Trends in Graft Sources for Allogeneic Hematopoietic Stem Cell Transplantation (HCT): Everyone Has a Donor

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CIBMTR, Medical College of Wisconsin
September, 2016

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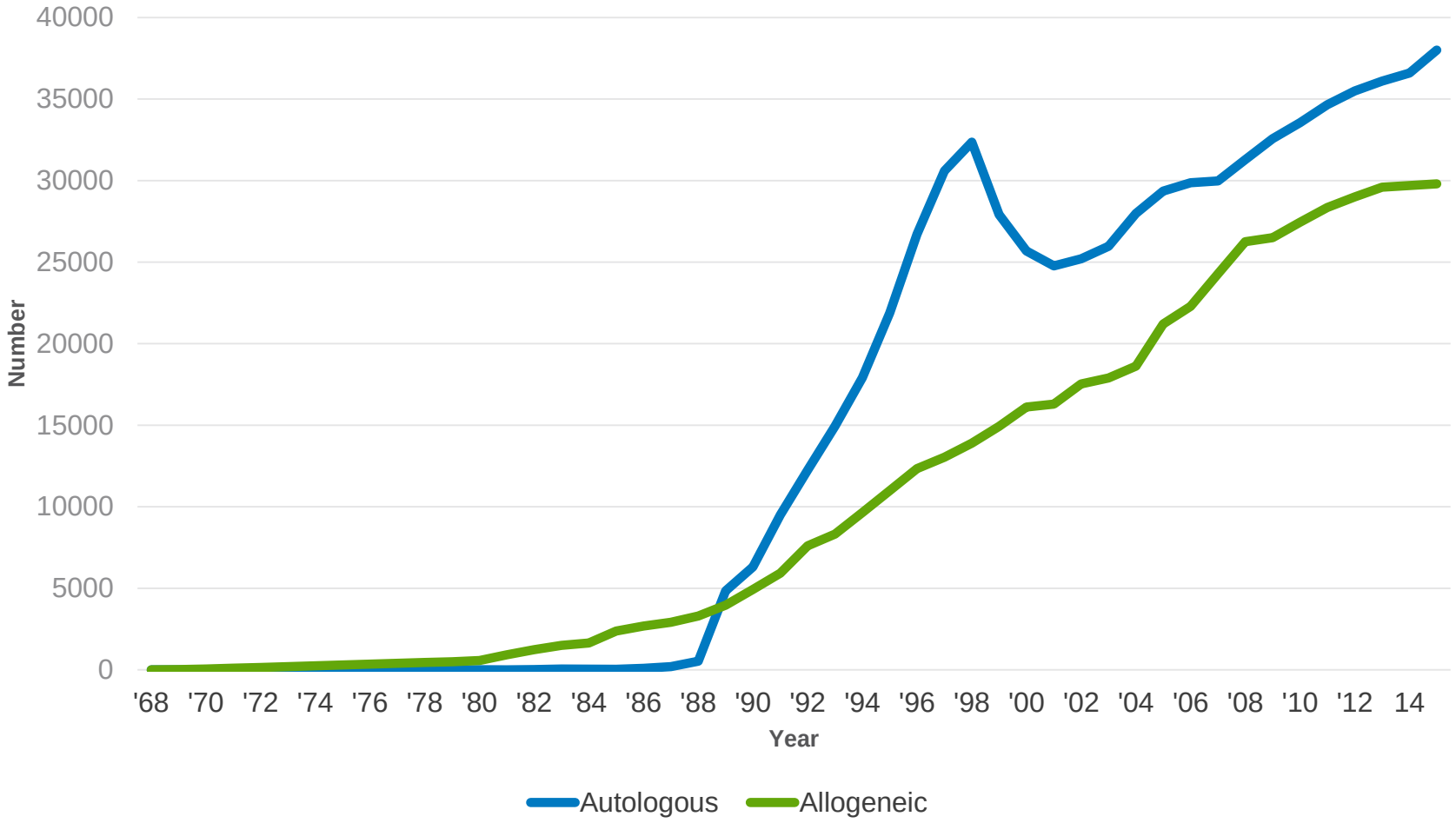
A research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin

Transplant Activity Worldwide1968-2015: increased use of both autologous and allogeneic HCT



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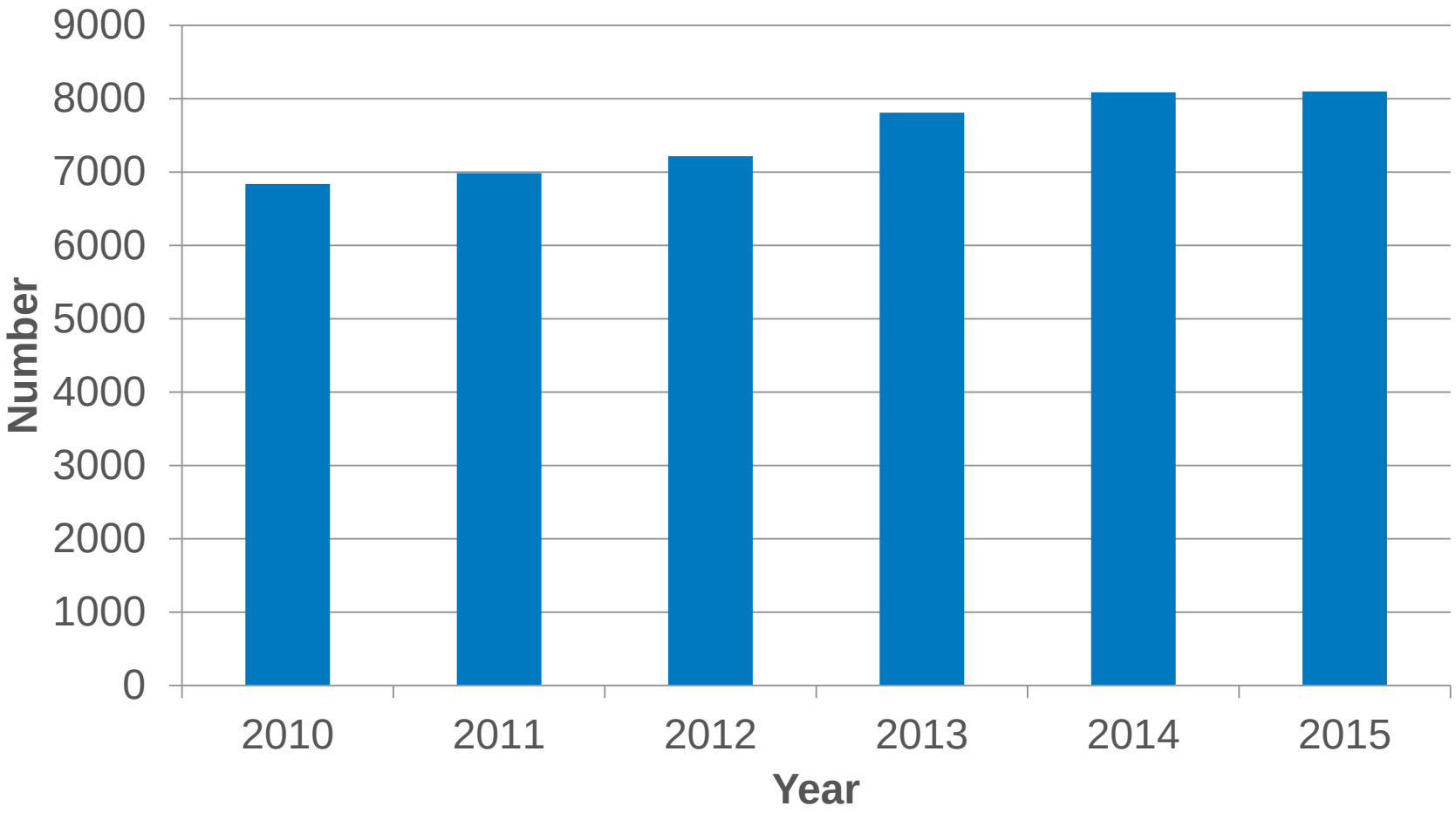
Number of First Allogeneic HCTs in the US By Year



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CIBMTR, unpublished data

Reasons for Increased Use

- Better outcomes
- Expanding Indications: MDS, follicular lymphoma, myeloma
- Expanding Age Range: up to 75 for both autos and allos
- Expanding Donor Availability

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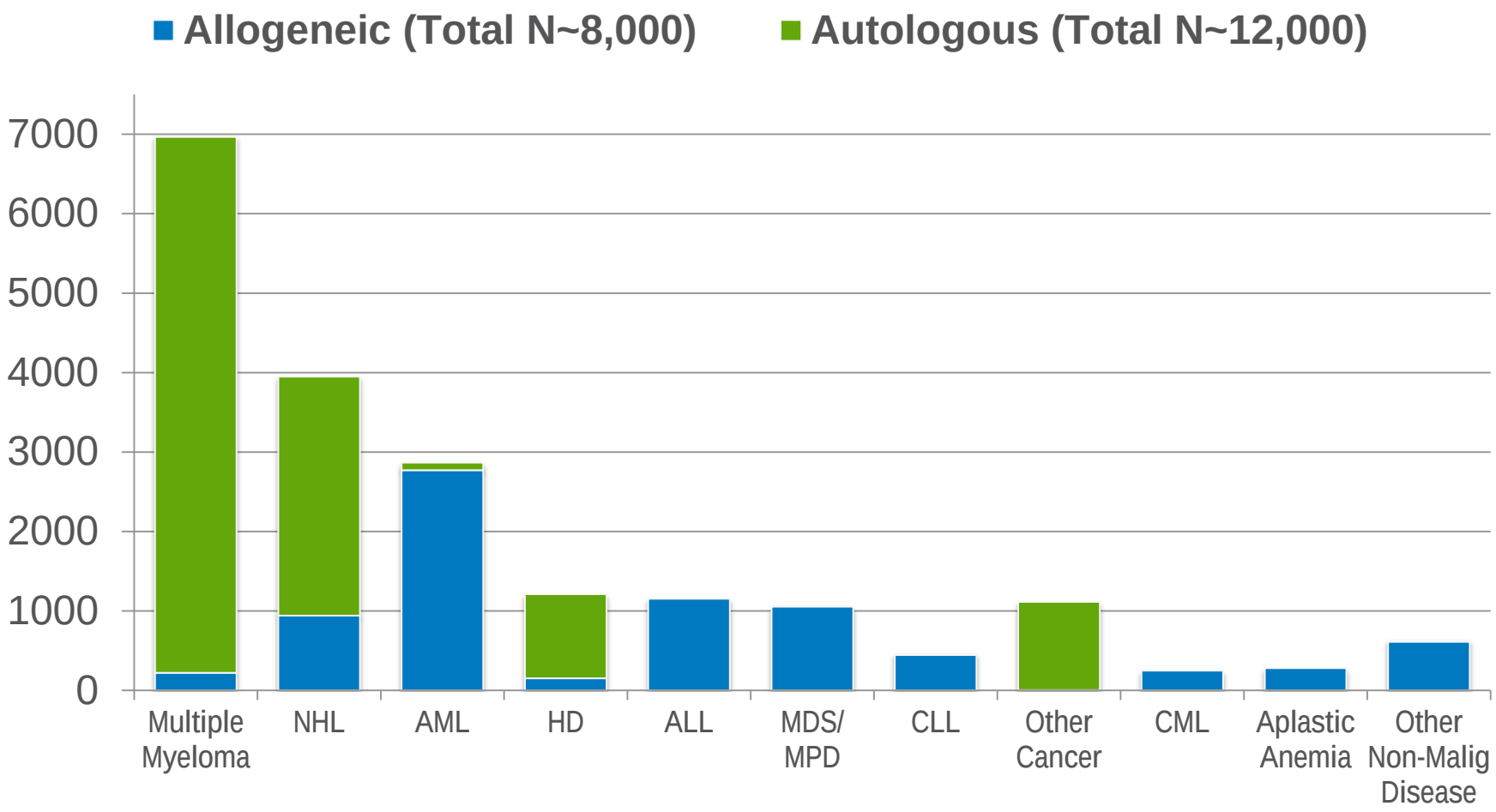
Indications for HCT in the US: Recent Growth in Allotransplants for MDS, NHL and CLL



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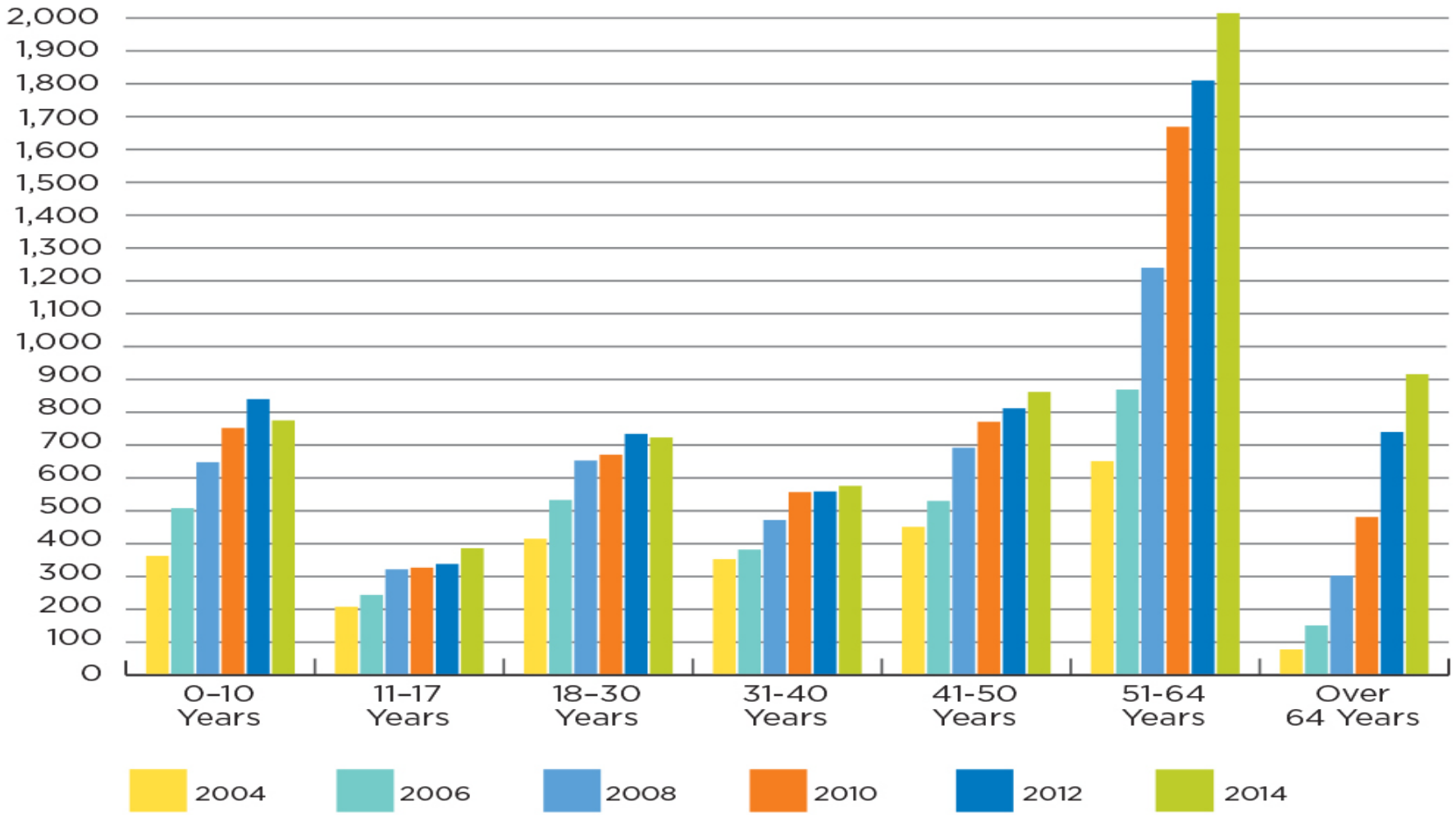
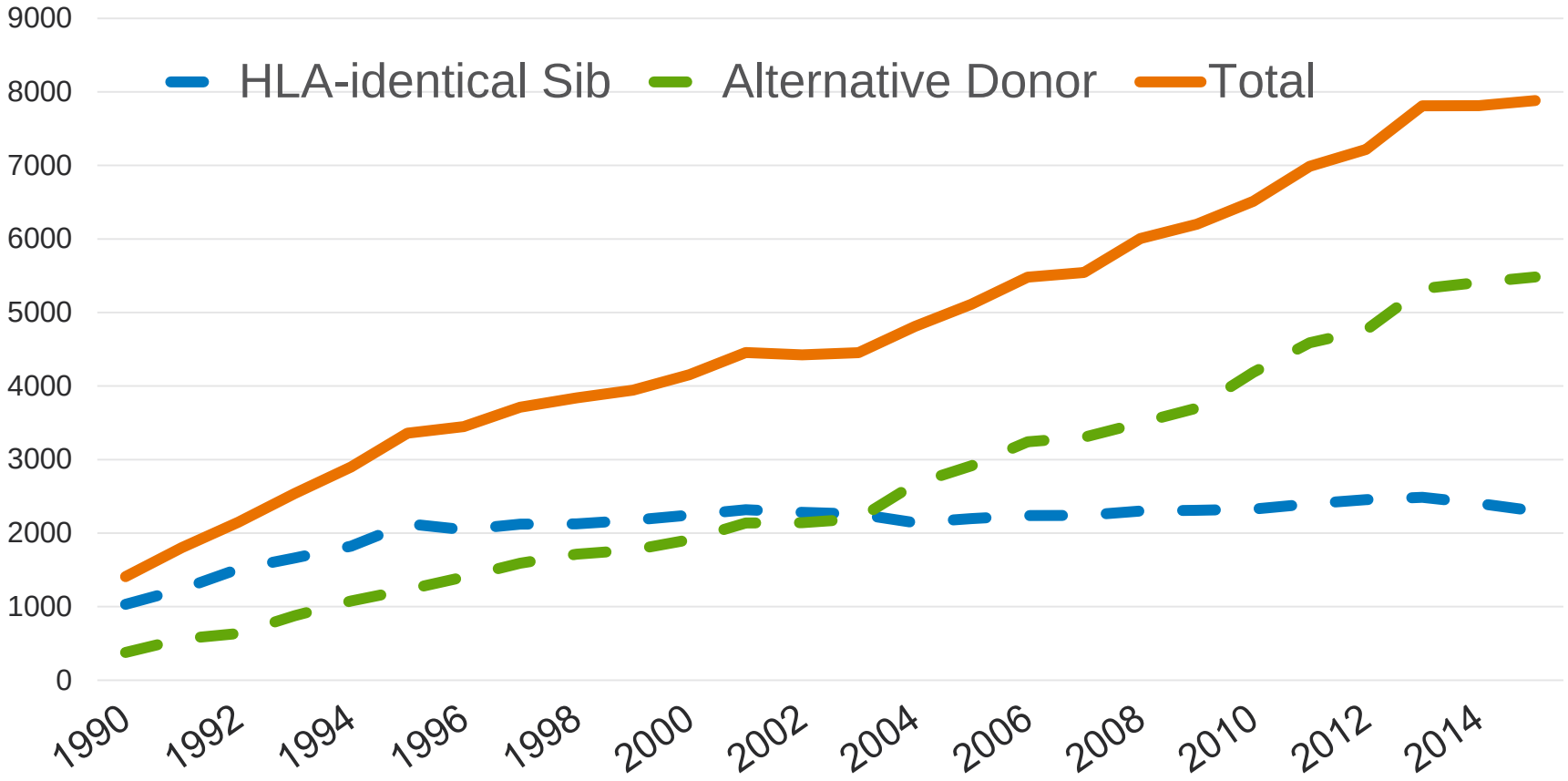
Unrelated Donor HCTs Facilitated by NMDP: Dramatic Growth in Use in Patients older than 50



Source: National Marrow Donor Program/Be The Match FY 2014

Allogeneic Transplant Recipients in the US, by Donor Type



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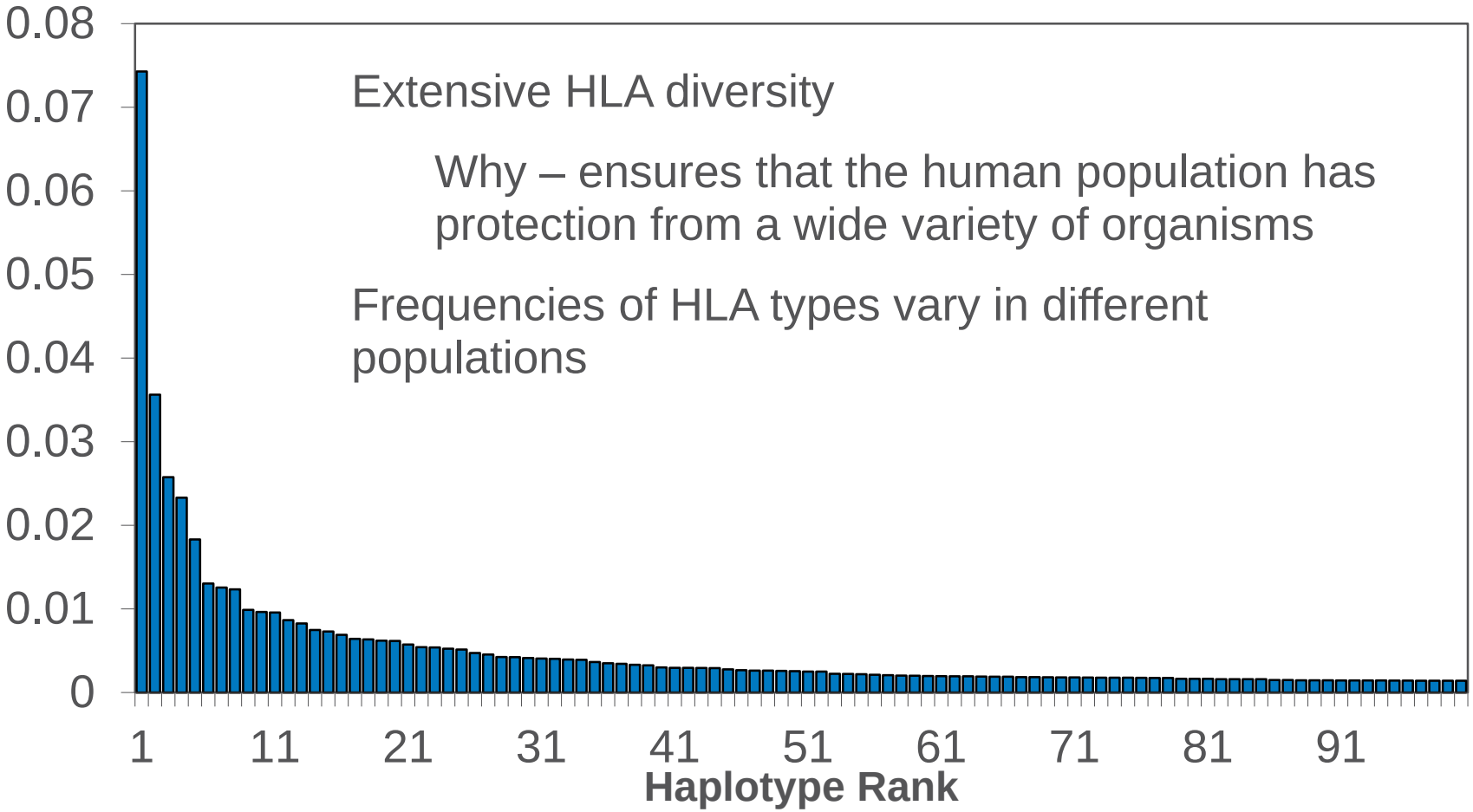
WHAT IS A SUITABLE DONOR?

- Source of hematopoietic stem cells that will provide durable engraftment, good immunologic recovery and acceptable risk of graft-versus-host disease.
- Requires donor-recipient matching for Human Leukocyte Antigens (HLA)
  - Gold standard: HLA-identical sibling
  - HLA-identical sibling available for about 30% of transplant candidates

Top 100 Caucasian A,B,C & DRB1 High-Resolution Haplotypes all have frequencies <8%; most <1%



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Bone Marrow Donors Worldwide – Adult Donors

- 28,273,571 unrelated donors
  - 74 stem cell donor registries from 53 countries

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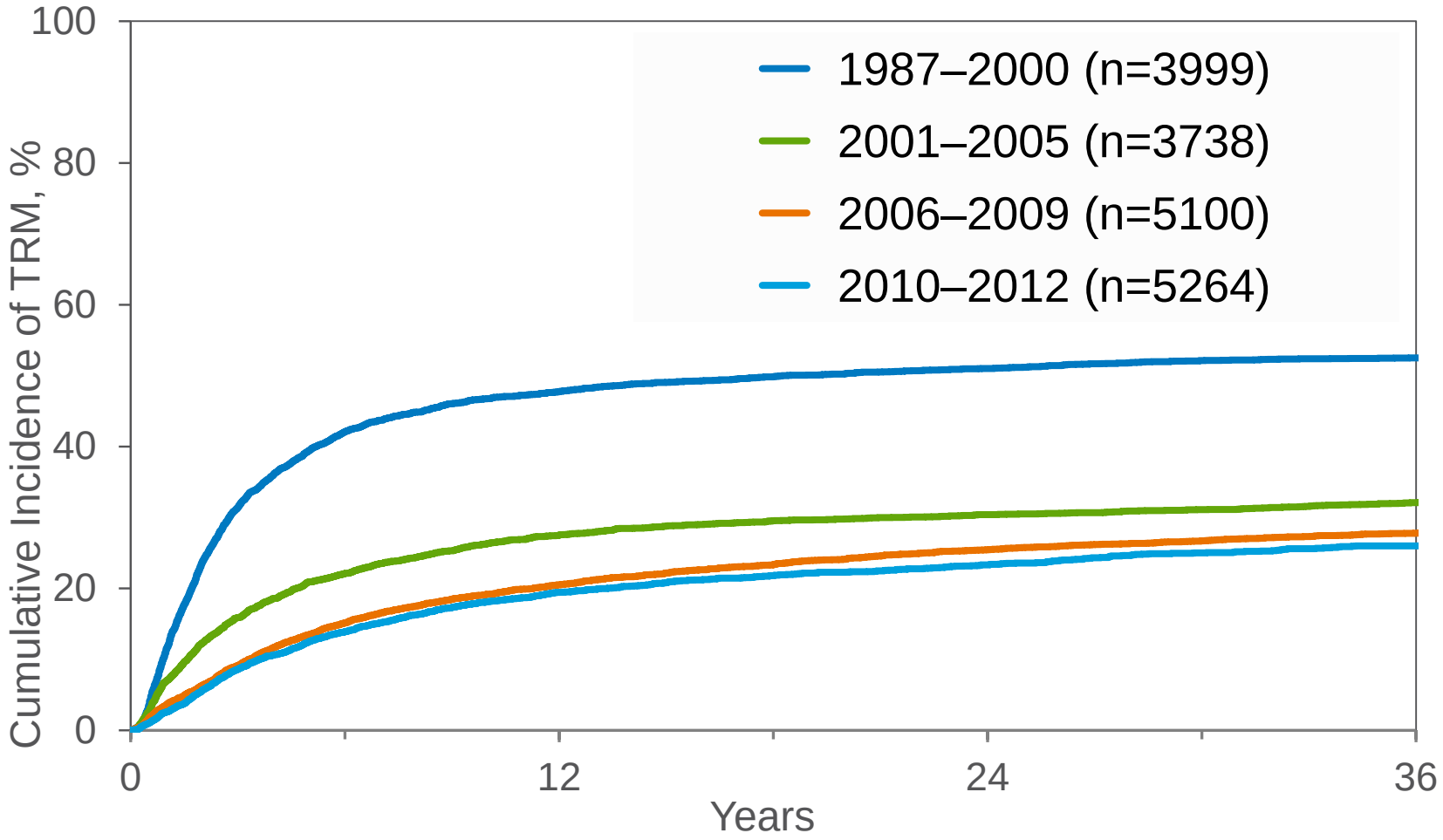
Treatment-Related Mortality after Unrelated Donor HCT for Leukemia or Lymphoma Has Decreased Substantially over Past 3 Decades From ~40% to ~20%



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1-Year Survival after Allogeneic HCT in the US in 2016 Center-Specific Outcomes Analysis

	2012		2013		2014	
	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)
Related donor	3036	73% (72-75%)	3182	72% (70-73%)	3262	73% (71-74%)
Unrelated donor	4248	65% (64-67%)	4675	67% (66-68%)	4601	66% (65-68%)

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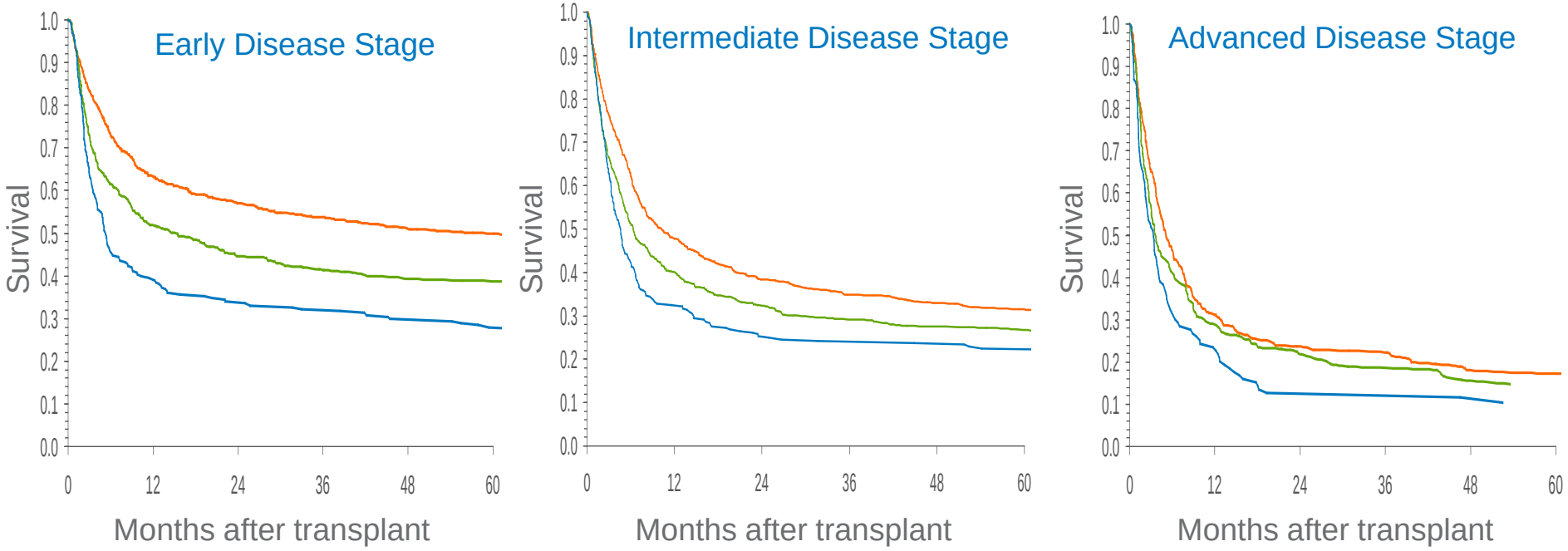
Influence of HLA match on Survival After Unrelated Donor HCT



S. Lee, et al. Blood 2007 Showed impact of single allele mismatch at A, B, C and DRB1; no difference between antigen and allele level matching

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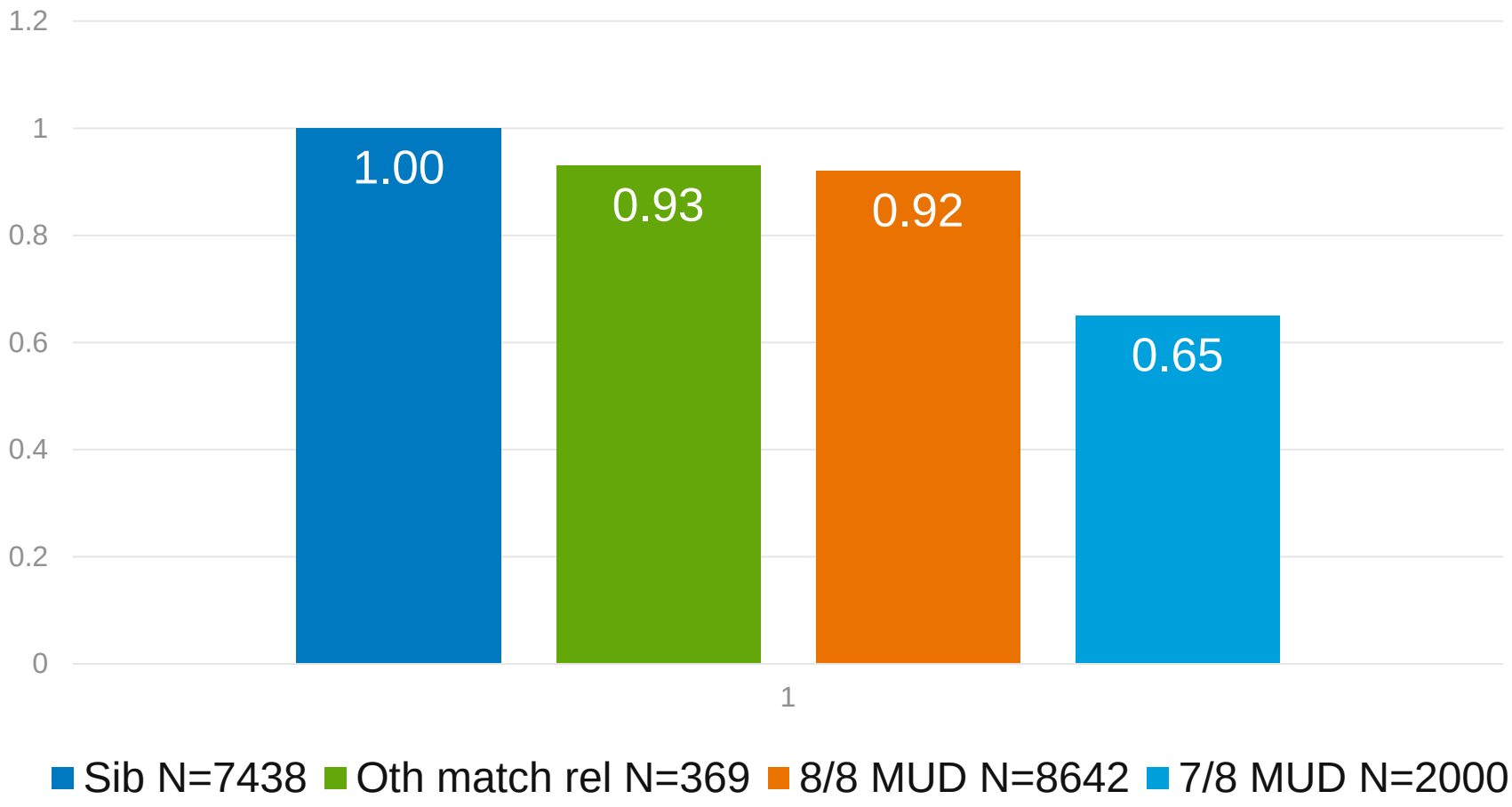
Impact of Donor Type on one-year mortality of after HCTs done in 2012-2014



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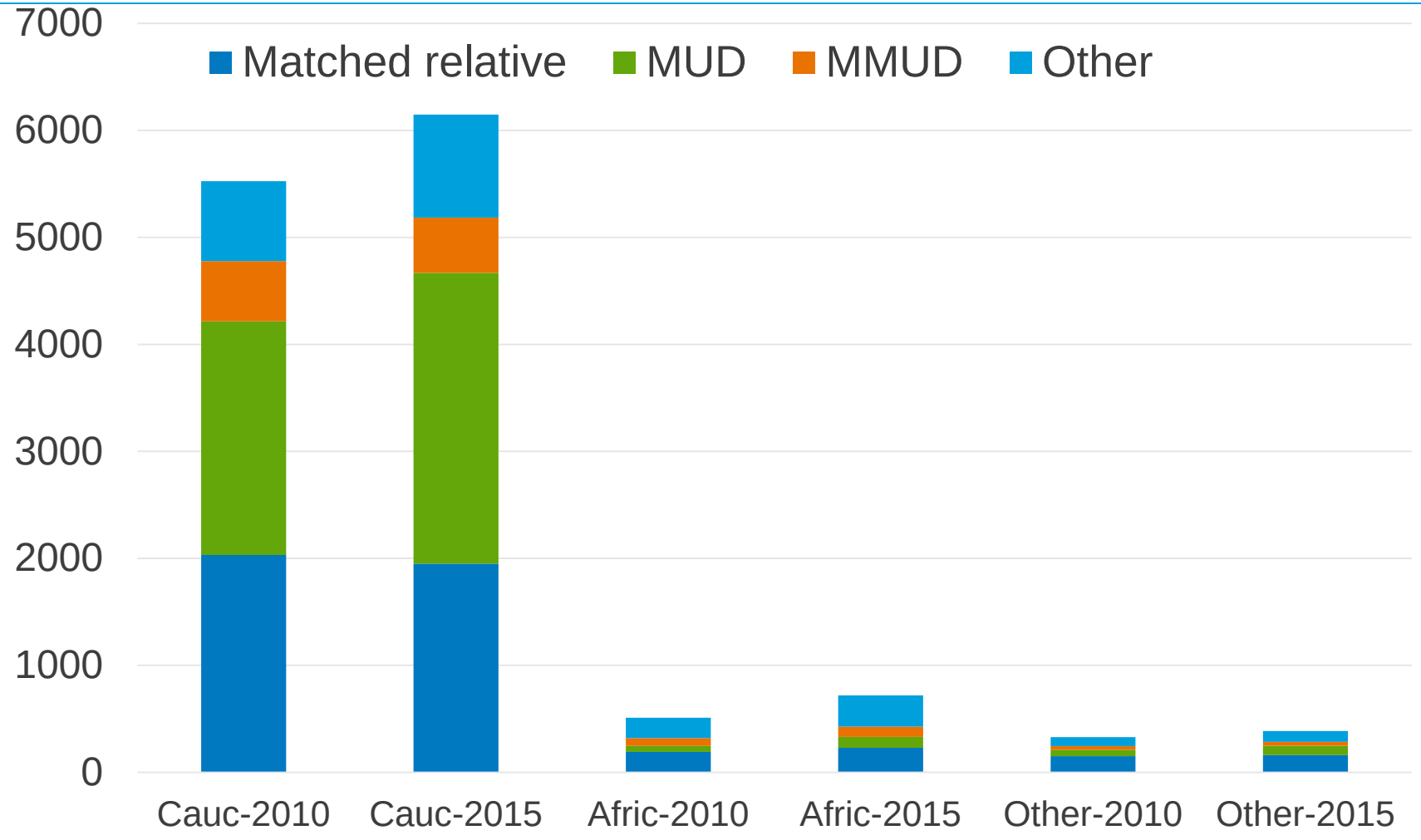
US Transplants by Race, Year and Donor Type



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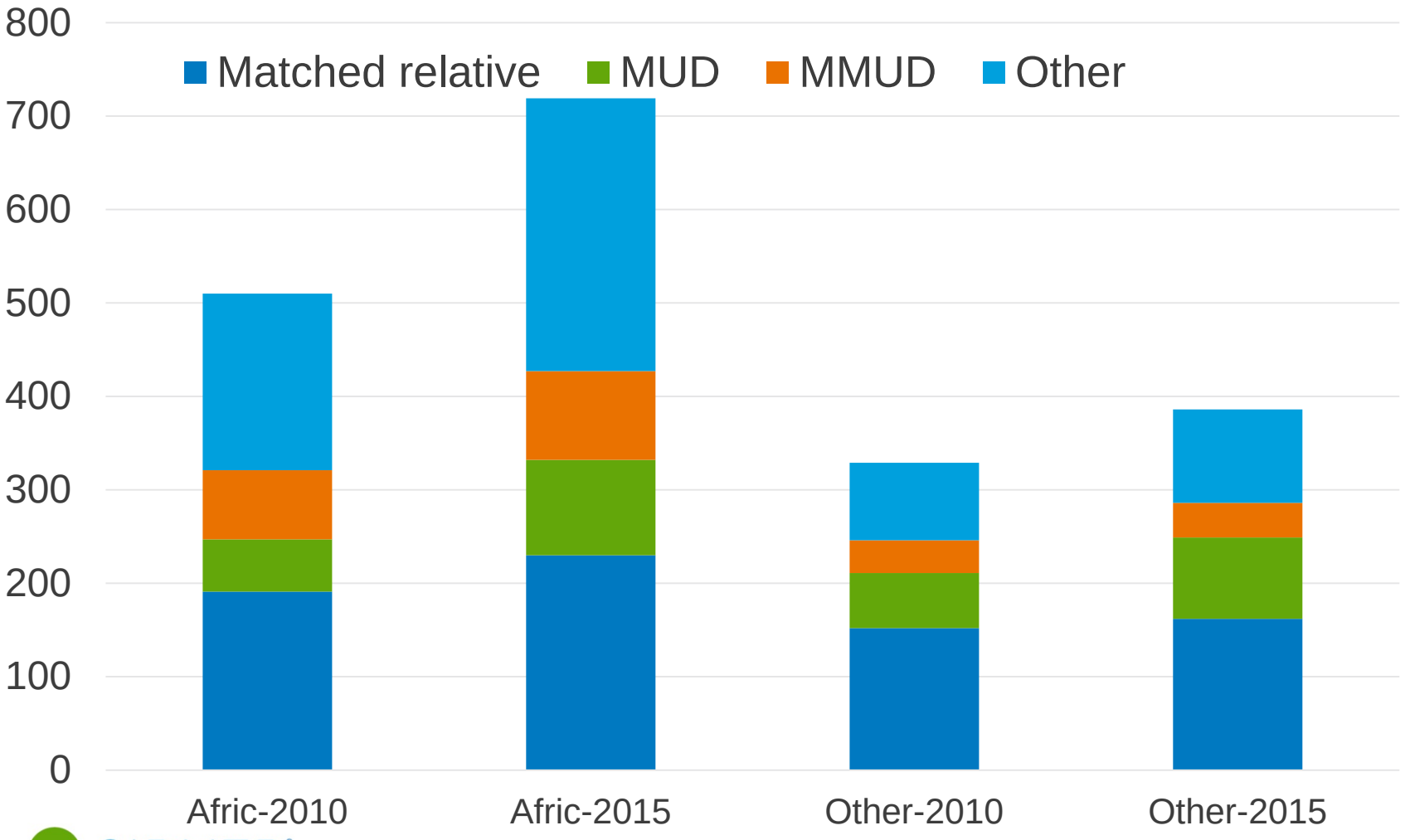
US Transplants in non-Caucasians by Year and Donor Type



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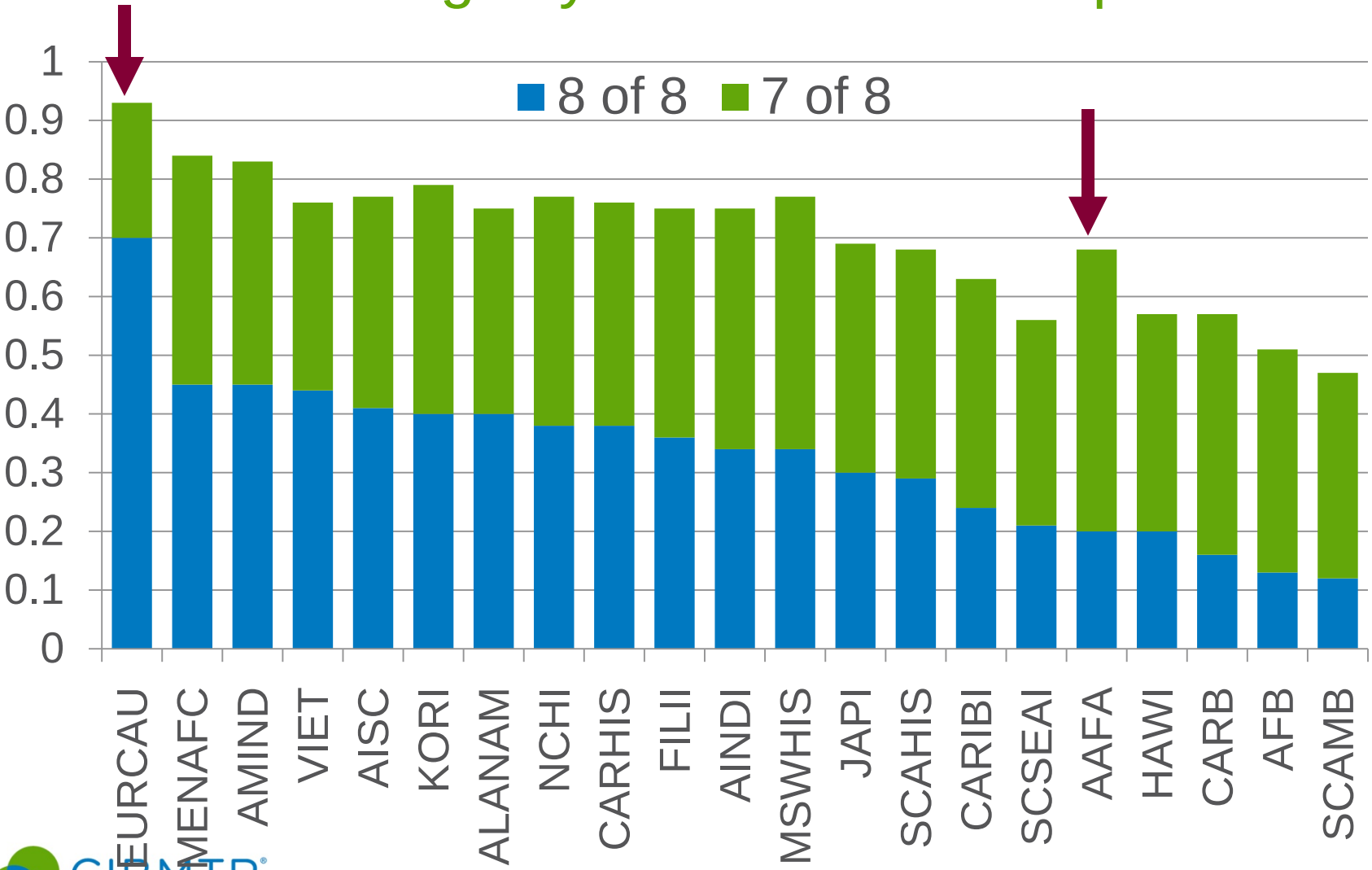
7/8 and 8/8 Allele, Available-Match Rates in the Adult Donor Registry in 21 Different Populations



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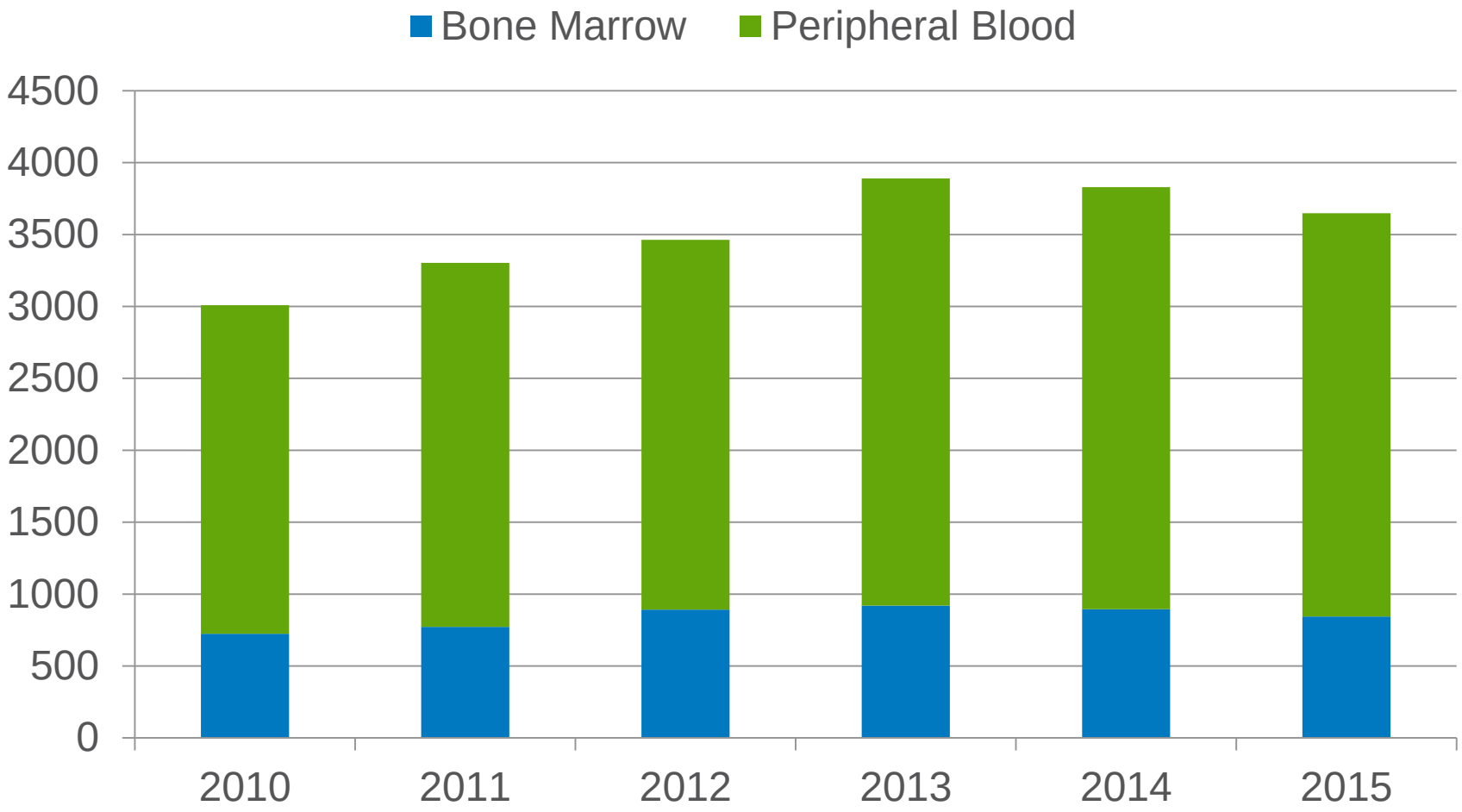
Gragert, NEJM 2014

Unrelated Adult Donor Transplants in the US by Graft Type: BM vs PB



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BMT CTN 0201: BM vs PB (Anasetti, et al. NEJM 2012)

- Randomized trial of unrelated donor bone marrow vs. peripheral blood for transplantation for hematologic malignancies
- **Results showed similar survival, DFS, TRM**
- BM had a higher rate of graft failure (9% vs. 3%, p=0.002)
- **PB had a higher rate of chronic GVHD (53% vs. 41%, p=0.01)**

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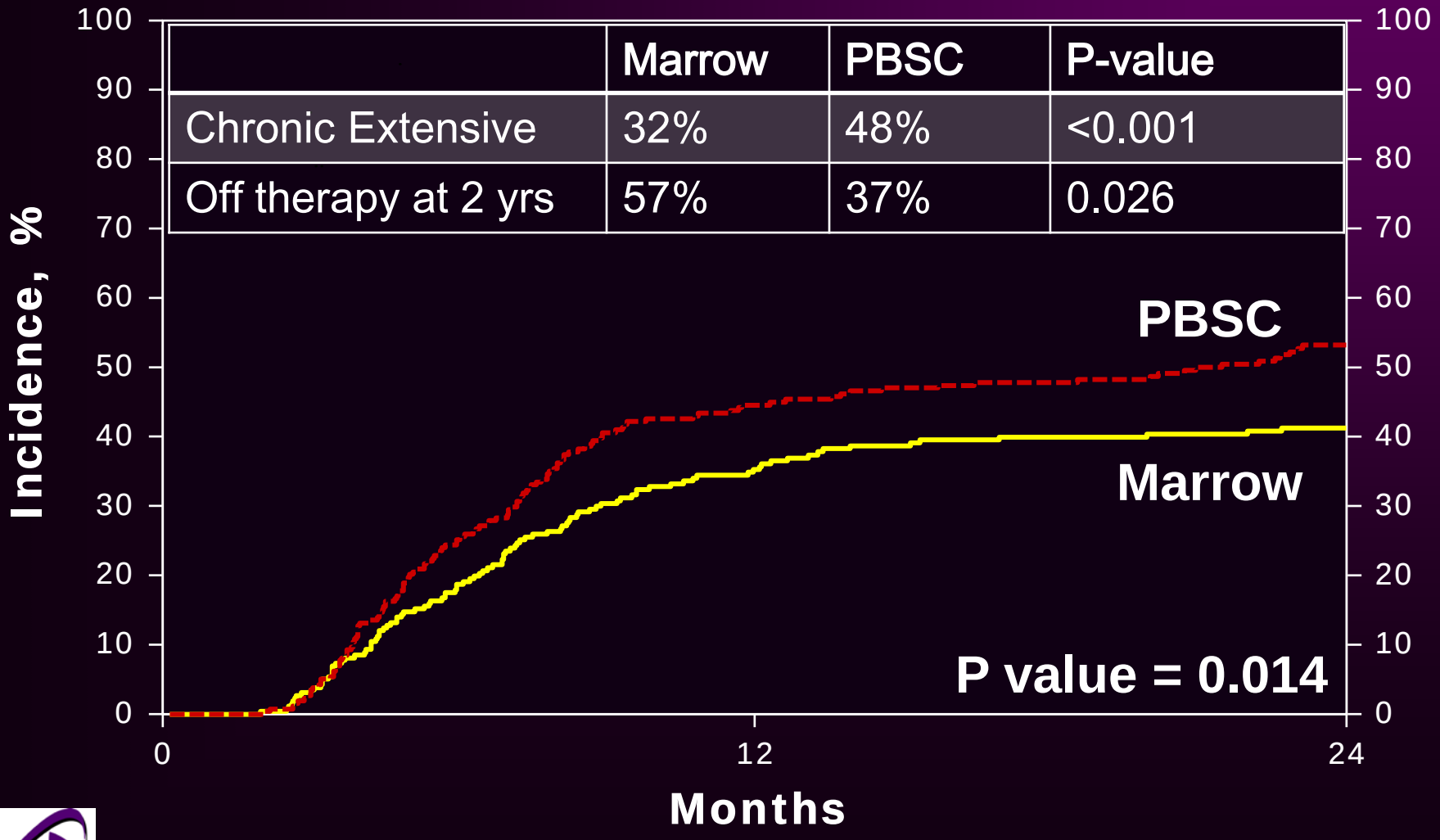
Chronic GVHD

	Marrow	PBSC	P-value
Chronic Extensive	32%	48%	<0.001
Off therapy at 2 yrs	57%	37%	0.026



Parent Trial Eligibility Criteria

- Age up to 66 years
- First transplant
- Acute and chronic leukemia, MDS, MF
- 5/6 or 6/6 match at HLA-A, B, DRB1
  - 98% 7/8 or 8/8 matched
- No active infection

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Parent Trial Study Design

- Four myeloablative/RIC regimens allowed
  - Cyclophosphamide/TBI
  - Cyclophosphamie/Busulfan
  - Fludarabine/Busulfan/ATG
  - Fludarabine/Melphalan
- Two GVHD prophylaxis regimens
  - Cyclosporine/methotrexate +/- others
  - Tacrolimus/methotrexate +/- others

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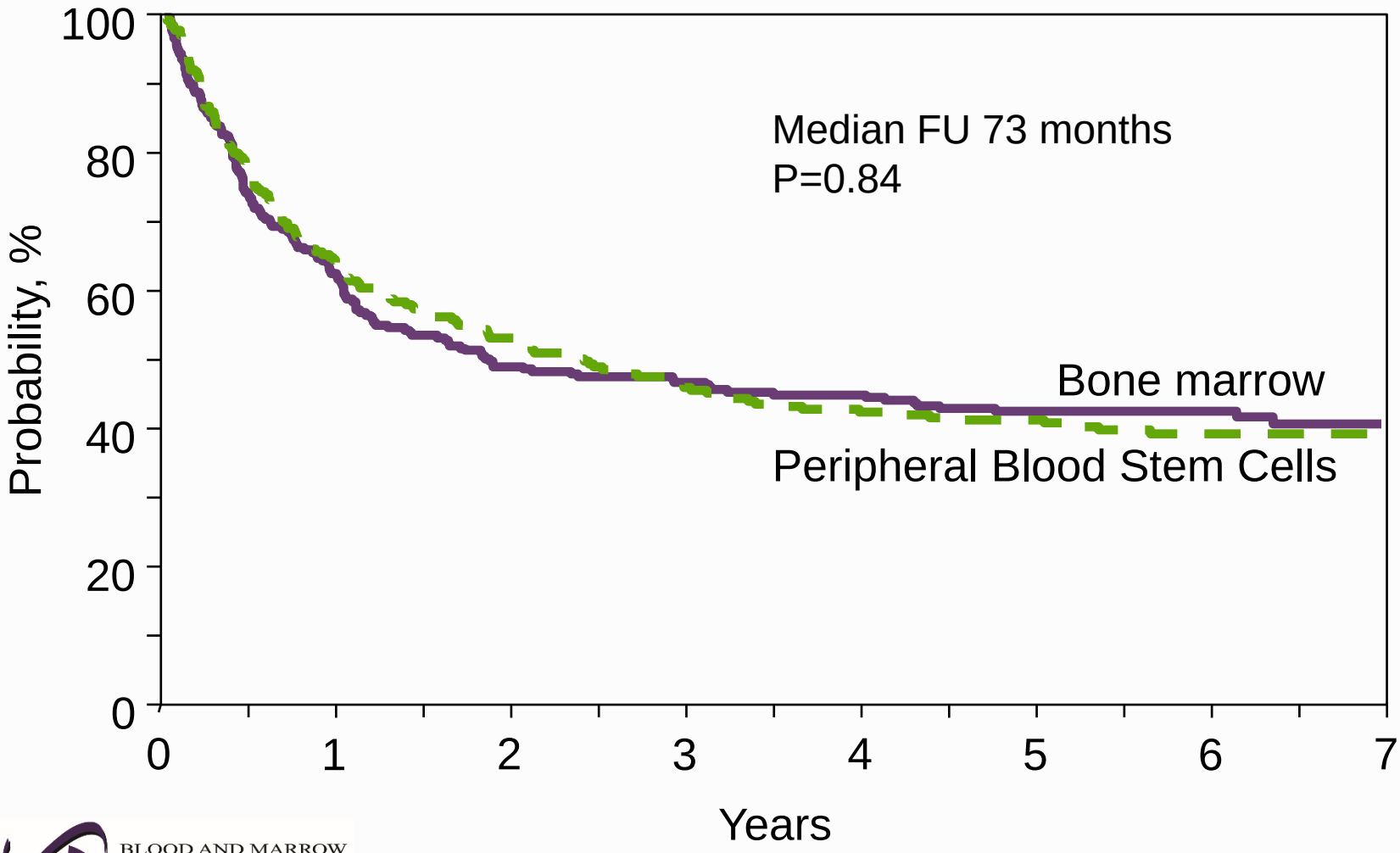
Overall Survival with 5 Years Minimum Follow-up



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Five year QOL data with BM vs PB (76% Response Rate)

QOL scale	Bone marrow (n=102)	Peripheral blood (n=93)	P value	Difference between BM and PB (95% CI)[2]
FACT-BMT TOI (↑ better) Mean +/- SE	**76.7 +/- 1.6 (n=79)**	**70.5 +/- 1.9 (n=69)**	**0.014**	**6.2 (1.3-11.1)**
MHI – Psychological well-being (↑ better) Mean +/- SE	**78.9 +/- 1.7 (n=80)**	**72.2 +/- 1.9 (n=72)**	**0.011**	**6.7 (1.6-11.8)**
MHI-Psychological Distress (↓ better) Mean +/- SE	**16.0 +/- 1.3 (n=80)**	**19.0 +/- 1.5 (n=71)**	**0.128**	**-3.0 (-6.8,0.9)**
Chronic GVHD symptoms (↓better) Mean +/- SE	**13.1 +/- 1.5 (n=80)**	**19.3 +/- 1.6 (n=72)**	**0.004**	**-6.3 (-10.5, -2.0)**

FACT-BMT TOI, Functional Assessment of Cancer Therapy, Bone Marrow Transplant Trial Outcome Index; MHI, Mental Health Inventory; GVHD, Graft-versus-Host Disease; SE, standard error

[1]0.5 x STD

[2]Adjusted for enrollment values and missing data using inverse probability weighting using significant clinical characteristics

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Return to work

- Likelihood of return to full or part time work outside the home was higher for BM
  - RR 1.5, 95% CI 1.2-2.0, p=0.002
  - Adjusted for work status before transplant
  - Missing data imputed based on graft source, disease risk, and age

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Conclusions

- At 5 years after HCT, recipients of unrelated donor BM, compared with PB, have:
  - Better psychological well-being
  - Less burdensome chronic GVHD symptoms
  - Are 50% more likely to go back to work
  - Similar survival, relapse, TRM
- No outcome for which PB was better
- PB is still used for >70% of unrelated donor transplants – cause for concern?

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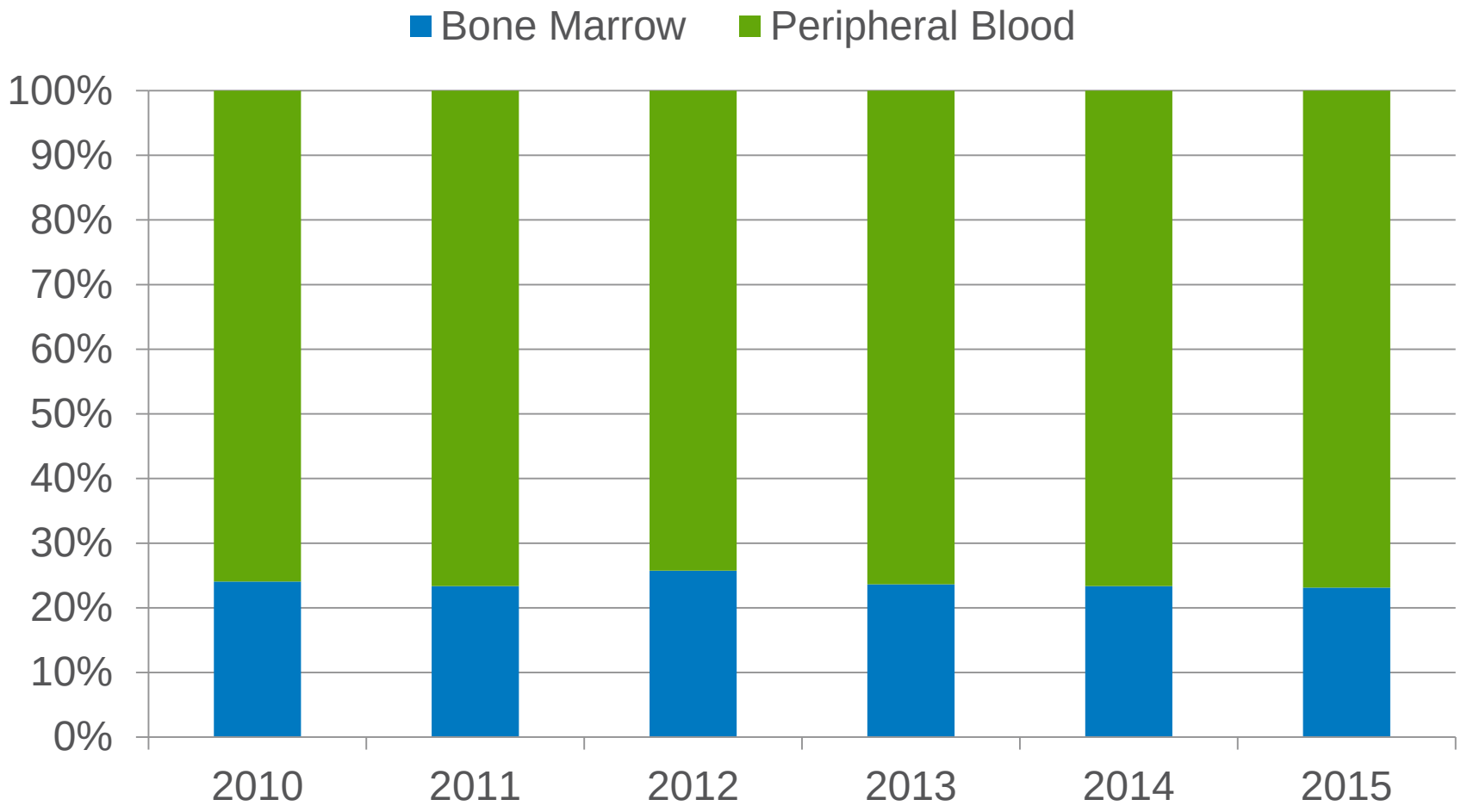
Unrelated Adult Donor Transplants in the US by Graft Type: Percent BM vs PB



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Other HLA/Donor Characteristics Associated with Outcome

- Low-expression HLA alleles (DQ, DP, DRB3,4,5)
  - Permissive versus non-permissive DP mismatches
  - Multiple mismatches
- **Donor age – age >46 about equivalent to a single locus mismatch**
- Non-HLA genomics – KIR Phenotype
- Others – CMV, sex-match, ABO-match

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Donor Availability

- HLA-matched relative 25-30%
- Unrelated donor 40-90%
  - Optimally selected* 10-60%

*HLA-matched, permissive DP mismatch, age <30, (ABO, CMV, sex)

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Patients Without an Adult Donor May be Helped by Banked Umbilical Cord Blood

Advantages:

- Immediately available (important for patients with rapidly progressive diseases)
- No risk to donor
- Allows more HLA-mismatch with lower risk of GVHD

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Bone Marrow Donors Worldwide – Cord Blood Units

- 28,273,571 unrelated donors
- **697,698 CBU**
- 74 stem cell donor registries from 53 countries
- **49 cord blood banks from 33 countries**

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Cord Blood Transplantation

- Multiple studies from individual centers, Eurocord, the NYBC, EBMT and CIBMTR document that Umbilical Cord Blood cells
  - Can establish durable hematopoiesis
  - Have potent graft-versus-tumor effects
  - Can lead to successful transplant outcomes in a variety of malignant and non-malignant diseases in adults and children
- Outcomes of UCB transplants have improved over time

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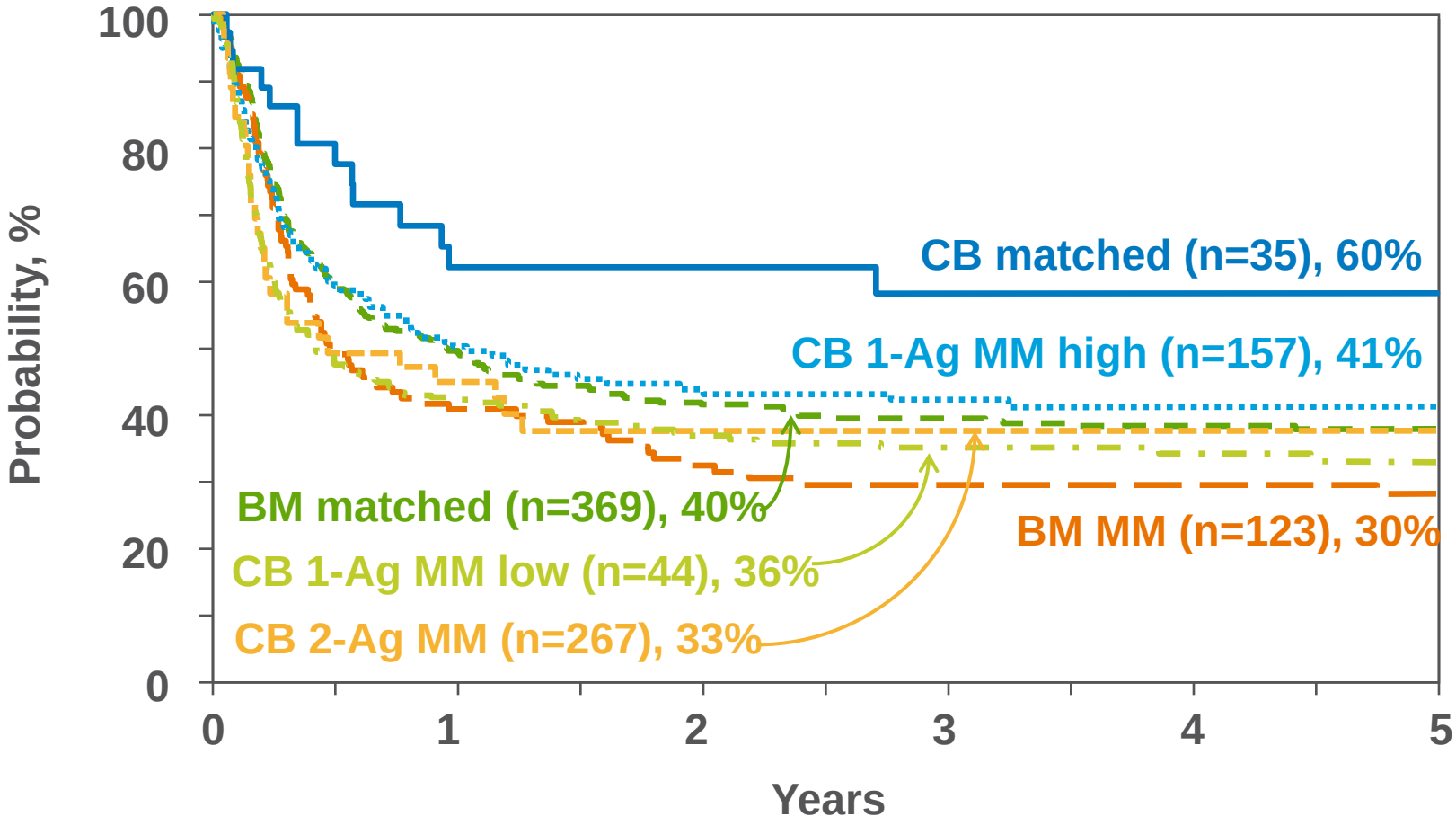
Leukemia-free Survival in Children – depends on HLA Match and Cell Dose: Better, the Same or Slightly Worse than Matched Bone Marrow (Eapen, Lancet, 2007)



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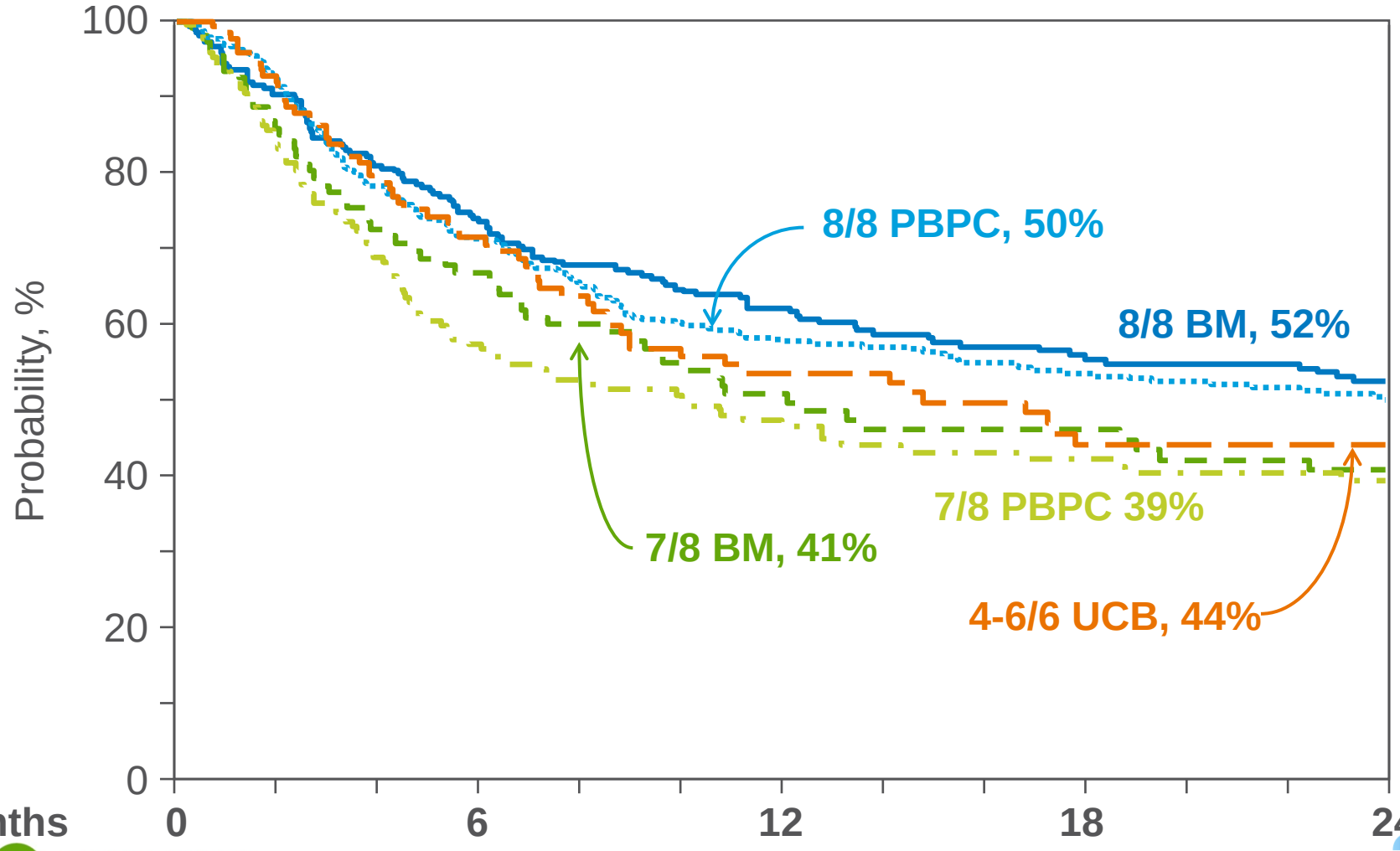
New York Blood Center

Leukemia-free Survival In Adults

Transplantation in Remission: Slightly worse than Matched Marrow of Peripheral Blood



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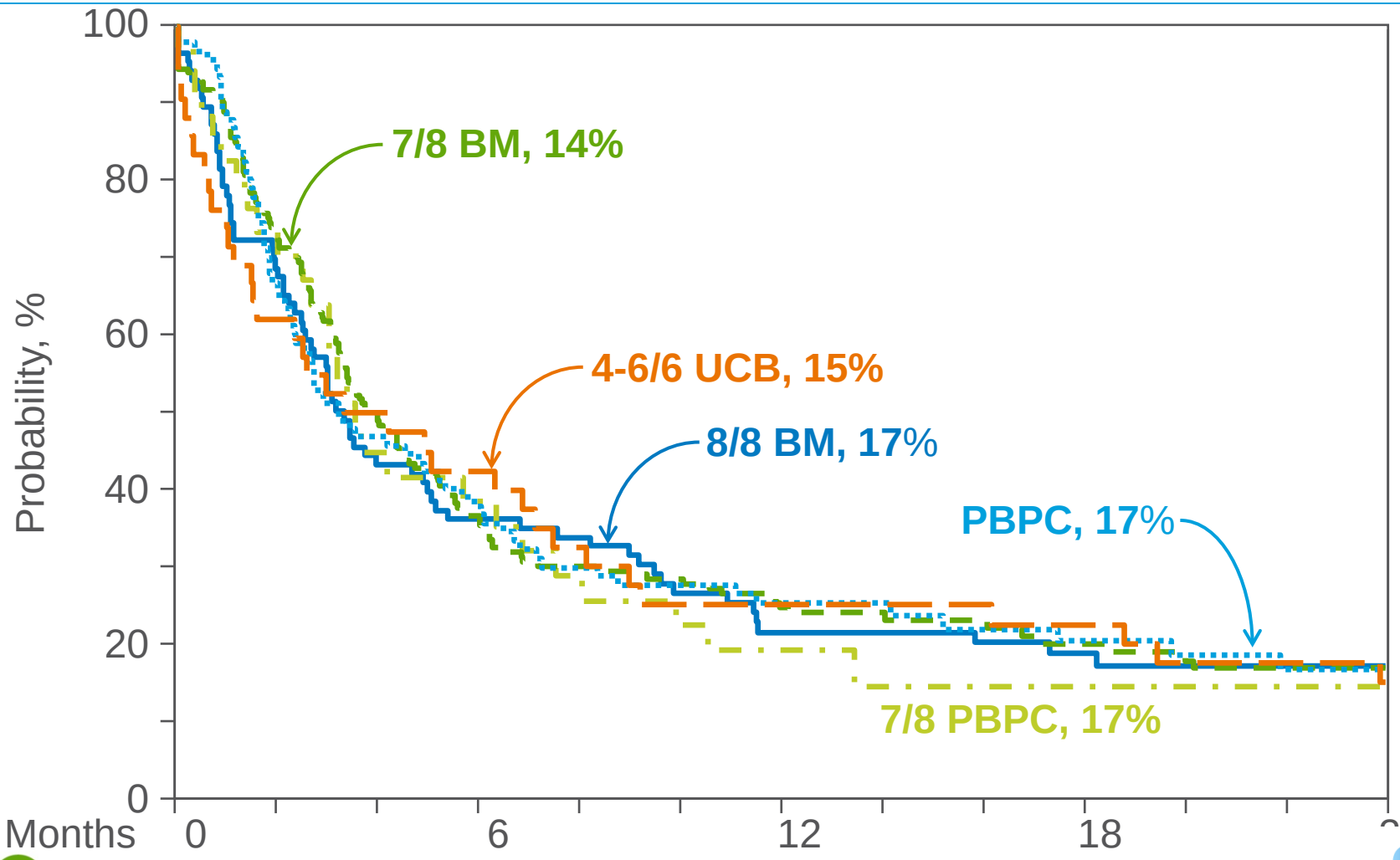
Eapen et al; Lancet Oncol 2010

eurocord

Leukemia-free Survival in Adults:

Transplantation Not in Remission: Similar to Matched or Mismatched BM or PB



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Eapen et al; Lancet Oncol 2010

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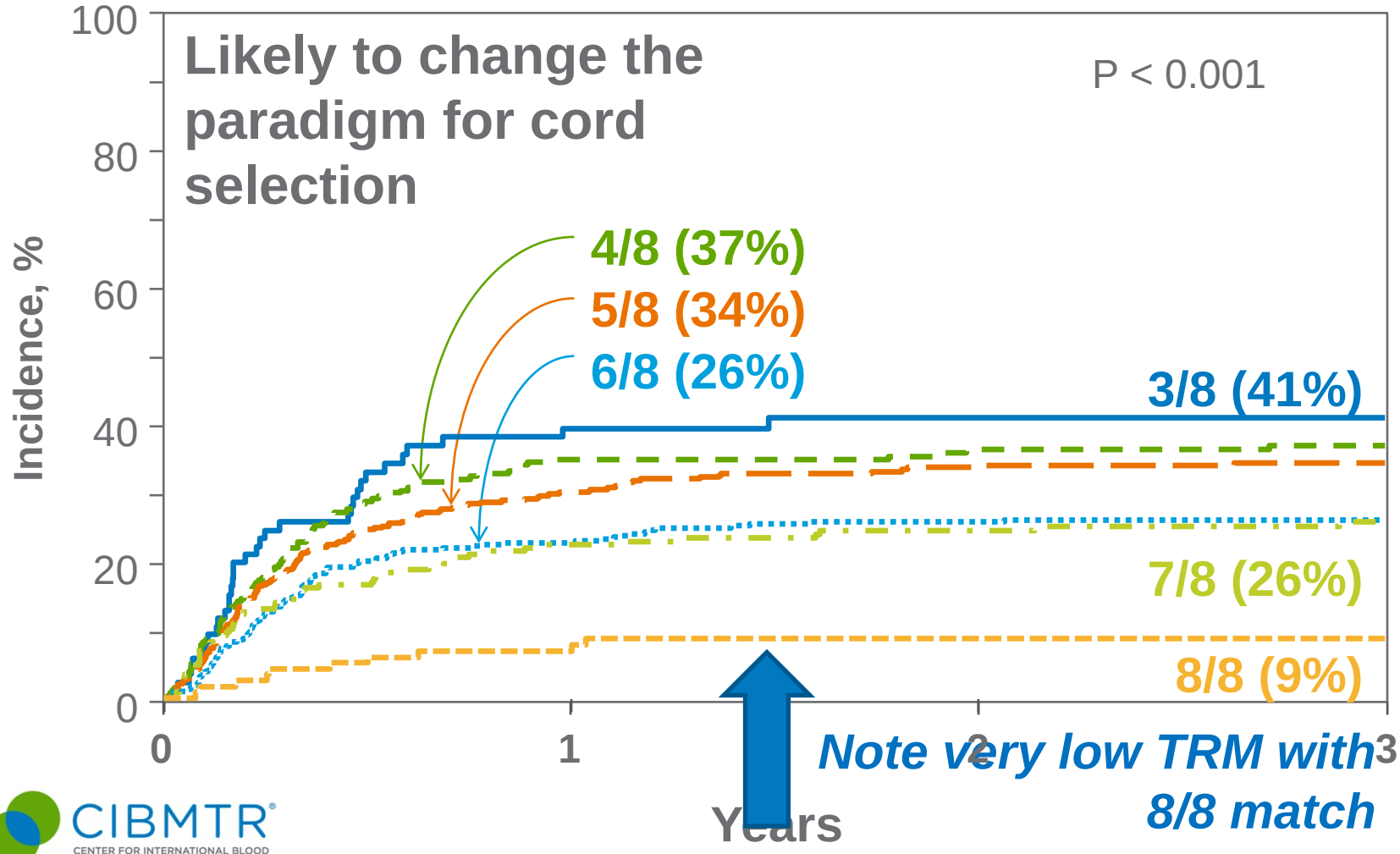
Effect of Allele-level Matching at A, B, C, DRB1 on Transplant-related Mortality after Cord Blood Transplantation (Eapen, Blood, 2014)



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Lesser (intermediate resolution A, B; high resolution DRB1) vs. Allele-level HLA-match

Loci mis-matched using usual typing	Loci mismatched using high resolution typing for A, B, C, DRB1					
	5	4	3	2	1	0
2	11%	31%	49%	**10%**	—	—
1	1%	8%	22%	44%	**25%**	—
0	—	—	4%	18%	24%	**54%**

Cord Blood Availability in the US

	Likelihood of suitable unit		
	8/8	7/8	6/8
African American	5%	33%	80%
South East Asian	7%	33%	75%
Alaskan Native	11%	42%	83%
Native American Indian	10%	44%	85%
Caucasian	36%	81%	98%

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Cell Dose

- Major limitation to Cord Blood Transplantation is the small number of cells in each unit
  - Slow hematopoietic recovery
  - Slow immune recovery
  - Graft failure
- Strategies:
  - Selection of large units
  - Double cord transplantation (expensive)
  - Expansion and homing techniques (in development, often requires two units)

The “New” Alternative – Haploidentical

- Europe: haplo-transplants using T-depleted peripheral blood grafts long used for a small but important proportion of transplants
- China: intensive immune suppression allows successful haplo-transplantation
- US: very few haplo-transplants until last 6 years
  - No approved CD34 selection or T-depletion device
  - Hopkins approach using post-transplant cyclophosphamide increased interest
  - Technically simple, costs similar to HLA-identical sib transplantation

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BMT CTN 0603 and 0604: Parallel Single Arm Studies of Haplo and CB Transplants

- Age ≤ 70
- Diseases
  - Leukemia: high risk, in remission
  - Lymphoma
    - Hodgkin, mantle cell, or large cell: chemosensitive relapse, not eligible for autologous SCT
    - Follicular or marginal zone: multiply relapsed
- Adequate organ function, performance score >60%
- N=50 in each trial
- Primary endpoint: 6-month survival

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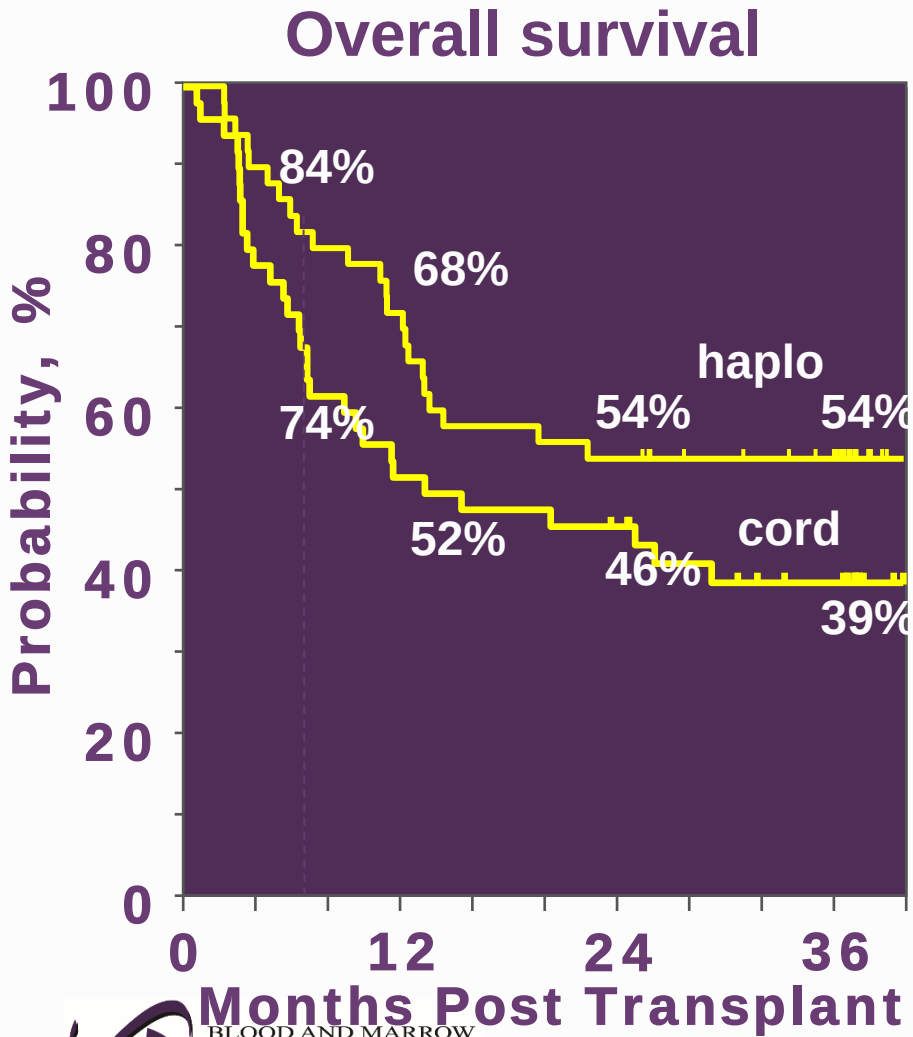
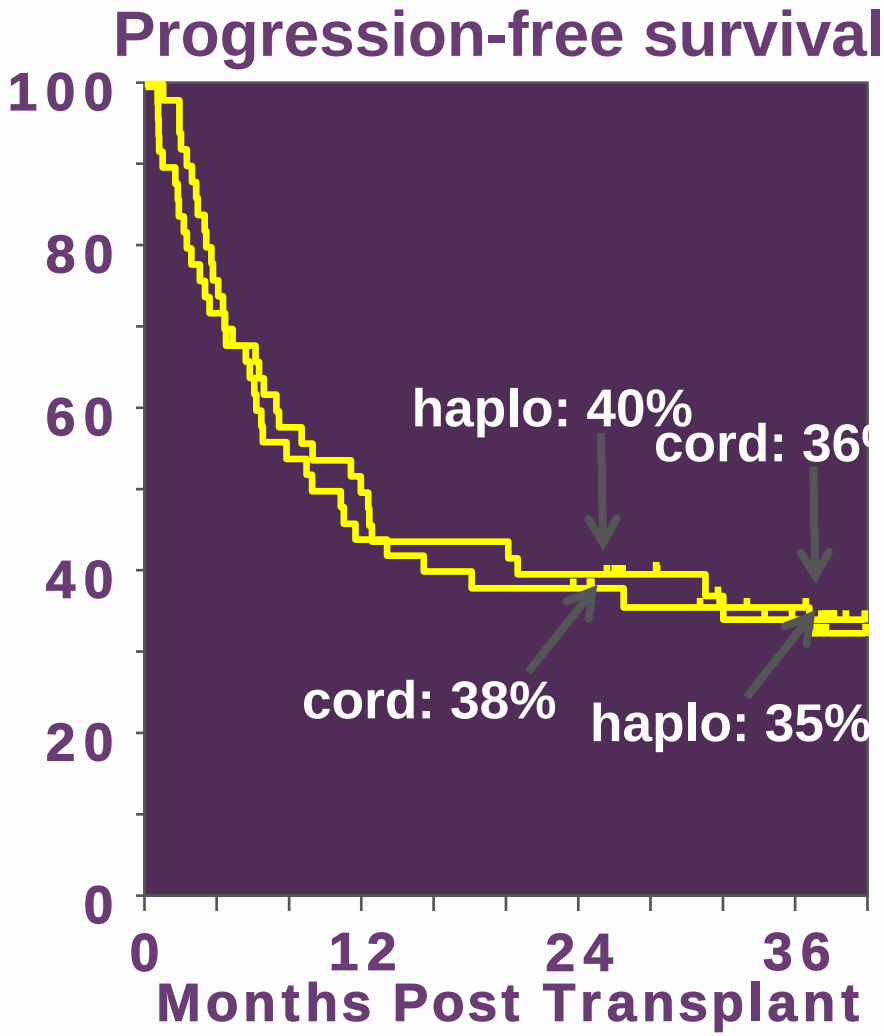
Comparisons of clinical outcomes: CB vs Haplo (BMT CTN 0603/0604)





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BMT CTN 1101: Randomized Comparison of Haplo and Double Cord HCT

- Primary: 2 year Progression-free survival
- Secondary: Engraftment, hematopoietic recovery, GVHD, TRM, relapse/progression, infections, hospitalizations, health-related quality of life
- *Planned ancillary studies:*
- Immune reconstitution
- Cost effectiveness
- 267 of 410 patients accrued to date

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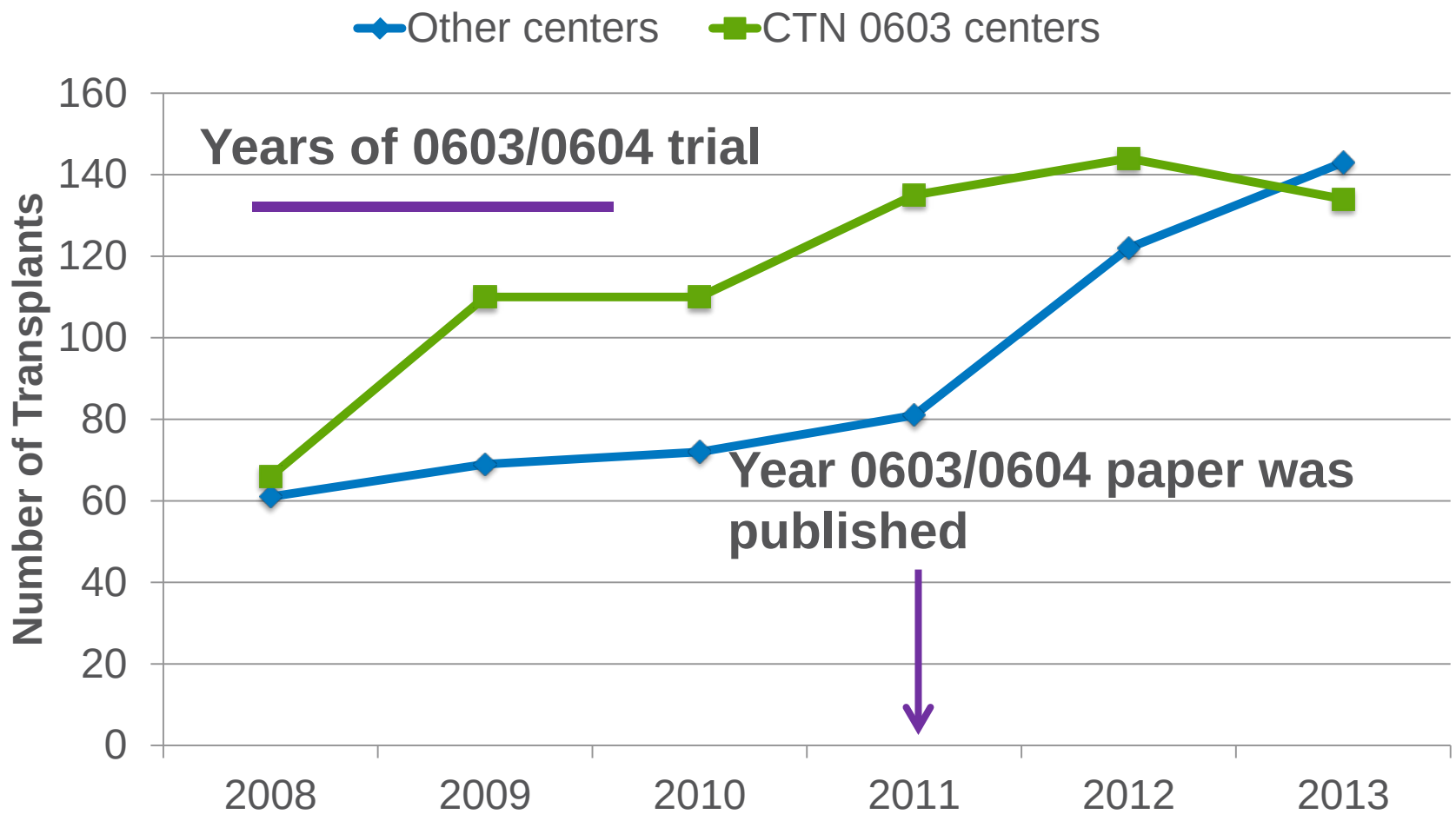
Haploidentical Transplantations for Hematologic Malignancy



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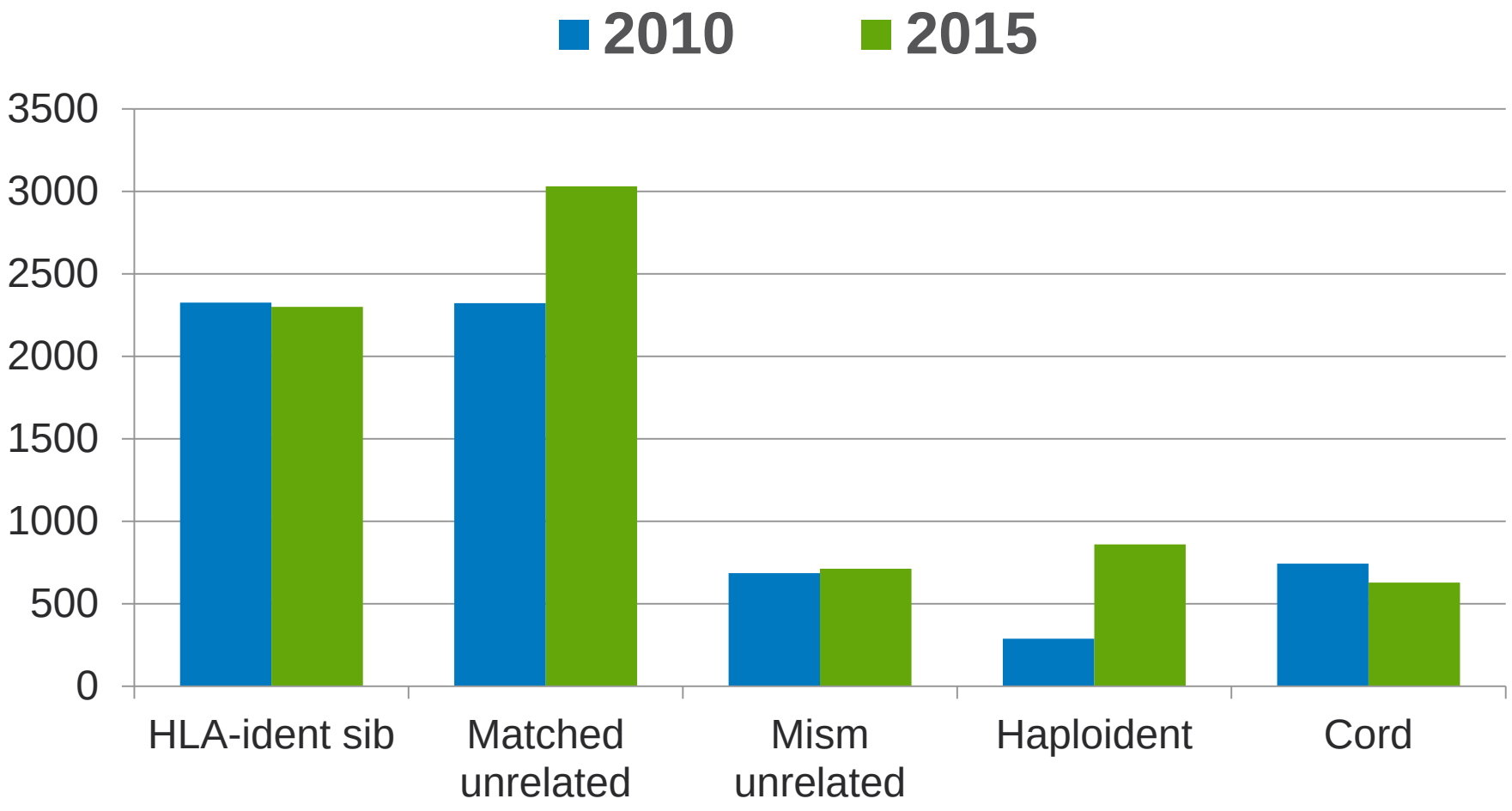
Distribution of Graft Sources: 2015 vs 2010



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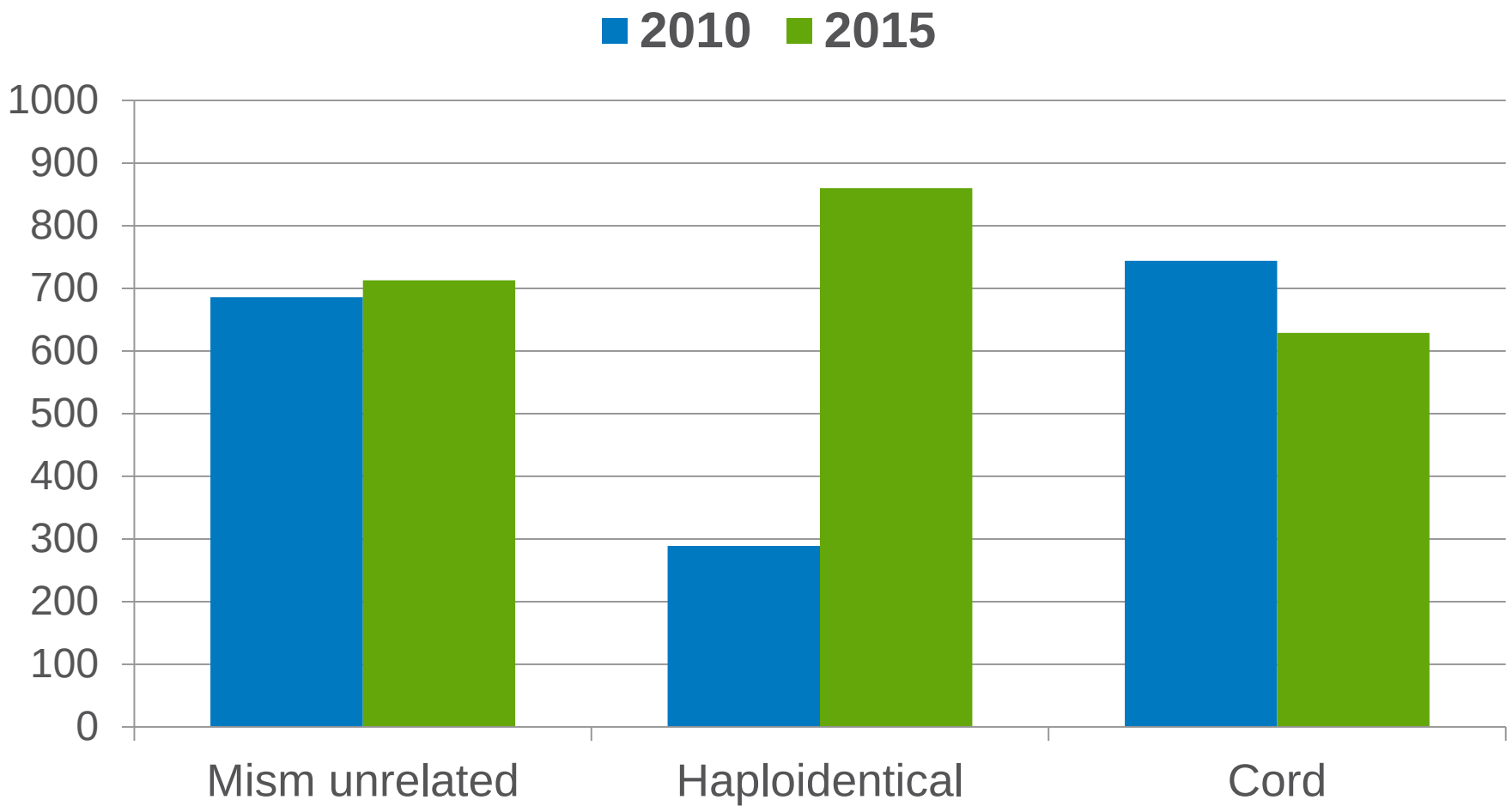
Distribution of Alternative (not an HLA-matched adult donor) Graft Sources - 1



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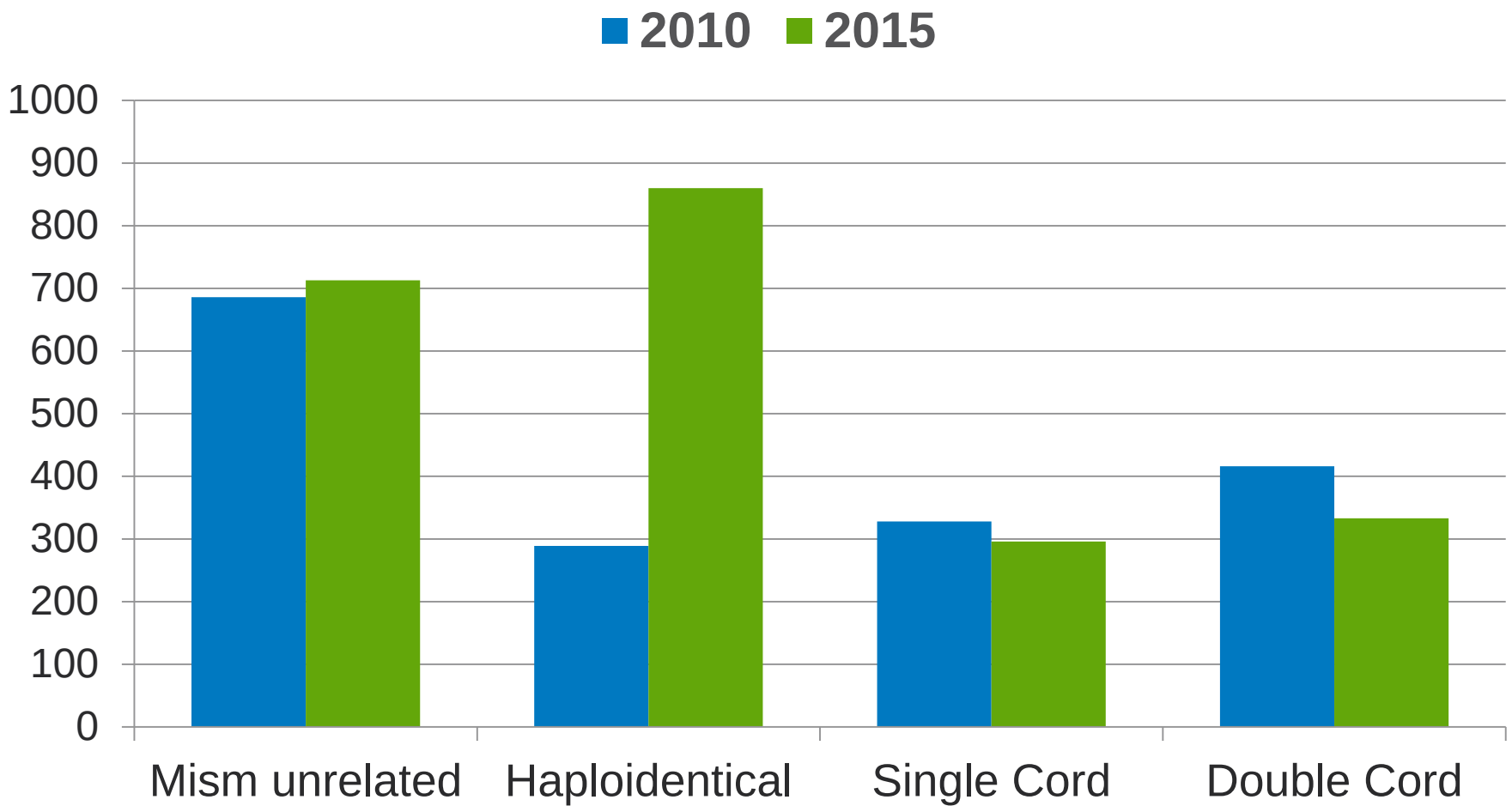
Distribution of Alternative (not an HLA-matched adult donor) Graft Sources - 2



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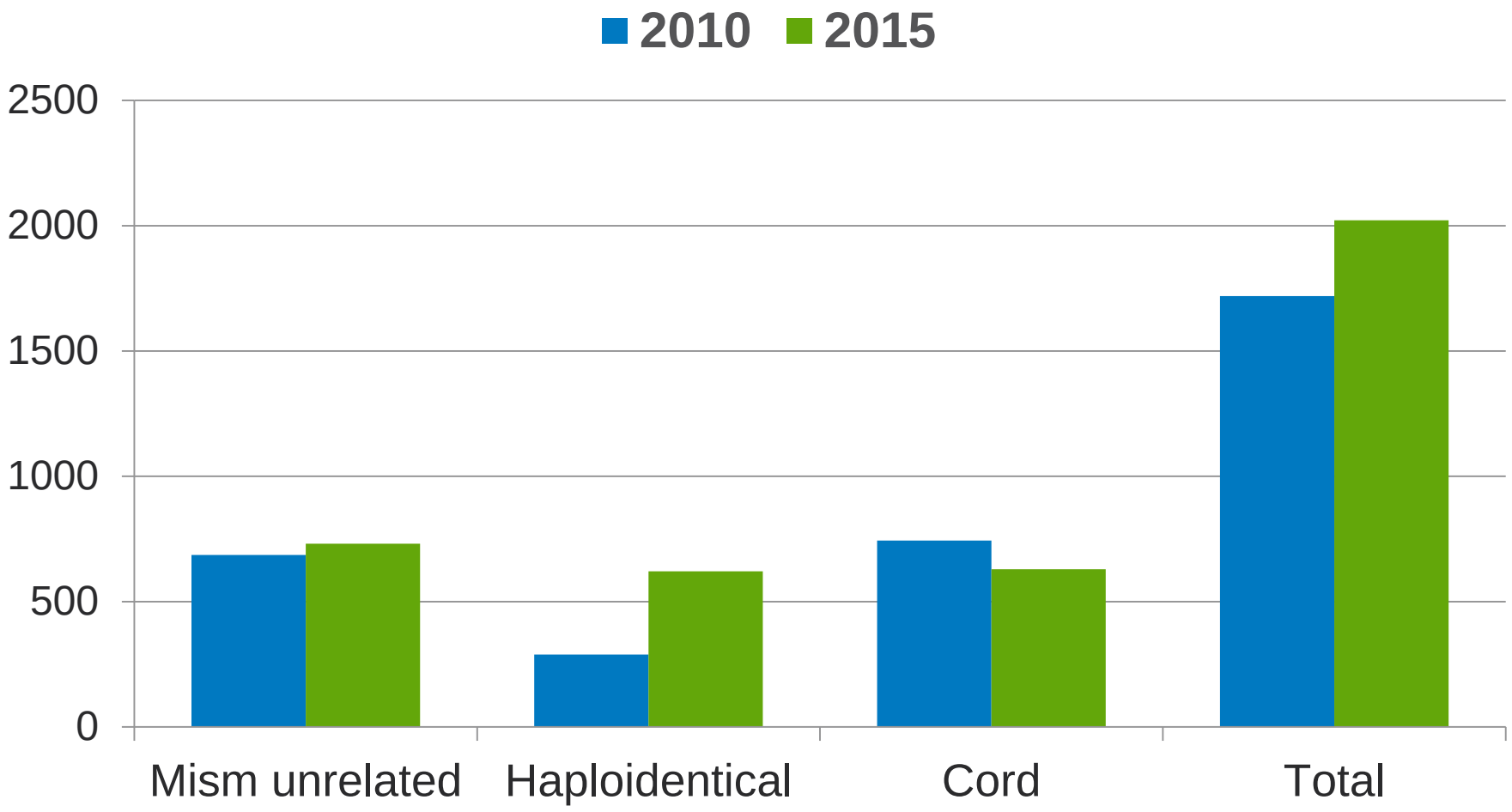
Distribution of Alternative (not an HLA-matched adult donor) Graft Sources - 3



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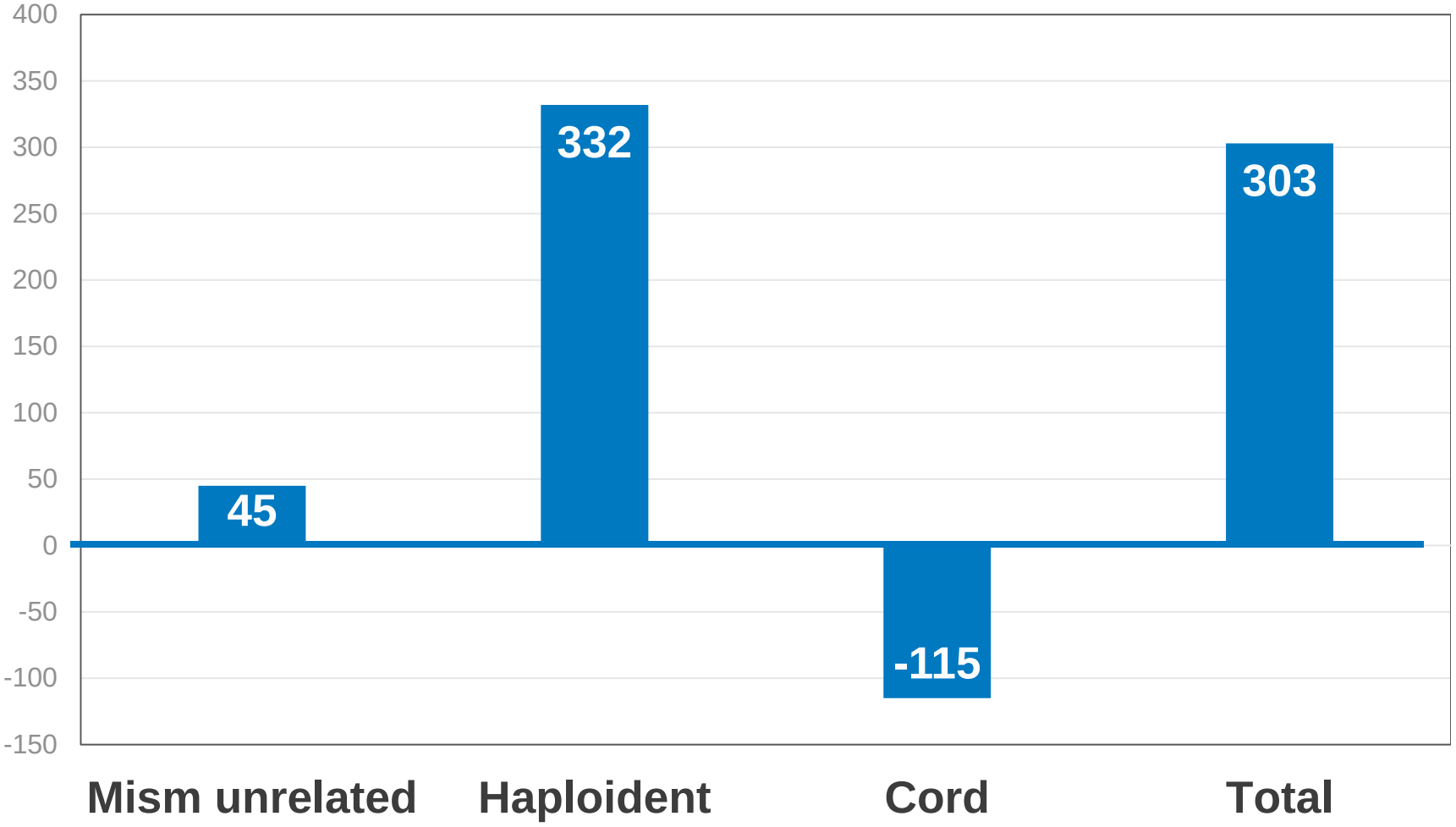
Change From 2010 to 2015



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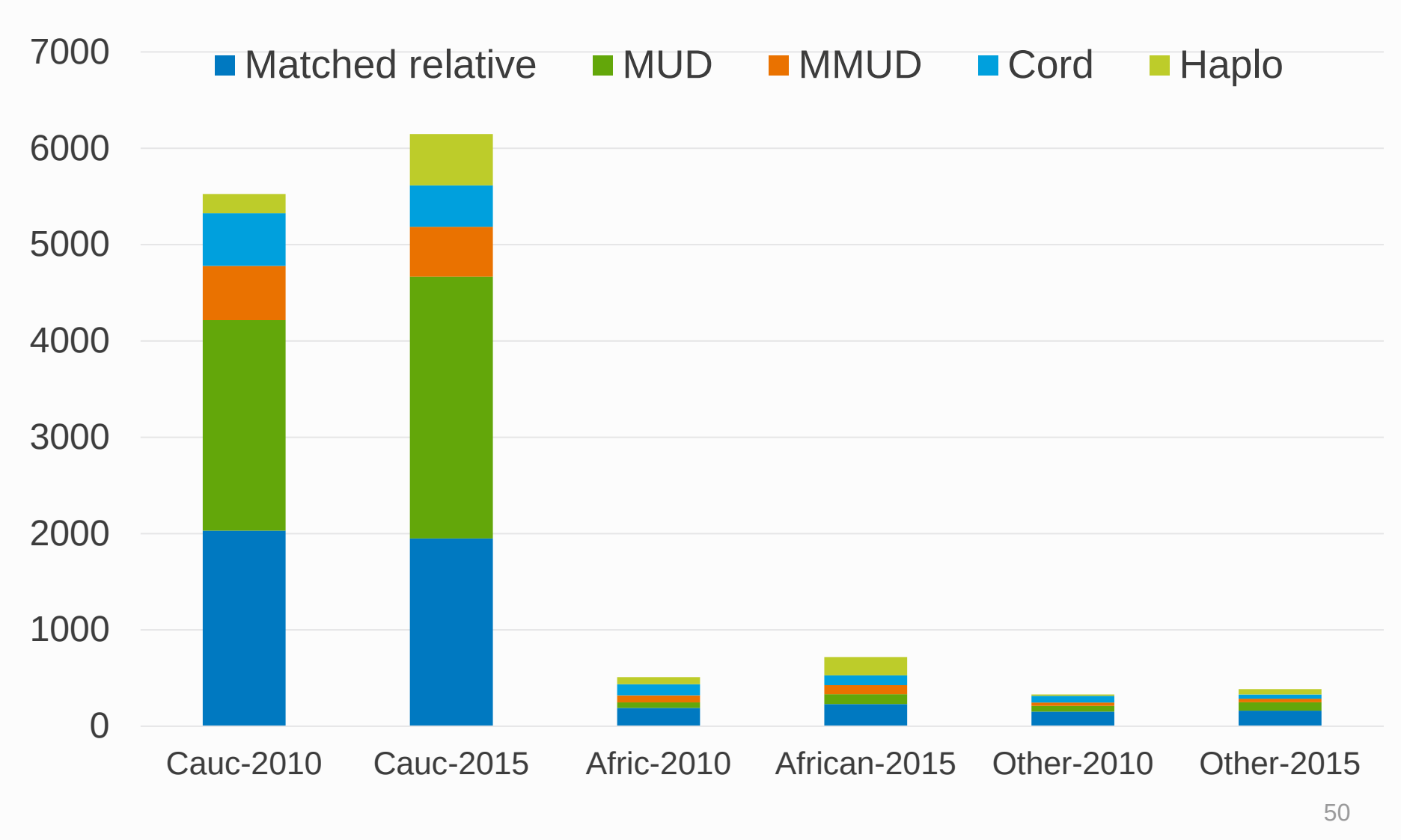
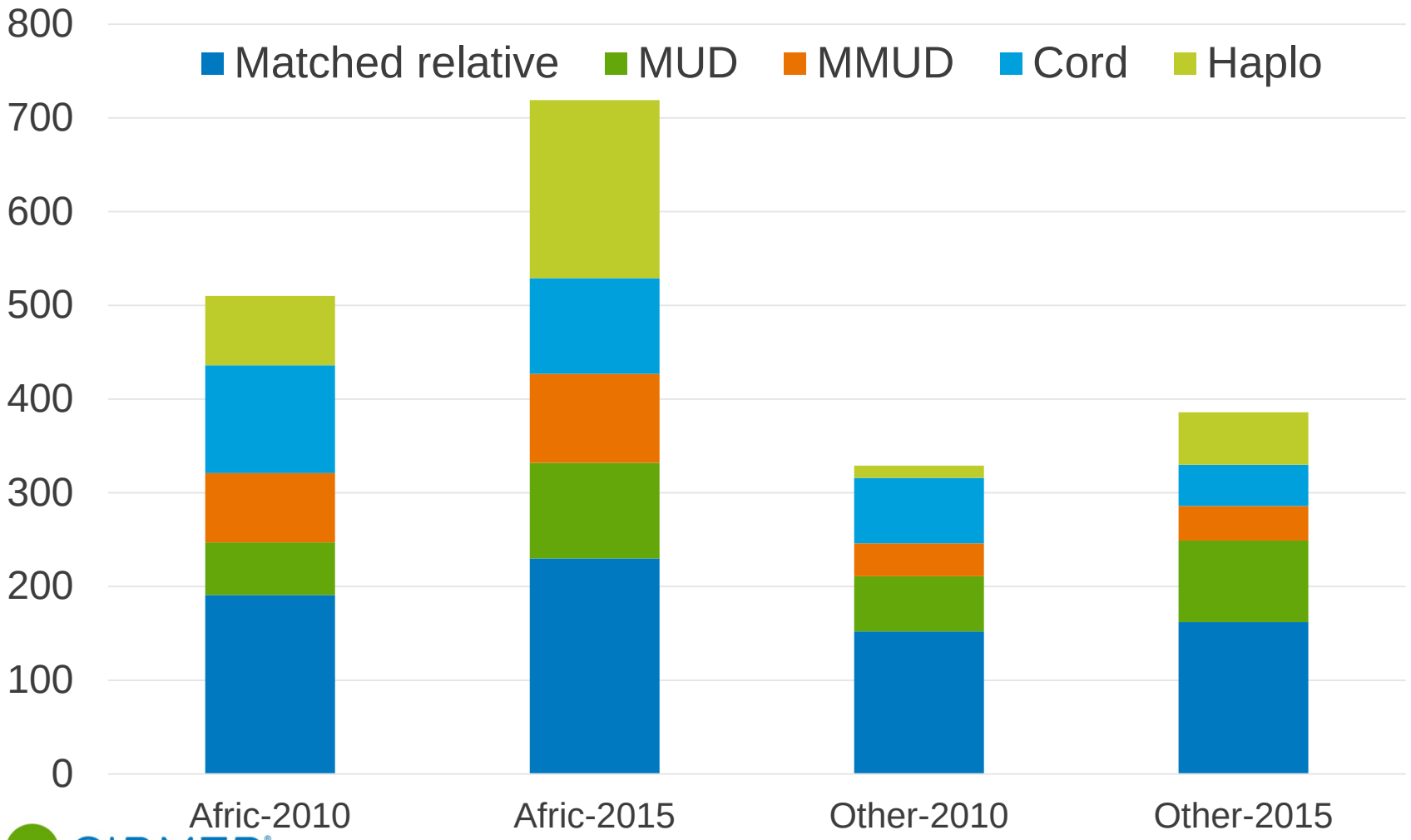
US Transplants by Race, Year and Donor Type (2)



US Transplants in non-Caucasians by Year and Donor Type (2)



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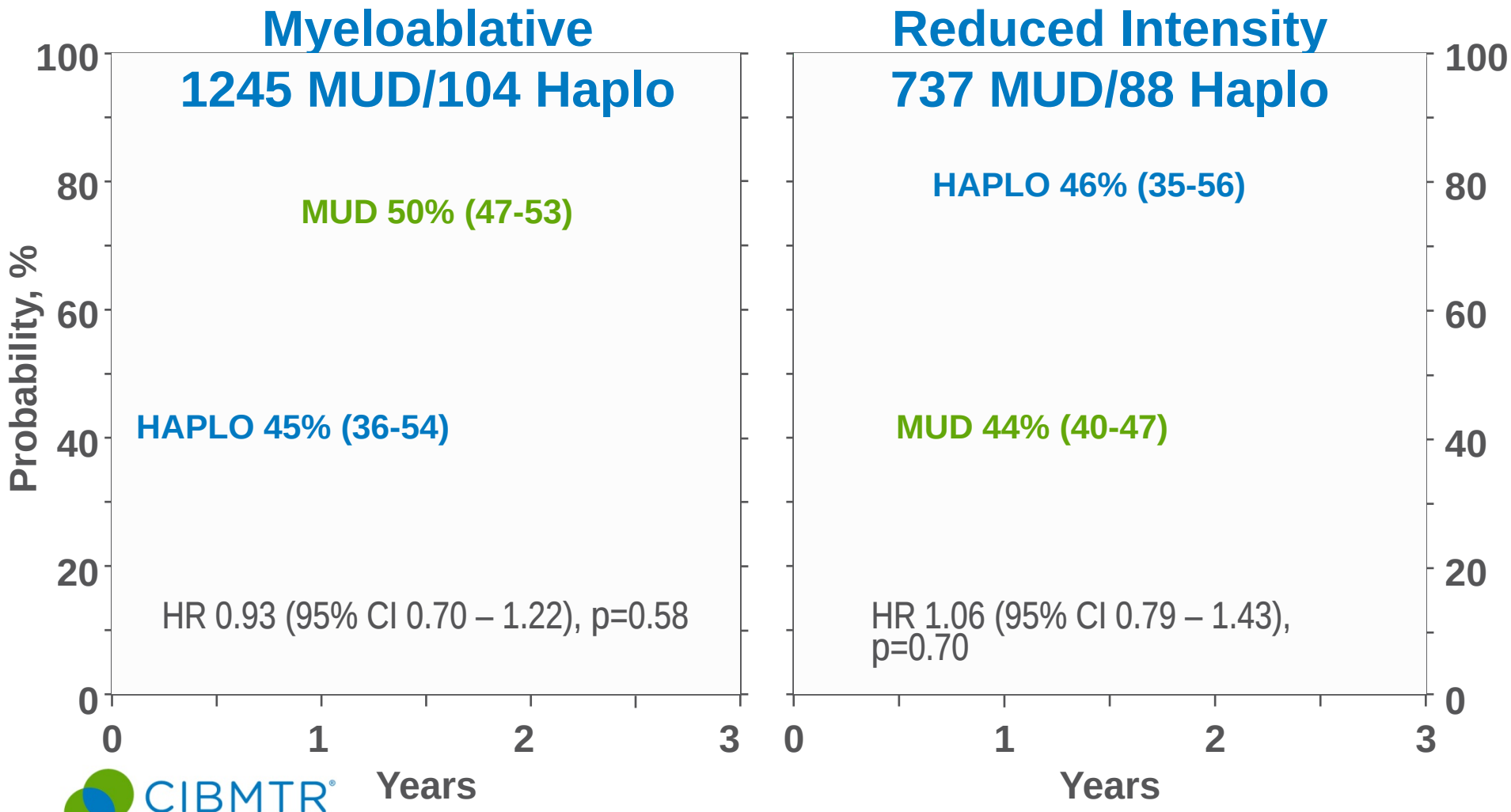
Overall Survival, Adjusted for Age, Disease Risk, Secondary AML (Ciurea, Blood, 2015)



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Limitation of this Analysis - POWER

COMPARISONS OF 3-Year SURVIVAL						
	Myeloablative: **1245** MUD/**104** Haplo			Reduced Intensity: **737** MUD/**88** Haplo		
	Point Estimate	Lower Bound	Upper Bound	Point Estimate	Lower Bound	Upper Bound
Matched Unrelated	50%	47%	53%	44%	40%	47%
Haploidentical	45%	**36%**	**54%**	46%	**35%**	**56%**

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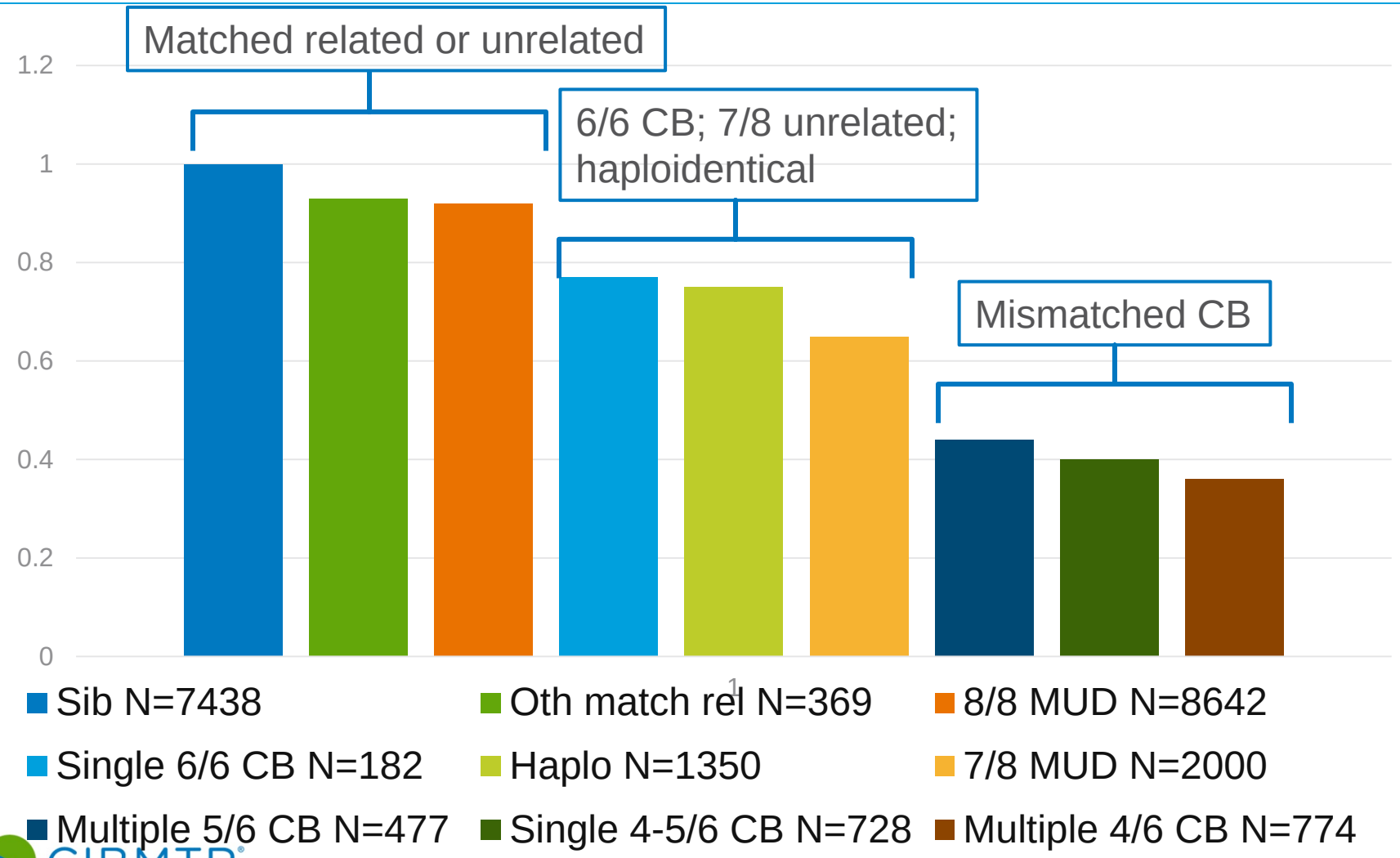
Impact of Donor Type on one-year mortality after HCTs done in 2012-2014



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What Do We Know About Haplos with Post-tx Cyclophosphamide?

- Haploidentical HCT can be performed with low GVHD and low early TRM and acceptable 2-3 year overall mortality, when used with postCy
- Haploidentical HCT is increasingly used, predominantly for adult patients who do not have an HLA-matched adult donor – and some who do

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Some Unknowns About Haplos with Post-tx Cyclophosphamide

- Long-term control of malignancy
- Engraftment in non-malignant diseases
- Optimal graft type (PB or BM) or conditioning regimen
- Suitability of Older Donors
  - More graft failure
  - Clonal hematopoiesis more common with older donors – uncertain significance

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Some Other Important Unknowns About Post-tx Cyclophosphamide

- Roles in HLA-mismatched unrelated donor transplantation
- Role in HLA-matched related and unrelated donor transplantation
- Viral immunity
- Are the same donor and recipient risk factors important for TRM, relapse and survival

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US National Trials Addressing Some of These Issues

- BMT CTN 1101: Haplo vs Cord with **reduced intensity conditioning**
- BMT CTN 1203: PostCy as GVHD prophylaxis with **matched** donors and **reduced intensity** conditioning
- BMT CTN 1301: PostCy as GVHD prophylaxis with **matched** donors and **myeloablative** conditioning
- BMT CTN 1502: Haplo with PostCy and UCB for **aplastic anemia**
- BMT CTN 1507: Haplo with PostCy in **Sickle Cell Disease**
- RCI BMT MMUD: PostCy as GVHD prophylaxis with **multiply mismatched unrelated donors**

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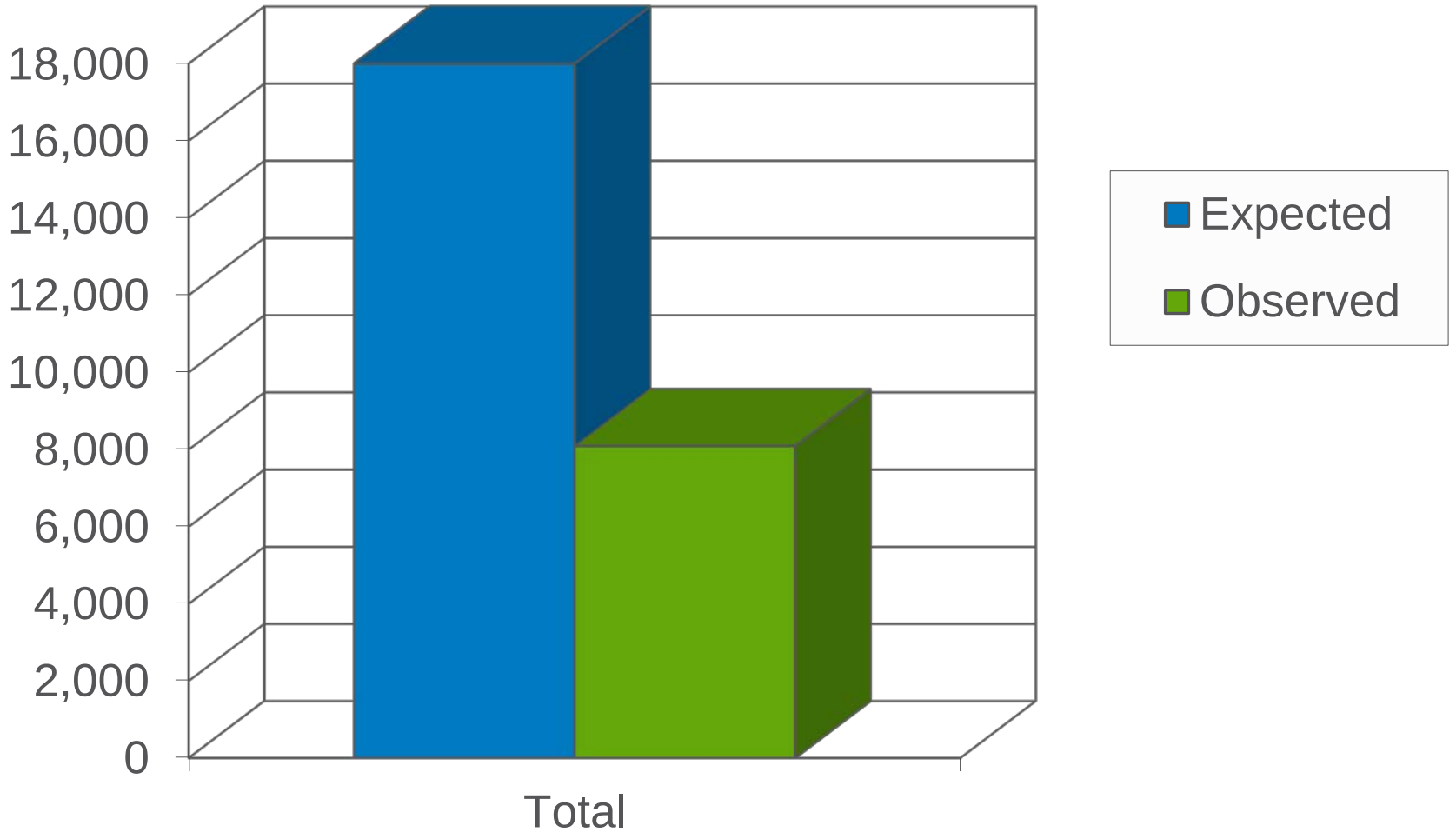
Allogeneic HCTs for all Standard Indications



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Conclusions

- **Few patients lack an acceptable donor**
- All donors (8/8, 7/8 adult, haplo, cord) produce outcomes that, if not identical, are in same range
  - Maximum differences in survival, compared to 8/8 adult donor, are in the range of 10%-15%
- Donor availability cannot fully account for differences in access to HCT in diverse ethnic and racial groups

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