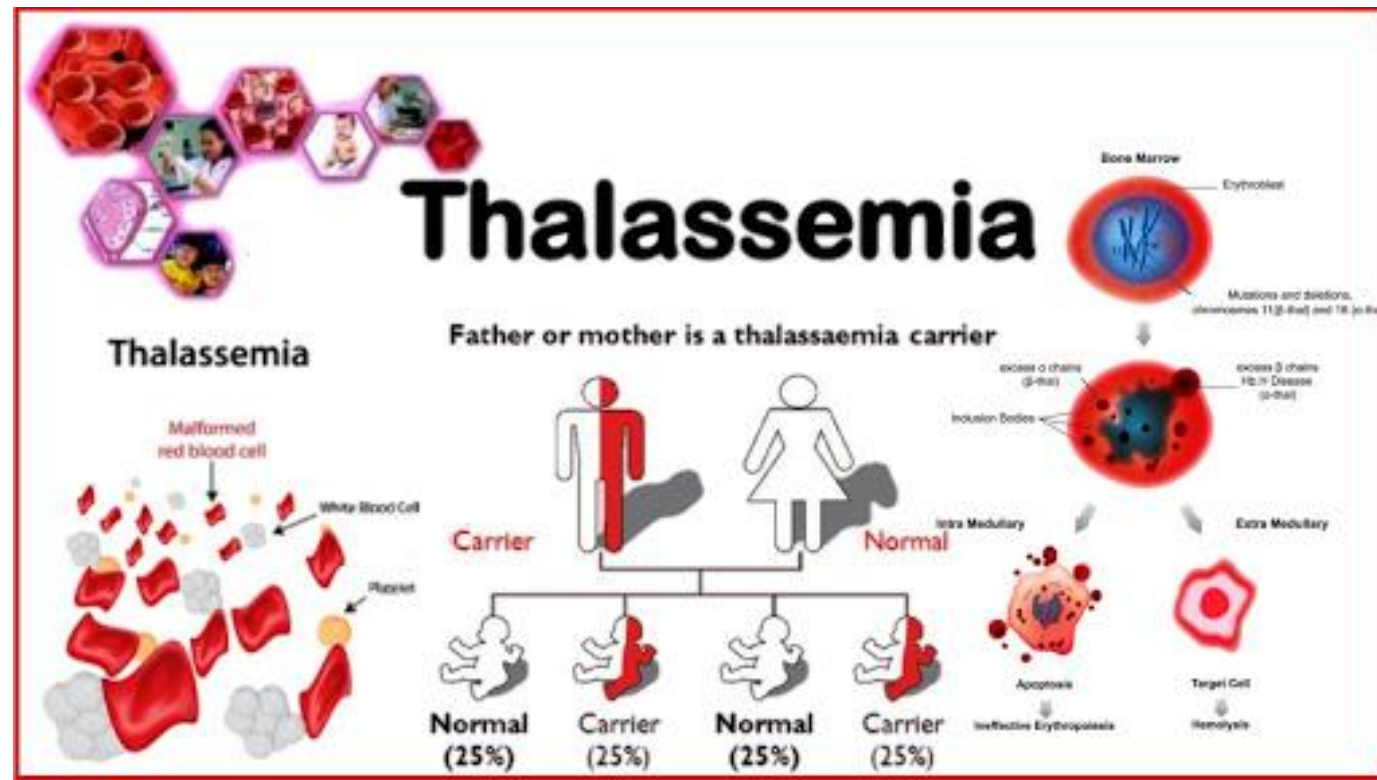




ΑΙΜΟΣΦΑΙΡΙΝΟΠΑΘΕΙΕΣ ΜΕΣΟΓΕΙΑΚΑ ΣΥΝΔΡΟΜΑ

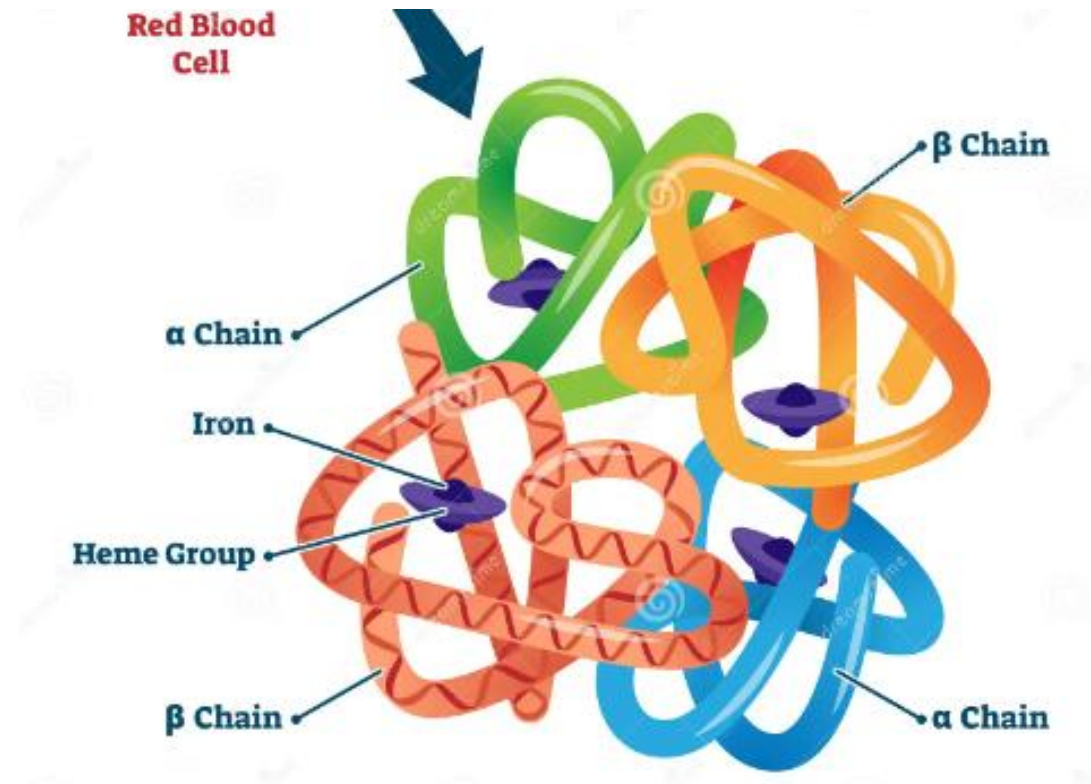
Δελαπόρτα Πολυξένη

Παιδίατρος, PhD

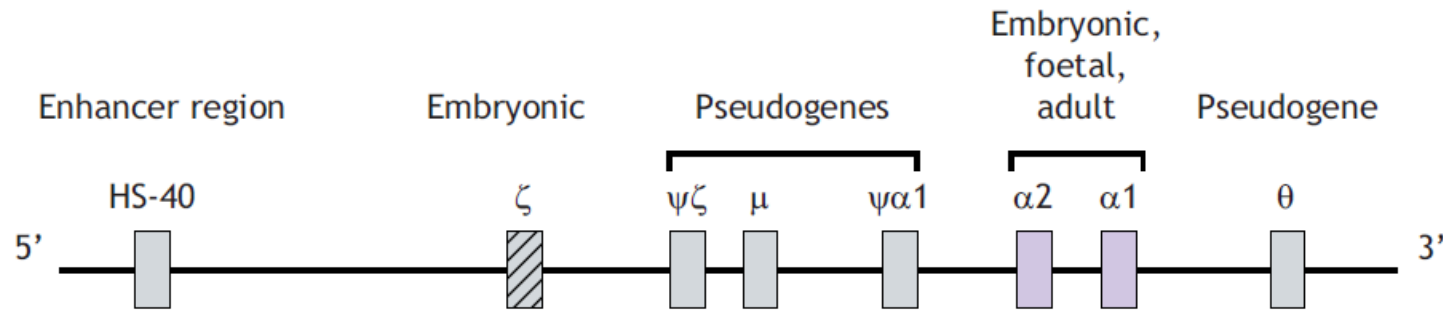
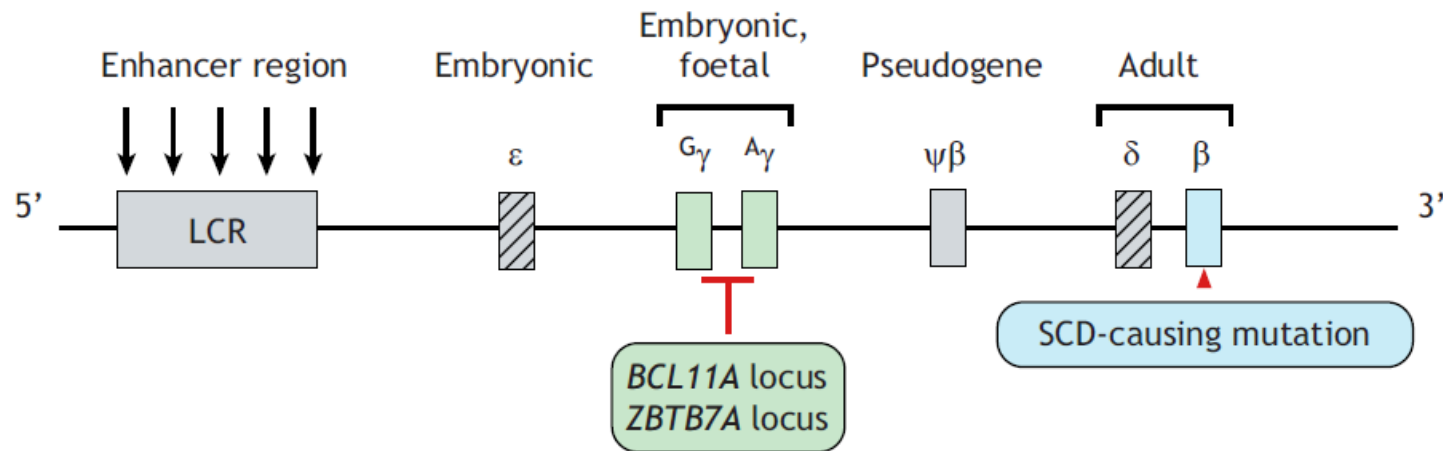
Επιμελήτρια Β', Μονάδα Μεσογειακής Αναιμίας, Α' Παιδιατρική Κλινική
Πανεπιστημίου Αθηνών

Αιμοσφαιρίνη

- Τετραμερές μόριο που αποτελείται από δύο υπομονάδες α και 2 υπομονάδες β σφαιρίνης
- μαζί με την αίμη και τον σίδηρο
- μεταφορά οξυγόνου στα ερυθροκύτταρα

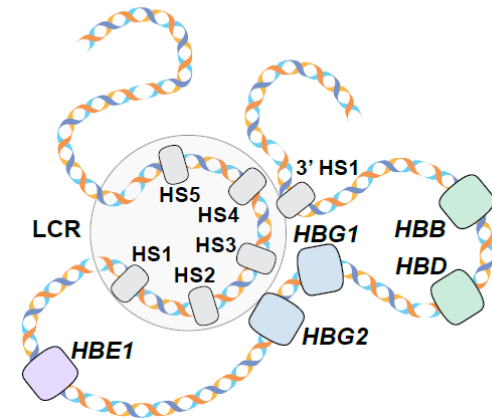


A

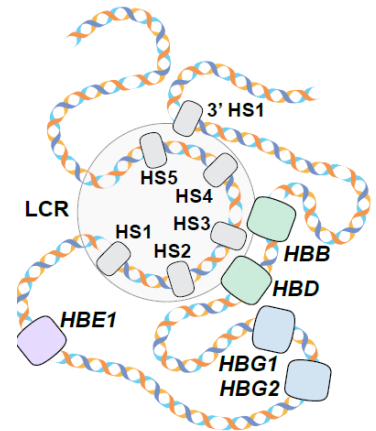
The α -globin cluster on chromosome 16The β -globin cluster on chromosome 11

3

Fetal

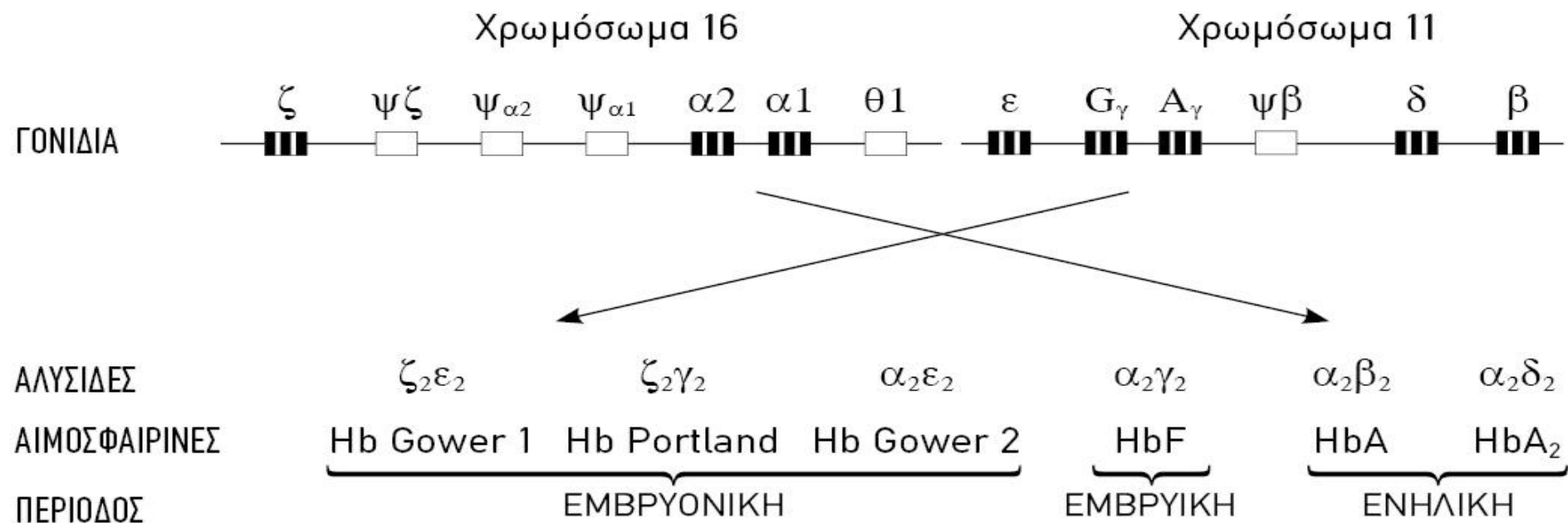


Adult



Η LCR, μαζί με μεταγραφικούς παράγοντες, συμπαράγοντες και δομικούς παράγοντες χρωματίνης, σχηματίζουν φυσικούς βρόχους που αλληλεπιδρούν με promoters (υποκινητές) των γονιδίων

Χρωμοσωμακή εντόπιση των γονιδίων και δομή των αιμοσφαιρινών



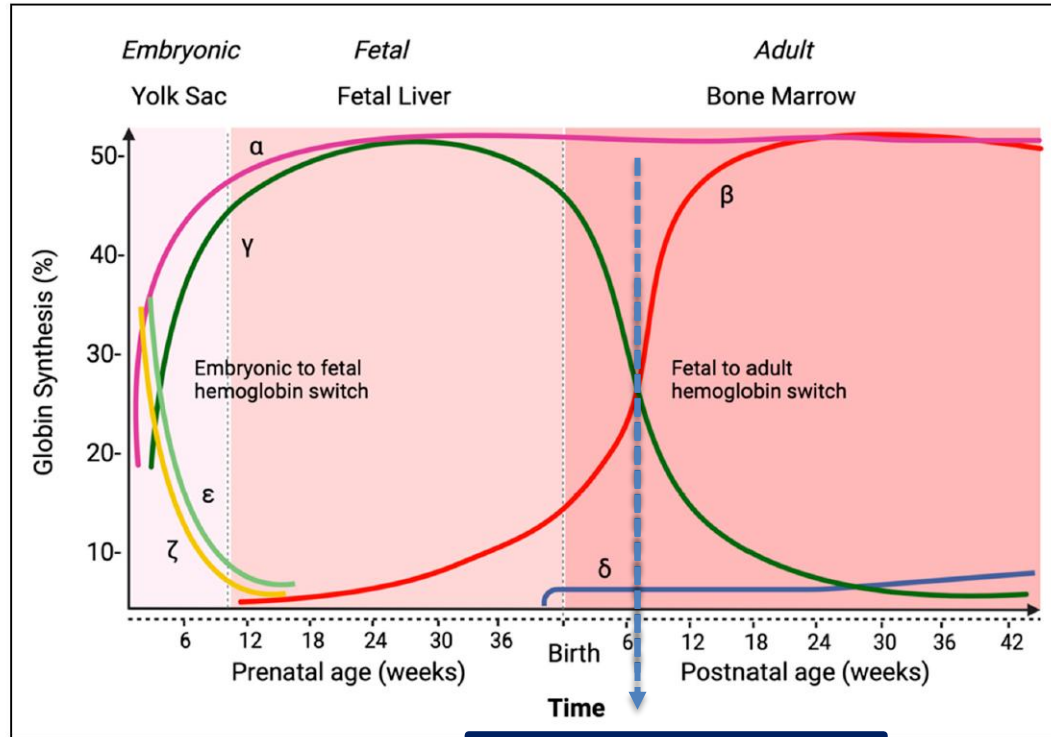
The hemoglobin types expressed during different stages of development are embryonic (Hb Gower-I [$\zeta_2\epsilon_2$], Hb Gower-II [$\alpha_2\epsilon_2$], and Hb Portland [$\zeta_2\gamma_2$]), fetal (HbF [$\alpha_2\gamma_2$]), and adult (HbA [$\alpha_2\beta_2$] and HbA₂ [$\alpha_2\delta_2$])

Πρωτεϊνική δομή φυσιολογικών αιμοσφαιρινών
Protein structure of normal hemoglobins

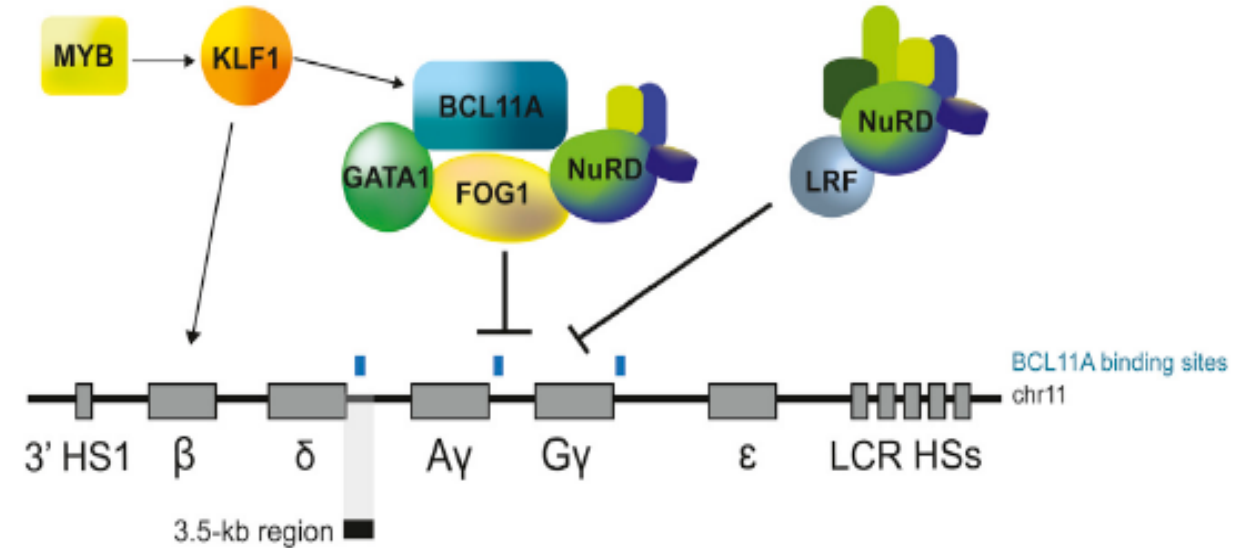
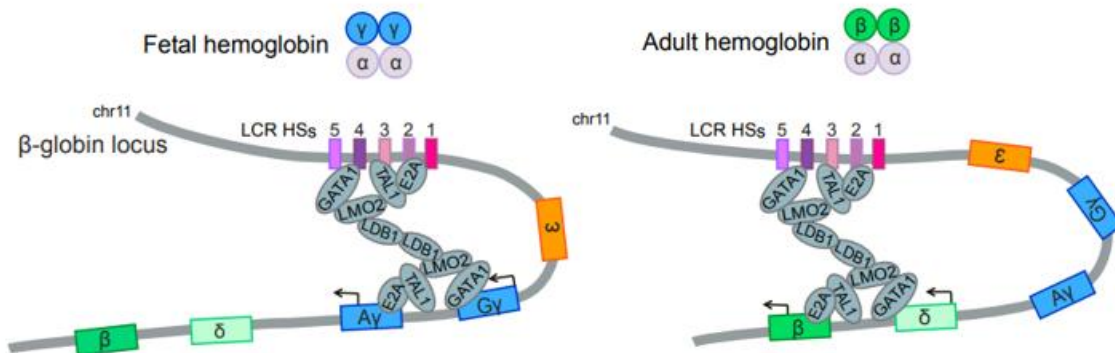
Είδος Hb	Ζεύγη πρωτεϊνικών Αλυσίδων
<u>Ενηλίκου</u>	
A 97%	$\alpha_2 \beta_2$
F <2%	$\alpha_2 \gamma_2$
A_2 <2-3.5%	$\alpha_2 \delta_2$
<u>Εμβρυονική</u>	
Gower 1	$\zeta_2 \epsilon_2$
Portland	$\zeta_2 \gamma_2$
Gower 2	$\alpha_2 \epsilon_2$

Hb Switching

Major Players in Fetal-to-Adult Hb Switching



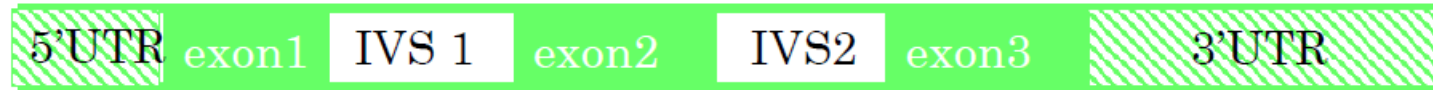
Onset of symptoms in β thalassemia and SCD



Fetal globin promoter

- ✓ BCL11A interacts with SOX6, GATA1, FOG1, and the NuRD repressor complex to repress the expression of g-globin genes
- ✓ BCL11A binding sites (light blue boxes) were mapped in the g-globin promoters and in a putative 3.5-kb HbF silencer (a black box).
- ✓ The expression of BCL11A is positively regulated by KLF1
- ✓ KLF1: directly activating b-globin gene expression
- ✓ LRF (TF): silences g-globin expression through the NuRD complex

Δομή γονιδίων αλύσεων β αιμοσφαιρίνης



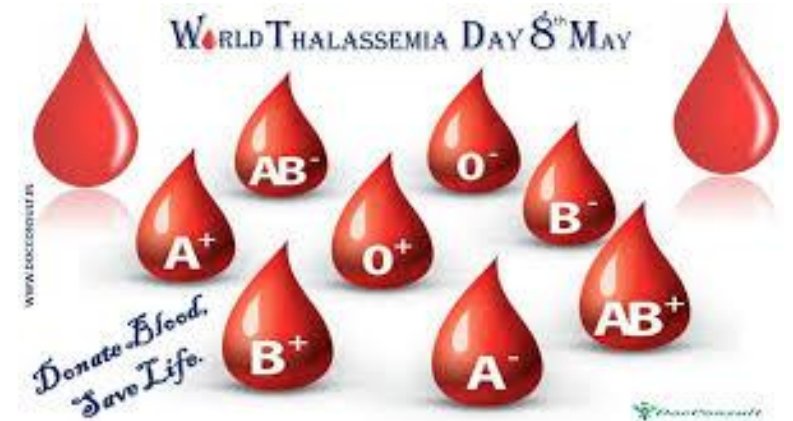
1.5kb long

3 exons

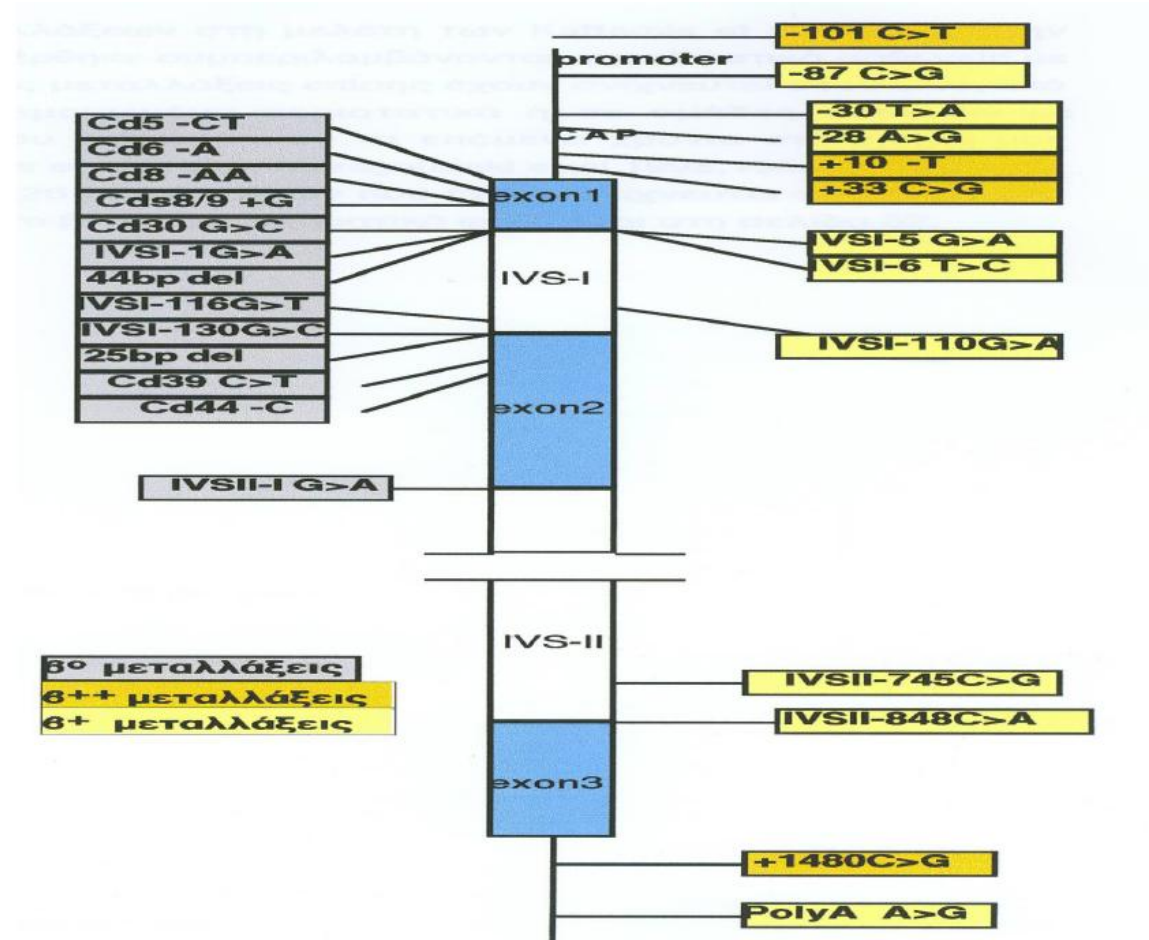
2 introns

Μεσογειακά Σύνδρομα

- Ευρύ φάσμα διαταραχών
- Χαρακτηρίζονται από μειωμένη σύνθεση μιας ή περισσότερων αλυσίδων αιμοσφαιρίνης
- Σχηματίζουν το μόριο της αιμοσφαιρίνης των ερυθρών κυττάρων

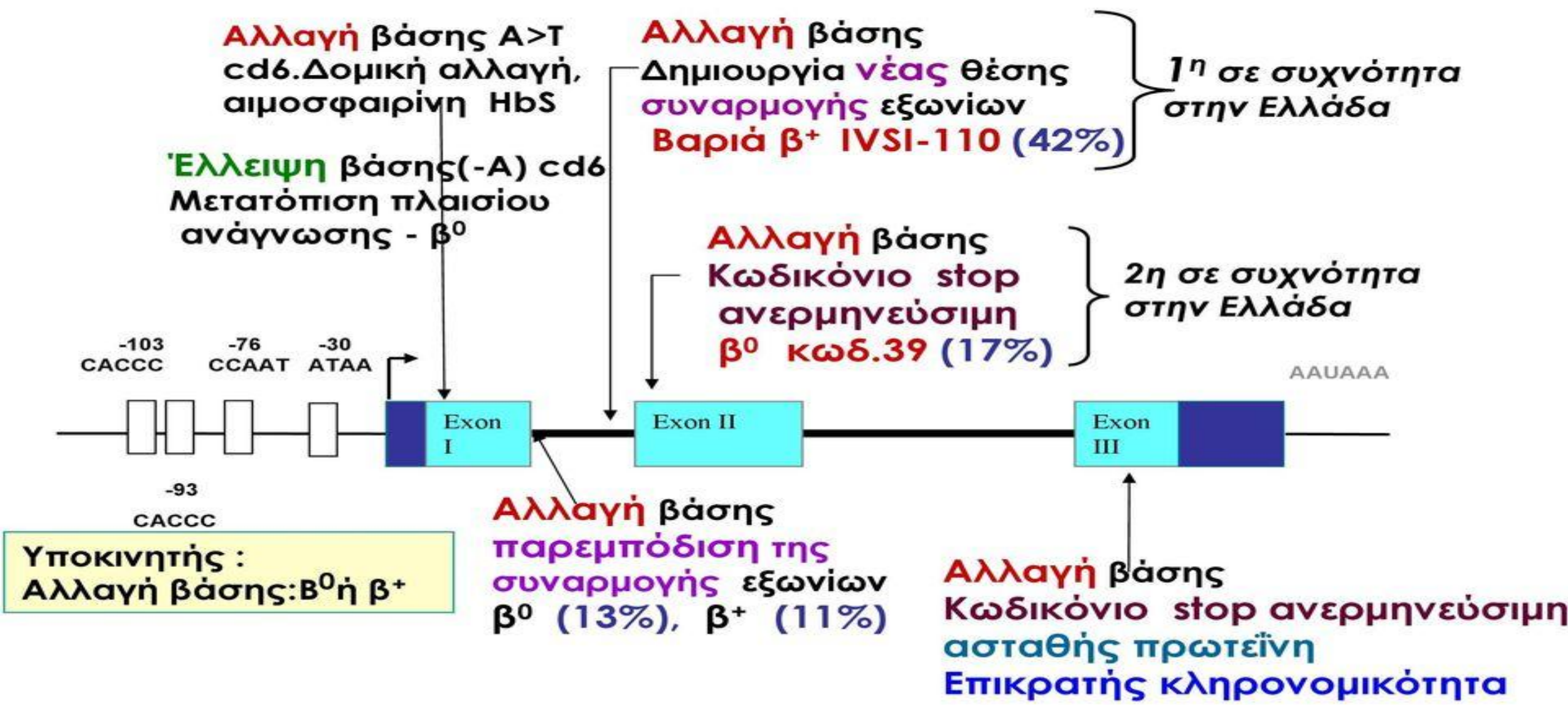


>400 μεταλλάξεις

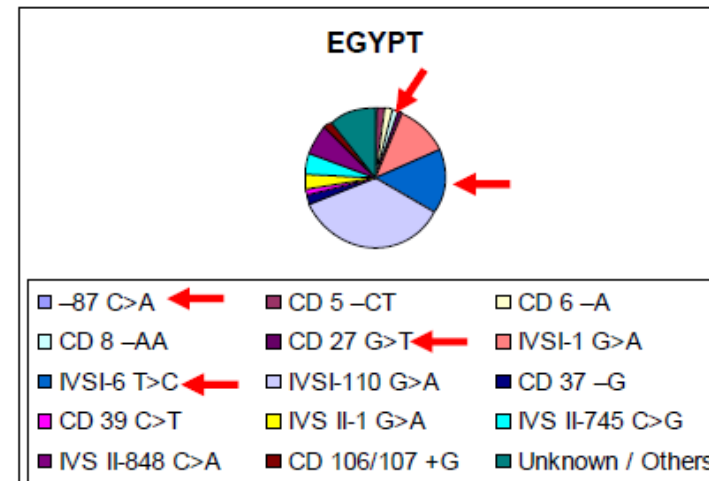
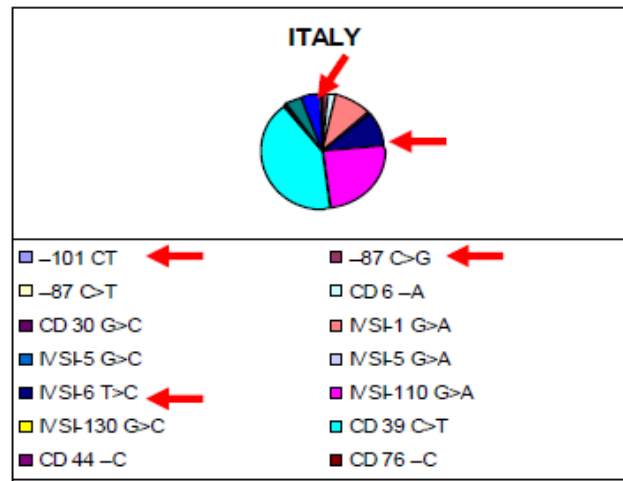
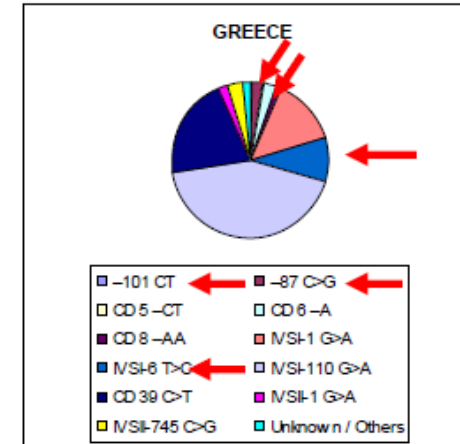
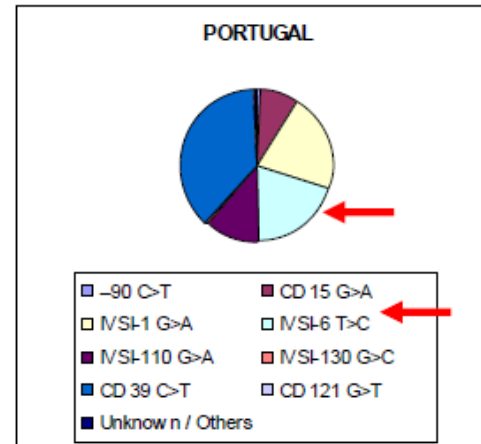
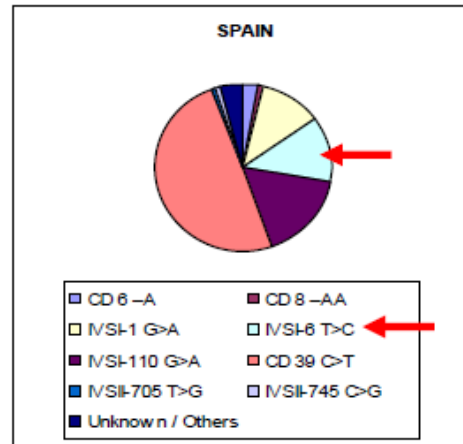


Μηχανισμοί δράσης των μεταλλάξεων β-Θαλασσαιμίας

- οι πιο συχνές στο Ελλαδικό χώρο



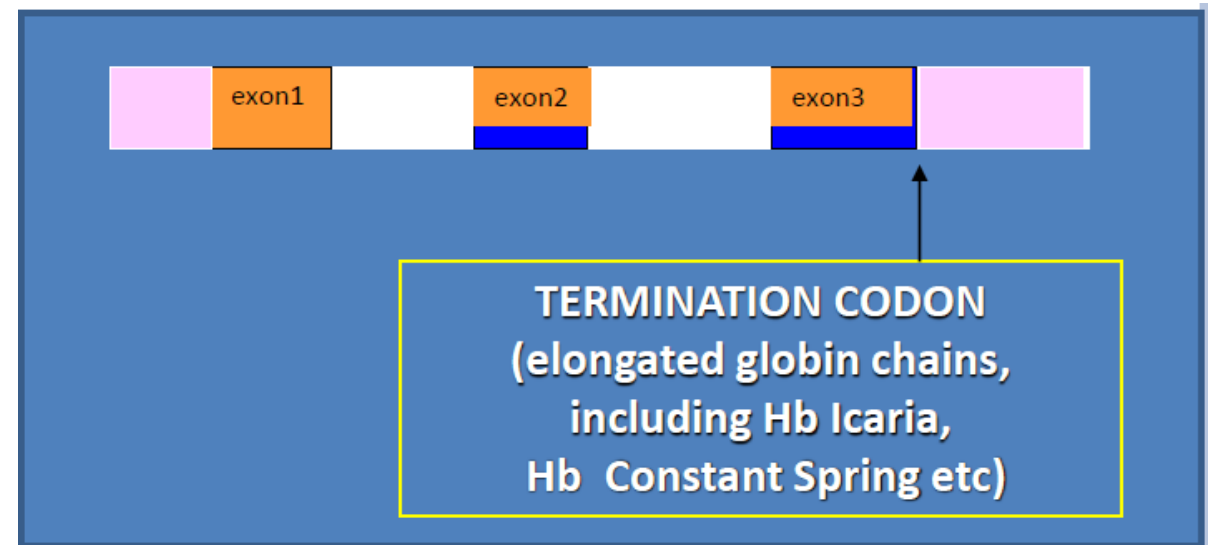
HBB gene mutations population-specific



←
Mild
mutations

➤ Termination codon mutations of the HBA2, such as Hb Constant Spring, Hb Icaria, Hb Seal Rock, Hb Paksé and Hb KoyaDora, alter the stop codon at position 142 into a coding sequence, which results in an elongated α -chain and a highly unstable hemoglobin variant expressed at low level.

➤ Pathophysiological mechanism: the transcription of an unstable mRNA with a shortened life span, unstable Hb variant precipitates

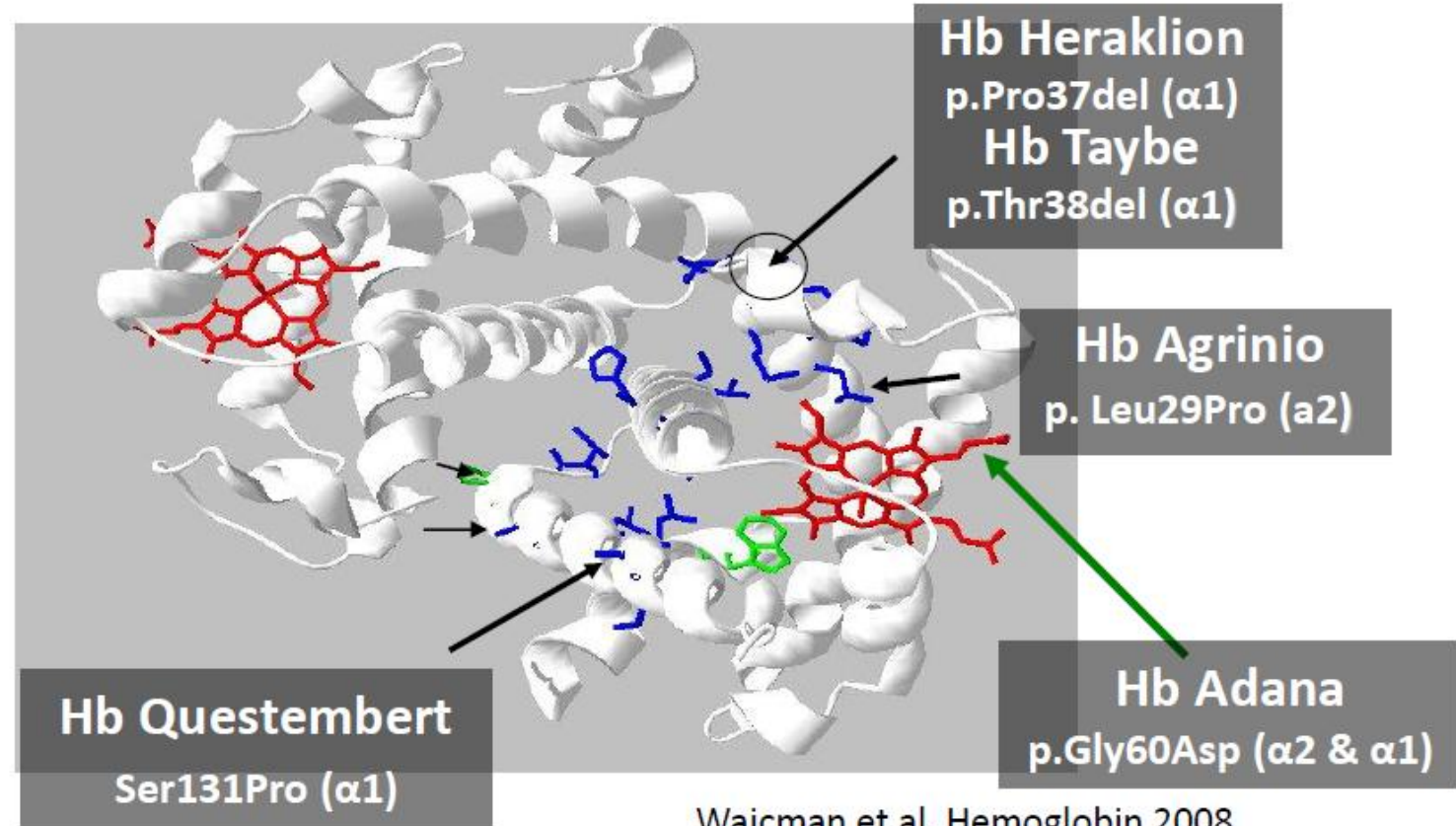


α -thalassaemia haemoglobinopathies involving hyperunstable α -globin variant alleles

Inhibit correct formation of Hb tetramer when in $\alpha 1\beta 1$ contact

and/or

Affect interaction of variant α -globin chain with AHSP

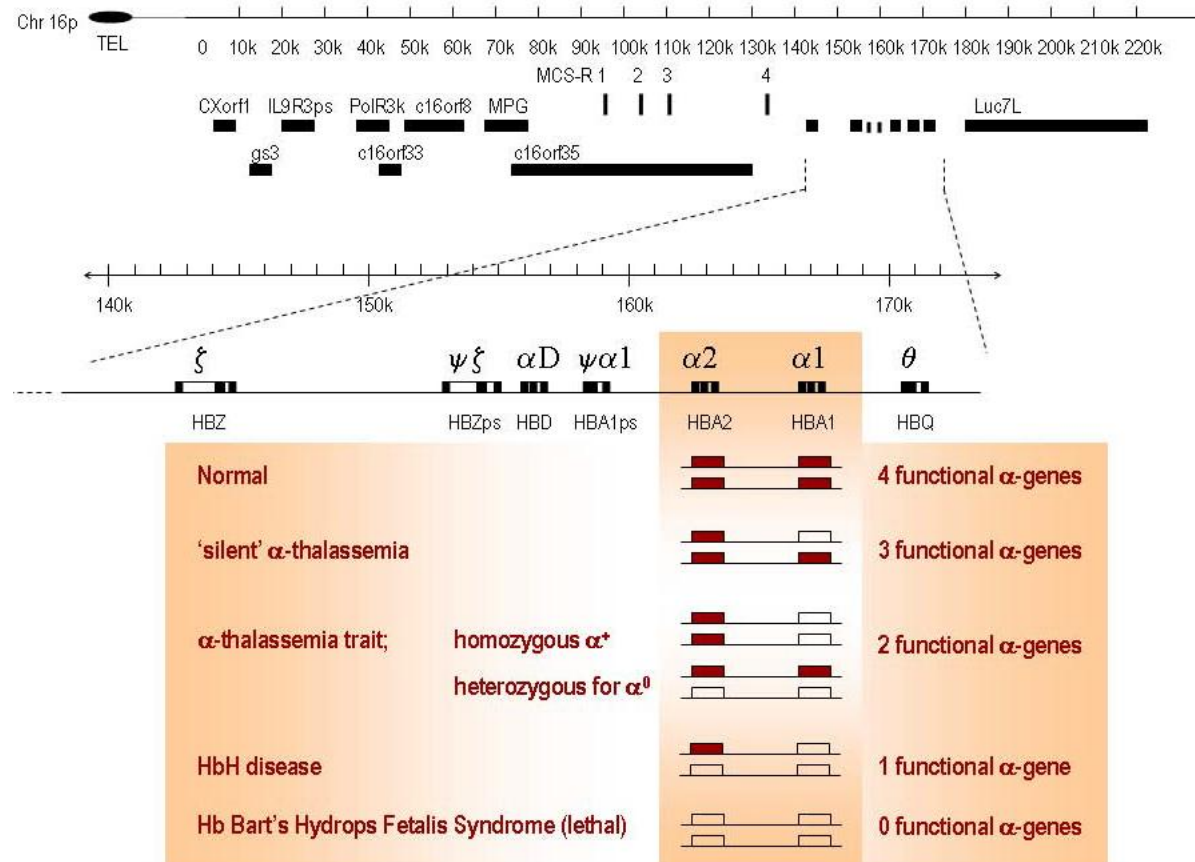


Wajcman et al, Hemoglobin 2008

Such unstable proteins may precipitate causing insoluble inclusion and damage the red cell membrane.

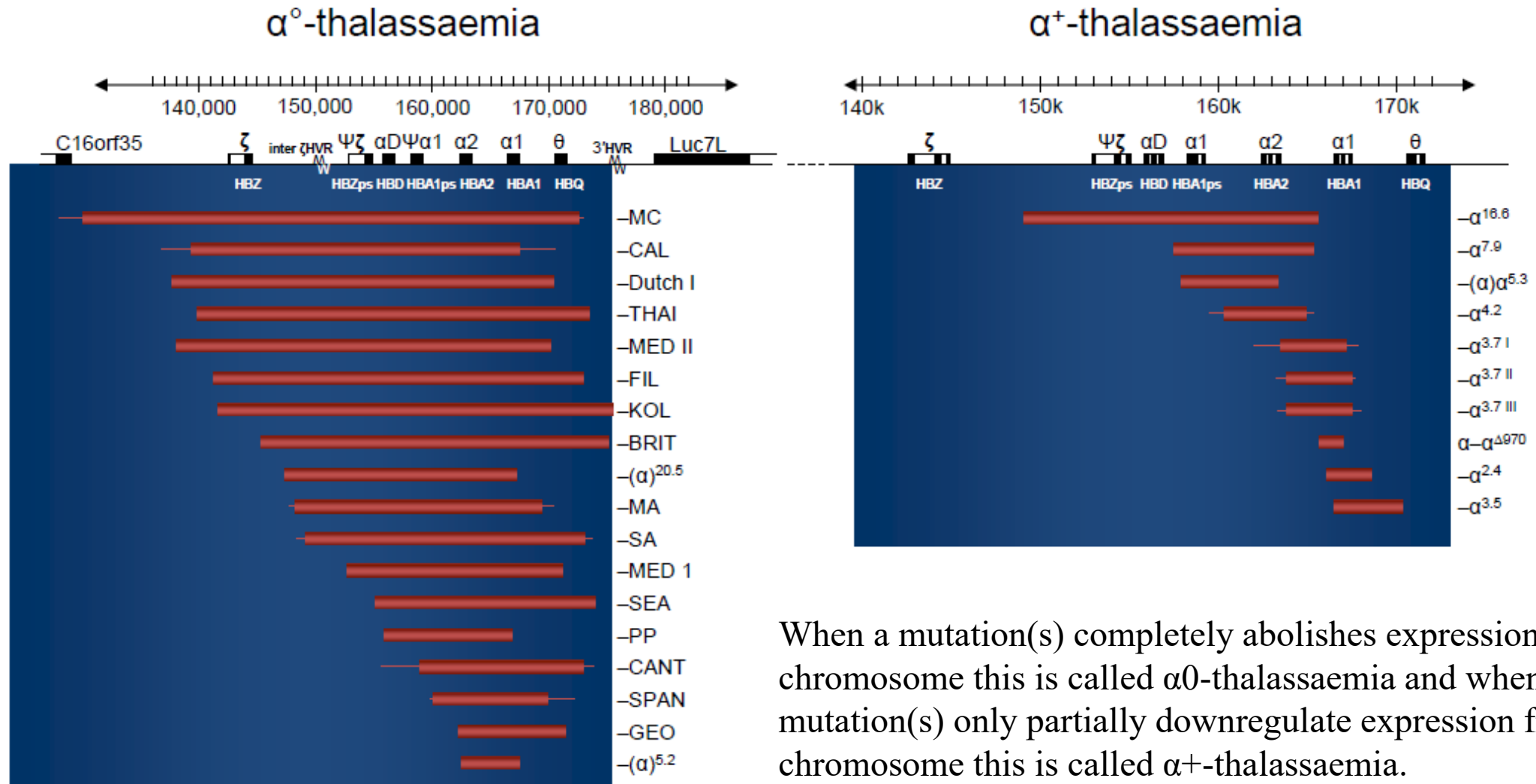
Traeger-Synodinos et al, 1999; Traeger-Synodinos et al, 2000; Oron-Karni et al, 2000; Stamoulakatou et al, 2004; Douna et al, 2008; Traeger-Synodinos et al, 2010

The structure of the α -globin gene cluster on chromosome 16



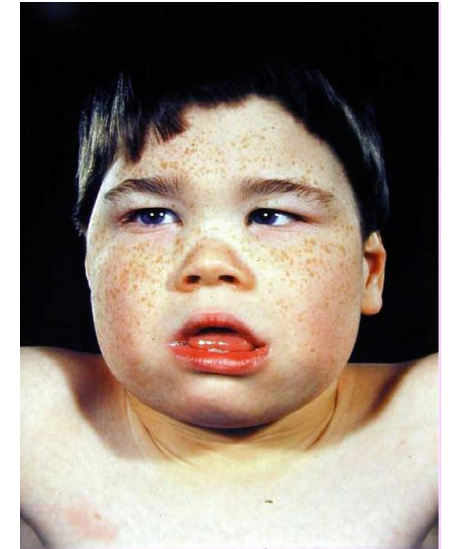
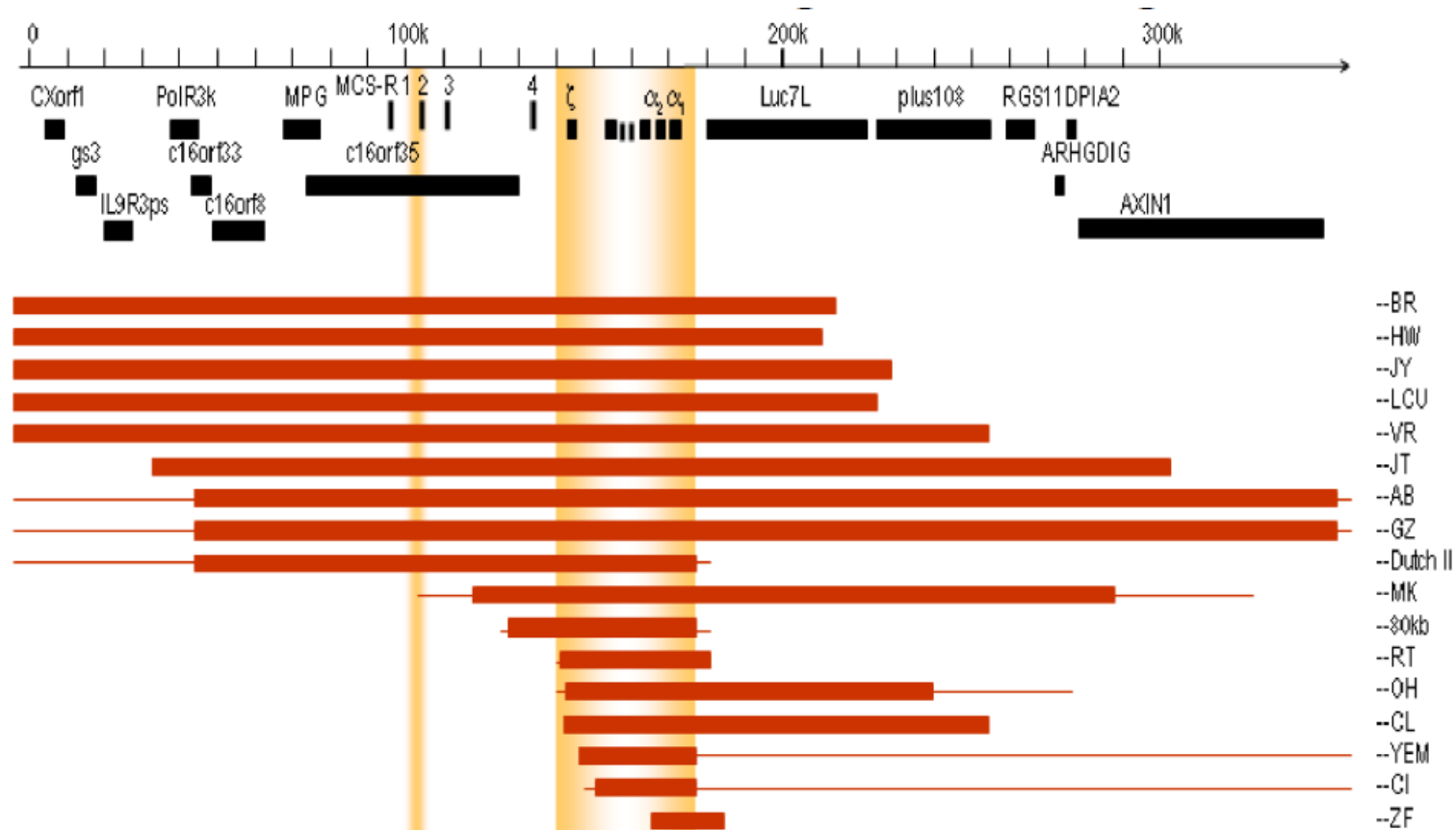
α -thalassaemic variants usually consist of deletion of one ($-\alpha$) or both ($-\alpha -$) α -globin genes of the chromosome

DELETIONS GIVING RISE TO ALPHA-THALASSEMIA



When a mutation(s) completely abolishes expression from a chromosome this is called α^0 -thalassaemia and when the mutation(s) only partially downregulate expression from the chromosome this is called α^+ -thalassaemia.

Rare deletions removing both *HBA* genes



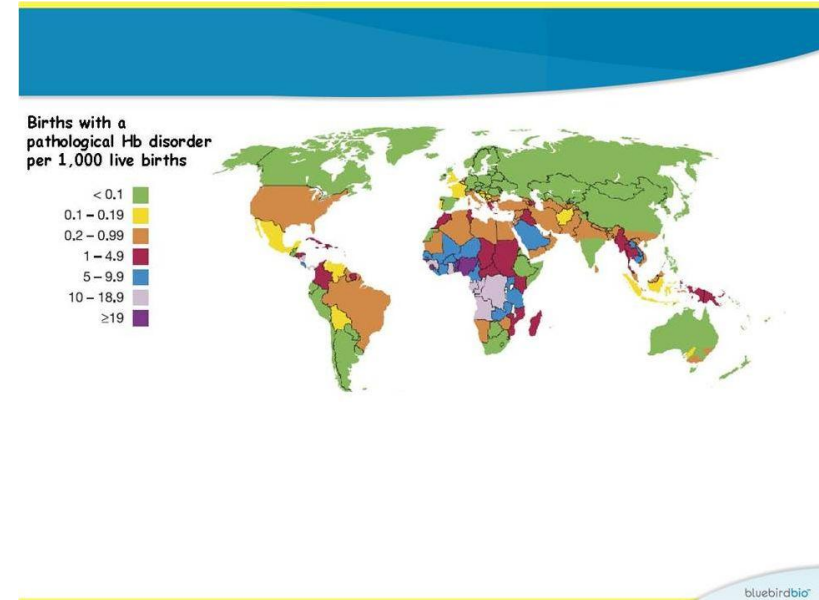
Σε ασθενείς με μεγάλα ελλείματα > 1Mb (μονοσωμία για ένα μεγάλο τμήμα 16p13,3) η α θαλασσαιμία σχετίζεται με αναπτυξιακές ανωμαλίες και διανοητική καθυστέρηση - γνωστό ως ATR-16 σύνδρομο

Μοριακές Βλάβες

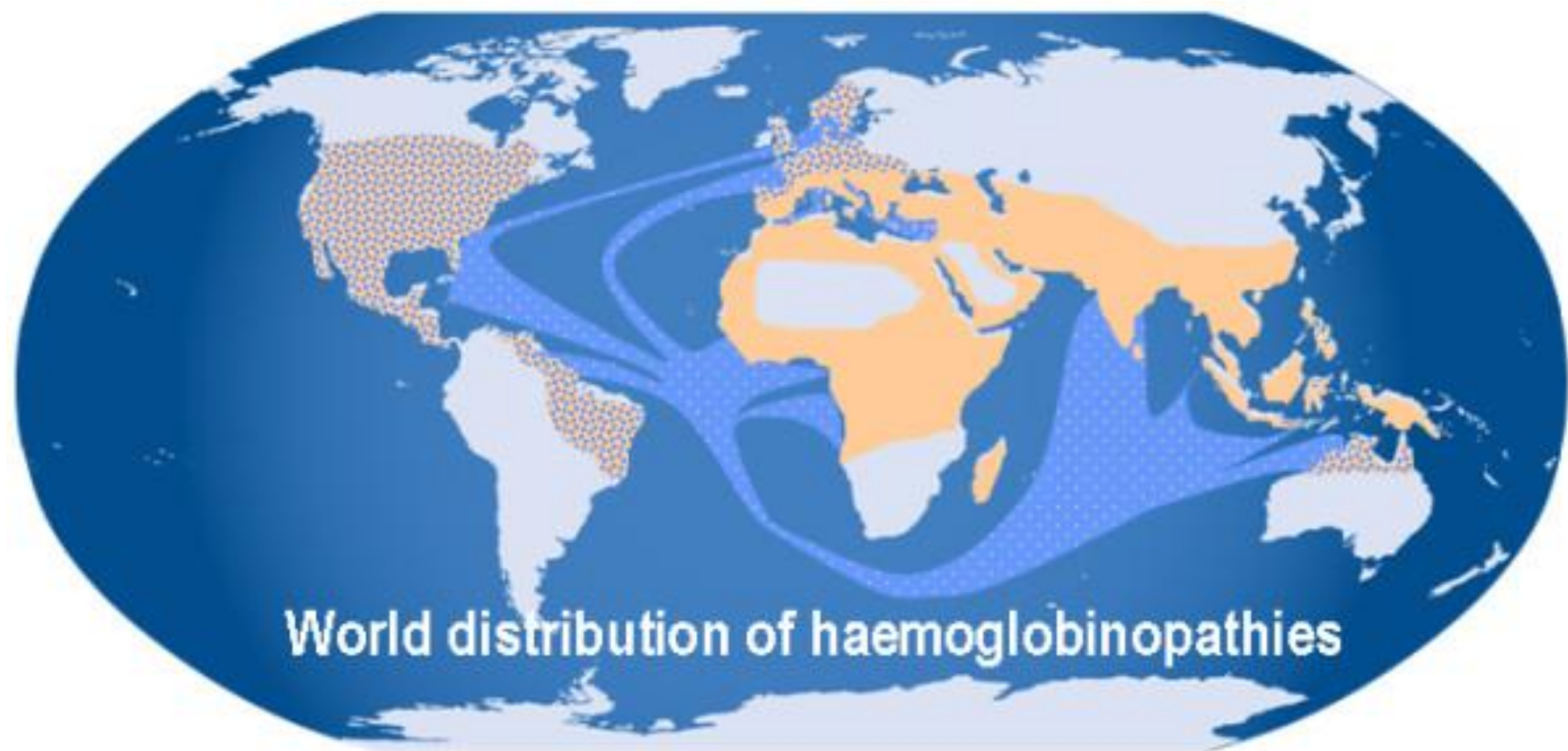
	Σημειακές μεταλ. ελλειμμα	
α-Thalassemia	++	+++
β- Thalassemia	++++	+
βδ- Thalassemia	++++	+

Επιδημιολογία Αιμοσφαιρινοπαθειών

- 7% του παγκόσμιου πληθυσμού είναι φορείς διαφόρων αιμοσφαιρινοπαθειών (~270.000.000)
- 1,5 % φορείς β-θαλασσαιμίας (~ 80-90.000.000)
- **330.000 νέες περιπτώσεις πασχόντων/έτος**
 - 280.000 : Δρεπανοκυτταρική νόσος
 - 42. 500 : β-θαλασσαιμία
 - 13.500 : α-θαλασσαιμία
- 90% Ασία, Ινδία, Μέση Ανατολή, Αφρική

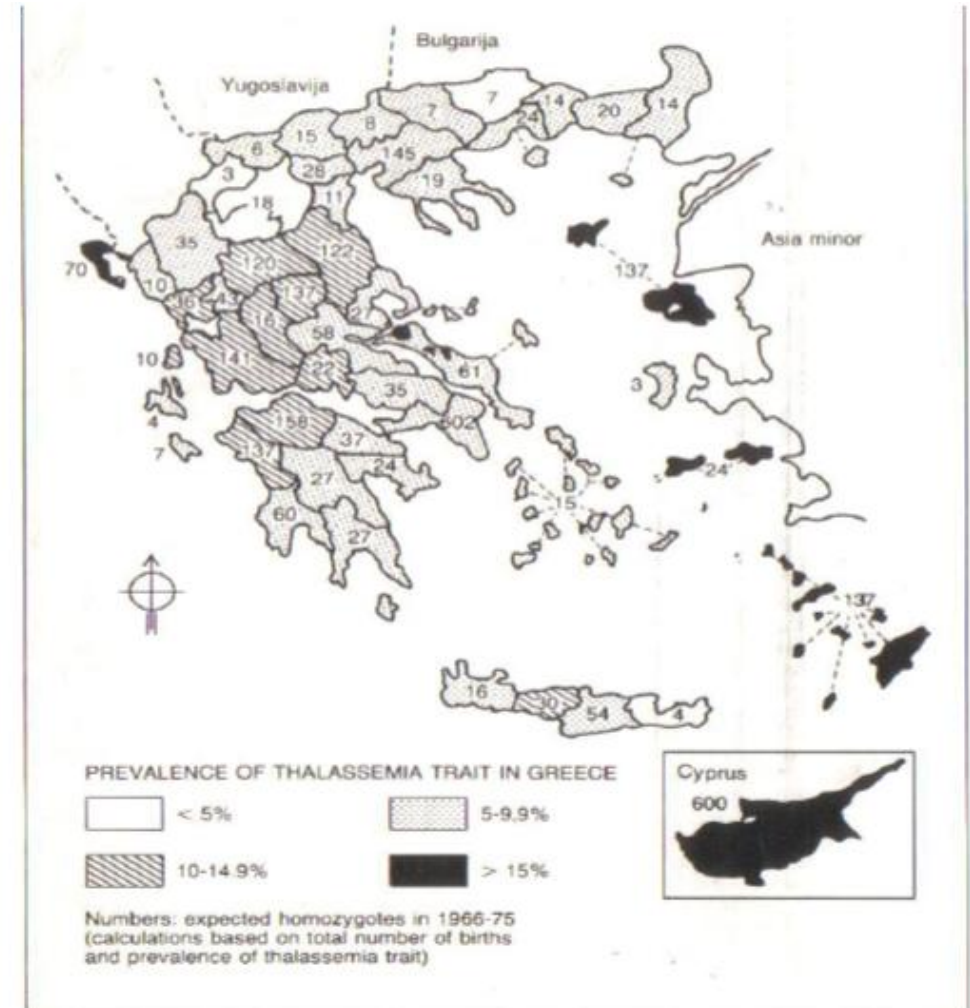


WHO Κατά προσέγγιση υπολογισμοί (2008)

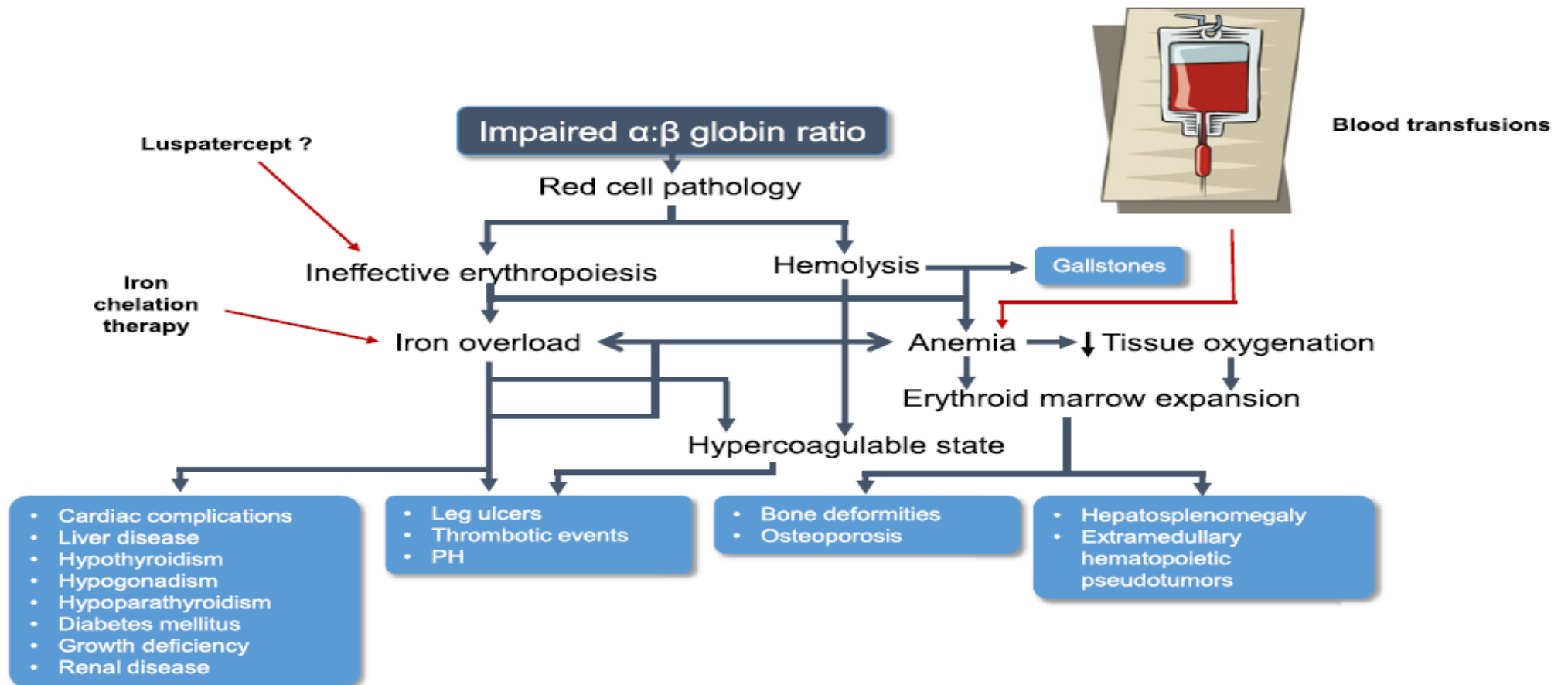


Incidence of thalassemia trait in the Greek population

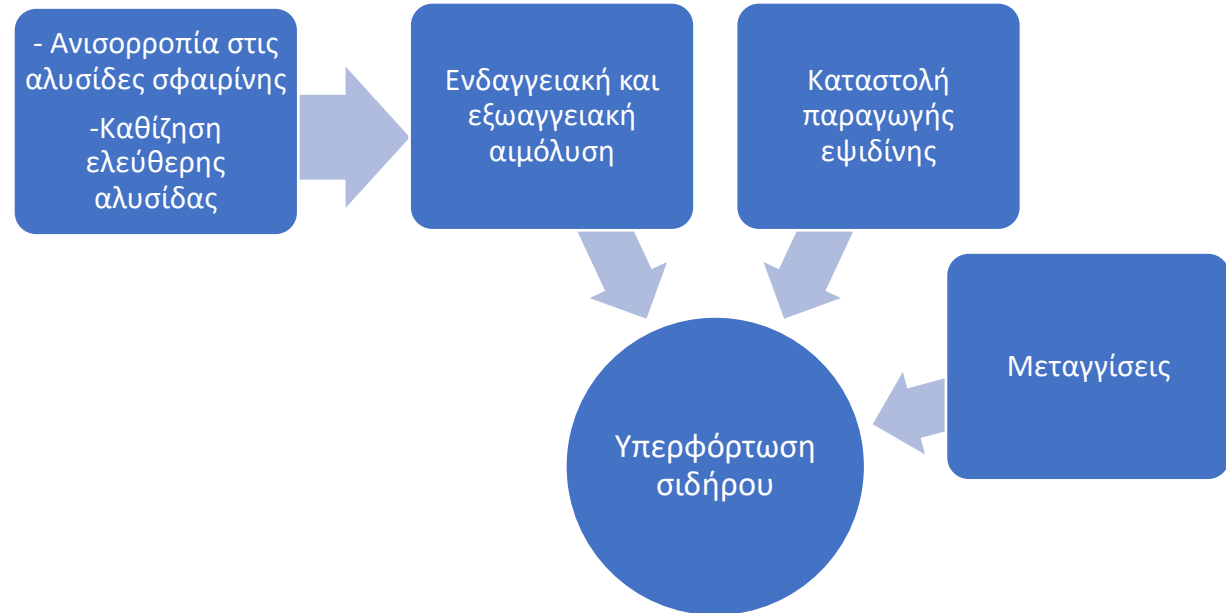
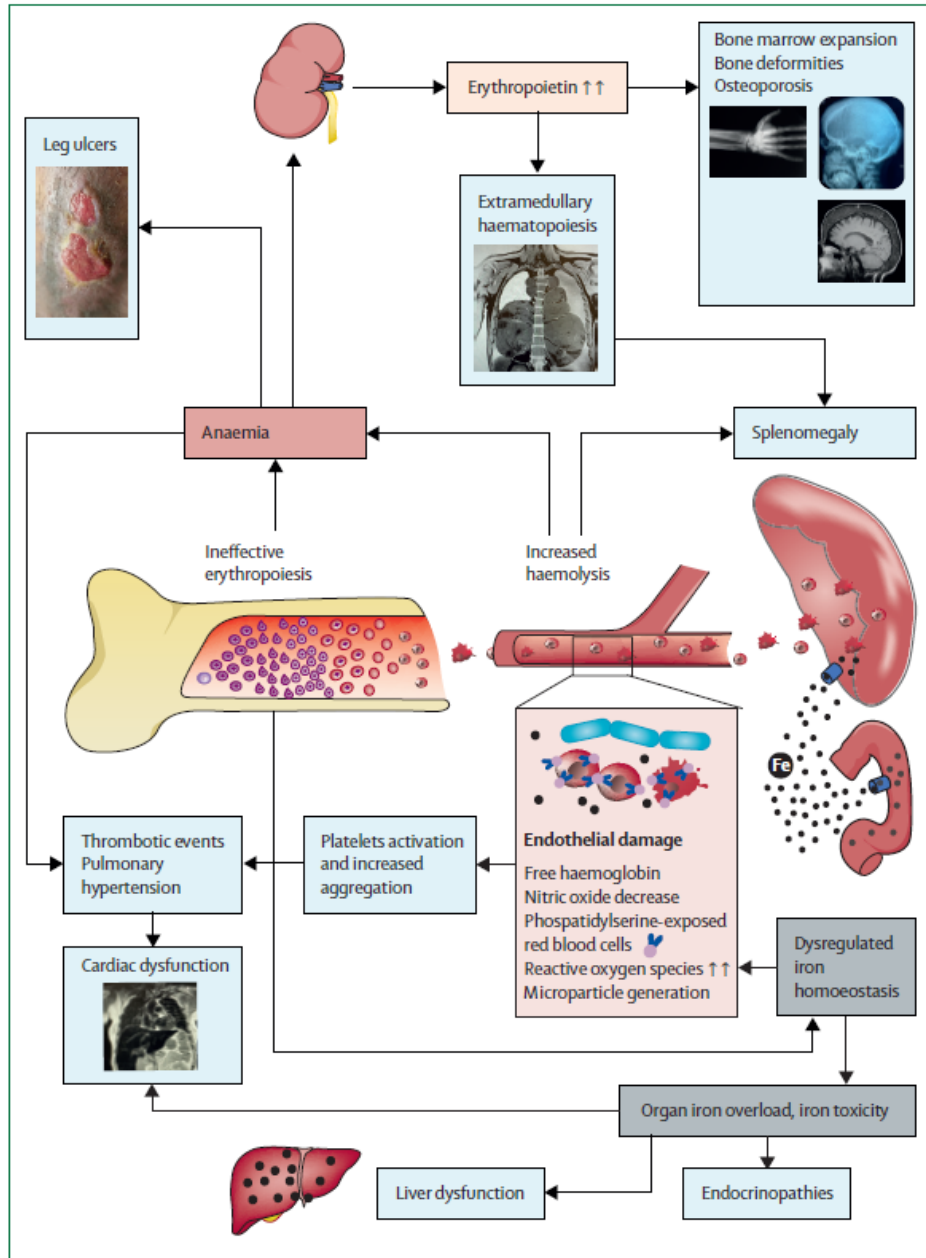
- ✓ β -thalassaemia trait 7.4%
- ✓ α -thalassaemia trait 8.5%
(α^+ : 7.1%, α^0 : 1.4%)
- ✓ HbS trait $\sim 1\%$
- ✓ Births of homozygotes during 1966–75:
2,850



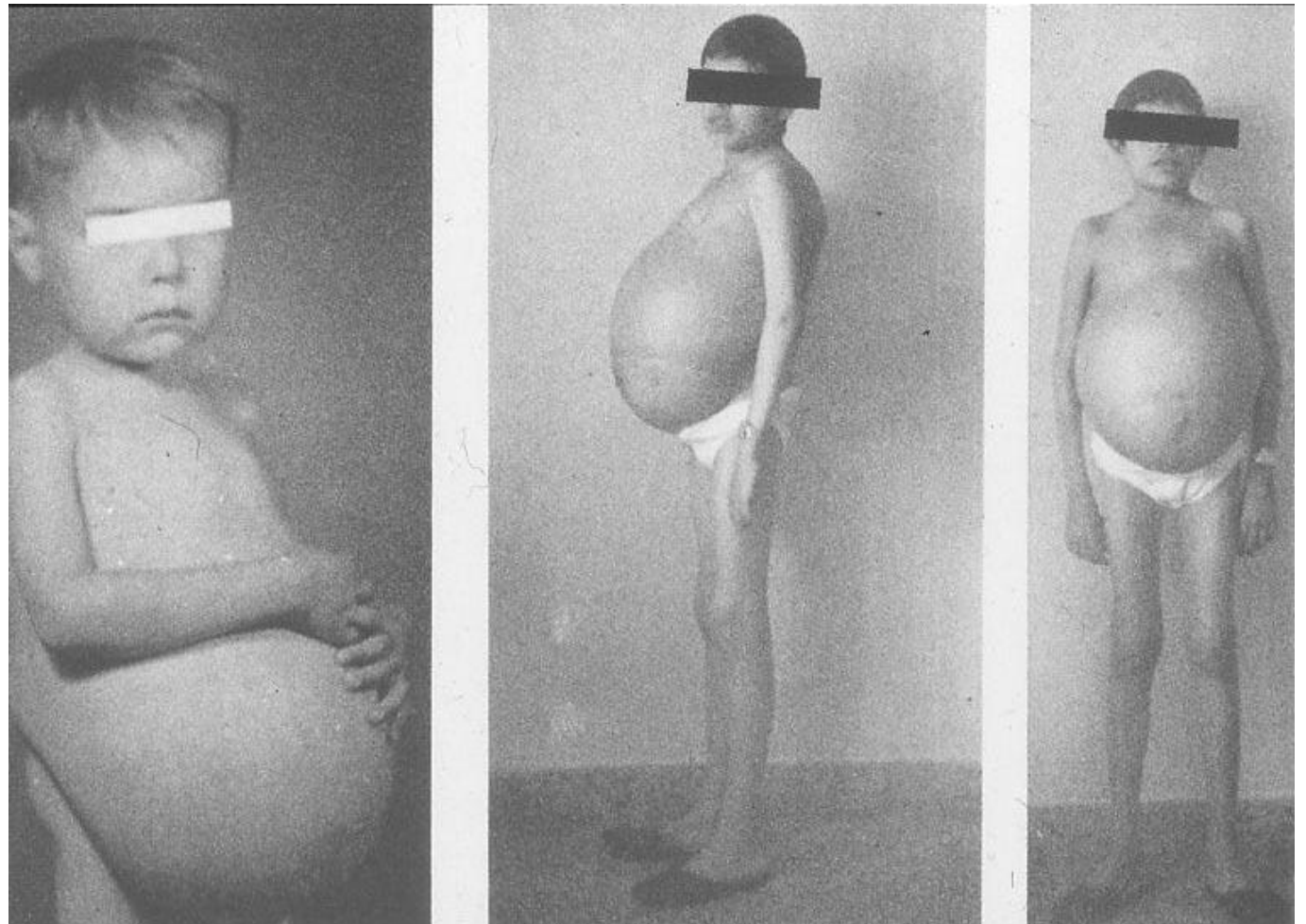
Παθοφυσιολογία



Παθοφυσιολογία Μεσογειακής Αναιμίας



- Σοβαρή Αναιμία
- Ηπατοσπληνομεγαλία
- Οστικές δυσμορφίες
- Υπέρχωση δέρματος
- Λευκοκυττάρωση-ερυθροκυττάρωση



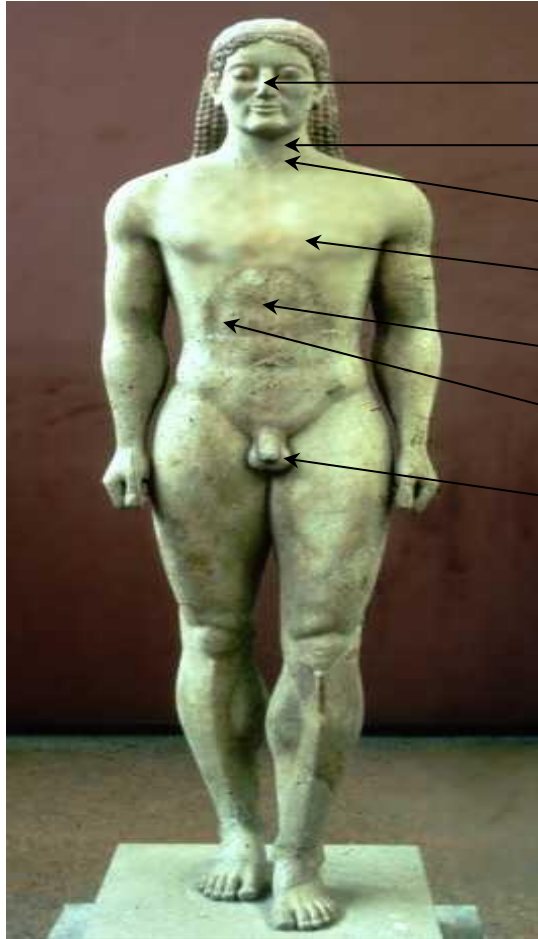
Cooley B and Lee P: American Pediatric Society, 1925

ΚΛΙΝΙΚΕΣ ΕΚΔΗΛΩΣΕΙΣ β-ΜΑ

- Αναιμία 1. Αδυναμία σύνθεσης β-αλύσων
2. Μη αποδοτική ερυθροποίηση [Μυελός]
3. Αιμόλυση [Περιφέρεια]
- Οστικές παραμορφώσεις: Αναιμία – Ιστική ανοξία –
Ερυθροποιητίνη – Υπερπλασία ΜΟ
- Διόγκωση ήπατος-σπληνός: Εξωμυελική ερυθροποίηση
- Αιμοσιδήρωση οργάνων: Αύξηση απορρόφησης Fe, Μεταγγίσεις
- Καθυστέρηση σωματικής αύξησης

* Η βαρύτητα των κλινικών εκδηλώσεων σχετίζεται με τη γενετική βλάβη

ΚΛΙΝΙΚΕΣ ΕΚΔΗΛΩΣΕΙΣ ΑΙΜΟΣΙΔΗΡΩΣΗΣ



pituitary gland (hypogonadotropic hypogonadism)

thyroid gland (hypothyroidism)

parathyroid gland (hypoparathyroidism)

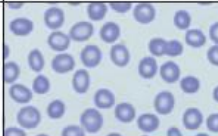
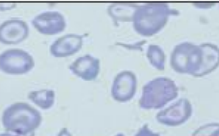
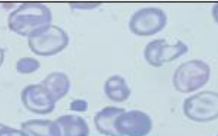
heart (cardiomyopathy)

pancreas (diabetes)

liver (cirrhosis, carcinoma)

gonads (hypogonadism)

Ταξινόμηση Μεσογειακής Αναιμίας

Globin chain balance						
Genotypes	β-thalassaemia	β/β ^{silent}	β/β ⁺ , β/β ⁰ , β/β ^E	Combination of β ^{Thal} /β with α-gene multiplication β ^{silent} /β ^{silent} , β ^{silent} /β ⁺ , β ^{silent} /β ⁰ , β ⁺ /β ⁺ , β ⁺ /β ⁰ , β ^E /β ⁺ , β ^E /β ⁰ , Combination of β ^{Thal} /β ^{Thal} with either α-thalassaemia or increased fetal haemoglobin production	β ⁺ /β ⁺ , β ⁺ /β ⁰ , β ^E /β ⁺ , β ^E /β ⁰ , β ⁰ /β ⁰ (β ^{silent} /β ^{silent} , β ^{silent} /β ⁺ , β ^{silent} /β ⁰ with α-globin gene multiplication)	
	α-thalassaemia	- α/αα	- α/- α, - -/αα	- -/- α, - α/α ND α, α ND α/α ND α, - -/α ND α	- -/- α, α ND α/α ND α, - -/α ND α, - -/- -	
Haematological indexes						
Clinical phenotype		Normal		Mild	Moderate	Severe
Transfusion requirements		None		Non-transfusion-dependent thalassaemia		Transfusion-dependent thalassaemia
				 None	 Rare	 Occasional
Thalassaemia		Minor		Intermedia		Major

Haematological and clinical phenotypes correlate with genotypes and severity of globin chain imbalance. ND=non deletional

Κλινικά κριτήρια TDT/NTDT

Clinical Criteria	TDT More Likely	NTDT More Likely
Age at presentation	≤2 years	>2 years
Degree of anemia at presentation	Severe	Mild to severe
Clinical anemia affecting daily living	Yes	No
Splenomegaly at presentation	Severe	Mild to severe
Jaundice	No	Mild
Skeletal deformities	Yes	Negative to mild
Growth retardation	Moderate to Severe	Negative to moderate
Transfusion requirements	Lifelong, dependence for survival	None, occasional, or frequent but temporary
Hb levels	6–7 gm/dL	8–10 gm/dL
Nucleated RBCs	Numerous	Negative to few
Reticulocytes	>10%	<10%

TDT: transfusion dependent thalassemia; NTDT: non-transfusion dependent thalassemia; RBCs: red blood cells.

Επιπλοκές

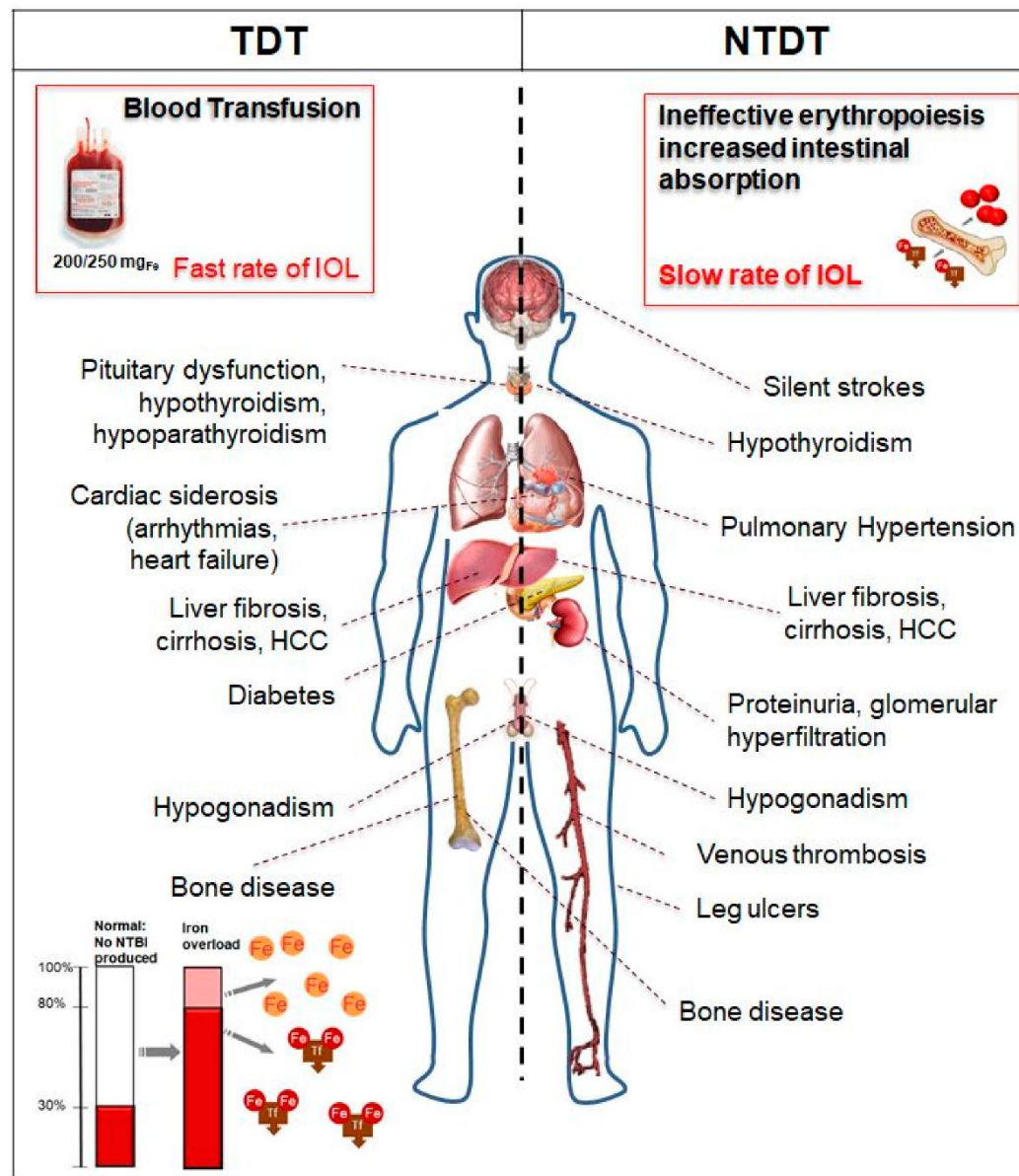
Table 1

The difference in complications between transfusion-dependent thalassemia and non-transfusion-dependent thalassemia

Complications	TDT	NTDT	Management
Cardiac dysfunction	+++	+	Iron chelation + standard care
Arrhythmias	+	++	Standard care
Viral hepatitis	+++	+	HBV vaccination, antiviral therapy
Hepatic fibrosis, cirrhosis, and cancer	++	+++	Standard care
Growth retardation Sexual development	++	+	Transfusion + chelation + hormones
Glucose intolerance/diabetes	++	+	Standard care
Bone disease	++	+++	Standard care + specific therapy
Extramedullary hematopoietic masses	+	+++	Hypertransfusion, HU, radiation
Thrombosis	+	+++	Anticoagulation, transfusion
Pulmonary hypertension	+	+++	Standard care, sildenafil, bosentan
Leg ulcers	+	++	Topic measures, HU

Abbreviations: HBV, hepatitis B virus; HU, hydroxyurea.

Επιπλοκές Μεσογειακής Αναιμίας



Επιπλοκές

		Επιπολασμός		
Καρδιακές επιπλοκές	υπερκοιλιακή αρρυθμία κολπική μαρμαρυγή, αρ. δυσλειτουργία κοιλίας	10%-39%	Koohi F et al. <i>Ann Hematol.</i> 2019	
Ενδοκρινολογικές	διαβήτης διαταραχή γλυκόζη νηστείας/ Αντίσταση στην ινσουλίνη άλλες ενδοκρινικές διαταραχές Κεντρικός υποθυρεοειδισμός ενήλικες/ παιδιά 4.8%/0.5%	6.5% 17.2% /12.5% 43.9% 4.8%/0.5%	He LN et al, <i>Biomed Res Int.</i> 2019 De Sanctis V et. al <i>Acta Biomed.</i> 2019	
Αγγειακά	ισχαιμικά εγκεφαλικά επεισόδια (0,5%), παροδικά ισχαιμικά (0,23%) και σιωπηλά εγκεφαλικά εμφράγματα (0,4%).	1.13%	Haghpanah S et al. <i>Blood Coagul Fibrinolysis.</i> 2012	
Νεφρικές διαταραχές	Σωληναριακή δυσλειτουργία (TDT)	60%	Ahmadzadeh A, et al. <i>Saudi J Kidney Dis Transpl.</i> 2011	
Νευροψυχιατρικές	Ασθενείς ηλικίας >65 χρόνια είχαν 2,24 φορές μεγαλύτερη πιθανότητα να αναπτύξουν άνοια (95% CI, 1.17-4.29)		Chen Yg et al <i>Eur J Intern Med.</i> 2015	
Ανοσοποίηση	Η αλλοανοσοποίηση ερυθροκυττάρων έναντι αντιγόνων του Rh (52,4%) και Kell (25,6%). TDT/NTDT (15,5% / 12,8%)	11.4% (95% CI, 9,3% -13,9%)	Franchini M et al. <i>Blood Transfus.</i> 2019	
Μυοσκελετικό	αρθροπάθεια που σχετίζεται με δεφεριπρόνη ασηπτική νέκρωση κεφαλής μηριαίου 14,5%, οστεοπόρωση /οστεοπενία, με συμβάντα 66% και 16,1%,	16-30% 14% 66% /16,1%,	Noureldine MHA,et al. <i>Rheumatology (Oxford).</i> 2018	
Ρευματολογικά	Ρευματοειδή αρθρίτιδα (Amer College of Rheumatology)	4/90	Pliakou Xi et al. <i>Rheumatol Int.</i> 2012	
Οφθαλμολογικά	ψευδοξανθώματα, ξηροφθαλμία, καταρράκτης , εκφύλιση ωχράς κηλίδας, διαταραχές οπτικών πεδίων TDT/NTDT 68.5% /19.4%	41-85%	Liaska Aet al. <i>BMC Ophthalmol.</i> 2016	

Alpha Thalassemia: *Pathogenesis and clinical presentations*

Author:

Yang (Steven) Liu

Reviewers:

Dex Arnold

Yan Yu

Sean Spence

Man-Chiu Poon*

* MD at time of publication

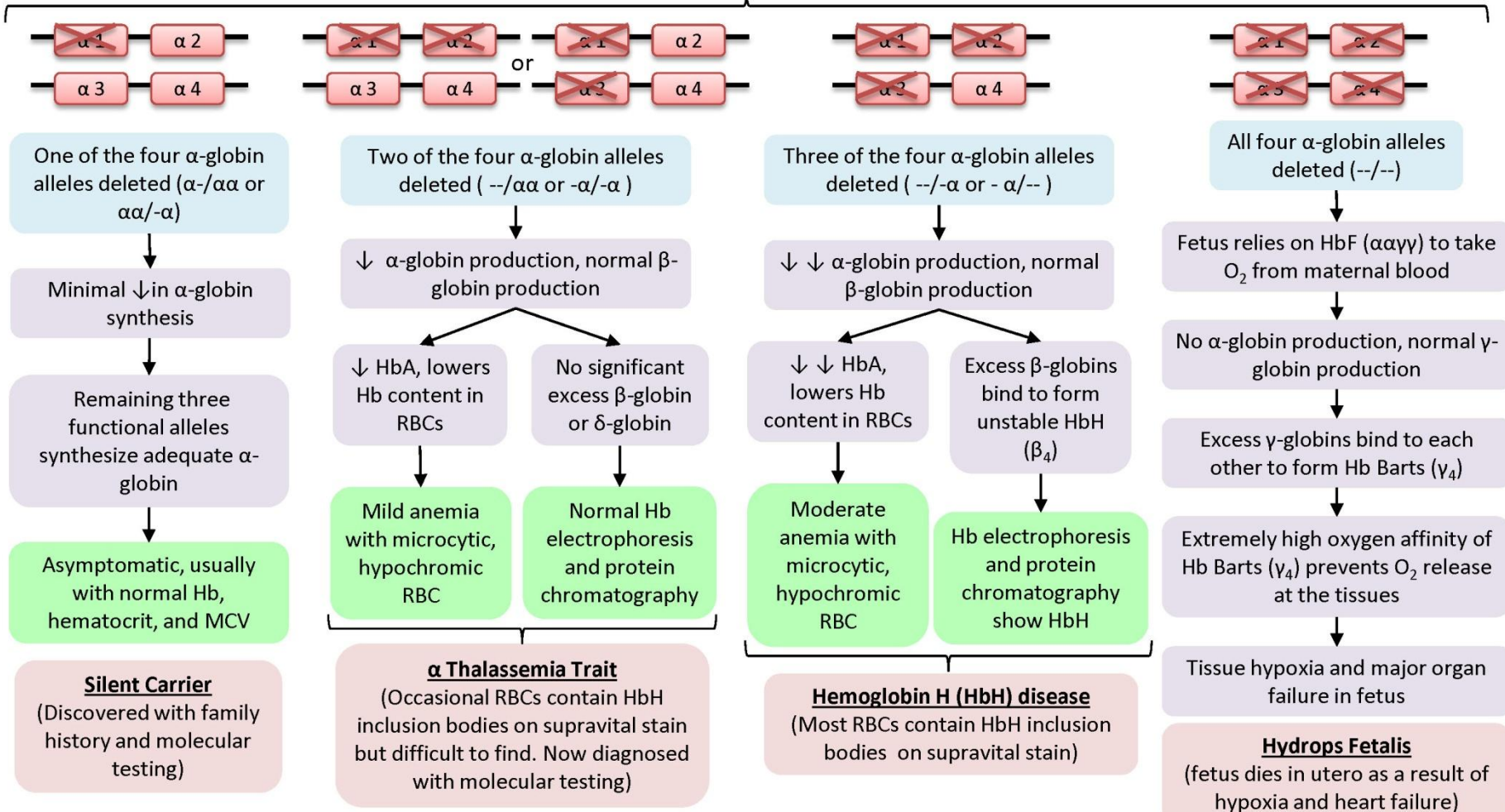
Normal adult hemoglobin (Hb) is

- 96% HbA ($\alpha\alpha\beta\beta = 2\alpha + 2\beta$ chains)
- 2% HbA₂ $\alpha\alpha\delta\delta$
- 2% HbF $\alpha\alpha\gamma\gamma$ (fetal hemoglobin)

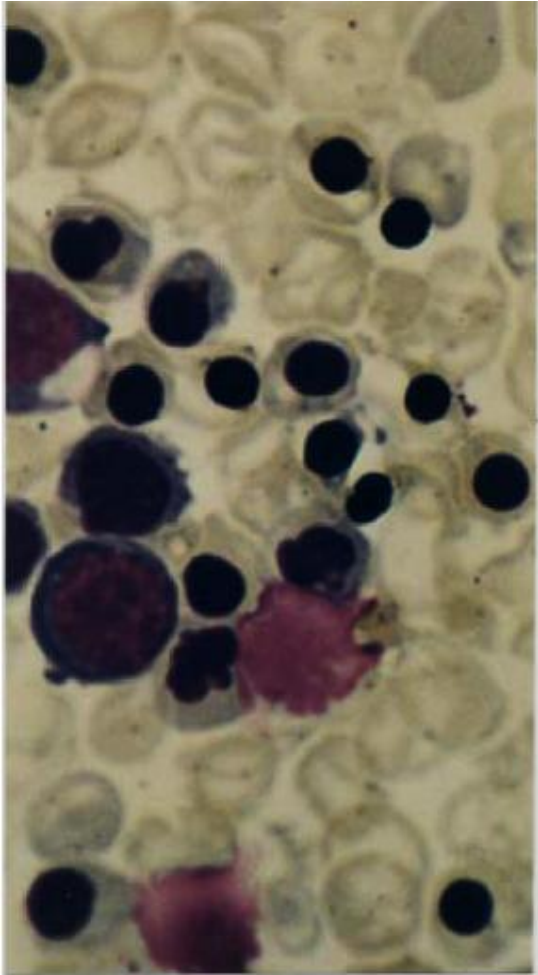
Two genes on chromosome 16 code for α -globin. Two copies of chromosome 16 in each diploid cell makes for four α -globin alleles.

Deletion mutation of one or more α -globin alleles

↓ in quantity of α -globin production



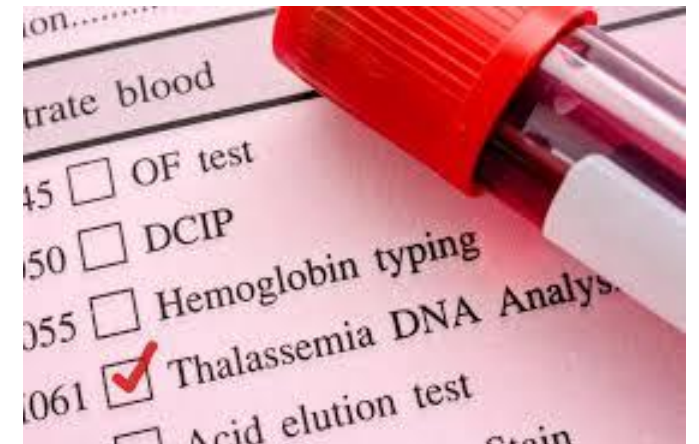
HEMOGLOBIN BART HYDROPS FETALIS SYNDROME



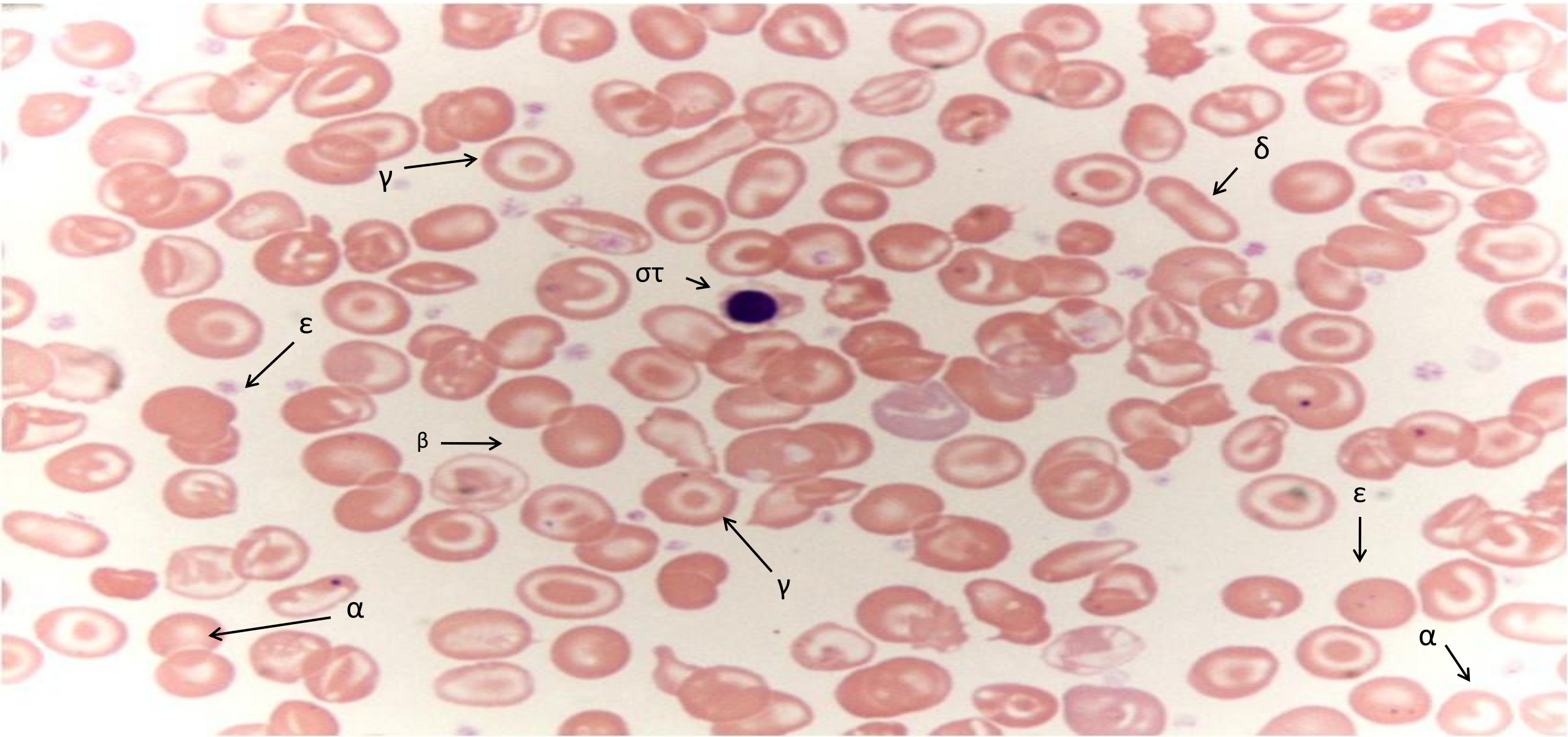
Deletion or inactivation of all four α -globin genes leads to haemoglobin Bart's hydrops fetalis, which typically results in death either in utero or soon after birth, unless the fetus is rescued with intrauterine transfusions

Διάγνωση

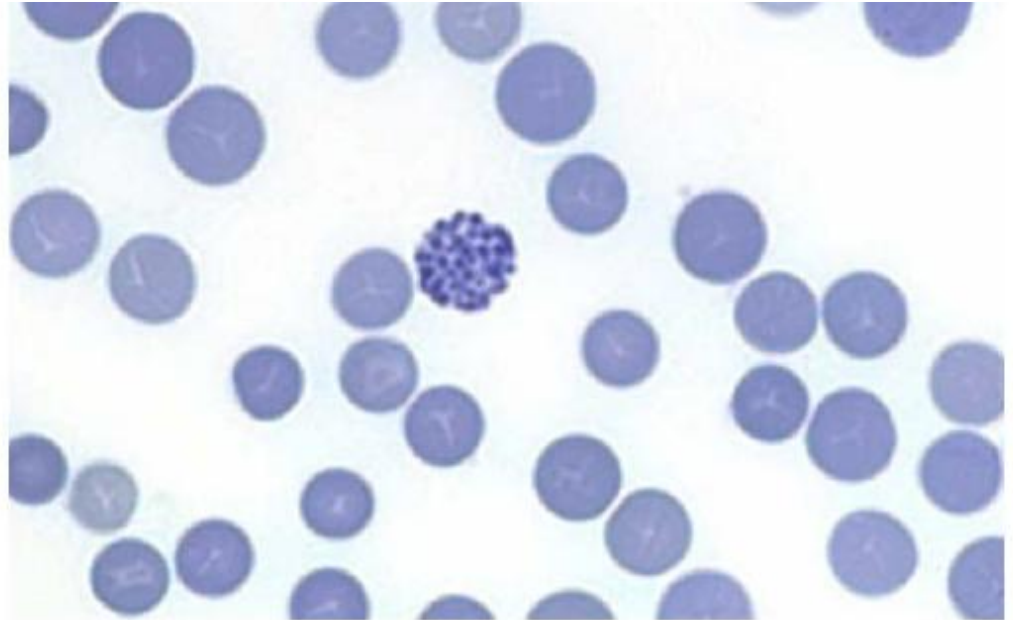
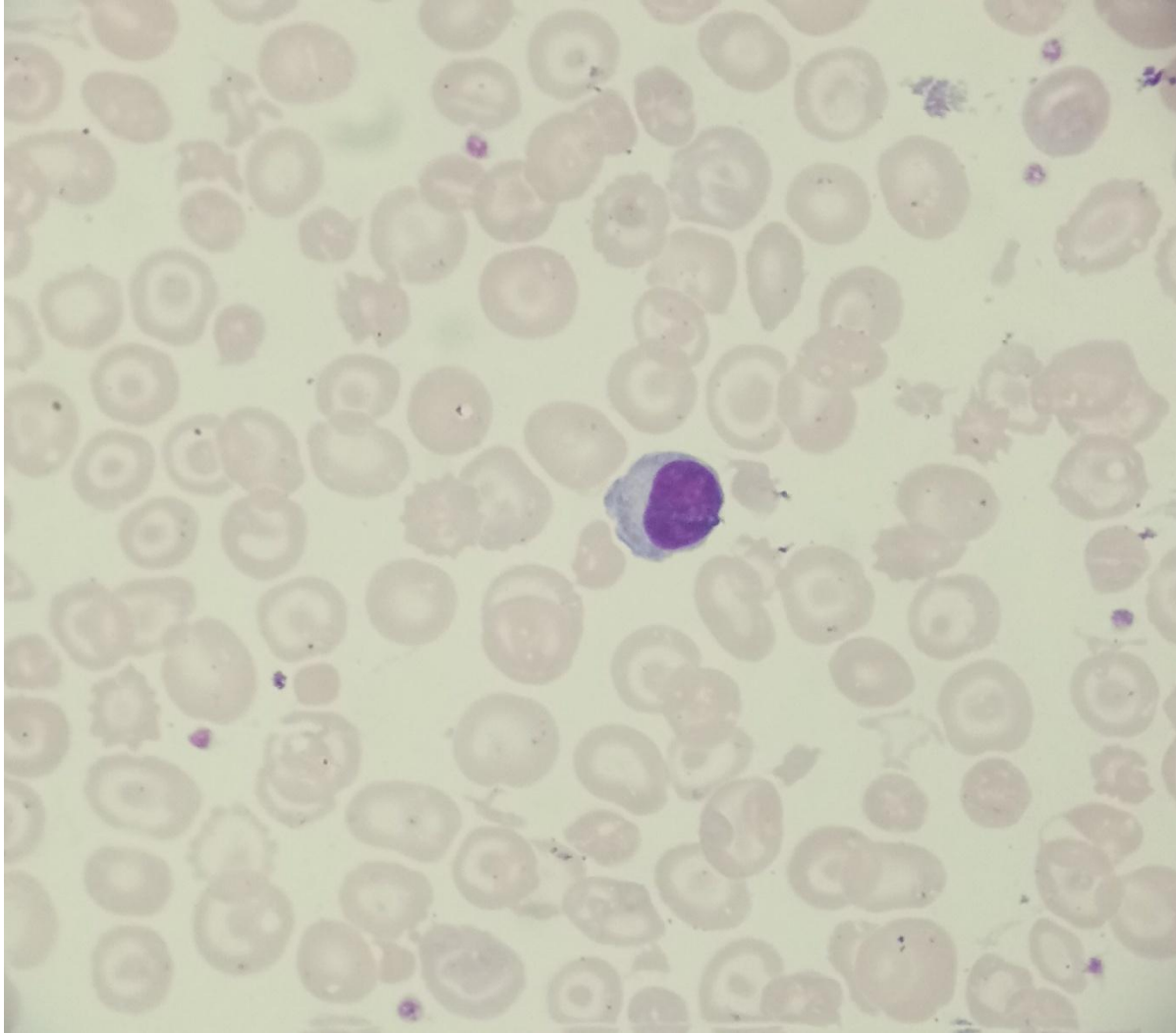
- Γενική Αίματος (complete blood count)
- ΔΕΚ (RET)
- Μορφολογία Μικροκυτταρική/ υπόχρωμη/ έντονες αλλοιώσεις
- Φερριτίνη (Ferritin)
- Ηλεκτροφόρηση (HPLC)
- Έγκλειστα inclusion bodies
- Έλεγχος γονέων
- Γονότυπος (genotype)



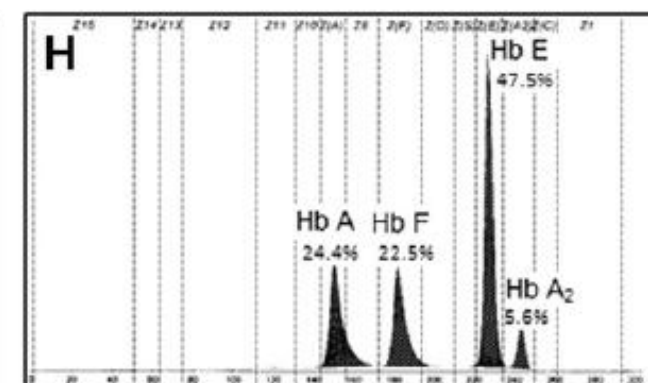
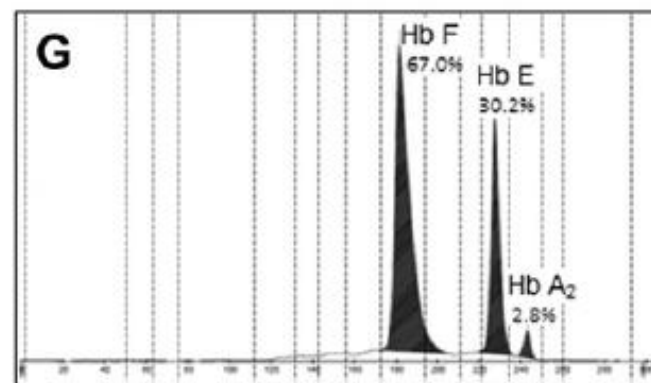
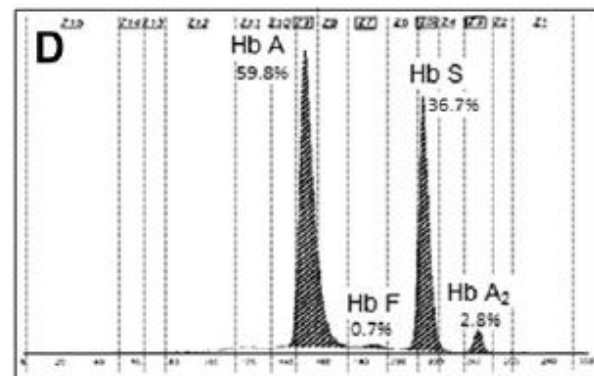
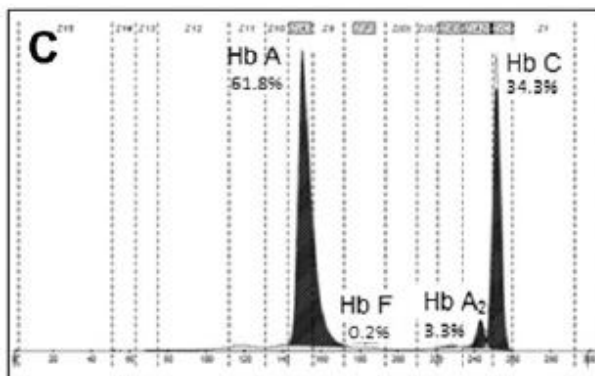
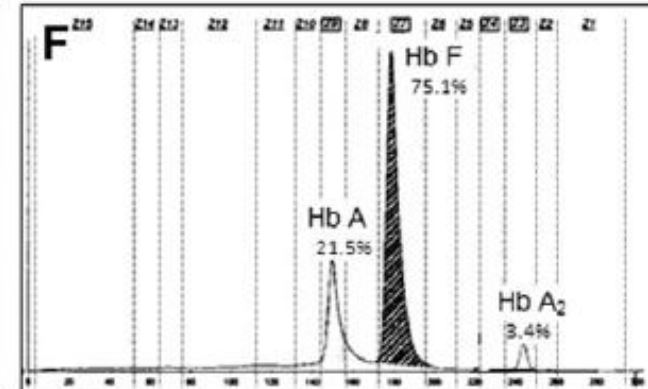
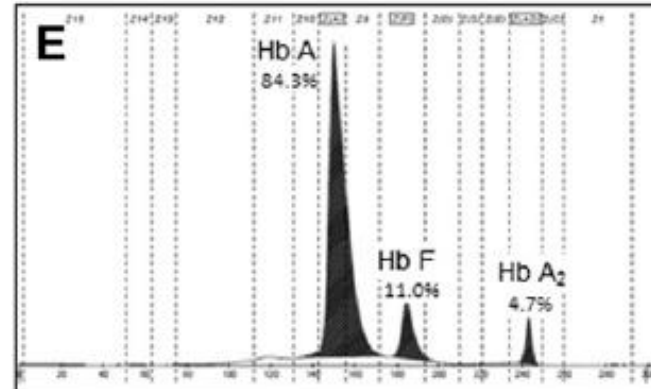
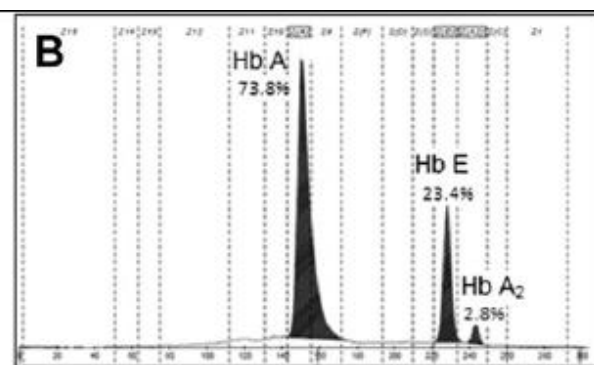
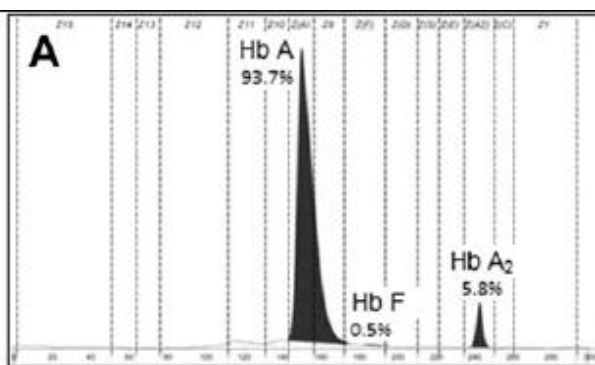
Μορφολογία ερυθρών αιμοσφαιρίων στην ομόζυγη β-θαλασσαιμία
(α) μικροκυτταρικά ερυθρά, (β) νορμόχρωμα ερυθρά, (γ) στοχοκύτταρα, (δ) ελλειπτοκύτταρα, (ε) σφαιροκύτταρα, (στ) ερυθροβλάστη.

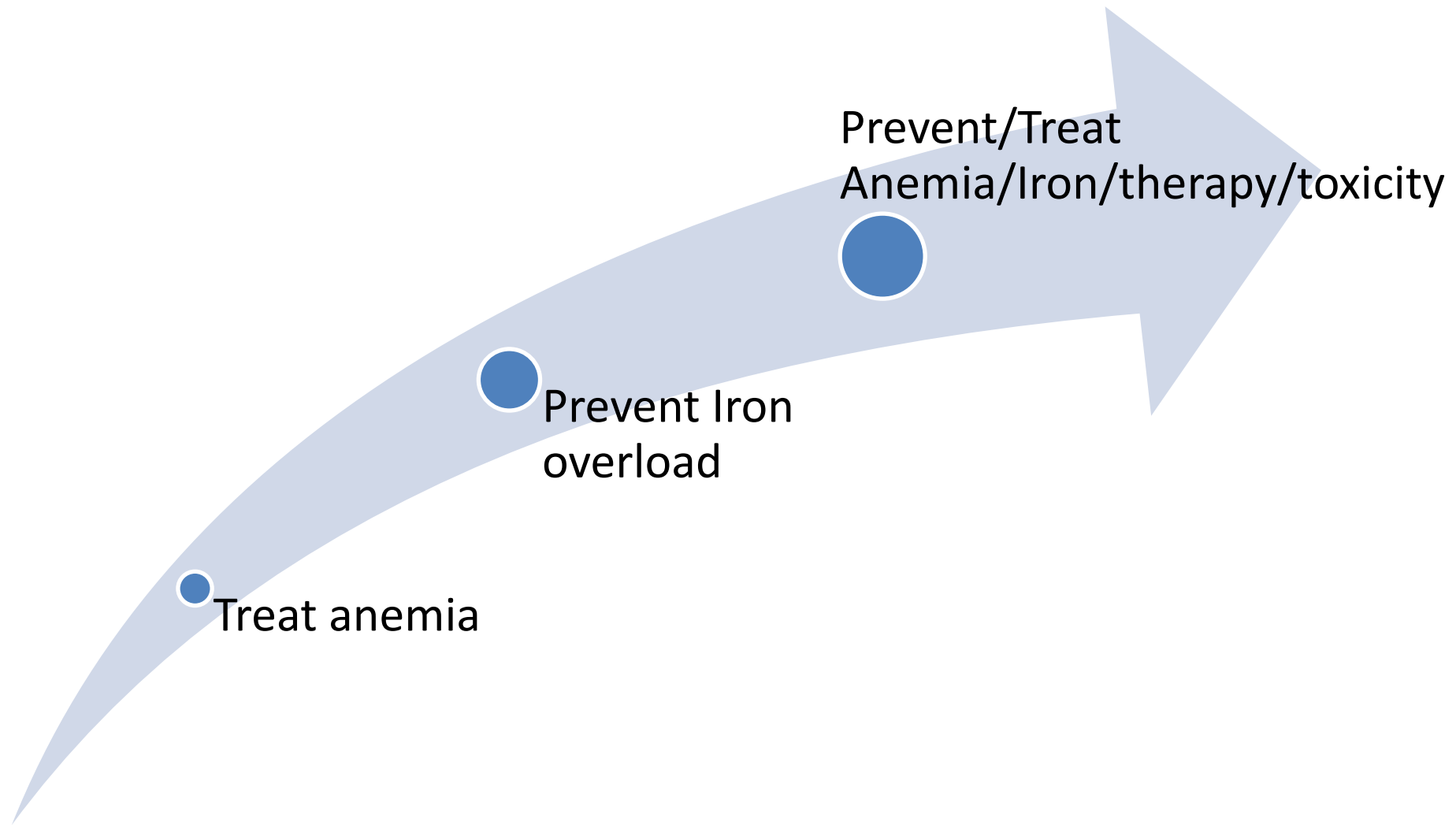


Αιμοσφαιρινοπάθεια Η



An inclusion body positive cell seen in Brilliant Cresyl Blue stained red cells of a α^0 -thalassaemia carrier





GROWTH PATTERN IN THALASSEMIA

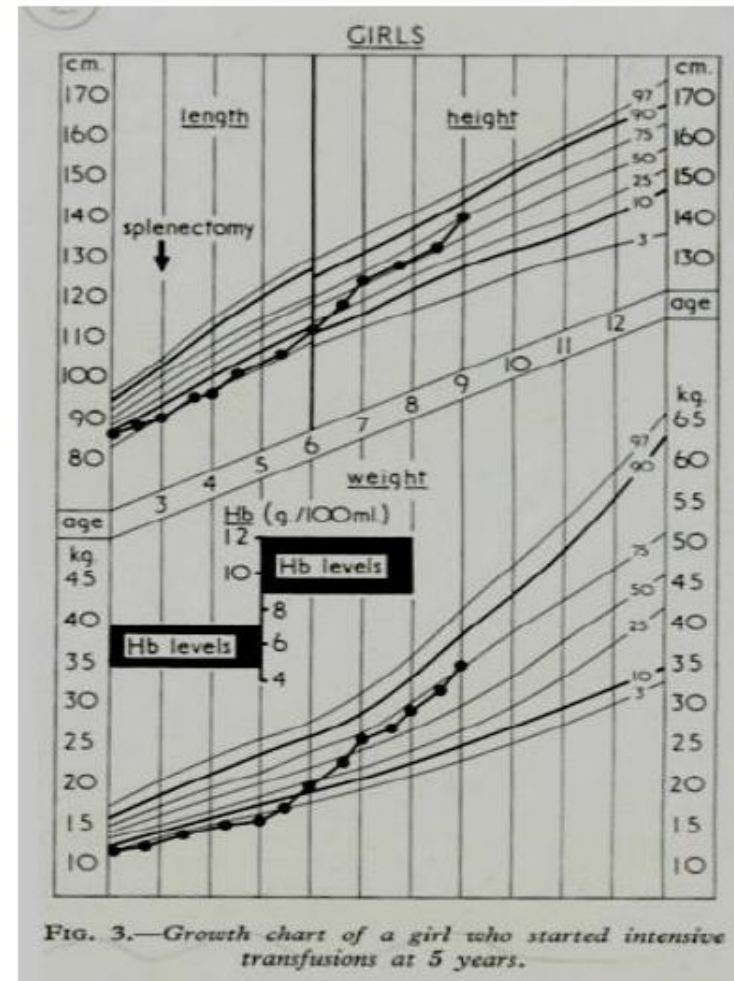
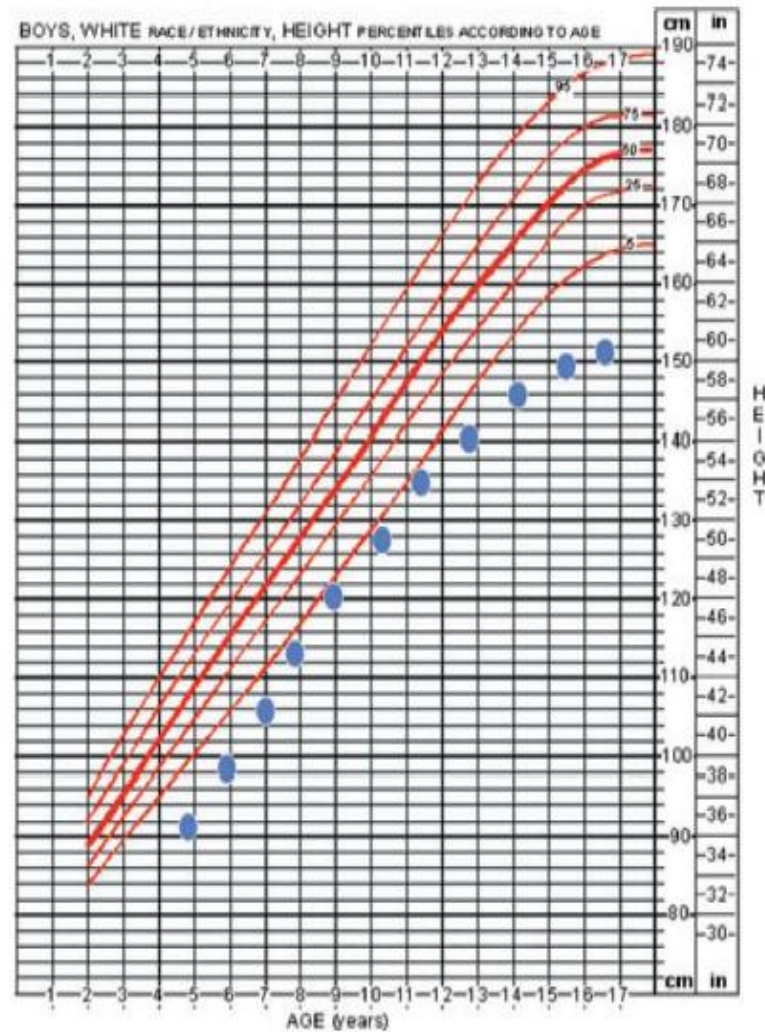
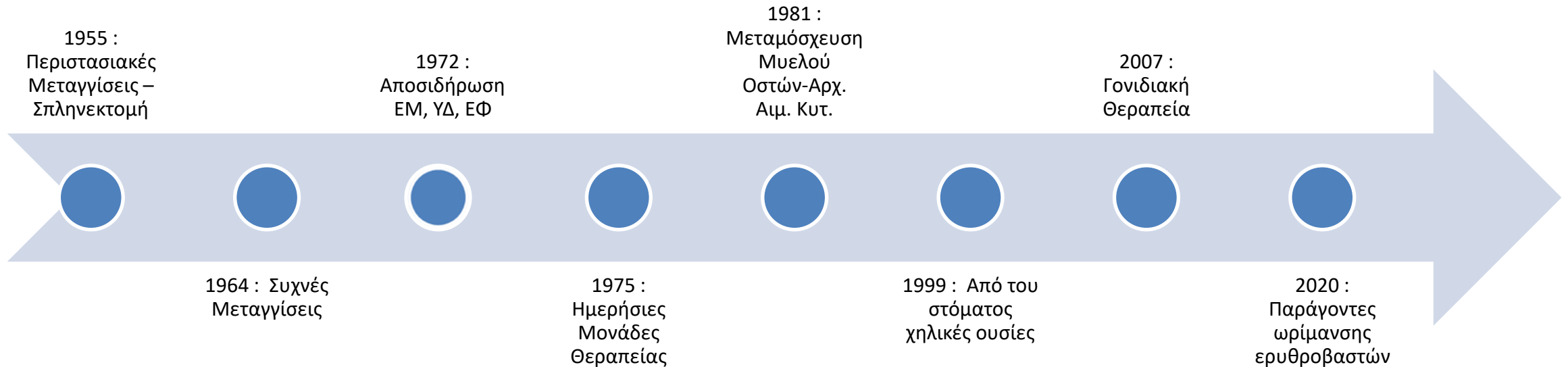


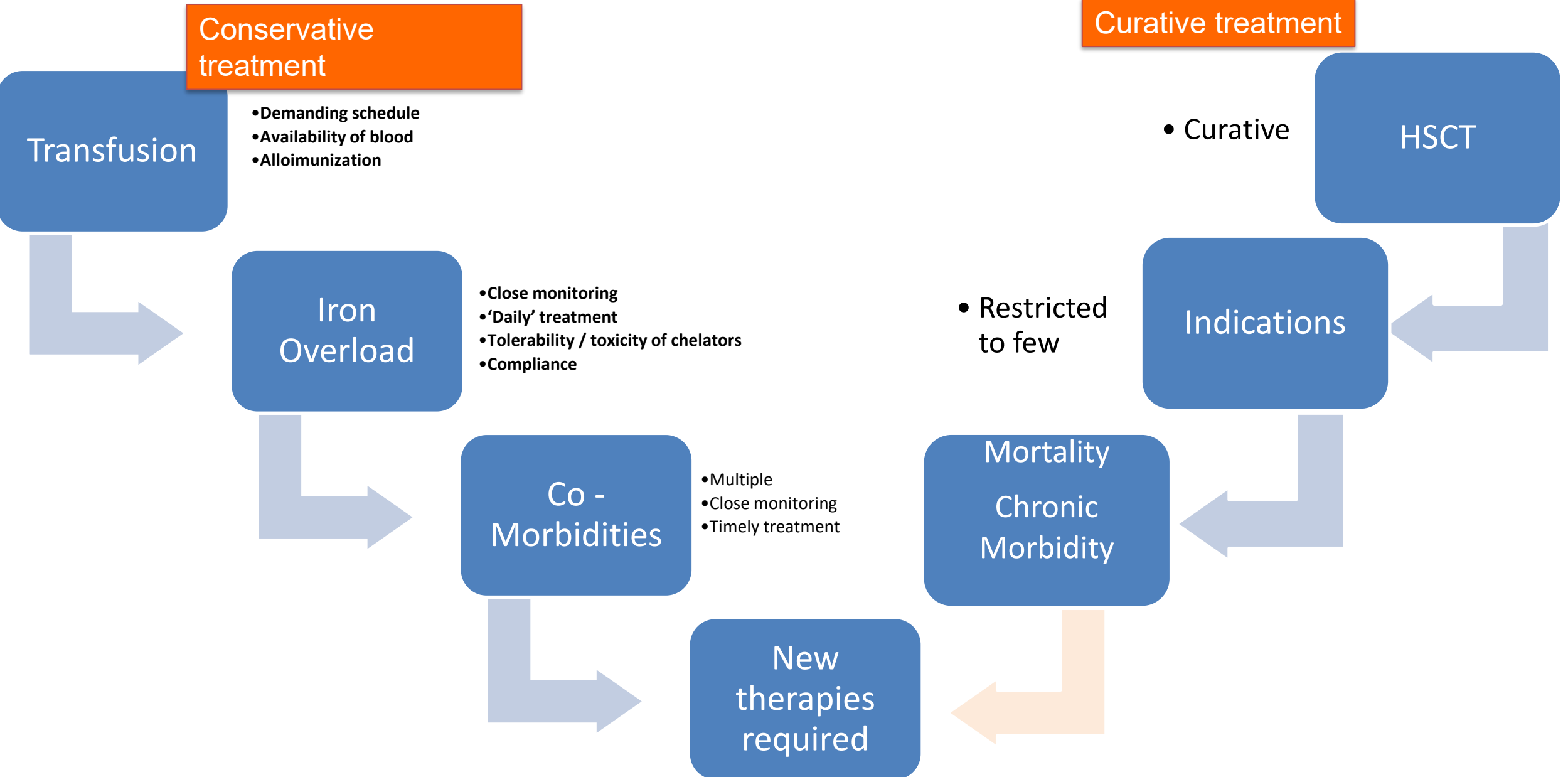
FIG. 3.—Growth chart of a girl who started intensive transfusions at 5 years.

Σταθμοί στην εξέλιξη και θεραπεία της Θαλασσαιμίας

Milestones in the evolution and treatment of Thalassemia



Management of TDT – Burden of Disease



Ποιόν θα μεταγγίσω?

- Confirmed genetic diagnosis of thalassaemia major¹
- Laboratory criteria¹
 - Hb < 7 g/dL on 2 occasions, > 2 weeks apart (excluding all other contributory causes such as infections)

OR

- Laboratory and clinical criteria, including¹
Hb > 7g/dL with
 - facial changes
 - poor growth
 - fractures
 - extramedullary haemopoiesis

Πότε θα ξεκινήσω μεταγγίσεις??

Age at first transfusion (years)	Alloimmunization rate (%)
< 1	7.7 ¹
> 1	27.9 ¹
< 3	20.9 ²
> 3	47.5 ²

- ✓ Έναρξη συστηματικών μεταγγίσεων για μείζων θαλασσαιμία < 2 χρόνια
- ✓ Ο κίνδυνος αλλοανοσοποίησης αυξάνεται όσο καθυστερεί η έναρξη των μεταγγίσεων

1. Machail-Merianou V, et al. Vox Sang. 1987;52:95-8. 2. Spanos T, et al. Vox Sang. 1990;58:50-5.3. Cappellini MD, et al. Guidelines for the management of

Μεταγγίσεις σε TDT ασθενείς

Συχνότητα Μεταγγίσεων

- Κάθε 3-5 εβδομάδες

Επίπεδα Αιμοσφαιρίνης προ της μετάγγισης

- > 9 -10.5 g/dL
- >11-12 g/dL για ασθενείς με καρδιακές παθήσεις ή άλλες ιατρικές παθήσεις καθώς και για εκείνους που δεν επιτυγχάνουν επαρκή καταστολή του μυελού των οστών σε χαμηλότερο επίπεδα αιμοσφαιρίνης

Επίπεδα Αιμοσφαιρίνης μετά τη μετάγγιση

- > 14 - 15 g/dL
- Παρακολουθείτε περιστασιακά έτσι ώστε να επιτρέψει την εκτίμηση του ρυθμού πτώσης της αιμοσφαιρίνης μεταξύ των μεταγγίσεων

Transfusion therapy results in iron overload

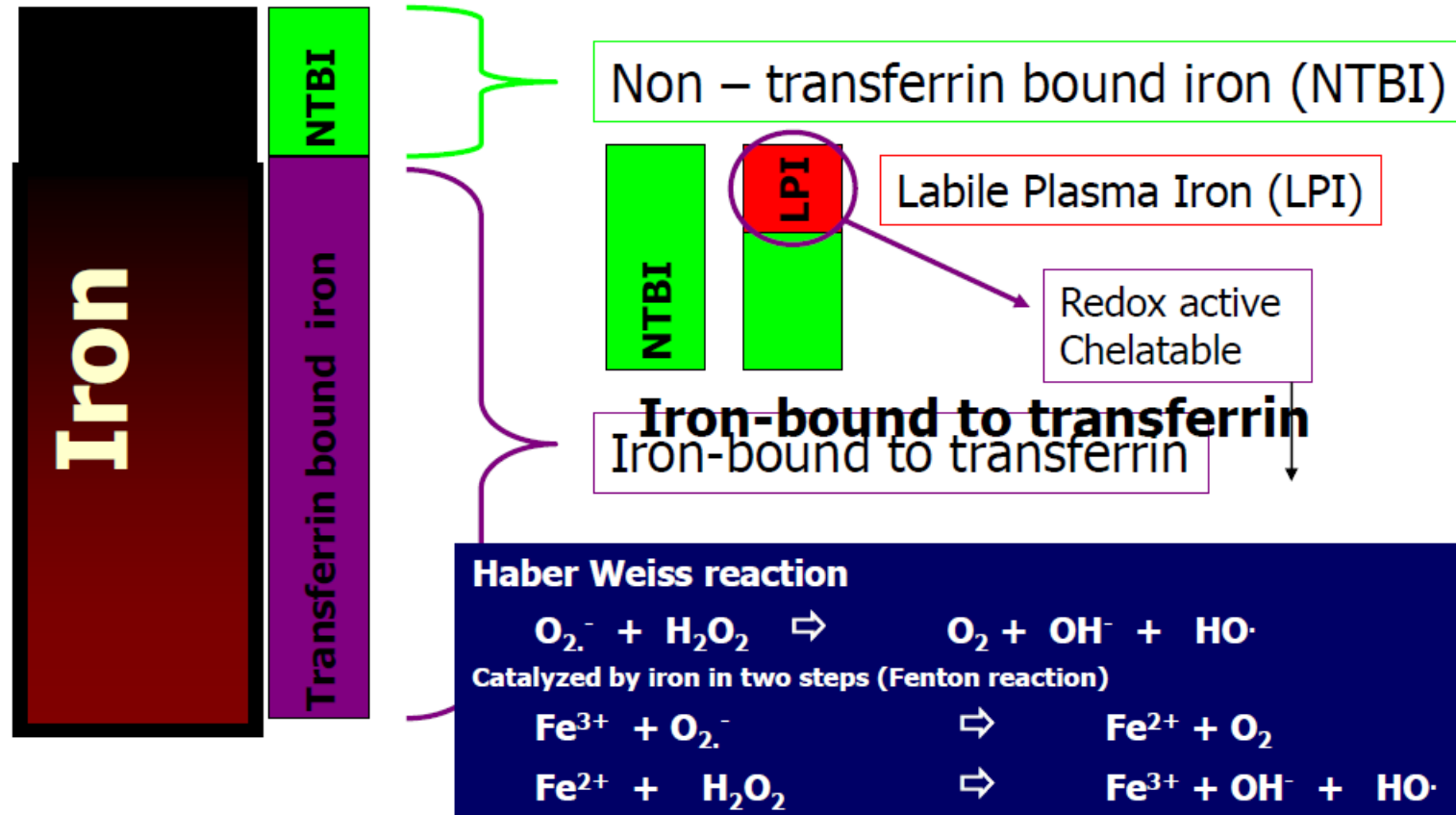


200–250 mg iron:
Whole blood: 0.47 mg iron/mL
'Pure' red cells: 1.16 mg iron/mL

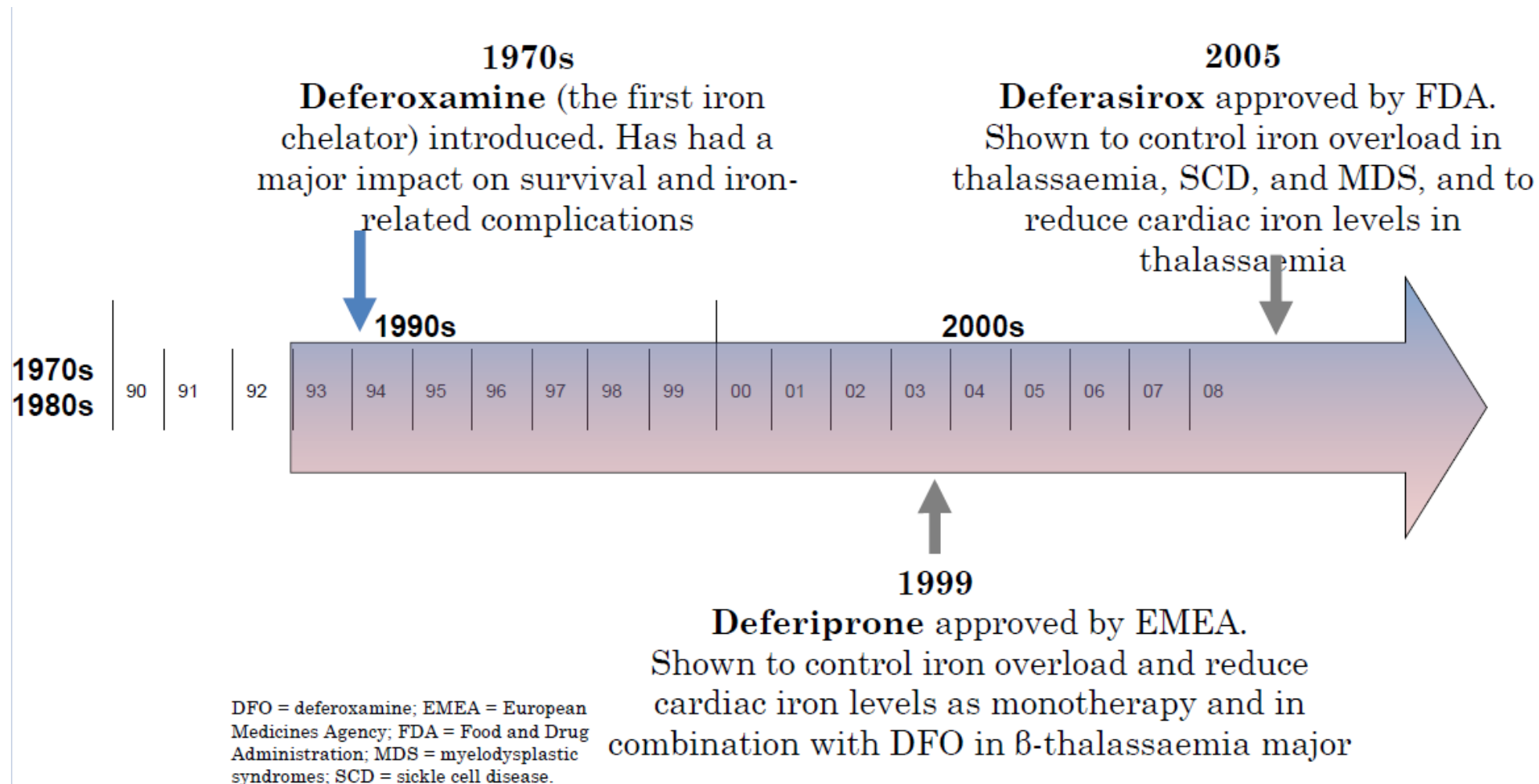
Porter JB. *Br J Haematol* 2001;115:239–252

- 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

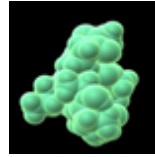
Iron overload is an inevitable consequence of multiple blood transfusions



Ιστορική εξέλιξη χηλικών ενώσεων



Available Chelators



Property	DFO	Deferiprone	Deferasirox
Iron binding	1:1	3:1	2:1
Route	s.c., i.v. over 8–12 hours, 5 days/week)	Oral 3 times daily	Oral Once daily
Half-life	20–30 minutes	3–4 hours	8–16 hours
Excretion	Urinary, faecal	Urinary	Faecal
Usual dose (mg/kg/day)	25–60	75–100	20–40
Main adverse effects in PI	Local reactions, ophthalmologic, auditory, growth retardation, allergic	Gastrointestinal disturbances, agranulocytosis/ neutropenia, arthralgia, elevated liver enzymes	Gastrointestinal disturbances, rash, rise in creatinine, renal dysfunction , elevated liver enzymes, ophthalmologic, auditory

Εργαστηριακή διερεύνηση αιμοσιδήρωσης

- **Φερριτίνη ορού**
- Σίδηρος ορού, Κορεσμός Τρανσφερίνης
- Δείκτες ελεύθερου σιδήρου (LPI, LIP)
- **Ηπατικός σίδηρος (LIC)**
 - Βιοψία
 - SQUID
 - MRI (T_2 , R_2 , T_2^* , SIR)
- **Καρδιακός σίδηρος**
 - MRI (T_2 , T_2^*), SIR (T_2)

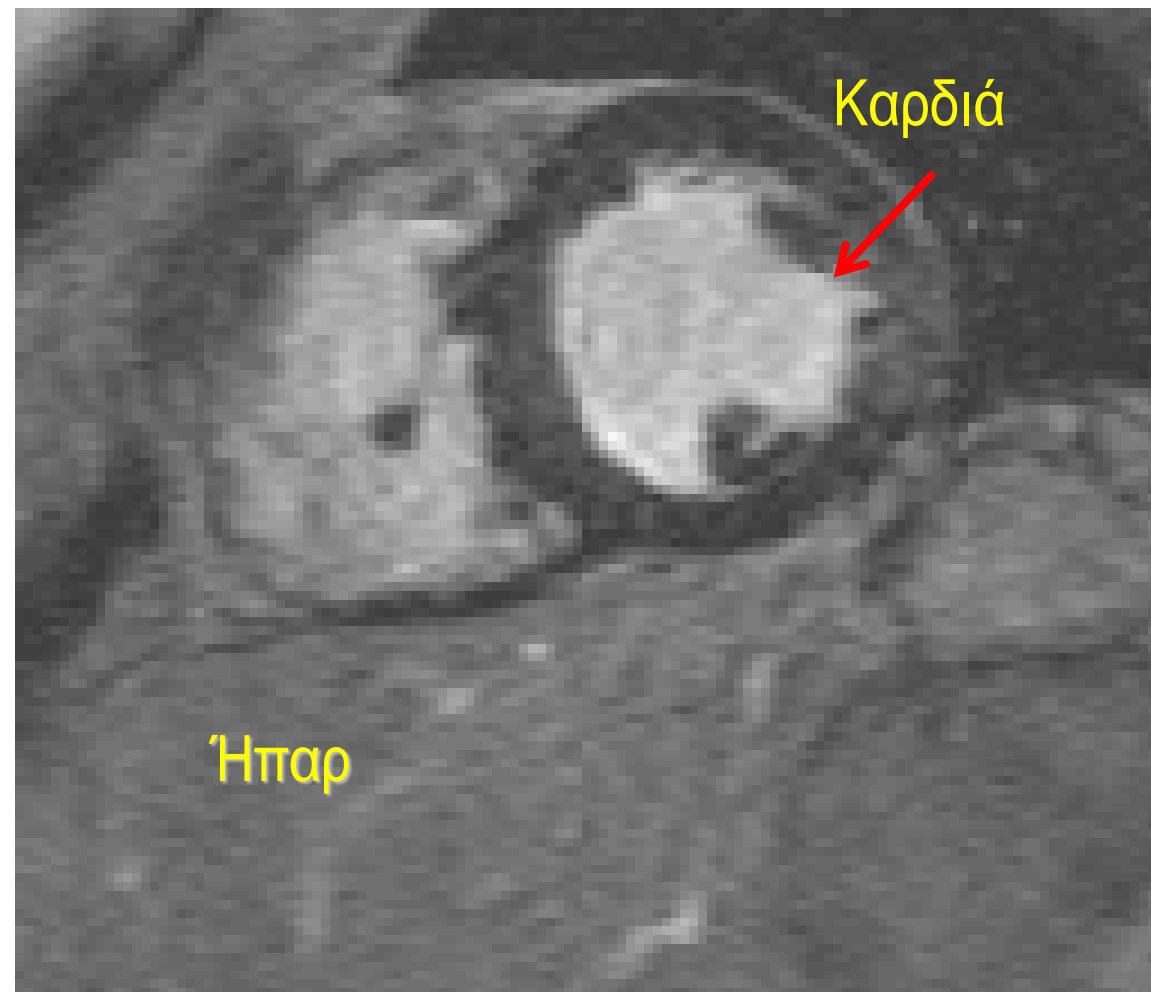
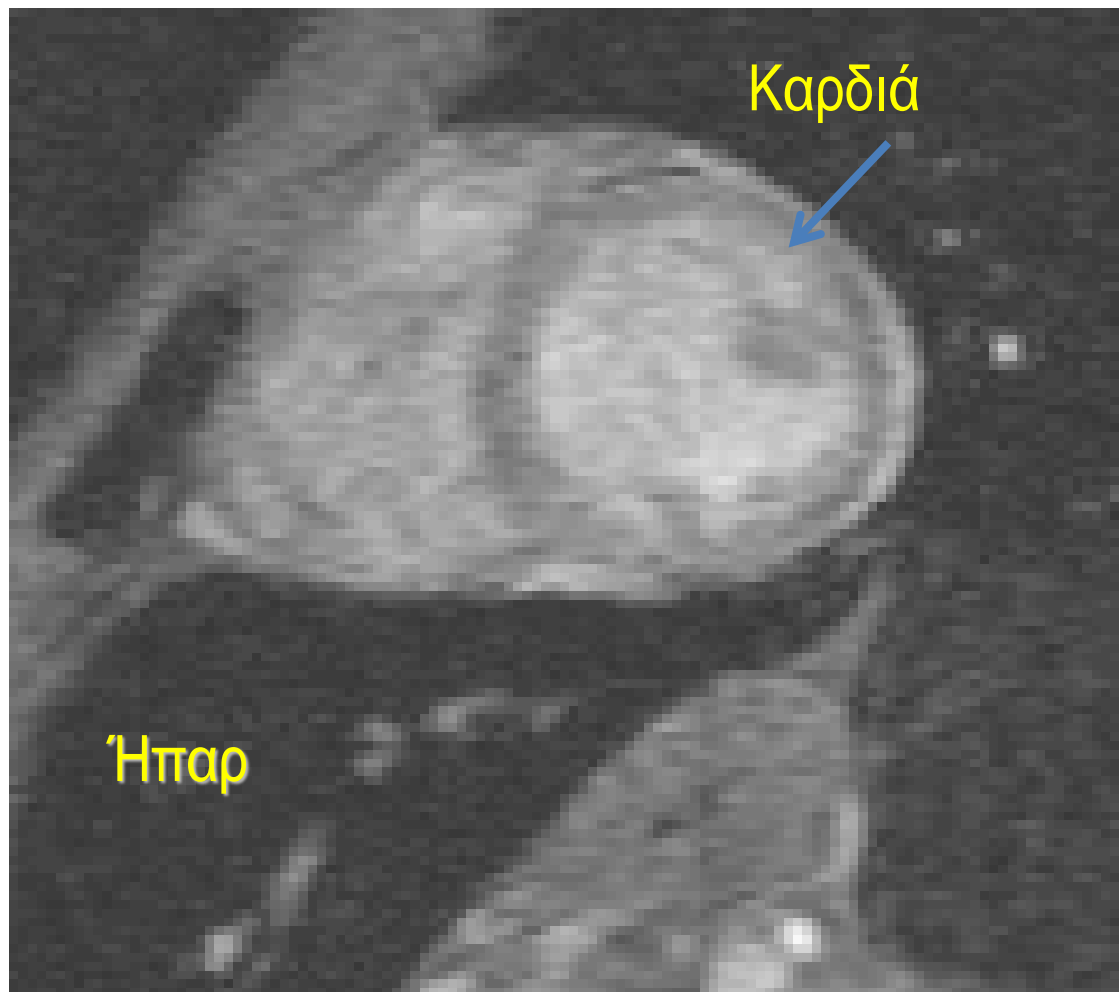
MRI: Magnetic Resonance Imaging

SIR: Signal Intensity Ratio

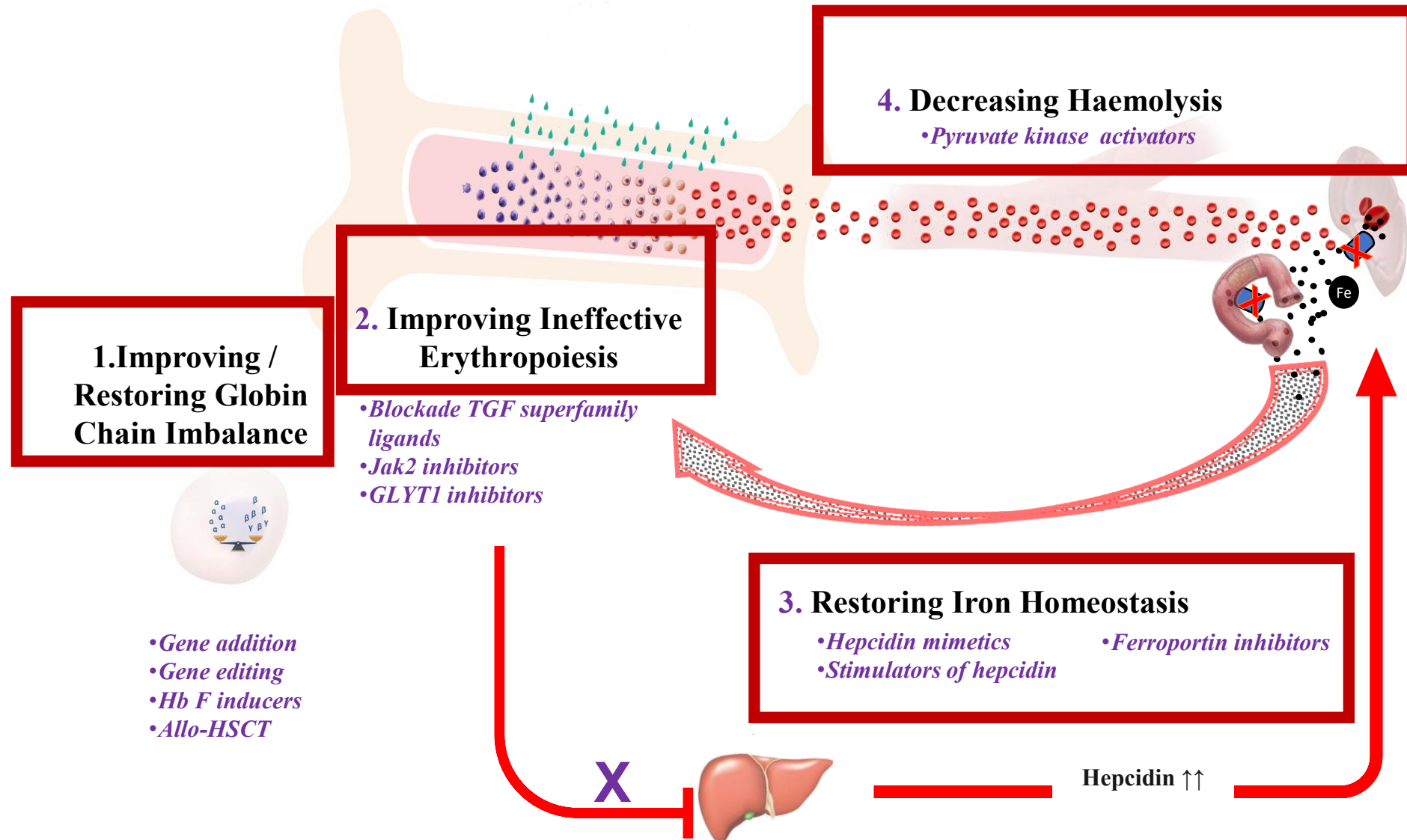
SQUID: Super Conducting Quantum Interface Device

Parameter	Normal	Iron-overloaded state		
		Mild	Moderate	Severe
LIC, mg Fe/g dw	<1.2	3–7	>7	>15
Serum ferritin, ng/mL	<300	>100 to <2500		>2500
Transferrin saturation, %	20–50	>50		
Myocardial T_2^* , ms	>20	8–20		<8
Alanine aminotransferase, U/L	<50	>50		
LPI, μ M	0–0.4	>0.4		

Απουσία συσχέτισης της συγκέντρωσης σιδήρου στο ήπαρ και την καρδιά

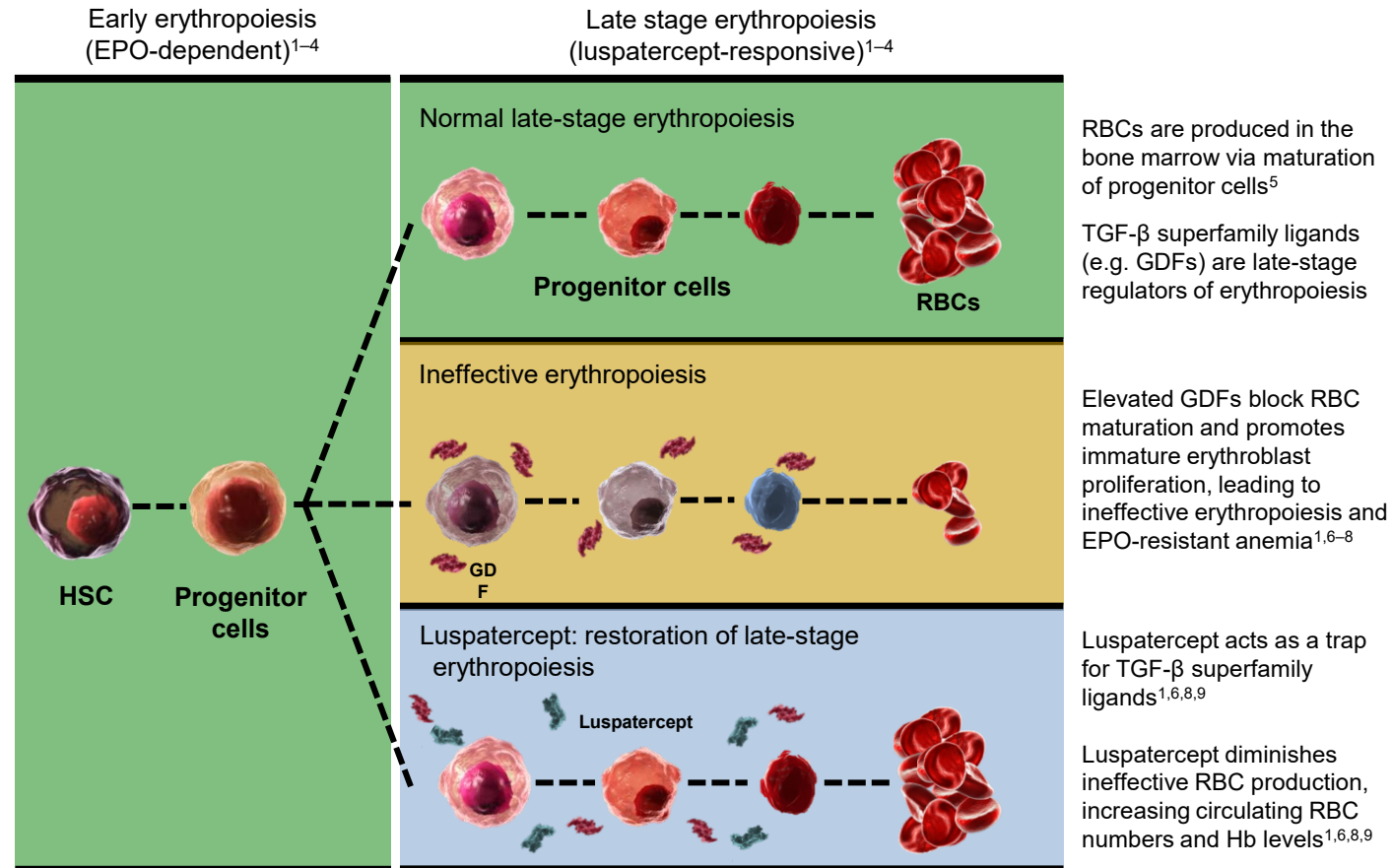


Θεραπευτικοί στόχοι-Therapeutic goals



Παράγοντες βελτίωσης αναιμίας

-Παράγοντας διαφοροποίησης ερυθροκυττάρων



1. Suragani et al. Nat Med. 2014;20:408-14. 2. Tsiftoglou et al. IUMBMB Life. 2009;61:800-30. 3. Singh et al. Adv Regen Med. 2014;2014:426520. 4. Zermati et al. Exp Hematol. 2000;28:885-94. 5. http://www.mds-foundation.org/wp-content/uploads/2014/06/Blood-Marrow-Booklet_English_ebook_5.02.2014.pdf. 6. Suragani et al. Blood. 2014;123:3864-72. 7. Zhou et al. Blood. 2008;112:3434-43. 8. Attie et al. Am J Hematol. 2014;89:766-70. 9. Sako et al. J Biol Chem. 2010;285:21037-48.

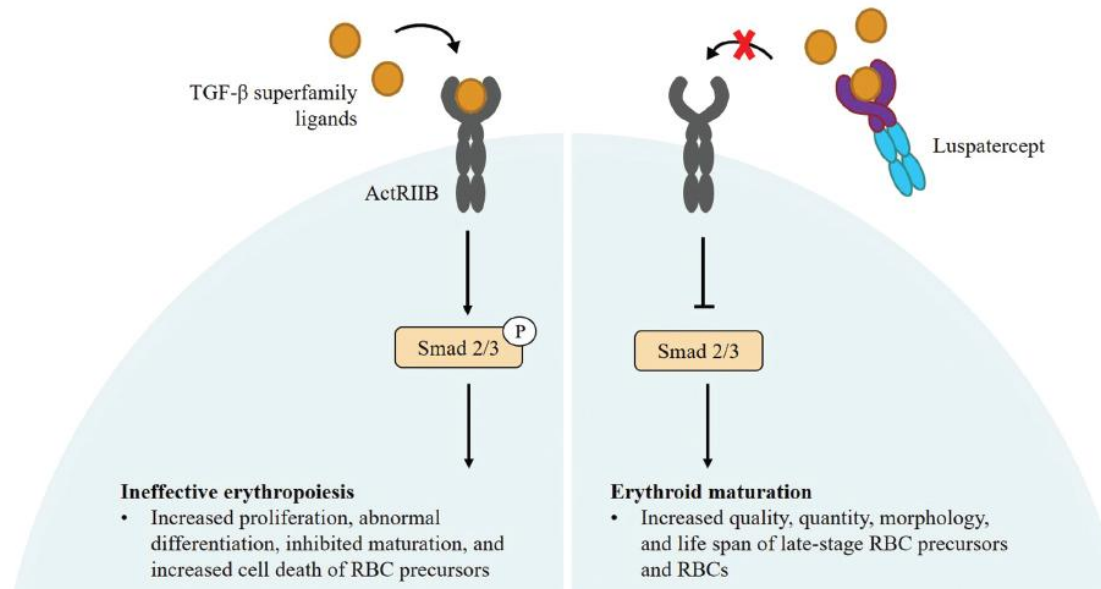
Luspatercept

- Έγκριση για τη θεραπεία της αναιμίας σε ενήλικες ασθενείς με β-TDT
- (FDA Νοέμβριο 2019, EMA Ιούνιο 2020)
- Χορηγείται υποδορίως κάθε 3 εβδομάδες
- Δόση 1-1.25 mg/kg



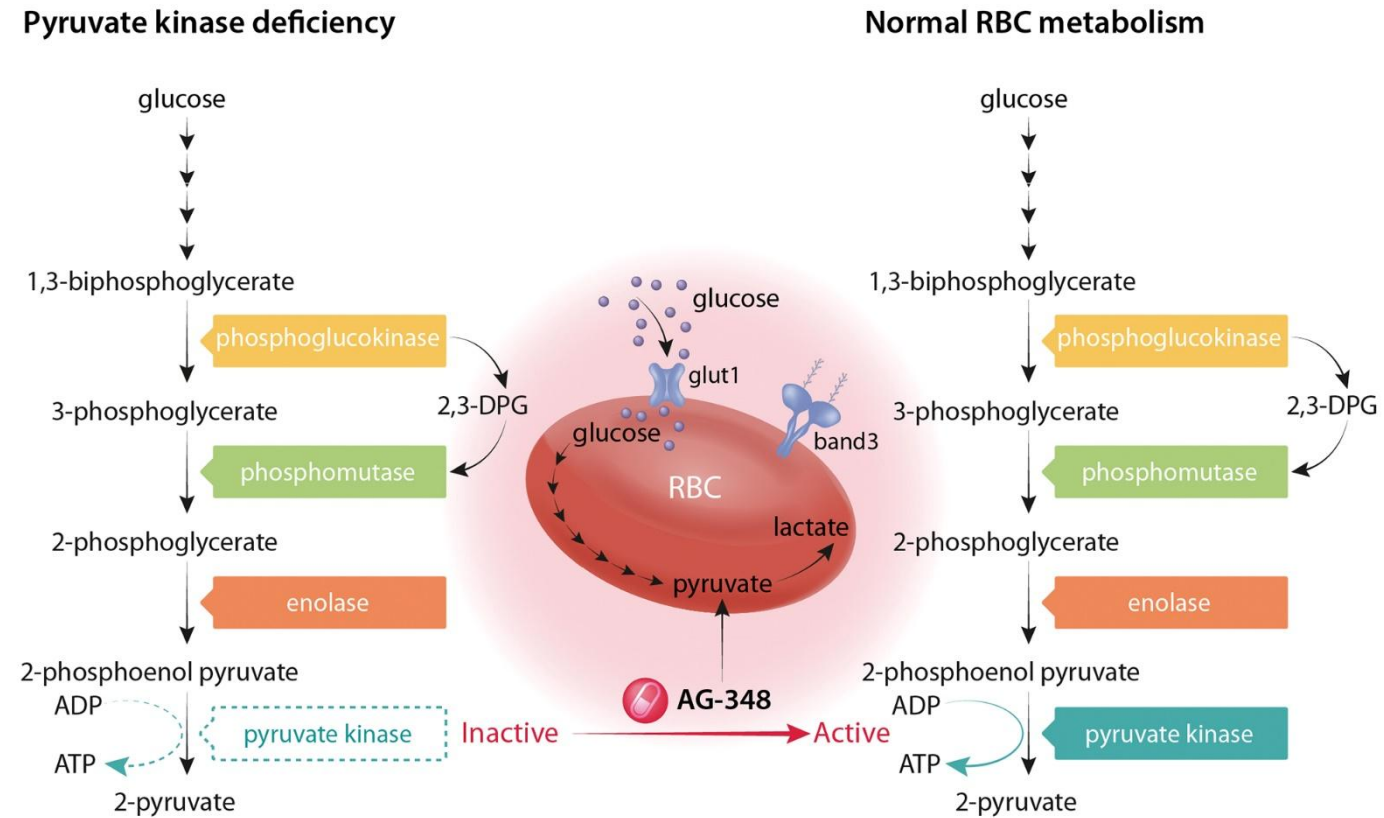
Luspatercept

- **ACE-536:** ανασυνδυασμένες πρωτεΐνες σύντηξης
 - τροποποιημένη μορφή της εξωκυττάριας περιοχής του ανθρώπινου ActRIIB συνδεδεμένη με την περιοχή Fc της ανθρώπινης ανοσοσφαιρίνης G1
- Τα μόρια TGF- β μέσω της δέσμευσής τους από τον υποδοχέα ακτιβίνης IIB (ActRIIB), εμπλέκονται στη διαφοροποίηση των τελικών μορφών των πρόδρομων ερυθροκυττάρων (SMAD2/3) που είναι ανεξάρτητες από την παραγωγή ερυθροποιητίνης.



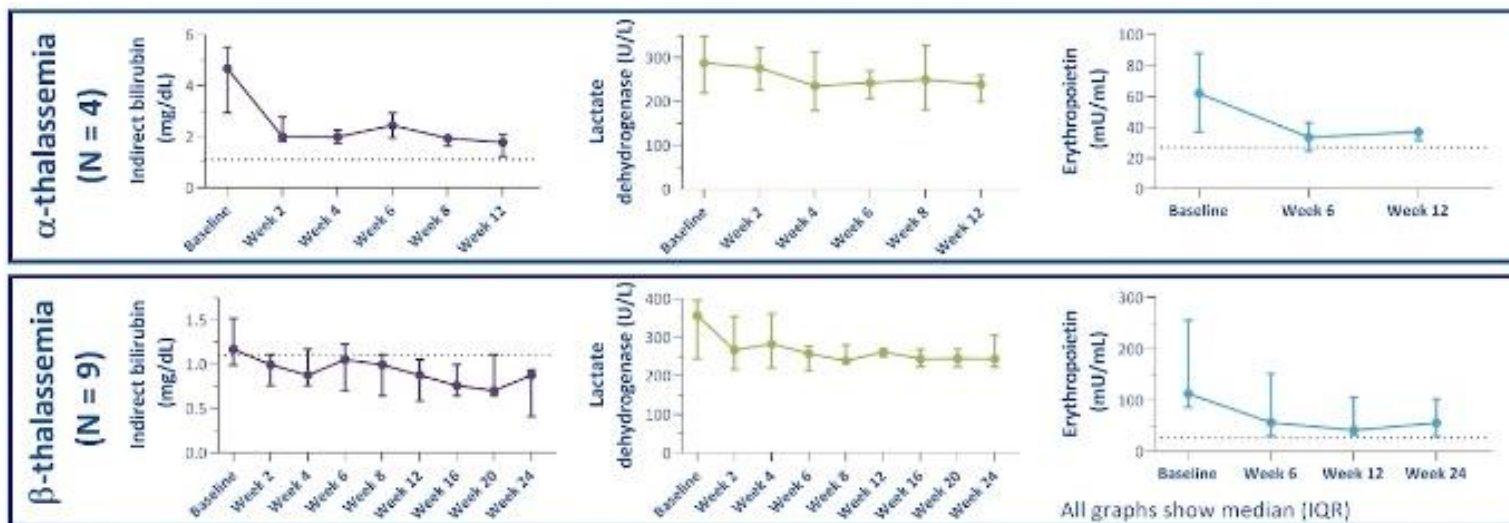
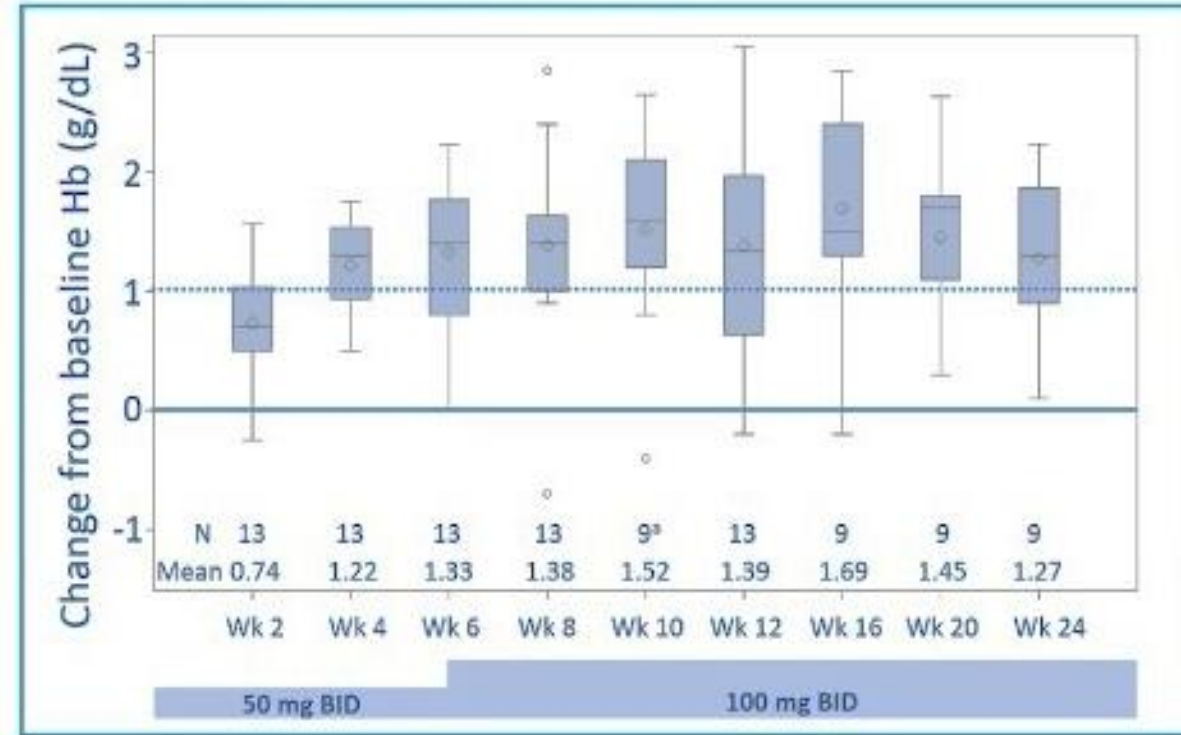
Ενεργοποιητές Πυρουβικής Κινάσης

- Το ένζυμο πυρουβική κινάση (PK) : παίζει σημαντικό ρόλο στο τελευταίο στάδιο της γλυκόλυσης στα RBC (παραγωγή ενέργειας)
- Η από του στόματος λήψη σε υγιή άτομα, ενός μορίου ενεργοποιητή της PK γνωστός ως AG-348 (mitarivat) αυξάνει το ATP και αποτελεσματικό και ασφαλές σε ασθενείς με ανεπάρκεια PK



Mitapivat

- Mitapivat (AG-348): ρος μικρός αλοστερικός ενεργοποιητής της πυρουβικής κινάσης
- Επίμυες με β-TDT: Αύξησε τα επίπεδα ATP& RBC , μείωσε την αναποτελεσματική ερυθροποίηση και αιμοσιδήρωση
- Θεραπεία NTDT ασθενών:
 - Αύξησε την αιμοσφαιρίνη
 - Μείωσε χολερυθρίνη, LDH



Ενεργοποιητές Πυρουβικής Κινάσης

PK activators				
Mitapivat (AG-348)	● NCT03692052	● Phase 2	● $n = 20$	● Hb increase ≥ 1 g/dl ^d
	● Active, not recruiting ^c	● Open-label	● NTDT (including α -thalassemia) with Hb ≤ 10 g/dl	● Hb, Reticulocytes, bilirubin, LDH, haptoglobin, ● EPO, nRPC, sTfR
			● ≥ 18 years	
	● ENERGIZE-T	● Phase 3	● $n = 240$	● Transfusion reduction ($\geq 50\%^d$, $\geq 33\%$) / ● independence
	● NCT04770779	● Randomized, placebo- controlled, double-blind	● TDT (including α -thalassemia)	● Transfusion requirement
	● Not yet recruiting		● ≥ 18 years	● SF, TSAT, TIBC
	● ENERGIZE	● Phase 3	● $n = 171$	● Hb increase ≥ 1 g/dl ^d
	● NCT04770753	● Randomized, placebo- controlled, double-blind	● NTDT (including α -thalassemia) with Hb ≤ 10 g/dl	● PRO
	● Not yet recruiting		● ≥ 18 years	● Hb, Hb increase ≥ 1.5 g/dl
				● Reticulocytes, bilirubin, LDH, haptoglobin, EPO,
				● SF, TSAT

Θεραπευτική αντιμετώπιση

➤ Αλλογενής Μεταμόσχευση Αρχέγονων Αιμοποιητικών Κυττάρων

- συγγενικός ιστοσυμβατός δότης (~20%)
- διεύρυνση δοτών (μη συγγενείς δότες)
- νέες πηγές αιμοποιητικών κυττάρων
- ασφαλέστερα πρωτόκολλα προετοιμασίας

➤ Γονιδιακή Θεραπεία

- Λεντιϊκοί μεταφορείς (προσθήκη γονιδίου β- ή γ-σφαιρίνης)
- Επιδιόρθωση μετάλλαξης Genome editing (CRISPR/Cas9)

Allogeneic Hematopoietic Stem Cell Transplantation

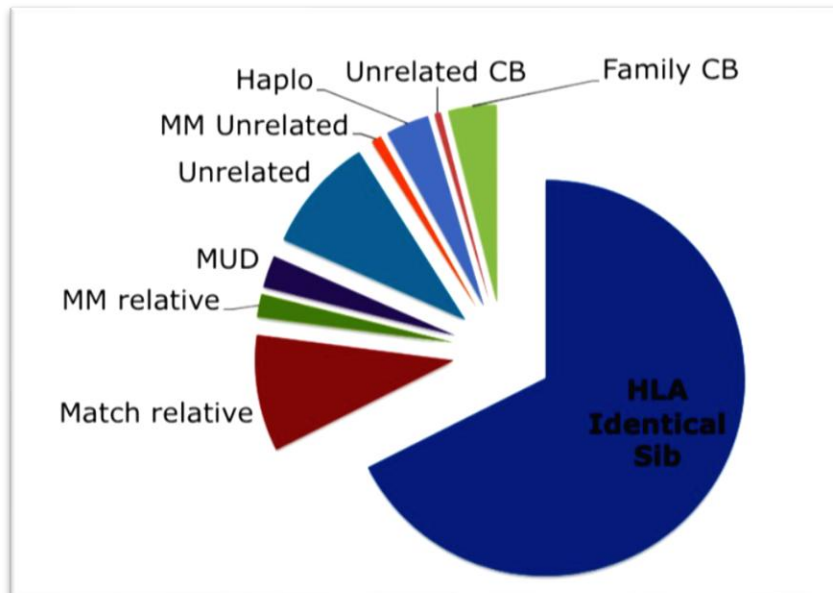
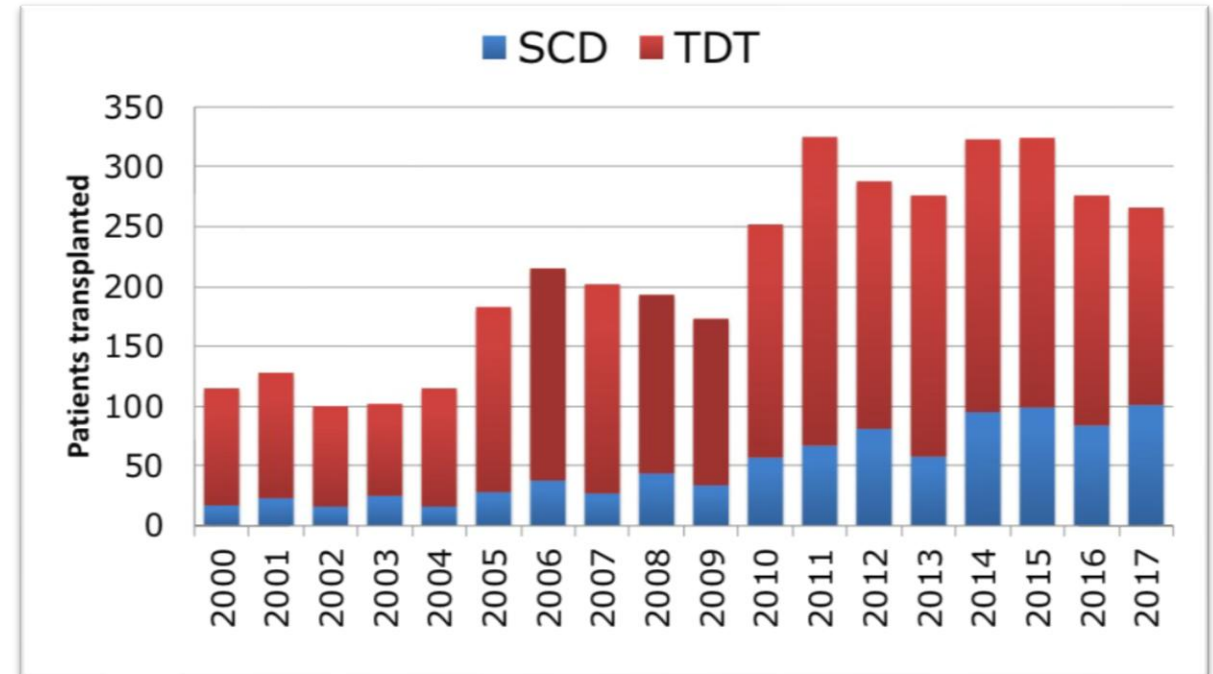
- matched related donor (~20%)
- expansion of donor options (unrelated donors)
- new sources of hematopoietic stem cells
- safer conditioning regimens

Gene Therapy

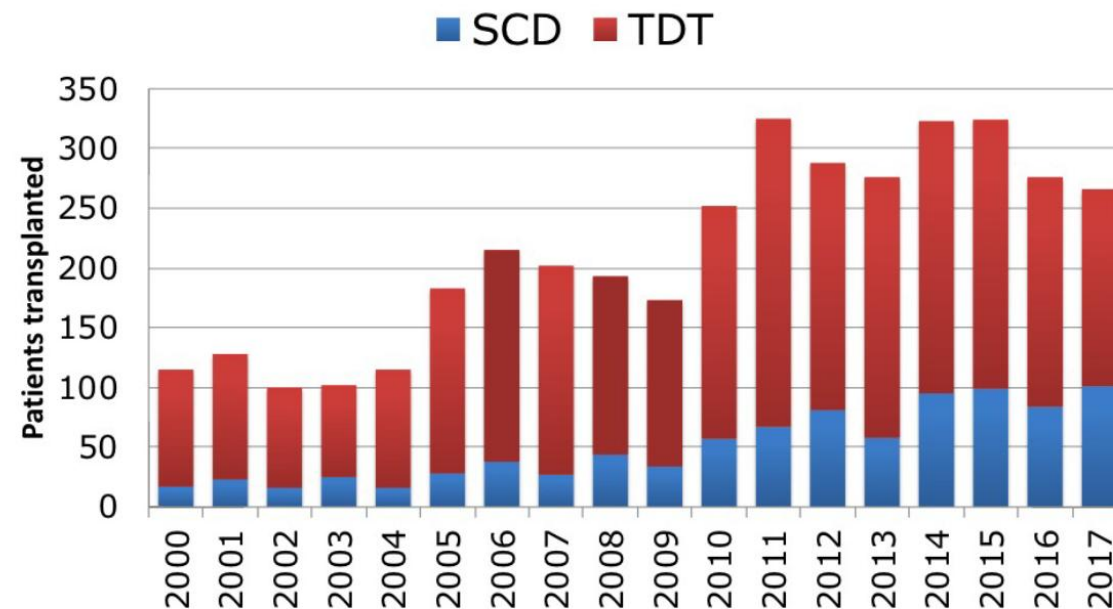
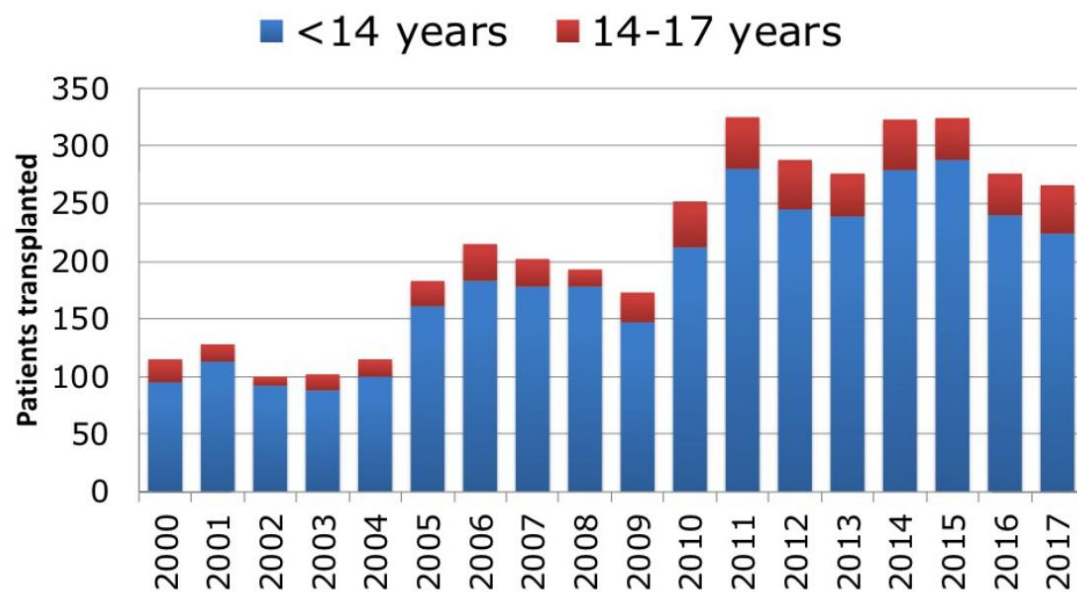
- Lentiviral vectors (addition of β- or γ-globin gene)
- Mutation correction – Genome editing (CRISPR/Cas9)

EBMT – results in 3856 patients

TDT	# 2936
SCD	# 920
Years	2000-2017
Male/Female	2064/1750
Median age	7.2 years (range 0.48- 17.9)
Median Follow up	23.8 months (range 0.63-264)

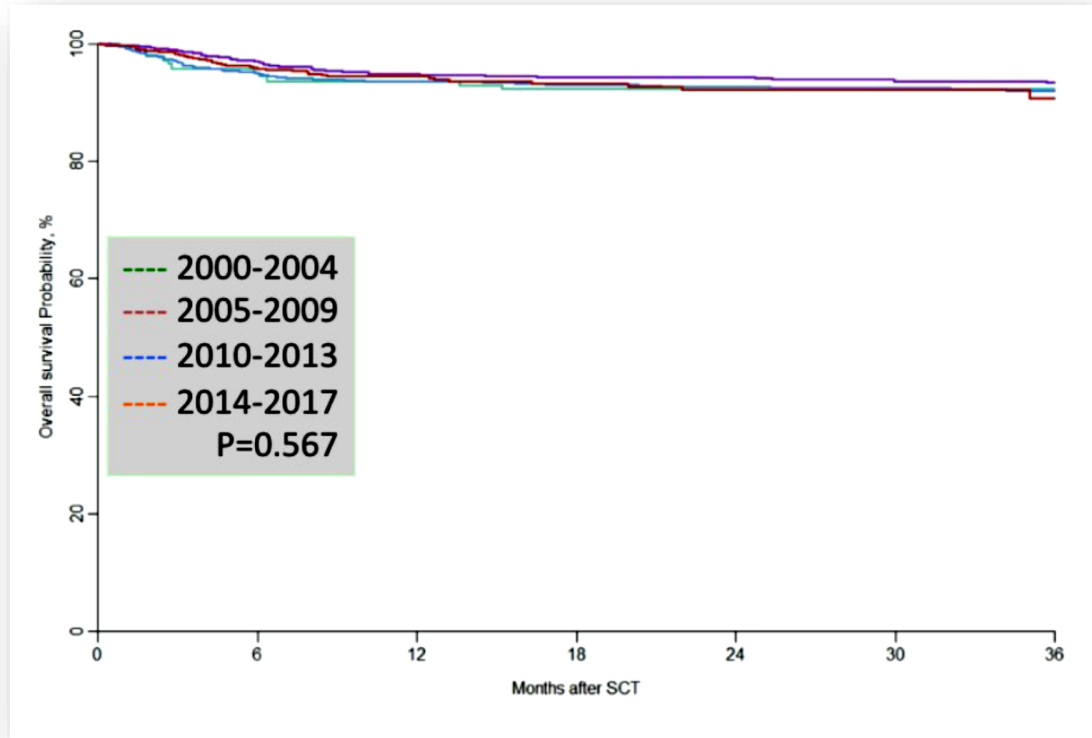


EBMT – results in 3856 patients

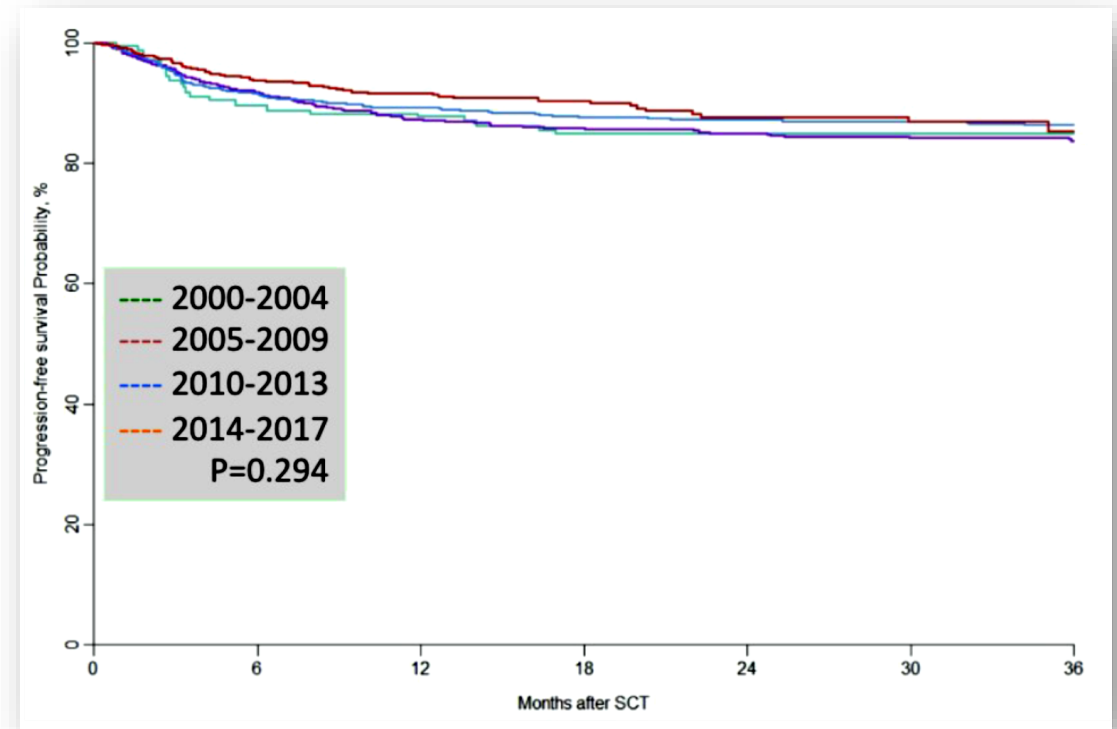


EBMT – αποτελέσματα σε 3856 ασθενείς με TDT/SCD

Overall Survival



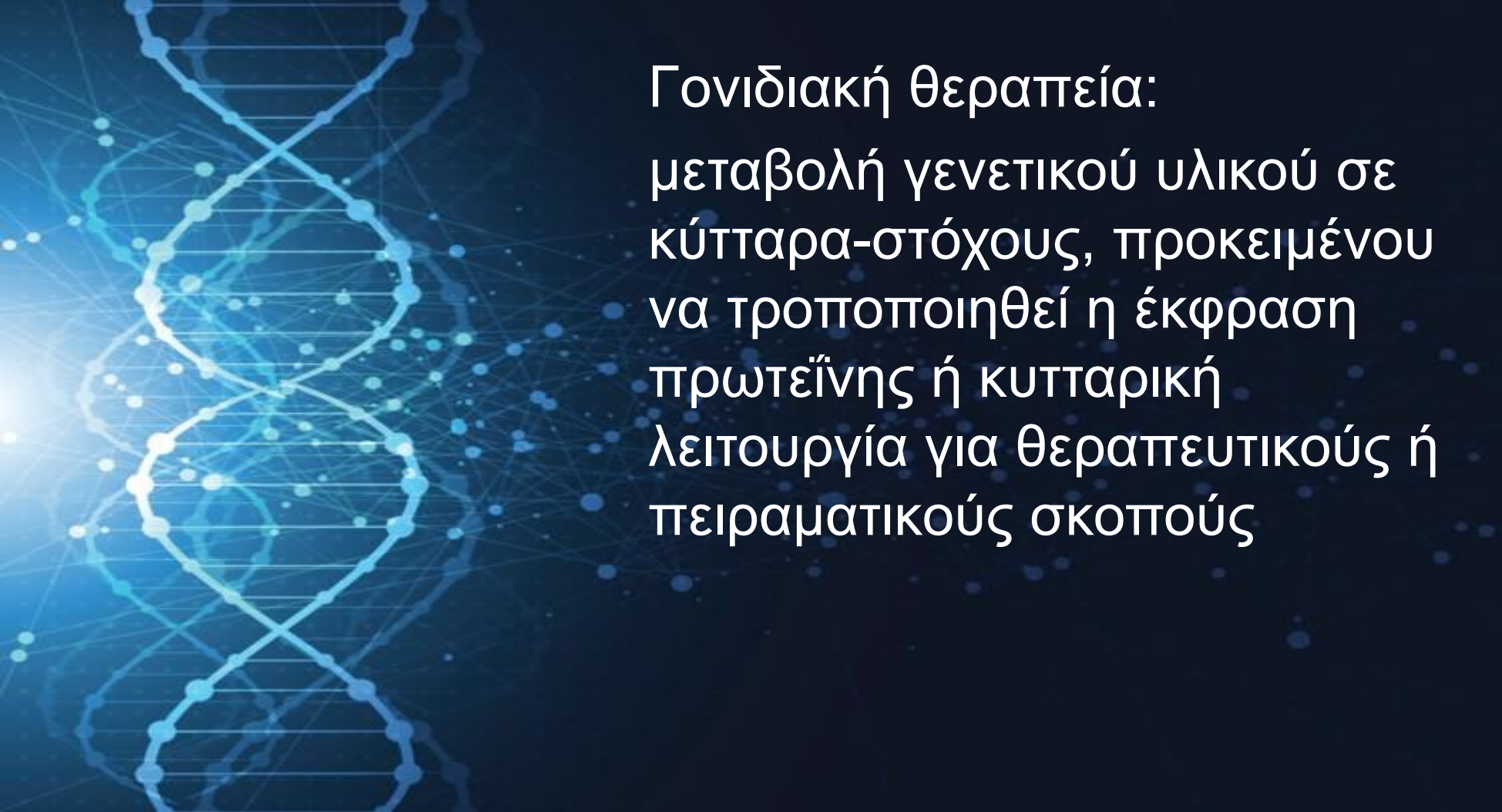
Event Free Survival



		Age <14 years	Age ≥14 years	
TDT	OS	91% (90-93)	83% (79-87)	P<0.001
	EFS	85% (83-86)	77% (72-82)	P<0.001

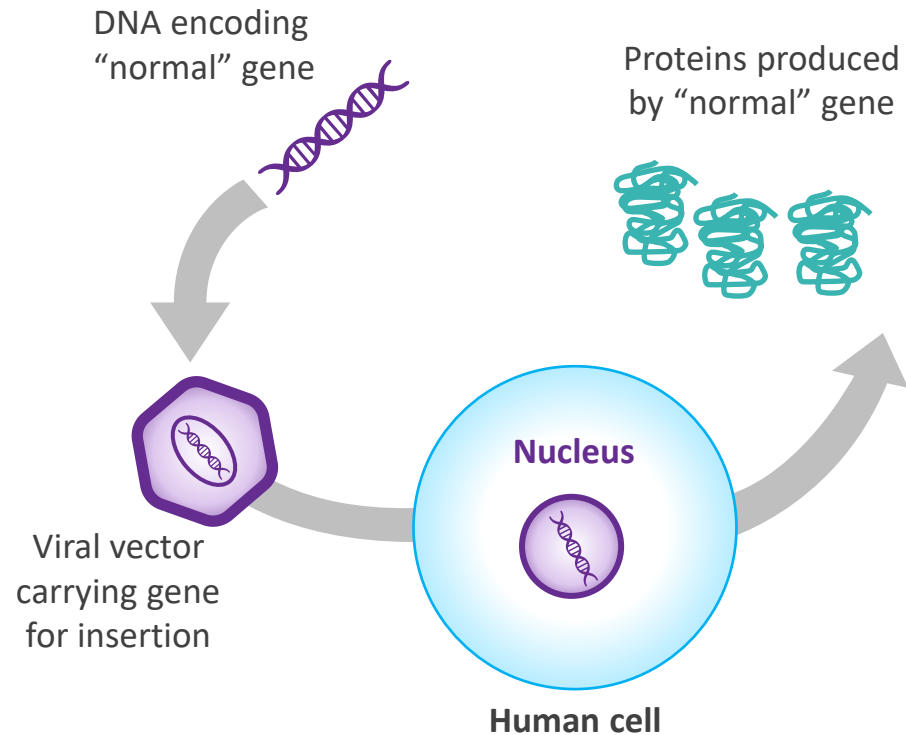
		Age <14yo	Age ≥14 years	
SCD	OS	95% (93-97)	90% (85-95)	p=0.001
	EFS	93% (90-95)	90% (84-96)	P=0.064

ΓΟΝΙΔΙΑΚΗ ΘΕΡΑΠΕΙΑ: ΟΡΙΣΜΟΣ



Γονιδιακή θεραπεία:
μεταβολή γενετικού υλικού σε
κύτταρα-στόχους, προκειμένου
να τροποποιηθεί η έκφραση
πρωτεΐνης ή κυτταρική
λειτουργία για θεραπευτικούς ή
πειραματικούς σκοπούς

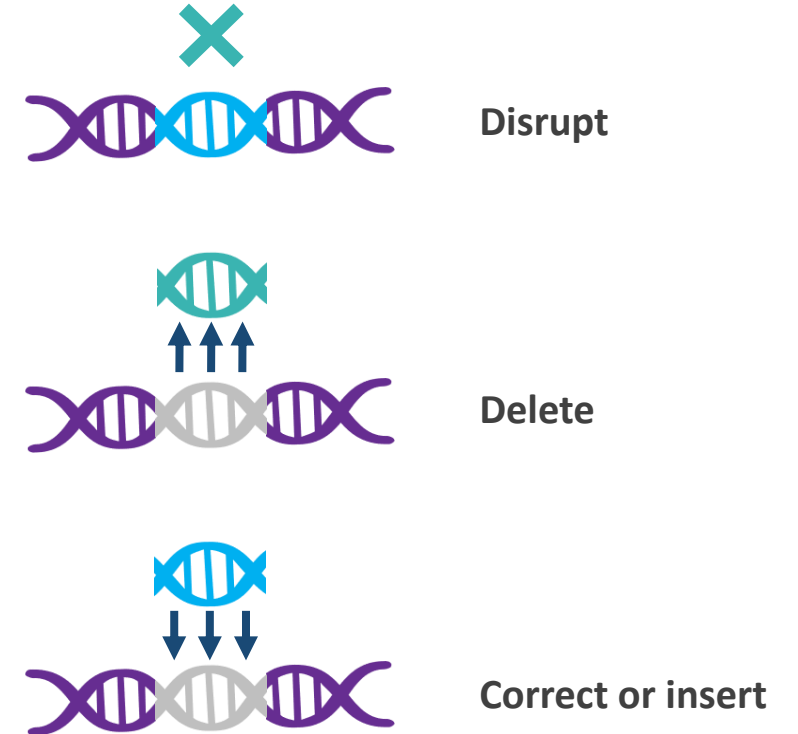
Gene addition involves adding an extra copy of a healthy gene into a cell to functionally replace the faulty gene



To be effective, the additional gene ideally needs to be expressed over the entire lifetime of the patient

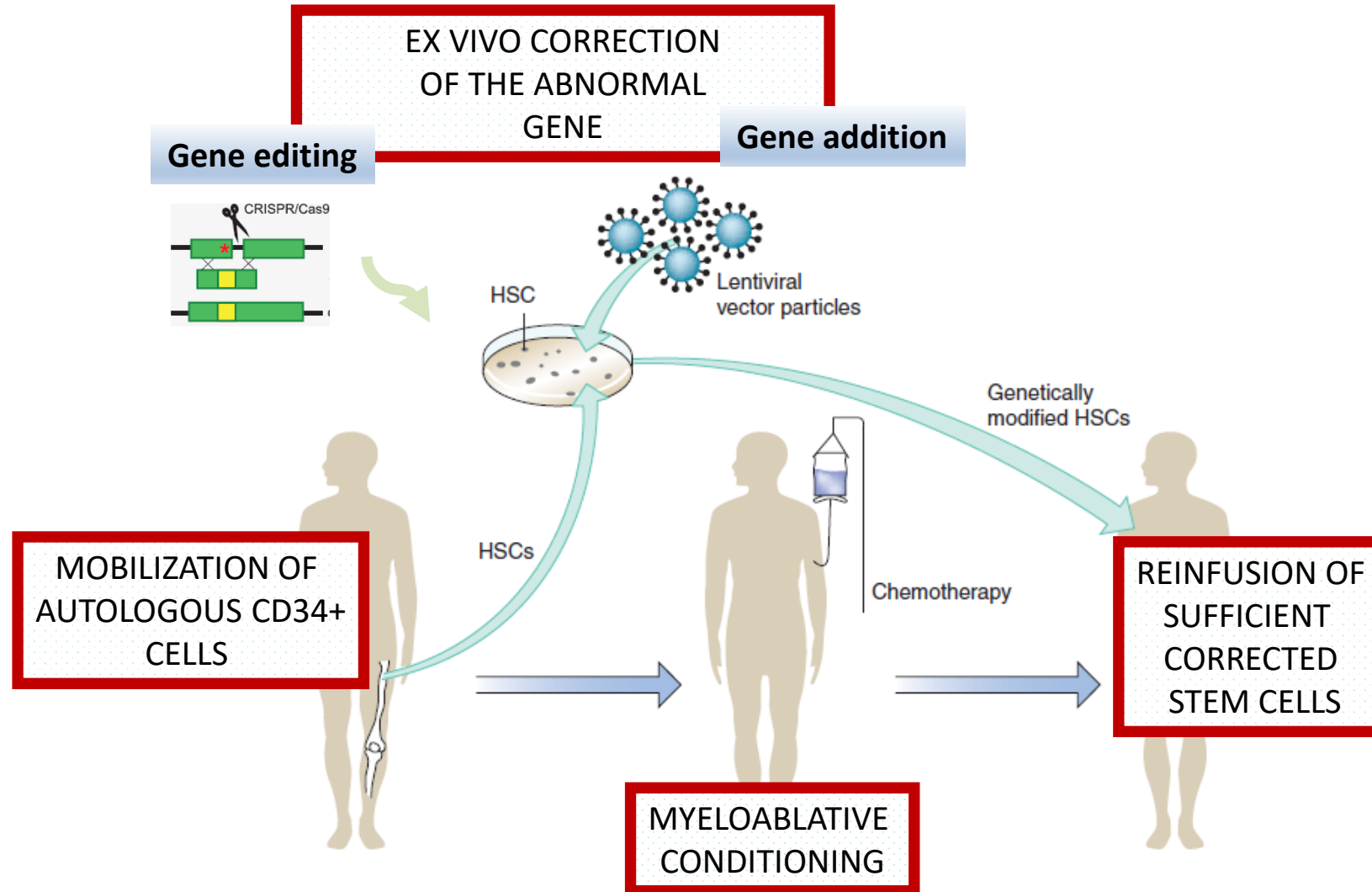


Gene editing alters the gene expression by disrupting, deleting, or correcting the faulty gene



Gene editing results in a permanent change to the transformed cells

Gene therapy in the clinic

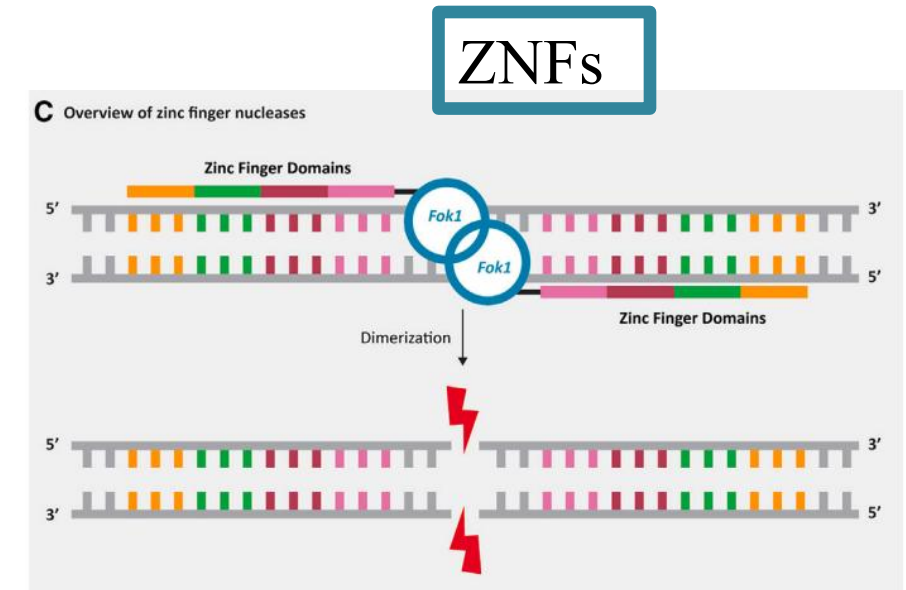
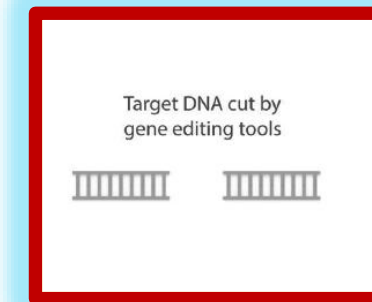
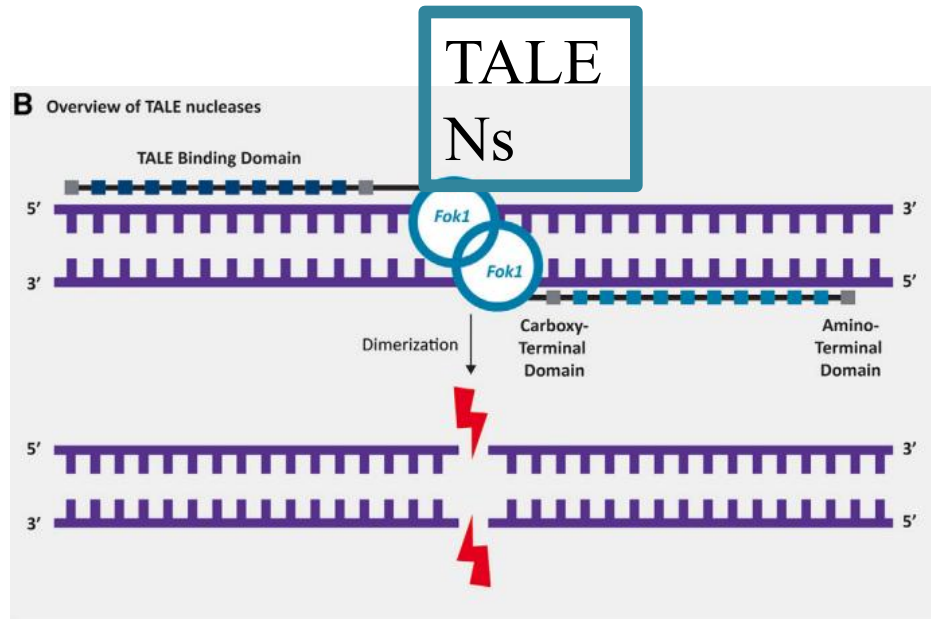




A stylized illustration on a light blue background depicting gene editing. A large blue DNA double helix is the central focus. A hand on the left uses scissors to cut the DNA. Another hand on the right uses a tool to insert a red segment into the helix. Various scientific icons are scattered around: a bar chart, a chemical ring, a heart with an ECG line, a brain, a plus sign, and a computer screen showing a DNA helix and equals signs. Dotted lines connect some of these elements.

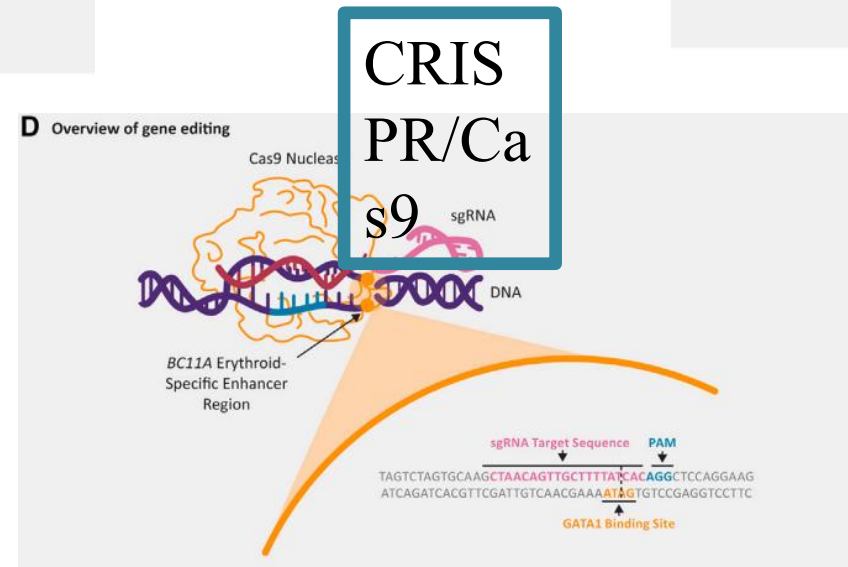
GENE EDITING

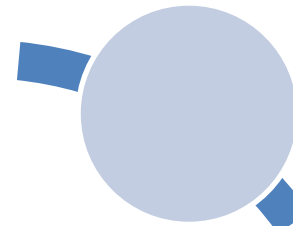
Genome editing techniques for correction of molecular defects



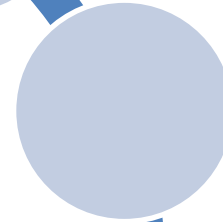
Several nucleases were developed for site-specific genomic modification:

- ✓ Zinc finger nucleases (ZFNs)
- ✓ Transcription activator-like effector nucleases (TALENs)
- ✓ Clustered regularly interspaced short palindromic repeat (CRISPR)-associated nuclease Cas9





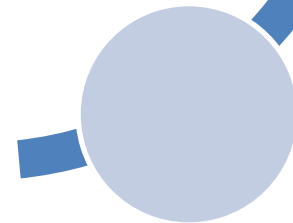
homologous recombination



transcription-activator like
effector nucleases (TALEN)



zinc-finger nucleases



CRISPR
/Cas9

Genetic engineering techniques

Time needed for an experiment

Zinc finger
nucleases



Months

TALENs

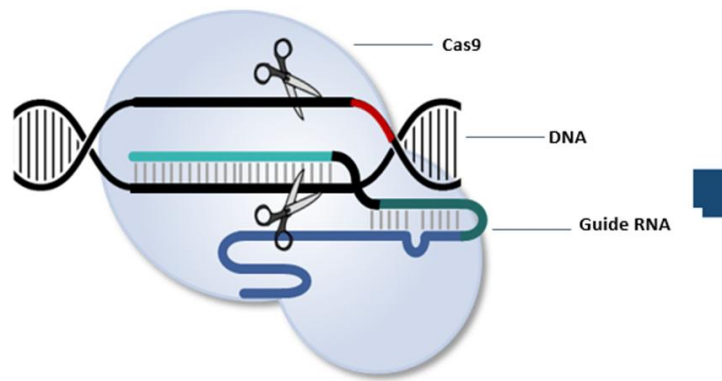


Weeks

CRISPR/Cas9

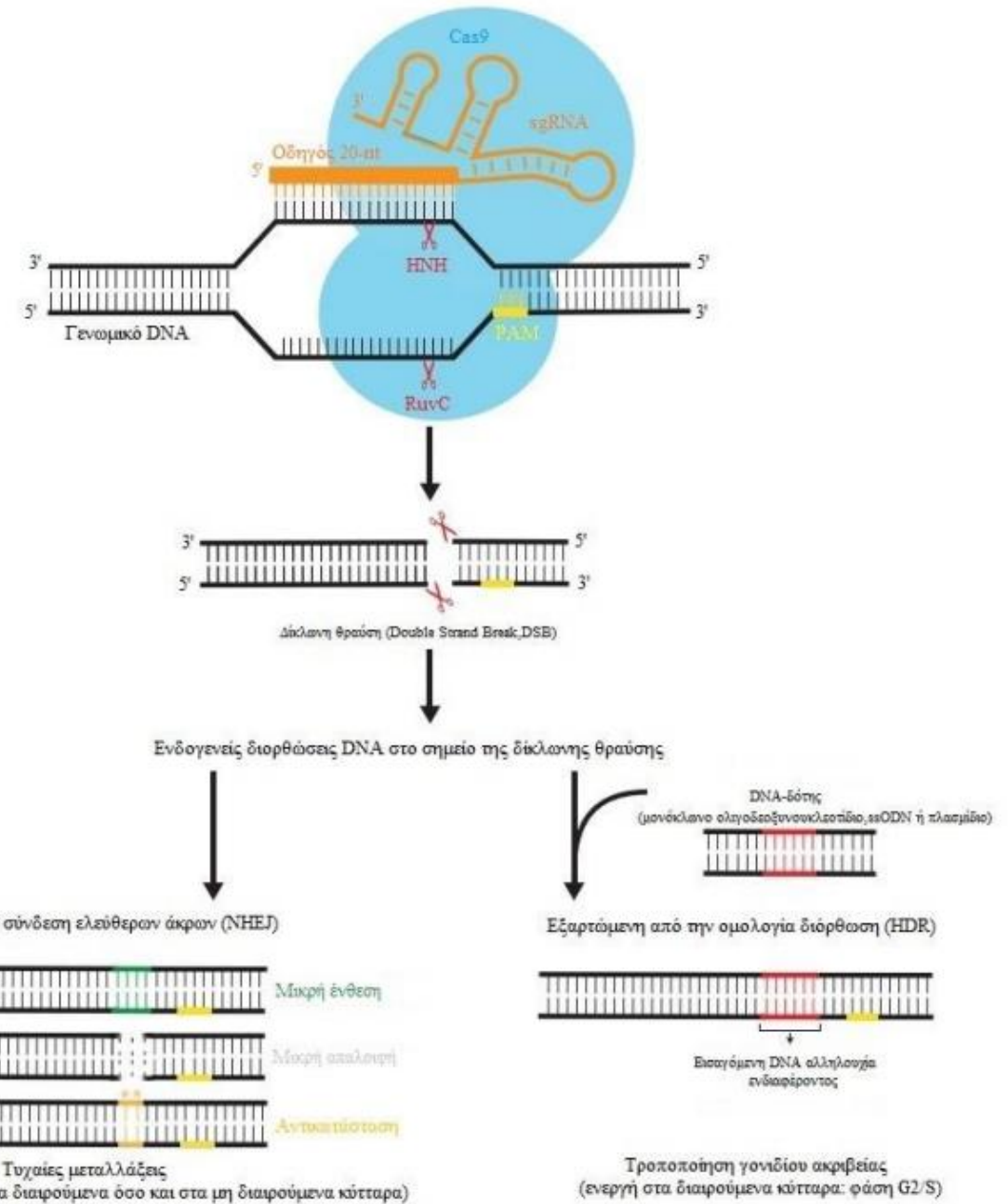


Days



- › The **CRISPR/Cas9 complex** is composed of a **single guide RNA (sgRNA)** and the **Cas9 endonuclease**
- › The sgRNA binds to a **specific sequence** of DNA
- › **Cas9 then creates a double strand DNA (DSB)** break at that precise sequence

Πρόκληση δίκλωνων θραύσεων στο DNA από το σύστημα CRISPR/Cas9 και ενδογενείς μηχανισμοί επιδιόρθωσης (NHEJ και HDR)



Exa-cel: Non-Viral, *Ex Vivo* CRISPR/Cas9-Mediated Editing of *BCL11A*

- **Editing of *BCL11A*** reactivates γ -globin expression and formation of HbF ($\alpha 2\gamma 2$) in mouse models⁴
- target a critical transcription factor binding site (GATA1) at an erythroid lineage-specific enhancer region
- Repair of the DSB by NHEJ results in DNA insertion/deletions (indels), disrupts GATA1 binding → lowering *BCL11A* transcription
- **Exa-cel** is produced using non-viral, *ex vivo* editing of the erythroid-specific enhancer region of *BCL11A* in CD34⁺ HSPCs and **reduces erythroid-specific expression of *BCL11A***

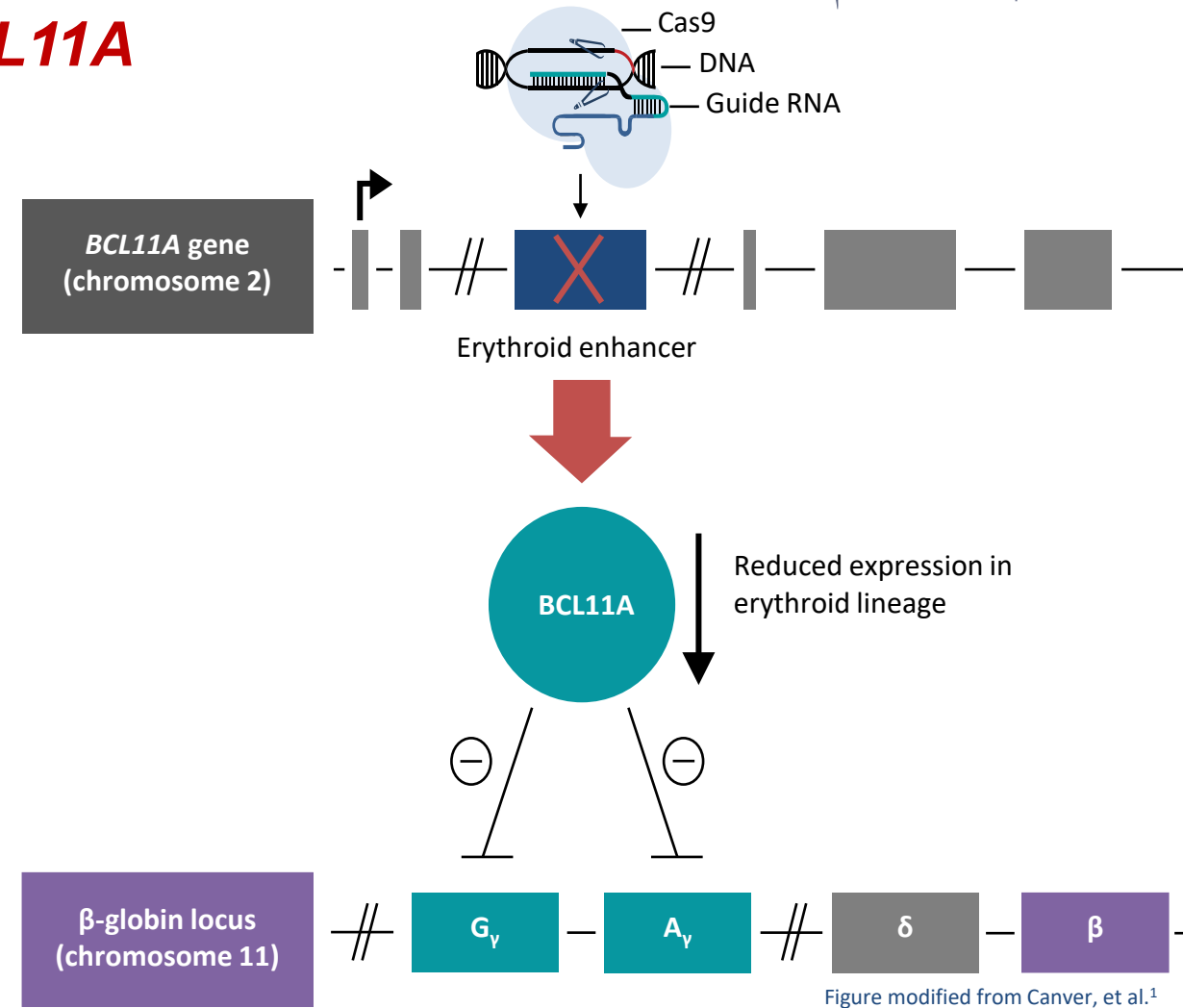


Figure modified from Canver, et al.¹

BCL11A, B-cell lymphoma/leukemia 11A; **CRISPR**, clustered regularly interspaced short palindromic repeats; **DNA**, deoxyribonucleic acid; **HbF**, fetal hemoglobin; **HSPC**, hematopoietic stem and progenitor cell; **RNA**, ribonucleic acid; **SCD**, sickle cell disease; **TDT**, transfusion dependent β -thalassemia.

1. Canver MC, et al. *Blood*. 2016;127:2536-2545; 2. Murray N, et al. *Br J Haematol*. 1988;69:89-92; 3. Bank A. *Blood*. 2006;107:435-443; 4. Bauer DE, et al. *Science*. 2013;342:253-257.

Study Endpoints



Primary Efficacy Endpoint

Proportion of participants **transfusion independent for 12 consecutive months** while maintaining a weighted average hemoglobin ≥ 9 g/dL (TI12)

- Assessed starting 60 days after last RBC transfusion for post-transplant support or TDT disease management

Proportion of participants **free of severe VOCs for ≥ 12 months (VF12)**

- Assessed starting 60 days after last RBC transfusion for post-transplant support or SCD disease management

Key Secondary Efficacy Endpoint

Proportion of participants **transfusion independent for 6 consecutive months** while maintaining a weighted average hemoglobin ≥ 9 g/dL (TI6)

- Assessed starting 60 days after last RBC transfusion for post-transplant support or TDT disease management

Proportion of participants **free from inpatient hospitalization for severe VOCs for ≥ 12 months (HF12)**

- Assessed starting 60 days after last RBC transfusion for post-transplant support or SCD disease management

Secondary & Other Efficacy Endpoints

- Total hemoglobin concentration
- Fetal hemoglobin concentration
- Proportion of F-cells
- Proportion of alleles with intended genetic modification in peripheral blood
- Proportion of alleles with intended genetic modification in CD34+ cells of the bone marrow
- Changes in markers of hemolysis (LDH, haptoglobin; CLIMB SCD-121 only)

Primary Safety Endpoints

- Neutrophil and platelet engraftment
- Safety and tolerability assessments, including adverse events, clinical laboratory values, and vital signs

ORIGINAL ARTICLE

Exagamglogene Autotemcel for Transfusion-Dependent β -Thalassemia

F. Locatelli, P. Lang, D. Wall, R. Meisel, S. Corbacioglu, A.M. Li, J. de la Fuente, A.J. Shah, B. Carpenter, J.L. Kwiatkowski, M. Mapara, R.I. Liem, M.D. Cappellini, M. Algeri, A. Kattamis, S. Sheth, S. Grupp, R. Handgretinger, P. Kohli, D. Shi, L. Ross, Y. Bobruff, C. Simard, L. Zhang, P.K. Morrow, W.E. Hobbs, and H. Frangoul, for the CLIMB THAL-111 Study Group*

ABSTRACT

BACKGROUND

Exagamglogene autotemcel (exa-cel) is a nonviral cell therapy designed to reactivate fetal hemoglobin synthesis through ex vivo clustered regularly interspaced short palindromic repeats (CRISPR)–Cas9 gene editing of the erythroid-specific enhancer region of *BCL11A* in autologous CD34+ hematopoietic stem and progenitor cells (HSPCs).

METHODS

We conducted an open-label, single-group, phase 3 study of exa-cel in patients 12 to 35 years of age with transfusion-dependent β -thalassemia and a β^0/β^0 , $\beta^0/\beta^{\text{low}}$ -like, or non- $\beta^0/\beta^{\text{low}}$ -like genotype. CD34+ HSPCs were edited by means of CRISPR–Cas9 with a guide mRNA. Before the exa-cel infusion, patients underwent myeloablative conditioning with pharmacokinetically dose-adjusted busulfan. The primary end point was transfusion independence, defined as a weighted average hemoglobin level of 9 g per deciliter or higher without red-cell transfusion for at least 12 consecutive months. Total and fetal hemoglobin concentrations and safety were also assessed.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Locatelli can be contacted at franco.locatelli@opbg.net or at the Department of Pediatric Hematology and Oncology, IRCCS Ospedale Pediatrico Bambino Gesù, Piazza Sant'Onofrio, 4, 00165 Rome, Italy.

*A list of the site investigators and coordinators from the CLIMB THAL-111 study group is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

This article was published on April 24, 2024, at NEJM.org.

N Engl J Med 2024;390:1663-76.
DOI: 10.1056/NEJMoa2309673
Copyright © 2024 Massachusetts Medical Society.

- ✓ Patients 12 to 35 years of age were eligible
- ✓ transfusion history of at least 100 ml of packed red cells per kilogram of body weight per year or 10 units of packed red cells per year for 2 years before screening.
- ✓ After completion of the 2-year study period, patients were offered enrollment in a 13-year long-term follow-up study (CLIMB-131; ClinicalTrials.gov number, NCT04208529).

- granulocyte-colony stimulating factor (G-CSF) and plerixafor for HSPC mobilization followed by apheresis for up to **3 consecutive days** to collect CD34+ HSPCs
- a myeloablative, pharmacokinetically adjusted busulfan conditioning regimen for **4 days**
- Exa-cel was infused intravenously through a central venous catheter at least 48 hours but no more than **7 days**

❖ ongoing phase 3, open label, single-dose study of exa-cel (CLIMB THAL111) at 13 sites

Demographics and Baseline Clinical Characteristics

	Full Analysis Set N = 52	Primary Efficacy Set N = 35
Age at baseline, years, mean (range)	21.5 (6.7)	21.1 (6.1)
≥12 and <18 years, n (%)	18 (34.6)	11 (31.4)
≥18 and ≤35 years, n (%)	34 (65.4)	24 (68.6)
Sex, n (%)		
Male	27 (51.9)	18 (51.4)
Female	25 (48.1)	17 (48.6)
Genotype, n (%)		
β ⁰ /β ⁰	19 (36.5)	10 (28.6)
β ⁰ /β ⁰ -like (β ⁰ /IVS-I-110; IVS-I-110/IVS-I-110)	12 (23.1)	10 (28.6)
Non-β ⁰ /β ⁰ -like	21 (40.4)	15 (42.9)
Historical RBC transfusions per year,^a units, mean (range)	36.0 (11.7)	37.1 (11.0)

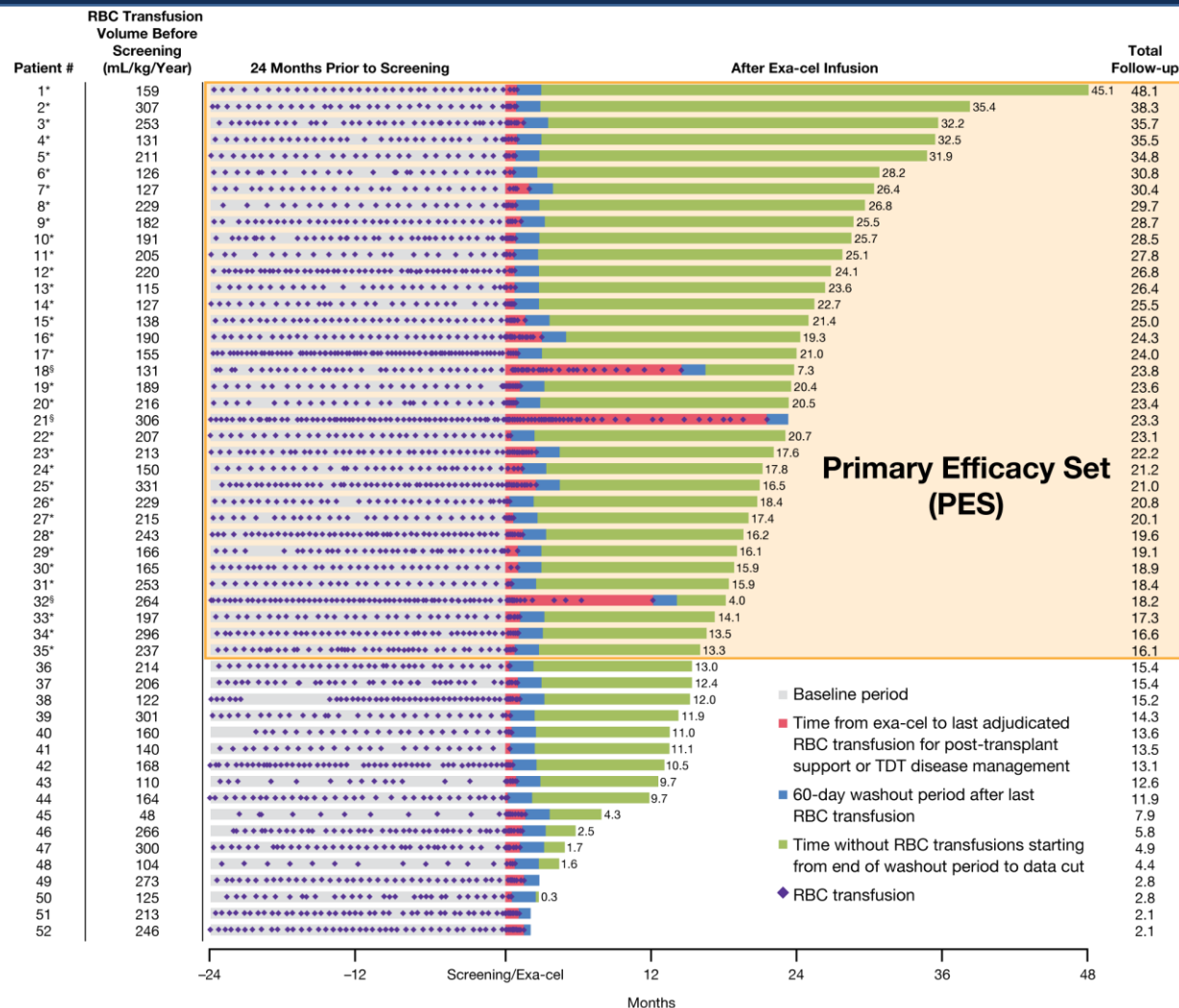
^a Annualized over 2 years before signing of the informed consent form; ^b Duration of follow-up include CLIMB SCD-131 trials.
RBC, red blood cell.

Treatment and Engraftment Results

	Full Analysis Set N = 52
Number of mobilization cycles, median (range)	1.0 (1, 4)
CD34 ⁺ cells x 10 ⁶ /kg drug product cell dose, median (range)	36.6 (10.9, 202.4)
Duration (months) of follow-up after exa-cel infusion, ^a median (range)	20.4 (2.1, 26.4)
Neutrophil Engraftment^b	
Time to neutrophil engraftment (days), median (min, max)	29.0 (12, 56)
Platelet Engraftment^c	
Time to platelet engraftment (days), median (min, max)	44 (20, 200)

^aDuration of follow-up include CLIMB SCD-131 trials. ^bDefined as the first day of 3 consecutive measurement of absolute neutrophil count ≥500 cells/μL on 3 different days. ^cDefined as the first day of 3 consecutive measurement of unsupported (no platelet transfusion in last 7days) platelet count ≥20,000/μL on 3 different days.

Patients Who Achieved Transfusion Independence (TI12) Maintained Transfusion Independence



Adolescents and Adults

- Participants **stopped transfusions** after a mean of 35.2 days; once T12 achieved, all participants **remained transfusion independent through follow-up**
- Three participants did not achieve TI12; however, had **substantial clinical benefit**
 - 1 participant had a relative reduction in annualized red blood cell transfusion volume of 83.9%
 - 2 participants stopped red blood cell transfusions 14.5 months and 12.2 months after exa-cel and have been transfusion-free for 7.3 months and 4.0 months, respectively

* patients who achieved TI12; §patients who did not achieve TI12

exa-cel, exagamglogene autotemcel; RBC, red blood cell; TDT, TDT, transfusion dependent β -thalassemia; TI12; proportion of participants transfusion independent for 12 consecutive months while maintaining a weighted average hemoglobin ≥ 9 g/dL.

Exa-cel Safety Profile Is Consistent With Myeloablative Busulfan Conditioning and Autologous HSCT

Post-exa-cel AE Overview	Exa-cel N = 52
Participants with	
Any AEs, n (%)	52 (100.0)
AEs related to exa-cel, n (%) ^a	13 (25.0)
AEs related to busulfan, n (%) ^a	51 (98.1)
AEs Grade 3/4, n (%)	46 (88.5)
SAEs, n (%)	17 (32.7)
SAEs related to exa-cel, n (%)	2 (3.8)
AEs leading to death, n (%) ^b	0
Any malignancies, n (%)	0

All participants engrafted neutrophils and platelets.
^a includes related and possibly related AEs and SAEs.
^b SAEs previously reported in 2 participant and fully resolved. One participant had SAEs starting per-engraftment and in context of HLH (HLH, acute respiratory distress syndrome, and headache were related to exa-cel; idiopathic pneumonia syndrome was related to exa-cel and busulfan). One participant had SAEs of delayed neutrophil engraftment and thrombocytopenia both related to exa-cel and busulfan (neutrophil engraftment achieved on Day 56 without use of backups cells).

Common Adverse Events: Preferred Term	Exa-cel N = 52
Febrile neutropenia	32 (61.5)
Headache	28 (53.8)
Stomatitis	26 (50.0)
Thrombocytopenia	25 (48.1)
Anemia	23 (44.2)
Mucosal inflammation	23 (44.2)
Nausea	22 (42.3)
Vomiting	21 (40.4)

Table includes common adverse events occurring in ≥40% of participants.

Most adverse events occurred within the first 6 months after the exa-cel infusion

AE, adverse event; **exa-cel**, exagamglogene autotemcel; **HLH**, hemophagocyticlymphohistiocytosis; **HSCT**, hematopoietic stem cell transplantation; **SAE**, serious adverse event.

Conclusions

- ✓ **91%** transfusion **independence** for at least 12 consecutive months.
- ✓ Patients **stopped transfusions** approximately **1 month after** the exa-cel infusion, and transfusion independence was durable, with a mean duration of 22.5 months (range, 13.3 to 45.1)
- ✓ **adverse events** occurring within the first **6 months** after the exa-cel infusion.
- ✓ **No** cases of **myelodysplasia** or other hematologic **cancer** occurred

Locatelli F et al. N Engl J Med. 2024 May 9;390(18):1663-1676.

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MAY 9, 2024

VOL. 390 NO. 18

Exagamglogene Autotemcel for Severe Sickle Cell Disease

H. Frangoul, F. Locatelli, A. Sharma, M. Bhatia, M. Mapara, L. Molinari, D. Wall, R.I. Liem, P. Telfer, A.J. Shah, M. Cavazzana, S. Corbacioglu, D. Rondelli, R. Meisel, L. Dedeken, S. Lobitz, M. de Montalembert, M.H. Steinberg, M.C. Walters, M.J. Eckrich, S. Imren, L. Bower, C. Simard, W. Zhou, F. Xuan, P.K. Morrow, W.E. Hobbs, and S.A. Grupp, for the CLIMB SCD-121 Study Group*

The study was designed by Vertex pharmaceuticals and CRISPR

- phase 3, open label, single-dose, 2-year study of exa-cel (CLIMB SCD-121) at 16 sites
- Patients 12 to 35 years of age with SCD
- history of at least two vaso-occlusive episodes per year during the 2 years before screening
- After completion of this study, patients were encouraged to enroll in the 13-year long-term follow-up study (CLIMB-131; ClinicalTrials.gov number, CT04208529)

- ✓ Autologous CD34+ HSPCs
- ✓ after **plerixafor** mobilization of HSPCs,
- ✓ apheresis for up to 3 consecutive days for each episode
- ✓ Exa-cel was manufactured from these CD34+ cells with the use of CRISPR-Cas9,
- ✓ with a single-guide RNA molecule selectively targeting the BCL11A
- ✓ erythroid-specific enhancer Before the exa-cel infusion, patients received myeloablative conditioning with pharmacokinetically adjusted single agent busulfan for 4 days

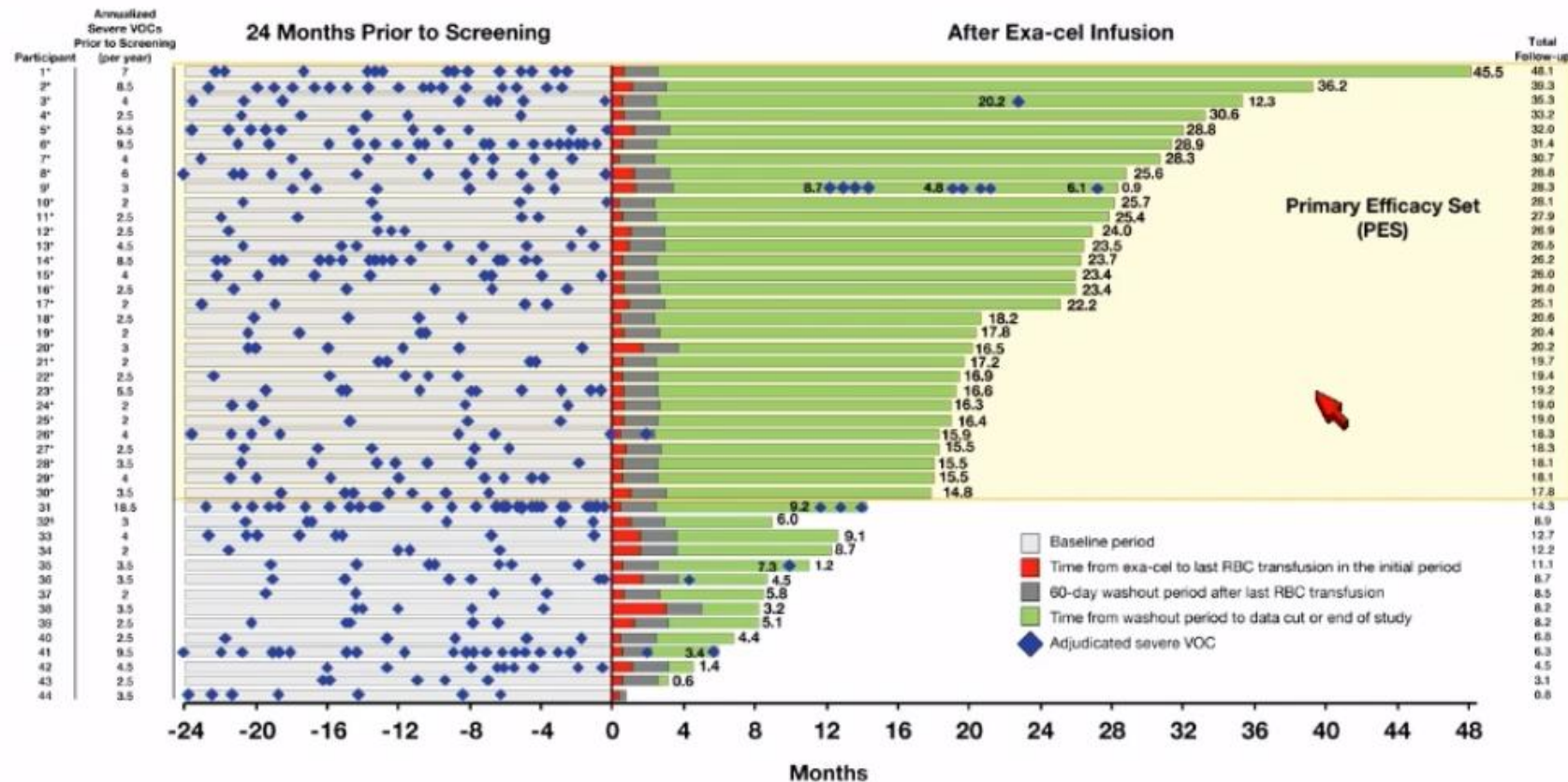
Demographics and Baseline Clinical Characteristics

	Full Analysis Set N = 44	Primary Efficacy Set N = 30
Age at screening, years, mean (SD)	21.2 (6.1)	22.1 (6.0)
≥12 and <18 years, n (%)	12 (27.3)	6 (20.0)
≥18 and ≤35 years, n (%)	32 (72.7)	24 (80.0)
Sex, n (%)		
Male	24 (54.5)	16 (53.3)
Female	20 (45.5)	14 (46.7)
Genotype, n (%)		
β^s/β^s	40 (90.9)	29 (96.7)
β^s/β^0	3 (6.8)	1 (3.3)
β^s/β^+	1 (2.3)	0
α-globin gene deletion status, n (%)		
One-gene deletion	15 (34.1)	9 (30.0)
Two-gene deletions	2 (4.5)	2 (6.7)
Historical VOC episodes per year,^a mean (range)	4.1 (2.0, 18.5)	3.9 (2.0, 9.5)
Historical in-patient hospitalizations for severe VOCs per year,^a mean (range)	2.7 (0.5, 9.5)	2.7 (0.5, 8.5)

Treatment and Engraftment Results

	Full Analysis Set N = 44
Number of mobilization cycles, median (range)	2.0 (1.00, 6.00)
Exa-cel dose: $10^6 \times \text{CD34}^+$ cells/kg, mean (range)	4.7 (2.9, 14.4)
Duration (months) of follow-up after exa-cel infusion ^a , mean (range)	20.1 (0.8, 48.1)
Neutrophil Engraftment^b	
Time to neutrophil engraftment (days), median (range)	27.0 (15, 40)
Platelet Engraftment^c	
Time to platelet engraftment (days), median (range)	35.0 (23, 126)

Participants Treated With Exa-cel Achieved Clinically Meaningful and Durable Benefit - Free From VOCs



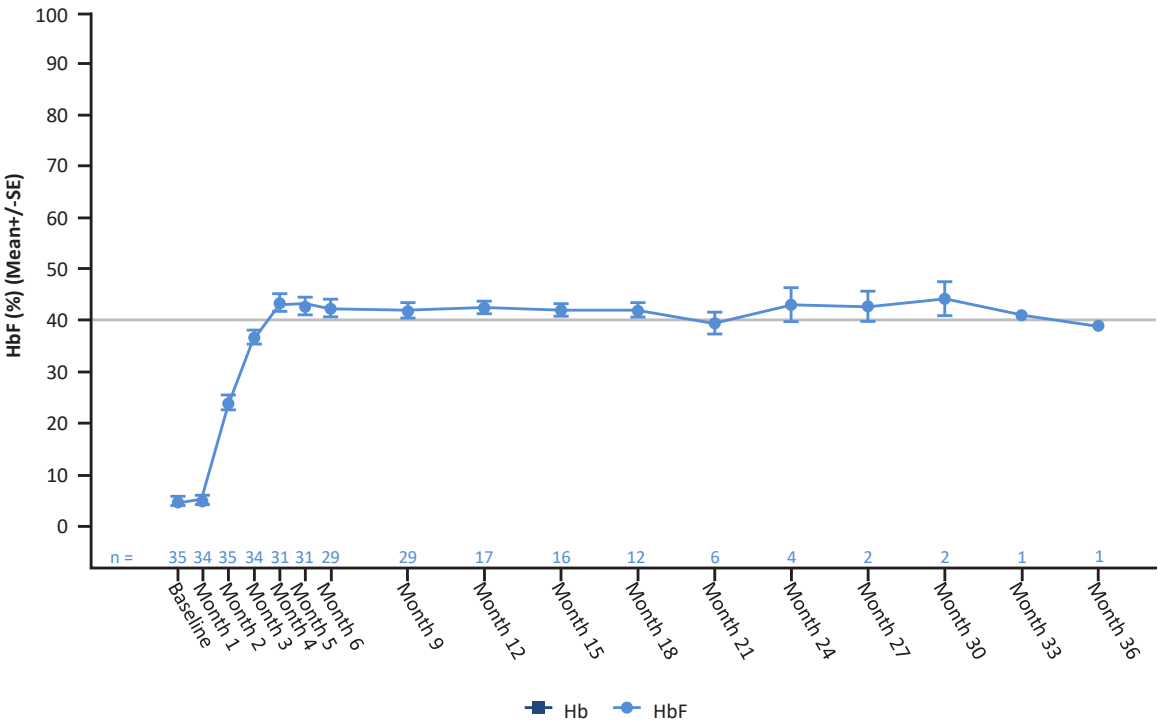
- Participants **stopped transfusions** after a median of 20 days
- One participant with **complex comorbidities and history of chronic pain** did not achieve VF12; however, **achieved HF12** and remains **free from hospitalization for severe VOCs (24.9 months)**
- **28 of 29 participants (PES)** remained **VOC-free through follow-up**; one participant had a **VOC** in the setting of a **parvovirus B19 infection** 22.7 months after exa-cel infusion, **fully recovered**, and has since been **VOC-free (12.3 months)**

*participants who achieved VF12; †participants who did not achieve VF12; §participant who died from respiratory failure due to COVID-19 infection; not related to exa-cel. Data shown is based on the Full Analysis Set.

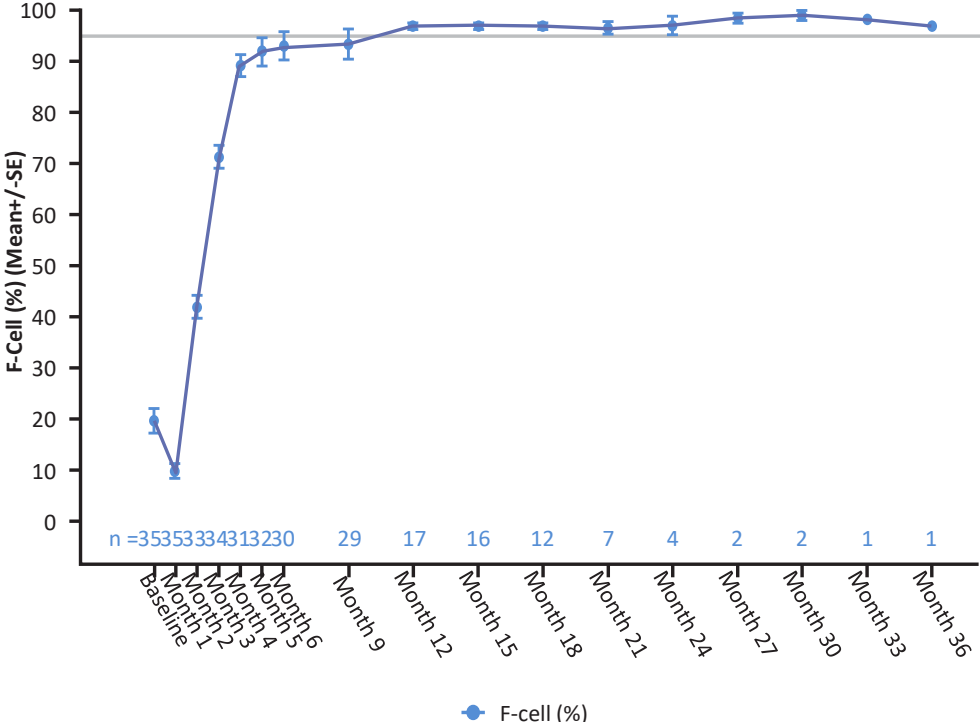
exa-cel, exagamglogene autotemcel; **HF12**, proportion of participants free from in-patient hospitalization for severe VOCs for ≥12 consecutive months; **PES**, Primary Efficacy Set; **VF12**, proportion of participants free of severe VOCs for ≥12 consecutive months; **RBC**, red blood cell; **VOC**, vaso-occlusive crisis.

SCD: Early and Sustained Increases in Total Hemoglobin and Fetal Hemoglobin in Pancellular Distribution Following Exa-Cel Infusion

Fetal Hemoglobin



Percent F-Cells



- Mean HbF was 36.8% at Month 3 and was then maintained at ~40.0% through follow-up
- Mean total Hb was 12.0 g/dL at Month 3 and was then maintained at ≥11.0 g/dL through follow-up
- Pancellular distribution of fetal hemoglobin (>95% of RBCs) observed early and maintained following exa-cel infusion

Exa-cel Safety Profile Consistent With Myeloablative Busulfan Conditioning and Autologous HSCT

Post Exa-cel Adverse Events: Overview	Exa-cel N = 44
Participants with	
Any AEs, n (%)	44 (100.0)
AEs related to exa-cel, n (%) ^a	13 (29.5)
AEs related to busulfan, n (%) ^a	44 (100.0)
AEs Grade 3/4, n (%)	42 (95.5)
SAEs, n (%)	20 (45.5)
SAEs related to exa-cel, n (%) ^a	0
AEs leading to death, n (%) ^b	1 (2.3)
Any malignancies, n (%)	0

All participants engrafted neutrophils and platelets.

^aincludes related and possibly related AEs.

^bOne death, from respiratory failure due to COVID-19, was not considered to be related to exa-cel.

Common Adverse Events: Preferred Term	Exa-cel N = 44
Nausea	31 (70.5)
Stomatitis	28 (63.6)
Vomiting	25 (56.8)
Febrile neutropenia	24 (54.5)
Abdominal pain	22 (50.0)
Headache	22 (50.0)
Pruritus	22 (50.0)

Table includes common adverse events occurring in ≥50% of participants.

One death from respiratory failure (SARS-CoV-2) in an adult patient (268 days after the exa-cel infusion)

- ✓ also had busulfan-associated lung injury
- ✓ preexisting lung disease

Conclusions

- Treatment with **exa-cel** **eliminated vaso-occlusive crises in 97%** of patients with sickle cell disease for a period of 12 months or more
- **100%** were **free** from inpatient **hospitalization** for severe vaso-occlusive crises for at least 12 months,
- Free from vaso-occlusive crises for a mean **duration of 22.4 months** (range, 14.8 to 45.5)
- Mean total **hemoglobin** level of **11.9±1.5 g** per deciliter at month 3 and **12.5±1.8 g** per deciliter at month 6

Conclusions on Exa-cel CLIMB THAL-111 and CLIMB SCD-121 Pivotal Trials

- Participants had **early and sustained increases in total hemoglobin and fetal hemoglobin with pancellular distribution**
- Stable proportions of *BCL11A* edited alleles were seen in bone marrow and peripheral blood, indicating **successful and durable editing of long-term HSCs** in TDT and SCD
- **Safety profile of exa-cel is consistent** with busulfan myeloablative conditioning and autologous hematopoietic stem cell transplantation, based on 48 participants with TDT and 35 participants with SCD who were dosed with exa-cel.

Exa-cel can provide a one-time functional cure to patients with TDT and SCD

FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease

[f Share](#) [X Post](#) [in LinkedIn](#) [Email](#) [Print](#)

For Immediate Release: December 08, 2023

Today, the U.S. Food and Drug Administration approved two milestone treatments, Casgevy and Lyfgenia, representing the first cell-based gene therapies for the treatment of sickle cell disease (SCD) in patients 12 years and older. Additionally, one of these therapies, Casgevy, is the first FDA-approved treatment to utilize a type of novel genome editing technology, signaling an innovative advancement in the field of gene therapy.

BREAKING | Vertex and CRISPR's Gene-editing Therapy Casgevy Receives Early FDA Approval for β -Thalassaemia Treatment

1 minute read



Casgevy received a conditional marketing authorisation valid throughout the **EMA on 9 February 2024.**

*On Tuesday, January 16, 2024, the FDA gave the green light to **Vertex Pharmaceuticals** and **CRISPR Therapeutics**' groundbreaking **Casgevy™ (exagamglogene autotemcel)** Cas9 gene-edited cell therapy. This one-time treatment is now approved for **transfusion-dependent β -thalassaemia** patients aged 12 and up.*

The Cost of Genetic Therapies to the Patients/Healthcare System

Lyfgenia will cost \$3.1 M

Casgevy will cost \$2.2 M

This is a huge burden on healthcare systems in the US

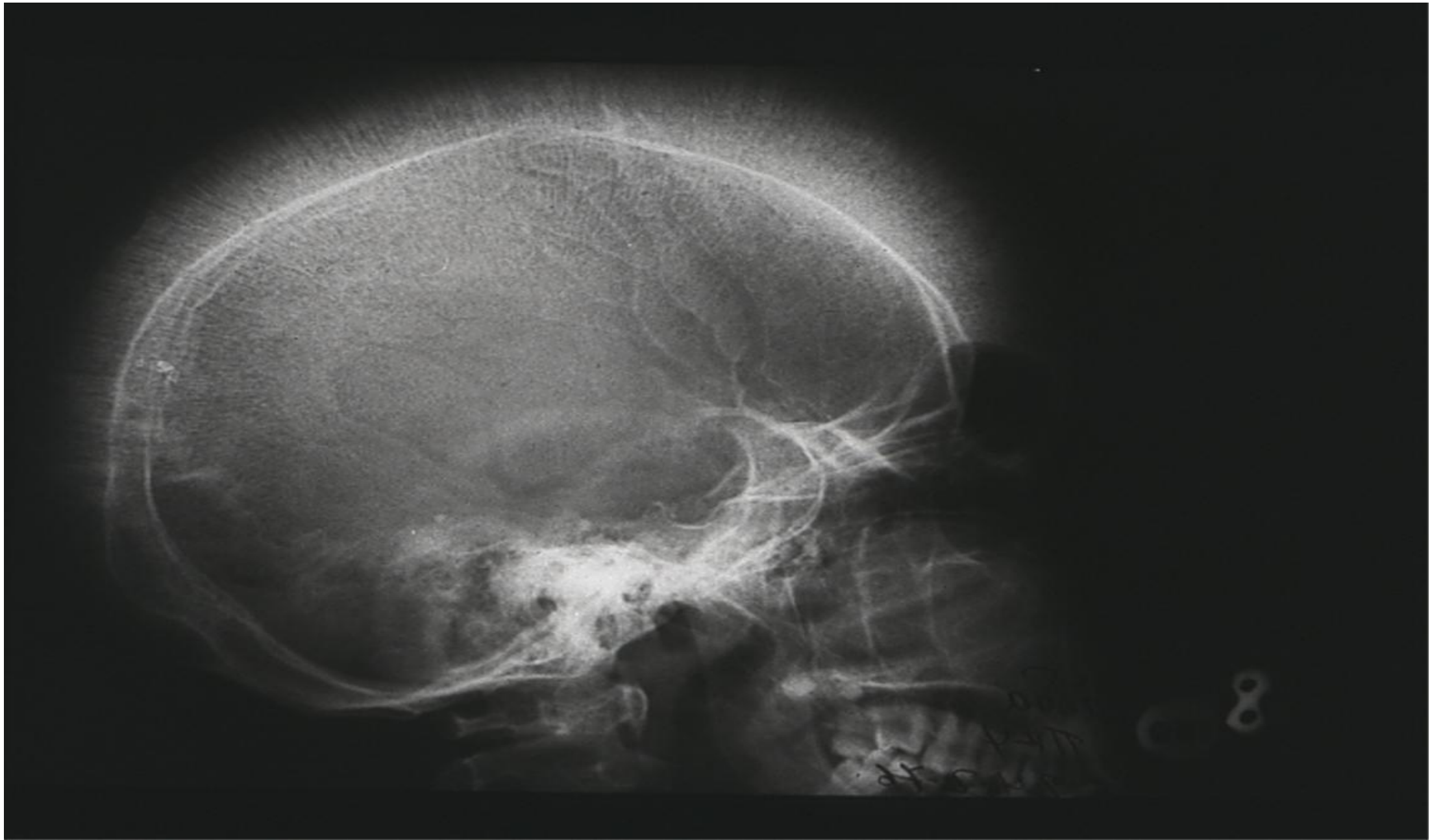
This is unaffordable in developing countries



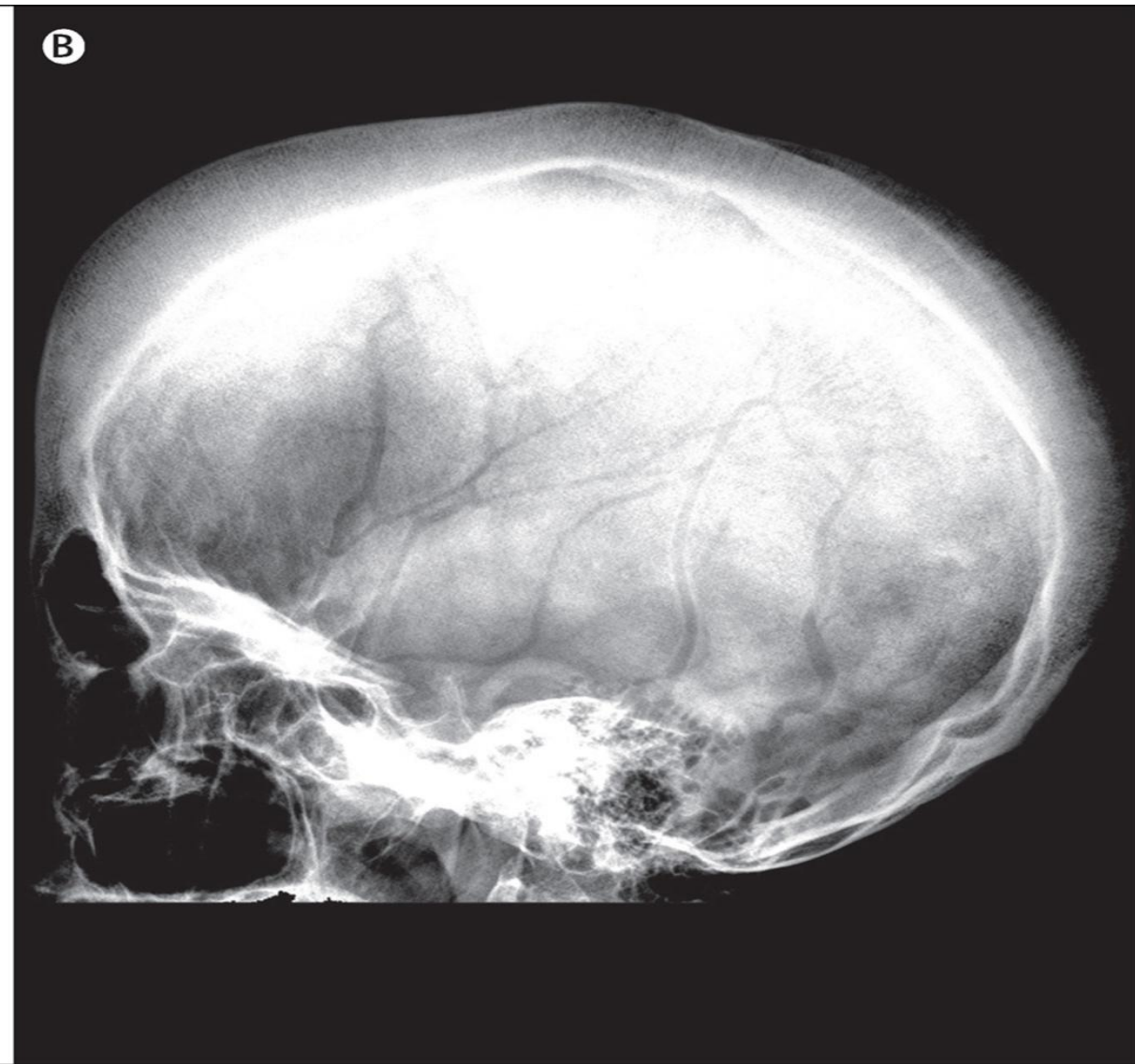
While exciting that genetic therapies are getting approved, efforts need to continue to cover the costs of these approved therapies so that they are accessible to all patients in the US

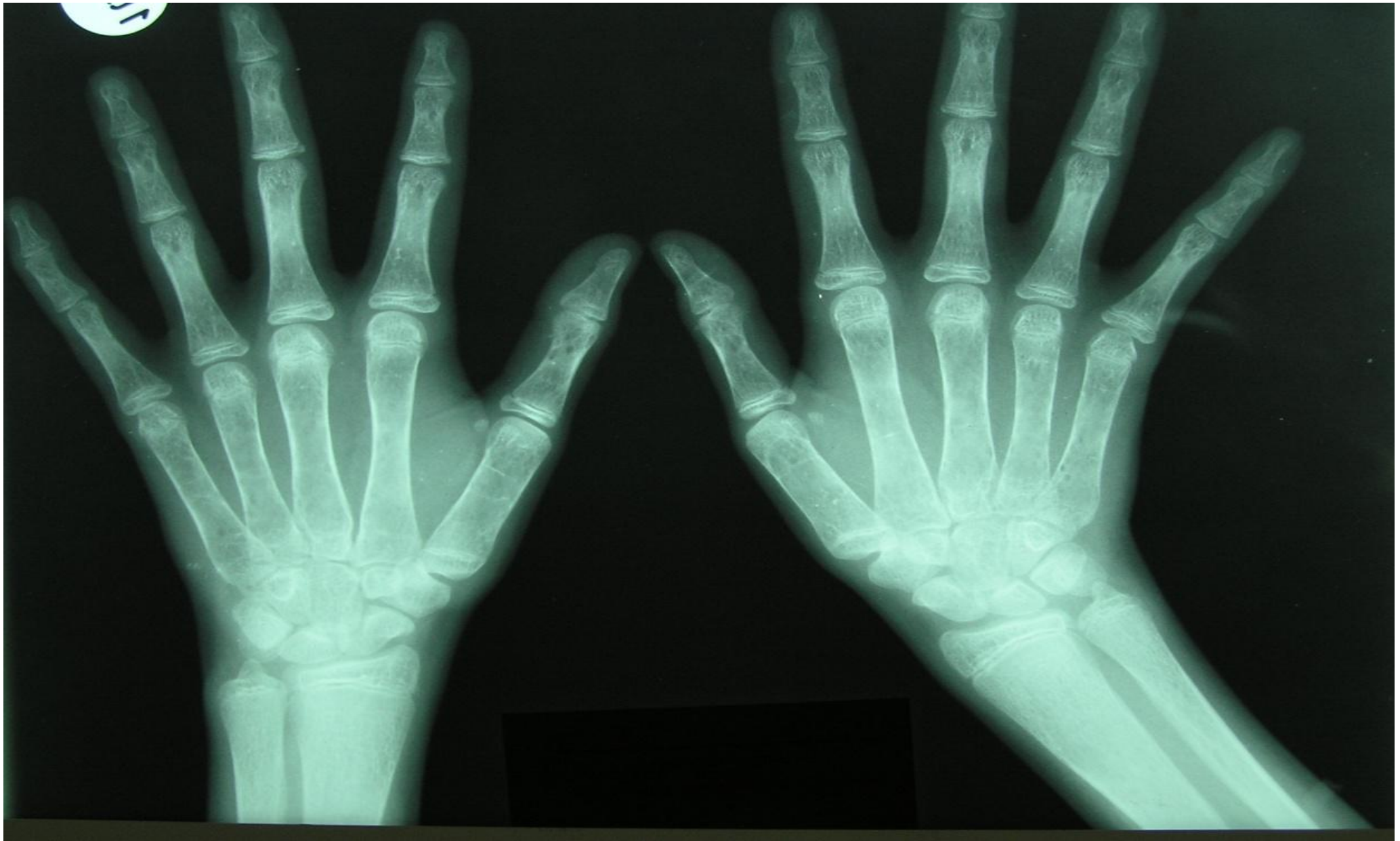
Efforts need to be made to reduce costs of genetic therapies



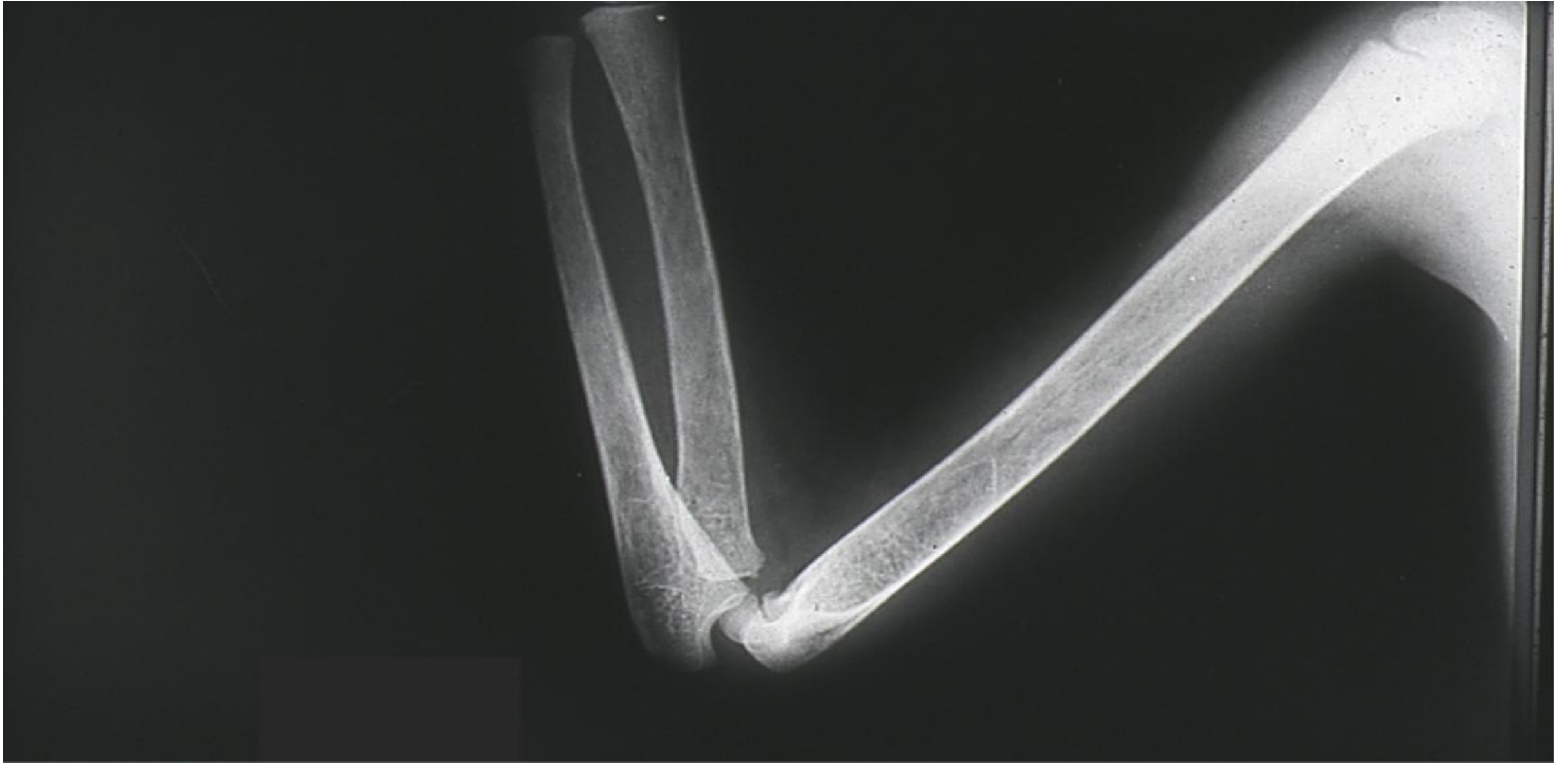


Thalassemia Unit, 1st Dept of Pediatrics, University of Athens.

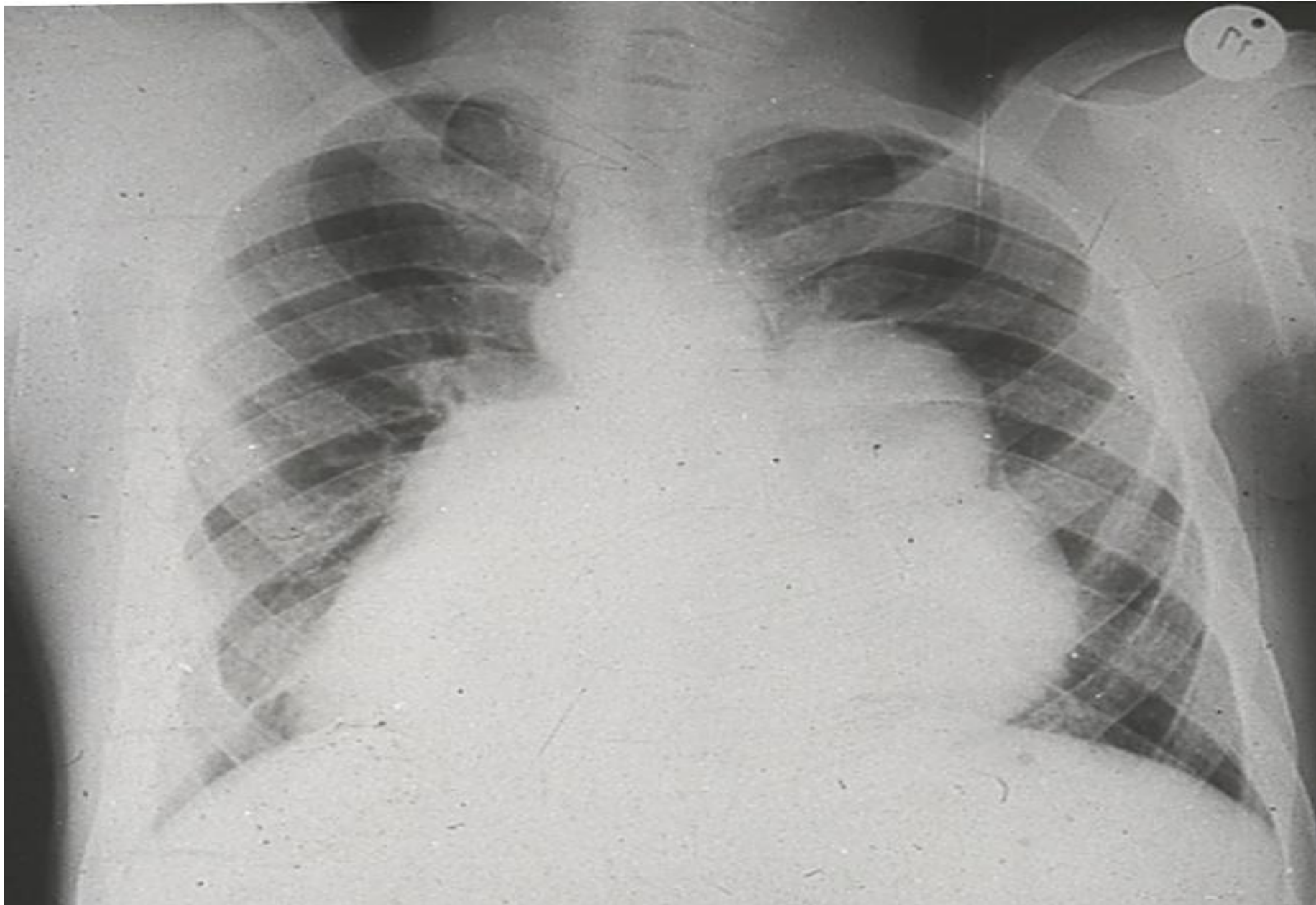




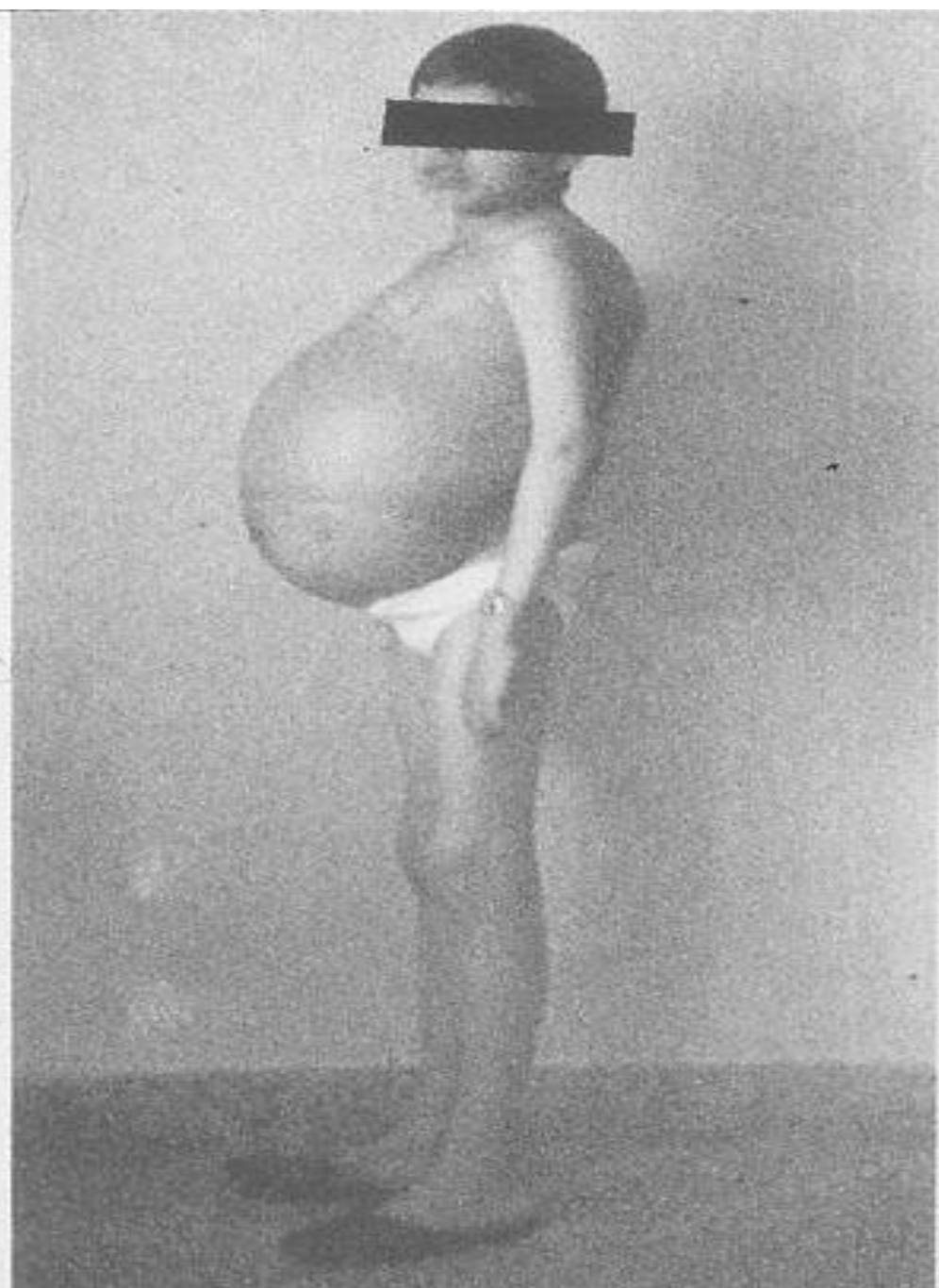
Thalassemia Unit, 1st Dept of Pediatrics, University of Athens.



Thalassemia Unit, 1st Dept of Pediatrics, University of Athens.



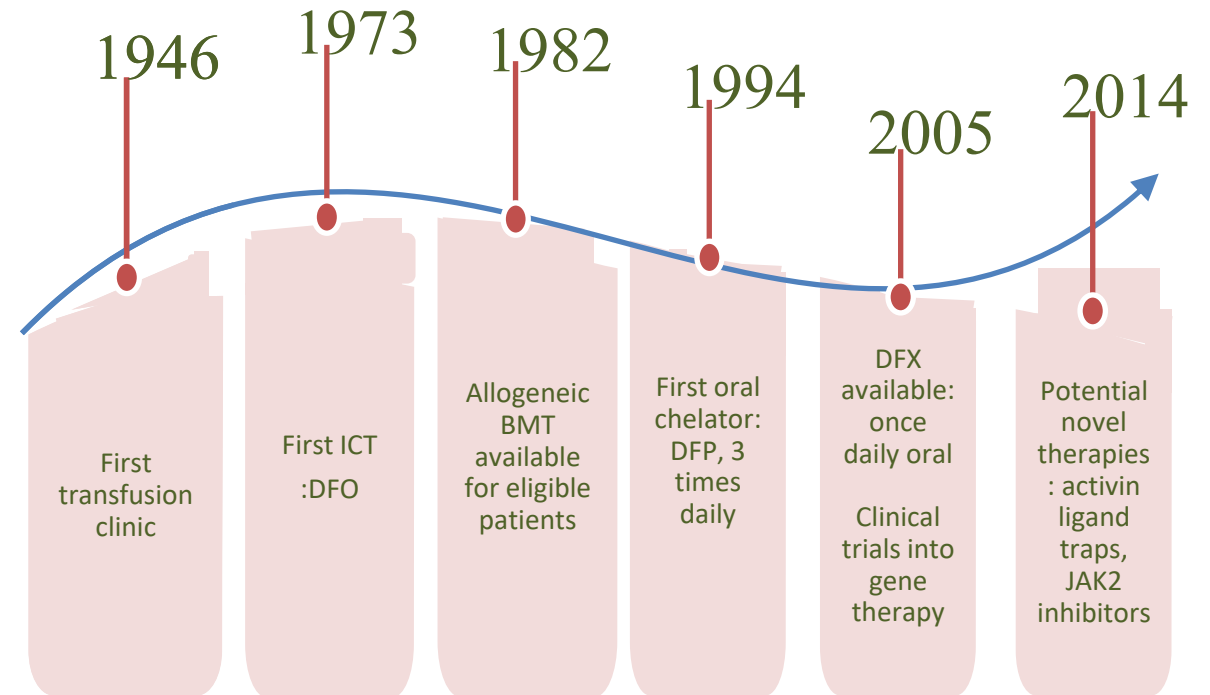
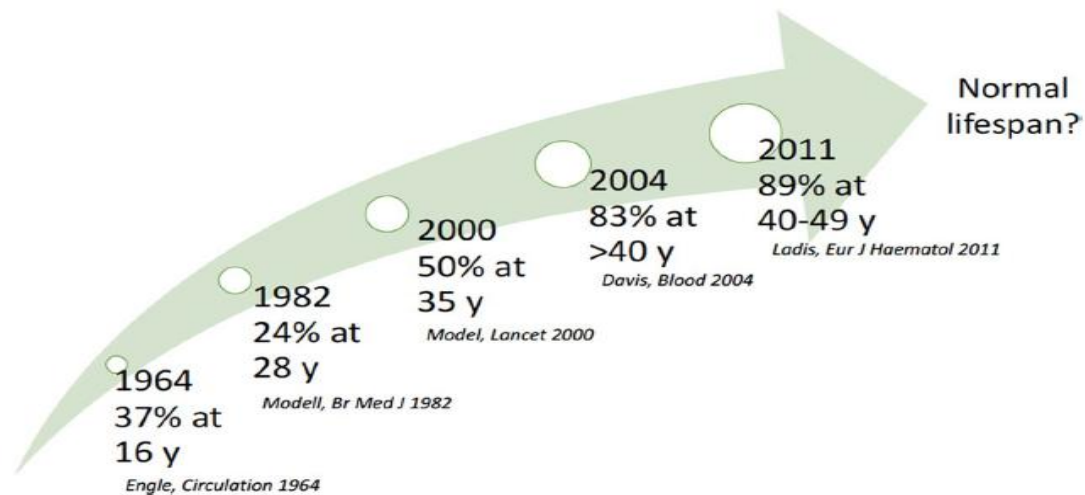
Thalassemia Unit, 1st Dept of Pediatrics, University of Athens.



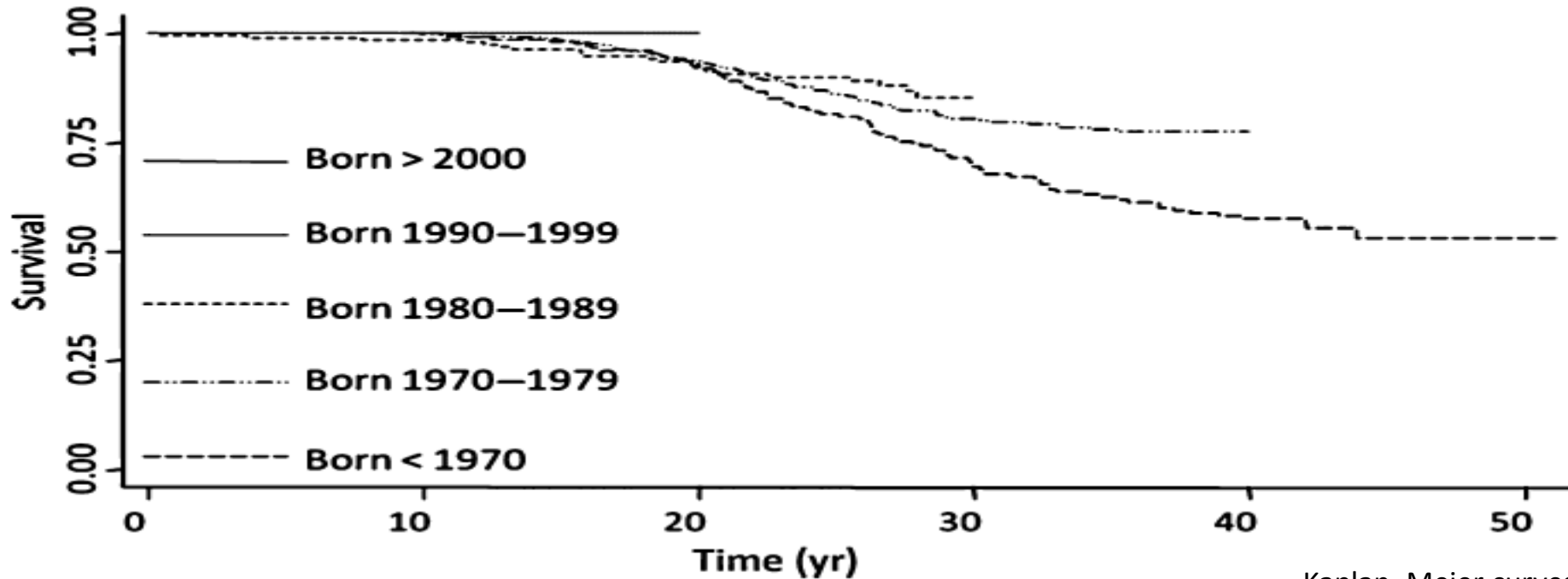


Εξέλιξη επιβίωσης

Improvement in survival



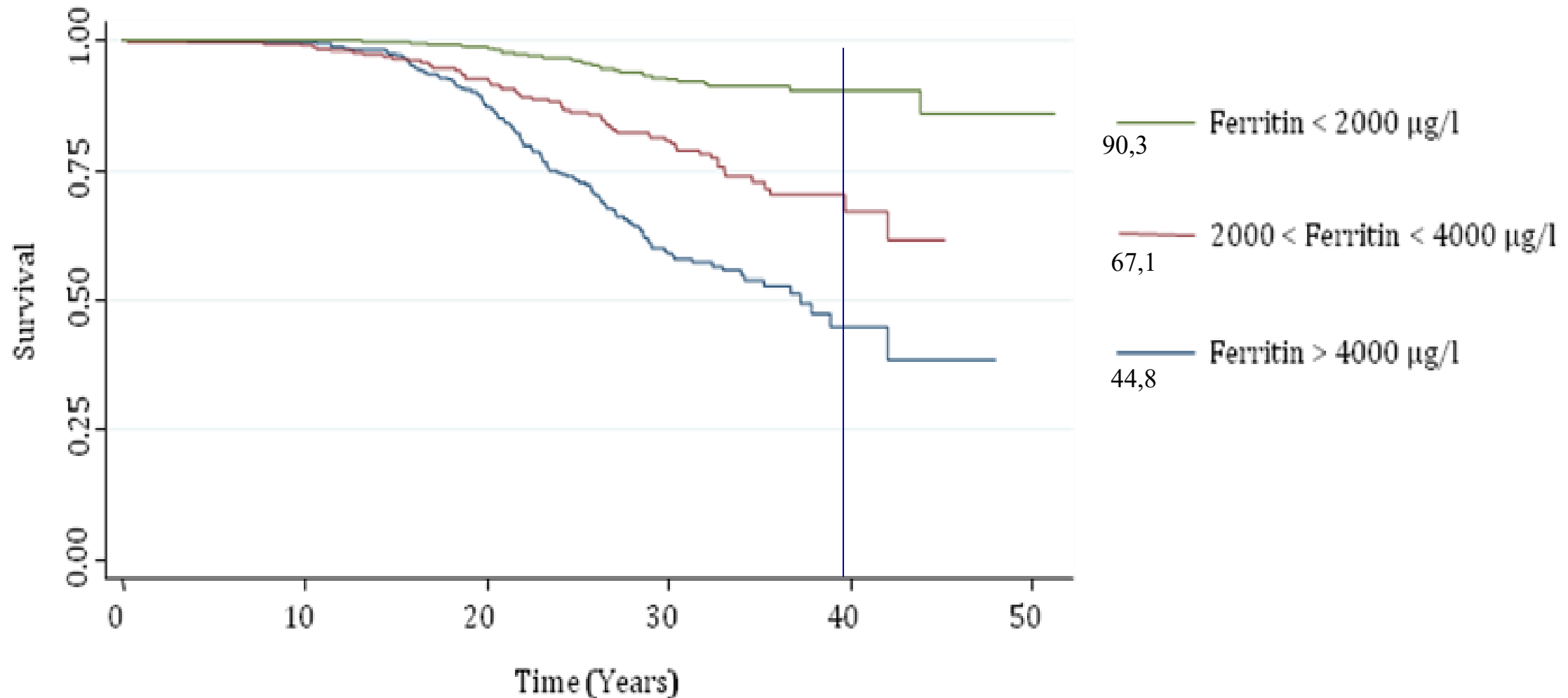
Ελληνικά δεδομένα Επιβίωσης



- ✓ 1044 ασθενείς
- ✓ Median time observation 28.4 yrs
- ✓ 65% των ασθενών αναμένεται να επιβιώσουν μέχρι την ηλικία των 50 ετών

Kaplan–Meier curves* of overall survival according to decade of birth. *Logrank test: P-value < 0.0001. *Test for trend: P-value < 0.0001

Προσδόκιμο επιβίωσης ανάλογα με τον βαθμό αιμοσιδήρωσης



Ελληνικό Μητρώο Καταγραφής Αιμοσφαιρινοπαθειών

Annals of Hematology
<https://doi.org/10.1007/s00277-018-3493-4>

ORIGINAL ARTICLE



National registry of hemoglobinopathies in Greece: updated demographics, current trends in affected births, and causes of mortality

Ersi Voskaridou¹ · Antonis Kattamis² · Christina Fragodimitri³ · Alexandra Kourakli⁴ · Panagiota Chalkia⁵ · Michael Diamantidis⁶ · Efthymia Vlachaki⁷ · Marouso Drosou⁸ · Stilianos Lafioniatis⁹ · Konstantinos Maragkos¹⁰ · Fotini Petropoulou¹¹ · Eftihios Eftihiadis¹² · Marina Economou⁷ · Evangelos Klironomos¹³ · Freideriki Koutsouka¹⁴ · Konstantina Nestora¹⁵ · Ioanna Tzoumari¹⁶ · Ourania Papageorgiou¹⁷ · Artemis Basileiadi¹⁸ · Ioannis Lafiatis¹⁹ · Efthymia Dimitriadou²⁰ · Anastasia Kalpaka²¹ · Chrysoula Kalkana²² · Georgios Xanthopoulos²³ · Ioannis Adamopoulos²⁴ · Panagiotis Kaias²⁵ · Aikaterini Mpitzioni²⁶ · Anastasia Goula²⁷ · Ioannis Kontonis²⁸ · Chrisoula Alepi²⁹ · Athanasios Anastasiadis³⁰ · Margarita Papadopoulou³¹ · Polixeni Maili³² · Dionisia Dionisopoulou³³ · Antigoni Tsirka³⁴ · Alexandros Makis³⁵ · Stavroula Kostaridou³⁶ · Marianna Politou³⁷ · Ioannis Papassotiriou³⁸ · on behalf of the Greek Haemoglobinopathies Study Group

Received: 12 May 2018 / Accepted: 31 August 2018
© Springer-Verlag GmbH Germany, part of Springer Nature 2018

Ελληνικό Μητρώο Καταγραφής Αιμοσφαιρινοπαθειών

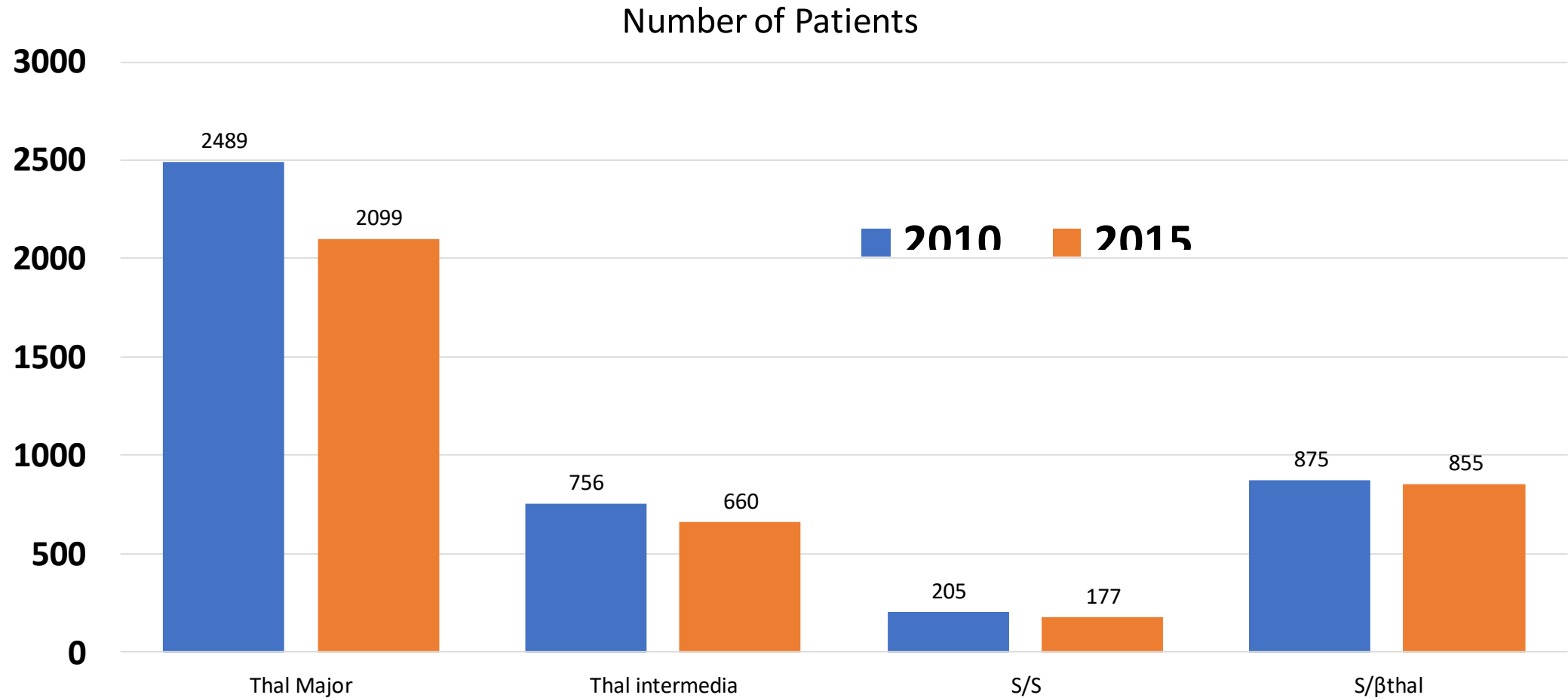
	Male			Female			Total		
	2000– 2010	2010– 2015	%	2000– 2010	2010– 2015	%	2000– 2010	2010– 2015	%
TM	1179	967	– 18	1301	1132	– 13	2485	2099	– 16
TI	326	293	– 10	427	366	– 14	756	660	– 13
HH	87	109	25	91	104	14	178	213	20
SCA	76	67	– 12	129	107	– 17	205	177	– 14
S/β-thal	381	366	– 4	490	483	– 1	875	855	– 2

Patients with missing data on sex or disease subtype are not included

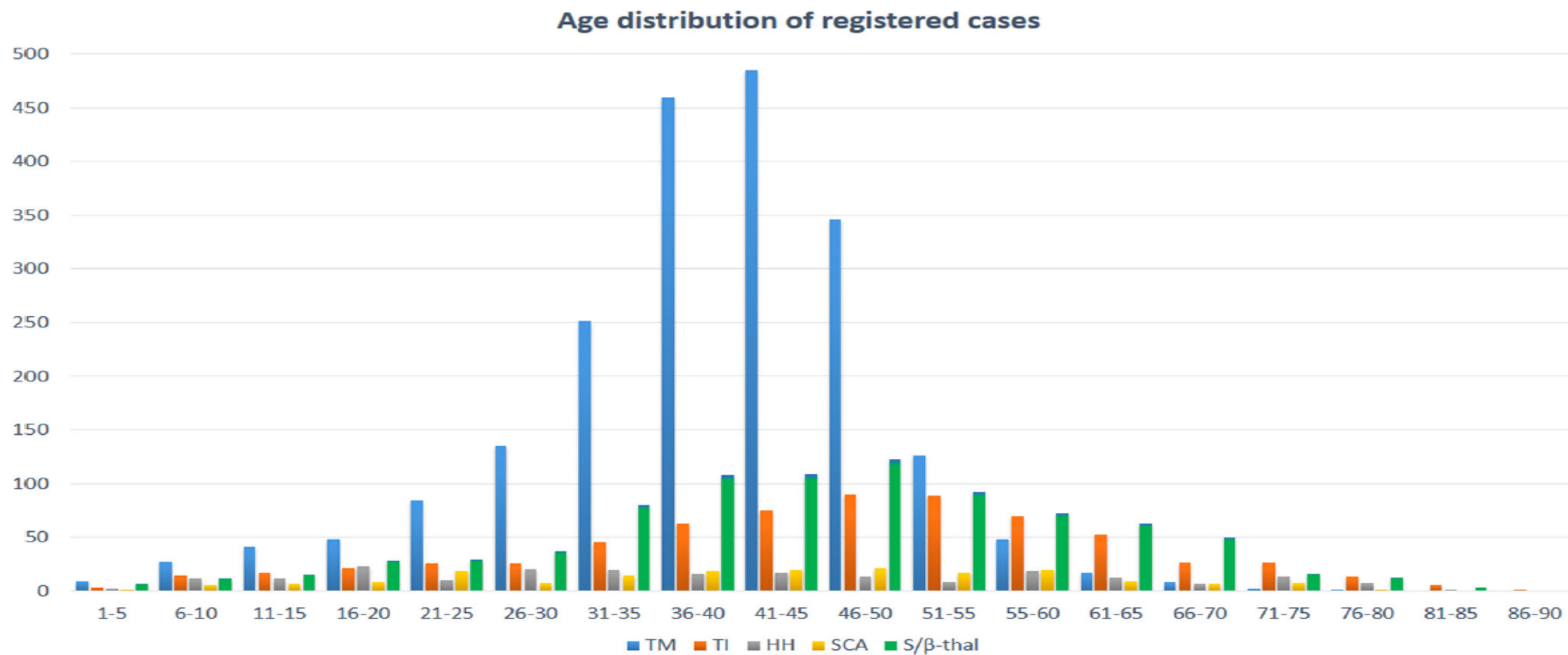
TM thalassemia major, TI thalassemia intermedia, HH hemoglobinopathy “H”, SCA sickle cell anemia, S/β-thal double heterozygous HbS and β-thal

✓ 4.506 ασθενείς
 ✓ 43 κέντρα
 θεραπείας
 ✓ πρόγραμμα
 πρόληψης από 1974
 ✓ 150 έως 200
 γεννήσεις
 αναμένονταν κάθε
 χρόνο
 ✓ 2000-2015: 319
 γεννήσεις

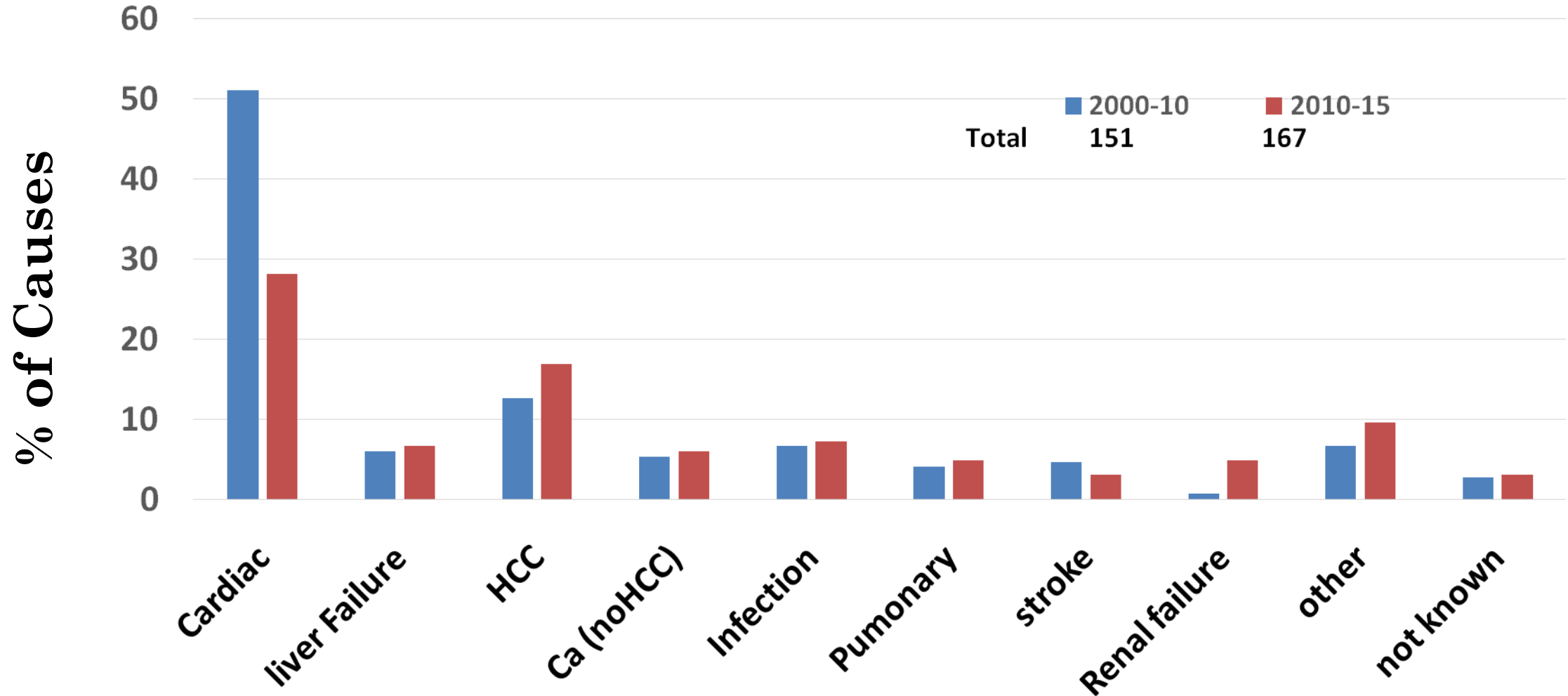
Ελληνικό Μητρώο Καταγραφής Αιμοσφαιρινοπαθειών



Ελληνικό Μητρώο Καταγραφής Αιμοσφαιρινοπαθειών



Ελληνικό Μητρώο Καταγραφής Αιμοσφαιρινοπαθειών-Αίτια Θανάτων



Επιμύθιο...

- Θαλασσαιμία: Μια χρόνια νόσος με ανάγκη συνεχούς ιατρικής φροντίδας και θεραπείας
- Οι νεώτερες γενεές θαλασσαιμικών καλύτερο αναμενόμενο προσδόκιμο ΕFS
- Ελλάδα: Όχι πια παιδιατρικό νόσημα.
- Συντηρητική Θεραπεία: Παράγοντες βελτίωσης αναιμίας / αποτελεσματική αποσιδήρωση
- Θεραπείες ίασης
- Προκλήσεις Παραμένουν ...