

Lobular carcinoma in situ

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Morphology • molecular biology • clinicopathologic interpretation

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Learning objectives

- Recognize classic LCIS and relate its morphology to loss of cell adhesion.
- Distinguish lobular neoplasia from ductal carcinoma in situ and invasive carcinoma.
- Interpret E-cadherin, hormone receptor status, and bilateral risk.
- Apply Robbins-based principles to core biopsy management.

Where LCIS belongs in breast pathology

Noninvasive lesion

Neoplastic epithelial proliferation remains within the ductal–lobular system.

Lobular phenotype

Discohesive epithelial cells;
Loss of E-cadherin is characteristic.

Risk indicator

Subsequent invasive carcinoma can occur in either breast.

The defining biological feature

Neoplastic cells are dyscohesive

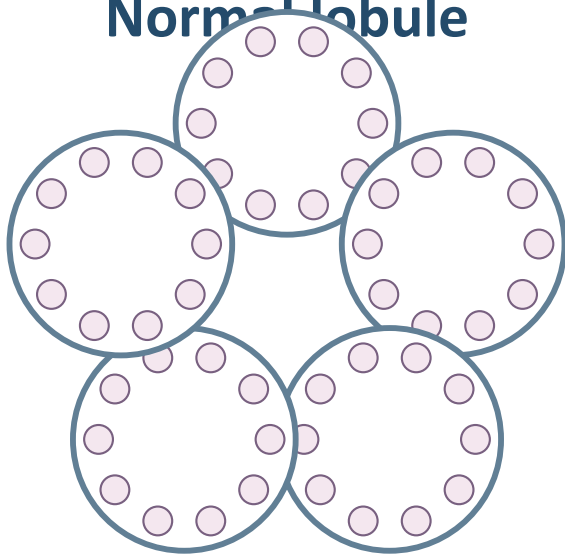
They proliferate within ducts and lobules without the cohesive epithelial arrangement of normal breast tissue.

The terminal duct–lobular unit is the setting

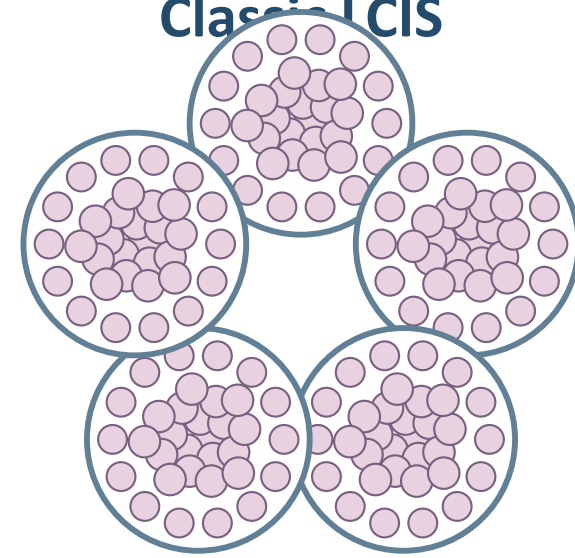
- Breast carcinoma in situ develops within the terminal duct–lobular unit.
- A terminal duct branches into groups of acini (the lobule).
- LCIS expands acini while recognizable lobular architecture remains.
- The intact boundary distinguishes an in situ proliferation from invasion.

Normal acini versus acini expanded by LCIS

Normal Lobule

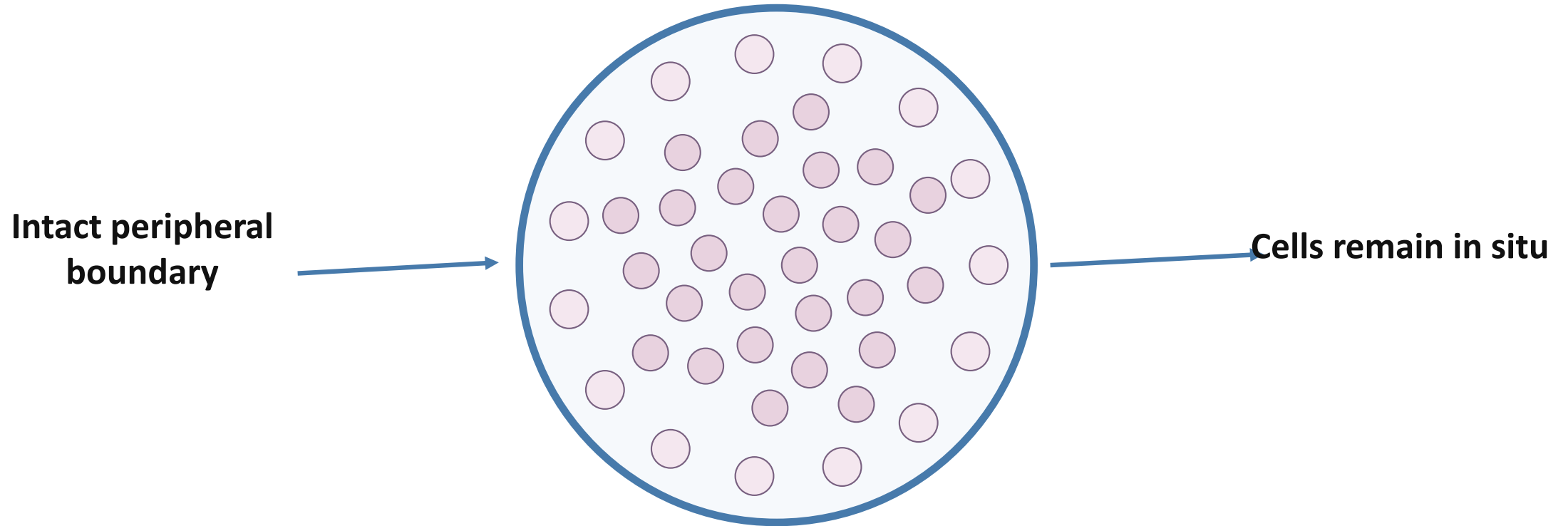


Classic LCIS



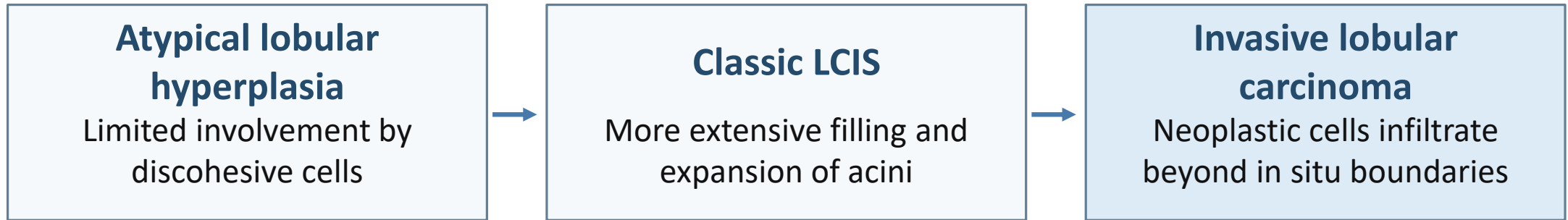
Schematic: Terminal duct–lobular units, not histologic specimens

What “in situ” does—and does not—mean



Schematic; Peripheral line represents the basement membrane

Lobular neoplasia is a morphologic continuum



These lesions can have similar cytology; Extent and tissue compartment are decisive.

Atypical lobular hyperplasia versus classic LCIS

Atypical lobular hyperplasia

- Small, round, dyscohesive neoplastic cells.
- Histologically identical cellular phenotype to classic LCIS.
- More limited extent within acini.

Classic LCIS

- Same characteristic dyscohesive cell type.
- Cells fill and expand more than half of acini in an involved lobular unit.
- Extent supports the LCIS designation.

The threshold is architectural extent

More than half of acini

The classic LCIS description uses filling and expansion of more than half the acini in a terminal duct–lobular unit.

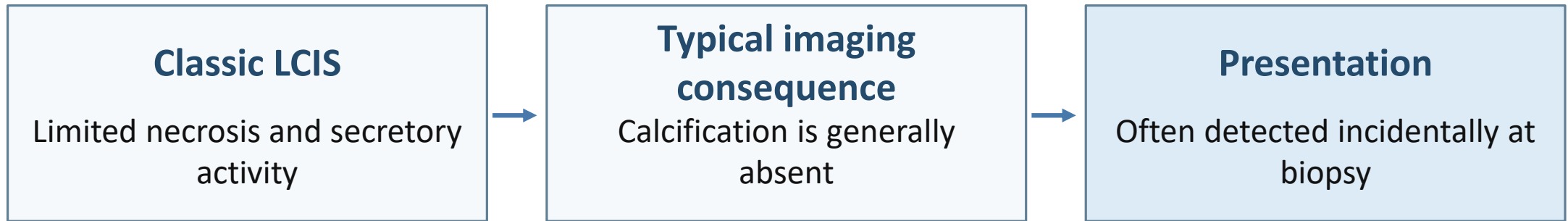
Cell identity alone cannot establish invasion

- Cells in atypical lobular hyperplasia, LCIS, and invasive lobular carcinoma may look alike.
- LCIS is distinguished from invasion by its confinement to ducts and lobules.
- Evaluation requires tissue architecture and the neoplastic cell distribution.
- Cytologic similarity does not make the three diagnoses interchangeable.

LCIS is commonly an incidental finding

- Most classic LCIS is discovered in tissue sampled for another reason.
- The lesion seldom produces the microcalcifications that prompt mammography-directed biopsy.
- Stromal reactions causing mammographic densities are also usually absent.
- Clinical and imaging silence follows from its morphology.

Why screening often does not identify classic LCIS



This describes the usual pattern; Aggressive variants may calcify.

Reported frequency has not risen with screening

- Robbins gives LCIS as approximately 1%–6% of all carcinomas in its discussion.
- Unlike mammographically visible DCIS, LCIS detection is often incidental.
- Its incidence has been unchanged by mammographic screening.
- Interpret this as a source-specific epidemiologic statement, not a new population estimate.

Classic LCIS and DCIS differ in detectability

Classic LCIS

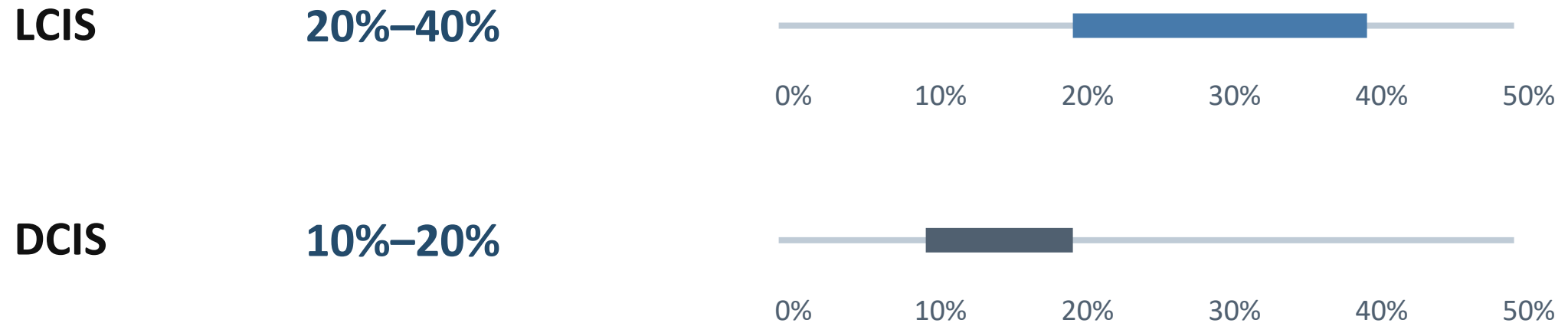
- Rare calcifications.
- Rare stromal reaction producing a radiologic density.
- Typically not the target of screening biopsy.

DCIS

- Frequently associated with calcifications.
- Usually identified on mammography.
- May occasionally produce a density or nipple-related presentation.

Bilateral involvement is an important clue

LCIS involvement on bilateral sampling

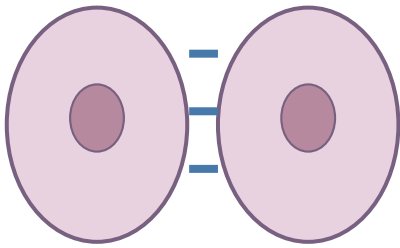


Intervals are reported ranges, not estimates of an individual patient's risk.

What bilateral involvement means

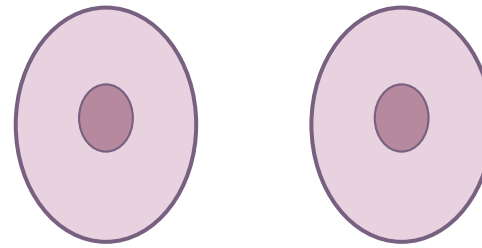
- LCIS is not necessarily restricted to the breast in which it is discovered.
- When both breasts are sampled, LCIS is reported in both in 20%–40% of cases.
- By comparison, bilateral DCIS in 10%–20%.
- These are frequencies of bilateral LCIS/DCIS findings on bilateral sampling, not lifetime invasive-cancer risks.

Dyscohesion arises from failed cell adhesion



Adhesion preserved

Cell–cell contact



Adhesion disrupted

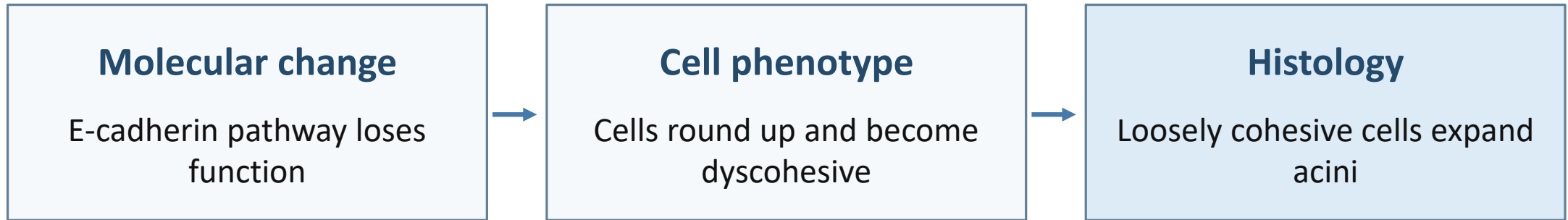
Rounded, dyscohesive cells

Schematic of E-cadherin-mediated adhesion

Normal function of E-cadherin

- E-cadherin is a transmembrane cell-adhesion protein.
- It helps breast epithelial cells maintain lateral contact with neighbors.
- E-cadherin-associated proteins support functional epithelial adhesion.
- Loss of this system explains rounded, loosely attached LCIS cells.

From adhesion loss to the LCIS appearance



Causal direction follows the explanation given.

CDH1 is the principal gene

- CDH1 encodes the E-cadherin adhesion protein.
- The gene at chromosome 16q22.1.
- Mutation or deletion of CDH1 commonly underlies E-cadherin loss.
- This is an adhesion-related tumor suppressor pathway in glandular epithelium.

Deletion and mutation are alternative routes

CDH1 mutation

- Altered CDH1 sequence can produce loss of normal E-cadherin function.
- The functional effect is impaired intercellular adhesion.

CDH1 deletion

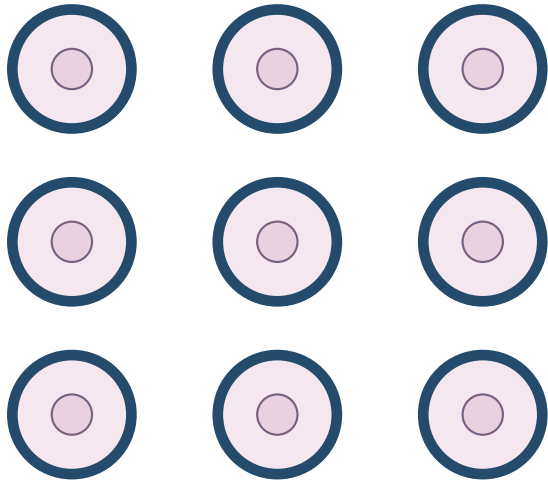
- Loss of genomic material may remove or disrupt CDH1.
- Chromosome 16q alterations also link LCIS with the low-grade pathway.

A negative E-cadherin stain is biologically meaningful

- Loss of membranous E-cadherin expression supports a lobular phenotype.
- Dyscohesive rounded morphology and loss of E-cadherin are concordant observations.
- Normal epithelial cells may retain expression and provide an internal contrast.
- Immunophenotype must be interpreted with tissue architecture.

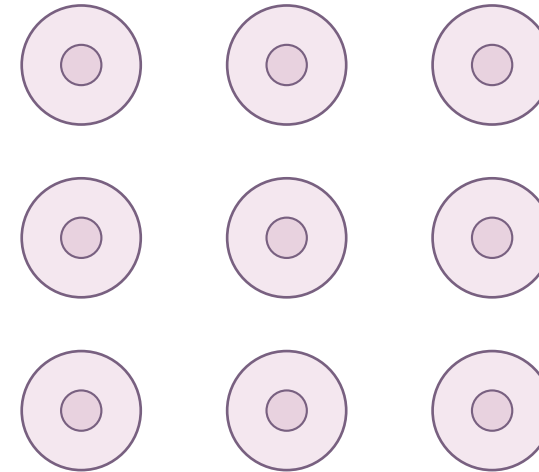
E-cadherin staining: Conceptual pattern

Adjacent normal luminal cells



Membranous E-cadherin retained

LCIS cells



E-cadherin expression lost

Schematic of the staining distinction — not an IHC photomicrograph

Rare non-CDH1 causes of failed adhesion

- Loss of E-cadherin function is usually the basis of dyscohesion, but not universally.
- Robbins also describes rare dysfunction in proteins needed for E-cadherin-mediated adhesion.
- β -catenin is named as one such associated protein.
- A mechanistic absence of adhesion need not always reflect direct CDH1 loss.

LCIS is linked to the low-grade pathway

- Low-grade breast neoplasia includes precursor lesions, classic LCIS, and some well-differentiated invasive cancers.
- Chromosome 16q deletion is a shared genomic alteration in this pathway.
- Atypical lobular hyperplasia also demonstrates E-cadherin loss.
- These similarities support a biological relationship across morphologic categories.

Molecular parallels with invasive carcinoma

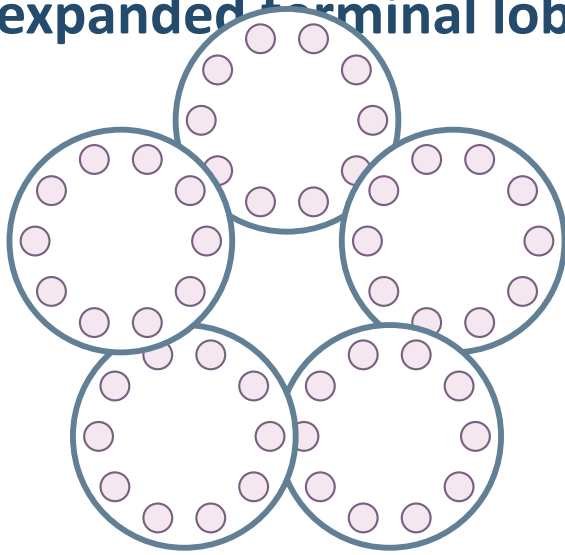
- LCIS may show a mutation spectrum like that of a synchronous invasive carcinoma.
- Shared molecular alterations suggest related neoplastic lineages.
- Molecular similarity does not establish invasion in a particular biopsy.
- The histologic distinction between in situ and invasive carcinoma remains essential.

Classic LCIS: Uniform epithelial population

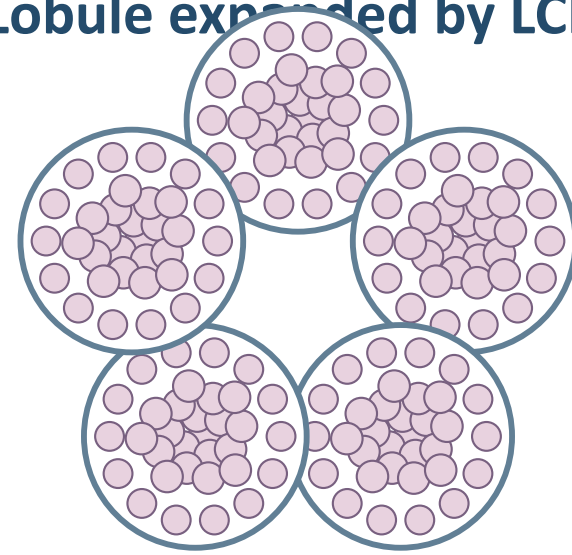
- A relatively monotonous population of epithelial cells fills involved acini.
- Nuclei are round or oval rather than strikingly pleomorphic.
- Nucleoli are generally small.
- The lobular outlines can still be identified despite luminal expansion.

Classic LCIS expands, rather than obliterates, lobules

Unexpanded terminal lobule



Lobule expanded by LCIS



Schematic: Terminal duct–lobular units, not histologic specimens

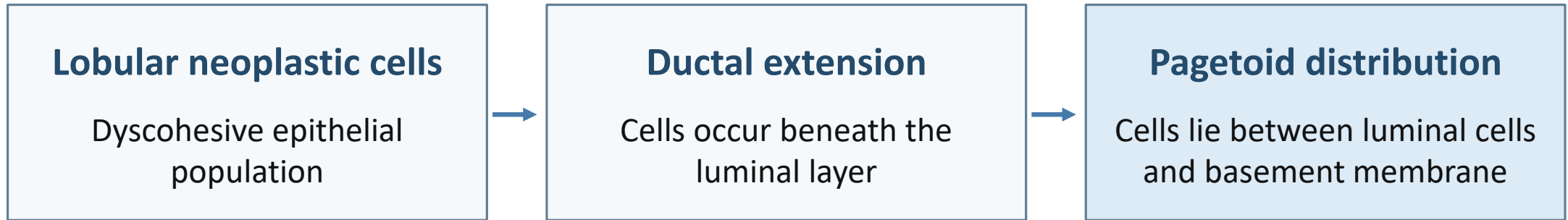
How the nuclear features fit the diagnosis

- Uniform nuclear size and shape are characteristic of classic LCIS.
- Round-to-oval nuclei are seen within dyscohesive epithelial cells.
- Small nucleoli accompany the relatively bland cytology.
- Architectural extent distinguishes classic LCIS from more limited lobular atypia.

Mucin-containing signet-ring cells can occur

- Mucin-positive signet-ring cells are commonly found in classic LCIS.
- Mucin within cytoplasm can displace a nucleus to the periphery.
- Their presence should be interpreted with the characteristic lobular architecture.
- A signet-ring appearance alone does not prove an invasive process.

Pagetoid spread can involve the ducts



Pagetoid ductal spread is not the same diagnosis as Paget disease of nipple skin.

Pagetoid ductal spread versus nipple Paget disease

Pagetoid spread in LCIS

- Neoplastic cells track beneath the ductal luminal epithelium.
- Seen commonly as duct involvement in lobular neoplasia.
- Defined by an intraductal location.

Paget disease of nipple

- Involves the epidermis of the nipple.
- Usually arises in association with DCIS.
- Nipple Paget disease is rare with LCIS.

Classic LCIS usually lacks necrosis

- Classical LCIS is typically not associated with necrosis.
- Intraluminal secretory activity is generally absent.
- Without these processes, calcifications are uncommon.
- The lack of calcification helps explain incidental presentation.

Pleomorphic LCIS differs from the classic form

Classic LCIS

- Usually uniform, relatively bland nuclei.
- Necrosis and calcifications generally absent.
- Commonly an incidental histologic diagnosis.

Pleomorphic LCIS

- Aggressive variant with larger pleomorphic cells.
- May show necrosis and calcifications.
- Requires a different clinical management approach.

Calcifications do not exclude lobular disease

- The usual absence of calcifications applies chiefly to classic LCIS.
- Pleomorphic LCIS can produce necrosis and calcifications.
- An imaging-visible lesion can therefore still be lobular in phenotype.
- Interpret imaging together with histologic subtype, rather than relying on a single screening expectation.

Hormone receptor profile of LCIS

ER

Almost always expressed in
LCIS

PR

Almost always expressed in
LCIS

HER2

Usually negative in LCIS

Pattern reported for LCIS; Not a stand-alone diagnostic criterion

ER and PR positivity connects to biology

- LCIS almost always expresses estrogen and progesterone receptors.
- The hormone receptor phenotype resembles that of lesions in the low-grade breast pathway.
- Hormone receptor expression does not by itself distinguish in situ from invasive carcinoma.
- Receptor results require integration with morphology and cell adhesion phenotype.

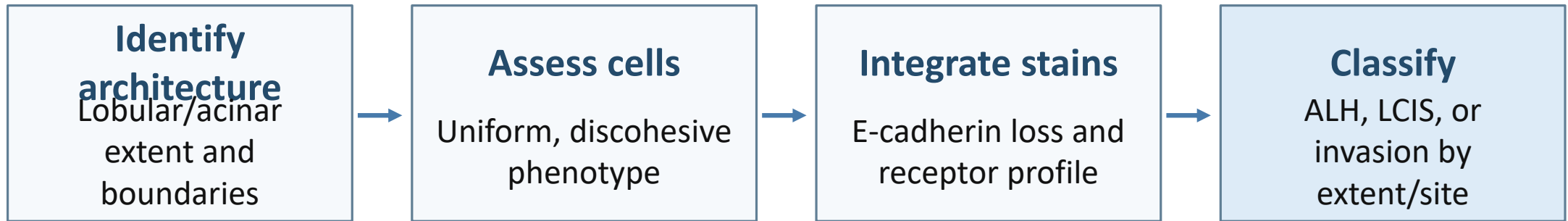
LCIS and DCIS: Essential diagnostic differences

Feature	Classic LCIS	DCIS
Cell cohesion	Dyscohesive	Typically cohesive epithelial proliferations
E-cadherin	Usually lost	Distinguishing expression pattern retained
Screening	Often incidental	Frequently mammographic calcifications
Risk distribution	Either breast	Often local ipsilateral recurrence risk

What immunohistochemistry can clarify

- E-cadherin can support lobular versus ductal epithelial differentiation.
- ER and PR describe a common receptor profile of LCIS.
- HER2 is usually negative in LCIS.
- Neither adhesion nor receptor staining replaces evaluation for invasion.

Classic lobular neoplasia: An interpretive sequence



Schematic reasoning aid derived from morphologic distinctions in the source; Not a formal clinical algorithm.

ALH versus LCIS: The decisive observation

What they share

- Round, relatively uniform epithelial cells.
- Loss of cohesion; Commonly loss of E-cadherin.
- Confinement to the ductal–lobular system.

What differs

- ALH is histologically less extensive.
- Classic LCIS fills and expands >50% of acini in a lobular unit.
- Classification depends on extent, not a novel cell type.

LCIS versus invasive lobular carcinoma

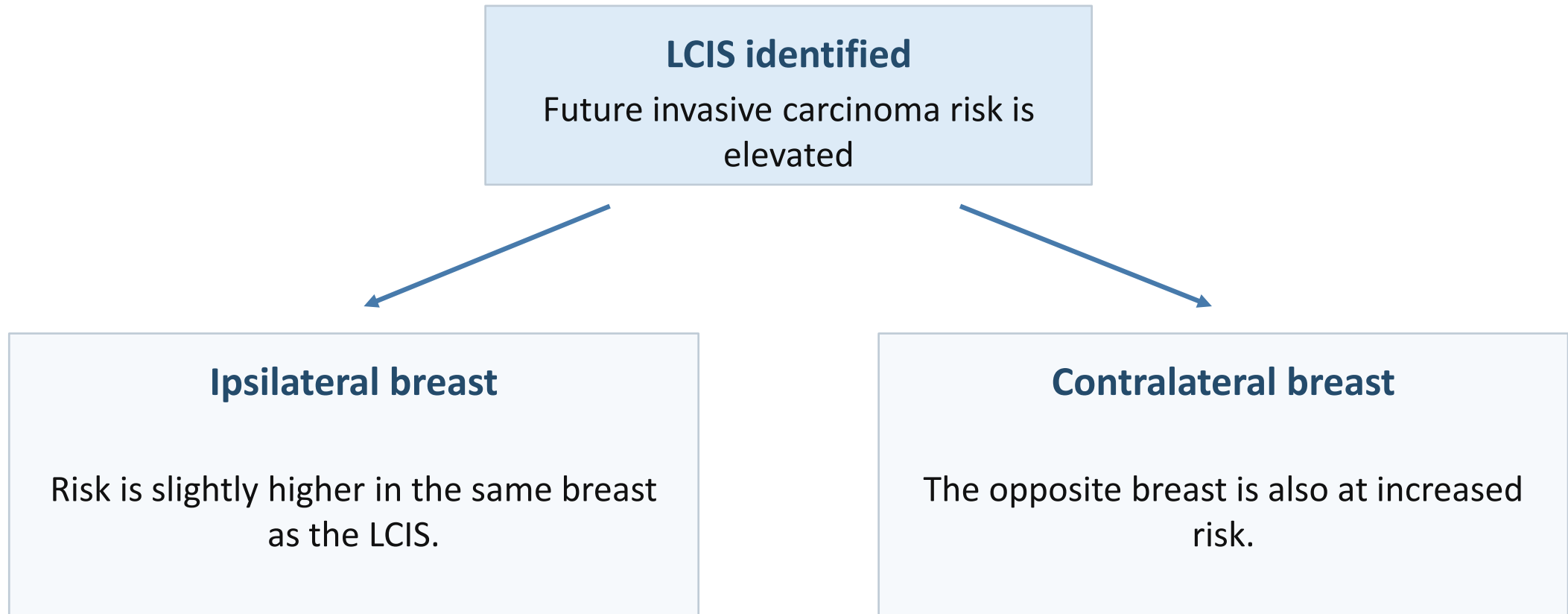
LCIS

- Cells occupy ductal and lobular compartments.
- The in situ basement membrane boundary remains.
- An in situ risk lesion with possible local precursor relationship.

Invasive lobular carcinoma

- Cells breach the in situ compartment and infiltrate stroma.
- Cytology may resemble that of LCIS.
- Invasion is an architectural, not merely nuclear, diagnosis.

LCIS predicts risk in either breast



Relative risk: Eight- to tenfold

8–10×

An 8- to 10-fold higher invasive breast carcinoma risk in patients with classic LCIS than in the general population.

Relative risk is not certainty of cancer

- An 8–10× relative risk compares populations, not a prediction for an individual patient.
- Relative risk must be distinguished from the annual rate at which cancers appear.
- Most risk discussions require patient-level context beyond a single tissue finding.
- LCIS is clinically important even though progression to invasion is not inevitable.

Reported invasive carcinoma rate

Approximately 1% per year

Robbins gives this approximate annual rate following classic LCIS; It is not a guarantee of a constant personal risk.

The annual rate resembles low-grade DCIS

Classic LCIS

- Invasive carcinoma appears at about 1% per year description.
- Subsequent disease may arise in either breast.

Untreated low-grade DCIS

- A similarly approximate annual invasion rate.
- Invasive carcinomas commonly occur in the same breast location.

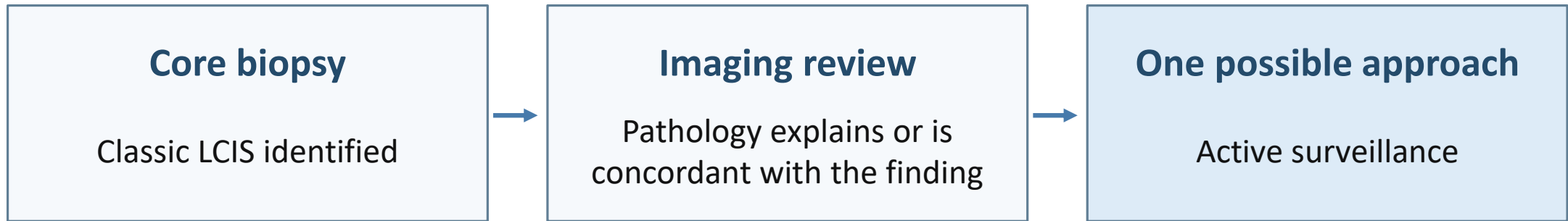
LCIS is both a risk marker and a possible precursor

- Bilateral risk supports the interpretation of LCIS as a marker of general breast susceptibility.
- Shared mutations with synchronous invasive carcinoma support a precursor relationship in some cases.
- These two roles are not mutually exclusive.
- The distinction matters when interpreting the value of local excision.

Why removing LCIS has an uncertain effect

- LCIS conveys risk to both breasts, not only the sampled focus.
- It remains unclear whether surgical removal reduces that risk.
- This differs from the rationale for routine local treatment of DCIS.
- Management therefore depends on LCIS subtype and clinicoradiologic context.

Classic LCIS on core biopsy: Imaging correlation

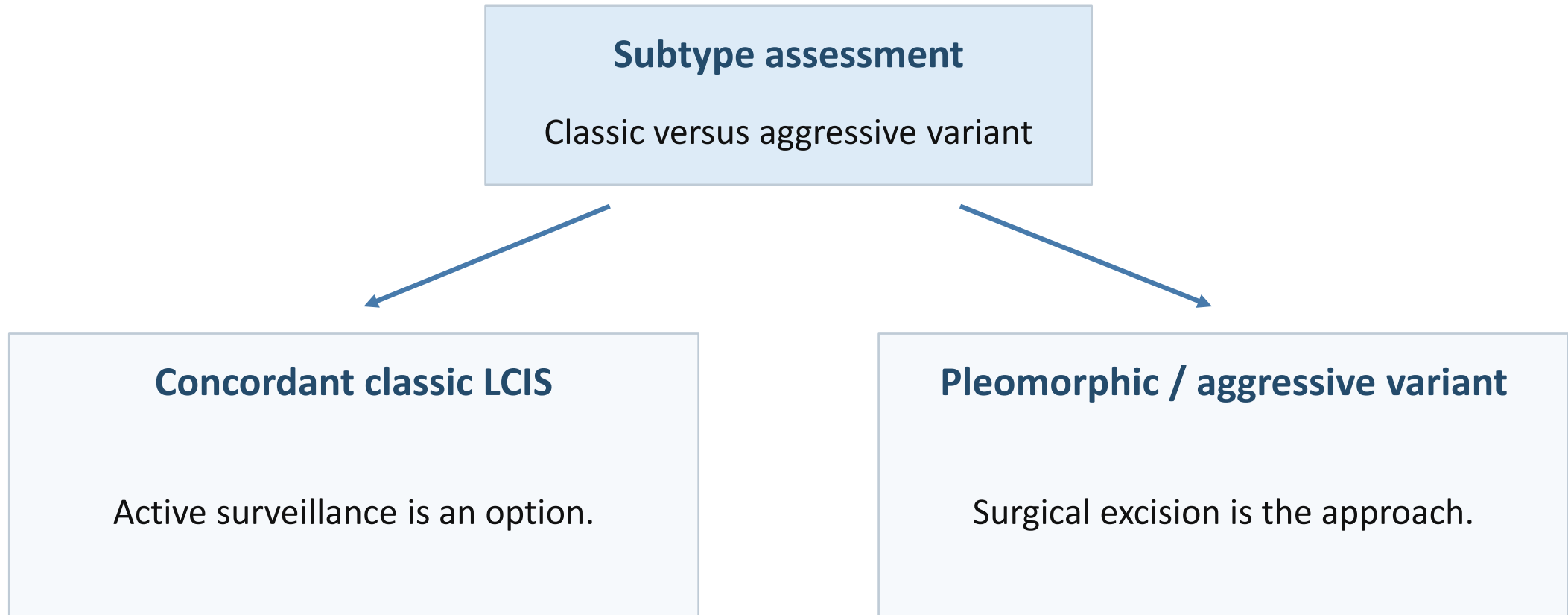


Surveillance in selected imaging-concordant classic LCIS; This is not a patient-specific recommendation.

Why concordance matters in core biopsy

- A classic LCIS diagnosis must be considered in the context of the lesion being sampled.
- In imaging-concordant cases, a very low probability of associated invasion.
- This explains why active surveillance may be appropriate for selected classic LCIS.
- The textbook does not supply a universal rule for all discordant cases.

Aggressive LCIS variants are treated differently



Reasons to excise pleomorphic LCIS

- Pleomorphic LCIS is classified among more aggressive lobular in situ variants.
- It may present with calcifications and necrosis, unlike classic LCIS.
- Robbins recommends surgical excision for more aggressive variants.
- Do not transfer the classic LCIS surveillance approach automatically to pleomorphic LCIS.

Other risk-management strategies

- Robbins mentions mastectomy in selected LCIS cases.
- The text also identifies endocrine therapy as an option for some patients.
- The adjacent precursor-lesion discussion names estrogen antagonists such as tamoxifen for risk reduction.
- These choices require individual clinical evaluation; This lecture does not prescribe therapy.

Local disease versus bilateral-risk strategy

DCIS — predominantly local strategy

- Subsequent invasive disease usually arises at the same site.
- Complete surgical removal is a central component of treatment.
- Local recurrence is a major management concern.

LCIS — bilateral-risk perspective

- Subsequent invasive disease can arise in either breast.
- Benefit of excision of classic LCIS is less certain.
- Risk reduction and surveillance become key considerations.

Case 1: An incidental lobular lesion

A screening-guided breast core biopsy performed for an unrelated radiologic finding contains small, uniform, loosely cohesive cells filling most acini. E-cadherin expression is lost. Imaging and pathology are concordant. Which interpretation best fits Robbins?

- Classic LCIS with surveillance as a possible option
- Invasive lobular carcinoma established by E-cadherin loss alone
- Mandatory excision because all LCIS behaves like high-grade DCIS

Case 1: Interpretation

Classic LCIS; Surveillance may be an option

- Characteristic dyscohesive cells fill/expand most acini.
- E-cadherin loss supports the lobular phenotype.
- No invasion is established by these data.
- Concordant classic LCIS on core biopsy is eligible for surveillance in selected cases.

Case 2: Calcifying in situ lobular lesion

A breast lesion has calcifications and necrosis. Histologic review identifies a pleomorphic lobular epithelial proliferation. Which source-based response is most appropriate?

- Classify it as classic LCIS because lobular lesions never calcify
- Recognize an aggressive LCIS variant and consider surgical excision
- Conclude automatically that the lesion is invasive carcinoma

Case 2: Interpretation

Consider pleomorphic LCIS and surgical excision

- Pleomorphic LCIS may show necrosis and calcifications.
- These features contradict the usual classic LCIS presentation, not the lobular diagnosis.
- Excision of aggressive variants from surveillance in selected classic LCIS.

Morphologic synthesis

Cells

Uniform round/oval cells,
small nucleoli, dyscohesion

Architecture

Acini filled and expanded;
Pagetoid ductal spread
possible

Stains

E-cadherin usually lost;
ER/PR often positive; HER2
usually negative

Applies principally to classic LCIS, with variant-specific exceptions.

Clinical synthesis

Recognition

Often incidental; Classic form rarely calcifies

Risk

8–10× increased risk; Either breast; Approximately 1%/year

Management

Surveillance can be considered for concordant classic LCIS; Aggressive variants are excised

Statistics and options reproduce Robbins, not externally updated guidance.

Source and further reading

- Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th edition (2026), Chapter 23: The Breast.
- LCIS subsection, printed page 953, continuing onto page 954.
- Relevant parent sections: precursor lesions, carcinoma in situ, and DCIS.
- Original textbook Fig. 23.14 should be consulted for genuine H&E and E-cadherin immunohistochemical examples.