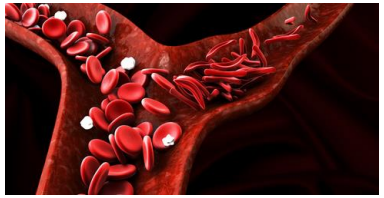
Challenges in treatment/drug development from a clinicians' perspective with regards to study design and endpoints used in clinical trials for management of paediatric sickle cell disease

Raffaella Colombatti, Mariane De Montalembert

European Haematology Association



July 1 st 2024, EMA Workshop

EMA
EUROPEAN MEDICINES AGENCY

EPIDEMIOLOGY

Rare Disease

UK 0.47:1000 births

Belgium 0.43:1000 births

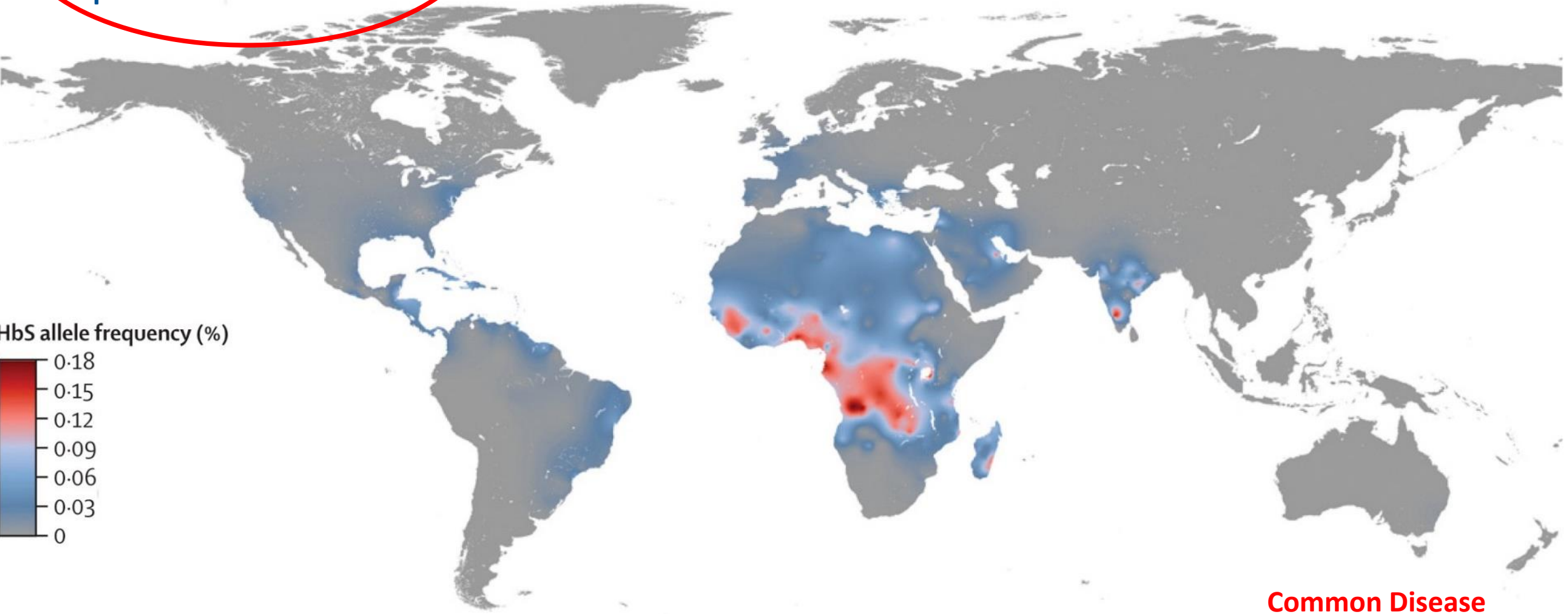
Spain 0.03-0.18:1000 births

Overall

100000 in the US

>60000 in Europe

60000-100000 Brazil



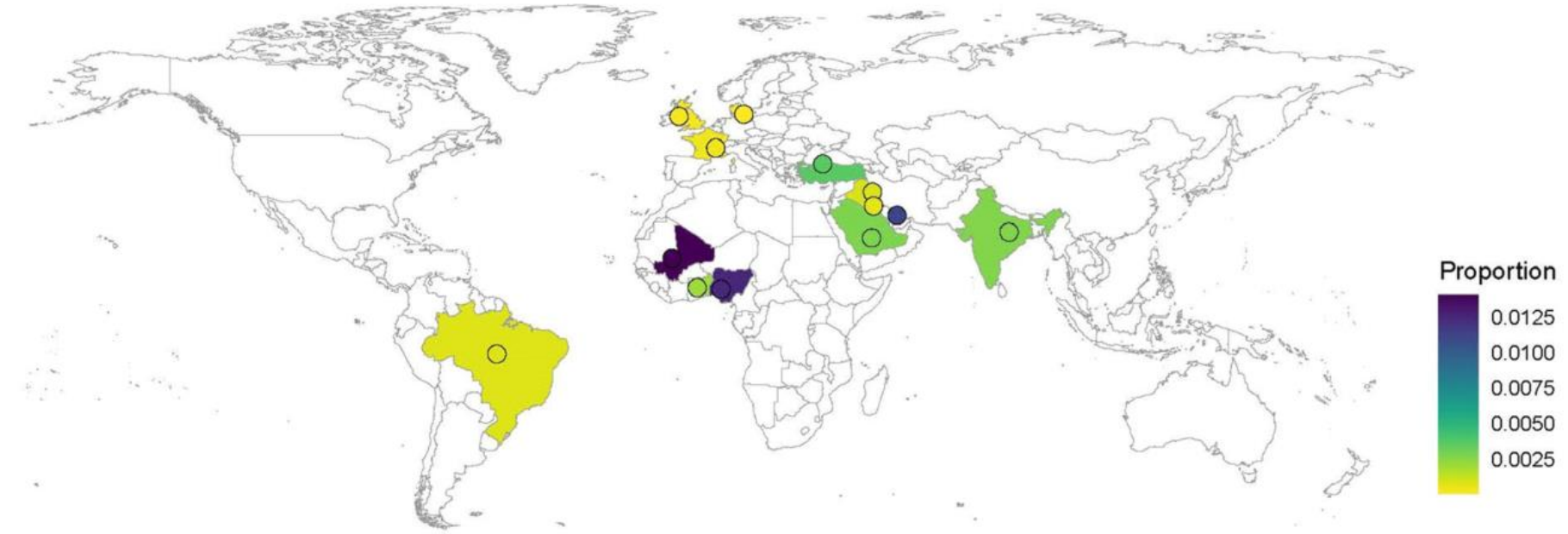
Common Disease

Ghana 18:1000 births

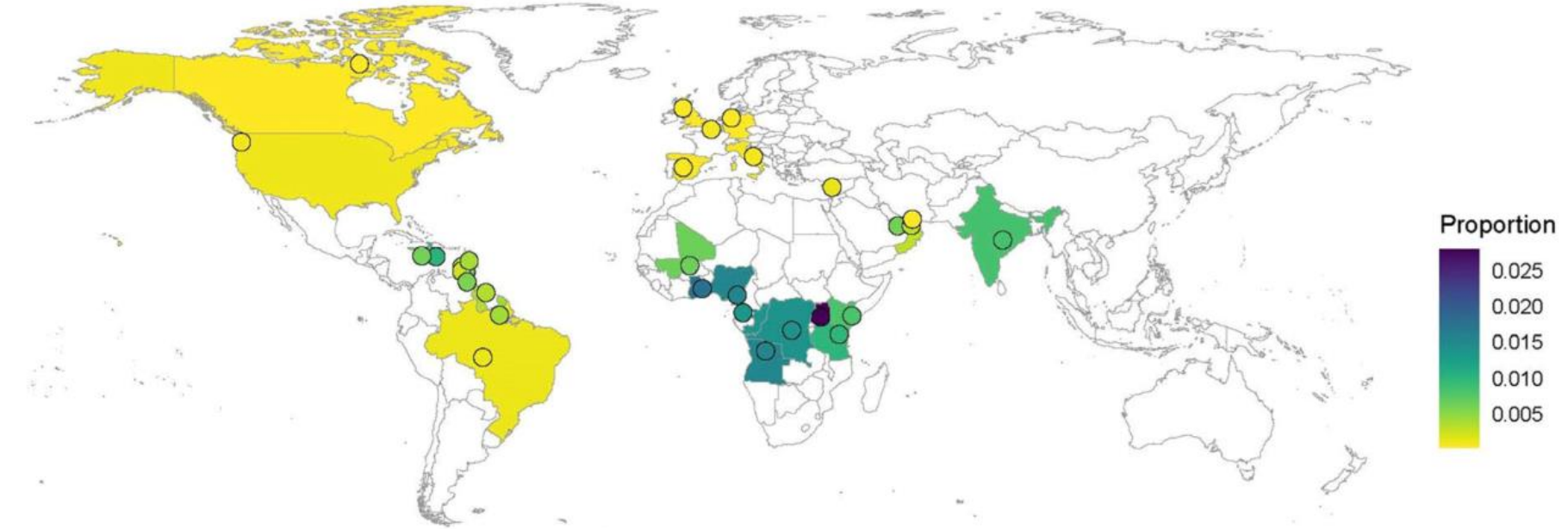
Tanzania 8:1000 births

Piel FB et al, Lancet 2013;381(9861):142-51; Le PQ et al. J. Med. Screen. 2018, 25, 57–63; Cela E et al. Pediatr Blood Cancer 2017. 64: e26322; M García-Morín et al.Annals of Hematology (2020) 99:1465–1474; Nkya S et al. Int Health. 2019;11(6):589-595; Segbefia CI et al. Pediatr Blood Cancer. 2021 Apr 23;e29068.
https://www.gov.uk/government/publications/sickle-cell-and-thalassaemia-screening-data-report-2018-to-2019

Prevalence of sickle cell disease (SCD)



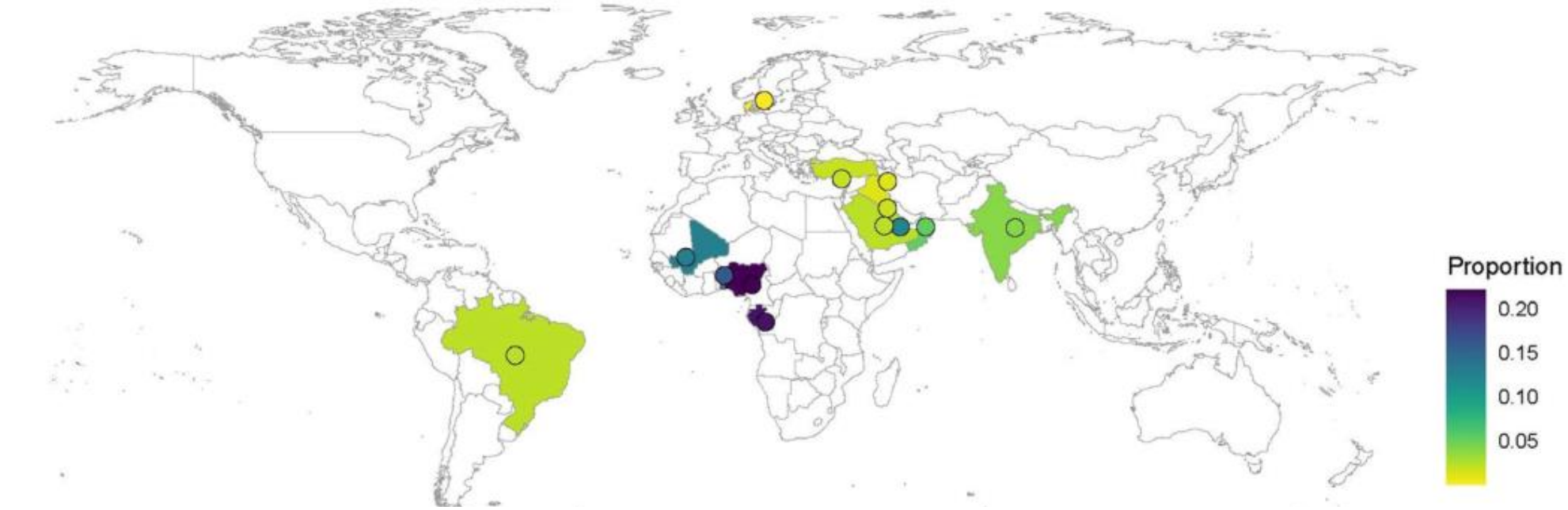
Birth prevalence of sickle cell disease (SCD)



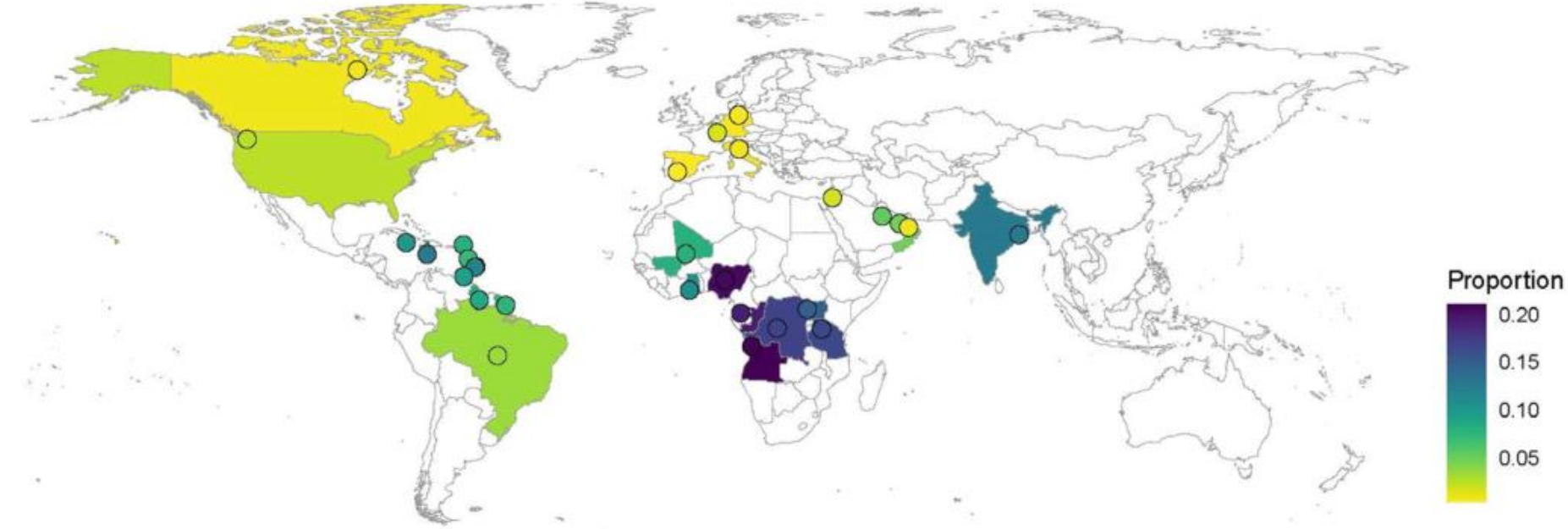
LACK OF DATA → EU-ERN-EHA iniciatives ongoing and scaling up on standardized data collection

Colombatti R, et al. Systematic Literature Review Shows Gaps in Data on Global Prevalence and Birth Prevalence of Sickle Cell Disease and Sickle Cell Trait: Call for Action to Scale Up and Harmonize Data Collection. J Clin Med. 2023 Aug 25;12(17):5538.

Prevalence of sickle cell trait (SCT)



Birth prevalence of sickle cell trait (SCT)



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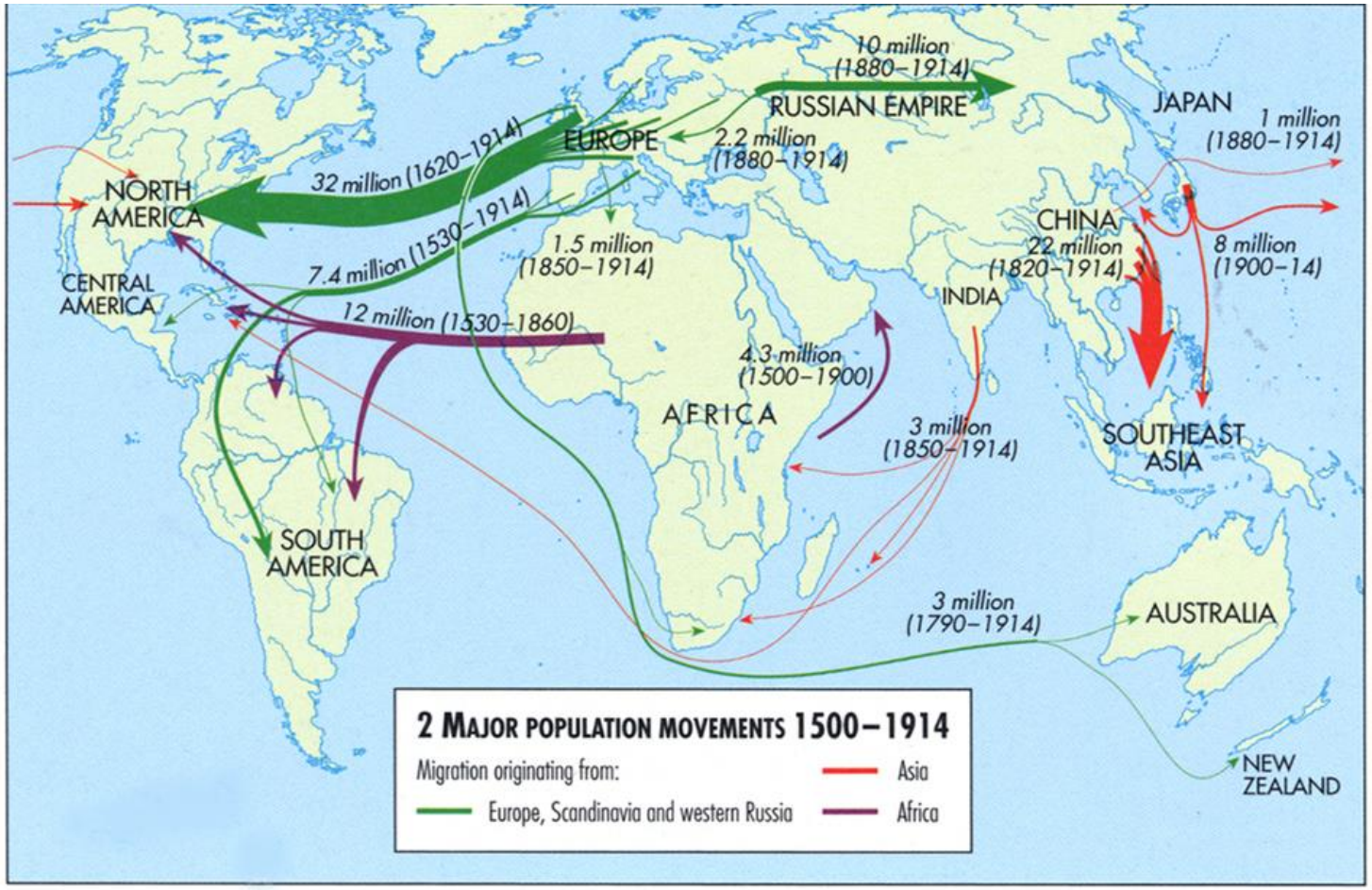
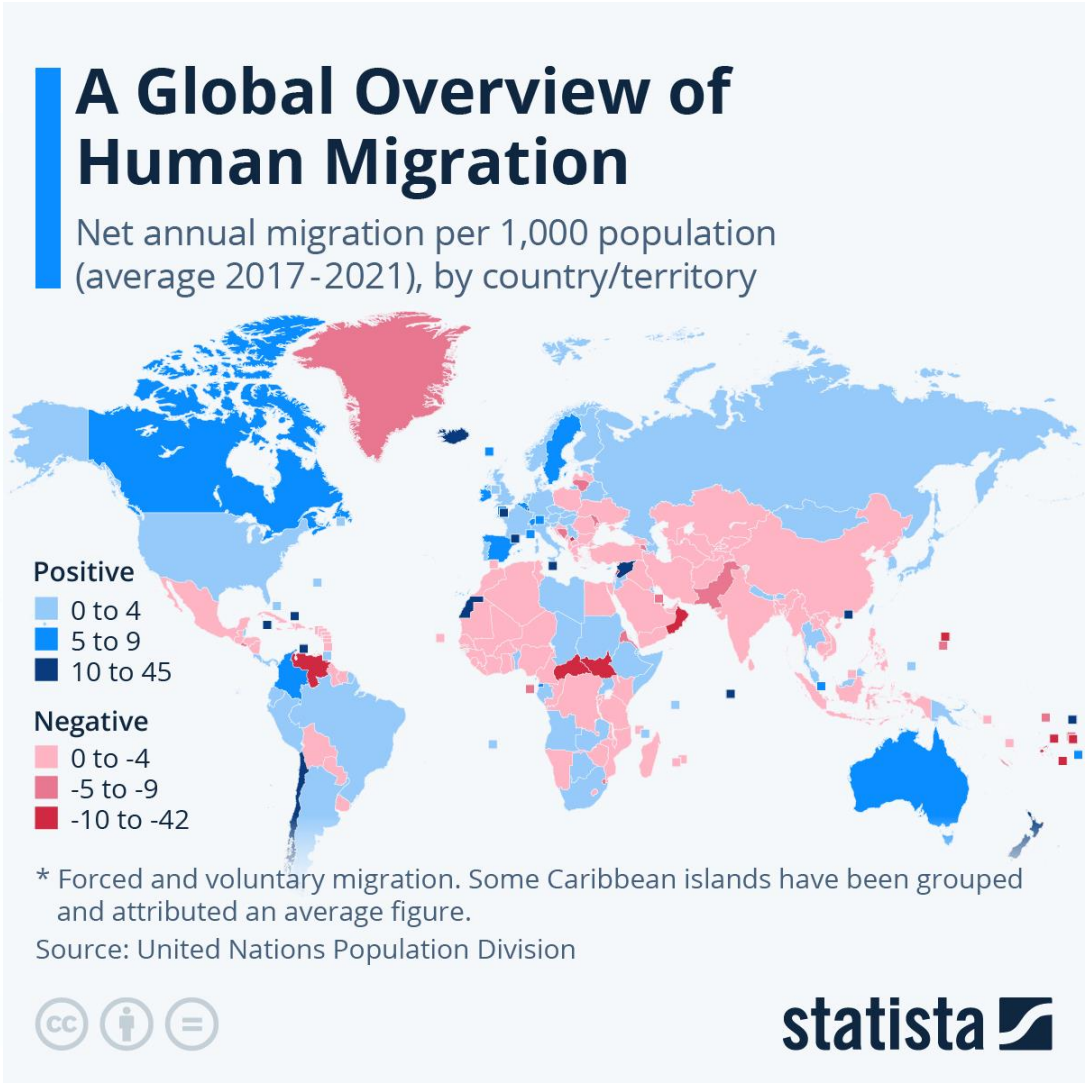
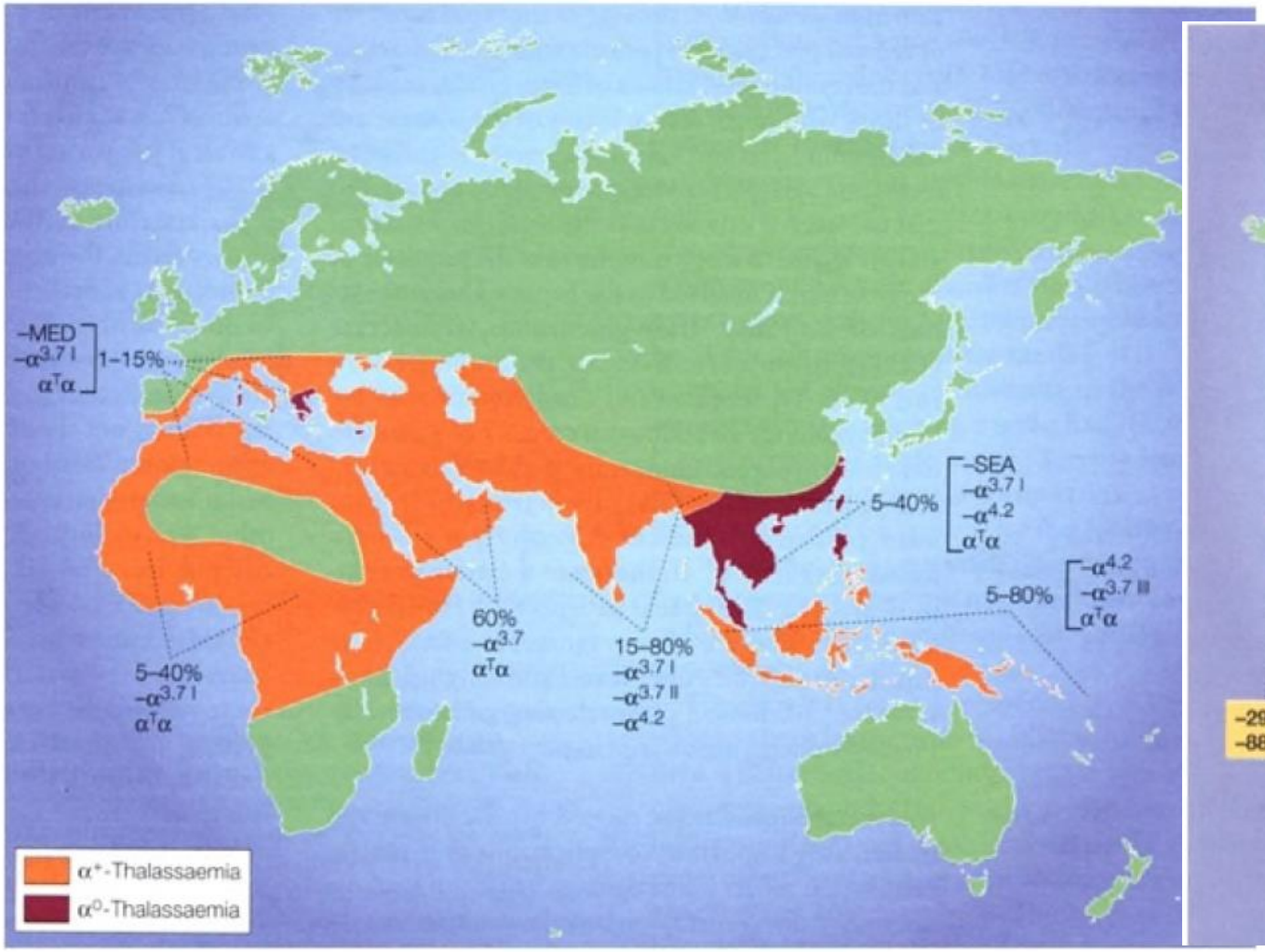
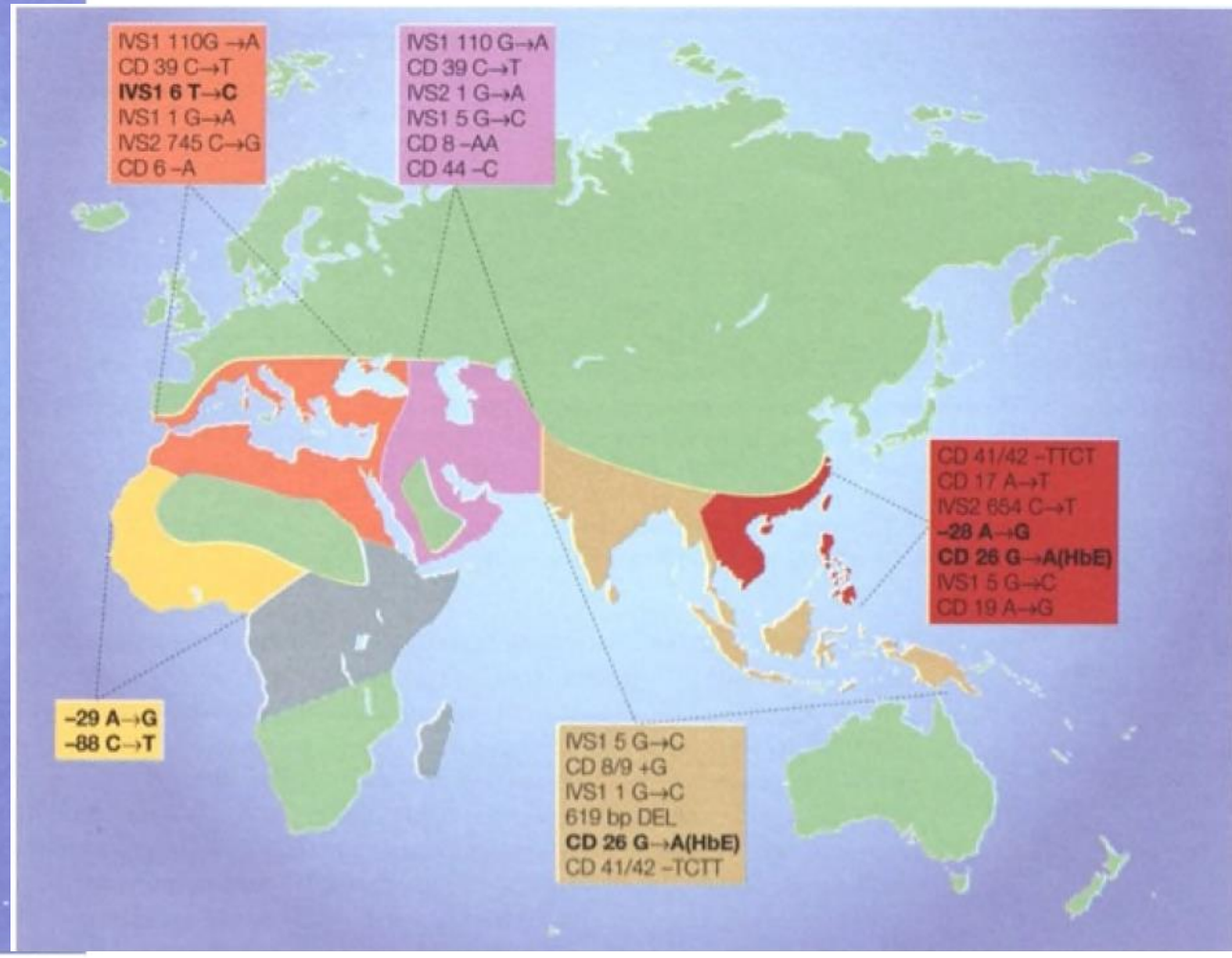
Global Population Movements





From a Global Perspective:
Thalassemia distribution is different in the various areas of the world—>impact on SCD

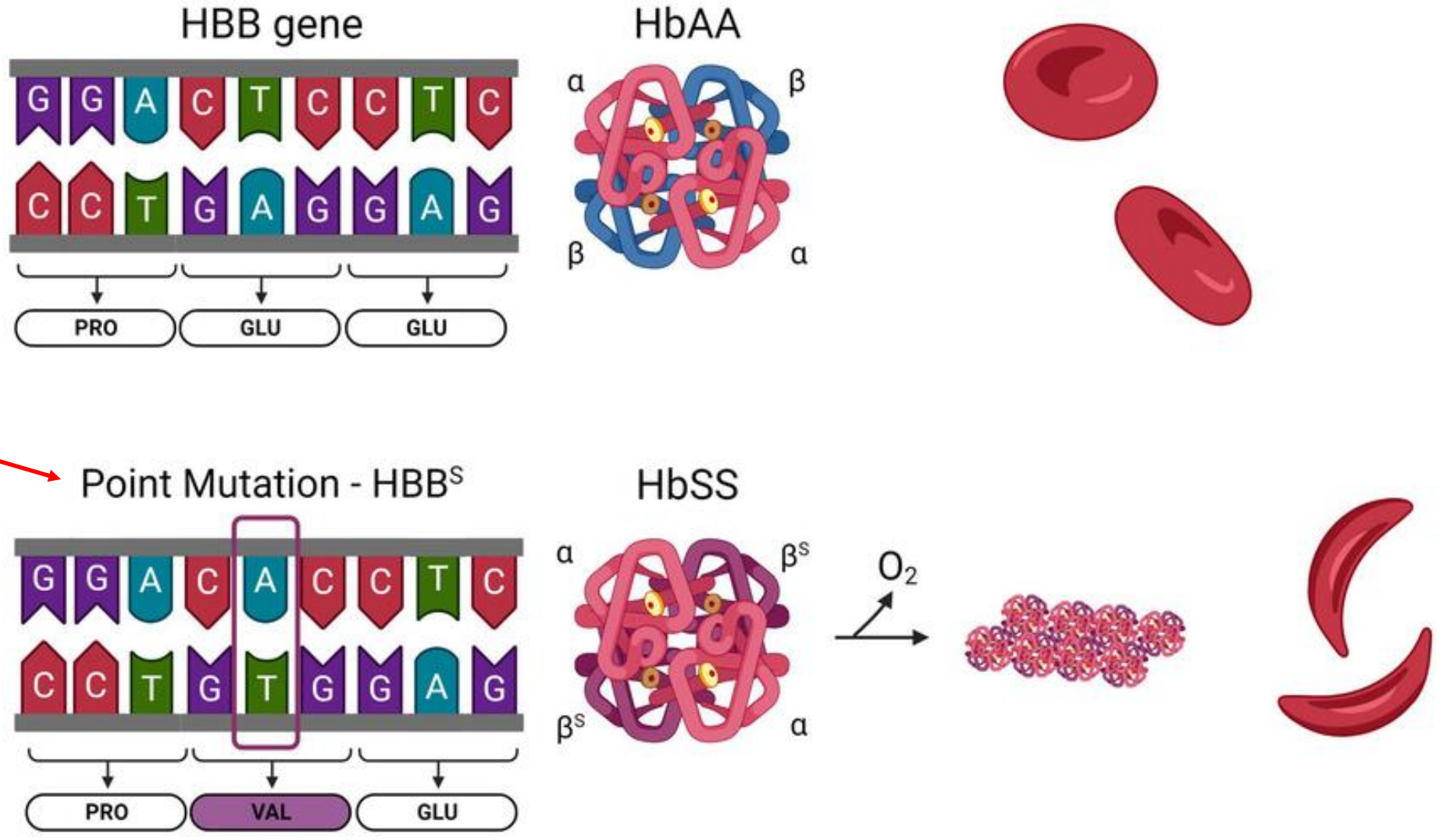




Approximate distribution of α (left) and β (right) Thalassemias

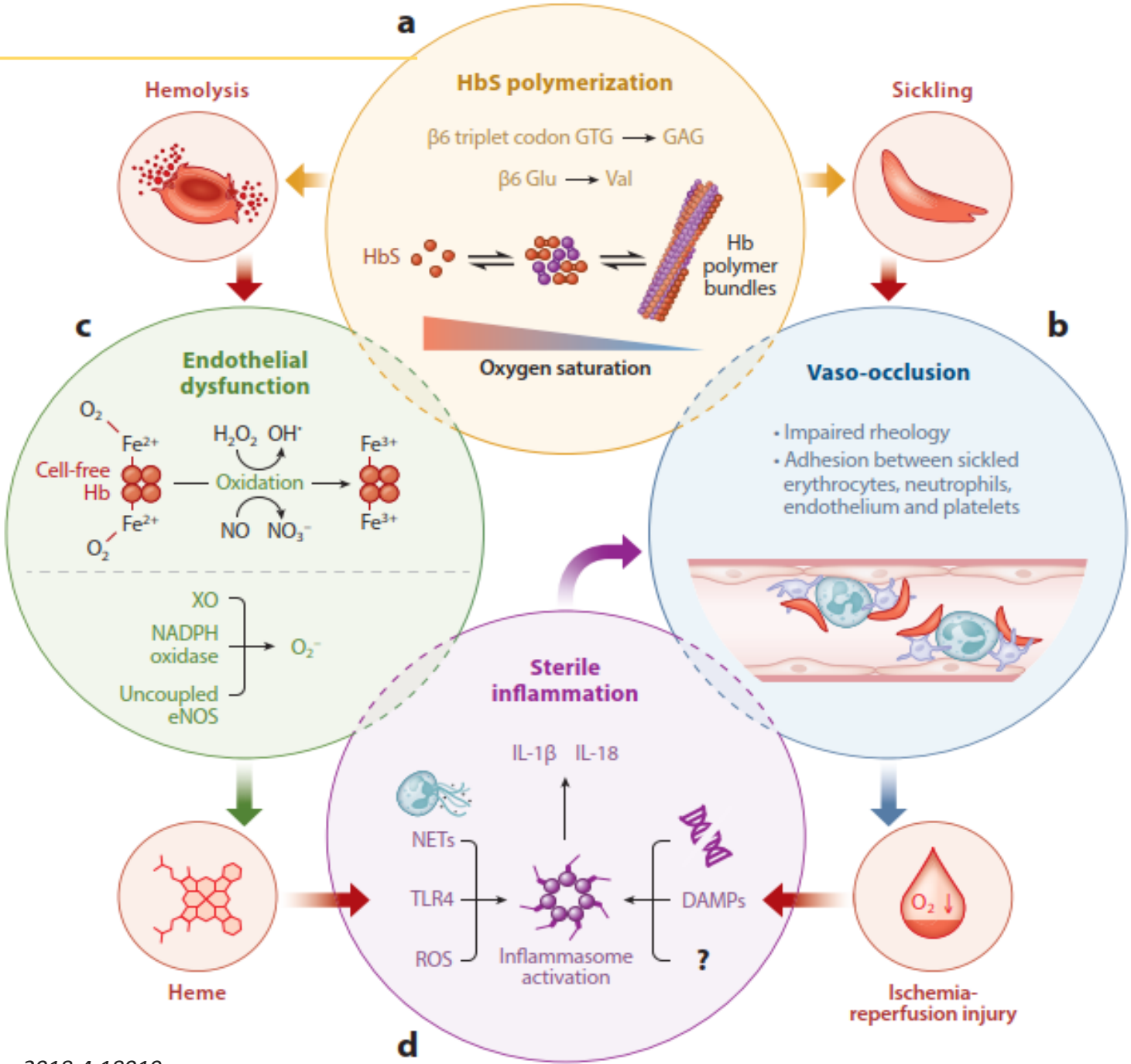
Weatherall DJ. The Evolving Spectrum of the Epidemiology of Thalassemia. Hematol Oncol Clin North Am. 2018 Apr;32(2):165-175

PATHOPYSIOLOGY
and
PHENOTYPIC VARIABILITY



Ramadas N et al Frontiers in Medicine 2024

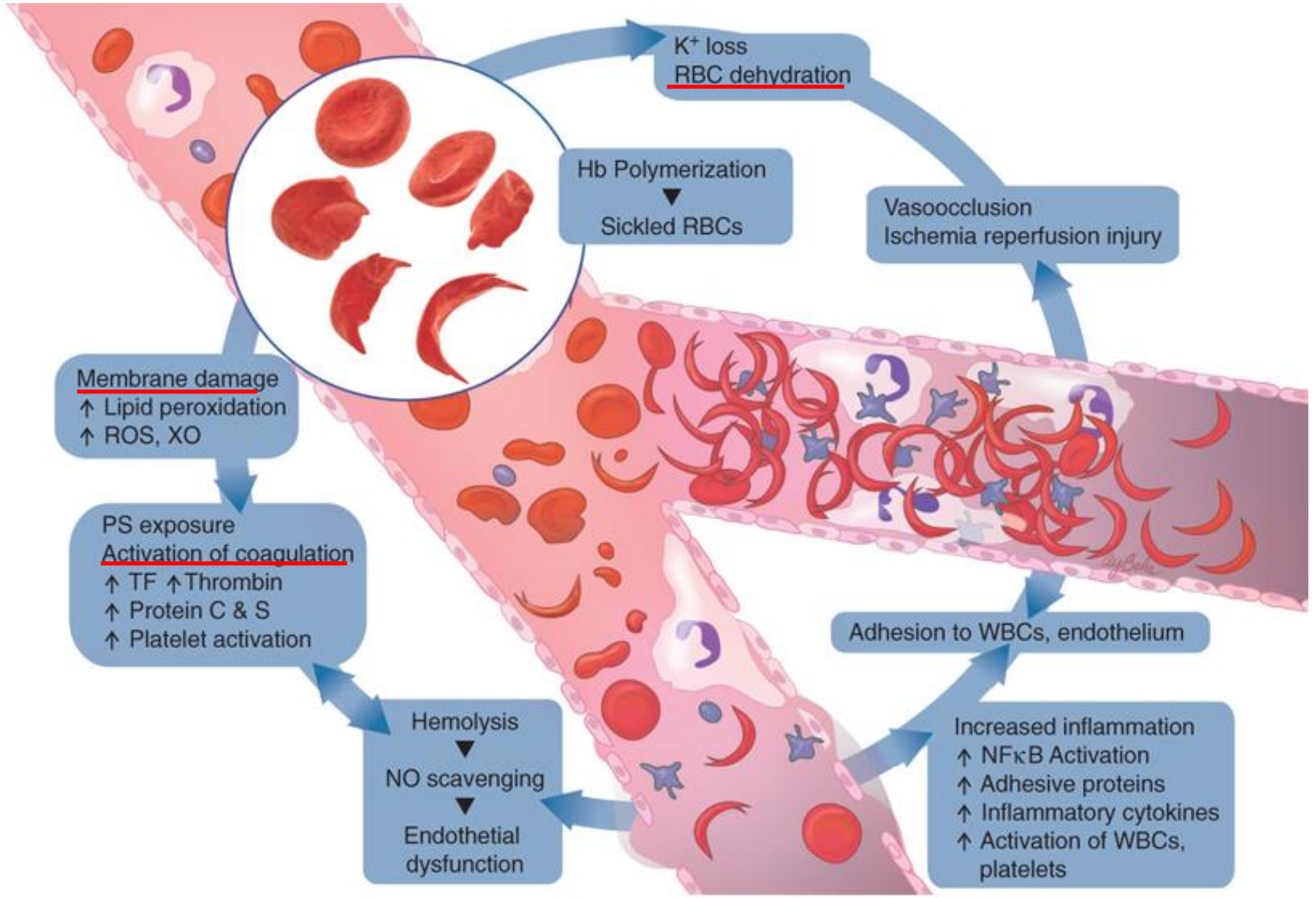
HbSS, HbSβ°
HbSC, HbSβ+
HbSD, HbSE, HbSOArab



Sundd P et al. Annu Rev Pathol. 2019;14:263-292; Kato GJ. Nat Rev Dis Primers. 2018;4:18010.

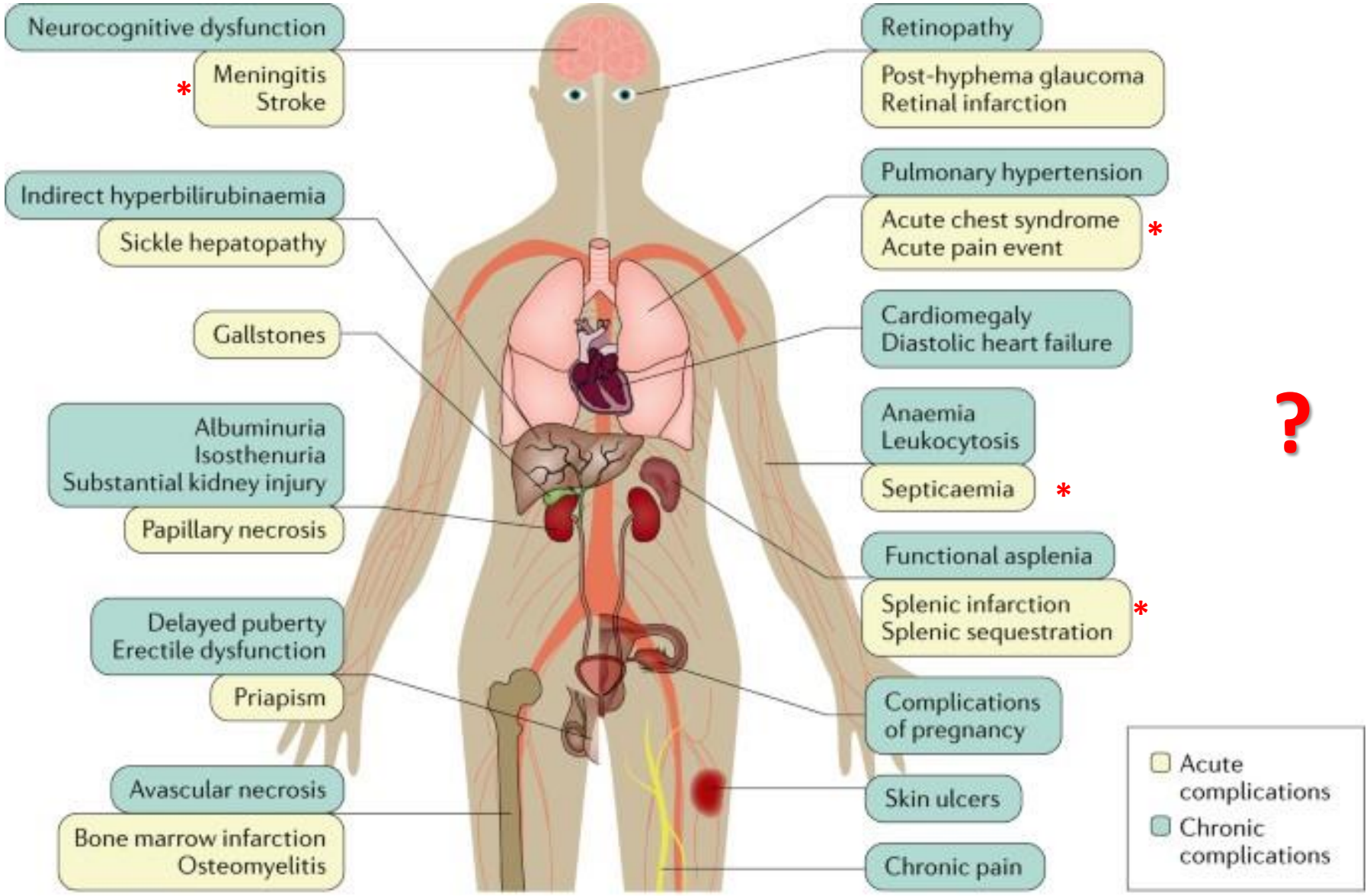
- Hemoglobinopathy
- **Complex pathophysiology**:
  - Vaso-occlusion
  - Chronic hemolytic anemia
  - Vasculopathy micro-macro circulation
  - Hypercoagulation
  - Inflammation

- **Extreme Phenotypic variability**
- **Each patient has a steady state**



Source: K. Kaushansky, M.A. Lichtman, J.T. Prchal, M.M. Levi, O.W. Press, L.J. Burns, M. Caligiuri: Williams Hematology, 9th edition
www.accessmedicine.com

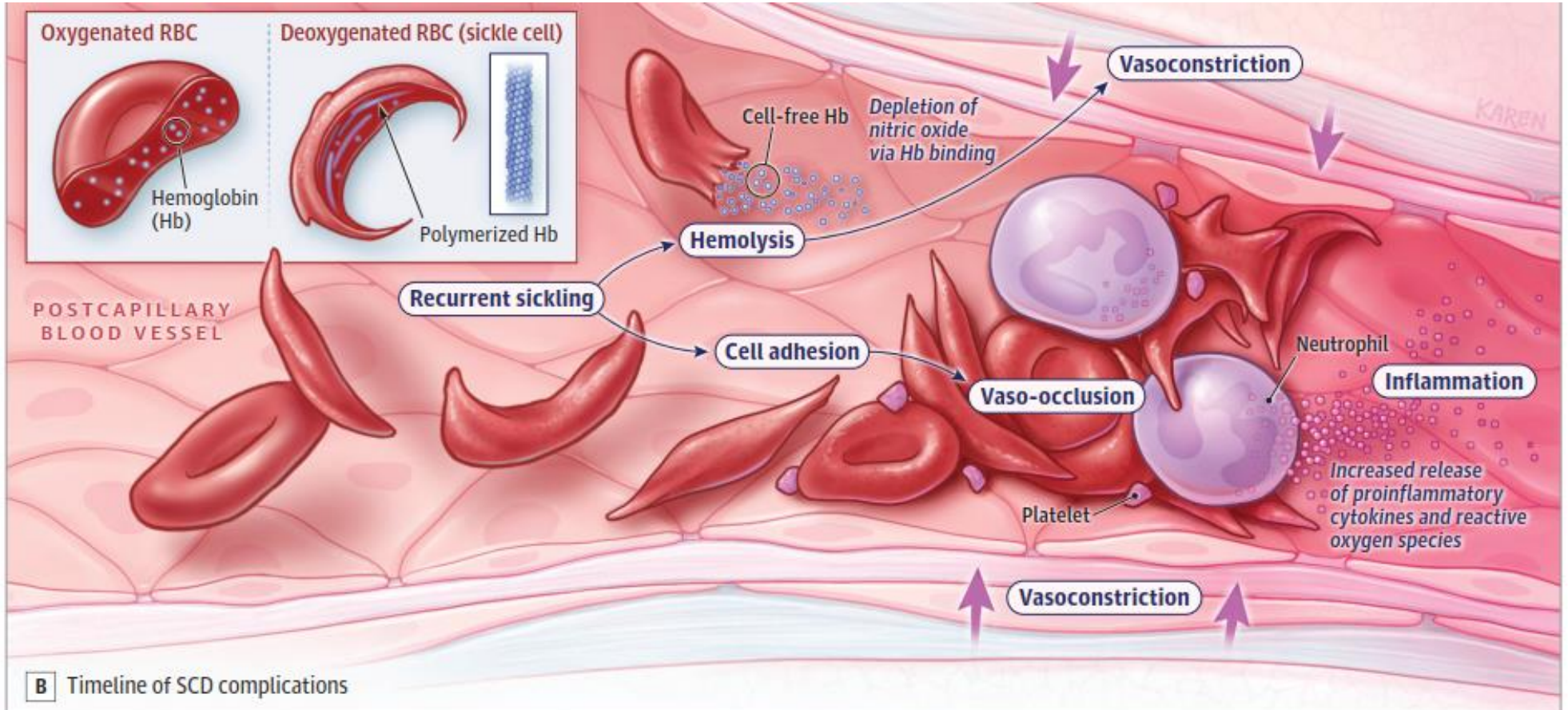
CLINICAL CARE
and CLINICAL CARE ORGANIZATION



Nature Reviews | Disease Primers

Kato GJ. Nat Rev Dis Primers. 2018;4:18010.

Clinical Manifestations Change Throughout the Lifespan



B Timeline of SCD complications

	Infancy and childhood	Adolescence	Adulthood
COMPLICATIONS			
During specific life stage	Delayed growth	Delayed puberty	Hemorrhagic stroke Leg ulcers Pulmonary hypertension Reproductive complications
During multiple life stages	Aplastic crisis Osteomyelitis Splenic sequestration Splenic infarction Sepsis	Avascular necrosis Cognitive dysfunction Chronic pain Gallstones Priapism Sickle nephropathy	Sickle retinopathy Venous thromboembolism
During all life stages	Acute pain - Acute chest syndrome - Ischemic stroke		

Kavanagh, P. L., et al (2022). Sickle Cell Disease: A Review. JAMA, 328(1), 57–68.

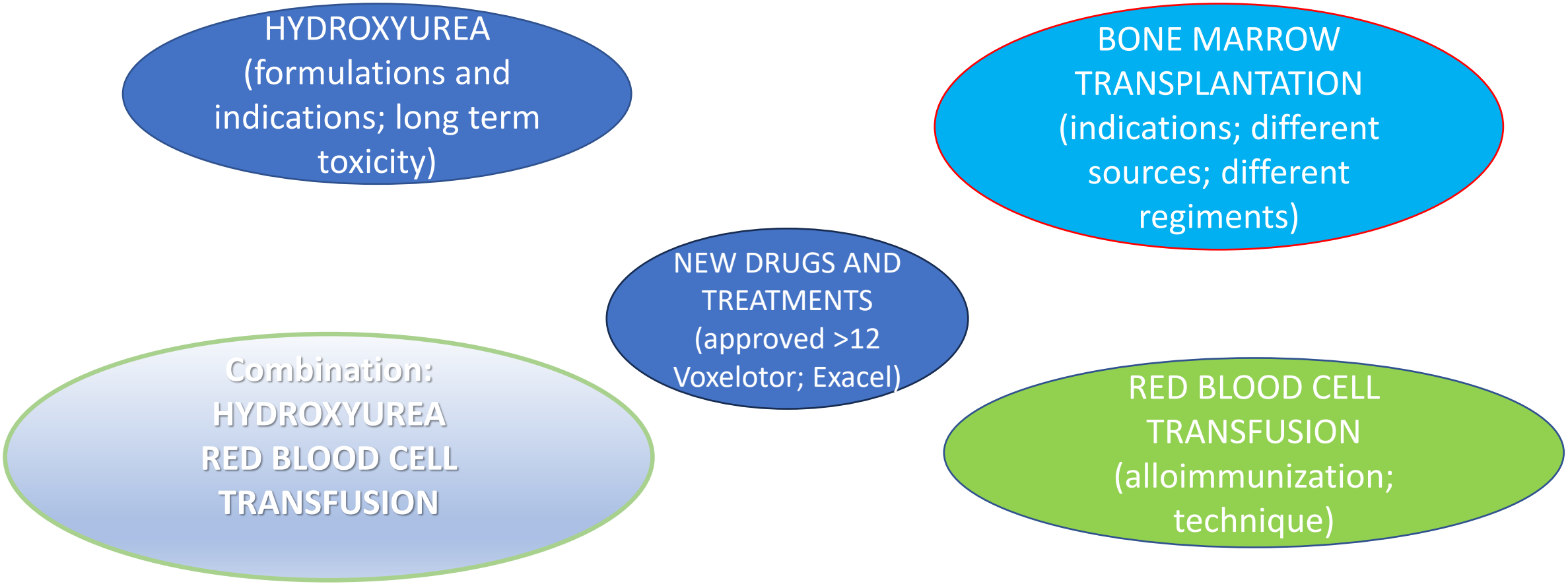
Standards of care

- **Newborn screening** → not available to all children
- H**ealth care plan for preventive** measures (antibiotic prophylaxis, vaccinations) → compliance not assessed everywhere
- **Transcranial doppler** for stroke prevention starting at age 2 years → low coverage; SCD protocol not always applied
- **Hydroxyurea** offered at 9 months of age SS/SB° → uneven access
- **Health care plan with acute complications**' management → Can be different in different countries
- **Health care plan with chronic complications**' management and organ damage monitoring (kidney, retina, brain, heart-lung)

- **Transition program** and plan → scarse
- Reproductive and pregnancy counselling

Brandow AM et al. *Blood Adv*. 2020;4(12):2656-2701. Kanter J et al. *Blood Adv*. 2020;4(16):3804-3813. Hulbert ML et al. *Pediatr Blood Cancer*. 2022;12:e29961.

STANDARD OF CARE
AVAILABLE TREATMENTS in the EU



Increasing access-indications and safety

CHALLENGES in SICKLE CELL DISEASE
Unmed Needs and Gaps in Europe

Rare disease with complex pathophysiology and estremely variable phenotype

Data fragmentation and difficulty to respond to open questions due to small subgroups of patients

Inequity of minimal standards of care availability → of early diagnosis and monitoring of complications

Only 30% of children are estimated to receive TCD screening and stroke prevention

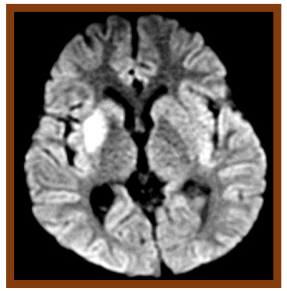
Inequity of access to treatment procedures and new drugs

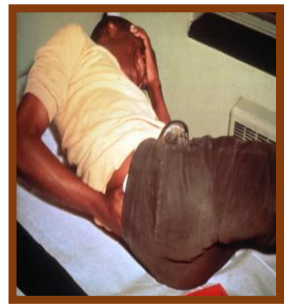
Less drugs/treatments approved by EMA compared to FDA (3 vs 6)

Approval for children is more long in EU compared to USA

Some endpoints are never considered (brain)

Morbidity and mortality of sickle cell disease in adults with SCD are still high





1

Death:
PHT
Stroke
Renal failure

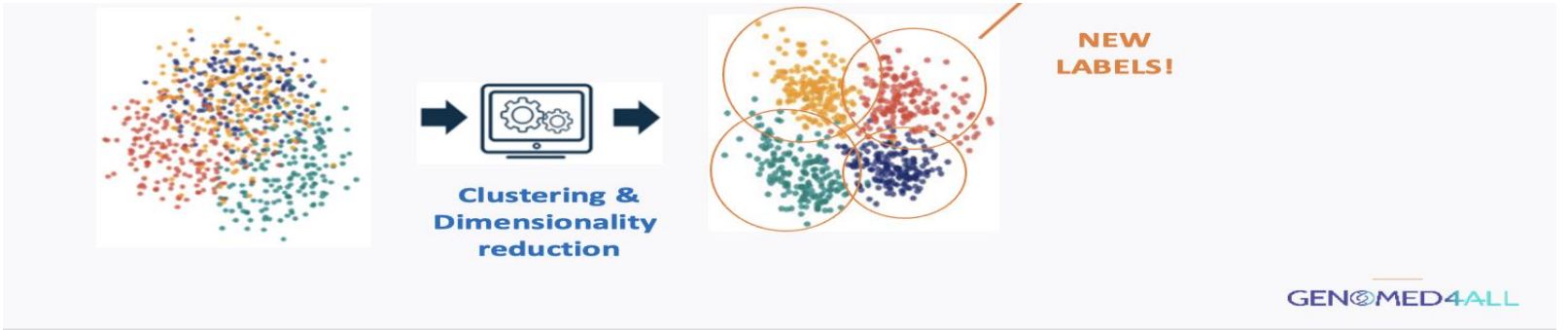
10 yrs | 20 yrs | 30 yrs | **41 yrs** [2]

1. 2.9 ± 2.2 painful days/ patient/per week (Osunkwo I, AJH 2021)
2. Median age at death in France in 2019. Habibi A et al, ASH, Abstract 1031

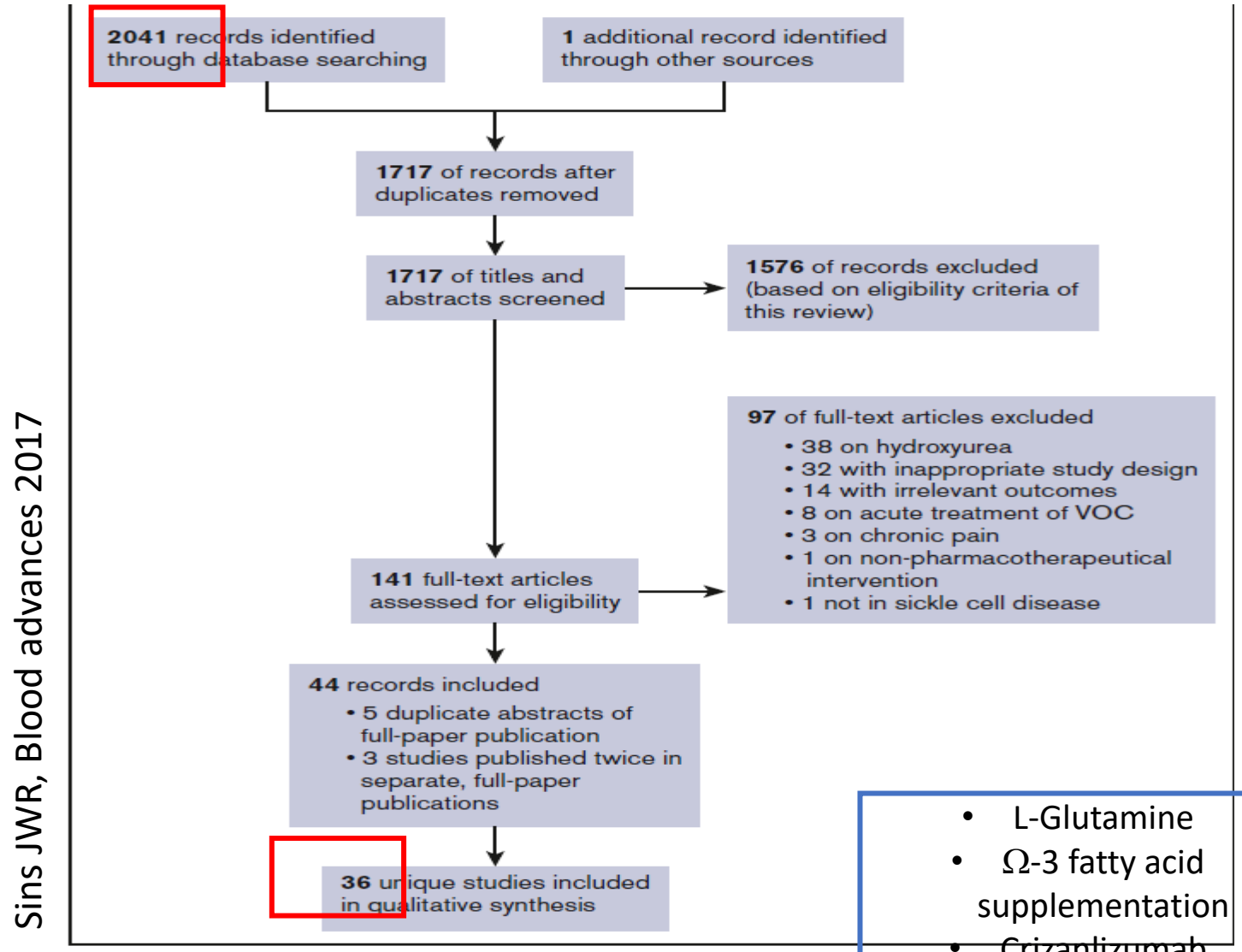
Biological markers (hemolysis and inflammation)
Classical genetic tests

Are weak predictors of individual prognosis

Contribution of AI?



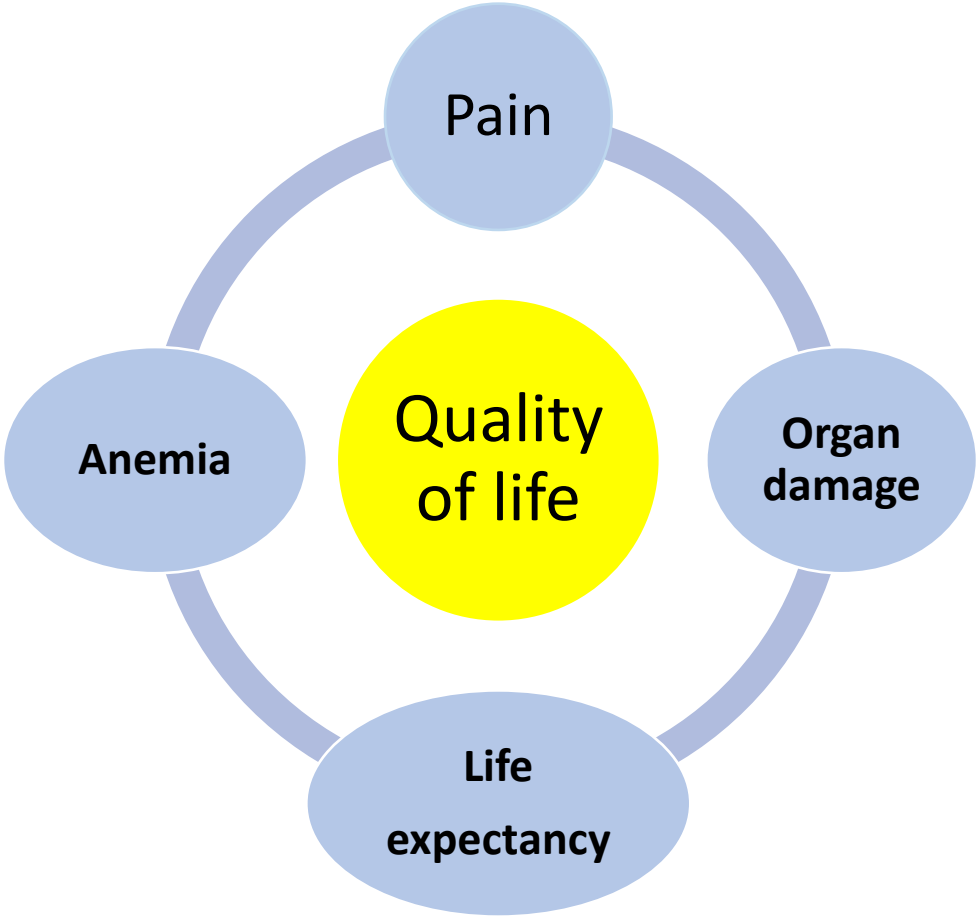
Scarcity of high-quality papers on pharmacotherapeutical strategies for SCD



- **Inappropriate study design**
- **Irrelevant outcomes**

- L-Glutamine
- Ω-3 fatty acid supplementation
- Crizanlizumab

Choice of endpoints in clinical trials for management of sickle cell disease



Pain

stress

Inhibition of HbS polymerization

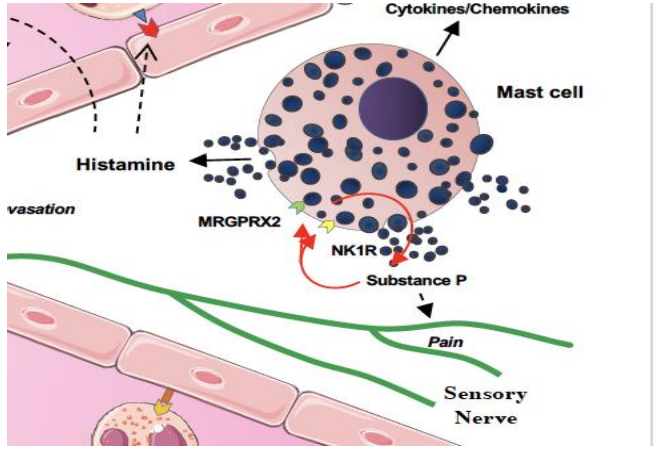
↑ HbF synthesis: **hydroxyurea**

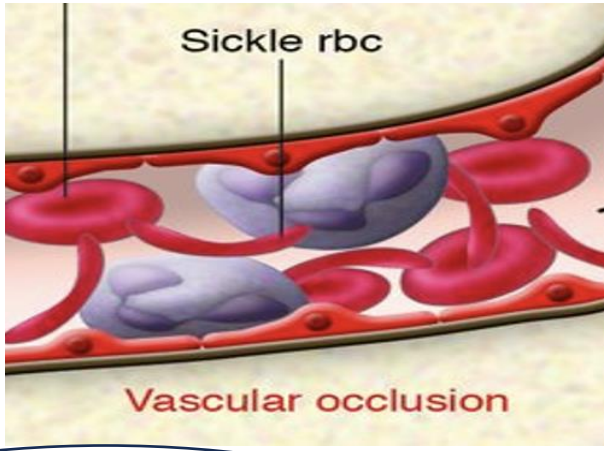
↑ O_2 affinity: voxelotor?

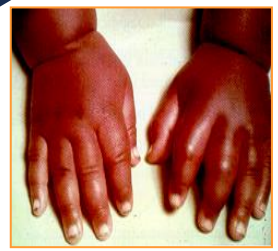
↓ concentration of 2,3 DPG? mitapivat, etavopivat

All preventive drugs

Cannabidiol?







Anti-oxidants?
L-glutamine

Anti-selectins?
- in prevention
- in acute pain, could be effective if given very early

Complement Pathway?

Challenges of using pain as an endpoint

- The definition of pain is subjective
- Chronic pain may have different triggers than acute pain
- Heterogeneity of pain scorings
- Difficulties in adjucating VOC

Inhibition of HbS polymerization

- ↑ HbF synthesis: **hydroxyurea**
- ↑ O_2 affinity: **voxelotor**
- ↓ concentration of 2,3 DPG **mitapivat, etavopivat**

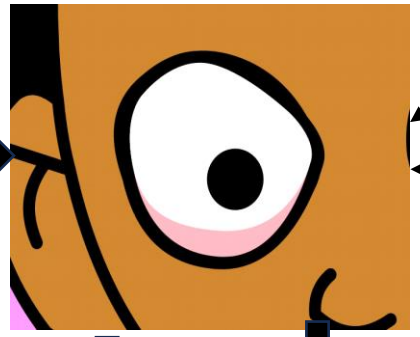
Anemia

chronic

Acute
-VOC
-Infection

Nutritional deficiencies

Hemolysis



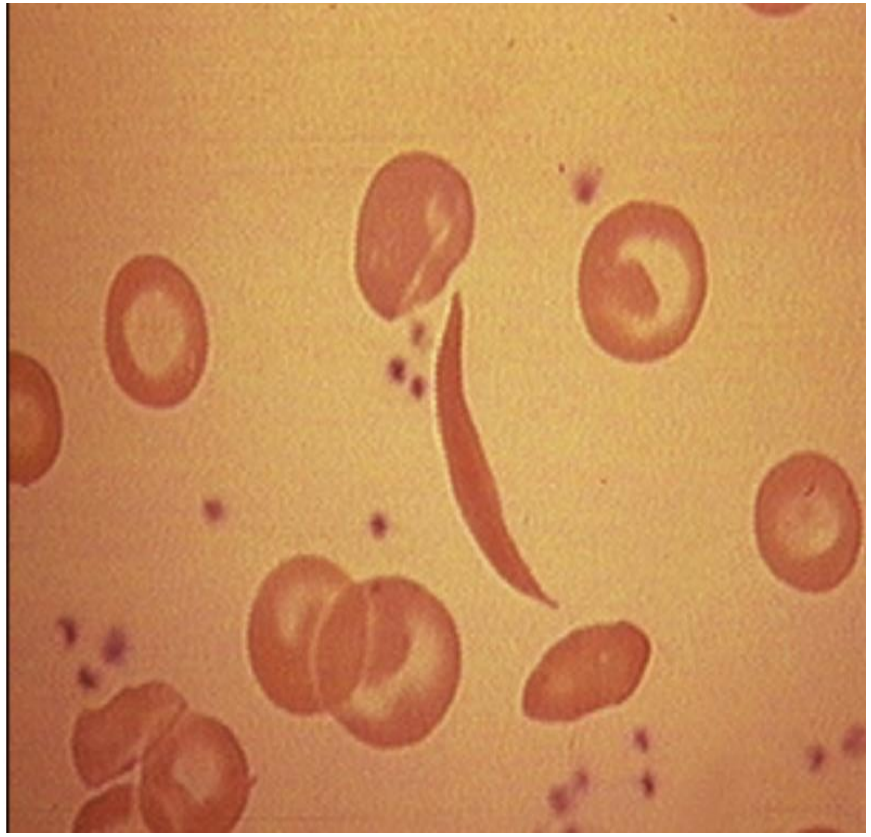
Ineffective erythropoesis

Organ damage
Stroke
Renal failure

Fatigue?[1]

1. Cheminet G, et al. Br J Haematol 2024

Challenges of using anemia as an endpoint



- The definitions of anemia and hemolysis are **objective**

- But anemia has <u>only</u> been shown to be strongly associated with cerebral and renal impairments [1,2]

Correlations with life expectancy and QoL in SCD are unclear

1. Rees DC, et al, *Br J Haematol*. 2012
2. Cheminet G, et al. Br J Haematol 2024

All patients are hoping for curative treatments

- More than 1000 allogenic bone marrow transplantations have been performed in SCD patients

OS (%)	EFS(%)	Graft rejection (%)	aGvH(%)	cGvH(%)
92.9	91.4	2.3	14.8	14.3

Gluckman E et al, Blood 2016

But ≤ 20% of patients have a suitable donor

- Haplo-identical and Non Myelo Ablative transplants are still experimental

Gene addition (Lovo-Cel)

Gene editing (exagamglogene autotemcel)[1]

- > 90% patients have no more pain
- low numbers: 44 patients
- short FU (1-48 m)
- high cost

1. Frangoul H et al. N Engl J Med 2024

In conclusion, although there are still many unmet needs, therapeutic research in SCD disease is difficult, because of the highly variable expression of the disease and the multiplicity of pathophysiological mechanisms

International collaboration involving patients is needed

Thank you!