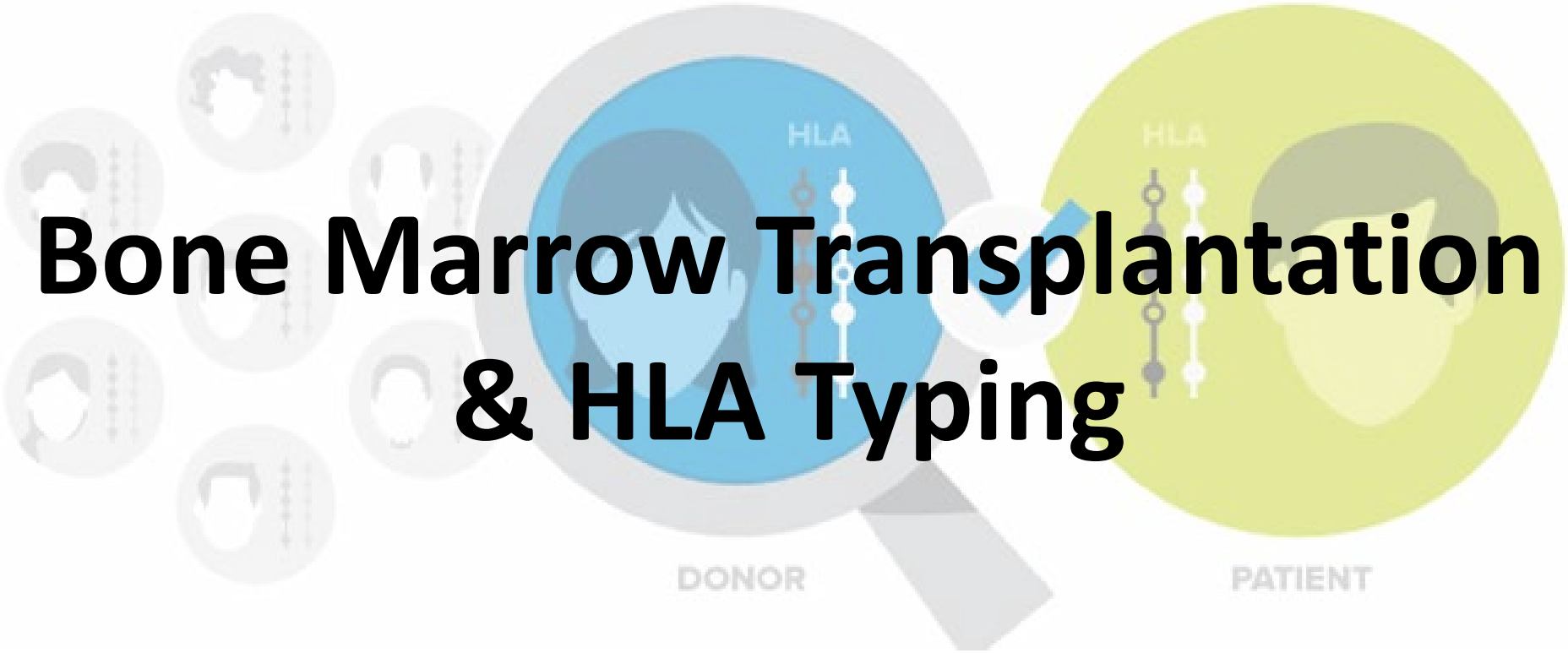

Bone Marrow Transplantation & HLA Typing

With backs to wall, Red Sox send Boddicker to face A's today - Playoff section, Pages 65-71

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The Boston Globe

SOUP TO NUTS
Tuesday: *AM fog/PM drizzle? 65*
Wednesday: *AM showers, 70-75*
High tide: *3:18 a.m., 3:31 p.m.*
Full report: *Page 64*

TUESDAY, OCTOBER 9, 1990

Boston doctor shares Nobel for medicine

Transplant work cited

By David L. Chandler
GLOBE STAFF

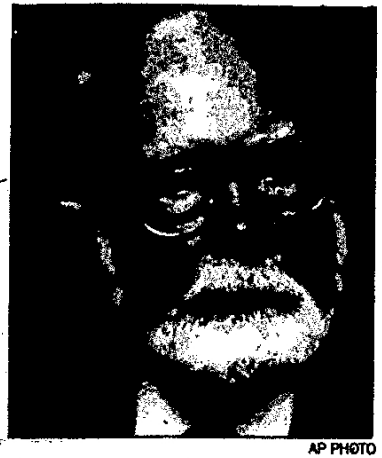
A doctor at Brigham and Women's Hospital was one of two American physicians awarded the Nobel Prize in Medicine yesterday for pioneering work that paved the way for now-commonplace organ and tissue transplants that have saved thousands of lives.

Joseph E. Murray, 71, of Wellesley, professor emeritus of plastic surgery at Brigham and Women's Hospital, and E. Donnall Thomas, 70, of Bellevue, Wash., received the honor for their work during the 1950s and 1960s on how to reduce the risk of organ rejection by the body's immune system. The two will share a prize worth about $700,000.

Murray performed the world's first successful organ transplant – a kidney from one identical twin to another – at the Peter Bent Brigham Hospital on Dec. 23, 1954.

NOBEL, Page 8

REUTERS PHOTO
Dr. Joseph E. Murray with his wife, Bobby, yesterday.



AP PHOTO
Dr. E. Donnall Thomas at a news conference in Seattle yesterday.

From unthinkable to commonplace

By Judy Foreman
GLOBE STAFF

It was two days before Christmas 1954.

Richard Herrick, 23, lay at Boston's Peter Bent Brigham Hospital – now called Brigham and Women's – facing death from kidney failure. His twin brother, Ronald, had just agreed to the unthinkable: removal of one of his kidneys to donate to Richard.

Kidney dialysis, so commonplace today, was still so new and clumsy that it was not considered a long-term option. The process had been invented in the Netherlands just after World War II.

Immunosuppressive drugs, the backbone of most of the more than 13,000 organ transplants done today in the United States, were barely a gleam in researchers' eyes.

And the idea that by 1990 Americans in every state would by law be able, more or less casually, to carry organ donor cards or donor stickers on drivers' licenses was too wild even for Dr. Joseph E. Murray, then 35 years old, to imagine.

TRANSPLANTS, Page 8

First reported therapeutic use of human bone marrow cells

INTRAVENOUS INFUSION OF BONE MARROW IN PATIENTS RECEIVING RADIATION AND CHEMOTHERAPY*

E. Donnall Thomas, M.D.,† Harry L. Lochte, Jr., M.D.,‡ Wan Ching Lu, Ph.D.,§ and Joseph W. Ferrebee, M.D.¶

COOPERSTOWN, NEW YORK, AND BOSTON, MASSACHUSETTS

After a lethal dose of radiation in rodents,[1] canines[2] or primates,[3] the destroyed bone marrow may be repopulated by intravenous infusion of cellular suspensions of marrow taken from healthy isologous, homologous[4] and, in some cases, heterologous[5] donors. Effective cells for these infusions may be stored by the Polge technic of freezing to −80°C. in glycerol.[6] Hosts seeded with donor marrow have some of the immunologic characteristics of the donors, and in some circumstances will take and hold homografts of other organs from them.[7]

Since cases of radiation disaster may occur, and since bone-marrow deficiency from radiation or chemotherapy does occur in the normal course of clinical medicine, an effort has been made to determine the availability and usefulness of bone-marrow infusions for the treatment of these conditions in man.

Experimental Considerations

Bone marrow was collected from fetal and adult cadavers, from ribs removed at surgery and from aspiration biopsy of the ilium. Irrespective of source, it was passed repeatedly through a stainless-steel screen[8] and broken into a smooth cellular suspension, and the fat, as a rule, removed by centrifugation. The cells, resuspended in tissue-culture fluid and serum, were administered intravenously or frozen in glycerol and stored at −80°C.

One may assess permissible periods of post-mortem

*From the Mary Imogene Bassett Hospital (affiliated with Columbia University), Cooperstown, and the Children's Cancer Research Foundation, Children's Medical Center, Boston, and Harvard Medical School.
Supported by research grants (C-2643 and H-607) from the United States Public Health Service and by contract AT (30-1)-2005 from the United States Atomic Energy Commission.

†Associate clinical professor of medicine, Columbia University College of Physicians and Surgeons; physician-in-chief, Mary Imogene Bassett Hospital.

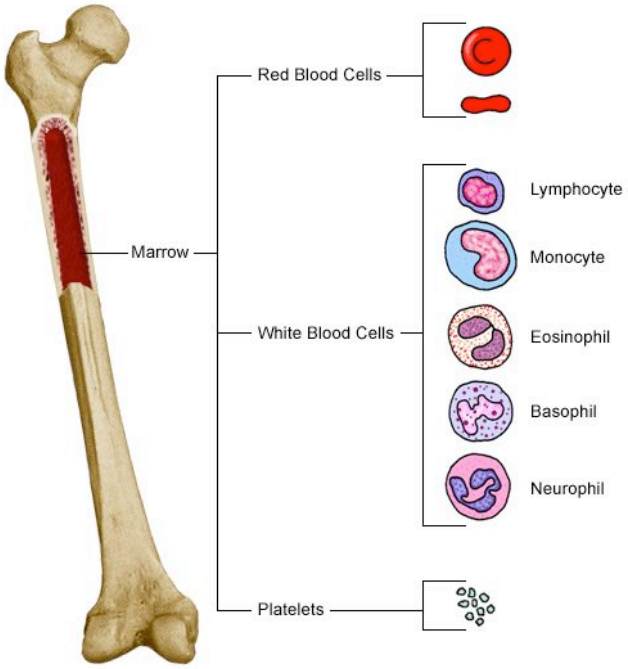
‡Public Health Service Research Fellow, National Heart Institute, National Institutes of Health, Bethesda, Maryland.

§Research assistant, Department of Pathology, Harvard Medical School; research assistant, Division of Laboratories and Research, Children's Medical Center.

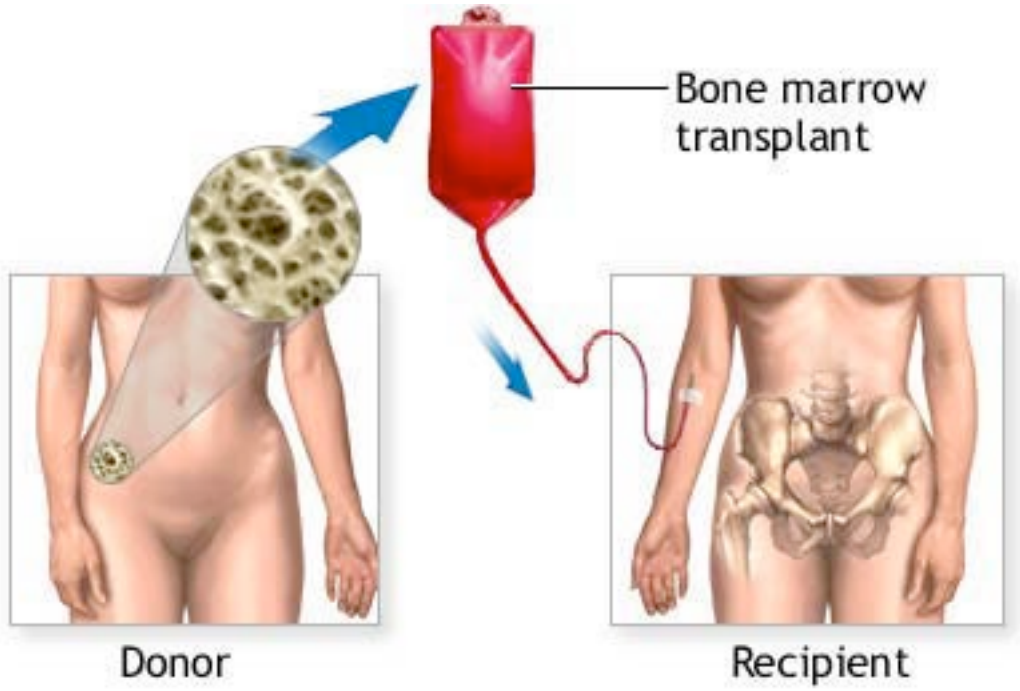
¶Associate clinical professor of medicine, Columbia University College of Physicians and Surgeons; research physician, Mary Imogene Bassett Hospital.

New England Journal of Medicine 257:491-496 (1957)

Hematopoietic cell transplantation for bone marrow failure – a simple concept

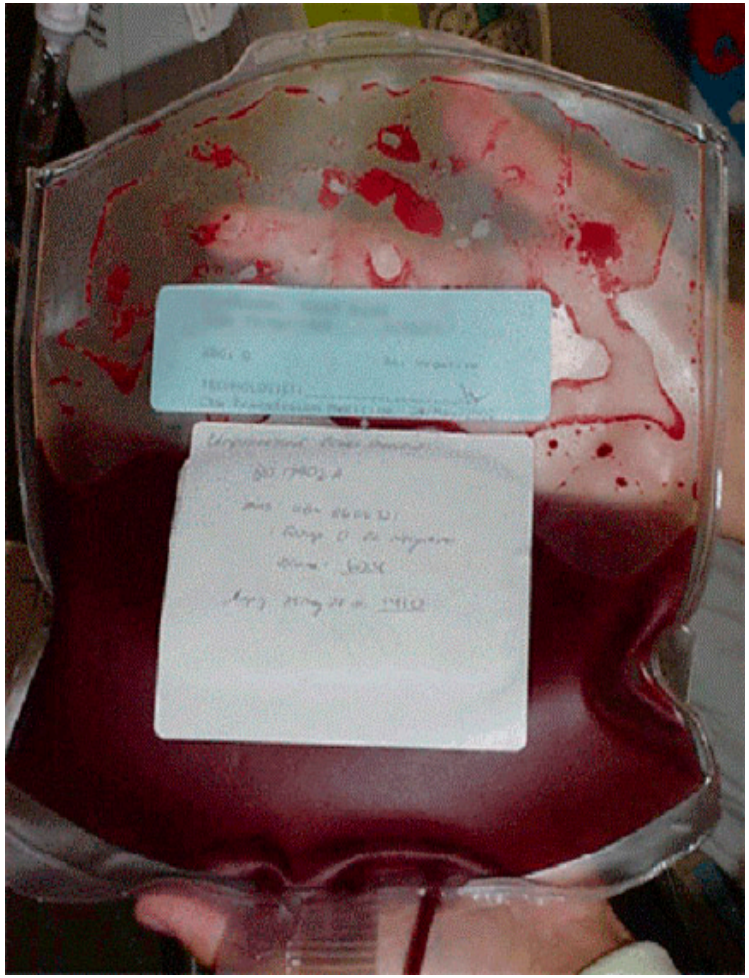


Bone marrow – the blood cell “factory” in postnatal life



Bone marrow is readily transplantable

Bone Marrow Harvest



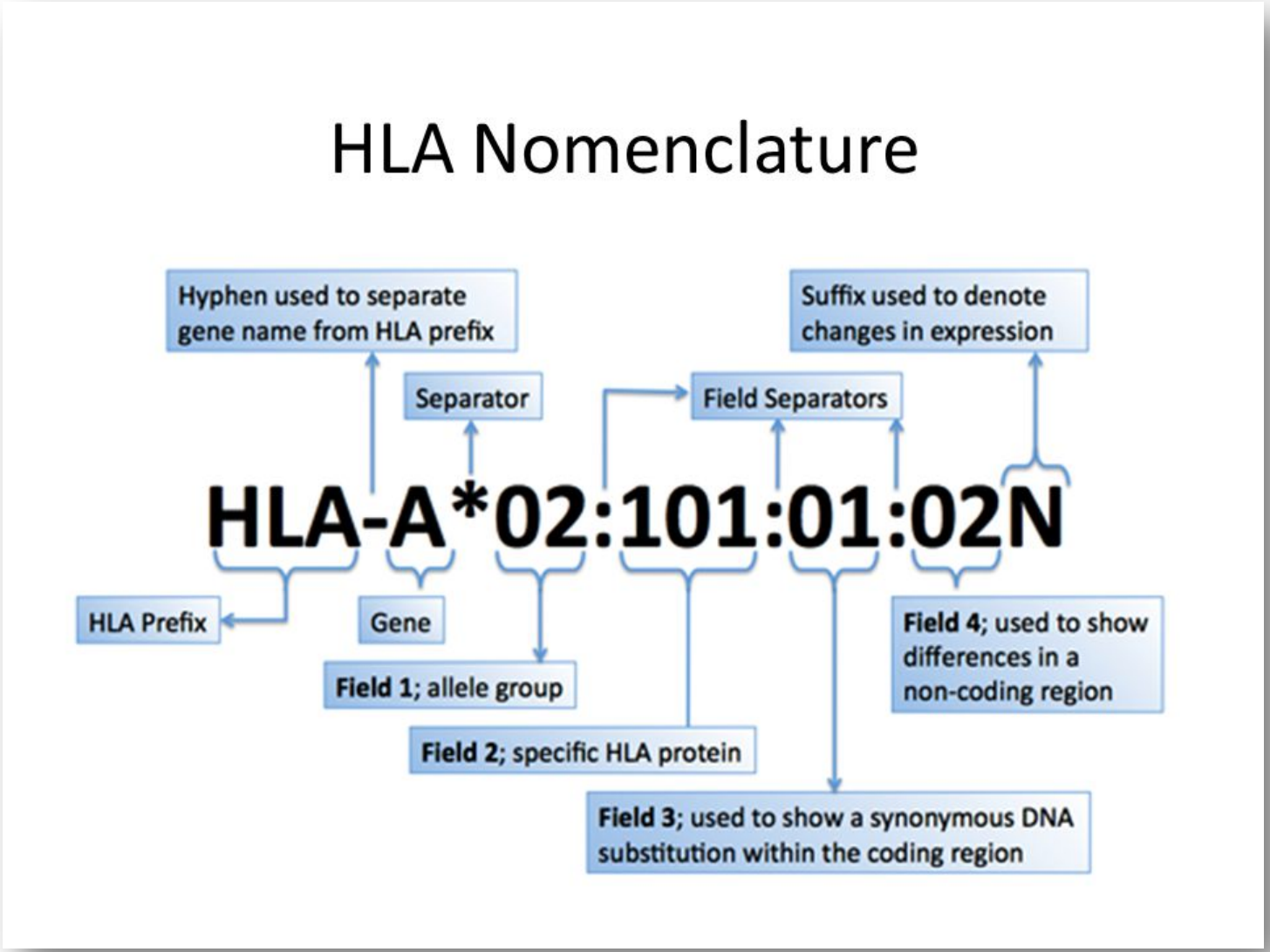
PBSC Collection

Cord Blood Unit

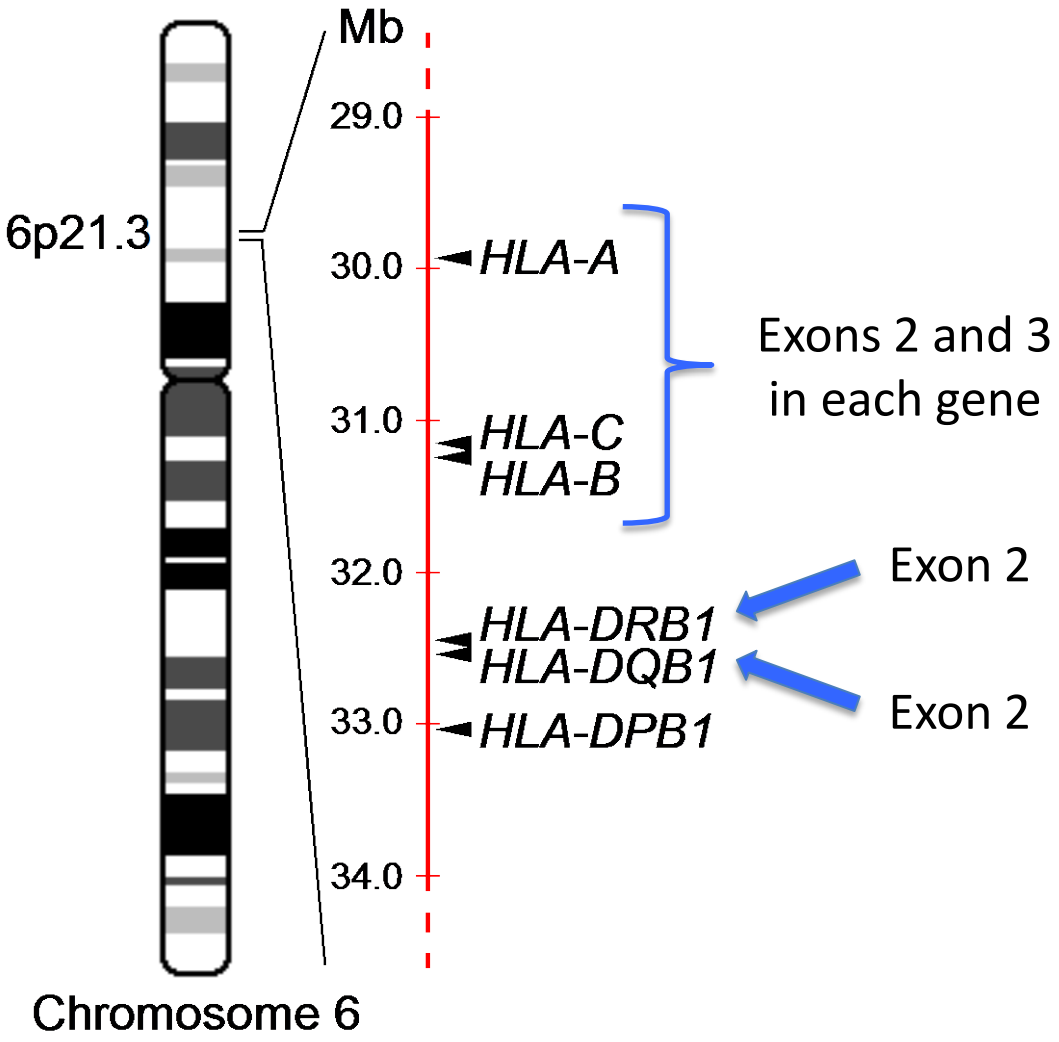
First home of the Seattle BMT unit, late 1960's

http://www.ci.seattle.wa.us/neighborhoods/preservation/images/large/PacMed3DON.jpg

First step is to perform HLA Typing



What is involved in HLA typing, anyway?



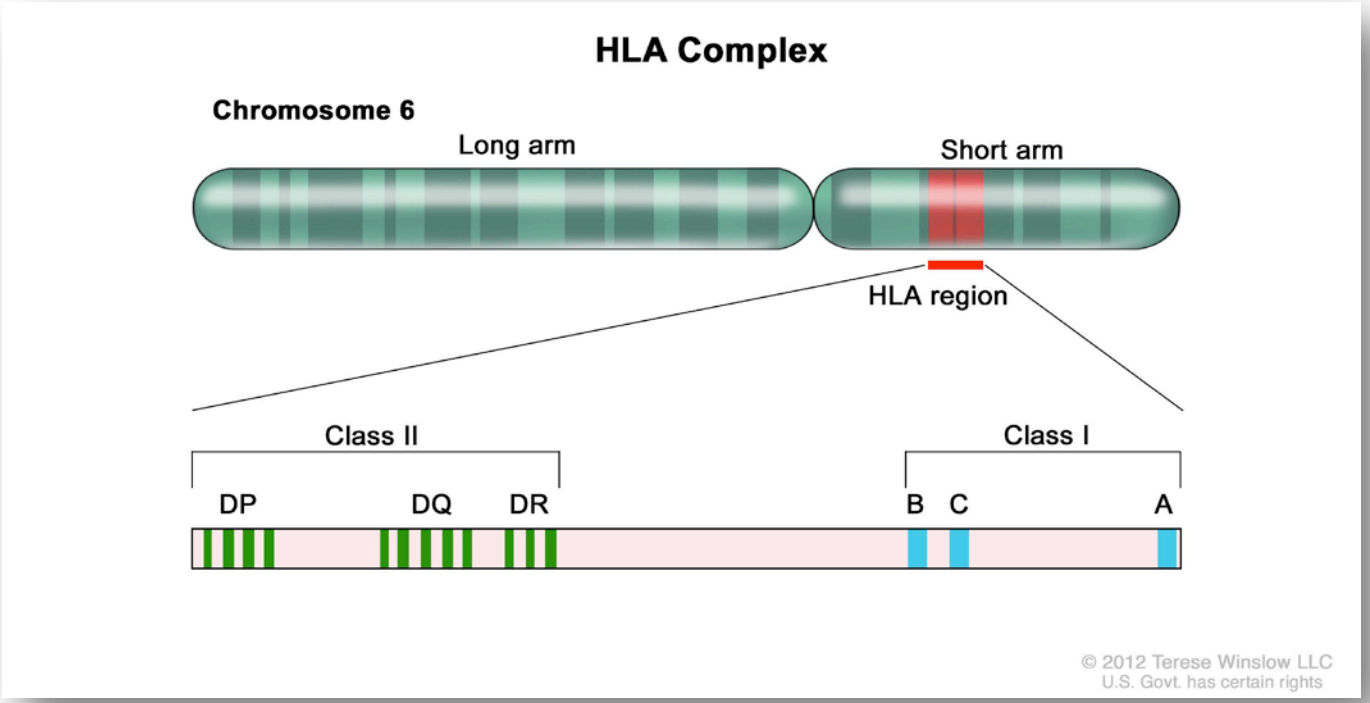
8 exons total

~275 nt each

TOTAL: 2,200 bp

Haploid genome: 3.3 x 10^9 bp

$< 1 \times 10^{-6}$ of the genome


HLA Complex
Chromosome 6
Long arm
Short arm
HLA region
Class II
Class I
DP
DQ
DR
B
C
A
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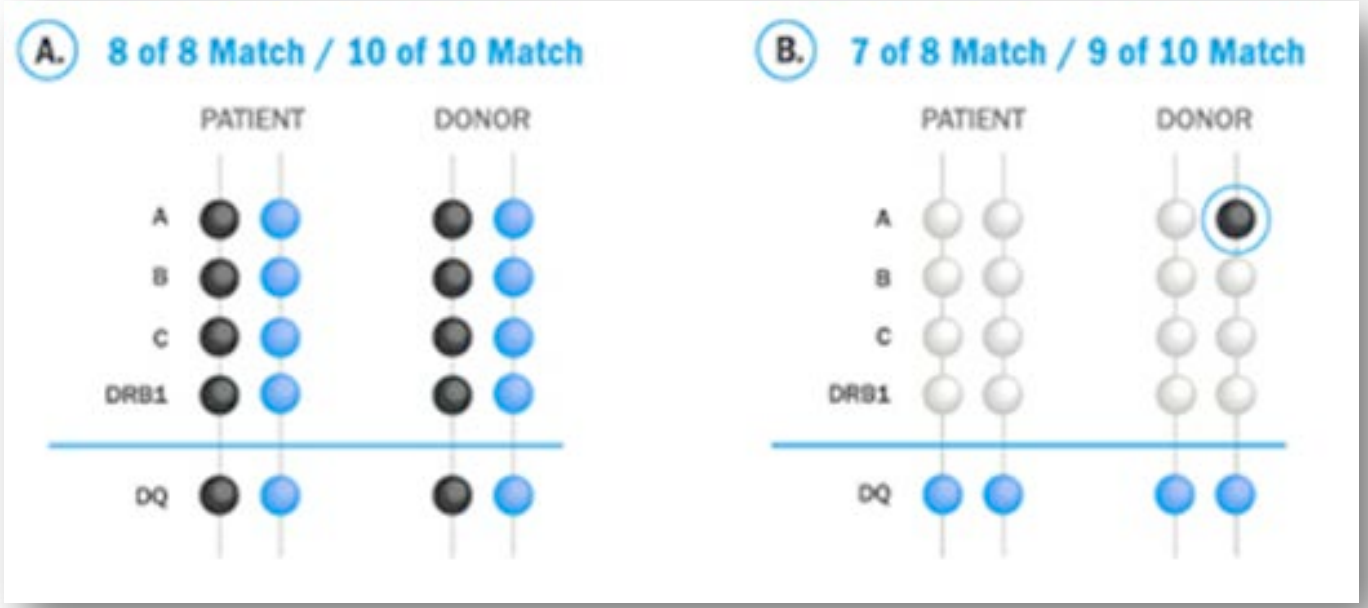
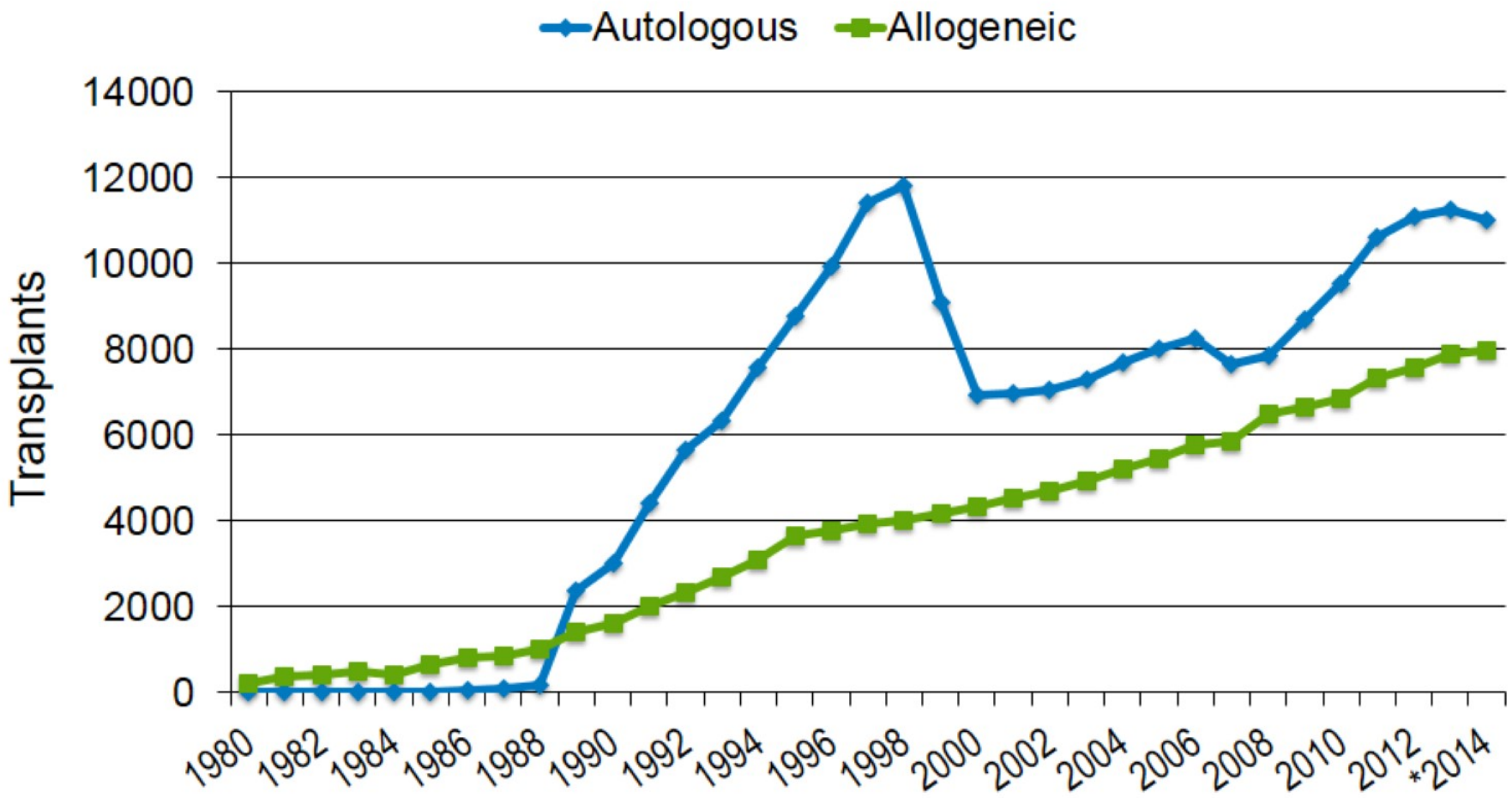

A.
8 of 8 Match / 10 of 10 Match
PATIENT
DONOR
A
B
C
DRB1
DQ
B.
7 of 8 Match / 9 of 10 Match
PATIENT
DONOR
A
B
C
DRB1
DQ

Hematopoiesis: some numbers

- Each day a typical adult produces:
  - 2×10^{11} red blood cells
  - 1×10^{11} white blood cells
  - 1×10^{11} platelets
- Over a lifetime: ~$4\text{-}8 \times 10^{15}$ blood cells
- Maintenance of basal hematopoiesis requires each human HSC to divide ~52 times
- Between the HSC and terminally differentiated circulating blood cells, there are between 17 and 19.5 effective cell divisions, with a net amplification of between ~170,000 and ~720,000

Rates of production can increase 10-fold

Annual Number of Transplant Recipients in the US by Transplant Type



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*2014 Data incomplete

Diseases commonly treated with allogeneic hematopoietic [stem] cell transplantation

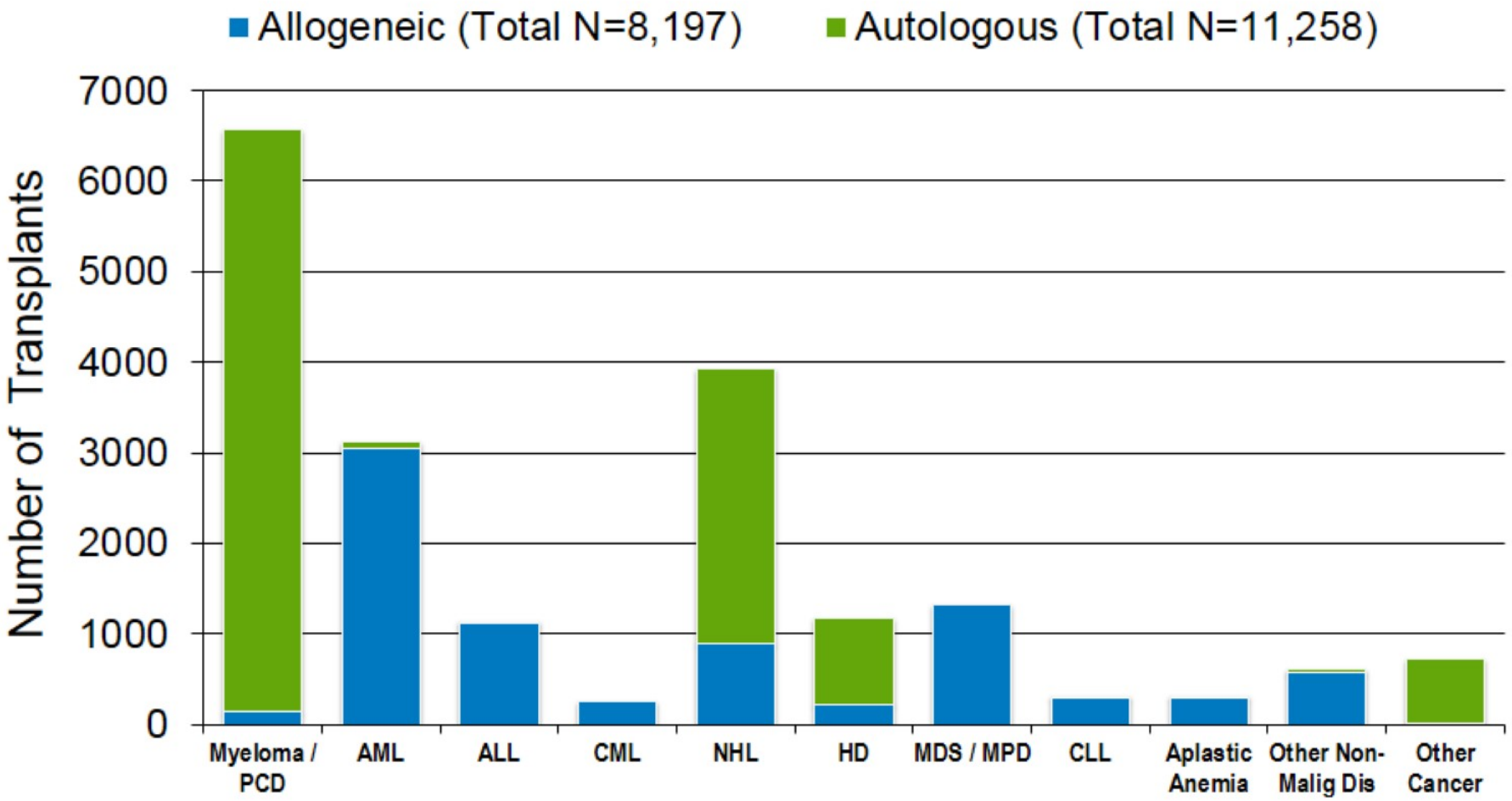
Cancers

- Acute myeloid leukemia
- Acute lymphoblastic leukemia
- Chronic myeloid leukemia
- Myelodysplastic syndromes
- Myeloproliferative disorders
- Non-Hodgkin lymphoma
- Hodgkin lymphoma
- Chronic lymphocytic leukemia
- Multiple myeloma
- Juvenile chronic myeloid leukemia

Non-malignant diseases

- Aplastic anemia
- Paroxysmal nocturnal hemoglobinuria
- Fanconi's anemia
- Blackfan-Diamond anemia
- Thalassemia major
- Sickle cell anemia
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome
- Inborn errors of metabolism

Indications for Hematopoietic Stem Cell Transplants in the US, 2013



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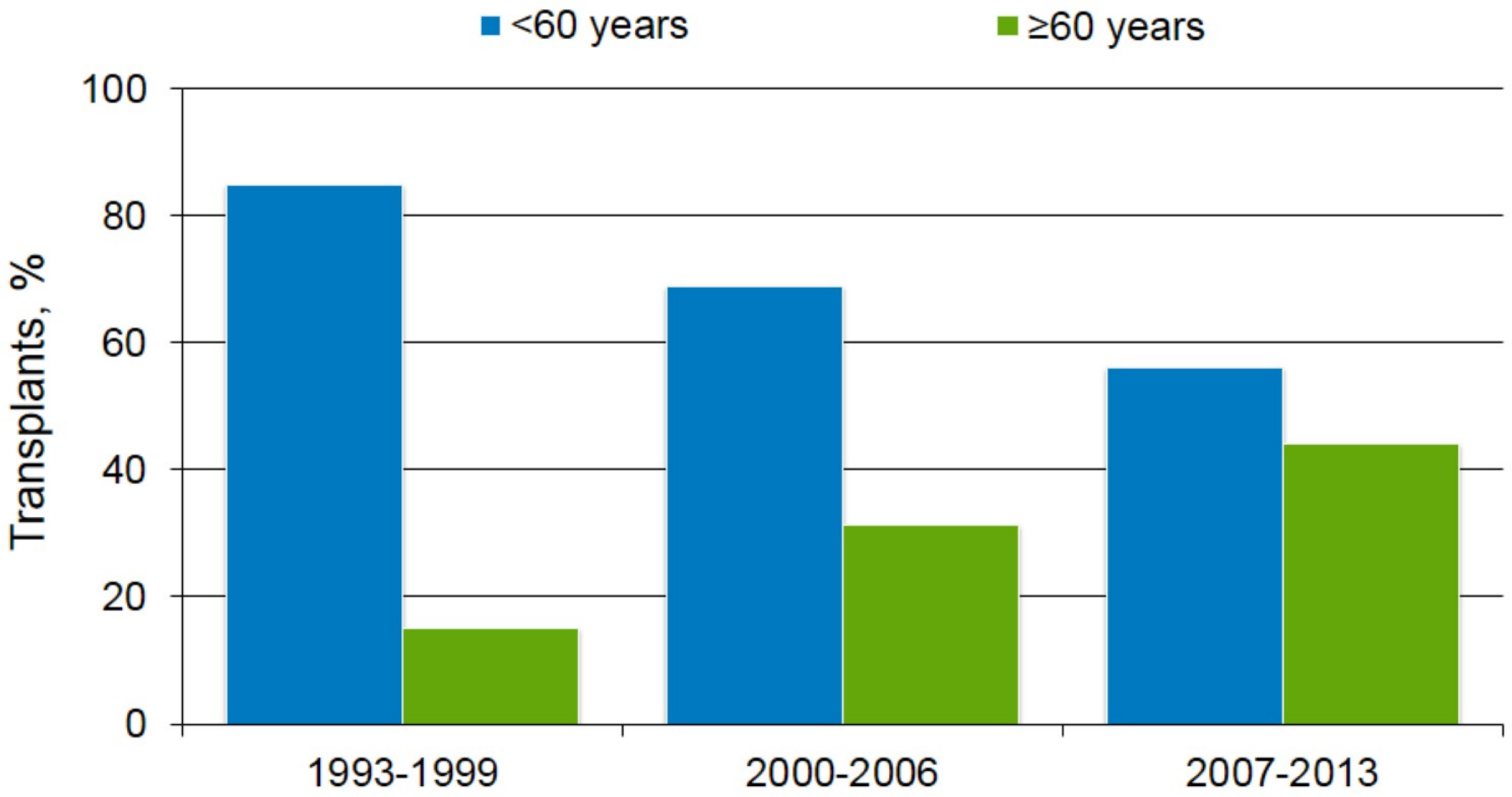
Trends in Autologous Transplants by Recipient Age*



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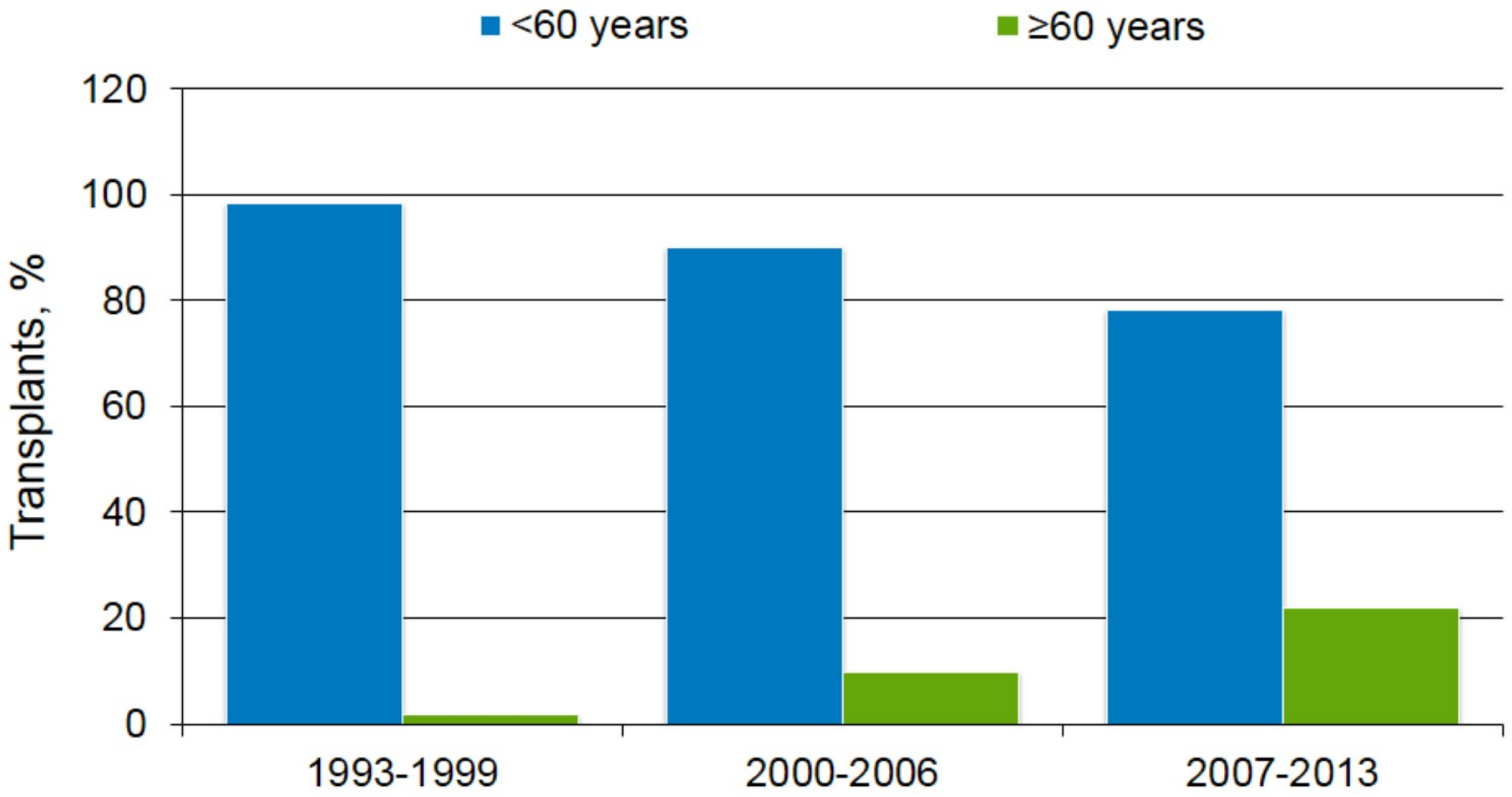
*Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

Trends in Allogeneic Transplants by Recipient Age*



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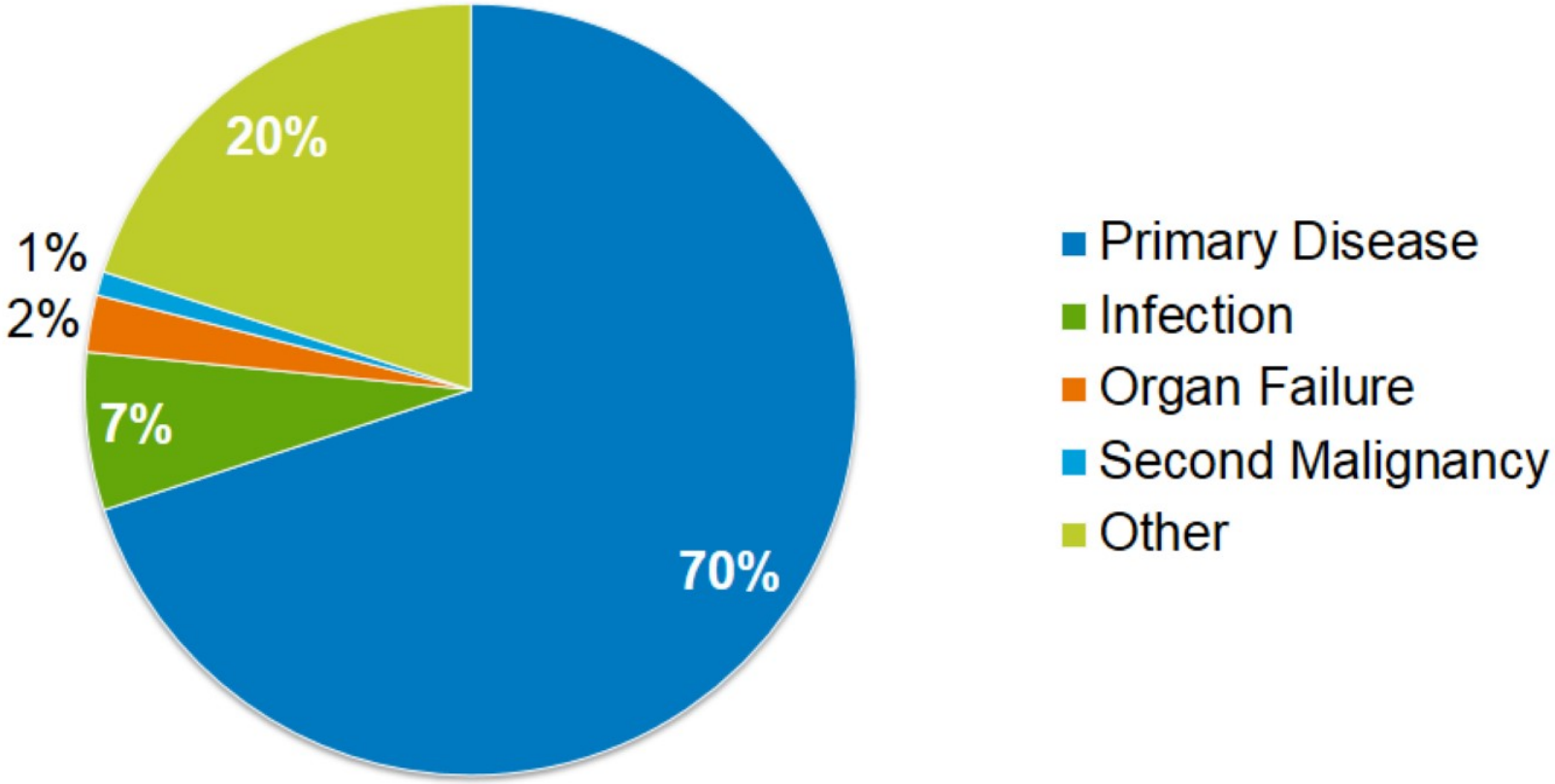
*Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

Causes of Death after Autologous Transplants done in 2012-2013



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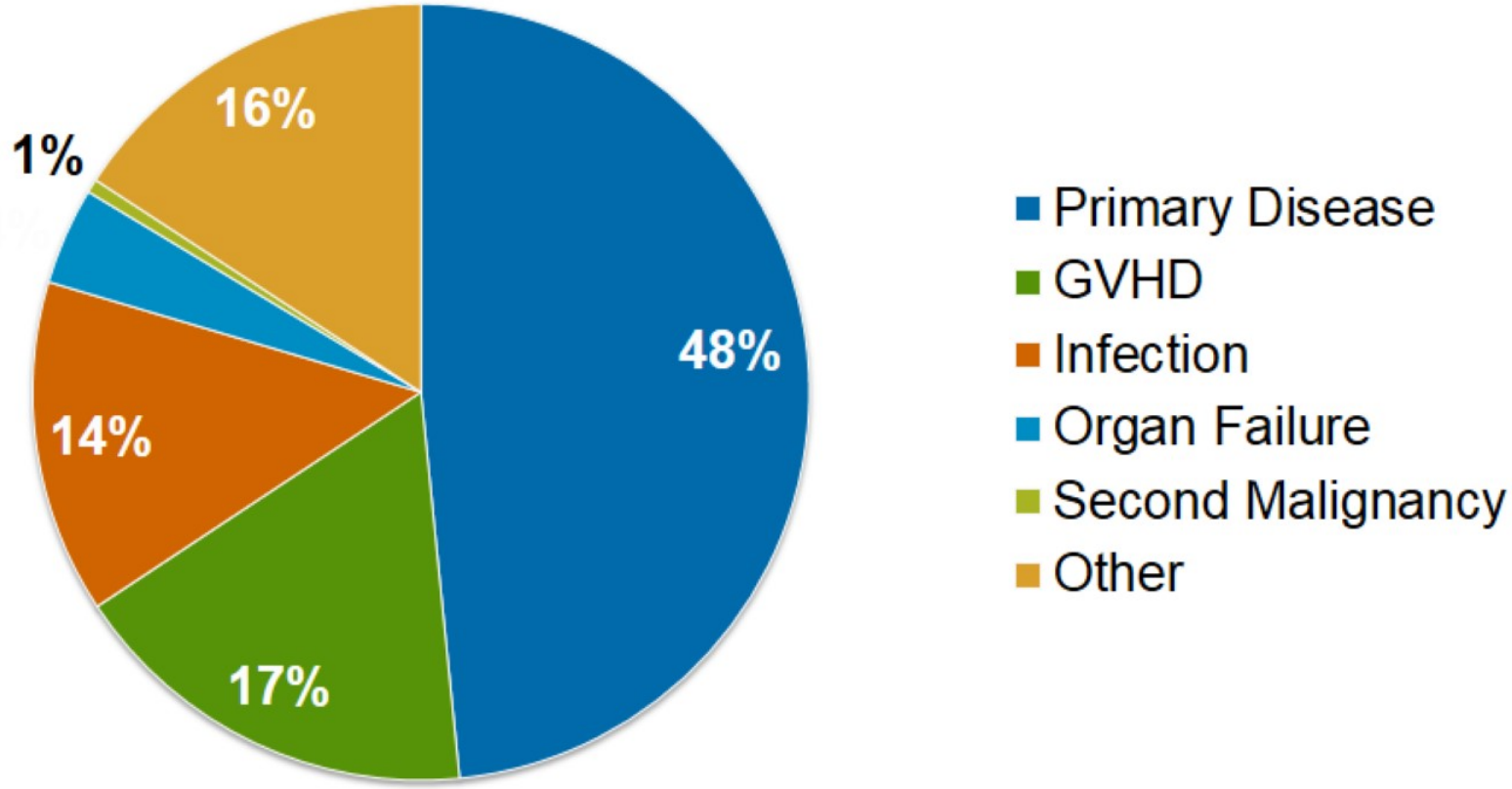
Causes of Death after HLA Match Sibling Transplants done in 2012-2013



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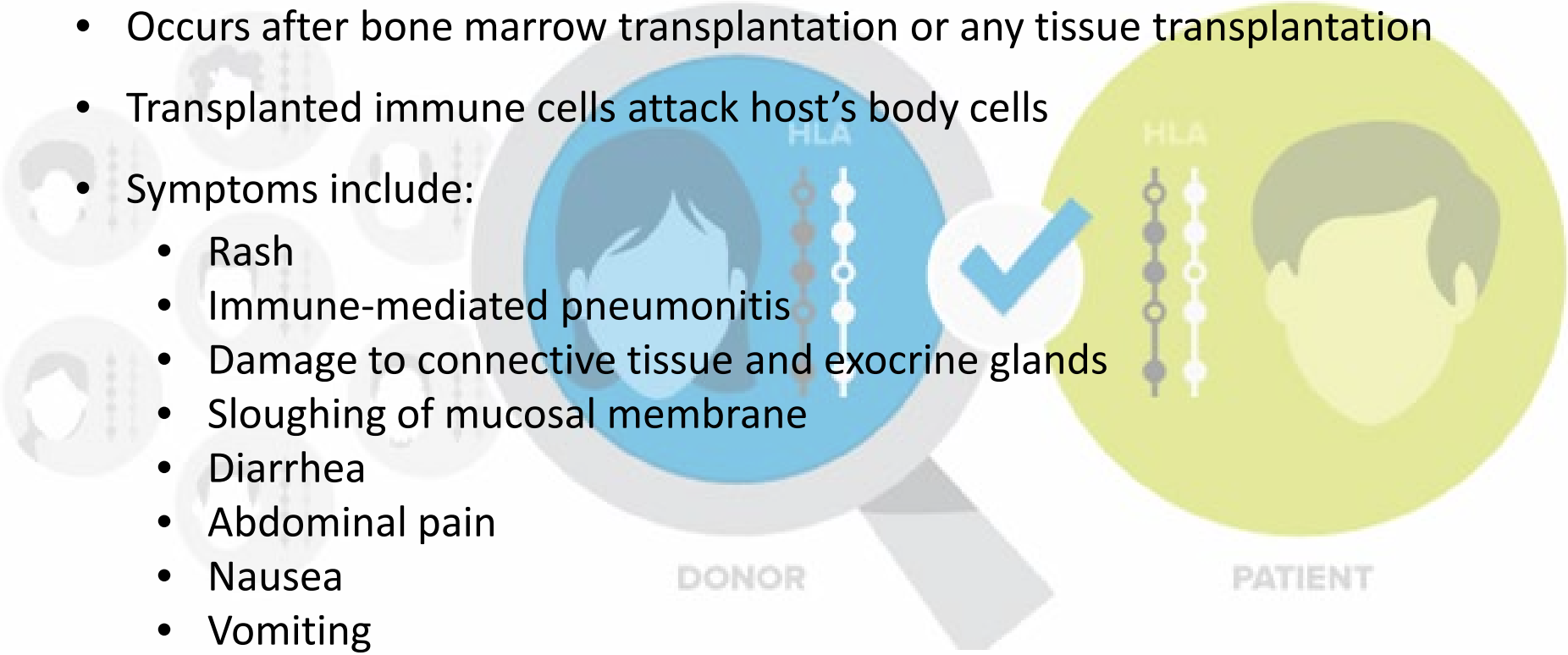
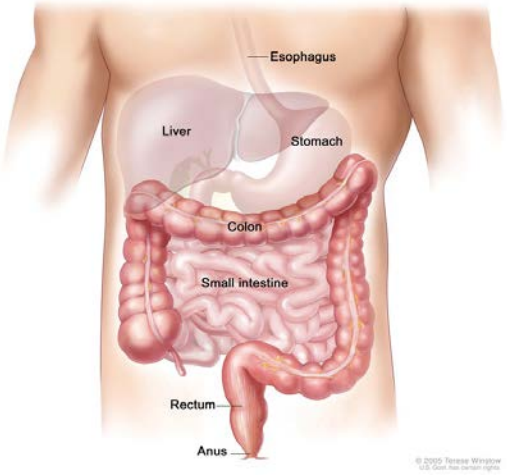
What is GVHD?

- Graft vs. Host Disease (GVHD)
- Occurs after bone marrow transplantation or any tissue transplantation
- Transplanted immune cells attack host's body cells
- Symptoms include:
  - Rash
  - Immune-mediated pneumonitis
  - Damage to connective tissue and exocrine glands
  - Sloughing of mucosal membrane
  - Diarrhea
  - Abdominal pain
  - Nausea
  - Vomiting
  - Eye irritation
- Can be fatal
- Treatment includes glucocorticoids such as prednisone

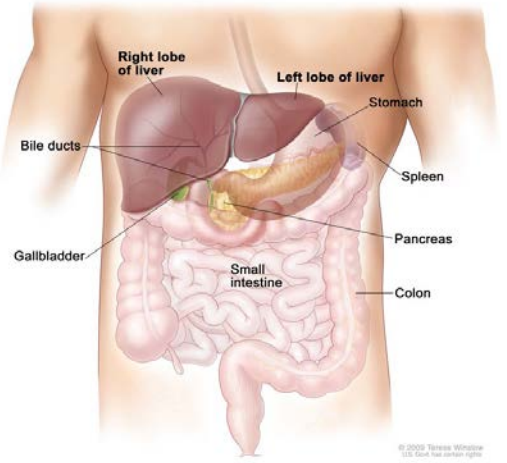


Major sites of graft-versus-host disease

Skin

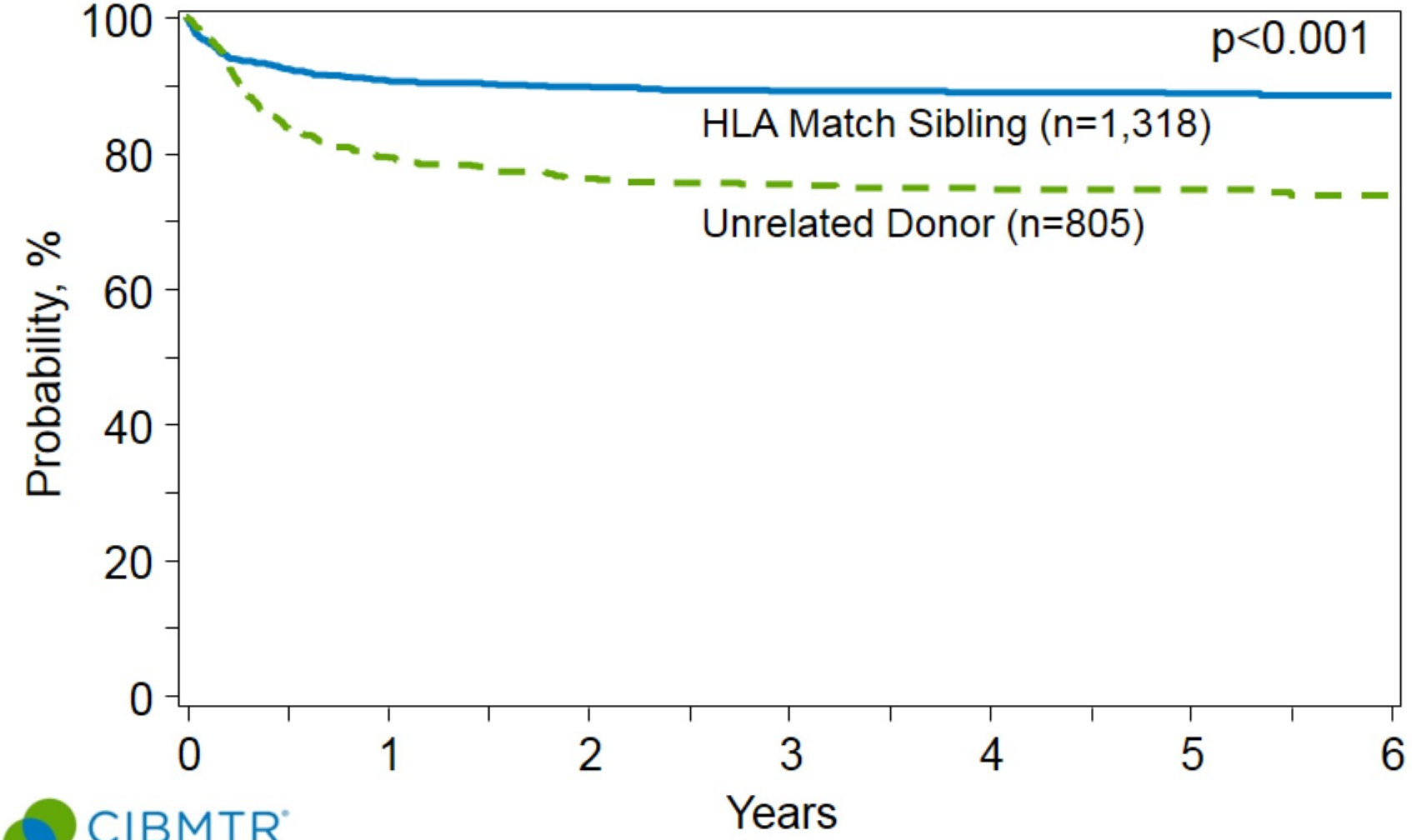


GI Tract



Liver

Survival after Allogeneic Transplants for Severe Aplastic Anemia, <20 Years, 2003-2013



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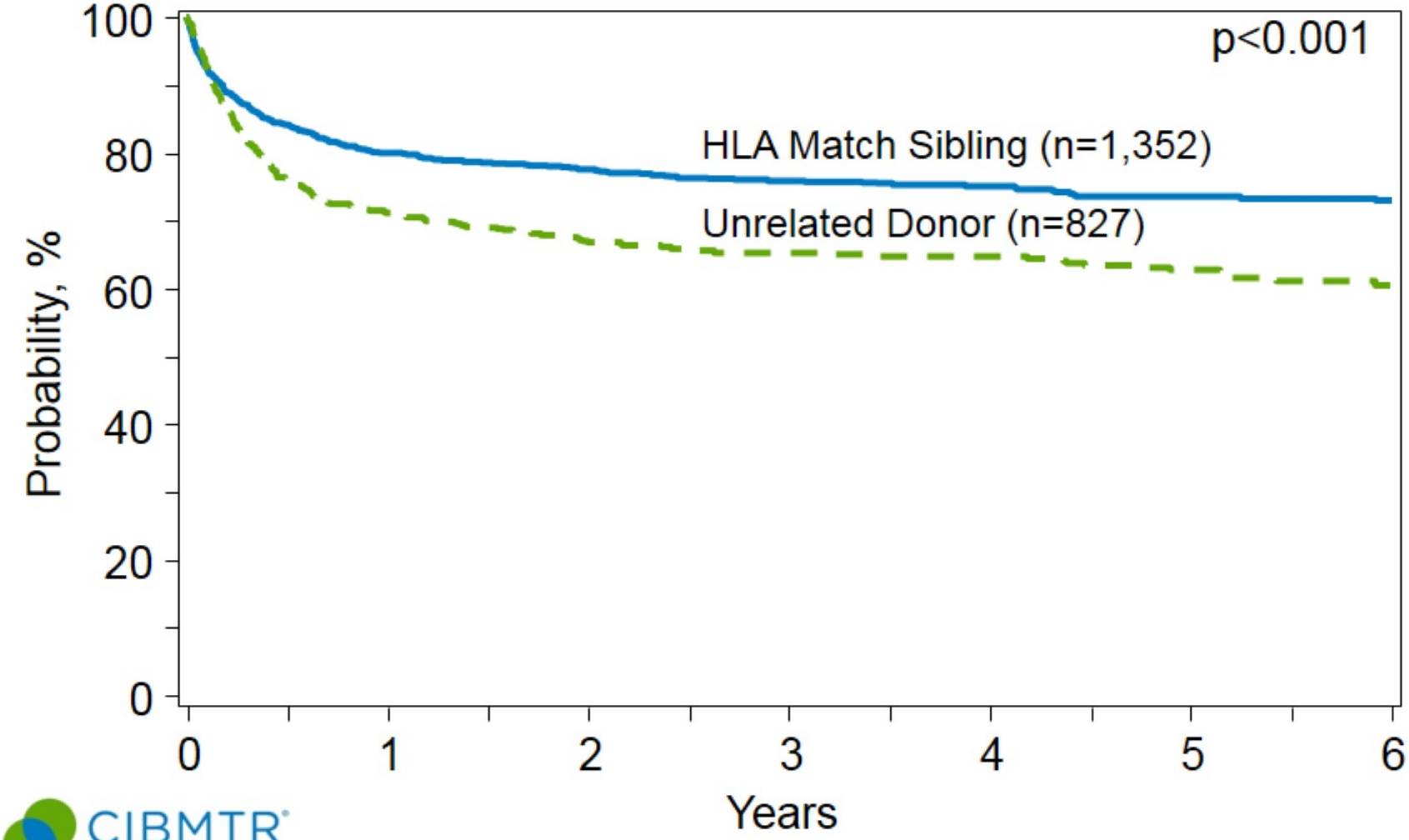
By Donor Type

Survival after Allogeneic Transplants for Severe Aplastic Anemia, ≥20 Years, 2003-2013



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By Donor Type

Summary

- Infusion of autologous and allogeneic hematopoietic stem cells is a standard and quite common procedure in contemporary hematology and oncology
- Histocompatibility is determined by genetic loci both within the MHC on chromosome 6p and at a large number of minor histocompatibility loci elsewhere in the genome (including the Y chromosome)
- Eradication of malignant cells in recipients of allogeneic HCT is mediated by the donor's immune system – providing the clearest example of effective cancer immunotherapy

References

- https://www.cibmtr.org
- https://bethematch.org/
- https://dreamerbiologist.wordpress.com/2013/04/19/hla-complex-in-predictive-medicine/
- Weilin Chen, Ph.D., Institue of Immunology, ZJU, http://slideplayer.com/slide/6086041/
- New England Journal of Medicine 257:491-496 (1957)
- http://www.ci.seattle.wa.us/neighborhoods/preservation/images/large/PacMed3DON.jpg
- https://en.wikipedia.org/wiki/Graft-versus-host_disease