Non-HLA donor characteristics

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Disclosures

The following faculty and planning committee staff have no financial disclosures:

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Bronwen Shaw, MD PhD	CIBMTR
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Martin Maiers	NMDP/Be The Match
Michael Wright	NMDP/Be The Match

Learning objectives

At the conclusion of this session, attendees will be able to:

- List multiple non-HLA donor characteristics that could influence transplant outcomes
- Identify key differences between how we self-report our ancestral origin and our genetic structure
- Prioritize donor characteristics to impact transplant outcome

Beyond HLA: What non-HLA characteristics are being considered in donor selection today?

Bronwen Shaw, MD PhD

Professor of Medicine, MCW
Senior Scientific Director, CIBMTR

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A research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin

Introduction

- HLA matching is the key variable when selecting an URD
- The ‘gold standard’ is an 8/8 match
- Other HLA loci may be considered
- Several studies show an impact of ‘secondary donor factors’
- These are especially important when more than one 8/8 URD is available:
  - Approximately 70% of Caucasian patients searches through NMDP, Kevin Tram, personal communication, July 2017

Which donor factors are we talking about?

- Age
- CMV serostatus
- Gender
- ABO type
- Is there an algorithm/hierarchy for selection

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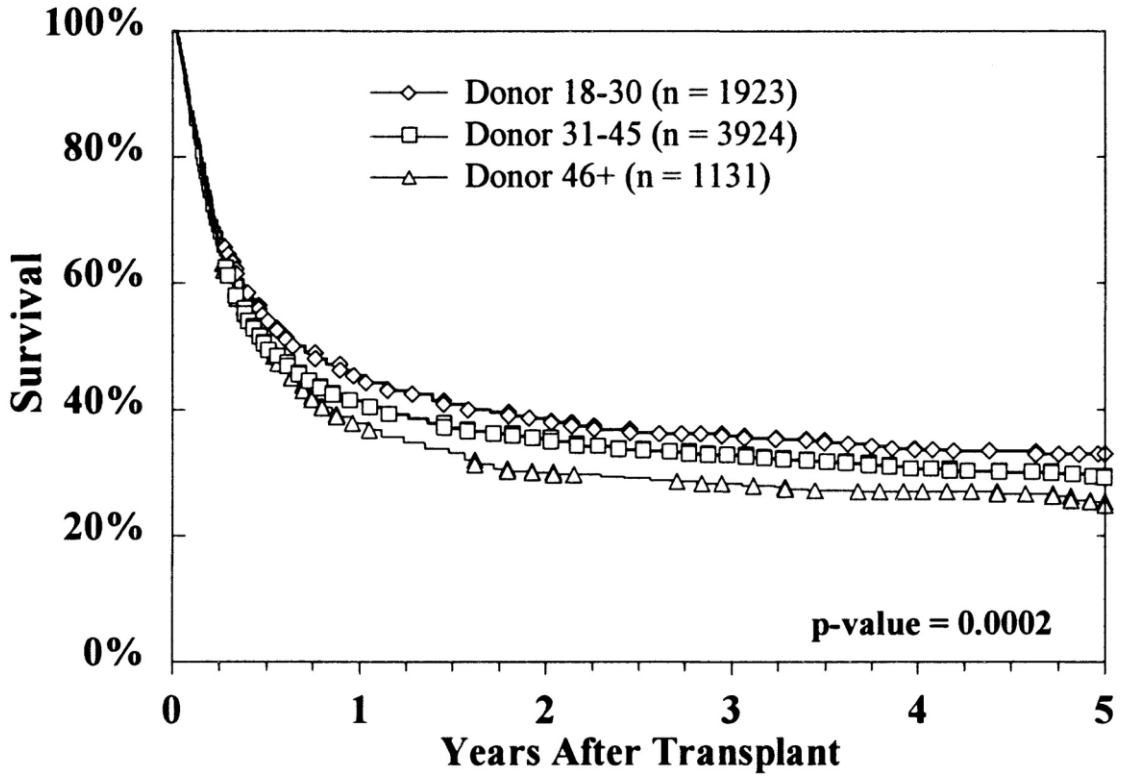
Donor Age: Does this affect OS?

- Several studies show that a younger donor results in a better survival
- 2001 NMDP study:
  - 6978 pts, 1987-1999, BM
- Updated population:
  - 6349 pts, 1988-2006, BM/PBSC
- Validation population:
  - 4690 pts, 2007-2011, BM/PBSC

Overall survival decreased with increasing donor age. This effect was highly significant.



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

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blood

Donor Age: Kollman 2001

Proportional hazards regression models for grade III or IV acute graft-versus-host disease (GVHD) (n = 6978) and chronic GVHD (n = 4819 evaluable patients surviving at least 80 days)

Factor	Grade III-IV acute GVHD				Chronic GVHD			
	RR	95% CI	*P*	Favorable factor	RR	95% CI	*P*	Favorable factor
Donor age (per decade)	1.08	1.03-1.14	.002	Younger	1.08	1.02-1.14	.005	Younger

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

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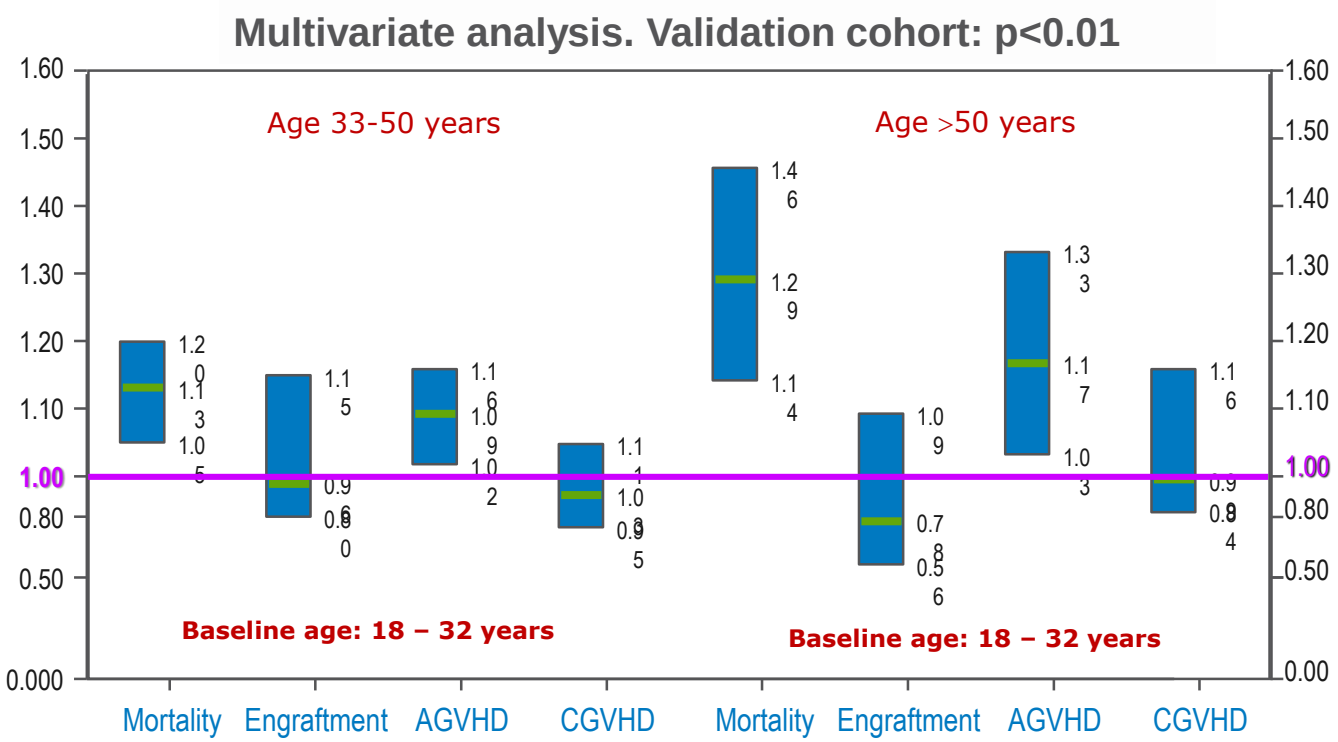
Donor Age: Kollman 2015



p<0.001.

Kollman, et al

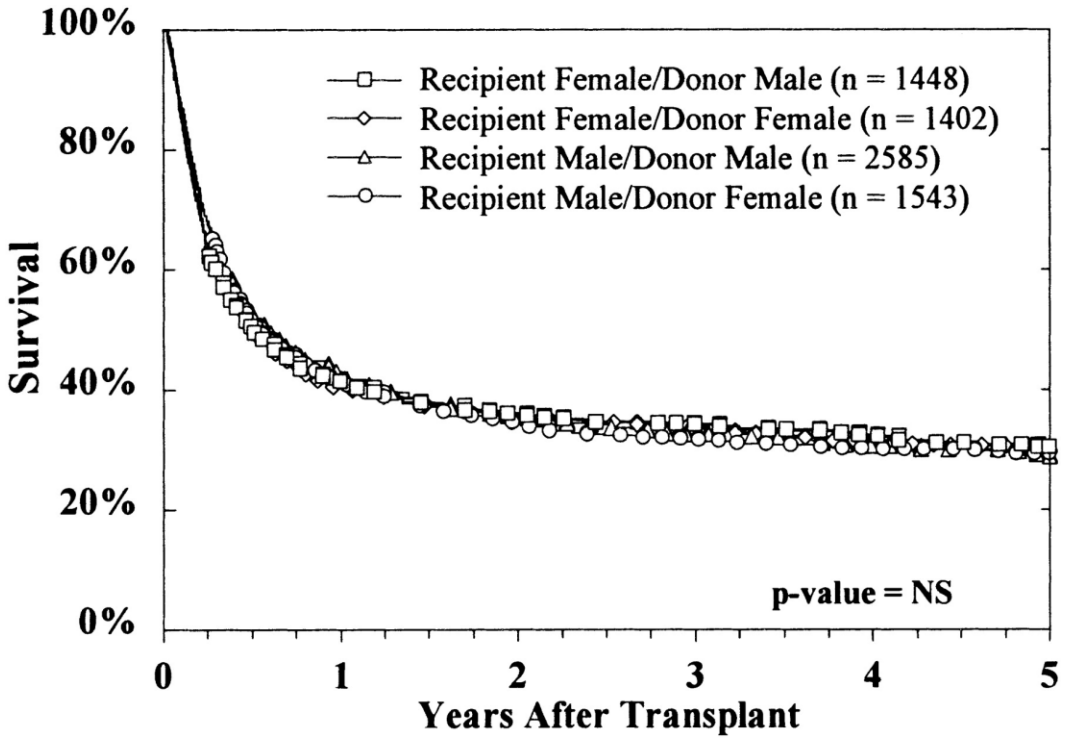
Summary: Donor Age

- This matters for all outcomes and should always be considered when selecting a donor
- Consider age next in importance after HLA for OS
- Every year younger is better:

  e.g. equal HLA match pick 19 yo before 33 yo

Donor Gender: Does this affect OS?

- Three CIBMTR studies mentioned
  - NO



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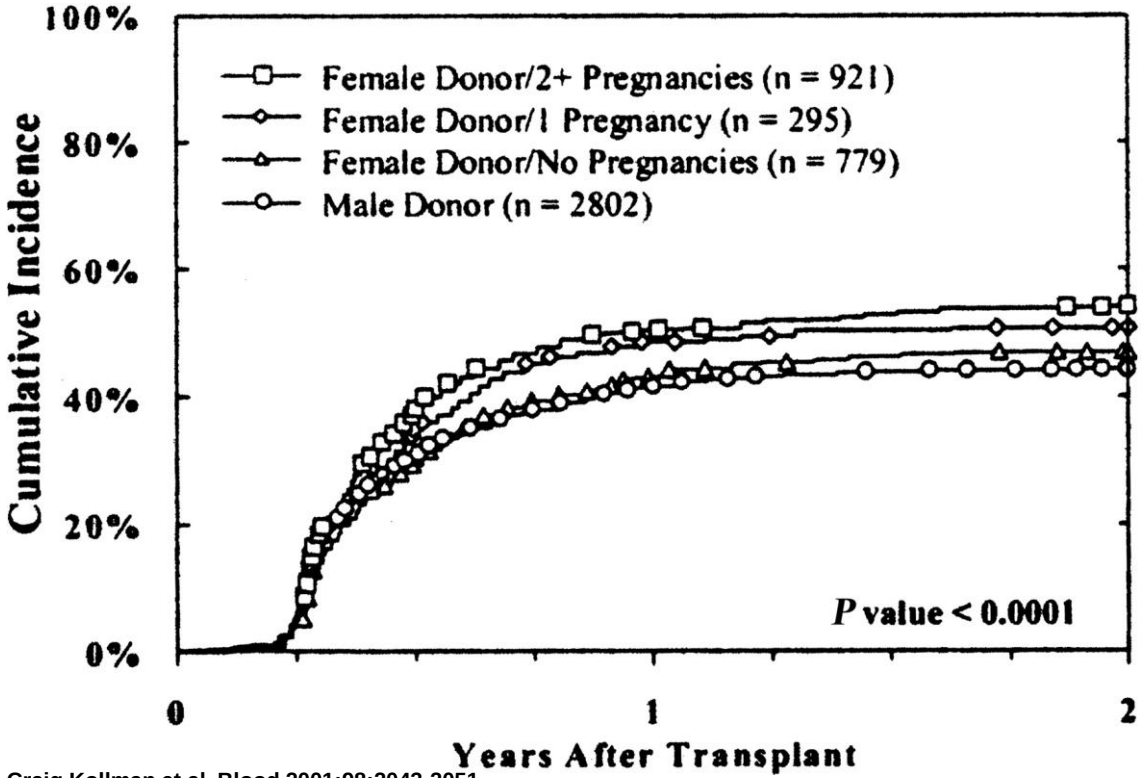
The cumulative incidence of chronic GVHD was higher with multiparous female donors. Results with male donors and female donors without pregnancies were similar, whereas an increasing incidence of chronic GVHD was associated with female donors with one or more pregnancies



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

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blood

Kollman 2015: Donor gender

Non-relapse Mortality		
Male	1.00	
Female, no pregnancies	1.02 (0.91 – 1.14)	0.75
Female, 1 or more pregnancies	1.29 (1.18 – 1.41)	<0.001
Chronic GvHD		
Male	1.00	
Female, no pregnancies	1.01 (0.91 – 1.12)	0.88
Female, 1 or more pregnancies	1.22 (1.11 – 1.34)	<0.001
Relapse		
Male	1.00	
Female, no pregnancies	0.96 (0.84 – 1.10)	0.57
Female, 1 or more pregnancies	0.84 (0.74 – 0.95)	0.007

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No impact on Overall Survival

Donor Gender: Does this affect other outcomes?

Male vs Female donor

- Higher cell numbers – may be related to weight and difference between patient and donor weight*
- Higher engraftment rates
- Less primary graft failure
- No difference in acute GVHD
- Lower Chronic GVHD than females with 1 or more pregnancies
- Female donor into male recipient: Some studies show higher GVHD

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* Billen, Transfusion, 2014

Summary: Donor Gender

- Does not impact survival, but may impact other outcomes
- Due to lower cell numbers and weight MIGHT prefer PBSC
- Is lower on the list of factors to consider

CMV serostatus: Does this affect OS?

- Three NMDP/CIBMTR studies mentioned
  - NO
- Other studies do show a difference
  - 8003 AL, CML, MDS: worst outcome in CMV R+/D-(Pidala, 2014)
  - Large EBMT study, 49542 showed: R+/ D+ had improved OS (HR, 0.92; 95% CI, .86-.98; P < .01) compared with R+/D- (Ljungman, 2014)
  - Anthony Nolan cohort (2016)

- Controversial results GVHD/Relapse

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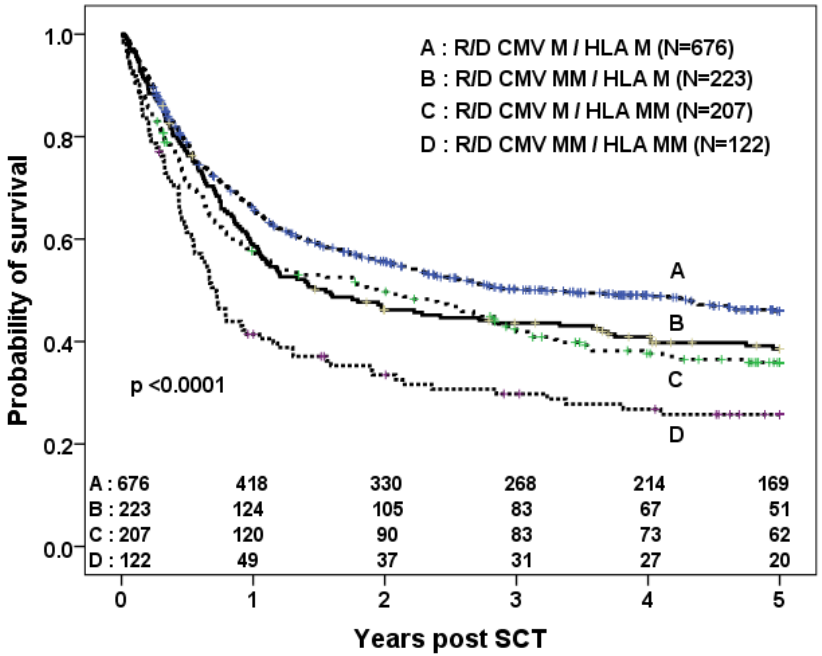
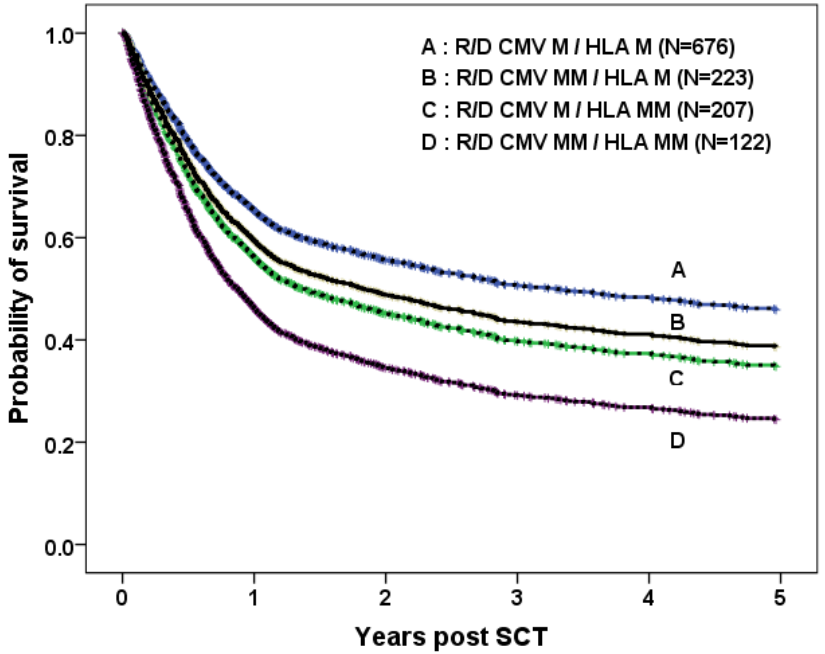
CMV serostatus: Does this affect OS?



Shaw, BMT, 2016

CMV serostatus: Does this affect OS?



Shaw, BMT, 2016

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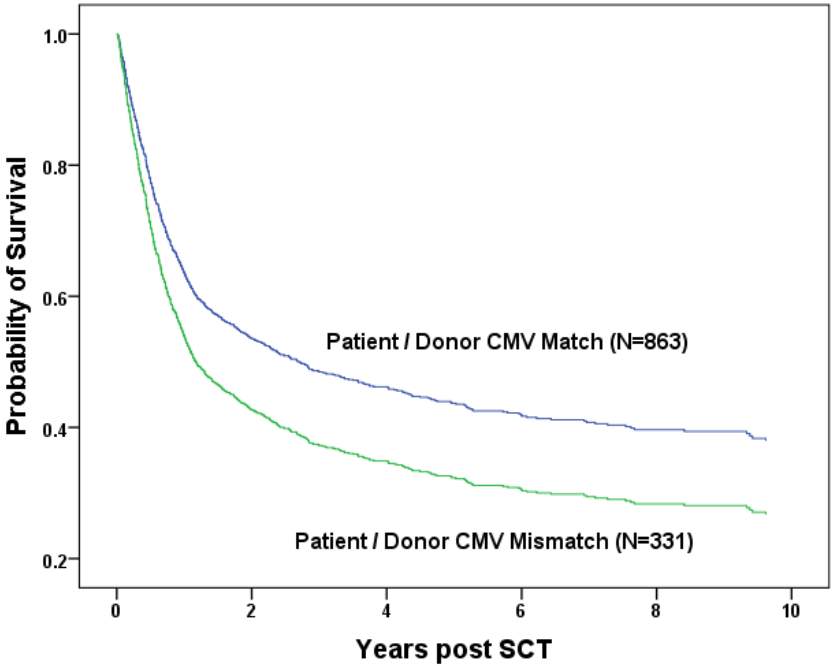
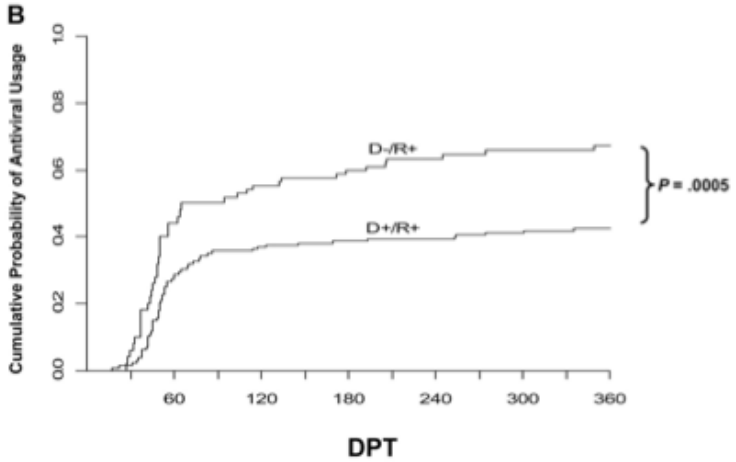


Shaw, BMT, 2016

CMV serostatus: Does this make the transplant more difficult for everyone?

- Post transplant CMV reactivation and persistent more common in R+/D- than R+/D-
  - No CMV specific T cells if D-/multiple reactivations
  - Increase morbidity with CMV treatment



Wendi Zhou et al. Blood 2009;113:6465-6476

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Summary: Donor CMV status

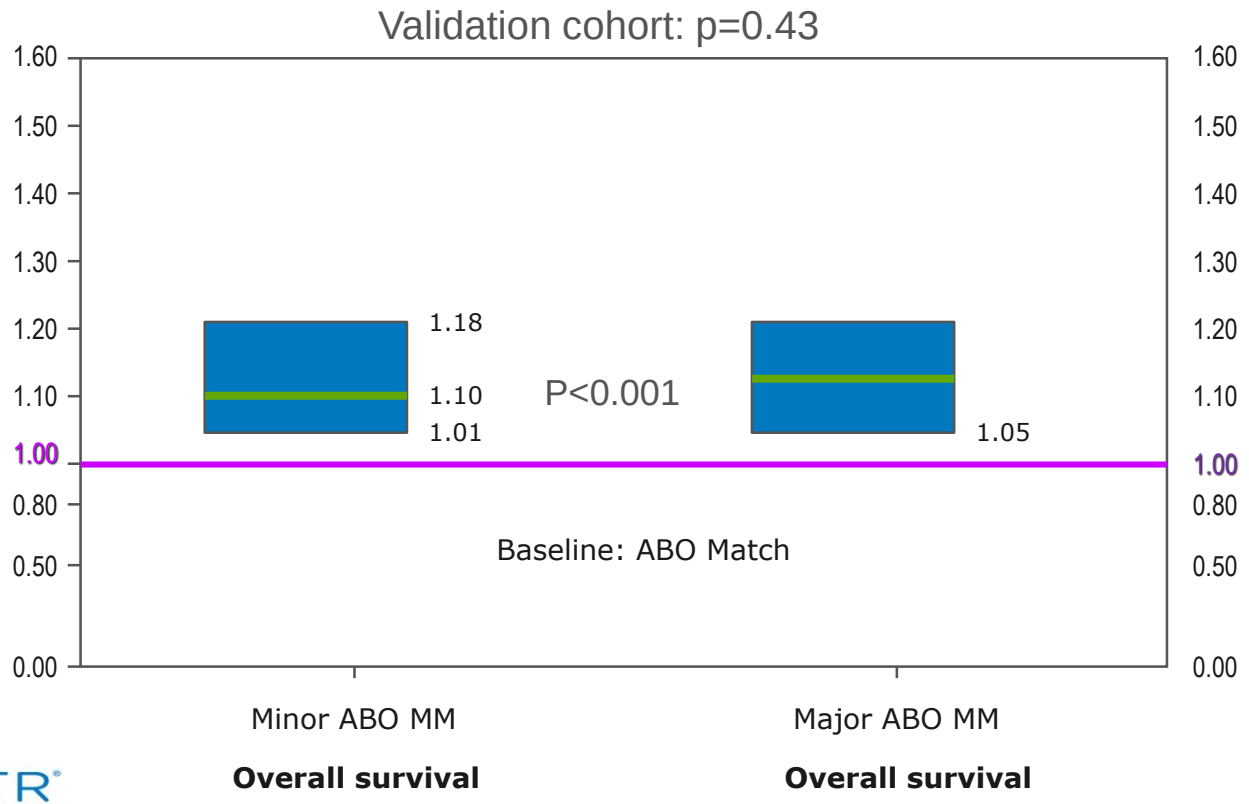
- Impact may be very dependent on the type of transplantation (e.g. conditioning/T cell depletion)
- A match is better than a mismatch if possible

ABO Match: Does this affect OS?

- Kollman, 2001 and validation, 2015 CIBMTR:
  - NO
- Second study:
  - ~10% increase mortality with ABO mismatch
- Variable results in other studies
  - 5179, all AML or MDS, major mm = ~ 20% increase TRM (Luger, 2012)
  - 1679 lymphoma, minor mm = shorter OS
  - 8003 AL, CML, MDS, any mm = ~10% increased mortality (Pidala, 2014)
- Several other studies show no impact

Multivariate Analysis

- Donor-recipient ABO match -



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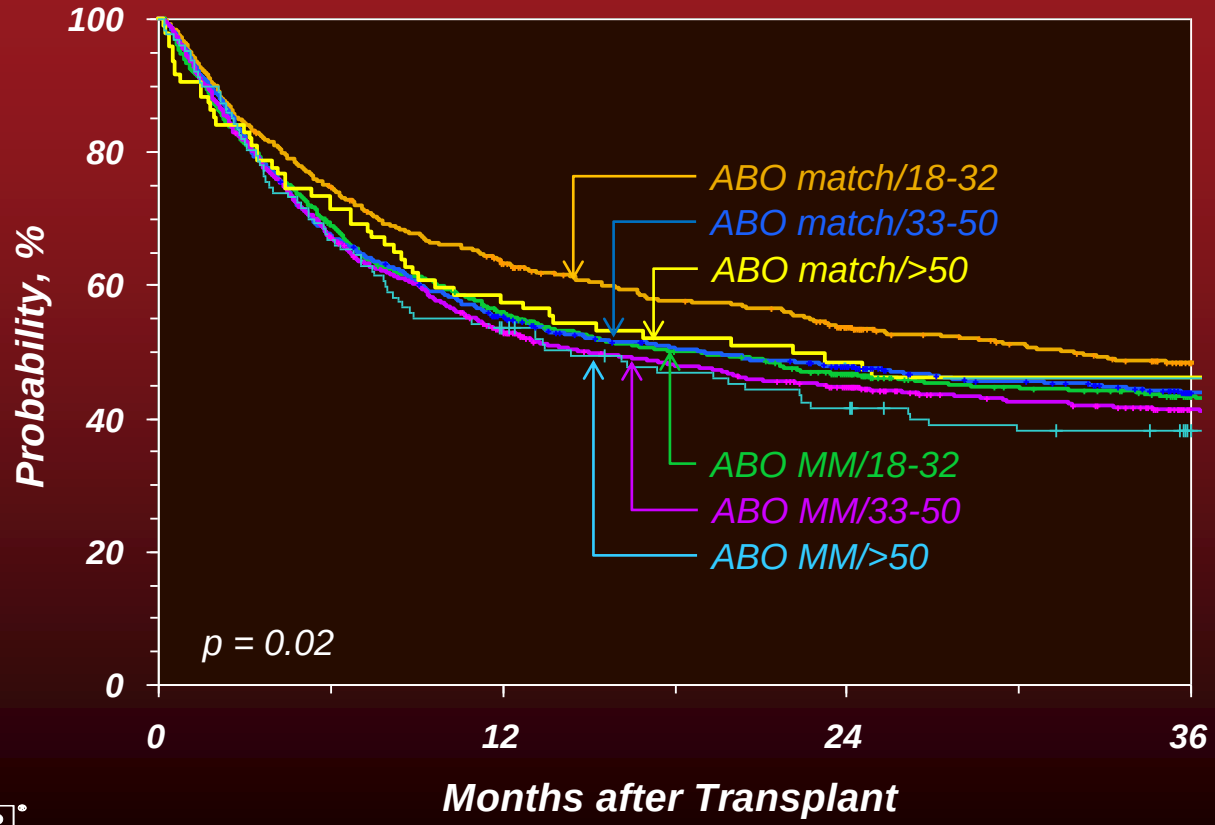
Kollman, et al

Overall Survival
8/8 HLA-matched Transplants



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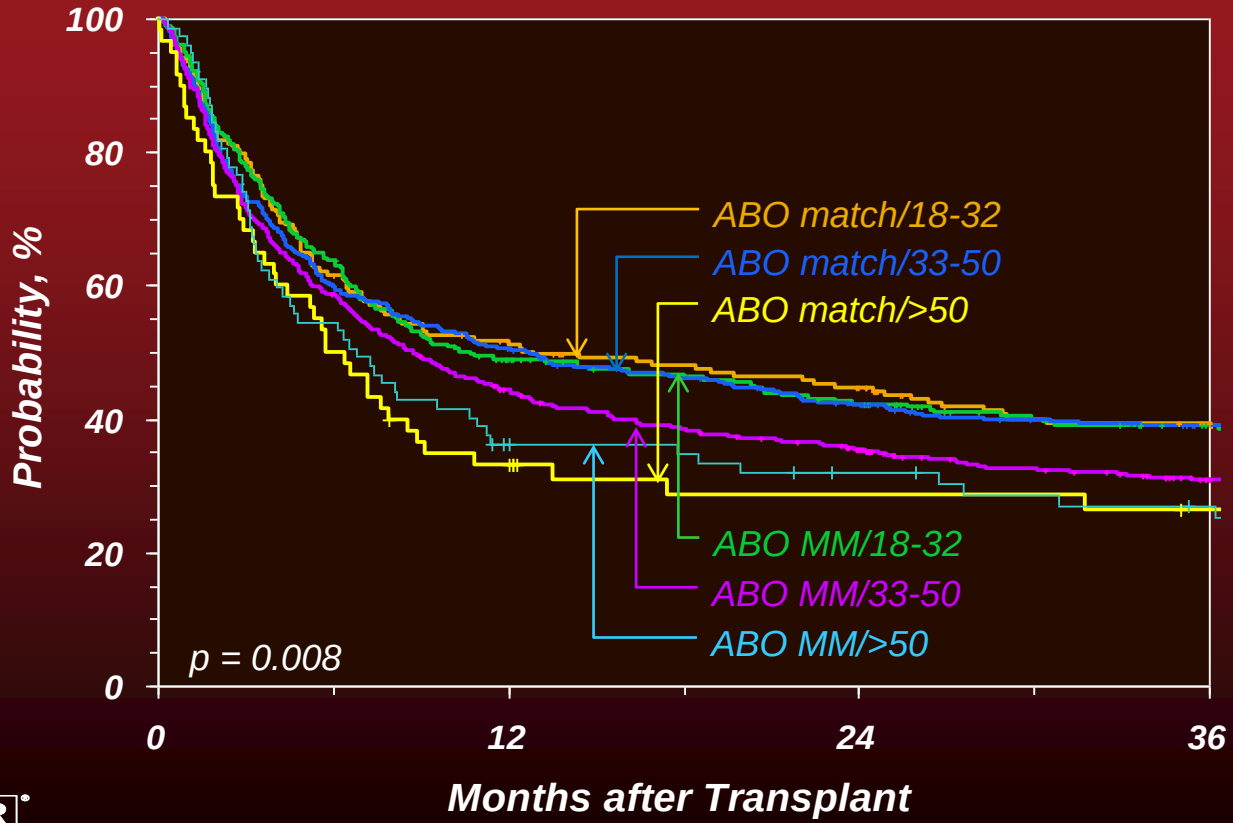
Overall Survival
7/8 HLA-matched Transplants



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ABO Match: Does this affect other outcomes?

Table I. *Nomenclature for ABO Mismatching Observed and Theoretical Adverse Outcomes in Allogeneic BMT Reported in Previous Studies*

ABO Mismatch	Donor	Recipient	Known and Postulated Consequences
Minor	O	A, B or AB	Recipient hemolysis
	A, B	AB	Reports of increased GVHD
Major	A, B or AB	O	Posttransplantation pure red blood cell aplasia
	AB	A, B	Reports of impaired engraftment and increased GVHD
Bidirectional	A	B	Recipient hemolysis and red blood cell aplasia
	B	A	Reports of reduced overall survival
			Reports of impaired engraftment and increased GVHD

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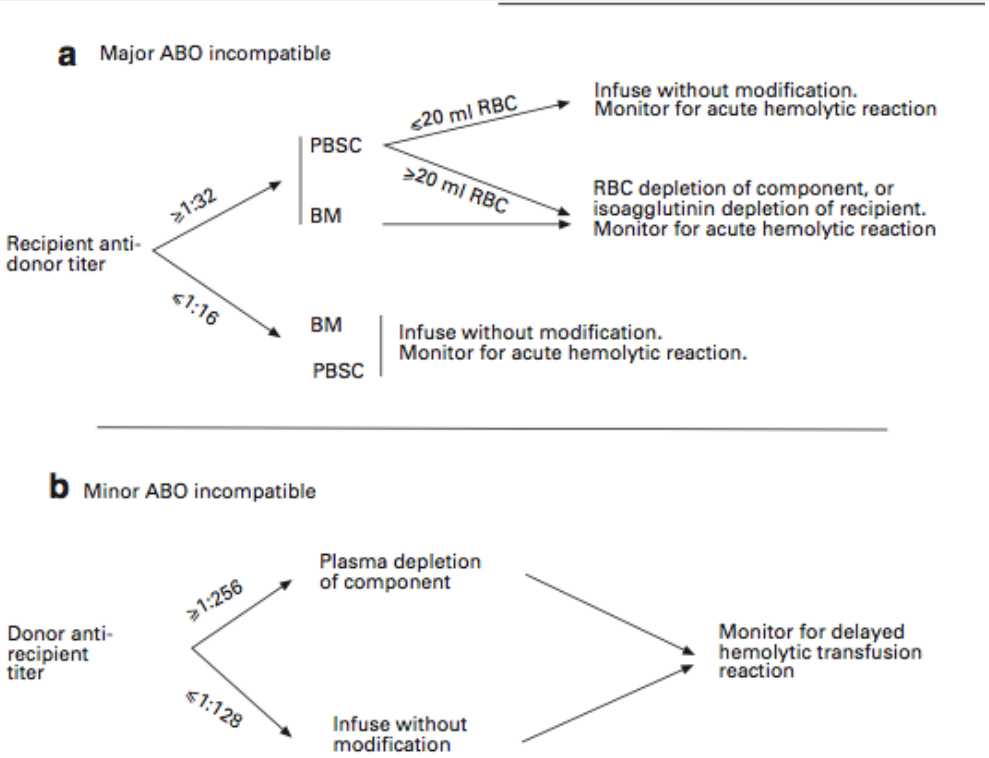
Seebach et al, BBMT 2005

ABO Match: Does this make the transplant more difficult for everyone?



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Rowley, BMT 2001

Summary: non-HLA

- Not controversial: it matters for outcomes!
  - Age
- Controversial impact on OS and other outcomes – selection practice relatively consistent – even if for logistic reasons
  - CMV serostatus: match is better
  - ABO type: match is better
- May not affect outcomes – selection practice varies
  - Gender: may impact cell numbers/GvHD (parity only)
- Other considerations
  - DSA, race/ethnicity, donor weight/discrepancy

Summary

- Some factors are interdependent
  - ABO or CMV match may ‘matter’ more depending on HLA match status
  - Gender and ABO may matter more in BM vs PBSC for logistic reasons
- Unfavorable donor characteristics are often a ‘package’
- Factors may differ in different transplant settings
  - BM vs PBSC
  - TCD vs T cell replete
  - Disease stage

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Is there an algorithm? My thoughts

- First tier (survival benefit repeatedly shown):
  - 8/8 HLA match

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- First tier (survival benefit repeatedly shown):
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  - Donor age = linear effect (younger is better)

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- First tier (survival benefit repeatedly shown):
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- Second tier (survival benefit repeatedly shown):
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- Third tier (survival benefit inconsistent):
  - DPB1 TCE permissive/match
  - CMV
  - ABO
  - Males or non-parous females

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  - ABO
  - Males or non-parous females
- Fourth tier (survival benefit not shown)
  - Gender
  - DQB1

Is there an algorithm? My thoughts

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  - Gender
  - DQB1
- TRUMPS
  - DSA/Clinical trial

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Effect of Genetic Ancestry on HSCT Outcome

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Senior Bioinformatics Scientist
Bioinformatics Research, CIBMTR

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Race and HCT outcomes

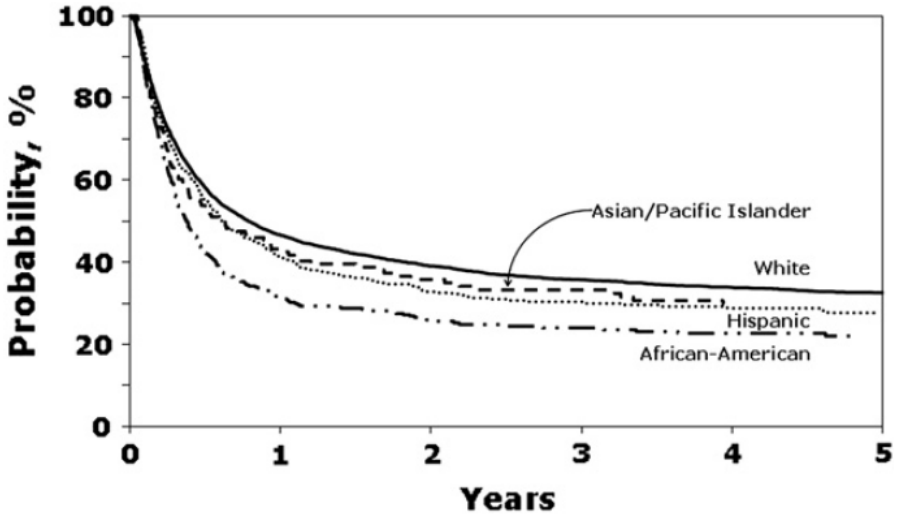
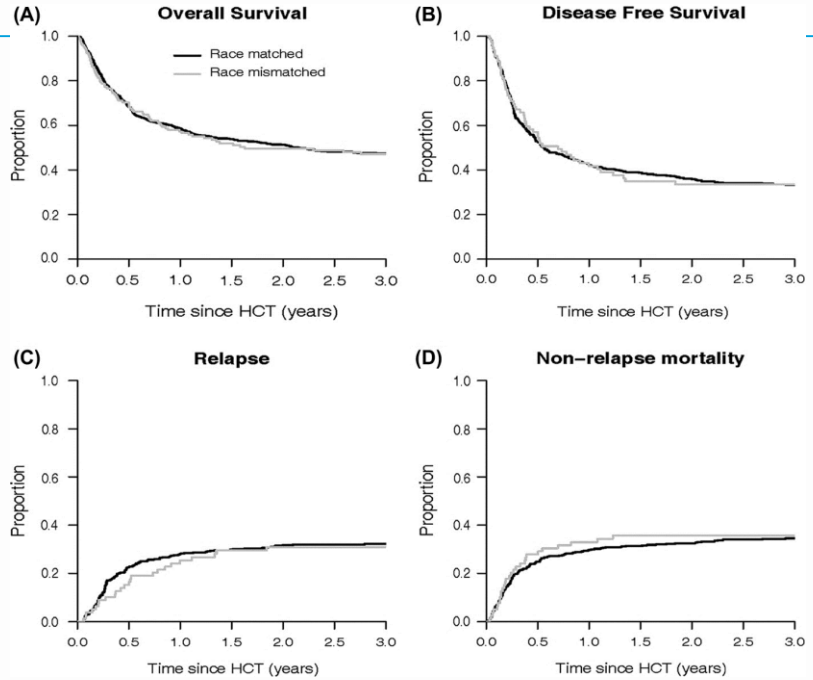


Figure 1. Probability of OS by race.

Baker et al, BBMT 2009



Ustun et al, *Leukemia & Lymphoma 2013*

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Race and HCT

Does race influence HCT outcome?

Yes

Does race matching influence HCT outcome?

We don’t know

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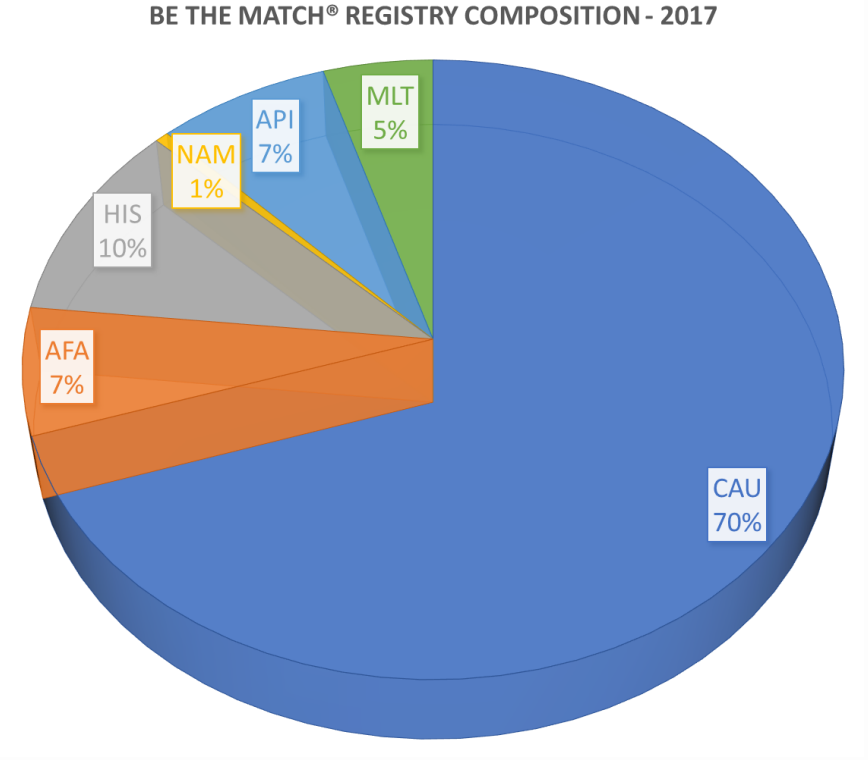
This is important

- HapLogic® starts by searching potentially matched donors of the same race group as the patient.
- The odds are higher to find a match within the same race group as the patient.
- We have more European Caucasian donors. HLA-matched/race-mismatched transplants often happer
- Prior studies addressed racial disparities in HLA matched HCT outcome.
- No studies to date analyzed disparities due to genetically defined ancestral groups.



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The Study

Biol Blood Marrow Transplant 23 (2017) 1029–1037

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Investigating the Association of Genetic Admixture and Donor/Recipient Genetic Disparity with Transplant Outcomes

Abeer Madbouly [1,*], Tao Wang [2], Michael Haagenson [3], Vanja Paunic [1], Cynthia Vierra-Green [3], Katharina Fleischhauer [4], Katharine C. Hsu [5], Michael R. Verneris [6], Navneet S. Majhail [7], Stephanie J. Lee [2,8], Stephen R. Spellman [3], Martin Maiers [1]

[1] *National Marrow Donor Program/Be The Match, Minneapolis, Minnesota*
[2] *Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin*
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[5] *Memorial Sloan Kettering Cancer Center, New York, New York*
[6] *University of Colorado-Denver, Denver, Colorado*
[7] *Cleveland Clinic, Cleveland, Ohio*
[8] *Fred Hutchinson Cancer Research Center, Seattle, Washington*

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Study Objectives

- Does difference in donor/recipient genetic ancestry affect HCT outcome?
- Does recipient/donor genetic ancestry affect HCT outcomes?

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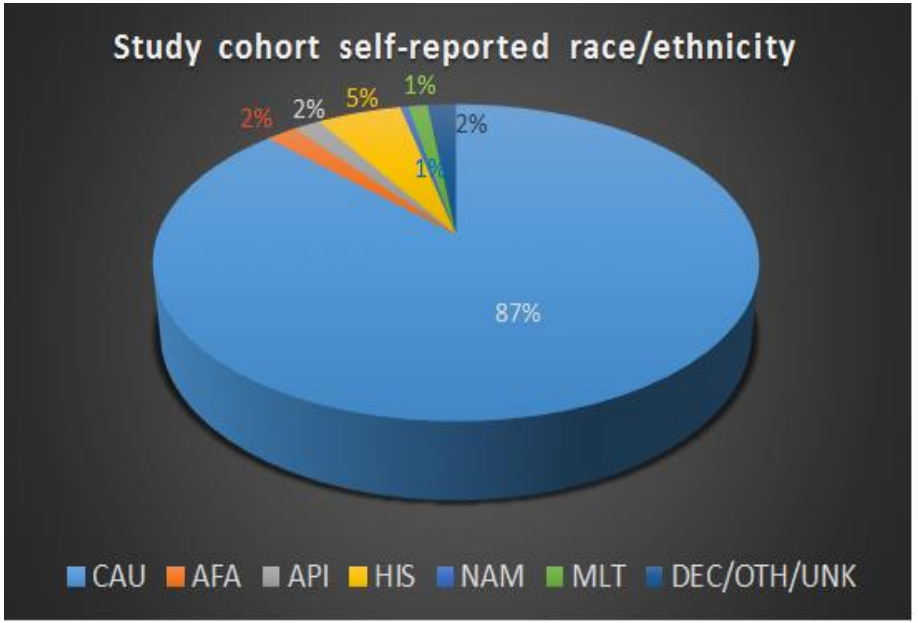
- Does recipient/donor genetic ancestry affect HCT outcomes?

Study cohort

Variable	N (%)
Number of patients	1378
Number of centers	146
Age, median (range), years	39 (<1-70)
Disease at transplant	
AML	461 (33)
ALL	216 (16)
CML	436 (32)
MDS	265 (19)
Graft type	
Bone marrow	777 (56)
Peripheral blood	601 (44)



1378 10/10 HLA matched donor/recipient pairs

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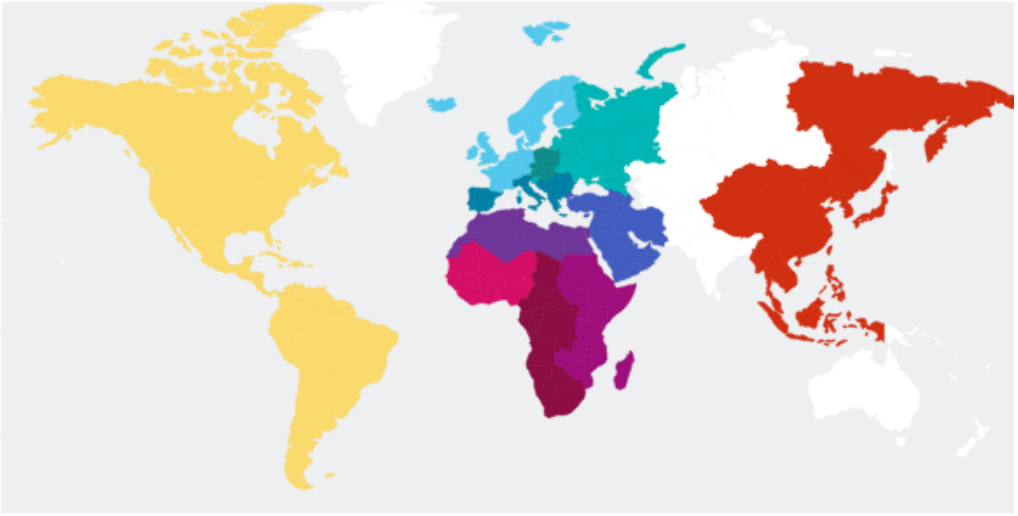
What did we study?

- We genotyped the study samples for 500 Ancestry Informative Markers (AIMs) single nucleotide polymorphisms (SNPs)
  - Genetic markers that differ in allele frequencies across different populations within or across world continents.
  - Designed to distinguish continental and/or sub-continental groups
- What does this mean?
- What does this look like?

Your genetic admixture

Abeer Madbouly	100%
Middle Eastern & North African	93.8%
Sub-Saharan African	4.2%
European	1.6%
East Asian & Native American	< 0.1%



This is a consumer genetics example. We have the same pipeline in-house.

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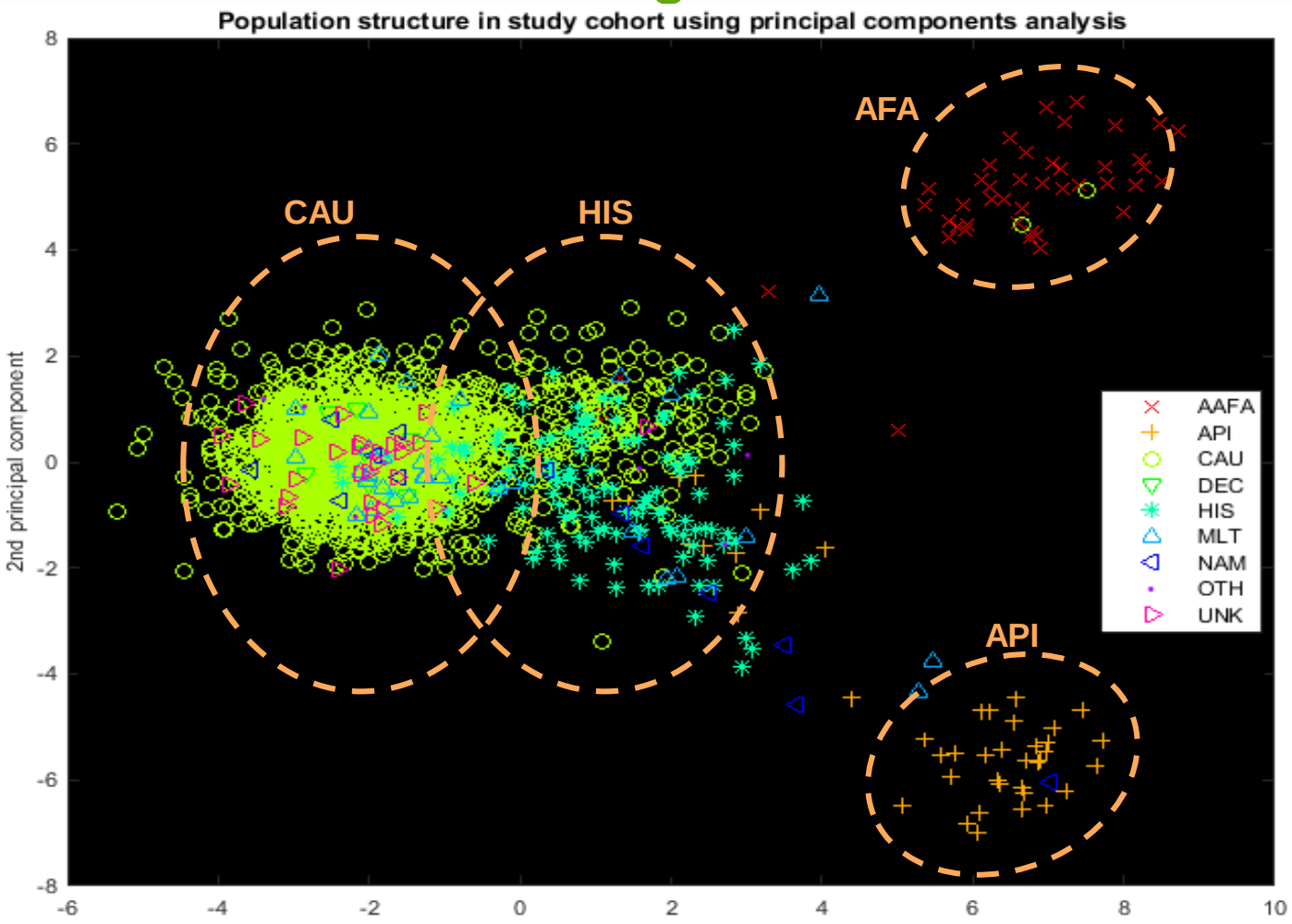
Does our race reflect our genetic admixture?



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Clinical Results

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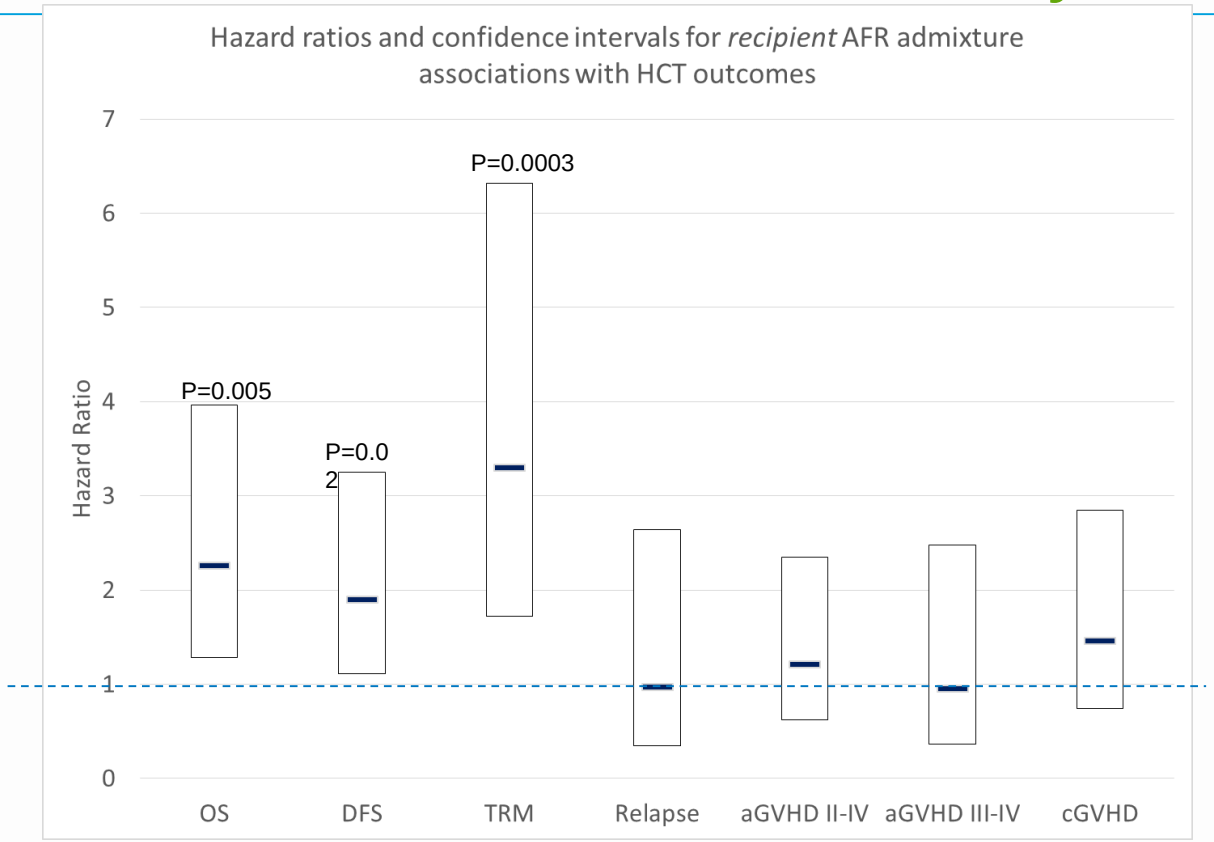
Genetic Admixture

- Studied the following genetic admixtures for donors and recipients:
  - European (EUR)
  - African (AFR)
  - Asian (ASI)
  - South European/Amerindian (SEUR/AMER)
- *Recipient* EUR and ASI failed linearity test and were excluded

Recipient admixture – multivariate analysis



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Recipient admixture

- When evaluated as a continuous variable, increasing recipient **AFR** admixture was associated with worse **OS** and **TRM** at p<0.01
- When tested as categorical variables, no significant associations were found
- Because of this discrepancy, we tested for a cut-point for AFR admixture.
- The optimal cut point was >14% AFR admixture
- This *risk group* included **2.8%** of the study population (N=34 recipients) and **90%** of the self-identified African-American recipients in the study

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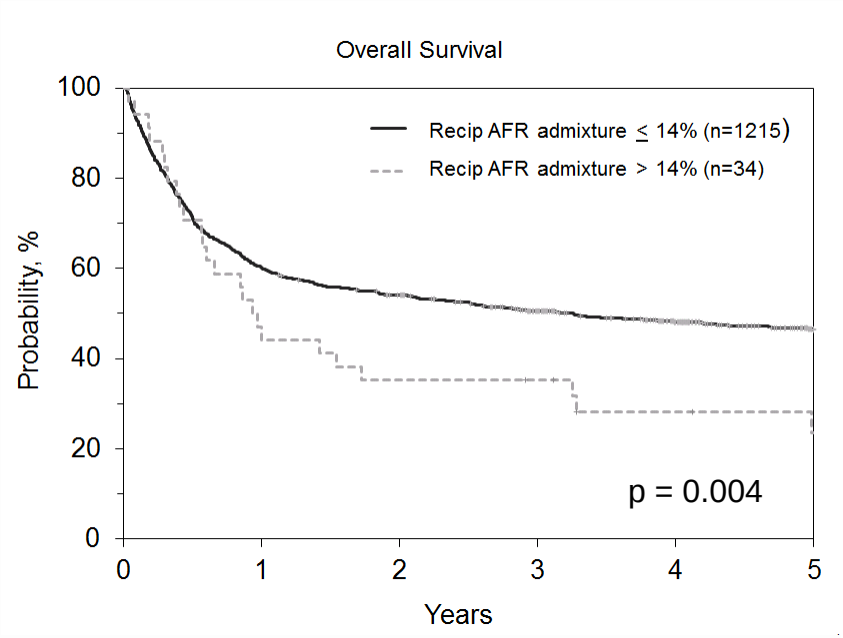
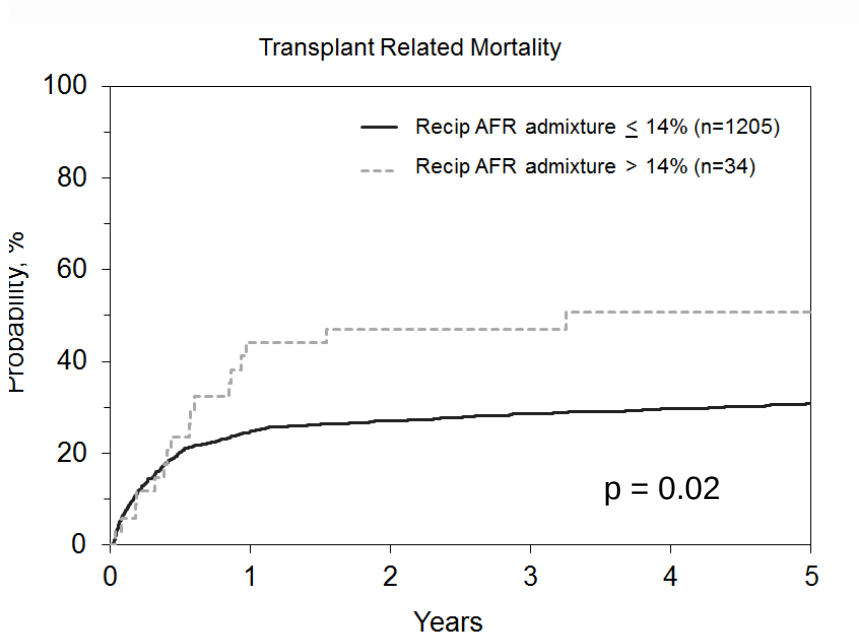
Recipient admixture





p – values shown for 5-year OS and TRM.

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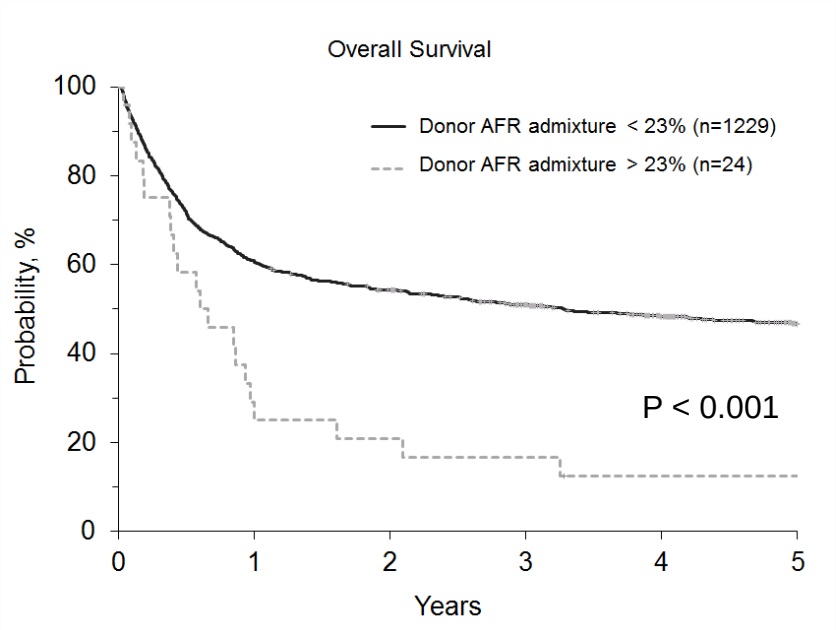
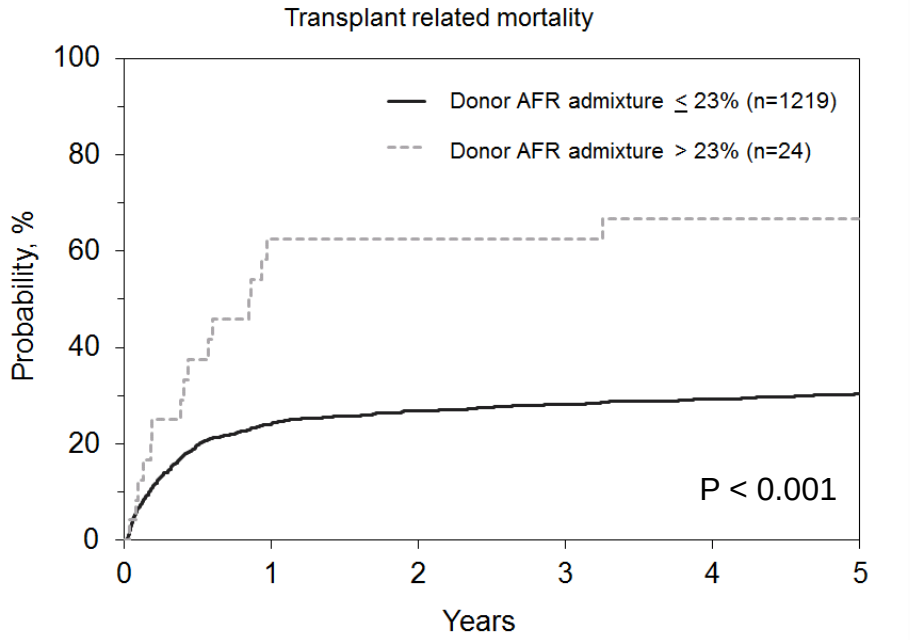
Donor admixture

- Similar effects were seen in the multivariate analysis when admixture was analyzed as a continuous variable but not categorical
- We tested for a cut-point for the donor AFR admixture.
- The optimal cut point was >23% AFR admixture
- This included 2% of the study population (N=24 donor) and 89% of the self-identified African-American donors

Donor admixture





p – values shown for 5-year OS and TRM.

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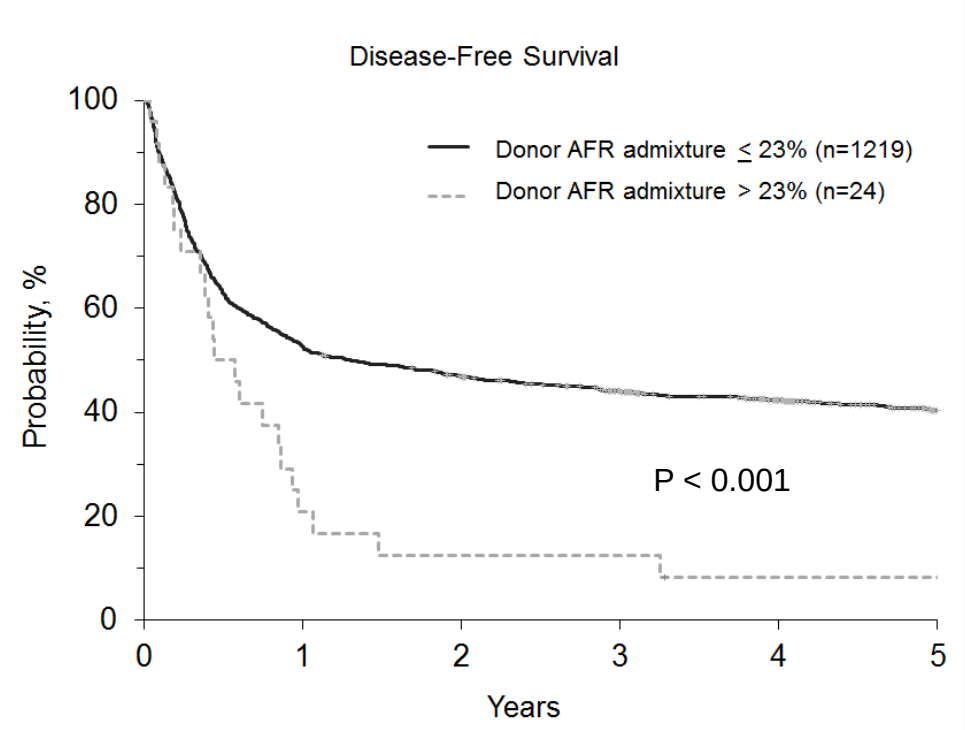
Donor admixture



p – value shown for 5-year DFS.

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Putting it all together

- Investigated effect of genetic ancestry and donor/recipient genetic distance on HCT outcome
- No association was found between genetic distance and outcome
- Increased *recipient* AFR admixture was found to have an adverse effect on OS and TRM
- Increased *donor* AFR admixture was found to have an adverse effect on OS, DFS and TRM

Donor Genetic Driver? **Hard to tell**

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Race, ethnicity and genetics

- The average AFR admixture in self-identified African-Americans in the US ranges from 73% to 93% (Bryc et al., AJHG 2015)
- Admixture thresholds (>14% and >23%) in this study are cohort driven, and **ARE NOT** indicative of African-American race (or any other group).
- AFR admixture of >14% can exist in several Latino populations or multiethnic individuals.
- However, high-risk groups included 89% self-identified African-American individuals. This was mainly driven by the study design.

Impact on HCT - Caution

- One should be careful when considering the findings of this study in selecting 10/10 matched donors for HCT, especially if multiple 10/10 donors of different race/ethnicity are available and the recipient is of AFA race.

- While the findings are in favor of selecting a non-AFA donor, the sample size driving these findings is NOT sufficiently large to settle this issue. Further analysis is required to validate these findings.

Study limitations

- Cohort 10/10 HLA allele-matched URD transplants, therefore a small subset of individuals was of non-CAU race/ethnicity.
- A larger, more diverse sample could help validate our findings
- The 10/10 HLA allele-matched selection criteria raised the odds of race-matched donor-recipient pairs.
- Expanding the study to mismatched transplants could increase the diversity in the sample race groups and race/ethnic match patterns.

Messages

- Genetic ancestry matters
- Self-identified race is complicated and occasionally misleading
- We need to collect race information in more detailed and consistent ways
- Transplant outcomes are affected by ancestry
- More work and bigger, more diverse cohorts are needed to investigate the effect on outcomes

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Evaluation Reminder

Please complete the Council Meeting 2017 evaluation in order to receive continuing education credits and to provide suggestions for future topics.

We appreciate your feedback!