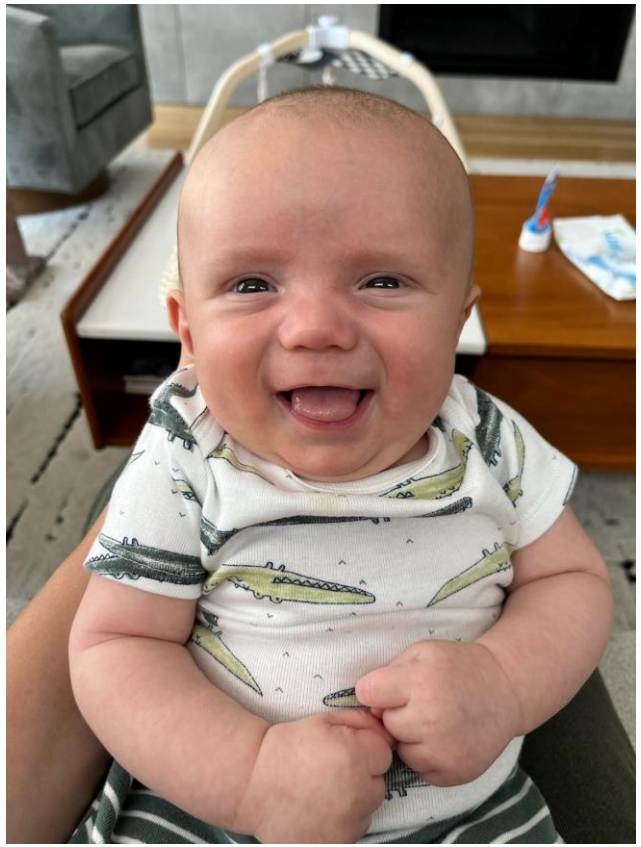
Stem cell transplants and cell therapies for MDS

Andrew Kent MD PhD

Assistant professor

Hematology/BMT Division

Liam 7/9/24



Outline

1. History of stem cell transplants
2. Current clinical practice in the world and at UCH
3. Future cell therapies?

First attempts at transplants

Aplasia noted after lethal irradiation by atomic bombs

Early clinical studies

1957-1967: 200 patients received bone marrow transplants after lethal irradiation

Intravenous Infusion of Bone Marrow in Patients Receiving Radiation and Chemotherapy

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

Article Figures/Media

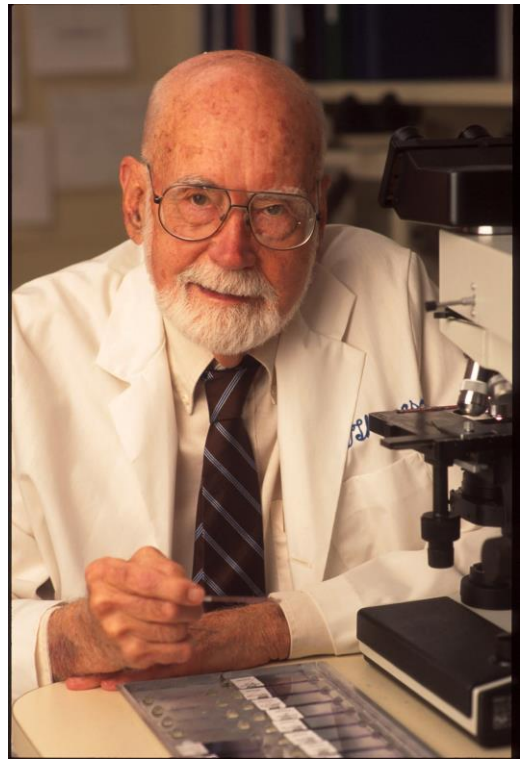
September 12, 1957
N Engl J Med 1957; 257:491-496
DOI: 10.1056/NEJM195709122571102

> Cancer Res. 1965 Oct;25(9):1525-31.

Adoptive immunotherapy of acute leukemia: experimental and clinical results

G Mathé, J L Amiel, L Schwarzenberg, A Cattan, M Schneider

PMID: 5323965



onnall Thomas (1920-2012):
Professor at U Washington, then director of emeritus of clinical research division at Fred Hutch
1990: Nobel Prize, shared with Joseph Murray (Harvard, first renal transplant)

https://pubmed.ncbi.nlm.nih.gov/4911417/

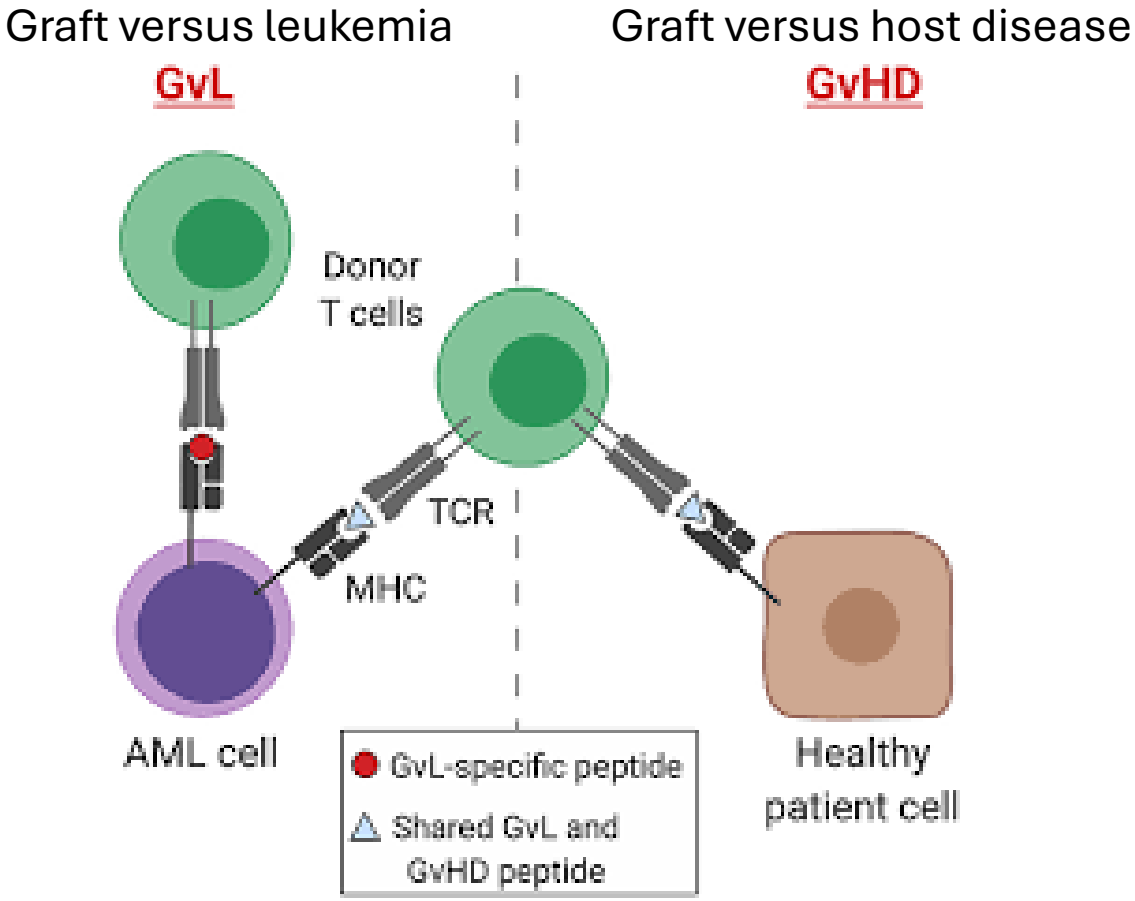
HLA system: crucial to transplant success

- Human leukocyte antigens (HLA)
  - Aka Major histocompatibility complex (MHC) in humans
- Set of genes on chromosome 6 that code for proteins that present antigens – crucial for immune recognition and function
  - Individuals inherit one set of HLA genes (haplotype) from each parent
- 10 Most clinically relevant HLA genes:
    - HLA A, B, C
    - HLA DR, DQ, (and DP)
- Mismatch: causes graft rejection and graft-versus-host disease

Importance of HLA: GVHD and GVL

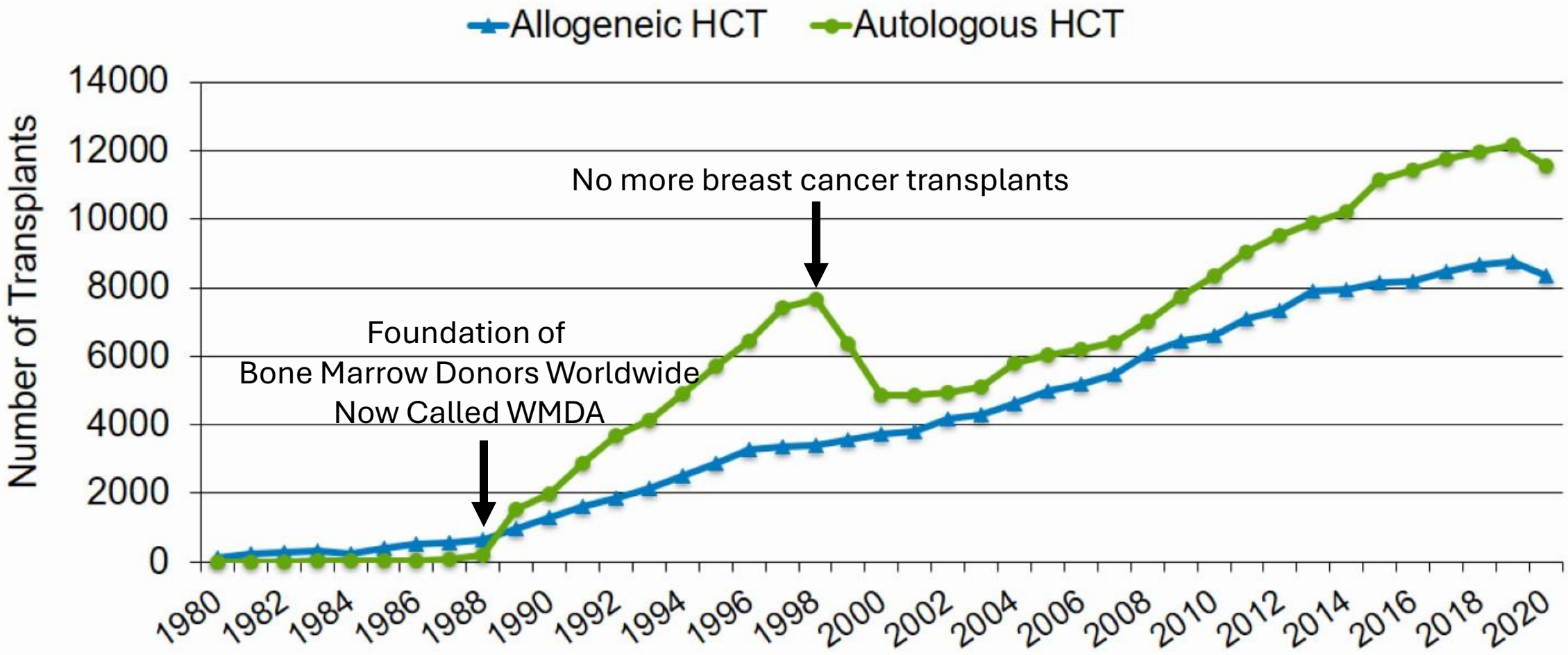
Graft versus leukemia effect: Thought to be how transplants actually cure people

Full match now: 10/10 HLA genes



https://www.frontiersin.org/articles/10.3389/fonc.2019.01217/full

Number of HCTs in the US Reported to CIBMTR by Transplant Type



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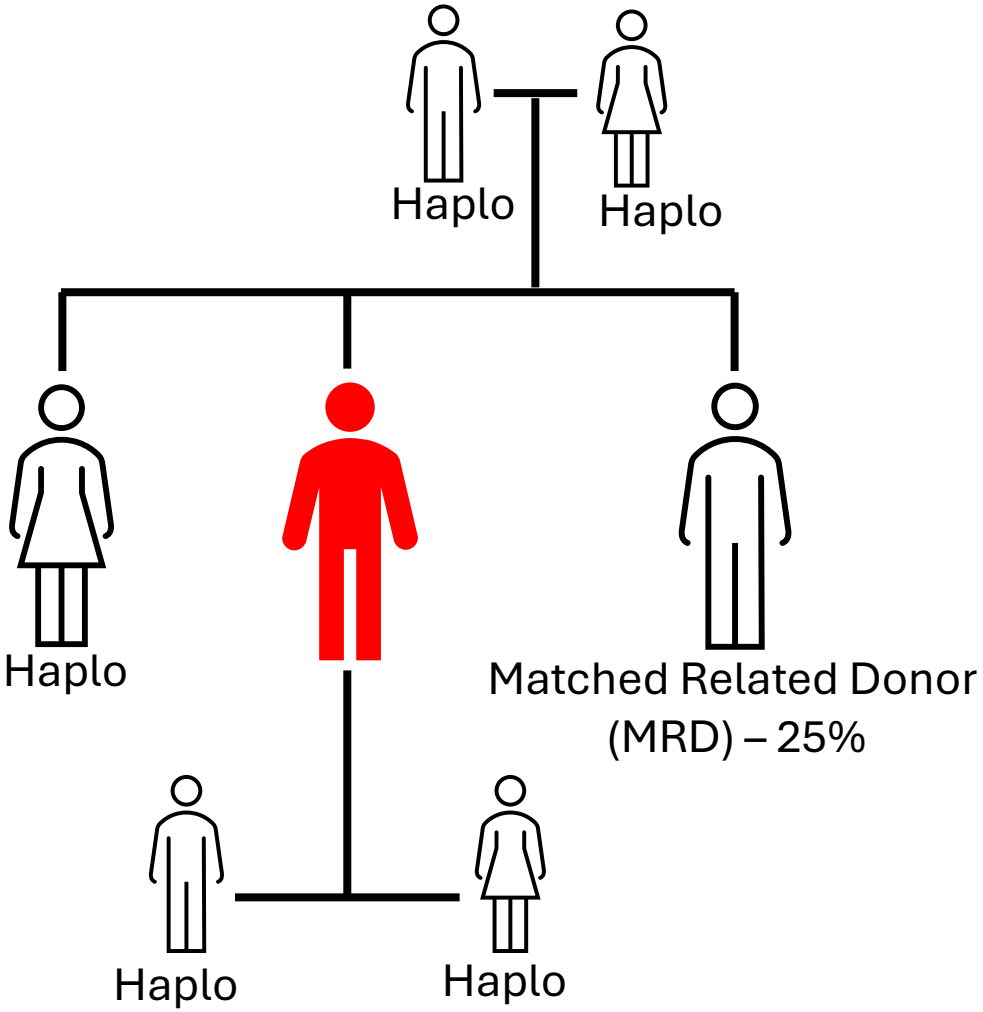
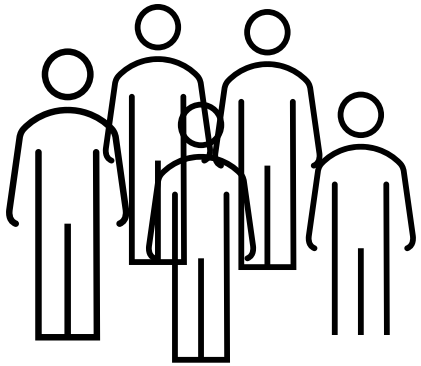
Types of stem cell transplants



Matched Related Donor (MRD) – 25%

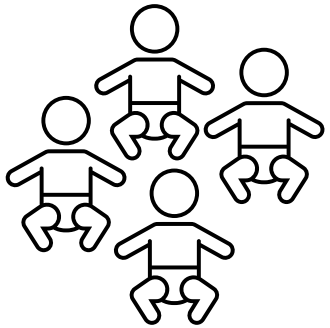
Matched Unrelated Donor (MUD) or mismatched unrelated donor (MMUD)



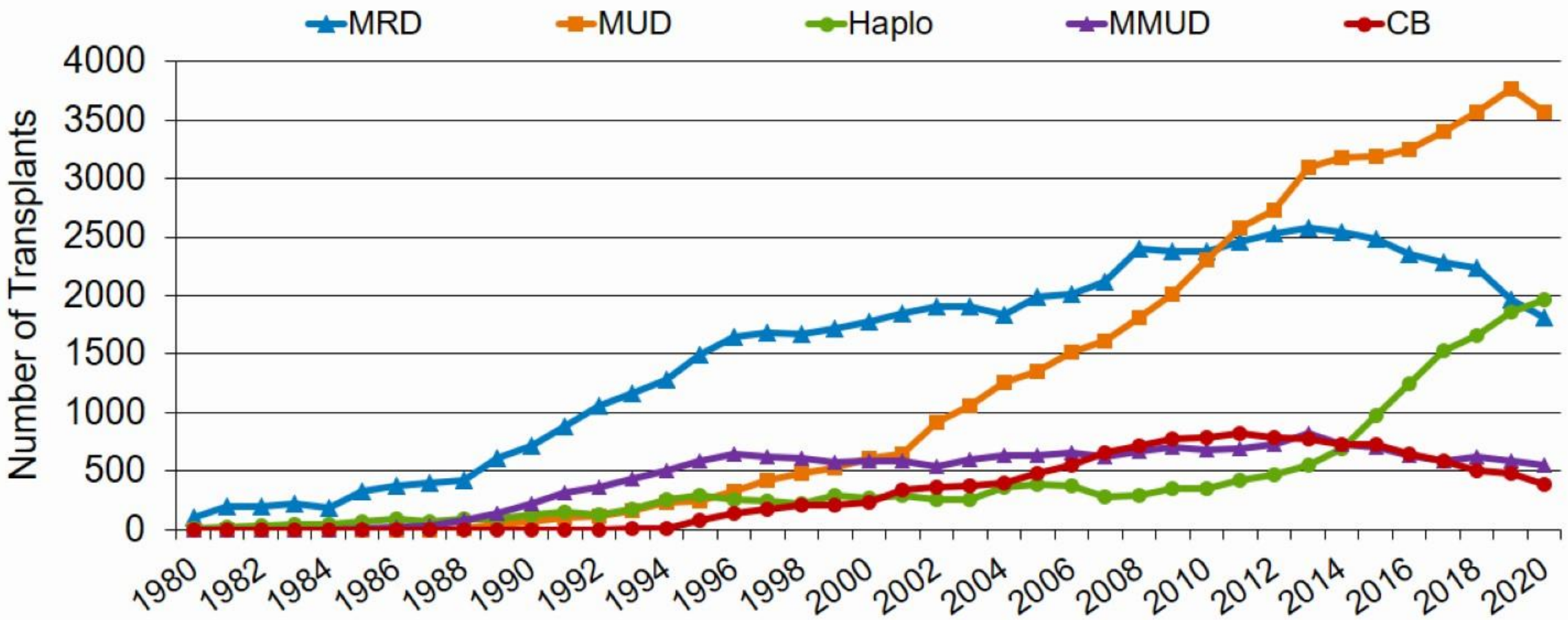
NATIONAL MARROW DONOR PROGRAM®

BE THE MATCH®

Cord blood



Number of Allogeneic HCTs in the US by Donor Type



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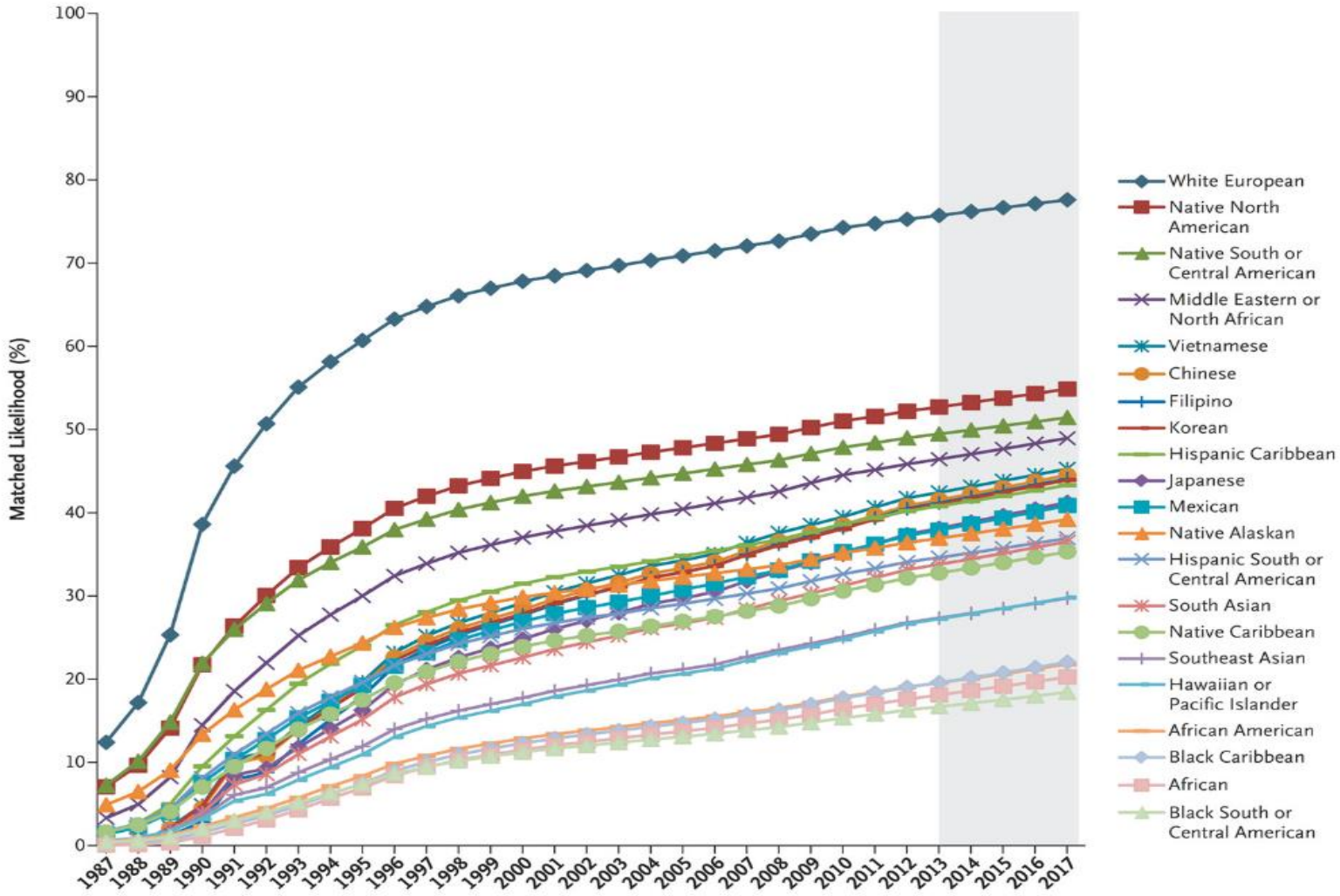
Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor;
Haplo: Haploidentical donor (includes all mismatched related donors); MMUD: Mismatched unrelated donor; CB: Cord blood

NMDP WMDP – donor programs

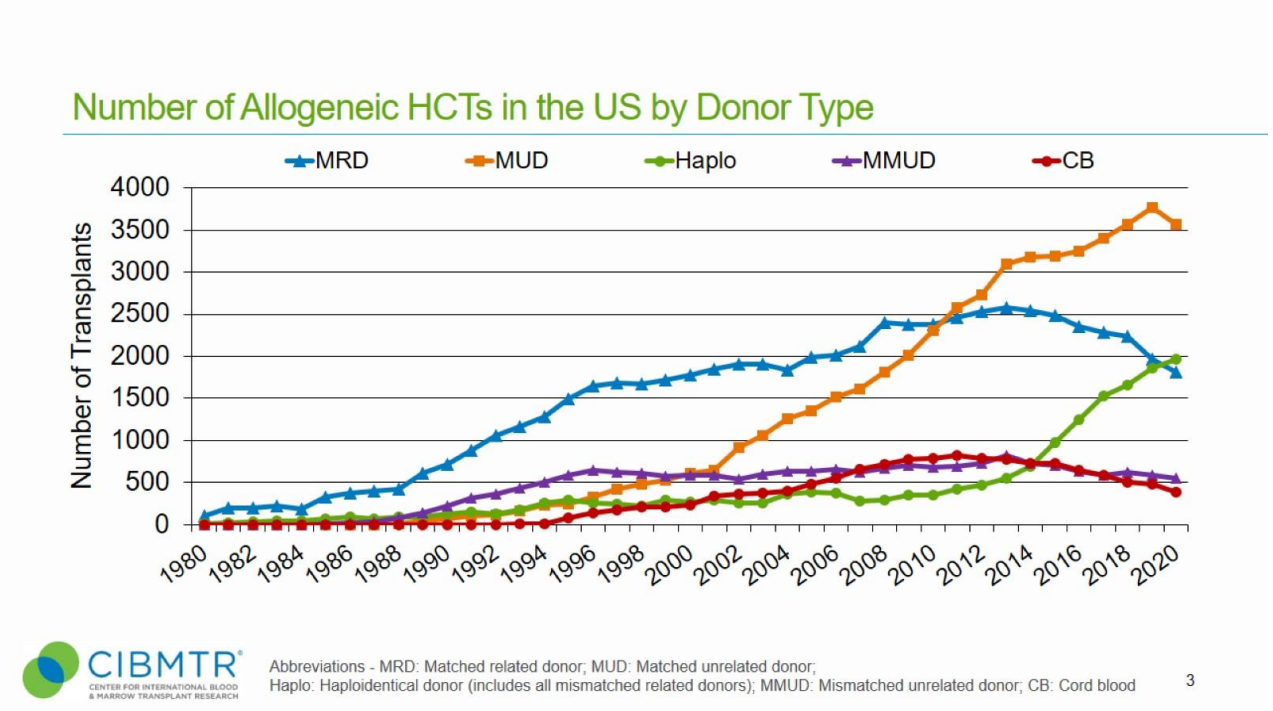
https://wmda.info/ https://www.nmdp.org/

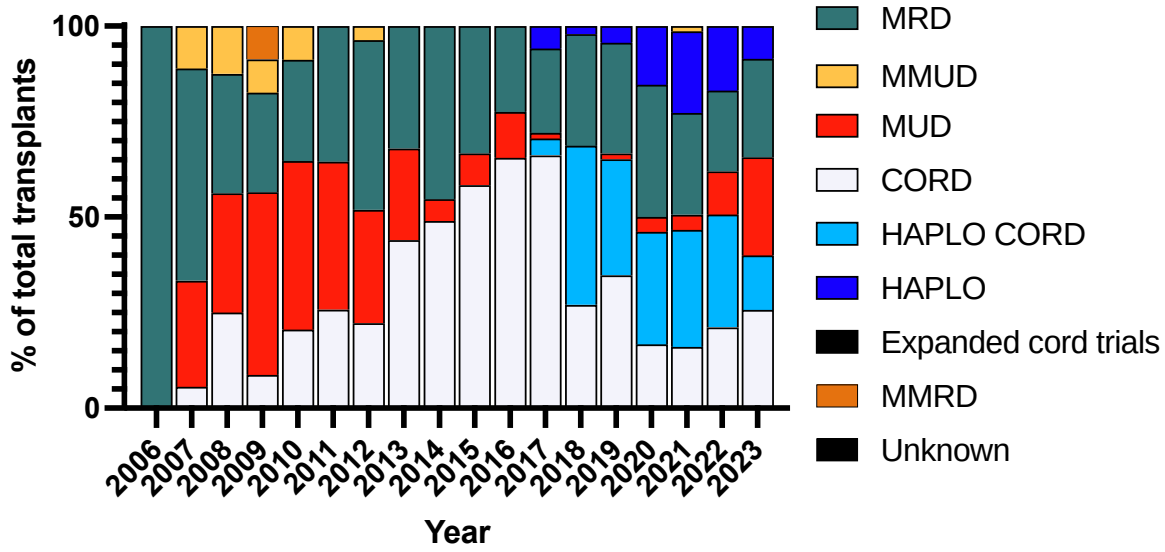
Donor Selection: Odds of match by ethnicity



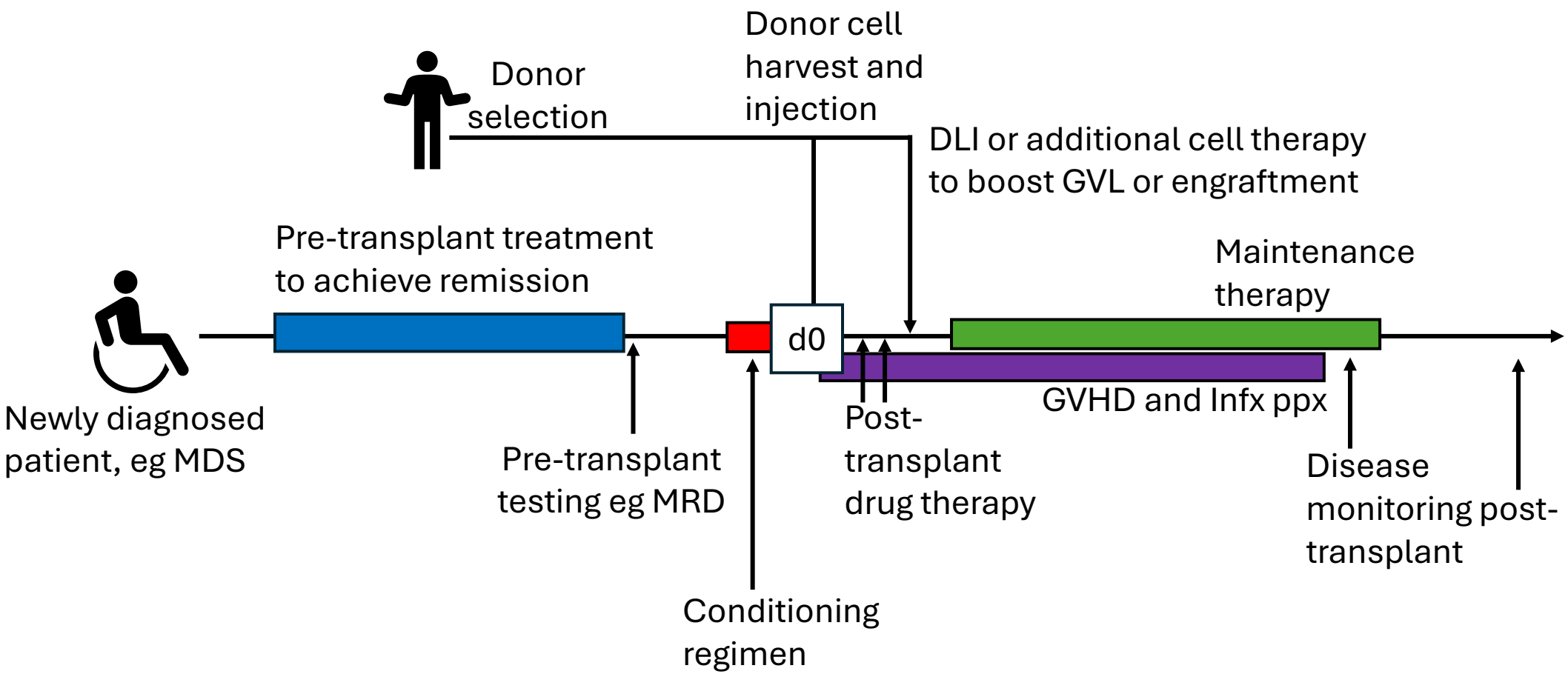
https://www.nejm.org/doi/full/10.1056/NEJMsa1311707

Allo transplant types by year at CU

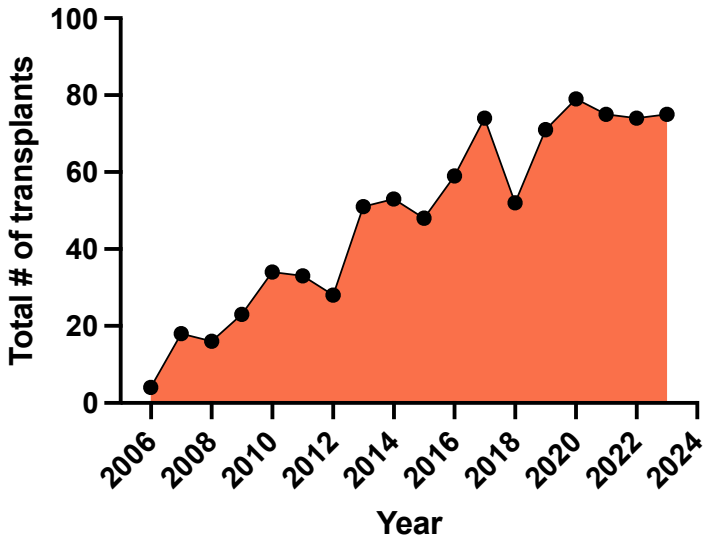


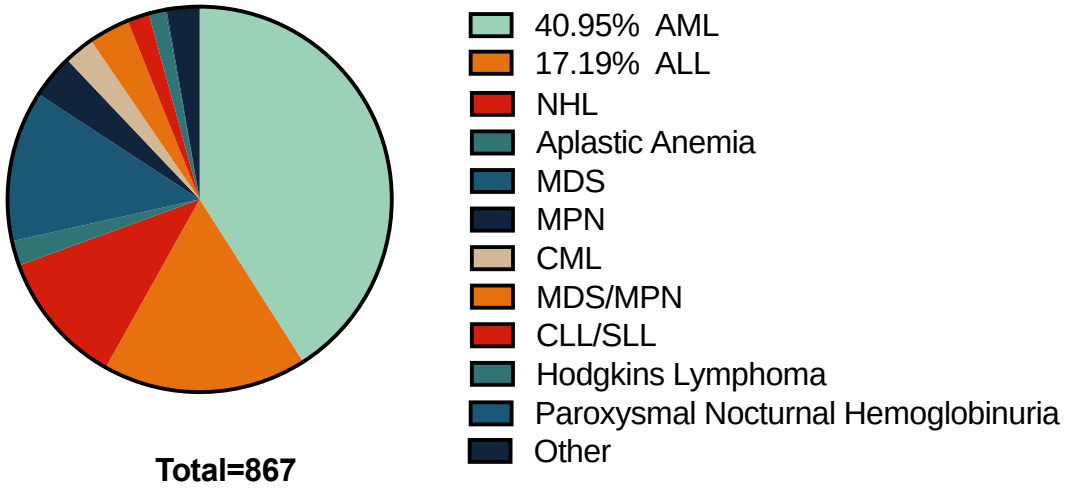


Typical transplant course

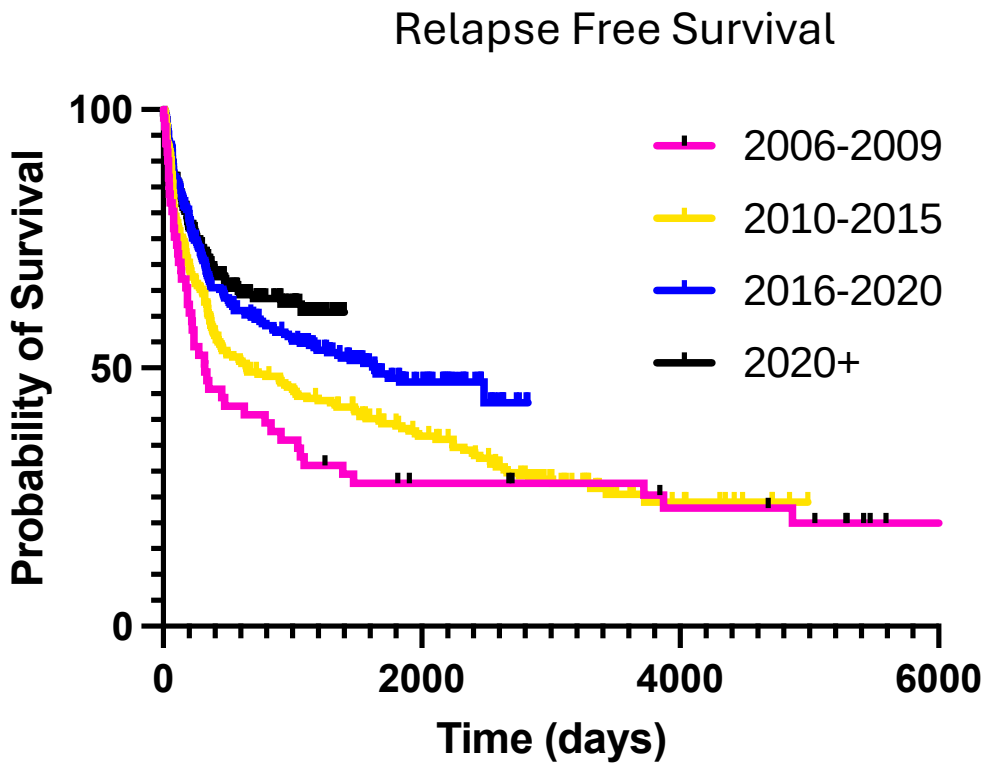


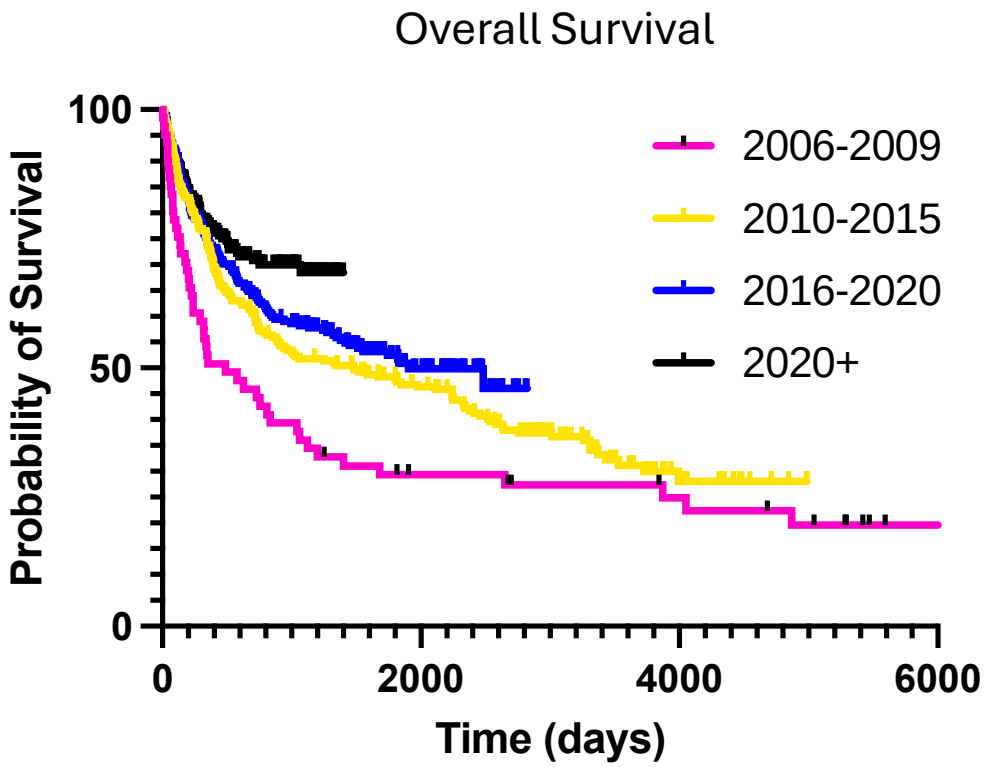
Total allo transplants and diseases that get transplants at UCH





Transplant outcomes over time at CU





Health Resources & Services Administration

HRSA

Blood Stem Cell

National Metrics 2023

Performance metric: actual outcomes/expected outcomes based on disease classification

Table 6c. Summary of transplant center performance status from 2014-2023 analyses among the centers that were identified as over-performing in the 2023 analysis

Center code	Center name	n	Actual survival (%)	Predicted survival (%)	95% CI lower	95% CI upper	'14	'15	'16	'17	'18	'19	'20	'21	'22	'23
17	Orlando Health Cancer Institute Bone Marrow Transplant and Cellular Therapy	20	80.0	60.1	38.6	78.3										1
98	Indiana Blood & Marrow Transplantation	108	87.0	73.7	65.5	81.5	0	0	0	0	-1	-1	-1	0	0	1
108	Cedars-Sinai Medical Center	127	85.8	76.1	68.8	83.1	-1	-1	-1	0	0	0	1	1	1	1
121	USC BMT Program	151	89.2	79.0	72.7	85.2	0	0	0	0	0	0	1	1	1	1
148	University of Colorado Hospital	224	79.3	72.7	67.1	78.3	1	1	1	1	0	0	0	0	0	1
154	Massachusetts General Hospital	264	82.1	76.5	71.5	81.4	0	1	0	1	1	1	1	1	0	1
157	The Blood and Marrow Transplant Program at Northside Hospital	271	81.9	72.4	67.3	77.5	1	1	1	1	1	1	1	1	1	1
172	Moffitt Cancer Center	566	78.7	73.3	69.9	76.9	0	0	0	0	1	1	1	1	1	1
174	The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	649	81.8	78.2	75.2	81.3	0	0	0	0	1	1	0	0	1	1
175	Fred Hutchinson Cancer Center	672	81.9	76.9	73.9	80.0	1	1	1	1	1	0	0	0	1	1
176	Dana-Farber Brigham Cancer Center	759	79.3	74.1	71.2	77.2	1	1	1	0	1	0	1	1	1	1
178	City of Hope National Medical Center	1077	79.0	76.0	73.6	78.5	1	1	1	1	1	1	0	1	1	1

Note: -1 indicates under-performing; 1 indicates over-performing; 0 indicates performing as predicted. The report year indicated in the header applies to unrelated and related HCTs performed in a 3-year period preceding the report year with a 1-year gap, e.g., 2014 includes unrelated and related HCTs performed in 2010-2012.

30th overall in terms of volume of transplants

C.W. Bill Young Cell Transplantation Program (CWBYCTP)

Stem Cell Therapeutic Outcomes Database (SCTOD)

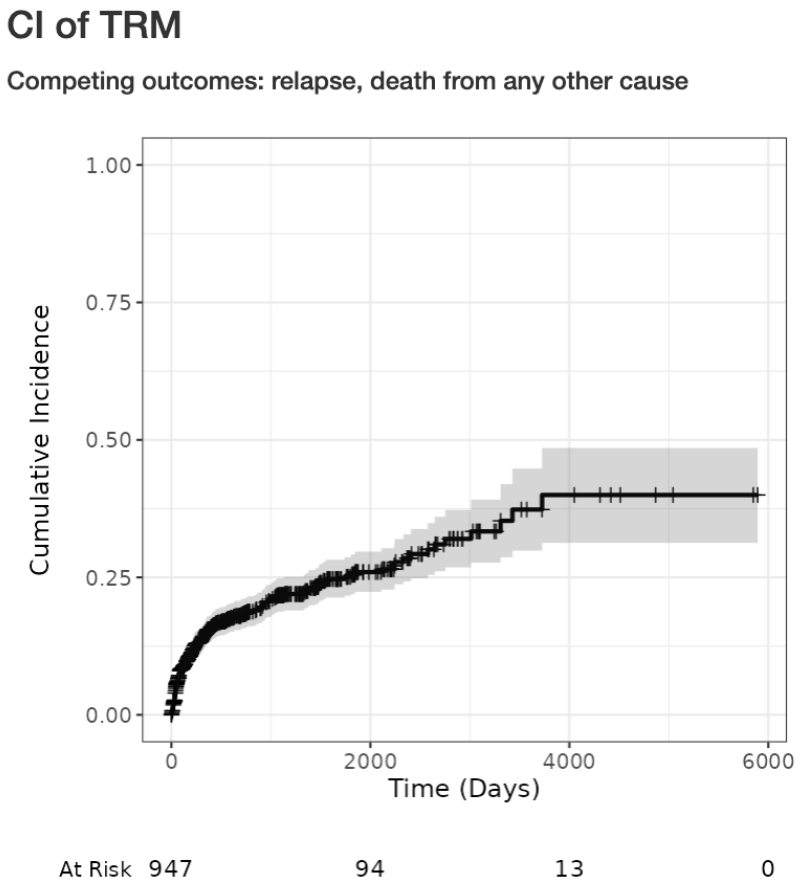
Important consideration for transplant, particularly in MDS:

Does the risk of doing the transplant outweigh the risks of the disease?

1. Older patient, lower risk disease – transplant likely will not provide benefit
2. Younger, higher risk disease – transplant likely will benefit
3. Younger, lower risk disease?
4. Middle age, moderate risk disease?

Why don’t we do transplants for everyone?

- Significant treatment related mortality (TRM)

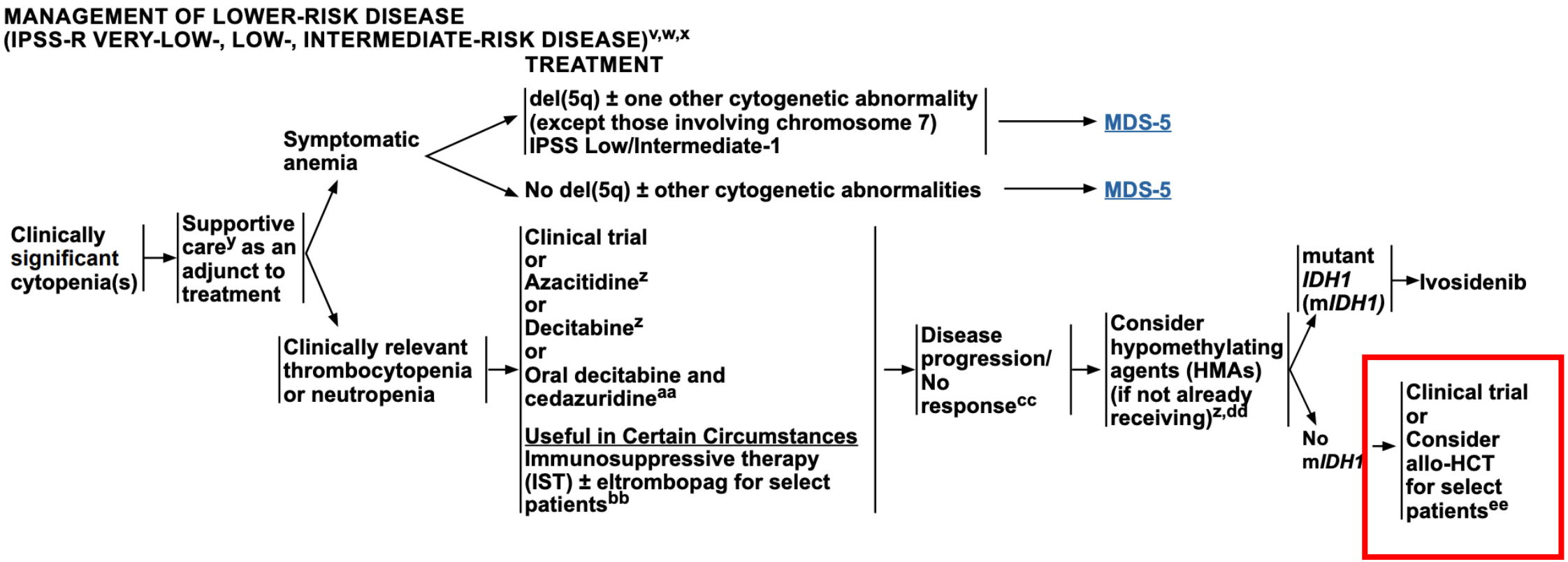


Major causes of TRM:

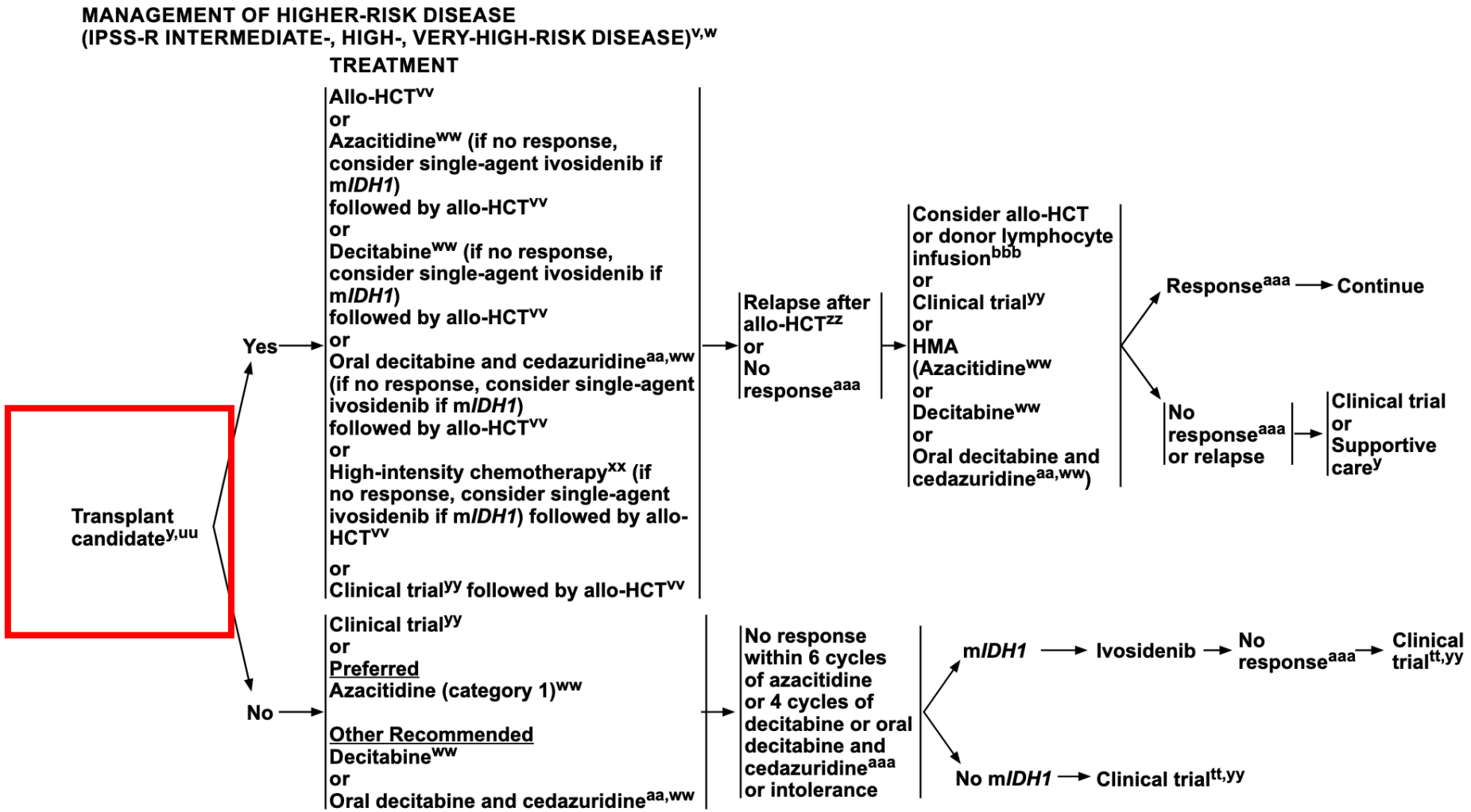
1. Infections post-transplant
2. GVHD
3. Complications due to anemia and low platelets
4. Graft failure

Clinical trials: ongoing to reduce TRM, reduce GVHD, improve cure rates
- not MDS specific, but could help for patients with MDS

NCCN guidelines for lower-risk MDS



NCCN guidelines for higher-risk MDS



Chasing the cure: Cell therapies?

The graft-versus-leukemic effect of transplant is thought to be the main cure for MDS

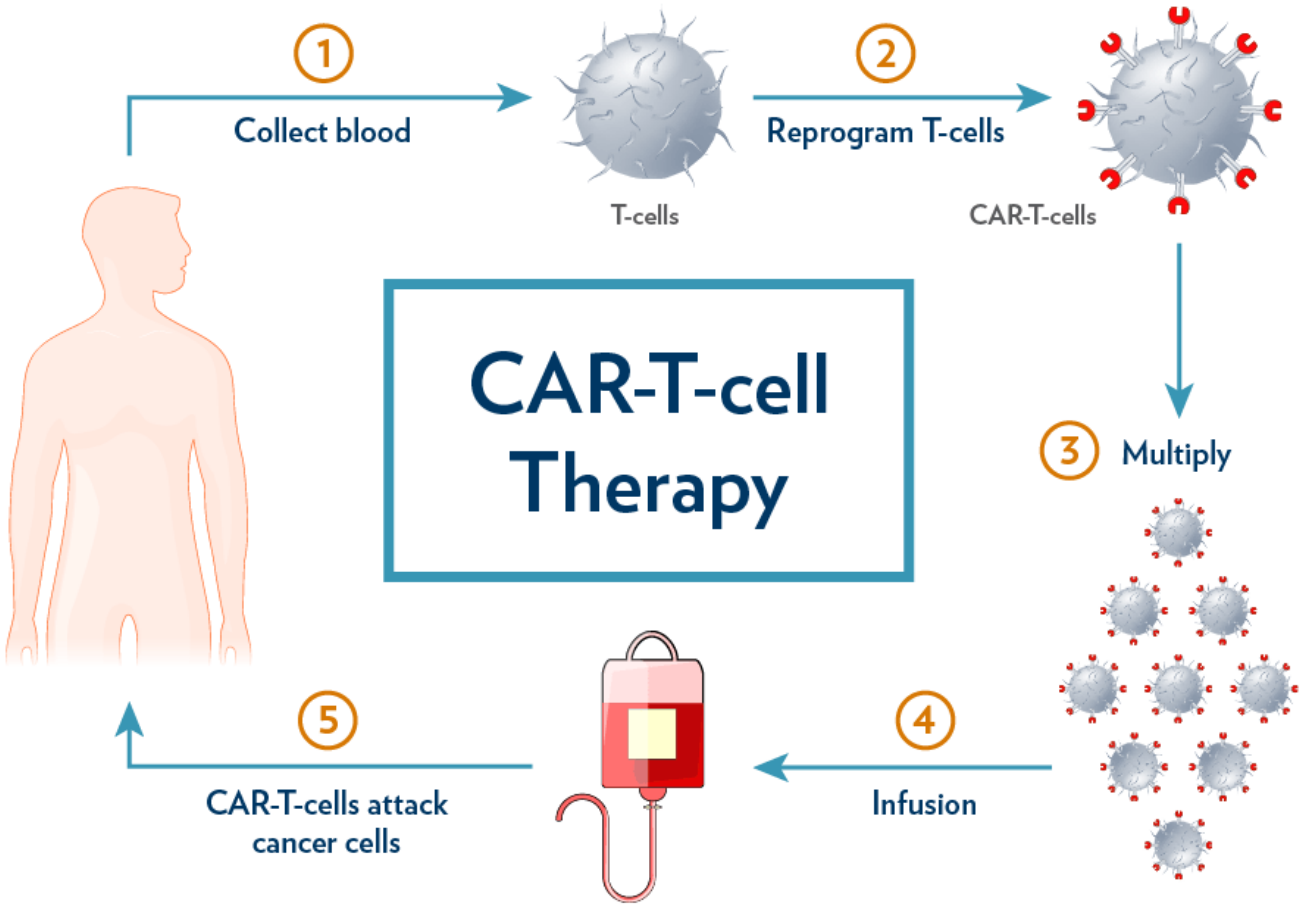
How can we harness this immune effect?

Proof of concept: Chimeric antigen receptor (CAR) T cells in Lymphoma and myeloma

- **Many FDA approved, hundreds of trials ongoing**

Barrier in myeloid diseases: stem cell disease so cell therapies destroy the whole blood/immune system

- Can do this, but have to follow with transplant



CAR-T clinical trial for MDS

Clinical Trial > Lancet Haematol. 2023 Mar;10(3):e191-e202.
doi: 10.1016/S2352-3026(22)00378-7. Epub 2023 Feb 7.

CYAD-01, an autologous NKG2D-based CAR T-cell therapy, in relapsed or refractory acute myeloid leukaemia and myelodysplastic syndromes or multiple myeloma (THINK): haematological cohorts of the dose escalation segment of a phase 1 trial

David A Sallman [1], Tessa Kerre [2], Violaine Havelange [3], Xavier Poiré [3], Philippe Lewalle [4], Eunice S Wang [5], Jason B Brayer [6], Marco L Davila [5], Ine Moors [2], Jean-Pascal Machiels [3], Ahmad Awada [4], Erik M Alcantar-Orozco [7], Rossitza Borissova [7], Nathalie Braun [7], Marie-Sophie Dheur [7], David E Gilham [7], Caroline Lonez [7], Frédéric F Lehmann [7], Anne Flament [7]

25% response rate in r/r AML and MDS (only 1) patients
No treatment related deaths

Emerging issue with CAR-Ts:

Front Oncol. 2023; 13: 1036455. PMCID: PMC9897055
Published online 2023 Jan 20. doi: 10.3389/fonc.2023.1036455 PMID: 36741006

High risk-myelodysplastic syndrome following CAR T-cell therapy in a patient with relapsed diffuse large B cell lymphoma: A case report and literature review

Eugenia Accorsi Buttini,[1,*] Mirko Farina, [1] Luisa Lorenzi, [2] Nicola Polverelli, [1] Vera Radici, [1] Enrico Morello, [1] Federica Colnaghi, [1] Camillo Almici, [3] Emilio Ferrari, [3] Andrea Bianchetti, [3] Alessandro Leoni, [1,4] Federica Re, [1,4] Katia Bosio, [1,4] Simona Bernardi, [1,4] Michele Malagola, [1] Alessandro Re, [5] and Domenico Russo [1]

Conclusions:

- **Transplants are not for everyone**
  - **can be curative but carry significant risk**
- **Ongoing studies in transplant to reduce relapse and improve safety**
- **CAR-Ts and other cell therapies might work, but several hurdles to success**

THANKS/Questions?