Anemia: Importance of correct diagnosis and the approach to common pediatric cases

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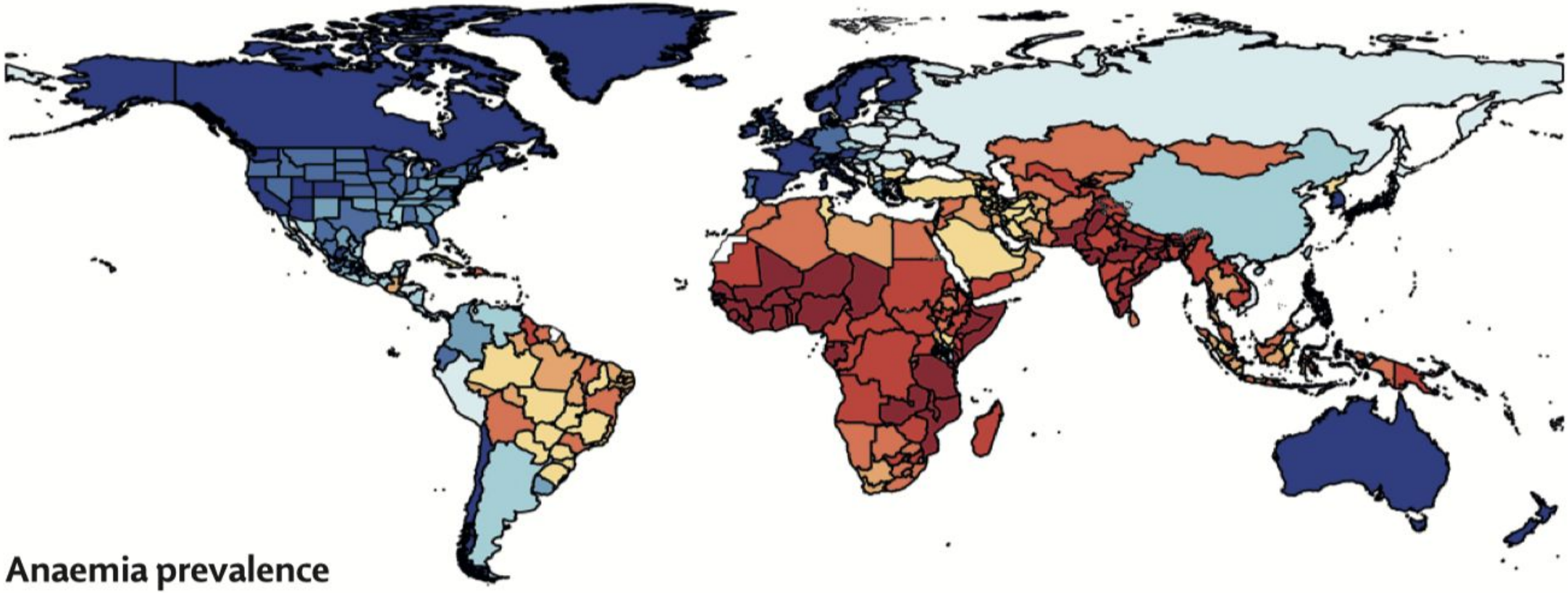
Conflicts

- Chiesi Farma
- Bristol Meyers Squibb
- Agios

Perhaps stating the obvious:

- ✔ **Anemia** can be defined as an insufficient circulating hemoglobin to meet tissue oxygen delivery requirements at rest and during stress or exercise.
- ✔ The pathological consequences of anemia depend on the severity of the hemoglobin deficit, the rapidity with which anemia develops, the duration of exposure to impaired oxygen delivery, and the underlying etiology of the anemia.
- ✔ Importantly, the diagnosis and the need for intervention are not determined solely by population-based statistical definitions of “normal” hemoglobin levels.

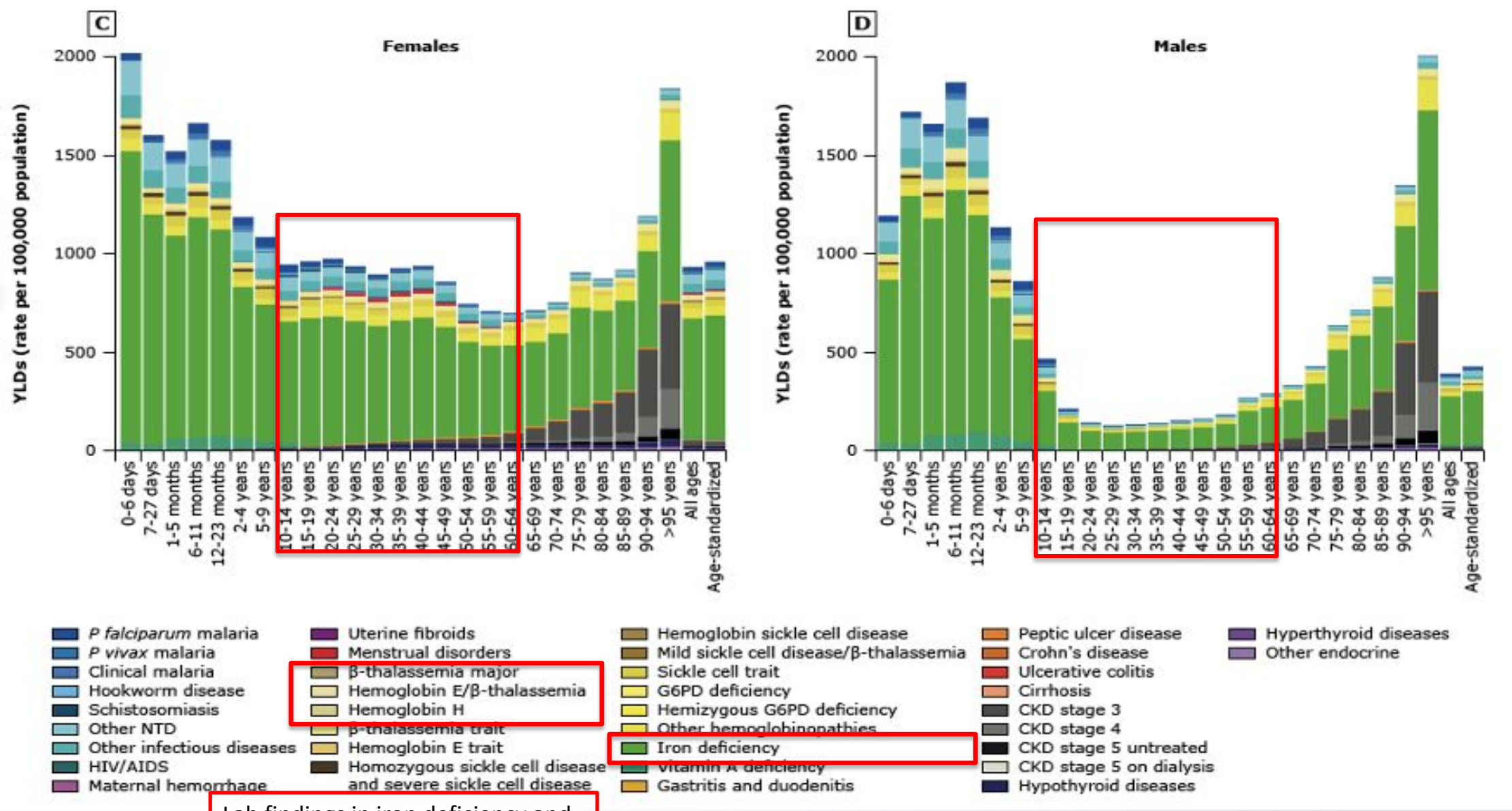
Worldwide prevalence of anemia



Global prevalence of anemia across all ages in 2021 was 24 %, corresponding to 1·92 billion cases,

GBD Anemia Collaborators, 2023 Lancet Heam 10(9) e713

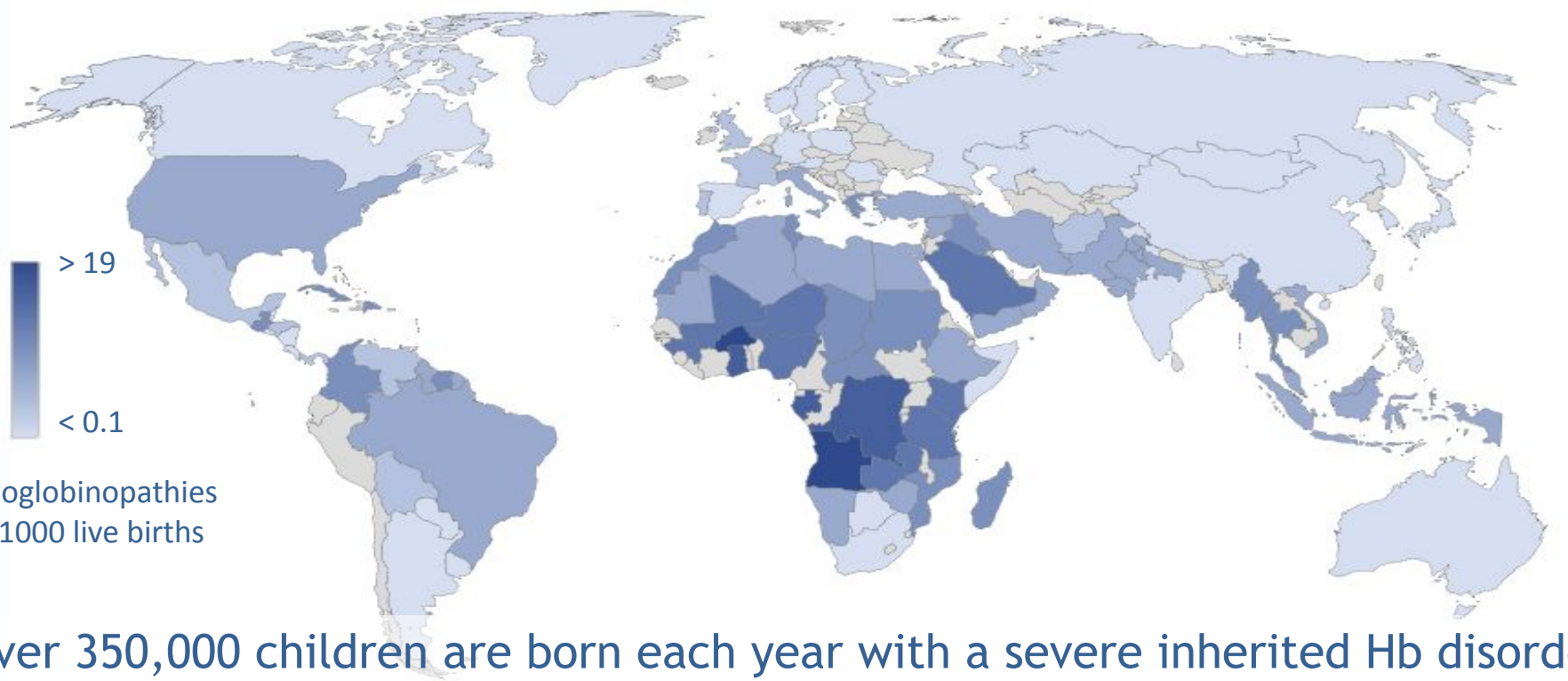
Years Lived with Disability (YLD)



Lab findings in iron deficiency and thalassemia can be similar

GBD Anemia Collaborators, 2023 Lancet Heam 10(9) e713

About 7% of the world's population has a significant hemoglobin variant

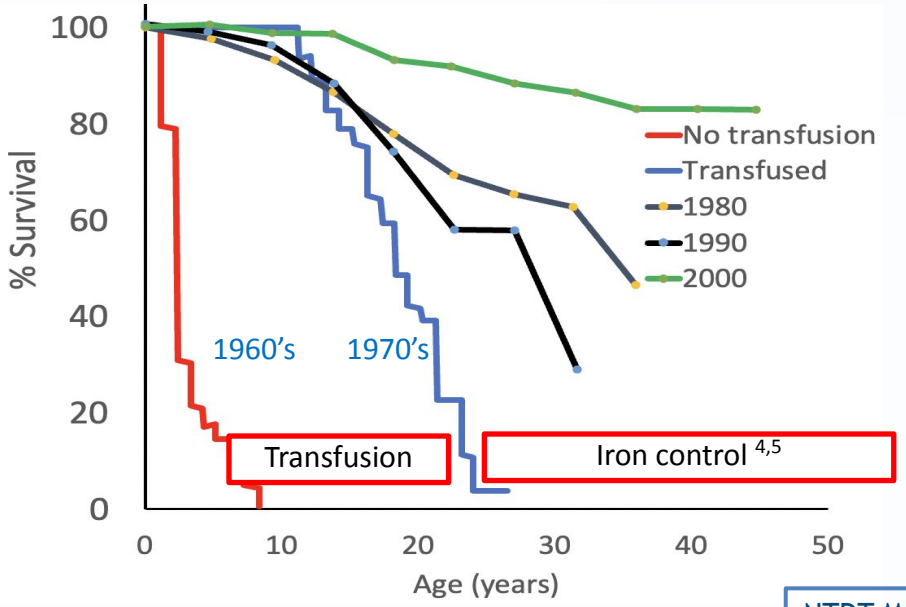


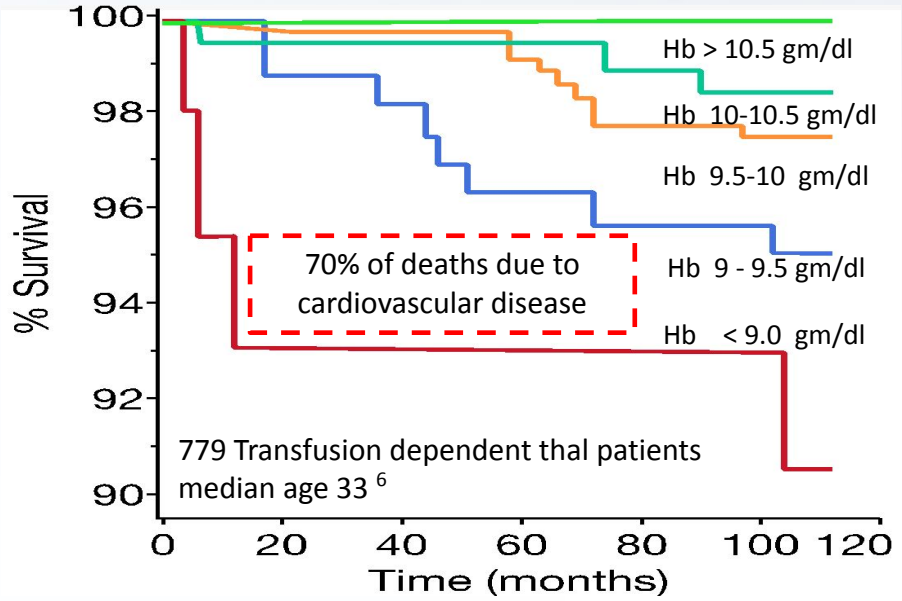
- Over 350,000 children are born each year with a severe inherited Hb disorder
- About 3 % of the world population is heterozygous for beta thalassemia.
- High prevalence of thalassemia in Southeast Asia, China, Indonesia, Mediterranean
- 75% of immigrants to the United States are from areas where thalassemia is prevalent

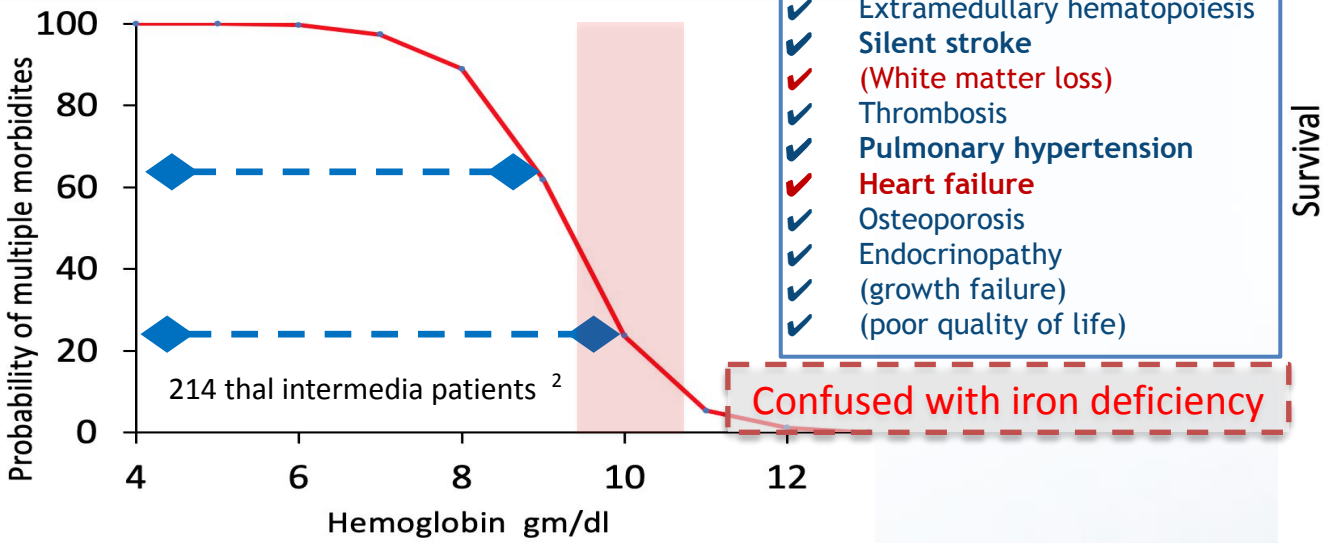
Weatherall DJ, 2010, Blood 115(22) 4331,
Piel FB 2016, Hematol Oncol Clin N Am30(2) 327

What can we learn about anemia from genetic disorders of hemoglobin ("human knock-outs")

Morbidity and survival in thalassemia is related to the degree of anemia

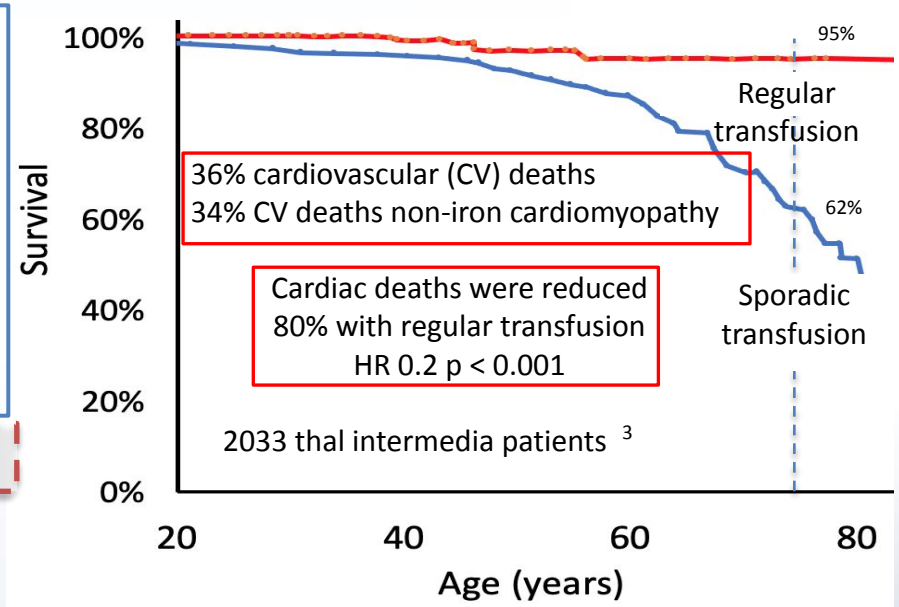






NTDT Morbidity
- ✔ Extramedullary hematopoiesis
- ✔ **Silent stroke**
- ✔ (White matter loss)
- ✔ Thrombosis
- ✔ **Pulmonary hypertension**
- ✔ **Heart failure**
- ✔ Osteoporosis
- ✔ Endocrinopathy
- ✔ (growth failure)
- ✔ (poor quality of life)

Confused with iron deficiency



1. Musallam KM, et al. Ann Hematol 2022 101(1):203; 2. Musallam KM, et al. Ann Hematol 2021 100(7):1903. 3 Musallam / Maggio et al 2021 Haematologica 106(9): 2489
4. Modell et a 2008 J Cardiovasc Magn Reson 10(1) 42 5 Modell 1984 6 . Musallam et al, 2024, Blood 143(10) ; 930-932. 7. Coates TD, 2024 Blood, 143(10), 884

Mild to moderate anemia over decades is not good

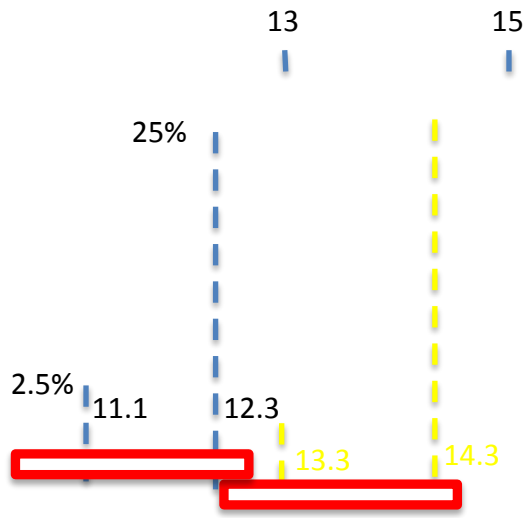
Kids can seem OK during 18 years of pediatric follow-up, but growth and exercise tolerance can be affected

Identification and diagnosis of genetic chronic anemia syndromes in childhood can have a significant effect on ultimate morbidity and survival

There is now treatment for mild thalassemia syndromes

What is the laboratory definition of “anemia”

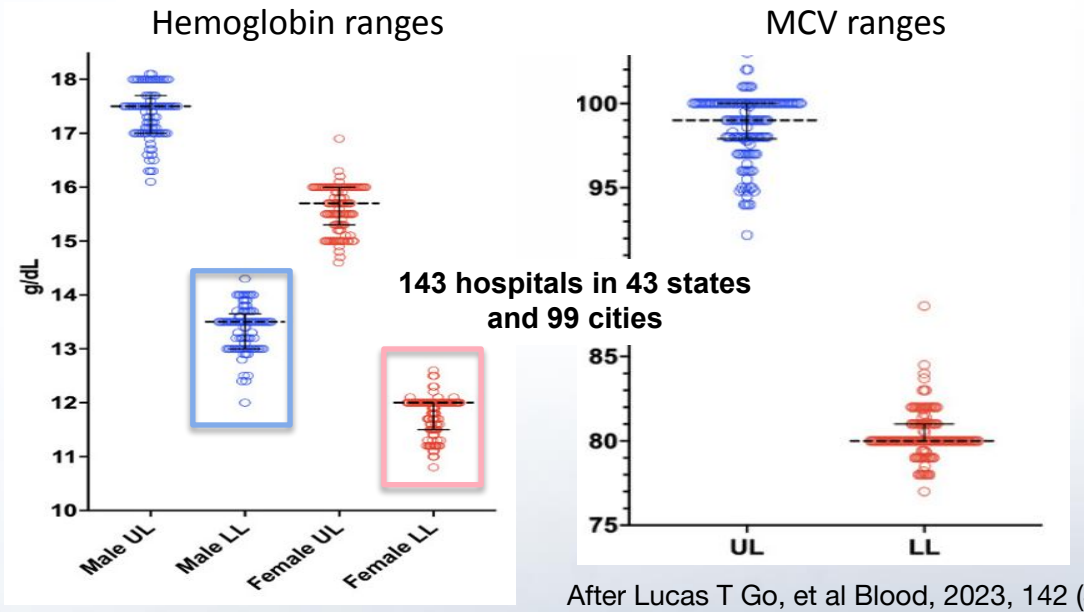
Age	Hemoglobin (g/dL)		Hematocrit (%)		MCV (fL)		RDW (%)	
	Lower limit	Upper limit	Lower limit	Upper limit	Lower limit	Upper limit	Lower limit	Upper limit
6 months to <2 years*	11.0¶	13.5	31	42	73	85	12.3	15.6
2 to 6 years	11.0¶	13.7	34	44	75	86	12.0	14.6
6 to 12 years	11.2	14.5	35	44	78	90	11.9	13.8
12 to <18 years								
Female	11.4	14.7	36	46	80	96	11.9	14.6
Male	12.4	16.4	40	51	80	96	11.9	13.7



Over 90% of the variability in hemoglobin is from non-hemoglobin genes

Use published ranges based on normal populations

”Normal ranges” are reset at each lab and can vary tremendously.



Powers, J Up To Date 2025 Anemia in children
Means R, Brodsky R UptoDate 2025 Anemia in adults

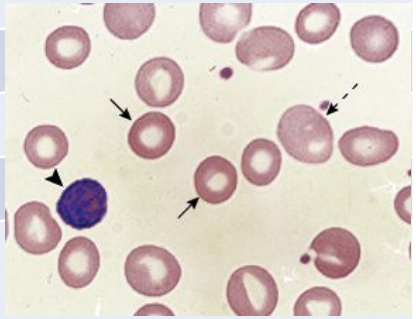
After Lucas T Go, et al Blood, 2023, 142 (Supp1):3701

Initial evaluation of anemia: History & Physical

	History/physical		
History	Jaundice	Requiring lights in NICU, intermittent with illness, family Hx	Possible hemolytic disease
	Unusual diet, excessive milk intake, pica, weight loss	How much milk/day	Dietary causes rare > 3 yo.
	Previous history of anemia, transfusion,		
	Diarrhea, constipation, abdominal pain, arthritis	GI and rheumatologic disorders can present as anemia	Crohn's, celiac disease, IBD May have no GI sx
	Pallor, fatigue, headache, bruising, blood loss	Duration, onset, other acute viral illness, Heavy periods patient or mom Specifically ask about mucosal bleeding	Possible blood loss, marrow suppression from virus
	Family history of anemia, cholecystectomy, splenectomy	Ask about ~~malignancy~~ serious illness or deaths in family < 50 yo.	Hemolytic disease, familial cancer or anemia.
Physical	Growth failure, dysmorphia, developmental delay	Genetic anemias can have dysmorphia	Bone marrow failure
	Presence of scleral icterus		
	Palpable spleen		Hemolytic disease

Initial evaluation of anemia: Lab data

		Comments
Phase I studies	Hemoglobin (Hb) g/dL	Venous sample is best for all CBC values. Serial monitoring can be very helpful,
	Hematocrit (Hct)	Is 3 x the hemoglobin level. Calculated, not measured.
	Red cell count cells x 10^9/dL	Relatively high in thalassemia, correlates with Hb otherwise.
	Reticulocyte count %	Should be done anytime CBC is done for anemia
	Reticulocyte count abs	Should be done anytime CBC is done for anemia
	Mean cell volume (MCV)	High in DNA synthesis issues, low in iron deficiency and thalassemia Normal MCV rules out almost NOTHING
	Mean Cellular Hb concentration (MCHC)	MCHC/MCV > 0.36 suggests spherocytosis (>97% sensitive, specific, and negative prediction :PMID 26009624)
	Blood smear	Not that helpful, especially in newborns, even with path review.
	Sedimentation rate and CRP	Inflammation affects CBC and iron studies. Marker for systemic disease
Selected Phase II	Iron	Acutely drops with fever, acutely increases with iron ingestion
	Transferrin saturation	Marker for available iron. Acutely drops with inflammation, increases in hours after oral iron
	Total iron binding capacity	Elevated with iron deficiency, normal with chronic inflammation
	ferritin	Very low ~ iron deficiency, increased by inflammation,
	Methylmalonic acid, homocysteine	Most sensitive markers of B12 and folate deficiency
	Hemoglobin electrophoresis	Hb A2 elevated in β-thal, normal in α-thal.
	Pre-GI referral studies	Stool calprotectin, H-pylori-DAA, (occult blood).



Hematological characteristics of thalassemia

			-2 α-genes	-3 α-genes (H)		
	Normal	Iron deficiency	β thal trait	β trait α-triple	β thal intermedia	β thal major
RBC	4.5	3.2 ↓ MI=20	6.5 ↑↑	5.6 ↑↑	5.6 ↑↑. MI=11	5.1 ↑↑
Hb	14	8.5 ↓↓	10.5 ↓	8.5 ↓↓	8.5 ↓↓	6.0 ↓↓↓
Hct	42	25.5	31.5	25.5	25.5	18
MCV	85	69 ↓↓	66 ↓↓↓	66 ↓↓↓	66 ↓↓↓	66 ↓↓↓
Fe Saturation	35	9 % ↓↓	35	50	60 ↑	80 ↑↑↑
TIBC	300	512 ↑	300	250	250	250
Ferritin	50	8 ↓↓	50	200 ↑	250 ↑	1000 ↑↑
Hb A2	0	0	6%↑ (β-only)	6% ↑ (β-only)	6% ↑	6% ↑
β gene	normal	normal	β hetero	β hetero	β^+/β^+ or + Hb E etc	β^0/β^0
α genes	4	4	4 (-2 α-trait)	> 4 (1 α HβH)	4	4

Screen for thalassemia: First: RBC, Hb, Hct, MCV, Hb Electrophoresis (Hb A2), Fe, TIBC, Saturation, ferritin Second: β-gene analysis (thal mutations, HbE, S other abnormal hemoglobin), α-gene duplication assay

Mentzer index (MI)
MCV/RBC < 13 ~ thal

α or β thalassemia trait never results in a hemoglobin < 10 mg/dl

If both parents are significantly microcytic, α and β gene analysis is critical

Let’s go over on some scenarios related to anemia that might be encountered in general practice.

Anemia with severe microcytosis in a Chinese girl

Tiffany is a 3 yo girl of Chinese descent born in China who comes to you for pallor noted by mom. She is clinically doing very well but is drinking 32 oz of milk a day. Mom is a 32 yo G2 P1 A1 who has always been told she has iron deficiency. She had a spontaneous abortion at 24 weeks in China. Dad has been told he is iron deficient as well. You started oral iron and told mom to decrease milk consumption.

WBC	5.75
HGB	9.3 (11.5-14)
RBC	6.3. (4.0 – 5.3)
MCV	59 (78-96)
Plts	550
Retic	56.9 (1.3%)
ESR	10
Bili	0.5
Fe	27
Sat	5%
TIBC	520
ferritin	5 (12-90)

- ☒ Counsel mom this is only iron iron deficiency from too much milk
- ☒ Get hemoglobin electrophoresis, it is likely just thal-trait
- ☒ This is likely thalassemia major and will require transplant
- ☐ Refer to heme because of recurrent low iron
- ☐ Request focused exome for iron genes
- ☒ Request CBC results from Mom and Dad to look at the MCV & RBC
- ☒ Continue oral iron
- ☐ Start aspirin because of high platelets

If both parents are microcytic, you must do α-globin gene analysis on both parents
If both parents have a CIS-2-gene α deletion, there is 1:4 chance of hydrops fetalis

3-8% South China

Newborn with elevated bilirubin and reticulocytosis

A 3 day old 38-wk gestation female was noted to be jaundiced by the parents and was seen by the pediatrician. Labs showed elevated total bilirubin and mild reticulocytosis and the child was placed on phototherapy. There was no ABO setup and DAT was negative. The father had an episode of jaundice with mononucleosis as a teenager and had his gall bladder removed at age 36.

	3 days
WBC	15000
HGB	14
RBC	4.1
MCV	90
MCHC	35
MCHC/MCV	0.38 (NL < 0.36)
Plts	320
Retic	6.1%
ABS retic	246 (100-300)
Bili	19
Smear	No spheres, "bite cells", schistocytes.

Likely hereditary spherocytosis

- ☒ Immediate Red cell enzymes, ~~osmotic fragility,~~ hemoglobin electrophoresis, EMA binding, RBC-gene analysis
- ☒ follow serial CBC, retic, bili, **feeding & growth**
- ☒ Refer to heme if persistent reticulocytosis, recurrent jaundice
- ☒ Request focused exome for RBC defects
- ☒ This is not spherocytosis as no spheres were seen on smear
- ☒ Counsel patients RE anemia/jaundice with viral illness as there may be an underlying hemolytic disorder.
- ☒ Email your friendly neighborhood hematologist re additional labs to order in preparation for heme consult

The trajectory of the Hb and retic helps us determine how far to go with fancy tests.

Possible iron deficiency no anemia

Johnny is a 12-year-old boy who is being followed for a number of issues including a neurological movement disorder. His parents, questioned a possible relationship between some of his problems and iron deficiency. He was noted to have low transferrin saturation, and lowish ferritin, indicative of iron deficiency. (Peterson B 2006 ; PMID 16816233)

He has a normal diet. There is no history of easy bruising, epistaxis, melena, or other bleeding diatheses, no GI complaints.

WBC	5.75
HGB	12.8 (12-15)
MCV	82 (78-96)
Plts	243
Retic	1.3% (abs 56.9)
ESR	10
Bili	0.5
Fe	54
Sat	15%. (> 20%)
TIBC	361
ferritin	18 (12-90)

- ☐ Do nothing, there is no anemia or iron deficiency
- ☐ Do nothing, iron for movement disorders is controversial
- ☒ Refer to heme because of recurrent low iron
- ☐ Request focused exome for iron genes
- ☒ Do GI workup for causes of iron loss (FOB, calprotectin, Hpylori DAA)
- ☒ Continue oral iron
- ☐ Give IV iron

Hb increase with iron administration indicates iron deficiency

Anemia with high iron and low retic in a toddler

Mary is a 3 yo Caucasian female who had a mild febrile illness a month earlier and a CBC was done. She was asymptomatic but was noted to be have a hemoglobin somewhat lower than usual, so a follow up CBC was done two weeks later, and the hemoglobin had dropped, but she was clinically well with normal exam except pallor.

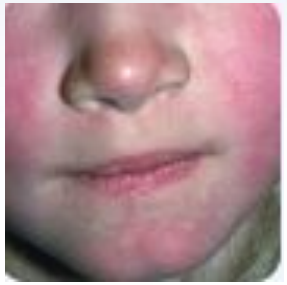
		+ 3 weeks
WBC	5.75	5.3
HGB	10.0	7.6
MCV	94 (78-96)	96
Plts	243	251
Retic	0.0%	0.01 %
ESR	15	11
Bili	0.5	.9
Fe	54	65
Sat	55%. (< 50)	70 %
TIBC	361	310
ferritin	80 (12-90)	200

- ☒ Do a bone marrow aspirate looking for nuclear inclusions
- ☒ Check parvovirus B19 PCR
- ☑ Continue to monitor CBC and retic
- ☐ Refer to heme because of high iron
- ☐ Request focused exome for iron genes and RBC defects causing hemolysis
- ☐ Do workup for causes of iron overload
- ☐ Continue oral iron
- ☒ Give IV iron
- ☐ Transfuse

Transient erythroblastopenia of childhood (TEC)

Anemia in a 6 yo with parvovirus infection

Julio is a 6 yo boy who had a low-grade temp in the office when his mom brought him in for a rash on his face. You diagnosed fifth disease (erythema infectiosum), told the mom not to worry, got a parvovirus B19 PCR, and asked mom if he had been near pregnant women. He was not pale. Eight days later he was back and was very pale and fatigued but had no other symptoms.



WBC	5.75
HGB	4.5
MCV	89
MCHC	35
Plts	243
Retic	0.1 %
ESR	16
Bili	3.5
Fe	54
Sat	50%
TIBC	361
ferritin	100 (12-90)
B19 PCR	> 100,000 copies

MCHC/ MCV 0.39

- ❑ Transfuse and follow CBC, this is likely TEC (transient erythroblastopenia of childhood)
- ☒ Give acyclovir
- ☒ Obtain detailed history: ? neonatal jaundice, ? family history of gall stones
- ☒ Test for reduced eosin-5'-maleomide (EMA) binding to band 3 for spherocytosis.
- ❑ Request focused exome for genes associated with anemia.
- ☒ Do GI workup for causes of iron loss (FOB, calprotectin, Hpylori DAA)
- ☒ Hematology consult for bone marrow before giving steroids
- ☒ Give IV iron

Hereditary spherocytosis

Significant Hb drop post infection suggests underlying hemolytic disorder

Failure to thrive and developmental delay

Tommy is a 9-mo exclusively breast fed male evaluated by a CHLA hematology grad in a neighboring state for significant FTT and only 4 months development at 9 mo of age. Mild leukopenia and thrombocytopenia but otherwise unremarkable CBC with no macrocytosis. Colon biopsy showed flattened villi but B12 was normal. He was given IM B12 and sent by car to CHLA heme for admission and a second opinion.

	CHLA day 1 9mo
WBC	4.00
HGB	10.0 (12-15)
MCV	89 (78-96)
Plts	100
Retic	1.3%
LDH	2500 (<950)
Bili	3.1
Fe	107
Sat	80%
TIBC	182
ferritin	159 (12-90)
Dev age	4 mo
B12	[240] Normal

- ☒ This not related to B12, no macrocytosis and B12 level normal
- ☐ Consult oncology because of low plts and high LDH
- ☐ Get a brain MRI and neuro consult because of development
- ☐ Request focused exome for iron genes because of iron overload
- ☒ Get methylmalonic acid, homocysteine levels STAT and consider gene analysis of B12 pathways
- ☒ Continue parenteral B12 or hydroxy cobalamin supplementation
- ☒ Start iron chelation

He has severe B12 deficiency
We subsequently diagnosed pernicious anemia in his Mom.

Complex chronic anemia

Juan is a 9-year-old male who is noted by mom to be less active than usual. Has had some aphthous ulcers and non-specific joint pains. He had a hemoglobin of 9.0 g/DL and was started on oral iron in the ER several months ago when he was seen for abdominal discomfort. He has no diarrhea or blood in the stool, and in fact is a bit constipated. He has lost some weight since his ER visit.

WBC	5.75
HGB	9.0 (12-15)
MCV	82 (78-96)
Plts	400
Retic	56.9 (1.3%)
ESR	40
Bili	0.5
Fe	32
Sat	13%
TIBC	250
ferritin	60 (12-90)

- ❑ Continue him on oral iron, he is just a picky eater
- ❑ ✗ Reassure mom his abdominal pain is from the oral iron and try a different oral preparation
- ❑ ✓ Refer to heme because of nonresponse to iron
- ❑ Request focused exome for iron genes
- ❑ ✓ Do workup for GI causes of iron loss (FOB, calprotectin, Hpylori DAA) in preparation for referral to IBD clinic.
- ❑ ✗ Give him steroids because his ESR is high
- ❑ ✓ Give IV iron

He has inflammatory anemia AND iron deficiency
He also has B12 deficiency with normal serum B12

The future is bright for patients with chronic anemia.

- Gene sequencing is clinically available to establish diagnoses
- Marrow transplant cures many chronic anemias
- Gene therapy for sickle cell and thalassemia is now FDA approved and ongoing at CHLA
- Pyruvate kinase activators are now approved and show great promise in many anemias including thalassemia intermedia and sickle cell disease.
- Drugs that target iron regulatory genes show promise for chronic inflammatory anemia
- There are active research studies ongoing at CHLA in hematology and cardiology related to physiology and treatment of chronic anemia.

Quaerite Veritatem:

Seek the Truth

(And stay as far away as possible from those who think they have found it…)

Thank you for your attention

α- thalassemia severity is correlated with the number and type of affected alleles[1]

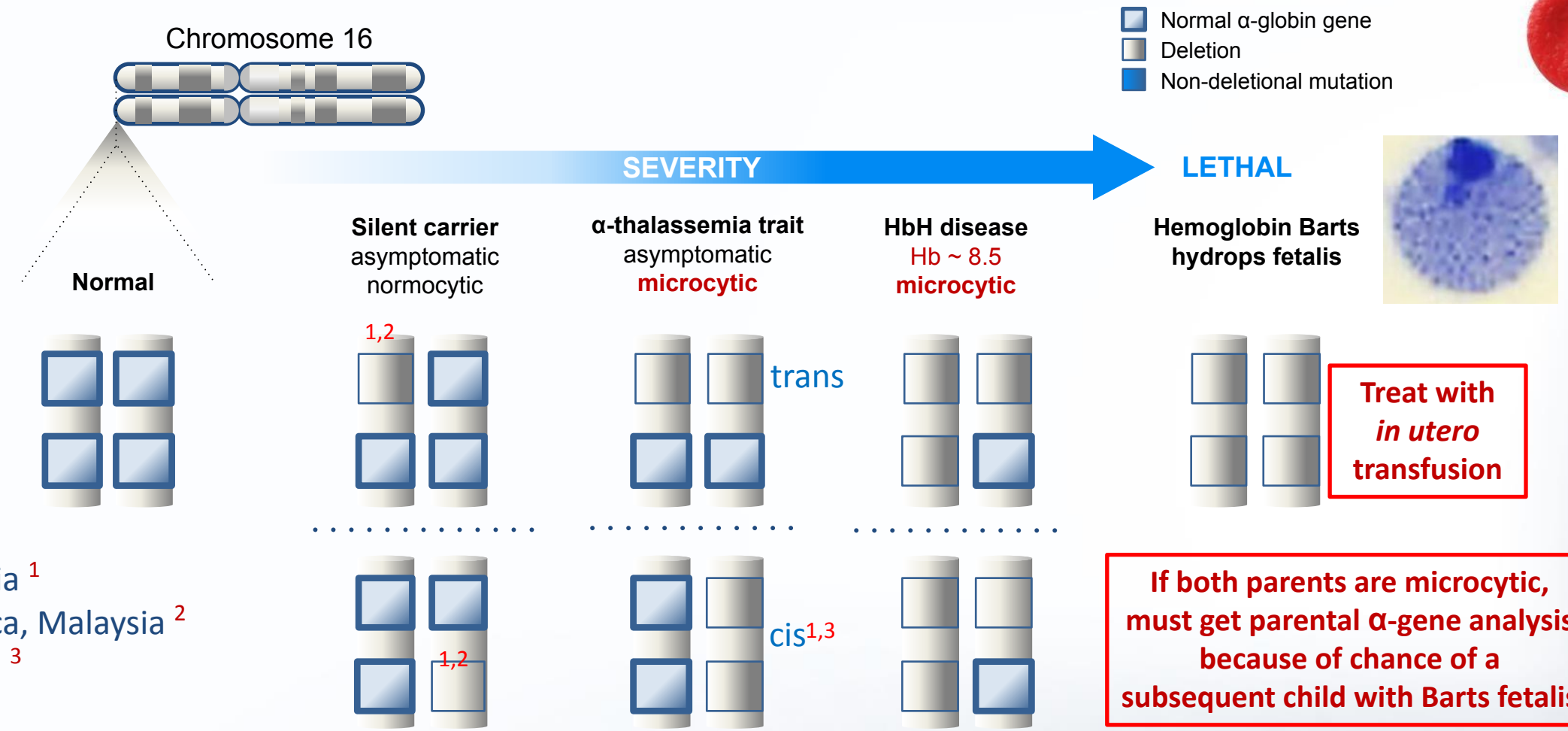


Figure adapted from Piel FB et al. *N Engl J Med*. 2014;371:1908–1916.

Hb-Barts and Hb-H do not release oxygen

Adapted from α-thal working group (ATWG) educational resource, 2023, Al-Samkari, Capellini, Coates, Kuo, Musallam, Sheth, Taher, Viprakasit