

Myeloid Neoplasms

Clonal stem-cell disease • differentiation • marrow output

A pathology framework for AML, MDS, and MPN

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Learning objectives

Classify myeloid tumors by the dominant defect in blood-cell production.

Link progenitor-cell mutations to differentiation, marrow morphology, and peripheral counts.

Interpret the AML–MDS–MPN spectrum, clonal evolution, and selected diagnostic pitfalls.

Apply a source-grounded approach to laboratory, marrow, and molecular findings.

Three major categories arise from myeloid progenitors

Acute myeloid leukemia

Accumulating blasts; Loss of effective mature-cell production

Myelodysplastic neoplasms

Disordered maturation;
Ineffective hematopoiesis

Myeloproliferative neoplasms

Growth-factor-independent expansion;
Increased mature cells

The dominant biological defect is more informative than the label “myeloid.”

Their common starting point is a transformed progenitor

Each family originates in a hematopoietic progenitor with acquired oncogenic alterations.

Bone marrow is usually the principal site of disease.

A neoplastic clone competes with or suppresses normal stem cells and progenitors.

Clinical manifestations follow the pattern of disturbed blood-cell production.

Clone determines output

Mutant progenitor

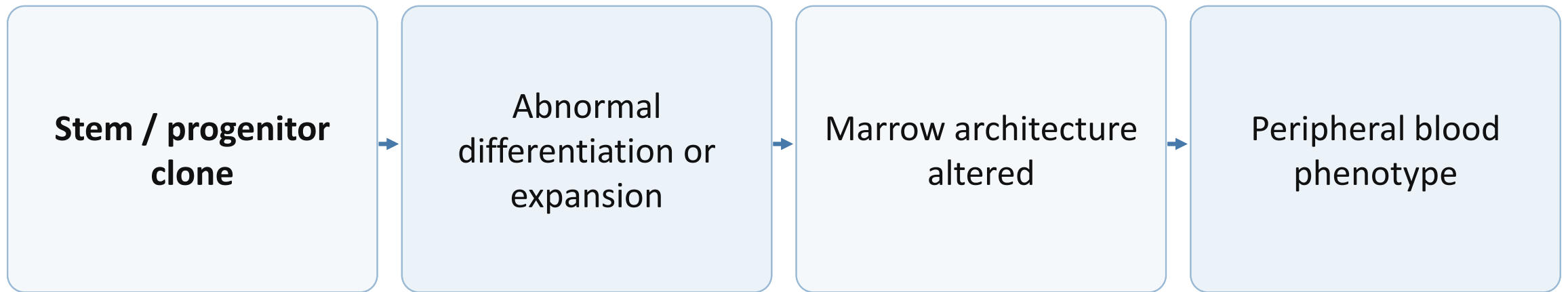


Clonal offspring



Altered output

The marrow is both factory and disease compartment



The blood count is an output signal; Marrow biology explains its cause.

Secondary hematopoietic organs can become involved

The spleen and liver may support extramedullary hematopoiesis.

Lymph nodes can be involved, usually less prominently.

Organomegaly is particularly relevant to proliferative and fibrosing disorders.

The pattern depends on the neoplasm and the degree of marrow displacement.

Sites of involvement

Bone marrow



Spleen



Liver / nodes

A CBC does not directly measure marrow productivity

High counts

Often reflect expanded output in myeloproliferation

Low counts

May reflect ineffective maturation or blast-mediated suppression

Mixed counts

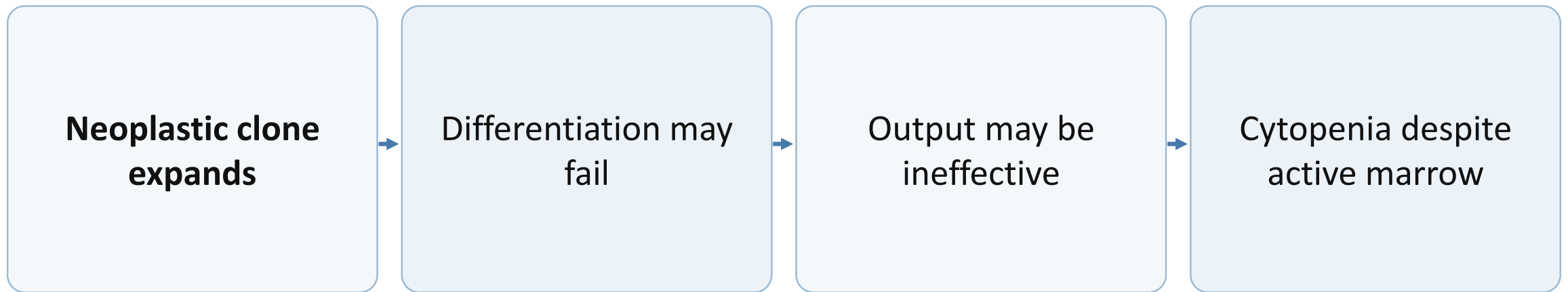
Can occur with skewed lineages, progression, or overlap

Interpret counts alongside smear, marrow, and molecular findings.

AML, MDS, and MPN: The central biological contrast

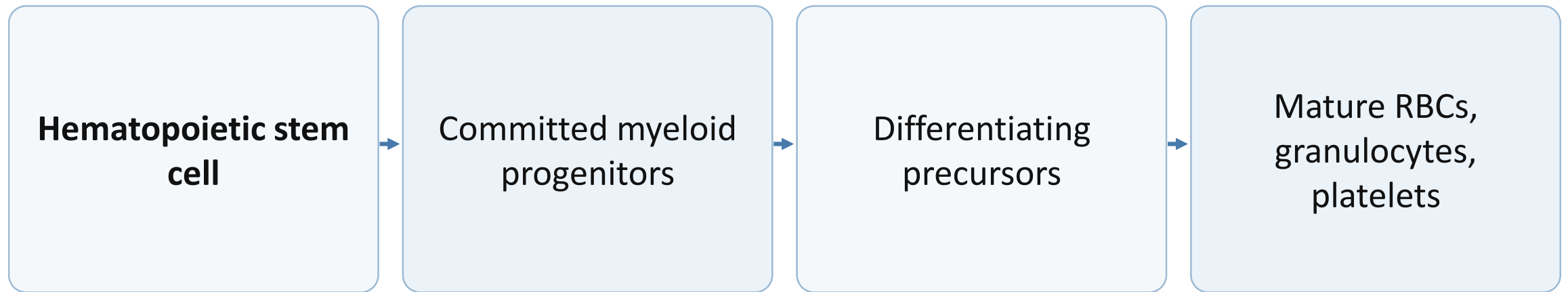
Dimension	AML	MDS	MPN
Dominant defect	Blast accumulation	Ineffective maturation	Uncontrolled expansion
Peripheral pattern	Often cytopenias	Usually cytopenias	Often increased cell counts
Marrow clue	Immature blasts	Dysplastic forms	Proliferating maturing cells
Important trajectory	Marrow failure	AML evolution	Fibrosis or acute leukemia

Cell number and cell function are different variables



A hypercellular marrow may coexist with low circulating counts, particularly in MDS.

Normal blood formation is hierarchical



The transformed cell's position in this hierarchy influences disease phenotype.

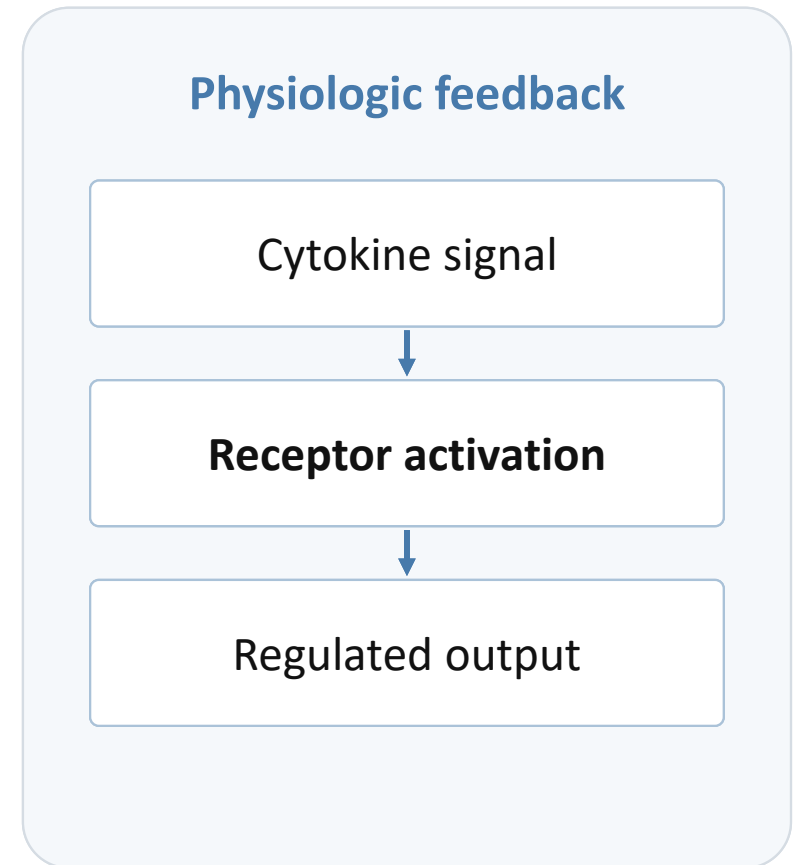
Homeostasis couples demand to blood-cell output

Growth factors and cytokines regulate normal marrow proliferation and maturation.

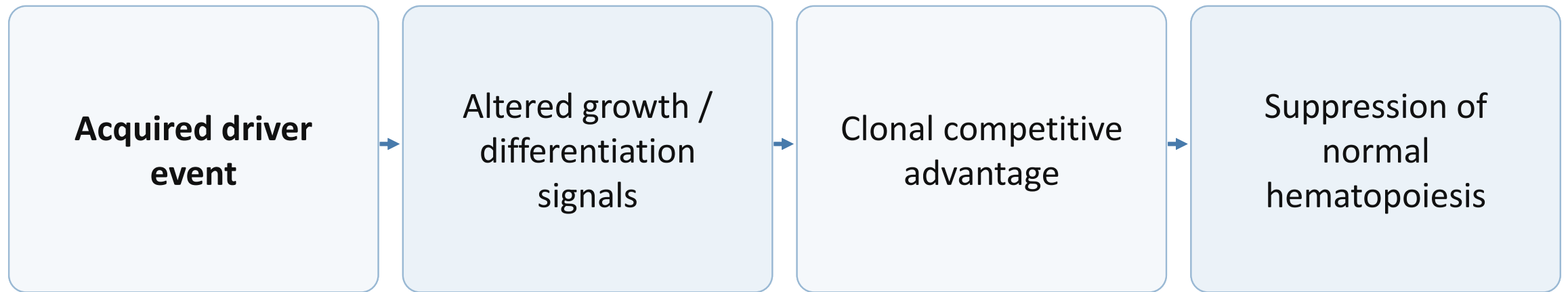
Feedback adjusts red cell, granulocyte, and platelet production to physiologic needs.

The response requires intact signaling and an orderly differentiation program.

Myeloid tumors partially escape these controls.



Neoplastic cells escape feedback control



“Clonality” alone does not specify whether the output will be blastic, dysplastic, or proliferative.

Cell of origin shapes clinical behavior

Pluripotent HSC

Can retain both myeloid and lymphoid differentiation potential

Myeloid-committed progenitor

Phenotype is generally restricted to myeloid production

Later myeloid precursor

Mutation effects depend on the maturation program available

Differentiation is the second major axis

Blocked

Immature forms
accumulate; AML archetype

Disordered

Abnormal maturation with
ineffective output; MDS
archetype

Largely preserved

Many mature elements
produced; MPN archetype

The model is a teaching simplification: Actual tumors are genetically and clinically heterogeneous.

Why myeloid tumors cause cytopenias

Leukemic blasts can crowd and suppress normal hematopoiesis.

Dysplastic progenitors may fail to generate effective mature cells.

Fibrotic replacement displaces functional marrow late in some MPNs.

The same low count can therefore arise through very different mechanisms.

Different roads to low counts

Blasts / dysplasia



Ineffective output



Cytopenias

Why some myeloid tumors cause cytoses

Constitutively active signaling can bypass normal growth-factor requirements.

When maturation remains largely intact, mature blood elements accumulate.

The dominant expanded lineage helps distinguish MPN phenotypes.

High cell counts do not imply that blood cells function normally.

Differentiation persists

Constitutive signal



Mature cell excess



Cytosis

Blood counts are a phenotype, not a lineage diagnosis

Finding	Possible mechanism	Context needed
Anemia	Ineffective erythropoiesis / crowding / fibrosis	Smear + marrow
Neutropenia	Production failure or blast expansion	Differential + marrow
Leukocytosis	Mature-cell proliferation or leukemic cells	Cell identification + molecular
Thrombocytosis	Clonal MPN or reactive change	Marrow + clinical exclusions
Thrombocytopenia	Marrow failure or advanced fibrosis	Marrow and disease course

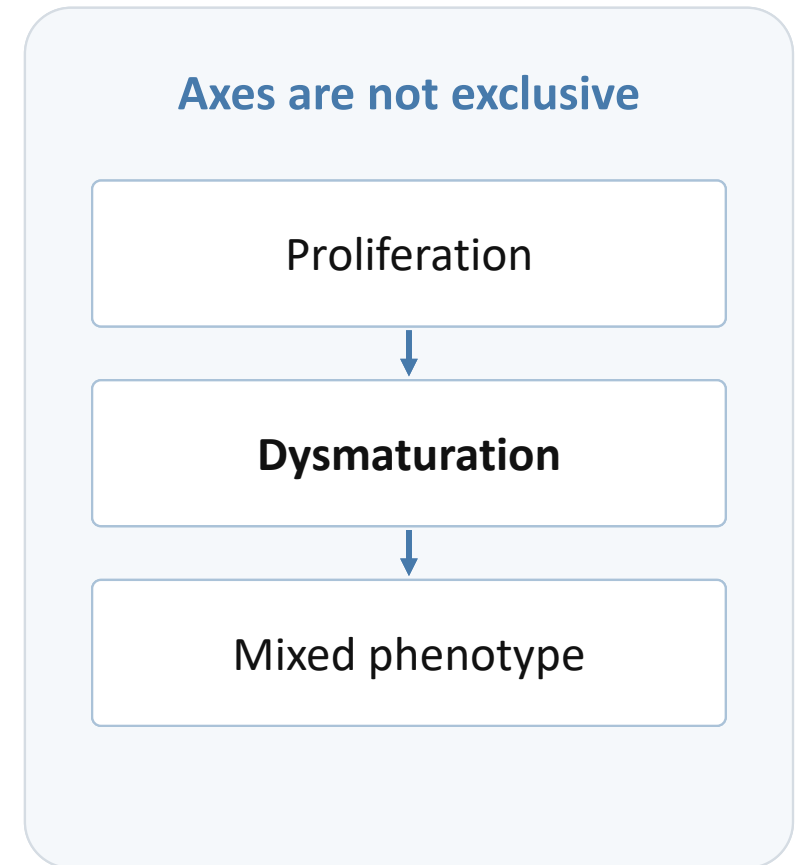
Categorical boundaries can overlap

Mutations influence both proliferative capacity and differentiation.

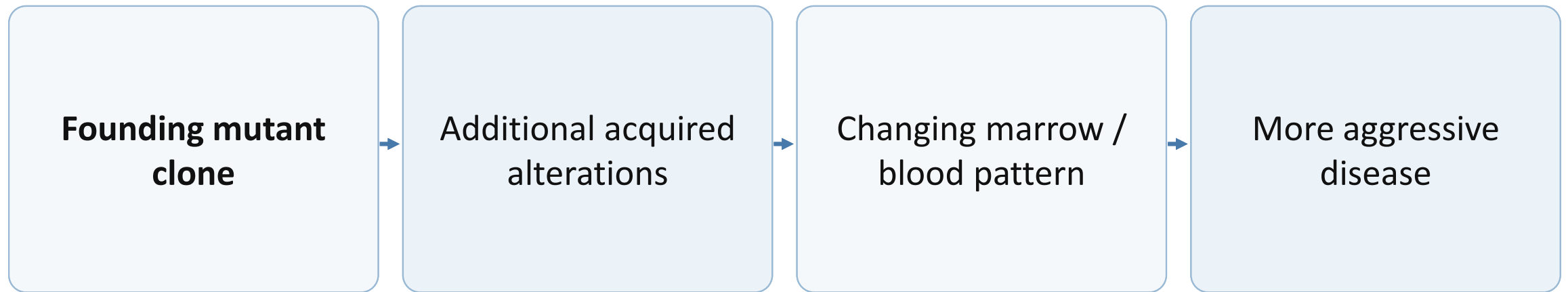
Some myeloid disorders display mixed myelodysplastic and myeloproliferative features.

Morphology and molecular findings may place a case between familiar patterns.

A single count should not override the integrated clinicopathologic picture.



A clonal disorder can evolve over time



Progression commonly involves the emergence or expansion of genetically altered subclones.

AML is a frequent endpoint of progression

Both MDS and several MPNs can transform to acute myeloid leukemia.

Progression is accompanied by increasing blast production and loss of effective hematopoiesis.

The risk and tempo vary substantially among underlying diseases.

A change in counts, symptoms, or blast burden may signal biological evolution.

Clonal progression

Stable clone

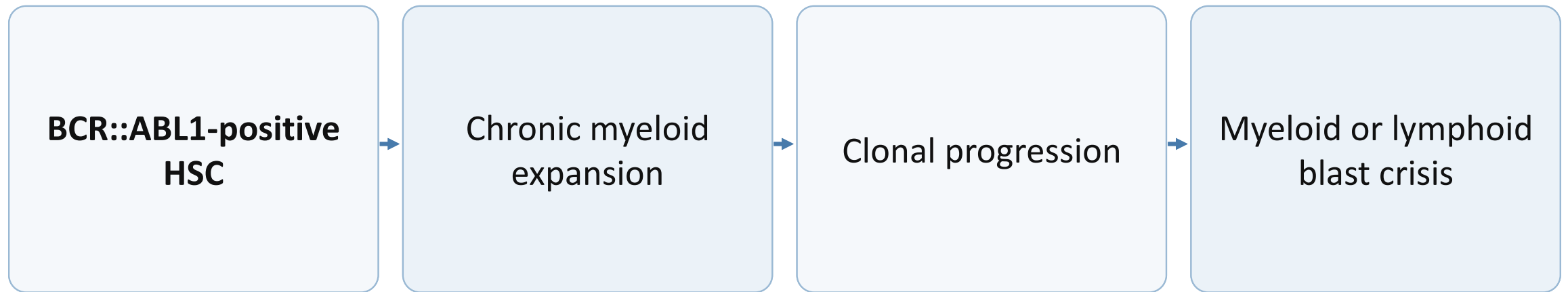


Subclone expands



AML transformation

CML demonstrates pluripotent stem-cell origin



Lymphoid blast crisis supports origin upstream of myeloid / lymphoid lineage commitment.

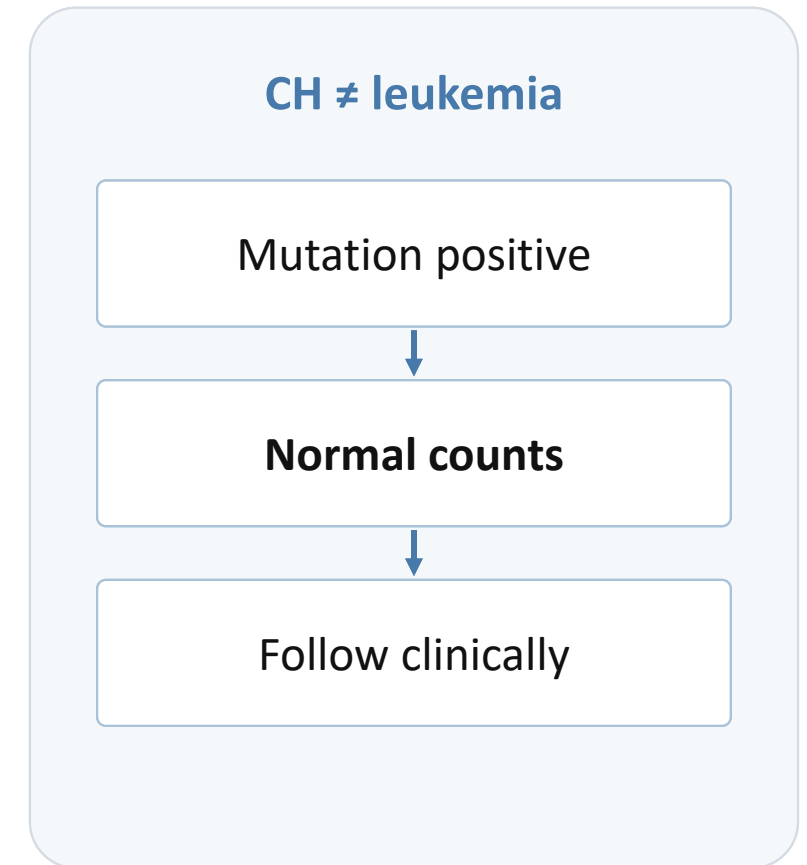
Clonal hematopoiesis may precede overt malignancy

Acquired cancer-gene mutations can create a detectable blood-cell clone before cytopenias appear.

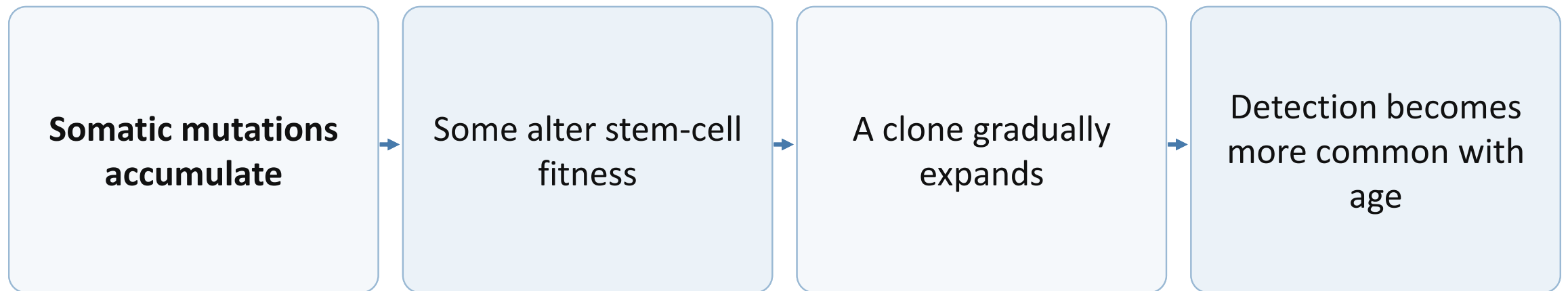
This state in people whose blood counts remain normal.

It is a precursor state, not itself equivalent to AML, MDS, or MPN.

Additional biological context determines whether progression occurs.



Age expands the opportunity for selected clones



Frequent involvement of DNMT3A and TET2 in clonal hematopoiesis.

Clonal hematopoiesis: What the definition requires

Acquired mutation

At least one pathogenic alteration in a cancer-associated gene

Detectable clone

The chapter discusses a conventional sequence-read fraction threshold

Normal counts

No overt count abnormality defining a myeloid malignancy

Mutation detection must be interpreted in clinical context, not as an automatic cancer diagnosis.

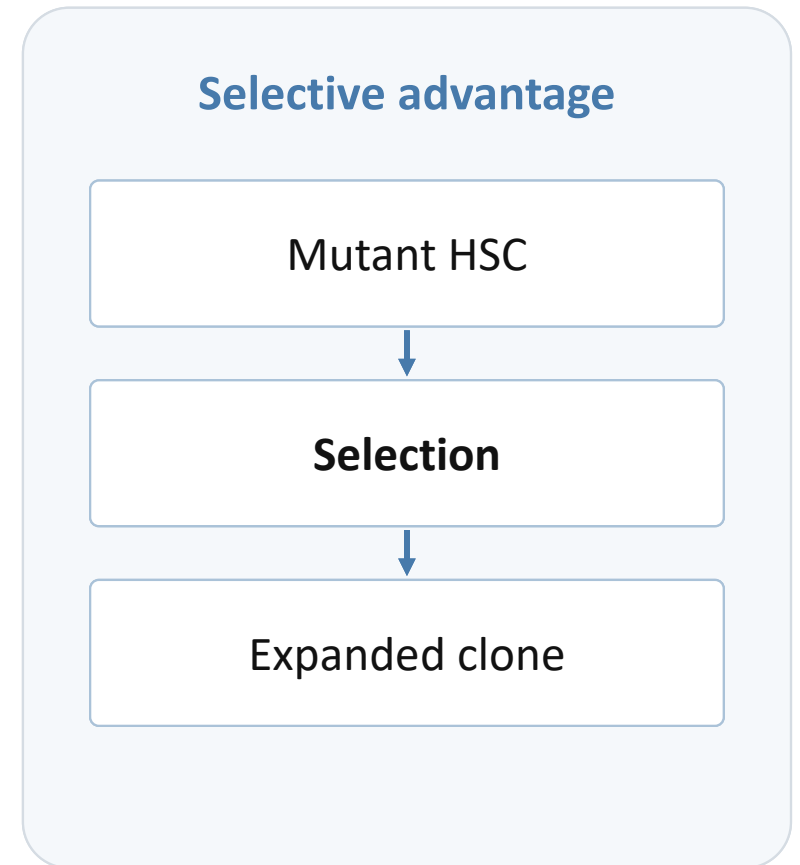
The biology of clonal hematopoiesis is selective

Most mutations arising over life do not confer an advantage.

Occasional changes in oncogenes or tumor suppressors promote stem-cell survival or growth.

TET2 and DNMT3A regulate epigenetic programs that influence differentiation.

Expanded clone size can increase the likelihood of later neoplasia.



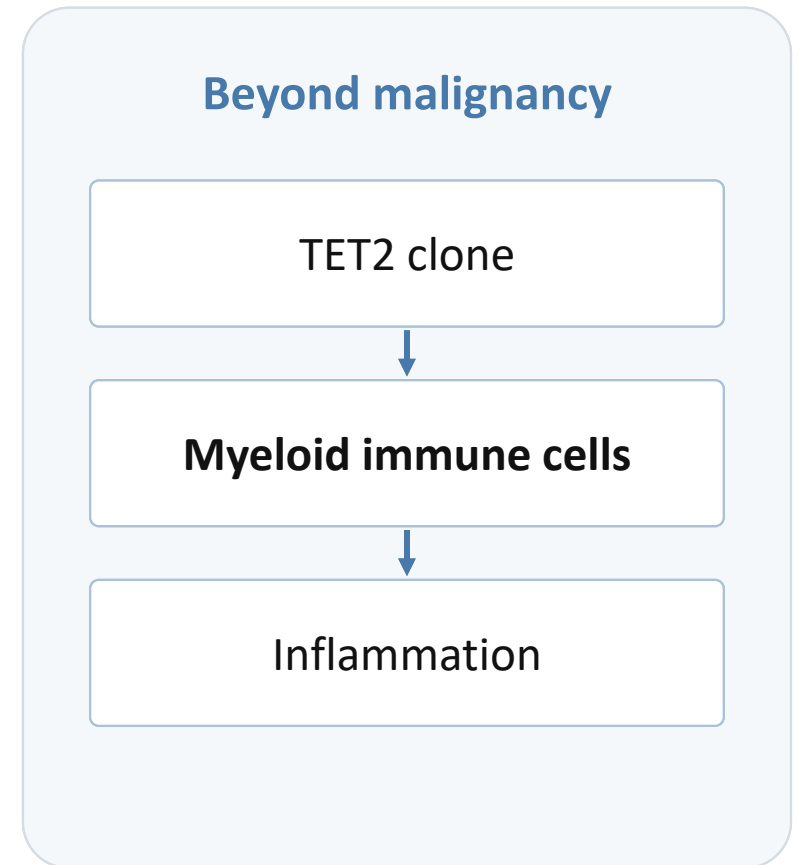
Clonal hematopoiesis has consequences beyond cancer

The chapter associates clonal hematopoiesis with systemic proinflammatory effects.

Clones carrying TET2 alterations are especially linked to monocyte/macrophage reprogramming.

Reported associations include greater severity of atherosclerosis and other inflammatory disease.

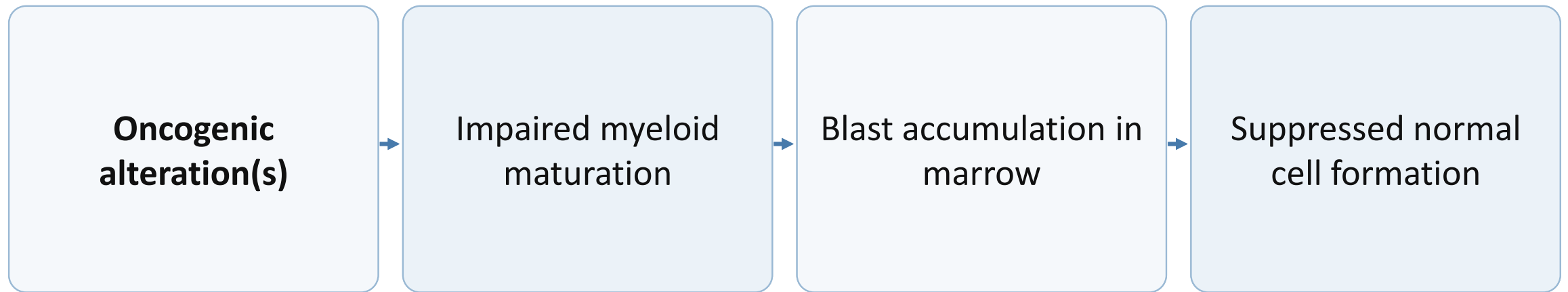
Association is not synonymous with inevitable malignant transformation.



Clonal precursor, dysplasia, and leukemia differ

State	Peripheral counts	Dominant marrow event
Clonal hematopoiesis	Normal by definition	Selected mutation-bearing clone
MDS	Cytopenias common	Dysmaturation / ineffective hematopoiesis
AML	Cytopenias common	Expansion of immature blasts

Acute myeloid leukemia arrests differentiation



AML is defined by immature myeloid progenitors, not merely by a high circulating leukocyte count.

Marrow failure drives many AML symptoms

Anemia contributes to fatigue and weakness.

Neutropenia or dysfunctional granulocytes increase infection susceptibility.

Thrombocytopenia produces mucosal bleeding, petechiae, and ecchymoses.

Symptoms may develop over weeks to months as marrow replacement advances.

Loss of normal production

Blasts



Marrow failure



Infection / bleeding

AML morphology centers on immature myeloid cells

Myeloblasts often show delicate nuclear chromatin and prominent nucleoli.

Azurophilic cytoplasmic granules may be visible.

Auer rods support myeloid differentiation when identified.

Blood blast counts vary widely; Marrow evaluation may be decisive.

Morphology → workup

Immature cells



Granules ± Auer rods



Lineage confirmation

Auer rods are a useful diagnostic clue

Appearance

Needle-like azurophilic cytoplasmic inclusions

Interpretation

Strongly support myeloid differentiation in a blast

Context

Especially conspicuous in acute promyelocytic leukemia

Morphologic description only; No synthetic specimen is presented.

Lineage confirmation combines morphology and markers

Blasts can be difficult to classify as myeloid versus lymphoid by appearance alone.

Myeloperoxidase and myeloid surface antigens contribute to identification.

Flow cytometry defines populations and degrees of maturation.

Genetic findings then refine the disease category and clinical implications.

Integrated lineage workup

Immature population



Myeloid markers

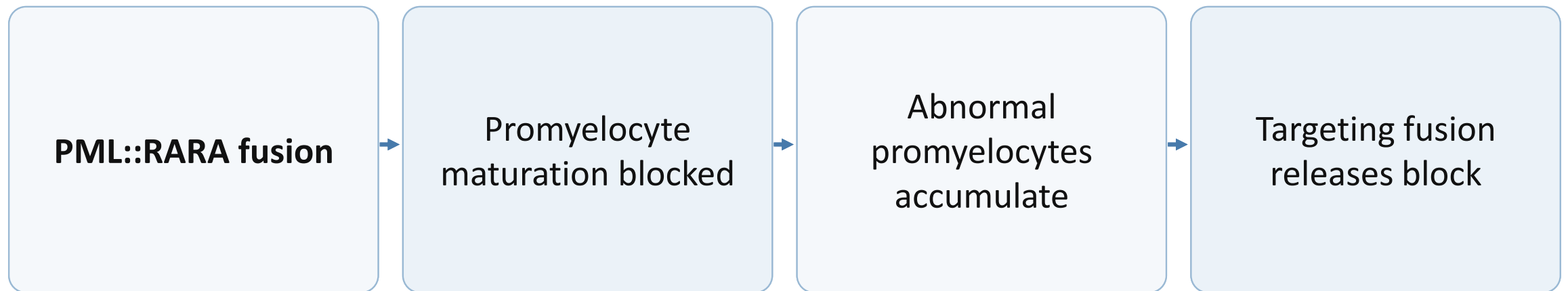


Genetic subtyping

Molecular lesions in AML are functionally diverse

Altered program	Examples in Robbins	Biological effect
Transcription factors	RUNX1::RUNX1T1, CBFB::MYH11	Impaired differentiation
Signaling	FLT3, RAS alterations	Growth / survival drive
Epigenetic regulation	IDH1, IDH2; chromatin regulators	Altered gene-expression state
Genome surveillance	TP53 dysfunction	High-risk biology

Acute promyelocytic leukemia is mechanistically distinctive



All-trans-retinoic acid and arsenic trioxide as therapies that counter this lesion.

APL carries a particular bleeding danger

Promyelocytic leukemia can produce prominent coagulation abnormalities.

Disseminated intravascular coagulation is a major early risk.

Promyelocytes may contain numerous Auer rods, sometimes in bundles.

Recognizing the subtype has immediate clinicopathologic significance.

Early recognition matters

APL clone



Procoagulant effects



Bleeding / DIC

AML is classified increasingly by genetics

AML into genetically defined and differentiation-defined groups.

Recurrent fusions and gene mutations can define biologically distinct entities.

Cytogenetic and molecular results can also inform prognosis and targeted treatment.

Morphology remains necessary but is not sufficient for comprehensive classification.

Complementary evidence

Morphology



Cytogenetics



Molecular profile

Clinical setting adds information in AML

De novo disease

Some younger patients have recurrent balanced rearrangements

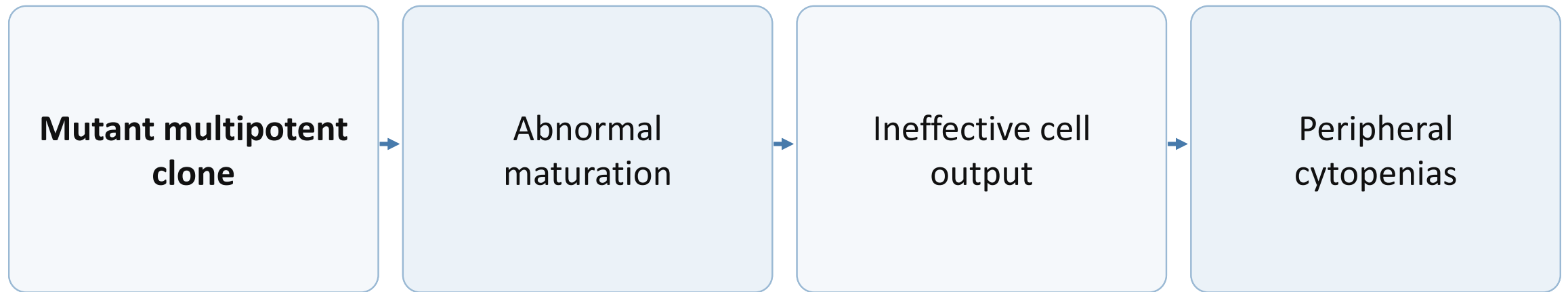
After genotoxic therapy

Chromosome 5 / 7 abnormalities and TP53 lesions may occur

Older adulthood

Mutations overlapping clonal hematopoiesis or MDS are common

Myelodysplastic neoplasms produce cells inefficiently



A marrow rich in precursors can coexist with anemia, neutropenia, and thrombocytopenia.

MDS is clonal and may affect several lineages

Erythroid, granulocytic, monocytic, and megakaryocytic maturation may be disordered.

The pattern and severity of dysplasia vary by patient.

Marrow is usually hypercellular but may be normocellular or hypocellular.

Cytopenias are often the clinical consequence of ineffective hematopoiesis.

Marrow–blood discordance

Dysplastic precursor



Ineffective output



Cytopenias

Erythroid dysplasia has specific morphologic patterns

Erythroblasts may have irregular or budding nuclei.

Megaloblastoid change reflects disordered nuclear/cytoplasmic maturation.

Ring sideroblasts reflect perinuclear iron-laden mitochondria on iron staining.

These features must be interpreted with the overall workup, not in isolation.

Erythroid dysmaturation

Abnormal nuclei



Ring sideroblasts



Anemia

Granulocytic dysplasia can be recognized in blood

Hypogranulation reflects abnormal granulocyte maturation.

Pseudo–Pelger-Huët neutrophils show markedly reduced nuclear segmentation.

Abnormal granulation and other cytoplasmic changes may occur.

Peripheral smear abnormalities can direct attention to marrow dysplasia.

Granulocyte dysmaturation

Hyposegmentation



Hypogranulation



Dysplasia

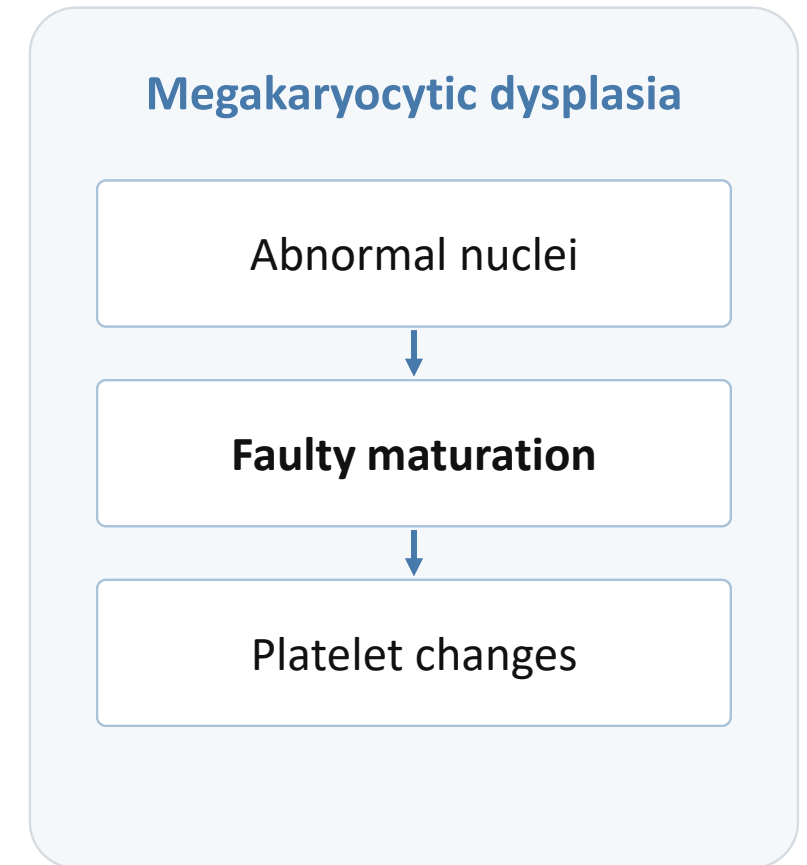
Megakaryocytic dysplasia alters nuclear architecture

Some megakaryocytes have a single, poorly lobated nucleus.

Others show multiple separate nuclei rather than one multilobated nucleus.

Platelet abnormalities can accompany dysplastic megakaryopoiesis.

Dysplasia in multiple lineages strengthens a coherent MDS interpretation.



MDS is associated with several molecular programs

Epigenetic regulators

DNA methylation, histone and chromatin regulation

Splicing factors

RNA-processing abnormalities; Significance varies

Transcription factors

Disordered lineage maturation; RUNX1 example

No single listed mutation is by itself a substitute for integrated diagnosis.

Genotoxic exposure changes the MDS context

MDS can arise without known prior therapy or after cytotoxic treatment / radiation.

Therapy-related cases tend to have adverse cytogenetic or molecular features.

The source identifies recurrent chromosome 5 and 7 abnormalities.

Previous treatment history is integral to marrow evaluation.

Clinical context matters

Prior genotoxicity



Acquired clonal injury



MDS risk

MDS prognosis reflects severity and clonal genetics

Blast burden

Higher blasts indicate more advanced biology

Cytopenias

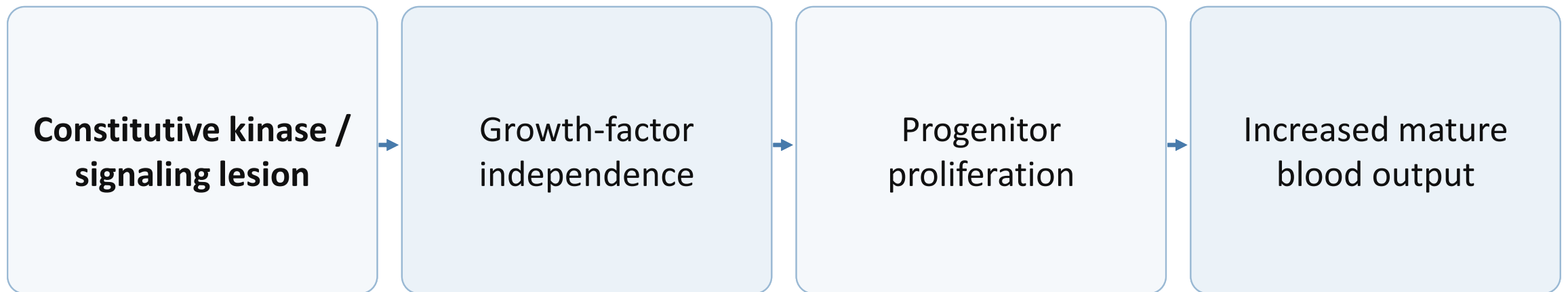
More severe deficits increase clinical consequences

Cytogenetics

Complex abnormalities often indicate worse outcomes

Substantial heterogeneity in progression to AML.

Myeloproliferative neoplasms escape growth control

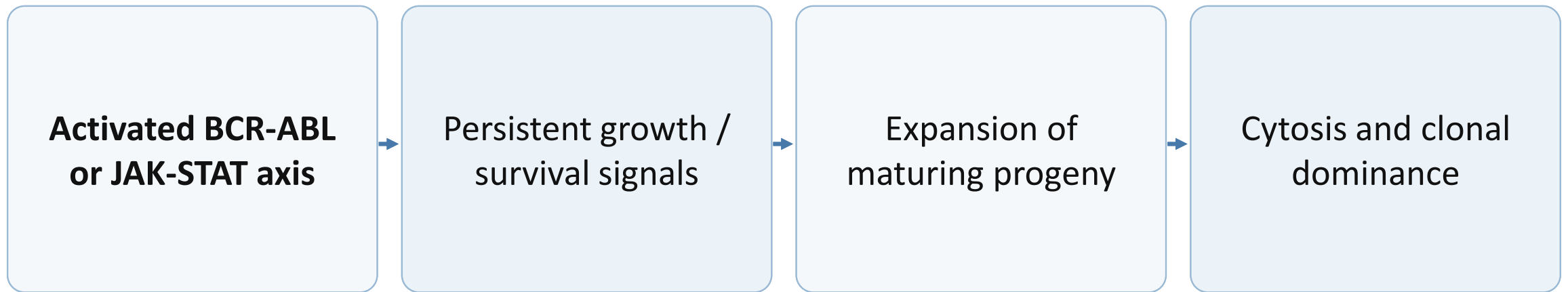


Unlike classic AML, differentiation is generally preserved in chronic-phase MPNs.

The main MPNs differ by dominant lineage

Disorder	Driver context	Dominant clinical / pathologic pattern
CML	BCR::ABL1	Granulocytic proliferation
Polycythemia vera	Usually JAK2	Red-cell excess / panmyelosis
Essential thrombocythemia	JAK2, CALR, or MPL	Platelet excess
Primary myelofibrosis	JAK2, CALR, or MPL often	Atypical megakaryocytes / fibrosis

Ligand-independent signaling explains proliferative output



The figure abstracts several kinase-driven pathways; Individual lesions are not interchangeable.

BCR::ABL1 is the defining CML lesion

A fusion of sequences from BCR and ABL1 encodes an active tyrosine kinase.

The classic Philadelphia rearrangement is t(9;22).

Cryptic rearrangements may require molecular testing.

The kinase promotes pathways supporting progenitor proliferation and survival.

CML-defining fusion

T(9;22)



BCR::ABL1



Active kinase

CML marrow and blood show granulocytic expansion

Marrow contains abundant maturing granulocytic precursors.

Circulating granulocytes appear at several stages of maturation.

Basophilia and frequently thrombocytosis accompany the pattern.

Splenic enlargement may follow extramedullary hematopoiesis.

Chronic phenotype

Myeloid expansion

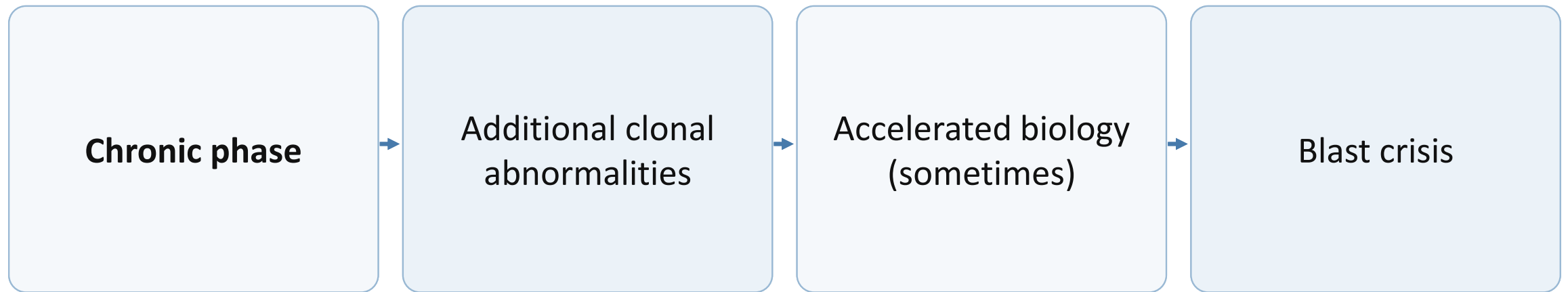


Left shift / basophilia



Splenomegaly

CML can progress from chronic disease to blast crisis



Blast crisis can be myeloid or lymphoid, reflecting an early stem-cell origin.

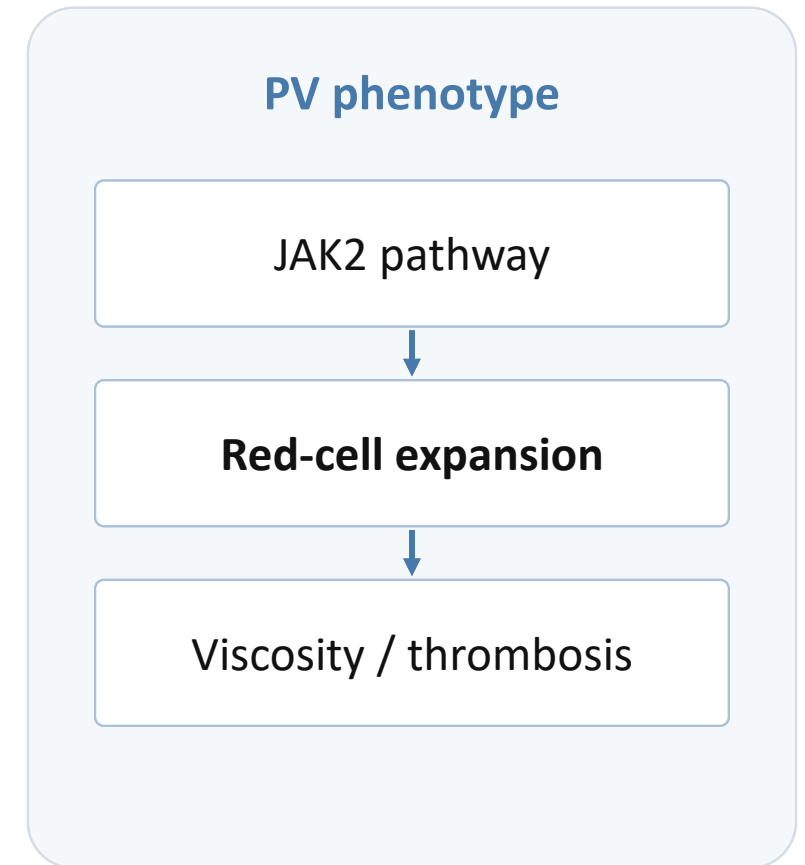
Polycythemia vera is more than isolated erythrocytosis

The textbook characterizes marrow production as panmyelosis.

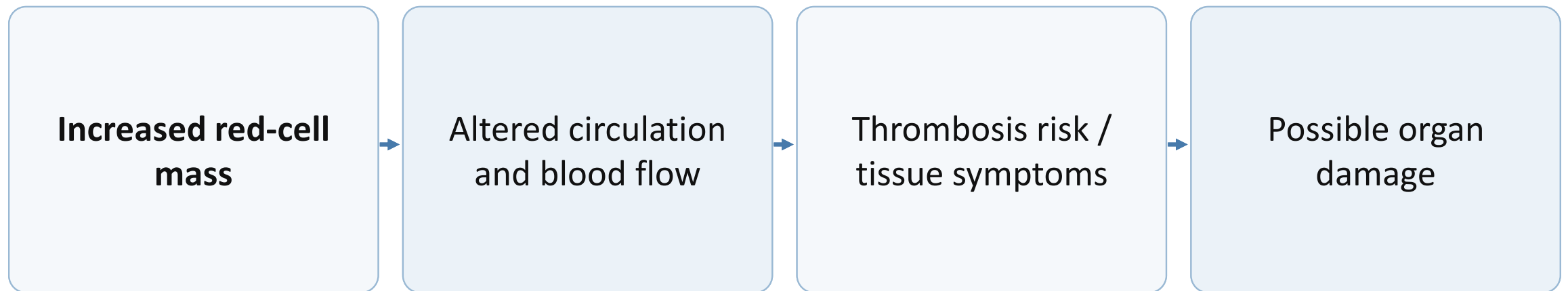
Red-cell mass is the chief determinant of hyperviscosity symptoms.

JAK2 activation reduces dependence on erythropoietin signaling.

Thrombotic and bleeding events are important complications.



In polycythemia vera, viscosity drives injury



A normal-looking hematocrit does not exclude PV when iron deficiency modifies erythrocyte production.

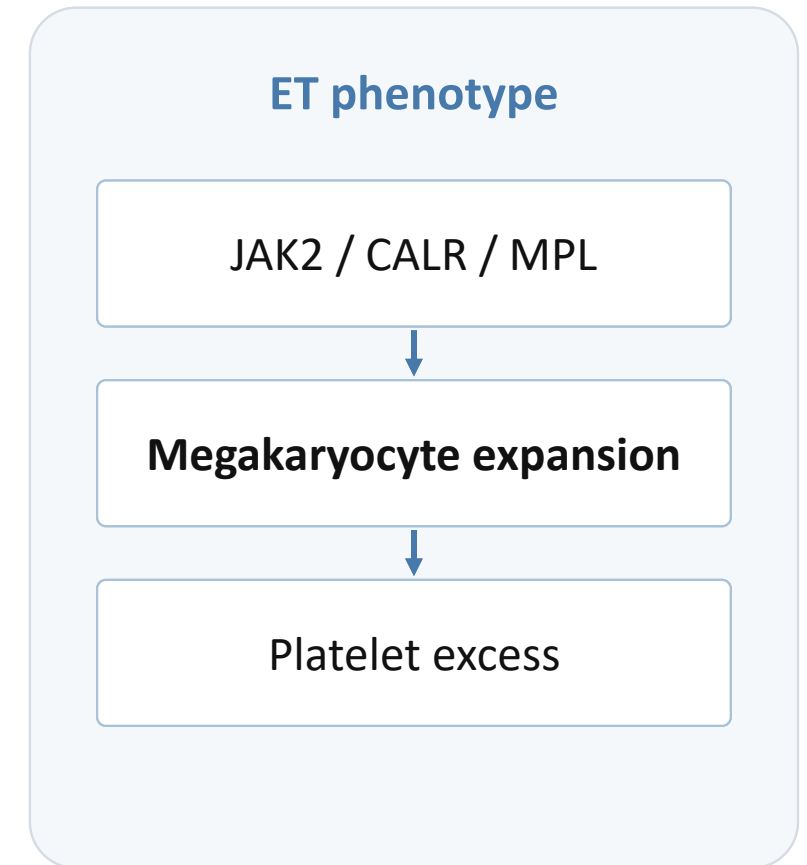
Essential thrombocythemia is clonal thrombopoiesis

Platelet production is increased despite normal growth controls.

JAK2, CALR, and MPL mutations converge on thrombopoietin-related signaling.

Marrow shows increased megakaryocytes, often unusually large.

Relative absence of overt fibrosis separates ET from fibrotic myelofibrosis.



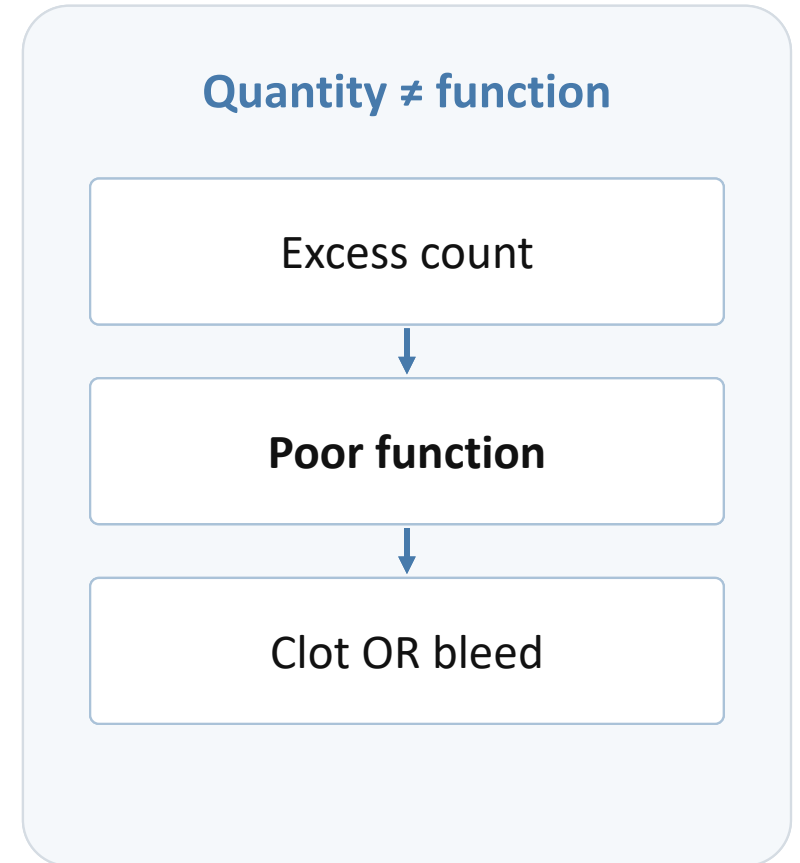
Excess platelets can coexist with bleeding

The platelets may be both numerous and functionally abnormal.

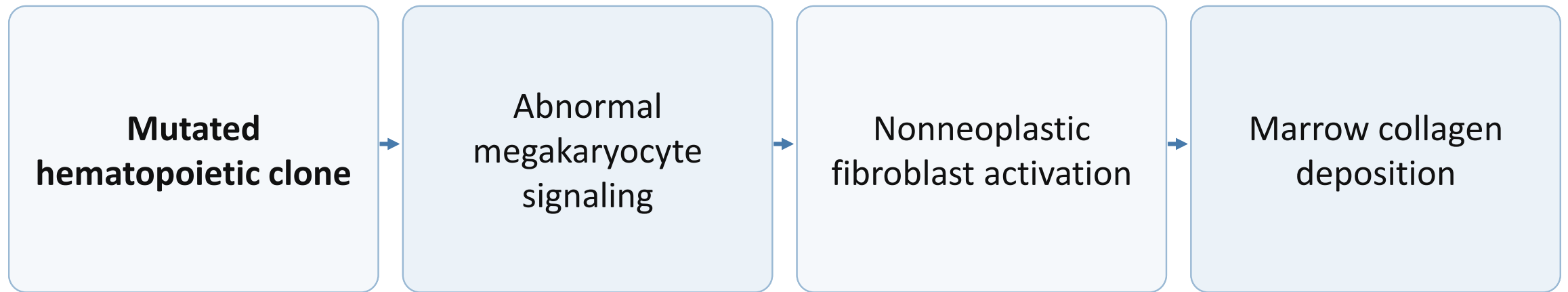
ET produces thromboses as well as spontaneous bleeding.

Acquired von Willebrand disease can contribute to bleeding in some patients.

Reactive thrombocytosis must be excluded when appropriate.



Primary myelofibrosis begins with a neoplastic clone



Fibroblasts depositing collagen are reactive rather than the primary neoplastic population.

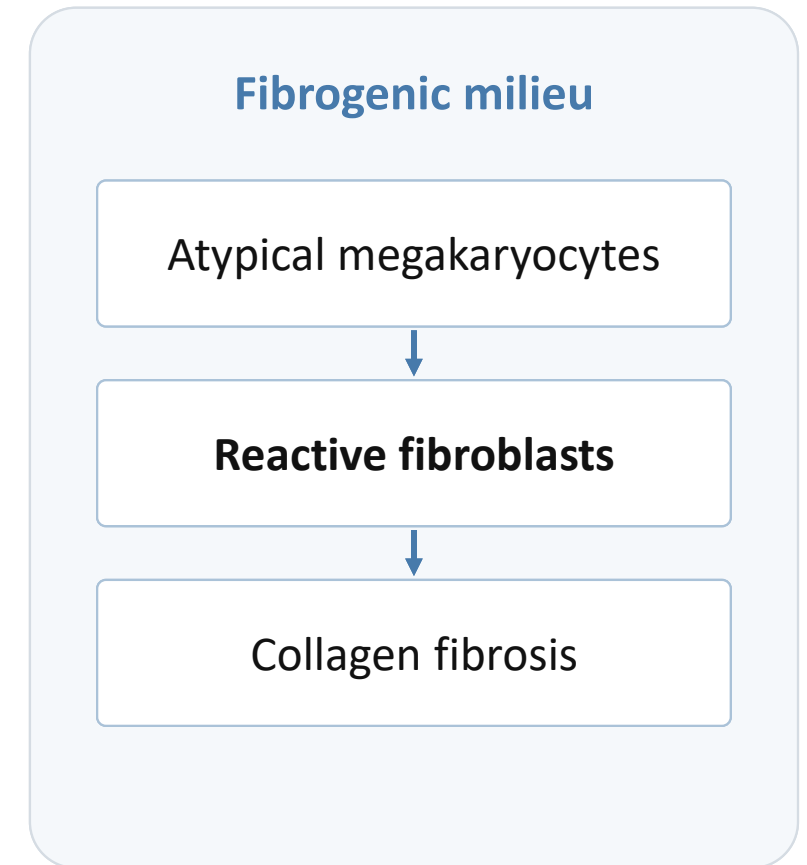
Myelofibrosis distorts marrow architecture

Megakaryocytes can be clustered with atypical bulbous or cloud-like nuclei.

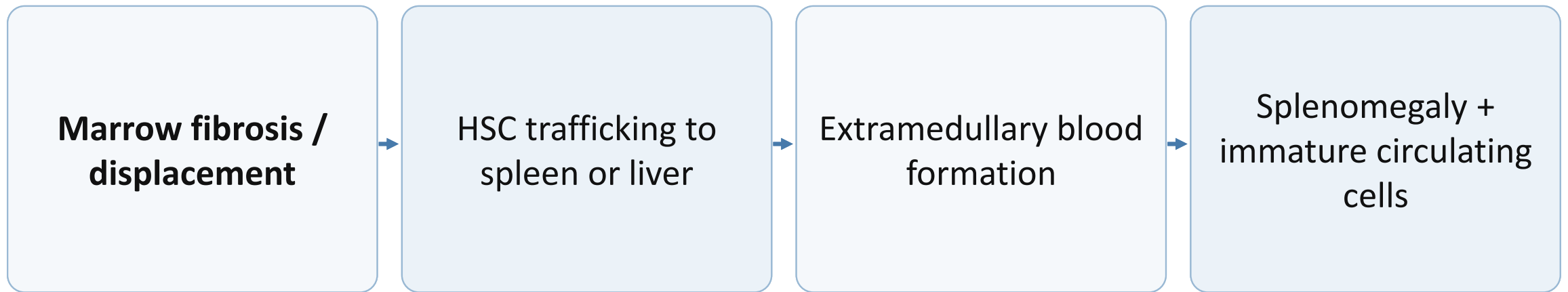
Increasing fibrous tissue displaces functional hematopoietic spaces.

Advanced cases may have marked cytopenias and even osteosclerosis.

Bone marrow biopsy is essential to define the process.



Extramedullary hematopoiesis changes the blood picture



The source associates fibrosed marrow with leukoerythroblastosis and dacryocytes.

Teardrop cells are not specific for myelofibrosis

Dacryocytes may arise during abnormal red-cell transit through distorted marrow.

Nucleated red cells and early granulocytes can enter the blood.

Together these features create a leukoerythroblastic picture.

Other marrow infiltrative diseases can produce the same findings.

Suggestive, not unique

Distorted marrow



Cell deformation

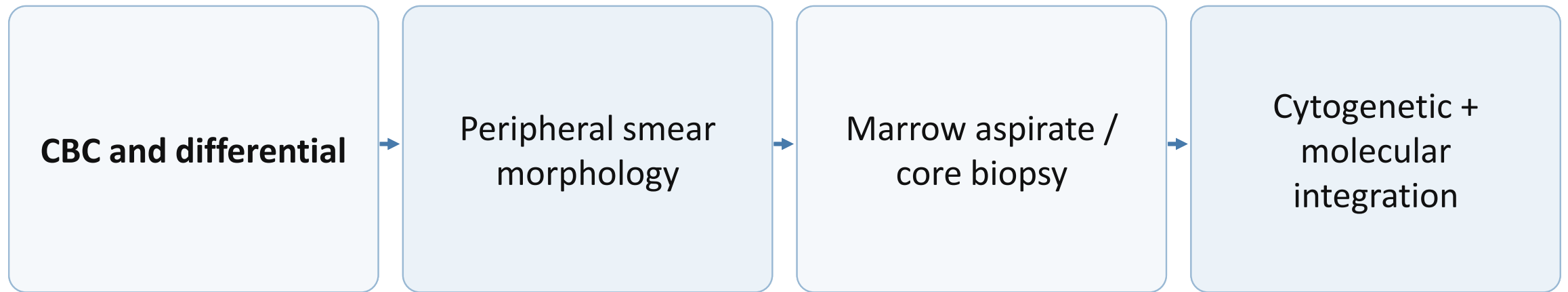


Dacryocytes

MPNs share complications but not identical mechanisms

Phenotype	Dominant mechanism	Representative concern
CML	BCR-ABL kinase / granulocytic output	Progression to blast crisis
PV	JAK2-associated erythroid excess	Thrombosis / hyperviscosity
ET	Megakaryocytic output + platelet dysfunction	Thrombosis or hemorrhage
PMF	Megakaryocyte-driven stromal fibrosis	Marrow failure / splenomegaly

Start diagnosis with the dominant blood phenotype



The order is a diagnostic framework, not a replacement for entity-specific criteria.

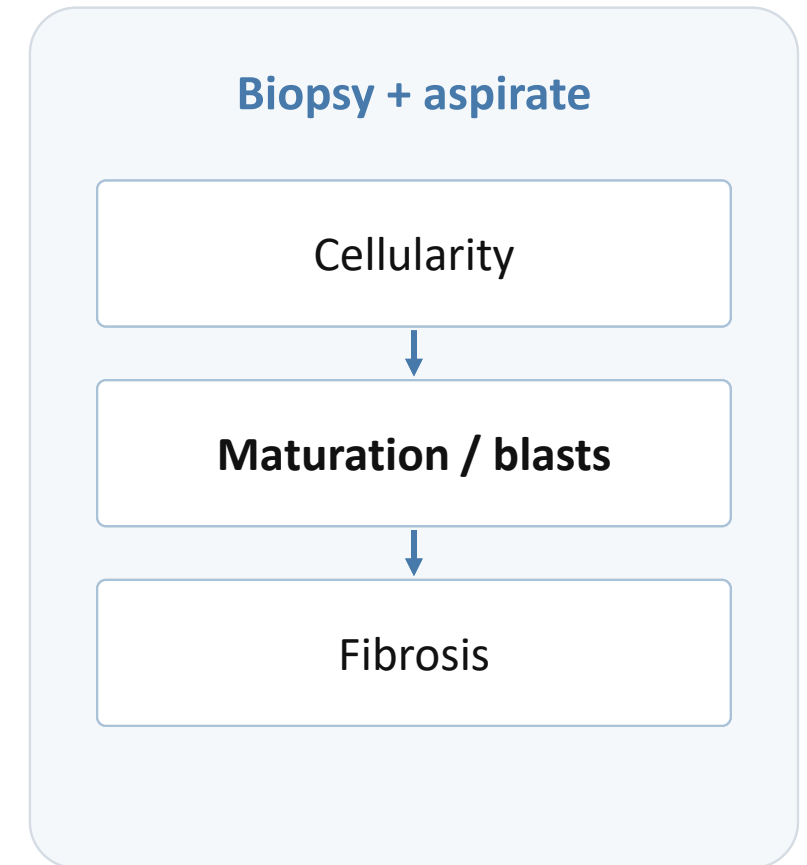
Marrow morphology resolves apparently contradictory counts

Identify blasts, differentiated precursors, dysplasia, and megakaryocytic pattern.

Assess marrow cellularity and architecture rather than counts alone.

Evaluate stromal fibrosis when clinically indicated.

Interpret the marrow in the setting of circulating counts and symptoms.



Molecular testing establishes identity and mechanism

Clinical suspicion	Key molecular context	Diagnostic value
CML	BCR::ABL1	Defines the disease
Classic Ph-negative MPN	JAK2 / CALR / MPL	Supports clonal kinase signaling
AML	Recurrent fusions / mutated genes	Subtype and risk information
MDS	Mutation profile + cytogenetics	Supports integrated classification

Important interpretation traps

A normal leukocyte count does not exclude AML when blasts remain in marrow.

A hypercellular marrow does not guarantee effective peripheral production.

Reactive thrombocytosis can resemble ET.

Iron deficiency may mask erythrocytosis; Dacryocytes are not unique to PMF.

Integrate evidence

Single test



Context missing



Wrong category

Case: Cytopenias with circulating blasts

Clinical pattern

New fatigue, mucosal bleeding, low platelets; Marrow contains many immature cells.

Reasoning

AML is favored: An immature myeloid clone suppresses normal hematopoiesis. Confirm lineage and genetics.

The source does not support diagnosis from symptoms alone.

Case: Hypercellular marrow with peripheral anemia

Clinical pattern

Persistent cytopenia; Marrow contains numerous precursors with dysplastic nuclei.

Reasoning

Consider MDS: Precursor expansion coexists with ineffective output. Exclude mimics and integrate genetics.

Hypocellularity is not a prerequisite for MDS.

Case: Leukocytosis with left-shifted granulocytes

Clinical pattern

Marked granulocytic proliferation, basophilia, splenic enlargement.

Reasoning

CML enters the differential. BCR::ABL1 detection establishes the defining molecular lesion.

Mature granulocytic expansion differs from an undifferentiated blast population.

Case: Splenomegaly, anemia, dacryocytes

Clinical pattern

Leukoerythroblastosis, teardrop erythrocytes, and a large spleen.

Reasoning

Marrow fibrosis / displacement is likely. Assess megakaryocytes, reticulin, and alternative infiltrative causes.

The smear suggests a mechanism; It does not independently prove primary myelofibrosis.

A single explanatory model organizes the family

Proliferation

How strongly does the clone expand?

Differentiation

Are mature cells produced normally, poorly, or not at all?

Evolution

Has the clone acquired fibrosing or blast-transforming behavior?

These three questions organize phenotype without replacing disease-specific diagnostic criteria.

The major patterns in one view

Family	Dominant problem	Typical clue	Potential course
AML	Blast arrest	Marrow failure	Rapid clinical deterioration
MDS	Ineffective maturation	Dysplasia + cytopenias	AML progression
MPN	Excess mature-cell output	Cytoses / extramedullary sites	Spent fibrosis or leukemia

Final synthesis: Diagnose the mechanism and its stage

Establish whether the dominant process is blastic, dysplastic, or proliferative.

Relate the phenotype to its progenitor compartment and mutated cellular program.

Read the smear, marrow, and molecular findings together.

Account for overlap and clonal evolution rather than assuming static boundaries.

Principal reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).

Chapter 13: Diseases of White Blood Cells, Lymph Nodes, Spleen, and Thymus.

Myeloid Neoplasms, pp. 560–561; contextual disease sections, pp. 561–571.

Text and concepts are paraphrased; diagrams are original editable teaching schematics.