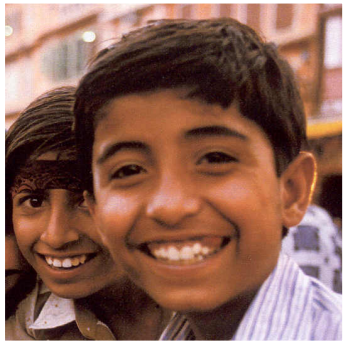
Le Anemie Congenite del Migrante

Le Emoglobinopatie

Maria Domenica Cappellini
Fondazione Ca Granda Policlinico
Università di Milano

Ravenna 25 marzo 2017



Emoglobinopatie

- Sindromi Talassemiche:
  - TDT
  - NTDT
- Varianti Emoglobiniche

Spectrum of clinical disorders due to structural Hb variants

- **Hemolytic anemia**
  sickling disorders, HbC
  Unstable variants
- **Abnormal oxygen transport**
  high affinity variants
  low affinity variants
- **Thalassemia phenotypes**
  HbE, Hb Knossos, Hb Indianapolis

Emoglobinopatie

- Sindromi Talassemiche:
  - TDT
  - NTDT
- Varianti Emoglobiniche: HbE

Worldwide Status of Hemoglobin disorders

- 270 million carriers of Hb disorders
- 300000 affected births per year total
- 60-70000 births of Thalassaemics: most of these die in early life, often with no diagnosis and no or inadequate treatment
- About 200000 new cases of SCD per year.

Agastiniotis M. WHO Report 2010

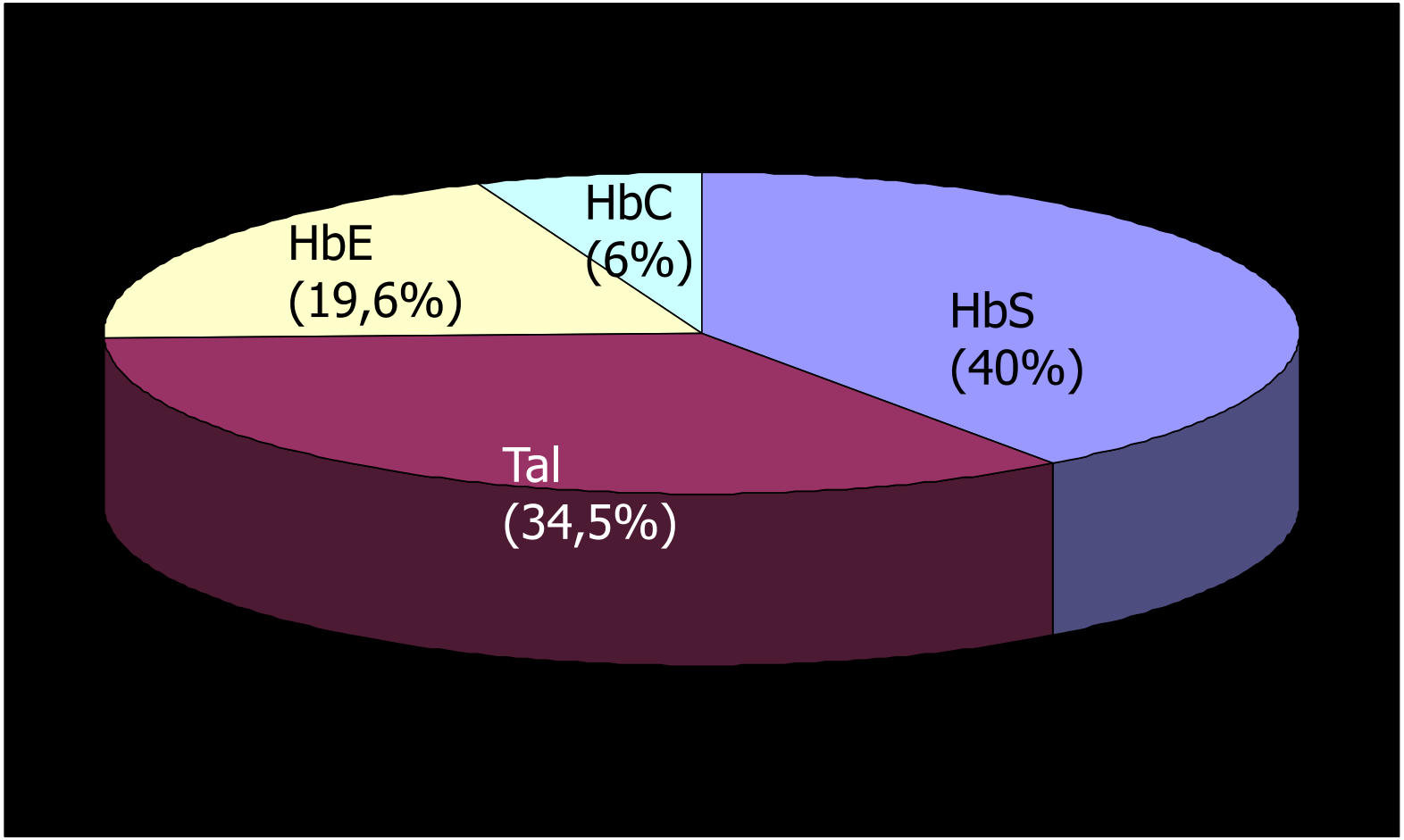
GLOBAL REGIONS

- The northern Mediterranean-carriers 1-19%
- The Arab world- carriers around 3%
- Central Asia- carriers 4-10%
- The Indian Subcontinent- carriers 1-40%
- S.E.Asia and China- carriers 1-30%
- The Americas- old immigrants
- N.Europe, Australia, S.Africa- recent migration
- Sub-Saharan Africa- SCD

Agastiniotis M. WHO Report 2010

EPIDEMIOLOGIA

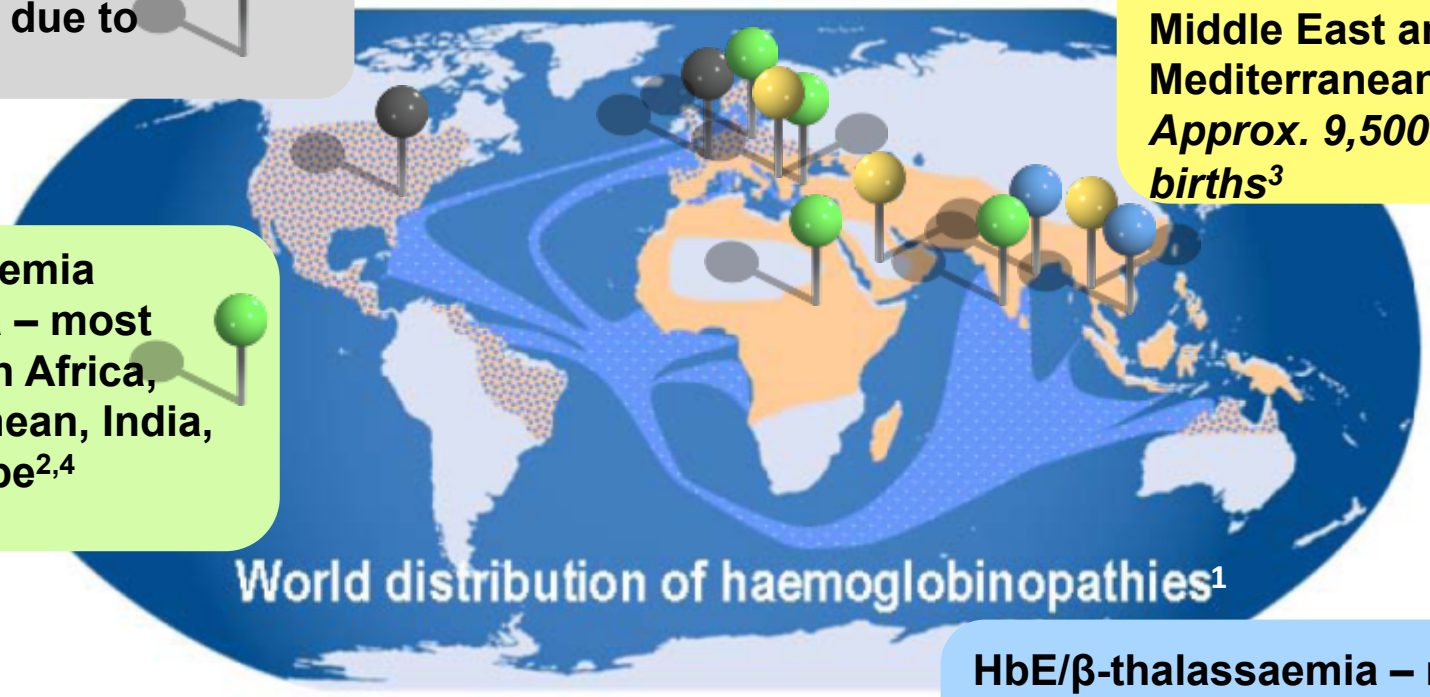
Il 4,83 % della popolazione mondiale è portatore di varianti emoglobiniche



Prevalence of thalassaemia world-wide

Prevalence in Europe and North America increasing due to migration[1]

HbH – most common in Southeast Asia, Middle East and Mediterranean[1]
Approx. 9,500 annual births[3]



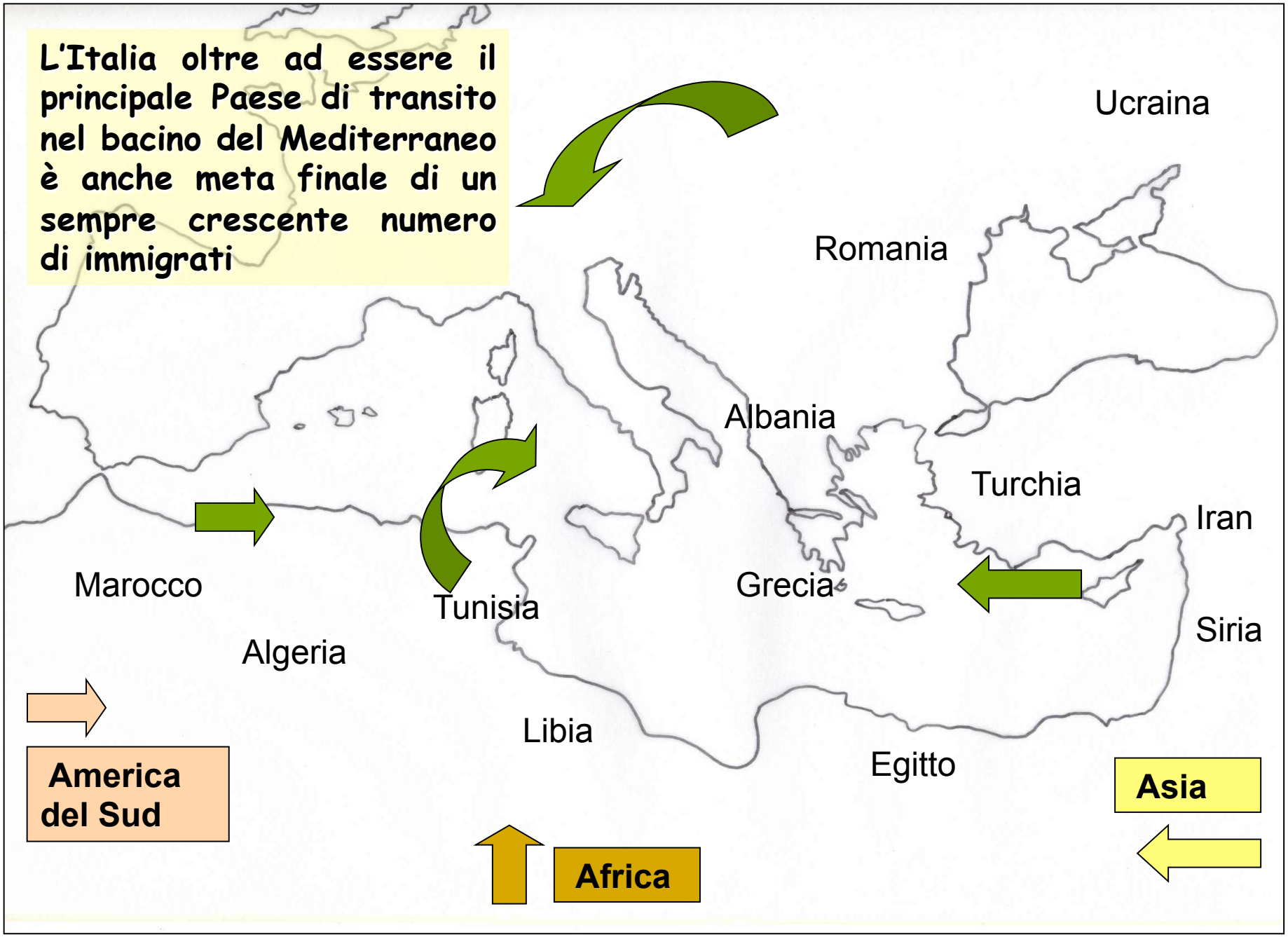
β-thalassaemia intermedia – most common in Africa, Mediterranean, India, East Europe[2,4]

HbE/β-thalassaemia – most common in East India, Bangladesh and SE Asia[2]
Approx. 19,000 annual births[3]

[1]Harteveld C & Higgs D. *Orphanet Journal of Rare Diseases* 2010;5:13; [2]Weatherall DJ. *Blood Rev* 2012;26S:S3–S6; [3]Weatherall DJ. *Blood* 2010;115:4331–4336; [4]http://emedicine.medscape.com/article/959122-overview#a0156.

OLD MIGRATIONS

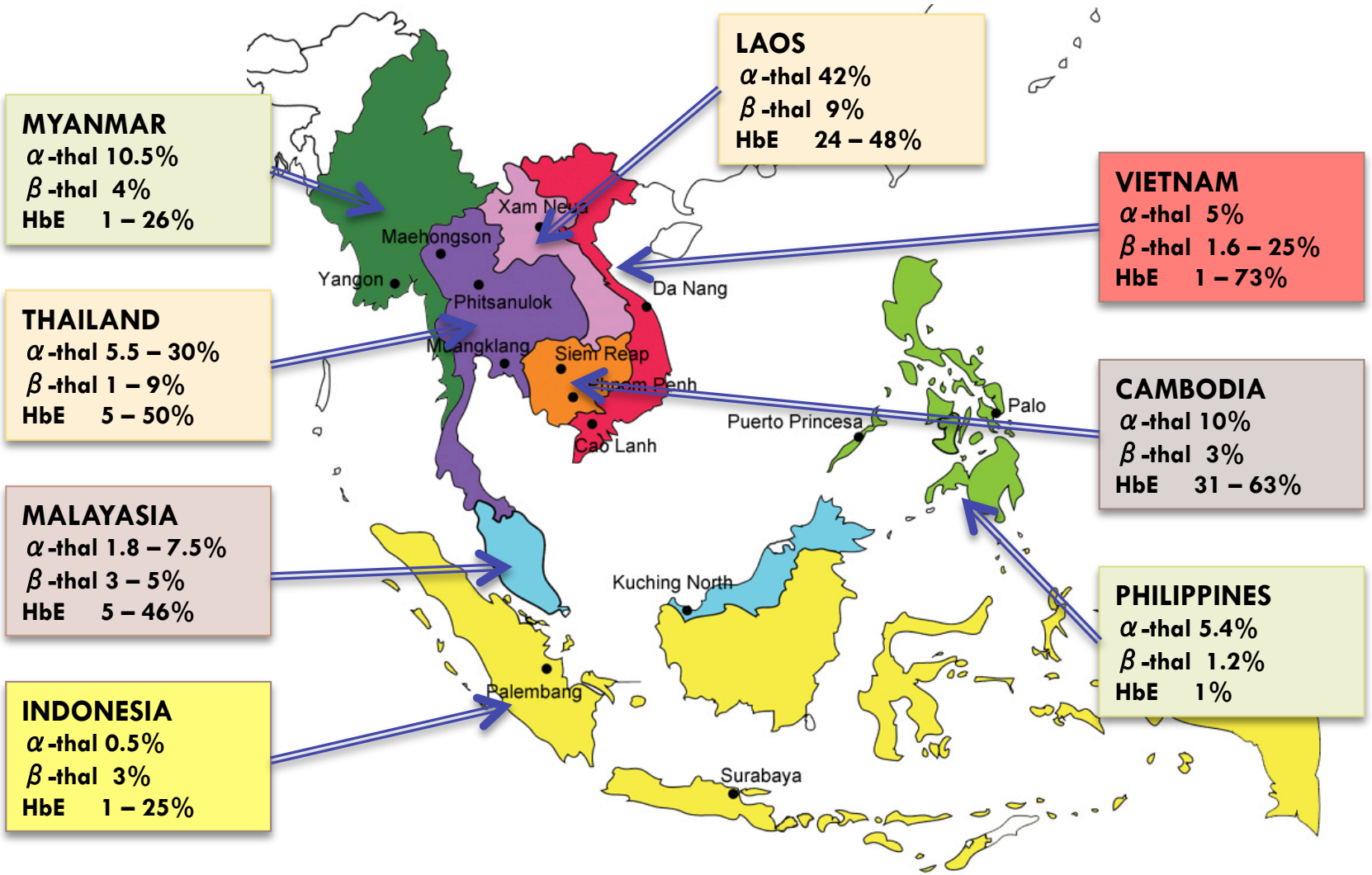
NEW MIGRATIONS


L'Italia oltre ad essere il principale Paese di transito nel bacino del Mediterraneo è anche meta finale di un sempre crescente numero di immigrati
Ucraina
Romania
Albania
Turchia
Iran
Marocco
Tunisia
Grecia
Siria
Algeria
Libia
Egitto
America del Sud
Africa
Asia

PROVENIENZE e PERCENTUALI PER MACRO-AREE

Nord-Ovest	31.4%
Nord-Est	24.5%
Centro	28.0%
Sud	10.5%
Isole	3.7%

Prevalence of thalassaemia and hemoglobinopathy in South East Asian countries



Viprakasit V et al. *Int J Hematol* 2009; 90(4):435-45.

Epidemiology of thalassaemia syndromes in Thailand

Diseases	Pregnancy at risk	New cases	Surviving cases
β-TM	2,500	625	6,250
Hb Bart's hydrops	5,000	1,250	0
β-Thal/HbE	13,000	3,250	97,500
HbH disease	28,000	7,000	420,000
Total	48,500	12,125	523,750

- At least **800,000 patients** are thalassaemia patients in Thailand
- At least **20 million HbE traits** worldwide and nearly **1 million** are at risk of HbE/b-thalassaemia

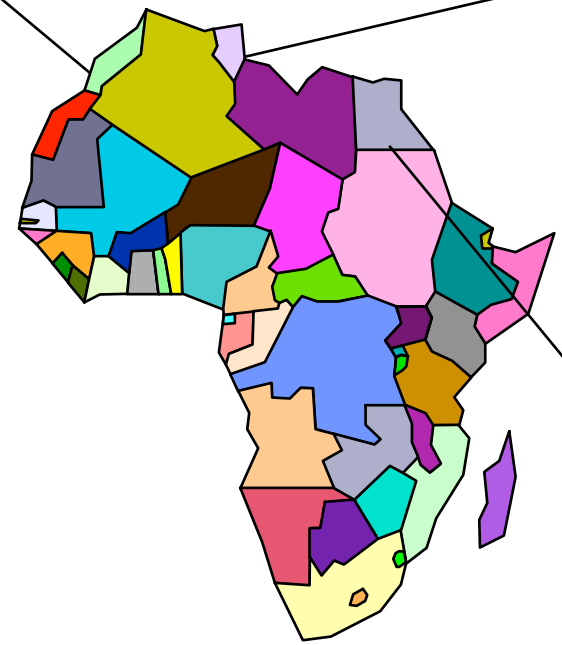
Thal, thalassaemia.

Source: Thalassaemia Foundation of Thailand 1998.

Prevalenza delle principali emoglobinopatie in Egitto, Marocco e Tunisia

MAROCCO
Pop: 26 milioni

Carriers	**7%**
HbS	**2%**
HbE/HbC	**2%**
β tal	**3%**
α tal	**0**



TUNISIA
Pop: 8 milioni

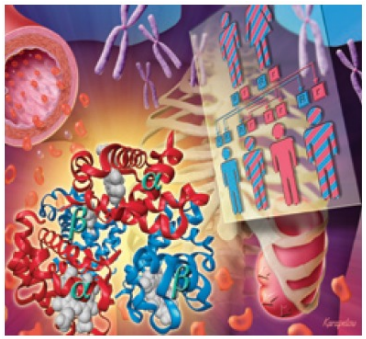
Carriers	**6%**
HbS	**2%**
HbE/HbC	**1%**
β tal	**3%**
α tal	**0**

EGITTO
Pop: 55 milioni

Carriers	**3%**
HbS	**0**
HbE/HbC	**0**
β tal	**3%**
α tal	**0**

Thalassemias are a group of inherited hemoglobinopathies

Absence or reduced synthesis of α chains of Hb



Absence or reduced synthesis of β chains of Hb

α thalassemias[1]

- α thalassemia silent carrier (single α gene deletion)
- α thalassemia trait – minor (double *α* gene deletion)
- Hb constant spring (reduced output of α globin)
- Hb H disease (triple *α* gene deletion)
- Hb Barts Hydrops (absence of *α* genes)

β thalassemias[2]

- β thalassemia minor (silent or carrier)
- β thalassemia intermedia
- β thalassemia minor
- β thalassemia with Hb anomalies
  - Hb C/β thalassemia
  - Hb E/β thalassemia
  - Hb S/β thalassemia
- Hereditary Hb F and β thalassemia
- β-thalassemia associated with
  - Trichothiodystrophy
  - X-linked thrombocytopenia

1. Muncie HL and Campbell JS. *Am Fam Physician* 2009;80:339–344;
2. Galanello R and Origa R. *Orphanet J Rare Dis* 2010;5:11.

Thalassemia phenotype is influenced by multiple genetic factors

	Variant	Genotype	Phenotype
α-thalassemia[1,2]	Normal	αα/αα	Normal
	Silent carrier	-α/αα	Insignificant hematologic findings
	Minor	-α/-α , --/αα	Borderline anemia, as well as microcytic and hypochromic red blood cells
	HbH disease	--/,-α , --/$\alpha^{cs}\alpha$	Moderate anemia and marked microcytosis and hypochromia
	Barts Hydrops Fetalis	--/--	Most develop hydrops fetalis syndrome and die *in utero* during pregnancy, or shortly after birth
β-thalassemia[1,3,4]	Normal	β/β	Normal
	Minor	β/β^{+}, β/β^{0}	Borderline anemia
	β-thalassemia intermedia	β^{0}/β^{+}	Severity is very variable. Clinical picture ranges between thalassemia minor to thalassemia major
	Major	$\beta^{0}\beta^{0}$, β^{+}/β^{+}	Severe anemia requiring regular transfusions
HbE thalassemia[5,6]	HbE trait	β^{E}/β	Asymptomatic condition with no clinical relevance
	Homo. HbE	β^{E}/β^{E}	Usually completely asymptomatic with no anemia and hemolysis
	HbE/β-thalassemia	β^{E}/β^{+}, β^{E}/β^{0}	Severity is very variable. Clinical picture ranges from thalassemia minor to thalassemia major
	HbS/β-thalassemia	β^{E}/β^{S}	Similar to sickle cell disease usually with rare vaso-occlusive crisis

[1]Muncie HL & Campbell JS. *Am Fam Physician* 2009;80:339–344; [2]Harteveld & Higgs*Orphanet Journal of Rare Diseases* 2010;5:13; [3]Galanello & Origa. *Orphanet Journal of Rare Diseases* 2010;5:11[4]Thein SL. *Hematology Am Soc Hematol Educ Program* 2005;31–37; [5]Vichinsky E *Hematology Am Soc Hematol Educ Program* 2007;79–83; [6]Gurkan E. *Am J Hematol* 2006;81:149–156.

Problemi

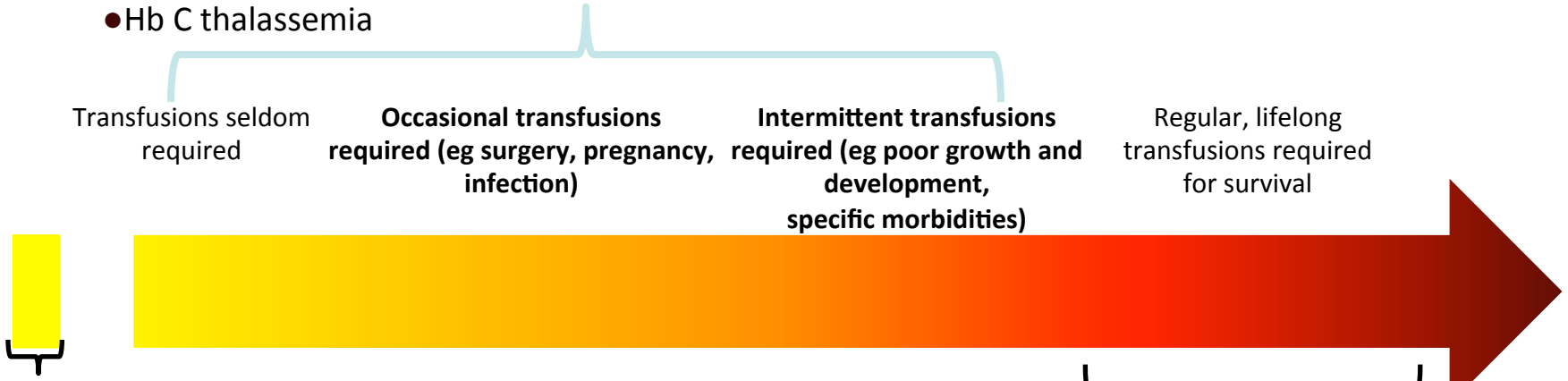
- Diagnosi
- Terapia
- Consulenza genetica

Thalassemia has a broad clinical spectrum, complicating diagnosis and management

NTDT patients do not require regular red cell transfusions but may require occasional transfusions for growth failure, pregnancy, infections and other specific situations[1–4]

NTDT

- β thalassemia intermedia
- Mild/moderate Hb E/β thalassemia
- Hb H disease (α thalassemia)
- Hb S β thalassemia
- Hb C thalassemia



Transfusions not required

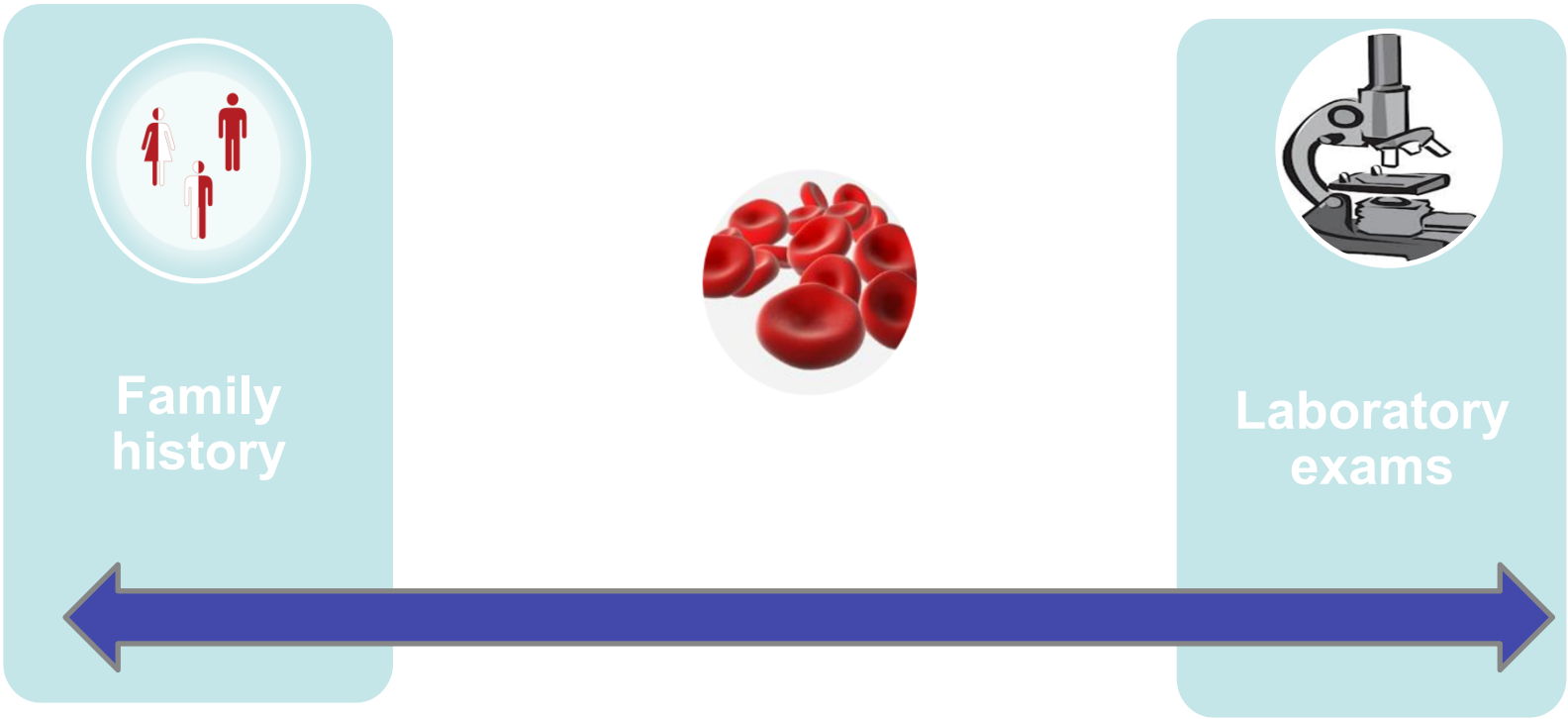
- α thalassemia trait
- β thalassemia minor

Transfusion-dependent thalassemia (TDT)

- β thalassemia major
- Severe Hb E/β thalassemia
- Hb Barts hydrops (α thalassemia major)

1.Taher AT *et al. Br J Haematol* 2011;152:512–523; 2. Galanello R and Origa R. *Orphanet Journal of Rare Diseases* 2010;5:11; 3. Vichinsky E. *Hematology Am Soc Hematol Educ Program* 2007;79–83; 4. Muncie HL and Campbell JS. *Am Fam Physician* 2009;80:339–344; 5. Figure adapted from Musallam KM *et al*. *Haematologica* 2013;98:833–844.

Several assessments can assist diagnosis



- Diagnosis should incorporate as much information as possible, utilizing family history, and laboratory examinations

1. Taher A *et al*. Guidelines for the management of NTDT. 2013;TIF Publication No. 19;
2. Weatherall DJ. *Blood Rev* 2012;26S:S3–S6.

Primary haematology tests

Full medical history and family history
Complete blood cell count with erythrocyte indices
Blood smear/ BCB staining

→ Other causes of anaemia?

↓

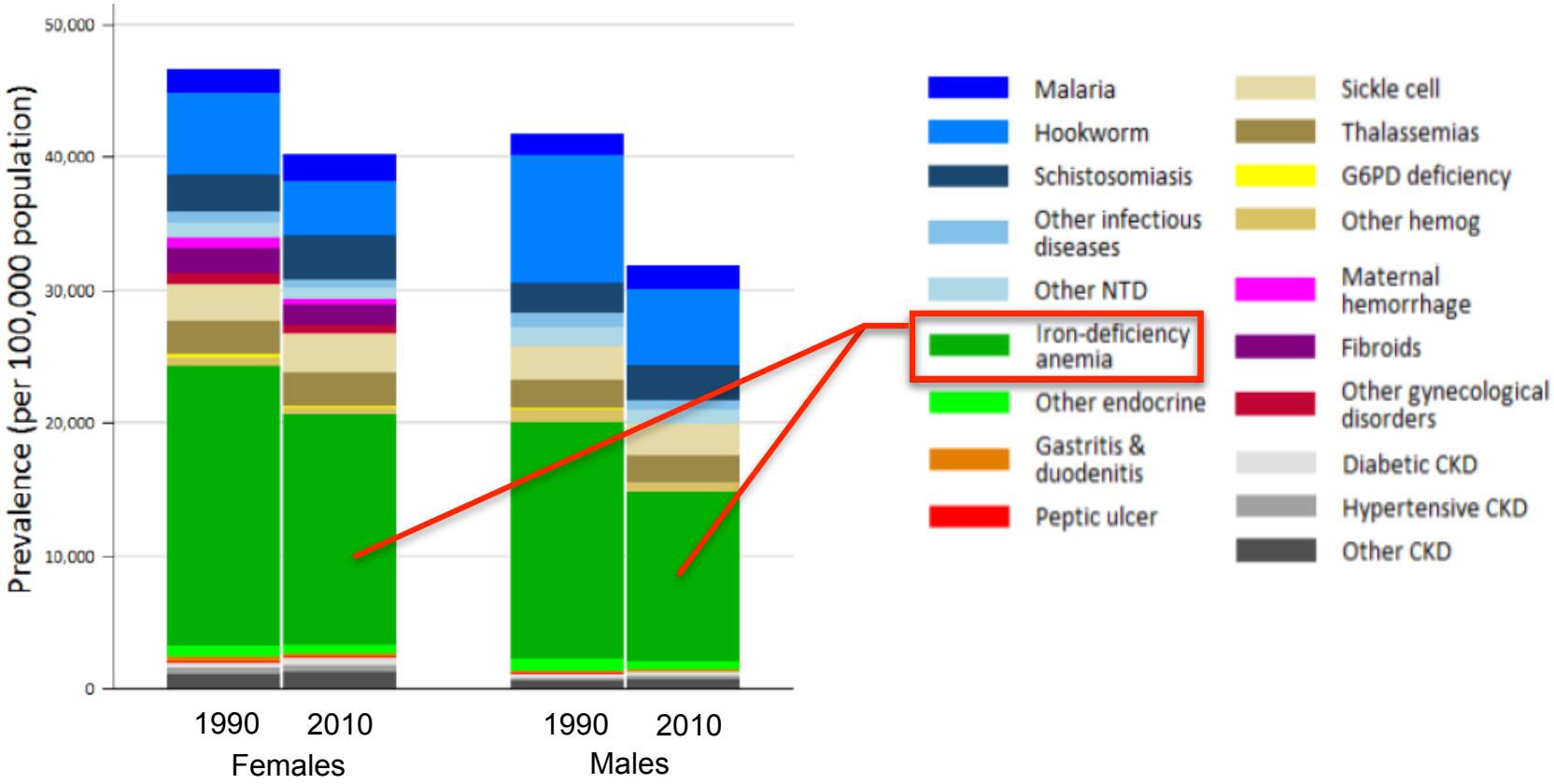
Low MCV (<80 fl) + Low MCH (<27 pg)

→ **Serum ferritin ≤12 ng/mL**

- Microcytosis
- Hypochromia

Consider iron deficiency anaemia

Prevalence of anaemia by aetiology



Kassebaum NJ, et al. Blood 2014;123:615-24

Primary haematology tests

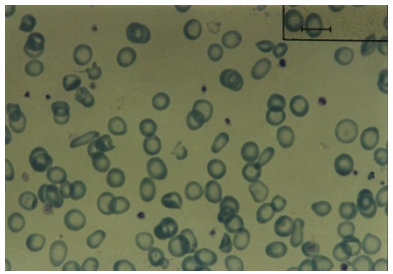
Full medical history and family history
Complete blood cell count with erythrocyte indices
Blood smear/ BCB staining

→ Other causes of anaemia?

↓

Low MCV (<80 fl) + Low MCH (<27 pg)

→ **Serum ferritin ≤12 ng/mL**



- Microcytosis
- Hypochromia

Consider iron deficiency anemia

Adequate iron supplement for 3 months

Primary haematology tests

Full medical history and family history
Complete blood cell count with erythrocyte indices
Blood smear/ BCB staining

→ Other causes of anaemia?

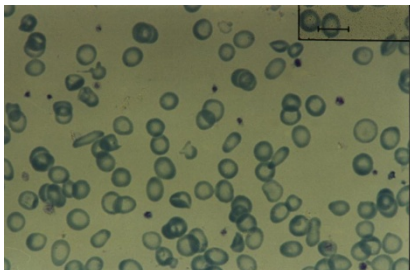
↓

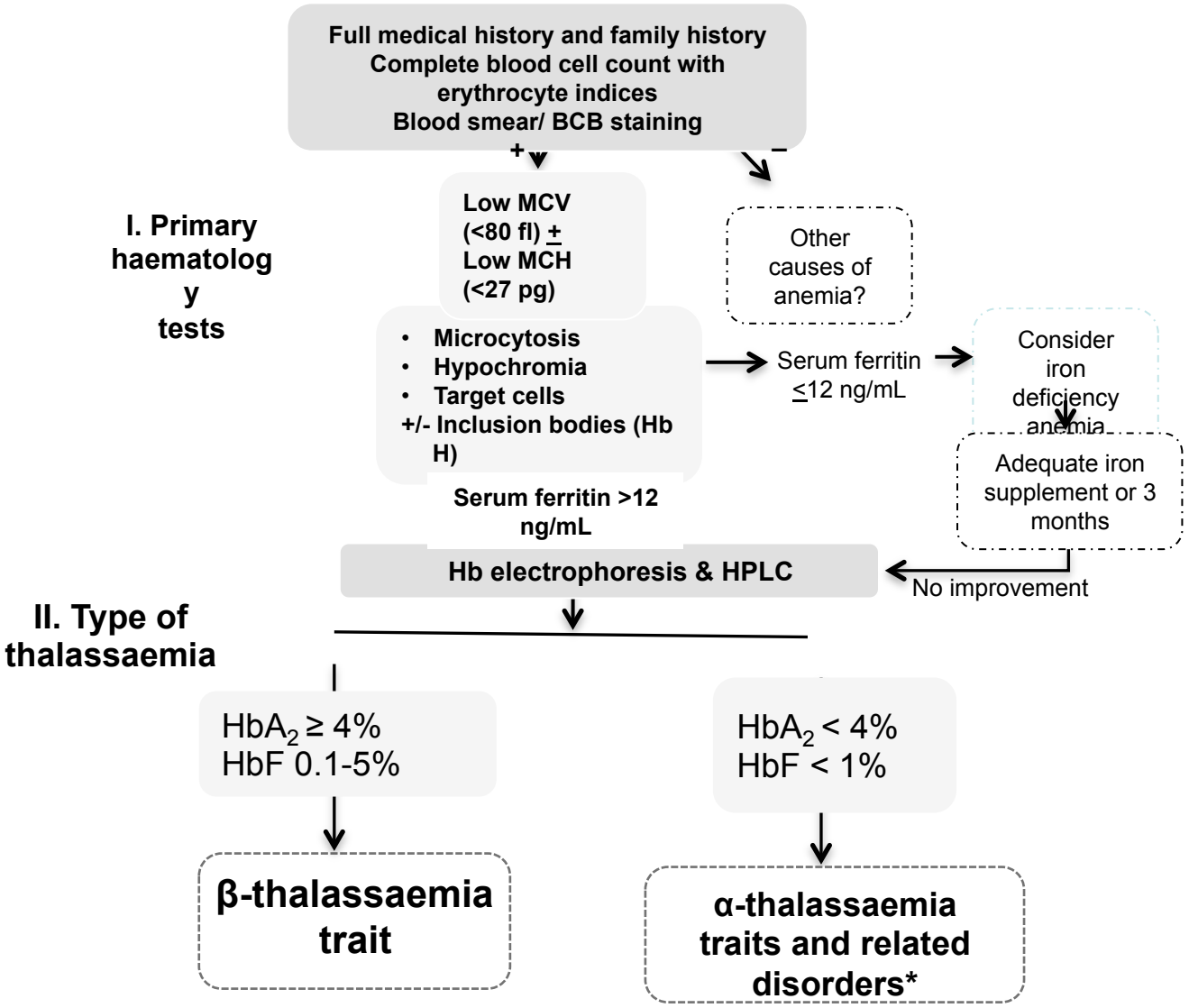
Low MCV (<80 fl) ± Low MCH (<27 pg)

→ **Serum ferritin < 12 ng/mL**

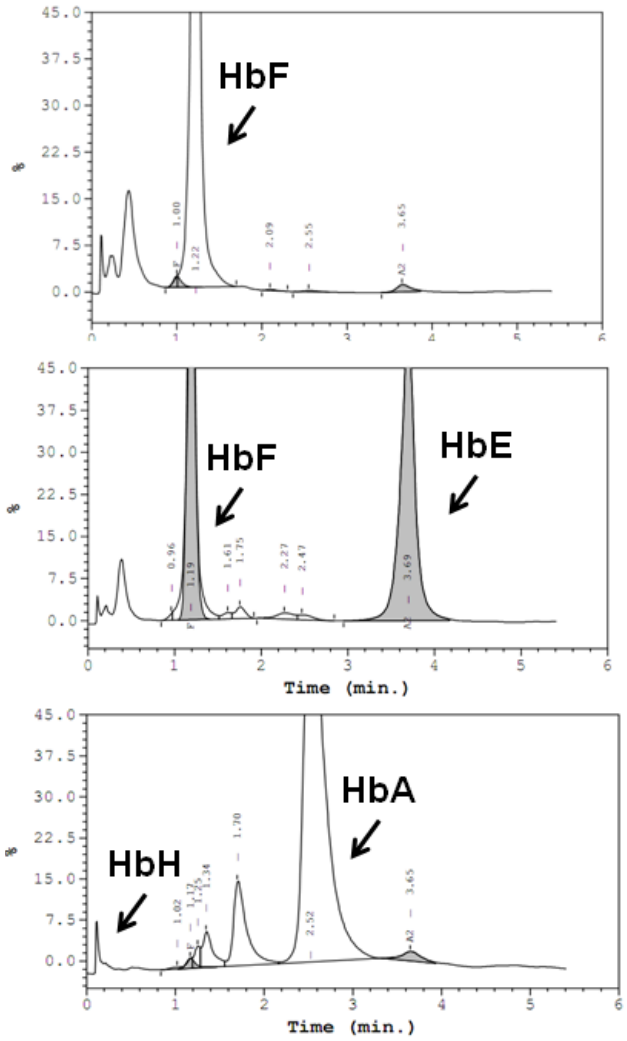
- Microcytosis
- Hypochromia
- Target cells

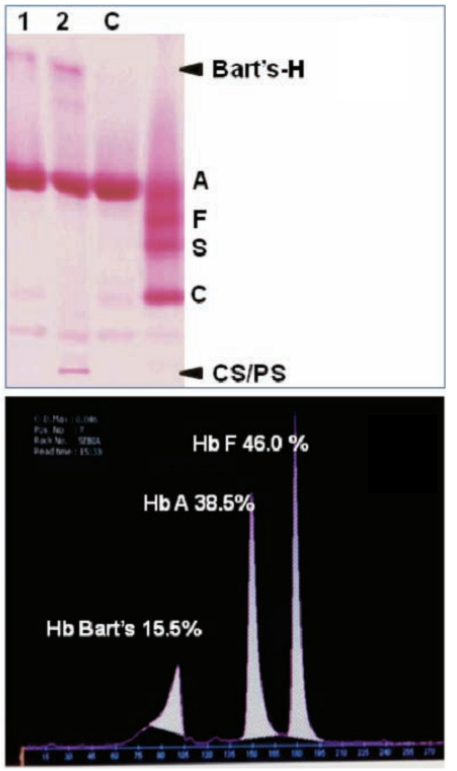
+/- Inclusion bodies (Hb H)




Full medical history and family history
Complete blood cell count with erythrocyte indices
Blood smear/ BCB staining
+
–
I. Primary haematology tests
Low MCV (<80 fl) + Low MCH (<27 pg)
Other causes of anemia?
• Microcytosis
• Hypochromia
• Target cells
+/- Inclusion bodies (Hb H)
Serum ferritin ≤12 ng/mL
Consider iron deficiency anemia
Adequate iron supplement or 3 months
No improvement
Serum ferritin >12 ng/mL
Hb electrophoresis & HPLC
II. Type of thalassaemia
HbA2 ≥ 4%
HbF 0.1-5%
HbA2 < 4%
HbF < 1%
β-thalassaemia trait
α-thalassaemia traits and related disorders*

HPLC and electrophoresis examples

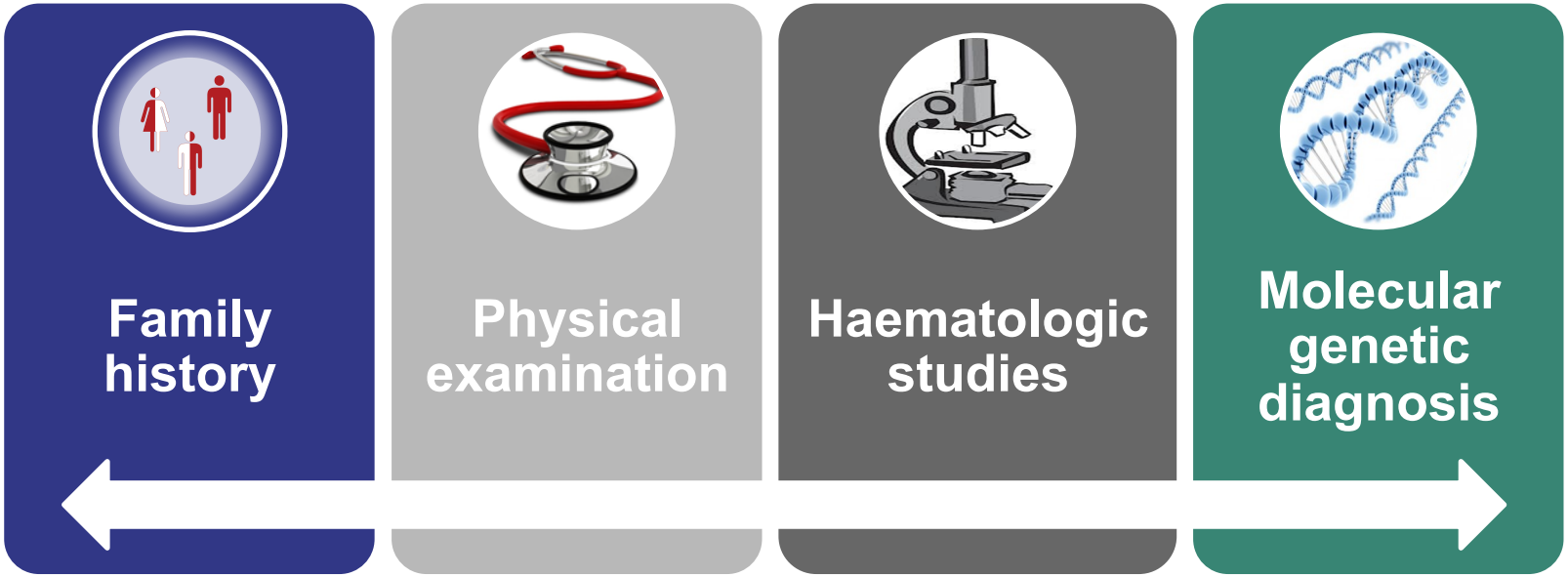




Hb electrophoresis of Hb H disease

Vip Viprakasit. EHA Educational Book 2013.

Main steps in diagnosing TDT



- Thalassaemia patients may be diagnosed before birth through prenatal and neonatal screening

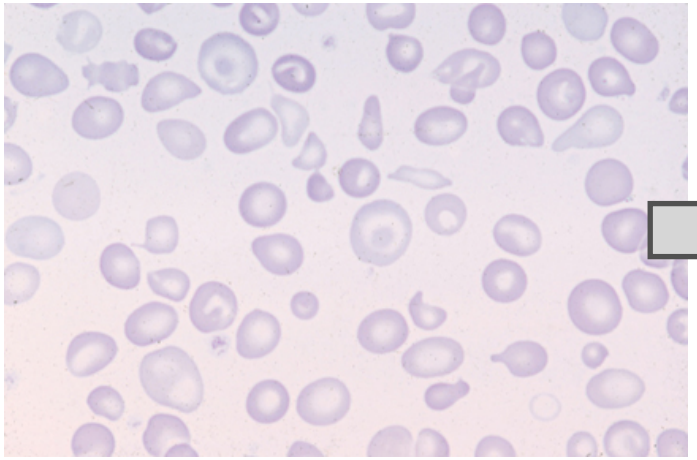
Complete blood count

	β thalassaemia major[1,2]	Severe Hb E/ β thalassaemia[3]	Hb Barts hydrops
Hb level* (g/dL)	<7	4–6	2–8
MCV (fL)	50–70	67	85–105
MCH (pg)	12–20	18	19–25
RDW	↑ (extreme anisocytosis)	35	25–30
WBC count	↑ (partly due to miscounting nucleated RBCs as leukocytes)	↑ (partly due to miscounting nucleated RBCs as leukocytes)	↑↑↑ (due to miscounting of very high numbers of nucleated RBCs)
Platelet count	Normal/increased, except in cases of splenomegaly		↑↑↑
Reticulocyte	↑↑	↑↑	↑↑↑ (up to 60%)

*Diagnosis should not be made on a single Hb measurement.
MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RDW, Red blood cell distribution width; WBC, white blood cell count

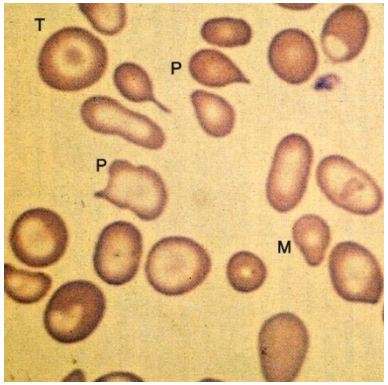
1. Galanello R and Origa R. *Orphanet J Rare Dis* 2010;5:11–26;
2. Steinberg MH *et al*. Disorders of Hemoglobin; 2nd edition 2009; Cambridge University Press.
3. Viprakasit V *et al*. *Blood* 2004;103:3296–3299.

Blood smear: β thalassaemia major

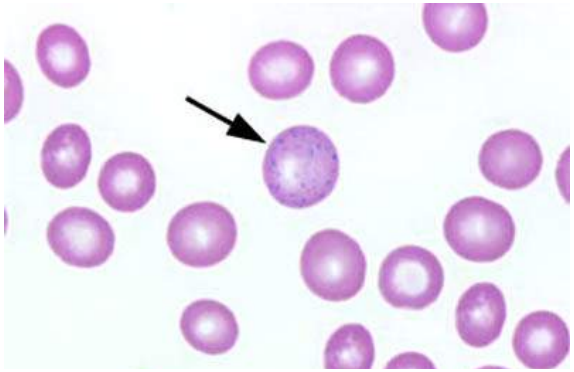


β thalassaemia major is characterized by severe degree of:

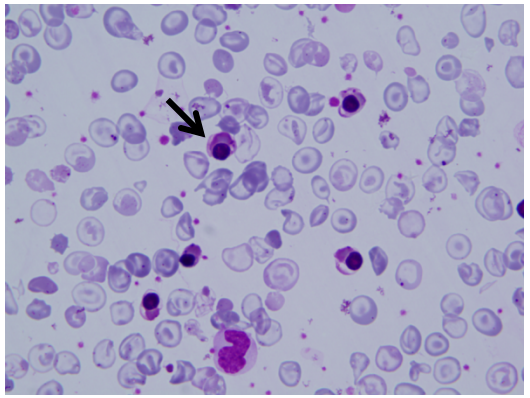
- Microcytosis
- Hypochromia
- Hypochromic macrocytes
- Poikilocytosis
- Nucleated red blood cells
- Basophilic stippling



Basophilic stippling



Nucleated red blood cell

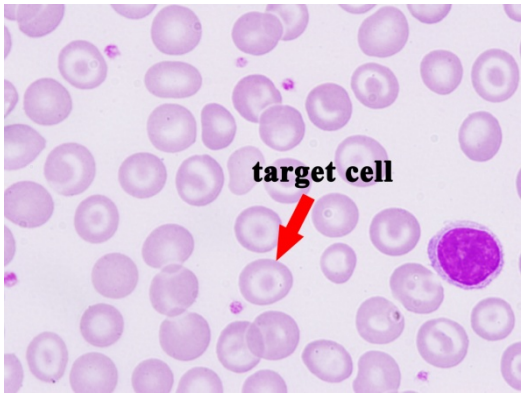


M, microcytosis; P, anisopoikilocytosis;
T, target cells,

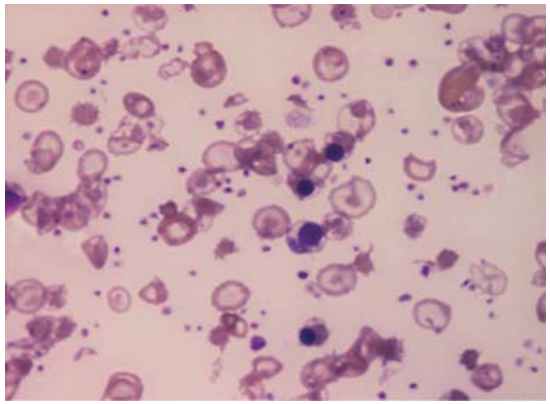
1. Steinberg MH *et al*. Disorders of Hemoglobin; 2nd edition 2009; Cambridge University Press

Blood smear: severe Hb E/ β thalassaemia

Homozygous state for Hb E showing large numbers of target cells[1]



Nucleated red cells and platelets in Hb E/β thalassaemia after splenectomy[1]



The main blood smear features for severe Hb E/β thalassaemia include:

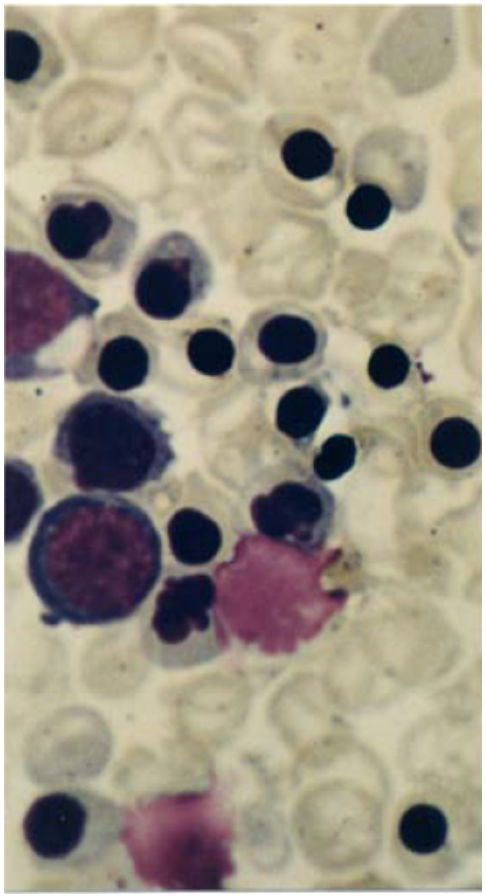
- Target cells[2]
- Nucleated red blood cells[1,2]
- Microcytes[2]
- Irregularly contracted RBC[2]

1. Fuchareon S and Weatherall DJ. *Cold Spring Harb Perspect Med* 2012;2:a011734;
2. Vichinsky E. *Hematology* 2007:79–83.

Blood smear: Hb Barts hydrops

Hb Barts hydrops shows high degree of:[1]

- Large hypochromic red cells
- Immature red cell precursors
- Anisocytosis
- Poikilocytosis
- Increased reticulocytes (up to 60%)



1. Harteveld C and Higgs DR. *Orphanet J Rare Dis* 2010;5:13.

Hb analysis by HPLC or electrophoresis

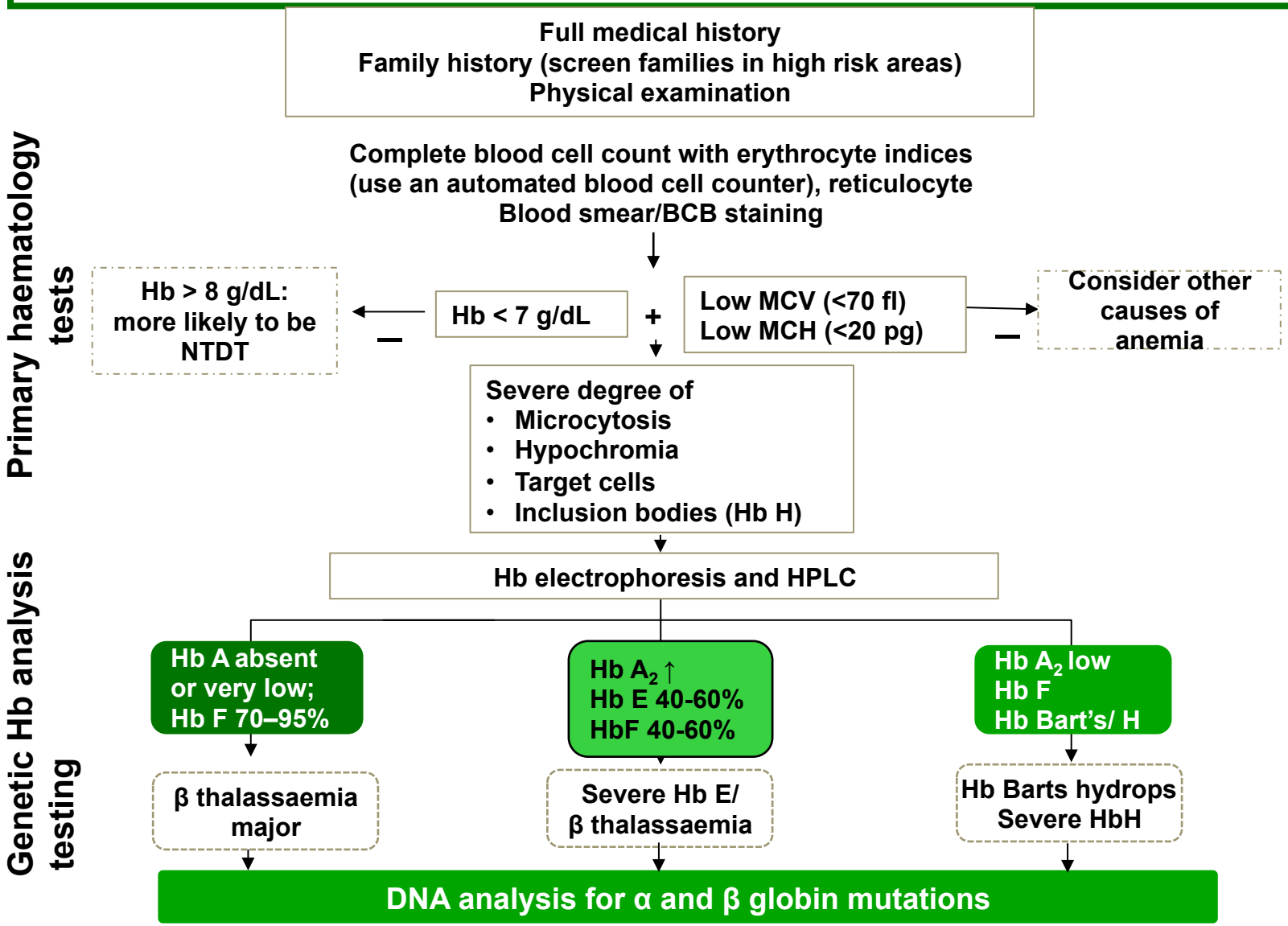
- Hb analysis by cellulose acetate and starch gel electrophoresis or HPLC identifies the amount and type of Hb fraction.
- Anti-coagulated blood sample should be obtained before start of transfusion

	β thalassaemia major[1]	Severe Hb E/ β thalassaemia[2]	Hb Barts hydrops[3]
Hb A_2	Variable	increased	Low
Hb Barts / Hb H	–	None	70-80% / 0.8–30.0%
Hb F	70–95%	40–60%	–
Hb E	–	40–60%	–
Others	Absent or very low Hb A	Absent or very low Hb A	–

HPLC, high-performance liquid chromatography

1. Galanello and Origa. *Orphanet J Rare Dis* 2010;5:11–26;
2. Vichinsky E. *Hematology* 2007:79–83;
3. Harteveld C and Higgs D. *Orphanet J Rare Dis* 2010;5:13.

Diagnostic work-up for TDT



NTDT, non-transfusion-dependent thalassemia

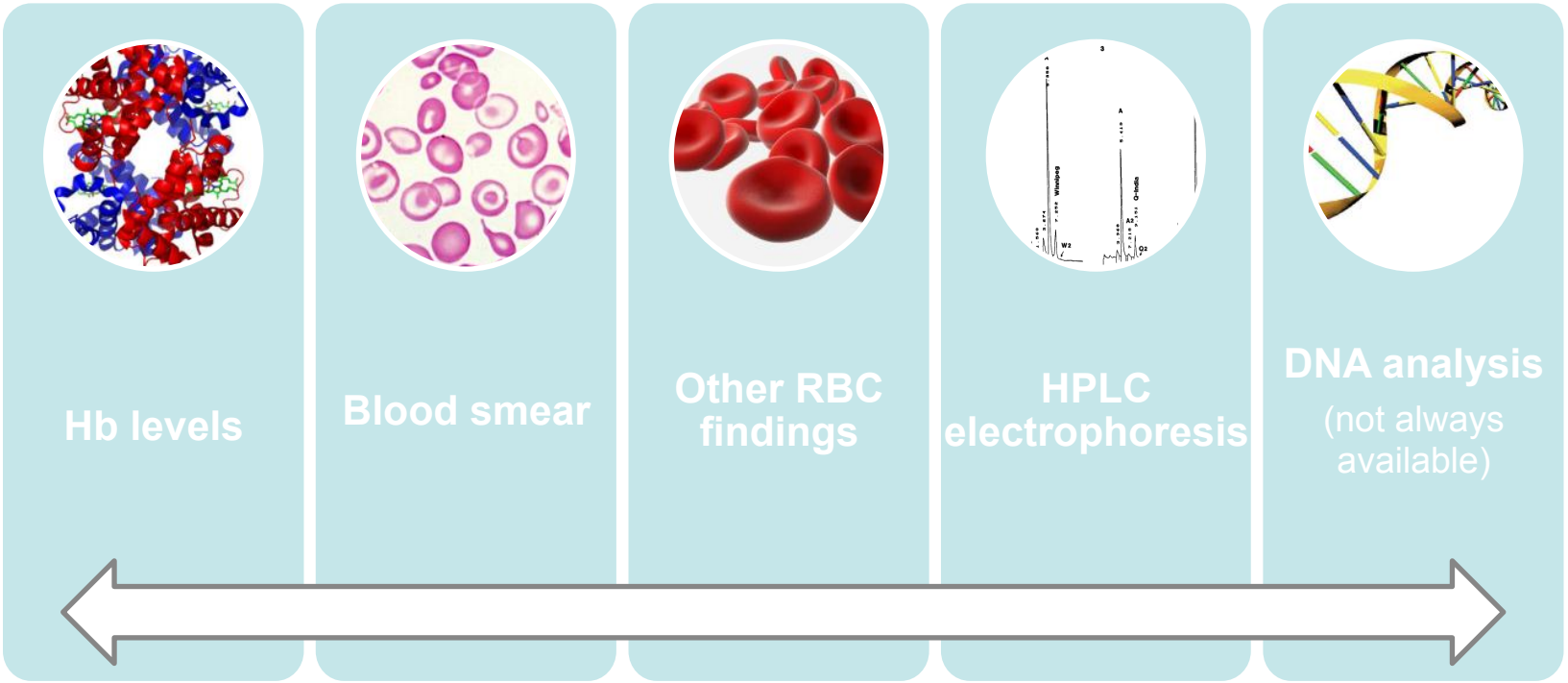
Introduction to molecular genetic diagnosis

- Molecular genetic diagnosis is required for ;
  - complementary part of diagnostic work-up
  - prenatal diagnosis
- The prevalence of a limited number of mutations in each ethnic group has greatly facilitated molecular genetic testing[1]
- Commonly occurring mutations of the globin gene are detected by PCR-based procedures[2]

PCR, polymerase chain reaction

1. Galanello and Origa. *Orphanet J Rare Dis.* 2010, 5:11–26.
2. Vrettou C *et al*. *Clin Chem*. 2003;49:769–776.

Several laboratory tests are available which together contribute to an NTDT diagnosis



Diagnosis should incorporate as much information as possible, utilizing patient history, physical and laboratory examinations

HPLC, high-performance liquid chromatography;
RBC, red blood cells

1. Taher AT *et al. Blood Cells Mol Dis* 2006;37:12–20;
2. Galanello R and Origa R. *Orphanet J Rare Dis* 2010;5:11;
3. Harteveld C and Higgs D. *Orphanet J Rare Dis* 2010;5:13.

Physical examination: common symptoms that can help distinguish and diagnose different forms of NTDT

	β TI	Hb E/β thalassemia	Hb H
Splenomegaly	Varying degree of enlargement[1]	Common[2]	Common[3,4]
Hepatobiliary	Gallstones[4] Moderate to severe liver enlargement[4]	Gallstones[2]	Gallstones[3,5] Variable jaundice[3,5] Enlarged liver[6]
Skeletal	Growth retardation[1] Expansion of facial bones[1] Obliteration of maxillary sinuses[1] Protrusion of upper jaw[1] Extramedullary hematopoiesis[1]	Growth retardation[2] Extramedullary hematopoiesis[2]	Growth retardation[3,5] Dysmorphic facial features[6]
Infections	Increased susceptibility[1] Leg ulcers[1]	Septicemia[2] Leg ulcers[2]	Infections[5] Leg ulcers[5]
Vascular/heart	Pulmonary hypertension[1] Cardiovascular disease[1]	Congestive heart failure[2]	–

Hb, hemoglobin

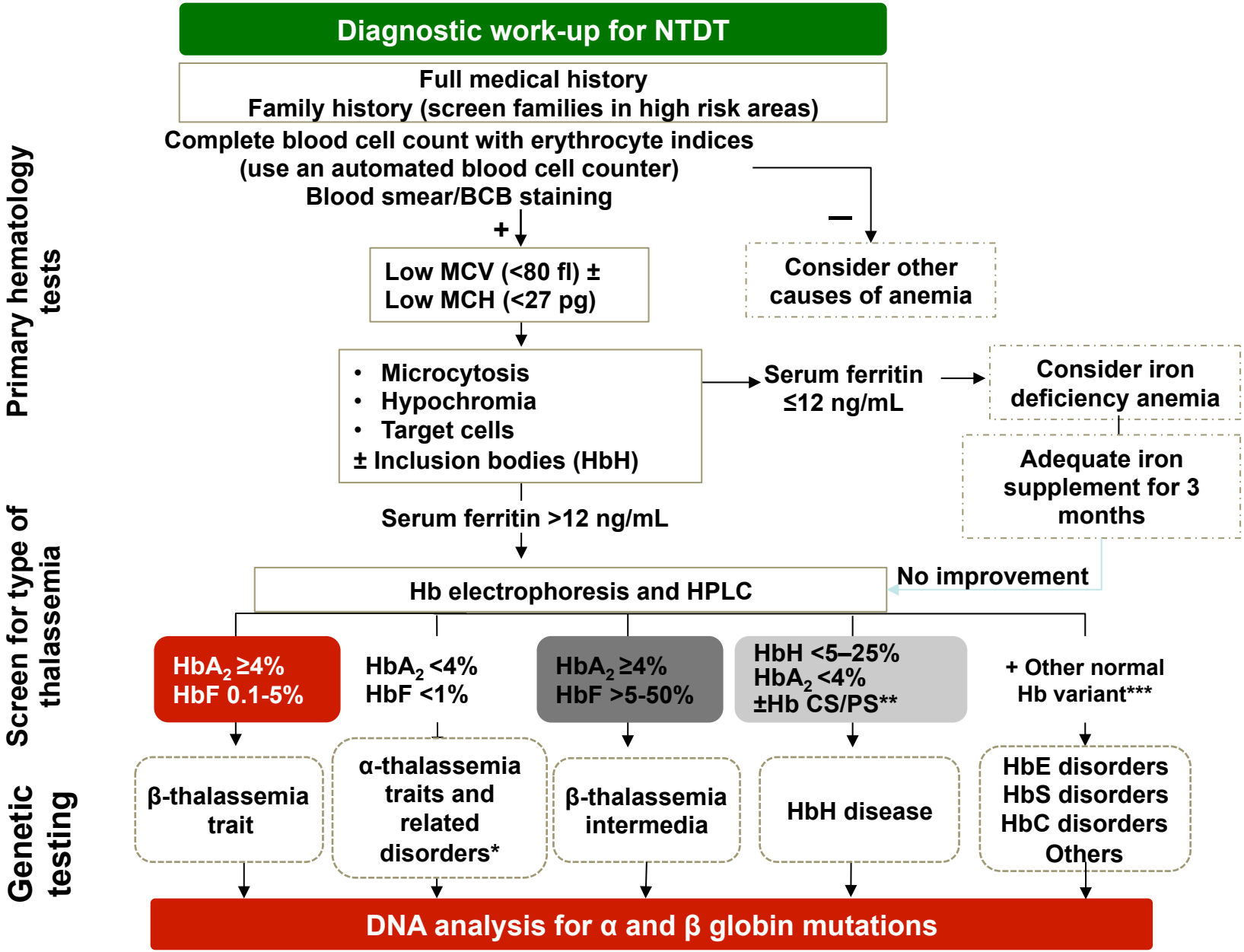
1. Taher AT *et al*. *Blood Cells Mol Dis* 2006;37:12–20;
2. Fucharoen S *et al*. *J Pediatr Hematol Oncol* 2000;22:552–557;
3. Fucharoen S and Viprakasit V. *Hematology Am Soc Hematol Educ Program* 2009:26–34;
4. Thalassaemia International Federation. Guidelines for the Clinical Management of thalassaemia, 2nd edition revised 2008;
5. Harteveld C and Higgs D. *Orphanet J Rare Dis* 2010;5:13–34;
6. Laosombat V *et al*. *Ann Hem* 2009;88:1185–1192.

Laboratory examination: parameters that can help distinguish and diagnose different forms of NTDT

	β TI	Hb E/β thalassemia		Hb H
Hb levels	~7–10 g/dL[1]	Mild[2]	9–12 g/dL	2.6–13.3 g/dL[3]
		Moderately Severe[2]	6–7 g/dL	
		Severe[2]	4–5 g/dL	
Blood smear	Basophilic stippling[6] Nucleated RBC[6]	Target cells[7] Red cell hypochromia[7] Microcytes[7] Nucleated RBC[7] hemolysis[4]		Microcytosis[8] Hypochromia[8] Target cells[8] Inclusion bodies[8] Irregularly crenated RBC[8] Increased reticulocytes (5–10%)[8]
HPLC electrophoresis	Hb F 10–50% (up to 100%)[5] Hb A_2 >4%[5]	Hb E and F[6] Hb $A_2\uparrow$[9]		α/β-globin chain synthesis ratio measurement[3] RBC indices[3] Hb $A_2\downarrow$[3] Variable Hb H (0.8–40%) and occasional Hb Barts hydrops[3]
DNA analysis	Genetic analysis should be performed in event of abnormal hematology findings[2]	To distinguish between different Hb E disorders[4]		Gap-PCR developed for seven common α thalassemia[3] For unknown rearrangements, Southern Blotting or MLPA analysis required[3]

MLPA, multiplex ligation-dependent probe amplification
PCR, polymerase chain reaction

1. Taher AT *et al*. *Blood Cells Mol Dis* 2006;37:12–20; 2. Galanello R *et al*. *Orphanet J Rare Dis* 2010;5:11; 3. Harteveld C *et al*. *Orphanet J Rare Dis* 2010;5:13; 4.Vichinsky E. *Hematology Am Soc Hematol Educ Program* 2007;79–83; 5. Thalassaemia International Federation. Guidelines for the Clinical Management of thalassaemia, 2nd edition revised 2008; 6. Yaish HM *et al*. http://emedicine.medscape.com/article/959122-overview; 7. www.Medialabinc.Net/spg469619/hemoglobin_e_hb_e_and_hbebeta_thalassaemia.Aspx; 8. http://www.hoslink.com/pathology/labresults/haematologic.htm#THE%20thalassaemiaS; 9. Fucharoen S *et al*. *Clin Chem* 1998;44:740–748.

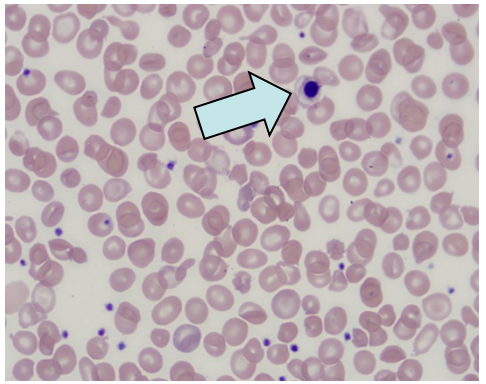


Prof. Taher & Prof. Viprakasit, personal communication

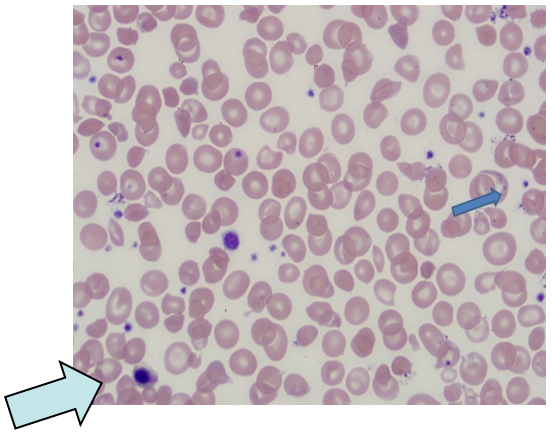
In β TI, red blood cell abnormalities can help distinguish the disease; however, diagnosis remains largely a clinical decision

- Diagnoses remains largely clinical
- Characterized by:
  - Hb levels maintained ~7–10 g/dL without need for regular transfusions[1]
  - More severe red blood cell abnormalities than thalassemia minor
  - Varying degree of spleen enlargement
  - Increased susceptibility to infections
  - Skeletal changes[1]

Basophilic stippling[2]



Nucleated RBC[2]



1. Taher AT *et al*. *Blood Cells Mol Dis* 2006;37:12–20;
2. Yaish HM *et al*. http://emedicine.medscape.com/article/959122-overview.

Both clinical and laboratory parameters can help distinguish the diverse spectrum of β thalassemias

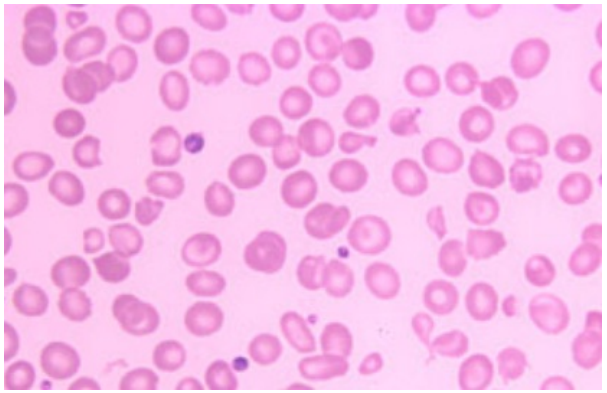
	β TM more likely	β TI more likely
Clinical		
Presentation (years)	<2	>2
Hb levels (g/dL)	6–7	8–10
Liver/spleen enlargement	Severe	Moderate to severe
Hematologic		
Hb F (%)	>50	10–50 (may be up to 100%)
Hb A_2 (%)	<4	>4
Genetic		
Parents	Both carriers of high Hb A_2 β thalassemia	1 or both atypical carriers: – High Hb F β thalassemia – Borderline Hb A_2
Molecular		
Type of mutation	Severe	Mild/silent
Co-inheritance of α thalassemia	No	Yes
Hereditary persistence of		
Hb F	No	Yes
δβ thalassemia	No	Yes
Gγ XMN1 polymorphism	No	Yes

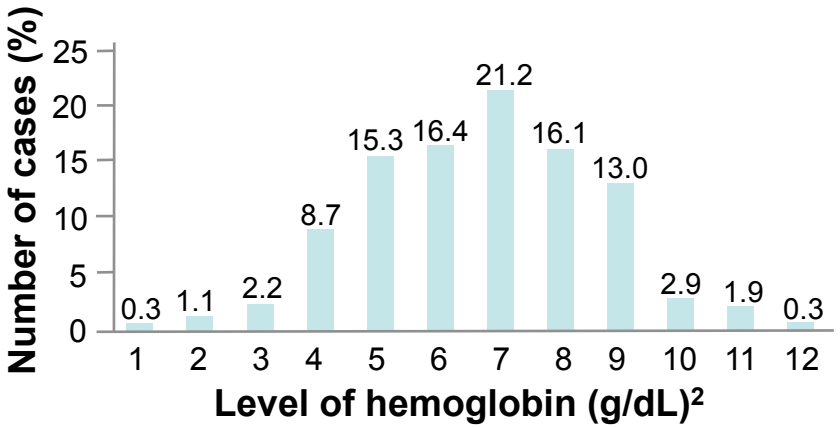
1. Thalassaemia International Federation. Guidelines for the clinical management of thalassaemia, 2nd Edition revised 2008.

Diagnosis of Hb E/β thalassemia is based on a variable anemia and laboratory profile

Blood smear

- Target cells, microspherocytes, red cell hypochromia, red blood cell fragments, nucleated red blood cells[1]



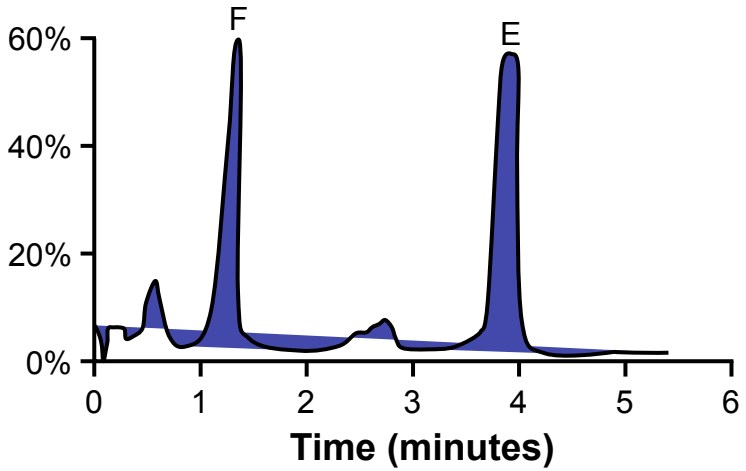


Hb electrophoresis and HPLC

- Hb E and F[3]
- Hb A_2 ↑

Hemolysis[2]

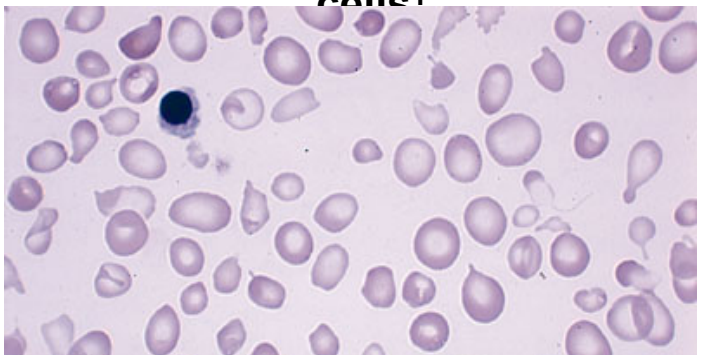
DNA analysis to distinguish syndromes



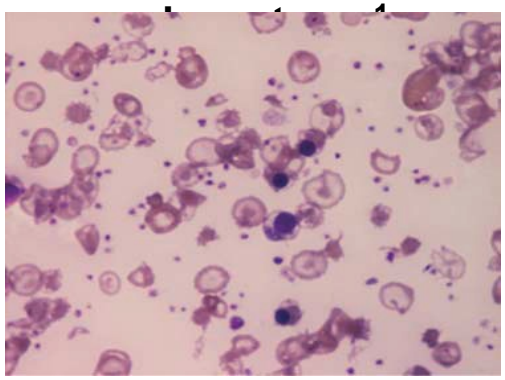
1. http://www.medialabinc.net/spg469619/hemoglobin_e_hb_e_and_hbebeta_thalassaemia.aspx;
2. Vichinsky *E. Hematology* 2007;79–83;
3. Fucharoen S *et al. Clin Chem* 1998;44:740–748.

Blood smear: severe Hb E/ β thalassemia

Homozygous state for Hb E showing large numbers of target cells[1]



Nucleated red cells and platelets in Hb E/β thalassemia after



The main blood smear features for severe Hb E/β thalassemia include:

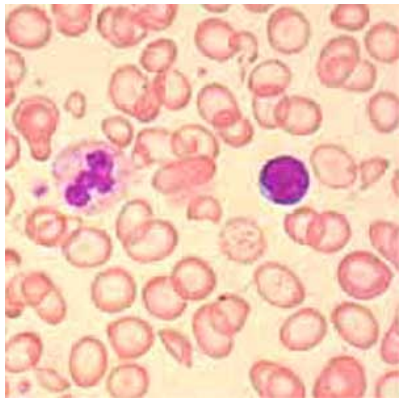
- Target cells[2]
- Nucleated red blood cells[1,2]
- Microcytes[2]
- Irregularly contracted RBC[2]

1. Fuchareon S and Weatherall DJ. *Cold Spring Harb Perspect Med* 2012;2:a011734;
2. Vichinsky E. *Hematology* 2007:79–83.

Clinical features and laboratory abnormalities may contribute to a diagnosis of Hb H disease

- Characterized by:[1]
  - Hb levels ~3–13 g/dL, variable amounts of Hb H (0.8-40%), occasionally Hb Barts hydrops
  - Splenomegaly (may be severe), occasionally complicated by hypersplenism
  - Jaundice in variable degrees
  - Children may show growth retardation
- Severity of clinical features related to molecular bass of disease[1]

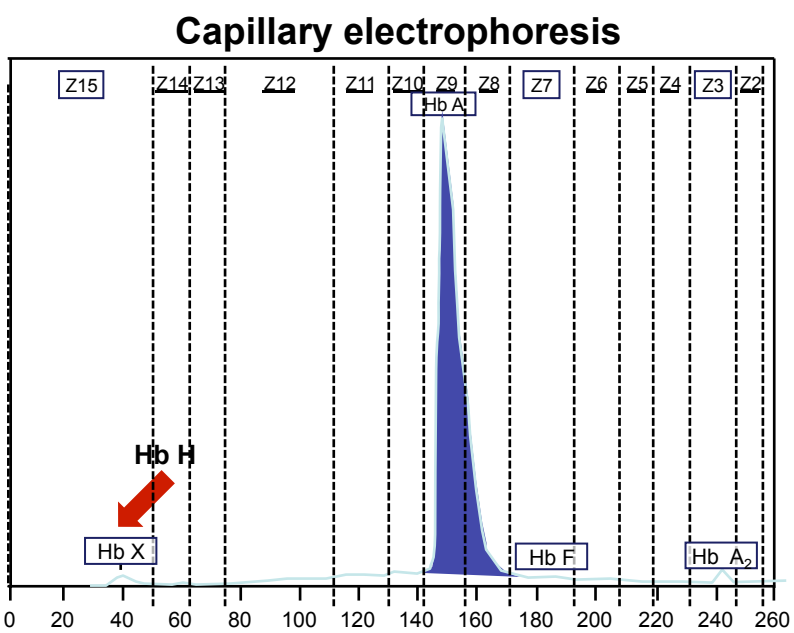
- Blood smear[2]
  - Microcytosis, hypochromia
  - Target cells
  - Inclusion bodies
  - Hemolysis
  - Hb Barts hydrops (γ tetramers)
  - Hb H (β tetramers)

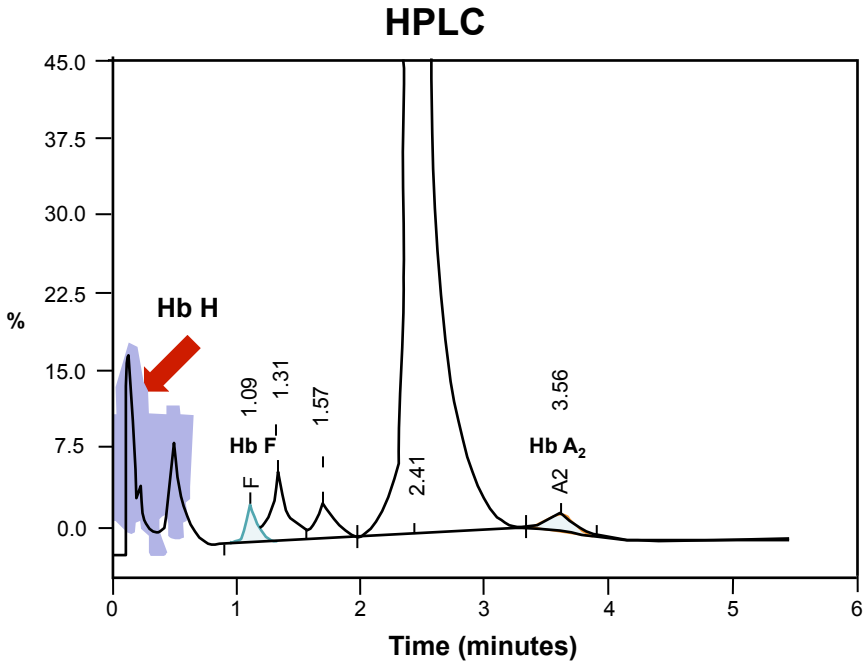


1. Harteveld C and Higgs D. *Orphanet J Rare* Dis 2010;5:13;
2. http://www.hoslink.com/labresults/haematologic.htm#THE thalassaemiaS.

Diagnosis of Hb H may require HPLC or electrophoresis to help distinguish Hb abnormalities

- Hb electrophoresis or HPLC (Hb A_2↓, Hb Barts hydrops, Hb H)
- DNA analysis
  - Gap-PCR
  - MLPA/Southern blot
  - Sequencing





1. Harteveld C and Higgs D. *Orphanet J Rare Dis* 2010;5:13.

Genotype-phenotype association in the β thalassemias lead to a varying clinical severity

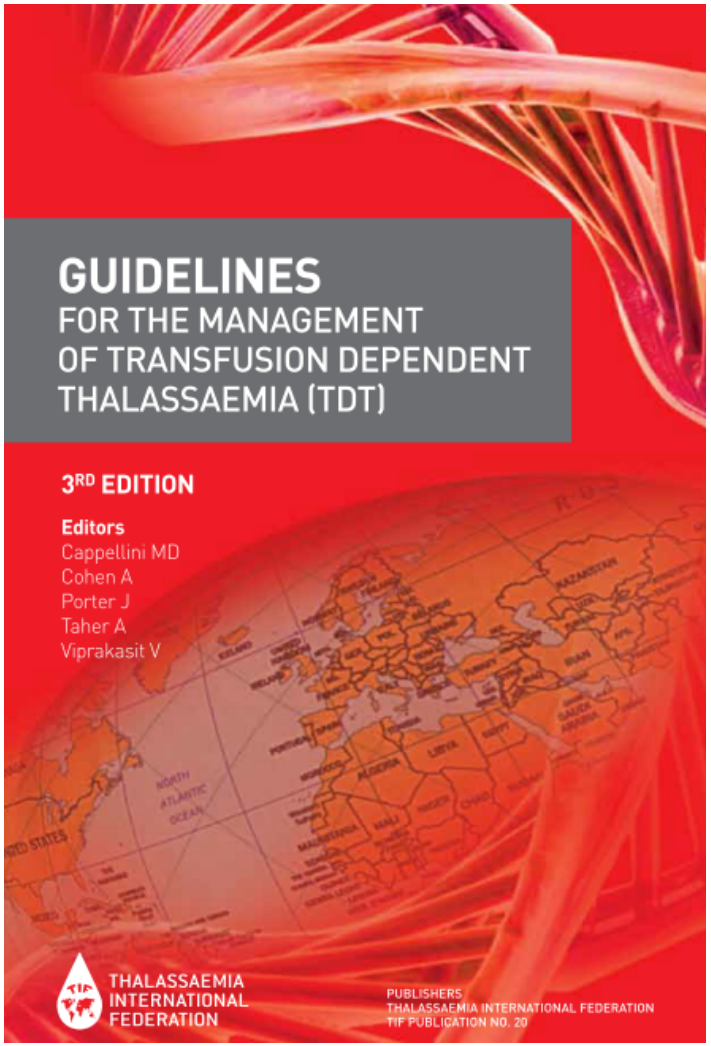
Phenotype	Genotype	Clinical severity
Major	• β^0/β^0, β^+/β^+, or β^0/β^+	• Early presentation • Severe anemia • Transfusion dependent
Intermedia	• β^0/mild β^+, β^+/mild β^+, or mild β^+/mild β^+ • β^0/silent β, β^+/silent β, mild β^+/silent β, or silent β/silent β • β^0/β^0, β^+/β^+, or β^0/β^+ and deletion or nondeletion α-thalassemia • β^0/β^0, β^+/β^+, or β^0/β^+ and increased capacity for γ chain synthesis • Deletion forms of δβ thalassemia and HPFH • β^0/β or β^+/β and ααα or αααα duplications • Dominant β thalassemia (inclusion body)	• Late presentation • Mild-to-moderate anemia • Transfusion independent • Clinical severity is variable and ranges between minor to major
Trait/minor	• β^0/β, β^+/β, or mild β^+/β	• Borderline asymptomatic anemia • Microcytosis and hypochromia
Silent carrier	• silent β/β	• Asymptomatic • No hematological abnormalities

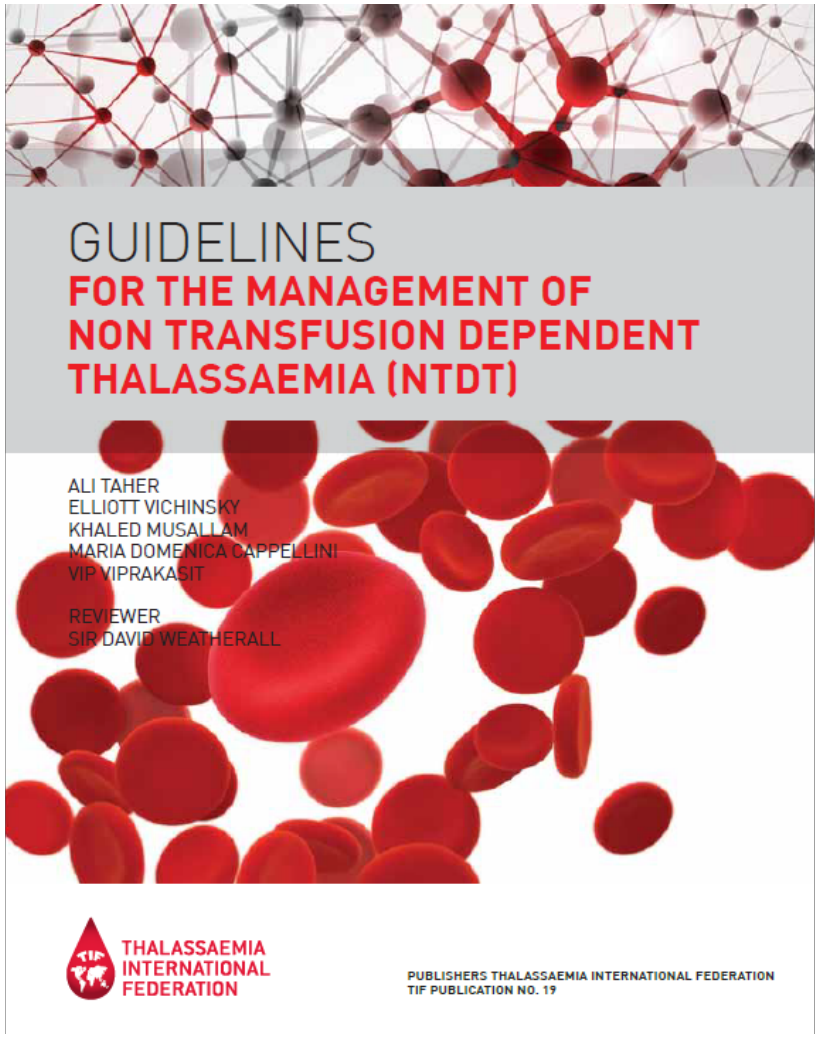
NTDT

Severity of disease

1. Musallam KM *et al*. *Haematologica* 2013;98:833–844.

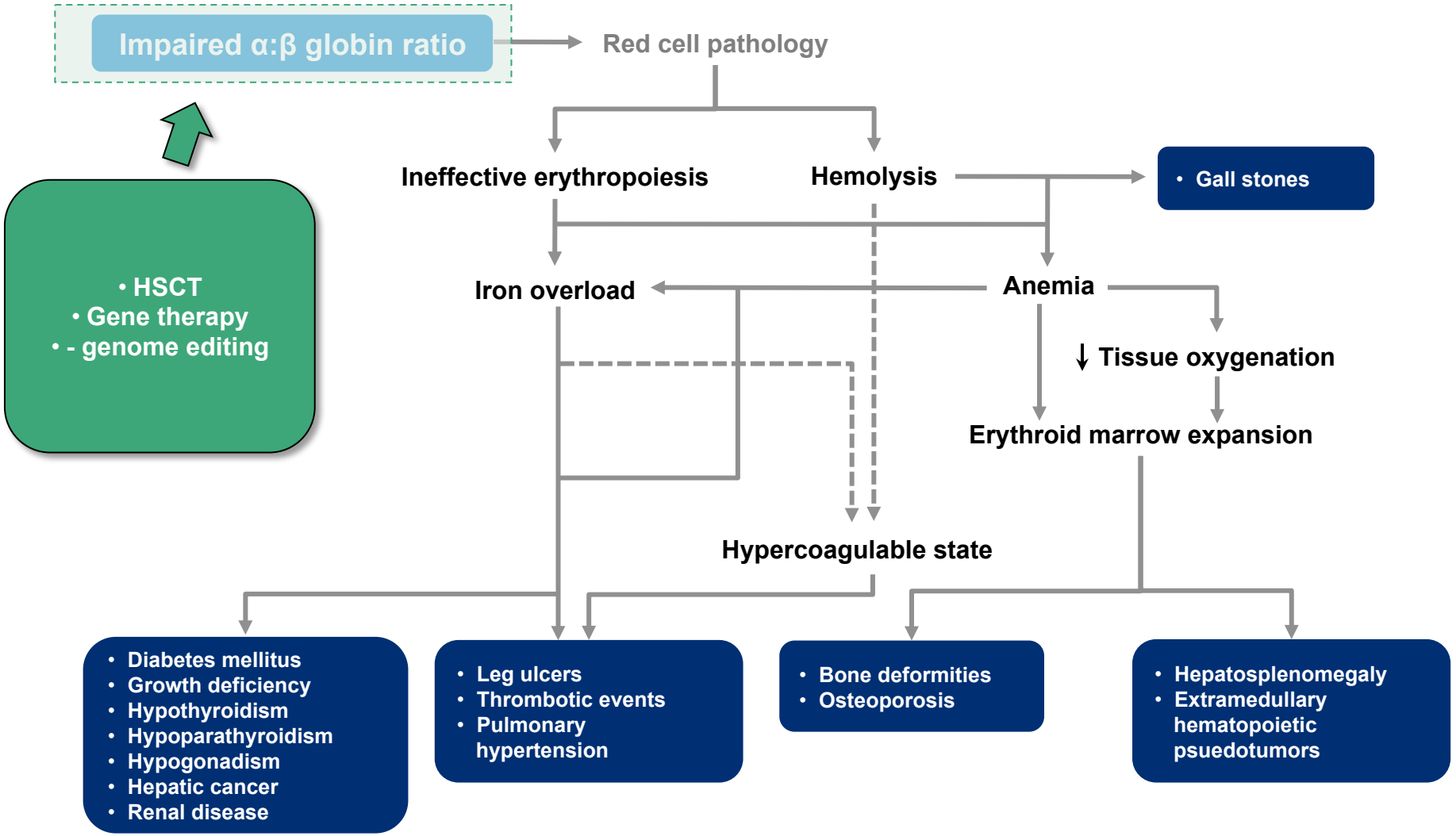
TIF 2014 guidelines





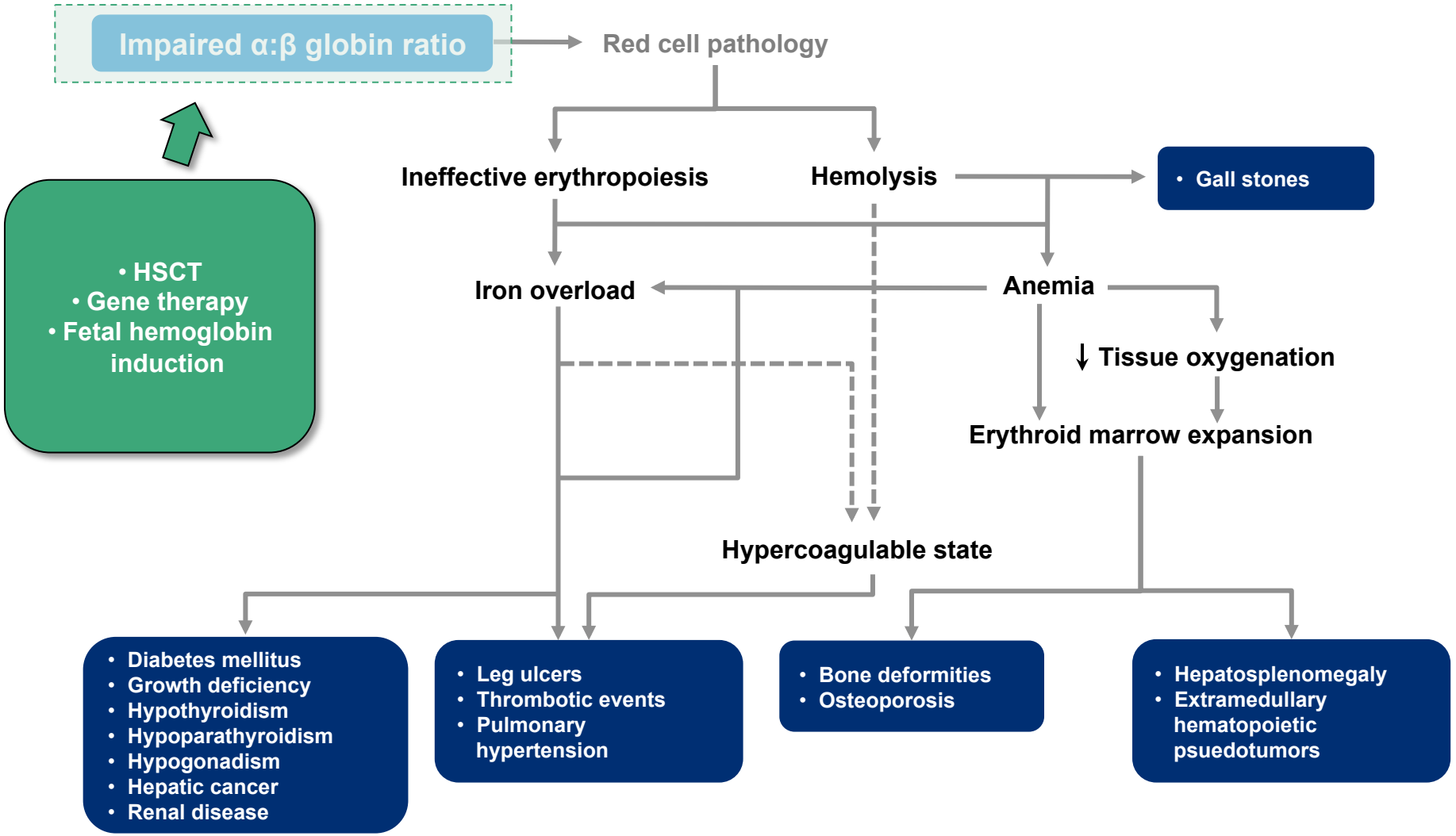
TIF, Thalassaemia International Federation.

Targeting α/β chain imbalance



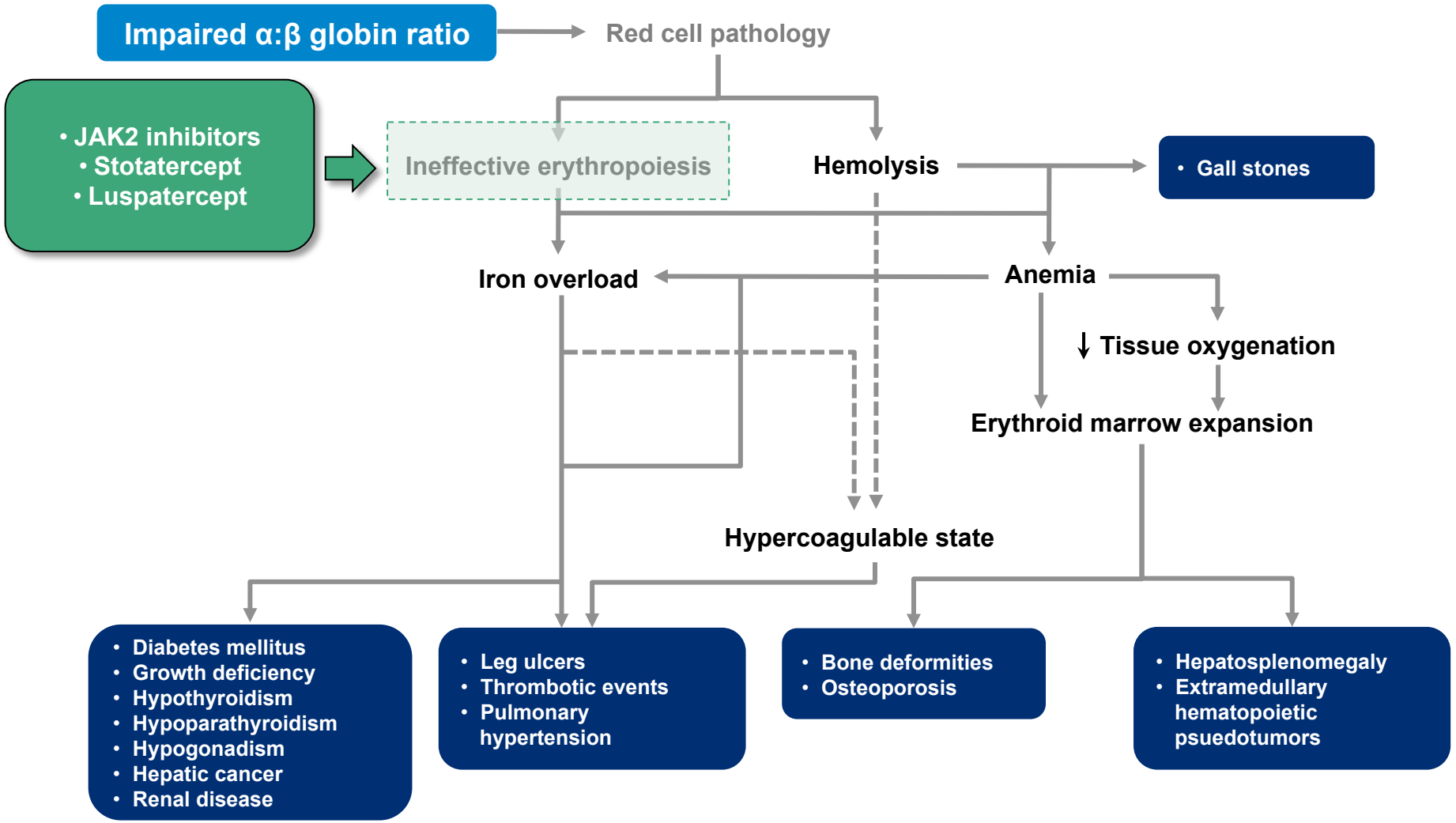
Musallam KM, et al. Haematologica. 2013;98:833-4.

Targeting α/β chain imbalance



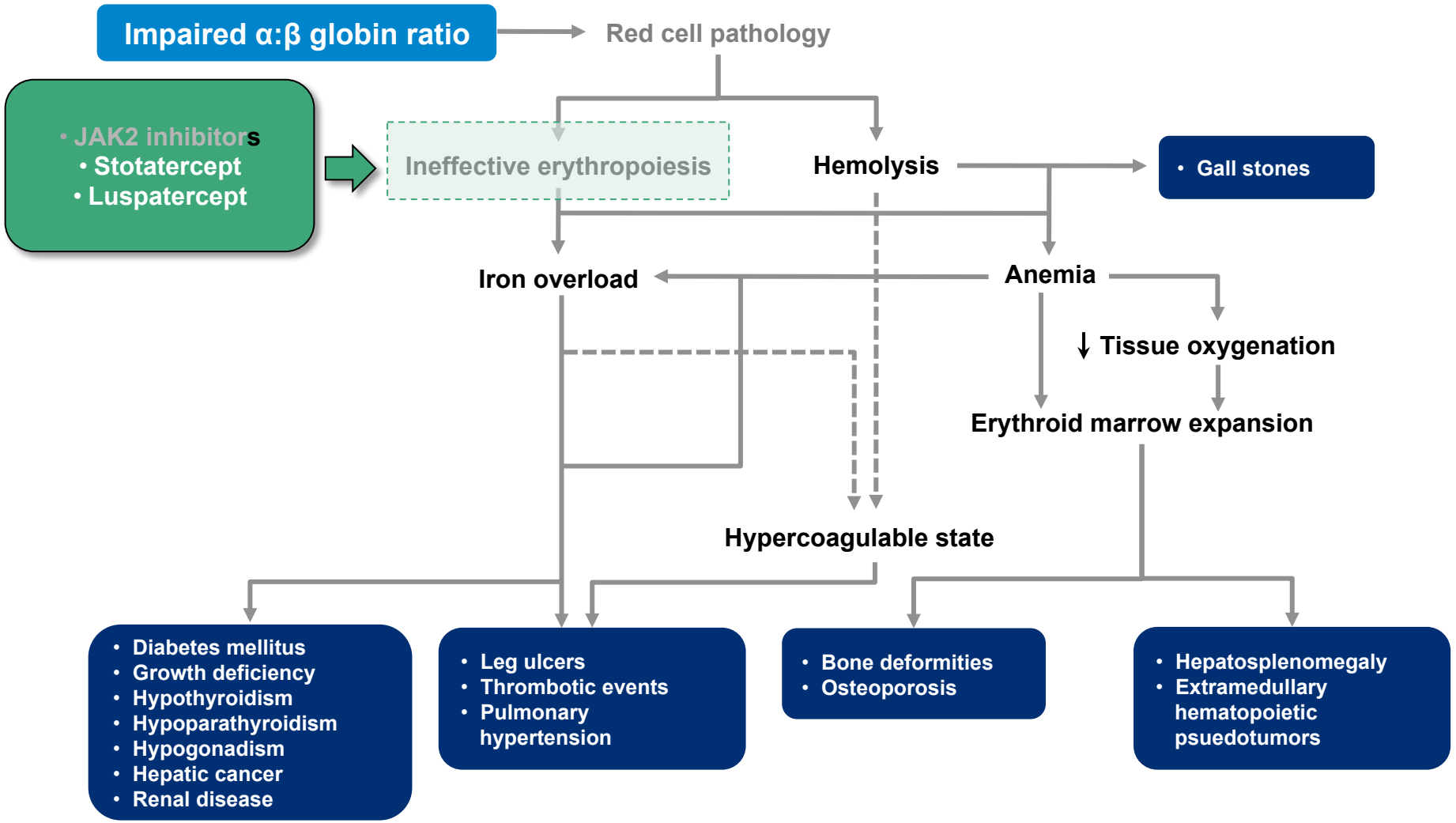
Musallam KM, et al. Haematologica. 2013;98:833-4.

Targeting ineffective erythropoiesis



Musallam KM, et al. Haematologica. 2013;98:833-4.

Targeting ineffective erythropoiesis



Musallam KM, et al. Haematologica. 2013;98:833-4.

GRAZIE