Bone Marrow Transplantation For Sickle Cell Anemia

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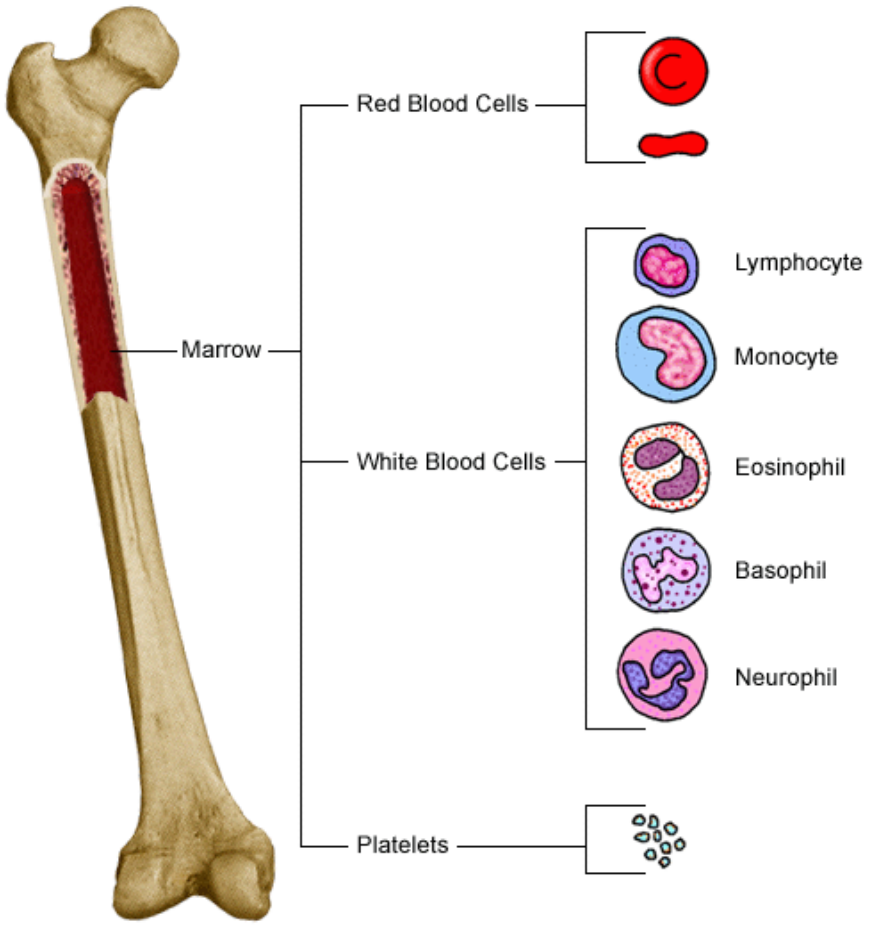
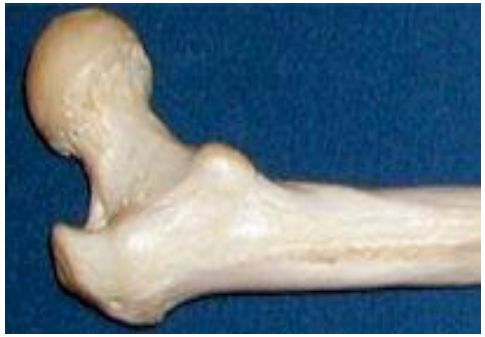
Pediatric Hematopoietic Stem Cell Transplantation

Stem Cell Transplantation

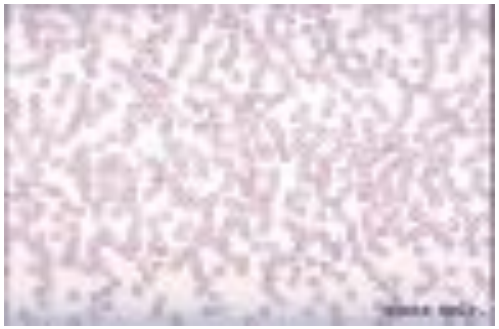
Replacement of recipient's bone marrow stem cells with those from an unaffected donor



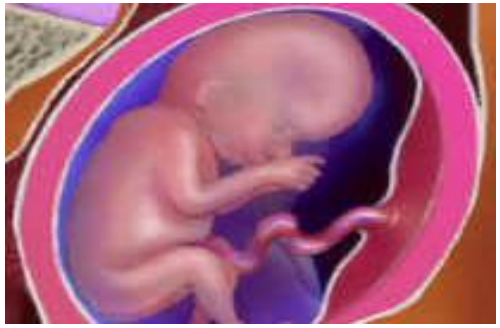
Sources of Stem Cells



Bone Marrow

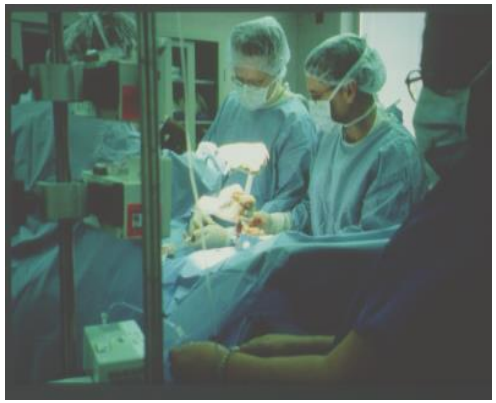


Peripheral Blood

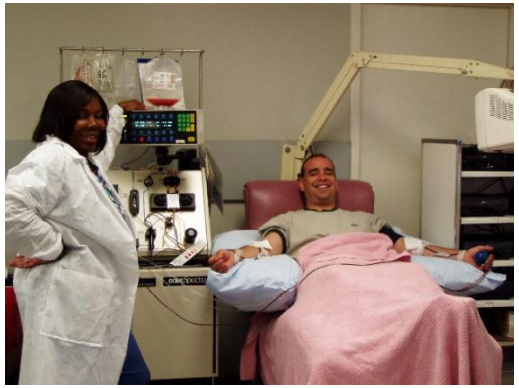


Placental blood

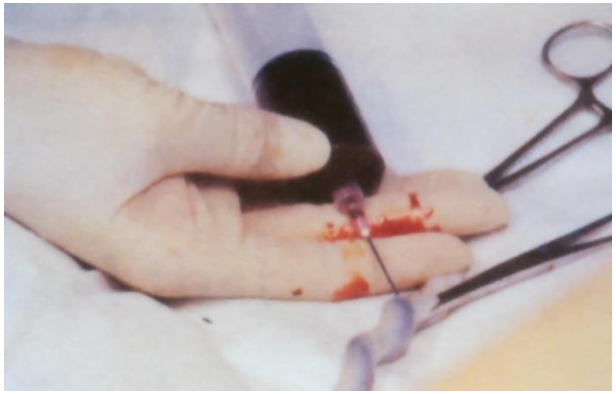
Harvesting Techniques



Bone Marrow



Peripheral Blood

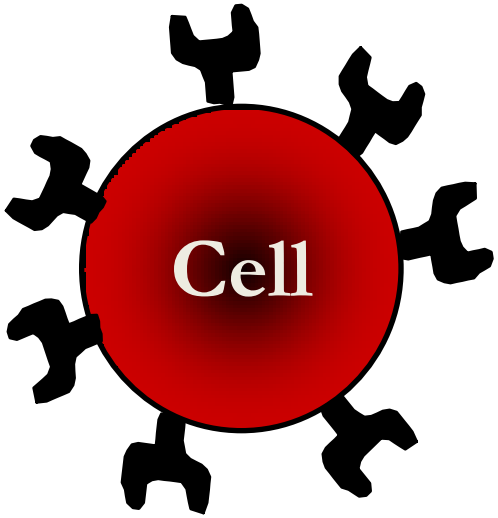


Placental blood

Stem Cell Donors

- Autologous: Patient's own stem cells
- Allogeneic: Another person's stem cells
  - Sibling Donors
    - Syngeneic = Identical twins
    - HLA matched:
      - 25% Chance for each full sibling to match
  - Parental donors
    - Haplo-identical: 50% genetic match
  - Unrelated donors
    - NMDP: ~9 million donors
    - Cord bloods and adults

HLA Proteins Expressed on Cells



Class I
A
B
C

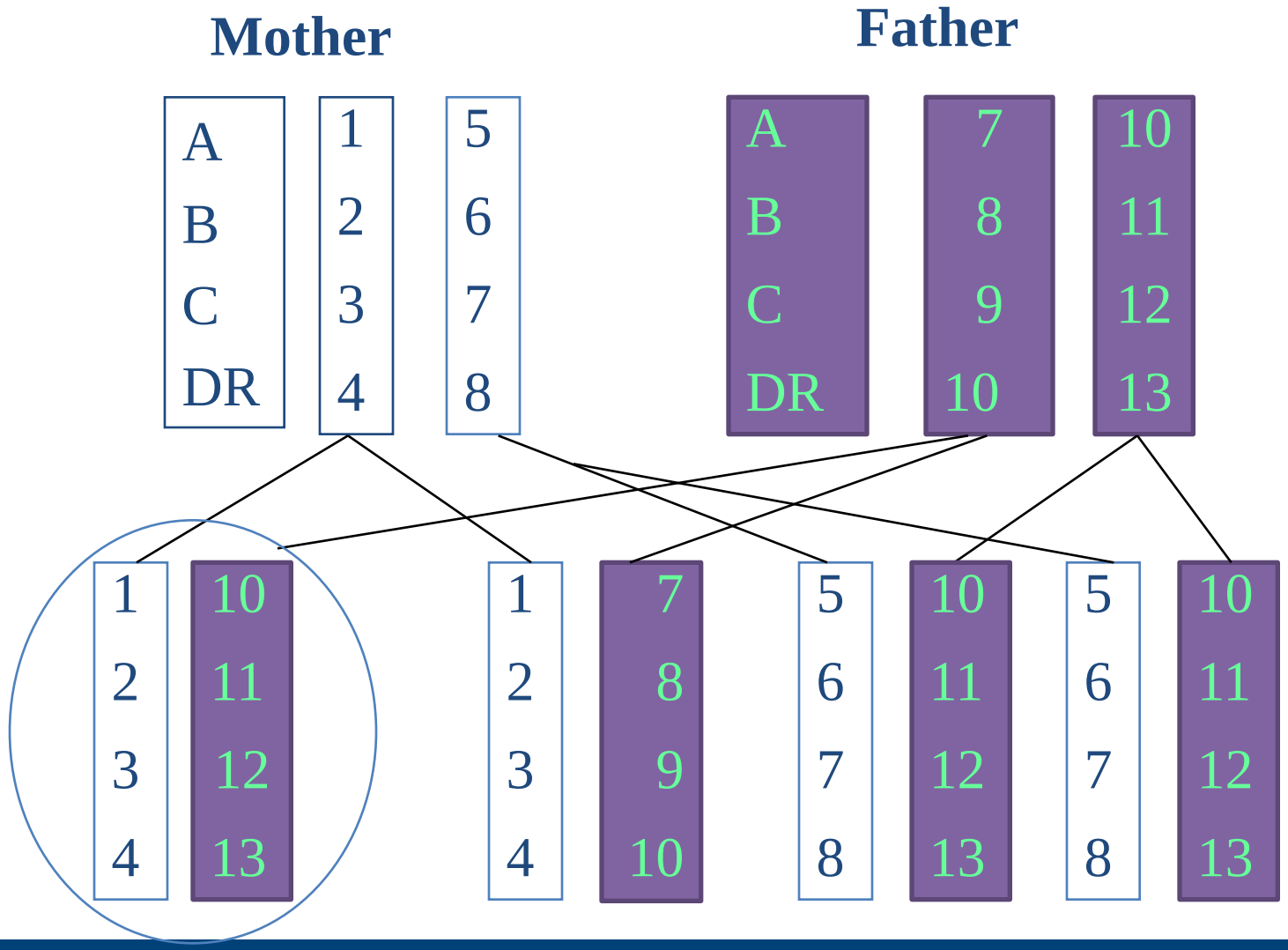
Class II*
DR

DQ
DP

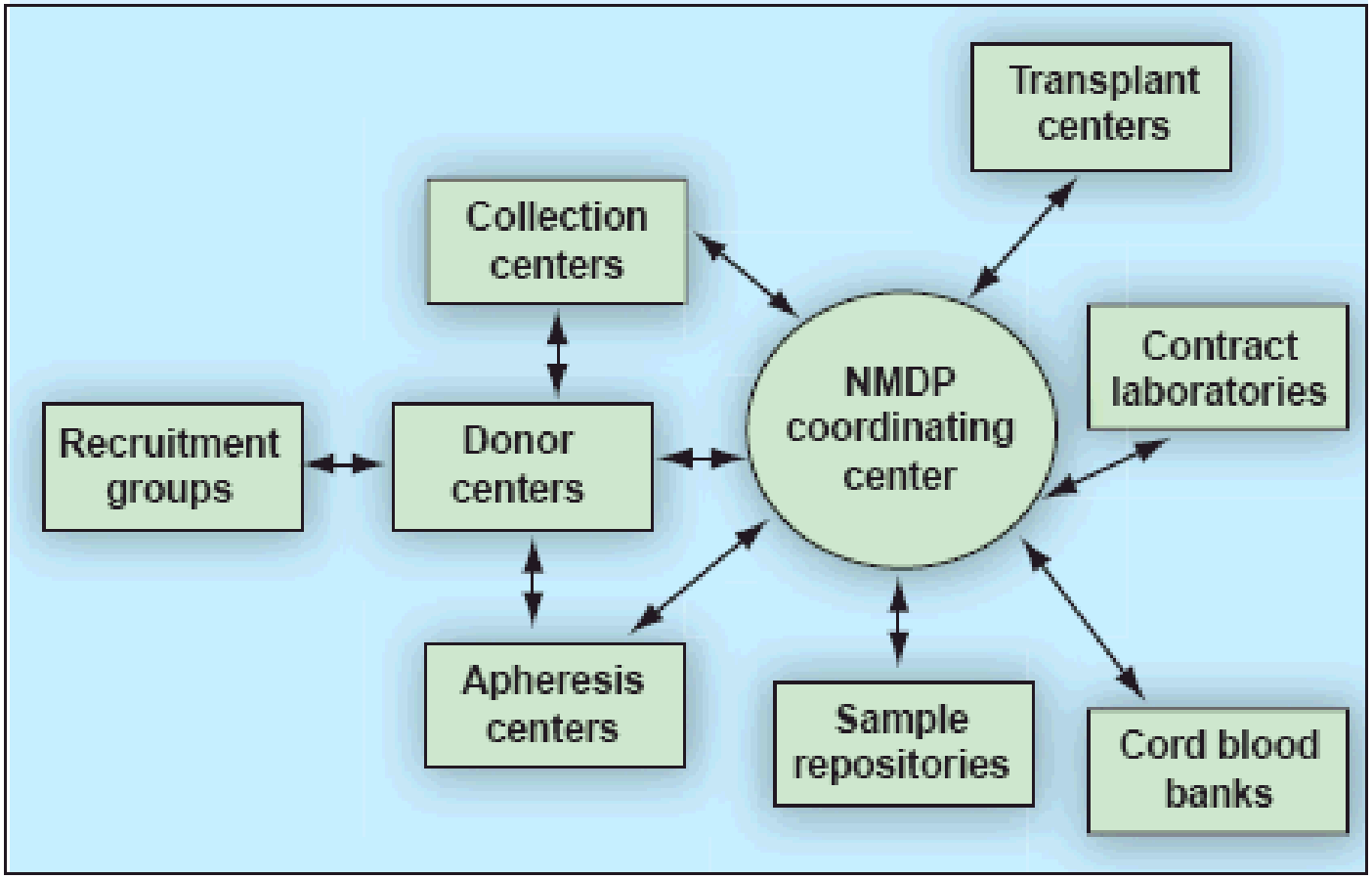
***Only on some cell types (T lymphocytes)**

Inheritance of HLA types

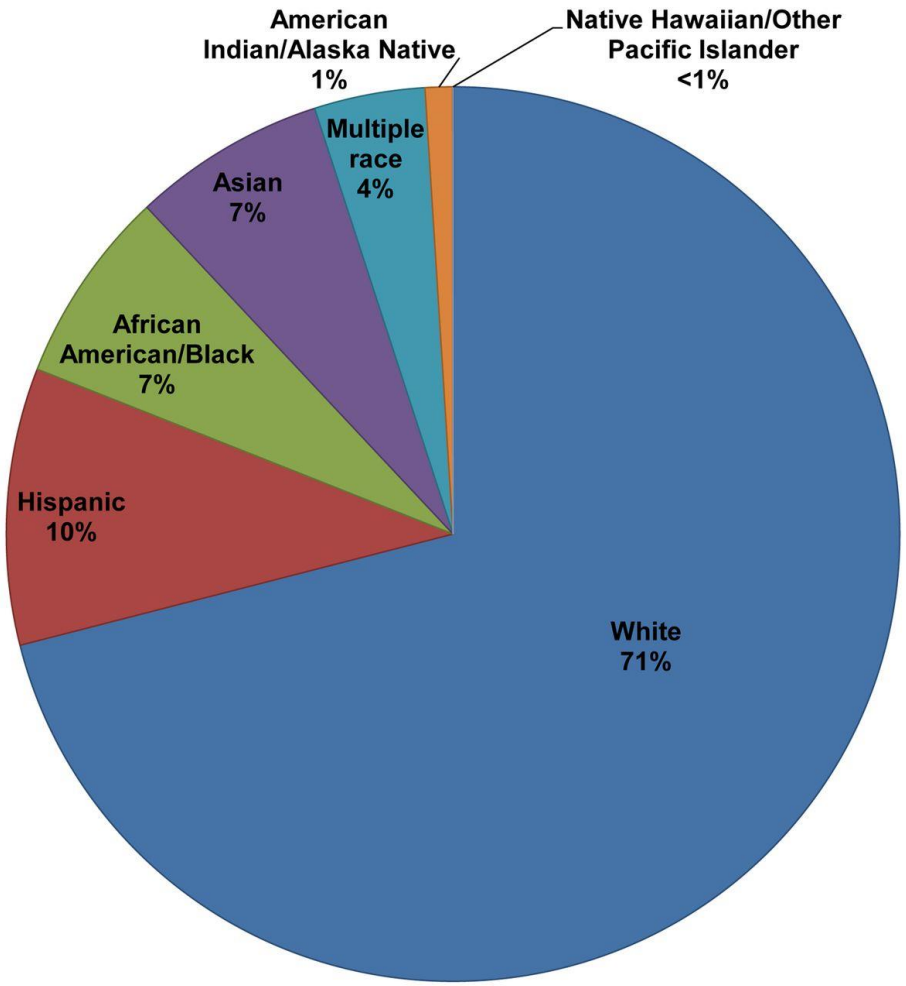
Patient's HLA type- A 1,10; B 2,11; C 3, 12; DR 4, 13



National Marrow Donor Program (NMDP) Network



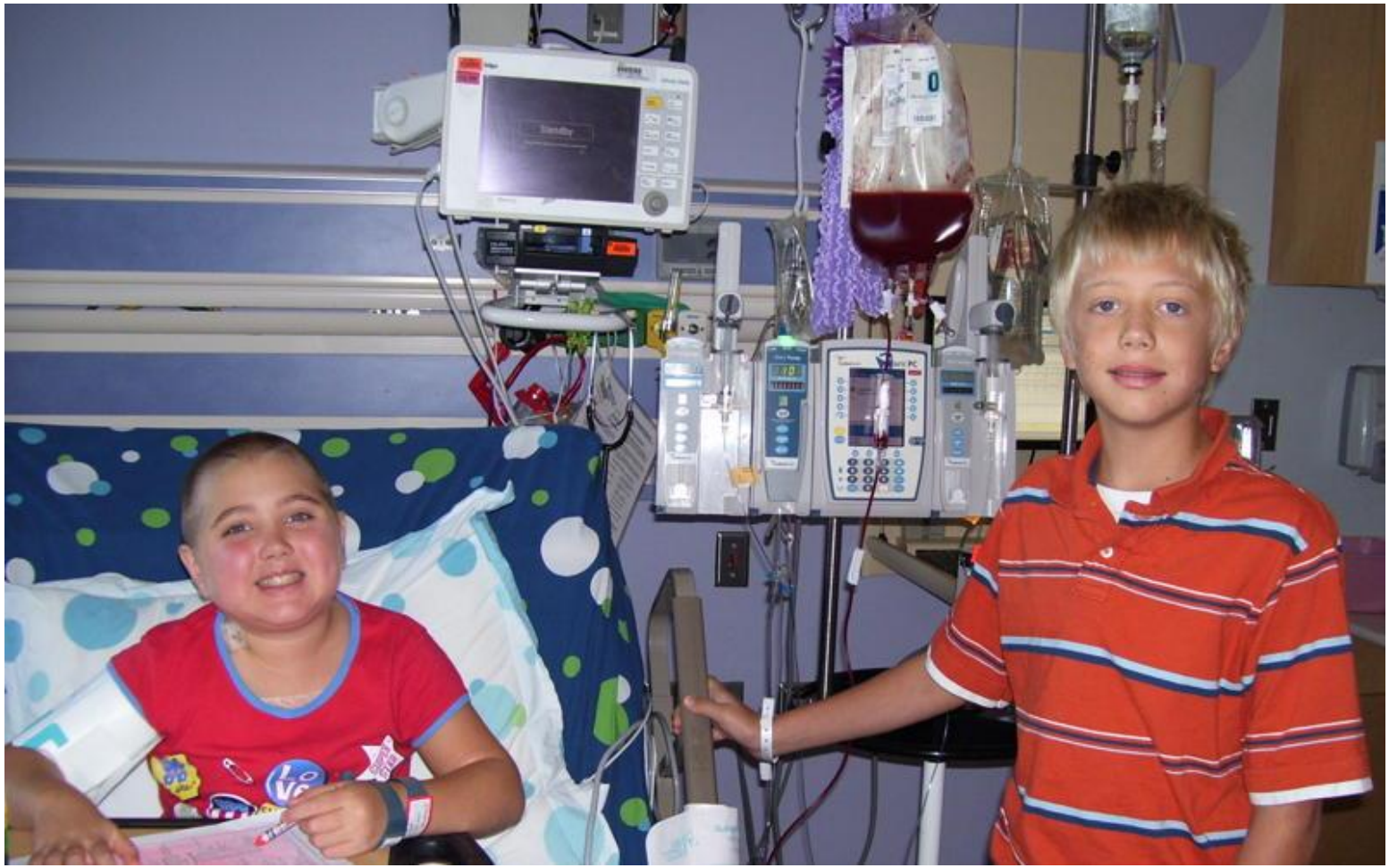
Racial/ethnic distribution of potential donors in the NMDP registry



Phases of SCT

- Conditioning
  - –High-dose chemotherapy ± radiation to ablate recipient's own marrow
  - –Reduced intensity regimens
- Transplant
  - –Infusion of donor stem cells
- Engraftment
  - –Recovery of bone marrow function
- Supportive Care
  - –Immunosuppression for Graft-vs.-Host disease
  - –Management of infection risk

Stem Cell Infusion



Complications of Stem Cell Infusions

- Transfusion reactions
  - Fever, chills, rash
  - Transmission of infection
    - Occasional positive cultures (esp. P acnes)
- Infusion of DMSO
  - Headache, shortness of breath, chest pain
  - Slow infusion
- Graft failure
  - Complete
  - Mixed chimerism

Mixed Chimerism

- Durable engraftment of both host and donor stem cells
- May need small amount of donor engraftment to correct non-malignancies
  - –Only need about 20-30% engraftment to cure sickle cell disease

Complications of SCT

- Short-Term Complications
  - –Transplant-related mortality 5-10%
  - –Graft failure/rejection
  - –Viral infections
  - –Acute Graft-versus-Host disease
- Long-Term Sequelae
  - –Chronic Graft-versus-Host disease
  - –Gonadal dysfunction/sterility
  - –Growth failure
  - –Secondary malignancies

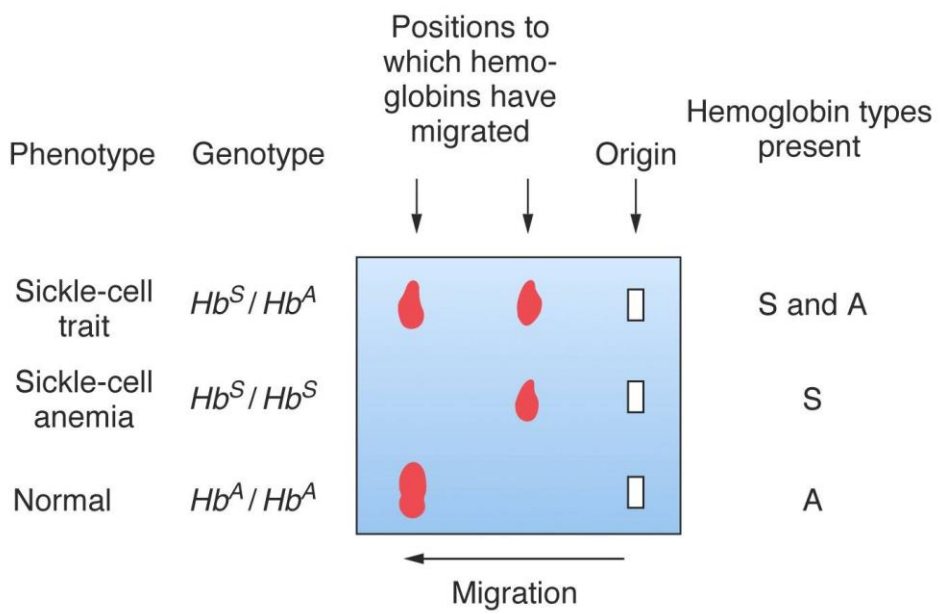
Sickle Cell Anemia

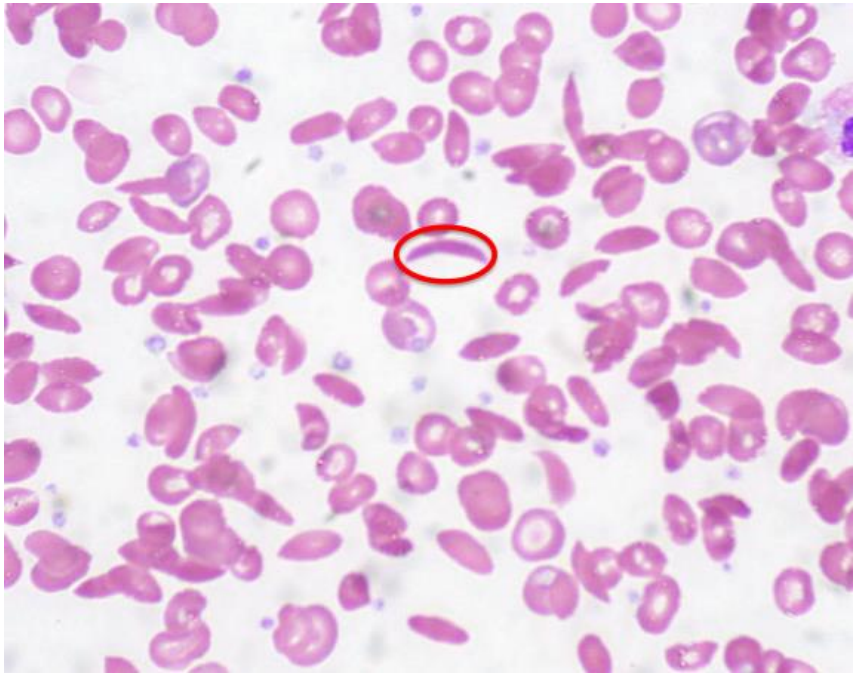
- Disease description
  - Chronic hemolytic anemia due to abnormal hemoglobin
    - Abnormal Hgb S “sickles” under stress conditions
  - Incidence ~ 1 in 400 in African Americans
    - Autosomal recessive inheritance
- Homozygous Sickle cell anemia most severe form
- Other forms (SC disease, SD, etc.) less severe
- Sickle cell trait
  - Most patients asymptomatic
  - Some sickling may occur in stress conditions

Sickle Cell Anemia

- Clinical signs and symptoms
  - Symptoms rare before 4 months of age
  - Severe complications
    - Dactylitis in young children
    - Recurrent painful episodes
    - Acute chest syndrome
    - Stroke
    - Splenic sequestration
    - Aplastic crisis
    - Recurrent priapism

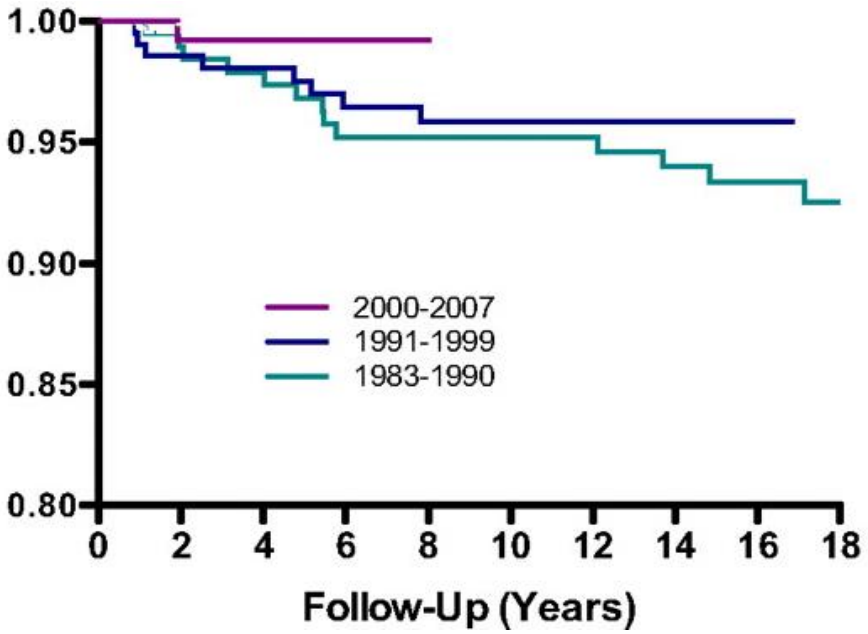
How is Sickle Cell Anemia Diagnosed?





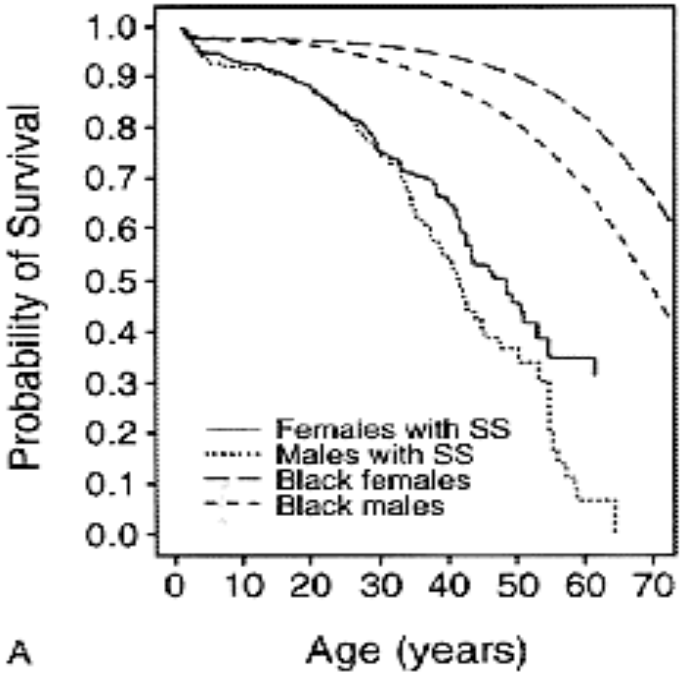
Impact of Newborn Screening on Children with Sickle Cell Anemia

- Newborn screening in Texas started in 1983
- Early referral to pediatric sickle cell center
- Implementation of preventive care



Sickle Cell Disease

- Shortened median life expectancy
  - Males 42 yrs
  - Females 48 yrs
- Causes of Death
  - Early childhood: Sepsis
    - Largely eliminated by penicillin prophylaxis
  - Later childhood:
    - Acute chest syndrome
    - Stroke
  - Adults:
    - Chronic organ failure
    - Sudden cardiac death



Current Treatment Options for SS Disease

- Supportive care
  - Prophylactic antibiotics
  - Pain medications
  - Blood transfusions
- Hydroxyurea
  - Increases fetal Hemoglobin
- Chronic transfusion
  - Reduces hemoglobin S
  - Iron overload
- Bone marrow transplant
  - Only curative option!!!

Indications for SCT in Sickle Cell Anemia

- Any child with a matched sibling
- Stroke or hemorrhage
- Abnormal cerebral MRI scan
- Increased blood flow velocity on trans-cranial doppler
- Acute chest syndrome with history of recurrent hospitalization or prior exchange transfusion
- Multiple RBC antibodies in patients requiring chronic transfusion therapy

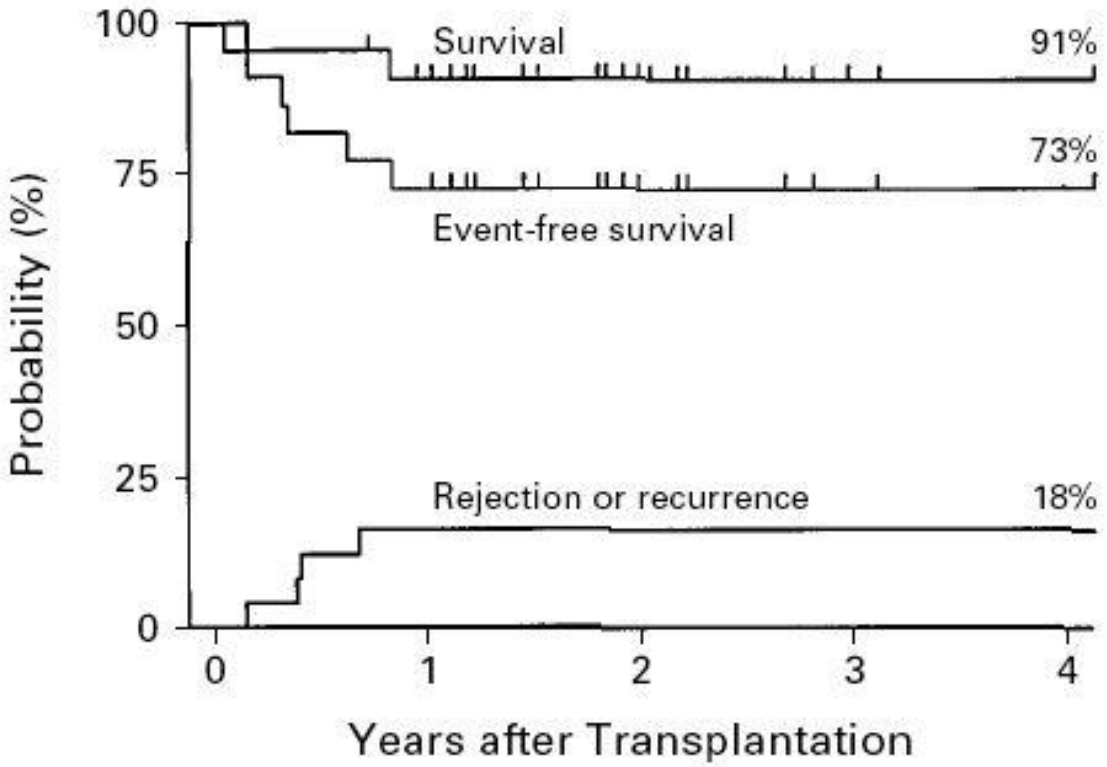
SCT in Sickle Cell Patients

- Multicenter Investigation of BMT for SCD
  - 50 children with SCD
  - Allogeneic BMT from an HLA-matched sibling
  - Results
    - 3 deaths (1 intracranial hemorrhage, 2 GVHD)
    - 5 graft rejection and recurrence of SCD
    - 47 surviving patients
      - 38 full donor chimerism
      - 4 stable mixed chimerism
      - 5 recurrent SCD

} Free of SCD

Blood 95:1918-1924, 2000

Outcome After Matched Donor SCT



Long Term Outcomes after SCT

- 28 patients with a median follow-up of 50.3 (range 26-80) months
- No new neurologic events in patients with prior stroke who engrafted
- Among women, 5/7 tested had elevated LH/FSH and 6 had primary amenorrhea
- Among 7 males, 0/4 had elevated LH/FSH

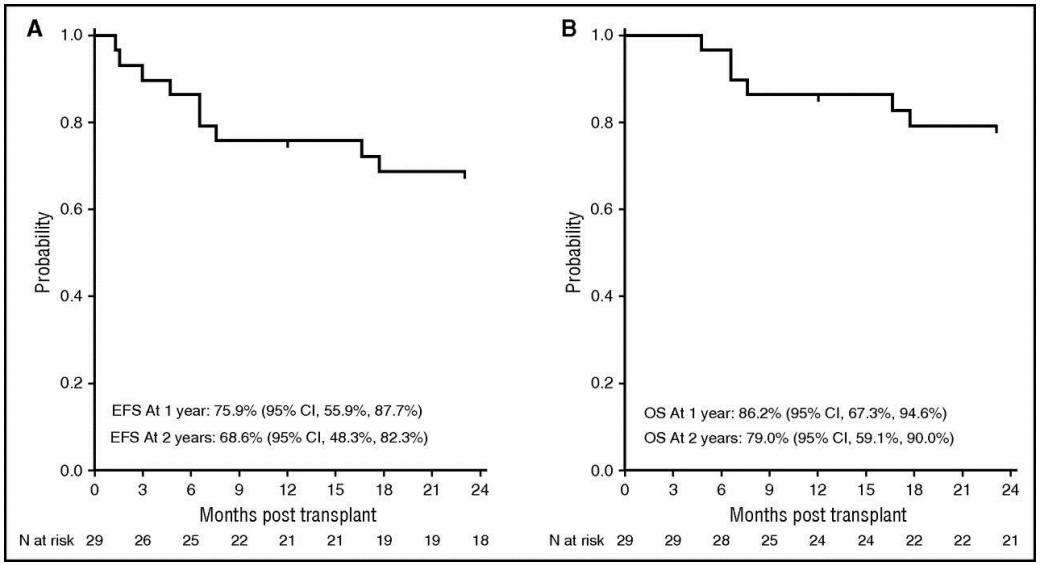
Reduced Intensity Transplant (RIC)

- Concept
  - –Non-myeloablative chemotherapy
  - –Infusion of donor hematopoietic stem cells
  - –Immunologic manipulation to promote graft survival

- Goal
  - –Cure SCD
  - –Induce stable “mixed chimerism”
  - –Decrease regimen-related morbidity and mortality

Unrelated Donor Transplant for SS Disease

- Phase II study involving 29 patients
- Unrelated stem cell transplantation in children with severe sickle cell disease who lack a matched sibling



Blood. 2016 Nov 24;128(21):2561-7

Increased Risk for GVHD in Patients with SS Disease

- Increased risk of GVHD
  - 31% with severe acute graft versus host disease
  - 66% with chronic graft versus host disease
  - 38% with extensive chronic graft versus host disease
- All deaths due to graft versus host disease

Blood. 2016 Nov 24;128(21):2561-7

Use of Haploidentical Transplant in SS Disease

- John Hopkins Study
  - –14 patients enrolled
  - –6 of 14 had graft failure
  - –2 of 14 could not stop immunosuppressive drugs because of poor donor chimerism
  - –Only 6 of 14 (42%) patients were free of both transfusion and immunosuppression

Blood. 2012;120(22):4285-91

How Do We Make Transplant Available to All Children with SS?

- Make transplants safer
  - –Use of reduced intensity regimens
  - –Better treatment of GVHD
- Develop ways to predict children at highest risk of severe SS
- Expand the donor pool to allow for better matched donors
- Gene therapy

Questions?