Thalassemia for the Primary Care Provider

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Disclosures

- Jeanne Boudreaux, MD, has disclosed that she has received consulting fees from Bluebird Bio, Vertex, Chiesi, and Celgene/BMS
- She has also served on the DSMB for Chiesi

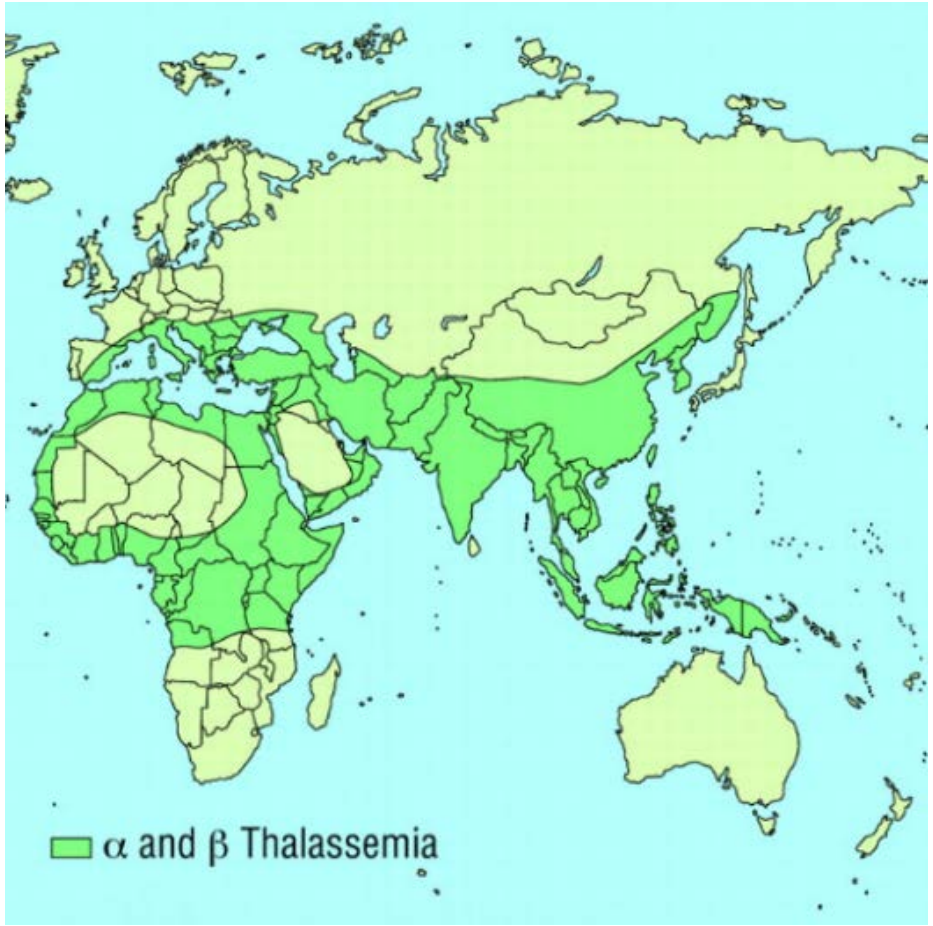
Learning Objectives

Participants should be able to:

- Describe the changing demographics and racial and ethnic disparities faced by thalassemia patients
- Accurately diagnose thalassemia and describe the pathophysiology of this disease
- Aid the hematologist in the care of thalassemia patients through the understanding of the various treatment options. This includes knowing when to refer these patients
- Have a working knowledge of the newer therapies in development

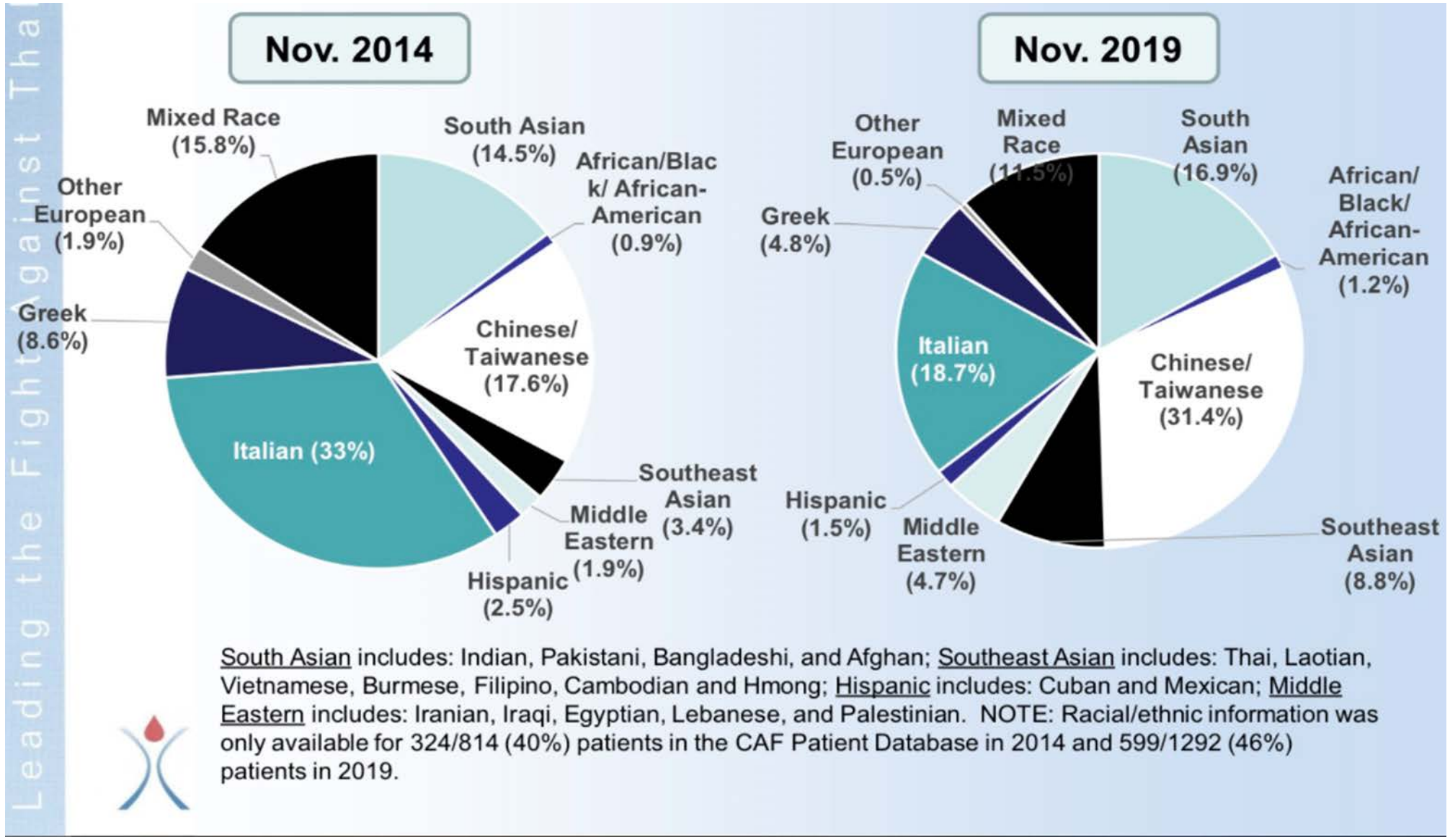
Worldwide Distribution of β-Thalassemia

- High prevalence in Asia—South and Southeast Asia, China[1]
- 80-90 million carriers worldwide (~ 1.5% of population)[1]
- 60,000 affected individuals born annually[1]
- Estimated prevalence in Italy: ~ 6000[3]
- Exact prevalence in US unknown; estimated to be ~ 2000 individuals[2]
  CAF in contact with 1408 pts (2021)



1. Galanello. Orphanet J Rare Dis. 2010;5:11. 2. Centers for Disease Control and Prevention. Thalassemia Awareness. 3. Angelucci. Blood. 2016;128:3533.

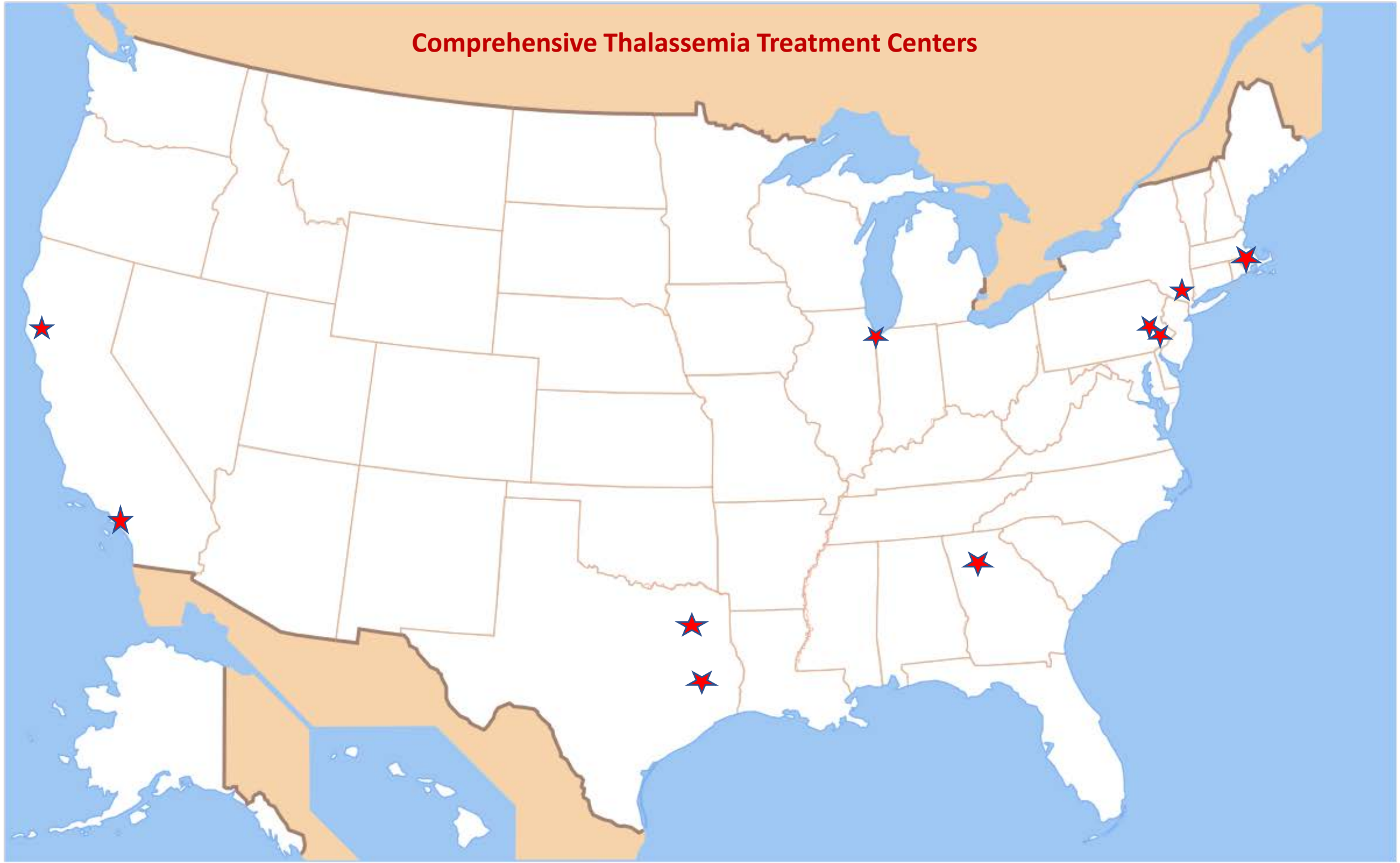
Changing Demographics



Demographics in Georgia

- Unpublished data from our center
  - We have 20x the national average of Black thalassemia patients
  - Only 20% have known relatives with Sickle cell disease
  - Most identify as African American
  - Have a higher rate of splenomegaly and bony changes
  - May be more likely due to their race to be inappropriately treated as a sickle cell patient

Comprehensive Thalassemia Treatment Centers



Racial and Ethnic disparities

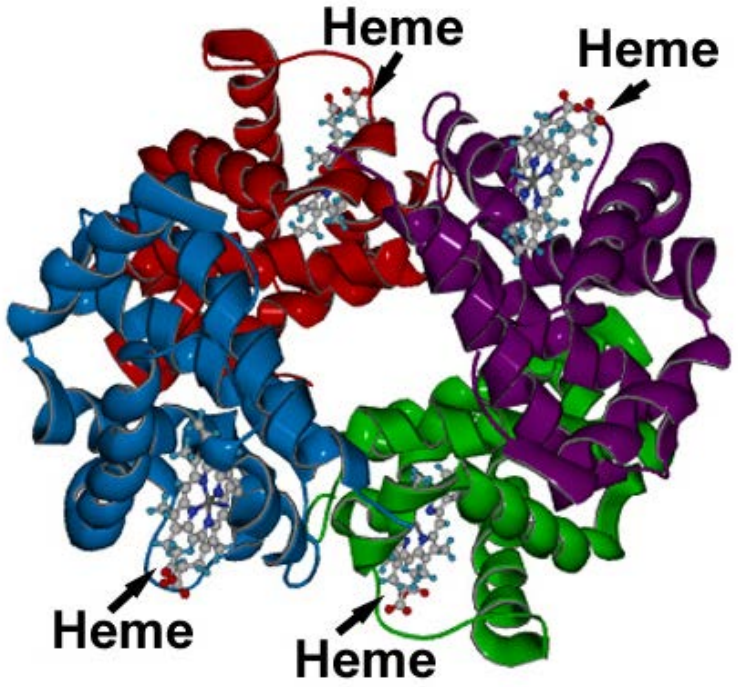
- Thalassemia patients are **racially diverse**: Asian (near and far-east), Mediterranean, Middle eastern, Black (rarely Northern European)
- **Unconscious bias**: Marginalized populations are often blamed for their own poor health outcomes believed to be due to behavioral choice or poor medication adherence
- **Treated like sickle cell** disease patients
  - Sickle cell disease is 50X more common than Thalassemia
  - Especially true for black and brown patients
- **Language** barriers
  - Refugees from other countries
- **Cultural** differences
  - Approach to disease influenced by cultural differences

Racial and Ethnic disparities

- Lack of ethnic diversity in **blood donation**:
  - Better antigen matched blood if patient and donor or from the same ethnic group
- **Access to BMT** as a curative option
  - Many patients are adopted (esp. China) so no access to potential matched siblings as donors
  - Most patients with thalassemia are members of ethnicities that are significantly under-represented in BM registries
- Access to **clinical trials**
  - Patients must be consented in their native language
  - Translating complex medical concepts can be difficult e.g. Phase 1 vs 2 vs 3, how the treatment process works in e.g. Gene editing

Hemoglobin Disorders

There are more mutations and more diseases described for Hemoglobin than any other gene family



- **Qualitative disorders**
  - Point mutations in globin genes
  - Hemoglobinopathies (eg, sickle cell disease, Hb CC, Hb EE)
- **Quantitative disorders**
  - Larger mutations or abnormalities in globin gene promoters that lead to decreased expression of or absent globin chains
  - **α-thalassemia or β-thalassemia, or more rarely, γ-thalassemia and δ-thalassemia**
  - There are > 200 mutations involving either the alpha of beta globin genes leading to thalassemia

Challenges in diagnosis using Newborn Screen

- In the U.S., there is currently **no standard** for newborn screening, and testing vary from state to state.
- The detection of **Hb Barts** (tetramers of γ-globin) on the newborn screen facilitates the early diagnosis of α-thalassemia trait or Hb H disease, but requires hemoglobin quantitation, not performed universally. **GA: present vs >25%**
- The most severe form of **β-thalassemia**, β0/β0-thalassemia, can be suspected by the absence of HbA on the newborn screen (F only). Less severe forms of β-thalassemia could also be detected using molecular typing, used by few states. (**NOT done in GA**). Beta thal trait relies on increased Hgb A2 which is in very small amounts in the fetus (< 0.5%) thus cannot be detected with standard methods.
- Individuals with **HbE β0** and **Hgb EE** both have no HbA (FE). Similarly, HbE β+ may be misdiagnosed as Hgb E trait (FAE)
- Caveats to testing
  - Some commercial labs only test for the more common thalassemia genotypes
  - γδβ thalassemia

Benson JM, Therrell BL. History and current status of newborn screening for hemoglobinopathies. Semin Perinatol. 2010;34(2):134-144.
Fogel BN, Nguyen HLT, Smink G, Sekhar DL. Variability in state-based recommendations for management of alpha thalassemia trait and silent carrier.

Alpha Thalassemia

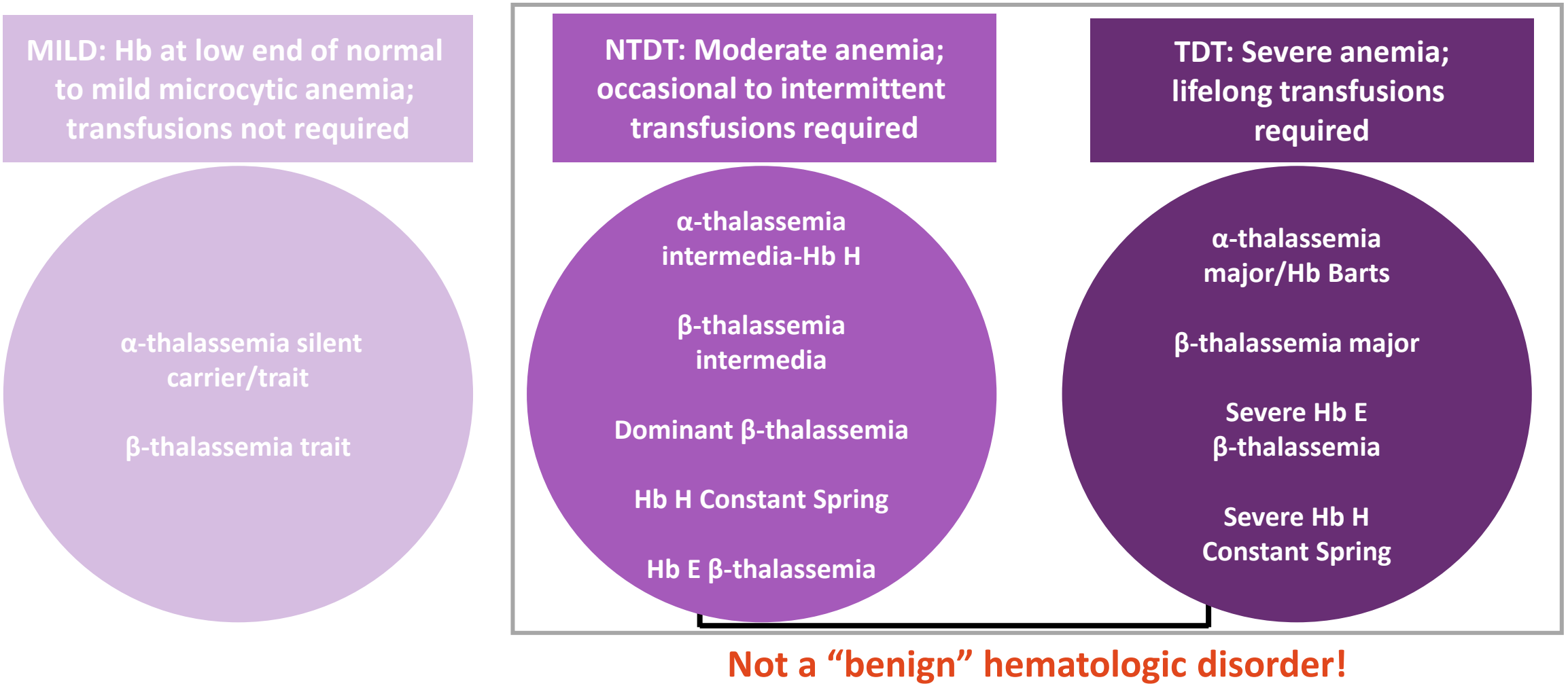
Classification	Genotype	Number of genes affected, severity
Silent Carrier	αα/α–	1 gene silent
Alpha thal trait	α–/α– αα/––	2 genes minor
Hgb H disease	α–/––	3 genes intermedia
Hgb Barts ds Hydrops Fetalis Alpha thal major	––/––	4 genes major

Hgb H = 4 β chains
Hgb Bart's = 4 γ chains

Beta Thalassemia

Classification	Genotype	Number of genes affected, severity
Beta thal trait	β/β+ β/β0	1 gene minor
Beta thal intermedia	β+/β+ β+/β0	2 genes intermedia
Beta thal major	β+/β0 β0/β0	2 genes major

Genotype–Phenotype Associations

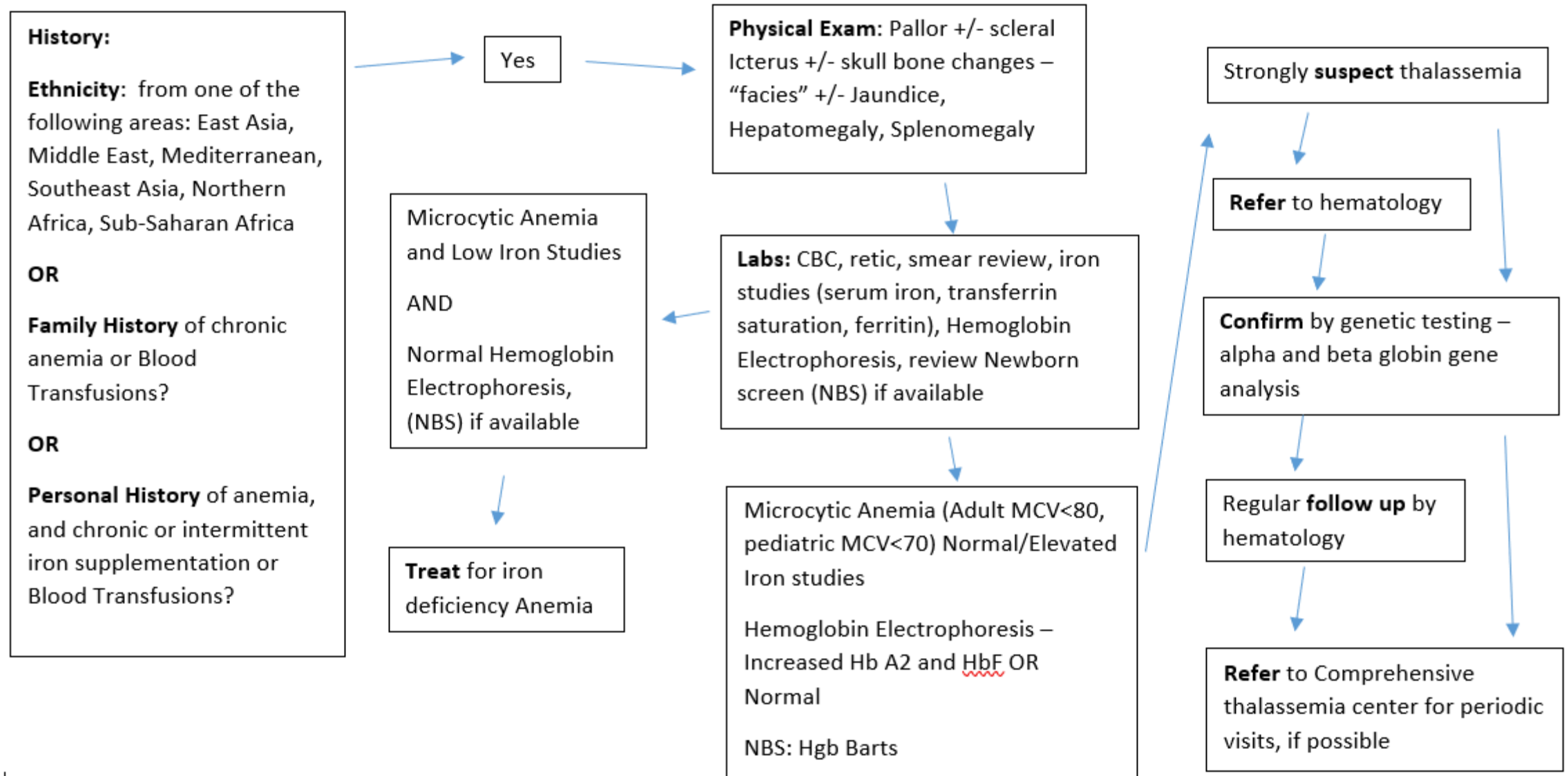


Not a "benign" hematologic disorder!

Proposed algorithm for primary care providers

- It has proved difficult to find and accurately identify thalassemia patients by searching various data bases due to multiple factors including incorrect ICD-9/10 diagnosis code assignments, rare need for hospitalization
- ***We must depend on the primary care provider to have an index of suspicion, do the appropriate work-up and refer to the Hematologist***
- Multiple thalassemia centers via the Redhott study have developed an algorithm to try to identify thalassemia patients

Screening/Diagnosis for Thalassemia



Alpha Thalassemia Hemoglobin patterns

Deletion	Genotype	Disease	Clinical	MCV	Electro.	% Bart's
0	αα/αα	None	Normal	Normal	Normal	0-2%
1	- α/αα	Silent Carrier	Normal	Normal	Normal	1-4%
2	- α/- α Blacks	α^+ Thal Trait	Mild Anemia	Low	Normal	3-8%
	- -/αα Asians	α° Thal Trait	Mild Anemia	Low	Normal	5-10%
3	- -/- α	Hb H	Mod Anemia	Low	Bart's Hb H	20-40%
4	- -/ - -		Death in utero	Low	Bart's	>80%

Hgb Bart's (γ) disappears shortly after birth. It is replaced by Hgb H in Hgb H ds

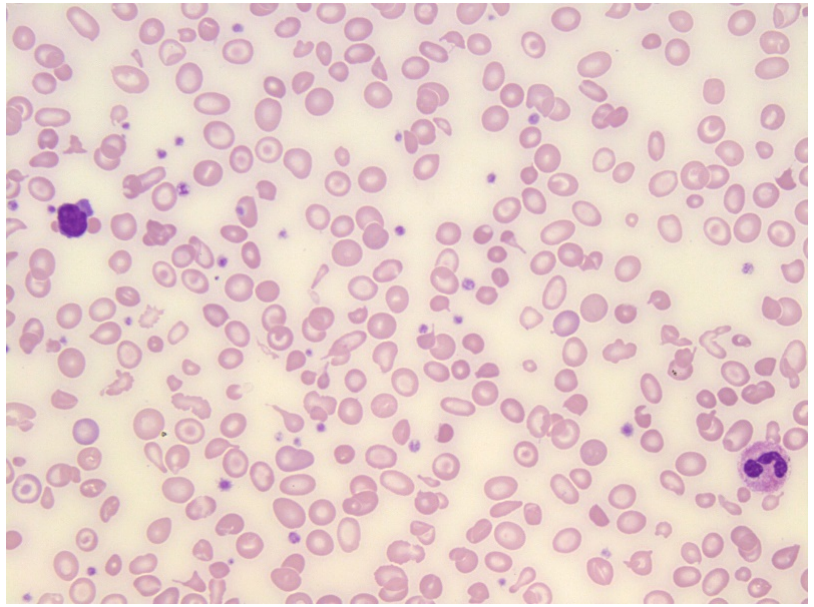
Beta Thalassemia Hemoglobin patterns

Hemoglobin	Normal	β^0/β^0	Non-β^0/β^0	Trait
Hb A %	96-98	0	10-30	92-95
Hb F %	<1	95-98	70-90	0.5-4
Hb A_2 %	2-3	2-5	2-5	>3.5

NTDT vs TDT

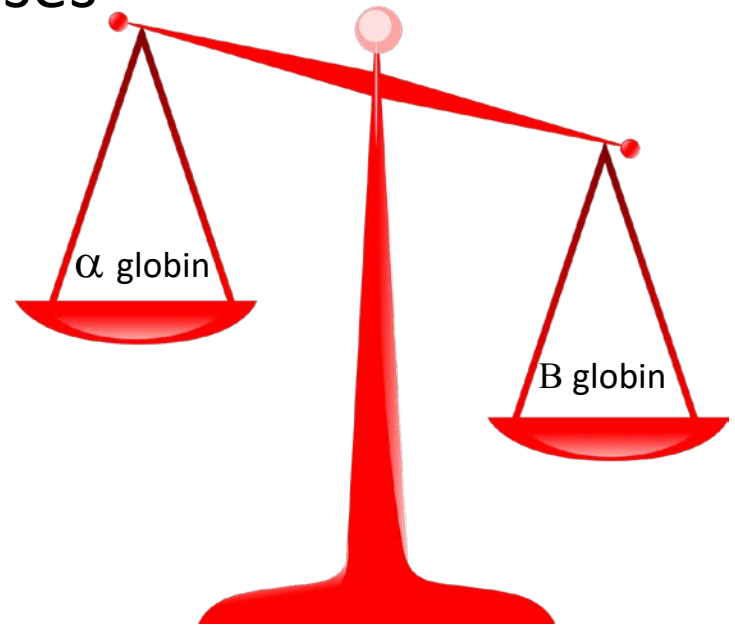
- NTDT= Non Transfusion Dependent Thalassemia
- TDT= Transfusion Dependent Thalassemia
- Phenotypic definition
- Influenced by the genes inherited ***but determined*** either by the depth of anemia and/or by co-morbidities e.g. poor growth, bony changes, extramedullary hematopoiesis, etc.
- NTDT -> TDT

Anemia in Thalassemia



The degree of anemia is influenced by:

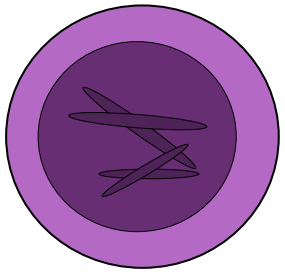
- The **types** of genes: e.g. Beta 0 vs Beta +
- **Co-inheritance** of modifying genetic polymorphisms e.g. Xmn1, BCL-11A
- Resultant **imbalance** between alpha & β chains causes
  - Ineffective erythropoiesis: impaired ability of the body to make blood efficiently
  - Excessive hemolysis: increased breakdown of manufactured red cells
  - Dysregulation of iron control

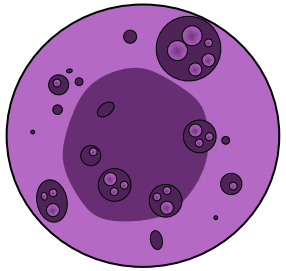


Features of Ineffective Erythropoiesis

Bone Marrow

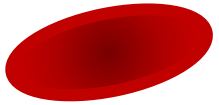
β-Thalassemia Erythroblast:
Mutations/deletions in β-globin gene on chromosome 11





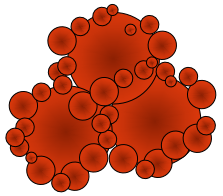
Reduced β-globin subunit production; accumulation and aggregation of unpaired α-globin chains form toxic hemichromes

Extramedullary:
RBC survival shortened



RBC → hemolysis

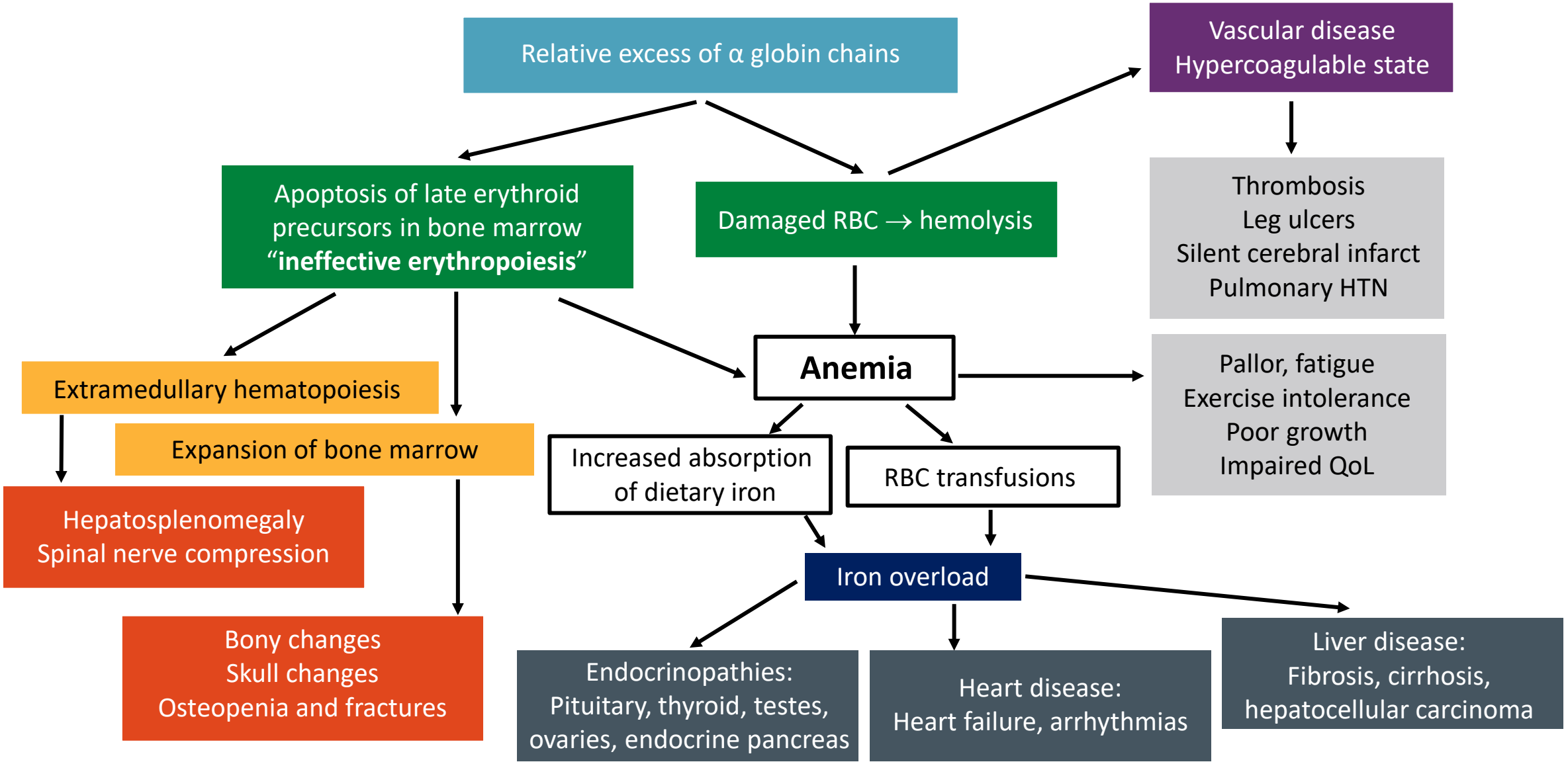
Intramedullary:
Premature erythroid precursor death



Anemia → increased erythropoietic drive

Apoptosis → ineffective erythropoiesis
→ extramedullary hematopoiesis
→ dysregulation of iron metabolism

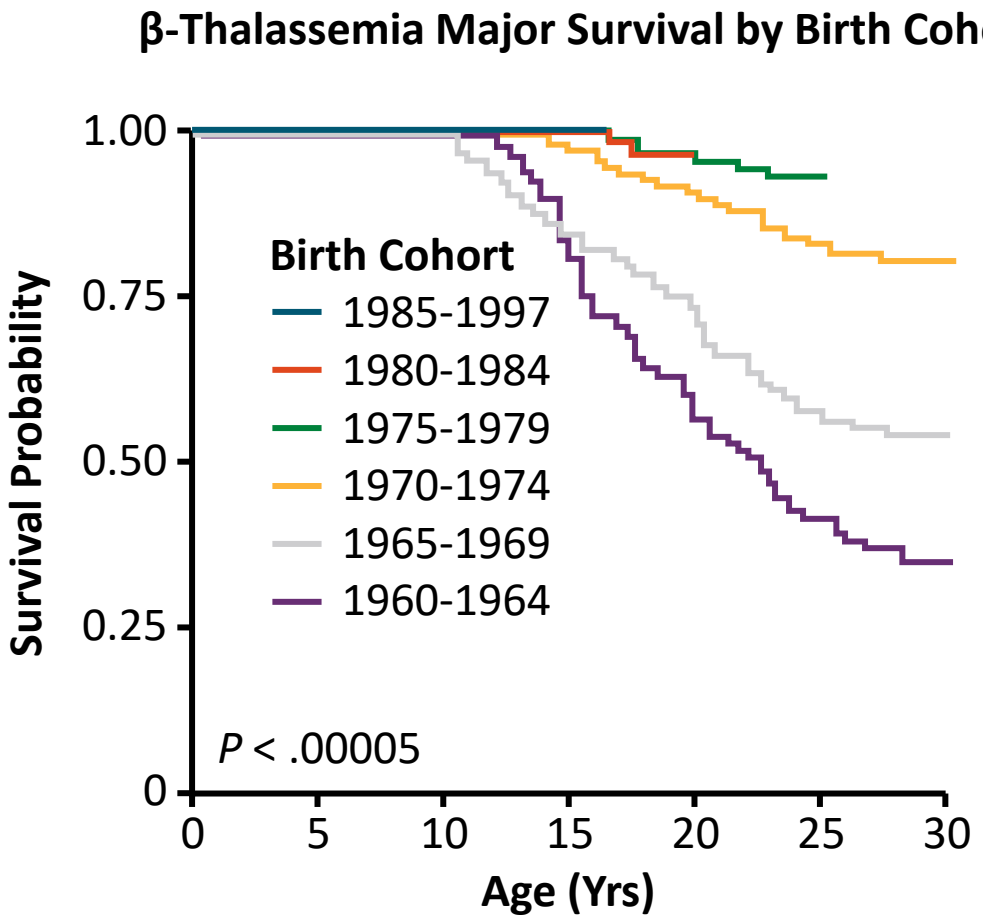
Pathophysiology and Clinical Features



Therapy Advances for Thalassemia

- Improved safety of blood supply
- Reduced incidence of alloimmunization
- Oral iron chelation, combination chelator regimens
- Improved monitoring of iron overload to enable individualized tailoring of treatment regimen
- Improved treatment for hepatitis
- Improved outcomes for stem cell transplantation

Survival



- Without treatment
  - β^0/β^0: die in first 2-5 yrs
  - Non-β^0/β^0: variable clinical spectrum with complications
- β^0/β^0 and non-β^0/β^0 with treatment
  - Improving survival
  - Significant morbidity but with decreasing incidence
  - Deaths related to complications

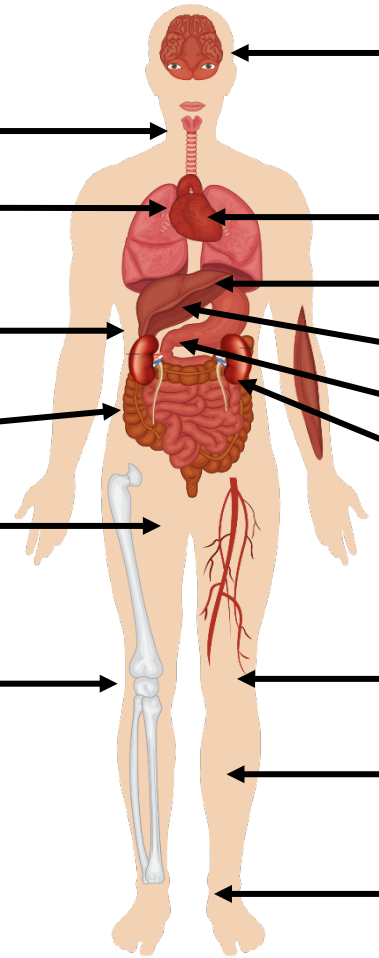
*Kaplan-Meier analysis included 977 patients who survived beyond first decade of life.

Borgna-Pignatti. Haematologica. 2004;89:1187. Galanello. Orphanet J Rare Dis. 2010;5:11.

Complications

Transfusion Dependent

- Hypothyroidism
- Hypoparathyroidism
- Cardiac siderosis
- Left-sided heart failure
- Hepatic failure
- Viral hepatitis
- Diabetes mellitus
- Hypogonadism
- Osteoporosis
- Transfusion reactions
- Alloimmunization



Nontransfusion Dependent

- Silent cerebral ischemia
- PHT
- Right-sided heart failure
- Extramedullary hematopoietic pseudotumors
- Hepatic fibrosis, cirrhosis, and cancer
- Gallstones
- Splenomegaly
- Osteoporosis
- Venous thrombosis
- Leg ulcers

Musallam. Acta Haematol. 2013;130:64. Musallam. Haematologica. 2013;98:833.

Conventional Management of NTDT

- **Supportive care**: bone health, vitamin D, and folic acid supplementation
- **Transfusions** (periodic): growth issues, fatigue, QoL, leg ulcers, splenomegaly, EMH tumors, pulmonary HTN, pregnancy, surgery, worsened anemia
- Monitor for **iron overload**: ferritin (> 500 ng/mL), MRI
- Iron **chelation** therapy
- **Splenectomy**: consider ONLY in select cases (severe anemia and massive splenomegaly); if done, need thromboprophylaxis
- **Induction of HbF**: hydroxyurea, 5'azacytidine, decitabine, butyrate

* *The management of NTDT is more complex than TDT* – J Boudreaux

Conventional Management of TDT

- Regular blood **transfusions**: every 2-4 wks with extended RBC-matched blood
- **Splenectomy** in certain circumstances
- Monitor for **iron overload**: MRI (annually)
- Iron **chelation** therapy
- **Monitor for AEs** of chelation (monthly)
- Monitor for **complications** of disease and treatments (at least annually)
- Hematopoietic stem cell **transplantation**

MRI: Abdomen **MRI: Heart**

Images courtesy of Sujit Sheth, MD. Weill Cornell Medicine.

Criteria for initiating chronic transfusion

- Confirmed diagnosis of Thalassemia. For severe genotypes, transfusion usually begins age < 1-2 yr
- **Lab criteria**: Hgb < 7 g/dL (beta thal, Hgb H CS), < 6-7 g/dL (E beta thal) on 2 occasions at least 2 wks apart, not attributed to other causes (e.g. infection) **AND/OR**
- **Clinical criteria**:
  - Symptomatic anemia
  - FTT/ decelerating growth
  - Excessive intramedullary hematopoiesis (bossing, facial changes, fractures)
  - Excessive extramedullary hematopoiesis (massive splenomegaly, EMH tumors)
- TDT $\geq$ 8 transfusions/yr

Capellini et al for TIF 2021 Guidelines for the management of TDT

Transfusion frequency and targets

- **Frequency** is typically every 2-4 wks to keep pre-transfusion Hgb 9.5-10.5 g/dL (different from sickle cell)
  - **Suppresses ineffective erythropoiesis (IEE) to 1-2X normal and extramedullary hematopoiesis (EMH)**
  - Promotes normal growth, allows for normal physical activity and adequately suppresses bone marrow activity while minimizing iron accumulation
  - Higher targets (11-12 g/dL) may be indicated in Alpha Thal major, clinically significant heart disease, EMH tumors, in pregnancy and before BMT/Gene therapy.
  - Increased frequency (shorter intervals) may reduce overall blood requirements but must be balanced with patient's work/school schedule

Guidelines for Managing Transfusion Therapy for TDT

Pretransfusion Hb Level	Action	Rationale
< 8.5 g/dL*	▪ Increase transfusion volume by 15% to 20% for children and by 1 unit for adults, not exceeding 20 mL/kg per transfusion ▪ If patient/family schedule permits, consider scheduling next transfusion 1 wk early ▪ Increase frequency of transfusions if Hb level consistently in this range	Hb level is well below target
8.5-9.4 g/dL	▪ Increase transfusion volume by 15% to 20% for children and consider increasing by 1 unit for adults, not exceeding 20 mL/kg per transfusion ▪ Consider increasing frequency of transfusions if Hb level consistently in this range	Hb level is below target
9.5-10.5 g/dL†	▪ Maintain current transfusion volume and frequency ▪ Typical transfusion volumes: for children, ~ 15 mL/kg (range: 10-20 mL/kg); for older children and adults, ~ 2-4 units	Hb level is in target range
> 10.5 g/dL	▪ Reduce transfusion volume by 15% to 20% ▪ Consider increasing interval between transfusions if Hb level consistently in this range	Reduce volume vs postpone transfusion to minimize disruption to patient/family schedules

*If Hb level unexpectedly low, investigate for causes (eg, recent illness, new red cell antibody, splenomegaly).

†This is generally considered the ideal pretransfusion Hb target range, but some patients may require higher Hb levels due to clinical complications (eg, heart failure).

Thalassemia Management Checklists. Thalassemia.org.

Transfusion volumes

- Clear recommendations are difficult to multiple variables including:
  - Variability in the minimal acceptable donor Hct, volume collected, type of anticoagulant storage solution used and whole blood vs PRBC's

		HAEMATOCRIT OF DONOR RED CELLS			
		50%	60%	75%	80%
Target increase in haemoglobin level	20 g/l	12 ml/kg	10 ml/kg	8 ml/kg	7.5 ml/kg
	30 g/l	18 ml/kg	15 ml/kg	12 ml/kg	11.2 ml/kg
	40 g/l	24 ml/kg	20 ml/kg	16 ml/kg	15 ml/kg

Capellini et al for TIF 2021 Guidelines for the management of TDT

Transfusion Rate & Volumes

- **Rate**: Dependent on local center policies
  - Some centers will transfuse each unit in 60-90 minutes
  - Others will cap the rate at 3-5 ml/kg/hour
- Rates should be slower in patients with cardiac failure or with significantly lower pre-transfusion Hgb
- **Volume**: To limit donor exposure, use whole units, based on the size of the patient and the patient's pre-transfusion Hgb. Maximum volume 20 ml/kg
  - Smaller, young patients may need transfusion using ml/kg
  - Other factors include degree of hypersplenism or unexpected/unexplained response to the previous transfusion

The correct Volume and Frequency for an individual patient is one that consistently achieves the desired target Hgb while minimizing transfusional iron accumulation and promoting normal growth and well-being

Spleen

- Transfusion requirements are higher in unsplenectomized patients (30%) and iron accumulation is higher (avg 39%)
  - **NOT a justification** for routine splenectomy due to the potential downsides including increased risk of infections, thrombosis and pulmonary hypertension
  - Hypertransfusion can decrease enlargement
  - Annual transfusion volumes significantly >200 ml/kg/year: *May* consider splenectomy

Cohen et al Blood 2008; 111 (2), 583-87; Graziano et al J Ped 1981; 99 (5) 695-99.

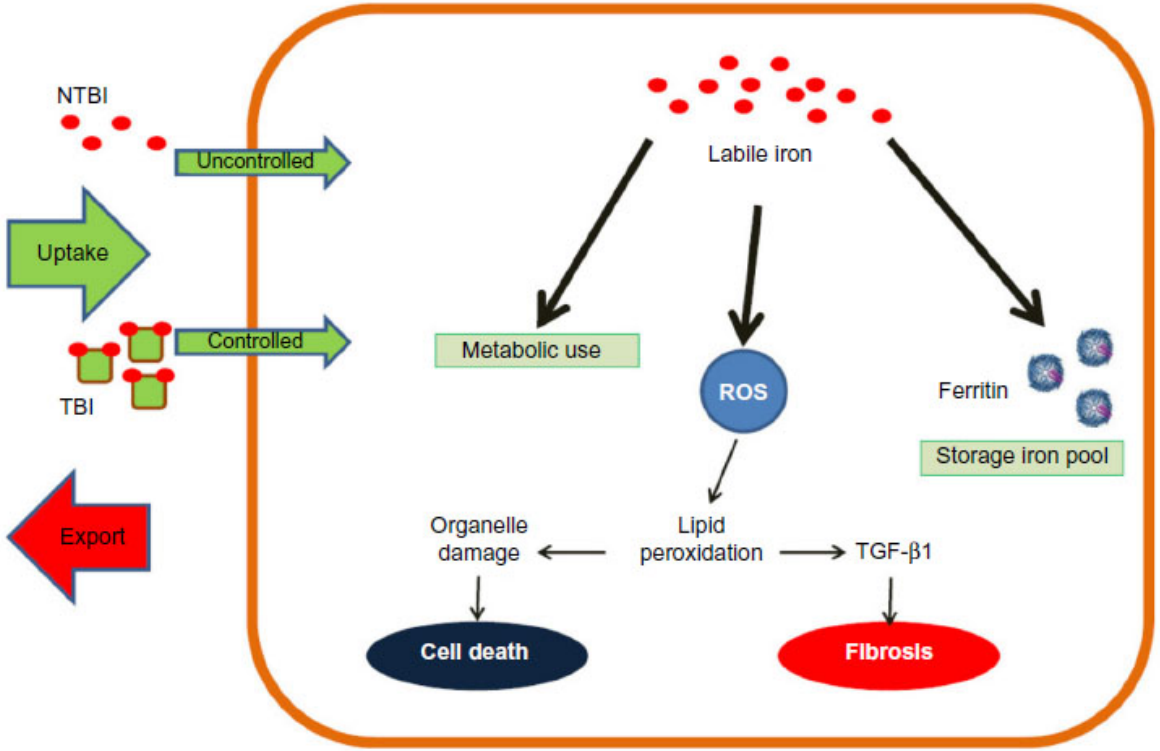
Compatibility testing

- **Alloimmunization** varies widely among centers due to the degree of homogeneity of the donor and recipient population.
- Anti-E, anti-c and anti-Kell are the most common (90%), therefore all patients should have extended RBC Ag typing for **at least ABO, CcDEe and Kell.** Full pheno/genotype panel preferred.
  - If already transfused, testing must be by molecular, not by serologic methods
- Development of either warm or cold antibodies of unidentified specificity
- Historical records of Ag testing, Ab formation and any reactions should be kept and shared with other centers if the patient is transfused at a different location

Safe collection, Testing and Storage

- Collected from carefully selected voluntary, unpaid donors, processed, stored and distributed from dedicated centers with well established quality assurance programs
- Pre-storage **Leukodepletion** to < 1 x 10^6/L per unit is the critical threshold for eliminating the adverse reactions caused by contaminating WBC's
- **Washing** removes plasma proteins. Indicated only in:
    - IgA deficiency (patient has preformed IgA antibody)
    - Patients with repeated severe urticarial, allergic reactions despite premedication
- **Irradiation** indicated only in patients with T-cell dysfunction (e.g. Hodgkin Lymphoma, BMT)

Why is Iron Overload 'bad'



- Iron as a part of RBC's is not harmful
- The small amount of iron that is freed up in the normal death of RBC's is usually bound up by proteins and recycled
- But there is a limit to the amount of this free iron that our bodies can bind up by proteins in macrophages to keep from being toxic
- "Free iron" is toxic to our tissues (e.g.**NTBI**)
- Our body resorts to storing it in places where it is toxic (liver cells, heart cells, pancreas, etc.)

What causes Iron Overload

- Normally our body only absorbs what it needs through signals to our intestines (1-2 mg/day)
- Transfusion dependent patients take in 1 mg Fe for every ml blood transfused (15-30 mg/day)
- *Thalassemia patients have abnormal gut signaling and inappropriately absorb iron (5 mg/day)*

Monitoring Iron Overload in TDT

Level of Iron Overload	Iron Overload Measurements	Frequency of MRI Testing
Target	▪ LIC 2-5 mg/g dw ▪ T2* > 20 msecs ▪ Ferritin < 1000 ng/mL	▪ Check LIC when chelation is first initiated and every yr thereafter ▪ Check cardiac T2* at age 10, then every 2 yrs thereafter
Moderately elevated	▪ LIC 5-10 mg/g dw ▪ T2* > 20 msecs ▪ Ferritin 1000 to 2500 ng/mL	▪ Check LIC when chelation is first initiated and every yr thereafter ▪ Check cardiac T2* at age 10, then every 1-2 yrs thereafter based on LIC trends
Seriously elevated	▪ LIC > 10 mg/g dw ▪ T2* < 20 msecs ▪ Ferritin > 2,500 ng/mL	▪ Check LIC when chelation is first initiated and every 6 mos thereafter if on intensive chelation ▪ Check cardiac T2* at age 10 and every yr thereafter based on LIC trends
Mild cardiac iron overload with normal cardiac function	▪ T2* 10-20 msecs	▪ Check LIC and cardiac T2* when chelation is first initiated and every 6-12 mos thereafter while on intensive chelation ▪ Monitor cardiac function (MRI/ECHO) every 6 mos
Severe cardiac iron overload with or without cardiac dysfunction	▪ T2* < 10 msecs	▪ Check LIC and cardiac T2* when chelation is first initiated and every 6 mos thereafter on intensive chelation ▪ Monitor cardiac function (MRI/ECHO) every 6 mos with cardiac specialist

Thalassemia Management Checklists. Thalassemia.org.

Ferritin: Friend or Foe?

- One of the proteins that stores iron
- **Pros:**
  - Cheap, readily available blood test
  - In most patients, can be used to “trend” iron overload
- **Cons:**
  - Cannot be used to “measure” iron overload
  - Significantly underestimates the degree of iron overload in NTDT
  - In some patients, has little correlation with iron overload
  - Is an acute phase reactant

Chelation

When to start:

- ≥ 2 yo
- > 10-20 transfusions
- ? Ferritin > 1000
- Liver Iron > 5 mg/g dry weight

Goal: Keep a “safe level” of Fe

- Prevent iron build up
- Remove the built up iron in order to reverse organ injury
- Bind up “free iron” (NTBI) to make it less toxic to tissues

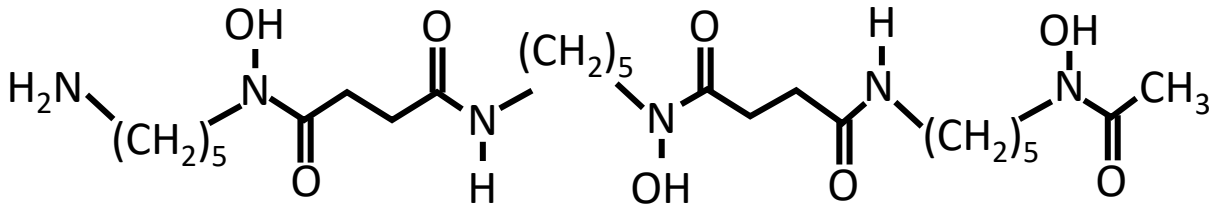
Chelation adjustment

- When iron levels are **too high:**
  - Address adherence
  - Increase dose if possible
  - Add a second chelator
  - Special challenge: when liver iron decreases to goal but cardiac is still too high
- When iron levels are **too low:**
  - Contrary to drug labeling and insurance policies, do not interrupt chelation
  - “free Iron” (NTBI)
  - Get out of the habit
  - Solution: reduce the dose

FDA-Approved Agents for Iron Chelation

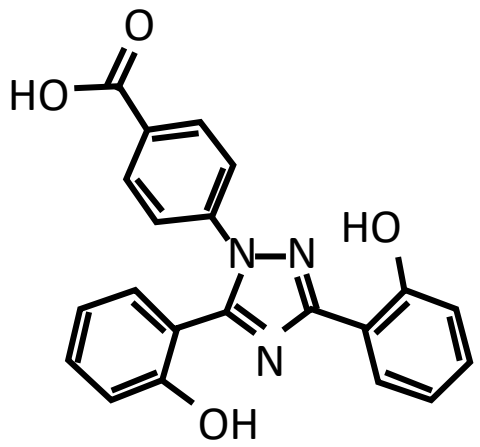
Deferoxamine

- FDA approved: 1968
- Delivery: SQ, IM, IV



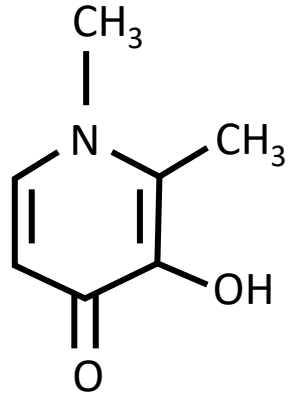
Deferasirox

- FDA approved: 2005, 2015, 2017
- Delivery: oral



Deferiprone

- FDA approved: 2011, 2015, 2020
- Delivery: oral



No new chelators currently in the pipeline

Deferoxamine (DFO)

- Advantages
  - Very good at chelating from the liver, good at chelating from the heart
  - ***Does not depend on oral absorption***
- Disadvantages
  - ***Short half-life***: ***slow SQ infusion*** 8-10 hrs, 5-7 nights/wk; Infusion-site reactions; pain; high frequency hearing loss; color and night vision changes; growth plate issues in children 2-3 yrs of age
  - ***High degree of noncompliance***

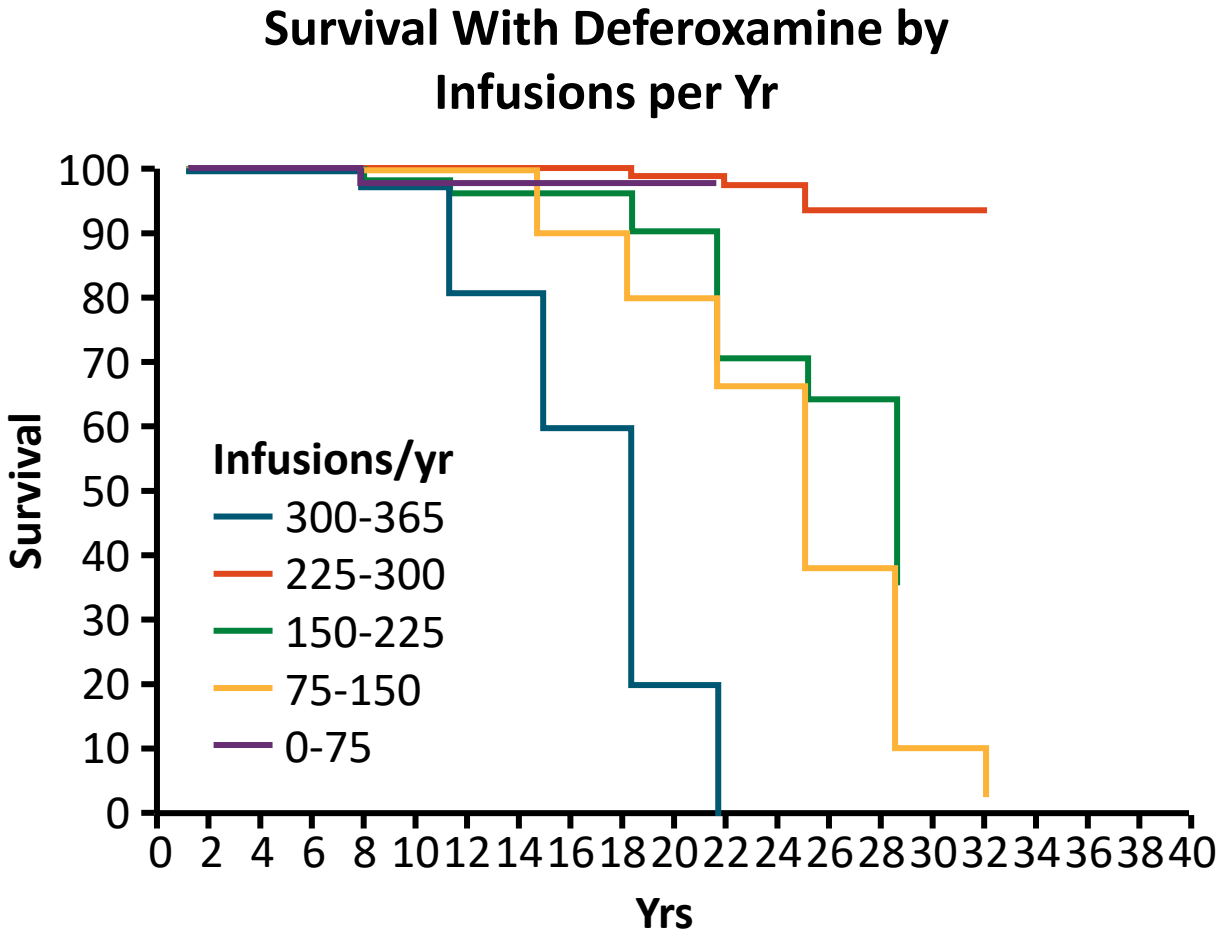


Figure modified from Wood. Blood. 2008;112:2973.

Deferasirox (DFX)

- Advantages
  - ***Oral, once daily,*** dispersible tab, coated tab, sprinkles
  - Wide therapeutic index, dose range
  - Demonstrated equivalent efficacy vs deferoxamine in cardiac iron removal

- Disadvantages
  - Dependent on oral absorption
  - Nausea, vomiting, abdominal pain
  - Liver toxicity: often transient
  - Rash: transient
  - ***Renal toxicity:*** Fanconi syndrome (more likely at high doses in low iron overload setting)

Deferiprone (DFP)

- Advantages
  - Oral
  - ***More effective in removing cardiac iron***

- Disadvantages
  - ***TID*** for pill and oral solution; new ***BID*** pill
  - Less effective at reducing LIC
  - Nausea, vomiting, abdominal pain
  - Liver toxicity
  - Arthralgia
  - Neutropenia/***agranulocytosis***
    - CBCD recommended every 7-10 days for 6 months, every 2 weeks for 6 months, then just with transfusions

Combination Chelator Regimens

- Advantages
  - Additive and synergistic: **DFX + DFP** > DFO + DFP > DFO + DFX[1]
  - Lower doses of each drug can decrease AEs
  - Capitalize on the advantages of each drug
  - Achieve negative iron balance in patients with highest transfusion needs
  - Make faster strides in decreasing iron in cases of severe iron overload
- Disadvantages
  - Adds complexity for the patient
  - Insurance companies often require LOMN, justification

1. Koumoutsea. Br J Haematol. 2015;170:874.

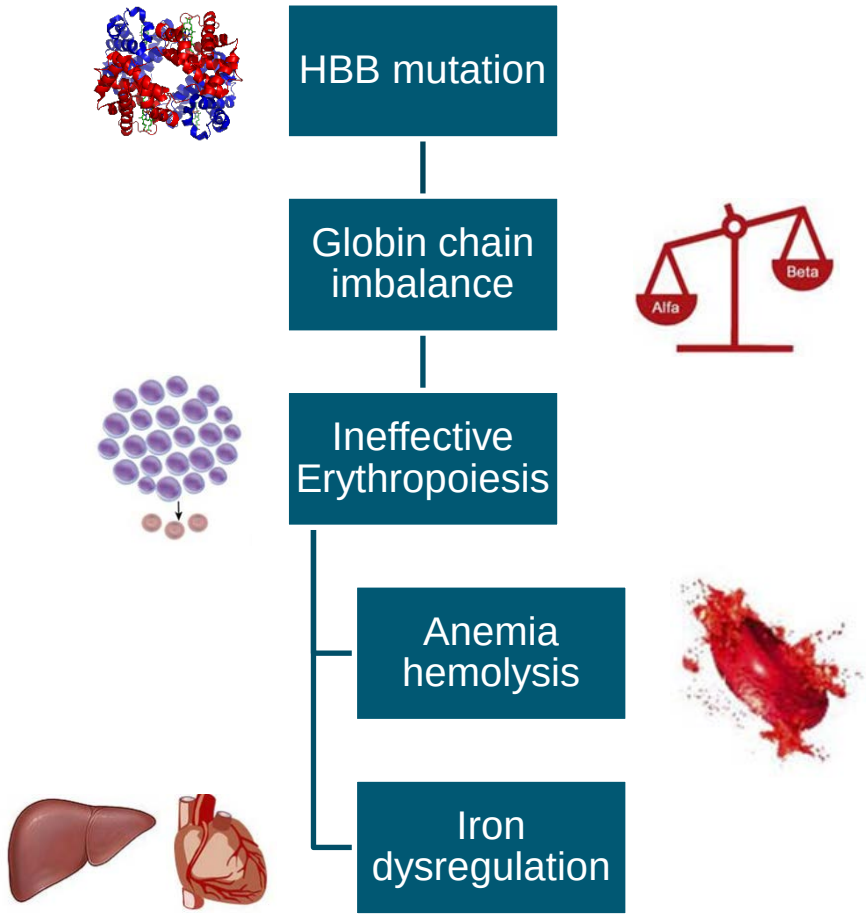
Patient Adherence

- ***Lifelong compliance*** with these medications is hard
  - Compliance is REALLY HARD if there are significant AEs
- Addressing the etiology of nonadherence is “the art of medicine”
- Discuss **barriers** to taking, suggest tools that are “age appropriate”
- Address GI AEs:
  - Take with food, increase liquids, drink slowly or split doses, suspend deferasirox in warm water, take at a different time of day, etc
  - Add antiemetics, acid suppressants; treat *H pylori*

Special population: Alpha Thal Major

- Hydrops fetalis is universally fatal due to the in utero hypoxia
- **If suspected** based on ethnicity and **detected early in pregnancy**, serial in utero transfusions can be instituted. ***All couples of Chinese and SE Asian decent should be screened.***
- In utero "BMT" using mom's stem cells is currently in trials
- At birth, transfusions are continued using mom as the first donor with a higher pre-transfusion hgb target (d/t Hgb H which cannot carry O2)
- Transfusions are continued until BMT (age 2y with a matched sib)
- Chelation is started earlier (age 1y) d/t the transfusion burden
- The early in utero hypoxia can cause GU anomalies (males)

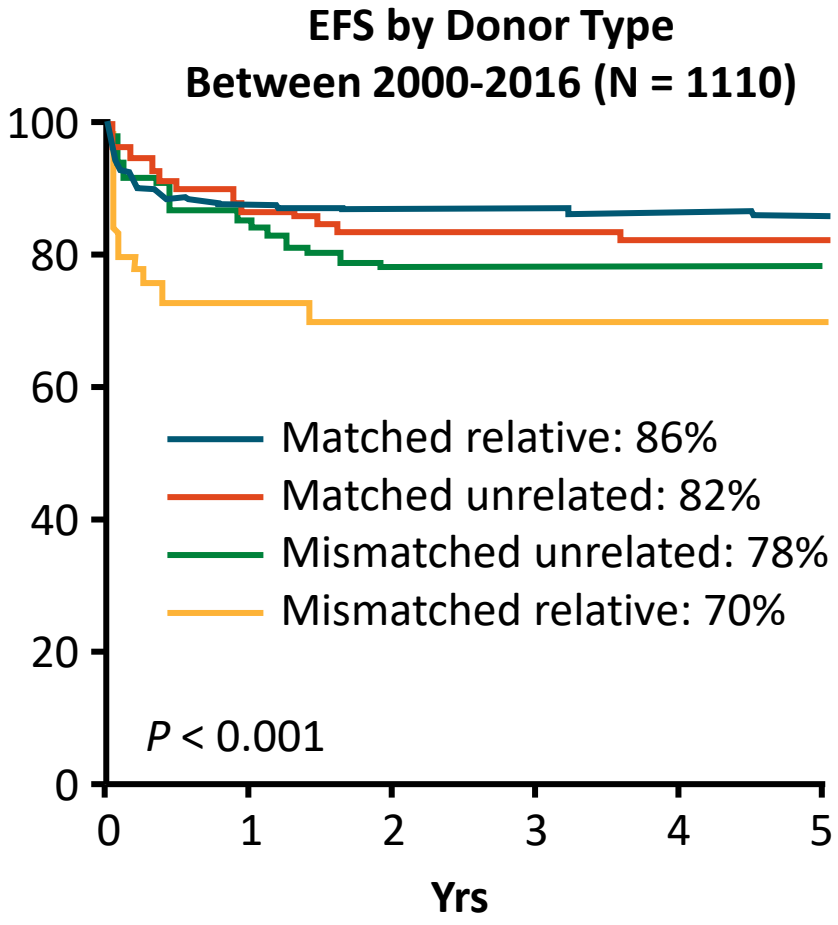
Treatments based on Pathophysiology



Current	In trials
BMT	BMT Gene therapy
Hgb F Inducer	Hgb F Inducer
Erythrocyte maturation	Erythrocyte maturation Hepcidin mimetic TMPRSS6 inhibitor
Transfusions	Modified Blood
Chelators	Modified chelators

Stem Cell Transplantation in Thalassemia

- Currently only available curative option **in the US**
- Pretransplant organ function and iron status important; younger patients do better
- Excellent outcomes with matched sibling donors (including umbilical cord blood): 85% to 95% TFS
  - Matched unrelated donors: 68% to 80% TFS
- Nonmyeloablative regimens in clinical trials
- Alternative donor sources in clinical trials: Unrelated PBSC, UCB; Haploidentical donors
- In utero transplant in alpha thalassemia major in trials



Li. Blood Adv. 2019;3:2562. Baronciani. ASH 2018. Abstr 168. Mohamed. Hematol Oncol Stem Cell Ther. 2017;10:290.

Gene Therapy

2 types of Gene Therapy

- Gene addition
- Gene editing

3 techniques to achieve

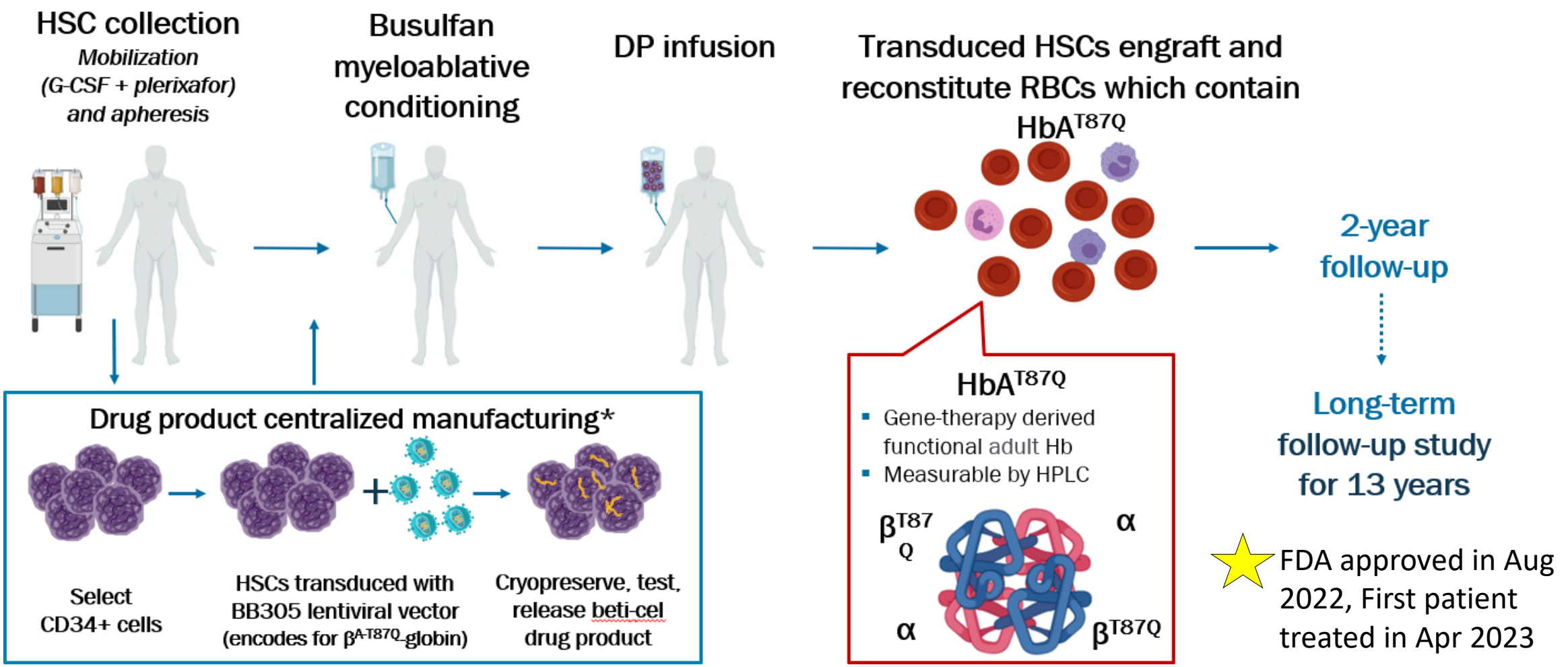
- Gene insertion: add functioning genetic material to do the work of a faulty gene
- Gene disruption: inactivates a gene that is contributing to disease
- Gene correction: replaces a faulty disease-causing gene with a functioning copy of the gene

Hematopoietic Stem Cell Transplantation (HSCT) vs Gene Therapy

Parameter	HSCT	Gene Therapy	Gene Editing
Chemotherapy	✓	✓	✓
Immunosuppression	✓	None	None
Graft-vs-host disease	✓	None	None
Medication burden	Higher	Lower	Lower
Donor availability	Allogeneic	Autologous	Autologous
Insertional mutation	None	Possible	None
Off-target editing	None	None	Possible
Phenotype Correction	Complete*	Partial/Sufficient	Partial/Sufficient
Long term data	Available	Limited	Limited

* Assumes full chimerism

Gene therapy: Beti-cel



★ FDA approved in Aug 2022, First patient treated in Apr 2023

Gene therapy: Beti-cel results

Durable transfusion independence (TI) (hgb >9) across ages and genotypes with up to 7 yrs follow-up.

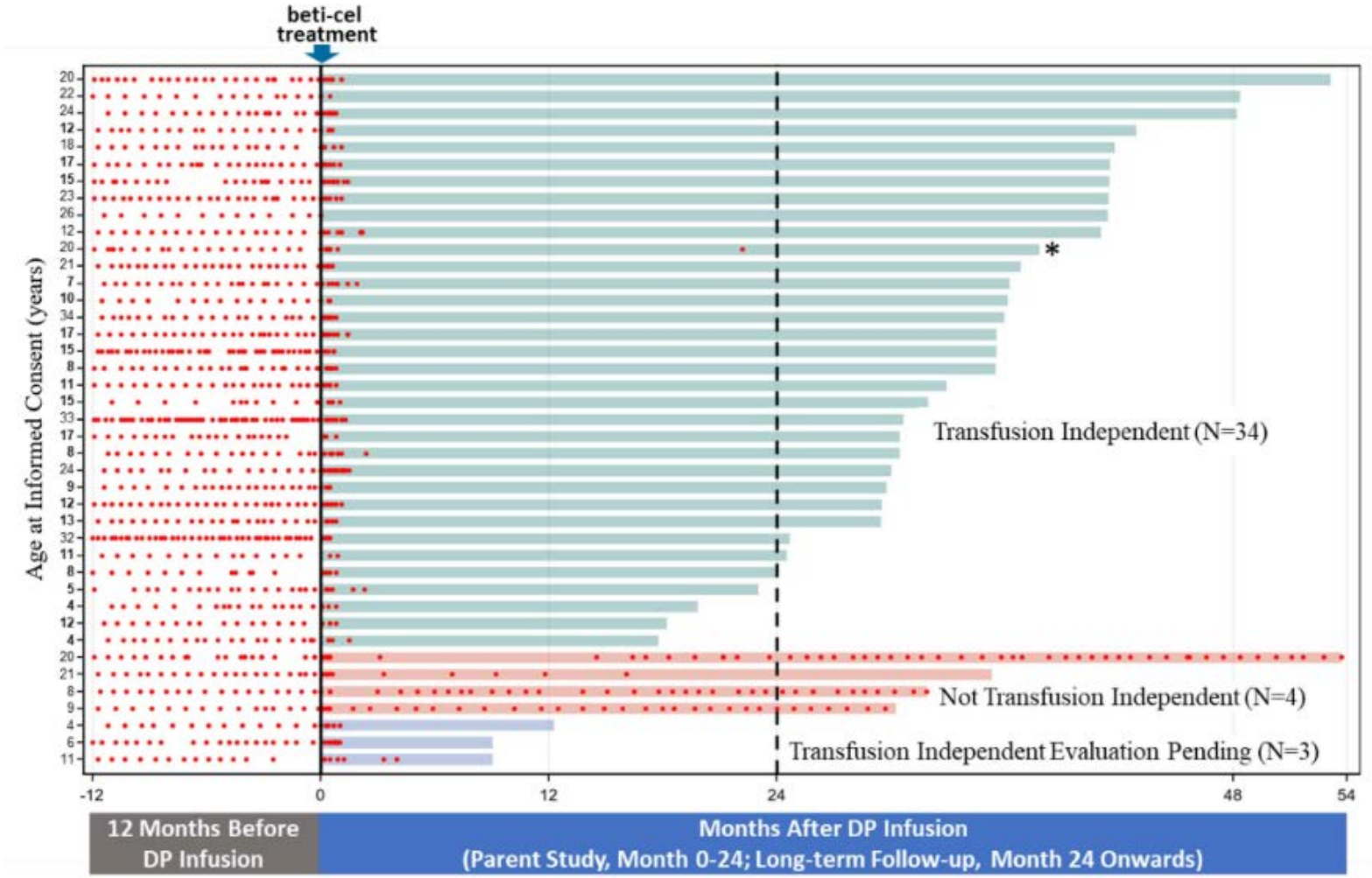
TI was observed in phase 3 trial (**34/38; 89.5%)**

No malignancies, insertional oncogenesis, vector-derived replication competent lentivirus, or clonal predominance was observed.

Safety: due to the known side effects of stem cell collection and the Busulfan conditioning regimen.

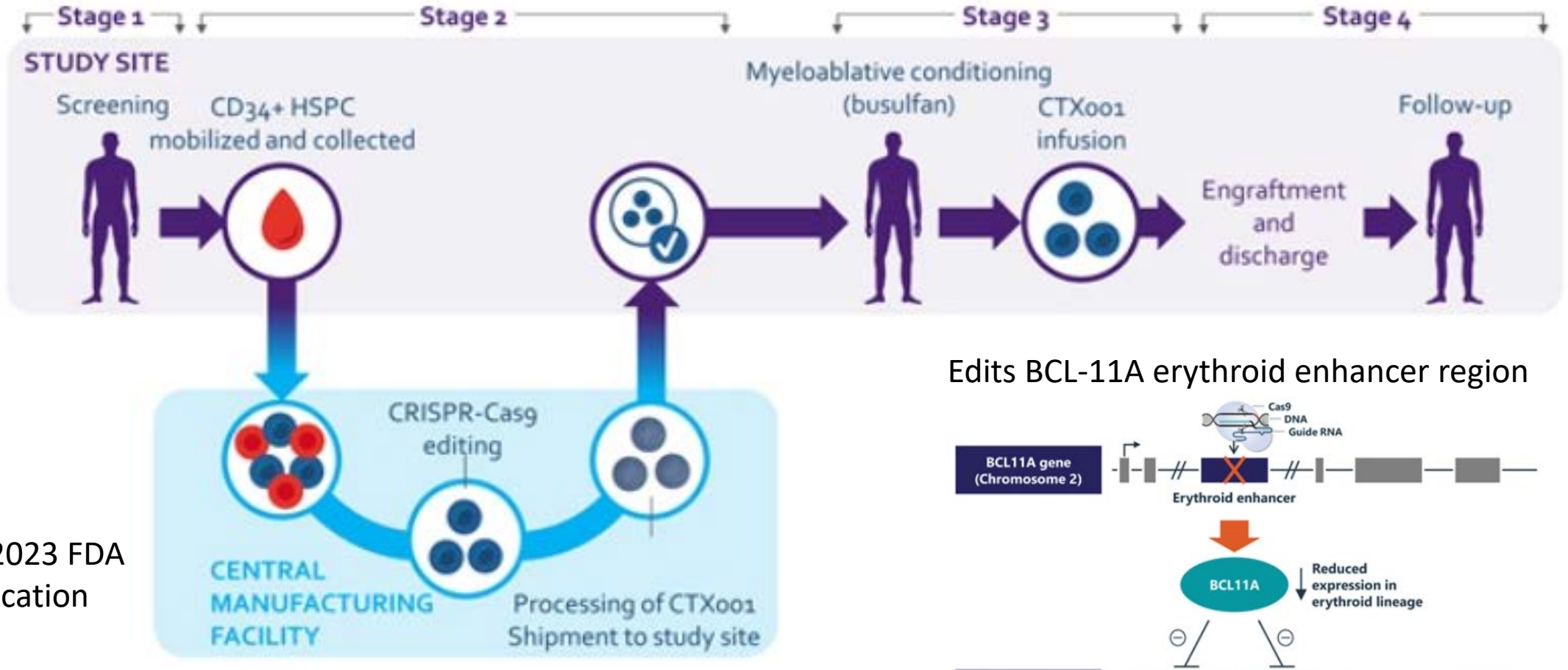
Transduction rate was the best predictor of success

Figure 1A. Transfusion Status in Phase 3 Patients

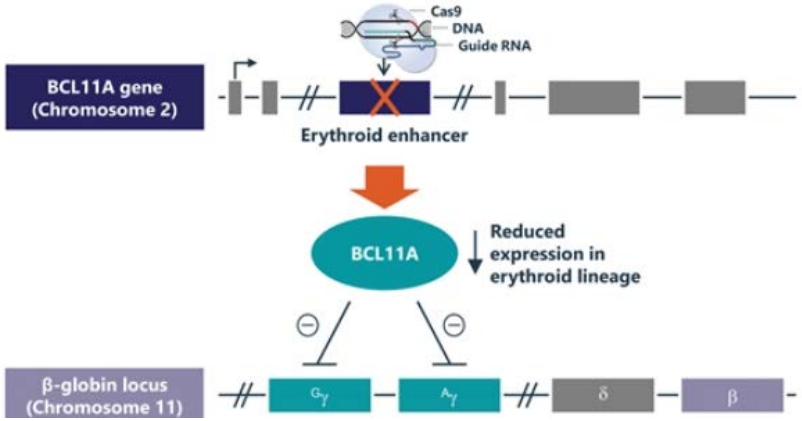


Walters, et al, American Society of Hematology, Dec 2022

Gene editing: CTX-001



Edits BCL-11A erythroid enhancer region

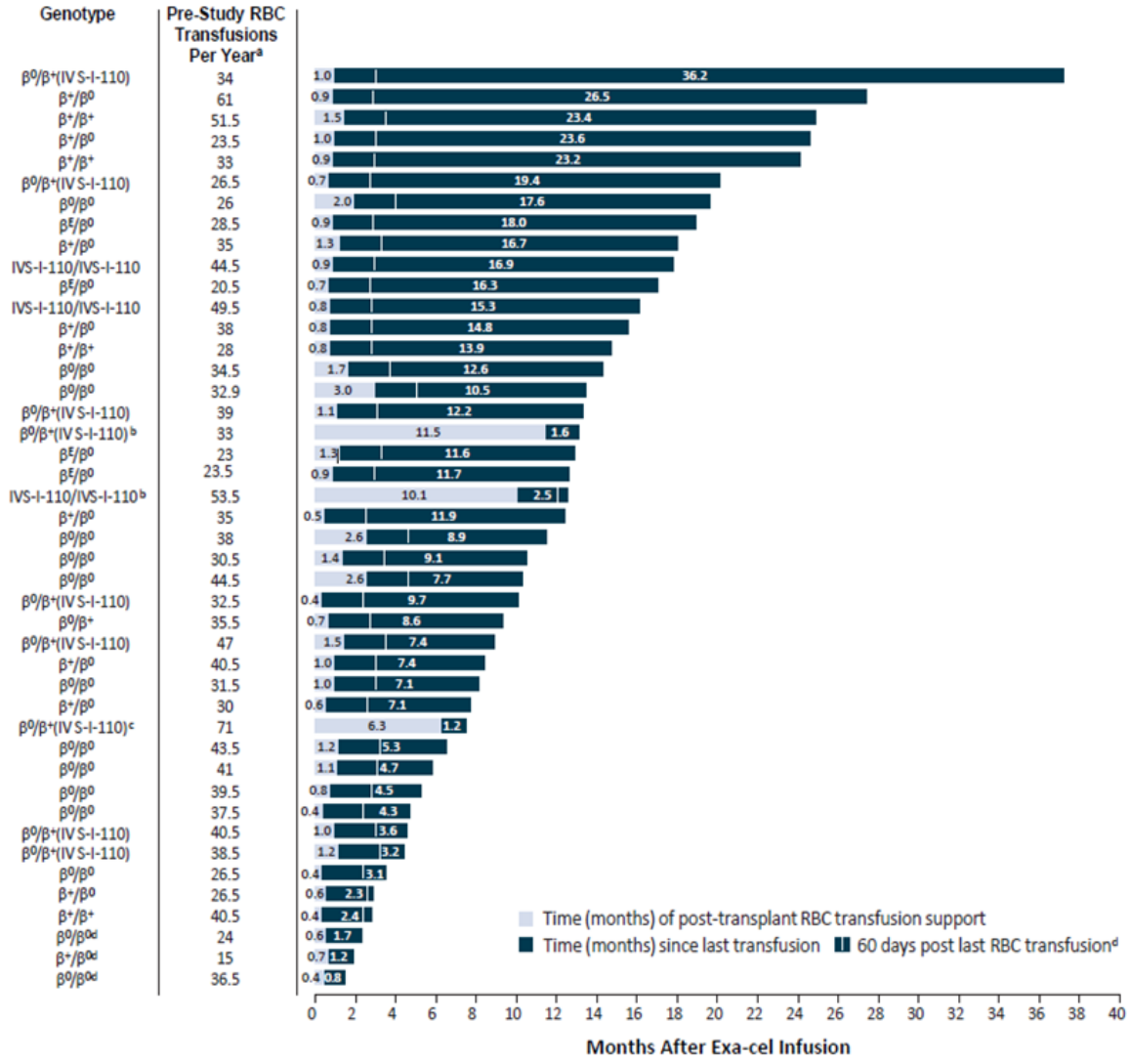


Jun 2023 FDA application

Locatelli et al EHA abstract June 2021 EP73

Gene Editing: CTX-001 Results

- **42 of 44** patients stopped RBC transfusions (duration 0.8-36.2 months)
- Two patients had not yet stopped transfusions but have 75% and 89% reductions in transfusion volume



Locatelli et al, 27th Congress of the European Hematology Assn (EHA) 2022; June 9–17, 2022

Ineffective erythropoiesis: Erythroid maturation

- **Luspatercept**
  - Activin Receptor Trap Ligands
  - Q3 wk SQ injection
  - Approved for use in Adults with TDT
  - Believe Trial (adults TDT)
    - Reduction of transfusion by 33% in 70% of pts, by 50% in 40% of pts
    - AE's transient bone pain, arthralgia, dizziness, HTN, and hyperuricemia; thrombosis in 3.6% patients s/p splenectomy + additional thrombosis risks
  - Beyond Trial (adults NTDT)
    - improved Hgb $\geq$1.0 in 77% of pts but BMS chose not to pursue FDA approval
  - Pediatric TDT, Phase 2, recruiting

Globin chain imbalance: Hydroxyurea

- Benefit of Hydroxyurea is uneven
- Certain mutations predict better response: Hgb E beta thalassemia, *Xmn*I polymorphism, Lepore or δβ-thalassemia
- Patients with asymptomatic extramedullary pseudotumors
- Starting dose of 10 mg/kg/day, not exceeding 20 mg/kg/day
  - Response evaluated after 3 and 6 months of therapy
  - Hemoglobin level increase of >1 g/dl at 6 months
  - Discontinue in patients not showing response

Globin chain imbalance: Hgb F inducers in trials

- **Benserazide (PB04-001)**
  - Currently to treat Parkinson's & Restless leg syndrome
  - Downregulates BCL11A, LSD1 and HDAC3 on the promoter region of the gamma globin gene
  - Phase 1/2, Oral, daily
- **Sirolimus**
  - Immunosuppressive agent in transplants and in vascular anomalies
  - Acts via mTOR inhibitor pathway activating autophagy
  - Phase 2, Oral, daily
- **Thalidomide (low dose) + HU** Phase 2/3 completed in Asia, no results

Ineffective erythropoiesis: PK activator

- **Mitapivat (AG-348)**
  - Oral daily agent
  - Phase 3, finished recruitment, adults, NTDT and TDT adults, **alpha** and beta thal
  - Phase 2 in NTDT adults: 80% had ≥1g increase in Hgb (x 1 in 5/5 α, 100%; 11/15 β 73%; x2 in 5/5 α, 100%; 8/15 β 53%; mean hgb 1.3 g); AE include initial insomnia, dizziness, HA
- **Etavopivat**
  - Oral daily agent
  - Phase 2, older child and adults, NTDT and TDT adults, **alpha** and beta thal

Ineffective erythropoiesis: Hepcidin mimetics

VIT-2763 & PTG-300

- Both completed Phase 2, further trials withdrawn due to “strategic reasons”

Apotransferrin

- Phase 2 trial terminated

Ineffective erythropoiesis: TMPRSS6 inhibitors

Sapablursen

- Phase 2 trial terminated

SLN-124

- Phase 1 trial terminated

Transfusions: modified blood products

Hemanext

- Study showed that using hypoxic (low oxygen) storage may improve post-transfusion recovery
- New processing system launched in Europe

Iron dysregulation/overload: modified chelator

DST-0509

- Deferasirox with potentially improved absorption characteristics
- Completed Phase 2, TDT, peds and adult

Resources

- Cooley's Anemia Foundation www.thalassemia.org
- Thalassemia International Federation www.thalassaemia.org.cy
- CDC
- ASH publications
- Up-to-Date

Thank You & Questions