

Thalassemia

Inherited disorders of globin-chain synthesis

α -thalassemia • β -thalassemia

Molecular basis | Pathogenesis | Morphology | Clinical correlation

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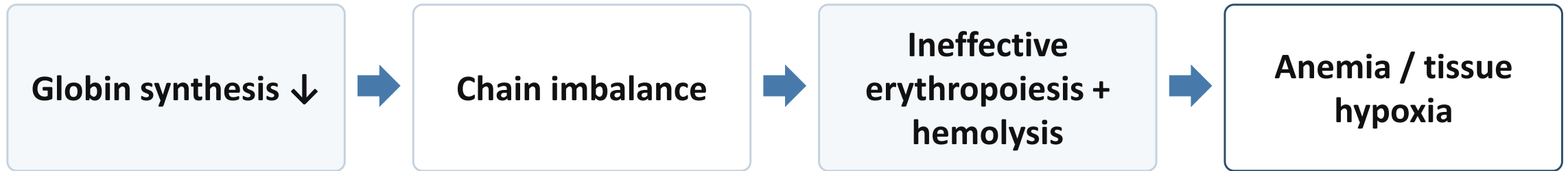
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Learning objectives

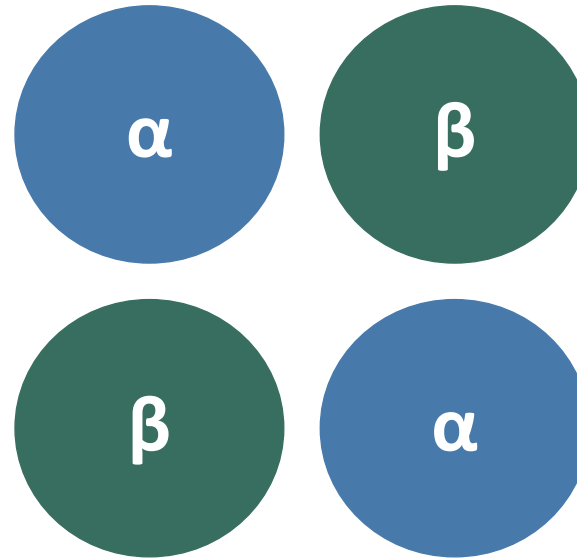
- Distinguish α - and β -thalassemia at the gene and chain levels
- Explain ineffective erythropoiesis, hemolysis, and tissue injury
- Connect phenotype and morphology to molecular genotype
- Interpret characteristic laboratory patterns and clinical complications

Thalassemia: A quantitative globin defect



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- Germline variants reduce production of one major globin chain
 - Deficient hemoglobin synthesis produces microcytic, hypochromic cells
 - Excess unmatched chains damage erythroid precursors or circulating RBCs

Hemoglobin A contains two paired chains

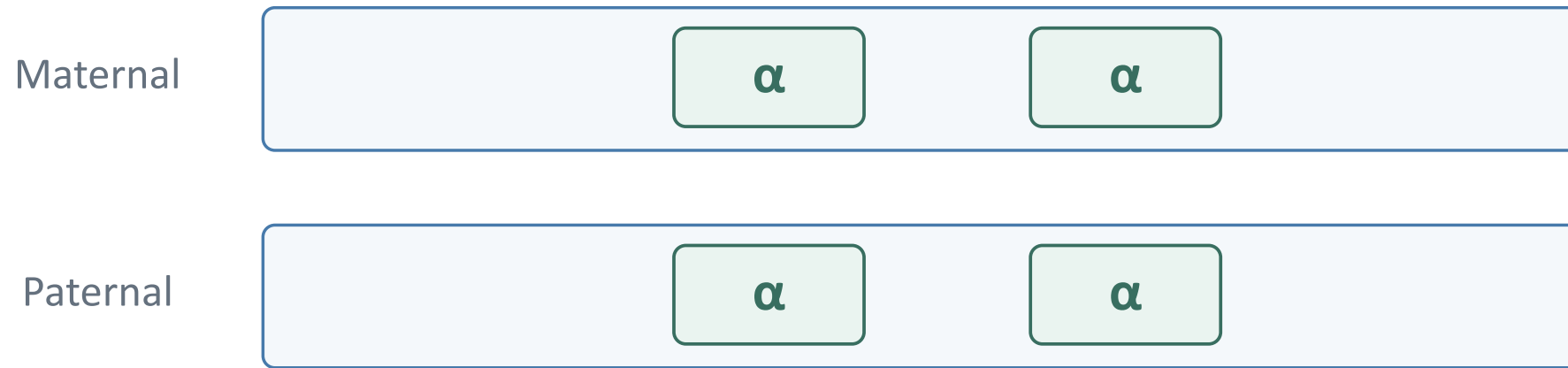


Hemoglobin A: $\alpha_2\beta_2$

The tetramer is conceptual, not a molecular-structure rendering.

α -globin genes are duplicated on each chromosome 16

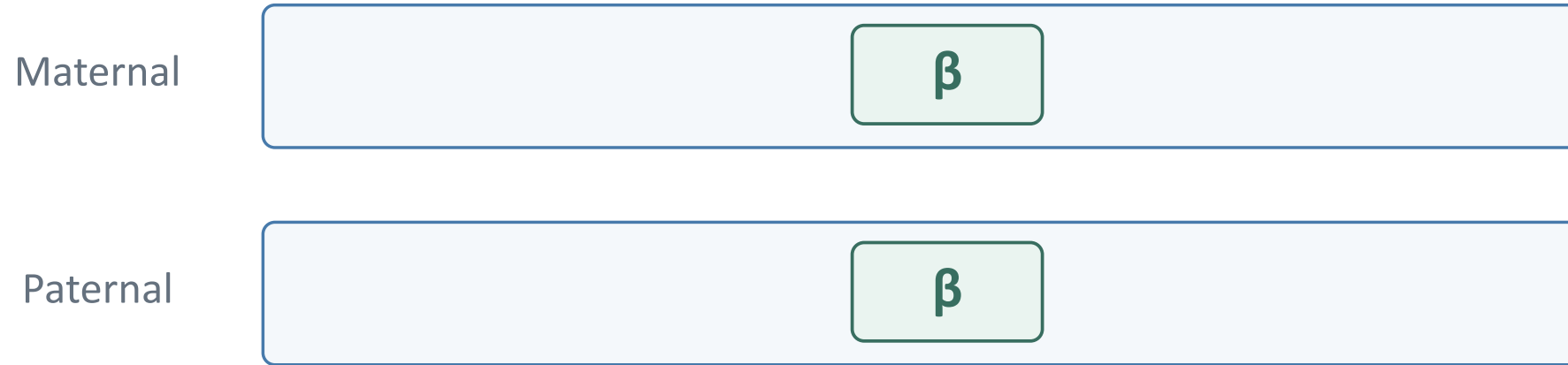
Two homologous chromosomes 16



- Two α -globin genes occur on each chromosome 16
- A diploid genome normally contains four functional α -globin genes
- Gene deletions form the principal molecular basis of α -thalassemia

β -globin is encoded at chromosome 11

Two homologous chromosomes 11



- One β -globin gene is present on each chromosome 11
- A diploid genome normally has two β -globin alleles
- β -thalassemia usually results from mutations that impair β -globin gene expression

Two distinct mechanisms produce thalassemic anemia

Reduced synthesis

Hypochromic microcytic erythrocytes

Low oxygen transport

Reduced cell survival

Precursor loss in the marrow

Peripheral hemolysis

The relative importance of these mechanisms differs by thalassemia type

The geographic distribution reflects genetic selection

- Thalassemias are common in the Mediterranean, Middle East, Africa, India, and Asia
- Together, they are among the most frequent inherited disorders worldwide
- Carrier prevalence is linked to protection against malaria

α and β defects have a shared starting point

β -thalassemia

β chains ↓

Free α chains ↑

Insoluble intracellular aggregates

α -thalassemia

α chains ↓

Free γ (fetus) or β (adult) ↑

Relatively stable homotetramers

Free α is especially insoluble and damaging to erythroblasts

β^0 versus β^+ : Residual synthesis matters

β^0 allele

Functional β output: Absent

Often terminator or severe splice defects

β^+ allele

Functional β output: Reduced

Often promoter or partially preserved splice defects

Phenotype also depends on the balance of other globin chains

Three molecular classes cause β -thalassemia

Splicing

Normal mRNA formation
impaired

Promoter

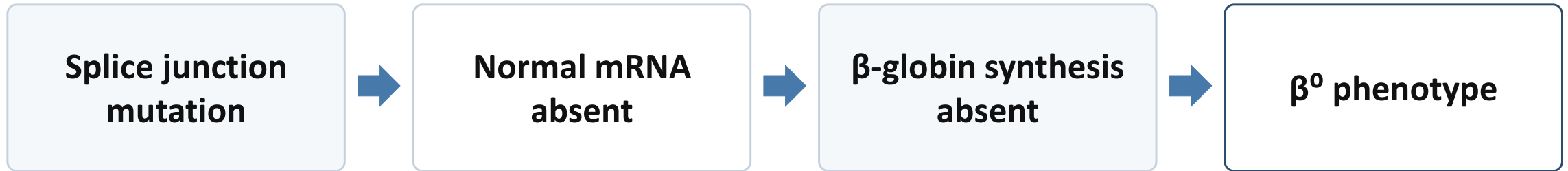
Transcription reduced

Terminator

Protein translation
interrupted

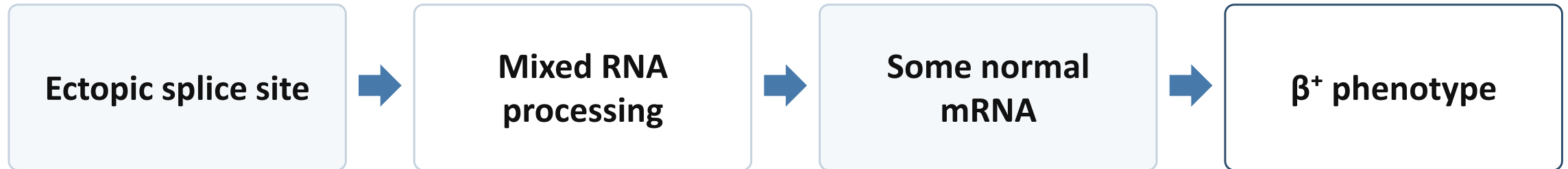
- RNA-splicing variants alter maturation of β -globin mRNA
- Promoter variants impair transcription
- Premature termination or frameshift variants block functional translation
- Most reported β -thalassemia variants are small sequence changes

Disrupted normal splicing may create β^0 -thalassemia



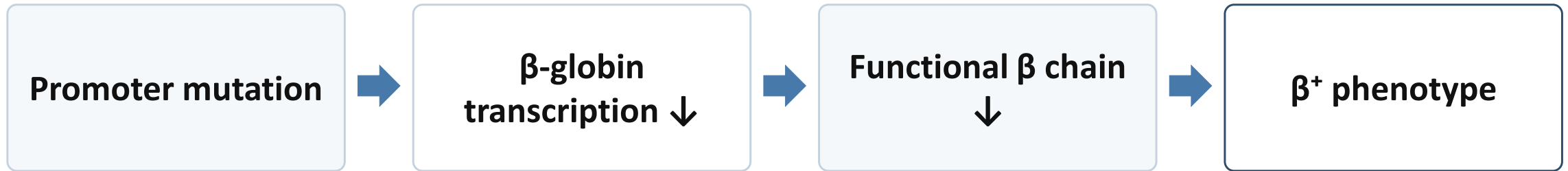
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- Normal splice junctions are necessary to make mature β -globin mRNA
 - A severe splice-junction mutation prevents formation of normal mRNA
 - The affected allele produces no functional β chain

An ectopic splice site may preserve partial expression



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- A mutation can create an abnormal splice site inside an intron
 - Both normal and abnormal splicing may then occur
 - Some normal β-globin mRNA is retained, producing a β⁺ phenotype

Promoter variants reduce β -globin transcription



- A promoter alteration decreases the amount of β -globin mRNA made
- The supplied Robbins section describes a roughly 75–80% transcription reduction
- Residual normal globin synthesis corresponds to β^+ -thalassemia

Premature stops and frameshifts favor β^0 -thalassemia

Nonsense variant

Premature stop codon

Truncated or absent functional β

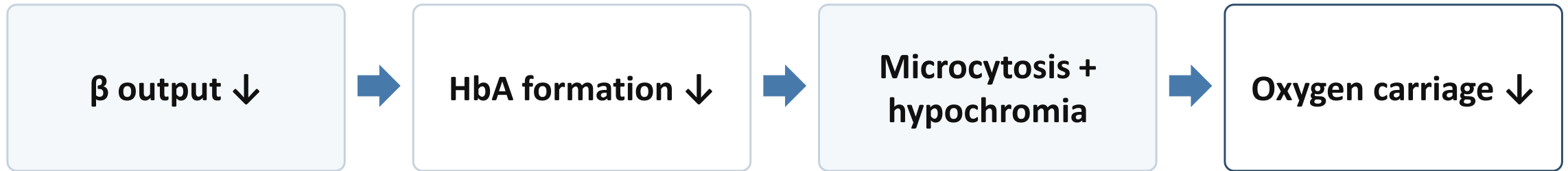
Frameshift variant

Changed translation reading frame

No functional β chain from allele

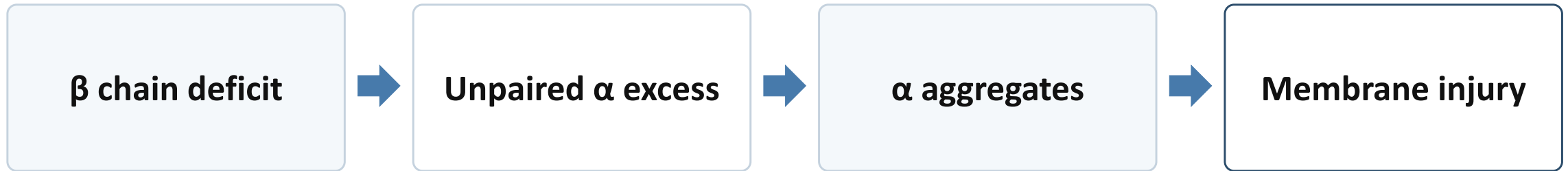
Functional β -globin translation may be completely blocked

The first β -thalassemia consequence is HbA deficiency



- A shortage of β chains limits assembly of HbA ($\alpha_2\beta_2$)
- Affected red cells are poorly hemoglobinized
- Hypochromia and microcytosis are direct consequences

Free α chains are the chief cytotoxic lesion



-
- β production falls while α -chain synthesis continues
 - Unpaired α chains precipitate as insoluble aggregates
 - These aggregates initiate oxidative and membrane injury

Membrane injury kills developing erythroblasts

Marrow response

Erythroblast proliferation ↑

Large erythroid precursor pool

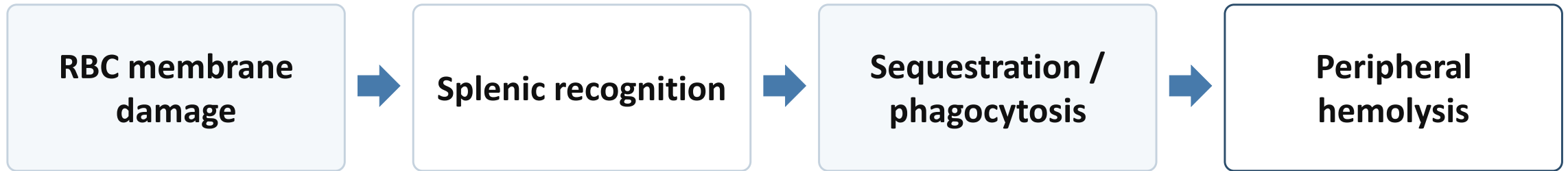
Functional result

Membrane injury / apoptosis

Few mature circulating cells per precursor

Marrow expansion therefore does not guarantee effective RBC output

Surviving RBCs remain vulnerable to the spleen



-
- Some damaged erythrocytes are released from marrow despite inclusions
 - Altered membranes promote splenic sequestration
 - Phagocytic removal shortens circulating RBC lifespan

Ineffective erythropoiesis and hemolysis coexist

Inside marrow

Precursor apoptosis

Ineffective erythropoiesis

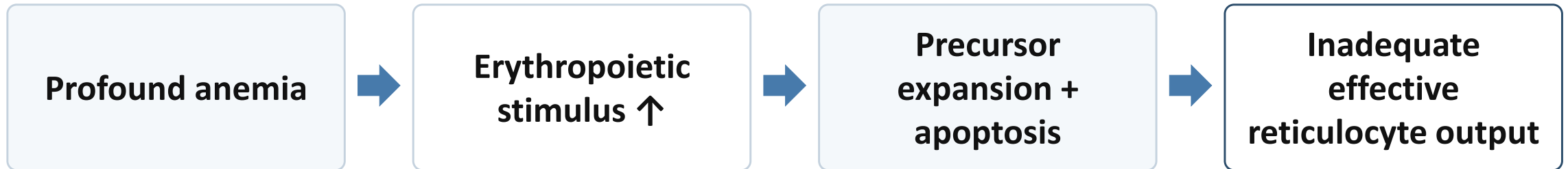
In circulation

Damaged circulating cells

Splenic hemolysis

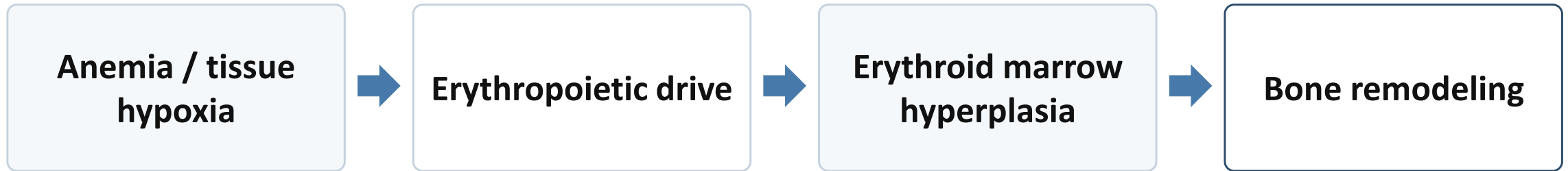
Together with reduced Hb synthesis, these sustain chronic anemia

Reticulocytosis does not fully compensate



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- The marrow is stimulated by severe anemia
 - Reticulocyte numbers may rise, yet remain inappropriately low for anemia severity
 - The discrepancy is explained by erythroblast destruction before maturation

Anemia drives marked erythroid marrow expansion



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- Oxygen deprivation amplifies erythropoietic drive
 - Erythroid precursors massively expand in active marrow
 - Marrow expansion can erode cortical bone and deform the skeleton

Marrow hyperplasia alters the skull and face

- Expanded marrow cavities thin and remodel cortical bone
- Facial prominences can enlarge or become distorted
- Skull radiographs may show a characteristic “crewcut” pattern
- These changes are most conspicuous when severe anemia is untreated

Extramedullary hematopoiesis enlarges organs

Liver

Hematopoiesis outside marrow

Spleen

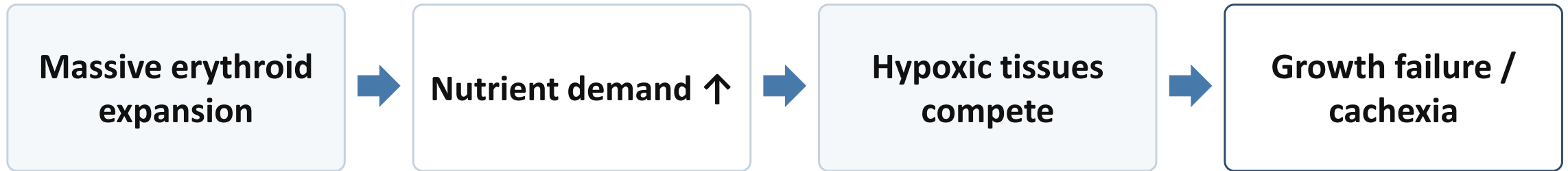
Hematopoiesis + phagocytic activity

Lymph nodes / masses

Additional hematopoietic sites

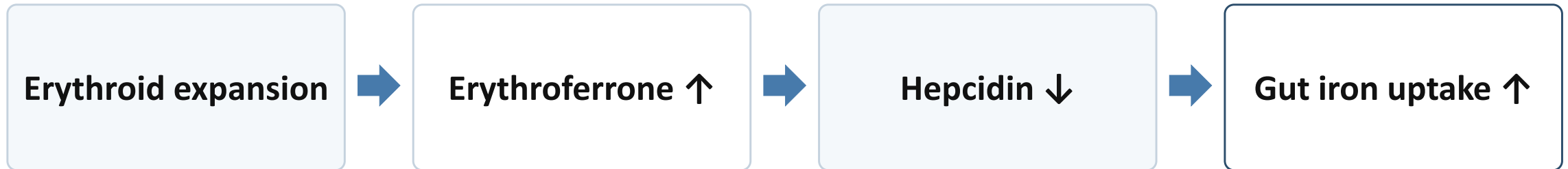
- Severe erythropoietic demand recruits liver, spleen, and lymph nodes
- Hepatosplenomegaly is common in severe forms
- In extensive disease, extraosseous hematopoietic masses can develop

Expanded erythropoiesis can consume tissue resources



- Large populations of metabolically active erythroid precursors require nutrients
- Other tissues simultaneously experience reduced oxygen delivery
- Untreated severe disease may therefore lead to growth impairment and cachexia

Ineffective erythropoiesis suppresses hepcidin



-
- Expanded erythroid progenitors release erythroferrone
 - Erythroferrone inhibits hepatic hepcidin production
 - Reduced hepcidin permits increased intestinal iron absorption

Iron absorption rises despite ineffective use

Iron entry

Absorption from gut ↑

Hepcidin restraint ↓

Iron use

Effective RBC output ↓

Iron gradually accumulates

The mismatch between uptake and utilization contributes to iron overload

Transfusions create a second route to iron excess

Endogenous pathway

Erythroferrone ↑

Hepcidin ↓ → absorption ↑

Treatment-associated pathway

Repeated RBC transfusions

Cumulative transfusional iron

Without iron-control measures, both sources can drive systemic overload

Chronic iron overload damages parenchymal organs

Heart

Cardiac injury

Liver

Hepatic iron toxicity

Pancreas

Pancreatic iron deposition

- Iron deposition can progress to secondary hemochromatosis
- Heart, liver, and pancreas are particularly vulnerable
- Cardiac disease due to iron overload is a major complication of β -thalassemia major

β -thalassemia spans three clinical phenotypes

Major

Severe; Regular transfusions

Intermedia

Moderate; Variable
genotype

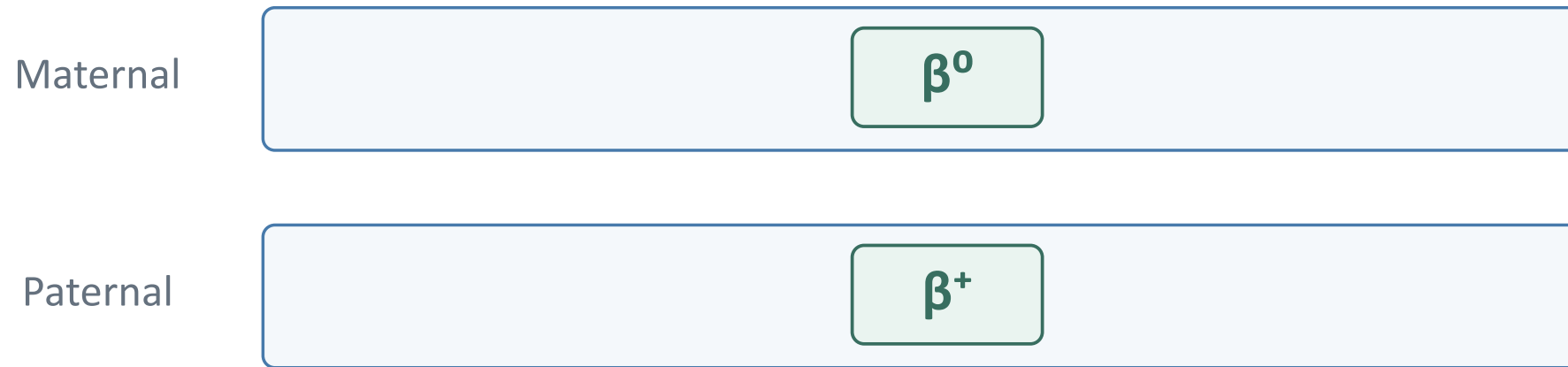
Minor / trait

Carrier phenotype

- β -thalassemia major: Severe, usually transfusion-dependent anemia
- β -thalassemia intermedia: Intermediate clinical severity, usually without regular transfusion requirement
- β -thalassemia minor (trait): Asymptomatic or mild microcytic anemia
- These are clinical categories; Genotype alone does not determine every case

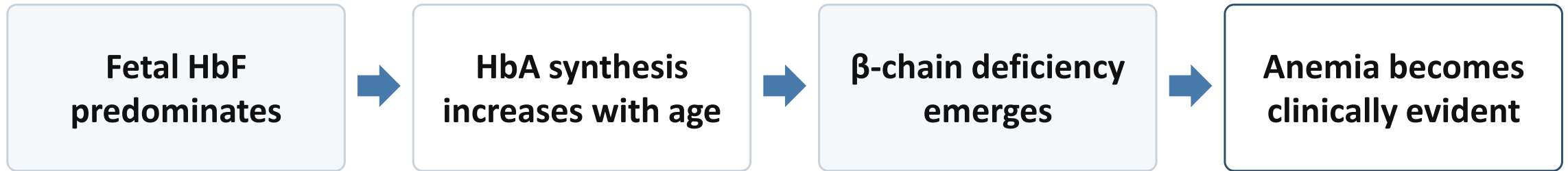
β -thalassemia major generally involves two affected alleles

Two homologous chromosomes 11



- Common genotypes include β^0/β^0 , β^0/β^+ , or β^+/β^+
- Severe reduction in β -chain supply produces major chain imbalance
- The phenotype is usually transfusion-dependent

β -thalassemia major emerges after infancy



-
- Neonatal hemoglobin contains a large fetal component, HbF
 - The switch toward HbA exposes inadequate β -chain synthesis
 - Onset around 6–9 months after birth

Hemoglobin fractions help explain severe β disease

β^0/β^0

HbA may be absent

HbF predominates

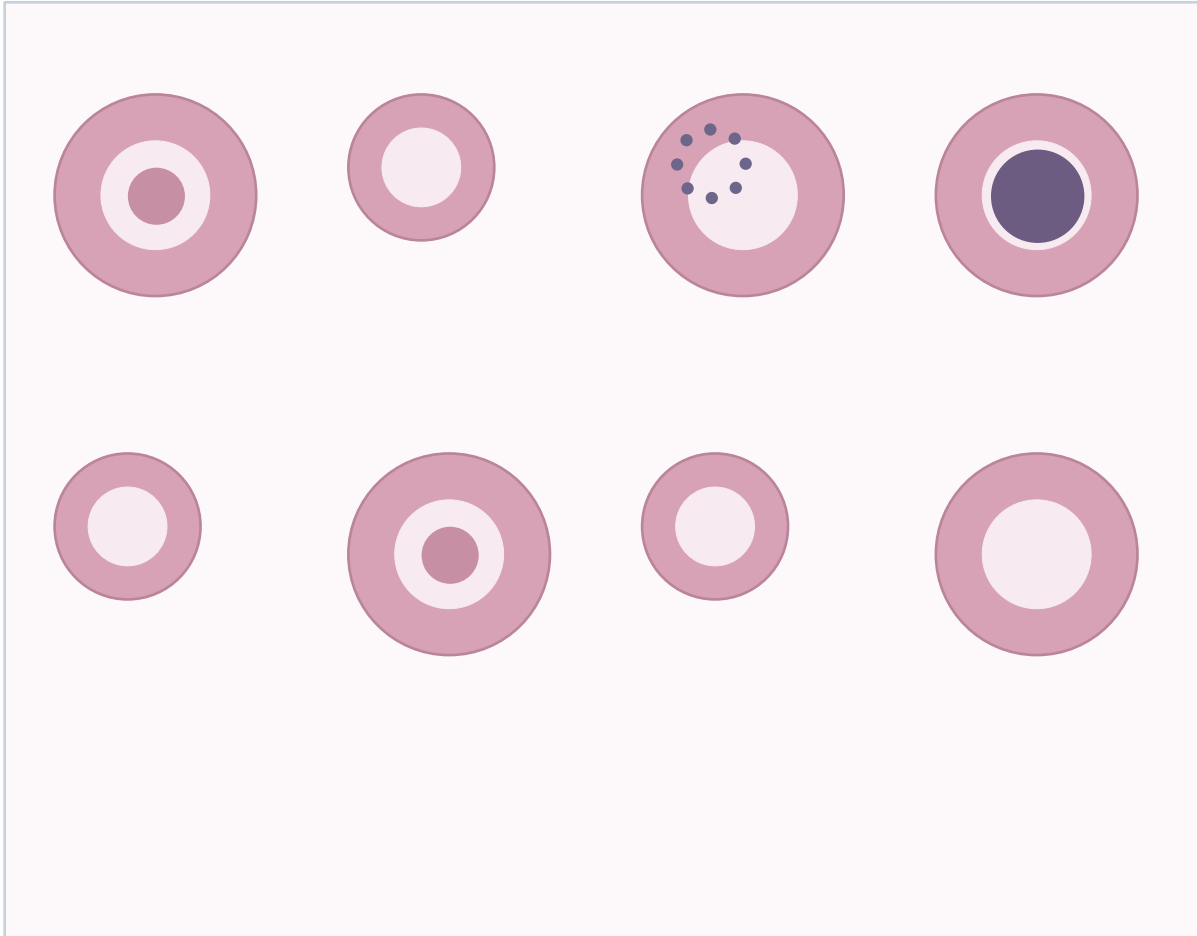
β^+ -containing genotype

Some HbA may persist

HbF remains substantially elevated

An untransfused major phenotype may have hemoglobin around 3–6 g/dL

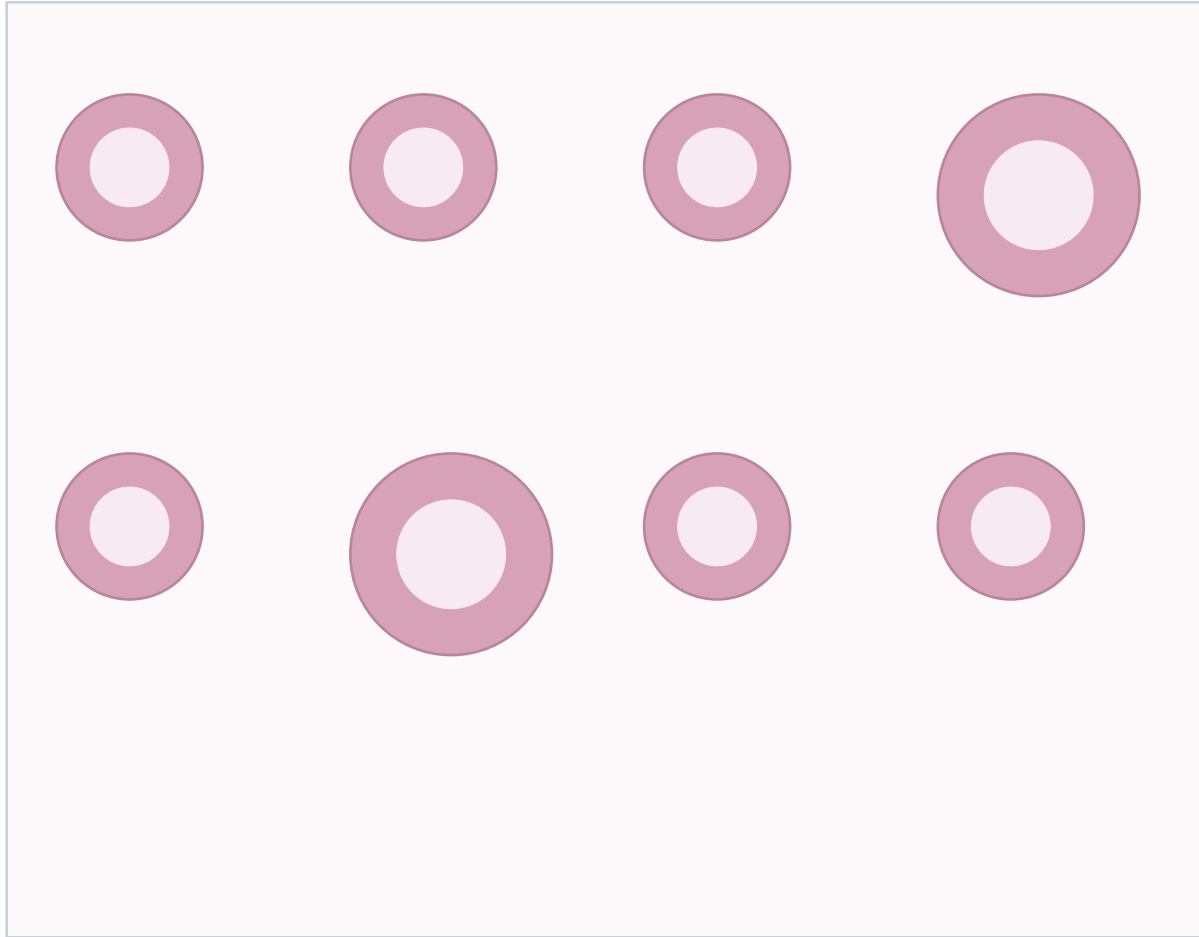
β -thalassemia major has a complex smear pattern



Illustrative RBC morphology — schematic, not a blood specimen

- Prominent anisocytosis and poikilocytosis
- Marked microcytosis and hypochromia
- Target cells, basophilic stippling, and fragmented RBCs
- Circulating nucleated RBCs may reflect stress hematopoiesis

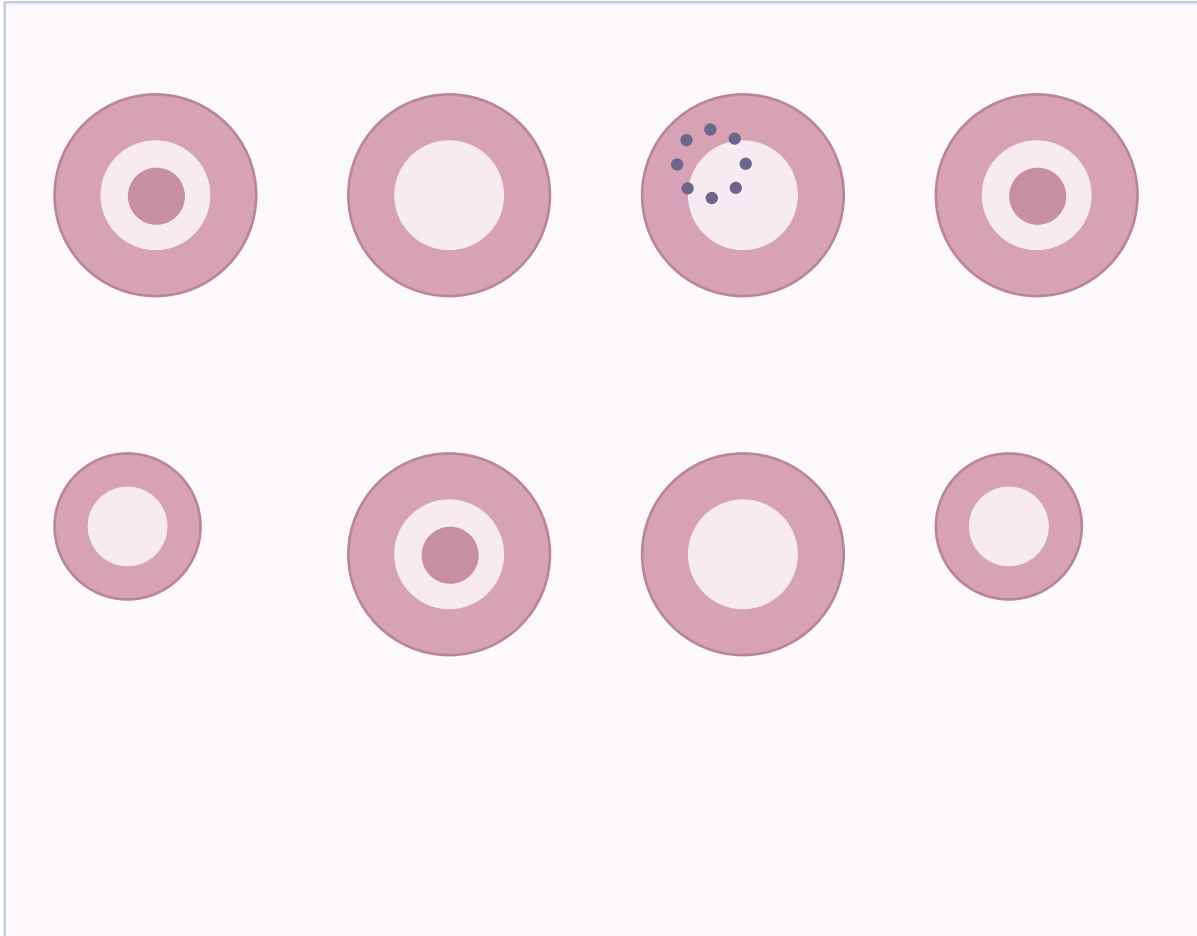
Microcytosis and hypochromia indicate deficient Hb



Illustrative RBC morphology — schematic, not a blood specimen

- Reduced globin synthesis lowers hemoglobin available per erythrocyte
- Small red cells and increased central pallor follow
- These signs are not specific to thalassemia and require a differential diagnosis

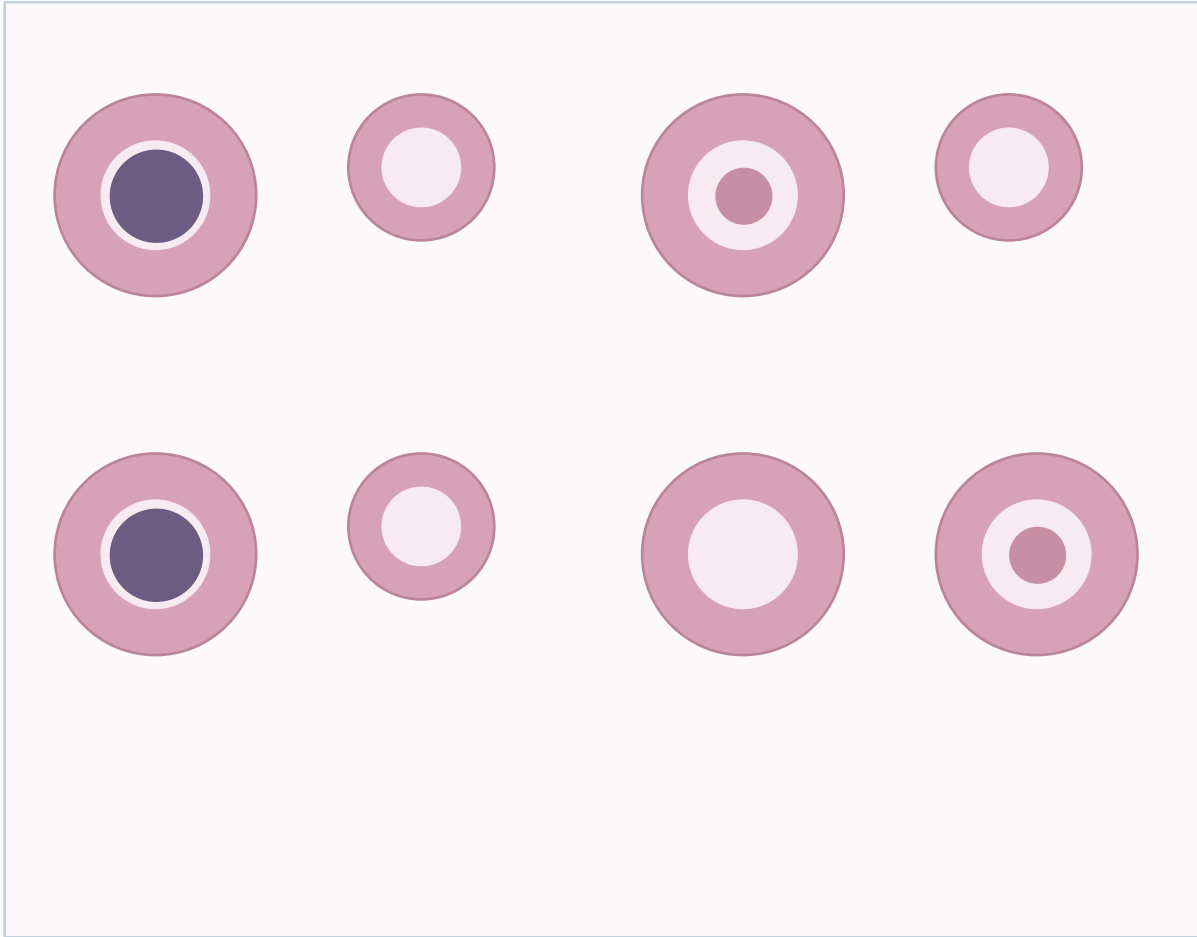
Target cells and stippling support, but do not prove, thalassemia



Illustrative RBC morphology — schematic, not a blood specimen

- Target cells show a central hemoglobinized area surrounded by pallor
- Basophilic stippling can occur in affected cells
- Neither feature uniquely identifies a thalassemia genotype

Nucleated RBCs signal severe erythropoietic stress



Illustrative RBC morphology — schematic, not a blood specimen

- Poorly hemoglobinized normoblasts may be present in peripheral blood
- Marrow stress and extramedullary hematopoiesis contribute to their release
- Their presence should be interpreted with overall severity and clinical context

Spleen and marrow changes reflect chronic turnover

Marrow

Expanded erythroblasts

Bone cortical remodeling

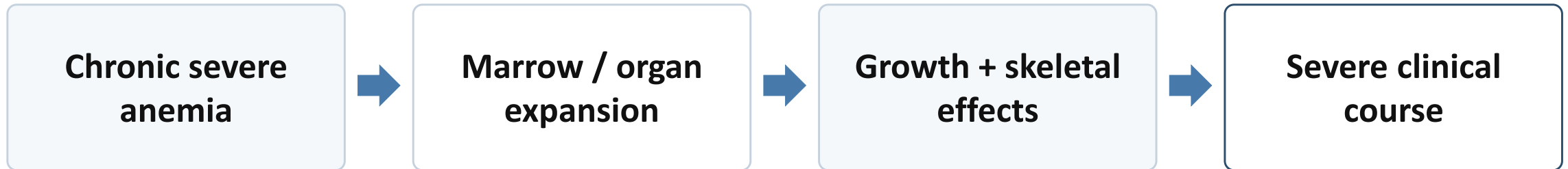
Spleen

Extravascular RBC clearance

Extramedullary hematopoiesis

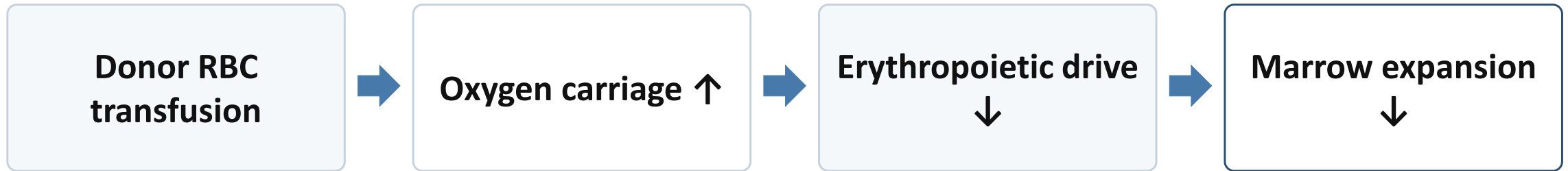
Extramedullary hematopoiesis further enlarges the spleen and liver

Untreated major disease has severe systemic consequences



-
- Growth retardation and skeletal deformities arise from longstanding anemia
 - Hepatosplenomegaly reflects extramedullary hematopoiesis
 - Early mortality can result from uncompensated severe anemia

RBC transfusion reduces erythropoietic stress



- Transfusion raises circulating functional hemoglobin
- Improvement of anemia reduces hypoxic stimulation
- Suppressing excess erythropoiesis can limit marrow and skeletal complications

Transfusion is beneficial but adds iron

Therapeutic benefit

Anemia less severe

Marrow expansion reduced

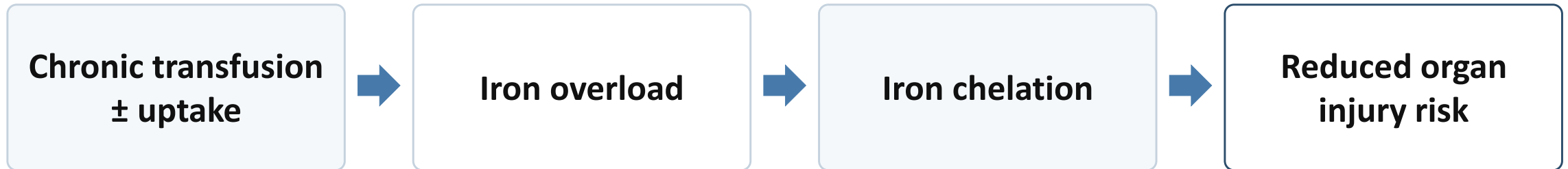
Complication

Transfusional iron loading

Risk of secondary hemochromatosis

The balance makes iron monitoring and chelation essential in treated patients

Chelation is central to preventing iron toxicity

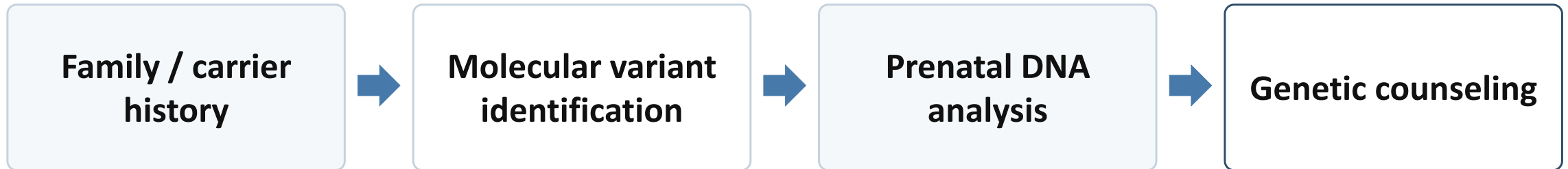


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- Iron deposition occurs unless overload is actively prevented
 - Chelation reduces risk of injury to heart and other organs
 - The source emphasizes combining appropriate transfusions with iron chelation

Curative approaches target hematopoietic stem cells

- Hematopoietic stem cell transplantation can be curative
- Gene-addition therapy introduces functional β -globin into stem cells
- The source also mentions CRISPR-based therapeutic strategies
- Access and very high cost constrain use in resource-limited settings

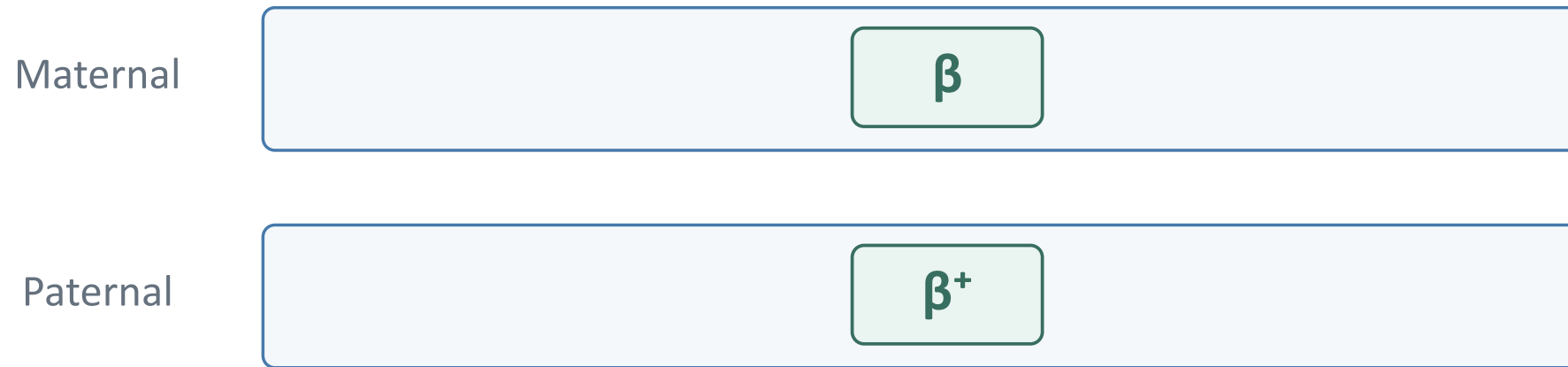
Prenatal molecular diagnosis is possible



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- Pathogenic β -globin variants can be identified by DNA analysis
 - Genetic characterization can support reproductive counseling
 - This is especially relevant when both parents carry affected alleles

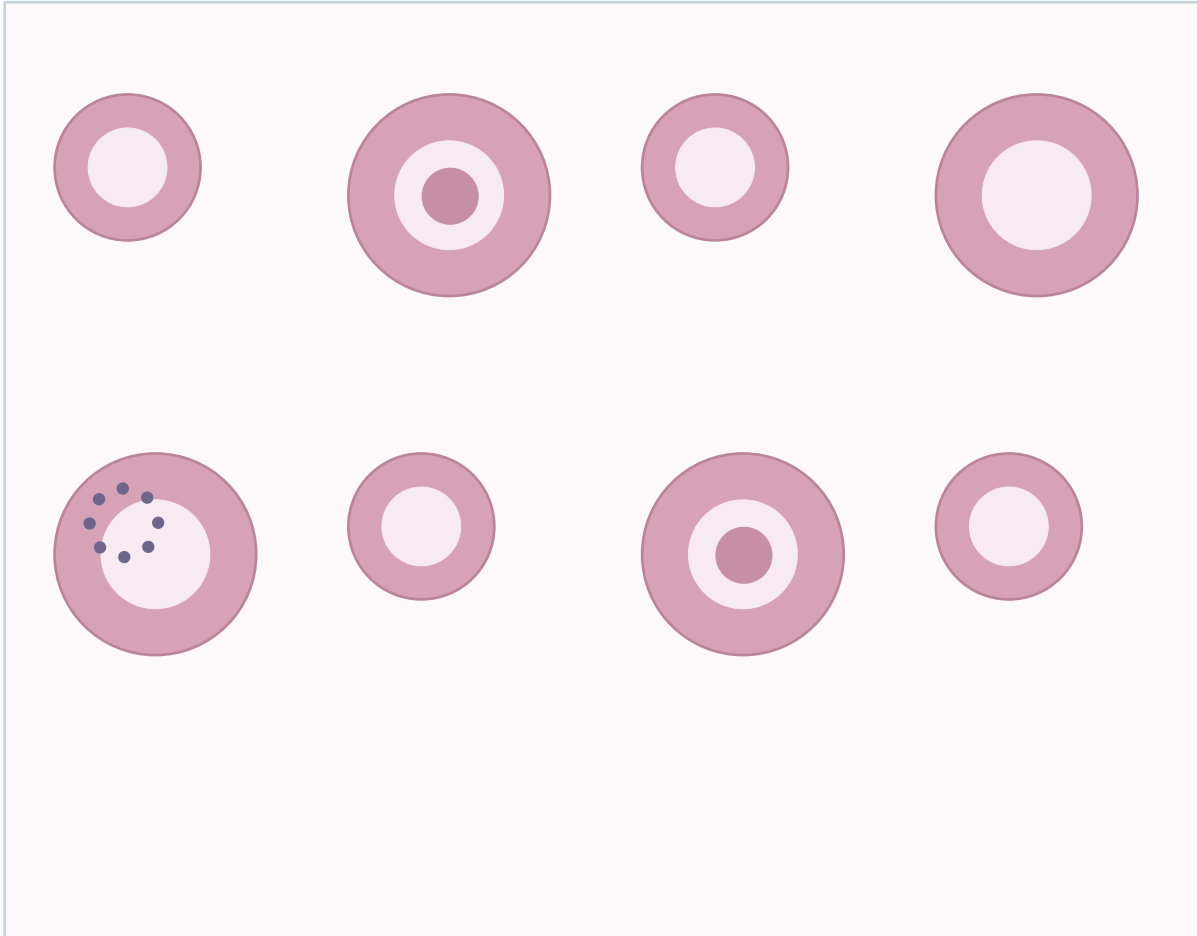
β -thalassemia trait usually causes little morbidity

Two homologous chromosomes 11



- Typically one β^0 or β^+ allele and one functional allele
- Individuals are generally asymptomatic
- Mild anemia or isolated microcytosis may be detected incidentally

β -thalassemia minor has recognizable red-cell changes



Illustrative RBC morphology — schematic, not a blood specimen

- Microcytosis and hypochromia commonly persist
- Target cells and basophilic stippling may be seen
- Marrow erythroid hyperplasia is usually mild
- Morphology must be interpreted alongside iron studies and Hb fractions

Elevated HbA₂ is a clue to β -thalassemia trait

- Hemoglobin analysis typically shows increased HbA₂
- Robbins gives an illustrative range of 4–8% of total hemoglobin
- HbF is usually normal or only slightly increased
- HbA₂ interpretation belongs with overall laboratory context

Differentiate β -thalassemia trait from iron deficiency

Finding	β -thalassemia trait	Iron deficiency
Microcytosis	Typical	Typical
HbA ₂	Often increased	Not diagnostic
Iron studies	Assess to exclude deficiency	Demonstrate iron deficiency
Context	Inherited carrier state	Acquired iron depletion

β -thalassemia intermedia has variable genotypes

Genes

Variable defective alleles

Hemoglobin

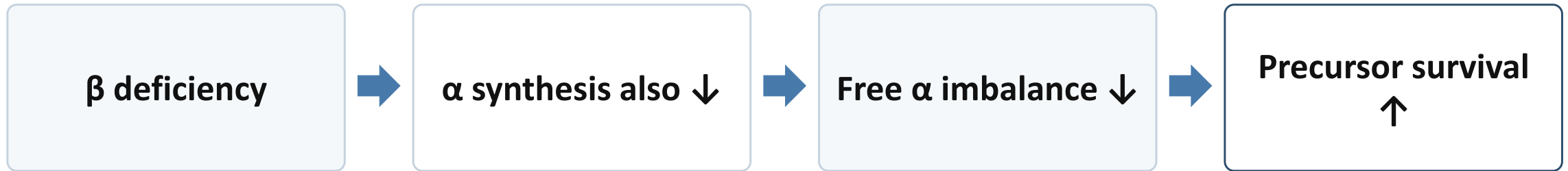
Moderately reduced
effective output

Clinical course

Intermediate severity

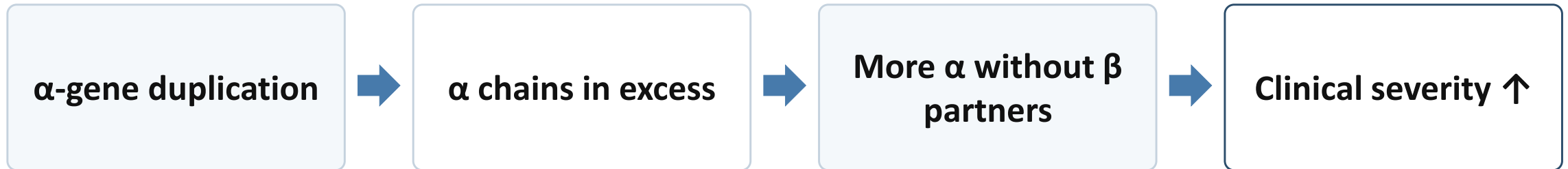
- Clinical severity is intermediate between major and trait
- Biallelic mild defects or selected heterozygous configurations may produce it
- It is often not dependent on regular blood transfusions
- Modifiers that alter globin-chain balance help explain variability

Coinherited α -thalassemia can ameliorate β disease



- Decreasing α synthesis reduces excess unpaired α chains
- This can lessen erythroid precursor damage
- Some patients with two β -thalassemia alleles therefore have a milder phenotype

Extra α -globin genes can worsen β -chain imbalance



-
- An α -gene duplication increases α -chain output
 - With one defective β allele, the extra α supply can worsen chain imbalance
 - The example demonstrates that phenotype depends on relative chain abundance

β -thalassemia phenotype is not a simple allele count

Underlying determinants

β^0 / β^+ expression

α -chain gene dosage

Observed phenotype

Mild trait

Intermedia or major

Clinical classification captures the net physiological effect

α -thalassemia severity follows four-gene dosage

Two homologous chromosomes 16

Maternal



Paternal



The phenotype depends on how many of these four gene copies are deleted.

Deficient α chains leave γ or β chains unmatched

Fetal period

Unpaired γ chains

γ_4 = Hb Barts

After birth

Unpaired β chains

β_4 = HbH

Neither tetramer delivers oxygen normally

α -thalassemia generally causes less precursor toxicity

Excess α (β defect)

Insoluble aggregates

Prominent precursor injury

Excess non- α (α defect)

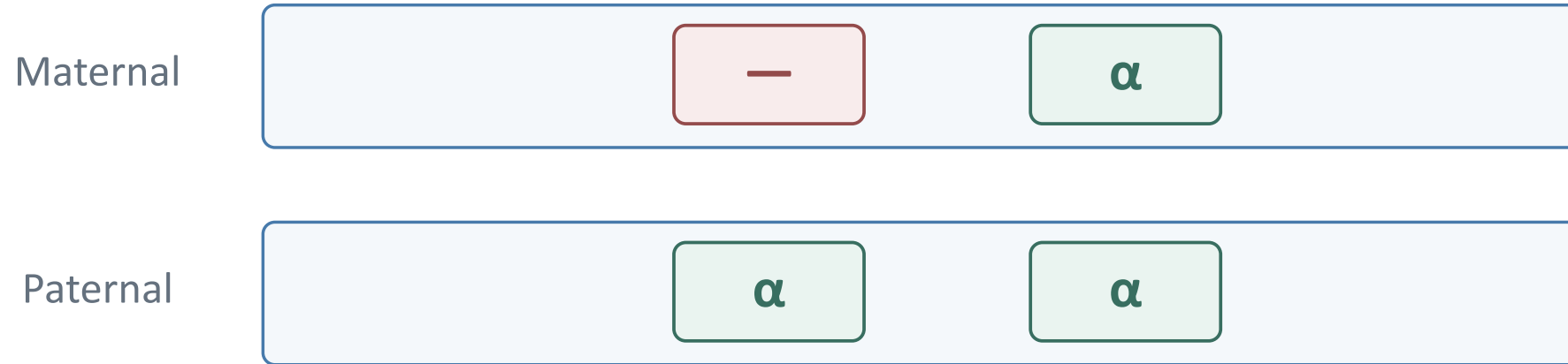
β_4 / γ_4 tetramers

High oxygen affinity / instability

Severe α -gene loss nevertheless has major physiological consequences

One α -gene deletion: Silent carrier

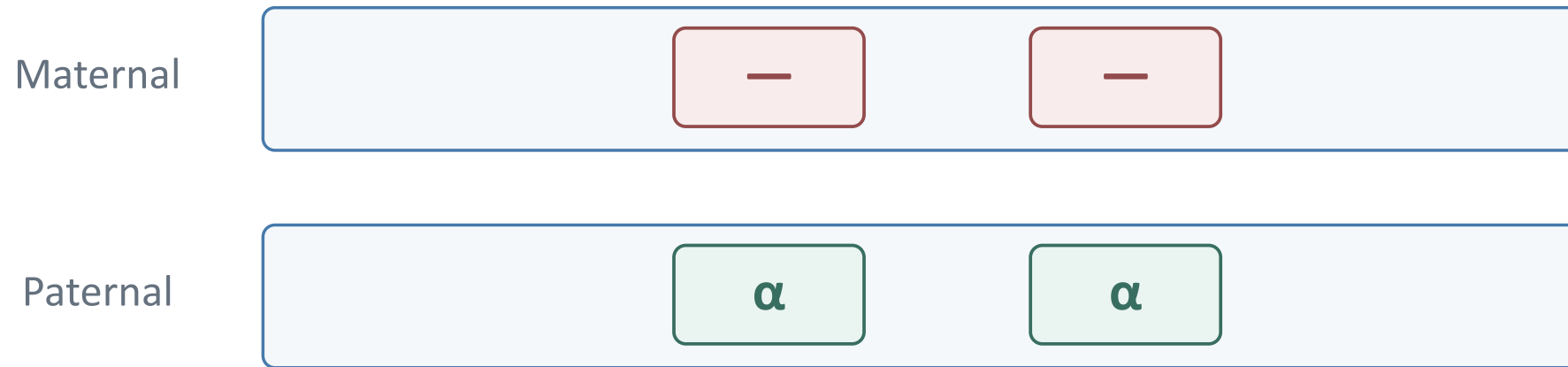
Two homologous chromosomes 16



- Three of four α -globin genes remain
- No clinically important anemia or physical signs are expected
- Very slight microcytosis may be detectable

Two α -gene deletions: α -thalassemia trait

Two homologous chromosomes 16



- α -chain output is lower, causing microcytosis
- Anemia is absent or minimal; Physical signs are usually lacking
- HbA₂ is typically normal or low
- Two deletions can occur in cis or in trans

The arrangement of two deletions matters

Cis deletion

-- / $\alpha\alpha$

One chromosome lacks both genes

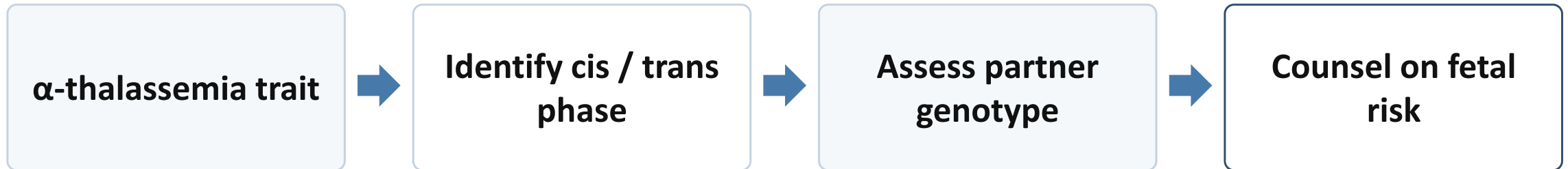
Trans deletion

- α / - α

Each chromosome has one gene

Their reproductive risks differ substantially

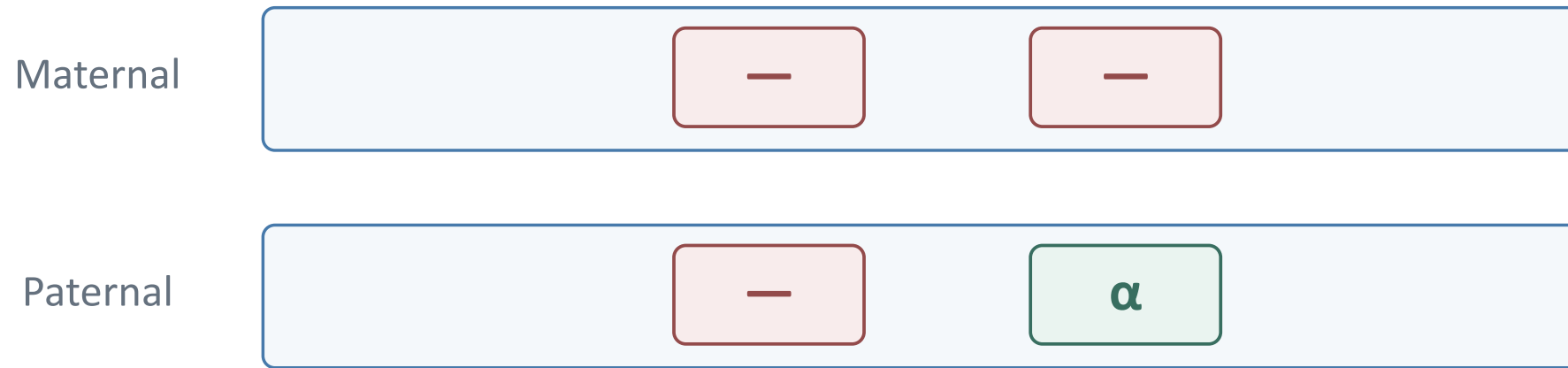
Cis α -gene deletions change fetal risk



-
- A parental chromosome lacking both α genes can transmit a two-gene deletion
 - The partner's α -globin genotype determines risk of HbH disease or α -thalassemia major
 - Genotyping is therefore more informative than red-cell indices alone for reproductive counseling

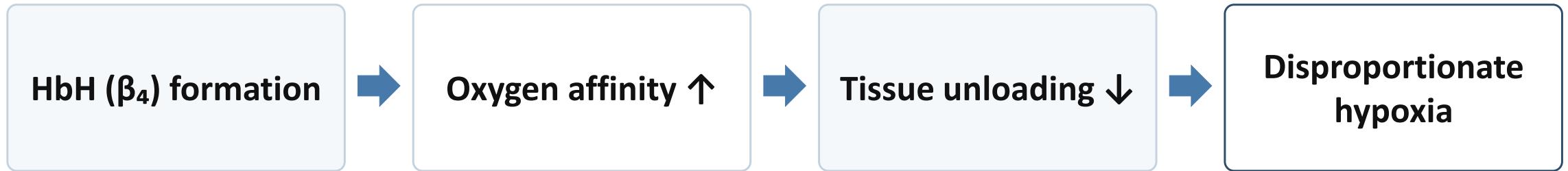
Three α -gene deletions cause HbH disease

Two homologous chromosomes 16



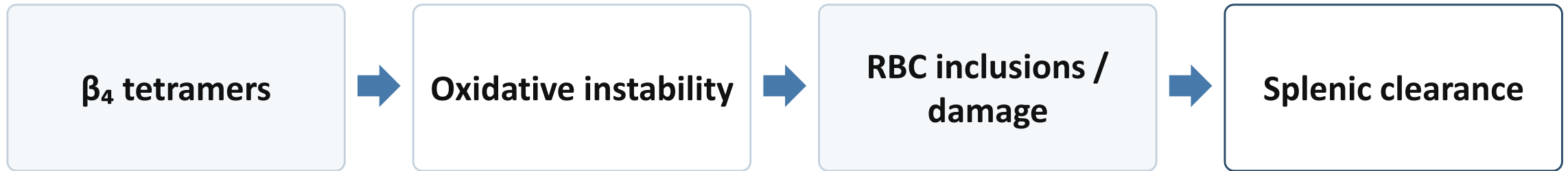
- Only one α -globin gene remains functional
- β -chain excess forms β_4 tetramers
- The resulting anemia resembles β -thalassemia intermedia in severity

HbH delivers oxygen poorly to tissues



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- β₄ tetramers have unusually high oxygen affinity
 - Oxygen unloading is inefficient
 - Tissue hypoxia may exceed what the measured hemoglobin level suggests

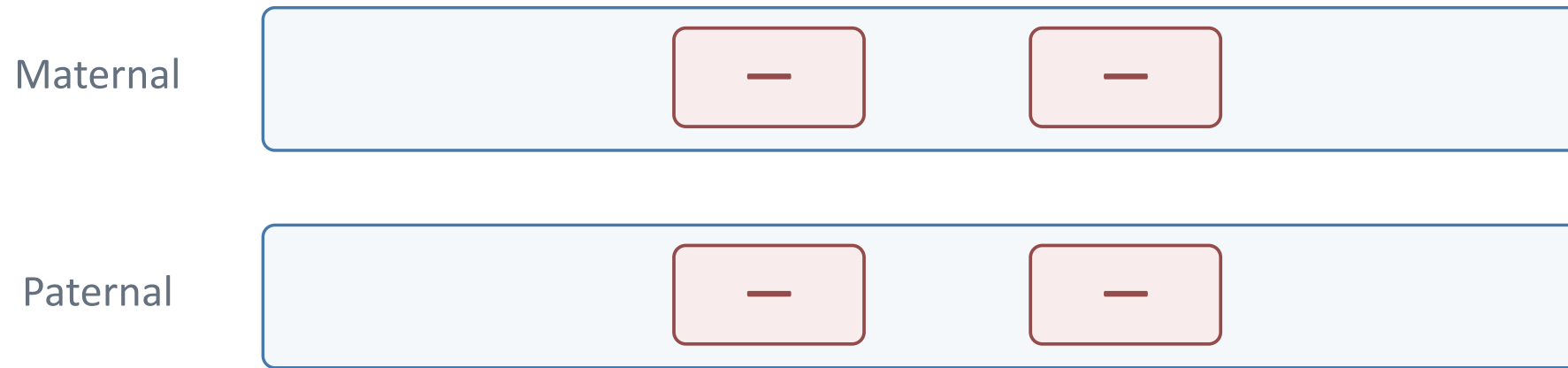
HbH instability promotes splenic destruction



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- HbH is susceptible to oxidation
 - Oxidation leads to intracellular precipitation and inclusions
 - Abnormal RBCs undergo sequestration and phagocytosis in the spleen

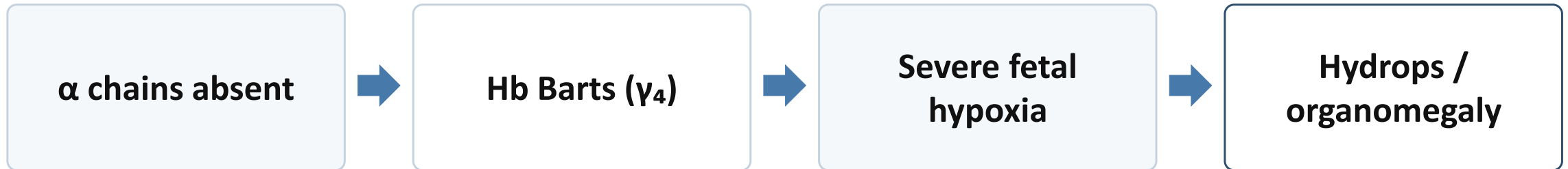
Loss of all four α genes causes α -thalassemia major

Two homologous chromosomes 16



- No α -globin synthesis occurs from the normal four-gene cluster
- Fetal excess γ chains form Hb Barts (γ_4)
- High-affinity Hb Barts does not release oxygen effectively to tissues

α -thalassemia major threatens fetal oxygenation

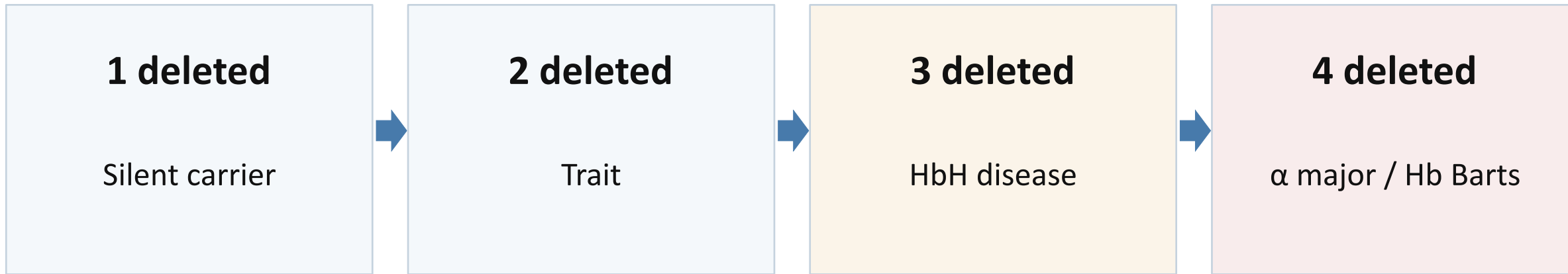


- Severe tissue anoxia becomes evident during pregnancy
- Typical findings include pallor, generalized edema, and massive hepatosplenomegaly
- Severe disease historically caused intrauterine or early neonatal death

Fetal survival and intervention can change outcome

- Embryonic ζ chains initially pair with γ chains to support oxygen transfer
- Signs of severe disease typically appear later in gestation
- Intrauterine transfusions can allow survival in some affected fetuses
- Survivors may require ongoing transfusion; Stem cell transplant can be curative

α -thalassemia phenotypes form a gene-dose sequence

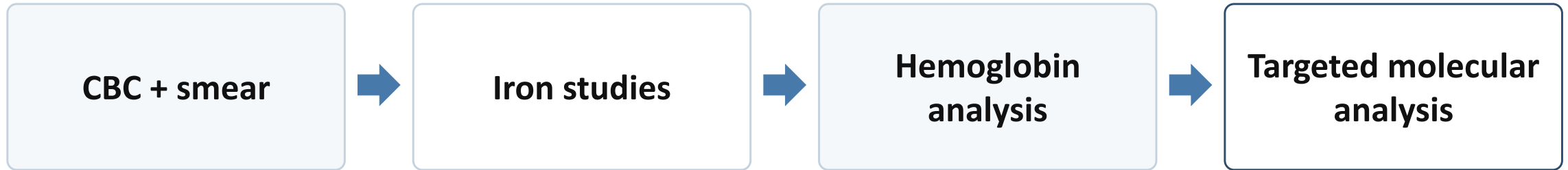


Increasing loss of α -globin gene function → generally increasing severity

β and α thalassemia differ in their toxic partner chains

Feature	β -thalassemia	α -thalassemia
Principal mutation	Often point mutation	Usually gene deletion
Excess chain	α	β or γ
Key mechanism	α precipitation + apoptosis	Tetramers + impaired O ₂ unloading
Severe form	β major	α major / Hb Barts

Clinical workup integrates morphology, fractions, and genes



-
- Recognize microcytosis and hypochromia
 - Evaluate iron deficiency rather than assuming the cause
 - Analyze hemoglobin fractions when appropriate

Case: Microcytosis with elevated HbA₂

- A clinically well adult has persistent microcytosis
- Hemoglobin analysis shows elevated HbA₂
- Iron status does not support iron deficiency
- Most compatible textbook classification: β -thalassemia trait

Which finding most strongly supports the carrier diagnosis?

Answer and reasoning in presenter notes

Case: Severe anemia emerging late in infancy

- An infant becomes markedly anemic after the HbF-to-HbA transition
- Smear shows target cells, hypochromia, and marked size variation
- HbF is predominant; HbA is greatly reduced
- Pattern is compatible with β -thalassemia major

Why does clinical disease emerge months after birth?

Answer and reasoning in presenter notes

Case: Hypoxia disproportionate to hemoglobin

- A patient has an α -globin deletion syndrome with HbH (β_4)
- The anemia is moderately severe
- Tissue oxygen delivery is poorer than the hemoglobin level alone implies
- High-affinity HbH accounts for the discrepancy

What molecular property explains poor oxygen delivery?

Answer and reasoning in presenter notes

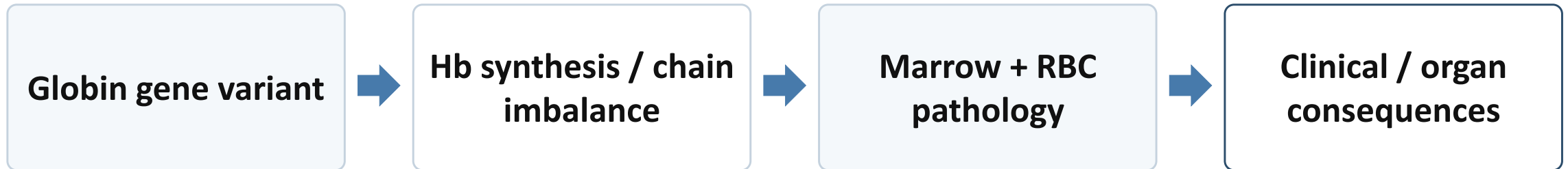
Case: α -thalassemia trait and family planning

- Two individuals have similar mild microcytosis
- One carries $--/\alpha\alpha$; The other $-\alpha/-\alpha$
- Blood indices alone cannot distinguish these arrangements
- DNA-level phase informs offspring risk

Why distinguish cis from trans two-gene deletions?

Answer and reasoning in presenter notes

Integrating thalassemic anemia from gene to organ



-
- Gene-level deficit causes reduced hemoglobin synthesis
 - Chain excess injures erythroblasts or disrupts oxygen unloading
 - Anemia stimulates marrow and extramedullary hematopoiesis

Core distinctions for diagnosis and teaching

- Thalassemia is a defect in globin quantity, not simply an abnormal Hb structure
- β -thalassemia severity is driven strongly by unmatched α chains
- α -thalassemia severity correlates with deletion count and gene arrangement
- Always consider iron deficiency in microcytic anemia

Primary reference

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Chapter 14: Red Blood Cell and Bleeding Disorders.
- Section: Thalassemia (printed pp. 585–589).
- Source-derived clinical classifications and numerical values retain the textbook framing.