

Endometrioid Endometrial Carcinoma

Etiopathogenesis · precursor lesions · molecular alterations · morphology · clinical correlation

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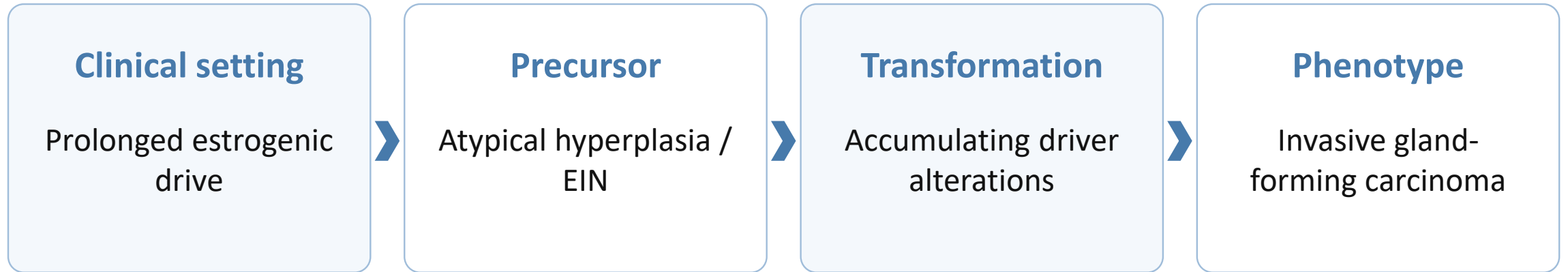
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Learning objectives

After this lecture, learners should be able to:

- Explain the relationship among unopposed estrogen, atypical hyperplasia, and carcinoma.
- Interpret major PI3K/AKT, genomic-instability, and molecular-subtype alterations.
- Recognize glandular architecture, solid growth, and histologic grading.
- Relate invasion, abnormal bleeding, specimen diagnosis, and outcome determinants.

The disease in four linked dimensions



The sequence is a teaching model; Not every tumor follows one obligatory linear trajectory.

Dominant histologic subtype

Endometrioid carcinoma predominates among endometrial cancers.

- Accounts for approximately 80%–85% of endometrial carcinomas.
- Many tumors are well differentiated and resemble proliferative endometrial glands.
- The name describes the endometrial gland-like architecture, not merely tumor location.
- Endometrioid and serous carcinomas have distinct typical biology.

Endometrioid versus serous carcinoma

Endometrioid subtype

- Often in a hyperplasia-related setting
- Frequently estrogen-associated
- Gland-forming appearance is common
- PI3K/AKT alterations prominent

Serous subtype

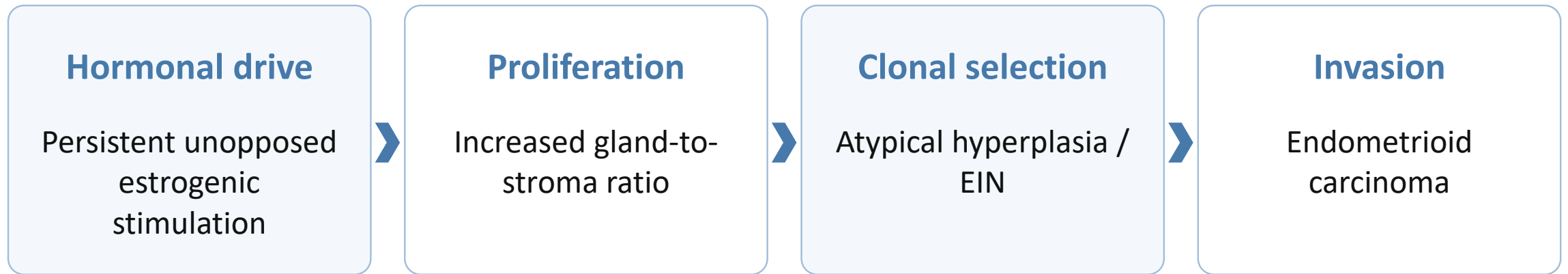
- Typically arises in atrophic endometrium
- Generally occurs at older ages
- High-grade cytology regardless of growth pattern
- Strongly associated with TP53 alterations

What “endometrioid” signifies

Architecture supplies the defining morphological resemblance.

- Well-formed tubular glands resemble those of proliferative endometrium.
- Tumor may form packed, complex, confluent, or invasive glands.
- Increasing solid epithelial growth corresponds to reduced glandular differentiation.
- Grade, extent of spread, and molecular features are separate dimensions.

Estrogen exposure and neoplastic progression



“Precursor” describes risk and clonal linkage; Morphology alone cannot establish that every hyperplasia will become malignant.

Why obesity matters

Peripheral estrogen formation increases the trophic drive on endometrium.

- Obesity as a major association with this carcinoma type.
- Obesity is linked to peripheral conversion of androgens to estrogens.
- Unopposed estrogen stimulation favors endometrial gland proliferation.
- The association with obesity also explains frequent coexistence with metabolic disorders.

Conditions associated with persistent estrogenic stimulation

Endogenous factors

- Obesity: Peripheral estrogen synthesis
- Anovulation and polycystic ovarian syndrome
- Estrogen-producing ovarian processes
- Menopausal hormonal imbalance

Exogenous / contextual factors

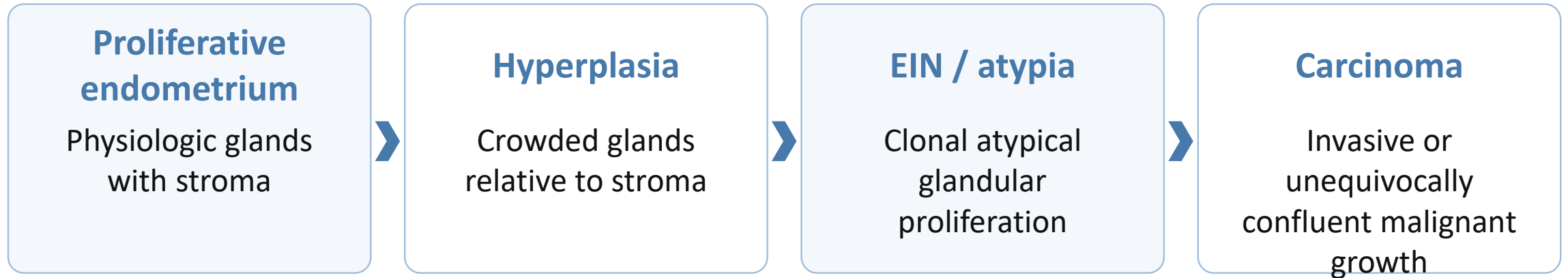
- Prolonged estrogenic medication exposure
- Unopposed estrogenic stimulation is the unifying mechanism
- Individual factors are associations, not equivalent risk magnitude
- Clinical risk assessment needs the full history

Metabolic comorbidity

Do not confuse co-occurrence with histologic diagnostic criteria.

- Hypertension and type 2 diabetes frequently coexist with endometrioid carcinoma.
- Robbins relates this clustering substantially to obesity.
- Neither hypertension nor diabetes identifies an endometrioid tumor histologically.
- Pathologic diagnosis still rests on tissue architecture and cytology.

Precursor-to-carcinoma model



The last distinction can be difficult in limited biopsies.

Hyperplasia without atypia versus atypical hyperplasia

Without atypia

- Increased gland-to-stroma ratio
- Variable gland size; Cystic dilation possible
- Intervening stroma is typically retained
- Progression to cancer is uncommon

Atypical hyperplasia / EIN

- Complex, crowded back-to-back glands
- Nuclear rounding and vesicular chromatin
- Conspicuous nucleoli may be present
- Substantial morphologic overlap with carcinoma

Atypical hyperplasia can coexist with carcinoma

Sampling limitations matter.

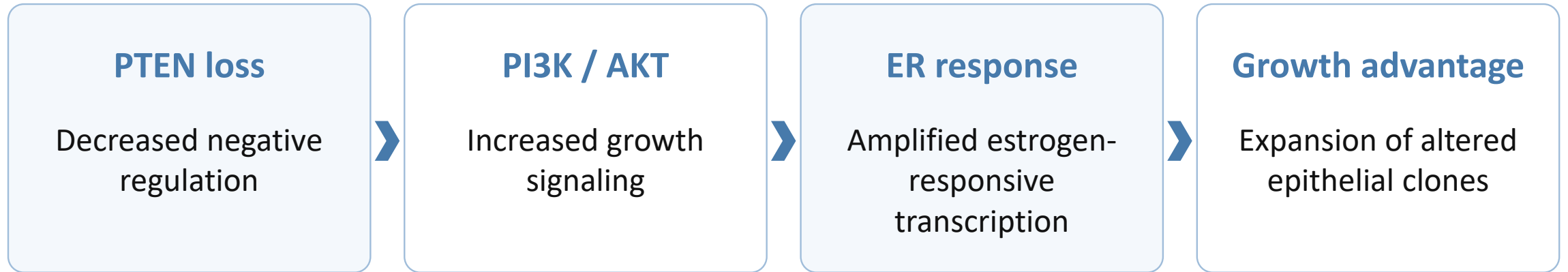
- Carcinoma at hysterectomy in up to 40% of patients diagnosed with atypical hyperplasia.
- The biopsy may sample an atypical precursor while missing a more advanced component.
- Complex crowded glands with atypia warrant careful search for unequivocal carcinoma.
- The estimate is from the source; It is not a universal predictive percentage.

Shared driver mutations establish clonal continuity

Precursor and carcinoma may carry identical acquired mutations.

- Matched atypical hyperplasia and carcinoma have shown shared PTEN, ARID1A, PIK3CA, and KRAS alterations.
- This supports clonal progression rather than merely incidental coexistence.
- Genetic alterations may precede overt invasive carcinoma.
- Additional events contribute to tumor progression.

Central growth-regulatory mechanism



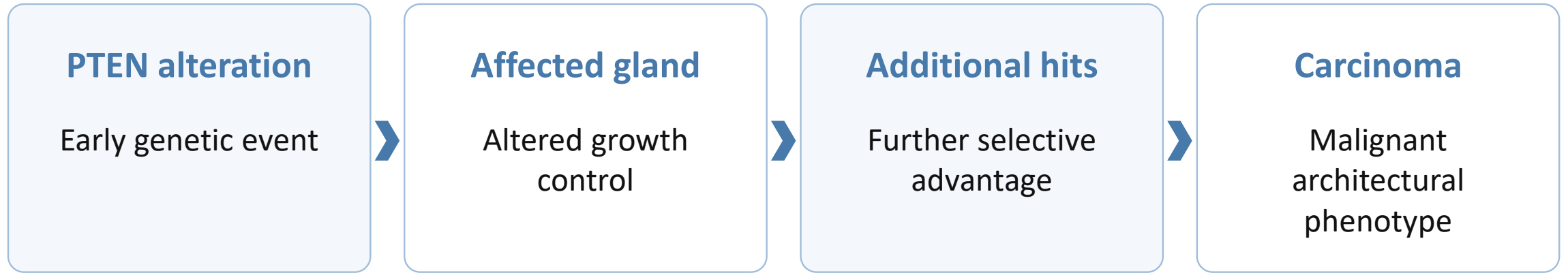
Different molecular lesions can increase signaling through the same pathway.

PTEN: Removal of a critical brake

PTEN normally restrains PI3K/AKT signaling.

- PTEN encodes a lipid phosphatase and acts as a tumor suppressor.
- Loss of PTEN increases PI3K/AKT pathway activity.
- Mutations are found in roughly 30%–80% of endometrioid carcinomas.
- The broad range reflects source-reported variation; It is not a single laboratory cutoff.

PTEN loss does not equal inevitable cancer



PTEN mutations in hyperplasia are not individually predictive of progression.

PIK3CA: Activation of a signaling enzyme

A direct pathway accelerator.

- PIK3CA encodes the catalytic subunit of phosphatidylinositol 3-kinase.
- Activating PIK3CA mutations occur in approximately 40% of endometrioid carcinomas.
- The change increases signaling along the PI3K/AKT axis.
- It may coexist with other mutations that stimulate the same pathway.

KRAS: An additional signaling input

Multiple upstream mutations can converge on a proliferative pathway.

- Activating KRAS mutations occur in approximately one-quarter of cases.
- KRAS activation can also stimulate PI3K/AKT signaling.
- KRAS, PIK3CA, and PTEN changes should not be represented as mutually exclusive.
- Concurrent pathway hits help explain progressive signal intensification.

ARID1A: Chromatin-regulatory alteration

Disordered transcriptional regulation joins signaling activation.

- ARID1A regulates chromatin structure and is inactivated in about one-third of tumors.
- The source links ARID1A loss to oncogenic transcriptional changes associated with PI3K/AKT.
- The precise mechanism is described as unclear.
- ARID1A alterations are also observed in some endometriosis-associated ovarian carcinomas.

Converging molecular drivers

PTEN

Tumor suppressor
loss
Releases a signaling
brake

PIK3CA

Oncogenic activation
Boosts PI3K signaling

KRAS

Upstream activation
Adds proliferative
input

ARID1A

Chromatin
dysregulation
Alters gene
expression

These are not four exclusive genetic categories; Co-occurrence is possible.

Why several mutations may coexist

The amount of pathway signaling can matter, not only its presence.

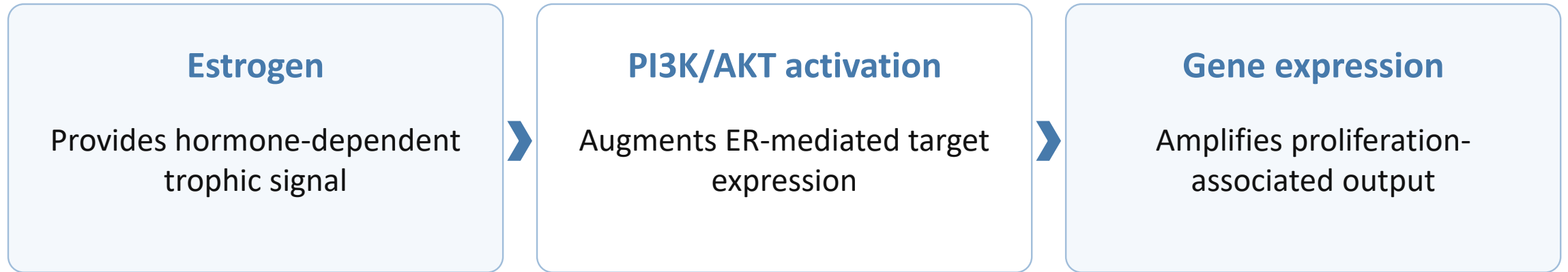
- Individual endometrioid carcinomas may contain multiple PI3K/AKT–enhancing alterations.
- Robbins suggests sequential increases in signal strength foster tumor evolution.
- The observed combinations support a multistep process.
- Do not infer a universal temporal order for PTEN, PIK3CA, KRAS, and ARID1A.

Selected alterations: Textbook frequencies

Alteration	Approximate source frequency	Principal implication
PTEN	30%–80%	Loss of PI3K/AKT restraint
PIK3CA	~40%	Activating PI3K signaling
KRAS	~25%	Oncogenic signaling input
ARID1A	About one-third	Chromatin regulation / transcription

Percentages describe different alteration groups and can overlap; They must not be added.

Estrogen receptor and PI3K/AKT cross-talk



The pathway is biologically linked to the hormonal environment.

Genomic instability can accelerate tumor evolution

Altered DNA maintenance produces a mutator phenotype.

- Defects in DNA repair and replication fidelity increase the burden of somatic mutations.
- This expands opportunities to acquire driver mutations.
- Endometrioid carcinomas include mismatch-repair-deficient and polymerase- ϵ -altered subsets.
- High mutation burden is a molecular characteristic, not synonymous with high histologic grade.

Mismatch repair loss: Mechanism

MMR defect

Reduced correction of
replication errors



Microsatellite instability

Accumulating sequence errors



Hypermutated tumor

Increased somatic mutation
burden

Sporadic promoter methylation and inherited predisposition are distinct etiologic routes.

Sporadic mismatch repair defects

Epigenetic silencing may disable a repair protein.

- Mismatch repair defects in approximately 20% of sporadic endometrioid carcinomas.
- Loss of MLH1 expression commonly results from promoter hypermethylation in sporadic tumors.
- Mismatch repair defects can also arise in Lynch syndrome.
- A tumor MMR abnormality alone does not prove a germline pathogenic variant.

Lynch syndrome association

Syndromic risk deserves separate recognition.

- Endometrial carcinoma can develop in patients with inherited mismatch repair predisposition.
- Lynch syndrome in approximately 3%–5% of females with endometrial cancer.
- The syndrome also confers important risk of colorectal carcinoma.
- Tumor mismatch repair assessment supports identification of potentially affected patients.

MMR assessment at diagnosis

Pathology connects tumor phenotype with hereditary risk.

- Robbins recommends examining endometrioid carcinoma for DNA mismatch repair defects.
- An abnormal tumor result requires appropriate subsequent clinical interpretation.
- Sporadic MLH1 promoter methylation is a relevant alternative to hereditary MMR loss.
- The source does not supply a complete reflex-testing algorithm; None is invented here.

POLE proofreading alteration

POLE exonuclease defect

Impaired polymerase
proofreading



DNA replication errors

Many somatic point mutations



Ultramutated phenotype

Exceptionally high mutation
burden

The key distinction is altered replication fidelity, not just greater proliferation.

Polymerase ϵ –altered tumors

A small subset with exceptional point mutation burden.

- Proofreading-disrupting POLE mutations in fewer than 10% of endometrial carcinomas.
- These tumors can carry extremely high somatic point mutation burdens.
- The POLE-defined molecular category is termed ultramutated.
- Molecular class should not be guessed from microscopic grade alone.

TP53 in progression of high-grade endometrioid tumors

Timing differs from typical serous carcinoma.

- TP53 loss-of-function mutations in about half of poorly differentiated endometrioid carcinomas.
- TP53 mutations are absent from most well-differentiated endometrioid tumors.
- This pattern suggests later involvement in progression of some tumors.
- By contrast, TP53 mutations are frequent early events in serous carcinoma.

Four molecular patterns in endometrial carcinoma

POLE

Ultramutated
Proofreading error

MMR-deficient / MSI

Hypermuted
Repair deficiency

Copy-number low / NSMP

Often endometrioid
PI3K/AKT drivers

Copy-number high / p53

Often aggressive
TP53 alteration

Histologic subtype and molecular classification are related but not interchangeable.

POLE molecular class

Defining event: Pathogenic proofreading-associated POLE alteration.

- The central biological effect is an exceptionally high burden of mutations.
- Tumors may still show endometrioid glandular or solid histology.
- Diagnosis of this molecular class requires appropriate molecular evidence.
- Textbook description is not a substitute for a current validated testing specification.

Mismatch-repair-deficient molecular class

Defining biological mechanism: Defective DNA repair.

- Microsatellite instability is linked to a hypermutated phenotype.
- The cause may be sporadic or hereditary.
- These tumors with prominent infiltrating T cells in some cases.
- The presence of T cells is a clue, not a molecular diagnostic assay.

Copy-number-low / NSMP pattern

A frequent pattern with endometrioid morphology.

- This group is associated with mutations upregulating PI3K/AKT signaling.
- The name refers to a molecular category, not an independent architectural grade.
- Absence of a defining POLE, MMR, or p53 result cannot be asserted without testing.
- Morphologic gland formation and molecular class are distinct observations.

Copy-number-high / p53-abnormal pattern

Aggressive biology can cross histologic boundaries.

- Classically associated with serous carcinoma and some high-grade endometrioid tumors.
- TP53 alterations coexist with many chromosomal copy-number changes.
- High-grade morphology alone is not proof of the category.
- The category helps illustrate why a purely gland-based classification is incomplete.

Histology and molecular type answer different questions

Histologic assessment	Molecular assessment
Architecture: Gland-forming versus solid	POLE proofreading status
Cytologic atypia / differentiation	DNA mismatch repair or MSI status
Squamous elements and invasion	P53 / copy-number-associated pattern
Tumor grade and local extent	Biological classification independent of grade

Tumor-infiltrating lymphocytes

Genomic instability can alter tumor immunogenicity.

- POLE-mutant and mismatch-repair-deficient tumors with numerous infiltrating T lymphocytes.
- High mutation burden may produce proteins with novel antigenic sequences.
- The described inflammatory infiltrate is interpreted as an ineffective host response in the text.
- Lymphocyte density alone should not be used to assign a POLE or MMR category.

Gross growth patterns

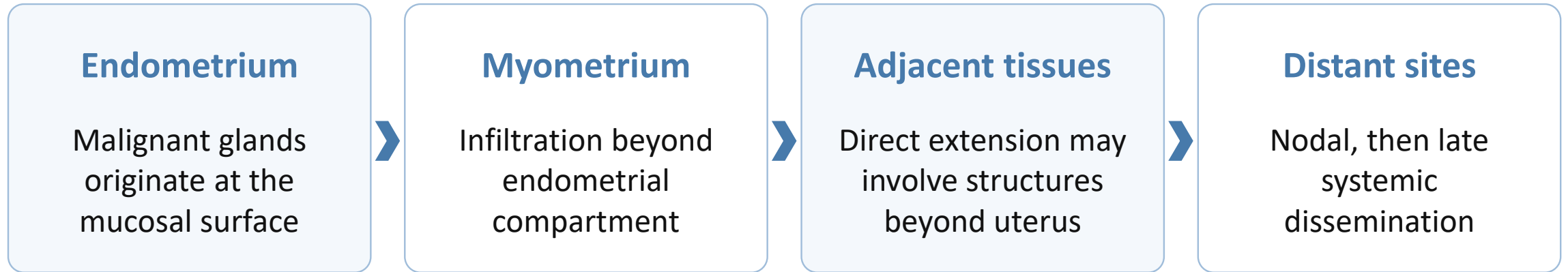
Localized / polypoid lesion

- Focal exophytic mass into uterine cavity
- May have a broad-based or protruding configuration
- An example is a fundal fungating mass
- Gross distribution does not define grade

Diffuse endometrial involvement

- Tumor may involve much of the endometrial lining
- Subsequent myometrial invasion changes stage
- Architectural tumor type must be confirmed microscopically
- Gross mapping assists extent assessment

Anatomic progression of invasion



This summarizes the spread sequence and is not an individual-patient prediction.

Myometrial invasion changes the disease extent

The same histologic tumor can occupy very different anatomic compartments.

- Endometrioid carcinoma can invade into the underlying myometrium.
- Beyond the uterine wall, extension may involve neighboring structures or organs.
- Broad-ligament involvement can produce a palpable mass.
- Anatomic extent should be reported independently from histologic grade.

Routes and destinations of spread

Location of tumor cells matters for staging and prognosis.

- Direct contiguous invasion can precede involvement of adjacent structures.
- Regional lymph-node dissemination can occur.
- Late distant metastatic sites include lung, liver, and bone.
- This description gives a typical sequence, not a deterministic pathway.

Architecture under the microscope

Gland formation

Well-formed malignant glands



Complexity

Back-to-back or confluent structures

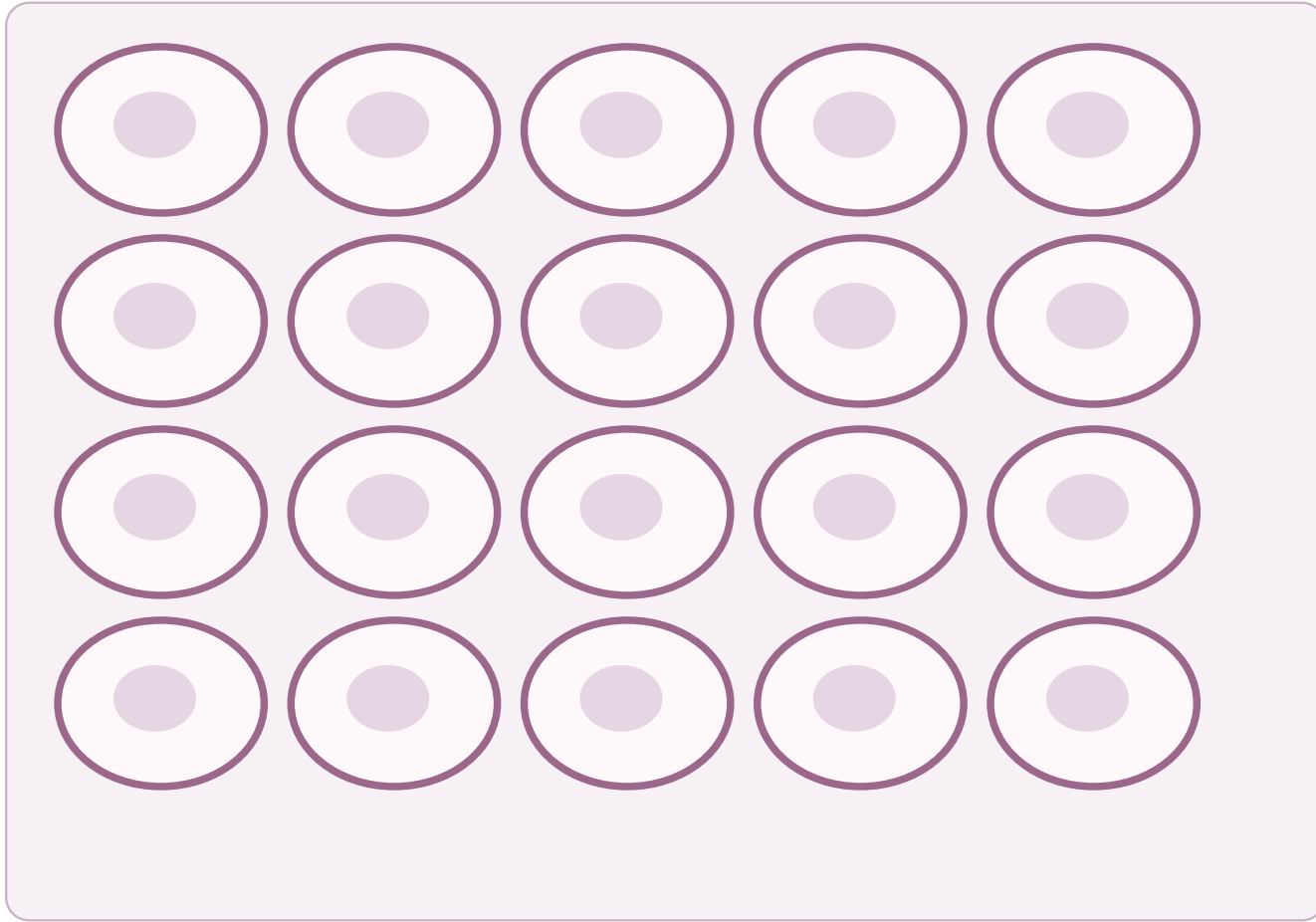


Solid growth

Loss of recognizably glandular architecture

The proportion of solid epithelial tumor determines the histologic grade in the source scheme.

Grade 1: Predominantly gland-forming



Simplified architectural schematic — not a photomicrograph

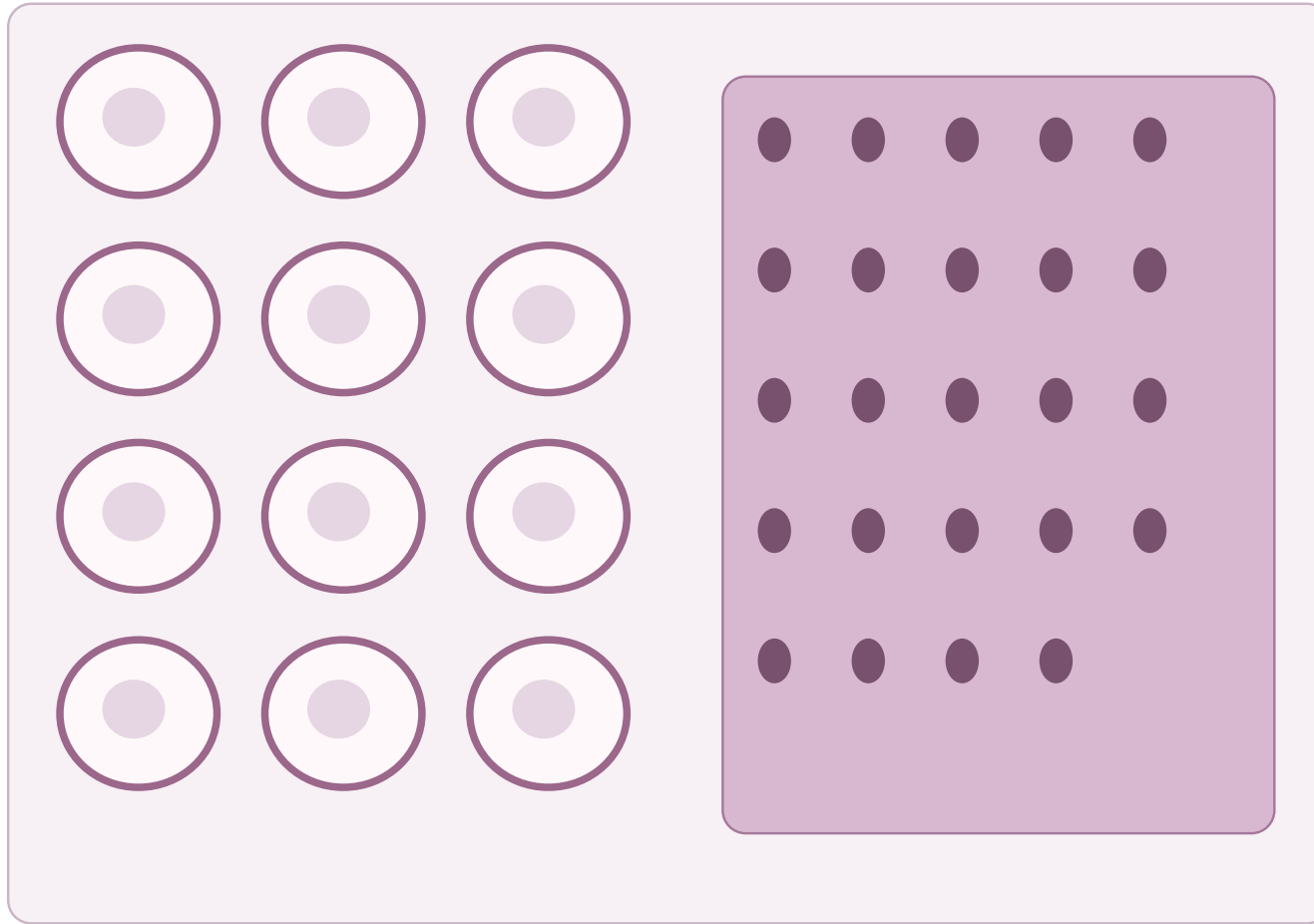
- Predominantly well-formed glands
- Very little solid epithelial growth
- Preserved glandular differentiation

Grade 1: What supports the interpretation

Look for malignant architecture even when cells appear deceptively bland.

- The majority of the tumor consists of well-formed glands.
- Intervening stromal boundaries may be lost within confluent malignant glands.
- Desmoplastic stromal reaction favors carcinoma over hyperplasia where demonstrable.
- The schematic is architectural only: Real H&E remains necessary for diagnosis.

Grade 2: Glands mixed with solid areas



Simplified architectural schematic — not a photomicrograph

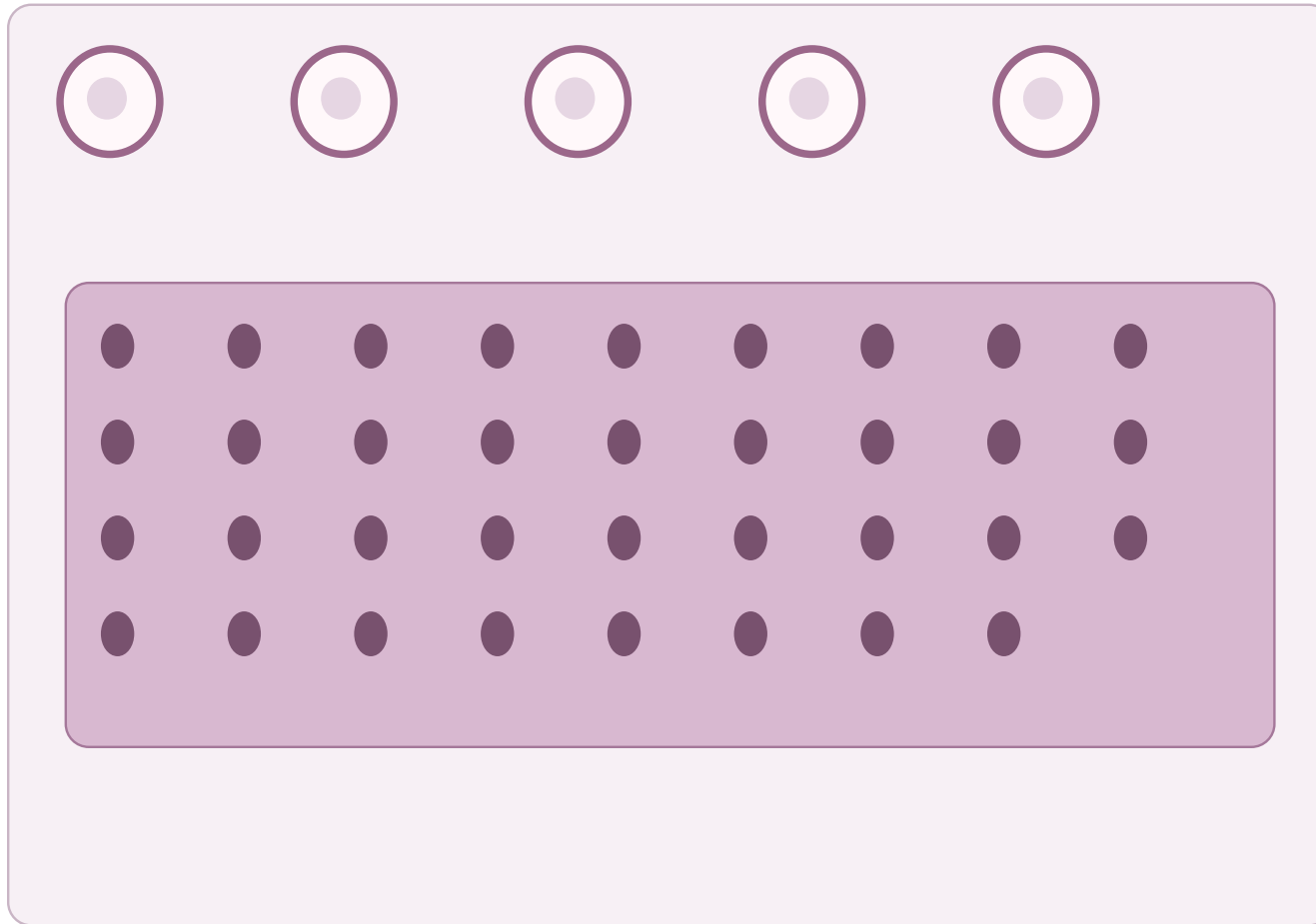
- Glands coexist with solid tumor
- Intermediate reduction in gland formation
- Architectural heterogeneity is central

Grade 2: Architectural heterogeneity

Both glandular and solid components should be evaluated.

- Well-formed glands coexist with sheets of solid tumor cells.
- Solid growth accounts for no more than half of the tumor in grade 2.
- Grade 2 retains appreciable glandular differentiation.
- Only the tumor epithelial architecture—not squamous areas—should control grading.

Grade 3: Predominantly solid tumor



Simplified architectural schematic — not a photomicrograph

- Solid growth dominates
- More than 50% solid architecture
- Glandular differentiation may be limited

Grade 3: Reduced glandular differentiation

Solid growth predominates by definition scheme.

- More than 50% of the tumor shows a solid growth pattern.
- Limited glandular elements may remain, requiring careful tumor typing.
- High-grade endometrioid carcinoma can contain TP53 alterations.
- Morphology must be integrated with other evidence rather than assuming serous histology.

Morphologic grades: The source-based distinction

Grade	Architectural pattern	Essential observation
1 — well differentiated	Nearly entirely well-formed glands	Predominantly glandular
2 — moderately differentiated	Glands admixed with solid growth	Solid component $\leq 50\%$
3 — poorly differentiated	Predominantly solid epithelial growth	Solid component $> 50\%$

This reproduces the simplified Robbins description, not a comprehensive current grading protocol.

Binary grade concept

Why some reporting frameworks group grades.

- Advocacy for a two-tier interpretation.
- Grades 1 and 2 may be combined as low-grade endometrioid carcinoma.
- Grade 3 is treated as high-grade disease in this binary approach.
- Histologic grading and molecular classification should still be reported as different attributes.

Atypical hyperplasia versus well-differentiated carcinoma

Atypical hyperplasia / EIN

- Crowded and complex glands with nuclear atypia
- Back-to-back growth can occur
- Limited samples may be ambiguous
- No unequivocal stromal invasion shown

Well-differentiated carcinoma

- Confluent or complex malignant glandular growth
- Desmoplastic stroma favors invasion
- Complex papillary arrangements may support carcinoma
- Examination of a larger specimen can clarify extent

The carcinoma–EIN interface is a sampling problem

A biopsy is a sample, not a complete architectural map.

- Some EIN foci closely resemble well-differentiated carcinoma.
- Textbook emphasizes complexity of reliably distinguishing the two in limited material.
- Findings supporting invasion must be evaluated in the actual tissue.
- A hysterectomy specimen may reveal carcinoma missed at initial biopsy.

Squamous differentiation in endometrioid carcinoma

A separate morphologic element can appear within the tumor.

- Up to approximately 20% contain squamous foci.
- Squamous areas can appear cytologically bland in low-grade tumors.
- Squamous elements may look overtly malignant in poorly differentiated tumors.
- Squamous differentiation does not by itself define an additional molecular subtype.

Do not grade the squamous component

Gland-forming tumor architecture remains the basis of grade.

- The source explicitly states that areas of squamous differentiation are ignored for grading.
- Grade 1–3 is based on non-squamous glandular versus solid growth.
- Failure to exclude squamous nests can falsely increase apparent solid fraction.
- Quantitative grading must use the specified tumor component.

Clinical presentation

Abnormal uterine bleeding is the central warning symptom.

- Carcinoma may be initially asymptomatic.
- Irregular bleeding and postmenopausal vaginal bleeding are characteristic presentations.
- Bleeding often prompts early evaluation while disease is confined to the uterus.
- Symptoms establish an indication for investigation, not a histologic diagnosis.

Age and clinical context

Epidemiology guides suspicion but is not diagnostic.

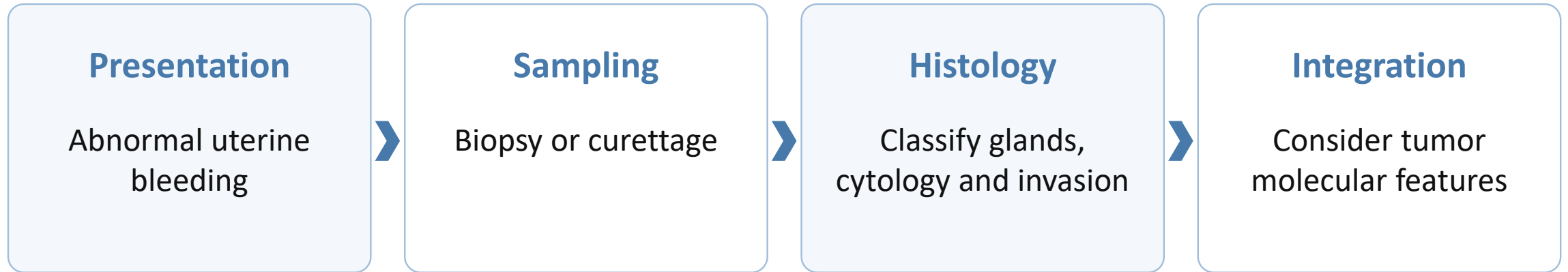
- A peak among postmenopausal females approximately 55–65 years old.
- Endometrial carcinoma can also occur in younger females.
- Increasing incidence in younger patients.
- Risk factors and age should guide evaluation of bleeding without substituting for biopsy.

There is no established general screening test in the source

Symptom-triggered assessment is therefore central.

- No screening test is available for endometrial carcinoma.
- Patients may experience bleeding before spread becomes extensive.
- Clinical suspicion should lead to appropriate tissue investigation.
- Hereditary-risk management protocols are separate from population screening statements.

From bleeding to tissue diagnosis



This educational sequence is not a comprehensive clinical management algorithm.

Why histology is essential

The diagnosis must be established in sampled tissue.

- Endometrial biopsy or curettage provides tissue for microscopic evaluation.
- Architecture distinguishes glandular crowding, EIN, and overt carcinoma.
- Limited fragments can constrain assessment of invasion.
- Biopsy-based morphology may be complemented by surgical resection findings.

Three axes of outcome assessment

Stage

Extent of disease in and beyond the uterus

Histologic grade

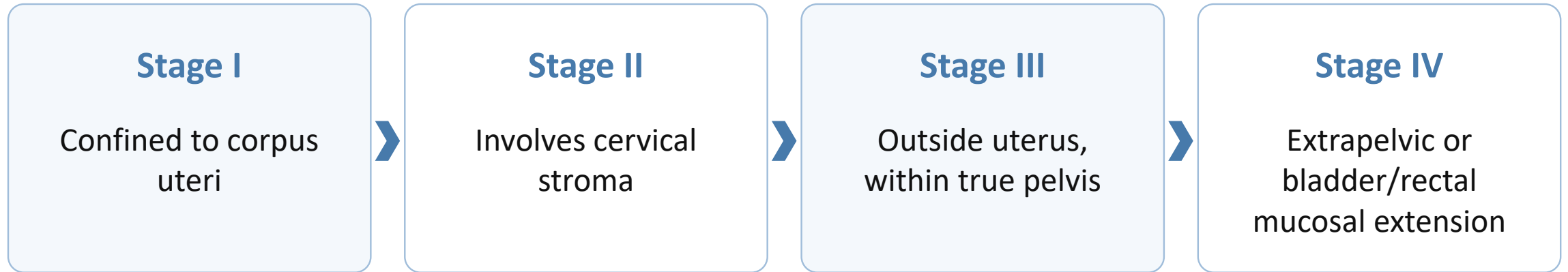
Relative glandular differentiation versus solid growth

Histologic / molecular type

Biologic pattern of the tumor

These dimensions should be integrated, not substituted for one another.

Source-based anatomic stage concepts



Simplified anatomic schema as printed; Not presented as the current comprehensive FIGO 2023 staging system.

Why early recognition affects outcome

Localized disease is generally more amenable to curative management.

- Bleeding can lead to histologic diagnosis before extensive spread.
- Outcome strongly with stage at diagnosis.
- Grade and tumor subtype also affect outcome.
- This lecture does not substitute historical survival estimates for individualized prediction.

Therapeutic implications: Principles only

Pathology informs the treatment pathway, but treatment is stage-dependent.

- Surgery as a major treatment modality for endometrioid carcinoma.
- Radiation may be used to reduce local recurrence in selected cases.
- Systemic therapy is considered when disease extends beyond the uterus.
- Current regimen selection and molecular treatment criteria require guideline verification.

Application case: Bleeding and obesity

Illustrative teaching vignette

A 61-year-old postmenopausal patient with obesity has intermittent vaginal bleeding. Endometrial sampling is planned.

What sequence of mechanisms links this clinical setting to endometrioid carcinoma?

Case analysis: Estrogen and clonal selection

The case establishes a mechanism of risk, not a final diagnosis.

- Adipose-associated estrogen production can produce persistent stimulation of endometrial glands.
- Hyperplasia, particularly atypical hyperplasia / EIN, is an important precursor setting.
- PTEN and related signaling alterations may be acquired before overt carcinoma.
- Histologic sampling is needed to identify the actual lesion.

Application case: Grade from architecture

Illustrative teaching vignette

An endometrial malignancy shows many abnormal glands and a substantial, but nonpredominant, solid epithelial component. Separate squamous nests are also present.

Which elements determine its grade, and what must be excluded from the estimate?

Case analysis: Grade versus squamous component

Architectural assessment is intentionally selective.

- Grade is determined by the non-squamous glandular/solid component.
- A solid fraction at or below one-half is compatible with grade 2 if a substantial solid component is present.
- Squamous foci are excluded from grading.
- Exact grading may require evaluation of the full sampled tumor.

Application case: Mismatch repair result

Illustrative teaching vignette

An endometrioid carcinoma is found to lack expression of a mismatch repair protein on tumor testing. The clinical team asks whether Lynch syndrome is established.

Why is a tumor MMR abnormality not automatically a hereditary diagnosis?

Case analysis: Sporadic versus inherited MMR loss

A shared tumor phenotype can have distinct causes.

- Abnormal MMR testing indicates a repair-deficient tumor phenotype.
- MLH1 silencing through promoter methylation is a common sporadic cause.
- Lynch syndrome is a separate inherited predisposition involving MMR genes.
- Appropriate downstream evaluation is needed; Tumor results alone do not specify inheritance.

Integrated morphology-to-mechanism recap

Observed feature	Mechanistic or interpretive link
Atypical gland crowding	Clonal precursor lesion may precede carcinoma
Confluent glands / desmoplasia	Supports carcinoma rather than simple atypical hyperplasia
Progressively solid architecture	Reduced glandular differentiation and increased grade
Many infiltrating T cells	May accompany MMR-deficient or POLE-altered tumors
Myometrial invasion	Greater anatomic disease extent

Five conclusions to retain

Integrate the precursor, molecular, and morphologic narratives.

- Most endometrial carcinomas are endometrioid and often related to hyperplasia.
- Unopposed estrogen and convergent PI3K/AKT alterations provide mechanistic context.
- MMR, POLE, and p53 alterations distinguish biologically important molecular patterns.
- Histologic grade reflects glandular versus solid growth; Squamous areas do not count.
- Stage, grade, and subtype influence prognosis; Biopsy establishes diagnosis.

Selected reading and source scope

Primary textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 22, The Female Genital Tract.

Read in context

Endometrial hyperplasia; carcinoma of the endometrium; endometrioid and serous carcinoma; grading and clinical features in adjacent text.

Scope of this lecture

Textbook-based histopathology and pathogenesis; not an updated FIGO staging or treatment guideline.