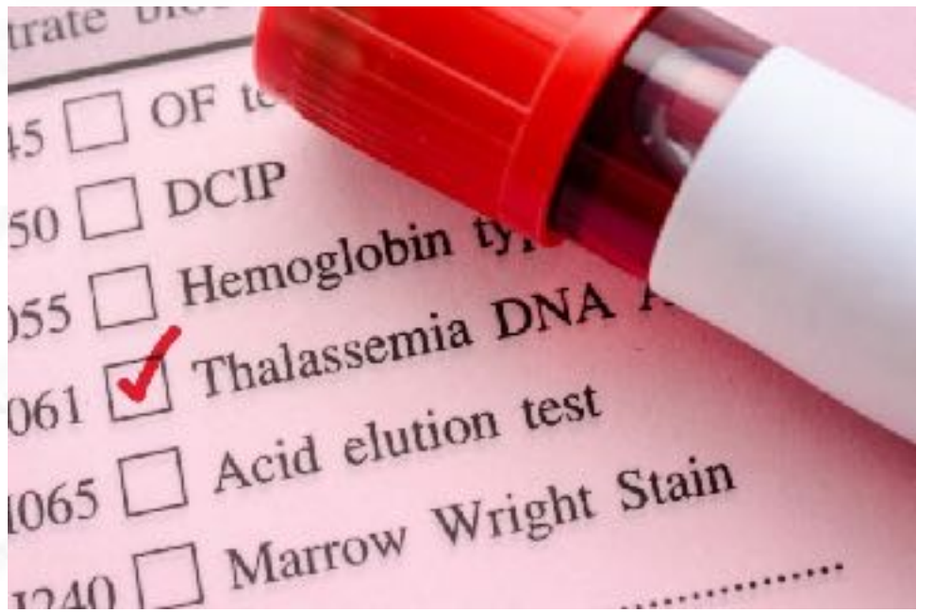


Thalassemia

What you ~~should~~ must know…

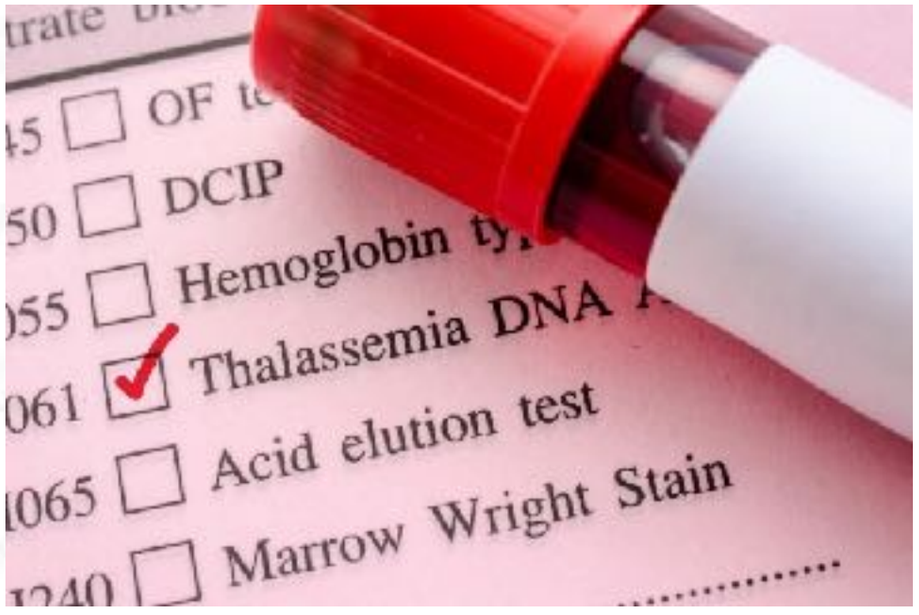
Apichat Photi-A MD.
Pediatric Hematology and Oncology Unit
Department of Pediatrics
Phramongkutklao Hospital

Learning objectives

Overview of Thalassemia and diagnostic test

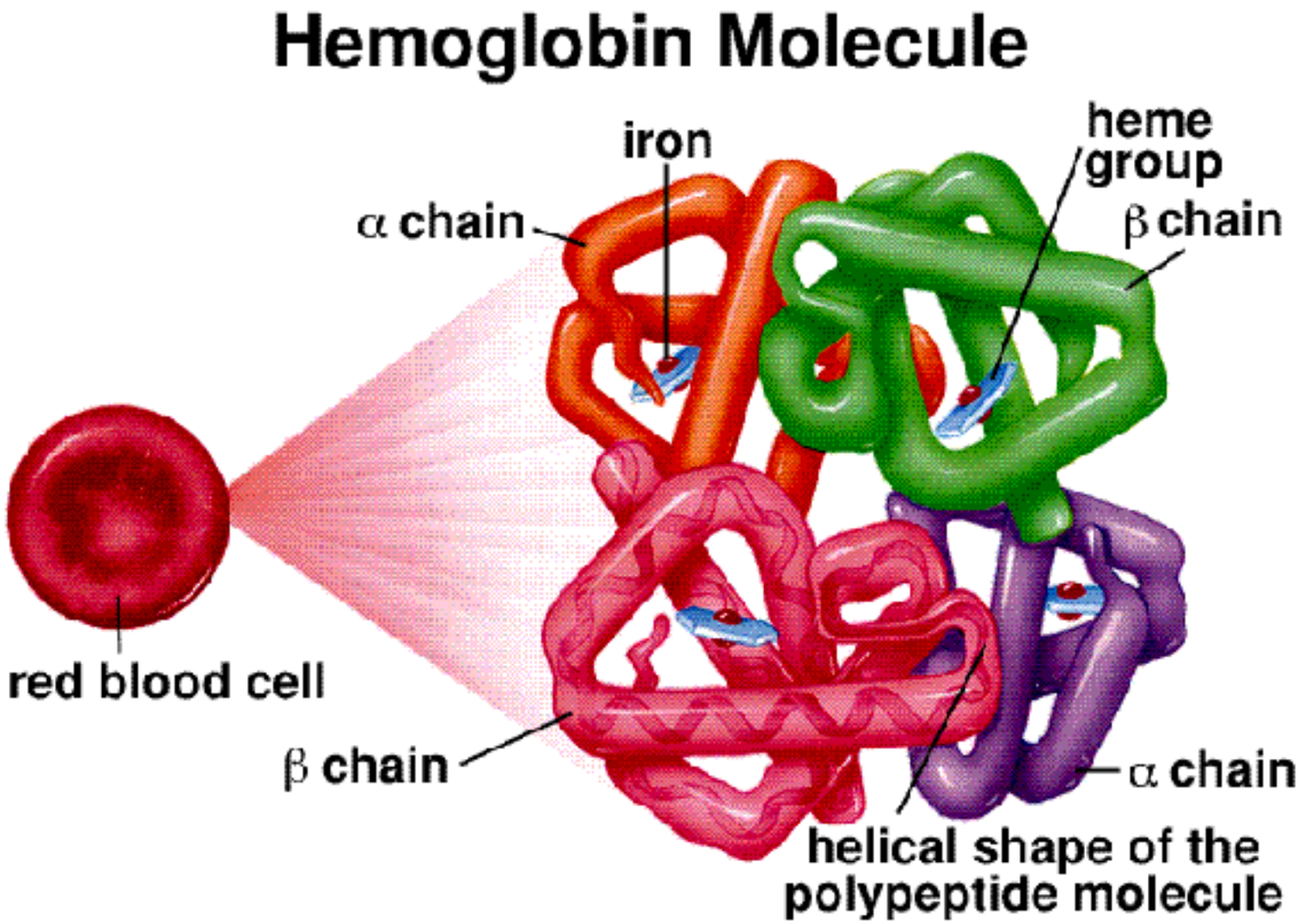
Treatment and complication

New coming treatment agents



Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Structure of Hemoglobin



Hb consists of 4 subunits

- 2 α-chain/ α-like chain
- 2 ß-chain/ ß-like chain

Structure of Hemoglobin

Type of "Globin chain"

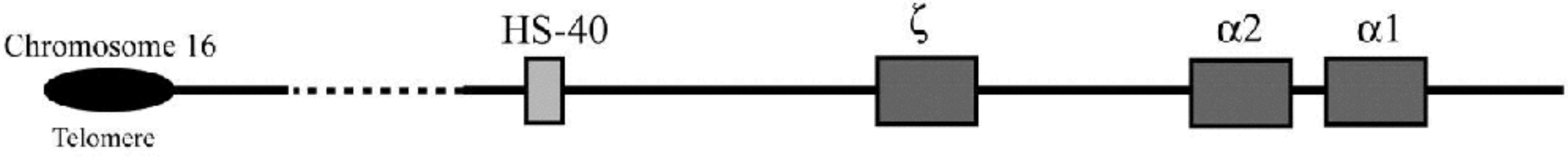
α(Alpha)-globin chain and **ζ(Zeta)**-globin chain consist of 141 Amino acids

- located on the short arm of ***Chromosome 16***

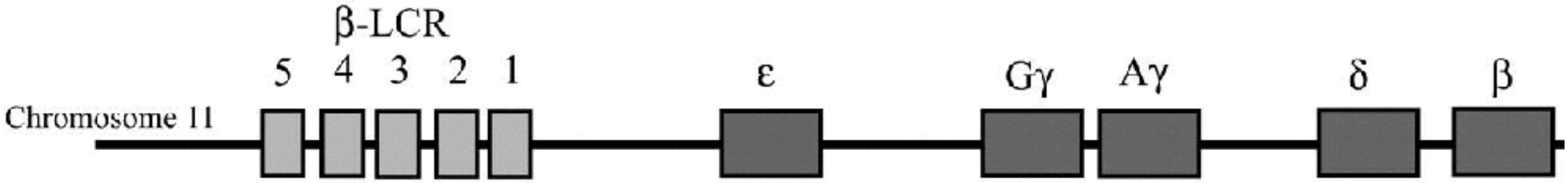
β(Beta), ɣ(Gamma), δ(Delta), ε(Epsilon)-globin chain consist of **146 Amino acids**

- located on the short arm of ***Chromosome 11***

Globin genes



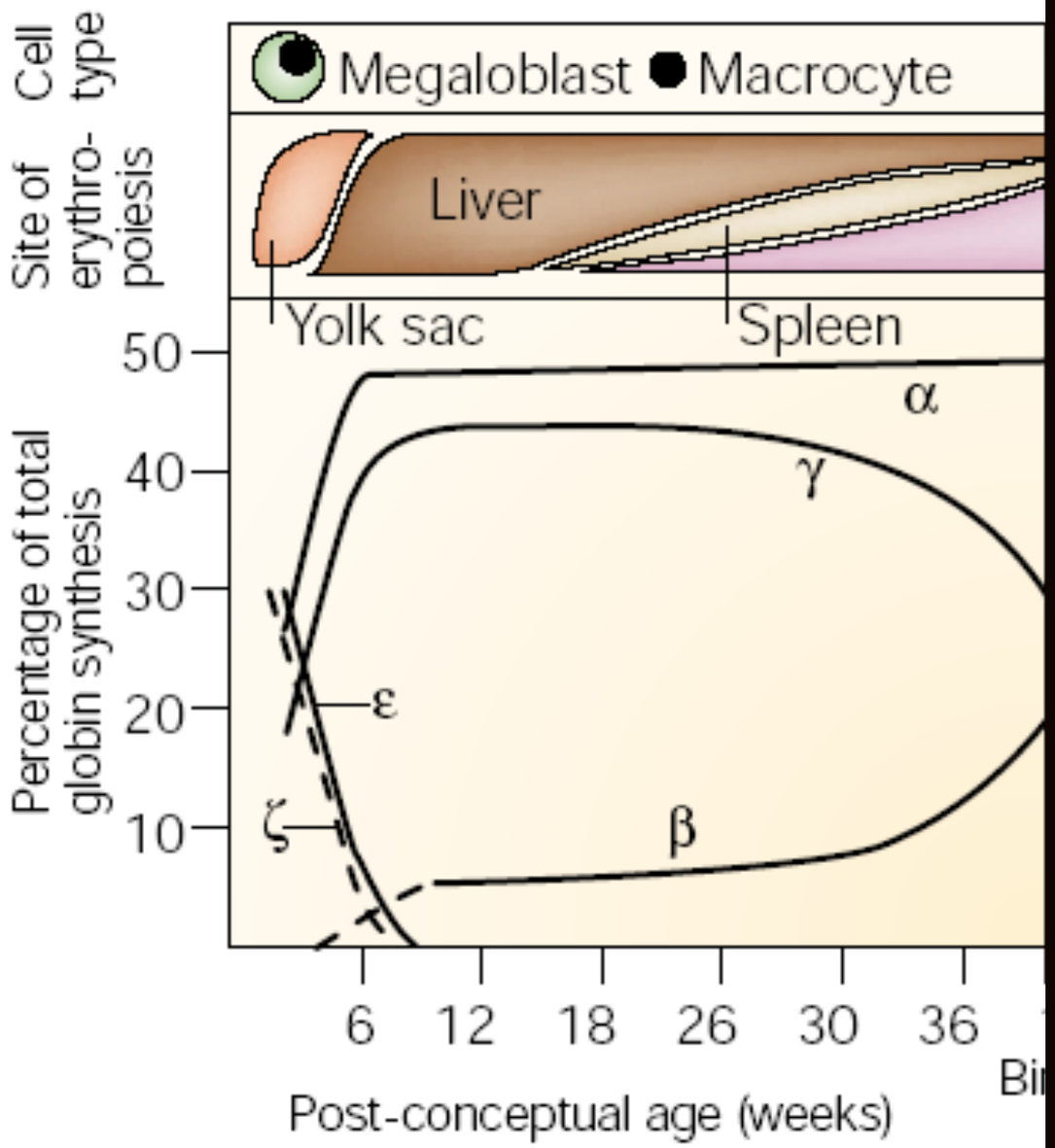
EMBRYO	FETUS	ADULT
ζ2ε2	α2γ2	α2β2
α2ε2		α2δ2
ζ2γ2		



Approximate scale:

10 kb

Globin gene synthesis



Embryonic Hemoglobin

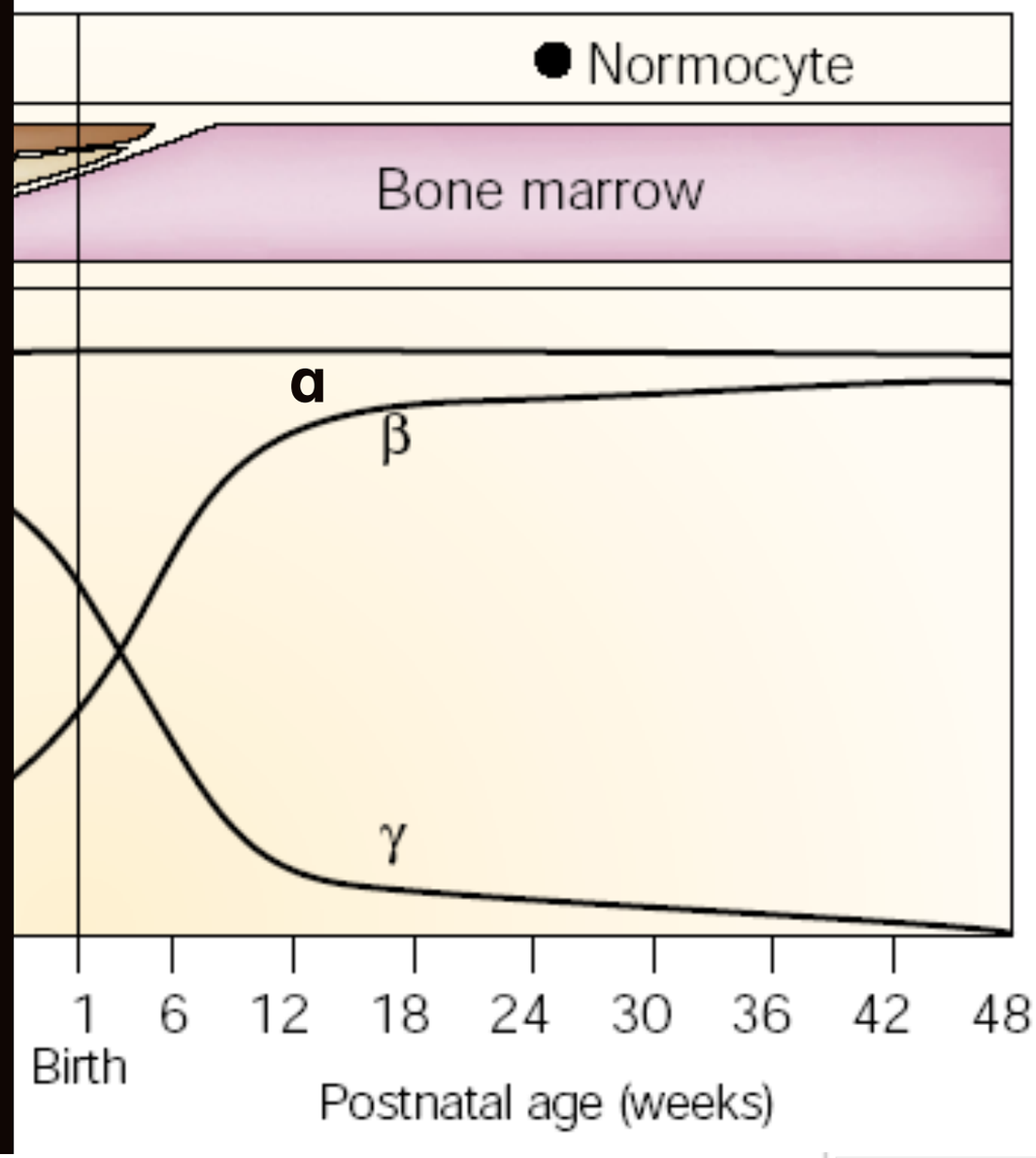
- ***Hb Gower I*** : ζ2 ε2
- ***Hb Gower II*** : α2 ε2
- ***Hb Portland*** : ζ2 ɣ2

Ref: Lessons from the thalasemia. Nature Reviews, Genetics, volume2, 2001

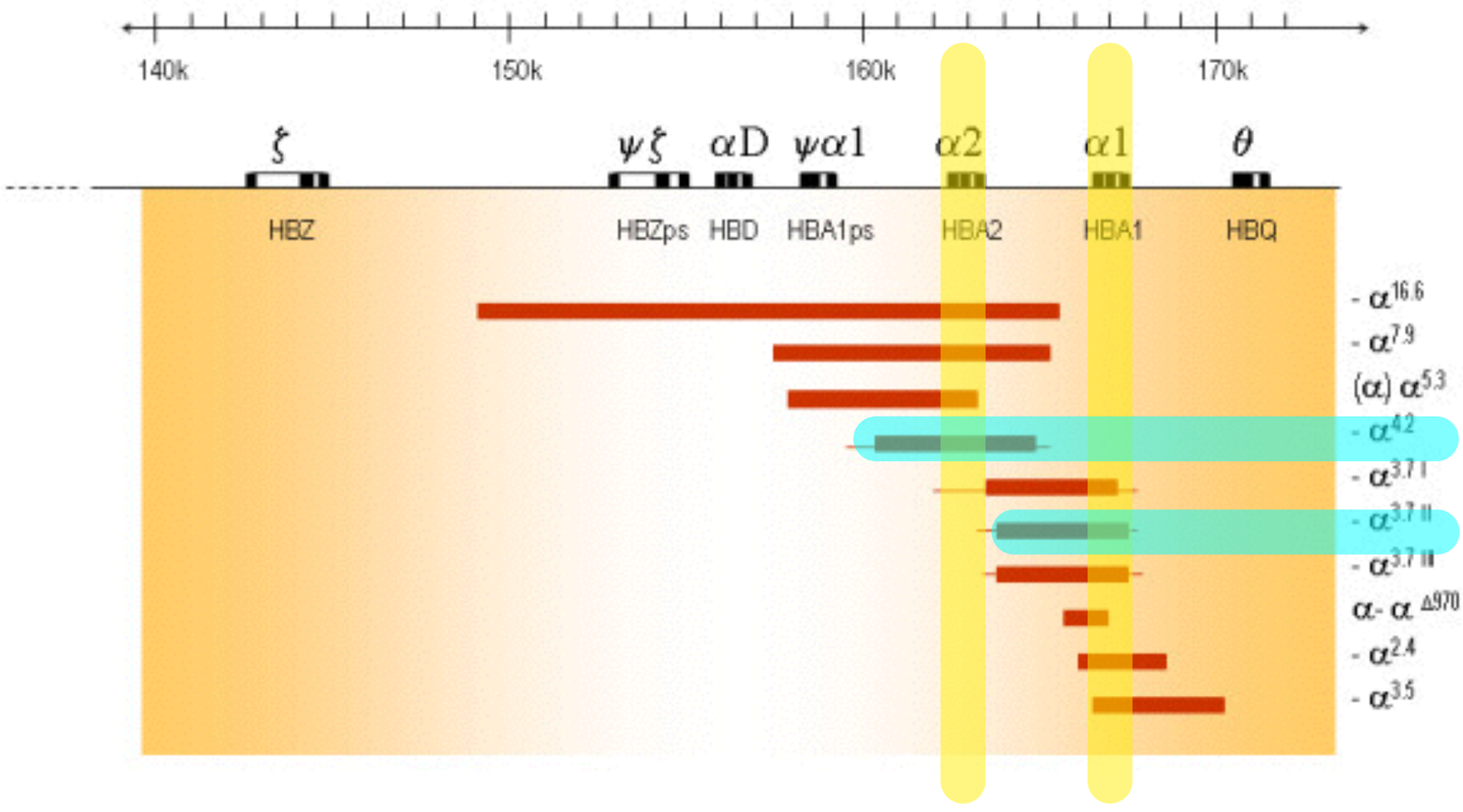
Globin gene synthesis

Fetal Hemoglobin

- ***Hb F*** : α2 ɣ2
- ***Hb A*** : α2 β2
- ***Hb A2*** : α2 δ2



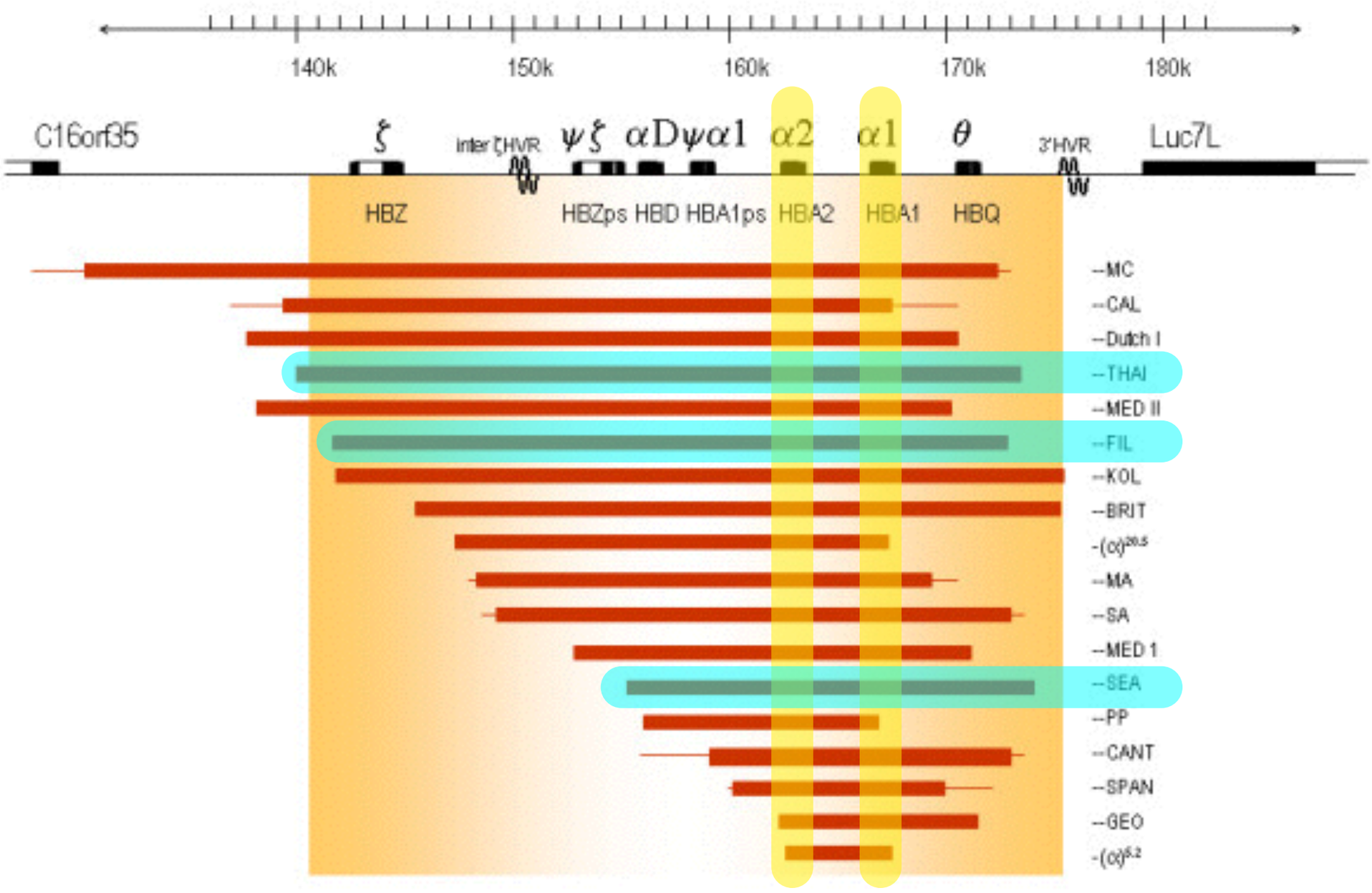
Deletion of alpha globin gene



Deletion of one alpha gene giving rise to alpha^{+}-thalassemia / alpha thal-2 deletion

Ref : Harteveld CL and Higgs DR, Orphanet J Rare 2010;5;13-33.

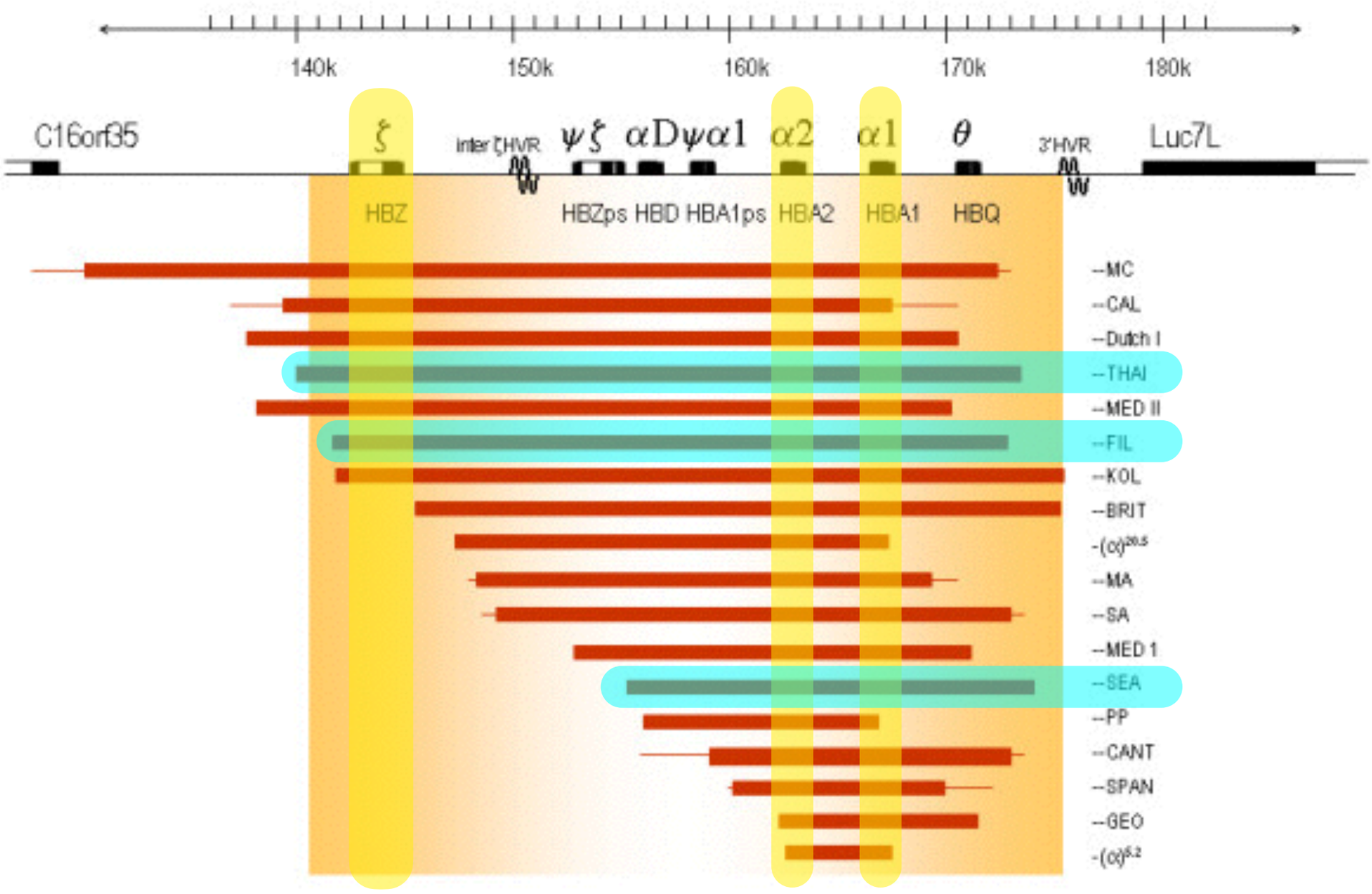
Deletion of alpha globin gene



Deletion of two alpha gene giving rise to alpha^{0}-thalassemia / alpha thal-1 deletion

Ref : Harteveld CL and Higgs DR, Orphanet J Rare 2010;5;13-33.

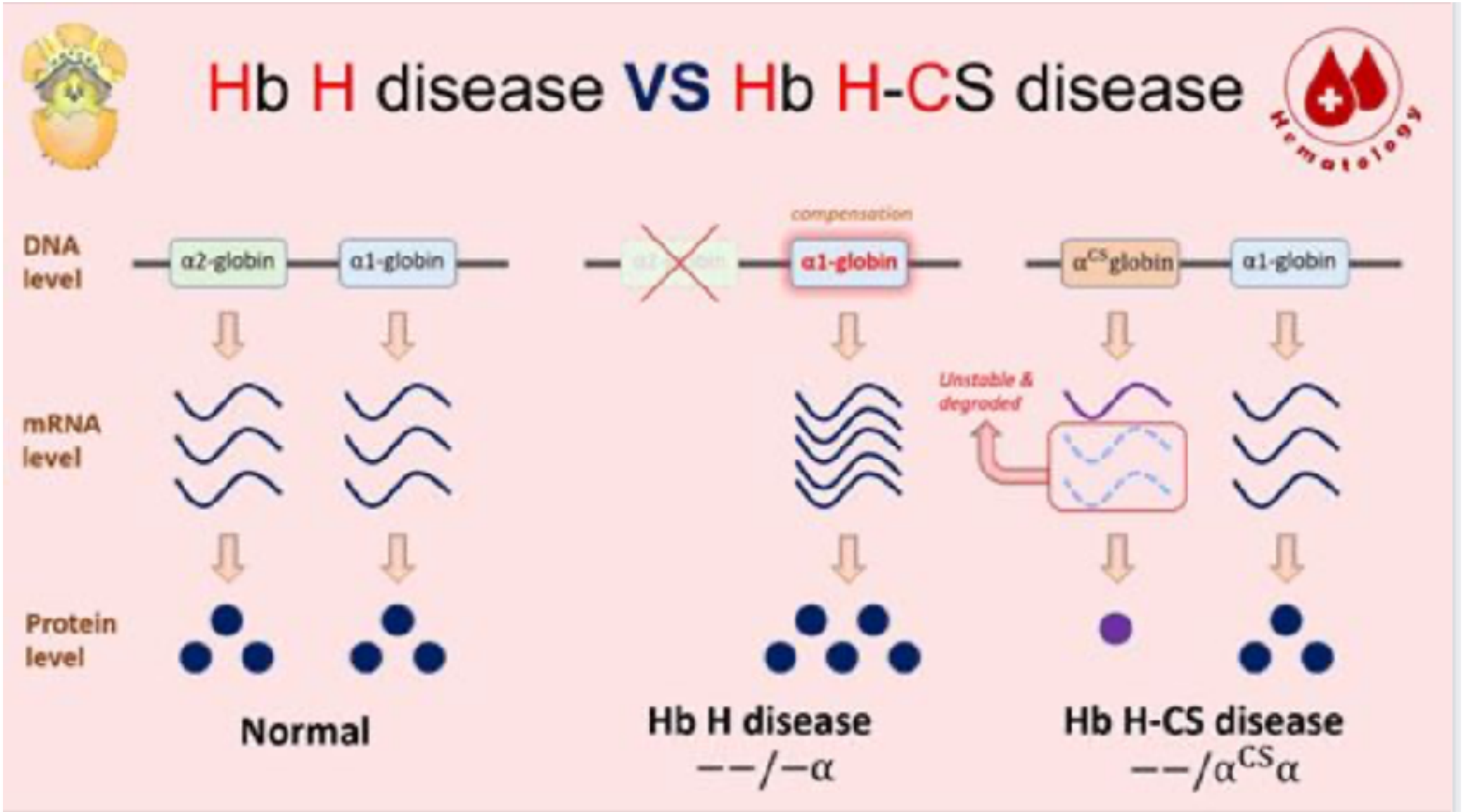
Deletion of alpha globin gene



Deletion of two alpha gene giving rise to alpha^{0}-thalassemia / alpha thal-1 deletion

Ref : Harteveld CL and Higgs DR, Orphanet J Rare 2010;5;13-33.

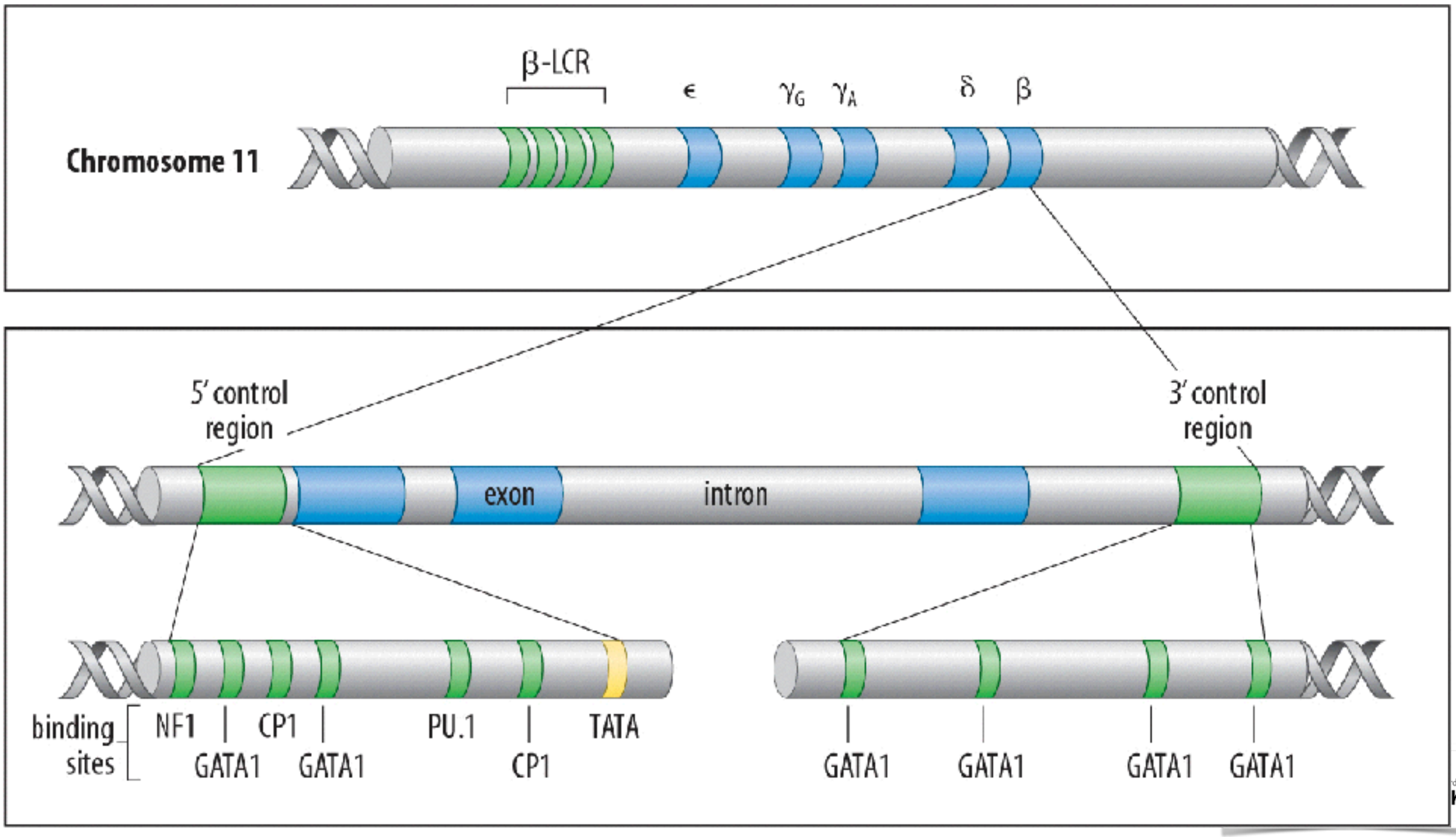
Non-deletion of alpha globin gene



Non-deletion of alpha gene giving the compensation from another alpha gene

Ref : Harteveld CL and Higgs DR, Orphanet J Rare 2010;5;13-33.

Mutation of Beta globin gene



Thalassemia disease

Thalassemia Major

Tranfusion-Dependent Thalassemia
TDT

- **Severe anemia presenting early in life**
- **Require lifelong RBC transfusion**
- **If untreated, lead to dead in first decade of life**

Homozygous Beta thalassemia (β^0/β^0)

Beta thalassemia/Hb E (β^0/β^E)

Bart's hydrops fetalis

Thalassemia Intermedia

Non-Transfusion-Dependent Thalassemia
NTDT

- **Mild anemia**
- **Diagnosed usually in late childhood**
- **Occasional blood transfusion may be required**

Beta thalassemia intermedia (β^0/β^+ or β^+/β^+)

Beta thalassemia/Hb E (β^0/β^Eor β^+/β^E)

Hemoglobin H disease

Beta thalassemia

β^0-thalassemia mutation	β^+-thalassemia mutation
Codon 41/42 deletion (-CTTT)	Codon 19 (A>G)
Codon 17 (A>T)	IVS I nt-5 (G>C)
Codon 35 (C>A)	IVS II nt-654 (C>T)
Codon 71/72 (+A)	Codon 26 (G>A)

Prevalence of alpha thalassemia

The Application of Clinical Genetics

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Clinical and molecular genetic features of Hb H and AE Bart's diseases in central Thai children

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Piya Rujkijyanont[1]
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*These authors contributed equally to this work

Prevalence of alpha thalassemia

Background: α-Thalassemia, one of the major thalassemia types in Thailand, is caused by either deletion or non-deletional mutation of one or both α-globin genes. Inactivation of three α-globin genes causes hemoglobin H (Hb H) disease, and the combination of Hb H disease with heterozygous hemoglobin E (Hb E) results in AE Bart's disease.

Objective: This study aimed to characterize the clinical and hematological manifestations of 76 pediatric patients with Hb H and AE Bart's diseases treated at Phramongkutklao Hospital,

- ***76 patients*** with Hb H and AE Bart's disease
- ***Non deletional*** Hb H and AE Bart's disease ***had severe symptoms*** than ***deletional types***.

patients with deletional AE Bart's disease. Non-deletional AE Bart's disease also had a history of urgent blood transfusion with the average of 6±0.9 times compared to 1±0.3 times in patients with deletional Hb H disease. The difference was statistically significant.

Conclusion: This study revealed the differences in clinical spectrum between patients with Hb H disease and those with AE Bart's disease in central Thailand. The differentiation of α-thalassemia is essential for appropriate management of patients. The molecular diagnosis is useful for diagnostic confirmation and genotype–phenotype correlation.

Keywords: genotype, phenotype, Hb H disease, AE Bart's disease, Thai children

Prevalence of beta thalassemia

Molecular analysis of beta-globin gene mutations among Thai beta-thalassemia children: results from a single center study

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Prevalence of beta thalassemia

Table 1 Genotype of 65 clinically manifested beta-thalassemia patients

Genotype	N (%)
Beta-thalassemia major	60 (92.3)
Codon 71/72 (+A)/beta[E]	1 (1.5)
Codon 19 (A>G) or Hb Malay/beta[E]	1 (1.5)
Beta-thalassemia intermedia	5 (7.7)
Codon 41/42 (-TCTT)/beta[E]	1 (1.5)
3.4 kb deletion/beta[E]	2 (3.1)
Codon 17 (A>T)/beta[E]	1 (1.5)
IVS-I-1 (G>T)/beta[E]	1 (1.5)
Total	65 (100)

Abbreviations: HbE, hemoglobin E; Hb, hemoglobin.

Table 2 The frequency of beta-thalassemia mutations in 88 alleles

Beta-thalassemia mutations	Type	Number of alleles (%)
Six common mutations		
Codon 41/42 (-TCTT)	0	33 (37.5)
Codon 17 (A>T)	0	23 (26.1)
IVS-I-5 (G>C)	+ (severe)	7 (8.0)
IVS-II-654 (C>T)	0	6 (6.8)
IVS-I-1 (G>T)	0	4 (4.5)
Codon 71/72 (+A)	0	2 (2.3)
Total		88 (100)

Abbreviation: Hb, hemoglobin.

Prevalence of Thalassemia

NORTH

α-thalassemia	30%
α^0-thal.	5-12%
α^+-thal.	19-26%
β-thalassemia	9-10%
Hb E	8%

CENTRAL

α-thalassemia	20-25%
α^0-thal.	3.5%
α^+-thal.	16%
β-thalassemia	3%
Hb E	13-19%

NORTHEAST

α-thalassemia	20%
α^0-thal.	3%
α^+-thal.	12%
β-thalassemia	6%
Hb E	20-60%

SOUTH

α-thalassemia	16%
α^0-thal.	2.5%
α^+-thal.	14%
β-thalassemia	2-4%
Hb E	9-11%

Courtesy of Thalassemia Foundation of Thailand

Prevalence of Thalassemia

Disease	Couple at risk (per year)	Birth (per year)	Living Patient
Hb H disease	28,000	7,000	420,000
Total	48,500	12,125	523,750

มีการศึกษาพบว่า การรักษาผู้ป่วย *Beta thal/Hb E* หนึ่งรายตลอดอายุขัย *30* ปี จะเสียค่ารักษาพยาบาลเป็นเงิน *20,825,000* บาท

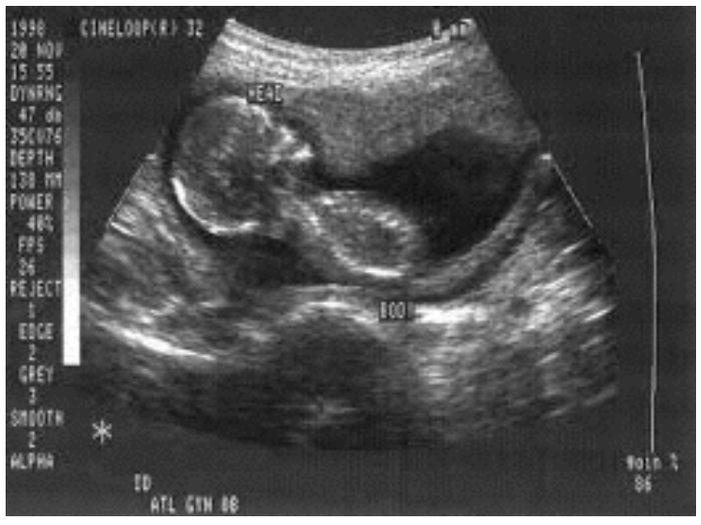
Ref : แนวทางการวินิจฉัยโรคธาลัสซีเมีย พุทธศักราช 2557

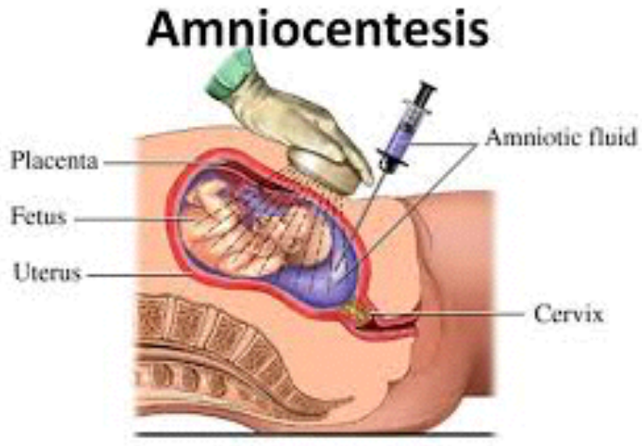
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

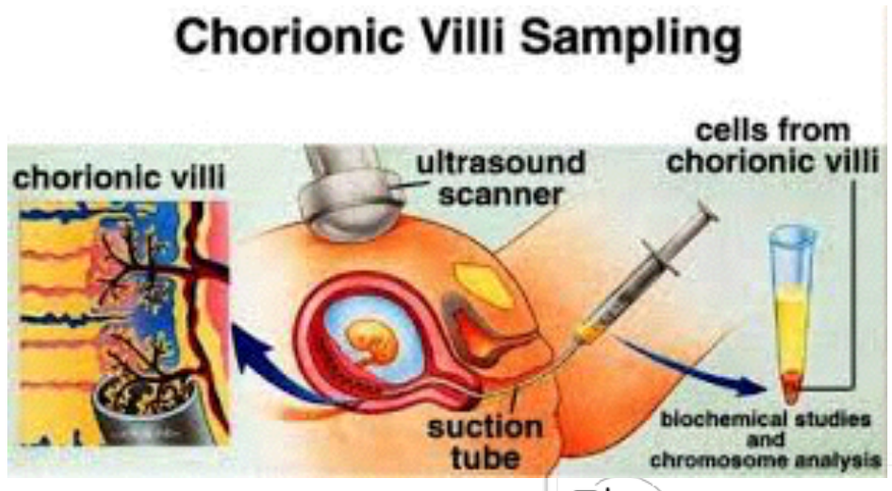
Prenatal Diagnosis

เป้าหมายการตรวจเพื่อคัดกรอง

- **Hb Bart's hydrop fetalis**
- **Homozygous beta thalassemia**
- **Beta thalassemia / Hemoglobin E**



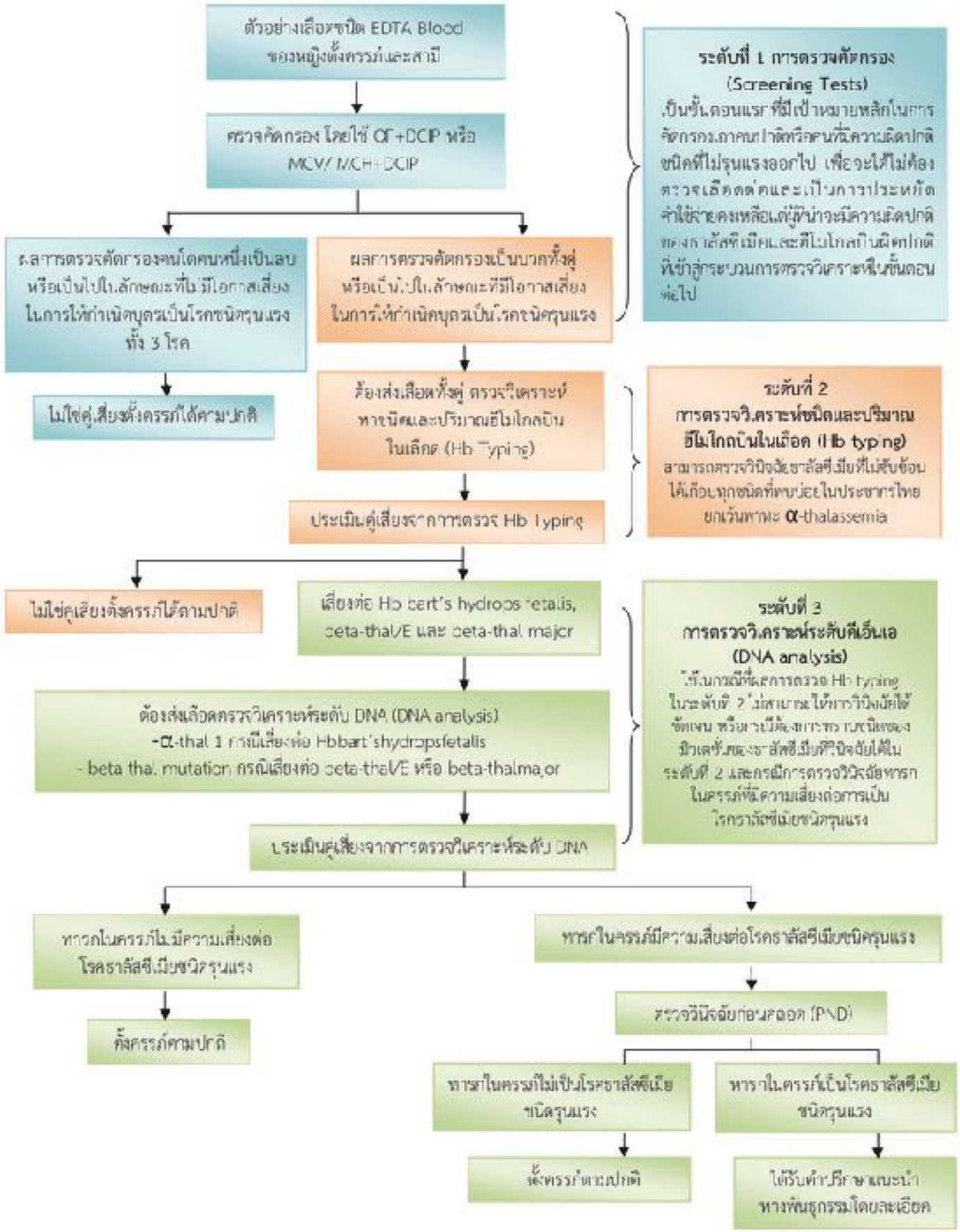




Prenatal Diagnosis

การเก็บตัวอย่างทารก

วิธี	GA	Risk	สิ่งที่ได้	สามารถส่งตรวจ	Point
Amniocentesis	16-20	0.5%	Cell	DNA Study	ถ้า + อาจต้องใช้เวลา repeat
Chorionic Villus Sampling	10-13	0.5-1%	Cell	DNA Study	ถ้า GA มากกว่านี้ DNA อาจไม่ค่อยดี
Cordocentesis	18-22	2.5%	Cell + Blood	DNA Study + Hb Typing	GA<18 : Cord เล็ก ดูดยาก GA>22 : ถ้า + ทำอะไรต่อไม่ได้แล้ว



ภาพที่ 3: ขั้นตอนการตรวจทางห้องปฏิบัติการเพื่อวินิจฉัยธาลัสซีเมียและฮีโมโกลบินผิดปกติในหญิงตั้งครรภ์และสามี

NHSO Protocol

การป้องกันและควบคุมโรคโลหิตจางธาลัสซีเมีย

Screening : OF/ DCIP/ MCV and MCH

If abnormal : checked husband

Confirmation : Hb typing for **Bart's hydrop fetalis, Homo Beta, B thal/Hb E**

Confirm with DNA : **alpha thal-1 del, beta thal**

Prenatal diagnosis : CVS, Amniocentesis, Cordocentesis

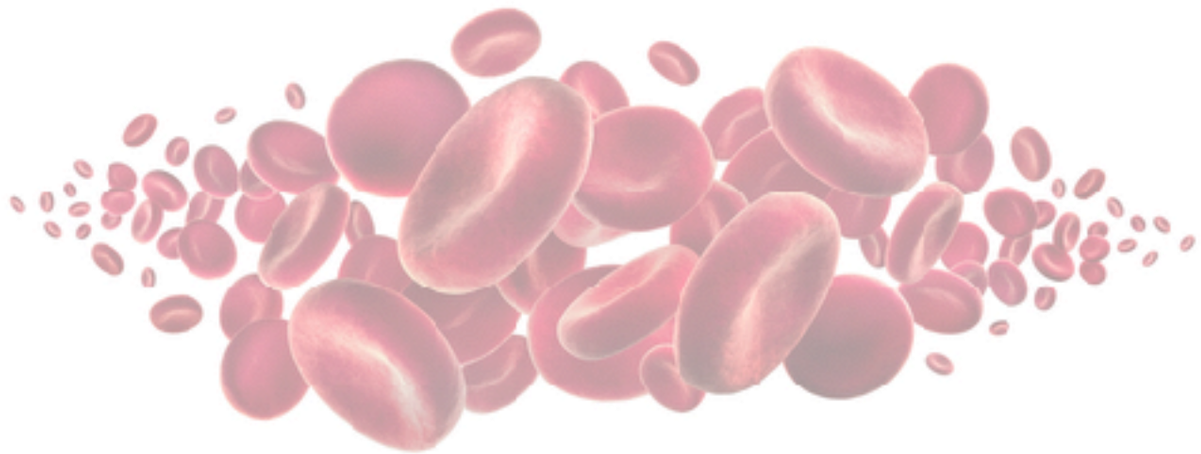
งบประมาณที่ใช้ไป : **2557** 28M // **2558-2559** 37M // **2560** 40M

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

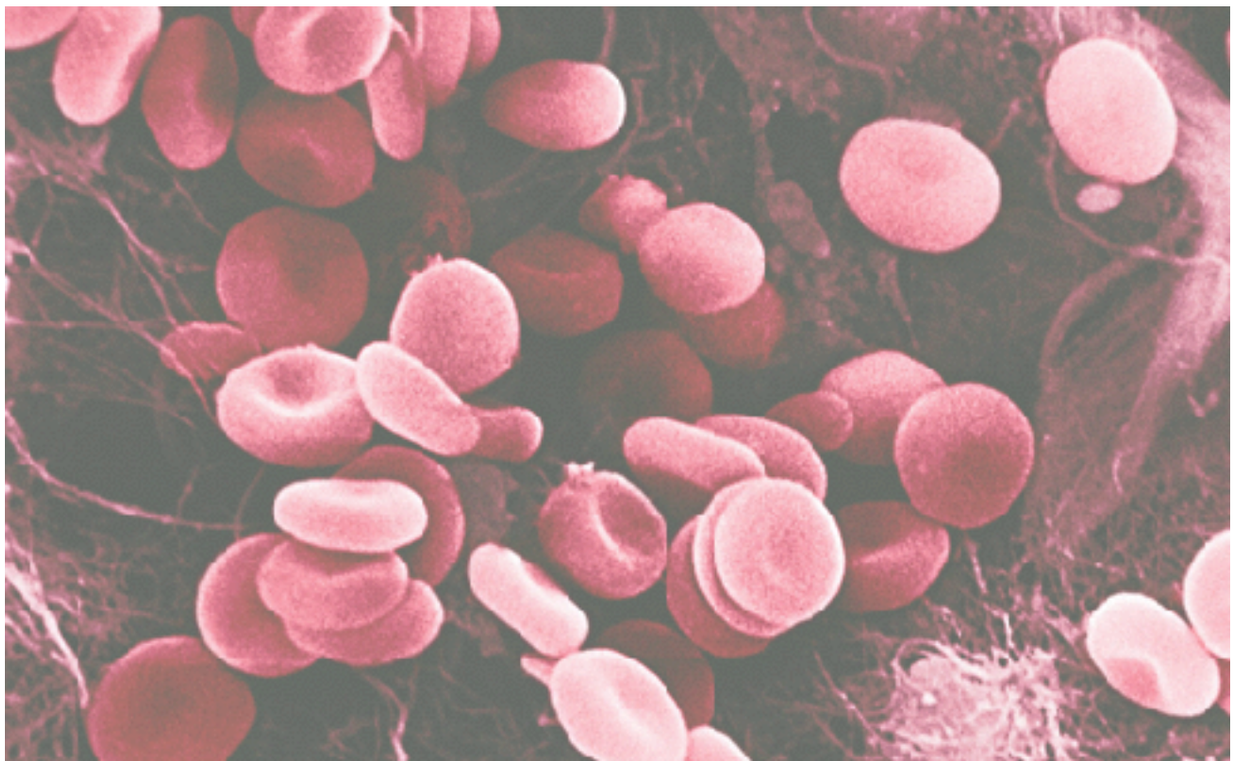
NHSO Protocol

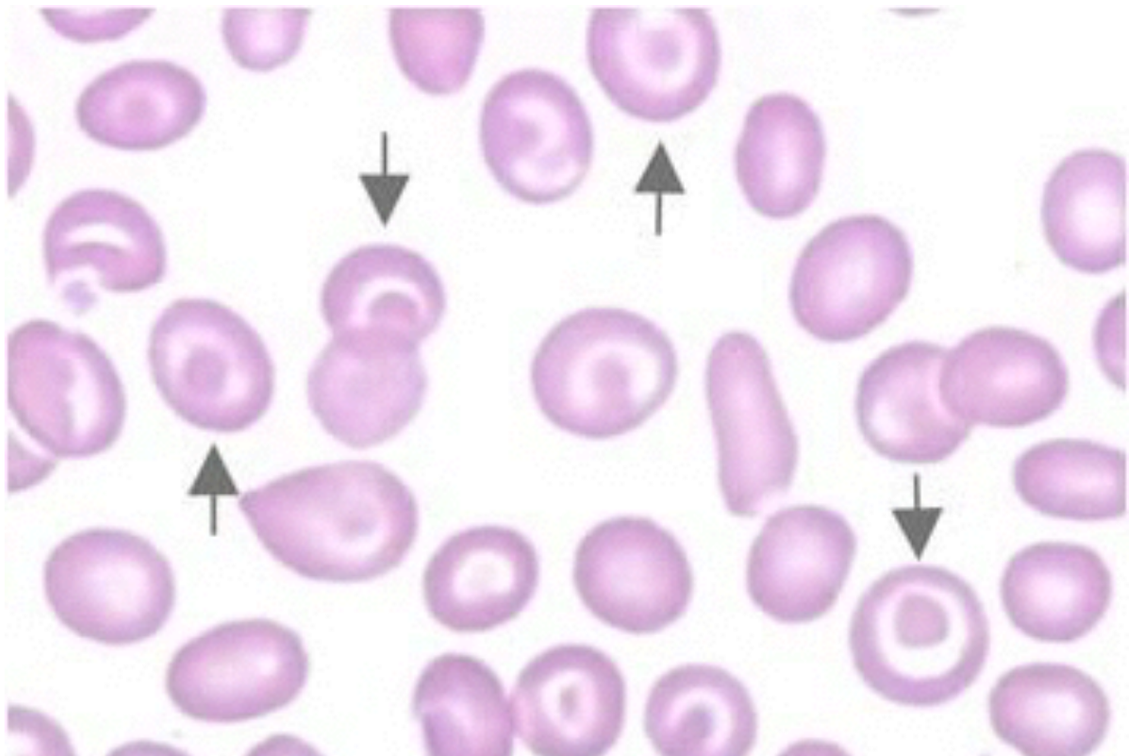
การสนับสนุนแก่หน่วยบริการที่ลงทะเบียน
ผู้ป่วยโรคโลหิตจางธาลัสซีเมียชนิดรุนแรง
ที่ต้องได้รับเลือดประจำ (regular transfusion)
เพื่อรักษาระดับ Hb 9.5-10.5 g/dl

ปี	จำนวนผู้ป่วย (ราย)	งบประมาณ (ล้านบาท)
2557	4532	10
2558	9835	40
2559	11940	40
2560	11439	130

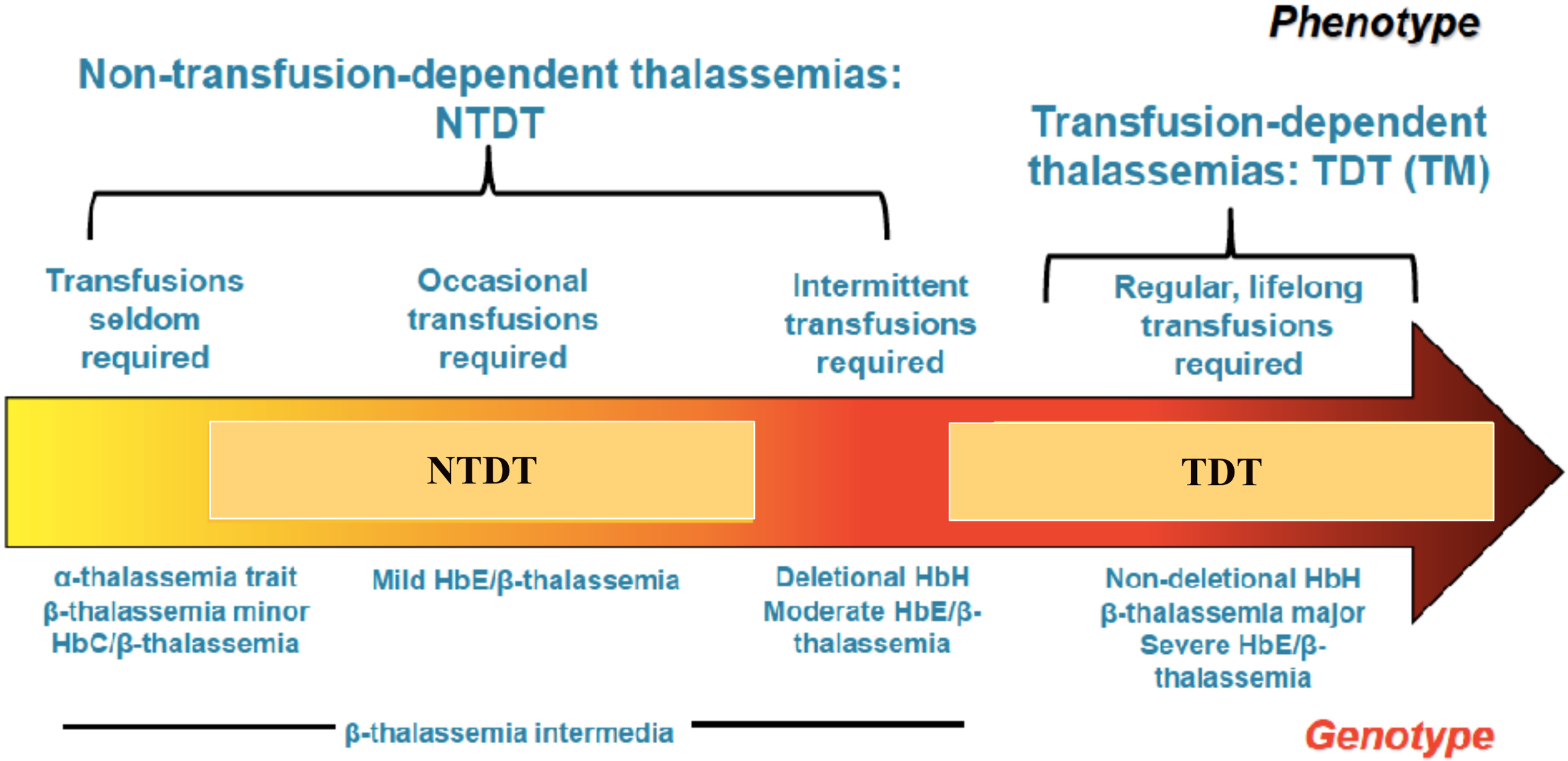


Clinical features

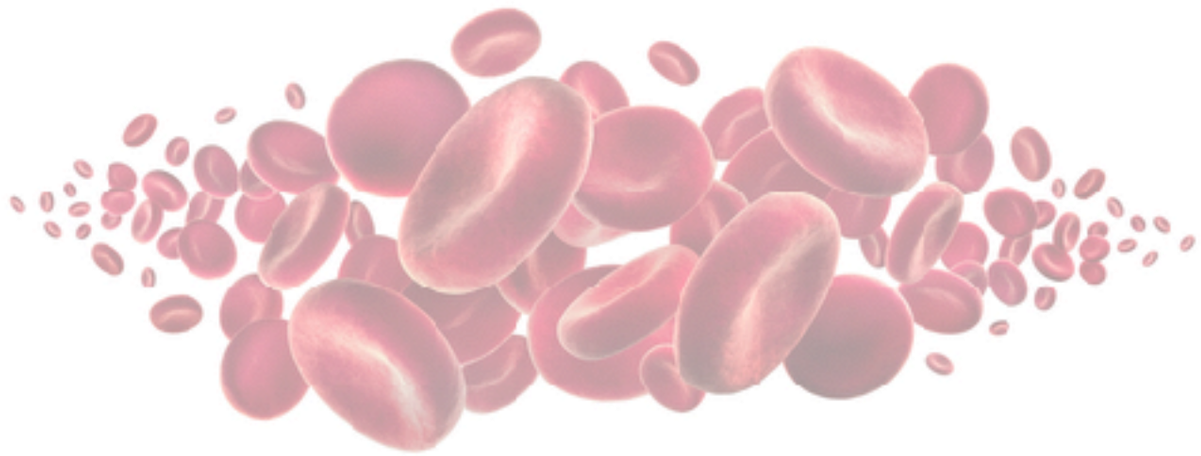




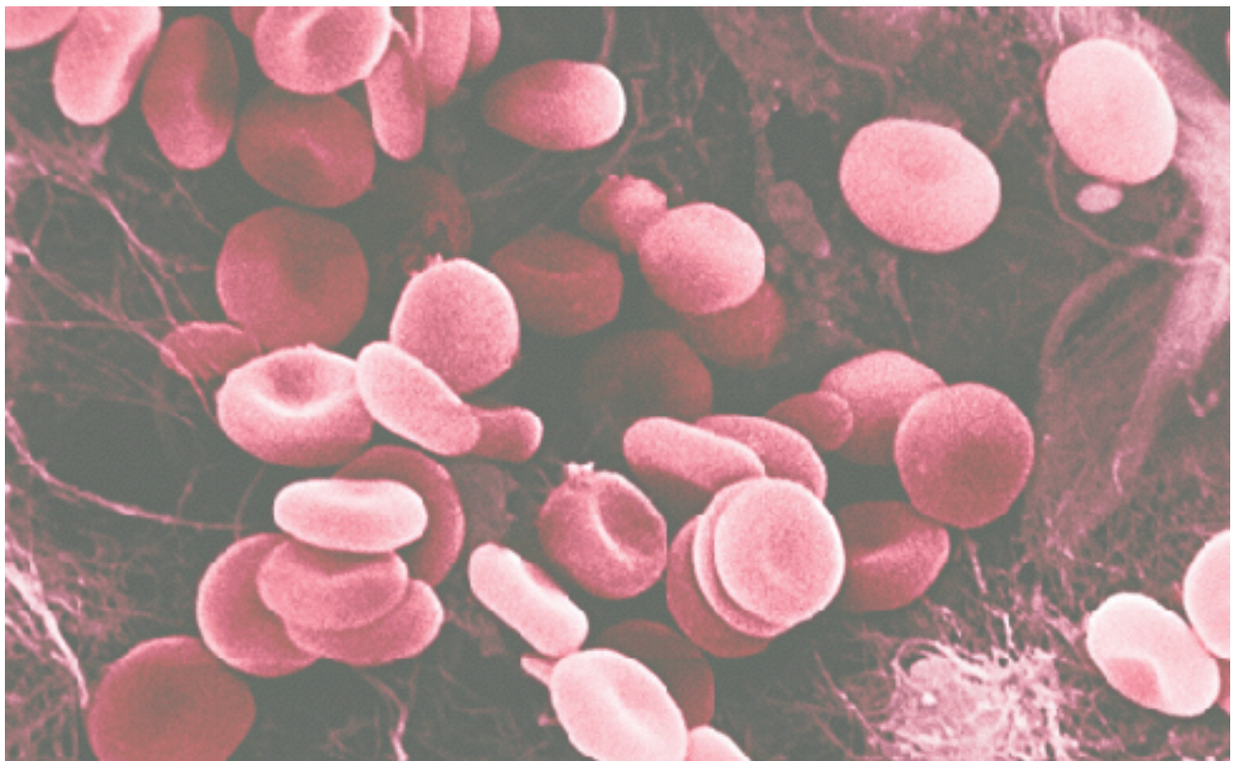
Spectrum of Thalassemia

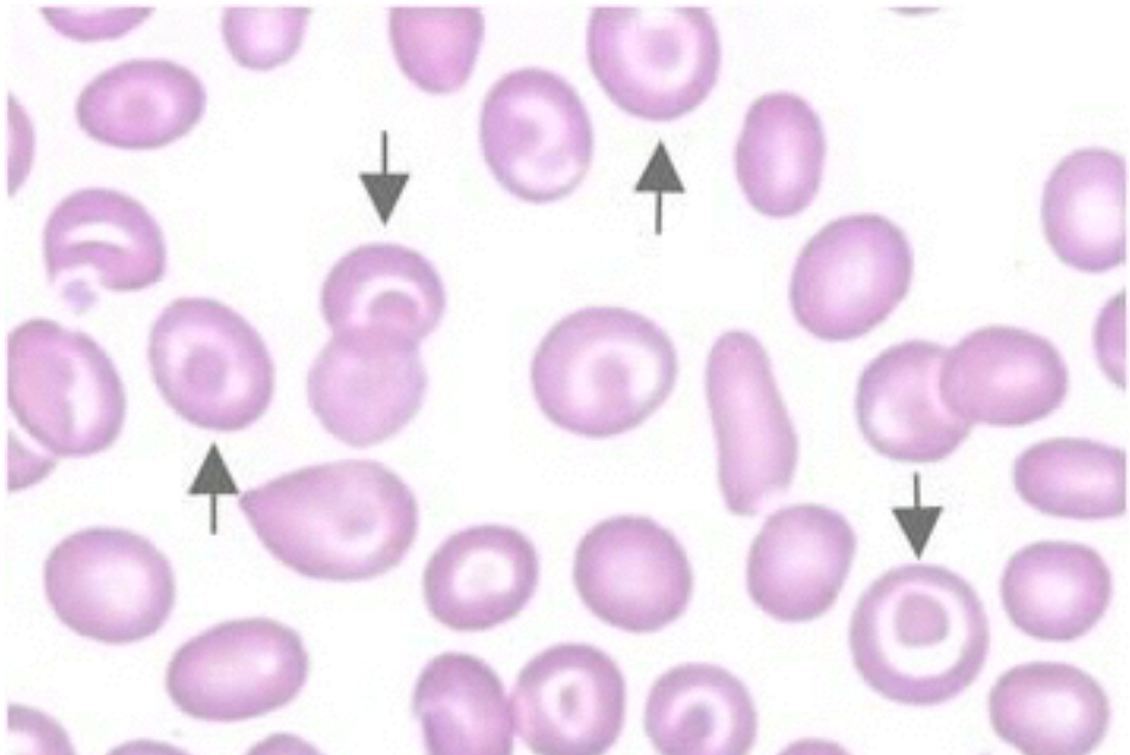


[1]Muncie HL *et al. Am Fam Physician* 2009;80:339; [2]Galanello R *et al. Orphanet J Rare Dis* 2010, 5:11; [3]Harteveld C *et al. Orphanet J Rare Dis* 2010, 5:13; [4]Cohen AR *et al. Hematology Am Soc Hematol Educ Program* 2004;14



Diagnosis

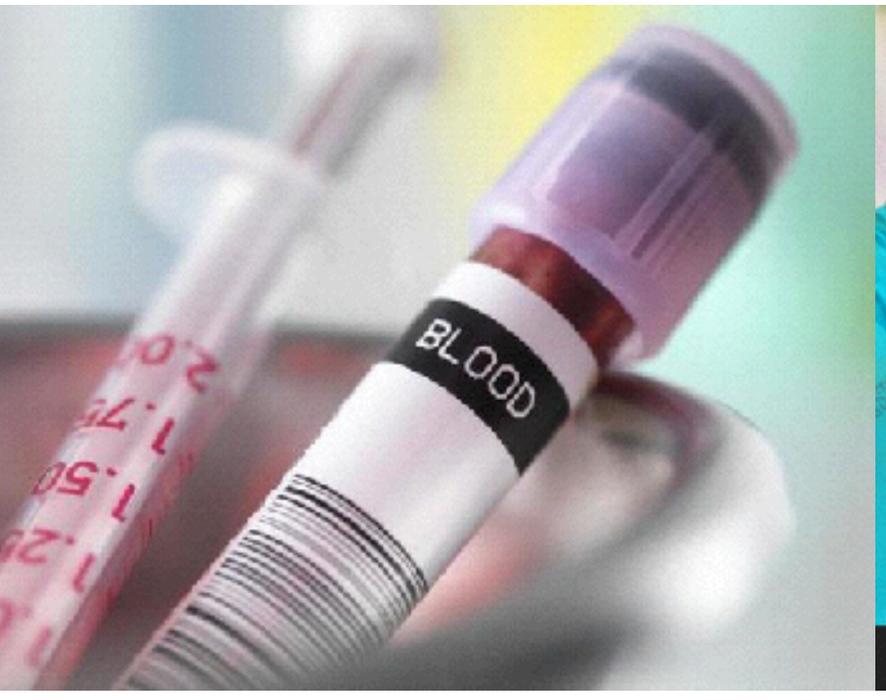




Screening Test

Screening test for Thalassemia *(2 tests for screening)*

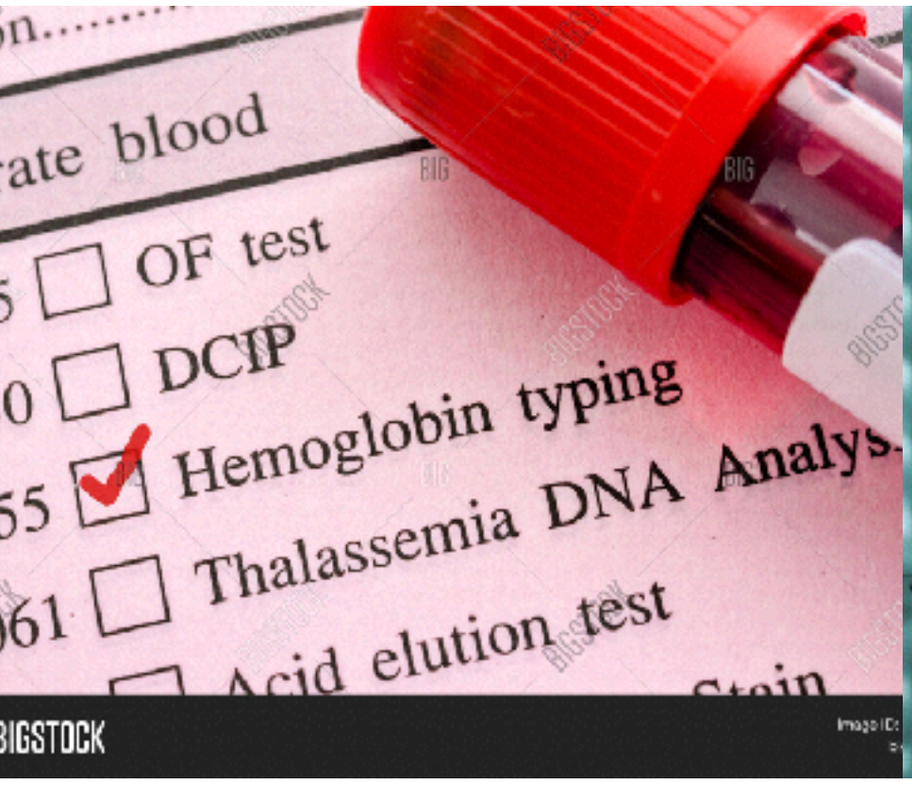
- Red cell Indices (MCV, MCH)
- One tube osmotic fragility test
- DCIP - DiChlorophenolIndoPhenol preparation test

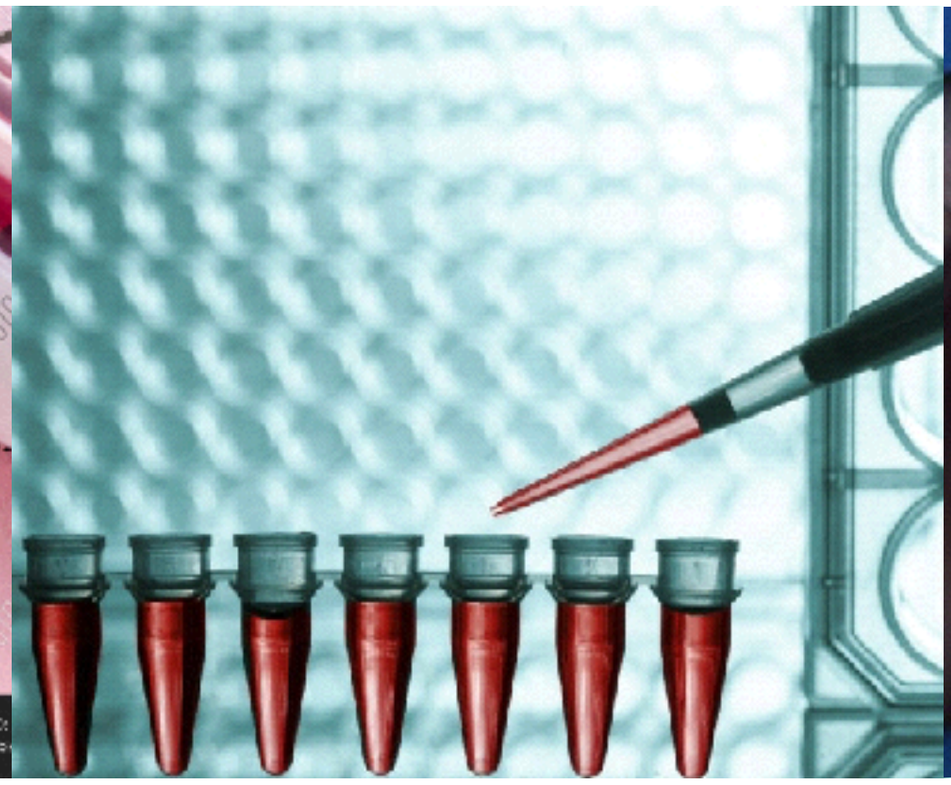


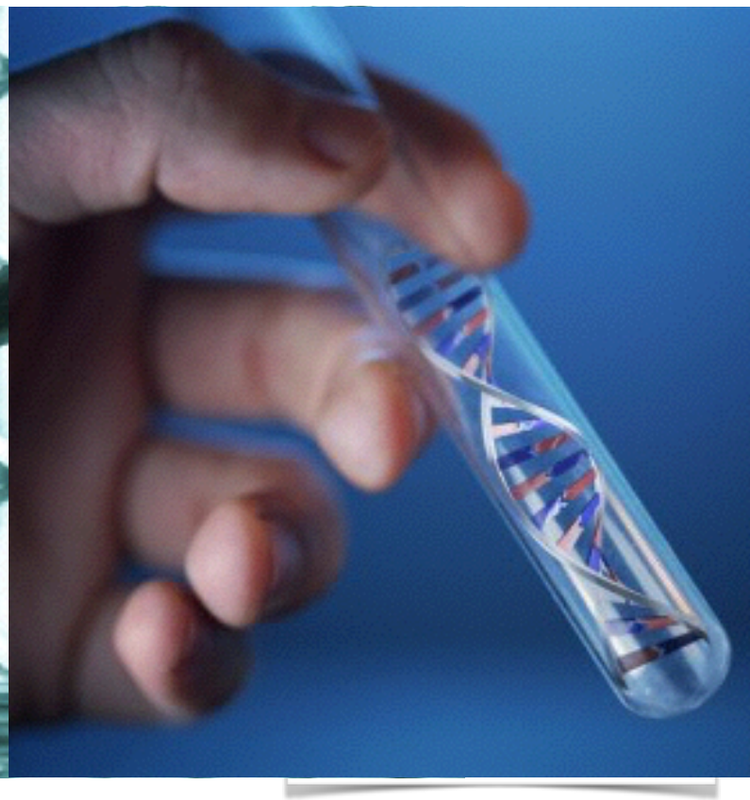
Confirmation Test

Confirmation test for Thalassemia

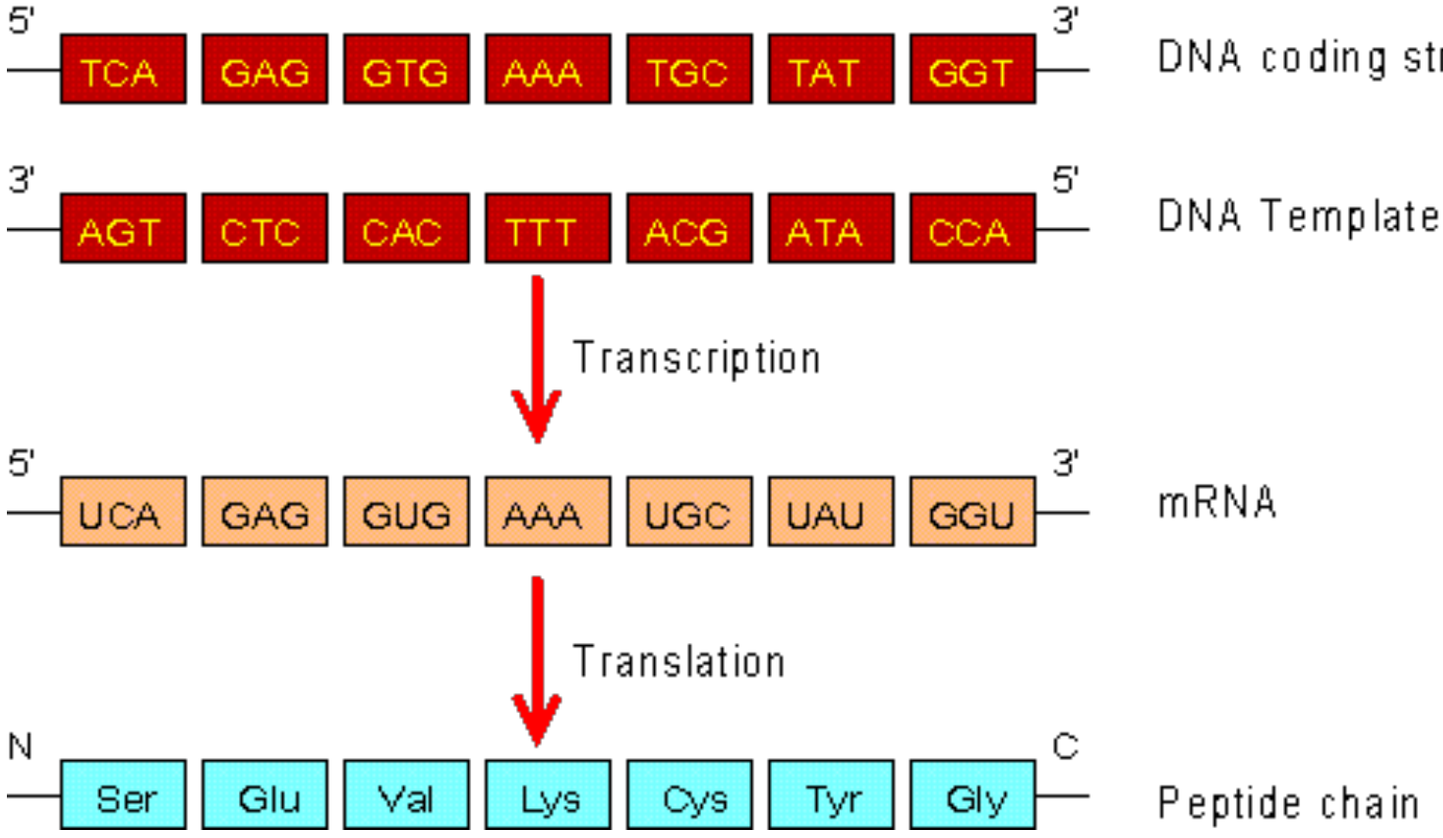
- Hemoglobin typing
- Molecular testing







Confirmation Test

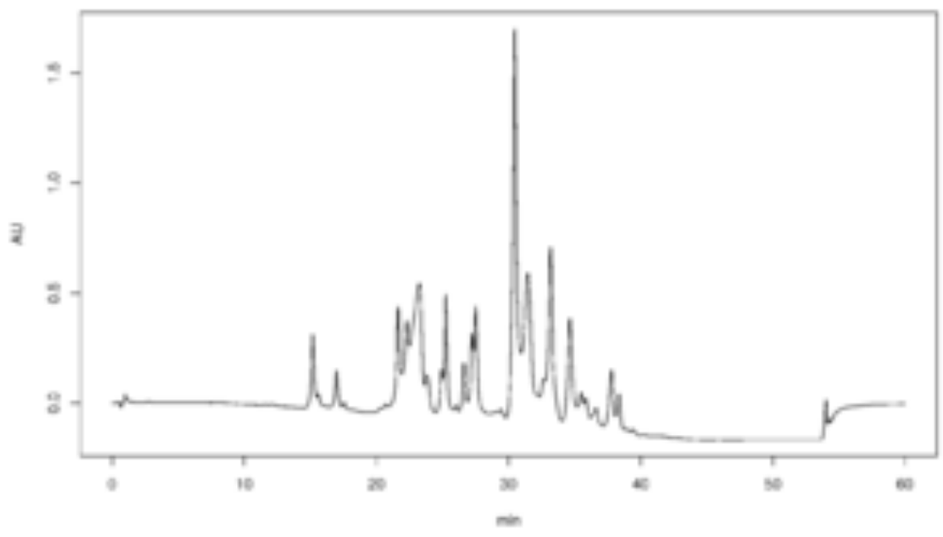


Genetic testing

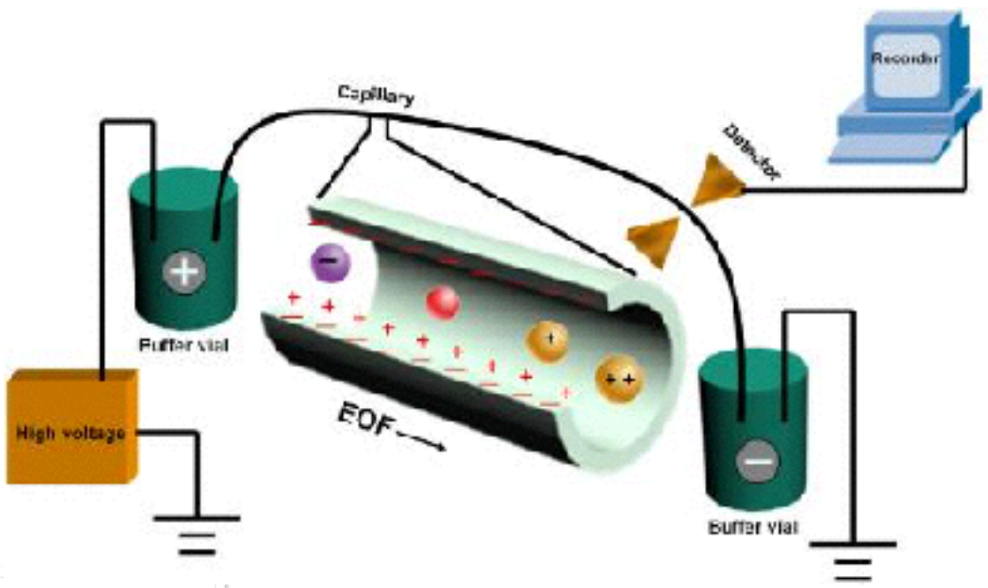
Hb typing

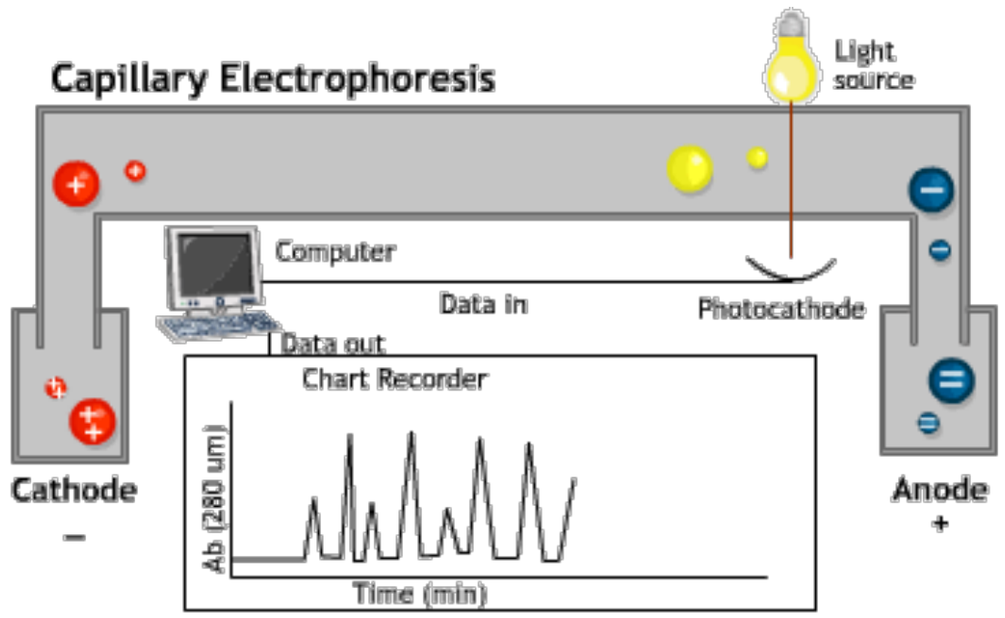
Hemoglobin typing

HPLC



Capillary Electropheresis

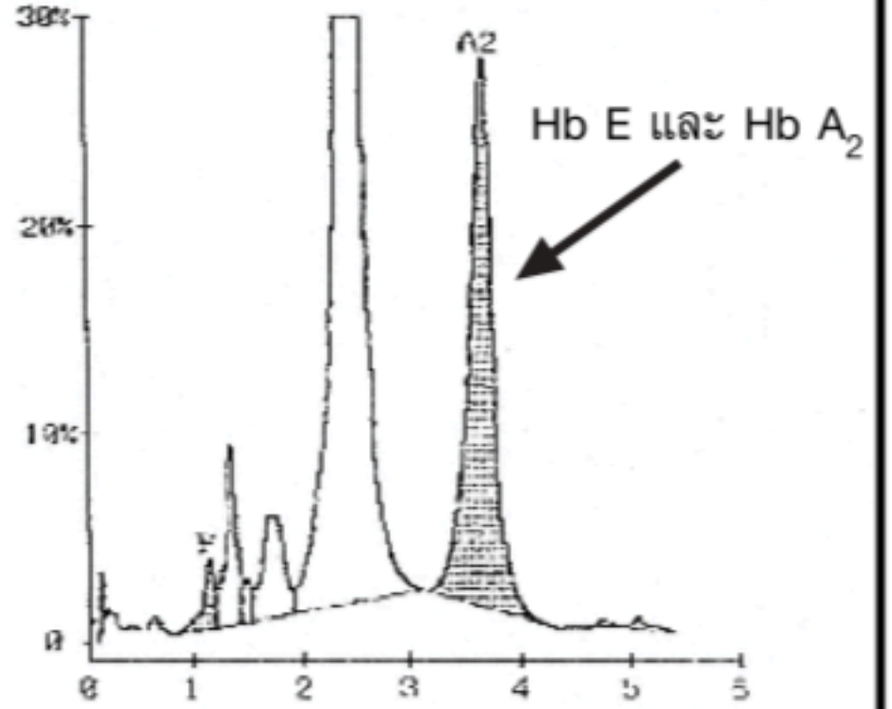




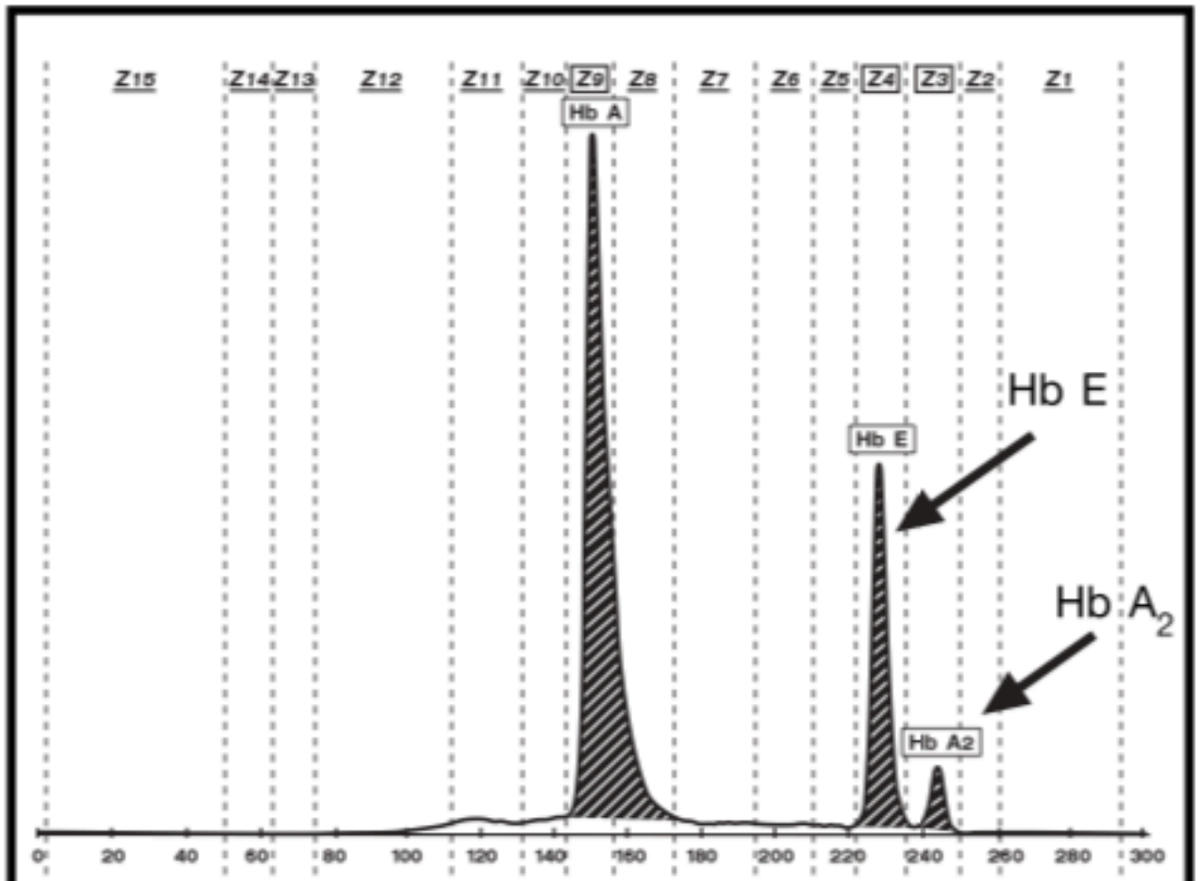
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Hemoglobin typing

ANALYTE ID	%	TIME	AREA
F	1.3	1.12	32713
P2	3.4	1.32	84862
Unknown 1	0.7	1.44	17745
P3	4.1	1.67	101871
Ao	62.4	2.43	1548798
A2	28.1	3.60	697043
	TOTAL AREA		2392232
F	1.3%	A2	28.1%



High Pressure Liquid Chromatography



Hemoglobin Electrophoresis

Fractions	%	Ref. %	Ref. g/dl
Hb A	72.5		
Hb E	23.7		
Hb A2	3.8		

Capillary Electrophoresis

Hemoglobin typing

Must know!!!			
Hb A	α2 β2	**Hb H**	β4
Hb A2	α2 δ2	**Hb Bart's**	ɣ4
Hb F	α2 ɣ2		

Normal : (αα,αα)(β,β)

A. Decrease production : ปริมาณ *Hb*

B. Abnormal production *(amino acid)*

Variant Hb Ex; Hb E, Hb Cs

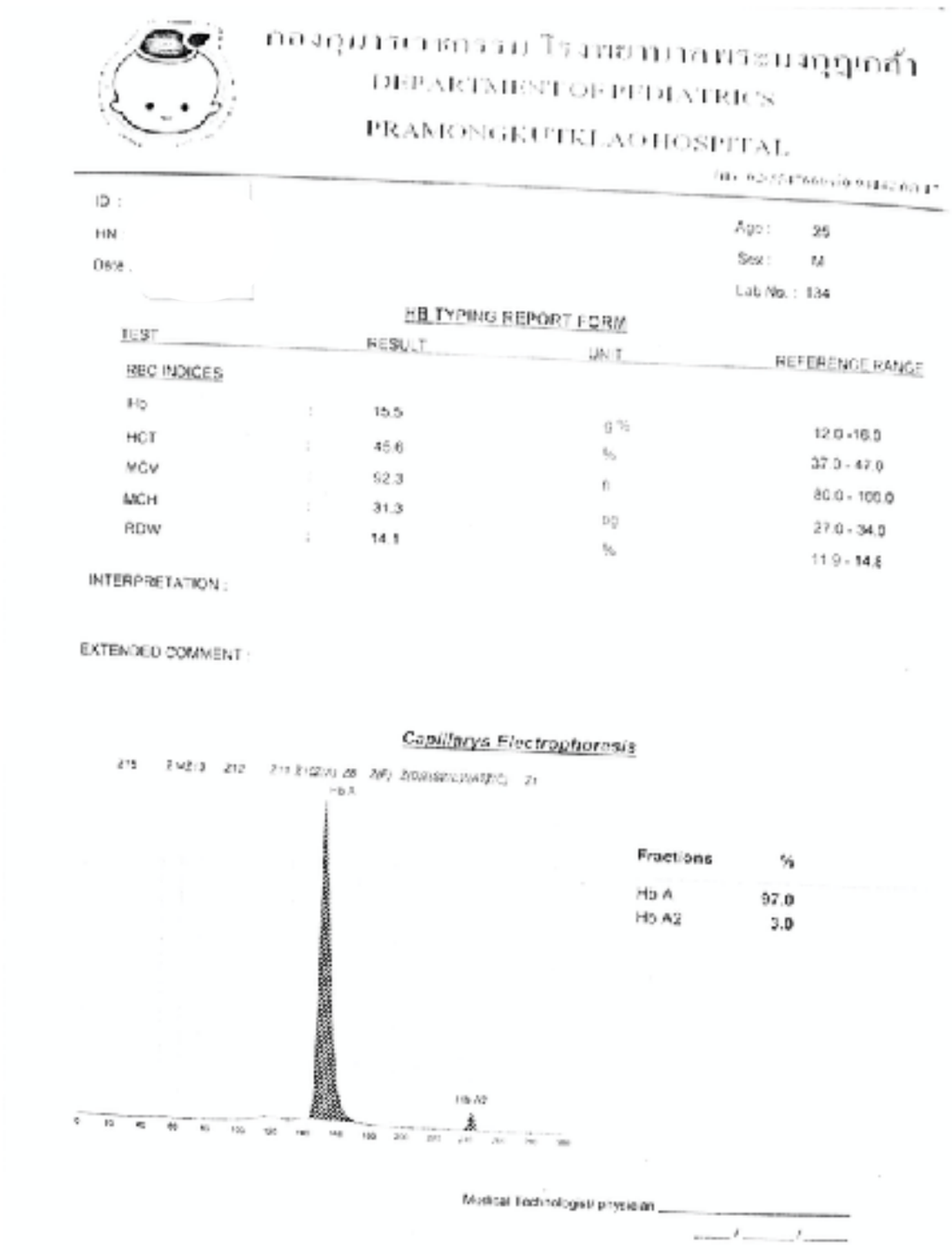
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Thalassemia

Hb type: Criteria for diagnosis

Condition	Hb typing
Normal	A_2 A (A_2 2.5-3.5%)
a-thal 1 trait	A_2 A (A_2 2.5-3.5%)*
a-thal 2 trait	A_2 A (A_2 2.5-3.5%)*
b-thal trait	A_2 A (A_2 > 4%)
Hb E trait	EA (E= 25- 35 %)
Hb E homozygous	EE (E >85%)
Hb CS trait	CS A_2 A (CS 1-2 %)
Hb CS homozygous	CS A_2 A (CS 3-6%

Interpretation!!!



DEPARTMENT OF PEDIATRICS

PRAMONGKUTKLAO HOSPITAL

ID :

HN

Date :

Age : 25

Sex : M

Lab No. : 134

HB TYPING REPORT FORM

TEST	RESULT	UNIT	REFERENCE RANGE
RBC INDICES			
Hb	15.5	g %	12.0 - 16.0
HCT	45.6	%	37.0 - 47.0
MCV	92.3	fl	80.0 - 100.0
MCH	31.3	pg	27.0 - 34.0
RDW	14.1	%	11.9 - 14.6

INTERPRETATION :

EXTENDED COMMENT :

Capillarys Electrophoresis

Fractions	%
Hb A	97.0
Hb A2	3.0

Medical technologist/ physician _____

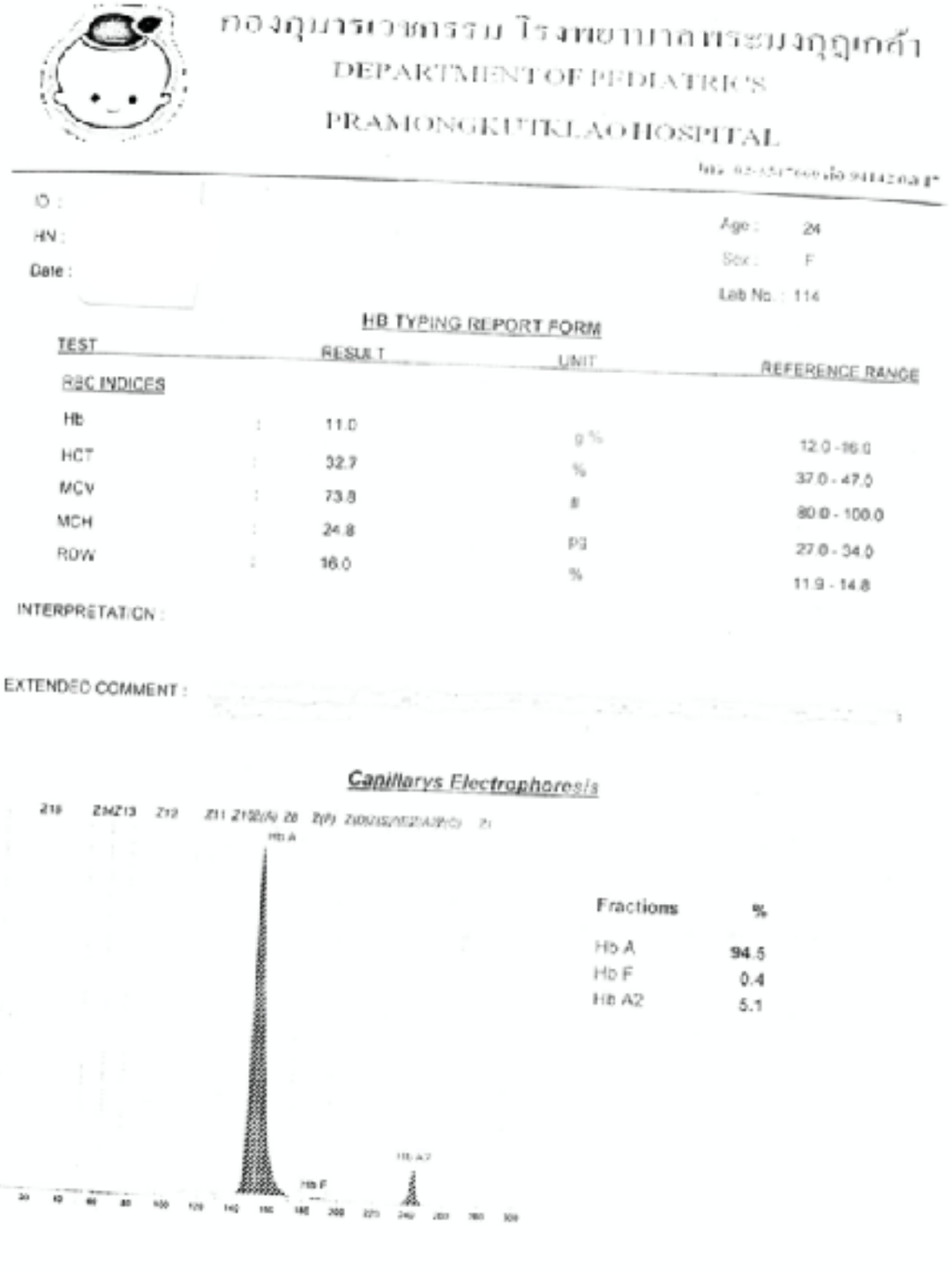
____ / ____ / ____

Hb	15.5 g/dl
Hct	45.6 %
MCV	92.3 fl
MCH	31.3 Pg
RDW	14.1 %

Hb A	97.0	%
Hb A2	3.0	%

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Interpretation!!!



กองกุมารเวชกรรม โรงพยาบาลพระมงกุฎเกล้า
DEPARTMENT OF PEDIATRICS
PRAMONGKUTKLAO HOSPITAL

ID :
HN :
Date :

Age : 24
Sex : F
Lab No. : 114

HB TYPING REPORT FORM

TEST		RESULT	UNIT	REFERENCE RANGE
RBC INDICES				
Hb	:	11.0	g %	12.0 - 16.0
HCT	:	32.7	%	37.0 - 47.0
MCV	:	73.8	fl	80.0 - 100.0
MCH	:	24.8	Pg	27.0 - 34.0
RDW	:	16.0	%	11.9 - 14.8

INTERPRETATION :

EXTENDED COMMENT :

Capillarys Electrophoresis

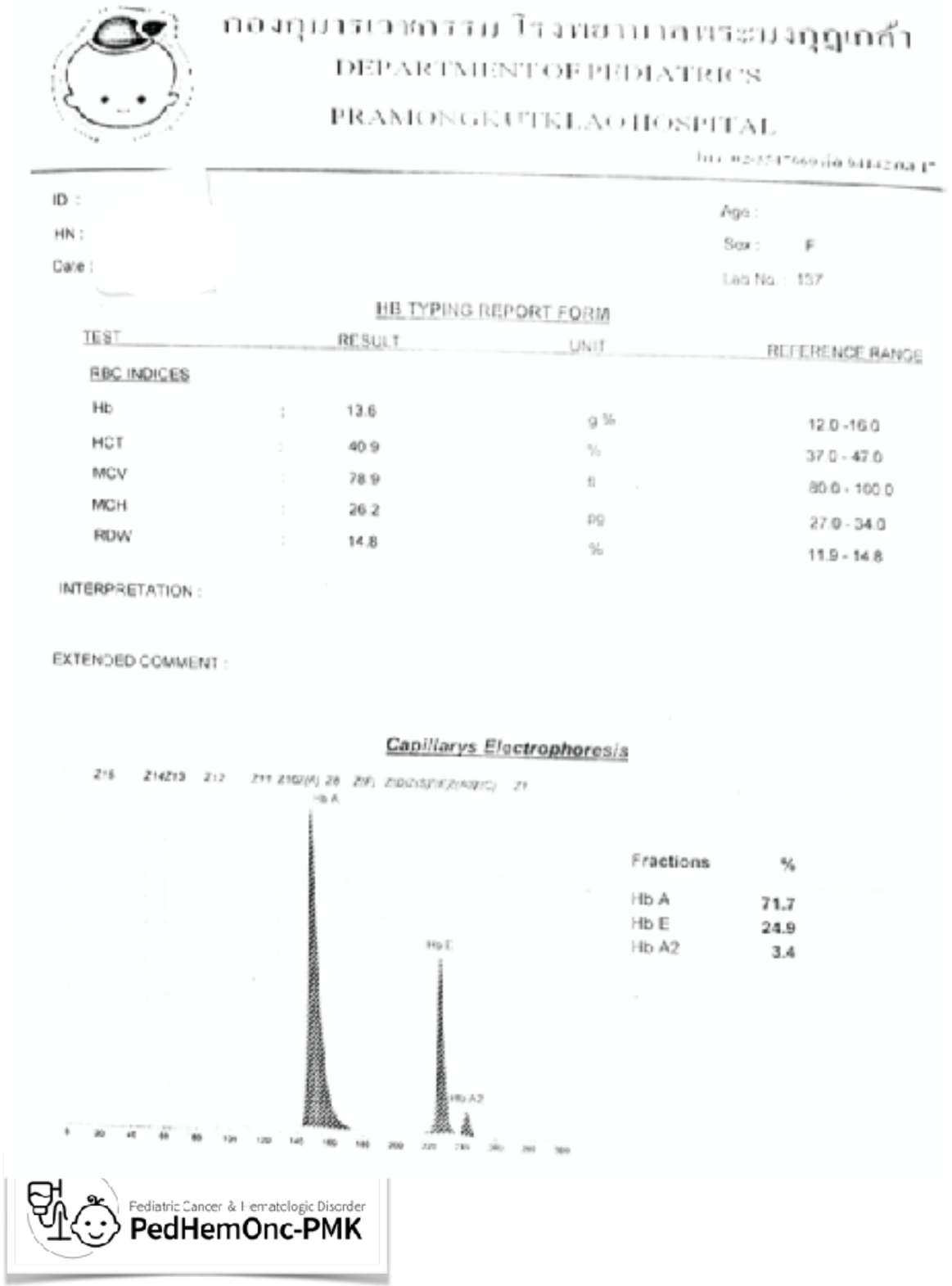
Fractions	%
Hb A	94.5
Hb F	0.4
Hb A2	5.1

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Hb	11.0	g/dl
Hct	32.7	%
MCV	73.8	fl
MCH	24.8	Pg
RDW	16.0	%

Hb A	94.5	%
Hb F	0.4	%
Hb A2	5.1	%

Interpretation!!!



ภาควิชากุมารเวชศาสตร์ โรงพยาบาลพระมงกุฎเกล้า
DEPARTMENT OF PEDIATRICS
PRAMONGKUTKLAO HOSPITAL

ID :
HN :
Date :
Age :
Sex : F
Lab No. : 157

HB TYPING REPORT FORM

TEST		RESULT	UNIT	REFERENCE RANGE
RBC INDICES				
Hb	:	13.6	g %	12.0 -16.0
HCT	:	40.9	%	37.0 - 47.0
MCV	:	78.9	fl	80.0 - 100.0
MCH	:	26.2	pg	27.0 - 34.0
RDW	:	14.8	%	11.9 - 14.8

INTERPRETATION :

EXTENDED COMMENT :

Capillarys Electrophoresis

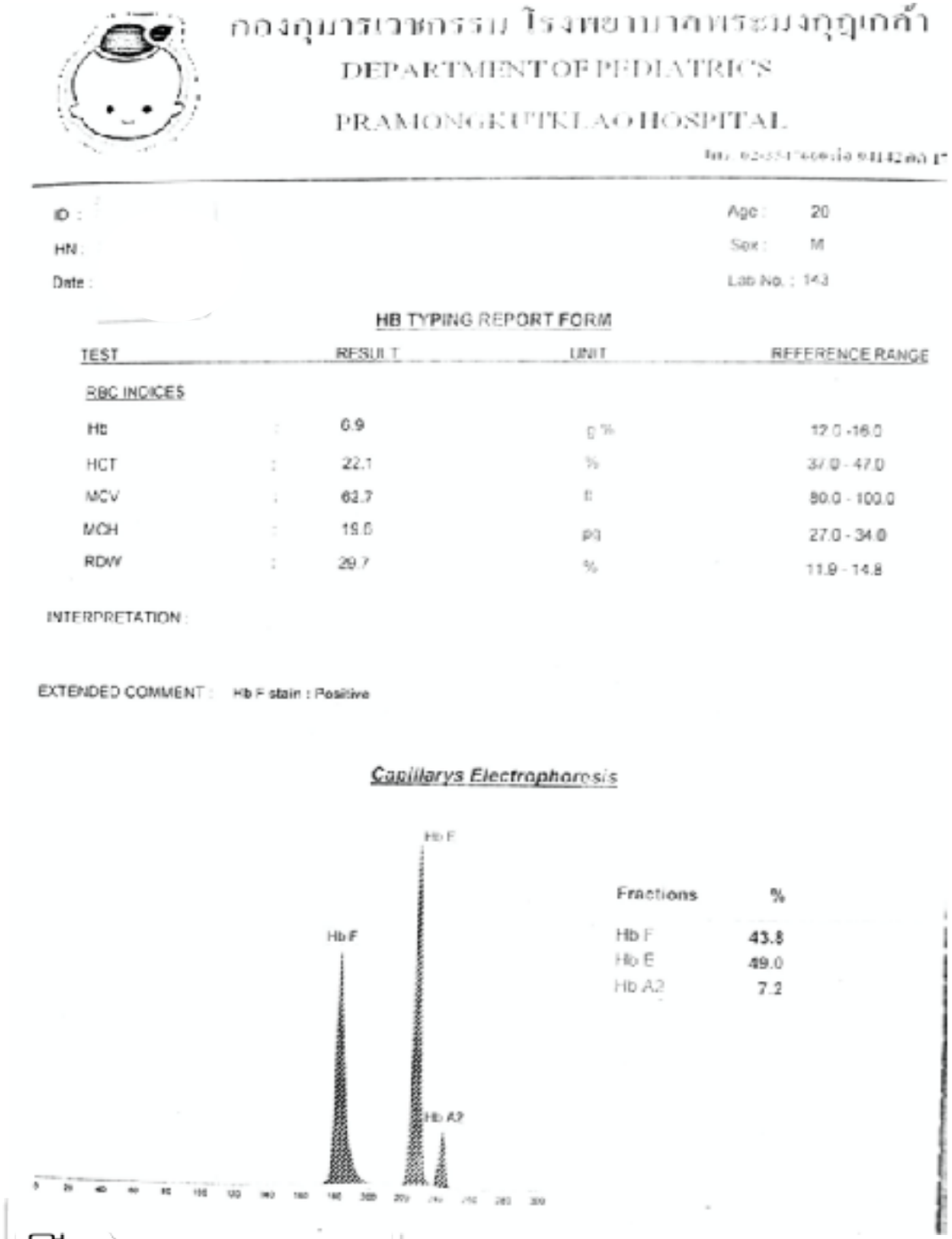
Fractions	%
Hb A	71.7
Hb E	24.9
Hb A2	3.4

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Hb	13.6	g/dl
Hct	40.9	%
MCV	78.9	fl
MCH	26.2	Pg
RDW	14.8	%

Hb A	71.7	%
Hb F	24.9	%
Hb A2	3.4	%

Interpretation!!!



กองกุมารเวชกรรม โรงพยาบาลพระมงกุฎเกล้า
DEPARTMENT OF PEDIATRICS
PRAMONGKUTKLAO HOSPITAL

ID :
HN :
Date :

Age : 20
Sex : M
Lab No. : 143

HB TYPING REPORT FORM

TEST		RESULT	UNIT	REFERENCE RANGE
RBC INDICES				
Hb	:	6.9	g %	12.0 -16.0
HCT	:	22.1	%	37.0 - 47.0
MCV	:	62.7	fl	80.0 - 100.0
MCH	:	19.6	pg	27.0 - 34.0
RDW	:	29.7	%	11.9 - 14.8

INTERPRETATION :

EXTENDED COMMENT : Hb F stain : Positive

Capillarys Electrophoresis

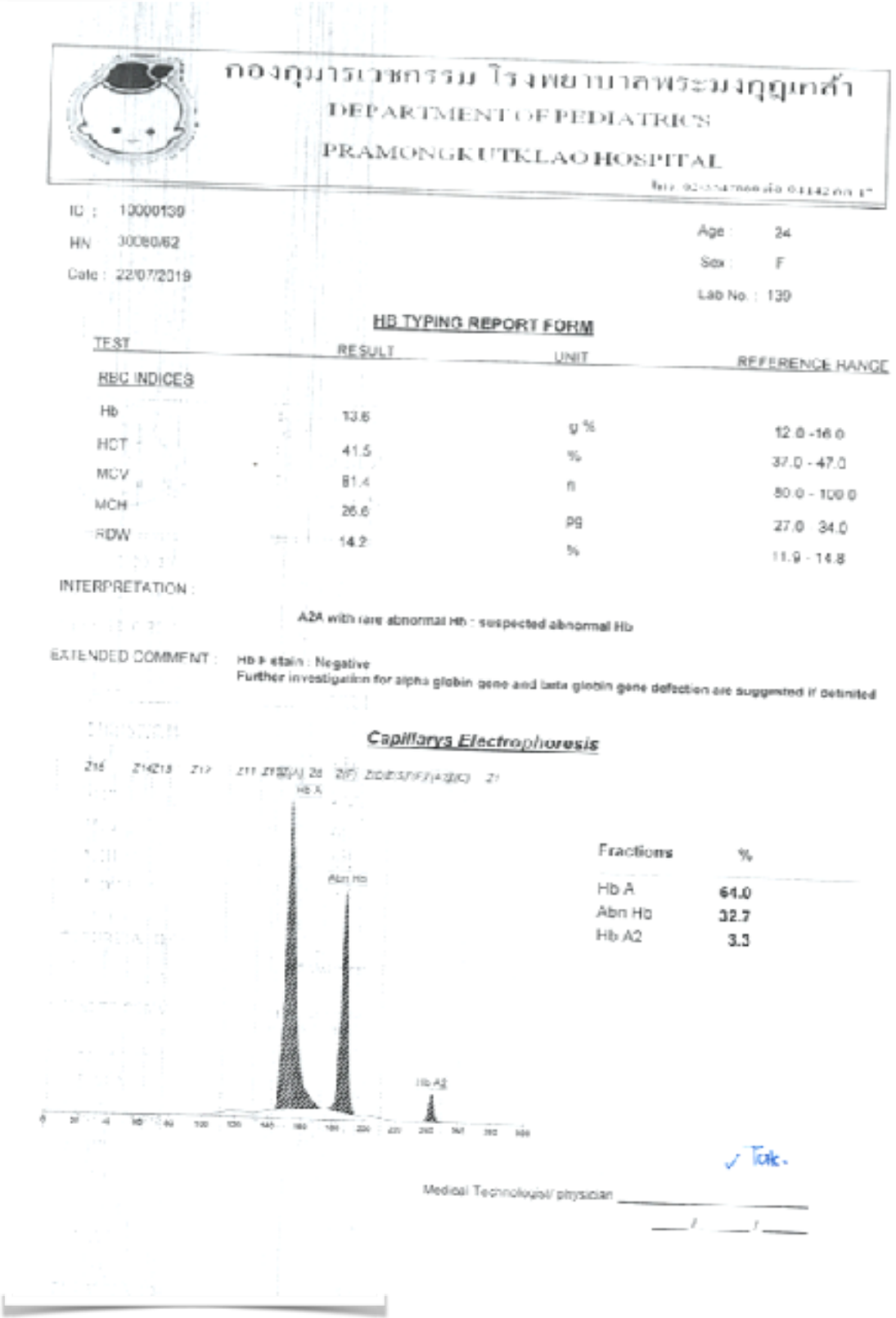
Fractions	%
Hb F	43.8
Hb E	49.0
Hb A2	7.2

Fediatric Cancer & Hematclogic Disorder
PedHemOnc-PMK

Hb	6.9	g/dl
Hct	22.1	%
MCV	62.7	fl
MCH	19.6	Pg
RDW	29.7	%

Hb F	43.8	%
Hb E	49	%
Hb A2	7.2	%

Interpretation!!!



กองกุมารเวชกรรม โรงพยาบาลพระมงกุฎเกล้า
DEPARTMENT OF PEDIATRICS
PRAMONGKUTKLAO HOSPITAL

ID : 10000139
HN 30080/62
Date : 22/07/2019

Age : 24
Sex : F
Lab No. : 139

HB TYPING REPORT FORM

TEST	RESULT	UNIT	REFERENCE RANGE
RBC INDICES			
Hb	13.6	g %	12.0 -16.0
HCT	41.5	%	37.0 - 47.0
MCV	81.4	fl	80.0 - 100.0
MCH	26.6	Pg	27.0 - 34.0
RDW	14.2	%	11.9 - 14.8

INTERPRETATION :

A2A with rare abnormal Hb : suspected abnormal Hb

EXTENDED COMMENT : Hb F stain : Negative
Further investigation for alpha globin gene and beta globin gene defection are suggested if detected

Capillarys Electrophoresis

Fractions	%
Hb A	64.0
Abn Hb	32.7
Hb A2	3.3

✓ Tak.

Medical Technologist/ physician _____
___/___/___

Hb	13.6	g/dl
Hct	41.5	%
MCV	81.4	fl
MCH	26.6	Pg
RDW	14.2	%

Hb A	64.0	%
Abn Hb	32.7	%
Hb A2	3.3	%

Others Detecting Techniques

Alpha globin gene

Alpha thal-1 deletion

Alpha thal-2 deletion

Multiplex Gap PCR

Uncommon large deletion or alpha-globing gene triplication

Multiplex ligation-dependent probe amplification (MLPA)

Beta globin gene

Deletion of beta gene

ARMS PCR

Reverse dot blot

Uncommon large deletion

Deletion

Non-deletion

Common known point mutation; CS, PS, QS

The amplification-refractory mutation system (ARMS) PCR

Point mutation

Uncommon point mutation; Unknown

Alpha-globin gene sequencing

Common known point mutation

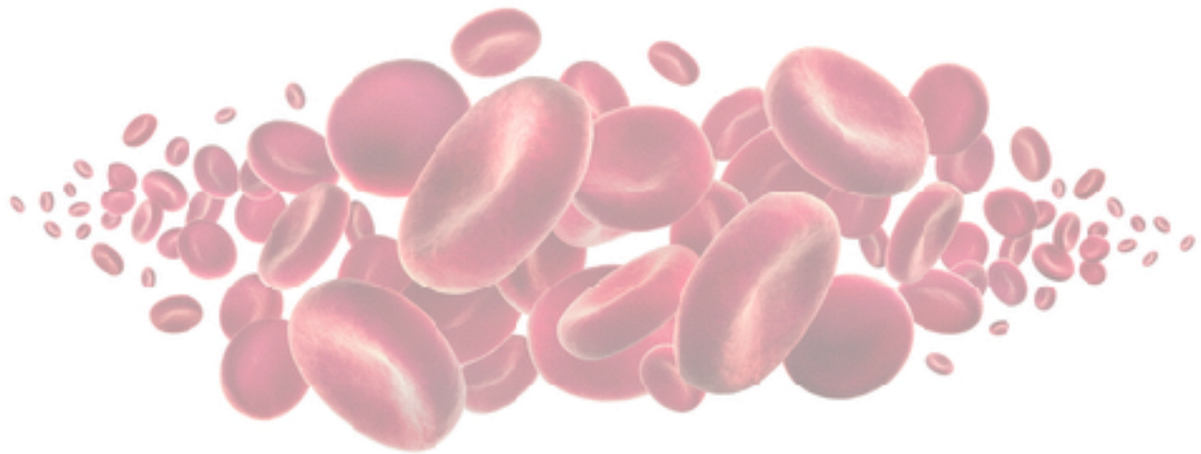
ARMS PCR

High resolution melting (HRM) analysis

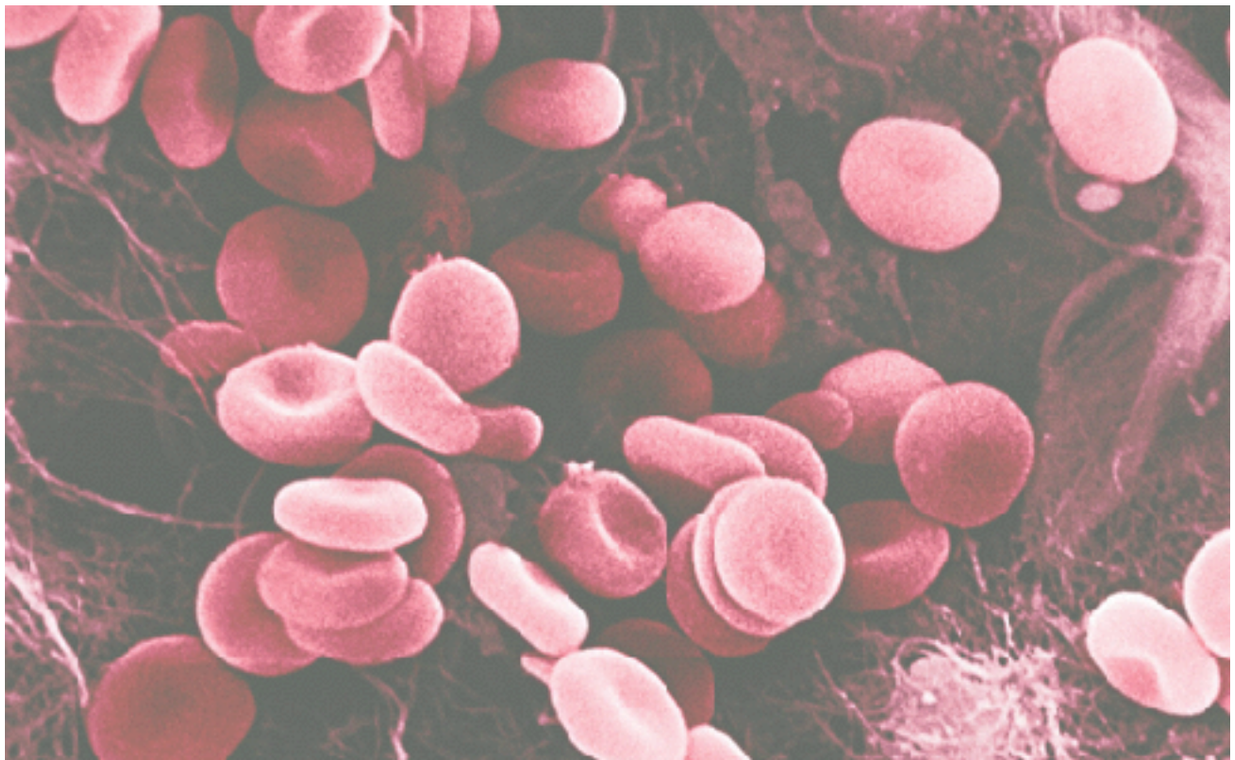
Point mutation

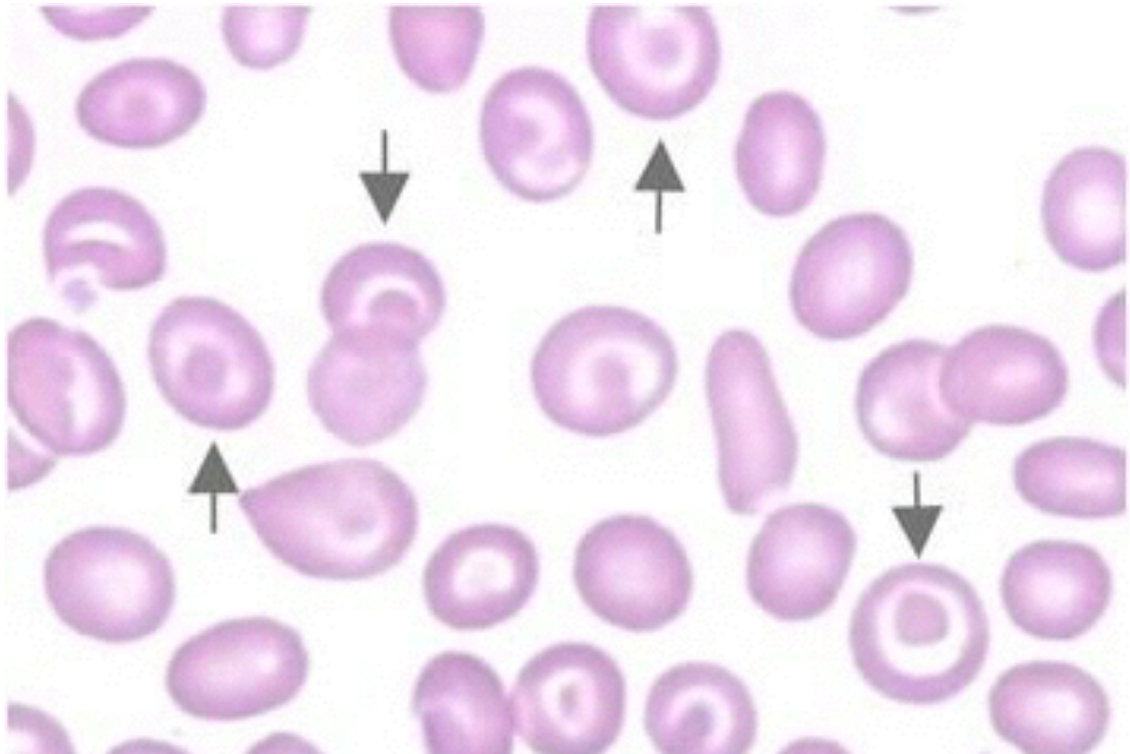
Uncommon point mutation; Unknown

Beta-globin gene sequencing



Treatment





Treatment

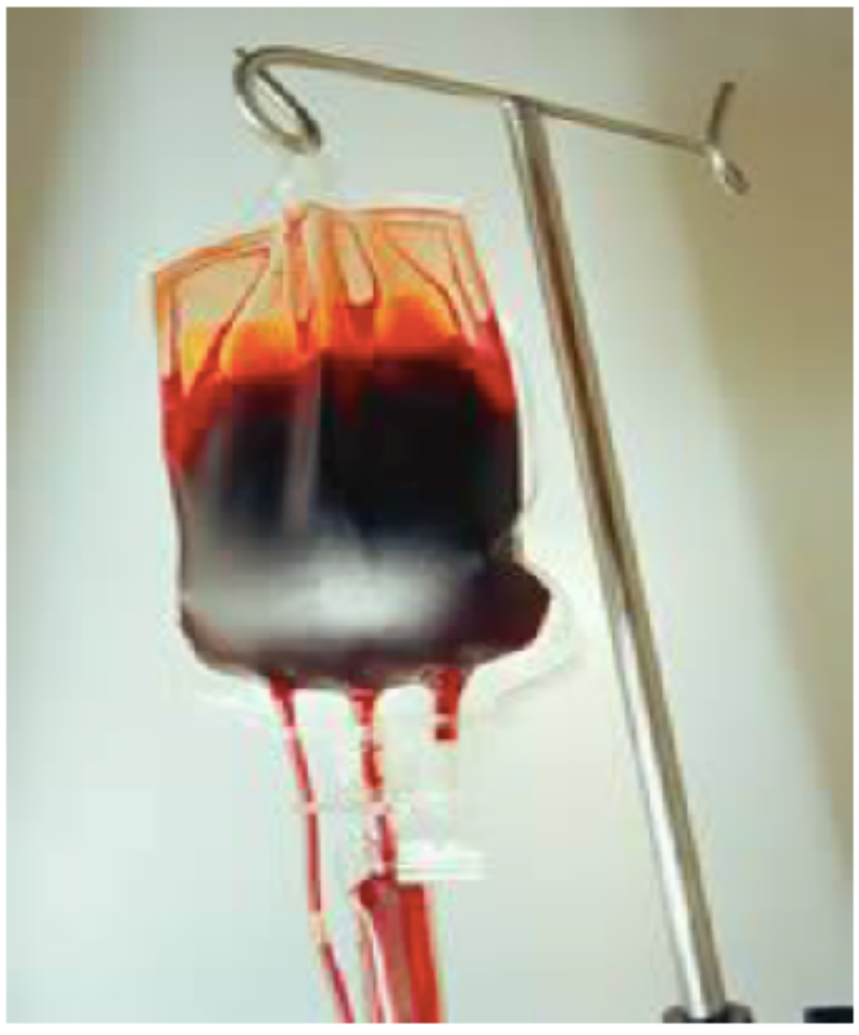
Curative treatment

- Hematopoietic stem cell transplantation
- Gene therapy

Standard treatment

- Education and genetic counseling
- Regular blood transfusion to maintain Hb 13-14 g/dL post transfusion and 9-10 at all time
- Supportive treatment : Folic acid, MTV
- Iron chelation

Blood transfusion



200–250 mg iron:
Whole blood: 0.47 mg iron/mL
'Pure' red cells: 1.16 mg iron/mL

Porter JB. *Br J Haematol* 2001;115:239–252

- 1 blood unit contains 200 mg iron
- A 60 kg patient with thalassemia receiving 45 units of blood annually has transfusional iron intake of 9 g iron/year
  - 0.4 mg iron/kg body wt/day
- In addition, up to 4 mg/day may be absorbed from the gut
  - Up to 1.5 g iron/year
- Overload can occur after 10–20 transfusions

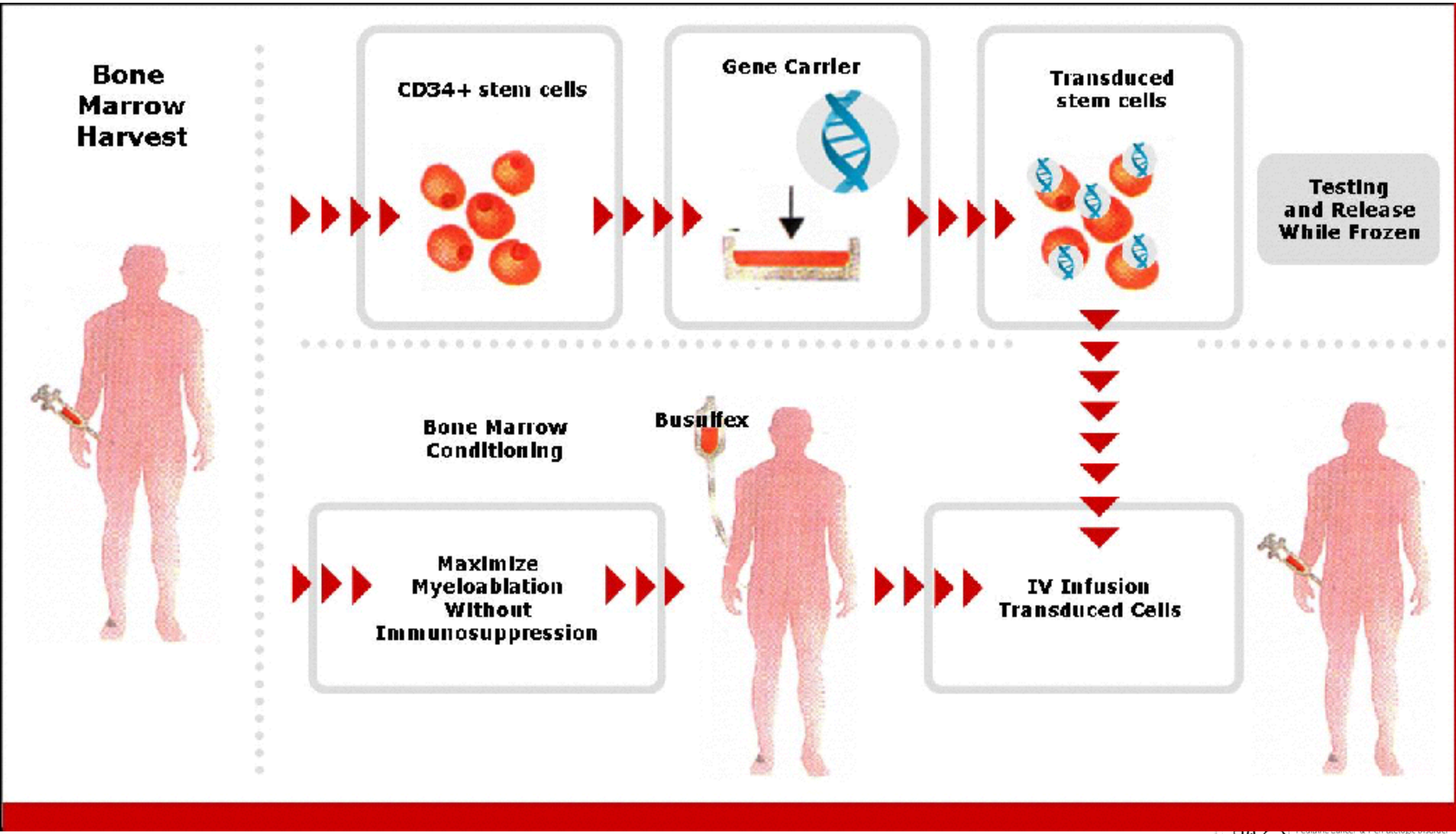
Iron overload is an inevitable consequence of multiple blood transfusions

Transfusion regimen

- การให้เลือดเพื่อยับยั้งการสร้างเม็ดเลือดแดง อย่างสม่ำเสมอ (regular transfusion) ควรให้ในผู้ป่วยธาลัสซีเมียรุนแรงหรือ ชนิดพึ่งพาเลือด (Transfusion dependent thalassemia; TDT) ซึ่งได้รับการวินิจฉัยใหม่
- จุดมุ่งหมายคือรักษาค่า IIb ของผู้ป่วย**สูงกว่า 9 กรัม/ดล.** ตลอดเวลา และไม่ให้เกิน 14 กรัม/ดล
- โดยให้ เลือดกรอง หรือปั่นแยกเม็ดเลือดขาวออก ขนาด 12-15 มล./กก. หรือ 1-3 ยูนิตในผู้ใหญ่ **ทุก 2-6 สัปดาห์** ทำให้ผู้ป่วยมีคุณภาพชีวิตที่ดี การเจริญเติบโตปกติ โดยเฉพาะผู้ป่วยเด็ก

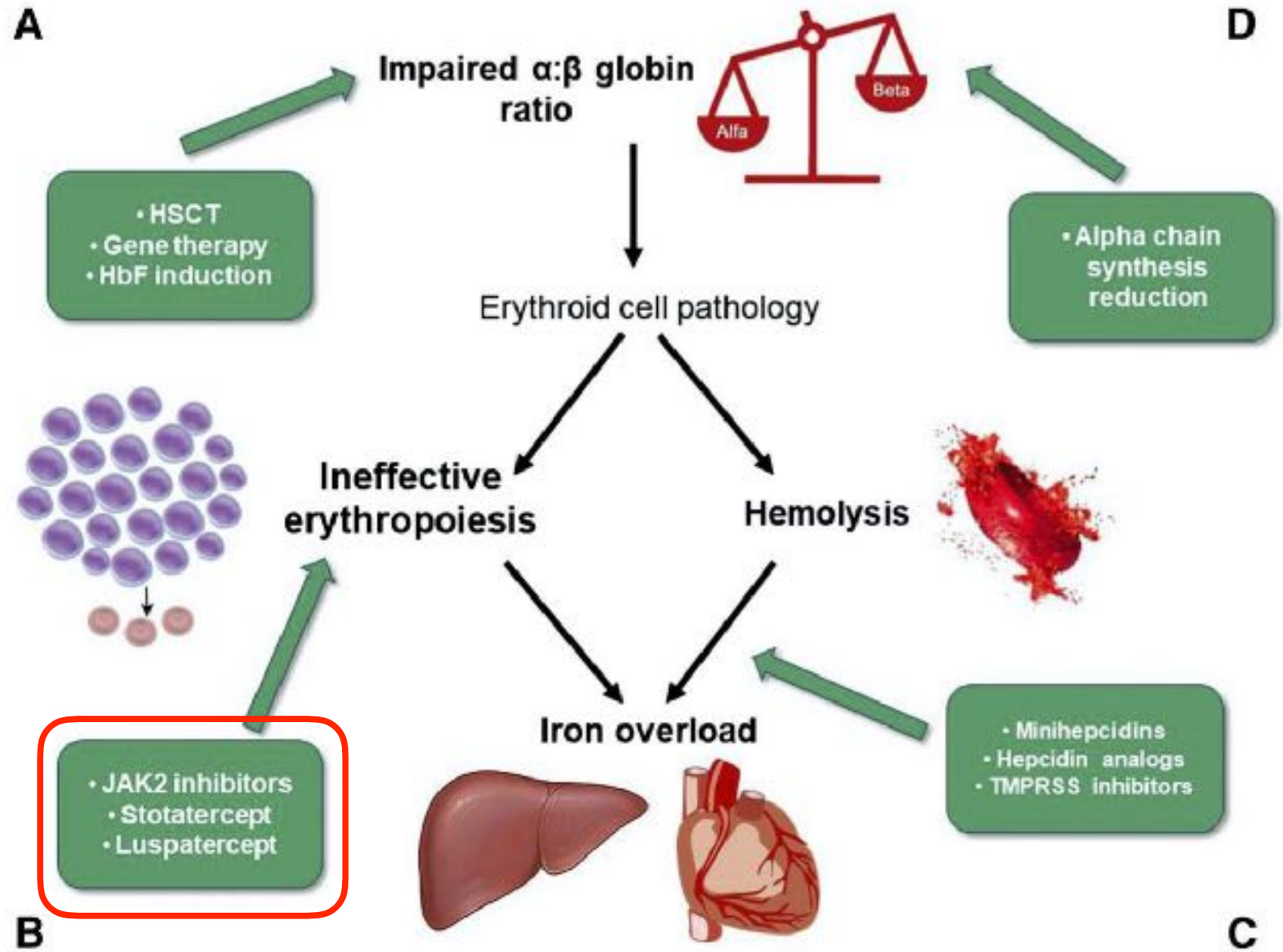
แนวทางการวินิจฉัยและการรักษาโรคโลหิตจางธาลัสซีเมีย พฤศจิกายน 2557

Gene Therapy



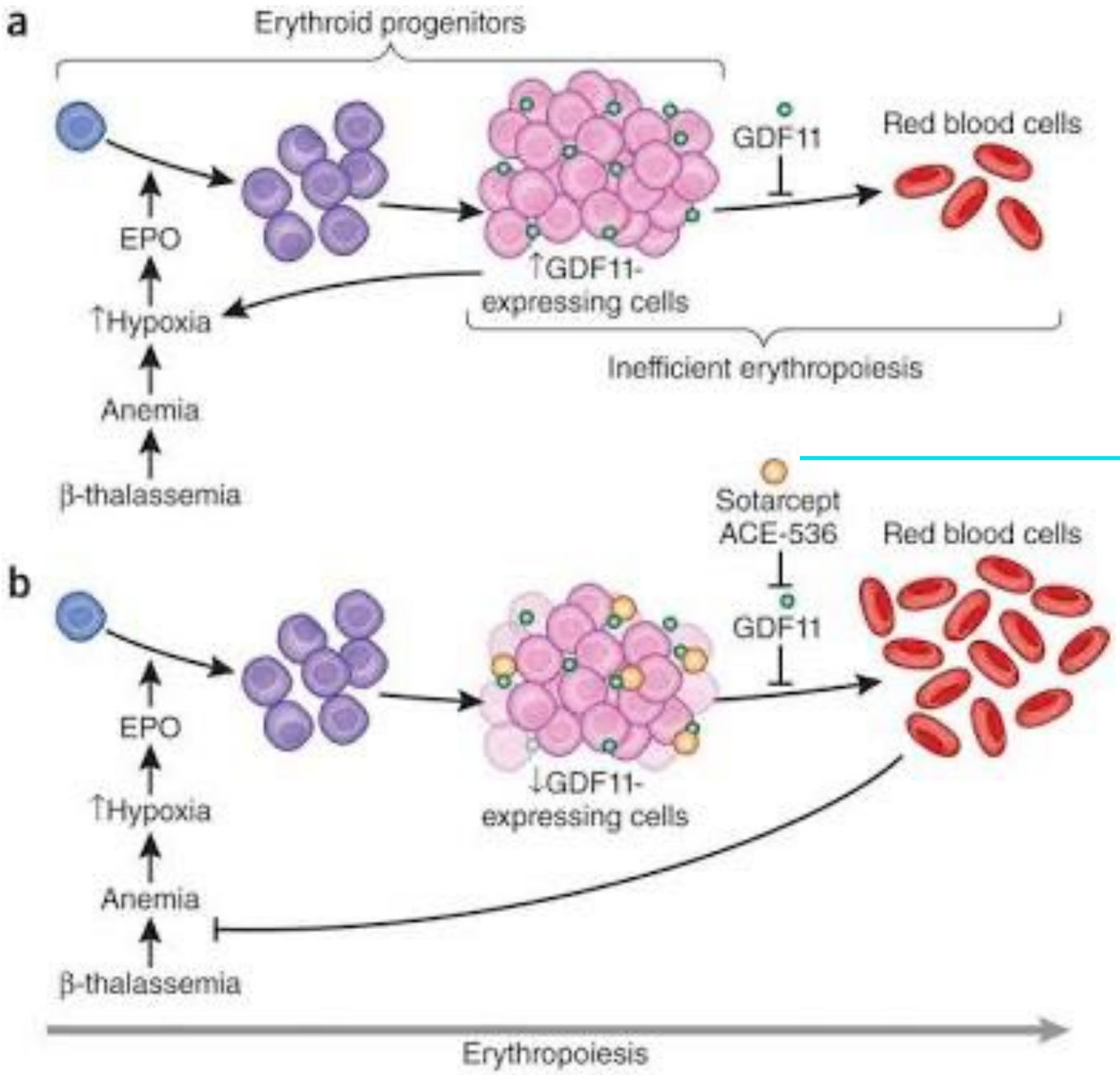
Novel therapy

New therapeutic targets in β-thalassemias: (A,D) impaired α:β-globin ratio, (B) ineffective erythropoiesis, and (C) iron metabolism and hemolysis.



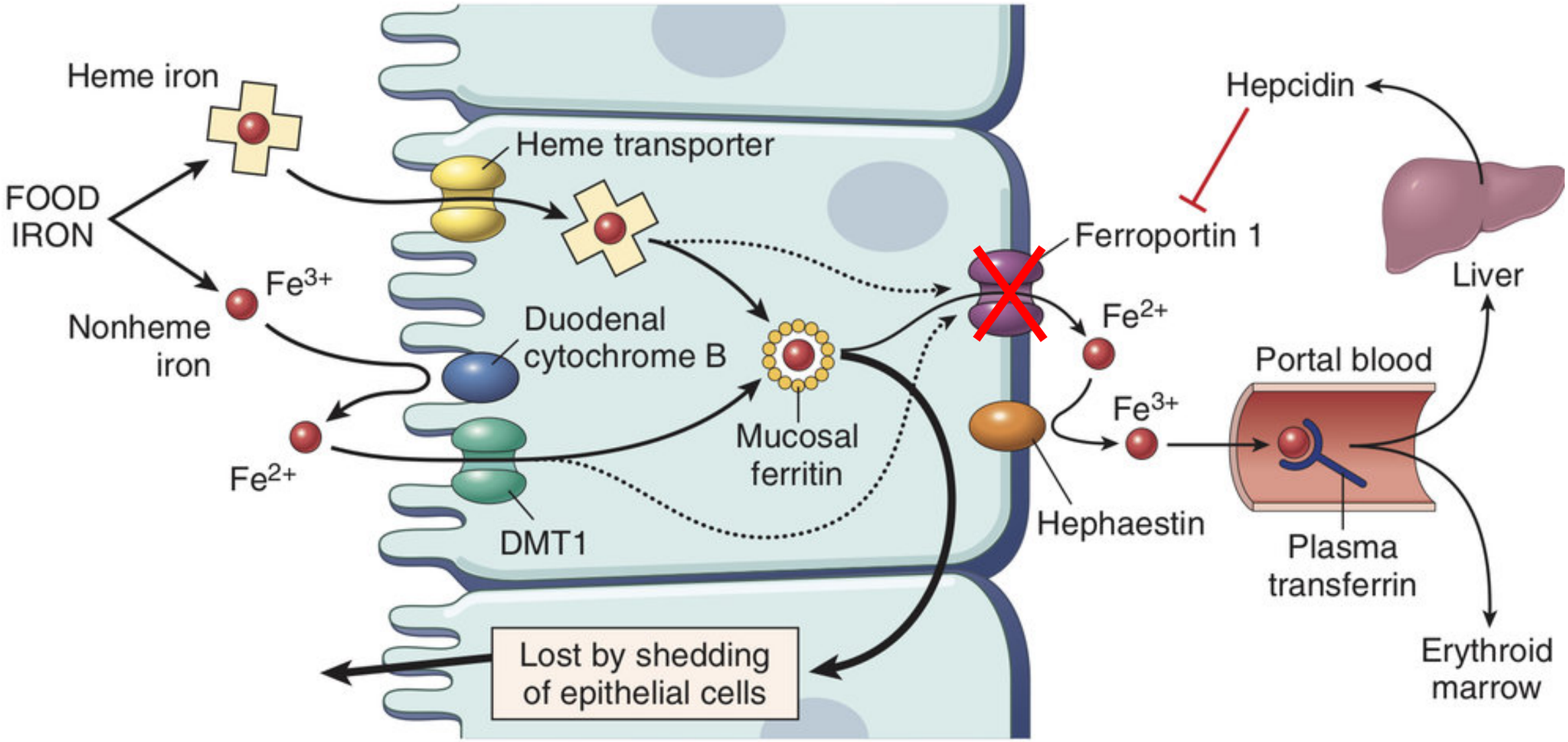
M. Domenica Cappellini, and Irene Motta Hematology 2017;2017:278-283

GDF-11 Antagonists



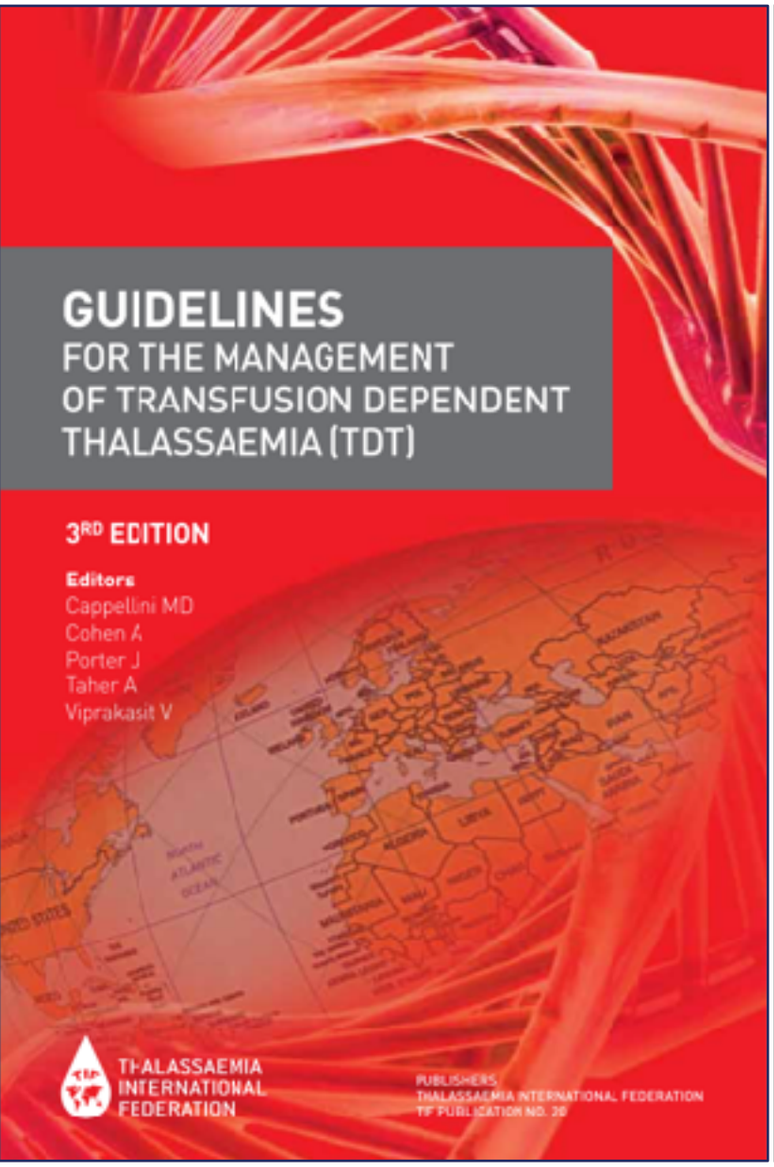
Stotatercept
Luspatercept (ACE-536)

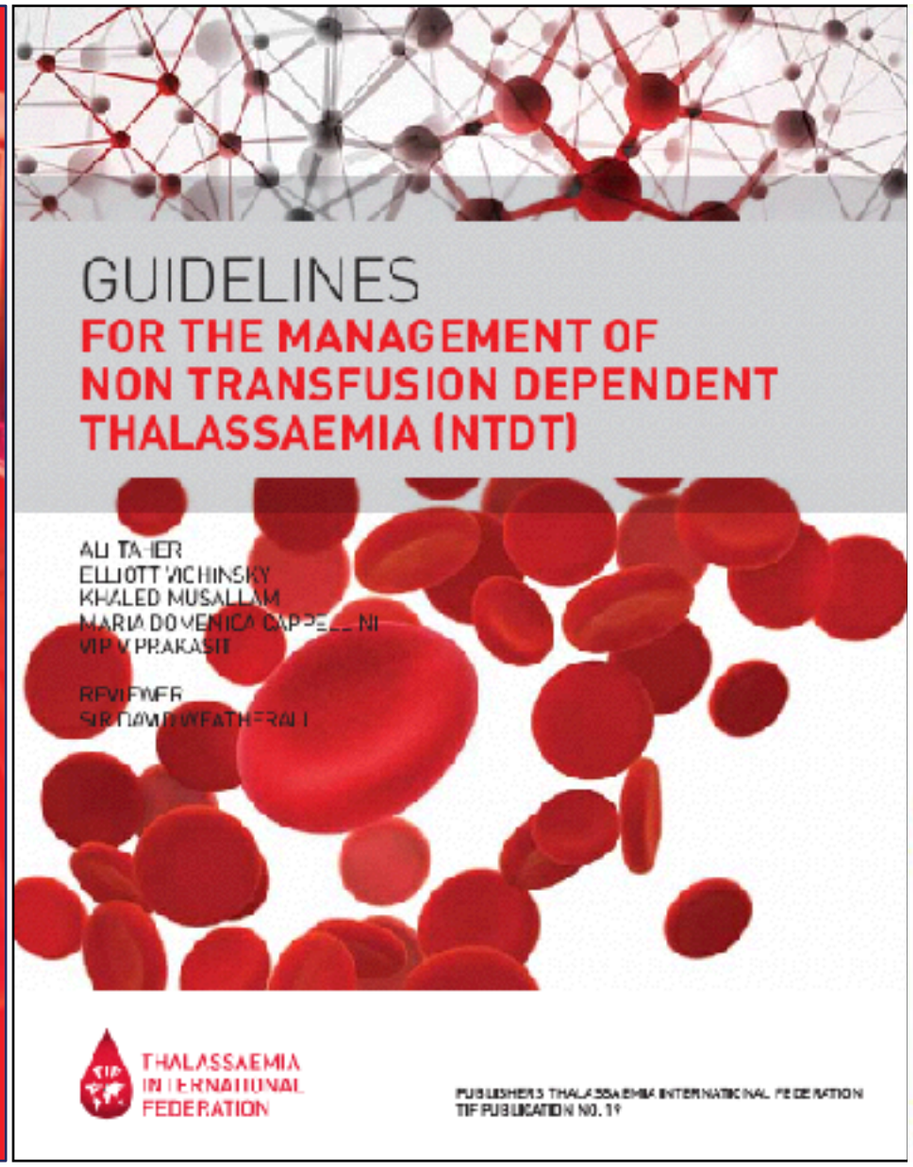
Minihepcidins

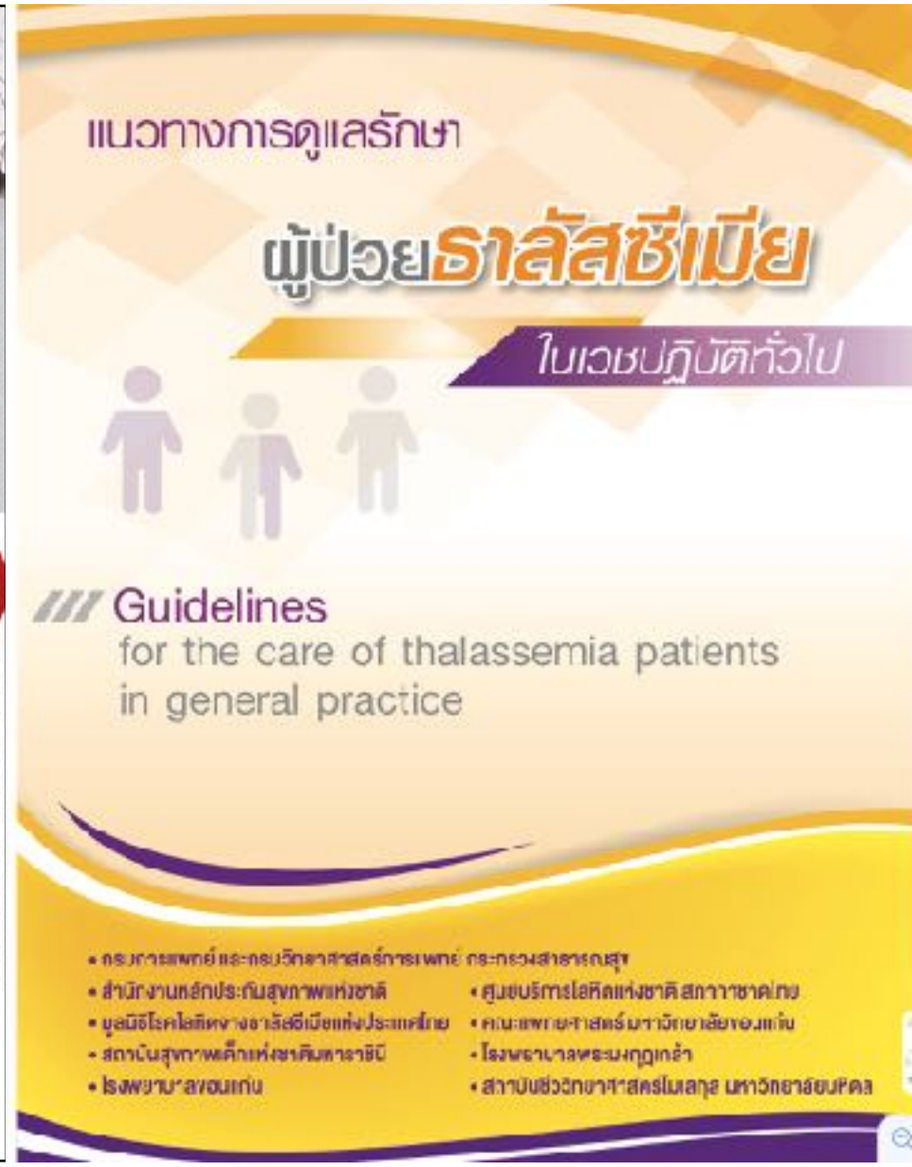


Ref: Robbins Basic Pathology (9th Edition)

Reference







Thank you for your kind attention

หากน้องๆพบผู้ป่วย**เด็กหญิง อายุ 12-18 ปี**มาตรวจที่โอพีดี หรือแอดมิทหอผู้ป่วย ในกรุณาแจ้ง **คุณหมอโดนัท** เพื่อประเมินผู้ป่วยเข้าร่วมโครงการวิจัย...

“การศึกษาความสัมพันธ์ระหว่างค่า reticulocyte hemoglobin equivalent และภาวะโลหิตจางจากการขาดธาตุเหล็กในหญิงวัยรุ่นไทยอายุ 12-18 ปี"

Handout