α-thalassemia

Disease state educational resource

THA-ALL-0035 November 2022

Disclaimers

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Learning objectives

Provide a better understanding of the genetic etiology of α-thalassemia and how this influences its global epidemiology

Describe how α-thalassemia is diagnosed

Describe the pathophysiology of α-thalassemia and how this gives rise to its clinical profile

Understand the current approaches to managing α-thalassemia through long-term supportive care

Describe the clinical presentation of α-thalassemia, including acute and chronic symptoms and complications

Overall, this educational resource should provide an understanding of the burden of α-thalassemia on patients, while highlighting important unmet needs and gaps both in the understanding of this disease and its clinical management

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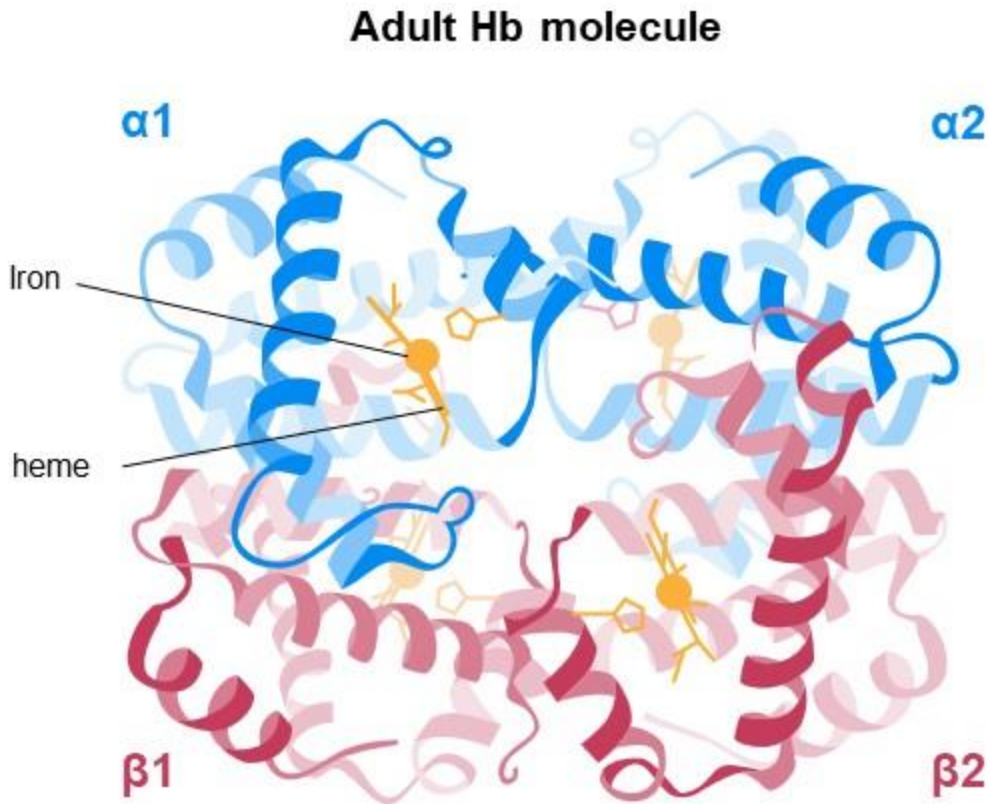
α-thalassemia genetics and epidemiology

Section 1

α- and β-thalassemias comprise a group of inherited Hb disorders[1]



Reduced or absent synthesis of α-chains of Hb → α-thalassemias

Reduced or absent synthesis of β-chains of Hb → β-thalassemias

1. Greer JP et al. *Wintrobe's Clinical Hematology*. 13th ed. Lippincott Williams & Wilkins; 2014.

Globin synthesis changes in early development[1]

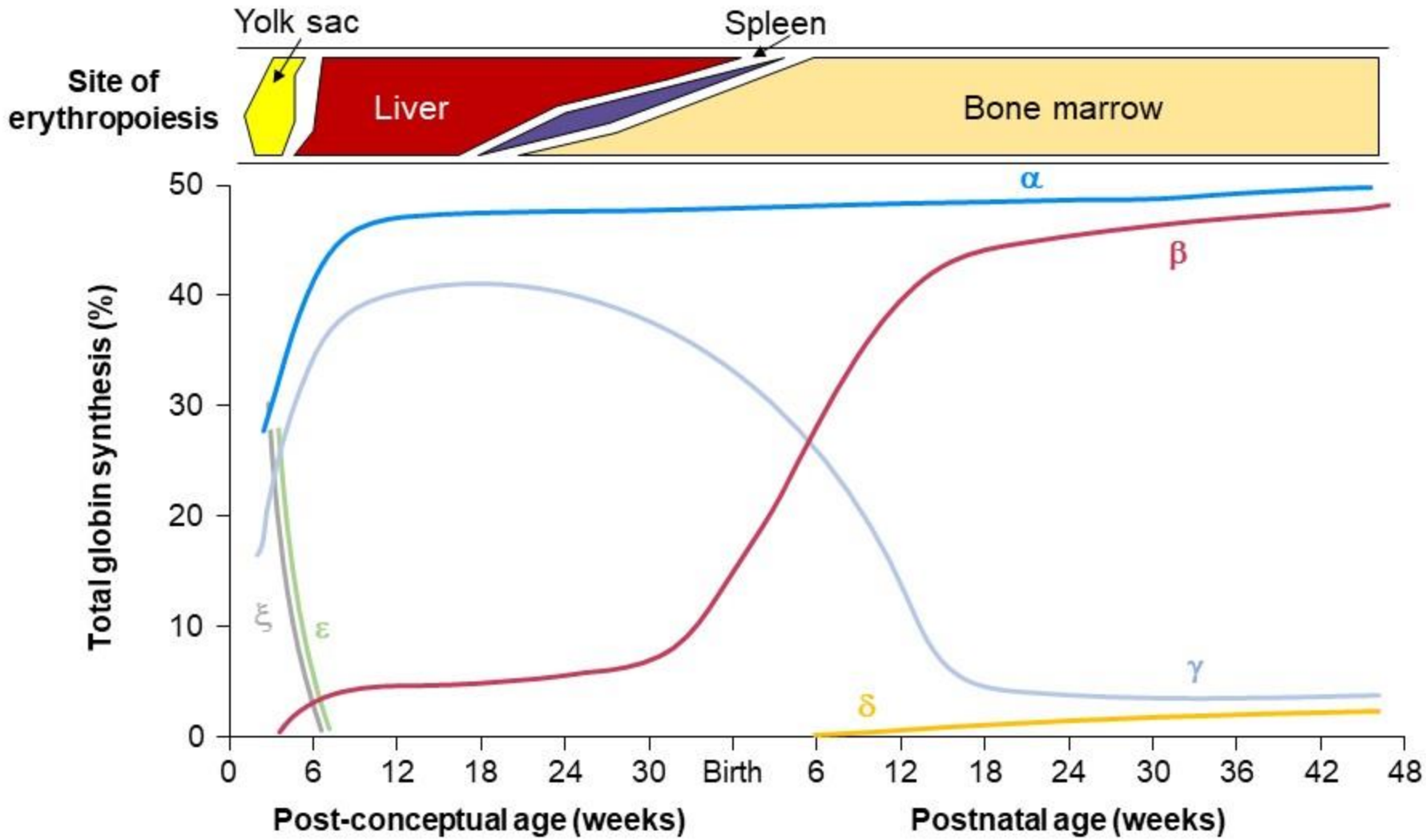


Figure adapted from Taher AT et al. Lancet. 2018;391:155–167.

1. Greer JP et al. *Wintrobe's Clinical Hematology*. 13th ed. Lippincott Williams & Wilkins; 2014.

Gene clusters on chromosome 16 and 11 encode the α- and β-globin chains[1]

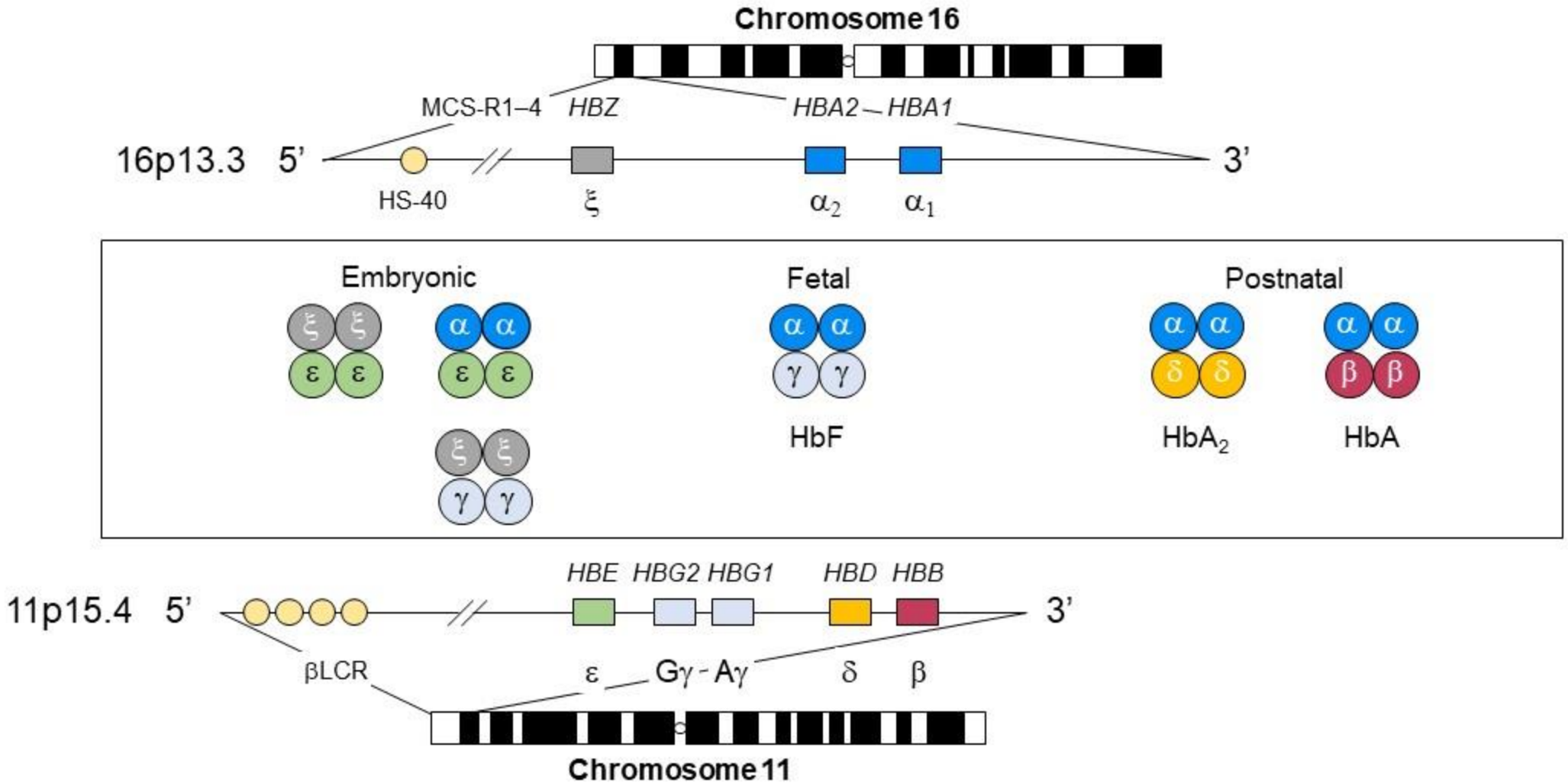


Figure adapted from Farashi S et al. *Blood Cells Mol Dis*. 2018;70:43–53.

1. Farashi S et al. *Blood Cells Mol Dis*. 2018;70:43–53.

α-thalassemia results from mutations or deletions of α-globin genes[1]

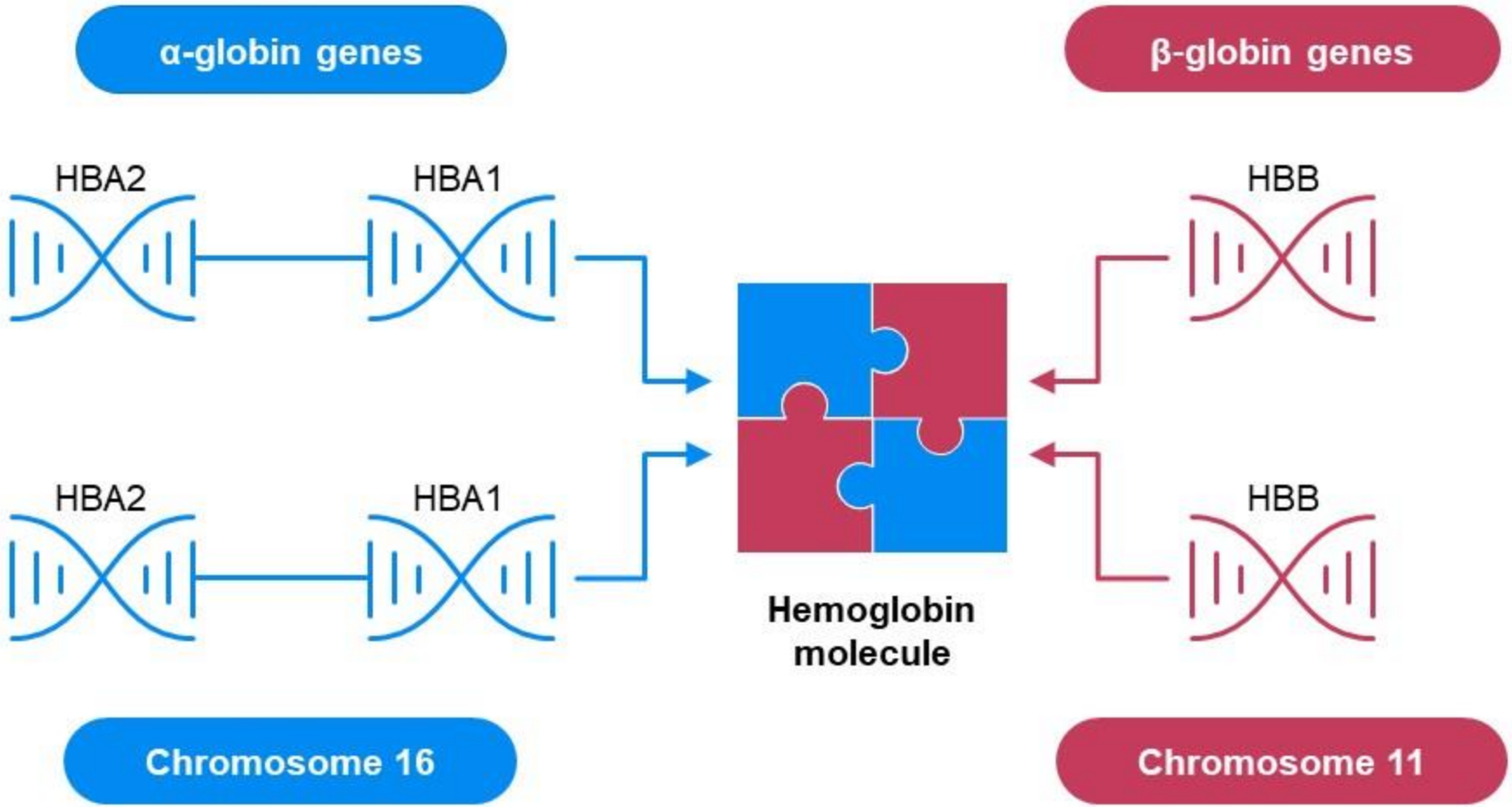
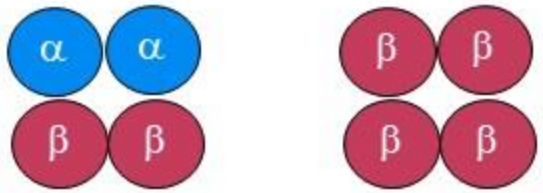


Figure adapted from Kalle Kwaifa I et al. *Orphanet J Rare Dis*. 2020;15:166.

1. Kalle Kwaifa I et al. *Orphanet J Rare Dis*. 2020;15:166.

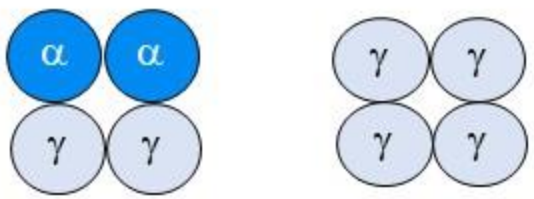
Reduced synthesis of α-globin chains leads to a globin chain imbalance[1,2]

Adult Hb



HbA (healthy) HbH

Fetal Hb

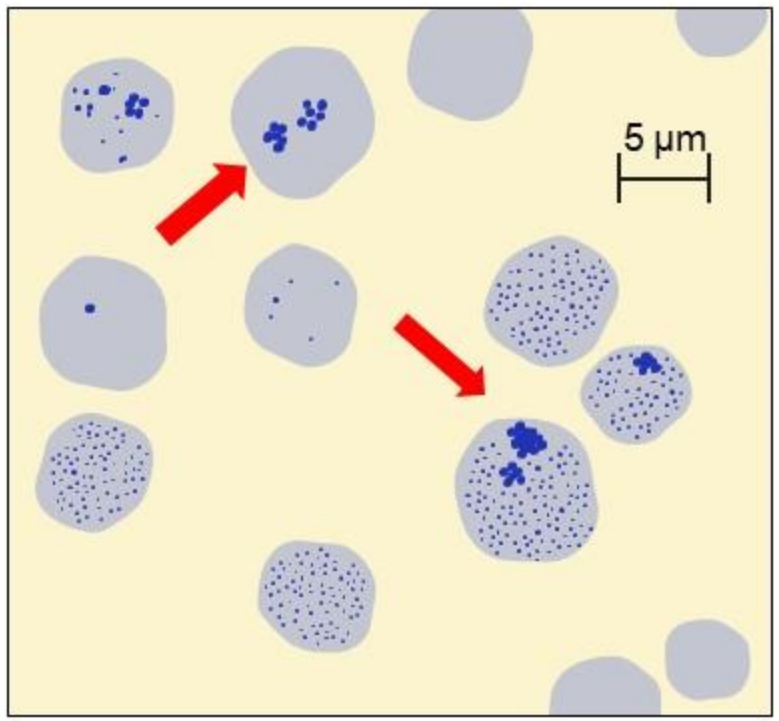


HbF (healthy) Hb Barts

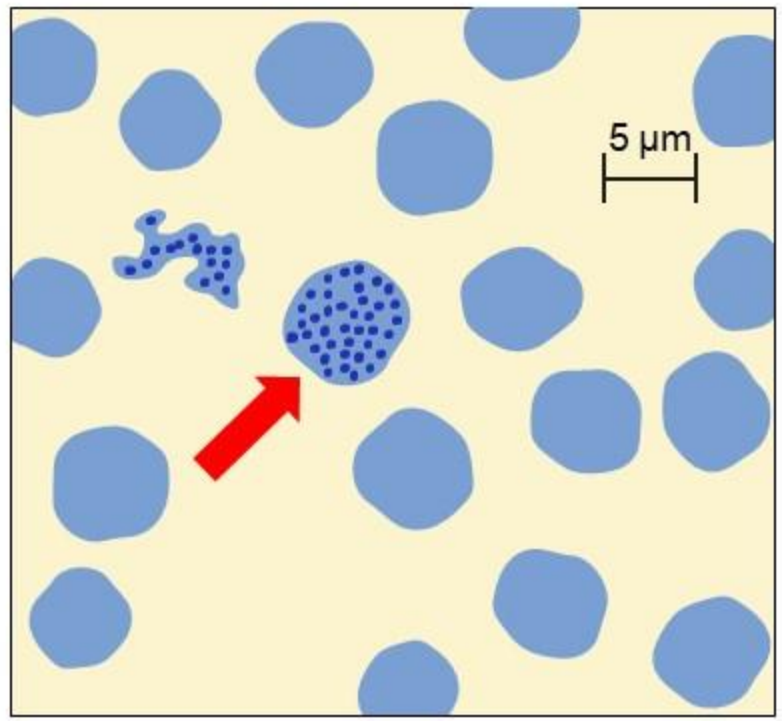
- **Healthy RBCs**: α- and β-globin chains are balanced in a 1:1 ratio[3,4]
- **α-thalassemic RBCs**: reduced or absent synthesis of the α-globin chain, or alterations of α-globin chain stability or binding to β-globin, leads to a relative excess of the β-globin and γ-globin chains[3,4]

1. Waye JS, Chui DH. *Clin Invest Med*. 2001;24:103–109. **2**. Piel FB et al. *N Engl J Med*. 2014;371:1908–1916.
3. Angastiniotis M et al. *Int J Neonatal Screen*. 2019;5:16. **4**. Kalle Kwaifa I et al. *Orphanet J Rare Dis*. 2020;15:166.

Globin chain imbalance causes reduction in functional Hb and impaired RBC function and survival[1]



Inclusion body positive cells in HbH disease



Occasional inclusion body positive cell in carrier

Hematology[2]

- ↓ in MCV (microcytosis)
- ↓ in MCH (hypochromia)
- ↓ in Hb (anemia)
- Slight ↑ in RBC count
- Presence of inclusion bodies with Brilliant Cresyl Blue stain

1. Angastiniotis M et al. *Int J Neonatal Screen*. 2019;5:16. **2**. Farashi S et al. *Blood Cells Mol Dis*. 2018;70:43–53.

α-thalassemia is an autosomal recessive disorder

Inheritance patterns depend on exact genotype of both parents[1]

>120 different mutations reported to date[1]

Types of mutations[2,3]

- **Deletional type (−):** involving one or both α-globin genes
- **Non-deletional type (α^T):** alterations in regions critical for gene expression and protein stability
- **Homozygous/*trans*:** one gene/both chromosomes (−α/−α)
- **Heterozygous/*cis*:** both genes/same chromosome (−−/αα)

1. Kalle Kwaifa I et al. *Orphanet J Rare Dis*. 2020;15:166. **2.** Galanello R et al. *Genet Med*. 2011;13:83–88. **3.** Piel FB et al. *N Engl J Med*. 2014;371:1908–1916.

Clinical severity is correlated with the number and type of affected alleles[1]

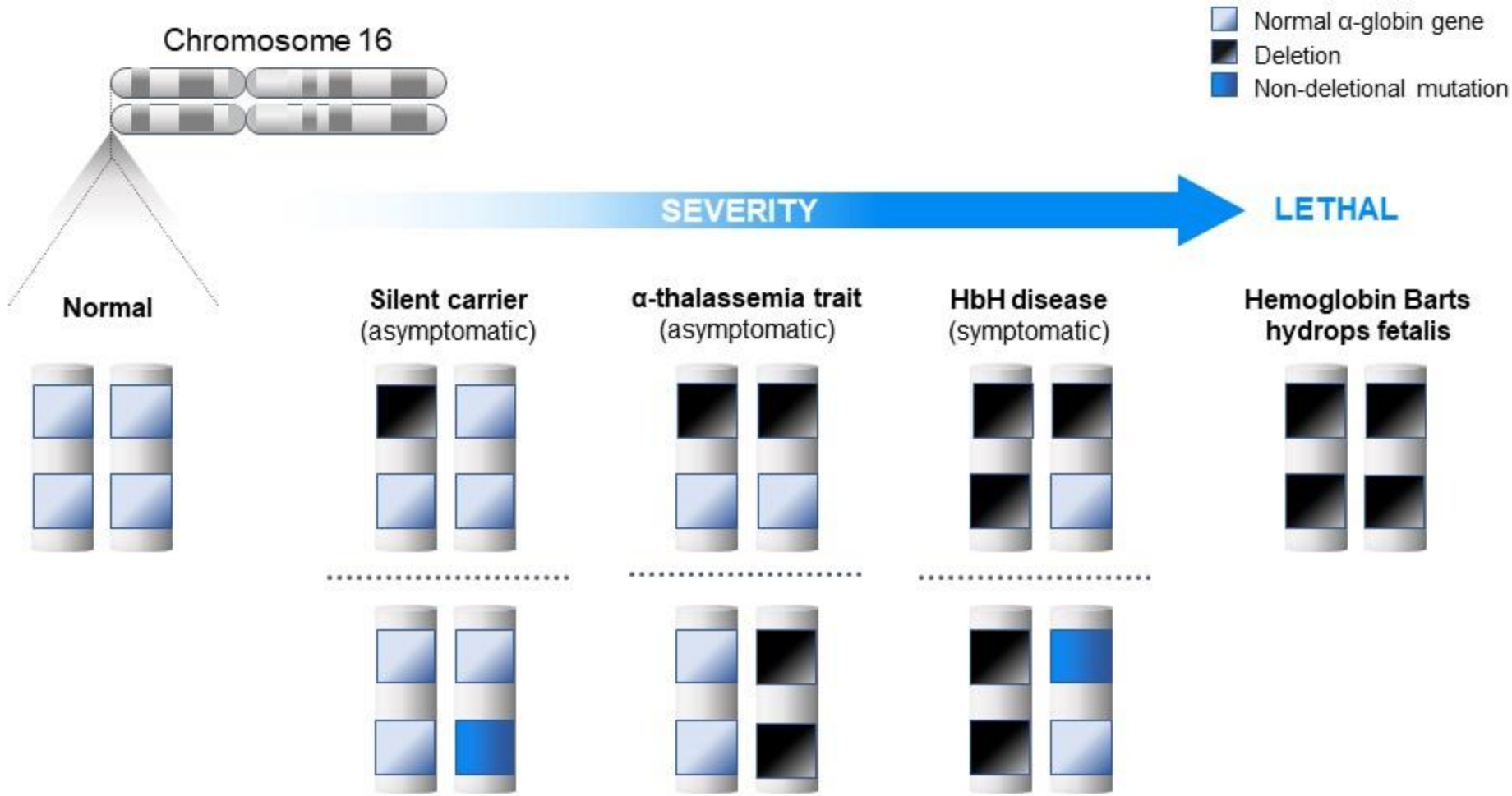
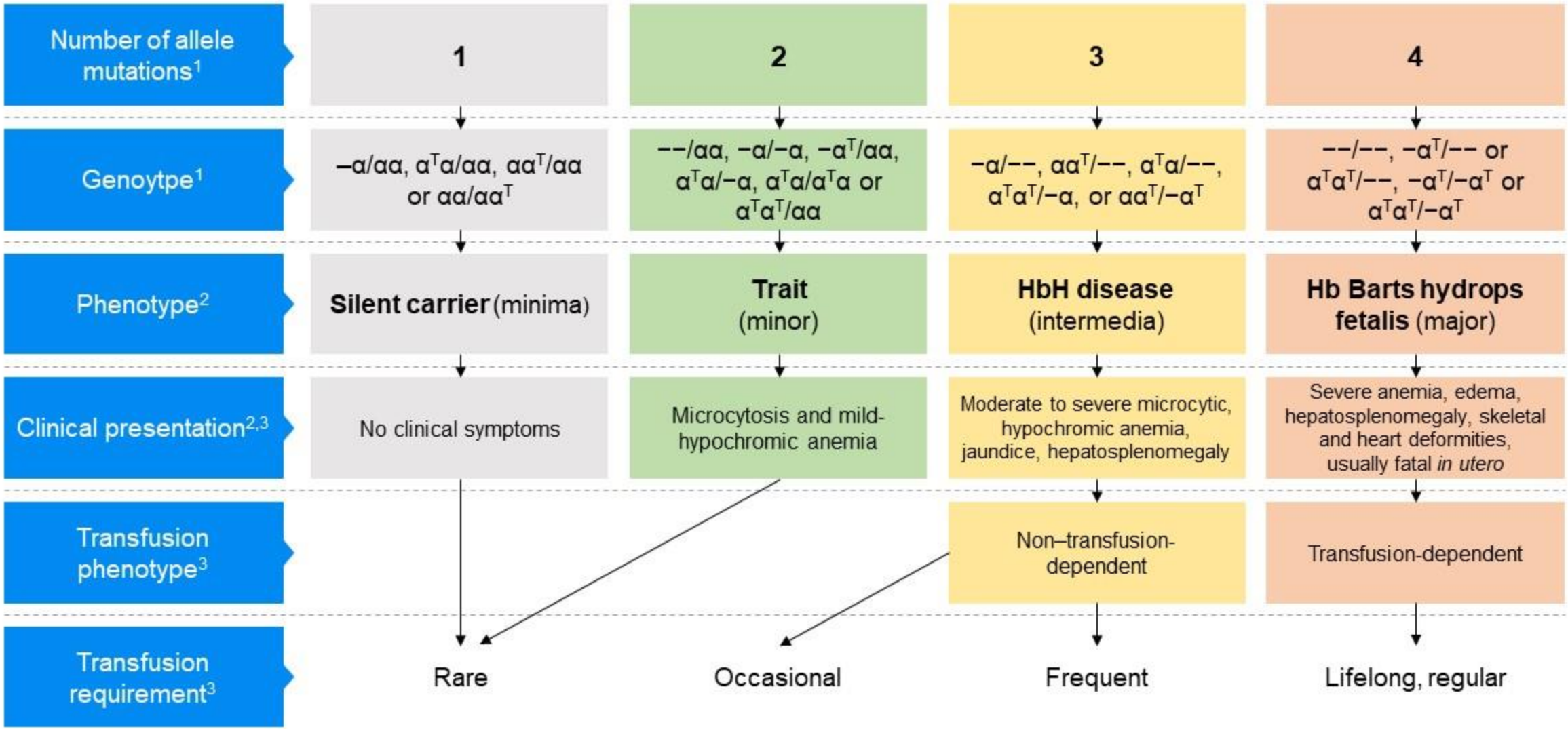


Figure adapted from Piel FB et al. *N Engl J Med*. 2014;371:1908–1916.

1. Piel FB et al. *N Engl J Med*. 2014;371:1908–1916.

Clinical severity ranges from asymptomatic to very severe



1. Kalle Kwaifa I et al. *Orphanet J Rare Dis*. 2020;15:166. **2**. Galanello R et al. *Genet Med*. 2011;13:83–88. **3.** Musallam KM et al. *Haematologica*. 2013;98:833–844.

α-thalassemia mutations are historically more prevalent in areas where malaria is endemic[1,2]

Carrier frequencies of thalassemia alleles (%)[2]

Region	α^0-thalassemia	α^+-thalassemia
Americas	0–5	0–40
Eastern Mediterranean	0–2	1–60
Europe	1–2	0–12
Southeast Asia	1–30	3–40
Sub-Saharan Africa	0	10–50
Western Pacific	0	2–60

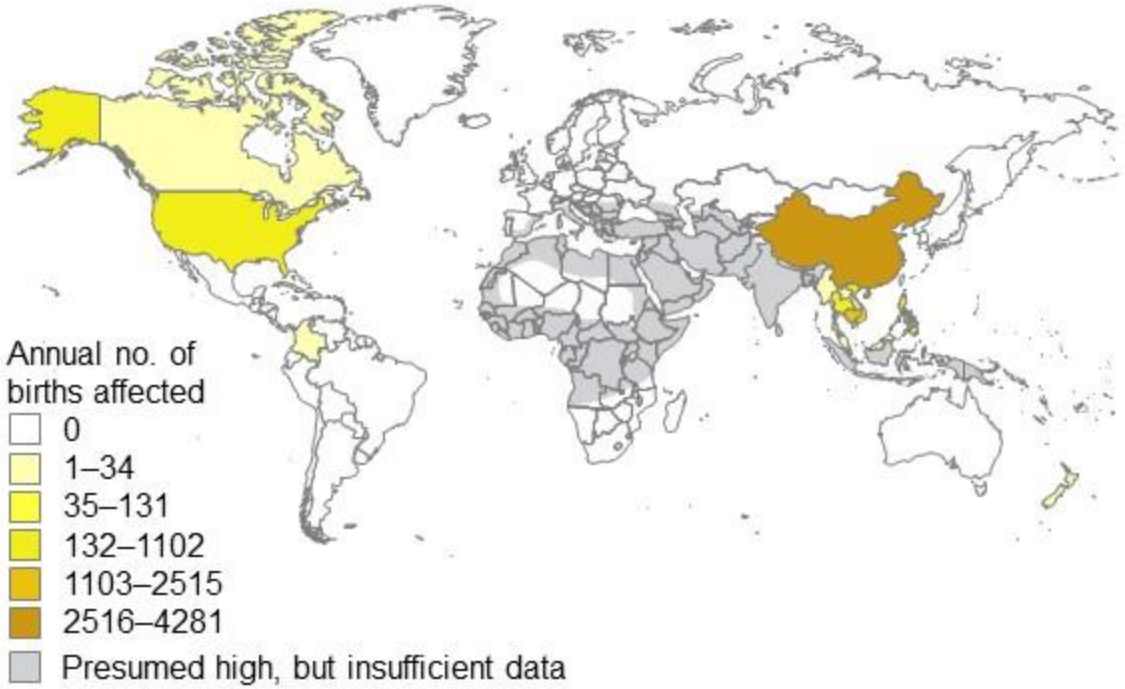
- Global prevalence is not well understood[1]
- Substantial heterogeneity within and between regions[1,2]
- More research is needed to quantify populations at risk for HbH disease and Hb Barts hydrops fetalis[1]

α^0 = both genes impacted
α^+ = one gene impacted

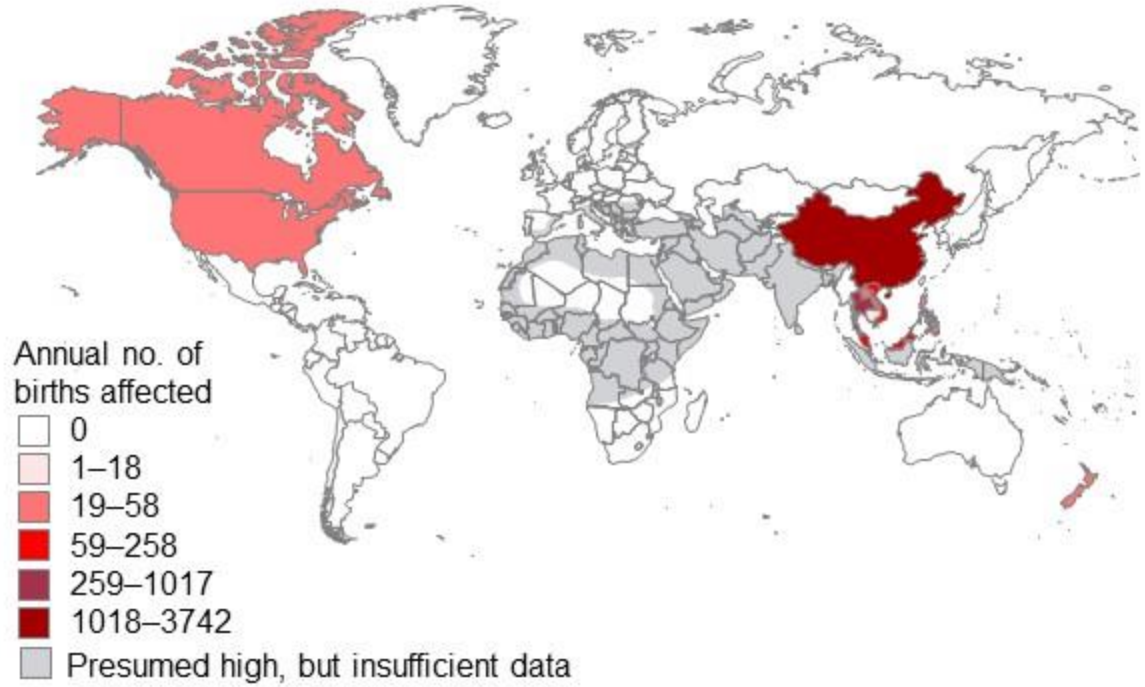
1. Piel FB et al. *N Engl J Med.* 2014;371:1908–1916. **2.** Weatherall D et al. *New York: Oxford University Press*; 2006:663–680.

Approximately 13,500 conceptions are affected annually by HbH disease or Hb Bart's hydrops fetalis[1]

HbH disease



Hb Bart's hydrops fetalis



- The most common variants of α-thalassemia are more prevalent in Southeast Asia, the Mediterranean, the Middle East, and Africa[2]
- Deletional HbH is more prevalent than non-deletional HbH disease[3]
  - Non-deletional HbH disease (eg, Constant Spring) found in populations from Southeast Asia, China, and the Mediterranean
- Prevalence has increased in Northern Europe and North America due to migration[3,4]

Maps adapted from Piel FB et al. N Engl J Med. 2014;371:1908–1916.

1. Modell B, Darlison M. *Bull World Health Organ*. 2008;86:480–487. **2**. Piel FB et al. *N Engl J Med*. 2014;371:1908–1916. **3.** Kalle Kwaifa I et al. *Orphanet J Rare Dis*. 2020;15:166. **4**. Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13.

Section 1: Key takeaways

Mutations in the α-globin genes (HBA1 and HBA2) cause reduced or absent synthesis of the α-globin chains and an accumulation of the β- or γ-globin chains

This globin chain imbalance results in reduced levels of functional Hb, which limits the RBCs' capacity to transport oxygen to the tissues

Genotype classification is based on the number (1–4) and type of affected alleles, which is also highly correlated with clinical severity

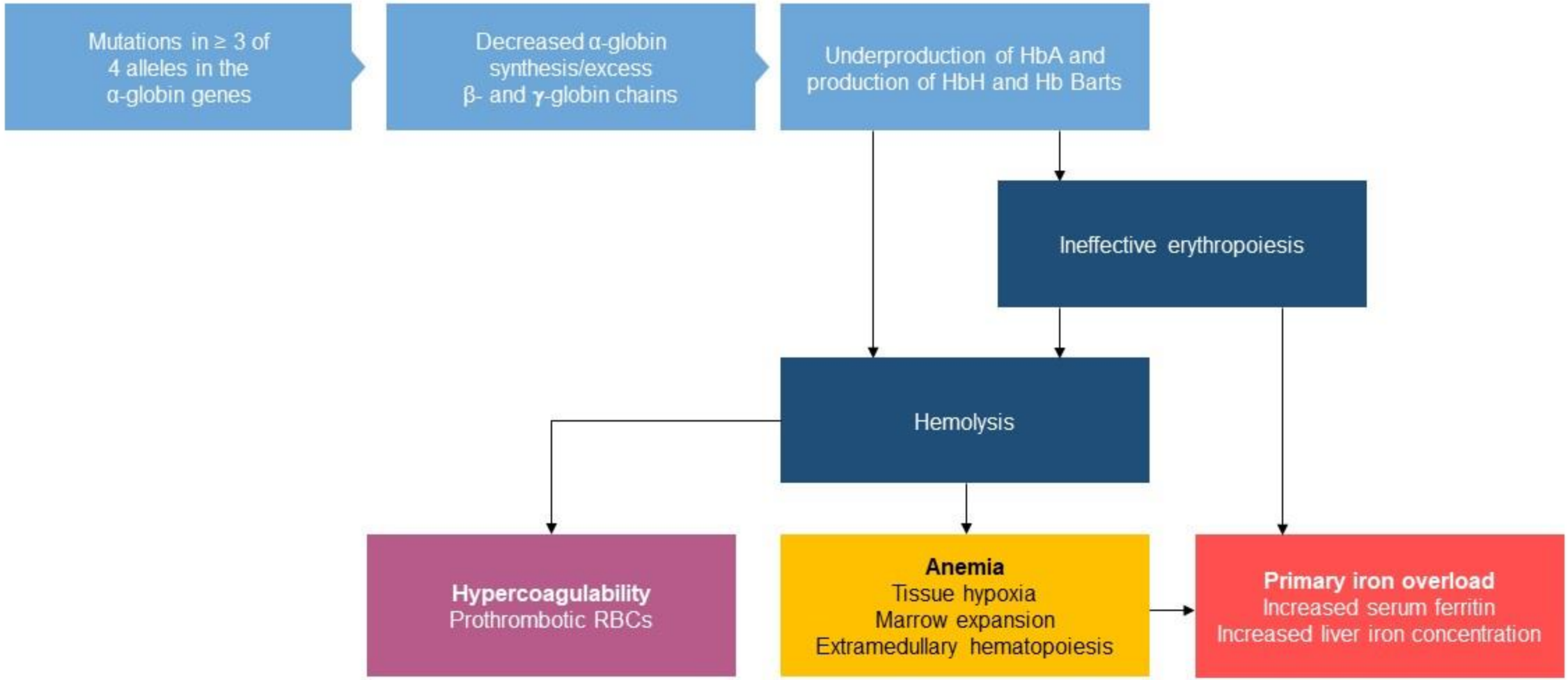
α-thalassemia is an autosomal recessive disorder that is most prevalent in regions where malaria is endemic

There is substantial heterogeneity within and between regions, and the global prevalence of α-thalassemia is not well understood

Pathophysiology and clinical presentation of α-thalassemia

Section 2

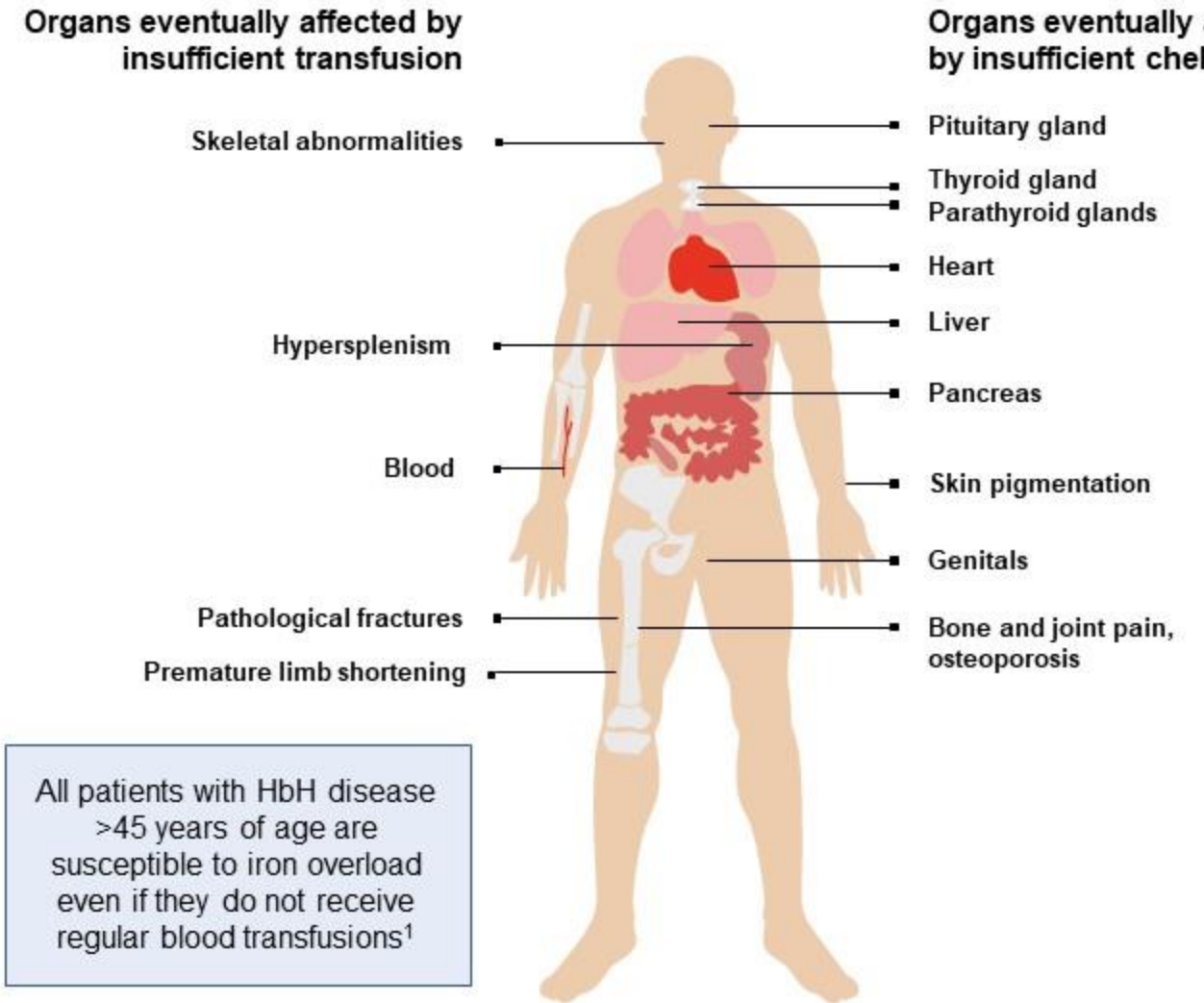
Globin chain imbalance and loss of functional Hb results in hemolysis, ineffective erythropoiesis, anemia, and their complications[1]



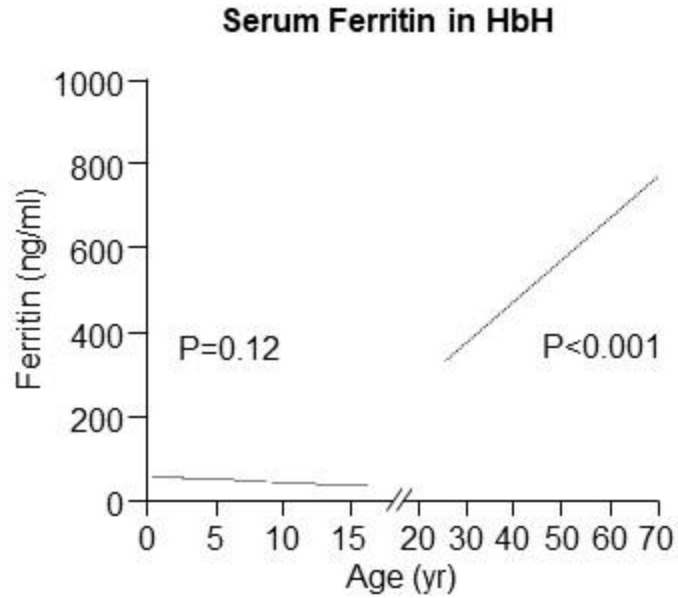
Adapted from Taher AT et al. *N Engl J Med*. 2021;384:727–743.

1. Taher AT et al. *Lancet*. 2018;391:155–167.

Complications of iron overload increase with advancing age without iron chelation therapy[1]



All patients with HbH disease >45 years of age are susceptible to iron overload even if they do not receive regular blood transfusions[1]



Left figure adapted from Machin A. *InnovAiT*. 2014;7:558–565. Right figure adapted from Lal A et al. *N Engl J Med*. 2011;364:710–718.

1. Viprakasit V et al. Orphanet J Rare Dis. 2014;9:131.

Management guidelines primarily based on data for β-thalassemia

People with silent carrier or trait are mostly asymptomatic, but are at risk of having children with HbH or Hb Barts disease

Classification	Laboratory results	Symptoms and complications	Risk to offspring
Silent carrier[1,2] (1 mutated allele)	Normal Hb Low to normal MCV	Asymptomatic Can act as a genetic modifier of other inherited disorders (eg, β-thalassemia and sickle cell)	HbH disease
Trait[1,2] (2 mutated alleles)	Normal or slightly low Hb Low MCV and MCH	Asymptomatic or mild anemia Can act as a genetic modifier of other inherited disorders (eg, β-thalassemia and sickle cell)	HbH disease Hb Barts

1. Kalle Kwaifa I et al. *Orphanet J Rare Dis*. 2020;15:166. **2.** Piel FB et al. *N Engl J Med*. 2014;371:1908–1916.

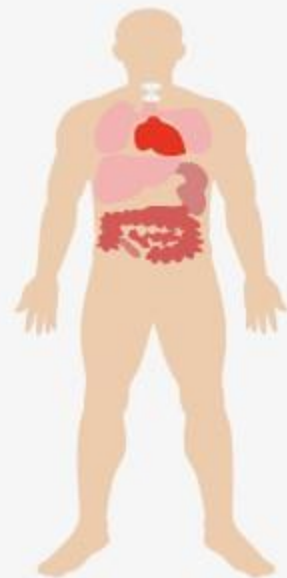
Patients with HbH disease may present with a wide range of symptoms and complications

Classification	Laboratory results	Symptoms and complications	Risk to offspring
HbH disease[1–7] (3 mutated alleles)	Low Hb and MCV	Moderate-to-severe anemia Hepatosplenomegaly Acute hemolytic events Leg ulcers Jaundice Cholecystitis (with or without gallstones) Folic acid deficiency Iron overload (older patients) Growth delays/endocrinopathies (younger patients) Decreased bone mineral density Thrombosis	HbH disease Hb Barts hydrops fetalis

1. Vichinsky EP. *Cold Spring Harb Perspect Med*. 2013;3:a011742. **2.** Piel FB et al. *N Engl J Med*. 2014;371:1908–1916. **3.** Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13. **4.** Kalle Kwaifa I et al. *Orphanet J Rare Dis*. 2020;15:166. **5.** Galanello R et al. *Genet Med*. 2011;13:83–88. **6.** Lal A et al. *N Engl J Med*. 2011;364:710–718. **7.** Ekwattanakit S et al. *Am J Hematol*. 2018;93:623–629.

Complications of HbH disease are associated with the severity of chronic anemia and increase with advancing age[1,2]

Characteristics and complications	α-thalassemia syndromes
Presenting age (years)	Usually > 2
Presenting Hb level (g/dL)	8–11
HbF (%)	Not raised, but HbH ($ß_4$) and Hb Barts (Y_4) present
HbA2/HbE (%)	< 2
Jaundice	■■■■
Growth retardation	■
Bone and skeletal abnormalities	■■■■
Splenomegaly	■■
Leg ulcers	■
Cholelithiasis	■■
Acute hemolytic episodes	■■■
Thrombotic events	■
Extramedullary hematopoiesis	■
Pulmonary hypertension	■



Number of ■ represent frequency of occurrence:
0-10% ■
10-30% ■■
30-60% ■■■
60-100% ■■■■

1. Viprakasit V et al. *Orphanet J Rare Dis*. 2014;9:131. **2.** Taher AT et al. *Vox Sang*. 2014;108:1–10.

Non-deletional HbH presents as more severe disease than deletional HbH[1,2]

- More severe anemia and jaundice, at a younger age
- Lower height Z-score
- Larger spleen and liver with increased rates of splenectomy
- More likely to require RBC transfusions, at a younger age
- Increased risk of hemolytic crisis
- Some of these differences can be detected at neonatal age
- Increased risk of cholelithiasis

1. Viprakasit V. Alpha-thalassemia syndromes: From Clinical and Molecular Diagnosis to Bedside Management. EHA Library 2013. Available at: https://library.ehaweb.org/eha/2013/18th/31667/vip.viprakasit.alpha-thalassemia.syndromes.from.clinical.and.molecular.html. Accessed 14 June 2022.
2. Viprakasit V et al. *Orphanet J Rare Dis*. 2014;9:131.

Non-deletional HbH presents as more severe disease than deletional HbH (continued)

Clinical manifestation	Deletional HbH	Non-deletional HbH
Hb, g/dL (range)[1]	8.5 (6.9–10.7)	7.2 (3.8–8.7)
Mean corpuscular volume[1], fL (range)	54.0 (46.0–76.0)	65.2 (48.7–80.7)
Mean corpuscular Hb[1], pg (range)	16.6 (14.3–24.7)	18.6 (14.8–24.8)
Anemia[2], %	58	65
Jaundice[2], %	24	27
Hepatomegaly[2], %	6	11
Reticulocytosis[1]	Less common	More common
Hypochromia[1]	More common	Less common
Splenomegaly[2], %	15	24
Gallstones[2], %	10	28
Growth delays[2], %	Rare	15
Decreased BMD[1]	Rare	Common
Liver iron overload[3], %	48	79
Age at first RBC transfusion[1,2], year	11±5.5	1.5±2.1
History of RBC transfusion[2], %	29	50

1. Vichinsky EP. *Cold Spring Harb Perspect Med.* 2013;3:a011742. **2.** Fucharoen S, Viprakasit V. *Hematology Am Soc Hematol Educ Program.* 2009:26–34.
3. Chan LKL et al. *Br J Haematol.* 2021;192:171–178.

Hb Barts hydrops fetalis can result in death *in utero* or shortly after birth without timely intervention

Classification	Laboratory results	Symptoms and complications
Hb Barts hydrops fetalis[1–3] (4 mutated alleles)	Very low Hb, MCV, and MCH High WBC count Increased bilirubin Normal platelet and reticulocyte counts	Very severe anemia and hypoxia Severe hepatosplenomegaly Brain, skeletal, and cardiovascular deformities Placental enlargement Maternal complications include severe anemia in pregnancy, preeclampsia, polyhydramnios, and difficult delivery due to enlarged placenta Typically results in death in utero or shortly after birth without timely intervention Long-term complications in survivors include congenital abnormalities, particularly urogenital and limb abnormalities, and growth/neurodevelopmental impairment[4]

1. Farashi S et al. *Blood Cells Mol Dis*. 2018;70:43–53. **2.** Piel FB et al. *N Engl J Med*. 2014;371:1908–1916. **3.** Kalle Kwaifa I et al. *Orphanet J Rare Dis*. 2020;15:166.
4. Songdej D et al. *Blood*. 2017;129:1251–1259.

Thalassemic anemia may be a component of α-thalassemia X-linked intellectual disability syndrome (ATR-X syndrome)[1]

- Mild α-thalassemia, in addition to craniofacial, genital, and developmental features in up to 75% of affected males
  - HbH RBC inclusions on peripheral blood smear
  - Microcytic hypochromic anemia on CBC
- Diagnosis of ATR-X syndrome
  - Male with suggestive clinical findings
  - Molecular genetic testing shows hemizygous pathogenic variant in ATR-X

Incidence of characteristic features in ATR-X syndrome[2]

Clinical feature	Incidence (%)
Profound mental retardation	95
Characteristic facial anomalies	94
Skeletal abnormalities	91
HbH inclusions	87
Motor deficits (eg, neonatal hypotonia)	85
Genital abnormalities	80
Microcephaly	76
Gut dysmotility	75
Short stature	66
Seizures	35
Cardiac defects	18
Renal and urinary abnormalities	14

1. Stevenson RE. *Gene Reviews.* 2000 [updated 2020]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1449/. Accessed 5 June 2022. 2. Hettiarachchi D et al. *Case Rep Genet.* 2019;2019:2687595.

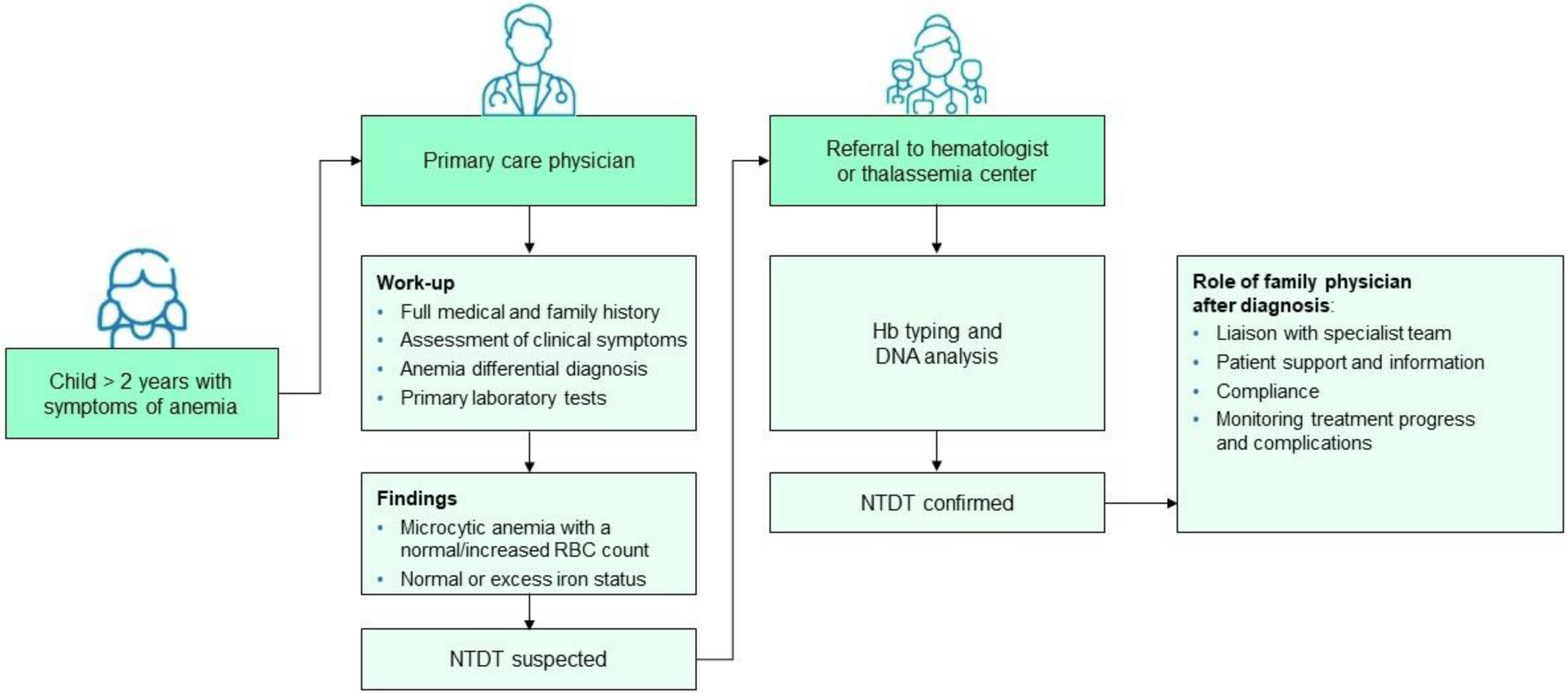
Section 2: Key takeaways

Globin chain imbalance leads to the underproduction of HbA and production of two types of nonfunctional Hb called Hb Barts and HbH
Hemolysis and ineffective erythropoiesis contribute to anemia, hypercoagulability, primary iron overload, and associated acute and long-term complications
Individuals with α-thalassemia minor/trait generally do not have visible symptoms, but their mutations may act as genetic modifiers for other inherited disorders, and their offspring may be at risk for HbH disease or Hb Barts hydrops fetalis
Deletional and non-deletional HbH present as a spectrum of distinct disorders; patients with non-deletional HbH are prone to more severe anemia and associated complications
In Hb Barts hydrops fetalis, severe anemia occurs *in utero* and usually results in death before or shortly after birth without timely intervention

Diagnosis of α-thalassemia

Section 3

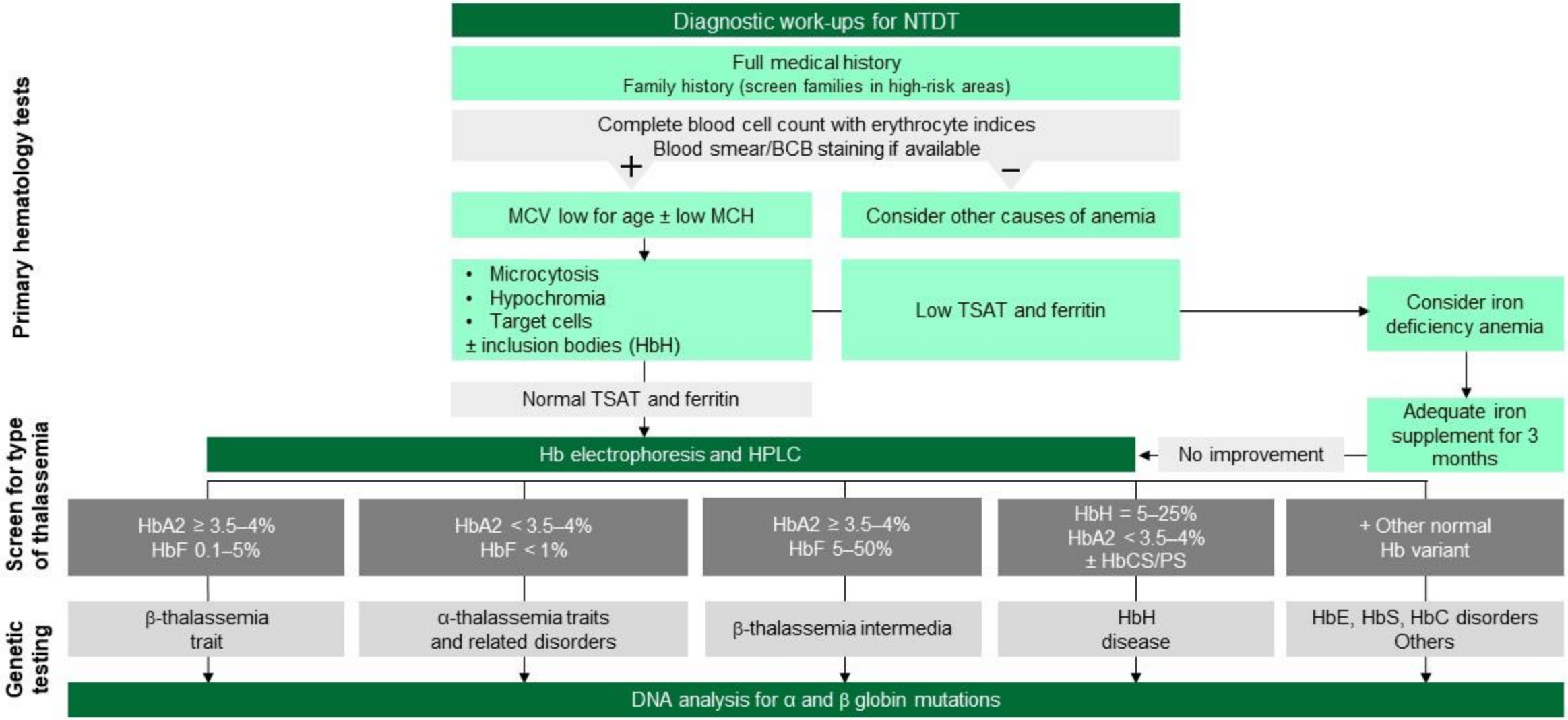
The role of the primary care physician is vital for identifying the α-thalassemia patient[1]



Adapted from Viprakasit V et al. *Orphanet J Rare Dis*. 2014;9:131.

1. Viprakasit V et al. *Orphanet J Rare Dis*. 2014;9:131.

The diagnostic work-up for α-thalassemia uses complete blood cell counts with erythrocyte indices[1]



Adapted from Viprakasit V et al. *Orphanet J Rare Dis*. 2014;9:131.

1. Viprakasit V et al. *Orphanet J Rare Dis*. 2014;9:131.

An array of complementary laboratory tests can be used to diagnose α-thalassemia[1,2]

COMPLETE BLOOD COUNT

- Low MCV for age, low MCH levels, and normal/elevated RBC count
- Test results may be due to iron deficiency anemia, thus confirmatory tests are needed

BLOOD SMEAR

- Check for microcytic anemia, anisocytosis, and poikilocytosis
- Inclusion bodies indicate presence of HbH

HPLC

- Measures Hb level, HbA2, HbF, and other Hb variants
- Limited in detecting HbH and Hb Barts percentage
- Low sensitivity to non-deletional forms of HbH (eg, Constant Spring)
- Can make a presumptive diagnosis of α-thalassemia

CAPILLARY/GEL ELECTROPHORESIS

- Quantifies HbA2, HbE, HbF, HbH, Hb Barts and some Hb variants
- Can make a presumptive diagnosis of α-thalassemia

MOLECULAR GENETIC TESTING

- Required to definitively confirm a diagnosis
- May help predict clinical phenotype (or disease severity)

1. Vijian D et al. *Medeni Med J*. 2021;36:257–269. **2**. Papadakis MA et al. *Current Medical Diagnosis & Treatment*. 58th ed. McGraw Hill-Education; 2019.

Laboratory tests used to diagnose α-thalassemia include CBC and blood smear[1-3]

COMPLETE BLOOD COUNT

- Low MCV for age, low MCH levels, and normal/elevated RBC count
- Test results may be due to iron deficiency anemia, thus confirmatory tests are needed

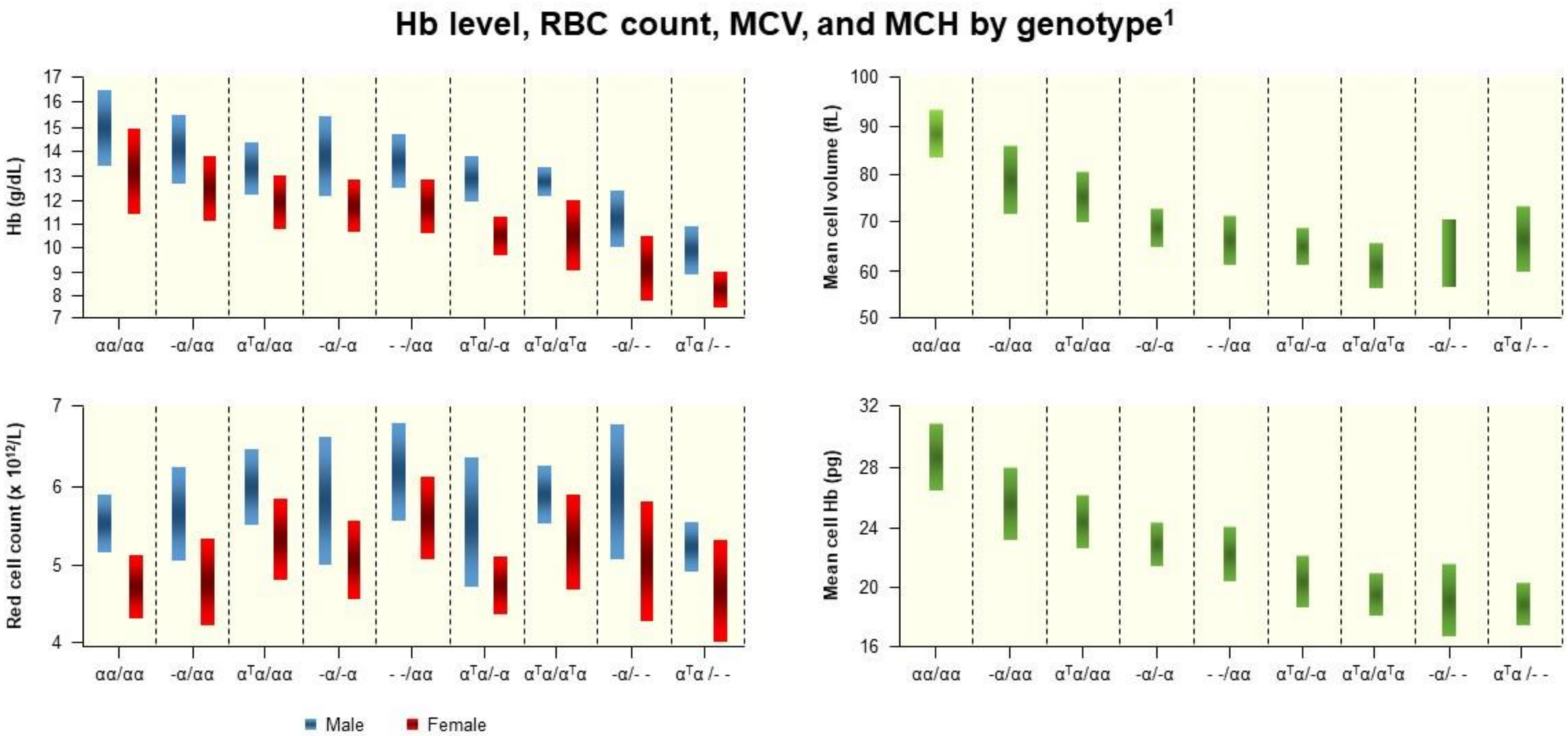
BLOOD SMEAR

- Check for microcytosis, hypochromic anemia, anisocytosis, and poikilocytosis
- Inclusion bodies indicate presence of HbH

- Degree of microcytic, hypochromic anemia is correlated with the number of affected alleles
- α-thalassemia minor/trait is sometimes misdiagnosed as iron deficiency anemia
  - Determining a patient's iron status by measuring their ferritin is recommended for differential diagnosis

1. Vijian D et al. *Medeni Med J*. 2021;36:257–269. **2.** Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13. **3.** Papadakis MA et al. Current Medical Diagnosis & Treatment. 58th ed. McGraw Hill-Education; 2019.

Significant CBC parameters include Hb level, RBC count, MCV, and MCH[1]



Adapted from Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13.

1. Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13.

Laboratory tests used to diagnose α-thalassemia include HPLC and capillary/gel electrophoresis[1,2]

HPLC

- Measures Hb level, HbA2, HbF, and other Hb variants
- Limited in detecting HbH and Hb Barts percentage
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- Can make a presumptive diagnosis of α-thalassemia

CAPILLARY/GEL ELECTROPHORESIS

- Quantifies HbA2, HbE, HbF, HbH, Hb Barts and some Hb variants
- Can make a presumptive diagnosis of α-thalassemia

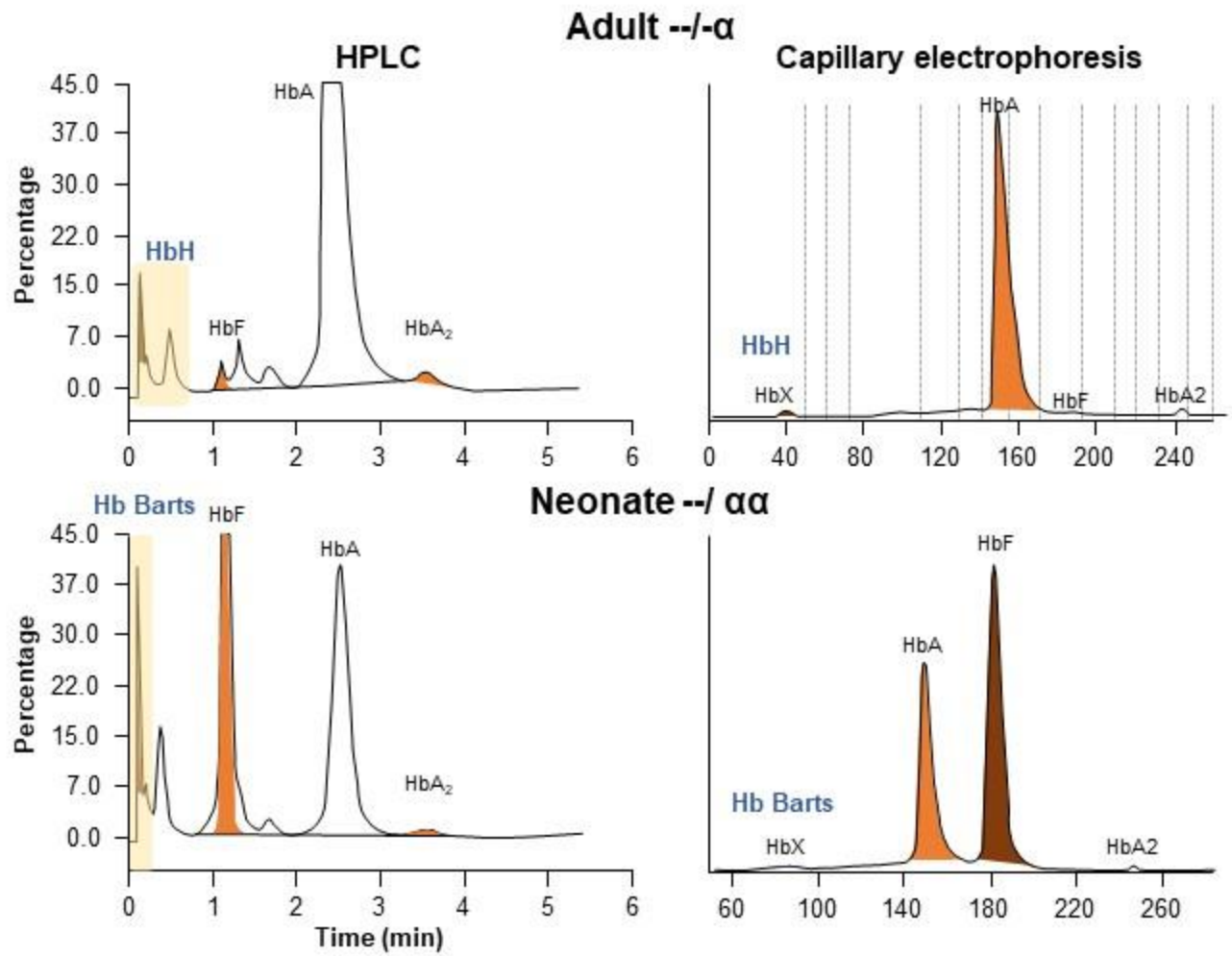


Figure adapted from Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13.

1. Vijian D et al. *Medeni Med J*. 2021;36:257–269. **2.** Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13.

Laboratory tests used to diagnose α-thalassemia include molecular genetic testing[1]

MOLECULAR GENETIC TESTING

- Required to definitively confirm a diagnosis
- May help predict clinical phenotype (or disease severity)

Molecular genetic tests

	Detects deletional mutations	Detects non-deletional mutations
Detects common mutations only	• Gap-PCR • Single-tube multiplex PCR	• Single-tube multiplex PCR
Detects rare/unknown mutations	• MLPA • LAMP • NGS	• Sanger sequencing • NGS • Reverse dot blot

1. Vijian D et al. *Medeni Med J*. 2021;36:257–269.

Prenatal screening and genetic counseling for high-risk couples may prevent or prepare for Hb Barts pregnancy

If both parents carry cis mutations (−−/αα), the fetus has a 25% risk of inheriting four non-functioning gene copies (Hb Barts)

These pregnancies are extremely high risk for both fetus and mother[1]

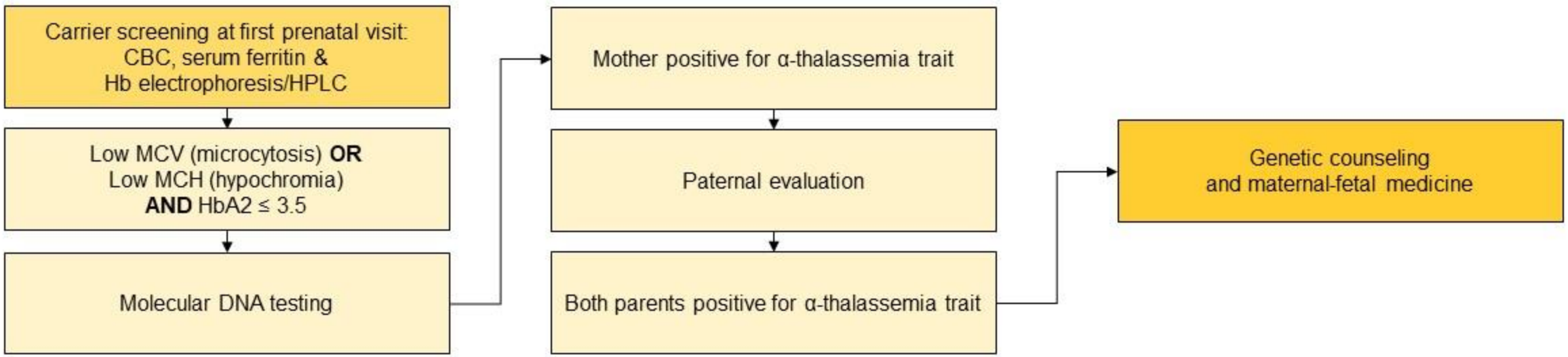
Prenatal screening is recommended for high-risk couples with ancestry from Asia, the Pacific Islands, the Mediterranean, the Middle East, or Africa[2]

- Preliminary screening of parents is performed with a CBC
- Microcytosis (reduced MCV) in parents with normal iron status and absence of iron deficiency should be followed by specific testing for hereditary anemias including α-thalassemia
- Molecular DNA testing is required to confirm the α-globin gene status in both parents

Counseling resources include The National Society of Genetic Counselors and The American Board of Genetic Counseling, Inc.

1. Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13. **2.** UCSF Fetal Treatment Center and UCSF Benioff Children's Hospitals. Available at: https://fetus.ucsf.edu/alpha-thalassemia. Accessed 25 April 2022.

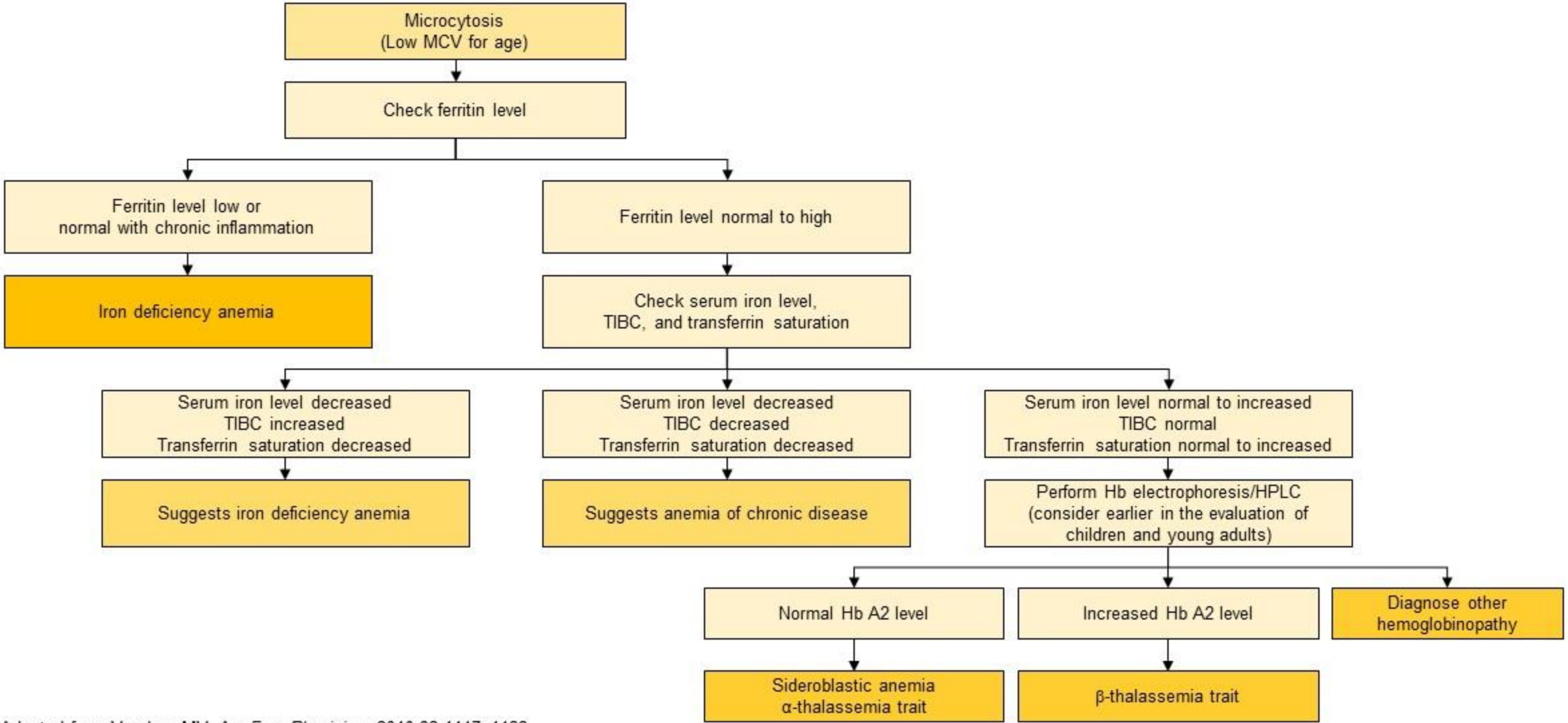
Prenatal screening and genetic counseling should be offered to pregnant women from high-risk geographic ancestry[1]



Adapted from Horvei P et al. *Hematology*. 2021;2021:592–599.

1. UCSF Fetal Treatment Center and UCSF Benioff Children's Hospitals. Available at: https://fetus.ucsf.edu/alpha-thalassemia/. Accessed 25 April 2022.

Microcytosis in the absence of iron deficiency may indicate a Hb disorder[1]



Adapted from Vranken MV. *Am Fam Physician*. 2010;82:1117–1122.

1. Vranken MV. *Am Fam Physician*. 2010;82:1117–1122.

Section 3: Key takeaways

α-thalassemia trait (two allele mutations) is sometimes misdiagnosed as iron deficiency, as the two disorders show similar hematological results
Laboratory tests to presumptively diagnose α-thalassemia include complete blood count, blood smear, HPLC, and capillary/gel electrophoresis
Molecular genetic testing is required to understand the clinical phenotype and definitively confirm a diagnosis of α-thalassemia
To reduce the risk of morbidity and mortality from Hb Barts hydrops fetalis to the mother and child, prenatal screening and genetic counseling when indicated is recommended for high-risk populations

Clinical management of α-thalassemia

Section 4

Clinical management of α-thalassemia silent carrier and trait is usually not indicated

Classification	Number of allele mutations	Therapeutic approach	Considerations and challenges
Silent carrier[1]	1	None	• Risk of affected offspring • Indication for prenatal screening
Trait[1,2]	2	Not generally indicated	• Risk of affected offspring • Indication for prenatal screening • Undiagnosed patients with anemia due to nutritional deficiencies (Vitamin B12, folate, or iron) at risk of excess iron supplementation

1. Farashi S et al. *Blood Cells Mol Dis*. 2018;70:43–53. **2.** Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13.

Clinical management of α-thalassemia HbH disease depends on phenotypic severity

Classification		Number of allele mutations	Therapeutic approach	Considerations and challenges
HbH disease[1–6]	Deletional - - / - α	3	NTDT • Episodic RBC transfusions • Folic acid supplementation • Iron chelation therapy	• Avoidance or precautions with oxidant therapies due to increased risk of hemolytic crisis • Development of primary iron overload in third decade of life[4]
	Non-deletional - - / α^T α	3	NTDT or TDT • Regular or intermittent RBC transfusions • Iron chelation therapy • Possible splenectomy	• Acute hemolytic crisis necessitating urgent transfusion[4] • Early development of iron overload (within first decade of life)[4] • Increased morbidity and mortality due to uncontrolled anemia in patients who do not receive regular transfusions[6] • Increased risk of sepsis and venous thrombosis with splenectomy

1. Fucharoen S, Viprakasit V. *Hematology Am Soc Hematol Educ Program*. 2009;26–34. **2.** Galanello R et al. *Genet Med*. 2011;13:83–88. **3.** Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13. **4.** Lal A et al. *N Engl J Med*. 2011;364:710–718. **5.** Taher A et al. Guidelines for the management of non-transfusion dependent thalassemias. 2017. Available at: https://thalassaemia.org.cy/wp-content/uploads/2017/10/NTDT-final-combined-1.pdf. Accessed 18 April 2022. **6.** Musallam KM et al. *Haematologica*. 2021;106:2489–2492.

In-utero clinical management of Hb Barts hydrops fetalis may improve fetal survival

Classification	Number of allele mutations	Therapeutic approach	Considerations and challenges
Hb Barts hydrops fetalis[1–3]	4	• Genetic counseling for at-risk couples • Intrauterine RBC transfusions • Iron chelation therapy • HSCT may be an option for affected infants	• Need for lifelong transfusions and iron chelation therapy in patients who survive due to intra-uterine RBC transfusions • Severe congenital abnormalities and cognitive/motor delays in surviving infants despite intrauterine transfusion

1. Piel FB et al. *N Engl J Med*. 2014;371:1908–1916. **2.** Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13. **3.** Farashi S et al. *Blood Cells Mol Dis*. 2018;70:43–53.

The clinical management of α-thalassemia correlates with the number and type of allele mutations

Classification		No. of allele mutations	Therapeutic approach	Considerations and challenges
Silent carrier		1	• None	• Risk of affected offspring
Trait[1,2]		2	• No treatment required	• Risk of affected offspring • Risk of overtreatment with iron supplementation
HbH disease[1–6]	Deletional	3	• Supportive with folic acid and vitamin supplementation • NTDT: episodic RBC transfusions	• Oxidative therapies may increase risk of hemolytic crisis • Iron overload can develop in third decade of life[5]
	Non-deletional	3	• Intermittent or regular RBC transfusions • Iron chelation therapy • Splenectomy in rare cases	• Iron overload can develop in first decade of life[5] • In patients who do not receive regular transfusions, uncontrolled anemia can result in increased morbidity and mortality compared with regularly transfused patients[6] • Splenectomy increases risk of sepsis and venous thrombosis
Hb Barts hydrops fetalis[1,2,7]		4	• Genetic counseling • Intrauterine RBC transfusions • Iron chelation therapy • HSCT	• Need for lifelong, regular RBC transfusions • Congenital abnormalities and delays in cognitive and motor functions

SEVERITY

1. Farashi S et al. *Blood Cells Mol Dis*. 2018;70:43–53. **2.** Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13. **3.** Fucharoen S, Viprakasit V. *Hematology Am Soc Hematol Educ Program*. 2009:26–34. **4.** Galanello R et al. *Genet Med*. 2011;13:83–88. **5.** Lal A et al. *N Engl J Med*. 2011;364:710–718. **6.** Musallam KM et al. *Haematologica*. 2021;106:2489–2492. **7.** Piel FB et al. *N Engl J Med*. 2014;371:1908–1916.

The management of α-thalassemia syndromes is usually supportive and symptomatic[1]

Most patients with deletional HbH disease only require

- Folic acid supplementation (2–5 mg/day)
- Multivitamin and vitamin E supplementation
- On-demand transfusions for acute anemia due to hemolytic crisis

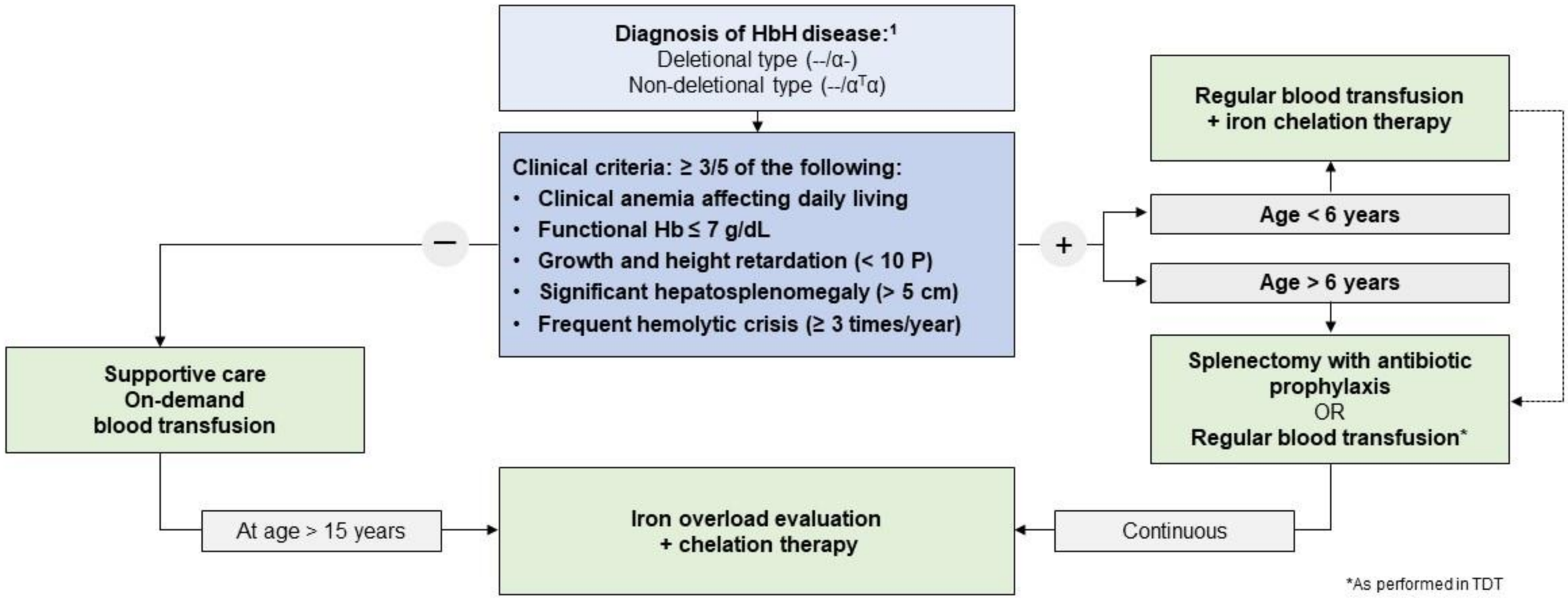
Patients with non-deletional type HbH disease may additionally require:

- Short-term regular transfusions in severe cases
- Lifelong blood transfusions for TDT or hydrops fetalis
- Splenectomy in selective cases

All patients with HbH disease require monitoring and appropriate management for evidence of iron overload

1. Viprakasit V. Alpha-thalassemia syndromes: from clinical and molecular diagnosis to bedside management. 2013. Available at: https://library.ehaweb.org/eha/2013/18th/31667/vip.viprakasit.alpha-thalassemia.syndromes.from.clinical.and.molecular.html. Accessed 3 June 2022.

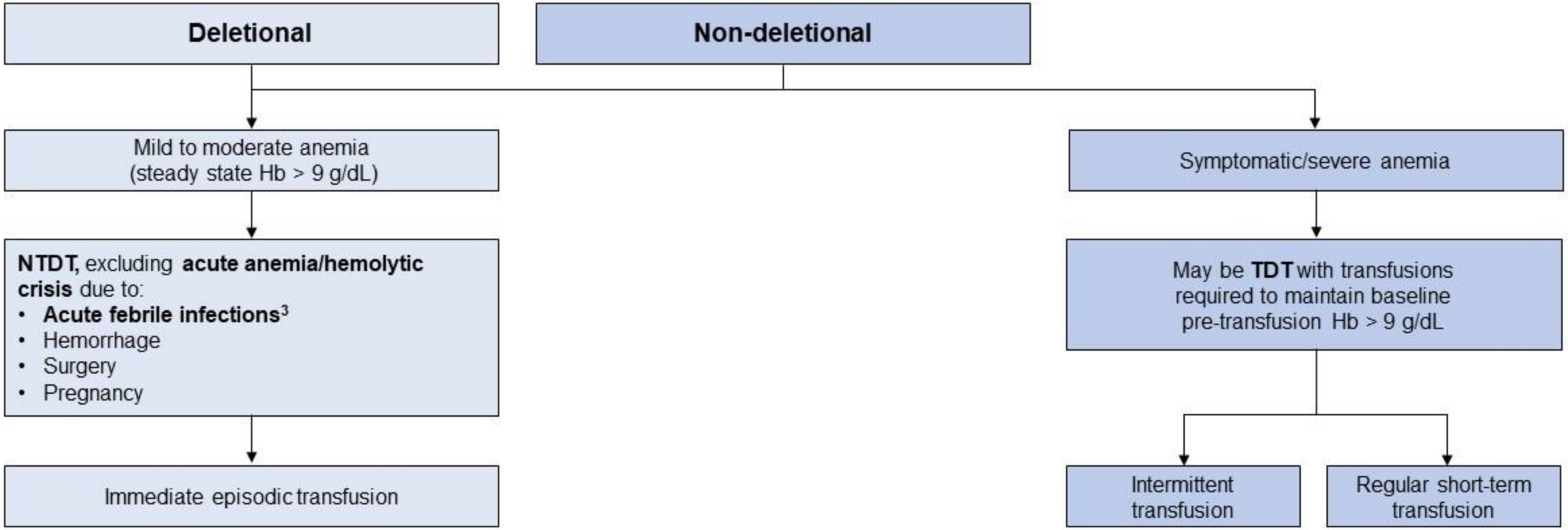
The clinical heterogeneity of HbH disease can affect its management



Adapted from Viprakasit V. Presentation at EHA 2013. Available at: https://library.ehaweb.org/conference/documents/97379/red_cell_disease_2_alpha-thalassemia_syndromes_-_from_clinical_and_molecular_diagnosis_to_bedside_management.pdf. Accessed 3 June 2022.

1. Viprakasit V. Presentation at EHA 2013. Available at: https://library.ehaweb.org/conference/documents/97379/red_cell_disease_2_alpha-thalassemia_syndromes_-_from_clinical_and_molecular_diagnosis_to_bedside_management.pdf. Accessed 3 June 2022.

Transfusion therapy is indicated for severe or symptomatic anemia in HbH disease[1,2]



1. Cappellini MD et al. Guidelines for the Management of Transfusion Dependent Thalassemias. 2021. Available at: https://www.thalassemia.org/boduw/wp-content/uploads/2021/06/TIF-2021-Guidelines-for-Mgmt-of-TDT.pdf. Accessed 21 April 2022.
2. Fucharoen S, Viprakasit V. *Hematology Am Soc Hematol Educ Program*. 2009:26–34. **3**. Taher A et al. Guidelines for the Management of Non-Transfusion Dependent Thalassemias. 2017.Available at: https://thalassaemia.org.cy/wp-content/uploads/2017/10/NTDT-final-combined-1.pdf. Accessed 21 April 2022.

Management guidelines primarily based on data for β-thalassemia

The decision to initiate transfusions balances benefits, risks, and other considerations[1-3]

BENEFITS

- Improvement in anemia, hemolysis, and ineffective erythropoiesis
- Prevention and management of complications and comorbidities

RISKS

- Iron overload
- Alloimmunization
- Adverse transfusion reactions

CONSIDERATIONS

- Close monitoring and individualized tailoring for desired patient outcome
- Hb level not the sole determinant of therapeutic initiation
- Careful assessment of newly diagnosed children to determine transfusion requirements

1. Cappellini MD et al. Guidelines for the Management of Transfusion Dependent Thalassemias. 2021. Available at: https://issuu.com/internationalthalassaemiafederation/docs/final_guideline_4th. Accessed 21 April 2022. **2.** Fucharoen S, Viprakasit V. *Hematology Am Soc Hematol Educ Program*. 2009:26–34. 3. . Taher A et al. Guidelines for the Management of Non-Transfusion Dependent Thalassemias. 2017.Available at: https://thalassaemia.org.cy/wp-content/uploads/2017/10/NTDT-final-combined-1.pdf. Accessed 18 April 2022.

Iron chelation is the treatment of choice for iron overload in HbH disease

NTDT[1,2]

All patients ≥ 15 years of age should be assessed for iron overload with measurement of LIC by MRI

- Although SF is a less reliable indicator, the rate of increase in SF level can be used if LIC measurement is unavailable
- Correlation with degree of ineffective erythropoiesis (eg, reticulocyte count or severity of bone disease) may be useful

Initiate iron chelation when:

- LIC ≥ 5 mg Fe/g dry weight
- SF ≥ 800 ng/mL

Reassess with MRI LIC in 1 year

TDT[3]

- All patients receiving regular transfusions should be assessed for iron overload with measurement of LIC by MRI after 10–12 transfusions
- Cardiac T2* MRI should be performed for all patients by 10 years of age

Initiate iron chelation after 12–15 transfusions:

- MRI LIC should be obtained when starting iron chelation
- Reassess with MRI LIC annually if possible or at least every 2 years

1. Taher A et al. Guidelines for the Management of Non-Transfusion Dependent Thalassemias. 2017.Available at: https://thalassaemia.org.cy/wp-content/uploads/2017/10/NTDT-final-combined-1.pdf. Accessed 18 April 2022. **2**. Taher A et al. *N Engl J Med.* 2021;384:727–743. **3**. Cappellini MD et al. Guidelines for the Management of Transfusion Dependent Thalassemias. 2021. Available at: https://www.thalassemia.org/boduw/wp-content/uploads/2021/06/TIF-2021-Guidelines-for-Mgmt-of-TDT.pdf. Accessed 21 April 2022.

Management guidelines primarily based on data for β-thalassemia

Splenectomy can lower transfusion burden in select symptomatic patients with HbH disease[1,2]

INDICATIONS[3]

Severe non-deletional HbH disease (baseline Hb < 7 g/dL) with:

- Significant hepatosplenomegaly
- Possible hypersplenism
- Abdominal discomfort
- Growth retardation
- Frequent transfusions (10–12/year)

RISKS

- Post-splenectomy infection and sepsis
- Post-splenectomy thrombosis

CONSIDERATIONS

- Avoid in children < 6 years of age (risk of fulminant sepsis)
- Prior evaluation for gallstones/cholecystectomy
- Antibiotic prophylaxis
- Pneumococcal and meningococcal vaccination
- Aspirin therapy for thrombocytosis (platelet count > 1,000,000/mm^3)

1. Taher A et al. Guidelines for the management of non-transfusion dependent thalassemias. 2017. Available at: https://thalassaemia.org.cy/wp-content/uploads/2017/10/NTDT-final-combined-1.pdf. Accessed 18 April 2022. **2.** Cappellini MD et al. Guidelines for the management of transfusion dependent thalassemias. 2021. Available at: https://www.thalassemia.org/boduw/wp-content/uploads/2021/06/TIF-2021-Guidelines-for-Mgmt-of-TDT.pdf. Accessed 21 April 2022. **3.** Fucharoen S, Viprakasit V. *Hematology Am Soc Hematol Educ Program*. 2009:26–34.

The clinical management of Hb Barts hydrops fetalis with intrauterine transfusion has improved fetal survival

Hb Barts hydrops fetalis[1–3]

- Management with intrauterine transfusion and transcranial doppler monitoring
- At least 60 surviving cases identified worldwide
- Survivors require regular lifelong transfusions and iron chelation therapy
- Splenectomy is reserved for selective cases of symptomatic hypersplenism[2]
- > 15 patients have been successfully cured by hematopoietic stem cell transplantation
- Other possible complications, include neurodevelopmental, limb, and genitourinary anomalies in survivors
- An international registry of survivors is now ongoing

1. Viprakasit V. Presentation at EHA 2013. Available at: https://library.ehaweb.org/eha/2013/18th/31667/vip.viprakasit.alpha-thalassemia.syndromes.from.clinical.and.molecular.html. Accessed 22 July 2022.**2.** Viprakasit V. Paper presented at EHA 2013. **3.** Kreger EM et al. *Prenat Diagn*. 2016;36:1242–1249.

Hematopoietic stem cell transplantation may be a cure for Hb Barts hydrops fetalis

Allogeneic HSCT is the only curative treatment available for α-thalassemia[1]

Pre-transplant[2]

Workup:
- Pre-HSCT evaluation
- Liver iron load (MRI)
- Cardiac iron load (cardiac MRI)

HSCT[2]

HLA-matched sibling donors

- Include preparatory conditioning regimens, such as busulfan (marrow ablation) and cyclophosphamide (immunosuppression), plus the potential addition of thiotepa in Pesaro class 3 patients
- Thalassemia-free survival rate of > 80%

HLA-matched unrelated donors

- Select donor using high-resolution molecular typing of HLA I and II
- Conditioning regimens including busulfan/cyclophosphamide, busulfan/fludarabine and/or thiotepa
- In phenotypically matched related donors, ~ 6% mortality risk

Follow-up[2]

- Monitoring of hematological and engraftment parameters, infectious complications, and GvHD
- Monitoring for evaluation of complications related to thalassemia
- Phlebotomy

1. Horvei P et al. *Hematology*. 2021;2021:592–599. **2.** Cappellini MD et al. Guidelines for the management of transfusion dependent thalassemias. 2021. Available at: https://www.thalassemia.org/boduw/wp-content/uploads/2021/06/TIF-2021-Guidelines-for-Mgmt-of-TDT.pdf. Accessed 21 April 2022.

Prevention and management of common complications requires routine evaluation and monitoring[1]

Complications	Assessment	Management
Cardiac dysfunction/arrhythmia	Electrocardiogram (routine), electrocardiography (routine)	As per standard of care
Pulmonary hypertension	Tricuspid regurgitant jet velocity (routine), right-heart catheterization (routine)	As per standard of care, sildenafil citrate, bosentan
Cerebrovascular events	MRI and MRA (high risk)	As per standard of care, antiplatelet prophylaxis
Venous thrombosis	Standard imaging	Anticoagulation, medical/surgical prophylaxis
Leg ulcers	Routine physical examination	Topical measures, pentoxifylline, hydroxycarbamide, hyperoxygenation
Viral hepatitis	Viral serology (routine in transfused patients), viral PCR if positive	Hepatitis B vaccination, antiviral therapy
Hepatic fibrosis, cirrhosis, and cancer	Liver function testing (routine) Ultrasound, α-fetoprotein (high-risk) Transient elastography (investigational)	As per standard of care
Endocrine disease	Growth retardation, sexual development, endocrine function tests, bone mineral density (routine)	As per standard of care
Bone disease	Bone mineral density (routine)	As per standard of care, bisphosphonates
Pregnancy	As per high-risk pregnancy	Revisit iron chelation, anticoagulation prophylaxis, maintenance of hemoglobin concentration and heart function
Extramedullary hematopoietic pseudotumors	Physical examination and imaging to rule out compression (suggestive signs and symptoms)	Hypertransfusion, radiation, surgery
Hemolytic crisis	Infection screening, electrolytes	Adequate hydration, correction of electrolytes, control body temperature, antibiotics or antivirals

1. Taher AT et al. *Lancet*. 2018;391:155–167.

Management guidelines primarily based on data for β-thalassemia

Section 4: Key takeaways

Individuals with α-thalassemia trait generally do not require treatment, but iron supplementation needs to be carefully managed if they present with anemia
Patients with HbH disease will mostly be non–transfusion-dependent, though some patients with non-deletional HbH may become transfusion-dependent; splenectomy may be an option for some NTDT patients in rare cases
Patients with Hb Barts hydrops fetalis who survive will be transfusion-dependent for life
Both patients with NTDT and patients with TDT are at risk for iron overload and will likely require close monitoring
Routine evaluation and monitoring for anemia, liver disease, pulmonary hypertension, leg ulcers, and growth delays and endocrinopathies may be indicated

α-thalassemia: Overall key takeaways

Section 5

Overall key takeaways of α-thalassemia pathophysiology, clinical presentation, and management

Characteristics	α-thalassemia[1,2]
Definition	Reduced or absent synthesis of the α-globin chains
Cause	Mutations/deletions in the α-globin genes on chromosome 16
Pathophysiology	Accumulation of beta and gamma globin chains. Globin chain imbalance leads to ineffective erythropoiesis and hemolysis, resulting in chronic anemia, iron overload, and associated short- and long-term complications
Classification	Silent carrier (1 mutated/deleted allele), trait (2 mutated/deleted alleles), HbH disease (3 mutated/deleted alleles), Hb Barts hydrops fetalis (4 mutated/deleted alleles)
Symptoms and complications	**Silent carrier/trait:** none or mild microcytic anemia, no long-term complications, offspring may be at risk for HbH or Hb Barts, based on partner genotype
	HbH disease (both parents are carriers): chronic moderate anemia; acute-on-chronic anemic events in response to infections; leg ulcers, jaundice, gallbladder disease, iron overload, growth delays/endocrinopathies, decreased BMD, thrombosis
	Hb Barts hydrops fetalis: Severe anemia; usually results in death *in utero* or shortly after birth without timely intervention. If fetus is able to receive intrauterine transfusions and survives, becomes transfusion dependent postnatally. Complications related to disease and underlying ineffective erythropoiesis, and transfusional iron overload
Diagnosis	CBC, blood smear, HPLC, capillary/gel electrophoresis; genetic testing required for definitive diagnosis
Conventional treatment	RBC transfusions (HbH patients are usually NTDT; Hb Barts patients are TDT), iron chelation, splenectomy in rare cases, genetic counseling, HSCT for some patients with Hb Barts hydrops fetalis

1. Piel FB et al. *N Engl J Med*. 2014;371:1908–1916. **2.** Harteveld CL et al. *Orphanet J Rare Dis*. 2010;5:13.

Additional resources

- Thalassaemia International Federation: The Thalassaemia International Federation (TIF) is a non-profit, non-governmental organization founded in 1986 by a small group of patients and parents representing mainly national thalassemia associations in Cyprus, Greece, UK, USA and Italy
- Cooley's Anemia Foundation: For more than 60 years, the Cooley's Anemia Foundation, a non-profit organization, has been a strong and supportive partner for families living with thalassemia

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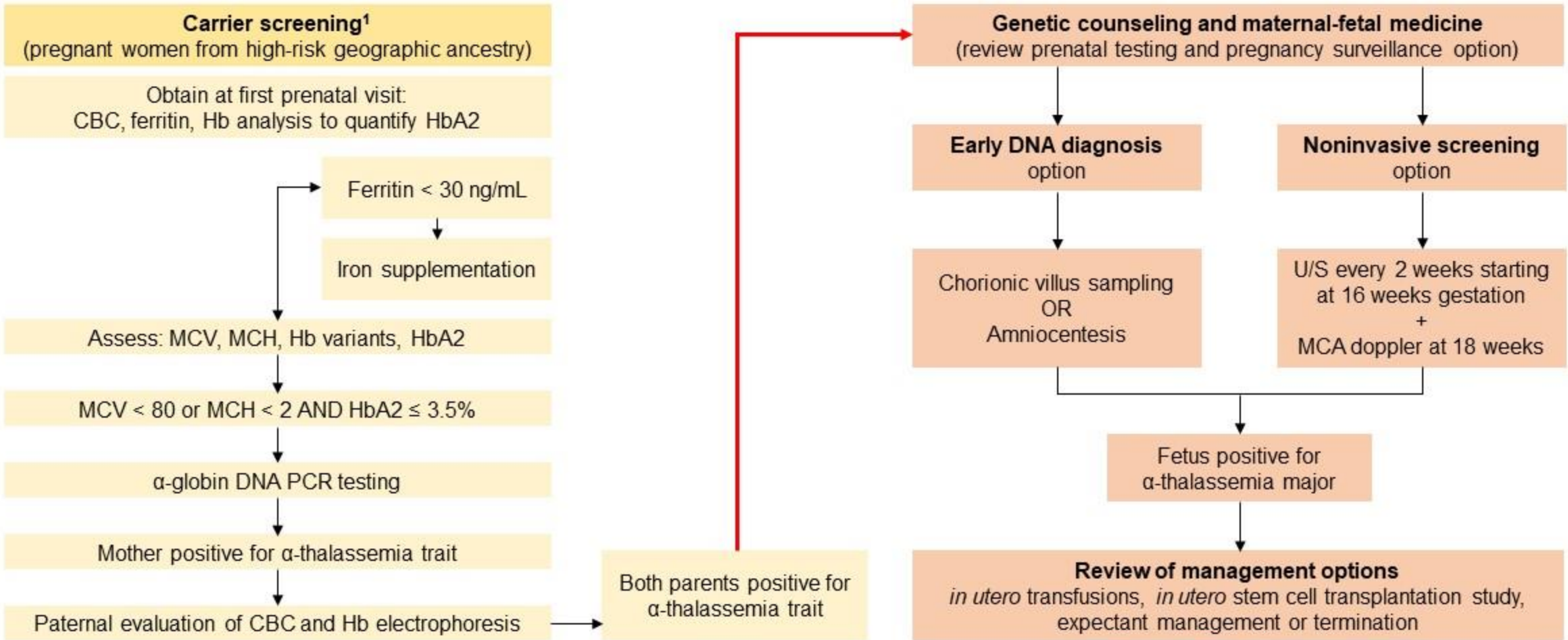
Appendix

Genetic counseling and prenatal screening



Adapted from Horvei P et al. *Hematology*. 2021;2021:592–599.

1. UCSF Fetal Treatment Center and UCSF Benioff Children's Hospitals. Available at: https://fetus.ucsf.edu/alpha-thalassemia/. Accessed 25 April 2022.

Case study: What is the most likely diagnosis in this patient?

A 10-year-old, previously healthy Vietnamese girl presents to clinic for body aches and marked fatigue that started 4 days ago. Her mother also notes that her skin has appeared yellowish for the past few days

Past medical and family history are otherwise unremarkable

The child appears short for her age, with apparent dysmorphic facial features, including maxillary hypertrophy and prominent malar eminences bilaterally

Mild jaundice and splenomegaly are also noted on physical examination

What key lab findings implicate a thalassemic disorder?[1-5]

Laboratory parameters	Patient results	Reference range
WBC	7.9	3.3–9.3 × 10^3/µL
RBC	6.52	4.21–5.61 × 10^3/µL
Hemoglobin	6.5	12.3–16.3 g/dL
Hematocrit	20.5	37.4–47.0%
MCV	60.5	79.0–95.0 fL
MCH	19.0	26.0–32.6 pg
MCHC	25.5	31.7–35.5 g/dL
RDW	21.2	10.7–15.5%
Nucleated RBCs	1.2	0.0%
Reticulocyte count	3.75	0.60–2.06%
Platelet count	170	143-398 × 10^3/µL
Neutrophil	52	40–60%
Bands	2	0–5%
Lymphocyte	25	20-40%
Monocyte	5	4–8%
Bilirubin, total	2.4	0.2–1.1 mg/dL
Ferritin	100	10–210 ng/mL
Haptoglobin	10	41-165 mg/dL
LDH	420	110-295 U/L

Red text signifies abnormal values.

1. Brit SS et al. *Lab Med.* 2010;41:78–82. **2**. Viprakasit V. Presentation at EHA 2013. Available at: https://library.ehaweb.org/eha/2013/18th/31667/vip.viprakasit.alpha-thalassemia.syndromes.from.clinical.and.molecular.html. Accessed 25 July 2022. **3**. Healthline. https://www.healthline.com/health/lactate-dehydrogenase-test#results. Accessed 30 November 2022. **4**. ATSU.edu. https://www.atsu.edu/faculty/chamberlain/Website/Sparks/Laborato/cbcsp.htm. Accessed 30 November 2022. 5. Mount Sinai.org. https://www.mountsinai.org/health-library/tests/haptoglobin-blood-test. Accessed 1 December 2022.

How can we confirm a diagnosis of HbH disease?

The CBC showed a hypochromic, microcytic anemia in the absence of iron deficiency, indicative of thalassemias

A peripheral blood smear demonstrated target cells and RBC inclusion bodies found in HbH disease

Hb analysis with electrophoresis and capillary electrophoresis was utilized to confirm the diagnosis of HbH disease in this patient

Fractions	%
HbH	12.0
Hb Bart's	2.0
Denatured HbA	1.1
HbA	82.4
HbF	1.5
HbA2	1.0

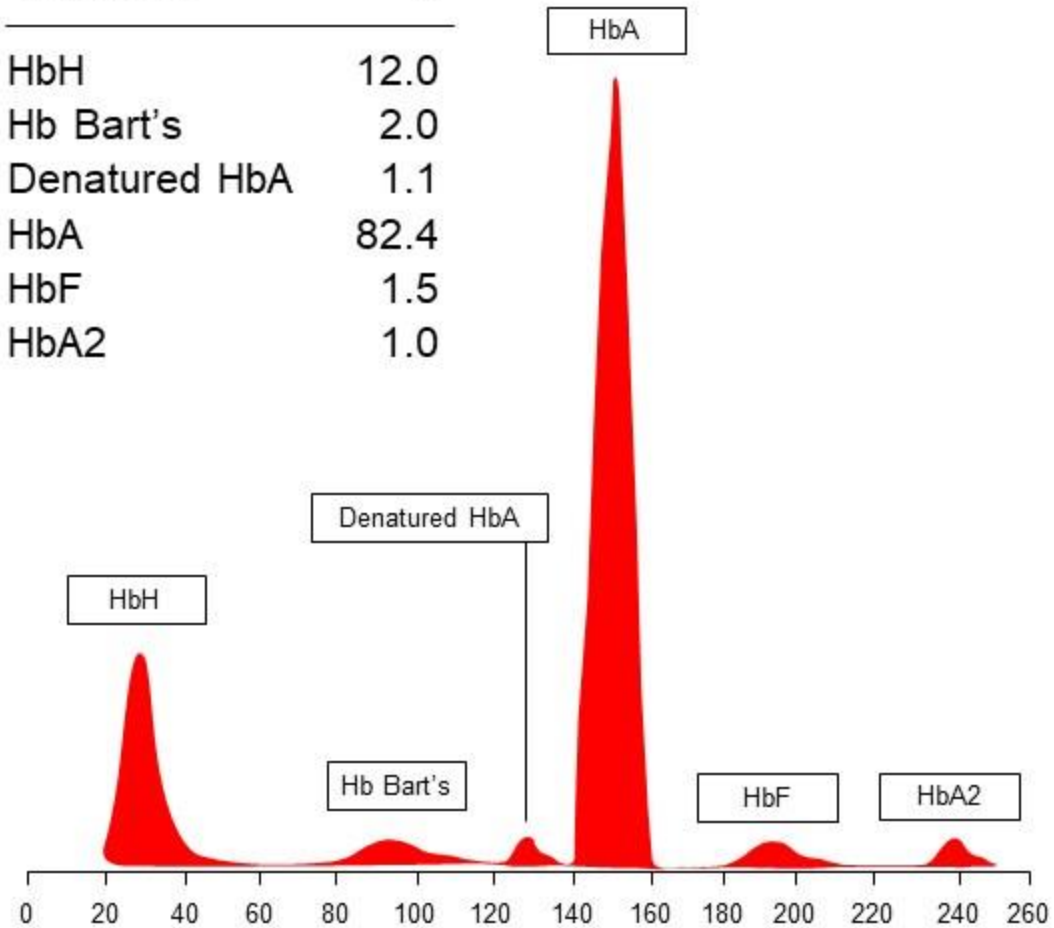


Figure adapted from Songdej D, Fucharoen S. *Thalass Rep.* 2022,12:157–172.

FAQs

What is the pathophysiology of α-thalassemia?

When should a patient be directed for prenatal screening or genetic counseling

What history, examination, and laboratory findings are typical of patients with α-thalassemia?

What are the management options for α-thalassemia?

When should α-thalassemia be suspected in an otherwise healthy patient?

How can care coordination be enhanced amongst the interprofessional team to improve delivery of care?