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BLOOD & MARROW TRANSPLANT INFORMATION NETWORK

Treatment Options for Patients with Sickle Cell Disease

Hosted by **Blood & Marrow Transplant Information Network**

Transplant and sickle cell survivor, Maxwell Monroe

Our thanks to bluebird bio for supporting this webinar.

Webcast will begin 7:00 pm ET, 6:00 pm CT, 5:00 pm MT, 4:00 pm PT

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Meet Tonight's Speakers

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Nationwide Children's Hospital
Columbus, Ohio

Emerging Curative Options for Sickle Cell Disease:

Bone Marrow Transplant and Gene Therapy

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NATIONWIDE CHILDREN'S HOSPITAL, COLUMBUS, OH

Sickle Cell Transplant Advocacy & Research Alliance

Conflict of Interest and Disclosures

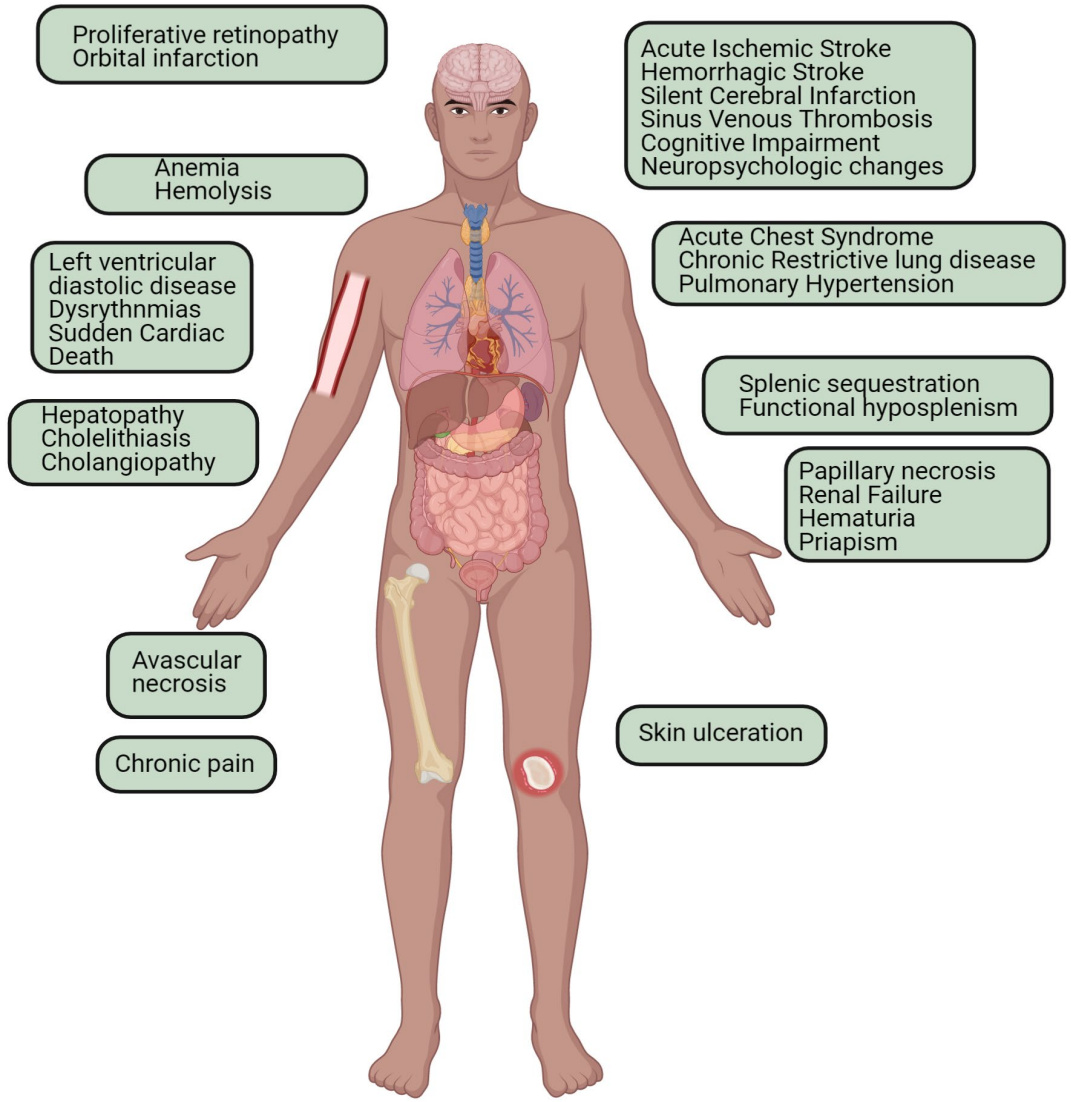
- Conflict of Interest:
  - Dr. Rangarajan: Honorary Consultant for Medexus (Treosulfan)
  - Alison Towerman: None
- May discuss off-label use of some medications

Learning Objectives

- Provide an overview and describe the process of bone marrow transplant (BMT) and gene therapy for sickle cell disease (SCD)
- Summarize outcomes of BMT in SCD from both matched sibling and non-matched sibling donors
- Compare outcomes of gene therapy with BMT for SCD

Overview of Sickle Cell Disease

- Inherited disorder that affects red blood cells
- Affects ~100,000 Americans (CDC, 2020)



- Defect in hemoglobin (protein) inside red cell = Sickle Hemoglobin

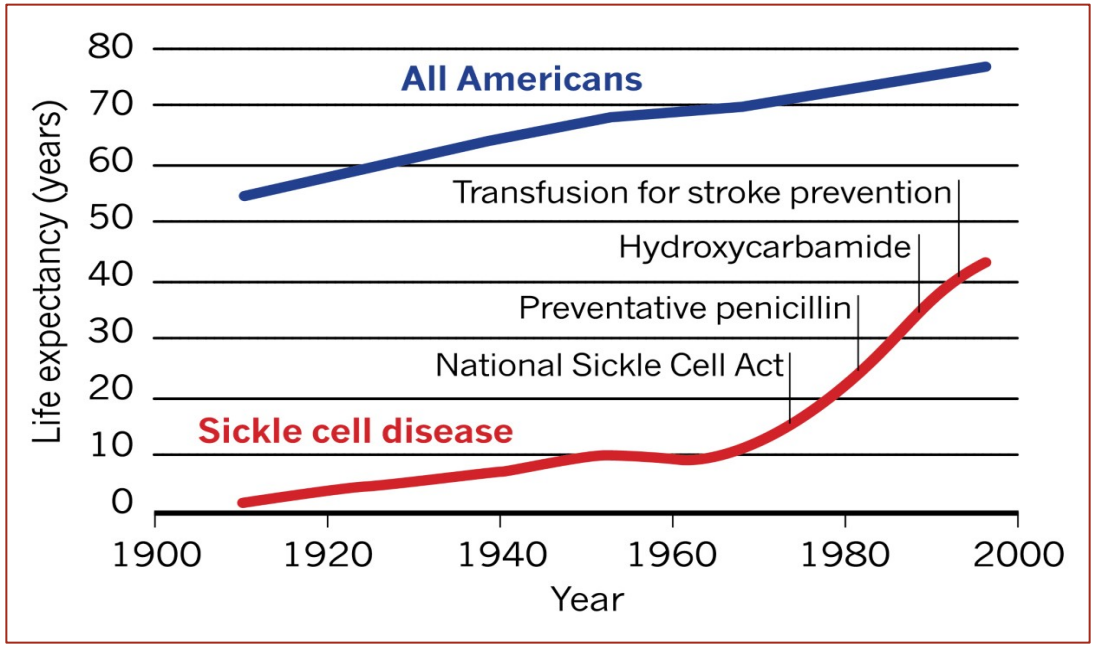
Normal red blood cell

Sickle red blood cell

Adapted from Piel FB, et al. *N Engl J Med.* 2017;376:1561-1573

Sickle Cell Disease: Progress and Problems

- Progress:
  - Improved childhood survival
  - Early diagnosis
  - Supportive care
  - Disease modifying therapies



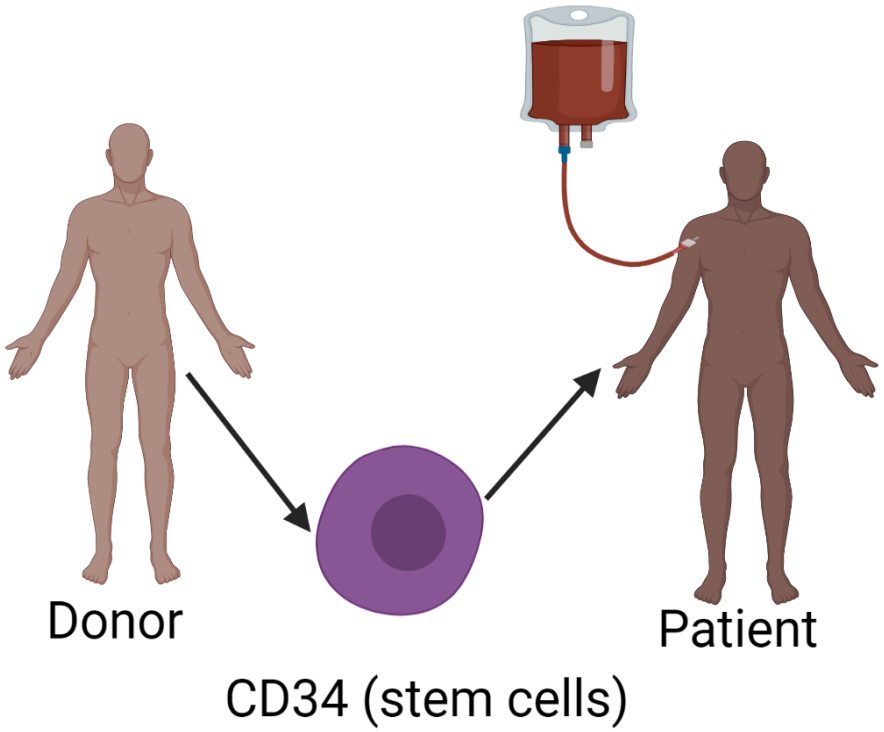
- Problems:
  - Early mortality
  - Median age of survival: 48 years (1990s to 2019)

Pleasants, S. *Nature.* 515,S2(2014)

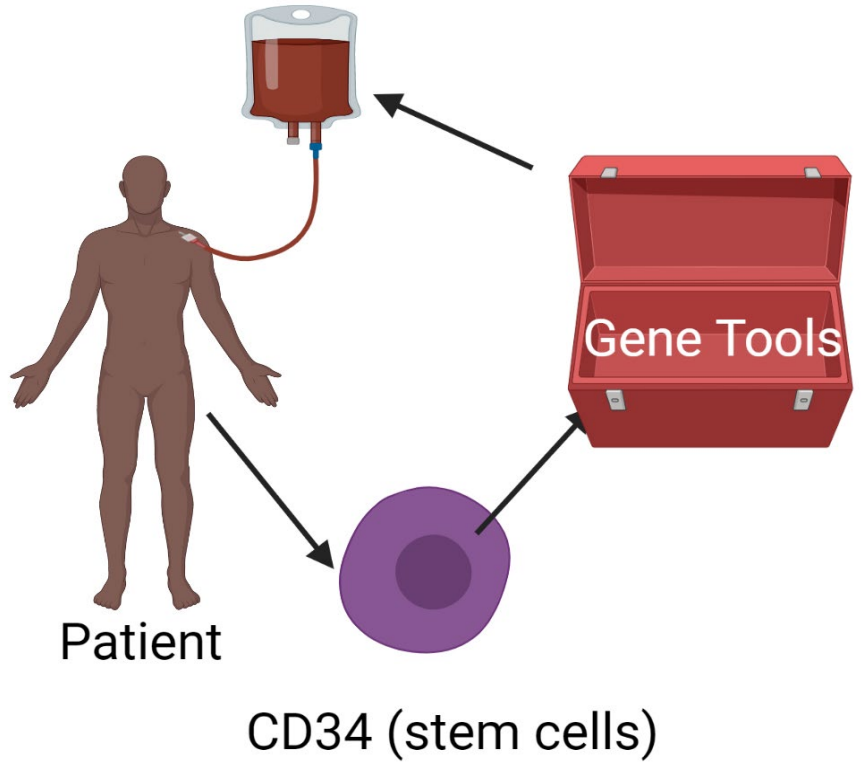
Platt OS, et al. *N Engl J Med*. 1994;330:1639-44.
DeBaun M, et al. *Blood.* 2019;133:615-617.

Forward Steps: Cure a Reality

Bone Marrow Transplant

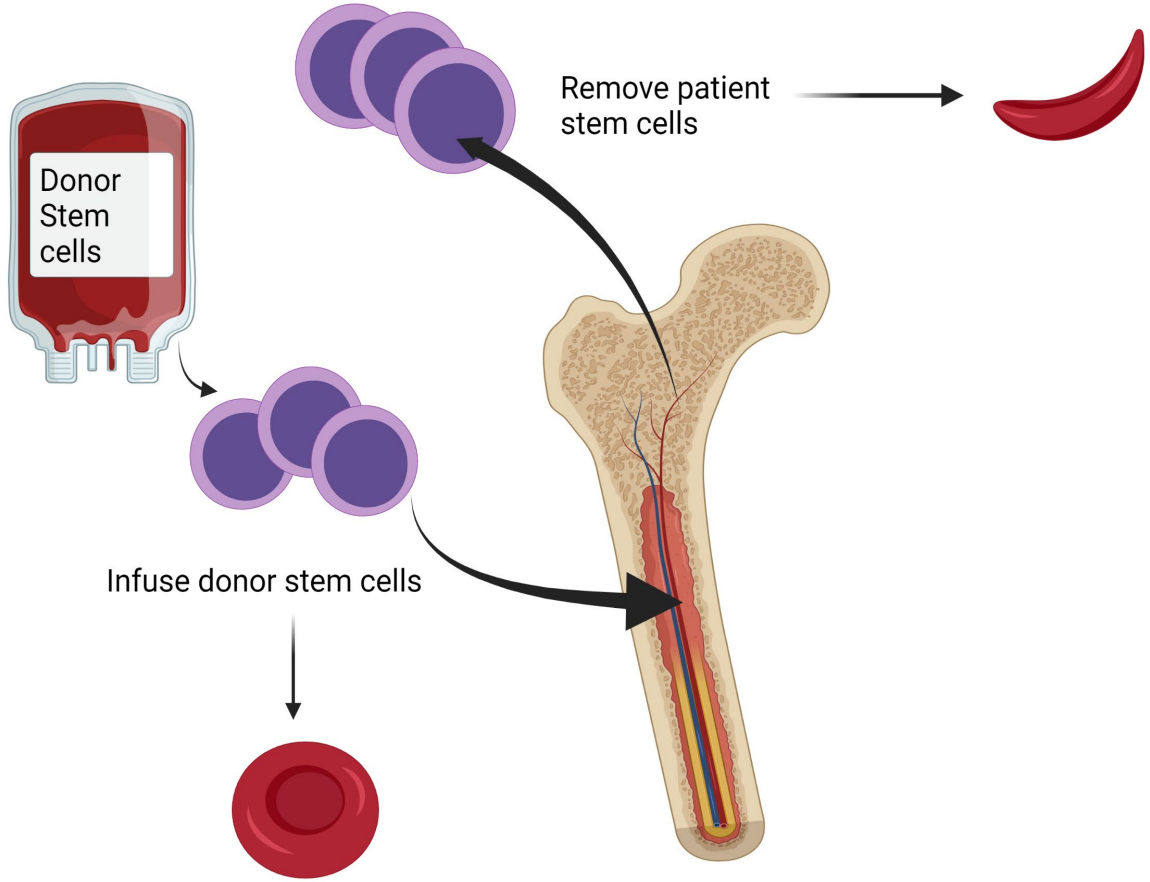


Gene Therapy



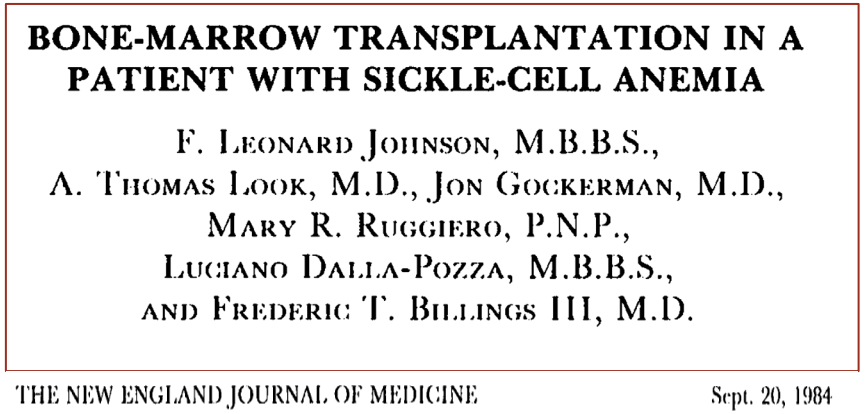
The Bone Marrow Transplant Process

- Stem cells housed in bone marrow give rise to different cells in body
- In sickle cell disease RED CELL is defective
- Therefore, replacing stem cells = cure
- Bone marrow transplant replaces patient's stem cells with those from another person (nor self)
- Chemotherapy creates space in the bone marrow for new cells to set up factory and star production



BMT in Sickle Cell Disease: Background

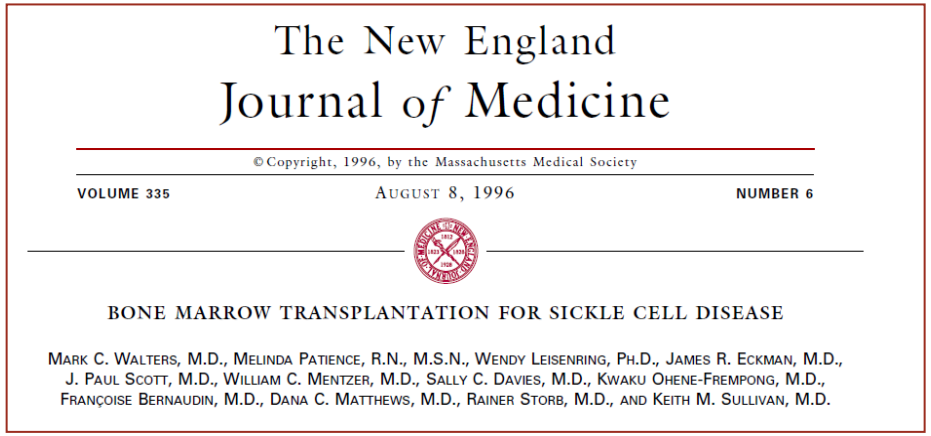
- First patient cured of sickle cell disease through bone marrow transplant described in 1984
- First international multi-center clinical trial in 1996
- Advances in treatment regimens
- Ability to use donors other than sibling donors
- <3000 patients worldwide



BONE-MARROW TRANSPLANTATION IN A PATIENT WITH SICKLE-CELL ANEMIA

F. Leonard Johnson, M.B.B.S., A. Thomas Look, M.D., Jon Gockerman, M.D., Mary R. Ruggiero, P.N.P., Luciano Dalla-Pozza, M.B.B.S., and Frederic T. Billings III, M.D.

THE NEW ENGLAND JOURNAL OF MEDICINE Sept. 20, 1984



The New England Journal of Medicine

VOLUME 335 AUGUST 8, 1996 NUMBER 6

BONE MARROW TRANSPLANTATION FOR SICKLE CELL DISEASE

Mark C. Walters, M.D., Melinda Patience, R.N., M.S.N., Wendy Leisenring, Ph.D., James R. Eckman, M.D., J. Paul Scott, M.D., William C. Mentzer, M.D., Sally C. Davies, M.D., Kwaku Ohene-Frempong, M.D., Françoise Bernaudin, M.D., Dana C. Matthews, M.D., Rainer Storb, M.D., and Keith M. Sullivan, M.D.

Johnson L, et al. *N Engl J Med*. 1984;311:781-783.
Walter M, et al. *N Engl J Med.* 1996;335:369-376
Cimpeanu et al.*Blood Rev*. 2021; 100868..

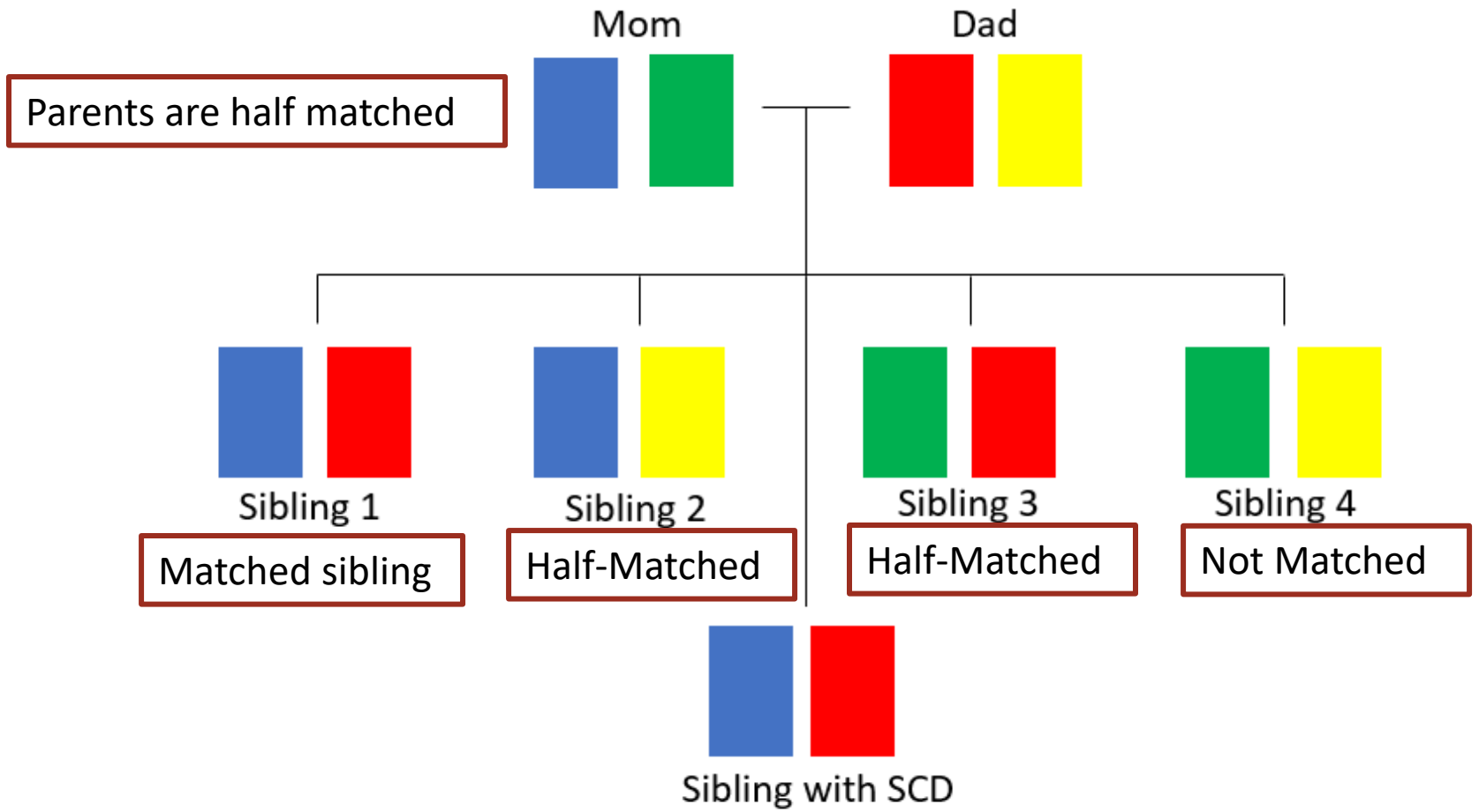
Bone Marrow Transplant for SCD: Eligibility

- Medical indications: Severe disease
  - 1 stroke
  - 2 acute chest syndrome episodes
  - > 3 pain crises (prior 1-2 years)
  - Irreversible organ damage
- Patient motivation
- Support system

Children	Adults (age 15-40 years)
Stroke or central nervous system event lasting longer than 24 hours	Clinically significant neurological event (stroke) or any neurological deficit lasting >24 hours
Impaired neuropsychological function with abnormal cerebral MRI imaging and angiography	History of 2 or more episodes of acute chest syndrome for 2 years, despite support care measures
Recurrent acute chest syndrome	History of 3+ severe pain crises per year for 2 years, despite supportive care measures
Stage I or II sickle lung disease	Red cell transfusion therapy 8 or more times per year for 1 year or more to prevent vaso-occlusive complications
Recurrent vaso-occlusive painful episodes or recurrent priapism	Tricuspid valve regurgitant > 2.7 m/s on Echocardiogram
Sickle nephropathy (glomerular filtration rate 30-50% of predicted normal)	

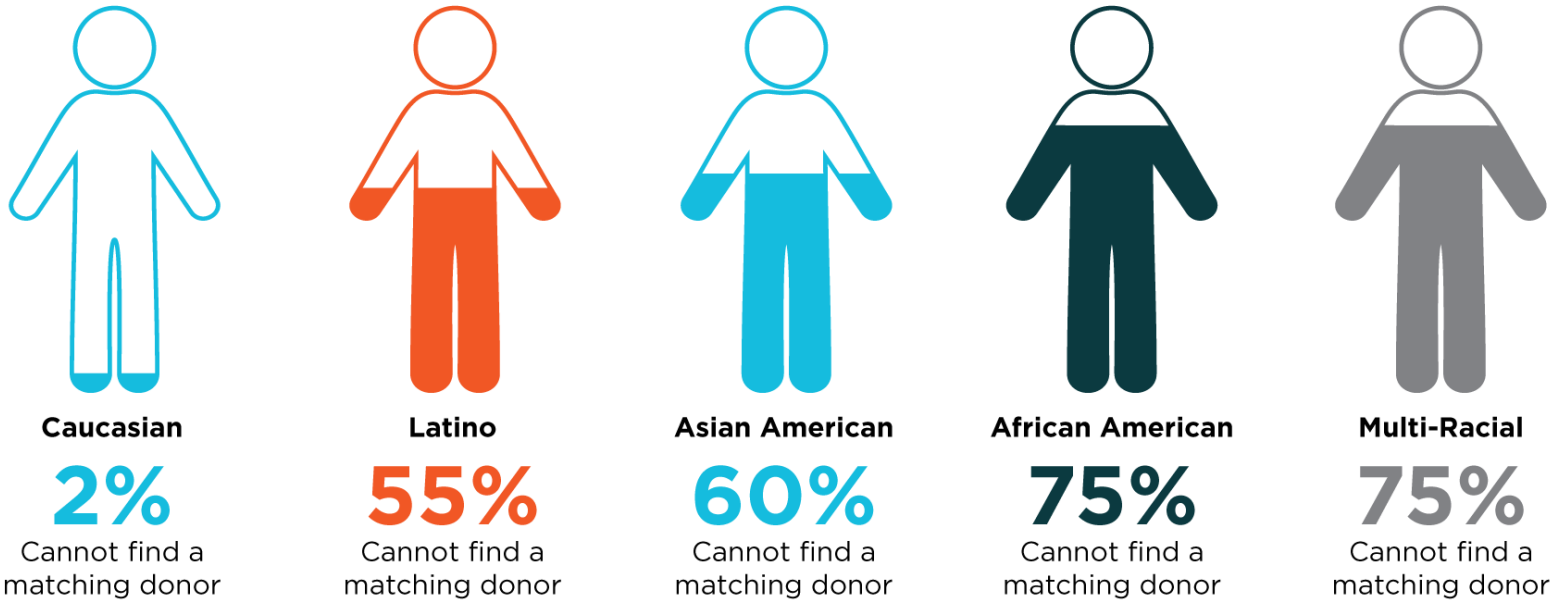
Arnold SD, et al. *Br J Haematol.* 2016; 174:515-525.

Ideal Donor: Matched Sibling



Difficulty Finding a Matched Donor for African Americans

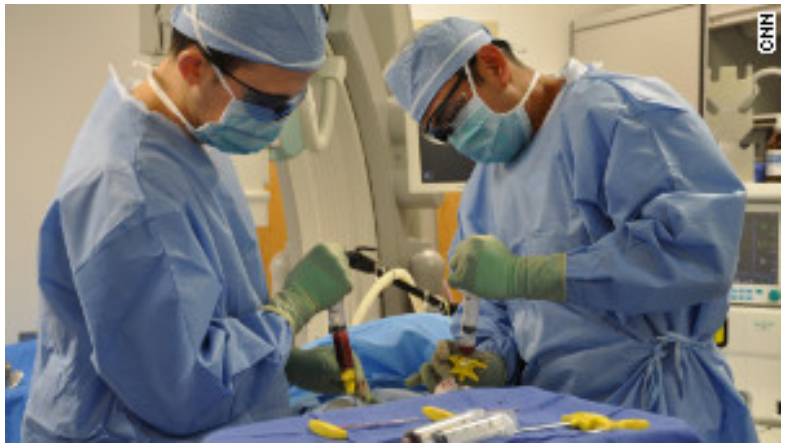
- Likelihood of finding
  - matched sibling donor ~18%
  - matched unrelated donor <18%
  - half-matched donor: universal availability



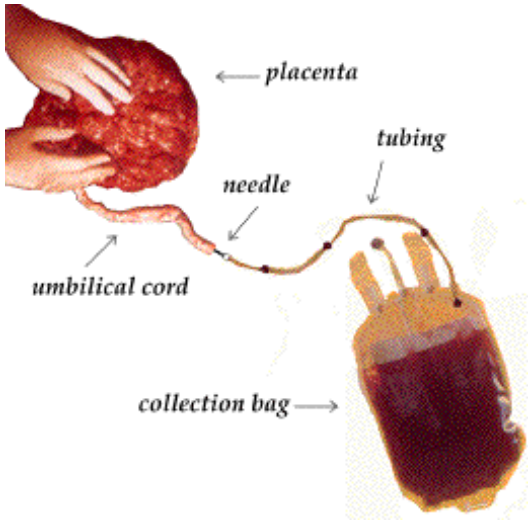
Mentzer WC,et al. *Am J Pedatric Hematol Oncol*. 1994;16:27-29.

Stem Cell Sources

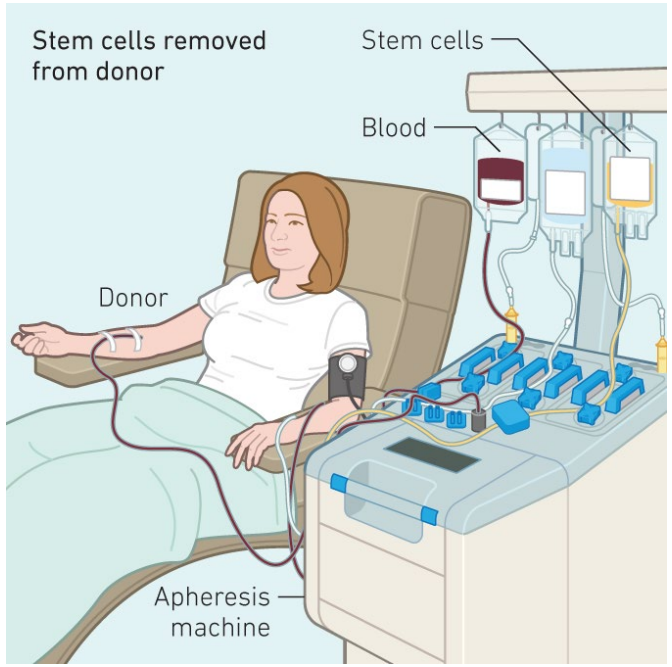
Bone Marrow Harvest



Umbilical Cord Blood



Peripheral Blood



Bone Marrow Transplant Process

1. Pre transplant workup: 1-3 months prior to transplant
2. Preparative regimen (combination of chemotherapy ± radiation): 1-3 weeks before transplant
3. Transplant: Day 0
4. Engraftment: 2-6 weeks after transplant
5. Early recovery post-transplant: 1-6 months after transplant
6. Late recovery post-transplant: 6 months to years after transplant

- Not a surgery!

Maryland Sickle Cell Disease Association, 2017

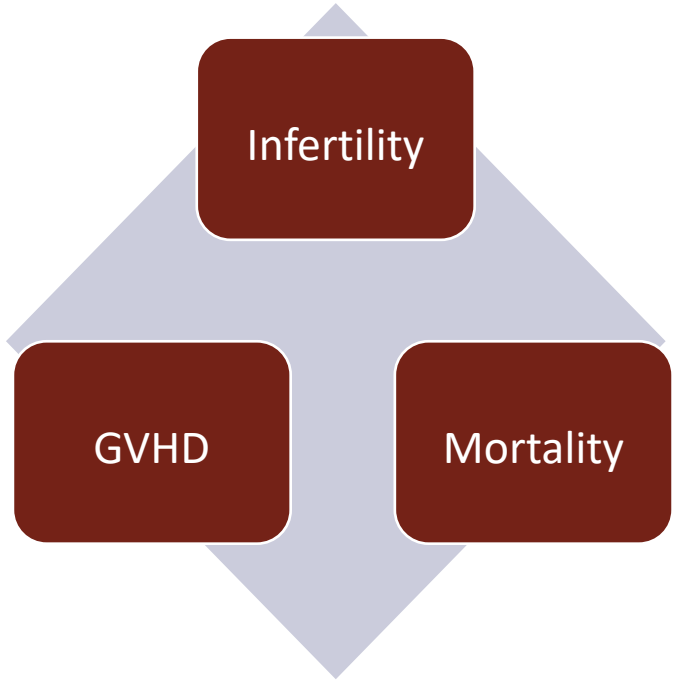
Benefits of Bone Marrow Transplant in SCD

- Prevent further organ damage
- Stable to improved:
  - Lung, heart and spleen function
  - Brain imaging, Transcranial dopplers
- Prevention of cognitive decline
- Health Related Quality of Life
  - General health
  - Decreased pain
  - Physical
  - Emotional
  - Psychosocial
- Chance for a cure!

Adapted from Badaway, SM, et al. *Blood Adv.* 2021; 5(2):570-583.

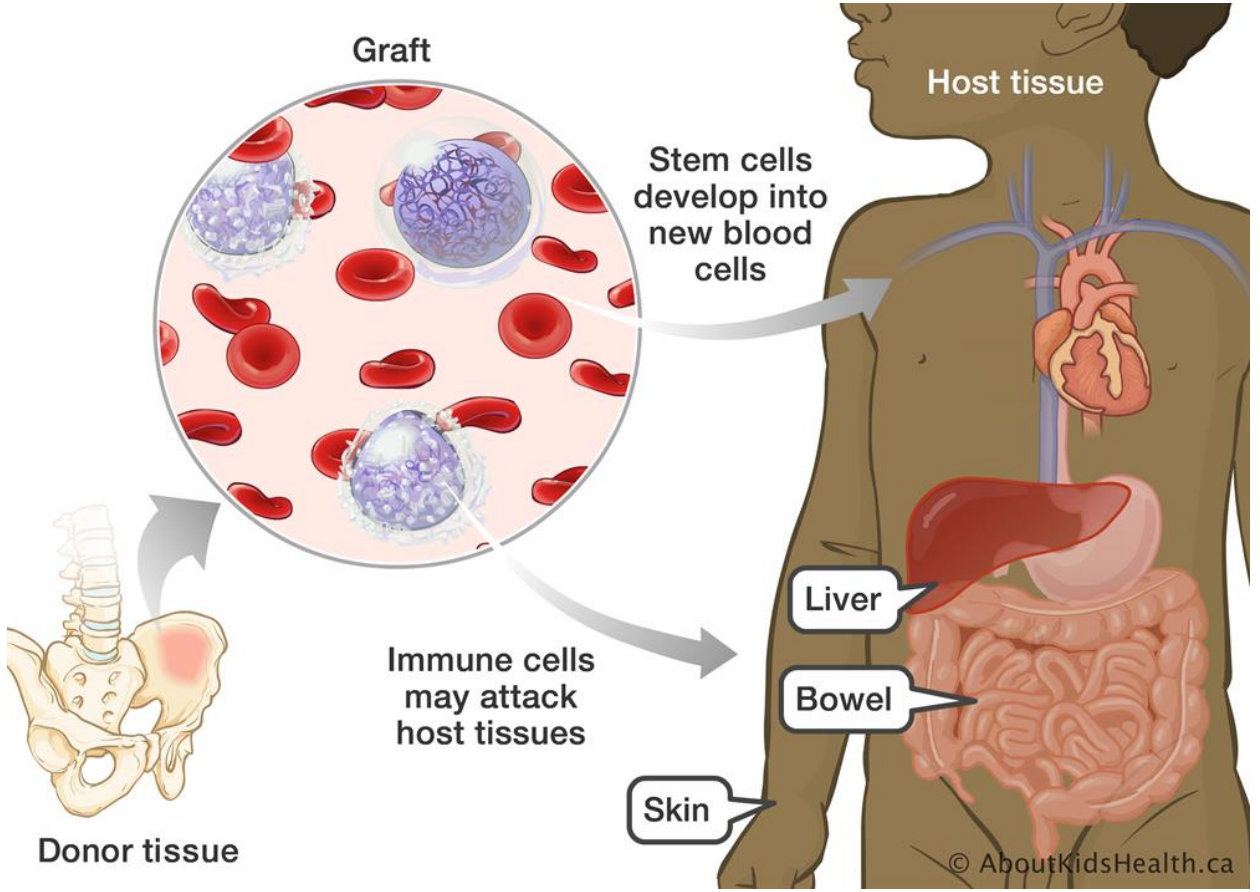
Bone Marrow Transplant in SCD: Risks

- **Immediate**
  - Chemotherapy side effects
  - Infection
  - Graft-versus-host disease
  - Rejection (Failure of Transplant)
  - Social and emotional issues
- **Long term side effects**
  - Impaired organ function
  - Infertility
  - Risk of cancers (due to chemotherapy: very low)
- **Death**



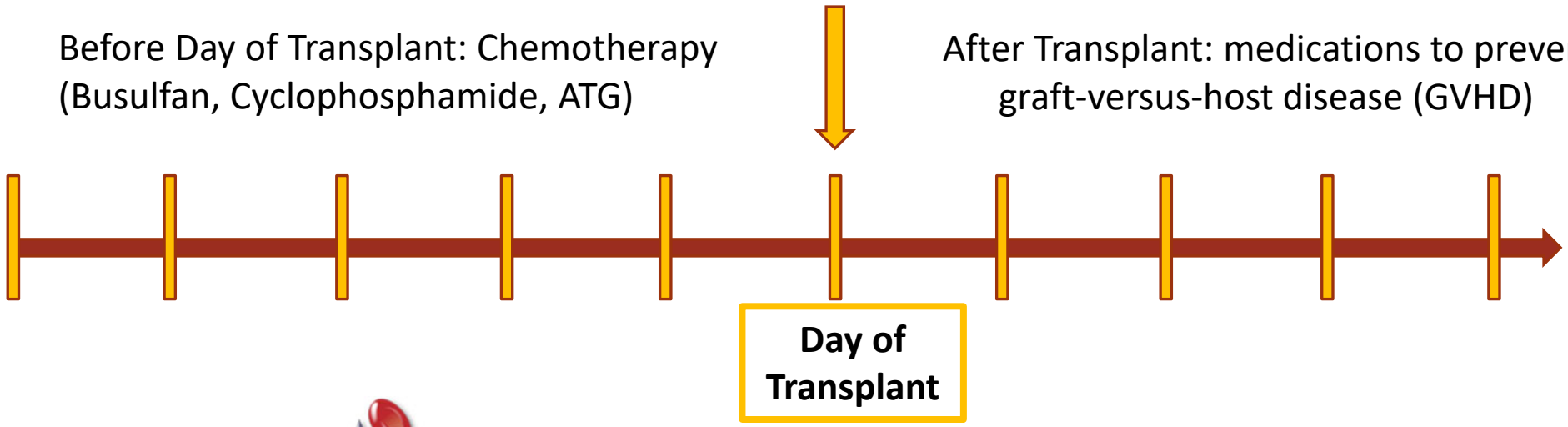
Graft Versus Host Disease (GVHD)

- Complication of BMT
- New (donor) white cells see patient tissues/cells as foreign/non-self and attacks them
- Can affect any organ eventually
- Acute (early after transplant)
- Chronic (late after transplant)
- Treatment: Medicines that suppress the immune system



Traditional Bone Marrow Transplant in SCD

- Strong Chemotherapy: Busulfan, Cyclophosphamide, Anti-thymocyte globulin (ATG)
- First transplants used matched sibling donors (MSD)
- Prevention of Graft versus Host Disease (GVHD): Tacrolimus or Cyclosporine & Methotrexate



Outcomes in Matched Sibling Donor Transplants Strong Chemotherapy (earlier studies)

Study, Year	# of patients	Median Age	Graft Failure	Overall Survival	Event-Free Survival	GVHD
Vermylen, 1998	50	7.5 years	10%	93%	82%	20%
Walters, 2000	50	9.4 years	10%	94%	84%	12%
Bernaudin, 2010	144	9 years	<2%	95%	93%	23%

Follow up ranging from 3 year to 5.5 years

Graft failure: Transplant did not work

Overall Survival: Alive with or without SCD disease

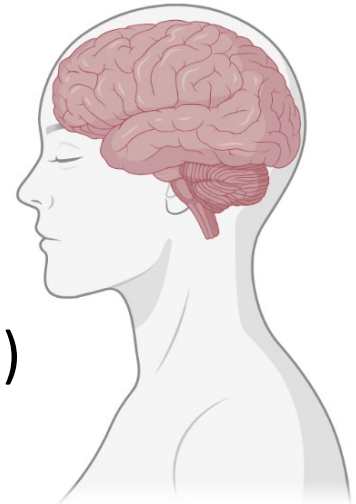
Event Free Survival: Alive without SCD

GVHD: Graft versus host disease

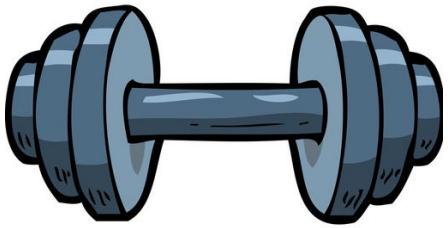
Vermylen C, et al. *Bone Marrow Transplant.* 1998; 22: 1-6.
Walters M, et al. *Blood*.2000; 95:1918-1924.
Bernaudin F, et al. *Blood* 2010; 116:3518.

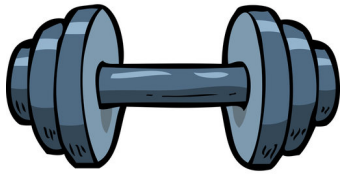
Traditional BMTs: Strong Chemotherapy

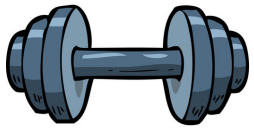
- Matched sibling donor: Bone marrow (BM) = umbilical cord blood (UCB)
- Umbilical cord blood : Prefer to wait till donor is older & use BM alone or BM+ UCB
- Complications
  - Infertility
  - GVHD, Mortality
  - **Neurological (brain) complication**: 20-38% (seizures, headaches, bleeds)
- Therefore, **need for less toxic chemotherapy regimens**



Strength of Chemotherapy Regimens







Myeloablative (MA)

Reduced intensity (RIC)

NMA*

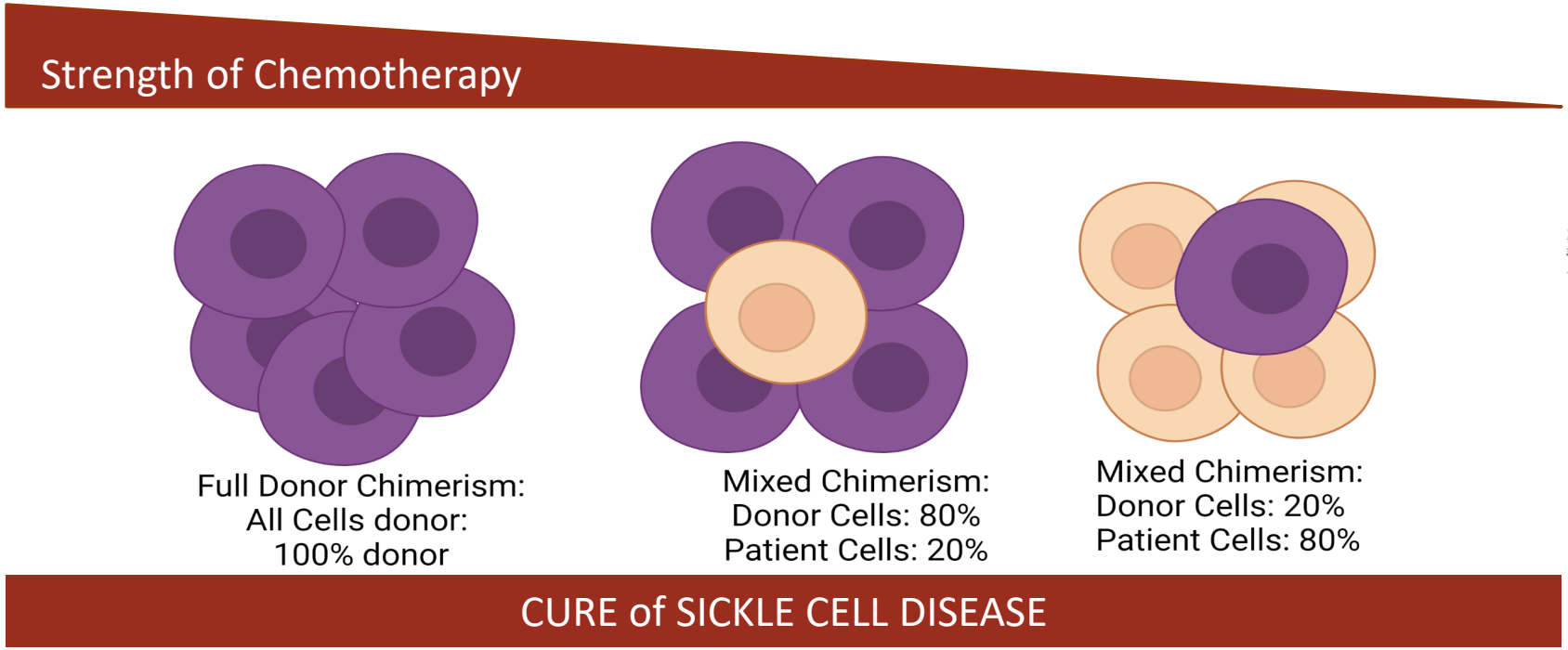
* Non-myeloablative

RISKS and TOXICITIES

Infections
?Infertility
Death
GVHD

Minimum Number of Donor Cells Sufficient for Cure

- Minimum percentage of donor cells for CURE: **20% donor cells sufficient!**
- Donor red cells survive longer than Sickle red cells.



Walters M et al, *Biol Blood Marrow Transplant.* 2001; 7: 665-673.
Abraham A et al, *Biol Blood Marrow Transplant*. 2017; 12: 2178-2183.
Fitzhugh C et al *Blood*, 2017; 130: 1946-1948

Reduced Intensity matched sibling BMT (medium strength)

Study Year	Number of Patients	Median Age	Graft Failure	Overall Survival	Event-Free Survival	GVHD
Bhatia, 2014	18	8.9 years	0%	100%	100%	17%
King 2015*	43	13years	1.9%	93%	91%	23%
Strocchio, 2014	30	8.4 years	7%	100%	93%	3%
Krishnamurti, 2019	22	22 years	0%	91%	94%	20%

Follow up ranging from 3 year to 10 years

Graft failure: Transplant did not work
Overall Survival: Alive with or without sickle cell disease
Event Free Survival: Alive without sickle cell disease
GVHD: Graft versus host disease

- Outcomes similar to strong regimens
- Neurological (brain) toxicity: 4.5 to 11%
- *Menstrual cycles resumed in 4 females

Bhatia M, et al. *Bone Marrow Transplant*.2014; 49:913-920.
King A, et al. *Am. J. Hematol.* 2015;90:1093-1098.
Strocchio L, et al. *Br J Haematol*. 2015; 169: 726 -236.
Krishnamurti L, et al. *Am J Hematol*.2019; 94: 446-454.

Least Intense Matched Sibling BMT: Minimal Toxicity

Author, Year	Number of patients	Median Age	Graft Failure %	GVHD %	Deaths %
Hsieh 2014 (updated w/ permission)	58	28.5 years	14	0	0
Saraf, 2016	13	30 years	7.7	0	0
Guilcher, 2019	16	12 years	0	0	0
*Alzharani, 2021	122	29 years	13	1.6	5.7

Follow up ranging from 18 months to 3 years

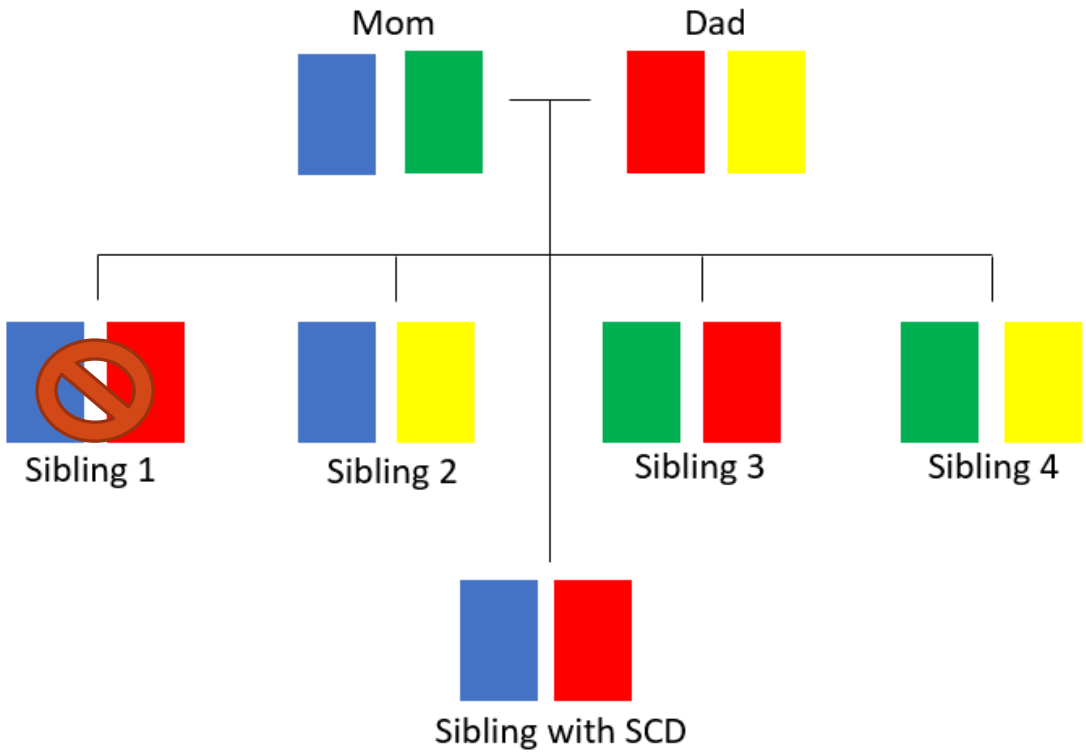
Graft Failure: Transplant not working
GVHD: Graft Versus Host Disease

- Minimal to no GVHD
- Slightly higher risk of Graft failure
- Risk of death: low
- Event Free Survival (Alive without SCD) 87% -100%
- * 21 pregnancies reported in one study

Hsieh M, et al. JAMA.2014; 312: 48-56
Saraf S, et al. *Biol Blood Marrow Transplant*. 2016; 22: 441-8
Guilcher G M, et al *Biol Blood Marrow Transplant* 2019; 25: 1179-1186
Alzahrani, et al. *Blood* 2020. 136; SI: 1-2

BMT from Non-Matched Sibling Donors
Alternative donors

- Matched Unrelated donors (bone marrow or peripheral blood)
- Umbilical Cord blood (not related to patient)
- Haploidentical donors (related donor but only half-matched)



Gold Standard: Matched sibling donors

Matched Unrelated Donors: High Risk of GVHD

Study Year	Number of Patients	Median Age in years	Graft Failure	Overall Survival	Event-free survival	GVHD
Shenoy, 2016	29	14 years	10%	79%	69%	**62% (38 % severe)**
Gluckman, 2020	70	Unknown	Unknown	86%	72%	**24%**
Ngwube, 2020	14	13 years	7%	100%	93%	**57% (All mild except 1 patient)**

Follow up ranging from 1.5 year to 2 years

Graft failure: Transplant did not work
Overall Survival: Alive with or without SCD
Event Free Survival: Alive without SCD
GVHD: Graft versus host disease

Shenoy S ,et al. *Blood* 2016;128: 2561-7.
Gluckman E, et al. Hematol Onc Stem Cell Ther 2020; 181-188
Ngwube A, et al. *Blood Adv*. 2020; 4: 3894-99

Unrelated Umbilical Cord Blood Donor: Risk of Graft Failure

Study Year	Number Patients	Median age in years	Graft Failure	Event-Free Survival	Overall Survival	GVHD
Ruggeri, 2011	16	6	**44%**	50%	94%	**Unknown**
Kamani, 2012	8	13.7	**63%**	25%	88%	**0**
Abraham, 2017	9	4	**22%**	78%	100%	**33%**
Parikh, 2021	13	4	**8%**	85%	85%	**69%**

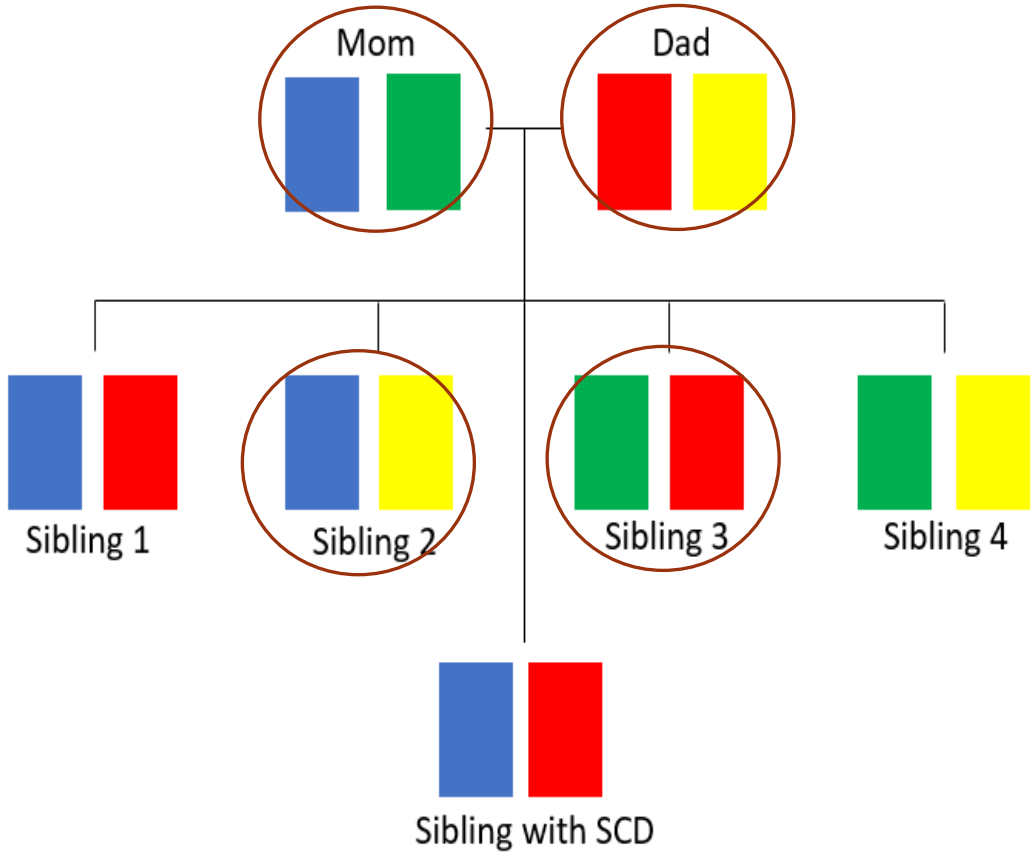
Graft failure: Transplant did not work
Overall Survival: Surviving with or without disease
Event Free Survival: Surviving without disease
GVHD: Graft versus host disease

Follow up ranging from 2 to 3 years

Ruggeri A, et al. *Biol Blood Marrow Transplant*. 2011; 17: 1375-1382.
Kamani NR, et al. *Biol Blood Marrow Transplant*. 2012; 18:1265-1272.
Abraham A, et al. *Biol Blood Marrow Transplant*. 2017; 23: 1580-1596
Parikh S, et al.Blood Adv 2021, 5: 843–852.

Haploidentical: Half-Matched Related Donors
A Donor for All

- Early studies high risk of graft failure (transplant not working) and GVHD (caused by white cells)
- Improvements over time: Getting rid of white blood cells responsible for failure and GVHD
- Two approaches:
  - Use chemotherapy (cyclophosphamide) after transplant to destroy white blood cells
  - Remove white blood cells before the "graft" is infused to patient



Outcomes Following Half-Matched Related BMT

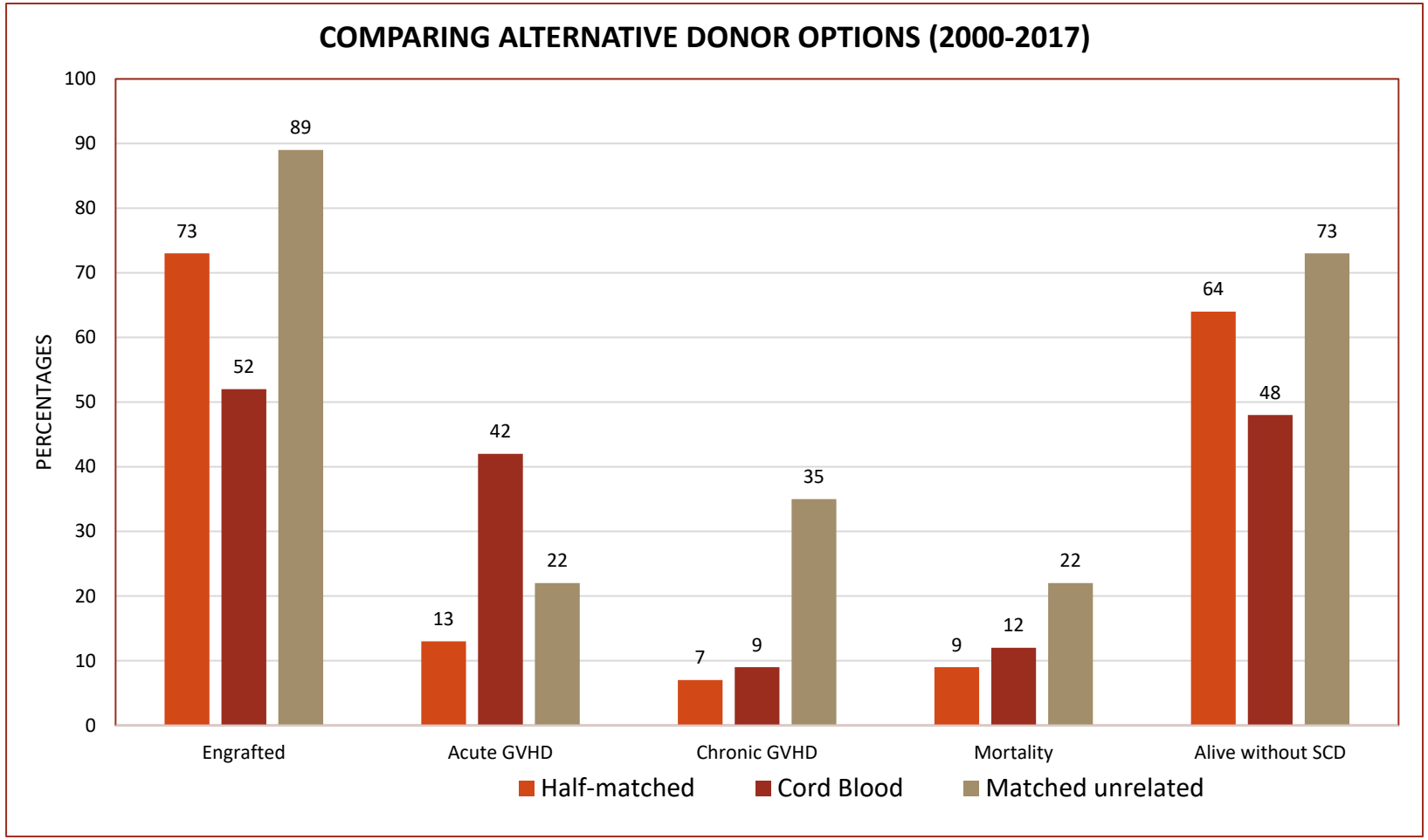
Study Year	# Patients	Median age	Graft Failure	Overall Survival	Event-Free Survival	GVHD
De La Fuente, 2018	18	21 years	7%	100%	93%	33%
Bolanos- Meade, 2019	12	16 years	8%	100%	92%	29%
Foel, 2019	20	14 years	10%	90%	90%	25%
Talano, 2020	19	13 years	0%	84%	84%	6.7%

Follow up ranging from 1 to 2 years

Graft failure: Transplant did not work
Overall Survival: Alive with or without SCD
Event Free Survival: Alive without SCD
GVHD: Graft versus host disease

De La Fuente, et al. *Biol Blood Marrow Transplant*. 2019;25:1197-1209
Bolanos-Meade et al. *Lancet Hematol*. 2019; 6: e183-93.
Foel J, et al. *Bone Marrow Transplant* .2019; 54:1859-1867.
Cairo M, et al. JAMA Pediatr. 2020;174(2):195-197.

Outcomes: Non-Matched Sibling Transplants



- Recommend on a clinical trial
- Currently no one donor is better than the other
- Choice
  - Transplant center preference/ experience
  - Available clinical trials
  - Family preference

Adapted from Joseph J et al. Semi Hematol, 2018: 94-101
Eapen M, et al. *Lancet Hematol*. 2019; 6: e585-e596.

Factors Impacting Outcome after BMT for SCD

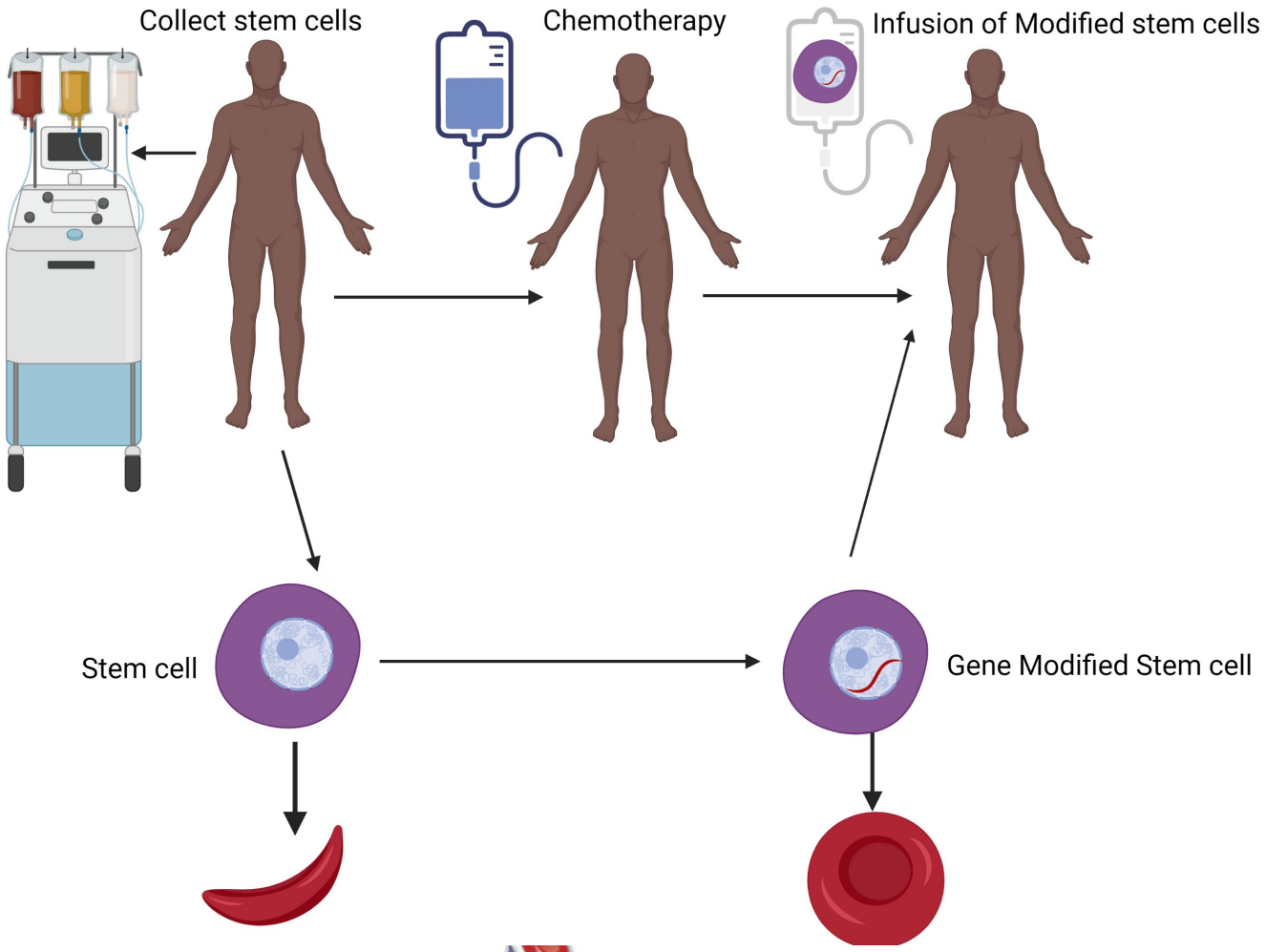
- **Younger Age:**
  - Every 1-year increase in age at time of transplant increases risk of transplant failure or death by 9%
- **Donor Type**
  - Matched Sibling Donor = Best outcomes
    - We can now consider **BMT in patients with less severe disease.**
  - Non-sibling donors: No one is better than the other based on current data.
- **≤ 12 years AND matched sibling donor = best outcomes**.

Gluckman E et al. *Blood.* 2017; 129:1548-1556
Nickel RS,et al. *Blood.* 2014;124: 861-866.
Eapen M, et al. *Lancet Hematol*. 2019; 6: e585-e596.

What is Gene Therapy?

- An experimental technique using genes to treat patients with diseases such as sickle cell disease
- Approaches being studied include:
  - **Replacing** a defective gene that causes disease with a healthy copy of the gene.
  - **Inactivating,** or "knocking out," a gene that is functioning improperly or controlling the production of another gene.
  - **Introducing** a new gene into the body to help fight a disease.

Gene Therapy for Sickle Cell Disease: The Process



- Collect stem cells: may need more than 1 session
- Medicine for collection: plerixafor
- Still need chemotherapy

Gene Therapy: Pros and Cons

Pros

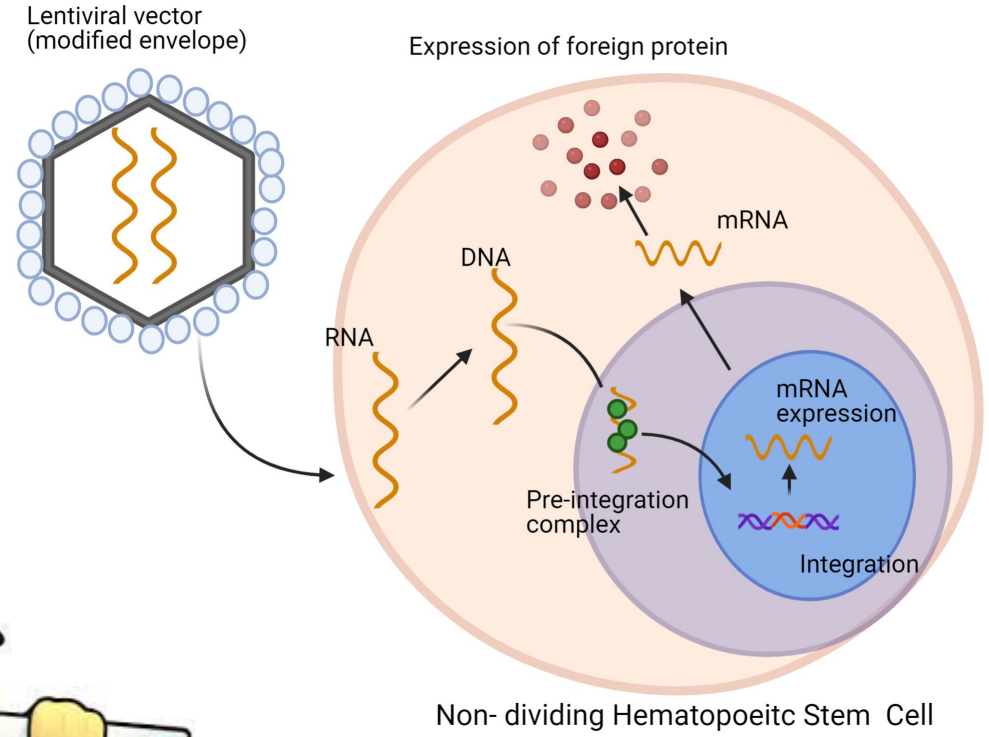
- No need to search for donor
- No graft-versus-host disease

Cons

- Still need chemotherapy
  - Infertility
- High cost, only on research trials
- Long term effects unknown
  - Need long follow up (15 yrs)
- Monitor for Cancers

Gene Tool: Lentiviral Vector (Postman)

- Carry gene (message) of interest and deliver it to target cells (stem cell)
- Insert/introduce genes (message) that code for hemoglobin (protein) that does not cause the red cell to sickle.
- 1st patient: 13-year-old reported in 2017



Adapted from Amado R et al. *Science.* 1999: 285 ;674-676.

Turn off a Switch to Allow/Reawaken Baby hemoglobin (HbF) production

Time	Type of Globin (protein) in Red Blood Cell	Properties of the Red Cell
Before Birth	Baby (fetal)Hemoglobin γγ	Does not sickle
After Birth Unaffected person	Adult hemoglobin $\beta^A \beta^A$	Does not sickle
Person with Sickle Cell Trait	$\beta^A\beta^s$	Does not sickle
Person with Sickle Cell Disease	Sickle Hemoglobin $\beta^s\beta^s$	Red Cells Sickle

- **BCL11A: Switch in the gene c**ontrolling HbF production
- More HbF: improved survival, less symptoms, less hospitalization

Baby Hemoglobin strong anti-sickling hemoglobin

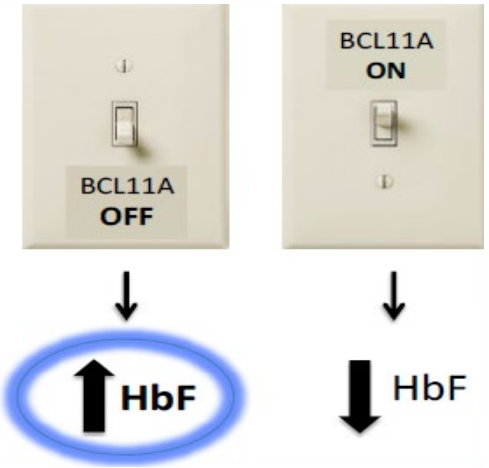


Image Courtesy of Drs. E. Esrick and D Bauer.

Genome Editing Tools: Using Genetic Scissors

- **Nucleases (Genetic Scissors):** e.g., CRISPR
- "Cut" Piece of gene carrying Master switch (BCL11A): "release brakes" and allow Baby hemoglobin production
- " Cut and copy, paste" Use Scissors to remove defective gene, then copy a healthy gene and paste/insert it (replace)

Cut: BCL11A (master switch), increase baby hemoglobin production

OR

Cut, copy, paste/insert Repair sickle mutation

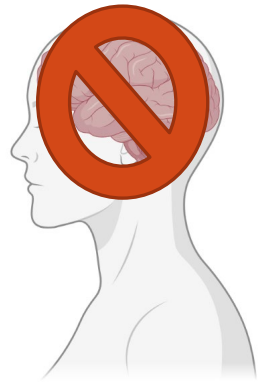
Who is Eligible for Current Gene Therapy Trials

Eligible

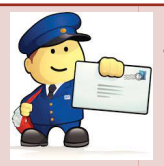
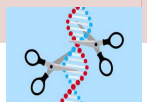
- Severe Disease
  - ≥ 2 Vaso-occlusive crisis (Pain, acute chest syndrome, etc.) in the last 2 years
  - Failure or intolerance of hydroxyurea
- Age ≥ 18 and ≤ 50 years with some trials including ≥ 7 or ≥ 12 years

Ineligible (currently)

- Central nervous system (brain) disease (stroke, silent infarct, Moya Moya)
- Prior bone marrow transplant
- Available matched sibling donor

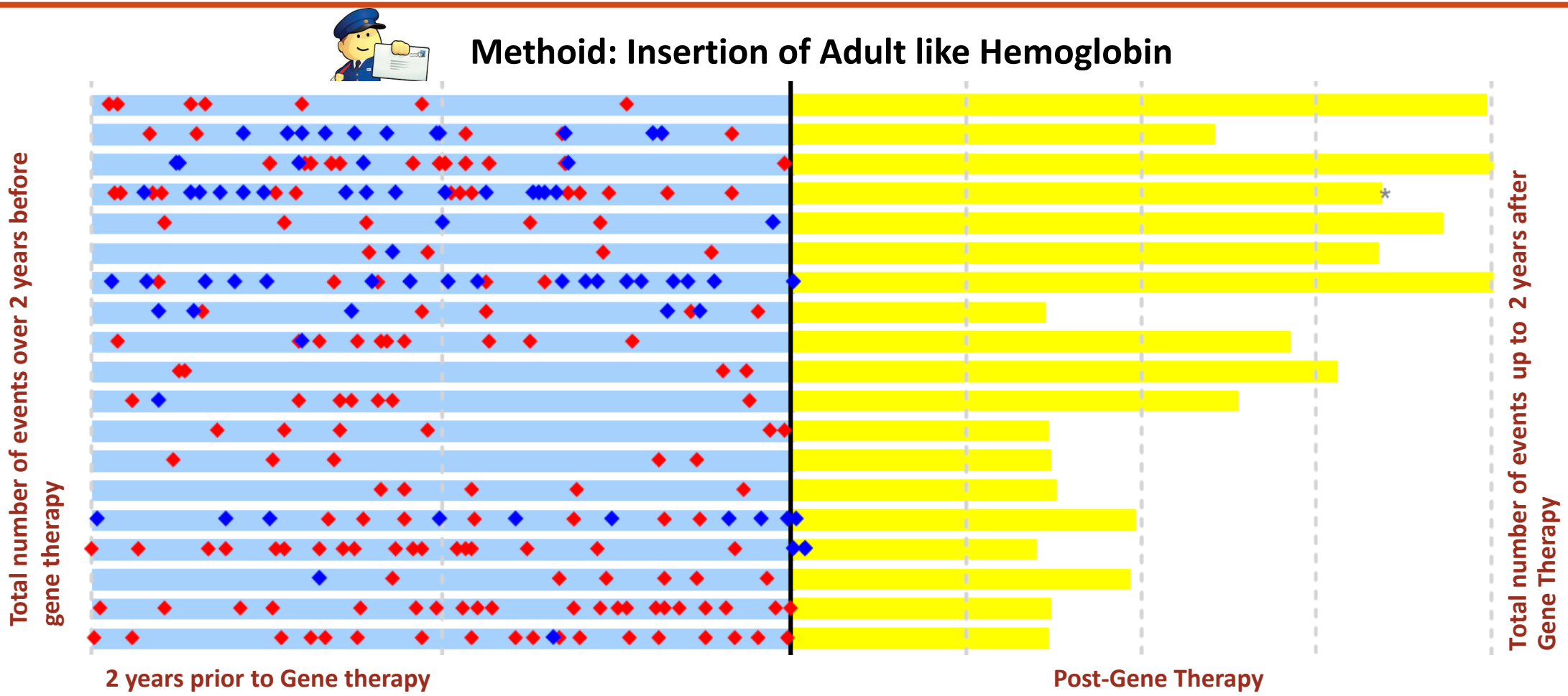


Gene Therapy Trials for SCD: Reported Outcomes

Clinical Trial	Strategy	# Patients	Chemotherapy	Comments
NCT 02151526	Adult like hemoglobin 	3 patients (13-21 years)	Strong	All surviving. 1 patient: pain 30 months after gene therapy, and 2nd patient: acute chest 6 months after gene therapy
NCT02140554	Adult like hemoglobin 	36 patients (12-50 years)	Strong	2 Death: 1 due to heart issues, 1 due to blood cancer 1 another patient with blood cancer (alive) 1 patient: Needing transfusions All unrelated to gene therapy
NCT03282656	Delete Master Switch 	6 patients (7-25 years)	Strong	All surviving 1 patient: sickle cell crisis 8 month after gene therapy
NCT03745287	Snip off Master Switch 	3 patients (22-33 years)	Strong	All surviving None
NCT02186418	Baby like hemoglobin 	3 patients (19-34 years)	Medium intensity	All surviving None

Median follow up for all above studies: 3-4 years

Sickle Cell Crisis-Free Period after Gene Therapy



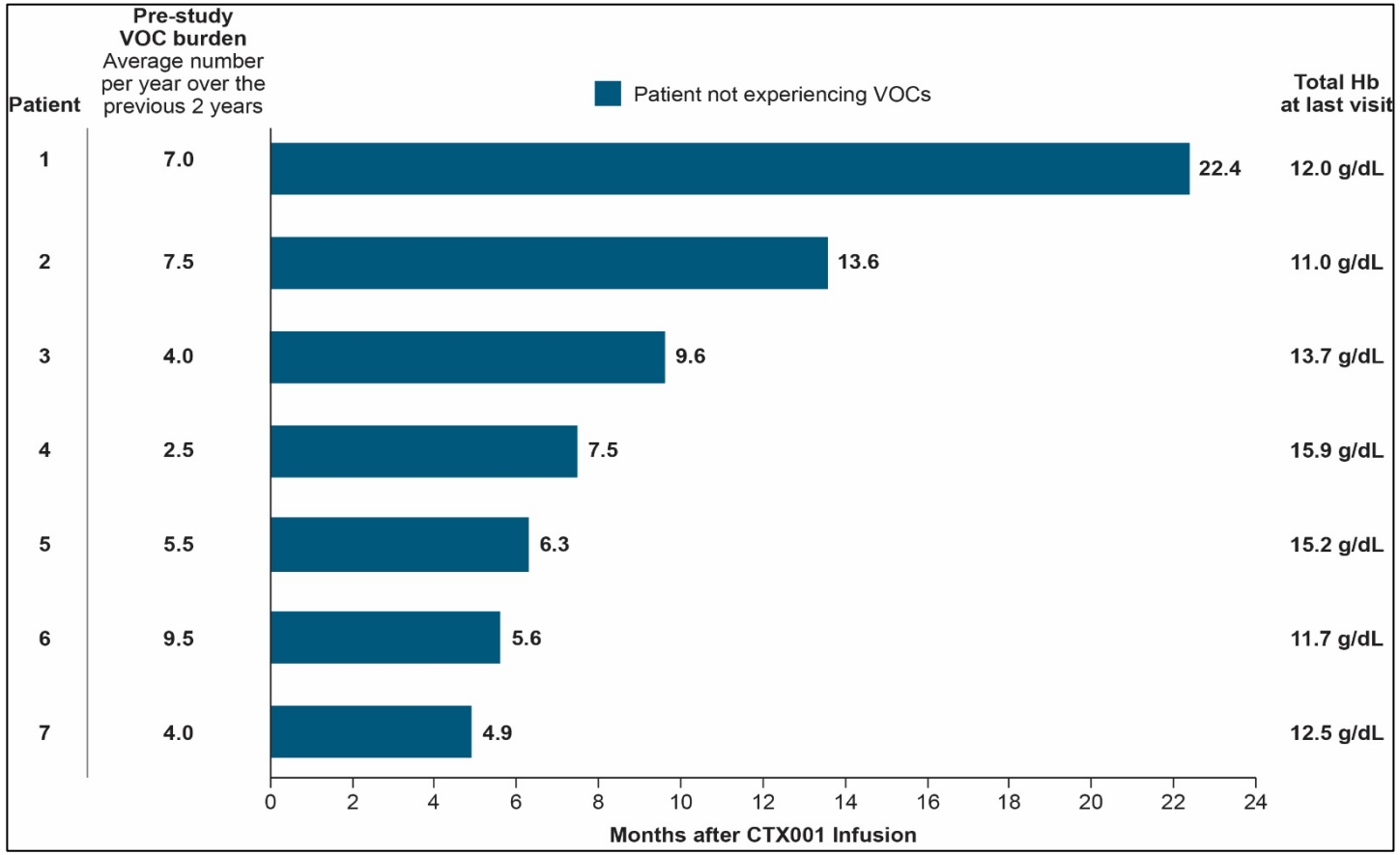
Each dot represents a sickle cell crisis event. Each horizontal bar a patient (total 19 patients)

Note there are no events after Gene therapy : Severe ◆ All other ◆

Thompson A, et al. *Blood* 2020. 136; S1:16-17.
Image Courtesy of Dr. A Thompson.

Sickle Cell Crisis-Free Period after Gene Therapy

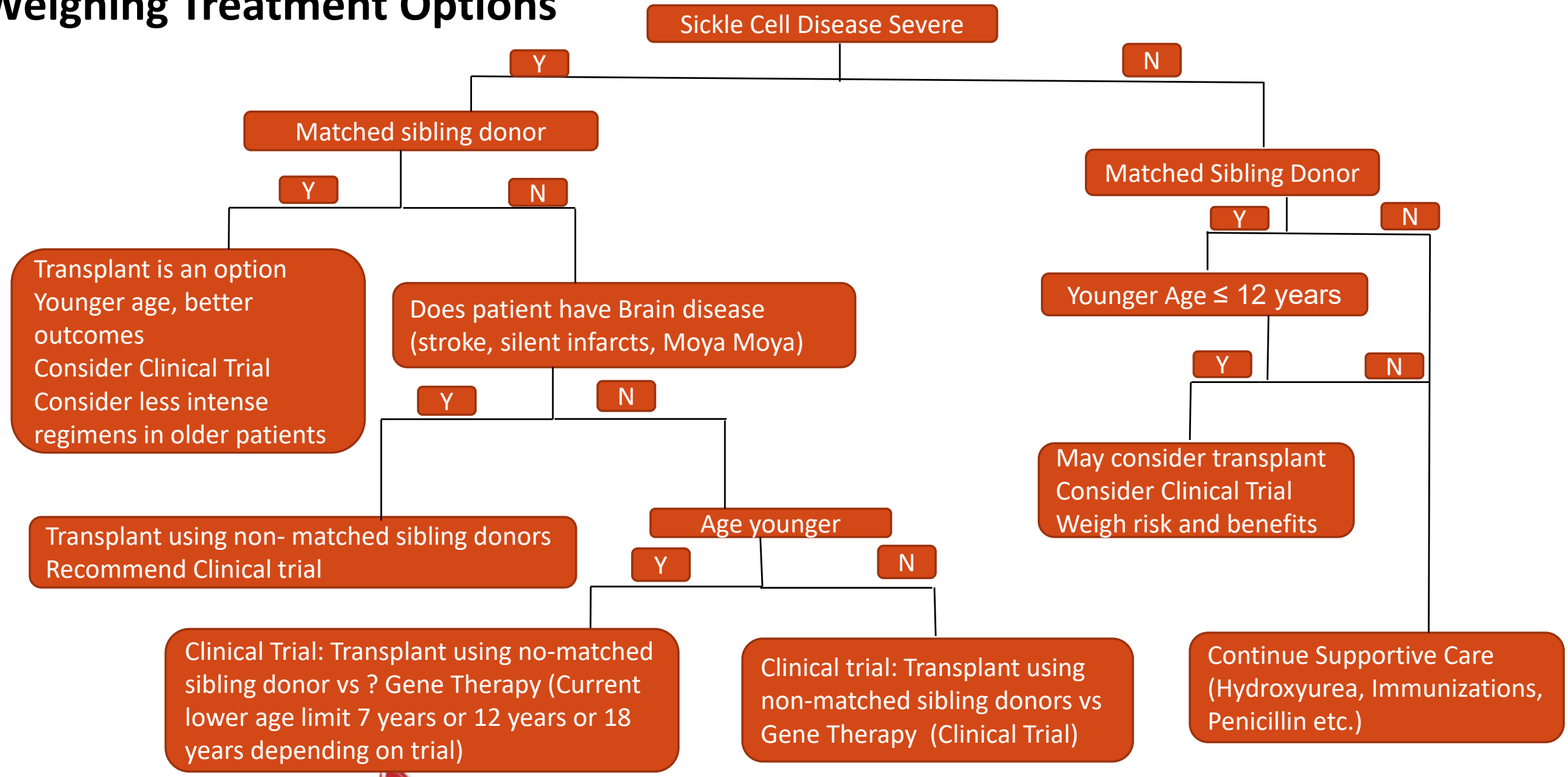
Method: Deleting Master Switch and allowing baby hemoglobin production



Number of months patients have remained free of Vaso-occlusive crisis (VOC) i.e Sickle cell crisis after Gene therapy
Each horizontal bar represents a patient (total number of patients=7)

Figures with permission from Frangoul H.

Weighing Treatment Options



Conclusions

- Matched sibling donor bone marrow transplant in sickle cell disease provides excellent outcomes, being considered in less severe disease
- Younger age donor (matched sibling and non-sibling) associated with improved outcomes
- Current data does not favor one non-matched sibling donor over another
- Gene therapy: rapid strides are being made, however longer follow up is needed

RESOURCES

Sickle Cell Transplant Advocacy & Research Alliance (STAR): curesicklenow.org

- Transplant for sickle cell disease educational materials & clinical trials information

American Society of Gene and Cell Therapy: ASGCT.org

- Gene therapy for SCD : asgct.org/research/news/september-2020/patient-education-sickle-cell
- Clinical trials: Gene therapy for sickle cell disease: asgct.careboxhealth.com

Be The Match: bethematch.org, 888-999-6743

- Information about transplant and sickle cell disease

Blood & Marrow Transplant Information Network (BMT InfoNet) (bmtinfonet.org) 888-597-7674

- Information about what's involved in having a bone marrow transplant
- One-on-one peer-support program

Jason Carter Clinical Trial Search and Support Program: ctsearchsupport.org/sickle-cell 888-814-8610

BMTinfonet.org
30 YEARS
EMPOWERING PATIENTS
BLOOD & MARROW TRANSPLANT INFORMATION NETWORK

Questions?

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This webinar was recorded and will be available for viewing on the BMT InfoNet website shortly.

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Sue Stewart, BMT InfoNet

Many thanks to bluebird bio for supporting this webinar.