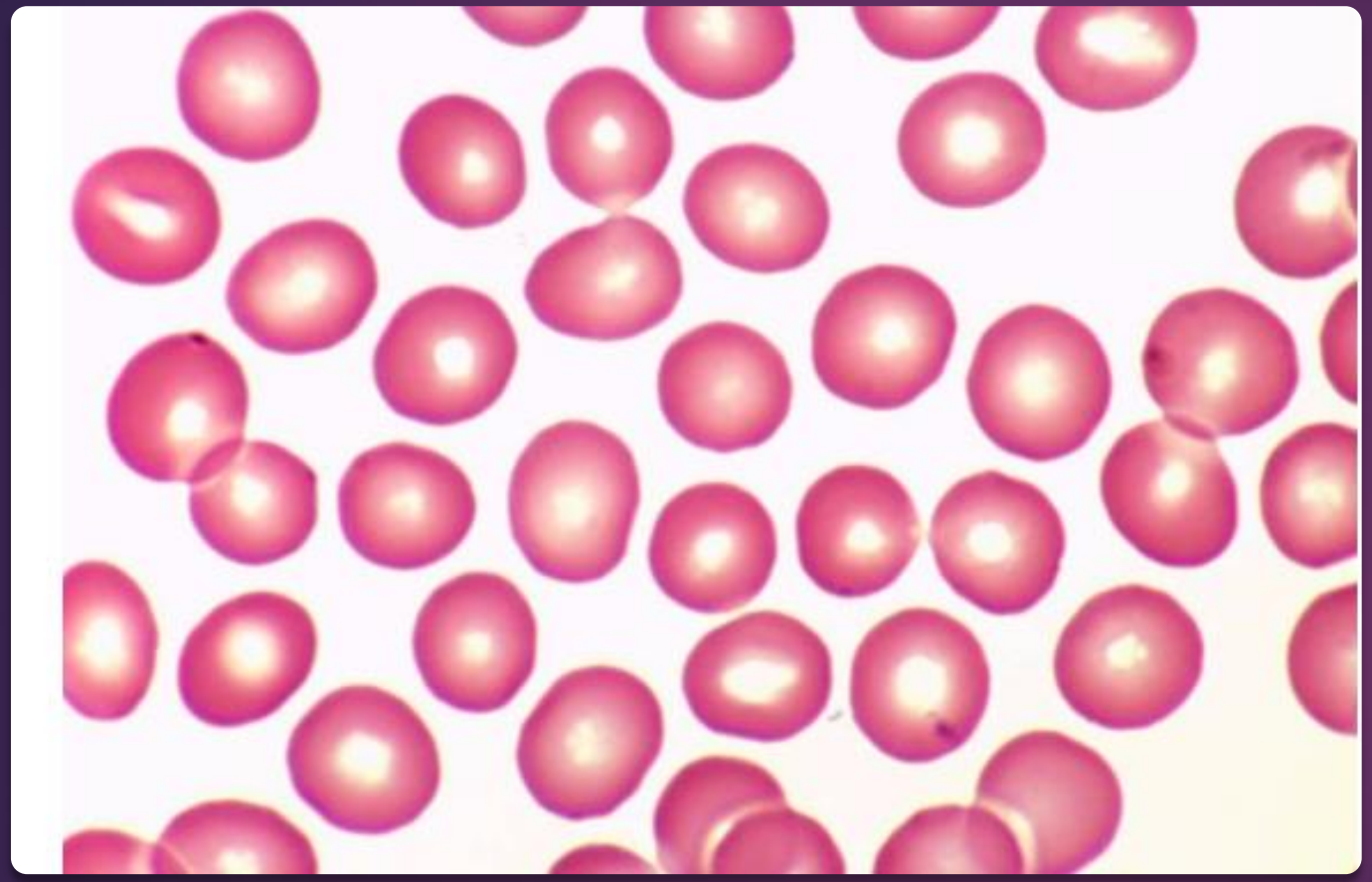
Thalassemia

KRYSTAL PEARCE, MHS, MLS(ASCP)CM

ASSISTANT PROFESSOR
MEDICAL LABORATORY SCIENCE PROGRAM
SCHOOL OF ALLIED HEALTH PROFESSIONS
LSU HEALTH SHREVEPORT

Objectives:

- Define Thalassemia
- Compare and Contrast different types of thalassemia
- Describe typical laboratory findings associated with thalassemia



Red Blood Cells and Hemoglobin

Composition of hemoglobin types

TABLE 6.2 Comparative Chain Composition of Hemoglobin Types

Hemoglobin Type	Symbol	Polypeptide (Globin) Chains
Embryonic		
Gower-1	$\zeta_2 \varepsilon_2$	2 zeta 2 epsilon
Gower-2	$\alpha_2 \varepsilon_2$	2 alpha 2 epsilon
Portland-1	$\zeta_2 \gamma_2$	2 zeta 2 gamma
Hemoglobin F	$\alpha_2 \gamma_2$	2 alpha 2 gamma
Hemoglobin A	$\alpha_2 \beta_2$	2 alpha 2 beta
Hemoglobin A_2	$\alpha_2 \delta_2$	2 alpha 2 delta

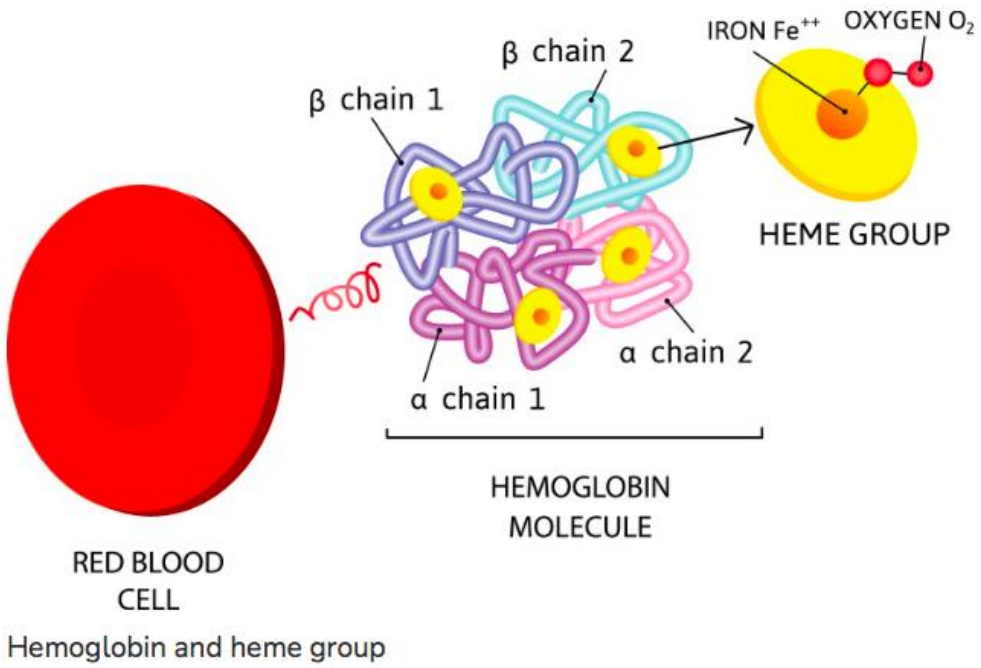
Hemoglobin Composition and Configuration

- Hemoglobin F
  - 2 Alpha chains
  - 2 gamma chains

Hemoglobin Composition and Configuration

- Normal Adult Hemoglobin (Hemoglobin A) consist of four heme groups and four polypeptide chains.

- The polypeptide chains
  - 2 Alpha chains
  - 2 Beta chains



Hemoglobin and heme group

Hemoglobin Composition and Configuration

- Hemoglobin A_2
  - 2 Alpha Chains
  - 2 Delta Chains
    - 2.5%

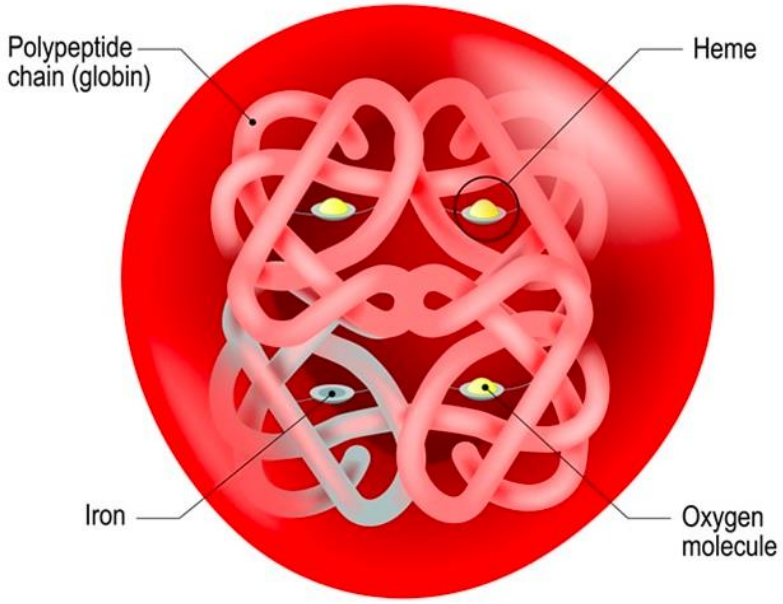


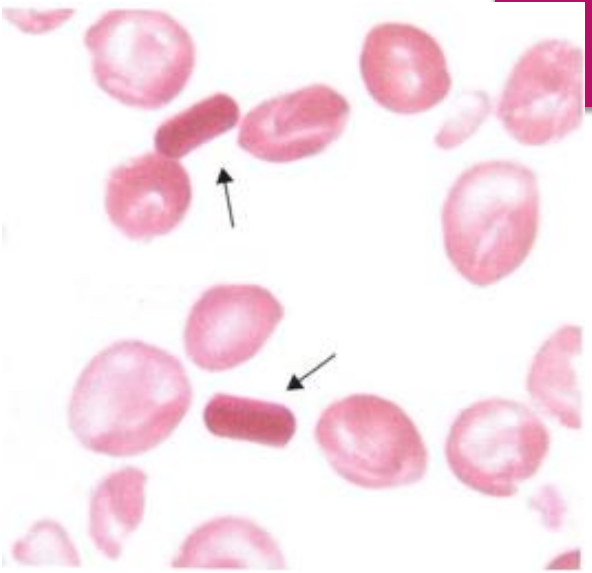
Image Credit: Designua / Shutterstock

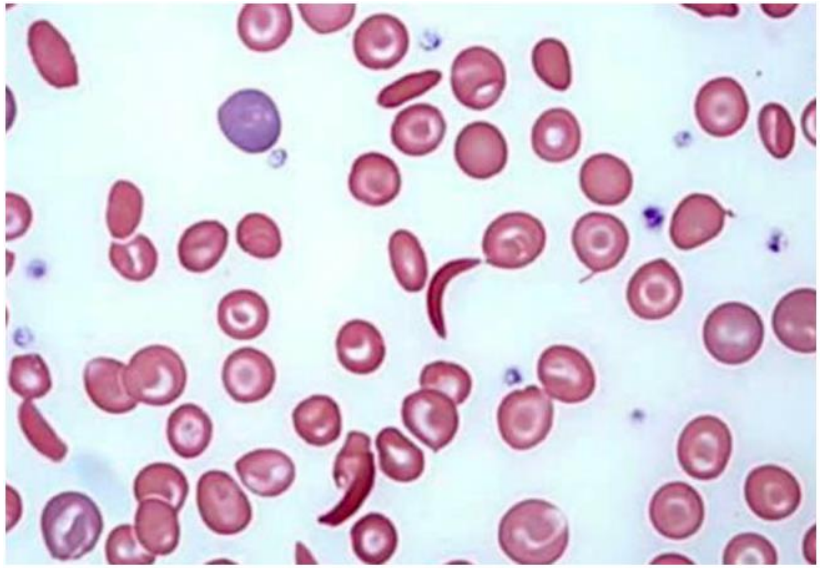
Hemoglobinopathies

- Qualitative vs. Quantitative Disorders

Qualitative Hemoglobinopathies

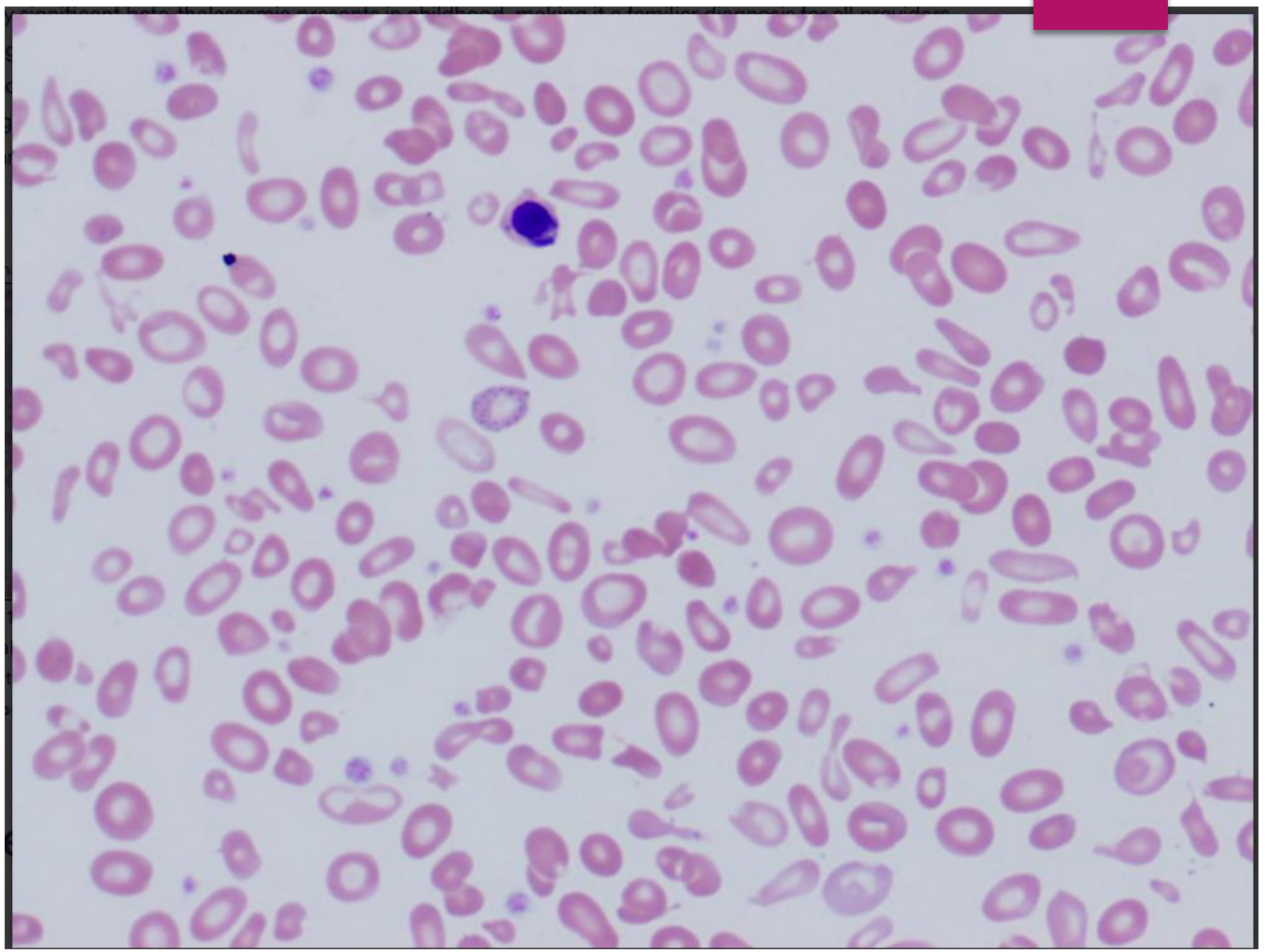
- Qualitatively abnormal hemoglobin molecules are the result of genetic mutations in which amino acid substitutions or deletions result in structural variants of the Hgb molecule
  - Hgb S (most common)
  - Hgb C





Quantitative Hemoglobinopathies

- Quantitative globulin disorders are the result of various genetic defects that cause decreased synthesis of normal globin chains. They are known as Thalassemias
  - Alpha Thalassemia
  - Beta Thalassemia



Thalassemia

- Are a group of inherited disorders of hemoglobin synthesis
  - Decreased rate of synthesis of one or more polypeptide chains (quantitative)
  - Classified according to the polypeptide chain or chains involved

Thalassemia Inheritance and pathophysiology

- Genetics
  - Structural gene deletion (partial or total)
- Pathophysiology
  - Characterized by absence or decrease in synthesis of one of the two constituent globulin subunits of a normal hemoglobin molecule

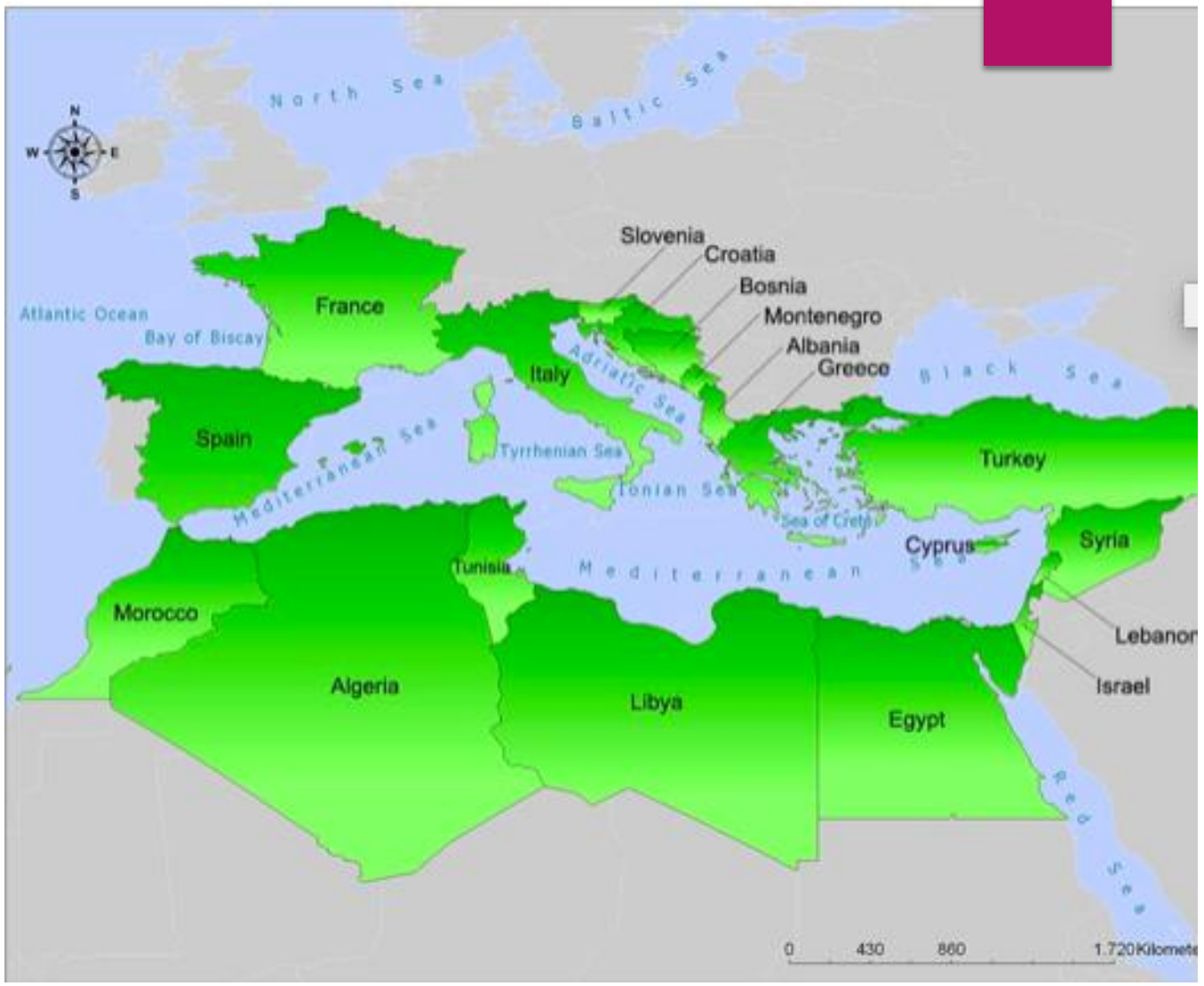
Major vs Minor

- In general, heterozygous inheritance of a thalassemia gene produces thalassemia minor (no clinical symptoms) while homozygous or doubly heterozygous thalassemia produces thalassemia major (more clinically severe)
- Combination hemoglobinopathies result from a combination of a globulin defect and another type of hemoglobinopathy

Beta-Thalassemia

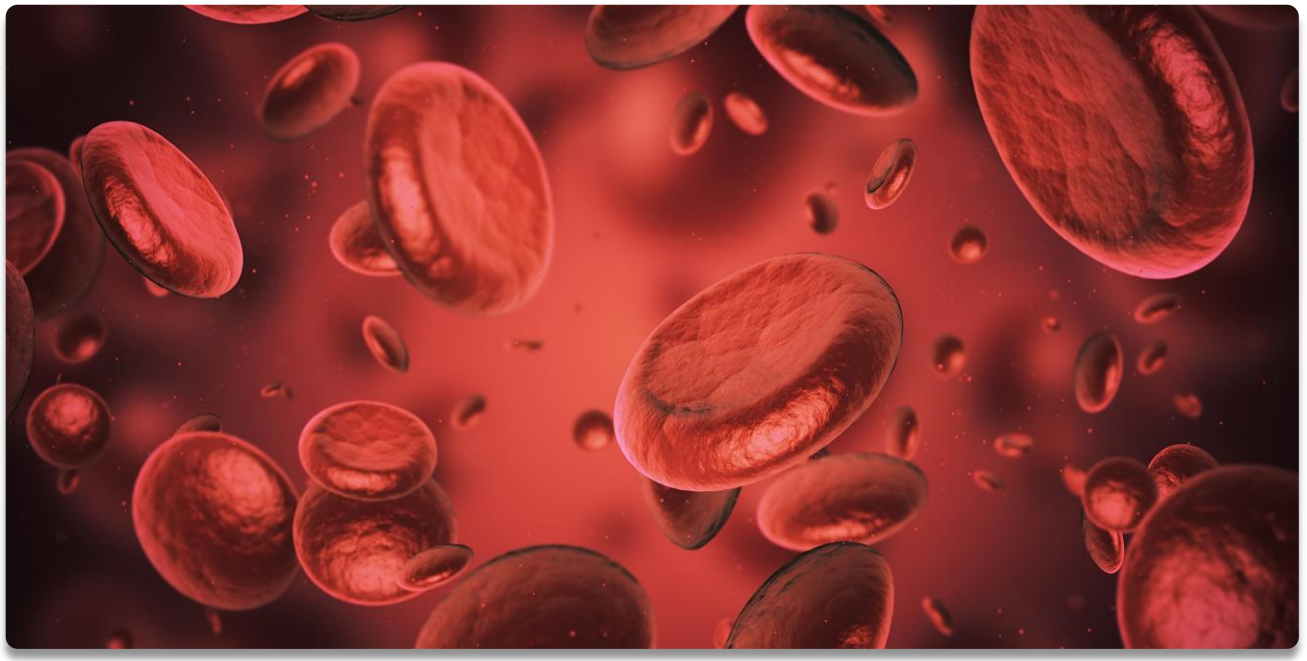
- One of most common single-gene disorders
- Point mutations (more than 200)
- Decreased production of Beta globulin

- The highest prevalence of beta-thalassemia mutations is in people of Mediterranean, Middle Eastern, and Asian descent



Variants of Beta-thalassemia

- Beta-thalassemia minor
- Beta-thalassemia intermedia
- Beta-Thalassemia Major (Cooley's Anemia)

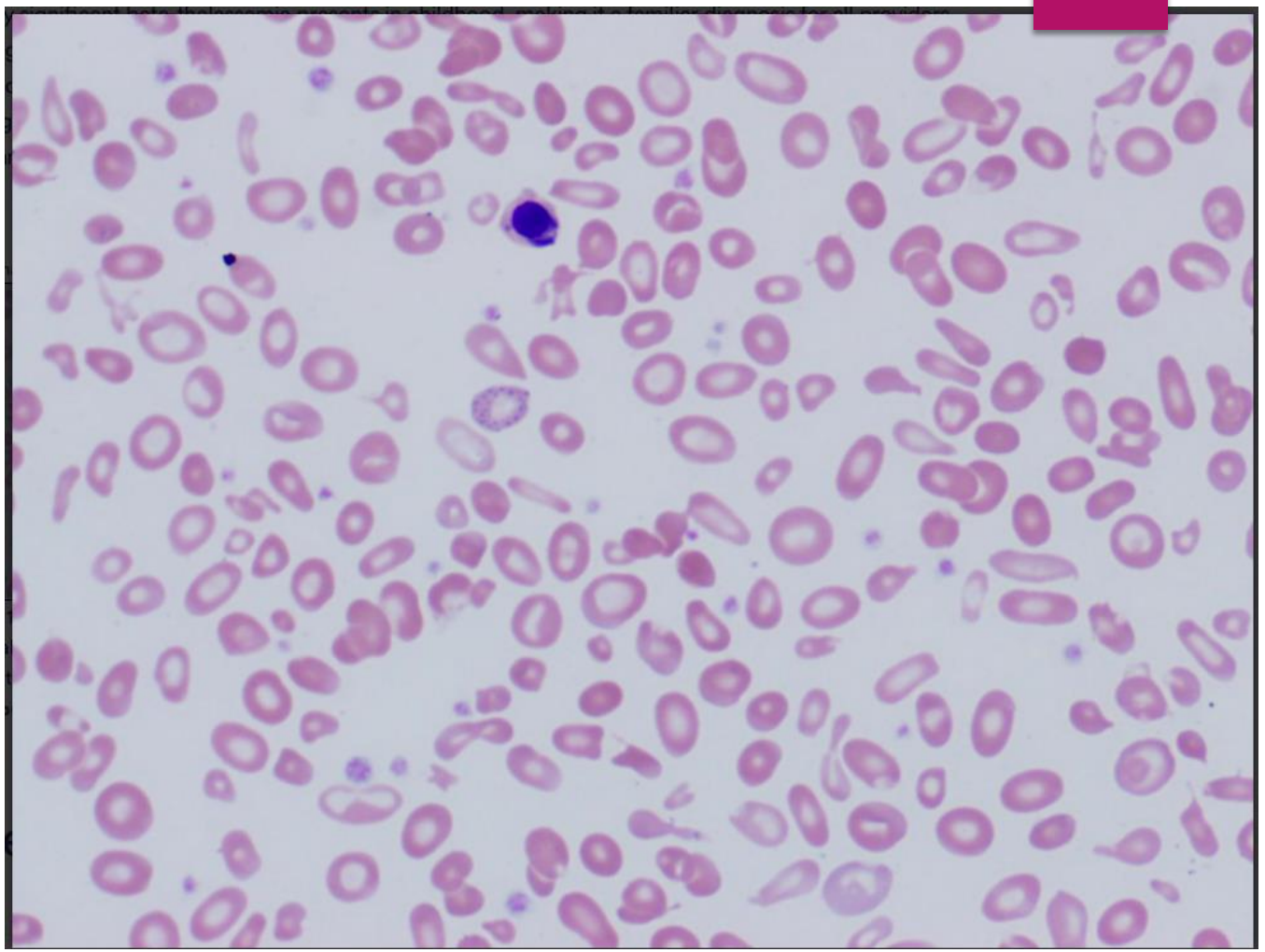


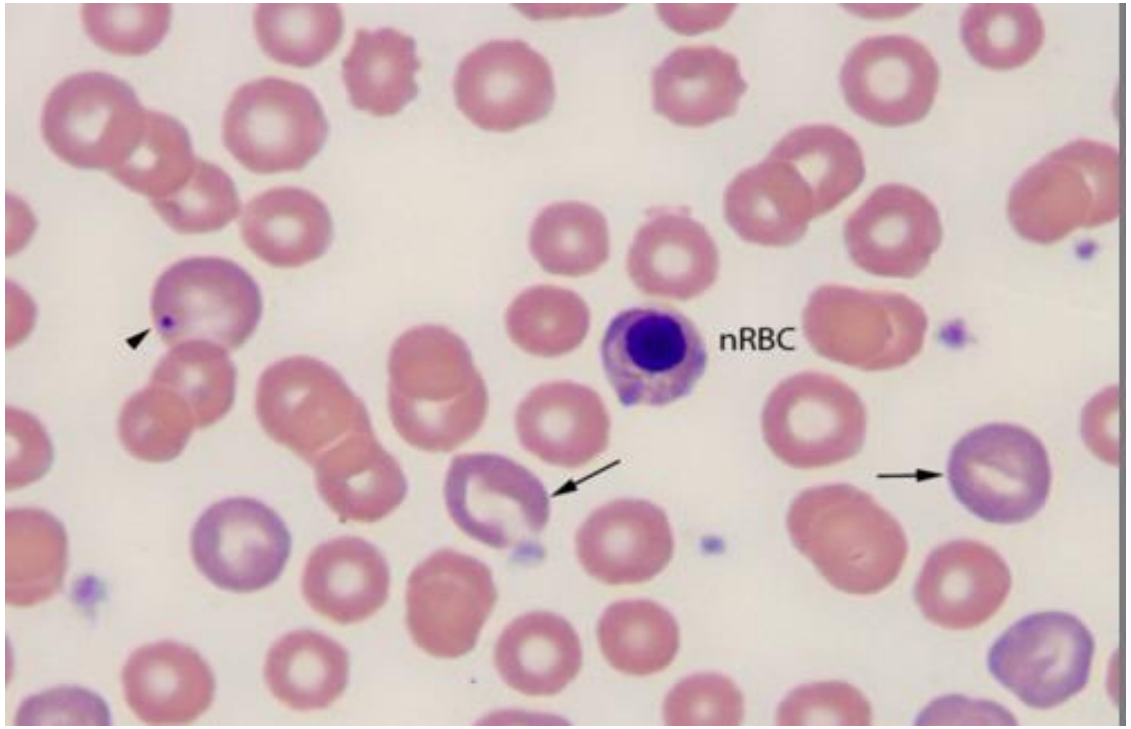
Laboratory Findings

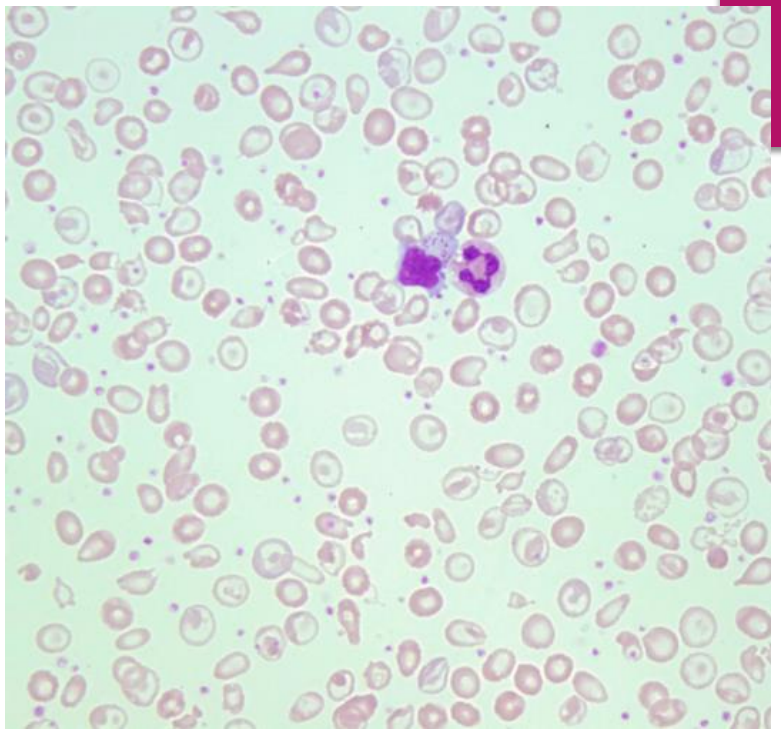
- Hematological findings
  - Decreased Hemoglobin and Hematocrit
  - Decreased RBC count
  - RBC indices
    - MCV
    - MCH
    - MCHC
    - RDW

Peripheral Smear

- Micro/hypo
- Anisocytosis
- Pokilocytosis
- Target
- Polychromasia
- NRBC's




nRBC

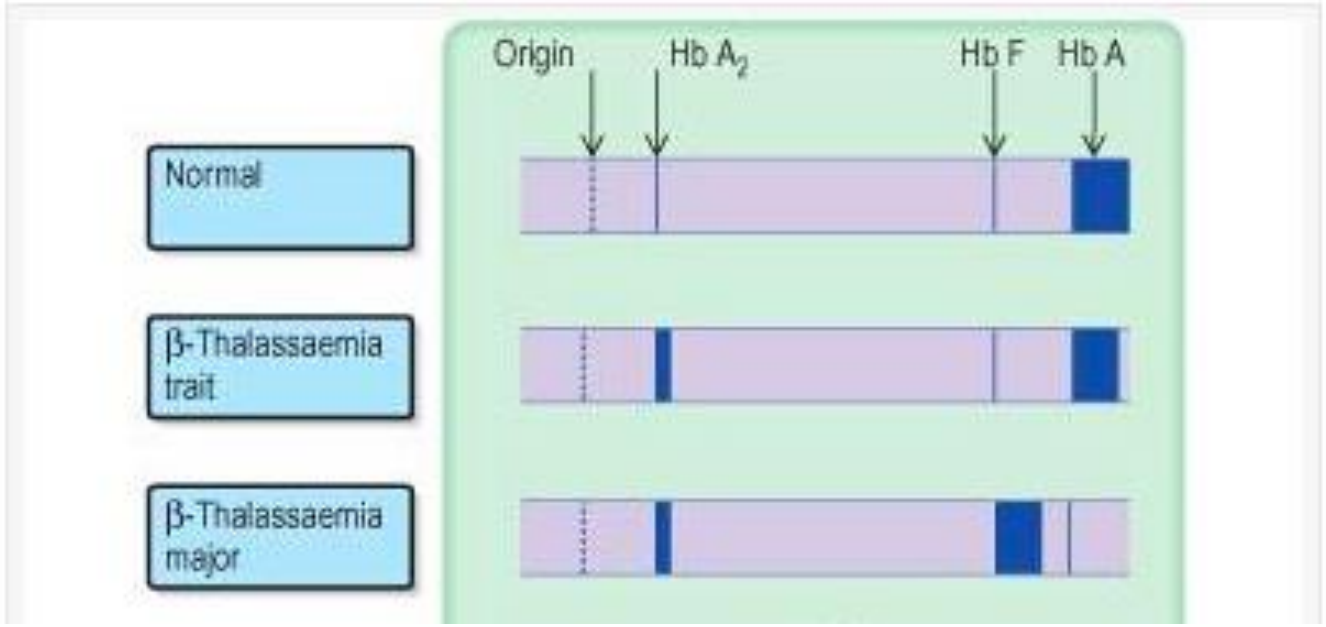


Other Lab Findings

- Bilirubin
- Serum iron
- TIBC
- Ferritin

Electrophoresis

- Typically with Beta-Thalassemia
  - Decreased A
  - Increased F
  - Elevated A_2



Association of Beta-Thalassemia with hemoglobinopathies

- Hgb S-Sickle Cell Thalassemia
- Hgb C-Thalassemia
- HgbE-Thalassemia

Treatment

Transformed from a lethal disease of infancy into a chronic disease of adulthood with a dramatic increase in both survival and life expectancy.

Blood transfusions

Iron chelation

Bone Marrow Transplant

Gene Therapy

Alpha Thalassemia

- Major cause is deletions that remove one or both alpha globulin genes from the affected chromosome.

- Found primarily in individuals of Mediterranean, Asia and African ancestry
- California

Types of Alpha-Thalassemia

- Silent Carrier (one inactive gene)
- Alpha-Thalassemia Trait (2 inactive genes)
- Hb H Disease (Three inactive genes)
- Hydrops fetalis with Hb Bart (4 inactive genes)

Silent Carrier State

- Missing only 1 of 4 genes
- 3 remaining genes compensate
- No clinical manifestations of hemoglobinopathy

Alpha Thalassemia Trait

- 2 Missing alpha genes
- Imbalance of alpha and beta chain synthesis creates an imbalance

Hemoglobin H Disease

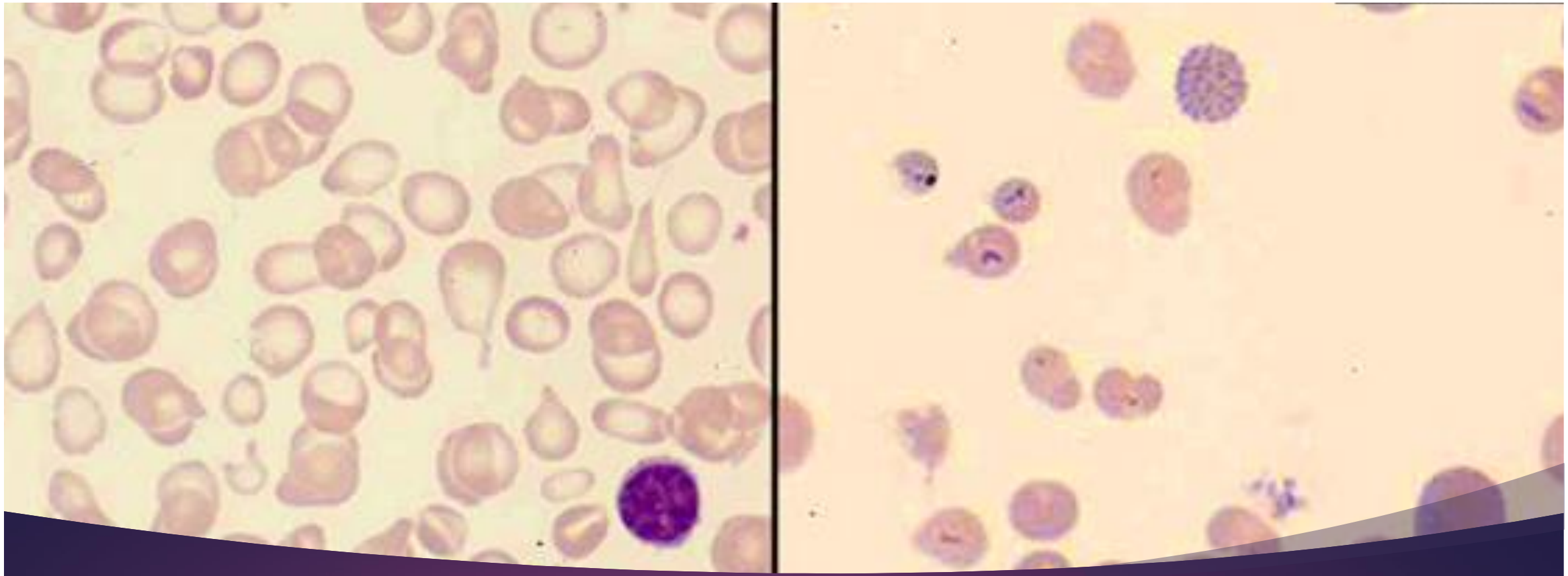
- 3 gene deletion
- Hgb H is a tetramer of four normal beta chains
- Prevalent in Southeast Asia, Mid. East, Greece and Cypress
- Micro/hypo, target cells, and tiny misshaped red cells
- Incubate cells with brilliant cresyl blue to demonstrate inclusions
- Hgb H characteristics

Hemoglobin Bart's

- An abnormal hemoglobin which is composed of four gamma chains
- Formed in alpha thalassemia minor
- Occurring in anemic, stillborn infants
- Hgb Bart's essentially useless as an oxygen-transport protein
- hydrops fetalis

Lab Results

- Peripheral Smear
- Micro/Hypo
- Anisocytosis
- Poikilocytosis
- RBC Indices



Hemoglobin H

Electrophoresis

Electrophoresis Patterns in Hemoglobinopathies					
	Hb A ($\alpha_2\beta_2$) (%)	HbA2 ($\alpha_2\delta_2$) (%)	HbF ($\alpha_2\gamma_2$) (%)	HbH (β_4) (%)	Hb Barts (γ_4) (%)
Normal	>95	2–3	<1	0	0
Alpha Thal (0)	0	0	0	<10	>90
Alpha Thal Major	60–90	2–3	0	5–30	2–5
Alpha Thal Trait	95	3–4	<1	0	0
Beta Thal Major	0–5	0–5	>90	0	0
Beta Thal Intermedia	5–90	0–5	10–90*	0	0
Beta Thal Minor	90–95	3–10	2–3	0	0

Alpha chain variants

- Hgb H Constant Springs
- Newborn screenings

Treatment

References

- McKenzie, S. B., Williams, J. L., & Landis-Piwowar, K. (2020). *Clinical laboratory hematology*.
- Turgeon, Mary Louise. **Clinical Hematology: Theory and Procedures.** 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2018.
- www.statpearls.com
- http://www.medical-labs.net/hemoglobin-electrophoresis-949/
- https://www.brown.edu/academics/biomed/departments/pathology/residency/digital-pathology-library/hematopoietic-and-lymphoid/blood-cell-anomalies/alpha-thalassemia
- https://doctorlib.info/oncology/pocket-oncology/132.html