

Cytogenetics and Genetics

Acute myeloid leukemia: molecular basis, disease classification, and clinicopathologic significance

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Learning objectives

- Explain how acquired genomic lesions define AML subgroups and disrupt myeloid differentiation.
- Relate recurrent chromosomal abnormalities to morphology, clinical setting, and outcome.
- Distinguish transcriptional, signaling, epigenetic, and p53-related driver mechanisms.
- Interpret molecular findings together with marrow morphology and immunophenotype.

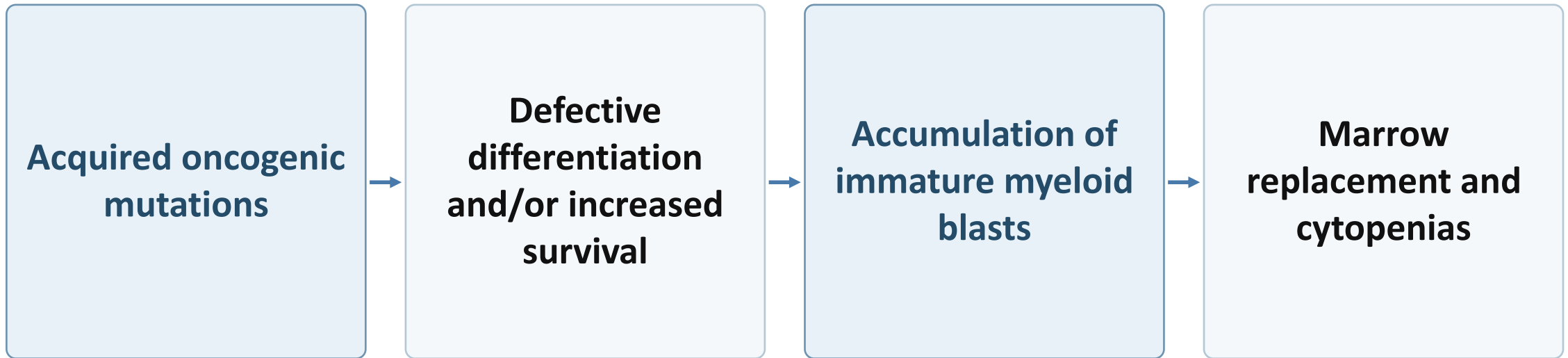
Emphasis: Genomic findings must be integrated—not interpreted in isolation.

Why cytogenetics matters in AML

- Genetic heterogeneity reflects the complexity of normal myeloid maturation.
- Recurrent abnormalities identify biologically distinct leukemias.
- Cytogenetic and molecular data contribute to classification, prognosis, and treatment selection.
- The same morphologic diagnosis may encompass different driver mechanisms.

Genetics is a disease-defining axis of AML classification.

The genetic basis of acute myeloid leukemia



Conceptual sequence / schematic

Disease phenotype follows from mutated hematopoietic progenitors.

Genetics does not replace pathologic evaluation

- Bone marrow examination documents increased myeloid blasts and evaluates lineage maturation.
- Immunophenotyping establishes myeloid differentiation when blast morphology is equivocal.
- Cytogenetic analysis detects structural and numerical chromosome abnormalities.
- DNA-based analyses identify pathogenic gene mutations and molecularly defined classes.

These modalities answer complementary questions.

Two major AML classification approaches

Genetically defined AML

- Specific recurrent genetic abnormalities define categories.
- Genotype can explain morphology and therapeutic vulnerability.
- Examples: RUNX1::RUNX1T1, CBFB::MYH11, PML::RARA.

AML defined by differentiation

- Used when qualifying defining genetic lesions are absent.
- Subgroups reflect myelocytic, monocytic, erythroid, or megakaryocytic patterns.
- Requires morphology and immunophenotypic lineage assessment.

This is the two-part framework described in the supplied Robbins table.

The same chromosomal finding can influence several decisions

- Classification: Places an AML into a genetically defined group.
- Morphologic expectation: Predicts characteristic patterns in several subtypes.
- Prognostic interpretation: Separates favorable and high-risk disease associations.
- Therapeutic relevance: Some lesions enable mechanism-directed treatment.

A lesion can carry diagnostic, prognostic, and predictive relevance.

Chromosomal abnormalities are common

- Conventional cytogenetics detects chromosomal aberrations in 50%–70% of AML cases in the Robbins description.
- Special high-resolution banding is reported to detect abnormalities in approximately 90%.
- These figures refer to the techniques and source context described.
- A case without an identified visible abnormality may still have pathogenic gene mutations.

Do not confuse cytogenetically normal results with biologically normal genomes.

Karyotypic changes versus sequence-level changes

Chromosomal alterations

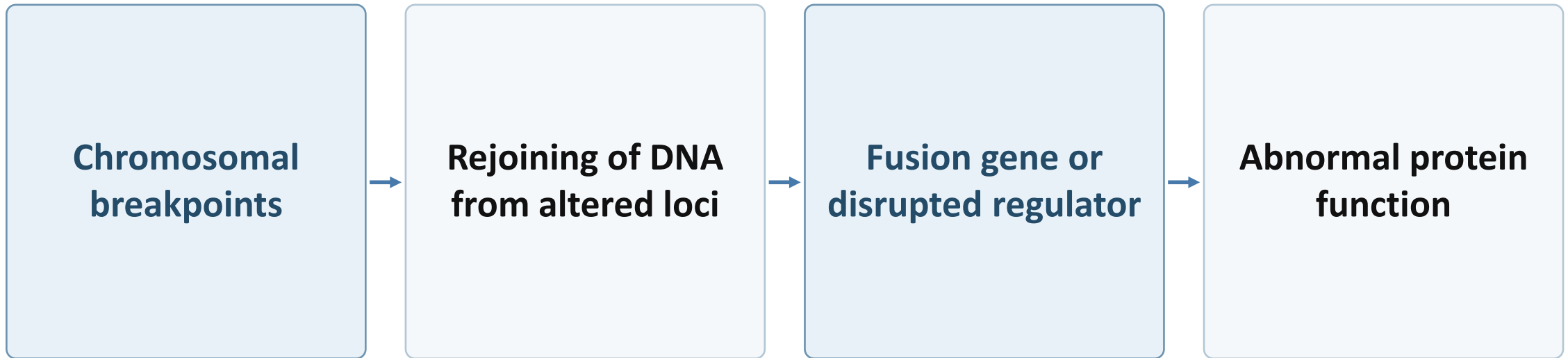
- Translocations and inversions may create chimeric genes.
- Deletions and monosomies remove chromosomal material.
- Multiple structural/numerical abnormalities can produce complex karyotypes.

Gene-level mutations

- Single genes can be altered without a visible chromosome change.
- Examples: NPM1, FLT3, IDH1/IDH2, TP53.
- Sequencing supplies information distinct from banded karyotypes.

Diagnostic interpretation requires both the scale and effect of a lesion.

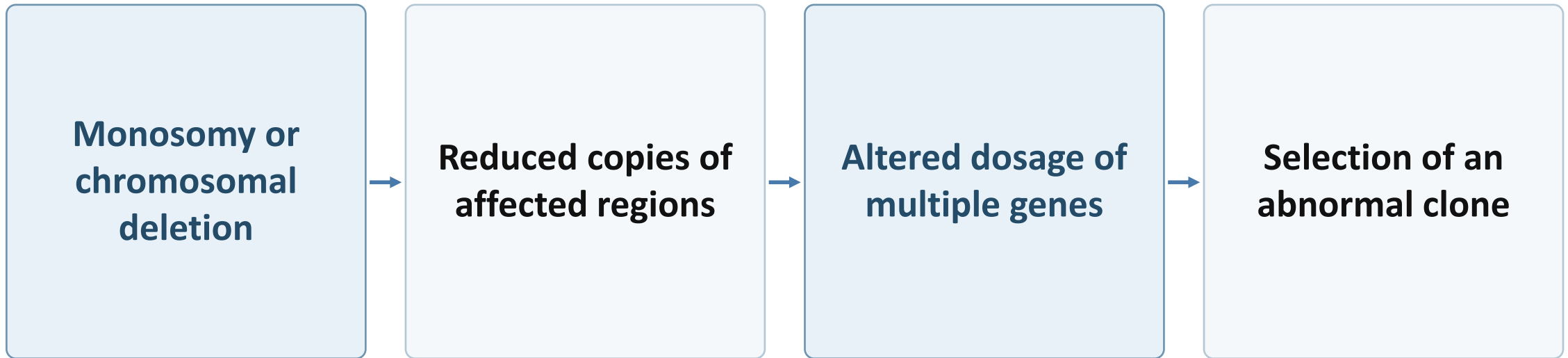
Rearrangement as a fusion-gene mechanism



Conceptual sequence / schematic

Schematic principle; Particular rearrangements have different consequences.

Gene dosage through chromosome loss



Conceptual sequence / schematic

The precise causal contribution of individual lost genes may remain uncertain.

Three common lesion classes

Balanced rearrangement

T(8;21) or t(15;17)

Usually creates a rearranged gene product.

Inversion

Inv(16)

Rearrangement within one chromosome.

Copy-number loss

-5, -7 or segmental deletion

Loss of chromosomal material;
Often therapy-related.

Different cytogenetic signatures require different biological interpretation.

Four groups of AML driver mutations

- Transcriptional regulators that interfere with maturation.
- Signaling proteins that promote growth or survival.
- Epigenomic regulators affecting DNA methylation or chromatin organization.
- TP53 or other regulators of p53 tumor-suppressor function.

The four-group framework comes from the AML pathogenesis section.

Driver classes and their primary effects

Transcription factors

Differentiation block

RUNX1/CBFB, PML::RARA

Signaling

Proliferation / survival

FLT3, RAS

Epigenome

Altered transcriptional regulation

IDH1/2, cohesin-related genes

P53 axis

Defective tumor suppression

TP53

Multiple abnormalities may coexist within the same AML.

Why cooperation between drivers matters

- A maturation block alone does not necessarily produce fully developed AML.
- Activated growth/survival signaling can act alongside differentiation-blocking mutations.
- Experimental cooperation between PML::RARA and activated FLT3 in mice.
- This is an example—not a universal fixed two-mutation model for every AML.

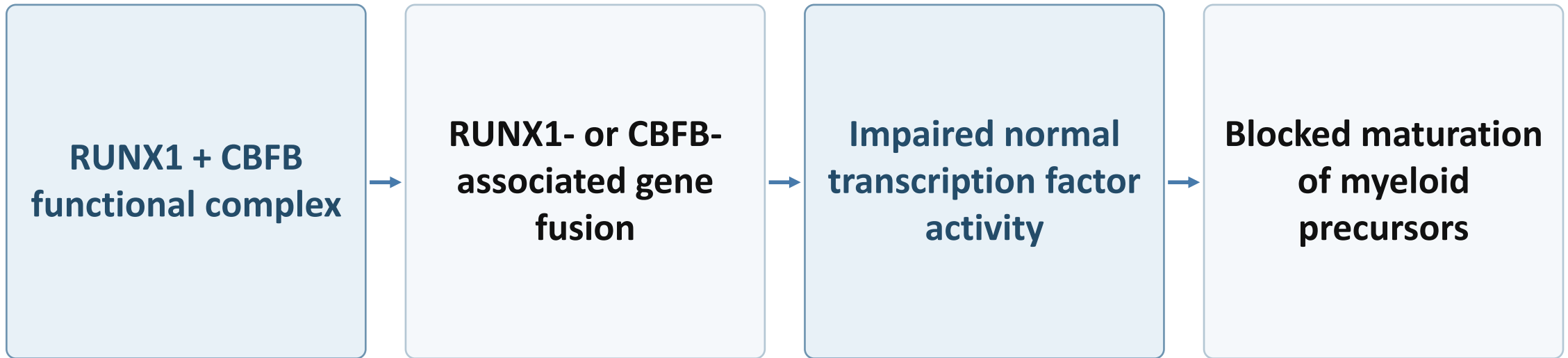
Avoid assuming that one genetic aberration explains every cancer hallmark.

RUNX1 and CBFB: A normal transcription factor complex

- RUNX1 and CBFB encode interacting proteins required for normal hematopoiesis.
- Together they form the core-binding-factor transcriptional complex.
- Normal function contributes to orderly differentiation of myeloid precursors.
- Rearrangements of either component can interfere with the complex.

The affected genes are biologically linked despite different chromosomal lesions.

Core-binding-factor disruption



Conceptual sequence / schematic

Schematic relationship based on the Robbins pathogenesis discussion.

AML with t(8;21): Fusion and mechanism

- T(8;21) creates a RUNX1::RUNX1T1 fusion gene.
- The rearrangement disrupts a normal RUNX1-associated transcriptional program.
- The fusion protein interferes with maturation of myeloid cells.
- This AML falls among the genetically defined disease classes.

Mechanistic class: Differentiation-associated transcription factor abnormality.

T(8;21): Genotype and expected phenotype

Genetic finding

- Recurrent t(8;21) rearrangement.
- RUNX1::RUNX1T1 fusion.
- Core-binding-factor pathway affected.

Morphologic correlation

- Myelocytic differentiation over a broad maturation range.
- Auer rods can be readily identified.
- Abnormal cytoplasmic granules are reported.

The morphologic pattern is supportive, not a substitute for genetic identification.

T(8;21): Prognostic interpretation

- The Robbins AML table places this class in a favorable prognostic group.
- The favorable association is relative to other AML genomic classes.
- Cytogenetics is interpreted alongside the full clinical and pathologic setting.
- Avoid treating any favorable label as a guarantee for an individual patient.

Use disease-specific context when discussing prognosis.

AML with inv(16): Fusion and mechanism

- Inv(16) produces a CBFB::MYH11 fusion gene.
- Normal CBFB participates in the RUNX1/CBFB transcriptional complex.
- The aberrant fusion interferes with core-binding-factor function.
- Failure of appropriate myeloid maturation contributes to AML.

A chromosome inversion can be a disease-defining lesion.

Inv(16): Genotype and expected phenotype

Genetic finding

- Inv(16) structural rearrangement.
- CBFB::MYH11 fusion.
- Core-binding-factor-associated AML.

Morphologic correlation

- Both myelocytic and monocytic differentiation.
- Abnormal eosinophilic precursors.
- These eosinophils may show aberrant basophilic granules.

The combination of lineages may suggest this class before molecular confirmation.

Comparison of core-binding-factor AML

Feature	t(8;21)	inv(16)
Fusion	RUNX1::RUNX1T1	CBFB::MYH11
Regulatory axis	RUNX1–CBFB	RUNX1–CBFB
Morphology	Myeloid maturation; Auer rods	Myelomonocytic; abnormal eosinophils
Robbins prognosis	Favorable	Favorable

Biologically connected mechanisms can have different morphologic clues.

Core-binding-factor AML: Interpretation limits

- RUNX1 and CBFB are normal cooperating proteins, not interchangeable genes.
- T(8;21) and inv(16) yield distinct fusion products.
- The same functional complex is perturbed through different genetic events.
- Neither cytology alone nor a generic “CBF abnormality” reports the exact molecular subtype.

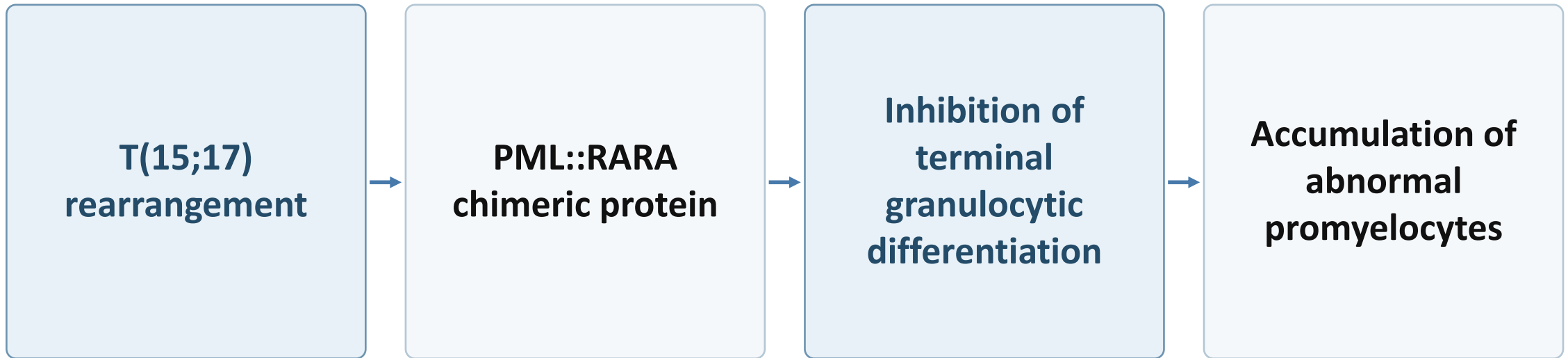
Report the precise rearrangement when known.

Acute promyelocytic leukemia: Defining genetics

- Acute promyelocytic leukemia (APL) is a distinctive subtype of AML.
- It is associated with t(15;17) and a PML::RARA fusion.
- The fusion incorporates retinoic-acid receptor α and PML components.
- Abnormal regulation interferes with terminal granulocytic differentiation.

Genotype directly explains a maturation-arrest phenotype.

PML::RARA and maturation arrest



Conceptual sequence / schematic

A differentiation-blocking lesion defines APL.

APL: Genetic lesion to pathologic phenotype

Underlying mechanism

- PML::RARA interferes with normal transcriptional regulation.
- Maturation is arrested near the promyelocyte stage.
- A defining fusion provides a treatment target.

Expected morphology

- Abnormal promyelocytes with coarse azurophilic granules.
- Auer rods may be abundant and occur in bundles.
- A microgranular variant may have inconspicuous primary granules.

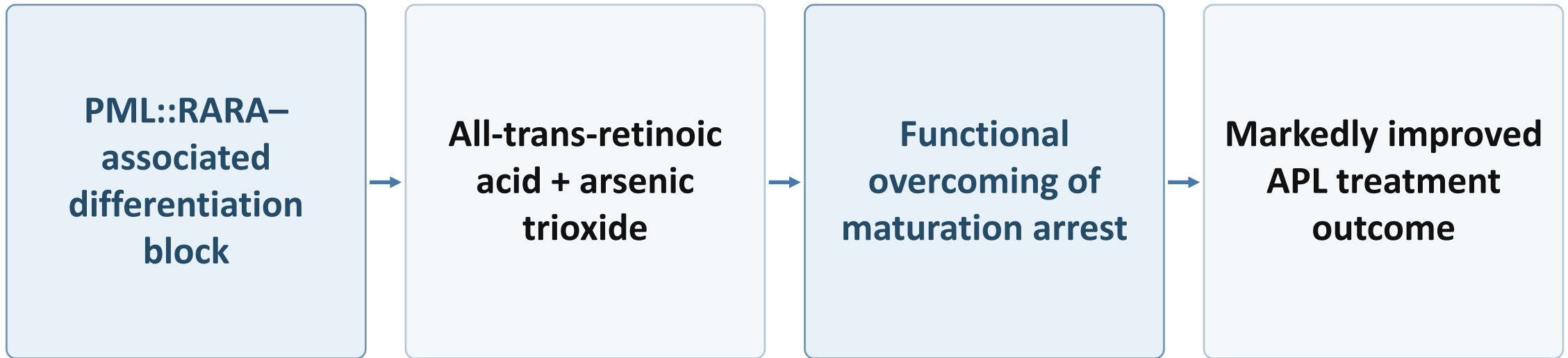
Morphologic heterogeneity does not negate a shared defining fusion.

APL: A genetic result with urgent clinical implications

- APL carries a high incidence of disseminated intravascular coagulation.
- Leukemic-cell procoagulants and fibrinolytic factors worsen bleeding tendency.
- Morphologic suspicion plus characteristic genetic context is clinically consequential.
- The Robbins table describes APL as very favorable when effectively treated.

Bleeding biology is a major clinical correlation of this genetic subtype.

Targeted differentiation in APL



Conceptual sequence / schematic

Treated APL is curable in over 90% of patients; This is a source-specific statement.

Why PML::RARA is more than a diagnostic marker

- Diagnostic relevance: Supports a genetically defined AML entity.
- Mechanistic relevance: Explains blocked promyelocyte maturation.
- Predictive relevance: The lesion identifies a therapy-responsive biology.
- Clinical relevance: Coagulopathy requires prompt recognition.

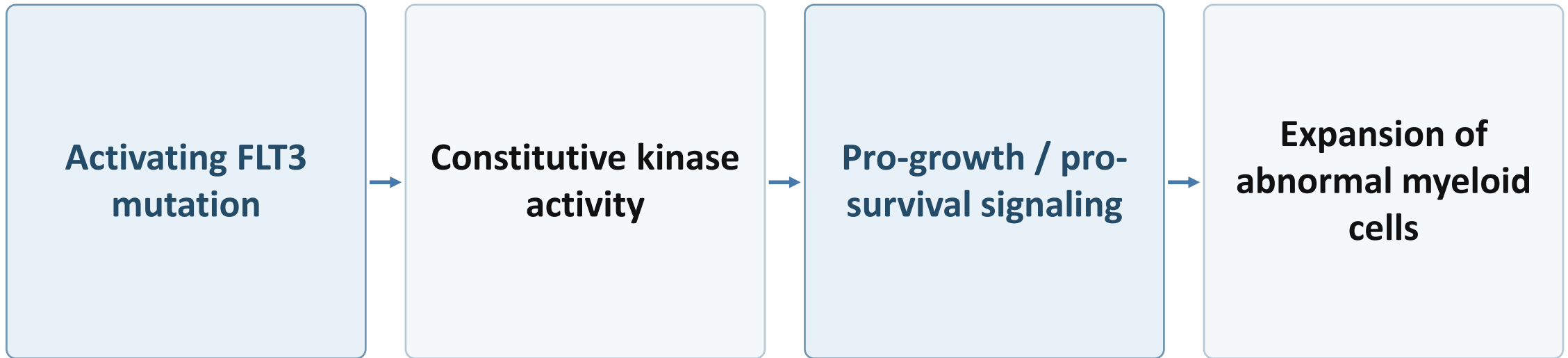
The same fusion connects mechanism, diagnosis, and treatment.

FLT3: A growth-factor signaling lesion

- FLT3 encodes a receptor tyrosine kinase involved in signaling.
- Activating alterations can mimic normal growth factor inputs.
- Constitutive signaling supports proliferation and survival.
- FLT3 alterations may coexist with APL-associated PML::RARA.

Signaling lesions differ in function from differentiation-blocking fusions.

Activated FLT3 promotes leukemic fitness



Conceptual sequence / schematic

Do not equate increased proliferation with an independent maturation block.

Cooperativity: PML::RARA and FLT3

- In the mouse model discussed by Robbins, PML::RARA alone is weakly leukemogenic.
- Combining PML::RARA with activated FLT3 is a potent inducer of AML.
- The fusion affects differentiation; The kinase affects growth and survival.
- This experimentally supports cooperative oncogenesis in AML.

Distinguish the demonstrated model from an assertion about all human cases.

RAS-pathway mutations in AML

- Mutations in several progrowth signaling genes occur in subsets of AML.
- RAS among the important signaling examples.
- These lesions act through growth and survival pathways rather than a fusion-mediated differentiation block.
- Their presence illustrates the functional diversity of AML driver mutations.

Driver pathways—not merely mutation lists—explain phenotype.

Differentiation lesions versus signaling lesions

Differentiation-associated

- RUNX1::RUNX1T1, CBFB::MYH11, PML::RARA.
- Interfere with appropriate myeloid maturation.
- Often create characteristic morphologic patterns.

Signaling-associated

- FLT3 activation and RAS alterations.
- Drive proliferative and survival advantage.
- May cooperate with other pathogenic changes.

These are functional categories, not mutually exclusive patient groups.

Epigenomic dysregulation in AML

- Some AML mutations affect proteins that regulate DNA methylation.
- Others alter chromatin organization and the nuclear epigenome.
- Such changes can disturb patterns of gene expression.
- Robbins cautions that their precise pathogenic mechanisms remain incompletely understood.

Avoid portraying epigenomic disruption as a fully resolved linear pathway.

Three epigenomic concepts

DNA methylation

Abnormal regulatory patterns

Impacts transcriptional programs

Chromatin architecture

Cohesin-family proteins

Affects 3D chromatin organization

Metabolic–epigenetic link

IDH1 or IDH2 mutations

Produces 2-hydroxyglutarate

The book groups these mechanisms under epigenomic regulation.

DNA methylation and myeloid clone biology

- DNA methylation modifies how genes are expressed without changing base sequence.
- The clonal hematopoiesis section highlights TET2 and DNMT3A as methylation regulators.
- Mutations in such regulators may confer a clonal growth or survival advantage.
- Overlap among clonal hematopoiesis, MDS, and AML gives developmental context.

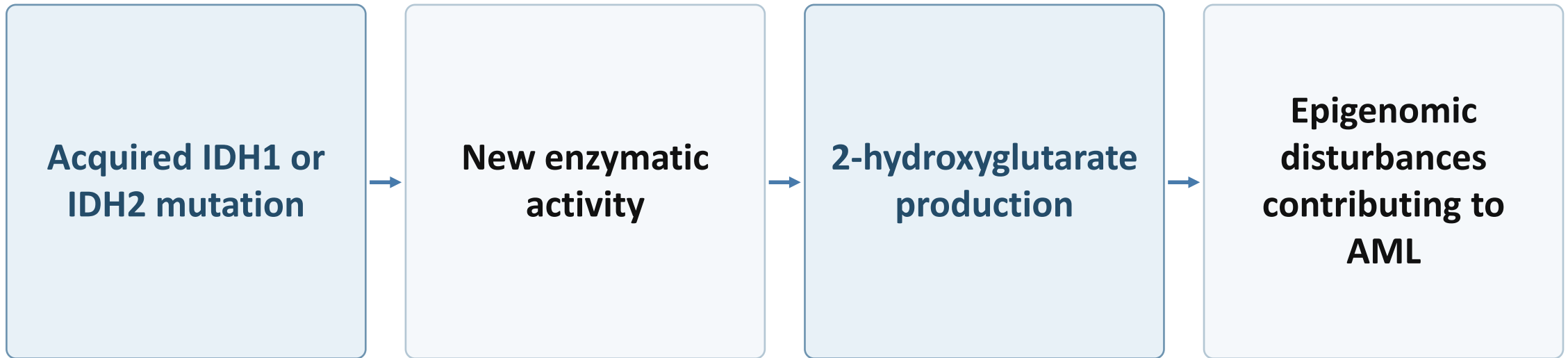
An early clonal mutation is not by itself proof of overt AML.

Cohesin and chromatin topology

- Cohesin proteins help regulate the three-dimensional organization of chromatin.
- AML can harbor mutations that alter this regulatory system.
- Abnormal topology may disturb gene-expression programs during myelopoiesis.
- Robbins does not assign one complete causal mechanism to all cohesin alterations.

Chromatin architecture is a functional layer of genetic pathogenesis.

Mutant IDH and oncometabolite generation



Conceptual sequence / schematic

The book describes 2-hydroxyglutarate as an oncometabolite.

IDH alterations: Therapeutic connection

- Mutant IDH enzymes gain an abnormal metabolic activity.
- Inhibitors of the mutated enzymes can treat IDH-mutated AML.
- Clinically meaningful responses to IDH-directed treatment.
- A treatment target does not automatically define all other prognostic properties.

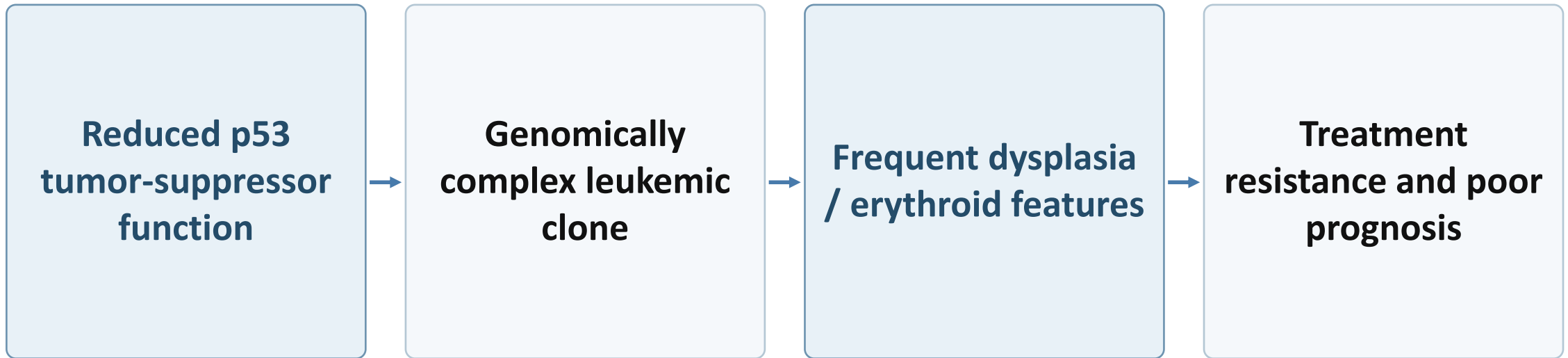
Molecular classification can expose actionable vulnerabilities.

TP53: A biologically distinct AML subgroup

- TP53 mutations or lesions impairing the p53 pathway occur in AML.
- They are associated with complex karyotypes.
- The textbook also links them to dysplasia and erythroid differentiation.
- These tumors have particularly poor outcomes with standard treatment.

Do not confuse adverse genetic biology with morphology alone.

P53 pathway impairment: Clinicopathologic association



Conceptual sequence / schematic

This is an association-based schematic, not a complete causal proof for each link.

Complex versus balanced cytogenetic patterns

Selected balanced rearrangements

- Often characteristic of de novo AML in younger adults.
- Examples: T(8;21), inv(16), t(15;17).
- Include several favorable subtype associations.

Complex / chromosome-loss patterns

- Often encountered after genotoxic therapy.
- Loss of chromosome 5 or 7 material is prominent.
- May accompany p53 pathway dysfunction and adverse outcome.

Patient context can guide—but does not replace—genetic testing.

TP53-associated AML: Interpretive caution

- Complex karyotype and TP53 impairment are correlated.
- An erythroid or dysplastic pattern may raise suspicion for this biology.
- Neither morphology nor therapy history uniquely establishes TP53 status.
- A prognosis label describes a group-level association, not certain individual outcome.

Use confirmed genetic findings to support biologic attribution.

De novo AML in younger adults

- AML arising de novo in younger individuals commonly features balanced rearrangements.
- T(8;21), inv(16), and t(15;17).
- These correspond to specific fusion-associated AML entities.
- Age and de novo presentation suggest patterns but are not definitive genetic tests.

Epidemiologic setting should inform, not dictate, expectations.

Genotoxic therapy-associated AML

- AML after many DNA-damaging treatments shows chromosome losses or deletions.
- Chromosomes 5 and 7 are repeatedly implicated.
- Mutations disrupting p53 function are frequent in this context.
- These abnormalities contribute to generally adverse disease associations.

Prior treatment exposure is clinically relevant to genetic interpretation.

Monosomy and deletion: What do the terms mean?

Monosomy

- Loss of a whole chromosome.
- Common examples cited: Monosomy 5 or 7.
- Affects genetic dosage across the chromosome.

Segmental deletion

- Loss of part of a chromosome arm.
- Examples in related MDS context: Del(5q), del(7q).
- Can affect genes within a specific region.

Both represent copy-number losses; They are not balanced rearrangements.

Topoisomerase II inhibitor: The exception

- Therapy-associated AML does not uniformly show chromosomes 5/7 loss.
- AML following topoisomerase II inhibitor exposure is linked to rearrangements of KMT2A.
- KMT2A resides at chromosome 11q23.
- This as an important exception to the common therapy-related pattern.

The source excerpt contains a likely KMT2A transcription typo; The neighboring table uses KMT2A.

KMT2A-rearranged AML

- Rearrangements involving KMT2A define a distinct genomic AML category.
- The Robbins table lists t(11q23;variable partner) among major examples.
- Some monocytic differentiation is often present.
- The source assigns an unfavorable prognosis to this class.

Gene rearrangement, exposure history, and phenotype may converge.

Clinical setting and typical genetic associations

Clinical context	Frequent association	Interpretive point
Younger de novo AML	t(8;21), inv(16), t(15;17)	Balanced rearrangements
Most genotoxic therapies	-5/-7, del(5q)/del(7q); p53	Loss/complexity
Topoisomerase II inhibitors	KMT2A (11q23) rearrangement	Important exception
Older adults	CH/MDS-overlapping mutations	Clonal history matters

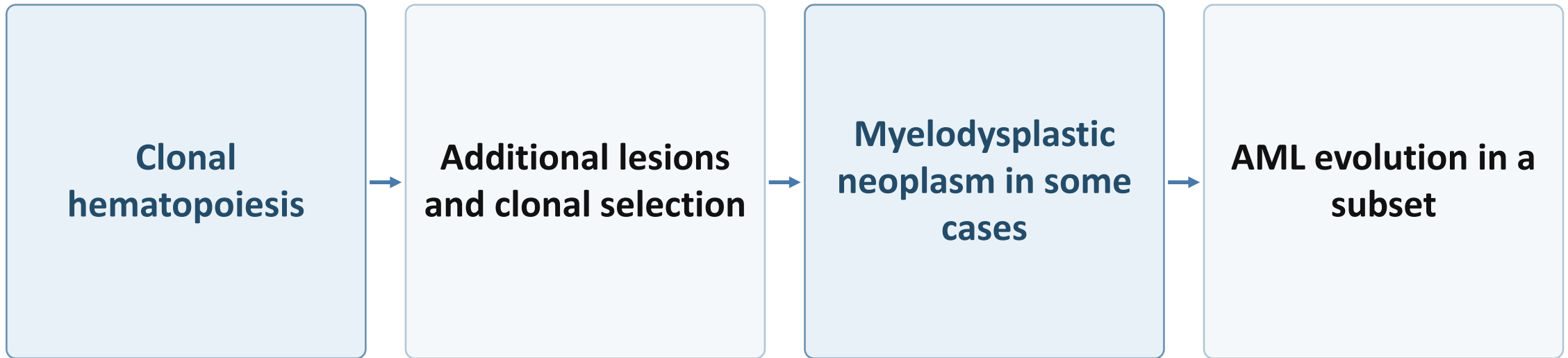
These are associations, not one-to-one deterministic rules.

AML in older adults: Evolutionary context

- Overlap with mutations found in clonal hematopoiesis and MDS.
- Increasing age is linked to different genomic contexts than classic younger de novo AML.
- An antecedent clonal disorder may contribute an earlier mutation background.
- Genetic assessment helps distinguish subgroup biology beyond age itself.

Age is a contextual variable; Genotype remains central.

A possible clonal progression pathway



Conceptual sequence / schematic

A possible progression route; Not every clone becomes MDS or AML.

Clonal hematopoiesis is not overt AML

- Clonal hematopoiesis occurs in individuals with normal blood counts at diagnosis.
- It involves an expanded hematopoietic clone with acquired pathogenic mutations.
- TET2 and DNMT3A among common genes.
- Some clones later acquire additional genetic changes and evolve into neoplasia.

Avoid labeling isolated clonal hematopoiesis as acute leukemia.

MDS shares—but does not duplicate—AML genetics

- MDS and AML share lesions affecting epigenomic regulators.
- RNA-splicing genes are a prominent mutation class in MDS.
- Common balanced AML rearrangements are not characteristic of MDS.
- TP53 abnormalities and complex cytogenetics have adverse associations in both.

Shared drivers can reflect biological continuity without diagnostic equivalence.

Myelodysplasia-related genetic abnormalities

- Del(5q) or del(7q) among the associated cytogenetic abnormalities.
- Associated sequence-level genes include SRSF2, SF3B1, U2AF1, and ZRSR2.
- The table also lists ASXL1, EZH2, BCOR, and STAG2.
- The source describes this AML class as having an unfavorable prognosis.

This is the gene list table; Classification details can be edition-dependent.

Disease groups: Genetics and phenotype

Feature	Clonal hematopoiesis	MDS	AML
Blood counts	Normal at definition	Cytopenias common	Often cytopenias
Marrow state	Clonal cells; no overt neoplasm	Ineffective / dysplastic maturation	Blast accumulation
Gene overlap	TET2, DNMT3A	Epigenetic/splicing/TP53	Multiple driver classes
Relationship	Potential precursor	May transform to AML	Acute myeloid neoplasm

Categories are biologically related but require distinct diagnostic criteria.

Morphology remains a genomic clue

- Auer rods in abnormal promyelocytes support consideration of APL.
- Myelomonocytic differentiation with unusual eosinophils can suggest inv(16).
- Abundant maturation and abnormal cytoplasmic granules can suggest t(8;21).
- Dysplasia and erythroid features can occur with p53 pathway abnormalities.

Visual features suggest—not definitively identify—specific lesions.

Immunophenotype and genetics answer different questions

- Morphologic overlap between myeloblasts and lymphoblasts can be substantial.
- Myeloid antigen studies establish lineage differentiation.
- The Robbins AML figure describes expression of CD34 and CD33 in an illustrative blast population.
- A chromosome or mutation result identifies a distinct layer of disease identity.

Lineage confirmation should not be conflated with molecular subtype.

Genetic AML subtypes in the Robbins framework

Genetic subtype	Genetic lesion	Source prognosis
Core-binding factor AML	RUNX1::RUNX1T1	Favorable
Core-binding factor AML	CBFB::MYH11	Favorable
Acute promyelocytic leukemia	PML::RARA	Very favorable
KMT2A-rearranged AML	KMT2A rearrangement	Poor
NPM1-mutated AML	NPM1 mutation	Favorable
MDS-related genetics	Defined mutations / 5q or 7q loss	Poor

These are textbook group-level labels, not a replacement for individualized risk assessment.

NPM1-mutated AML in the classification table

- The Robbins table includes an AML category defined by NPM1 mutation.
- Detection is described through DNA sequencing.
- The listed prognosis is favorable for this class in the source framework.
- This illustrates why gene-level testing complements chromosome banding.

A defining mutation may be invisible on routine cytogenetic analysis.

Why survival and treatment outcomes differ

- Different AML subtypes have distinct mechanisms of disease maintenance.
- APL responds to treatment directed toward its fusion-associated maturation block.
- IDH-mutated and FLT3-mutated AML can have targeted-therapy opportunities.
- High-risk TP53-associated and genotoxic-treatment-associated forms have poorer outcomes.

Biologic diversity is clinically consequential.

Genetic findings: Distinct clinical roles

Disease assignment

- Fusion genes can establish AML subtype.
- Some genetic definitions modify reliance on a simple blast threshold.
- Class assignment helps organize diagnostic information.

Clinical management

- Genomic subgroup informs prognosis.
- Some alterations identify targeted drug mechanisms.
- Therapy history and phenotype alter the interpretation of risk.

Classification and management are related but not identical uses of genomics.

Blast percentage is not the entire diagnosis

- 20% marrow blasts as the usual AML threshold.
- The source WHO framework permits certain genetically defined AML diagnoses below that blast percentage.
- This illustrates that disease-defining genetics may take precedence over a uniform blast count.
- Actual cutoffs are classification- and edition-specific; Do not generalize across systems.

Genetic context can change how morphologic findings are classified.

Case interpretation: Promyelocytic morphology

Clinical vignette

A marrow contains abnormal promyelocytes with coarse granules and bundles of Auer rods; Bleeding is prominent.

Interpretive task

Which fusion should be investigated, and what clinical hazard does the appearance raise?

Resolution

PML::RARA (t(15;17)); Acute promyelocytic leukemia with major coagulopathy risk.

Case interpretation: Myelomonocytic pattern

Clinical vignette

A marrow shows granulocytic and monocytic differentiation, with abnormal eosinophilic precursors containing basophilic granules.

Interpretive task

Which recurrent genomic lesion is the characteristic correlate?

Resolution

Inv(16), producing CBFB::MYH11.

Case interpretation: Preceding chemotherapy

Clinical vignette

AML occurs after prior cytotoxic treatment. The karyotype includes losses involving chromosomes 5 and 7 and several additional abnormalities.

Interpretive task

Which pathway defect is particularly important to consider?

Resolution

TP53/p53 pathway impairment; Complex, therapy-related genomic context.

Case interpretation: Exposure-specific exception

Clinical vignette

A patient develops AML after exposure to a topoisomerase II inhibitor and has evidence of a chromosome 11q23 rearrangement.

Interpretive task

Which gene is strongly associated with this exception?

Resolution

KMT2A rearrangement; Often associated with monocytic differentiation.

Case interpretation: Normal-looking chromosomes

Clinical vignette

An AML sample has no identified abnormality on routine karyotyping, but sequencing reveals a pathogenic NPM1 mutation.

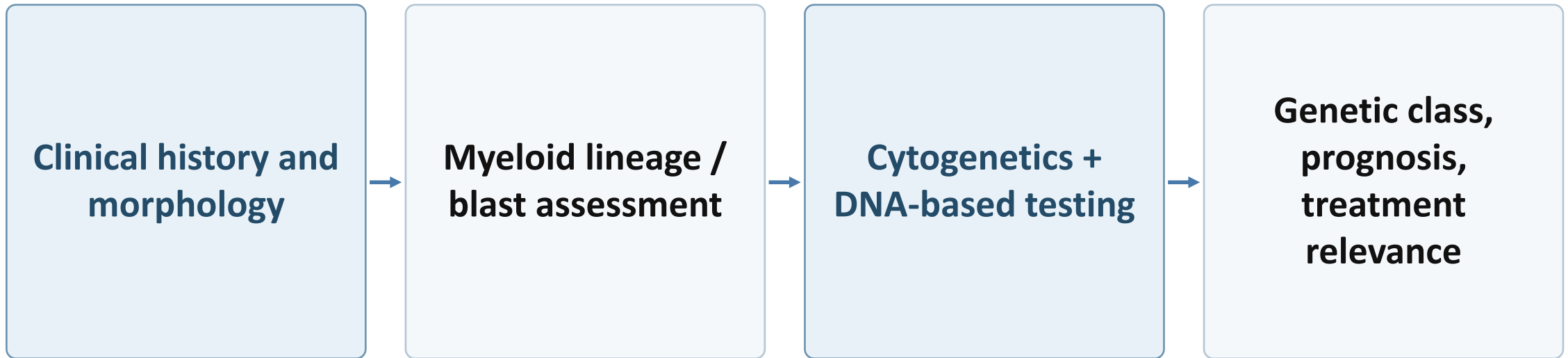
Interpretive task

Does absence of a visible cytogenetic lesion exclude a genetic AML subtype?

Resolution

No. NPM1-mutated AML illustrates sequence-defined disease beyond conventional karyotyping.

Integrated interpretation of an AML genetic report



Conceptual sequence / schematic

The report is most useful when multiple diagnostic streams are reconciled.

Five durable lessons

1 · Define

AML can be genetically defined.

Morphology alone is incomplete.

2 · Mechanize

**Fusions, signaling, epigenome,
p53.**

Drivers differ functionally.

3 · Correlate

**Genotype can predict
phenotype.**

Correlations have exceptions.

4 · Contextualize

**Age and therapy exposure
matter.**

Do not overinterpret setting.

5 · Apply

**Prognosis and therapies can
differ.**

Avoid generic AML risk claims.

Read molecular lesions through disease biology and clinical context.

Reference and evidentiary boundary

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Primary section: “Cytogenetics and Genetics,” within Acute Myeloid Leukemia.
- Related source sections: AML classification/pathogenesis/morphology; Clonal Hematopoiesis; Myelodysplastic Neoplasms.
- Genetic classification and prognostic labels reflect the supplied textbook; external guideline updates were not incorporated.

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