

Pathogenesis of Breast Cancer

Molecular evolution • inherited susceptibility • tumour microenvironment

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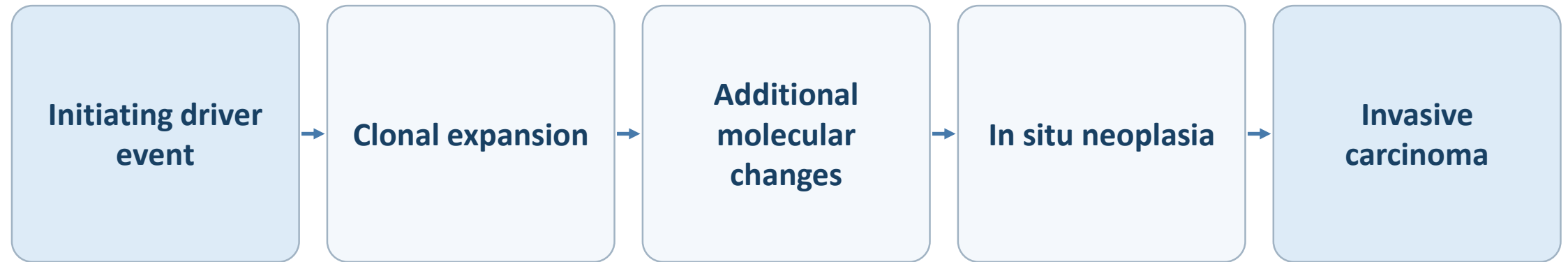
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What this lecture explains

- How initiating genomic events and cell context shape breast carcinoma phenotype.
- Why low-grade and high-grade neoplasia often follow different evolutionary pathways.
- How inherited susceptibility, hormones, and acquired alterations converge.
- Why invasion also depends on epithelial–stromal and immune interactions.

Breast cancer is an evolutionary process



A useful conceptual model—not every tumor passes through a morphologically identifiable precursor.

Initiation is not independent of cell context

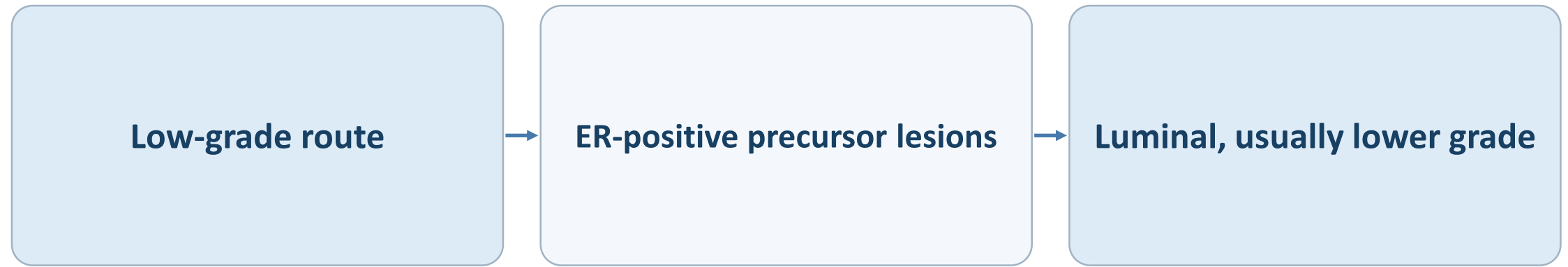
Initiating alteration

- An inherited or acquired driver can establish the first transformed clone.
- Its molecular consequences constrain later evolutionary options.

Epithelial context

- The epithelial cell in which the event occurs may influence phenotype.
- Different lineages and differentiation states can yield different outcomes.

Two major evolutionary routes



In parallel: A high-grade route leads to heterogeneous luminal B, HER2-positive, or triple-negative tumors;
The routes can intersect.

Why terminal duct–lobular anatomy matters

- Most breast carcinomas are thought to arise in the terminal duct–lobular unit.
- “Ductal” and “lobular” describe growth and cohesion patterns, not necessarily distinct cells of origin.
- In situ disease remains bounded by a basement membrane; Invasion breaches that interface.
- Myoepithelial and stromal interactions help maintain normal compartmental architecture.

Three clinical molecular categories

Luminal

ER-positive / HER2-negative

Typically hormone-dependent

HER2-positive

**HER2 amplified /
overexpressed**

ER may be positive or negative

Triple-negative

ER-, PR-, HER2-negative

Molecularly heterogeneous

Clinical biomarker categories overlap imperfectly with intrinsic expression subtypes.

Biomarker groups $\neq$ expression signatures

Routine biomarker grouping

- ER, PR and HER2 protein/gene status guide clinical grouping.
- Provides practical information about biological dependencies.

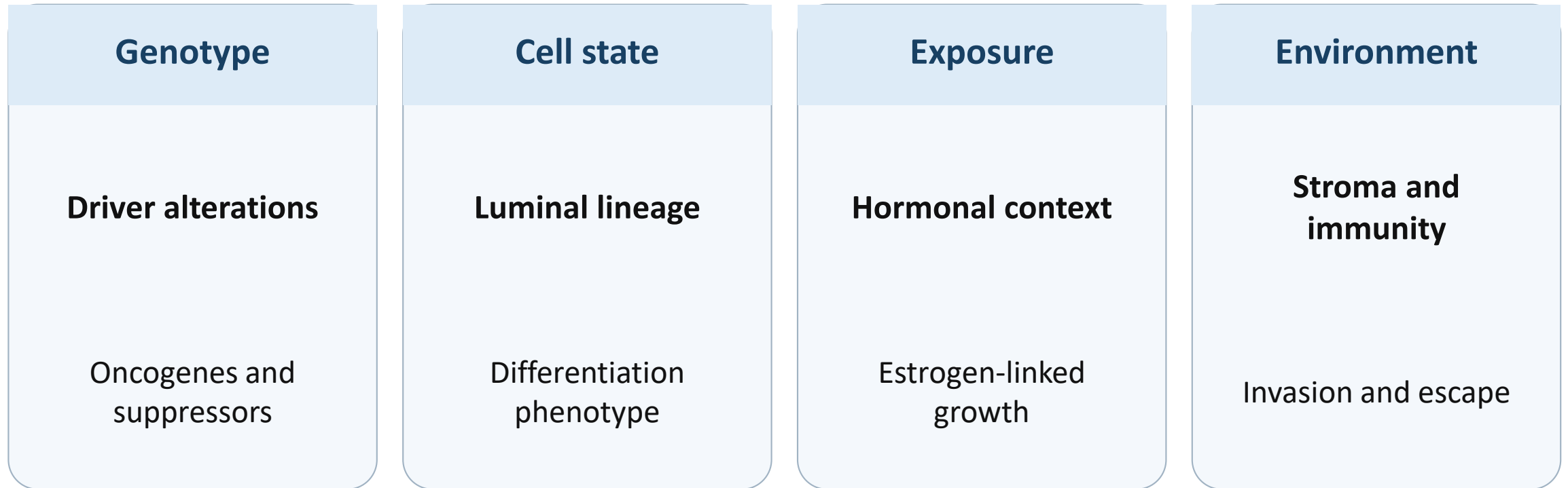
Intrinsic molecular grouping

- Gene-expression profiling distinguishes luminal A, luminal B and basal-like patterns.
- The two frameworks overlap, but are not perfectly interchangeable.

Evolution is heterogeneous, not a single sequence

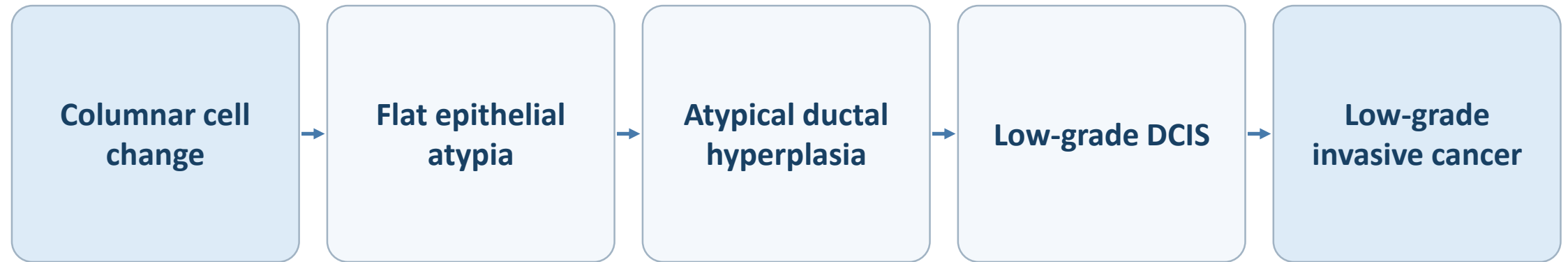
- Low-grade and high-grade tumors commonly have different genomic architectures.
- Tumor cell proliferation, DNA repair capacity, and selective pressures shape progression.
- Atypical lesions may remain noninvasive; Progression is not inevitable.
- A subset of lower-grade tumors can acquire high-grade molecular changes.

Four interlocking determinants of pathogenesis



Breast carcinoma phenotype is a systems-level product of these influences.

Low-grade pathway: A multistep model



Schematic sequence: The pathway is associated with ER-positive luminal neoplasia; Individual lesions do not inevitably progress.

Columnar cell lesions: Earliest recognizable changes

- Variably dilated acini are lined by columnar epithelial cells.
- Microcalcifications may draw attention to these lesions on screening.
- Some lesions belong to the low-grade neoplastic continuum.
- Their appearance provides morphological evidence of early epithelial change.

Flat epithelial atypia versus atypical hyperplasia

Flat epithelial atypia

- Columnar cell lesion with cytologic atypia.
- Does not show the architectural complexity of atypical ductal hyperplasia.

Atypical ductal hyperplasia

- Monomorphic cells in organized patterns, often cribriform or micropapillary.
- Resembles low-grade DCIS but is limited in extent.

Ductal and lobular atypia are related—not identical

Atypical ductal hyperplasia

- Cohesive, regular population with low-grade ductal-type architecture.
- Morphologically related to low-grade DCIS.

Atypical lobular hyperplasia

- Dyscohesive epithelial population within duct–lobular spaces.
- Morphologically resembles classic LCIS but is less extensive.

Carcinoma in situ has already acquired cancer features

- Neoplastic epithelial cells remain within ducts or lobules enclosed by basement membrane.
- Many molecular driver changes are shared with the associated invasive carcinoma.
- The in situ designation is defined by location, not biological innocuousness.
- An intact barrier is the defining distinction from invasive carcinoma.

Low-grade in situ neoplasia is not one uniform entity

Low-grade DCIS

Ductal-type architecture

A common precursor of low-grade invasion

Classic LCIS

Dyscohesive luminal cells

Lobular neoplasia pathway

Atypical lesions

Partial neoplastic features

Risk and precursor significance

These lesions share ER-positive low-grade biology but should not be forced into one linear chain.

Low-grade pathway: Genomic fingerprint

16q loss

Copy-number loss

Characteristic genomic event

1q gain

Copy-number gain

Characteristic genomic event

Luminal program

ER-associated transcription

Characteristic expression pattern

The recurring molecular signature supports relatedness among low-grade precursors and invasive lesions.

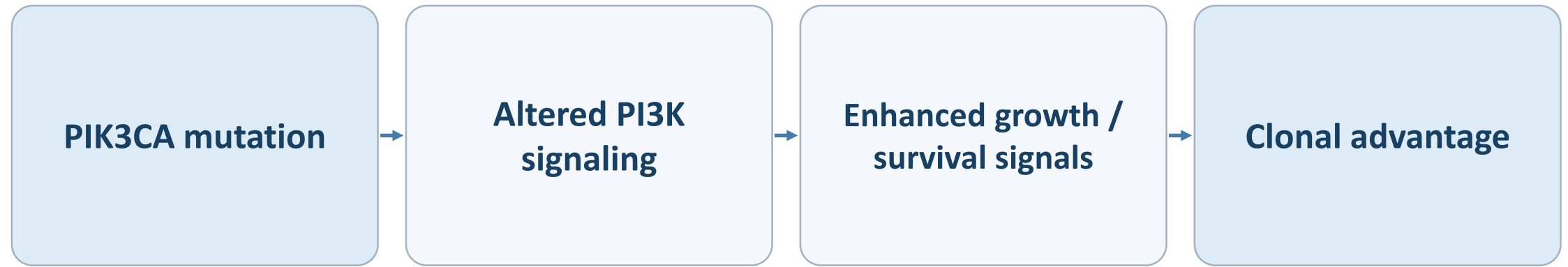
Loss of chromosome arm 16q: A recurring clue

- Loss of 16q is characteristic of the low-grade neoplasia pathway.
- The alteration is detected at the genomic level rather than inferred from microscopic appearance alone.
- It can occur in noninvasive lesions, consistent with early clonal evolution.
- Its presence alone does not prove inevitable invasion.

Gain of chromosome arm 1q: Clonal progression

- Gain of 1q commonly accompanies the low-grade molecular pathway.
- Copy-number change may precede the development of invasive disease.
- Recurrent low-grade alterations help distinguish this route from genomically chaotic high-grade neoplasia.
- Copy-number patterns are not stand-alone clinical diagnostic tests in this lecture.

PIK3CA activation provides growth signaling



PIK3CA mutations are common in luminal A cancers; This schematic simplifies the downstream network.

The luminal expression program is an identity

- Luminal cancers express genes regulated by estrogen receptor signaling.
- Hormone-responsive transcription is a molecular phenotype, not merely a positive stain.
- ER expression links lineage differentiation to growth dependence.
- Degree of proliferation helps distinguish lower- from higher-risk luminal programs.

Risk lesion does not mean predestined cancer

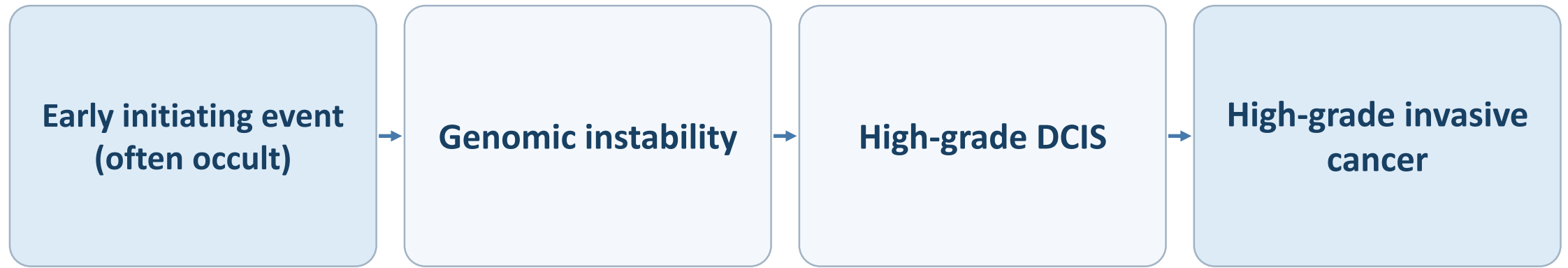
What precursor lesions establish

- A clone with recognizable neoplastic features exists.
- Its genotype can overlap with later carcinoma.

What precursor lesions do not establish

- That every lesion will progress to carcinoma.
- That invasion requires a new universally identifiable driver mutation.

High-grade pathway: The broad model



Earlier high-grade precursors are incompletely defined; The model does not assert a mandatory sequence.

The earliest high-grade precursor remains uncertain

- High-grade DCIS is a recognized major noninvasive counterpart of high-grade invasion.
- Morphologically earlier precursor lesions are much less well characterized.
- Rapid progression before detection may obscure intermediate steps.
- Absence of a recognized precursor is not evidence that there was no precursor.

Low-grade versus high-grade evolution

Low-grade route

- Recognizable atypical and low-grade in situ lesions.
- Often ER-positive with 1q gain / 16q loss.
- Generally less genomic instability.

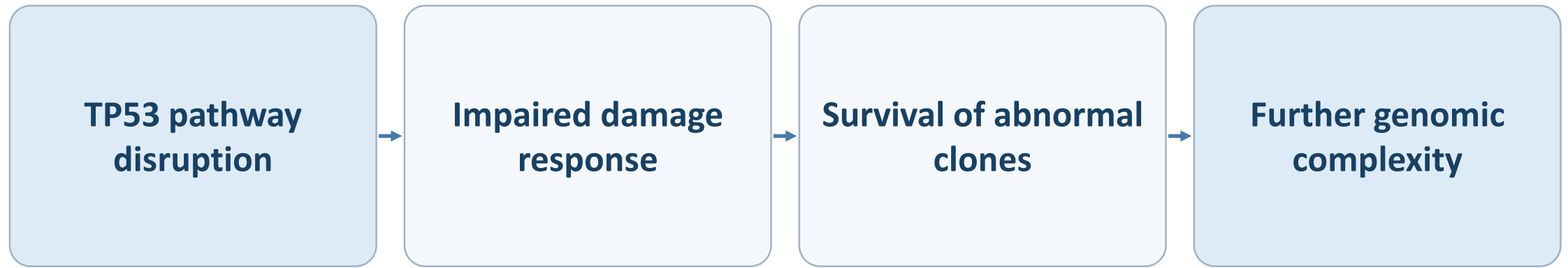
High-grade route

- Earlier steps frequently unrecognized.
- High-grade DCIS often demonstrable.
- More genomic abnormalities and proliferation-associated expression.

High-grade genomic instability is foundational

- High-grade tumors frequently show complex copy-number alterations and rearrangements.
- Genomic instability creates new variants from which selection can act.
- DNA-repair failure and disrupted cell-cycle checkpoints can amplify genomic disruption.
- The degree of instability differs among molecular subtypes.

TP53 dysfunction favors genomic evolution



TP53 mutations occur frequently in high-grade pathways, particularly many triple-negative tumors.

Reported high-grade genomic changes

13q loss

Copy-number loss

Associated with high-grade
pathway

11q13 gain

Copy-number gain

Reported high-grade alteration

17q12 gain

HER2 region

Amplification in HER2-driven
cancers

These are associations evolutionary model—not a universal diagnostic panel.

Low-grade and high-grade routes can intersect

- Largely separate but not mutually exclusive trajectories.
- Some luminal cancers acquire additional abnormalities and become more proliferative.
- Acquired defects in genome-stability pathways may enable grade progression.
- A higher-grade phenotype need not imply a wholly independent cell of origin.

High-grade biology yields multiple phenotypes

Luminal B

ER-associated, higher proliferation

May evolve from luminal lesions

HER2 positive

ERBB2 amplification

Receptor-driven signaling

Triple-negative

Often HR repair defective

ER-independent and HER2-negative

The shared feature is not one mutation, but frequently accelerated evolution and genomic complexity.

Familial and sporadic cancers converge

Inherited susceptibility

- Constitutional variant predisposes epithelial clones.
- Subsequent somatic events complete tumor evolution.
- Often affects DNA repair / genomic stability.

Sporadic development

- Driver events accumulate without a recognized highly penetrant inherited syndrome.
- Hormonal influences and acquired genomic changes remain important.
- Can converge on similar molecular phenotypes.

Family history is biologically informative

- Inherited susceptibility contributes through rare high-penetrance genes and lower-penetrance variants.
- A positive family history may reflect multiple interacting risk alleles.
- Absence of a striking pedigree does not rule out a genetic contribution.
- “Familial” is broader than BRCA-associated cancer.

Penetrance is a probability, not a destiny

- Penetrance is the risk that a carrier of a susceptibility variant develops cancer.
- Risk depends on the variant and potentially other inherited factors.
- High- and moderate-penetrance genes differ in effect magnitude.
- A germline pathogenic variant is susceptibility—not itself a diagnosis of carcinoma.

Inherited tumor-suppressor defects: Two hits



Autosomal dominant inheritance of cancer susceptibility can coexist with recessive gene inactivation within the tumor.

BRCA1 and BRCA2: Central susceptibility genes

- BRCA1 and BRCA2 account for a major fraction of single-gene hereditary breast cancer.
- Both proteins contribute to repair of double-strand DNA breaks by homologous recombination.
- Pathogenic variants also confer susceptibility to selected cancers outside the breast.
- The resulting breast cancer phenotype differs between BRCA1 and BRCA2 carriers.

BRCA1-associated versus BRCA2-associated cancer

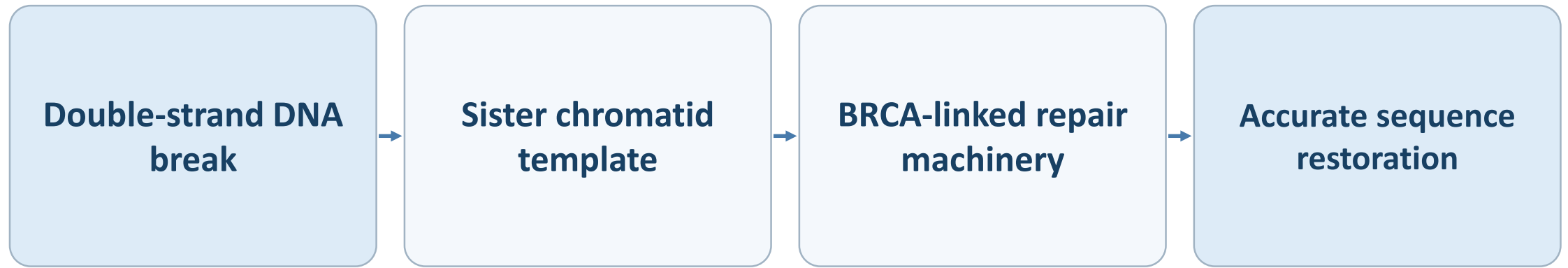
BRCA1-associated tumors

- Frequently triple negative description.
- May arise from defects affecting breast progenitor differentiation.
- Homologous recombination repair is compromised.

BRCA2-associated tumors

- A majority are ER-positive.
- Luminal B-type biology can be observed.
- Homologous recombination repair is compromised.

Homologous recombination repairs double-strand breaks



Homologous recombination is especially important for maintaining genomic integrity during cell replication.

DNA-repair susceptibility is a network

BRCA1 / BRCA2

Homologous recombination

Core breast predisposition genes

PALB2 / RAD51C / RAD51D

Repair-associated proteins

Genome maintenance

ATM / CHEK2

Damage response

Checkpoint and repair context

These interconnected genes are associated with familial susceptibility in the source text.

Biallelic DNA-repair loss accelerates instability

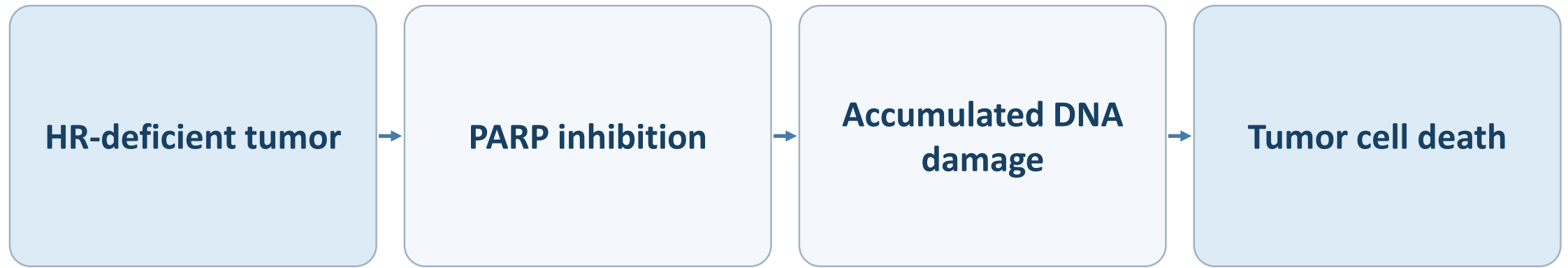


The defining mechanism is genome maintenance failure, not a specific histologic architecture.

Synthetic lethality exploits repair dependence

- Homologous-recombination-deficient tumor cells already lack a major DNA-repair pathway.
- PARP inhibitors disrupt repair of additional DNA lesions.
- Combined defects can create lethal genomic damage selectively in vulnerable tumors.
- Normal cells with intact homologous recombination retain an alternative repair capacity.

PARP inhibition: Mechanism in four stages



Simplified mechanism underlying sensitivity to PARP inhibition; Not a comprehensive treatment selection guideline.

Why BRCA loss predisposes to breast cancer is unresolved

- BRCA proteins function widely throughout the body, yet cancer susceptibility is tissue biased.
- Proposed explanations include lineage-specific differentiation and hormonal survival signals.
- Epithelial tissues may differ in the DNA damage types they experience.
- These ideas are hypotheses, not a settled single mechanism.

A proposed BRCA1–progenitor link



Hypothesis: Impaired differentiation following BRCA1 loss may leave a genetically unstable progenitor compartment; This causal model remains tentative.

Risk architecture: Monogenic and polygenic

Single-gene high/moderate effects

- Loss-of-function variants in genes regulating stability or growth.
- Often recognizable through familial clustering or associated cancer syndromes.

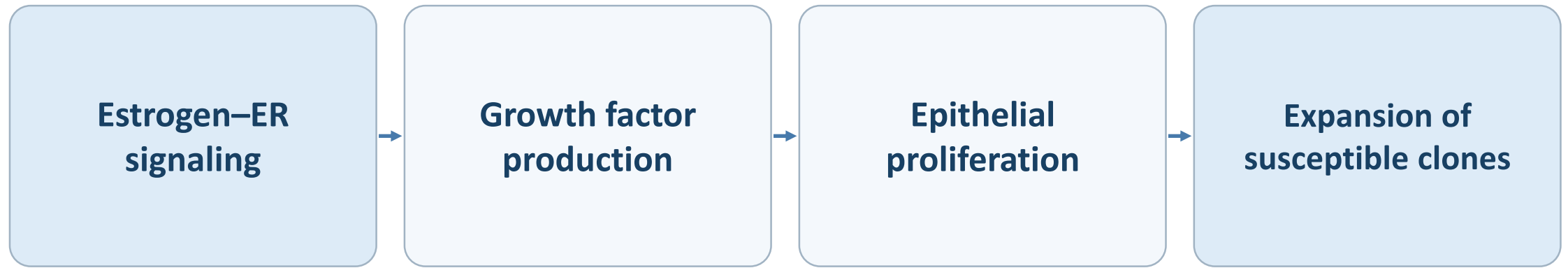
Lower-penetrance combinations

- Multiple polymorphic variants can jointly modify susceptibility.
- One variant may have only a modest measurable impact on individual risk.

Sporadic luminal cancer is hormone linked

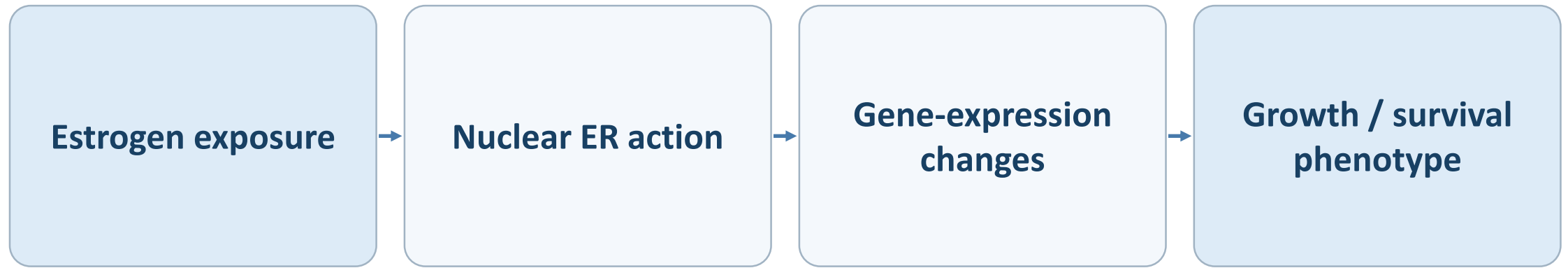
- The luminal ER-positive/HER2-negative pathway accounts for a large proportion of breast cancers.
- Cumulative estrogen exposure is a major biologic risk factor.
- Estrogen may influence both emergence and subsequent growth of mutated clones.
- Hormone antagonism provides clinical evidence of estrogen dependence.

Estrogen can amplify local growth signals



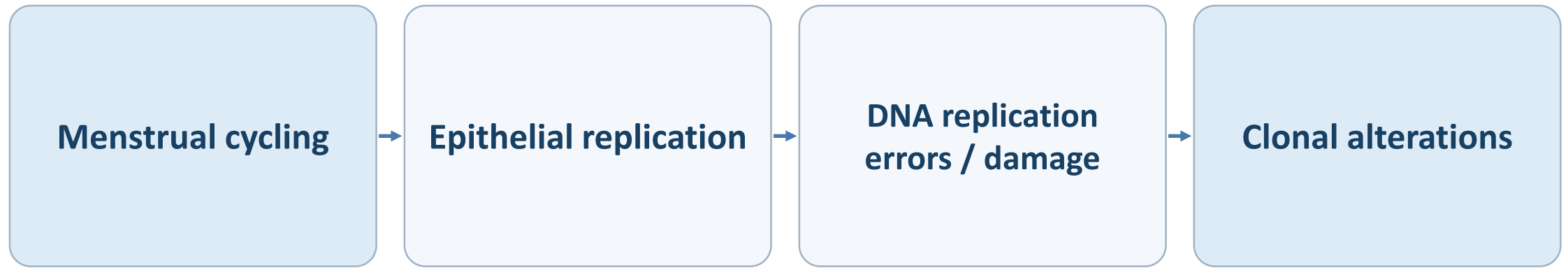
TGF- α , PDGF and FGF among estrogen-associated local growth factors.

Estrogen acts as a transcriptional regulator



Many ER-regulated genes can contribute to epithelial growth and cancer evolution.

Repeated proliferation increases mutation opportunity

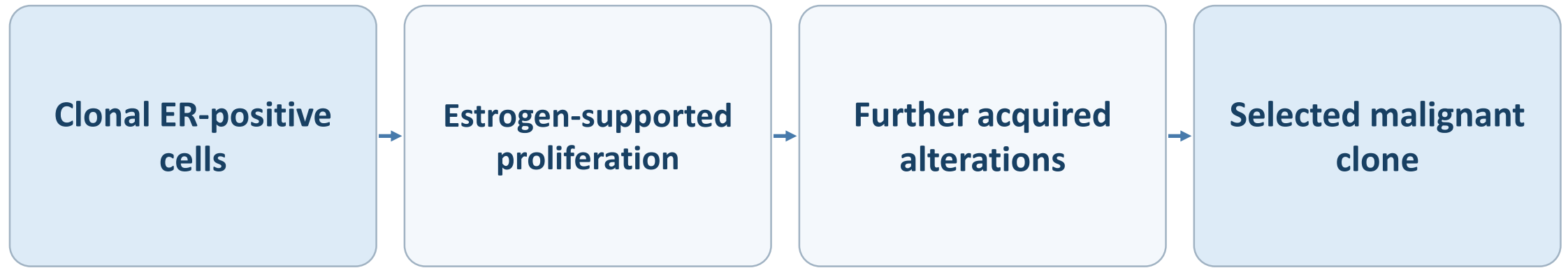


The proposed link is increased opportunities for mutation and fixation during repeated cycles; This is mechanistic interpretation.

Reproductive and environmental context modifies risk

- Earlier menarche and later menopause increase cumulative menstrual cycling.
- Late first pregnancy and nulliparity are associated with increased risk.
- Prolonged breastfeeding and early pregnancy are associated with lower risk.
- Postmenopausal obesity, activity and alcohol are modifiable influences described in the text.

A hormone-responsive clone still needs other events



Most low-grade precursor lesions never develop invasive cancer; ER stimulation alone is not sufficient.

Luminal A: Differentiated, hormone-regulated program

- Strong expression of estrogen-regulated and luminal genes.
- Often strongly ER-positive and PR-positive.
- Typically lower proliferation and well-differentiated morphology.
- Frequent alterations include 1q gain, 16q loss and PIK3CA activation.

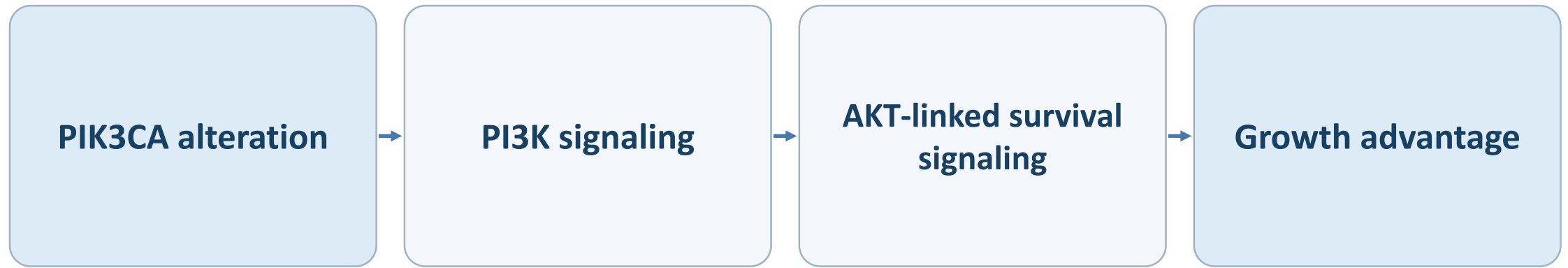
Luminal B: A more proliferative luminal state

- Retains a luminal component but expresses more proliferation-associated genes.
- Usually higher grade, with lower ER/PR expression than luminal A.
- More chromosomal aberrations are often present.
- Can arise after additional genetic changes in a luminal precursor population.

Luminal A and B: Biological contrasts

Feature	Luminal A tendency	Luminal B tendency
Gene program	Strong ER-regulated	Proliferation enriched
Proliferation	Lower	Higher
Differentiation	Better	Less differentiated
Genomic burden	Often lower	Often greater

PI3K activation links genotype to phenotype

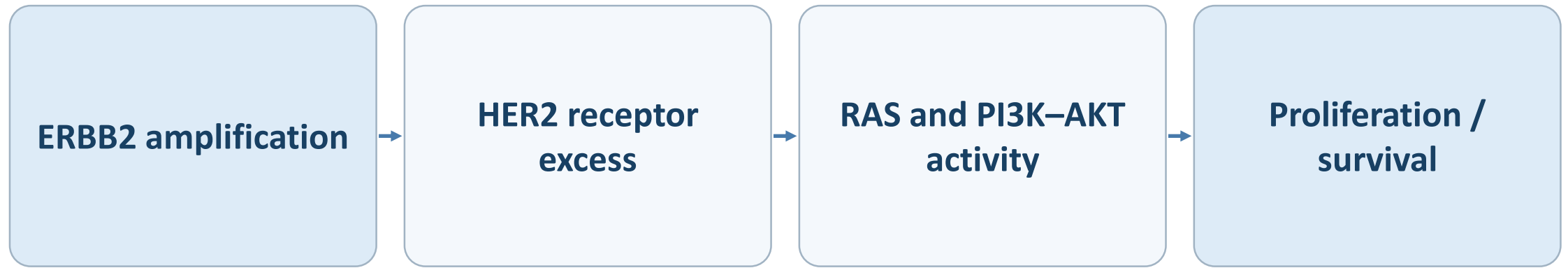


A conceptual molecular axis; The complete pathway contains additional receptors and feedback loops.

HER2-positive carcinoma is gene-amplification driven

- Amplification of the ERBB2 / HER2 region on chromosome 17q is central.
- HER2 is a receptor tyrosine kinase with growth-promoting activity.
- HER2-positive cancers may express ER or be ER-negative.
- Gene amplification underlies the great majority of HER2 protein overexpression in the source.

HER2 drives mitogenic and survival pathways



Conceptual receptor signaling chain; HER2-driven tumors often show additional genomic alterations.

HER2 tumors combine signaling with instability

- HER2 amplification is often accompanied by complex chromosomal rearrangements.
- TP53 and PIK3CA mutations are frequently observed.
- Amplified oncogenic signaling increases proliferation and opposes apoptosis.
- The high-grade phenotype reflects both receptor activity and accumulated genomic change.

HER2 molecular change versus its detection

Underlying mechanism

- ERBB2 locus amplification increases gene copy number.
- HER2 receptor overexpression drives downstream signaling.

Observable clinical biomarkers

- IHC can demonstrate protein overexpression.
- In situ hybridization can assess gene amplification.
- These are related but technically distinct assays.

Triple-negative cancer is defined by what it lacks

- No detectable ER, PR or HER2 by the defining clinical biomarker criteria.
- The group is heterogeneous and not one molecular disease.
- Most common high-grade triple-negative cancers have an ER-independent phenotype.
- A minority of special low-grade histologic tumors are also triple-negative.

Triple-negative is not synonymous with basal-like

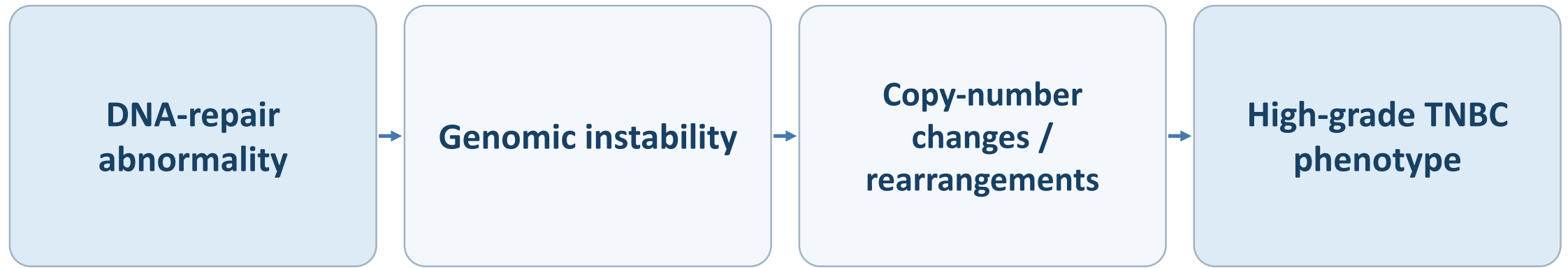
Triple-negative biomarker phenotype

- Defined by absence of ER, PR and HER2.
- Comprises biologically distinct tumors.

Basal-like expression subtype

- Defined by a molecular expression program.
- Often expresses basal / myoepithelial-associated genes.
- Overlaps substantially, but incompletely, with TNBC.

Homologous recombination deficiency in TNBC

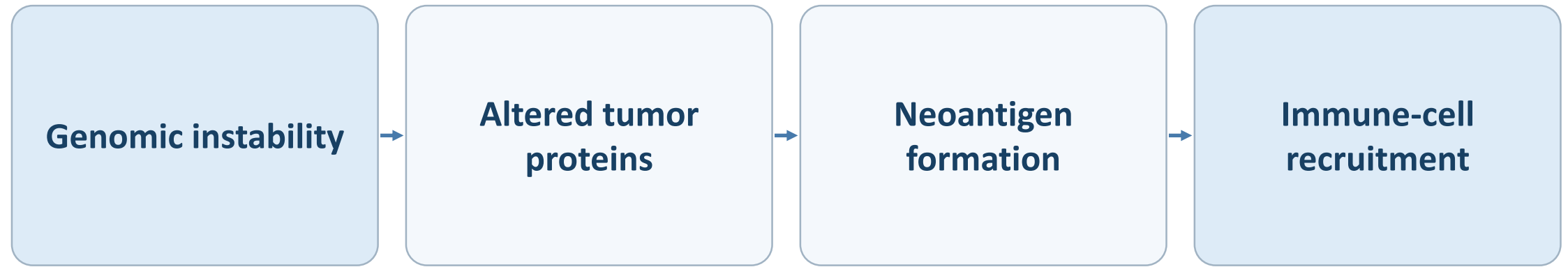


In familial tumors BRCA mutations may cause repair deficiency; Sporadic TNBC more often shows other mechanisms including BRCA1 silencing.

TP53 and structural change dominate many TNBCs

- TP53 is the only cancer gene mutated in the majority of TNBCs described in the source.
- Other driving changes may involve rearrangements and copy-number variation.
- Many TNBCs show marked cytologic atypia, brisk proliferation and necrosis.
- A high burden of genome damage helps shape tumor immunogenicity.

Genome instability can expose tumor neoantigens



This mechanism helps explain prominent immune infiltration in many high-grade TNBCs.

High-grade TNBC frequently engages immunity

- Tumor neoantigens can stimulate immune recognition.
- Some triple-negative tumors contain conspicuous tumor-infiltrating lymphocytes.
- Tumor immune evasion can occur despite immune-cell recruitment.
- Biological immune responsiveness provides a rationale for immunotherapy in appropriate settings.

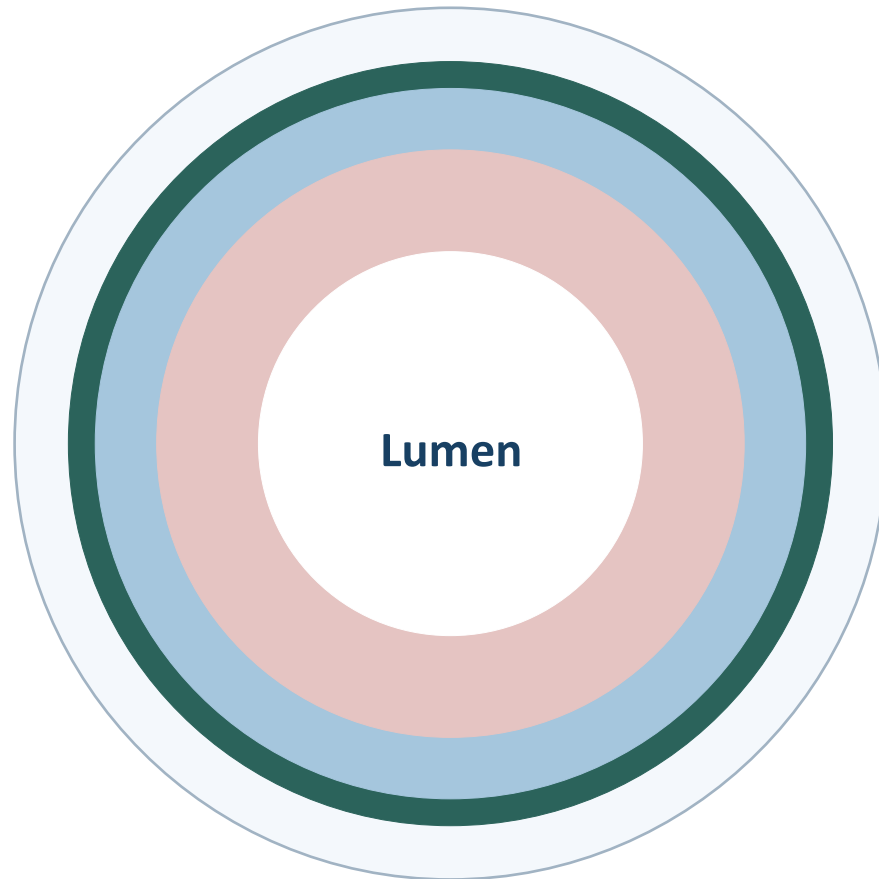
Not every triple-negative cancer is aggressive

- Some special histologic types are triple-negative yet behave favorably.
- The low-grade subset is morphologically and genetically distinct from common high-grade TNBC.
- Biomarker negativity does not substitute for histologic classification.
- Adenoid cystic, secretory and low-grade adenosquamous examples.

Invasion is a biological paradox

- Many genomic alterations in invasive breast cancer are detectable in carcinoma in situ.
- No universal invasion-specific genomic change has been identified.
- An invasive transition cannot be explained by driver acquisition alone.
- Microenvironmental interactions are plausible determinants of basement membrane breach.

Normal tissue integrity is cooperative



 **Luminal epithelial cells**

Inner epithelial ring

 **Myoepithelial cells**

Outer epithelial layer

 **Basement membrane**

Structural boundary

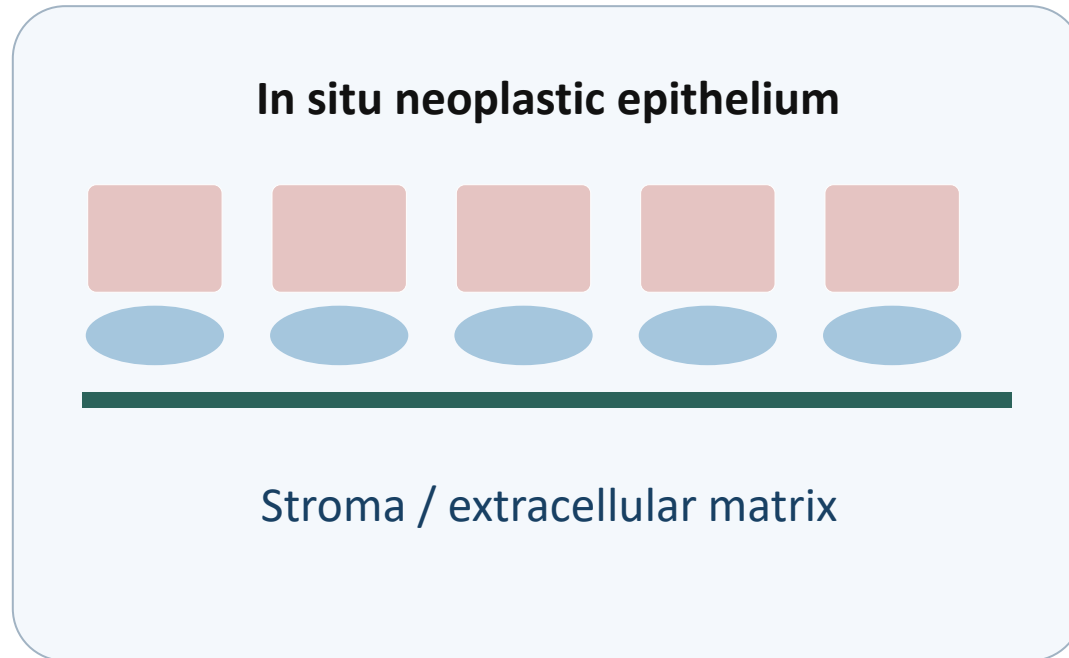
 **Stroma / matrix**

Local support environment

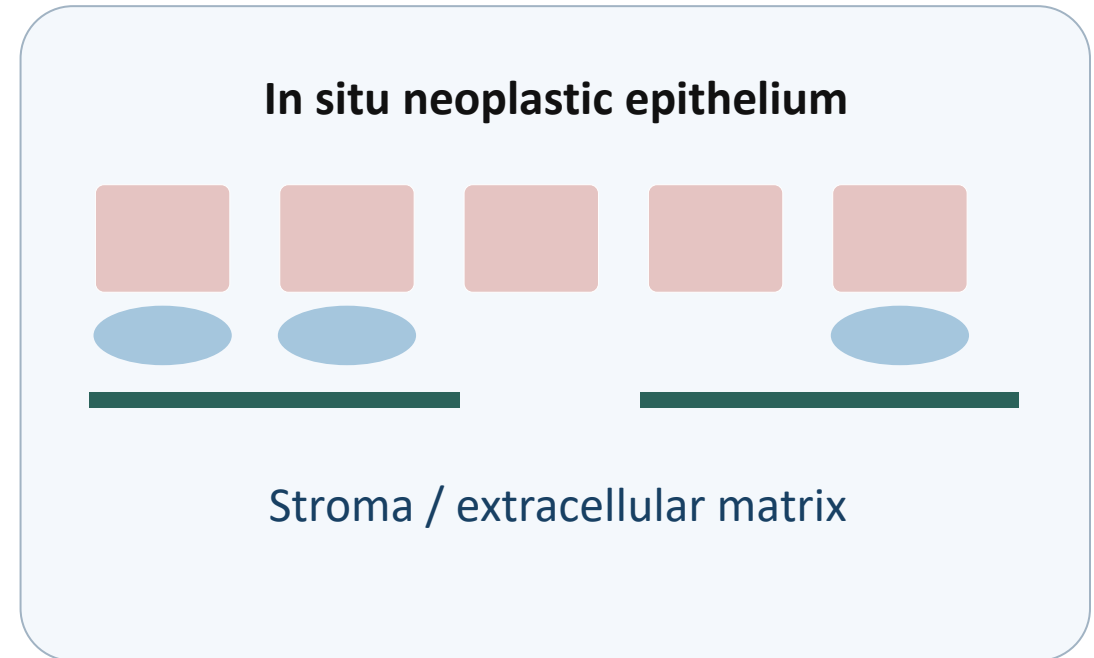
Schematic transverse model: Normal barrier integrity depends on multiple interacting cell compartments.

One route toward basement membrane failure

Preserved epithelial boundary



Proposed disruption in some lesions

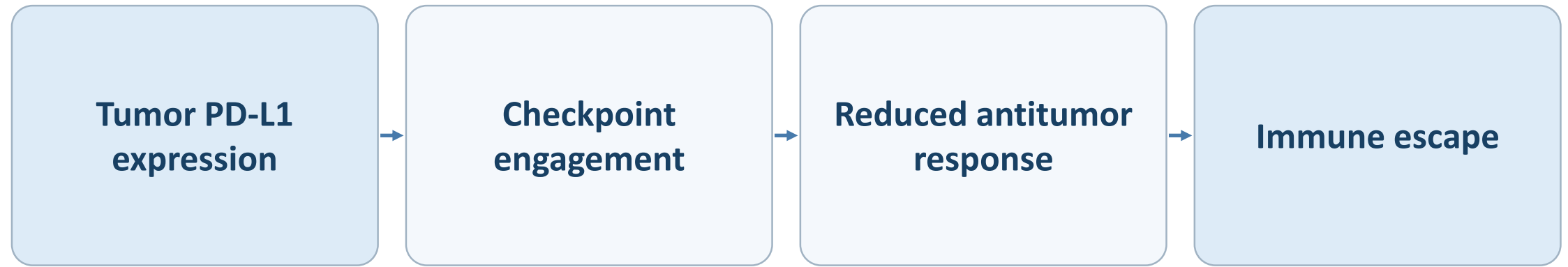


Schematic hypothesis: Myoepithelial depletion and focal basement membrane defects may facilitate invasion.

Cancer-associated fibroblasts support progression

- Activated stromal fibroblasts can facilitate tumor-cell adhesion.
- Extracellular matrix remodeling alters mechanical and signaling interfaces.
- Fibroblasts may support a locally immunosuppressive environment.
- Tumor and stroma can mutually reshape the niche during progression.

Immune evasion can be locally engineered



The source cites upregulation of PD-L1 as one possible mechanism among several.

Microenvironment integrates three barriers

Physical

Basement membrane

Preserves epithelial boundaries

Biochemical

ECM and fibroblasts

Modulates invasion-associated signals

Immunologic

Immune cells / PD-L1

Constrains or permits tumor survival

Invasive behavior emerges from interactions, not a single isolated molecular switch.

Major breast cancer pathways: Synthesis

Feature	Low-grade luminal	High-grade luminal / HER2 / TNBC
Precursors	Often recognizable	Earlier stages poorly defined
Genomics	1q gain / 16q loss	Greater structural complexity
Key signaling	ER / PI3K	Proliferation, HER2 or HR defect
In situ link	Low-grade DCIS / classic LCIS	High-grade DCIS

Case: A low-grade luminal evolutionary pattern

A biopsy shows a monomorphic ER-positive ductal proliferation with limited low-grade architectural atypia. Molecular evaluation finds gain of 1q and loss of 16q.

Interpret:

- Which evolutionary route is most consistent?
- Why does atypia not prove inevitable invasion?

Case: Inherited repair vulnerability

A patient carries a pathogenic germline BRCA1 variant. The carcinoma is high grade and triple-negative; Tumor cells show impaired homologous recombination.

Interpret:

- Which inherited-somatic sequence can establish repair deficiency?
- Why can PARP inhibition be effective?

Case: Amplification and signaling

An invasive high-grade breast carcinoma shows strong HER2 protein expression and increased ERBB2 gene copies.

Interpret:

- What genomic mechanism explains the phenotype?
- Which downstream pathways mediate growth advantage?

Mechanisms to retain

- The initiating event and epithelial context influence tumor phenotype.
- Low-grade and high-grade trajectories differ but can intersect.
- BRCA-linked homologous recombination, estrogen–ER signaling and HER2 amplification are distinct pathogenic axes.
- Microenvironmental remodeling and immune escape help explain the transition to invasion.

Primary reading

Robbins, Cotran & Kumar

Pathologic Basis of Disease, 11th edition (2026)

The Breast — pathogenesis of breast cancer, including the familial and sporadic pathways.

Source locators, extraction boundaries, and visual provenance are recorded in the speaker notes.