
Nucleotide Excision Repair Factors

UV-induced DNA damage, repair failure and cancer predisposition

Molecular pathology and clinicopathologic correlations

Dr Abu Suraih Sakhri

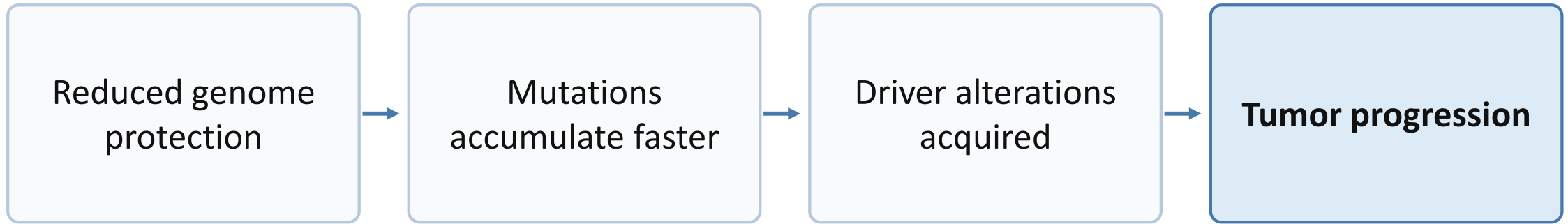
MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain how UV-induced pyrimidine dimers interfere with DNA replication.
- Connect nucleotide excision repair failure to xeroderma pigmentosum and skin cancer.
- Distinguish nucleotide excision repair from the other genomic stability pathways.
- Use molecular injury–repair logic to interpret clinical and pathological examples.

Genomic instability accelerates cancer evolution

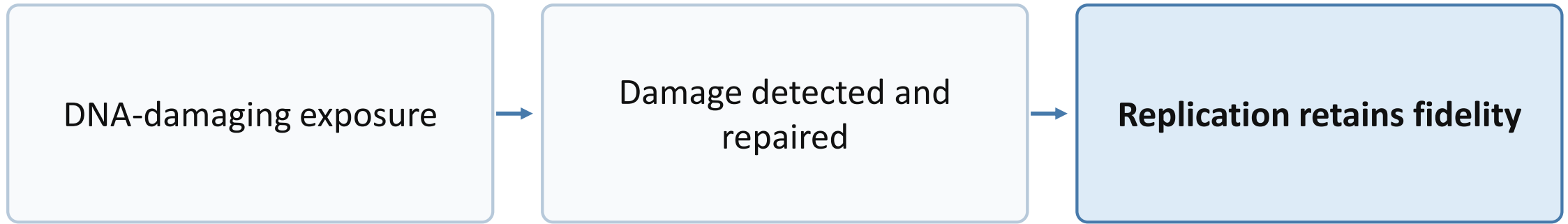


Schematic

Mutation rates matter as well as mutation identity

- Cancer requires genetic alterations that confer a selective growth or survival advantage.
- Genome-protective machinery normally restrains the rate at which new variants appear.
- When repair fails, additional potential driver events can accumulate more rapidly.
- This accelerated state as a “mutator” phenotype.

DNA injury does not necessarily become a fixed mutation



Schematic

The carcinogenic risk increases when damaging lesions persist or are repaired inaccurately.

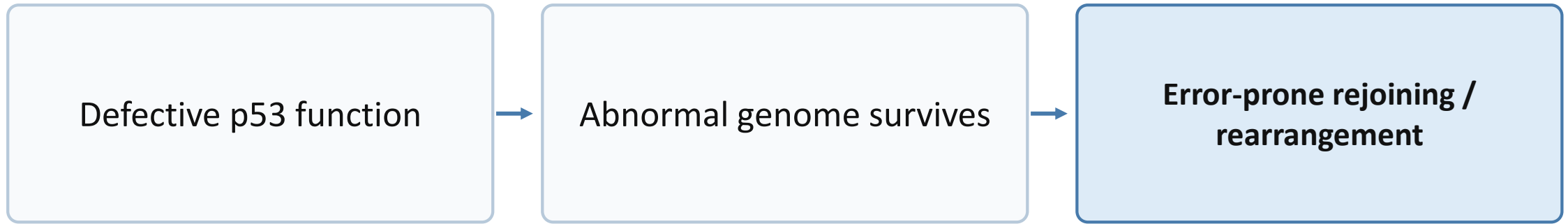
P53 links DNA damage to cell fate



Schematic

If the genome is irreparably damaged, p53 can instead initiate apoptosis.

Loss of p53 permits damaged cells to persist



Schematic

P53 loss with aneuploidy and complex chromosomal alterations.

Different DNA lesions recruit different safeguards

Predominant problem	Protective process
UV-induced pyrimidine dimers	Nucleotide excision repair
Incorrect base pairing during replication	Mismatch repair
Double-strand breaks and covalent cross-links	Homologous recombination pathways
DNA polymerase copying errors	Polymerase proofreading

Why UV injury is the central NER example

- Ultraviolet radiation can generate covalent links between adjacent pyrimidines.
- The resulting abnormal DNA structure interferes with faithful replication.
- The nucleotide excision repair pathway normally corrects this class of injury.
- Failure is illustrated clinically by xeroderma pigmentosum.

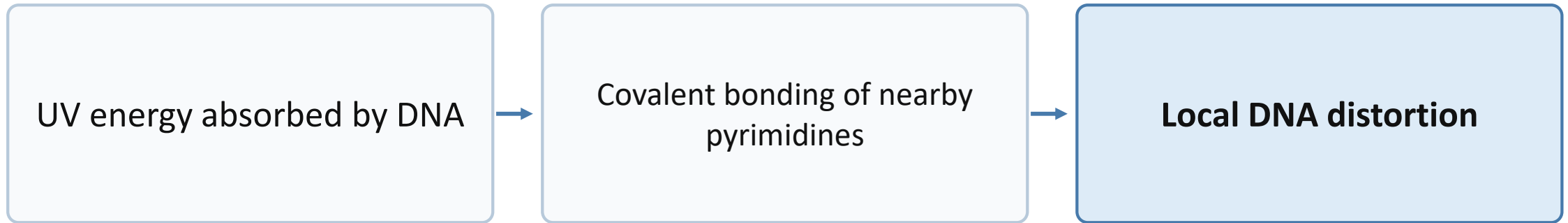
Ultraviolet wavelengths have different biological reach

Band	Wavelength	Relevance in Robbins
UVA	320–400 nm	Part of sunlight reaching the skin
UVB	280–320 nm	Major direct pyrimidine-dimer carcinogen in skin
UVC	200–280 nm	Mutagenic, but normally filtered by ozone

UV-associated skin cancer risk is contextual

- Intensity and pattern of UV exposure affect carcinogenic opportunity.
- Pigmentation modifies risk: Melanin absorbs UV photons.
- Fair skin that burns readily is less protected against sunlight.
- UV exposure contributes to squamous cell carcinoma, basal cell carcinoma and melanoma.

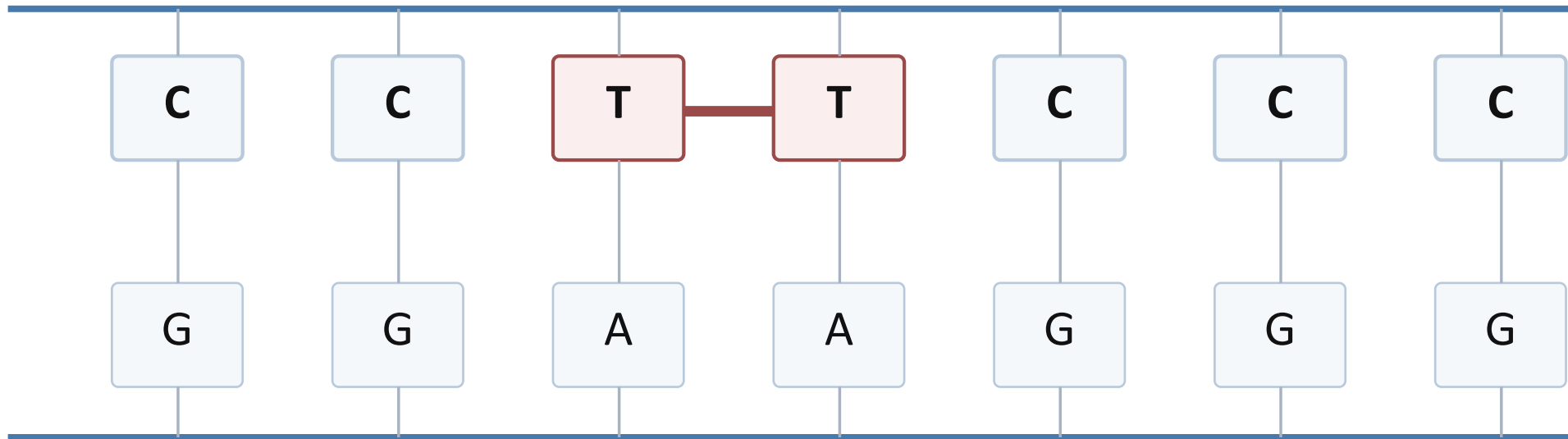
From a UV photon to a DNA lesion



Schematic

A pyrimidine dimer links adjacent bases on one strand

Covalent linkage of adjacent thymines



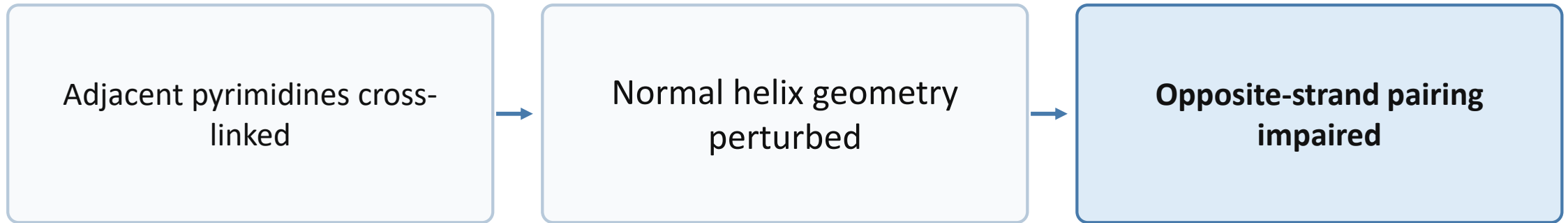
Damage lies within a strand, not between opposite strands

Schematic

The location of the dimer is mechanistically important

- Covalent linking of pyrimidines on the same DNA strand.
- Adjacent thymidine residues are a particularly important target.
- This is not a normal Watson–Crick base pair between opposite strands.
- The covalent dimer is a lesion within a strand, disrupting normal duplex geometry.

A pyrimidine dimer distorts the DNA helix

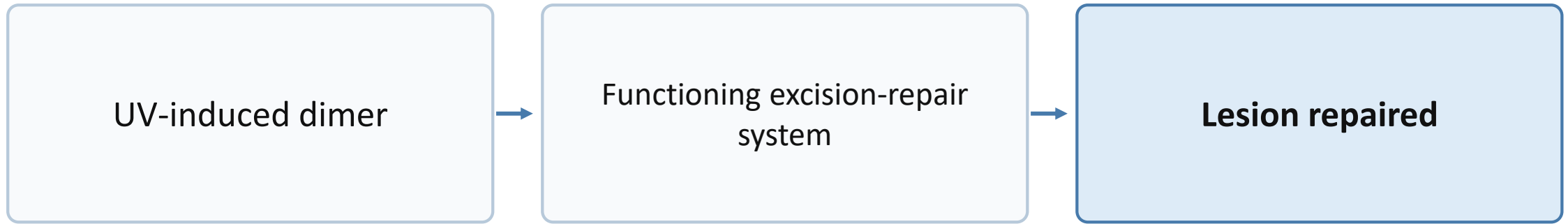


Schematic

Why base-pair distortion threatens replication

- DNA replication uses the existing strands as templates.
- Pyrimidine dimers impede correct pairing opposite the damaged segment.
- The structural defect can prevent normal DNA synthesis.
- Repair before successful copying helps avoid mutation fixation.

DNA repair can break the mutation pathway



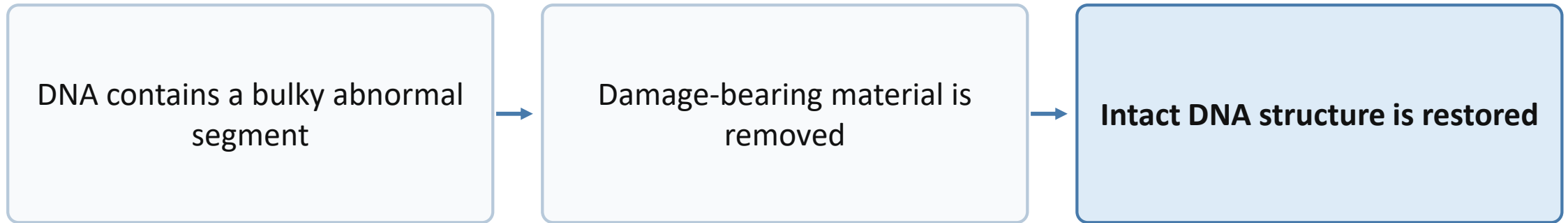
Schematic

Schematic abstraction; Robbins does not enumerate the individual enzymatic steps in this excerpt.

The nucleotide excision repair system is multicomponent

- More than 30 proteins participating in nucleotide excision repair.
- Several distinct genes encode factors required for normal pathway operation.
- This molecular complexity explains why inherited dysfunction is genetically heterogeneous.
- The provided NER passage does not specify the full protein-by-protein reaction sequence.

“Excision” captures the essential repair principle



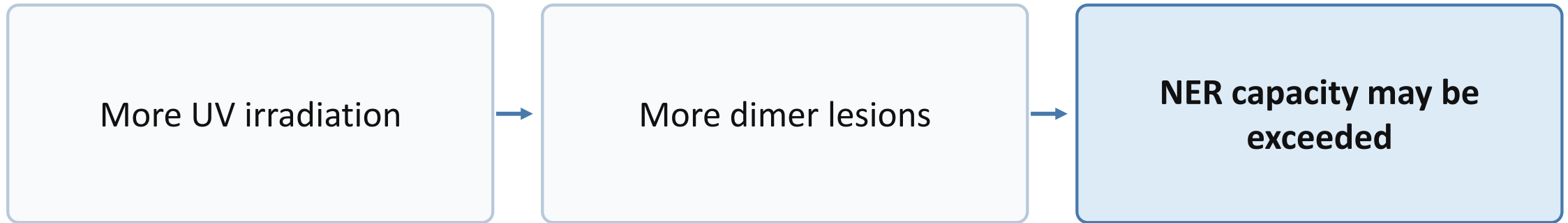
Schematic

Conceptual mechanism, not a depiction of specific NER protein order.

Repair failure differs from replication proofreading

Question	Nucleotide excision repair	Polymerase proofreading
What is corrected?	UV-induced helix-distorting damage	Misincorporated bases during copying
When is it useful?	After lesion formation	During DNA replication
Cancer example	Xeroderma pigmentosum	Polymerase-mutated colon/endometrial cancers

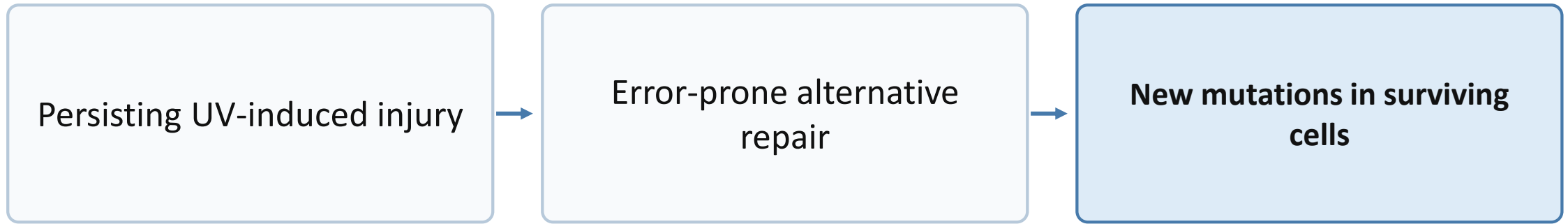
Excessive UV exposure challenges repair capacity



Schematic

Pathway saturation during excessive exposure as a proposed mechanism.

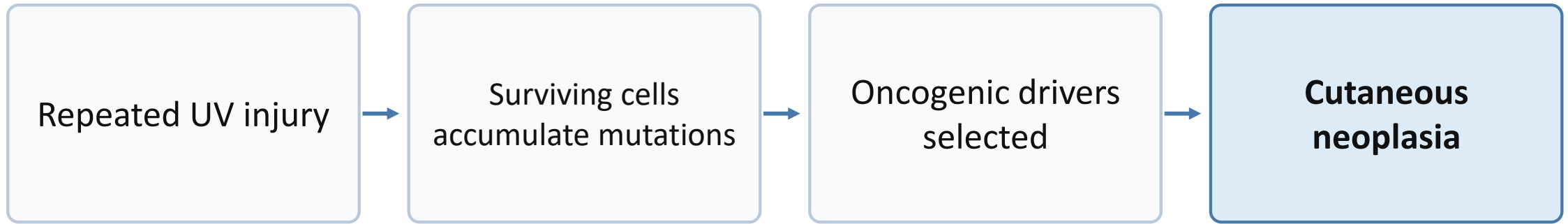
Inaccurate repair may preserve viability yet create risk



Schematic

This mechanism as postulated, not as a quantified certainty.

UV carcinogenesis requires lesion persistence and selection



Schematic

A UV mutational signature provides causal evidence

- Sequencing of sun-exposed melanomas reveals very large numbers of mutations.
- The mutation patterns are characteristic of pyrimidine-dimer damage and error-prone repair.
- This links UV exposure to molecular alterations observed in the tumor genome.
- The evidence supports an etiologic role of sunlight in melanoma.

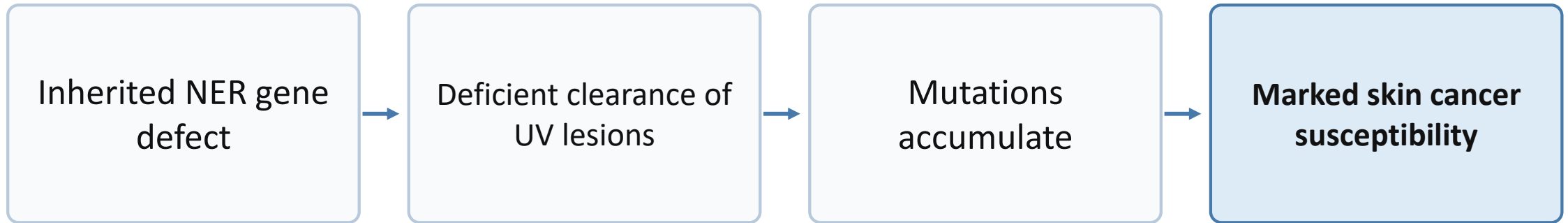
Skin cancers associated with sunlight

Tumor	Robbins association with UV / NER
Cutaneous squamous cell carcinoma	UV-induced DNA injury; increased risk with NER dysfunction
Basal cell carcinoma	Frequent on sun-exposed skin; increased with NER dysfunction
Melanoma	UV-associated mutational patterns, especially sun-exposed lesions

Xeroderma pigmentosum is a repair-deficiency syndrome

- Inherited loss-of-function variants affecting nucleotide excision repair cause the syndrome.
- The pathway fails to remove UV-induced pyrimidine dimers effectively.
- Patients therefore develop an extraordinarily high risk of cutaneous malignancy.
- It provides a human illustration of genome maintenance as a tumor-suppressive function.

The genotype–phenotype chain in xeroderma pigmentosum



Schematic

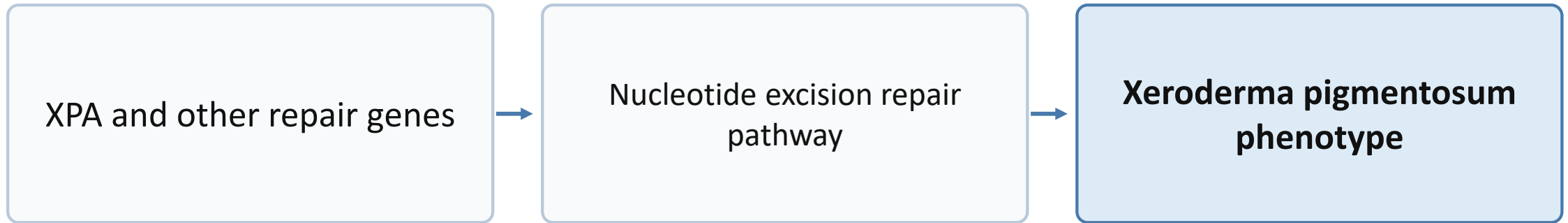
Xeroderma pigmentosum is genetically heterogeneous

- Robbins explicitly refers to several nucleotide excision repair genes.
- Different loss-of-function gene defects can produce the same syndrome.
- The shared phenotype is explained by failure of a common repair process.
- The topic excerpt does not provide a complete list of the implicated loci.

Xeroderma pigmentosum: Inheritance matters

- Robbins' hereditary skin cancer table identifies autosomal recessive inheritance.
- Inheritance of defective repair capacity creates constitutional susceptibility.
- UV exposure supplies a repeated tissue-specific mutagenic challenge.
- The interaction helps explain predominance of tumors in sun-exposed skin.

XPA is one documented genetic example



Schematic

XPA among associated genes; This is not an exhaustive molecular classification.

The cancer predisposition is particularly cutaneous

- Cancers arising in UV-light–exposed skin.
- Squamous cell carcinoma and basal cell carcinoma are specifically highlighted.
- The inherited pathway defect does not itself select a particular driver mutation.
- Chronic UV mutagenesis creates repeated opportunities for oncogenic change.

Squamous versus basal cell carcinoma in this setting

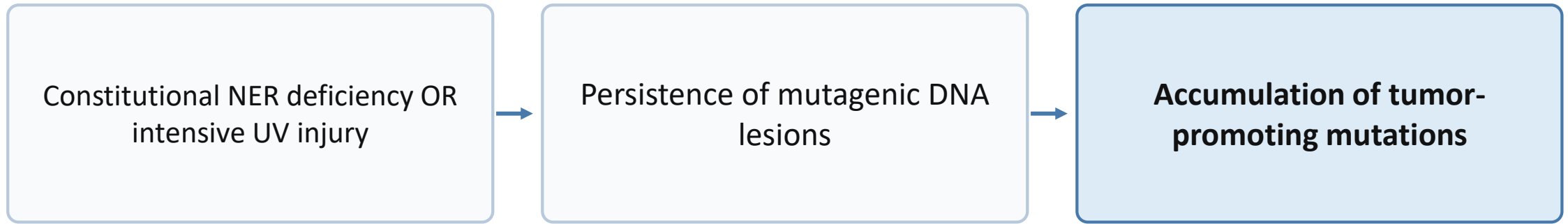
Squamous cell carcinoma

- High risk in xeroderma pigmentosum
- Can develop through UV-damaged keratinocyte precursors
- TP53 defects occur early in many UV-related precursors

Basal cell carcinoma

- High risk in xeroderma pigmentosum
- Typically affects sun-exposed skin
- A distinct molecular driver pathway often involves Hedgehog activation

Inherited repair failure and sporadic UV cancer converge



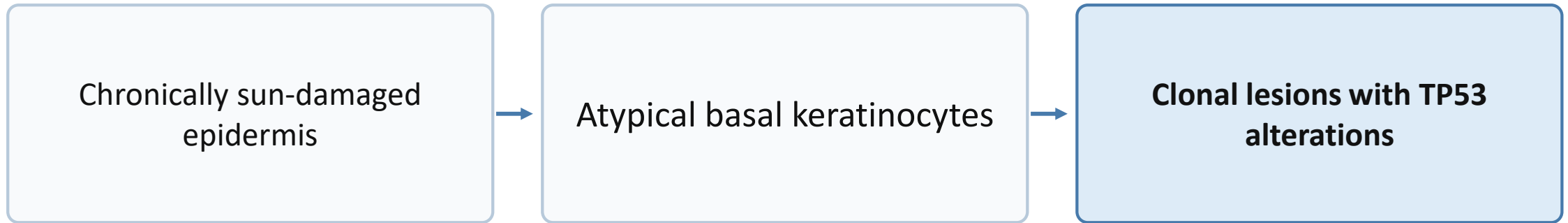
Schematic

Different initiating circumstances can converge on UV-driven genomic damage.

TP53 changes link UV injury to squamous precursors

- Actinic keratoses are precursor lesions in sun-damaged skin.
- Mutations of TP53 occur frequently in actinic keratoses of lightly pigmented individuals.
- Many TP53 alterations occur at pyrimidine-dimer sites.
- This provides a mechanistic link between UV injury and loss of p53 protection.

Actinic keratosis: An early example of UV-driven change



Schematic

Microscopic actinic keratosis reflects dysregulated maturation

- Basal-cell atypia (dysplasia) occurs within UV-damaged epidermis.
- Hyperkeratosis and parakeratosis can be prominent.
- Solar elastosis may occur in the superficial dermis.
- These changes are not, by themselves, proof of invasive carcinoma.

Actinic keratosis versus squamous carcinoma in situ

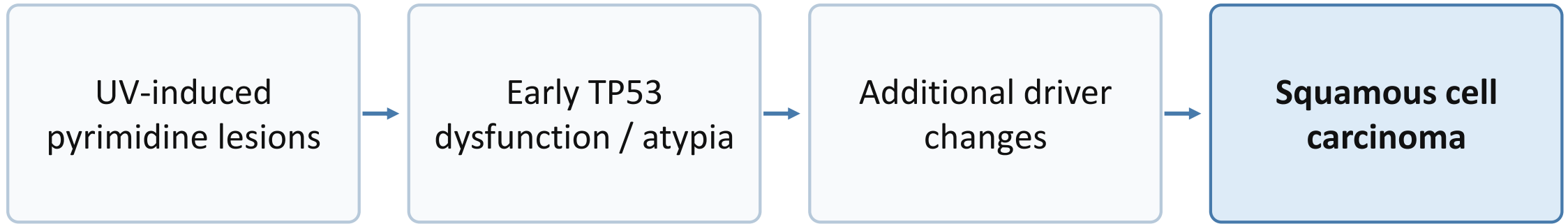
Actinic keratosis

- Basal-layer dysplasia predominates
- Hyperkeratosis and parakeratosis may accompany
- Superficial epidermal maturation can persist

Squamous carcinoma in situ

- Full-thickness nuclear atypia
- Atypia spans the epidermal thickness
- Invasion is not implied by an in-situ diagnosis

A skin-cancer progression model



Schematic

Conceptual sequence; Not every actinic keratosis progresses to carcinoma.

Squamous carcinogenesis usually requires multiple hits

- Cutaneous squamous cell carcinoma involves more than a single mutation.
- Additional increases in RAS signaling and decreases in NOTCH signaling.
- Loss of p53 protection and accumulating mutations can cooperate.
- No single molecular change explains every sporadic or inherited case.

Basal cell carcinoma illustrates pathway diversity

- Basal cell carcinoma is associated with activating changes in Hedgehog signaling.
- It commonly arises on sun-exposed skin in lightly pigmented adults.
- The risk is elevated in DNA-repair disorders including xeroderma pigmentosum.
- UV injury and specific oncogenic pathway selection are related but distinct concepts.

Genetic susceptibility is not the same as an acquired driver

Feature	Constitutional NER defect	Tumor-associated driver
Where present?	Inherited predisposition in the individual	Acquired in the evolving tumor clone
Main effect	High background vulnerability to DNA injury	Confers a growth/survival advantage
Representative example	Xeroderma pigmentosum repair defect	TP53 defect or Hedgehog pathway activation

Clinical application: Multiple UV-site skin tumors

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A patient develops numerous cutaneous squamous and basal cell carcinomas at UV-exposed sites. Family history suggests a hereditary disorder.

Question

Which genome-maintenance pathway should be considered?

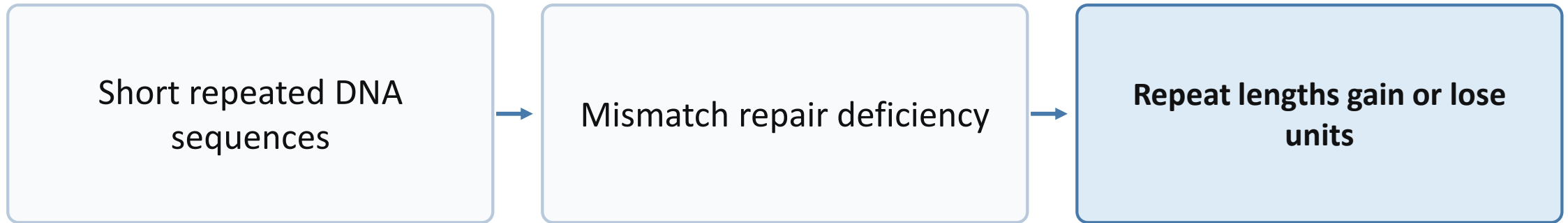
Clinical interpretation: Why this history is informative

- The combination of sunlight-exposed tumors and inherited susceptibility points to failure of UV-lesion removal.
- An NER defect is a mechanism-based explanation, not a histologic diagnosis from one tumor alone.
- Squamous and basal cell carcinoma remain distinct tumor types.
- Identification of a hereditary syndrome and characterization of a lesion are separate tasks.

Mismatch repair guards against copying errors

- Mismatch repair removes incorrectly paired bases during replication.
- A G–T mismatch instead of an A–T pair.
- Failure allows errors to accumulate across the genome.
- It protects a different class of DNA defect from nucleotide excision repair.

Microsatellite instability reveals mismatch repair failure

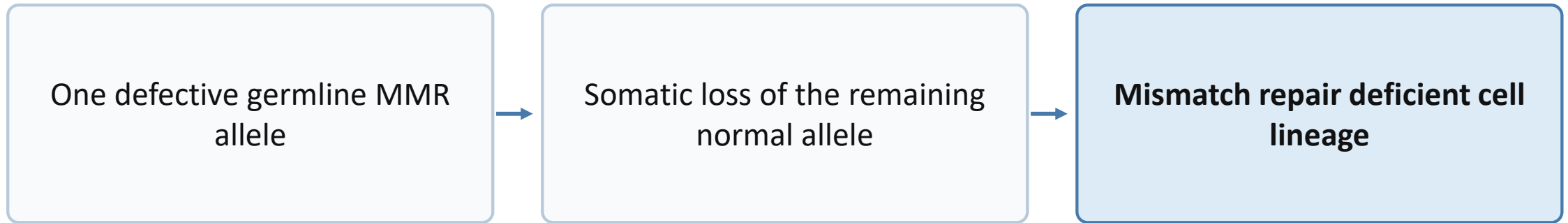


Schematic

Lynch syndrome illustrates inherited mismatch repair failure

- Robbins also uses the name hereditary nonpolyposis colorectal cancer (HNPCC).
- The syndrome is autosomal dominant at the family level.
- MSH2 and MLH1 are commonly affected mismatch repair genes.
- Tumors often occur in the proximal colon.

A two-hit sequence explains inherited Lynch susceptibility



Schematic

Sporadic microsatellite instability has a different route

- Microsatellite instability is not restricted to inherited Lynch syndrome.
- Sporadic colorectal carcinomas with mismatch repair deficiency.
- Epigenetic silencing of MLH1 is a typical mechanism in sporadic tumors.
- Identical instability phenotypes can arise from distinct inherited/acquired mechanisms.

NER and mismatch repair should not be conflated

Characteristic	NER deficiency	MMR deficiency
Predominant damaged substrate	UV-related pyrimidine dimers	Replication base mismatches / repeat errors
Recognized inherited setting	Xeroderma pigmentosum	Lynch syndrome
Cancer emphasis	Cutaneous SCC/BCC	Colorectal and other Lynch-associated cancers
Molecular readout in Robbins	Failure to repair UV dimers	Microsatellite instability

Homologous recombination responds to severe DNA injury

- Double-stranded breaks and covalent cross-links in this repair context.
- Defects in homologous recombination factors predispose to malignancy.
- These damage classes differ from the UV-associated pyrimidine dimers central to NER.
- Pathway comparisons should be based on substrate rather than the presence of cancer alone.

Homologous recombination–associated syndromes

Condition	Affected safeguard	Salient consequences
Bloom syndrome	Helicase involved in homologous recombination	Developmental anomalies; broad cancer susceptibility
Ataxia-telangiectasia	ATM damage-response kinase	Ataxia, immune deficiency, radiation sensitivity, cancers
Fanconi anemia	DNA cross-link response pathway	Developmental anomalies, marrow failure, leukemia
Inherited BRCA1/2 defects	Homologous recombination repair	Hereditary breast/ovarian and other cancers

ATM loss explains a different sensitivity pattern

- ATM acts in signaling responses to double-strand DNA damage.
- Ataxia-telangiectasia includes cerebellar neurodegeneration and immunodeficiency.
- Patients are highly sensitive to ionizing radiation.
- Leukemia and lymphoma are important cancer associations.

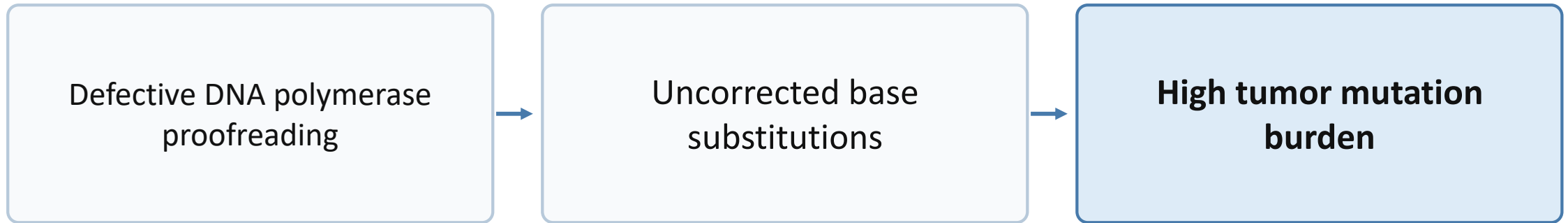
Fanconi anemia connects cross-link repair and marrow failure

- Multiple Fanconi-associated proteins function in repair of DNA cross-links.
- Developmental abnormalities and hypersensitivity to cross-linking agents occur.
- Bone marrow failure and leukemic transformation are major consequences.
- This syndrome should not be equated with UV-specific NER deficiency.

BRCA proteins help maintain chromosome integrity

- BRCA1 and BRCA2 participate in homologous recombination DNA repair.
- Inherited variants are associated with familial breast and other cancer risks.
- Failure shifts the repair balance toward more error-prone pathways.
- Chromosomal rearrangements and aneuploidy can follow.

Proofreading errors are another source of the mutator phenotype

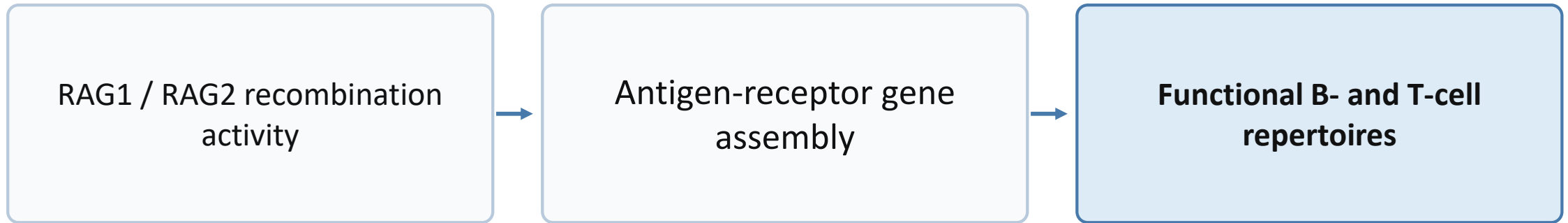


Schematic

Polymerase proofreading defects have tumor-level effects

- These variants in subsets of endometrial and colorectal carcinoma.
- A loss of proofreading function increases point substitutions.
- Extremely high mutation burdens can generate many neoantigens.
- The text links such tumors to generally strong checkpoint inhibitor responses.

Lymphocytes deliberately rearrange DNA



Schematic

AID introduces additional purposeful B-cell genome changes

- Activation-induced cytosine deaminase (AID) is expressed in activated mature B cells.
- It is required for class-switch recombination and somatic hypermutation.
- These physiological processes are intrinsically error-prone.
- Errors can produce chromosomal changes associated with lymphoid neoplasms.

Choose the relevant instability mechanism

Finding	Most directly implicated pathway
Sunlight / pyrimidine-dimer damage	Nucleotide excision repair
Unstable length of short DNA repeats	Mismatch repair
Sensitivity to double-strand break injury	Homologous recombination / damage response
Excess point mutations from replicative copying	DNA polymerase proofreading
Antigen-receptor translocations in lymphoid tumors	Programmed recombination / mutagenesis

Mechanism-based question: DNA lesion classification

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Two neoplasms show genomic instability. One follows intense UV exposure; The other has altered lengths of short nucleotide repeats.

Question

Which pathway is most relevant in each?

Mechanism-based question: Interpreting a skin precursor

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An actinic keratosis contains atypical basal keratinocytes, and sequencing identifies TP53 alteration at a UV-dimer-associated site.

Question

What does the molecular result suggest?

Integrated conclusions

- UVB-induced pyrimidine dimers distort DNA and threaten faithful replication.
- Nucleotide excision repair is a multigene barrier against these lesions.
- Xeroderma pigmentosum demonstrates the cancer risk of inherited NER failure.
- Mutational damage, cell-cycle protection and repair fidelity jointly shape tumor evolution.
- Other repair defects produce distinctive lesion types and cancer syndromes.

References and scope

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 7: Neoplasia — Genomic Instability (pp. 280–282) and Ultraviolet Rays (p. 289).

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 25: The Skin — Actinic Keratosis, Squamous Cell Carcinoma and Basal Cell Carcinoma (pp. 1040–1041).

Chapter 7 also discusses DNA mismatch repair, homologous recombination, polymerase proofreading and regulated genomic instability in lymphoid cells.