

Corso di Formazione **GITMO**

Trapianto e terapie cellulari: cellule, donatori e condizionamenti

Quesito: priorità all'età o all'HLA
compatibilità nella scelta del donatore?

Nicola Polverelli

Unit of BMT and Cellular Therapies

Fondazione IRCCS Policlinico San Matteo

n.polverelli@smatteo.pv.it

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Aula Polifunzionale Ospedale di Udine

Disclosures of Nicola Polverelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis			X		X	X	
GSK						X	X
Sanofi							X
Neovii							X
Kite-Gilead							X
Medac			X			X	X
Arog			X				

Which donor would you prioritize?

PATIENT PROFILE

65 **65-year-old woman**
High-risk AML (ELN) • First complete remission

Related donor available
Brother, 70 years • ABO compatible
No children

No 8/8 unrelated donor
One 7/8 unrelated donor identified

DISEASE CONTEXT

Diagnosis

AML, high-risk by ELN

Current disease status

First complete remission (CR1)

Transplant decision

Donor prioritization

RELATED DONOR OPTION: SIBLING

Brother, 70 years

ABO compatible

Eligibility to be assessed

Older donor age

VS

UNRELATED DONOR OPTION: 7/8 MMUD

Male, 27 years

7/8 HLA matched • ABO matched • 75 kg

Young donor age

One HLA allele mismatch

DECISION POINT: SHOULD A YOUNGER 7/8 MMUD OUTWEIGH AN OLDER RELATED DONOR IN AML CR1?

HLA mismatch and survival after transplant: the GITMO report

STUDY COHORT

1,788 adult recipients

39 Italian transplant centres · 2012–2015

High-resolution HLA typing

A, B, C, DRB1 and DQB1

Disease mix

AML 40% · ALL 15% · MDS/MPN 18%

Lymphoma/myeloma 24%

Transplant platform

MAC 71% · PBSC 82% · ATG 90%

Median age: recipient 49 y · donor 29 y

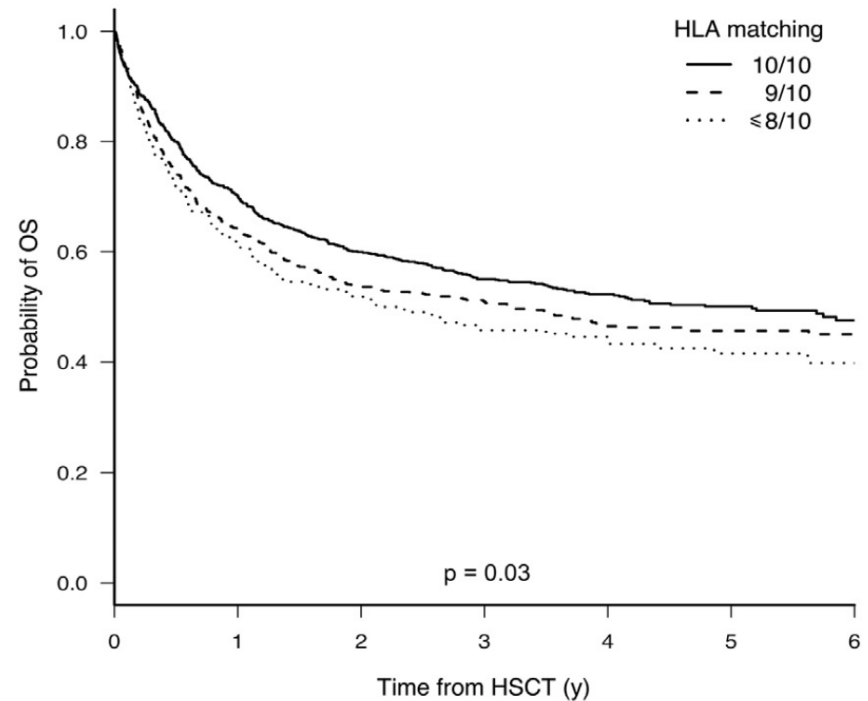
HLA MATCHING

50% 10/10 **38%** 9/10

12% ≤8/10

UNADJUSTED OVERALL SURVIVAL

Kaplan–Meier curves by overall HLA matching · log-rank P = 0.03



	Number at risk						
10/10	890	616	514	415	281	156	62
9/10	677	428	350	294	199	118	50
≤8/10	221	135	113	93	69	38	18

ADJUSTED EFFECT ON OS

Multivariable model, reference: 10/10

One allelic mismatch

9/10 vs 10/10 HR 1.16

95% CI 1.004–1.34 · P = 0.04

Two or more mismatches

≤8/10 vs 10/10 HR 1.32

95% CI 1.08–1.60 · P = 0.007

Early/intermediate disease

9/10 vs 10/10 HR 1.22

95% CI 1.02–1.46 · P = 0.03

No significant OS difference:

≤8/10 vs 9/10 · HR 1.10 · P = 0.25

In this predominantly ATG-based cohort, **10/10 matching** was associated with **better OS** and lower alloreactivity

What EBMT guidelines suggest for adult patients with malignancies

Algorithm for donor selection for adult patients with hematological malignancies

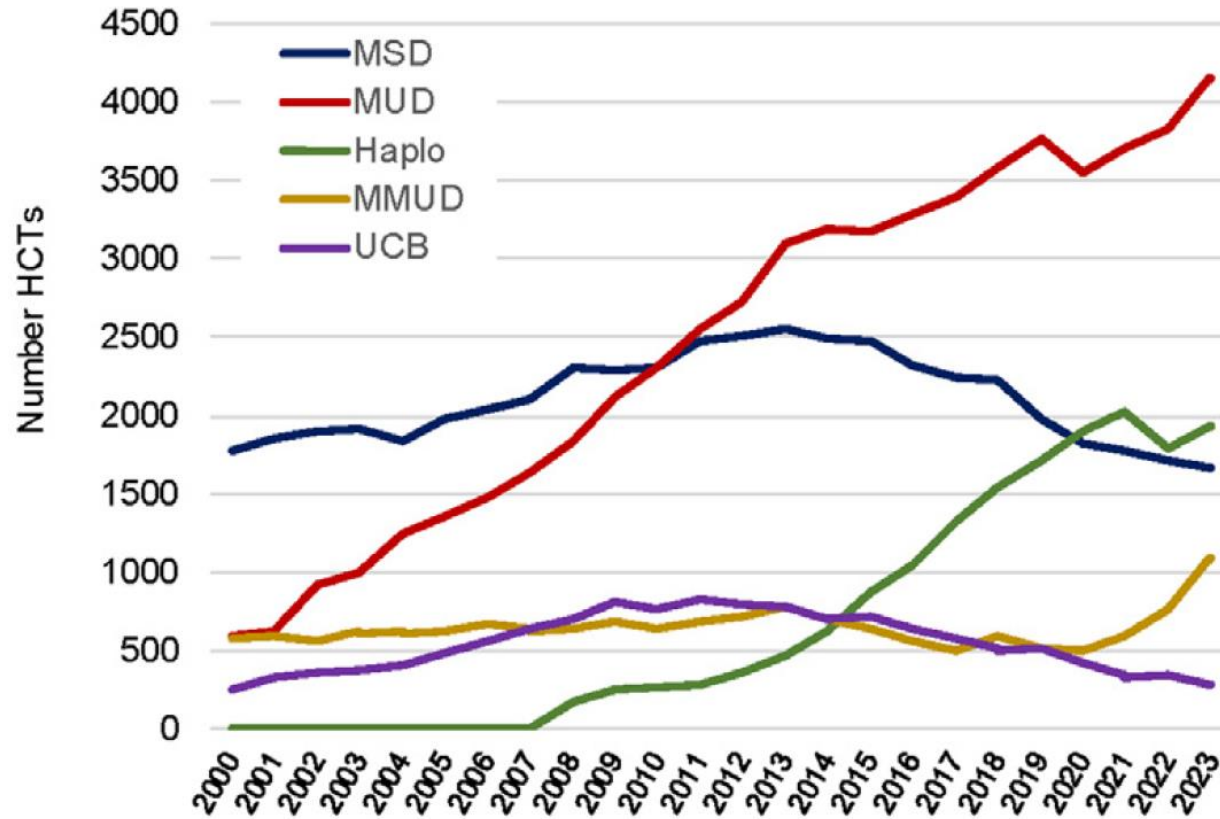
HLA-identical sibling donor

HLA-10/10 matched unrelated donor
Beyond HLA: donor age > CMV-matching, sex-matching, ABO-matching

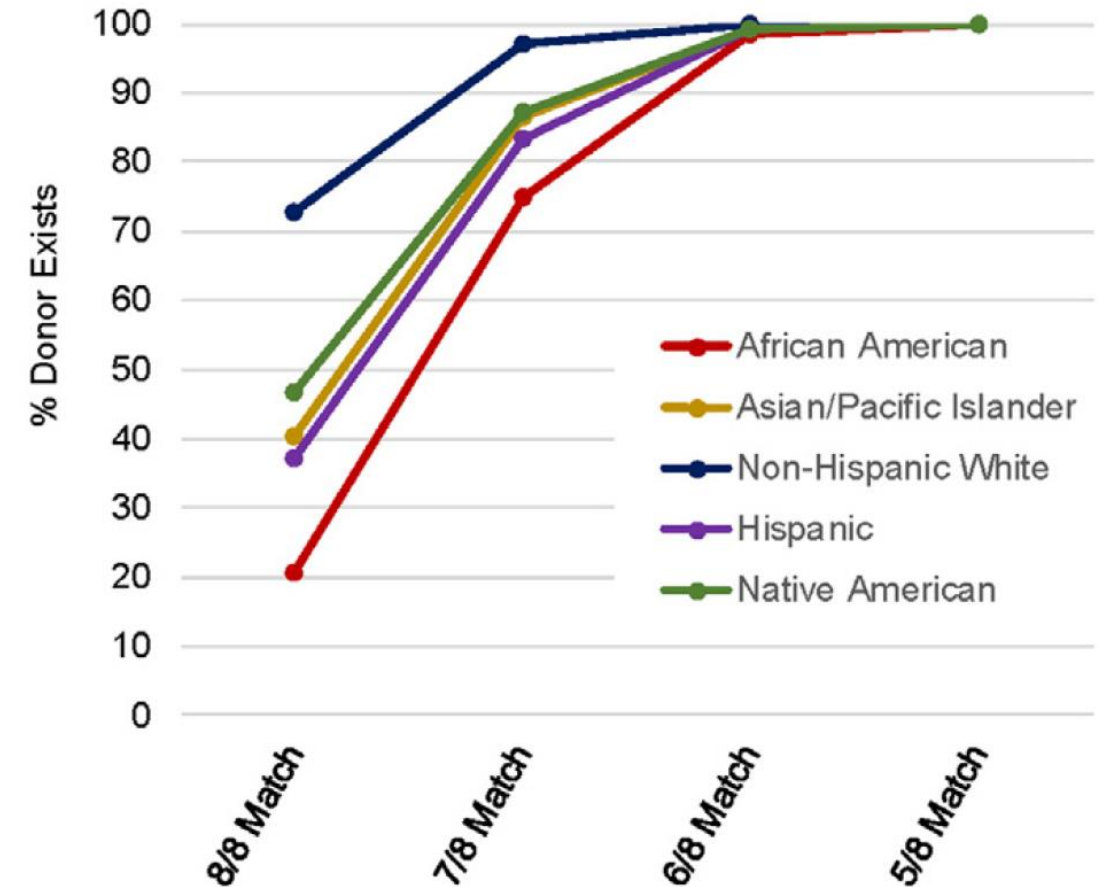
HLA-9/10 matched unrelated donor; HLA-mismatched or haploidentical related donor; cord blood
Beyond HLA: donor age, donor specific antibodies, specific center experience

An 8/8 MUD is not guaranteed for every patient

Donor source use over time

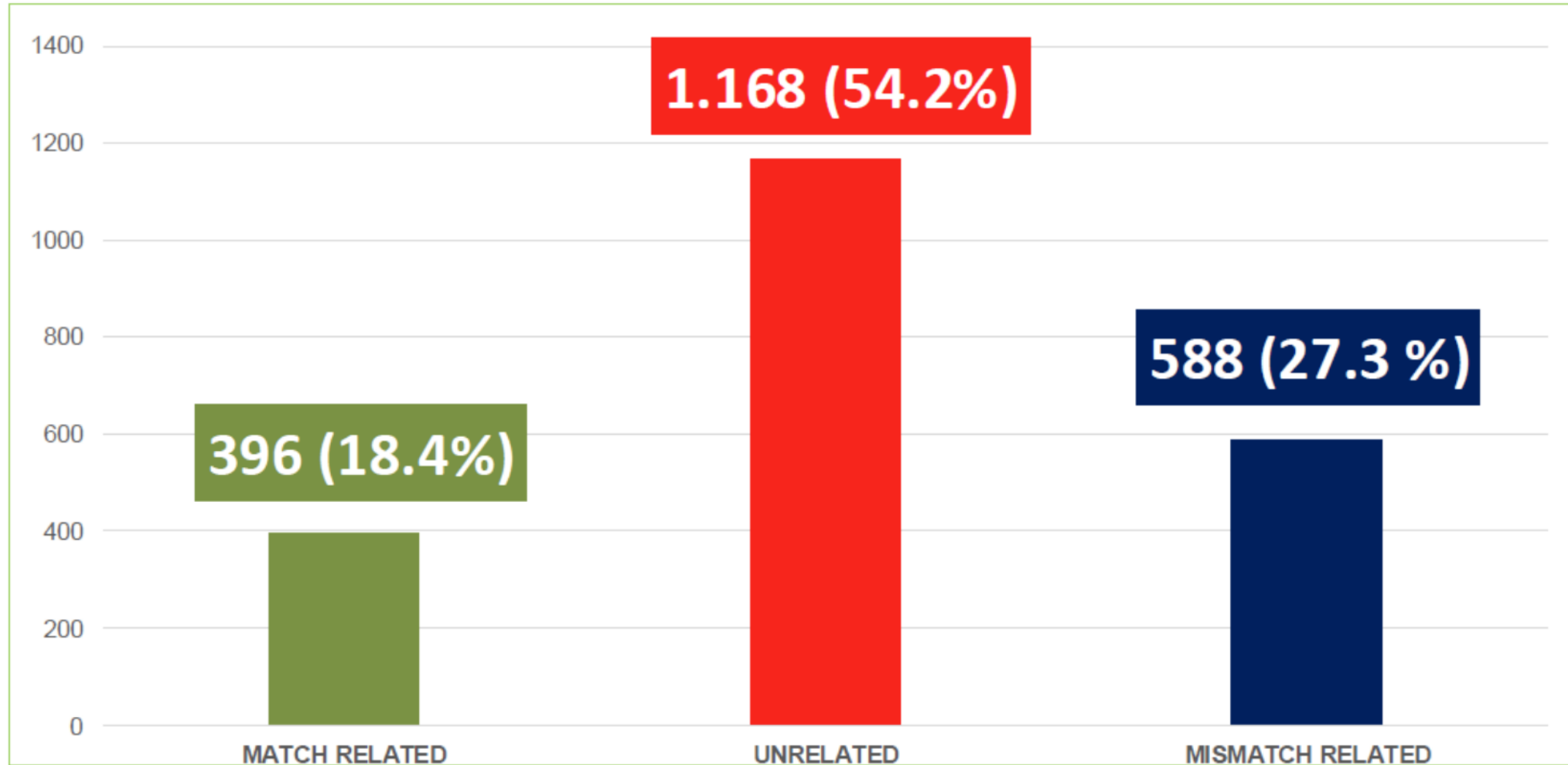


8/8 MUD access varies by ancestry



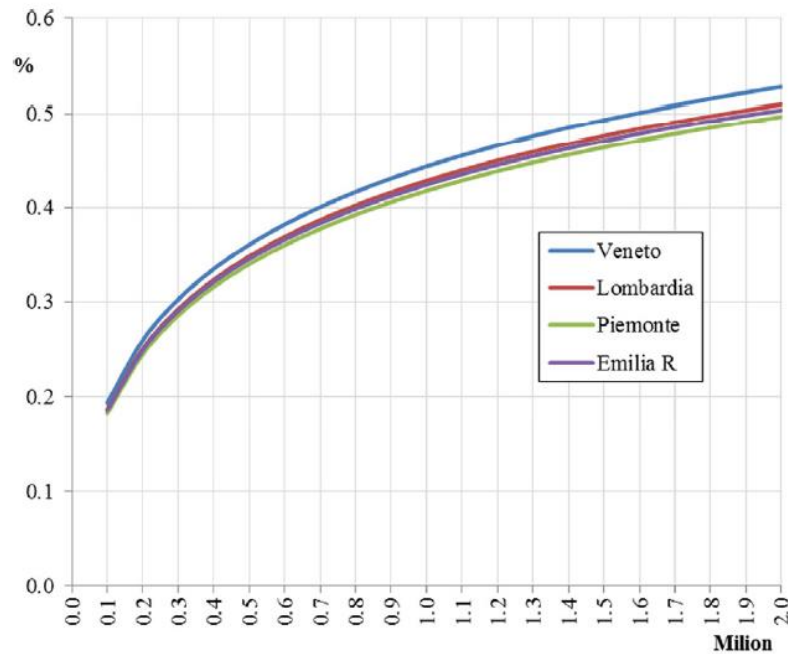
8/8 MUD access is not 100%; it ranges from approximately **20% to 72%** across ancestry groups

2025 GITMO transplants according to type of donor

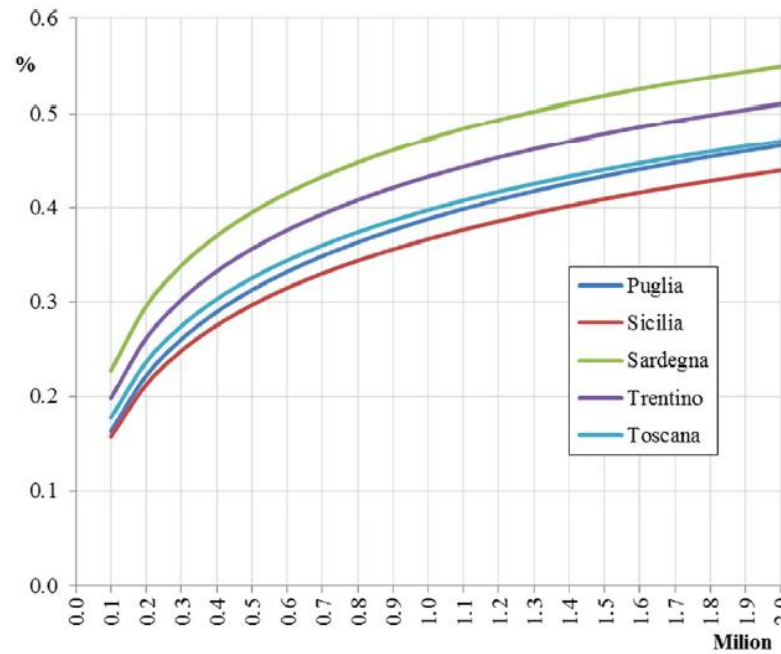


Availability of HLA-matched unrelated donors: the Italian population

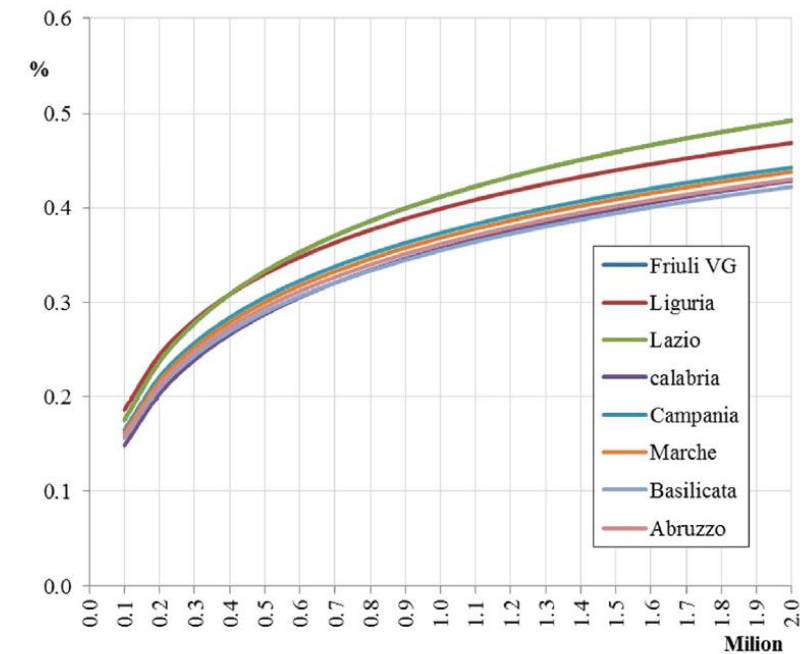
Based on high-resolution HLA data from >100,000 Italian donors, the study estimated matching probability by IBMDR registry size



a) Italian regions with >10,000 donors



b) Italian regions with 4,000 - 10,000 donors



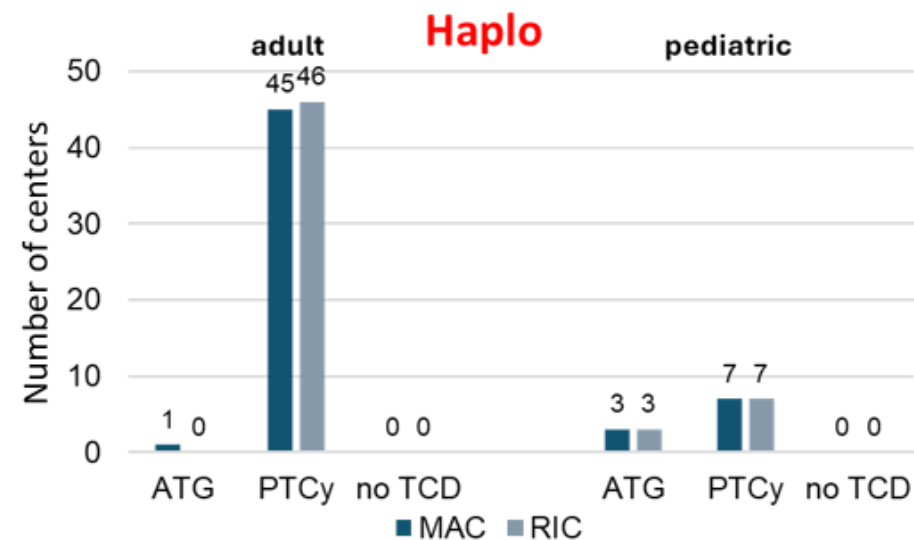
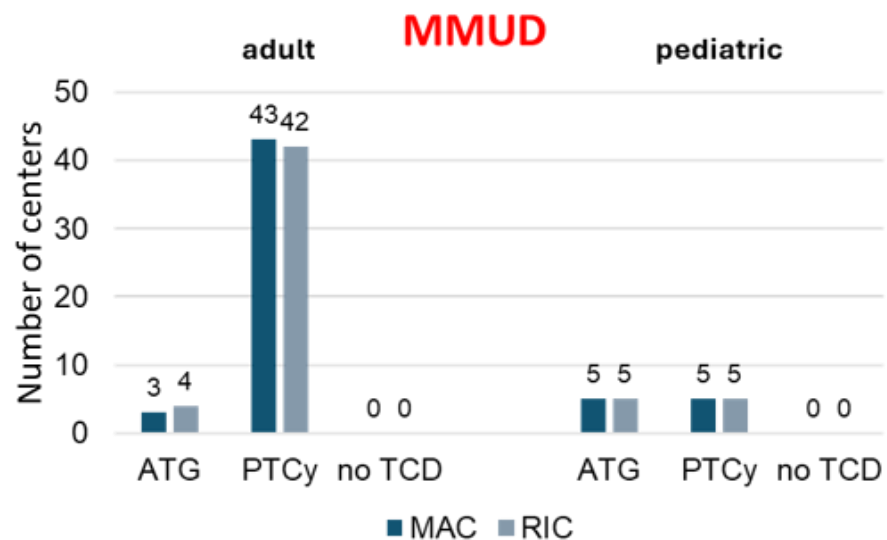
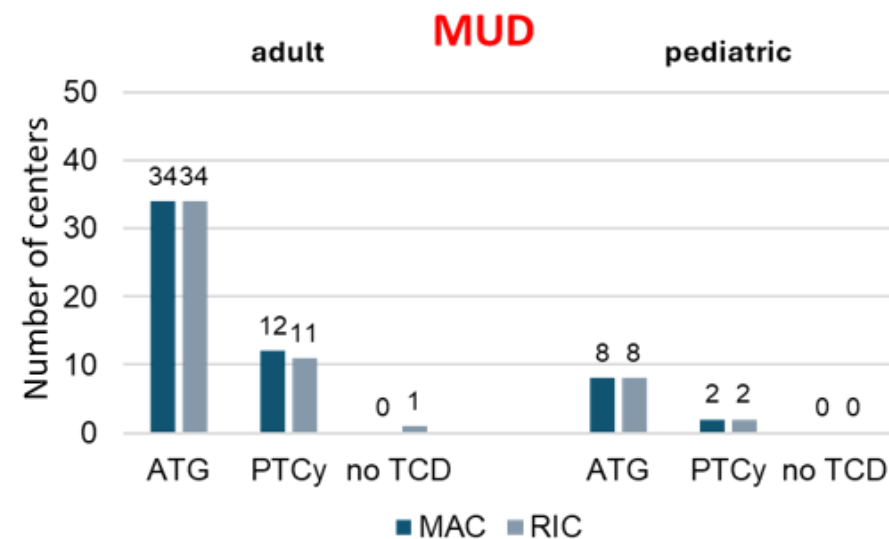
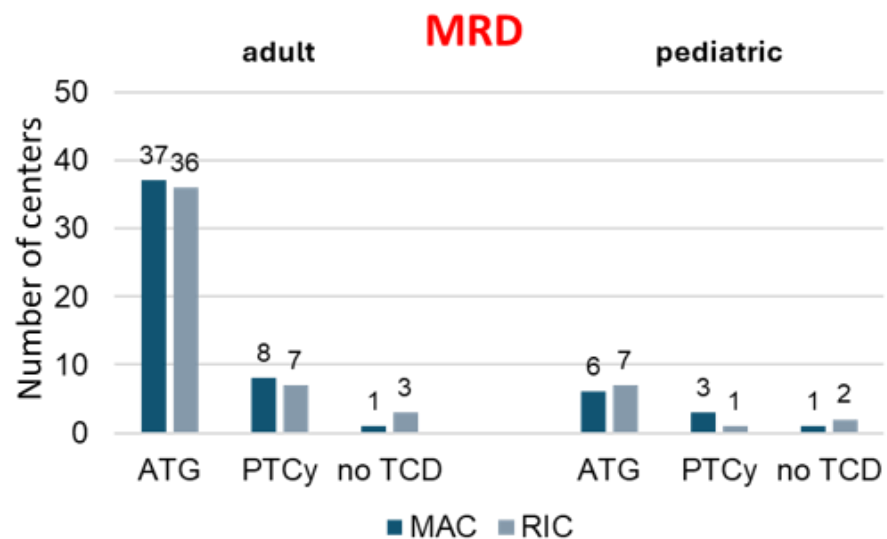
c) Italian regions with 1,000-3,999 donors

National IBMDR estimates: with **500,000 donors**, the probability of identifying an **8/8 donor** is **33.4%** and of identifying a **≥7/8 donor** is **73.7%**.

The current recommendations on GVHD prophylaxis

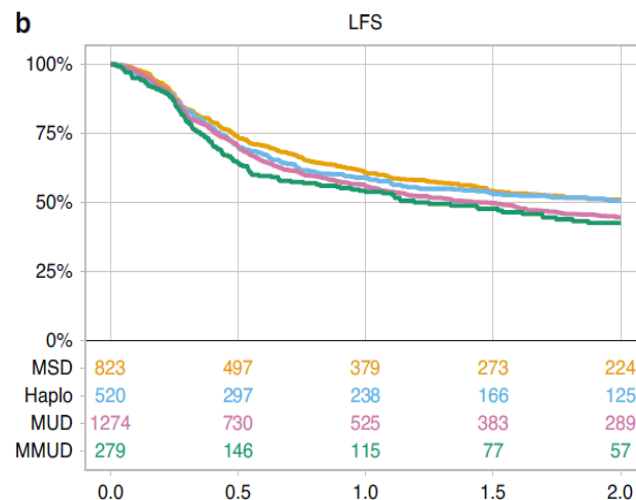
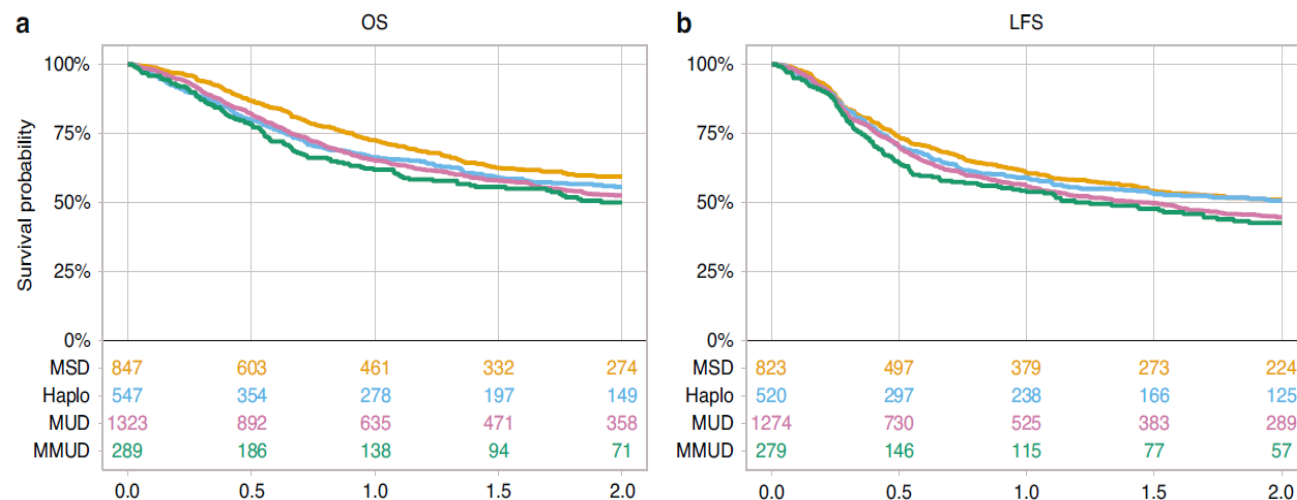
DONOR SETTING	EBMT 2024	NCCN v 3.2026
MRD	PTCy should not be preferred to rATG Grade 2A	PTCy-based CNI-based T-cell depletion/graft-engineering are accepted
MUD	PTCy or rATG preferred over prophylaxis without either in-vivo agent Grade 1	PTCy-based CNI-based T-cell depletion/graft-engineering are accepted
MMUD	PTCy or rATG preferred over prophylaxis without either in-vivo agent Grade 2A	PTCy-based prophylaxis preferred CNI & T-cell depletion-based: alternatives
MMRD	Not covered	PTCy-based prophylaxis preferred T-cell depletion: alternative platform

GVHD prophylaxis in contemporary Italian transplant practice



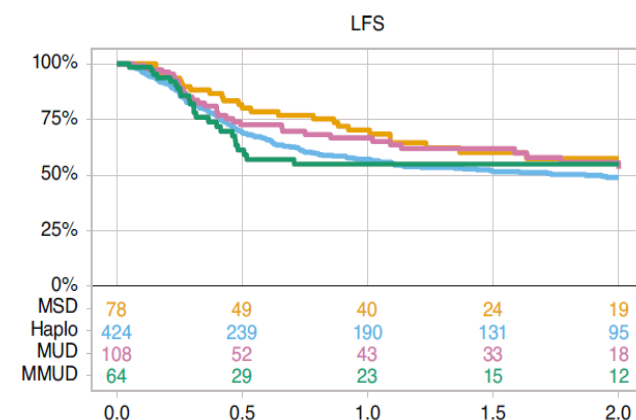
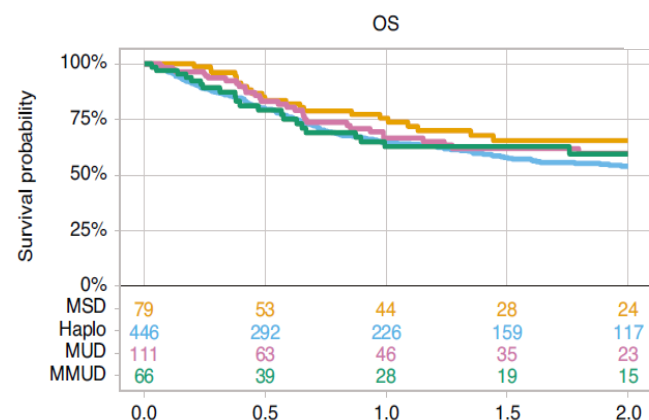
AML Transplant outcomes according to type of donor

EBMT cohort of 3006 adult **high risk cytogenetics AML** in CR1, submitted to transplant between 2017 and 2022



Multivariate analysis

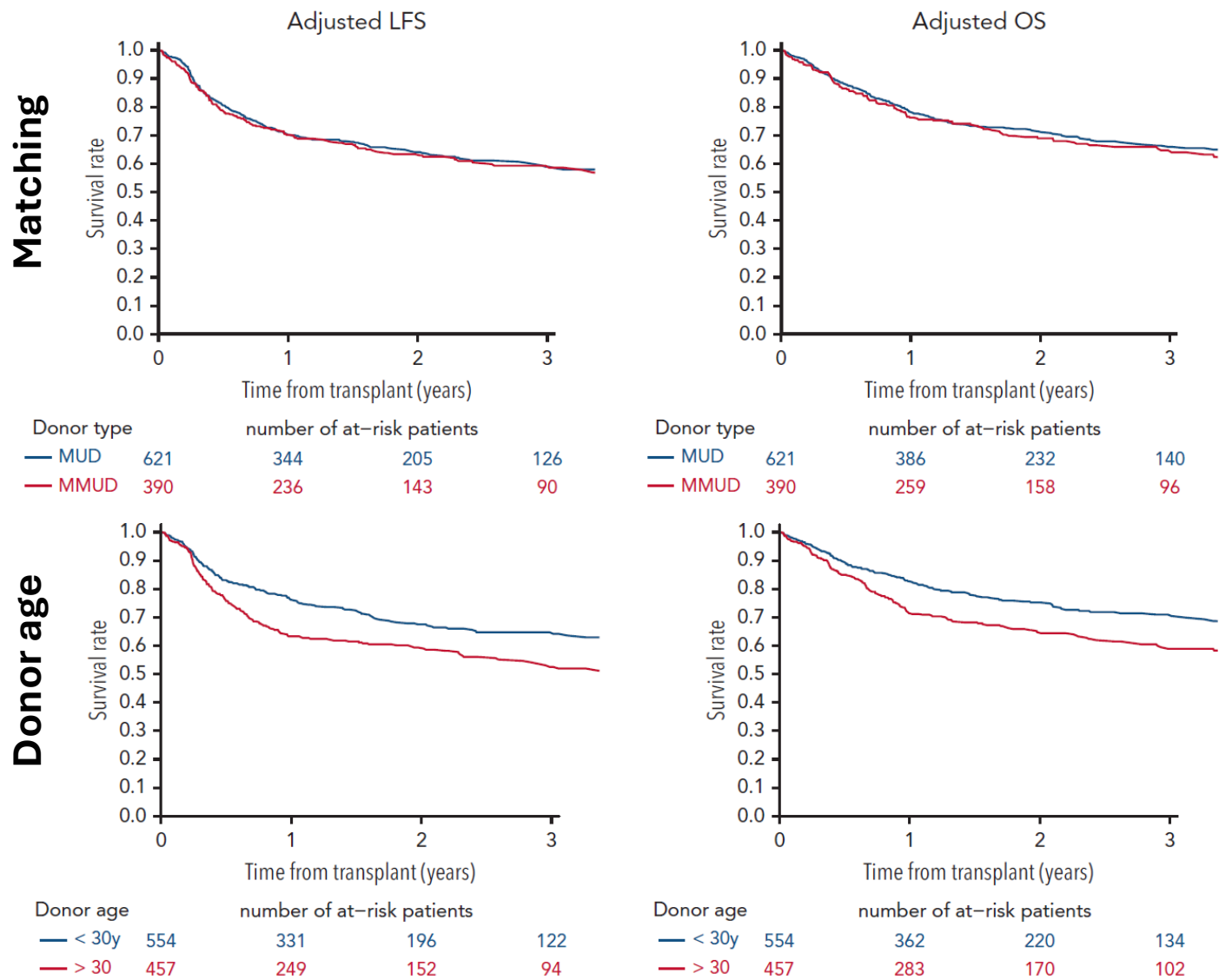
All	HR versus MSD
OS	MUD 1.36; MMUD 1.40; haplo 1.33
LFS	Not significant
NRM	MUD 2.26; MMUD 2.90; haplo 3.85



PTCy cohort	HR versus MSD
OS	Not significant
LFS	Not significant
NRM	haplo 3.22

AML Transplant outcomes according to UD match in PTCy era

Characteristic	CR1/2 AML (1011)
Follow-up in months, median (IQR)	26 (24–29)
Age, median (range), y	54 (18–77)
Sex, n (%)	
Male	566 (56)
KPS at transplant, n (%)	
≥90	744 (75)
HCT-CI, n (%)	
0	510 (50)
1–2	237 (23)
≥3	264 (26)
Cytogenetic risk, n (%)	
Adverse	213 (24)
Disease status at transplant, n (%)	
CR1	837 (83)
CR2	174 (17)
Conditioning intensity, n (%)	
Myeloablative	548 (54)
Reduced intensity	463 (46)

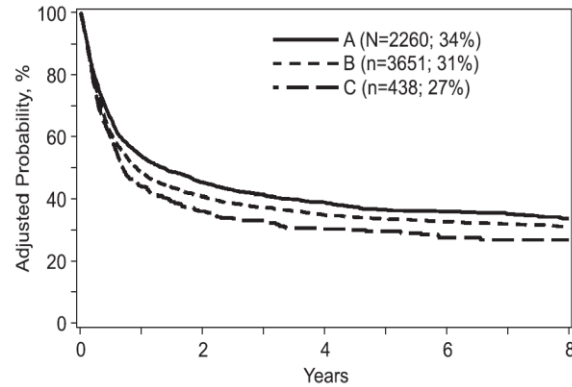


Donor age is a key determinant for transplant outcomes

Kollman et al. • Blood 2016

Unrelated donor transplantation

Overall survival by donor-age group



5-year OS: 36% → 29%

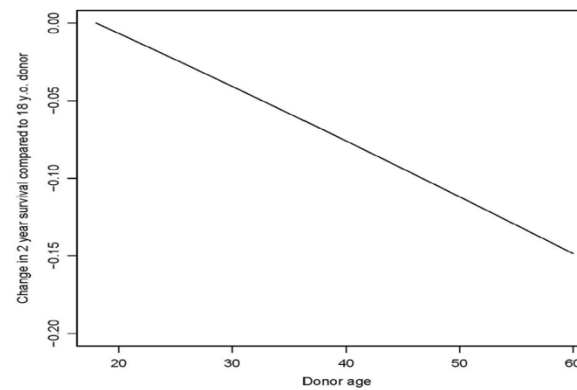
Young donors (18–32 y) vs donors >50 y

Mortality HR: 1.055 per 10-year increase

Shaw et al. • BBMT 2018

8/8 HLA-matched unrelated donors

Decline in 2-year survival with increasing donor age



≈3% higher 2-year OS

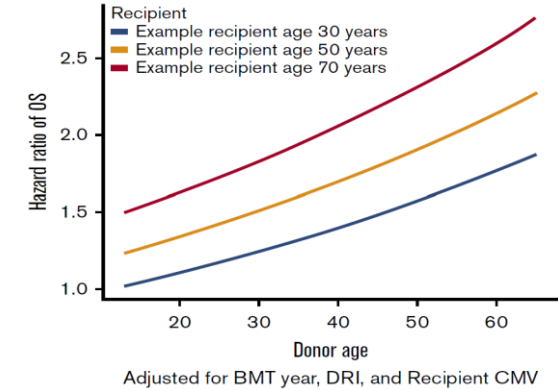
For a donor 10 years younger

Age was the only reproducible donor factor

DeZern et al. • Blood Adv 2021

Haploidentical BMT + PTCy

Relative mortality risk according to donor age



OS HR 1.13 per 10 years

Increasing donor age independently worsened OS

p = 0.0015 • n = 889

CLINICAL TAKE-HOME

HLA match remains foundational; when donor options are comparable, prioritize the youngest suitable donor.

Evidence shown: unrelated HCT (Kollman; Shaw) and haploidentical BMT with PTCy (DeZern).

Machine learning refined unrelated donor selection

COHORT DEFINITION

 **11,818**
first HCT recipients

 **8/8 HLA-matched**
unrelated donors

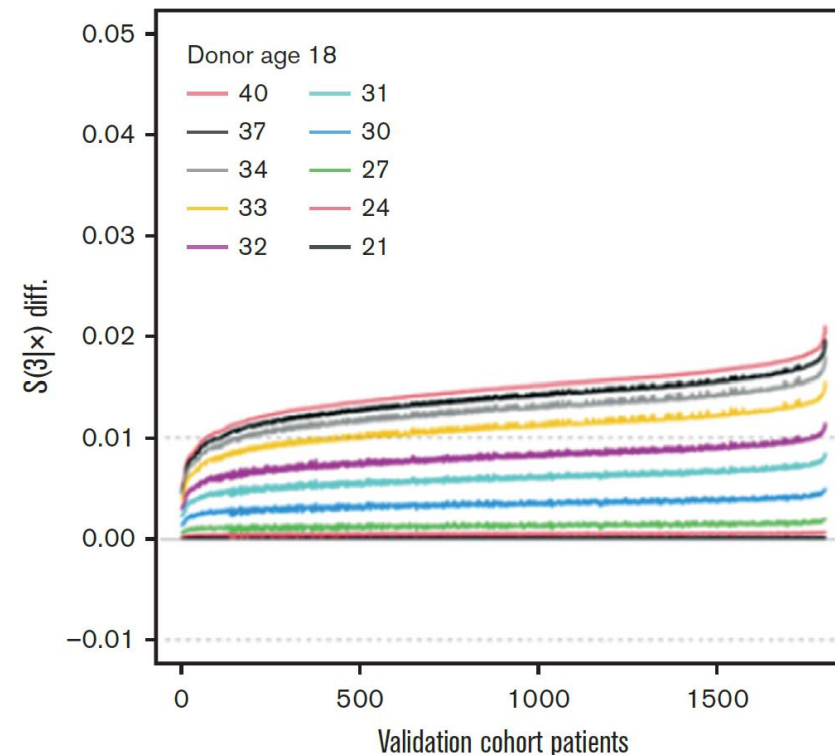
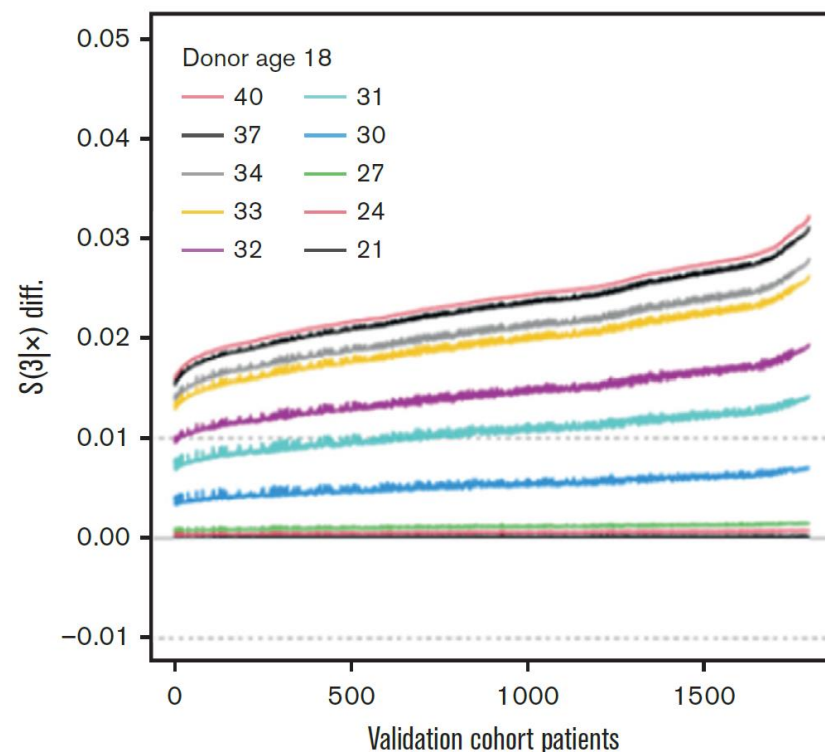
 **CIBMTR registry,**
2016–2019

 **Training: 10,016 |**
Validation: 1,802

 **Median donor age:**
27 years (range 18–60)

 **NFT-BART**
machine-learning
survival model

Contemporary 8/8 MUD CIBMTR transplant between 2016 and 2019



Select the earliest available 8/8 matched donor aged 18–30 years.

If several donors are available,
a male donor may optimize EFS.

Do not delay HCT for minor
differences within this age range.

GITMO AI-Assisted Donor Selection: Comparing Two Candidates

1 Cohort definition

26.911
registry records

15.023
Completed cases

7.609
Final analytical cohort

MSD	MUD	MMUD	MMRD
1388 (18.2%)	2443 (32.1%)	1720 (22.6%)	2058 (27.0%)

85 GITMO Centers 2011-2024

2 Model architecture



Patient + disease +
donor + transplant
variables

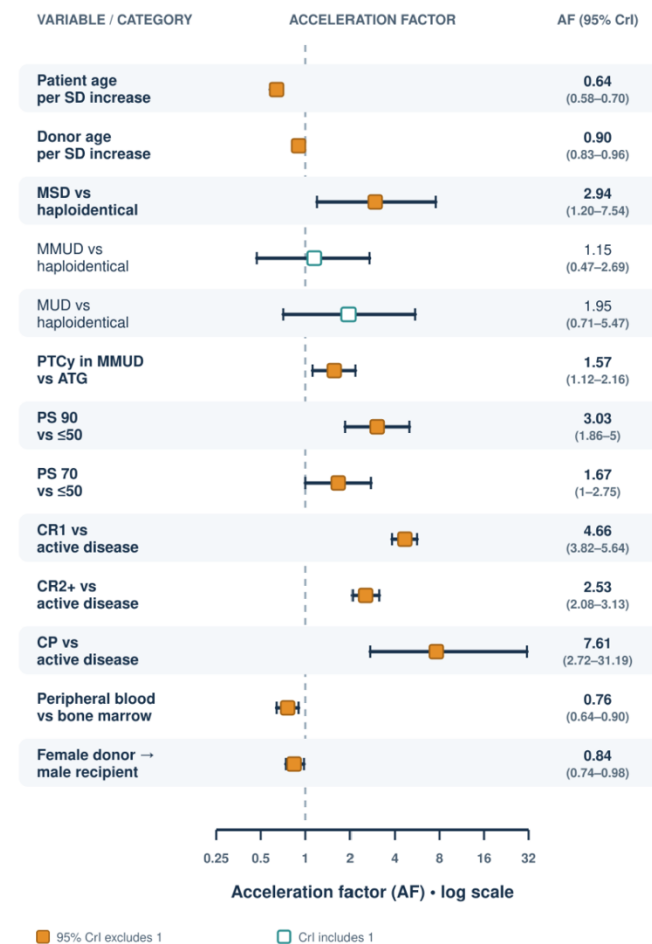


Bayesian hierarchical
heteroscedastic log-
normal AFT model



Personalized survival
curves + 95%
credible intervals +
SHAP explanations

3 Fixed effect estimates



Practical Application to the Presented Case

1) Patient Data

Patient_age
65

PS_grouped
90

Status_disease
CR1

Diagnosis
Acute leukemia

CIC_1_collapsed
Select...

Donor 1

Donor_age
70

HLA_cat
match_related

Stem_cell_source
Peripheral Blood

Score_sexcomb
Other combinations

regimen_gvhd
ATG

CNI
Yes

MTX_MMF
Yes

Donor 2

Donor_age
27

HLA_cat
MMUD

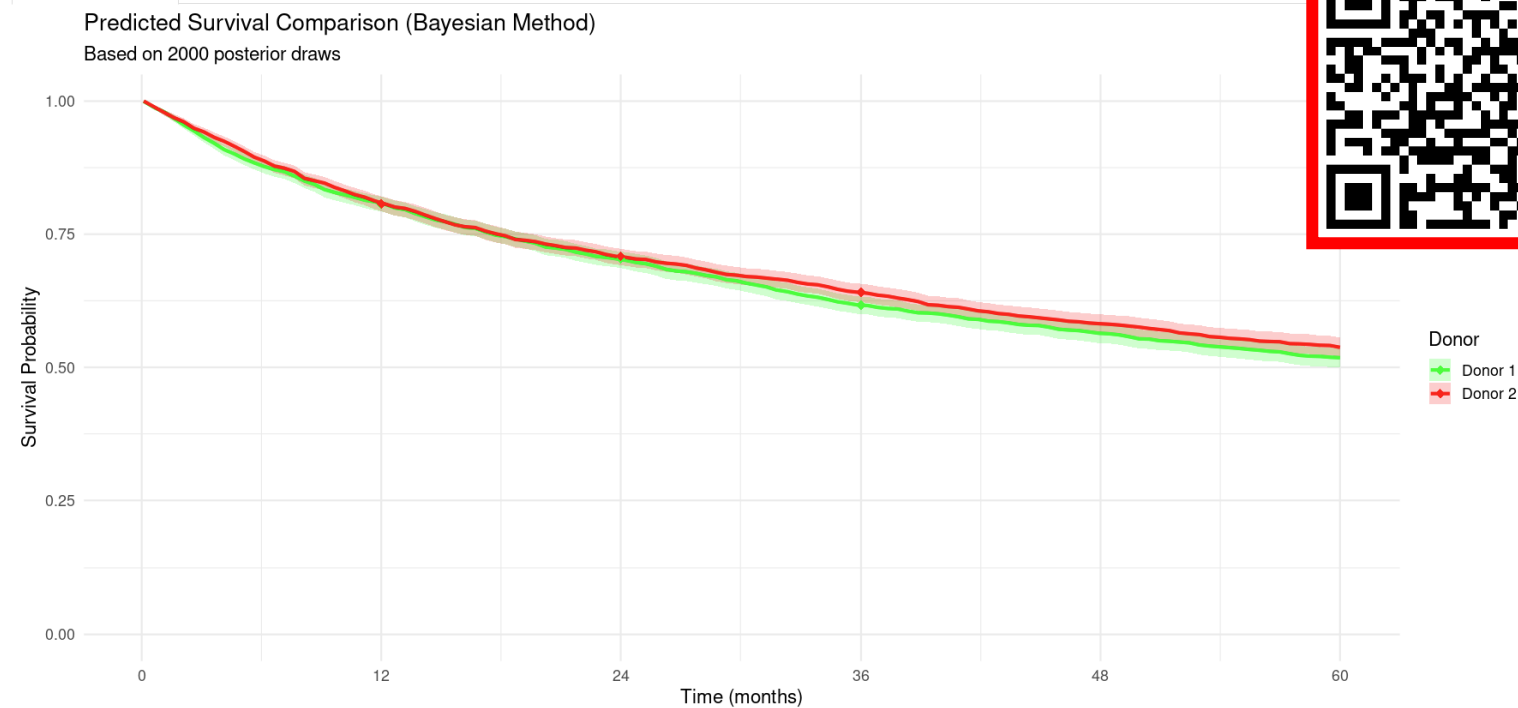
Stem_cell_source
Peripheral Blood

Score_sexcomb
Other combinations

regimen_gvhd
PTCy

CNI
Yes

MTX_MMF
Yes



Donor 1 Results

Donor 1 – Predicted survival:

	Horizon	Median	CI_low	CI_high
1	1 year(s)	80.7%	79.1%	81.9%
2	2 year(s)	70.4%	68.8%	71.9%
3	3 year(s)	61.7%	60.1%	63.3%

Draws used: 2000

Donor 2 Results

Donor 2 – Predicted survival:

	Horizon	Median	CI_low	CI_high
1	1 year(s)	80.7%	79.1%	82%
2	2 year(s)	70.9%	69.3%	72.4%
3	3 year(s)	64.1%	62.3%	65.8%

Draws used: 2000

Survival determinants: SHAP waterfall

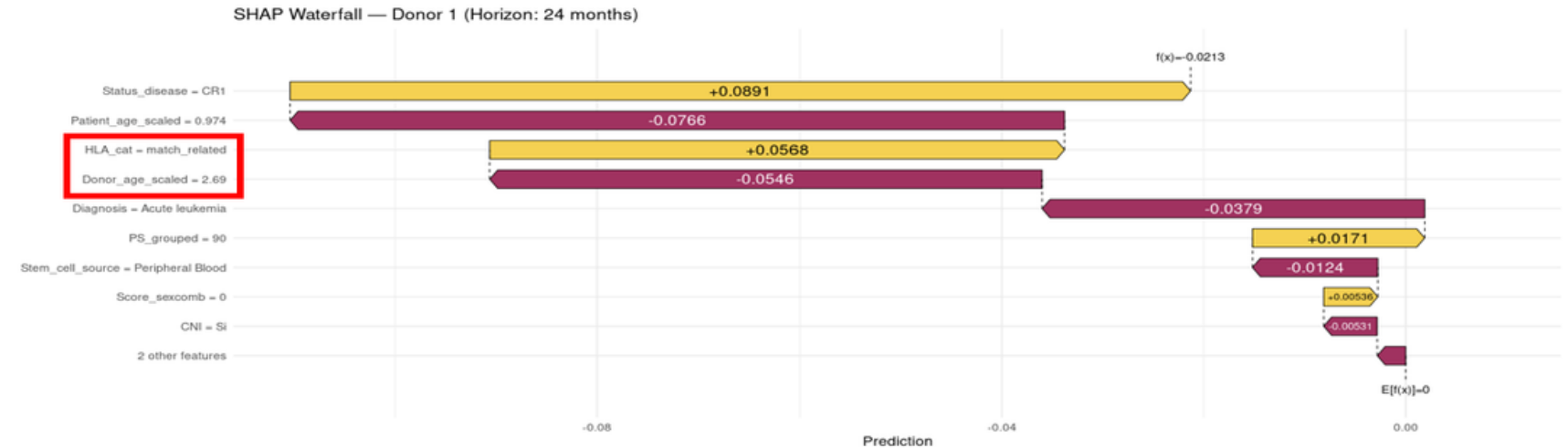
DONOR 1

Older matched sibling

HLA match favours OS

Older donor age penalises OS

Donor 1 — Waterfall



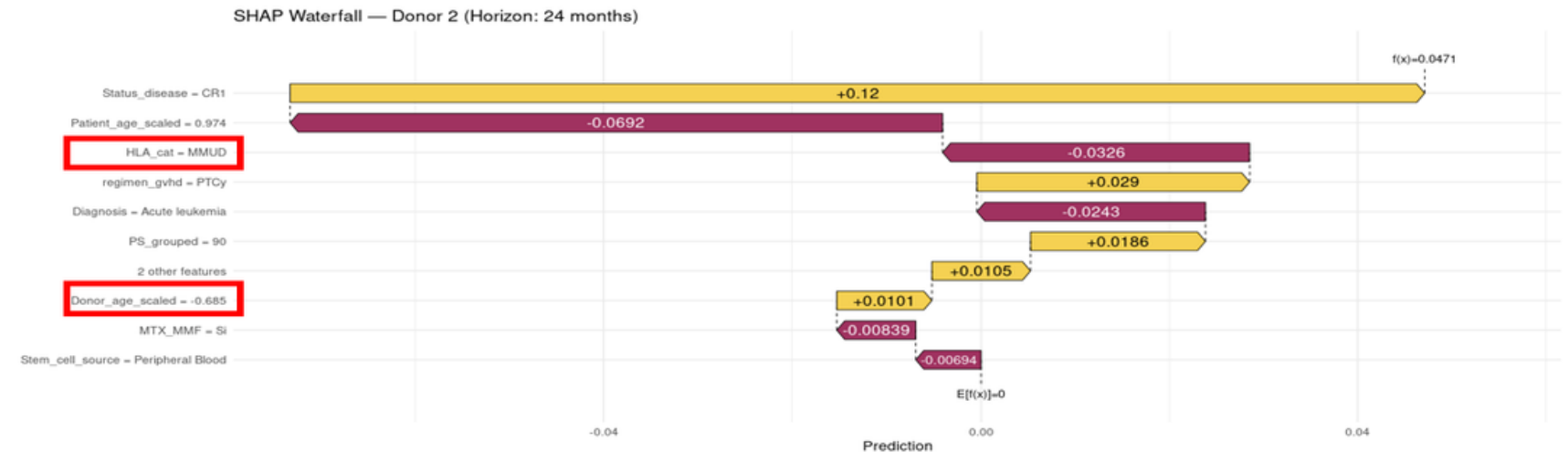
DONOR 2

Younger 9/10 MUD, PTCy

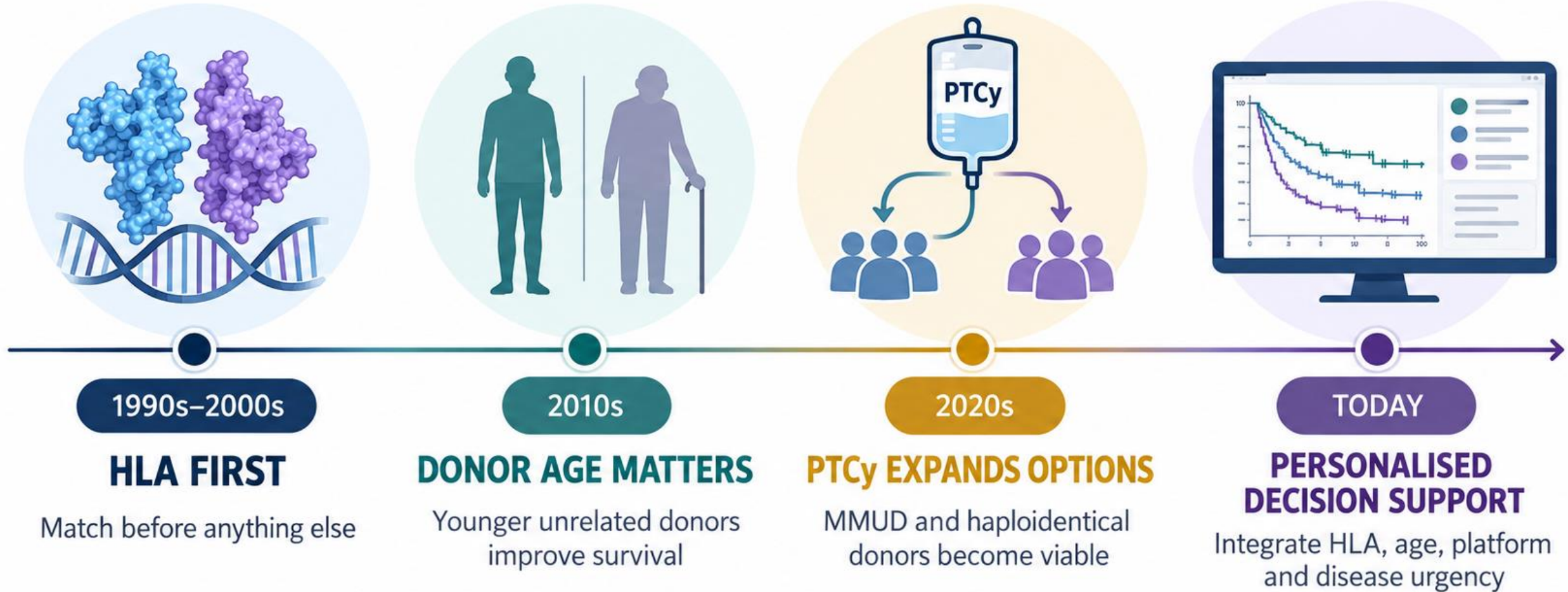
Young age and PTCy favour OS

HLA mismatch penalises OS

Donor 2 — Waterfall



Donor selection: from a fixed hierarchy to personalised choice



WHY NOW?

More donor sources and PTCy make one-size-fits-all rules inadequate.



Fondazione IRCCS
Policlinico San Matteo

Sistema Socio Sanitario



Regione
Lombardia

Transplant Team

Nicola Polverelli
Antonio Bianchessi
Irene Defrancesco
Gianluca Martini
Caterina Zerbi
Maria Grazia Benevento

Case Managers and Nurses

Angela Correddu
Valentina Zoboli
Luciana Dellepiane

Data Manager

Sofia Perrone

Hematology Team

Luca Malcovati
Luca Arcaini



Unit of BMT and Cellular Therapies



Thank you!!

