In Situ Lesions of the Breast

Normal Anatomy

Terminal Duct Lobular Unit (TDLU)
Increasingly small branching ducts terminate in clusters of acini called lobules.

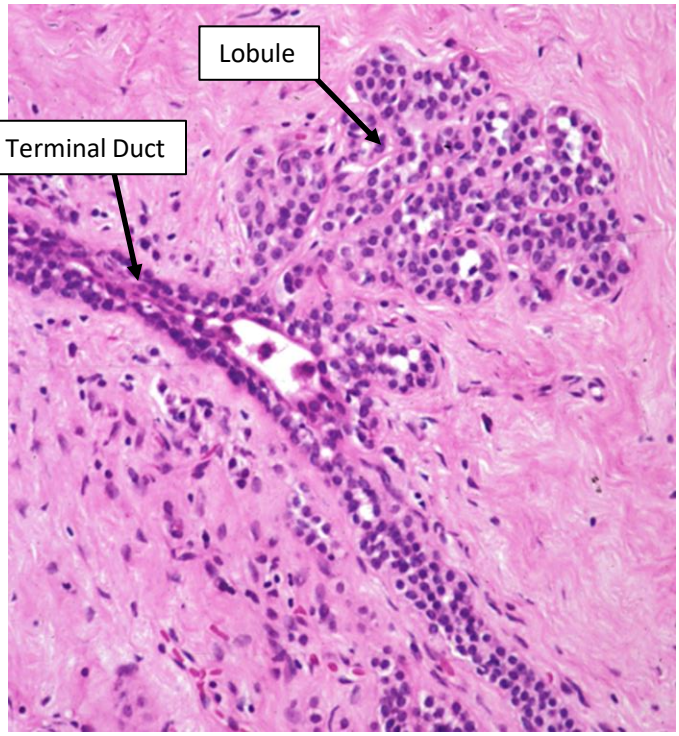
Milk flow: Acini→ ducts→ collecting ducts → Nipple

Set in fibrous stroma with varying amounts of adipose tissue

Two cell layers:

1) Inner Epithelial cell
Cuboidal to columnar cells with eosinophilic cytoplasm and oval nuclei.
Stain with LMW cytokeratins (e.g., CK7)

2) Outer myoepithelial cell
Flat (sometimes barely visible) to plump with abundant clear cytoplasm. Stain with Actin, calponin, SMMHC, p63, CK5/6, S100



In Situ Lesions

Usual Ductal Hyperplasia (UDH)

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

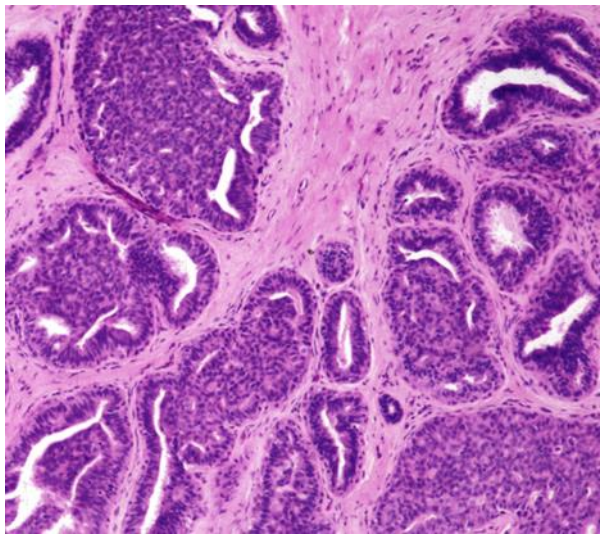
Think: "*Polyclonal*"

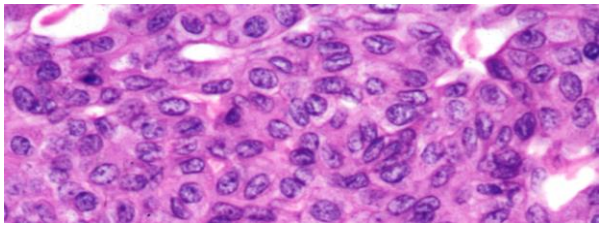
Cohesive proliferation with **haphazard** architecture
Irregular, slit-like lumina, often peripherally located
Streaming, syncytial pattern
Variably sized cells with indistinct borders
Overlapping nuclei
Frequent nuclear grooves, some pseudoinclusions

Any bridges are thin and stretched
Any micropapillae have broad bases and narrow tips with small pyknotic nuclei

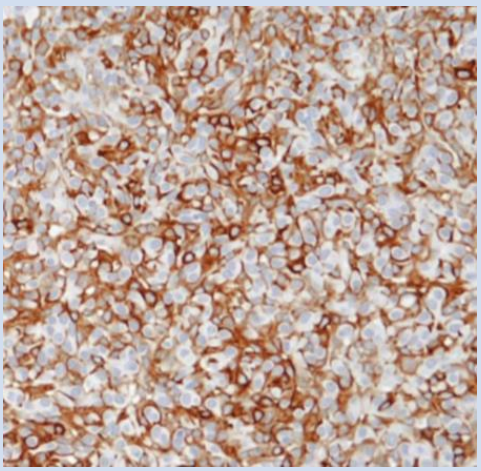
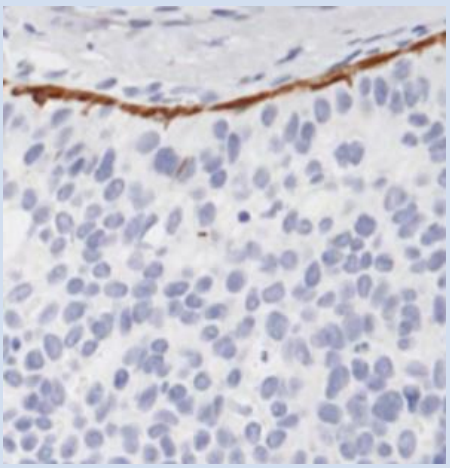
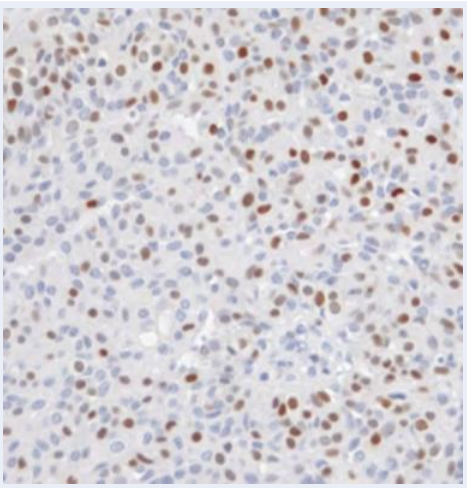
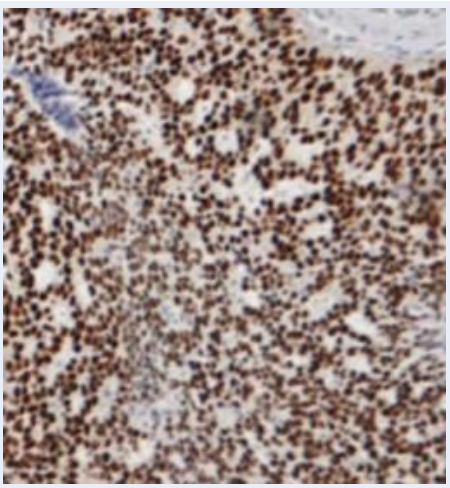
Cells stain with a mixture of low-molecular weight cytokeratins (e.g., CK7) and high-molecular with CKs (e.g., CK5/6). Heterogeneous ER staining.

~2x Relative Risk of Developing Cancer
Treatment: None needed





UDH	Low-grade DCIS
Think: "**Polyclonal**"	Think: "**Monoclonal**"
Irregular, Slit-like lumina, often peripheral	Regular, punched out lumina, often central
Streaming architecture, minimal polarization	Prominent polarization
Variation in cell size/shape	Monomorphic cells/shape
Indistinct cell margins	Distinct cell margins
Admixture of cell types (epithelial, myoepithelial and/or apocrine): Stain with high and low-molecular weight cytokeratins	Proliferating cells are epithelial. Myoepithelial cells are against the basement membrane: Epithelium stains with low-molecular weight cytokeratins only
Heterogeneous ER staining	Strong, diffuse ER staining

	UDH	Low-grade DCIS
CK5/6		
ER		

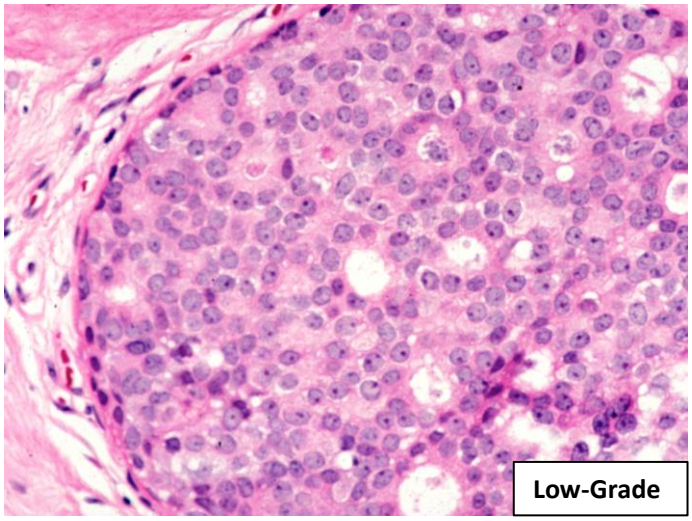
Ductal Carcinoma In Situ (DCIS)

Non-invasive neoplastic epithelial proliferation

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

Often 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)

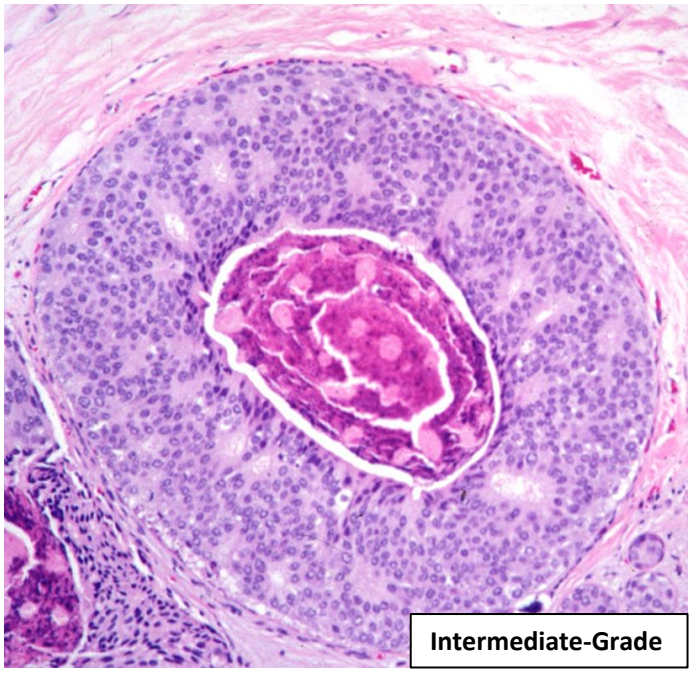


Low-grade DCIS

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

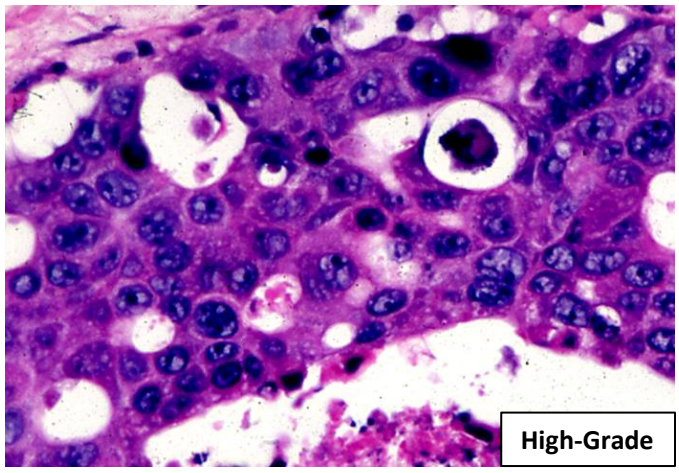


High-grade DCIS:

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 "wide" negative margins**
Possibly +/- radiation and/or hormone therapy

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 DCIS (similar cytology and architecture), **BUT** less developed in architecture or extent

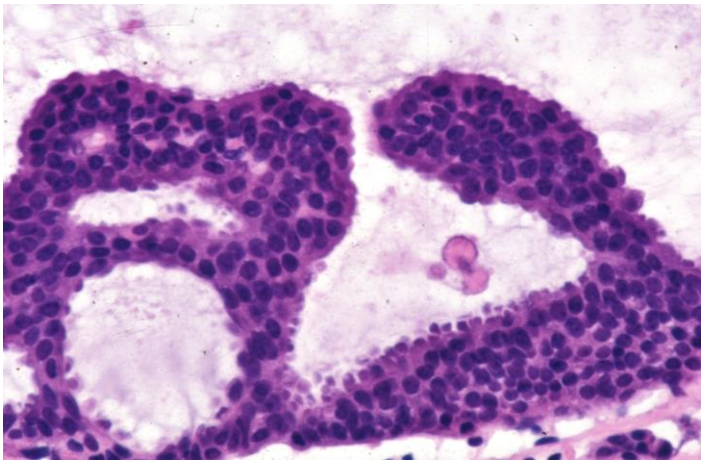
Similarly genetically to low-grade DCIS→ clonally related, just smaller or questionable architecture

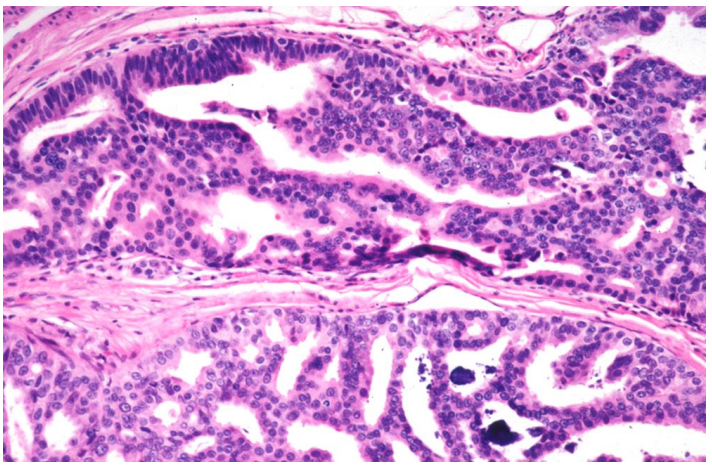
Size: ≤2mm and <2 duct spaces

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

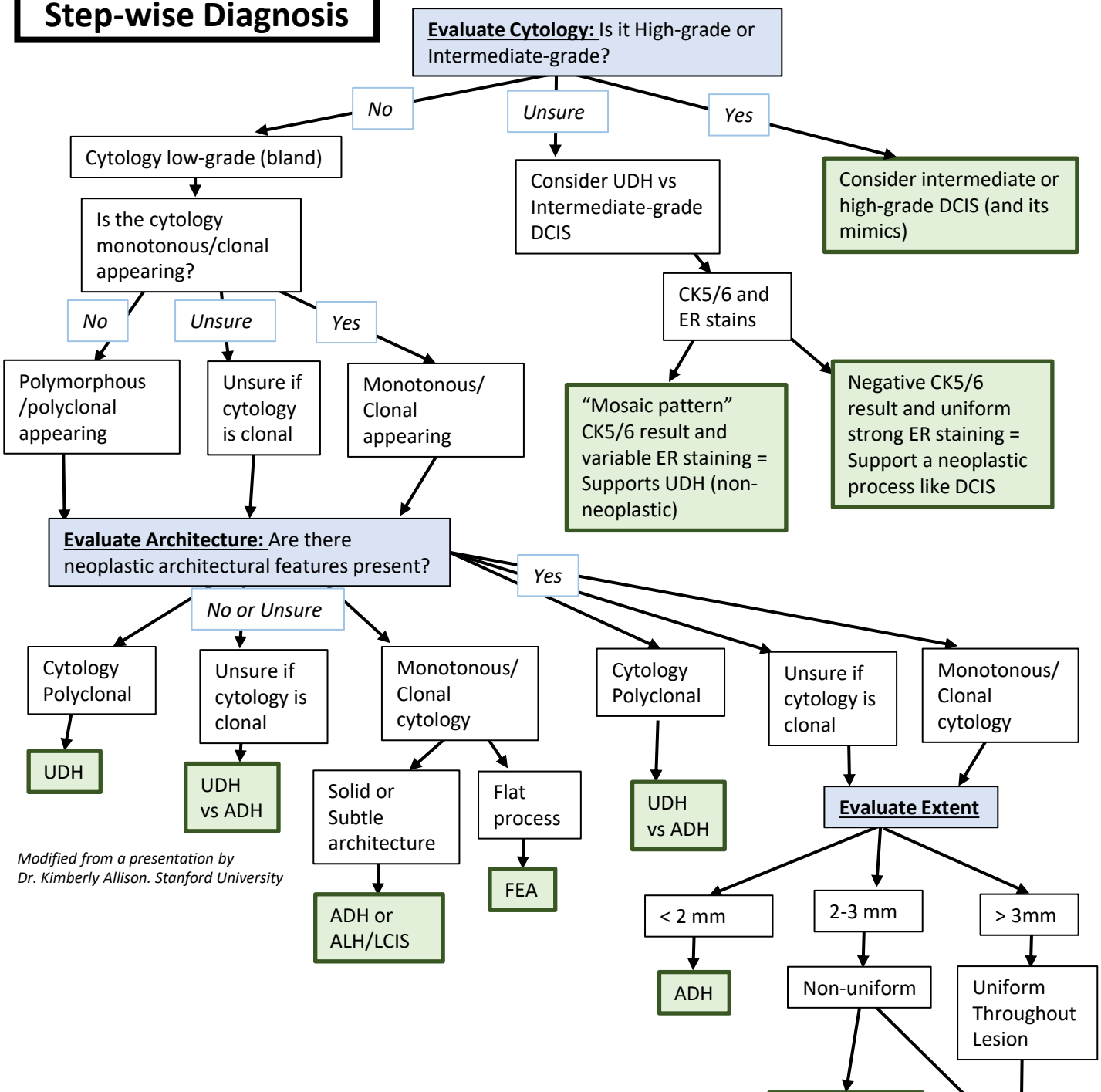
Architecture:
- **Cribriform**
- **Rigid bridges**, arcades, and bars
- **Bulbous micropapillae** (with narrow bases and wide tips)

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





Step-wise Diagnosis

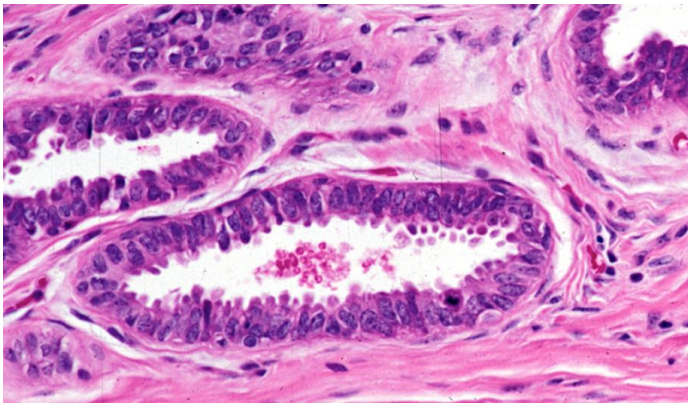


Modified from a presentation by Dr. Kimberly Allison. Stanford University

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

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

Apical snouts, secretions and calcification are often present

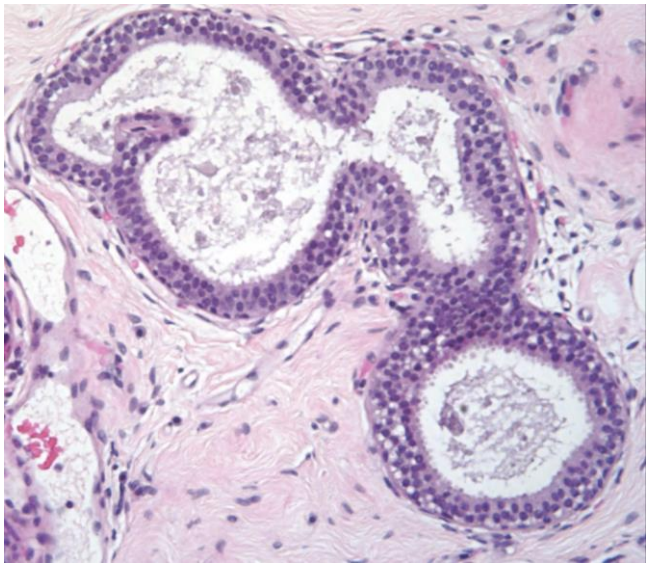
Earliest step in low-grade carcinoma pathway

Not infrequently associated with ADH, low grade DCIS, or invasive carcinoma, but risk of developing a subsequent carcinoma is negligible, so excision is not indicated

More than 2 cell layers thick?
→ Columnar cell *hyperplasia*

More complex architecture? → ADH

Flat Epithelial Atypia (FEA)



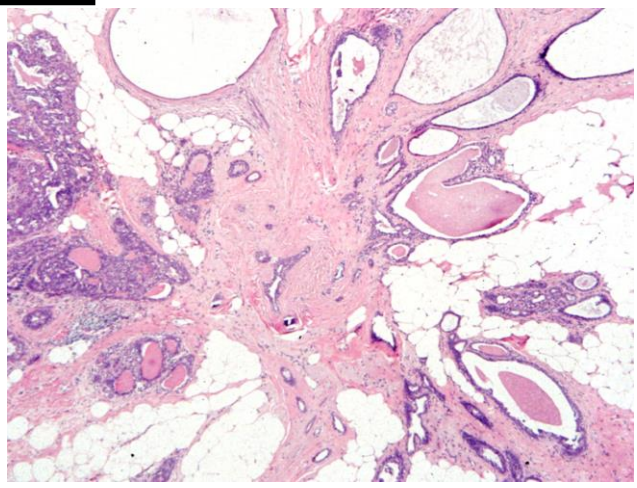
Similar to columnar cell change (in dilated TDLUs), but lined by **1-2 layers of cells with enlarged round to oval nuclei**
(same cells as in ADH/low grade DCIS!)

Complex architecture of the type seen in ADH/low grade DCIS is not allowed

Apical snouts, secretions and calcification may be present

Frequently associated with DCIS/cancer, so if found on core biopsy, it is an indication for excision (to exclude a worse lesion nearby). No further treatment on excision.

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 and more disorganized

Dense, hyalinized, elastotic stroma

Two cell layers maintained throughout

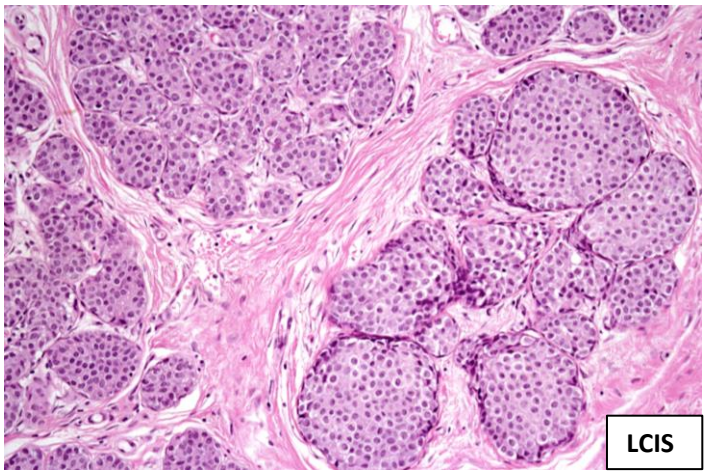
Excision somewhat controversial, often excised

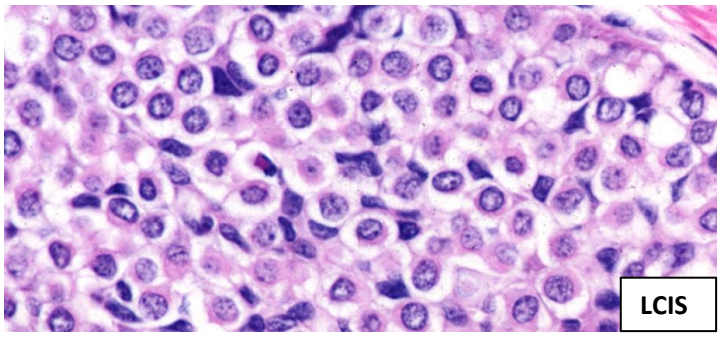
Often may want to do myoepithelial stains to confirm no invasive component given complexity

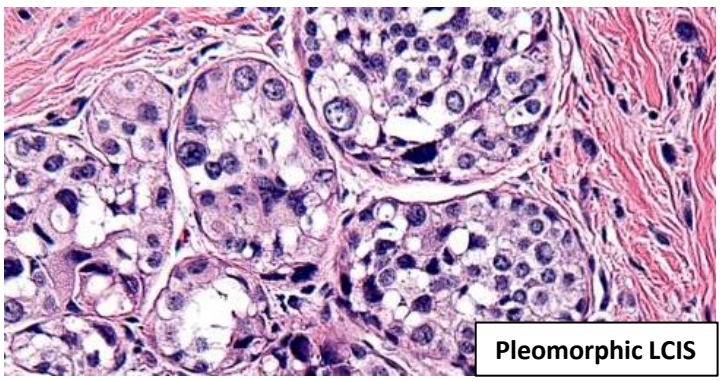
Lobular Neoplasia In Situ

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

- **Small, discohesive monomorphic cells**
- **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)


LCIS


LCIS


Pleomorphic LCIS

Atypical Lobular Hyperplasia (ALH)

Solid proliferation of discohesive, monomorphic epithelial cells expanding <50% of the acini in a TDLU
If incidental on a biopsy, no need to excise

Lobular Carcinoma In Situ (LCIS)

>50% of the acini are filled and expanded
Often >8 cells thick
Non-obligate precursor to invasive lobular carcinoma
~8-10x Relative Risk of Cancer
If incidental on a biopsy, no need to excise
On excision, margins don't matter

LCIS Subtypes:

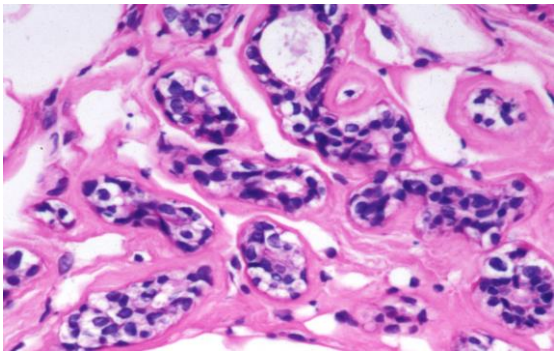
Pleomorphic LCIS—composed of large cells (>4x size of a lymphocyte) with marked nuclear pleomorphism

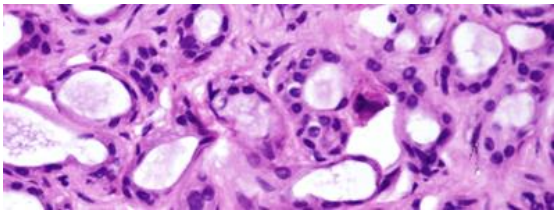
Florid LCIS—classic LCIS cells, but forming a confluent mass-like lesion with little to no intervening stroma between distended TDLUs (often ~50 cells in diameter)

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

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





Very common
Lobulocentric proliferation of acini and tubules accompanied by <u>compressing fibrosis</u>

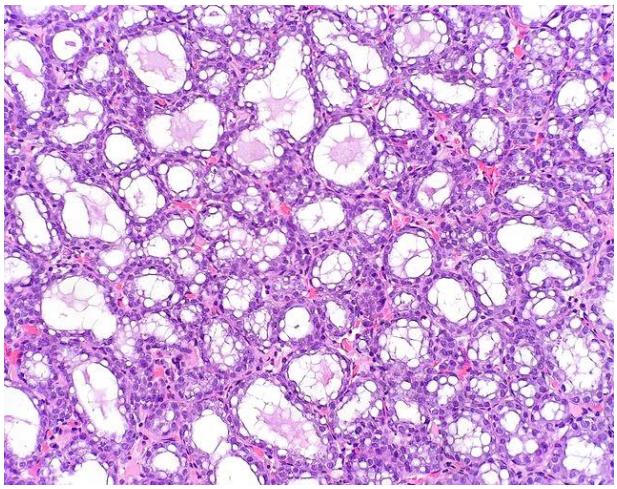
Epithelial cells are often cuboidal, small, and bland
Myoepithelial cells have spindled, hyperchromatic nuclei and inconspicuous to prominent clear cytoplasm
Can highlight myoep's with IHC stains if necessary

Microcalcifications are common
Can extend into fat occasionally

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

Primarily significant as it can be ***<u>confused</u>*** with carcinoma

Lactating Adenoma



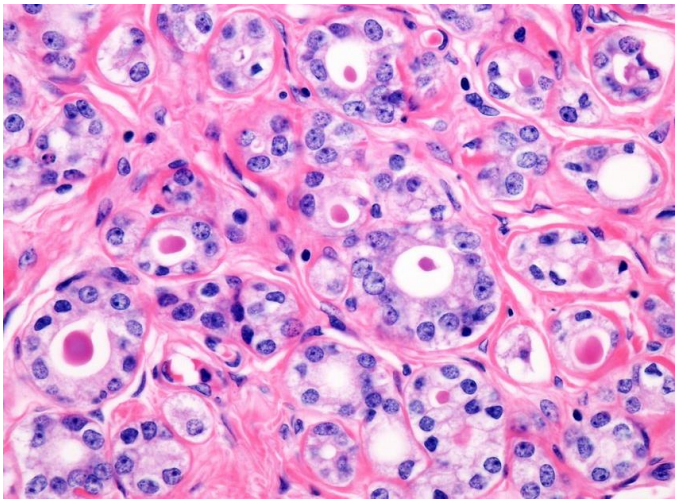
Benign breast nodule **diagnosed during pregnancy or breast feeding**, that is composed of an **<u>aggregate of glands with lactational change</u>**

<u>Well-circumscribed</u> proliferation of closely packed <u>hyperplastic secretory lobules</u> separated by delicate connective tissue

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

Spontaneously regress when done lactating

Microglandular adenosis



<u>Haphazard</u> proliferation of **small, round, uniform, tubular glands composed of a single layer of epithelium** (<u>*without* associated myoepithelial cells!</u>)

Luminal spaces are open and often contain an **eosinophilic colloid-like secretion**

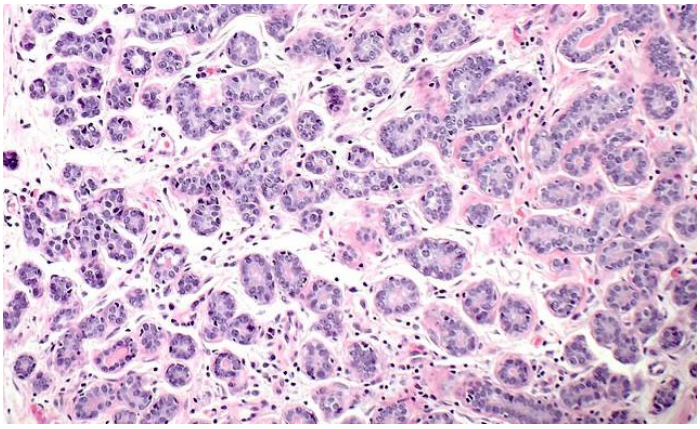
Small bland nuclei with amphophilic cytoplasm

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

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

Tubular Adenoma



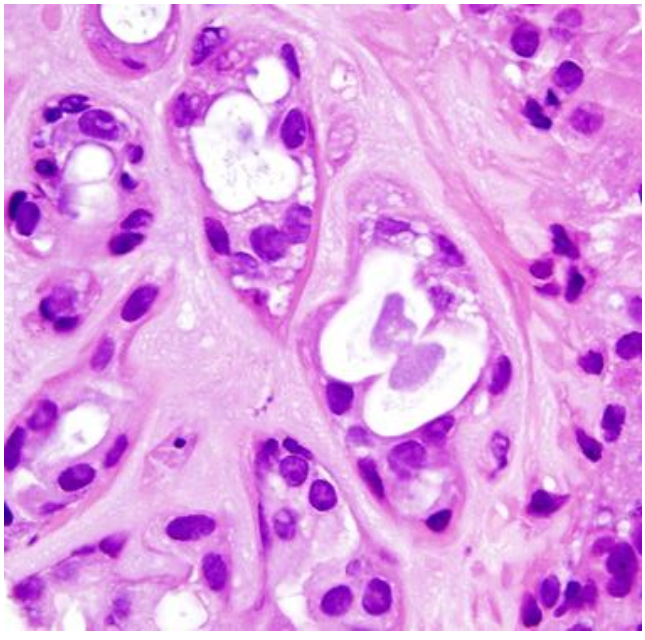
Benign. Usually Younger women. Uncommon.

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)

Apocrine Adenosis



= Apocrine metaplasia + Sclerosing adenosis

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

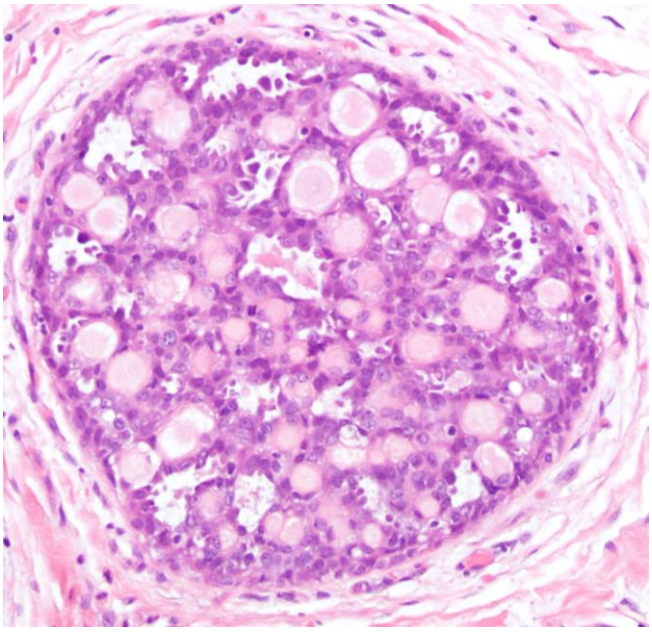
Enlarged, round nuclei with prominent nucleoli
Often have apical "snouts"
Intact myoepithelial cells→ can highlight with IHC

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

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

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

Collagenous Spherulosis

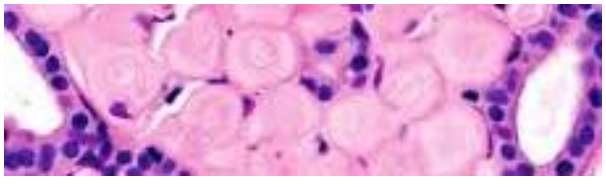


Intraductal deposits of basement membrane: Appear as hyaline, acellular, eosinophilic spherules or fibropapillary, amorphous eosinophilic to mucoid material

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



Gynecomastia

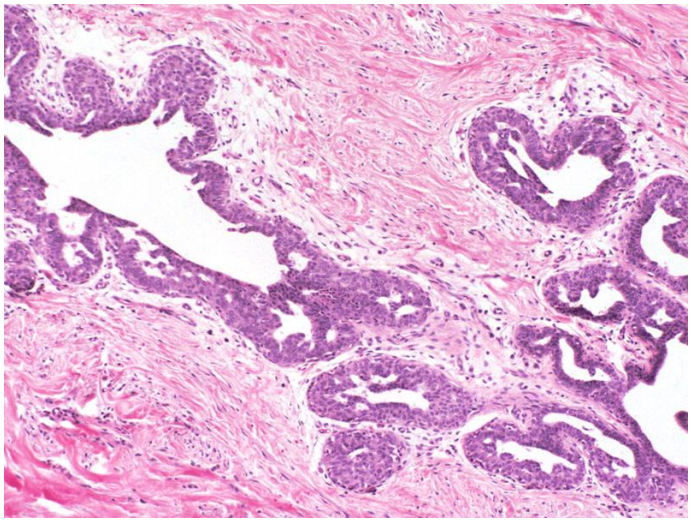
Bilateral, diffuse or discrete **retroareolar masses**.
Most common lesion of the **male breast.**

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:
Early
Loose periductal stroma
Mixed chronic inflammatory infiltrate
Extensive epithelial hyperplasia 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 se pseudoangiomatous hyperplasia (PASH)

Not associated with any risk of cancer
Usually no treatment necessary



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