

Clonal Hematopoiesis

Aging • mutant stem-cell selection • neoplastic risk • inflammation

Acquired mutation

Molecular origin

Clonal expansion

Stem-cell fitness

Clinical impact

Malignancy and inflammation

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Learning objectives

- Define clonal hematopoiesis in terms of mutation, clone and blood counts.
- Explain age dependence, HSC selection and the principal epigenetic genes.
- Relate mutant clone biology to malignancy and inflammatory disease.
- Interpret molecular findings without mistaking a clone for overt cancer.

1

Definition

2

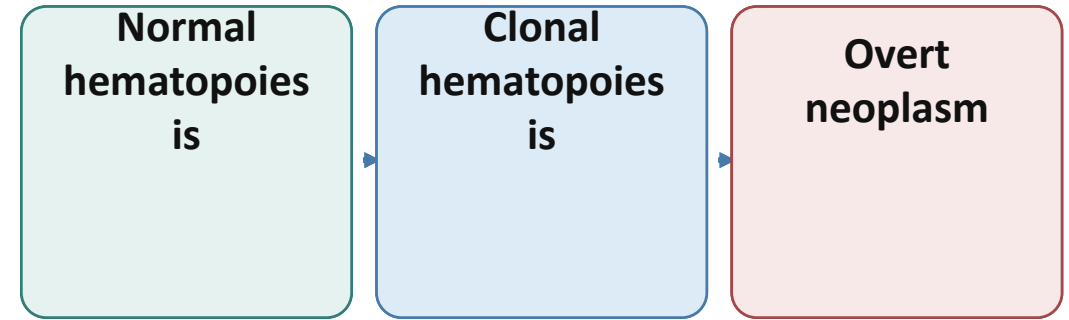
Mechanism

3

Clinical
significance

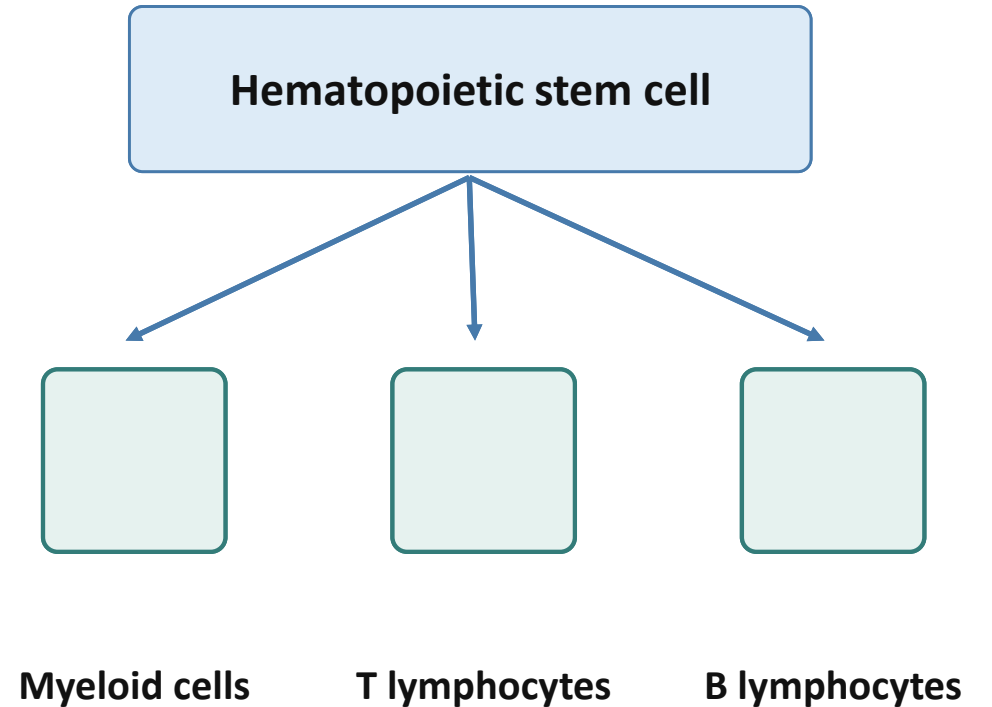
Position in hematopathology

- Clonal hematopoiesis may precede overt hematologic malignancy.
- It is encountered in individuals without abnormal blood counts.
- Its discussion precedes acute and chronic myeloid neoplasms because of the precursor relationship.



Normal hematopoiesis is hierarchical

- Hematopoietic stem cells generate committed progenitors.
- Progenitors mature into circulating myeloid and lymphoid cells.
- A genetic change in an upstream HSC can be represented across differentiated lineages.



Schematic: Lineage output from an upstream HSC

Homeostatic control versus clonal selection

- Normal hematopoiesis responds to growth factors and feedback controls.
- A mutant stem-cell population may expand because of increased fitness.
- The mere presence of a clone does not establish malignant marrow failure.

**Feedback-
regulated blood
cell production**

**Selective
expansion of one
mutated lineage**

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Core definition

- An acquired pathogenic mutation occurs in a hematopoietic clone.
- The affected gene is implicated in cancer biology.
- Peripheral blood counts remain normal definition.

Acquired mutation



Clonally expanded hematopoiesis



Normal blood counts

Three defining requirements

- Somatic genetic lesion: Not simply an inherited germline variant.
- Clonality: Mutant cells are present as an expanded population.
- No hematologic count abnormality at diagnosis in this definition.

1

Acquired
lesion

2

Clonal
expansion

3

Normal
counts

Clonal hematopoiesis is not leukemia

- A cancer-associated mutation can exist before malignancy.
- Leukemia requires disease-specific neoplastic features, not mutation detection alone.
- Normal counts and lack of hematologic symptoms distinguish the textbook-described state.

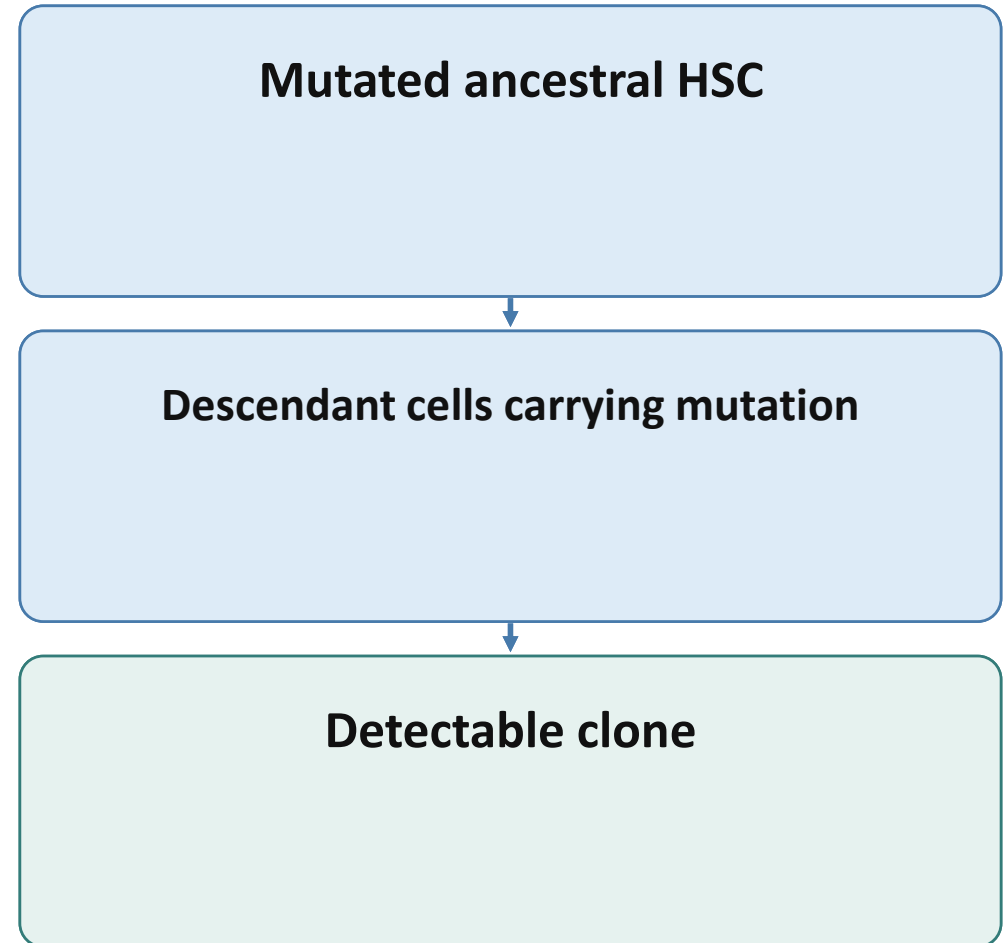
**Mutation-
positive clone**

**Clinically
apparent
hematologic
neoplasm**

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What constitutes a hematopoietic clone?

- A group of blood-producing cells descends from a mutated ancestral cell.
- Its cells share an acquired molecular alteration.
- Expansion means this lineage contributes a detectable share of hematopoiesis.



Acquired and inherited variants differ

- An acquired mutation develops during the individual's lifetime.
- A germline variant is present from conception across many tissues.
- Interpretation of blood sequencing must preserve this distinction.

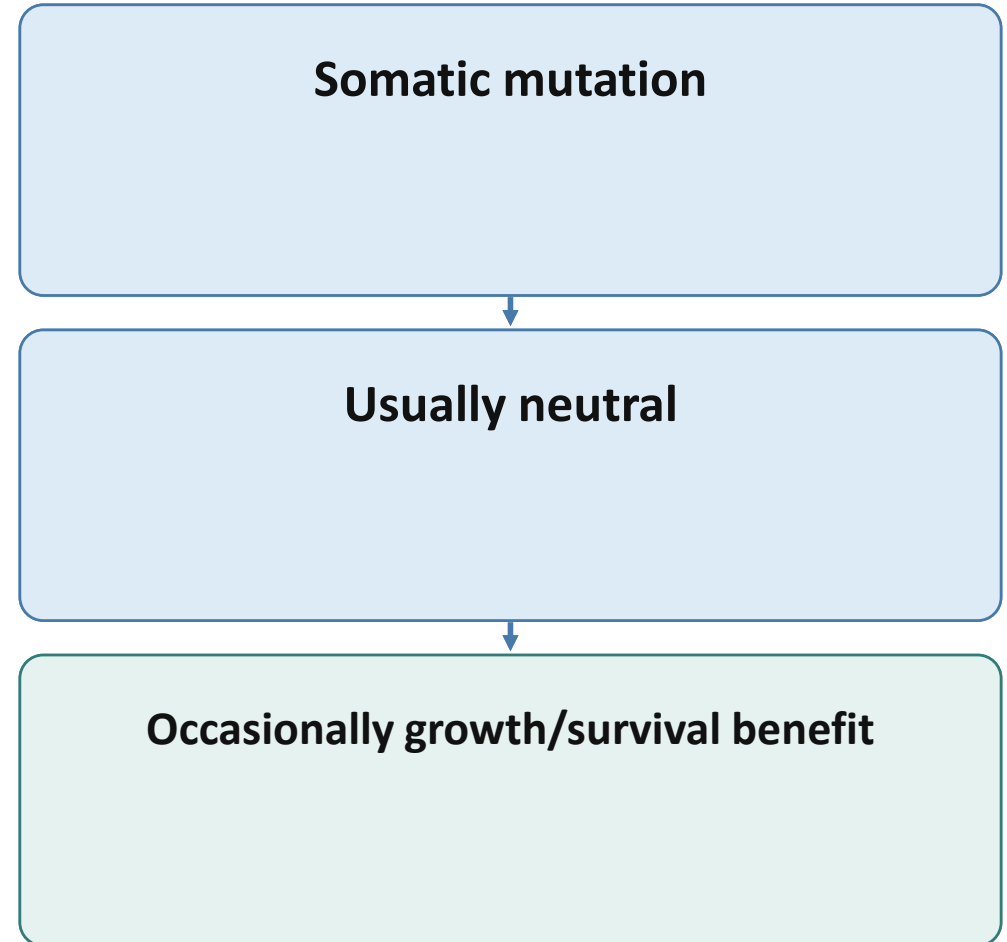
**Somatic
mutation in
blood-cell
lineage**

**Constitutional
inherited variant**

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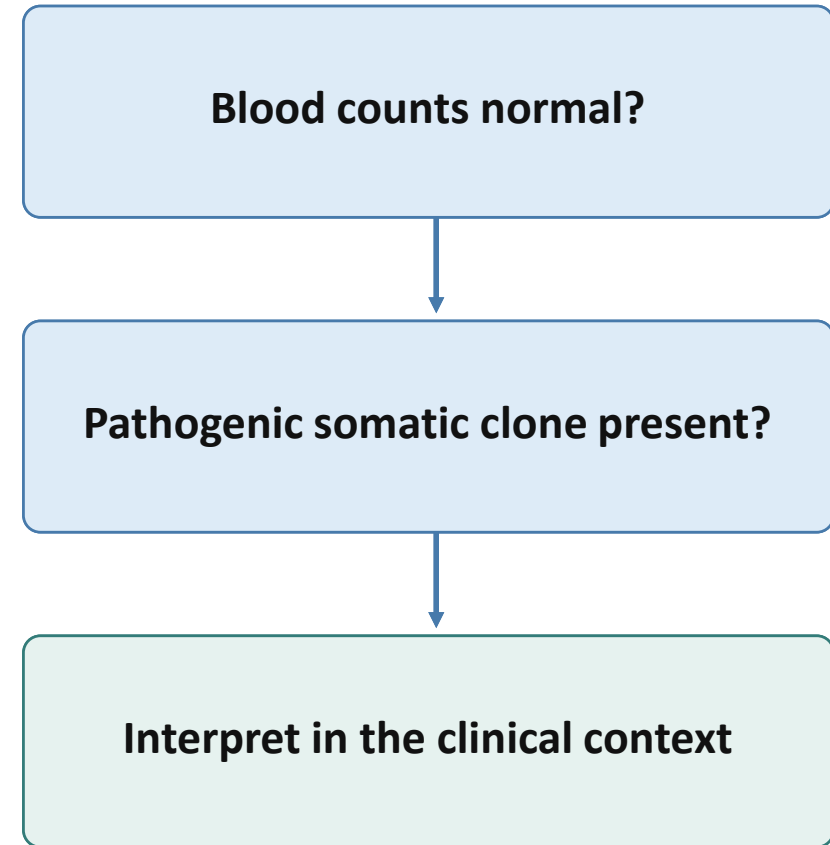
A cancer gene mutation is not sufficient

- Somatic mutations arise continually as cells age.
- Most do not give rise to clinically significant clones.
- Selection requires a favorable effect on stem-cell growth or survival.



The normal blood count requirement

- Normal blood counts are part of the textbook's working definition.
- An affected person need not have clinical hematologic symptoms.
- Molecular alterations can precede changes detected by routine hematology.



Sequencing defines the measurable clone

- DNA sequencing examines blood- or marrow-derived cells.
- Mutant sequence reads reveal the variant in a cell population.
- The source specifies a mutant-read fraction threshold for the working definition.

DNA from blood / marrow cells



Short sequencing reads



≥2% mutant sequencing reads

The operational 2% threshold

- At least 2% of sequencing reads as the diagnostic convention.
- The threshold is explicitly described as somewhat arbitrary.
- A threshold convention is not a biologic switch between health and malignancy.

**Below working
cutoff**

**At or above the
2% read
threshold**

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Read fraction is not a cell count

- A fraction of mutant DNA reads is a sequencing measurement.
- It should not automatically be equated with the percentage of marrow cells in the clone.
- Interpret clone size in the context of the measurement being reported.

DNA from blood / marrow cells



Short sequencing reads



Mutation detected in a subset of reads

A molecular finding needs context

- Detection establishes that a variant is in the specimen.
- Clonal hematopoiesis interpretation additionally requires normal blood counts and suitable biological context.
- The same gene may carry alterations in hematologic or nonhematologic neoplasms.

Where did the sampled DNA originate?



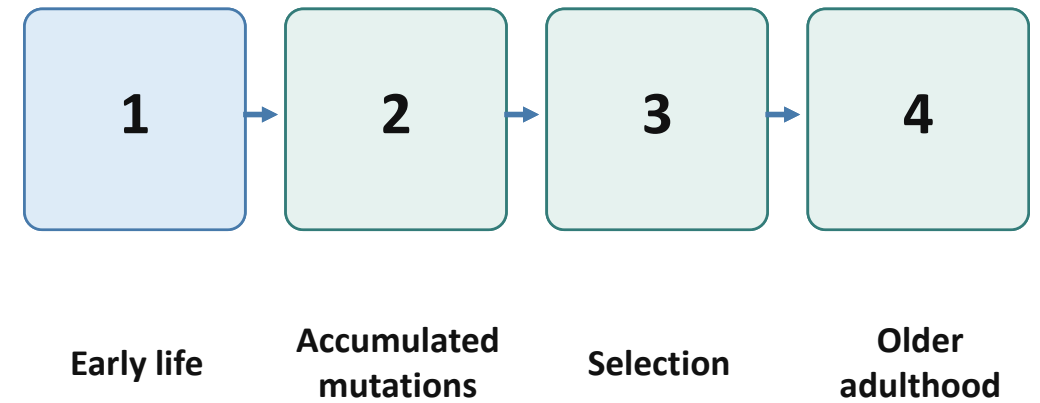
Are blood counts normal?



Which tissue harbors the variant?

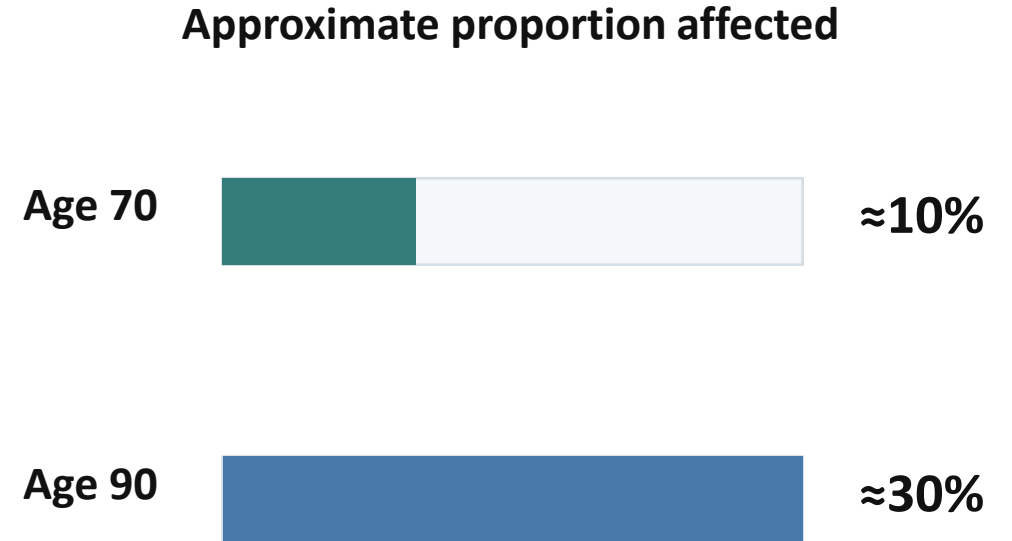
Age is the dominant epidemiologic pattern

- Clonal hematopoiesis is uncommon before age 50 years.
- Frequency increases progressively in later life.
- Aging supplies time for mutations and selection of advantaged stem-cell clones.



Prevalence rises markedly with age

- Approximately 10% are affected by age 70 estimate.
- The estimate approaches 30% by age 90.
- These are age-specific approximations, not a patient-specific prediction.



Not a continuous interpolated curve

Age and mutation accumulation

- The source describes spontaneous base deamination throughout life.
- Accumulation of genetic variants does not imply that all confer fitness.
- Occasional driver mutations may produce selective expansion.

Mutations arise over time



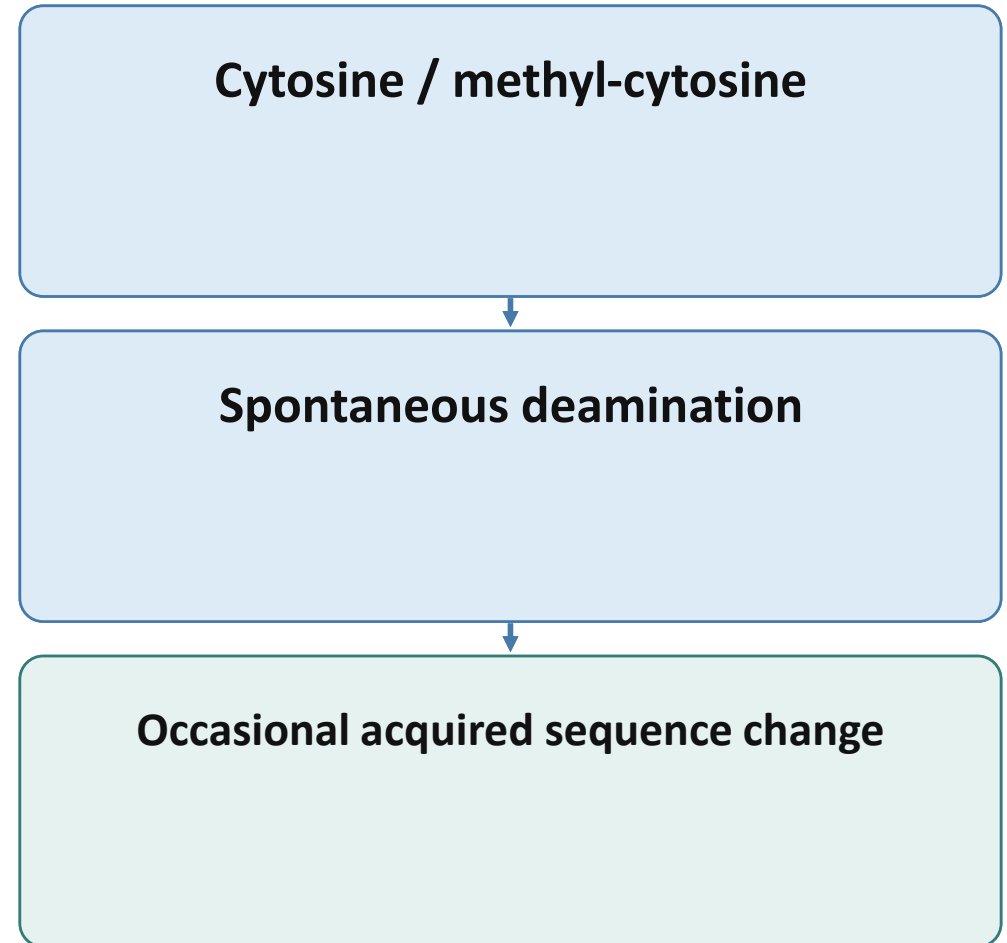
Most are inconsequential



Rare beneficial variants expand

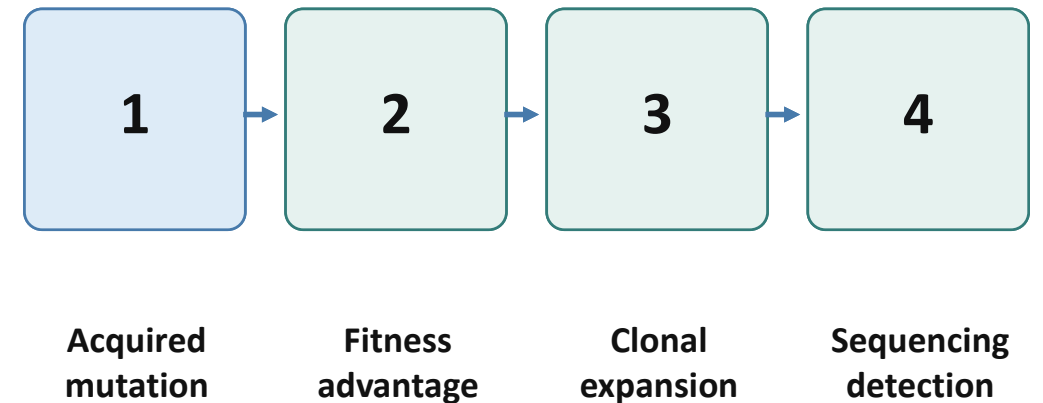
Mutational origin: Spontaneous deamination

- Cytosine or methyl-cytosine can undergo spontaneous deamination.
- This is described as an ongoing process in multiple cell types.
- Hematopoietic stem cells acquire such lesions during life.



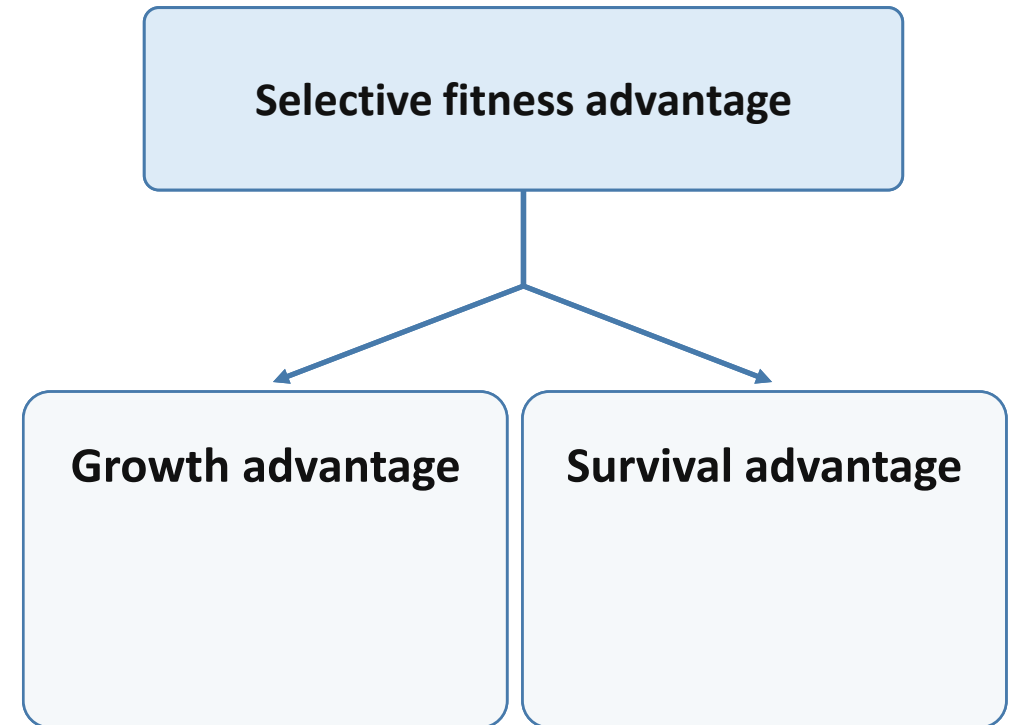
Mutation is followed by selection

- Mutation generation and clonal expansion are separate processes.
- A change that improves stem-cell fitness can increase the size of its descendant population.
- The resulting clone may be detected without blood-count abnormalities.



Growth and survival advantages

- A mutated stem cell may proliferate more effectively than competitors.
- Alternatively, greater survival may allow progressive representation.
- Both lead to disproportionate contribution to hematopoiesis.



Most somatic mutations do not expand

- Cells accumulate changes without necessarily altering tissue behavior.
- Only some changes modify oncogene or tumor-suppressor function.
- A detectable clone therefore reflects mutation plus selection and persistence.

Many acquired variants



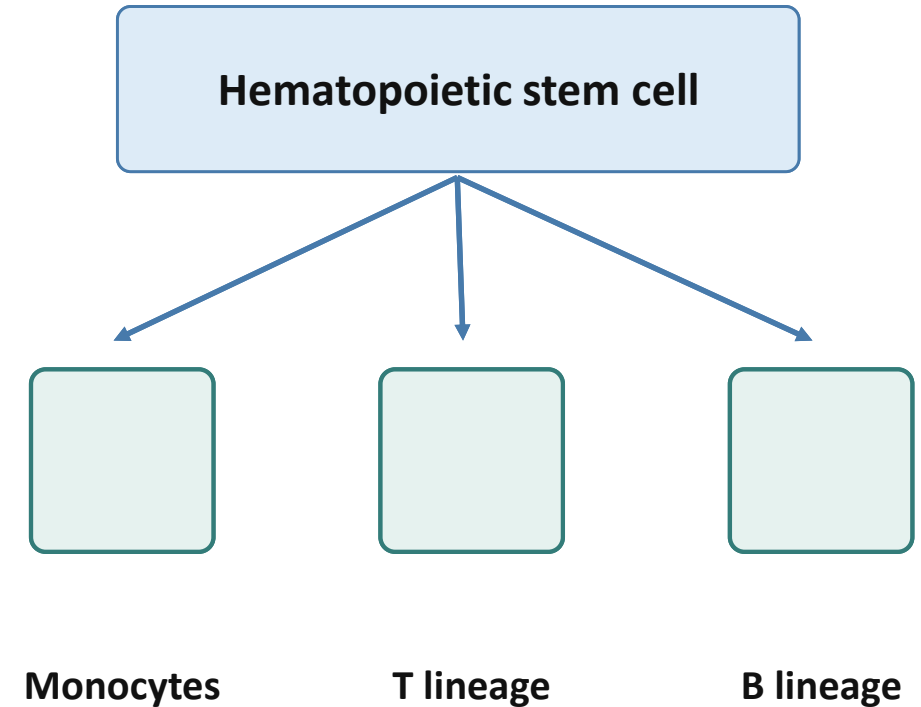
Few alter cellular fitness



Selected clone persists

The stem-cell compartment matters

- An affected HSC can persist and continuously supply differentiated progeny.
- An early mutation can be shared across different blood-cell lineages.
- This explains why blood-cell mutation signals may antedate distinct neoplasms.



Schematic: Lineage output from an upstream HSC

Clonal expansion is not synonymous with blasts

- Expansion of mature blood-cell progeny may coexist with normal counts.
- Myeloid leukemia instead features abnormal immature myeloid-cell accumulation.
- The essential comparison is a precursor clone versus a manifested neoplasm.

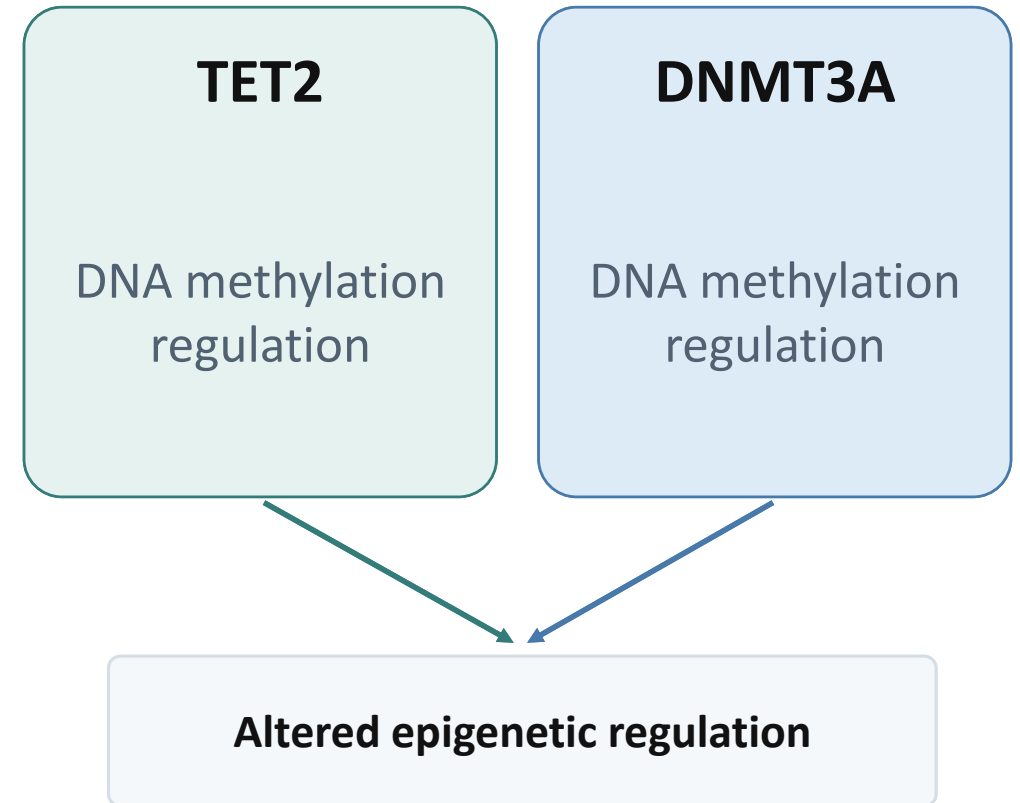
**Expanded
molecular clone**

**Abnormal blast
accumulation**

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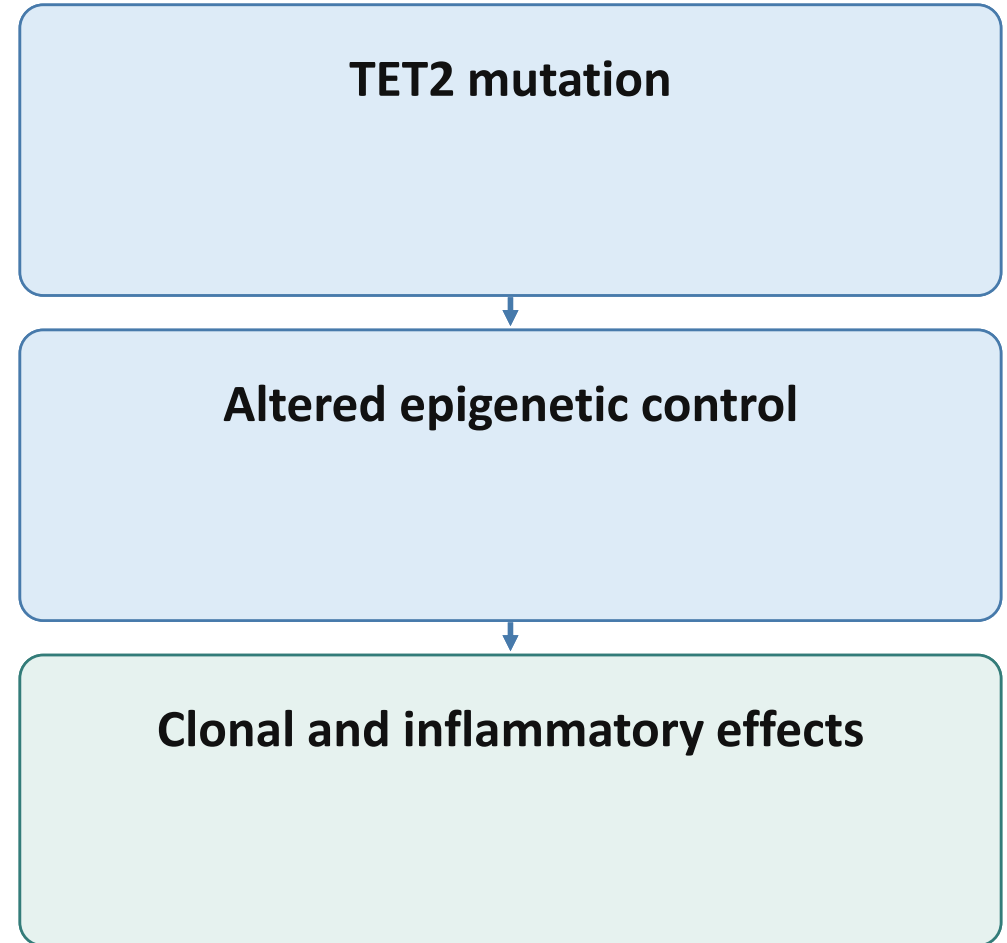
TET2 and DNMT3A predominate

- TET2 and DNMT3A are the most commonly mutated genes named in the source.
- Both participate in regulation of DNA methylation.
- Their disruption alters epigenetic control relevant to cell state and differentiation.



TET2: A recurrent epigenetic driver

- TET2 is identified as a tumor-suppressor gene.
- It regulates the DNA methylation landscape.
- TET2-mutated clones are particularly associated with inflammatory consequences.



DNMT3A: Another major driver

- DNMT3A is a tumor-suppressor gene emphasized by Robbins.
- It regulates DNA methylation-dependent gene expression.
- Altered stem-cell regulation can favor clonal persistence or expansion.

DNMT3A mutation



DNA methylation dysregulation



HSC clonal selection

Why DNA methylation matters

- DNA methylation is a chemical modification with effects on gene expression.
- Gene-expression programs influence hematopoietic maturation.
- Mutations in epigenetic regulators can change cell behavior without altering blood counts initially.

DNA methylation programs



Regulated gene expression



Differentiation and cell fitness

A gene is not a diagnosis

- The same recurrent gene may be mutated in clonal hematopoiesis and malignancy.
- A mutation must be interpreted with the blood count and overall disease phenotype.
- TET2 or DNMT3A positivity alone does not prove leukemia.

**TET2 / DNMT3A
variant**

**Diagnostic
integration is
required**

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Clonal hematopoiesis creates cancer risk

- Most affected individuals do not immediately develop a neoplasm.
- The textbook gives an approximate overall hematologic-neoplasm risk of 1% per year.
- Risk varies substantially by clone size and mutation identity.

Baseline estimate

≈1% / year

Higher concern

Large clones

Higher concern

Splicing-factor variants

The overall risk estimate is an average

- Approximately 1% per year is a population-level textbook estimate.
- Individual risk may be considerably above or below that figure.
- It must not be applied uniformly to every molecular finding.

**Average
population
estimate**

**Heterogeneous
individual risk**

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Clone size influences progression risk

- Larger clones are associated with a greater neoplastic risk.
- Clones involving 20% or more of marrow cells.
- This cell-based description is different from the 2% mutant-read cutoff.

Larger clonal contribution



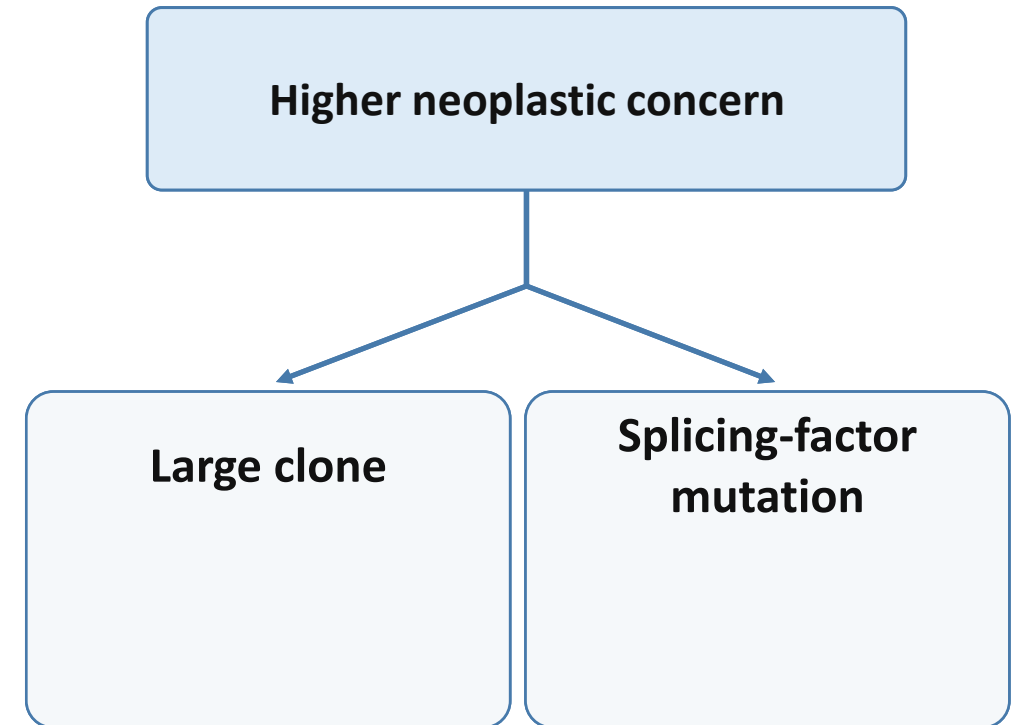
Greater high-risk representation



Higher progression concern

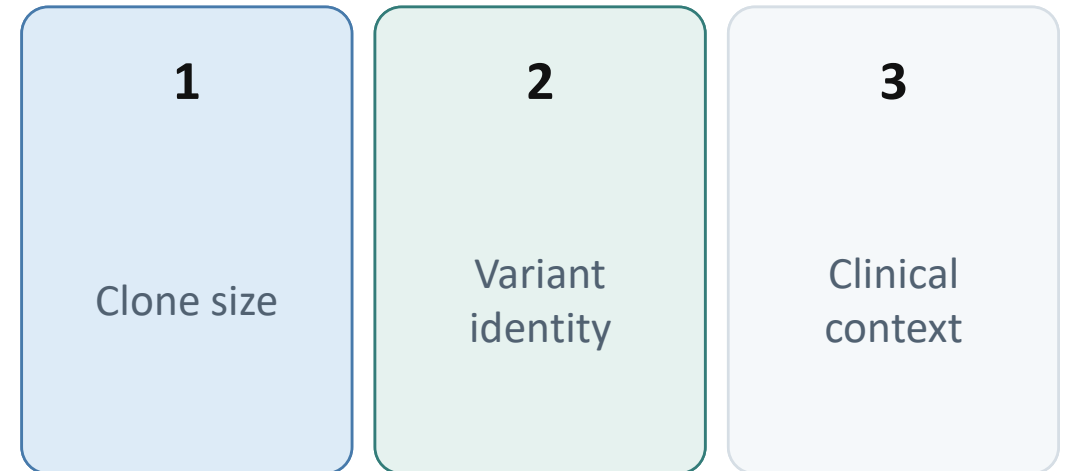
Mutation identity also influences risk

- Cancer-gene mutations do not have identical clinical implications.
- Mutations encoding RNA splicing factors are particularly associated with increased risk.
- Risk interpretation should combine variant identity with clone size.



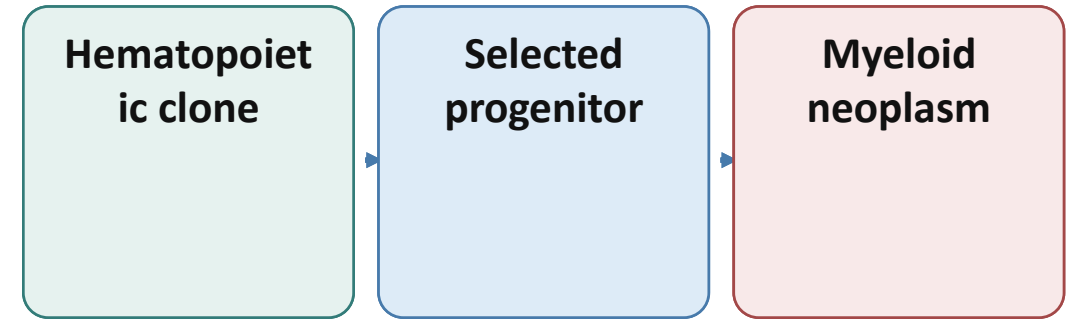
Risk factors should be integrated

- A low-level mutation and a large clone need not carry the same prognosis.
- Variant identity adds risk information that clone burden alone cannot supply.
- The textbook advocates improved prediction models for complication risk.



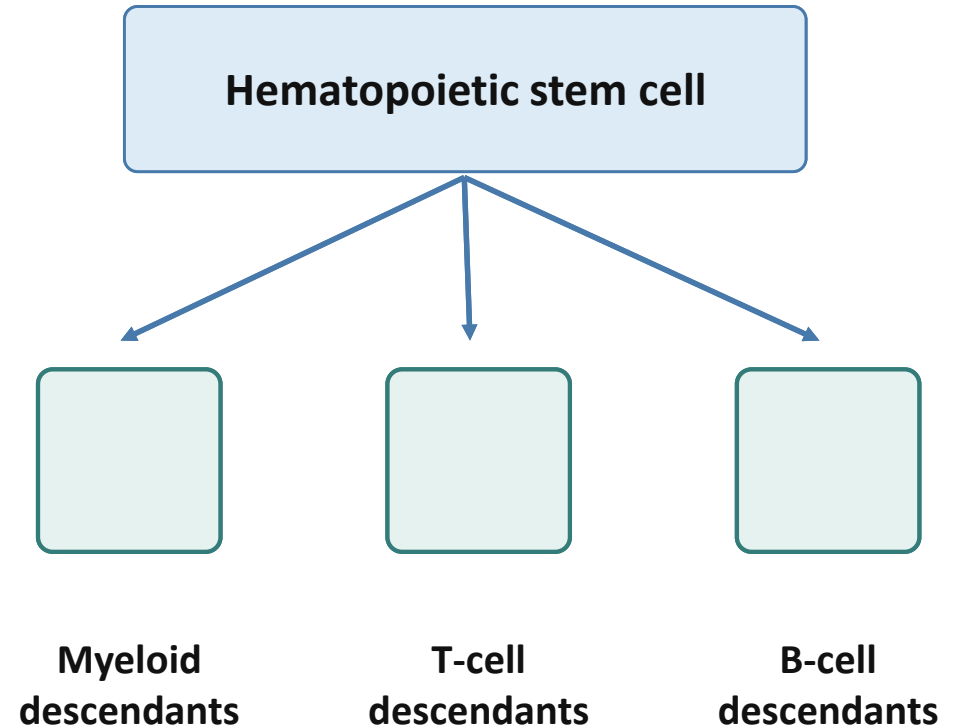
Myeloid neoplasms are the principal outcome

- Myeloid neoplasms occur most frequently among subsequent hematologic cancers.
- Their cell of origin is within the hematopoietic progenitor hierarchy.
- The antecedent clone can carry mutations retained in the malignancy.



Lymphoid neoplasms also show association

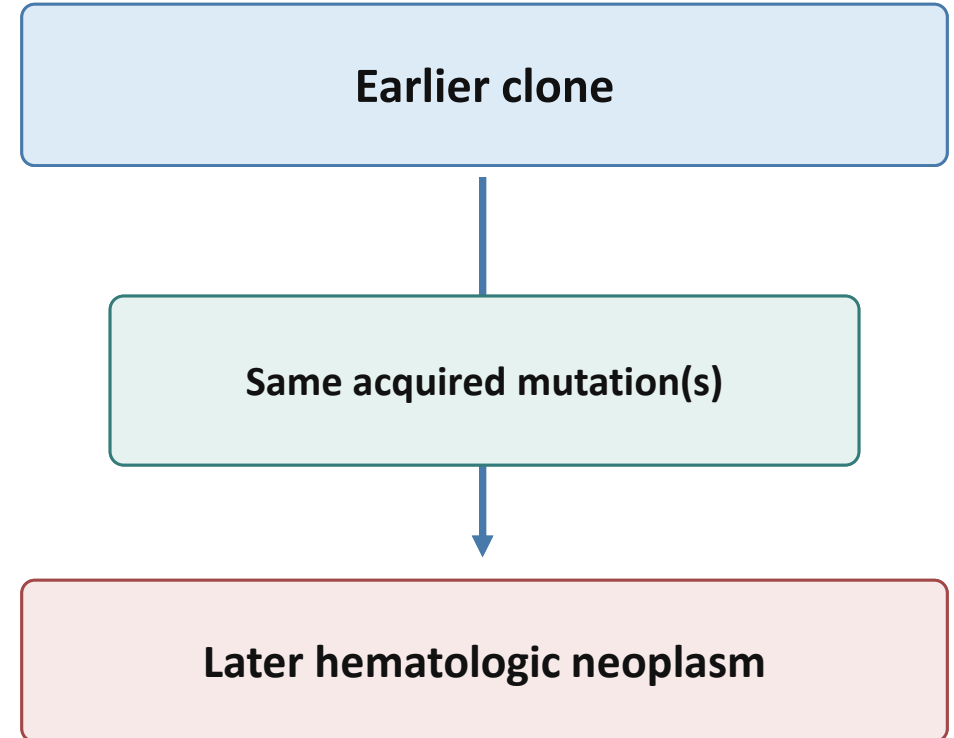
- Risks of T-cell tumors and B-cell tumors are also increased.
- This is consistent with mutation occurring in an upstream multipotent stem cell.
- A precursor lesion can therefore predate tumors of different lineages.



Schematic: Lineage output from an upstream HSC

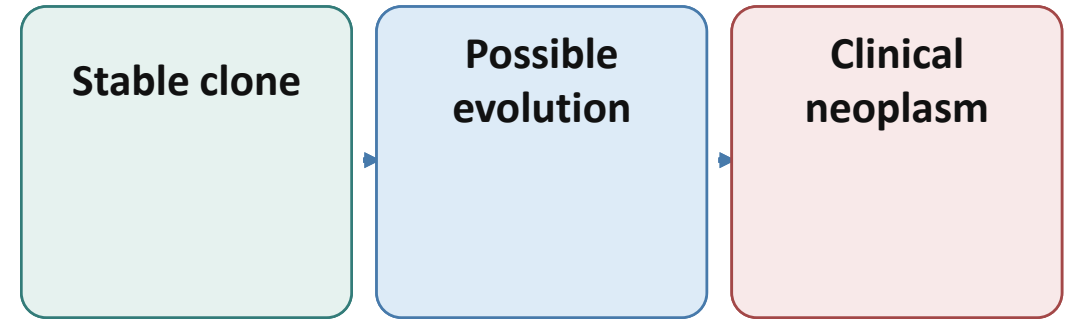
Shared variants support a precursor relationship

- Subsequent neoplasms commonly contain mutations present in the prior clone.
- This continuity supports a precursor–product relationship.
- A shared molecular lesion is more informative than simple chronological coincidence.



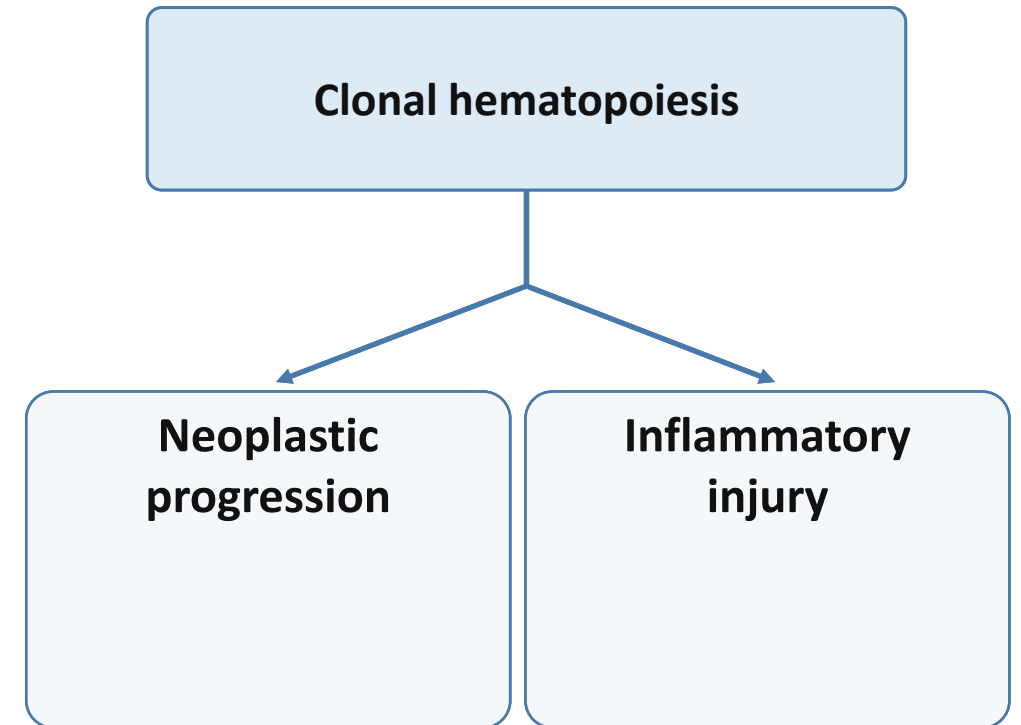
Clonal evolution is not inevitable

- An advantaged clone may remain clinically silent.
- A precursor–product relationship does not imply that every clone progresses.
- The textbook supports increased risk, not certainty of transformation.



Two major consequence pathways

- One branch concerns transformation into hematologic neoplasia.
- A second branch concerns inflammation and chronic organ disease.
- Both may arise despite initially normal blood counts.



Inflammation is a major noncancer effect

- Clonal hematopoiesis is associated with a systemic proinflammatory state.
- Mutant hematopoietic cells can alter inflammatory responses.
- This may increase the severity of prevalent chronic disorders.

Mutant blood-cell descendants



Amplified inflammation



Chronic tissue damage

TET2 links clones to innate immunity

- The TET2 association is especially strong for inflammatory disease.
- The source implicates epigenetic reprogramming of monocytes and macrophages.
- This modifies how these cells respond to inflammatory stimulation.

TET2-mutant hematopoiesis



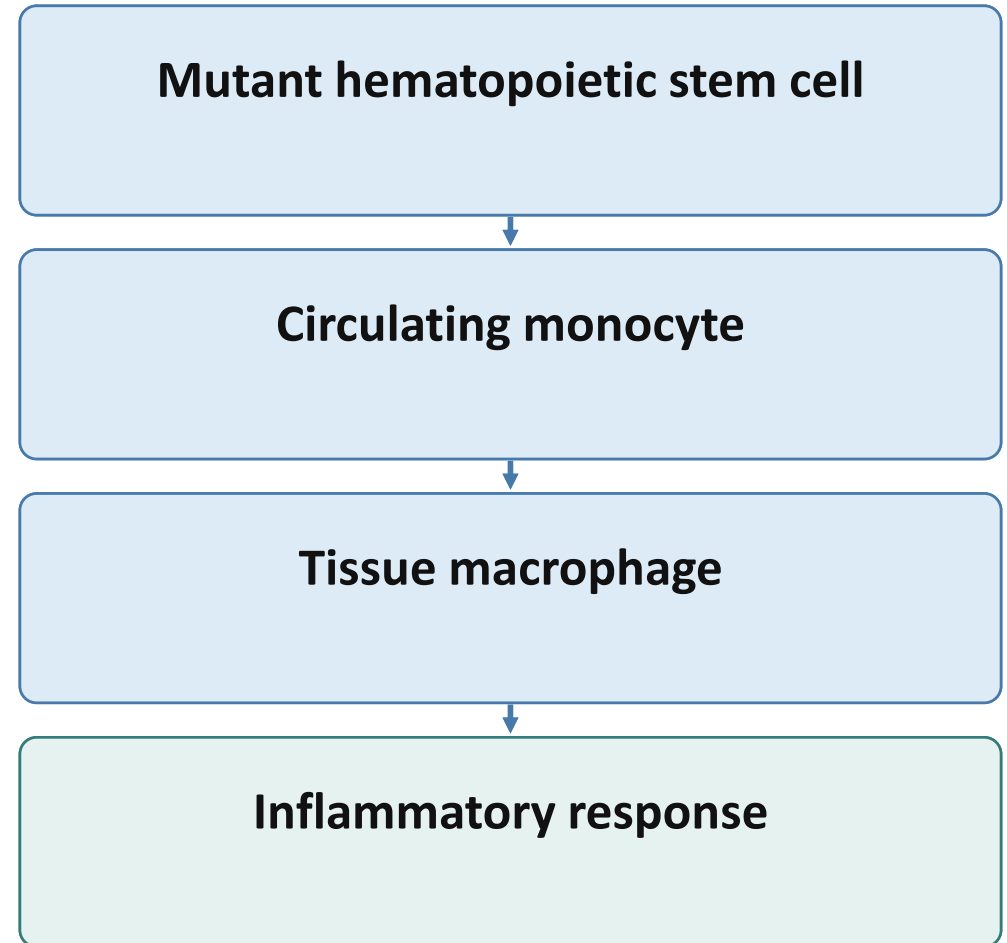
Monocytes / macrophages



Altered inflammatory responsiveness

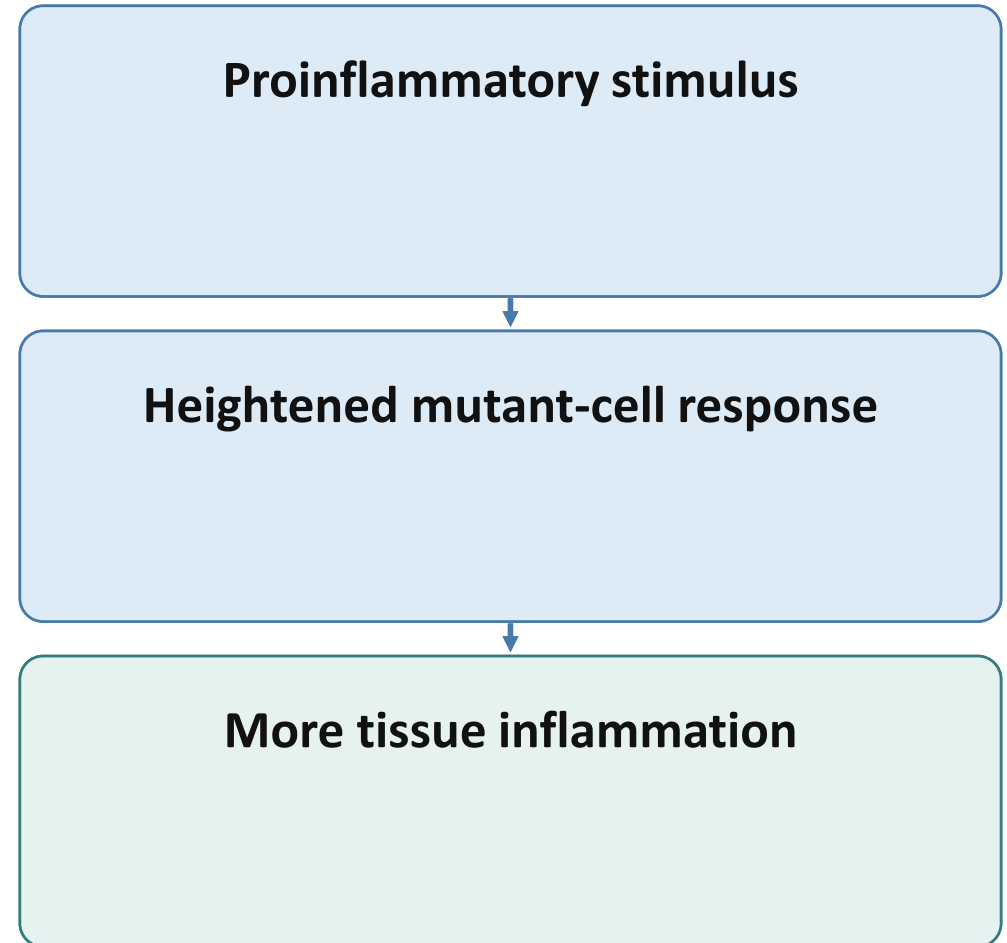
Monocytes and macrophages as effectors

- They arise from hematopoietic lineages and participate in tissue inflammation.
- Epigenetic changes can alter the intensity of their responses.
- The consequence extends outside the bone marrow to organ injury.



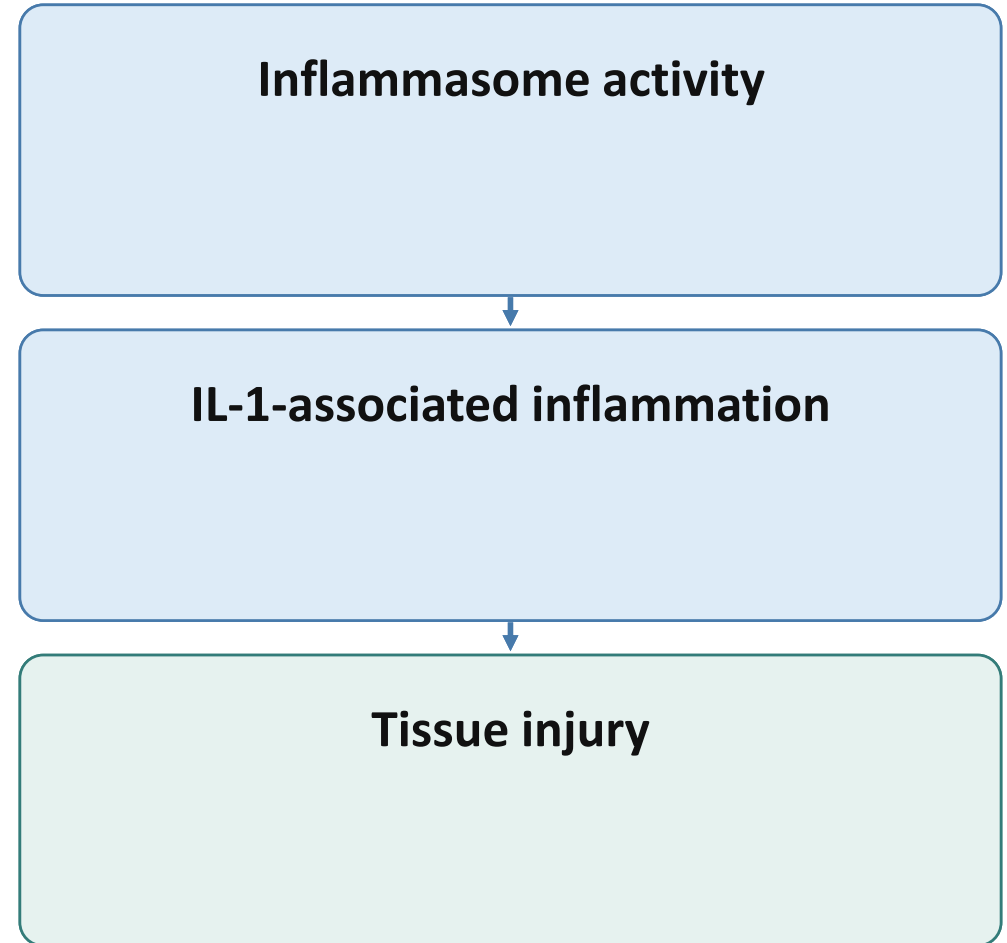
Hypersensitivity to inflammatory stimuli

- TET2-associated programming renders monocytes and macrophages unusually responsive.
- Greater inflammatory reactivity provides a plausible disease-amplification mechanism.
- This as an apparent mechanism rather than a complete causal account.



The inflammasome–IL-1 pathway

- IL-1 signaling and inflammasome activity are involved in experimental inflammation.
- In animal models, their inhibition protects against tissue damage.
- Animal-model protection is not equivalent to proven routine human preventive therapy.



Atherosclerosis association

- Clonal hematopoiesis is linked to greater severity of atherosclerotic disease.
- The proposed connection involves inflammation from mutant myeloid-cell descendants.
- Cardiovascular consequences are clinically important beyond cancer risk.

Clonal hematopoiesis



Proinflammatory cells



Atherosclerotic injury

Chronic liver disease association

- Nonalcoholic liver disease among affected chronic disorders.
- Amplified inflammatory responses offer a proposed shared mechanism.
- This association does not establish the clone as the sole cause of liver disease.

Mutant hematopoietic cells



Increased inflammatory tone



Liver disease severity

Chronic obstructive pulmonary disease

- Chronic obstructive pulmonary disease is also among the associated conditions.
- Altered host inflammatory reactivity may amplify tissue injury.
- The association broadens the clinical relevance beyond marrow pathology.

CH-associated inflammation



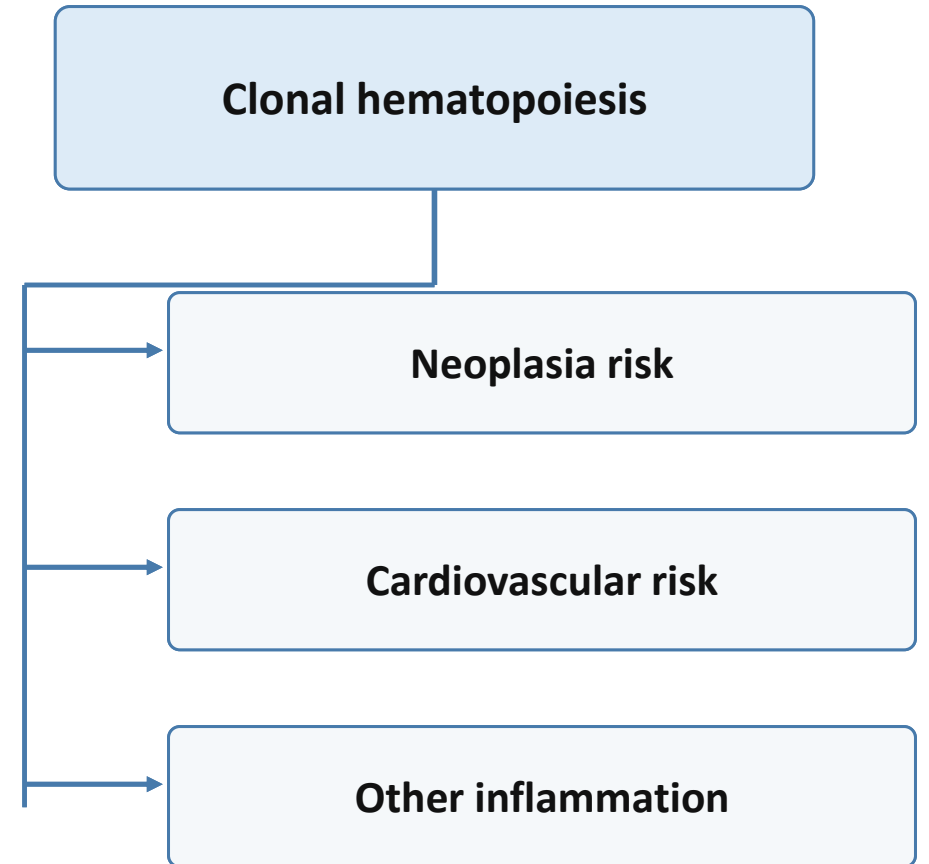
Lung tissue inflammatory response



Greater COPD severity

Consequences are not restricted to cancer

- Noncancer mortality is increased in individuals with clonal hematopoiesis.
- Cardiovascular disease is a prominent contributor.
- This changes the clinical interpretation of a superficially silent molecular state.



Symptoms may be absent at diagnosis

- Individuals usually lack symptoms attributable to hematologic abnormalities.
- Normal blood counts are expected in the definition employed here.
- Biological risk may nonetheless be clinically relevant.

**Silent
hematologic
presentation**

**Potential long-
term
complications**

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Red cell distribution width association

- A higher RDW is associated with clonal hematopoiesis.
- The basis for the association remains uncertain.
- RDW is also independently associated with mortality.

Elevated RDW



Observed association

Mechanistic basis unresolved

RDW should not be used alone

- RDW is an indirect hematology measure, not a clone-specific molecular assay.
- An increased RDW is not sufficient to diagnose clonal hematopoiesis.
- Its mechanistic association with the clone is unresolved.

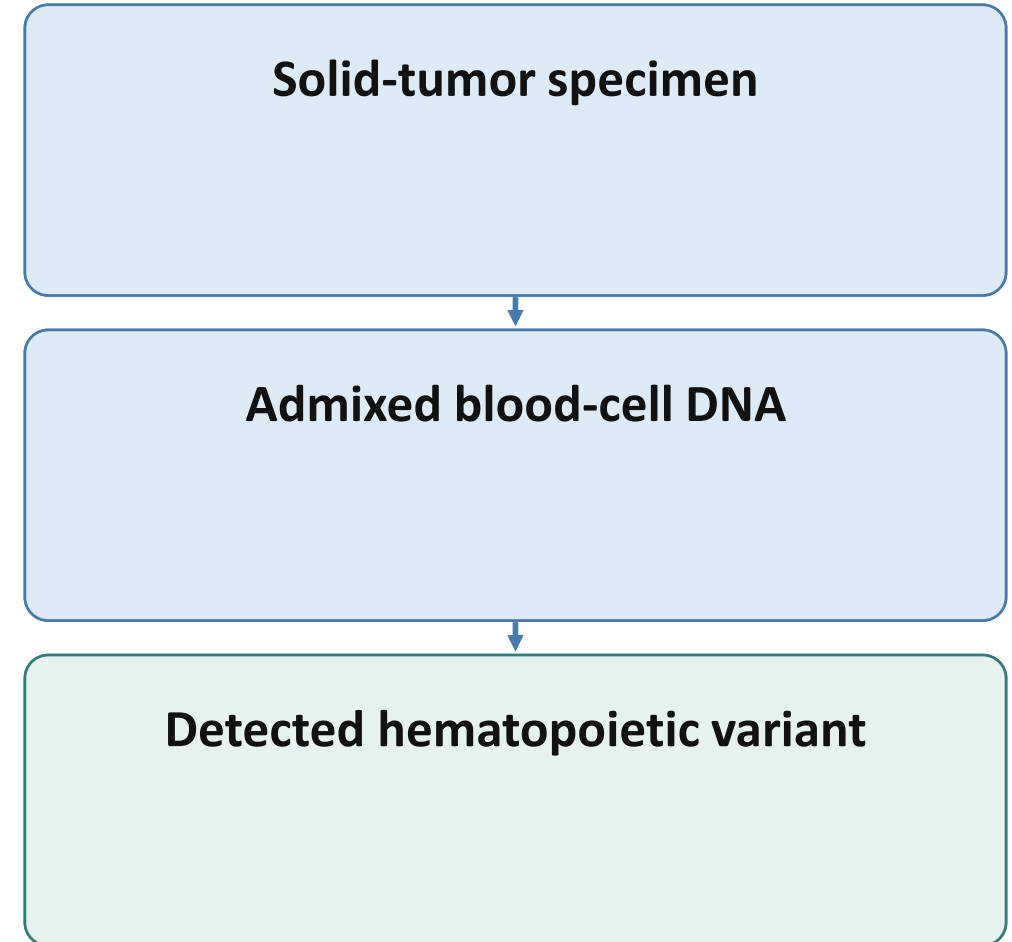
**Nonspecific RDW
association**

**Mutation-based
clonal
identification**

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Incidental detection in tumor sequencing

- Sequencing of solid malignancies can incidentally detect blood-cell mutations.
- Infiltrating leukocytes can contribute DNA to the specimen.
- TET2 or DNMT3A calls may therefore derive from blood cells rather than carcinoma cells.



Distinguish tumor from hematopoietic DNA

- A mutation reported in tumor sequencing is not automatically tumor-intrinsic.
- The cellular source must be considered when clonal-hematopoiesis genes are found.
- Molecular interpretation should be integrated with the sampled tissue and hematology data.

Was the assay performed on mixed-cell tissue?



Could the variant be hematopoietic?



Correlate with blood and tumor context

Teaching case: Incidental blood finding

- Scenario: An older adult with normal blood counts undergoes blood sequencing.
- A pathogenic acquired TET2 variant is detected above the textbook threshold.
- Question: Does this finding alone establish leukemia?

Teaching scenario

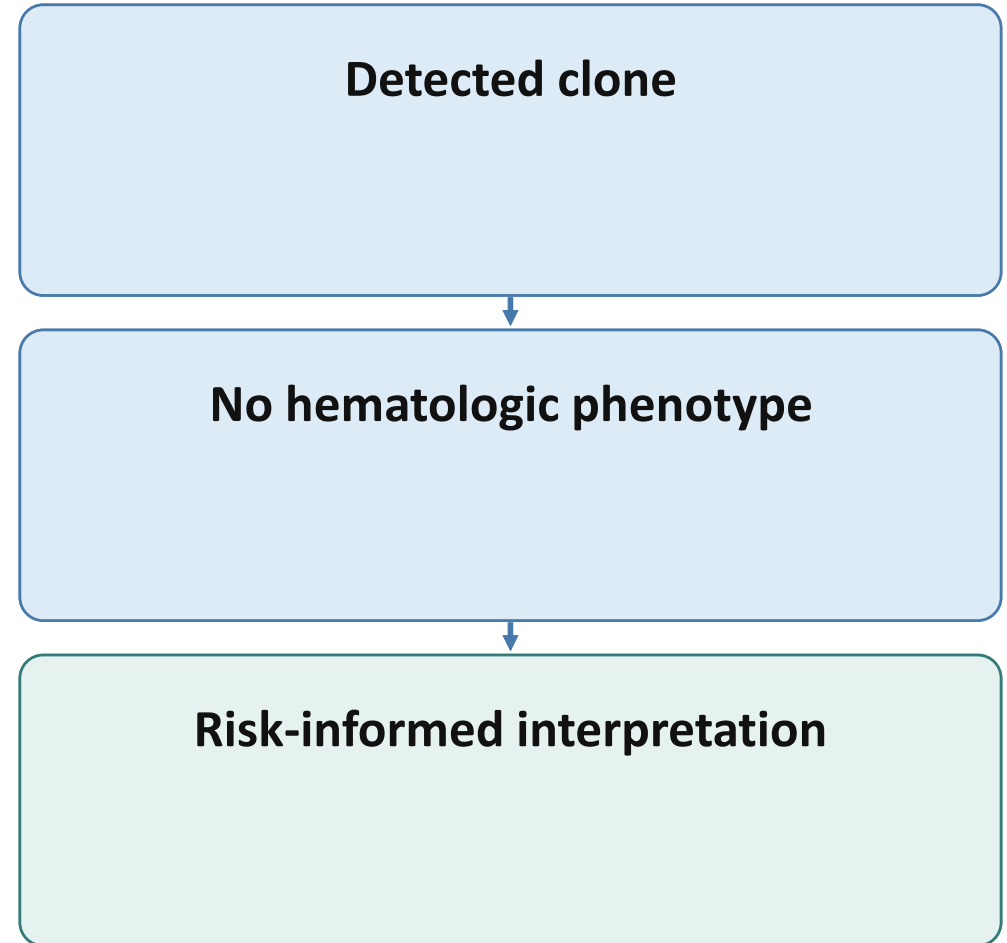
Older adult; Normal blood counts

Somatic TET2-positive clone

No signs of hematologic disease

Case interpretation: A precursor, not cancer

- The described pattern is compatible with clonal hematopoiesis.
- The clone confers risk but does not prove an overt neoplasm.
- Counseling must distinguish an estimated population risk from an individual prediction.



Teaching case: A lung tumor sequence

- Scenario: DNA from a lung carcinoma sample contains a DNMT3A mutation.
- The sample may include nonmalignant blood cells.
- Question: Can the sequencing call automatically be assigned to the carcinoma?

Teaching scenario

Lung carcinoma specimen

DNMT3A variant reported

Leukocytes may contribute DNA

Case interpretation: Determine cell origin

- Hematopoietic contamination is a recognized explanation.
- A detected cancer-associated gene is not necessarily altered in the solid-tumor cells.
- Avoid attributing biology or therapy implications to the tumor without support.

Variant detected in bulk tissue



Consider admixed blood cells



Do not assume tumor origin

Teaching case: Contrasting clone risks

- Scenario A: A small clone with a common epigenetic-driver variant.
- Scenario B: A much larger clone with a splicing-factor variant.
- Question: Should both be assigned identical neoplastic risk?

Teaching scenario

Different clone burdens

Different mutation classes

Normal counts at diagnosis

Case interpretation: Risk is heterogeneous

- Large clones and splicing-factor mutations as higher-risk features.
- The overall $\approx 1\%$ annual estimate cannot capture all risk strata.
- Prediction is a research focus; Avoid claiming precise individualized probabilities.

Baseline estimate

$\approx 1\%$ / year

Higher concern

Large clones

Higher concern

Splicing-factor variants

Prevention remains an evolving field

- Risk-stratification models are under development.
- Anti-inflammatory interventions are being investigated as potential prevention strategies.
- Animal-model evidence cannot be presented as a proven standard-of-care indication.

Identify higher-risk subgroups



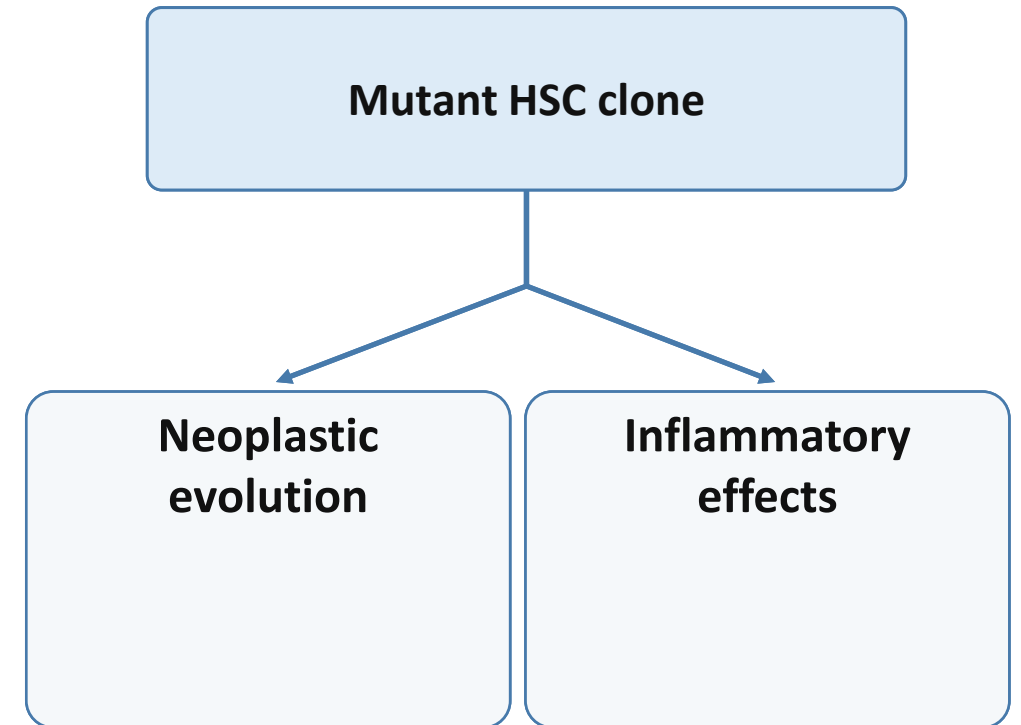
Study prevention strategies



Require clinical validation

Integrated mechanism map

- Somatic mutation and stem-cell selection create a stable clone.
- Clone-associated outcomes include hematologic evolution and inflammation.
- Interpretation combines clinical hematology and the molecular specimen context.



Five clinicopathologic take-home points

- Clonal hematopoiesis can be present with normal counts.
- Age, TET2 / DNMT3A and stem-cell selection explain much of the biology.
- Hematologic progression risk varies with clone burden and gene identity.
- Cardiovascular and chronic inflammatory disease associations are clinically relevant.
- Incidental molecular findings demand cell-of-origin interpretation.

1

Identify

2

Risk stratify

3

Interpret

Foundational reading

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 13 discussion of myeloid neoplasms and clonal hematopoiesis.
- This lecture follows the supplied textbook excerpt; no external classification updates are substituted.

Textbook chapter



Clonal hematopoiesis section



Parent myeloid-neoplasm context