

Polycythemia Vera

Clonal panmyelosis · JAK2 signaling · Vascular complications

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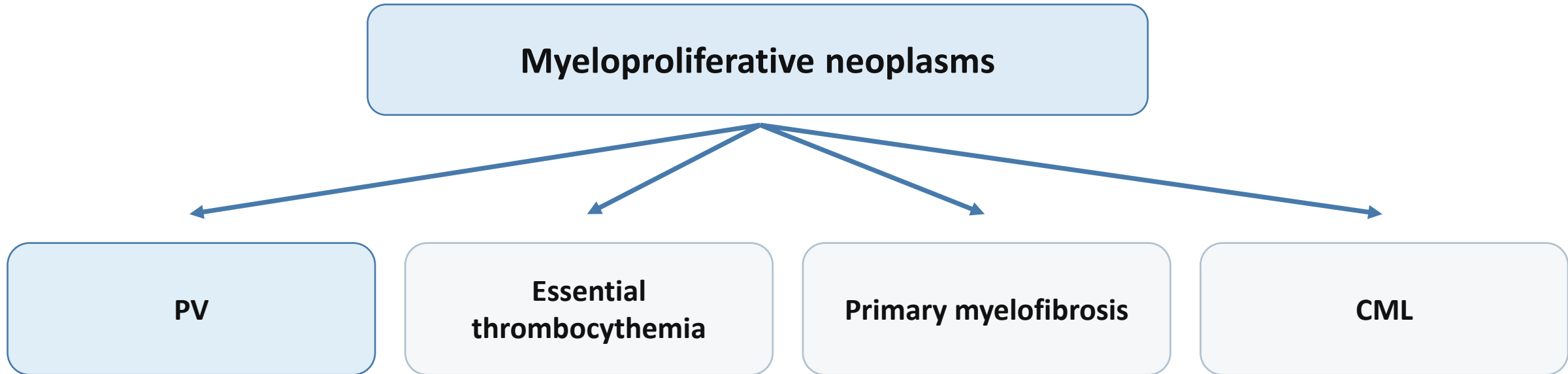
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Learning objectives

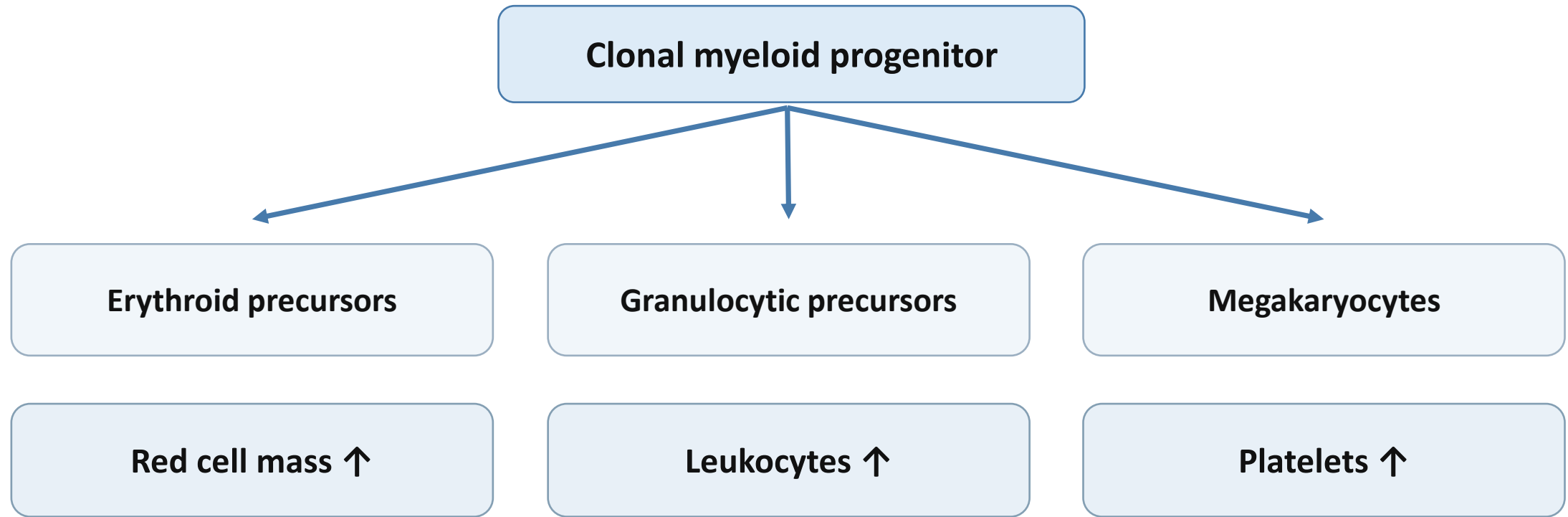
- Explain how JAK2 activation produces growth-factor–independent hematopoiesis.
- Recognize panmyelosis and its marrow and blood manifestations.
- Connect erythrocytosis and platelet dysfunction to vascular events.
- Distinguish PV from relative/secondary polycythemia and related MPNs.
- Describe post-PV myelofibrosis and leukemic transformation.

PV within the myeloproliferative neoplasms



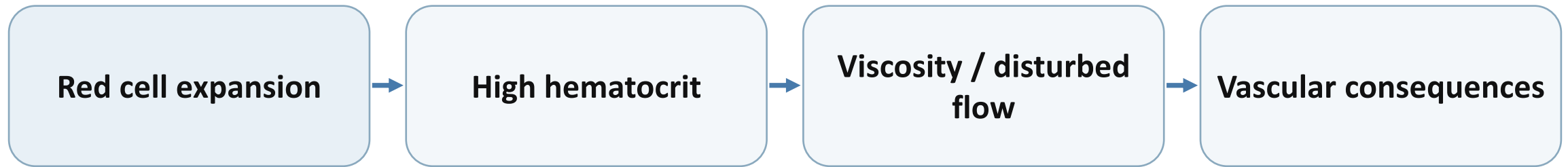
Classification context: Kinase signaling abnormalities with overlapping phenotypes

The defining marrow phenotype is panmyelosis



Simplified lineage model — not a marrow section

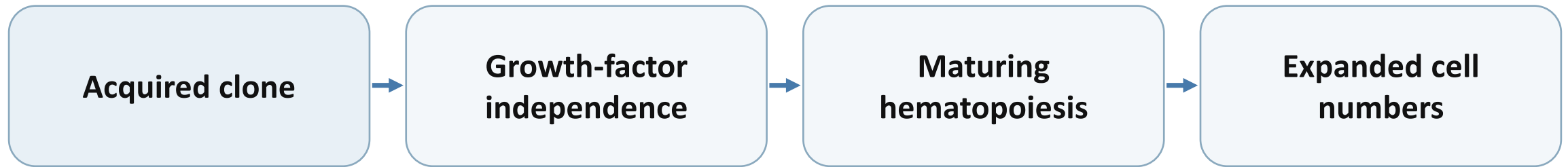
Why red cell expansion matters most



Conceptual causal sequence — native, editable schematic

- Increased red cell mass elevates the hematocrit.
- Viscosity and altered microvascular flow connect cell production to symptoms.
- The other two lineages contribute to thrombosis and hemorrhage.

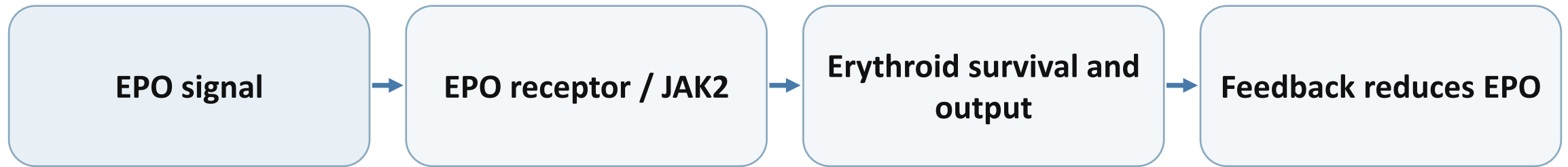
PV is clonal rather than a physiologic response



Conceptual causal sequence — native, editable schematic

- The proliferating progenitor has acquired an oncogenic signaling alteration.
- The cell responds less to normal hematopoietic growth-factor control.
- Mature circulating cells increase because differentiation is largely preserved.

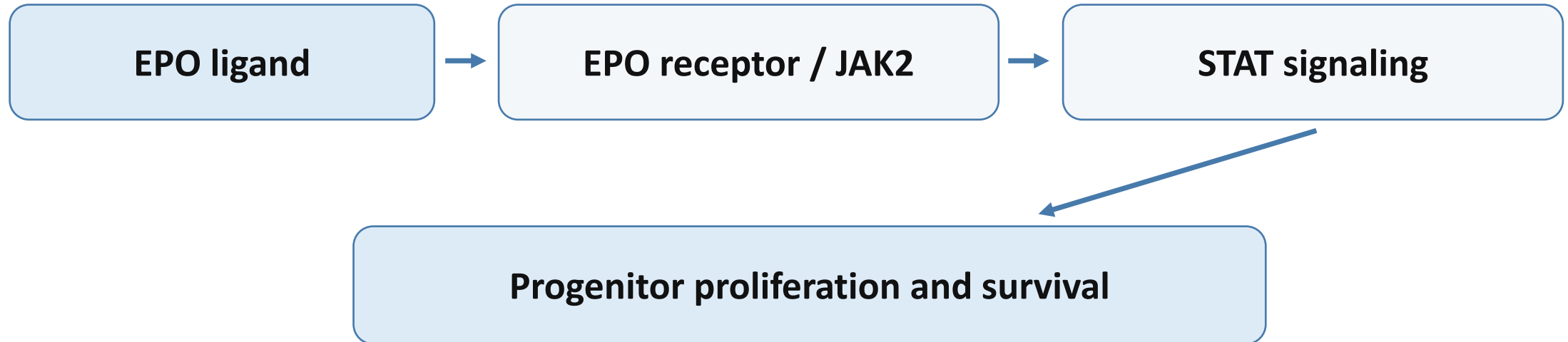
Normal erythropoiesis is EPO responsive



Conceptual causal sequence — native, editable schematic

- Erythropoietin (EPO) stimulates erythroid progenitors through the EPO receptor.
- Intracellular JAK2 participates in receptor-linked growth signaling.
- Rising red cell mass normally suppresses further EPO production.

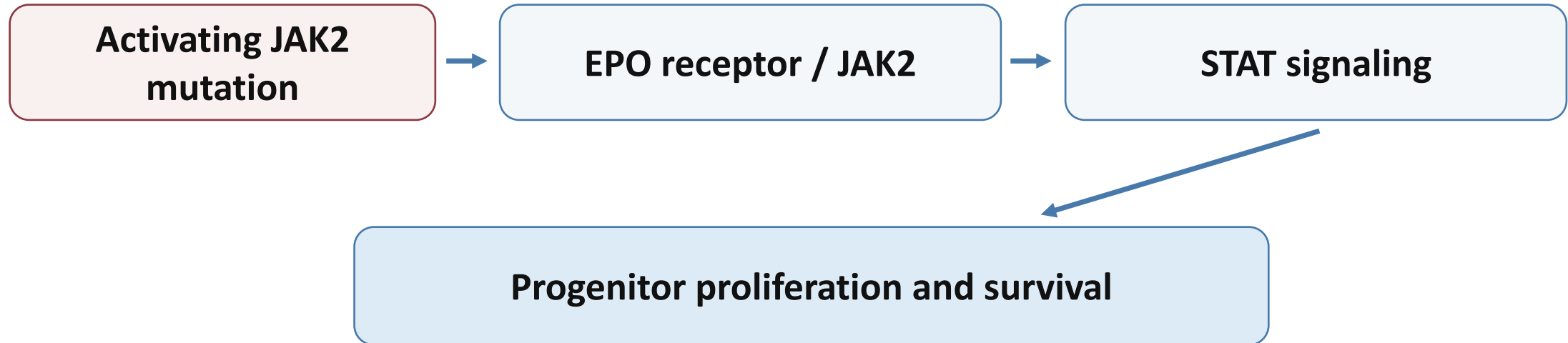
The JAK–STAT axis links receptors to gene expression



- Normal EPO ligand binding activates the receptor-linked JAK2 pathway.
- Activated STAT proteins support erythroid progenitor survival and growth.

Normal receptor signaling schematic

Activating JAK2 mutations bypass normal restraint



- Mutant JAK2 permits signaling with markedly reduced EPO dependence.
- Persistent signaling drives clonal expansion of mature blood elements.

JAK2 V617F is the predominant driver

JAK2 V617F

Valine (V)



Phenylalanine (F)

Residue 617 substitution — not a sequence-scale representation

The JAK2 variant is not the same as the blood-count phenotype

Driver genotype

The mutation establishes proliferative signaling potential.

Disease phenotype

Cell lineage output and marrow context determine observed counts.

The same JAK2 mutation may also occur in related MPN phenotypes.

Growth-factor independence is relative at the bedside

Physiologic erythropoiesis

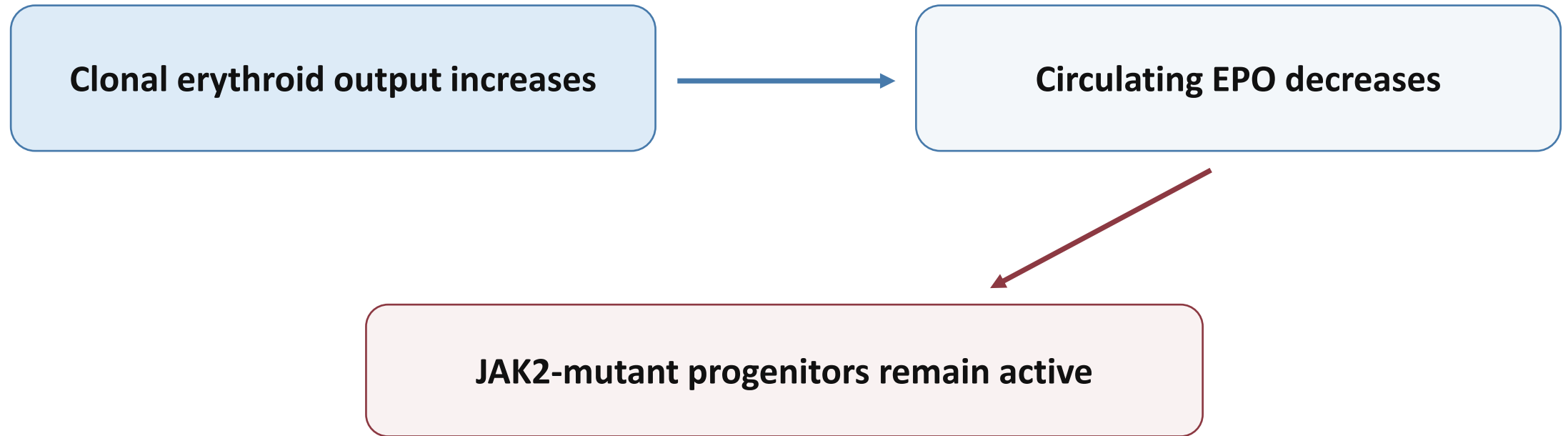
PV progenitors have markedly reduced growth-factor requirements.

PV erythropoiesis

The clinical clue is inappropriate erythropoiesis despite suppressed EPO.

Do not equate a suppressed EPO with absent receptor-signaling activity.

Serum EPO is often suppressed in PV



Suppressed EPO does not switch off an autonomous JAK2 clone

PV and secondary erythrocytosis have opposite EPO logic

PV: Low EPO

PV: An autonomous marrow clone expands red cells despite low EPO.

Secondary: Elevated EPO

Secondary erythrocytosis: Increased EPO drives a compensatory red cell response.

EPO is a discriminating clue, not a stand-alone diagnosis.

Additional JAK2 alleles can influence the phenotype

One mutated allele

The source describes two mutant JAK2 copies in approximately 25%–30% of cases.

Two mutated alleles

Such cases were associated with higher leukocyte counts, splenomegaly, pruritus, and fibrotic progression.

This association is not an individual prognosis for a new patient.

PV proliferates less aggressively than CML

PV / JAK2

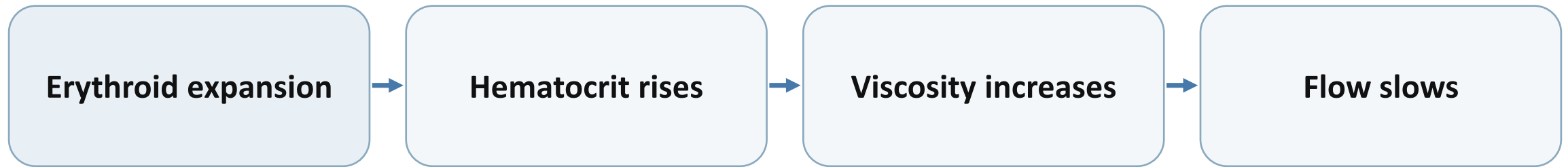
PV generally has less striking leukocytosis and marrow hypercellularity.

CML / BCR::ABL

CML is driven by BCR::ABL and often has pronounced granulocytic expansion.

The two kinases produce distinguishable clinicopathologic phenotypes.

Hematocrit links marrow output to viscosity



Conceptual causal sequence — native, editable schematic

- Higher red cell fraction increases resistance to blood flow.
- Blood sludging becomes particularly relevant in low-pressure vascular beds.
- This hemodynamic change contributes to microvascular and major vascular events.

The venous circulation is especially vulnerable

RBC-rich blood in low-pressure peripheral vessels



Distension + sluggish transit → increased local deoxygenation

Circulatory illustration — not an anatomic vessel cross-section

Platelets are numerous but not necessarily normal

Platelet quantity ↑

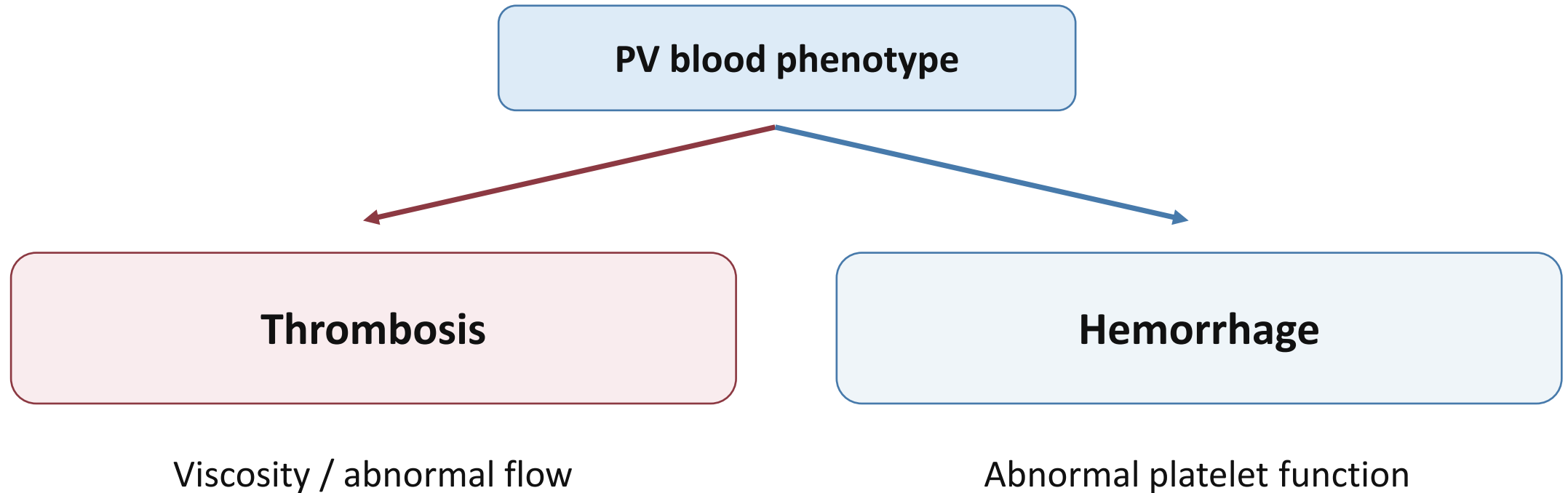
Thrombocytosis frequently accompanies erythrocytosis.

Platelet quality impaired

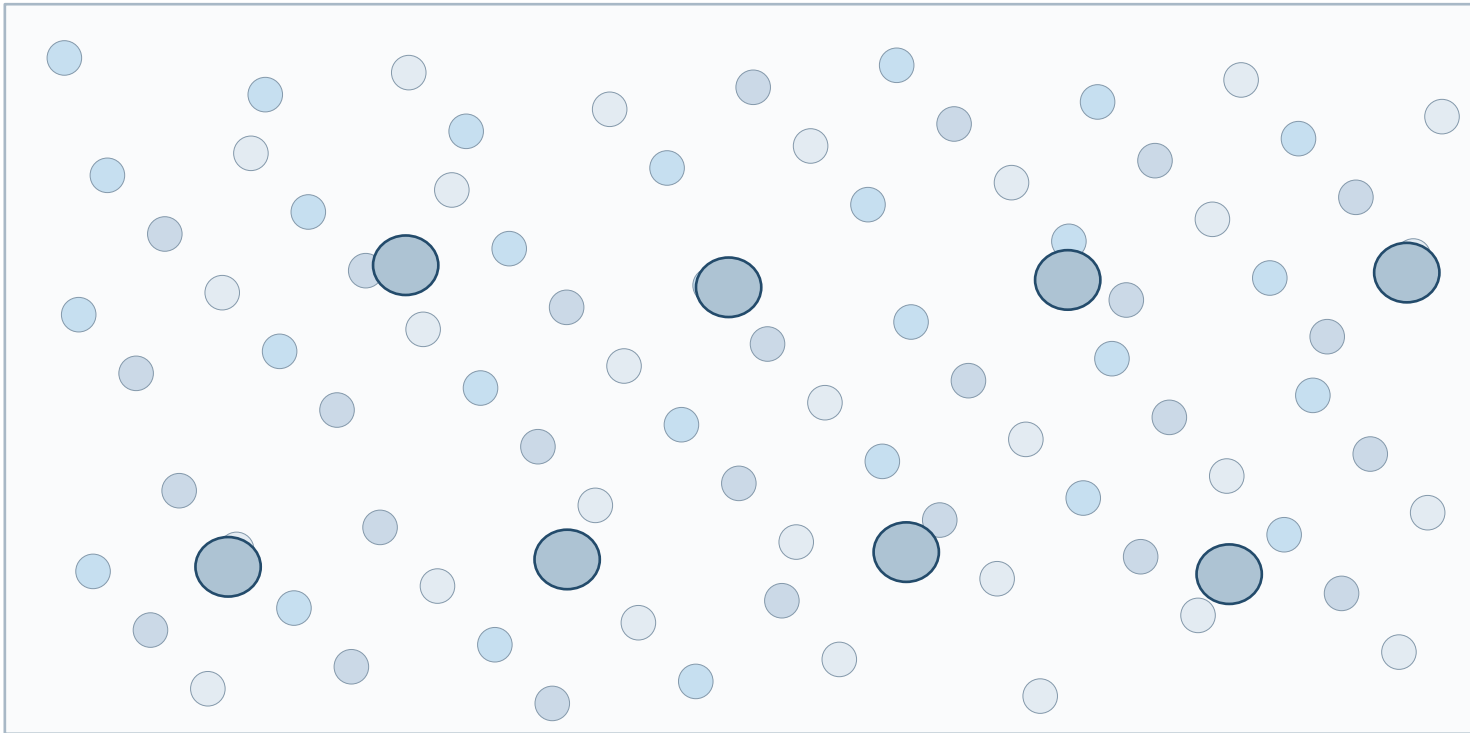
Large, morphologically abnormal platelets may circulate.

Aggregation studies can demonstrate qualitative platelet defects.

Thrombosis and hemorrhage can coexist



Bone marrow morphology: Hypercellularity



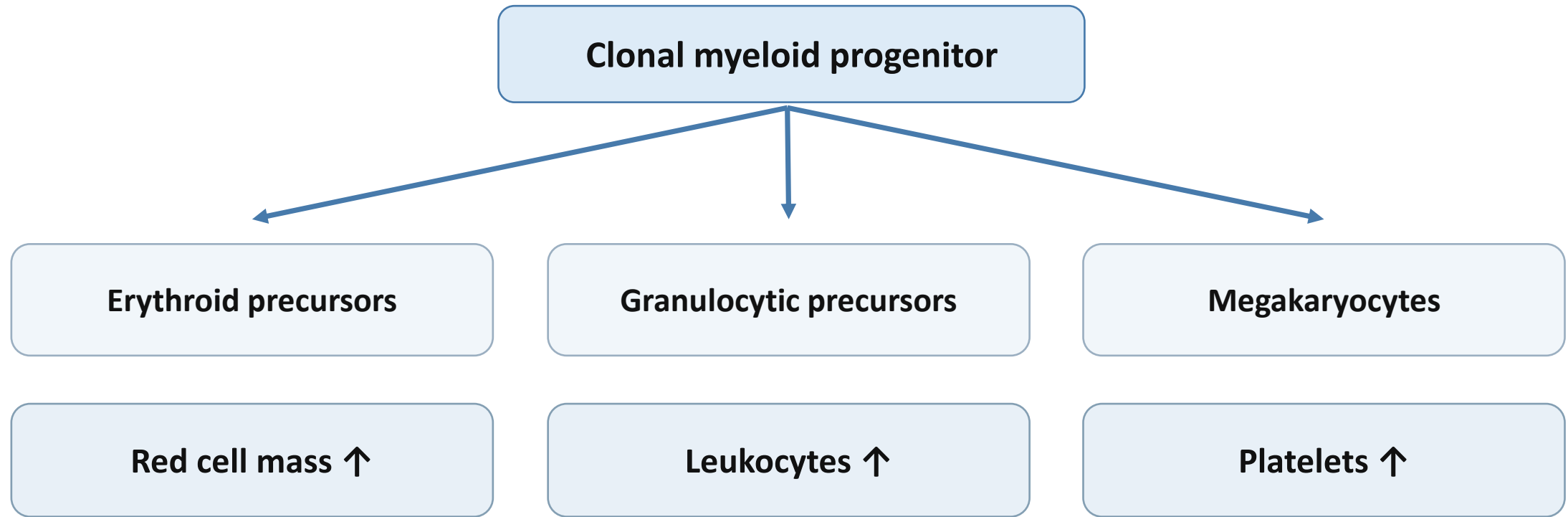
Hypercellular marrow

Some residual fat

Trilineage expansion

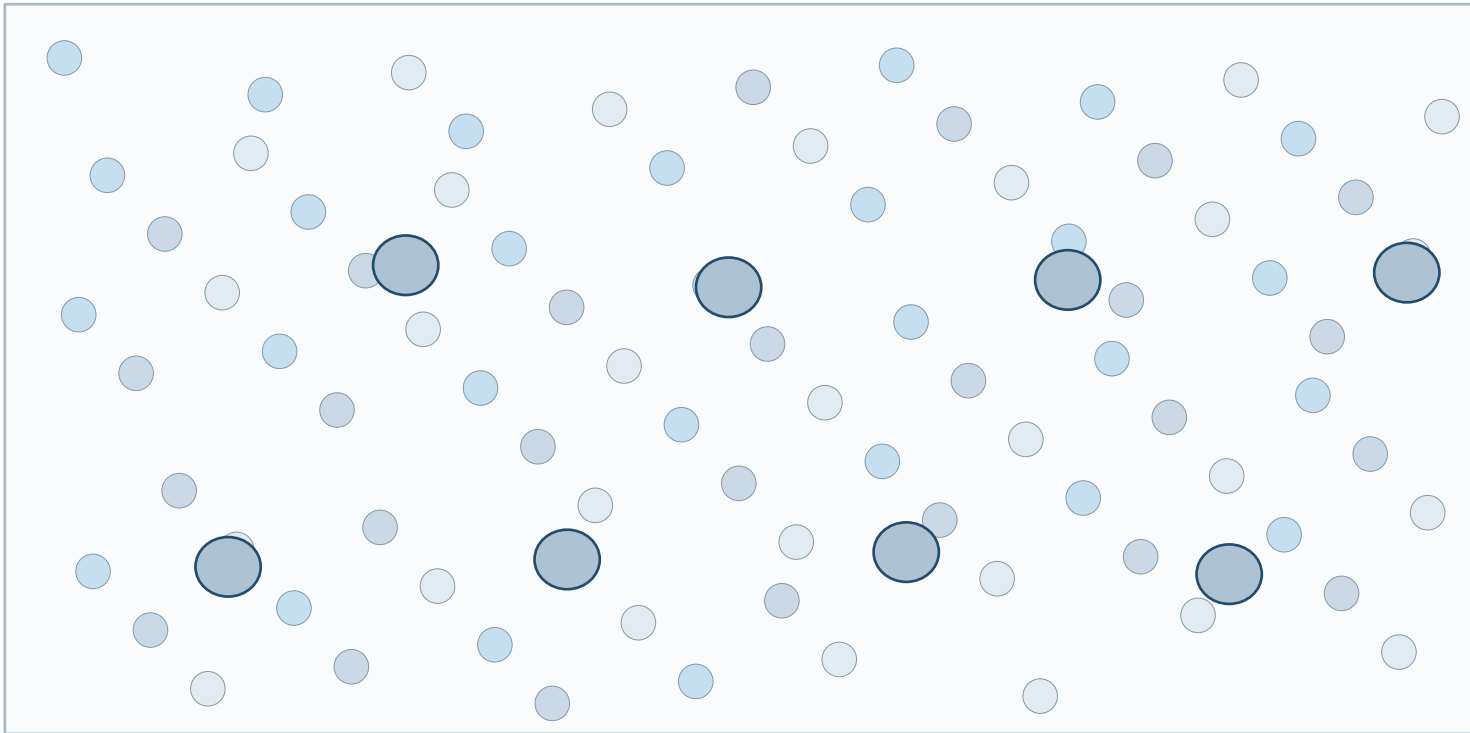
Simplified editable cellularity schematic — not genuine H&E

Recognize the three expanding hematopoietic lineages



Simplified lineage model — not a marrow section

Erythroid expansion can appear subtle in biopsy



Subtle erythroid expansion

Read all three lineages

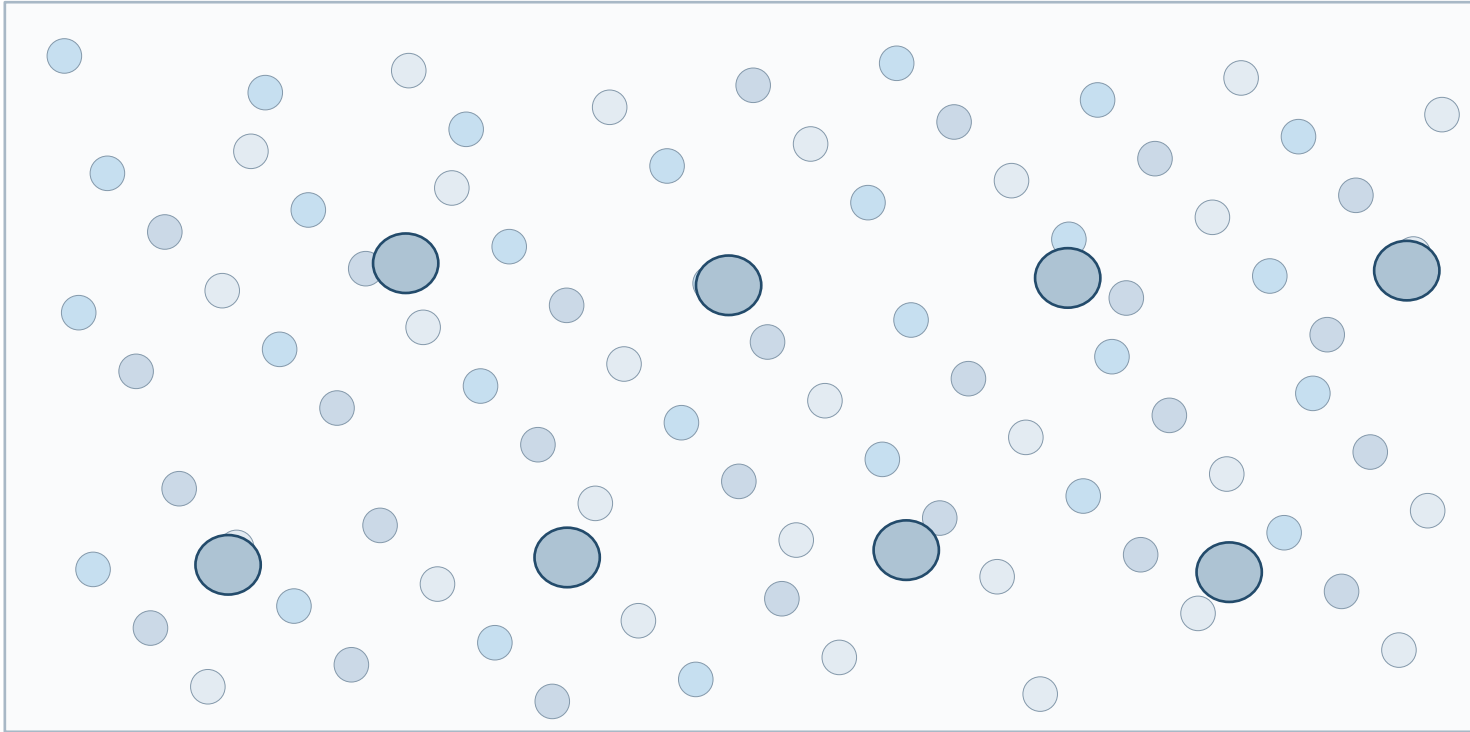
Correlate with counts

Simplified editable cellularity schematic — not genuine H&E

Granulocytic expansion accompanies erythrocytosis

- The marrow often contains increased granulocytic precursors.
- Mature blood granulocytes may also be elevated.
- Panmyelosis is therefore not synonymous with isolated erythroid hyperplasia.

Megakaryocytes add a distinct morphologic clue



Megakaryocytes ↑

Giant platelets possible

Assess panmyelosis

Simplified editable cellularity schematic — not genuine H&E

Residual marrow fat need not disappear

Normal-context marrow

PV marrow can be hypercellular with residual adipose spaces.

PV marrow

The pattern is not the uniformly packed marrow often seen in untreated CML.

Degree of cellularity must be judged in clinical and age context.

Reticulin increase may occur at diagnosis

- Moderate-to-marked reticulin in about 10% of presenting marrow samples.
- Reticulin increase is not automatically equivalent to post-PV myelofibrosis.
- Stage interpretation requires the broader clinicopathologic picture.

Early organomegaly need not mean extensive EMH

Early congestion

Mild organomegaly can reflect vascular congestion early in PV.

Advanced EMH

Extramedullary hematopoiesis (EMH) is limited in this phase.

In advanced myelofibrosis, EMH becomes much more prominent.

Peripheral blood: Think beyond RBC count

Increased basophils may be present.

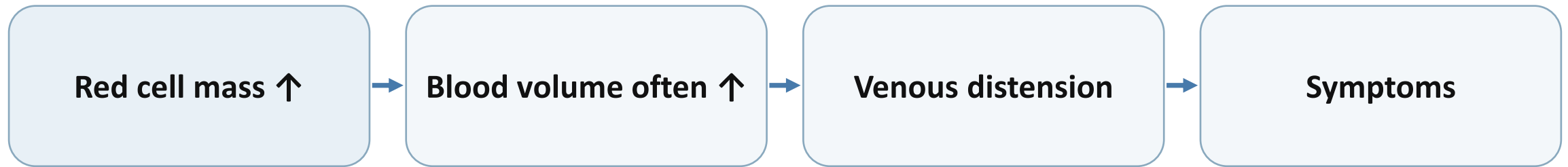
Platelets can be abnormally large.

A smear complements the complete blood count but does not establish PV by itself.

Insidious onset in later adulthood

- PV most often in adults of late middle age.
- The reported U.S. Incidence is approximately 1–3 per 100,000 people per year.
- Symptoms may evolve before the myeloproliferative disorder is recognized.

A raised red cell mass changes the circulating volume



Conceptual causal sequence — native, editable schematic

- Total blood volume is commonly increased in PV.
- Venous distension and diminished flow efficiency help explain physical findings.
- Volume expansion and viscosity should be considered together.

Plethora and cyanosis reflect peripheral stasis

RBC-rich blood in low-pressure peripheral vessels



Distension + sluggish transit → increased local deoxygenation

Circulatory illustration — not an anatomic vessel cross-section

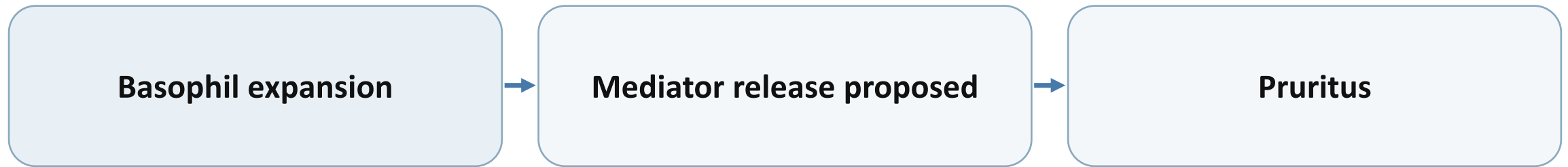
Headache and dizziness are hemodynamic clues

- Disordered microvascular flow provides a mechanistic explanation.
- These symptoms are common but are nonspecific.
- Their value increases when accompanied by elevated hematocrit and other PV findings.

Hypertension and gastrointestinal complaints may occur

- Expanded blood volume is relevant to blood-pressure changes.
- Gastrointestinal symptoms are among the clinical manifestations described.
- Neither feature is independently diagnostic.

Pruritus may relate to basophil mediators



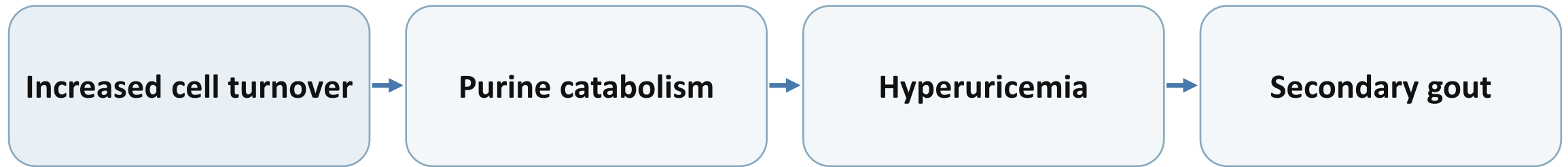
Conceptual causal sequence — native, editable schematic

- The textbook links intense pruritus possibly to basophil histamine release.
- Basophils may be elevated in peripheral blood.
- This proposed mechanism is a possibility, not proof of a single pathway.

Peptic ulceration is another possible mediator effect

- Peptic ulceration occurs in the clinical description of PV.
- Histamine release from basophils is offered as a possible mechanism.
- The causal explanation should be taught as uncertain.

High turnover can produce hyperuricemia



Conceptual causal sequence — native, editable schematic

- Increased blood-cell production also increases cellular turnover.
- Purine breakdown can elevate serum uric acid.
- Symptomatic secondary gout in about 5%–10% of cases.

Major thrombosis may be the first presentation

Approximately one-quarter of patients presenting with a vascular event.

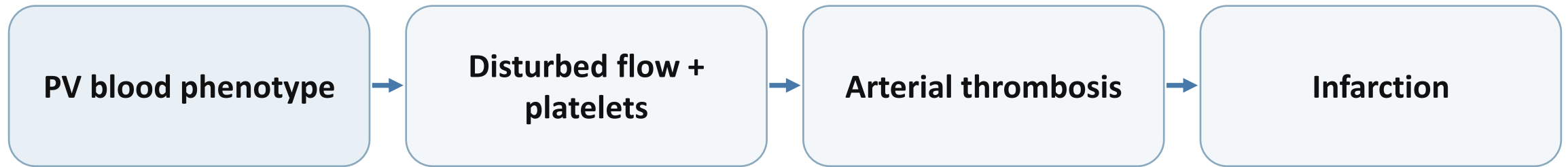
Deep venous thrombosis, myocardial infarction, and stroke are examples.

Thrombosis can precede obvious hematologic abnormalities.

Venous thrombosis has several clinical faces

- Deep venous thrombosis is an important presenting manifestation.
- Venous stasis is a plausible contributor, alongside cellular and platelet changes.
- The clot location influences symptoms and the diagnostic pathway.

Arterial events are part of the same disease spectrum



Conceptual causal sequence — native, editable schematic

- Myocardial infarction and stroke may bring PV to attention.
- High hematocrit and abnormal platelet biology are both relevant.
- A vascular event should prompt evaluation of otherwise unexplained erythrocytosis.

Splanchnic thrombosis deserves attention

Hepatic vein thrombosis may produce Budd–Chiari syndrome.

Portal and mesenteric venous thromboses are also described.

Mesenteric venous occlusion can progress to bowel infarction.

Do not wait for classic blood counts after thrombosis

- Thrombotic episodes may precede the textbook hematologic pattern.
- A single hematocrit measurement must be interpreted in context.
- Clinical suspicion may remain high despite initially ambiguous counts.

Bleeding commonly involves mucosal surfaces

Epistaxis and gum bleeding are frequently described.

Major bleeding is less common but can be life-threatening.

The textbook estimates life-threatening hemorrhage in roughly 5%–10% of cases.

The platelet paradox is functional, not numerical

More platelets

Elevated platelet count does not exclude impaired aggregation.

Impaired function

Large forms and abnormal functional tests indicate dysregulated megakaryopoiesis.

Bleeding and thrombosis are therefore not mutually exclusive outcomes.

Hemoglobin and hematocrit: Typical textbook findings

Hemoglobin: Often >16 g/dL

Hematocrit: Often $\geq 55\%$

Descriptive textbook values — not formal diagnostic criteria

Leukocyte and platelet abnormalities support panmyelosis

WBC: 12,000–50,000/mm³

Platelets: Often >500,000/mm³

Descriptive textbook values — not formal diagnostic criteria

Iron deficiency can disguise red cell overproduction

- Chronic blood loss may deplete iron stores.
- Restricted hemoglobin synthesis can reduce the measured hematocrit.
- Underlying PV can therefore coexist with a deceptively normal hematocrit.

Two abnormalities can counteract on a blood test

PV: Erythroid drive ↑

Iron deficiency: Hb synthesis ↓

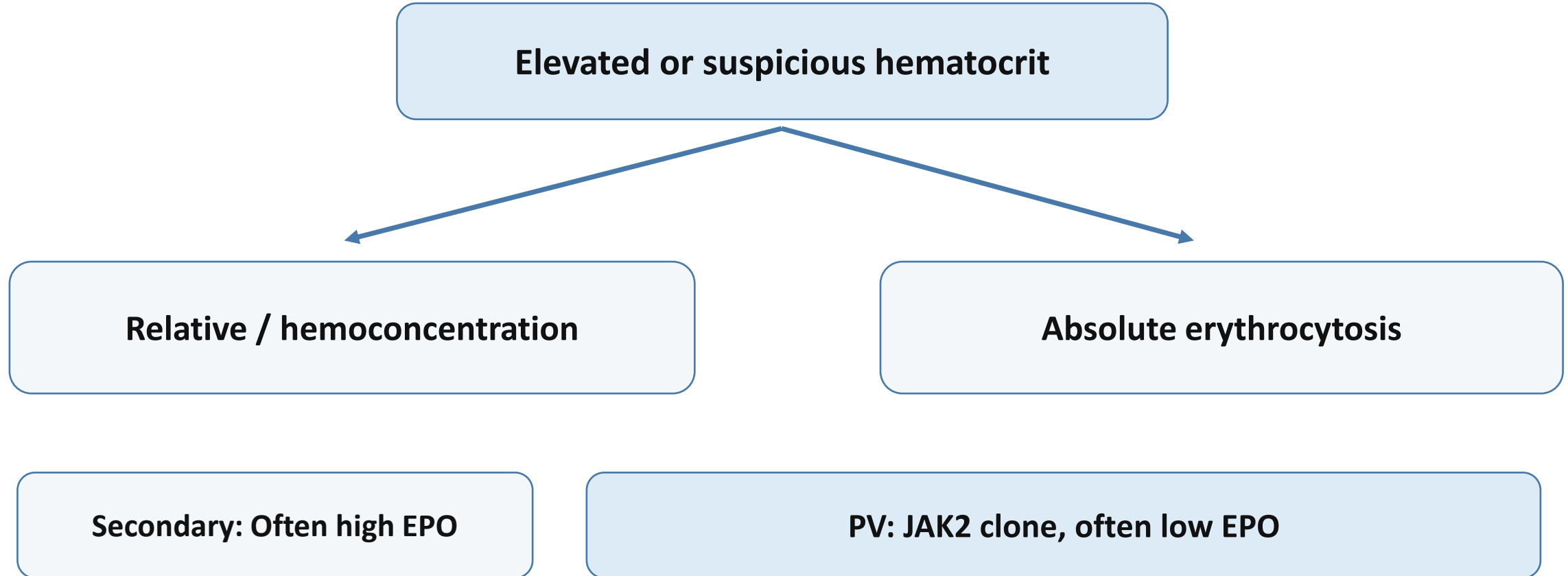
Measured hematocrit can appear normal

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graph TD; A[PV: Erythroid drive ↑] --> D[Measured hematocrit can appear normal]; B[Iron deficiency: Hb synthesis ↓] --> D;
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Interpret the CBC as a pattern, not a verdict

- Assess red cell indices, white cell count, and platelet count together.
- Link blood counts with marrow morphology and molecular findings.
- Review iron status when counts and the clinical pattern appear discordant.

First differentiate relative from absolute polycythemia



Conceptual diagnostic classification; Not a validated clinical algorithm

Secondary erythrocytosis is not PV

Clonal PV

Secondary forms are stimulated by elevated EPO, unlike the usual low EPO of PV.

EPO-mediated erythrocytosis

Physiologic or pathological drivers outside a JAK2-mutant marrow must be evaluated.

The textbook directs readers to the subsequent erythrocytosis chapter.

Integrated diagnostic reasoning for suspected PV

- An elevated hematocrit triggers evaluation, not an automatic PV label.
- Consider hemoconcentration, secondary erythrocytosis, and masking iron deficiency.
- Integrate JAK2 mutation testing, EPO, peripheral counts, and marrow findings.

PV versus essential thrombocythemia

Polycythemia vera

Both can harbor JAK2 mutations and have high platelet counts.

Essential thrombocythemia

PV has erythrocytosis with panmyelosis; ET is clinically platelet-dominant.

Iron deficiency can obscure the erythrocytosis of PV.

PV versus chronic myeloid leukemia

JAK2 / PV

JAK2-driven PV commonly produces erythrocytosis and trilineage proliferation.

BCR::ABL / CML

BCR::ABL-driven CML usually produces far greater granulocytic proliferation.

Molecular markers distinguish their defining oncogenic pathways.

PV versus primary myelofibrosis

PV phase

Early PV emphasizes increased red cell mass and panmyelosis.

Primary myelofibrosis

Primary myelofibrosis is a separate MPN with a fibrotic marrow phenotype.

Post-PV myelofibrosis is an acquired late disease phase, not an initial synonym.

Case 1: An unexpected venous thrombosis

- A late-middle-aged adult develops hepatic vein thrombosis.
- Investigations reveal an elevated hematocrit and increased platelet count.
- What pathophysiologic links and diagnostic distinctions should be considered?

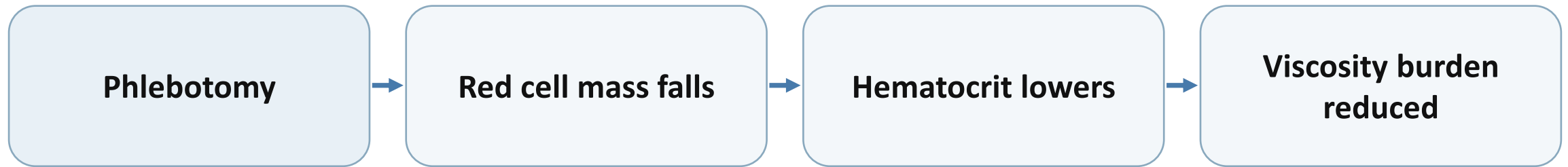
Discussion: Form a mechanistic differential

Case 1: Reasoning from the vascular event

- Unusual venous thrombosis is a recognized PV presentation.
- Increased red cell mass can raise viscosity; Platelet abnormalities add risk.
- Differentiate relative and secondary erythrocytosis before concluding PV.

Discussion: Expected reasoning

Phlebotomy targets the red cell burden



Conceptual causal sequence — native, editable schematic

- Reducing red cell mass addresses the principal hemodynamic driver.
- Phlebotomy as a major strategy for PV control.
- Treatment targets should follow current specialty guidance, not a descriptive hematocrit from the excerpt.

Low-dose aspirin addresses vascular risk

Red cell component

The Robbins treatment discussion pairs phlebotomy with low-dose aspirin.

Platelet component

The rationale is mitigation of platelet-mediated thrombotic risk.

Clinical use must account for bleeding risk and current guidance.

Current practice: JAK inhibitor eligibility differs

Robbins textbook framing

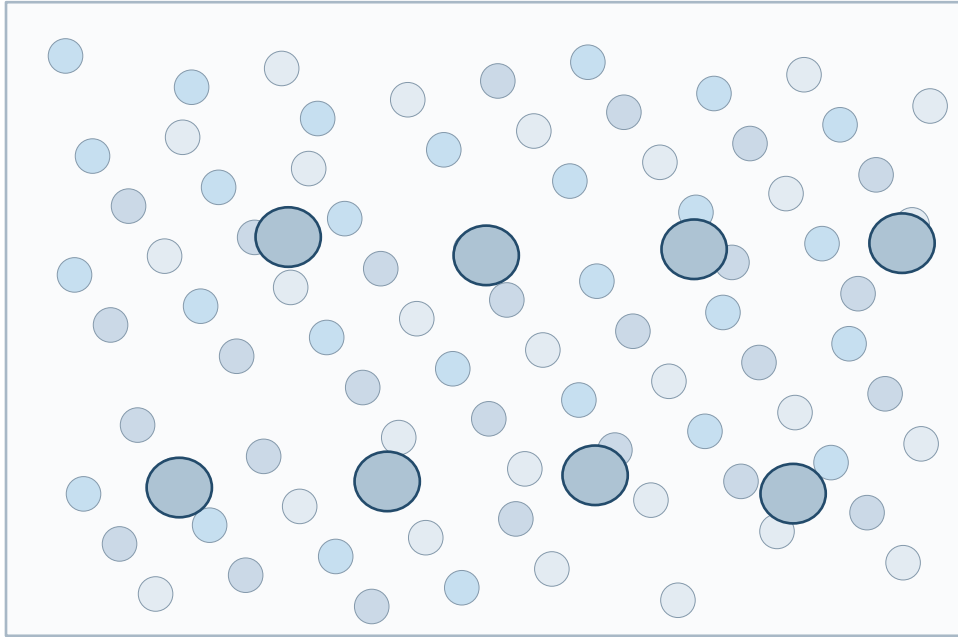
Describes use of JAK2 inhibitors primarily after progression to a fibrotic phase.

Verified 2026 U.S. Label

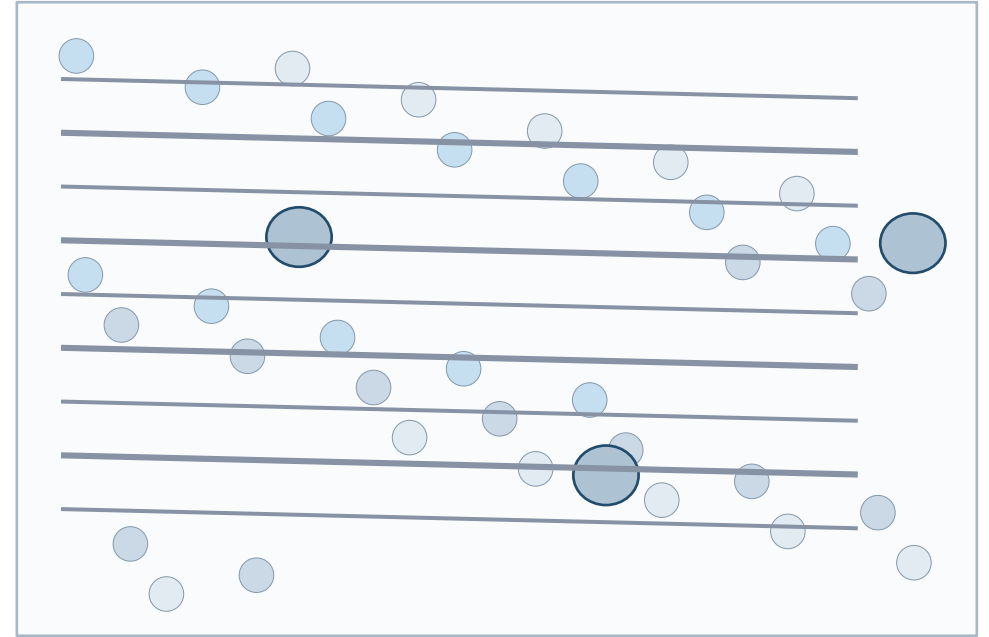
Ruxolitinib is also indicated for adult PV after inadequate response or intolerance to hydroxyurea.

Separately sourced contemporary clarification

Post-PV myelofibrosis changes the marrow architecture



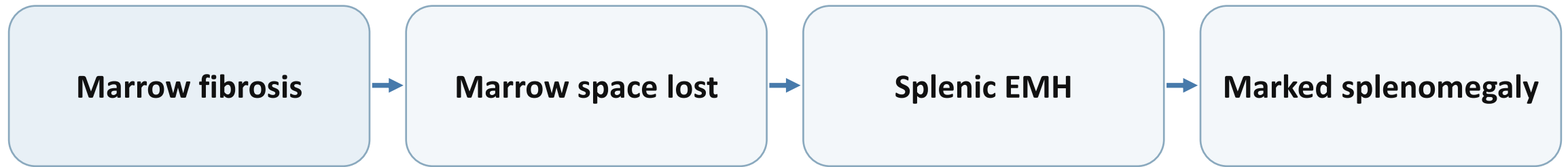
Proliferative phase



Fibrotic "spent" phase

Stage schematic; Not histologic evidence or measured fibrosis

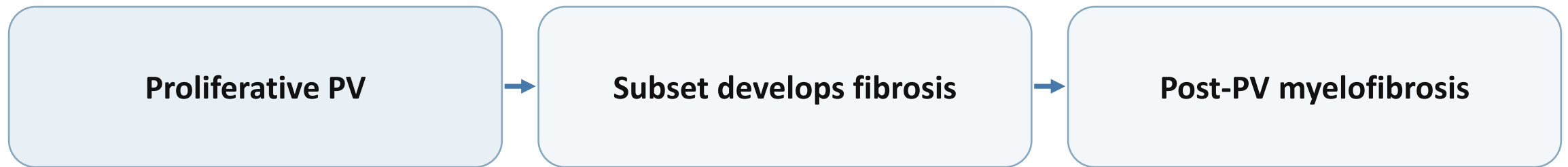
The spleen can become a major hematopoietic site



Conceptual causal sequence — native, editable schematic

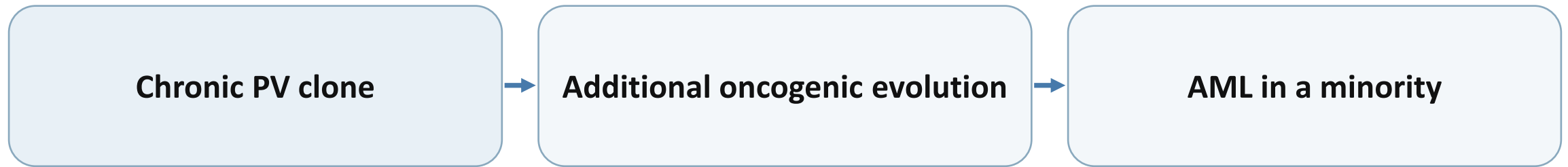
- As marrow function becomes impaired, extramedullary hematopoiesis increases.
- The spleen may enlarge dramatically during the spent phase.
- Late splenomegaly reflects a different mechanism from early congestion.

The transition to a spent phase is not universal



Robbins: Fibrosis in ~15%–20% after an average of ~10 years

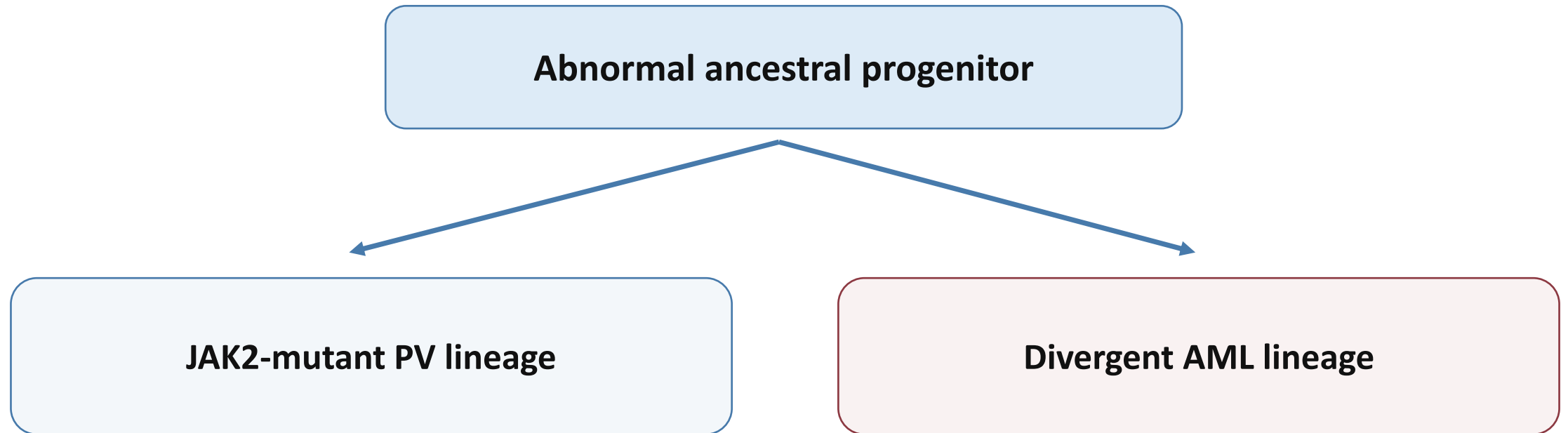
Acute myeloid leukemia is an uncommon outcome



Conceptual causal sequence — native, editable schematic

- A small fraction of PV patients develop AML.
- The extracted textbook passages report discordant approximate frequencies (1% and 2%).
- A single precise transformation percentage is therefore deliberately not presented.

Leukemic clones may not retain the JAK2 alteration



Mechanistic model inferred from discordant JAK2 status in some AML clones

The proposed cell of origin remains a mechanistic inference

- The text favors an abnormal progenitor with myeloid commitment for PV.
- Transformation to acute lymphoblastic leukemia is rare, unlike the broader lineage potential in CML.
- Clonal evolution is more complex than a linear JAK2-only model.

Case 2: A “normal” hematocrit with clues to PV

- A patient has pruritus, thrombocytosis, leukocytosis, and iron deficiency.
- The hematocrit is not markedly increased despite other myeloproliferative clues.
- What could be masking red cell expansion?

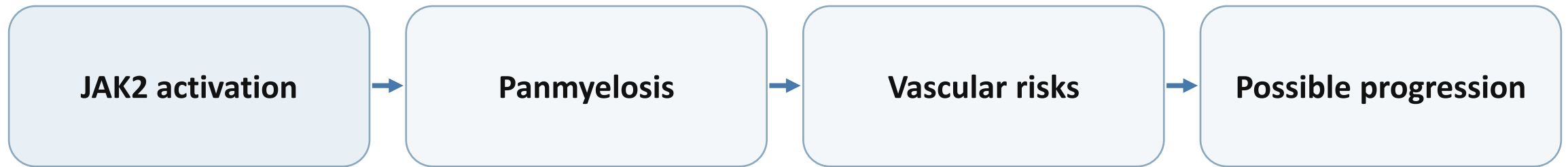
Discussion: Form a mechanistic differential

Case 2: Interpret the countervailing defects

- Iron deficiency can limit erythropoiesis enough to lower the hematocrit.
- Consider masked PV instead of assuming isolated thrombocythemia.
- The full work-up requires integrated blood, marrow, EPO, and molecular data.

Discussion: Expected reasoning

Polycythemia vera: Integrated disease sequence



Diagnosis requires integrated clinicopathologic interpretation.

Reference and interpretation notes

- Primary text: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed., Chapter 13, pp. 568–569.
- Treatment update: U.S. FDA ruxolitinib label (2026), adults with inadequate response/intolerance to hydroxyurea.
- Textbook numerical observations are distinguished from formal diagnostic criteria.
- No chapter PDF was supplied; source passages were reconstructed from column-interleaved Markdown.