Trends in Hematopoietic Cell Transplantation

- AAMAC Patient Education Day Oct 2014

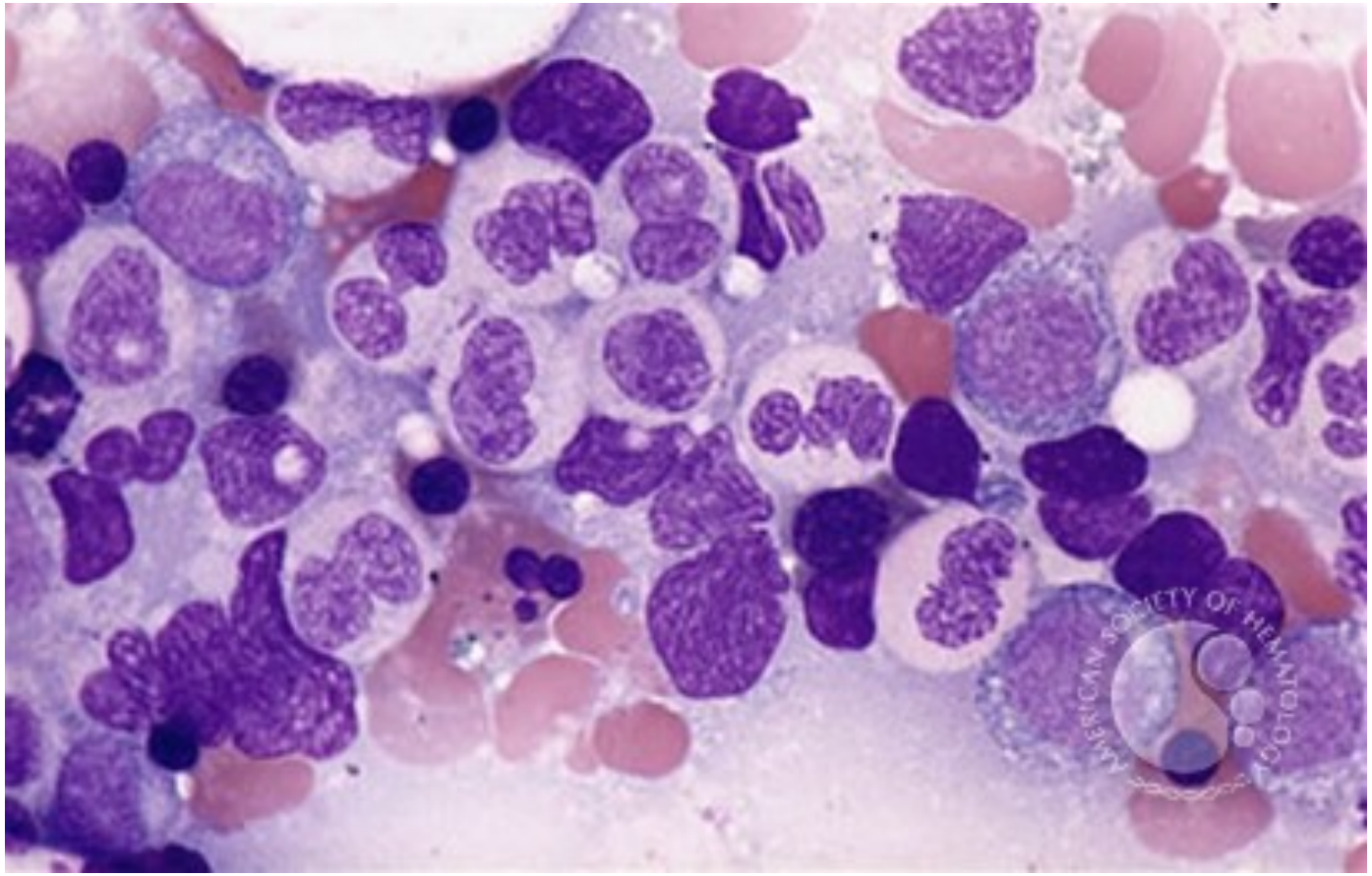
Objectives

- Review the principles behind allogeneic stem cell transplantation
- Outline the process of transplant, some of the potential benefits and risks
- Describe new trends in hematopoietic cell transplantation

Case 1

- 46 yo woman comes to her doctor after noticing a week of skin rash and easy bruising. She is pale. CBC shows:
- Hemoglobin 68
- Platelets 8
- Neutrophil count 0.6
- Diagnostic test: Bone marrow

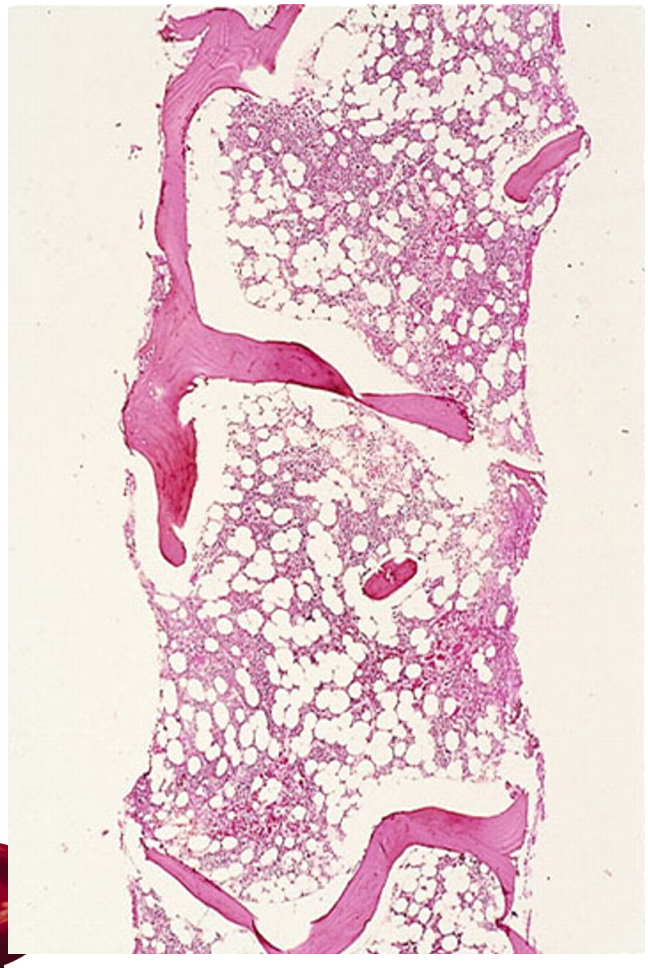
High Risk Myelodysplastic Syndrome with increased blasts



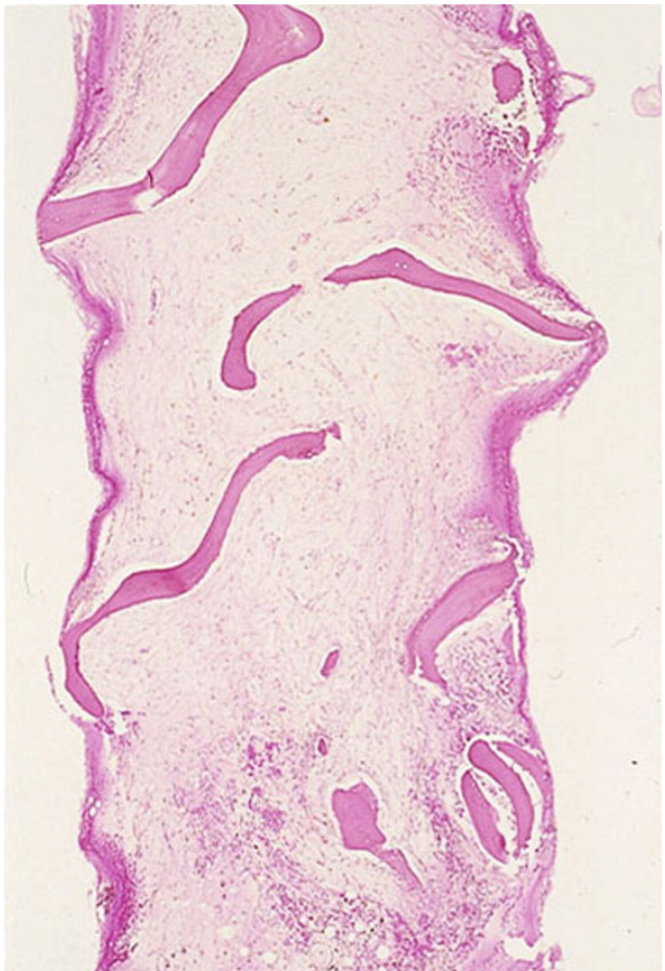
- Cytogenetic testing shows high risk chromosome abnormalities

Bone Marrow Biopsy

Normal Bone Marrow Biopsy

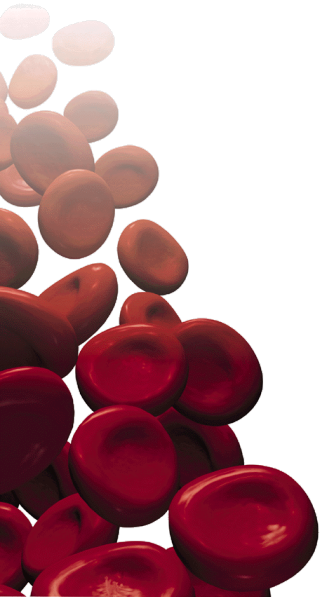


Aplastic Anemia

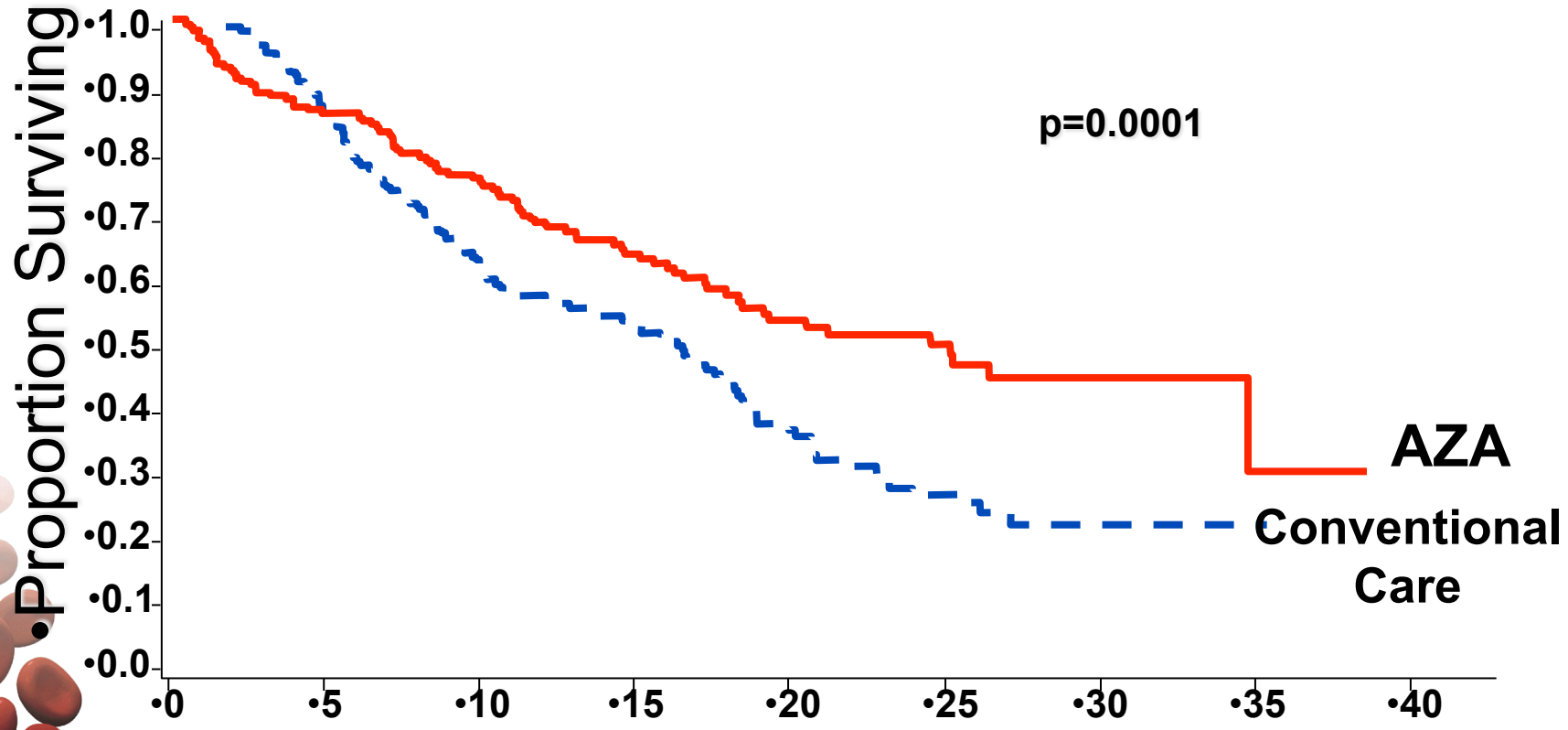


What are her treatment options now?

- Supportive Care
- Transfusions
- Antibiotics
- Growth Factors
- Hypomethylating agents
- Chemotherapy
- Transplantation



•Overall Survival: Azacitidine vs Conventional Care Regimen



•Time (months) from Randomization

- **•Survival Difference 9.4 months**
- **•HR = 0.58 [95% CI: 0.43, 0.77]**

•Lancet Oncol 2009; 10:223-32.

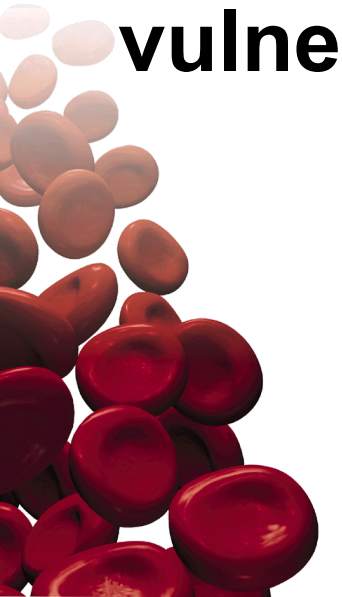
Between a rock and a hard place

Transplantation is currently the only curative therapy for myelodysplastic syndromes

Median age at diagnosis is 65-70
Toxicity of transplantation can be prohibitive

Original principle of stem cell transplant in malignancy

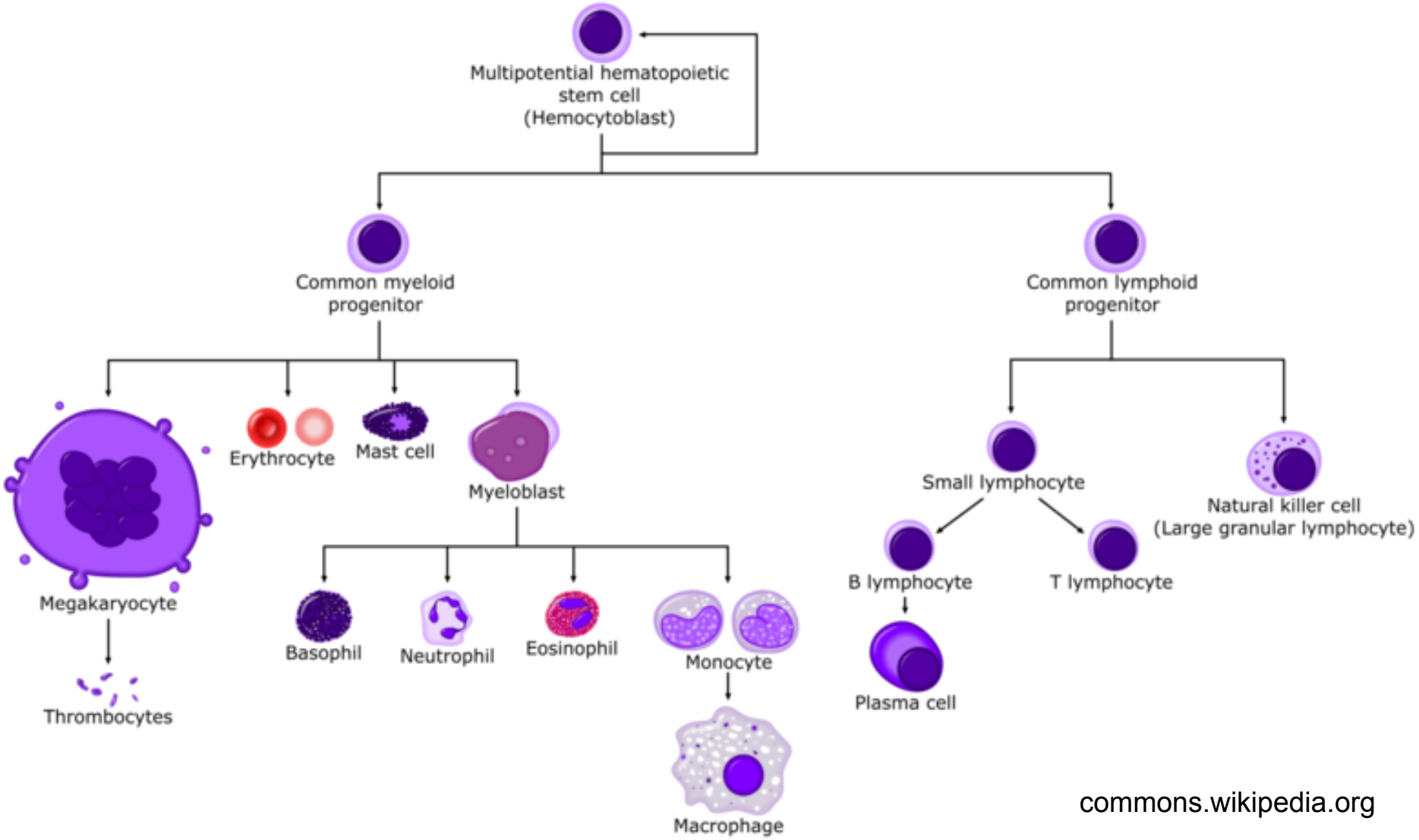
To allow delivery of curative doses of anticancer agents which would otherwise destroy the bone marrow, the most vulnerable tissue.



Process of Hematopoietic Stem Cell Transplantation

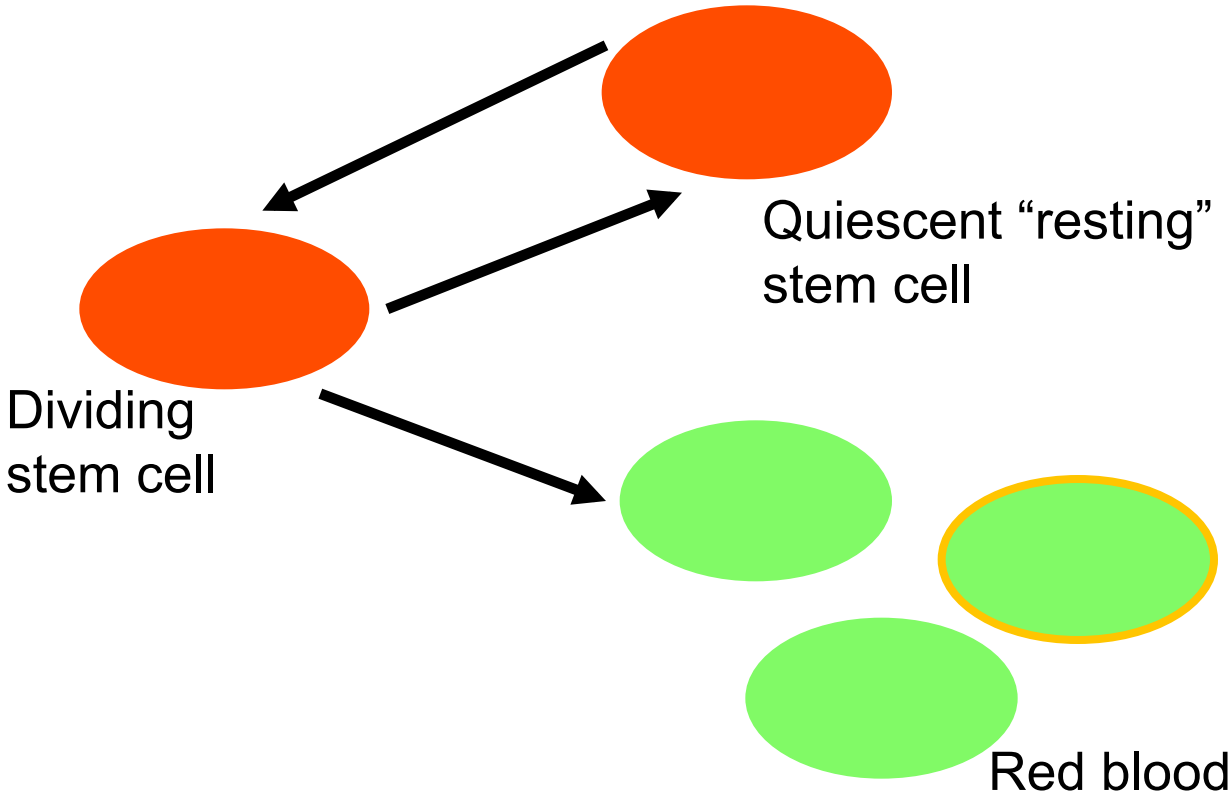
- A patient is given high doses of chemotherapy ± radiation effective against tumor or abnormal marrow "conditioning"
- Bone marrow toxicity is dose-limiting
- Stem cells are then infused after chemotherapy and/or total body irradiation to salvage marrow function

Hematopoiesis



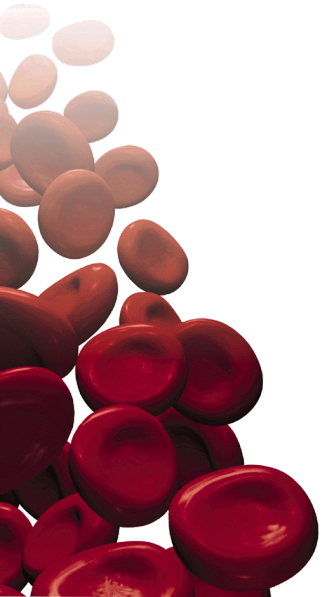
commons.wikipedia.org

Hematopoietic Stem Cells are Self-Renewing

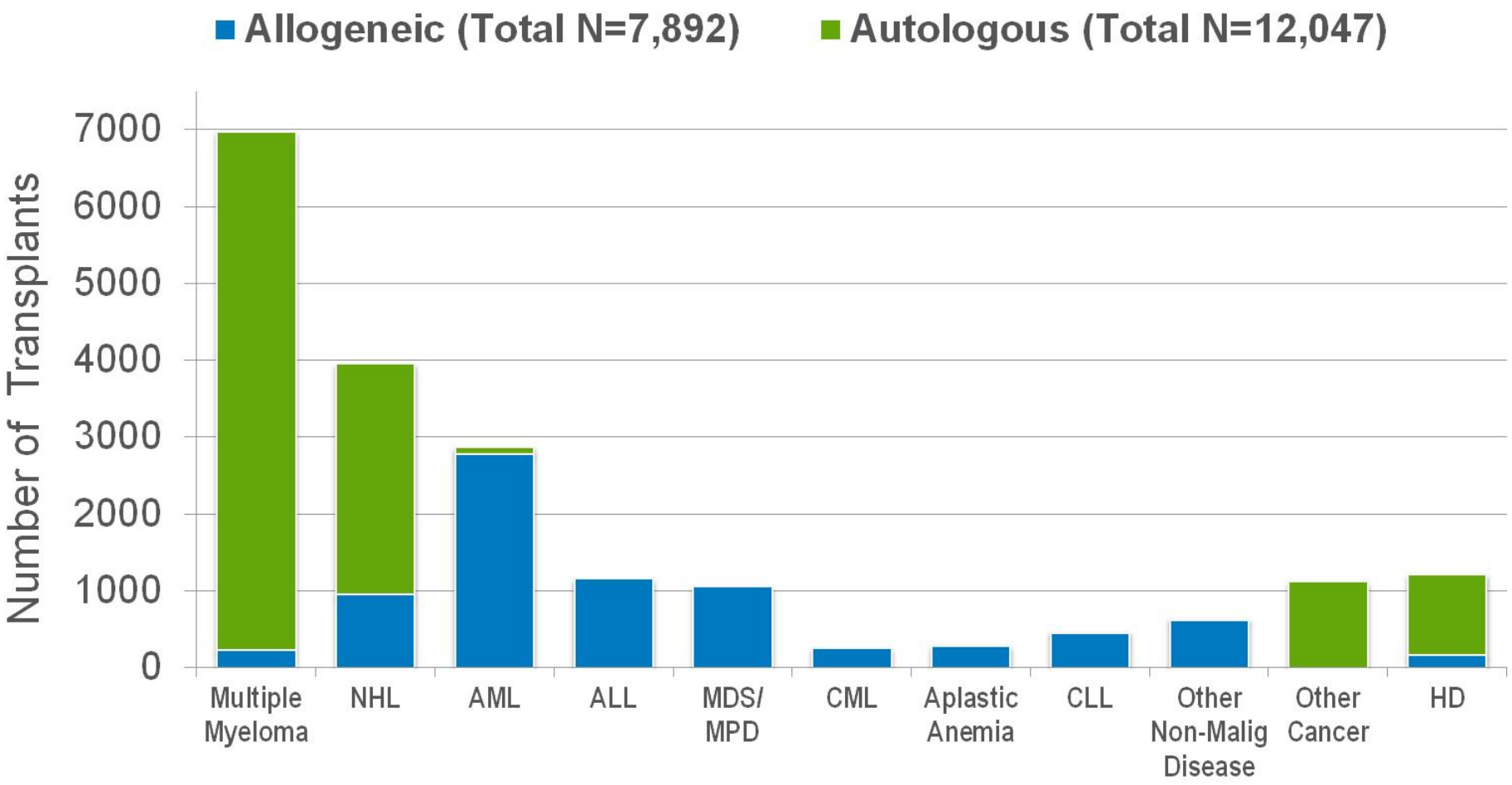


A transplant is not a transplant is not a transplant...

- Autologous – patient's own cells
- Allogeneic – donor cells
  - Bone marrow source
  - Peripheral blood (mobilized with G-CSF)
  - Umbilical cord
- Syngeneic – identical twin



Indications for Hematopoietic Stem Cell Transplants in the US, 2011



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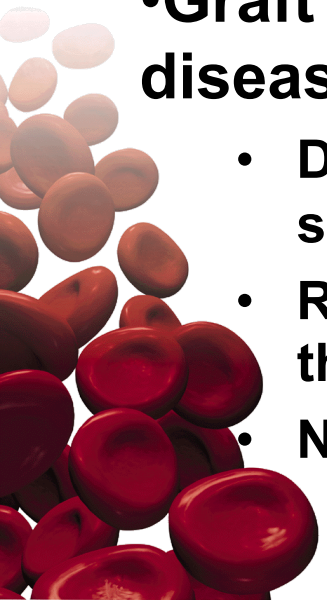
Allogeneic Stem Cell Transplantation

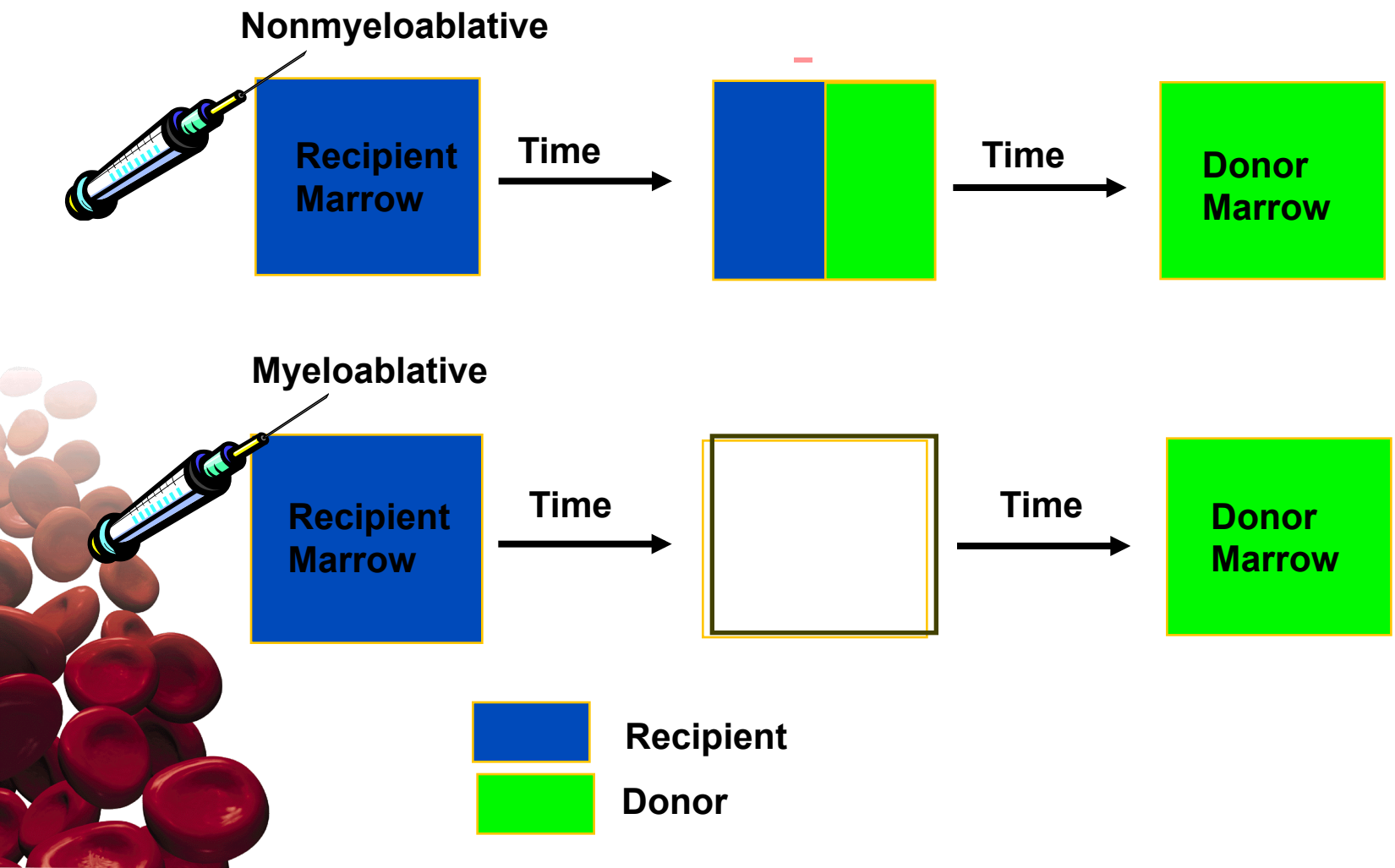
- **Chemotherapy and/or total body irradiation**
  - **Eradicate malignancy in patients with cancer**
  - **Suppress immune system to prevent rejection of donor cells**
- **Donor stem cells are not contaminated with tumor**
- **Graft vs leukemia effect can be helpful in malignant disease**
  - **Donor immune system can fight residual malignant cells it sees as non-self/abnormal**
  - **Reduced intensity conditioning regimens take advantage of this principle**
  - **No effect for non-malignant disease like aplastic anemia**



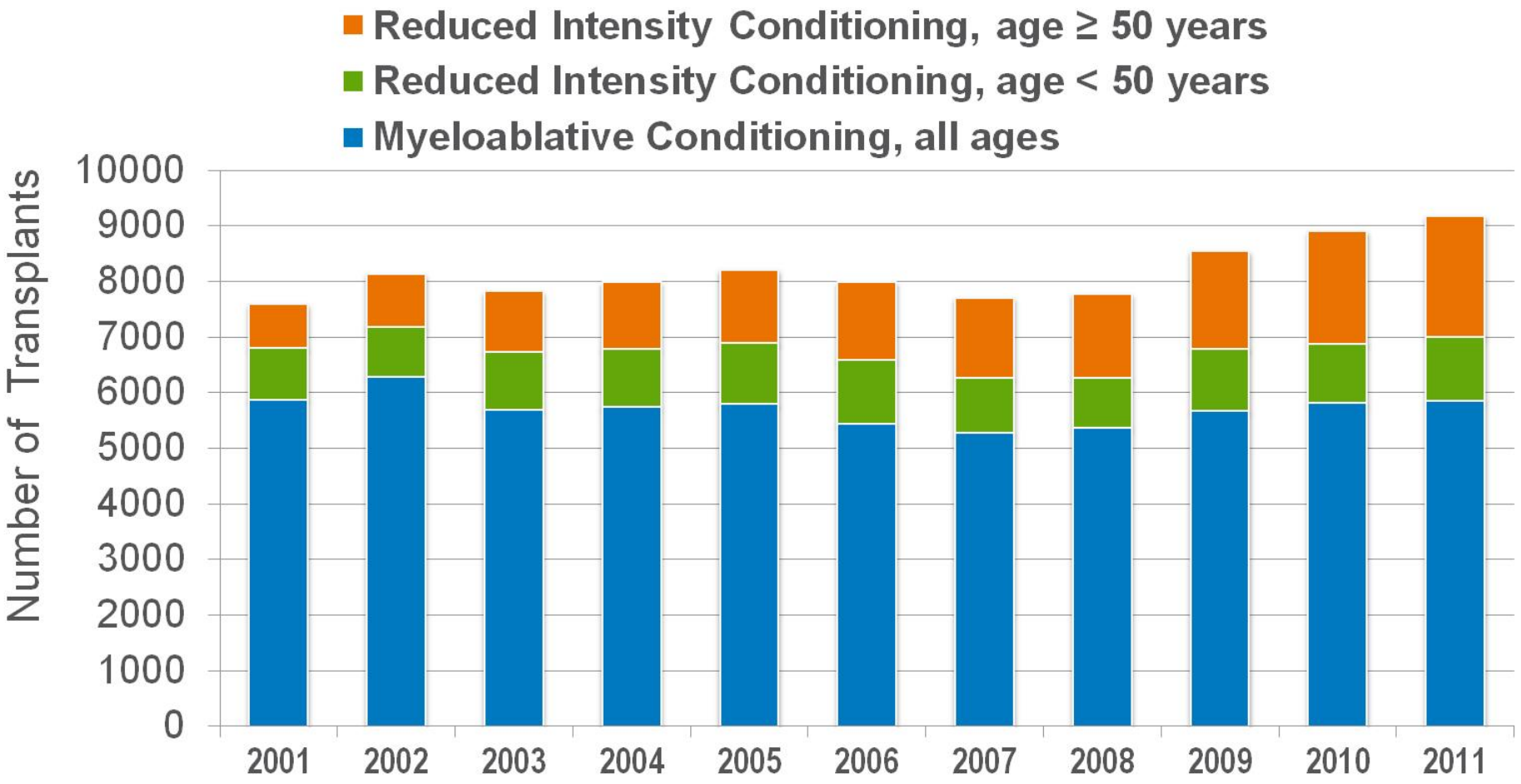
Reduced Intensity Conditioning (RIC) Transplantation

- Lower doses of chemotherapy ± radiation to immune suppress patient and allow engraftment of donor stem cells.
- Gradual increase in engraftment over months
- Relies on graft vs. disease effect rather than high dose chemotherapy as major mediator of effect.

Nonmyeloablative (RIC) Stem Cell Transplantation



Allogeneic Transplants Registered with the CIBMTR



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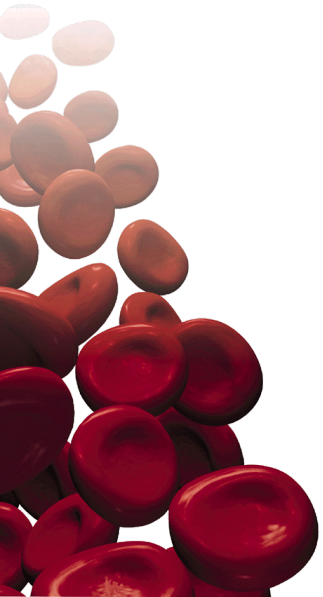
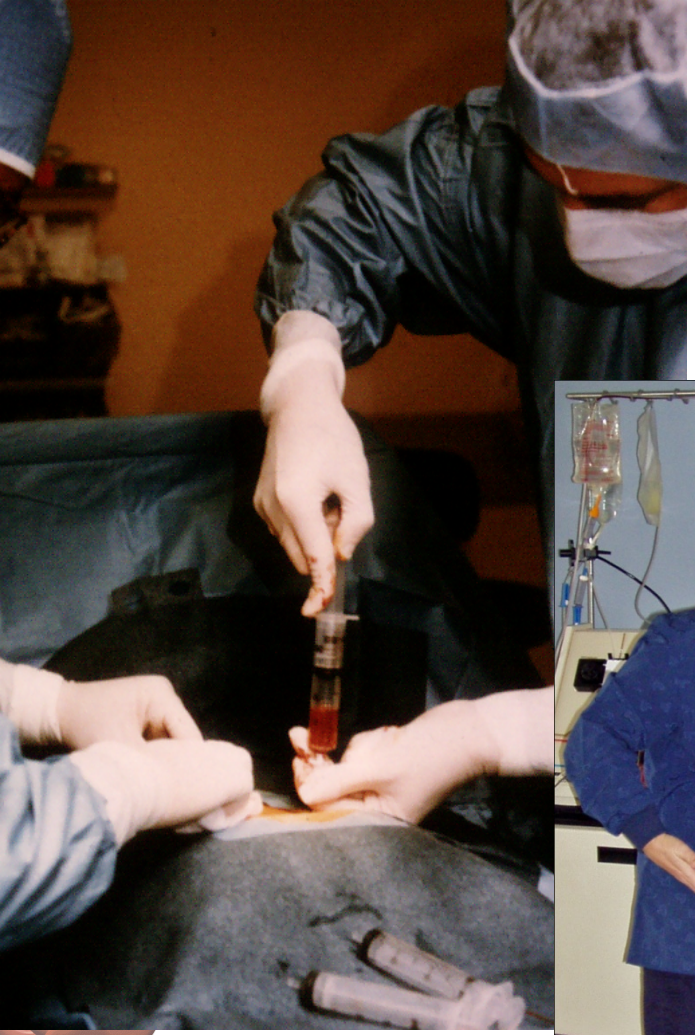
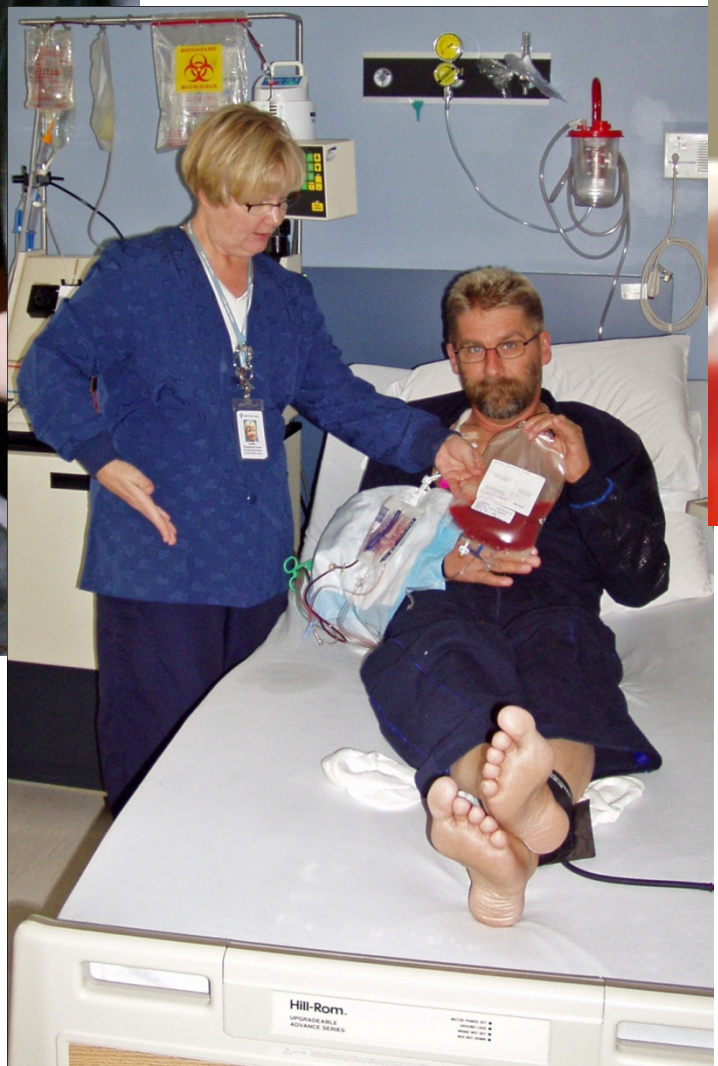
by Conditioning Regimen Intensity & Age

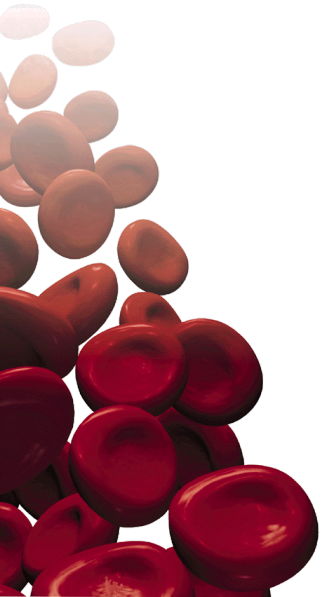
How are stem cells collected?







What advantages could there be to different stem cell sources for allotransplantation?

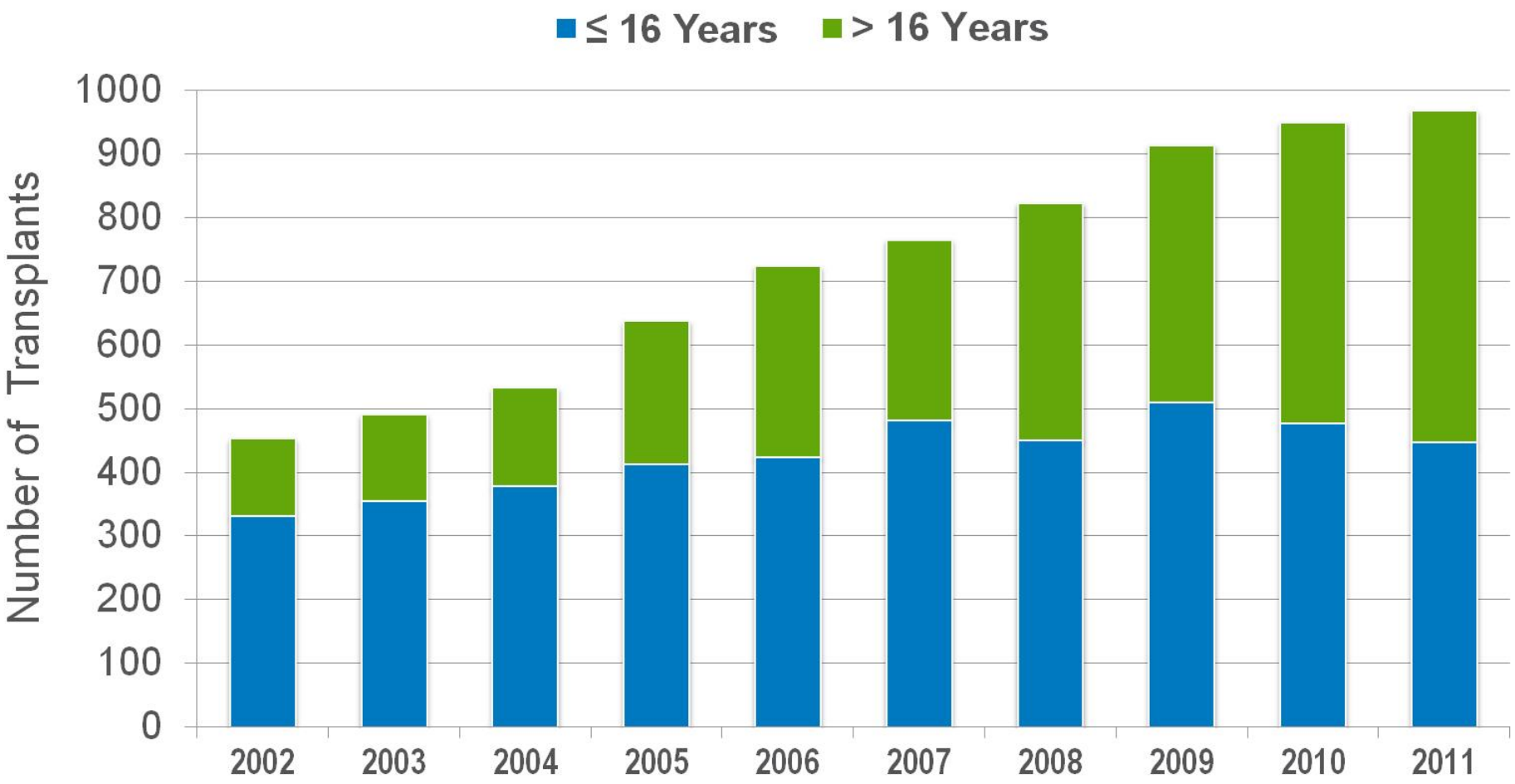


Collection of Stem Cell Sources

	Blood	Bone Marrow	Umbilical cord
Drugs	GCSF	General anesthetic	None
Invasive Procedure	IVs	Multiple bone punctures	none
More cells available	Yes	Yes	No
Outcomes	More graft vs host disease	Slightly higher relapse	Less GVHD, more infections

Umbilical cord stem cells samples are presumed free of viral infections ie cytomegalovirus

Unrelated Cord Blood Transplants by Age Registered with the CIBMTR



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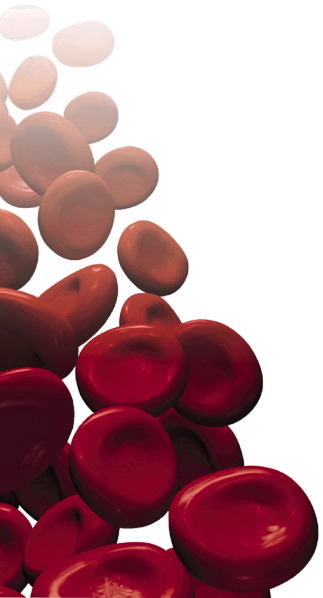
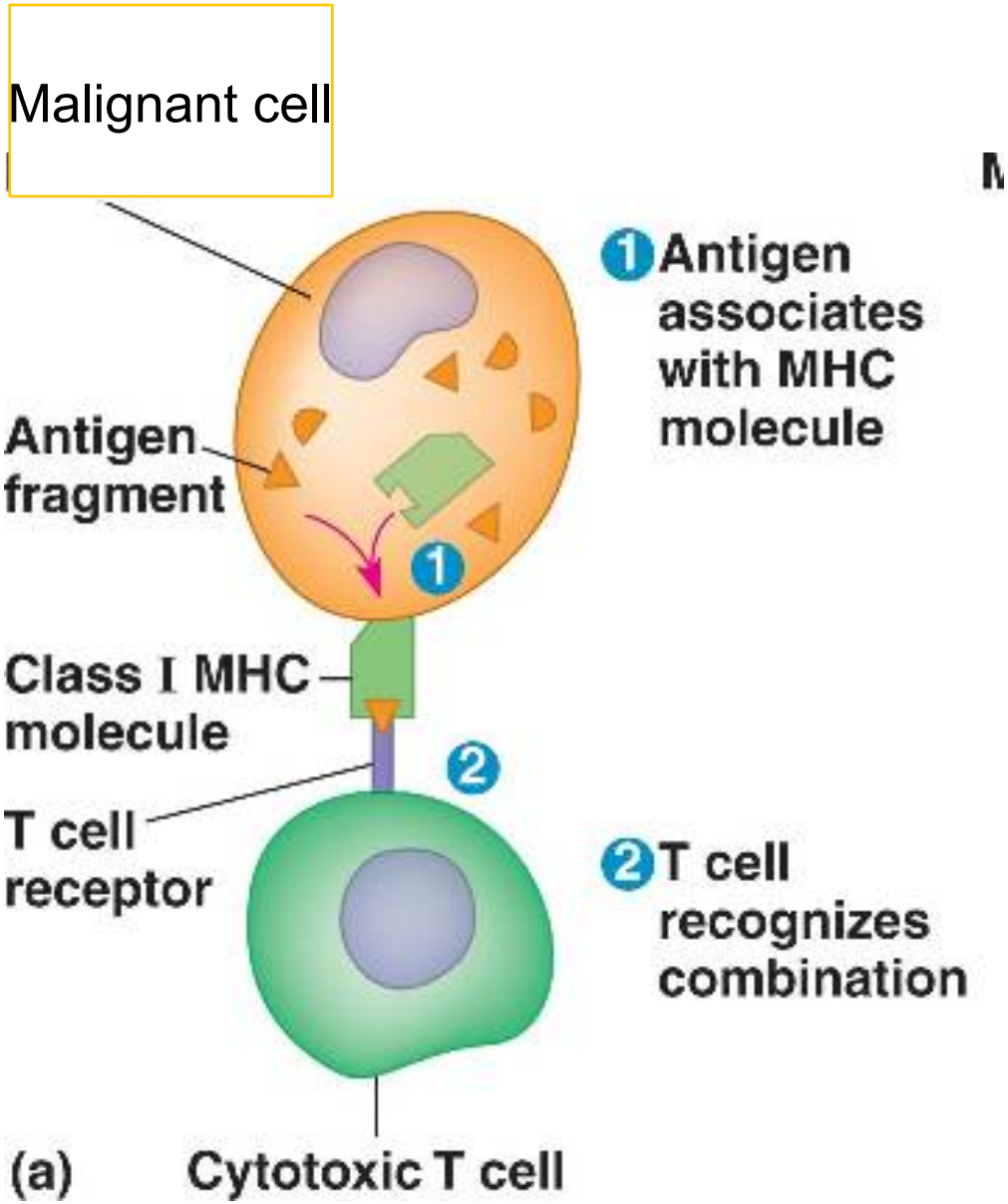
Until 1970s, no long term survivors of unrelated donor transplants – WHY?

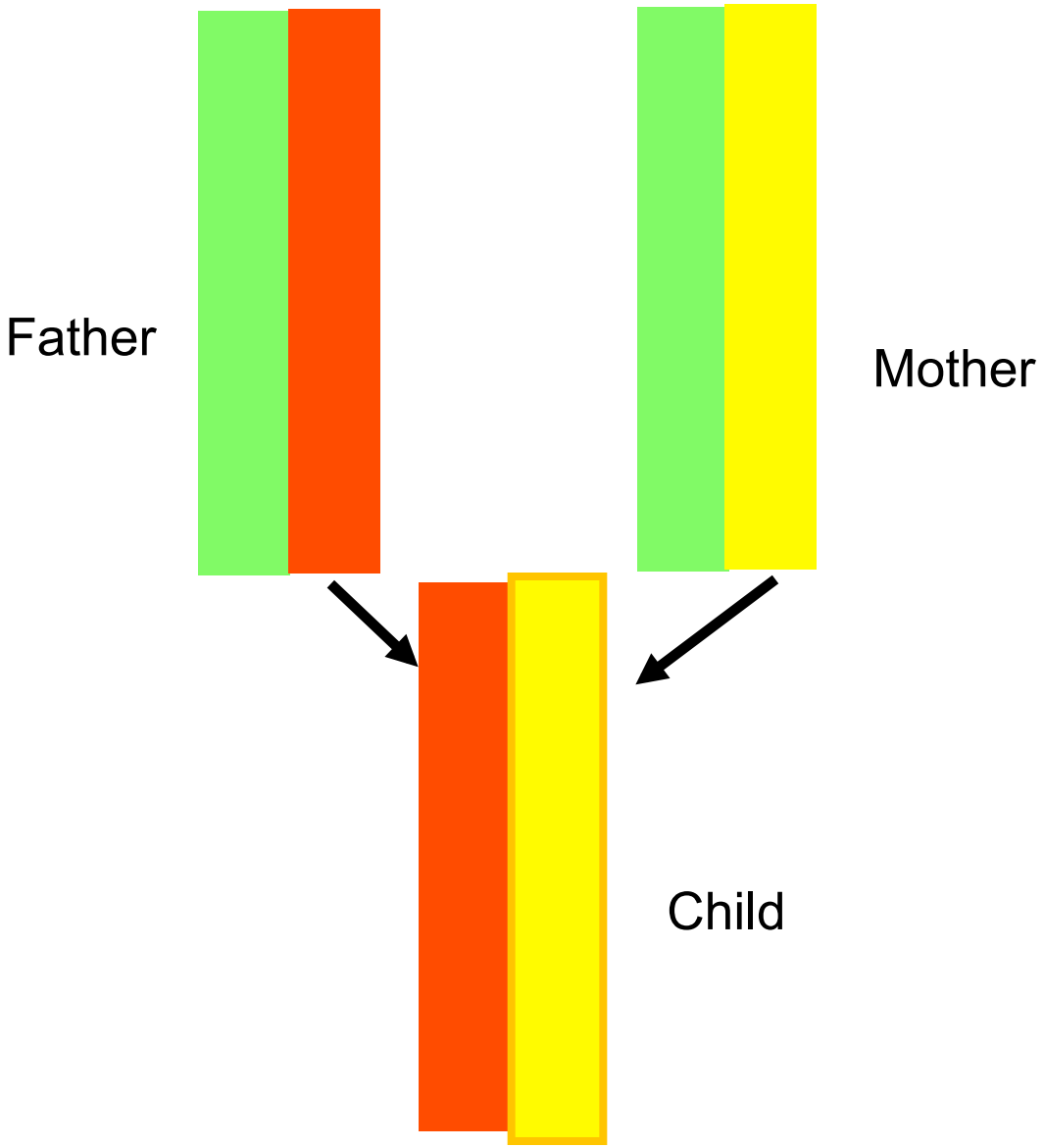


Human Leukocyte Antigen Typing

- **HLA genes on chromosome 6 are inherited as haplotypes**
- **Encode major histocompatibility complexes that present antigens to helper T cells and cytotoxic T cells**
  - **Label self and nonself**
  - **Protect against infection/malignancy**



Inheritance of HLA Genes



Donor Selection

- 30% of patients have a matched sibling donor
- 70% of patients have a fully matched donor on the unrelated donor registry
  - >10 million people on unrelated donor registry
  - Patients of minority/mixed ethnic groups less likely to have donor (linkage dysequilibrium)
  - Generally accept 1 antigen mismatch if no 10/10 full match but increased toxicity
- 95% of patients have a 4/6 matched cord, almost all patients have haploidentical donors

Haploidentical Transplants

- 3/6 match – anyone with a parent, child or sibling will have a haploidentical donor
- Risk of graft vs host disease higher – very intensive immunosuppression given with the transplant
- Clinical trial ongoing in Calgary and Winnipeg

•Survival by donor status in 1210 patients post haploidentical transplant

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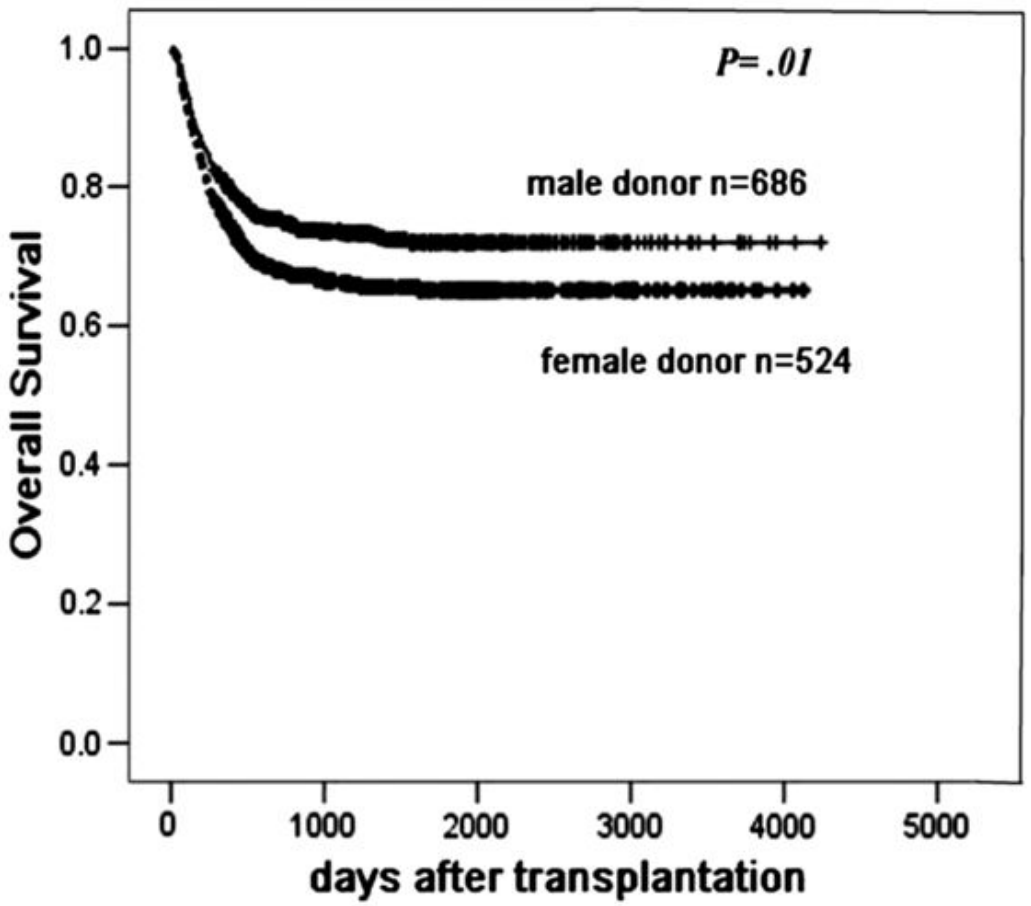
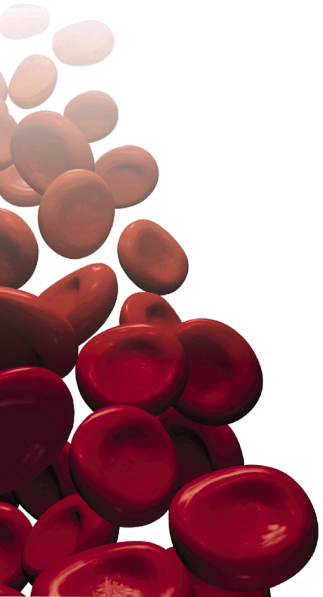
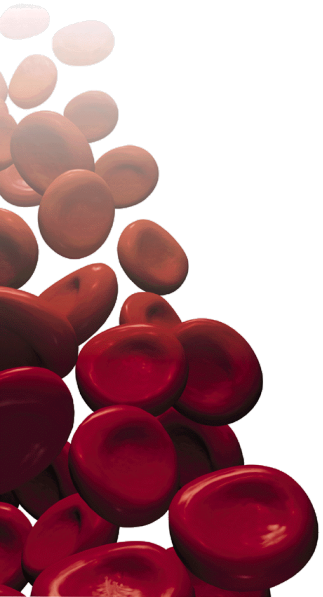


•Wang Y et al. Blood 2014;124:843-850

Complications of allogeneic HCT



Graft vs Host Disease

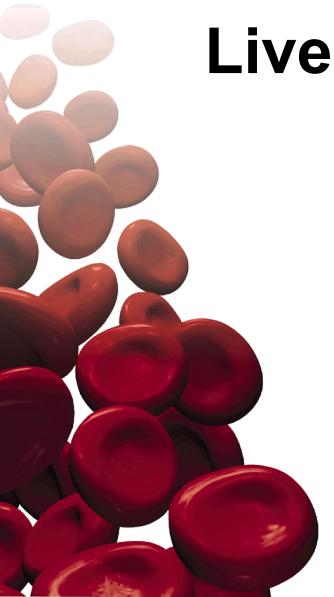


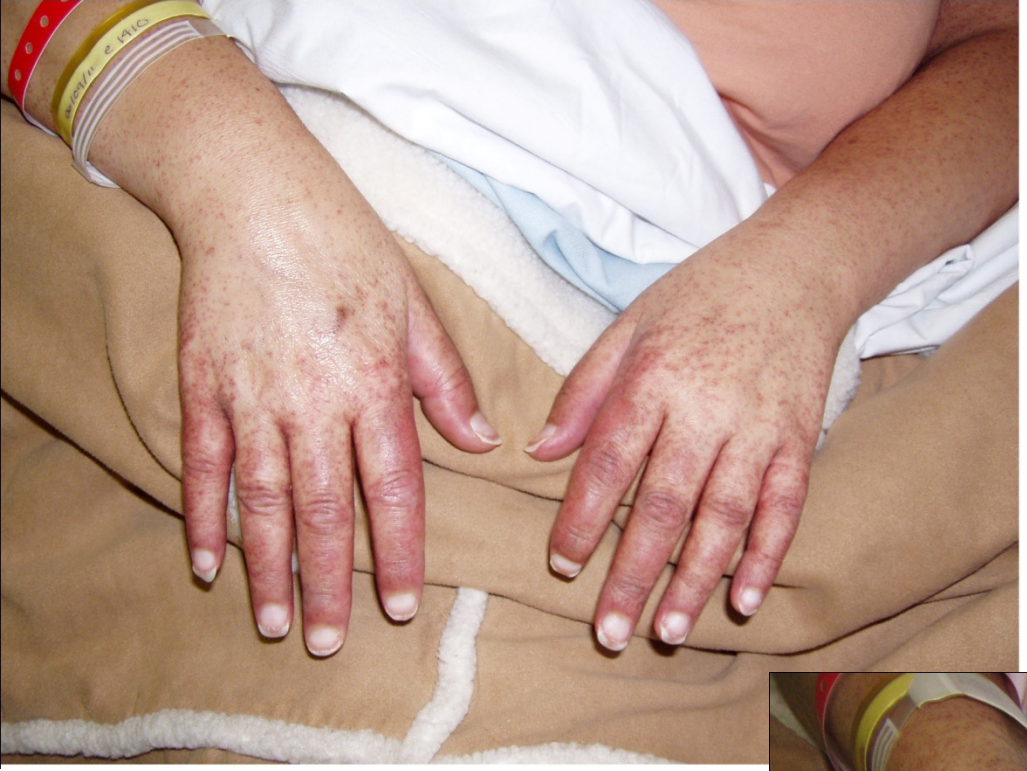
Acute graft vs host disease

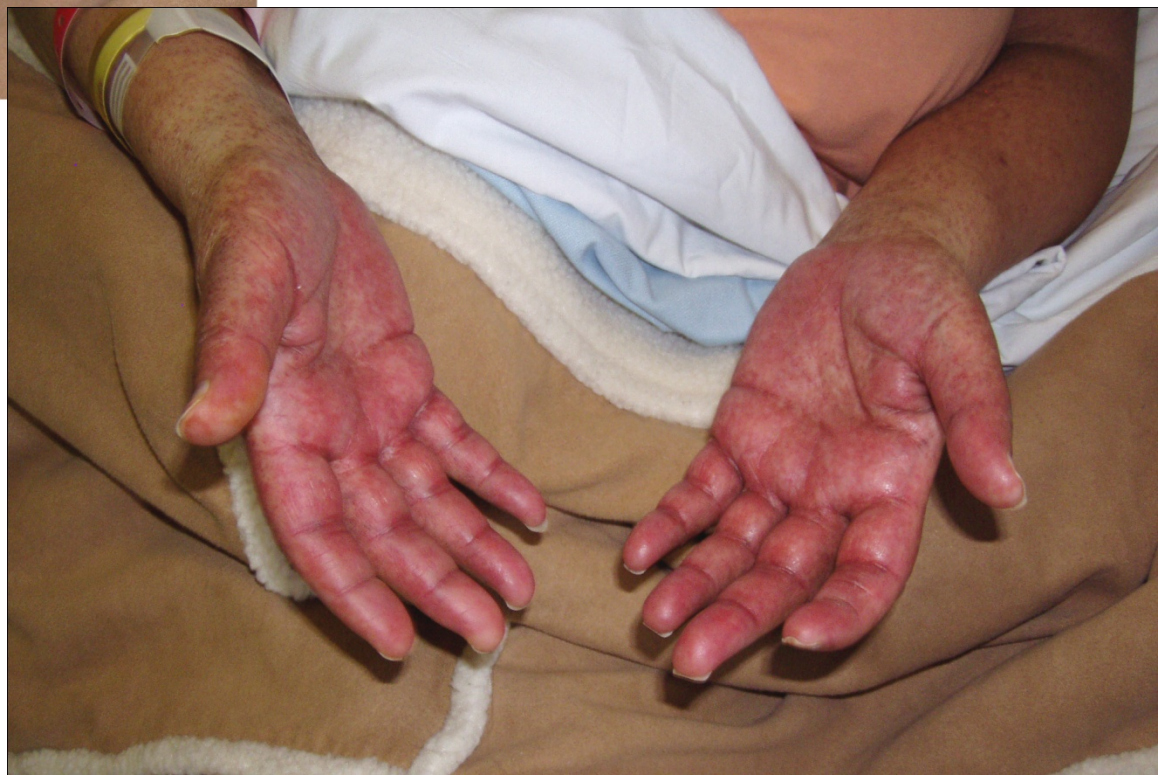
- Occurs in 1st 100 days after allogeneic transplantation
- Donor immune system activated by antigens on host cells (HLA or minor antigens)
  - "rejects" tissues in recipient
- Major cause of morbidity and mortality for allogeneic transplants

Acute graft-versus-host disease (GVHD)

ORGAN AFFECTED	MANIFESTATION
Skin	Rash
Gut	Diarrhea
Liver	Jaundice
	Abnormal liver function tests

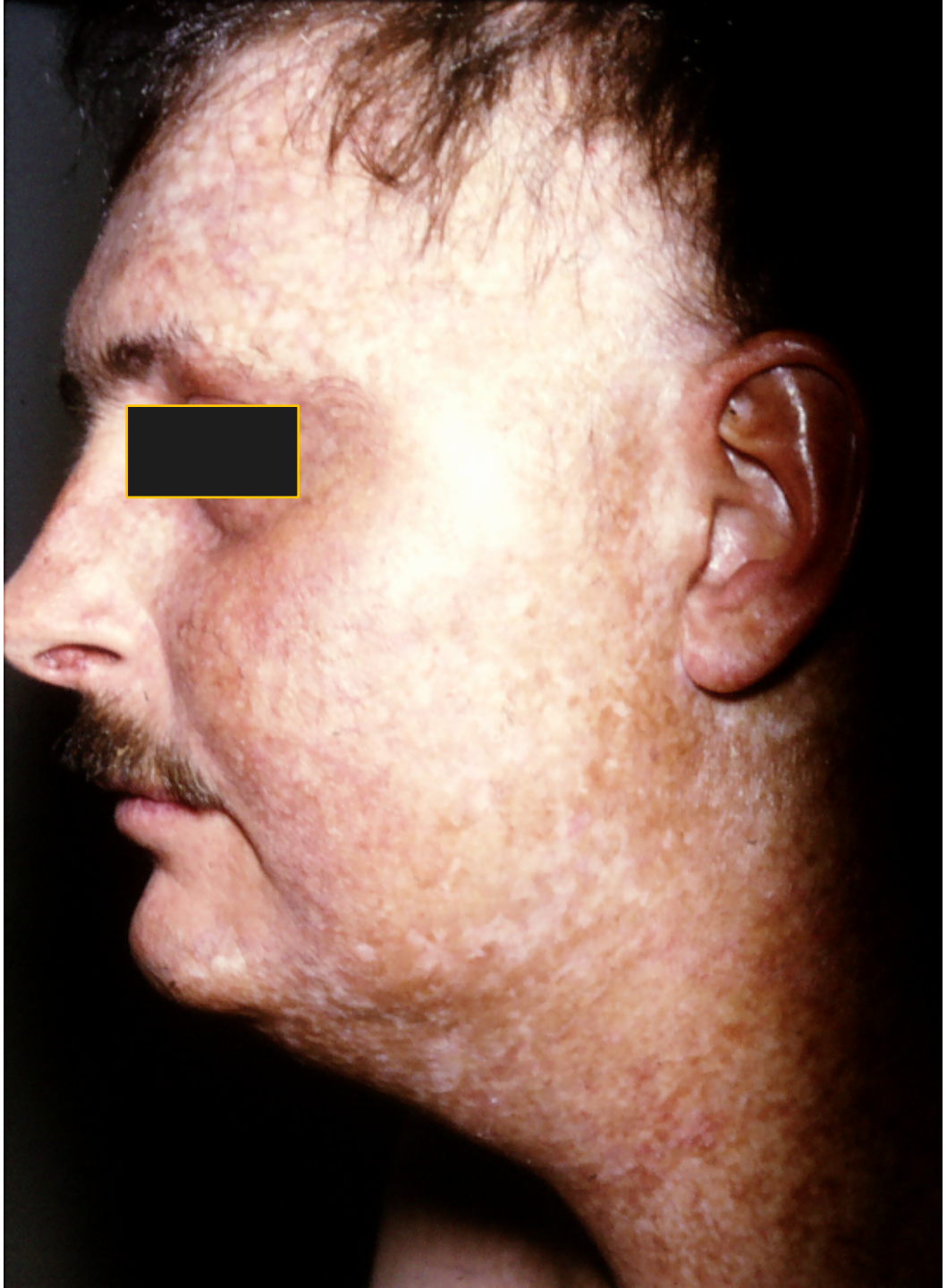






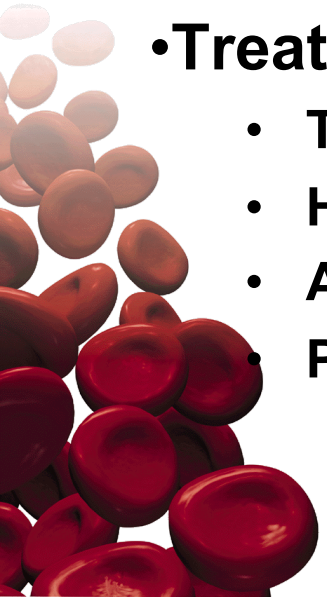
Chronic graft vs host disease (>100 days post BMT)

- Lungs – shortness of breath, cough, chest infiltrates, infections
- Skin – pigmentation changes, thickening of skin and soft tissue with contractures
- Eyes – dryness, pain, tearing, corneal abrasions
- Mouth – dryness, pain



Prevention and treatment of graft vs host disease

- **Prevention:**
  - **HLA match**
  - **Immune suppressant drugs eg. methotrexate, cyclosporine are routinely given**
  - **T cell depletion of graft by antibodies against T cells ie ATG**
- **Treatment:**
  - **Topical steroids, UV light therapy to skin**
  - **High dose steroids**
  - **Additional immunosuppressant drugs**
  - **Photopheresis**



Infections post HCT

Bacterial – irritated mucous membranes, IV catheters

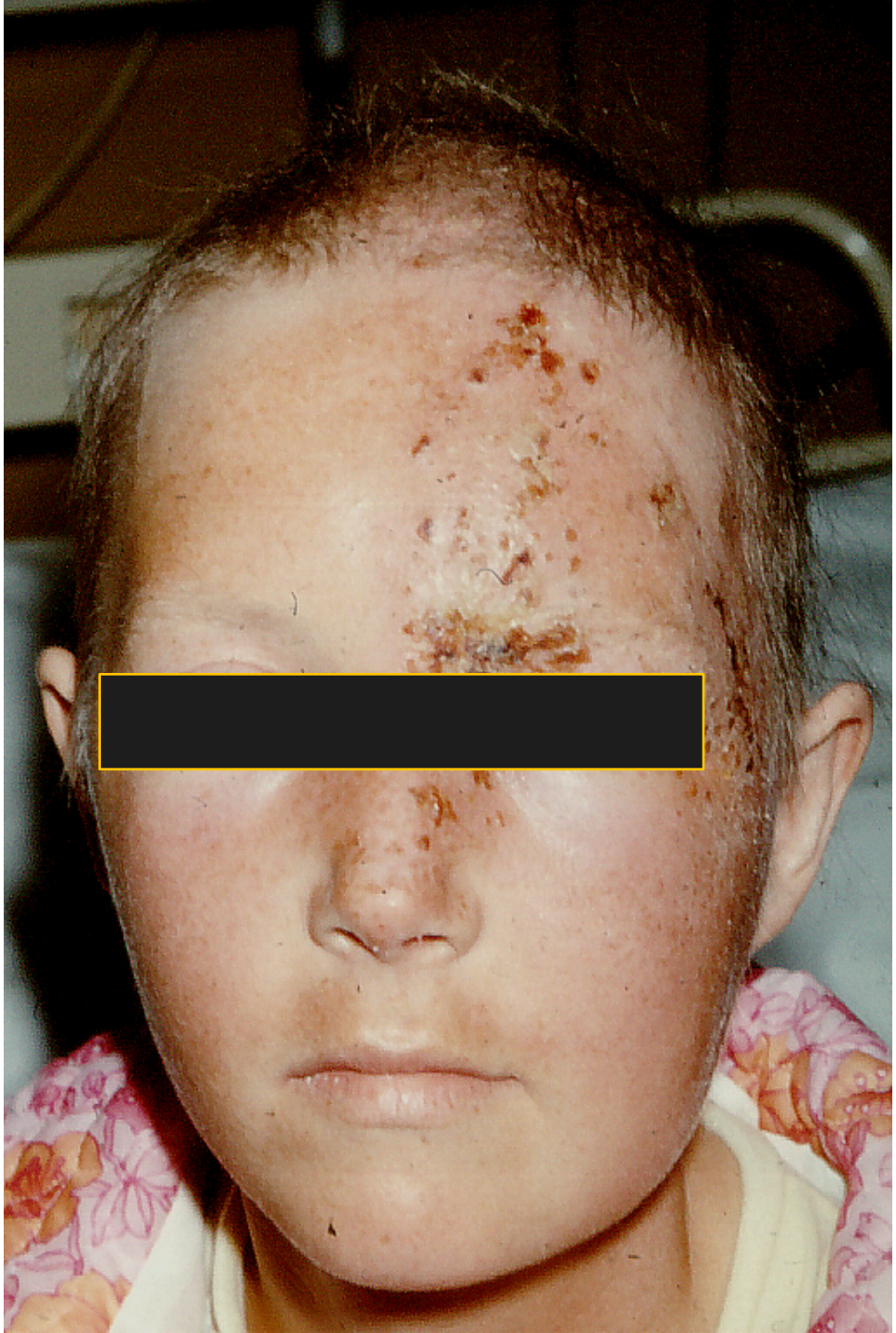
- **Low white blood cells 1st 3-4 weeks**
- **Antibody production is decreased, require revaccination**

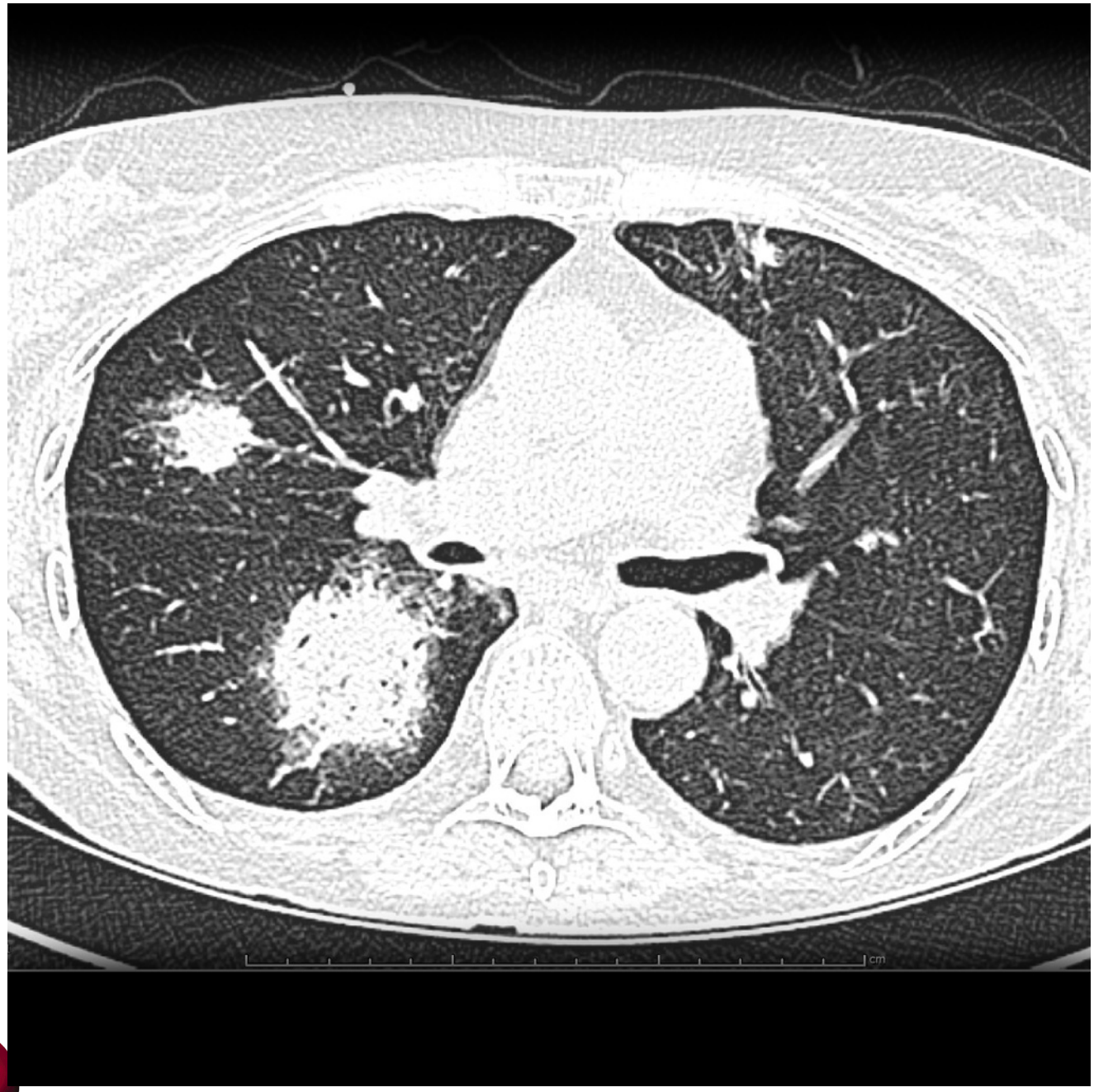
Viral –cold sores, CMV, shingles

- **T cell mediated immunity profoundly depressed even up to 1 year post allotransplant or longer**

Fungal and Parasitic

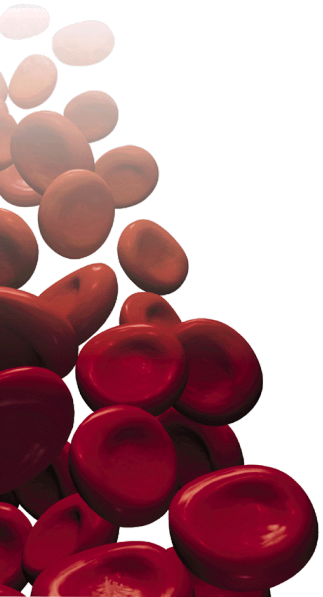
- **Prolonged immunosuppression allows opportunistic organisms**



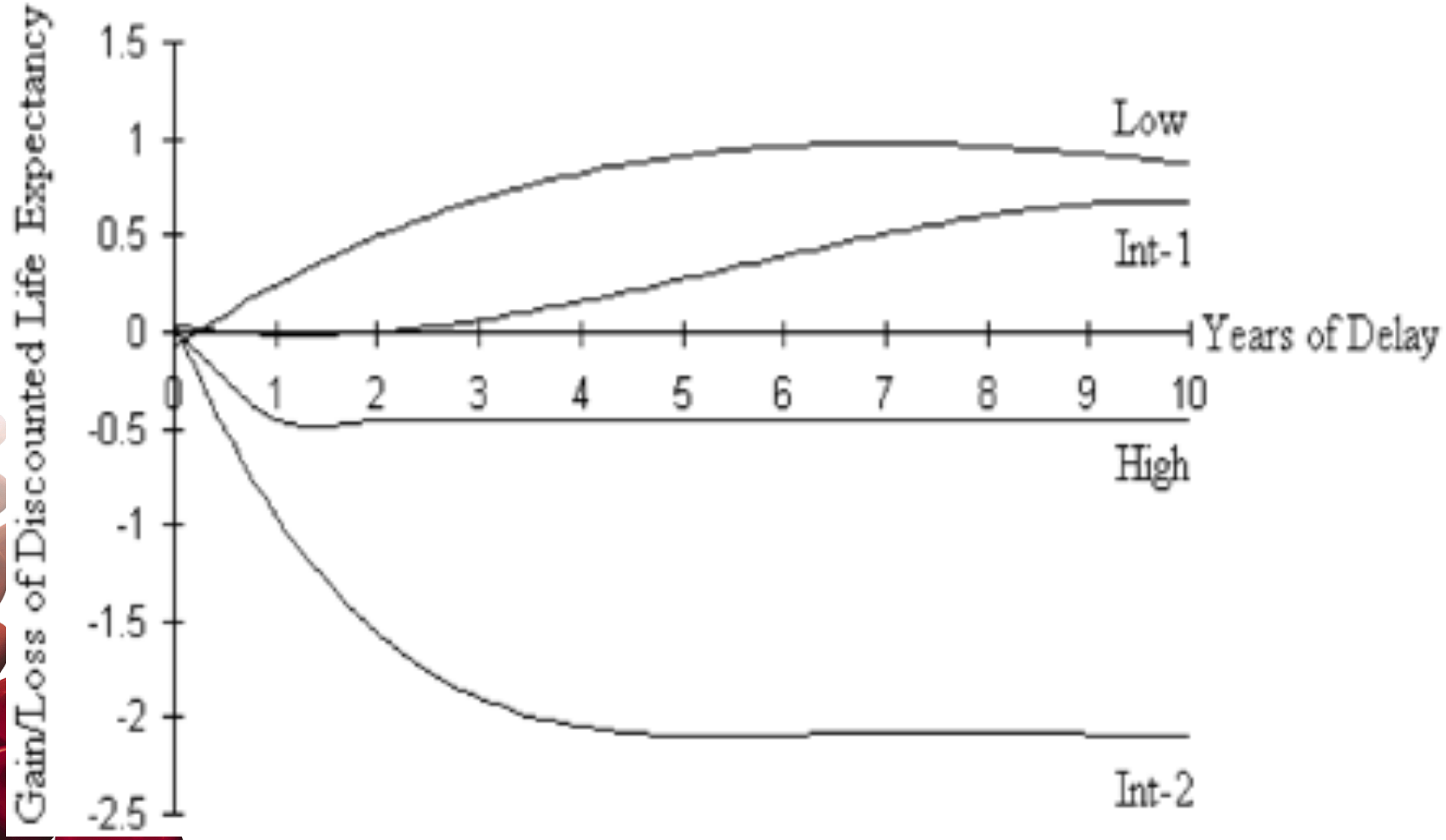


Survivorship Clinics and Survivorship Issues

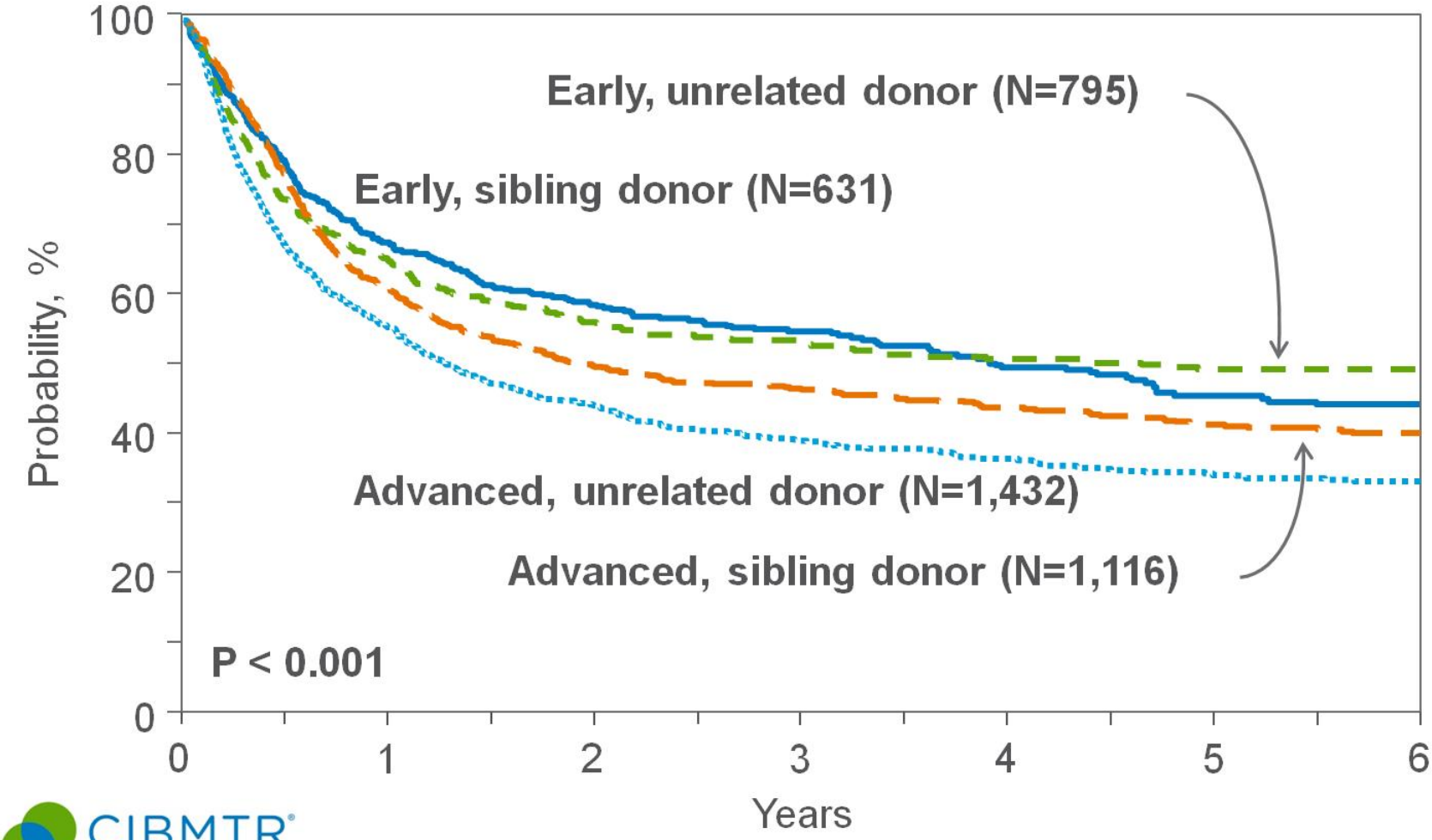
- **Treatment-related toxicities:**
  - **Cataracts**
  - **Second malignancy**
  - **Endocrine (thyroid, ovarian)**
  - **etc**
- **Chronic GVHD**
- **Treatment of GVHD**



Int-2 and High Risk IPSS benefit with HCT early



Survival after Allogeneic Transplants for MDS, 2001-2011



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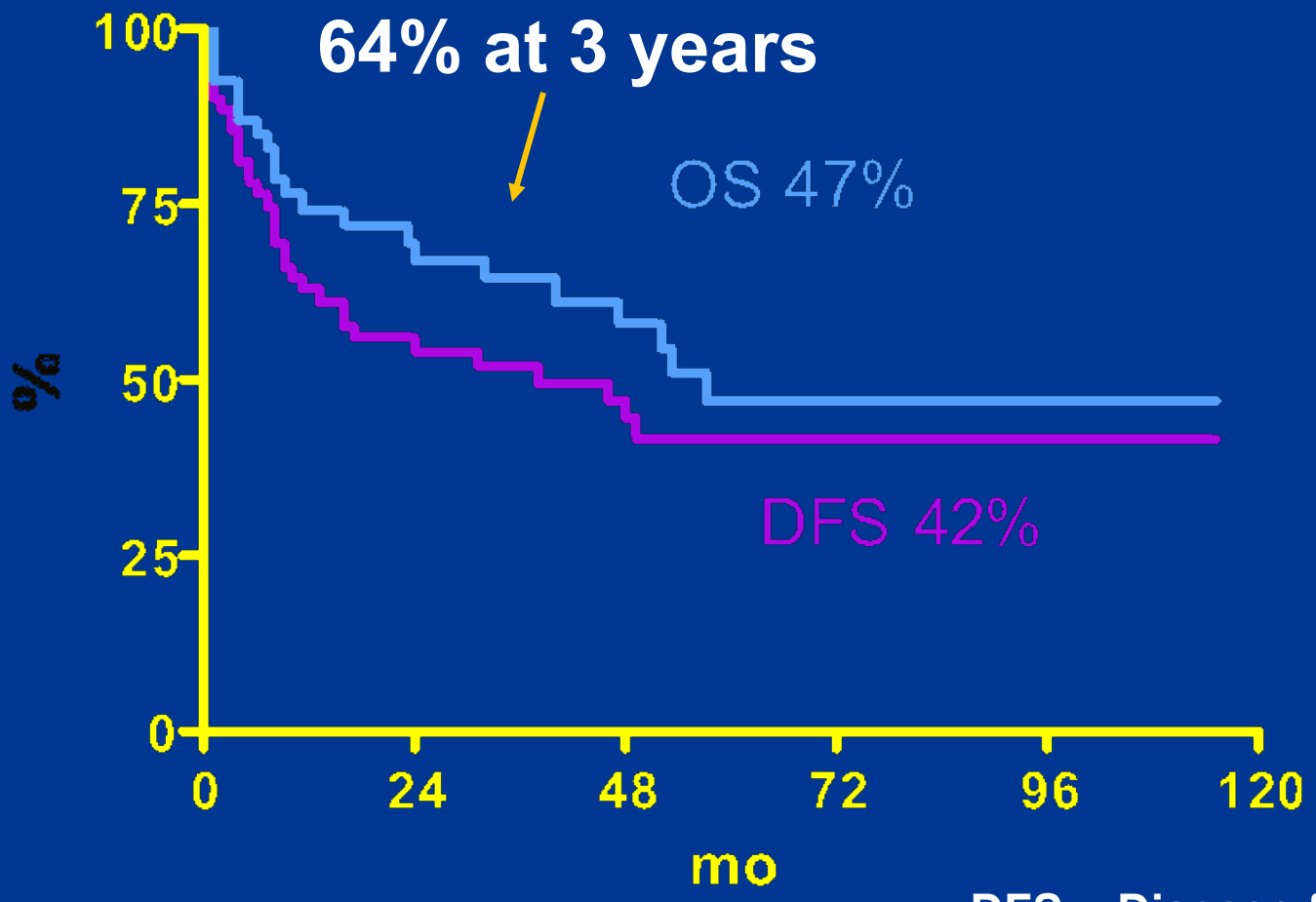
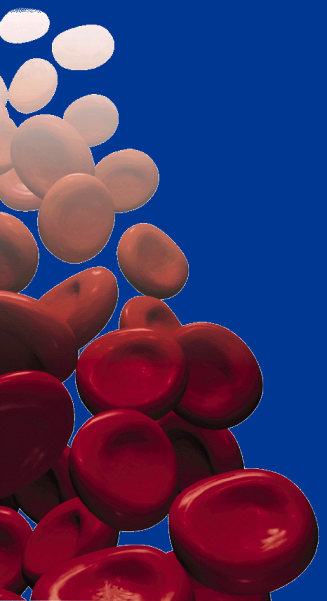
By Disease Status and Donor Type

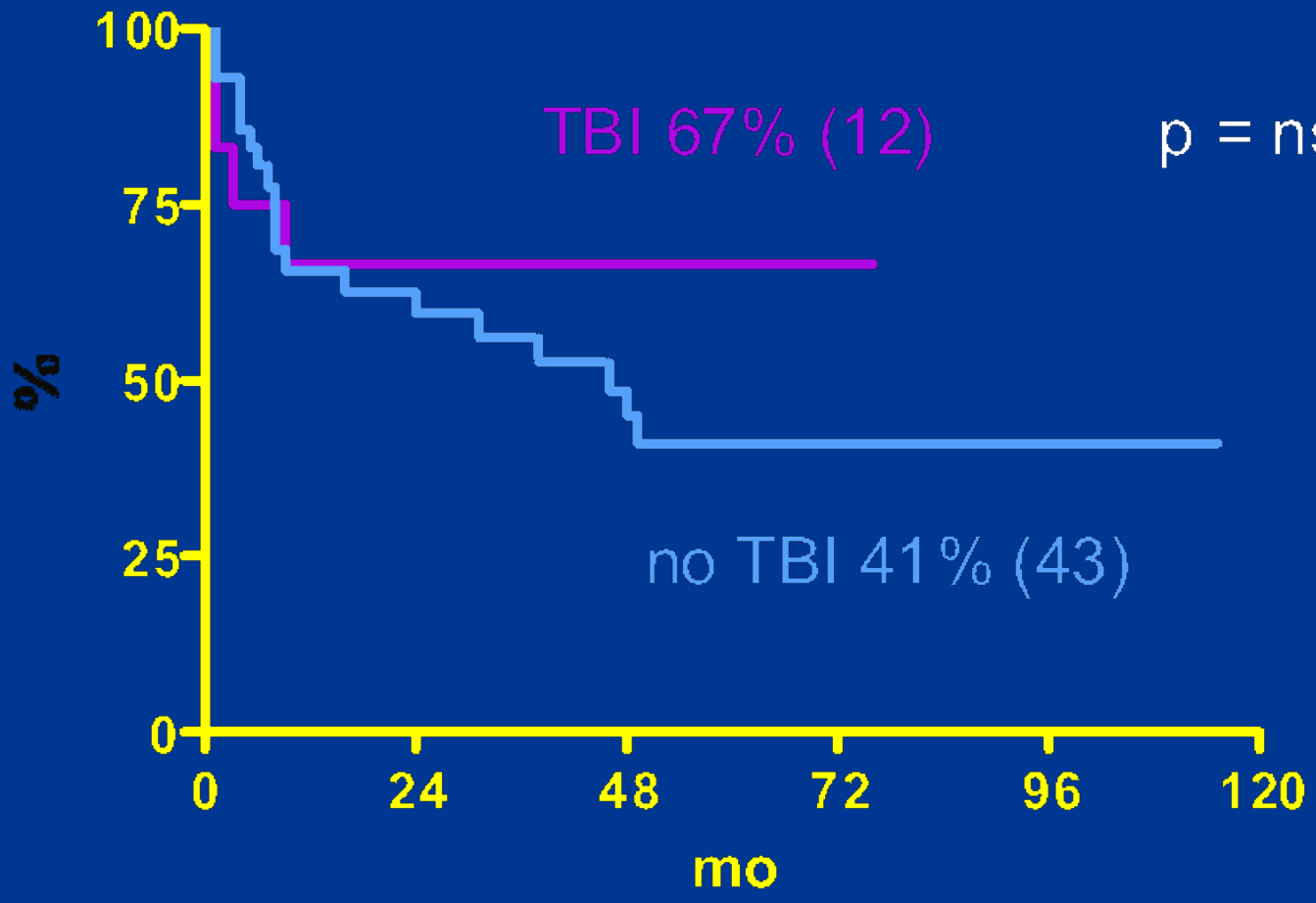
Adult HCT for MDS 1999-2010



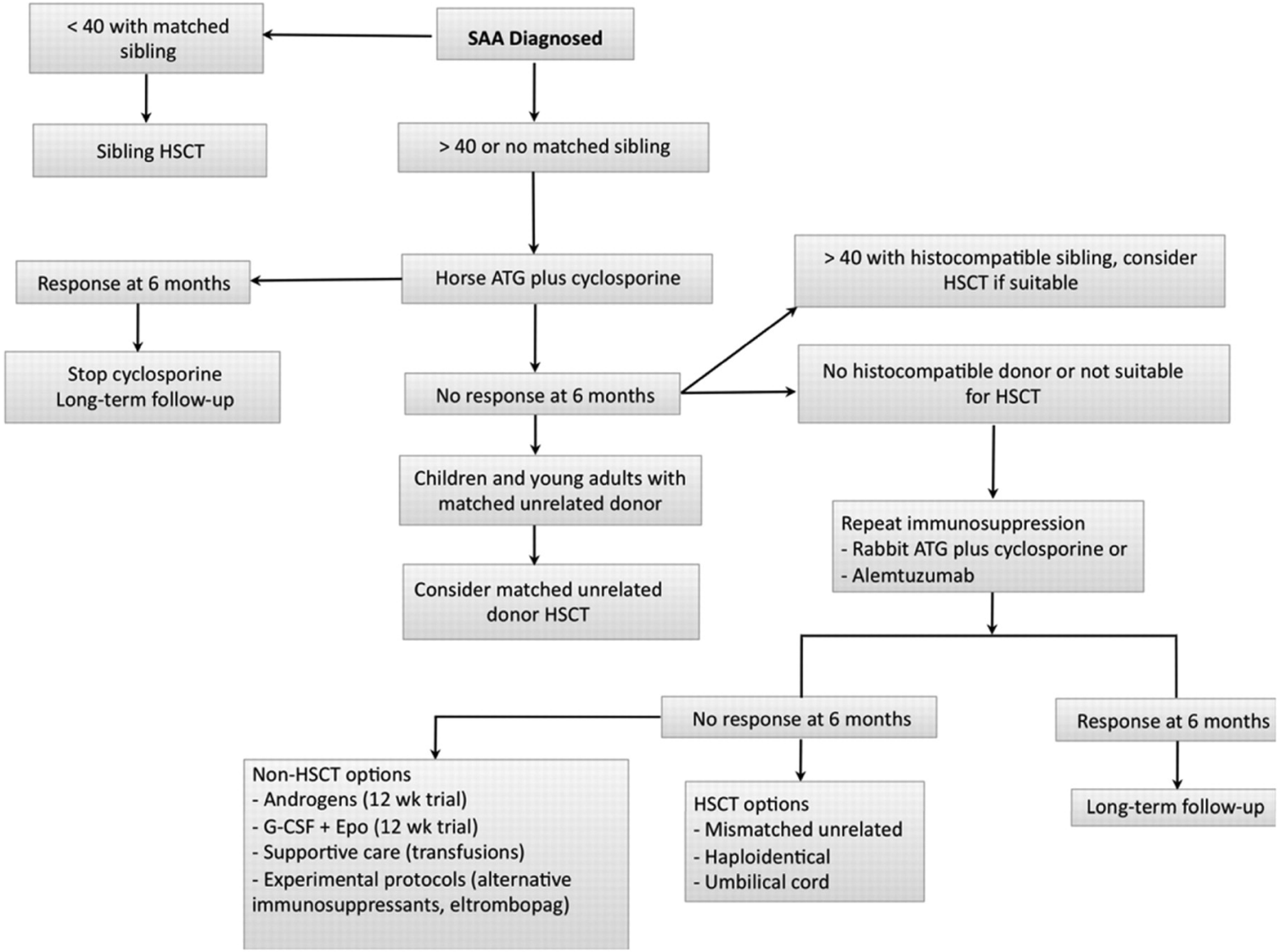
DFS = Disease free survival
OS = Overall survival

Disease Free Survival Adult HCT for MDS 1999-2010



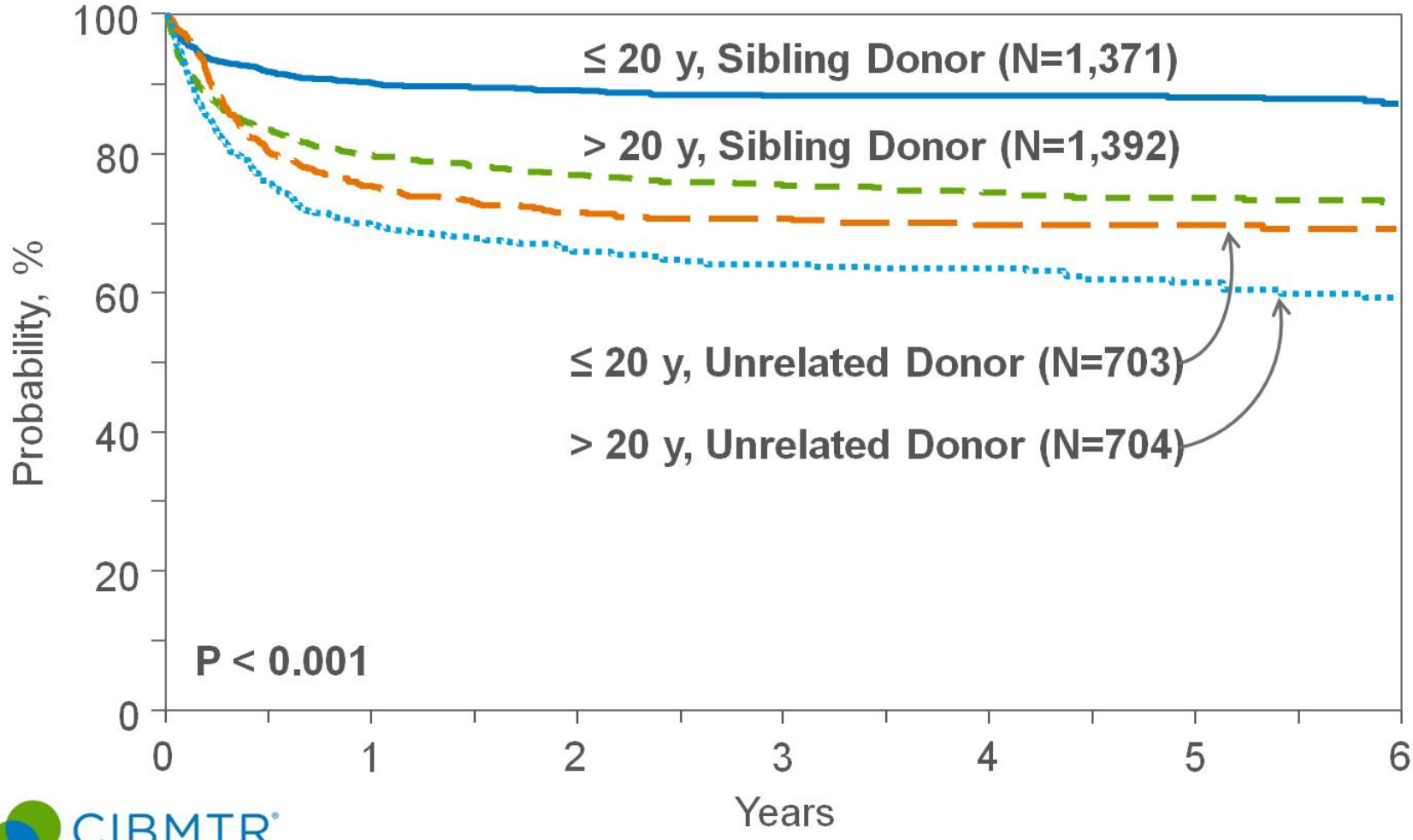


Algorithm for Aplastic Anemia



•Scheinberg P , and Young N S Blood 2012;120:1185

Survival after Allogeneic Transplants for SAA, 2001-2011



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By Donor Type and Age

Questions?