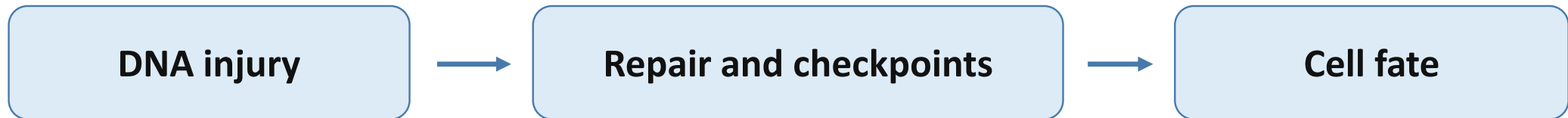


DNA Damage and Carcinogenesis

Ionizing radiation • DNA repair fidelity • genomic instability



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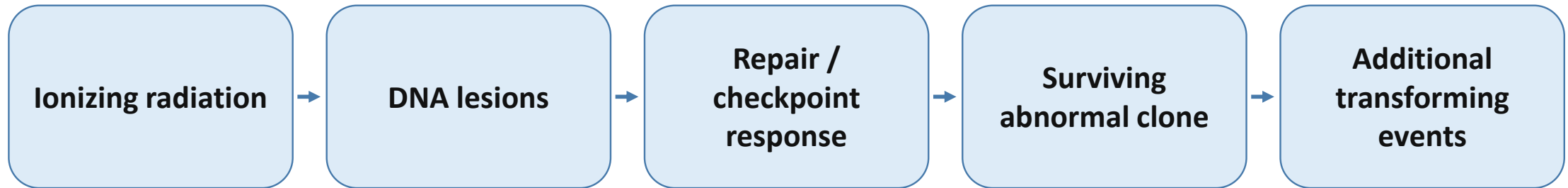
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Learning objectives

- Identify the principal DNA lesions produced by ionizing radiation.
- Compare homologous recombination with nonhomologous end joining.
- Explain how checkpoints prevent propagation of chromosomal damage.
- Connect persistent damage to genomic instability and delayed neoplasia.

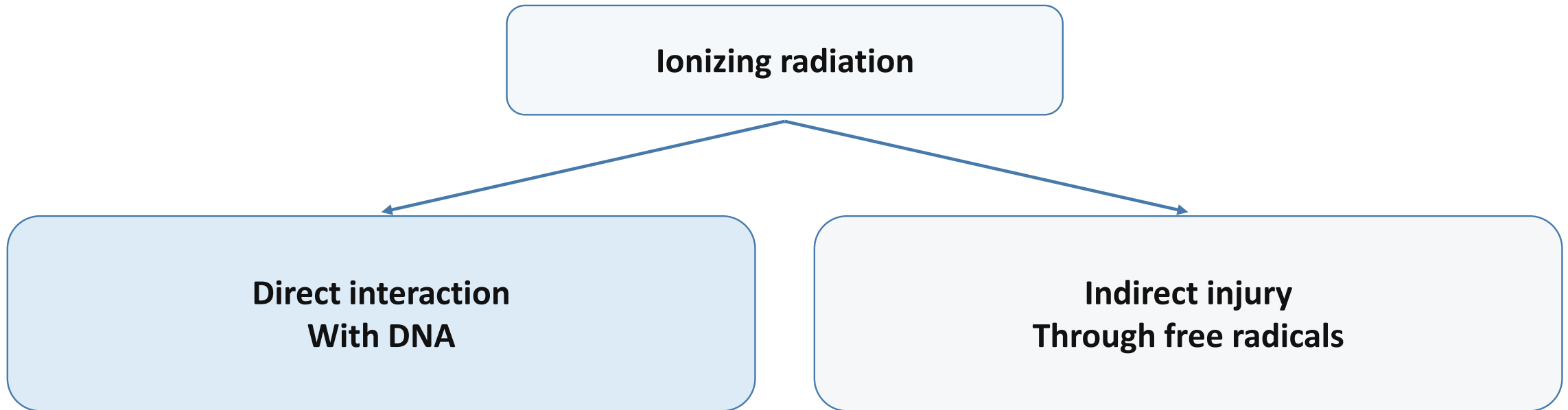
The radiation-to-cancer sequence

A multistep pathway: Exposure alone does not imply inevitable malignancy.



- DNA injury is an initiating event, not a cancer diagnosis.
- Damage outcome depends on repair fidelity and cell-cycle control.
- Persistence and selection of abnormal clones permit later transformation.

Ionizing radiation as a genotoxic agent



- Ionization transfers sufficient energy to disrupt molecular structures.
- DNA can be damaged by direct energy deposition or indirect chemical reactions.
- Radiation is used medically, yet can induce mutagenesis and carcinogenesis.

Direct DNA injury

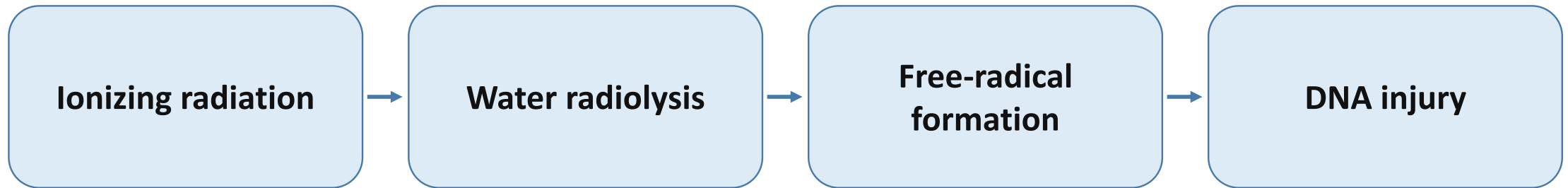
- Energy is deposited in DNA or its immediate molecular environment.
- Ionizing events can alter bases or disrupt the sugar–phosphate backbone.
- The biological effect is determined by the lesion and its subsequent processing.

Schematic DNA lesion



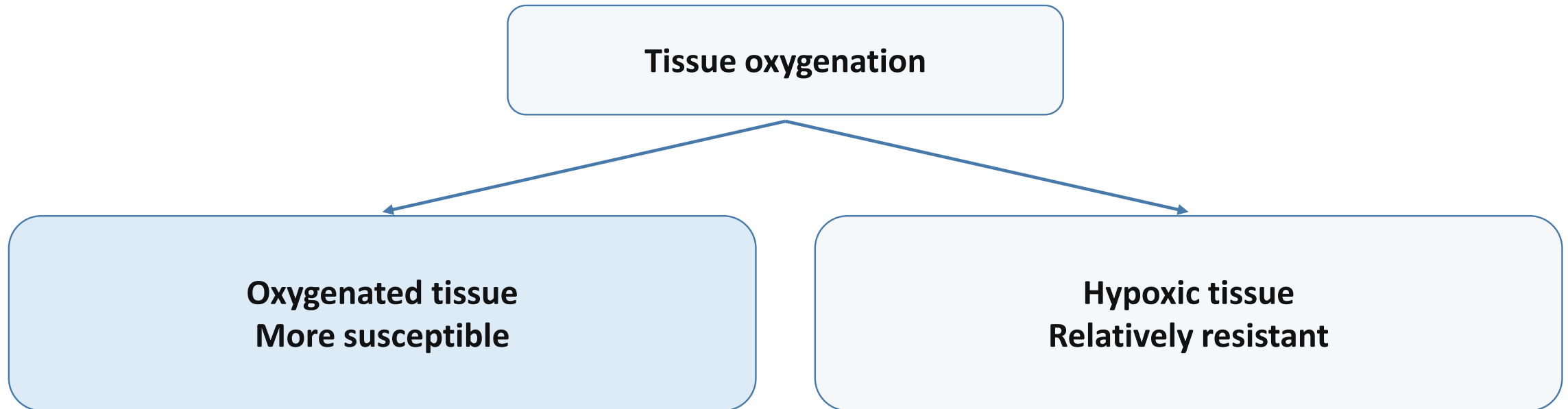
Direct energy deposition may alter DNA

Indirect DNA injury through water radiolysis



- Radiation generates highly reactive species through radiolysis of water.
- Free radicals then react with nearby macromolecules, including DNA.
- This indirect route is prominent in the Robbins radiation-injury model.

Oxygen amplifies indirect injury



- Reactive oxygen species contribute substantially to radiation-related DNA damage.
- Well-oxygenated tissue is generally more radiosensitive than hypoxic tissue.
- Oxygen status therefore changes the biological consequences of exposure.

Multiple lesions can follow one exposure

DNA lesion	Primary consequence
Base damage	Altered nucleotide chemistry
Single-strand break	One interrupted backbone
Double-strand break	Both strands disrupted
DNA–protein crosslink	Protein covalently associated with DNA

Single-base lesions affect individual nucleotides.

Single-base damage

- Damage limited to one base need not disrupt both DNA strands.
- Enzymatic repair systems can correct many simpler lesions.
- Uncorrected base injury may be copied as a sequence alteration.

Schematic DNA lesion

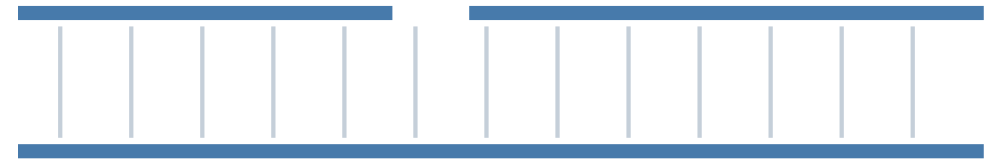


Base lesion

Single-strand breaks

- A single-strand break interrupts one backbone while the partner remains intact.
- Many simple lesions can be repaired by mammalian enzymatic systems.
- The context and completion of repair determine residual genomic injury.

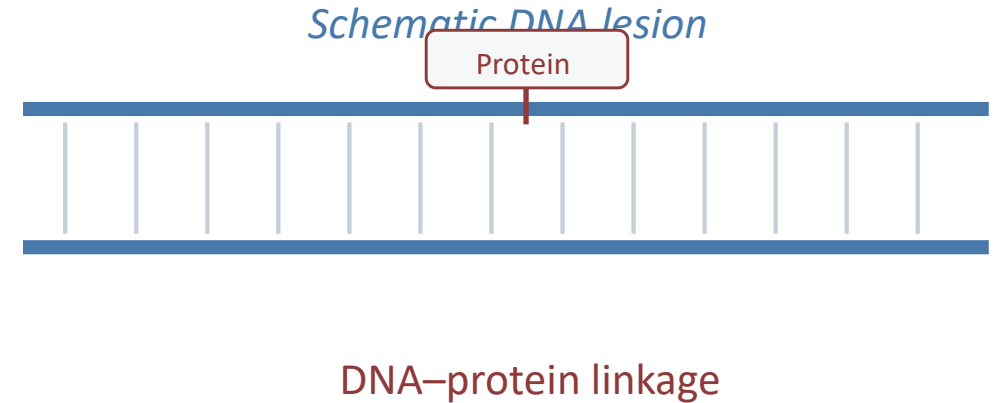
Schematic DNA lesion



One backbone interrupted

DNA–protein crosslinks

- Ionizing radiation can produce DNA–protein crosslinking.
- The covalent attachment can impede DNA transactions.
- Crosslinks belong to the radiation lesion spectrum; They are not synonymous with DSBs.



Double-strand breaks are especially consequential

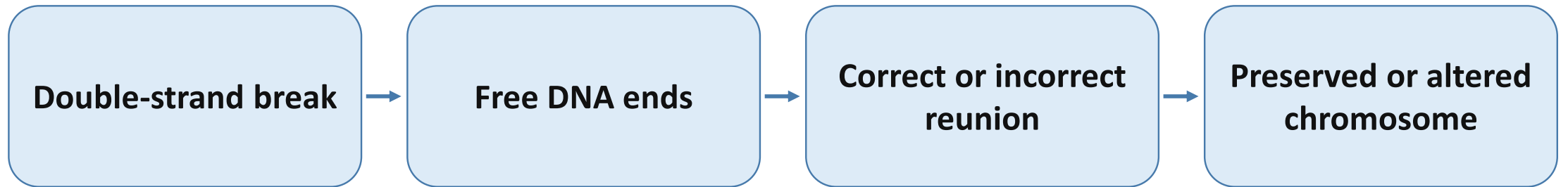
- Both strands of the helix are severed.
- An incorrect rejoining event can change chromosomal structure.
- DSBs as the most serious radiation-induced DNA lesions.

Schematic DNA lesion



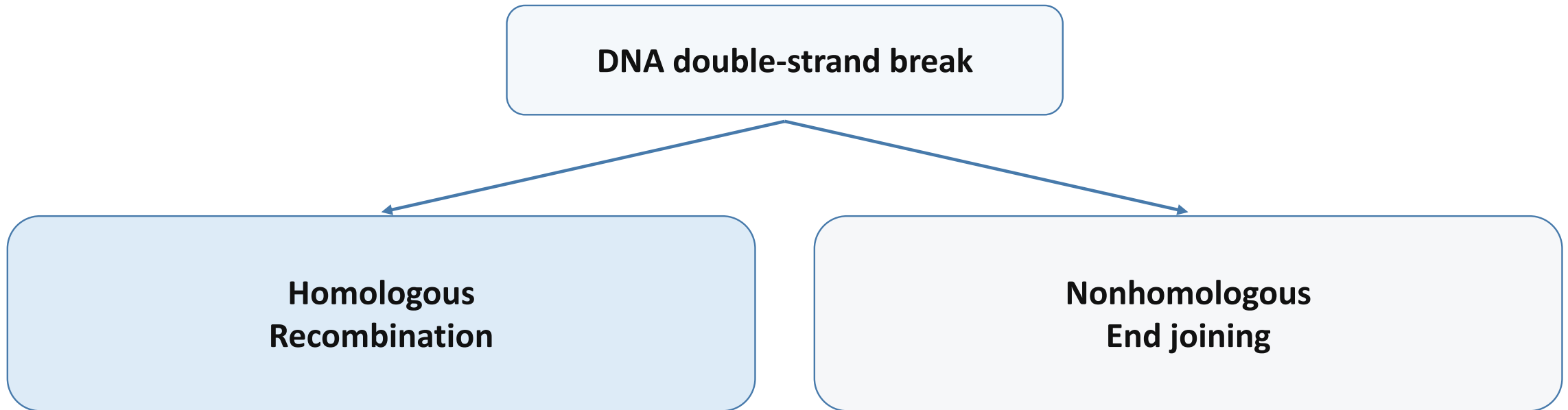
Both strands broken

Why DSBs threaten chromosome integrity



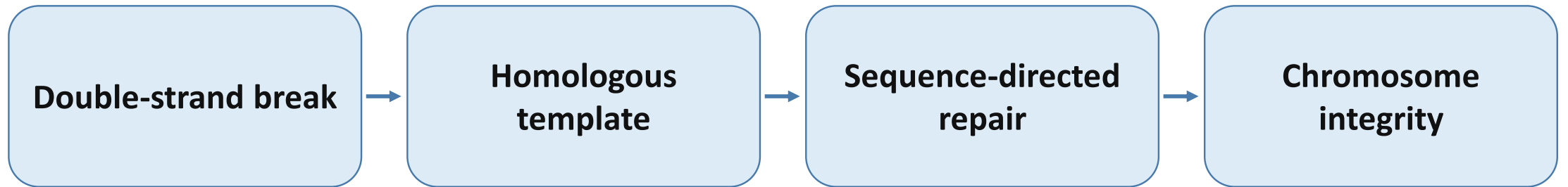
- Broken ends must be reconnected in the correct configuration.
- End joining between inappropriate partners can rearrange chromosomes.
- The danger persists if damaged cells continue cycling.

Two major mechanisms repair DSBs



- Homologous recombination is a template-guided pathway.
- Nonhomologous end joining directly rejoins DNA ends.
- The pathways differ in dependence on homology and potential fidelity.

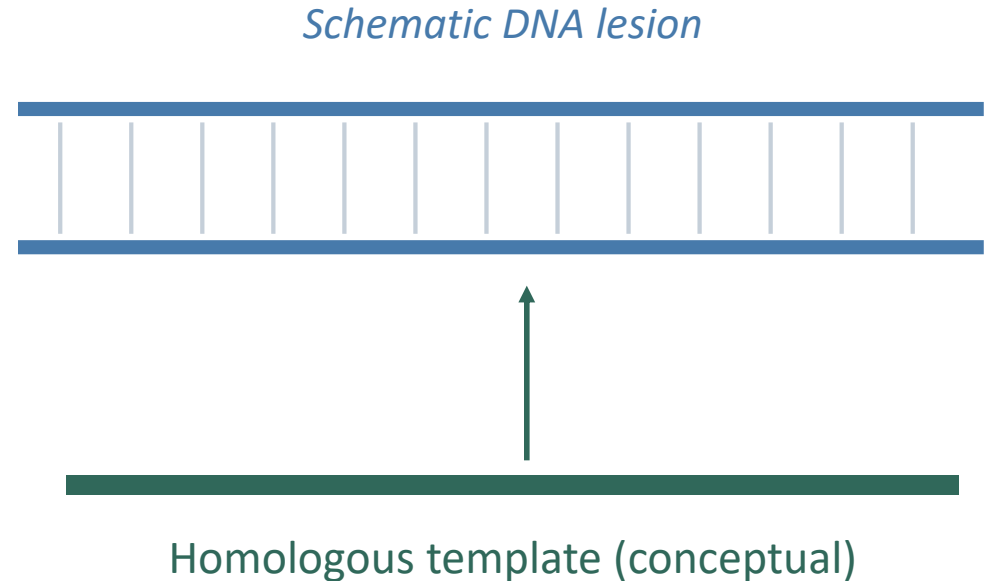
Homologous recombination: Core principle



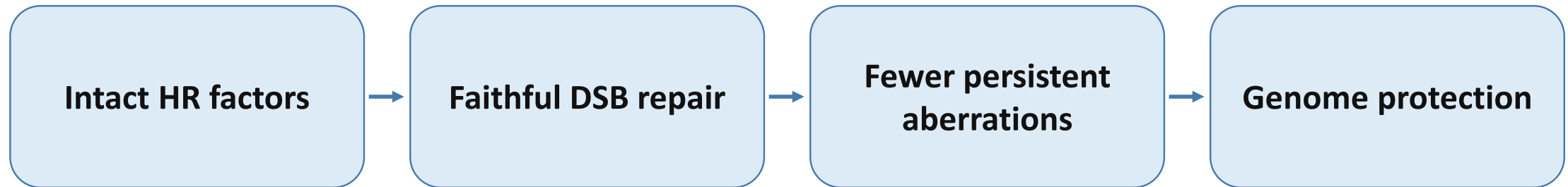
- A homologous DNA sequence provides a reference for repair.
- This strategy can restore lost information with high fidelity.
- Homologous recombination defects with cancer predisposition.

Homology supplies the missing information

- A homologous template can guide restoration of the disrupted sequence.
- Template use distinguishes homologous recombination from simple end joining.
- Availability of an appropriate template constrains pathway choice.

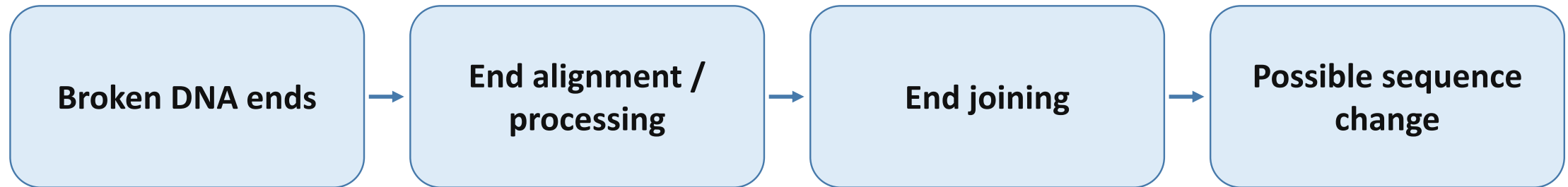


Homologous repair protects genome stability



- Accurate restoration limits formation of rearrangements.
- Defective homologous repair shifts damaged cells toward more error-prone repair.
- Cancer risk rises when high-fidelity repair pathways fail.

Nonhomologous end joining: Core principle



- Broken DNA ends are reunited without a homologous template.
- NHEJ as the most common DSB-repair pathway.
- Rejoined DNA can contain new sequence or structural errors.

NHEJ repairs damage but may introduce mutations

- End processing or joining can change the original sequence.
- Short deletions and duplications are examples of possible outcomes.
- The existence of a repaired chromosome does not prove accurate restoration.

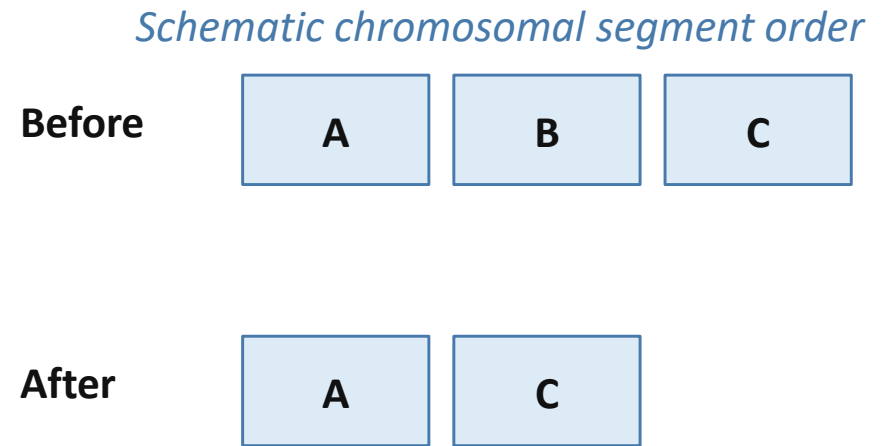
Schematic DNA lesion



Both strands broken

Short deletion following end joining

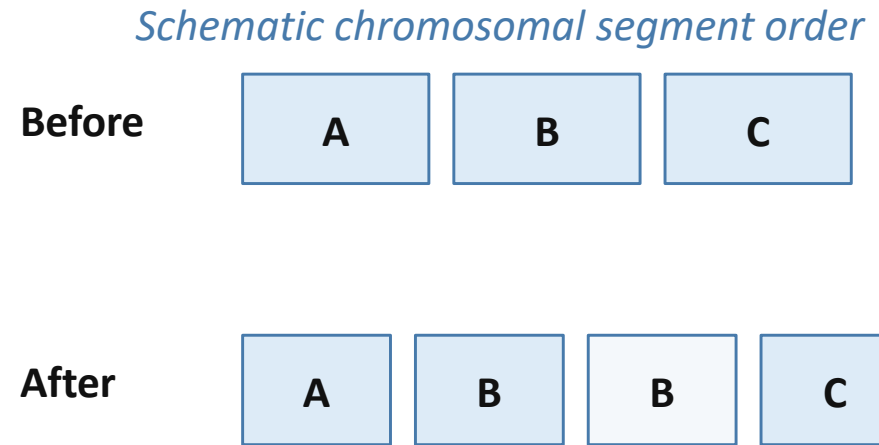
- Loss of bases during break repair yields a deletion.
- A short deletion can change coding or regulatory sequence if it occurs there.
- Robbins explicitly identifies short deletions among NHEJ-associated changes.



The B segment is deleted at the repair junction.

Short duplication following end joining

- A segment may be repeated at the repaired junction.
- The result is a local change in copy number or sequence arrangement.
- This is one described mutational outcome of NHEJ.

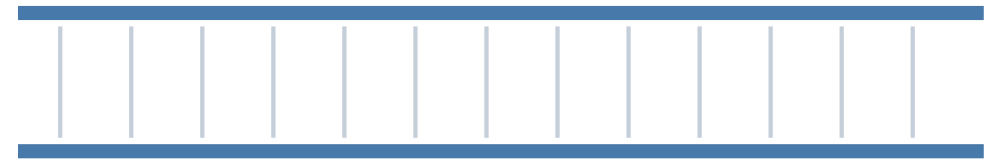


An extra copy of segment B appears.

Chromosomal translocation

- Misjoining ends from different chromosomes can produce a translocation.
- The rearrangement may alter gene regulation or generate abnormal fusion contexts.
- Translocations among radiation-associated repair aberrations.

Schematic DNA lesion

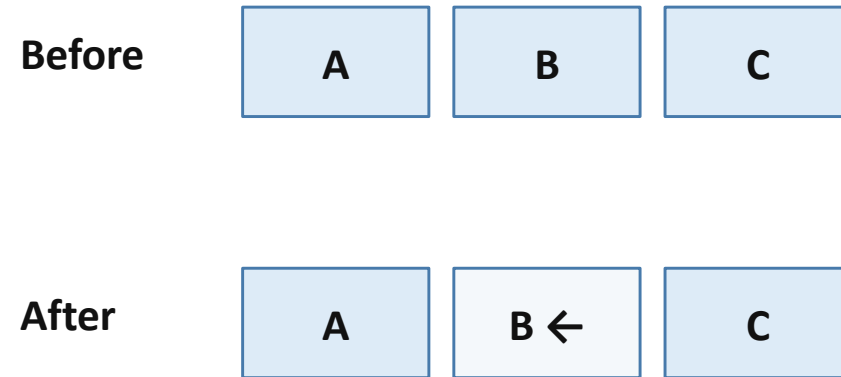


Joined fragments from different chromosomes

Chromosomal inversion

- A DNA segment may reintegrate in the reverse orientation.
- Sequence order is altered even if DNA content is not obviously lost.
- Inversions are another chromosomal aberration linked to NHEJ.

Schematic chromosomal segment order



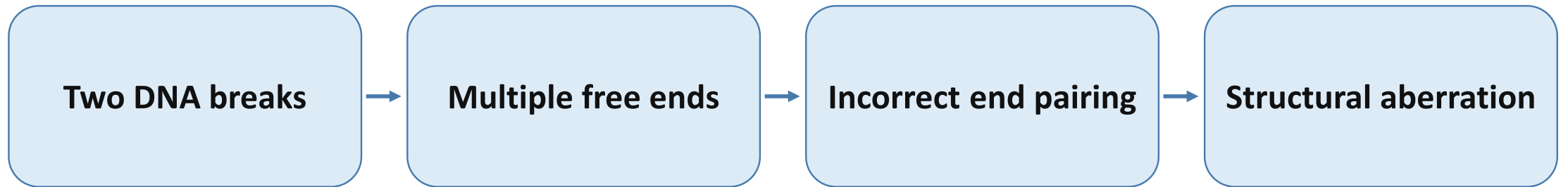
B reverses orientation; A and C retain their positions.

Deletion and duplication versus rearrangement

Alteration	Illustrative effect
Short deletion	Sequence removed near a repaired junction
Short duplication	Sequence repeated near a junction
Translocation	Segments joined between chromosomes
Inversion	Segment orientation reversed

Small insertions/deletions change local sequence length.

Misjoining changes chromosome topology



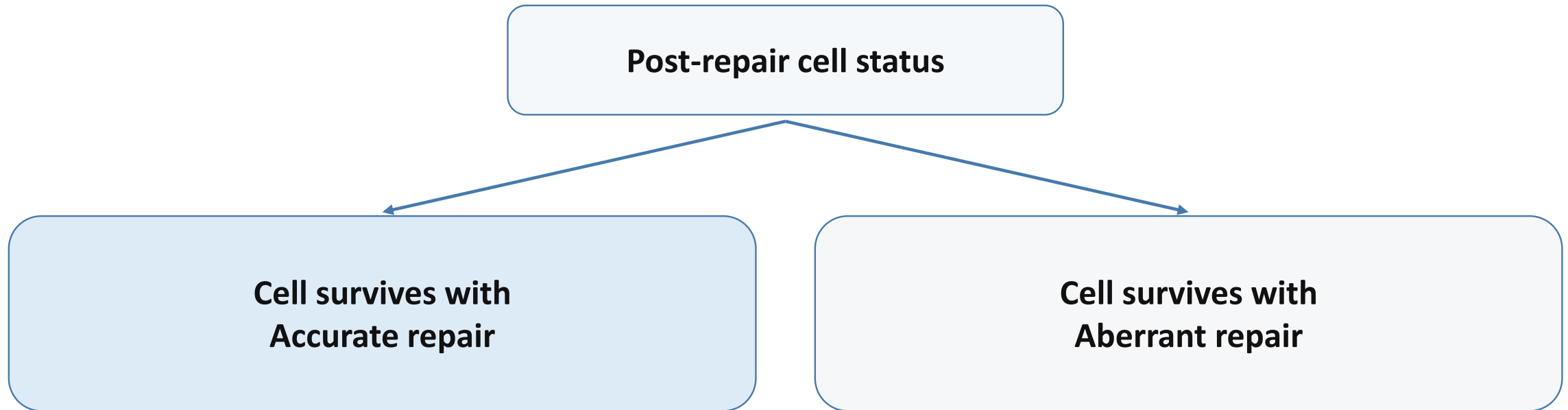
- Two independent breaks generate several free ends.
- Pairing the wrong ends creates structural rearrangement.
- Preserved cell viability is compatible with a persistently abnormal genome.

Comparing the two DSB repair strategies

Feature	Homologous recombination	NHEJ
Repair principle	Template-guided	Direct end joining
Template	Homologous sequence	No homologous template required
Fidelity	Potentially high	May be error-prone
Cancer relevance	Defects predispose to cancer	Aberrant joining can alter chromosomes

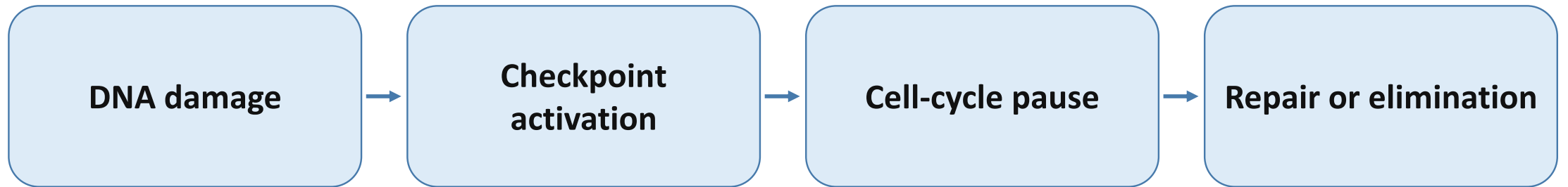
Both pathways can resolve a DNA double-strand break.

Repair success is not a binary concept



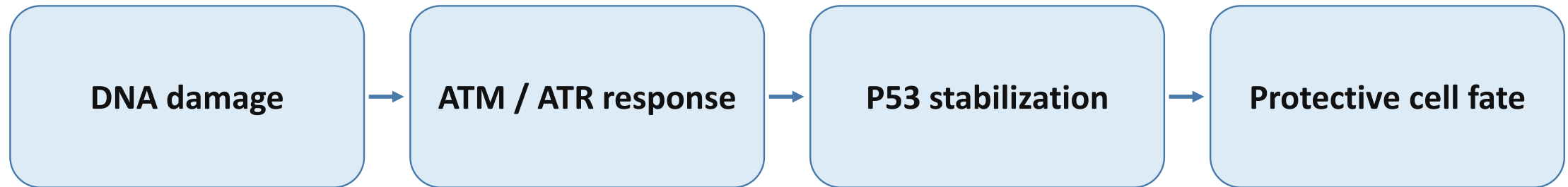
- A chromosome may be reconnected while its sequence is altered.
- Mutagenic repair may support cell survival but retain carcinogenic potential.
- The relevant endpoints are survival, sequence accuracy, and chromosome architecture.

Cell-cycle checkpoints prevent error propagation



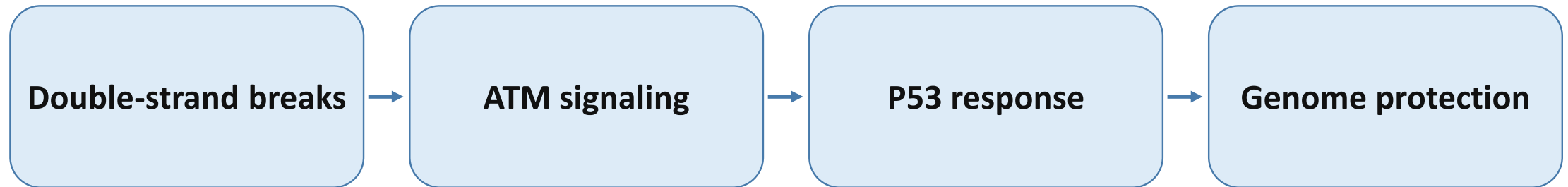
- A cell with unrepaired DSBs should not proceed unchecked through replication.
- Checkpoint controls create time for repair or direct a protective cell fate.
- Failure lets chromosomal abnormalities persist in daughter cells.

The DNA damage response activates p53



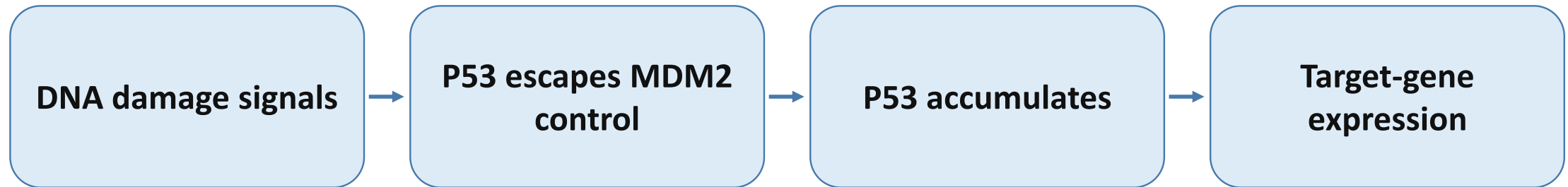
- ATM and ATR are stress-responsive protein kinases upstream of p53.
- Kinase signaling stabilizes p53 following DNA damage.
- Activated p53 directs arrest, repair-associated programs, senescence, or apoptosis.

ATM is linked directly to DSB surveillance



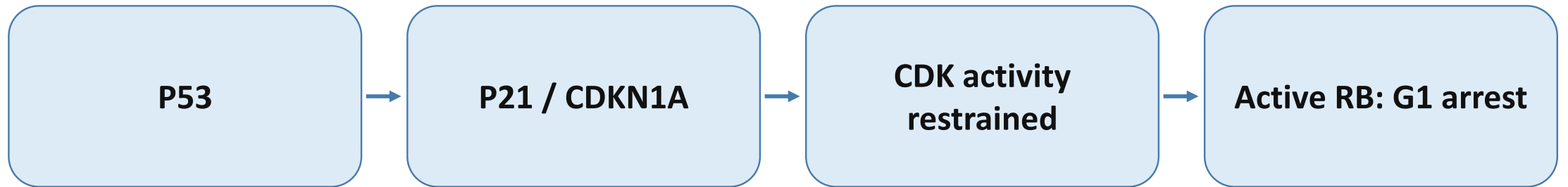
- ATM is a kinase in the DNA damage response.
- Defects in ATM impair responses to DNA double-strand breaks.
- Ataxia-telangiectasia illustrates the link between DNA-repair failure and cancer.

P53 stabilization changes transcriptional programs



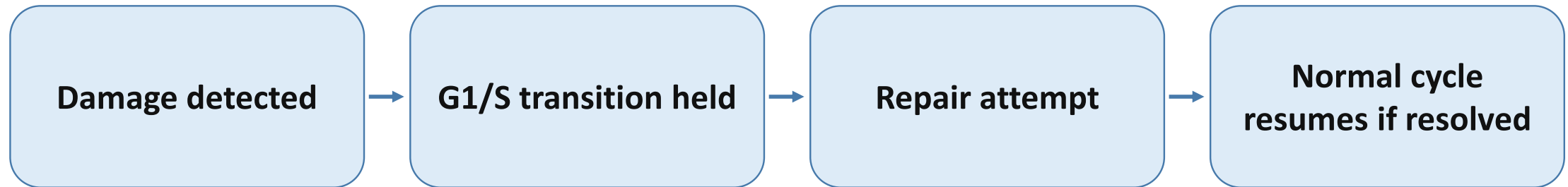
- MDM2 normally promotes p53 degradation in unstressed cells.
- DNA damage signaling reduces MDM2-mediated suppression.
- Accumulated p53 acts as a transcription factor for protective responses.

P21 links p53 to G1 arrest



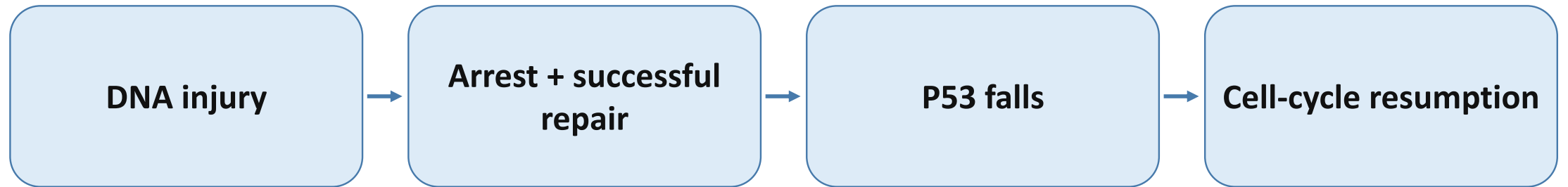
- P53 induces CDKN1A, encoding the CDK inhibitor p21.
- P21 inhibits cyclin D–CDK4 activity.
- RB remains active and restricts passage from G1 into S phase.

The G1/S pause limits replication of damaged DNA



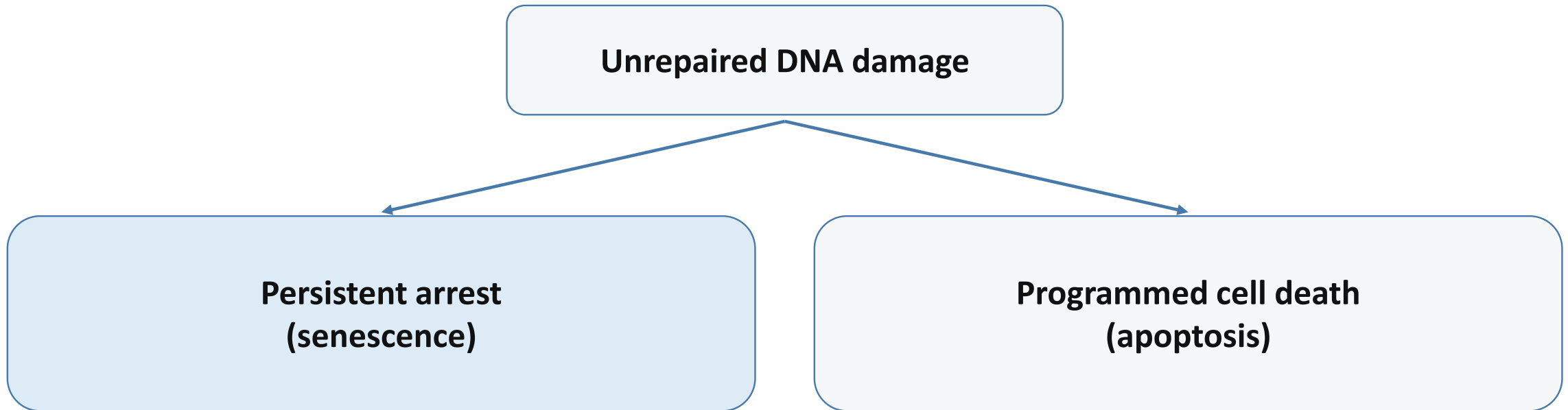
- The transition into S phase commits DNA to replication.
- A checkpoint pause delays copying of a damaged genome.
- Repair can return the cell to normal proliferation after damage is resolved.

Successful repair ends the checkpoint signal



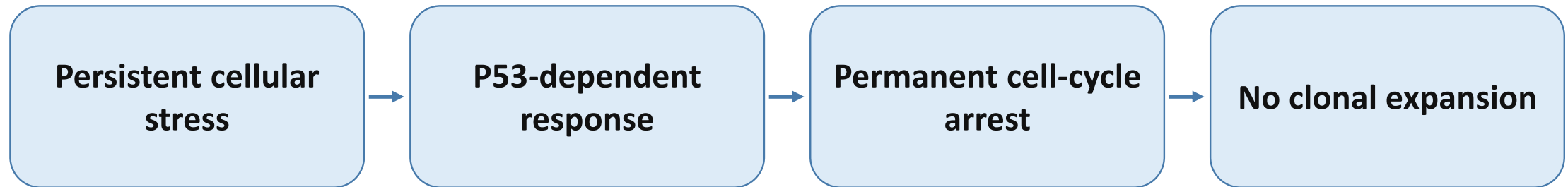
- Resolution of damage reduces signals stabilizing p53.
- Declining p53 releases the reversible cell-cycle block.
- The cell may re-enter a normal proliferative state.

Persistent damage triggers additional protection



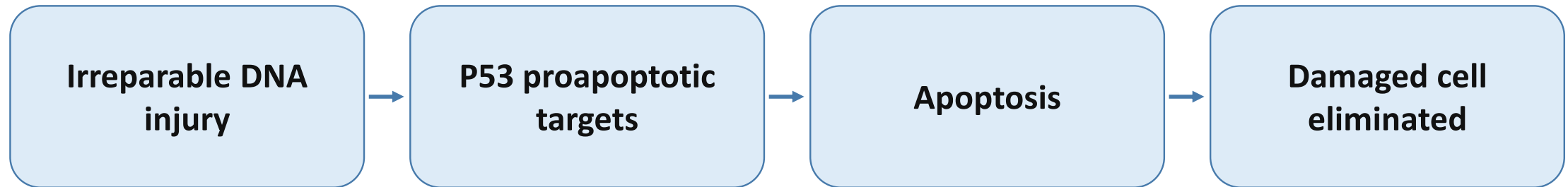
- Uncorrected DNA damage can maintain p53 activation.
- Possible outcomes include permanent growth arrest or apoptosis.
- Which outcome predominates varies with damage and cell context.

Senescence prevents replication of an unstable genome



- Senescence is a durable, essentially permanent cell-cycle arrest.
- Cells may survive but lose proliferative capacity.
- This prevents transmission of persistent genome damage to a clone.

Apoptosis removes irreparably damaged cells



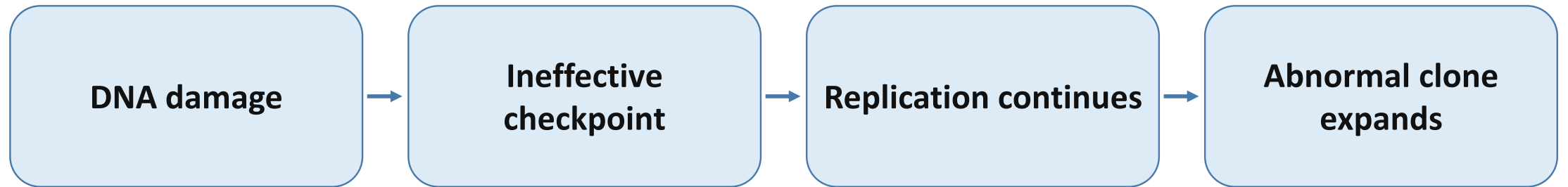
- P53 induces proapoptotic genes, including BAX and PUMA.
- The intrinsic apoptotic pathway can eliminate cells with serious damage.
- Cell elimination is protective against malignant transformation.

Three p53-dependent responses

Response	Consequence	Genomic benefit
Reversible arrest	Pause in cell cycling	Time for DNA repair
Senescence	Permanent growth arrest	No propagation of damage
Apoptosis	Cell elimination	Damaged genome removed

Transient arrest permits repair and continued survival.

Checkpoint loss converts damage into inherited instability



- Failure of p53-mediated arrest allows proliferation despite DNA injury.
- Chromosomal aberrations then persist across cell generations.
- Additional driver mutations can accumulate in surviving clones.

Wild-type versus defective checkpoint

Checkpoint intact

Replication can pause

Repair or elimination is promoted

Lower opportunity for clonal fixation

Checkpoint impaired

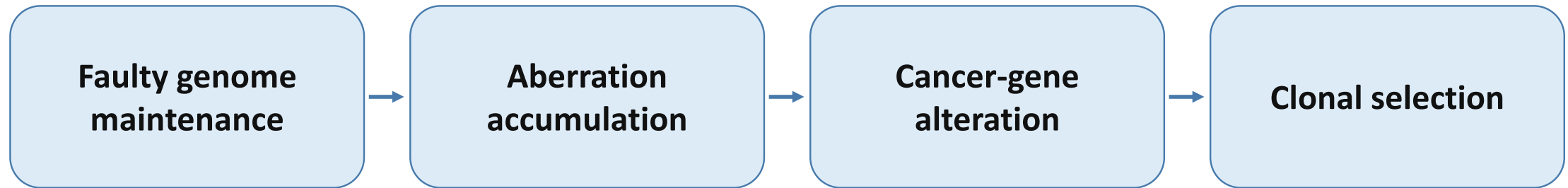
Division may continue

Mutated genomes can persist

More opportunity for additional drivers

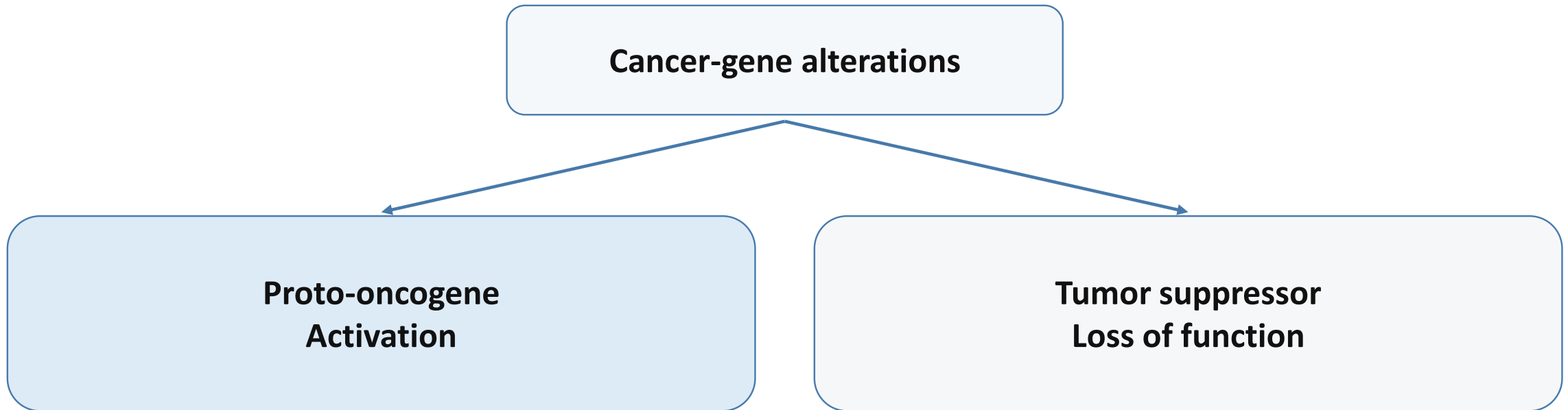
Functioning response: Stop, repair, senesce, or die.

Genomic instability accelerates carcinogenesis



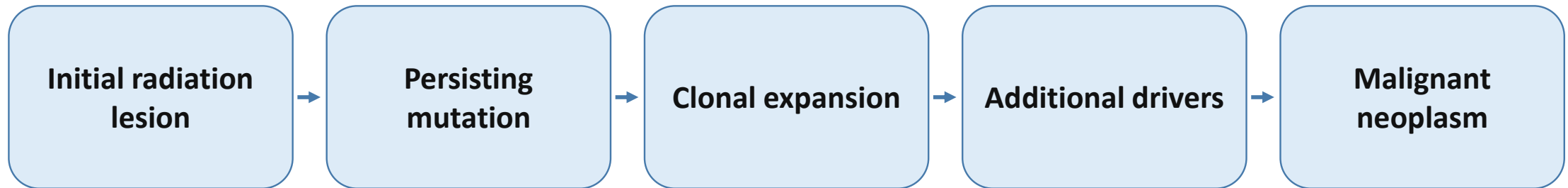
- Persistent DNA repair or checkpoint defects increase acquisition of genomic abnormalities.
- Aberrations can affect oncogenes or tumor suppressor genes.
- Additional mutations allow selection and progression of transformed clones.

Chromosome damage can affect cancer genes



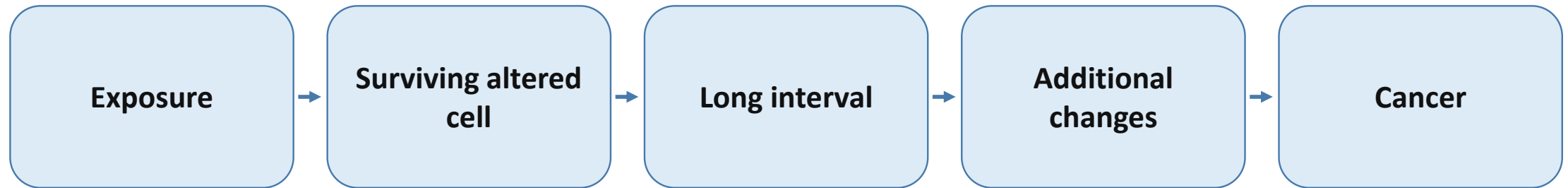
- A rearrangement is consequential when it changes important gene function.
- Proto-oncogenes may become dysregulated.
- Tumor suppressor function may be lost or reduced.
- Most DNA damage does not, by itself, establish malignant transformation.

Radiation carcinogenesis is a multistep process



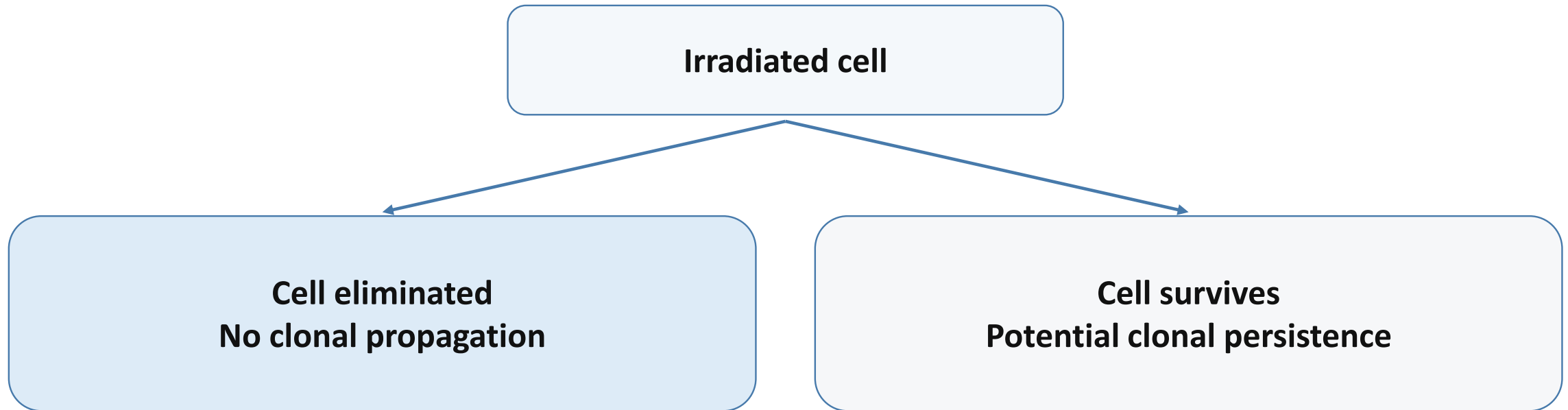
- A surviving damaged cell can initiate a lineage with an abnormal genome.
- Additional transforming events are required for malignant progression.
- The extended sequence helps explain long clinical latency.

Latency reflects delayed clonal evolution



- Chromosomal damage can remain in cells that survive irradiation.
- Years may pass before additional events produce overt cancer.
- Absence of immediate malignancy does not exclude later carcinogenic effects.

Only a surviving lineage can propagate damage



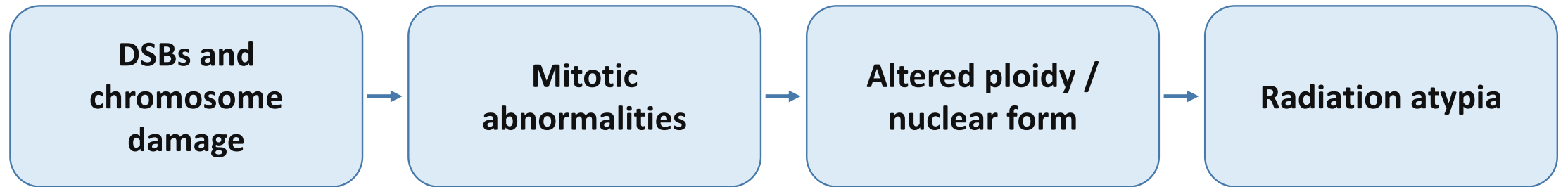
- Many severely injured cells die rather than form tumors.
- Carcinogenesis requires continued viability and potential proliferation.
- The fate of damaged cells matters as much as the initial lesion.

Radiation injury does not equal malignancy

Post-radiation finding	Interpretive caution
Enlarged or pleomorphic nuclei	Can reflect radiation effect
Abnormal mitotic figures	Not automatically a new tumor
Giant or multinucleated cells	May persist after exposure
True malignancy	Requires appropriate diagnostic evidence

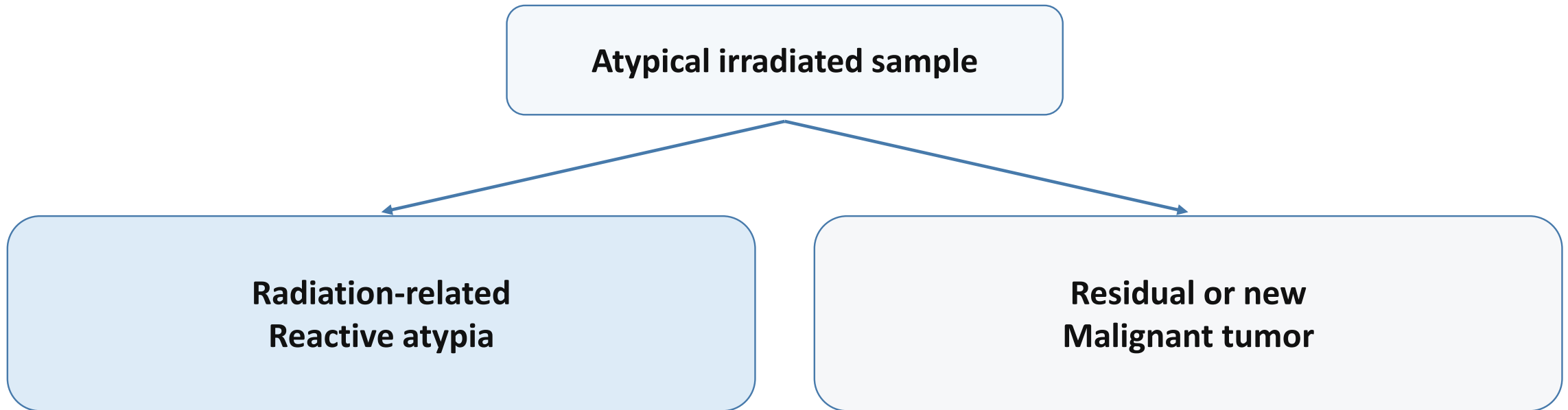
Radiation can produce cellular atypia and chromosomal abnormalities.

Chromosomal injury produces nuclear alterations



- DNA breaks are associated with deletions, translocations, and fragmentation.
- Spindle disorganization can accompany polyploidy and aneuploidy.
- These alterations can create striking abnormal nuclear morphology.

Cellular radiation atypia can mimic cancer



- Radiation may induce pleomorphic nuclei and giant cells.
- Abnormal mitoses can appear in previously irradiated tissue.
- A known radiation field is vital context when reviewing tissue sections.

Diagnostic pitfall in a treated tumor bed

Finding	Question for interpretation
Pleomorphic cells	Treatment effect or viable tumor?
Giant nuclei	Radiation-associated change?
Abnormal mitoses	Is there independent evidence of neoplasia?
Stromal fibrosis	Expected post-treatment injury?

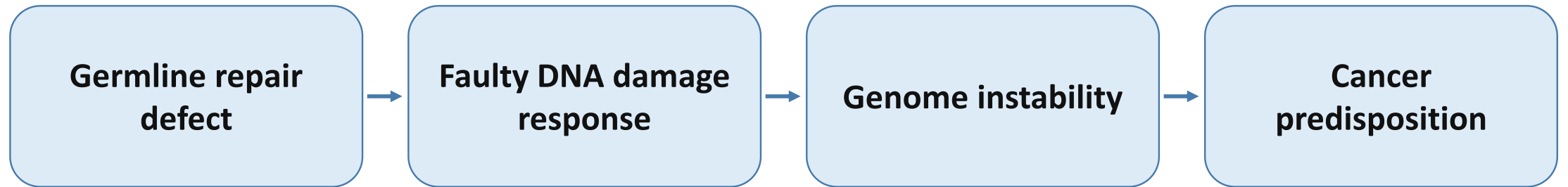
Postirradiation atypia may resemble malignant cytology.

Early cell killing and late cancer are different endpoints

Endpoint	Dominant mechanism	Timing concept
Acute tissue injury	Loss of sensitive cells	Early
Fibrosis	Vascular / parenchymal injury	Delayed
Cancer	Persisting mutations + progression	Often years later

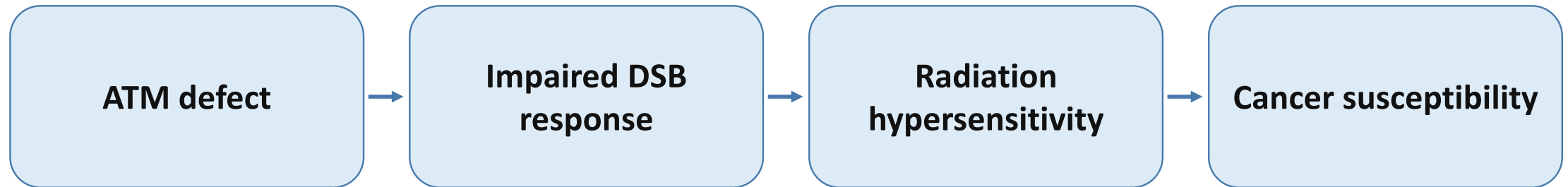
Acute injury reflects death or dysfunction in sensitive tissues.

Inherited repair defects reveal the pathway's importance



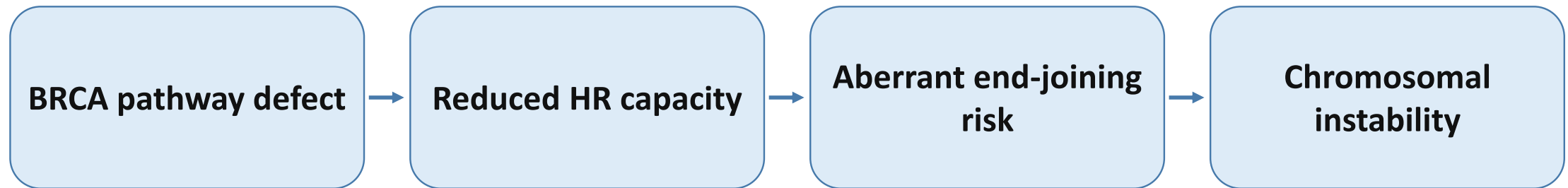
- Disorders involving repair genes provide natural evidence of genome protection.
- The diseases vary in phenotype and affected repair proteins.
- Cancer susceptibility rises when chromosomal damage is not handled correctly.

Ataxia-telangiectasia: Defective ATM signaling



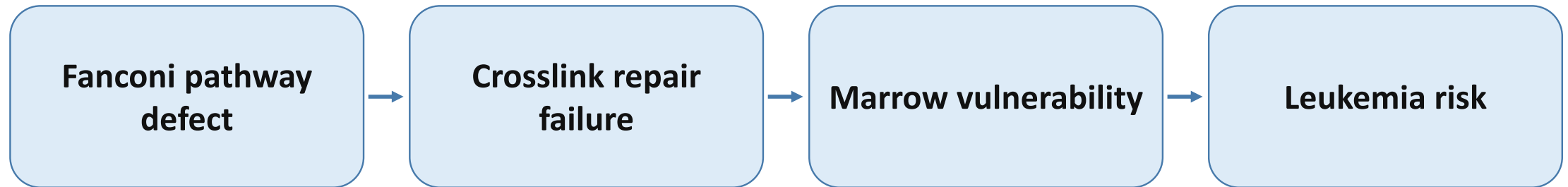
- Autosomal recessive ATM defects impair the DSB damage response.
- Clinical features include ataxia, immunodeficiency, and radiation hypersensitivity.
- Predisposition particularly includes lymphoid malignancies.

BRCA1 and BRCA2 support homologous repair



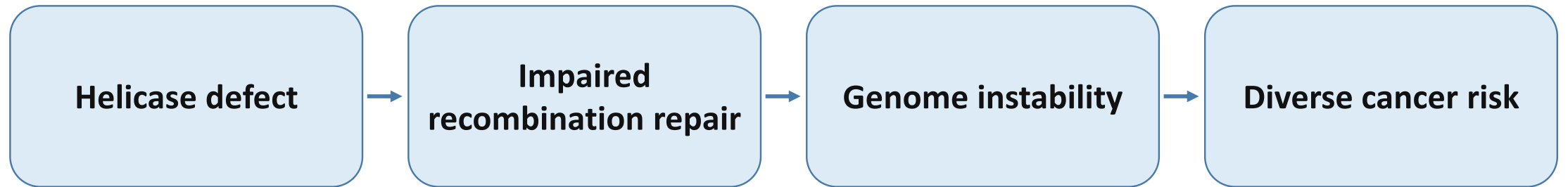
- BRCA proteins are required for homologous recombination repair.
- Defective pathway activity predisposes to several malignancies.
- Failure of the high-fidelity route favors aberrant repair and instability.

Fanconi anemia: Crosslink repair and marrow failure



- Multiple Fanconi genes act in a pathway repairing DNA crosslinks.
- The pathway cooperates with homologous recombination machinery.
- Affected patients can develop marrow aplasia and leukemia.

Bloom syndrome: Homologous repair vulnerability



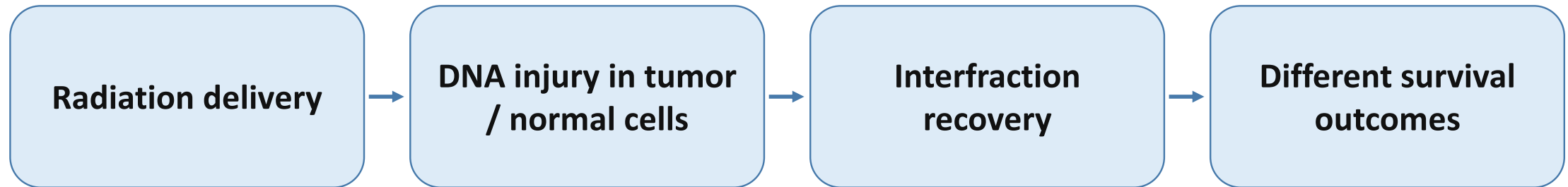
- Bloom syndrome is associated with loss of a repair-associated helicase.
- Developmental abnormalities accompany a broad cancer predisposition.
- It reinforces the importance of chromosome maintenance in tumor prevention.

Repair-deficiency syndromes in comparison

Syndrome / genes	Repair link	Teaching association
Ataxia-telangiectasia / ATM	DNA damage signaling	Radiation sensitivity; lymphoid cancer
BRCA1/BRCA2	Homologous recombination	Hereditary cancer predisposition
Fanconi anemia	Crosslink / HR-associated repair	Marrow failure and leukemia
Bloom syndrome	Repair-associated helicase	Broad malignancy predisposition

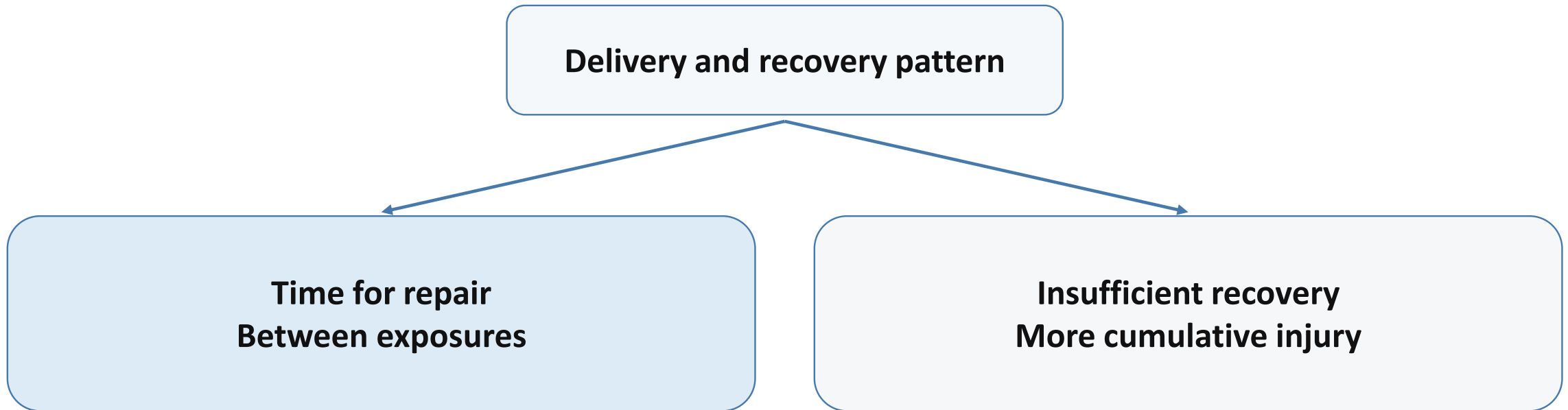
Different inherited disorders compromise different parts of DNA maintenance.

Radiotherapy exploits incomplete tumor recovery



- Radiation-induced DNA damage is essential to its antitumor action.
- Repair capacity and cell survival determine treatment response.
- Fractionation may allow normal tissue repair between exposures.

Dose rate and fractionation modify cell injury



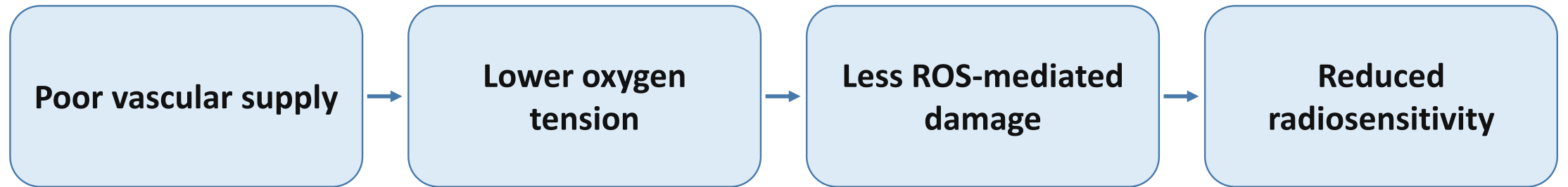
- Radiation effects are cumulative but influenced by dose delivery over time.
- Intervals can permit repair of some sublethal damage.
- Incomplete recovery permits accumulation of biologic injury.

Proliferating tissues are especially radiosensitive

Feature	Biological consequence
Rapid cell turnover	Early injury from cell loss
Quiescence	Relative resistance to cell killing
Persistent mutant dividing cells	Potential late neoplastic outcome

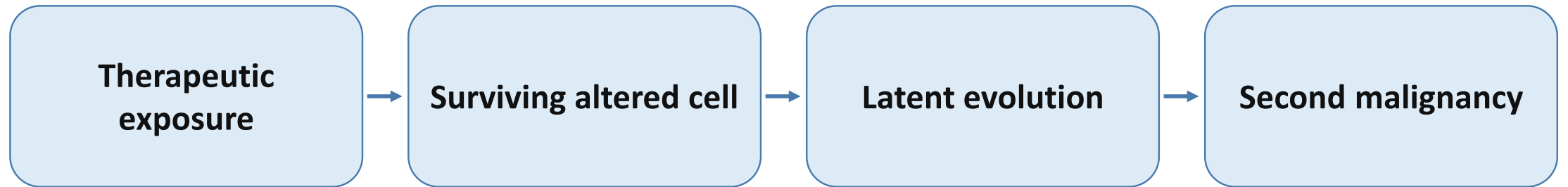
DNA replication makes dividing cells vulnerable to damage.

Tumor hypoxia can diminish radiation effectiveness



- Hypoxic regions generate less oxygen-dependent amplification of injury.
- Rapidly growing tumors may contain poorly vascularized areas.
- Relative radioresistance is one consequence of this microenvironment.

Irradiated fields can generate second neoplasms



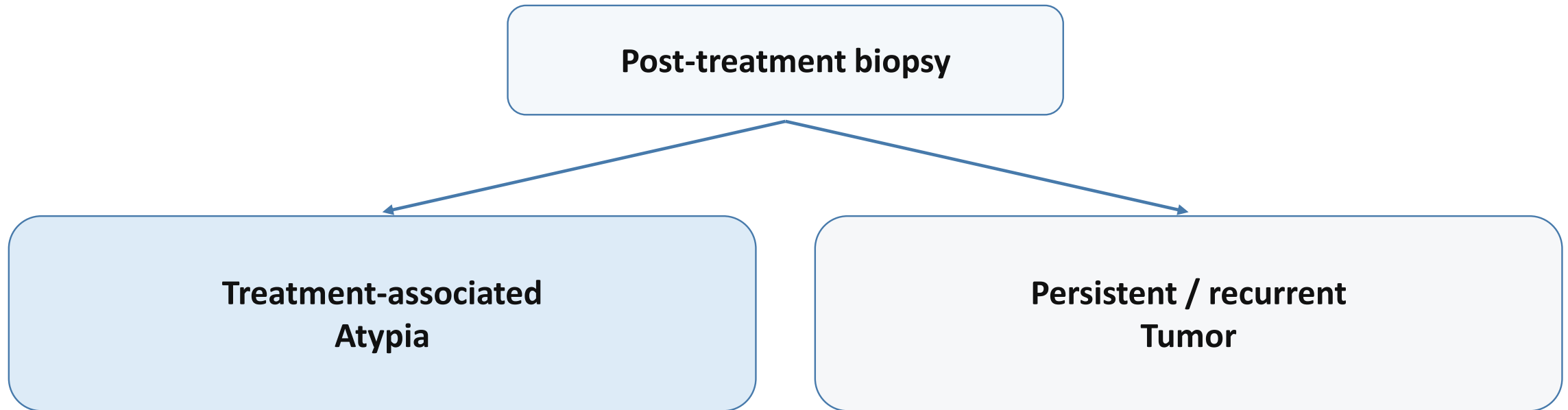
- A patient cured of the initial malignancy may later develop a distinct neoplasm.
- Persistent DNA damage provides a plausible mechanistic basis.
- Myeloid and solid second cancers after radiotherapy.

Human observations support radiation carcinogenesis

Exposure context	Cancers noted in Robbins
Hiroshima and Nagasaki survivors	Leukemias and multiple solid tumors
Chernobyl accident	Thyroid cancer
Therapeutic radiation	Second myeloid or solid malignancies

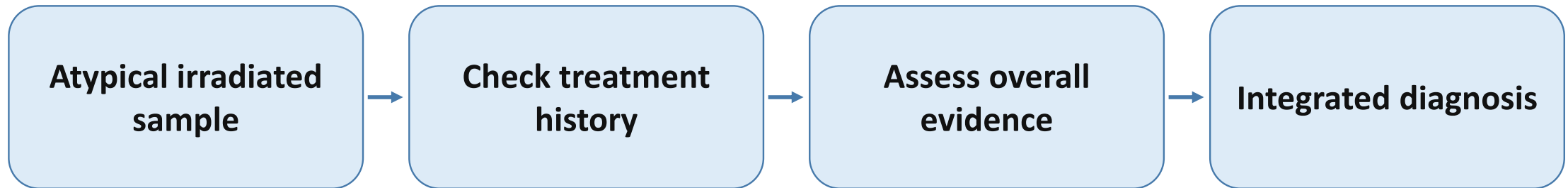
Excess leukemias and solid tumors in atomic-bomb survivors.

Case application: Radiation-treated tissue



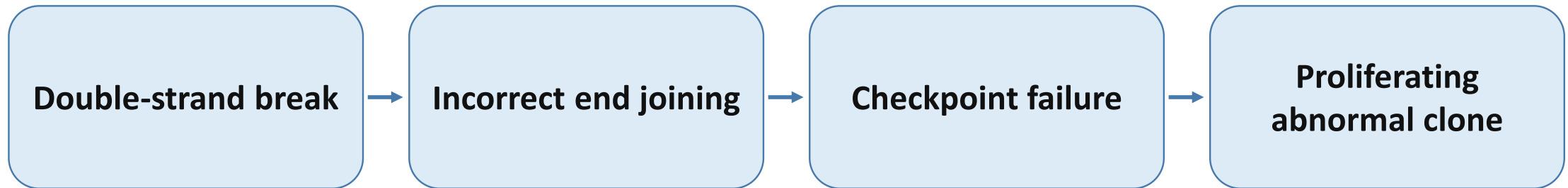
- A post-treatment biopsy shows giant pleomorphic cells and abnormal nuclei.
- The prior specimen was irradiated months earlier.
- What prevents immediate classification as recurrent malignancy?

Case resolution: Morphology needs context



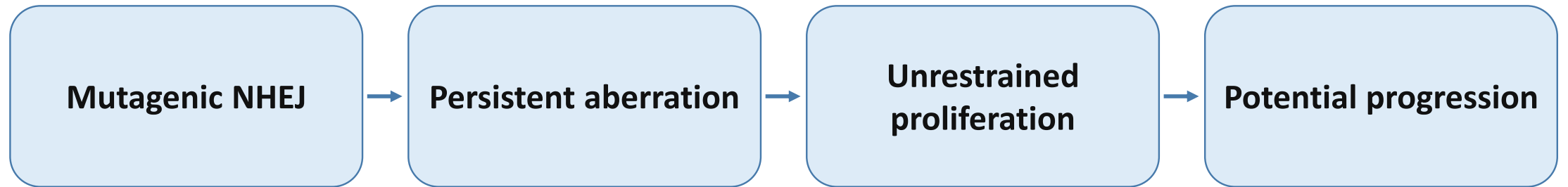
- Radiation effects can reproduce several cytologic signs of cancer.
- Review field history, timing, architecture, and independent tumor evidence.
- Do not equate postirradiation nuclear pleomorphism with neoplasia.

Case application: Damaged dividing cell



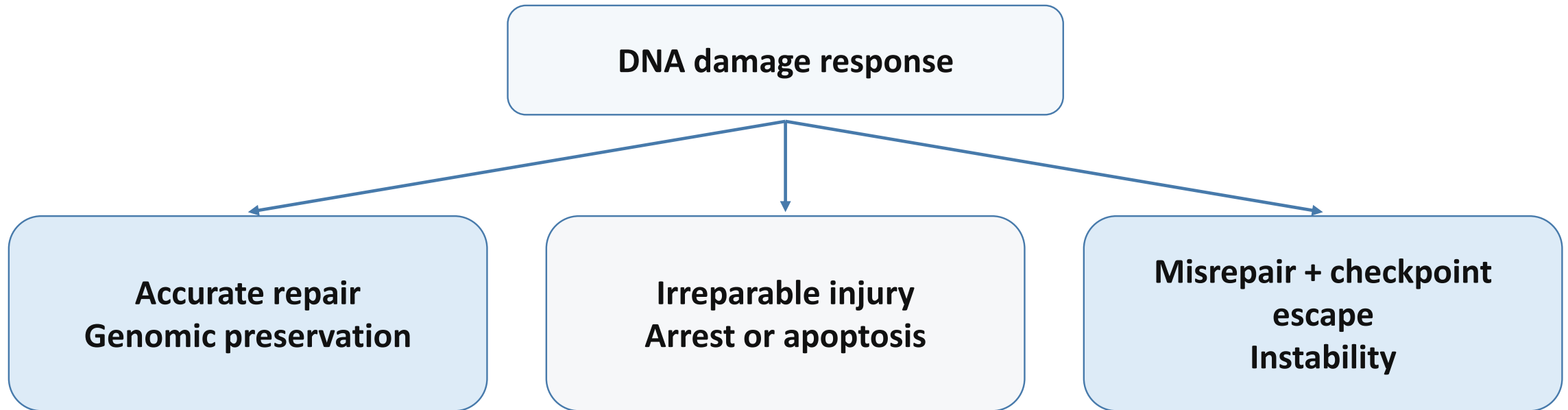
- A dividing cell incurs a DSB and rejoins two incorrect chromosome ends.
- Its p53-dependent checkpoint is defective, yet the cell survives.
- Explain the two failures that jointly increase oncogenic potential.

Case resolution: Mutagenic repair plus escape



- Misrepair creates the heritable chromosomal abnormality.
- Checkpoint escape permits replication of the altered genome.
- Further cancer-gene changes and selection are still needed for malignancy.

Integrated model of DNA injury and cell fate

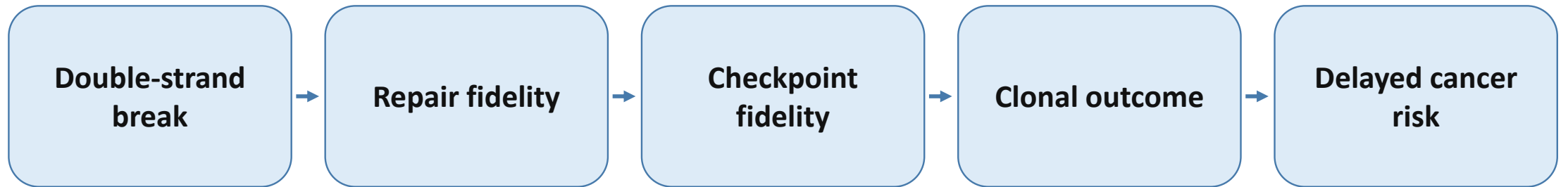


- Accurate repair preserves genome integrity.
- Severe damage may result in senescence or cell death.
- Aberrant repair plus failed checkpoint enables persistence and progression.

Six distinctions that prevent common errors

- DNA lesion $\neq$ fixed mutation.
- Successful end joining $\neq$ restoration of original sequence.
- Chromosomal aberration $\neq$ inevitable cancer.
- Radiation atypia $\neq$ histologic proof of malignant persistence.
- Acute radiosensitivity $\neq$ eventual cancer risk.
- Ionizing radiation's effects include both therapeutic killing and late mutagenesis.

Mechanistic synthesis



- Double-strand breaks are the central severe lesion emphasized by Robbins.
- NHEJ is common but may generate small mutations and major rearrangements.
- ATM–p53 checkpoints protect against propagation of damaged DNA.
- Surviving aberrant clones may acquire further events and form cancers after years.

Principal source and internal cross-reference

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026.
- Chapter 9: radiation injury and DNA damage–carcinogenesis pathway.
- Chapter 7: p53 responses, genomic instability, and repair-deficiency syndromes.
- Illustrations in this deck are original editable schematics; not histology specimens.