

Acute Lymphoblastic Leukemia / Lymphoma

Precursor B- and T-lineage lymphoid neoplasms

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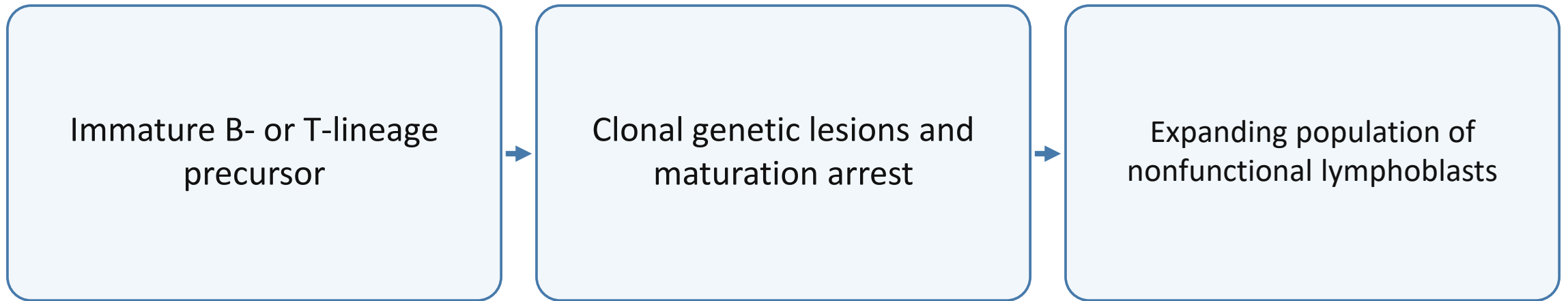
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Learning outcomes

- Explain how arrested lymphoid maturation produces B-ALL and T-ALL.
- Recognize marrow and blood morphology and lineage-defining immunophenotypes.
- Connect infiltration sites to clinical manifestations and complications.
- Interpret genetic, age-related and post-treatment prognostic findings.

ALL is a malignancy of lymphoblasts



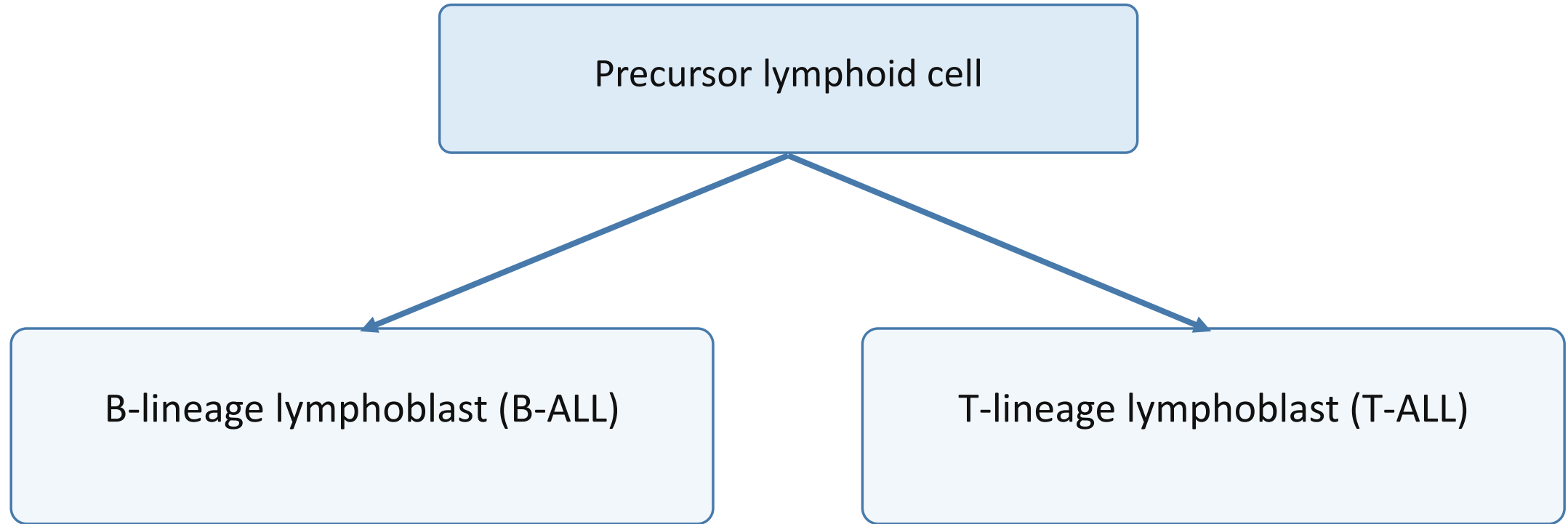
The defining cell is an immature lymphoid precursor—not a mature lymphocyte.

Leukemia and lymphoma describe a disease spectrum

Predominant form	Leukemic disease	Lymphomatous disease
Principal burden	Marrow and often peripheral blood	Discrete tissue mass
Shared biology	Immature lymphoid blasts	Immature lymphoid blasts
Possible evolution	Extramedullary lesions may occur	Marrow/blood dissemination may occur

Lineage and blast biology—not the initial site—establish the entity.

Two major precursor lineages



Similar blast morphology can conceal profoundly different lineage-specific genetics.

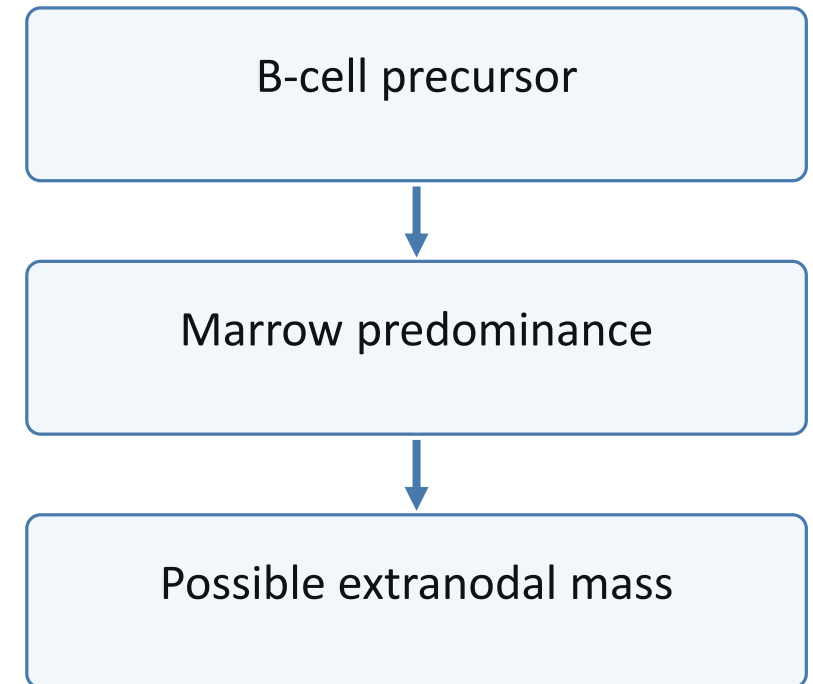
ALL predominates in childhood

- ALL is as the most common cancer of childhood.
- Most cases occur before age 15; Both B- and T-lineage disease can also affect adults.
- Incidence varies with age and shows a modest male predominance.

Age at onset helps frame probability but cannot assign lineage.

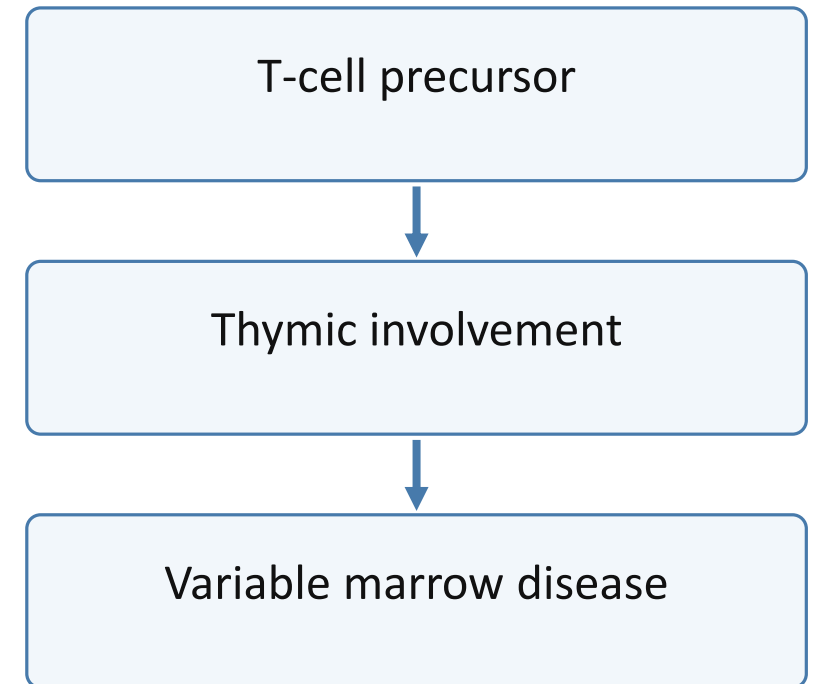
B-ALL usually presents as childhood leukemia

- Precursor B-cell neoplasms constitute the majority of ALL.
- Marrow-based disease is the usual presentation in children.
- Less commonly, B-ALL produces a localized skin or bone mass.



T-ALL frequently presents as a thymic mass

- T-ALL is less common than B-ALL.
- Adolescent males often present with a mediastinal/thymic mass.
- A leukemic phase can be present initially or develop later.



Typical presentations differ without being exclusive

Feature	B-ALL	T-ALL
Peak pattern	Early childhood	Adolescence
Common initial form	Acute leukemia	Thymic or mediastinal tumor
Site overlap	Occasional soft-tissue masses	Frequent marrow/blood involvement
Microscopic appearance	Lymphoblasts	Lymphoblasts

Clinical pattern suggests lineage; Immunophenotyping establishes it.

B-ALL peaks early in childhood

- The incidence peak at approximately age 3 years.
- The peak may reflect abundant normal pre-B precursors in early life.
- The putative link between precursor abundance and incidence is an explanatory hypothesis—not a deterministic rule.

T-ALL tracks thymic precursor biology

Thymus expands through
childhood



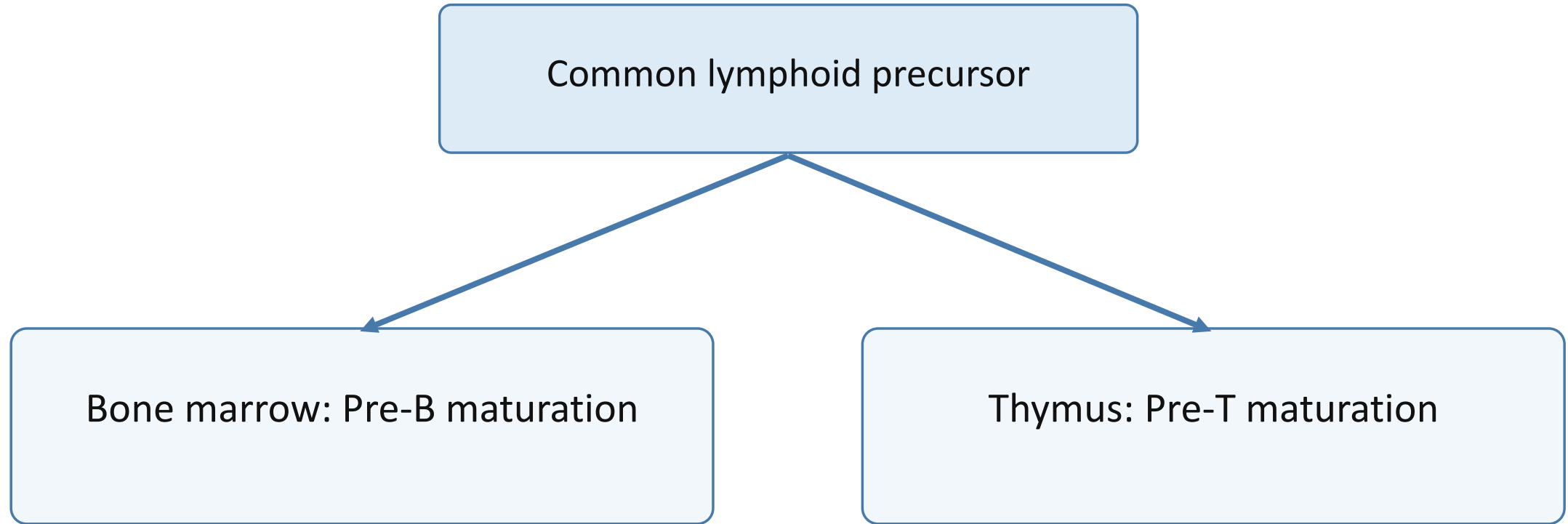
Pre-T-cell populations are
abundant in adolescence



T-ALL incidence peaks during
adolescence

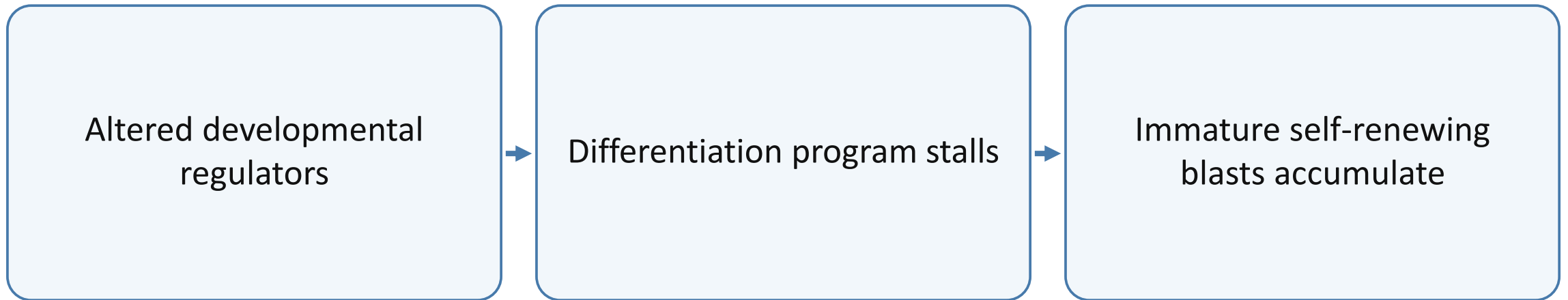
This age distribution is consistent with an origin in thymic precursors.

Normal differentiation supplies the cellular context



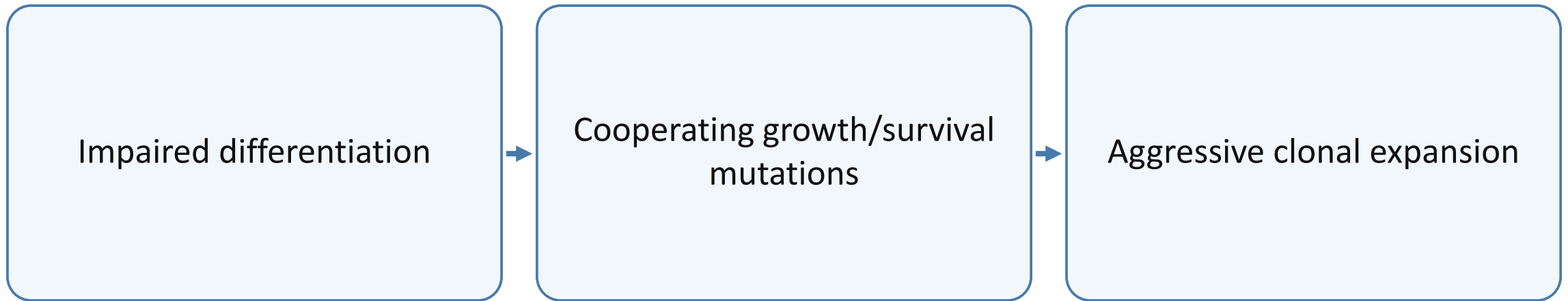
ALL arises at an immature stage along either of these lineages.

Maturation arrest is the central pathogenic lesion



Tumor cells retain a stem-cell-like phenotype instead of becoming functional lymphocytes.

A second class of alterations favors proliferation



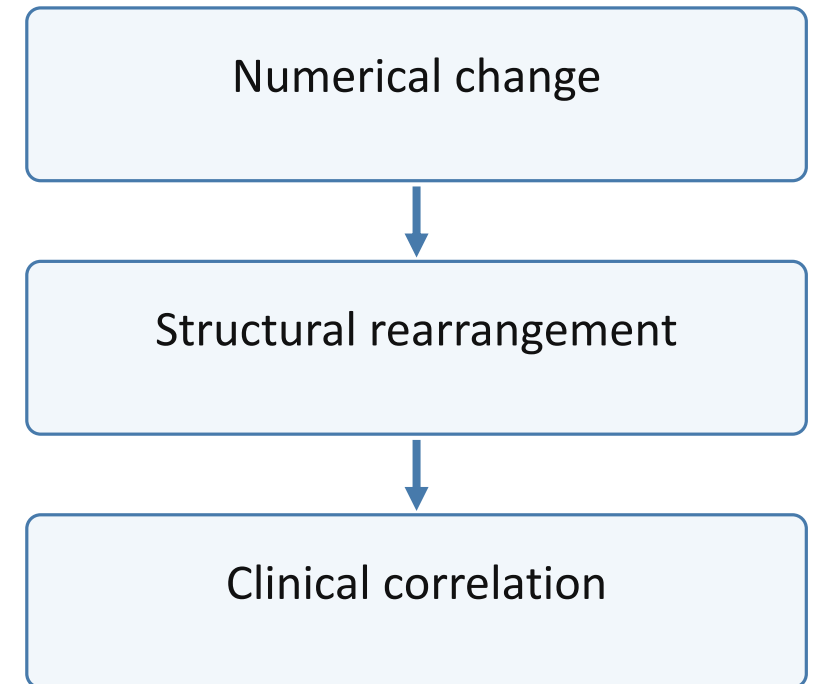
A developmental block alone is generally insufficient for overt ALL.

ALL follows a multistep oncogenic model

- One lesion perturbs differentiation or precursor-cell identity.
- Additional driver alterations promote proliferation, survival, or altered signaling.
- Sequencing evidence that relatively few driver mutations may suffice for overt ALL.

Chromosomal abnormalities are very common

- Approximately 90% of cases show numerical or structural changes.
- Aneuploidy and balanced translocations are recognized patterns.
- Their causal importance varies; Many also stratify immunophenotype or prognosis.

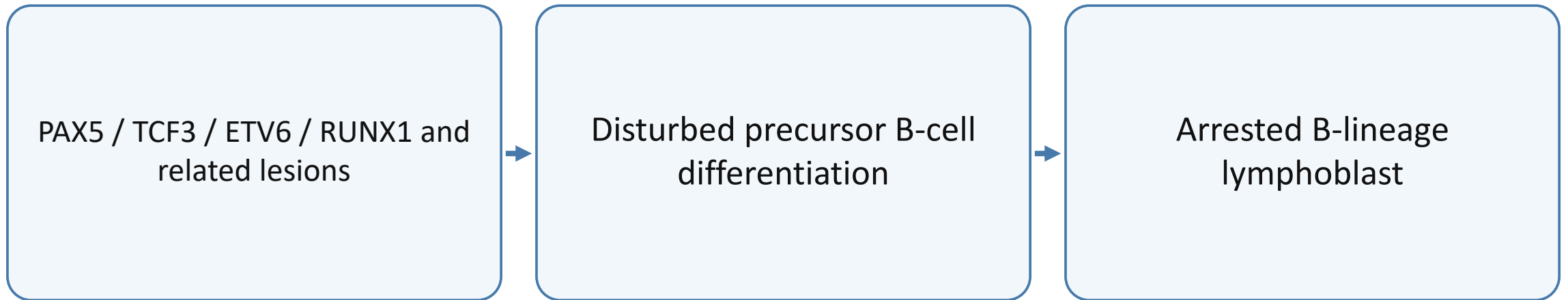


Hyperdiploidy and hypodiploidy are not equivalent

Feature	Hyperdiploidy	Hypodiploidy
Chromosome content	Increased number	Reduced number
Lineage	B-ALL	B-ALL
Prognostic direction	Generally favorable	Generally adverse
Interpretation	Correlate with context	Correlate with context

Aneuploid categories are prognostic descriptors, not morphologic diagnoses.

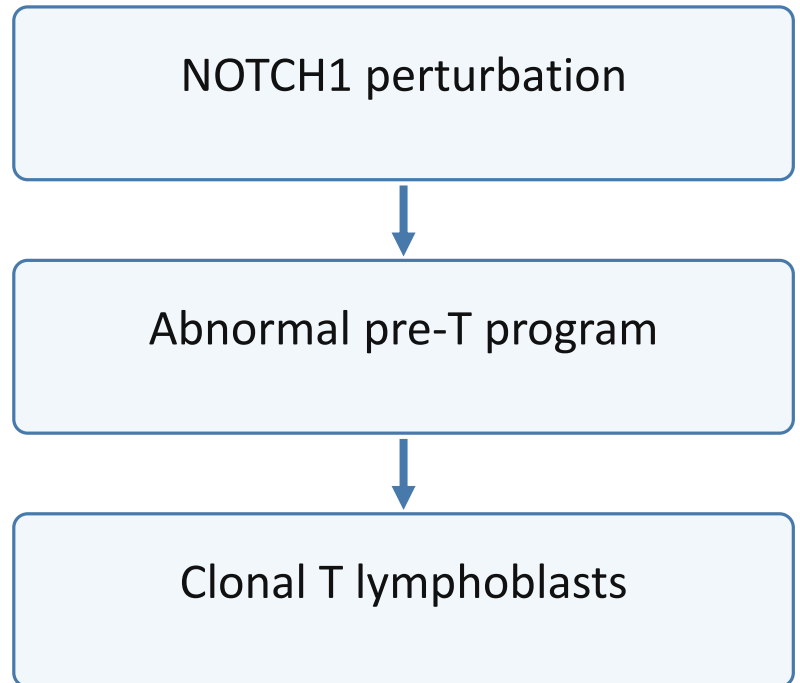
B-ALL disrupts early B-lineage regulation



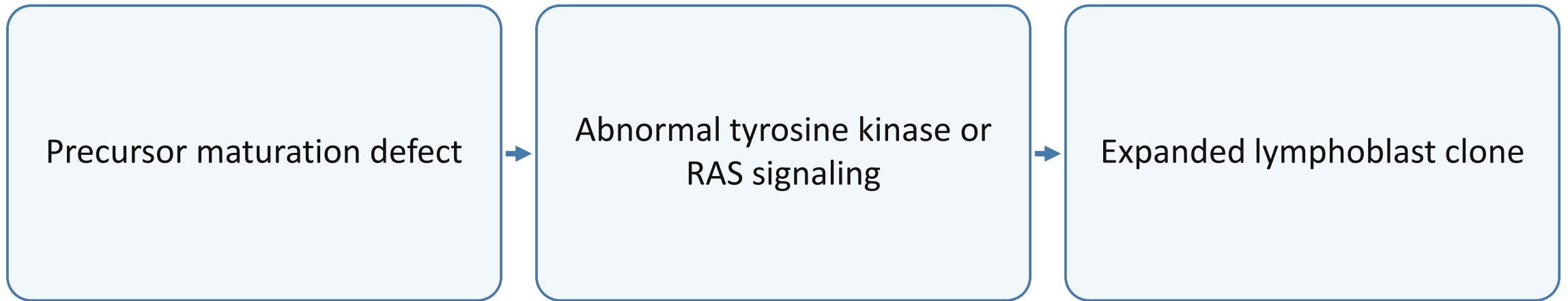
The source groups many B-ALL lesions around altered hematopoietic regulation.

T-ALL frequently involves NOTCH1

- NOTCH1 is crucial to normal T-cell development.
- Mutations in NOTCH1 are common in T-ALL.
- The molecular profile is distinct from the typical genetic lesions of B-ALL.



Growth pathways cooperate with lineage defects



The same clone can combine arrested differentiation with enhanced growth.

BCR::ABL1 creates a constitutively active kinase

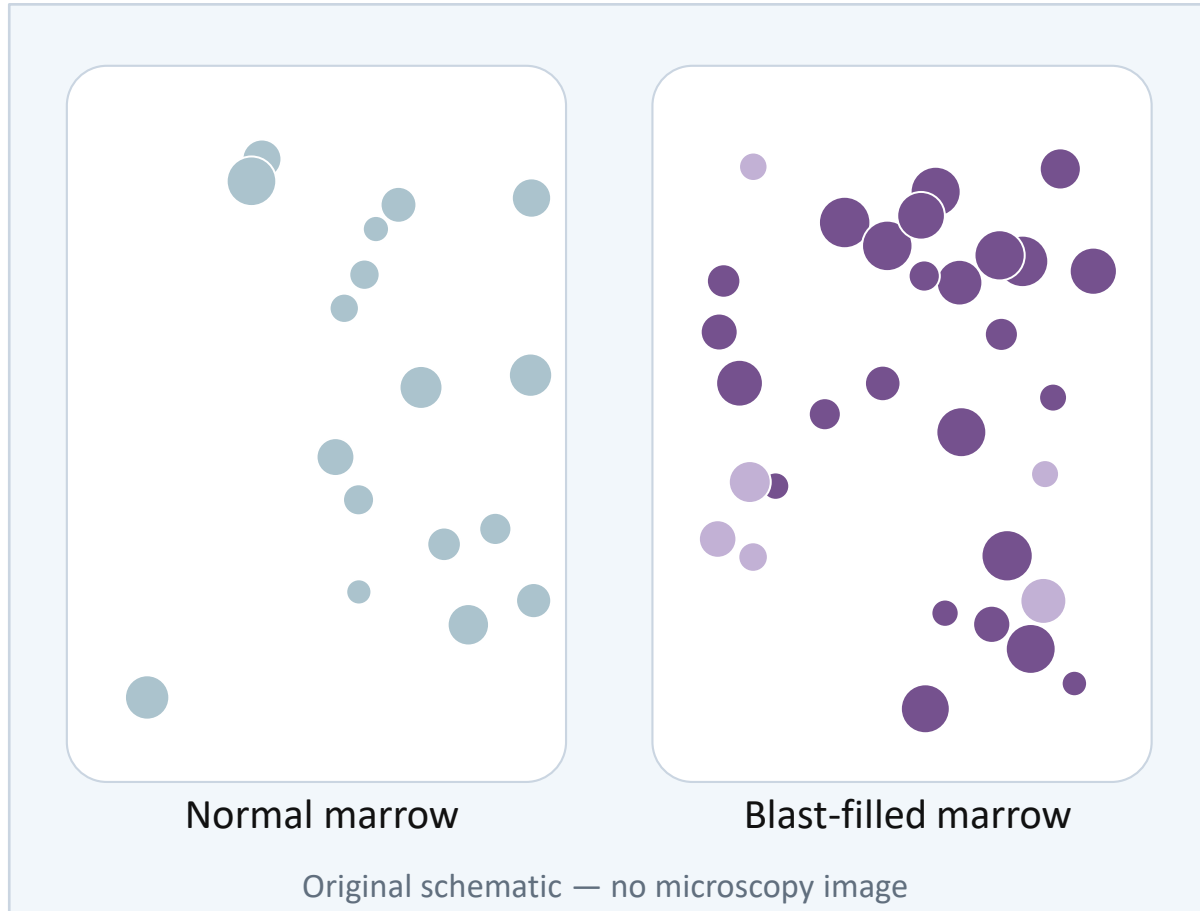


This alteration has direct therapeutic relevance in a subset of B-ALL.

Genetic identity separates morphologic look-alikes

Level	B-ALL	T-ALL
Precursor	Bone marrow pre-B cell	Often thymic pre-T cell
Frequent genetic theme	B-lineage developmental regulators	NOTCH1 and T-lineage lesions
Morphology	Immature lymphoblast	Immature lymphoblast
Required resolution	Lineage markers $\pm$ genetics	Lineage markers $\pm$ genetics

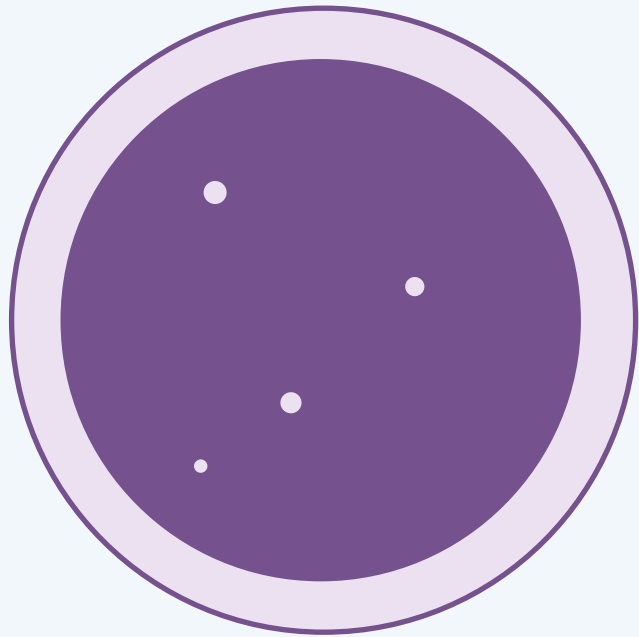
Marrow replacement explains the leukemic picture



- Leukemic marrow becomes hypercellular and densely infiltrated by lymphoblasts.
- Normal erythroid, myeloid and megakaryocytic production is suppressed.

Morphologic burden and hematopoietic failure are causally linked.

Lymphoblast cytology: Small cytoplasm, large nucleus



Schematic lymphoblast (not a specimen)

- Scant, usually basophilic cytoplasm with absent conspicuous granules.
- Finely stippled chromatin with small, sharply outlined nucleoli.
- Nuclear contour may be deeply indented or convoluted.

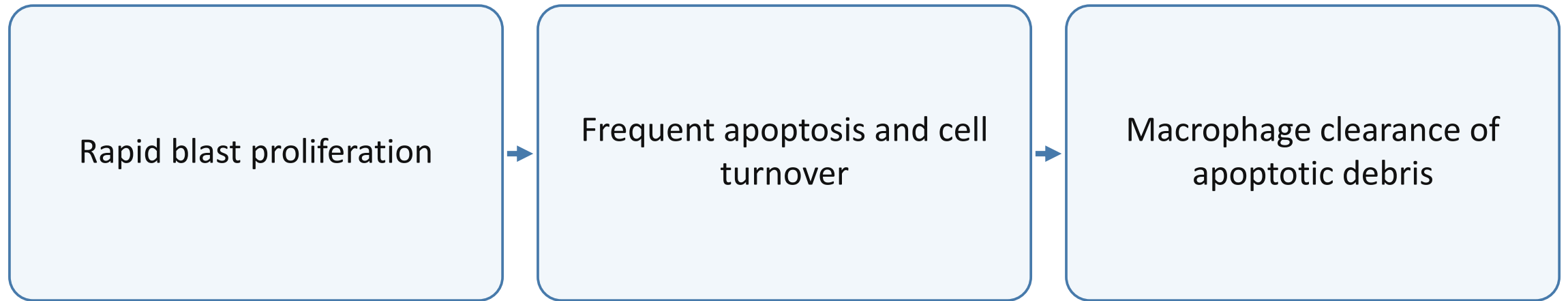
The schematic emphasizes classic features; Actual smears show a range of appearances.

Nuclear chromatin helps—but does not decide

- Lymphoblast nuclei commonly show more condensed chromatin than myeloblasts.
- Nucleoli tend to be less conspicuous and cytoplasm less abundant.
- There is important morphologic overlap between ALL and AML.

Do not make a definitive lineage call from H&E or cytology alone.

High mitotic activity reflects aggressive growth



Macrophage–blast admixture can create a “starry-sky” appearance.

A “starry sky” pattern is not lineage specific

- Pale macrophages contain ingested apoptotic tumor-cell debris.
- The surrounding field consists of numerous proliferating tumor cells.
- The pattern can occur in other high-turnover lymphoid tumors.

Dark blast-rich background



Pale scavenger macrophages



High cell turnover

This is a growth pattern, not an ALL-specific diagnostic criterion.

AML and ALL can be clinically indistinguishable

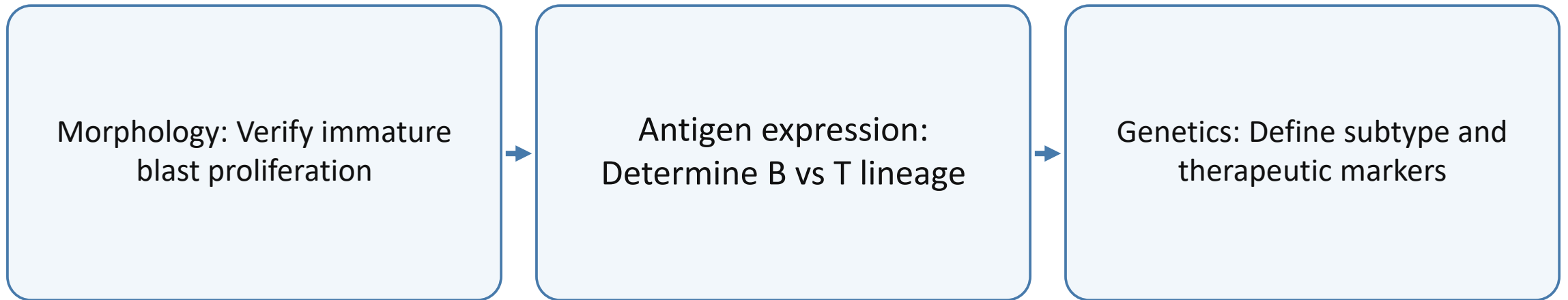
Feature	ALL	AML
Neoplastic cell	Lymphoblast	Myeloblast
Symptoms	Marrow failure $\pm$ infiltration	Marrow failure $\pm$ infiltration
Typical cytoplasm	Scant; Usually agranular	Often more abundant; Sometimes granular
Myeloperoxidase	Usually negative	Commonly positive in myeloid blasts
Final decision	Lineage immunophenotype	Lineage immunophenotype

Cytochemical clues complement antibody studies

Stain	Lymphoblasts	Myeloblasts
Myeloperoxidase	Negative	Often positive
Periodic acid–Schiff	May show positive cytoplasmic material	Not the defining lineage test
Interpretation	Supportive only	Supportive only

Cytochemistry cannot replace a coherent antigen-based diagnosis.

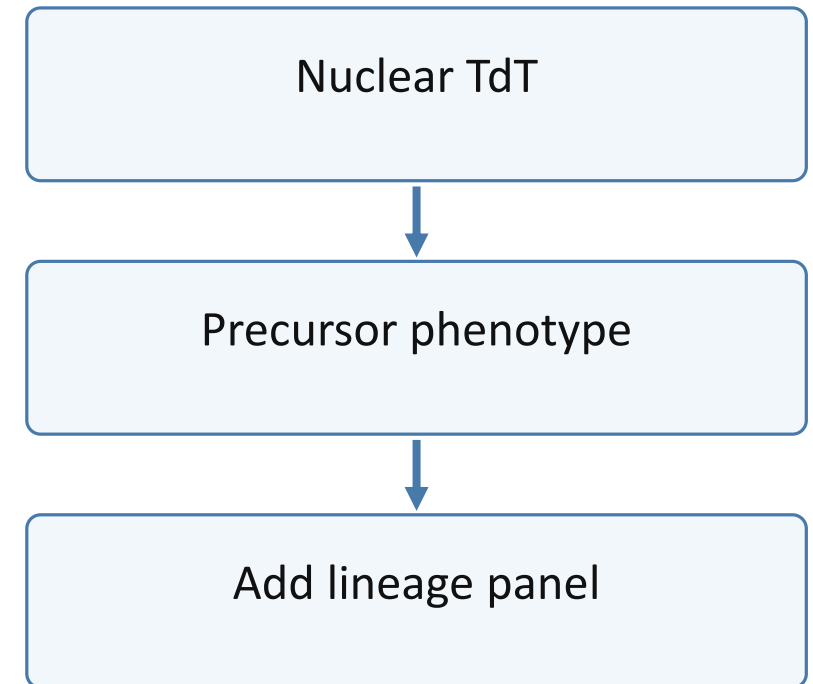
The diagnostic strategy integrates three data types



Every domain answers a different diagnostic question.

TdT is a major immaturity marker

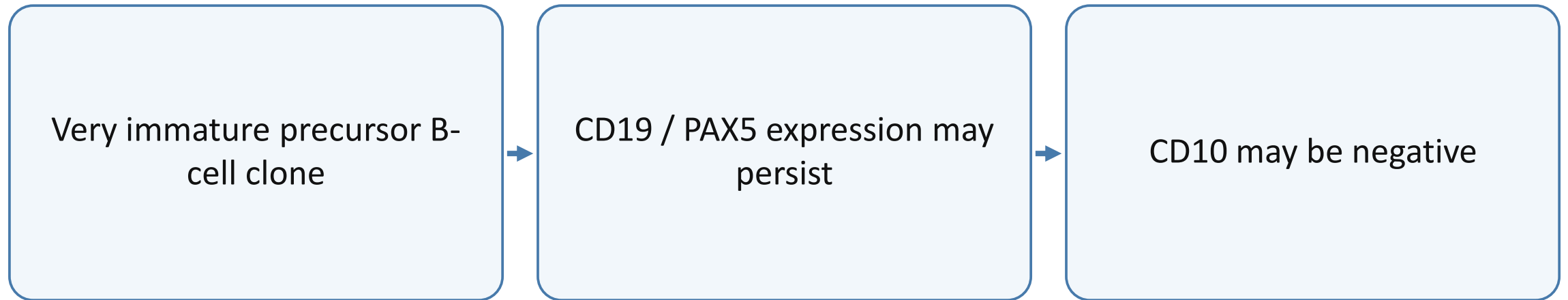
- Terminal deoxynucleotidyl transferase is a DNA polymerase characteristic of precursor lymphoblasts.
- TdT staining in more than 95% of ALL cases.
- TdT positivity supports immaturity but does not alone establish B or T lineage.



B-ALL: CD19 and PAX5 support B lineage

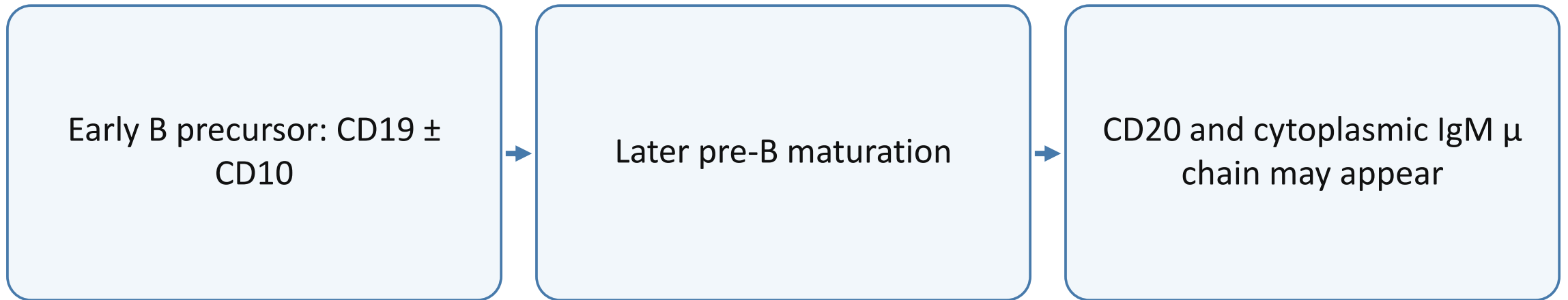
- B lymphoblasts commonly express CD19 and the transcription factor PAX5.
- CD10 is often present but may be absent in very immature cases.
- Marker patterns reflect developmental stage and may vary among tumors.

CD10 absence does not rule out B-ALL



Lineage assignment requires the full immunophenotype, not a single antigen.

Late pre-B tumors acquire additional markers



An ALL immunophenotype can be read as a snapshot of developmental arrest.

T-ALL: Characteristic precursor T-cell antigens

- Robbins commonly describes expression of CD1, CD2, CD5, and CD7.
- Expression varies with the stage at which maturation is interrupted.
- No single marker should be interpreted without the rest of the panel.

Surface markers change along T-cell maturation

Phenotype	Earlier precursor T-ALL	Later precursor T-ALL
Surface CD3	Usually absent	Can be positive
CD4 and CD8	Usually absent	May become positive
Precursor antigens	Commonly retained	Variable with maturation

Distinguish surface CD3 from any assay of cytoplasmic CD3.

B-ALL versus T-ALL: Practical marker map

Question	B-lineage evidence	T-lineage evidence
Immaturity	TdT often positive	TdT often positive
Lineage	CD19 / PAX5	CD2 / CD5 / CD7; CD3 stage-dependent
Maturation	CD10, CD20, cytoplasmic μ	CD1, CD4, CD8 variable
Interpretation	Pattern, not isolated stain	Pattern, not isolated stain

Do not infer lineage from one positive stain

Identify blasts
morphologically



Establish immaturity (e.g.,
TdT)



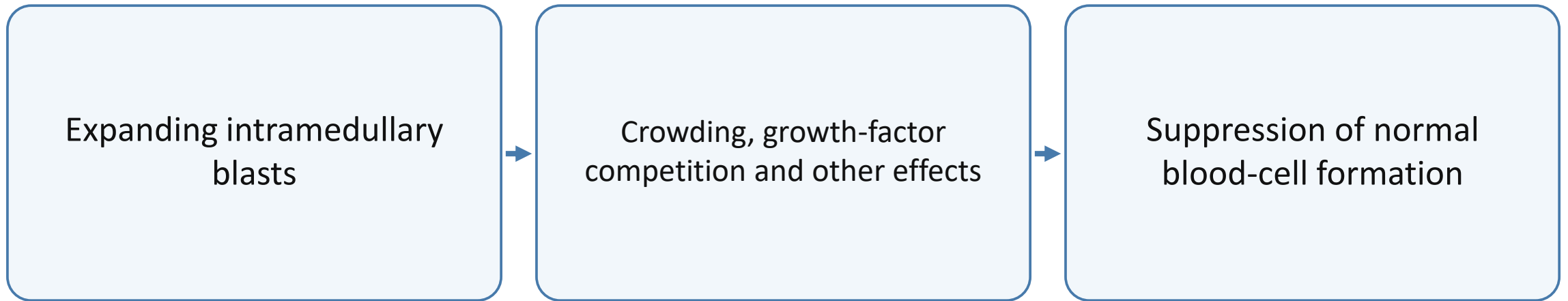
Integrate several lineage
markers

The phenotype is interpreted as a coordinated profile.

ALL often begins abruptly

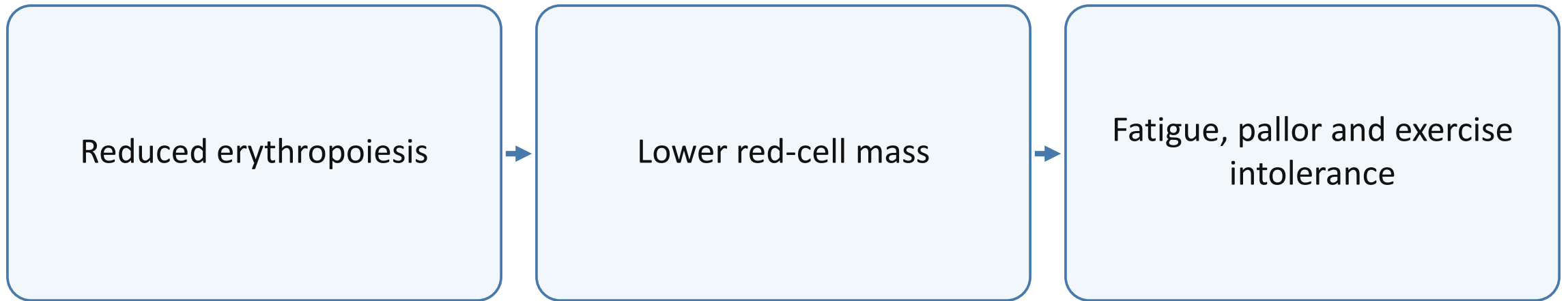
- Clinical illness may evolve over days to a few weeks.
- The presenting syndrome may resemble AML despite different lineage genetics.
- A rapidly developing constellation of cytopenias and infiltration signs should raise concern for acute leukemia.

Marrow failure results from blast accumulation



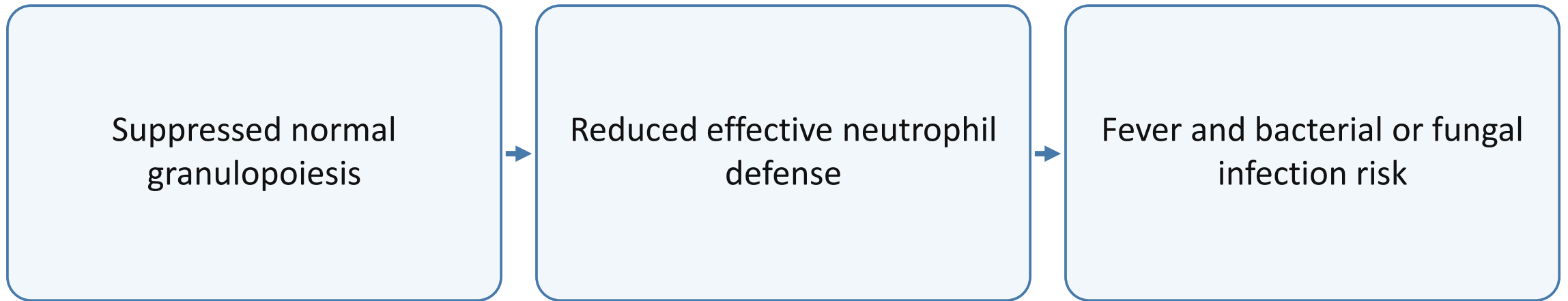
The hematologic phenotype is produced by loss of normal marrow function.

Anemia explains fatigue and reduced exercise capacity



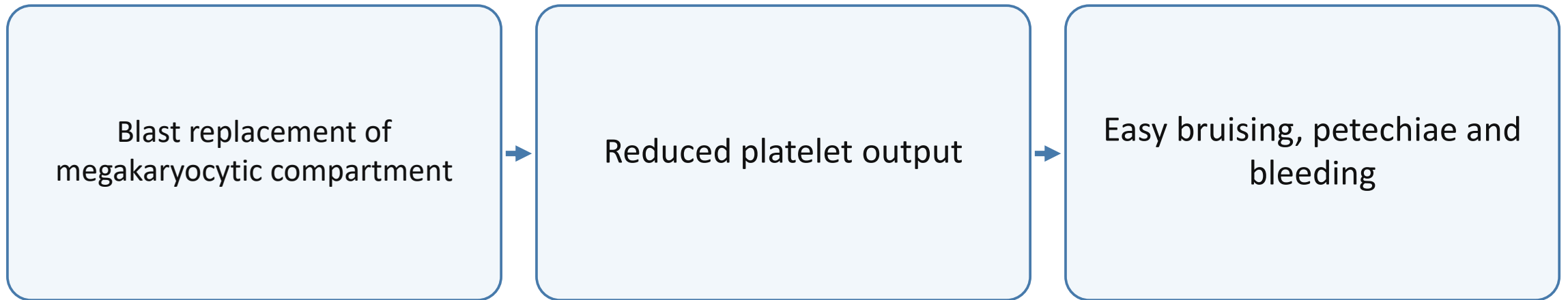
The marrow lesion has systemic physiologic consequences.

Neutropenia predisposes to febrile infection



Fever may reflect infection in a cytopenic patient rather than tumor fever.

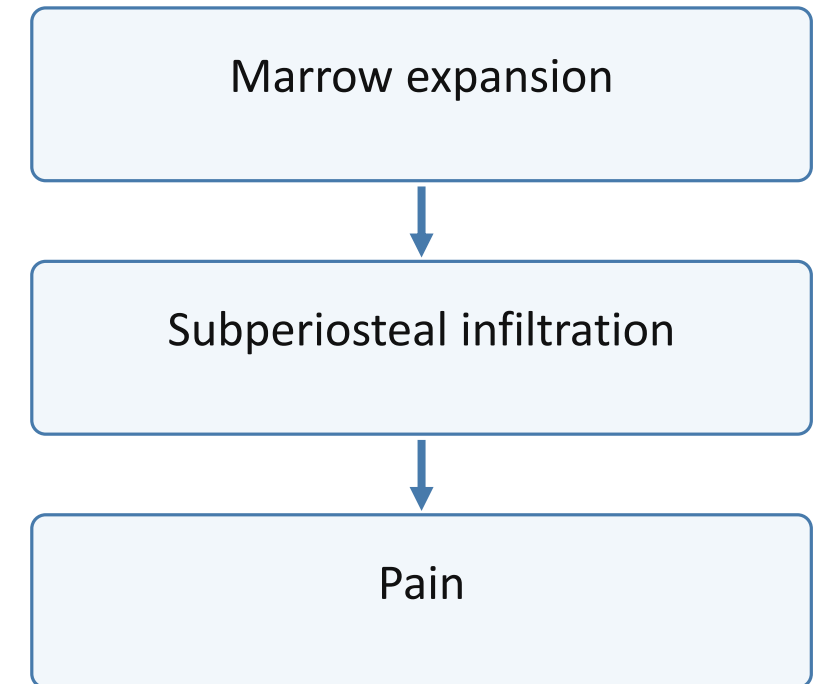
Thrombocytopenia explains mucocutaneous bleeding



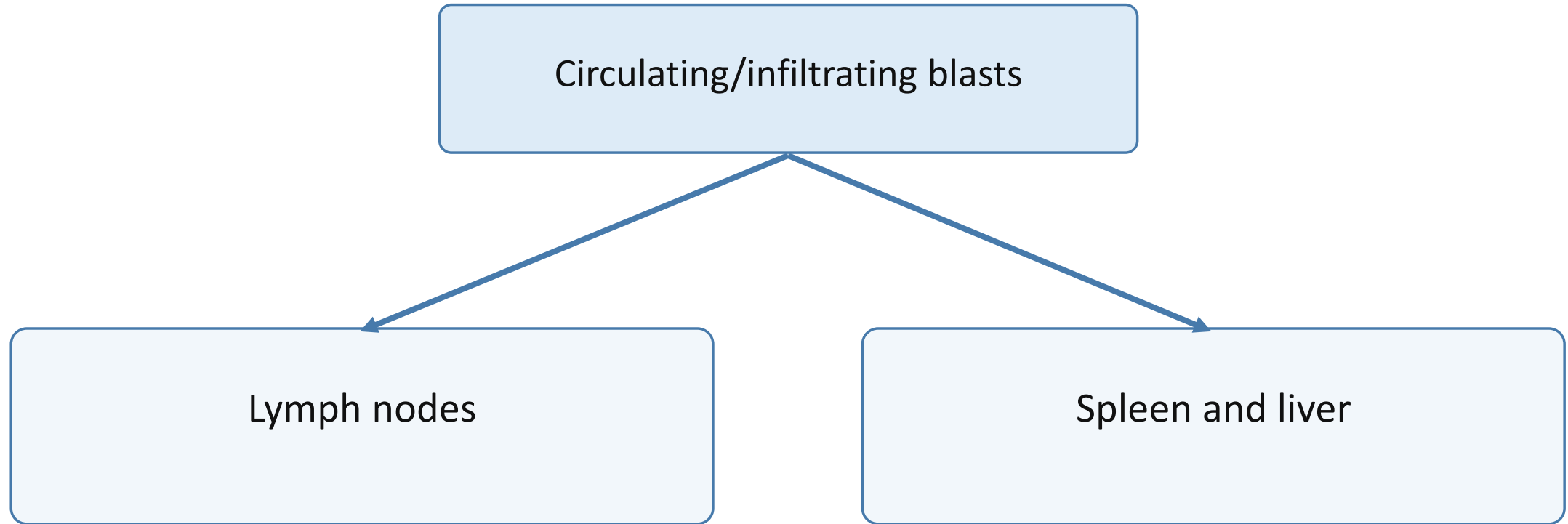
Blood-count abnormalities are mechanistically connected to marrow occupancy.

Bone pain signals marrow expansion and periosteal spread

- ALL frequently produces painful skeletal symptoms.
- Mechanism: Expanding blast population in marrow and infiltration beneath periosteum.
- This can be a prominent presenting clue in childhood disease.

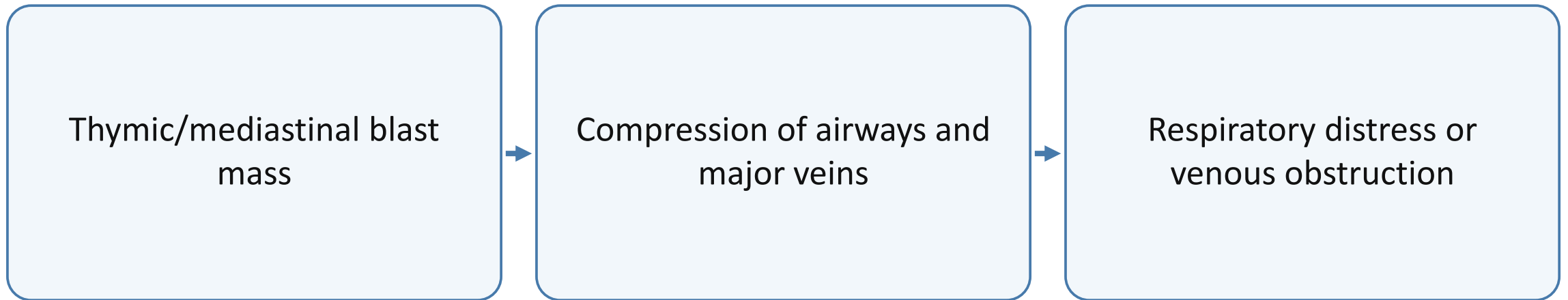


Nodal and visceral enlargement signal infiltration



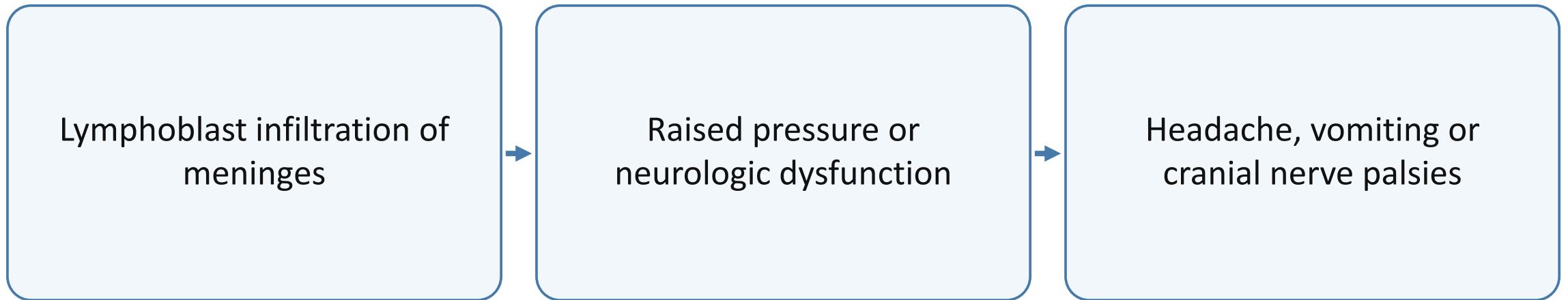
Generalized lymphadenopathy, splenomegaly and hepatomegaly may accompany ALL.

Mediastinal T-ALL creates compression risk



A mediastinal syndrome in an adolescent strongly raises concern for T-ALL.

CNS involvement results from meningeal spread



Neurologic symptoms have an anatomic basis in meningeal disease.

Testicular enlargement is another infiltration clue

- Testicular involvement can produce clinically apparent enlargement.
- It is an extramedullary manifestation of the same precursor-cell malignancy.
- Its presence reinforces the importance of examining sites outside marrow.

Symptoms can be classified by anatomic mechanism

Dominant site	Mechanism	Typical manifestation
Bone marrow	Hematopoietic suppression	Anemia, infections, bleeding
Bones	Expansion/subperiosteal disease	Bone pain
Mediastinum	Tumor mass, compression	Airway/vascular syndrome
Meninges	Lymphoblast infiltration	Headache, vomiting, palsies

ALL treatment outcomes differ strongly by age

- Major improvements with pediatric chemotherapy.
- Complete remission and cure are not synonymous.
- Outcomes remain substantially less favorable in adults in the cited source.

Pediatric: Frequent remission



Many children cured



Adults: More guarded

Pediatric remission and cure: Distinct endpoints

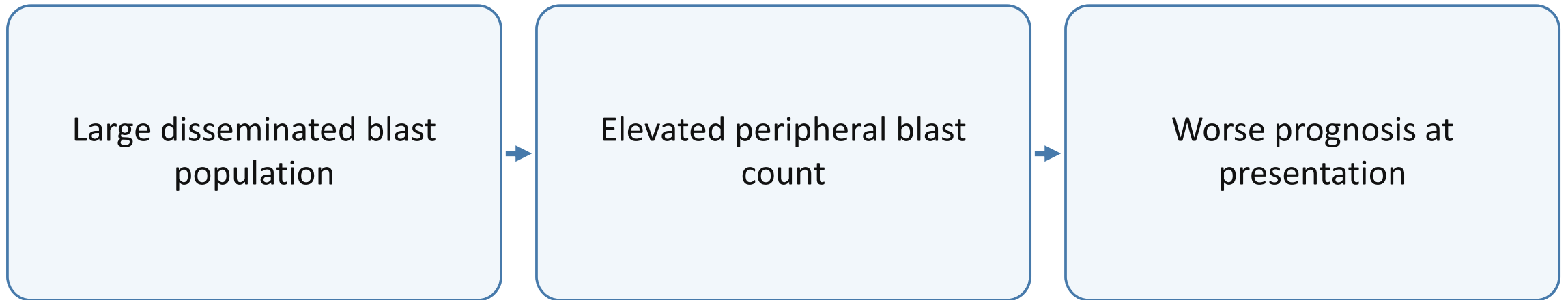
Outcome	Robbins 11th ed. Description	Interpretation
Complete remission	Approximately 95% of children	No clinically demonstrable disease by conventional criteria
Cure	Approximately 75–85% of children	Durable disease control
Adult cure	Fewer than half	Marked age-related difference

These are textbook-described values, not independently updated population estimates.

Age is a powerful prognostic variable

Age grouping	Source-described association	Context
Under 2 years	Adverse	KMT2A rearrangements and CNS disease enriched
2–10 years	Favorable	Better average prognosis
Adolescence or adulthood	Adverse	Higher-risk presentation and treatment challenges

High circulating blast count reflects burden

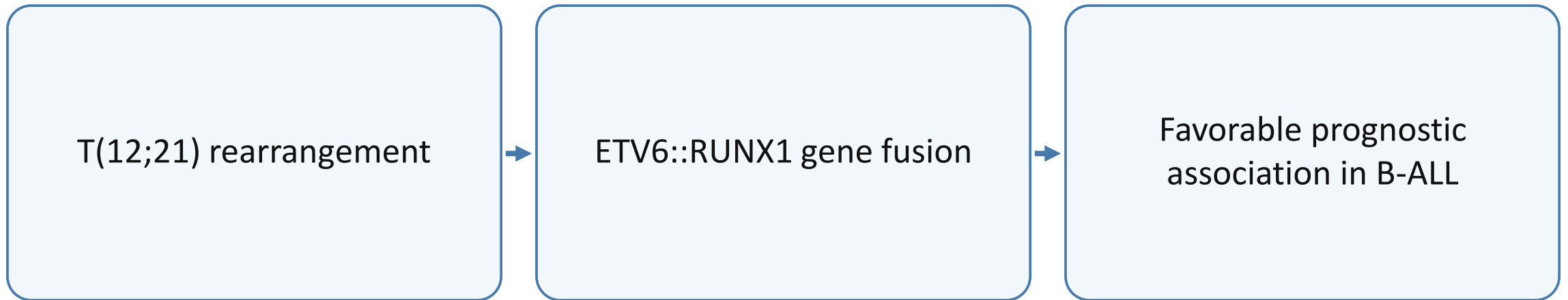


Counts >100,000 as an adverse feature; Verify units and laboratory context before clinical use.

Several B-ALL cytogenetic findings are favorable

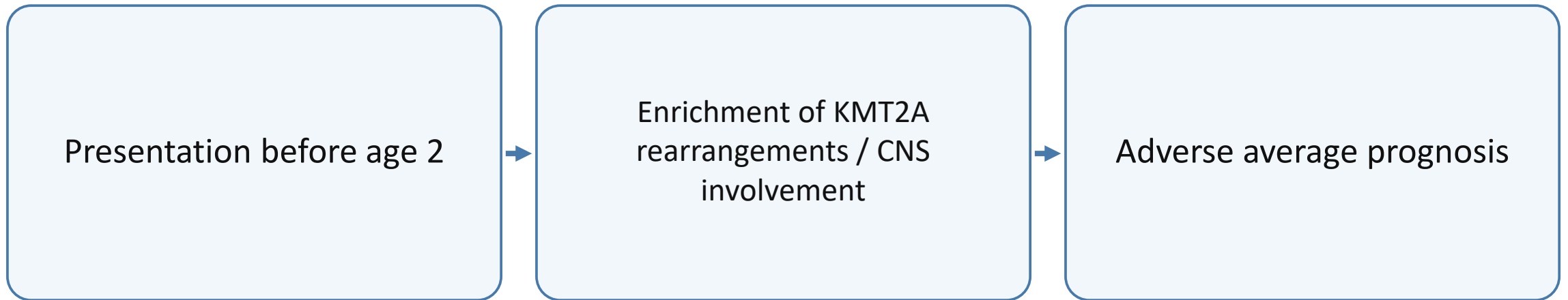
- Hyperdiploidy is described as favorable compared with hypodiploidy.
- Trisomy of chromosomes 4, 7 and 10 is a favorable constellation.
- ETV6::RUNX1 fusion is another favorable marker account.

ETV6::RUNX1 results from t(12;21)



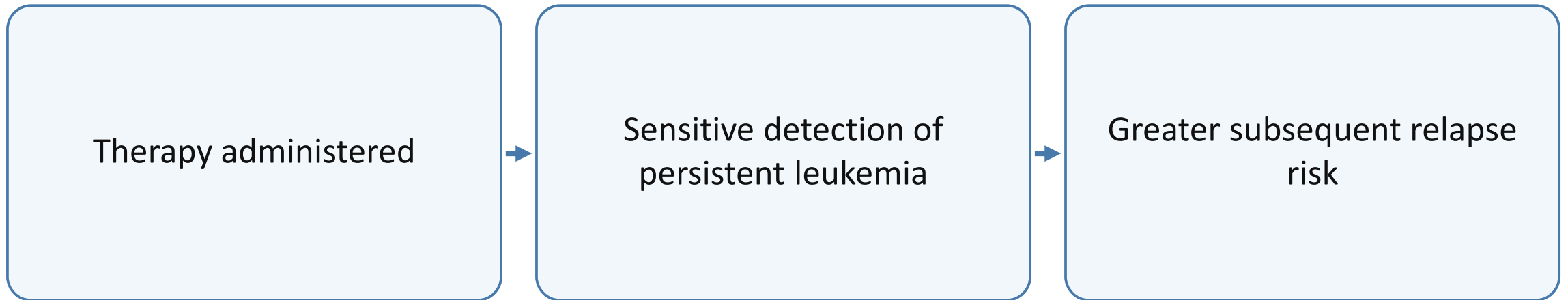
The molecular subtype has significance beyond its appearance on a blood smear.

Infantile disease often carries KMT2A lesions



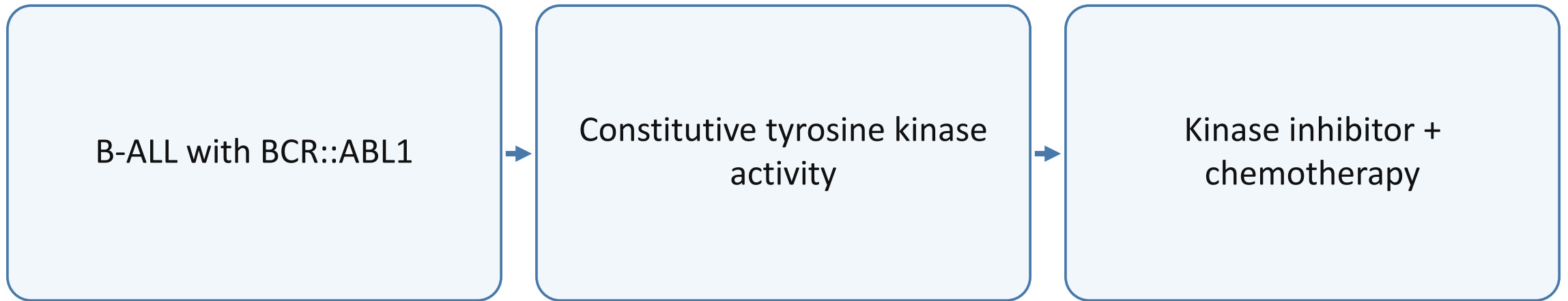
The source frames age-related risk partly through distinct molecular biology.

Minimal residual disease adds post-therapy prognosis



Molecular residual-disease assessment informs treatment decisions in both lineages.

BCR::ABL1 is both a lesion and a drug target

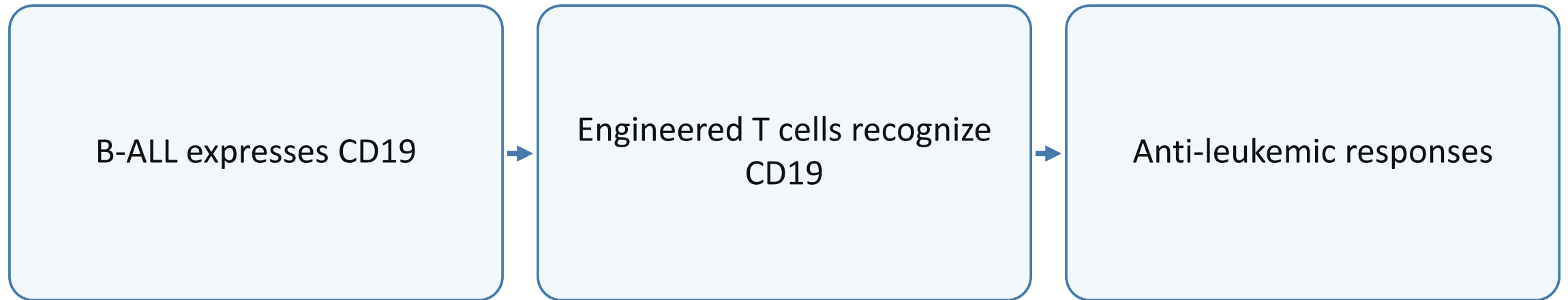


The molecular alteration supplies a mechanistic rationale for targeted treatment.

Other kinase rearrangements may be actionable

- Cryptic rearrangements of kinase-encoding genes beyond ABL.
- These are particularly relevant in adult B-ALL in the source text.
- Molecular characterization can therefore affect therapy, not only diagnosis.

CD19-directed CAR T-cell treatment



Robbins also emphasizes potential severe toxicities and high financial cost.

Why adult ALL remains challenging

- Adults differ from children in the molecular spectrum of ALL.
- Older patients may not tolerate intensive pediatric-type regimens.
- Absence of targetable lesions can limit therapeutic options.

Integrated case: Acute marrow failure

- A child presents with rapidly progressive fatigue, fever, petechiae and severe cytopenias.
- Marrow evaluation reveals an extensive population of immature blasts.

Which mechanism links the presenting symptoms to the marrow lesion?

Blast replacement suppresses erythropoiesis, granulopoiesis and platelet production.

Integrated case: A mediastinal syndrome

- An adolescent male develops respiratory symptoms and a large anterior mediastinal mass.
- Biopsy shows lymphoblasts; Marrow examination also reveals blasts.

What lineage should be investigated first, and how is it confirmed?

T-ALL is an important possibility; Confirm with an integrated precursor T-lineage antigen panel.

Integrated case: Uncertain blast lineage

- Marrow aspirate shows small agranular blasts with fine chromatin.
- TdT is positive; Myeloperoxidase is negative.

Can B-ALL versus T-ALL be established from these results?

No. Add B- and T-lineage markers (e.g., CD19/PAX5 and T-cell antigens).

The diagnostic and prognostic questions differ

Question	Main evidence	Clinical significance
Is this an acute blast neoplasm?	Marrow/blood morphology	Recognize disease process
B or T lineage?	Antigen-expression profile	Classify ALL
What genetic subtype?	Cytogenetics/molecular testing	Prognosis and treatment options
Is leukemia persisting?	Residual disease testing	Refine post-treatment risk

Core principles to retain

- ALL is an aggressive malignancy of immature B- or T-lineage lymphoblasts.
- Developmental blockade plus cooperating growth lesions creates an expanding blast clone.
- Marrow replacement causes cytopenias; Infiltration explains mass effects and CNS findings.
- Immunophenotyping resolves lineage; Genetics and residual-disease assays refine risk.

Primary reference and image provenance

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. Chapter 13, “Acute Lymphoblastic Leukemia/Lymphoma,” pp. 539–543.
- All illustrations in this lecture are original, editable educational schematics—not histologic or clinical specimens.
- Quantitative treatment/prognostic values are reported as described in the textbook and were not independently updated.