Mismatched Unrelated Donor (MMUD) Transplantation: An Overview

HRSA Advisory Council on Blood Stem Cell Transplantation

Sept. 25, 2020

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The CIBMTR® (Center for International Blood and Marrow Transplant Research®) is a research collaboration between the National Marrow Donor Program® (NMDP)/Be The Match® and the Medical College of Wisconsin (MCW).

Disclosures

- Stephen Spellman is an employee of the National Marrow Donor Program (NMDP) and serves as a Scientific Director in the Center for International Blood and Marrow Transplant Research (CIBMTR)

NMDP Donor-Recipient Pair Project and studies to address HLA (mis)matching

- Started in 1994 with funding from U.S. Office of Naval Research

- Goals:
  - Generate data to determine the impact of allele level matching of HLA-A ,B and DRB1 on HCT outcomes
  - Determine the contribution of matching at other loci (HLA-C, DPA1, DPB1, DQA1, and DQB1)

- Calcineurin inhibitor based GVHD prophylaxis (+/- T cell depletion with ATG/campath – up to a third of patients undergoing hematopoietic cell transplantation (HCT))

Impact of high-resolution matching

- N = 1,874
- US transplants between 1988 - 1996
- AML, ALL, CML, other
- 100% Bone marrow
- 100% Myeloablative transplants
- Median follow-up 9 years

Flomenberg et al., Blood 2004

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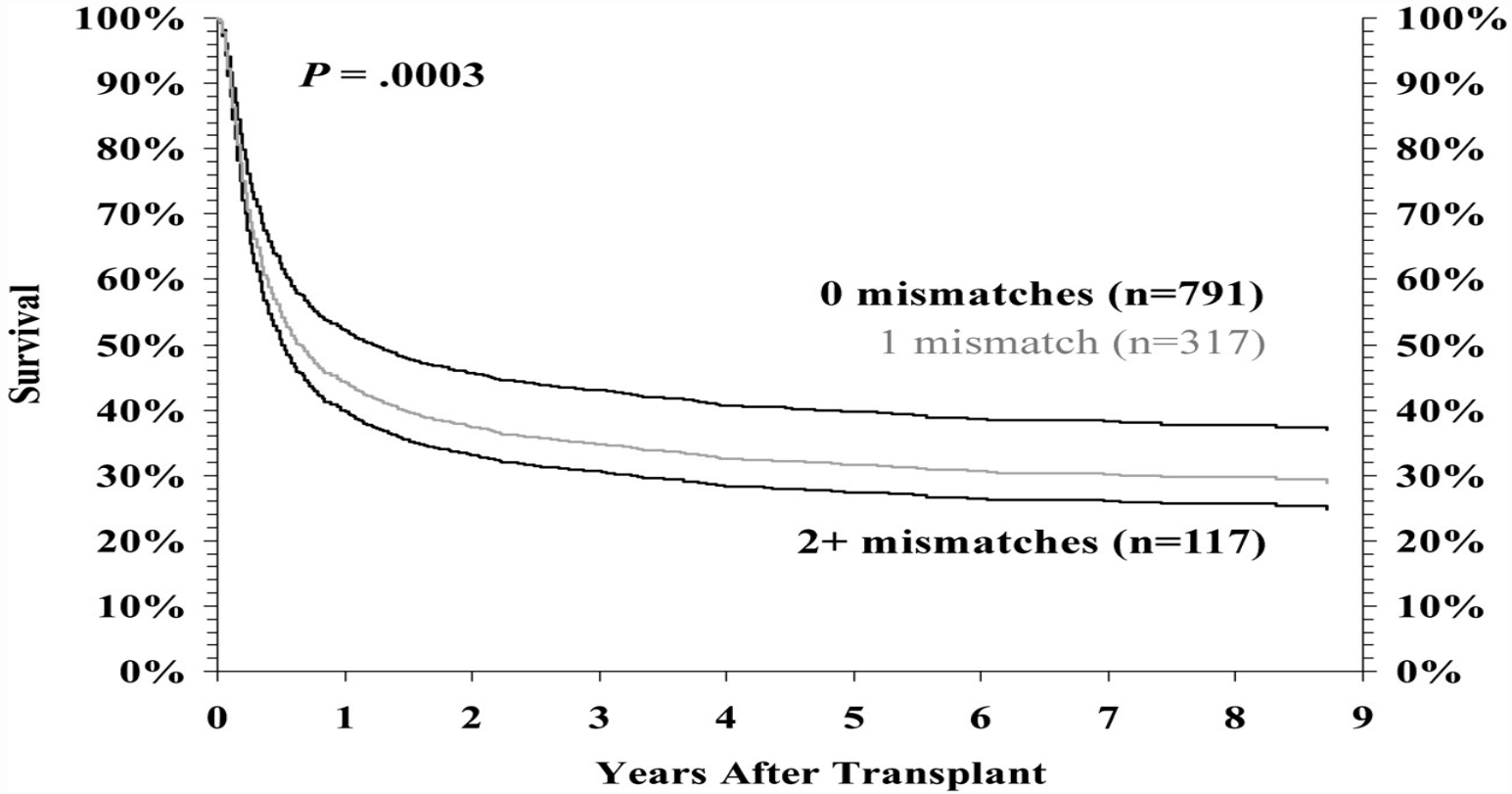
Mismatching at HLA-A, B, C and DRB1 impacts overall survival



Study demonstrated that:

- Matching at HLA-A, B, C and DRB1 impacted overall survival
- Single allele or antigen mismatches associated with an approx. 10% decrease in overall survival at 5 years

Flomenberg et al., Blood 2004

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Impact of high-resolution matching: additional loci

- N = 3860
- US transplants between 1988 - 2003
- AML, ALL, CML, MDS
- Myeloablative conditioning
- Bone marrow 94%
- Median follow-up 6 years

Lee et al., Blood 2007

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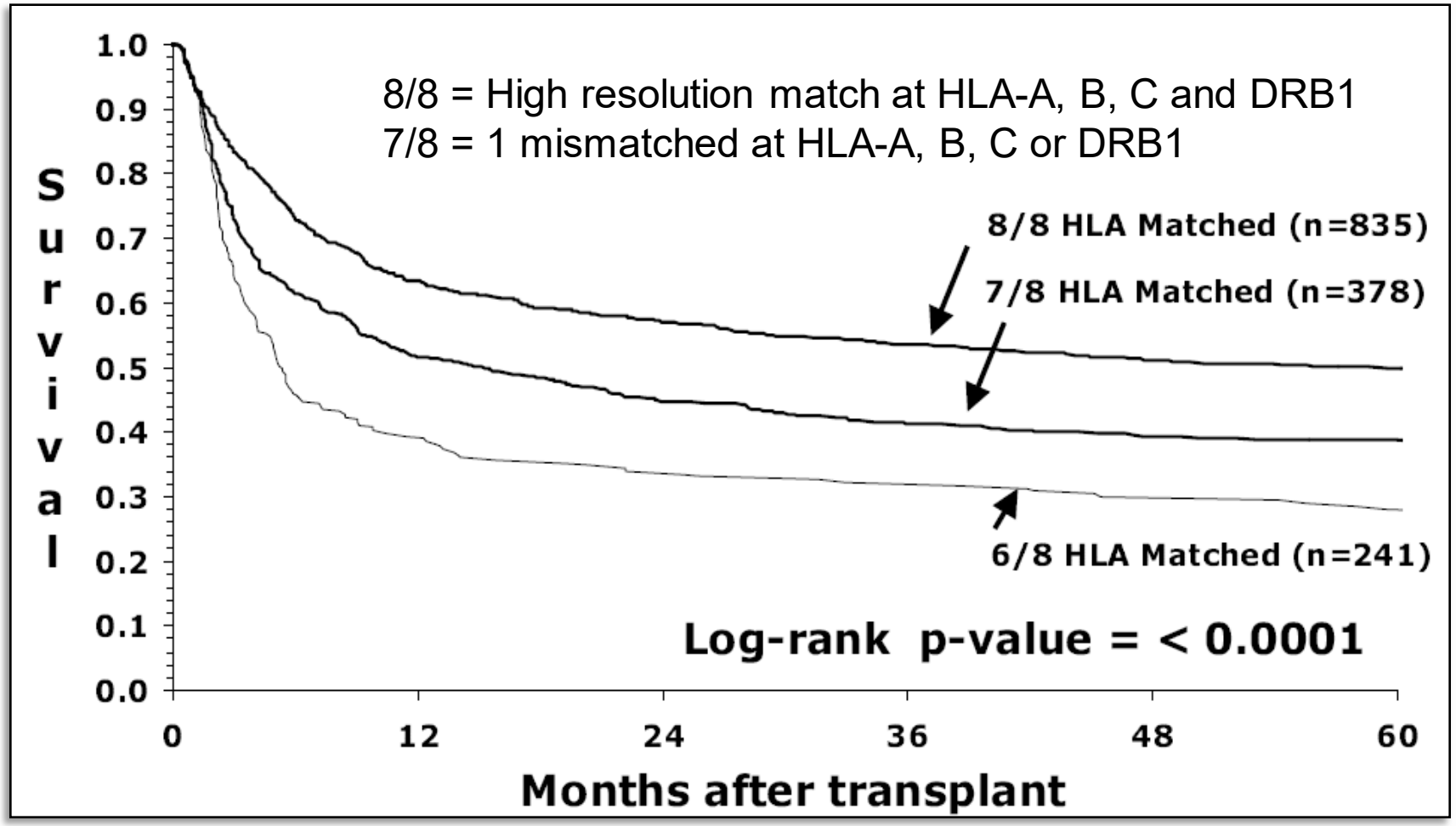
HLA impact on overall survival



Study demonstrated that:

- Matching at HLA-A, B, C and DRB1 impacted overall survival
- Single allele or antigen mismatches associated with an approx. 10% decrease in overall survival at 5 years
- >1 mismatch associated with an approx. 20% decrease in overall survival at 5 years

Lee et al., Blood 2007

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HLA-DQ Lacked Impact

As a Single Mismatch

	Survival		TRM		Acute GVHD	
	RR	p	RR	p	RR	p
10/10	1.00		1.00		1.00	
DQ MM	0.97	0.77	1.08	0.50	1.03	0.86

As a Second Mismatch

	8/10	9/10	RR (95% CI)	P-value
DQ MM	191	797	1.14 (0.94-1.38)	0.17

Lee et al., Blood 2007

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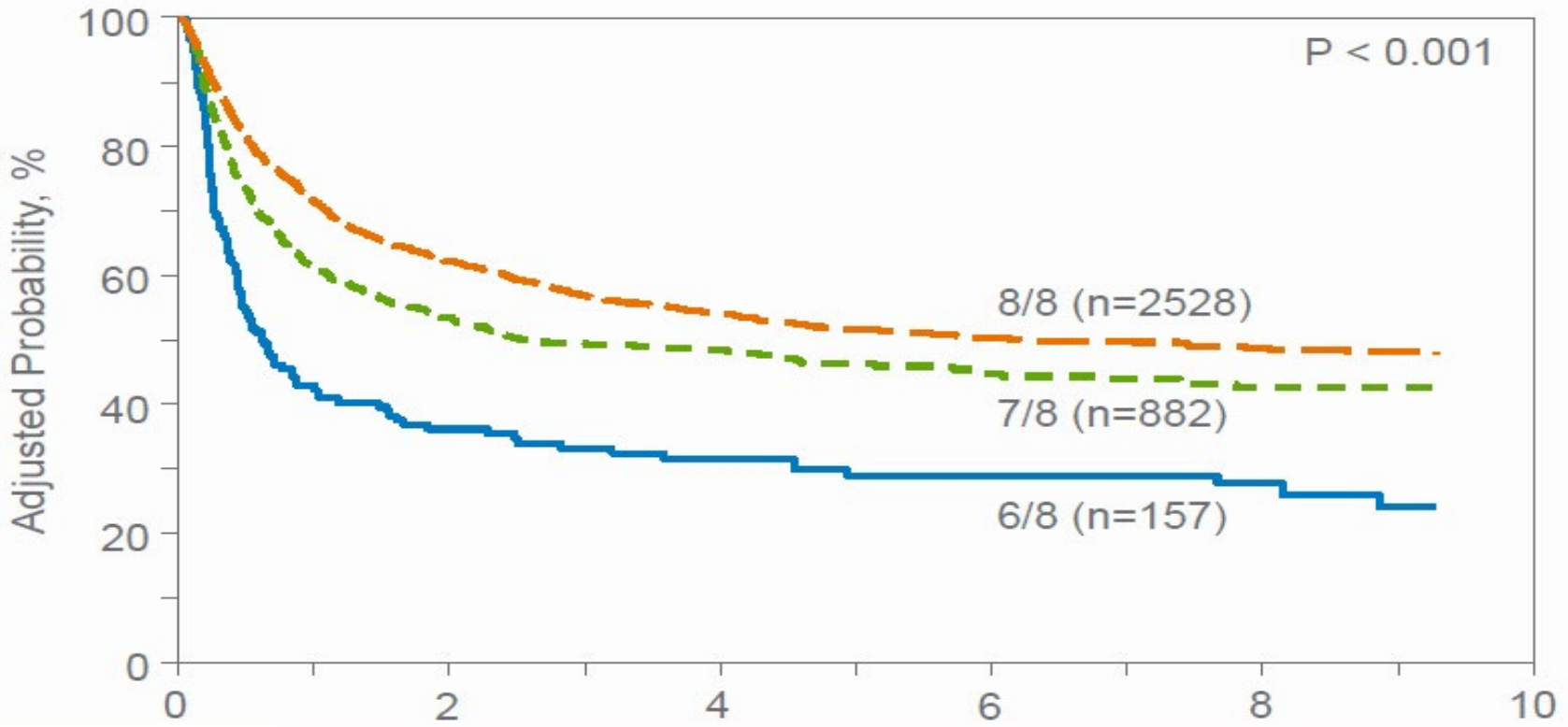
Validation: More recent dataset



Study validated the findings from earlier analyses:

- Matching at HLA-A, B, C and DRB1 impacted overall survival
- Single allele or antigen mismatches associated with an approx. 10% decrease in overall survival at 5 years
- >1 mismatch further increased the risk of mortality

Pidala et al., Blood 2014

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Evaluation of Permissive mismatches at HLA-A, B, C and DRB1

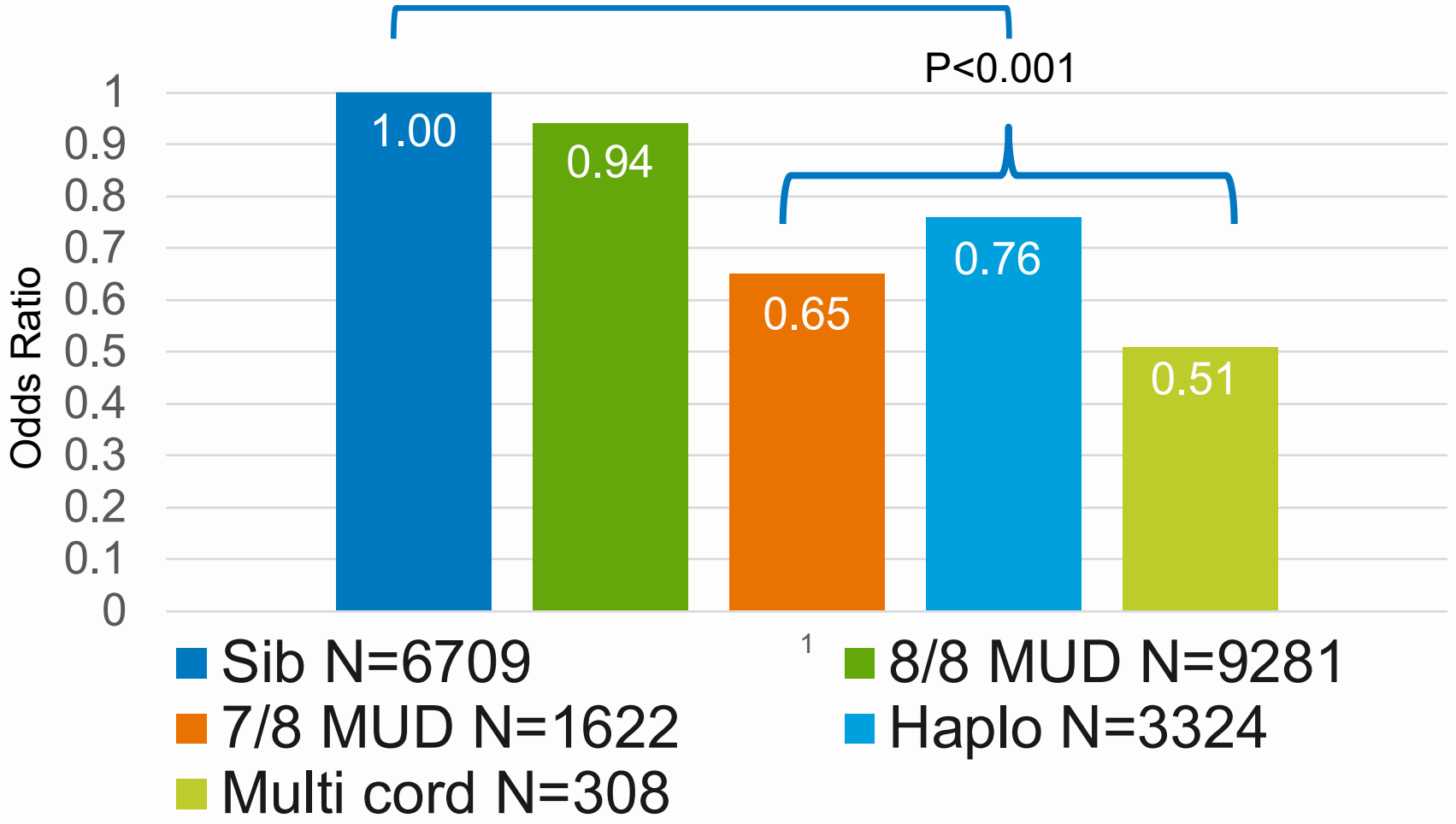
- Cross-reactive Antigen (CREG) groups (Wade et al Blood 2007)
- HLA Matchmaker (Duquesnoy et al BBMT 2008)
- Histocheck (Spellman et al BBMT 2012)
- Supertype matching (Lazaryan et al Haematologica 2016)
- Predicted indirectly recognizable HLA epitopes (PIRCHE) (Spierings et al BBMT 2017)

HLA Mismatch Algorithms - Results

Algorithm	Results vs 8/8 (or 10/10)	Results among mismatched groups
Cross-reactive Groups (CREG) (Wade et al Blood 2007)	p<0.001	p=0.47
HLA Matchmaker (Duquesnoy et al BBMT 2008)	p<0.01	p=0.62
Histocheck (Spellman et al BBMT 2012)	p<0.01	p=0.36
HLA Supertypes (Lazaryan et al Haem. 2016)	NT	Class I p>0.1 Class II p=0.04
Predicted indirectly recognizable HLA epitopes (PIRCHE) (Spierings et al BBMT 2017)	p<0.01	p>0.8

No studies have developed effective methods to define permissive mismatches at HLA-A, B, C or DRB1

Impact of Donor Type on One-year mortality after HCTs done in 2015-2017



[1]

The 2019 Center-Specific Outcome Analysis of 1-year mortality among all 1st allogeneic HCT performed in the U.S. shows:

- No significant difference between 8/8 MUD and HLA matched sibling HCT
- Significant risk of increased mortality with use of MMUD, haploidentical related and cord blood HCT

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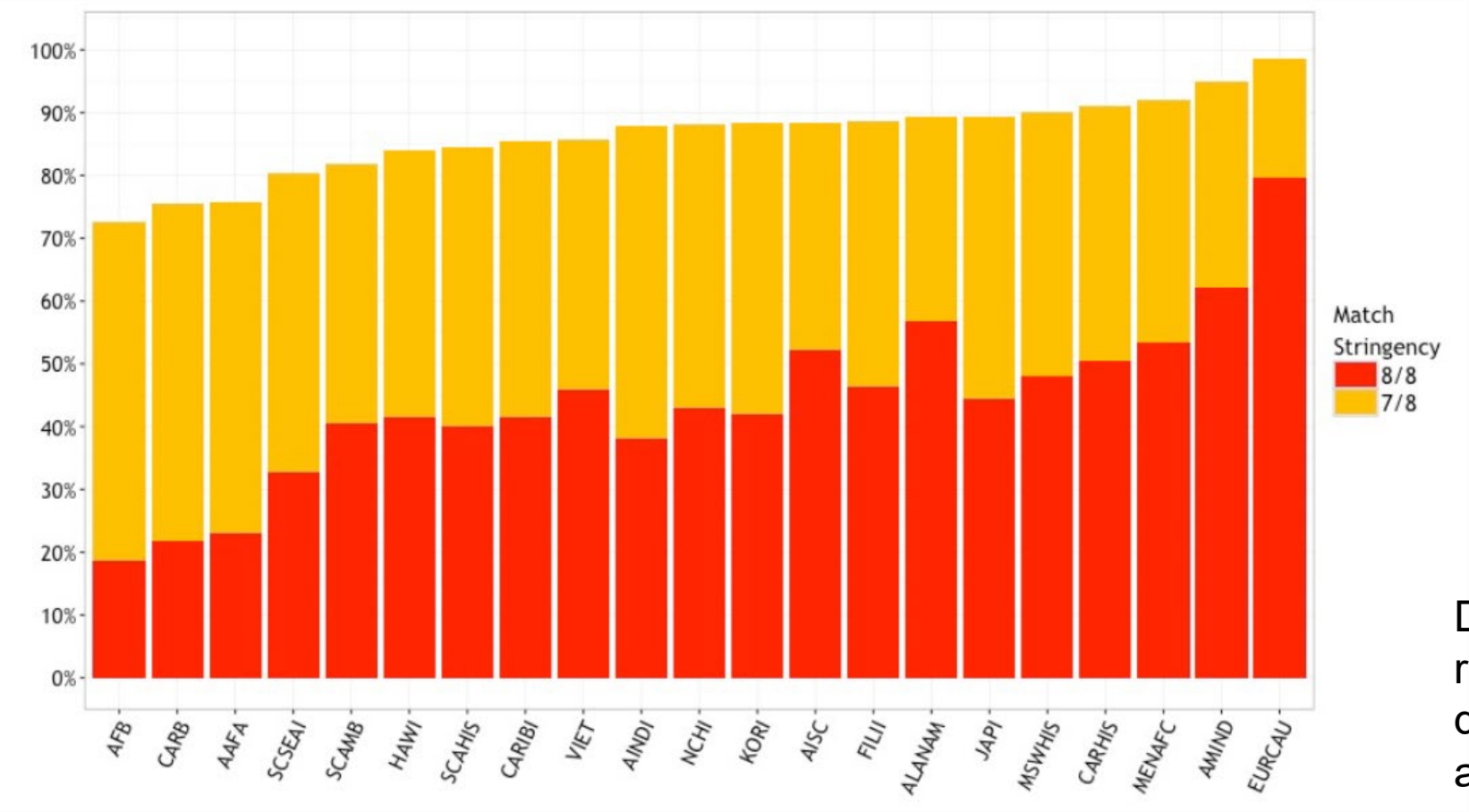
Likelihood of finding a match



- 8/8 – 20-70%
- 7/8 – 20-50%
- <7/8 – 10-30%

Despite best efforts to build a representative volunteer donor registry disparities still exist between racial and ethnic groups

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What novel approaches improve outcomes for mis-matched unrelated donor (MMUD) HCT?

- New research to minimize the impact of HLA mismatches using novel agents for GVHD prophylaxis
  - Post-transplant cyclophosphamide
  - Sirolimus
  - Abatacept
  - Graft engineering

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15-MMUD – PIs: B Shaw and J Bolañes-Meade (NCT02793544)

- Multi-center, single arm Phase II study to assess the safety and efficacy of MMUD (4/8 – 7/8) bone marrow transplantation using PTCy, sirolimus and MMF for GVHD prophylaxis
  - Patients with a suitable HLA matched related or URD were excluded.
  - Patients received a fresh BM graft, followed by PTCY on days +3, +4, Sirolimus/MMF starting on Day+5.
  - Regimen intensity was at the center's discretion.
- Enrolled 80 patients at 11 transplant centers in the U.S. between Dec 2016 and March 2019:
  - 40 full intensity conditioning [FIC]
  - 40 reduced intensity conditioning [RIC]

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Objective and hypotheses

- **Primary Objective:** The primary objective is to determine overall survival (OS) 1-year after HLA MMUD bone marrow transplantation using PTCy, sirolimus and MMF to prevent GVHD

- **Primary Hypothesis:** The primary hypothesis is that 1-year survival after HLA MMUD bone marrow transplantation is 65% or higher, similar to the 1-year survival observed after haploidentical (related) donor bone marrow transplantation

- **Secondary Hypotheses**
  - Greater than 90% of subjects will engraft and more than 80% of engrafting subjects will achieve ≥ 95% donor chimerism by Day+56
  - The incidence of grades III-IV GVHD will be less than 15% at Day+100

15MMUD - Population characteristics

	Full Intensity Conditioning	Reduced Intensity Conditioning	Total
Patient race/ethnicity	N (%)	N (%)	N (%)
Non-white	23 (58)	15 (37)	38 (48)
Disease			
Acute Leukemia	37 (92.5)	21 (52.5)	58 (72.5)
Patient age			
Median (min-max)	48.5 (18-66)	59.5 (23-70)	51.5 (18-70)
Donor age			
Median (min-max)	27 (18-56)	29 (21-44)	29 (18-56)
HLA Match			
7/8	26 (65)	23 (58)	49 (61)
≤6/8	14 (35)	17 (32)	31 (39)

Clinical Outcomes

	FIC (N = 40)		RIC (N = 40)		Total (N=80)	
Outcomes	**N**	**Prob (90% CI)**	**N**	**Prob (90% CI)**	**N**	**Prob (90% CI)**
Overall survival	40		40		80	
6 months		80 (68.7-89.3)%		90 (80.9-96.4)%		85 (77.9-90.9)%
1-year		72.3 (59.9-83.1)%		78.9 (66.9-88.8)%		75.7 (67.3-83.3)%
Non-relapse mortality	40		40		80	
100-day		5 (0.9-12.2)%		7.5 (2.1-15.8)%		6.3 (2.5-11.5)%
6 months		7.5 (2.1-15.8)%		7.5 (2.1-15.8)%		7.5 (3.4-13.1)%
1-year		7.5 (2.1-15.8)%		10 (3.6-19.2)%		8.8 (4.3-14.7)%
Relapse	40		40		80	
6 months		22.6 (12.6-34.5)%		20 (10.6-31.5)%		21.3 (14.2-29.4)%
1-year		30.4 (18.9-43.2)%		22.5 (12.6-34.3)%		26.4 (18.7-35)%
Progression-free survival	40		40		80	
6 months		69.9 (57.4-81.1)%		72.5 (60.3-83.2)%		71.2 (62.5-79.1)%
1-year		62.1 (49.2-74.3)%		67.5 (54.9-79)%		64.8 (55.8-73.3)%

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Clinical Outcomes

	FIC (N = 40)		RIC (N = 40)		Total (N=80)	
Outcomes	**N**	**Prob (90% CI)**	**N**	**Prob (90% CI)**	**N**	**Prob (90% CI)**
Grade II-IV acute GVHD	39		40		79	
100-day		44.7 (31.6-58.3)%		32.5 (20.9-45.4)%		38.5 (29.6-47.7)%
Grade III-IV acute GVHD	39		40		79	
100-day		20.5 (10.9-32.2)%		2.5 (0.1-8.2)%		11.4 (6.2-17.9)%
Chronic GVHD	39		40		79	
6 months		28.3 (17.1-41.2)%		10 (3.6-19.2)%		19 (12.3-26.9)%
1-year		36.5 (24-49.9)%		20 (10.6-31.5)%		28.1 (20.1-36.9)%
Neutrophil recovery	40		40		80	
100-day		97.5 (89.7-100)%		97.5 (89.8-100)%		97.5 (93-99.8)%
Median (range), days		17 (14-28)		18 (5-36)		18 (5-36)
Platelet recovery	40		40		80	
100-day		92.5 (83.3-98.2)%		97.5 (89.8-100)%		95 (89.8-98.4)%
Median (range), days		25 (4-99)		33.5 (8-73)		27.5 (4-99)
Primary graft failure	39		40		79	
56-day		0 (0-7.4)%		7.5* (2.1-18.3)%		3.8 (1.0-9.5)%

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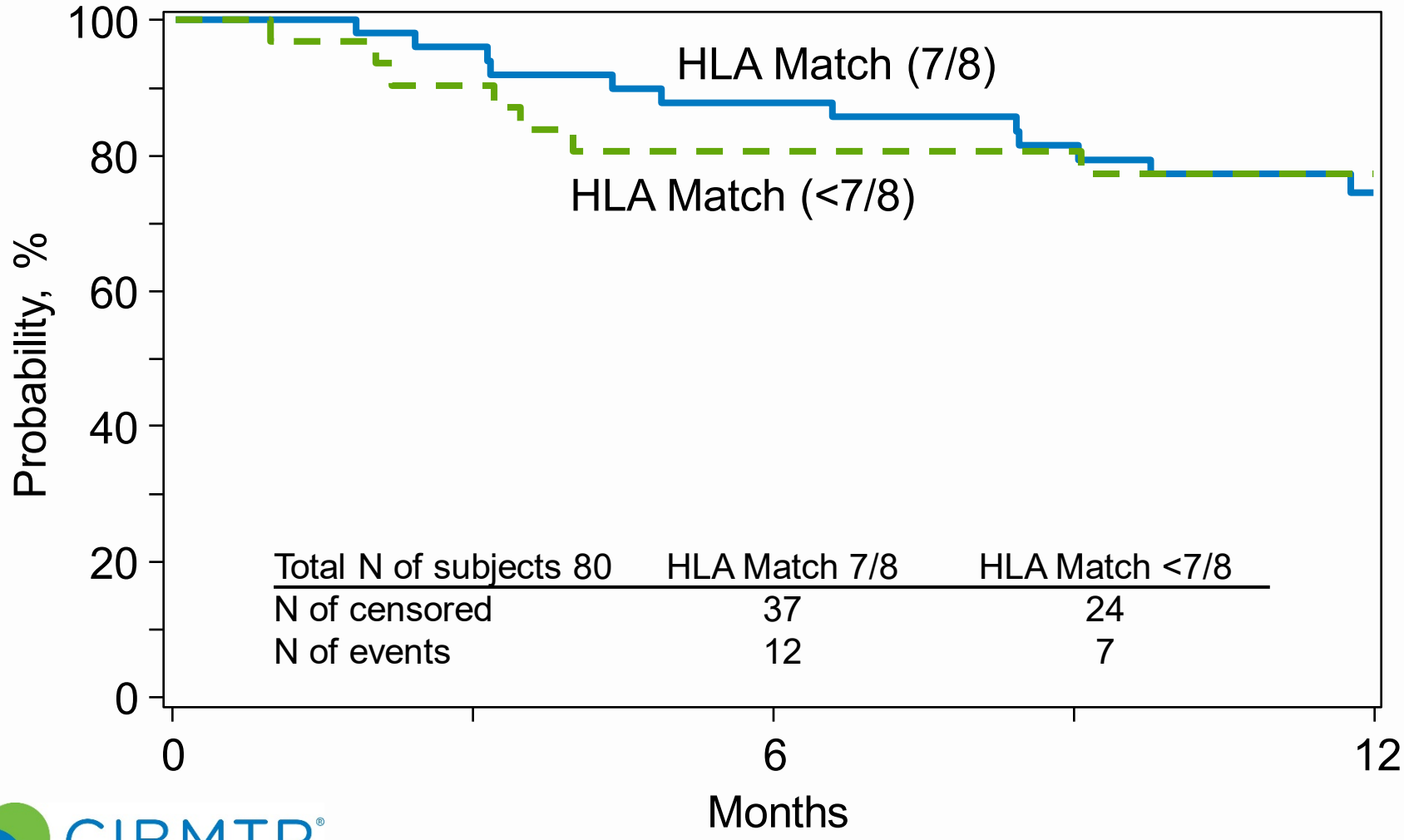
Overall Survival



Overall survival did not significantly differ by conditioning intensity (not shown in figure) or level of HLA mismatch

A follow-on study, sponsored by the NMDP, to evaluate the use of peripheral blood stem cell grafts (>80% of MUD products used annually) is in development and will begin enrollment in 2021

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Use of mismatched URD expands donor choice

- Younger age
- Sex match
- CMV status
- ABO match
- Avoid donor specific antibodies
- CCR5 Δ32 -/-
- KIR
- Other factors

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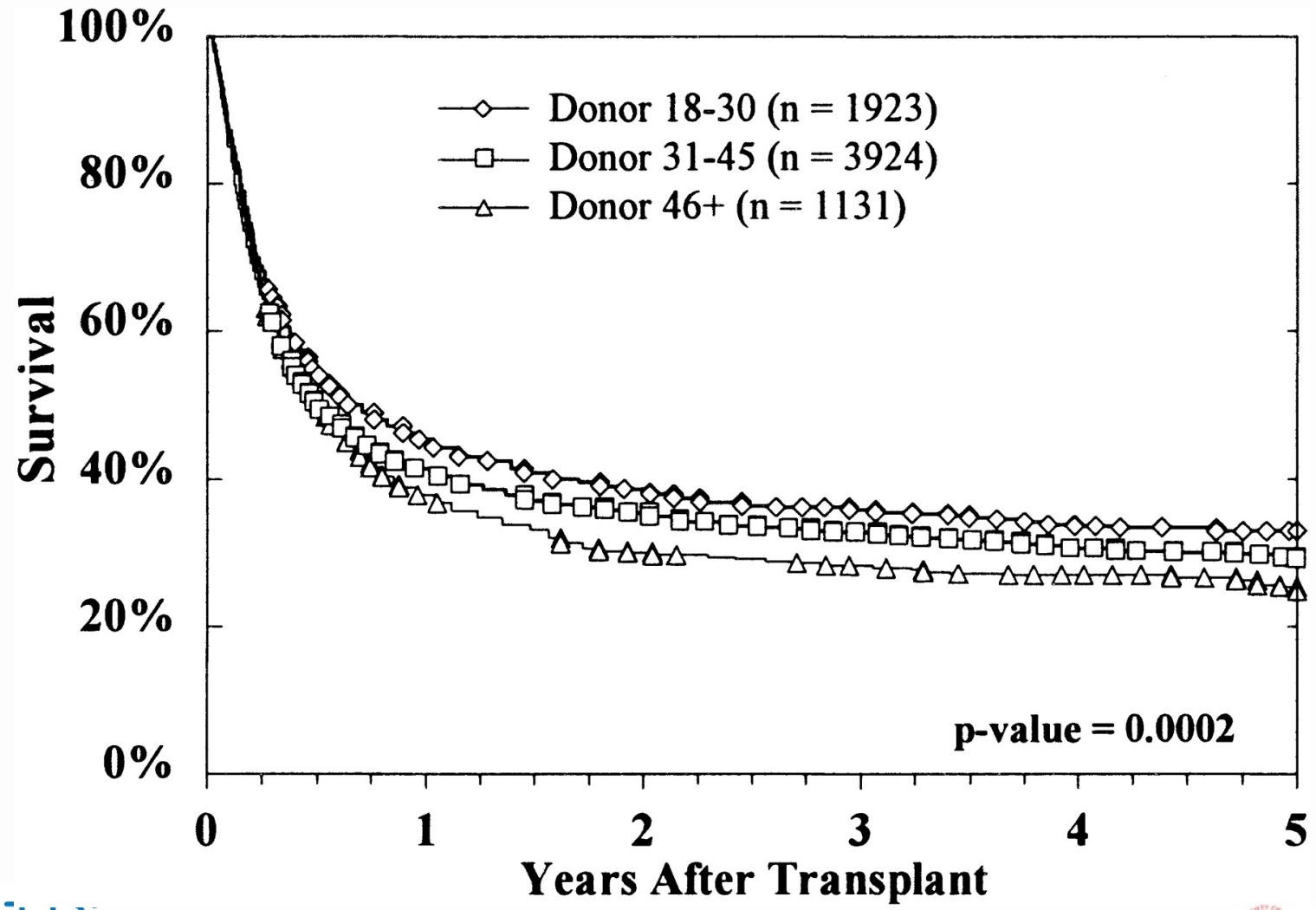
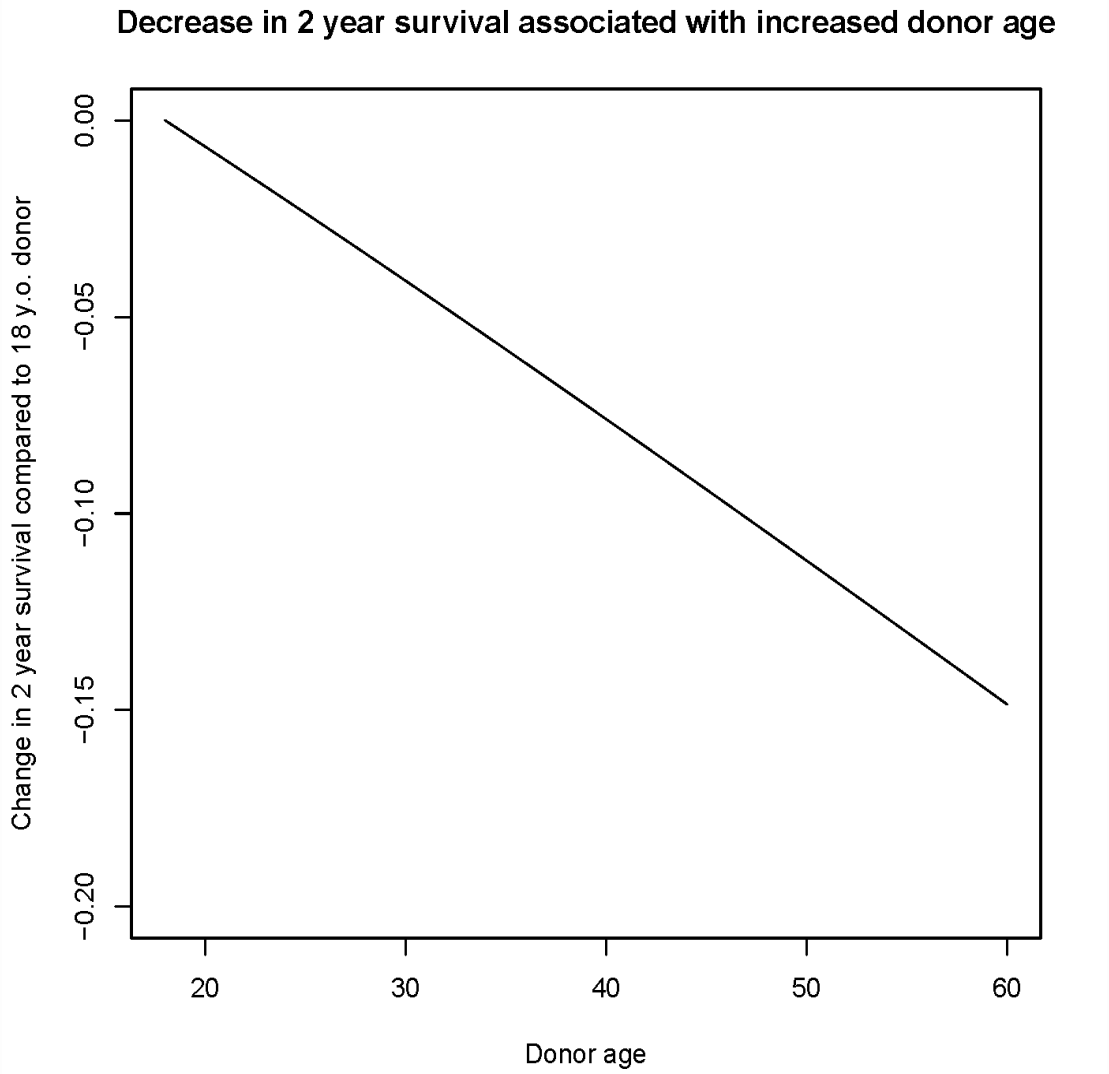
Increasing donor age impacts survival



HCT with unrelated donors 31-45 years old and >46 years old associated with higher mortality compared to donors 18-30 years old

Kollman et al. Blood 2001;98:2043-2051

Increasing unrelated donor age is associated with higher mortality



2-year survival decreased ~4% per decade of donor age

Shaw et al, BBMT, 2018

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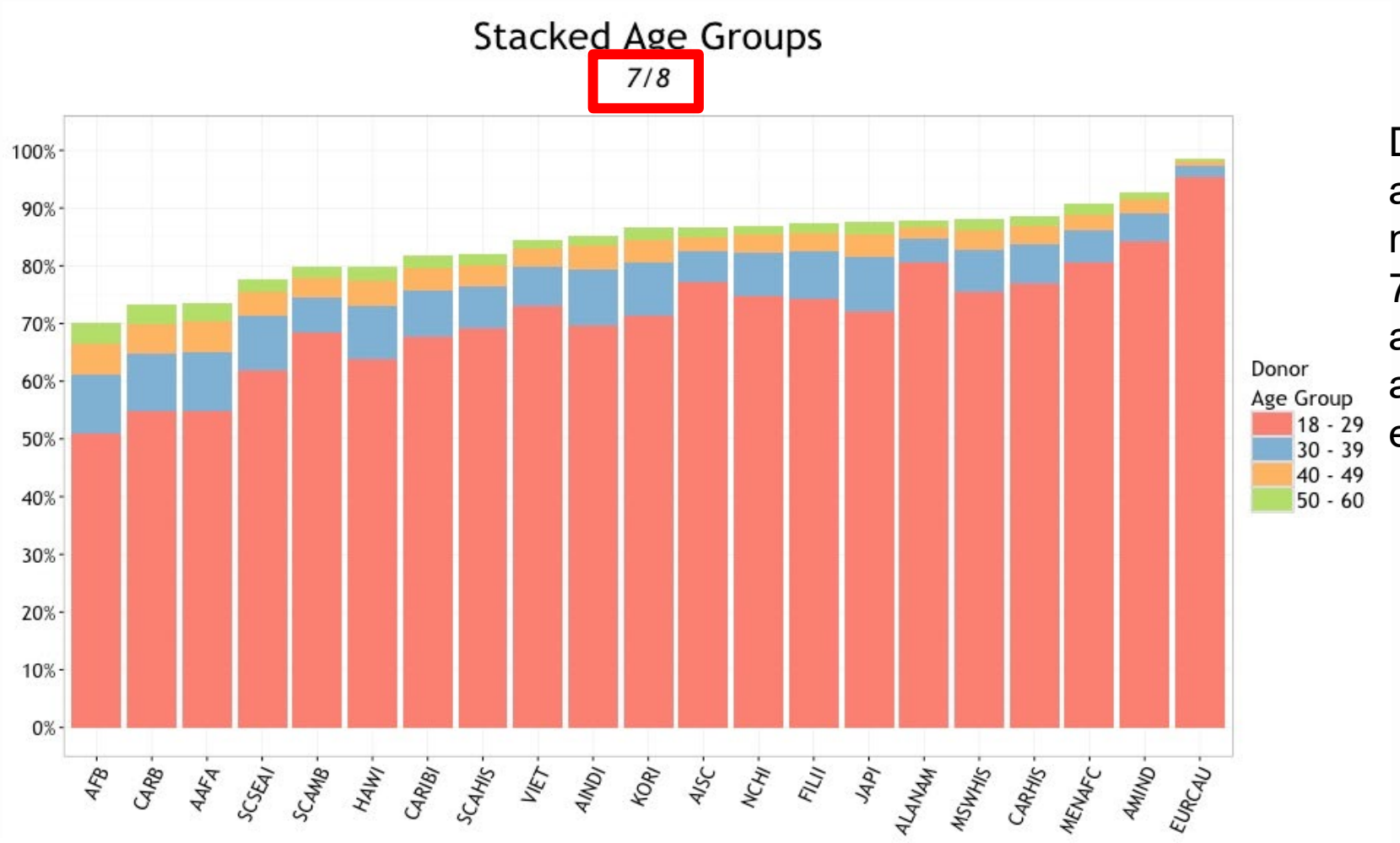
Likelihood of finding a donor in NMDP file



Donors 18-29 years old account for the vast majority (50 to >90%) of 7/8 matched donors available to patients across all race and ethnicity groups

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Impact of new approaches to prevent GVHD

- Potential to transplant across HLA barriers
- Expanded donor choice – younger donors
- Faster donor selection
- A donor available for all in need

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