

Brief history and emerging concepts in transplantation

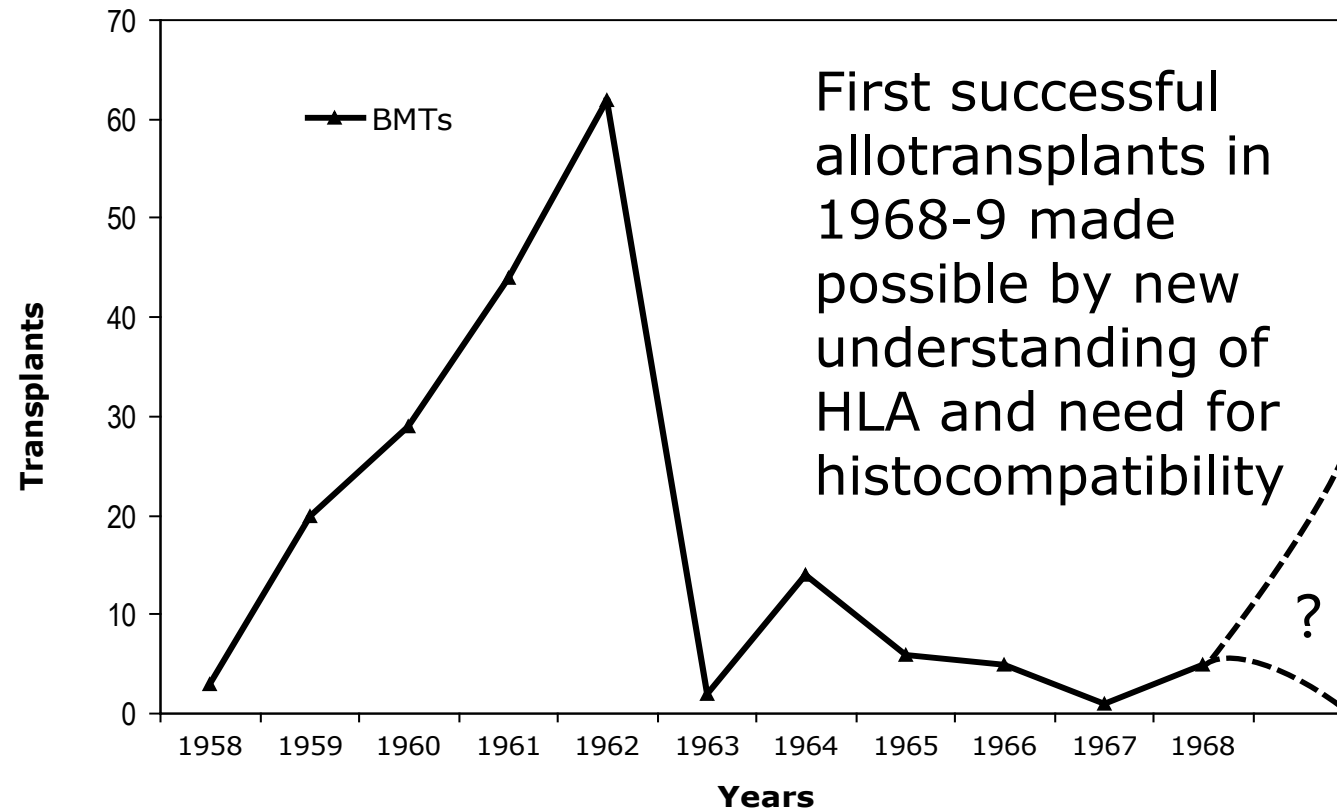
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Professor of Medicine, Froedtert and MCW

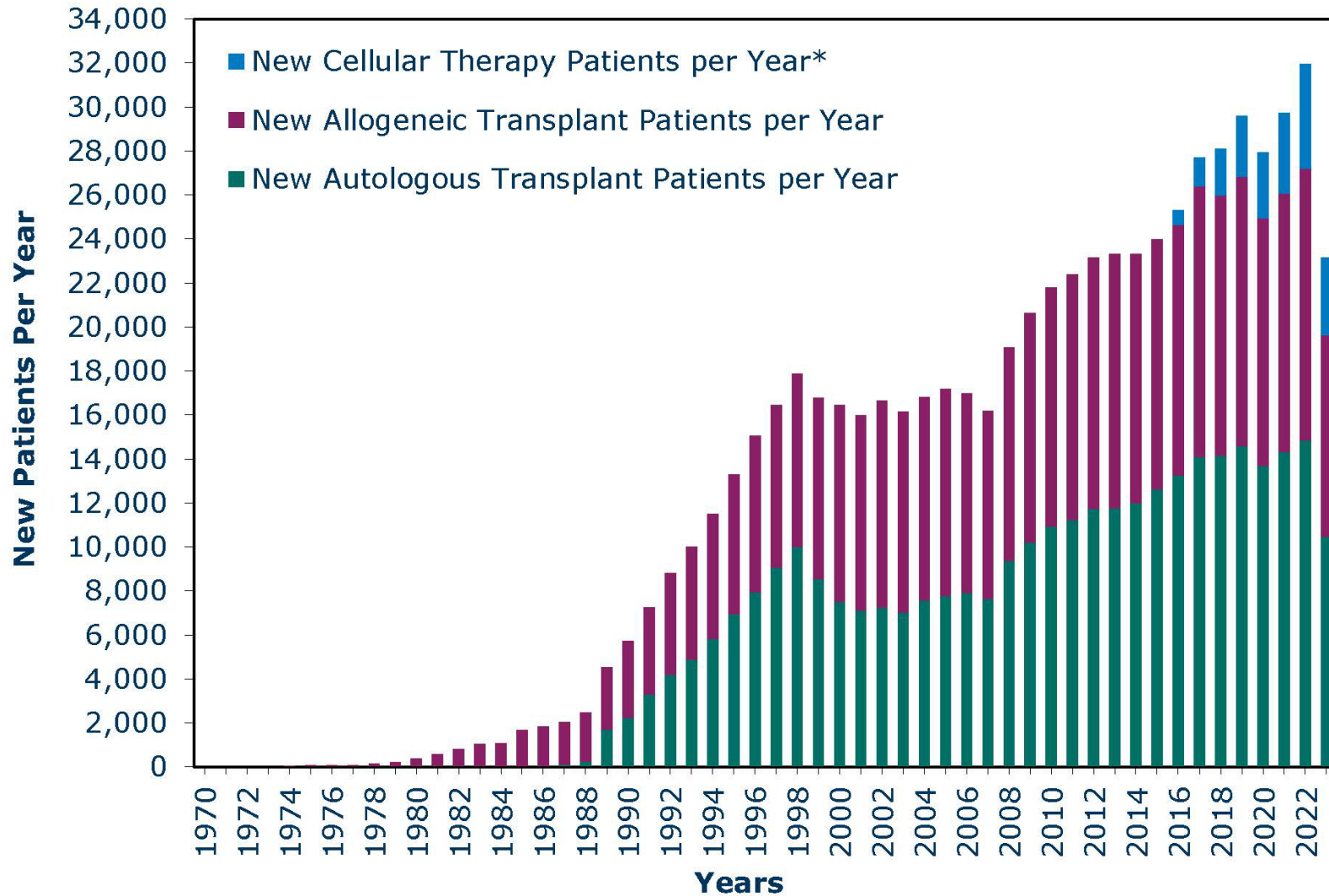
Foundations: advances in science and importance of collaboration

Early years of HCT

Reported Human Bone Marrow Transplants, 1958-1968



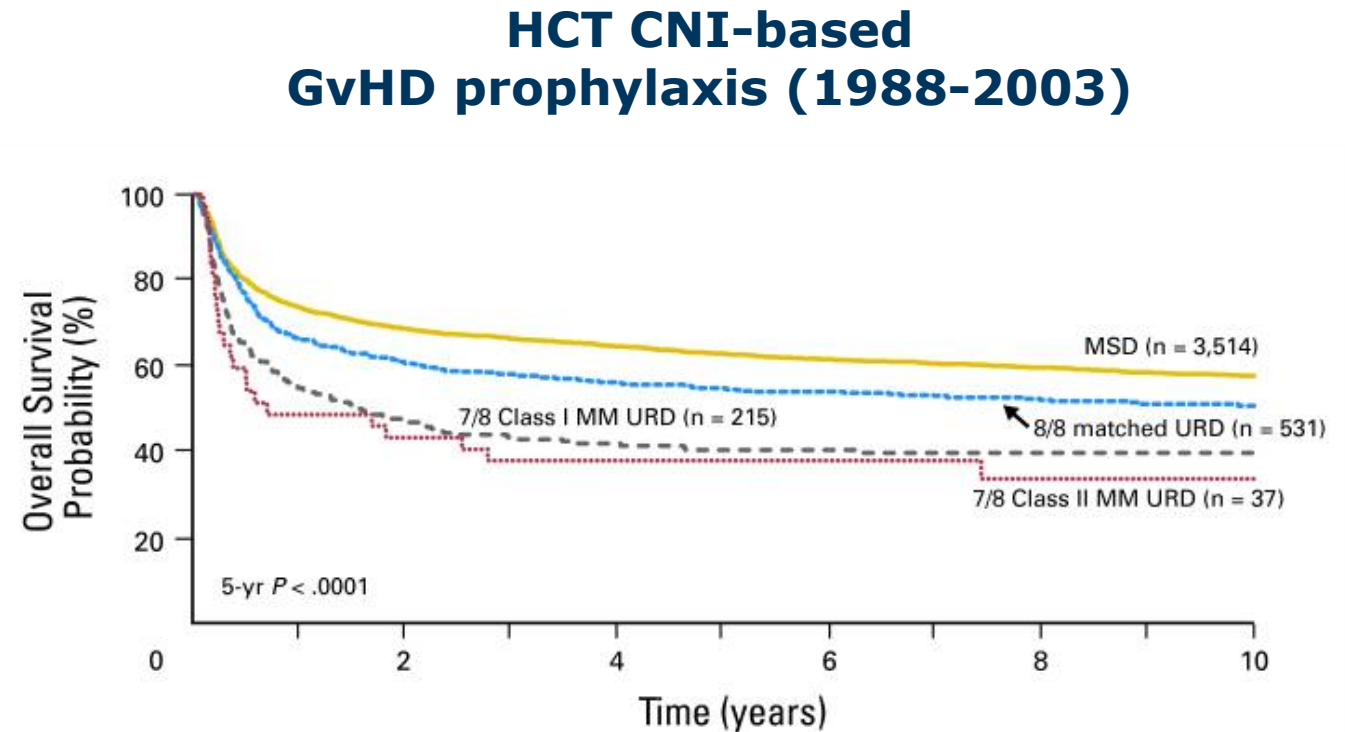
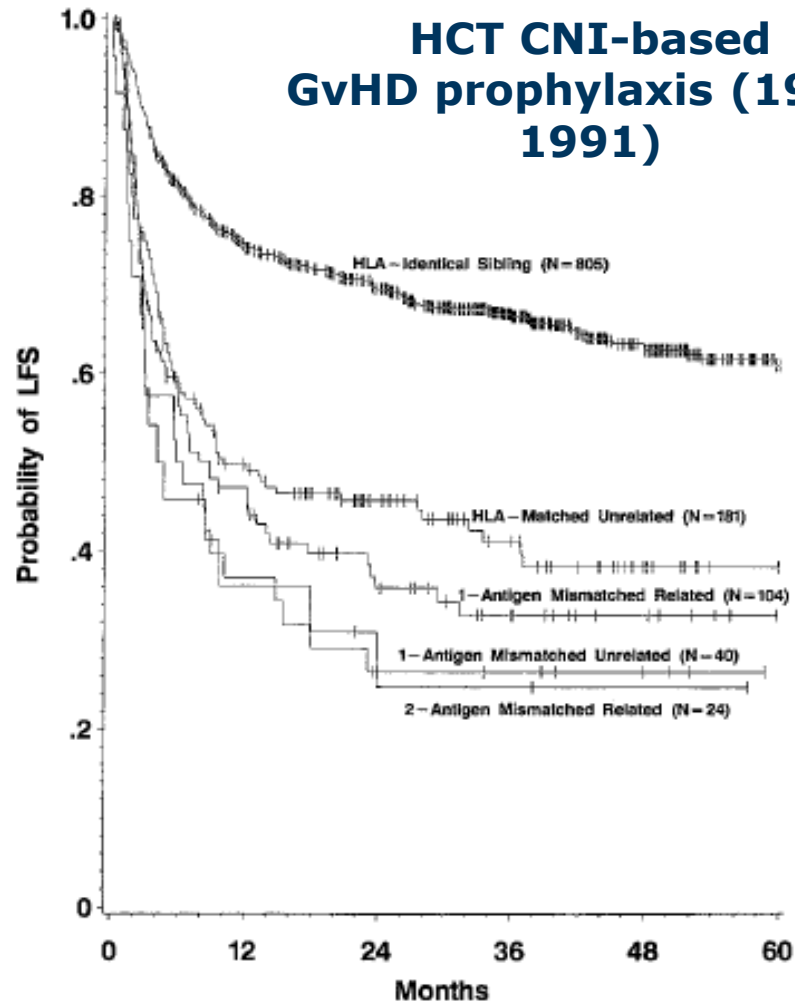
CIBMTR Number of Patients Registered, 1970-2023, Total = 673,545



*Includes CAR-T and genetically modified products

(Data are incomplete for 2023)

Outcomes improved, but were very variable depending on the donor type



GVHD prophylaxis approaches: Early strategies reduced GVHD and were used for years

T cell replete:
Calcineurin inhibitors +/- others

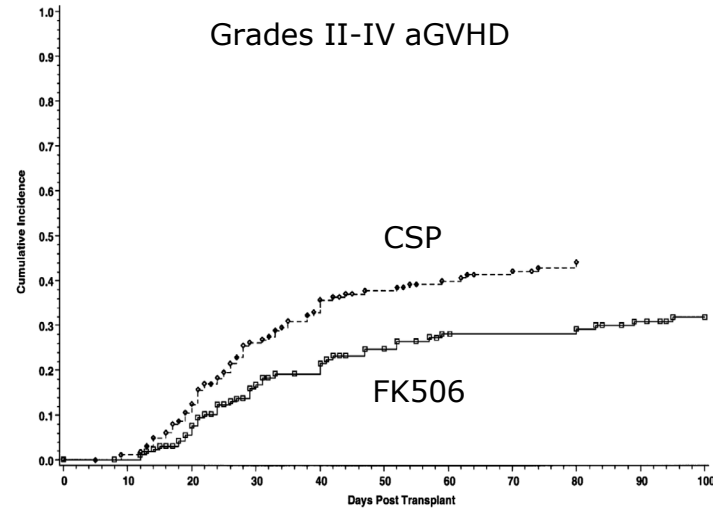
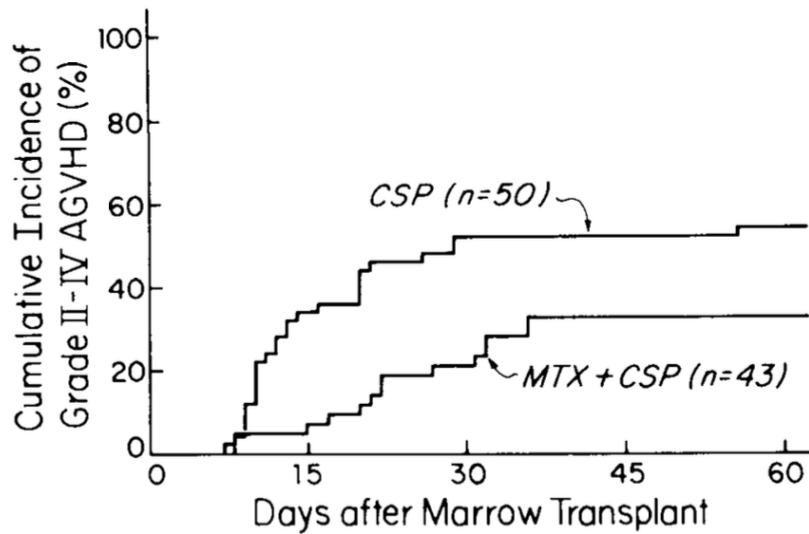
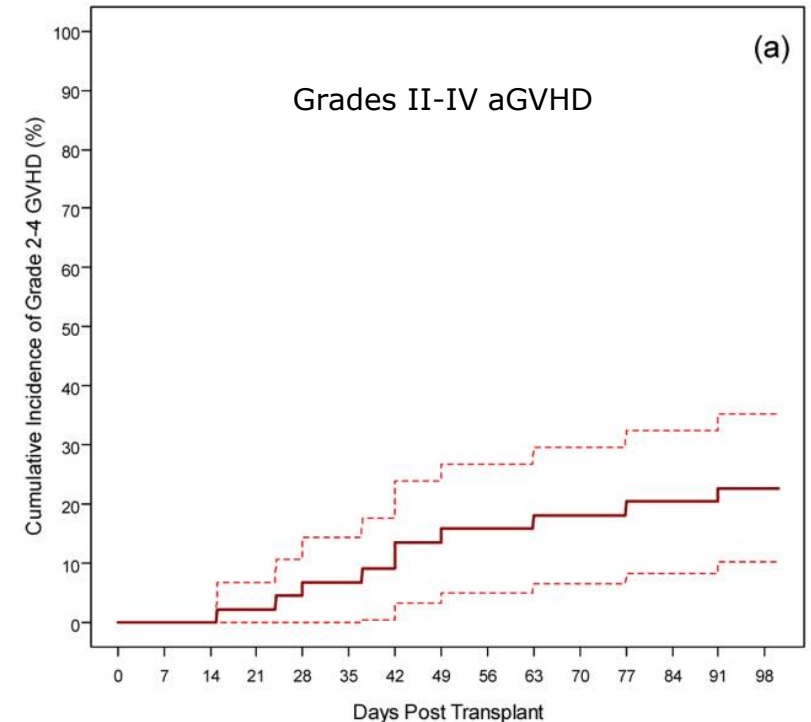
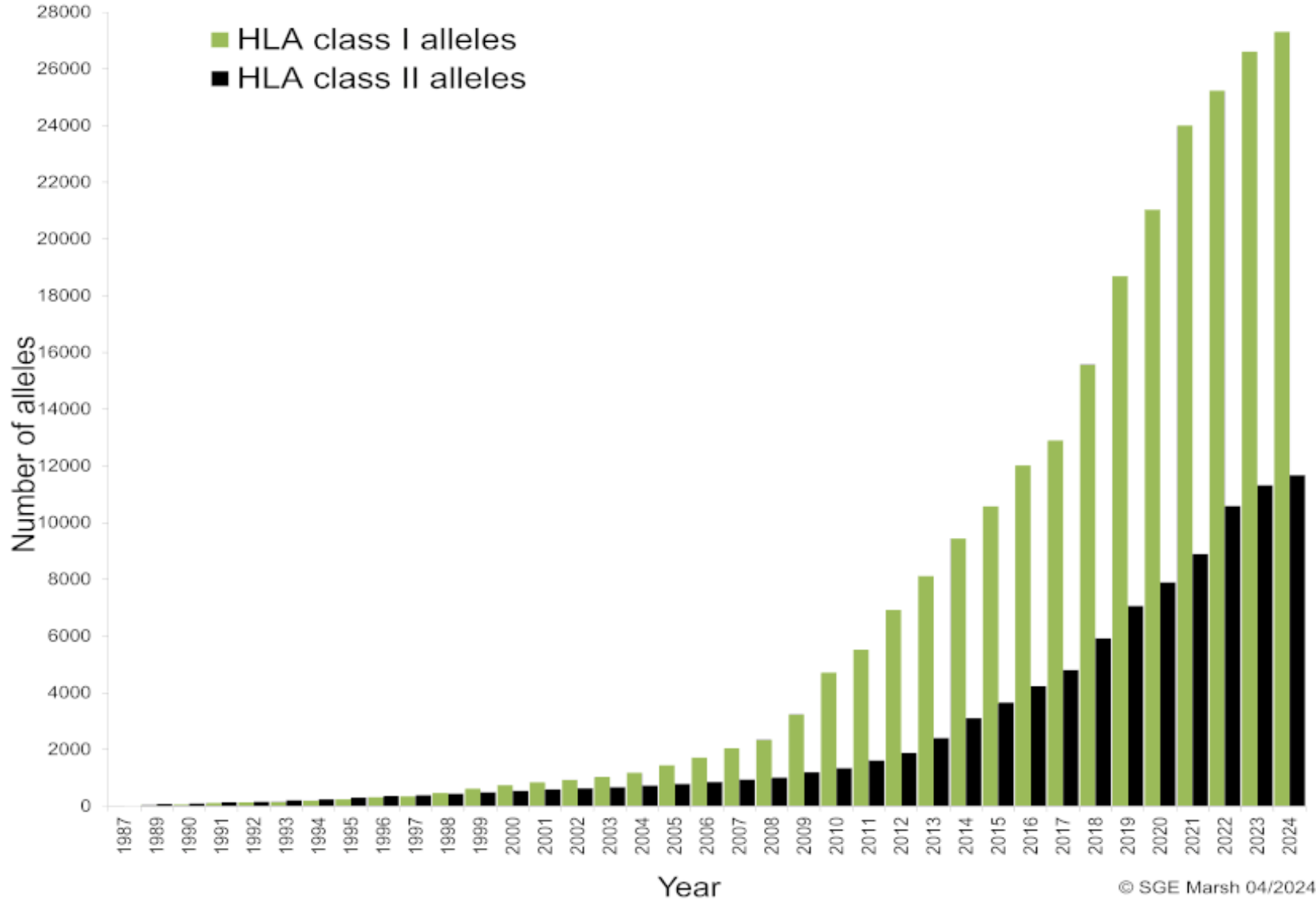


Fig 1. Cumulative incidence of grade II-IV acute GVHD of 165 patients who received cyclosporine/methotrexate, 44.4% (◇) and 164 patients who received tacrolimus/methotrexate, 31.9% (□); absolute difference = 12.5%, 95% CI = -23.9 to -1.2 (P = .01, Wilcoxon).

T cell depletion:
CD34-enriched, TCD

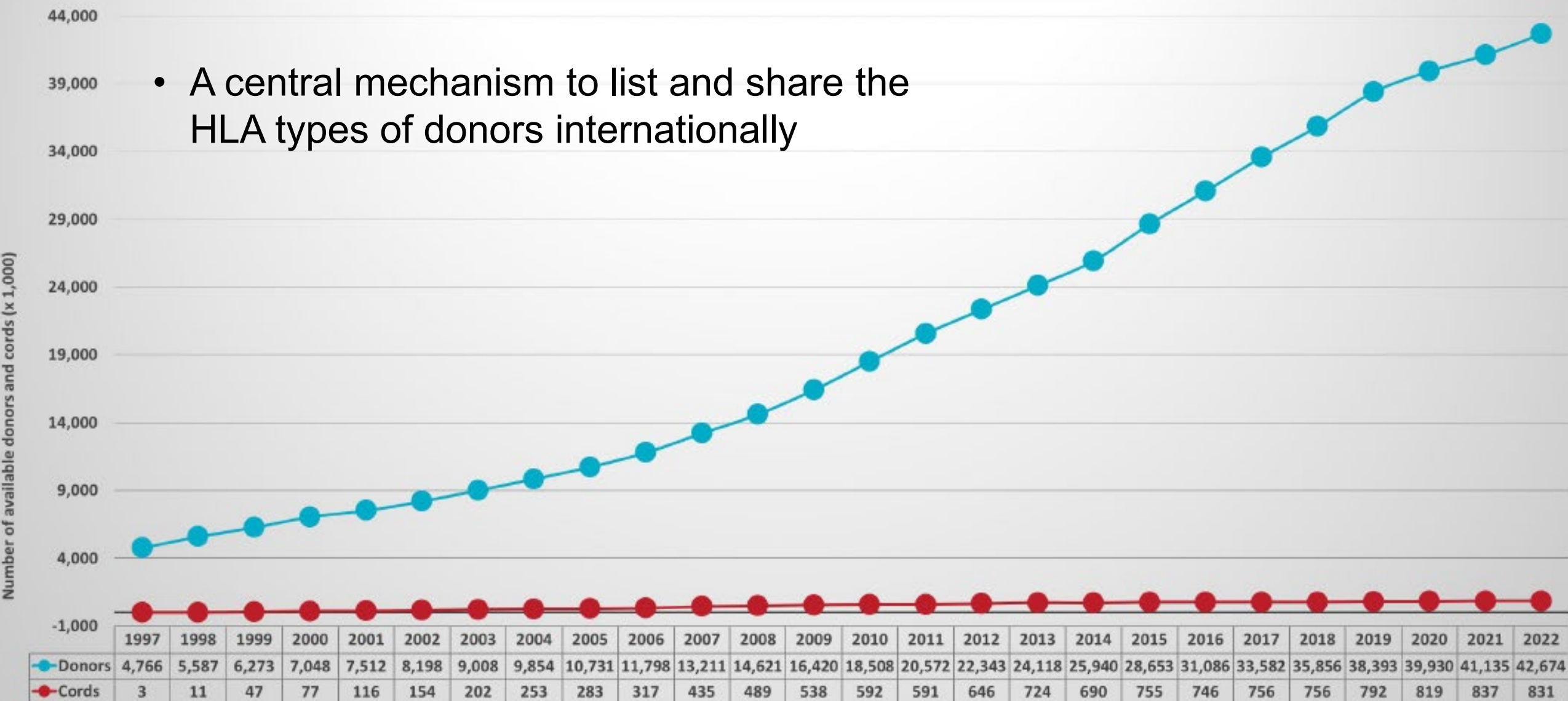


Dramatic improvement in technology: HLA ALLELES IDENTIFIED OVER TIME 1987-2024

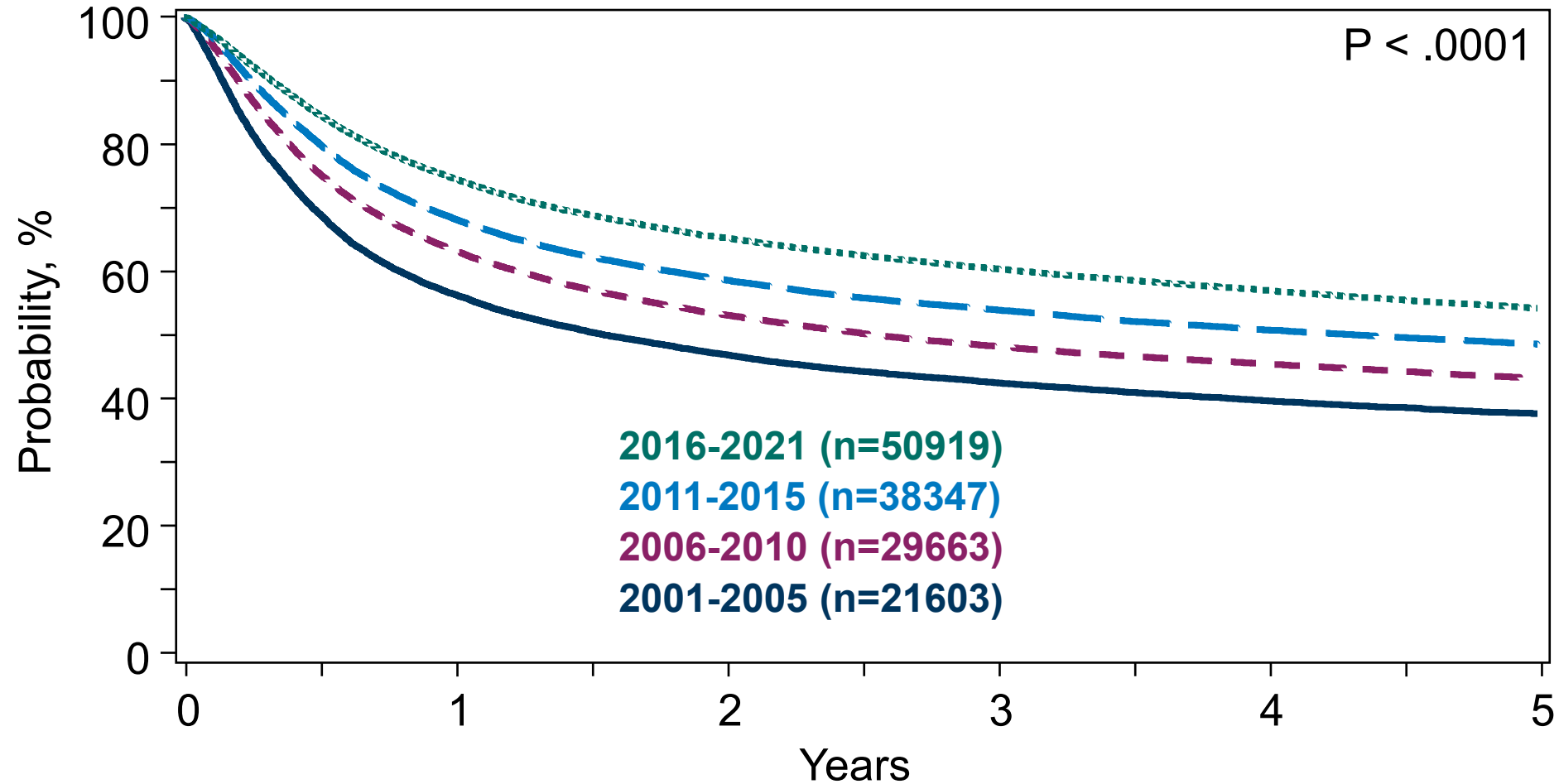


Number of unrelated blood stem cell donors and cord blood units available worldwide 1997-2022

- A central mechanism to list and share the HLA types of donors internationally

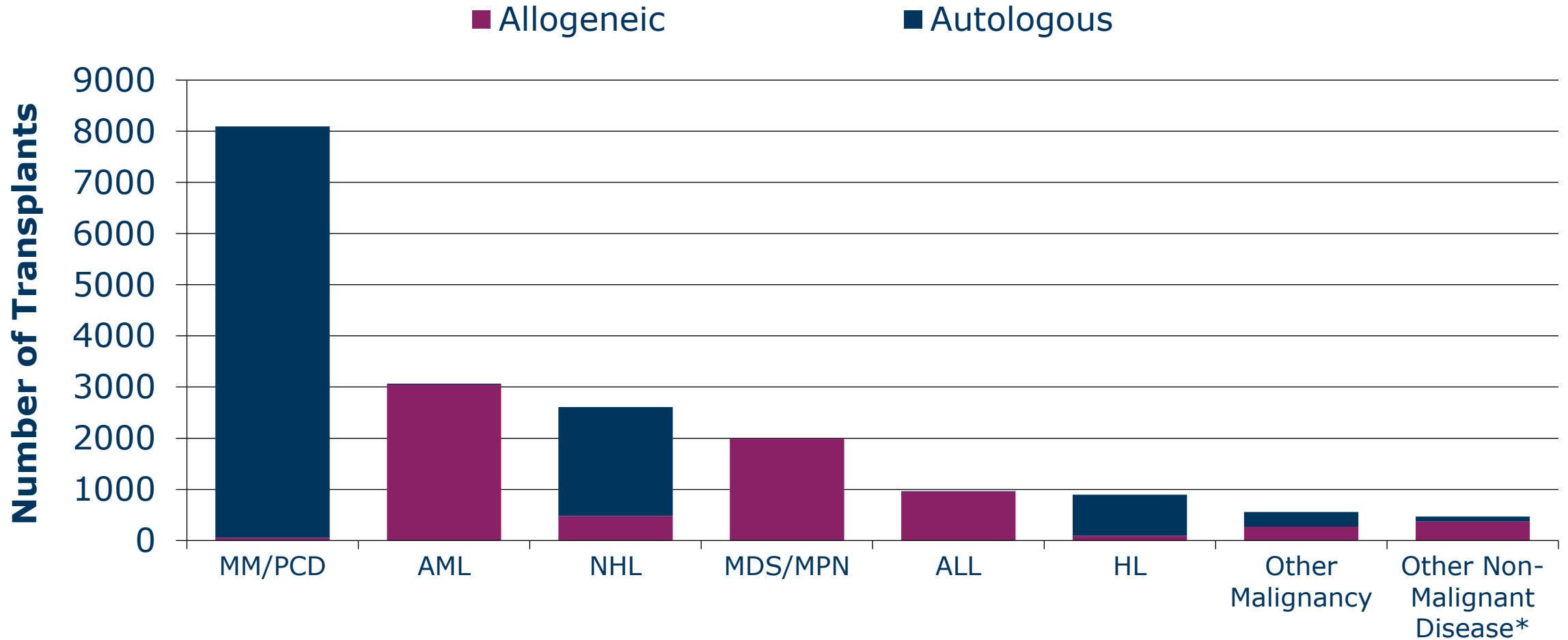


Significant improvement in overall survival after allogeneic HCT over several eras



Practice patterns in the USA and current SOC

Major indications for adult HCT in 2022 in the US

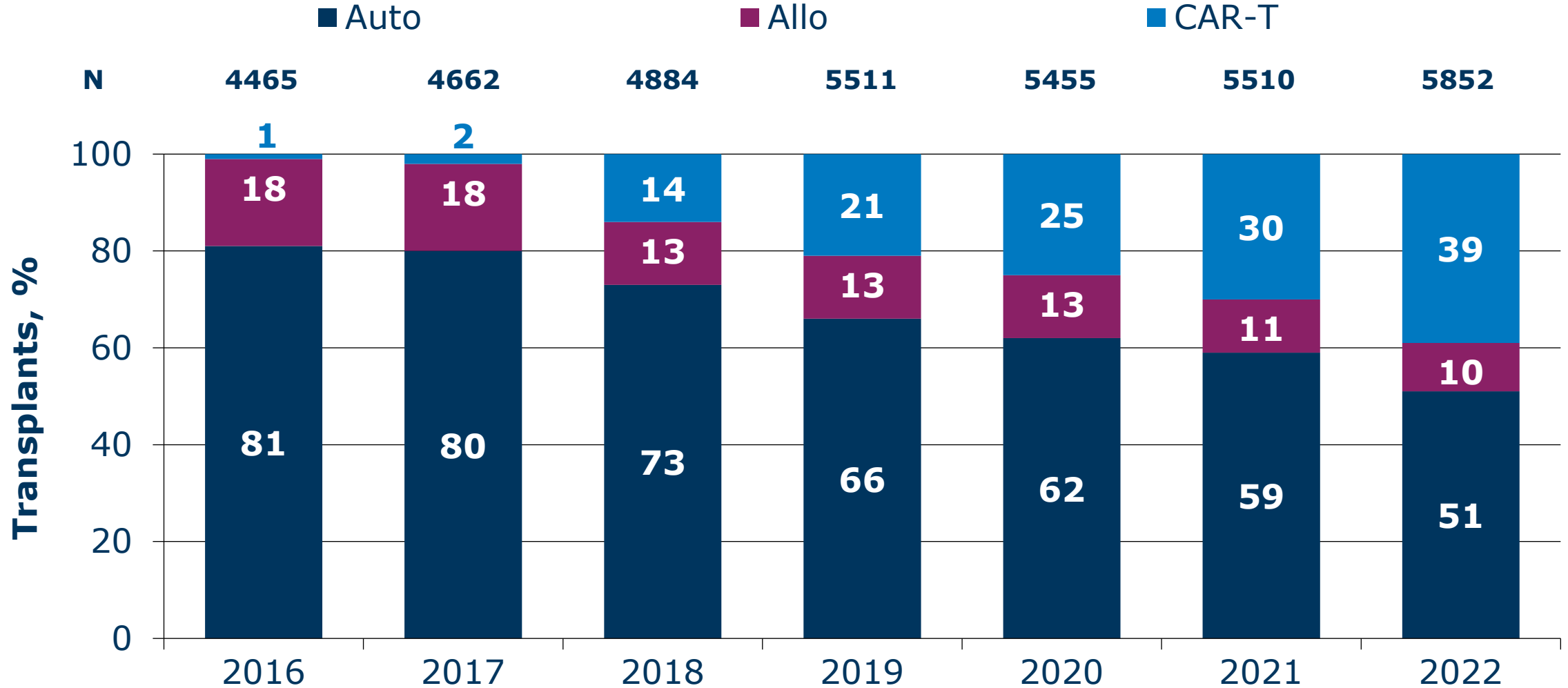


*Includes limited gene therapy events

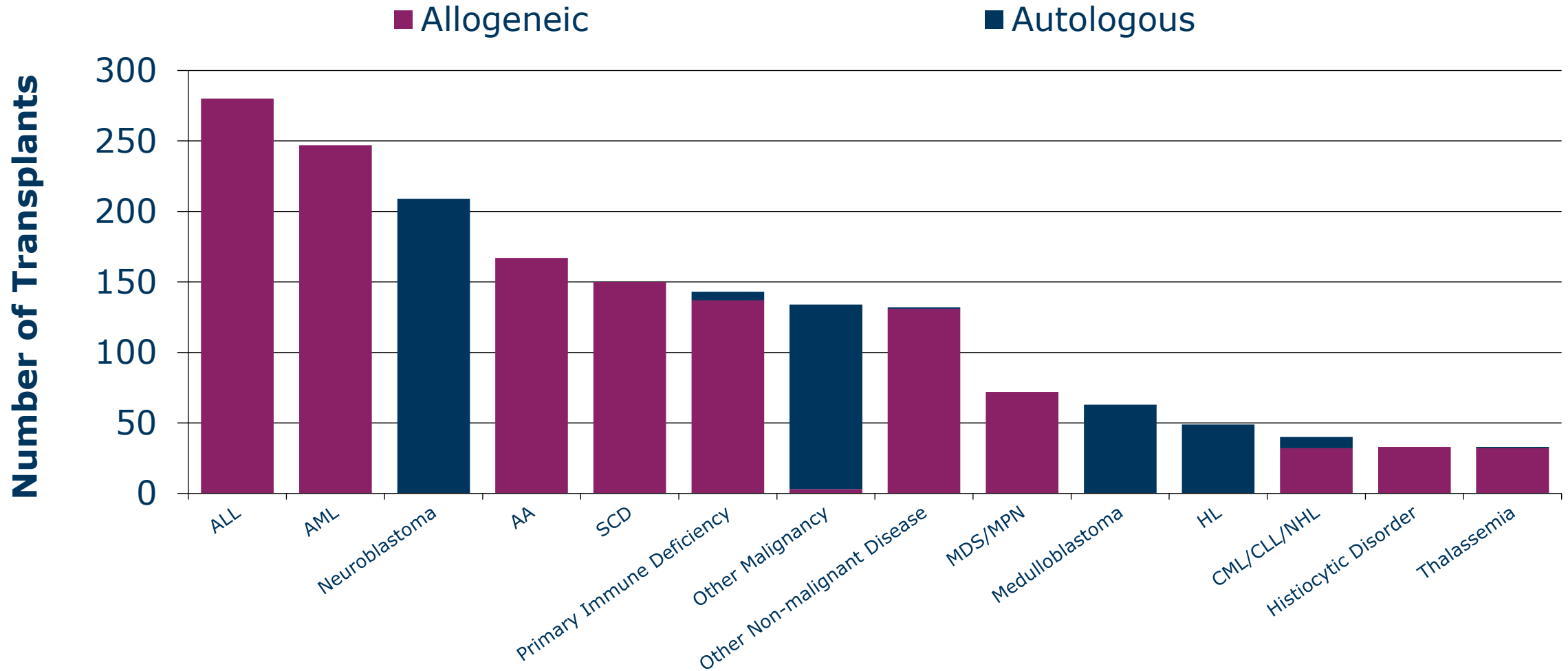
Abbreviations:
 ALL, acute lymphoblastic leukemia;
 AML, acute myeloid leukemia;
 CLL, chronic lymphocytic leukemia;
 HL, Hodgkin lymphoma;
 MDS, myelodysplastic syndromes;

MM, multiple myeloma;
 MPN, myeloproliferative neoplasms;
 NHL, non-Hodgkin lymphoma;
 PCD, plasma cell disorders.

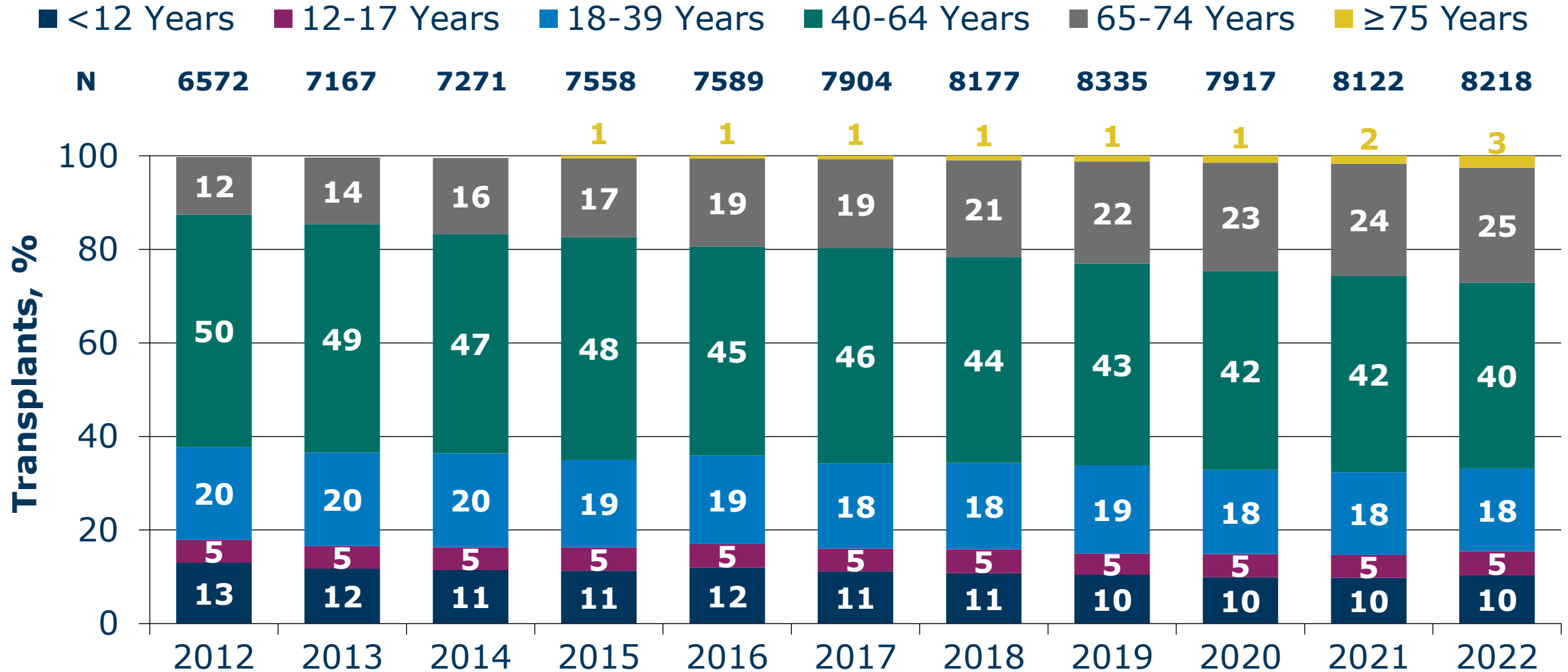
In certain diseases HCT activity is changing dramatically due to novel therapies e.g lymphoma



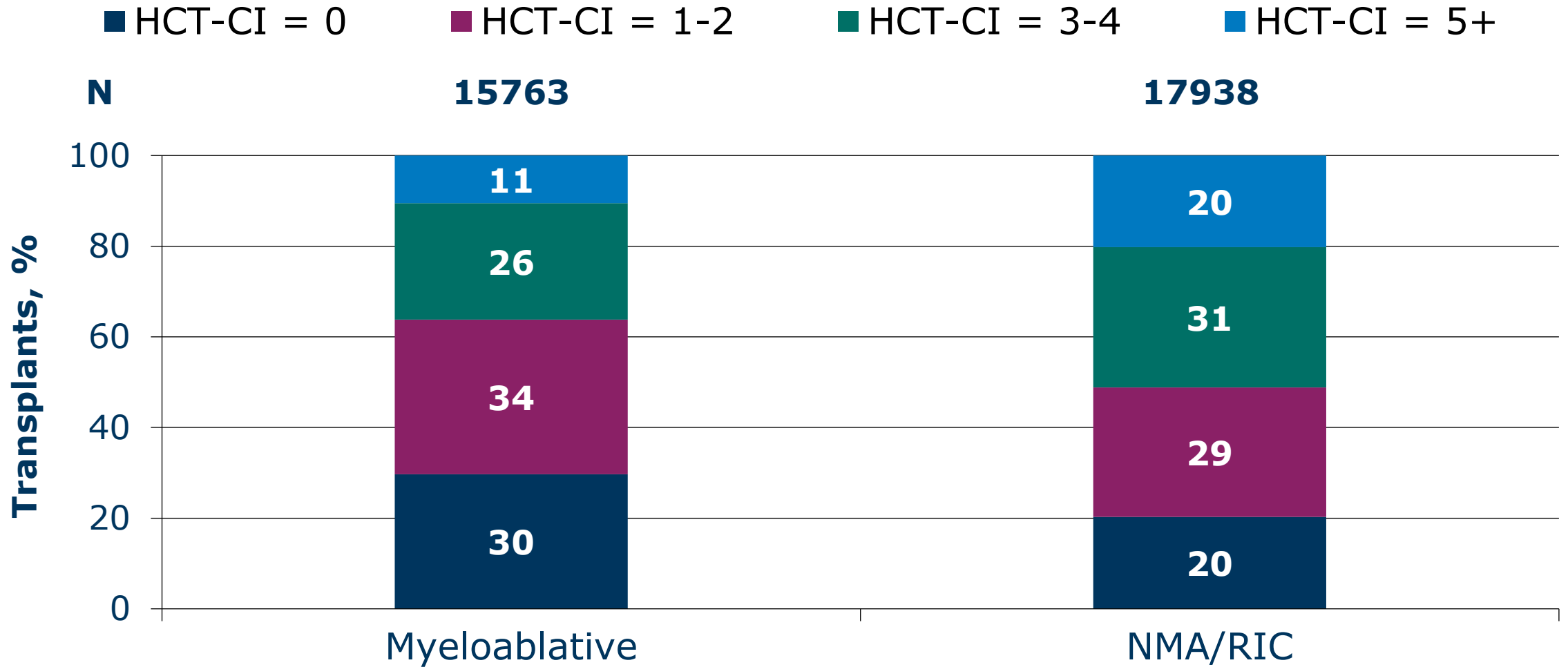
Major indications for pediatric HCT in 2022 in the US



We are transplanting a much older population

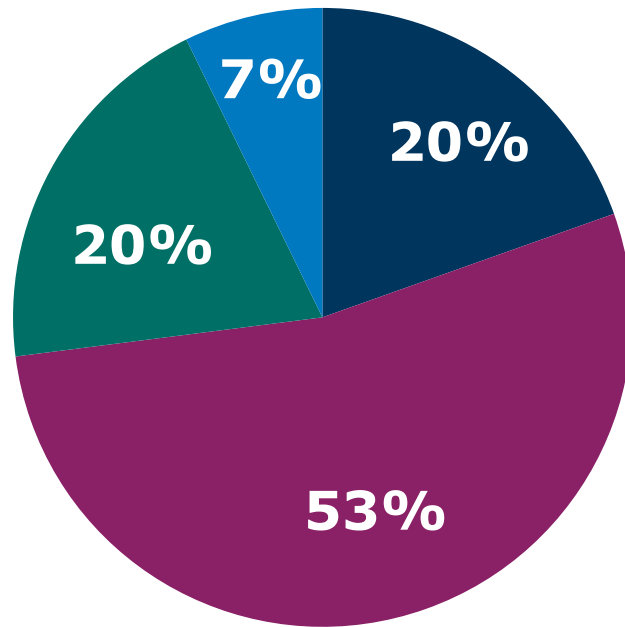


We are transplanting a much sicker population



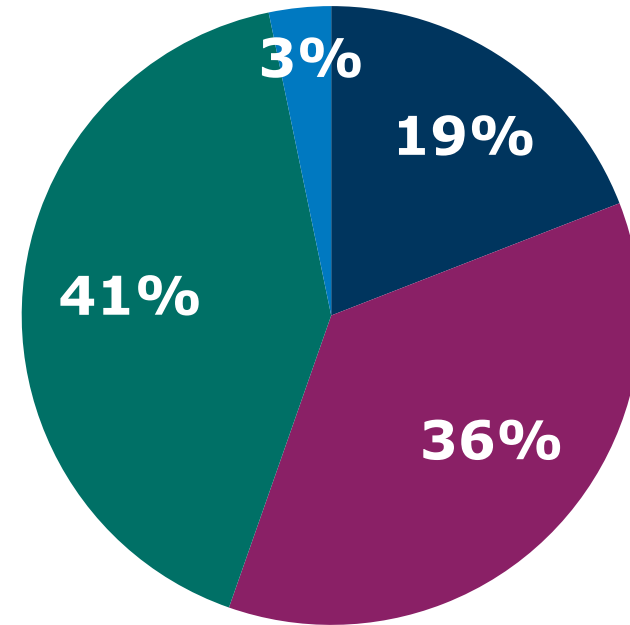
Common Conditioning Regimens in AML/MDS

MAC (n=8162)



- MAC Bu + Cy ± others
- MAC Bu + Flu ± others
- MAC TBI ± others
- MAC others

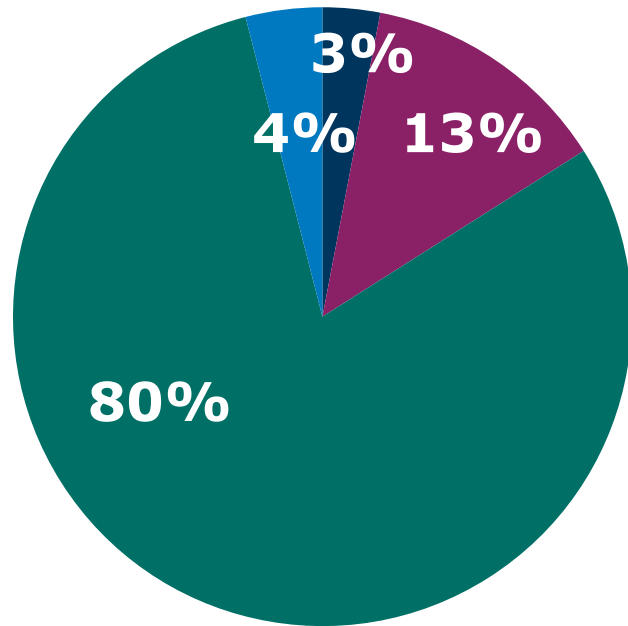
RIC/NMA (n=11508)



- RIC/NMA Bu + Flu ± others
- RIC/NMA Flu + Mel ± others
- RIC/NMA TBI ± others
- RIC/NMA others

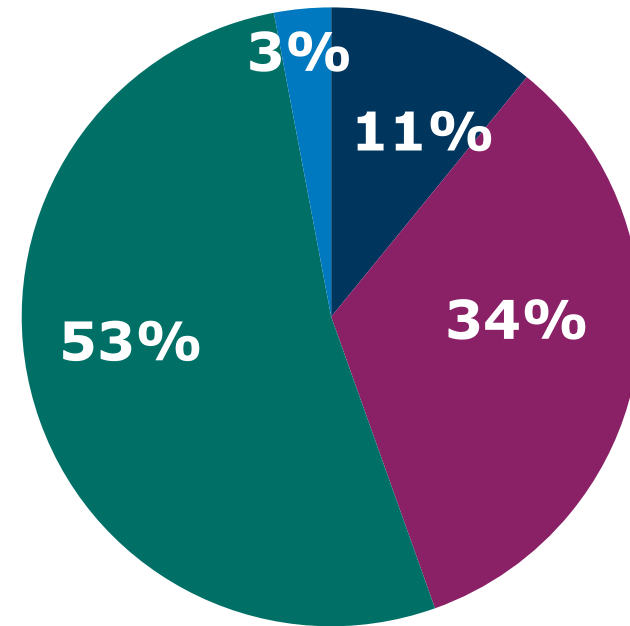
Common Conditioning Regimens in ALL

MAC (n=2688)



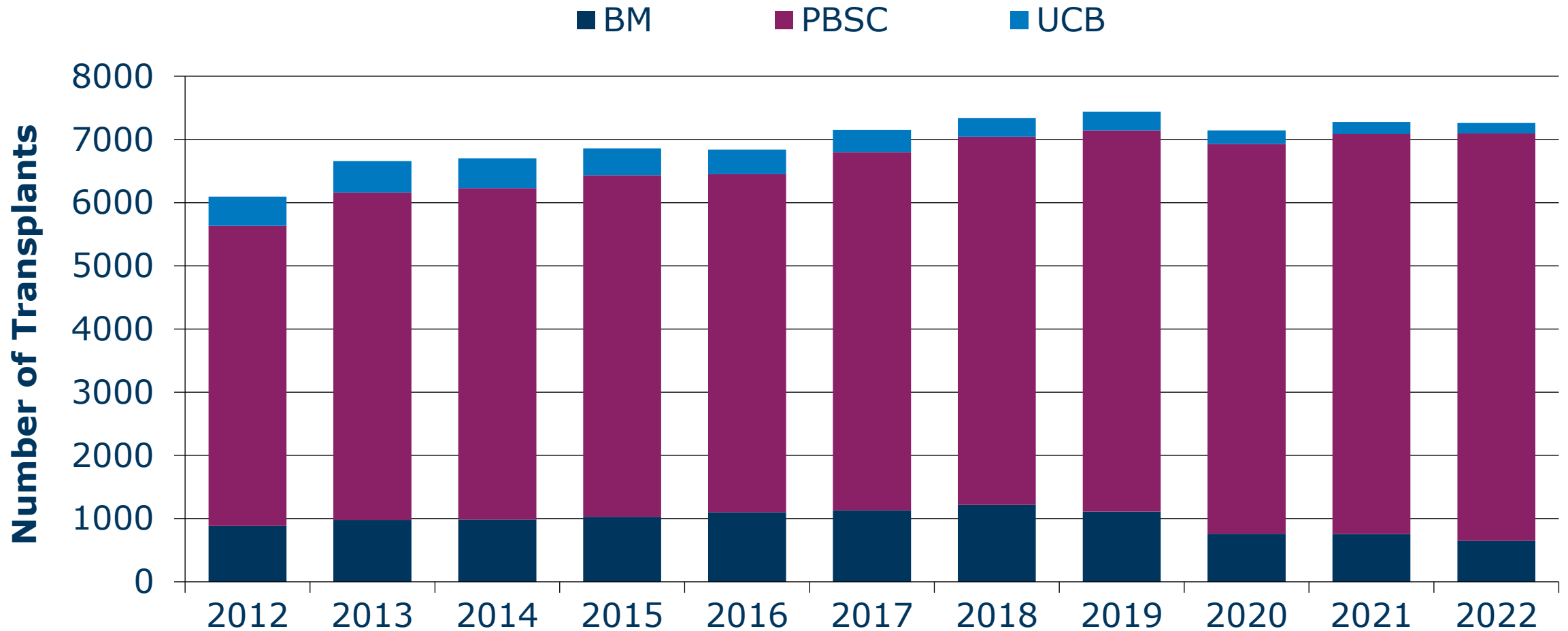
- MAC Bu + Cy ± others
- MAC Bu + Flu ± others
- MAC TBI ± others
- MAC others

RIC/NMA (n=1427)

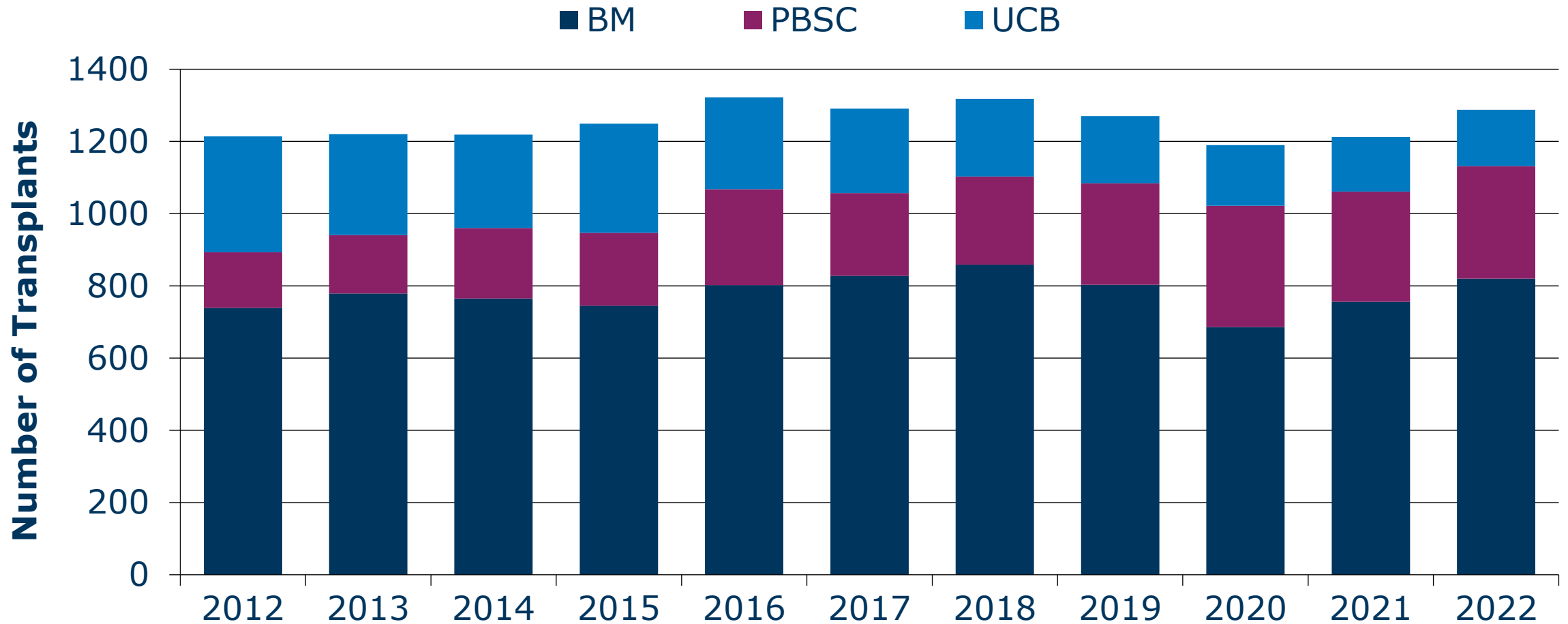


- RIC/NMA Bu + Flu ± others
- RIC/NMA Flu + Mel ± others
- RIC/NMA TBI ± others
- RIC/NMA Others

PBSC has been the SOC graft source in adult HCT (with a few specific exceptions) for >10 years



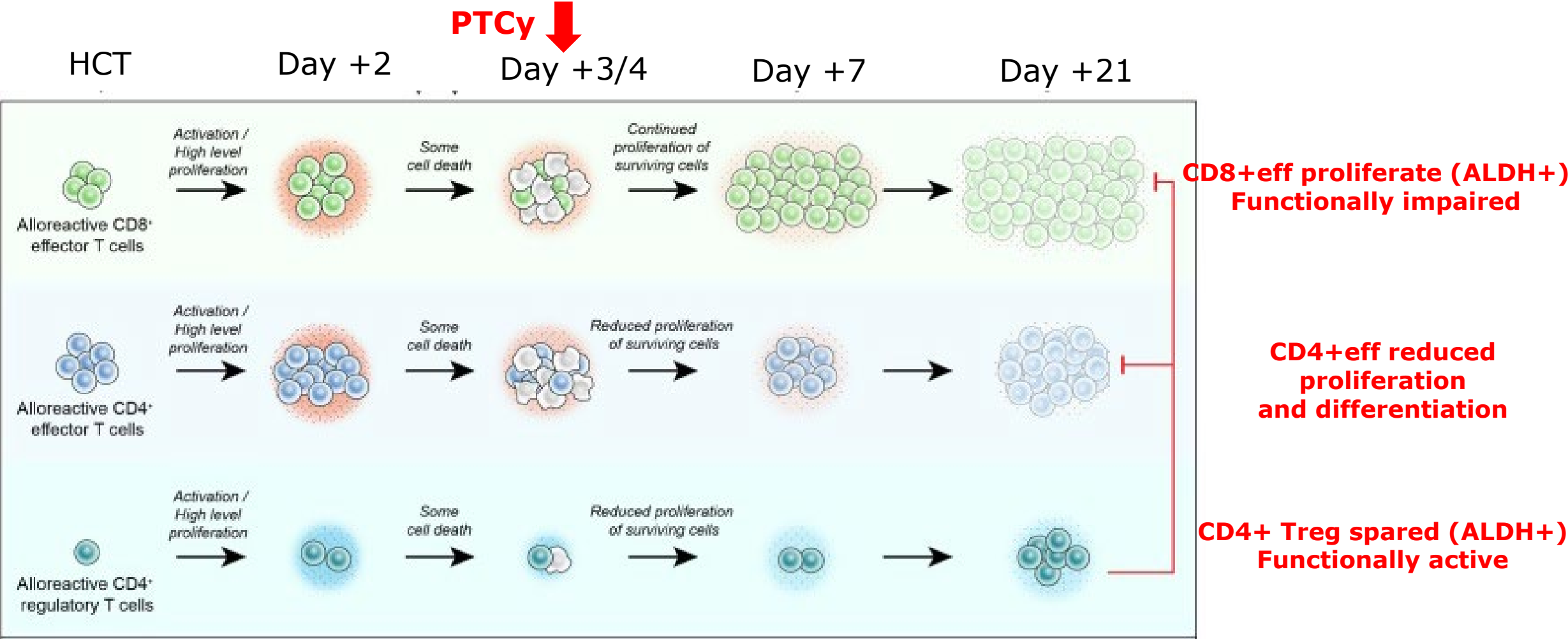
BM is still the most commonly used graft source in Pediatrics



What about GVHD prophylaxis?

PTCy: Dampening of Alloreactivity

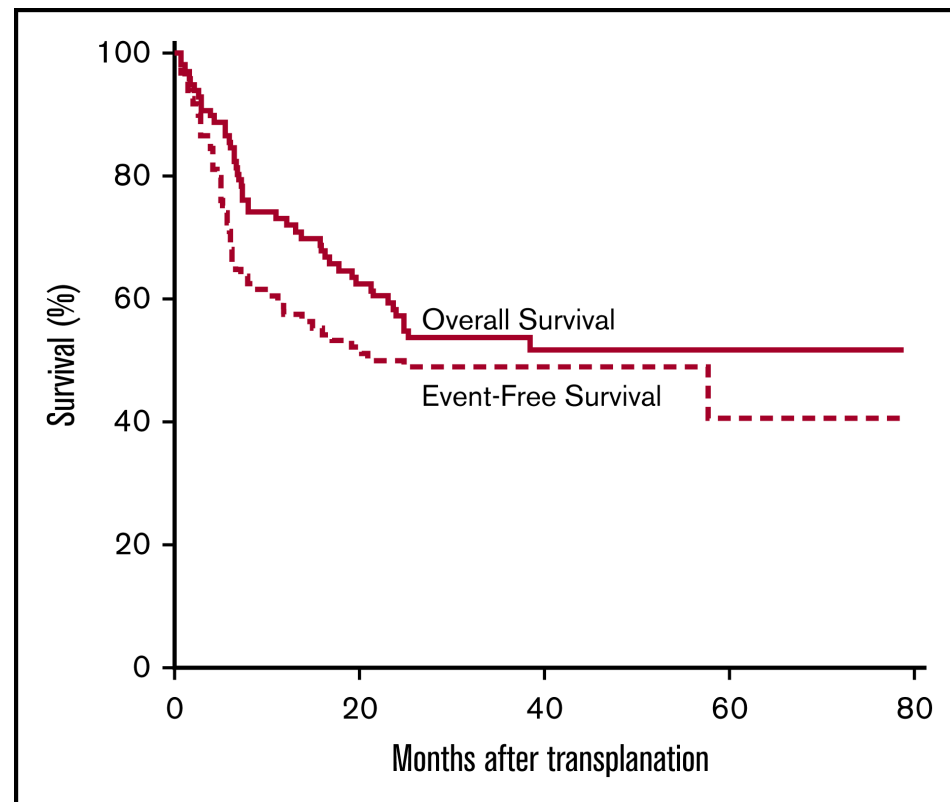
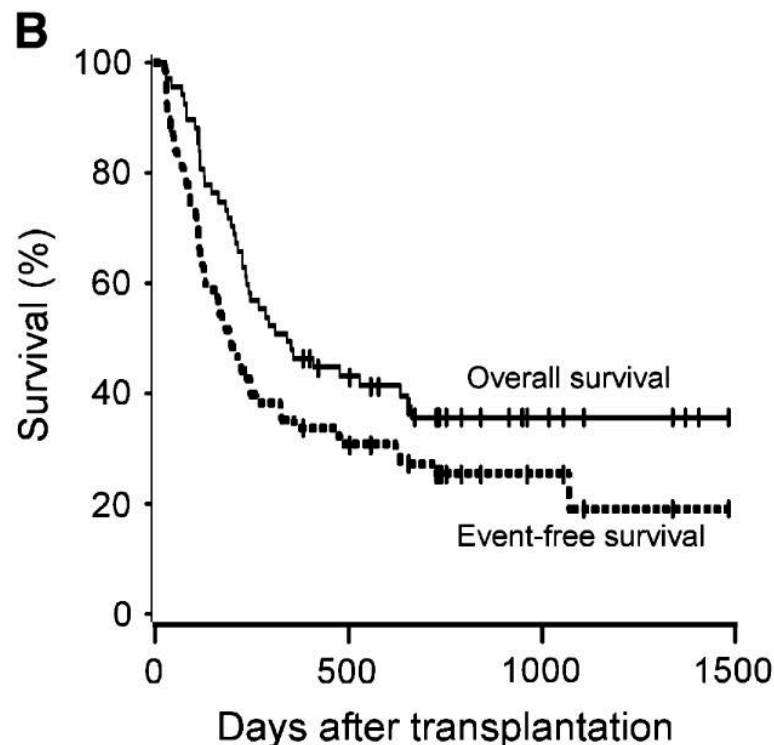
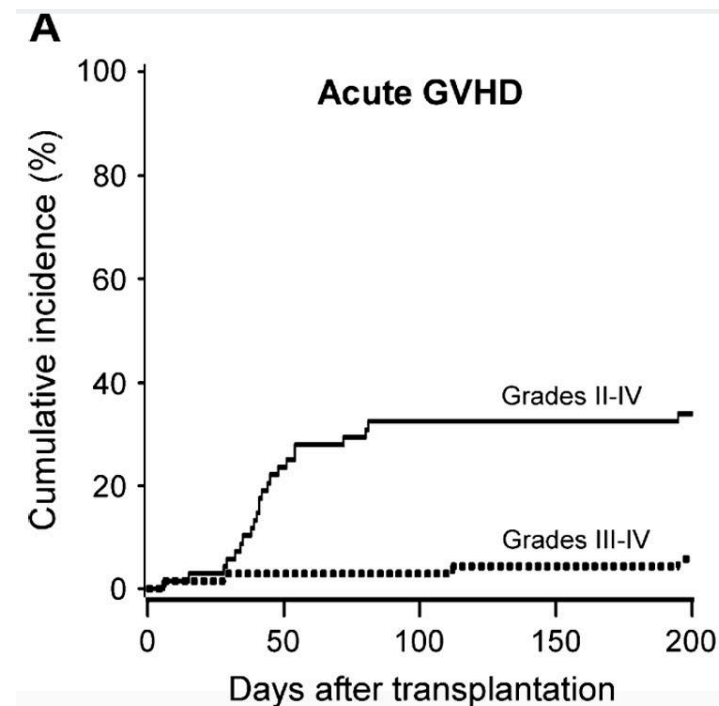
Also inexpensive, available and easy to give



PTCy was a game changer for haplo-identical HCT: Improved survival with significantly less GVHD

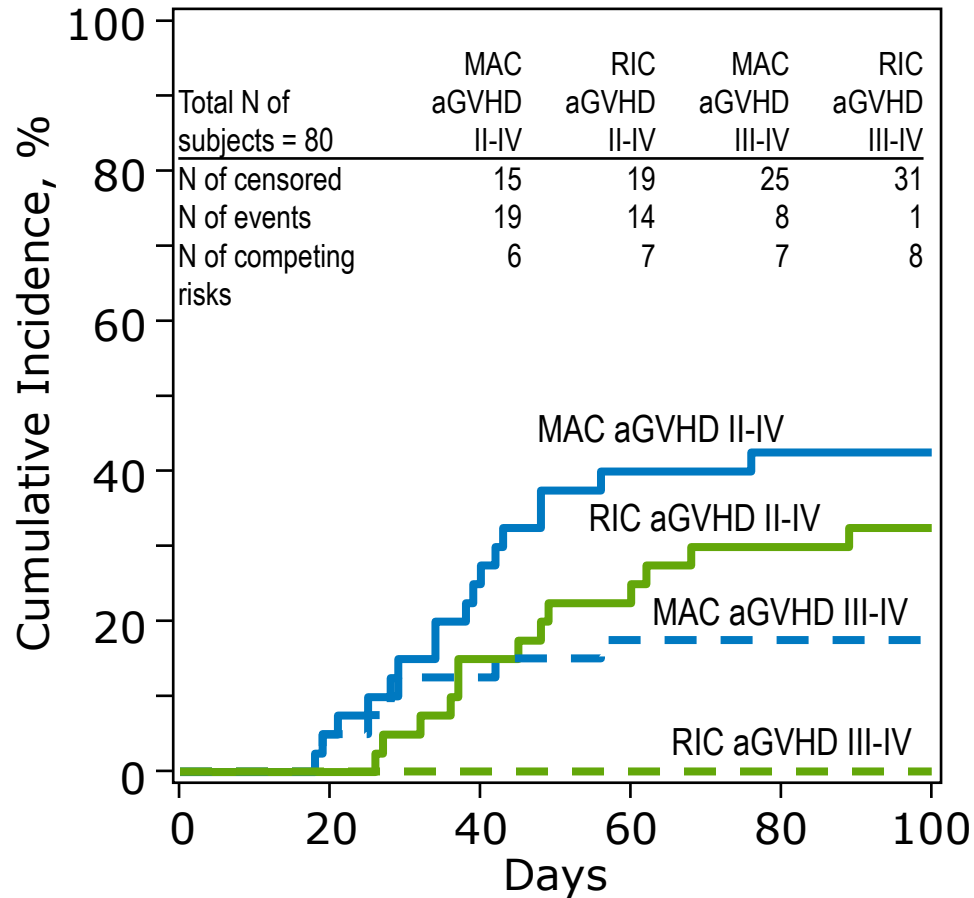
2008

2020

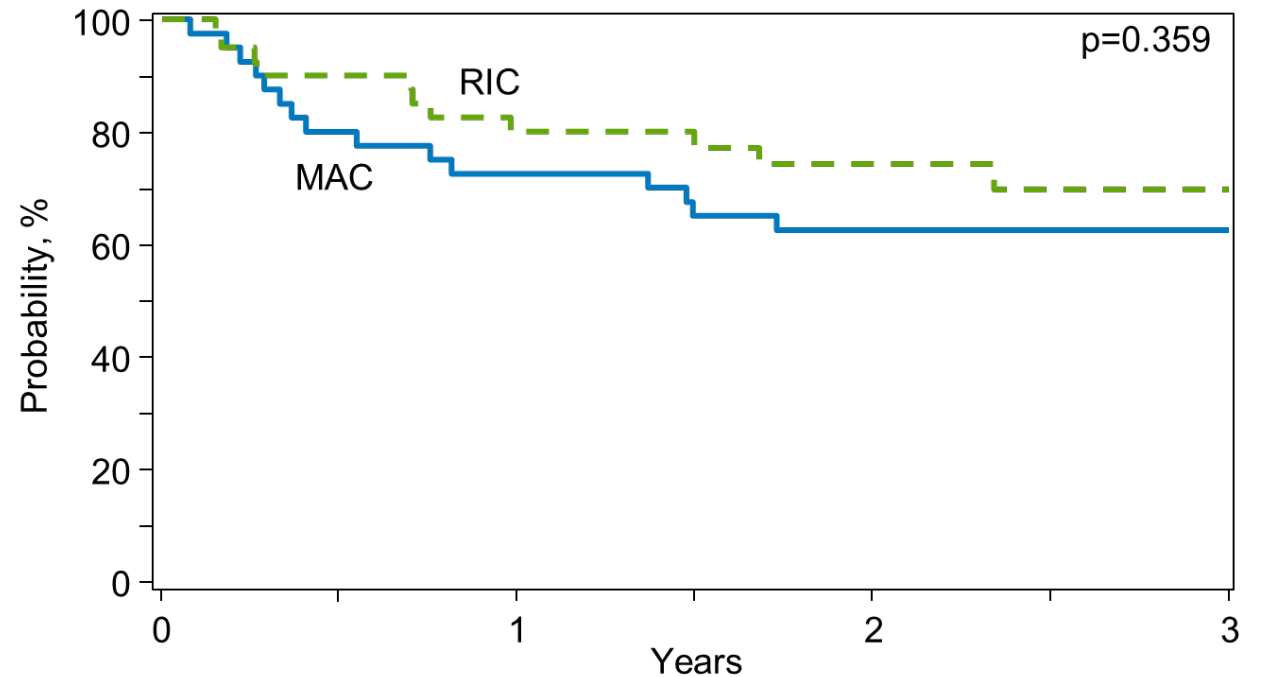


PTCy is also a successful approach in the MMUD setting: 15-MMUD study using bone marrow

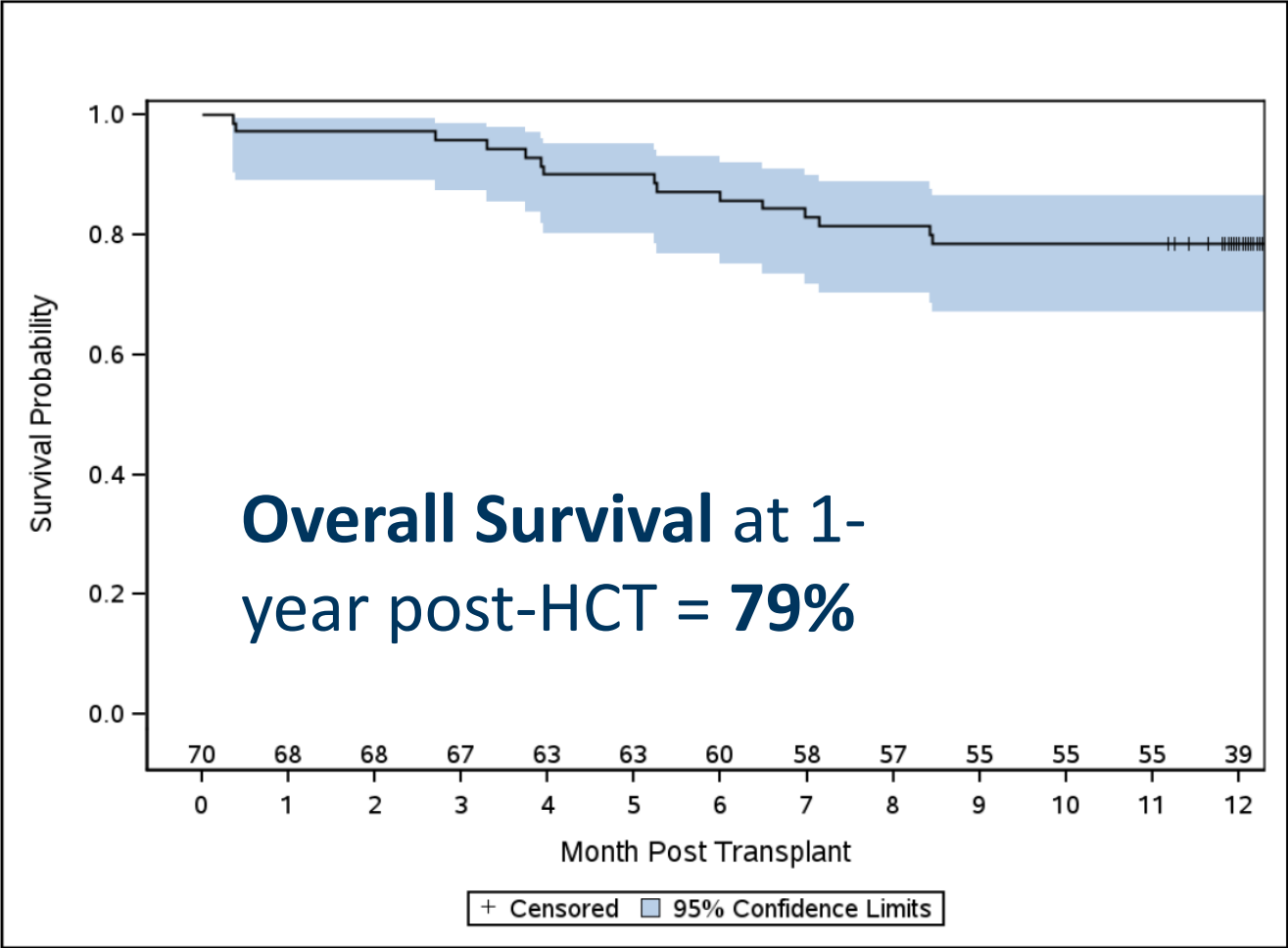
Acute GVHD



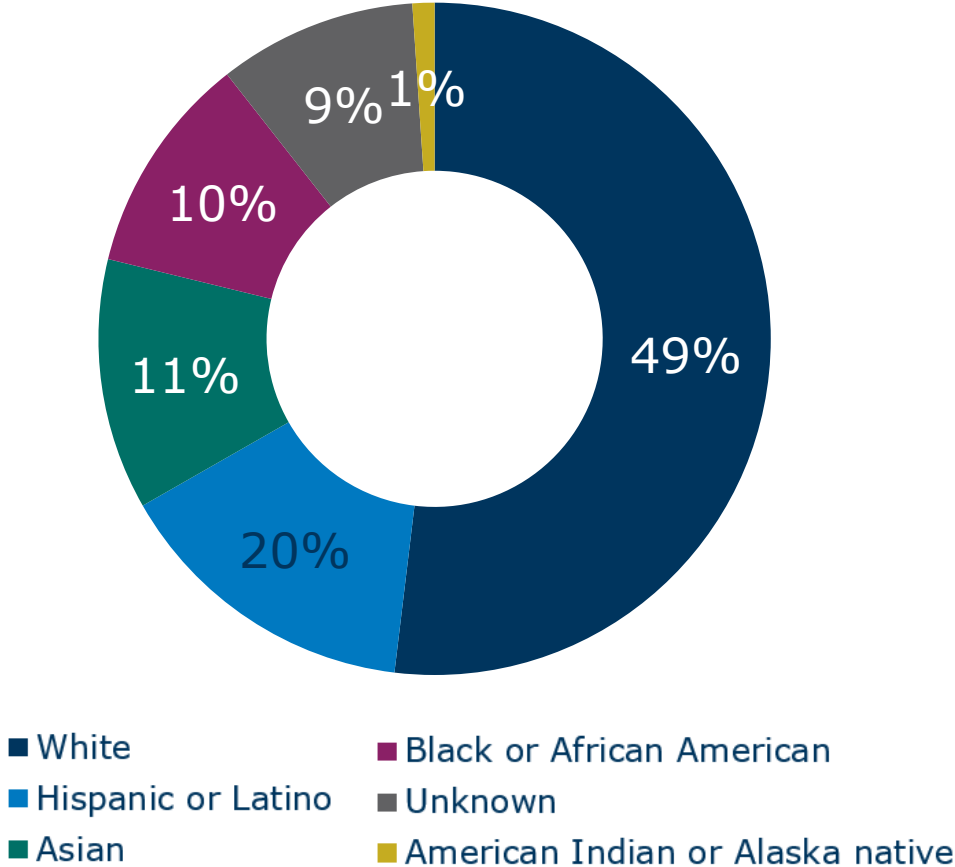
Overall survival by conditioning



CIBMTR ACCESS study shows similarly good results when using PBSC – increases access

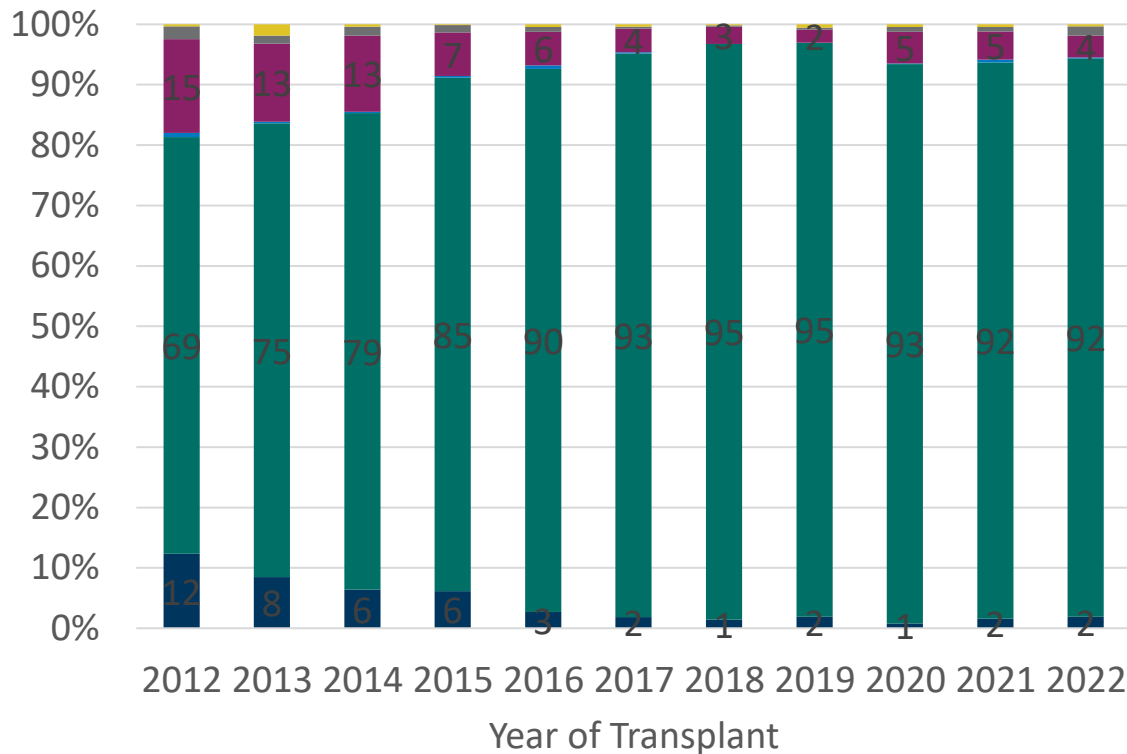


Patient Race and Ethnicity

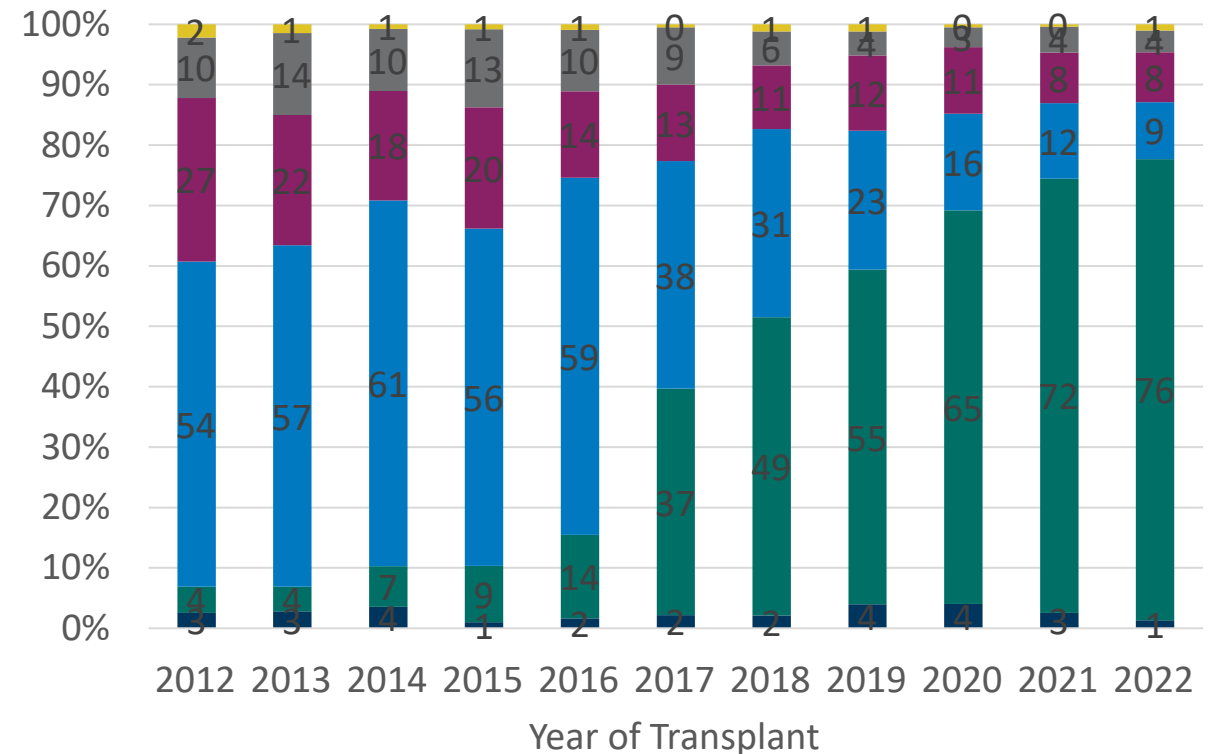


PTCy is now the predominant GvHD prophylaxis for all mismatched donor HCT

Haplo Donor

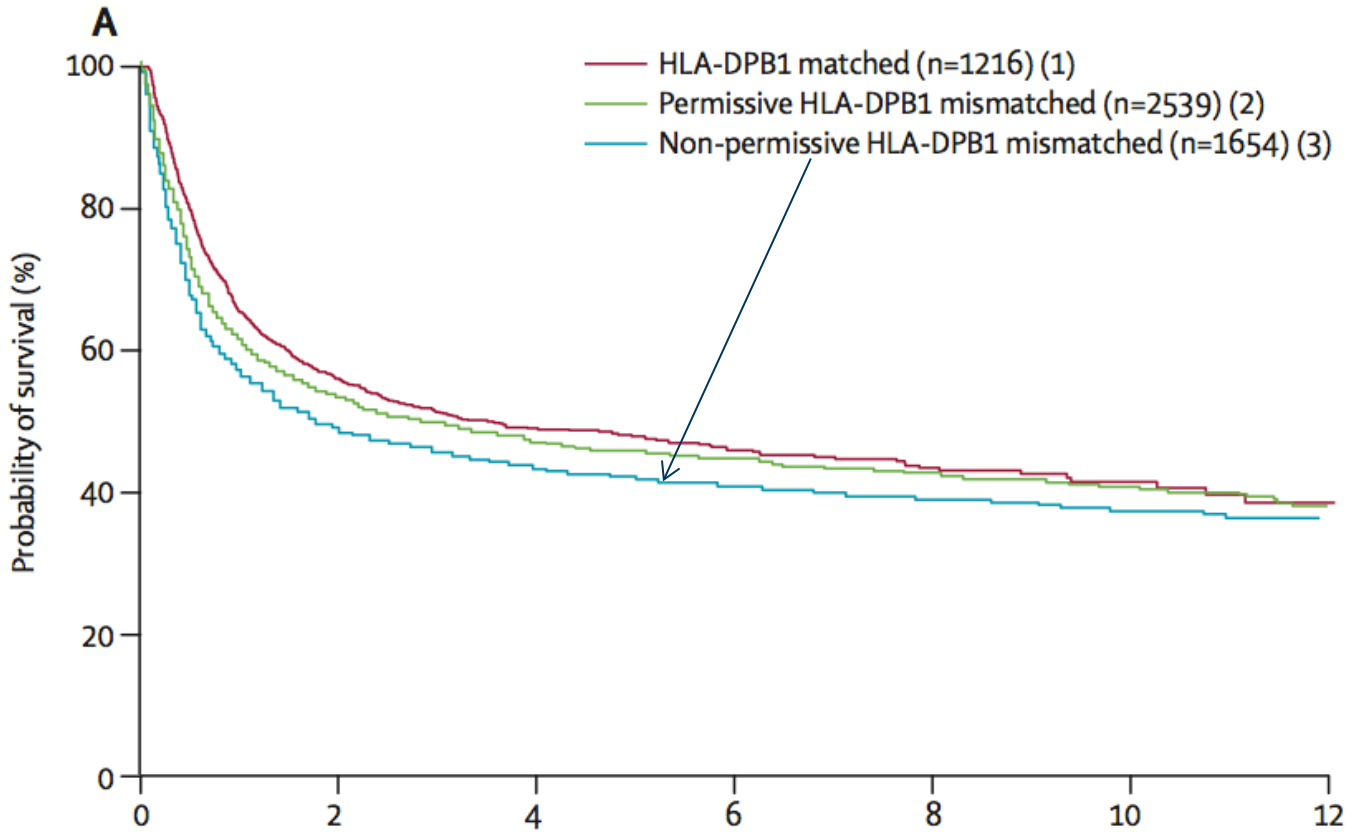


Mismatched Unrelated Donor



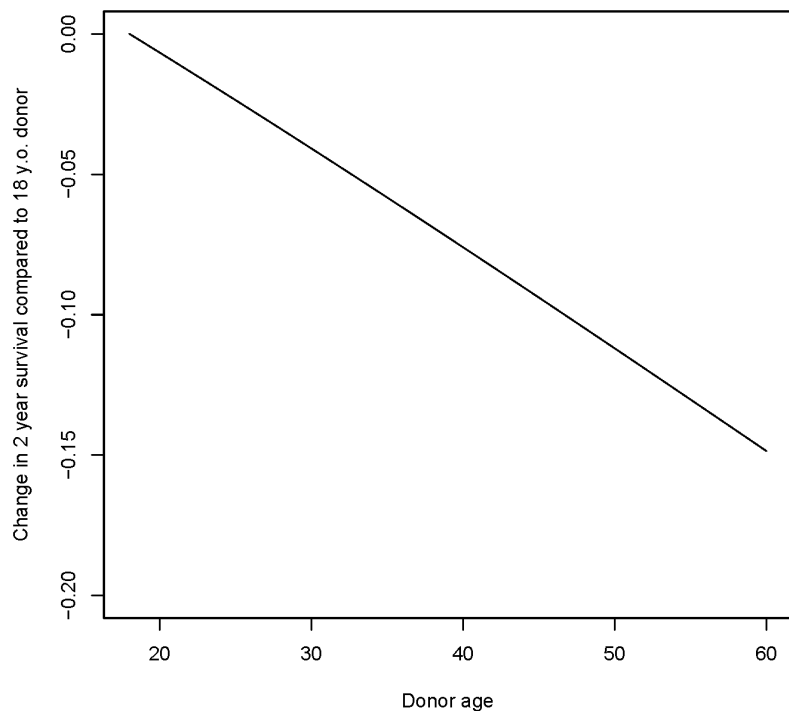
Donor secondary characteristics

Overall survival is worse in the setting of a non-permissive DPB1 mismatch (calcineurin inhibitor prophylaxis)



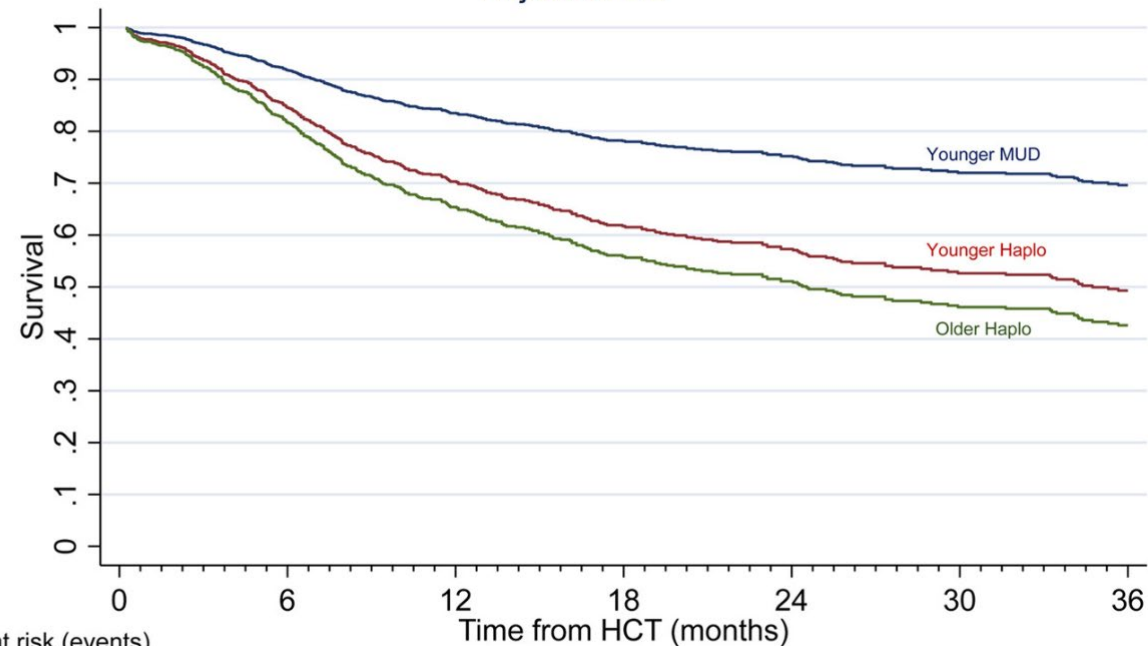
Younger unrelated and haplo donors result in better OS

Decrease in 2 year survival associated with increased donor age



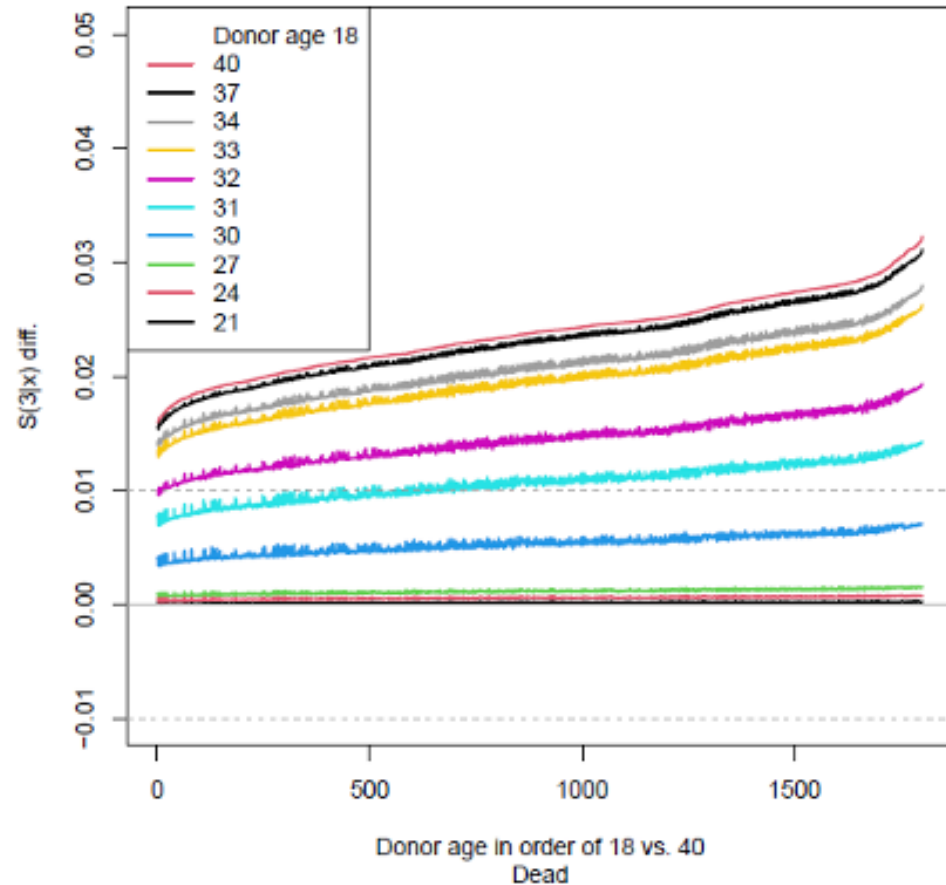
2-year survival is 3% better when an **unrelated donor** is 10 years younger, 7% with 20 years younger

Adjusted OS



	Number at risk (events)												
	0	6	12	18	24	30	36						
— Younger MUD	84	(9)	73	(7)	57	(4)	41	(0)	38	(1)	31	(1)	23
— Younger Haplo	302	(44)	253	(38)	190	(20)	125	(9)	108	(7)	73	(5)	57
— Older Haplo	389	(81)	301	(61)	210	(23)	153	(13)	127	(11)	94	(5)	68

Unrelated donors >30 years old are associated with worse survival

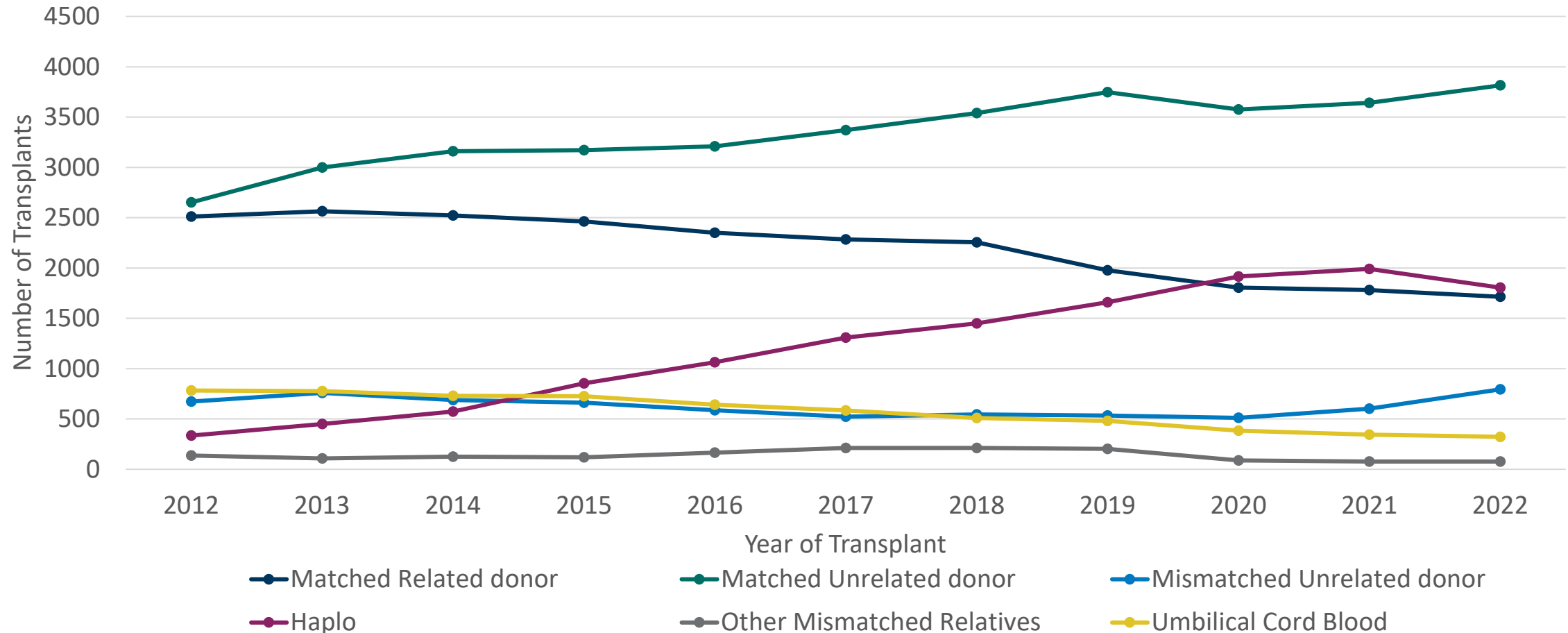


There is a <1% difference in OS when selecting any donor between 18-30

Don't delay donor selection waiting for the youngest donor within this range

CIBMTR registry data showing changes in donor use over the last 10 year

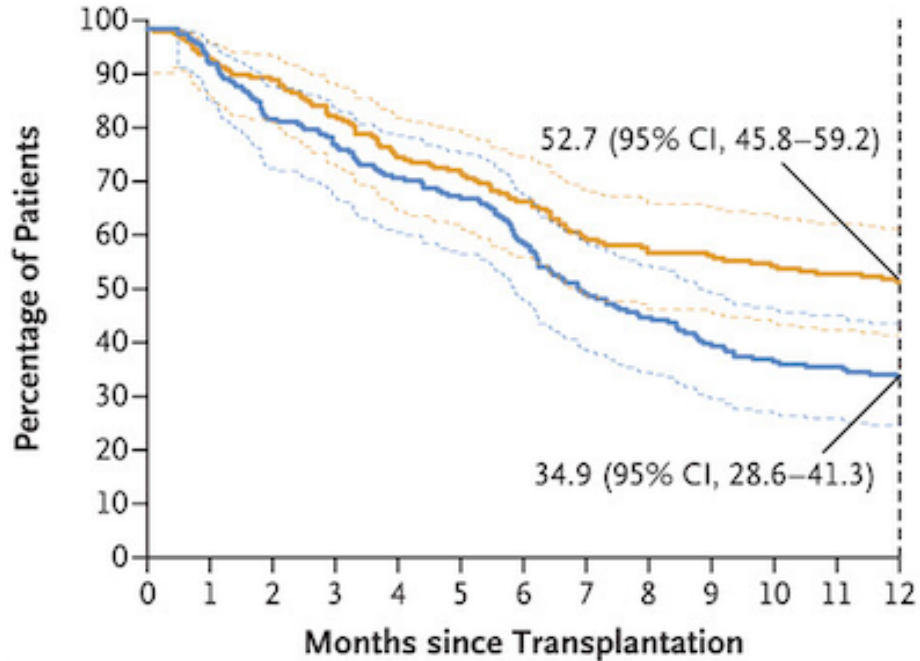
First allogeneic HCT in US by donor type, 2012-2022



The future: what are the important questions facing us

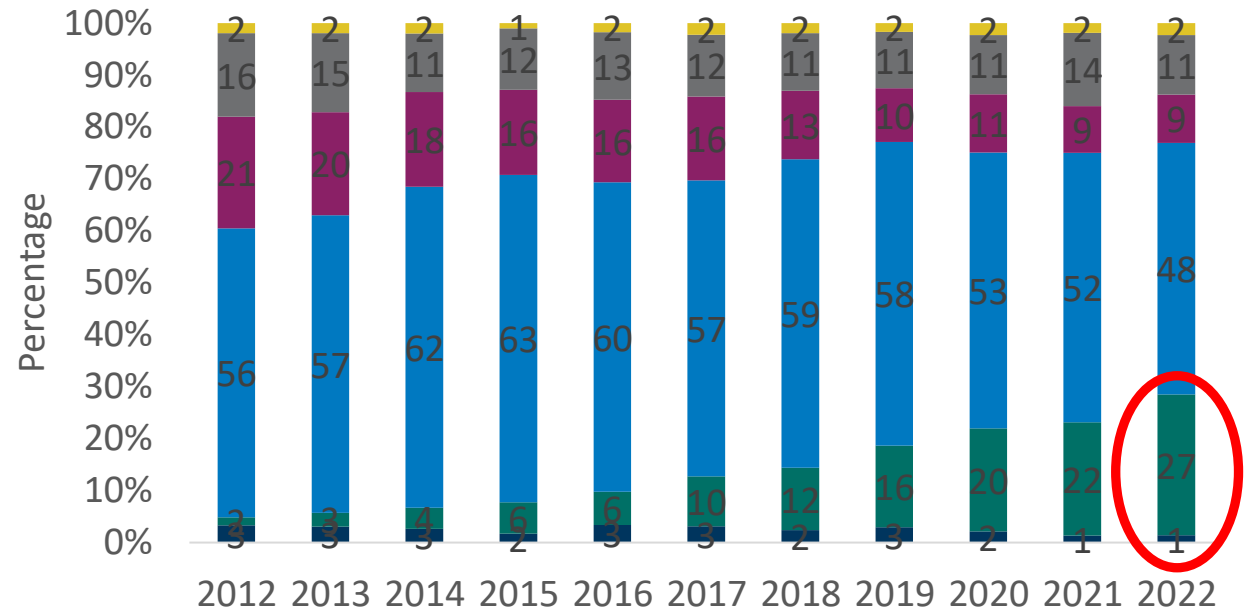
PTCy is moving to the matched donor setting: SOC in myeloablative HCT

A Adjusted GVHD-free, Relapse-free Survival



No. at Risk	0	1	2	3	4	5	6	7	8	9	10	11	12
Experimental prophylaxis	214	197	187	172	155	149	138	123	117	116	112	109	24
Standard prophylaxis	217	199	174	164	150	142	125	106	97	87	80	78	14

GVHD Prophylaxis of matched related donor HCT in US in Adults from 2012 to 2022



31% in MUD

- Ex Vivo and CD34
- PtCy
- CNI+MTX
- CNI+MMF
- CNI +/- others
- Others

PTCy does have toxicities: Several studies are testing reduced doses

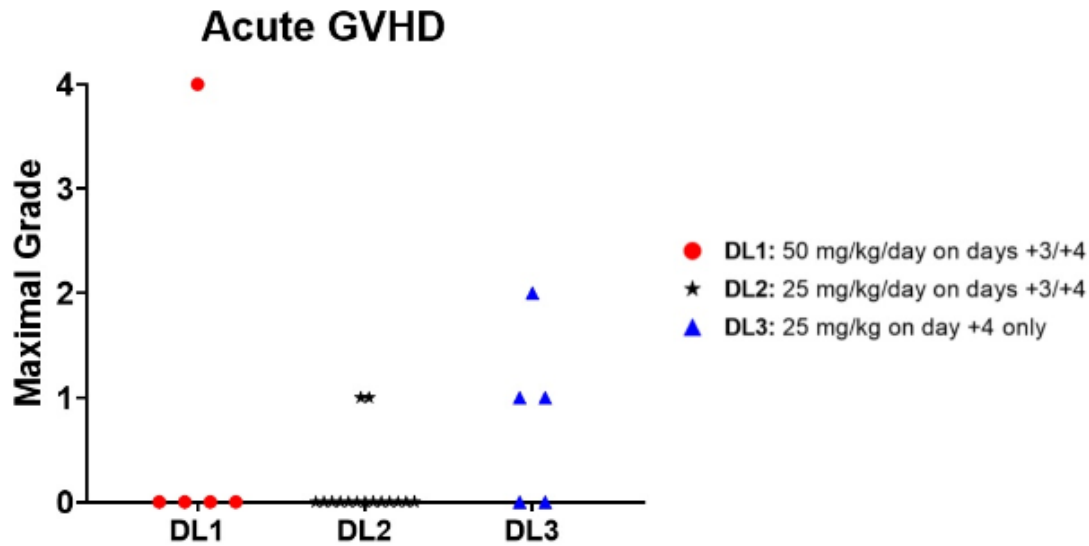
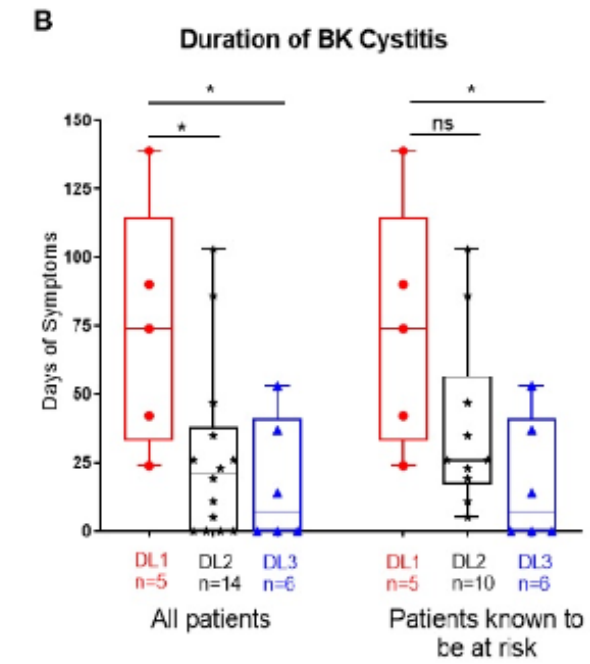


Figure 1. Maximal acute GVHD grade based on Keystone Criteria. Per the protocol, patients without acute GVHD but with graft failure, relapse, or death prior to day +60 were considered inevaluable for acute GVHD (the primary endpoint) and are not included here.

A CMV Reactivation

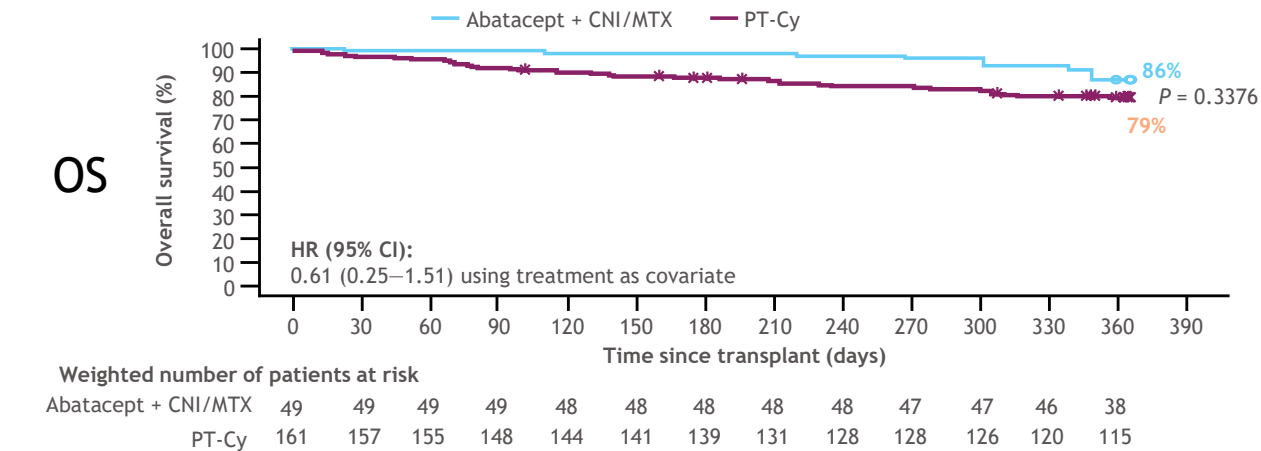
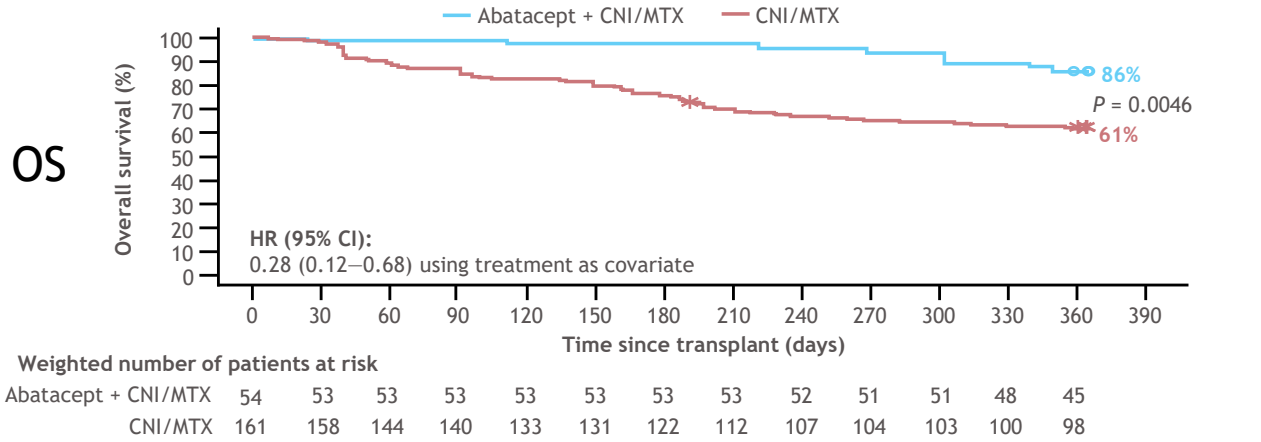
Dose Level	Recipient	Donor	CMV ppx (stop day)	Reactivation
Dose Level 1: 50 mg/kg/day on days +3/+4	-	+	None	Yes
	+	+	Letemovir, day +84	Yes
	+	+	Letemovir, day +80	Yes
	+	+	Letemovir, day +80	Yes
	+	+	Letemovir, day +131	Yes
Dose Level 2: 25 mg/kg/day on days +3/+4	+	+	Letemovir, day +77	No
	+	+	Letemovir, day +81	No
	+	+	Letemovir, day +73	No
	+	+	Letemovir, day +65	Yes
	+	+	Letemovir, day +71	Yes*
	+	+	Letemovir, day +73	No
	+	+	Letemovir, day +81	Yes
	-	+	Letemovir, day +71**	Yes**
Dose Level 3: 25 mg/kg/day on day +4	+	+	Letemovir, day +80	Yes
	+	+	Letemovir, day +33	No
	+	+	Letemovir, day +79	Yes*
	+	+	Letemovir, day +47	Yes*
	+	-	Letemovir, day +64	No
	+	+	Letemovir, day +60	No
+	+	Letemovir, day +75	Yes*	

*Occurred while on steroids.
**Primary infection at day +6. Letemovir started after treatment and then stopped due to intolerance.

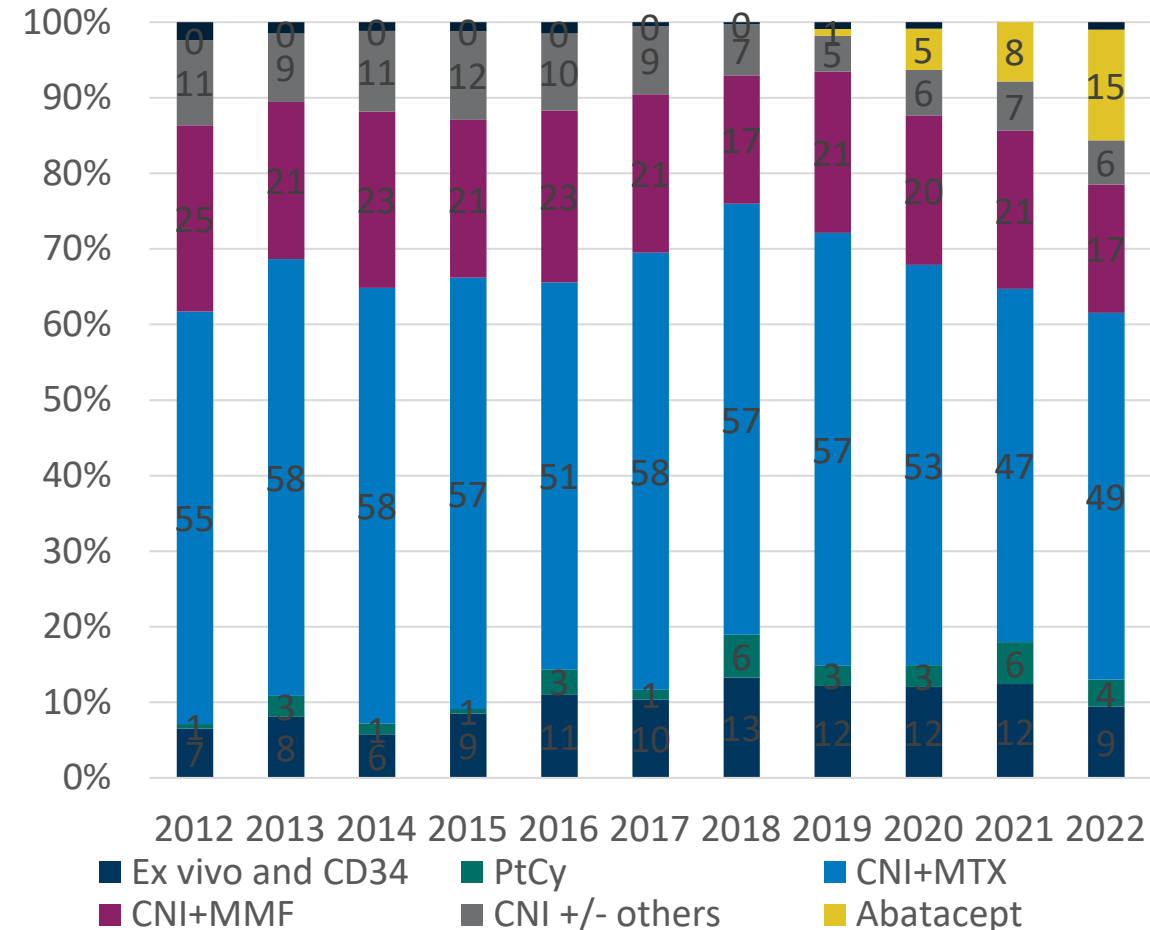


Other novel GVHD prophylaxis agents are showing promise in the mismatched and matched donor setting

7/8 MMUD

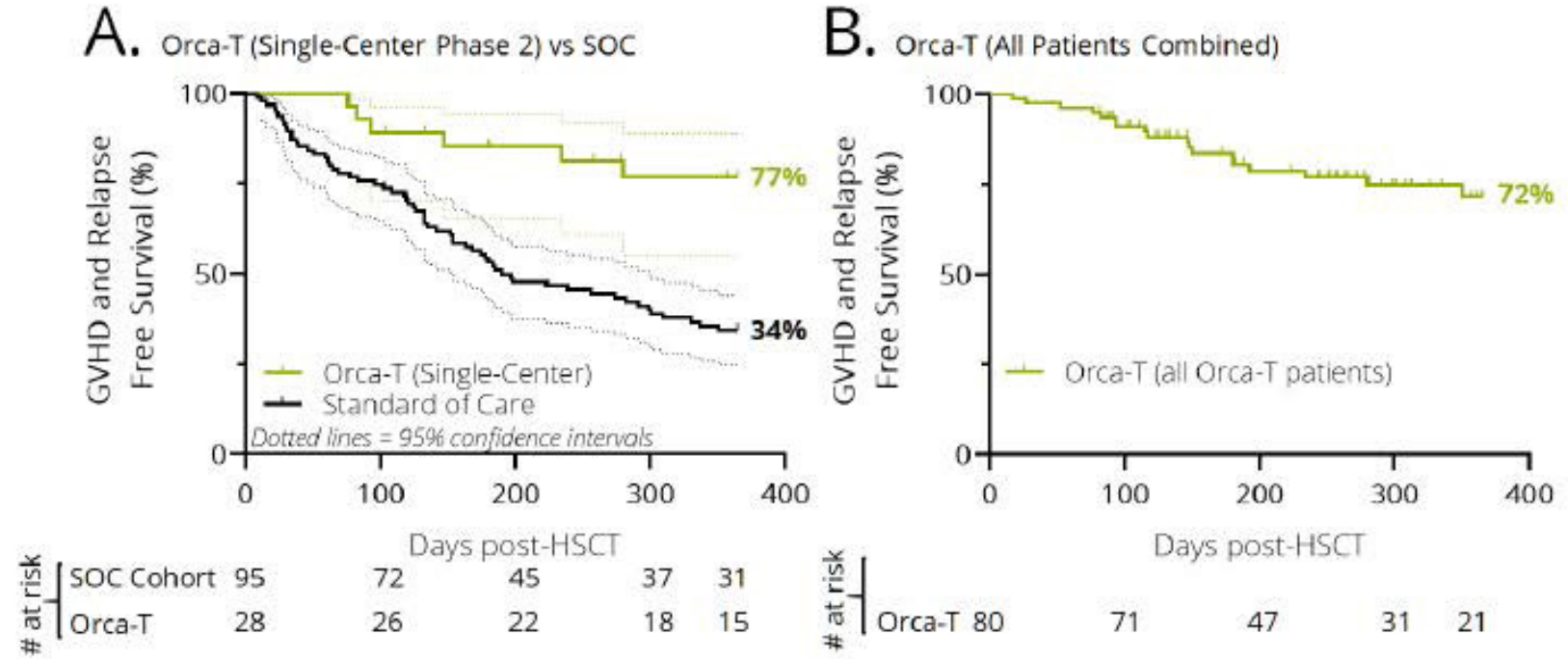


GVHD Prophylaxis of MUD HCT in Children



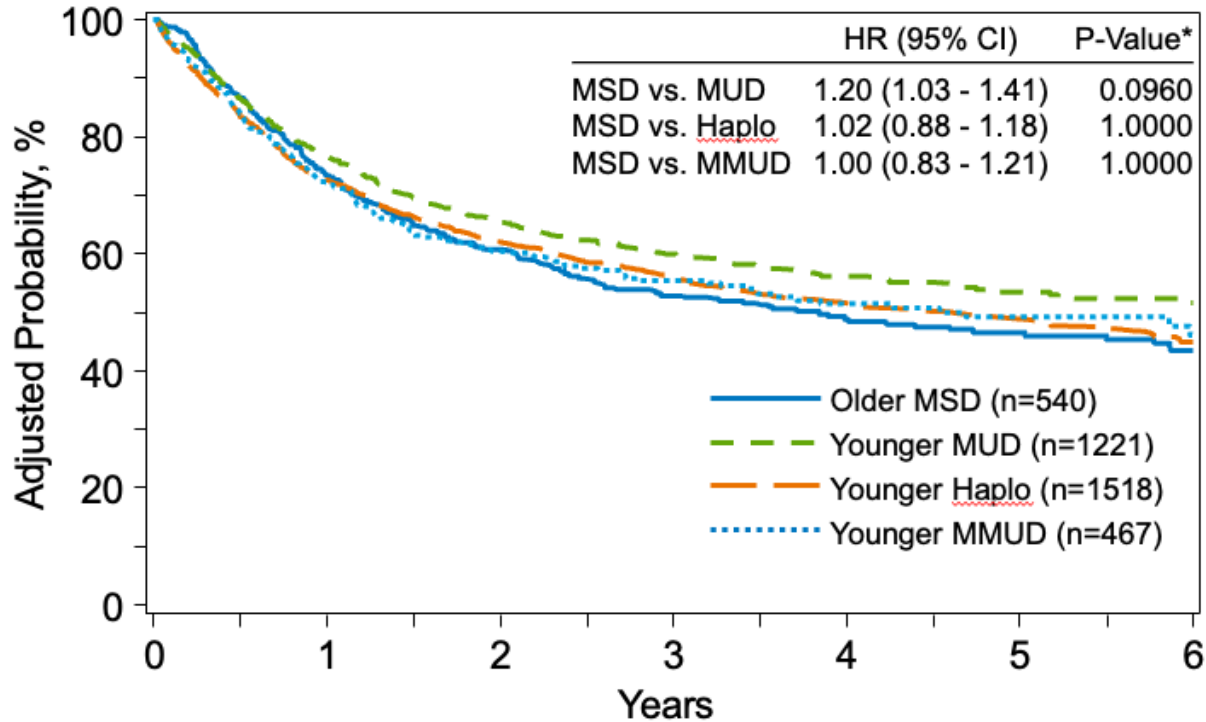
Graft manipulation strategies are showing promise in the mismatched and matched donor setting

FIGURE 1. A. GRFS (defined as survival free of Grade ≥ 3 aGVHD, moderate-to-severe cGVHD, or relapse) in the Single-Center Phase 2 Orca-T Study vs. SOC Cohort. B. GRFS in all patients receiving Orca-T (n=80).

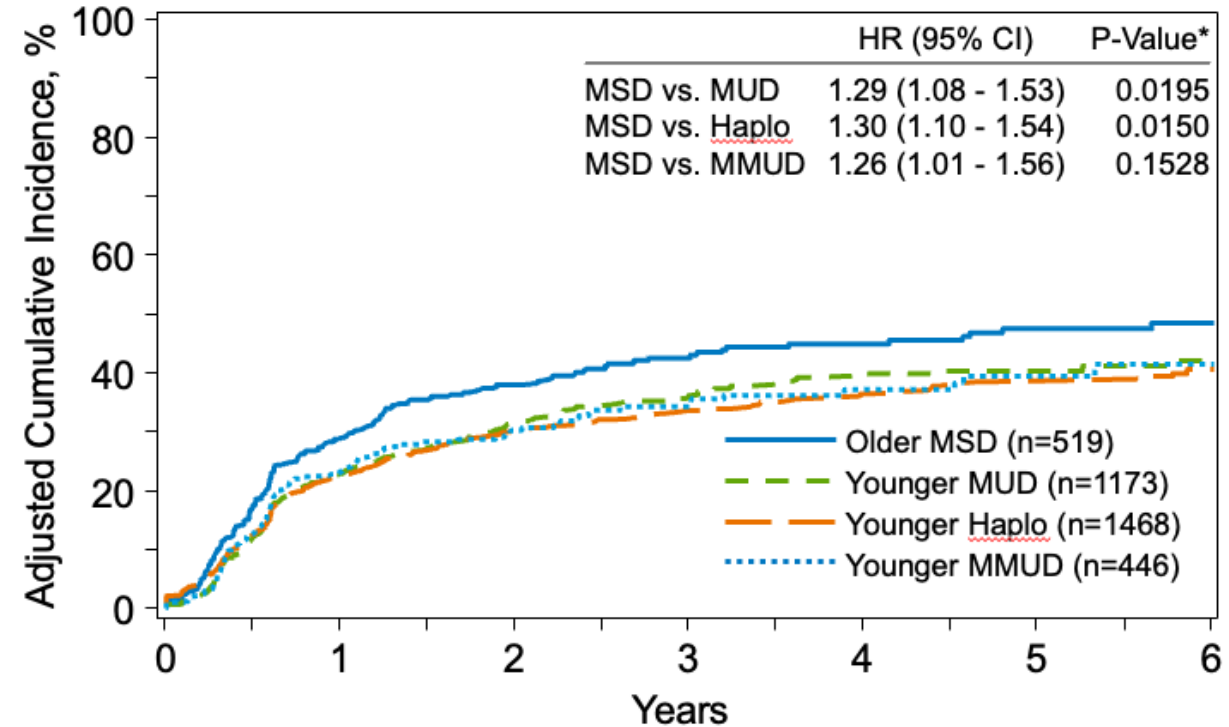


Donor age may be more important than HLA match or relationship

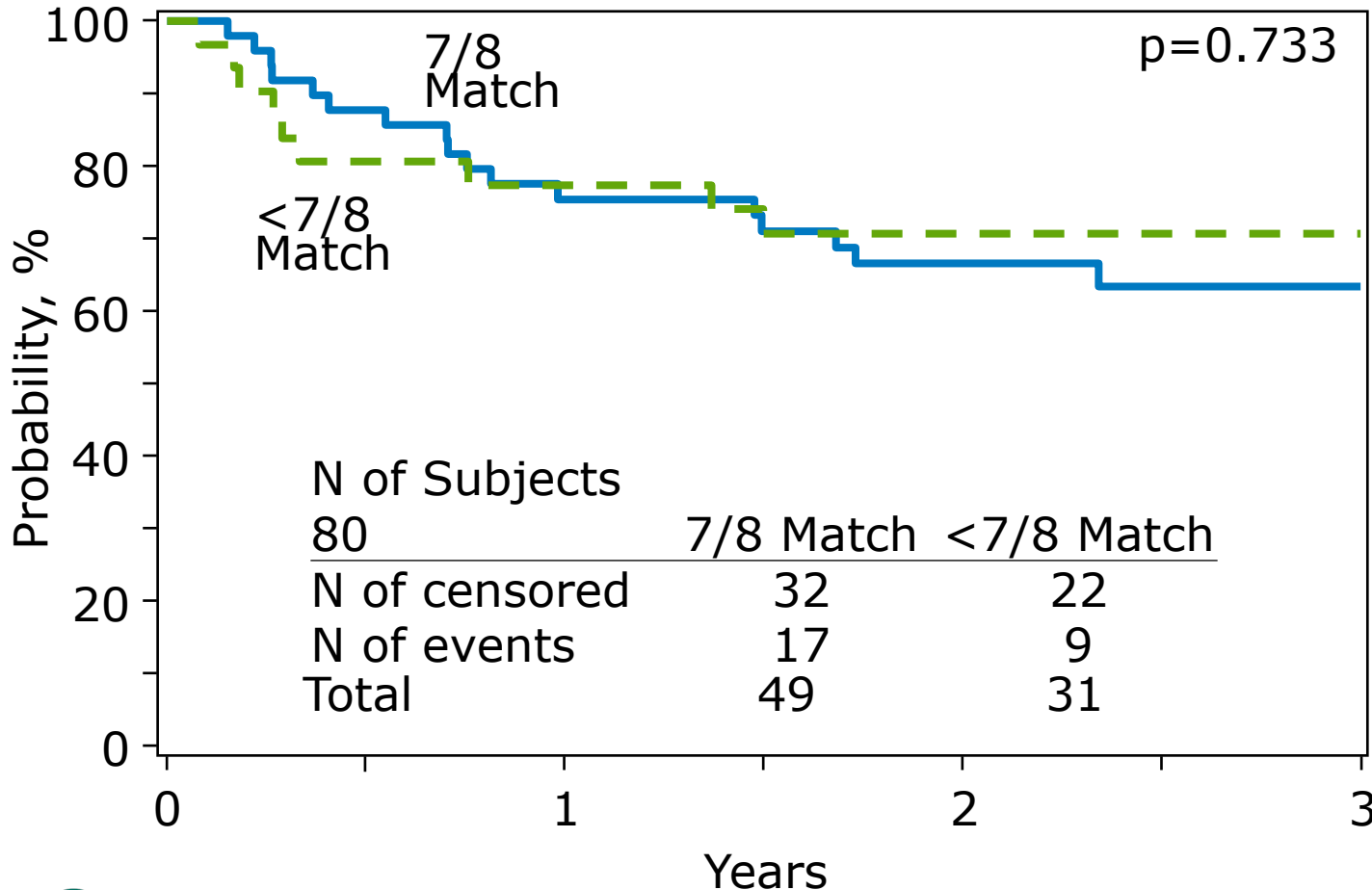
Overall survival



Relapse

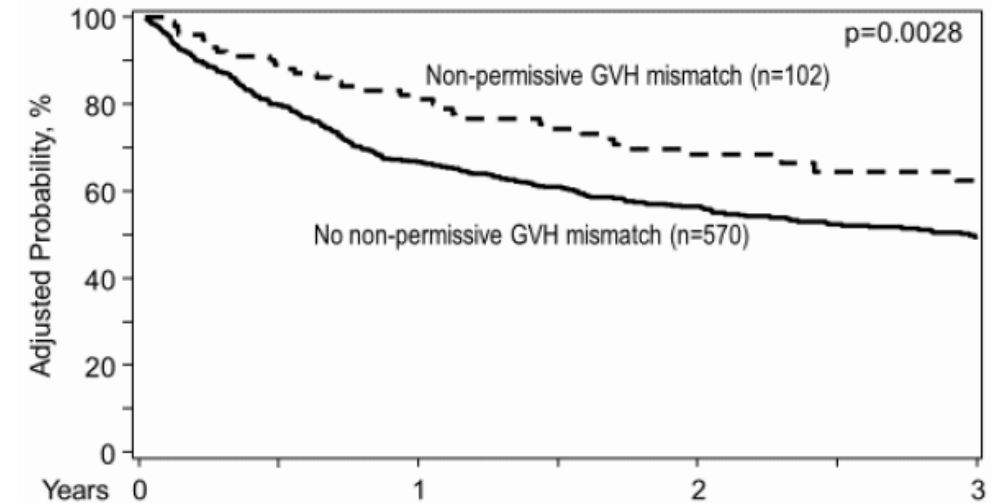


Mismatched donor setting: more mismatch may be beneficial (or not matter)



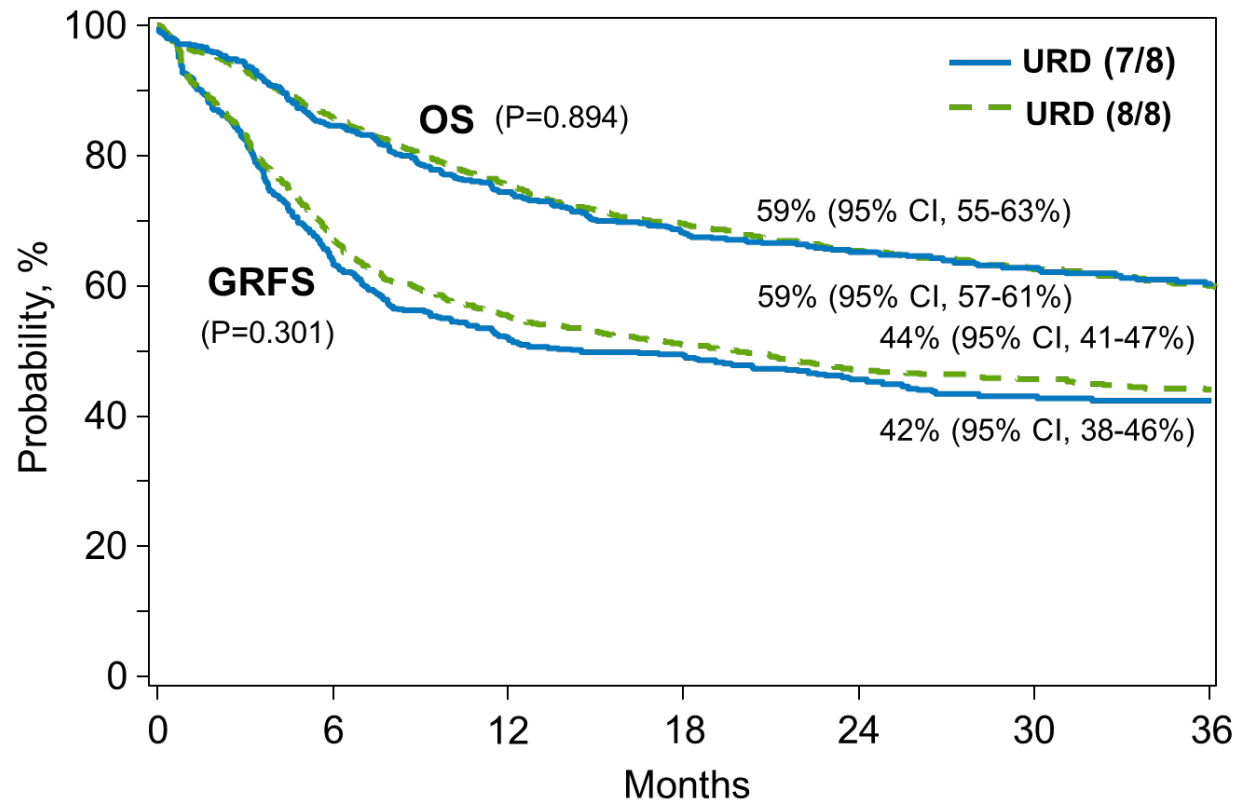
Retrospective cohort analysis of 1,434 **haploidentical** donor PTCy HCT: More mismatches = better OS

Overall Survival: DPB1 TCE matching



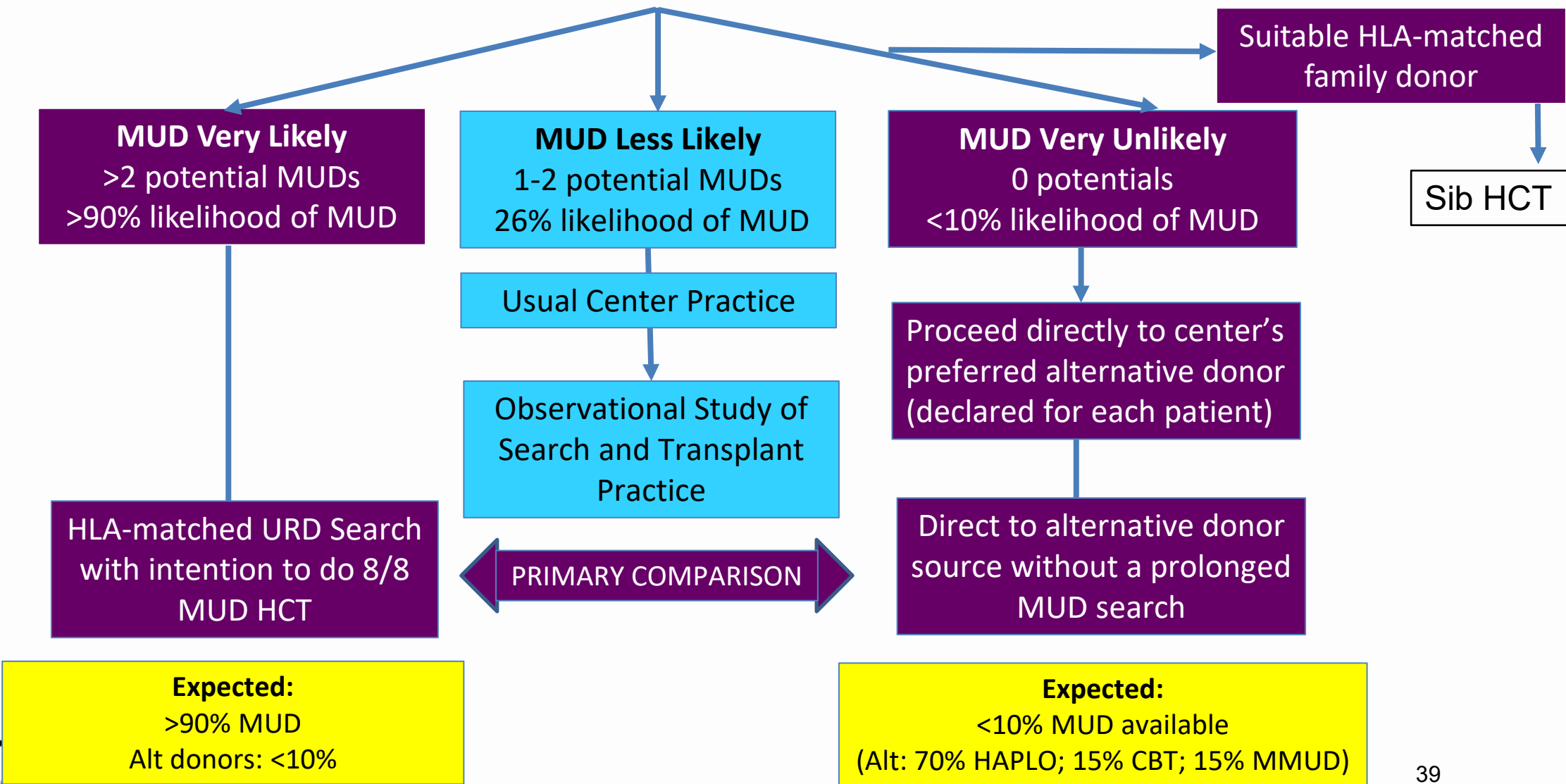
Using PTCy outcomes for MUD or MMUD may be the same

HCT PTCy GvHD prophylaxis (2017-2020)

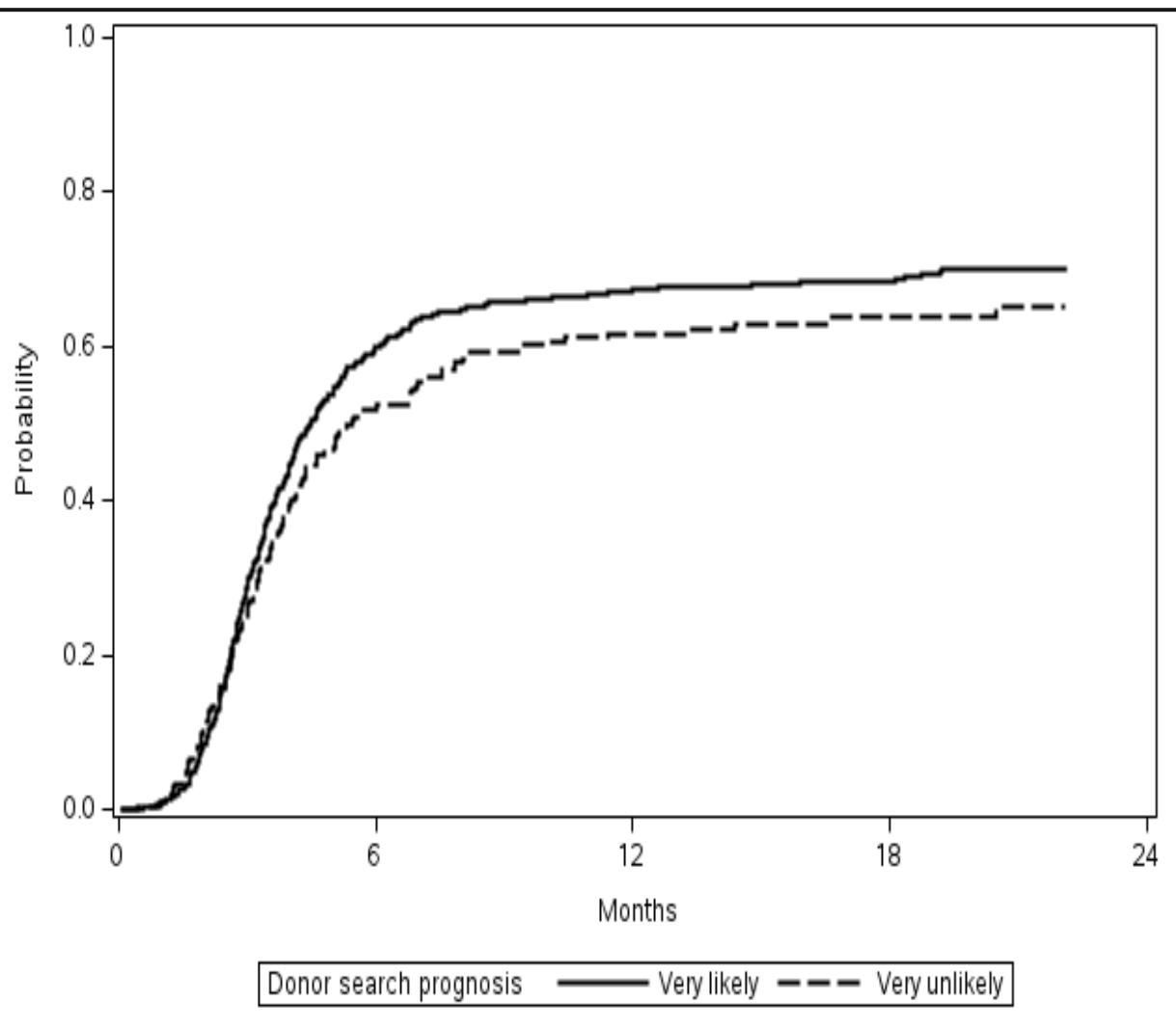


Using a search prognosis score upfront considers all donors simultaneously

Search prognosis score assigned at HLA typing



No significant difference in the adjusted cumulative incidence of receiving a transplant according to donor search prognosis



	Very likely		Very unlikely		
Outcomes	N	Prob (95% CI)	N	Prob (95% CI)	P Value
Transplant	958		276		0.105
6 months		59.8 (56.7–62.9)%		52.2 (46.0–58.4)%	
1-year		67.0 (64.0–70.0)%		61.3 (55.2–67.4)%	
2-year		70.1 (67.1–73.1)%		64.3 (58.1–70.4)%	

Conclusions

- HCT is a highly successful therapy
 - Outcomes continue to improve
 - Innovation and collaboration have been key to success
- Prospective clinical trials have been critical
- Registries (both clinical and donor) have been major contributors
- Donor choice and selection has changed significantly due to these advances and changes in GVHD prophylaxis
 - Numerous important questions remain to be tackled by the field