

Acute Myeloid Leukemia

Pathogenesis • classification • morphology • clinical correlations

A molecularly heterogeneous myeloid malignancy

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Learning objectives

- Relate acquired driver lesions to myeloid differentiation arrest.
- Use morphology and lineage markers to recognize AML.
- Distinguish major genetic and differentiation-defined patterns.
- Explain marrow failure, bleeding, infection and prognosis.

Three major myeloid neoplasms

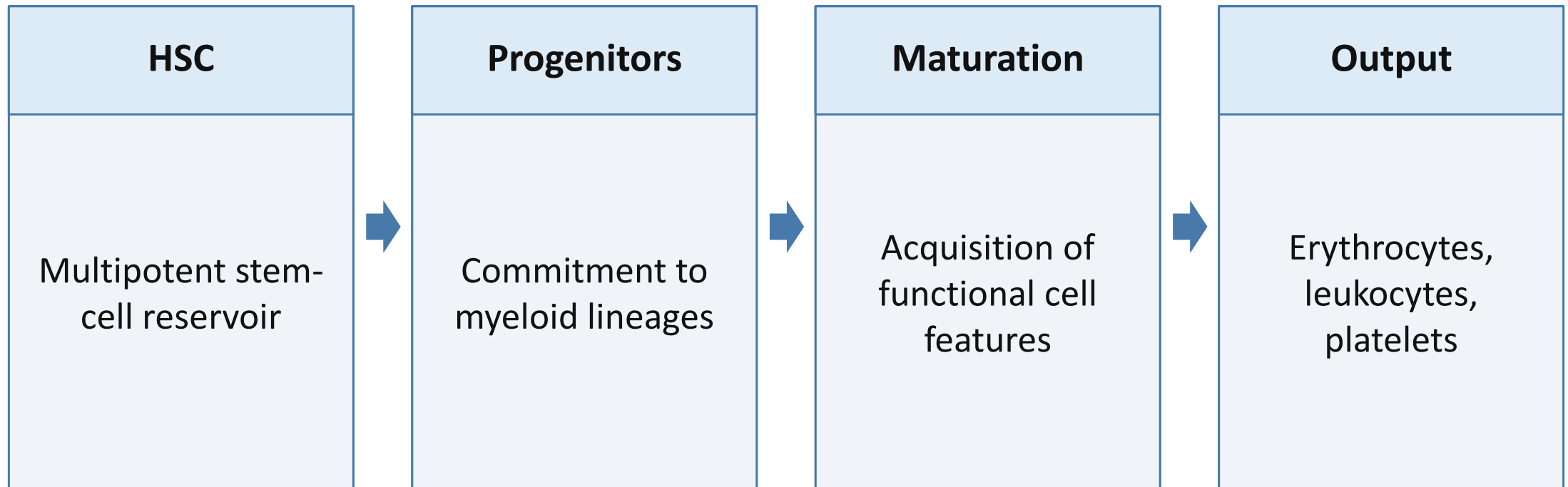
AML

- Immature myeloid blasts accumulate.
- Marrow failure dominates presentation.

Other myeloid neoplasms

- MDS: Ineffective, dysplastic hematopoiesis.
- MPN: Usually increased output of mature blood cells.

Normal blood-cell production

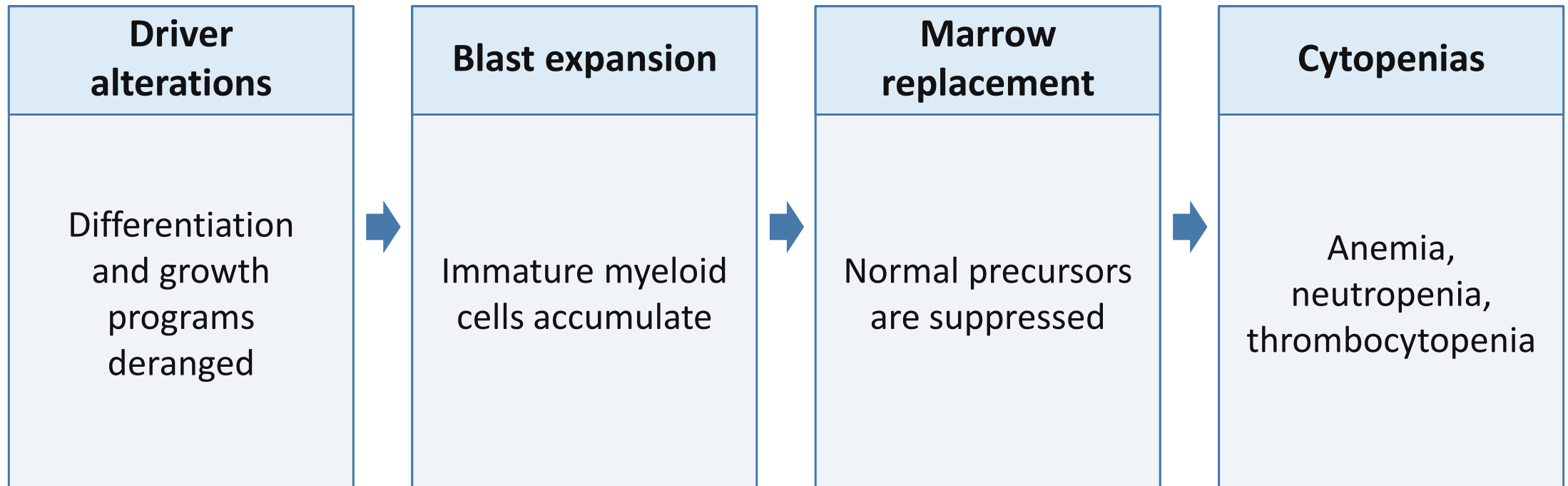


Schematic: Regulated differentiation sustains peripheral blood counts.

Defining lesion in AML

- A neoplasm of hematopoietic progenitor cells.
- Acquired oncogenic alterations impede myeloid differentiation.
- Immature blasts expand and replace functional marrow.
- The critical consequence is failure of normal hematopoiesis.

From mutations to marrow failure



Marrow failure can occur without marked peripheral leukocytosis.

Marrow failure has three major clinical outputs

Red-cell deficit

Reduced oxygen-carrying capacity → fatigue and pallor.

Neutrophil deficit

Reduced innate defense → fever and bacterial/fungal infections.

Platelet deficit

Impaired hemostasis → petechiae and mucosal bleeding.

Disease-related coagulopathy

Particularly important in acute promyelocytic leukemia.

Who develops AML?

- Disease can arise at any age.
- Incidence increases with age and peaks after 60 years.
- The clinical background often correlates with the molecular genotype.
- Age alone does not identify a genetic subtype.

AML is genetically heterogeneous

- Numerous different oncogenic lesions converge on the AML phenotype.
- Different clones are defined by their lineage maturation and genetics.
- Molecular testing is integral to classification and risk assessment.
- Morphology alone cannot identify every important genotype.

Four functional classes of AML drivers

Transcription factors

Disruption of lineage-specific maturation programs.

Growth signaling

Constitutive proliferation and survival signals.

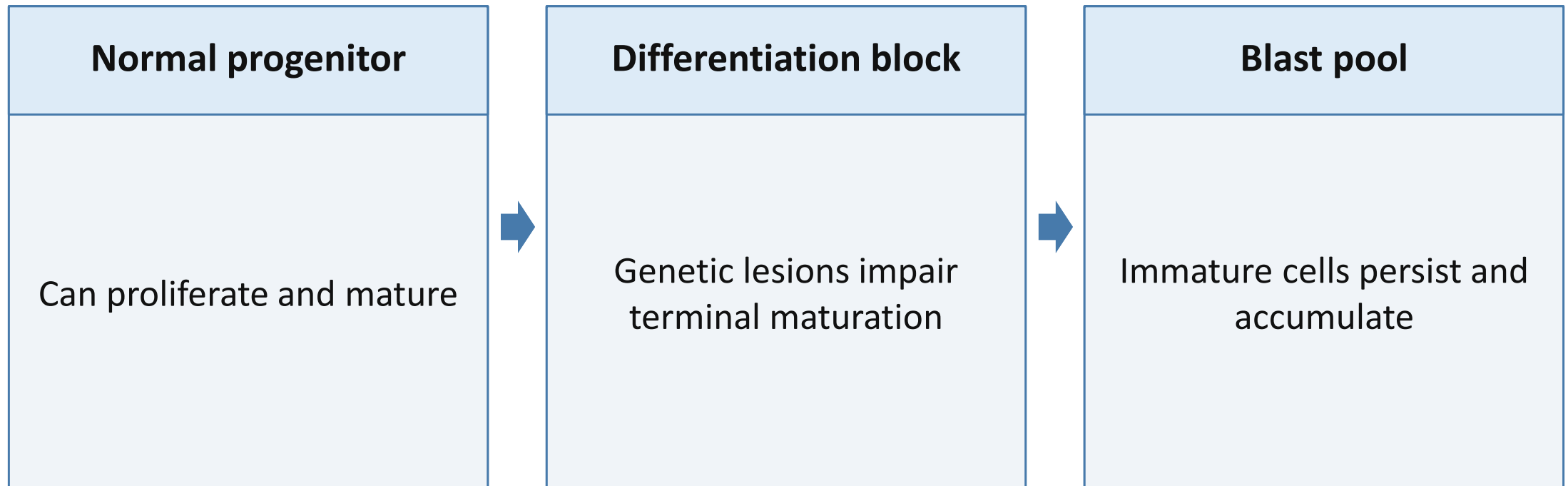
Epigenetic regulation

Disturbed methylation, chromatin architecture and gene expression.

P53 pathway

Impaired genome surveillance; Often therapy-resistant disease.

Differentiation arrest is the central mechanism



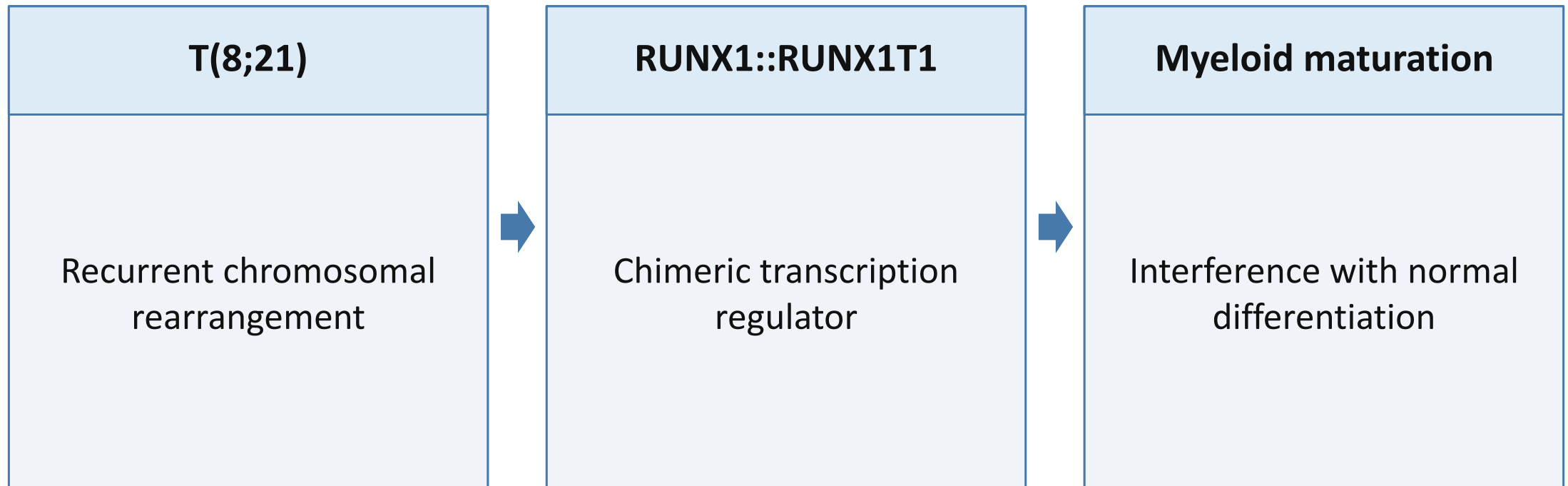
Failure to differentiate—not just rapid division—defines the phenotype.

RUNX1 and CBFB normally cooperate

RUNX1	CBFB	RUNX1–CBFB complex
DNA-binding transcription-factor component	Partner that forms a functional complex with RUNX1	Regulates normal hematopoietic differentiation

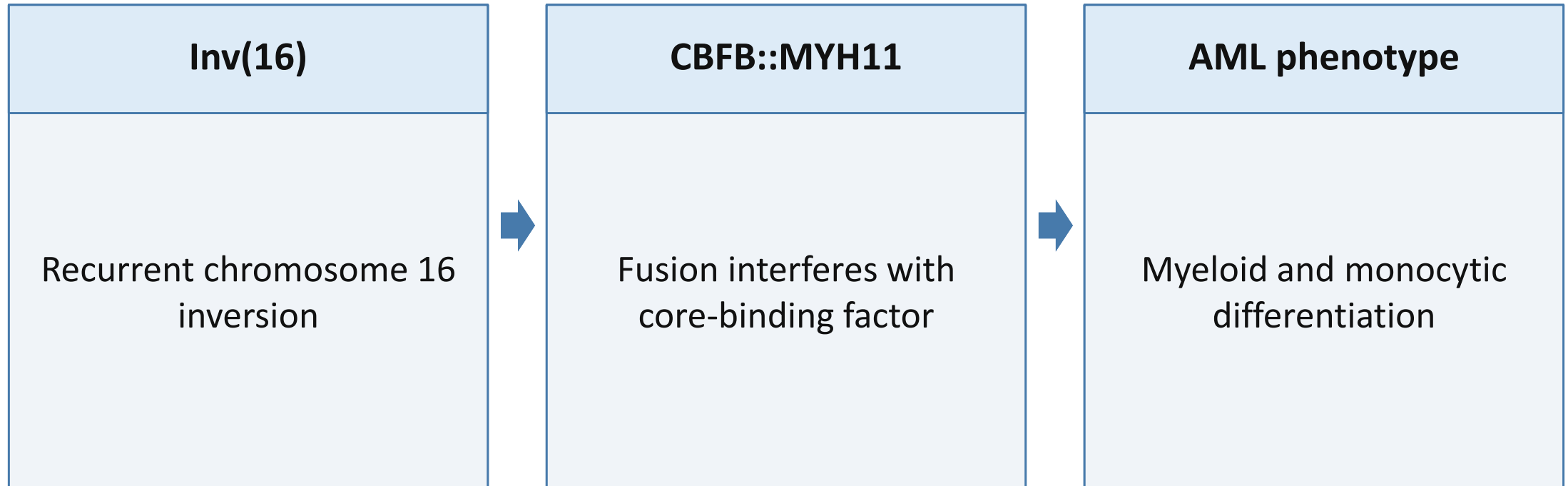
T(8;21) or inv(16) disrupts the cooperative transcriptional program.

T(8;21): A differentiation-blocking fusion



Textbook associates this genetic class with favorable prognosis.

Inv(16): Perturbed core-binding factor



Abnormal eosinophilic precursors may aid recognition.

Core-binding factor AML: Two pathways

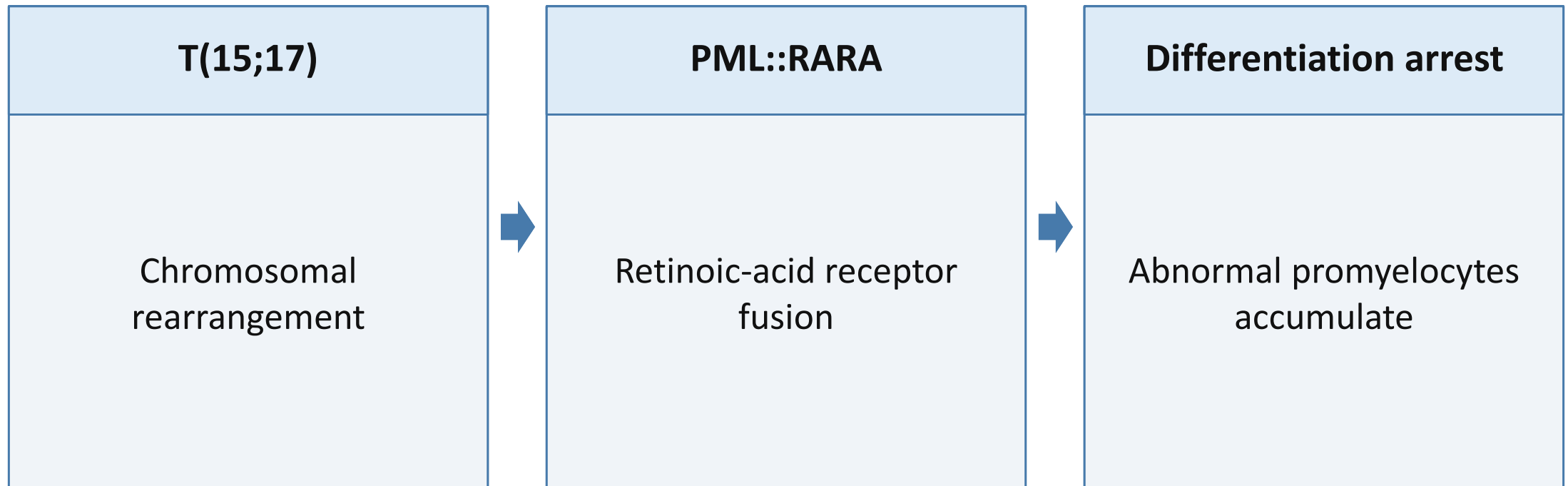
T(8;21)

- RUNX1::RUNX1T1 fusion.
- Often full spectrum of myeloid maturation.
- Auer rods and abnormal granules may be conspicuous.

Inv(16)

- CBFB::MYH11 fusion.
- Myelocytic plus monocytic differentiation.
- Abnormal eosinophil precursors may be present.

APL: The PML::RARA fusion



A distinctive AML subtype with clinically important coagulopathy.

Why retinoic acid and arsenic work in APL

- The PML::RARA fusion interferes with granulocytic differentiation.
- All-trans-retinoic acid targets the fusion-associated maturation block.
- Arsenic trioxide also targets the oncogenic fusion pathway.
- APL illustrates molecularly directed differentiation therapy.

FLT3: Constitutive survival signaling



FLT3 activation can coexist with PML::RARA in APL.

Cooperating mutations in leukemogenesis

Differentiation lesion

- Blocks progression toward mature myeloid cells.
- May leave proliferation/survival drive insufficient alone.

Signaling lesion

- Enhances growth-factor-like activity.
- Fosters survival and expansion of arrested precursors.

RAS-pathway dysregulation

- Driver changes also affect genes in progrowth signaling pathways.
- The RAS family is among the recurrently affected pathways.
- Growth-pathway activation is not synonymous with myeloid identity.
- Combined genetic events help explain AML's biologic diversity.

Epigenetic deregulation in AML

DNA methylation

Driver variants may disturb methylation programs.

Chromatin organization

Cohesin-family alterations affect three-dimensional genome architecture.

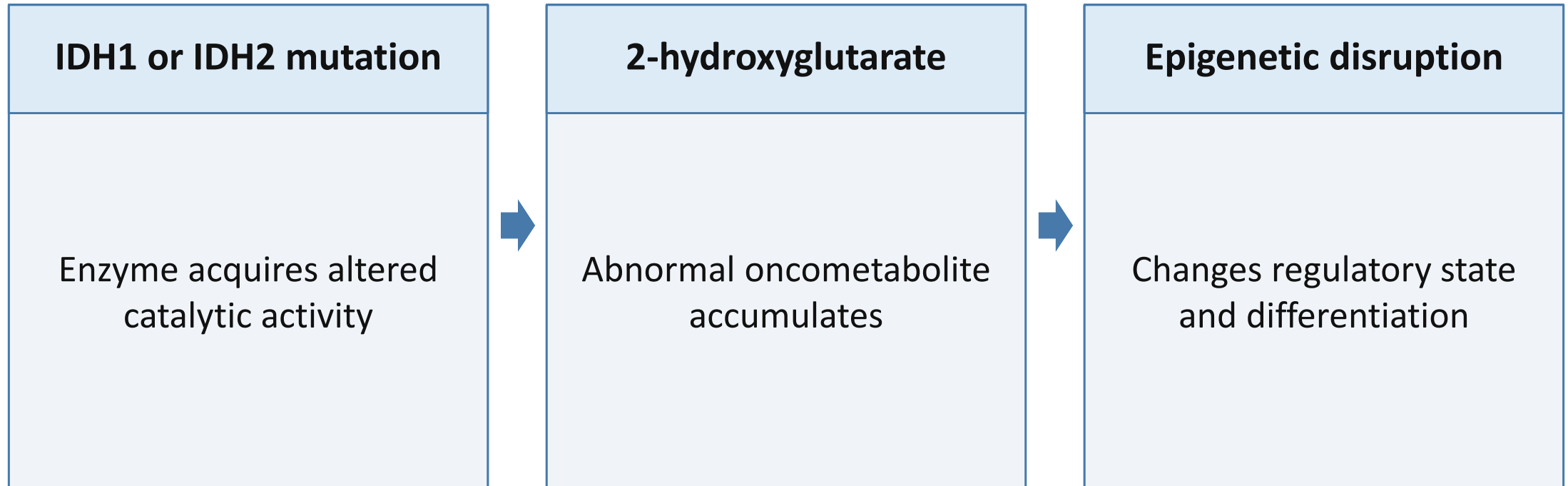
Histone programs

Epigenetic defects alter regulatory states.

Gene expression

The resulting transcriptional changes may support malignant phenotypes.

IDH-mutant AML: An oncometabolite pathway



Targeted mutant-IDH inhibition can induce clinical responses.

Cohesin alterations and chromatin topology

- Cohesin proteins organize chromatin in three dimensions.
- Some AML drivers affect members of the cohesin family.
- Disturbed chromosome topology may alter gene expression.
- The exact causal links between epigenetic changes and AML remain incompletely resolved.

TP53-mutated AML: A recognizable pattern

Genome

Frequently associated with complex karyotypes.

Morphology

Marked dysplasia and sometimes erythroid differentiation.

Clinical setting

Often seen following DNA-damaging therapy.

Outcome

Particularly poor response to standard treatment.

Not every mechanism is fully resolved

- Genetic lesions can be classified by their known molecular functions.
- The immediate consequences of some epigenetic disturbances remain uncertain.
- Cooperating events differ across patients and AML subtypes.
- Genotype–phenotype relationships are informative but not perfectly deterministic.

Integrated model of AML biology

Differentiation defects

Fusion transcription factors impair maturation

Growth advantage

Signaling alterations promote survival and proliferation

Other driver programs

Epigenetic and p53 pathway dysfunction

Functional classes may cooperate within the same AML clone.

Two complementary classification approaches

Genetically defined AML

- Entity anchored by a defining cytogenetic or molecular aberration.
- Often carries subtype-specific morphologic and prognostic clues.

Differentiation-defined AML

- Entity categorized by its morphologic lineage maturation.
- Used when specific defining genetic abnormalities are absent.

Why genetic classification is essential

- Morphologically similar AMLs may have different molecular drivers.
- Genetics can distinguish biologically coherent subtypes.
- Genotype influences prognosis and therapeutic choice.
- An integrated report includes morphology, immunophenotype and genetics.

Genetically defined AML: Core examples

Genetic lesion	Gene/fusion	Textbook pattern
t(8;21)	RUNX1::RUNX1T1	Maturing blasts; Auer rods
inv(16)	CBFB::MYH11	Myelomonocytic; abnormal eosinophils
t(15;17)	PML::RARA	Abnormal promyelocytes; DIC
11q23 rearrangement	KMT2A	Often monocytic differentiation

T(8;21) AML: Distinctive morphology

- A spectrum of myelocytic maturation may be apparent.
- Abnormal cytoplasmic granules are described.
- Auer rods are often readily identified.
- Molecular confirmation distinguishes this entity from morphology-only lookalikes.

Inv(16) AML: Eosinophilic clues

- Blasts may show granulocytic and monocytic differentiation.
- Abnormal eosinophilic precursors contain atypical basophilic granules.
- This clue should prompt a search for CBFB::MYH11.
- The characteristic genetics carry prognostic significance.

APL: Morphologic and clinical coupling

Blast stage

Neoplastic promyelocytes are prominent.

Granularity

Often abundant, coarse azurophilic granules.

Auer rods

May be numerous or form bundles.

Clinical hazard

Disseminated intravascular coagulation is an urgent concern.

KMT2A-rearranged AML

- The rearrangement involves 11q23 and the KMT2A gene.
- Many cases show monocytic differentiation.
- Robbins groups this pattern among unfavorable-risk examples.
- A history of topoisomerase II inhibitor exposure is relevant.

NPM1-mutant AML

- A genetically recognized subtype detected by molecular testing.
- A normal-appearing karyotype does not exclude driver mutations.
- Favorable outcomes in the overview table.
- Actual risk assignment requires the complete genetic and clinical context.

AML with myelodysplasia-related genetics

Chromosomes

Loss/deletion involving 5q or 7q may be seen.

Splicing

SRSF2, SF3B1, U2AF1 and ZRSR2 are listed.

Other drivers

ASXL1, EZH2, BCOR and STAG2 are listed.

Interpretation

Integrate the abnormalities with AML morphology and clinical background.

A useful distinction: Genotype versus maturation

Genetically defined entity

- RUNX1::RUNX1T1 and PML::RARA name molecular subtypes.
- The genetic event is central to subtype recognition.

Differentiation-defined entity

- Descriptions such as monocytic or megakaryocytic emphasize lineage features.
- Lineage is established through morphology and markers.

Differentiation-defined AML patterns

Pattern	Salient discriminating feature
Minimally differentiated	Myeloid lineage by antigen expression; MPO-negative
Without / with maturation	Limited blasts versus wider myelocytic maturation
Myelomonocytic / monocytic	Coexisting granulocytic/monocytic or predominant monocytic maturation
Erythroid / megakaryocytic	Erythroid phenotype or platelet-lineage antigens; fibrosis may occur

AML, minimally differentiated

- Morphology alone may be insufficient to establish myeloid lineage.
- Myeloperoxidase staining may be negative.
- Flow-cytometric identification of myeloid-associated antigens becomes essential.
- Avoid calling lineage based on one nonspecific morphologic feature.

AML without maturation

- Blast predominance reflects marked arrest in differentiation.
- Limited appearance of maturing granulocytic elements.
- Myeloperoxidase can support a myeloid assignment.
- Distinguish from minimally differentiated and acute lymphoblastic leukemia.

AML with maturation

- Granulocytic cells may span a wider differentiation spectrum.
- Myeloblasts coexist with recognizable maturing forms.
- Auer rods, when present, support myeloid lineage.
- A defining genetic lesion still takes precedence when identified.

Two mixed-lineage maturation patterns

Myelomonocytic AML

- Both granulocytic and monocytic maturation are present.
- Morphology should be integrated with appropriate lineage markers.

Monocytic AML

- Monoblasts and promonocytes predominate.
- Nonspecific esterase is a useful cytochemical correlate.

Monocytic AML: Why sites of infiltration matter

- Monocytic tumors may infiltrate the gingiva and skin.
- Normal monocytes are physiologically capable of tissue extravasation.
- Leukemia cutis and gingival enlargement may be clinical clues.
- Monocytic features alone do not define a single genetic subtype.

AML with erythroid differentiation

- Some AMLs contain a conspicuous neoplastic erythroid component.
- The erythroid phenotype may coexist with marked dysplasia.
- TP53-pathway alterations are particularly associated with such cases.
- Interpret lineage findings in the context of the full marrow and genetic results.

AML with megakaryocytic differentiation

- Blasts demonstrate megakaryocyte-lineage markers such as GPIIb/IIIa.
- Marrow fibrosis can obscure simple aspirate-based assessment.
- Fibrogenic cytokines released by leukemic cells contribute to fibrosis.
- Its association with Down syndrome.

Lineage-specific clues guide the laboratory

Myeloid

Azurophilic granules, Auer rods, myeloperoxidase.

Monocytic

Folded nuclei, monoblasts/promonocytes, nonspecific esterase.

Erythroid

Erythroid differentiation in the leukemic population.

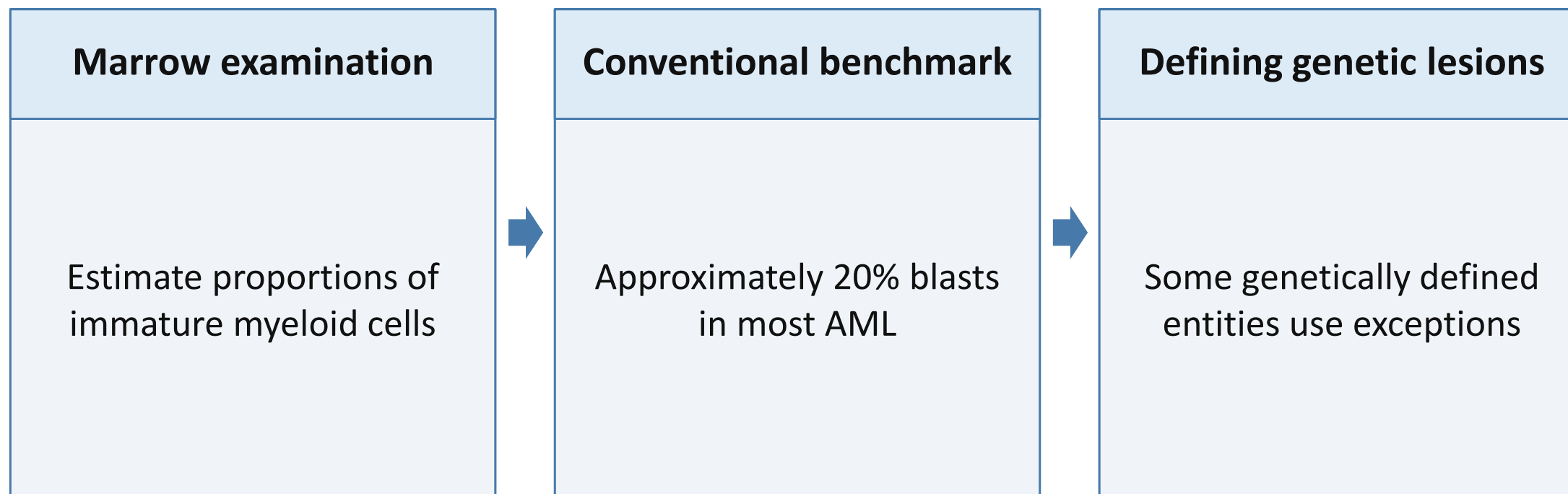
Megakaryocytic

Platelet-lineage antigens and possible marrow fibrosis.

Morphologic common denominator

- Every AML subtype increases immature myeloid cells in marrow.
- Blasts vary morphologically and can have hybrid features.
- The distribution between marrow and peripheral blood is variable.
- Morphology is the starting point, not the whole diagnosis.

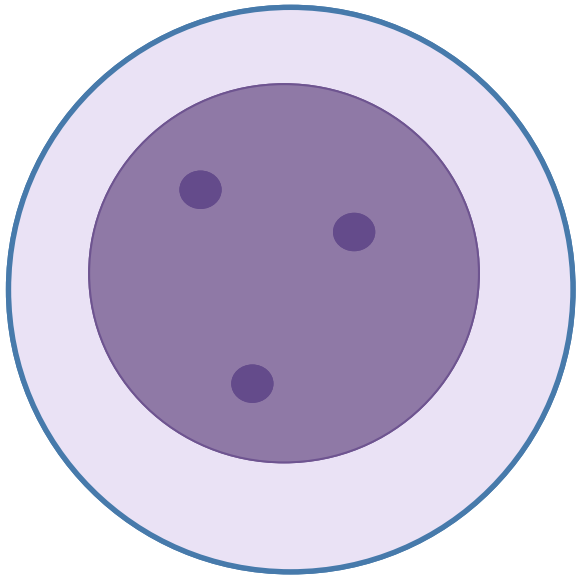
Blast percentage and genetic exceptions



Exact thresholds are classification- and entity-dependent; The textbook summary should not replace formal diagnostic criteria.

Recognizing a myeloblast

Schematic — not a clinical specimen

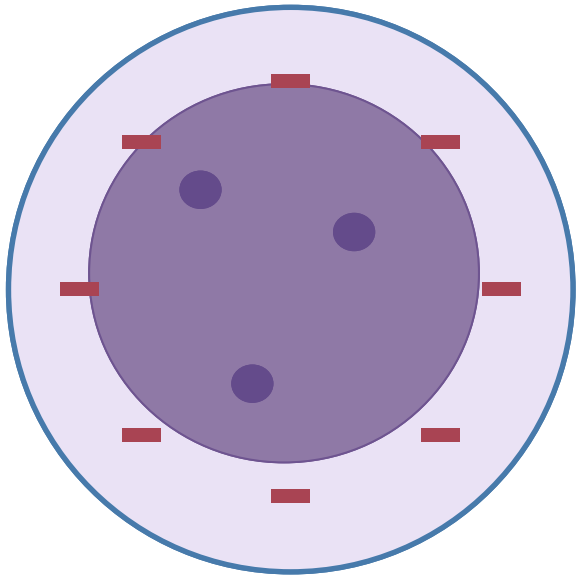


Features to recognize

- Delicate nuclear chromatin.
- Usually two to four nucleoli.
- Relatively abundant cytoplasm.
- Fine azurophilic granules may occur.

Why Auer rods matter

Schematic — not a clinical specimen



Features to recognize

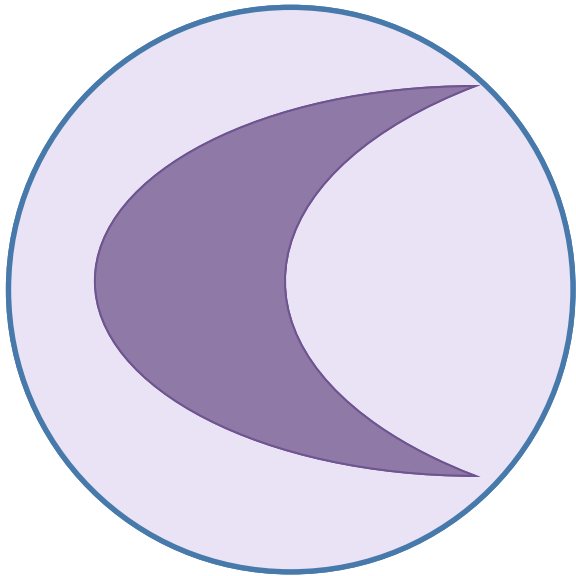
- Needle-like azurophilic inclusions.
- Support myeloid differentiation.
- Particularly numerous in APL.
- Absence does not exclude AML.

Auer rods: A useful but incomplete clue

- The inclusions represent distinctive needle-like azurophilic granules.
- Many, but not all, AML cases contain detectable Auer rods.
- Abundant clustered rods are strongly associated with APL.
- Diagnosis still requires integrated lineage and genetic testing.

Monoblast morphology

Schematic — not a clinical specimen



Features to recognize

- Folded or lobulated nuclear outline.
- No typical Auer rods.
- Nonspecific esterase-positive.
- Can coexist with promonocytes in blood.

Myeloblast versus monoblast

Myeloblast

- Delicate chromatin; Often visible nucleoli.
- Possible fine MPO-positive granules.
- Auer rods may be observed.

Monoblast

- Folded or lobulated nuclear membranes.
- Nonspecific esterase reactivity.
- Auer rods generally absent.

Marrow fibrosis in megakaryocytic AML

- Megakaryoblastic differentiation can be accompanied by fibrosis.
- Leukemic cells release factors with fibrogenic effects.
- Fibrosis may complicate marrow aspiration and interpretation.
- Lineage-specific antigen studies help establish the phenotype.

Peripheral counts cannot rule out AML

Leukemic cells circulate

- Some patients have striking numbers of blood blasts.
- Peripheral morphology may immediately suggest acute leukemia.

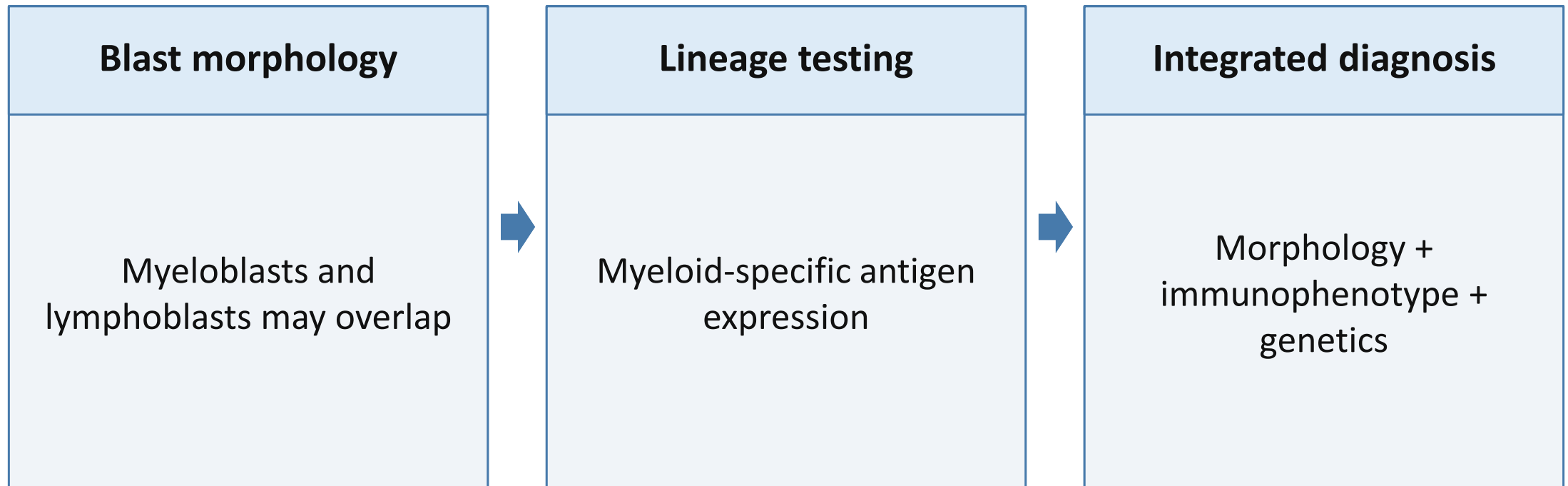
Leukemic cells scarcely circulate

- Blasts may be few or absent despite marrow disease.
- Pancytopenia requires marrow assessment when leukemia is suspected.

Aleukemic leukemia: A diagnostic trap

- The blood smear may lack visible circulating blasts.
- Anemia, neutropenia and thrombocytopenia can predominate.
- A reassuring peripheral blast count does not exclude AML.
- Bone marrow examination remains essential in suspicious pancytopenia.

Why immunophenotyping is necessary



Assigning myeloid lineage may require flow cytometry and/or cytochemistry.

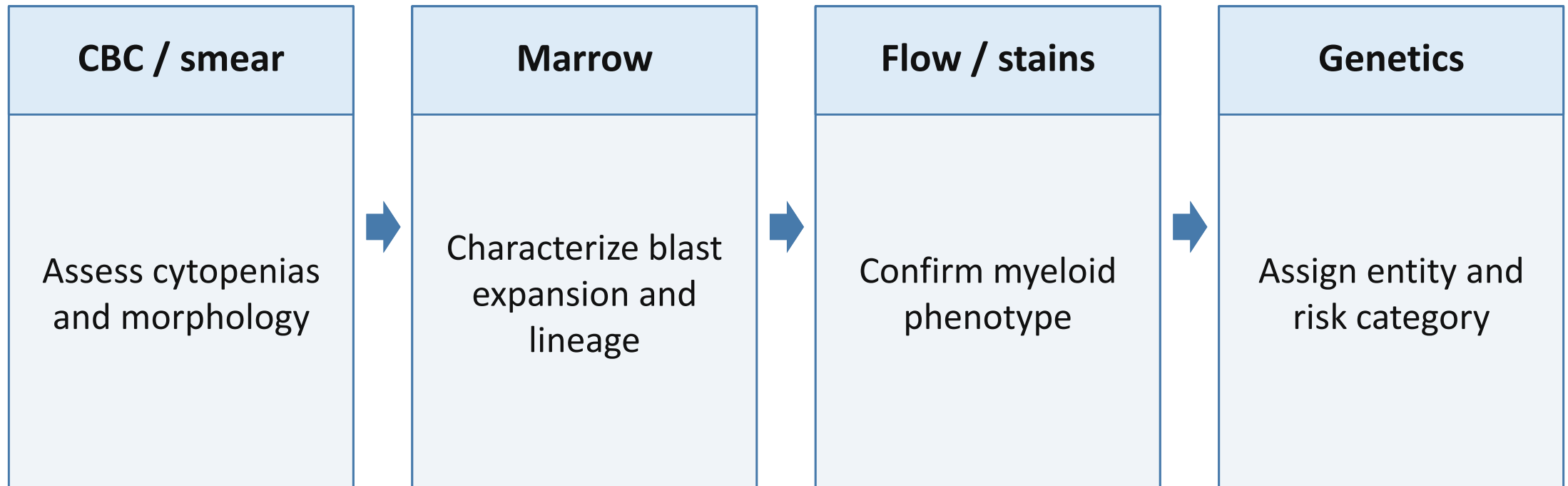
Flow cytometry: An illustrative Robbins example

Marker	Illustrated expression	Interpretive role
CD34	Positive	Stem/progenitor-associated blast marker
CD33	Positive	Myeloid-associated lineage marker
CD15	Subset positive	A measure of partial myeloid maturation
CD64	Negative	Lack of mature monocytic-marker expression

Cytochemistry contributes to lineage assignment

- Myeloperoxidase positivity supports granulocytic differentiation.
- Nonspecific esterase helps identify monocytic differentiation.
- Minimally differentiated AML can be MPO-negative.
- Flow-cytometric immunophenotyping is essential when morphology is equivocal.

A source-consistent diagnostic workflow



This is a teaching schematic; Testing choices should follow a current diagnostic protocol.

Clinical context predicts different genetics

Younger, de novo AML

- Balanced rearrangements such as t(8;21), inv(16), t(15;17) are relatively characteristic.
- A subset has favorable biology.

Older / prior hematologic disease

- Overlap with mutations in clonal hematopoiesis and MDS.
- Adverse molecular patterns become more common.

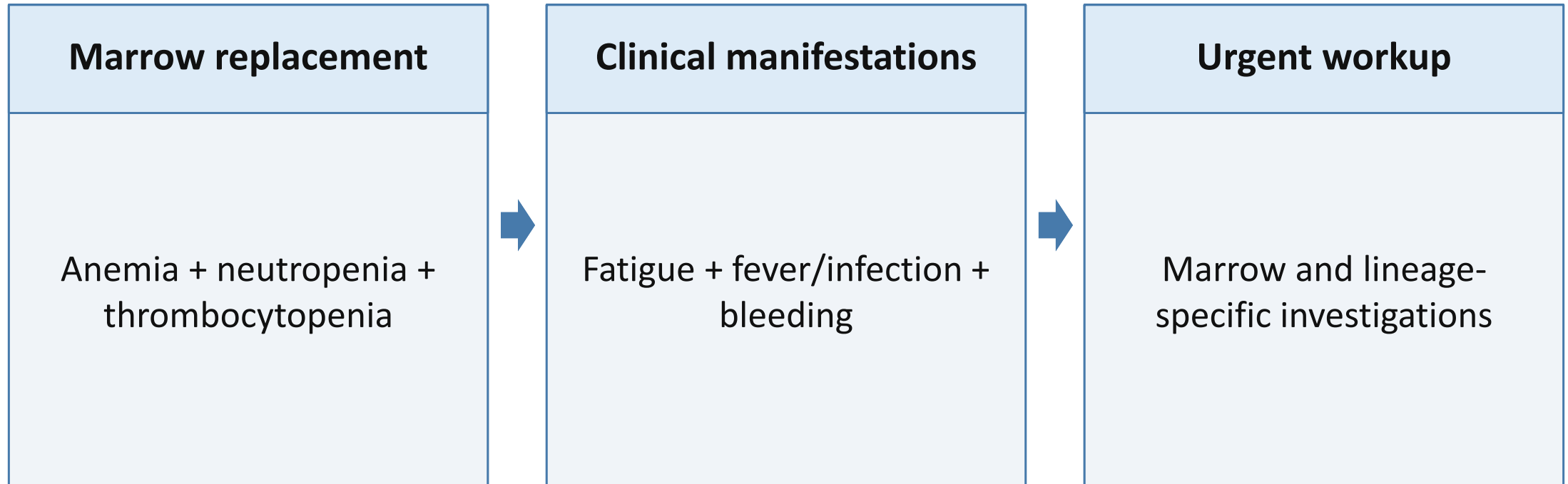
Therapy-related AML: Dominant patterns

- Prior chemotherapy or radiation exposure can precede AML.
- Most DNA-damaging exposures correlate with chromosome 5/7 lesions.
- TP53 dysfunction and complex karyotypes are frequent.
- The genetic signature contributes to an adverse clinical phenotype.

Topoisomerase II therapy: A notable exception

- AML after topoisomerase II inhibition can follow another genetic route.
- KMT2A translocations involving 11q23 are emphasized.
- Monocytic differentiation may accompany KMT2A rearrangement.
- Exposure history and genetics should be interpreted together.

Typical presentation evolves over weeks to months



Do not wait for leukocytosis or a large circulating blast fraction.

Symptoms reflect lost normal cell function

Anemia

Fatigue, decreased activity tolerance and pallor.

Neutropenia

Fever and susceptibility to infection.

Thrombocytopenia

Petechiae, ecchymoses and mucosal bleeding.

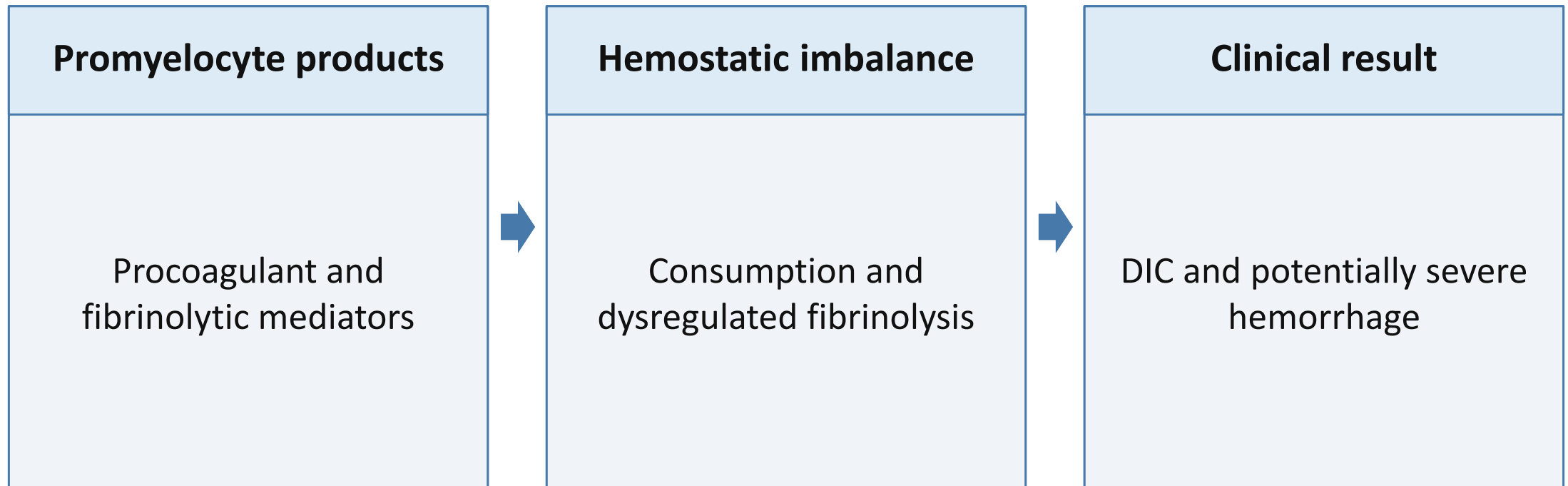
Blast-specific effect

Tissue infiltration and coagulopathy in some subtypes.

Hemorrhage in AML

- Thrombocytopenia reduces primary hemostatic capacity.
- Mucosal, cutaneous and serosal hemorrhage may occur.
- Bleeding can involve gingivae or urinary tract.
- APL adds a consumptive coagulopathy to the platelet deficit.

APL-related bleeding is mechanistically distinct



APL with suspected coagulopathy requires urgent clinical recognition.

Infections are a consequence of neutropenia

- Loss of functional neutrophils impairs antimicrobial defense.
- Infection commonly affects oral cavity, skin, lung and urinary tract.
- Gastrointestinal and renal/urinary infections are also described.
- Opportunistic fungi and Gram-negative bacteria may be involved.

Extramedullary manifestations

Gingival infiltration

Particularly relevant in monocytic differentiation.

Leukemia cutis

Skin involvement by leukemic cells.

Myeloid sarcoma

A localized soft-tissue tumor of myeloid blasts.

Central nervous system

Less frequent involvement than in acute lymphoblastic leukemia.

Myeloid sarcoma: A tissue-based presentation

- AML occasionally produces a localized soft-tissue mass.
- This mass may be recognized as myeloid sarcoma.
- A tissue lesion may occur before florid systemic AML is apparent.
- Without systemic treatment, progression to marrow disease is expected.

Acute myeloid versus acute lymphoblastic leukemia

Shared mechanisms

- Both can replace marrow and cause cytopenias.
- Both may present with fever, fatigue or bleeding.

Useful distinction

- Immunophenotype establishes myeloid or lymphoid lineage.
- CNS involvement is relatively less frequent in AML.

AML versus MDS in marrow failure

AML

- Accumulation of immature myeloid blasts.
- Abrupt clinical presentation is common.
- Many cases meet a high blast burden or defining genetic pattern.

MDS

- Defective maturation with ineffective production.
- Dysplastic elements predominate.
- May evolve into AML over time.

Why prognosis depends heavily on genotype

- Some rearrangements identify highly treatment-responsive disease.
- TP53 abnormalities and complex karyotypes predict resistance.
- Age, prior MDS and therapy-related disease shift genotype distribution.
- A single undifferentiated AML survival estimate conceals this heterogeneity.

Molecular categories and broad prognosis

Example	Textbook direction	Rationale
PML::RARA APL	Very favorable	Sensitive to ATRA / arsenic
t(8;21) or inv(16)	Favorable	Better conventional-therapy response
KMT2A / MDS-related AML	Often poor	Adverse molecular context
TP53-abnormal AML	Poor	Resistant disease; complex karyotype

APL is a paradigmatic molecular success

- PML::RARA is a specific therapeutic vulnerability.
- Retinoic acid and arsenic trioxide overcome the fusion-associated block.
- Cure in more than 90% of patients with this subtype.
- The immediate bleeding risk remains essential to clinical recognition.

Adverse-risk AML: The TP53 example

- P53 pathway impairment associates with genomic complexity.
- Marked dysplasia and erythroid differentiation may coexist.
- Standard therapies often perform poorly.
- Some high-risk or relapsed cases are considered for stem-cell transplantation.

Targeted AML therapeutics: Two examples

Mutant IDH1 / IDH2

- Altered metabolism yields 2-hydroxyglutarate.
- Mutant-IDH inhibitors may produce strong responses.

Activating FLT3

- Growth-factor-like signaling promotes blast survival.
- FLT3 kinase inhibitors target the activated signaling enzyme.

Other therapeutic concepts discussed

- Epigenetic-modifying agents are therapeutic options for some older adults.
- BCL2 inhibition can produce responses in AML.
- Responses in these settings may be transient.
- Treatment decisions depend on molecular risk and patient condition.

HSC transplantation: A selected strategy

- Used in some high-risk and relapsed AML settings.
- Patient factors, remission status and disease genetics influence eligibility.
- The treatment goal differs from purely symptom-directed management.
- A pathology lecture should distinguish risk assessment from prescribing.

Illustrative case: Promyelocytes and bleeding

A patient presents with new mucosal bleeding and cytopenias. Marrow shows many abnormal promyelocytes with dense granules and bundled Auer rods.

Discuss

- What molecular lesion should be prioritized?
- Which life-threatening hemostatic complication is associated?

Case interpretation: Suspect APL

Likely subtype

AML with PML::RARA associated with t(15;17).

Morphologic clue

Hypergranular promyelocytes and numerous Auer rods.

Immediate concern

Disseminated intravascular coagulation and hemorrhage.

Mechanistic therapy

Retinoic acid and arsenic act on the fusion-dependent block.

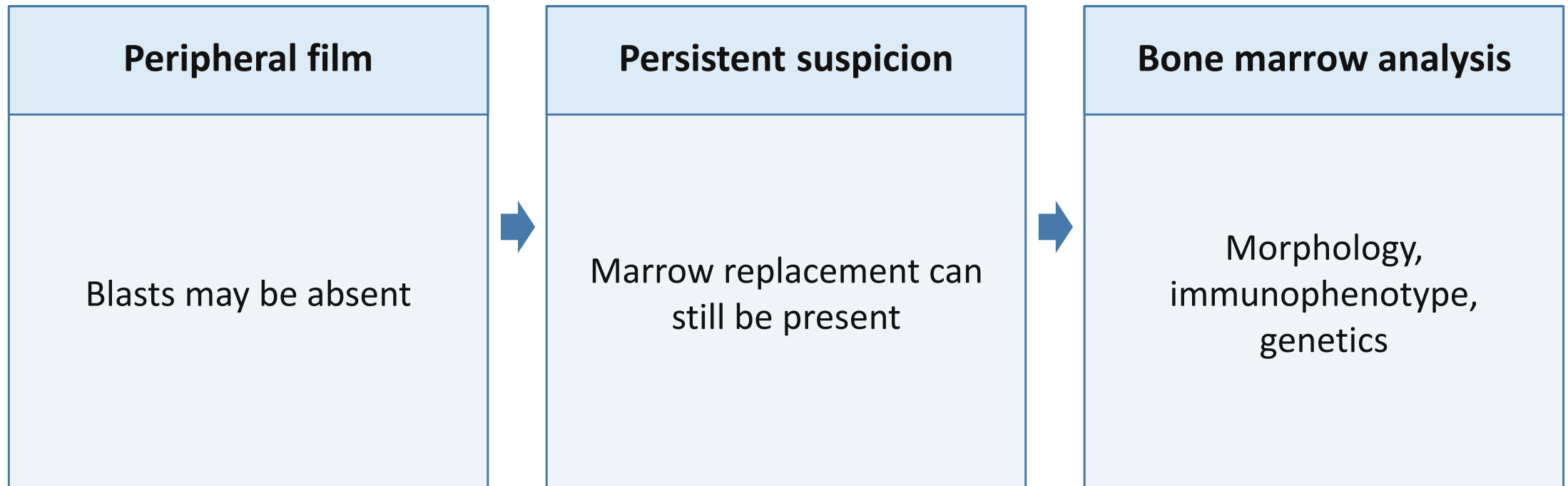
Illustrative case: Pancytopenia without blasts

An older adult has progressive fatigue, fever and widespread petechiae. The blood film shows pancytopenia but no unequivocal circulating blasts.

Discuss

- Does the absence of blood blasts exclude AML?
- Which specimen is essential for the diagnostic evaluation?

Case interpretation: Marrow remains decisive



Aleukemic presentation is a recognized diagnostic pitfall.

Illustrative case: Gingival and skin lesions

A patient with acute marrow failure has gingival thickening and skin nodules. Blasts have folded nuclear membranes and nonspecific esterase positivity.

Discuss

- Which lineage differentiation is favored?
- How does the normal behavior of that lineage help explain tissue infiltration?

Case interpretation: Monocytic AML

Lineage clue

Monoblasts or promonocytes with folded nuclei.

Cytochemistry

Nonspecific esterase supports monocytic differentiation.

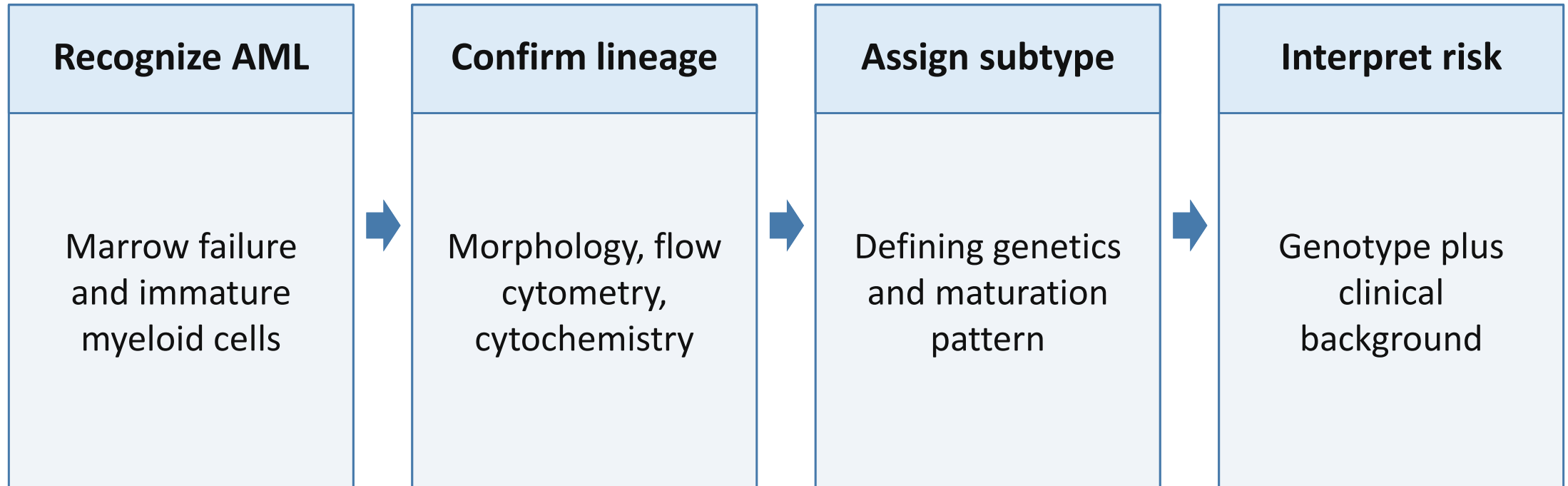
Clinical association

Gingival infiltration and leukemia cutis.

Mechanistic link

Monocytes normally extravasate into tissues.

Integrated diagnostic synthesis



Each layer contributes distinct information; None should be interpreted in isolation.

Five points to retain

- AML is differentiation-arrested myeloid neoplasia with marrow failure.
- Transcription-factor, signaling, epigenetic and TP53 alterations cooperate.
- Auer rods support myeloid lineage; Absence does not rule out AML.
- Molecular classification determines major biologic and therapeutic distinctions.
- APL is simultaneously a bleeding emergency and a highly targetable subtype.

Primary teaching reference

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition.
- Chapter 13: Diseases of White Blood Cells, Lymph Nodes, Spleen, and Thymus.
- Acute myeloid leukemia, classification, morphology and adjacent genetics/clinical features; printed pages 562–564.
- Source images from textbook figures were not reproduced; drawings are original editable schematics.