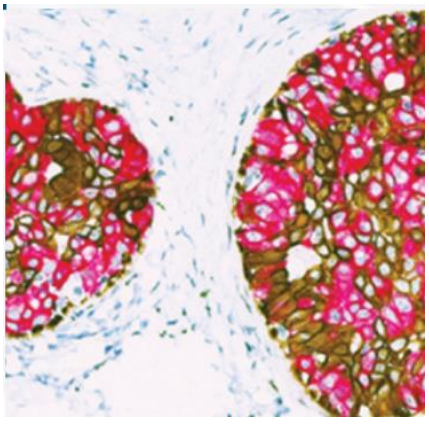
*Think: "**Monoclonal**"*

CK5/6: Proliferating cells are epithelial. Myoepithelial cells are against the basement membrane → CK5/6 highlights *myoepithelial* cells only



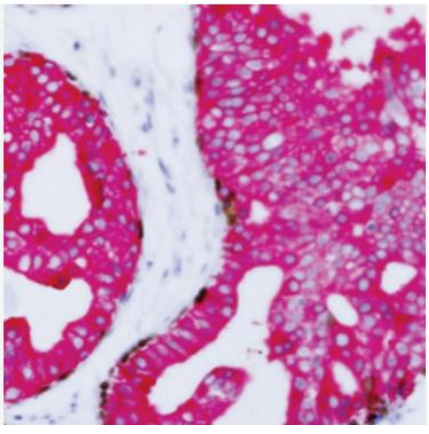
ER: Proliferating cells over-express ER → *Strong, diffuse ER staining*





Multiplex IHC can combine several antibodies to show similar findings.

This is an "ADH5" cocktail that combines HMWCK (including CK5) and p63 (brown) and a LMWCK (including CK7) (pink)



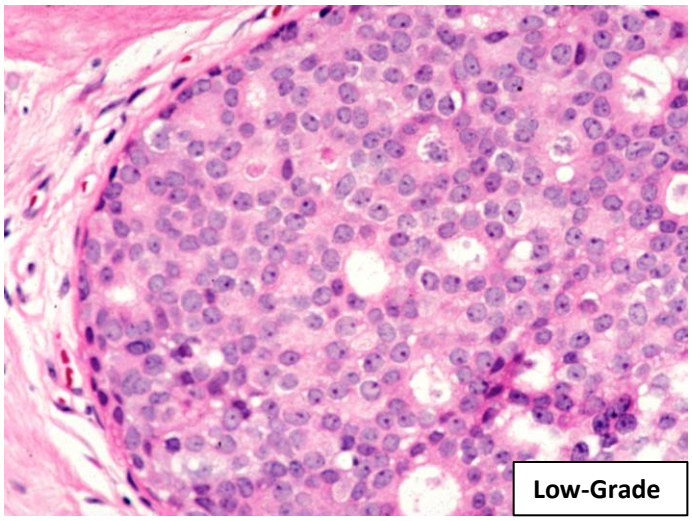
Ductal Carcinoma In Situ (DCIS)

Non-invasive neoplastic epithelial proliferation.
Non-obligate precursor to invasive carcinoma.

Often detected on mammography (e.g., linear calcifications)

Often unifocal, limited to one duct system, but can involve lobules ("Cancerization of the lobule") and/or can "skip" around in duct

Graded based on nuclear morphology, but can be varying grades within one case due to tumor heterogeneity (Grade NOT architecture based)

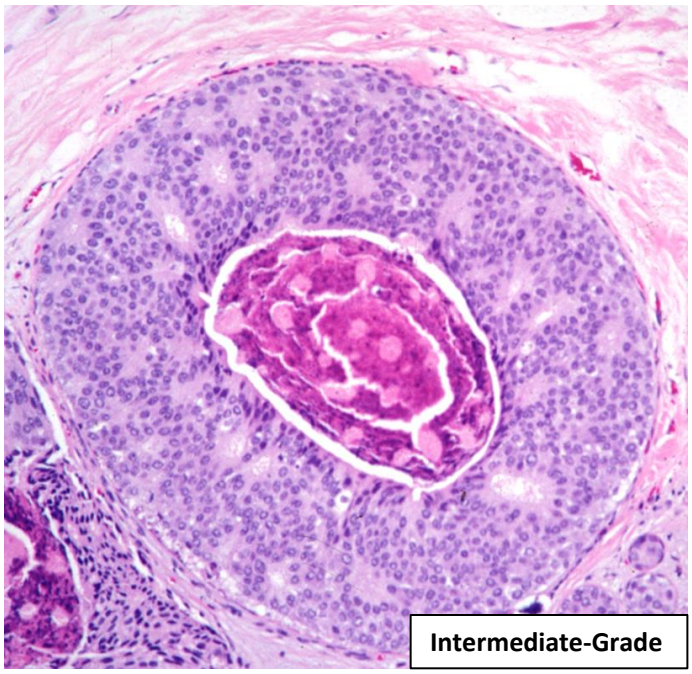


Low-grade DCIS

Think: "Monoclonal"
Small, monomorphic cells
- Uniform size and shape
- Regular chromatin; small nucleoli
- 1.5-2x size of RBC
- Rare mitoses

Often cribriform or micropapillary growth
- Often forms microrosettes/glands with **polarization** around the gland
- Sometimes solid growth

Calcifications common. Necrosis uncommon.
Size requirement: >2mm and involving more than two complete spaces

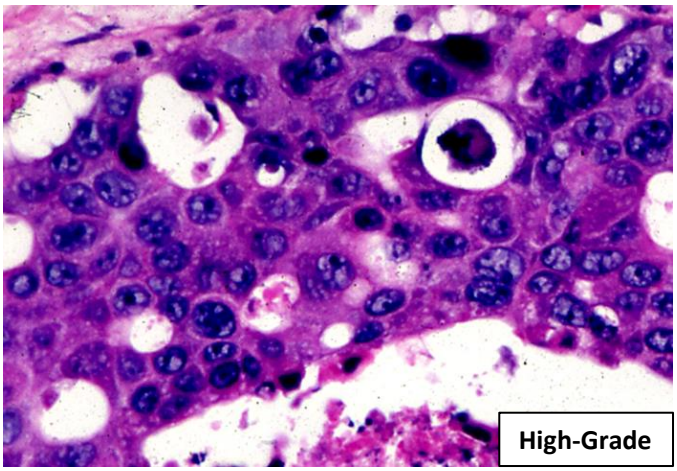


High-grade DCIS:

Think: "Pleomorphic, Ugly"
Large, ugly cells
- Irregular contours, course chromatin
- Often prominent nucleoli
- >2.5-3x the size of an RBC
- Lots of mitoses

Often solid architecture
- Minimal/no polarization
- Comedo necrosis common
- Sometimes single layer of cells ("Clinging carcinoma"). Uncommonly cribriform or micropapillary

Size requirement: None!!



Intermediate-grade DCIS:

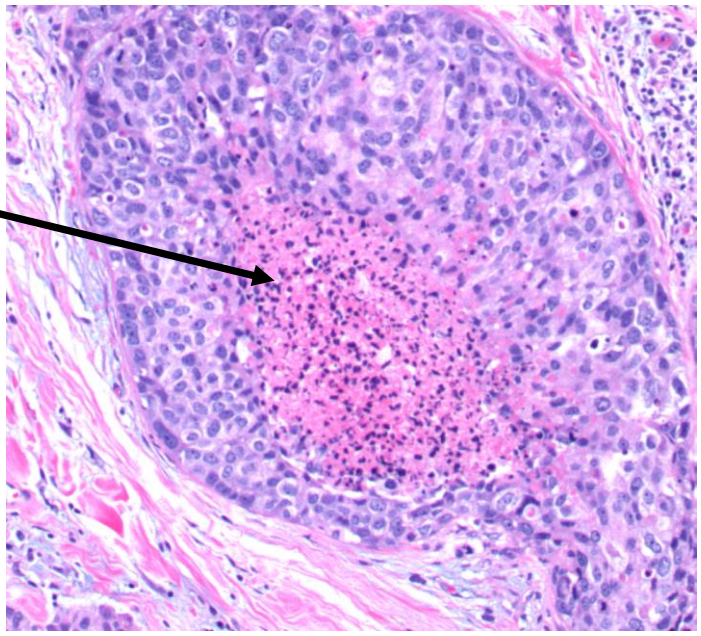
In between low and high-grade
Moderate variability, size, polarization
May have necrosis and/or calcifications

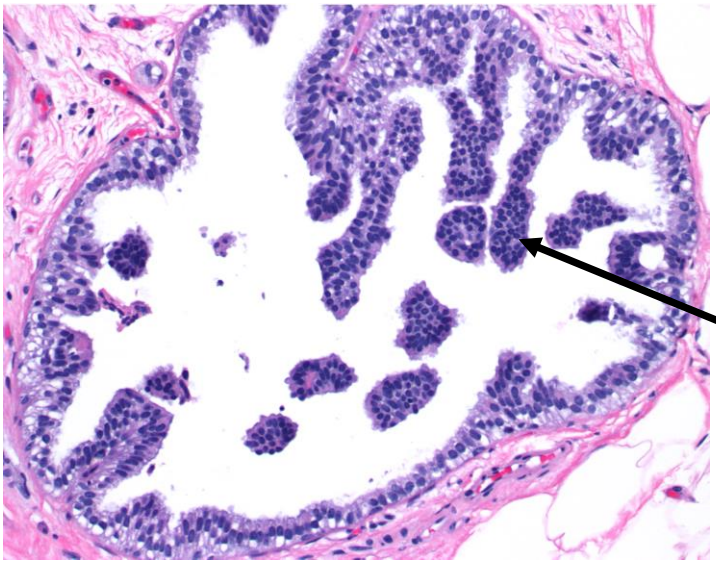
~10x Relative Risk of Cancer in ipsilateral breast

Treatment: **Excision with 2 mm tumor-free margins**
Possibly +/- radiation and/or hormone therapy

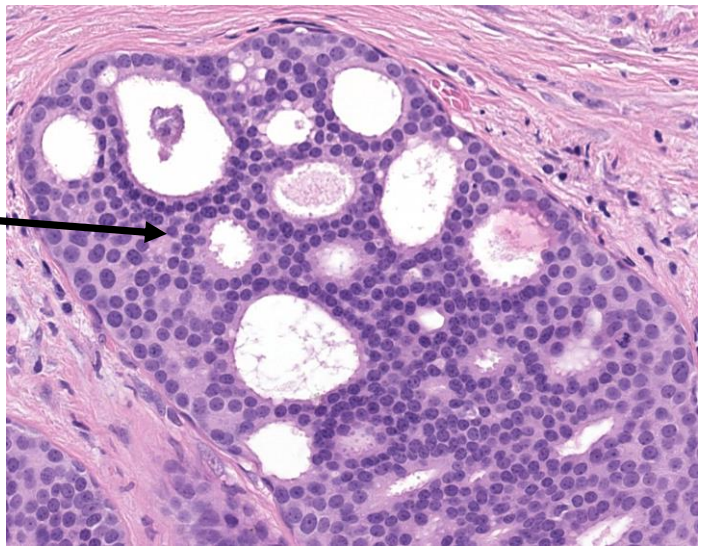
More DCIS examples:

Intermediate-grade DCIS with comedonecrosis
Comedonecrosis: granular eosinophilic material within the duct lumen with associated karyorrhectic/nuclear debris.
This case has solid architecture.

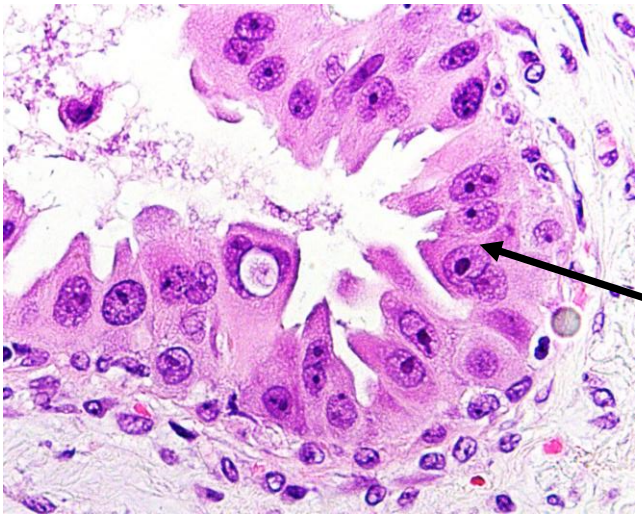




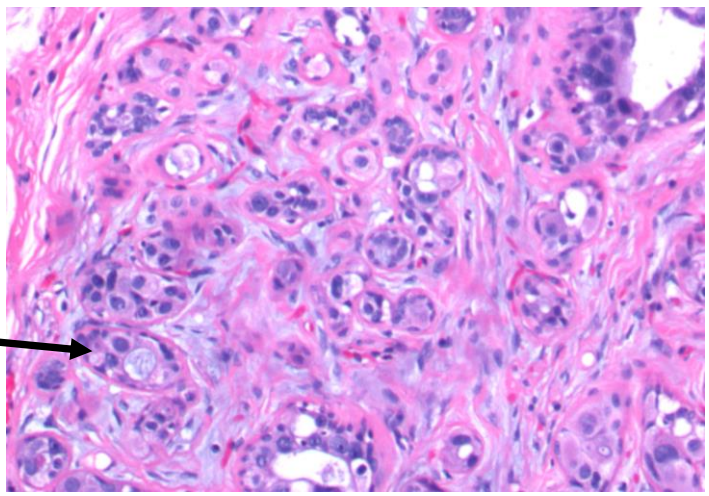
Low-grade DCIS with micropapillary architecture
Papillary projections without fibrovascular cores



Low-grade DCIS with cribriform architecture



High-grade apocrine DCIS



"Cancerization of the lobule"
Pagetoid spread of DCIS into lobules of TDLU

Virtual Slide 2 3 4

Low-grade DCIS	High-grade DCIS
Small, monomorphic cells 1.5-2x size of RBC Regular nuclear contours Even chromatin Inconspicuous nucleoli	**Large, pleomorphic cells** >2.5x size of RBC Irregular nuclear contours Course chromatin Prominent nucleoli
Usually cribriform or micropapillary growth	Usually solid growth, but any architecture can be present
Polarization around lumina	No polarization around lumina
Necrosis uncommon	Necrosis common
Must be >2mm	No size requirement
ER and PR positive frequently	ER and PR negative more frequently
HER2 negative frequently	HER2 positive frequently
Few mitoses	Many mitoses
Low-grade associated cancers	High-grade associated cancers

Atypical Ductal Hyperplasia (ADH)

Non-invasive neoplastic epithelial proliferation resembling low-grade DCIS (similar cytology and architecture), **BUT** less developed in architecture or extent

Similar genetically to low-grade DCIS→ clonally related, just smaller or questionable architecture

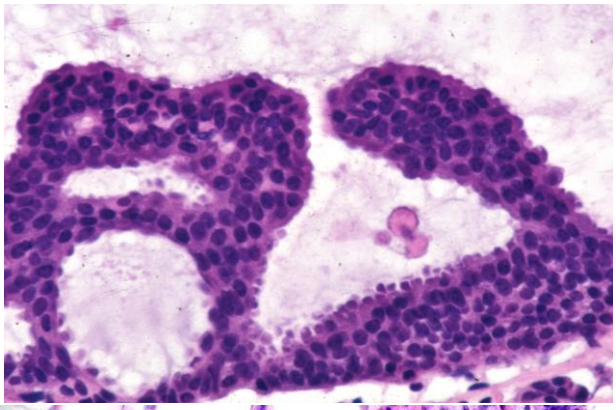
Size: partial involvement of multiple spaces; or uniformly involved duct spaces but measuring ≤ 2 mm in contiguous extent (≤ 3 mm in a papilloma).

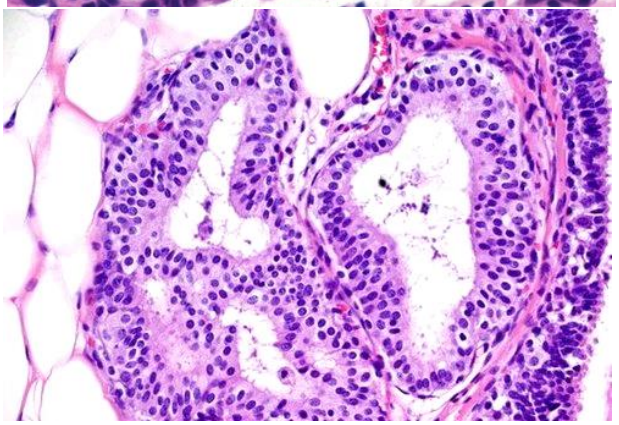
Cells (same as low-grade DCIS):
- Evenly spaced monotonous cells
- Round nuclei with dense chromatin
- Distinct cell borders

Architectural features:
- **Cribriform**
- **Rigid bridges**, arcades, and bars of uniform thickness
- **Bulbous micropapillae** (with narrow bases and wide tips)

IHC: Uniform ER positivity; CK5/6 (-)

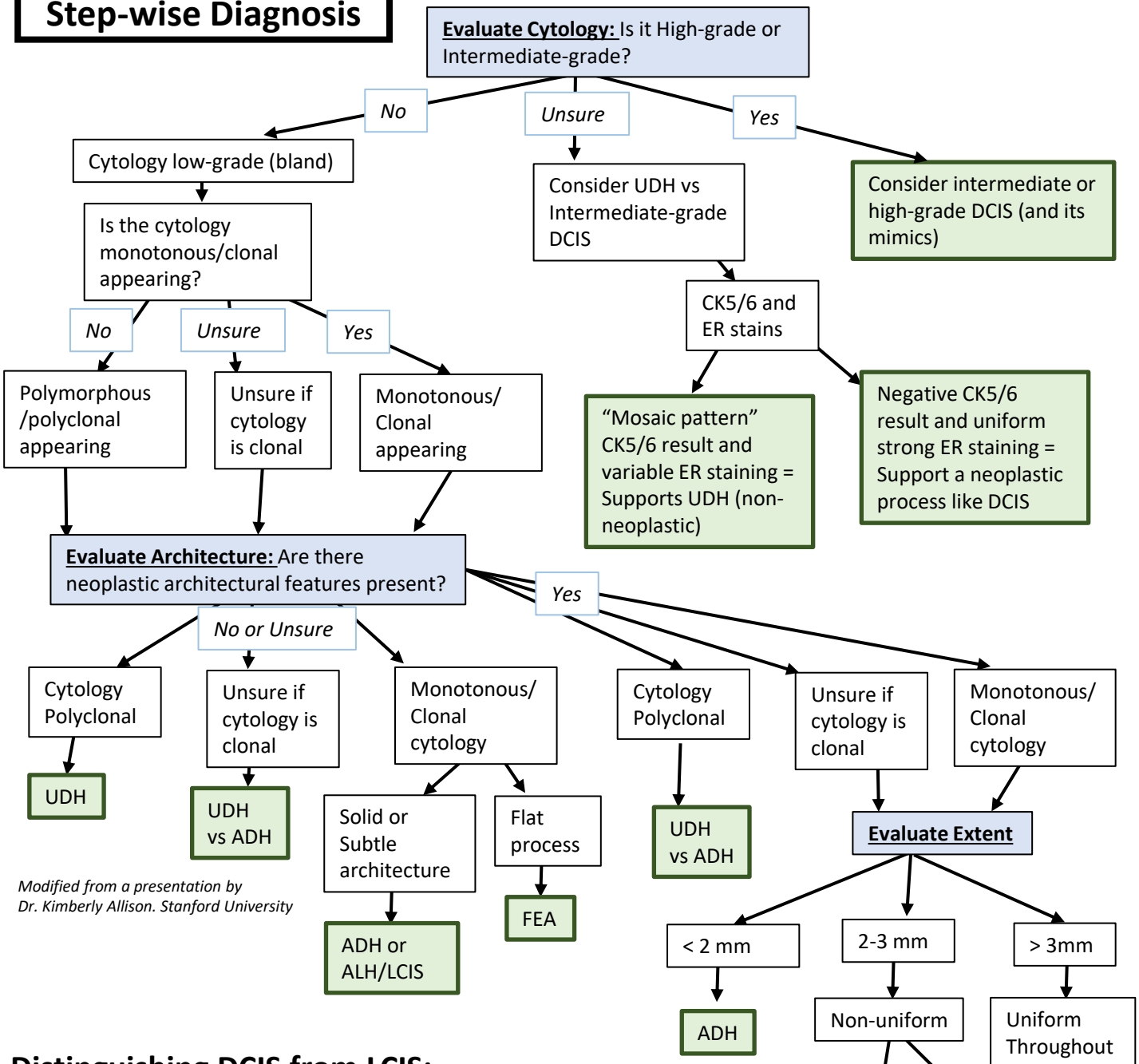
Virtual Slide





~4-5x relative risk of breast cancer
Treatment: if on Bx→ surgical excision to exclude DCIS/carcinoma;
On excision→ Nothing more

Step-wise Diagnosis



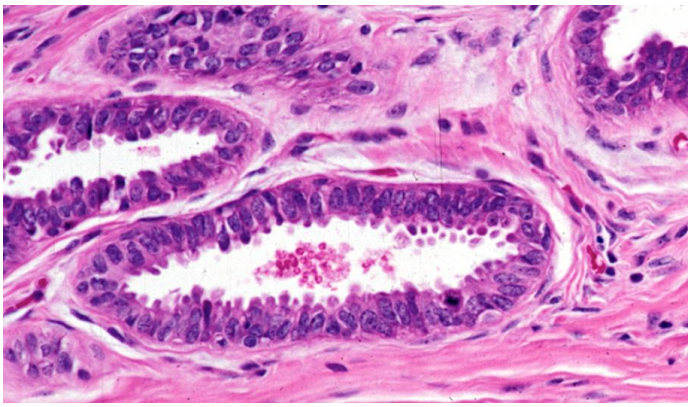
Modified from a presentation by Dr. Kimberly Allison. Stanford University

Distinguishing DCIS from LCIS:

Feature	LCIS	DCIS
Loss of cohesion	Present	Absent
Intracytoplasmic vacuoles	More common	Less common
Pagetoid ductal involvement	More common	Less common
Microacini	Absent	Present
Polarization at duct periphery	Absent	Present

Pro Tip: Consider LCIS whenever you're evaluating a solid intraductal lesion, like Solid-pattern DCIS. When you consider that DCIS is excised to negative margins, while LCIS isn't, this this distinction can make a big change in management. *Have a low threshold for getting an E-cadherin!*

Columnar Cell Change



Clonal alterations of the TDLU characterized by enlarged, variably dilated acini lined by **columnar epithelial cells arranged perpendicular to the basement membrane**; 1-2 cells thick
No Atypia.

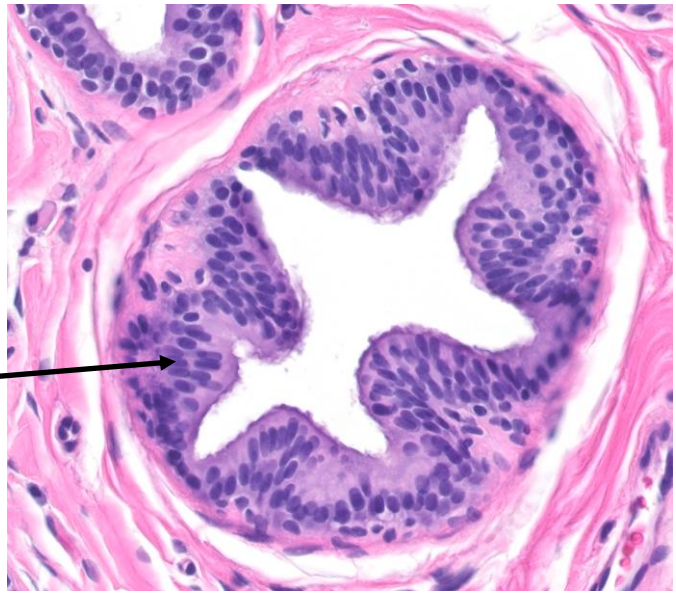
Apical snouts, secretions and calcification are often present

IHC: Usually Diffuse ER+;
Peripheral CK5/6 (myoepithelial cells)

Earliest step in low-grade carcinoma pathway → non-obligate precursor to ADH → DCIS → cancer

~1.5x Relative Risk of Developing Cancer
Treatment: None needed

Virtual Slide



Columnar cell *hyperplasia*

Columnar cell change with cellular stratification or tufting > 2 cell-layers thick

More complex architecture? → **ADH**
Cytologic atypia? → **FEA**

Criterion	Columnar cell change	Columnar cell hyperplasia	FEA	ADH
Internal contour	Irregular	Irregular	Smooth	Variable
Cell morphology	Columnar	Columnar	Columnar/cuboidal	Columnar/cuboidal
Epithelial cell layers	≥ 1	> 2	≥ 1	Variable
Nuclear atypia	Absent	Absent	Present (monomorphic)	Present (monomorphic)
N:C ratio	Normal	Normal	Increased	Increased
Architecture	Flat	Hyperplastic	Flat; an occasional focal tuft or mound Not complex	Complex

Modified from: WHO Classification of tumors of the Breast 6th edition (beta) online.

Flat Epithelial Atypia (FEA)

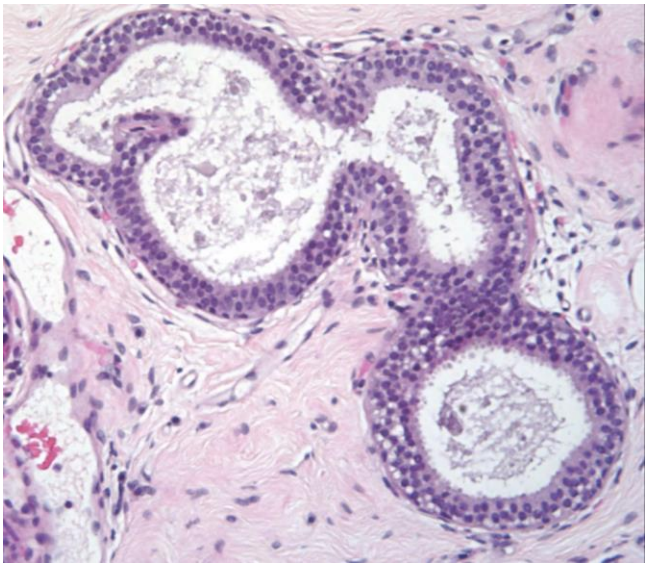
Flat proliferation of one or more layers of epithelial cells with low-grade (monomorphic) cytological atypia and no intraluminal architecture.
(same cells as in ADH/low grade DCIS!)

Similar to columnar cell change (in dilated TDLUs). Includes Columnar cell lesions with atypia. Complex architecture of the type seen in ADH/low grade DCIS is not allowed.

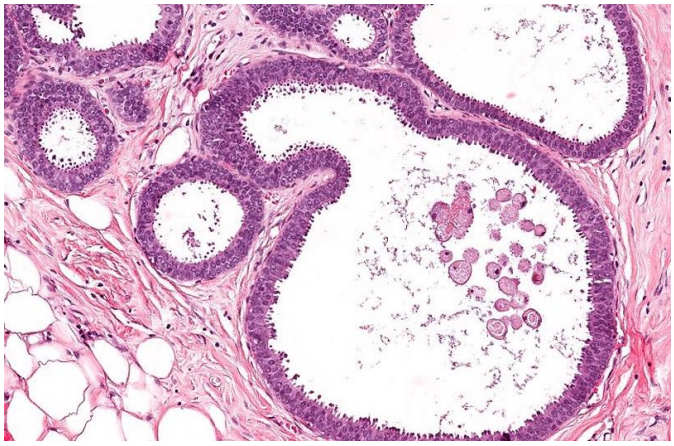
Apical snouts, secretions and calcification may be present.

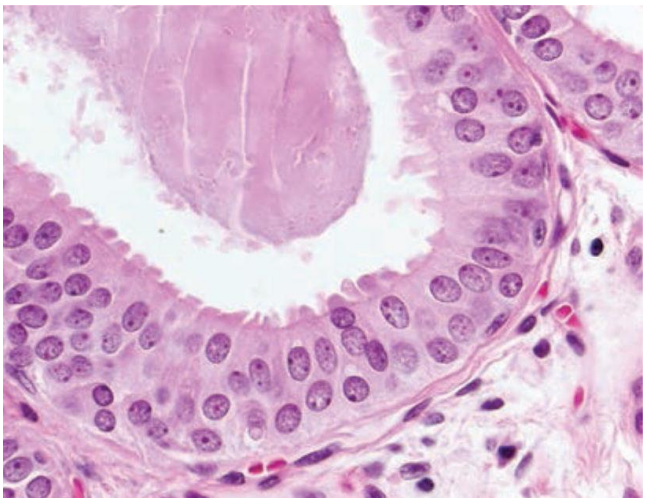
IHC: Usually Diffuse ER+; Negative for CK5/6

Treatment: Current recommendation is just imaging follow up (Not long ago, they'd excise if found on Bx).



Virtual Slide 2





Radial Scar / Complex Sclerosing Lesion

Benign lesion with **fibroelastosis with entrapped glandular structures**, ± Proliferative epithelial lesions (e.g., UDH)

Radial scar→ smaller with stellate configuration

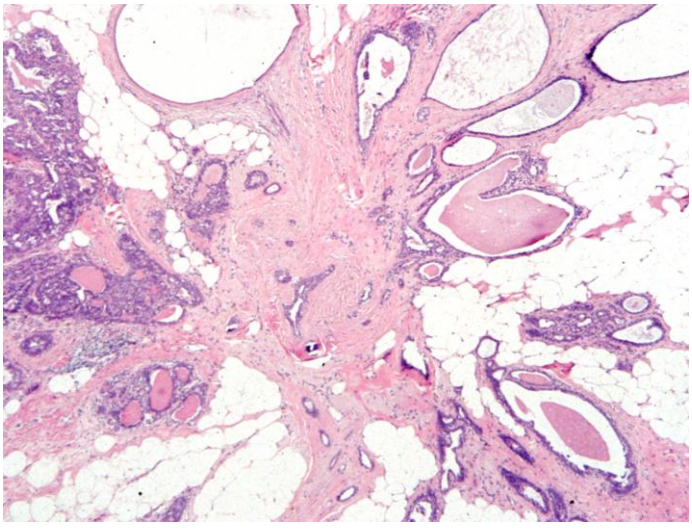
Complex sclerosing lesion→ larger (often > 10 mm) and more disorganized

Dense, hyalinized, elastotic stroma.
Maintained lobulocentric architecture

Two cell layers maintained throughout

Currently not recommended to be excised unless there is atypia, but this is a little controversial.

Virtual Slide

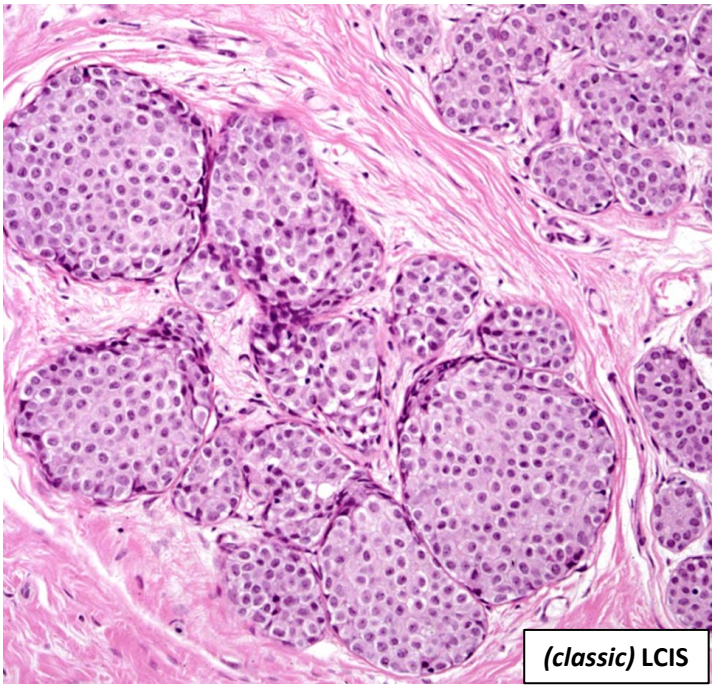


Often may want to do myoepithelial stains to confirm no invasive component given complexity

Lobular Neoplasia In Situ

Epithelial proliferations **originating in the TDLU** characterized by:

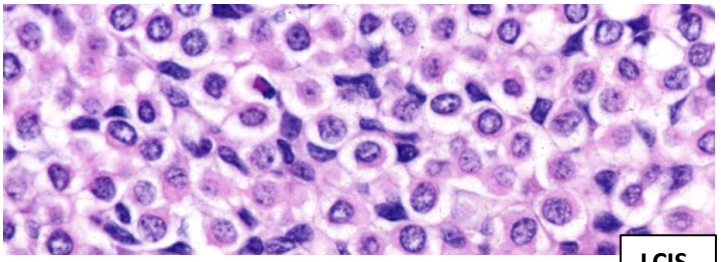
- **Small, discohesive monomorphic cells**
- Uniform hyperchromatic nuclei (type A) to slightly larger vesicular nuclei with mild variability (type B)
- Proliferate in/throughout TDLU → rounded, lobular architecture. Frequent pagetoid spread along ducts
- **E-cadherin inactivation** → Loss of membranous E-cadherin staining → cellular discohesion
    - *Note: Up to 15% of lobular lesions retain E-cad, but with an aberrant staining pattern*
- CDH1 mutations common (same gene as hereditary diffuse gastric cancer)



Atypical Lobular Hyperplasia (ALH)

Solid proliferation of discohesive, monomorphic epithelial cells expanding <50% of the acini in a TDLU

No need to excise if present on Bx. Virtual Slide



Lobular Carcinoma In Situ (LCIS) *("classic")*

>50% of the acini in a TDLU are filled and expanded

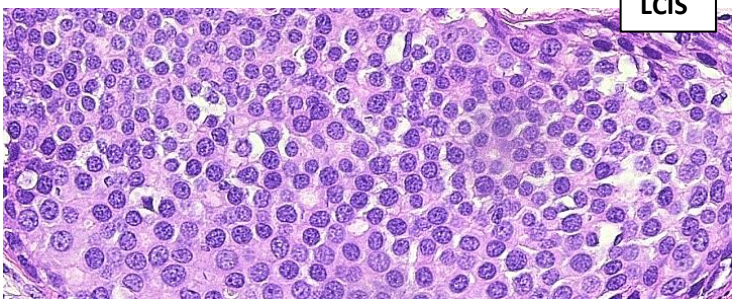
Often >8 cells thick

Non-obligate precursor to invasive lobular carcinoma Virtual Slide

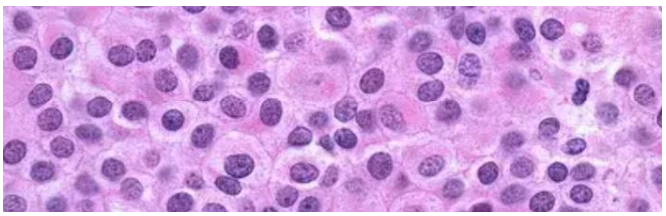
~8-10x Relative Risk of Cancer

If incidental on a biopsy, no need to excise

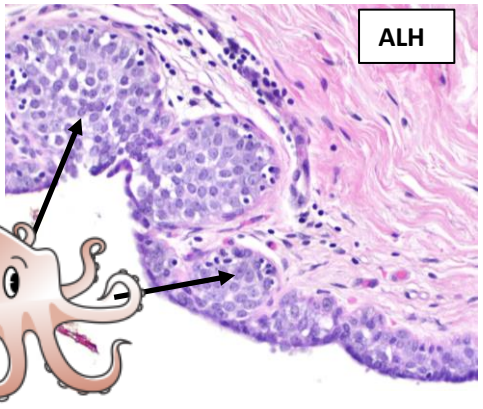
On excision, margins do not matter



Classic ALH and LCIS are collectively considered *"Lobular neoplasia"*



I think of ALH as sort of looking like an octopus with tentacles down various ducts and TDLUs



Pro Tip: Consider LCIS whenever you're evaluating a solid intraductal lesion, like Solid-pattern DCIS. When you consider that DCIS is excised to negative margins, while LCIS isn't, this this distinction can make a big change in management.

Have a low threshold for getting an E-cadherin!

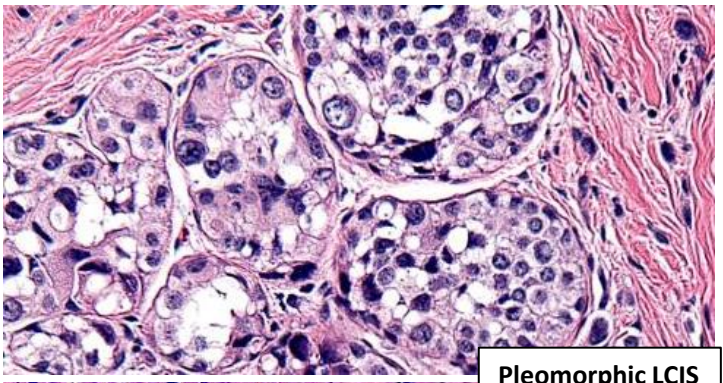
LCIS Subtypes:

Pleomorphic LCIS— large dyscohesive cells with pleomorphic nuclei > 4 times the size of a lymphocyte (equivalent to the nuclei of high-grade DCIS), with or without apocrine features.

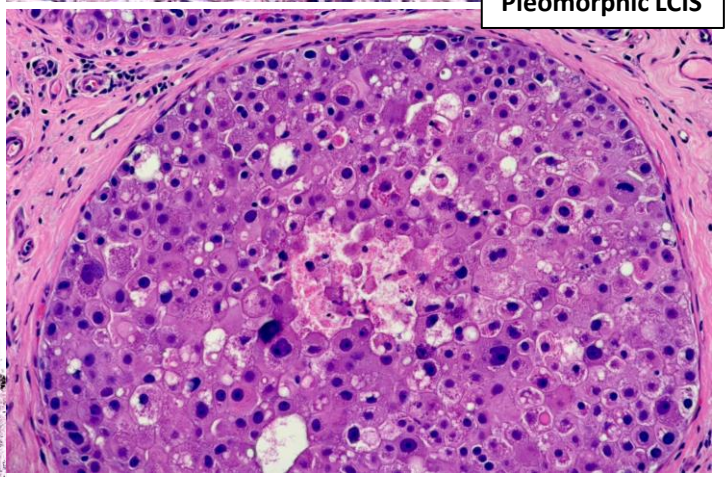
Florid LCIS—classic LCIS cells, but forming a confluent mass-like lesion with little to no intervening stroma between distended TDLUs (often ~50 cells in diameter)

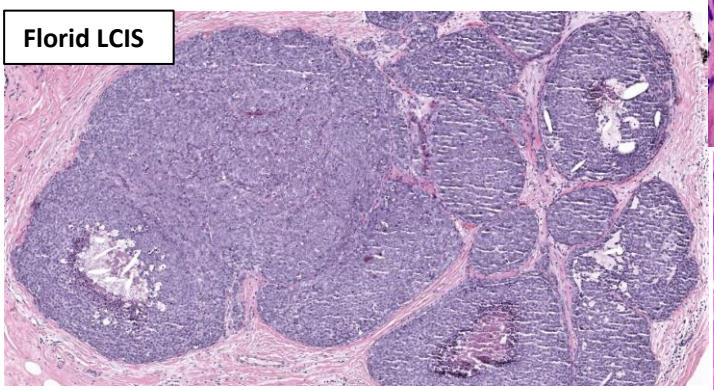
Pleomorphic LCIS and florid LCIS often demonstrate comedonecrosis and calcifications

Both of these subtypes exhibit greater genomic instability→ behave more aggressively→ **excise with negative margins**

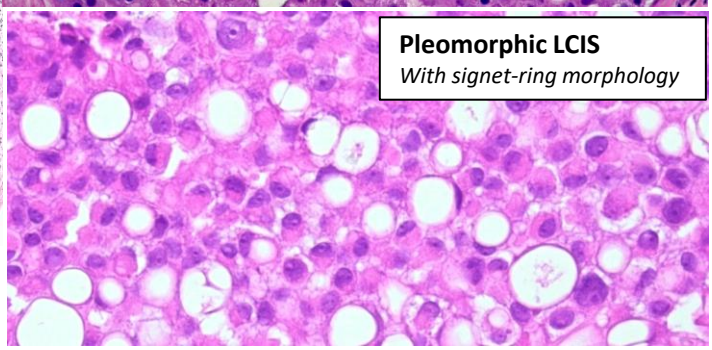


Pleomorphic LCIS





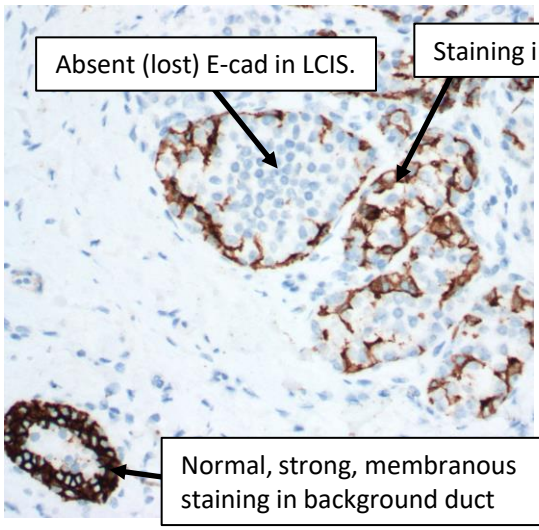
Florid LCIS



Pleomorphic LCIS
With signet-ring morphology

Immunohistochemistry of Lobular lesions:

Loss of membranous E-cadherin (*"E-cad"*) expression is the characteristic immunohistochemical feature for all types of LCIS. However, 15% of lobular lesions, the neoplastic cells have conserved but aberrant E-cadherin expression. Look for any abnormalities, such as fragmented, diminished, and/or cytoplasmic aberrant staining. When in doubt, consider getting a panel with p120 and/or β-catenin.



IHC Stain	Normal Epithelium	Lobular Neoplasia	DCIS
E-Cadherin	Membrane staining	Negative	Membrane staining
P120 catenin	Membrane staining	Cytoplasmic	Membrane staining
β-catenin	Membrane staining	Absence of membrane staining	Membrane staining

Sclerosing Adenosis

Non-neoplastic. Very common. Often incidental.

Lobulocentric proliferation of benign glandular structures distorted by sclerosis, arising from the TDLU.

Lobular (rounded, well-circumscribed) architecture;

Proliferation of **small, compressed glands** distorted by stromal collagen;
Epithelial cells are often cuboidal, small, and bland

Basement membrane and **retained myoepithelial cell layer** around glandular or acinar structures.

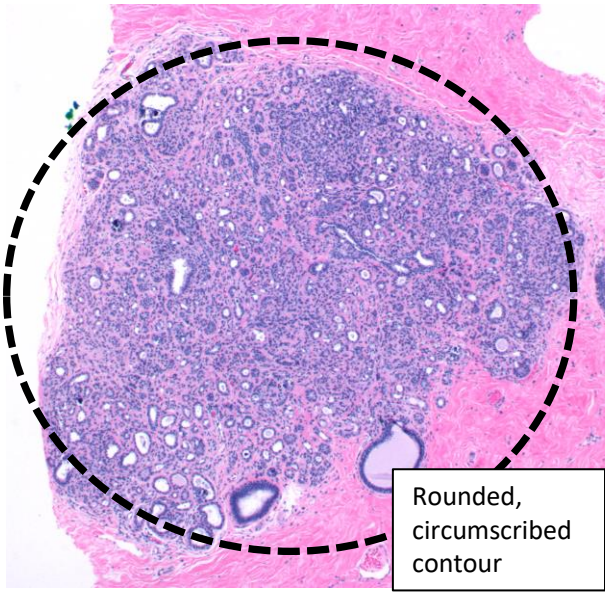
Myoepithelial cells have spindled, hyperchromatic nuclei and inconspicuous to prominent clear cytoplasm
Can highlight myoep's with IHC stains if necessary

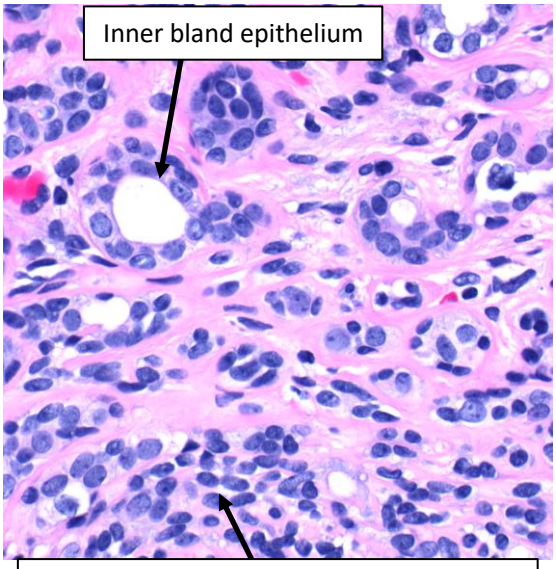
Microcalcifications are common
Can extend into fat occasionally

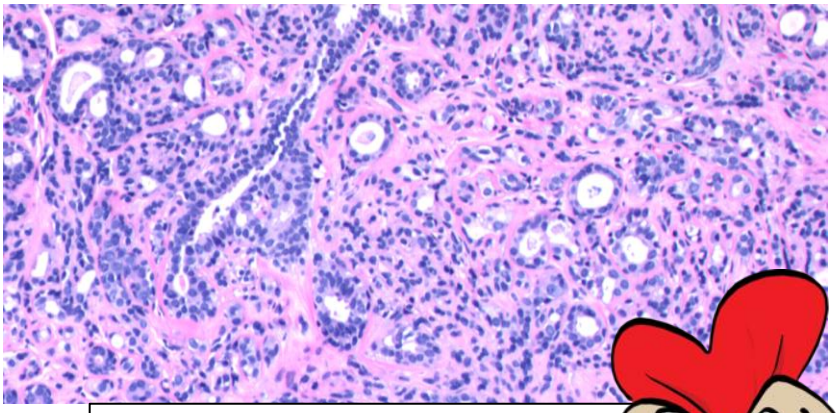
Can be involved by epithelial proliferations (e.g., UDH)

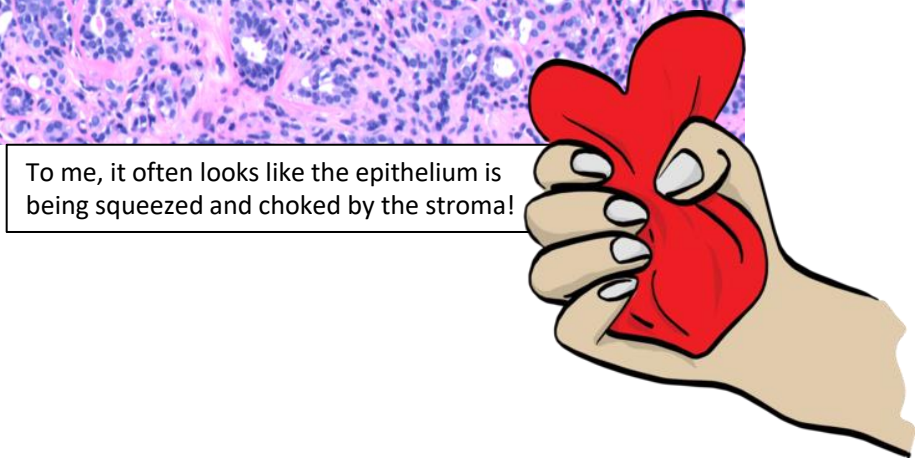
Most common benign breast lesion *confused* with carcinoma

Virtual Slide 2









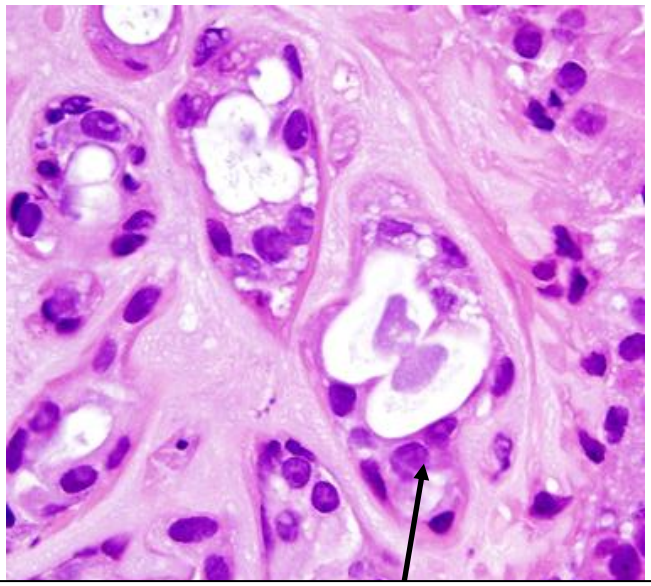
Apocrine Adenosis

= Apocrine metaplasia + Sclerosing adenosis

Lobulocentric proliferation of benign glandular structures composed of cells with abundant granular cytoplasm distorted by fibrosis

Abundant eosinophilic, granular, or foamy cytoplasm.
Enlarged, round nuclei with prominent nucleoli.
Should have even chromatin and <3x variation in nuclear size.
Often have apical "snouts"
Intact myoepithelial cells→ can highlight with IHC

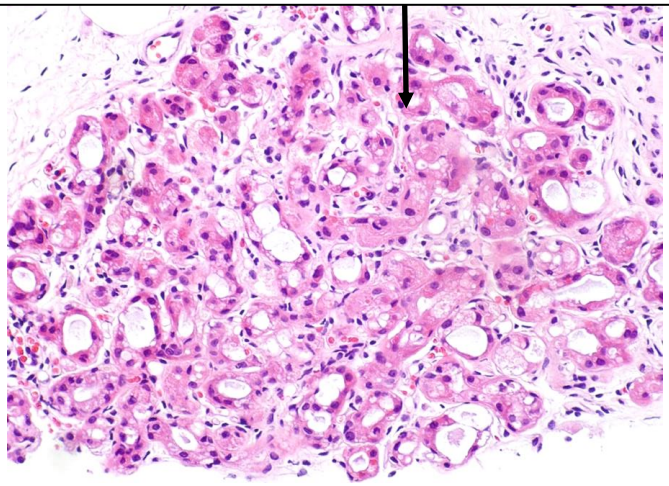
Cells typically **ER-negative, AR-positive**, and positive for GCDFP-15.



Apocrine Adenosis = Apocrine metaplasia + Sclerosing adenosis

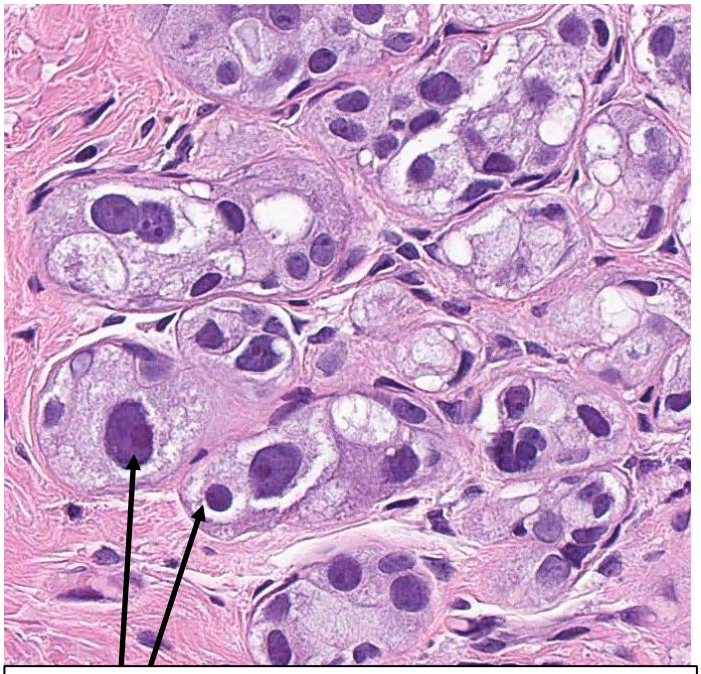
If significant cytologic atypia (>3:1 size variation, mitotic activity)→ ***Atypical Apocrine Adenosis*** *(Treated like ADH)*

If complex architecture (e.g., cribriform growth) or very marked pleomorphism, → ***Apocrine DCIS***



Apocrine adenoma: a well-delineated, benign tumor characterized by a proliferation of round and oval tubular structures, lined by luminal apocrine cells, with a peripheral attenuated layer of myoepithelial cells, and little background stroma.

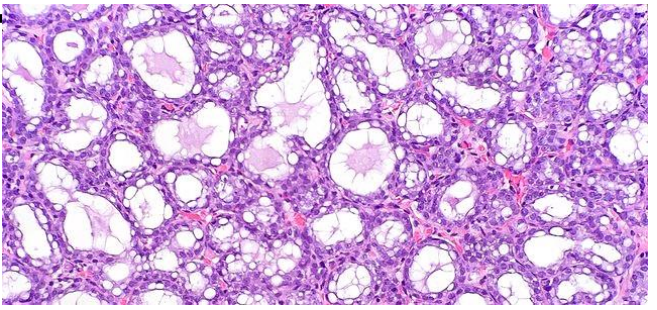
Pitfall alert: Myoepithelial cell layers may be attenuated or even partly lost in benign apocrine lesions!
(loss/partial loss ≠ malignancy!)

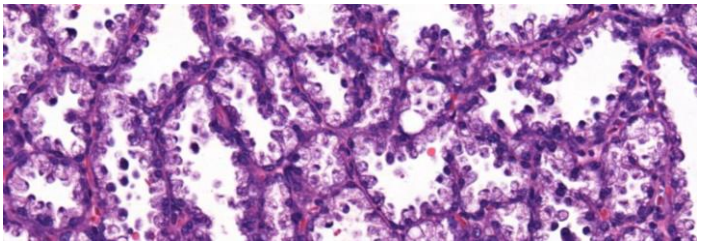


Atypical Apocrine Adenosis with >3x variation in cell size

Lactating Adenoma

Virtual Slide





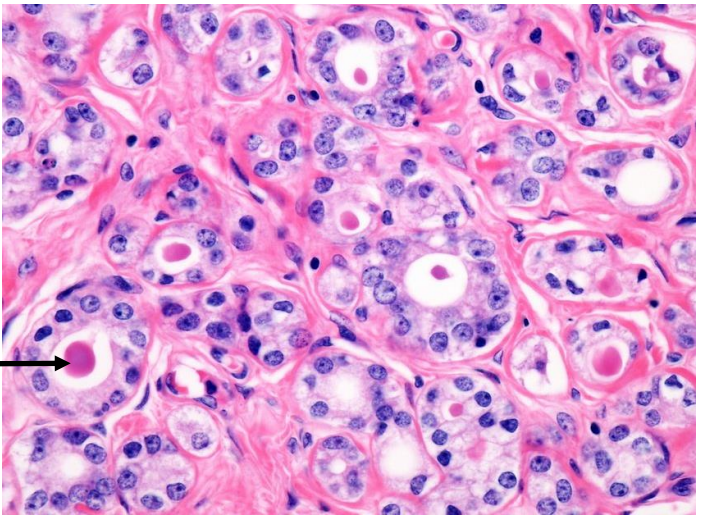
Benign breast nodule **diagnosed during pregnancy or breast feeding**, that is composed of an **aggregate of glands with lactational change.**

Well-circumscribed proliferation of closely packed hyperplastic secretory lobules separated by delicate connective tissue.

Cuboidal to hobnailed epithelial cells are bland with **vacuolated to granular cytoplasm and small, uniform, pinpoint nuclei.**

May spontaneously regress when done lactating.

Microglandular adenosis *"MGA"*



Non-Lobulocentric, infiltrating, Haphazard proliferation of **small, round, uniform, tubular glands composed of a single layer of epithelium** *without* associated myoepithelial cells, but surrounded entirely by basement membrane

Luminal spaces are open and often contain an **eosinophilic colloid-like secretion.** Glands are uniform and similar in size to normal acini.

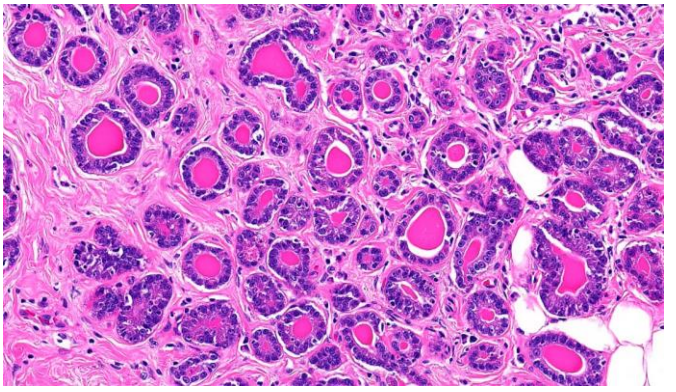
Small bland nuclei with amphophilic cytoplasm.

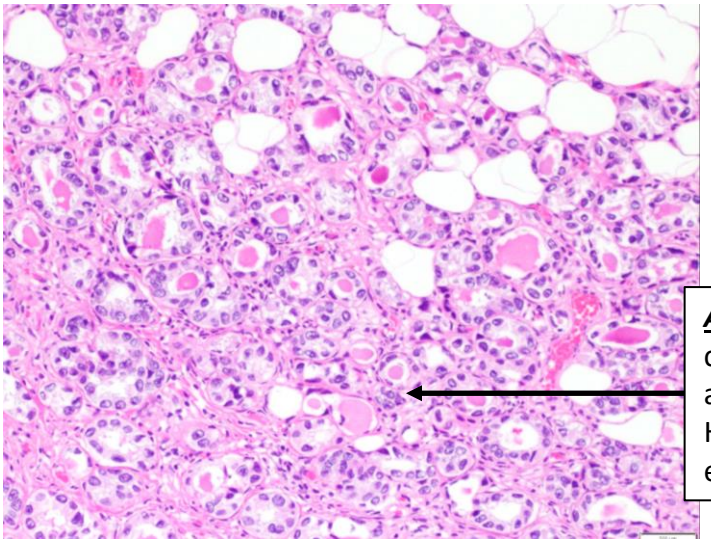
IHC: Cells stain with **CKs and S100**, Negative for ER, PR, and HER2 Myoepithelial stains negative

Virtual Slide

Benign, but thought to be a non-obligate precursor to basal-type breast cancer

***DDX*:**
Sclerosing adenosis → S100 Neg, Myoep intact
Tubular carcinoma → ER pos, S100 Neg

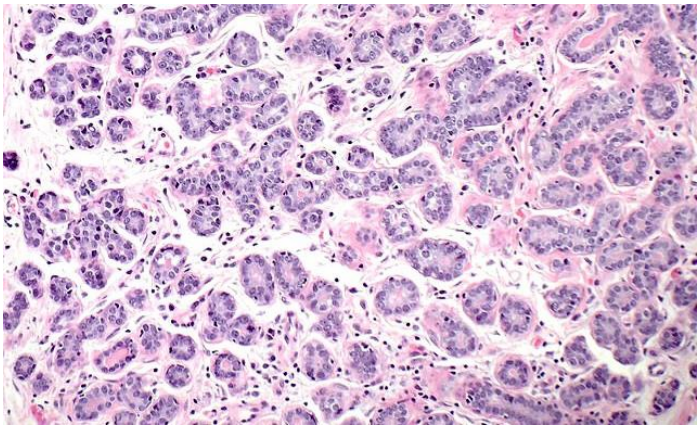




***Atypical* Microglandular adenosis**: similar to classic MGA but with increasing glandular crowding and complexity with greater cellular atypia. Higher Ki-67 proliferative index and greater p53 expression.

Tubular Adenoma

Virtual Slide

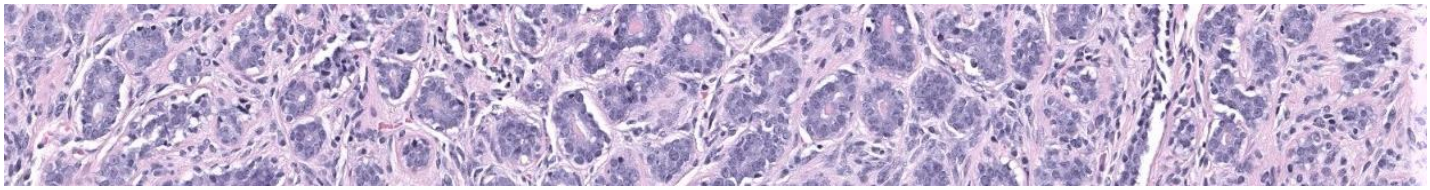


Benign. Usually Younger women. Uncommon.

Well-circumscribed, sharply demarcated, dense proliferation of closely approximated round to oval tubular structures with little background stroma

Glands have **usual two layers**: Epithelium and myoepithelium

May be related to fibroadenomas histogenetically (but just stroma poor)

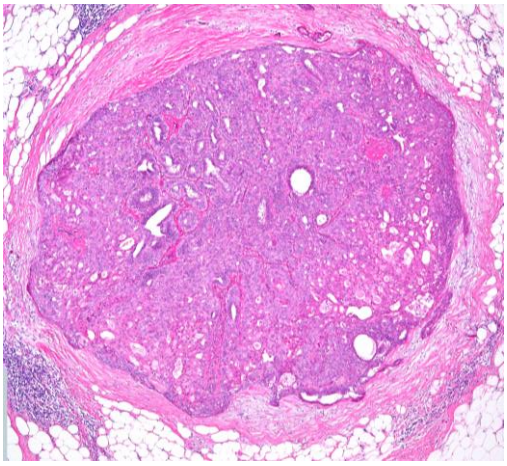


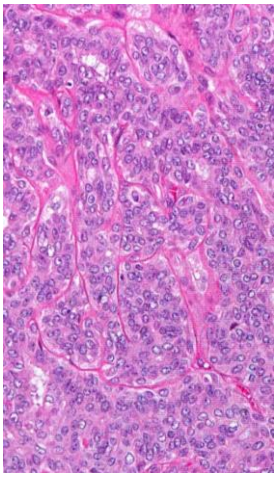
Ductal Adenoma

Rare. Benign. Usually older women.

Well-circumscribed, solitary. Adenomatous proliferation of round to oval, elongated to branched glands in parallel pattern, radiating outwards from the center to the periphery.

Surrounded by a laminated concentric fibrosclerotic wall. Usual 2 layers: luminal ductal and myoepithelial cells.
No atypia, rare mitoses.





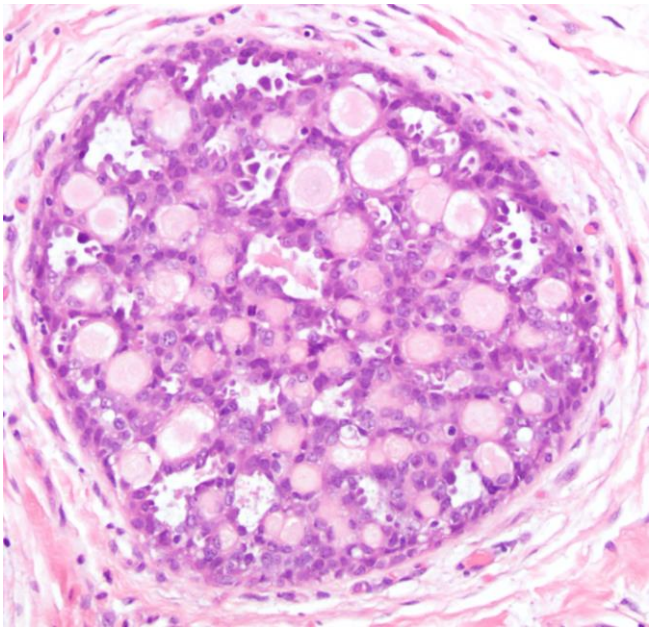
Collagenous Spherulosis

Intraductal deposits of basement membrane: Appear as hyaline, acellular, eosinophilic spherules or fibropapillary, amorphous eosinophilic to mucoid material

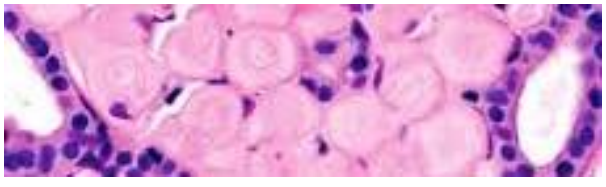
Myoepithelial cells surround the lumina and are often compressed and spindle-shaped.

Can be calcified. Commonly seen with papillomas, UDH, or sclerosing lesions.

Main importance is to recognize that it is benign and ***NOT*** DCIS or adenoid cystic carcinoma

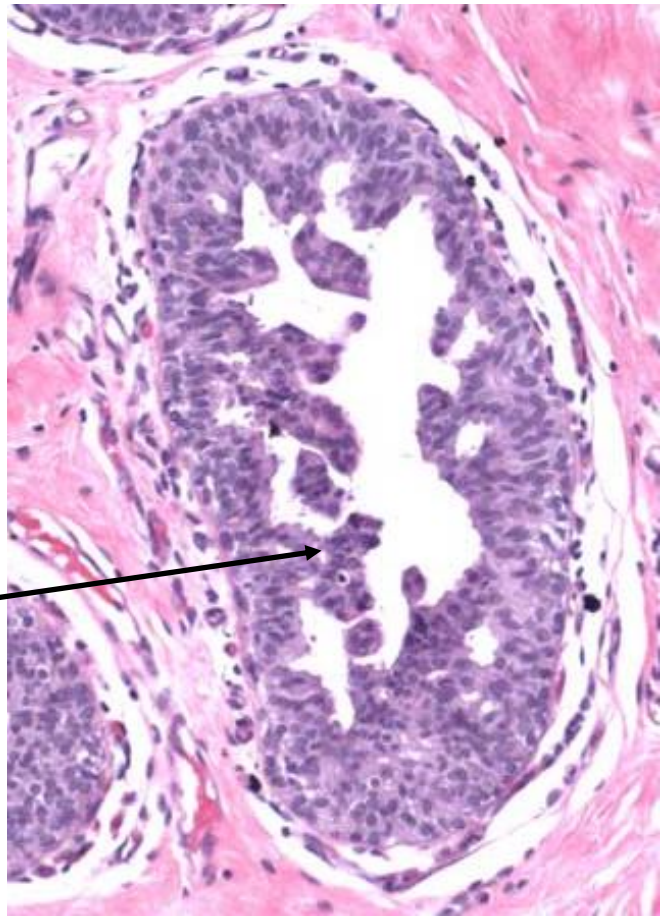


Virtual Slide



Gynecomastia

Male breast histology:
Contains fibrous stroma and branching ducts and terminal ductules, but extremely few (if any) acini.



Benign diffuse or focal **proliferation of glandular tissue of the male breast**.
Bilateral, diffuse or discrete **retroareolar masses**.

Caused by androgen/estrogen imbalance.
Physiologic in infants, children, and adolescents.
In a minority, often older age, it is pathologic and associated with endocrine abnormalities (Klinefelter syndrome, obesity, cirrhosis) and certain drugs (e.g., spironolactone and marijuana).

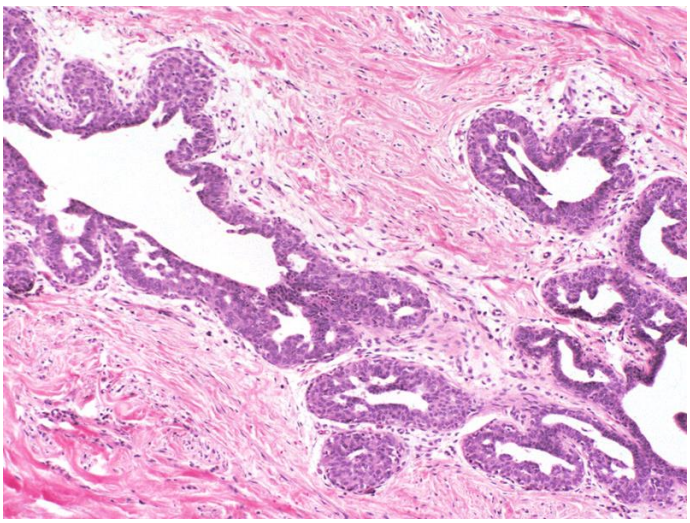
Histologic appearance varies with duration/stage:
Increased number of ducts

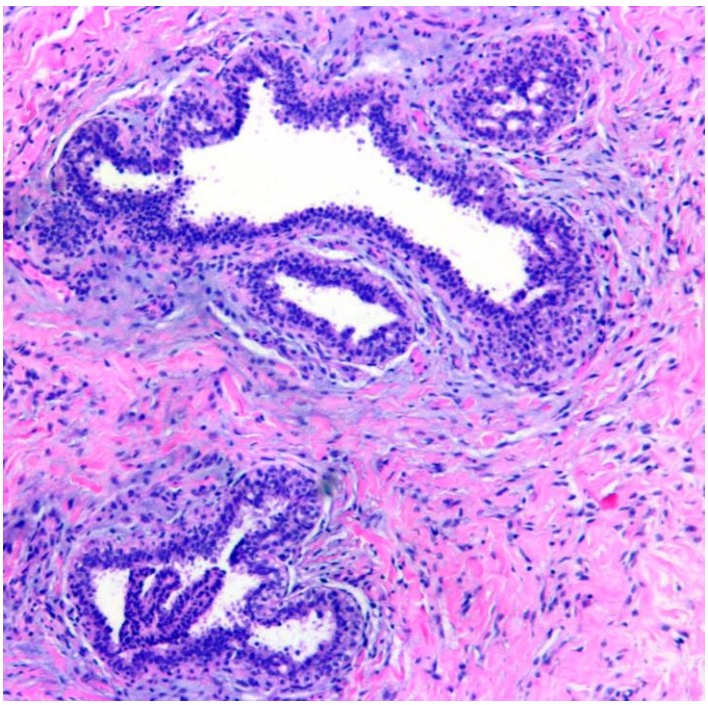
Virtual Slide 2

Early
Loose periductal stroma
Mixed chronic inflammatory infiltrate
Extensive epithelial hyperplasia (≥3 cells thick) with tapering tufts (**pyramid-shaped micropapillae**) and protrusion into lumen (like what is seen in juvenile fibroadenomas), so have a high threshold for calling DCIS/ADH

Late
Fibrosis and hyalinization of periductal stroma
Atrophy of epithelium
Can see Pseudoangiomatous stroma hyperplasia (PASH)

Not associated with any risk of cancer
Usually no treatment necessary





Summary of Surgical Management Recommendations for High-Risk Lesions of the Breast

THE AMERICAN SOCIETY OF Breast Surgeons | Resource Guide

Lesion	Recommendation[a]	Exceptions / Notes
ADH	Surgical excision	Patients who meet low-risk criteria can be considered for observation (see summary of data below)
Classic LCIS / ALH	No excision Observation with clinical and imaging follow-up[b,c]	Excision if other benign lesion with potential for upstaging is present or if not incidental (see summary of data below)
Non-classic LCIS (pleomorphic and florid)	Surgical excision to negative margins[d]	Similar for necrosis and other non-classical lesions
CCL without atypia	No excision Return to screening	
Pure FEA	No excision Observation with clinical and imaging follow-up[b,c]	Excision if extensive calcifications or not adequately sampled
Papilloma without atypia	No excision Observation with clinical and imaging follow-up[b,c]	Consider excision for symptomatic lesions
Papilloma with atypia	Surgical excision	
Complex sclerosing lesions (CSL)	No excision Observation with clinical and imaging follow-up[b,c]	Excision for CSL with atypia For CSL without atypia, consider excision if not adequately sampled or other concerning features
Mucocele-like lesions (MLL)	No excision Observation with clinical and imaging follow-up[b,c]	Surgical excision for MLL with atypia.
Desmoid tumors or fibromatosis	Observation with clinical and imaging follow up every 3-6 months[c] (breast imaging, MRI, CT as clinically indicated)	Excision for symptomatic lesions and those increasing in size (see summary of data below)
PASH	Clinical observation	Consider excision for symptomatic lesions

ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; CCL, columnar cell lesion; CT, computed tomography; FEA, flat epithelial atypia; LCIS, lobular carcinoma in situ; MRI; magnetic resonance imaging; PASH, pseudoangiomatous stromal hyperplasia

[a]Recommendation are for lesions for which radiologic pathologic concordance has been established

[b]Diagnostic imaging at 6, 12, and 24 months to establish stability is recommended based on American College of Radiology guidelines (see "Indications for excision: discordance and the risk of pathology upgrading")

[c]Strongly consider excision for lesion progression during follow up

[d]Data on appropriate margin width for PLCIS is limited (see "Non classic LCIS")

From: https://www.breastsurgeons.org/resources/statements/