Sickle Cell and Current Therapies

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Objectives

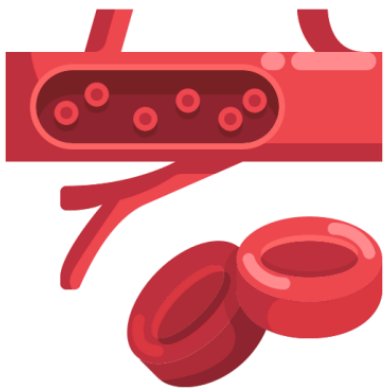
- Review the pathology, survival rates of sickle cell
- Discuss the historical barriers to care and the history of treatment
- Review Current Therapies and Clinical Trial Results of the recently approved gene therapies.
- Review the comprehensive care model and a call to action

Tammuella Chrisentery-Singleton, MD - Disclosures

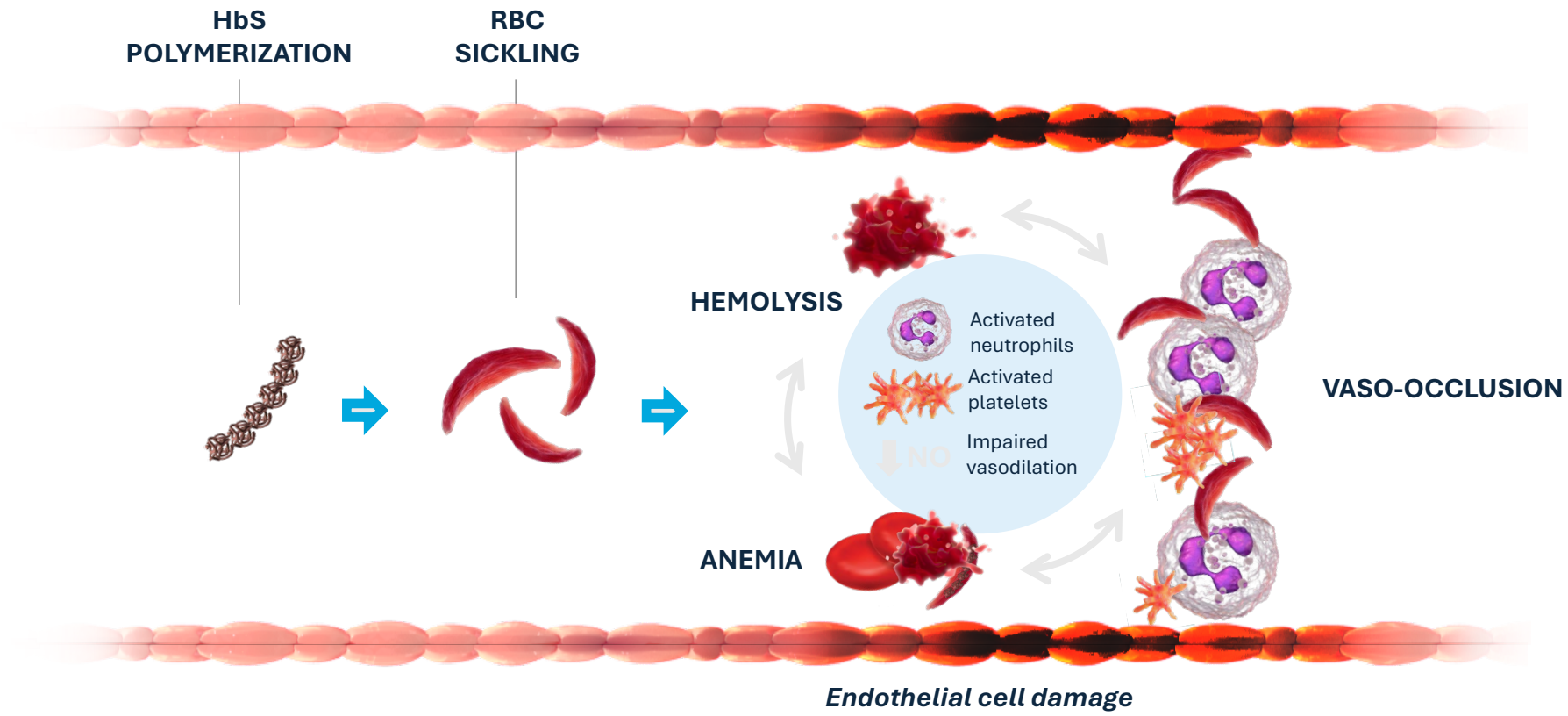
- **Consultant/Scientific Advisory Board** – Octapharma, Bayer, Novo-Nordisk, CSL Behring, Genentech, Biomarin, Takeda, Hema Biologics, Kedrion, Pfizer
- **Speakers Bureau** – Octapharma, Genentech, Biomarin, Novo Nordisk, CSL Behring, Takeda, Grifols, Spark
- **Honoraria** – Octapharma, Genentech, CSL Behring, Novo Nordisk, Takeda, BPL, Biomarin, Grifols, Pfizer
- **Research Funding** – Spark, Biomarin, Pfizer

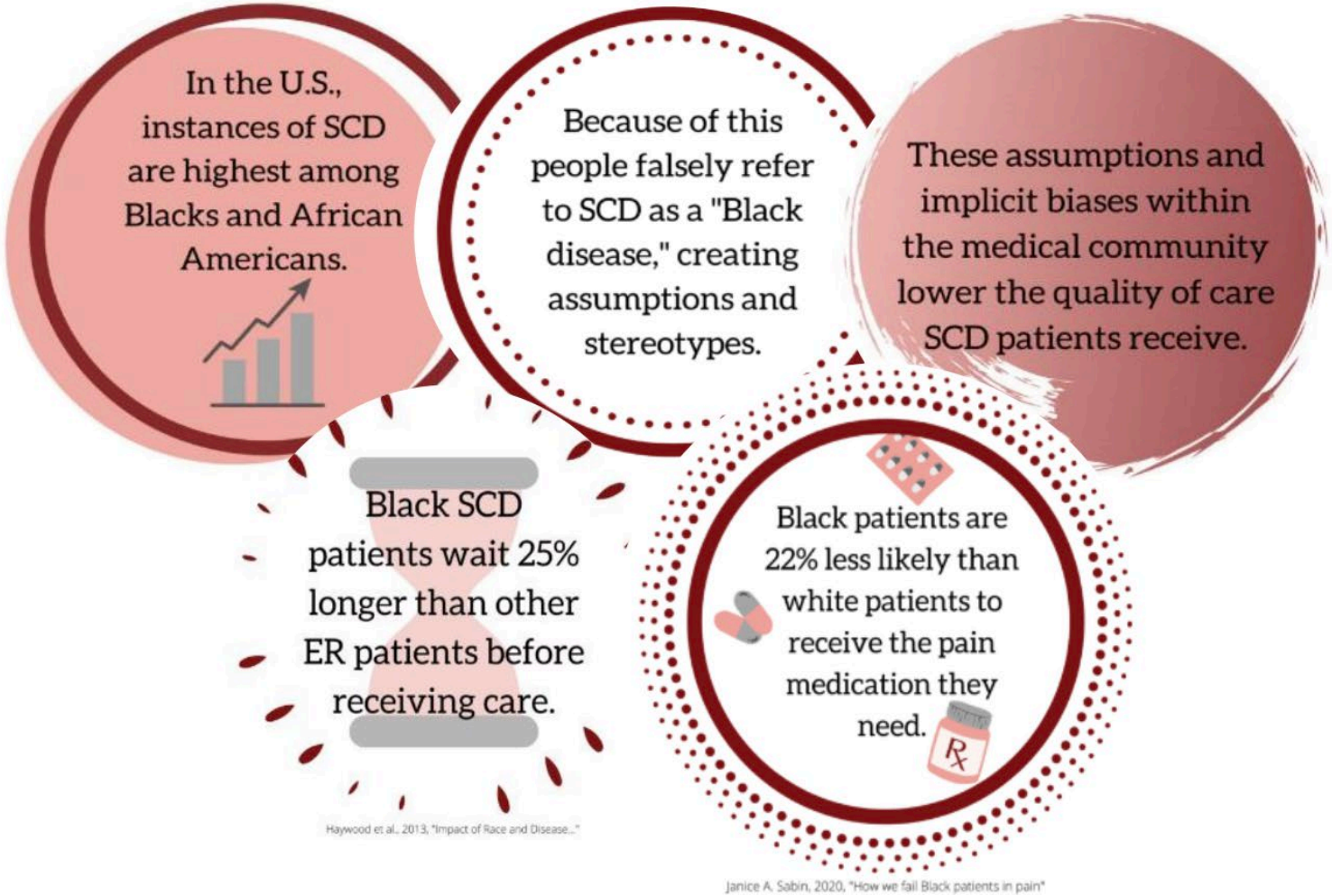
Background: Sickle Cell Disease

- Genetic mutations in the gene for the beta subunit of Hb leading to structural abnormalities of red blood cells (sickle-shape)
- Sickling leads to vascular obstruction and hemolysis
- Affects ~100,000 Americans
  - Most common in people of African descent
  - Higher prevalence globally
- $3 billion annual in direct health care costs (US)



HbS Polymerization Is the Root Cause of SCD Pathologies, Leading to Multiple Complications[1-3]

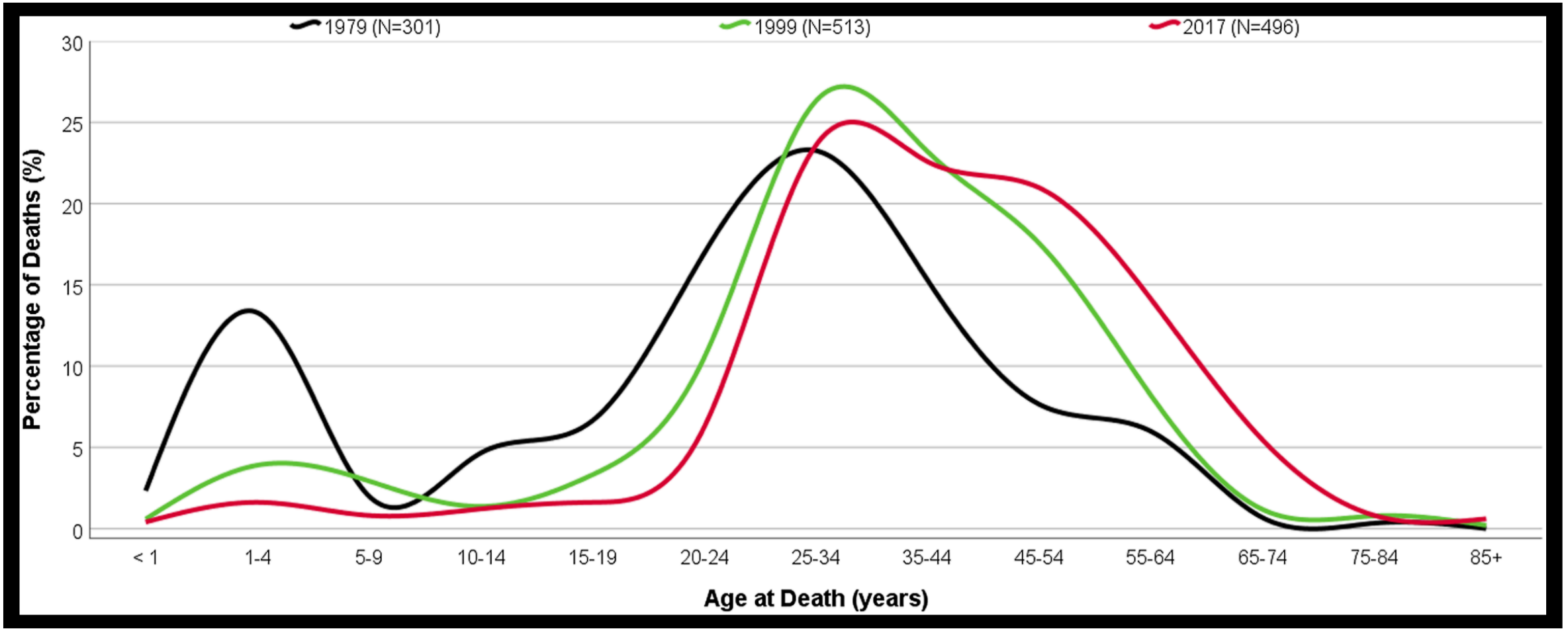




SICK CELLS

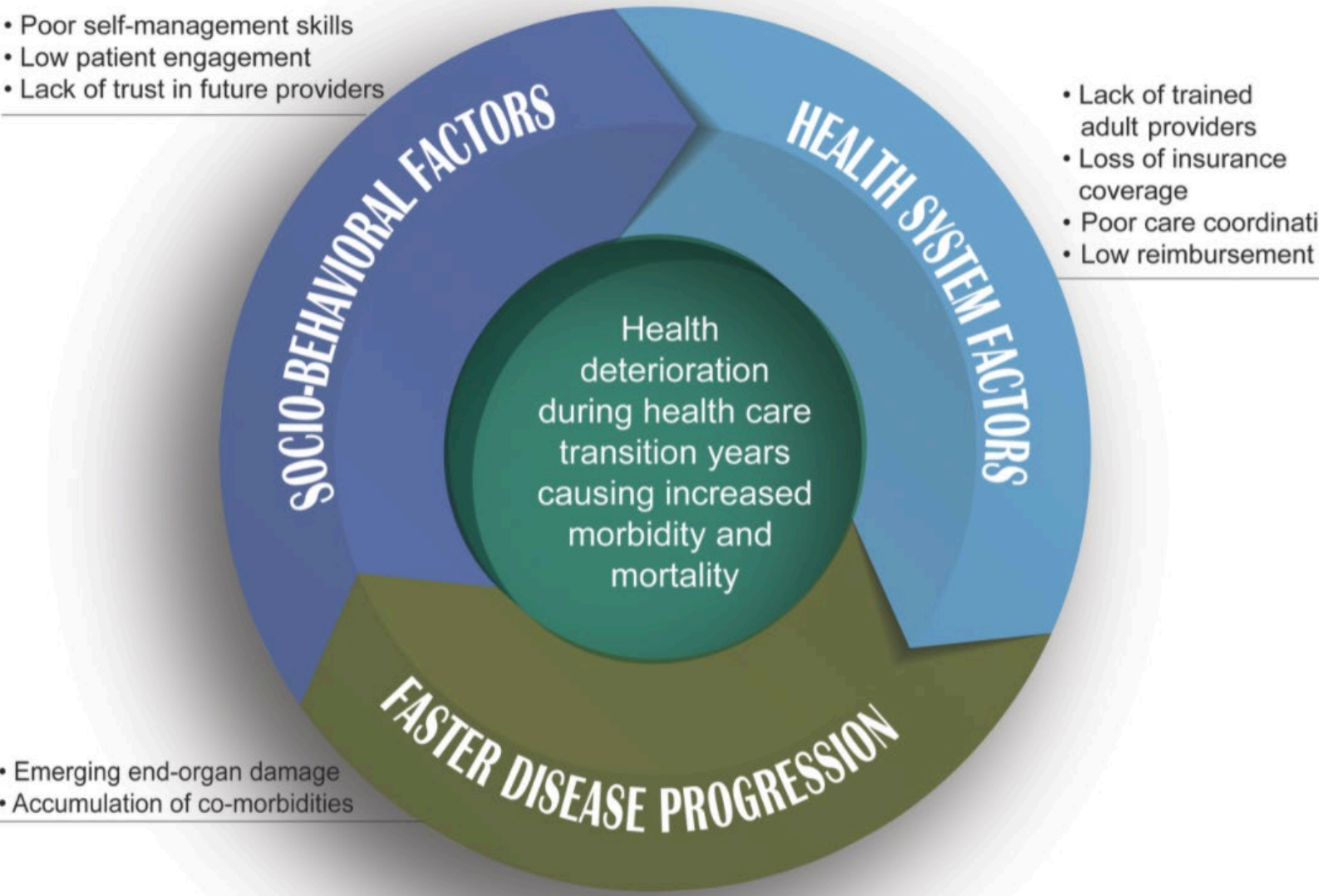
Adapted from ‘Racism in Sickle Cell: Why Black Lives in the Healthcare System are Forgotten’ by Sick Cells

Survival of Sickle Cell Disease



Proportion of deaths among individuals with SCD by age group. Adapted from Hassell[1] (source: wonder.cdc.gov) with permission.

Saulsberry, et al. *Hematology Am Soc Hematol Educ Program* (2019) 2019 (1): 496–504.

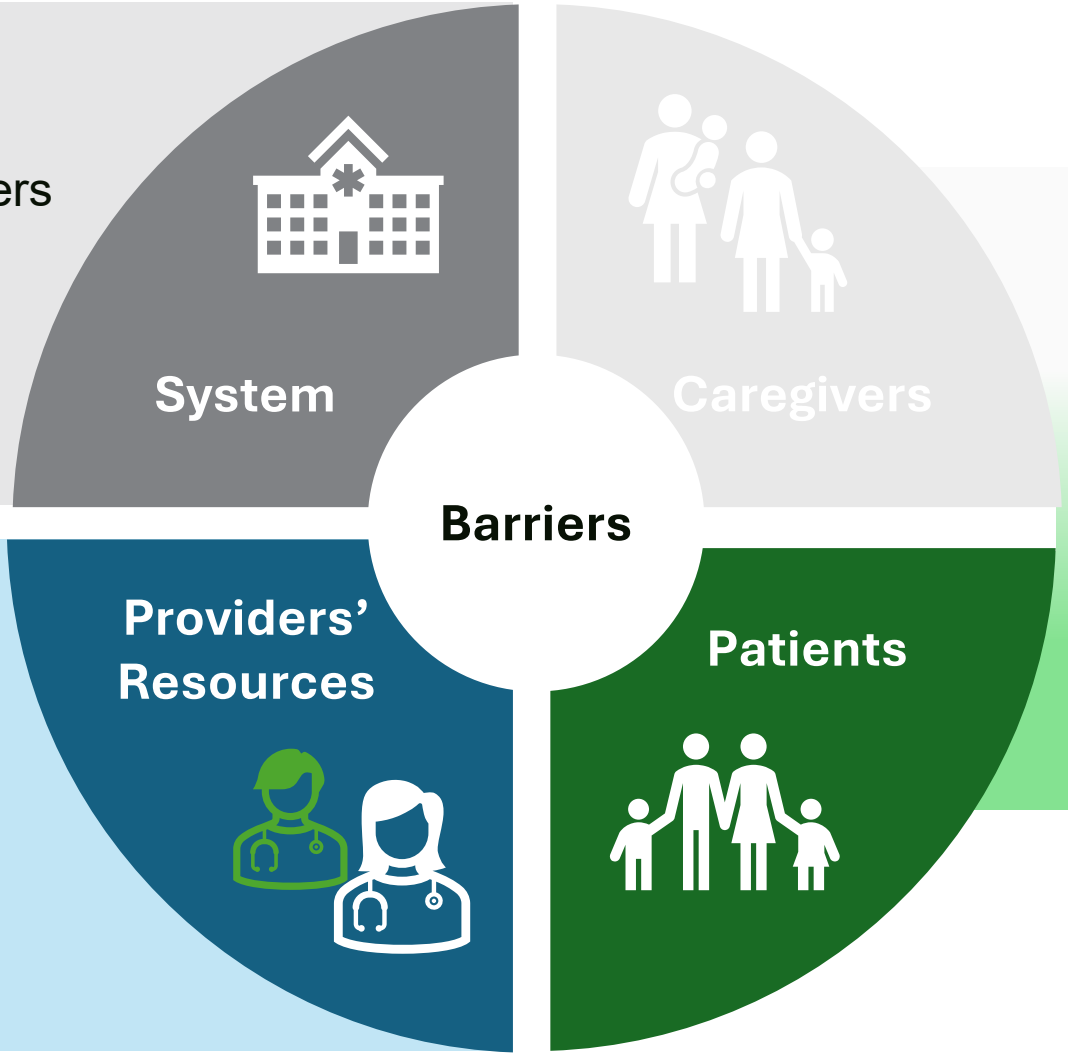


Why does transition to adult care fail?

- Saulsberry, et al. *Hematology Am Soc Hematol Educ Program* (2019) 2019 (1): 496–504.

Barriers to Treatment Remain for Patients With SCD

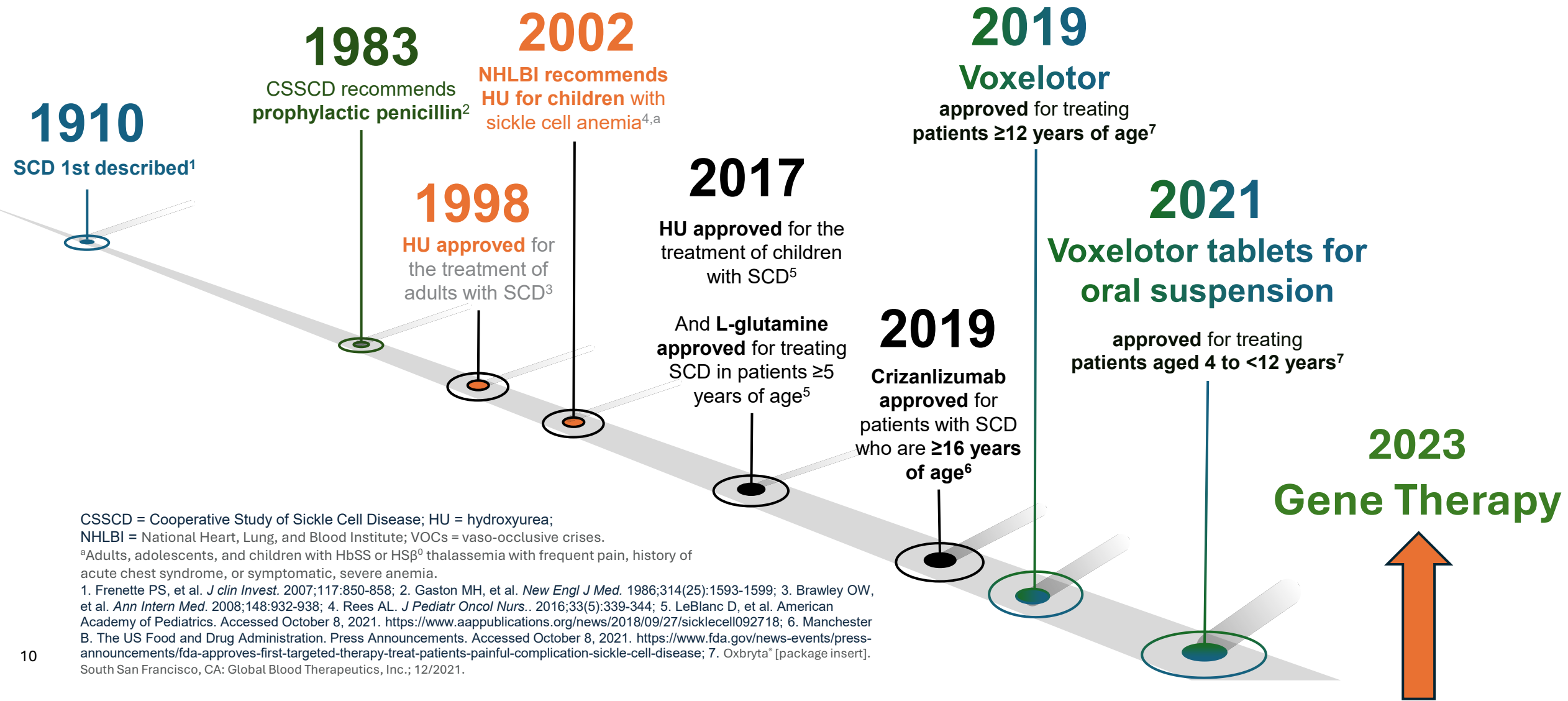
- **Financial barriers**
- **Limited access** to comprehensive care centers
- **Transitioning** from pediatric to adult care
- **Cultural and language barriers**



- **Difficulty in communication** between caregivers and patients
- **Patient concerns related to current treatment options**
- **Patient/caregiver lack of access to knowledge** about treatment options

- **Limited number of providers** who specialize in treating SCD
- **Limited resources**

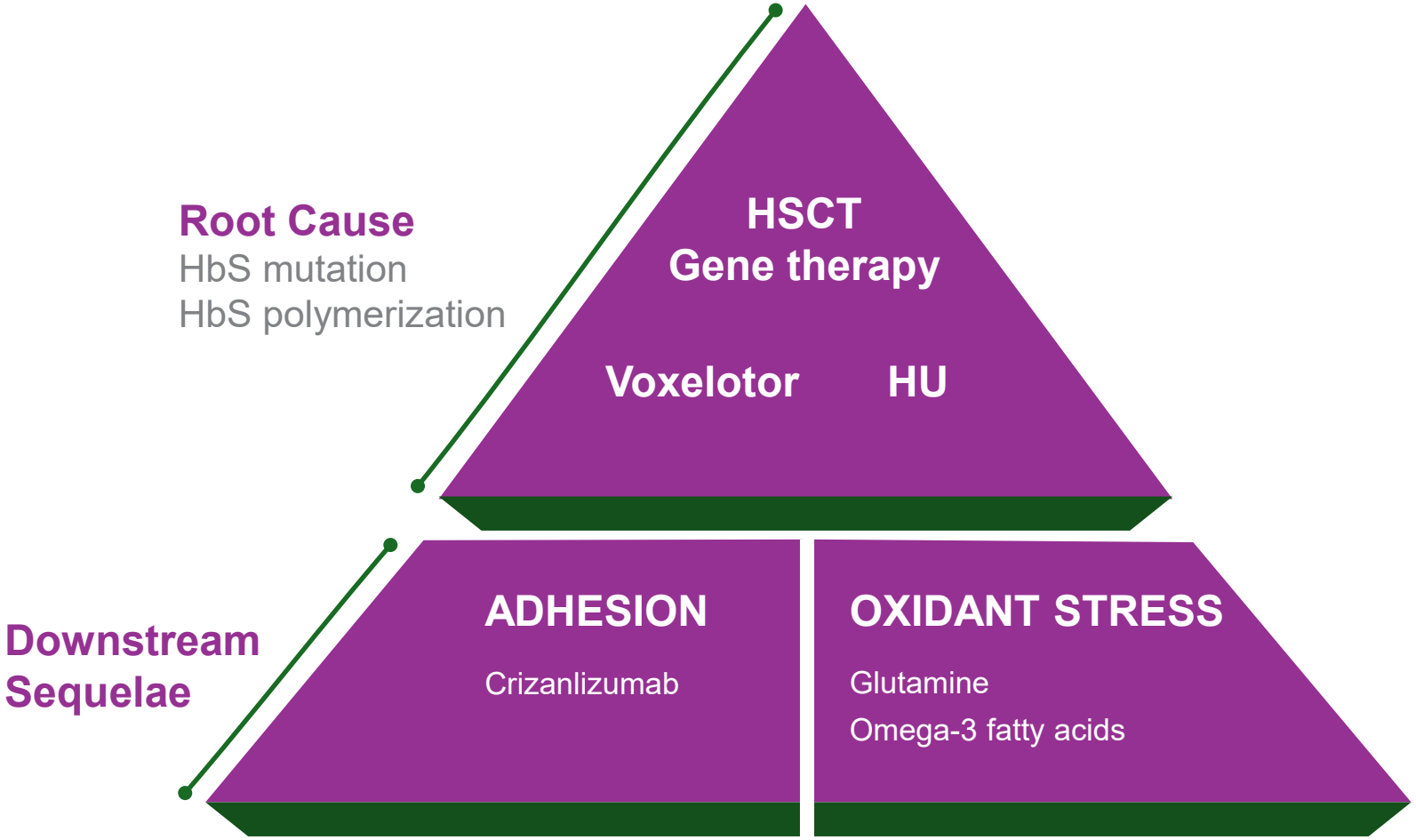
History



CSSCD = Cooperative Study of Sickle Cell Disease; HU = hydroxyurea;
NHLBI = National Heart, Lung, and Blood Institute; VOCs = vaso-occlusive crises.
[a]Adults, adolescents, and children with HbSS or HSβ^0 thalassemia with frequent pain, history of acute chest syndrome, or symptomatic, severe anemia.

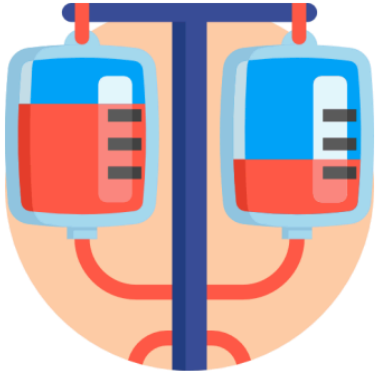
1. Frenette PS, et al. *J clin Invest*. 2007;117:850-858; 2. Gaston MH, et al. *New Engl J Med*. 1986;314(25):1593-1599; 3. Brawley OW, et al. *Ann Intern Med*. 2008;148:932-938; 4. Rees AL. *J Pediatr Oncol Nurs*.. 2016;33(5):339-344; 5. LeBlanc D, et al. American Academy of Pediatrics. Accessed October 8, 2021. https://www.aappublications.org/news/2018/09/27/sicklecell092718; 6. Manchester B. The US Food and Drug Administration. Press Announcements. Accessed October 8, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-therapy-treat-patients-painful-complication-sickle-cell-disease; 7. Oxbryta® [package insert]. South San Francisco, CA: Global Blood Therapeutics, Inc.; 12/2021.

Sickle Cell Treatment Options



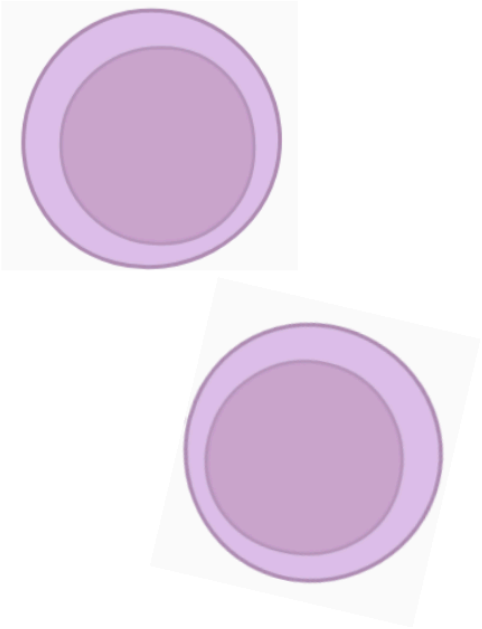
Current Standards of Care for Sickle Cell Disease

- Hydroxyurea, pain medication, blood transfusions, iron chelation therapy
- Other therapies (l-glutamine, crizanlizumab, voxelotor) have low uptake/ not cost-effective (ICER 2020 SCD Report)
- Even with treatment, numerous health consequences:
  - Severe and recurrent painful crises
  - Acute (e.g., stroke, infection) and chronic complications
  - Fertility and pregnancy-related concerns
  - Reduced health-related quality of life
  - Decreased life expectancy



Current Curative Therapy: HSCT

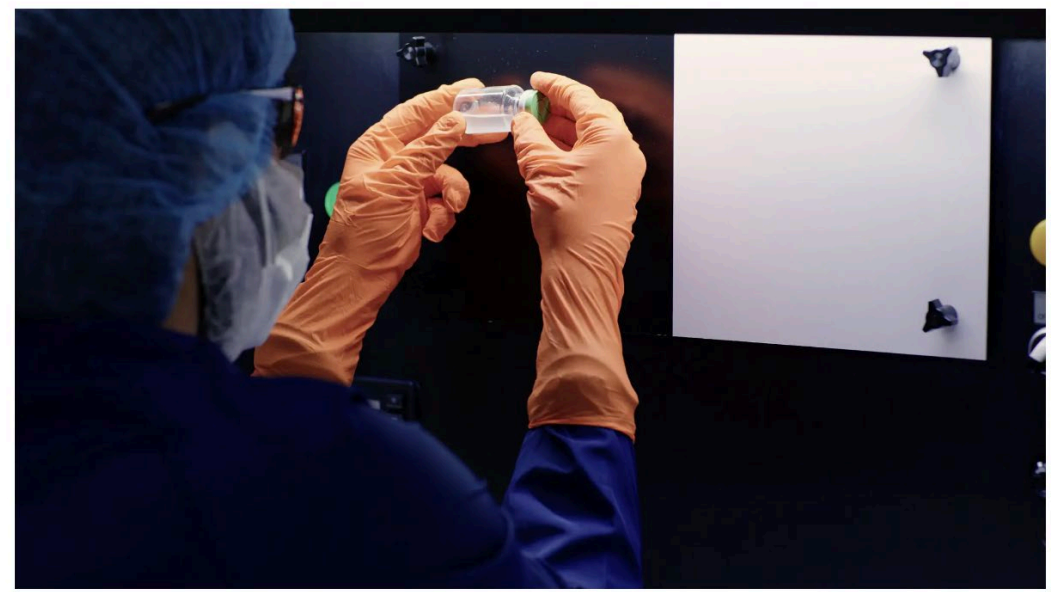
- Currently, the only **curative** option is hematopoietic stem cell transplant (HSCT *aka* Bone Marrow Transplant).
- HSCT requires a ‘match’, ideally a sibling
- Typically performed in childhood
- Requires myeloablative chemotherapy
- Risks = mortality, infection, GvHD, rejection, failure



The New York Times

F.D.A. Approves Sickle Cell Treatments, Including One That Uses CRISPR

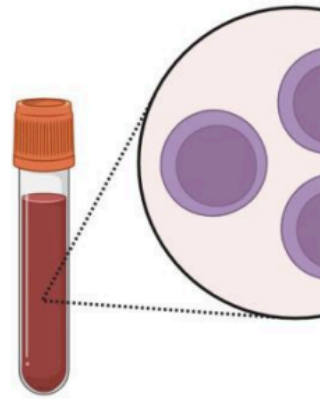
People with the genetic disease have new opportunities to eliminate their symptoms, but the treatments come with obstacles that limit their reach.



A vial of Vertex Pharmaceuticals's CRISPR Cas-9 gene therapy for sickle cell disease.
Vertex Pharmaceuticals

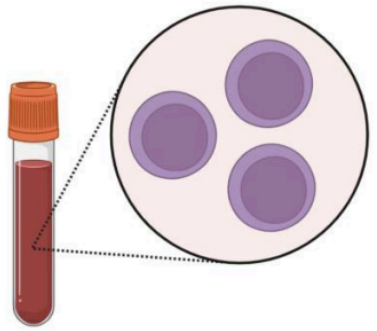
New Therapy: Lovotibeglogene autotemcel (lovo-c

- Utilizes autologous stem cell transplant
  - Stem cells modified *ex vivo* and then infused back into the patient
- Lentiviral vector used to insert functioning copies of the *HBB* gene into patients own stem cells
  - Production of modified anti-sickling adult hemoglobin, HbA^{T87Q}
- Requires myeloablative chemo/hospitalization



New Therapy: Exagamglogene autotemcel (exa-cel)

- Utilizes autologous stem cell transplant
- CRISPR/Cas9 gene-edited cell infusion therapy targeting *BCL11A* to increase fetal hemoglobin (HbF)
  - HbF≥30% considered to achieve clinical cure
- Requires myeloablative chemo / hospitalization



- Population:
  - Adolescents and adults with severe SCD (i.e., minimum of four severe vaso-occlusive events/ crises in the prior two years).
  - No access to or ineligible for HSCT (e.g., no available match)
- Interventions:
  - Lovotibeglogene autotemcel (lovo-cel)
  - Exagamglogene autotemcel (exa-cel)

- Comparators:
  - Standard of care (e.g., hydroxyurea, iron chelation, blood transfusions)

- Patient important outcomes:
  - Frequency of acute pain crisis (VOC/VOE)
  - Hospitalization
  - Ability to maintain education/employment
  - Quality of life, fertility
  - Adverse events (malignancies)
  - Mortality

-No universal definition of VOE/VOC
-All definitions included: acute chest syndrome, splenic sequestration, and priapism
-Visit to a medical facility part of the definition of severe VOC and VOEs

- Other outcomes: Hemoglobin levels, hemolysis markers, measures of gene editing durability, health services

Overview of Lovo-cel and Exa-cel Clinical Trials for Severe SCD

Intervention & Key Trial	Design	Follow-up	Primary Outcome	Age, Years (Range); % Female	Annualized Rate of VOCs/VOEs (Range)
lovo-cel **HGB-206** N=36 (Group C)*	Phase I/II, single-arm, open-label	24 months Current follow-up: 20.9 months (as of July 2021)	Proportion of participants free of (severe) VOEs	Median: 24 (12-38); 37% female	Median: 3 (0.5-13.5)
exa-cel **CLIMB-121** N=35	Phase I/II/III, single-arm, open-label	24 months Current follow-up: 11.6 months (as of September 2022)	Proportion of participants free of severe VOCs	Mean: 22.1 (12-34); 45% female	Mean: 4.2 (2-18.5)

SCD: sickle cell disease, VOC: vas-occlusive crisis, VOE: vaso-occlusive event
*earlier cohorts included Group A (N=7) and Group B (N=2), with a different manufacturing and administration process.

Key Trial Results: Lovo-cel

- Reduction in occurrence of vaso-occlusive events (VOEs)
  - 30/31 trial participants were free of severe VOEs between 6 and 18 months of follow-up
  - Median # of severe VOEs/year was reduced from 3 → 0
  - Reduction in the number of annual hospital admissions and days
  - Non-severe VOEs only reported in a small sample (n=10) with 90% free of any VOE

Lovo-cel Results

- Improvements in quality-of-life measurements
  - Reductions in pain intensity, improved Health Utility Index
  - Reduction in hours of work missed due to health problems
- Favorable Hematological Response
  - Increase in total Hb levels (8g/dL → 12g/dL, baseline to month 12)
  - Increase in levels of modified adult hemoglobin HbA^{T87Q}
  - Reduction in markers of hemolysis

- 100% of participants reported AEs
- >50% SAEs (stomatitis, thrombocytopenia, neutropenia)
- One death in Group C Cohort 20 months post-infusion, cardiac fibrosis deemed unrelated to lovo-cel.
- Two deaths related to hematologic malignancy in earlier cohort, no evidence of oncogenic insertion (Group A).
- Two cases of suspected MDS determined to be anemia from co-occurring alpha-thalassemia mutation

Key Trial Results: Exa-cel

- Reduction in occurrence of vaso-occlusive crises (VOC)
  - 16/17 trial participants (94.1%) who had at least 12 months of follow-up were free of *severe* VOCs (Sept. 2022)
    - No *hospitalization* for severe VOC during follow-up
  - Baseline average of 4.6 VOCs per year over two-year period before treatment

Key Trial Results: Exa-cel

- Improvements in quality-of-life measurements
  - Greater than minimum clinically important difference (MCID) in QoL measures (EQ VAS, FACT-G) by month six, sustained over 18 months
- Favorable Hematological Response
  - Increase in total Hb levels (9.1g/dL → 12.1g/dL, baseline to Month 3, → 11.0 g/dL during remainder follow-up)
  - Mean proportion of fetal Hb>30% by month three and through 24 months of follow-up

34.3% reported adverse events related to exa-cel treatment

40% reported SAEs (thrombocytopenia, neutropenia)

No malignancies as of September 2022

One death attributed to SARS-CoV-2 infection and potentially rel

busulfan lung injury

One patient treated required therapeutic phlebotomy

Controversies and Uncertainties

- Small sample size, insufficient data on long-term outcon durability
  - Experts suggested that long-term follow-up (>15 years) is requ establish precision around durability of treatment effect
- Effects in real-world settings and broader SCD populatic
- Comparative Effectiveness
  - Single arm trials; no comparison against HSCT or each other

Contextual Considerations

- SCD risk of many acute, severe complications (e.g., infection, stroke, myocardial infarction, blood clots, renal infarctions) that can lead to significant disability and death
- The cumulative burden of SCD disease is substantial

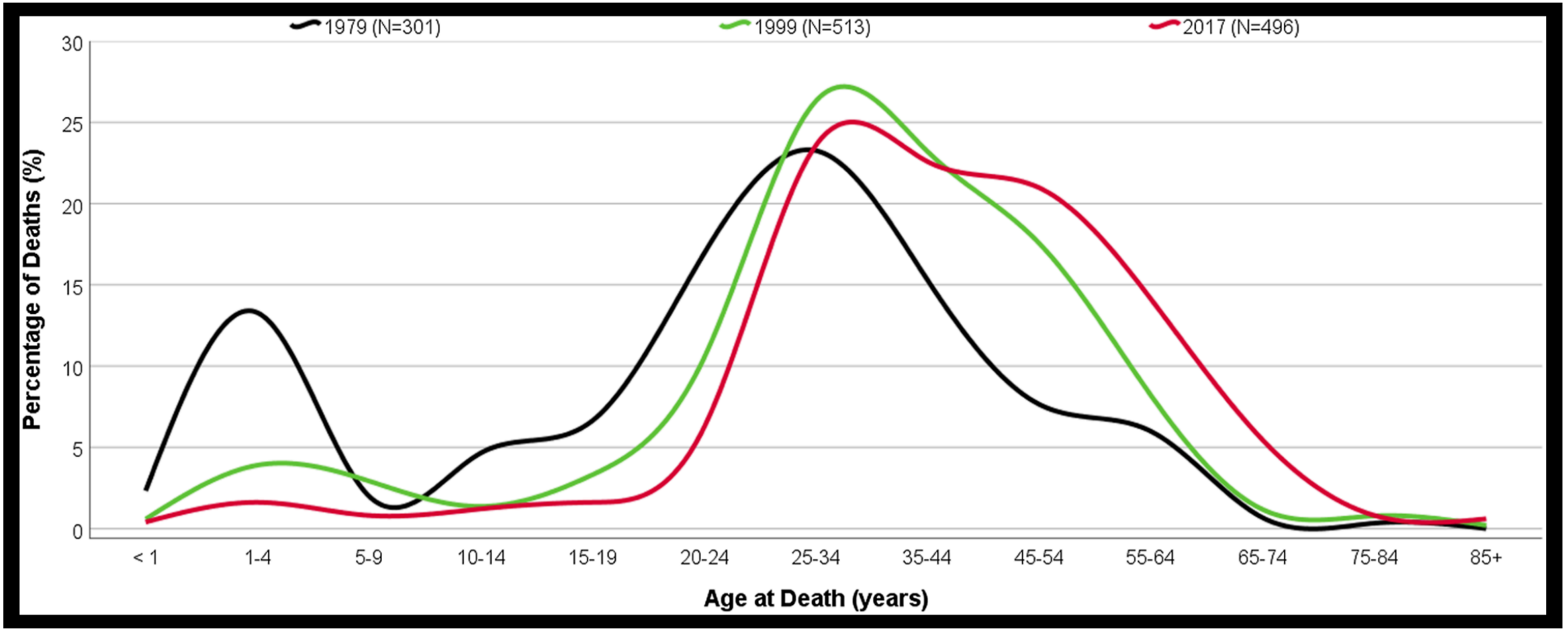
Potential Other Benefits or Disadvantages

- Benefits to potentially curative therapy:
  - QoL, ability to achieve major life goals related to education, work, or family life
  - High likelihood of improvement in caregivers' ability to return to school and/or work and overall productivity
  - Reduce the need for other long-term medical therapies (standard of care)
  - Addressing health inequities in a vulnerable population impacted by bias
- Disadvantages:
  - Requires lengthy hospitalization and myeloablation carries risks in the short-term (infection), but also long-term (fertility)

Summary: Gene therapies for Sickle Cell Disease

- Both **lovo-cel** and **exa-cel** demonstrate good efficacy in reducing severe VOE/VOCs.
- Safety outcomes have been consistent with those generally expected from myeloablative conditioning
- Careful monitoring required for risk of malignancy
- Durability and long-term safety need to be established over years of follow up, greater uncertainty with exa-cel as it would be first in class

Survival of Sickle Cell Disease



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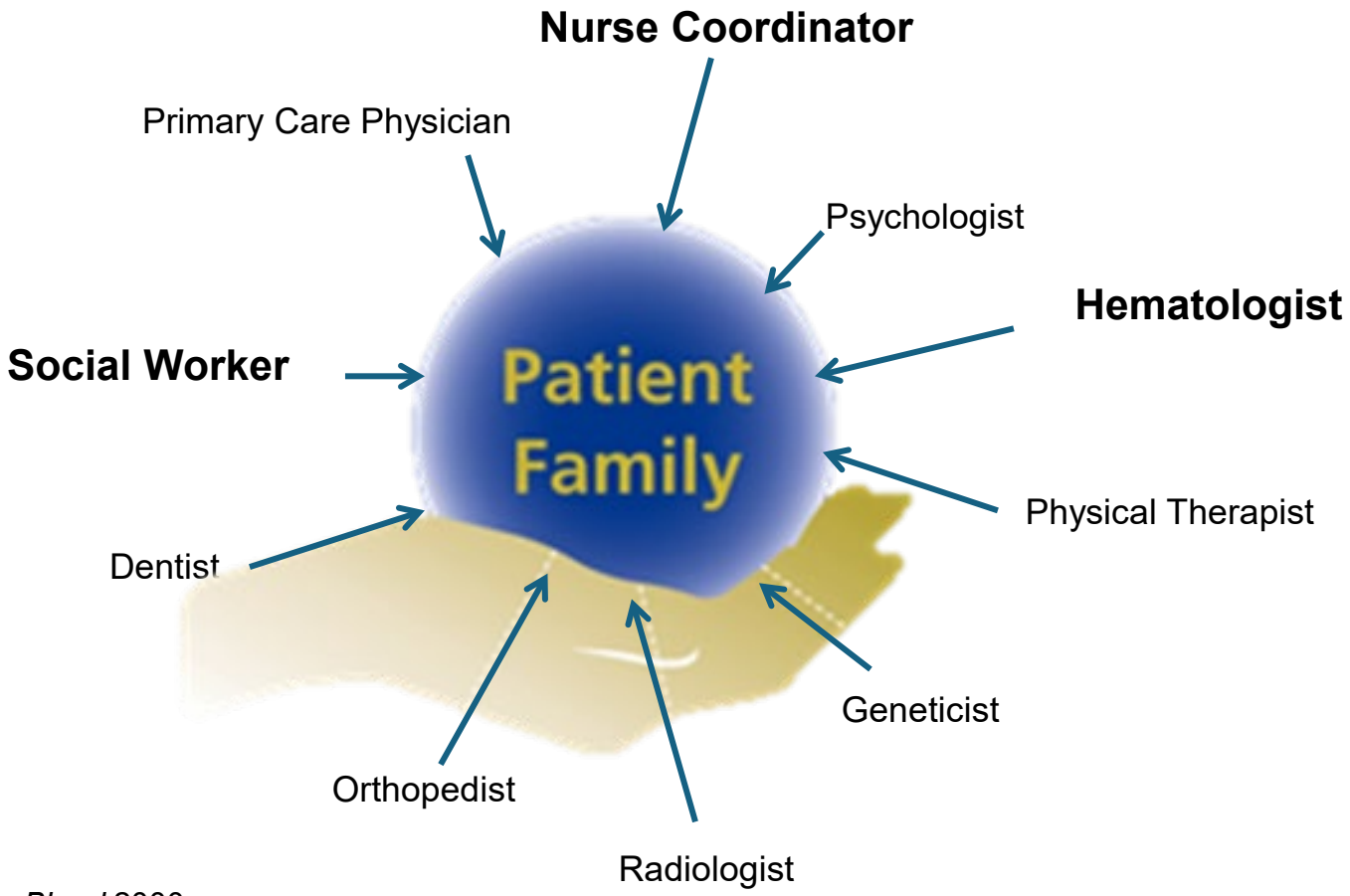
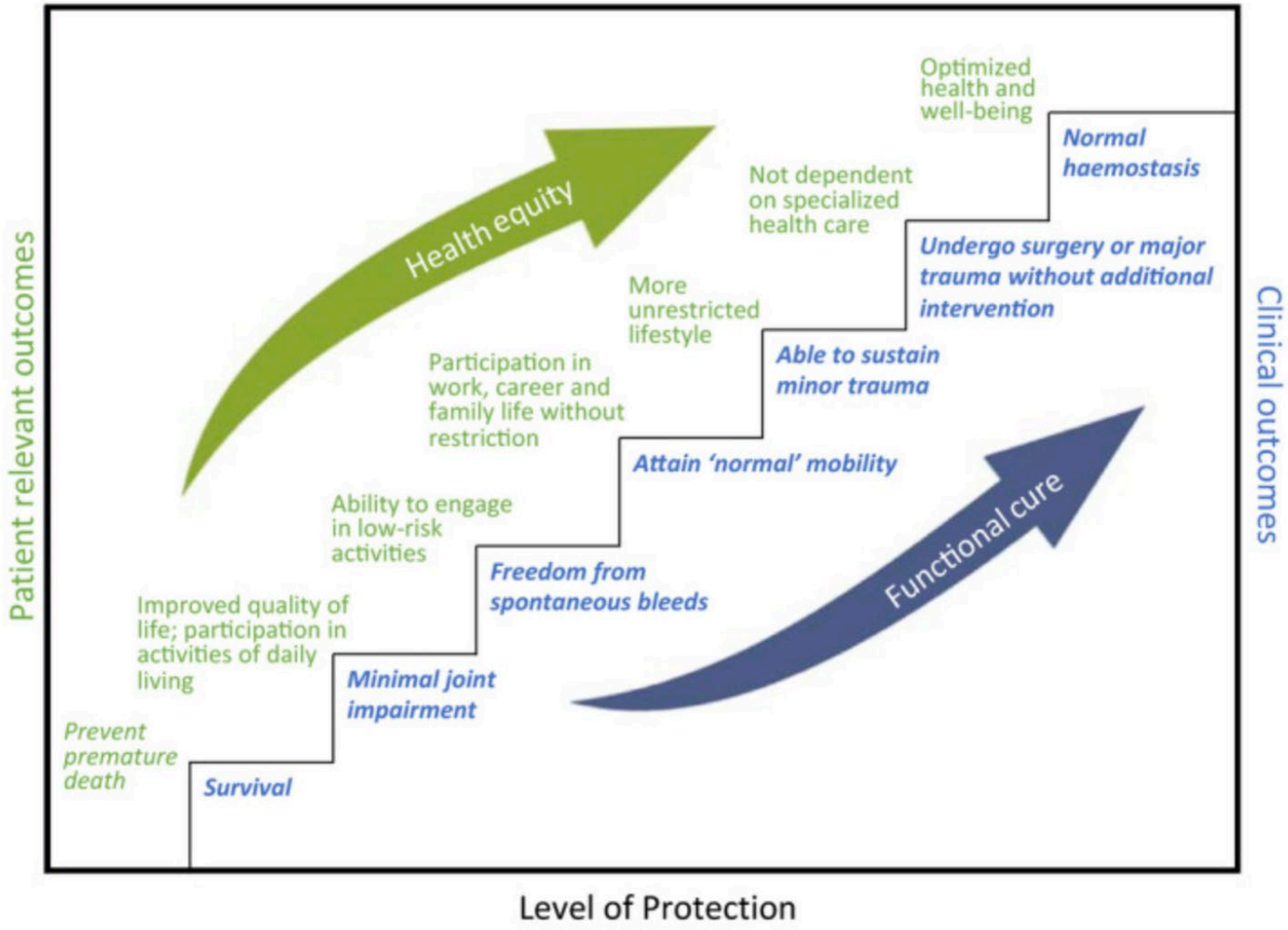
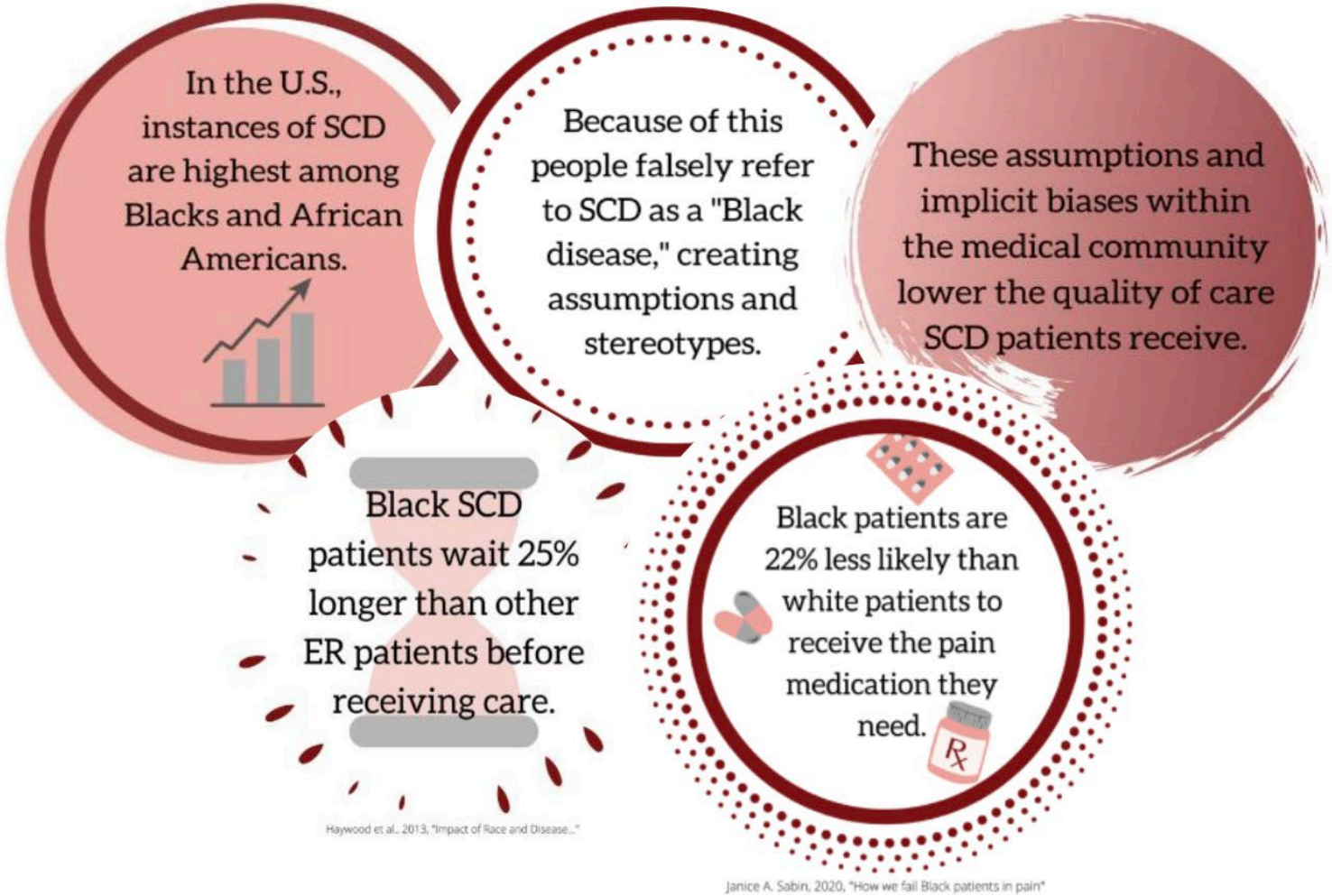
Comprehensive Care



Source: Soucie. *Blood* 2000; 96:437-442.



Haemophilia. 2020 Jan; 26(1): 17–24.



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Thank you!