Bone Marrow Transplantation: Risks and Benefits

Aplastic Anemia and MDS International Foundation

2019 Patient & Family Conference

July 20, 2019

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Medical College of Wisconsin

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Objectives

1. What is a bone marrow transplant (BMT)?
2. What are the complications of BMT?
3. Who should be considered for a BMT?
4. What are the outcomes of BMT in MDS and aplastic anemia?
5. What's next?

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What is a bone marrow transplant?

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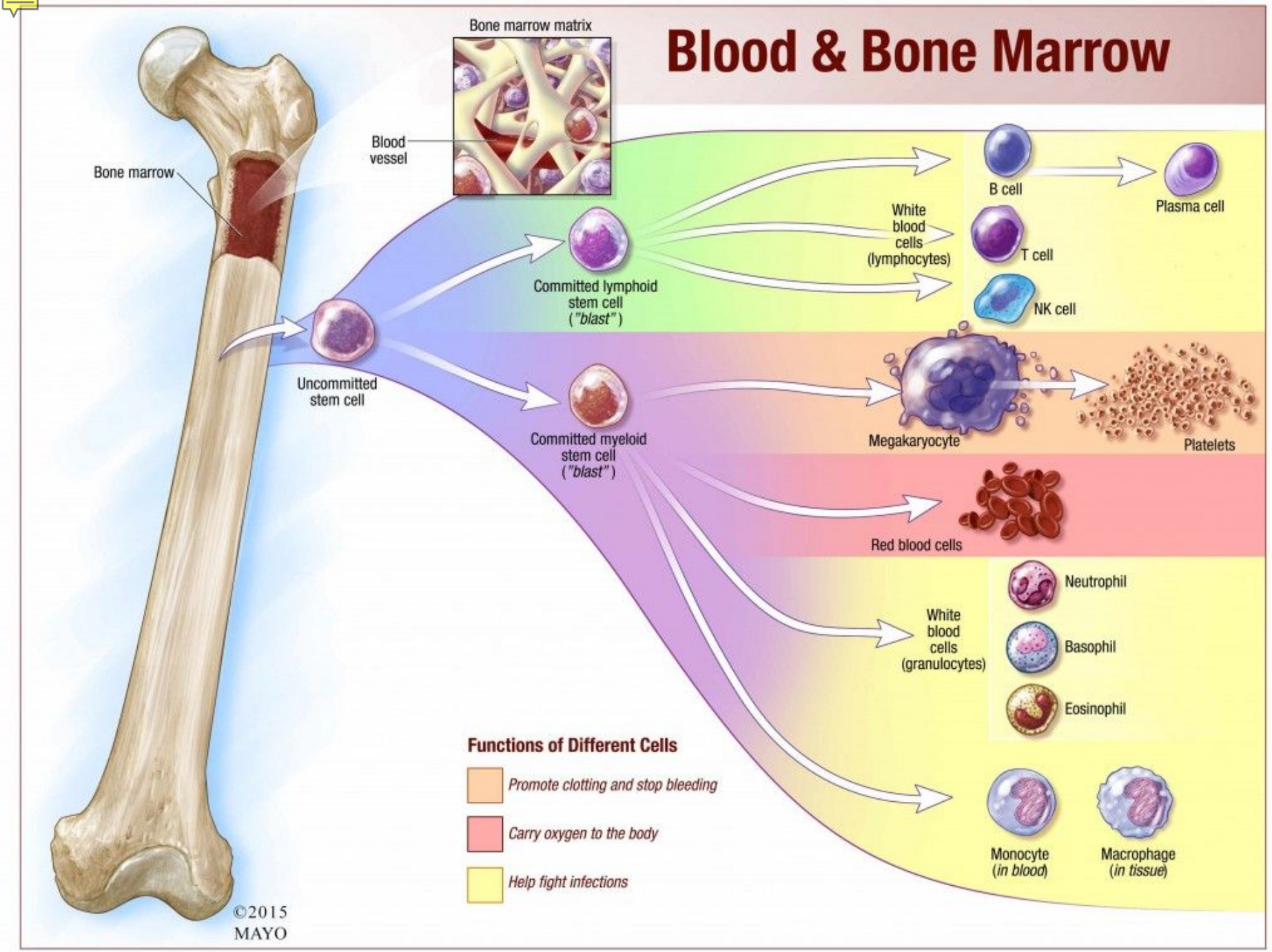

EACH DAY…

- 200 billion red cells
- 200 billion platelets
- 70 billion white cells

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Bone Marrow Transplant

Aka “Stem Cell Transplant” (SCT)

Aka “Hematopoietic Stem Cell Transplant” (HSCT)

1. Cancer
   - Tool to give more chemotherapy
   - Immune therapy against more resistant cancers
     - MDS
2. Immune deficiency
3. Replace dysfunctional marrow
   - Aplastic anemia
   - PNH

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Types of Transplant

I. MODALITY

- Autologous
  - Patient's own stem cells
- Allogeneic
  - Stem cells from a HLA matched donor
    - Match at HLA-A, B, C (class I MHC) AND
    - Match at DRB1, DQB1 (class II MHC)
- Syngeneic
  - Stem cells from an HLA identical donor (ie identical twin)

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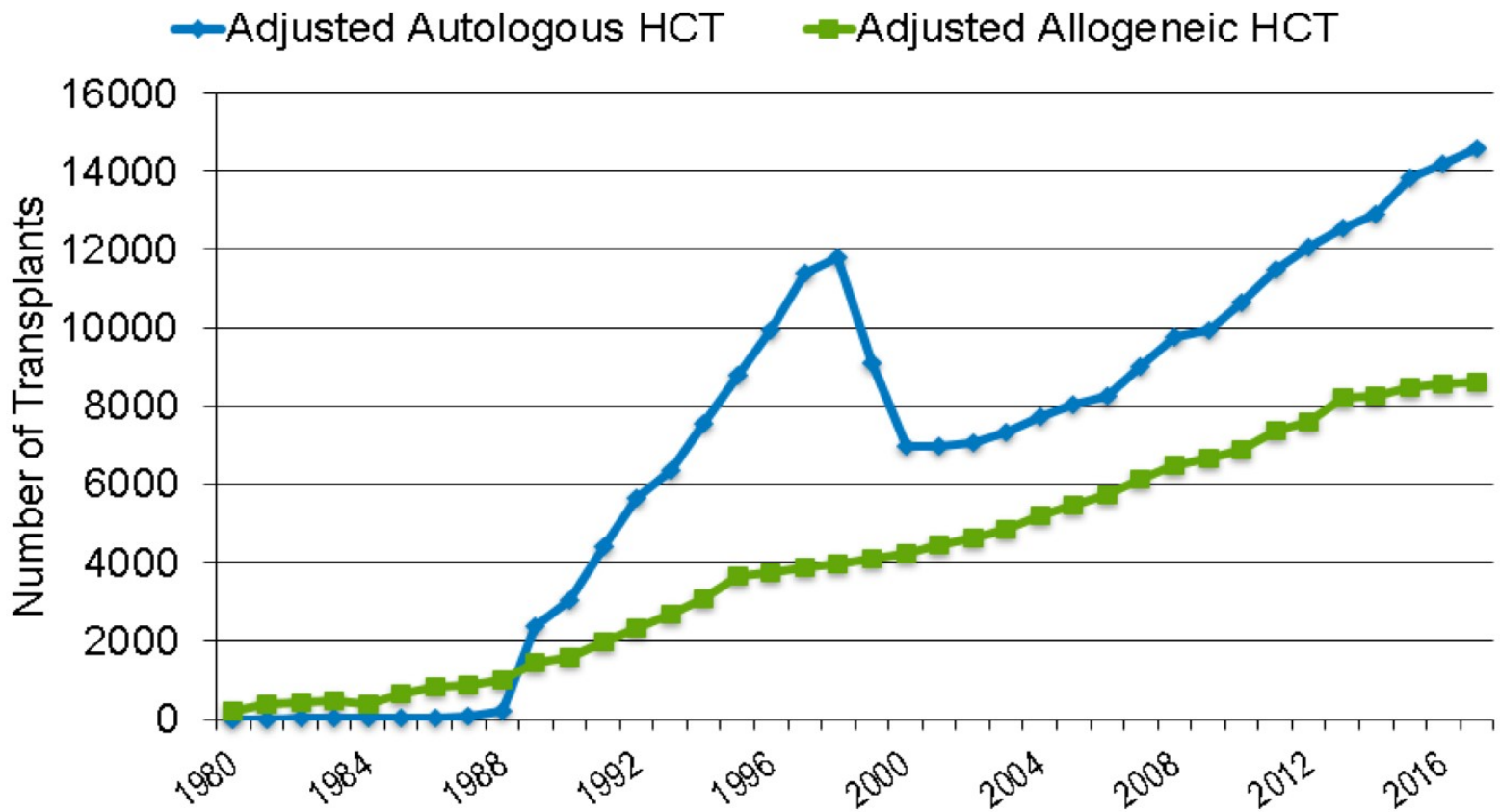
Annual Number of HCT Recipients in the US by Transplant Type



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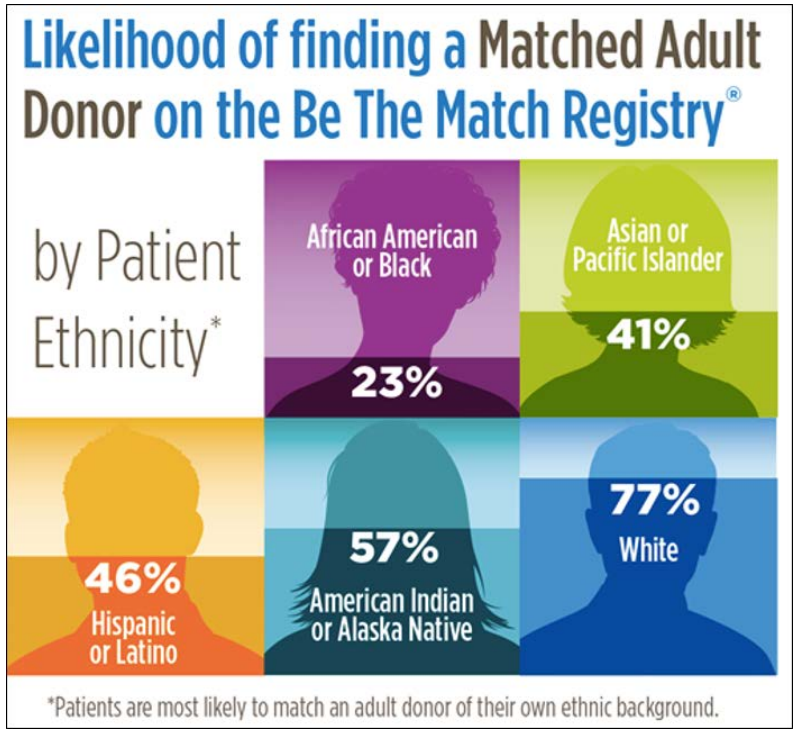
Types of Transplant



…for allogeneic only…

II. DONOR SOURCE

- Matched related
  - Related donor at least 8/8 HLA match
  - 25% chance of full sibling
- Matched unrelated
  - Unrelated donor who is at least an 8/8 HLA match
  - Chance related to ethnicity
- Mismatched
  - Donor who is < 8/8 HLA match with recipient
- Haploidentical
  - Related donor who is mismatched at as many as 3/6 HLA loci (HLA A, B, DR) – ie siblings, children, parents
- Umbilical cord blood
  - Stem cells collected from umbilical cord + placenta after baby is born; immaturity of immune system allows for higher level of HLA mismatch, requires at least 4/6 match (HLA-A, B, DRB1)

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HLA: Our Genetic "Fingerprint"

- **H**uman **L**eukocyte **A**ntigens (HLA) are proteins found on the surface of most cells in the body
- The immune system uses HLA to verify that a given cell is part of the body and not foreign
  - Grab on to foreign proteins in a way that allows immune cells to recognize and destroy them without destroying normal cells
- There are many different HLA proteins (HLA-A, -B, -C, -DRB1, -DQ, -DP) and there are many varieties of each one

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HLA: Our Genetic “Fingerprint”

- Alleles = Genes that control HLA antigens; are on chromosome 6
- Antigens = the proteins that are on the surface of cells

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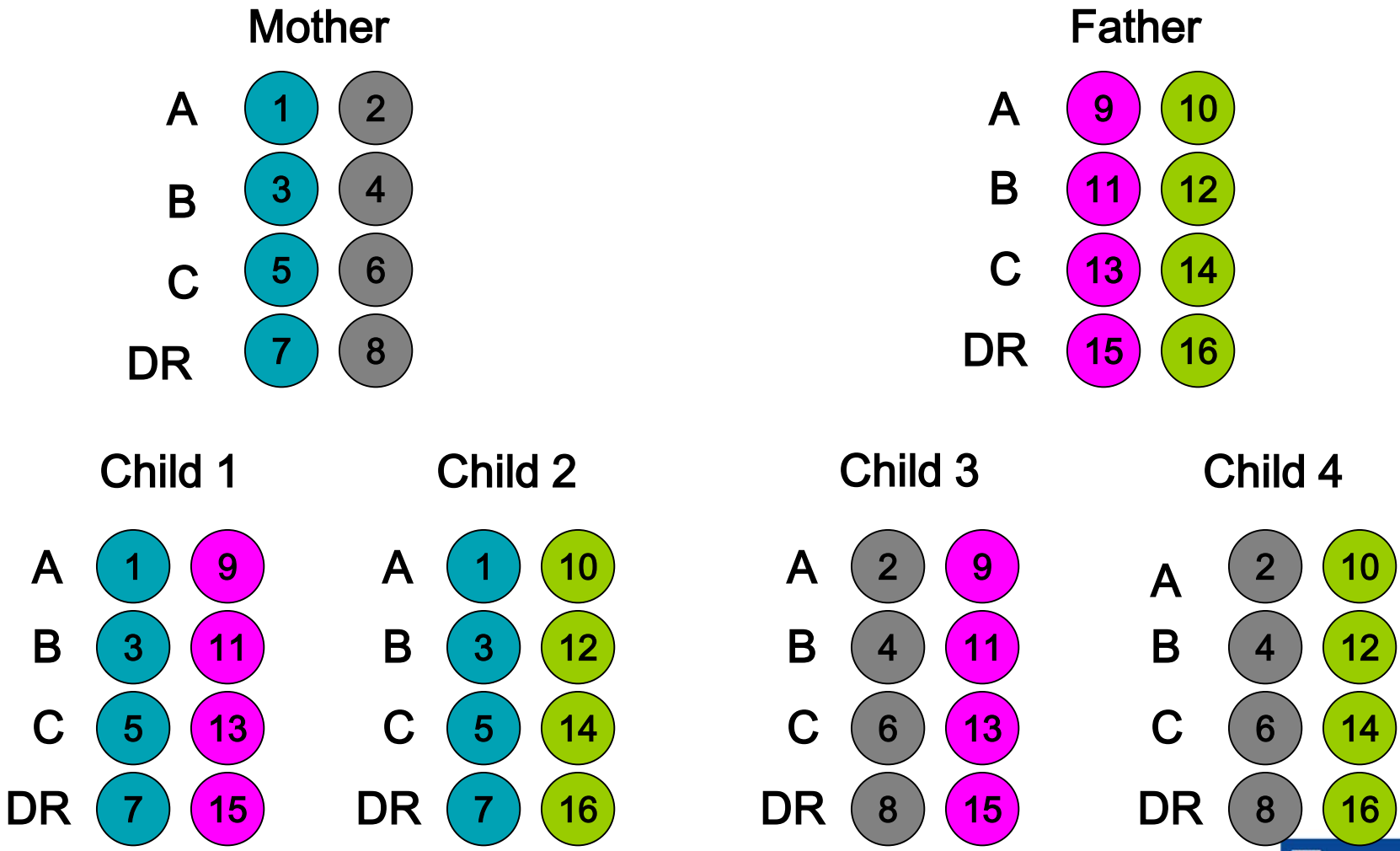
HLA Inheritance



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Why is HLA Matching Important?

- If donor stem cells are not the same HLA type as the recipient they will recognize the recipient as being different and attack – and vice versa
  - If the recipient cells win, you get graft rejection
  - If the donor cells win, you get graft-versus-host disease (GVHD)

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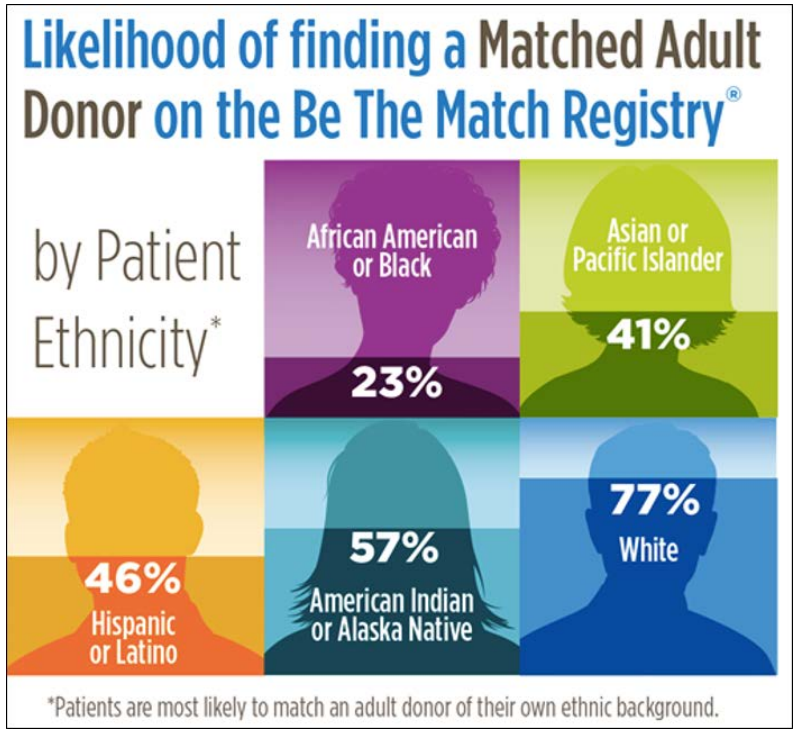
Types of Transplant



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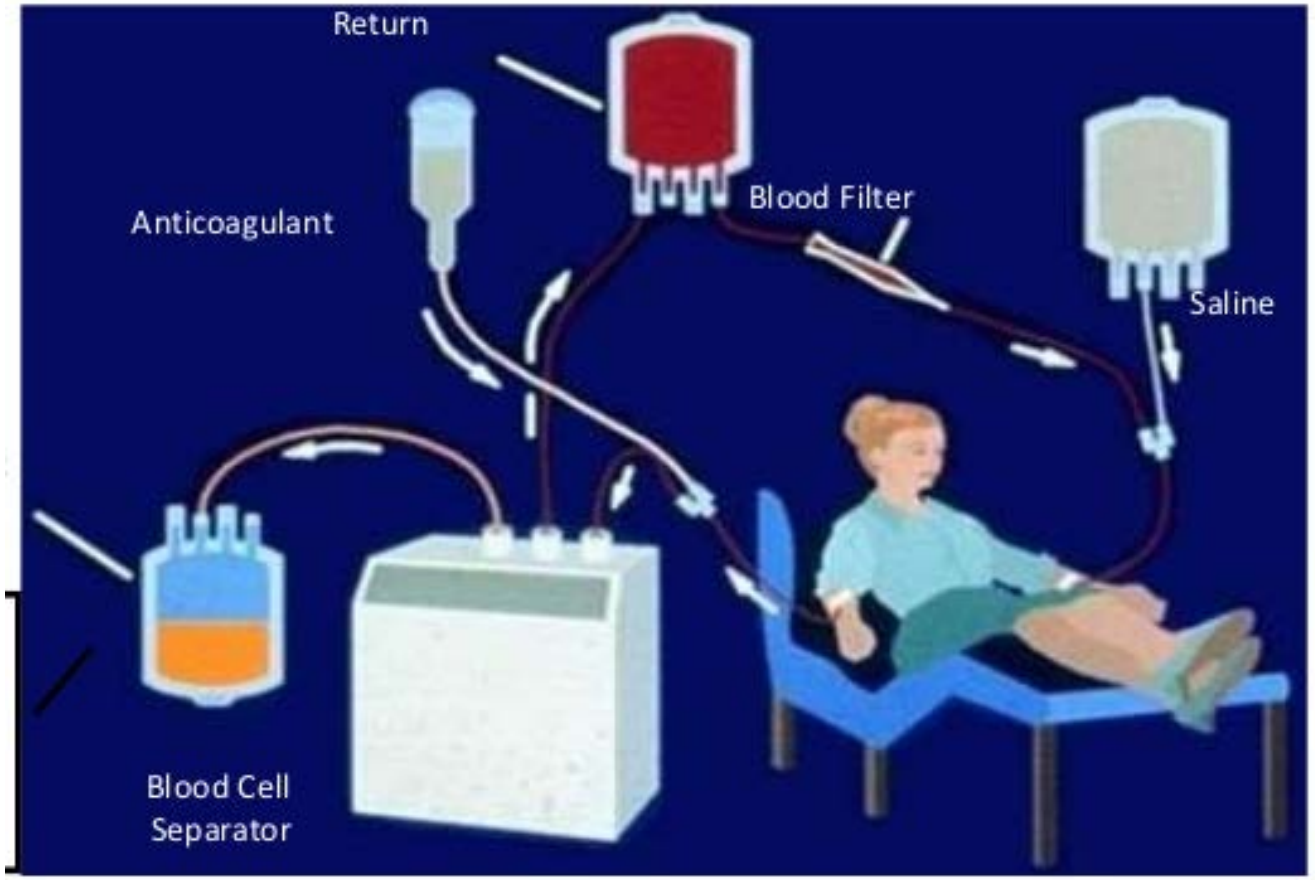
Types of Transplant

III. STEM CELL SOURCE

- Peripheral blood stem cells
  - Collected using a peripheral blood pheresis procedure after a chemokine-based or chemotherapy-based regimen
    - Common donor side effect: bony pain
    - Major side effect: low platelet counts, ?long term effects



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Types of Transplant

III. STEM CELL SOURCE

- Bone Marrow
  - Collected directly from the bone marrow – generally no pre-procedure mobilization but requires OR and general anesthesia
    - Common donor side effect: pain
    - Major side effect: significant bone, nerve, soft tissue injury

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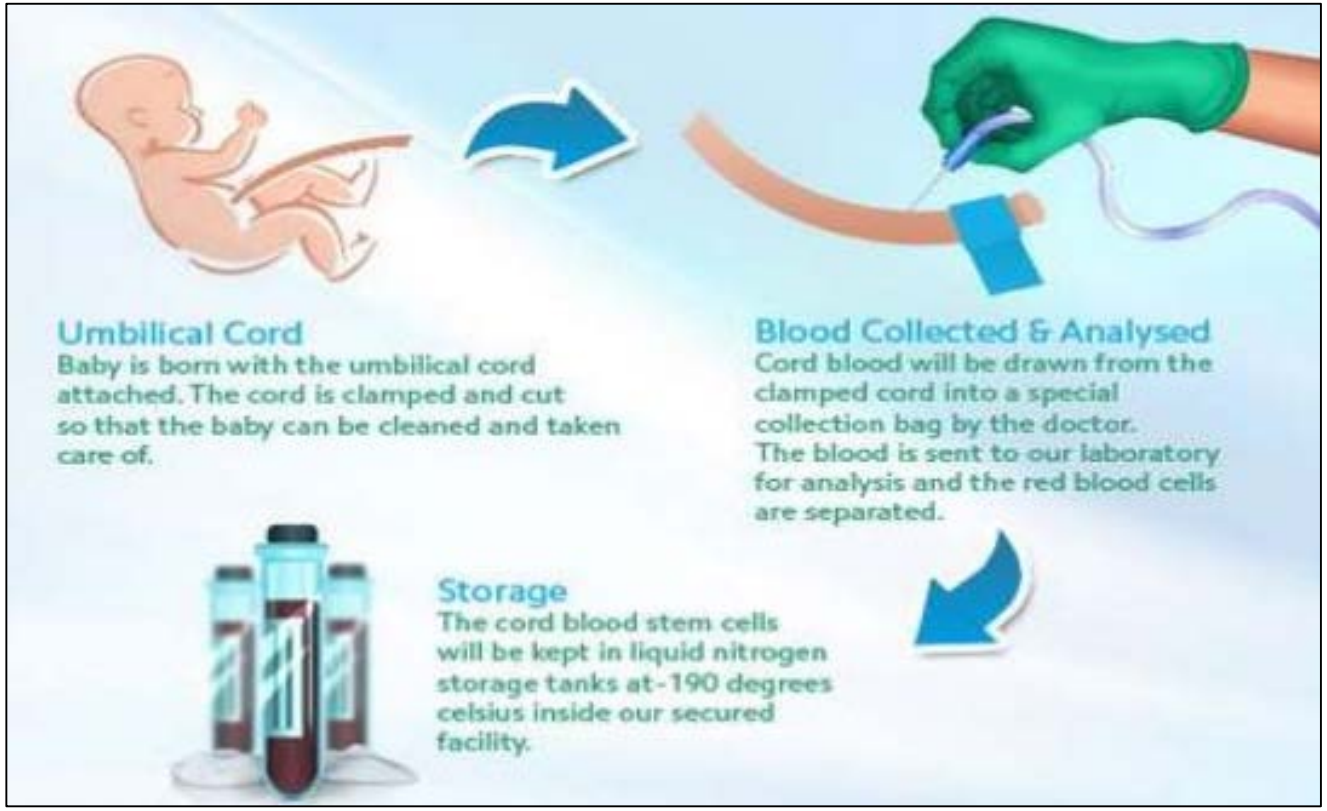
Types of Transplant

III. STEM CELL SOURCE

- Umbilical cord blood
  - Removed from umbilical cord and placenta after normal delivery of infant donor
  - Can be stored frozen for 10+ years
    - Common donor side effects: none
    - Major donor risks: none



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Transplant Logistics*

…full medical evaluation …		D-x CHEMO Aka "conditioning" →				
Rest Day	Day 0 HCT					
						Day 12… counts rising
		Day 15… Engraft?				Day 19… home?

- Generally inpatient for ~3 weeks *
- Need to live within ~45 minutes
- Need an adult caregiver through ~d90

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Day 0 – Day of Transplant

- Stem cells from marrow or peripheral blood are collected from donor the day before and/or the day of transplant
  - Transported to patient and administered like a blood transfusion
- Cord blood units are shipped to transplant center and stored before start of preparative regimen
- Side effects are usually the same as a blood transfusion and may include fever, chills and rash

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Recovery: Early Days after Transplant

- 14-21 days of extreme immune suppression:
  - Very low white blood cell, red blood cell & platelet counts
- At risk for serious infections, bleeding, and organ damage from the conditioning regimen
- Antibiotics given to prevent & treat infection
- Blood & platelet transfusions given as needed
- Closely monitored for organ damage and treated and supported as needed

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Transplant Logistics*

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Engraftment

- Term used to refer to the establishment of new stem cells within the bone marrow as evidenced by the appearance of (in order):
  - White blood cells
  - Platelets
  - Red blood cells
- Occurs 10-28 days after transplant
- Risk for infection and bleeding decreases following engraftment

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Transplant Logistics*

…full medical evaluation …		D-x CHEMO Aka "conditioning" →				
Rest Day	Day 0 HCT					
						Day 12…
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Getting Discharged

- You will be discharged from the hospital when:
  - You've engrafted –Absolute Neutrophil Count (ANC)>500
  - No active infection
  - No active Graft Versus Host Disease (GvHD)
  - Able to take foods and meds by mouth

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Life After Transplant

- The first 100 days
  - Close monitoring for complications such as GvHD and infections
  - Frequent clinic visits with possible readmission to the hospital for treatment of complications
- Don’t be discouraged by re-hospitalization: it’s very common
  - Restriction of activities
  - Need caregiver for transportation, shopping, cooking

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What are the complications of BMT?

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Complications

1. Low cell counts
2. Toxicity from the chemotherapy/conditioning
3. Graft failure
4. Graft-versus-host disease
5. Infection
6. Veno-occlusive disease
7. Relapse
8. Late effects

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Complications

1. Low cell counts
    - Secondary to the chemotherapy prior to transplant
        - Results in fatigue, bleeding, and infectious risk
        - Will be dependent on transfusion of RBCs and platelets during chemotherapy and prior to engraftment

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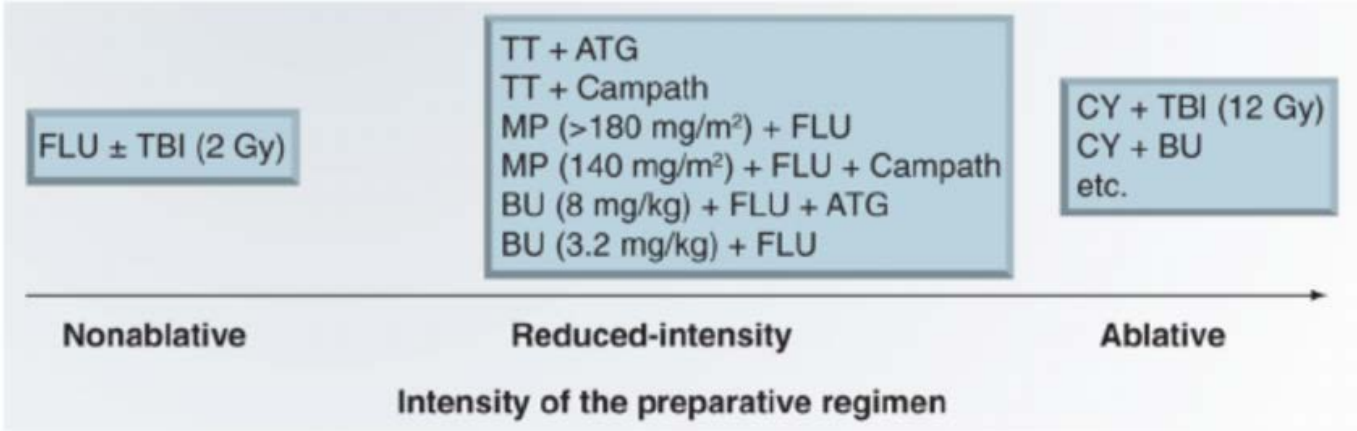
Complications

2. Toxicity from the chemotherapy/conditioning
   - Organ toxicity – heart/lung/liver/kidneys
   - Risk of seizure
   - Nausea/vomiting/diarrhea
   - Rash
   - Mouth sores

Higher dose chemo/XRT
Goal: Kill ALL stem cells/diseased cells
-more side effects



Lower dose chemo/XRT
Goal: Suppress recipient immune system to allow donor to engraft
-usually used in patients less likely to tolerate side effects of high dose transplant

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Complications

3. Graft failure

- Donor stem cells not engrafted within host marrow, fail to produce necessary hematopoietic elements
  - Primary: donor stem cells NEVER engrafted
  - Secondary: loss of donor cells after initial engraftment
- ~5% or less
- Higher risk with cord blood, reduced intensity transplants, certain disease states (ie MF)

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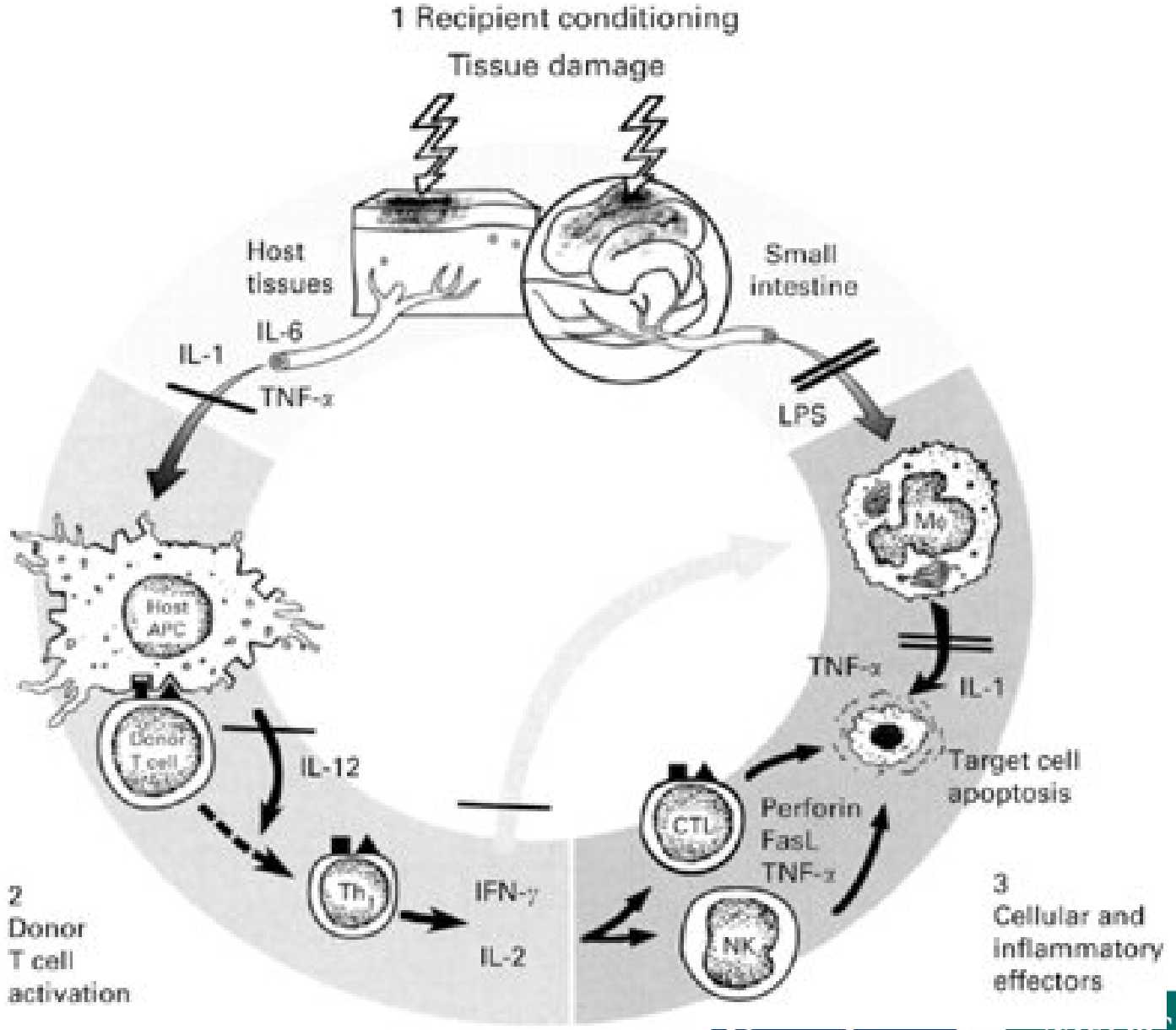
Complications

4. Graft-versus-host disease



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Complications -- GVHD

- Risk depends on:
  - Degree of HLA compatibility
  - >HLA compatibility = < GVHD
    - Related < unrelated
- Stem cell source
  - BM < GVHD vs PBSC
- Conditioning regimen
  - NMA/RIC < MA

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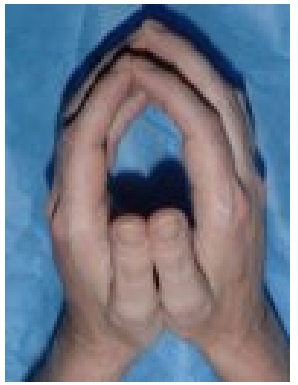
Complications -- GVHD



Acute

- <d100
- 40-70% of patients
- Skin -- rash
- GI – upper or LOWER GI, diarrhea
- Liver – increased bilirubin

Chronic

- >d100
- Skin – lichen planus, sclerosis, hyper- or hypo-pigmentation
- Eyes/mouth -- dry
- Liver – abnormal LFTs
- Lungs -- BO
- MSK – fasciitis, contractures

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Complications

5. Infections:

<u>Pre-engraftment period</u>

- Bacterial organisms from skin/oral/GI flora
- Invasive fungal infxn
- HSV

<u>Post-engraftment period</u>

- Impaired cell mediated immunity, humoral immunity and phagocyte function
- ?GVHD? Additional IS
- VIRAL – CMV, adeno, respiratory, HHV-6, BK
- Invasive fungal infxn
- PCP

<u>Late post-transplantation period</u>

- ?chronic GVHD – defects in cellular, humoral, barrier functions
- Skin infxn, upper and lower respiratory tract

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Complications

6. Veno-occlusive disease

- Painful hepatomegaly, ascites, jaundice, weight gain→fulminant liver failure; typically 3-21 days post-transplant
- Progressive injury in hepatic venous endothelium with progressive occlusion of venules + sinusoids
- Risk factors: pre-existing liver disease, hepatitis, conditioning regimen, prior treatments
- *Prevention*: minimize risks, ursodiol
- *Treatment*: Defibrotide

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Complications

7. Relapse

- 10-40% of undergoing allogeneic HCT
  - Donor lymphocyte infusions
    - Risks: GVHD, myelosuppression
  - Additional chemotherapy
  - Second transplant

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Complications

8. Late effects

- Late relapse
- Chronic GVHD
- Late infection
- Cardiovascular diseases – ischemic heart disease, cardiomyopathy
- Pulmonary toxicity
- Renal dysfunction
- Endocrinopathies – DM2, thyroid disease, osteopenia, infertility, hypogonadism, hypoadrenalism
- Treatment related malignancies
- Increased risk for secondary solid tumors

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Who should get a BMT?

Right disease, right patient…

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Indications

I. Autologous

- Malignant
  - **Myeloma**/other plasma cell disorders
  - Non-Hodgkins lymphoma – relapsed DLBCL, MCL, PTCL, +/- FL
  - Hodgkin's lymphoma
  - Relapsed germ cell tumors
  - Acute promyelocytic leukemia (APL)

Transplantation of Stem Cells Allows Us to Increase the Dose Intensity of Our Treatments

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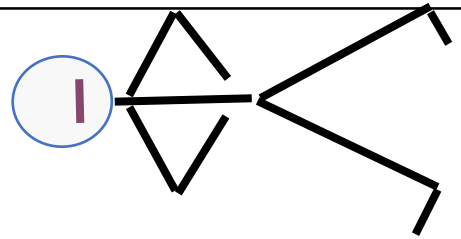
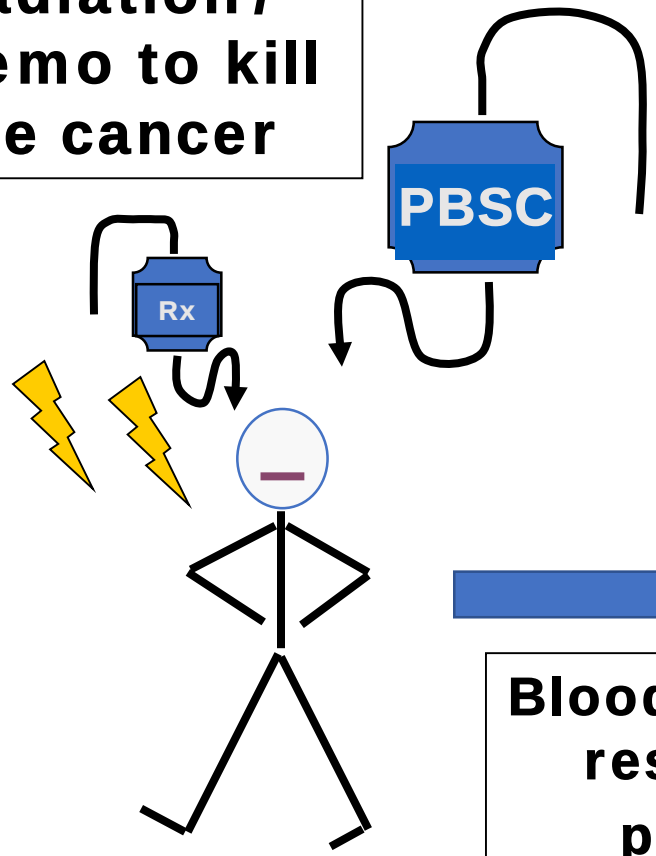
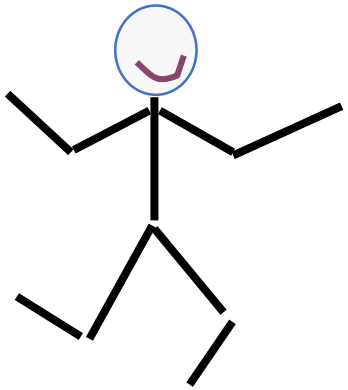
Patient as Donor:
Autologous Transplantation
Collect & freeze cells



Radiation / Chemo to kill the cancer



Support until recovery



Blood stem cells to restore blood production

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Indications

- Non-malignant
  - Autoimmune conditions -- ?immune re-set?

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Indications

II. Allogeneic

- Malignant -- GRAFT versus TUMOR effect
  - Acute leukemias – AML, ALL (APL)
  - *MDS/MPN*
  - CML
  - CLL
  - Myeloma
  - NHL
  - HL

Donor's immune cells can recognize and destroy cells of some kinds of cancer

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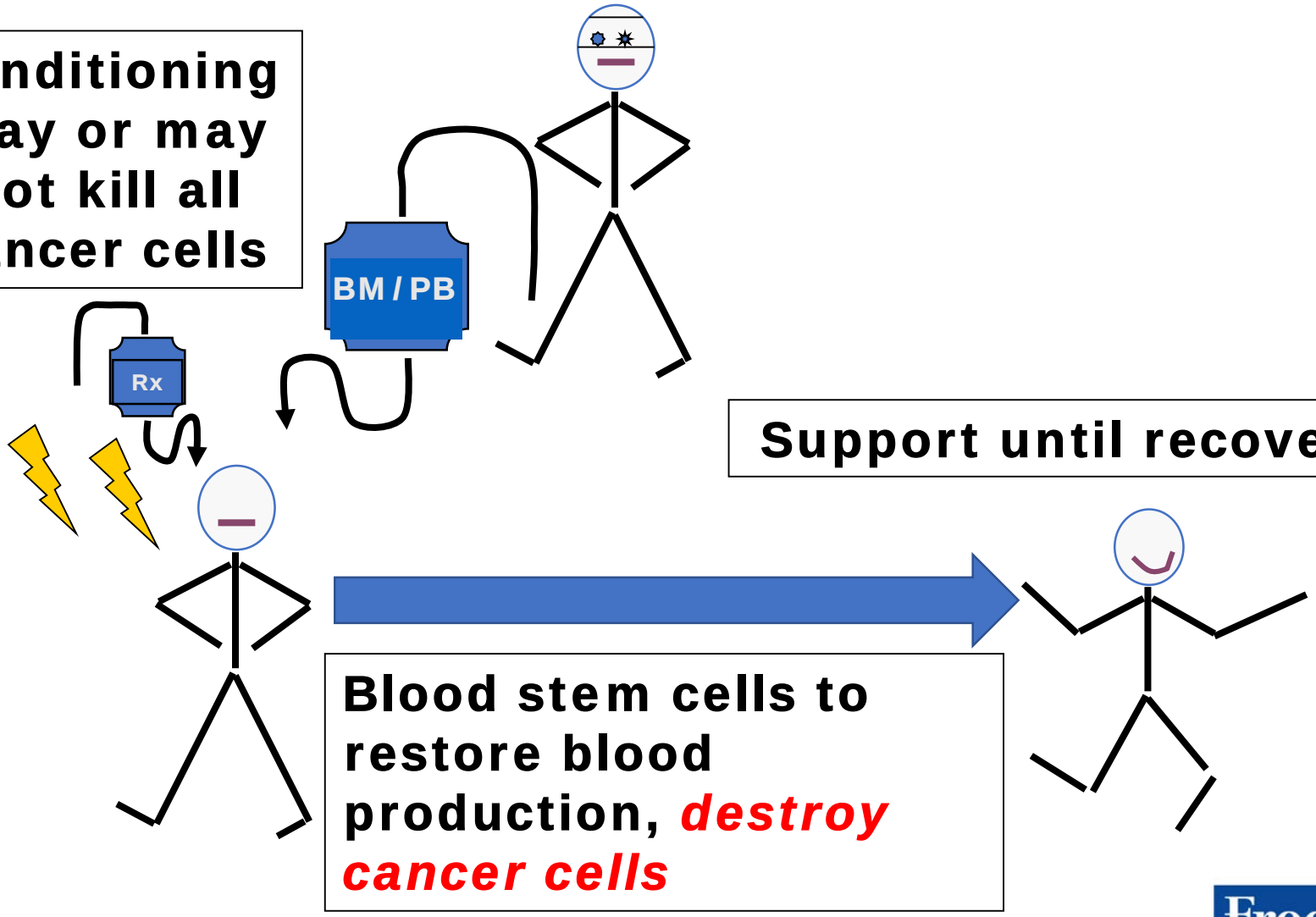
Healthy Donor: Allogeneic Graft

Conditioning may or may not kill all cancer cells



Support until recovery

Blood stem cells to restore blood production, *destroy cancer cells*

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Indications

- Benign – replacing diseased organ
  - *Aplastic anemia*
  - Congenital marrow failure syndromes
  - Hemoglobinopathies
  - Immunodeficiency syndromes

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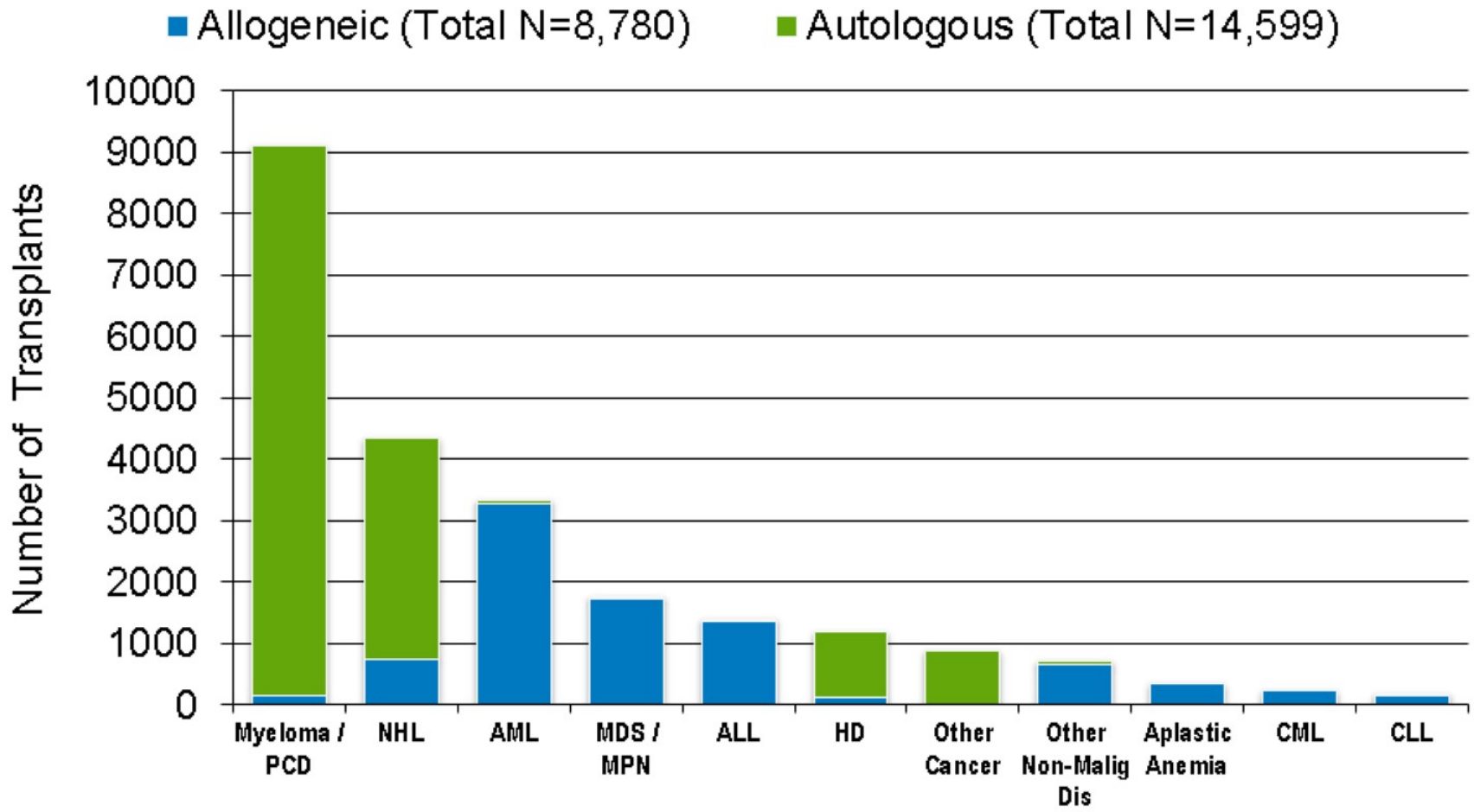
Indications for Hematopoietic Cell Transplant in the US, 2017



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Comorbidities

- **NOT** all about age
- Cardiac disease
- Inflammatory bowel disease
- Diabetes
- CVA
- Psychiatric illness
- Liver disease
- Kidney disease
- Pulmonary disease
- Obesity
- Uncontrolled infection
- Ulcer disease
- Rheumatologic disease
- Other cancers

These items will help determine conditioning intensity as well as candidacy for transplant overall

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When???

- For some diseases, transplant should be part of initial treatment
- For others, transplantation is appropriate when other drugs fail
- Whichever disease you have, it is good to have a consult with a transplant expert early on – to make sure that you get a transplant when you need it and when it is most likely to benefit you

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What are the outcomes of BMT in MDS and aplastic anemia?

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MDS

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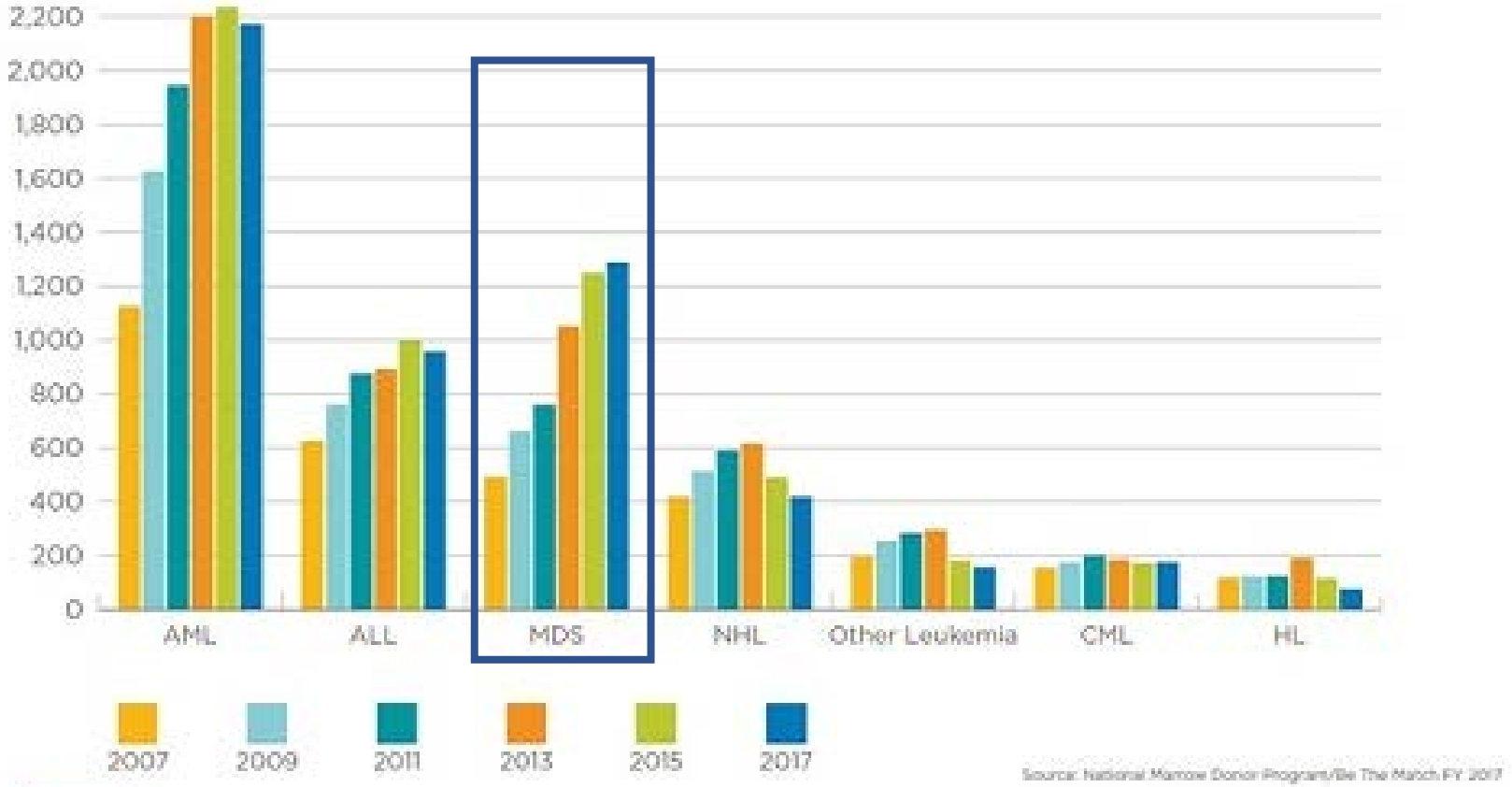
Transplants by Patient Diagnosis

Hematologic Malignancies

Unrelated Donor Transplants Facilitated by NMDP/Be The Match



Source: National Marrow Donor Program/Be The Match FY 2017

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Myelodysplastic / Myeloproliferative Diseases - Adult

Unrelated HCT Improved Survival Over Time

Transplants Facilitated by NMDP/Be The Match

Improved Survival Over Time – MDS/MPN			
YEAR OF HCT	NUMBER OF CASES	ONE-YEAR SURVIVAL	TWO-YEAR SURVIVAL
2013-2016	2,766	62%	52%
2009-2012	1,733	58%	48%
2004-2008	1,086	55%	46%
1987-2003	1,357	43%	37%

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SOURCE: CIBMTR®, the research program of NMDP/Be The Match

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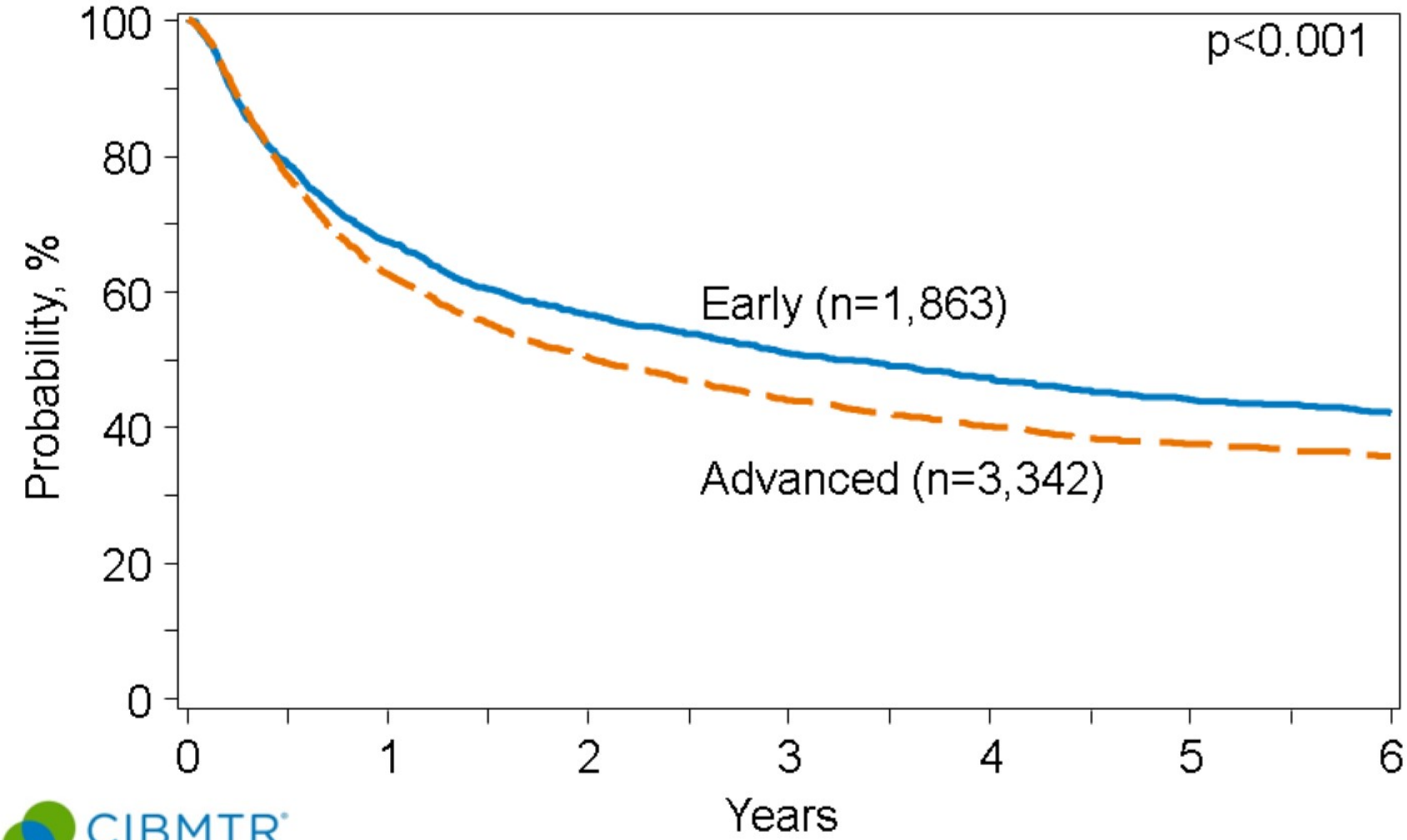
Survival after Unrelated Donor HCT for Myelodysplastic Syndrome (MDS), 2006-2016



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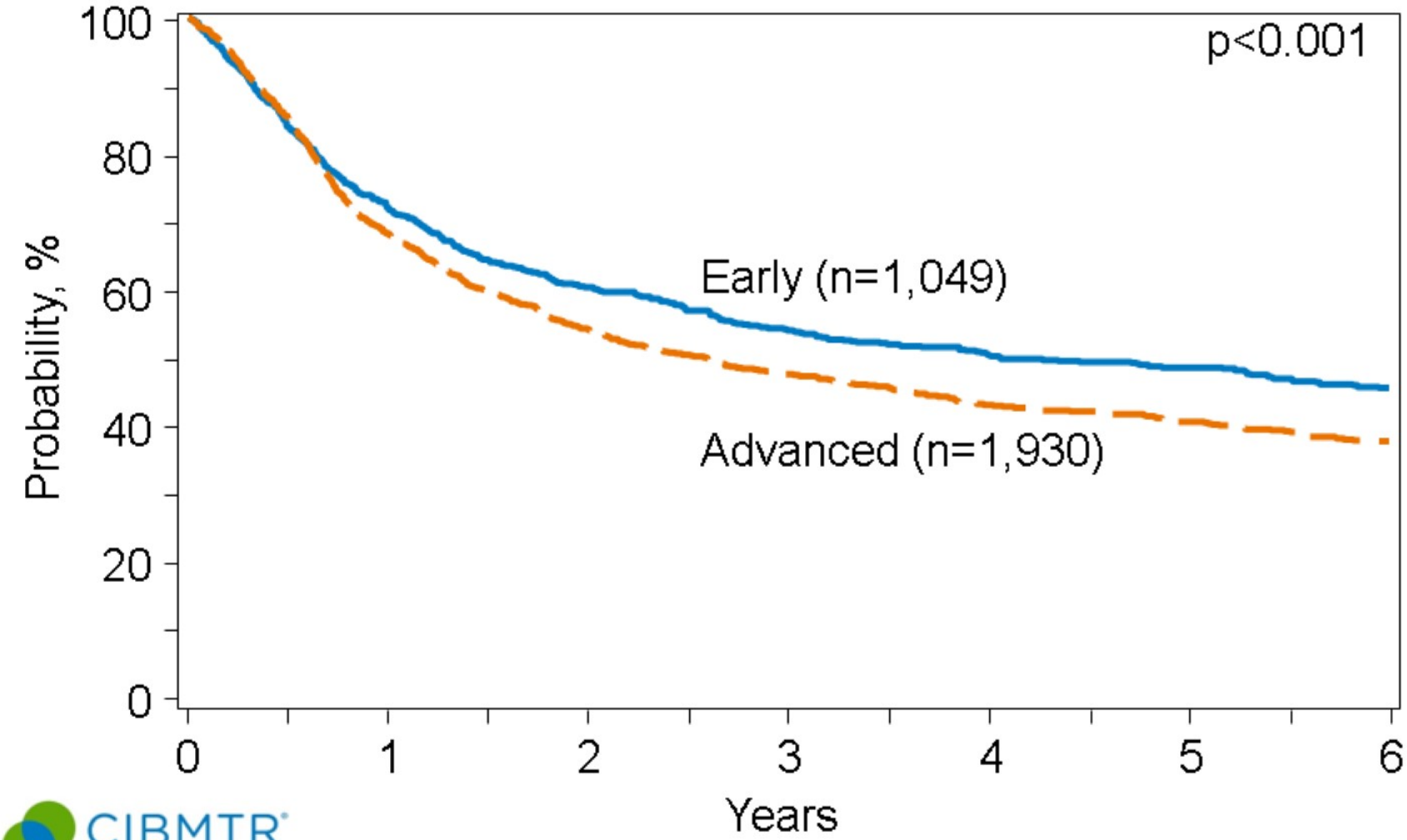
Survival after HLA-Matched Sibling HCT for Myelodysplastic Syndrome (MDS), 2006-2016



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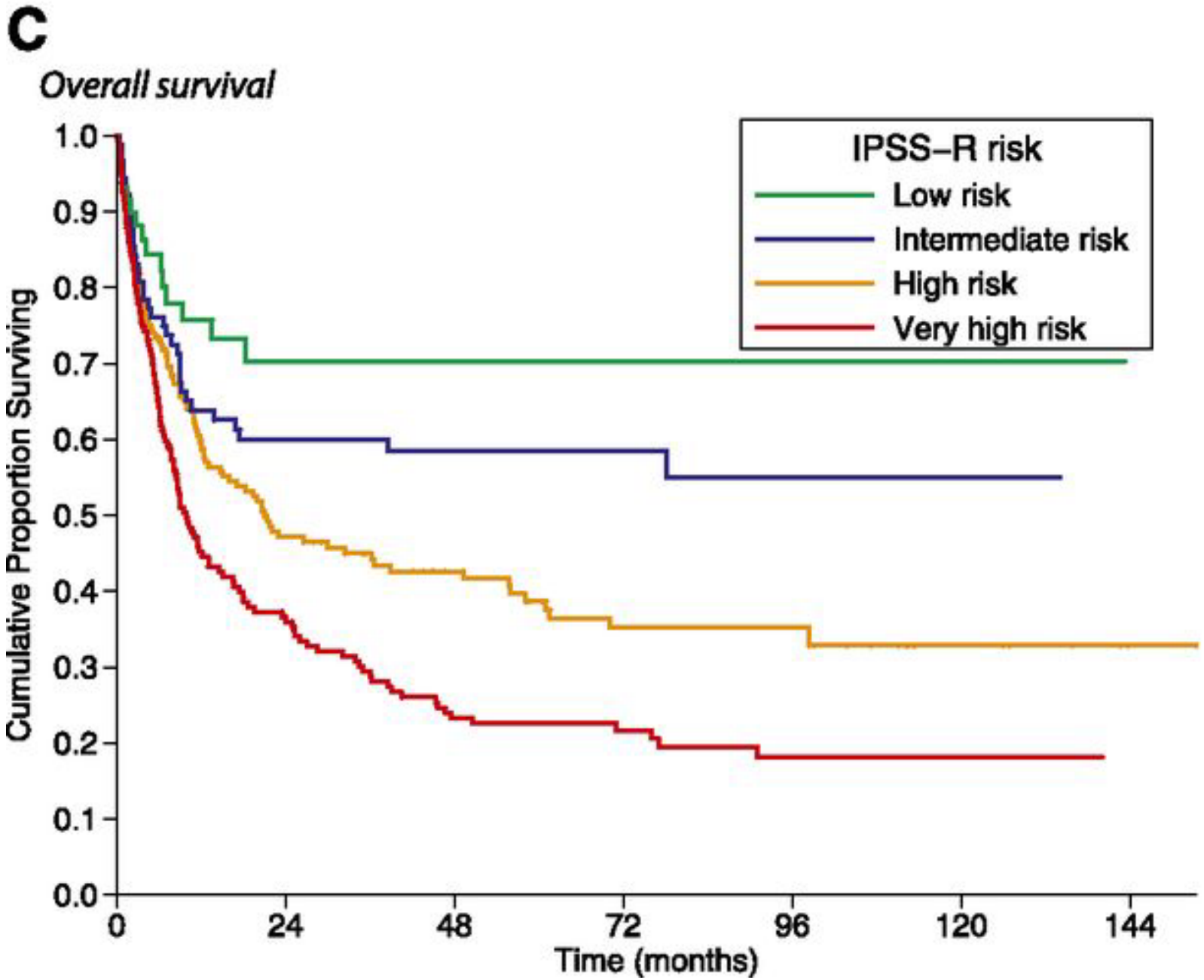

IPSS-R considers:

-degree of cytopenias

-blast percentage

-cytogenetic abnormalities

Della Porta et al. Blood 2014.

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But when??

	Immediate Transplant	Transplant at Progression
Low	6.51	7.21
Int-1	4.61	5.16
Int-2	4.93	2.84
High	3.2	2.75

WAIT

TRANSPLANT IMMEDIATELY

Cutler et al. Blood 2004.

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Aplastic Anemia

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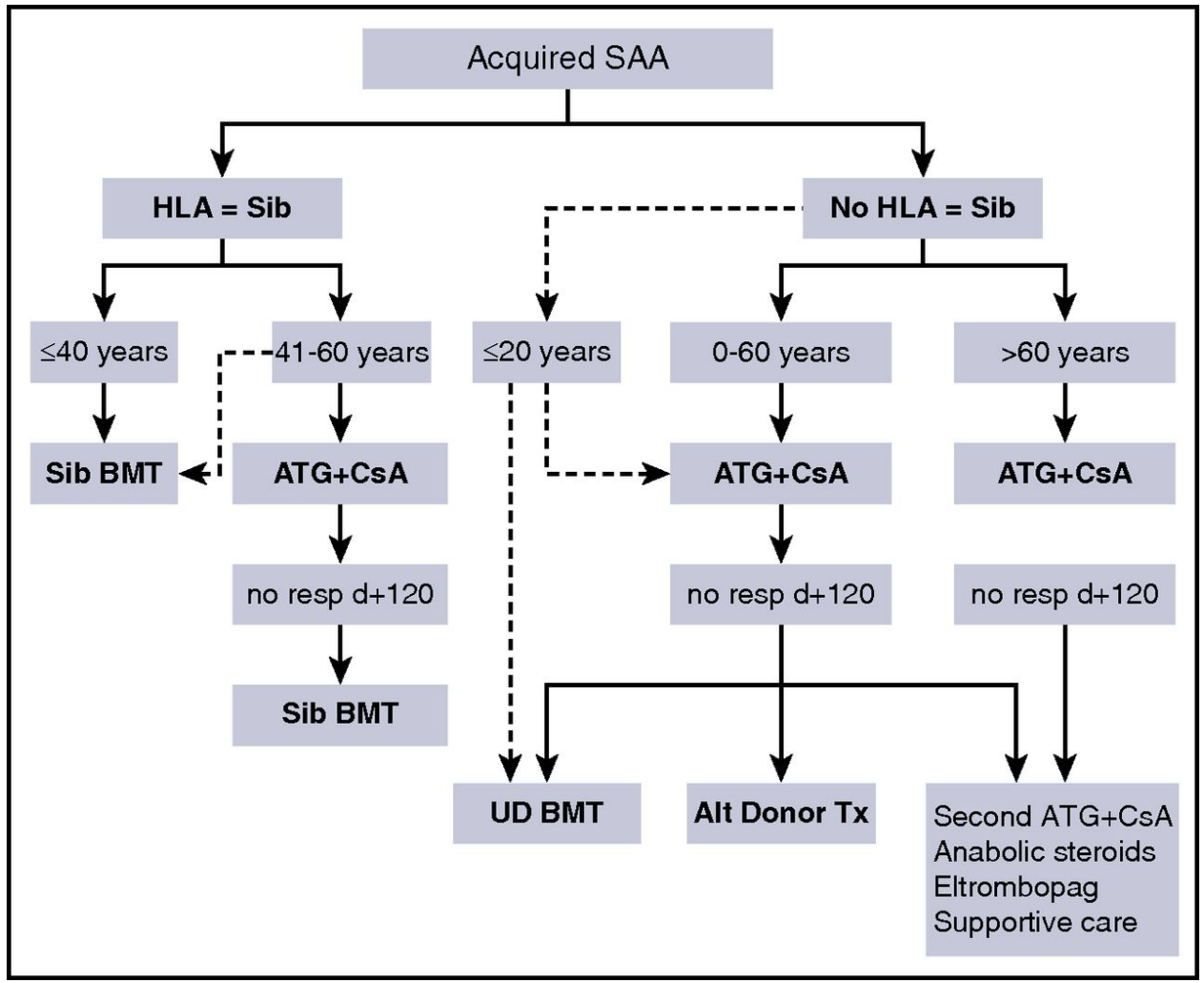
Management of Severe Aplastic Anemia



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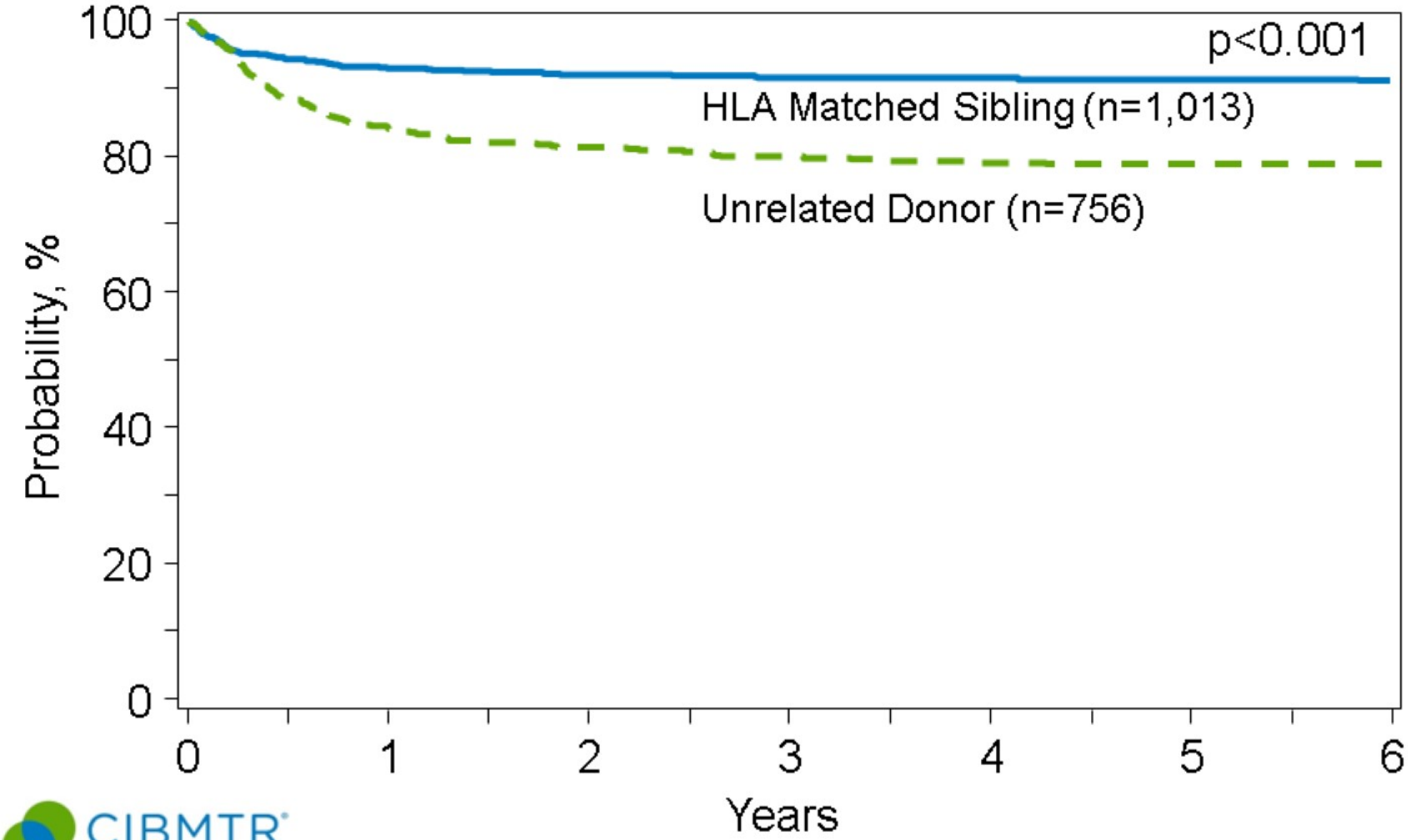
Survival after Allogeneic HCT for Severe Aplastic Anemia, <18 Years, 2006-2016



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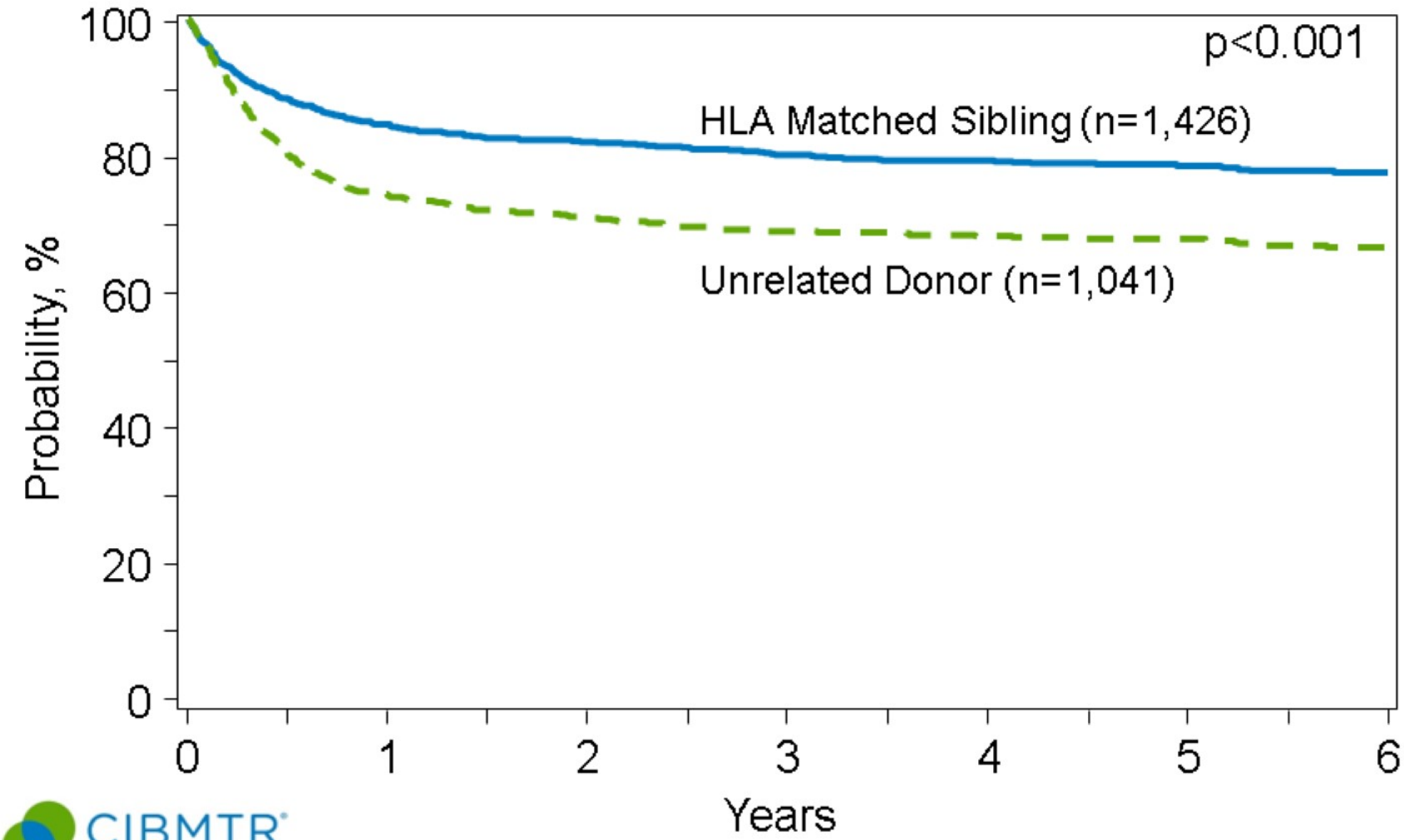

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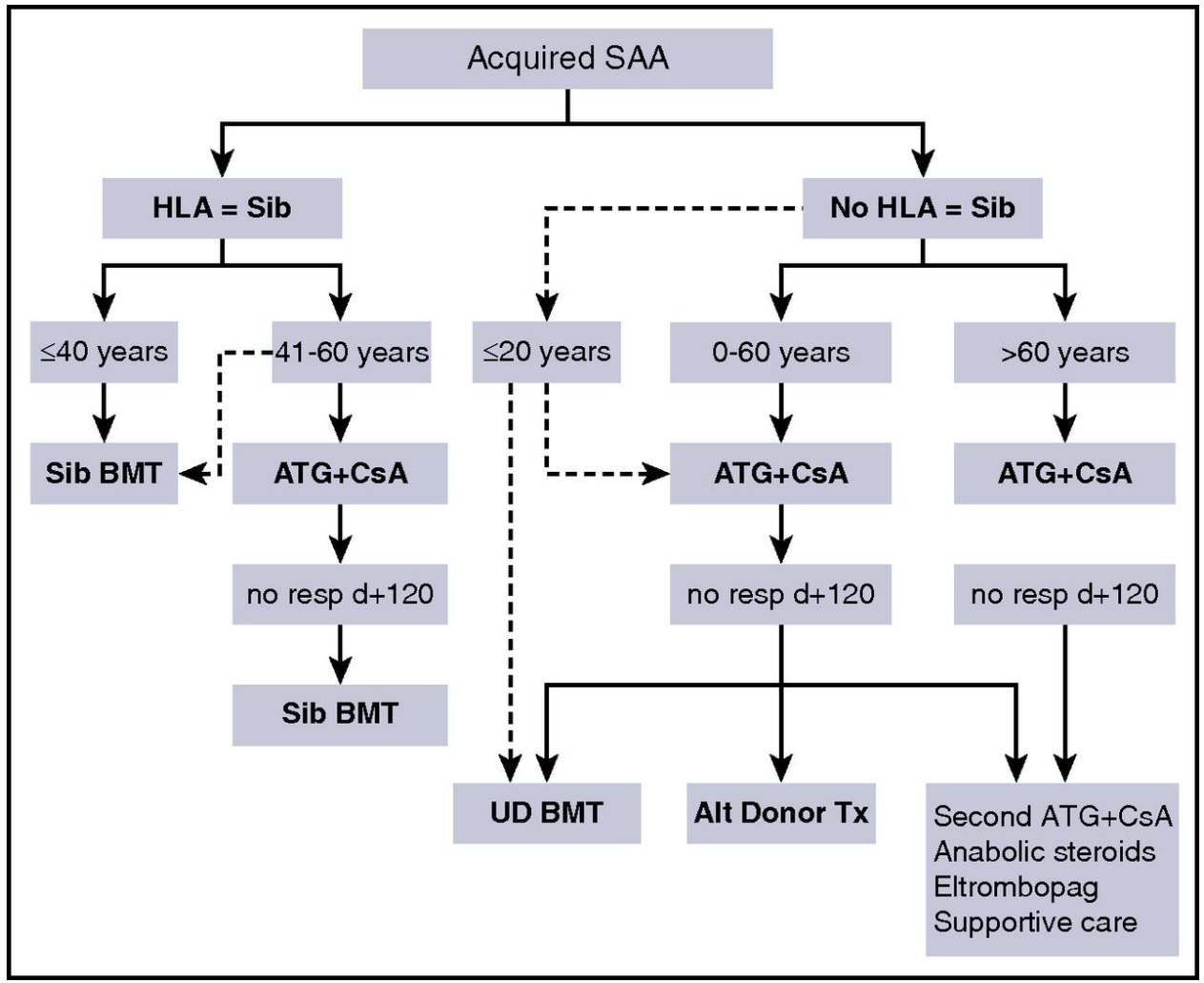
Management of Severe Aplastic Anemia



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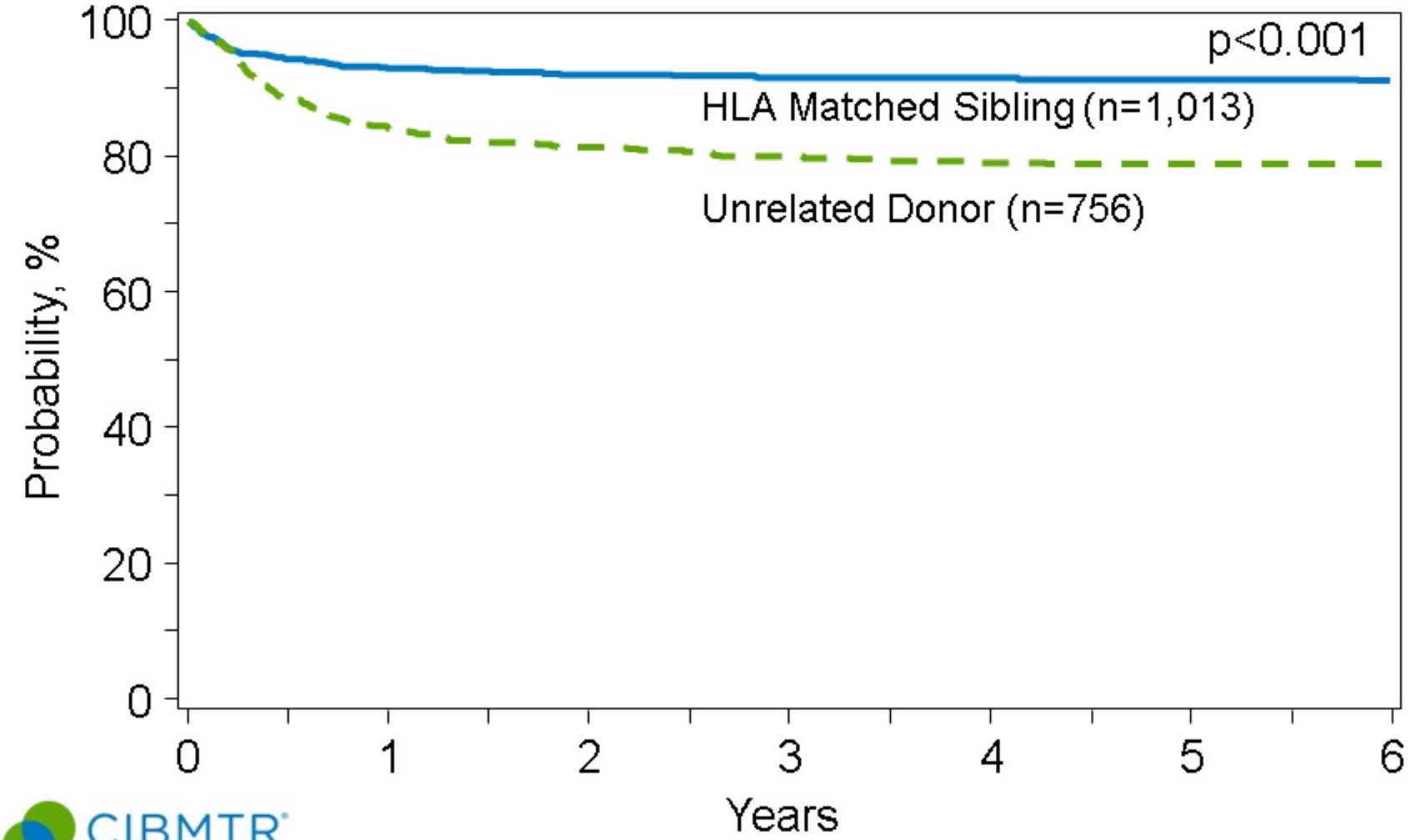
Survival after Allogeneic HCT for Severe Aplastic Anemia, <18 Years, 2006-2016



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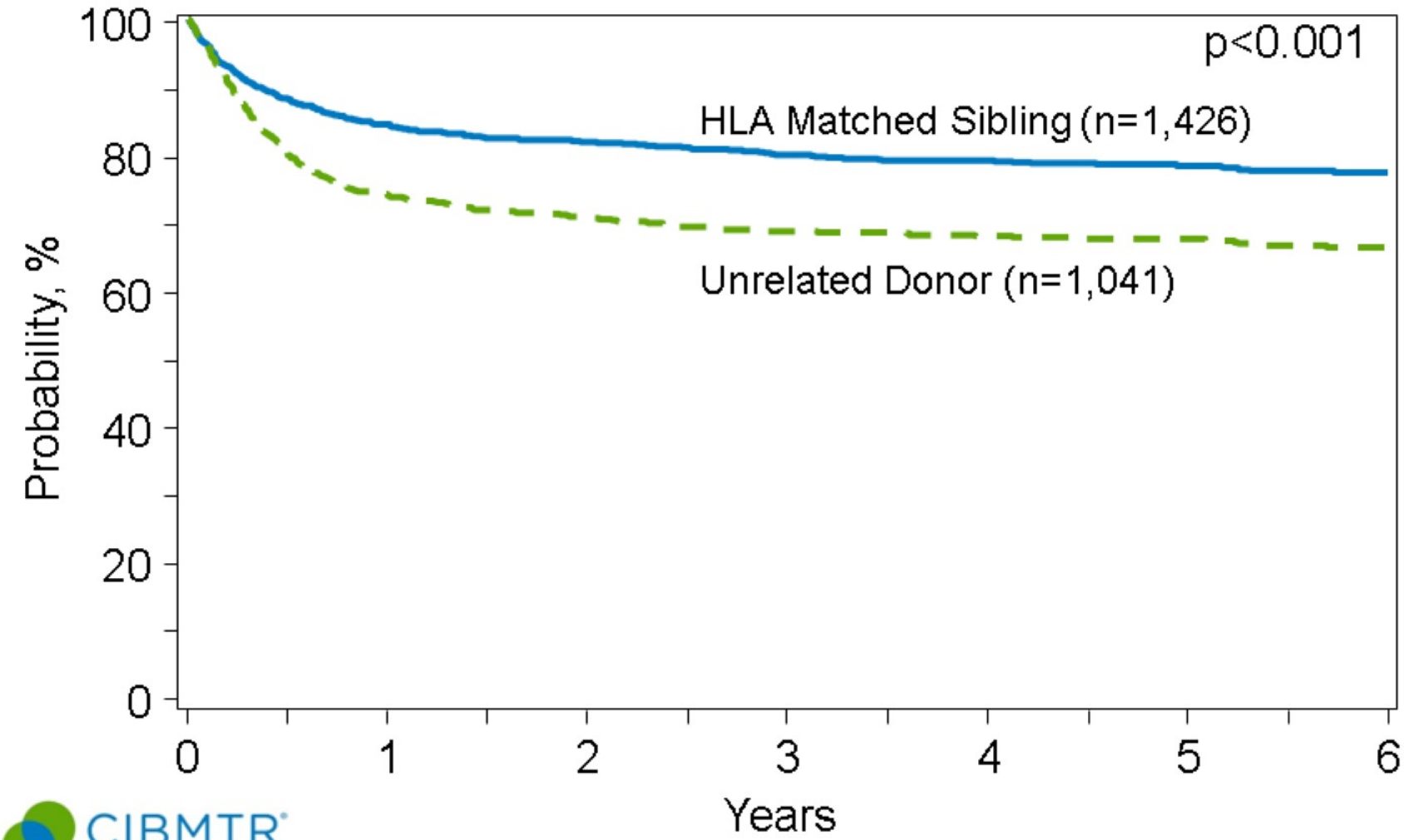
Survival after Allogeneic HCT for Severe Aplastic Anemia, ≥18 Years, 2006-2016



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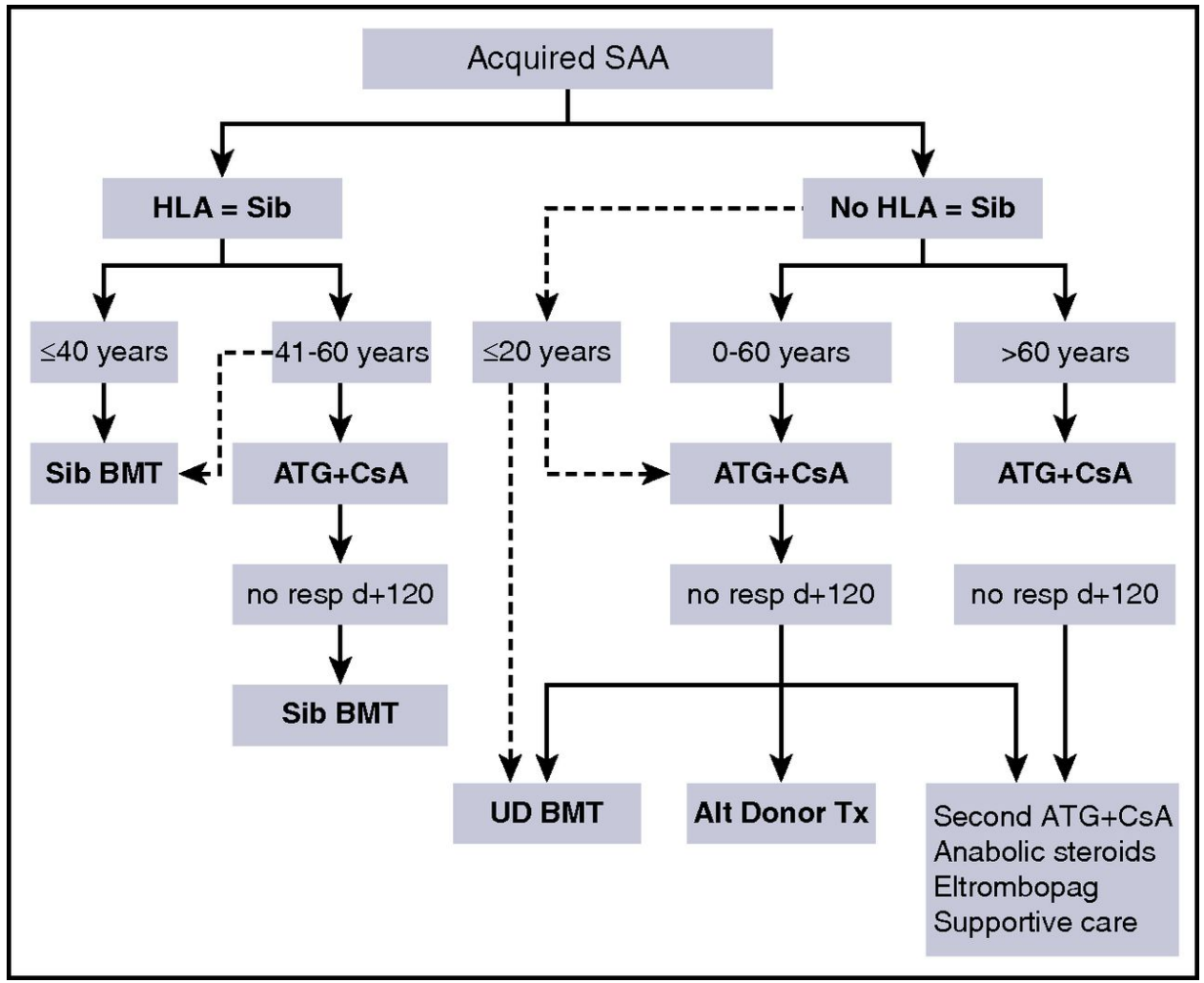

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What’s next?

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MDS

- **BMT CTN 1102** – A Multi-Center Biologic Assignment Trial Comparing Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients with Intermediate-2 and High Risk Myelodysplastic Syndrome – completed accrual, await results
- **French study** – low/intermediate risk MDS transplant/no transplant at diagnosis based on availability of a matched related or unrelated donor -- recruiting
- **Initial Cytoreductive Therapy for Myelodysplastic Syndrome Prior to Allogeneic Hematopoietic Cell Transplantation (the ICT-HCT Study) –** intensive versus less intensive chemotherapy prior to transplant in patients with MDS
  - Mayo Scottsdale, Cleveland Clinic, Fred Hutch, Kaiser Permanente Washington
- Strategies to make transplant SAFER – GVHD prevention, changes in conditioning, etc.

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Aplastic Anemia

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Optimizing Haploidentical Aplastic Anemia Transplantation (CHAMP):

BMT CTN 1502

- Phase II pivotal trial
  - Intended to provide evidence that the curative option available to SAA patients
  - Repeated IST is of less value for patients
- Addresses key need in rare patient population

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Study Design & Objectives

- **Study design:** Prospective, multicenter, phase II study in patients receiving haploidentical transplant for severe aplastic anemia
- **Primary objective:** Assess overall survival at one year post-HSCT in patients with SAA
- Secondary objectives include
  - Probability of being engrafted and alive at 1 year
  - Probabilities of GVHD

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Inclusion Criteria

1. ≤ 75 years of age
2. Confirmed diagnosis of acquired SAA
3. No suitable fully matched related (6/6) or unrelated donor (8/8) available
   - Ok to forego this donor search if the clinical situation dictates urgent transplant (low likelihood of identifying a suitable donor within 6-8 weeks)
4. **Refractory (at 3 months) or relapsed after at least one trial of immunosuppressive therapy directed at primary SAA**
5. Available HLA haplo first degree relatives (2, 3, or 4 mismatches, but with at least one allele identical at HLA-A, -B, -C, or DRB1)

Aplastic Anemia

- A Phase II Trial of Non-Myeloablative Conditioning and Transplantation of Partially HLA-Mismatched/Haploidentical Related or Matched Unrelated Bone Marrow for Patients with Refractory Severe Aplastic Anemia and Other Bone Marrow Failure Syndromes
  - Johns Hopkins + MCW

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Questions?

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