

Myelodysplastic Neoplasms

Clonal hematopoiesis · dysplasia · cytopenias · evolution

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

- Explain clonal ineffective hematopoiesis and its clinical effects.
- Relate molecular abnormalities to disordered differentiation.
- Identify characteristic erythroid, granulocytic and megakaryocytic dysplasia.
- Integrate morphology, genetics, prognosis and treatment concepts.

MDS requires a clinicopathologic and genetic synthesis.

Myeloid neoplasms: Three dominant phenotypes

Category	Primary abnormality	Typical blood consequence
Acute myeloid leukemia	Accumulation of immature myeloid blasts	Suppression of mature blood-cell production
Myelodysplastic neoplasms	Ineffective, dysplastic maturation	One or more cytopenias
Myeloproliferative neoplasms	Increased production of mature myeloid cells	Increased counts initially

The defining biological lesion

Clonal stem-cell disease

The marrow is populated by progeny of an altered multipotent hematopoietic stem cell.

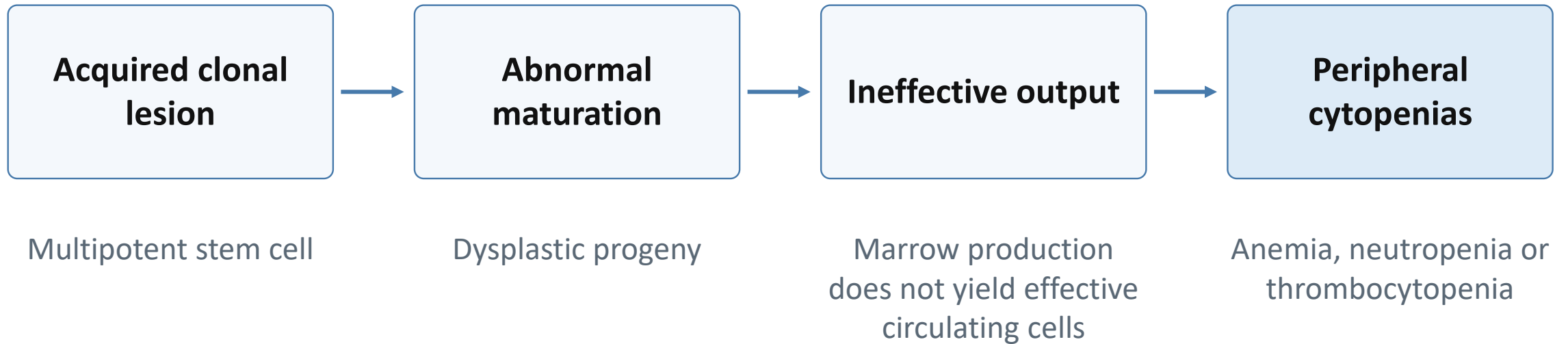
Differentiation is retained

Cells mature along myeloid lineages, but maturation is abnormal.

Production is ineffective

Marrow activity fails to generate adequate functional circulating cells.

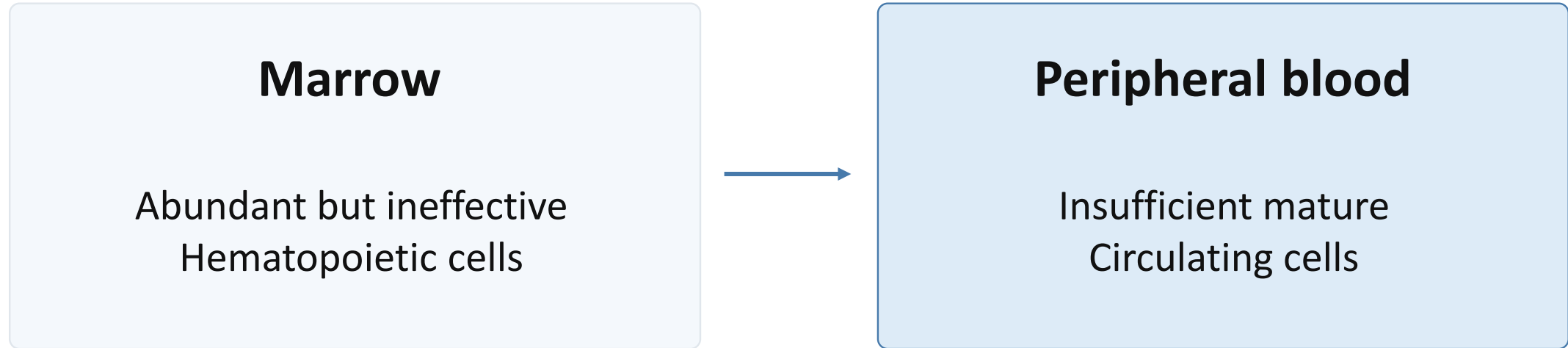
A clonal stem cell creates the MDS phenotype



Normal vs dysplastic hematopoiesis

Feature	Normal marrow	MDS
Hematopoietic clone	Regulated diverse progenitors	Expansion of neoplastic clone
Maturation	Orderly lineage progression	Disordered maturation
Output	Production meets blood-cell needs	Ineffective output despite marrow activity
Blood counts	Maintained by homeostasis	Cytopenia(s) of variable severity

Why a cellular marrow can produce cytopenias



Marrow cellularity and effective blood-cell output are not synonymous.

Three lineages explain the clinical syndrome

Red-cell lineage

Ineffective erythropoiesis → anemia and weakness.

Granulocytic lineage

Abnormal myeloid production → neutropenia and infection risk.

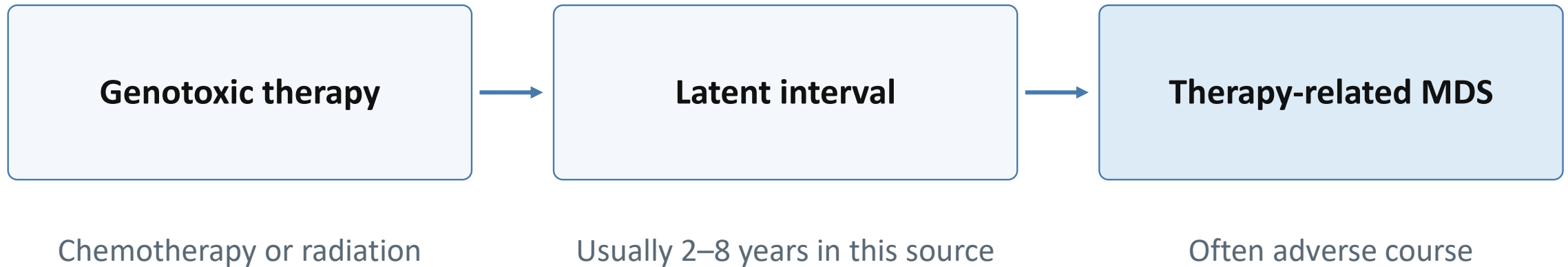
Megakaryocytic lineage

Defective platelet production → thrombocytopenia and bleeding.

Primary and therapy-related MDS

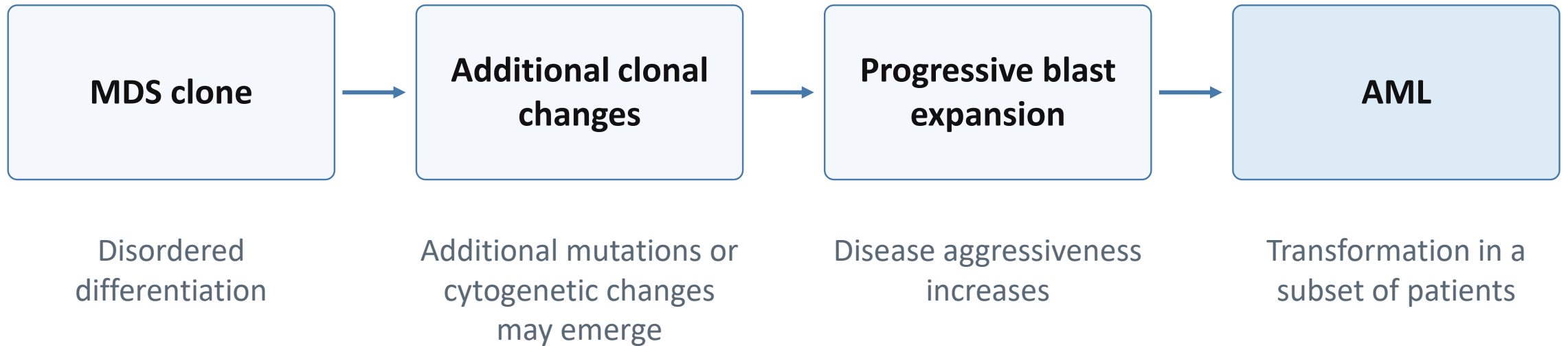
Aspect	Primary MDS	Therapy-related MDS
Clinical context	De novo; No identified genotoxic antecedent	After cytotoxic drugs or irradiation
Age	Predominantly older adults	Depends on previous treatment history
Course	Variable prognostic groups	Typically more adverse; Rapid AML progression

Exposure-associated disease has a latent interval



The latency is a population description—not a diagnostic requirement for an individual patient.

MDS is a potential antecedent of AML



Three broad categories of MDS drivers

Acquired mutations perturb the regulation of myeloid differentiation.

Epigenetic regulators

DNA methylation, histone modifications and chromatin organization.

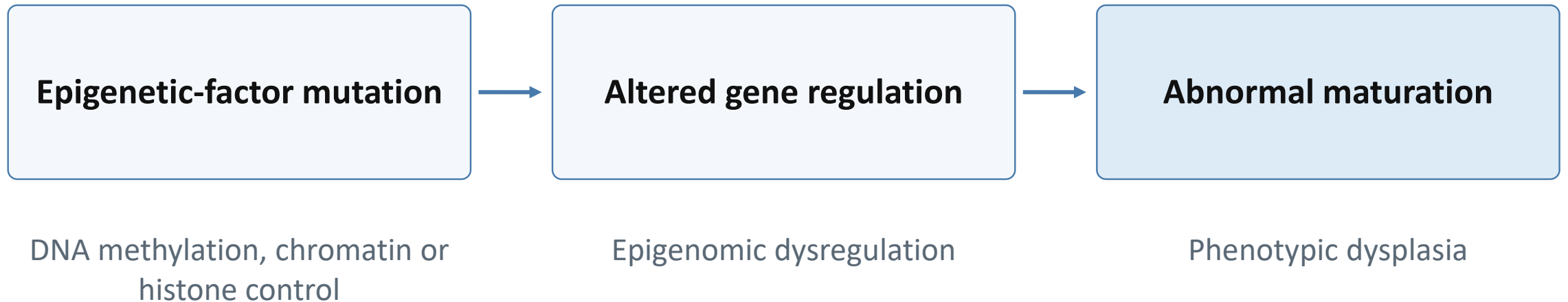
RNA splicing factors

Defects in the machinery that processes pre-mRNA.

Transcription factors

Disruption of programs needed for normal myelopoiesis.

Epigenetic disturbance can alter differentiation



A conceptual relation; This diagram does not specify an unverified gene-to-phenotype pathway.

Epigenetic regulators overlap with AML

- MDS and AML share abnormalities in epigenetic control pathways.
- Affected protein classes regulate DNA methylation, histone modifications and chromatin looping.
- This overlap is biologically consistent with progression of some MDS clones to AML.

Shared pathways do not imply that the same lesion predicts identical clinical behavior.

RNA splicing is another recurrent target

Spliceosome component mutation

A subset of MDS has splicing-factor gene defects

Altered RNA processing

The precise pathogenic contribution remains incompletely established

MDS-associated clone

Molecular evidence supports clonality

Clonal hematopoiesis links aging and MDS

- Age-associated mutant hematopoietic clones may be present with normal blood counts.
- Splicing-factor mutations in clonal hematopoiesis are associated with particularly high progression risk.
- Clonal hematopoiesis alone is not equivalent to symptomatic MDS.

Transition to MDS requires evidence beyond merely detecting a mutated clone.

Transcription-factor defects disturb maturation

Loss-of-function mutation

Example: RUNX1



**Disrupted transcriptional
program**

Normal differentiation requires
transcriptional control



Abnormal myelopoiesis

MDS phenotype may result

RUNX1 illustrates a transcription-factor lesion

- RUNX1 is required for normal myeloid development.
- MDS may harbor loss-of-function lesions involving RUNX1.
- The principal conceptual consequence is a defect in lineage differentiation.

Do not confuse RUNX1 loss-of-function with AML-associated balanced rearrangements.

Chromosomal changes: MDS vs de novo AML

Feature	MDS	Common de novo AML patterns
Prominent genetic change	Deletions, monosomies and other unbalanced aberrations	Specific balanced rearrangements in subsets
Examples emphasized	−5, −7, del(5q), del(7q), del(20q), +8	T(8;21), inv(16), t(15;17)
Interpretation	Different predominant genetic landscape	These typical AML rearrangements are not seen in MDS in this account

TP53 marks a clinically adverse subset

Approximately 10%

Loss-of-function TP53 mutations in roughly one-tenth of MDS cases.

Genetic association

Often accompanies a complex karyotype.

Clinical association

Correlates with particularly poor outcomes.

Complex karyotype is a prognostic warning

- Defined in the source as multiple chromosomal abnormalities.
- Associated with worse clinical outcomes across risk frameworks.
- Often present in TP53-mutated disease.

Prognostic significance depends on the integrated disease context.

Recurrent chromosome abnormalities in MDS

Whole-chromosome loss	Partial deletion	Chromosome gain
Monosomy 5	Del(5q)	Trisomy 8
Monosomy 7	Del(7q)	
	Del(20q)	

Copy-number changes alter gene dosage

Deletion/loss



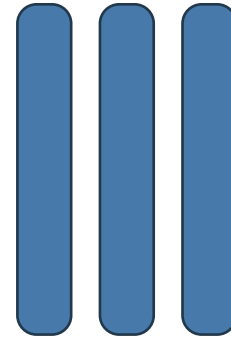
Single copy

Normal pair



Two copies

Trisomy

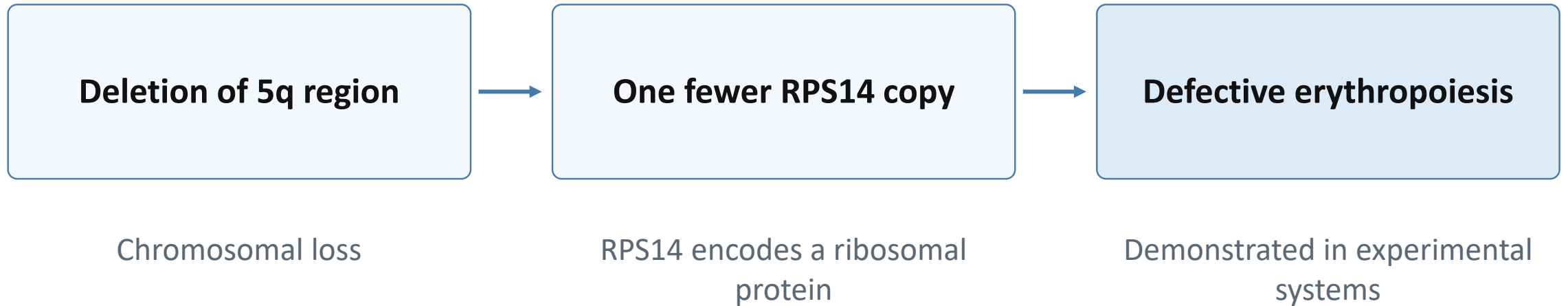


Three copies

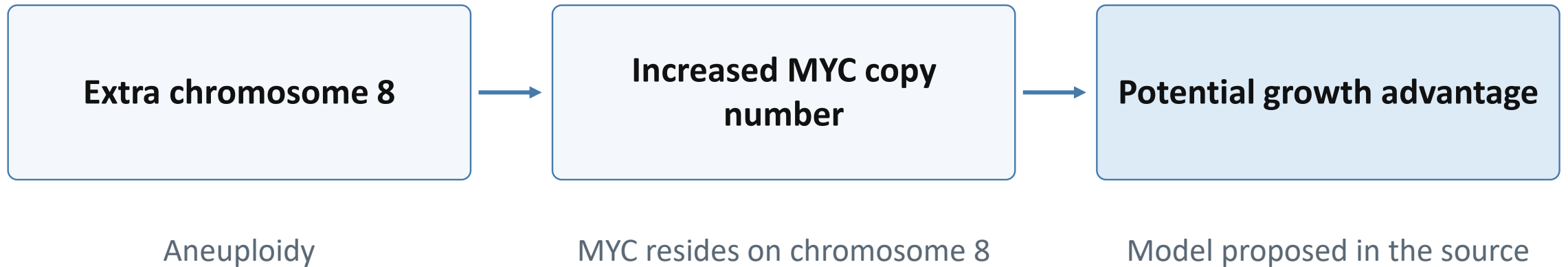
Concept: Changing gene dosage can confer a growth advantage; The exact contribution of most aneuploidies remains incompletely understood.

Schematic — not a clinical/histologic specimen

Deletion 5q: An illustrative mechanism



Trisomy 8: A gene-dosage hypothesis



Gene dosage is a proposed mechanism, not proof that MYC alone explains trisomy 8 disease.

Molecular tests have complementary roles

Cytogenetics

Detects recurrent gains, losses and complex karyotypes;
Contributes to prognosis.

DNA sequencing

Identifies acquired variants that can support clonal disease and classification.

Morphology

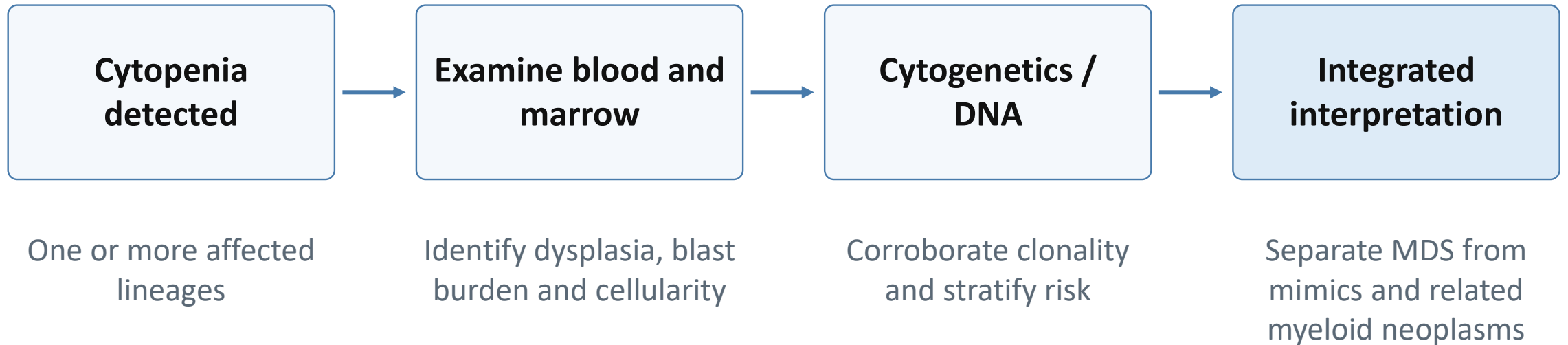
Shows abnormal maturation and lineage-specific dysplasia.

A mutation alone does not establish MDS

- Genetic clonality may also occur in people with normal blood counts.
- The MDS diagnosis requires correlation with peripheral counts and morphologic findings.
- Use cytogenetic and sequencing data to complement—not replace—clinical assessment.

Clinicopathologic interpretation prevents overcalling age-related clonal hematopoiesis.

An integrated diagnostic reasoning sequence



Bone marrow cellularity varies

Pattern	Status in the source	Interpretation
Hypercellular	Most common at diagnosis	Ineffective hematopoiesis despite increased marrow cellularity
Normocellular	Sometimes encountered	Does not exclude MDS
Hypocellular	Less common	Does not exclude MDS

MDS is a multilineage dysplasia

Assess erythroid, granulocytic, monocytic and megakaryocytic elements.

Erythroid

Abnormal nuclear maturation and iron distribution.

Granulocytic

Abnormal granulation and segmentation.

Megakaryocytic

Abnormal nuclear number and lobation.

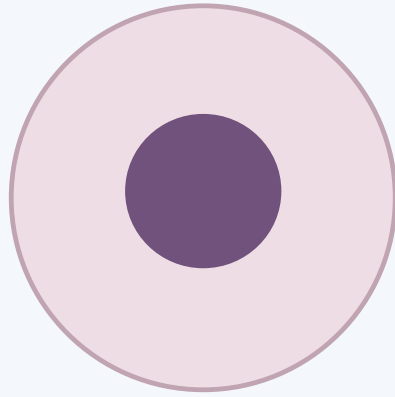
Erythroid abnormalities have several forms

- Ring sideroblasts: Perinuclear mitochondrial iron on Prussian blue stain.
- Megaloblastoid maturation: Resemblance to B12 or folate deficiency.
- Nuclear budding, multilobation and irregular polyploid nuclei.

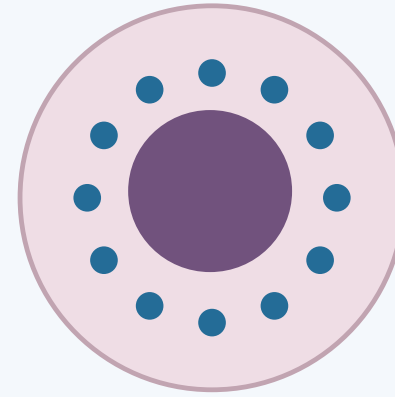
Different abnormalities may coexist in the same marrow.

Ring sideroblasts represent mitochondrial iron

Erythroblast



Ring sideroblast



Perinuclear iron is demonstrated with Prussian blue staining.

Schematic — not a clinical/histologic specimen

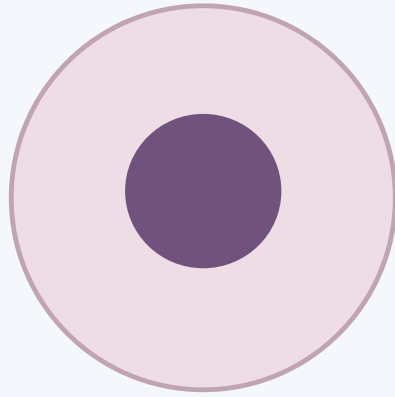
Prussian blue demonstrates abnormal iron distribution

- Ring sideroblasts are erythroid precursors, not mature circulating erythrocytes.
- Iron-laden mitochondria appear as blue perinuclear granules.
- The abnormal localization provides morphologic evidence of disordered erythropoiesis.

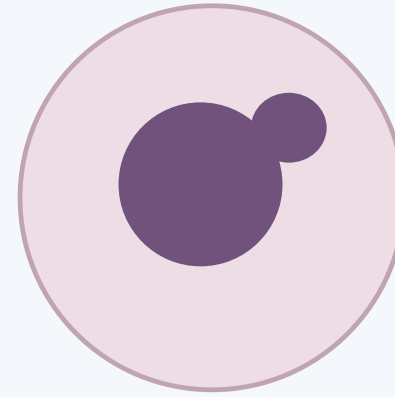
A ring pattern must be assessed in the correct cell and stain.

Abnormal erythroblast nuclei show budding

Single nucleus



Nuclear budding



The schematic illustrates an irregular erythroblast nuclear contour.

Schematic — not a clinical/histologic specimen

Megaloblastoid maturation is a morphologic mimic

Feature	MDS	Vitamin B12 / folate deficiency
Morphology	Can show megaloblastoid maturation	Can show megaloblastic maturation
Interpretive implication	Requires clonal/marrow context	Requires evaluation of a nutritional cause
Conclusion	Morphology by itself may overlap	Look beyond isolated nuclear appearance

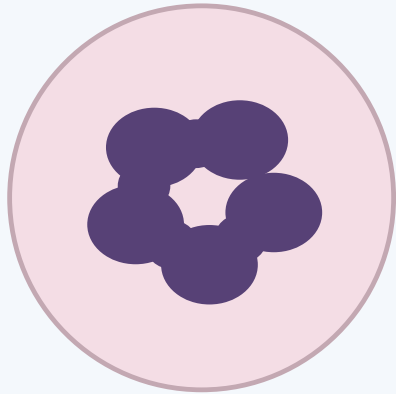
Granulocytic dysplasia affects granules and nuclei

- Neutrophils may have reduced secondary granules.
- Toxic granulation and Döhle bodies may also occur.
- Abnormal nuclear segmentation is exemplified by pseudo–Pelger-Huët cells.

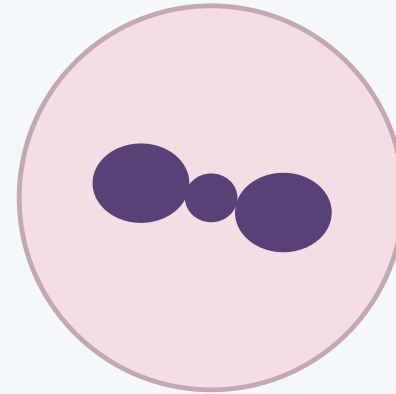
Evaluate the overall dysplastic pattern, not one cell in isolation.

Pseudo–Pelger-Huët neutrophils are bilobed

Normally segmented neutrophil



Pseudo–Pelger-Huët form



The abnormal neutrophil has two nuclear lobes rather than the usual three to five.

Schematic — not a clinical/histologic specimen

Pseudo–Pelger-Huët cells are useful smear clues

- They may be visible in peripheral blood as well as marrow.
- They have abnormally reduced nuclear segmentation; Some cells lack segmentation entirely.
- Their recognition should prompt review of other lineages and clinical data.

A characteristic clue is not a stand-alone diagnosis.

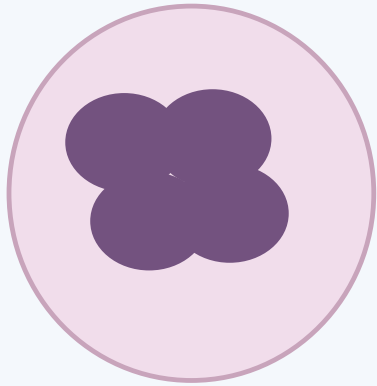
Megakaryocytic dysplasia has distinctive nuclei

- Some megakaryocytes have a single nuclear lobe.
- Others show multiple separate nuclei—the “pawn-ball” pattern.
- These findings differ from the normal large multilobated nucleus.

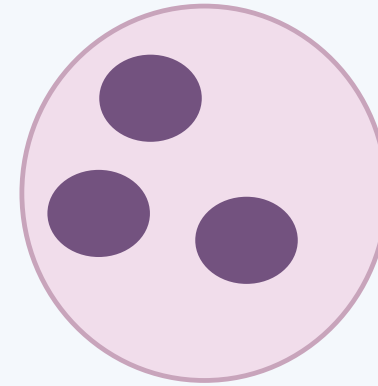
Megakaryocyte morphology is an important component of multilineage assessment.

Megakaryocytes may have separated nuclei

Typical multilobated nucleus



Dysplastic separate nuclei



Simplified nuclear topology; Actual cytologic diagnosis requires marrow assessment.

Schematic — not a clinical/histologic specimen

Peripheral blood can reveal multilineage dysplasia

Blood element	Representative source finding	Meaning
Red cells	Macrocytes and poikilocytes	Abnormal erythropoiesis
Neutrophils	Pseudo–Pelger-Huët cells	Abnormal granulocytic maturation
Platelets	Giant platelets	Megakaryocytic dysplasia
Monocytes	Relative or absolute monocytosis	Possible accompanying pattern

Macrocytosis and poikilocytosis warrant context

- Macrocytes are enlarged red cells.
- Poikilocytosis denotes variation in erythrocyte shape.
- In MDS, these smear findings can accompany marrow erythroid dysplasia.

Peripheral morphology is supportive, not pathognomonic.

Giant platelets are another peripheral clue

- Oversized platelets can be seen on blood smears.
- They complement marrow evidence of dysplastic megakaryocytes.
- Thrombocytopenia, when present, creates bleeding risk.

Recognize both qualitative morphology and quantitative platelet count.

Monocytic findings need integrated interpretation

- The blood may show relative or absolute monocytosis.
- MDS morphology can include abnormalities in the monocytic lineage.
- Monocytosis alone cannot define the disease subtype described here.

Robbins does not provide detailed monocytosis-based classification criteria in this section.

Blasts indicate disease burden—not all MDS is AML

Compartment	MDS statement in the source	Interpretive caution
Bone marrow	Myeloid blasts may increase, but are less than 20% of cellularity	Apply genetic exceptions and current classification carefully
Peripheral blood	Blasts usually comprise less than 10% of leukocytes	Peripheral percentages alone are insufficient

MDS and AML differ in dominant maturation phenotype

- MDS: Dysplastic but partially differentiated myeloid cells and ineffective production.
- AML: Accumulation of immature blasts that suppress normal hematopoiesis.
- The two share mutations and can be linked by clonal evolution.

A single blast cut-off is not a complete modern classification algorithm.

Morphology helps link a lineage to its output

Morphologic abnormality	Likely lineage affected	Potential clinical correlate
Megaloblastoid erythroblasts	Erythroid	Anemia / fatigue
Pseudo–Pelger-Huët cells	Granulocytic	Neutropenia / infection
Dysplastic megakaryocytes	Megakaryocytic	Thrombocytopenia / bleeding

MDS may be identified incidentally

Up to half

The source states that MDS may first be discovered during routine blood testing.

An abnormal complete blood count can precede overt symptoms.

Age distribution is strongly weighted to older adults

Mean age $\approx$ 70 years

Primary MDS predominantly presents in older adulthood.

Clinical implication

Persistent unexplained cytopenias in older adults warrant careful assessment.

Pancytopenia explains the symptom triad



Each symptom is linked to deficiency of a specific functional blood-cell compartment.

Anemia produces symptomatic weakness

- Ineffective erythropoiesis reduces functional circulating red cells.
- The resulting anemia contributes to weakness and fatigue.
- Erythroid dysplastic changes provide the marrow correlate.

Marrow erythroid activity cannot be equated with adequate red-cell output.

Neutropenia drives infectious complications

- Granulocytic maturation is dysplastic and may be ineffective.
- Reduced neutrophil availability predisposes to infections.
- Infection is a major source of morbidity and mortality in MDS.

Morphologic abnormalities and cell counts address different aspects of risk.

Thrombocytopenia drives hemorrhagic complications

- Dysplastic megakaryocytes may fail to support adequate platelet production.
- Thrombocytopenia increases bleeding risk.
- Bleeding contributes substantially to adverse outcomes.

Platelet size abnormalities do not substitute for a measured count.

Application: Unexplained multilineage cytopenia

An older adult has persistent cytopenias. The peripheral smear shows macrocytes and bilobed neutrophils; Marrow aspirate shows dysplastic megakaryocytes.

What unifying disease process should be considered?

MDS: Dysplasia across several lineages with ineffective hematopoiesis.

Three recurring prognostic dimensions

Risk estimation combines measurable disease burden and genetic complexity.

Blast burden

Increasing myeloid blasts suggests more advanced disease.

Cytopenia severity

More severe blood-cell deficits worsen clinical outlook.

Cytogenetic complexity

Multiple chromosomal abnormalities predict adverse outcomes.

Primary MDS has a broad survival spectrum

<6 months to >5 years

This median-survival range across prognostic groups of primary MDS.

Why this spread matters

MDS is biologically heterogeneous; Aggregate survival figures cannot describe one individual.

Therapy-related MDS has particularly poor outcomes

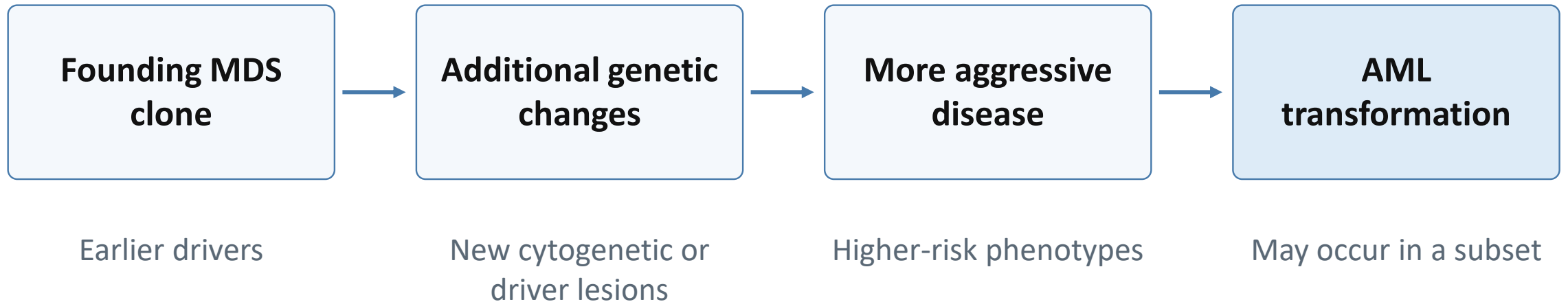
Median 4–8 months

A very unfavorable prognosis for therapy-related MDS.

Rapid transformation

In the source, progression to AML often occurs within 2–3 months of t-MDS diagnosis.

Clonal evolution underlies progression



Treatment choice reflects biology and fitness

Approach	Goal / rationale	Source context
Allogeneic HSC transplantation	Reconstitute normal hematopoiesis; Possible cure	Relatively young and fit patients
Supportive treatment	Manage infection and cytopenia complications	Older or medically frail patients
Hypomethylating agents	Improve effectiveness of hematopoiesis / counts	Responses in a subset
Thalidomide-like drugs	Genotype-correlated therapeutic response	Isolated del(5q)

Allogeneic transplantation targets the clone

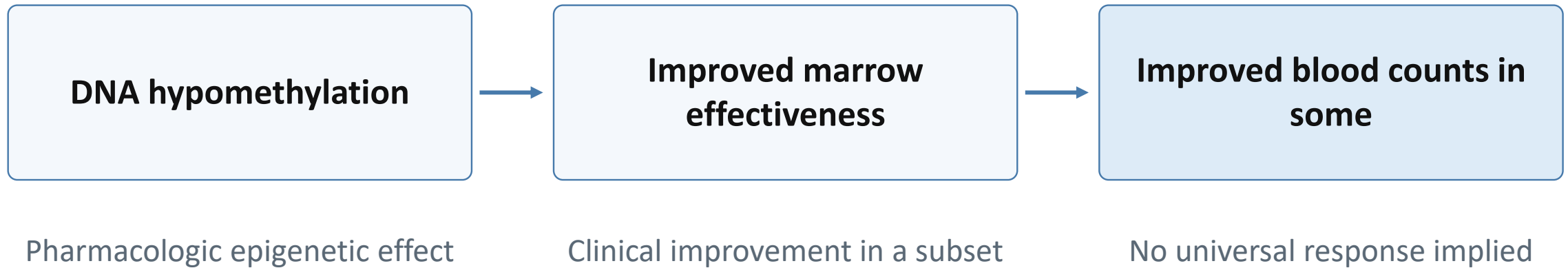


Supportive treatment addresses immediate risks

- Antibiotics may be needed to manage infectious complications.
- Blood-product transfusions support patients with severe cytopenias.
- Supportive approaches are especially important when curative therapy is not feasible.

Supportive care treats consequences of marrow failure, not necessarily the founding clone.

Hypomethylating agents address abnormal epigenetic control



Isolated del(5q) can inform treatment response

- The 5q chromosomal region contains RPS14, implicated in ineffective erythropoiesis.
- An isolated 5q deletion correlates with response to thalidomide-like drugs.
- The cytogenetic finding has both mechanistic and predictive clinical value.

Association with drug response is a predictive—not merely diagnostic—observation.

Genetic markers serve different purposes

Role	Question answered	MDS example in source
Diagnostic / classificatory	Is there a clonal pattern useful for classification?	Cytogenetic and molecular abnormalities
Prognostic	What predicts an adverse course?	Complex karyotype; TP53 association
Predictive	Who may respond to a treatment?	Isolated del(5q) and thalidomide-like drugs

Distinguishing MDS from selected alternatives

Feature	MDS	Comparator
Ineffective maturation	Central lesion	MPN: Often increased mature cell production
Multilineage dysplasia	Characteristic	Nutritional megaloblastosis may mimic erythroid change
Blast excess	Variable, below threshold in this account	AML: Accumulation of myeloid blasts
Molecular context	Overlapping drivers and chromosomal abnormalities	Clonal hematopoiesis can show mutations without cytopenia

Application: Therapy-related risk

A patient develops cytopenias several years after cytotoxic therapy. Marrow examination shows dysplasia and a complex karyotype.

What major clinical concern follows from this setting?

Therapy-related MDS may have rapid progression and poor prognosis.

Application: Monosomy versus translocation

A patient with morphologic MDS has monosomy 7. Another patient with a myeloid neoplasm has t(15;17).

Which finding is emphasized as recurrent in MDS?

Monosomy 7; T(15;17) is a characteristic rearrangement of an AML subtype.

Application: Prognostic reasoning

Two individuals have MDS. One has severe pancytopenia, increased blasts and several cytogenetic abnormalities; The other has milder blood abnormalities.

Which profile is associated with greater risk?

The patient with higher blast burden, worse cytopenias and complex cytogenetics.

Integrated diagnostic synthesis

A robust diagnosis combines the marrow phenotype with blood and genetic data.

Counts + symptoms

Define clinically significant marrow dysfunction.

Blood / marrow morphology

Identify dysplastic maturation and estimate blast burden.

Cytogenetics + DNA

Establish clonality and refine classification / prognosis.

Key concepts: Mechanism to morphology

- MDS is a clonal neoplasm with ineffective myeloid differentiation.
- Altered epigenetic regulation, RNA splicing and transcription are major pathogenetic themes.
- Dysplasia may involve erythroid, granulocytic, monocytic and megakaryocytic lineages.
- Characteristic blood findings include cytopenias and abnormal cell morphology.

The bone marrow phenotype must be interpreted with molecular and clinical context.

Key concepts: Prognosis and management

- The probability of AML evolution varies substantially by disease risk.
- More blasts, more severe cytopenias and complex cytogenetics are adverse features.
- Allogeneic transplant may be curative in selected fit patients.
- Supportive care and disease-modifying agents have distinct roles.

Management should not be inferred from morphology alone.

References and source boundaries

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026). Chapter 13: Myeloid Neoplasms; Myelodysplastic Neoplasms, pp. 560–566.
- Primary slide facts were derived from the supplied robbins.md text and the indexed teaching unit; no chapter PDF was supplied for figure verification.
- Microscopic concepts are shown with native editable schematics, not clinical micrographs. Subtype criteria and updated treatment guidelines were not independently reviewed.