

Pathogenesis of Sporadic (Nonfamilial) Breast Cancer

Molecular pathways • precursor lesions • tumor phenotype

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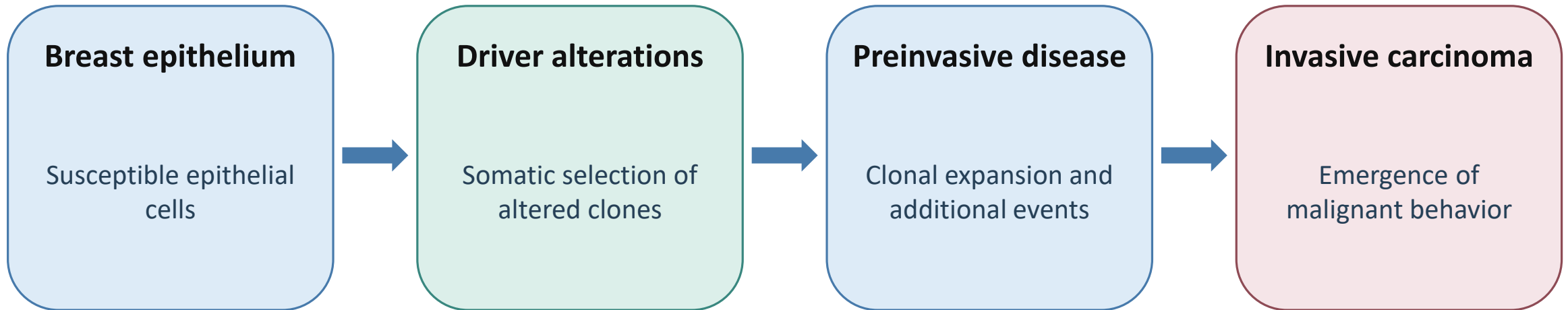
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Learning outcomes

- Contrast low- and high-grade evolutionary pathways
- Explain estrogen-related mechanisms in luminal cancer
- Relate HER2 and triple-negative molecular drivers to phenotype
- Integrate invasion, histology, biomarkers, and clinical implications

Breast carcinoma develops by stepwise clonal evolution



The sequence is a model; Not every lesion progresses.

The initiating event helps determine the final phenotype

Early influences

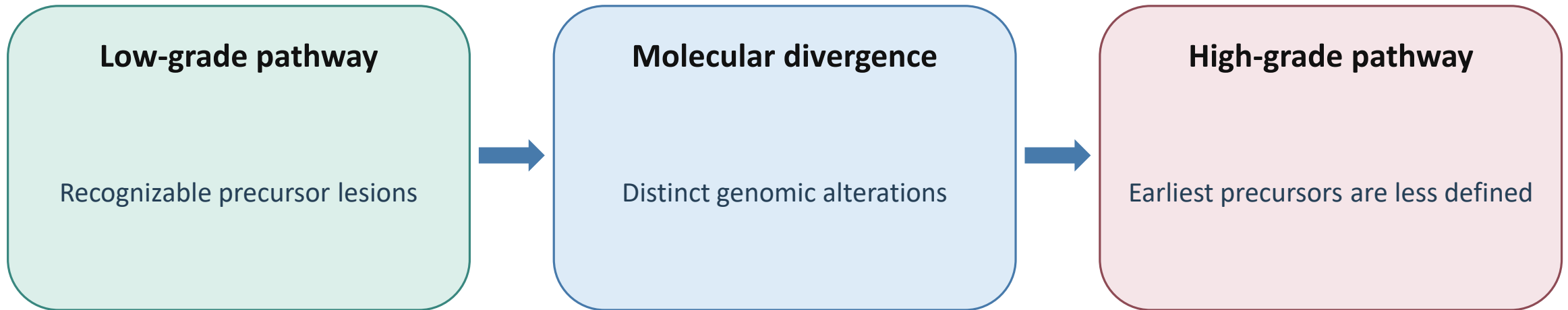
- Identity/state of the susceptible cell
- Nature of initial genomic alteration
- Subsequent selection under local signals

Later influences

- Accumulation of further genetic alterations
- Selection of subclones with growth advantage
- Interactions with the tumor microenvironment

A tumor subtype reflects both evolutionary history and current phenotype.

Histologic grade separates two broad evolutionary routes



These routes are useful models, not biologically sealed compartments.

Three clinically recognizable molecular phenotypes

Luminal

- ER-positive / HER2-negative
- Usually includes luminal A and luminal B gene-expression patterns

HER2-positive

- HER2 overexpression / gene amplification
- ER status can be positive or negative

Triple-negative

- ER-negative, PR-negative, HER2-negative
- Biologically heterogeneous

Receptor/IHC groups overlap with, but are not identical to, expression-defined classes.

Receptor assays and molecular profiling answer different questions

Routine tumor markers

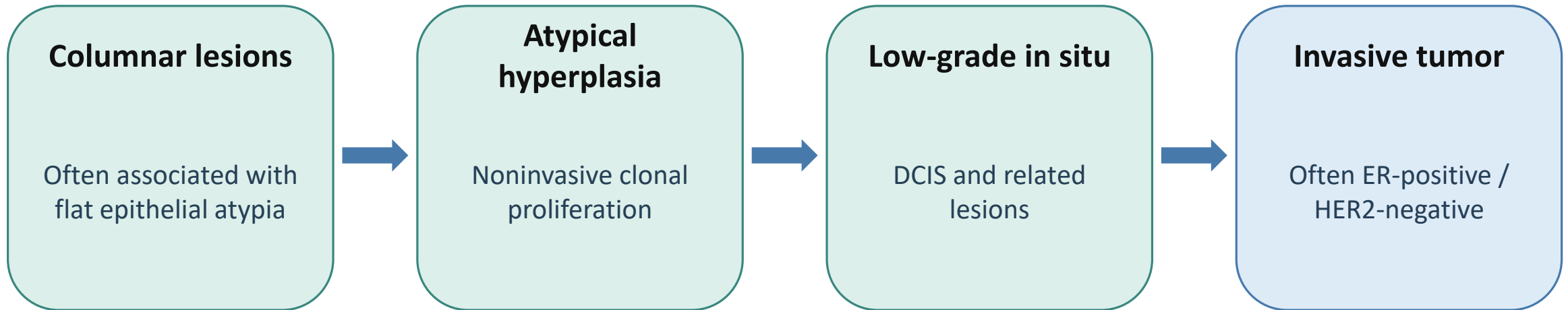
- ER and PR expression: Hormone receptor phenotype
- HER2 protein and/or gene status
- Help select biomarker-directed management

Expression profiling

- Multigene mRNA patterns
- Luminal A, luminal B, HER2-enriched, basal-like
- Groupings do not perfectly match receptor results

Do not equate an immunohistochemical subtype with an exact genomic-expression class.

Low-grade progression has recognizable precursor lesions



Progression is possible, not inevitable.

Flat epithelial atypia belongs to the low-grade pathway

- Columnar cell lesions may show epithelial atypia, termed flat epithelial atypia.
- The low-grade pathway often includes flat epithelial atypia before advanced lesions.
- This lesion is best understood as part of a proposed stepwise sequence—not a guaranteed precursor.

Interpretive limit

Histologic atypia alone
does not establish
invasive cancer.

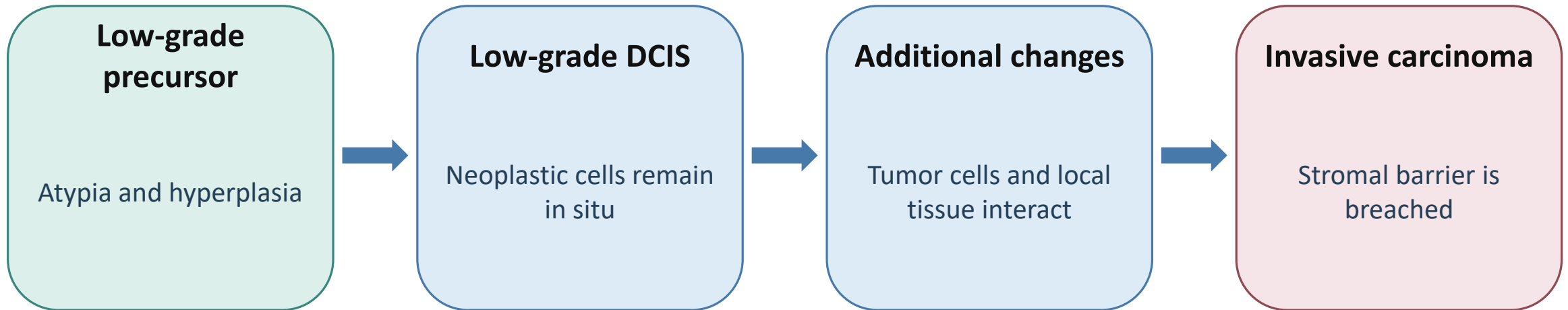
Atypical hyperplasia is an intermediate clonal lesion

- Atypical ductal and lobular hyperplasia participate in the low-grade neoplasia pathway.
- These lesions share parts of the genomic pattern found in low-grade invasive cancers.
- Only a minority of recognized precursor lesions evolve into malignancy.

Progression risk

Multiple additional events are usually required for invasive cancer.

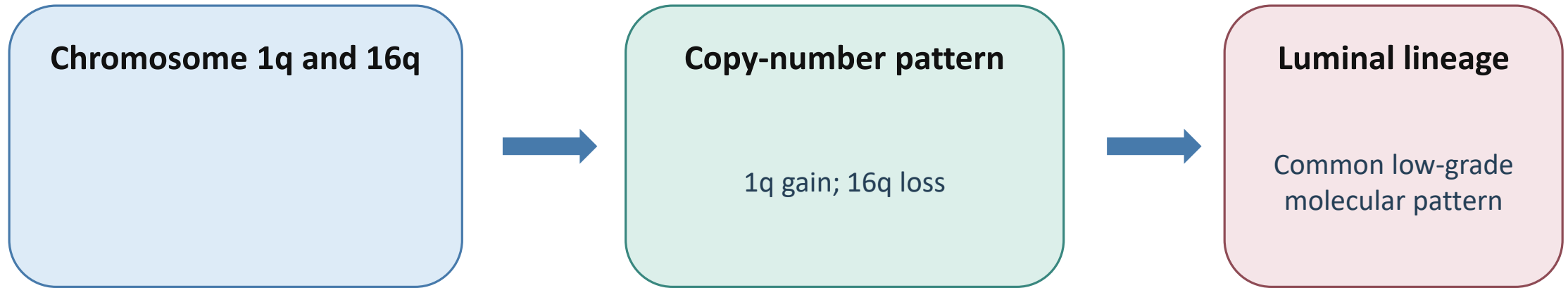
Low-grade DCIS precedes some ER-positive invasive cancers



There is no single known universal genetic switch that produces invasion.

Chromosome changes characterize low-grade neoplasia

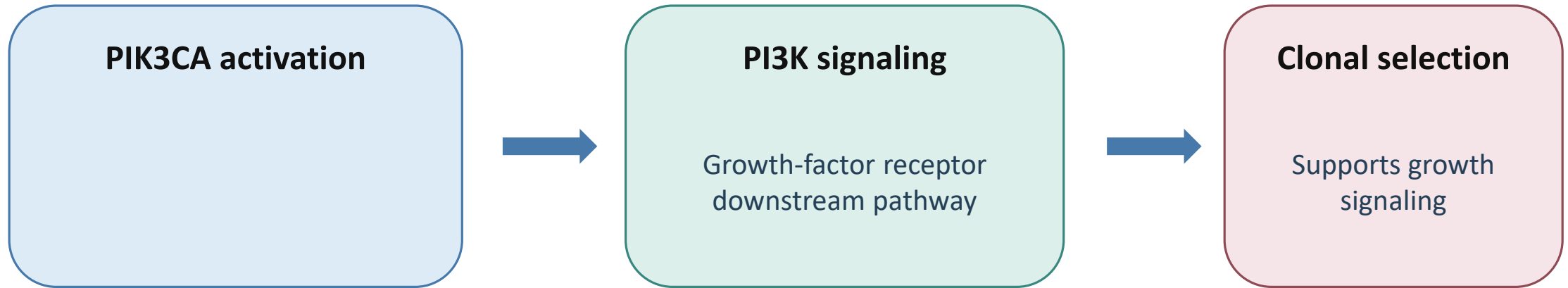
Biologic event



Low-grade tumors often carry fewer large-scale chromosomal rearrangements than high-grade tumors.

PIK3CA is a major luminal pathway alteration

Biologic event



PIK3CA encodes a central signaling enzyme; A mutation is not the whole causal story.

Genomic organization differs by tumor grade

Lower-grade tumors

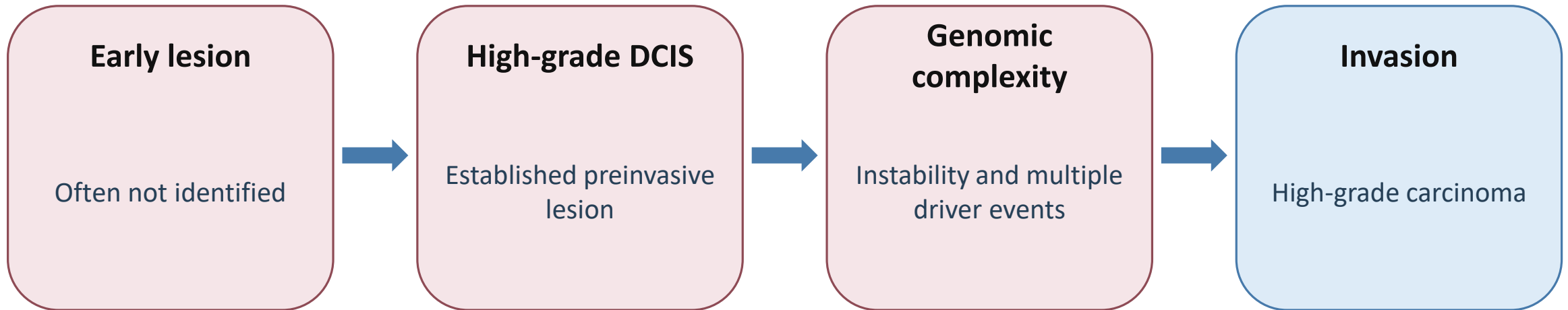
- Relatively “quiet” genomes
- 1q gain and 16q loss are characteristic
- Often strongly ER-positive

Higher-grade tumors

- Numerous chromosomal aberrations
- Greater structural genomic complexity
- High proliferation and more frequent TP53 alterations

These patterns are probabilistic associations, not immutable diagnostic rules.

High-grade evolution has less certain early steps



Unknown precursor ≠ absence of a precursor.

Why high-grade precursor lesions are difficult to identify

- The earliest lesion in the high-grade pathway remains poorly characterized.
- The source proposes that some precursor stages may progress before detection.
- High-grade DCIS is a recognized immediate noninvasive precursor.

Evidence boundary

The timing and identity of earliest high-grade precursor lesions remain uncertain.

High-grade DCIS links high-grade in situ and invasive disease

- High-grade DCIS shares many genomic abnormalities with associated invasive carcinoma.
- TP53 changes, increased genomic instability, and HER2 amplification occur in relevant high-grade branches.
- Molecular similarity does not identify a universal driver of basement membrane invasion.

Ductal confinement

DCIS denotes carcinoma confined within ductal structures.

Three genomic themes enrich the high-grade route

Genomic instability

- Complex copy-number profiles
- Chromosomal rearrangements

TP53 alteration

- Frequent in several high-grade phenotypes
- Loss of genomic surveillance

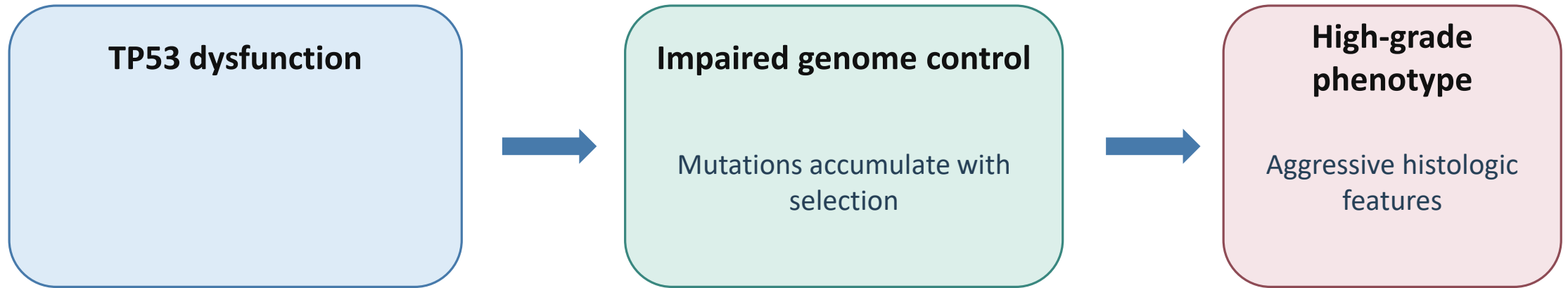
Selected growth drivers

- HER2 amplification in HER2-positive disease
- DNA repair pathway impairment in subsets

These processes frequently coexist in individual tumors.

TP53 alteration favors genomic instability

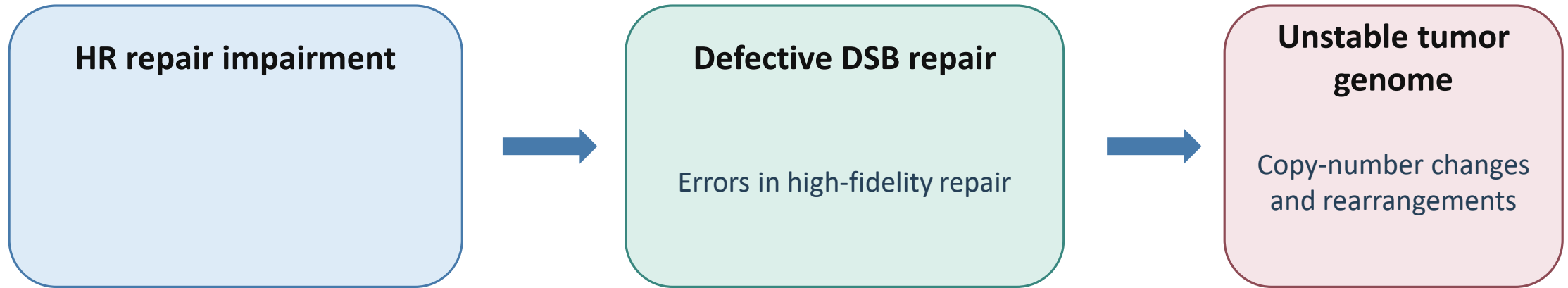
Biologic event



TP53 mutation is common in HER2-positive and high-grade triple-negative carcinomas.

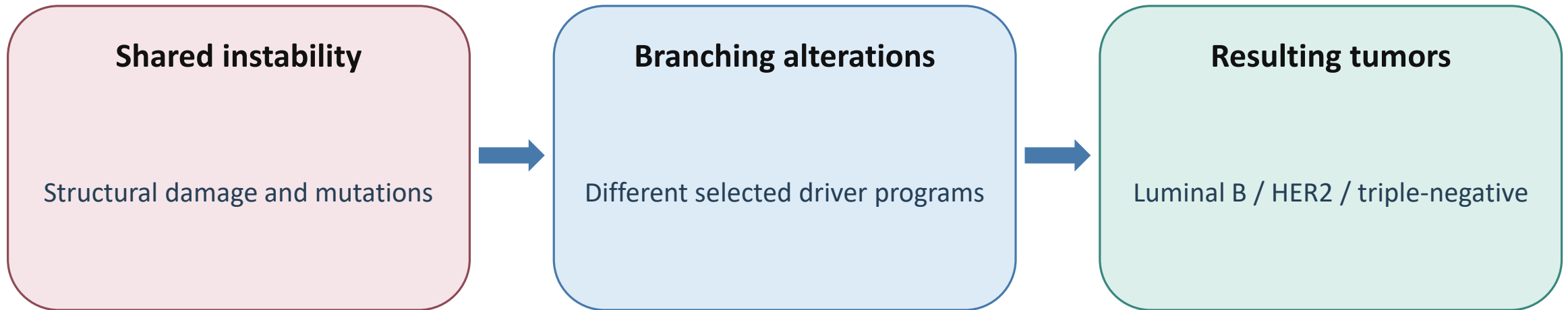
Homologous recombination defects permit chromosomal damage

Biologic event



Sporadic tumors can develop repair deficiencies without an inherited BRCA mutation.

The high-grade pathway can produce distinct phenotypes



There is no single molecular program shared by all high-grade cancers.

Low-grade tumors may progress toward high grade

Typical pattern

- Low-grade and high-grade pathways differ in molecular profile
- Each has characteristic histologic features

Important exception

- Low-grade lesions may acquire additional genomic alterations
- Some can progress to a more aggressive high-grade phenotype

Separate pathways are a simplification, not a barrier to evolutionary transition.

In situ–invasive transition is not explained by one new driver

What is observed

- Many genomic abnormalities of invasive cancer occur in its DCIS precursor
- Major driver mutations can precede invasion

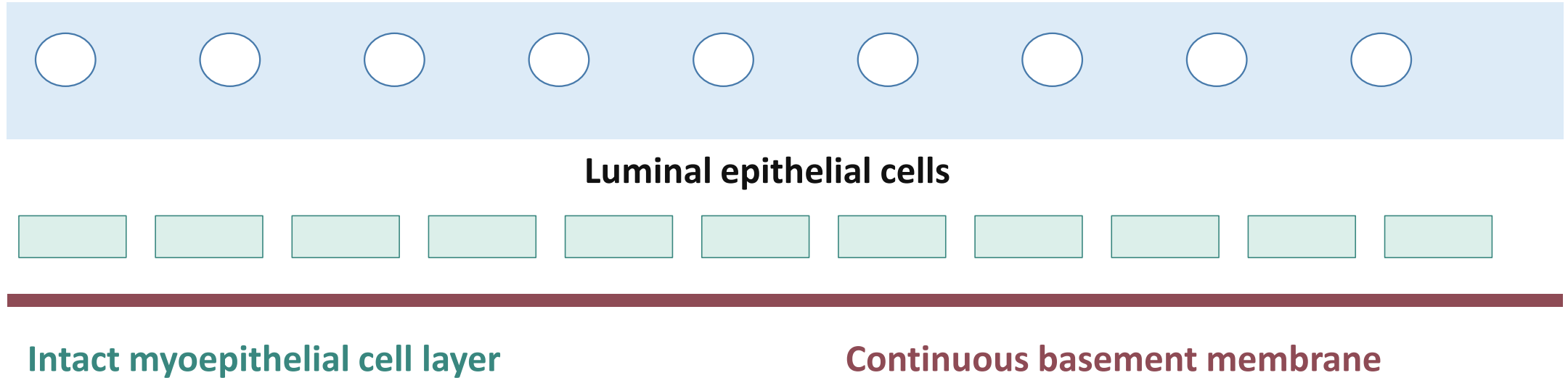
What remains uncertain

- No universal invasion-specific genomic alteration has been found
- Local tissue and microenvironmental events may be important

Do not present stromal invasion as the consequence of one named mutation.

A stable ductal boundary resists stromal invasion

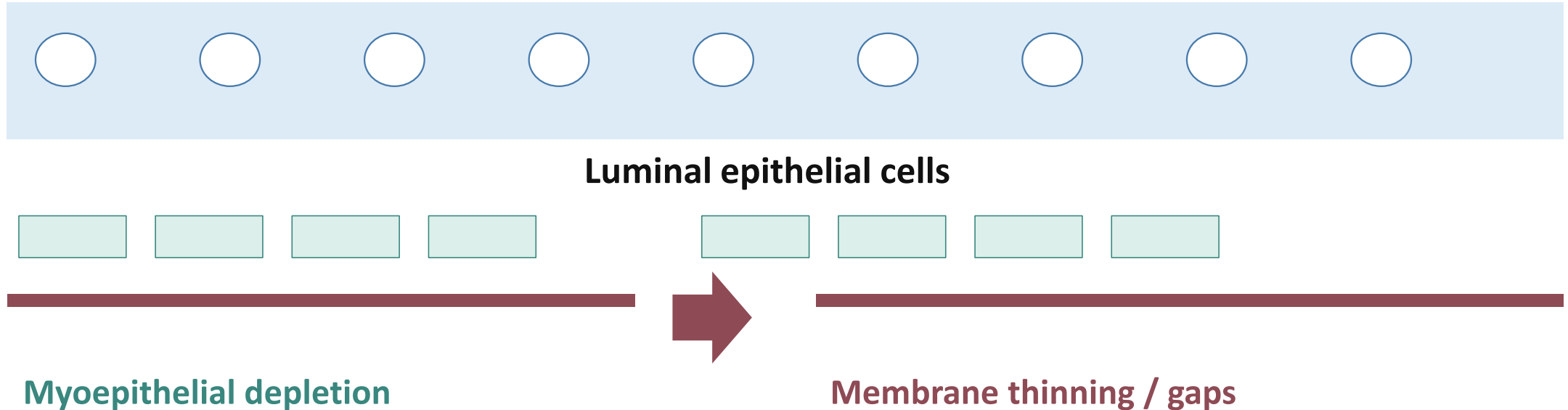
Schematic breast duct cross-section (not histology)



An intact myoepithelial–basement membrane unit constrains stromal invasion.

Myoepithelial loss and membrane gaps may facilitate invasion

Schematic breast duct cross-section (not histology)



Disrupted ductal support structures may help permit stromal entry.

Cancer-associated fibroblasts reshape the tumor environment

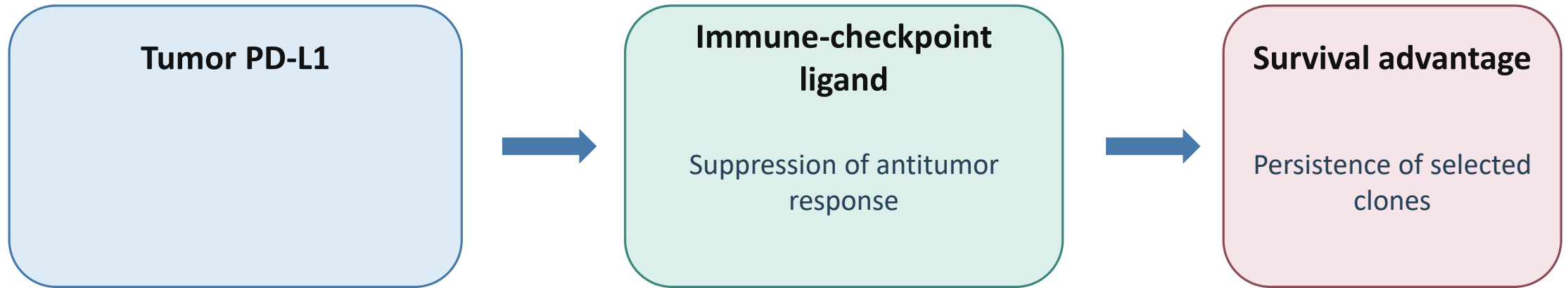
- Stromal fibroblasts interact with adjacent neoplastic epithelium.
- Cancer-associated fibroblasts can facilitate adhesion and extracellular matrix remodeling.
- The stromal response may also contribute to local immunosuppression.

Stromal contribution

Invasion is a tissue-level process, not just a tumor-cell genotype.

PD-L1 is an example of tumor immune evasion

Biologic event



Checkpoint ligand expression can weaken antitumor immunity.

Estrogen exposure is central to luminal cancer risk

- The dominant ER-positive pathway produces many luminal breast carcinomas.
- Estrogen acts through multiple biologic mechanisms rather than a single mutation.
- Cumulative exposure and cell proliferation help explain age-related risk.

Exposure and growth

Luminal cancer as the largest major subgroup.

Estrogen increases locally acting growth factors

Biologic event



Growth-factor induction is one mechanism linking estrogen to luminal growth.

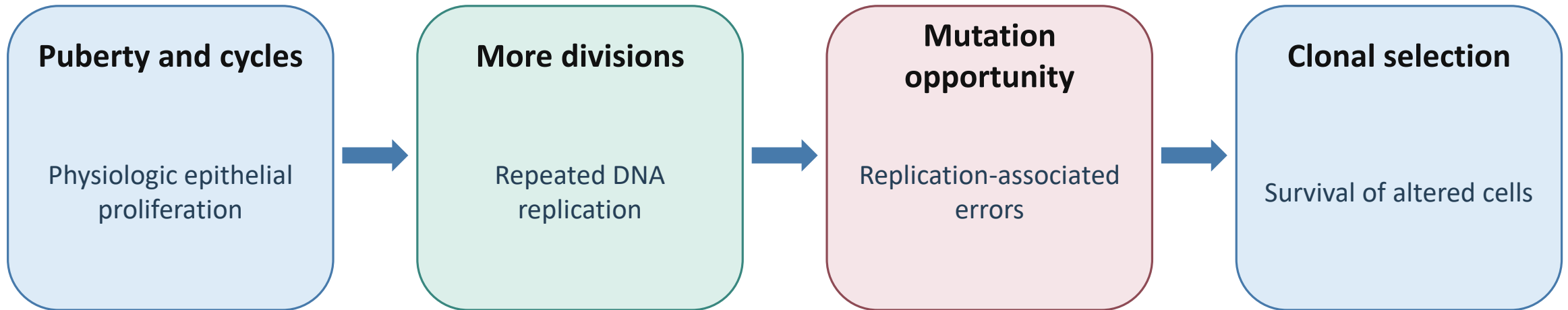
Estrogen regulates epithelial transcriptional programs

Biologic event



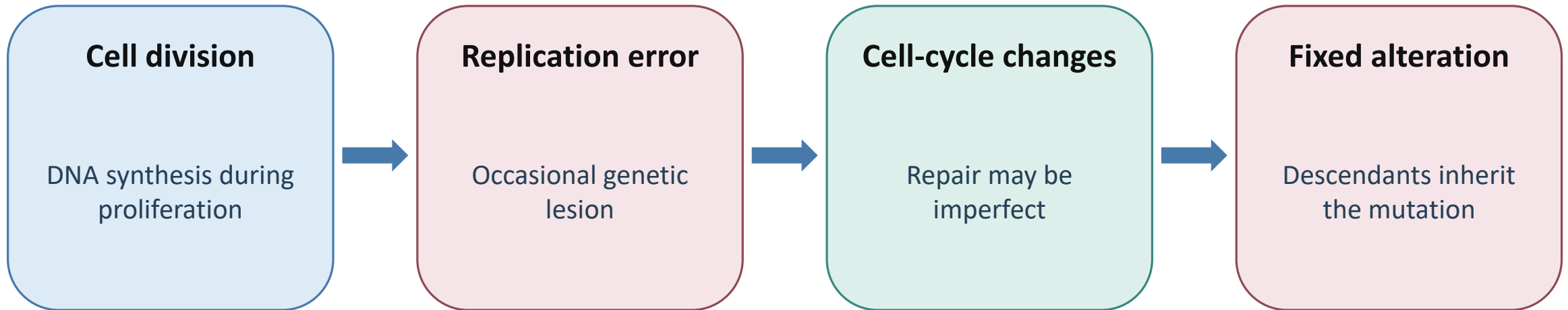
Luminal tumors preserve a recognizably estrogen-regulated transcriptomic program.

Estrogen also expands the at-risk epithelial population



Proliferation increases opportunities for mutation; It is not itself malignancy.

Repeated menstrual cycling may promote mutation fixation



Proposed mechanism: Imperfect repair can leave permanent DNA alterations.

Cumulative estrogenic exposure links age and risk

Exposure-associated factors

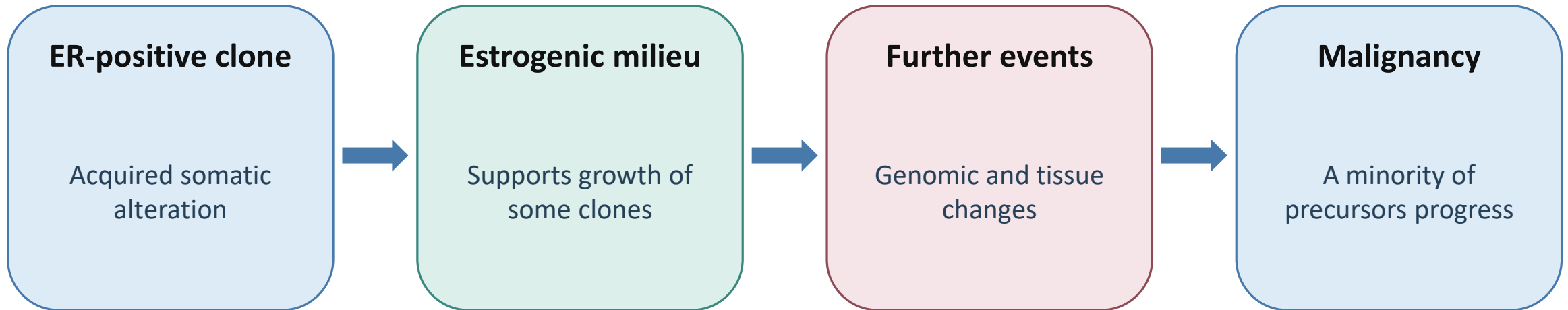
- A greater lifetime number of menstrual cycles
- Proliferative stimulation across reproductive life
- Postmenopausal hormone therapy in some contexts

Mechanistic interpretation

- More cells experience DNA replication
- Somatic alterations can accumulate over time
- ER-driven cell growth can favor selected clones

Association does not mean estrogen exposure alone causes every luminal carcinoma.

Precursor clones require additional evolution



Most low-grade precursor lesions do not become invasive cancers.

Endocrine epidemiology supports a causal estrogen role

Risk reduction evidence

- Estrogen antagonists lower development of luminal cancers in high-risk females
- Therapeutic benefit implicates ER signaling

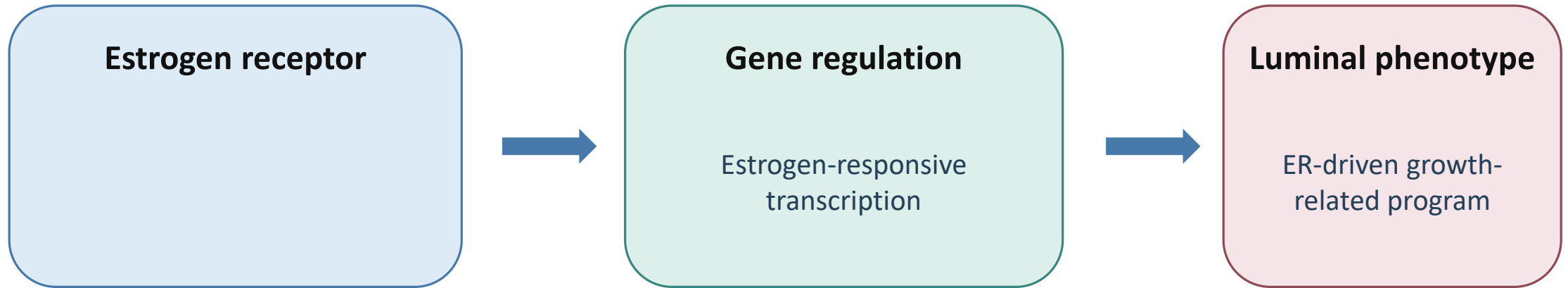
Risk increase evidence

- Luminal cancer incidence is higher in women receiving postmenopausal hormone therapy
- Pattern is consistent with hormonal promotion

These are convergent lines of evidence, not molecular proof of a single pathway.

ER is a ligand-regulated transcription factor

Biologic event



ER immunoreactivity indicates a potential endocrine-treatment target.

Luminal A has a strong estrogen-regulated gene signature

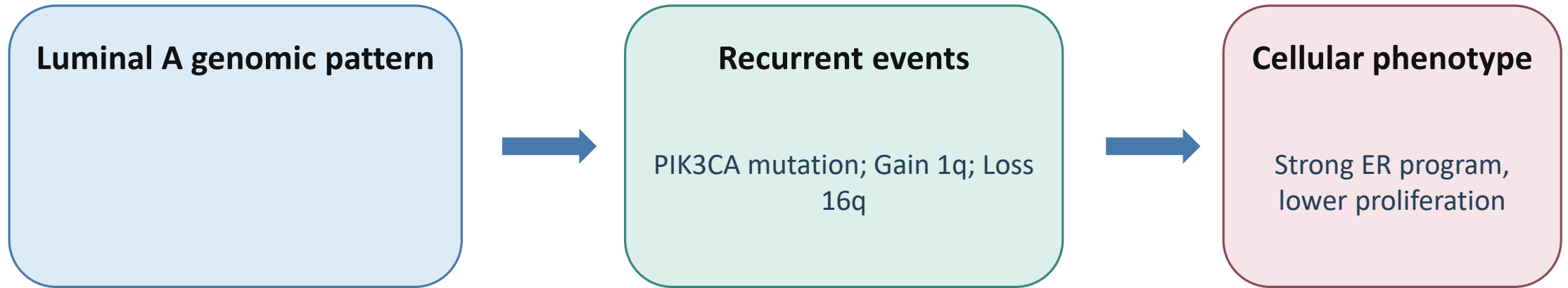
- Expression profiling shows high levels of estrogen-responsive transcripts.
- The estrogen receptor gene itself is part of this luminal program.
- Proliferation-associated gene expression is generally lower than in luminal B.

Expression-defined group

“Luminal A” is a gene-expression category with clinical-pathologic correlates.

Luminal A often carries PIK3CA mutation and 1q/16q change

Biologic event



Somatic PI3K-pathway activation complements estrogen-dependent growth.

Luminal A morphology tracks with differentiation

- Luminal A cancers tend to be well differentiated.
- Strong ER and progesterone receptor expression is typical.
- They commonly show low cellular proliferation.
- These are associations; Grade and Ki-67 can vary within luminal tumors.

Histologic correlate

Relatively organized histology reflects the less proliferative molecular phenotype.

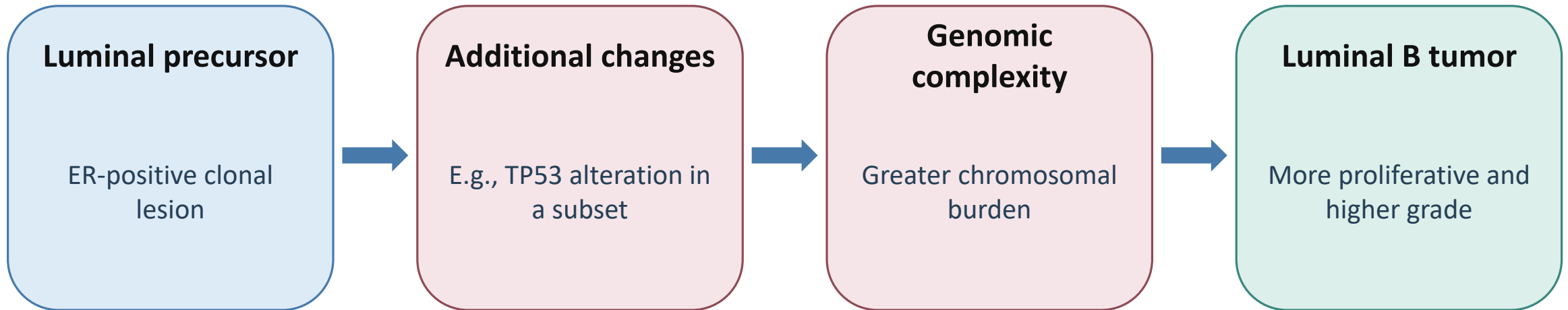
Luminal B expresses a stronger proliferation program

- Luminal B is defined by higher expression of proliferation-related genes.
- The luminal/estrogen-related expression program is usually less prominent than in luminal A.
- ER and PR protein levels tend to be lower, although ER expression remains relevant.

Classification caution

Expression-defined
luminal B is not
synonymous with HER2
positivity.

Luminal B may evolve with genomic destabilization



Luminal A-to-B progression is possible but not required.

Luminal A and luminal B: Major discriminators

Feature	Luminal A pattern	Luminal B pattern
ER-related genes	Prominent expression	Lower relative expression
Proliferation	Usually lower	Usually higher
Differentiation	Typically well-differentiated	Often less differentiated
Genomic burden	Relatively quiet	More chromosomal abnormalities

These are broad transcriptomic–pathologic correlations, not standalone assay cutoffs.

Several special histologies commonly map to luminal disease

Well-differentiated types

- Tubular carcinoma
- Cribriform carcinoma

Mucinous and papillary

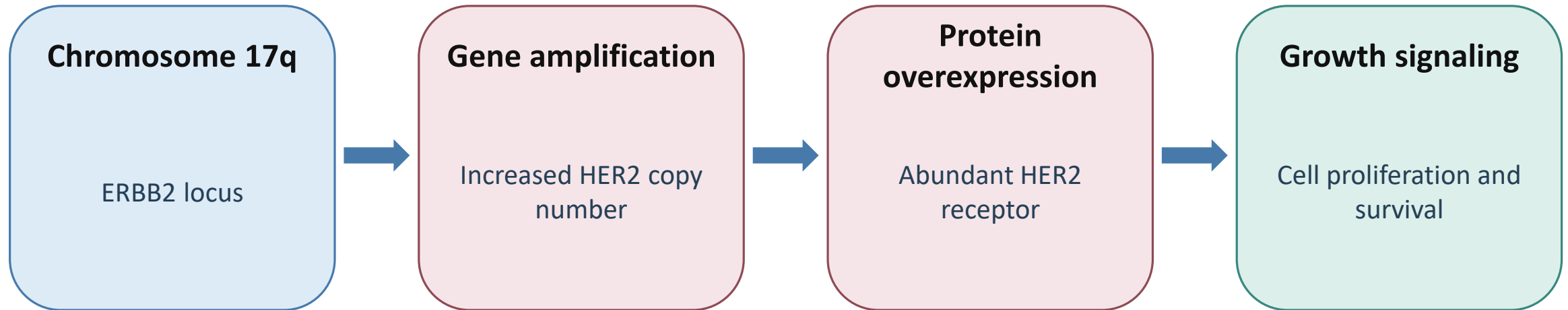
- Mucinous carcinoma
- Some papillary carcinomas

Lobular pattern

- Most lobular carcinomas are luminal
- A minority may show more aggressive biology

Morphologic subtype is informative but cannot replace ER, PR and HER2 testing.

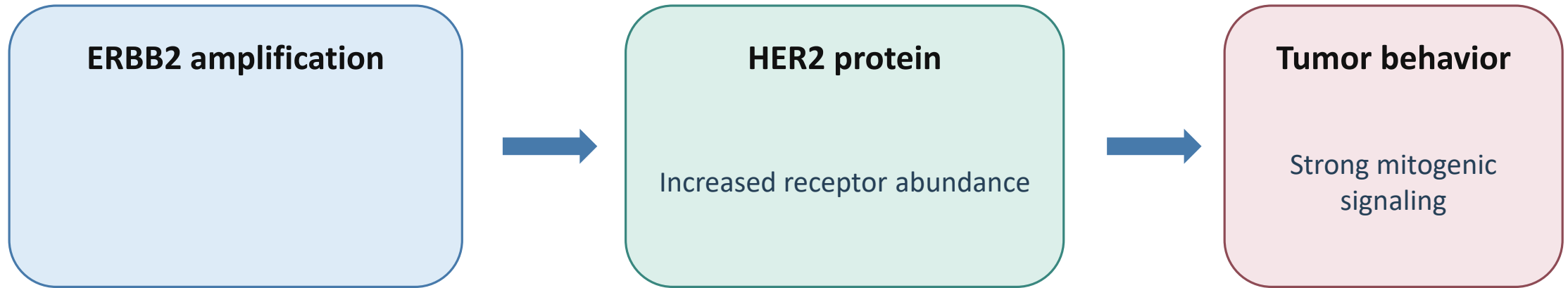
HER2-positive carcinomas are centered on ERBB2 amplification



ERBB2 is the gene encoding the HER2 receptor tyrosine kinase.

HER2 amplification is the usual route to HER2 protein excess

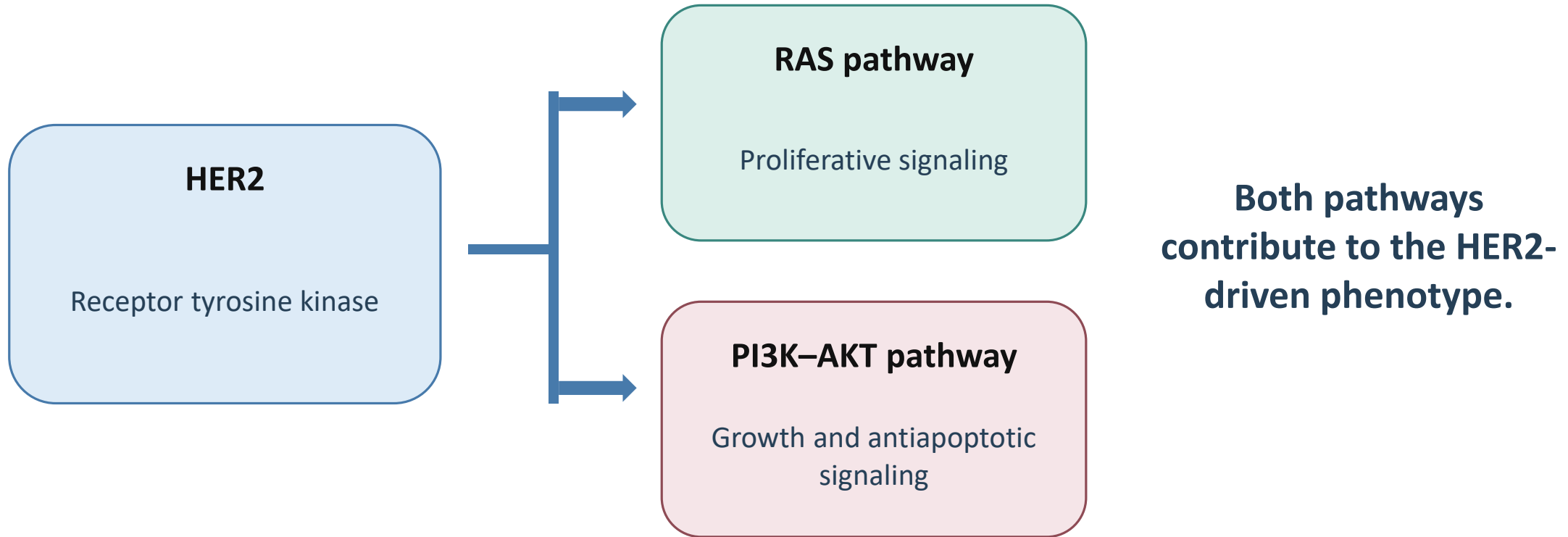
Biologic event



Gene amplification is the predominant mechanism of HER2 overexpression.

HER2 promotes growth through RAS and PI3K–AKT

Two signaling branches downstream of amplified HER2



Parallel outputs from HER2 signaling support proliferation and survival.

HER2 tumors combine growth signaling with genomic complexity

Amplification

- High-level ERBB2 copy-number gain
- Strong HER2 overexpression

Genome

- Complex rearrangements
- High burden of mutations

Coalterations

- TP53 frequently involved
- PIK3CA also altered

A high-grade genomic pattern frequently coexists with the principal HER2 driver.

HER2-positive tumors are frequently poorly differentiated

- HER2-positive breast carcinomas are typically high grade.
- A solid sheet-like growth pattern is described.
- Marked pleomorphism and brisk proliferation are common.
- Apocrine histology is a notable HER2-associated subtype.

Testing implication

Histologic suspicion
requires biomarker
confirmation.

HER2 protein and HER2 gene tests interrogate different levels

Immunohistochemistry

- Measures HER2 protein overexpression
- Provides localization in tumor cells
- A routine component of phenotyping

In situ hybridization

- Assesses ERBB2/HER2 gene amplification
- Assesses DNA-level copy-number state
- Complements protein-based assessment

Protein and gene-based assays measure complementary aspects of HER2 biology.

HER2-positive cancers are not uniformly ER-negative

ER-negative / HER2-positive

- Often classified near HER2-enriched expression pattern
- HER2-driven signaling predominates

ER-positive / HER2-positive

- Can overlap with a luminal B expression pattern
- Hormone receptor coexpression has biologic implications

HER2 status alone does not fully determine expression-based subtype.

Triple-negative cancer is defined by absent routine markers

- Triple-negative breast cancers lack ER, PR, and HER2 expression by clinical classification.
- They do not follow the estrogen-dependent luminal pathway.
- HER2 gene amplification is not the defining mechanism.

Heterogeneous category

Triple-negative is a receptor-defined umbrella, not one molecular disease.

Triple-negative tumors are biologically heterogeneous

Most TNBC

- High grade and rapidly proliferative
- Frequent genome instability
- Often basal-like at the RNA level

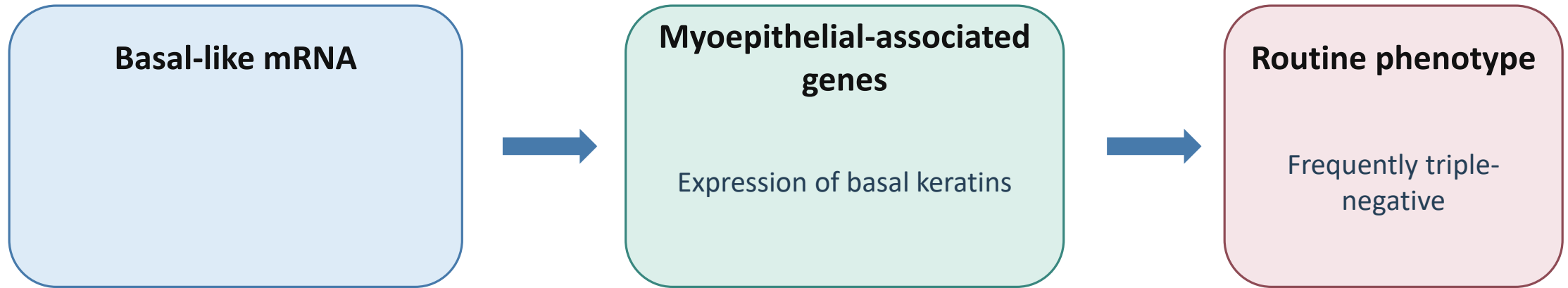
Uncommon TNBC variants

- Some rare histologic types are low grade
- Some behave much more favorably
- Not all use the same driver mechanisms

Avoid attributing uniform aggressiveness to every triple-negative histology.

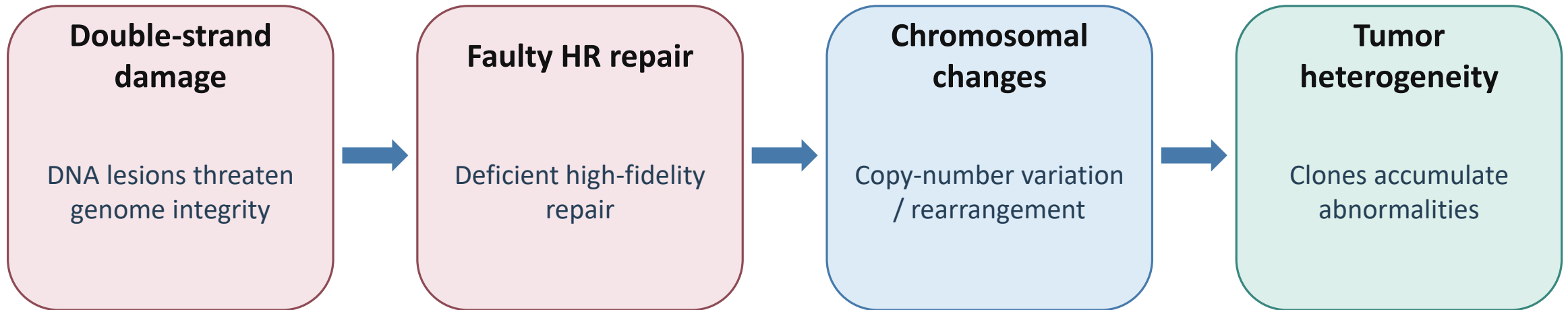
A basal-like expression program overlaps substantially with TNBC

Biologic event



“Basal-like” and “triple-negative” are related but nonidentical categories.

Defective homologous recombination creates a mutator phenotype



High-grade TNBC often shows this pattern.

Sporadic TNBC can inactivate BRCA1 without inherited mutation

Familial context

- Germline BRCA1 / BRCA2 variants can cause HR deficiency
- The inherited setting is taught separately

Sporadic context

- BRCA1 coding mutations are uncommon in sporadic TNBC
- Epigenetic silencing with allelic loss can impair BRCA1 function

Distinguish germline susceptibility from tumor-acquired repair deficiency.

TP53 is the most consistently mutated TNBC cancer gene

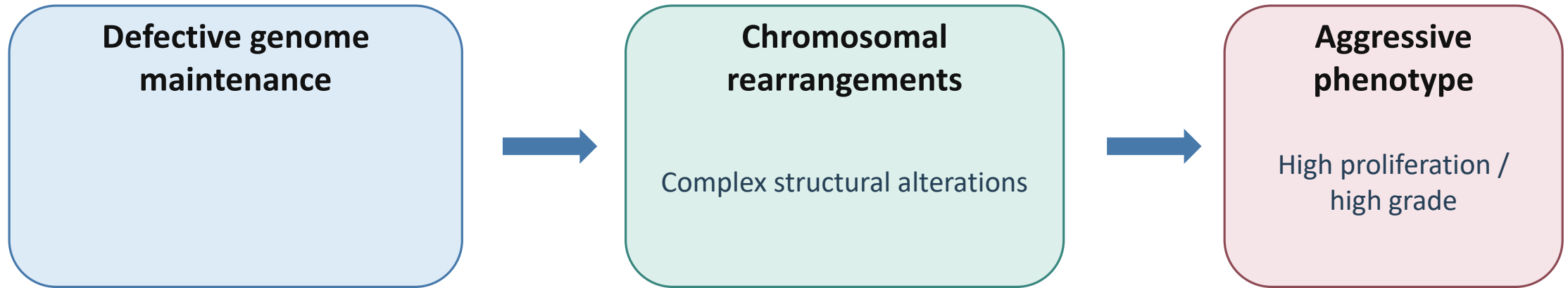
- TP53 is the only cancer gene described as mutated in a majority of TNBCs.
- Additional oncogenic effects may result from copy-number alterations and rearrangements.
- Mutational diversity contributes to a biologically heterogeneous group.

Mutation pattern

Do not assert that a particular single mutation is present in every TNBC.

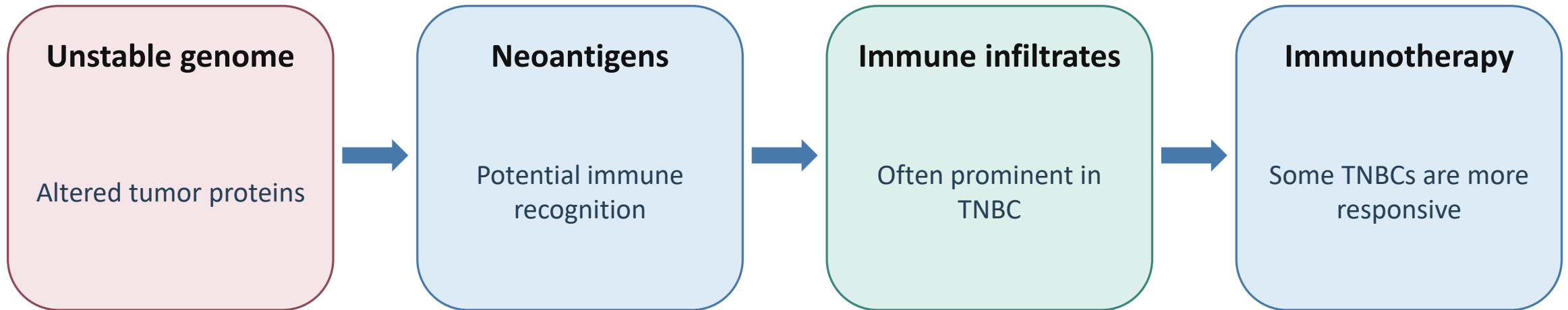
Structural genome disruption is a hallmark of high-grade TNBC

Biologic event



Copy-number alteration can contribute alongside point mutations.

Genomic instability can increase immune visibility



Greater immunogenicity does not mean universal immunotherapy benefit.

High-grade TNBC has characteristic—not unique—morphology

- Many tumors grow in solid sheets.
- Marked nuclear pleomorphism is common.
- Necrosis and very high proliferation are frequently seen.
- Some tumors show medullary-pattern features.

Diagnostic overlap

These features overlap with other high-grade carcinomas; Markers are needed.

A small subset of triple-negative tumors is relatively indolent

Special histologies

- Adenoid cystic carcinoma
- Secretory carcinoma

Other distinct forms

- Low-grade adenosquamous carcinoma
- Some salivary gland-like tumors

Interpretation

- Clinical behavior differs from usual high-grade TNBC
- Specific diagnosis matters

High-grade TNBC generalizations should not be applied to these rare entities.

Major phenotype comparison: Molecular drivers

Feature	Luminal ER+/HER2–	HER2-positive	High-grade TNBC
Receptors	ER+ / HER2–	HER2+; ER variable	ER– / HER2–
Growth pattern	ER program; PIK3CA	ERBB2 gain; PI3K / RAS	Genomic instability / HR defect
Genome	Quieter (A), complex (B)	Amplified ERBB2; complex	Large-scale instability
Typical grade	Lower (A), higher (B)	Usually high	Usually high

Phenotype groups differ in driver programs and genome architecture.

Predictive and prognostic information must be separated

Predictive relevance

- ER expression: Endocrine vulnerability
- HER2 protein/gene status: HER2-directed therapy eligibility
- TNBC immune biology: Potential immunotherapy relevance

Prognostic association

- Grade and proliferation correlate with aggressiveness
- Luminal A generally less proliferative than luminal B
- Triple-negative category includes uncommon favorable subtypes

Prediction of treatment response is different from natural-history prognosis.

Grade, phenotype and genomic classification are distinct axes

Pathologist-observed features

- Differentiation and nuclear features
- Mitoses, solid growth and necrosis
- In situ versus invasive anatomy

Molecular readouts

- ER and PR protein expression
- HER2 protein and ERBB2 copy number
- Gene-expression profiles and other alterations

A rigorous diagnosis integrates morphology with appropriately validated biomarkers.

Teaching case: Indolent luminal pattern

Hypothetical teaching case

An invasive carcinoma is well differentiated, strongly ER/PR positive, HER2 negative and shows low proliferation.

Which proposed pathway and molecular subtype best fit?

Formulate a mechanistic explanation using the supplied findings.

Teaching case: Signaling amplification

Hypothetical teaching case

A poorly differentiated tumor shows marked HER2 protein overexpression with ERBB2 amplification; ER expression is low.

Which genomic event best explains the receptor phenotype?

Formulate a mechanistic explanation using the supplied findings.

Teaching case: High-grade repair-deficient pattern

Hypothetical teaching case

A high-grade carcinoma lacks ER, PR and HER2, with extensive chromosomal complexity and conspicuous immune infiltrates.

Which mechanistic framework is most compatible?

Formulate a mechanistic explanation using the supplied findings.

Important uncertainties in sporadic breast cancer evolution

Supported conclusions

- Distinct low- versus high-grade pathways are useful models
- Certain driver and expression patterns cluster by subtype
- Microenvironmental remodeling can contribute to progression

Open questions

- Earliest high-grade precursor lesions are not well defined
- A universal invasion-specific driver is not established
- Not every lesion or tumor follows the canonical pathway

Mechanistic diagrams should distinguish inferred sequences from observed alterations.

Synthesis: three ways evolution shapes tumor phenotype

Selective signals

- Estrogenic transcription and proliferation
- ER-positive luminal programs

Driver signaling

- PIK3CA and ERBB2 pathway activation
- Genomic alterations affecting growth

Genome maintenance

- TP53 and DNA repair defects
- Instability and tumor heterogeneity

Breast cancer subtype emerges from interacting evolutionary processes.