2018 Donor and Cord Blood Selection Guidelines

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NATIONAL MARROW DONOR PROGRAM®

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Disclosures

The following faculty and planning committee staff have the following financial disclosures:

Name	Institution	Disclosure
Bernadette Anton	NMDP/Be The Match	None
Jason Dehn	NMDP/Be The Match	None
Janelle Olson	NMDP/Be The Match	None
Bronwen Shaw	CIBMTR	None

Objectives (part 1)

- ✓ Describe HLA typing considerations for patient and donor search
- ✓ Describe strategies to inform the search and time to transplant

History

- 2003 (Hurley et al, BBMT)
- 2008 (Bray et al, BBMT)
- 2012 (Spellman, Blood)
- 2018 (Dehn, TBD?)

A perspective on the selection of unrelated donors and cord blood units for transplantation

Stephen R. Spellman,[1] Mary Eapen,[2] Brent R. Logan,[3] Carlheinz Mueller,[4] Pablo Rubinstein,[5] Michelle I. Setterholm,[6] Ann E. Woolfrey,[7] Mary M. Horowitz,[2] Dennis L. Confer,[6] and Carolyn K. Hurley[8]

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Selection of a suitable graft for allogeneic hematopoietic stem cell transplantation involves consideration of both donor and recipient characteristics. Of primary importance is sufficient donor-recipient HLA matching to ensure engraftment and acceptable rates of GVHD. In this Perspective, the National Marrow Donor Program and the Center for International Blood and Marrow Transplant Research provide guidelines, based on large studies correlating graft characteristics with clinical transplantation outcomes, on appropriate typing strategies and matching criteria for unrelated adult donor and cord blood graft selection. (*Blood.* 2012;120(2):259-265)

Introduction

The National Marrow Donor Program (NMDP) facilitates identification and procurement of hematopoietic stem cell grafts for transplantation. The Center for International Blood and Marrow Transplant Research (CIBMTR) is a research affiliation of the NMDP and the Medical College of Wisconsin. The guidelines herein, which update those previously published in 2003[1] and in 2008,[2] are based on current and relevant data supporting optimal HLA donor-recipient matching criteria and other factors affecting graft selection.

HLA matching

What literature discusses the impact of HLA on hematopoietic cell transplantation outcome?

apply. One caveat to this is that graft-versus-tumor effects that offset some of the mortality associated with GVHD after transplantation for malignancies are of no benefit when treating nonmalignant diseases.

Which is the most important outcome to consider?

The outcome of primary importance after transplantation is survival. Survival is determined by multiple factors. Pretransplantation factors include donor-recipient HLA matching, graft cell-dose (particularly for umbilical cord blood grafts), recipient cytomegalovirus seropositivity, performance score, disease, and disease status. Posttransplantation factors include acute and chronic GVHD, infections, organ toxicity, and recurrent and second malignant neoplasms. When transplantation is being considered as a treatment option, early referral for transplantation, ensuring the recipient has

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Methods

- NMDP Histocompatibility Advisory Group
  - Key opinion leaders
  - Laboratory HLA science expertise
  - Clinical transplant expertise

- Focus on large registry studies and other evidence based research

HLA Typing Considerations: Patient and Donor

- Required: High resolution HLA-A, B, C, DRB1, DPB1
  - DNA based methods

- Recommended: HLA-DRB3/4/5, DQB1
  - Select among similar donors
  - Understand for HLA sensitized patient

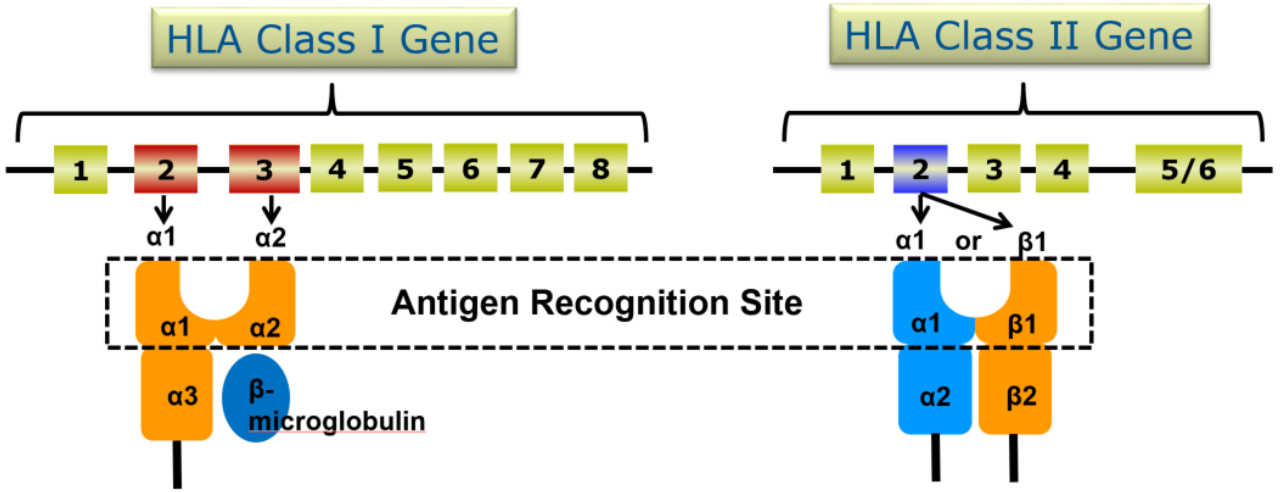
HLA Typing Considerations: Cord Blood

- Required: High resolution HLA-A, B, C, DRB1
  - DNA based methods

- NMDP CT pkg: includes HLA-DQB1+ DPB1

What is HR typing?

- Discriminates among protein differences
- Sequence differences inside the antigen recognition domain/site (ARD)
  - ‘G’ groups are identical
- Most current data suggests amino acid sequence outside the ARD does not impact allorecognition



URD Search: Considerations

- Patient Race/Ethnic group(s)
- HLA commonality
- Size of the donor population of interest
- Time to Transplant
- Acceptable stem cell products: 8/8 vs mismatched vs CBU vs Haplo

URD Search: Available Tools

- Search Prognosis Tool (http://search-prognosis.b12x.org)
  - Immediate assessment of likely outcome (8/8 or 7/8) based on patient race and HLA commonality

Individual Race Calculations

Classifier Table Information

The table below shows the search prognosis spread and scores for each available race. The Population Probability column is based on the selections above.

Population	Population Probability	Good	Fair	Poor	Search Prognosis
CAU	88.4%	99.6%	0.4%	0%	Good
HIS	8.4%	82.2%	16.1%	1.7%	Good
AFA	3.1%	71%	25.8%	3.1%	Good
API	0.1%	37.6%	50.8%	11.6%	Fair

URD Search: Available Tools

HapLogic

- Considers:
  - Patient Race/Ethnic group(s)
  - HLA commonality
  - Provides likelihood of acceptable stem cell products: 8/8 vs ≤7/8 vs CBU
  - Future application to all worldwide donors

URD Search: Time to Tx

- Early evaluation of case and discussion with clinical team
- Consider alternate products including concurrent searching early (URD + CB)
- Don’t wait for donors to be recruited!
- Ask NMDP for help
  - Search strategy
  - FastTrack search
  - HLA typing

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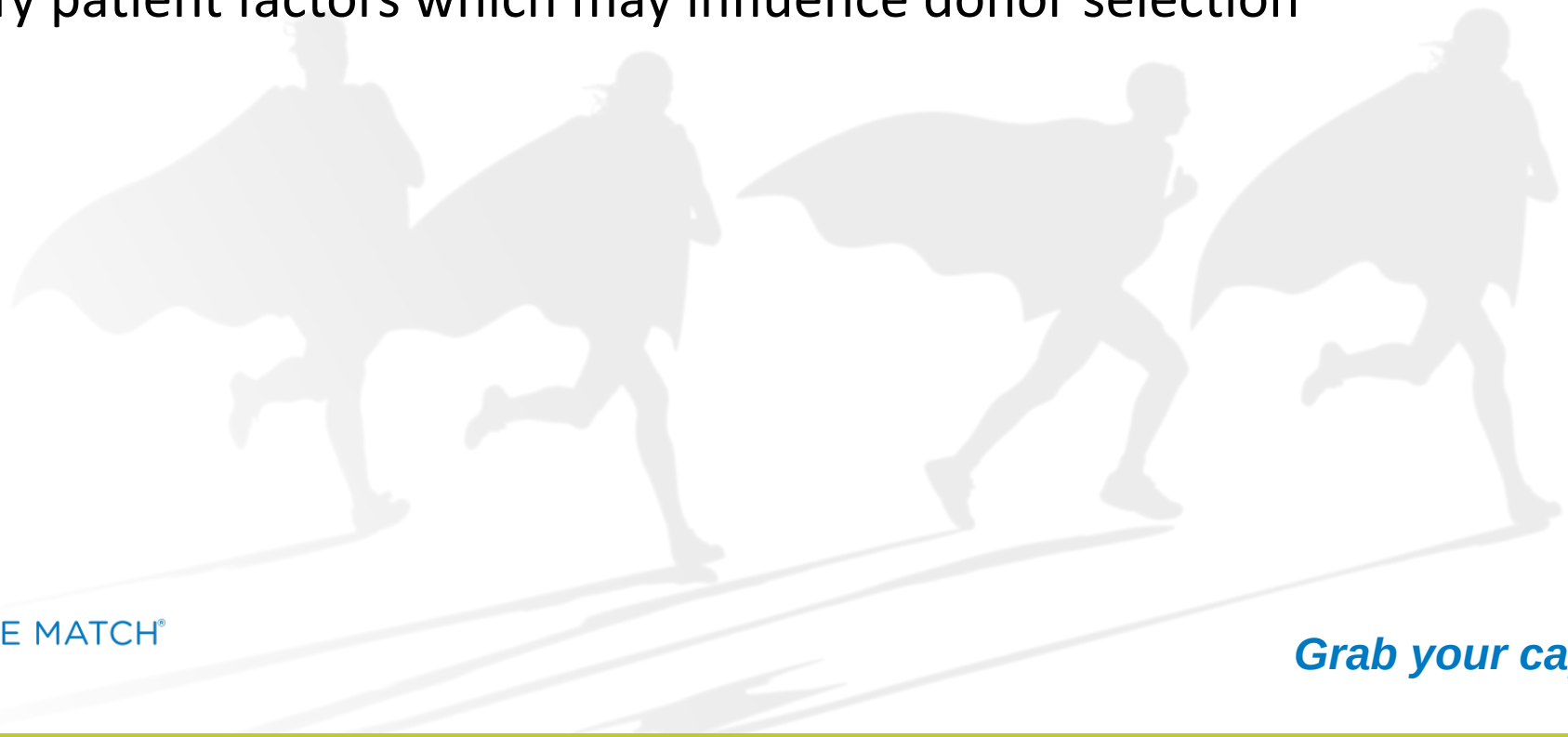
Objectives (part 2)

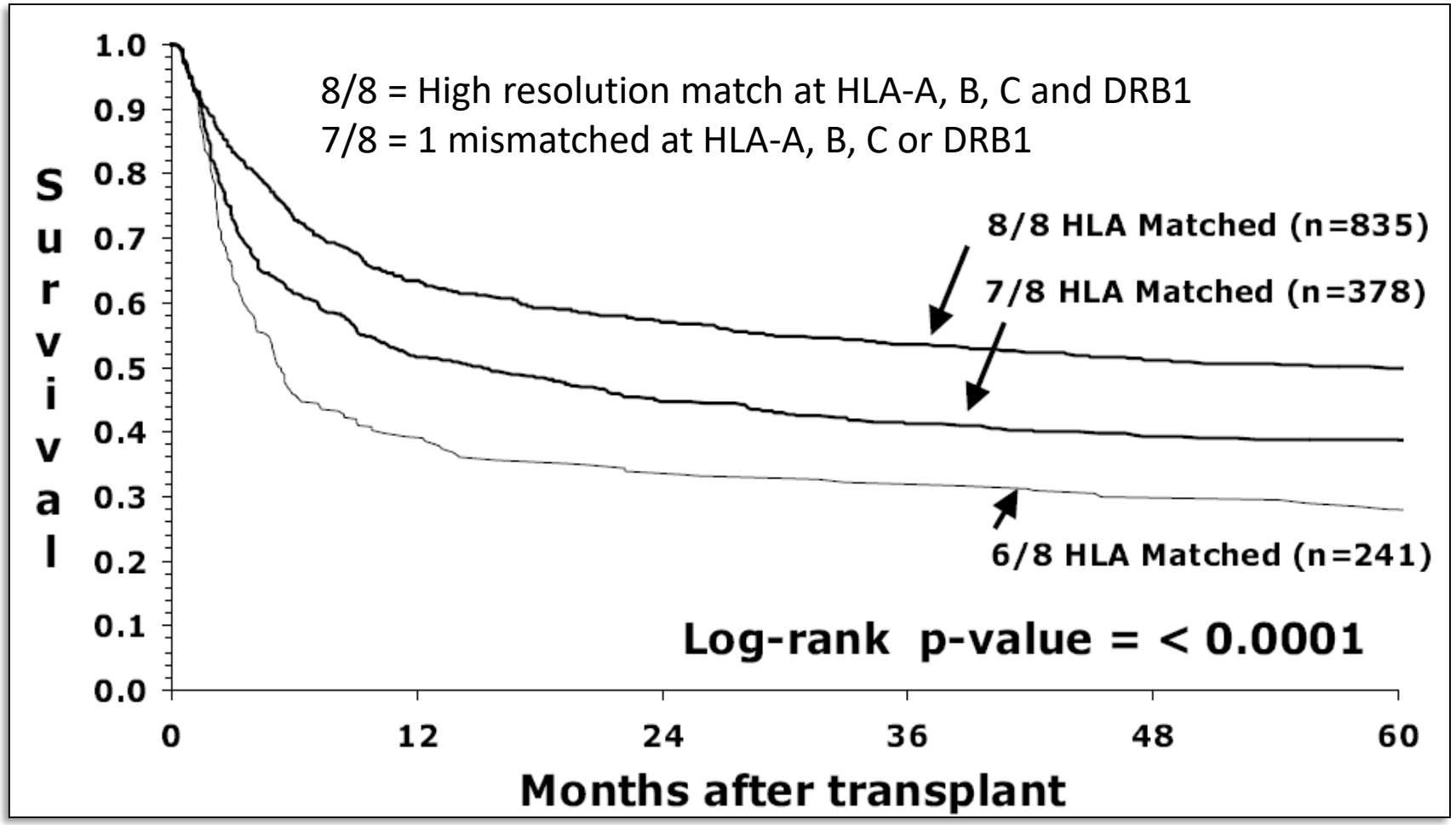
- ✓ Recognize factors which are important in the selection of unrelated donors
- ✓ Identify patient factors which may influence donor selection



Donor Selection

	Multiple HLA-A, -B, -C, -DRB1 (8/8) HLA matched unrelated donors available	8/8 match unavailable; multiple 7/8 unrelated donors available
1. Resolution of typing HLA-A,-B,-C,-DRB1	High resolution, matches for antigen recognition domains	High resolution, matches for antigen recognition domains for 7 matched alleles Select HLA-C*03:03 vs C*03:04 mismatch, if present; No other preference for mismatched loci (HLA-A/B/C/DRB1) or other allele combinations
2. Donor age	Select donors of younger age	Select donors of younger age
3. Permissive mismatching HLA-DPB1	Select matched/permissive DPB1 mismatch based on the algorithm developed by Crivello et al[44] (http://www.ebi.ac.uk/cgi-bin/ipd/imgt/hla/dpb_v2.cgi)	Select matched/permissive DPB1 mismatch based on the algorithm developed by Crivello et al[44] (http://www.ebi.ac.uk/cgi-bin/ipd/imgt/hla/dpb_v2.cgi)
4. Matching HLA-DRB3/4/5, -DQB1	Minimize mismatches at additional loci	Minimize mismatches at additional loci
5. Vector of mismatch	N/A	Select donor with single allele mismatched at patient's homozygous locus (HLA-A/B/C/DRB1), if applicable
6. Donor-specific antibody (DSA) in patient	Avoid mismatches of allotypes targeted by DSA, including DPA1 and DQA1	Avoid mismatches involving allotypes targeted by DSA, including DPA1 and DQA1
7. Transplant center practice may differ in additional considerations to use in the selection among multiple donors equivalent for the characteristics above		

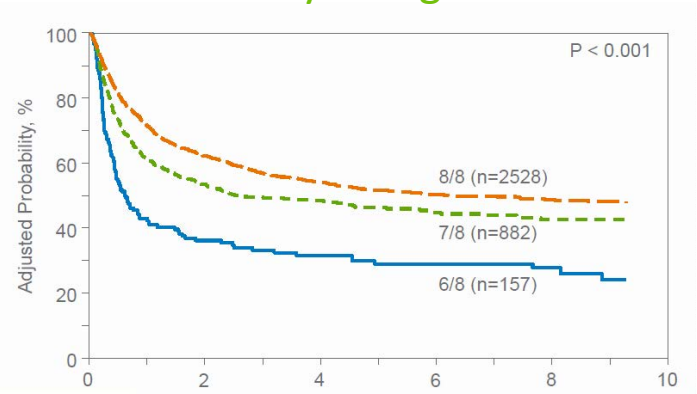
HLA impact on overall survival



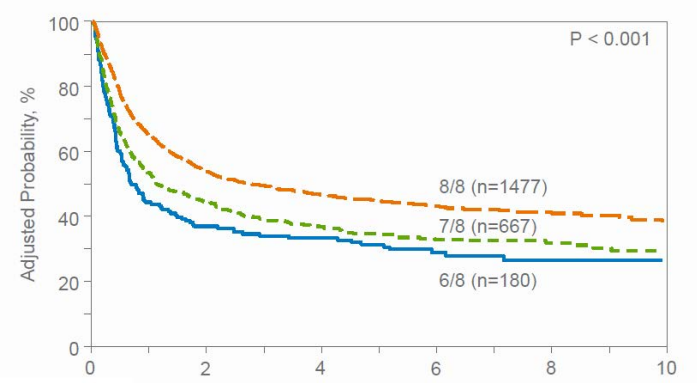
Lee et al., Blood 2007

Impact of HLA Matching varies by disease stage

Early - Stage

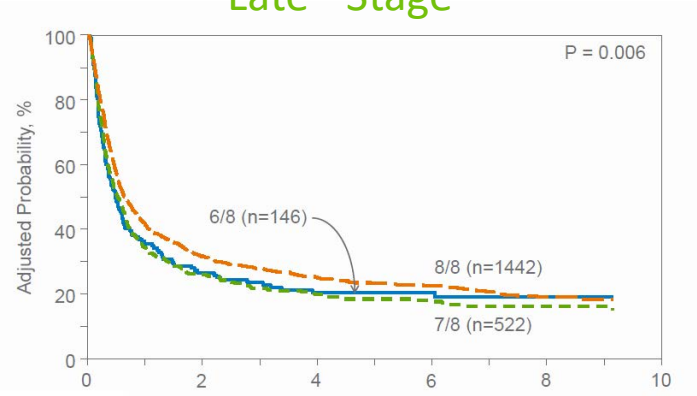


Intermediate - Stage



As before…..
benefits of HLA matching diminish as disease progresses

Late - Stage



Pidala et al., Blood 2014

Permissive HLA mismatch

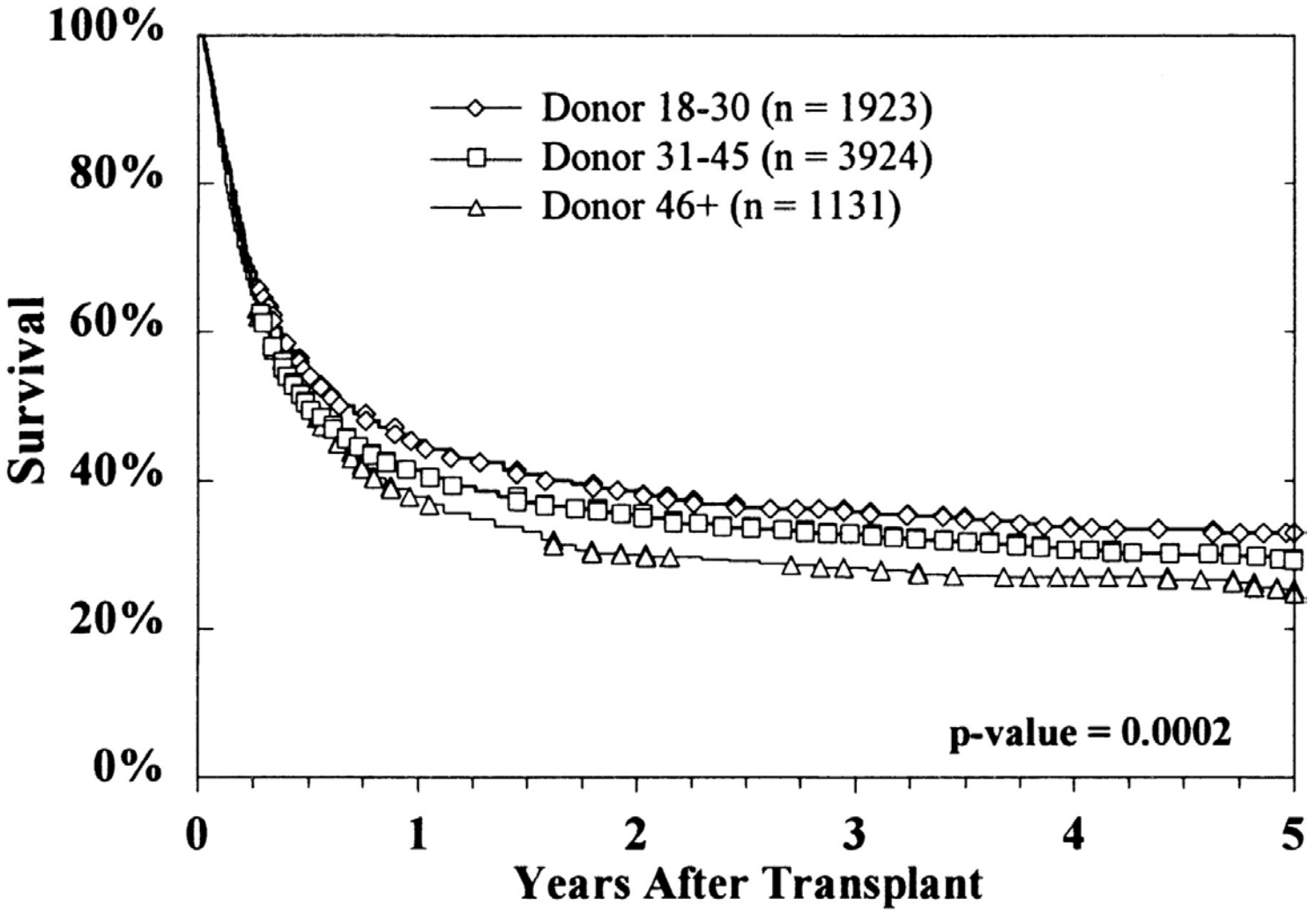
- C*03:03 vs C*03:04 mismatch (MM) DOES NOT elicit CTL responses (Oudshoorn, et. al. Human Immunology, 2002)

- Hypotheses:
  - C*03:03/03:04 is the predominant allele level MM in patients and donors with European ancestry
    - 69% of HLA-C MM in Lee, et al. Blood 2007 were C*03:03/03:04
  - C*03:03/03:04 MM is well tolerated in HCT
  - Other C-allele MM are as detrimental as C-antigen or HLA-A, B or DRB1 (other) MM

Validation: C*03:03/03:04 MM Permissive

Matching (8/8 baseline, N=5447)	RR (95% CI)	RR (95% CI)
03:03/03:04 mm (N=86)	1.1 (0.8-1.4)	0.98 (0.78-1.23)
Other C allele mm (N=74)	1.3 (1.0-1.8)	1.43 (1.06-1.92)
Other C Antigen mm (N=606)	1.4 (1.2-1.5)	1.37 (1.24-1.51)
Other non-C mm (N=1305)	1.2 (1.1-1.4)	1.30 (1.19-1.43)
	p<0.01	p<0.01
	Pidala Blood 2014	Fernandez-Viña Blood 2014

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



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

Donor Age: Kollman 2001

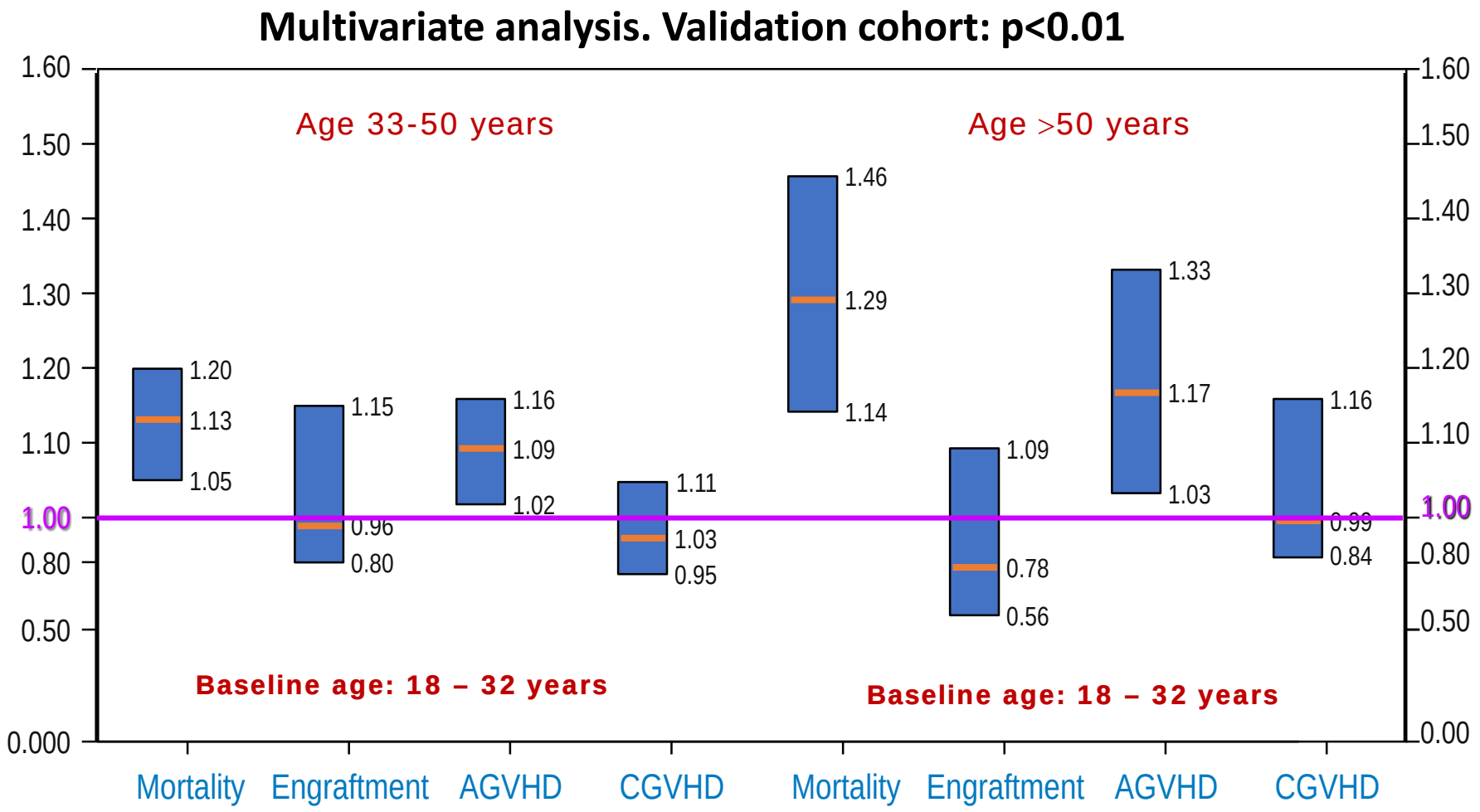
Proportional hazards regression models for grade III or IV acute graft-versus-host disease (GVHD) (n = 6978) and chronic GVHD (n = 4819 evaluable patients surviving at least 80 days)

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

blood

Donor Age: Kollman 2015



p<0.001.

Kollman, et al

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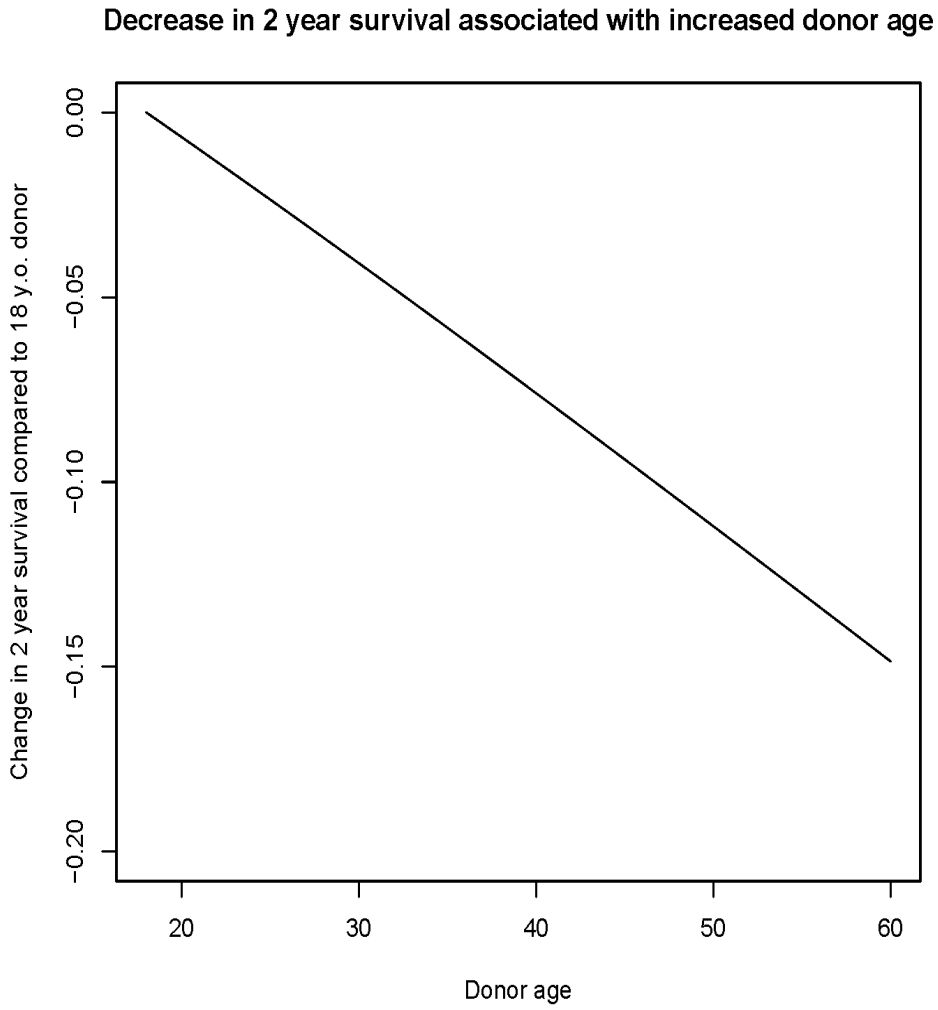
DEVELOPMENT AND VALIDATION OF A CLINICAL UNRELATED DONOR SELECTION SCORE

- Used existing validated data sets 1999-2011 (n=5952) all 8/8 matched
- Split into a training and testing cohort
- Factors which were significant in training set:
  - DPB1 TCE, Donor age, CMV match, ABO match significant for OS
- Validation failed to show same impact on OS
- Analysis redone with contemporary dataset 2012-2014 (n=4510)
  - No score validated
  - Only significant factor in training and testing set = younger donor age

DEVELOPMENT AND VALIDATION OF A CLINICAL UNRELATED DONOR SELECTION SCORE

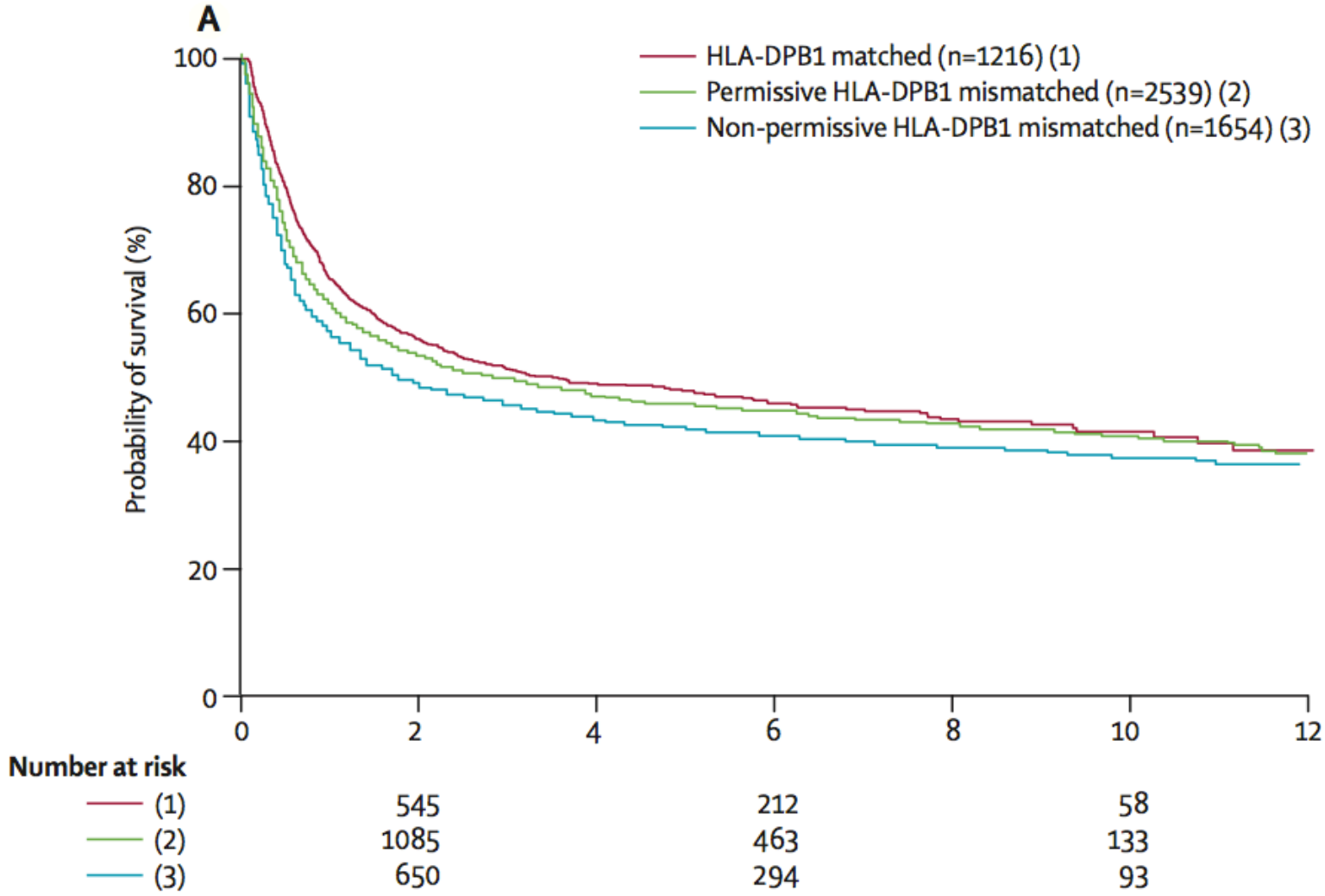


DPB1 TCE: Multivariate outcomes (10/10)

	HLA 10/10 match				
	Permissive HLA-DPB1 mismatch	HLA-DPB1 match		Non-permissive HLA-DPB1 mismatch	
		HR or OR	p value	HR or OR	p value
Overall mortality	1 (ref)	0·96 (0·87–1·06)	0·40	1·15 (1·05–1·25)	0·002
Non-relapse mortality	1 (ref)	0·86 (0·75–0·98)	0·03	1·28 (1·14–1·42)	<0·0001
Relapse*	1 (ref)	1·34 (1·17–1·54)	<0·0001	0·89 (0·77–1·02)	0·10
Grade 3–4 aGvHD	1 (ref)	0·84 (0·69–1·03)	0·09	1·31 (1·11–1·54)	0·001

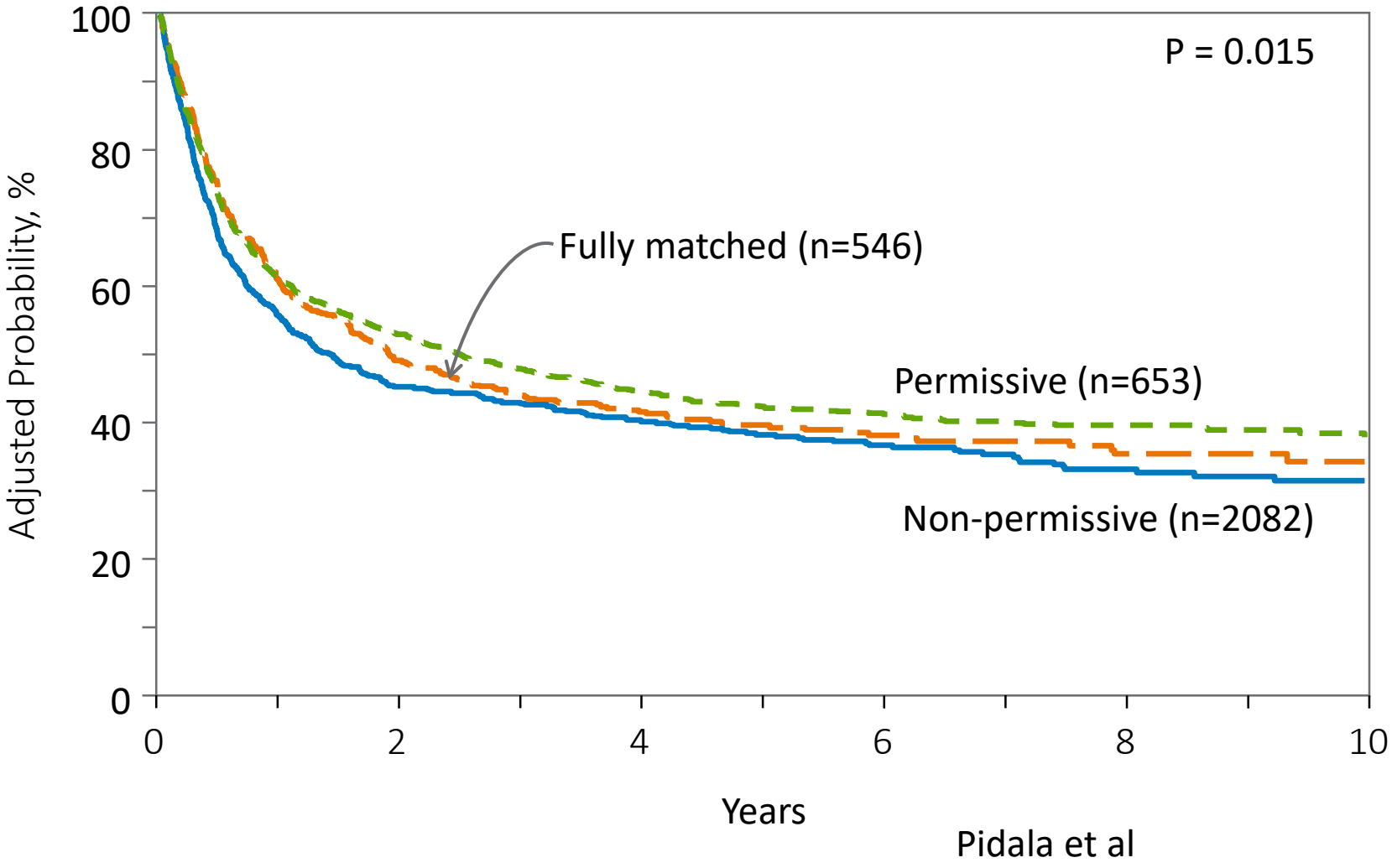
Fleischhauer&Shaw, 2012, Lancet Oncology

Overall survival



Fleischhauer&Shaw, 2012, Lancet Oncology

Validation: Benefit of Permissive DPB1 TCE mismatching on OS in 8/8



Pidala et al

HLA matching: Low expression Loci

- Low expression Loci
  - HLA-DQA1, -DQB1, DPA1, -DPB1, DRB3/4/5
- 3853, 1988-2003, 30%<20, BM (95%)

- 8/8 matched: LEL mismatches not associated with any adverse outcome
- 7/8 matched: 3 or more mismatches may adversely affect clinical outcome

Fernández-Viña et al, 2013

Vector of mismatch (GvH vs HvG)

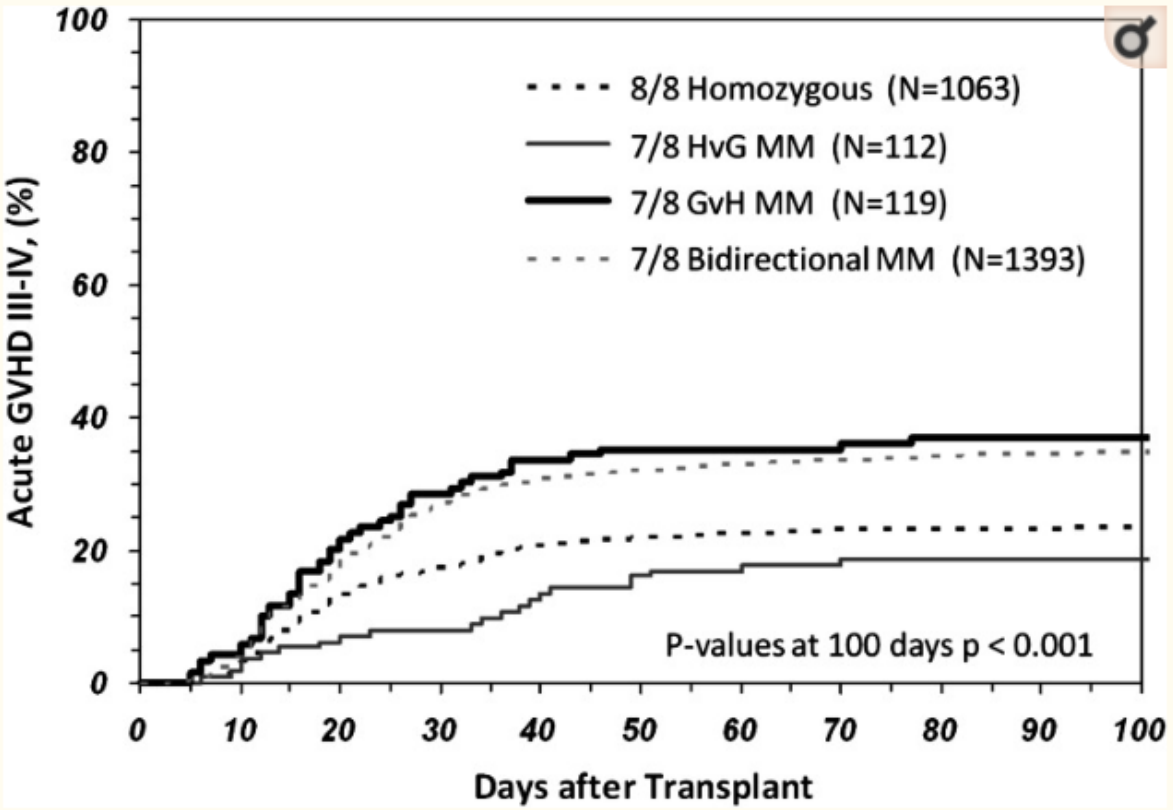


Figure 1

Cumulative incidence of acute GVHD grades III-IV during the first 100 days following a transplantation using an 8/8, 7/8 bidirectional MM, 7/8 GVH MM, or 7/8 HVG MM donor. Significant differences were observed between the 7/8 groups ($P = .0001$) and the 7/8 HVG group having a lower acute GVHD risk similar to the 8/8 group.

Hurley et al, Blood. 2013

Studies of DSA impact in different settings in AHSCT

Reference	Patients (*n*)	Stem cell source	Conditioning	Anti-HLA%	DSA%	Graft failure with/without DSA
Spellman et al.	115	Mismatched unrelated	RIC	ND	9	24 versus 1%
Ciurea et al.	592	10/10 and 9/10 unrelated	MAC or RIC	19.6	1.4	37.5 versus 2.7%

Table 3

Results of conditional logistic regression analysis evaluating the association of DSA directed against HLA class I and/or II and graft failure

	Odds ratio	95% confidence interval	*P*
Class I DSA	11.34	1.49-∞	.017
Class II DSA	12.00	1.46-551.97	.014
Class I and/or II DSA	22.84	3.57-∞	< .001

Morin-Zorman et al, Front Immunol. 2016; 7: 307.

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

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

Donor Selection

	Multiple HLA-A, -B, -C, -DRB1 (8/8) HLA matched unrelated donors available	8/8 match unavailable; multiple 7/8 unrelated donors available
1. Resolution of typing HLA-A,-B,-C,-DRB1	High resolution, matches for antigen recognition domains	High resolution, matches for antigen recognition domains for 7 matched alleles Select HLA-C*03:03 vs C*03:04 mismatch, if present; No other preference for mismatched loci (HLA-A/B/C/DRB1) or other allele combinations
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7. Transplant center practice may differ in additional considerations to use in the selection among multiple donors equivalent for the characteristics above		

Cord Blood Selection

developed by ASBMT CB Special Interest Group

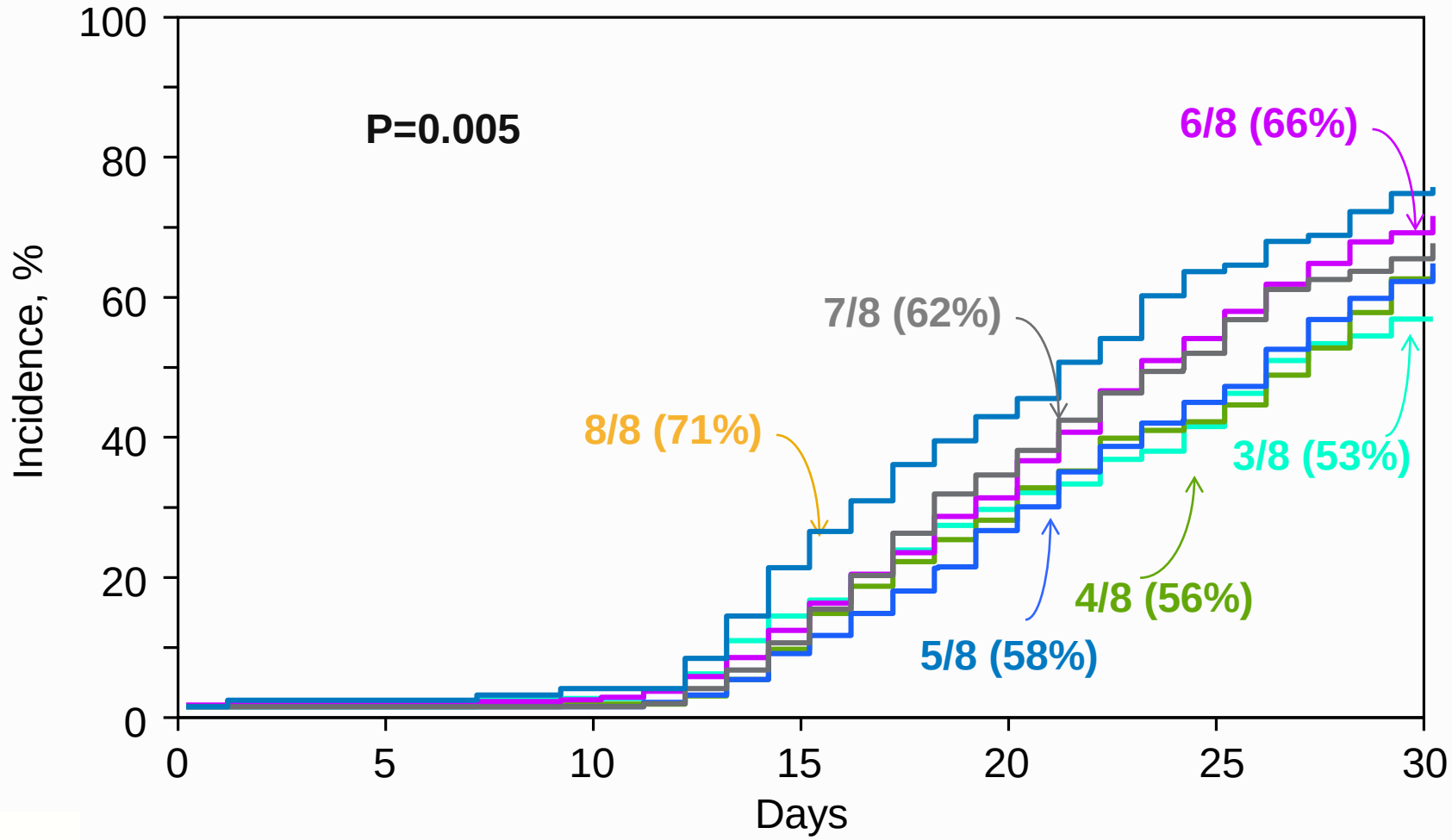
Bank Practices	Guidelines
Attached segment identity testing	Mandatory
Bank accreditation	Should be considered
Use of RBC replete units	Not recommended
Bank location	Either domestic or international units fulfilling selection criteria
Year of cryopreservation	More recent units may be linked to optimal banking practices depending on the bank
Processing/ Cryovolumes	Must be considered: automated processing with standard cryovolumes considered optimal eg ~25 ml/bag (or ~25 mls bag x 2 = ~ 50)

Cord Blood Selection

HLA-match	Guidelines
Resolution of HLA-typing	Minimum of 8 allele (HLA-A,-B,-C,-DRB1) for both patient & CB
Donor-recipient HLA-match	≥4/6 HLA-A,-B antigen, -DRB1 allele (Traditional Match) & ≥4/8 allele match (Some centers investigating use of 4/6 & 3/8 units if adequate dose)
Unit-unit HLA-match for DCB grafts	Not required
Avoidance of units against which recipient has DSA	Conflicting results in hematological malignancies; Discuss with laboratory Avoid if non-malignant diagnosis

Malignant diseases: Neutrophil Recovery

- Allele-level Matched at A, B, C, DRB1 -



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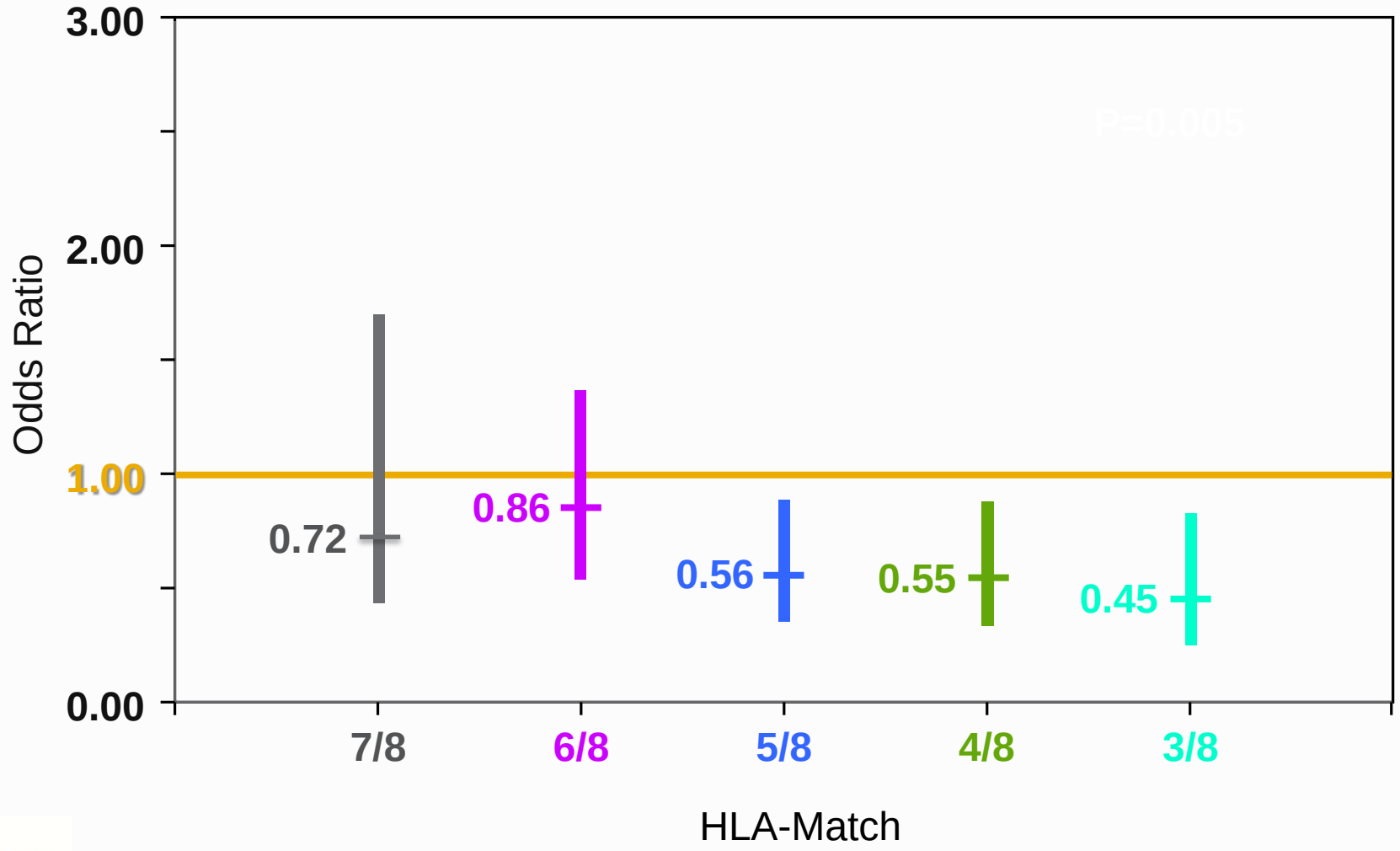
Eapen M et al; Blood 2014

eurocord

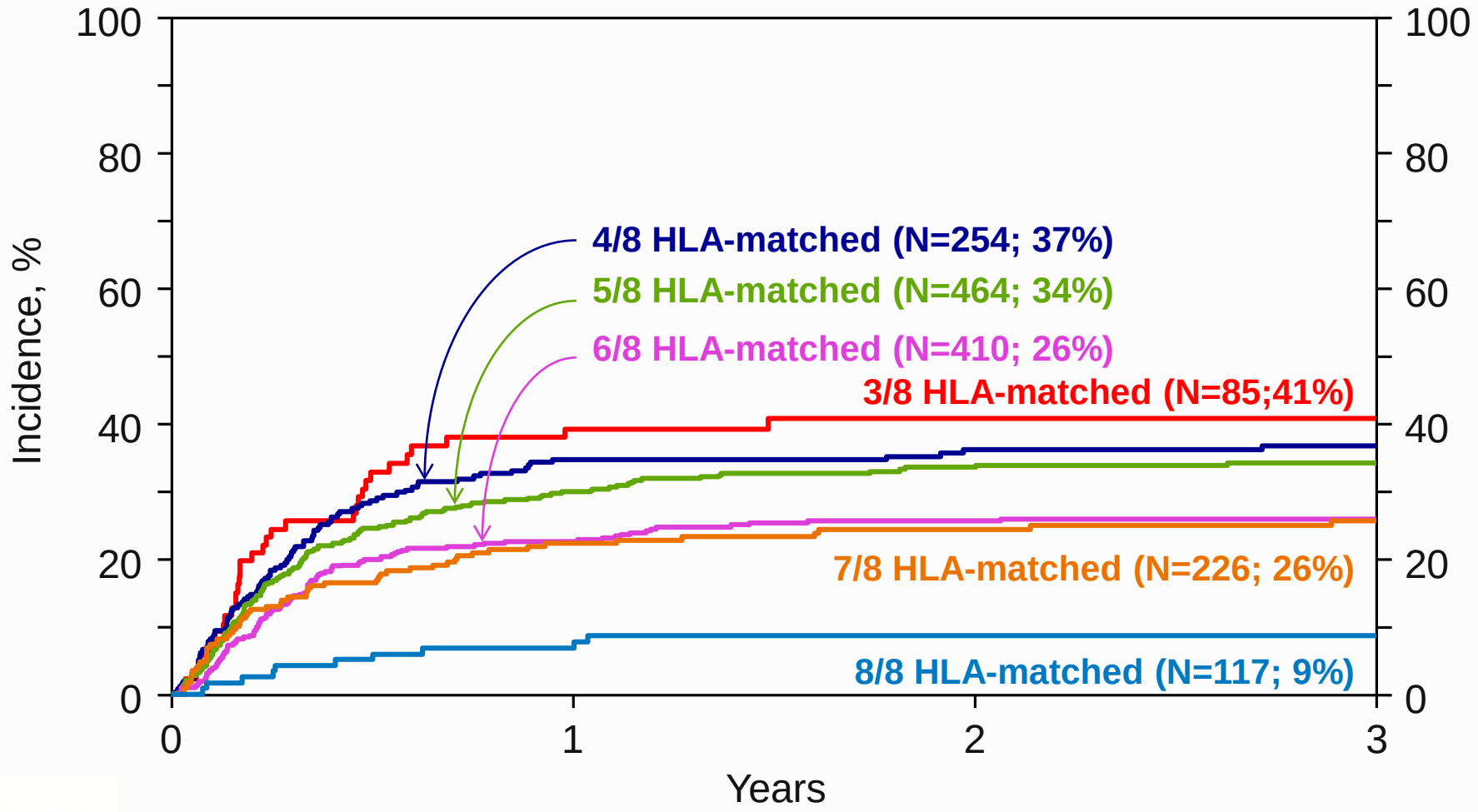
Neutrophil Recovery

- Allele-level Matched at A, B, C, DRB1 -



Eapen M et al; Blood 2014

Non-Relapse Mortality



Eapen M et al; Blood 2014

Non-Relapse Mortality

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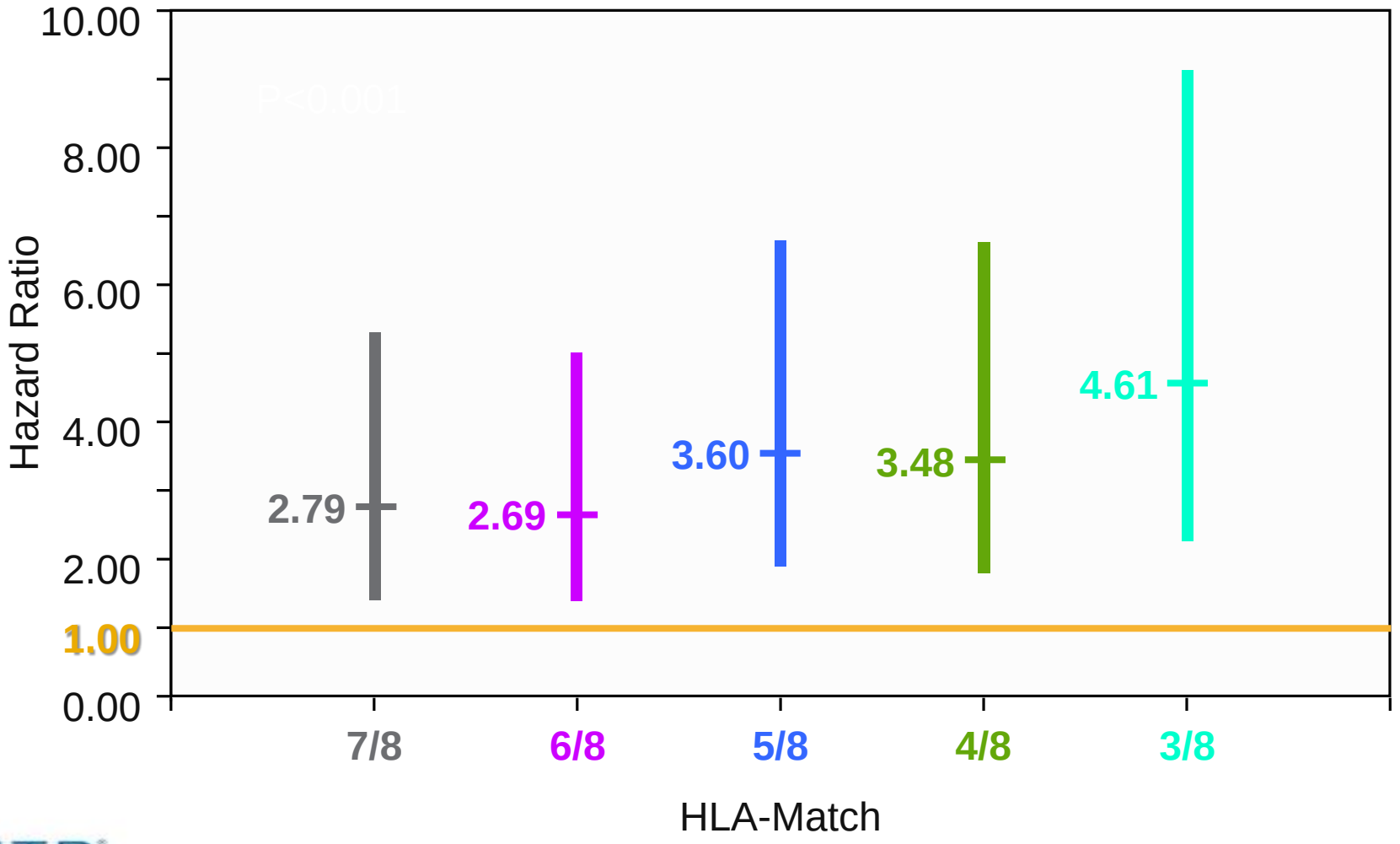

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Eapen M et al; Blood 2014

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Non-Relapse Mortality

- Effect of mismatch at single HLA-locus -

	HR	P-value
HLA-A match vs. mismatch 117 vs. 117	3.05	0.002
HLA-B match vs. mismatch 31 vs. 117	1.26	0.72
HLA-C match vs. mismatch 40 vs. 117	3.04	0.01
HLA-DRB1 match vs. mismatch 66 vs. 117	2.93	0.005

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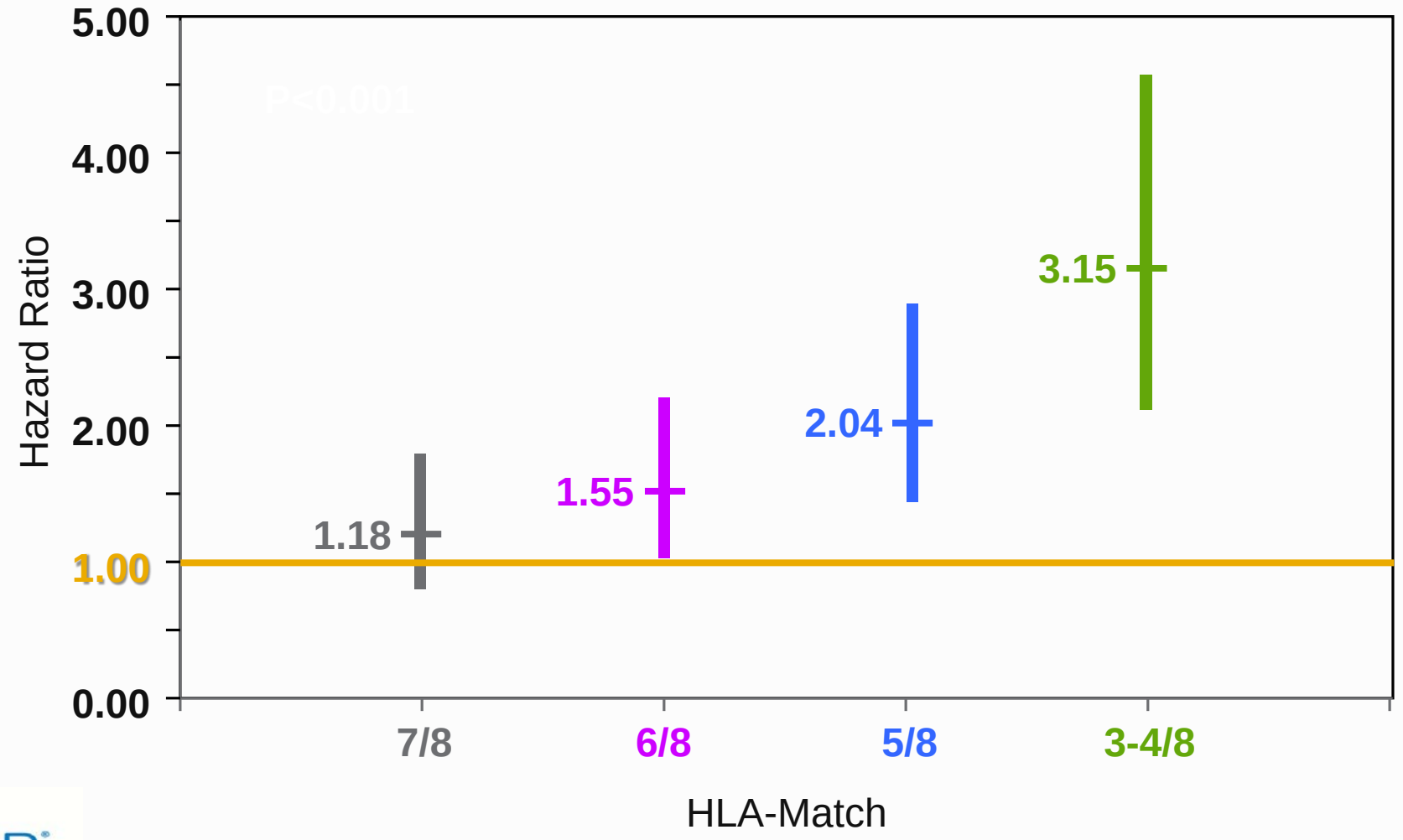
Eapen M et al; Blood 2014

eurocord

Non-malignant diseases: Overall Mortality

- Allele-level Matched at A, B, C, DRB1 -



Eapen M et al; Lancet Haematol 2017

Cord Blood Selection

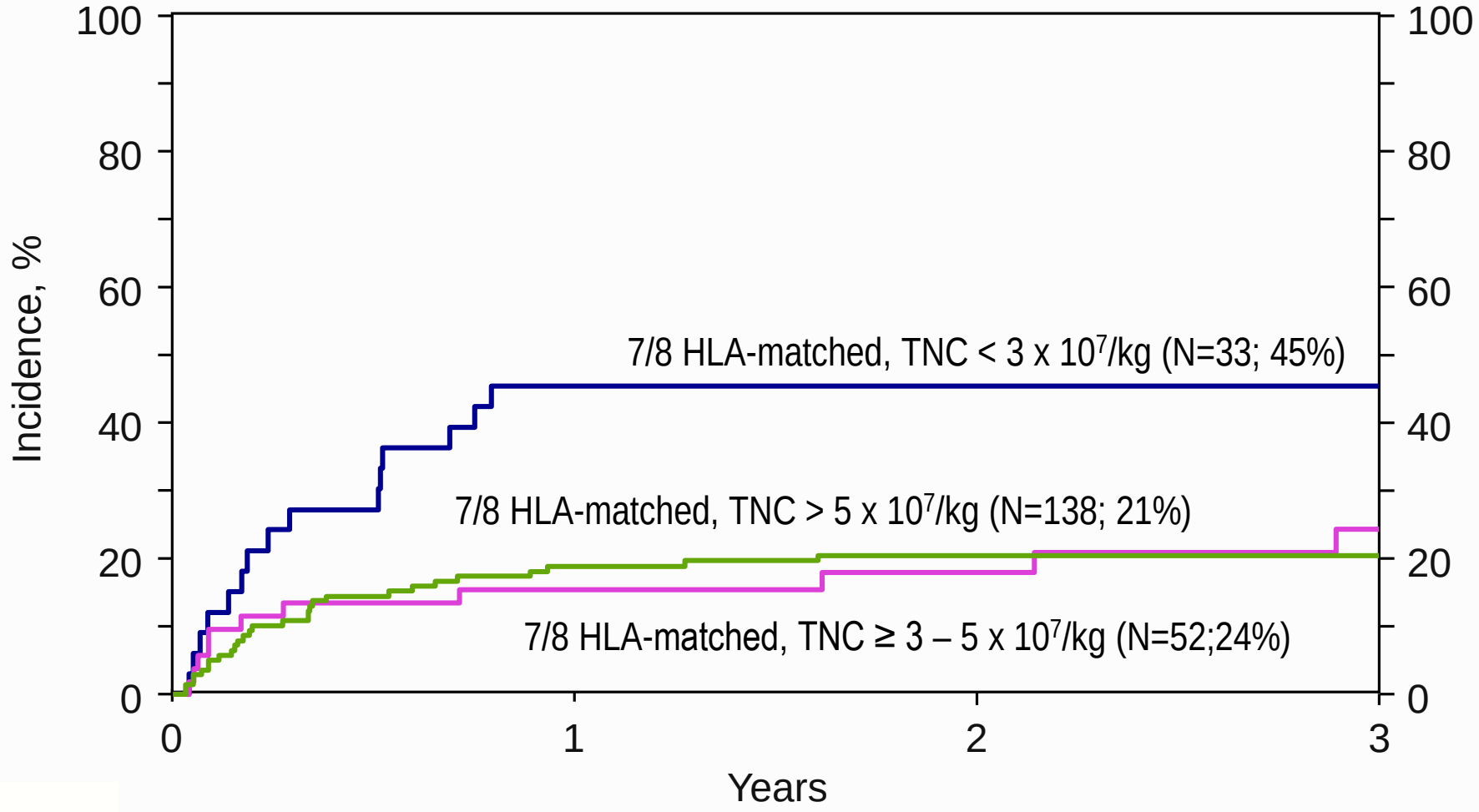
Cryopreserved Cell Dose	Guidelines
Single unit CBT: Minimum dose/ kg	TNC ≥2.5 x 10^7/kg & CD34+ cells ≥1.5 x 10^5/kg (Some centers recommend higher CD34+ dose as minimum)
Double unit CBT: Minimum dose/ kg/ unit	TNC ≥1.5 x 10^7/kg for each unit & CD34+ cells ≥1.0 x 10^5/kg for each unit (Some centers recommend higher CD34+ doses for each unit as minimum)

CB Unit Selection

Criteria	Boston	Duke	FHCRC	MDACC	MSKCC	U of MN
Resolution of HLA-typing	8-allele HLA-A, -B, -C, -DRB1					
Donor-recipient HLA-match	≥ 4/6 alleles	Traditional ≥ 4/6 & ≥ 3/8 alleles	Traditional ≥ 4/6		Traditional ≥ 4/6 & ≥ 3/8 alleles	Traditional ≥ 4/6 (& 8 allele)
Cell dose/kg: *single* unit	Singles not done	TNC ≥ 2.5				TNC ≥ 2.5 if ≥ 5-6/6 & ≥ 5.0 if 4/6. (CD34+ considered).
		CD34+ ≥ 1.5	CD34+ ≥ 2	CD34+ ≥ 1.0	CD34+ ≥ 1.5	
Cell dose/kg/unit: *double* unit	TNC ≥ 1.5/ unit	TNC ≥ 1.5/ unit				
		CD34+ ≥ 1.0/ unit	CD34+ ≥ 2.0/ unit	CD34+ ≥ 1.0	CD34+ ≥ 1.0/ unit	CD34+ considered.

8 allele match based selection. CD34+ dose universally considered. Dose 1st, match 2nd. Can use highly mismatched units. Doubles in wide use for adults. Definition of adequate single unclear.

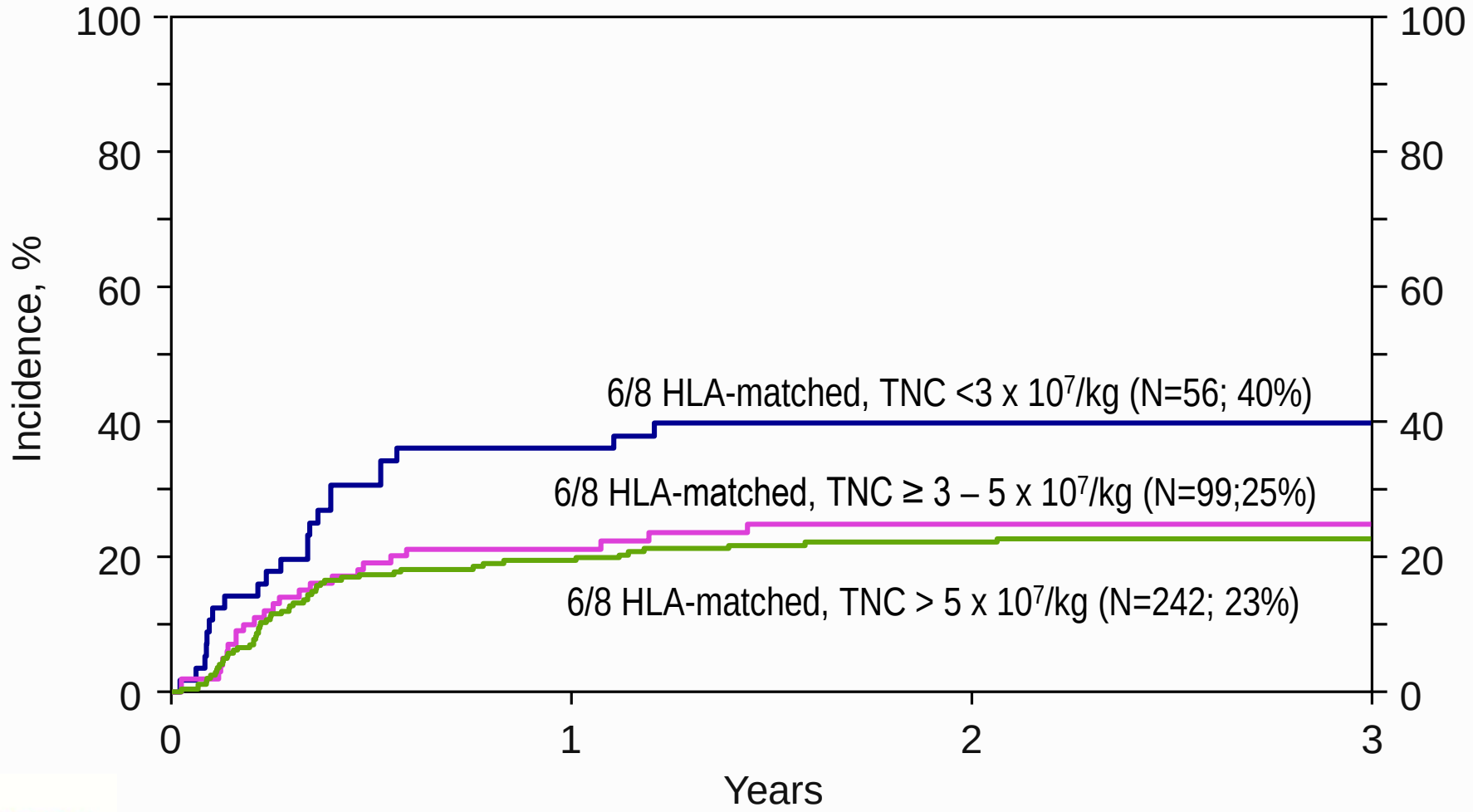
Can cell dose compensate for HLA mismatch: Non Relapse Mortality - Total Nucleated Cell Dose -



Eapen M et al; Blood 2014

Non Relapse Mortality

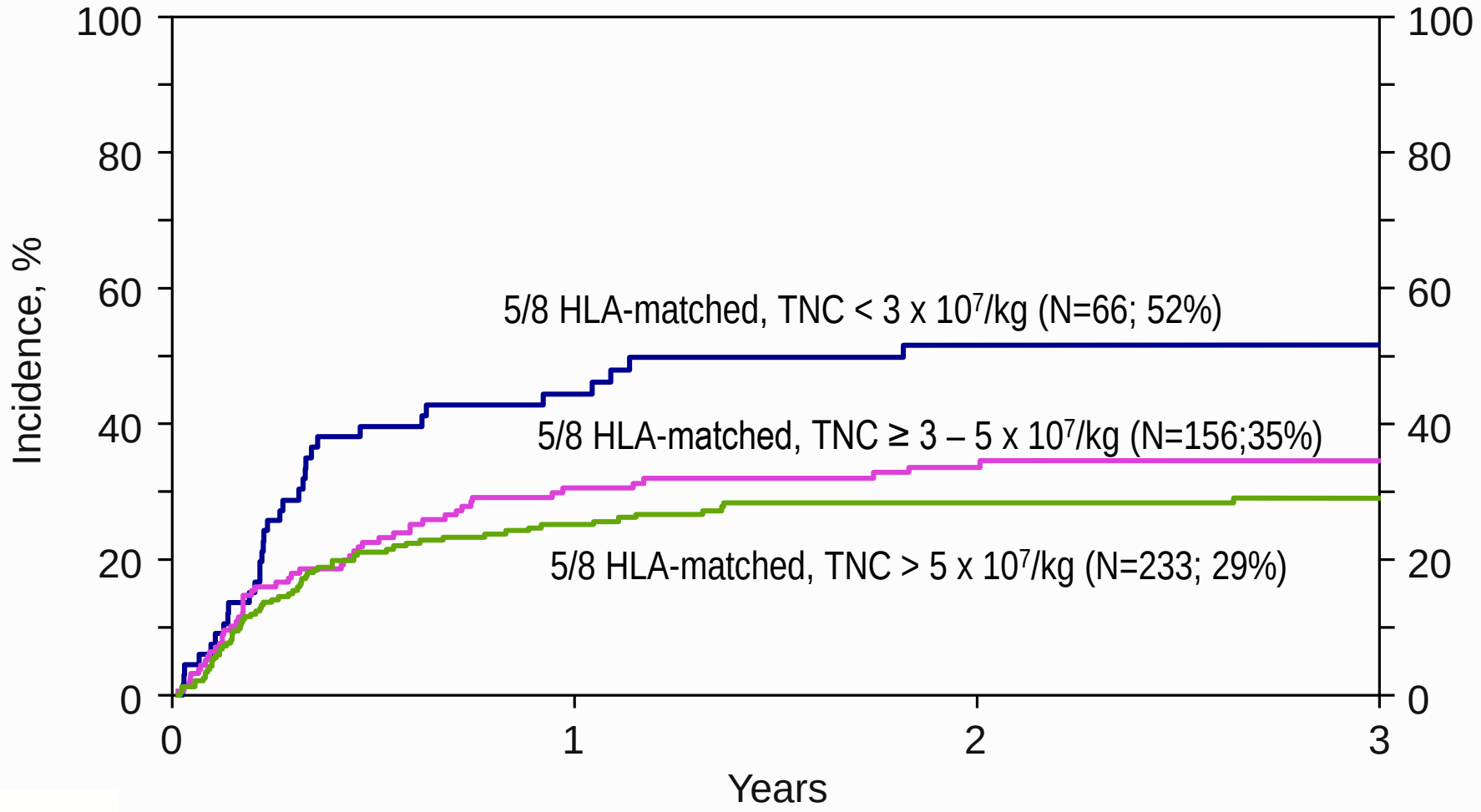
- Total Nucleated Cell Dose -



Eapen M et al; Blood 2014

Non Relapse Mortality

- Total Nucleated Cell Dose -



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