

Endometrial Hyperplasia

Mechanism • morphology • malignant potential • interpretation

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Learning outcomes

- Interpret the gland-to-stroma relationship in endometrial tissue.
- Explain persistent estrogenic stimulation and PTEN-related signaling.
- Differentiate hyperplasia without atypia from atypical hyperplasia/EIN.
- Connect morphology to carcinoma risk and clinical decisions.

The defining lesion

Abnormal proliferation of endometrial glands relative to the stroma

The diagnostic concept is architectural: Glands occupy disproportionately more tissue.

Two compartments of the endometrium

Glandular epithelium

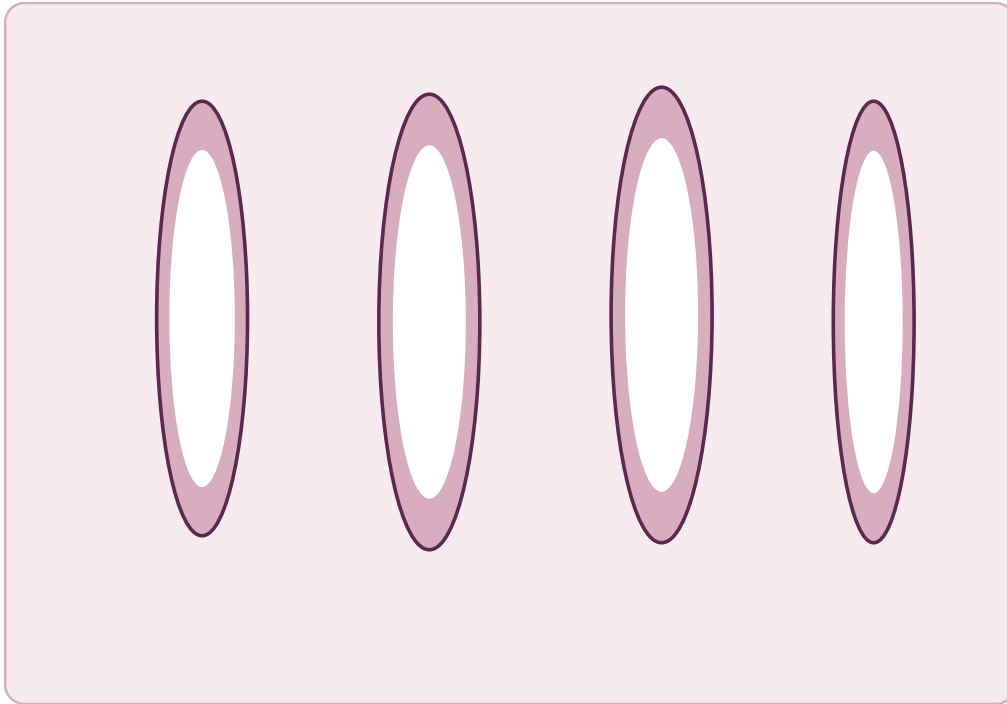
- Hormone-responsive epithelial structures
- Proliferation alters the glandular component

Endometrial stroma

- Cellular supporting tissue between glands
- Acts as the reference compartment for gland crowding

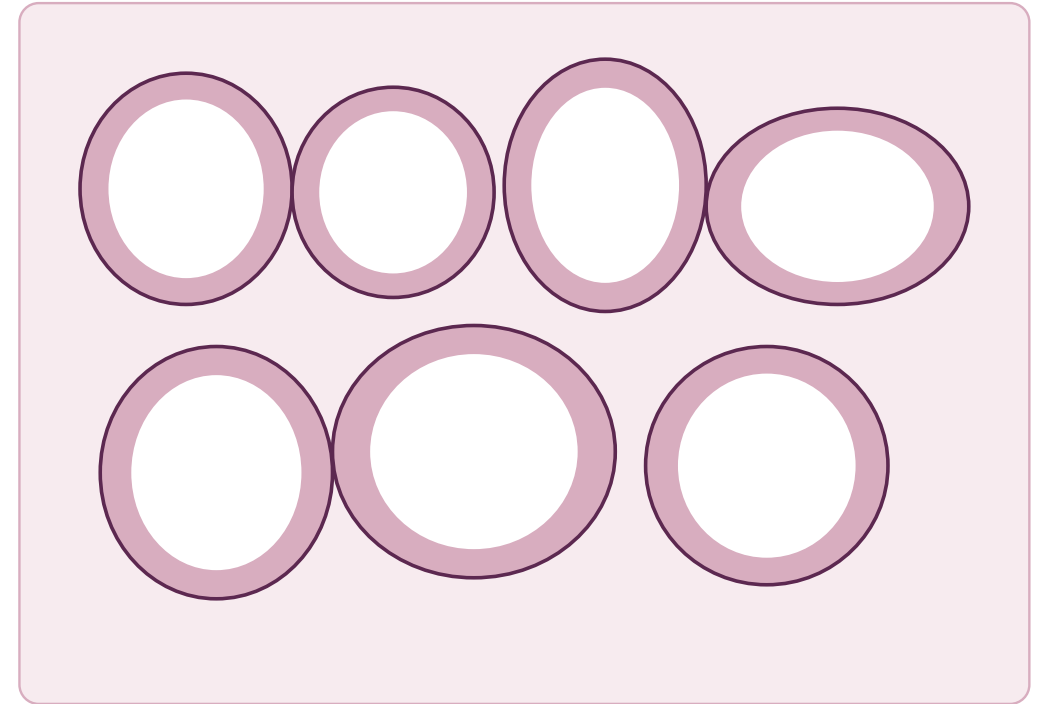
Architecture: Baseline versus hyperplasia

Reference



Original schematic — not an H&E micrograph

Hyperplasia



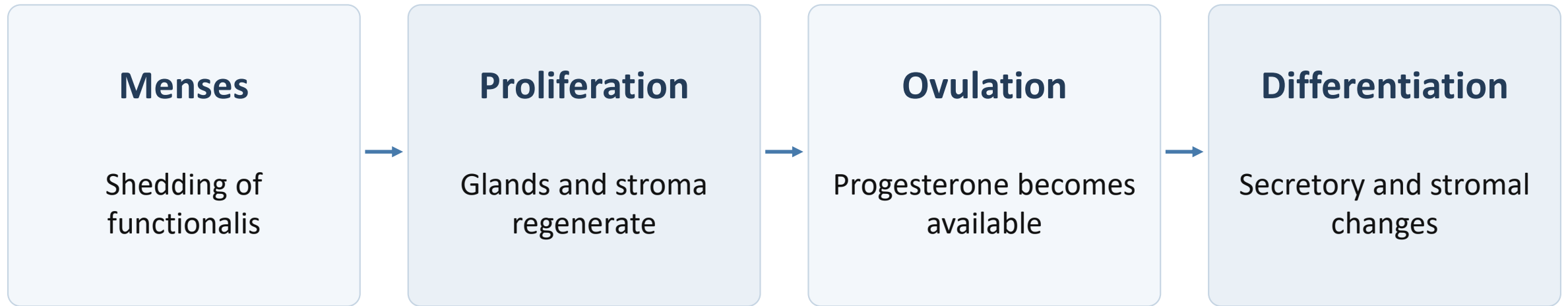
Original schematic — not an H&E micrograph

Compare the relative amount of stroma between gland profiles.

Abnormal uterine bleeding: A diagnostic clue

- Endometrial hyperplasia is a clinically important cause of abnormal bleeding.
- The same symptom may arise from hormonal disorders, polyps, inflammation or neoplasia.
- Histologic classification is needed because morphology predicts different clinical concerns.

Normal cycle: Gland proliferation and differentiation



Hyperplasia develops in a different hormonal context: Proliferation persists without adequate counter-regulation.

Proliferative endometrium is not hyperplasia

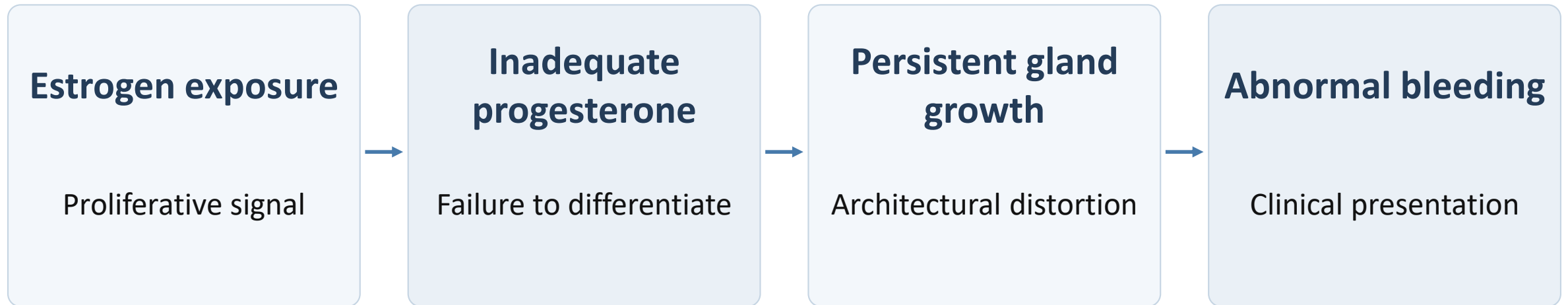
Physiologic proliferation

- Straight, tubular glands
- Regular pseudostratified epithelium
- Stroma also proliferates

Pathologic hyperplasia

- Glands increase relative to stroma
- Size and shape become irregular
- Estrogenic stimulation persists

Unopposed estrogen: The causal sequence



A hormonal imbalance can create the setting for both nonatypical hyperplasia and endometrioid tumorigenesis.

Anovulation prolongs estrogenic stimulation

- Anovulation means that no corpus luteum forms.
- The usual postovulatory progesterone-associated morphologic response does not develop.
- Repeated cycles of estrogen-dominant proliferation may cause architectural abnormalities.

Anovulatory endometrium versus hyperplasia

Anovulatory pattern

- Proliferative-type glands can persist
- Secretory transformation is absent
- Mild cystic changes may resolve

Hyperplastic lesion

- Gland-to-stroma proportion is increased
- Glands may be irregular or crowded
- Diagnostic focus includes atypia

Do not diagnose atypical hyperplasia from hormonal context alone.

Sources of prolonged estrogenic influence

Anovulation

Repeated cycles without a progesterone-dominant secretory phase.

Endogenous estrogen

Obesity and hormonally active ovarian conditions.

Exogenous exposure

Prolonged administration of estrogenic substances.

Obesity and peripheral estrogen generation

- Peripheral conversion of androgens to estrogens is a recognized mechanism.
- Excess estrogen availability can sustain endometrial proliferation.
- Obesity therefore contributes to the endocrine setting in which hyperplasia develops.

Polycystic ovarian syndrome

- PCOS is among the conditions linked to endometrial hyperplasia.
- Anovulation supplies the mechanistic connection in many affected individuals.
- Endometrial findings must be interpreted in the context of the hormone milieu.

Menopause and estrogen-associated exposure

- Menopause is listed among the clinical settings associated with hyperplasia.
- The relevant lesion-driving factor is persistent estrogenic stimulation, not age alone.
- Abnormal bleeding in this setting requires attention because carcinoma is a differential diagnosis.

Granulosa cell tumors as a hormonal source

- Functioning ovarian granulosa cell tumors can produce estrogen.
- Their endocrine activity can stimulate uterine glandular proliferation.
- An ovarian lesion may therefore underlie an endometrial abnormality.

Ovarian cortical stromal hyperplasia

- Excessive ovarian cortical function is included among the associated conditions.
- The pathophysiologic link is increased endogenous estrogenic activity.
- Etiologic assessment should not be confined to the endometrial compartment.

Exogenous estrogenic substances

- Prolonged estrogenic therapy can provide sustained proliferative signaling.
- The balance between estrogenic and progesterone-associated influences is clinically relevant.
- Exposure history is part of understanding the histologic lesion.

Etiology: Three useful mechanisms

Hormone-cycle failure

Anovulation prevents ordinary progesterone-linked differentiation.

Hormone overproduction

Adipose conversion or ovarian endocrine production raises estrogenic influence.

Hormone administration

Exogenous estrogen adds sustained stimulation.

Hormonal drive and genetic alteration

Hormonal background

- Provides a proliferative environment
- Includes anovulation and excess estrogen
- Helps explain benign glandular expansion

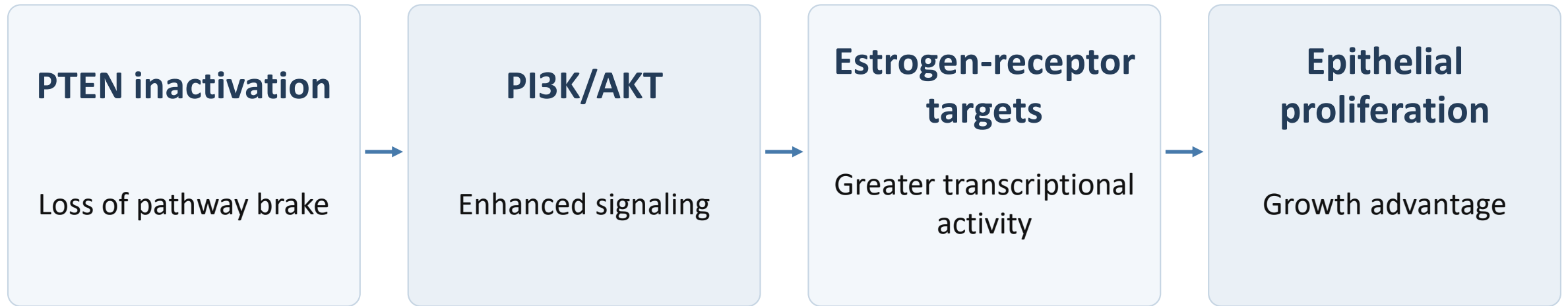
Molecular alteration

- Can establish clonal growth advantage
- May be shared with endometrioid carcinoma
- Does not itself confirm future progression

PTEN: Growth-suppressive function

- PTEN is a tumor suppressor encoding a lipid phosphatase.
- Its normal activity restrains PI3K/AKT signaling.
- Loss of PTEN removes an inhibitory control on cellular growth signaling.

PTEN loss and growth signaling



Conceptual mechanism based on the signaling relationships.

Estrogen-receptor and PI3K/AKT convergence

- PI3K/AKT signaling can enhance estrogen-receptor-dependent transcription.
- PTEN loss may amplify responses to estrogenic trophic signals.
- This provides a plausible link between molecular mutation and hormone-sensitive tissues.

PTEN mutations in hyperplasia

>20%

Hyperplasia lesions

PTEN mutations in more than one fifth of endometrial hyperplasias, with and without atypia. This is a frequency observation—not an individual risk estimate.

PTEN alterations in carcinoma

30–80%

Endometrial carcinomas

A broad reported range across endometrial carcinoma cohorts indicates that PTEN changes are common. The range must not be used as a progression probability.

An early molecular event is not a crystal ball

What PTEN supports

- An early role in endometrial neoplasia
- Mechanistic overlap between lesions
- Clonal molecular pathway relevance

What PTEN does not establish

- It does not predict which individual hyperplasia progresses
- A mutation alone does not diagnose carcinoma
- Mutation prevalence is not progression risk

Cowden syndrome: An inherited PTEN context

- Cowden syndrome is associated with germline PTEN alteration.
- Affected individuals have increased occurrence of endometrial carcinoma and certain other tumors.
- A germline predisposition is distinct from an acquired mutation within an endometrial lesion.

Germline and acquired PTEN alterations

Germline alteration

- Present in constitutional DNA
- Associated with inherited susceptibility
- Illustrated by Cowden syndrome

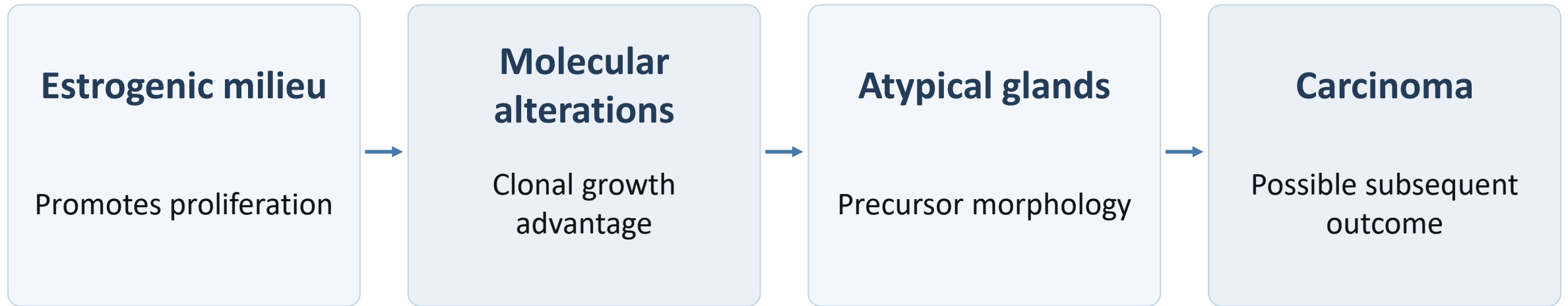
Somatic alteration

- Acquired within glandular cells
- Can occur in hyperplasia and carcinoma
- May contribute to clonal proliferation

Shared driver mutations support a precursor relationship

- Molecular studies identify acquired driver mutations in hyperplasia and carcinoma.
- Matching alterations in paired atypical hyperplasia and carcinoma support related clones.
- The evidence strengthens the concept of atypical hyperplasia/EIN as a precursor lesion.

From proliferation to neoplasia: Conceptual model



This conceptual progression is not inevitable; Many hyperplasias do not progress.

A classification with clinical consequences

Without atypia

Crowded glands with predominantly proliferative-type cytology; Low progression risk.

Atypical hyperplasia / EIN

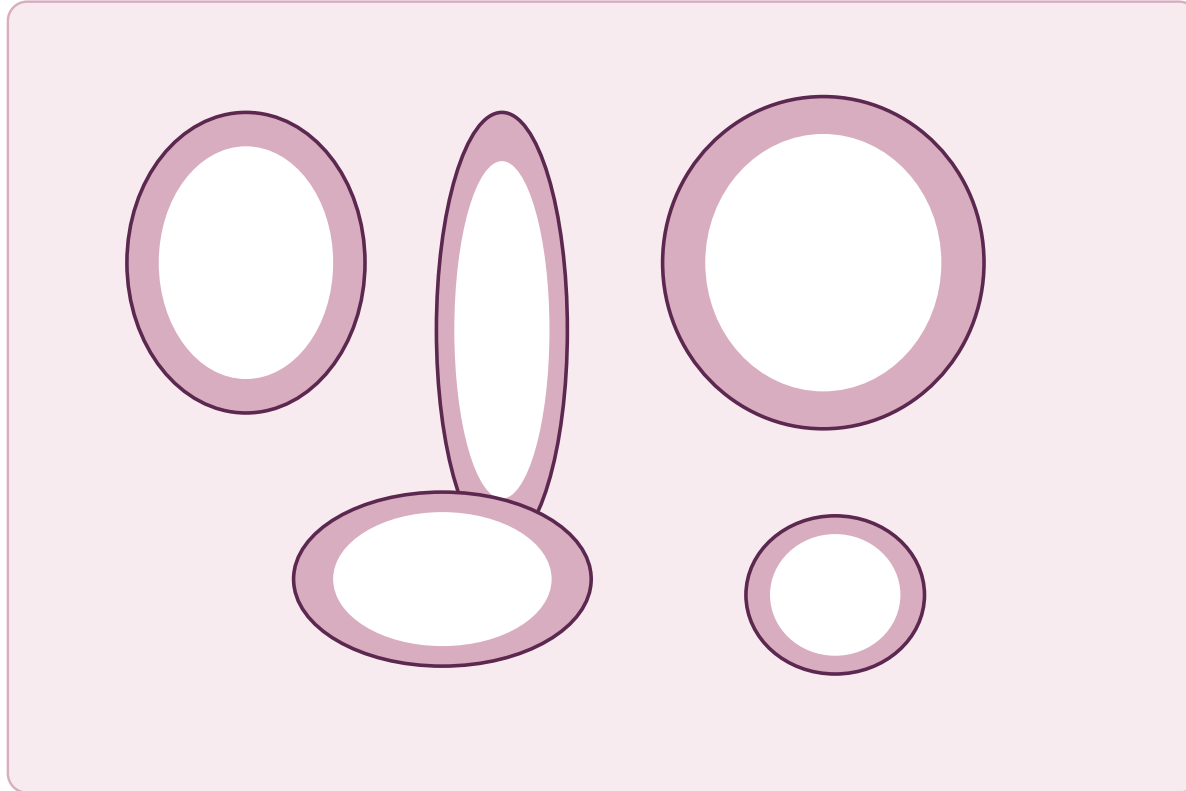
Complex crowded glands and cytologic atypia; Substantial carcinoma association.

Morphology begins with the ratio

More glands relative to intervening stroma

Architectural interpretation comes before assessing the epithelial nuclei.

Hyperplasia without atypia: Distribution of glands



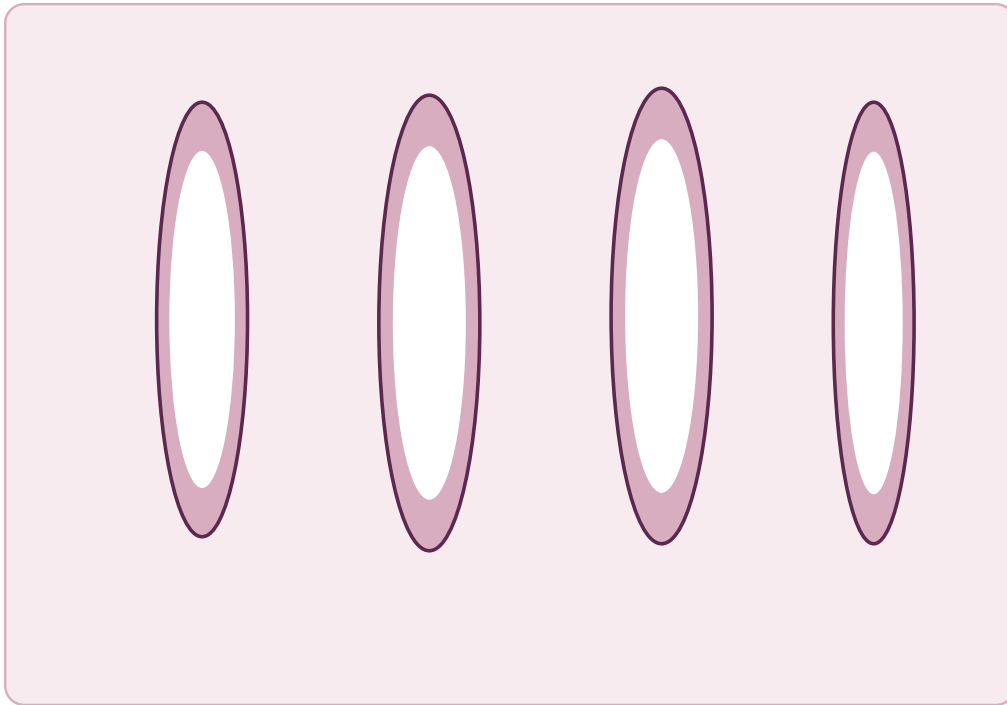
Original schematic — not an H&E micrograph

Crowding is variable

- A greater gland-to-stroma ratio than normal proliferation.
- Gland profiles differ in size and contour.
- Some intervening stroma is usually visible.

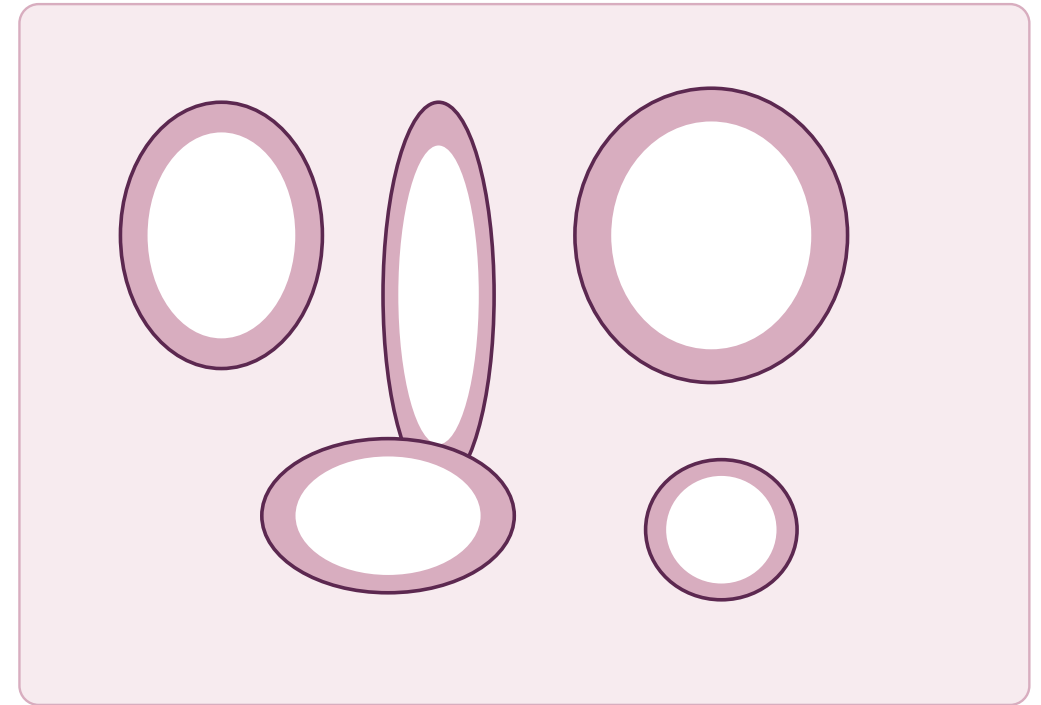
Gland size and shape: Schematic contrast

Typical profiles



Original schematic — not an H&E micrograph

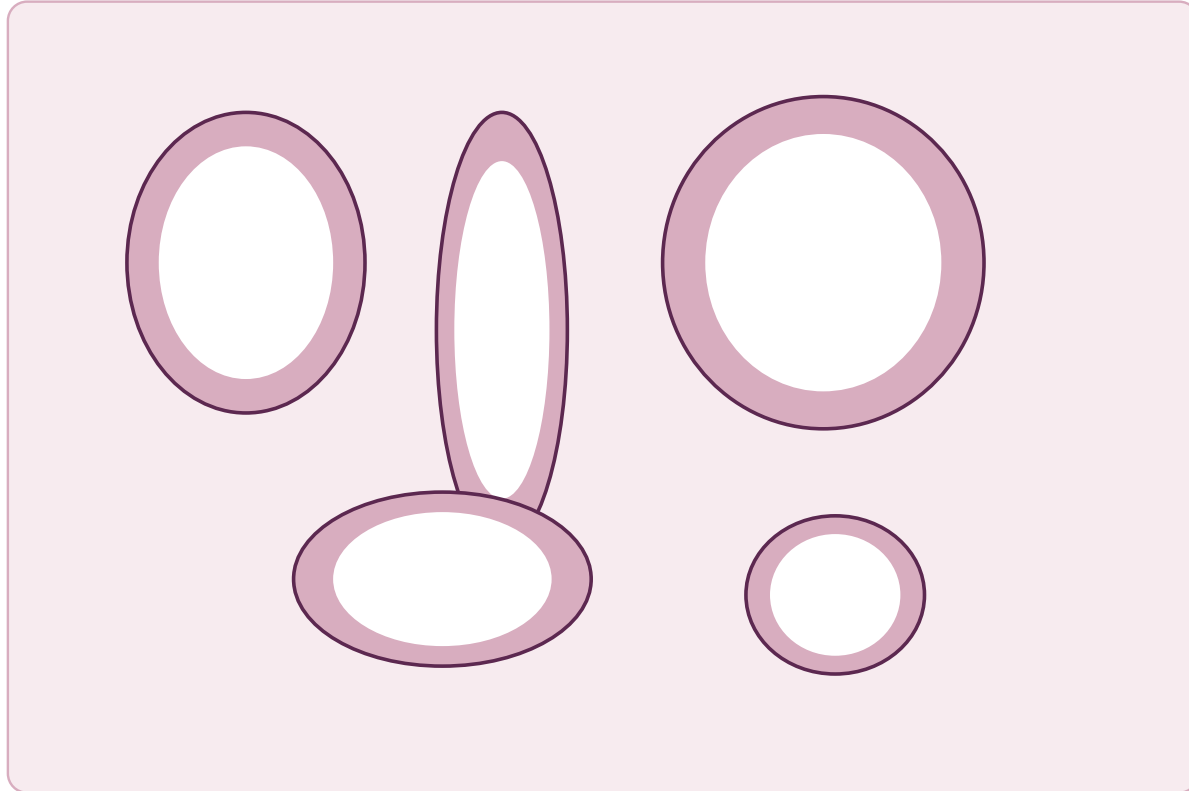
Variable profiles



Original schematic — not an H&E micrograph

In nonatypical hyperplasia, gland dilation and shape variability are typical features.

Cystically dilated glands



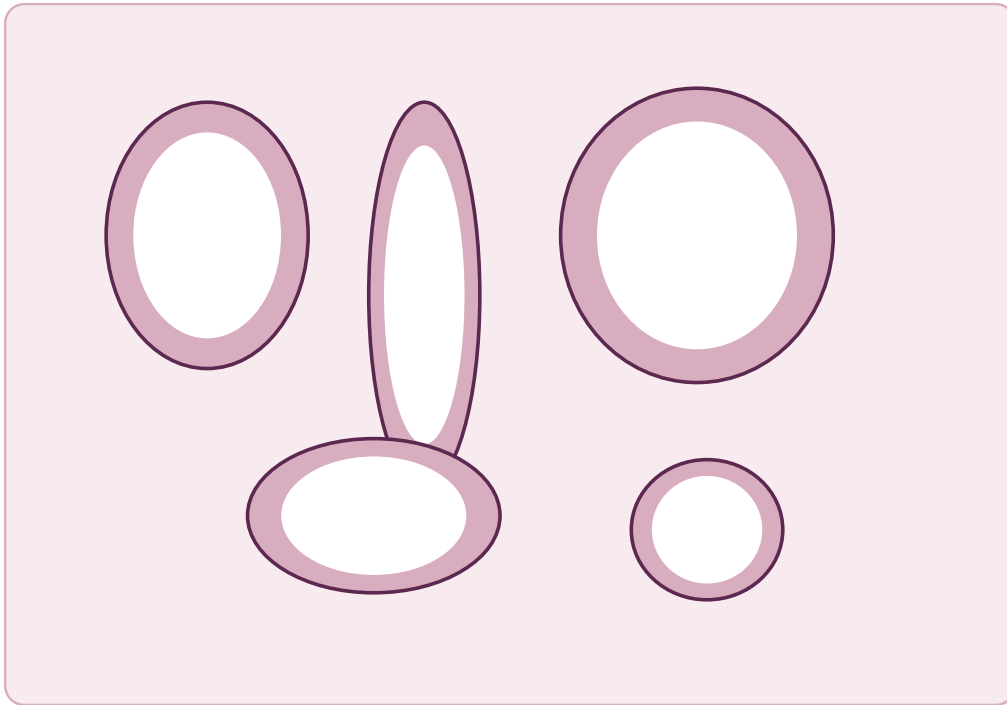
Original schematic — not an H&E micrograph

Dilated gland lumina

- Some glands are enlarged relative to adjacent glands.
- Dilation contributes to architectural irregularity.
- Gland dilation alone does not establish atypia.

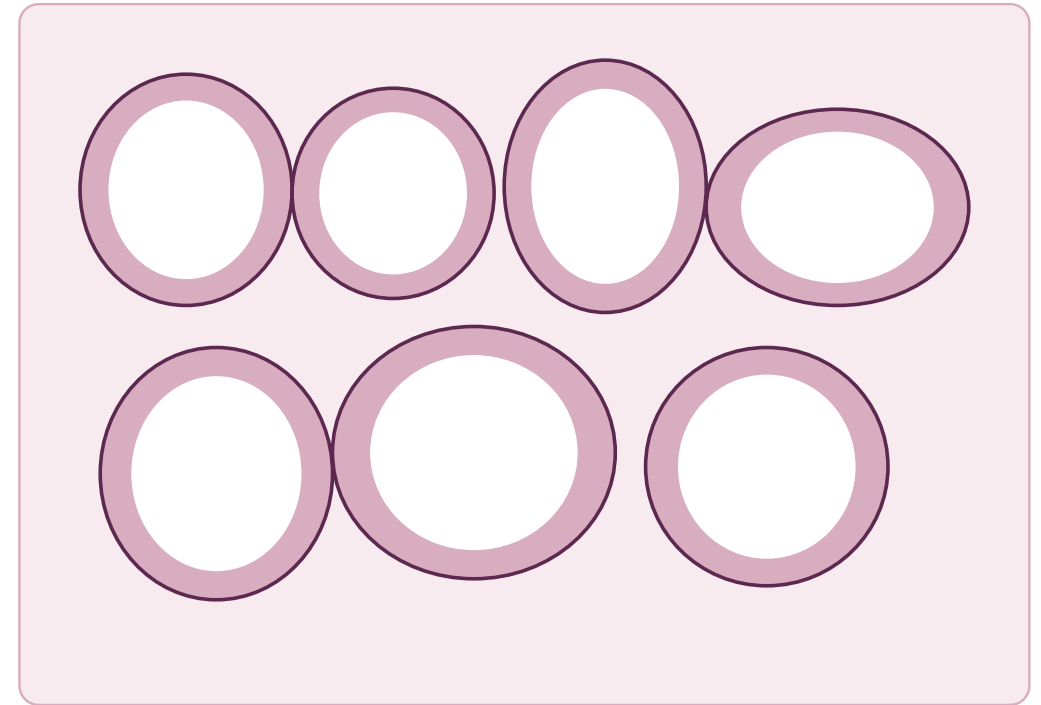
Focal back-to-back glands can occur without atypia

With stroma



Original schematic — not an H&E micrograph

Focally crowded



Original schematic — not an H&E micrograph

Focal crowding must be interpreted alongside the nuclear features.

Nuclei in hyperplasia without atypia

- Epithelial nuclei retain features resembling proliferative endometrium.
- Architectural complexity varies and is not synonymous with nuclear atypia.
- Nuclear morphology is therefore essential for the two-category classification.

After estrogen withdrawal: Cystic atrophy

- Nonatypical hyperplasia reflects persistent estrogenic stimulation.
- When estrogenic stimulation is withdrawn, hyperplasia may evolve into cystic atrophy.
- The tissue response illustrates the hormonal dependence of these lesions.

Progression of hyperplasia without atypia

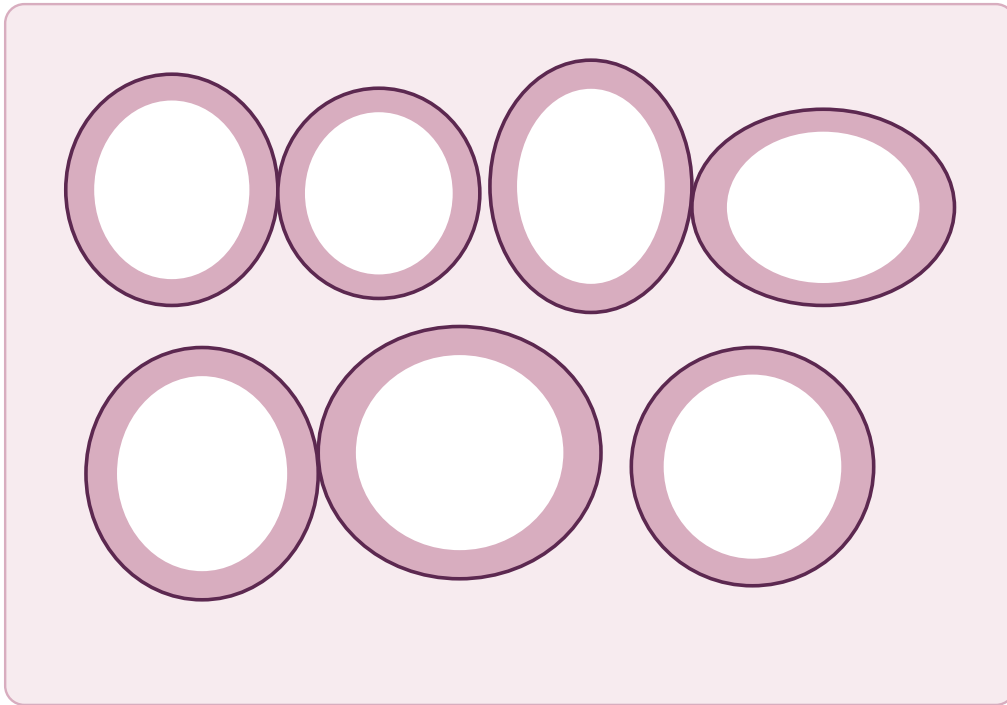
~1–3%

Reported progression

Robbins characterizes progression to adenocarcinoma as rare. This estimate refers to hyperplasia without atypia and must not be applied to atypical hyperplasia/EIN.

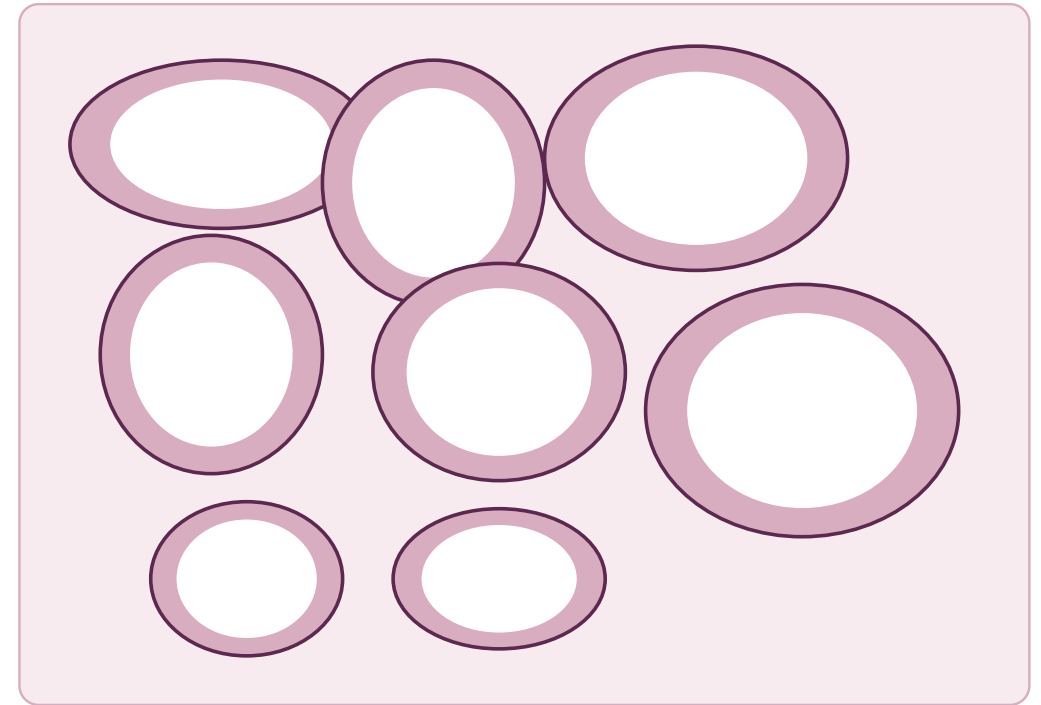
Atypical hyperplasia: Complex gland architecture

Without atypia



Original schematic — not an H&E micrograph

With atypia



Original schematic — not an H&E micrograph

Greater crowding and branching are features of atypical hyperplasia/EIN.

Architectural atypia: Branching and complexity

- Atypical hyperplasia contains complex patterns of proliferating glands.
- Glands are often arranged back-to-back.
- Irregular branching produces complex gland outlines.

Cellular orientation: The loss of polarity

- Normal endometrial glandular cells maintain orientation to the basement membrane.
- In atypical hyperplasia, epithelial cells become rounded and lose this orientation.
- This cytologic change adds evidence beyond gland crowding alone.

Atypical nuclei: Vesicular chromatin

- Nuclei may appear rounded with open, vesicular chromatin.
- Conspicuous nucleoli are an additional characteristic.
- Nuclear differences help separate atypical from nonatypical hyperplasia.

Architecture and cytology are complementary

Architectural axis

- Gland-to-stroma ratio
- Back-to-back glands
- Branching and irregular gland shape

Cytologic axis

- Cell polarity
- Nuclear shape and chromatin
- Visibility of nucleoli

Atypia is a nuclear diagnosis interpreted within glandular architecture.

WHO two-category classification

Feature	Without atypia	Atypical hyperplasia / EIN
Architecture	Crowding; Variable dilation	Complex; Often back-to-back
Nuclear appearance	Proliferative-like	Rounded; Vesicular; Nucleoli
Clonality	Not required for diagnosis	Clonal outgrowth emphasized
Clinical implication	Rare progression	High concern for carcinoma

Why EIN matters beyond morphology

- Atypical hyperplasia/EIN represents clonal proliferation with multiple genetic alterations.
- Its morphologic and molecular features overlap with well-differentiated endometrioid carcinoma.
- This explains both its precursor designation and the challenge of excluding carcinoma.

Atypical hyperplasia versus well-differentiated carcinoma

Atypical hyperplasia / EIN

- Complex, crowded glandular proliferation
- Nuclear atypia
- May coexist with carcinoma

Endometrioid carcinoma

- Morphologic and genetic overlap
- Cannot always be excluded in limited tissue
- Definitive distinction may require hysterectomy

Concurrent carcinoma at hysterectomy

**Up to
40%**

After an EIN diagnosis

That up to 40% of patients diagnosed with atypical hyperplasia have carcinoma identified in the hysterectomy specimen. This is a coexistence estimate, not a prospective progression rate.

Sampling can limit certainty

- A small sample provides only part of the endometrial tissue architecture.
- Atypical hyperplasia and well-differentiated carcinoma may be difficult to distinguish in that material.
- A final hysterectomy specimen can reveal carcinoma not established on the preceding biopsy.

Endometrioid carcinoma: The relevant malignant endpoint

- Endometrioid carcinoma is the most common endometrial carcinoma type.
- Many lesions occur in the same estrogen-associated context as endometrial hyperplasia.
- Atypical hyperplasia may represent an identifiable precursor to this carcinoma.

Shared mutations reinforce biologic continuity

- PTEN, ARID1A, PIK3CA and KRAS alterations in paired precursor and carcinoma components.
- Their shared presence supports a related clonal origin.
- These observations do not convert any single biomarker into a validated progression test.

Diffuse hyperplasia and a discrete polyp

Endometrial hyperplasia

- Defined by gland-stroma imbalance
- Patterns of gland proliferation and atypia
- Driven often by endocrine influences

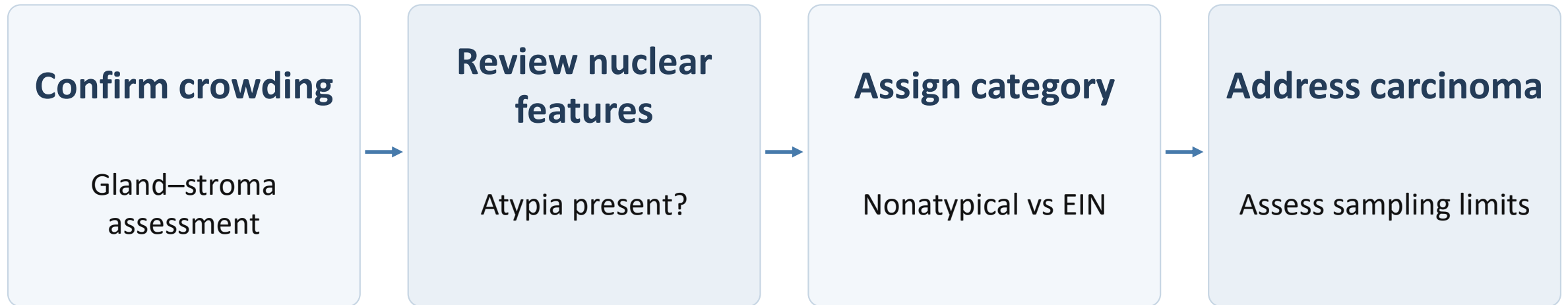
Endometrial polyp

- Localized exophytic endometrial mass
- Projects into uterine cavity
- Distinct gross architecture and possible other associations

Abnormal bleeding: Essential alternatives

Process	Source-based distinction
Anovulatory endometrium	Hormonal bleeding with persistent proliferative pattern
Endometrial polyp	Focal exophytic lesion in the cavity
Chronic endometritis	Inflammatory process with endometrial plasma cells
Endometrial hyperplasia	Increased gland-to-stroma ratio $\pm$ atypia
Endometrial carcinoma	Malignant neoplastic lesion

Teaching approach to a hyperplastic sample



Teaching sequence only—not a complete diagnostic or management guideline.

Why management differs by category

Without atypia

- Rare carcinoma progression
- Often hormonally responsive lesion
- Requires appropriate clinical interpretation

Atypical hyperplasia / EIN

- Substantial concurrent carcinoma concern
- Hysterectomy often used
- Fertility preservation needs close follow-up

Atypical hyperplasia: Hysterectomy

- Hysterectomy as a standard management option for atypical hyperplasia.
- The approach also addresses uncertainty about an unsampled carcinoma.
- Management is determined by clinical circumstances, not morphology alone.

Fertility-preserving approach in selected patients

- Young patients desiring fertility may receive a trial of progestin therapy.
- Close follow-up is necessary to evaluate lesion regression.
- This is a selected-patient alternative rather than equivalent exclusion of carcinoma.

Persistent atypia changes the management discussion

- Failure of regression after a fertility-preserving approach prompts consideration of uterine removal.
- Hysterectomy after unsuccessful progestin management.
- The pathologic endpoint of interest is resolution versus persistence of atypical disease.

Case 1: Hormonal setting

Illustrative teaching vignette

An adult with repeated anovulatory cycles develops irregular uterine bleeding. The sample contains enlarged irregular glands, but nuclei resemble proliferative endometrium.

Which classification is best supported—and why?

Case 1: Interpret both components

- The hormonal context supports prolonged estrogenic stimulation.
- Increased gland crowding with proliferative-type nuclear features is compatible with hyperplasia without atypia.
- Nuclear atypia is not established solely by gland shape or cystic dilation.

Case 2: Crowding plus atypia

Illustrative teaching vignette

An endometrial sample shows crowded branching glands, rounded nuclei, vesicular chromatin and conspicuous nucleoli.

What is the category, and what key limitation follows?

Case 2: Classify and interpret limitations

- The architectural and nuclear findings support atypical hyperplasia/EIN.
- Its overlap with well-differentiated endometrioid carcinoma prevents certainty in some limited samples.
- Carcinoma at hysterectomy in up to 40% of such cases.

Case 3: The PTEN inference trap

Illustrative teaching vignette

An endometrial hyperplasia sample carries a PTEN alteration. A colleague states that carcinoma progression is now inevitable.

Is that conclusion justified by Robbins?

Case 3: Mutation is not destiny

- PTEN inactivation is common in hyperplasia and carcinoma.
- Its occurrence supports an early molecular role in tumorigenesis.
- PTEN alteration does not predict which hyperplasia progresses to carcinoma.

Five diagnostic propositions

Hyperplasia is a gland-to-stroma imbalance.

Persistent estrogenic stimulation is the principal etiologic context.

PTEN–PI3K/AKT signaling provides a molecular growth mechanism.

Atypia, not crowding alone, separates the two WHO categories.

EIN requires special attention because concurrent carcinoma is common.

Principal reference and image limitation

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- The uterine corpus, hormonal disorders, hyperplasia and adjacent carcinoma text informed this lecture.
- All tissue architecture drawings are editable teaching schematics, not microscopic evidence.
- Robbins figure 22.23 is discussed conceptually; no copyrighted textbook photomicrographs have been reproduced.