BEYOND PAIN: Improving the Outcomes of Sickle Cell Disease with Therapeutics and Cellular Therapy in 2024

Arun Shet MD PhD

Bethesda, Maryland

Indy Hematology Review
Feb 24, 2024

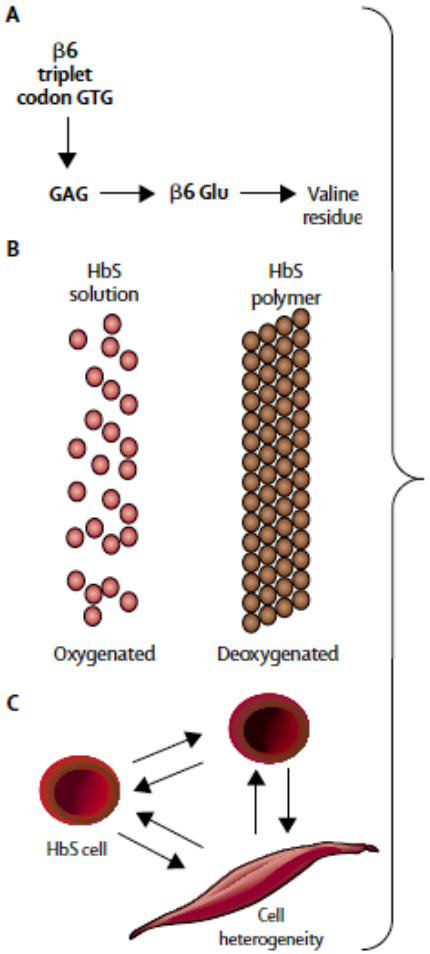
Disclosures

- No financial disclosures
- Sickle cell disease therapy that is not approved by the FDA or widely utilized will not be covered in this session

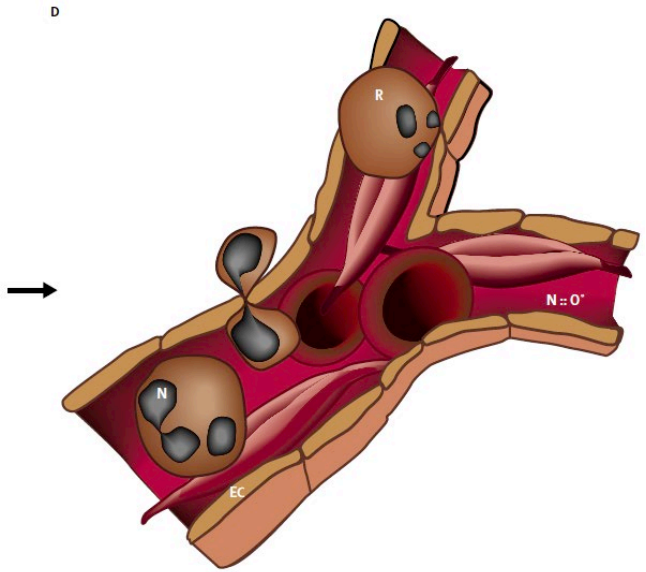
Learning objectives

- Define the pathophysiology and clinical manifestations of sickle cell disease and describe its global impact
- Evaluate current management strategies for sickle cell disease, with a focus on managing painful vasoocclusive crisis
- Appraise where cellular and gene directed therapy fits into the spectrum of therapeutics for patients with sickle cell disease

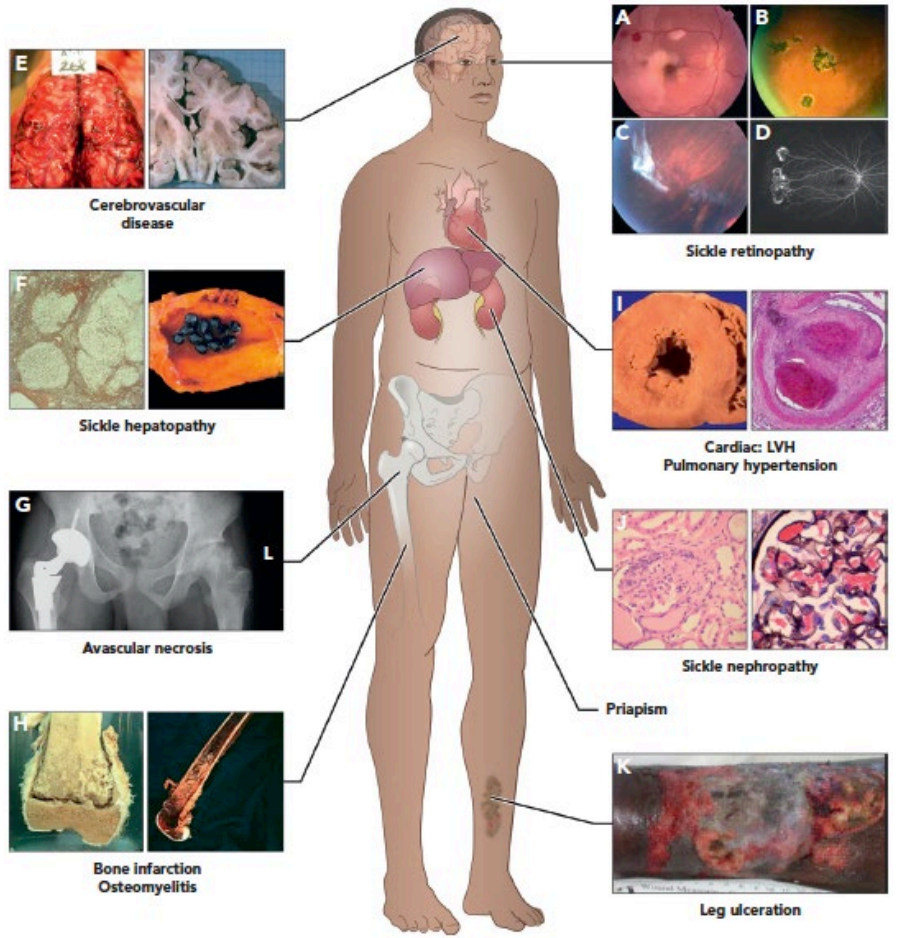
Single gene hemoglobin disorder with multiorgan dysfunction



Hb polymerization



Recurrent vasoocclusive crises



Multiorgan vasculopathy

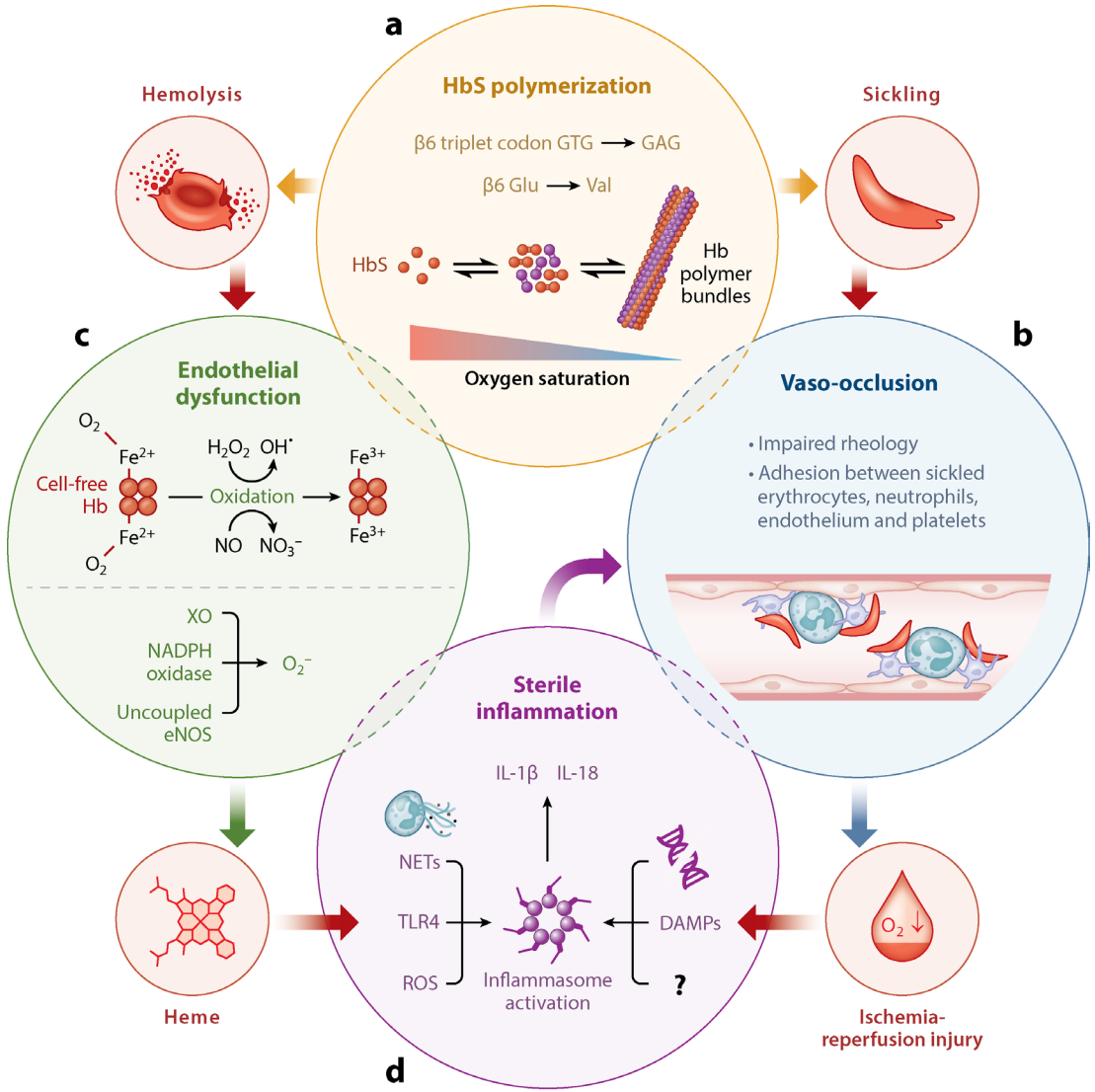
Stuart and Nagel Lancet 2004; Thein & Howard Blood 2019

Beyond borders: Geographic inequity

Globally the commonest genetic blood disorder

https://www.notaloneinsicklecell.com/Global-Impact-Of-SCD/

Sickle pathophysiology involves multiple parallel pathways

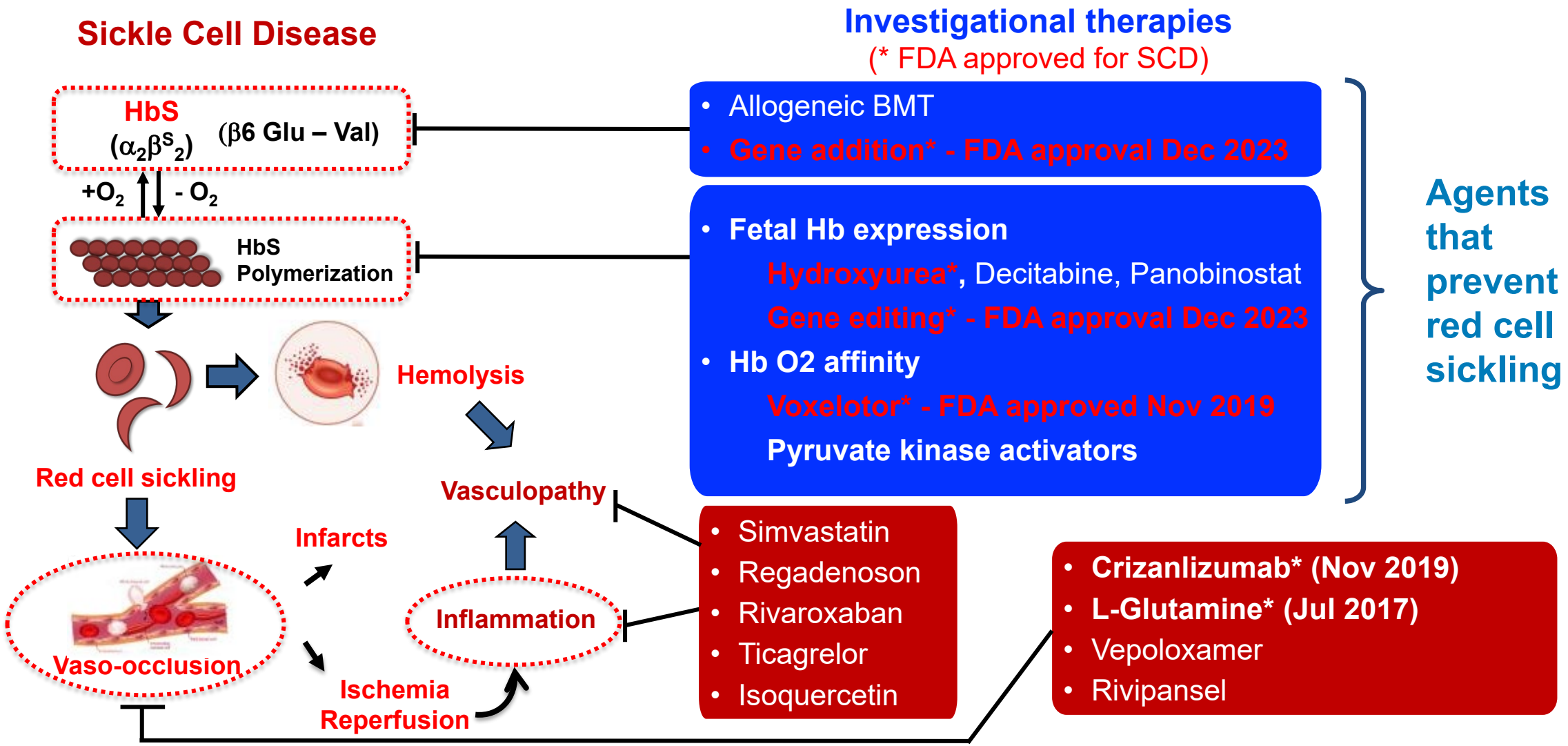


Sundd et al Annual Review of Medicine 2019

Phenotypic heterogeneity of SCD

- Persistence of fetal hemoglobin (HPFH)
- Mutations affecting fetal hemoglobin expression
- Coinheritance of alpha thalassemia
- HbSC and HbSβ^{+thal}
- Iron status
- Undefined factors

Current treatment targets and approved treatments



Hb, hemoglobin; HbS, sickle hemoglobin; Glu, glutamine; Val, valine; Slide courtesy Dr. Swee Lay Thein, modified 2024

Beyond Pain: Sickle Cell World Assessment Survey

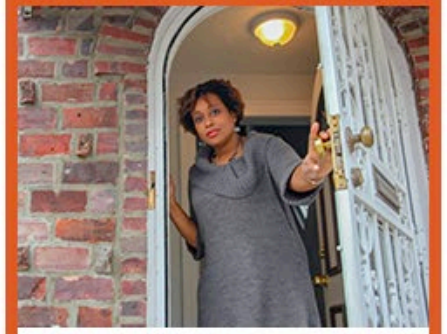
>2100 individuals surveyed from 16 countries

Physical Symptoms

90%

of people had at least 1 pain crisis in the past year

Daily Activities



38%

of people said sickle cell disease impacted their daily home activities

Emotional Life

59%

of people felt frustrated with their symptoms

Work and School

53%

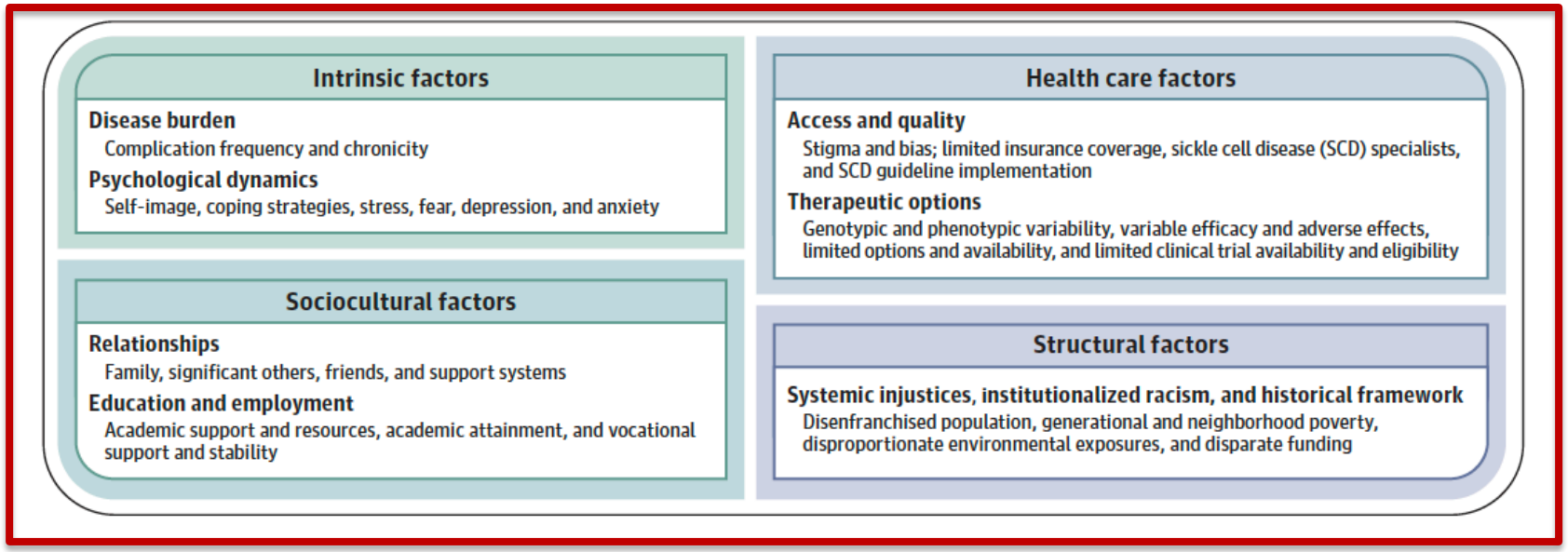
believed their income would be higher if they did not have sickle cell disease

Fatigue; Bone aches; headache
Fear of dying

https://www.notaloneinsicklecell.com/Impact-of-Pain-Crises/#sway; Osunkwo et al Amer J of Hematol 2021

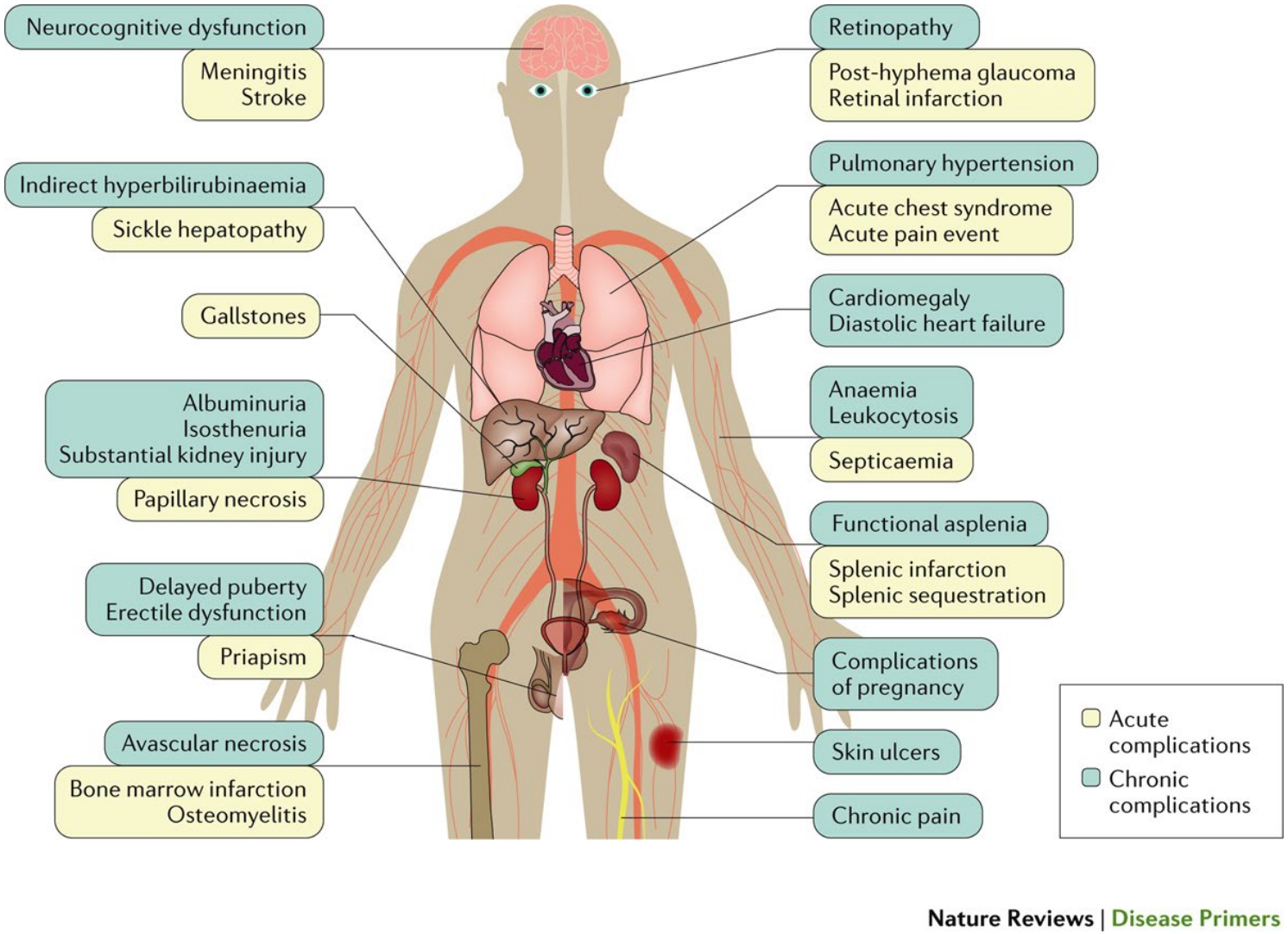
Complications occur at all life stages

COMPLICATIONS	Infancy and childhood	Adolescence	Adulthood
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		



Kavanaugh P et al JAMA 2022

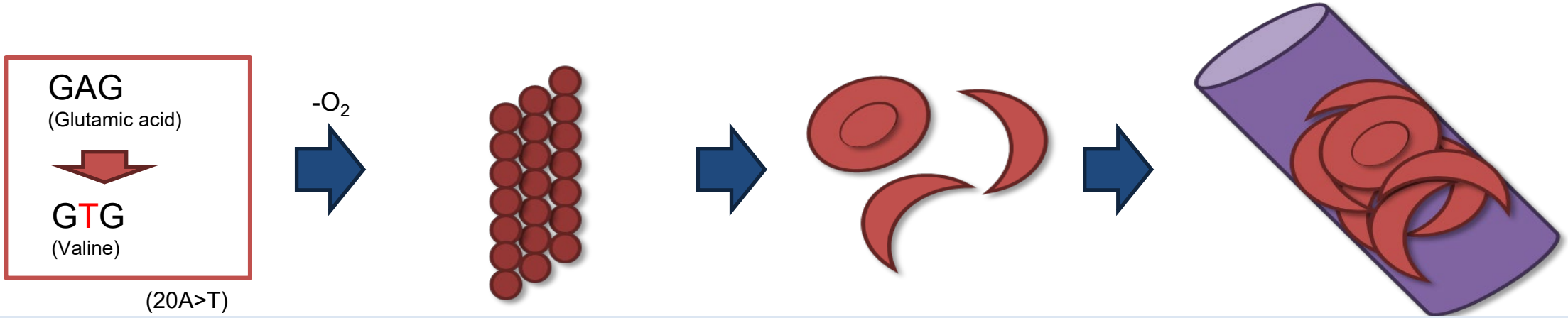
Acute and chronic complications of SCD



- 29 year old female with HbSS disease
- Presents to the ER with acute pain typical of her usual “crisis”
- She denies any obvious triggering factors
- She is not taking hydroxyurea or any other disease modifying therapy
- You admit her for management of an acute vasoocclusive event

Kato et al. Nature Reviews 2018

Sickle Cell Disease – VOC treatment is mostly symptomatic



β-globin gene mutation

(1 of 12 African Americans)

Hemoglobin S polymerization

Sickling of red cells / adhesion

Blood vessel occlusion

Recurrent painful crises

HSC transplantation
Gene directed therapy

Hydroxyurea
Voxelotor

Crizanlizumab
L-Glutamine

Symptomatic Rx

Slide courtesy Naoya Uchida 2018, modified 2019 & 2023; VOC, vasoocclusive crisis

Management of acute vasoocclusive crisis

Symptomatic management

- Rapid initiation of individualized opioid analgesia (<30 min) is desirable
- Adequate initial dosing; Repeated frequent administration until pain improves (?PCA)
- Patient-specific dosing protocols provide better clinical outcomes*
- Use NSAIDs as adjunct, if not contraindicated
- Adjuvants - fluid, oxygen, others

Disease modifying therapy

- Medication
  - Hydroxyurea
  - Crizanlizumab
  - L-Glutamine
  - Voxelotor
- Social factors impact treatment success
- Patient education

*Tanabe Eur J Haematol 2023; Masese et al *Blood* (2023) 142 (Supplement 1): 3671

Sickle cell disease modifying therapy

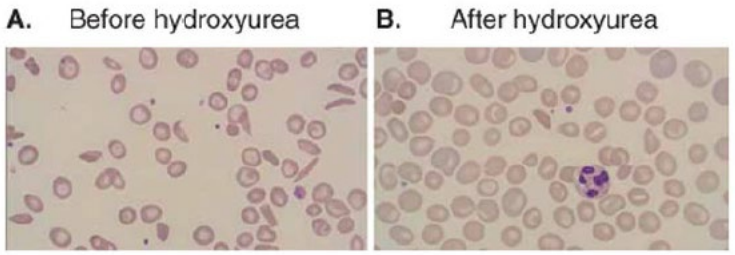
	Hydroxyurea* (hydroxycarbamide)	L-glutamine** (Endari)®	Crizanlizumab**** (Adakveo)®	Voxelotor*** (Oxbryta)®
Mechanism of action	Increases fetal Hb Reduce sickle Hb Reduces crisis	Unknown; provide amino acid source to red blood cells Reduces crisis	Reduces red, white, platelets sticking to blood vessel wall Reduces crisis	Hb binds to oxygen irreversibly Reduces sickling of Hb Reduces anemia
Predominant treatment effect	Patients (HU, n=152; placebo, n=147) had decrease in VOE from 4.5 to 2.5/y	Patients (Endari, n=152; placebo, n=78) had a 25% reduction in VOE 33% Reduction in hospitalization	Patients (Adakveo, n=67; placebo, n=65) had a reduction in VOE from 2.98 to 1.63/y)	Patients (Oxbryta, n=90; placebo, n=92) 51% had an increase in Hb ≥1 g/dL at 24 weeks
Formulation	Oral, daily	Oral, daily	Intravenous every 4 weeks	Oral, daily
Rx duration	Lifelong	Lifelong	Try for at least 3-6 months	Lifelong

*Charache et al. New Engl J Med 1995; **Niihara et al N Engl J Med 2018; *** Vichinsky et al N Engl J Med 2019; **** Ataga et al N Engl J Med 2017

Hydroxyurea: mechanism and efficacy

Hydroxyurea (HU) mechanism of action#

- Ribonuclease reductase inhibitor
- Induces HbF
- Reduced sickling
- Improved rheology
- Myelosuppression
- Nitric oxide donor
- Reduced adhesion



#McGann & Ware Expert Op on Drug Saf 2015

	*Multicenter HU study			**Baby HUG study		
	HU	Placebo	P value	HU	Placebo	P value
Number of patients	152	147		96	97	
Pain (VOC)	2.5/y	4.5/y	<0.001	177	372	0.002
Acute chest	25	51	<0.001	8	27	0.017
Dactylitis				24	123	<0.001
Hospitalization	1/y	2.4/y	<0.001	232	321	0.050
Transfusions	48	73	<0.001	35	60	0.033

*Charache et al. New Engl J Med 1995
**Wang et al. The Lancet 2011
Tshilolo et al New Engl J Med 2019 (REACH investigators)

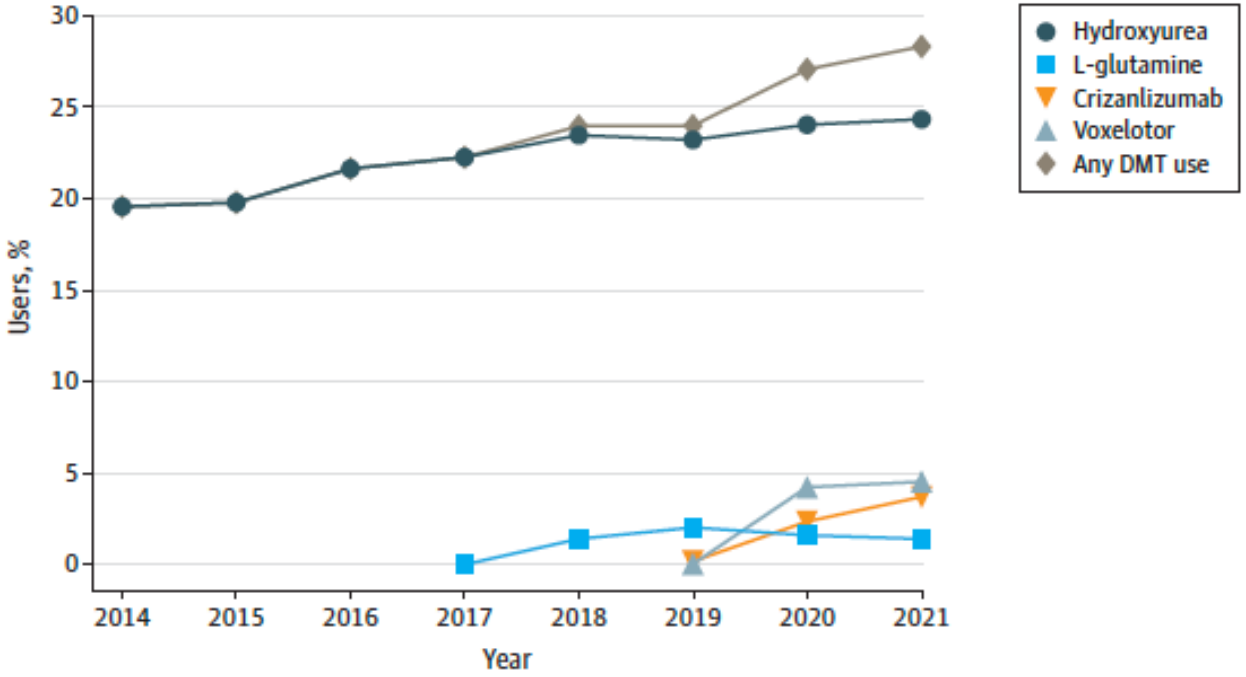
Underutilization persists since 2014 SCA treatment guidelines*

Table. Characteristics of 2086 Adults With Probable Sickle Cell Anemia (SCA) Reported in a Large Commercial Insurance Database Between January 1, 2009, and June 30, 2013

	Adults With Probable SCA[a]
Age, median (25th-75th percentile), y	39 (28-52)
Female sex	1231 (59.0) [56.9-61.1]
Duration of continuous enrollment, median (25th-75th percentile), mo	30.0 (13.9-52.9)
Filled ≥1 prescription for hydroxyurea during enrollment period	369 (17.7) [16.1-19.4]
Average number of emergency visits or hospitalizations for pain per year, median (25th-75th percentile)	0.70 (0-2.10)
Emergency visit or hospitalization for pain during enrollment period	
≥1	1420 (68.1) [66.0-70.1]
≥3 over 12 mo	677 (32.5) [30.5-34.5]

[a] Data are expressed as No. (%) [95% CI] unless otherwise indicated.

Gap in evidence based practice# ^



*Yawn et al JAMA 2014 NHLBI guideline summary; # Stetler et al, JAMA 2015; ^ Newman et al JAMA Open 2023

Case scenario 1

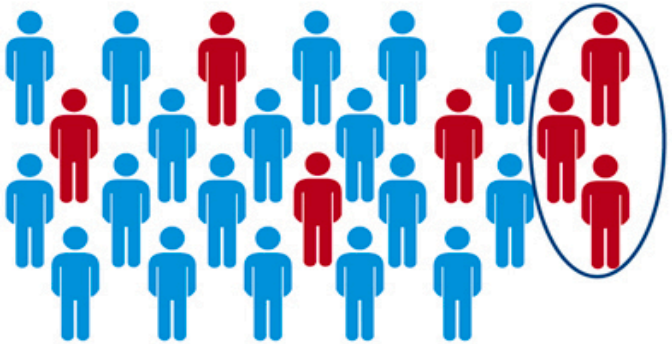
- She is not taking hydroxyurea or any other disease modifying therapy.
- She wants to know when she will be transfused. “she feels so much better with a unit of blood”.

- Recently moved to the United States (US)
- Does not have a primary care provider

11 years follow up

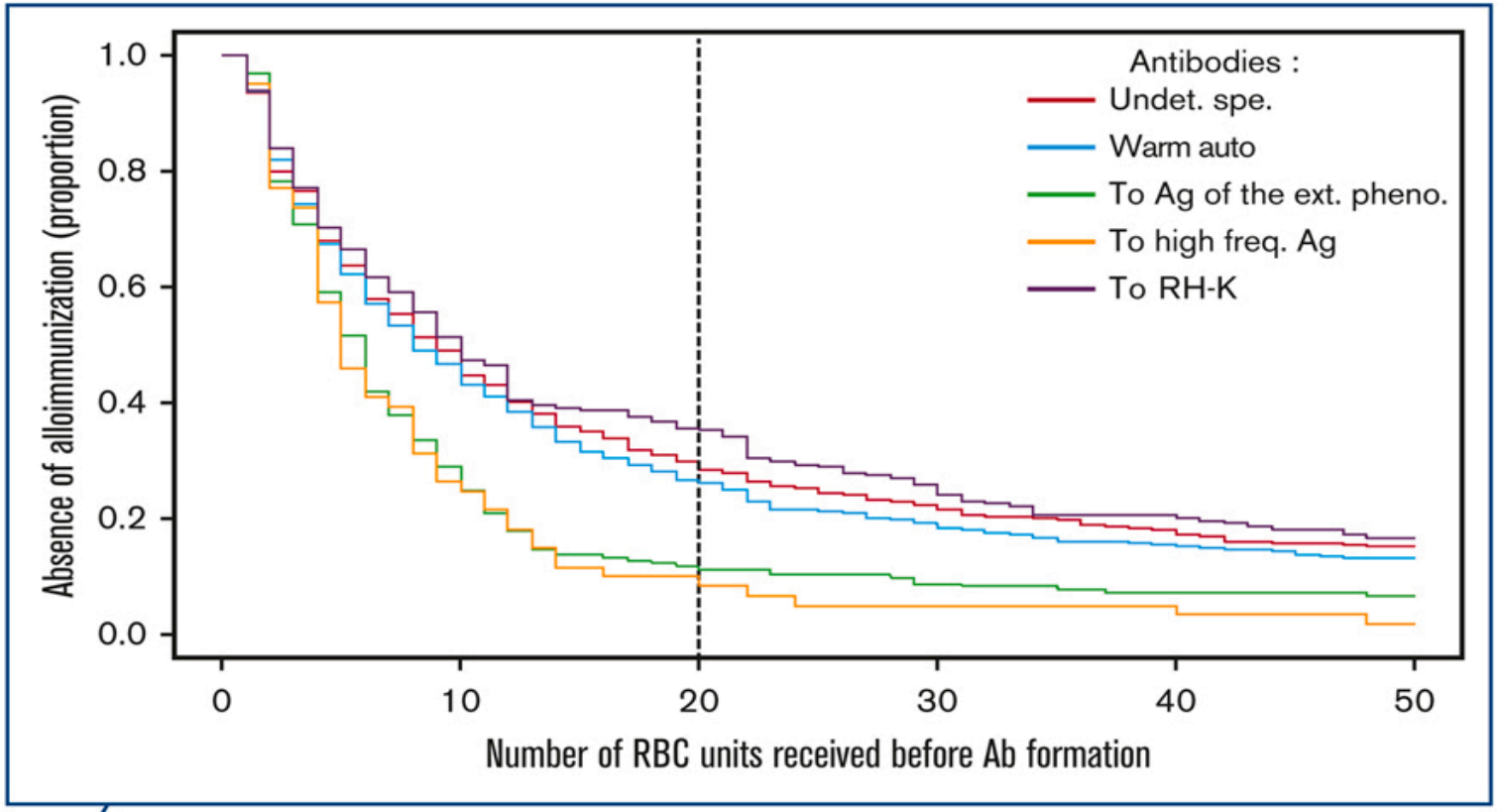
239 944 Red Blood Cell (RBC) units

6 496 patients with sickle cell disease



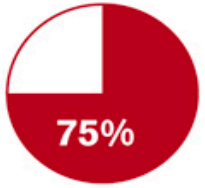
1 742 made antibodies to RBC antigens

643 patients : precise chronology of antibody formation



By the 20th RBC unit transfused :

- 75% of patients who will make an antibody (excluding warm auto antibodies) have made their first



- 90% of patients who will make an antibody to a high prevalence antigen or an antigen of the extended phenotype (Fy, Jk, S, s) have made their first antibody to these antigens

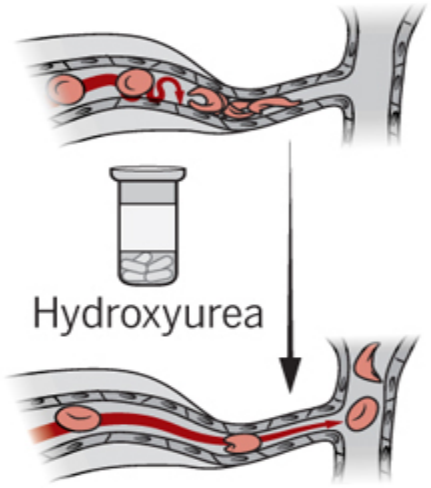
Current and future treatments for sickle cell anemia

Numerous advances in the understanding of sickle cell disease (SCD) have allowed the development of curative therapies through allogenic stem cell transplanation, with the promise of gene therapy–based treatments in the future.

Current treatments

Drug treatment

Aim to allow more cells to transit the microcirculation before sickling



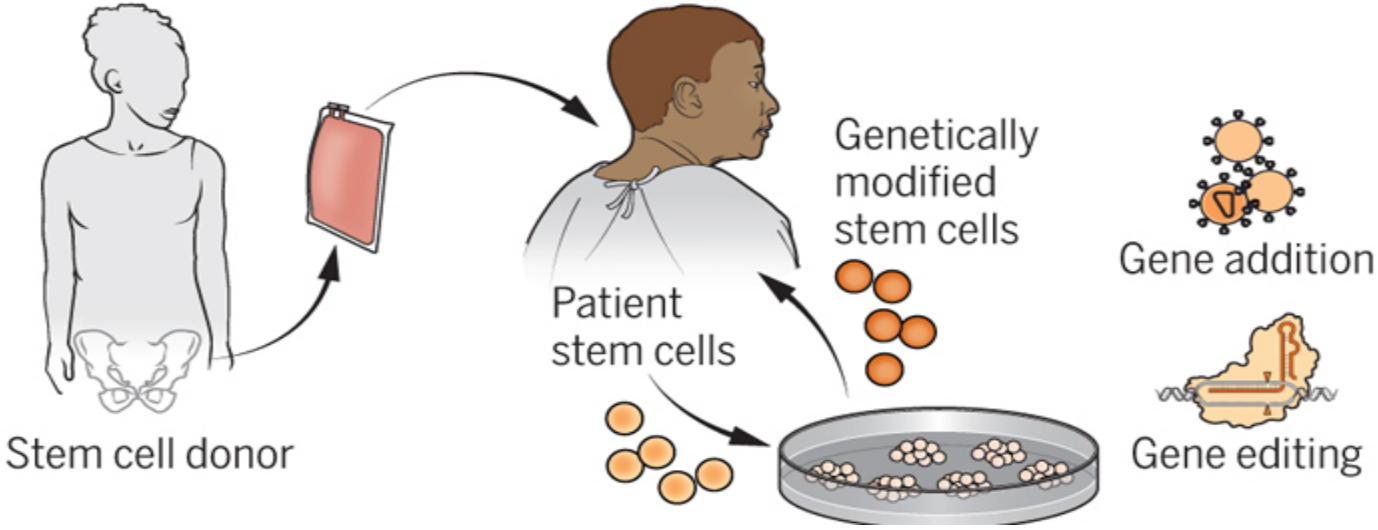
Future treatments

Allogeneic transplant

An established curative strategy using bone marrow stem cells from a donor without SCD

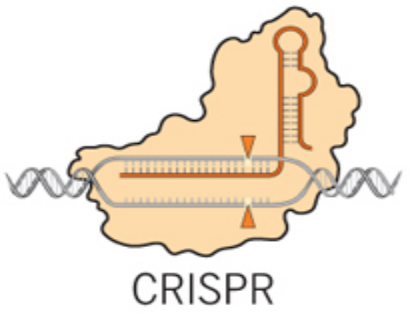
Ex vivo gene therapy

The patient's bone marrow cells are modified by adding a β-globin gene, using a retroviral vector or with gene editing, to reactivate fetal hemoglobin (HbF) or correct the disease mutation.



In vivo gene therapy

Direct gene editing in patients could circumvent the need for transplantation of modified patient cells if sufficient efficiency and safety can be achieved.



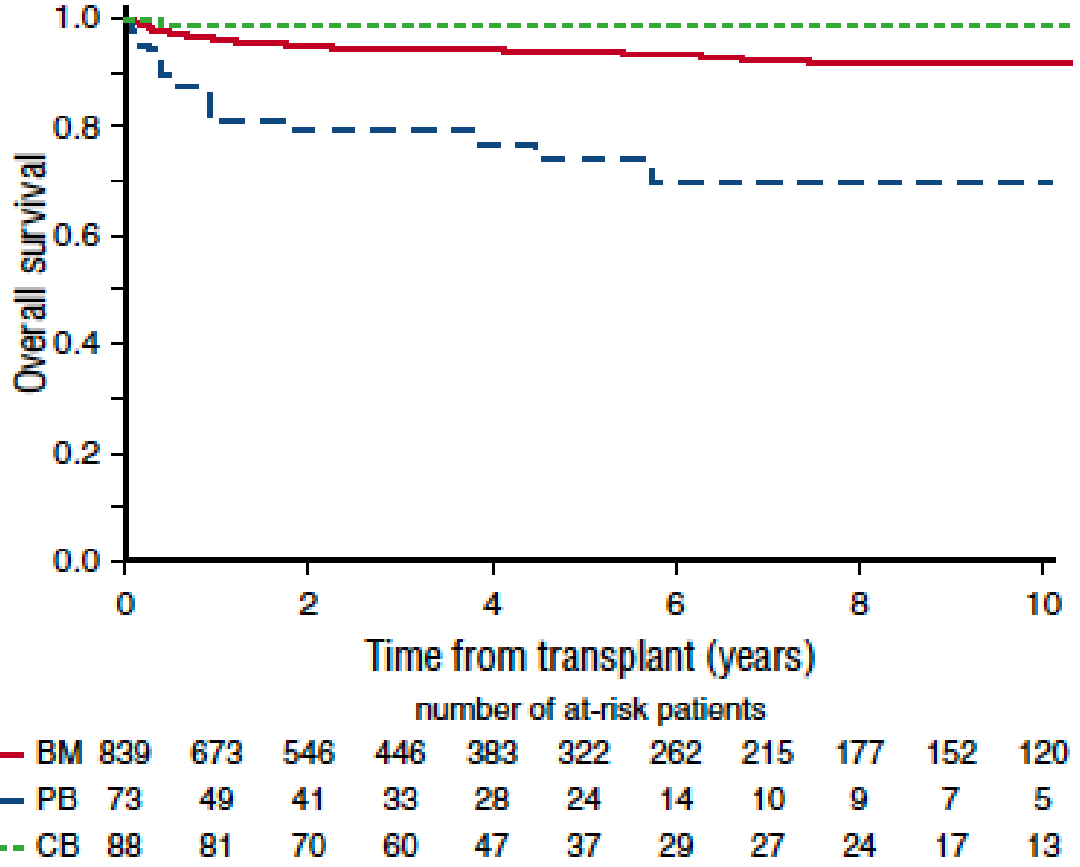
Tisdale et al. Treating Sickle Cell Anemia. Science 2020

Curative therapy: Stem cell transplantation

Allogeneic stem cell transplantation

- Eligibility: HbSS or HbSβ^{0thal}
  - Severe sickle cell disease
  - High risk individuals
- Must have a matched sibling donor
- Complications:
  - short term TRM
  - long term GVHD
- Cost: high burden on health system

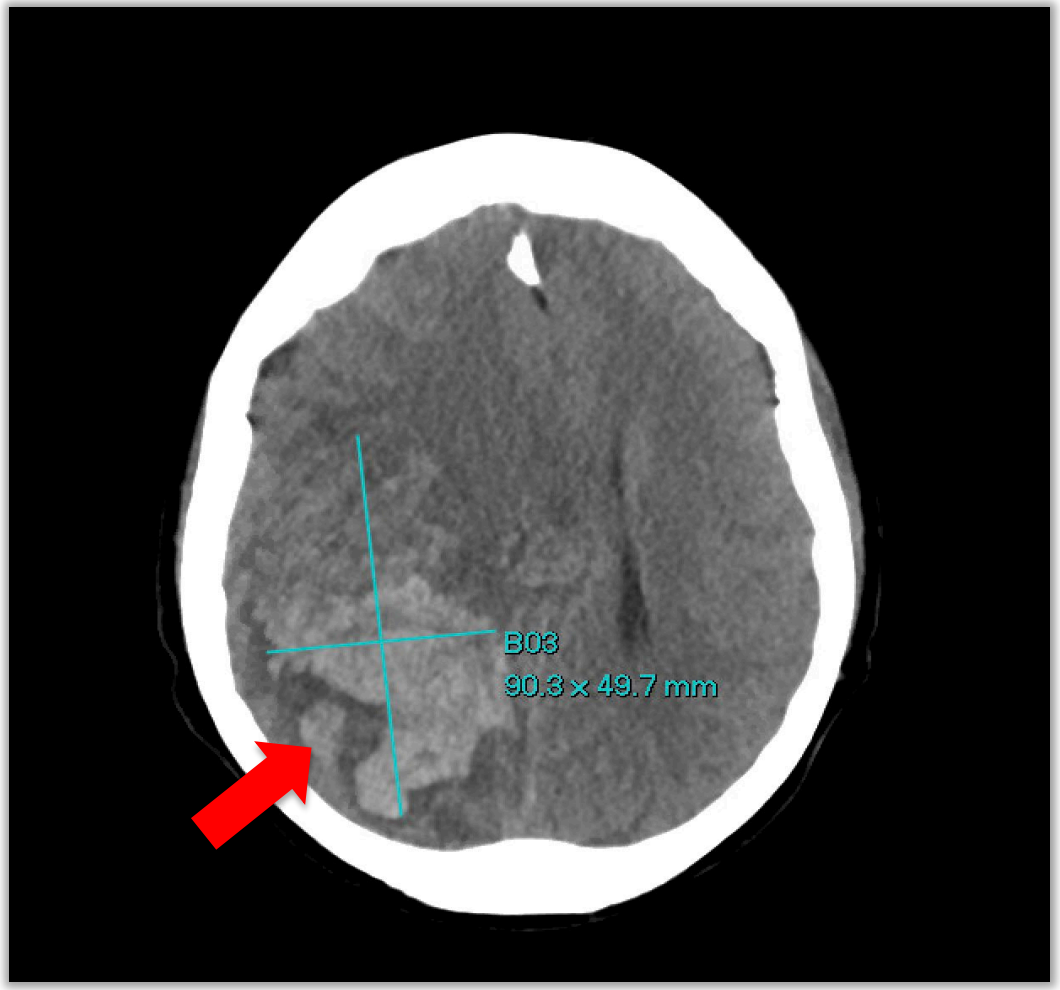
Outcomes



Gluckman et al Blood 2017; Registry data for HLA identical sibling HSCT; 1000 transplants between 1986 and 2013

Case scenario 2

- 36 y.o. F with HbSS and prior history of ACS x 2, VOC 3/year and life-threatening PE on lifelong anticoagulation and Rt heart catheterization documented Pulm Htn
- Underwent haploidentical-HSCT
  - Estimated 2-year EFS = 88% (95% CI: 73.5%, 94.8%)*
  - Durable donor engraftment at 2-years with low mortality.
  - The 2-year EFS and OS are comparable to that reported after MSD myeloablative HSCT
- On d+41 developed sudden loss of consciousness; CT brain shows intracranial hemorrhage



Case from Dr. Courtney Fitzhugh, CMTB, NHLBI

*Kassim et al: ASH 2023 LBA-4 Reduced Intensity Haploidentical Bone Marrow Transplantation in Adults with Severe SCD: BMT CTN 1507; n=54

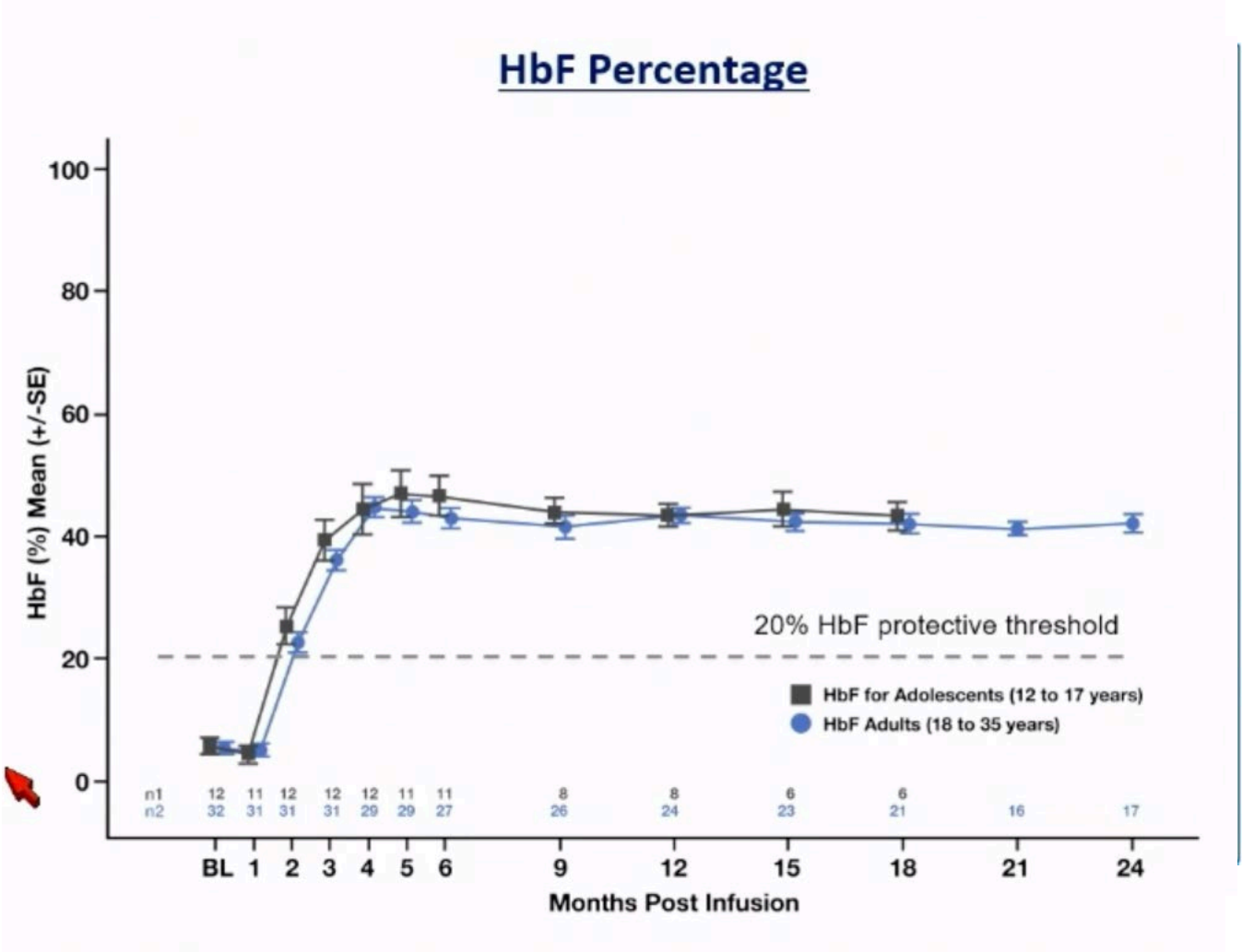
Curative therapy: Gene directed treatment

Gene addition (*ex vivo*)*

- Phase 2 study of Lovo-cel® infusion in 47 patients with 60 months follow-up (126 pt yrs)
- Reduction in VOE from 3.5/year to 0/year
- Over 40% of total hemoglobin was HbA^{T87Q}
- Toxicity mild; no malignancy in 37 months f/u.

Gene disruption (*ex vivo*)**

- CRISPR-Cas9 targeting of gene:
  - ***BCL11A* erythroid- enhancer
  - ***HBG1 & HBG2 gene promoters
- Phase 3 non viral, Exa-cel® infusion robustly induced HbF (n=44)
- VOE free = 97%; hospitalization free post infusion = 100%
- Toxicity mild; stable durable editing in HSPCs



*Kanter el al New Engl J Med 2022; **Frangoul et al New Engl J Med 2021; ***Sharma et al New Engl J Med 2023; Data from presentations made at ASH 2023

Life changing benefits versus massive costs

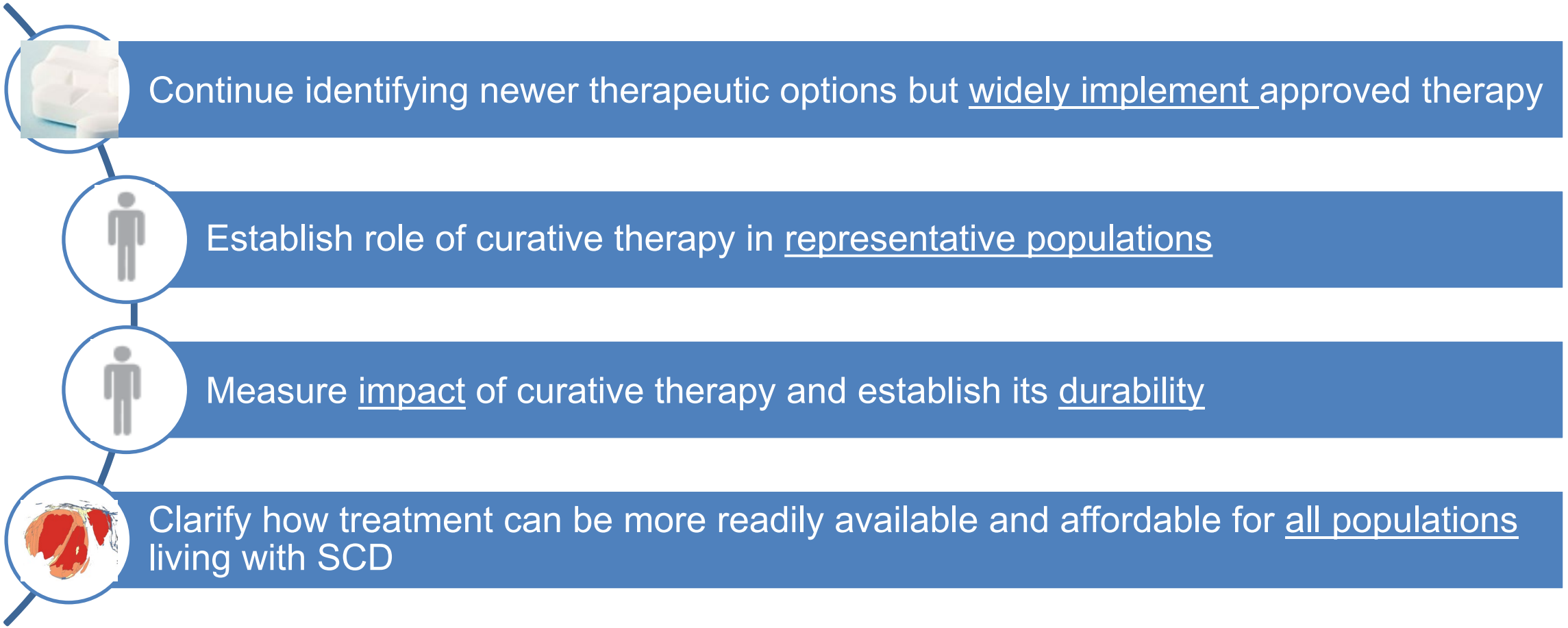
JAMA Pediatrics | Original Investigation

A Budget Impact Analysis of Gene Therapy for Sickle Cell Disease
The Medicaid Perspective

Patrick DeMartino, MD; Meredith B. Haag, MD, MPH; Alyssa R. Hersh, MD, MPH;
Aaron B. Caughey, MD, MPH, PhD; Joshua A. Roth, PhD, MHA

Hardy et al: Assessing Psychosocial Readiness for Gene Therapy in Sickle Cell Disease: A Consensus Statement ASH 2023

Incorporate the future of SCD treatment into current management



Summary

- Define the pathophysiology and clinical manifestations of sickle cell disease and describe its global impact
- Evaluate current management strategies for sickle cell disease, with a focus on managing painful vasoocclusive crisis
- Appraise where cellular and gene directed therapy fits into the spectrum of therapeutics for patients with sickle cell disease