

Carcinoma of the Endometrium

Pathogenesis • Molecular classification • Morphology • Clinical correlation

Pathology lecture

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Learning outcomes

- Distinguish endocrine-associated endometrioid carcinoma from serous carcinoma.
- Explain the four molecular classes and their biological basis.
- Recognize the implications of glandular architecture, invasion and cytologic grade.
- Relate abnormal uterine bleeding, histologic sampling and clinical extent to management.

Endometrial carcinoma: The disease entity

A malignant epithelial neoplasm arising in the lining of the uterine corpus.

- It is the leading invasive cancer of the female genital tract in the United States.
- The common morphologic types are endometrioid and serous carcinoma.
- Precursors and molecular alterations differ across biological subtypes.

Two complementary ways to classify disease

Histologic phenotype

- Architecture: Endometrioid vs serous morphology
- Differentiation and cytologic atypia
- Relation to precursor lesions

Molecular phenotype

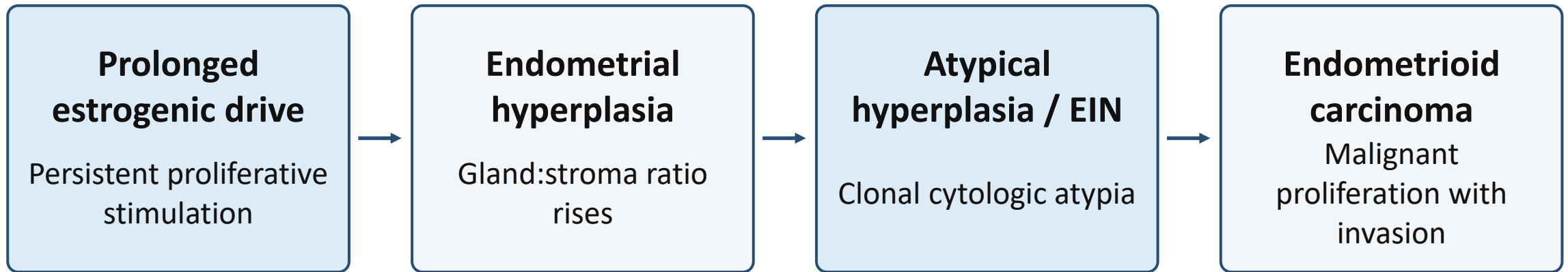
- POLE-ultramutated
- Mismatch repair-deficient / MSI
- Copy-number low / NSMP
- Copy-number high / TP53-abnormal

Histologic appearance and molecular subtype are related, but not identical.

Clinical importance: A changing epidemiologic pattern

- Endometrial carcinoma as more common than cervical carcinoma in the United States.
- Reduction in cervical precursor disease and increasing endometrial cancer in younger women contribute to the shift.
- Most cases are recognized following abnormal or postmenopausal vaginal bleeding.

One pathway to endometrioid malignancy



Atypical hyperplasia is an important precursor—not an inevitable outcome.

What “endometrial hyperplasia” means

- The endometrium has more proliferating glands relative to the intervening stroma.
- Abnormally crowded and irregularly shaped glands can cause abnormal bleeding.
- Hyperplasia without atypia and atypical hyperplasia differ in cancer risk.

Hyperplasia without atypia versus atypical hyperplasia

Without atypia

- Architectural crowding and variable gland size
- Cytology resembles proliferative endometrium
- Usually retains some intervening stroma
- Uncommon progression to carcinoma

Atypical hyperplasia / EIN

- Crowded, complex glands with nuclear atypia
- Clonal genetic alterations
- Overlaps morphologically with low-grade carcinoma
- Substantial concurrent carcinoma risk

Why atypical hyperplasia is a precursor

- Atypical hyperplasia and carcinoma may share mutations in PTEN, ARID1A, PIK3CA and KRAS.
- Shared abnormalities support a common evolving neoplastic clone.
- Coexistent invasive carcinoma can be missed in limited sampling.

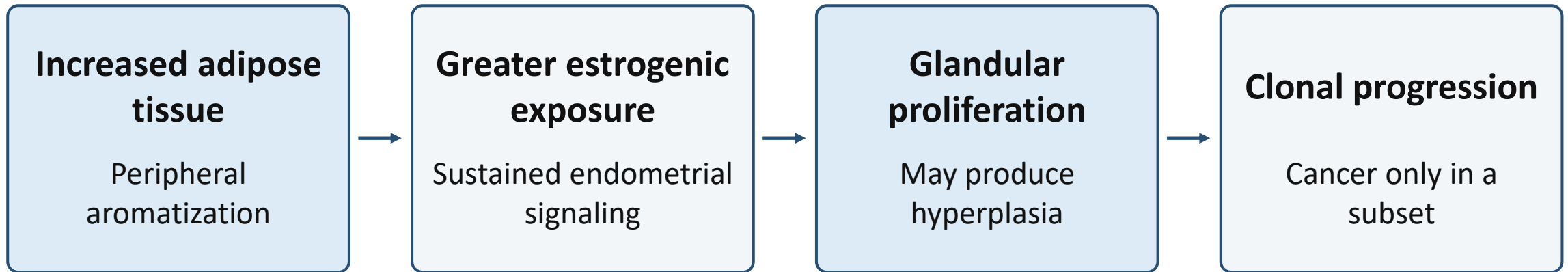
Carcinoma at hysterectomy in up to 40% diagnosed with atypical hyperplasia.

Sources of excess estrogenic stimulation

Metabolic	Ovarian	Exogenous
Obesity	Anovulation	Prolonged estrogen exposure
Peripheral androgen-to-estrogen conversion	Polycystic ovarian syndrome	Unopposed estrogenic substances
	Estrogen-producing tumors	

The pathway is especially relevant to endometrioid carcinoma.

Obesity and a proliferative endometrium



Metabolic associations require causal care

- Obesity is a major epidemiologic association for endometrioid carcinoma.
- Hypertension and type 2 diabetes commonly coexist in affected patients.
- Co-occurrence does not establish that hypertension independently causes the cancer.

Distinguish associated clinical conditions from established molecular tumor drivers.

Hereditary predisposition: Two distinct mechanisms

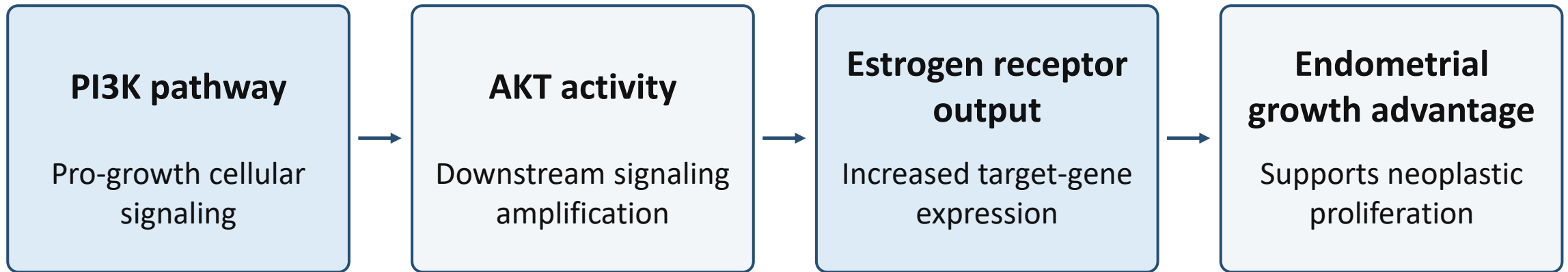
PTEN / Cowden syndrome

- Germline PTEN mutation
- Dysregulated PI3K/AKT signaling
- Higher risk of endometrial and certain other cancers

Mismatch repair / Lynch syndrome

- Heritable mismatch repair defect
- Microsatellite instability can develop
- Raises risk of endometrial and colorectal cancer

Growth signaling through PI3K and AKT



This is an original simplified pathway: No claim that each component acts in isolation.

PTEN: Loss of a growth-regulatory brake

- PTEN encodes a lipid phosphatase that restrains PI3K/AKT signaling.
- Loss of PTEN function releases this negative regulation.
- PTEN mutations are found in hyperplasia and many endometrioid carcinomas.
- Mutation alone does not predict which hyperplasias will progress.

PIK3CA and KRAS: Cooperating oncogenic alterations

PIK3CA

- Encodes a catalytic component of PI3K
- Activating alterations increase growth signaling
- Frequent in endometrioid carcinoma

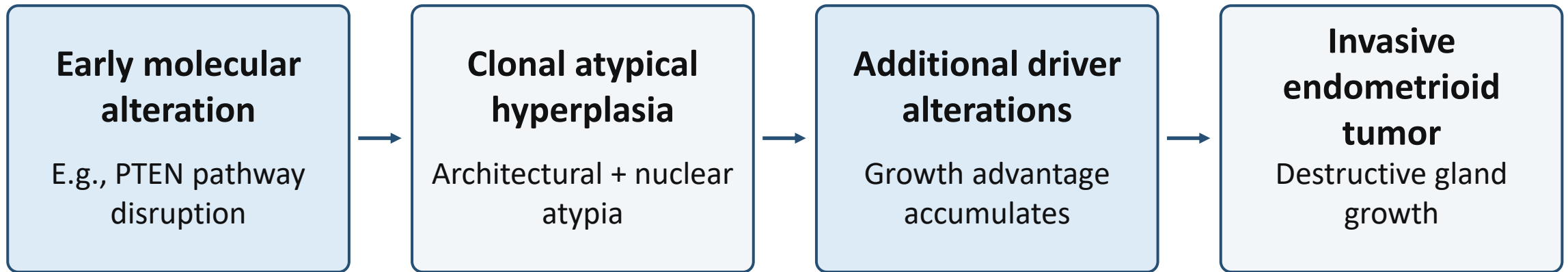
KRAS

- Oncogene with activating mutations in a subset
- Can also increase PI3K/AKT pathway output
- Tumors may acquire more than one pathway alteration

ARID1A: Chromatin regulation intersects signaling

- ARID1A participates in the regulation of chromatin structure.
- Loss-of-function alterations occur in many endometrioid carcinomas.
- ARID1A loss to pro-oncogenic PI3K/AKT-related gene expression, with the mechanism unresolved.

From precursor clone to overt carcinoma



Conceptual multistep progression; The exact order varies among tumors.

Four principal molecular classes

POLE-mutated	MMR-deficient	NSMP / copy-number low	P53-abnormal
DNA proofreading defect	Mismatch repair failure	Often endometrioid	Copy-number high
Ultramutated genome	Microsatellite instability	PI3K/AKT pathway	Often serous or high-grade

POLE-ultramutated endometrial tumors

- A pathogenic DNA polymerase ϵ proofreading defect generates an exceptionally high somatic mutation burden.
- Most of the acquired mutations are passengers rather than oncogenic drivers.
- Tumors with this phenotype can contain prominent infiltrating T cells.

MMR-deficient and MSI-hypermethylated tumors

- Mismatch repair normally corrects certain replication-associated DNA errors.
- Loss of repair activity leads to microsatellite instability and accumulation of mutations.
- Alterations may be sporadic, including MLH1 promoter methylation, or related to Lynch syndrome.

Copy-number low / NSMP endometrial carcinomas

- A common molecular phenotype among endometrioid tumors.
- It lacks the defining ultramutated, MMR-deficient or copy-number-high profile.
- Mutations favoring PI3K/AKT signaling are frequent in this group.

“NSMP” = no specific molecular profile; It does not mean no pathogenic mutations.

Copy-number high / TP53-mutated carcinomas

- Numerous genomic copy-number alterations reflect chromosomal instability.
- Disruptive TP53 mutation is a defining frequent feature.
- The group is enriched for serous and some high-grade endometrioid morphologies.

Molecular phenotype is not a histologic synonym

Molecular class	Molecular hallmark	Common morphologic setting
POLE-mutated	Proofreading defect / ultramutation	May be endometrioid
MMR-deficient	Repair dysfunction / MSI	Often endometrioid
NSMP	No class-defining feature	Usually endometrioid
P53-abnormal	TP53 disruption / copy-number high	Often serous; May be high-grade endometrioid

Genomic instability has different causes

Sequence-level instability

- POLE: Replication proofreading fails
- MMRd: Mismatch repair fails
- High numbers of sequence mutations

Chromosomal instability

- P53-abnormal: Broad copy-number changes
- Many gains and losses across the genome
- Often aggressive serous phenotype

Why immune infiltrates may be prominent

- Many somatic mutations can produce altered peptide sequences.
- Novel protein epitopes may be recognized as tumor neoantigens.
- Increased tumor-infiltrating T cells in POLE- and MMR-defective tumors.
- Their presence does not guarantee an effective anti-tumor immune response.

Endometrioid carcinoma: The dominant morphology

Approximately 80–85% of endometrial carcinomas.

- Tumor glands often resemble those of proliferative endometrium.
- Many cases arise in an estrogen-associated clinical setting.
- Grade varies with the proportion of glandular versus solid tumor growth.

Endometrioid carcinoma: Gross patterns

Localized growth

- Polypoid or fungating tumor mass
- May arise in the uterine fundus
- Can be detected during investigation of bleeding

Diffuse growth

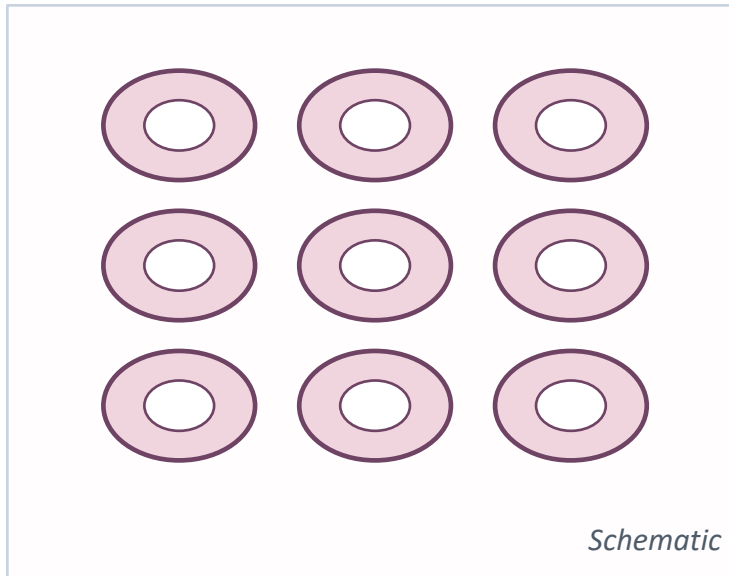
- Broader involvement of endometrial lining
- Potential progression to myometrial invasion
- Extension to adjacent tissues in advanced disease

Endometrioid histology: Architecture is central

- Neoplastic epithelium forms glands with resemblance to proliferative endometrium.
- Crowded glands may show complex or confluent growth.
- Solid tumor areas increase with decreasing glandular differentiation.
- Desmoplastic stroma or confluent growth may support carcinoma over hyperplasia.

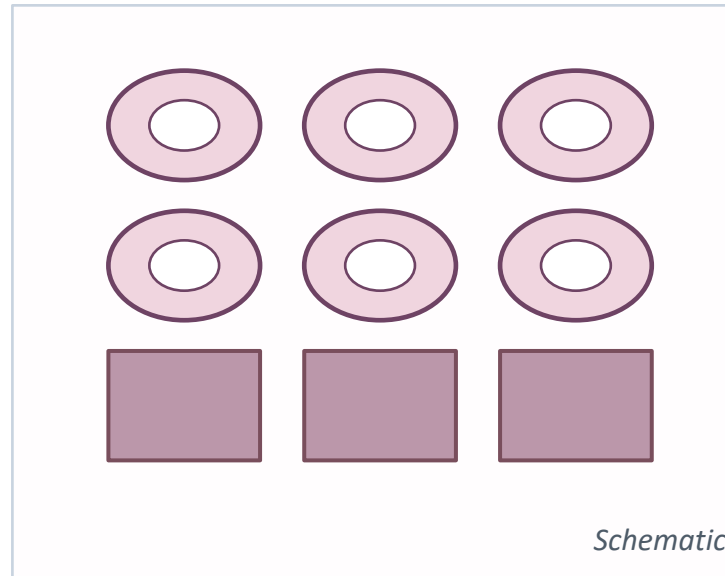
Grading endometrioid carcinoma: A visual model

Grade 1: Predominantly glands



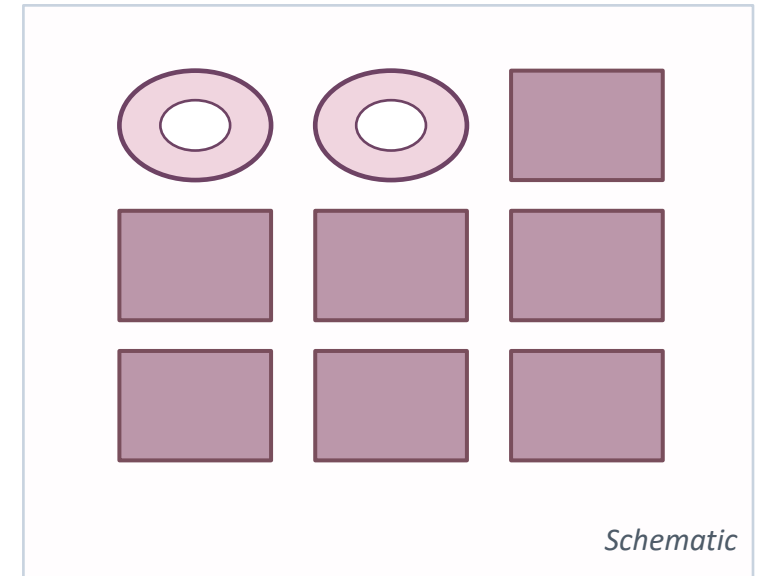
Well formed glandular architecture

Grade 2: Glands + solid growth



Solid areas present but $\leq 50\%$

Grade 3: Predominantly solid

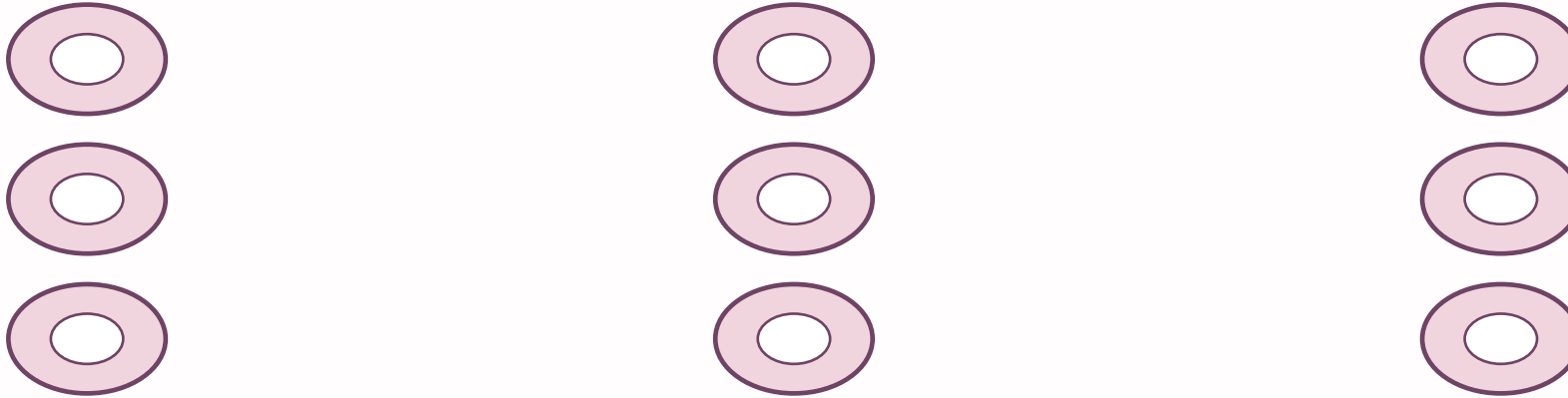


Solid growth $> 50\%$

Editable architectural schematics—not diagnostic histology or a substitute for microscopy.

Grade 1: Well-formed glandular architecture

Grade 1: Predominantly glands



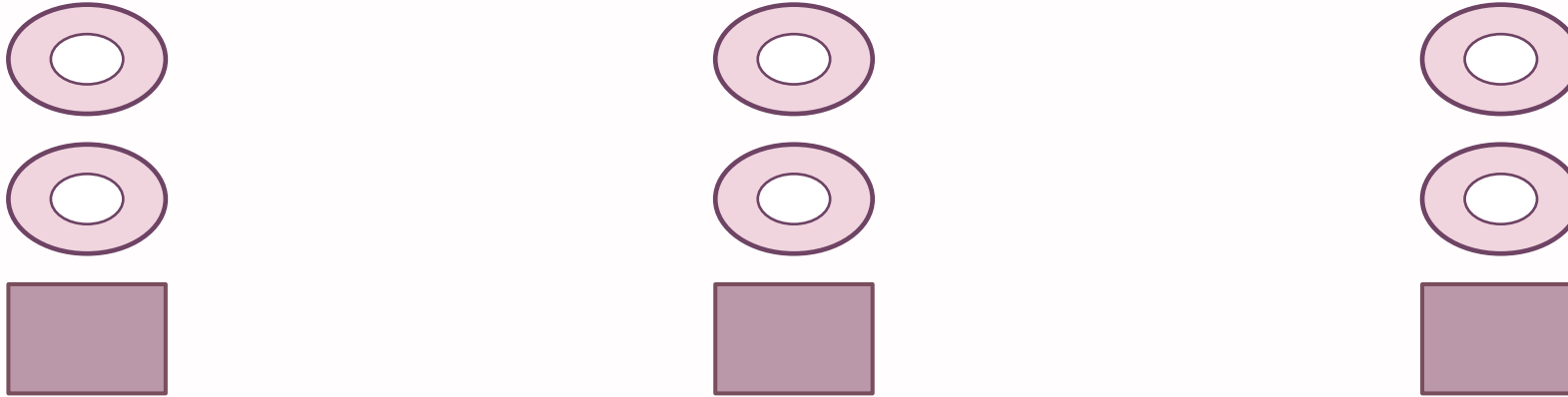
Schematic

Well formed glandular architecture

The well-differentiated pattern may resemble proliferative endometrial glands.

Grade 2: Mixed glandular and solid regions

Grade 2: Glands + solid growth



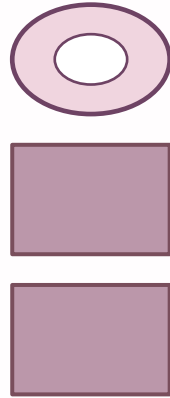
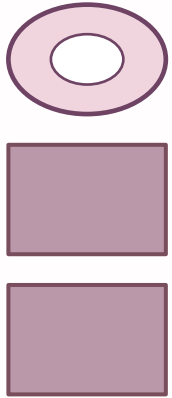
Schematic

Solid areas present but $\leq 50\%$

'three-tier' description, solid growth occupies no more than half the tumor.

Grade 3: Predominantly solid growth

Grade 3: Predominantly solid



Schematic

Solid growth > 50%

' three-tier description, solid growth accounts for more than half the tumor.

Architectural grade versus nuclear atypia

Architectural grading

- How much tumor forms glands?
- How much grows in solid sheets?
- This is the grading foundation

Cytologic assessment

- Nuclear variability and atypia
- Mitotic activity and high-grade features
- May raise concern about serous or other carcinoma

Grading rules depend on histotype and applicable classification criteria.

Squamous differentiation: An important exception

- A subset of endometrioid tumors contains squamous differentiation.
- Squamous components may appear bland or markedly malignant.
- Glandular differentiation—not the squamous component—determines the architectural grade.

Atypical hyperplasia versus carcinoma

Atypical hyperplasia / EIN

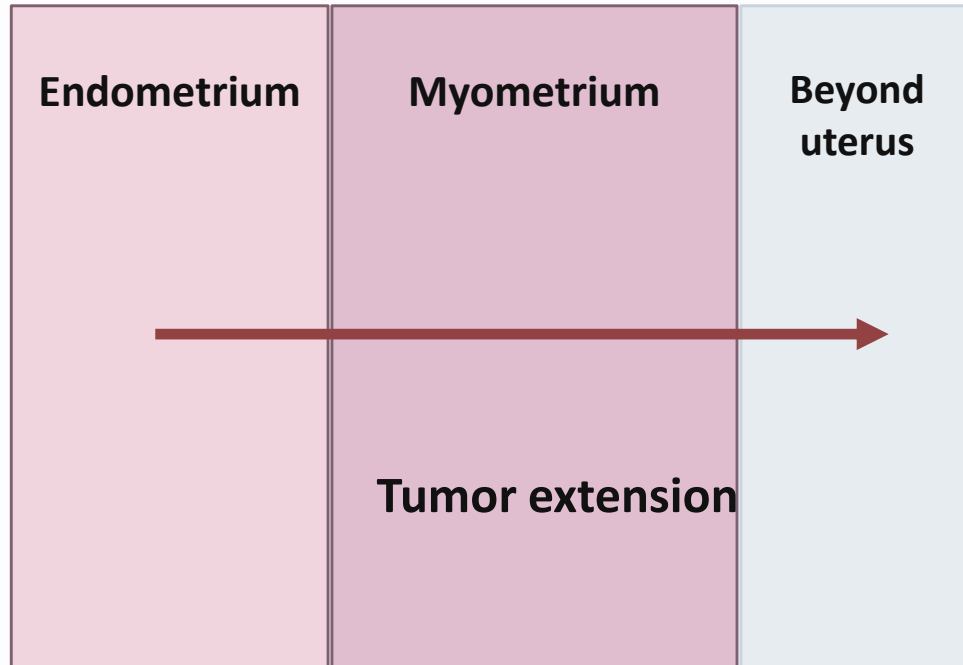
- Crowded clonal glands with cytologic atypia
- May be difficult to distinguish in limited material
- Concurrent carcinoma may be present elsewhere

Well-differentiated carcinoma

- Confluent or complex growth
- Desmoplastic stromal response may be present
- Definite invasion supports carcinoma

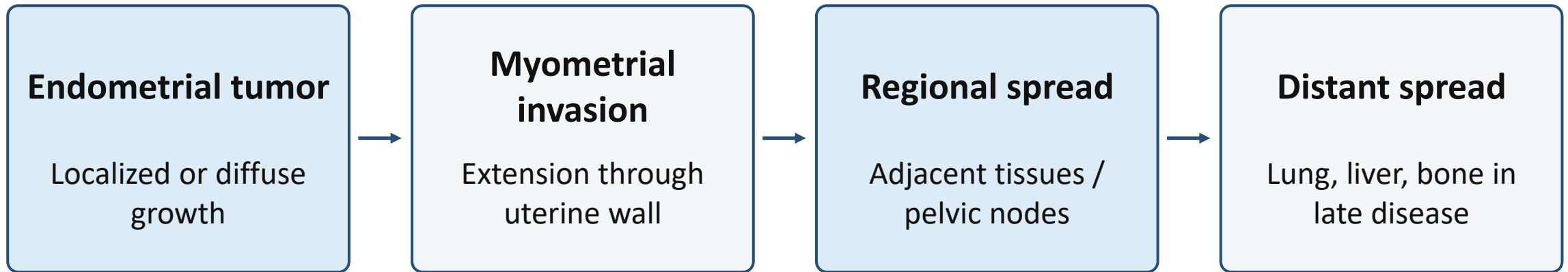
Adequacy of tissue sampling is central to the differential diagnosis.

Myometrial invasion changes anatomic extent



- Invasion beyond endometrium reaches uterine smooth muscle.
- Increasing local extension opens routes for regional spread.
- Anatomic invasion differs conceptually from architectural grade.

Endometrioid carcinoma: Routes of progression



The endocrine context is not universal

- Estrogen-related risk is especially characteristic of endometrioid carcinoma.
- Not all endometrial cancers arise from atypical hyperplasia.
- Serous tumors typically develop in an atrophic rather than hyperestrogenic background.

Serous carcinoma: Clinically aggressive histotype

A high-grade tumor with biology distinct from usual endometrioid carcinoma.

- That serous tumors account for about 15% of cases.
- Affected patients tend to be older than patients with endometrioid carcinoma.
- Deep invasion or extrauterine spread can already be present at diagnosis.

Endometrial background in two major histotypes

Endometrioid phenotype

- Often follows unopposed estrogenic stimulation
- May be preceded by atypical hyperplasia
- Frequently associated with PI3K/AKT pathway mutation

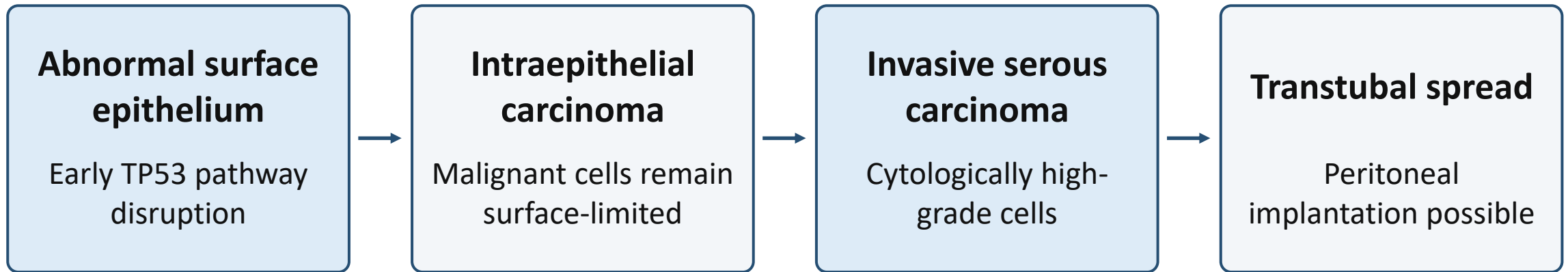
Serous phenotype

- Usually arises in atrophic endometrium
- Surface epithelial precursor is described
- TP53 alteration is strongly characteristic

TP53 dysfunction in serous carcinoma

- Disruptive TP53 alterations are found in the large majority of serous tumors.
- Many are missense mutations leading to accumulation of altered p53 protein.
- Aberrant p53 immunostaining can provide morphologic–molecular correlation.
- Broad copy-number alterations are characteristic of the subtype.

Serous intraepithelial lesion to disseminating carcinoma



Surface-limited disease can already be biologically dangerous.

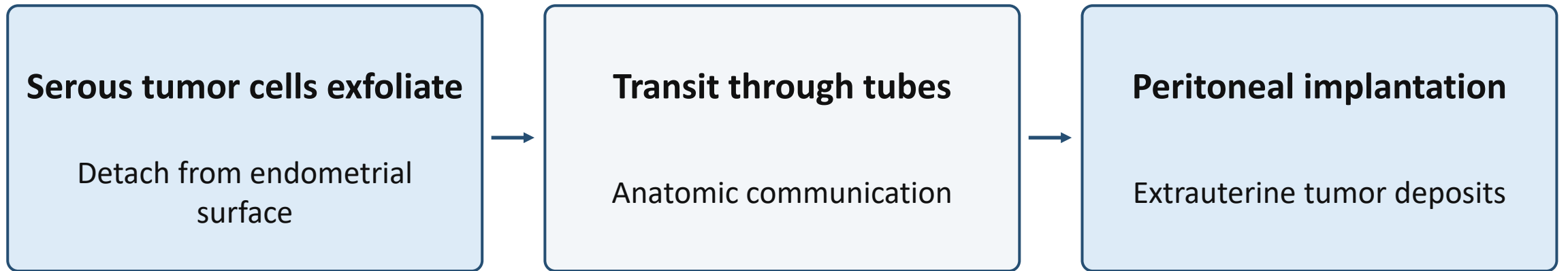
Serous carcinoma: Cytology can trump architecture

- Tumors may show papillary or glandular architecture.
- Cells are markedly atypical, hyperchromatic and often have high nuclear-to-cytoplasmic ratios.
- Atypical mitoses and prominent nucleoli reinforce high-grade morphology.
- A gland-forming growth pattern does not make serous carcinoma low grade.

All serous carcinomas are considered high grade

- The designation is based on intrinsic cytologic and biological features.
- Architectural patterns can vary within the tumor.
- Endometrioid three-tier glandular grading must not be applied to regrade a serous carcinoma.

Why extrauterine spread can precede deep invasion



A conceptual model of transtubal dissemination.

Endometrioid and serous carcinoma: Essential contrasts

Feature	Endometrioid	Serous
Typical substrate	Estrogenic drive / EIN	Atrophic endometrium
Genetic emphasis	PI3K/AKT, MMR, POLE	TP53, copy-number high
Histology	Glands $\pm$ solid areas	High-grade papillary or glandular
Grading	Architectural grades 1–3	Intrinsically high grade
Spread	Often invasion-led	Early extrauterine seeding possible

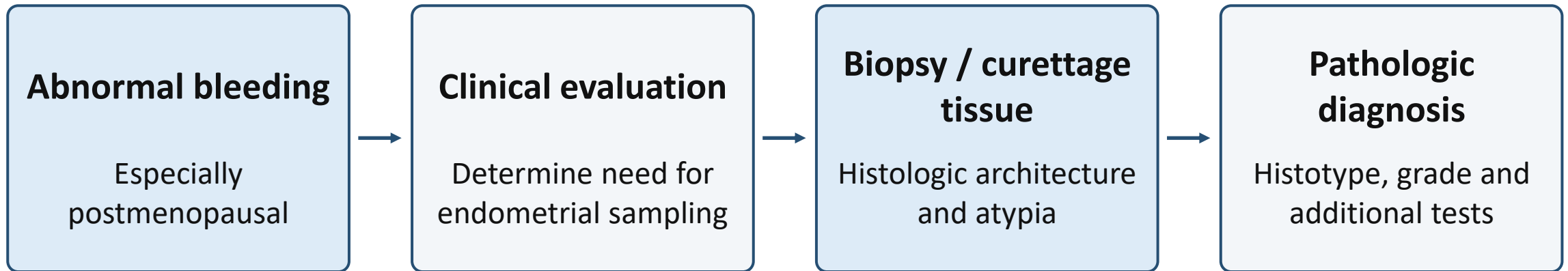
Other morphologic types share molecular pathways

- Robbins also names clear cell, undifferentiated/dedifferentiated and mesonephric-like carcinomas.
- Molecular profiling can place many uncommon histotypes into one of the four major classes.
- Morphologic recognition remains necessary; A molecular group alone is not the histotype.

Abnormal vaginal bleeding is the key clinical clue

- Presentation may include irregular bleeding during reproductive years.
- Postmenopausal bleeding is a frequent reason for evaluation.
- A tumor can initially be asymptomatic, so absence of bleeding does not exclude it.

How symptoms lead to tissue diagnosis



There is no routine screening test

- No screening test is available for endometrial cancer.
- Symptom-triggered evaluation therefore has practical importance.
- A negative routine cervical screening result does not establish the absence of endometrial cancer.

Histologic tissue sampling is indispensable

What sampling can establish

- Presence of atypical epithelial proliferation
- Morphologic carcinoma type
- Clues to grade and molecular assessment

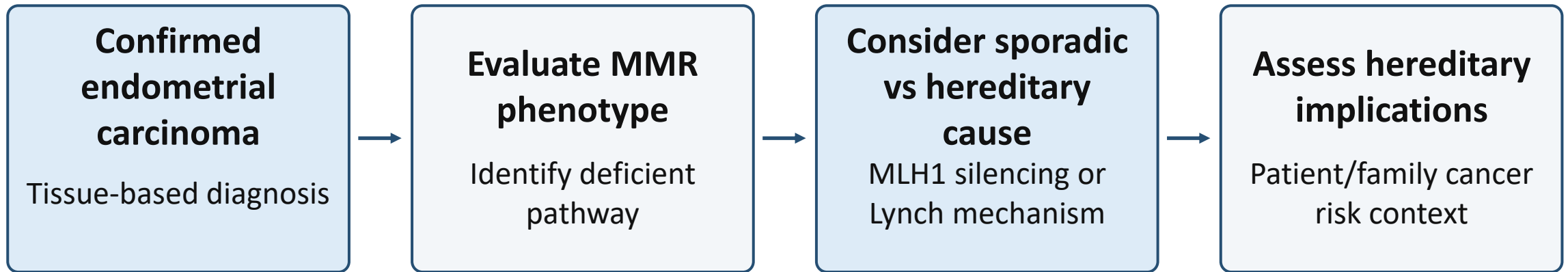
What limited samples may miss

- A focal coexistent carcinoma in EIN
- Definite myometrial invasion
- The full extent of extrauterine dissemination

Morphologic diagnosis and extent answer different questions

- Biopsy or curettage identifies the neoplasm and its cellular features.
- Assessment of myometrial or extrauterine invasion generally requires evaluation beyond surface tumor alone.
- Molecular findings refine classification but do not substitute for assessing anatomic extent.

MMR testing links tumor pathology to inherited risk



Why Lynch syndrome matters beyond the uterus

- Endometrial carcinoma can be a sentinel malignancy for Lynch syndrome.
- Hereditary Lynch syndrome among approximately 3–5% of patients with endometrial cancer.
- Recognition matters because associated colorectal and other cancer risks extend beyond the original tumor.

Grade and stage measure different disease properties

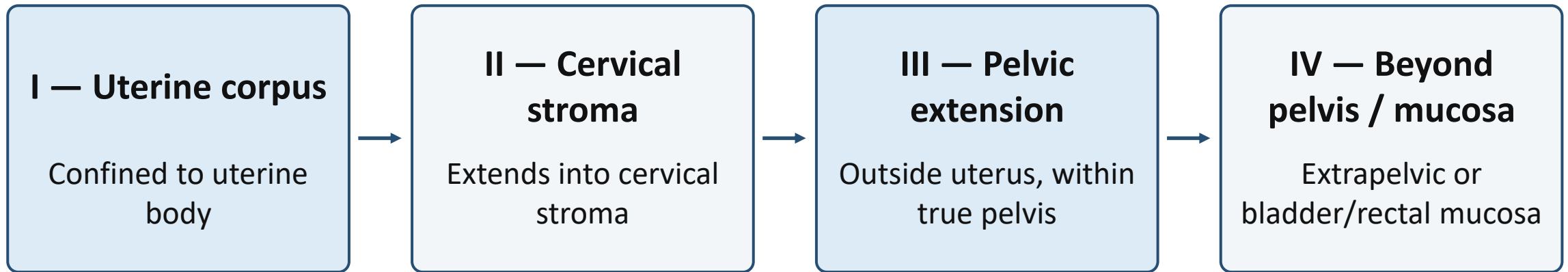
Histologic grade

- Differentiation of malignant epithelium
- For endometrioid tumors, mainly glandular versus solid growth
- Tumor-intrinsic phenotype

Anatomic stage

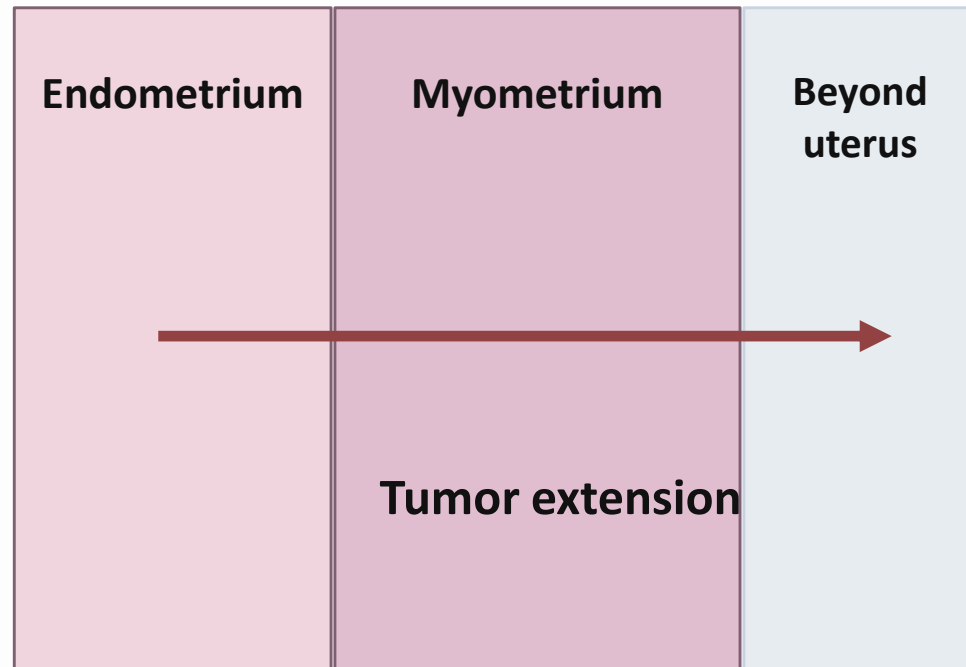
- How far the tumor has extended
- Uterine confinement vs cervical / extrauterine extension
- Requires information about tumor distribution

Anatomic stage: Simplified progression of extent



Simplified Robbins anatomic teaching scheme; Not the complete modern FIGO 2023 staging algorithm.

Local extension differs from distant dissemination



- Confined endometrial disease is anatomically different from cervical stromal extension.
- Regional extension may affect pelvic tissues and lymphatic drainage.
- Peritoneal or distant disease changes clinical stage and therapy planning.

Prognosis is multifactorial

Anatomic extent	Morphologic features	Molecular biology
Stage at detection Myometrial / extrauterine spread	Histotype Endometrioid grade	POLE, MMR, NSMP, p53 pathways Biological heterogeneity

Stage, grade and histologic subtype; Molecular class adds biological context.

Why serous carcinoma has a worse outcome

- Marked cytologic atypia and TP53-associated genomic instability accompany aggressive biology.
- Exfoliation and transtubal spread can cause extensive extrauterine disease despite limited primary uterine involvement.
- An apparently small uterine tumor must therefore not be assumed to represent low overall disease burden.

Treatment follows histotype and anatomic extent

Endometrioid carcinoma

- Surgery is a major primary modality
- Adjuvant treatment depends on recurrence risk and spread
- Extrauterine disease may require systemic treatment

Serous carcinoma

- Aggressive biological phenotype
- Systemic therapy may be considered even without overt distant disease
- Multimodal strategies reflect spread risk

Source-level principles only; Drug regimens and current treatment criteria require contemporary guideline review.

Molecular results can inform therapy

- Hypermutated MSI and POLE-ultramutated tumors with the use of checkpoint inhibition.
- HER2 amplification is described in a subset, especially among TP53-mutated tumors.
- Predictive utility, treatment eligibility and approvals must be evaluated using current evidence and guidance.

Case discussion: Abnormal bleeding and glandular atypia

A postmenopausal patient has irregular bleeding. Endometrial sampling reveals crowded atypical glands and foci of confluent epithelial growth.

What key diagnostic distinction must be resolved?

Discuss the underlying tissue findings and molecular rationale before revealing the answer.

Case reasoning: Atypical hyperplasia or carcinoma?

Consider atypical hyperplasia

- Crowded clonal glands with atypical nuclei
- Limited samples may not establish invasion
- Concurrent malignancy is possible

Consider carcinoma

- Confluent epithelial growth
- Desmoplasia or destructive invasion
- Extent may only be resolved with more tissue

Case discussion: High-grade tumor in an atrophic uterus

An older patient has a cytologically high-grade glandular endometrial tumor, abnormal p53 expression, and a relatively atrophic background.

Which morphologic–molecular phenotype is most likely?

Discuss the underlying tissue findings and molecular rationale before revealing the answer.

Case reasoning: Serous carcinoma

Supporting clues

- Atrophic endometrial background
- Marked nuclear pleomorphism despite gland formation
- TP53-associated phenotype

Immediate implications

- Treat as intrinsically high grade
- Assess extrauterine dissemination
- Avoid equating glandular growth with low-risk biology

Integrated pattern-recognition checklist

Question	Observation	Interpretive value
Clinical substrate?	Estrogenic vs atrophic	Suggests common histotype
Tumor structure?	Glands vs high-grade papillae	Histologic classification
Molecular profile?	POLE / MMR / NSMP / p53	Biological subgroup
Has it invaded?	Myometrium / beyond uterus	Anatomic extent
Inherited risk?	MMR abnormalities	Possible Lynch work-up

Synthesis: Three independent diagnostic axes

- Histotype: What the tumor looks like (endometrioid, serous or another form).
- Molecular class: The principal altered genomic process.
- Stage: Where the tumor is anatomically distributed.
- These axes provide complementary—not interchangeable—information.

Core concepts to retain

- Atypical hyperplasia / EIN is an important precursor to endometrioid carcinoma.
- PI3K/AKT dysregulation is central to many endometrioid tumors.
- Serous carcinoma is associated with TP53 abnormality and a risk of early extrauterine dissemination.
- Abnormal bleeding prompts tissue diagnosis; Stage and histotype are fundamental to prognosis.

References and teaching scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th edition.
- Carcinoma overview, endometrial hyperplasia and adjacent endometrioid / serous sections were used to support this lecture.
- All architectural and mechanistic illustrations are native editable PowerPoint schematics, not histologic specimens.
- Contemporary FIGO staging algorithms and management recommendations should be verified independently when required.