

# **Hematopoieticus őssejt- transzplantáció**

Belgyógyászati Szakvizsga Előkészítő Tanfolyam

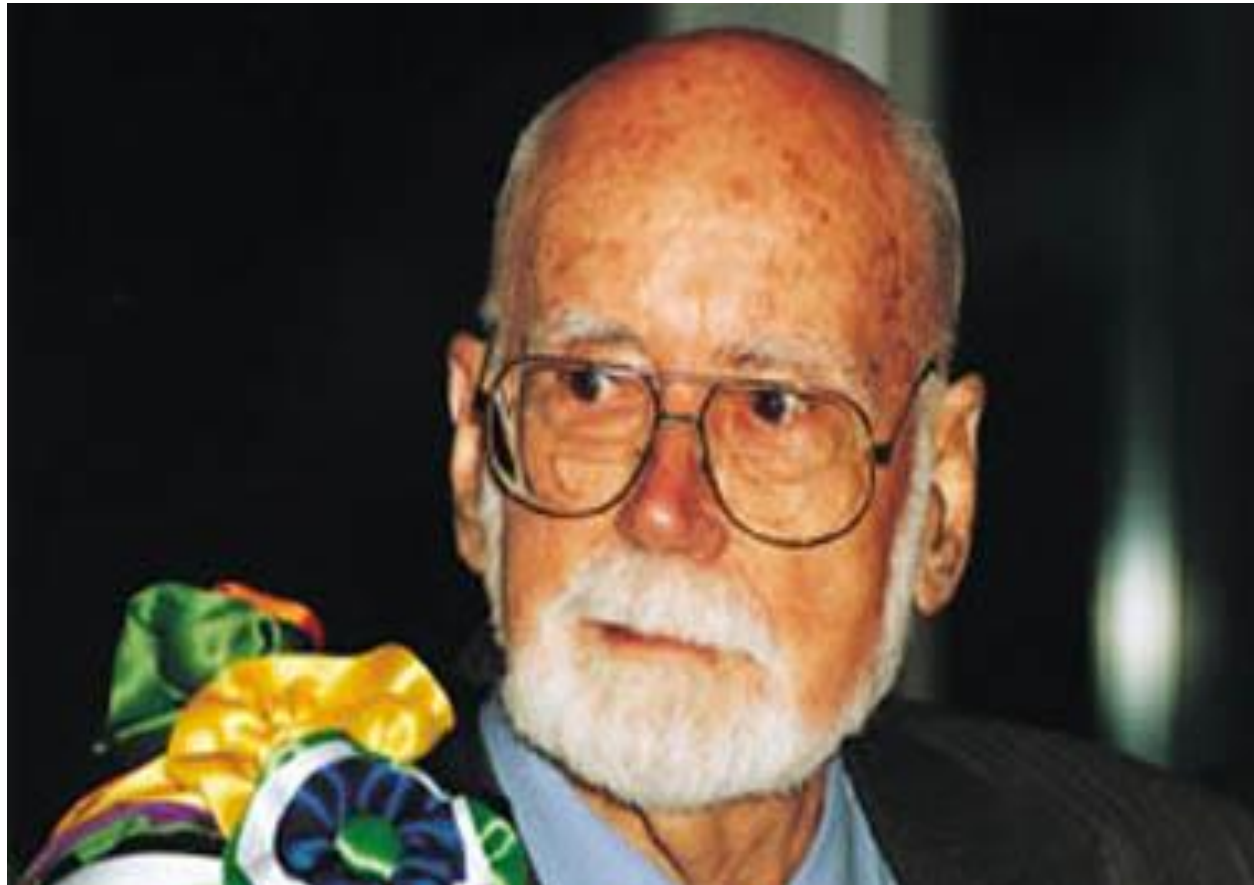
2021.05.17-Június 11.

Pécs

On-line tanfolyam

# Orvosi Nobel Díj 1990

**E. Donnall Thomas**

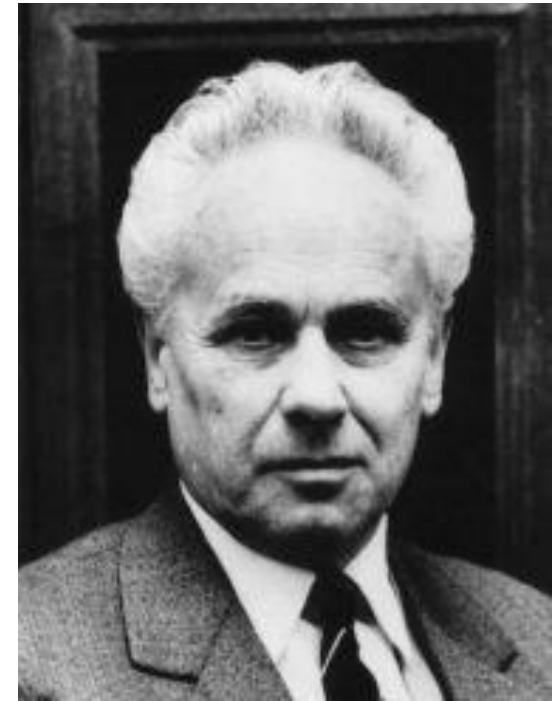


**Első sikeres allogén- HSCT akut leukaemiában:  
2 ALL: TBI + szingén BMT: 2 hét múlva megtapadás  
relapsus hónapok múlva - tumor eradikáció**

**Thomas ED, Lochte HL, Lu WC, Ferrebee JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. N. Engl. J. Med. 1957; 257: 491.**

# **Őssejt transzplantáció hazánkban**

**1974. Prof. Kelemen Endre 1. BMT  
(1921-2000)**



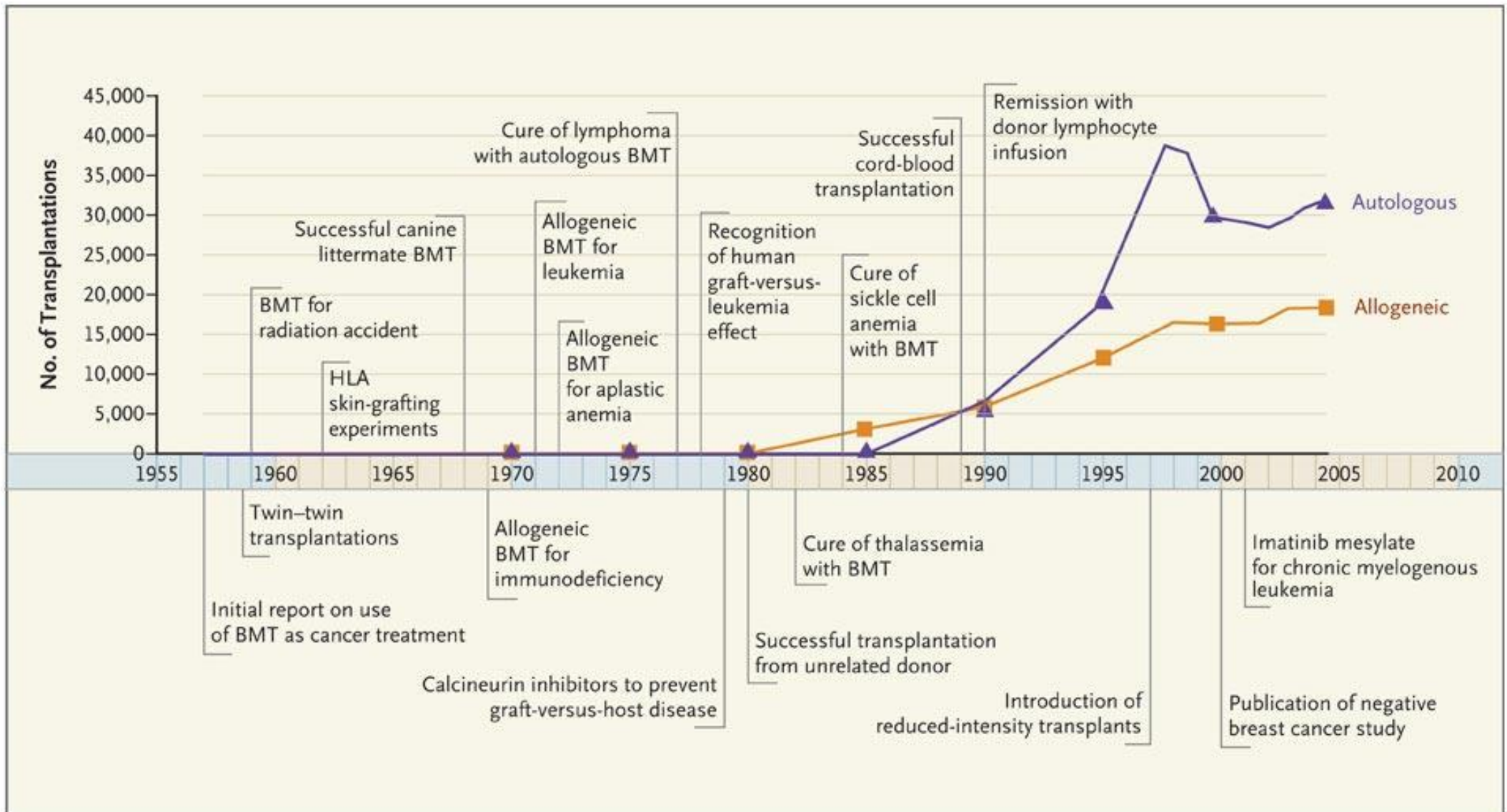
**Jelenleg 5 transzplantációs központban  
történik HSCT**

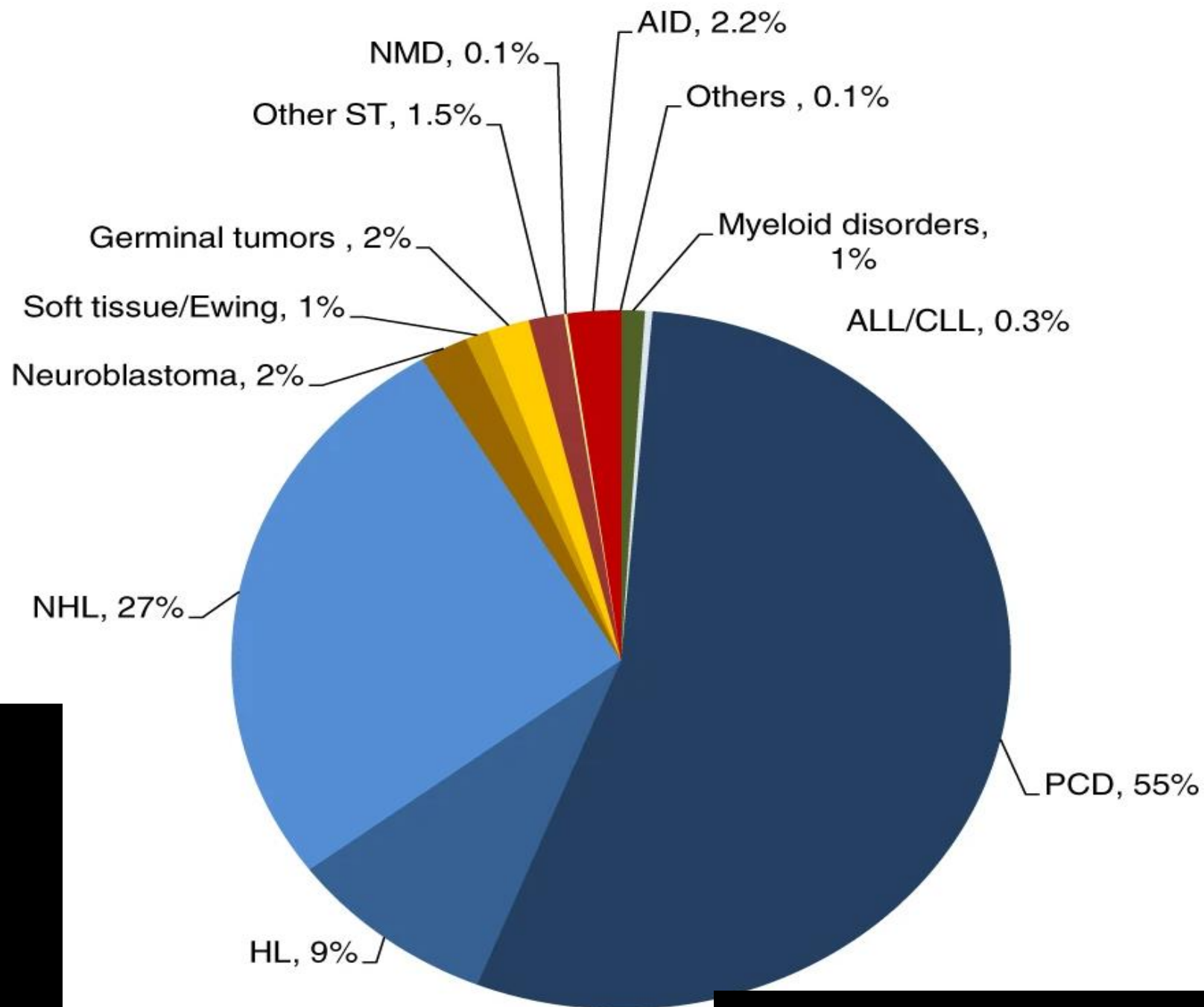
**Budapest (felnőtt, gyermek)**

**Miskolc (gyermek)**

**Pécs (1999), Debrecen (2003),**

**Szeged (2011)**

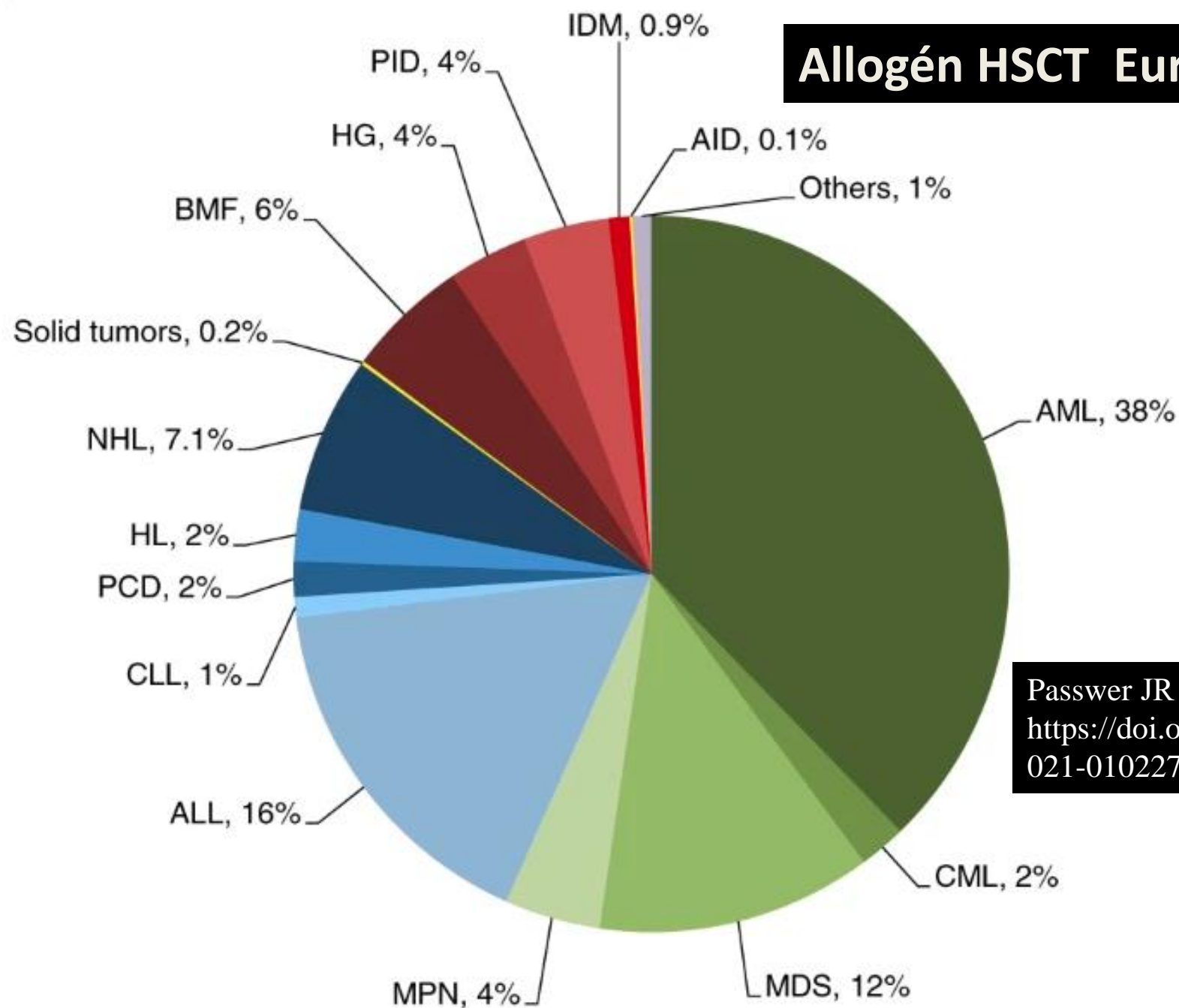




**Autológ  
HSCT  
Európában  
2019**

Fig. 1: Relative proportion of disease indications for HCT in Europe 2019.

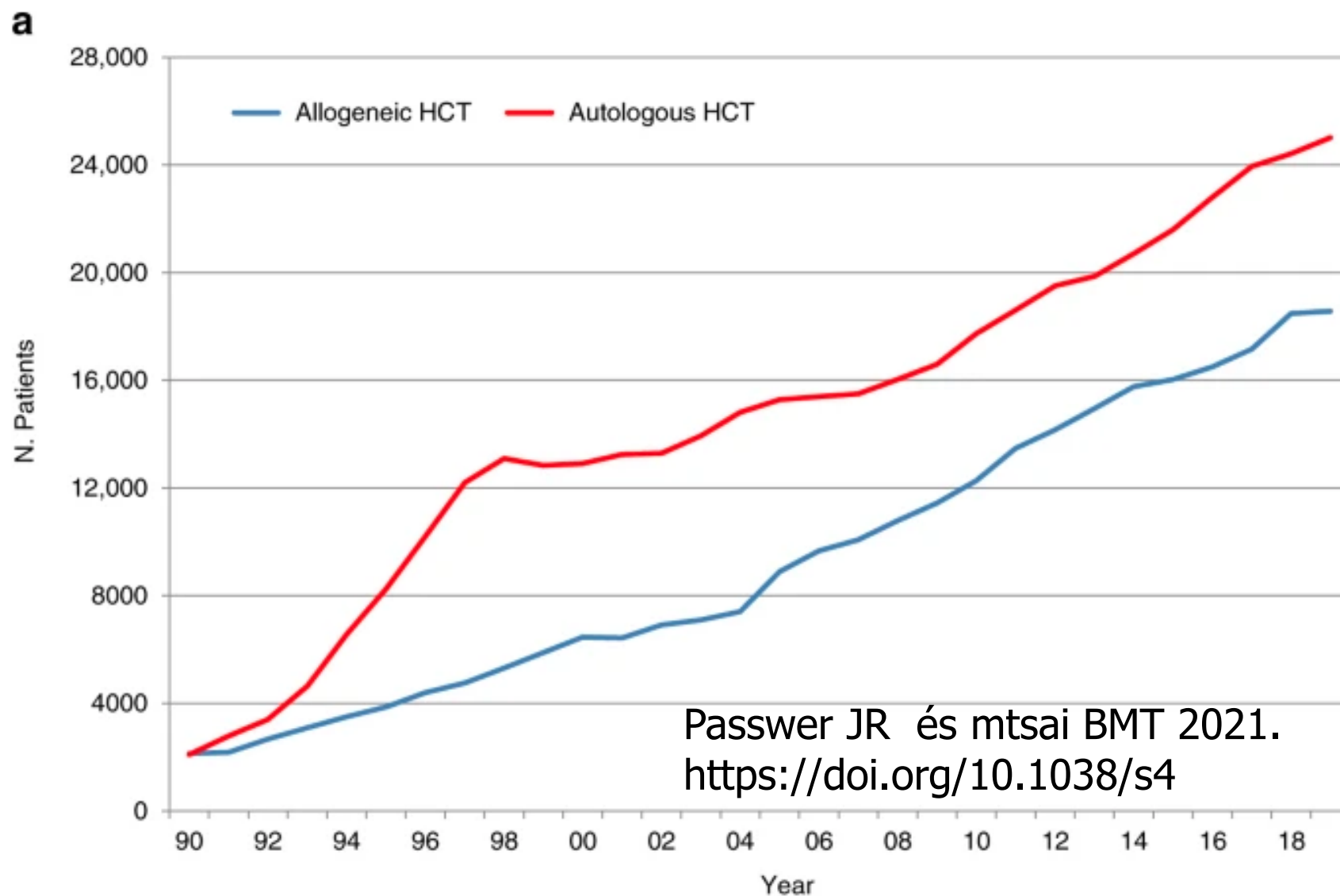
**a**



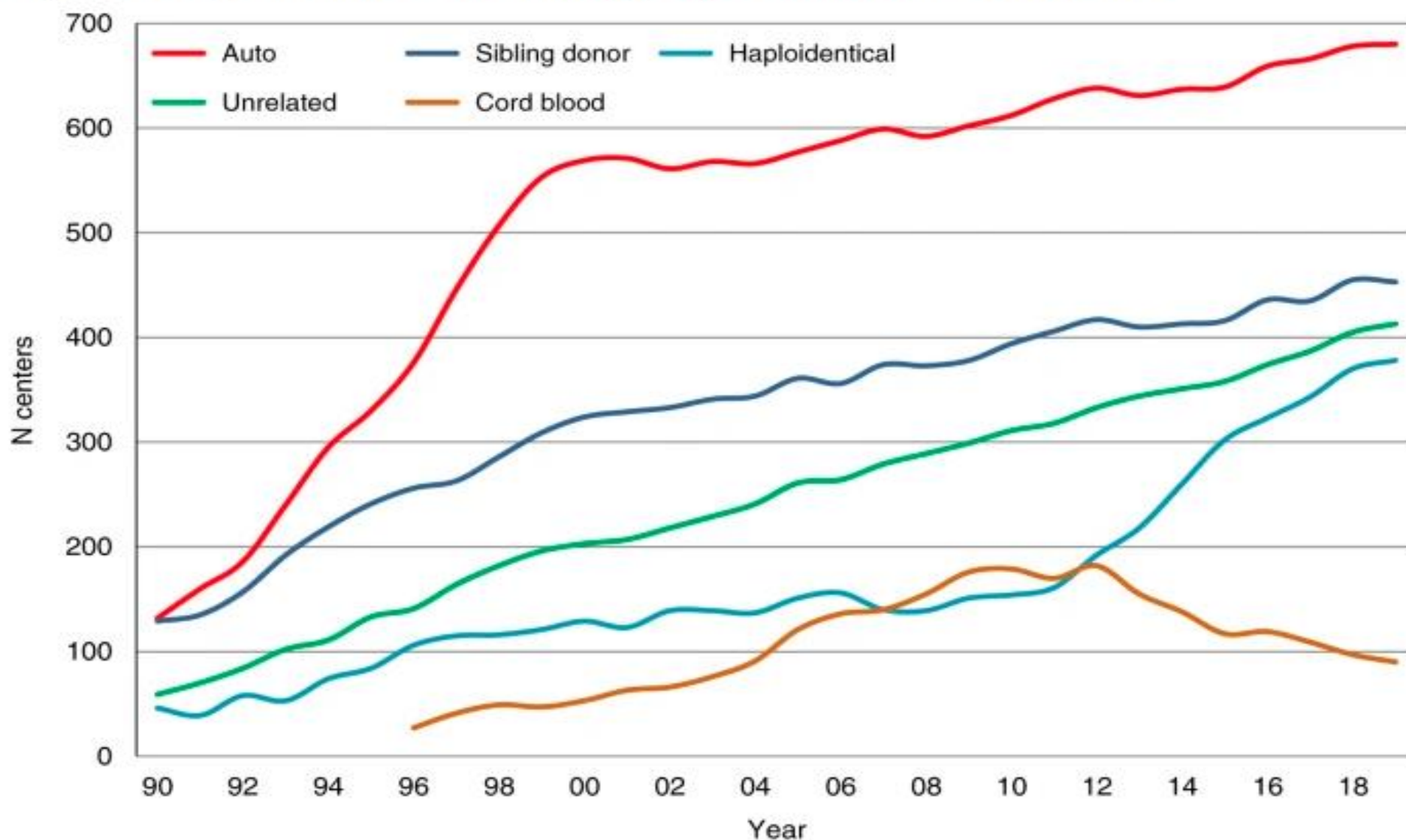
**Allogén HSCT Európában 2019**

Passwer JR és mtsai BMT 2021.  
<https://doi.org/10.1038/s41409-021-010227-8>

**Fig. 3: Development of HCT from 1990 to 2019.**

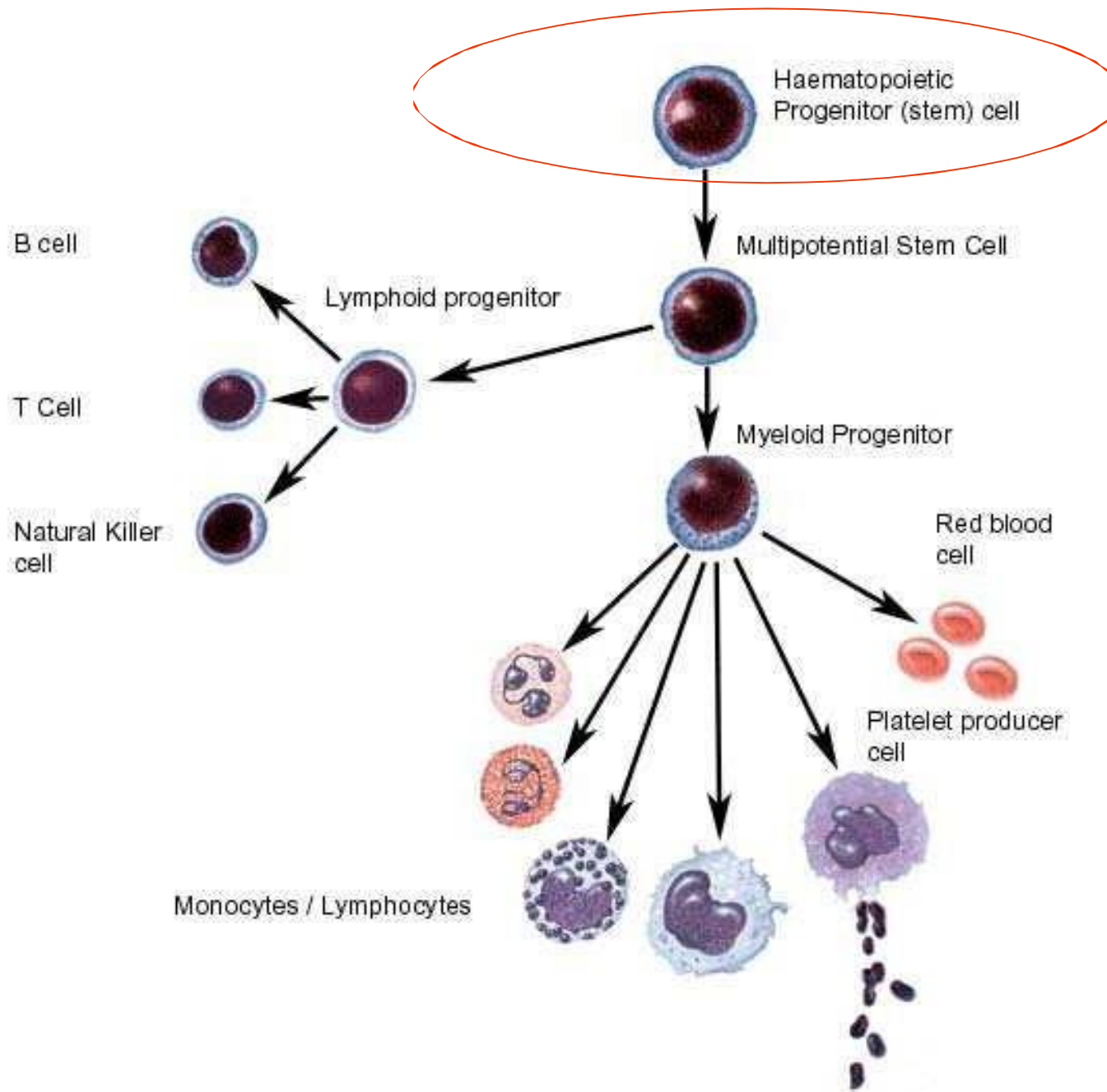


**Fig. 5: Change in choice of donor type by center from 1990 to 2019.**



The figure shows the numbers of centers and the type of donors selected for HCT over the 30 year period.

# Hematopoiesis



What is a stem cell?

A single cell that can

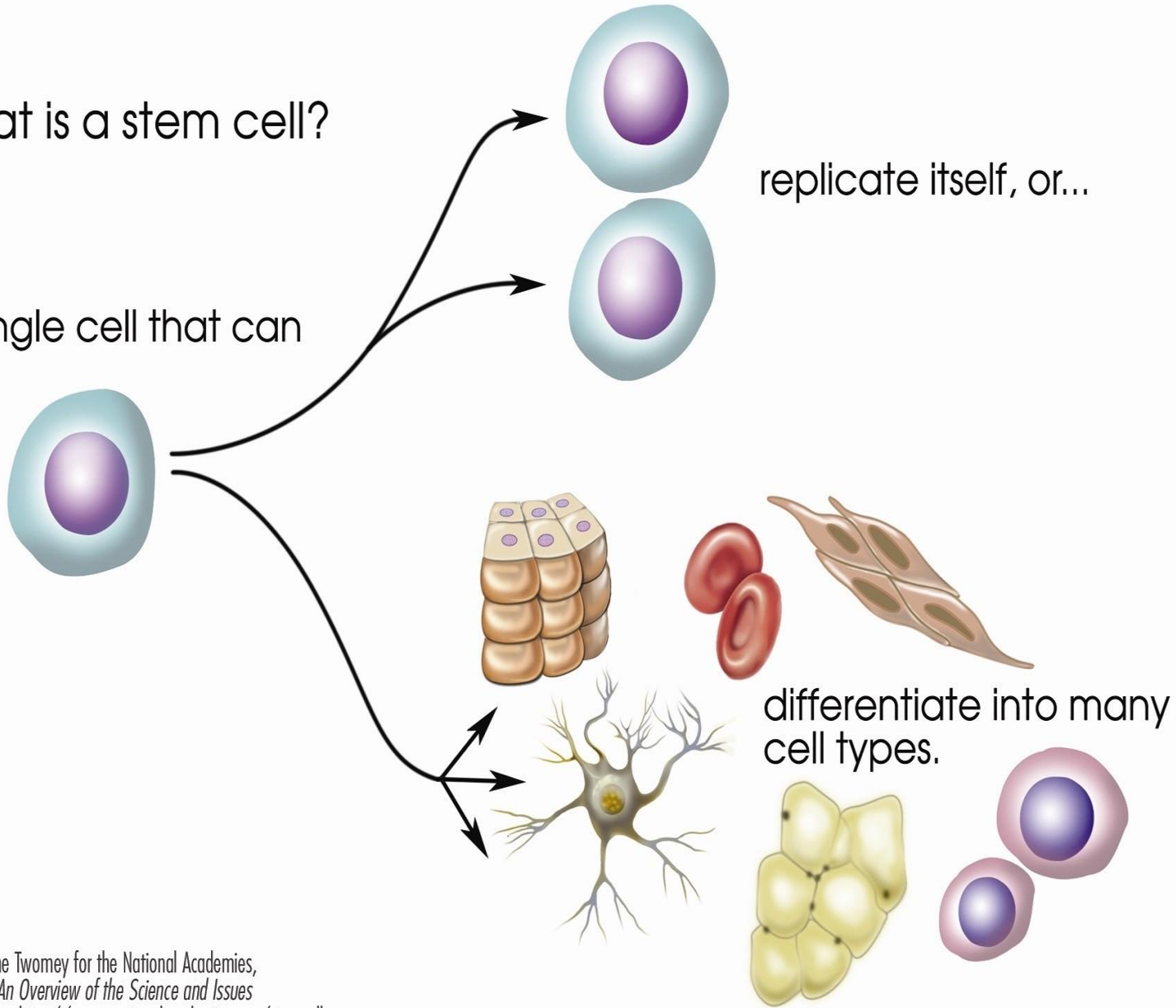


Image prepared by Catherine Twomey for the National Academies,  
*Understanding Stem Cells: An Overview of the Science and Issues*  
from the National Academies, <http://www.nationalacademies.org/stemcells>.  
Academic noncommercial use is permitted.

# Az őssejtek típusai

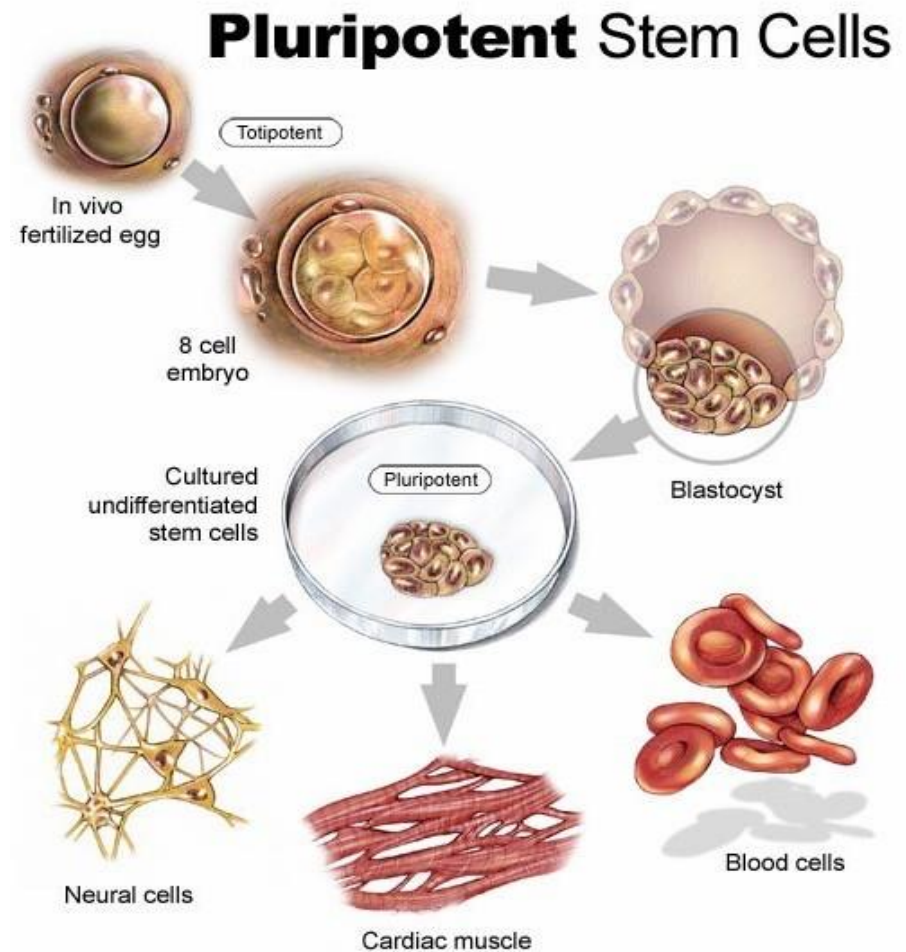
## 1. Embryonic stem cell (ES Cells) :

Are Pluripotent.

Can generate all tissues of body.

Derived from embryos(blastocyst).

Developed from in vitro fertilization.



# Az őssejtek típusai

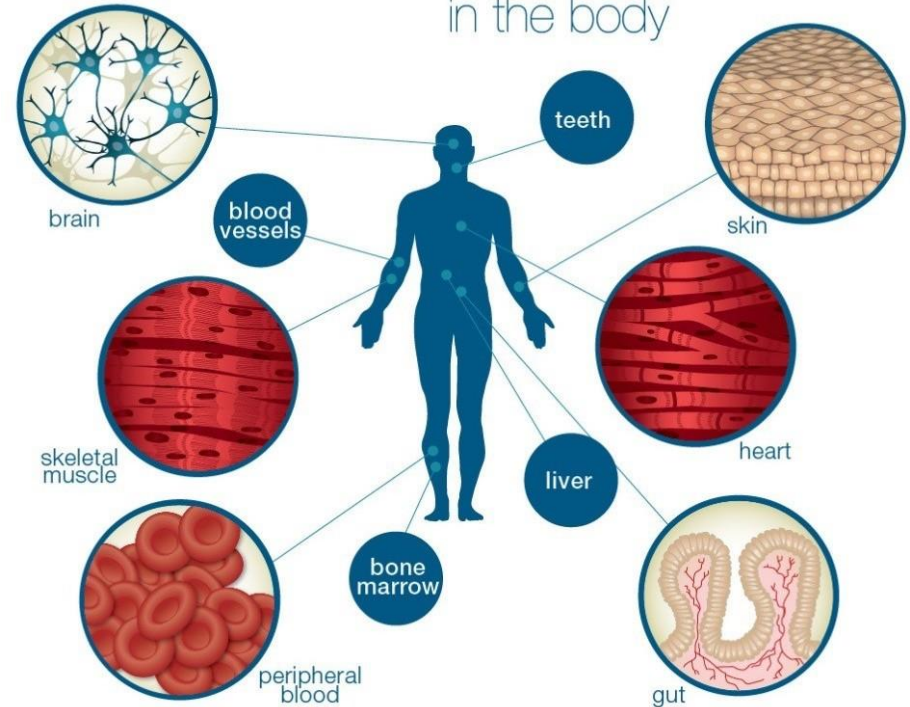
## 2. Adult stem cell ( somatic cell ) :

Undifferentiated cell found among differentiated cells in a tissue or organ.

Can renew it self in to specialized cells.

e.g. Bone marrow , Skin , lining of G.I.T., pancreas , liver adipose tissues & many others.

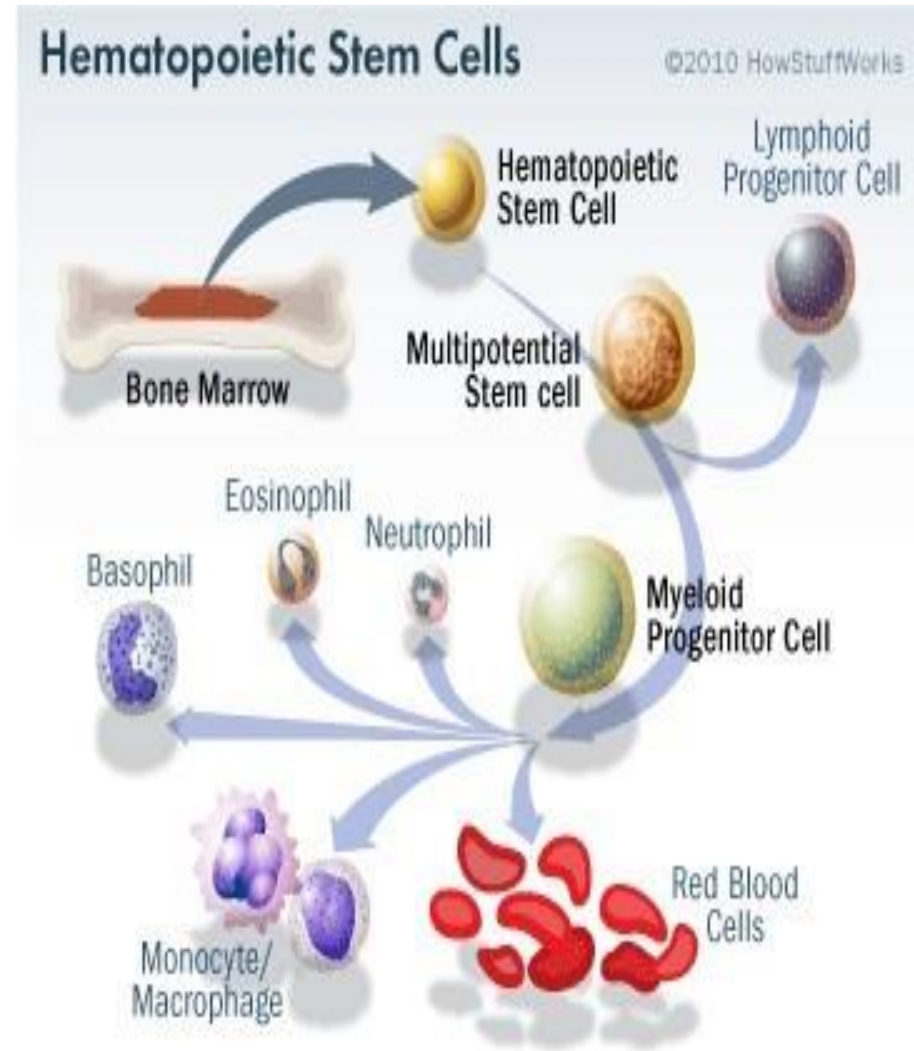
Locations of **Somatic Stem Cells** in the body



# Hematopoieticus őssejt (HSCT)

Adult stem cells that are found in bone marrow and blood.

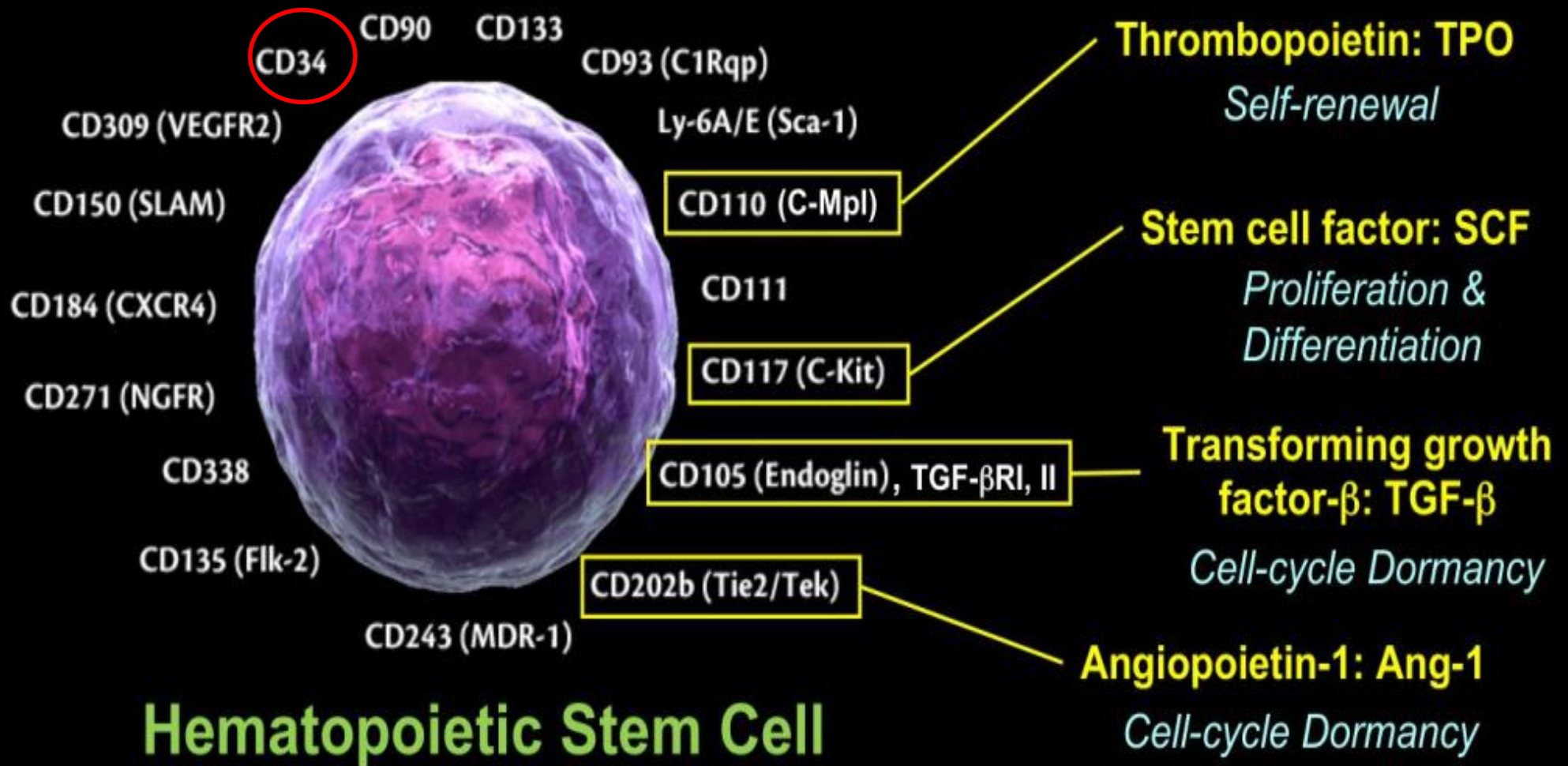
HSCs are capable of producing all of the cells that make up the blood and the immune system.



## Az őssejt

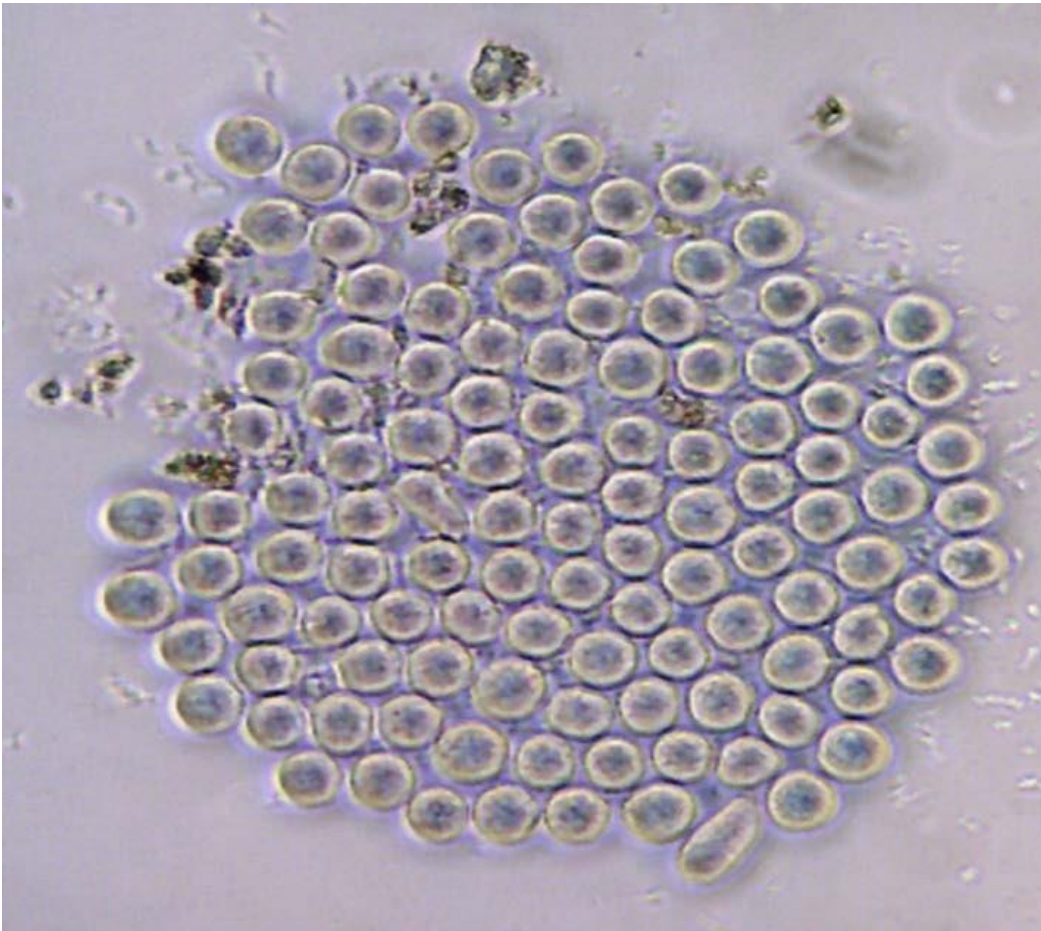
- ▶ Perifériás vérben 0,06 % a CD34+ sejt,  
3,8x10<sup>6</sup>/l az abszolút CD34+ sejt
  - ▶ Citokinek: G-CSF, G-CSF+GM-CSF, stem cell factor, flt3 ligand+G-CSF, rhTPO+G-CSF, IL-3 és G-CSF
  - ▶ Csontvelő 1990-es években döntő többség
  - ▶ Perifériás vér 2000-ben már 81 %-ban  
2007-ben auto: 98 %, allo: 71%
  - ▶ Embrionalis sejtek (köldökvér, máj)
- } Őssejt  
forrás

# Hematopoietikus őssejt



# **Hematopoieticus őssejt (HSCT)**

**1/ 25,000 - 1,00, 000 cells in the bone marrow**



## **Characteristic:**

- **CD34**
- **CD133**
- **C-kit (CD117)**
- **ADH**

## **A transzplantáció típusa**

Allogén (más személyből származó őssejtek)

Autológ (saját őssejtek)

Szingén (egypetűjű ikrek)

## **Donor típusa**

HLA identikus testvér vagy egyéb rokon

HLA identikus idegen donor

HLA nem identikus (pl. haploidentikus rokon)

HLA nem identikus idegen donor

# Őssejt mobilizáció sikeressége függ

Életkor

Alapbetegség (tumoros csontvelői érintettség)

Csv-i őssejt pool csökkenése (károsodás)

előző kemoth-k száma, hossza, összetevők,  
dózisok

„sejtvisszatérések” hossza korábban

korábbi csontvelőt érintő besugárzás

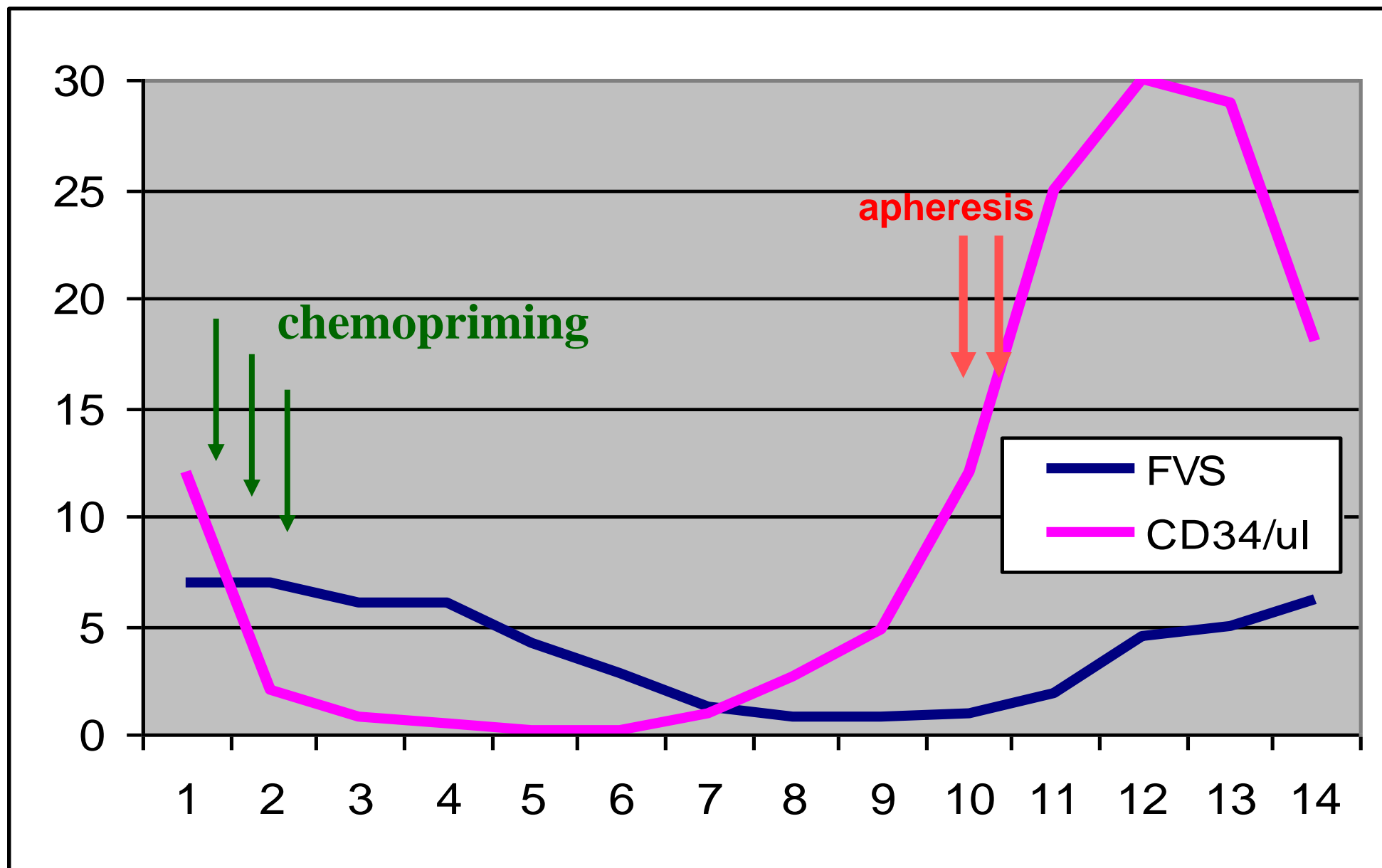


# **Tumor purging technikák**

- ▶ immunológiai (immunmágneses, high density microparticulum)
- ▶ farmakológiai
- ▶ fotoszenzitizedáló anyagokkal
- ▶ fizikai hatás, membránaktív anyagokkal
- ▶ molekuláris biológiai és gén transzdukciós eljárásokkal (anti sense technika)
- ▶ immuneffektor sejtekkel
- ▶ "long term" csontvelő kultúra

**Nem bizonyított a purging előnye (EBMT study)**

# Perifériás vérőssejt mobilizálás (chemotherapy utáni rebound)



# Cryopreservatio

1970-ben írták le a csontvelőgyűjtést (ACD vagy heparin)

Volumen redukció: hydroxyethyl starch ülepítés: VVT

$200 \times 10^6$  magvas sejt/ml az ideális végkoncentrárum

DMSO – cryoprotectans: jégkristály kialakulás ellen

Cső, vagy polyolefin zsák

Fagyasztás:  $1\text{ }^{\circ}\text{C/perc}$  -  $50\text{ }^{\circ}\text{C}$ -ig

$4\text{ }^{\circ}\text{C/perc}$  -  $150\text{ }^{\circ}\text{C}$ -ig

Tárolás folyékony nitrogénben (  $-196\text{ }^{\circ}\text{C}$ )







## Történelem

**A kezdetek:** The late **1940s** saw major research efforts directed at **repairing or preventing radiation damage to organs in response to observations made on survivors of the atomic bomb explosions in Japan.**

A pivotal report by Jacobson *et al.* in 1949 demonstrated protection of mice from lethal TBI damage to the bone marrow when shielding their spleens or femora with lead.

Two years later, Lorenz *et al.* saw similar protection when mice were given an iv. infusion of syngeneic marrow following TBI.

Jacobson & others attributed the radiation protection to some humoral factor present in spleen or bone marrow, the “**humoral hypothesis**”, as a ‘rescue’ of the irradiated mice had cellular origins.

In the mid-1950s several laboratories documented, with the help of blood genetic markers, that the radioprotection was due to repopulation of the irradiated marrow spaces by transplanted donor cells, thereby validating the “**cellular hypothesis**”.

In 1967 van Bekkum and de Vries wrote the book “Radiation Chimeras”.

High doses of chemoradiation therapy could be used both to destroy diseased marrow and suppress the host immune system, thereby preventing rejection of an infused marrow graft from a healthy donor.

## Történelem

**A kezdetek:** In 1957, Thomas *et al.* reported in *The New England Journal of Medicine* that **marrow could be infused into irradiated leukemia patients and then engraft, even though, in the end, the patients were not cured of their leukemia.**

In 1965, Mathé *et al.* described a **patient with acute leukemia who was given TBI followed by a marrow infusion from each of six relatives.** The marrow of one of the relatives engrafted. While the patient eventually succumbed to an immunologic complication, initially called secondary disease and now known as GvHD, his leukemia remained in remission (GvHD could lead to eradication of leukemic cells= “**graft-versus-leukemia**” effect) (Barnes and Loutit from 1956).

**All human allogeneic marrow grafts in these early years failed, as meticulously documented in a paper from 1970 by Bortin. Of the 200 patients reported between 1957 and 1967, 73 were transplanted for AA, 115 for advanced and refractory hematologic malignancies, and 12 for immunodeficiency diseases. In the end, all 200 patients died, 125 with graft failure, 47 with GvHD, and others with infections or recurrence of their underlying malignancies.**

These early human transplants were performed before a full understanding of conditioning regimens and GvHD prevention was achieved, and before the discovery of the importance of histocompatibility matching for the outcome of marrow transplantation.

The early transplants were based on observations in inbred mice, for which MHC matching was not an absolute requirement. As a result of the complete failure of translating findings from mice to humans, most investigators abandoned the idea that allogeneic HCT could ever become a valuable asset in clinical medicine, and prominent immunologists doubted that the immunological barrier from one human to another could ever be crossed.

## Történelem

**Vissza a laboratóriumba:** Discouraged by the disastrous clinical results, most investigators left the field, declaring it a dead end. However, a few small laboratories in Europe and the United States persisted in systematic efforts to understand and overcome the perceived “insurmountable” obstacles encountered in early human marrow transplantation. Much of the work was carried out in large animals, including monkeys and dogs. An important paper published in **1968 showed that canine littermates matched for the MHC antigens by *in vitro* tissue typing had far better HCT outcomes than MHC-mismatched recipients.**

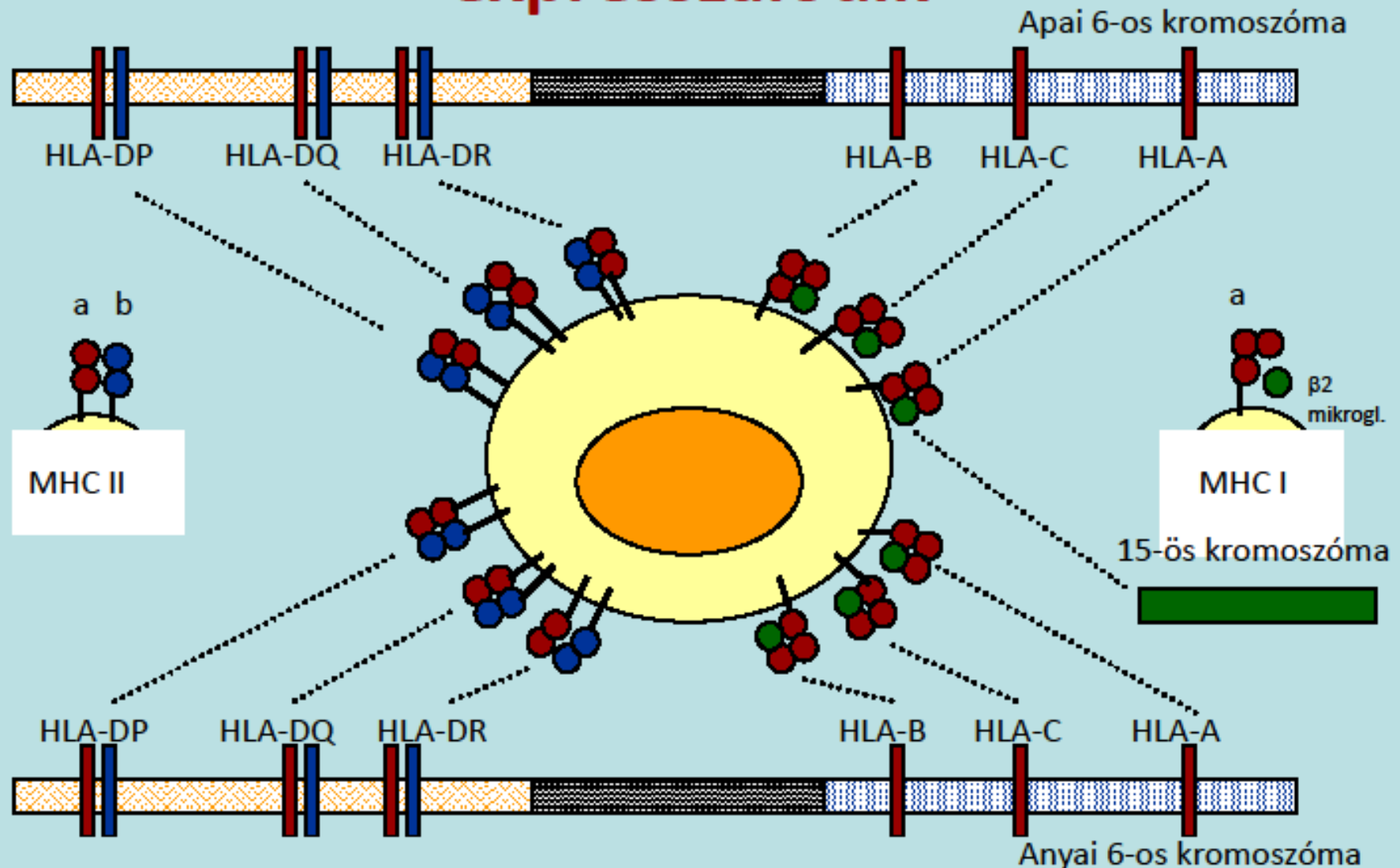
*In vitro* typing for the MHC, called HLA region in humans, H2 in mice, and DLA in dogs, was very primitive at the time and, moreover, the complexity of the MHC was not yet understood.

Typing consisted of serologic measurements using multi-specific antibodies collected from parous women or transfusion recipients in trypan blue exclusion or leuko-agglutination assays, combined with testing of donor and recipient lymphocytes for reactivity in a mixed leukocyte culture.

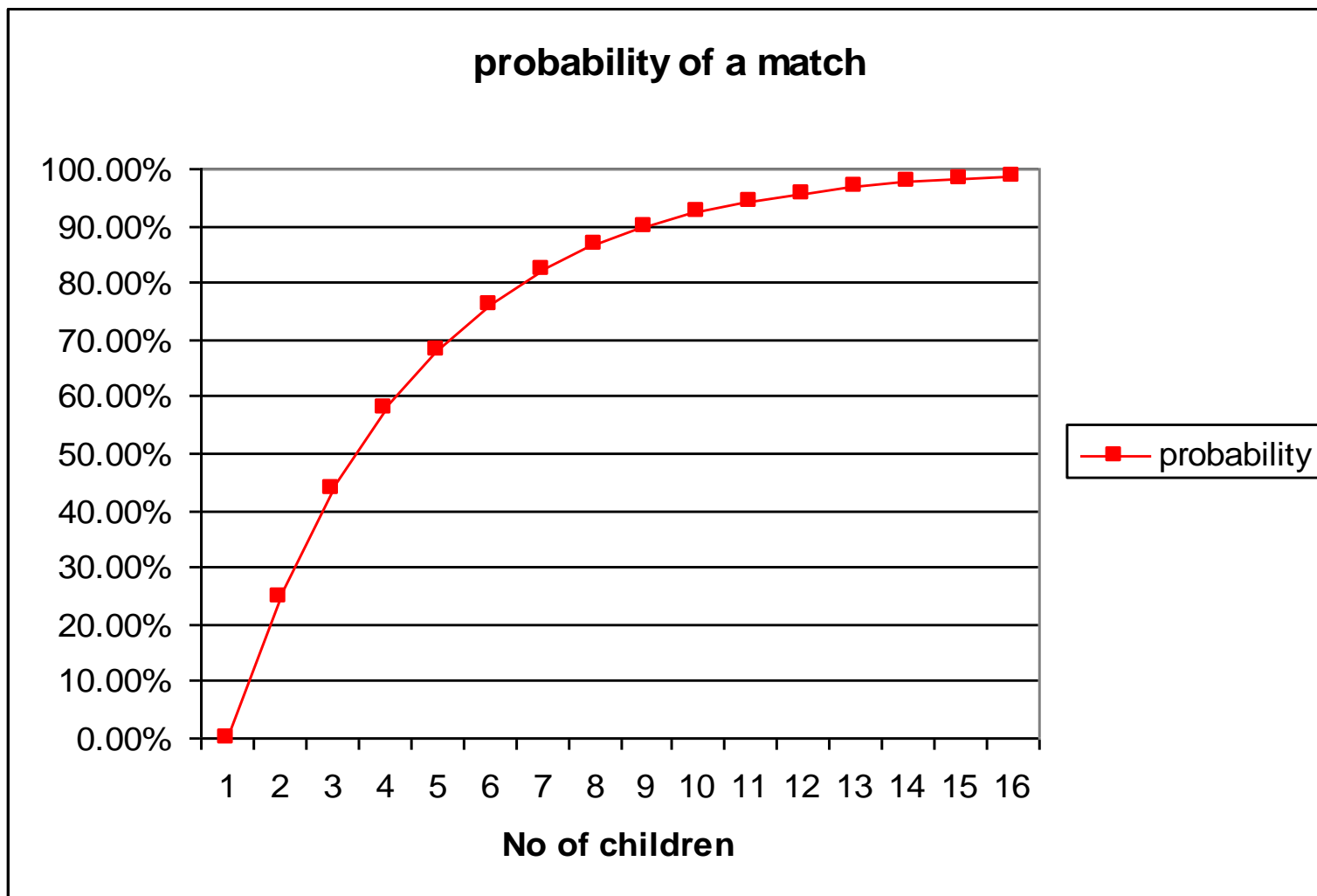
GvHD, either in acute, subacute or chronic form, developed in MHC-matched littermates, even though significantly later than in mismatched littermates.

This pointed out the need for investigating methods to prevent and control GvHD even in well-matched human donor-recipient combinations.

# A HLA gének terméke a sejtek felszínén kodominánsan jelenik meg



# Testvér donor valószínűsége



Probability =  $1 - (3/4)^{n-1}$  where n=number of children

## Történelem

### Vissza a laboratóriumba:

Studies of numerous **immunosuppressive agents** were conducted in a canine model that eventually led to identifying the antimetabolite methotrexate as the best drug for **GvHD prevention**.

By **balancing the drug's toxicities against its efficacy**, a regimen of intermittent **methotrexate** was established, with administration of the drug 1, 3, 6, and 11 days after transplantation and then weekly for at least 3 months. This regimen entered the clinic in 1969 and was used until the early 1980s.

Other research efforts focused on effective and tolerable conditioning regimens. In the beginning, single-dose TBI up to 10 Gray (Gy) was utilized. Extensive studies in canines revealed that delivering TBI in multiple fractions of 2 Gy each reduced damage to slow-responding tissues, such as liver, lung and others, while barely diminishing radiation effects on marrow and lymphoid tissues. Based on these studies, fractionating TBI has remained the standard.

Effective drug-based conditioning regimens were developed. Among those, cyclophosphamide has become the standard for patients with aplastic anemia since the drug had outstanding immunosuppressive qualities.

**Cyclophosphamide spared stem cells** and was not myeloablative, and so was not deemed suitable for conditioning patients with leukemia.

Another alkylating agent, busulfan, proved to be highly myeloablative but lacked the immunosuppressive qualities of cyclophosphamide or TBI. Prospective, randomized trials showed that busulfan was better tolerated than TBI and had equivalent efficacy to TBI for conditioning patients with myeloid malignancies, however, in order to ensure hematopoietic engraftment, busulfan needed to be combined with immunosuppressive drugs such as cyclophosphamide or fludarabine.

## Történelem

### Vissza a laboratóriumba:

Studies addressed **transfusion-induced sensitization to minor histocompatibility antigens**, which often resulted in marrow graft rejection among HLA-identical recipients with AA. Rejection rates in early transplants for AA ranged from 36% to 60%.

A more immunosuppressive conditioning regimen was developed that combined ATG with cyclophosphamide to minimize the risk of sensitization from transfusions.

Unlike in solid organ transplantation, **post-HCT immunosuppression was not required for the remainder of the patients' life** but could often be discontinued after 6 months. After 6 months, **donor-derived regulatory T cells** (“**suppressor T cells**”) were found in the peripheral blood, which were thought to enable and maintain a state of graft-*versus*-host tolerance; of note, these cells were absent in patients with chronic GvHD.

Successful grafts could be accomplished using hematopoietic cells derived from the peripheral blood in mice, dogs and baboons.

In later years, it was found that large numbers of these cells could be “mobilized” from the marrow into the **peripheral blood** (PBSC) with G-CSF).

## Történelem

### Vissza a laboratóriumba:

Since dogs share spontaneous blood disorders with humans, preclinical exploration of treating such diseases by allogeneic HCT was possible.

For example, dogs with SCID were cured by marrow transplants, as were dogs with severe hemolytic anemia due to pyruvate kinase deficiency.

The latter dogs had massive iron deposits in their inner organs from the severe hemolysis.

Long-term follow-up of transplanted dogs showed impressive resolution of iron deposits in the liver over time. This finding encouraged the first successful transplantation for multiply transfused human patients with **thalassemia major**.

Dogs with spontaneous NHL served to establish the value of autologous HCT in the treatment of this disease. Comparisons with results of allogeneic HCT confirmed the presence of **graft-versus-lymphoma** effects in dogs.

## Történelem

### Vissza a klinikára: 1960-1980

By 1968, the progress made in preclinical transplantation and the advances in the understanding of **HLA** set the stage for clinical trials to resume. In 1968/1969, three publications reported the first **successful marrow grafts for patients with primary immune deficiency disorders**.

During the subsequent years, most clinical transplants were performed in patients with advanced hematologic malignancies & SAA.

These early trials posed serious challenges not only in the field of transplantation biology but also in aspects of supportive care, especially infections and transfusion support. Therefore, these trials stimulated incredible progress in infectious disease and transfusion research.

Even though donors and recipients in nearly all early trials were HLA-identical siblings, and despite prophylaxis with methotrexate, GvHD occurred in almost half of the patients.

Major advances in **GvHD prevention and improvement in overall patient survival** were accomplished when, based on preclinical canine studies, **methotrexate** was combined with **calcineurin inhibitors** such as cyclosporine or tacrolimus (synergistic drug combinations).

## Történelem

### Vissza a klinikára: 1960-1980

**The first grading system for acute GvHD was described in 1974**, and the first effective treatment of acute GvHD with ATG was reported in the same year.

In those early years, ATG was not commercially available and the drug was produced in our laboratory by immunizing rabbits with human thymocytes.

Early results in patients with AA conditioned with cyclophosphamide showed **45%** long-term survival.

One reason for the disappointing findings was fatal GvHD. However, as predicted from canine studies, the most serious fatal complication was graft rejection due to sensitization through transfusions to minor histocompatibility antigens for which donors and recipients were disparate.

Changing transfusion support to leukocyte-depleted, *in vitro* irradiated platelet and red blood cell products reduced the risk of sensitization to minor antigens and, with it, the risk of graft rejection not only for patients with aplastic anemia but also those with hemoglobinopathies.

The newly developed cyclophosphamide/ATG regimen more effectively suppressed recipient immunity thereby enabling almost uniform marrow engraftment. The cumulative effects of these changes have resulted in **survivals** for patients with **AA** anemia given HLA-identical sibling marrow grafts ranging from **64% to 100%**.

## Történelem

### Vissza a klinikára: 1960-1980

All early transplantations for acute leukemia were performed in patients who were in refractory relapse. As a result, in addition to fatalities from GvHD, many patients died from post-transplantation relapse.

A decision in the mid-1970s to transplant patients earlier in the course of their disease, while the leukemia burden was low, reduced the relapse risk and led to a significant improvement in survival among patients with acute leukemias. Two pivotal publications from **1979 and 1981** in *The NEJM* described powerful **graft-versus-leukemia** effects associated with acute and chronic GvHD.

This work provided the rationale for the subsequent introduction of donor lymphocyte infusions in the 1990s to prevent or combat relapse after HCT. Some transplant centers focused on **removing T cells** from the marrow in order to reduce the risk of GvHD. However, initial studies showed unacceptably high incidences of mortality from graft rejection, disease relapse and infections.

## **Történelem**

### **Vissza a klinikára: 1960-1980**

When **T-cell depletion** was combined with high-intensity conditioning regimens before and careful monitoring after transplantation for recurrence of acute leukemia and prompt treatment by **DLIs**, outcomes were improved. This approach has remained an acceptable procedure in patients with acute leukemia.

In the **late 1980s**, **G-CSF-mobilized PBSC** were introduced for allogeneic transplants. Randomized, prospective trials showed marrow and PBSC to be equivalent as far as engraftment & OS were concerned. PBSC caused more chronic GvHD than marrow; because of this, marrow has remained the preferred source of stem cells for patients with non-malignant diseases such as aplastic anemia or hemoglobinopathies. PBSC continue to be the predominant graft source for patients with hematologic malignancies, in part due to donor preference.

## Történelem

### Vissza a klinikára: 1960-1980

One limitation in early allogeneic HCT was that only approximately **35%** of patients had **HLA-identical siblings** who could serve as marrow donors. In order to get around that limitation, and assisted by an increasing understanding of the genetics of the HLA region, along with improved HLA-typing techniques, registries were established in the 1980s that collected HLA data from unrelated volunteer donors, first in the UK with the Anthony Nolan Foundation, in the United States with the National Marrow Donor Registry, and then other national registries.

Early canine studies had already indicated the feasibility of “**matched**”, **unrelated HSCT**, and the first successful human transplant from an **HLA-matched unrelated donor was carried out in 1979 for a patient with ALL**.

Currently, HLA data from **more than 39 million** unrelated volunteers are accessible in the various national registries.

For Caucasian patients, the likelihood of finding an HLA-matched unrelated donor is approximately 80%; however, this percentage declines dramatically for patients from ethnic groups.

In order to provide potentially curative HCT for these otherwise unserved patients, transplant methods have been developed that use grafts either from unrelated UCB or from HLA-haploidentical relatives. This way donors can be found for 95% of transplant candidates regardless of age and ethnic background.

## Történelem

### Előre haladni: Az 1990-es évek

Over the past 25 years, more and more transplant centers have been established worldwide. In order to collect and analyze outcome data from the ever-increasing numbers of transplants, data registries have been set up, such as the EBMT & the Center for International Bone Marrow Transplant Research (CIBMTR). To date, information on 1.5 million HCT has been collected.

The 1990s saw many changes in the way transplantations have been carried out. Major advances in **infectious disease prevention and treatment** were made, including using acyclovir to prevent herpes simplex and varicella zoster virus reactivation, monitoring for CMV reactivation and, once reactivation occurred, preventing CMV disease with ganciclovir or foscarnet, preventing *Pneumocystis Jirovecii* infections with a synthetic antibacterial combination of sulfamethoxazole and trimethoprim, and introducing more effective anti-fungal agents and antibiotics.

Conditioning regimens were intensified to the upper limit of tolerability in order to optimize tumor cell kill; however, investigators began realizing that these intensive, myeloablative regimens, including cyclophosphamide/TBI or busulfan/cyclophosphamide were too toxic for elderly patients or for those with comorbid conditions (most hematologic malignancies happen to occur in older patients).

## Történelem

### Előre haladni: Az 1990-es évek

The problem was obvious when comparing the median ages of patients transplanted in those years at Fred Hutch (related grafts 40 years, and unrelated grafts 35 years) to the median patient age at diagnosis of the underlying hematologic malignancies (68 years). Most affected patients were excluded from transplantation.

In order to address this serious problem, and extend allogeneic HCT to include older or medically infirm patients, **less-intensive conditioning regimens** were introduced. These regimens shifted the burden of tumor kill from high-dose chemo-irradiation therapy toward graft *versus*- tumor effects. The regimens were facilitated by the development of a then new immunosuppressive agent, MMF, that blocked the *de novo* purine pathway needed for lymphocyte replication and worked in synergy with calcineurin inhibitors.

This synergistic drug combination was not only effective in preventing GvHD but, importantly, also enhanced hematopoietic engraftment. MMF also was synergistic with another agent, sirolimus, which reduced the sensitivity of T cells to interleukin-2 through mTor inhibition.

Combinations of these agents are now commonly used after allogeneic HCT, leading to relatively low and acceptable risk of non-relapse mortality (NRM).

# Történelem

## A 21. század:

The early years of the 21<sup>st</sup> century saw tremendous growth in allogeneic HCT, in part because of NMA or RIC conditioning regimens, which enabled extending allogeneic HCT to include older patients, and, in part, the growth was due to increased use of grafts from alternative donors, including **unrelated cord blood** (UCB) and **HLA-haploidentical relatives**.

Progress has been made in **GvHD prevention** among unrelated recipients. A recently published randomized, prospective phase III trial compared a commonly used drug combination of MMF and cyclosporine to a triple-drug regimen of MMF, cyclosporine, and sirolimus. Patients on the triple drug arm had a significant reduction in overall acute GvHD, and acute grade III-IV GvHD was seen in only 2% of patients. This resulted in a significant improvement in overall survival.

Another recent development has been the US FDA approval of ruxolitinib, a JAK2 inhibitor for the treatment of steroid-refractory acute GvHD. The approval was prompted by the favorable outcome of the single-arm, phase II REACH 1 (Research Evaluation and Commercialization Hub) study.

**Extracorporeal photopheresis** (ECP) has been used as an off-label second-line treatment for cutaneous manifestations of steroid-refractory acute and chronic GvHD since the early 2000s, with variable success. The introduction of the HCT comorbidity index (HCT-CI) in 2005 facilitated comparisons of results between centers worldwide, and has served as an important decision-making tool for choosing appropriate transplant regimens.

Serum biomarkers derived from the GIT, specifically ST2 and REG-3, have emerged as an additional method of predicting acute GvHD severity, as presented in a recent Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial. The application of this tool may enable tailored GvHD treatment and prediction of NRM.

## Történelem

### A 21. század:

**Minimal-intensity or RIC regimens:** One publication from 2013 reported outcomes in nearly 1,100 elderly or medically infirm patients with advanced hematologic malignancies who were given HLA-matched related or unrelated grafts after minimal-intensity conditioning with fludarabine and low-dose (2-3 Gy) TBI.

The oldest patients in that trial were 75 years of age. Half of the patients had serious comorbidities with HCT Comorbidity Index scores  $\geq 3$ . These transplants were designed as an outpatient procedure. Nearly half of the patients were never hospitalized while the remaining half had a median hospital stay of only 6 days. Living at home or in a private apartment and being able to move around freely were appreciated by patients and caregivers.

At a median follow-up of 5 yrs, depending on the relapse risk of the underlying malignancies and on the comorbidity score, lasting remissions were seen in 45-75% of patients and 5-yr survivals ranged from 25% to 60%. Overall 5-year NRM was 24%, for the most part associated with concurrent or preceding GvHD, and the overall relapse mortality was 34.5%. With the introduction of the triple-drug regimen of MMF, cyclosporine and sirolimus, the NRM has significantly declined among unrelated recipients.

## Történelem

### A jelenlegi trendek:

Early HCT involved grafts from HLA-identical sibling donors, from 2006 on unrelated donors became the most frequently used graft source in the USA with almost 4,500 transplants in 2018 alone.

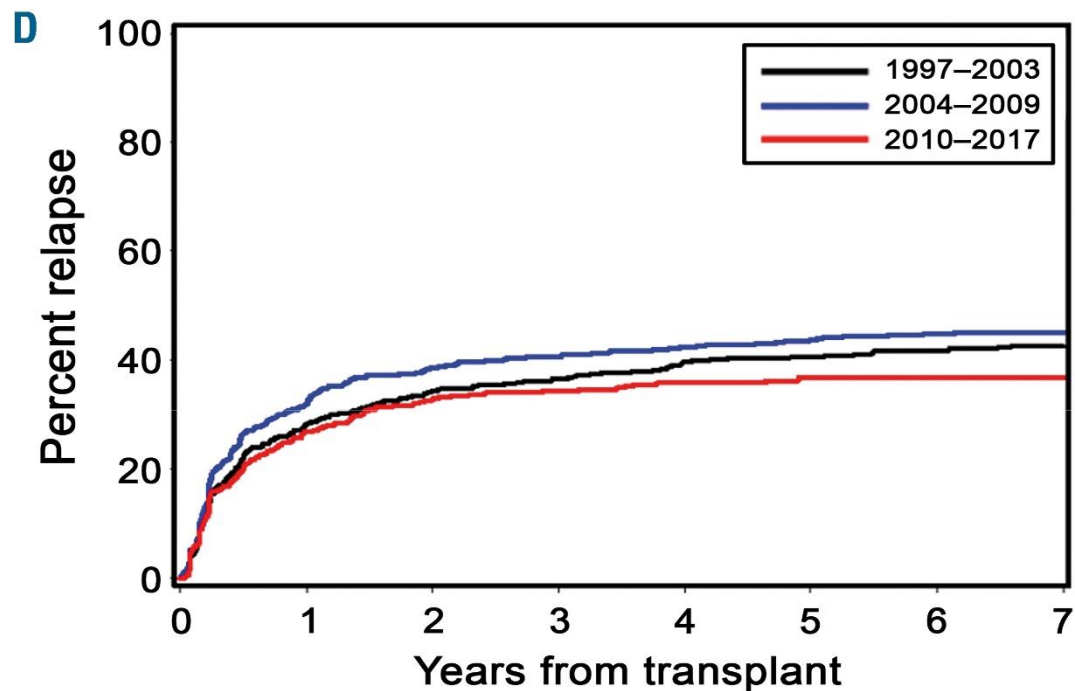
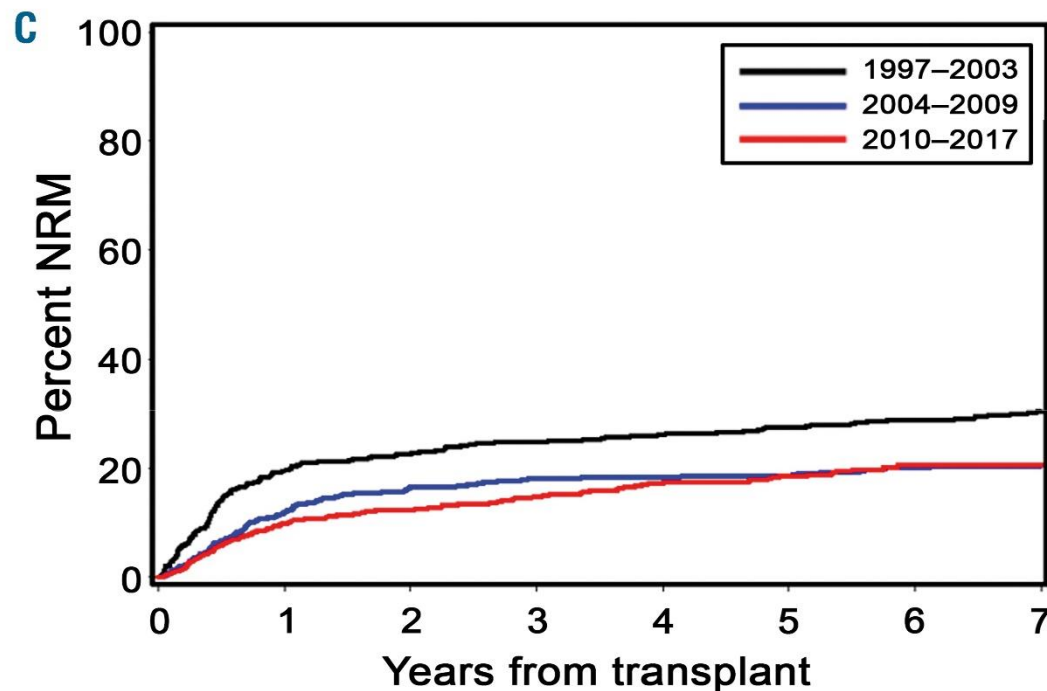
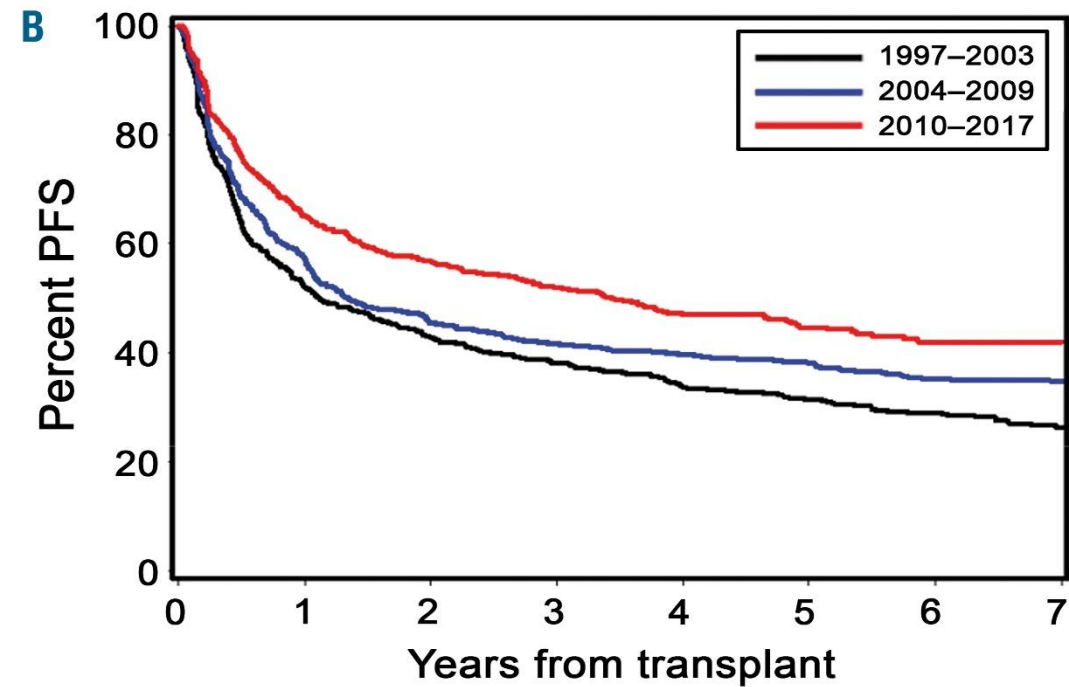
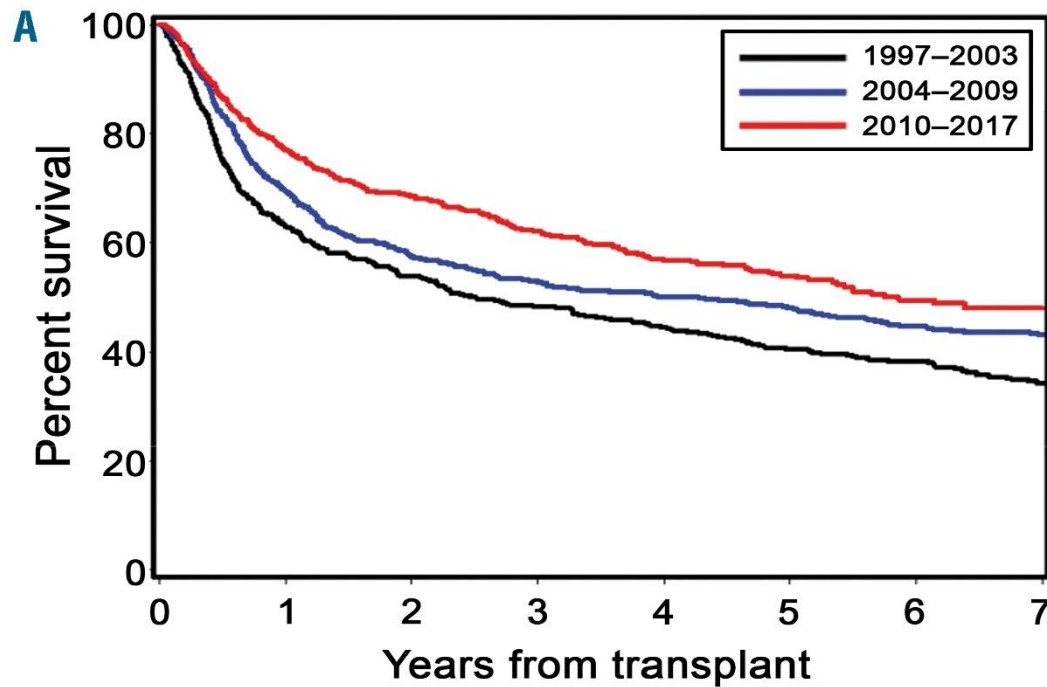
This increase could be attributed to: (i) the ever-larger number of unrelated, HLA-typed volunteers in the registries; (ii) advances in HLA-typing including the recognition of the importance of HLA-DPB1 expression for the development of GVHD; and (iii) increasing age of patients whose siblings were also older and often unfit to donate because of comorbidities.

A rise in the use of UCB during the early 2000s has been offset and reversed by the remarkable increase in HLA-haploidentical, related grafts after the introduction of **post-transplant cyclophosphamide for GvHD prevention**.

Post-HCT cyclophosphamide served to cause *in vivo* depletion of both donor-*versus*-host reactive T cells (GvHD prevention) and host-*versus*-donor T cells & NK cells (prevention of graft rejection).

An alternative regimen for HLA-haploidentical grafts has been reported by Chinese investigators. They conditioned patients by busulfan, cyclophosphamide, ME-CCNU and ATG and combined cyclosporine, MMF and a short course of methotrexate for GvHD prevention and reported favorable outcomes.

Improved outcomes of allogeneic hematopoietic cell transplantation with non-myeloablative conditioning for older and medically infirm patients with hematologic malignancies over two decades at Fred Hutchinson Cancer Research Center (WA, USA)



## **Történelem**

### **Jövőbeli irányok:**

For allogeneic HCT to become an even more relevant treatment modality, advances must be made in mitigating 3 major interrelated problems:

- 1. regimen-related toxicities,**
- 2. post-HCT relapse,**
- 3. cGvHD.**

Younger patients have traditionally received systemic, high-intensity conditioning regimens for maximal tumor cell kill before HCT & reducing the risk of relapse after HCT. Regimen intensity seems to be especially important for patients with AML. A recent, retrospective analysis of outcomes for patients with AML showed a clear advantage of MAC regimens in patients without MRD over RIC or NMA regimens both with respect to relapse and survival (this benefit was not seen in patients with MRD). Minimizing the systemic regimen intensity would markedly reduce the risks of shortand long-term toxicities, including secondary cancers. For this to become reality, the problem of post-HCT relapse needs to be harnessed. This could be accomplished by: (i) increasing graft-*versus*-tumor effects after HCT; (ii) reducing the tumor burden before HCT through adding targeted radioimmunotherapy with few off-target effects to low-intensity conditioning regimens; and (iii) administering maintenance therapy after HCT.

# Történelem

## Jövőbeli irányok:

Apart from relapse, cGvHD has remained the most challenging complication of allogeneic HCT.

The conundrum of preventing chronic GvHD while not sacrificing graft-*versus*-tumor effects has, as yet, not been satisfactorily resolved: global *in vivo* T-cell depletion with ATG or *in vitro* depletion of naïve T cells from the graft, have used high-intensity, MAC regimens to control post-HCT relapse, but this comes at the cost of regimen-related sequelae.

Therapies targeting alloreactive T cells, alloreactive and autoreactive B cells through direct depletion from stem cell grafts (e.g., post-transplantation cyclophosphamide, CD34 selection, IL-2 and IL-17 therapy), *in vivo* depletion (antiCD20 MoAbs), and signal inhibition (e.g., ITK, JAK 1/2, ROCK-II, BTK, SYK inhibition).

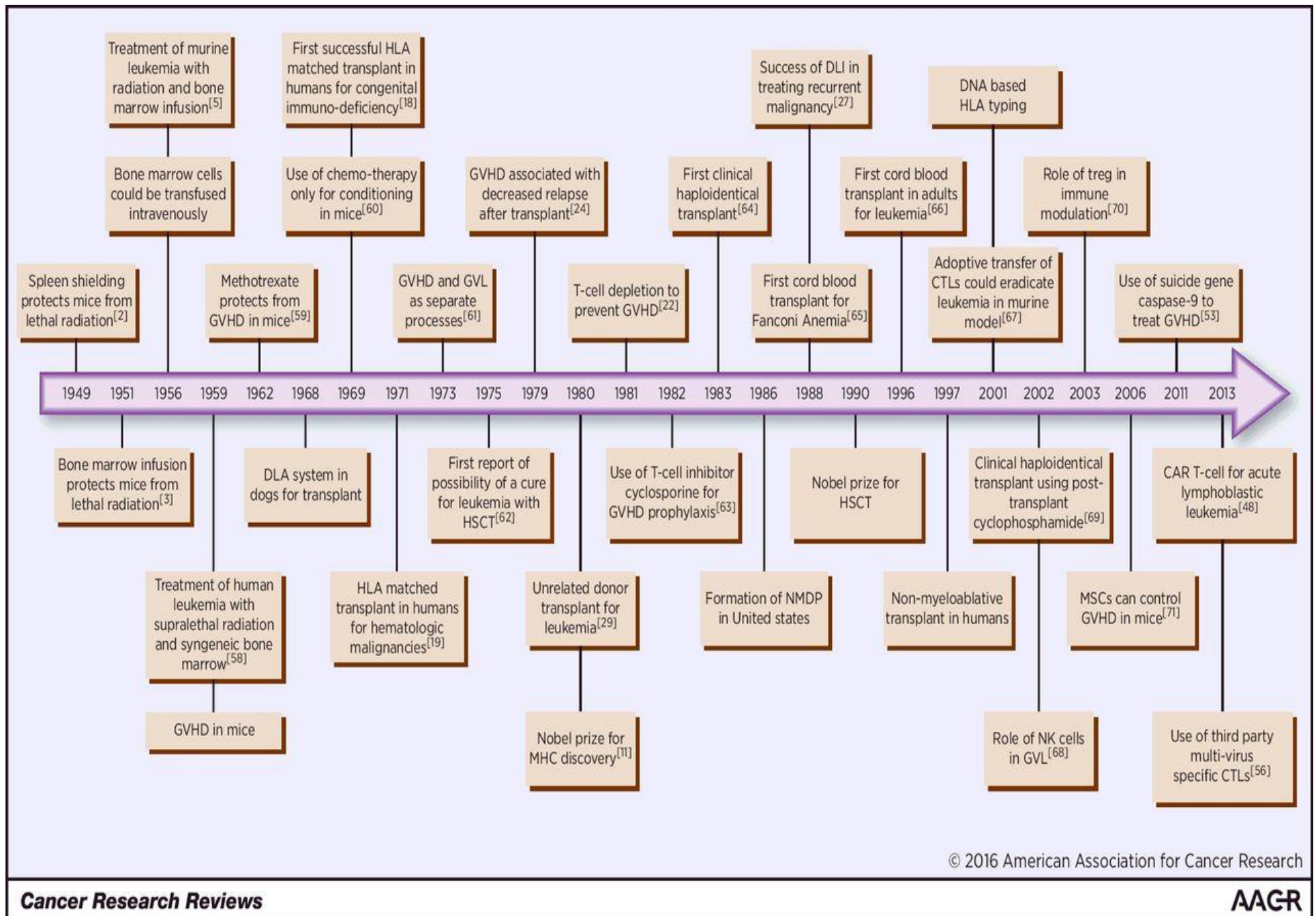
No single method is unequivocally effective.

Novel therapies focus on **adoptive transfer and expansion of regulatory T cells (Tregs) to prevent and treat chronic GvHD** through administration of low-dose IL-2 and T Tregs sparing therapy, e.g.; removal of naïve T cells from the graft has shown encouraging results for GvHD prevention in younger patients with high-risk leukemia.

These patients were conditioned with a very intensive conditioning regimen consisting of fludarabine, thiotepa and 13.2 Gy TBI. This approach reduced rates of chronic GvHD (9% at 2 years) while preserving immune reconstitution, without increasing relapse or NRM, though observation periods are still short.

Avoiding GvHD without compromising graft-*versus*-leukemia effects in HLA-haploidentical transplants by co-infusion of donor-derived Tregs & conventional T cells, and infusion of NK cells after transplantation, selective depletion of B cells & T cells by removal of CD45RA<sup>+</sup> or /<sup>+</sup> cells from the graft.

# Milestones in the field of allogeneic transplant.



## Timeline of list of notable events throughout the years

Year	Event
1949-1955	Evidence of hematopoietic cell recovery after exposure to lethal radiation <sup>2-6</sup>
1956	Bone marrow transplant induces graft- <i>versus</i> -host immune response (GvHD) <sup>10</sup>
1957	First human bone marrow transplantation <sup>8,153</sup>
1958	Major histocompatibility complex discovered: human leukocyte antigen (HLA) <sup>13,15,16,154,155</sup>
1958-1969	Major preparative regimens developed: total body irradiation (TBI), cyclophosphamide, busulfan <sup>156-160</sup>
1958-1970	Methotrexate for control GvHD in animal models <sup>19,161-163</sup>
1968	First allogeneic transplants for primary immunodeficiencies <sup>34-36</sup>
1971	First successful transplant for end-stage leukemia <sup>164</sup>
1972-1974	First allogeneic transplants for aplastic anemia, PNH and Fanconi anemia <sup>44,45</sup>
1973	GvHD and graft- <i>versus</i> -leukemia effects are separate reactions <sup>9,165</sup>
1974	Acute grading system and first effective treatment of acute GvHD <sup>42,43</sup>
1974	The first bone marrow donor registry was established by the Anthony Nolan Foundation
1975	Transplantation earlier in the course of leukemia <sup>27</sup>
1979-1981	Establishing graft- <i>versus</i> -leukemia effect in human patients <sup>56,57</sup>
1980	First successful unrelated HLA-matched transplant in acute leukemia patient <sup>67</sup>
1981	Establishment of conditioning regimen for non-malignant diseases leading to successful full immune reconstitution <sup>166</sup>
1981	First successful treatment of chronic GvHD with immunosuppression combination <sup>167</sup>
1981	Introduction of the concept of fractionated total body irradiation <sup>20</sup>
1981	Introduction of acyclovir for HSV and VZV prophylaxis <sup>79</sup>
1982	First successful transplant for thalassemia major <sup>33</sup>
1983	Busulfan-cyclophosphamide conditioning for acute myeloid leukemia <sup>23</sup>
1986	Establishment of the National Marrow Donor Program in the USA
1986	More effective acute GvHD prophylaxis with a combination of methotrexate and cyclosporine or tacrolimus <sup>40</sup>
1987-1993	HLA class I and HLA class II structures are defined, and HLA-typing transitions from cellular to DNA based <sup>62-64</sup>
1988	Standard treatment of chronic GvHD established; prednisone, cyclosporine <sup>168,169</sup>
1991	Early treatment with ganciclovir after allogeneic HCT to prevent CMV disease <sup>77</sup>
1995	Use of peripheral blood stem cells mobilized with granulocyte colony stimulating factor (G-CSF) <sup>30,31,170</sup>
1995	Donor lymphocyte infusions for disease relapse <sup>58,59</sup>
1997	Umbilical cord blood as an alternative source of hematopoietic cells <sup>101</sup>
1998	Impact of matching for class II HLA-DRB1, HLA-DQB1 and class I HLA-C <sup>171</sup>
1997-2001	Less toxic conditioning regimens expand allogeneic transplant for older patients <sup>172-176</sup>
1998	CMV monitoring assays <sup>177</sup>
1983-2005	HLA-haploidentical related grafts for severe combined immunodeficiency and leukemia patients <sup>178-181</sup>
2001	BMT CTN established
2002	Dramatic reduction in liver GvHD with ursodeoxycholic acid <sup>195</sup>
2005-2012	Novel antibacterial and antifungals improve transplantation outcomes <sup>74-76,78</sup>
2008	Improved outcomes of HLA-haploidentical transplants with post-transplant cyclophosphamide <sup>100</sup>
2009	More judicious dosing of systemic glucocorticoids for treatment of acute GvHD <sup>96,97</sup>
2012	Same outcomes with PBSC <i>versus</i> bone marrow from unrelated donors, and less chronic GvHD with bone marrow <sup>182</sup>
2014	Addition of sirolimus for control of GvHD <sup>83-85</sup>
2015	Introduction of novel therapies <sup>149,150</sup>
2017	Novel CMV prophylaxis with letermovir <sup>126</sup>
2018	Ruxolitinib for treatment of steroid-refractory acute GvHD <sup>87</sup>
2019-2020	Improved outcomes of aplastic anemia patients with HLA-haploidentical transplants <sup>123,124</sup>
2018-2020	CAR-T cell therapy as a 'bridge' to allogeneic HCT <sup>113-115</sup>

BMT CTN: The Blood and Marrow Transplant Clinical Trials Network; CAR T-cell: chimeric antigen receptor T-cell; CMV: cytomegalovirus; G-CSF: granulocyte-colony stimulating factor; GvHD: graft-*versus*-host disease; HCT: hematopoietic cell transplantation; HSV: herpes simplex virus; PBSC: peripheral blood stem cell; PNH: paroxysmal nocturnal hemoglobinuria; VZV: varicella zoster virus.

# ASTCT Definitions for Classifying Indications for HCT and IECT

Classification of Indication	Definition
Standard of care (S)	This category includes indications that are well defined and are generally supported by evidence in the form of high-quality clinical trials and/or observational studies (eg, through CIBMTR or European Society for Blood and Marrow Transplantation).
Standard of care, clinical evidence available (C)	This category includes indications for which large clinical trials and observational studies are not available. However, HCT/IECT has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single-center or multicenter cohort studies. HCT/IECT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits. As more evidence becomes available, some indications may be reclassified as “Standard of care.”
Standard of care, rare indication (R)	Indications included in this category are rare diseases for which clinical trials and observational studies with sufficient number of patients are not currently feasible because of their very low incidence. However, single-center or multicenter or registry studies in relatively small cohorts of patients have shown HCT/IECT to be effective treatment with acceptable risks of morbidity and mortality. For patients with diseases in this category, HCT/IECT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits.
Developmental (D)	Developmental indications include diseases where preclinical and/or early-phase clinical studies show HCT/IECT to be a promising treatment option. HCT/IECT is best pursued for these indications as part of a clinical trial. As more evidence becomes available, some indications may be reclassified as “Standard of care, clinical evidence available” or “Standard of care.”
Not generally recommended (N)	HCT/IECT is currently not recommended for these indications where evidence do not support the routine use. However, this recommendation does not preclude investigation of HCT/IECT as a potential treatment and may be pursued for these indications within the context of a clinical trial.

# Indications for IECT

IECT Category	Indication and Disease Status for Cellular Therapy	Pediatric	Adult
CAR-T therapy	ALL		
	Primary refractory, resistant (after 2 lines of therapy)	S <sup>†</sup>	S <sup>†</sup>
	Beyond second relapse	S <sup>†</sup>	S <sup>†</sup>
CAR-T therapy	Diffuse large B cell lymphoma/primary mediastinal B cell lymphoma		
	Primary refractory, resistant (after 2 lines of therapy)	NA	S
	First relapse, resistant	NA	S
	Beyond second relapse	NA	S
	Relapse after autologous transplant	NA	S
CAR-T therapy	High-grade B cell lymphoma, with <i>MYC</i> and <i>BCL2</i> and/or <i>BCL6</i> rearrangements		Abraham S. Kanate et al. <a href="https://doi.org/10.1016/j.bbmt.2020.03.002">https://doi.org/10.1016/j.bbmt.2020.03.002</a>
	Primary refractory, resistant (after 2 lines of therapy)	NA	S
	First relapse, resistant	NA	S
	Beyond second relapse	NA	S
	Relapse after autologous transplant	NA	S
CAR-T therapy	Follicular lymphoma		
	Transformation to large B cell lymphoma (beyond second relapse)	NA	S

Indications for HCT in Pediatric Patients (Generally Age < 18 Years)

Indication and Disease Status	Allogeneic HCT	Autologous HCT
Acute myeloid leukemia		
CR1, low risk	N	N
CR1, intermediate risk	C	N
CR1, high risk	S	N
CR2+	S	N
Not in remission	S	N
Acute promyelocytic leukemia, relapse	R	R
ALL		Abraham S. Kanate et al. <a href="https://doi.org/10.1016/j.bbmt.2020.03.002">https://doi.org/10.1016/j.bbmt.2020.03.002</a>
CR1, standard risk	N	N
CR1, high risk	S	N
CR2	S	N
CR3+	C	N
Not in remission	C*	N
Chronic myeloid leukemia		
Chronic phase	C	N
Accelerated phase	C	N
Blast phase	C	N

Indications for HCT in Pediatric Patients (Generally Age < 18 Years)

Myelodysplastic syndromes		
Low risk	C	N
High risk	S	N
Juvenile myelomonocytic leukemia	S	N
Therapy related	S	N
T cell non-Hodgkin lymphoma		
CR1, standard risk	N	R
CR1, high risk	R	R
CR2	S	C
CR3+	C	C
Not in remission	C	N
Burkitt lymphoma		
First remission	N	N
First or greater relapse, sensitive	C	C
First or greater relapse, resistant	C	N
Hodgkin lymphoma		
CR1	N	N
Primary refractory, sensitive	N	C
Primary refractory, resistant	C	N
First relapse, sensitive	N	S
First relapse, resistant	C	N
Second or greater relapse	C	C
Solid tumors		
Germ cell tumor, relapse	D	C
Germ cell tumor, refractory	D	C
Ewing sarcoma, high risk or relapse	D	S
Soft tissue sarcoma, high risk or relapse	D	D
Neuroblastoma, high risk or relapse	D	S†
Wilms tumor, relapse	N	C
Osteosarcoma, high risk	N	C
Medulloblastoma, high risk	N	C
Other malignant brain tumors	N	C

Abraham S. Kanate et al. <https://doi.org/10.1016/j.bbmt.2020.03.002>

Indications for HCT in Pediatric Patients (Generally Age < 18 Years)

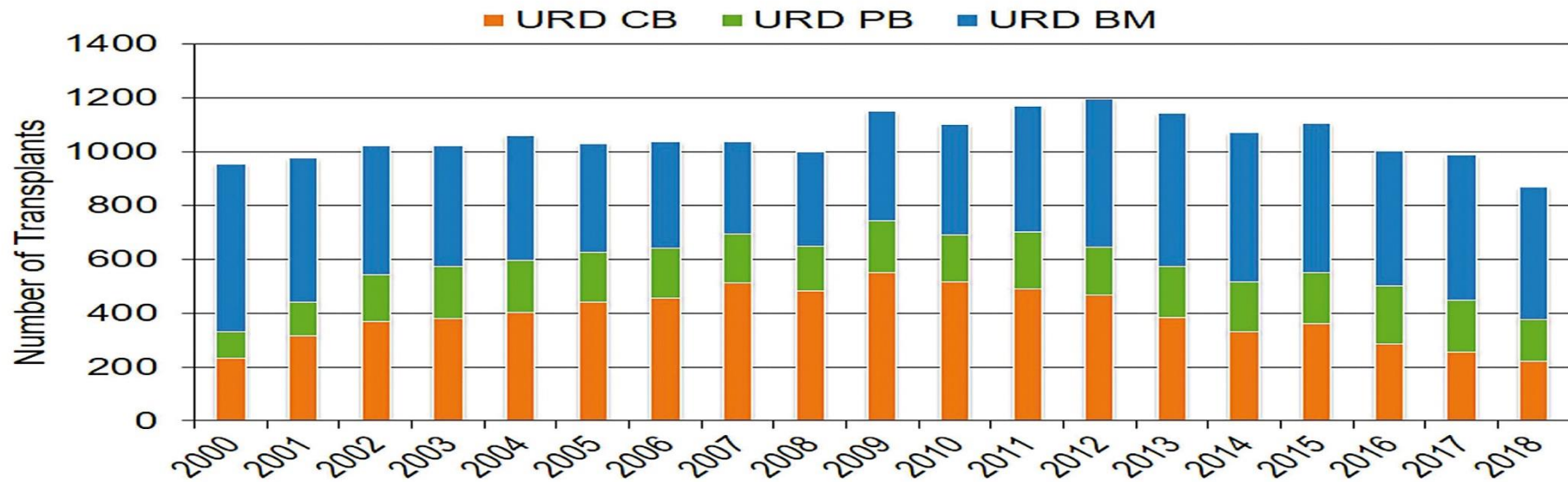
Nonmalignant diseases		
Severe aplastic anemia, new diagnosis	S	N
Severe aplastic anemia, relapse/refractory	S	N
Fanconi anemia	R	N
Other bone marrow failure syndrome <sup>‡</sup>	R	N
Sickle cell disease	C	N
Thalassemia	S	N
Congenital amegakaryocytic thrombocytopenia	R	N
SCID	R	N
T cell immunodeficiency, SCID variants	R	N
Wiskott-Aldrich syndrome	R	N
Hemophagocytic disorders	S	N
Severe congenital neutropenia	R	N
Chronic granulomatous disease	R	N
Other phagocytic cell disorders	R	N
IPEX syndrome	R	N
Juvenile rheumatoid arthritis	D	R
Systemic sclerosis	D	R

Abraham S. Kanate et al. <https://doi.org/10.1016/j.bbmt.2020.03.002>

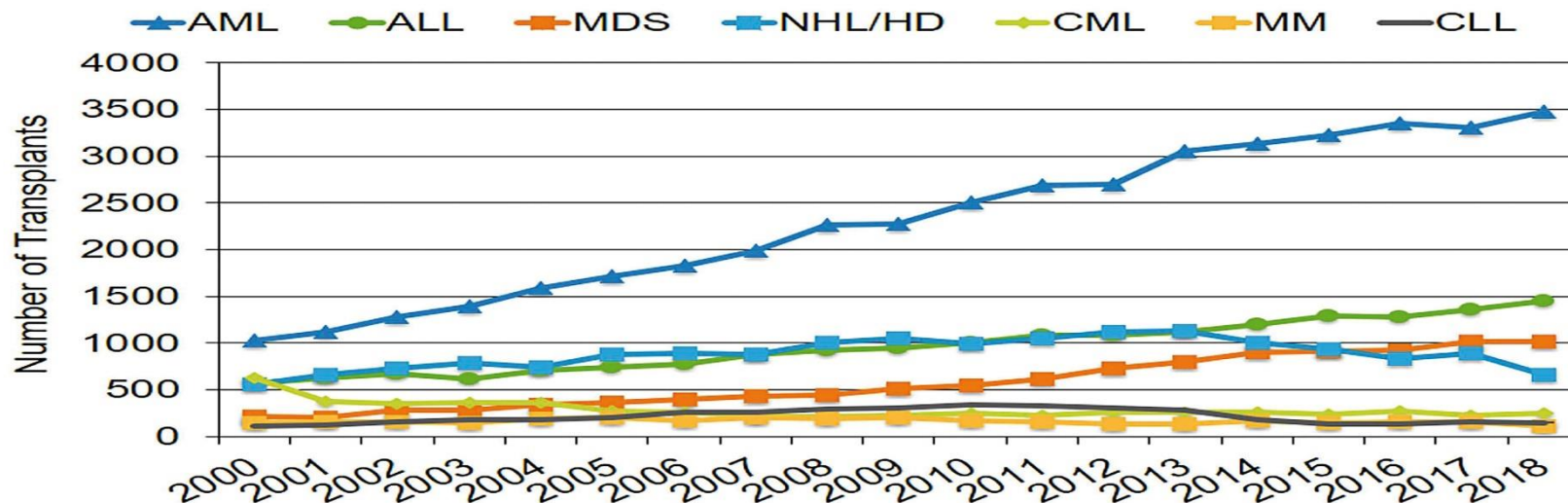
Indications for HCT in Pediatric Patients (Generally Age < 18 Years)

Other autoimmune and immune dysregulation disorders	R	N
Mucopolysaccharidosis I (severe; Hurler syndrome)	R	N
Other mucopolysaccharidoses (II, IV, VI)	D	N
Other lysosomal metabolic diseases	D	N
Osteopetrosis (severe, recessive)	R	N
Osteopetrosis (intermediate)	D	Abraham S. Kanate et al. <a href="https://doi.org/10.1016/j.bbmt.2020.03.002">https://doi.org/10.1016/j.bbmt.2020.03.002</a>
Globoid cell leukodystrophy	R	N
Metachromatic leukodystrophy	R	N
Cerebral X-linked adrenoleukodystrophy	R	N

## A Unrelated Donor Allogeneic HCT in Patients <18 Years

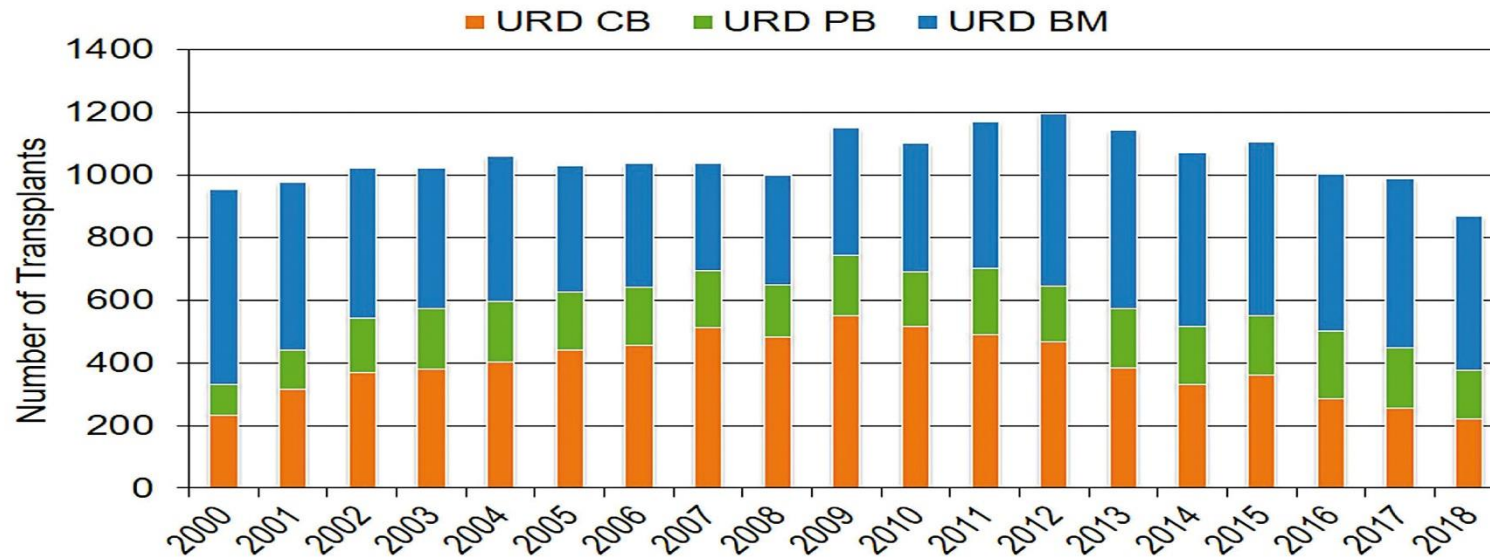


## B Selected Disease Trends for Allogeneic HCT in the US



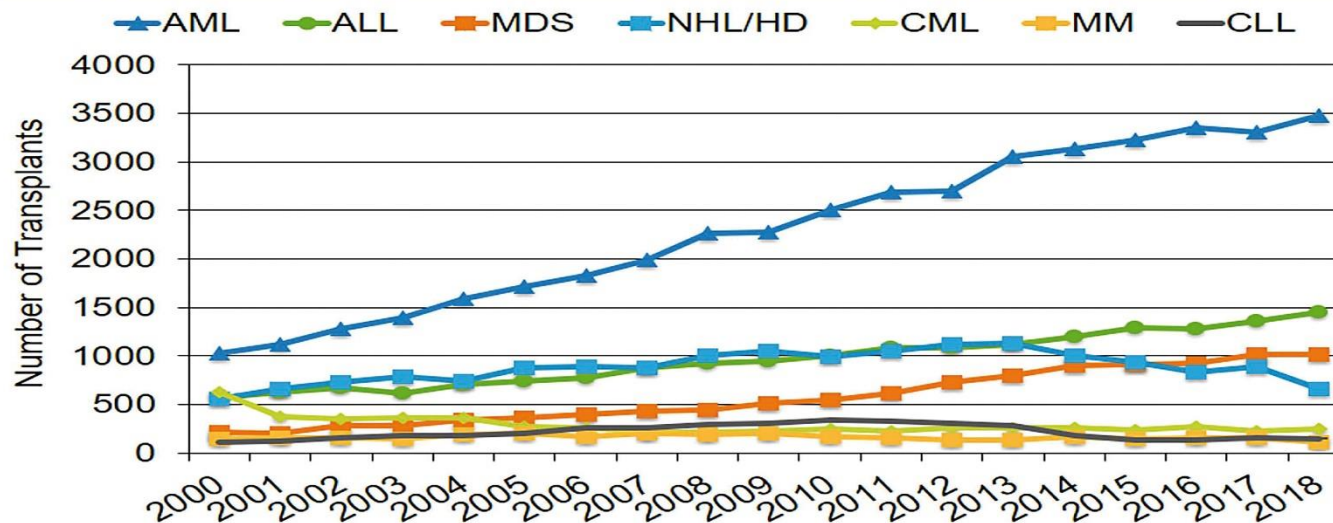
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## Unrelated Donor Allogeneic HCT in Patients <18 Years



B

## Selected Disease Trends for Allogeneic HCT in the US



# Indications for HCT in Adults (Generally Age ≥ 18 Years)

Indication and Disease Status	Allogeneic HCT	Autologous HCT
Acute myeloid leukemia		
CR1, low risk	N	C
CR1, intermediate risk	S	C
CR1, high risk	S	N
CR2	S	C
CR3+	S	N
Not in remission	S	N
Acute promyelocytic leukemia		
CR1	N	N
CR2, molecular remission	C	S
CR2, not in molecular remission	S	N
CR3+	C	N
Not in remission	C	N
Relapse after autologous transplant	C	N
Acute lymphoblastic leukemia		Abraham S. Kanate et al. <a href="https://doi.org/10.1016/j.bbmt.2020.03.002">https://doi.org/10.1016/j.bbmt.2020.03.002</a>
CR1, standard risk	S	N
CR1, high risk	S	N
CR2	S	N
CR3+	S	N
Not in remission	S*	N
Chronic myeloid leukemia		
Chronic phase 1, TKI intolerant	C	N
Chronic phase 1, TKI refractory	C	N
Chronic phase 2+	S	N
Accelerated phase	S	N
Blast phase	S	N
Myelodysplastic syndromes		
Low/intermediate-1 risk	C	N
Intermediate-2/high risk	S	N
Therapy-related acute myeloid leukemia/ myelodysplastic syndromes		
CR1	S	N
Myelofibrosis and myeloproliferative diseases		
Primary, low risk	C	N
Primary, intermediate/high risk	C	N
Secondary	C	N
Hypereosinophilic syndromes, refractory	R	N

Indications for HCT in Adults (Generally Age ≥ 18 Years)

Miscellaneous		
Systemic mastocytosis	R	N
Blastic plasmacytoid dendritic cell neoplasm	R	R
Plasma cell disorders		
Myeloma, initial response	D	S
Myeloma, sensitive relapse	S	S
Myeloma, refractory	C	C
Plasma cell leukemia	S	C
Amyloid light-chain amyloidosis	N	S
POEMS syndrome	N	C
Relapse after autologous transplant	C	C
Hodgkin lymphoma		Abraham S. Kanate et al. <a href="https://doi.org/10.1016/j.bbmt.2020.03.002">https://doi.org/10.1016/j.bbmt.2020.03.002</a>
CR1 (positron emission tomography negative)	N	N
Primary refractory, sensitive	C	S
Primary refractory, resistant	C	N
First relapse, sensitive	S	S
First relapse, resistant	C	N
Second or greater relapse	S	S
Relapse after autologous transplant	S	N

Indications for HCT in Adults (Generally Age ≥ 18 Years)

Diffuse large B cell lymphoma		
CR1 (positron emission tomography negative)	N	N
Primary refractory, sensitive	S	S
Primary refractory, resistant	S	N
First relapse, sensitive	S	S
First relapse, resistant	S	N
Second or greater relapse	S	S
Relapse after autologous transplant	S	N
High-grade B cell lymphoma, with <i>MYC</i> and <i>BCL2</i> and/or <i>BCL6</i> rearrangements		Abraham S. Kanate et al. <a href="https://doi.org/10.1016/j.bbmt.2020.03.002">https://doi.org/10.1016/j.bbmt.2020.03.002</a>
CR1 (positron emission tomography negative)	N	C
Primary refractory, sensitive	R	C
Primary refractory, resistant	R	N
First relapse, sensitive	R	C
First relapse, resistant	R	N
Second or greater relapse	R	C
Relapse after autologous transplant	R	N

## Indications for HCT in Adults (Generally Age ≥ 18 Years)

Primary central nervous system lymphoma		
CR1/first partial remission (consolidation)	N	C
Relapse, sensitive	N	C
Follicular lymphoma		
CR1	N	N
Primary refractory, sensitive	N	S
Primary refractory, resistant	S	N
First relapse, sensitive (including POD24)	N	S
First relapse, resistant	S	N
Second or greater relapse	S	S
Transformation to high grade lymphoma	C	S
Relapse after autologous transplant	S	N
Mantle cell lymphoma		Abraham S. Kanate et al. <a href="https://doi.org/10.1016/j.bbmt.2020.03.002">https://doi.org/10.1016/j.bbmt.2020.03.002</a>
CR1/first partial remission	C	S
Primary refractory, sensitive	S	S
Primary refractory, resistant	C	N
First relapse, sensitive	S	S
First relapse, resistant	C	N
Second or greater relapse	S	S
Relapse after autologous transplant	S	N

**Indications for HCT in Adults (Generally Age ≥ 18 Years)**

T cell lymphoma		
CR1/first partial remission	S	S
Primary refractory, sensitive	S	S
Primary refractory, resistant	C	N
First relapse, sensitive	S	S
First relapse, resistant	C	N
Second or greater relapse	S	C
Relapse after autologous transplant	S	N
Lymphoplasmacytic lymphoma/ Waldenstrom macroglobulinemia		Abraham S. Kanate et al. <a href="https://doi.org/10.1016/j.bbmt.2020.03.002">https://doi.org/10.1016/j.bbmt.2020.03.002</a>
CR1	N	N
Primary refractory, sensitive	N	C
Primary refractory, resistant	R	N
First or greater relapse, sensitive	C	S
First or greater relapse, resistant	R	N
Relapse after autologous transplant	C	N
Burkitt lymphoma		
CR1	N	N
First or greater relapse, sensitive	C	C
First or greater relapse, resistant	C	N
Relapse after autologous transplant	C	N
Cutaneous T cell lymphoma		
Relapse	S	C

# Indications for HCT in Adults (Generally Age ≥ 18 Years)

Plasmablastic lymphoma		
CR1	R	R
Relapse	R	C
Chronic lymphocytic leukemia		
High risk, first or greater remission	S	N
T cell prolymphocytic leukemia	S	R
B cell, prolymphocytic leukemia	R	R
Transformation to high-grade lymphoma	C	S
Hairy cell leukemia		Abraham S. Kanate et al. <a href="https://doi.org/10.1016/j.bbmt.2020.03.002">https://doi.org/10.1016/j.bbmt.2020.03.002</a>
First remission	N	N
Second remission	N	N
≥Third remission or refractory disease	R	N
Solid tumors		
Germ cell tumor, relapse	N	S
Germ cell tumor, refractory	N	S
Ewing's sarcoma, high risk	D	C
Breast cancer, adjuvant high risk	N	N
Breast cancer, metastatic	D	N
Renal cancer, metastatic	D	N

# Indications for HCT in Adults (Generally Age ≥ 18 Years)

Nonmalignant diseases		
Severe aplastic anemia, new diagnosis	S	N
Severe aplastic anemia, relapse/ refractory	S	N
Fanconi anemia	R	N
Dyskeratosis congenita	R	N
Sickle cell disease	S	N
Thalassemia	D	N
Hemophagocytic syndromes, refractory	S	N
Common variable immunodeficiency	R	N
Wiskott-Aldrich syndrome	C	N
Chronic granulomatous disease	R	N
Multiple sclerosis	N	C
Systemic sclerosis	N	S
Rheumatoid arthritis	N	D
Systemic lupus erythematosus	N	D
Crohn's disease	N	D
Polymyositis-dermatomyositis	N	D
Osteopetrosis (intermediate)	D	N
Cerebral X-linked adrenoleukodystrophy	R	N

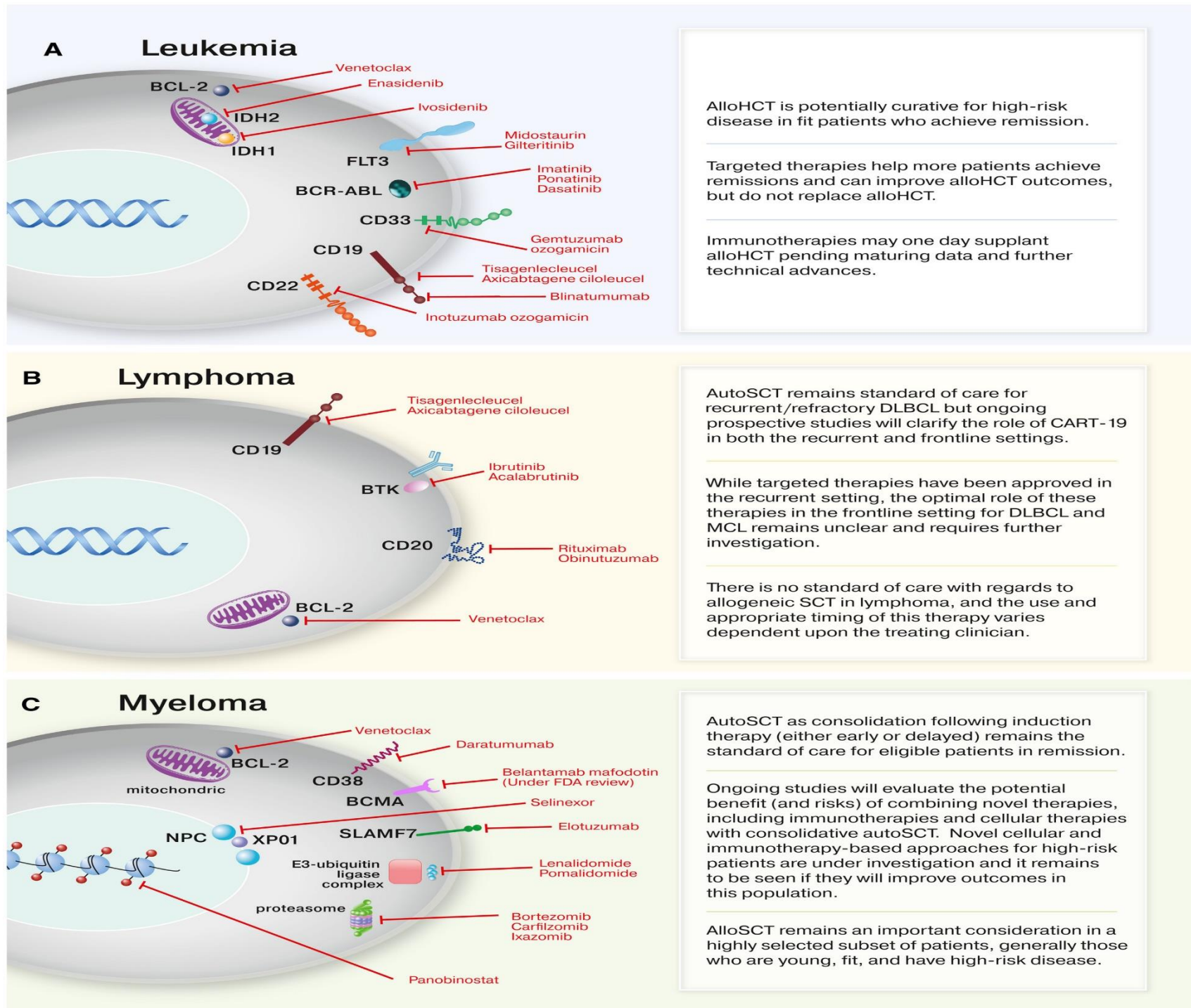
# Key Historical Studies Supporting the Role of HCT in Selected Hematologic Malignancies

Trial	Phase	No.	Comparison	Results
Acute leukemias				
Weiden 1979 <sup>1</sup>	NA	242	Retrospective comparison of the risk of recurrence after alloHCT in those who did and did not develop GVHD	GVHD associated with a 2.5 times reduction in risk of recurrence compared, providing evidence of graft-versus-leukemia effect
Cornelissen 2007 <sup>6</sup>	3	925	Patients in first remission with an identified HLA-identical donor underwent consolidation and alloHCT and those without an identified donor underwent consolidation without alloHCT	DFS (4-y): 48% vs 27% ( <i>P</i> < .001)
				OS (4-y): 54% vs 46% ( <i>P</i> = .07)
Koreth 2009 <sup>7</sup>	NA	6007	Large systematic review and meta-analysis evaluating RFS and OS for patients with good-, intermediate-, and poor-risk AML in first remission who undergo alloHCT vs those who do not (based on donor availability)	RFS among patients with good-, intermediate-, and poor-risk AML who undergo alloHCT in first remission compared with those who receive nontransplantation therapies (HRs of 0.69, 0.76, and 1.06, respectively)
				OS among patients with good-, intermediate-, and poor-risk AML who undergo alloHCT in first remission compared with those who receive nontransplantation therapies (HRs of 0.73, 0.83, and 1.07, respectively)
Pidala 2011 <sup>8</sup>	NA	3157	Systematic review evaluating efficacy of alloHCT compared with autoHCT for high-risk ALL in first remission	DFS among alloHCT vs autoHCT: HR, 0.82 ( <i>P</i> = .004)
				OS among alloHCT vs autoHCT: HR, 0.86 ( <i>P</i> = .01)
Aggressive B-cell lymphomas				
Philip 1995 <sup>9</sup>	3	215	DHAP × 6 cycles plus RT vs DHAP × 6 cycles plus RT and intensive chemotherapy plus autoHCT for R/R DLBCL	EFS (5-y): 12% vs 46% ( <i>P</i> = .001)
				OS (5-y): 32% vs 53% ( <i>P</i> = .04)
Stiff 2013 <sup>10</sup>	3	253	R-CHOP vs R-CHOP plus autoHCT for frontline DLBCL	PFS (2-y): 55% vs 69% ( <i>P</i> = .005)
				OS (2-y):71% vs 74% ( <i>P</i> = .3)

# Key Historical Studies Supporting the Role of HCT in Selected Hematologic Malignancies

Dreyling 2005 <a href="#">11</a>	3	269	Myeloablative radiochemotherapy plus autoHCT vs IFN- $\alpha$ maintenance in first remission MCL	PFS (3-y): 54% vs 25% ( $P = .01$ )
				OS (3-y): 83% vs 77% ( $P = .18$ )
Hermine 2016 <a href="#">12</a>	3	497	R-CHOP plus autoHCT vs R-CHOP/R-DHAP plus high-dose cytarabine and autoHCT for MCL in first remission	TTF: 3.9 y vs 9.1 y ( $P = .04$ )
Multiple myeloma				
Attal 1996 <a href="#">13</a>	3	200	VMCP/BVAP $\times$ 4-6 cycles and autoHCT vs VMCP/BVAP $\times$ 18 alternating cycles plus IFN	PFS (5-y): 28% vs 10% ( $P = .01$ )
				OS (5-y): 52% vs 12% ( $P = .03$ )
Palumbo 2014 <a href="#">14</a>	3	273	HDM followed by autoHCT vs MPR consolidation after induction, with or without lenalidomide maintenance	Median PFS: 43.0 mo vs 22.4 mo ( $P < .001$ )
				OS (4-y): 81.6% vs 65.3% ( $P = .02$ )
Gay 2015 <a href="#">15</a>	3	389	RD $\times$ 4 cycles followed by autoHCT vs RD $\times$ 4 cycles followed by RCD $\times$ 6 cycles, with or without lenalidomide maintenance	Median PFS: 43.3 mo vs 28.6 mo ( $P < .0001$ )
				OS (4-y): 86% vs 73% ( $P = .004$ )
Attal 2017 <a href="#">16</a>	3	700	RVD $\times$ 3 cycles plus autoHCT plus RVD $\times$ 2 cycles vs RVD $\times$ 8 cycles, with maintenance lenalidomide in both arms	Median PFS: 50 mo vs 36 mo ( $P < .001$ )
				OS (4-y): 81% vs 82% (NS)
Stadtmauer 2019 <a href="#">17</a>	3	758	Tandem autoHCT plus lenalidomide maintenance vs single autoHCT plus RVD $\times$ 4 cycles plus lenalidomide maintenance vs autoHCT plus lenalidomide maintenance	PFS (38-mo): 58.5% vs 57.8% vs 53.9% (NS)
				OS (38-mo): 81.8% vs 85.4% vs 83.7% (NS)

# Targeted and cellular therapy products currently approved by the FDA



# Selected Ongoing Trials Investigating Novel Therapies in Combination With or Compared With HCT in Hematologic Malignancies

Registration No.	Disease Type	Phase	Objective
Acute leukemias			
NCT03515512	IDH2-mutated AML	1	To evaluate the safety and efficacy of enasidenib as maintenance therapy for IDH2-mutated AML after alloHCT
NCT02117297	R/R AML	2	To evaluate the efficacy of standard-of-care alloHCT followed by gemtuzumab ozogamicin in average-risk AML/MDS
NCT03613532	AML, MDS	1	To examine the efficacy of venetoclax in combination with a standard alloHCT conditioning regimen prior to alloHCT
NCT03766126	R/R AML	1	To evaluate the efficacy of CD123 CAR T cells in R/R AML
NCT02577406	IDH2-mutated AML	3	IDHENTIFY Study: To evaluate the efficacy and safety of ivosidenib compared with conventional regimens in older patients with AML harboring an IDH2 mutation
NCT03173248	IDH1-mutated AML	3	AGILE Study: To compare the efficacy of ivosidenib and placebo in combination with azacitidine in patients with previously untreated IDH1-mutated AML
NCT02997202	FLT3-mutated AML	3	To evaluate the efficacy of gilteritinib administered as maintenance therapy after alloHCT in patients with AML harboring a FLT3 mutation
NCT02400255	FLT3-mutated AML	2	To evaluate the efficacy of crenolanib administered as maintenance therapy after alloHCT in patients with AML harboring a FLT3 mutation
NCT03735875	FLT3-mutated AML	1/2	To compare the efficacy of crenolanib with that of midostaurin when administered after induction chemotherapy, consolidation chemotherapy, and bone marrow transplantation in patients with newly diagnosed AML with a FLT3 mutation

## Selected Ongoing Trials Investigating Novel Therapies in Combination With or Compared With HCT in Hematologic Malignancies

Aggressive B-cell lymphomas			
NCT03575351	DLBCL	3	TRANSFORM: To compare the safety and efficacy of the standard-of-care strategy vs JCAR017 in patients with R/R aggressive B-cell non-Hodgkin lymphoma (JCAR017 vs HDT–autoHCT)
NCT03570892	DLBCL	3	BELINDA: To compare the efficacy, safety, and tolerability of tisagenlecleucel with standard of care in adult patients with aggressive B-cell non-Hodgkin lymphoma after failure of rituximab and anthracycline-containing frontline chemoimmunotherapy (tisagenlecleucel vs HDT–autoHCT)
NCT03391466	DLBCL	3	ZUMA-7: To evaluate the clinical efficacy of axicabtagene ciloleucel compared with standard-of-care second-line therapy in R/R DLBCL (axicabtagene ciloleucel vs autoHCT)
NCT02858258	MCL	3	To establish 1 of 3 study arms as standard of care: R-CHOP/R-DHAP plus autoHCT vs R-CHOP/R-DHAP plus ibrutinib vs R-CHOP/R-DHAP plus ibrutinib plus autoHCT
Multiple myeloma			
NCT03549442	High-risk multiple myeloma	1	To test CART-BCMA in combination with huCART19 as consolidation of early therapy for multiple myeloma in patients with high-risk disease
NCT02203643	Multiple myeloma	2	FORTE: Evaluate the efficacy and safety of induction with carfilzomib, lenalidomide (or cyclophosphamide), and dexamethasone (KRd or KCd) followed by autoHCT and KRd/KCd consolidation vs KRd without transplantation, each followed by maintenance
NCT03224507	Multiple myeloma	2	MASTER: To evaluate the efficacy of induction therapy with carfilzomib, lenalidomide, dexamethasone, and daratumumab with or without autoHCT
NCT02874742	Multiple myeloma	2	GRIFFIN: To evaluate the activity of D-VRd vs VRd in transplantation-eligible patients with multiple myeloma
NCT03601078	High-risk multiple myeloma	2	KarMMA-2: To evaluate the efficacy and safety of bb2121 in patients with early recurrence after 1 line of therapy (both including and excluding autoHCT as well as those with an inadequate response to initial therapy (including autoHCT)
Pending	High-risk multiple myeloma	2	BMT CTN 1901: To determine progression-free survival in patients with poor-risk myeloma undergoing BCMA CAR T-cell therapy after autologous transplantation
NCT01208662	Multiple myeloma	3	To compare outcomes in patients treated with induction therapy with bortezomib, lenalidomide, and dexamethasone followed by autoHCT and lenalidomide maintenance or no transplantation and lenalidomide maintenance

## A donor kiválasztása őssejtátültetéshez

Első választás: HLA azonos testvér



HLA egyező nem rokon donor

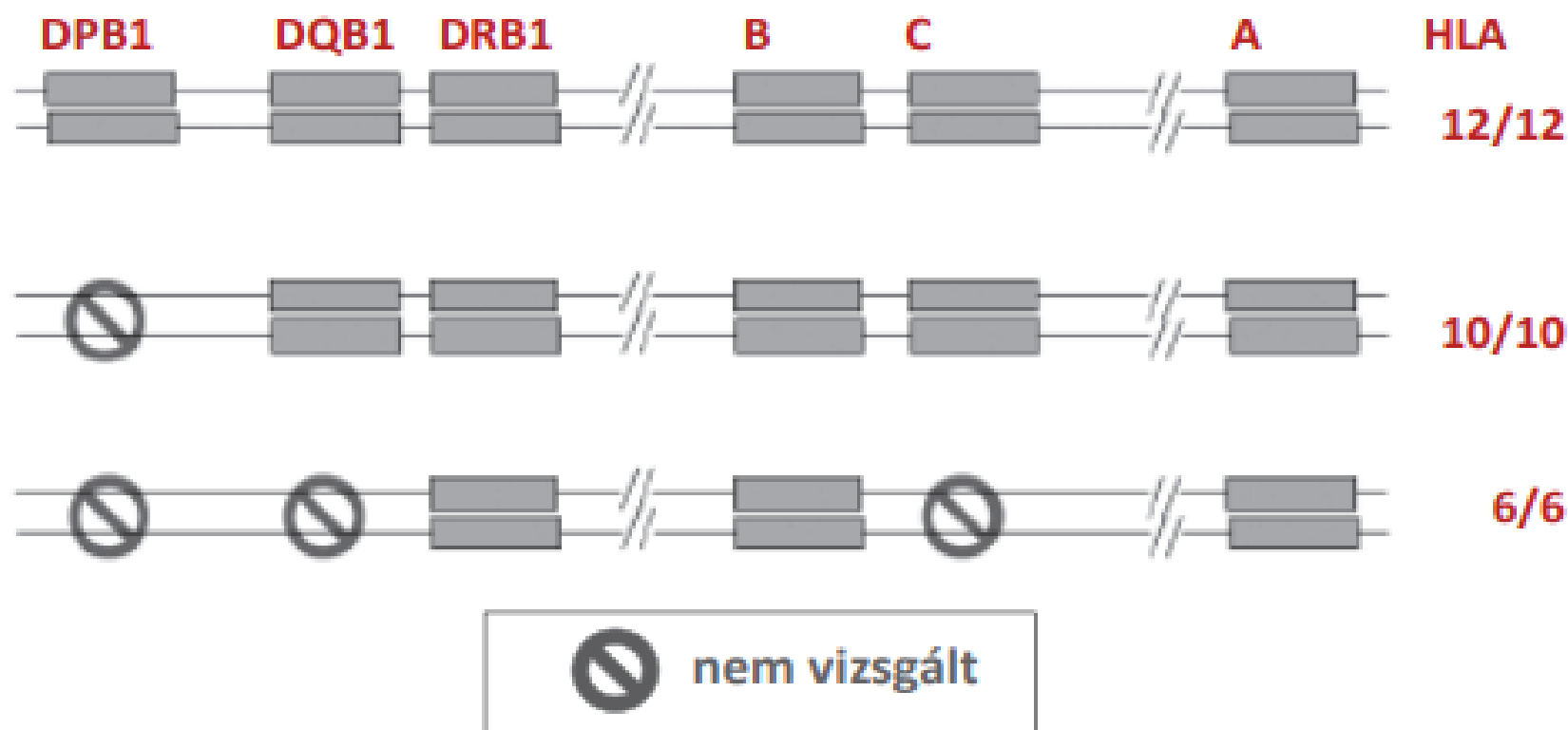


1-2 HLA tulajdonságban  
eltérő  
nem rokon donor

Köldökzsinórvér  
(1 vagy több egység)

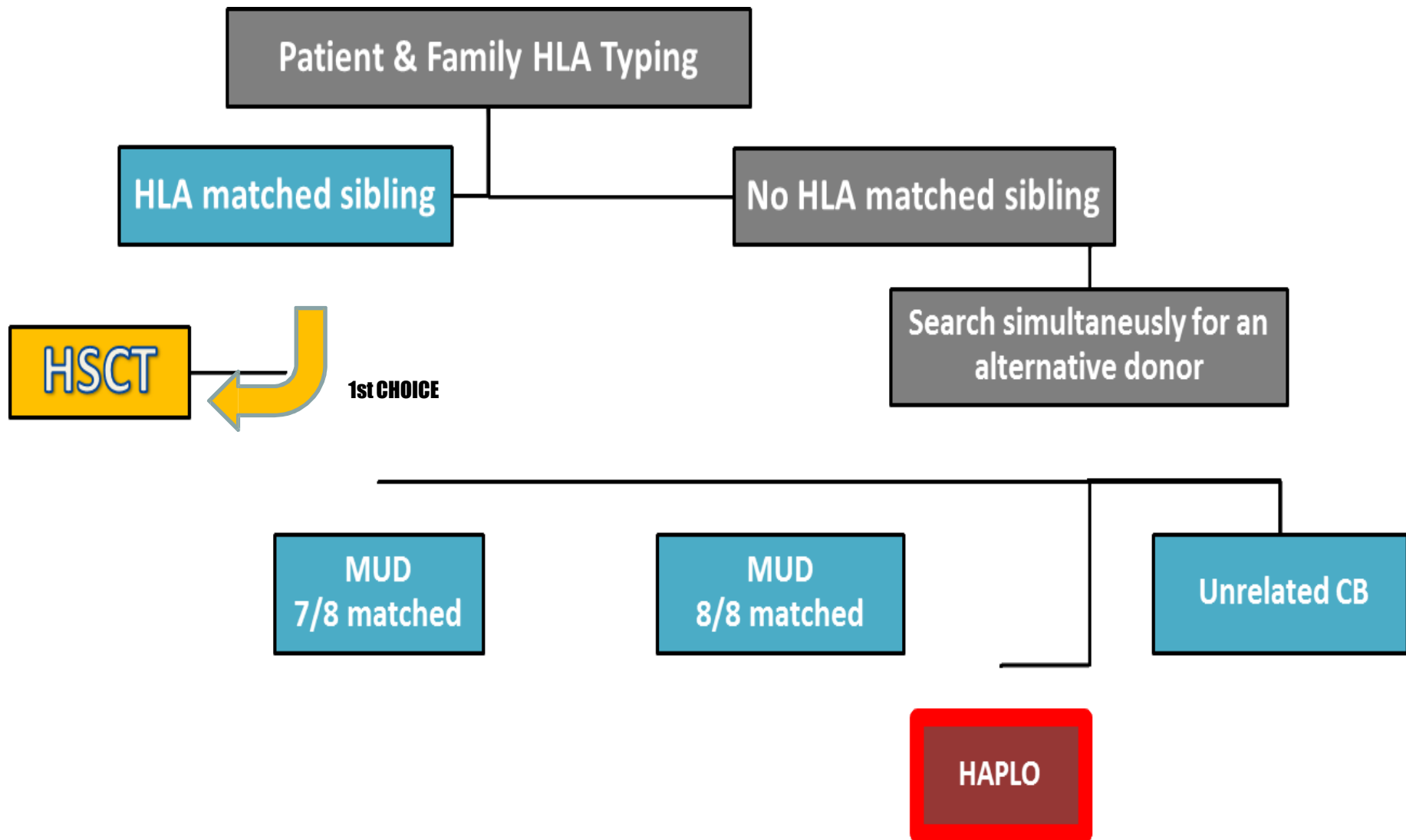
Haploidentikus  
(50%-ban egyező)  
családi donor

# Donorkeresés nem rokon donorral történő összejtátlításhoz a rendelkezésre álló adatok alapján

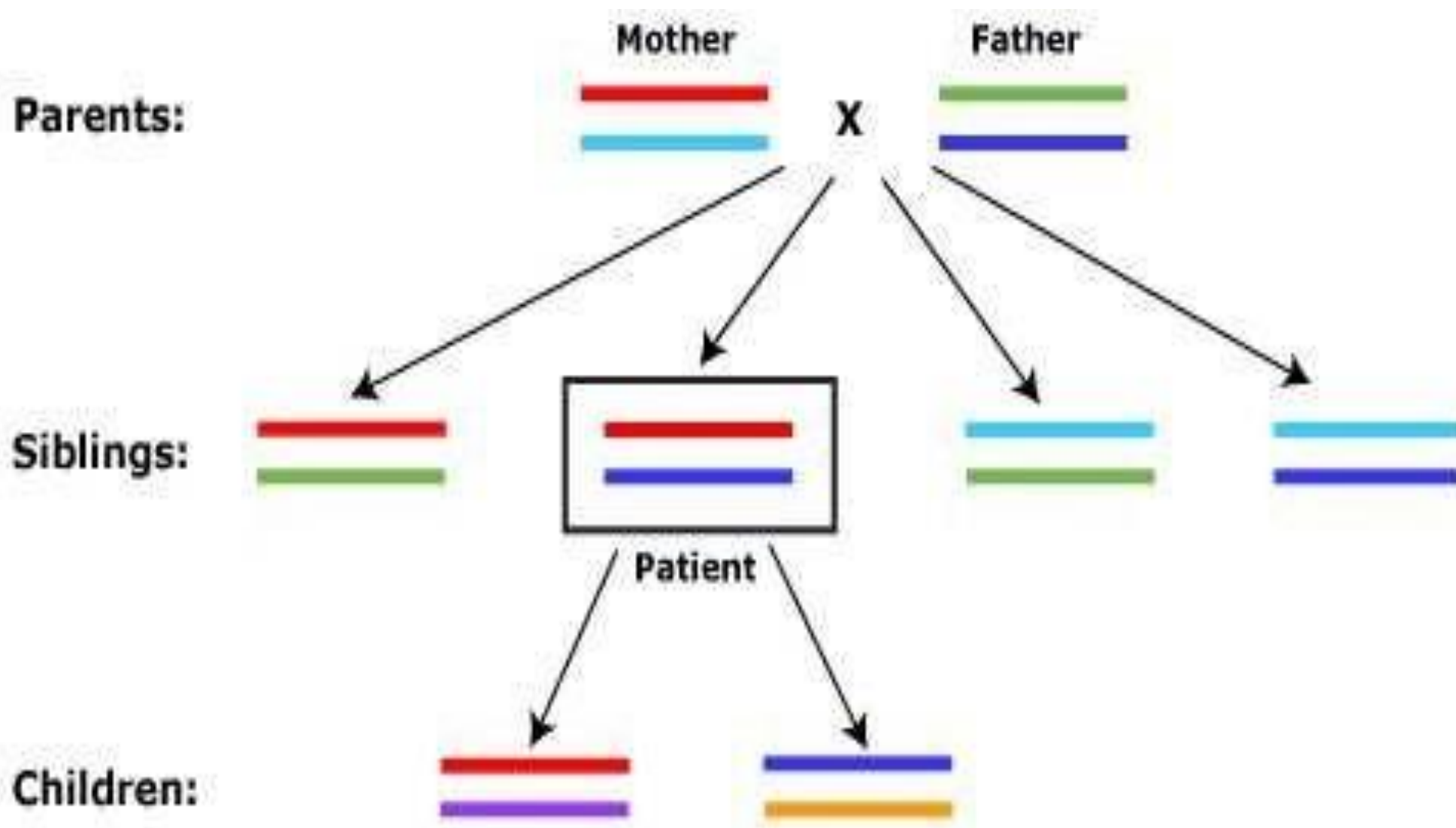


Egyeztetés 6, 8, 10 és végül 12 tulajdonság alapján

# Donor keresés



# Haploidentikus donorok a családban



# Korhatárok

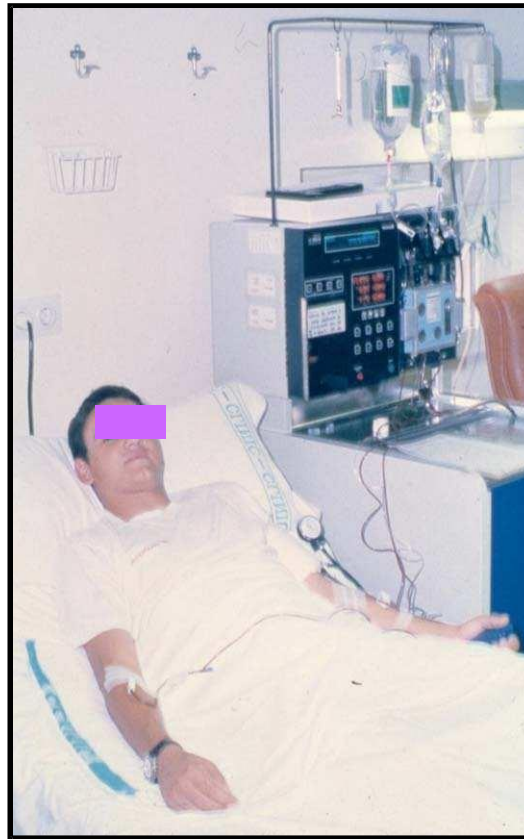
• Össejt-átültetés	KOR(év)
• Autológ	70
• Allogén (testvér donor)	60
• VUD (donor bankból)	50
• RIC allogén	70

# Össejt források

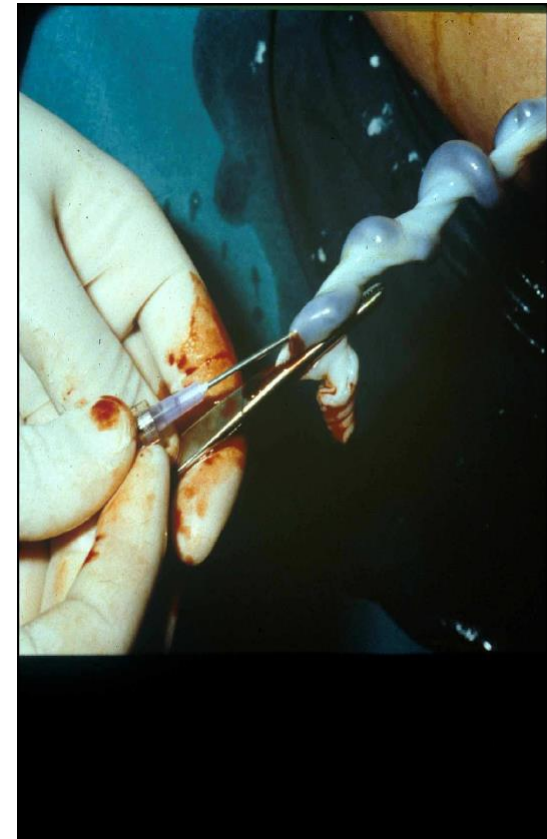
**Csontvelő**



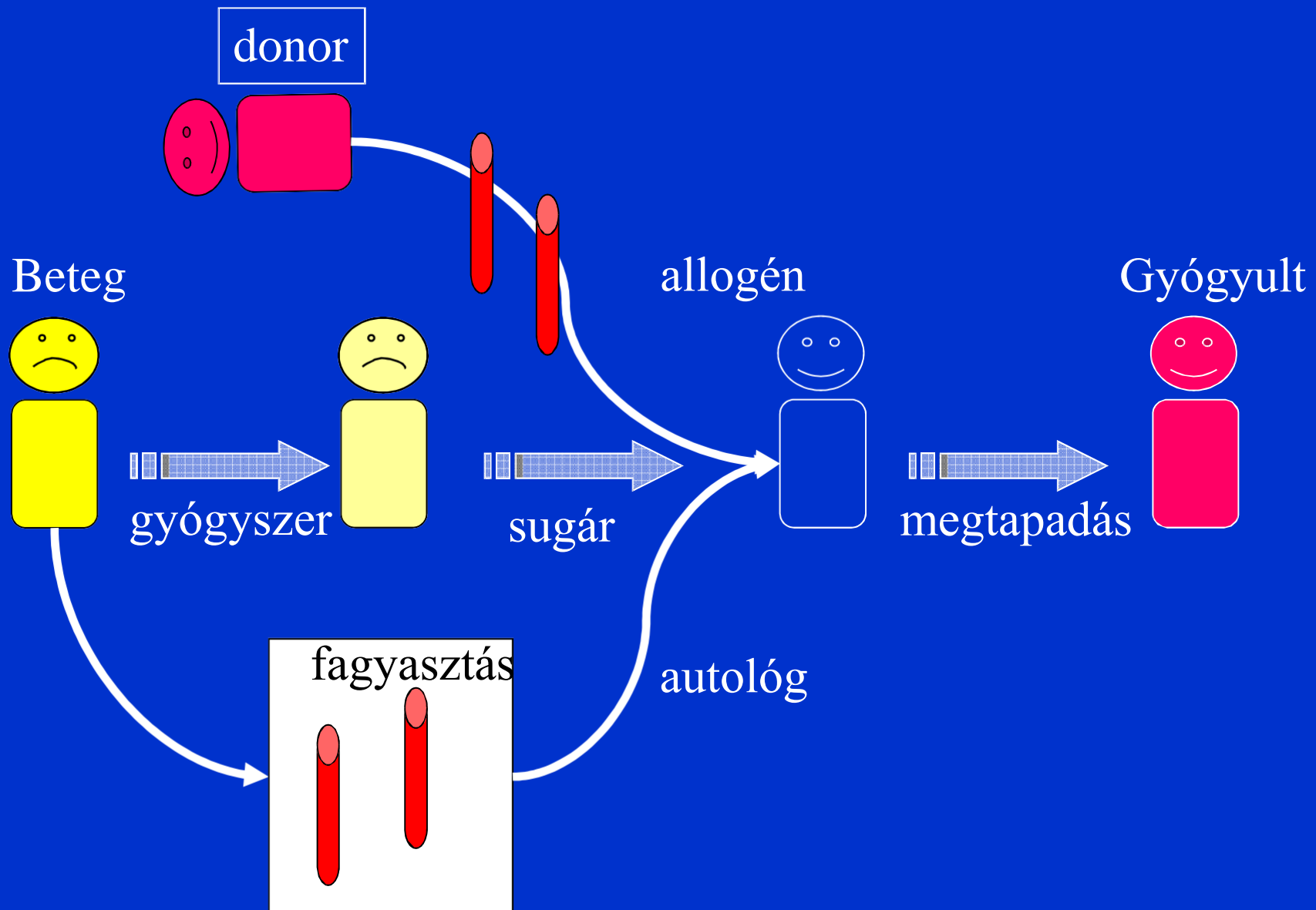
**Perifériás vér**



**Köldökvér**



# Az őssejtátültetés folyamata



# Perifériás őssejt átültetés előnyei és hátrányai

Előny:

gyorsabb megtapadás → rövidebb aplasia

kevesebb szövődmény

gyorsabb hazamenetel

kisebb költségek

ismételt ferezisekkel több sejt gyűjthető → graft manipuláció (CD34+ szelekció, T sejt mentesítés)

Allogén átültetéseknél a donor számára előnyt jelent, hogy nincs szükség műtetre, ambuláns formában alkalmazható, nagy donor-recipiens testtömeg különbségek esetén is lehetővé teszi a transzplantációt.

Hátrány:

gyakoribb cGVHD



**WMDA 2021.04.19.**

**38,772,360 önkéntes  
össajt donor**

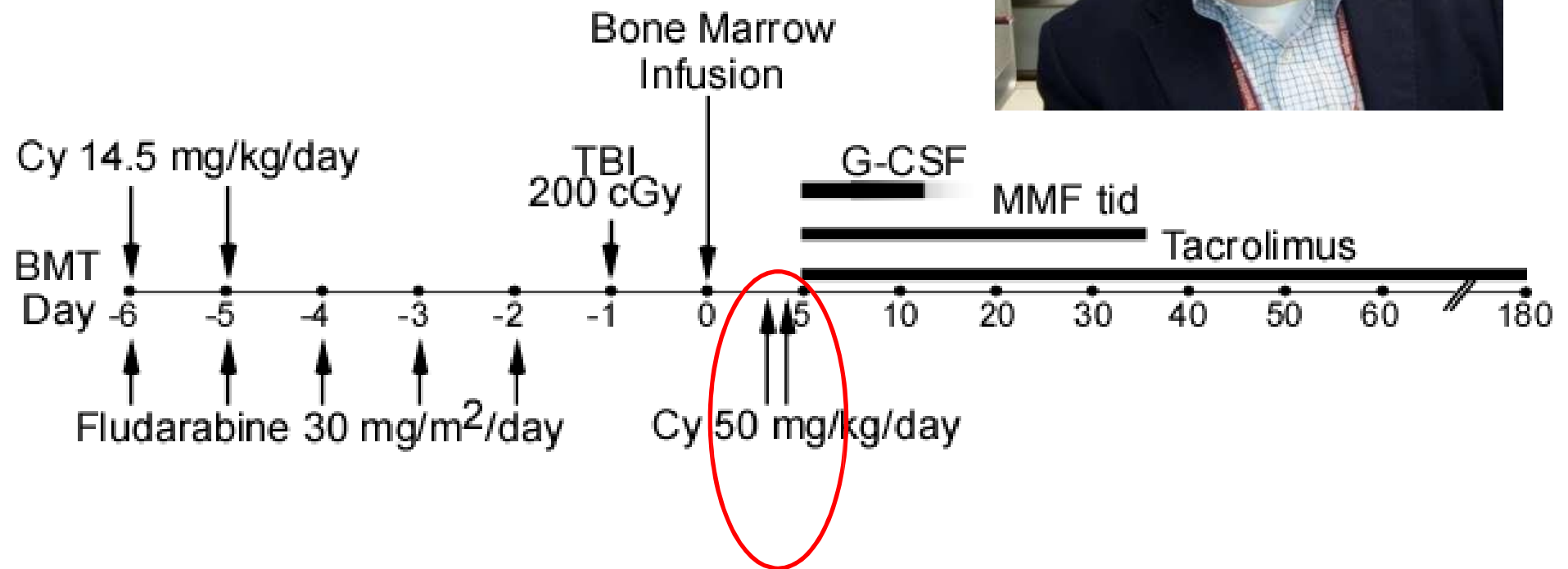
**Ebből 7,023 magyar**

**Németország  
>8 millió!**

# Haploidentikus SCT

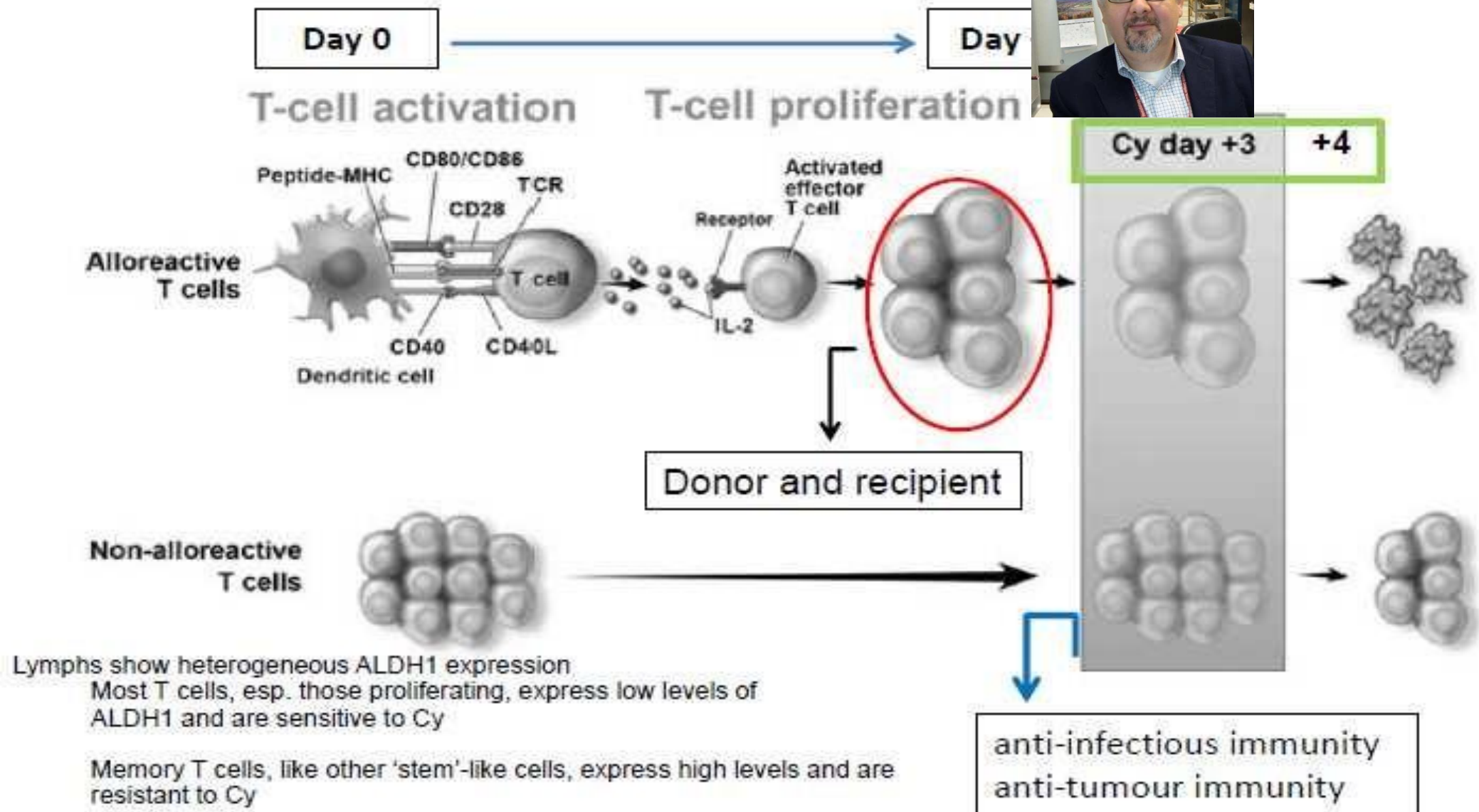
- **Ex vivo** T-cell depletion
  - Dárga, komplikált, lassú immun rekonstrukció,
- **In vivo** T-cell depletion ATG based
  - Dárga
- **In vivo** T-cell depletion post-transplant Cyclophosphamid adásával
  - Pofon egyszerű, olcsó, könnyen kivitelezhető

# Post-transplant cyclophosphamide

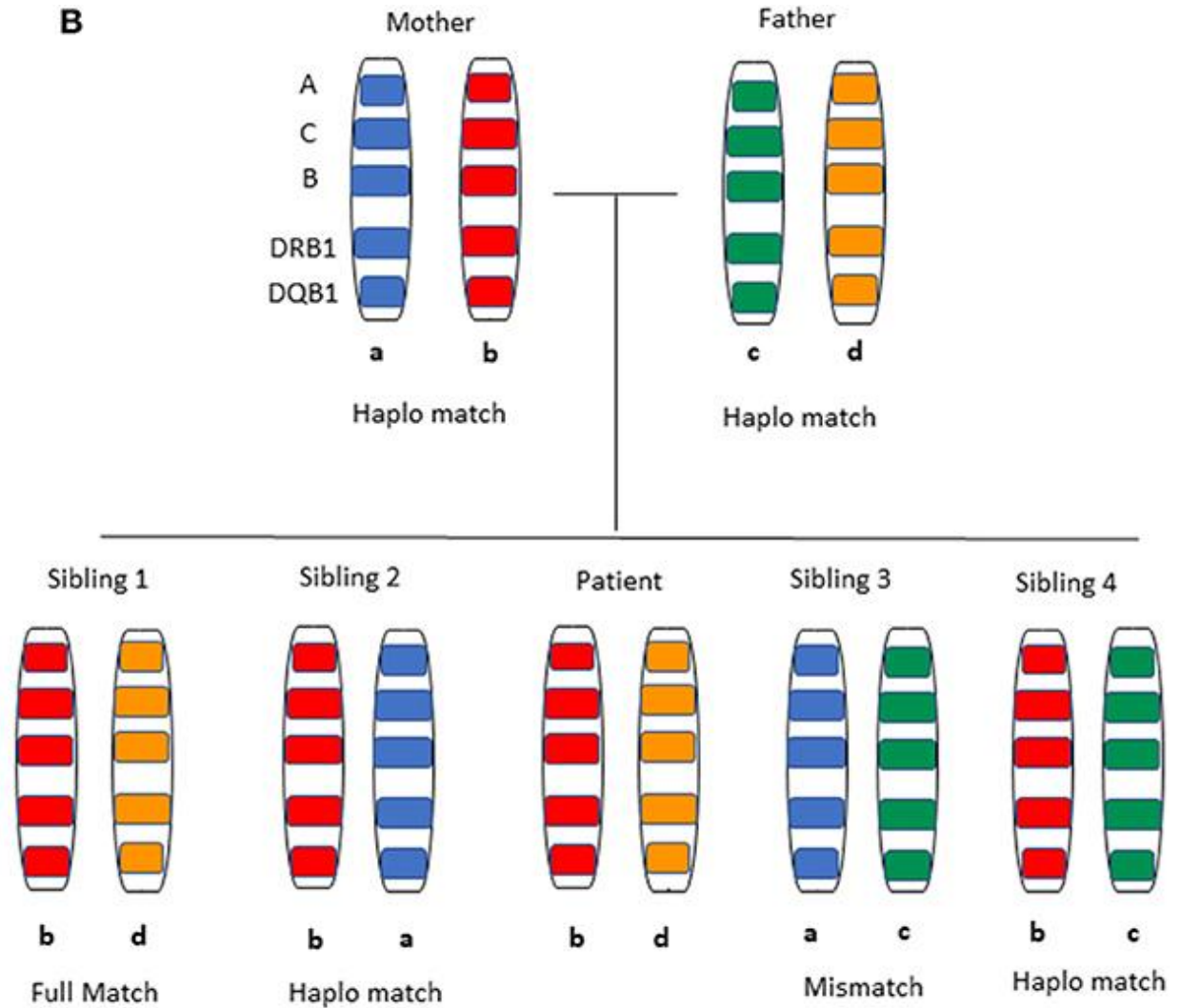
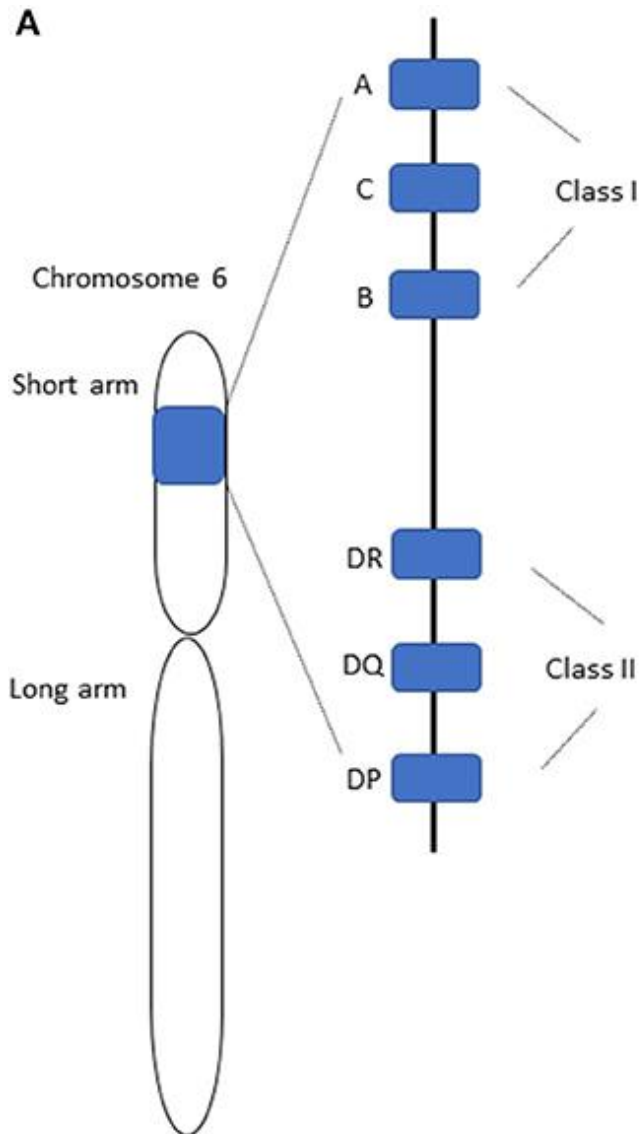


# Post transplant cyclophosphamide allodepletion of haplo BM

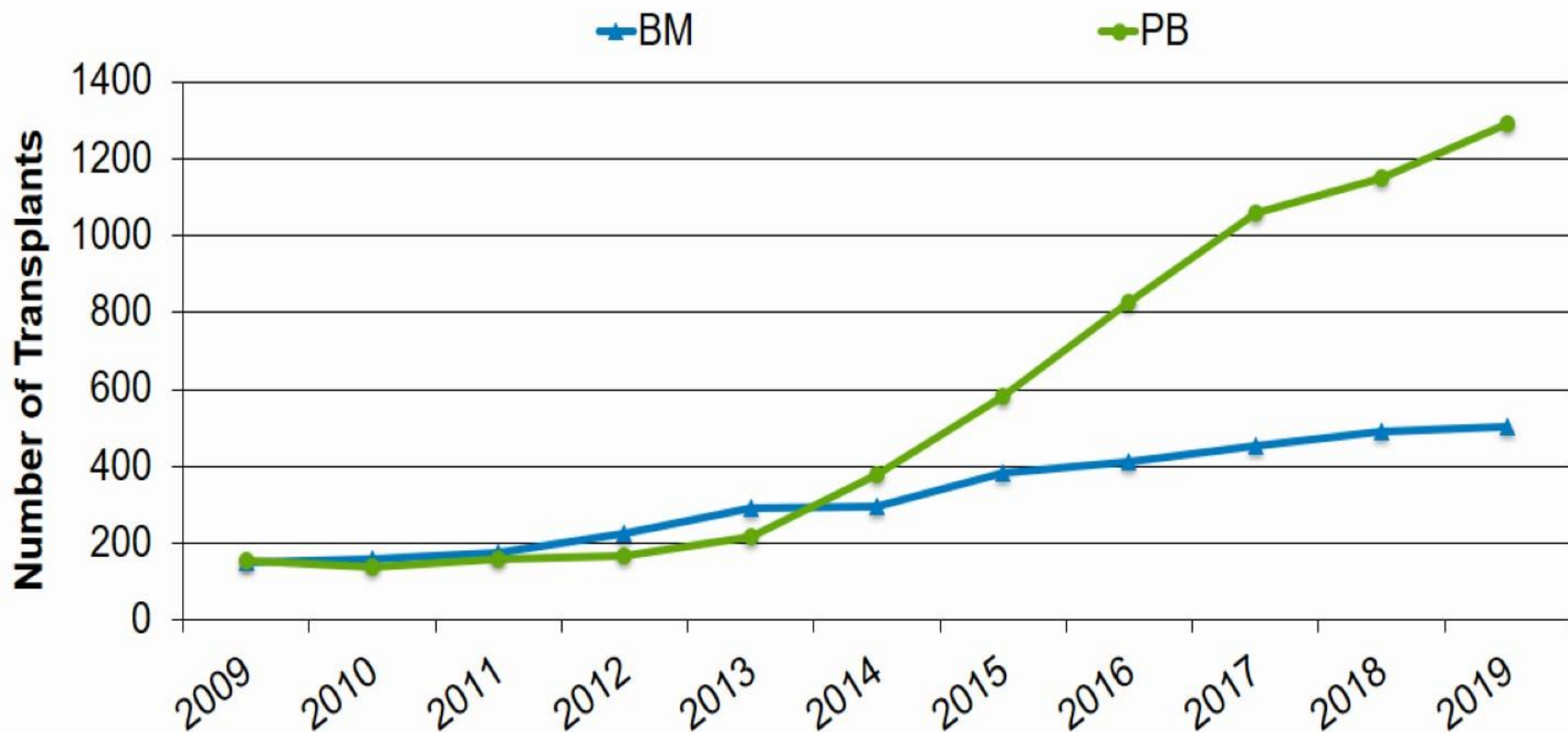
Luznik et al 2010



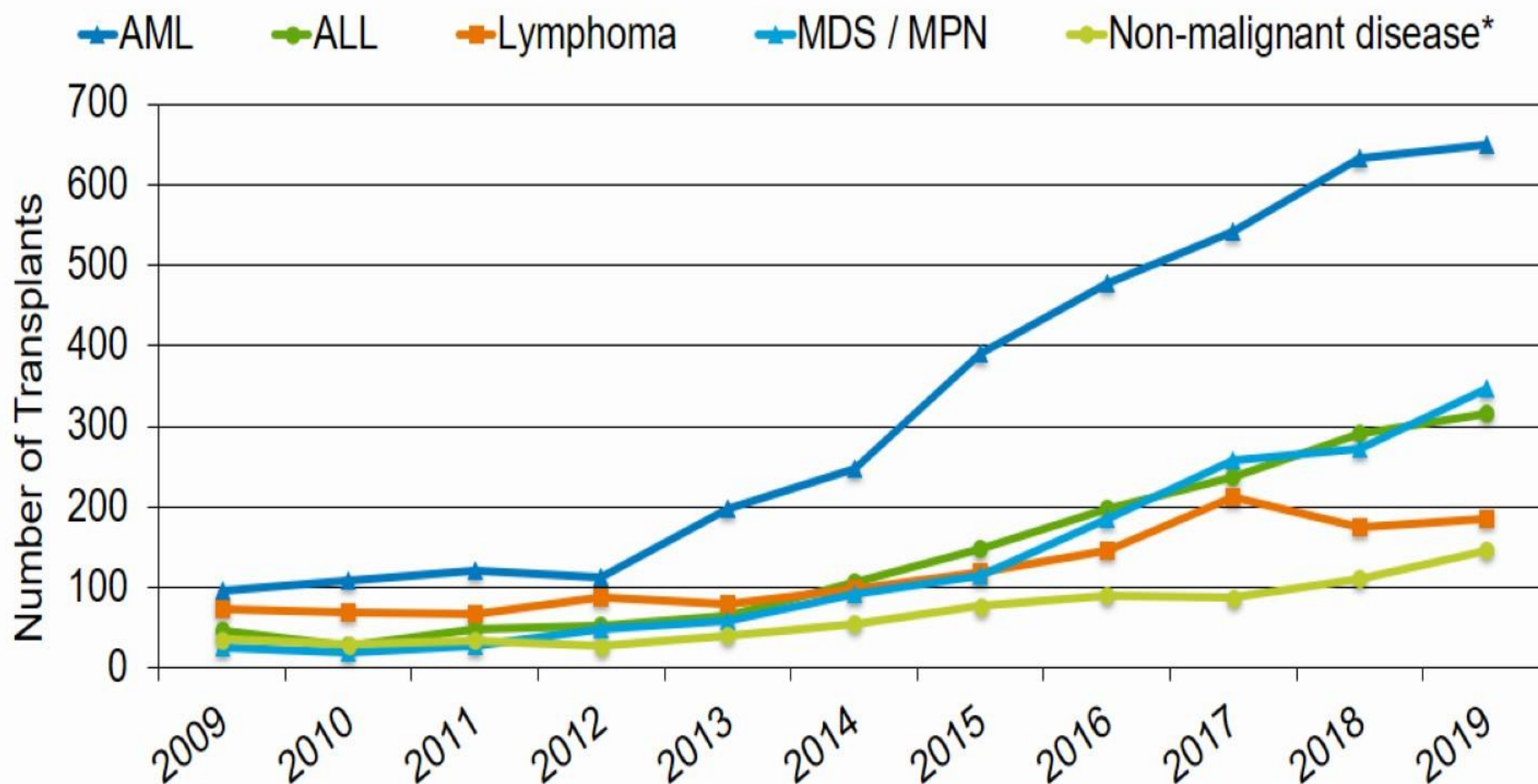
# Haploidentikus donor



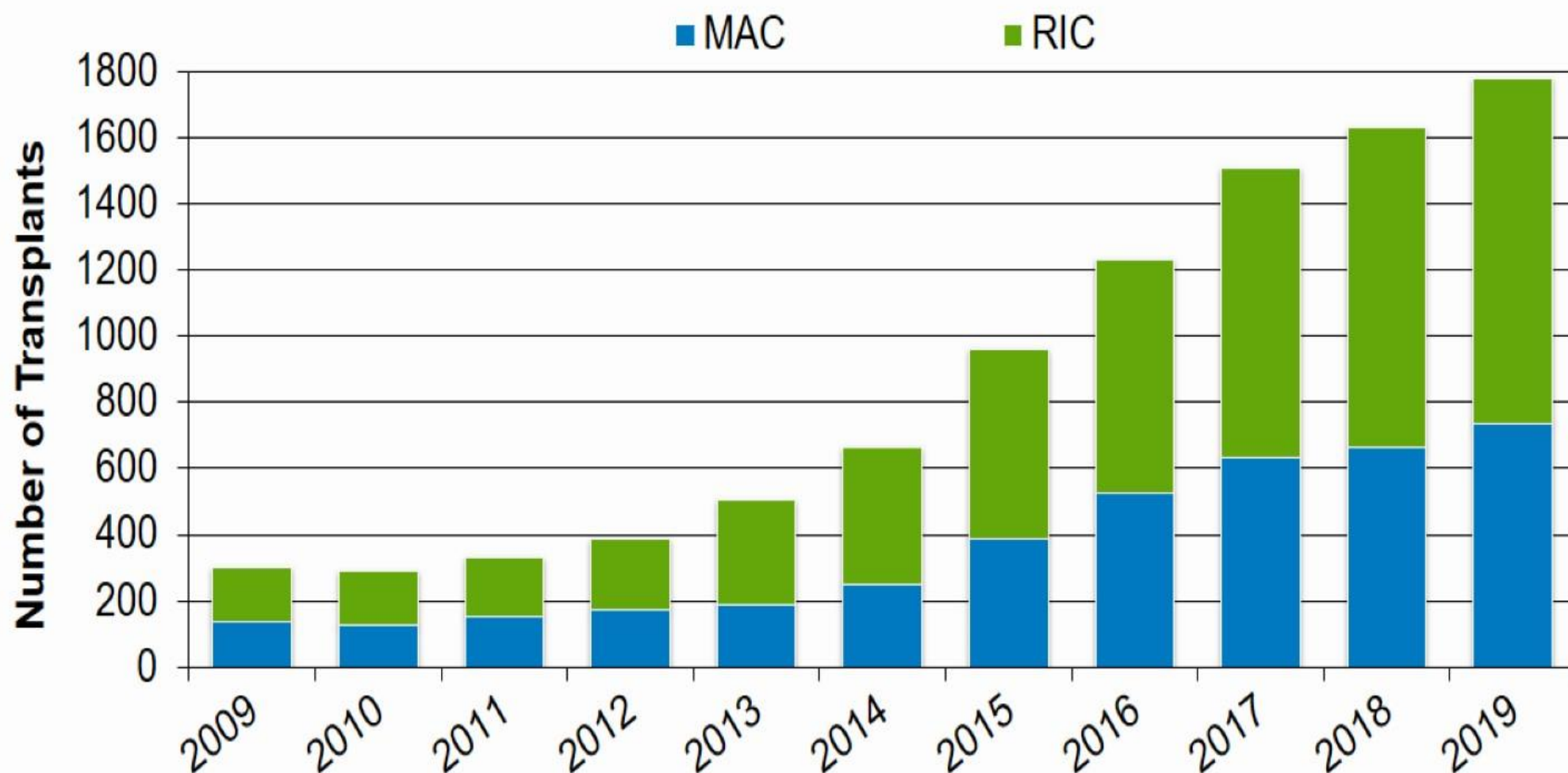
## Haploidentical HCT in the US by Graft Type



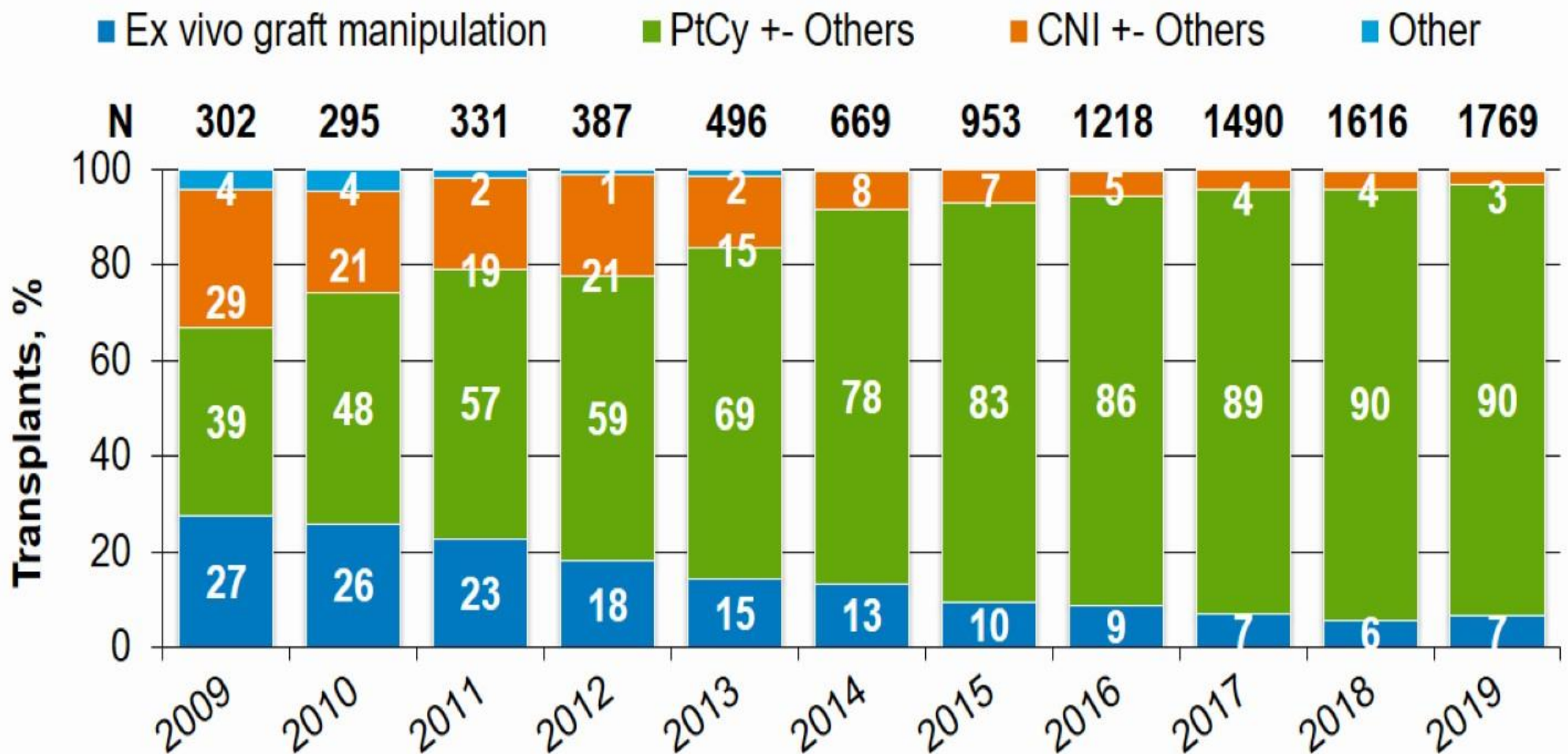
## Haploidentical HCT in the US by Disease



## Haploidentical HCT in the US by Conditioning Intensity



## Haploidentical HCT in the US by GVHD Prophylaxis



# Köldökvér bankok

- Allogén
  - Unrelated : *közösségi köldökvérbank*
  - orvosi indokkal, családi
- Autolog
  - Össejtátültetés
  - Regenerativ medicina



# Köldökvér őssejtek előnyei és hátrányai

## Előnyök:

könnyen, biztonságosan nyerhető és gyorsan felhasználható  
több éretlenebb őssejtet tartalmaz, jobb proliferációs kapacitás  
lymphocytái kevésbé alloreaktívak (↓ aGvH és cGvH))  
kisebb eséllyel közvetít fertőzést (pl. CMV)  
csekély toxicitás  
nem szükséges teljes HLA egyezés (az eredmények 1 antigén különbség és teljes HLA egyezés mellett azonosak), ezért nagyobb valószínűséggel találni alkalmas donort

## Hátrányok:

őssejt tartalma korlátozott  
megtapadás lassabb, elhúzódó immunrekonstitúció, több fertőzés  
DLI (donor lymphocyta infúzió) adása nem lehetséges  
genetikai betegségek átvitele

# Köldökvér bankok

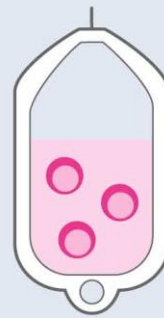
## Public/allo vs privát/auto

- Bizonyítottan hatásos
- Quality : akkreditált bankok
- Non-profit, közös pénzből
- Folytonosság garantált
- Szolidaritás
- Egyenlő esély a hozzáféréshez
- Pontos tájékoztatás
- Globális hozzáférhetőség
- Nem bizonyított hasznosság
- Bizonytalan minőség
- Magán pénzből , for profit
- A folytonosság nem biztos
- Donáció ellenes
- Egyenlőtlen esély
- Torzított információk
- Nincs hozzáférhetőség

Donor



**Stem cell  
collection**



# Allogén átültetés

**Stem cell  
infusion**

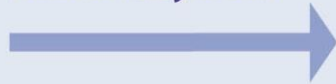


Patient without  
immune system

Patient



**Destroy  
leukemia cells  
and the patient's  
immune system**



**Rebuilding of the  
immune system  
with donor cells**



Patient with new  
hematopoietic  
system



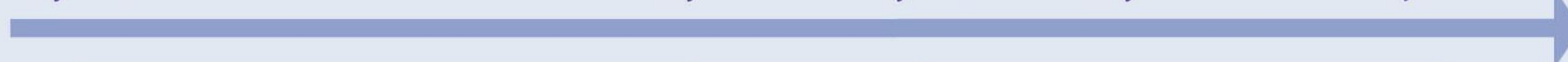
day -10

Infusion  
day 0

day 30

day 100

1 year



Conditioning

Engraftment

Immune recovery

Critical period for infections

Critical period for  
acute GVHD

Critical period for  
chronic GVHD

# **Transzplantáció szakaszai**

**Kondicionálás**

**Közvetlen poszttranszplantációs szak**

aplasia (0-30. nap)

**Korai poszttranszplantációs szak**

(30-100. nap)

**Kései poszttranszplantációs szak**

(100-365. nap)

# A kondicionáló kezelés célja

- A beteg sejtek elpusztítása
- A megtapadáshoz szükséges immunszuppresszió
- A beültetett sejtek csontvelői helyének kialakítása

Mega chemo-radioterápia

Cél:

Malignus sejtek elpusztítása

Immunszuppresszió (rejectio ↓)

„Hely” a donor vérképzés számára a csontvelői stromában.

# Kondicionáló kezelések lymphomában

B\*EAM: 300 mg/m<sup>2</sup> BCNU iv. – 7. nap

400 mg/m<sup>2</sup> Etoposide iv. – 6–3. nap

2 x 200 mg/m<sup>2</sup> cytosine Arabinosid iv. –6-3. nap

140 mg/m<sup>2</sup> Melphalane iv. –2. day

Bu-Cy: 4 mg/kg Busulphan per os – 9-6. nap iv

50 mg/kg Cyclophosphamide iv. – 5–2. nap

TBI-Cy: Frakcionált teljes test besugárzás TBI 12 Gy (napi 2x2 Gy),  
tüdőtakarással –3–1. nap

Cyclophosphamid 60 mg/kg –6–5. nap

CVB, BEAC, VP-16/CY/TBI, BU/CY/Thiotepa

(TBI helyett radiolabeled antibodies: Z-BEAM )

\* Jelenleg B=bendamustin 2 napig 100-200 mg/m<sup>2</sup>

# Engraftment syndrome

7-11. napon lép fel ( $> 15-20 \times 10^6/\text{kg}$  CD34)

Tünetek: láz

bőrkíütés

capillary leak syndrome

tüdőinfiltrátum

Kezelés: steroid (jól reagál)

# Egy kis görög mytológia

Echydna



Typhon



Echidna és Typhon számos gyermeket nemzett, ezek mind valamilyen szörnyek voltak!

# Kiméra



Oroszlán fej, kecske test és kígyó farok

# Szövődmények

Fertőzés

Vérzés

Gyógyszer mellékhatások

Graft versus host betegség

Graft rejekció

Késői mellékhatások

# Az őssejtátültetés szövődményei

Korai	késői
Gastroenteritis	
Mucositis	
Hemorrhágiás cystitis	
Venoocclusiv májbetegség	
Fokozott hajszálér permeabilitás	
Hemolízis	
Leukoencefalopátia	
Akut GvHD	
Graftelégtelenség	
Fertőzések	
Immundefektusok	
Intersticiális pneumonitis	
Csontvelői elégtelenség	
Pszicho-szociális defektusok	
Másodlagos malignitás	
Krónikus GVHD	
Krónikus tüdőbetegség	
Autoimmun betegség	
Endokrin működési rendellenesség	
Növekedési rendellenesség	
Infertilitás	
Katarakta	
Fogászati problémák	
Sugár okozta vesegyulladás	

# **Infekció-kontroll**

**Protektív környezet**

**Izolációs technikák:**

Egyágyas szoba, zsilip, fürdő  
steril box

HEPA-filter

túlnyomásos levegőbefúvás 0,5 bar  
lamináris áramlás

**Surveillance**

## **Aplasia időszaka (0-30. nap)**

Neutropenia

Thrombocytopenia

Anaemia

Gyógyszer mellékhatások (hemorrhagiás  
cystitis, máj-, vesetoxicitás, VOD-SOS)

Fertőzések (gomba, baktérium)

Akut GVHD

# Neutropeniás betegek fertőzéseinek jellegzetességei

**A fertőzés nem a megszokott, jellegzetes formában jelentkezik**



## **Neutropeniás betegek fertőzéseinek jellegzetességei**

A gyulladásos jelek és tünetek  
hiányozhatnak (↓ duzzanat, erythema,  
gennyképződés)

Mellkas rtg: nincs infiltrátum

Meningitis: liquor pleocytosis nélkül

Húgyúti fertőzés: pyuria nélkül

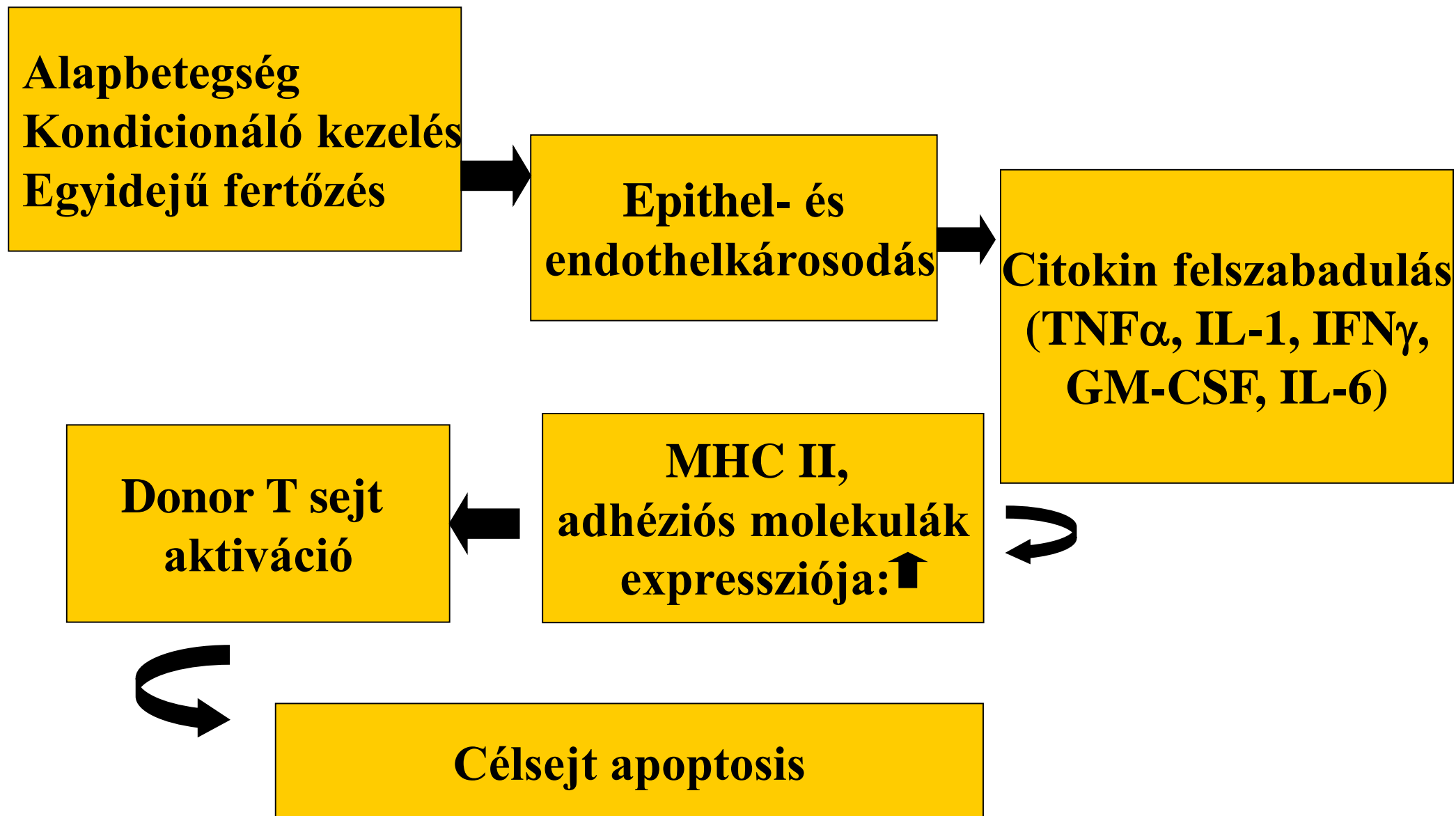
# **Akut Graft versus Host betegség (GvHD) feltételei**

A graft immun-kompetens sejteket  
tartalmazzon

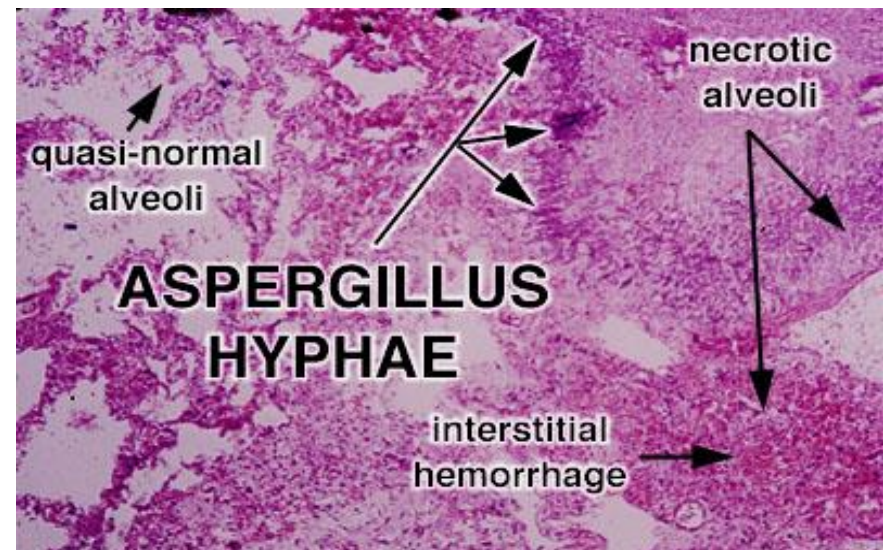
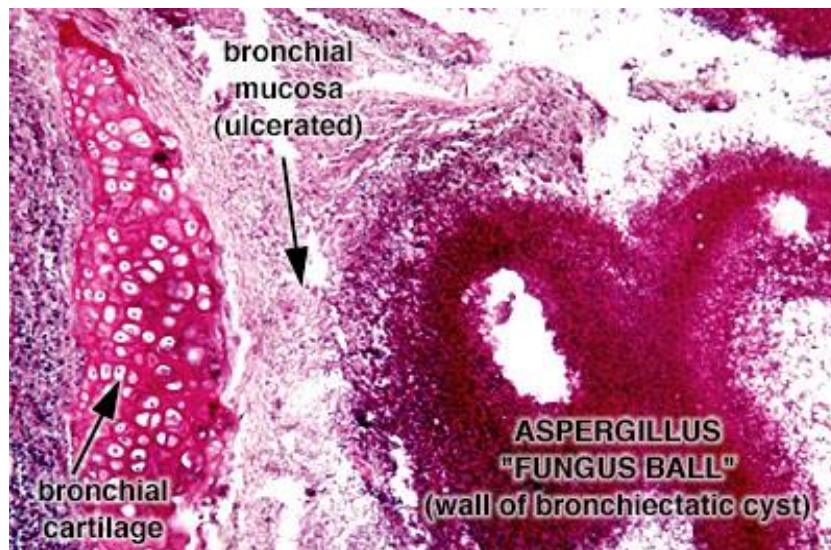
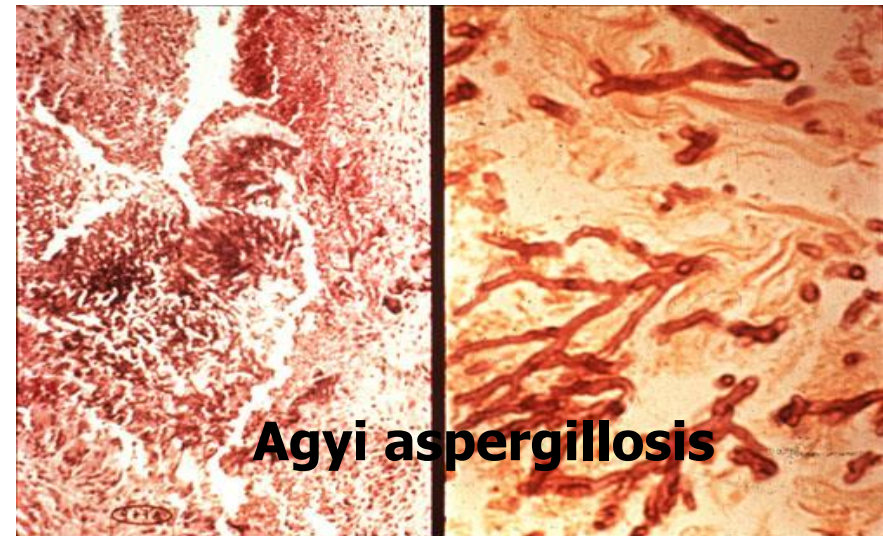
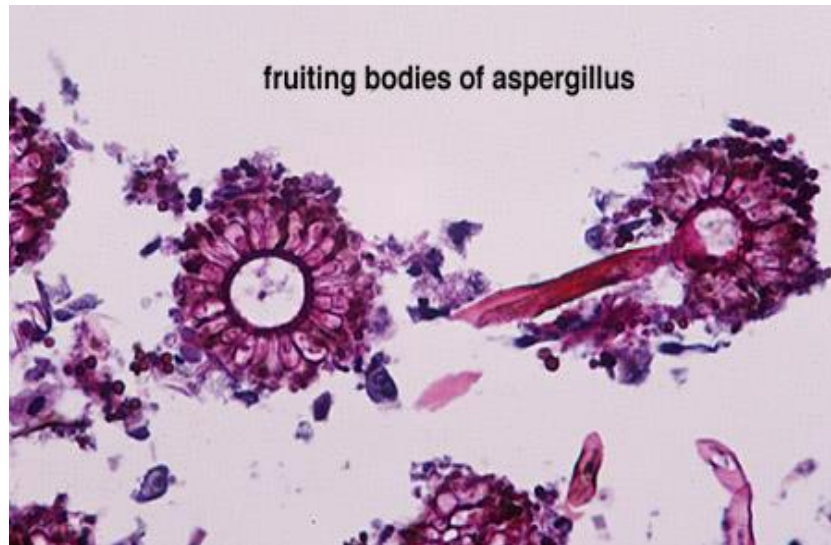
A graft és a host alloantigénjei  
különbözzenek

A host ne tudjon hatékony immunválaszt  
kiváltani a graft ellen (immundeficiens  
legyen)

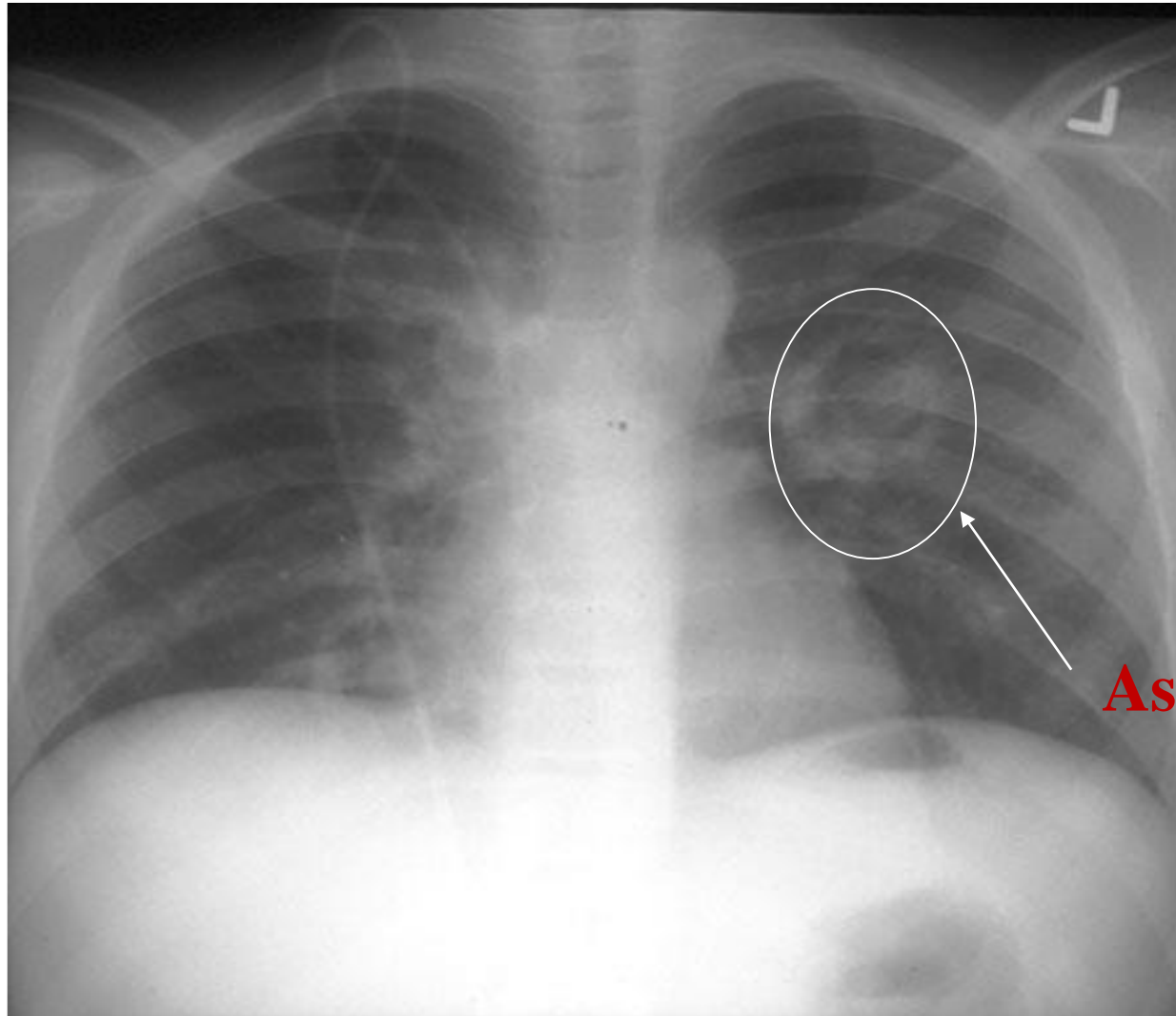
# Akut graft versus host betegség



# Aspergillosis

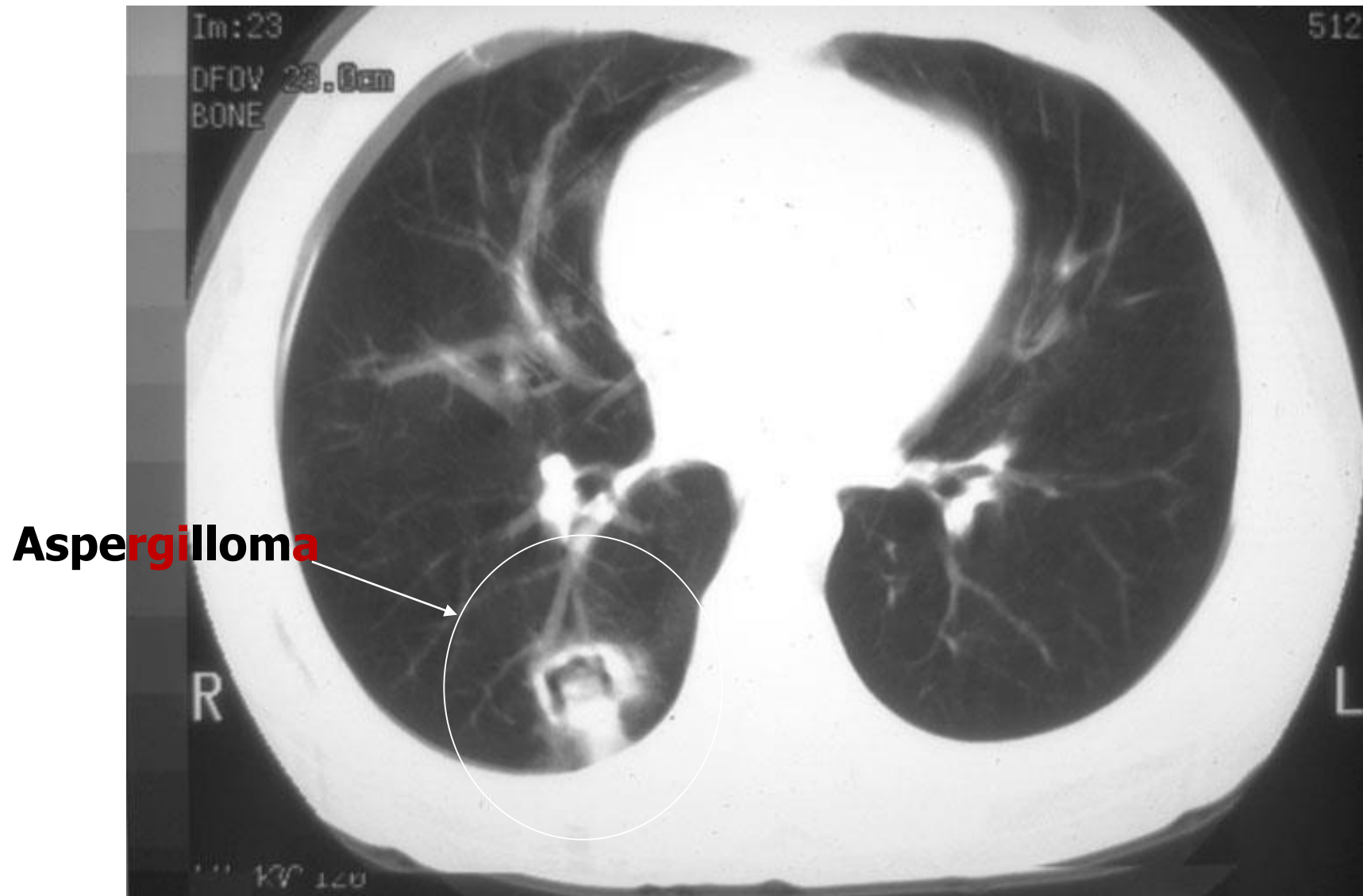


# Aspergillosis

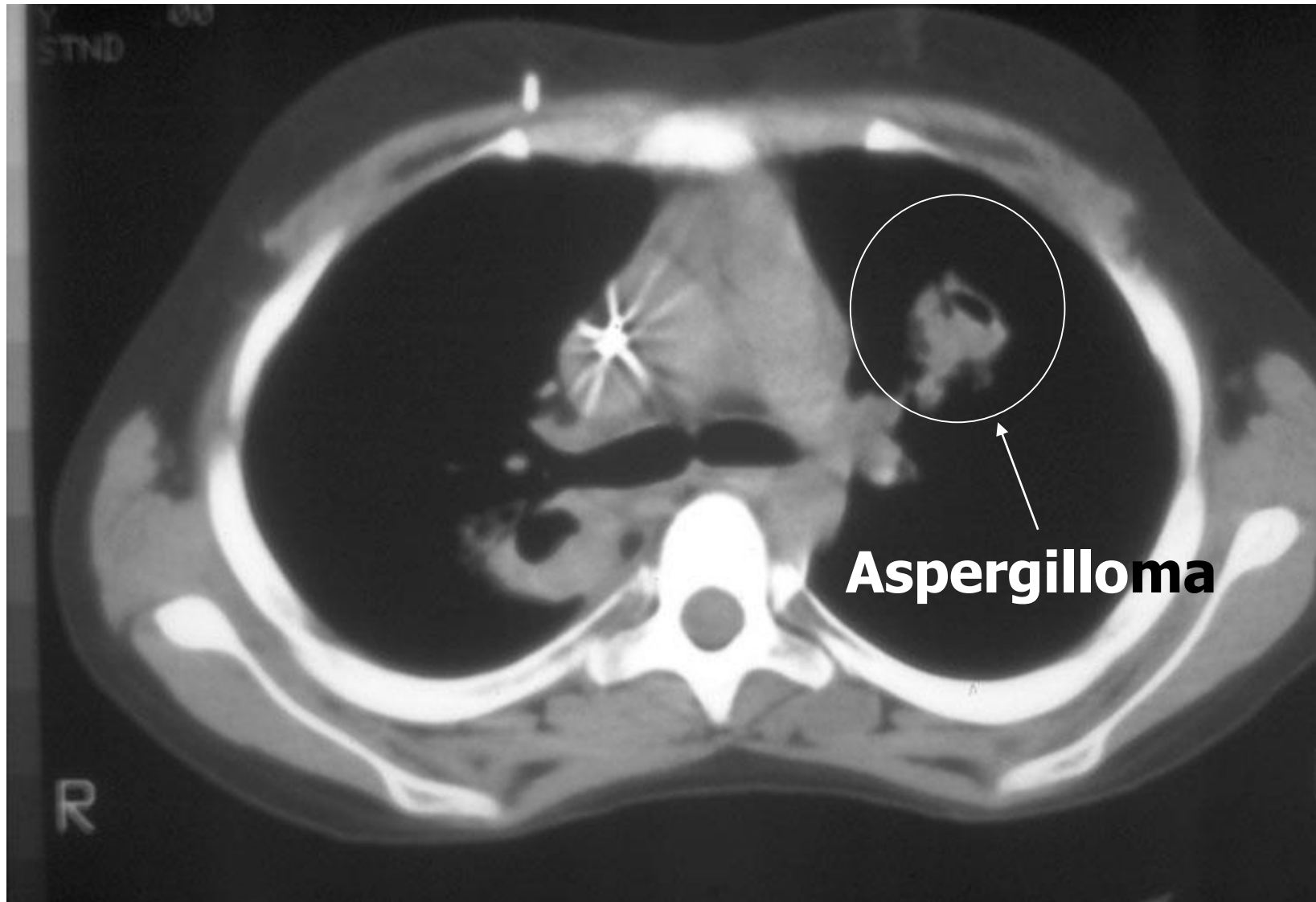


**Aspergilloma**

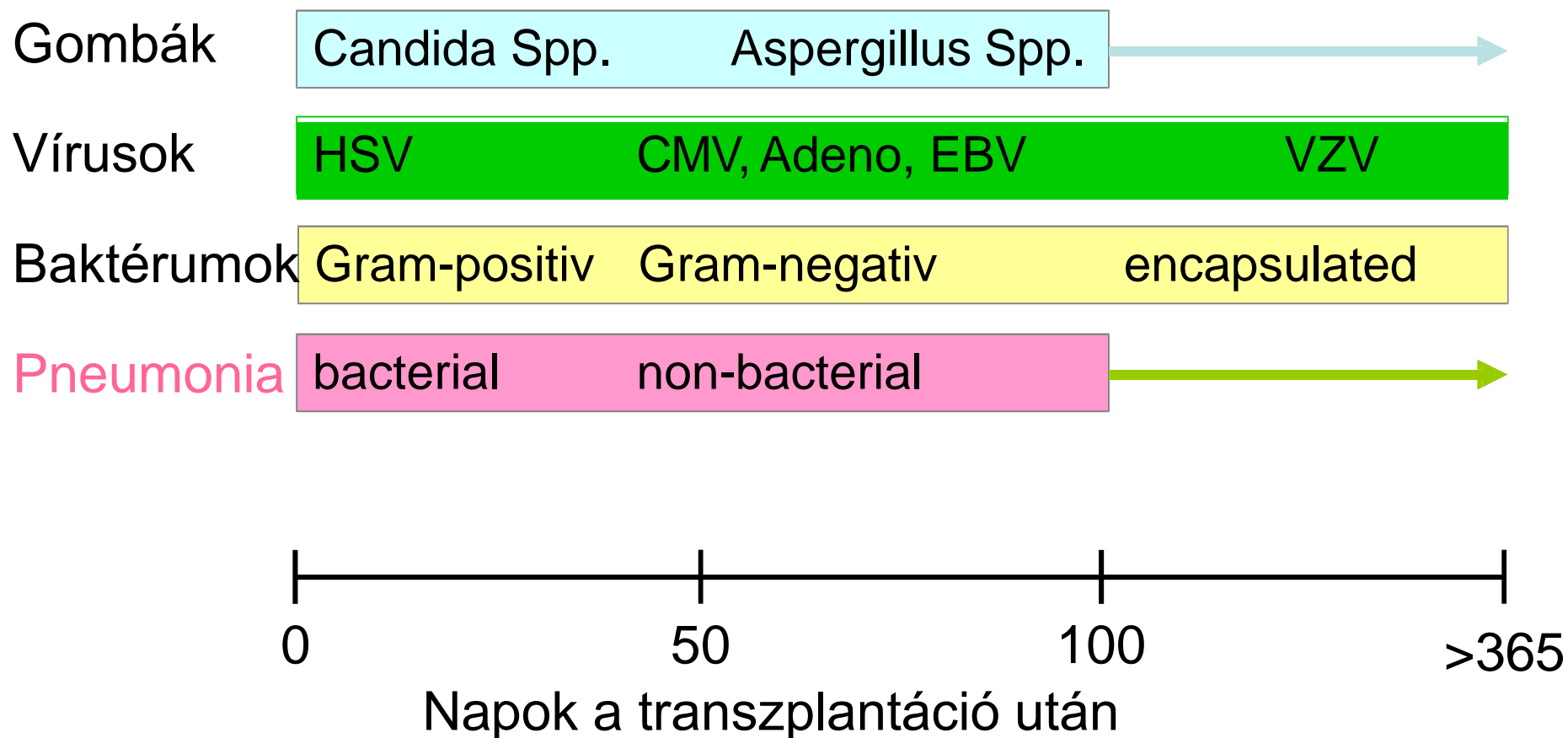
# Aspergillosis



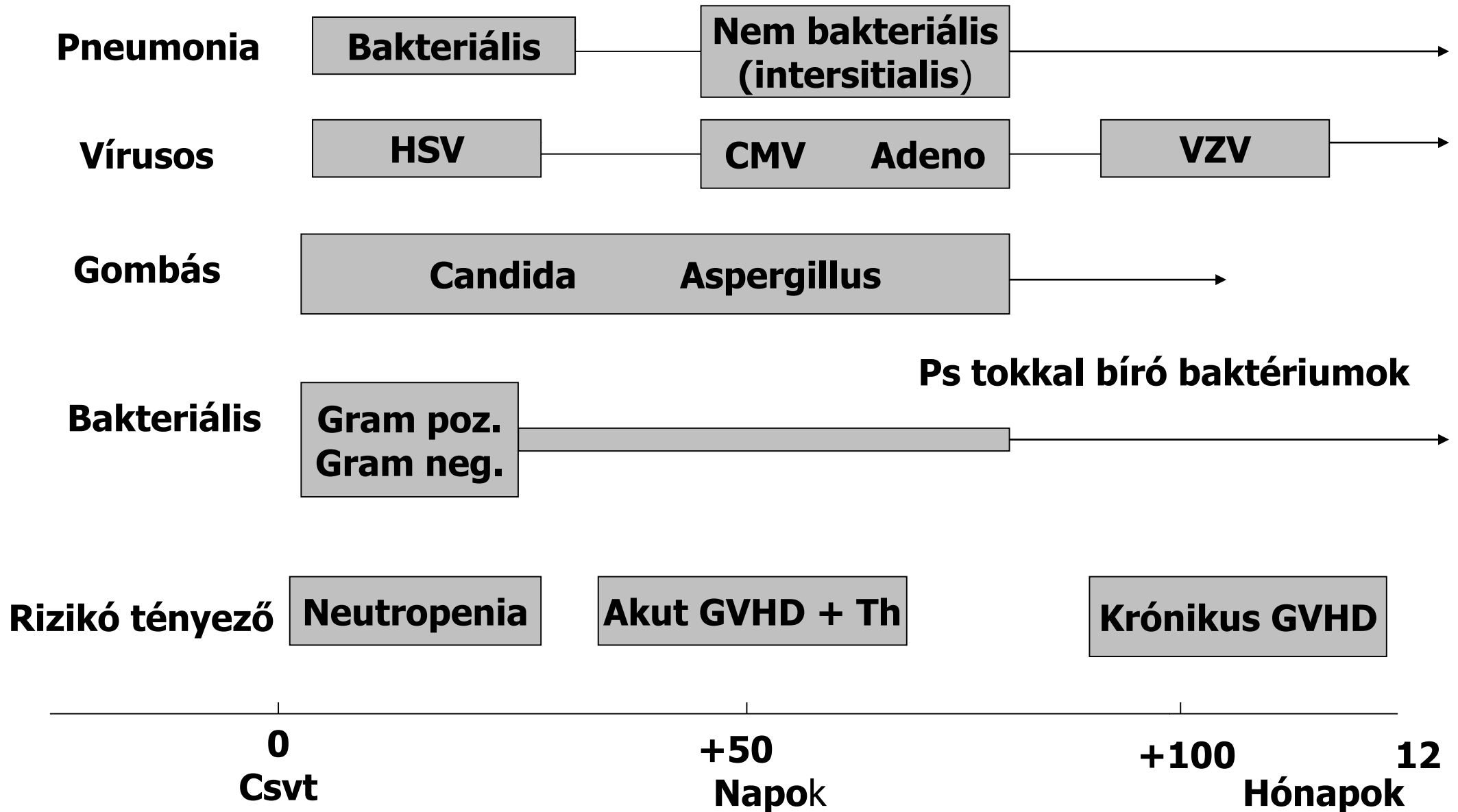
# Aspergillosis



# Infektív komplikációk Allogén SCT után



# Infekciók csontvelő-transzplantált betegekben



1. fázis: megtapadás előtt

2. fázis: megtapadás után

3. fázis: késői

Neutropenia,  
Barrierkárosodás  
(mucositis, centrális  
kanül)

Csökkent humorális és  
celluláris immunitás; először  
NK és sejtek jönnek, de  
korlátozott T sejt repertoár

Csökkent humorális és  
celluláris immunitás; B- és CD4  
T sejtszám lassan nő és a  
repertoár szélesedik

Baktérium

Gram negatív baktériumok

Gram pozitív baktériumok

Gastrointestinális streptococcusok

Tokos baktériumok

Vírus

Herpes simplex

CMV

Légúti és enterális vírusok

Egyéb vírusok: pl. HHV

Varicella zoster

EBV PTLD

Gomba

Aspergillus species

Candida species

Aspergillus species

Pneumocystis

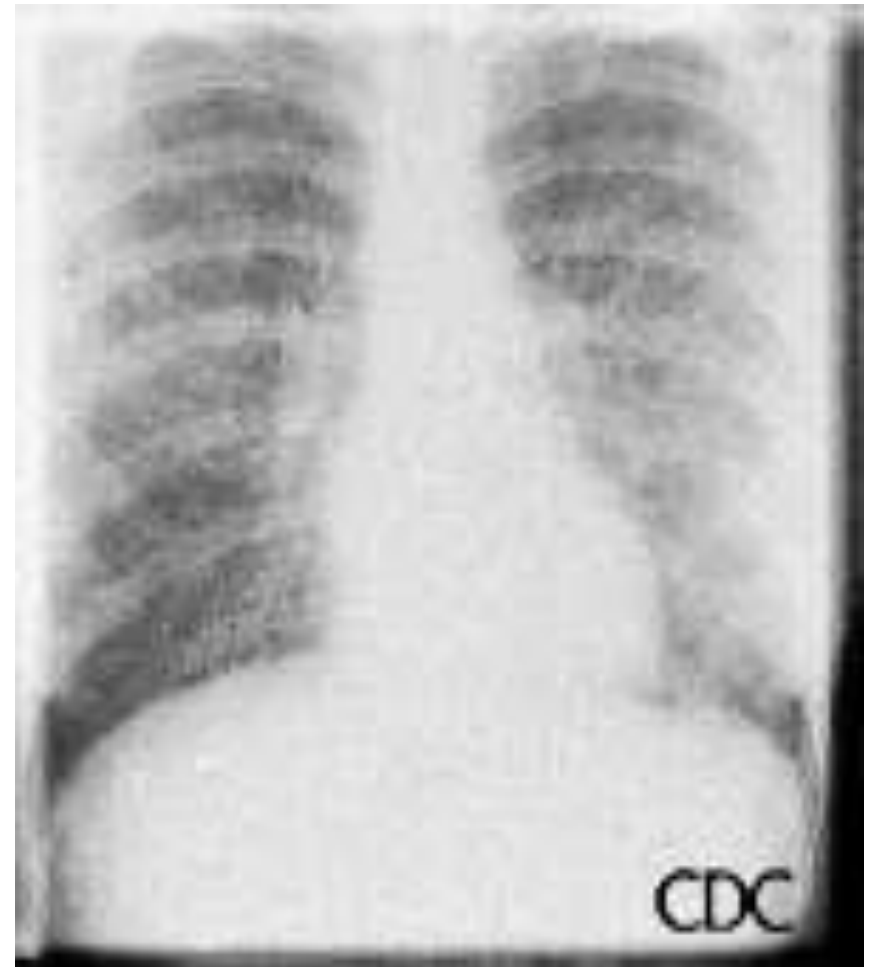
# CMV intersticiális pneumonia

Medián kezdet: 50 nap

Az intersticiális  
pneumóniák fele

Halálozás ~ 85%

A csontvelő utáni  
halálozás vezető oka









# Chronicus GvHD

Kezdetben lichen planusra emlékeztető  
elváltozások → poikiloderma

Lokalizált forma: epidermális atrophia, focalis  
fibrosis, morphea-szerű elváltozások, komoly  
gyulladás nélkül

Generalizált forma: gyulladásos elváltozások →  
kiterjedt fibrosis, scleroderma

# Késői mellékhatások

Krónikus graft versus host betegség

Immundefektus és fertőzések

Légúti és tüdőbetegségek

Autoimmun kórképek

Neuroendokrin működészavar

Növekedési és fejlődési zavar

Infertilitás

Szívbetegség

Szemészeti problémák

Mozgásszervi betegségek

Fogászati eltérések

Húgy-ivarrendszeri működészavarok

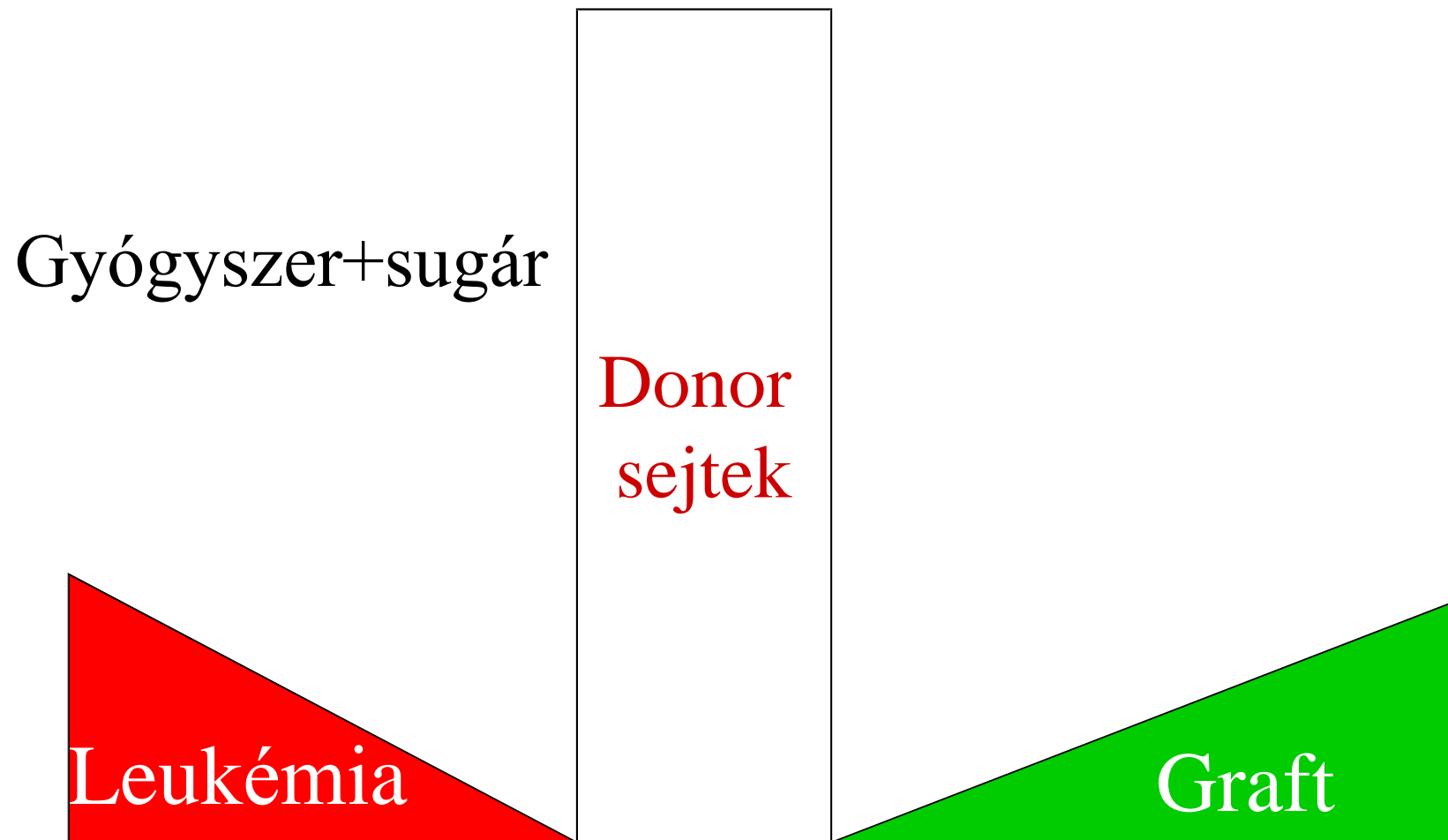
Gastrointestinális- és májműködési zavarok

Malignus betegségek

Központi- és perifériás idegrendszeri zavarok

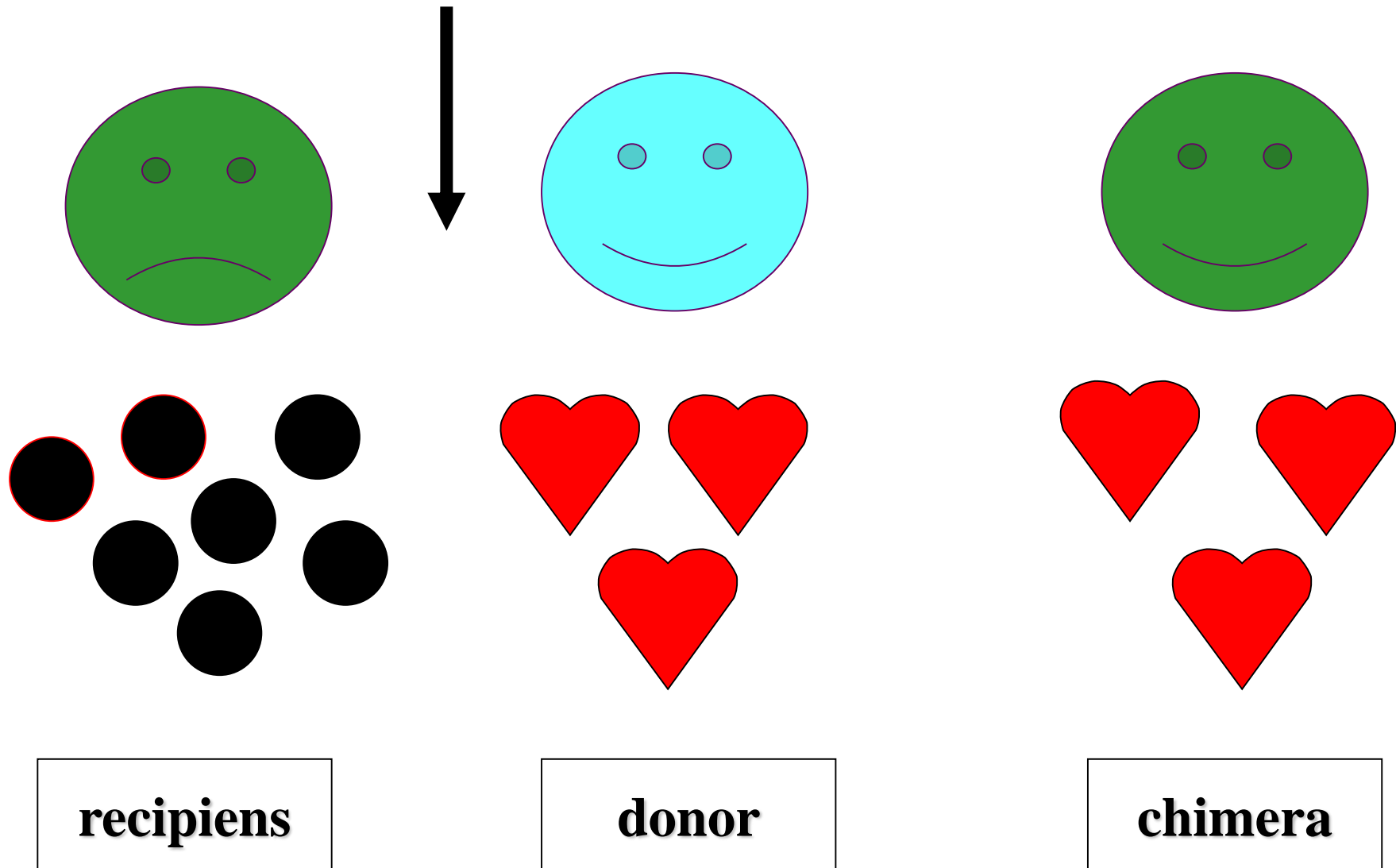
Pszichoszociális hatások

# Intenzív kondicionálás - kifejezett toxicitás



# Myeloablatív allogén őssejt-átültetés

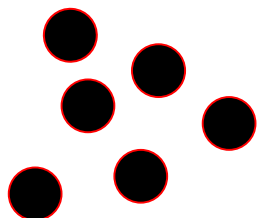
## Kondicionálás



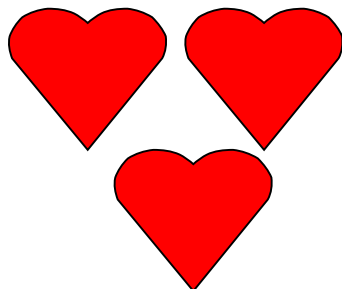
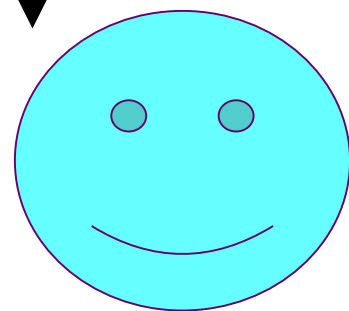
# Non-myeloablative őssejtátültetés

Őssejtátültetés  
(kondicionálás)

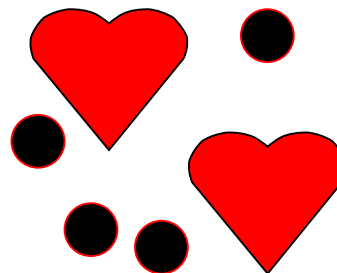
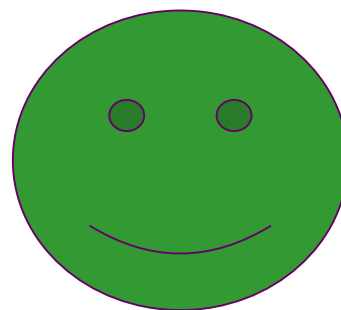
DLI



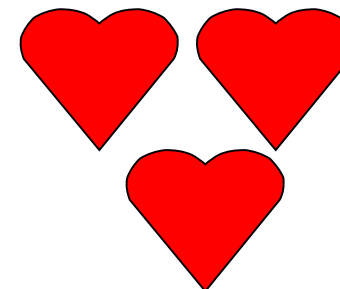
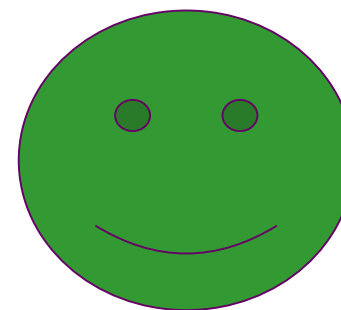
Recipiens



Donor



Kevert chimera



Teljes chimera

# Enyhébb kondicionálás - kevesebb toxicitás

Kevesebb  
Gyógyszer+sugár

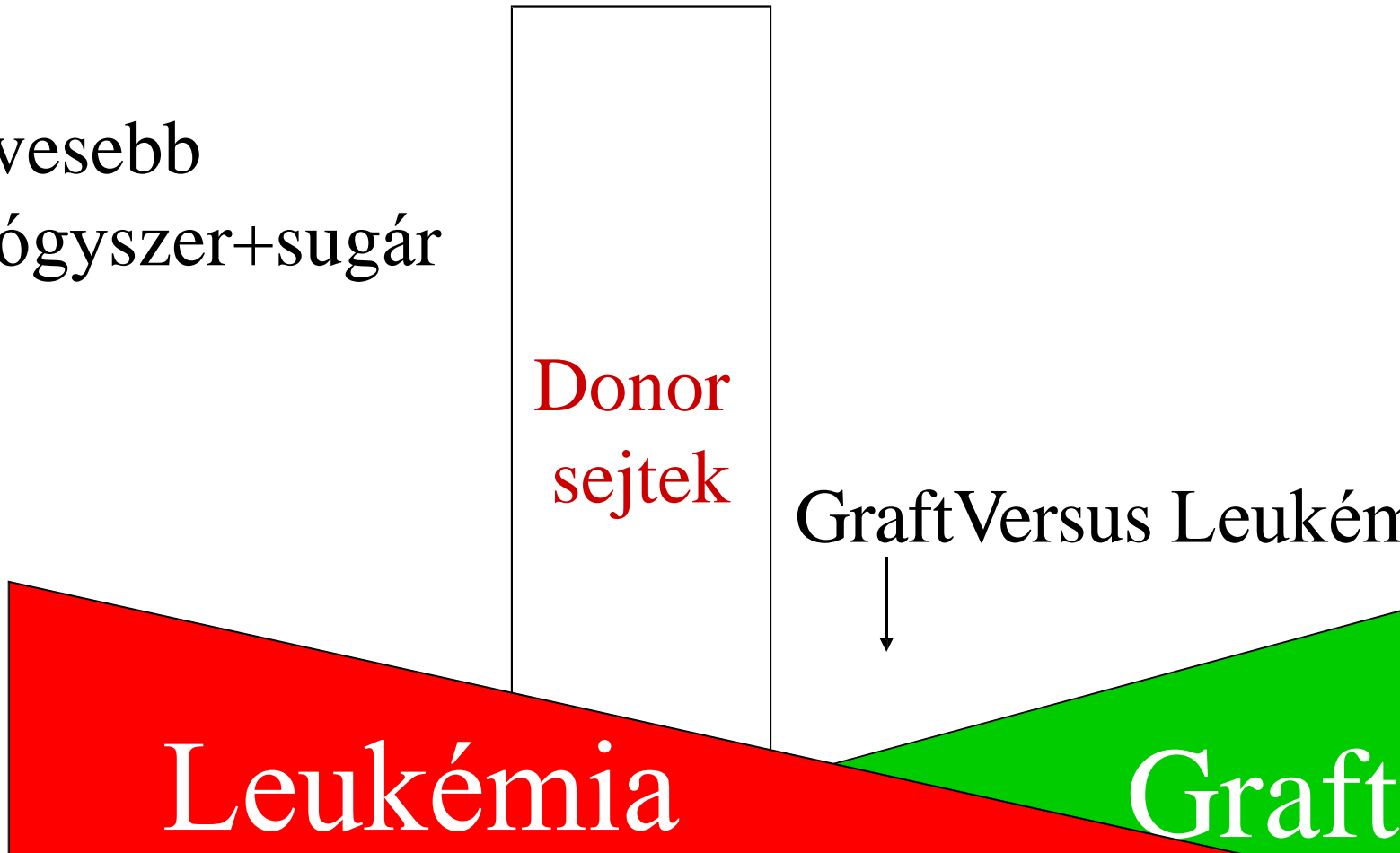
Donor  
sejtek

Graft Versus Leukémia

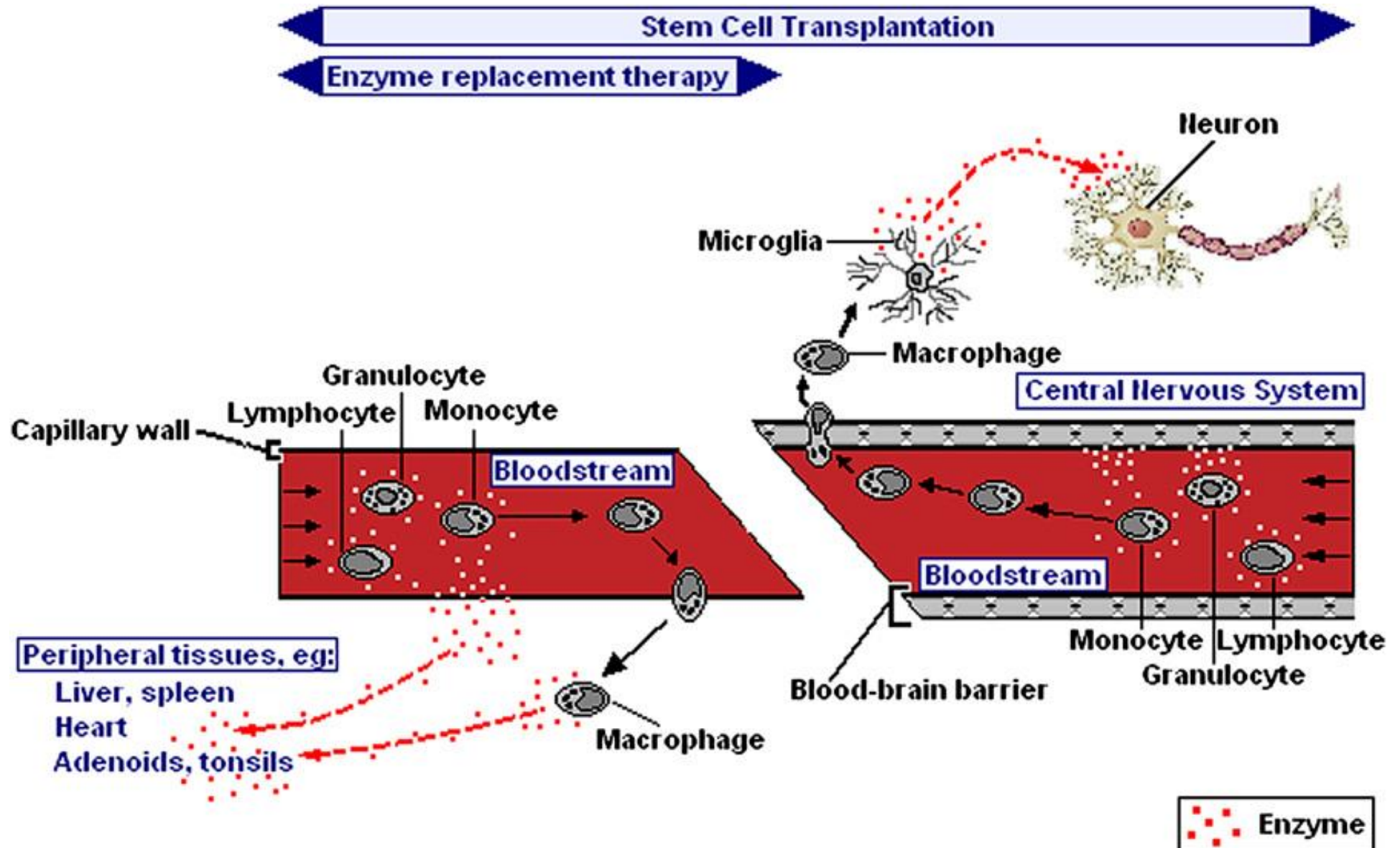


Leukémia

Graft



# Vérképző őssejt Txp tárolási betegségeiben



# **Allogén csontvelő-átültetés tárolási betegségben**

## **Feltételezett mechanizmusok:**

A beteg (recipiens) enzimhiányos csontvelői sejtjei kicserélődnek a donor egészséges csontvelői sejtjeire

A donor sejtjeiben termelődő enzim bejuthat a recipiens sejtjeibe (közvetlen sejt-sejt kontaktus vagy receptor-mediált úton)

„Metabolikus filtráció”: a keringő szubsztrátot a donor sejtjei bontják le

**Transzplantáció feltételei autoimmun betegségben**

Potenciálisan életveszélyes betegség

Hagyományos kezelés kudarca

Állapot reverzibilis legyen, kielégítő

életminőség biztosítása

Transzplantációra alkalmas állapot

# Patofiziológia

## Autológ

Intenzívebb immunszuppresszív kezelés

A korlátozott T sejt repertoár helyreállítása

A T- és B sejt szubpopulációkban a naív populáció növelése ( $\Leftrightarrow$  memória)

Thymusbeli „reprocessing”

A normális T reg sejtpopuláció helyreállítása

A kóros T reg populáció eltüntetése...

## Allogén

Előzöek + graft versus autoimmunitás hatás

# Az immunológiai rekonstitúciót meghatározó tényezők allo-Txp után

## **Transzplantáció:**

**Nincs klinikailag jelentős, tartós donor eredetű T- és B sejt immunválaszkészség**

**A recipiens lympho-haemopoetikus rendszere nagyrészt elpusztult (kondicionálás)**

**A lymphoid rekonstitúció során megismétlődik a lymphoid ontogenesis**

## **Transzplantáció előtti tényezők:**

HLA különbség a donor-recipiens között (MUD, haplo)

Recipiens thymus működése (életkor!)

A donor és a recipiens korábbi infekciói

## **Transzplantáció jellemzői:**

Graft T sejt mentesítése (normális IgG termelés 9→12 hónap)

Kondicionálás módja („mini”, TBI vagy kemoth.)

Anti-lymphocyta antitestek a kondicionálásban

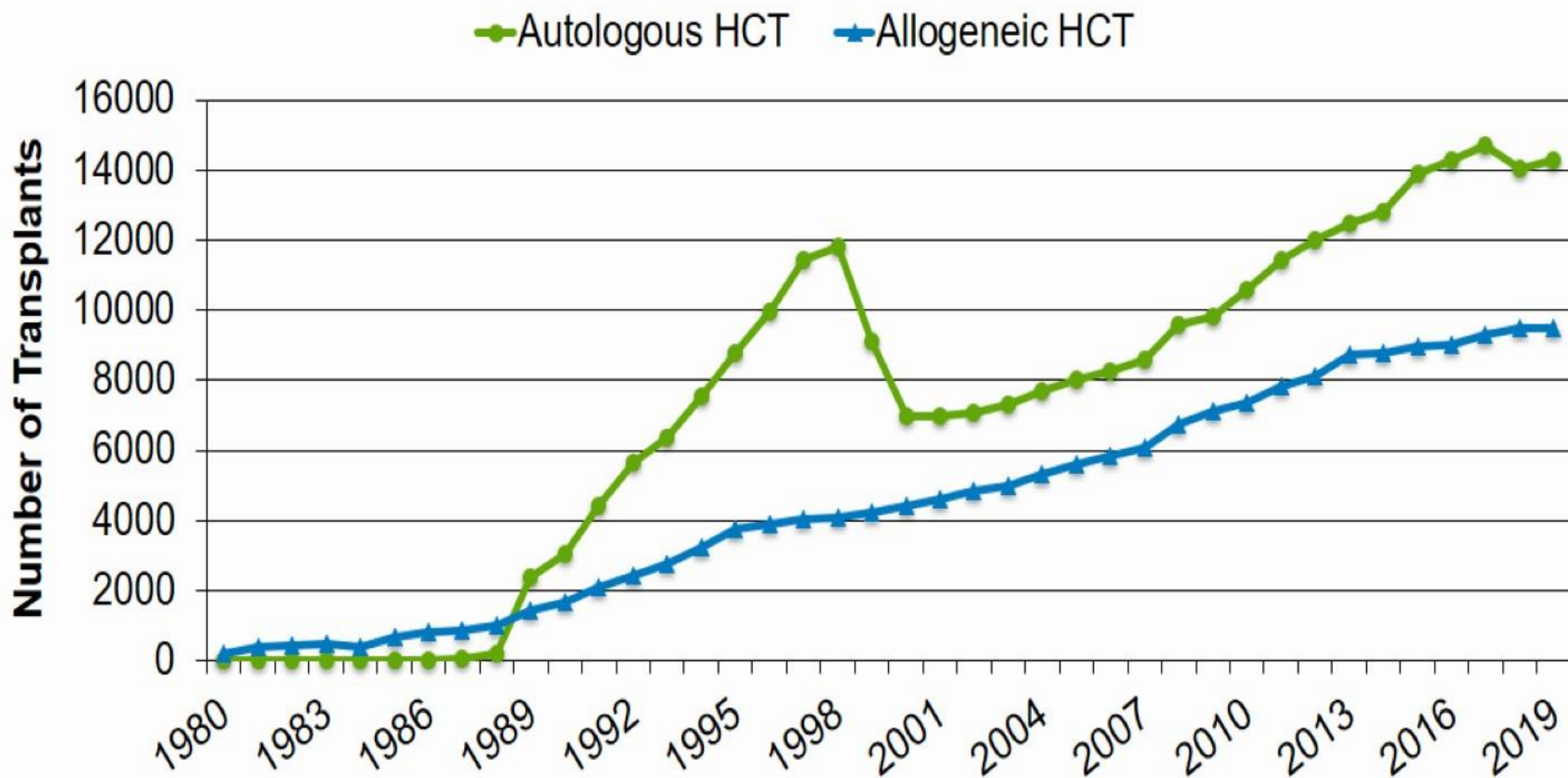
Őssejt forrás (periféria vs. csontvelő vs CBU)

## **Transzplantációt követő:**

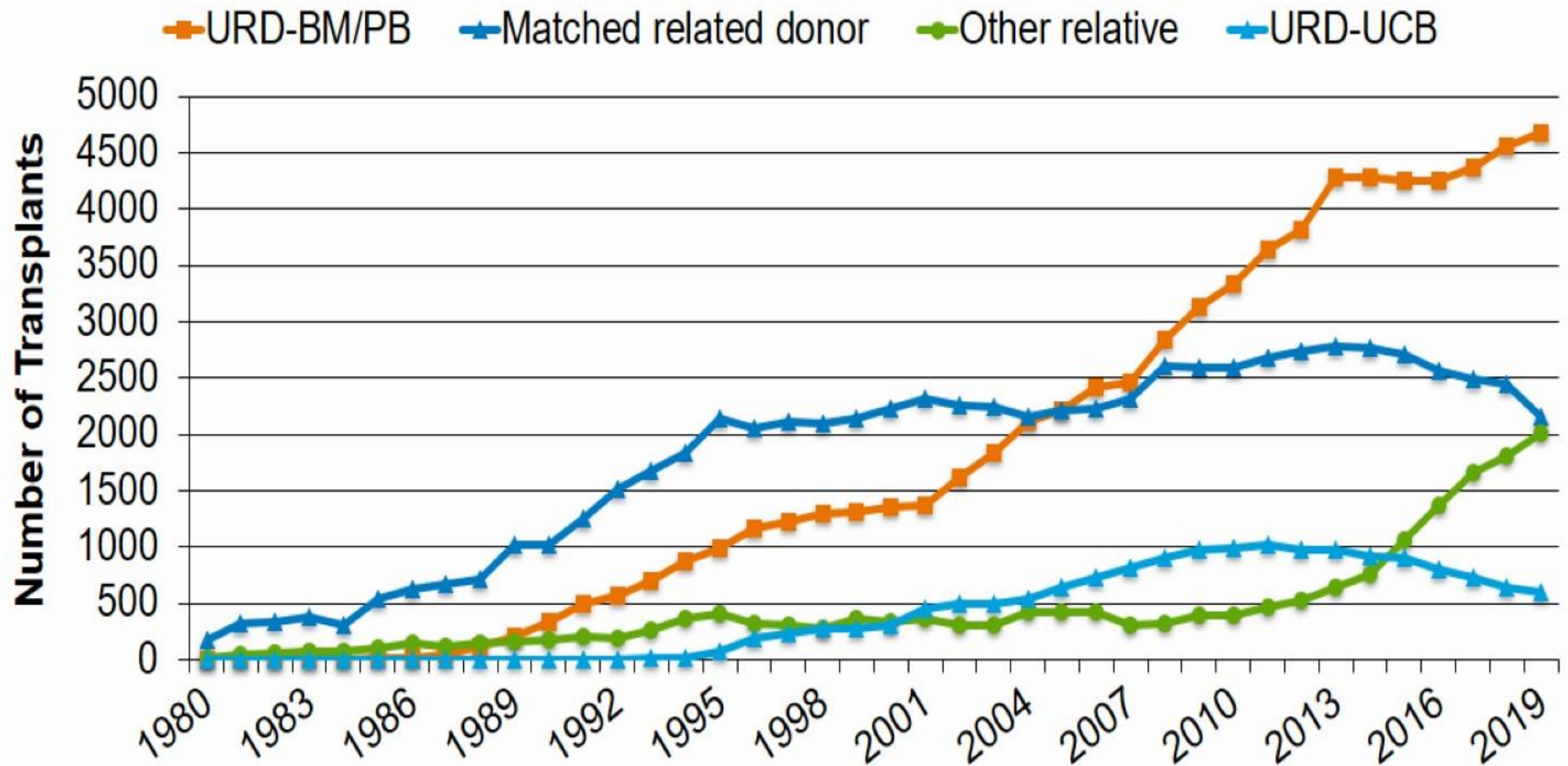
Akut és/vagy krónikus GvH (profilaxis és terápia)

Fertőzések (elsősorban CMV)

# Estimated Annual Number of HCT Recipients in the US by Transplant Type

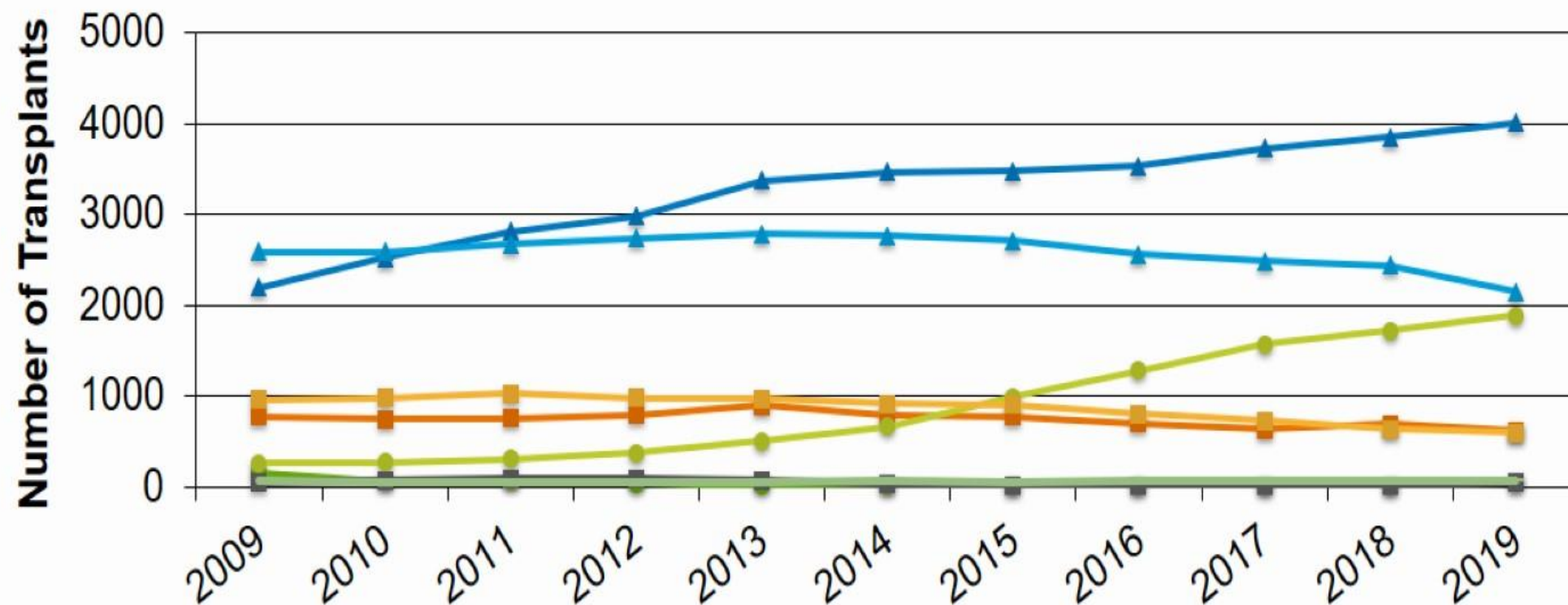


## Estimated Allogeneic HCT Recipients in the US by Donor Type

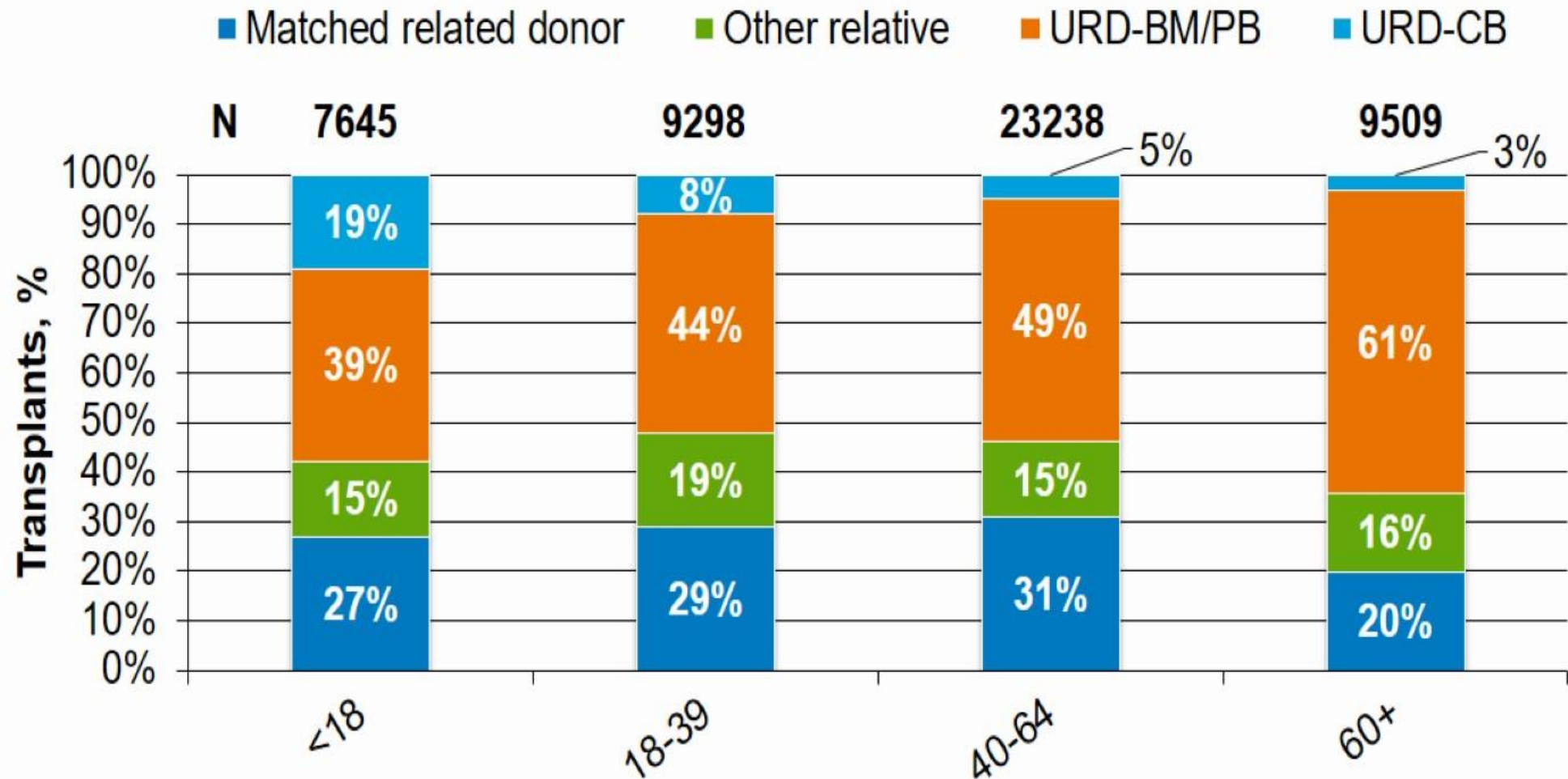


## Estimated Allogeneic HCT Recipients in the US by Donor Type

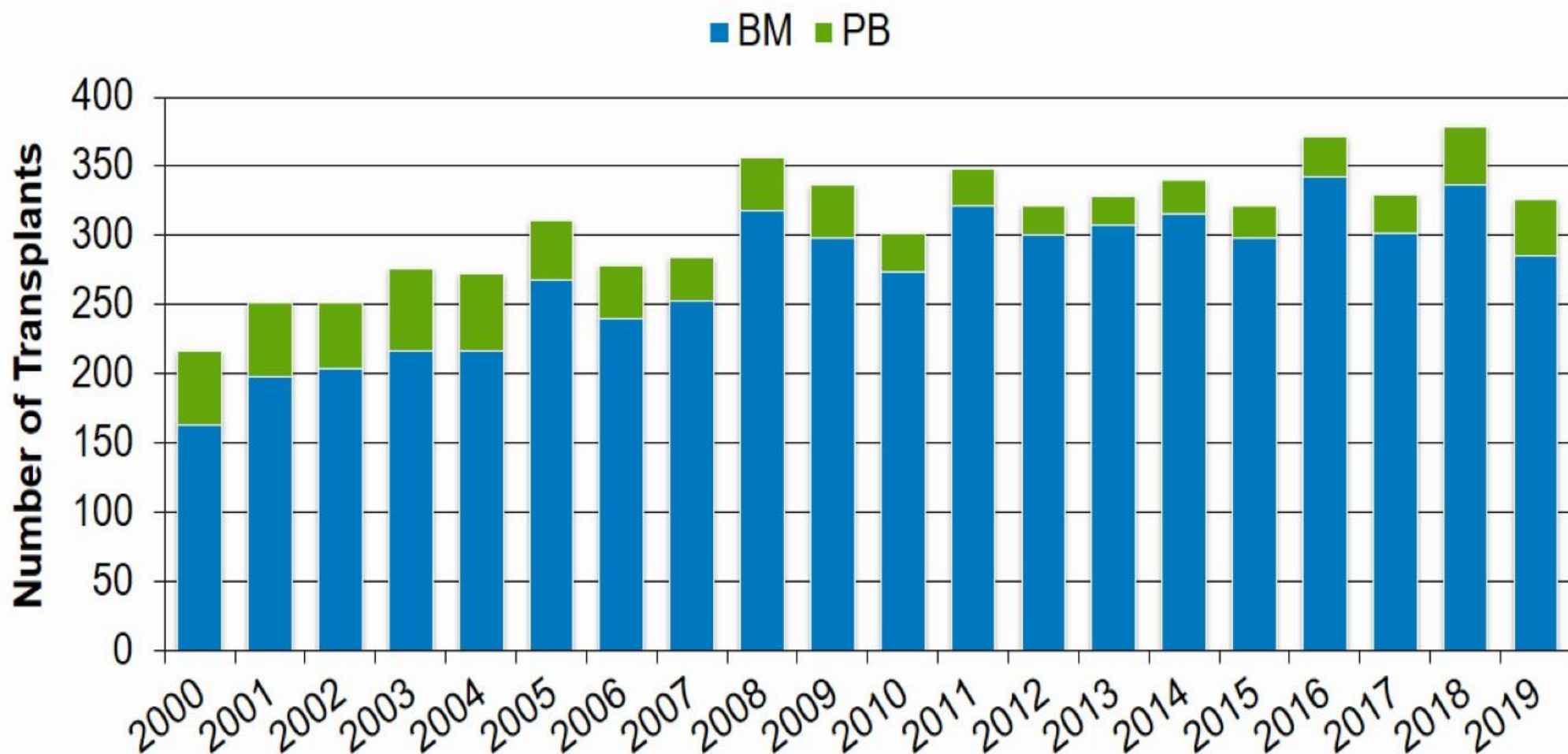
- URD-BM/PB, HLA-matched
- URD-BM/PB, HLA mismatched
- Haploidentical,  $\geq 2$  HLA antigen mismatch
- Other mismatched relative, HLA-match unknown
- URD-BM/PB, HLA match unknown
- Matched related donor
- URD-CB
- Haploidentical, 1 HLA antigen mismatch



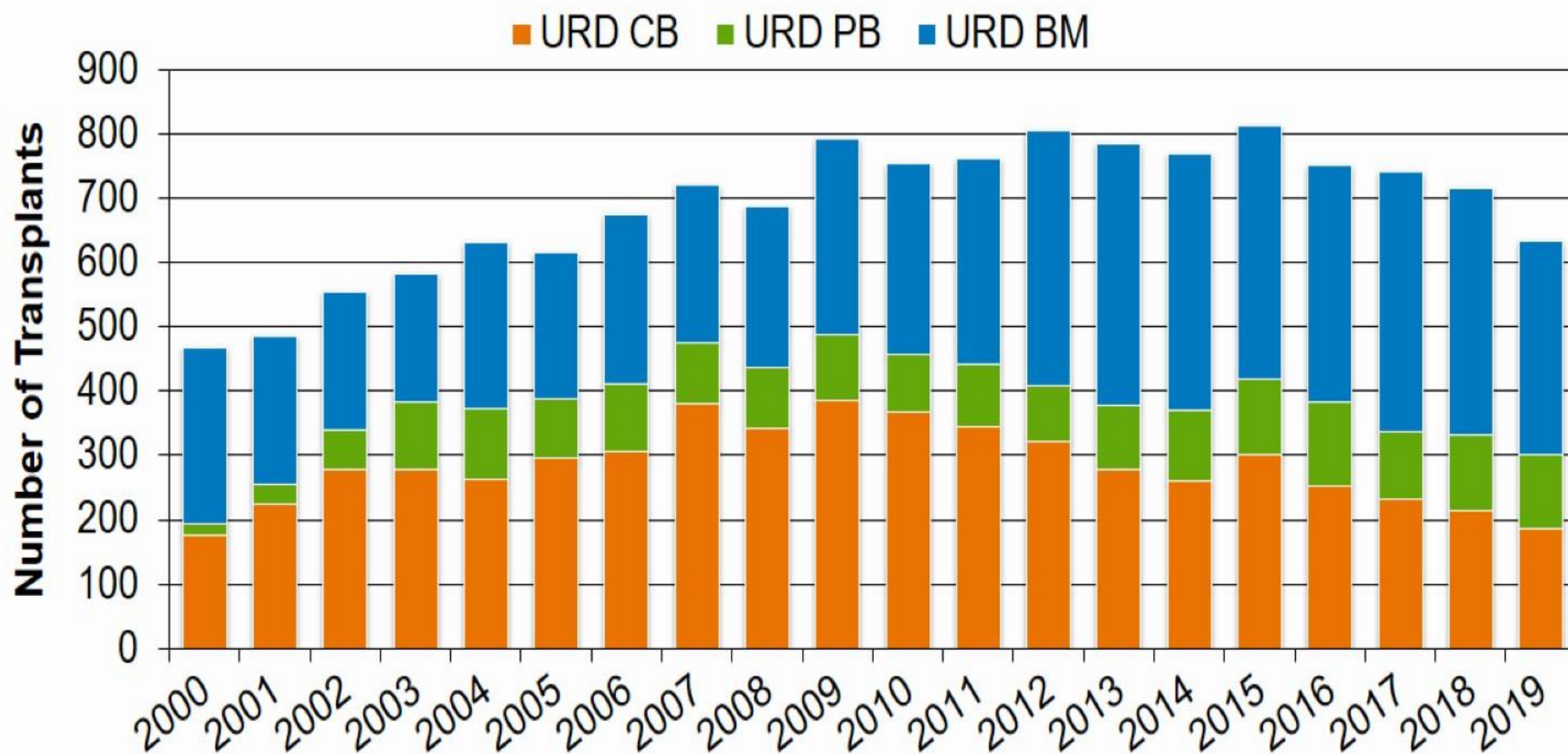
## HCT Recipient Donor Type in the US by Age Group 2014-2019



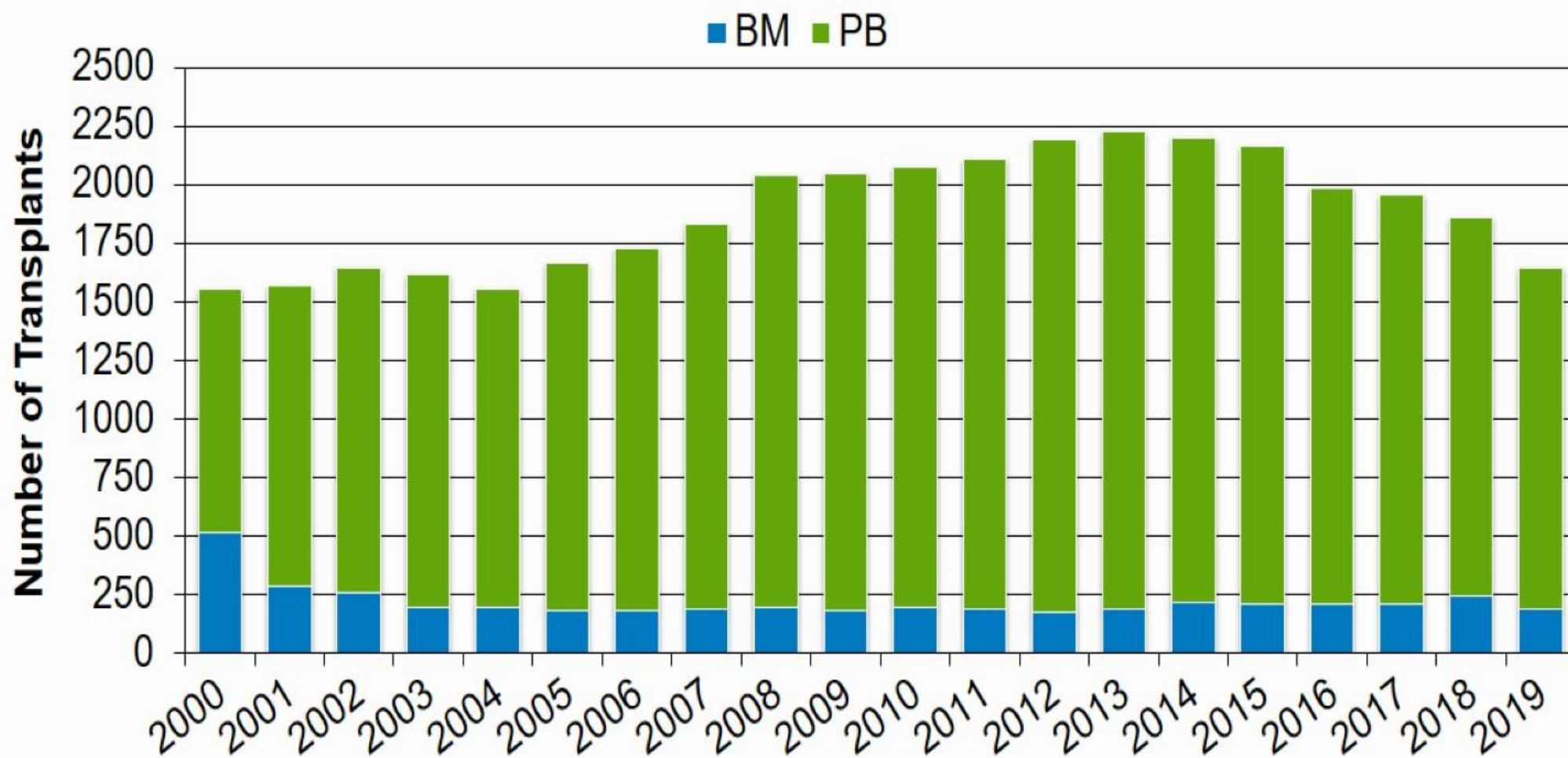
## Matched Related Donor Allogeneic HCT in the US in Patients <18 Years



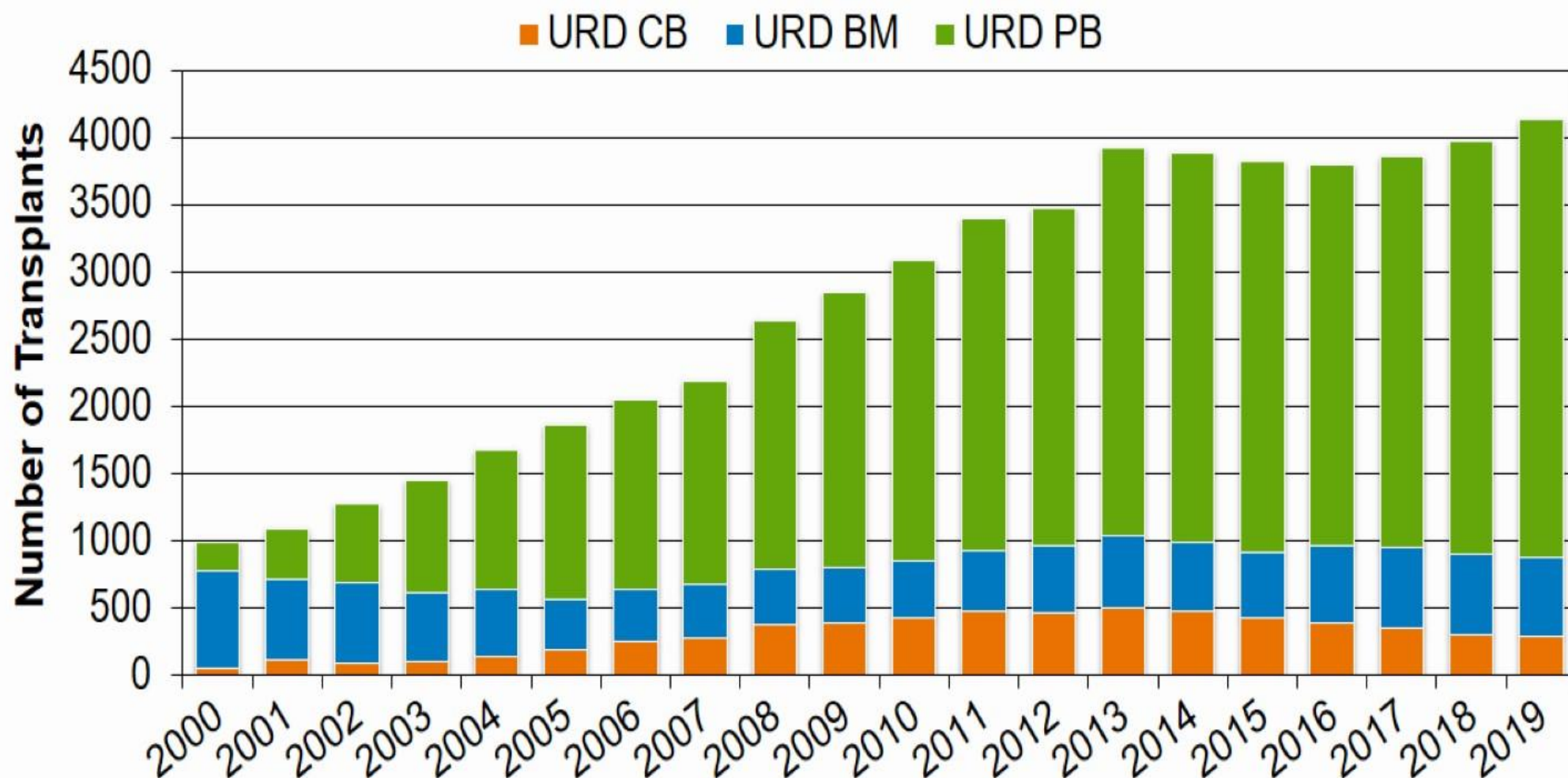
## Unrelated Donor Allogeneic HCT in the US in Patients <18 Years



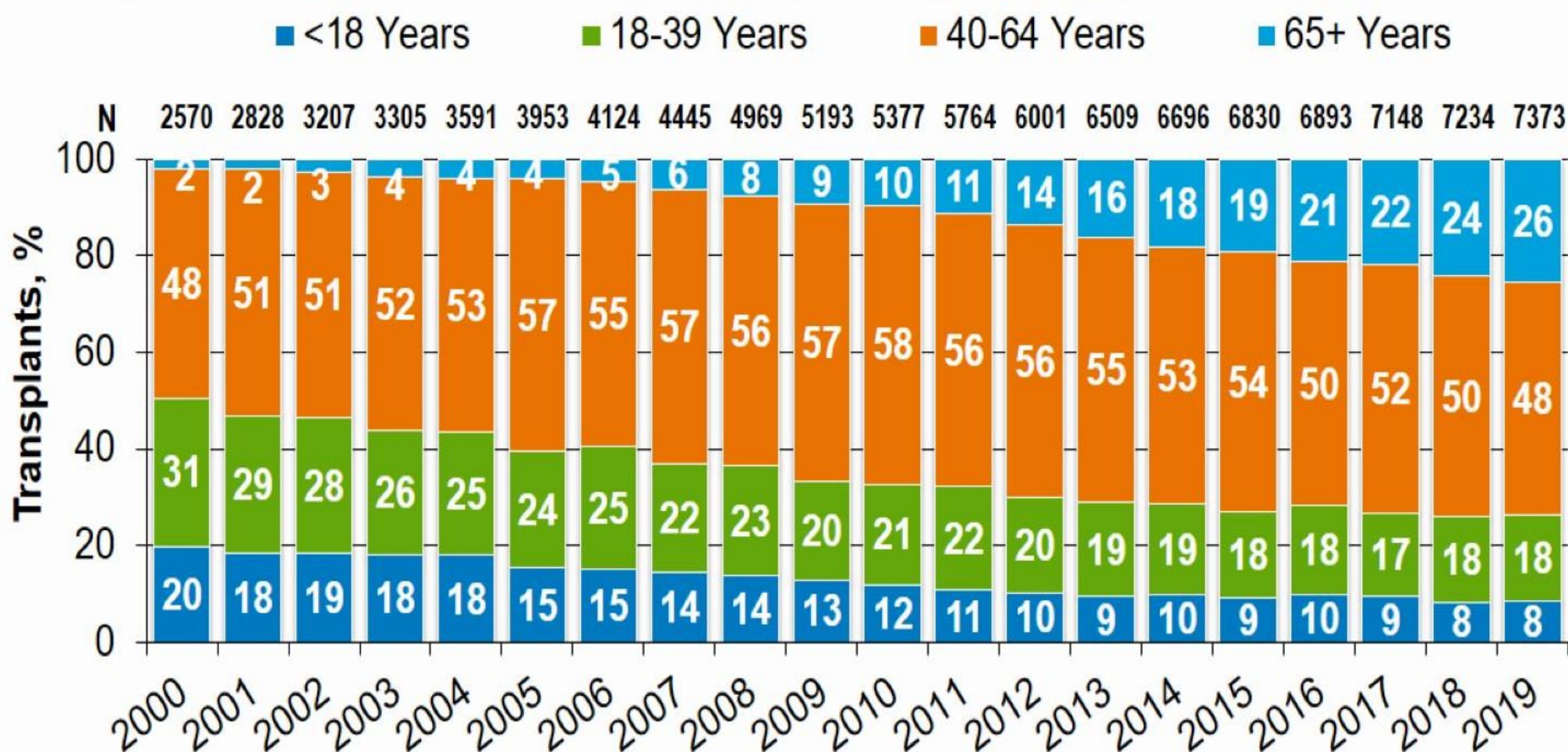
## Matched Related Donor Allogeneic HCT in the US in Patients $\geq 18$ Years



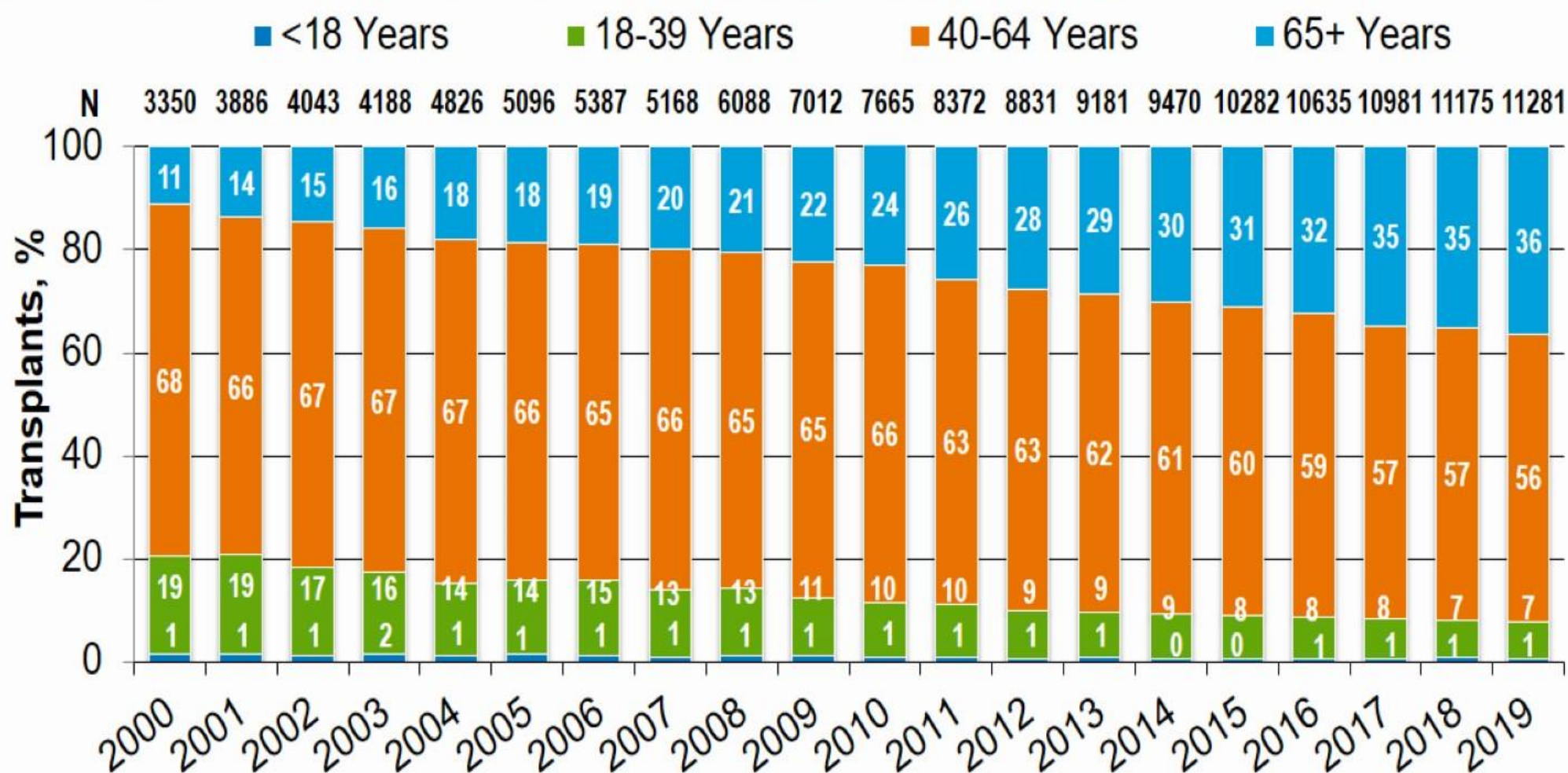
## Unrelated Donor Allogeneic HCT in the US in Patients $\geq 18$ Years



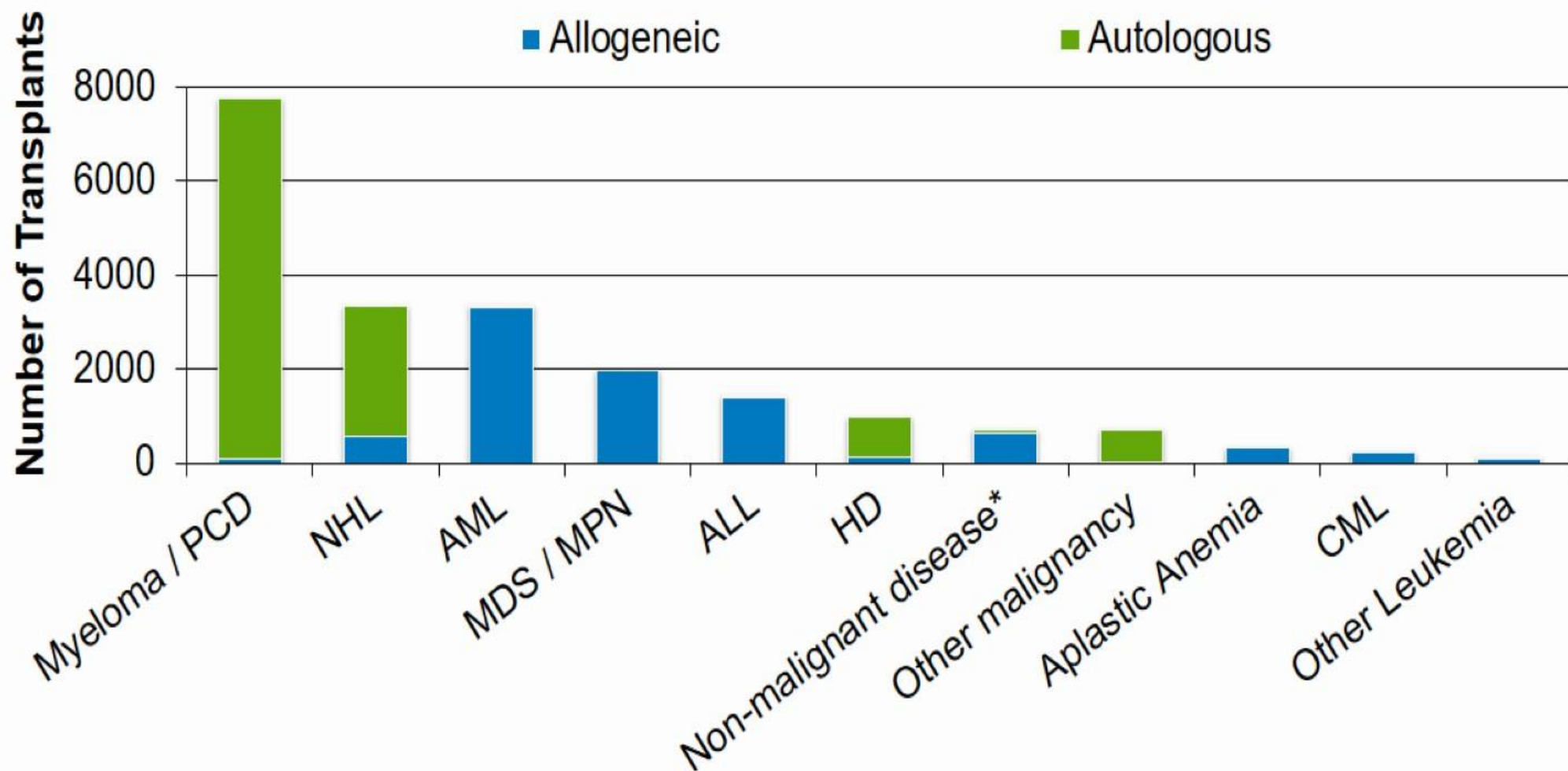
## Trends in Allogeneic HCT in the US by Recipient Age<sup>^</sup>



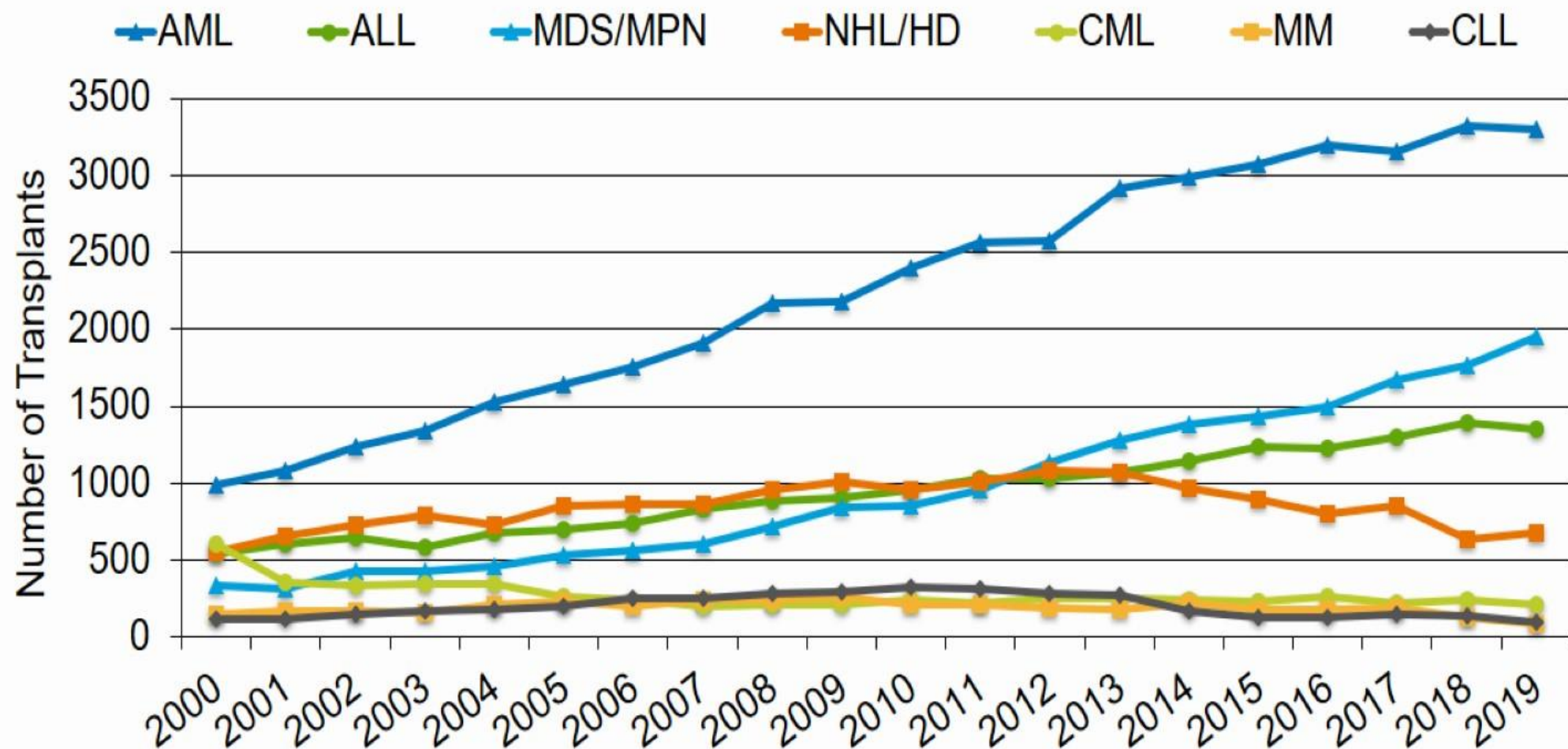
## Trends in Autologous HCT in the US by Recipient Age<sup>^</sup>



## Indications for Hematopoietic Cell Transplant in the US, 2019

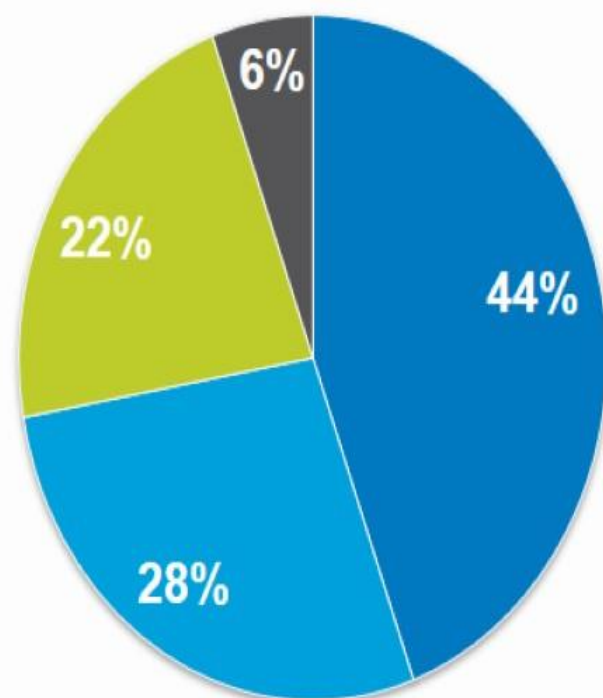


## Selected Disease Trends for Allogeneic HCT in the US



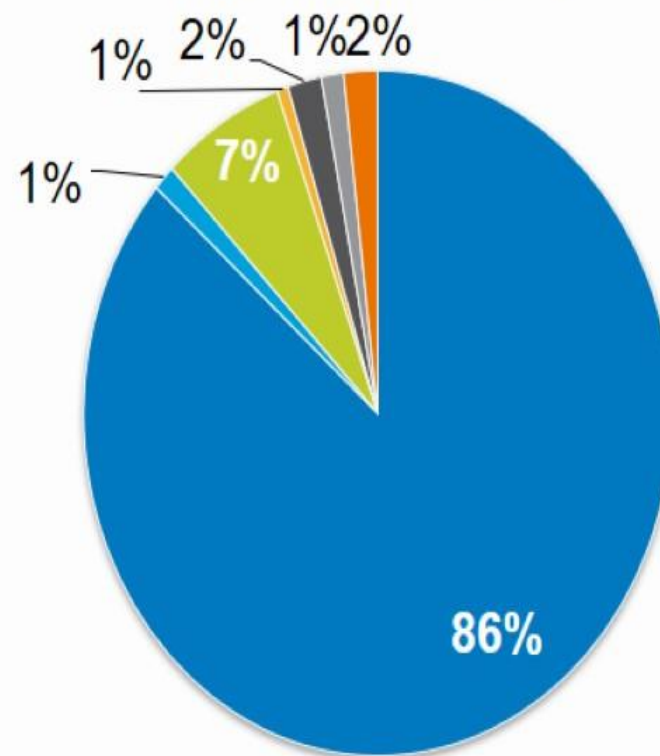
# Causes of Death after Pediatric (age <18) Autologous HCT in US, 2018-2019

Died within 100 days post-transplant



■ Primary Disease      ■ Infection  
■ Organ Failure      ■ Hemorrhage

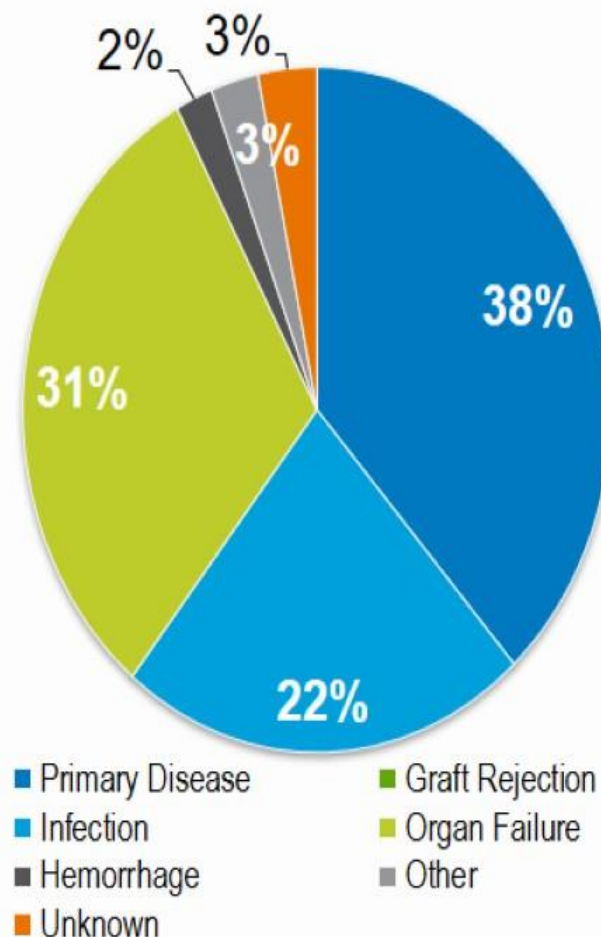
Died at or beyond 100 days post-transplant\*



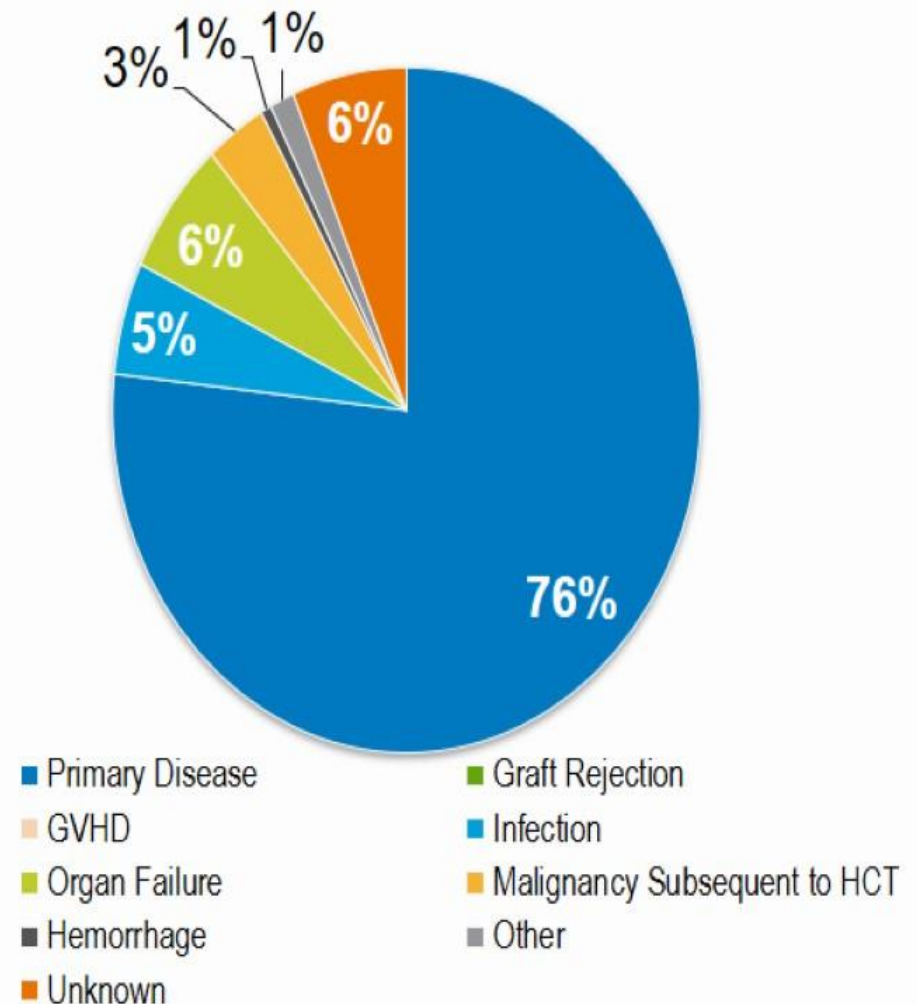
■ Primary Disease      ■ Infection  
■ Organ Failure      ■ Malignancy Subsequent to HCT  
■ Hemorrhage      ■ Other  
■ Unknown

# Causes of Death after Adult (age $\geq 18$ ) Autologous HCT in the US, 2018-2019

Died within 100 days post-transplant

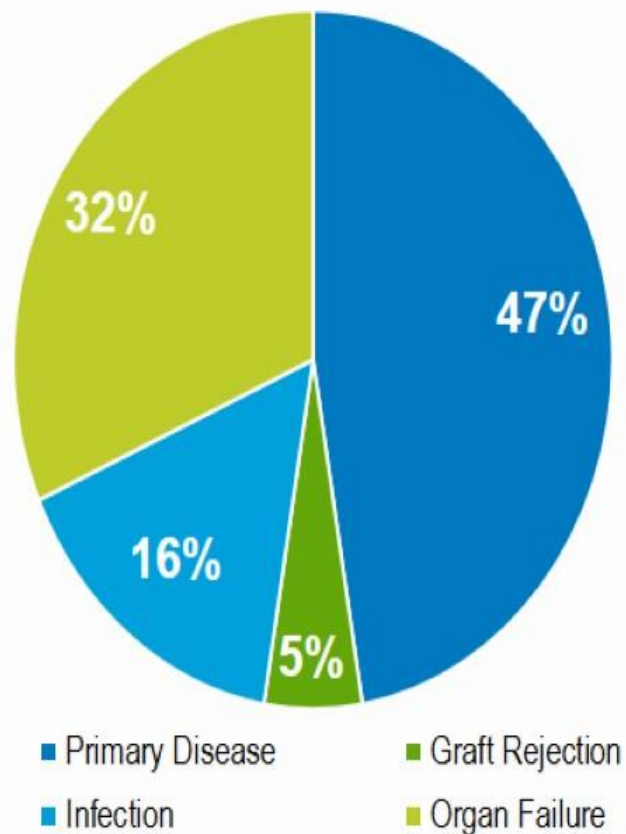


Died at or beyond 100 days post-transplant\*

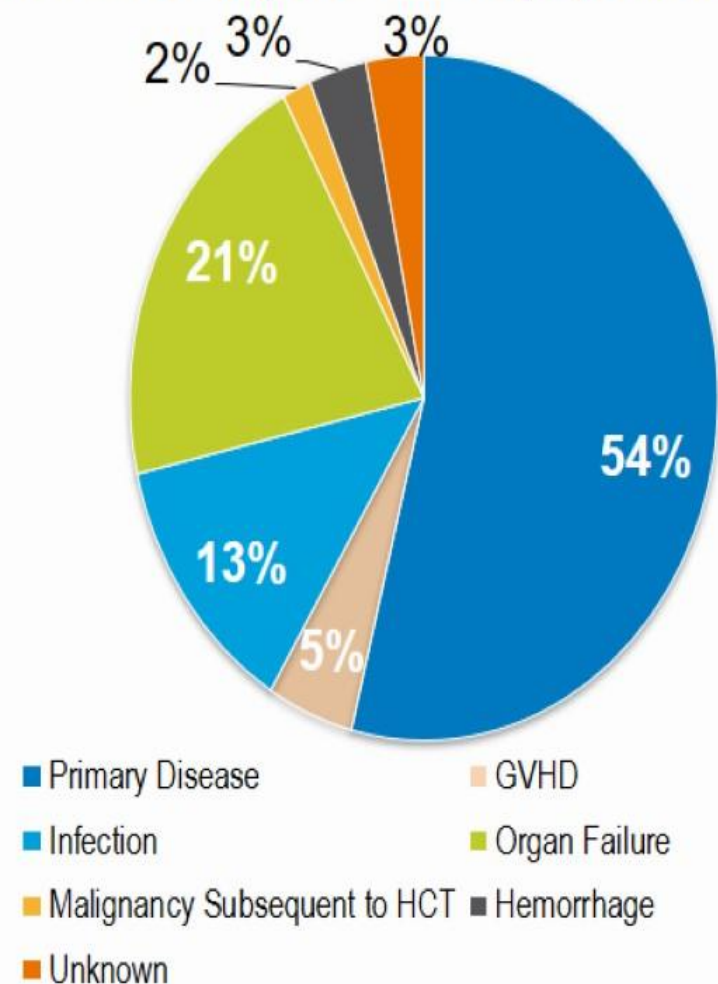


# Causes of Death after Pediatric (age <18) Matched Related HCT in the US, 2018-2019

Died within 100 days post-transplant

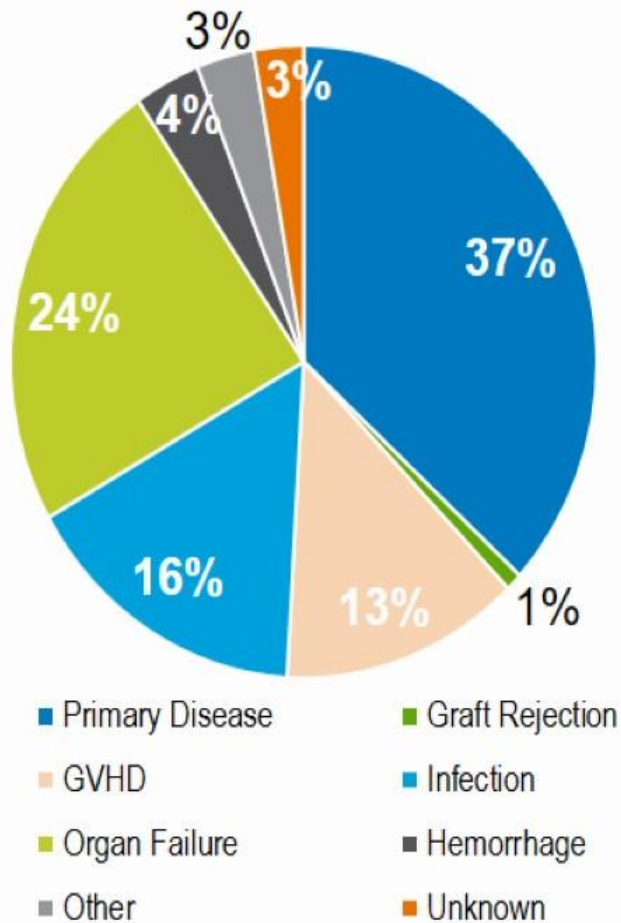


Died at or beyond 100 days post-transplant\*

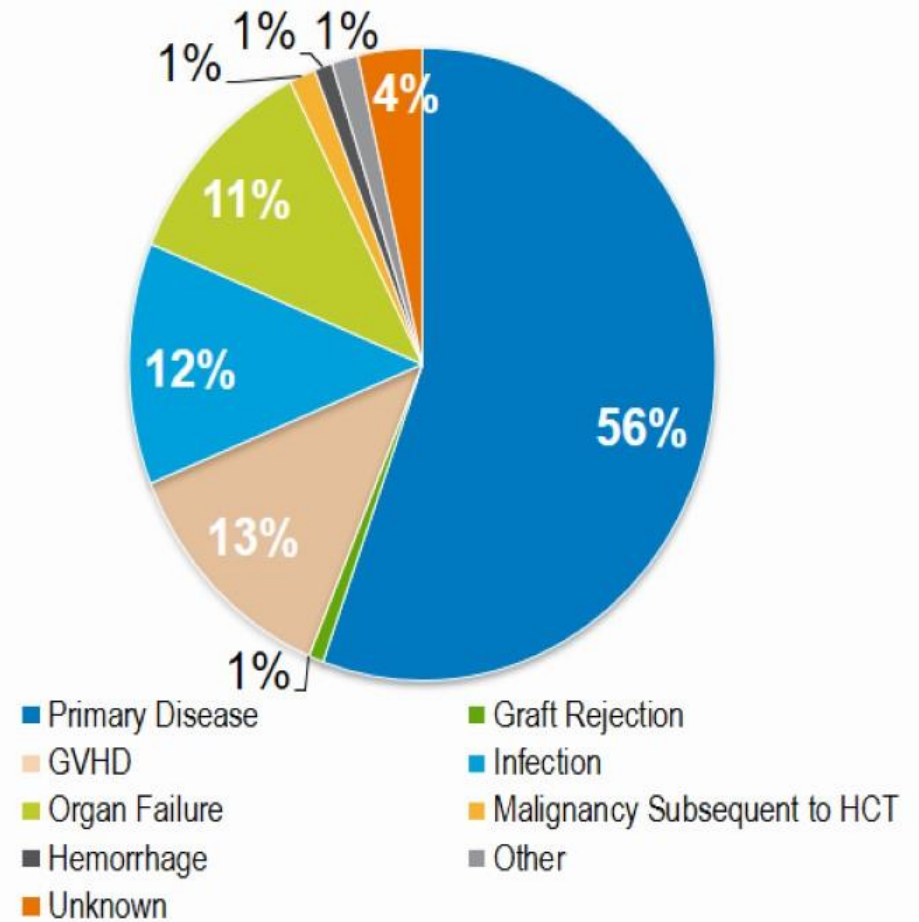


# Causes of Death after Adult (age $\geq 18$ ) Matched Related HCT in the US, 2018-2019

Died within 100 days post-transplant

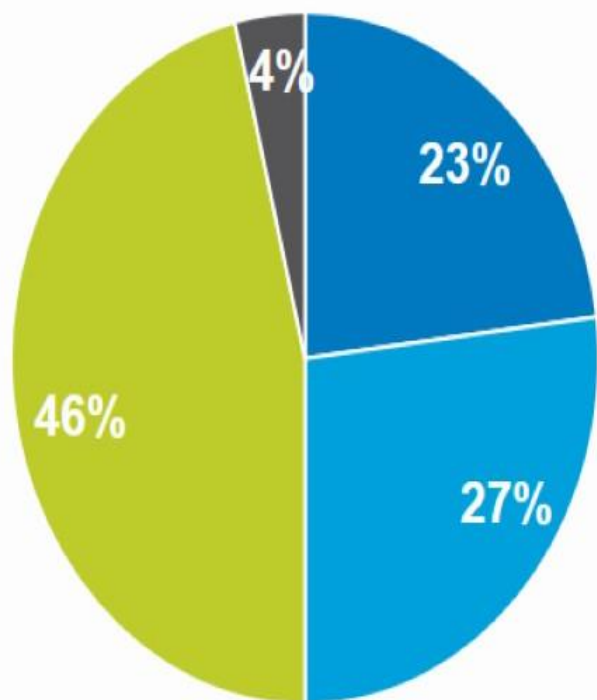


Died at or beyond 100 days post-transplant\*



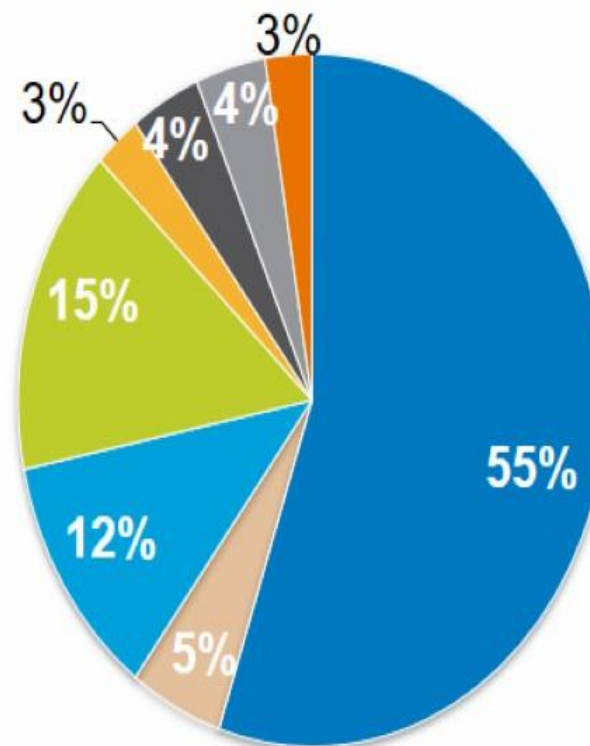
# Causes of Death after Pediatric (age <18) Haploidentical Donor HCT in the US, 2018-2019

Died within 100 days post-transplant



■ Primary Disease  
■ Infection  
■ Organ Failure  
■ Hemorrhage

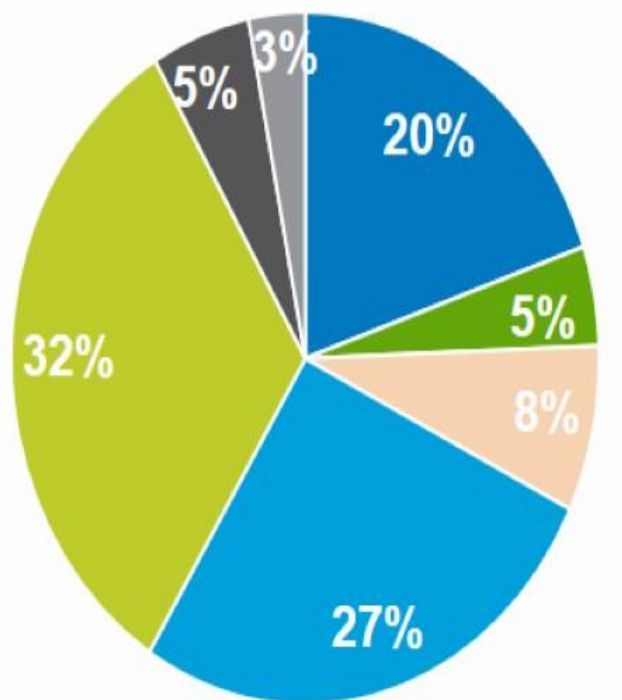
Died at or beyond 100 days post-transplant\*



■ Primary Disease  
■ Infection  
■ Malignancy Subsequent to HCT  
■ GVHD  
■ Organ Failure  
■ Hemorrhage  
■ Other  
■ Unknown

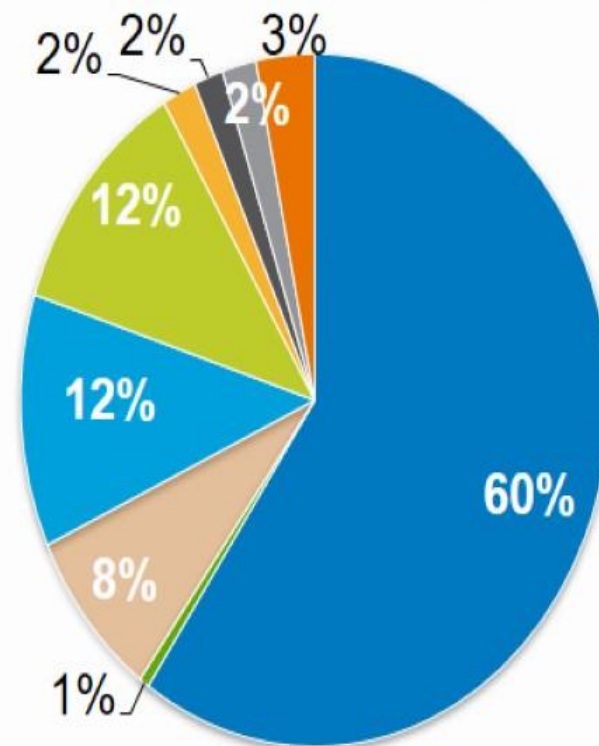
# Causes of Death after Adult (age $\geq 18$ ) Haploidentical Donor HCT in the US, 2018-2019

Died within 100 days post-transplant



- Primary Disease
- GVHD
- Organ Failure
- Other
- Graft Rejection
- Infection
- Hemorrhage
- Unknown

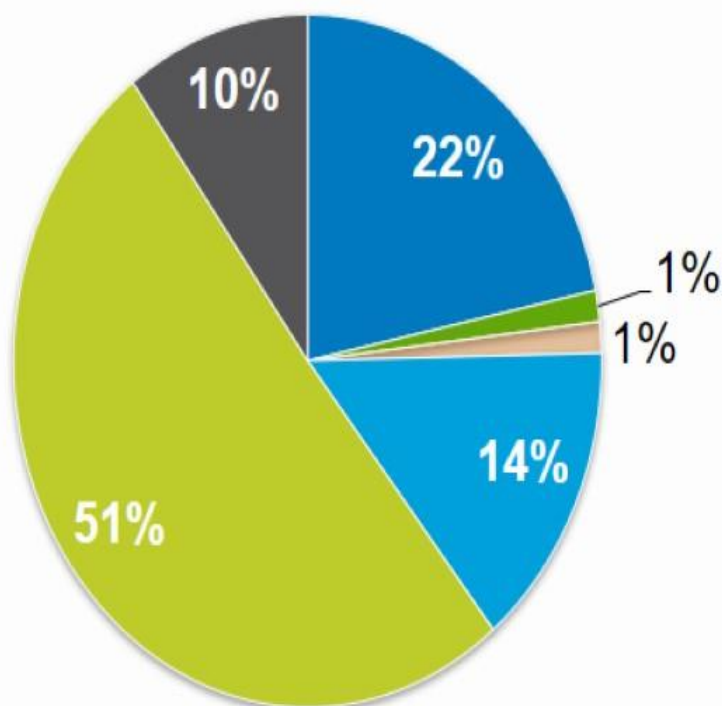
Died at or beyond 100 days post-transplant\*



- Primary Disease
- GVHD
- Organ Failure
- Hemorrhage
- Unknown
- Graft Rejection
- Infection
- Malignancy Subsequent to HCT
- Other

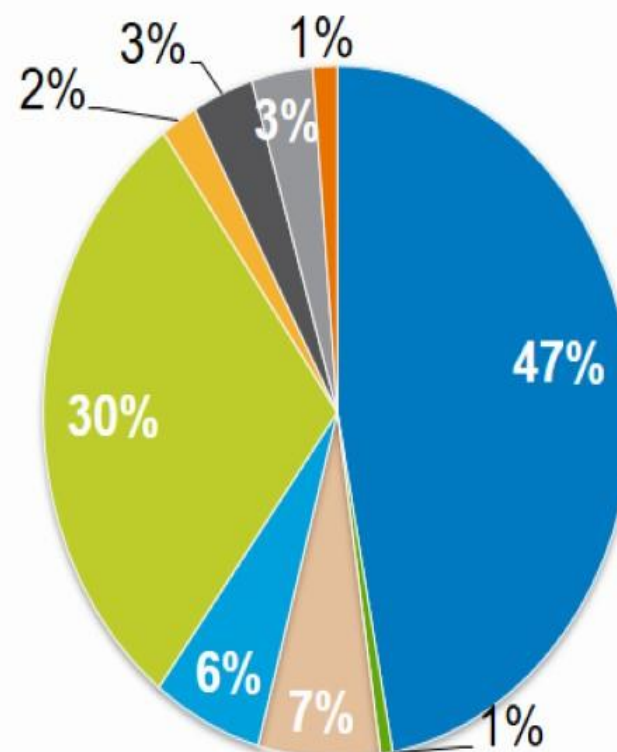
# Causes of Death after Pediatric (age <18) Unrelated Donor HCT in the US, 2018-2019

Died within 100 days post-transplant



- Primary Disease
- GVHD
- Organ Failure
- Graft Rejection
- Infection
- Hemorrhage

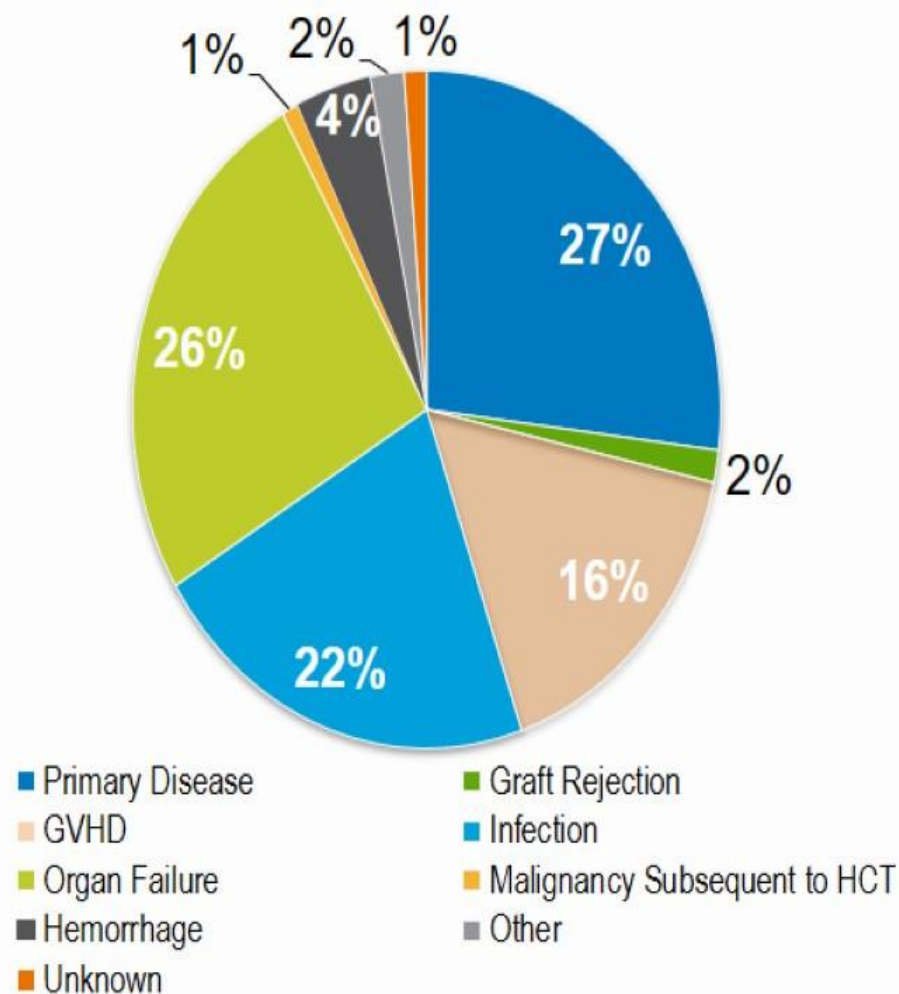
Died at or beyond 100 days post-transplant\*



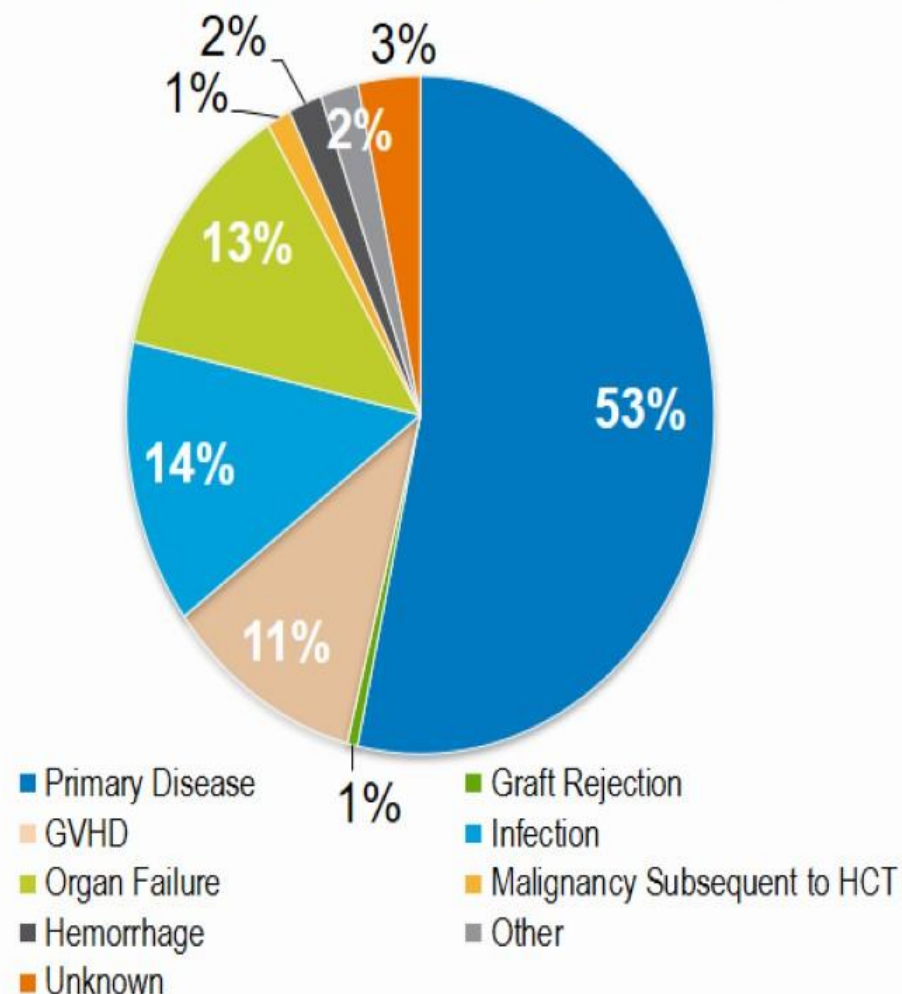
- Primary Disease
- GVHD
- Organ Failure
- Graft Rejection
- Infection
- Hemorrhage
- Malignancy Subsequent to HCT
- Other
- Unknown

# Causes of Death after Adult (age $\geq 18$ ) Unrelated Donor HCT in the US, 2018-2019

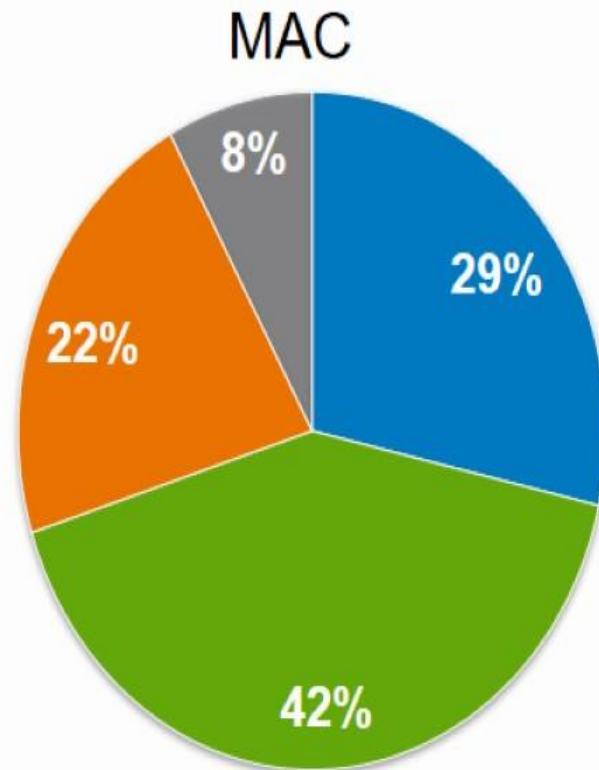
Died within 100 days post-transplant



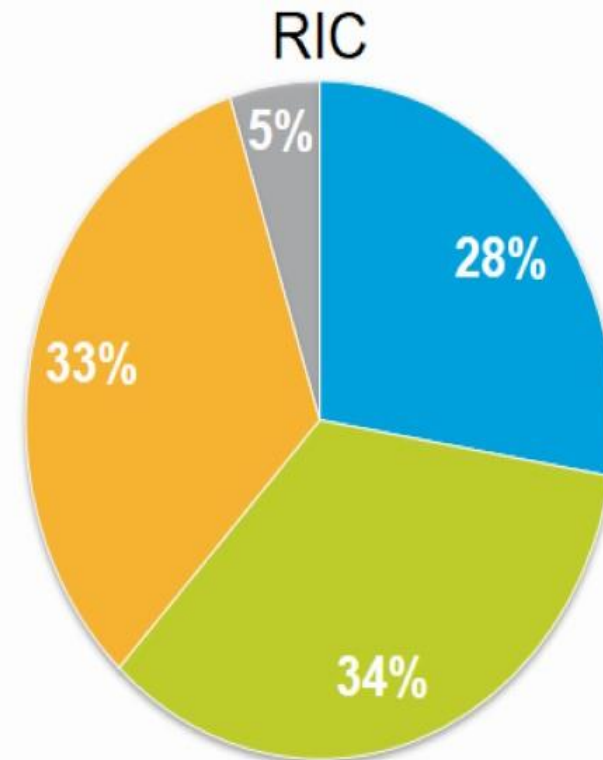
Died at or beyond 100 days post-transplant\*



# Common Conditioning Regimens in Acute Myelogenous Leukemia (AML) or Myelodysplastic Syndrome (MDS) Allogeneic HCT in the US, 2009-2019

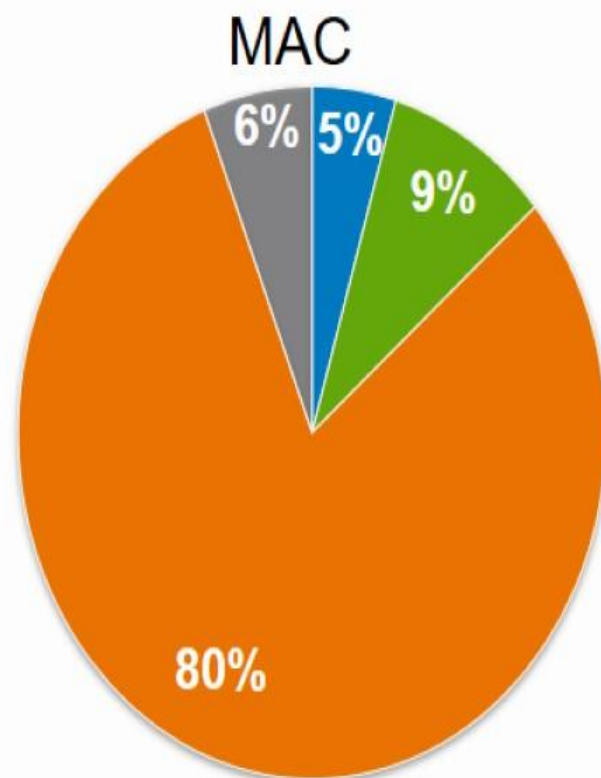


- MAC Bu+Cy+/-others
- MAC Bu+Flu+/-others
- MAC TBI+/-others
- MAC Others

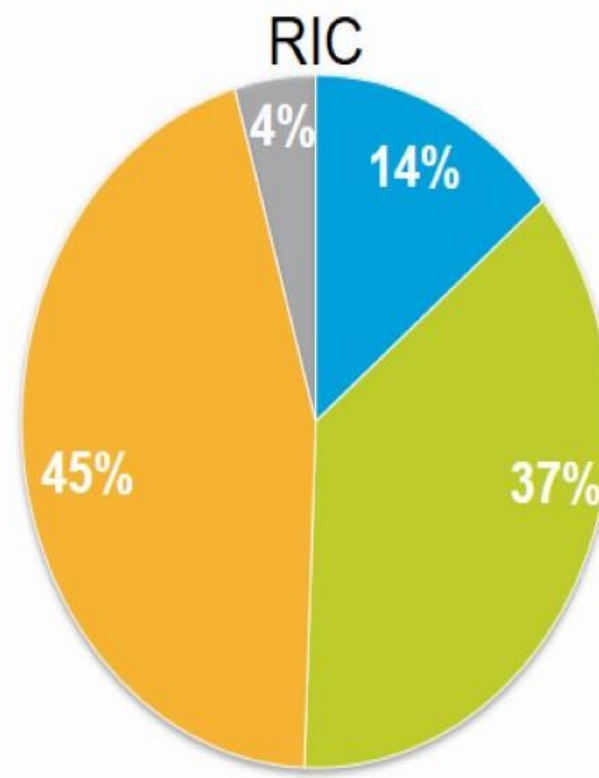


- RIC Bu+Flu+/-others
- RIC Flu+Mel+/-others
- RIC TBI+/-others
- RIC Others

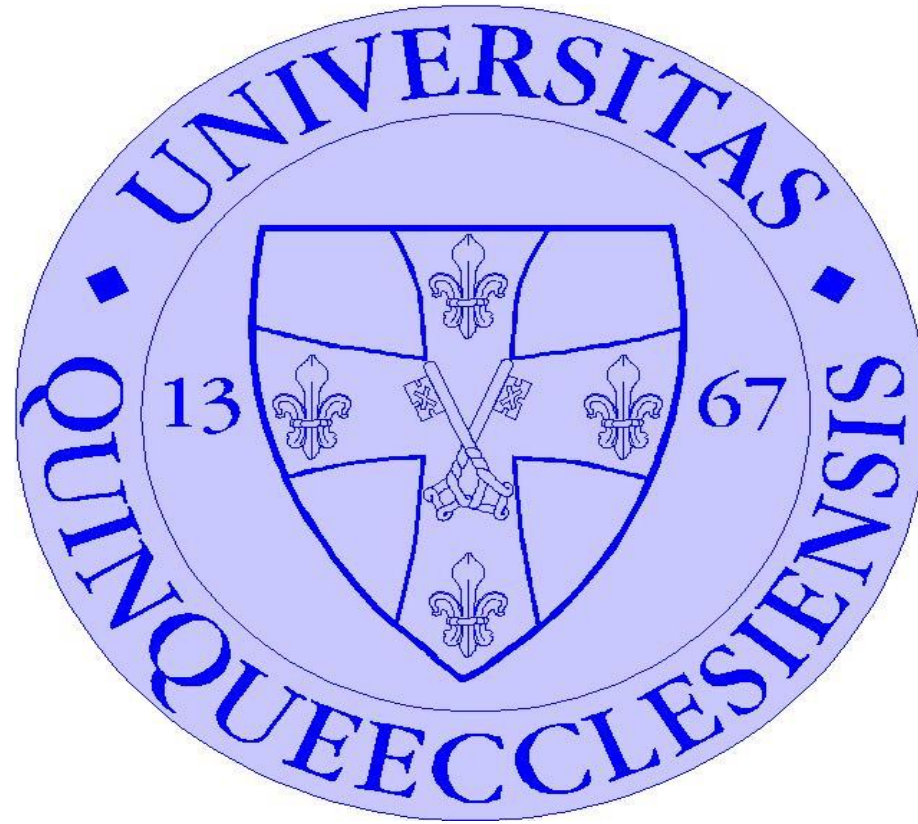
# Common Conditioning Regimens in Acute Lymphoblastic Leukemia (ALL) Allogeneic HCT in the US, 2009-2019



- MAC Bu+Cy+/-others
- MAC Bu+Flu+/-others
- MAC TBI+/-others
- MAC Others



- RIC Bu+Flu+/-others
- RIC Flu+Mel+/-others
- RIC TBI+/-others
- RIC Others



**Köszönöm a megtisztelő figyelmet!**