The Thalassemias in Clinical Practice

Ashutosh Lal, MD

Director

Comprehensive Thalassemia Program

UCSF Benioff Children's Hospital Oakland

Outline

- Thalassemia: definitions and pathophysiology
- Epidemiology
- Classification of thalassemia syndromes
- Diagnosis of thalassemia
- Treatment of thalassemia

Hemoglobin

- Hemoglobin is a tetramer of 2 pairs of unlike globin chains

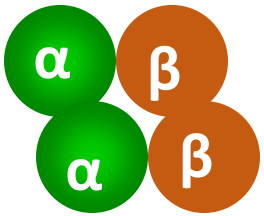
2 alpha chains	2 beta chains	$\alpha_2\beta_2$	Adult hemoglobin or **HbA**
2 alpha chains	2 gamma chains	$\alpha_2\gamma_2$	Fetal hemoglobin or **HbF**
2 alpha chains	2 delta chains	$\alpha_2\delta_2$	Minor adult hemoglobin or **HbA2**

Alpha genes are encoded on chromosome 16

There are 2 copies of alpha genes on each Ch.16

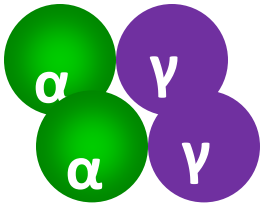
Gamma, delta and beta genes are encoded on chromosome 11

There is a single copy of each of these genes on each Ch.11



Adult

Hb A: α2 β2



Fetal

Hb F: α2 γ2

Thalassemias:
Quantitative defects of globin chain synthesis

Thalassemia

Inherited anemia

Inability to synthesize normal amounts of globin proteins

- **α thal: Decrease or absence of α-globin chains**
- **β thal: Decrease or absence of β-globin chains**

Thalassemia Trait

Heterozygote

Mild anemia that has insignificant effect on health

- **α thal trait**
- **β thal trait**

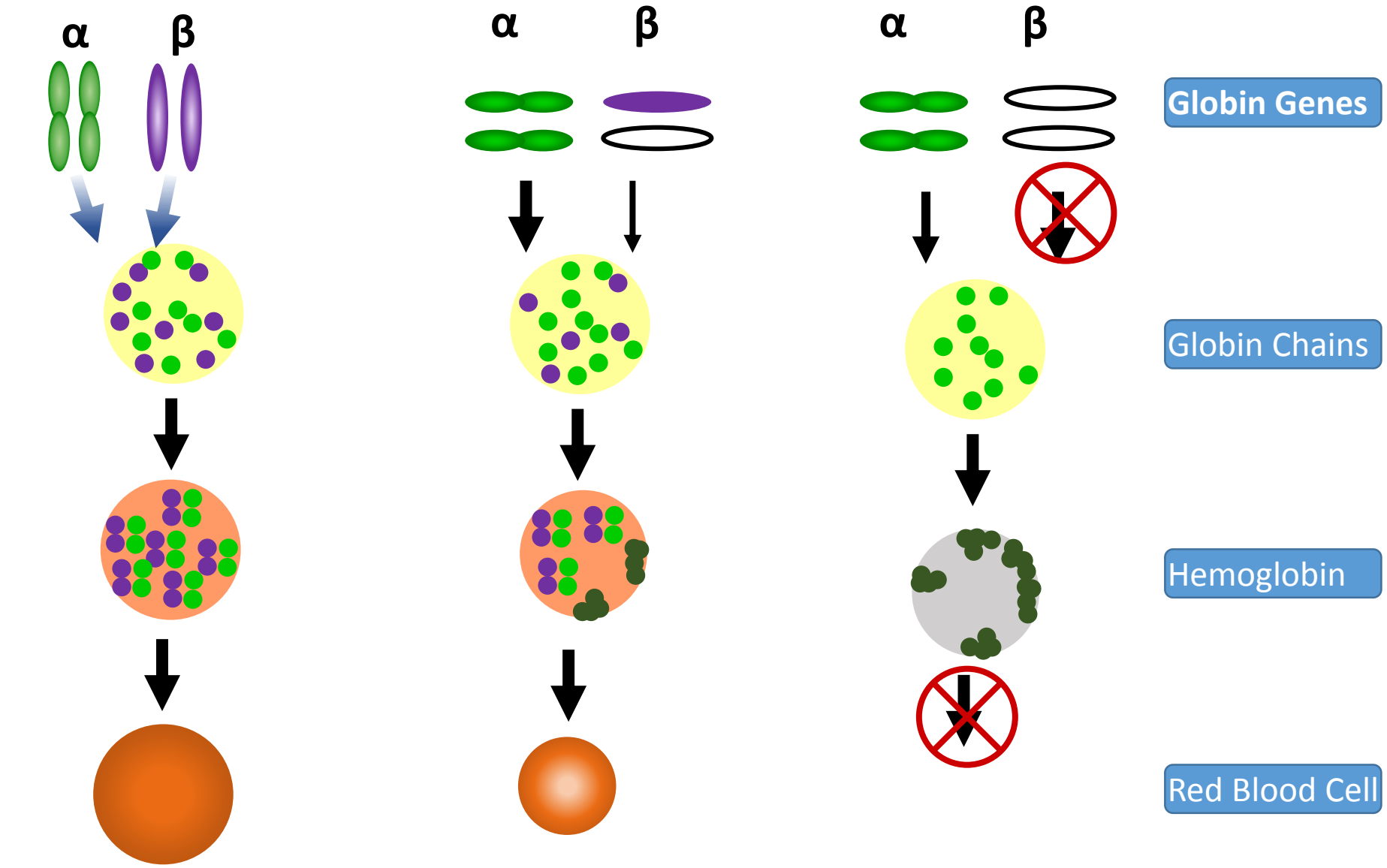
Thalassemia Disease

Heterozygote, Homozygote or Compound Heterozygote

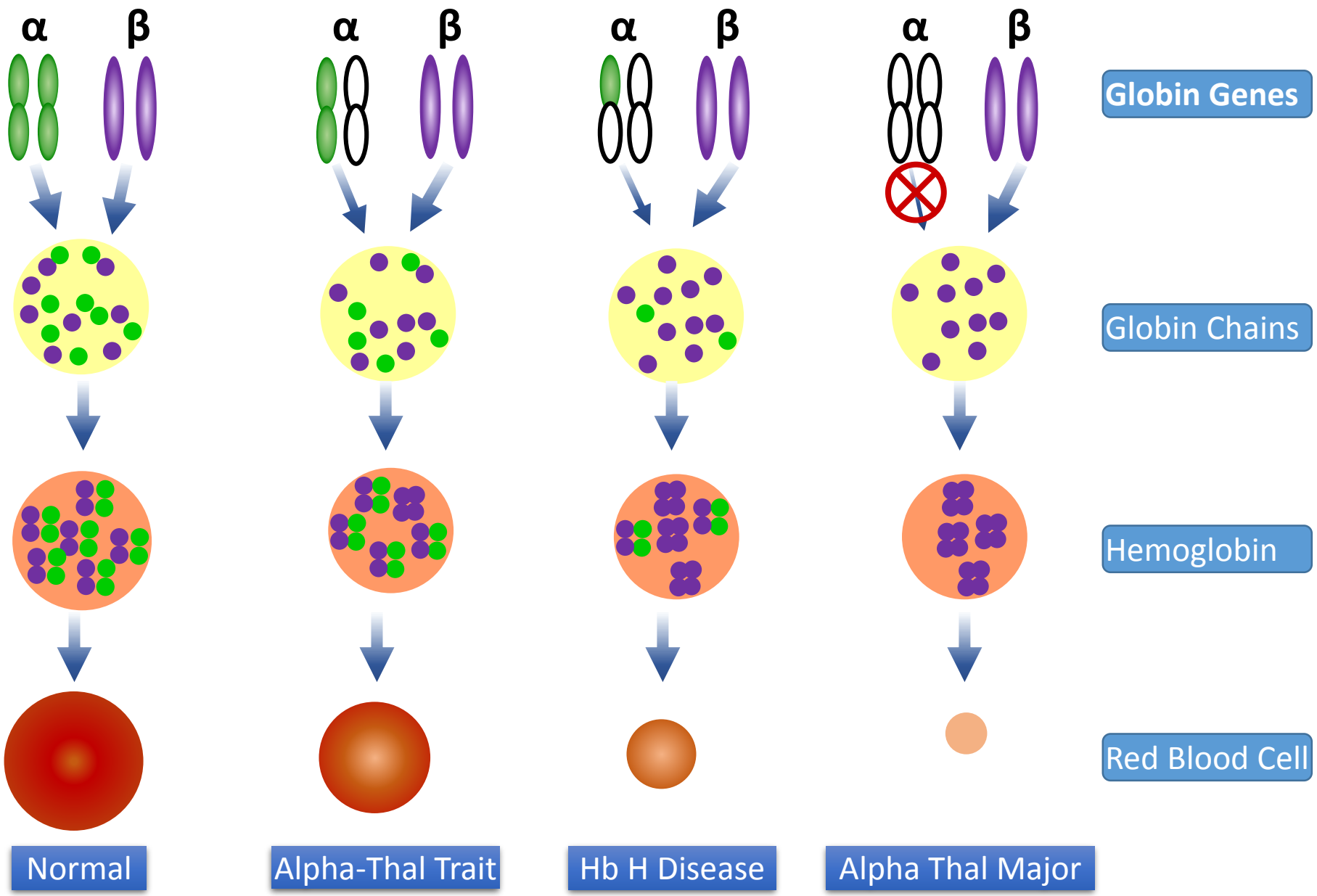
Moderate or severe anemia

- **May not require transfusion: Thalassemia intermedia**
- **Requires regular transfusions: Thalassemia major**

Molecular Pathogenesis: beta thalassemia



Molecular Pathogenesis: alpha thalassemia

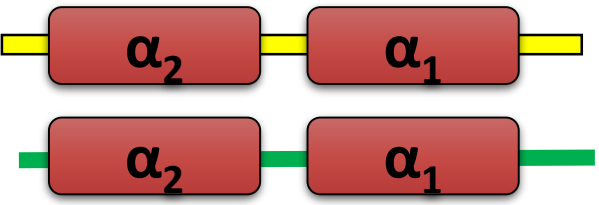


Genetic basis of α thalassemia

Two **α** genes (α2 and α1) are located on each Ch. 16

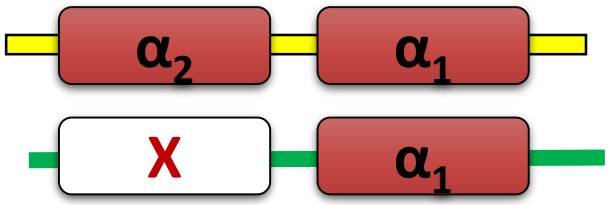
Common 1 gene deletions:
-3.7 Kb and -4.2 Kb
Common alpha mutation:
Constant Spring
Common 2 gene deletions:
SEA, MED, THAI, FIL

α^+: 1 intact α gene
α^0: 0 intact α genes



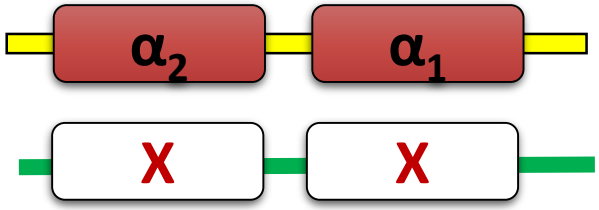
Normal

4 alpha genes
M: 14.5-16.5; F: 13-15



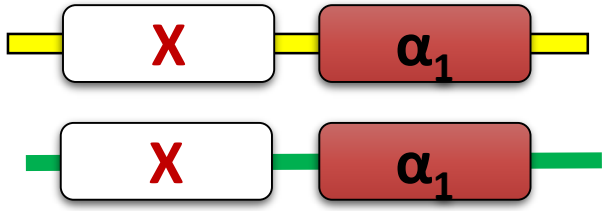
Silent Carrier

3 alpha genes, 1 del
M: 13-15.5; F: 11.5-13.5



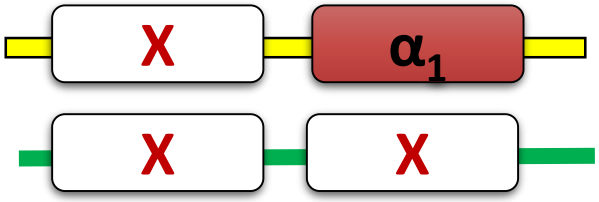
Heterozygous α^0 Trait

2 alpha genes, 2 del
M: 12-14; F: 10.5-12.5



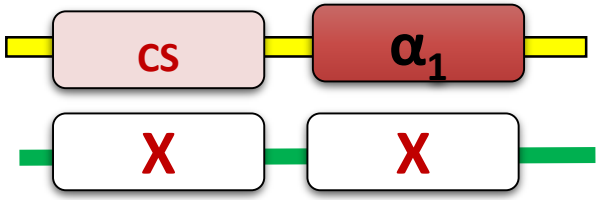
Homozygous α^+ Trait

2 alpha genes, 2 del
M: 12-14; F: 10.5-12.5



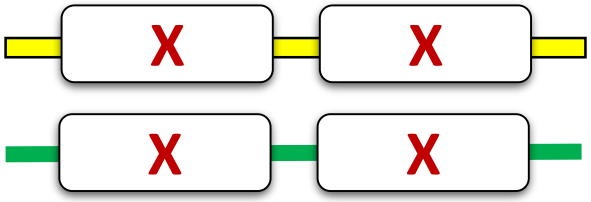
Hemoglobin H Disease

1 alpha gene, 3 del
M: 10-12; F: 8.5-10.5



Hemoglobin H Constant Spring

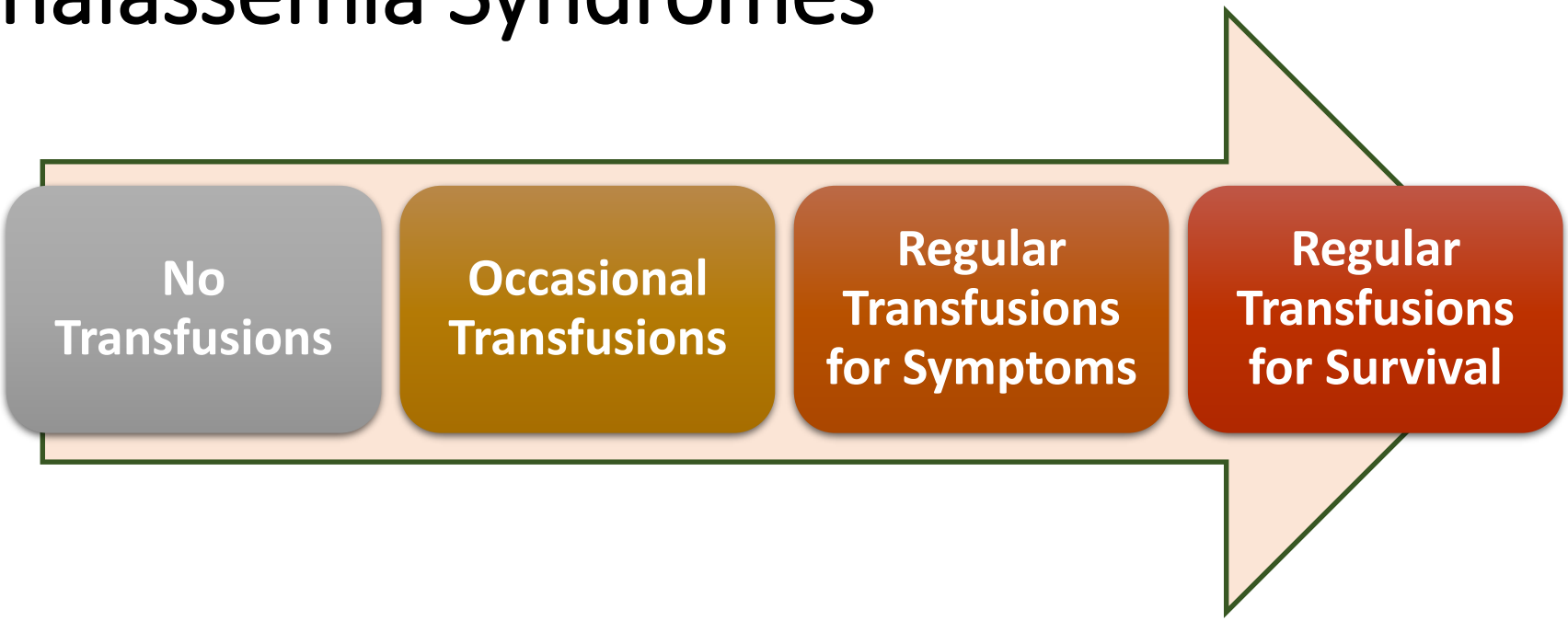
1 alpha gene, 1 mutation
M: 10-12; F: 8.5-10.5

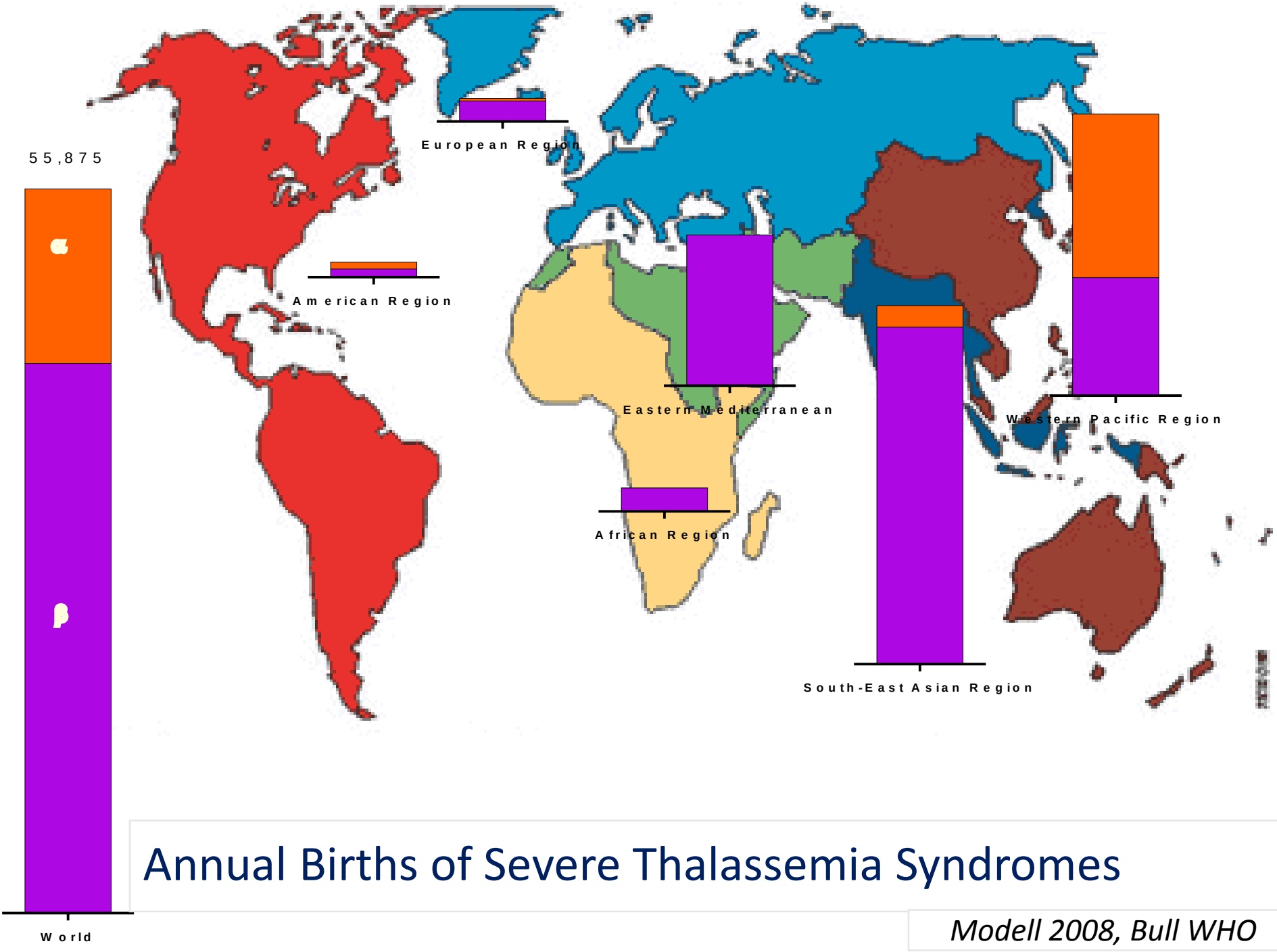


Alpha Thal Major

0 alpha genes, 4 del
Severe Anemia in Fetus

Transfusion Dependence in Thalassemia Syndromes





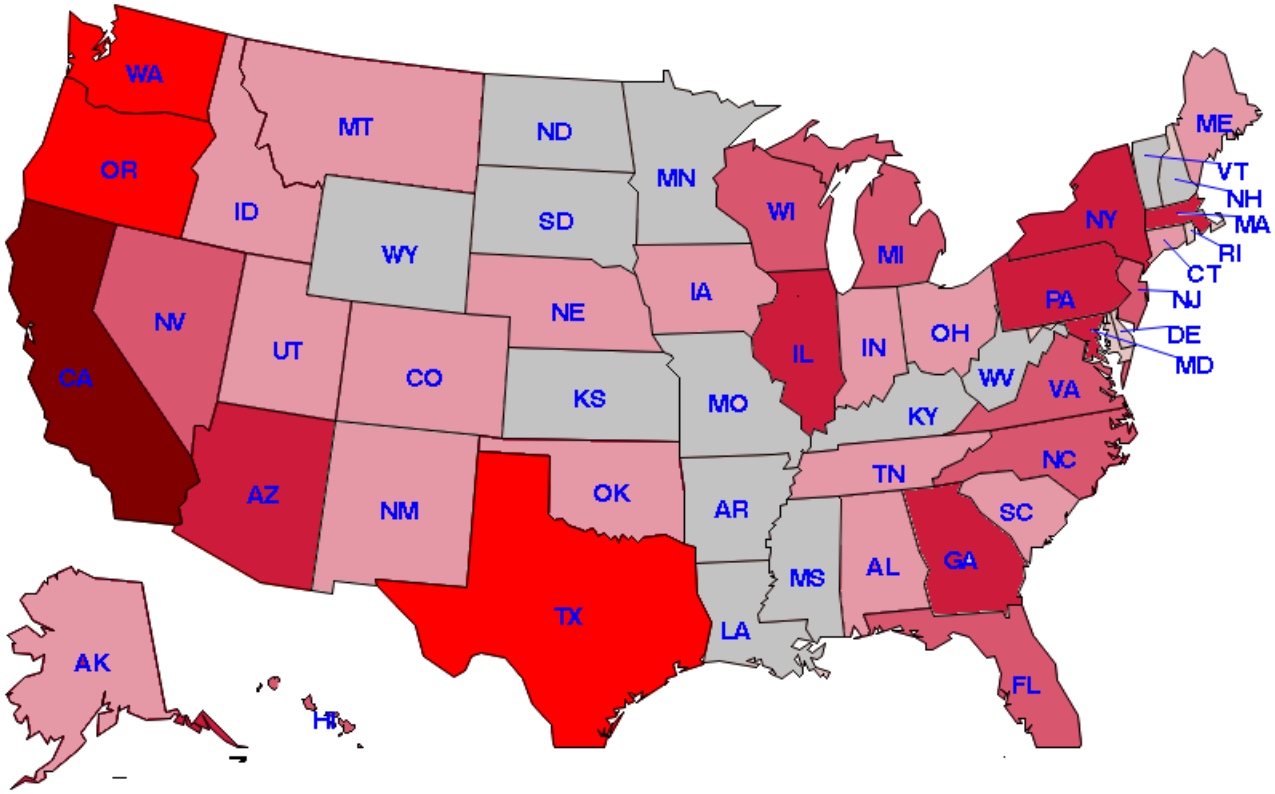
Annual Births of Severe Thalassemia Syndromes

Modell 2008, Bull WHO

Distribution of Thalassemia in China

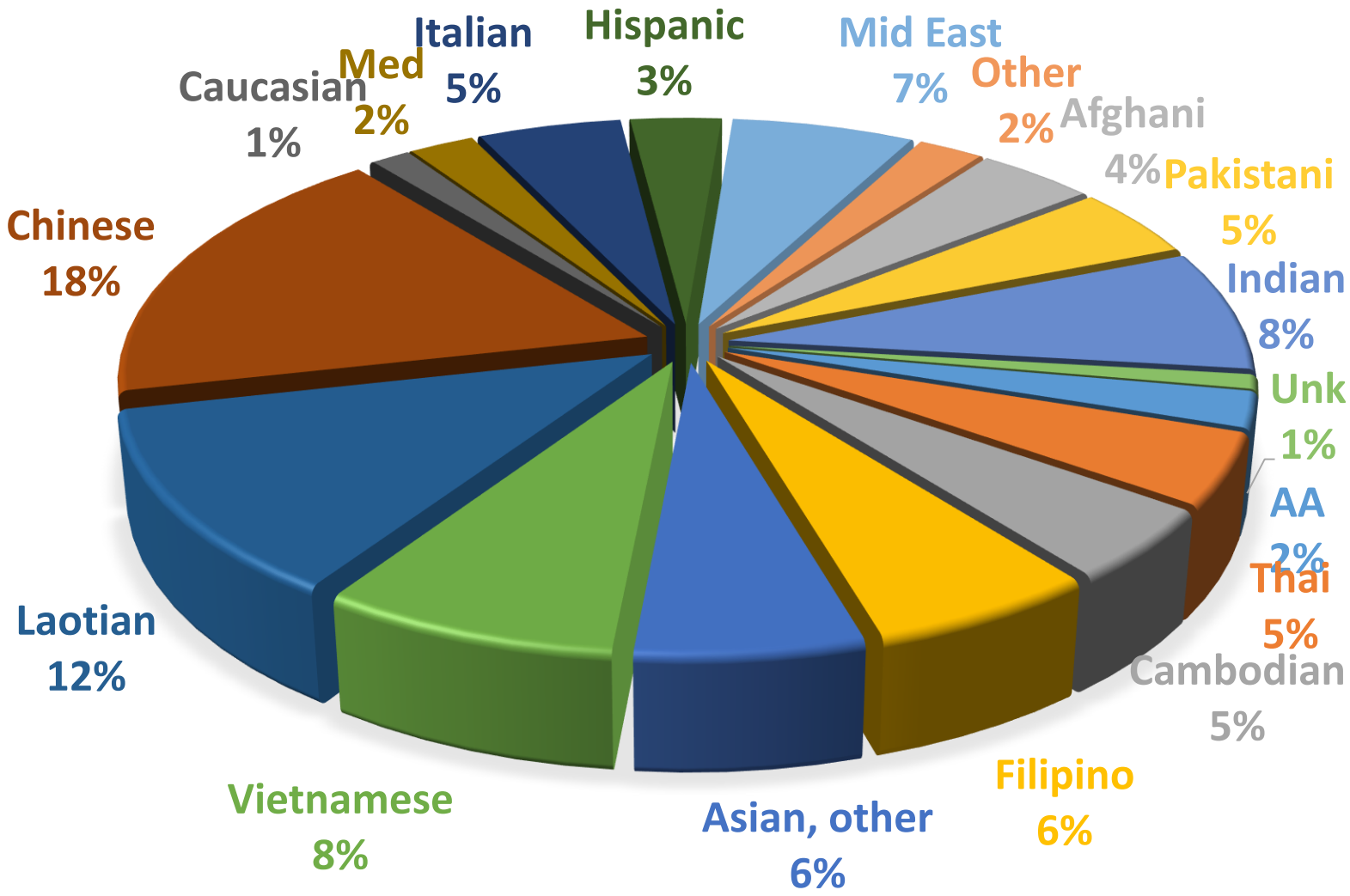
Adapted from Zeng & Huang. J Med Genet. 1987:578 and others

Distribution of Thalassemia in USA (estimated)



Oakland Data, HRSA, TCRN, plus extrapolation

Distribution of Ethnicities at Oakland



Diagnosis of Thalassemia: Thalassemia Trait

- When to suspect thalassemia trait
  - Mild anemia — Hemoglobin 10-12 g/dL
  - Microcytosis — MCV <80
  - Hypochromia — MCH <28
  - RBC count — Normal or Increased
  - RDW — Normal

- What is the best time to screen at risk population
  - Beta thal trait: at 1 year CBC
  - Alpha thal trait: At birth (currently not possible), otherwise at 1 year CBC
- Genetic counseling should follow screening
  - All activities should ideally take place in primary care practice
  - Prepare PCP's caring for at risk population to provide counseling for thalassemia trait
  - Different counseling for alpha and beta thalassemia

Diagnosis of Thalassemia Disease

- Prenatal diagnosis
  - When both parents are known carriers of thalassemia mutation
  - Test second parent if one parent is known thalassemia trait
  - Prenatal testing with CVS or amnio if both have beta trait or both have alpha trait
    - No consequence if one parent has alpha trait and one parent has beta trait
- Newborn screening for thalassemia syndromes
  - Possible to diagnose severe thalassemia syndromes
  - Alpha thalassemia: Hb Bart's
  - Beta Thalassemia: Hb F
  - E beta Thalassemia: Hb E
- Diagnosis of moderate or severe thal syndromes
  - CBC with hemoglobin <10 g/dL, microcytosis (sometimes mild), hypochromia, nucleated RBC
  - Splenomegaly, elevated bilirubin, growth impairment
  - Hemoglobin electrophoresis, DNA testing

Common Thalassemia Syndromes

- Beta thalassemias:

Condition	Genotype	Hemoglobin
Beta thal major	2 beta mutations	Hb <7 g/dL
Beta thal intermedia	2 beta mutations	Hb >7 g/dL
E beta thal	1 beta mutation with E mutation	Hb 4-9 g/dL

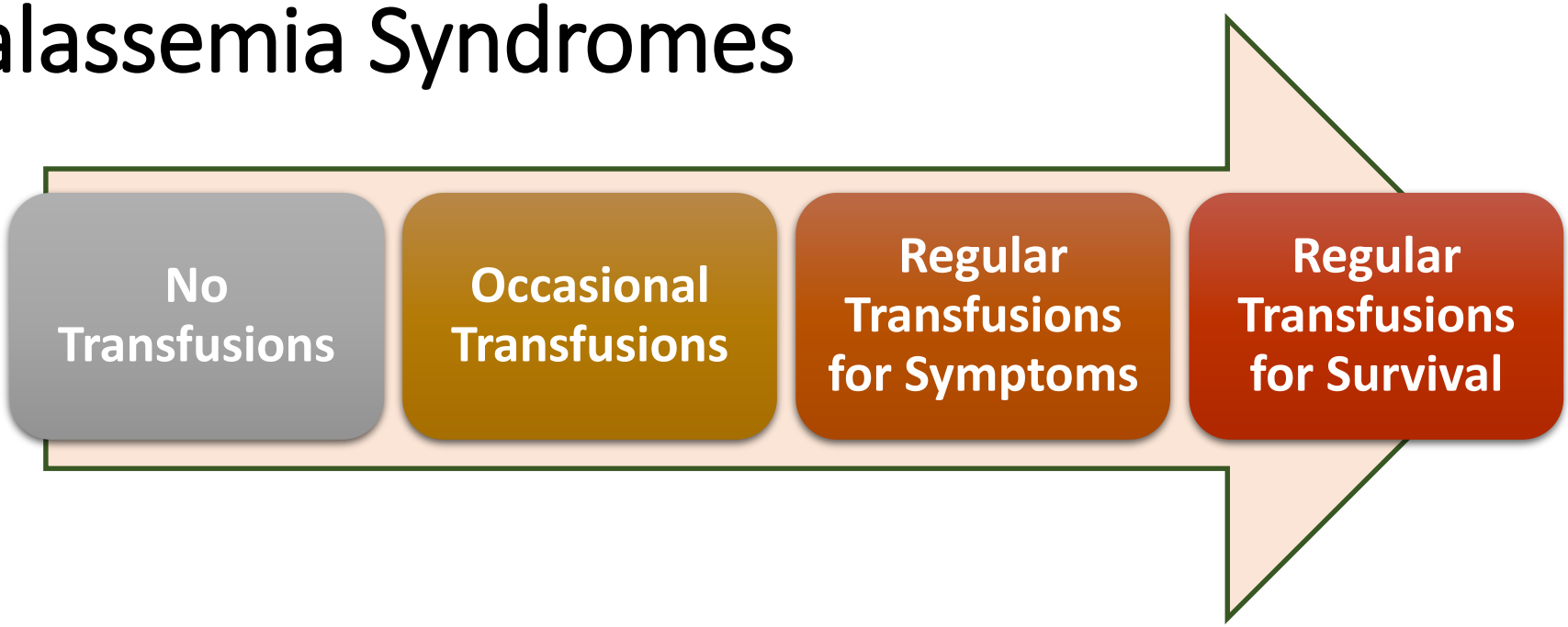
- Alpha thalassemias:

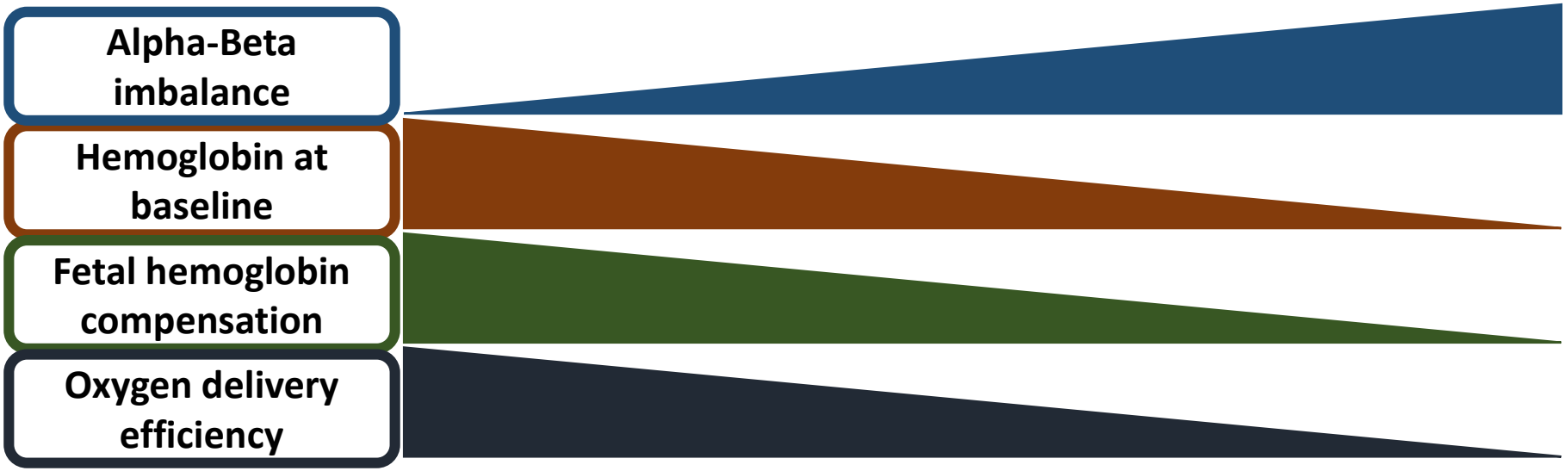
Condition	Genotype	Hemoglobin
HbH disease	3 alpha gene deletion	Hb 8-12 g/dL
HbH Constant Spring	2 alpha gene deletion + Constant Spring mutation	Hb 7-10 g/dL
Alpha thal major	4 alpha gene deletion	Fetal hydrops

Treatment of Thalassemia

- Deciding between regular transfusions and conservative management
- Pros and cons of transfusions
- Alternatives to transfusions
- Curative therapies

Transfusion Dependence in Thalassemia Syndromes





Comparison of Average Hemoglobin Levels

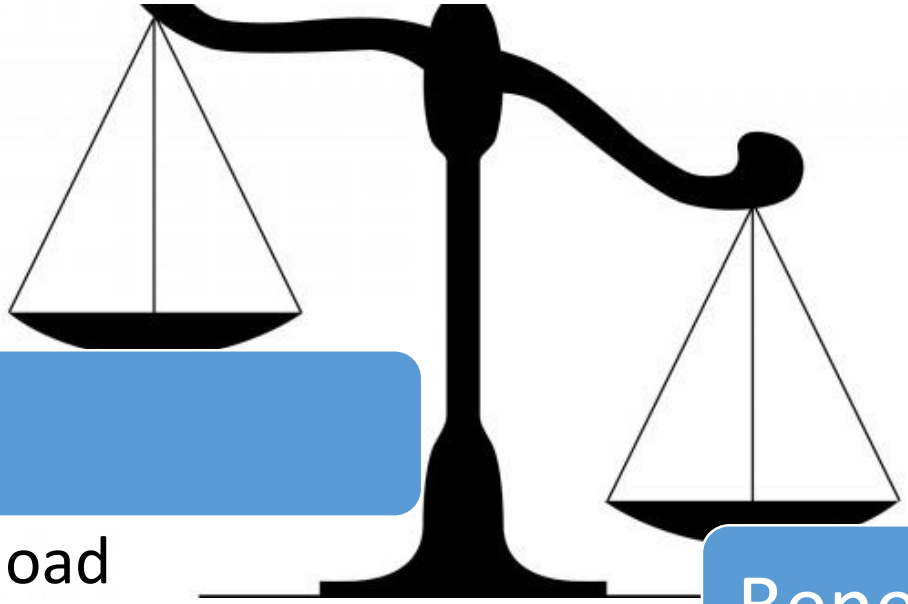
Individuals without thalassemia	• 13-16 g/dL
Thalassemia intermedia not receiving transfusions	• 6-9 g/dL
Thalassemia major receiving regular transfusions	• 11-12 g/dL

Why not transfuse all individuals with thalassemia intermedia?

Complications of Low Hemoglobin in Non-Transfused Thalassemia

Children	10-15 years	Adults
• Bone changes: face and head size • Feeding difficulties • Sweating • Lack of weight gain • Growth delay • Splenomegaly	• Growth delay • Pubertal delay • Progressive splenomegaly • Facial bone changes • Fatigue • Extramedullary masses	• Extra-medullary masses • Fatigue • Pain • Thrombosis • Pulmonary hypertension, • Cerebral vacsulopathy • Leg ulceration • Fractures

Transfusions have become very safe, but still have risks



Risks

- Iron overload
- Antibody formation
- Viral infections
- More hospital visits

Benefits

- Activity, appetite, growth
- Prevent bone changes
- Prevent spleen enlargement

Role of Splenectomy

- Splenectomy is no longer recommended to delay or prevent transfusions
  - Transfusions are safer
  - More risks of splenectomy in the long term
  - Many patients will still require transfusions later on
- But, progressive splenomegaly worsens anemia
  - So, splenomegaly should be prevented by early recognition and starting transfusions
  - Splenomegaly is reversible in the first decade, but not later on

Deciding on chronic transfusions

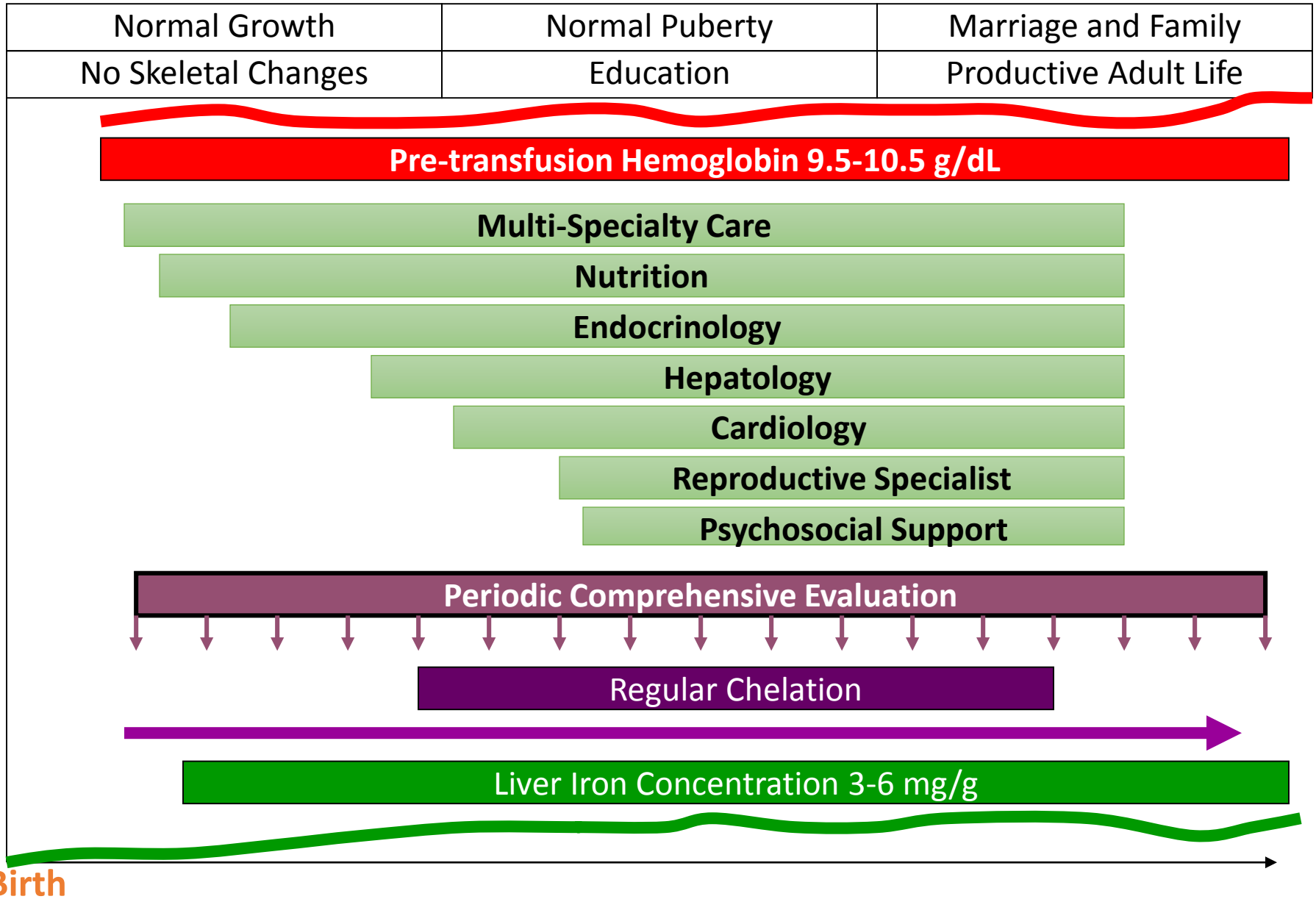
- Beta/Beta thalassemia
  - Baseline hemoglobin <7 g/dL, with or without symptoms

    Or
  - Baseline hemoglobin >7 g/dL AND ***symptoms of anemia***

- E Beta Thalassemia
  - Symptoms of anemia

- Hemoglobin H Disease
  - Intermittent transfusions in Hb H Constant Spring
  - Transfusions are not needed in deletional Hb H disease

Beta Thalassemia Major: Natural History
Transfused & Chelated



Options for Non-Transfused Thalassemia

- Hydroxyurea
  - Effective in a subgroup of patients with beta thalassemia intermedia
- Luspatercept (investigational)
  - Improves survival of red blood cell that are forming in the bone marrow
  - Initial clinical trial in transfusion-dependent thalassemia
  - Future trial in non-transfused thalassemia
- Hepcidin or hepcidin-mimics (investigational)
  - Expected to improve alpha:beta imbalance
  - No current clinical trials in non-transfused thalassemia

Cure for thalassemia

- Bone marrow transplant
  - Siblings
  - Unrelated donors
- Gene therapy
  - Lentiviral vectors
  - Gene Editing