

Pathogenesis of Familial Breast Cancer

Inheritance • tumor-suppressor loss • DNA repair • therapeutic vulnerability

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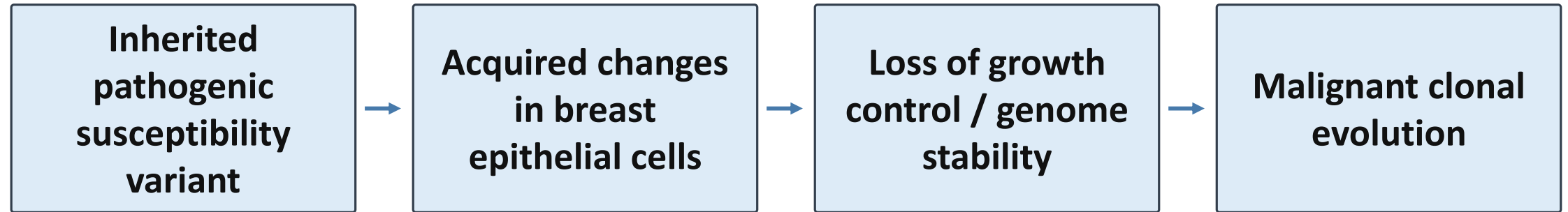
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Learning objectives

- Distinguish inherited susceptibility from an established breast carcinoma.
- Explain autosomal-dominant predisposition and biallelic tumor-suppressor inactivation.
- Connect BRCA-associated homologous recombination failure to genomic instability.
- Interpret major hereditary genes, tumor phenotypes, and synthetic lethality.

Familial cancer begins with susceptibility, not a tumor



A germline variant increases risk; Additional somatic events are required for cancer.

Hereditary contribution is broader than single-gene syndromes

25–35%

Breast cancers estimated
to involve inherited
susceptibility variants

8–17%

Breast cancers associated
with moderate- or high-
penetrance single-gene
mutations

15–20%

Additional familial
susceptibility described
beyond monogenic forms

The source describes partially overlapping conceptual risk categories; Do not add them as independent totals.

Penetrance expresses the probability of disease

Genotype

A person inherits a susceptibility variant.

The inherited allele is present in normal cells.

Inheritance alone does not prove cancer will develop.

Phenotype

Penetrance: Risk of developing disease in a carrier.

Age and specific mutation influence observed risk.

The same gene can have different penetrance across variants.

Penetrance is a probabilistic property, not a binary prediction.

High penetrance versus moderate and low penetrance

High / moderate penetrance

Larger risk attributable to an individual allele.

May form a recognizable familial cancer syndrome.

Tumor suppressor defects often affect repair or growth control.

Low penetrance / polygenic susceptibility

Single variants usually confer smaller increments of risk.

Combinations of polymorphisms may interact.

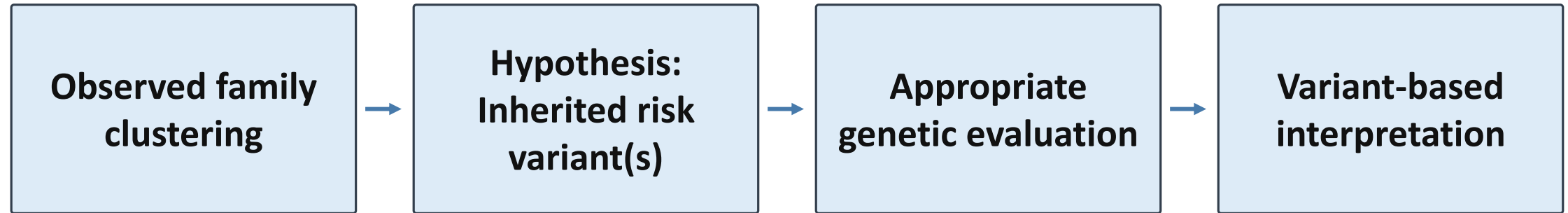
May explain familial clustering without a classic monogenic syndrome.

Risk magnitude and familial aggregation are not synonymous.

Family history acts as a clinical clue

- Breast cancer in a first-degree relative (mother, sister, or daughter).
- Multiple affected relatives across a family.
- Cancer diagnosed at an unusually early age.
- These patterns raise suspicion but do not establish a pathogenic variant.

Family history and molecular inheritance are different observations



Clinical pedigree information suggests inherited susceptibility; Molecular testing addresses genotype.

Hereditary predisposition follows autosomal-dominant segregation

At the family level

A pathogenic allele can be inherited from one affected or unaffected carrier parent.

Risk can occur across generations.

Inheritance of one mutant allele is sufficient to create susceptibility.

At the neoplastic-cell level

The intact allele continues to provide tumor-suppressor function.

Tumor evolution commonly involves acquired loss of that remaining allele.

Biallelic loss produces the cellular defect.

Dominant inherited predisposition and recessive cellular tumor-suppressor loss are compatible.

Inheritance is not equivalent to inevitable disease

- Not every carrier has the same age-specific cancer risk.
- The exact BRCA1/BRCA2 variant influences penetrance and age of onset.
- Other genetic factors may modify individual risk.
- Disease phenotype emerges through subsequent tumor evolution.

Recognize two classes of inherited risk

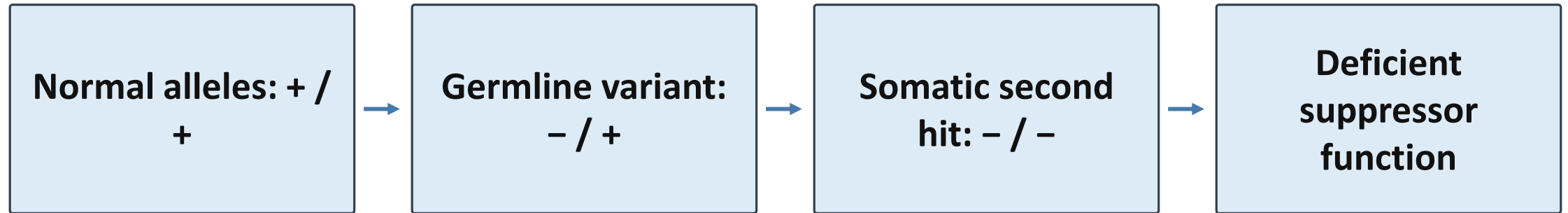
Characteristic	Monogenic higher-risk	Polygenic / lower-risk
Molecular basis	One pathogenic susceptibility allele	Multiple low-effect variants
Family pattern	Sometimes a strong recognizable pedigree	May be more subtle or complex
Risk estimate	Depends on gene and variant	Depends on combined variant effects
Cancer emergence	Somatic evolution still required	Somatic evolution still required

Conceptual comparison; No polygenic numerical risk score is assumed.

The inherited lesion usually affects a tumor suppressor

- Important high-penetrance genes participate in genomic stability or cell-growth control.
- Risk-conferring inherited alleles typically contain loss-of-function mutations.
- Inactivation of a second allele can eliminate the remaining protective function.
- Genomic instability helps epithelial cells accumulate transforming alterations.

A tumor suppressor requires two functional hits for loss



Schematic allele states: + = functioning allele; - = loss-of-function allele.

Inherited first hit: Every cell carries the susceptible state

Carrier normal tissue

One inherited defective susceptibility-gene copy.

A functional allele remains.

Normal tissues may still maintain DNA repair.

Emerging neoplastic clone

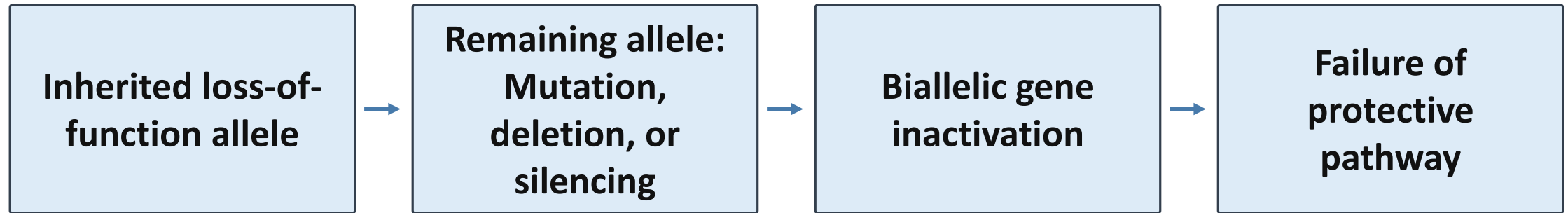
A vulnerable cell acquires additional lesions.

Loss of the remaining allele may confer a strong selective advantage.

The deficient lineage can expand.

This is a two-hit mechanism for tumor suppressors; It does not imply all tissues form tumors.

The second hit can arise by multiple mechanisms



Methylation-dependent silencing is one described route to loss of remaining-allele function.

Mutation, deletion, and epigenetic silencing are distinct

Second-hit mechanism	Molecular consequence	Pathogenic interpretation
Somatic mutation	Sequence alteration of intact allele	Protein function may be lost
Deletion	Physical loss of the remaining allele	No intact gene copy retained
Methylation-dependent silencing	Suppressed expression without required sequence deletion	Functionally inactivated allele

All are listed by Robbins as possible mechanisms for the remaining tumor-suppressor allele.

A two-hit model explains cancer development in carriers

Starting condition

One pathogenic allele is inherited.

Normal cellular growth control can persist.

Risk is elevated before a tumor exists.

A breast epithelial cell acquires a second hit



Protective gene function is lost



**Genomic damage or proliferative escape
increases**

Schematic causal chain; Additional oncogenic events are required for malignancy.

Inherited predisposition and somatic driver accumulation cooperate



The initiating inherited genotype influences subsequent cancer phenotype, but does not determine it absolutely.

BRCA1 and BRCA2 dominate monogenic familial disease

80–90%

Single-gene familial breast
cancers attributed to
BRCA1 or BRCA2
mutations

3–6%

All breast cancers
attributed to
BRCA1/BRCA2 germline
mutations

These figures have different denominators; They are not directly comparable percentages.

BRCA1 and BRCA2 occupy different chromosomal loci

BRCA1

Chromosome 17q21.

Large susceptibility gene with many pathogenic sequence variants.

Encoded product is important for genomic maintenance.

BRCA2

Chromosome 13q12.3.

Large susceptibility gene with many pathogenic sequence variants.

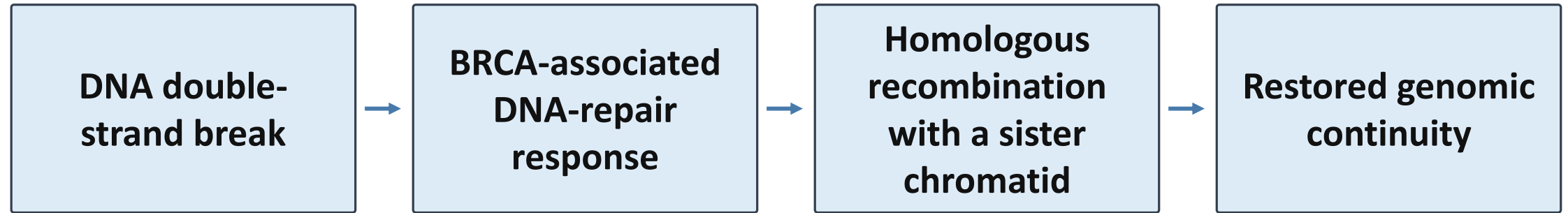
Encoded product is important for genomic maintenance.

The presence of many variants makes interpretation of a genetic test more demanding.

BRCA1 and BRCA2 variants are heterogeneous

- Hundreds of disease-associated variants are distributed across the coding regions.
- Different pathogenic variants can confer different risks and ages of onset.
- Inconsequential polymorphisms are also common.
- Identifying a sequence change is not the same as establishing clinical pathogenicity.

The BRCA genes protect against loss of genomic integrity



Schematic normal pathway, deliberately omitting unverified mechanistic substeps.

BRCA deficiency changes the consequence of DNA damage

Functional BRCA repair pathway

Homologous recombination is available.

An intact sister-chromatid template can guide accurate repair.

Damage is less likely to persist as a driver of instability.

BRCA-deficient tumor cell

Double-strand repair is compromised.

Genomic abnormalities can accumulate.

Clonal selection may favor cells acquiring further oncogenic changes.

Mechanism is the key link between inherited genotype and malignant evolution.

BRCA1- and BRCA2-associated tumors need not look alike

BRCA1-associated phenotype

Most cancers in carriers are triple-negative.

Triple-negative: ER-negative, PR-negative and HER2-negative.

Reflects an association, not an exclusive diagnosis.

BRCA2-associated phenotype

Most breast cancers in carriers are ER-positive.

Hormone-receptor expression does not rule out hereditary BRCA2 disease.

Variant-specific effects remain relevant.

Tumor phenotype suggests biological pathways but cannot establish germline status alone.

Tumor subtype and germline genotype are different tests

Clinical question	Relevant evidence	What it cannot prove alone
What phenotype has developed?	Tumor ER / PR / HER2 assessment	Presence of a germline pathogenic variant
What risk allele is inherited?	Germline molecular analysis	Actual phenotype of a tumor
What pathway is defective in tumor?	Integrated molecular and pathology interpretation	Every repair-deficient tumor has a BRCA mutation

ER, estrogen receptor; PR, progesterone receptor; HER2, ERBB2 protein.

BRCA-associated susceptibility extends beyond the breast

- Ovarian and related epithelial malignancies are important associated cancers.
- Pancreatic and prostatic cancer risks are also increased.
- Male BRCA2 carriers have increased susceptibility to breast cancer.
- The tumor spectrum differs between genes and inherited variants.

The sex of a carrier changes expression of risk

Female carriers

Breast cancer is a major associated malignancy.

Age-specific penetrance varies substantially.

Ovarian cancer susceptibility may coexist.

Male carriers

BRCA2 variants increase male breast-cancer risk.

Prostate and pancreatic risks may also be elevated.

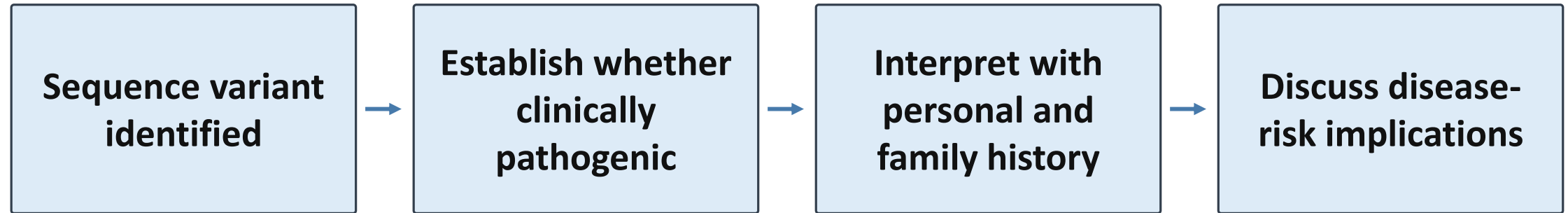
Carrier status matters even without female breast cancer.

Sex-specific clinical expression does not alter autosomal inheritance.

BRCA penetrance should not be presented as one fixed percentage

- Risk depends on the precise pathogenic allele.
- Different variants can have different onset distributions.
- Other susceptibility alleles can modify familial risk.
- A population average cannot be converted into certainty for an individual carrier.

Genetic-test interpretation requires a meaningful variant classification



Numerous disease-associated variants and common inconsequential polymorphisms.

Founder variants illustrate ancestry-specific genetic risk

~1 in 400

General-population
frequency of BRCA variants
that increase risk, as

~1 in 40

Ashkenazi Jewish
population frequency of
three founder variants in
the source

These figures are textbook estimates, not individual predictive probabilities or a current population screening recommendation.

Founder mutations do not represent all pathogenic BRCA variants

Founder-variant testing

Targets recurrent variants in a particular ancestral population.

Useful for understanding why variant prevalence can vary by ancestry.

A negative founder-variant result is not the same as absence of all hereditary risk.

Broad sequence evaluation

Large genes harbor many variants across coding regions.

Interpretation must separate disease-causing changes from polymorphisms.

Clinical context remains essential.

The three Ashkenazi-associated founder variants described: Two in BRCA1, one in BRCA2.

The susceptibility-gene spectrum has several functional classes

Biological role	Important examples	Main teaching implication
DNA repair / DNA-damage response	BRCA1, BRCA2, PALB2, ATM, CHEK2, RAD51C, RAD51D	Failure of genomic maintenance
Other growth / genome surveillance	TP53, PTEN, STK11, NF1	Altered checkpoint or growth-control pathways
Cell-cell adhesion	CDH1	Distinctive lobular breast-cancer association

Functional grouping is simplified; Several gene products have multiple interacting roles.

Hereditary susceptibility genes do not confer identical risk

Higher-penetrance syndromes

BRCA1, BRCA2, PALB2.

TP53, PTEN, STK11, CDH1.

Gene-specific cancer spectrum often helps define the syndrome.

Moderate-penetrance susceptibility

ATM, CHEK2, NF1, RAD51C and RAD51D.

Usually smaller individual breast-cancer risk effect than BRCA1/BRCA2.

Cancer associations and phenotypes still differ by gene.

This grouping follows the hereditary susceptibility table in the source; Exact individualized risk is not inferred.

PALB2 links hereditary breast cancer to DNA-repair failure

PALB2

Mechanistic role

Participates in the homologous recombination DNA-repair system. Interacts functionally with BRCA-associated genome-maintenance pathways.

Associated tumor pattern / spectrum

Tumors may be ER-positive or triple-negative.

Breast and additional epithelial cancer susceptibility is described.

Clinical interpretation

Biallelic inherited abnormalities can produce a Fanconi anemia phenotype.

Genetic context determines whether a variant is disease-causing.

The OCR table spells “PALPB2”; The surrounding source prose consistently identifies PALB2.

ATM coordinates response to DNA damage

ATM

Mechanistic role

DNA-damage response linked to homologous recombination and checkpoint signaling.
Loss impairs appropriate response to DNA double-strand breaks.

Associated tumor pattern / spectrum

Most associated breast cancers express estrogen receptor.
Included among moderate-penetrance predisposition genes.

Clinical interpretation

Biallelic germline abnormalities can cause ataxia-telangiectasia.
Carrier-associated cancer risk is distinct from the recessive syndrome.

CHEK2 connects damage signaling with cell-cycle control

CHEK2

Mechanistic role

Checkpoint pathway involved in genome surveillance after DNA damage.
Works in an interconnected DNA-damage response network.

Associated tumor pattern / spectrum

Associated breast cancers are often ER-positive.

Additional cancer associations are reported in the source table.

Clinical interpretation

Moderate-penetrance susceptibility gene.

Tumor receptor phenotype alone is insufficient to determine genotype.

RAD51C and RAD51D connect susceptibility with repair

RAD51C / RAD51D

Mechanistic role

Proteins associated with homologous recombination repair.
Maintain the response to DNA double-strand breaks.

Associated tumor pattern / spectrum

Breast tumors may be triple-negative.

Ovarian and fallopian-tube cancer
susceptibility is noted.

Clinical interpretation

Grouped among moderate-penetrance breast-
cancer genes.

A tumor phenotype cannot uniquely identify
an inherited gene.

BRCA2 and PALB2 deficiency can have biallelic germline effects

Monoallelic inherited defect

Predisposes to adult cancer after somatic evolution.

A second hit in tumor tissue can inactivate repair.

A typical hereditary tumor-predisposition model.

Biallelic germline defect

The source associates BRCA2 and PALB2 biallelic variants with Fanconi anemia.

The phenotype is not simply “twice the carrier risk.”

Illustrates how genotype dosage changes disease mechanism.

Distinguish recessive constitutional disease from dominant cancer susceptibility.

TP53-associated familial breast cancer is a different pathway

TP53

Mechanistic role

Tumor suppressor governing responses to genomic damage and cellular stress.
Broad cancer predisposition differs from BRCA-centered repair deficiency.

Associated tumor pattern / spectrum

Associated with Li–Fraumeni syndrome.

Associated breast cancers often express both ER and HER2.

Clinical interpretation

Sarcomas, leukemia, and brain tumors occur in the cancer spectrum.

Family phenotype must be interpreted across organ systems.

PTEN-associated predisposition combines neoplasia and growth control

PTEN

Mechanistic role

Tumor-suppressive regulation of cellular growth signaling.
Biology differs from core homologous recombination proteins.

Associated tumor pattern / spectrum

Cowden syndrome association.

Benign tumors and thyroid/endometrial malignancies are described.

Clinical interpretation

Breast carcinomas can show apocrine differentiation.

Breast cancer is one component of a multisystem syndrome.

STK11-associated predisposition is syndromic

STK11

Mechanistic role

Tumor-suppressor pathway regulating cell-growth programs.
Not classified as a core BRCA homologous-recombination gene.

Associated tumor pattern / spectrum

Peutz–Jeghers syndrome.

Susceptibility also includes ovarian, pancreatic and colonic neoplasms.

Clinical interpretation

Associated with benign gastrointestinal polyps.

Extra-breast manifestations can identify syndromic susceptibility.

CDH1-associated hereditary cancers have a lobular pattern

CDH1

Mechanistic role

Encodes an epithelial cell-adhesion factor.
Loss alters intercellular cohesion rather than BRCA-like repair directly.

Associated tumor pattern / spectrum

Breast carcinomas are predominantly lobular.

Syndromic association with diffuse gastric carcinoma.

Clinical interpretation

A tumor's lobular histology may point toward this gene.

Histologic association is not sufficient to diagnose inherited CDH1 susceptibility.

NF1-associated breast cancer is part of a wider syndrome

NF1

Mechanistic role

Tumor-suppressive control of growth-related signaling.
Listed among moderate-penetrance susceptibility genes.

Associated tumor pattern / spectrum

Neurofibromatosis type 1 with multiple neurofibromas and cutaneous findings.
Other associated neoplasms include neural-system tumors.

Clinical interpretation

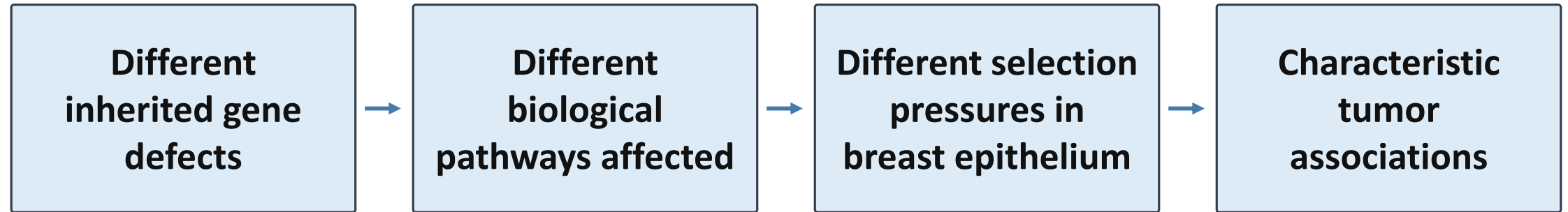
Non-breast clinical findings may inform genetic evaluation.
A syndrome-level clinical assessment is more useful than subtype alone.

Different genes predict different associated neoplasms

Germline susceptibility	Associated cancer pattern in source	Breast phenotype clue
BRCA1	Ovarian, pancreatic, prostate	Often triple-negative
BRCA2	Ovarian, pancreatic, prostate	Often ER-positive; Male breast risk
TP53	Sarcoma, leukemia, brain	Often ER-positive / HER2-positive
CDH1	Diffuse gastric carcinoma	Often lobular type
PTEN	Thyroid, endometrium	May be apocrine

Phenotype clues are tendencies, not diagnostic criteria.

Why genotype and morphology are related but not interchangeable

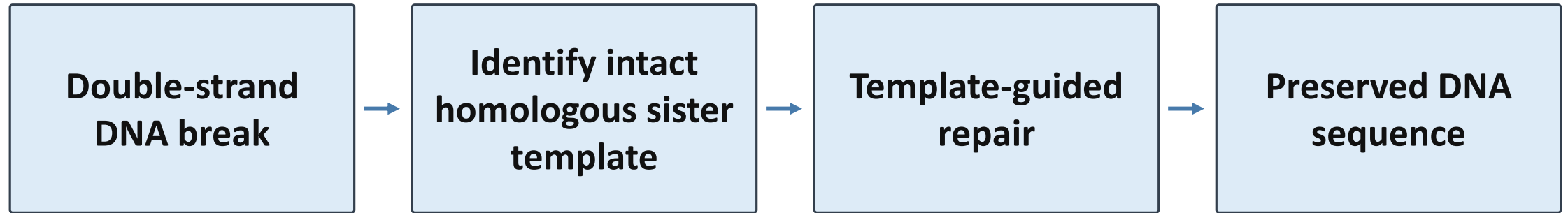


Many tumors deviate from characteristic patterns; Molecular and morphologic evidence are complementary.

Double-strand breaks threaten genomic continuity

- DNA double-strand breaks interrupt both strands of a DNA duplex.
- Incorrect or incomplete repair can destabilize the genome.
- BRCA-associated pathways help preserve genomic information after injury.
- The resulting repair phenotype links hereditary risk to therapeutic vulnerability.

Homologous recombination uses a sister-chromatid template



Conceptual schematic; The textbook provides the template-guided principle, not every enzymatic step.

Homologous recombination differs from single-strand repair

Double-strand break repair

Repair using a normal sister chromatid is homologous recombination.

BRCA1, BRCA2 and related genes are central to this response.

Loss causes homologous recombination deficiency.

Single-strand repair mechanisms

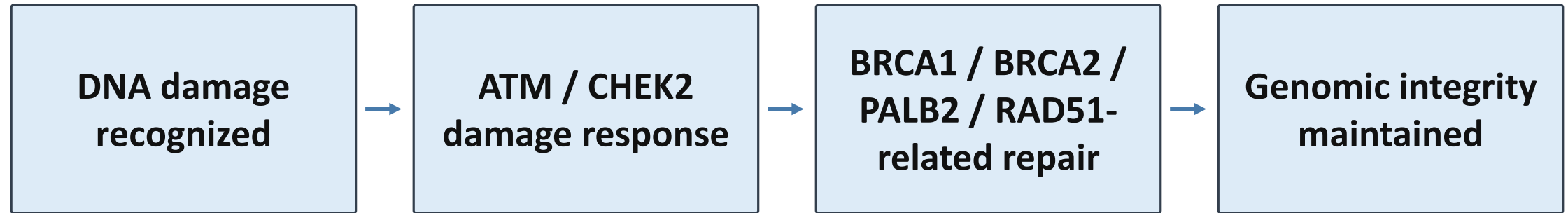
PARP participates in repair pathways dealing with single-strand lesions.

Inhibition can increase damage burden.

Repair-pathway redundancy can determine whether a cell survives.

This distinction is the core of the textbook PARP synthetic-lethality explanation.

A network of susceptibility genes supports genome maintenance



Simplified functional grouping: ATM and CHEK2 act prominently in DNA-damage signaling; Not identical biochemical roles.

Loss of repair capacity facilitates oncogenic evolution



Genome instability increases opportunity for additional driver alterations; It is not itself the sole defining cause of cancer.

What is homologous recombination deficiency?

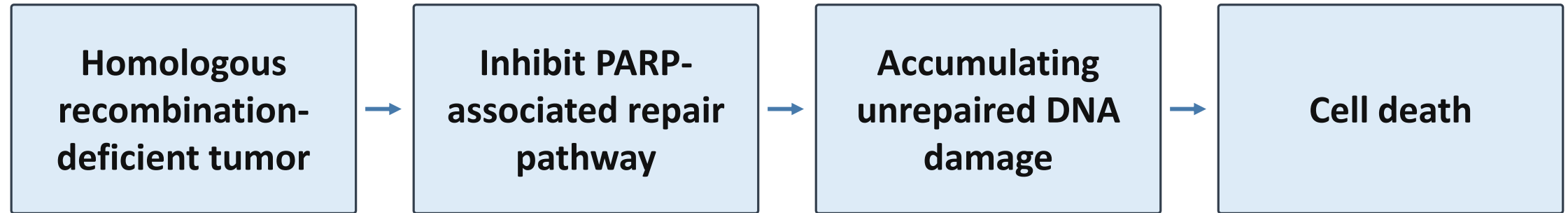
- Tumor cells lack effective homologous recombination repair of DNA double-strand breaks.
- BRCA1 or BRCA2 biallelic loss is a canonical route to deficiency.
- Other genes in the DNA-damage response network may produce related deficits.
- This is a tumor functional phenotype, not just a germline family-history category.

Repair-intact and repair-deficient cells face different options

Cellular condition	Double-strand repair reserve	Potential consequence
Normal repair-intact cell	Homologous recombination available	Can tolerate repair-pathway stress better
Repair-deficient tumor cell	Homologous recombination compromised	Greater dependence on residual repair routes
Repair-deficient + PARP inhibition	Multiple pathways stressed	DNA damage may become lethal

Educational mechanism; No drug-response rate or universal sensitivity is implied.

PARP inhibition creates a repair-pathway dependency



The source models PARP inhibitor susceptibility through repair-pathway loss and synthetic lethality.

Synthetic lethality is a genetic interaction

Single defect: Often survivable

A cell may survive loss of one compensatory repair pathway.

Alternative pathways preserve a degree of viability.

A functioning pathway can buffer another defect.

Combined defects: Potentially lethal

Tumor: Homologous recombination deficient.

Treatment: Pharmacologic PARP-pathway inhibition.

The combined repair impairment can trigger tumor cell death.

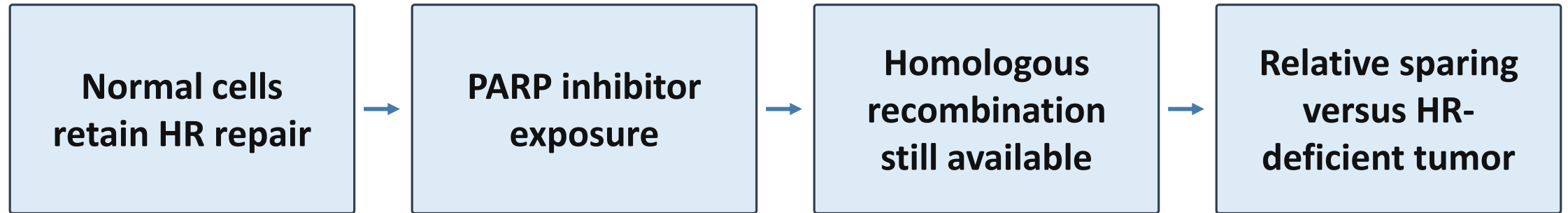
Synthetic lethality describes the interaction of two perturbations, not the toxicity of a drug in all cells.

The synthetic-lethality logic can be represented as a matrix

Homologous recombination	PARP-related function	Expected qualitative outcome
Intact	Available	DNA repair capacity preserved
Deficient	Available	Tumor may remain viable
Intact	Inhibited	Alternate repair remains available
Deficient	Inhibited	High vulnerability to lethal DNA damage

Schematic expectation, not clinical response percentages; Resistance and context are not represented.

Therapeutic selectivity follows the preexisting repair defect



Relative therapeutic selectivity is the textbook mechanism; Normal cells are not guaranteed to be unaffected.

BRCA mutation and PARP sensitivity are related, not synonymous

- Germline BRCA status describes inherited susceptibility.
- Tumor biallelic loss creates a potential homologous recombination defect.
- PARP inhibitors act on a repair vulnerability in malignant cells.
- Individual therapeutic response cannot be inferred from gene name alone.

Genetic testing has both familial and therapeutic applications

Hereditary-risk evaluation

Strong personal or family history may prompt germline evaluation.

Interpret pathogenicity and familial implications.

The source describes focused testing in high-risk contexts.

Cancer-therapy selection

Some breast-cancer patients undergo germline BRCA sequencing.

Pathogenic variants can inform consideration of targeted treatment.

HER2-negative metastatic disease as one example.

This is a textbook-context overview, not a current prescribing or screening guideline.

A pathology report should separate three kinds of molecular information

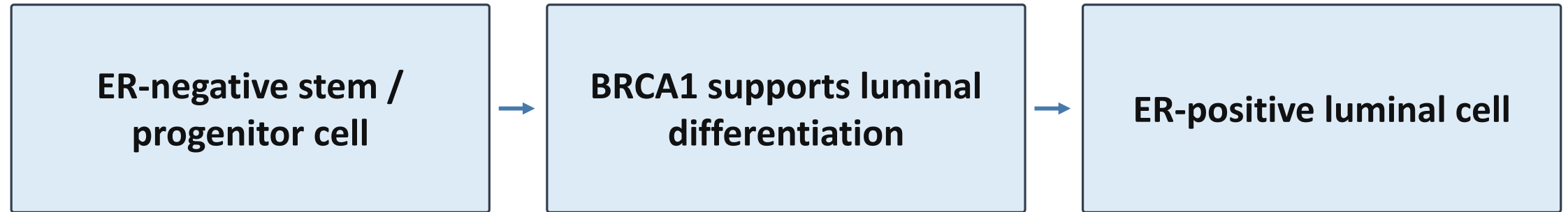
Type of information	Example	Interpretation
Inherited susceptibility	Germline BRCA1/BRCA2 pathogenic variant	Risk to carrier and relatives
Tumor biology	Defective homologous recombination pathway	Mechanistic phenotype of cancer
Potential therapeutic vulnerability	PARP-associated synthetic lethality	Possible treatment relevance requiring clinical context

Risk prediction, tumor classification, and drug sensitivity are different clinical inferences.

Why does a ubiquitous repair defect preferentially affect breast?

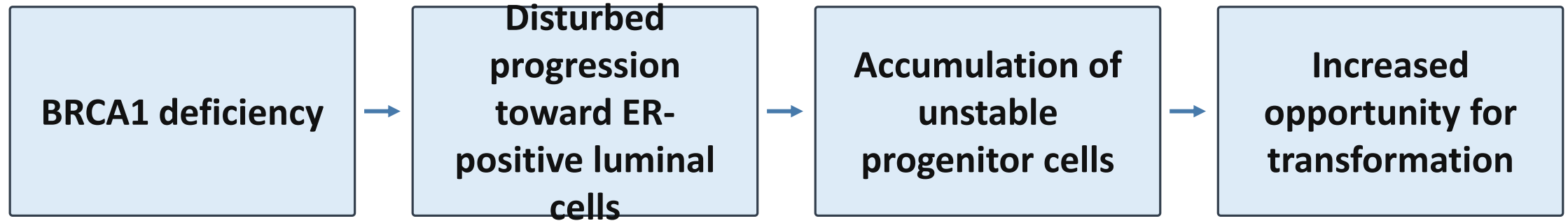
- BRCA1 and BRCA2 are expressed throughout the body.
- Nevertheless, inherited loss preferentially predisposes to breast and certain other epithelial cancers.
- The precise cause of this tissue selectivity remains unresolved.
- Several nonexclusive mechanistic hypotheses.

Hypothesis 1: BRCA1 influences luminal differentiation



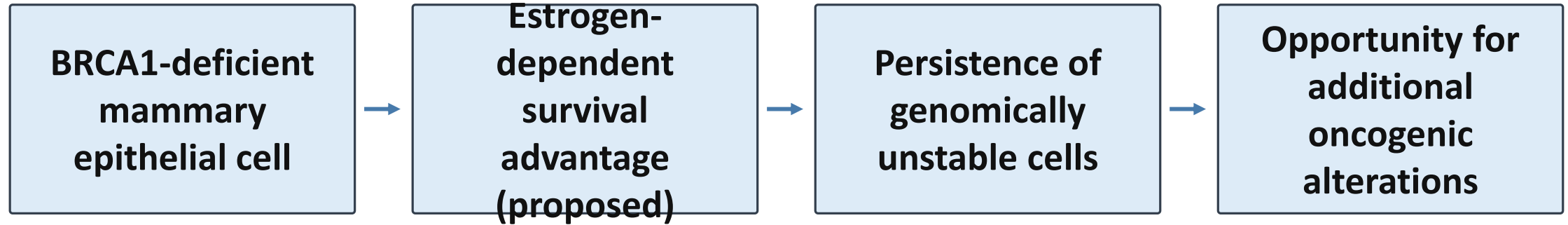
Proposed biological contribution of BRCA1; Evidence is not presented as a settled explanation of tissue specificity.

Hypothesis 1: Loss may retain an unstable progenitor pool



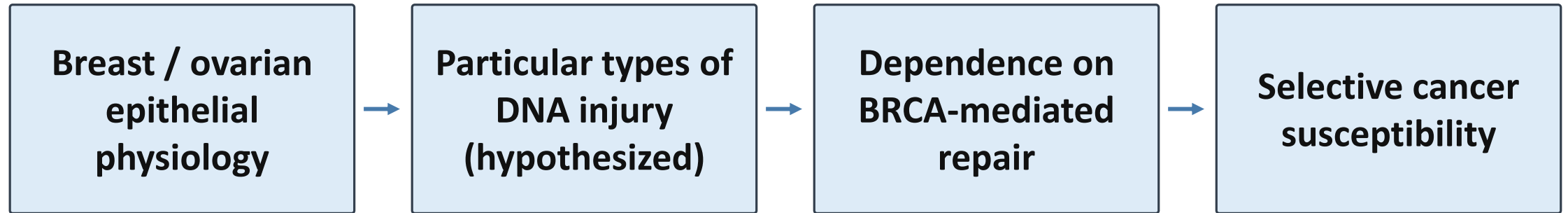
A model proposed by Robbins, not an experimentally quantified timeline or universal cell-of-origin claim.

Hypothesis 2: Estrogen may sustain BRCA1-deficient cells



The textbook explicitly frames the estrogen-survival model as a suggestion rather than established fact.

Hypothesis 3: Epithelial context influences DNA damage



Tissue-specific damage mechanism remains hypothetical in the source; No quantitative rates are asserted.

Three proposed explanations may cooperate

Hypothesis	Specific proposed link	Evidence status in source
Differentiation	BRCA1 supports ER-negative progenitor → ER-positive luminal progression	Proposed
Hormonal survival	Estrogen may aid BRCA1-deficient cell survival	Suggested
Tissue damage context	Breast / ovary may accumulate BRCA-requiring lesions	Proposed

These hypotheses are not proven to be exhaustive or mutually exclusive.

Familial and sporadic tumors may converge on repair defects

Inherited origin

Pathogenic germline susceptibility allele precedes tumor development.

Tumor evolution often requires inactivation of the remaining allele.

Family history may be a relevant clue.

Somatically acquired origin

Both alleles can potentially become inactivated through somatic events.

Molecular phenotype may resemble a hereditary repair-deficient tumor.

Absence of a germline defect does not prove an intact tumor repair pathway.

Convergence on pathway failure does not establish identical etiology or management.

Clinical vignette: Multigenerational breast cancer

A patient reports breast carcinoma in her mother and sister; One relative was diagnosed at a young age. No molecular testing is yet available.

What conclusion is best supported by the family history?

- Strong suspicion of an inherited predisposition.
- A specific pathogenic BRCA variant cannot yet be assigned.

Case interpretation: Pedigree is the starting point

- A first-degree affected relative and young age strengthen concern for familial susceptibility.
- Syndromic and multigene etiologies are possible.
- Hereditary risk cannot be converted into a precise genotype from history alone.
- Genetic interpretation requires a documented disease-associated variant.

Clinical vignette: BRCA-associated tumor phenotype

A breast carcinoma has a triple-negative phenotype. The patient also has several relatives affected by breast or ovarian cancer.

Which biological interpretation is reasonable?

- BRCA1-associated susceptibility is a consideration.
- Triple-negative morphology does not establish a BRCA1 germline variant.

Case interpretation: Phenotype should not substitute for testing

- BRCA1-associated breast cancers are frequently triple-negative.
- Other hereditary and nonhereditary pathways can produce the same phenotype.
- ER-positive tumors remain compatible with BRCA2-associated predisposition.
- Pathology, pedigree, and molecular analysis provide different evidence.

Clinical vignette: Synthetic lethality

A malignant clone has lost homologous recombination repair function. Nearby nonneoplastic cells retain an intact homologous recombination pathway.

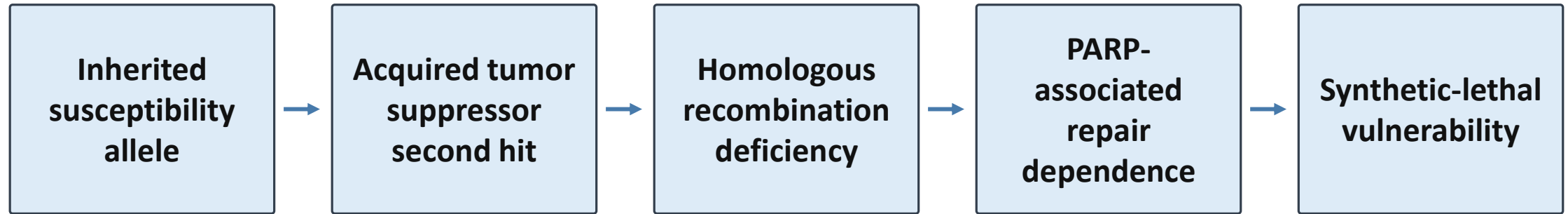
Why could inhibition of PARP-associated repair preferentially injure the tumor?

- The tumor has already lost an alternative high-fidelity repair route.
- Combined repair impairment can generate lethal DNA damage.

Case interpretation: Selective toxicity follows repair redundancy

- A preexisting homologous recombination defect creates dependency on remaining repair processes.
- PARP inhibition increases the burden of unrepaired DNA lesions.
- An intact homologous recombination pathway offers normal cells a relative survival advantage.
- This establishes a rationale for therapy, not a guarantee of clinical response.

Mechanistic summary: From germline allele to treatment vulnerability



This pathway particularly illustrates BRCA-related hereditary breast cancer; Not all susceptibility genes act through HR.

Five distinctions to retain in clinical pathology

- Inherited predisposition ≠ inevitable breast cancer.
- Autosomal-dominant risk ≠ single-hit cellular tumorigenesis.
- BRCA1 phenotype ≠ BRCA2 phenotype.
- Germline pathogenic variant ≠ demonstration of tumor repair deficiency.
- Drug mechanism ≠ patient-specific treatment response.

References and source scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026). Chapter 23, The Breast.
- Core subsection: “Pathogenesis of Familial Breast Cancer” (pp. 956–957).
- Supplemental chapter context: “Pathogenesis of Breast Cancer” and Table 23.3 (printed p. 958 in the supplied extraction).
- Diagrams: newly authored, editable schematic teaching illustrations; no diagnostic specimen images are included.

Risk figures and syndromic associations reflect the supplied edition, not independently updated clinical guidelines.