Center for International Blood and Marrow Transplant Research – Trends in Use of Haploidentical Transplantation

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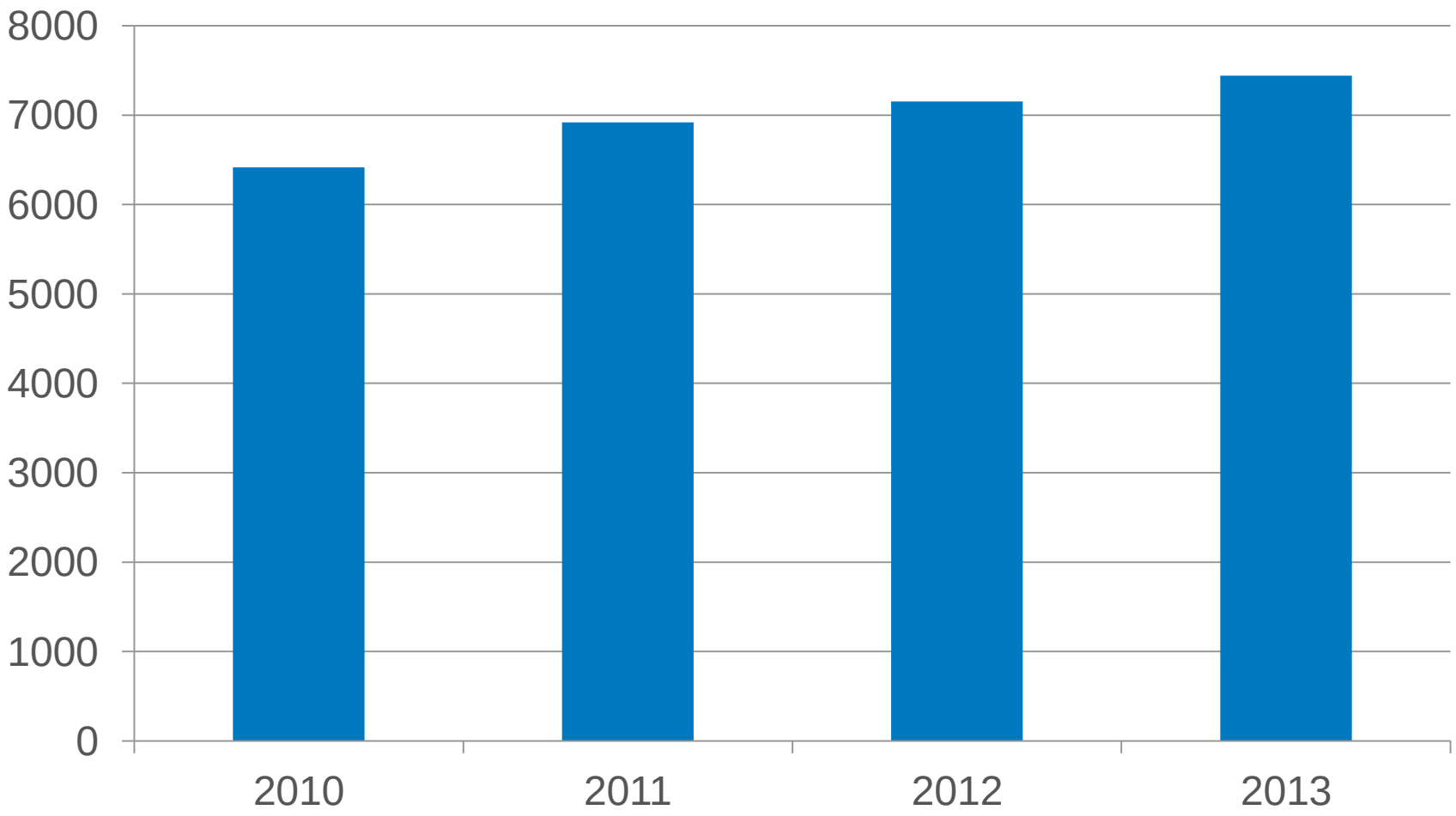
A research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin

Number of First Allogeneic HCTs in the US By Year



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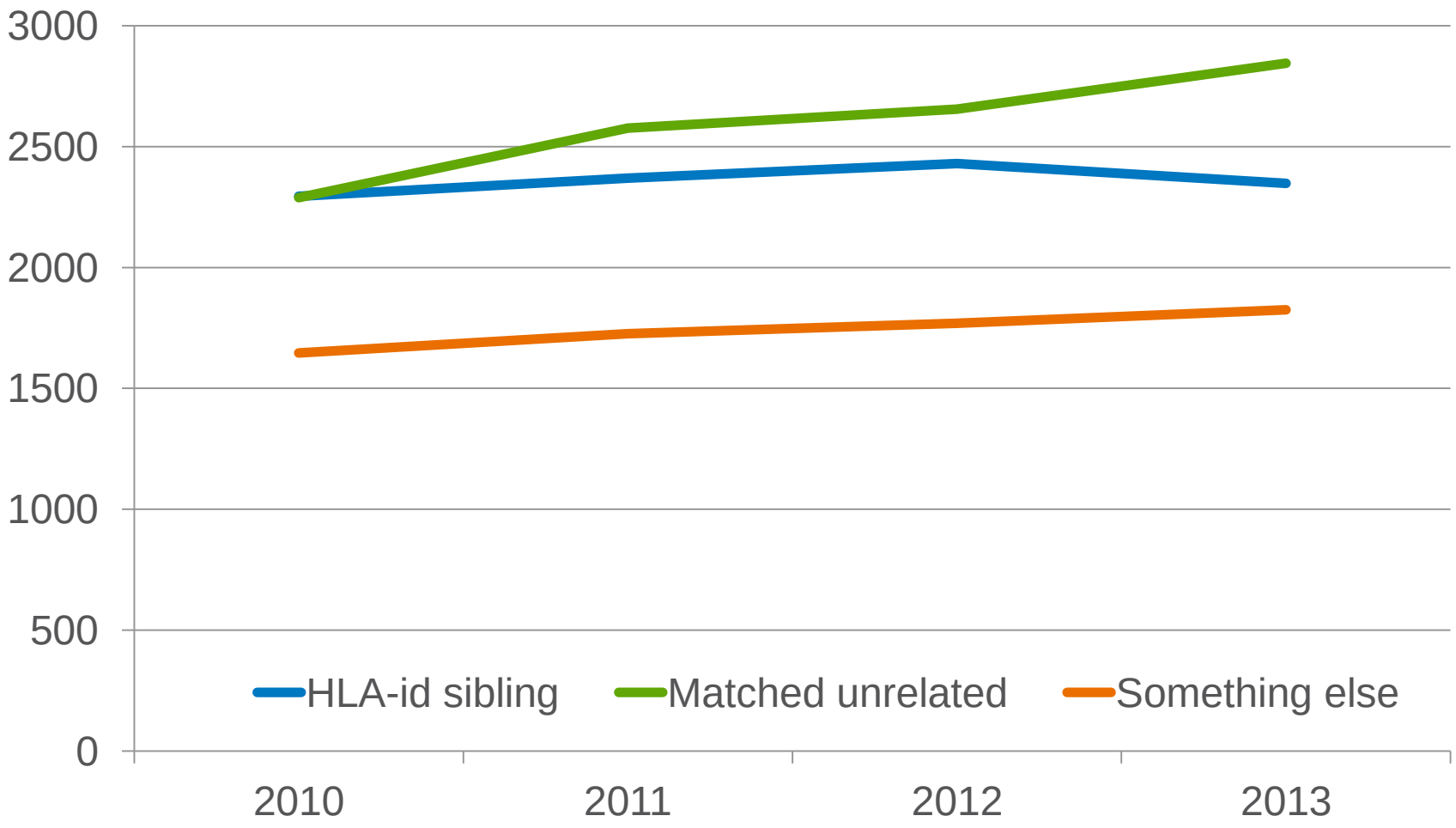
CIBMTR, unpublished data

Numbers of Allogeneic HCTs in the US By Year and Donor Type



Excludes twins, related CB, 0-1 mism relatives

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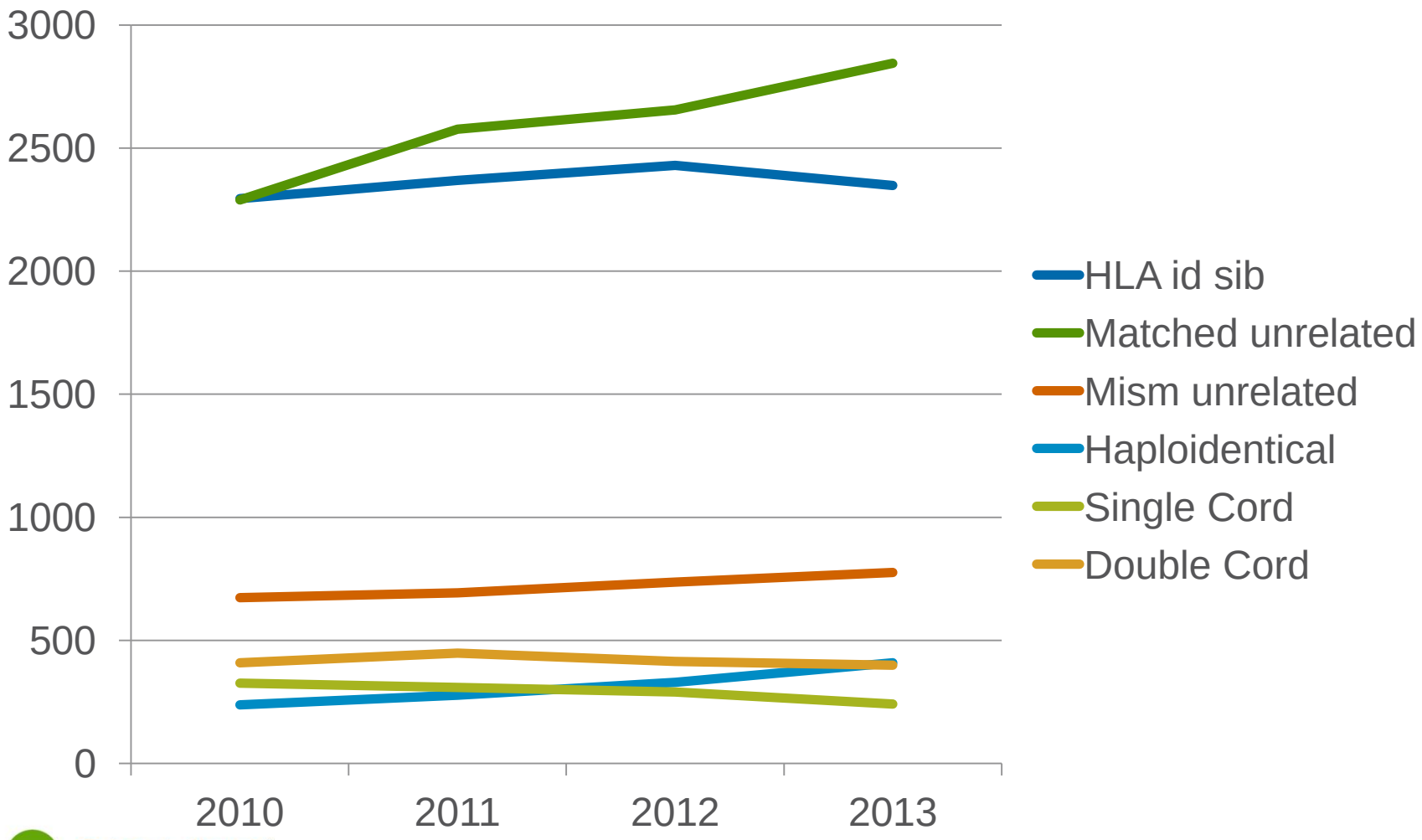
Numbers of Allogeneic HCTs in the US By Year and Donor Type



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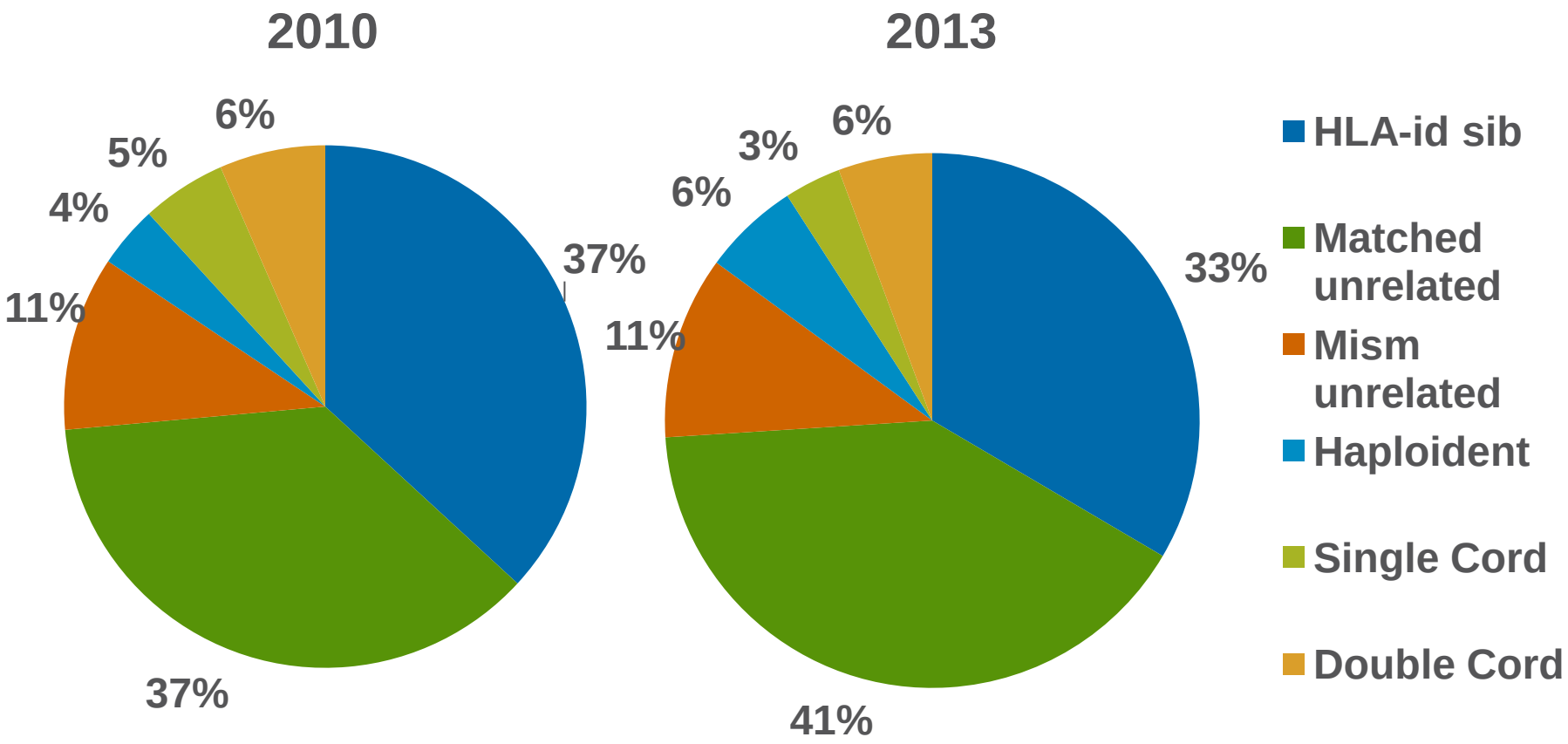
Excludes twins, related CB, 0-1 mism relatives

Distribution of Graft Sources



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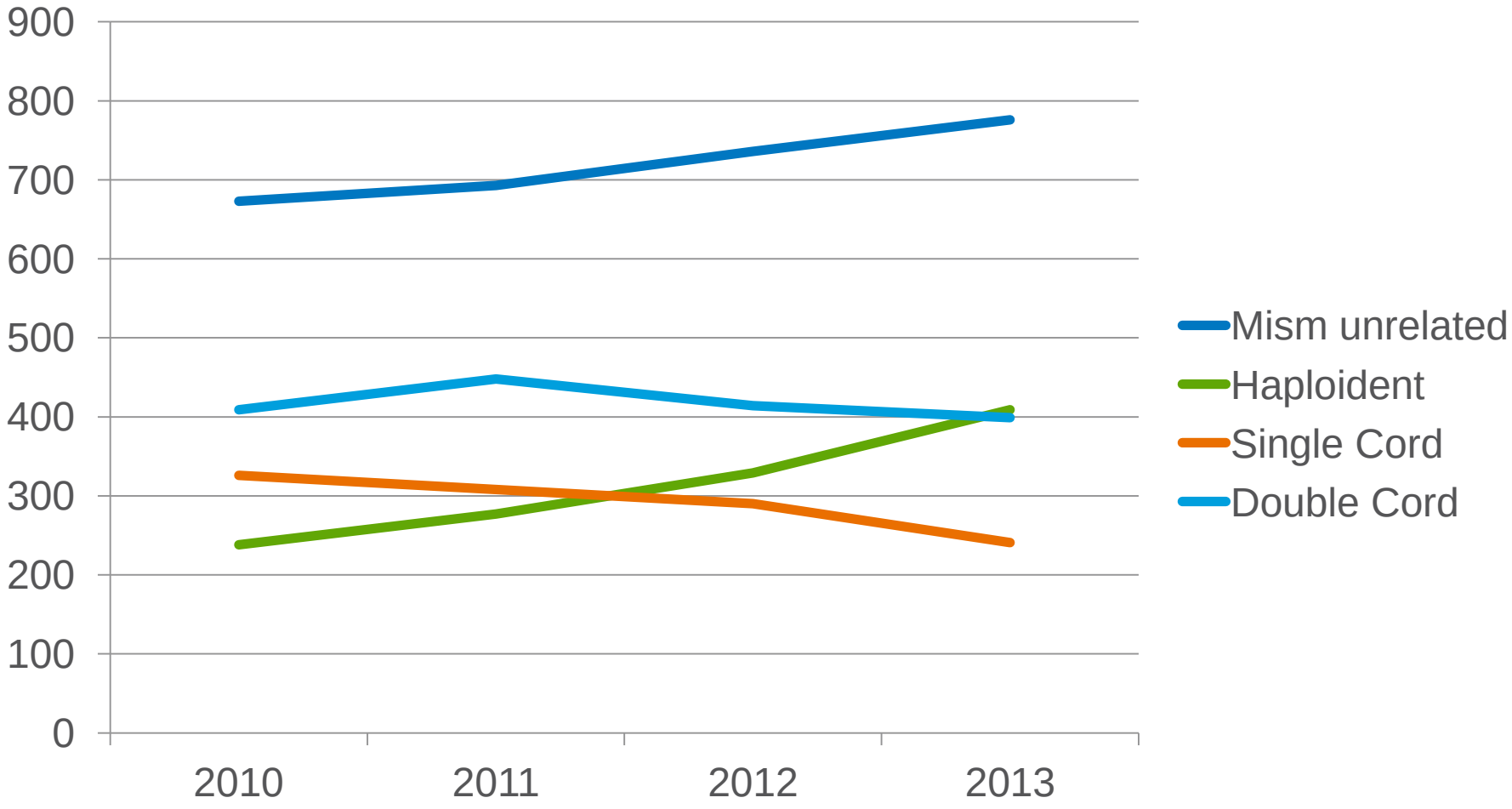
“Alternative Donor” Transplants in the US by Year and Graft Type



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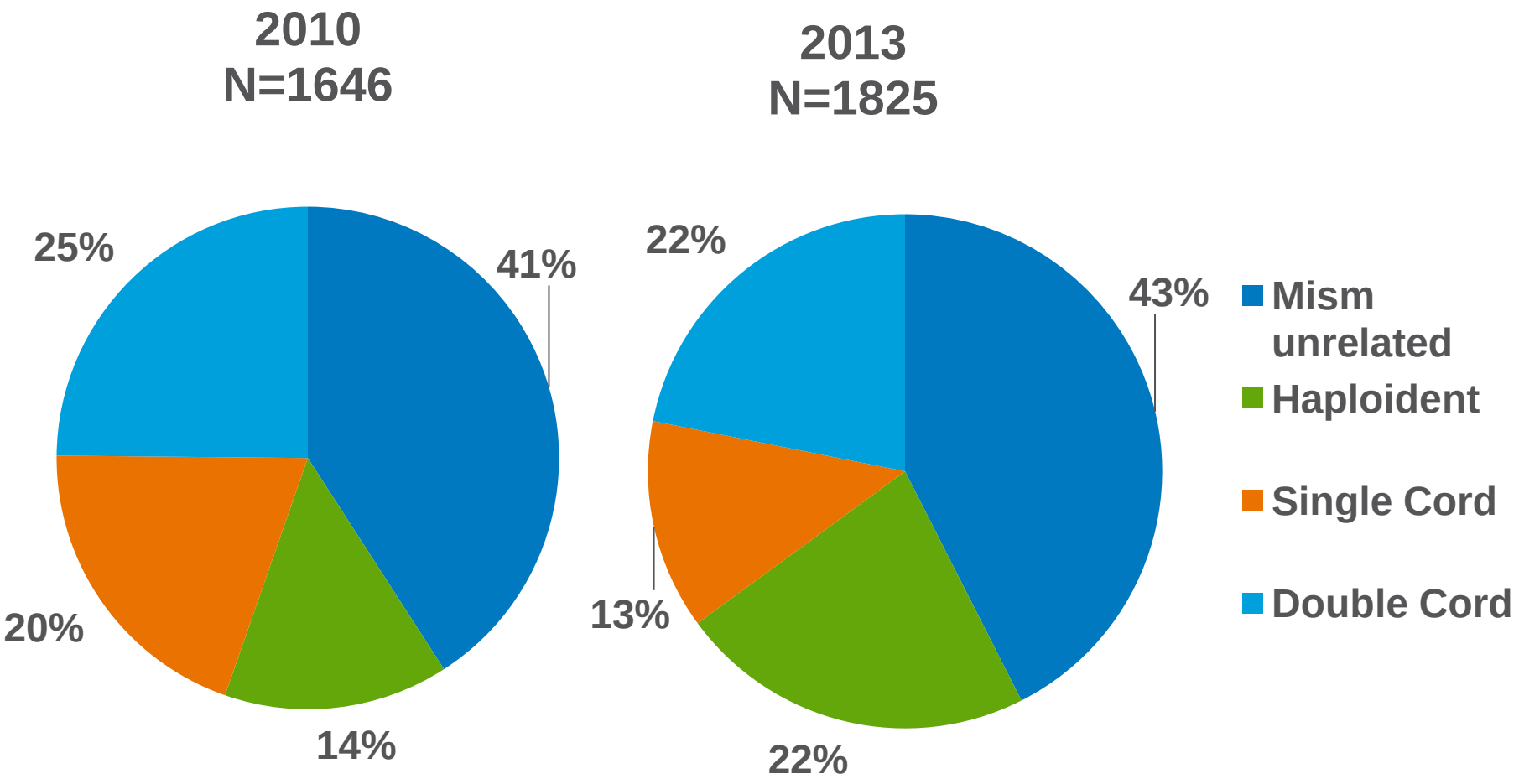
Distribution of Alternative Graft Sources



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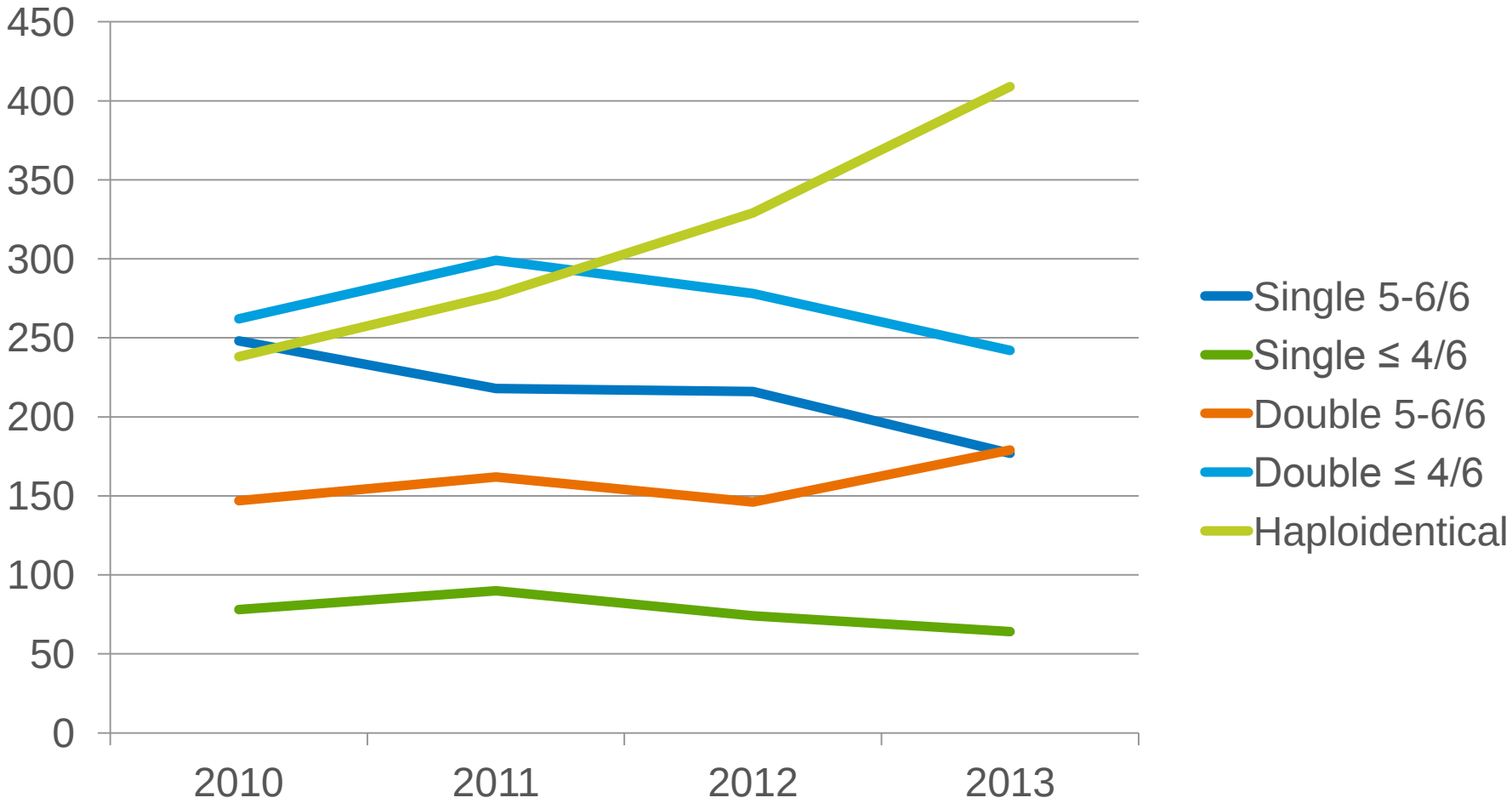
Umbilical Cord Blood & Haploidentical Transplants in the US by Year & HLA Match



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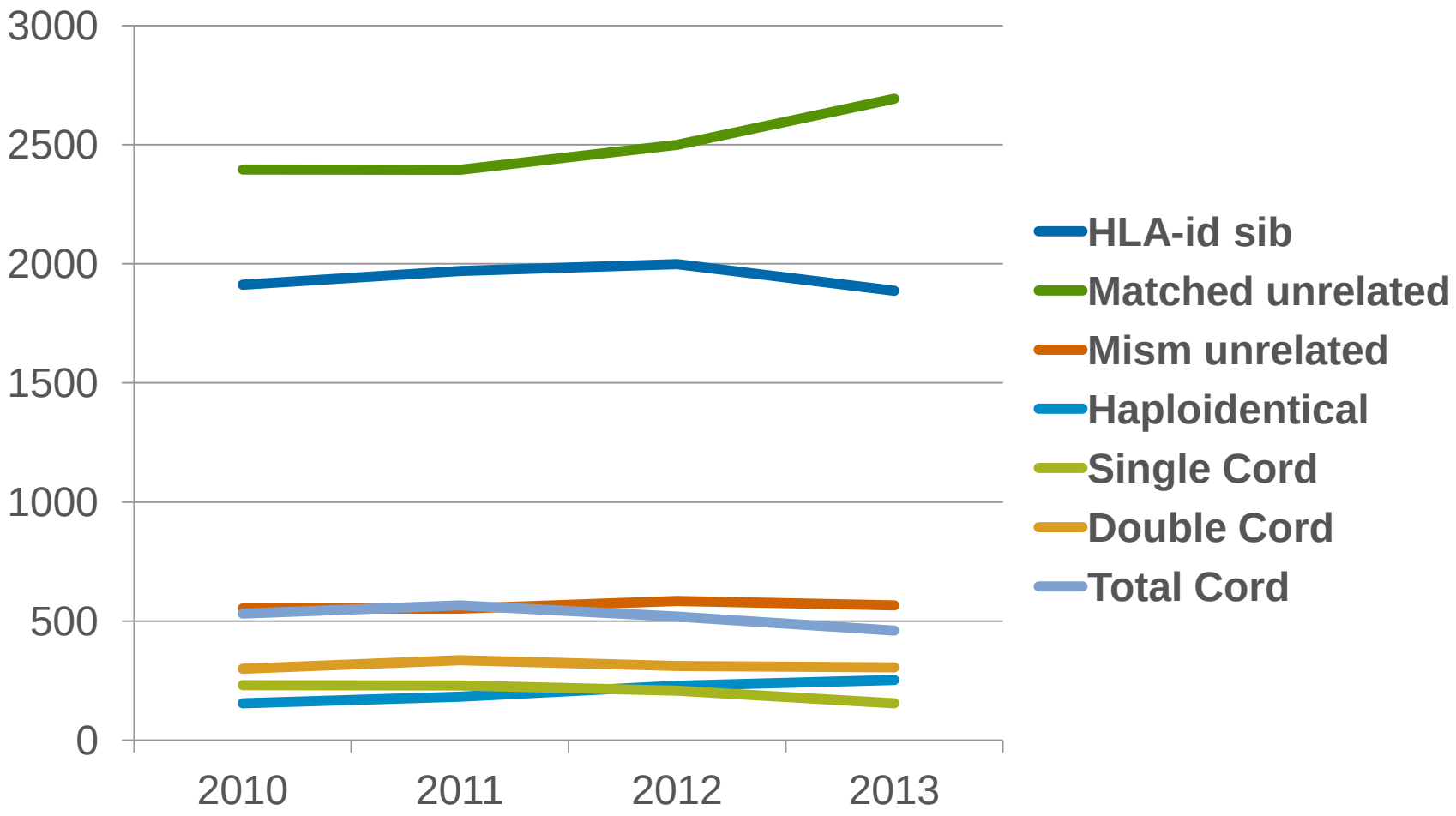
Numbers of Allogeneic HCTs in US Caucasians By Year and Donor type



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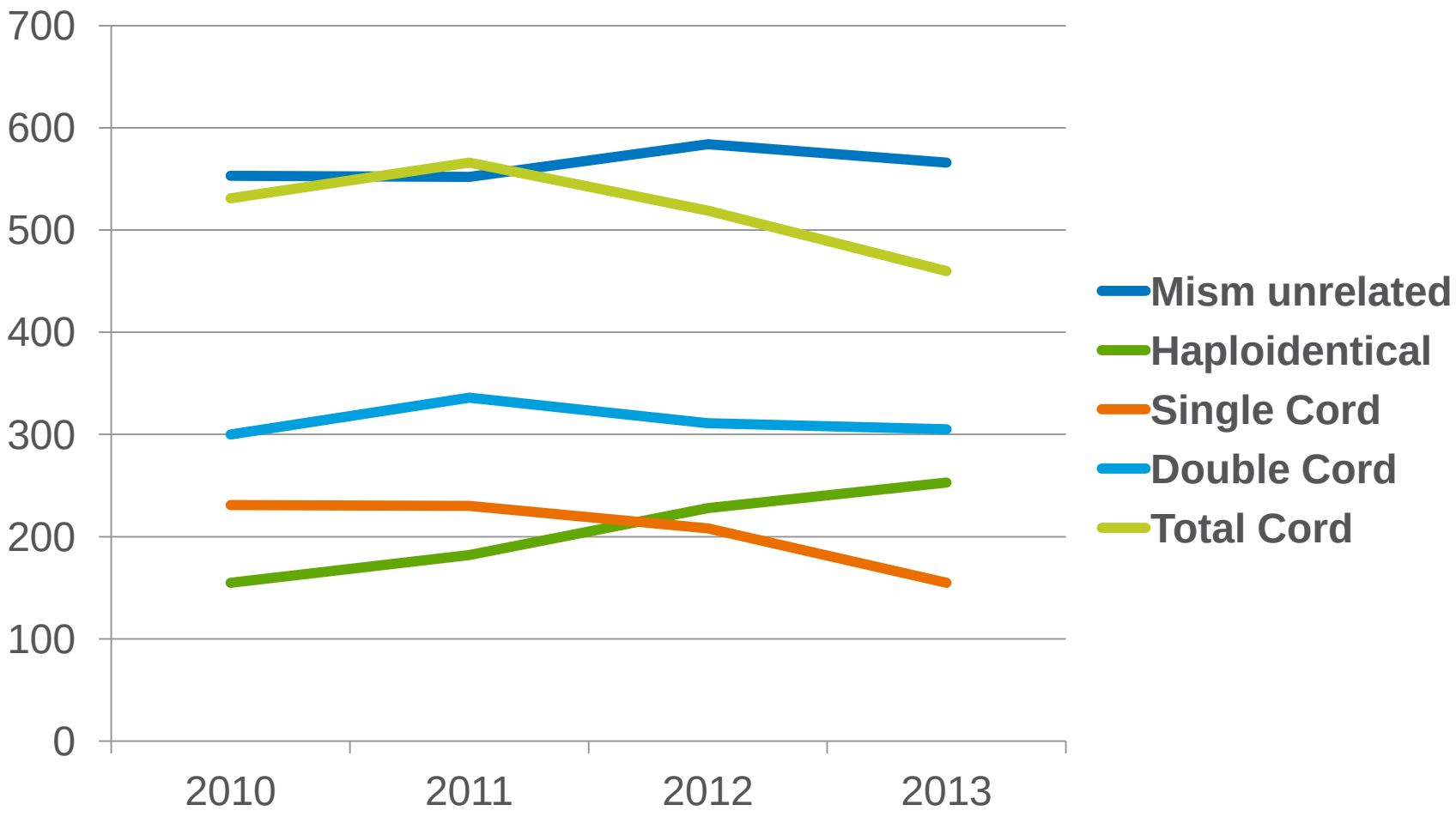
Numbers of Alternative Donor HCTs in US Caucasians By Year and Donor type



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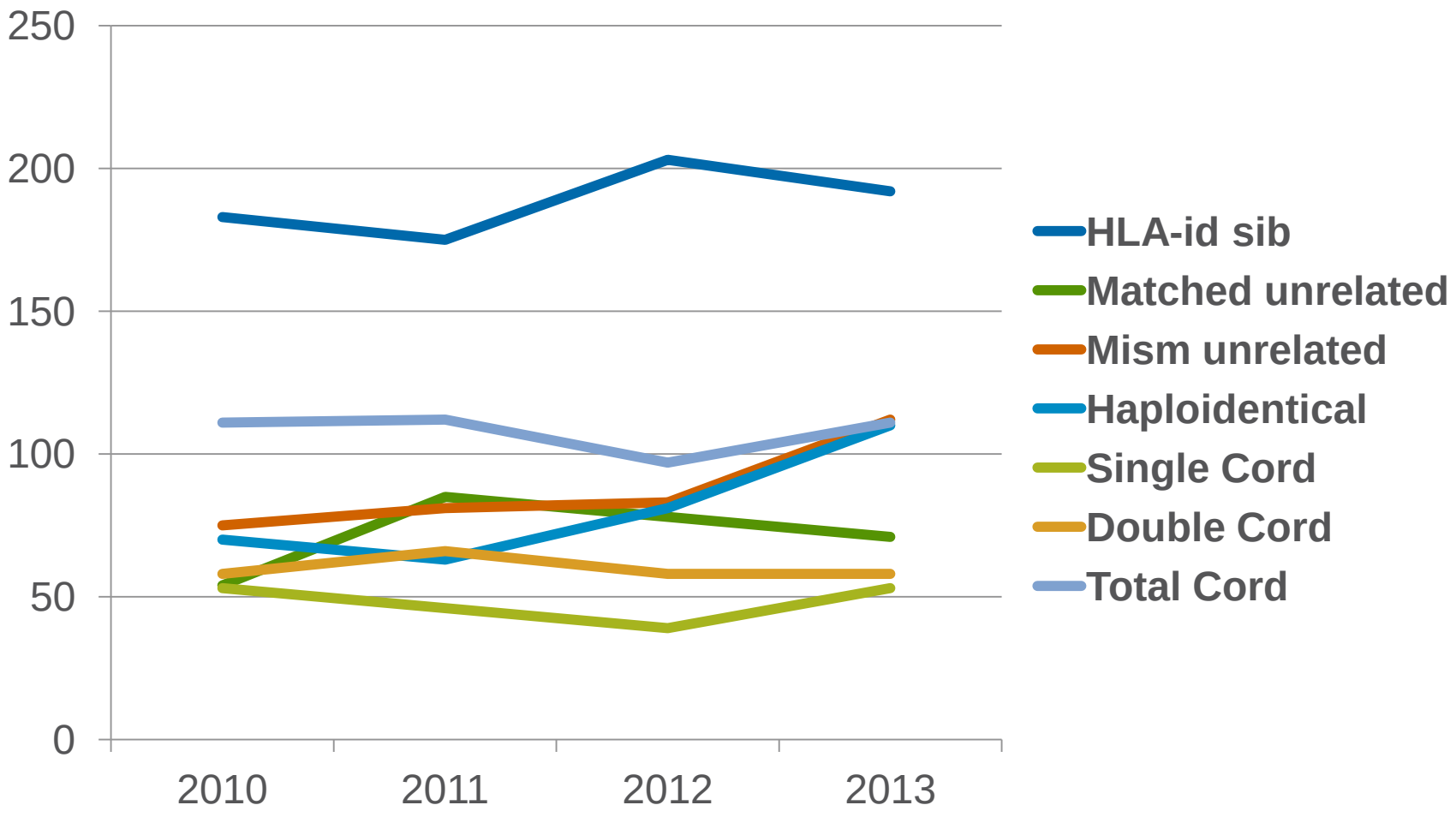
Numbers of Allogeneic HCTs in African-Americans By Year and Donor type



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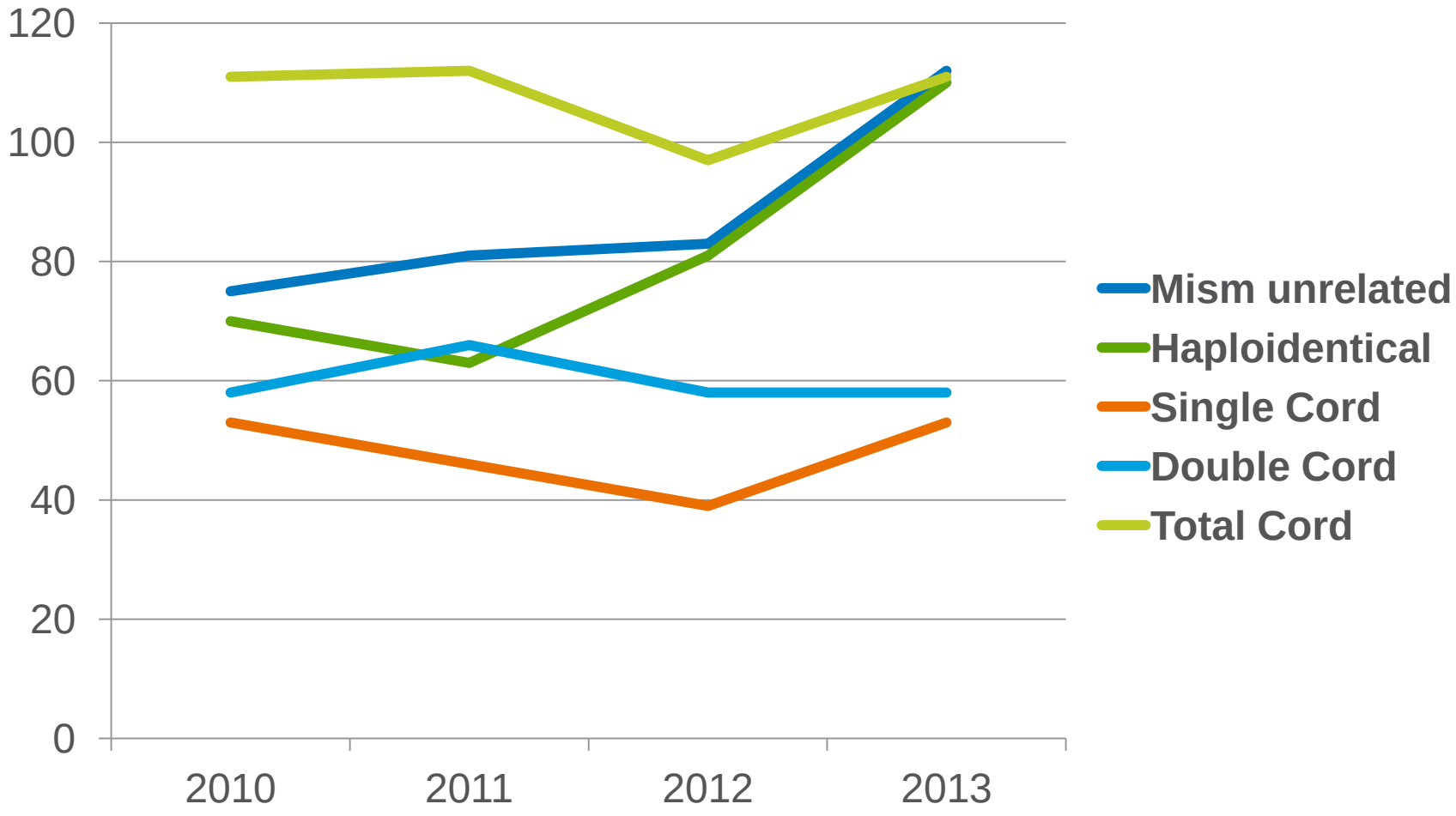
Numbers of Alternative Donor HCTs in African-Americans By Year & Donor type



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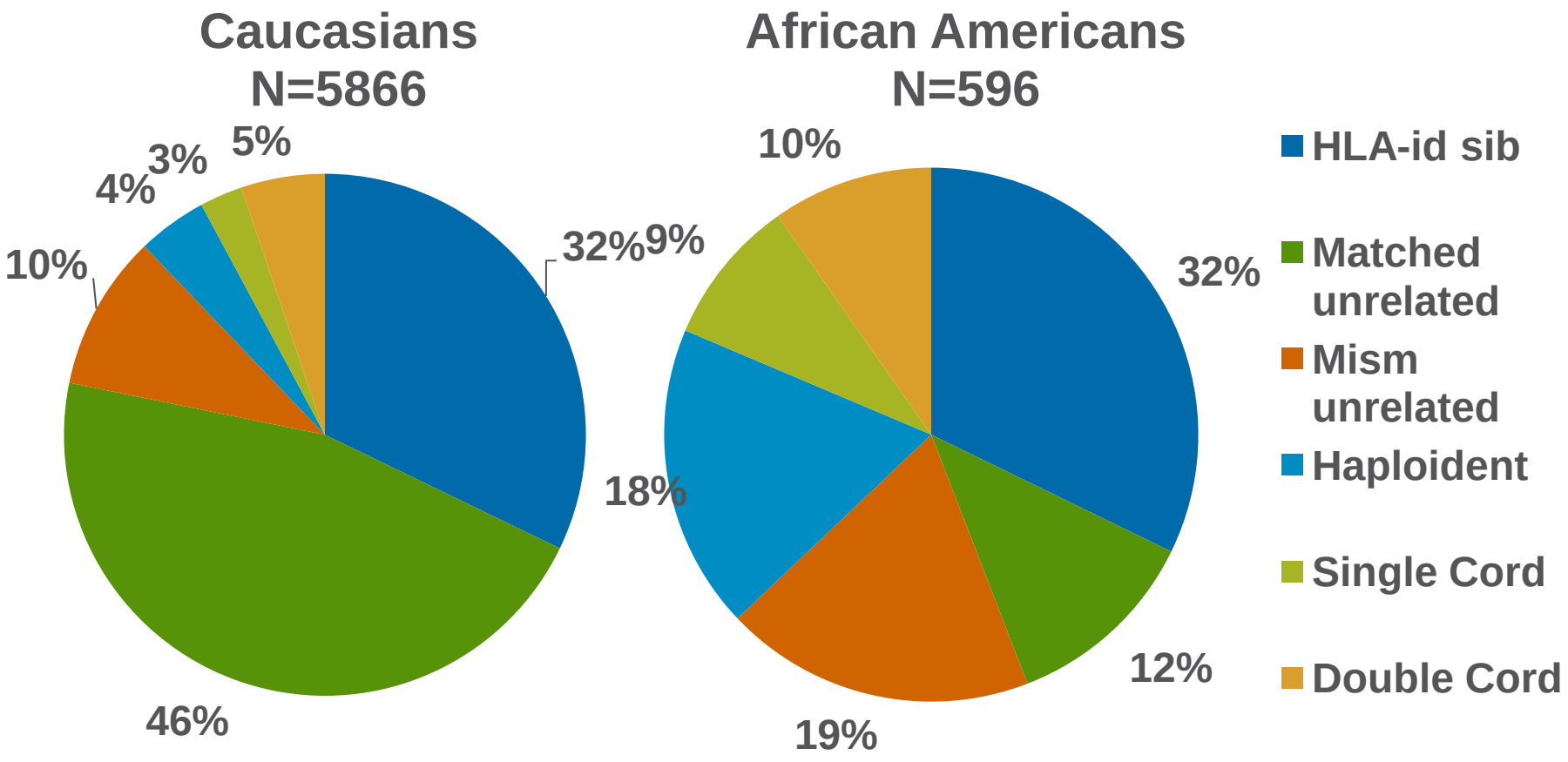
Distribution of Graft Sources – 2013



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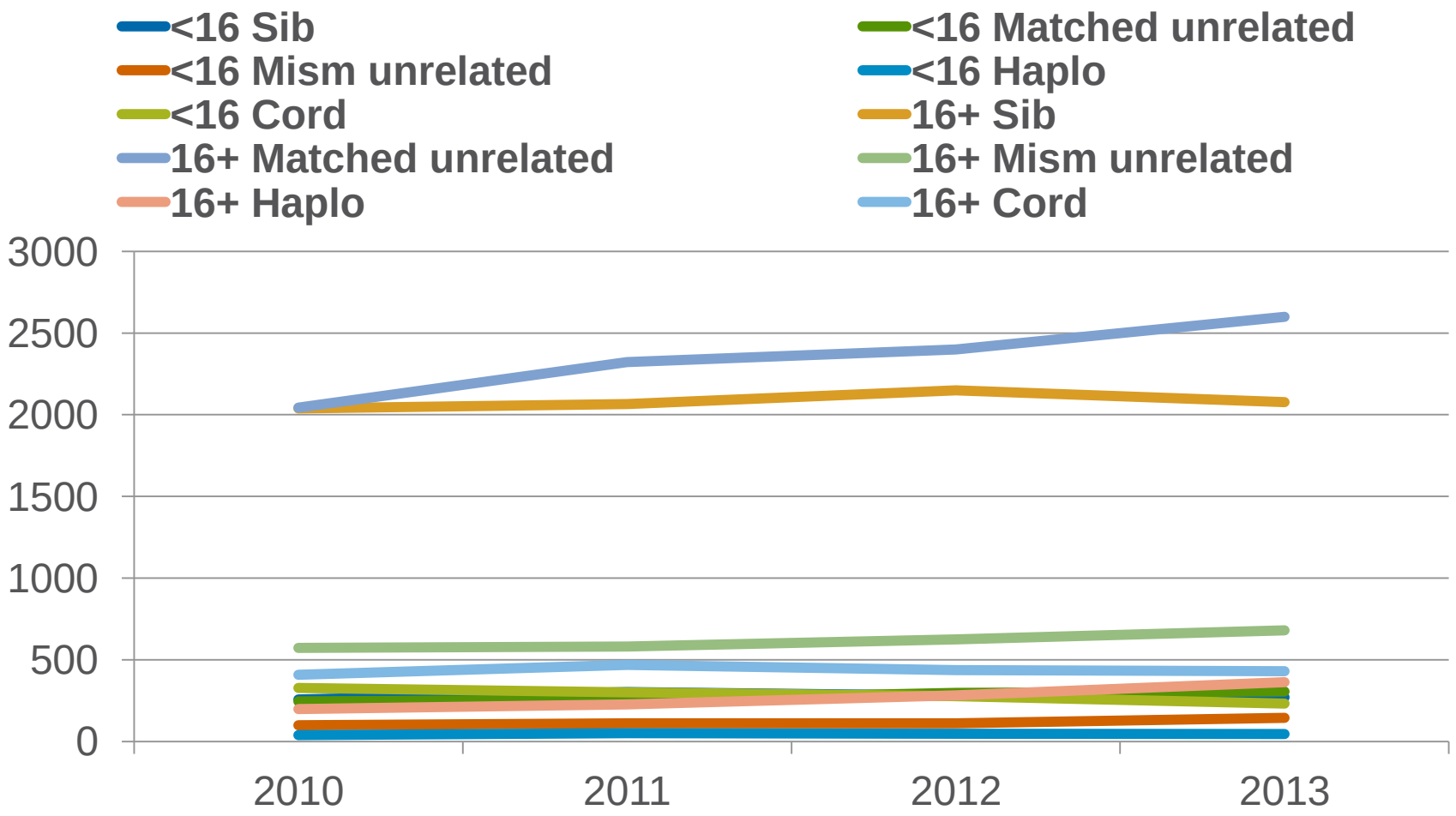
Numbers of Allogeneic HCTs by Age, Year and Donor type



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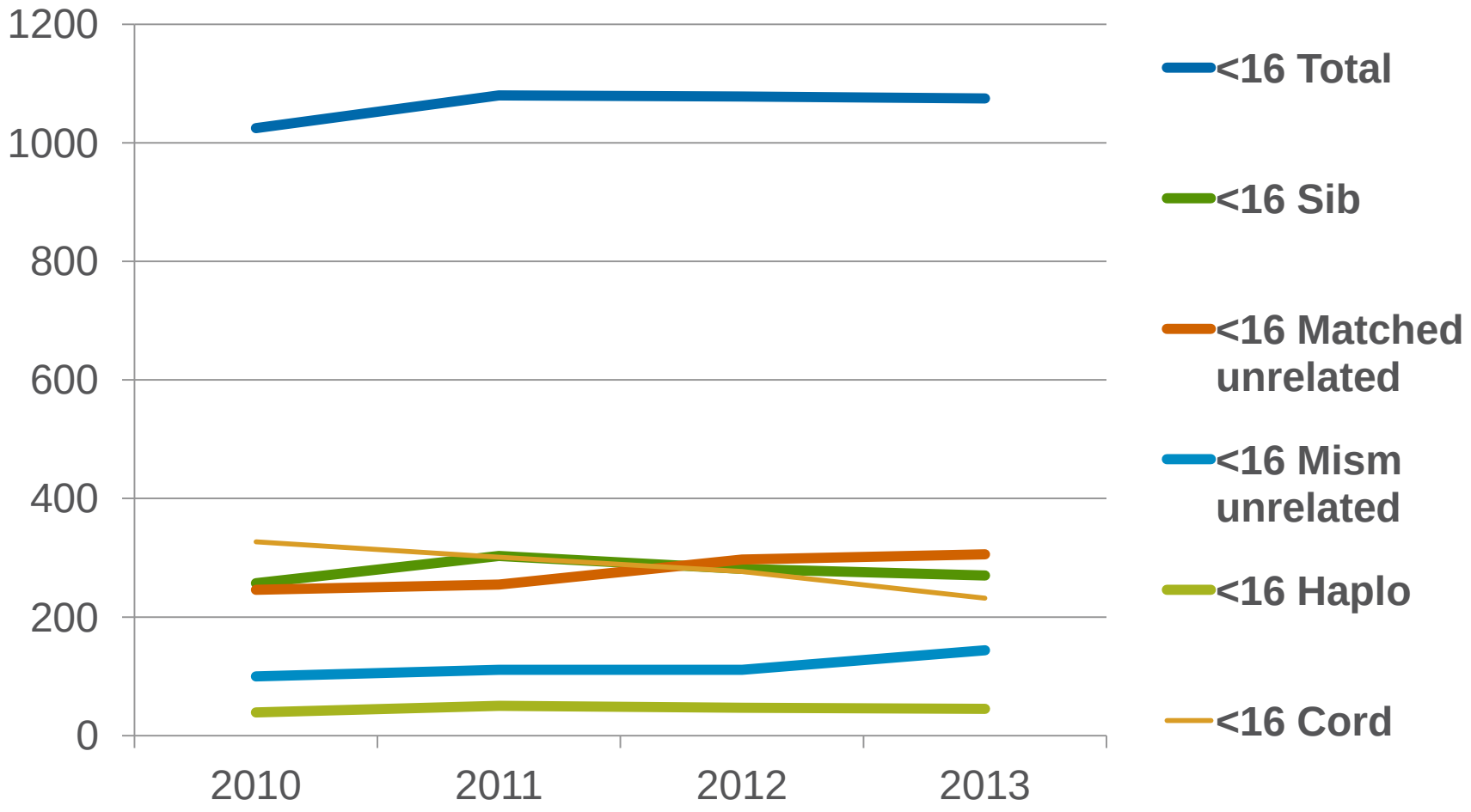
Numbers of Allogeneic HCTs in Children by Year and Donor type



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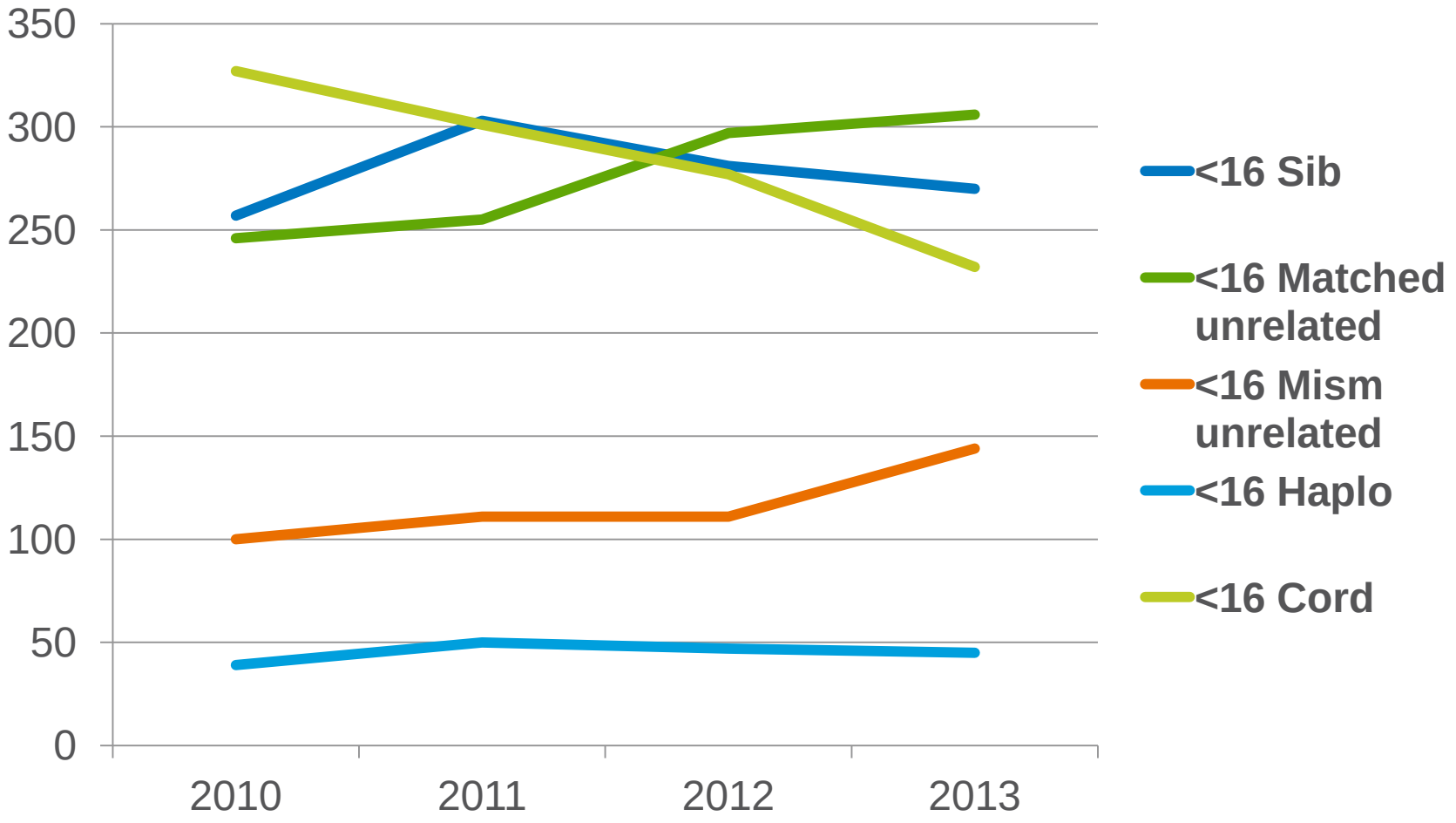
Numbers of Allogeneic HCTs in Children by Year and Donor type



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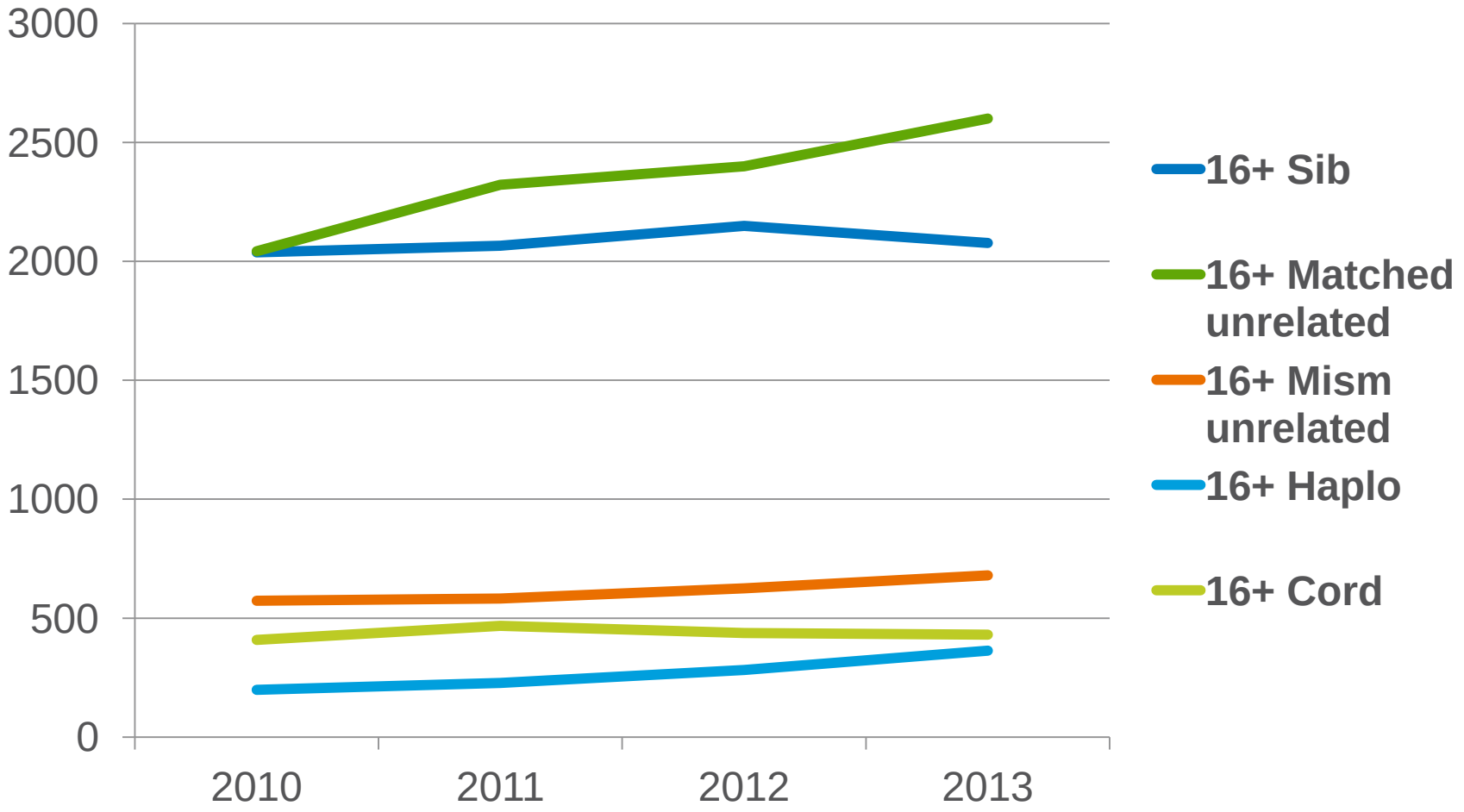
Numbers of Allogeneic HCTs in Adults by Year and Donor type



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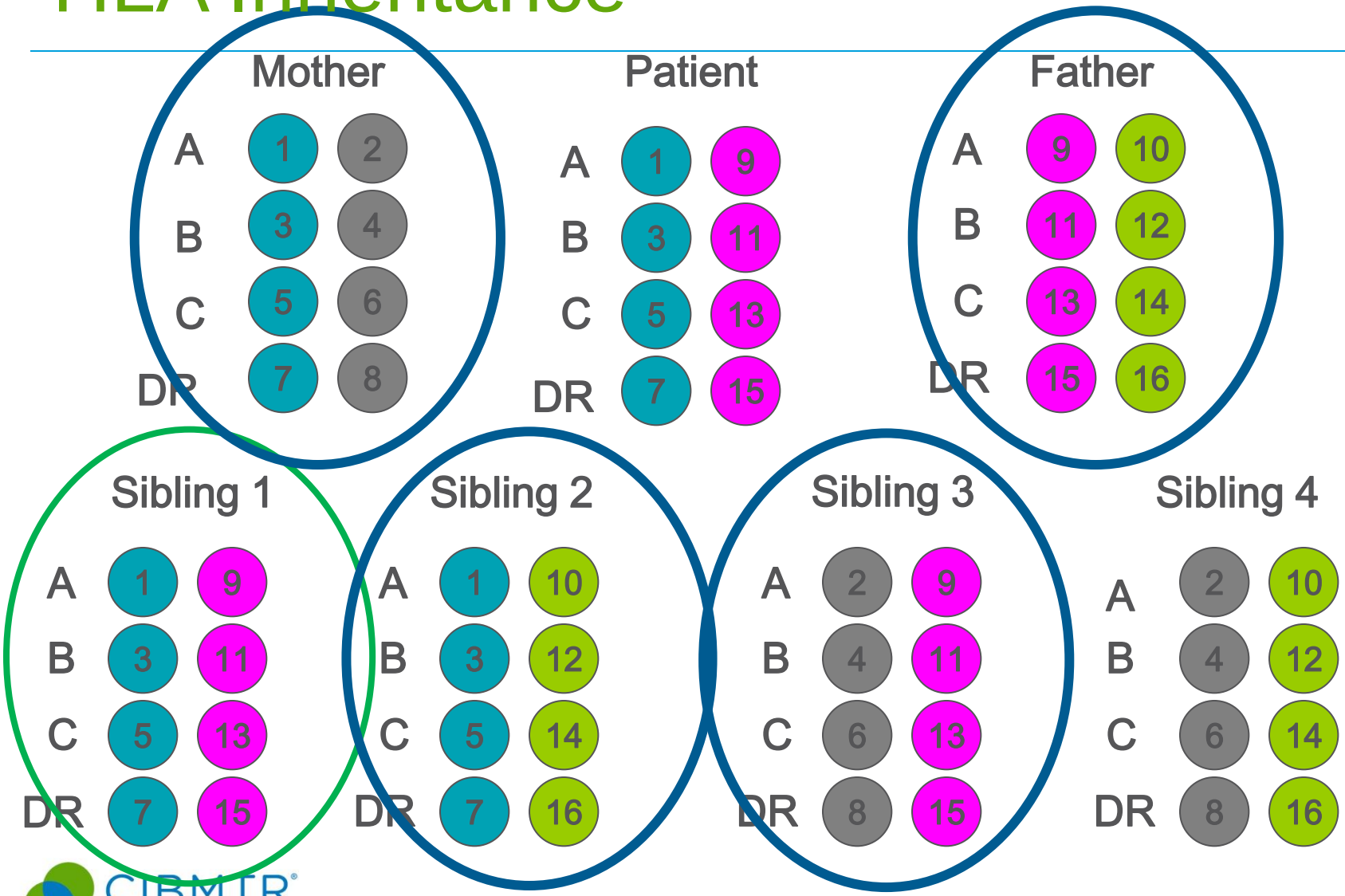
HLA Inheritance



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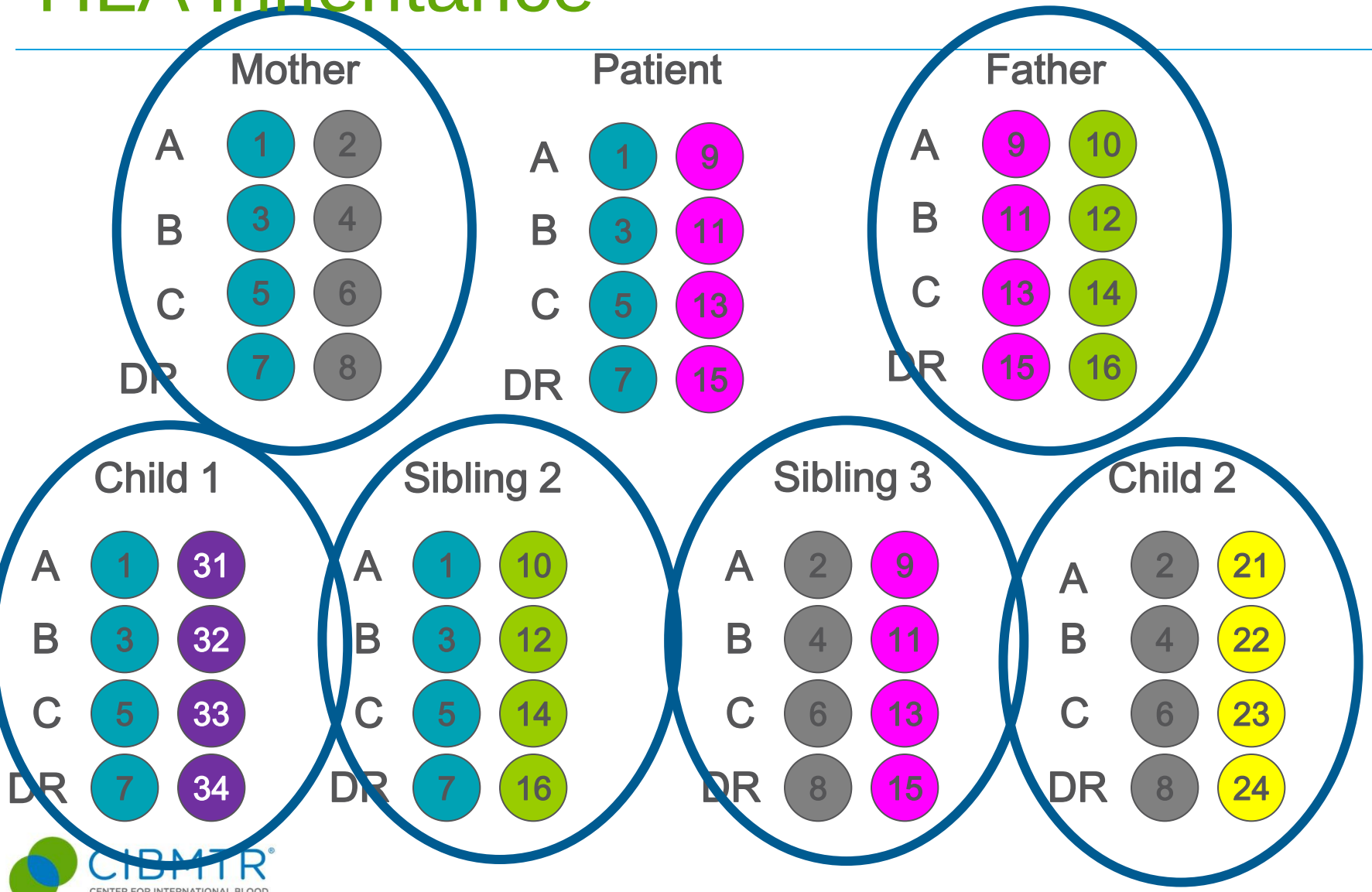
HLA Inheritance



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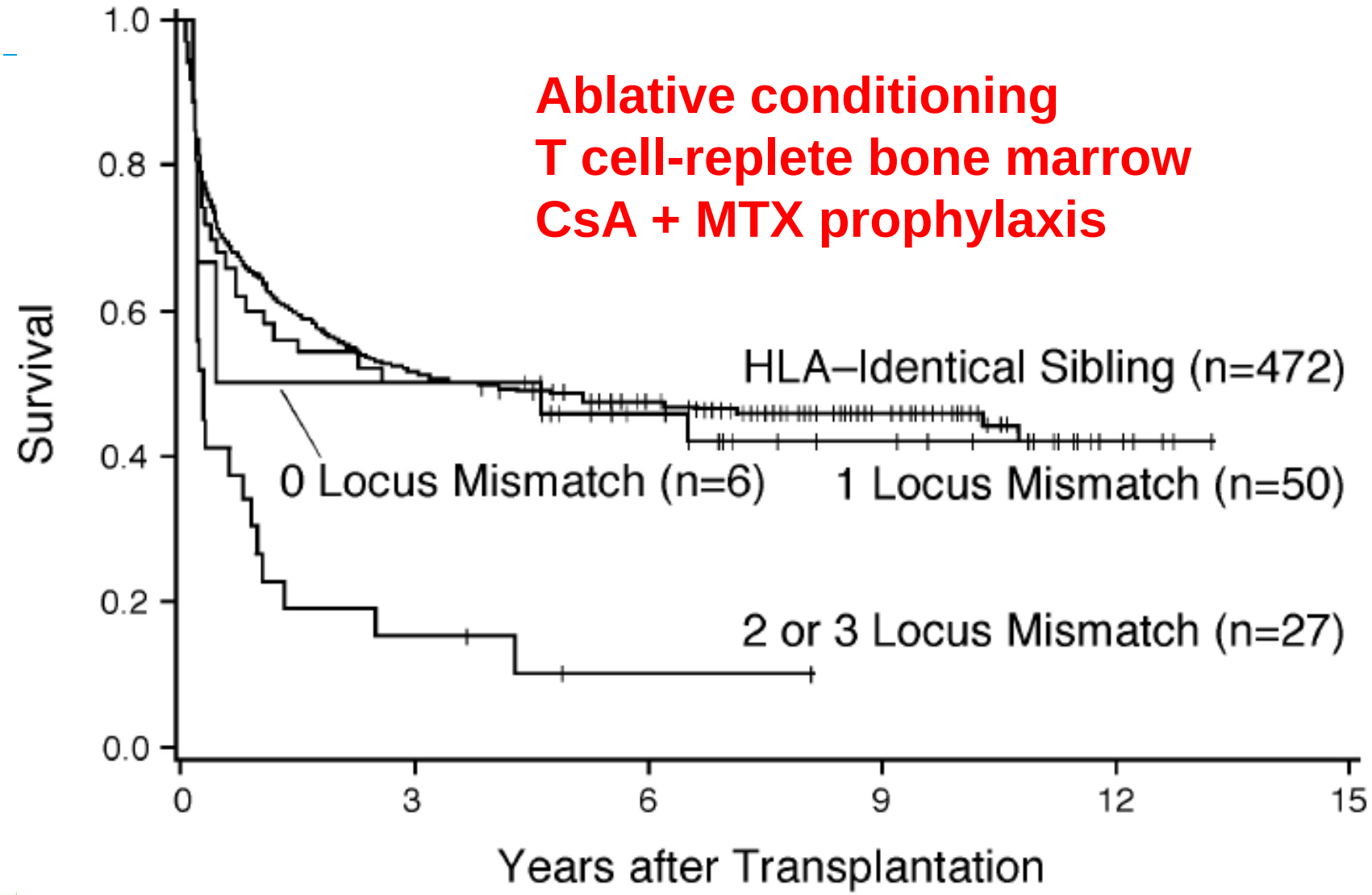
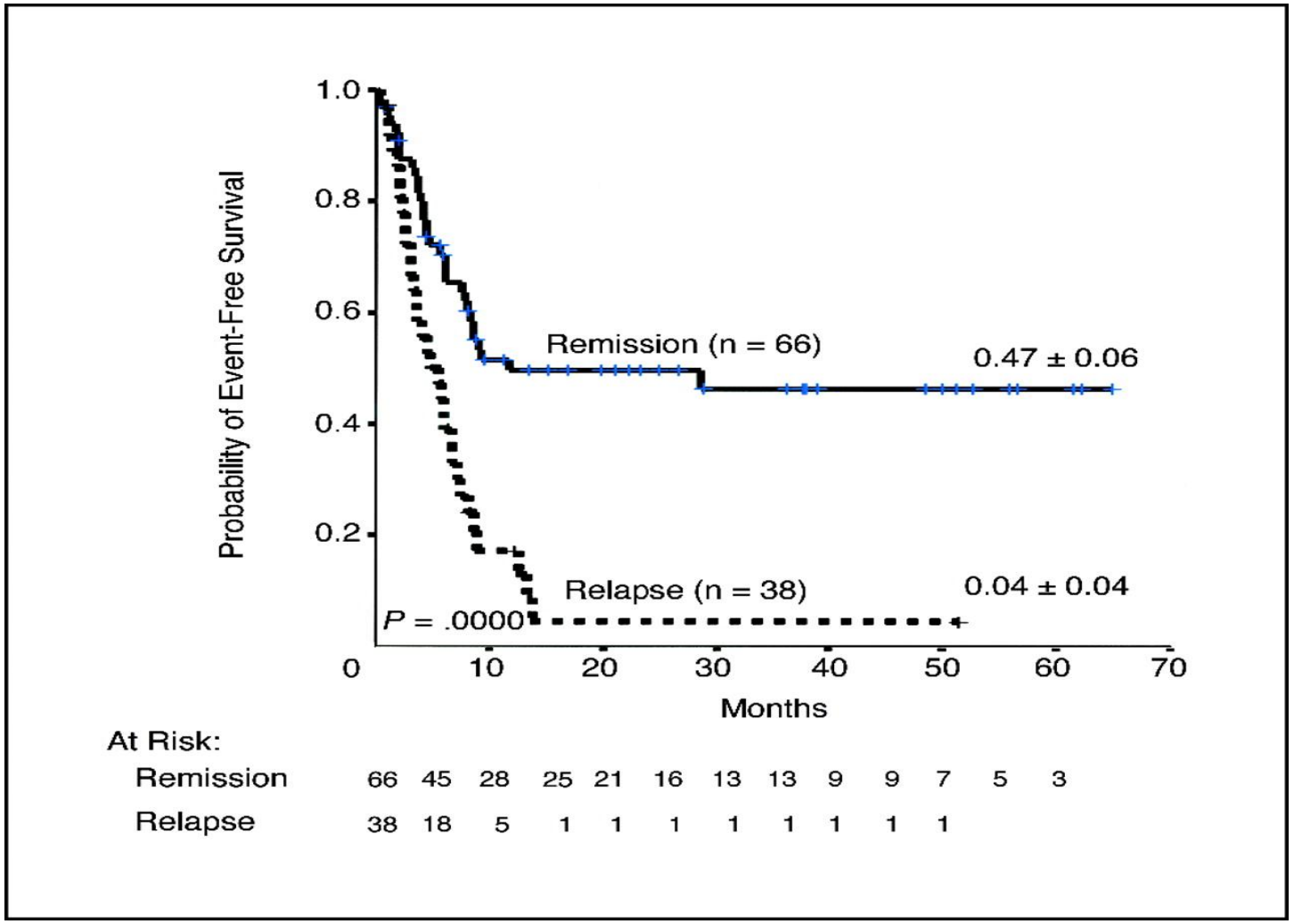
HLA-haploidentical BMT *circa 1990*



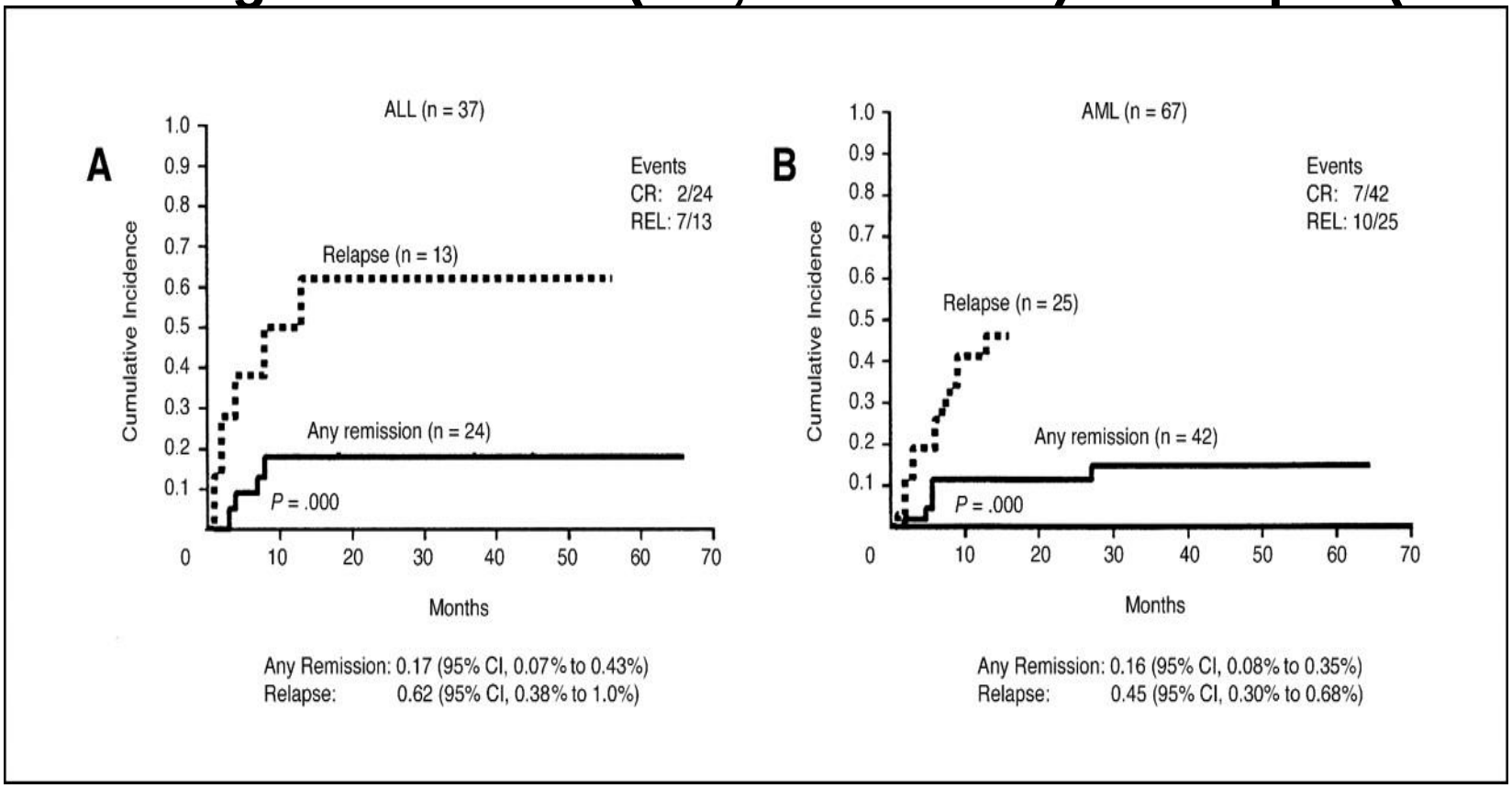
C Anasetti et al., Hum Immunol 29:79, 1990

Probability of event-free survival in 66 patients who received transplantation in remission and 38 patients who received transplantation in relapse.



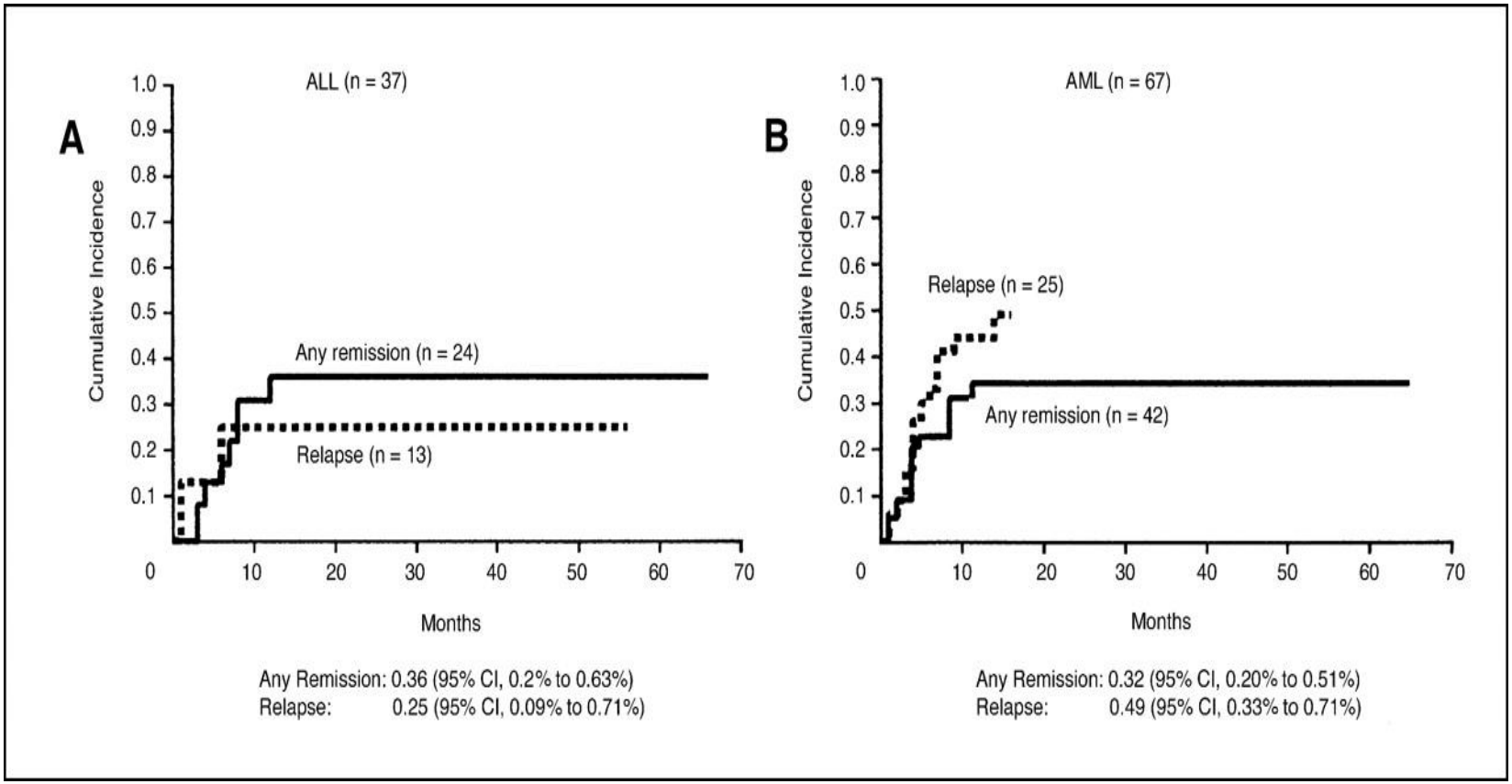
Aversa F et al. JCO 2005;23:3447-3454

Cumulative incidence of leukemia relapse at 2 years for patients with acute lymphoblastic leukemia (ALL; A) or acute myeloid leukemia (AML; B) who were in either hematologic remission (CR; solid lines) or relapse (REL;



Aversa F et al. JCO 2005;23:3447-3454

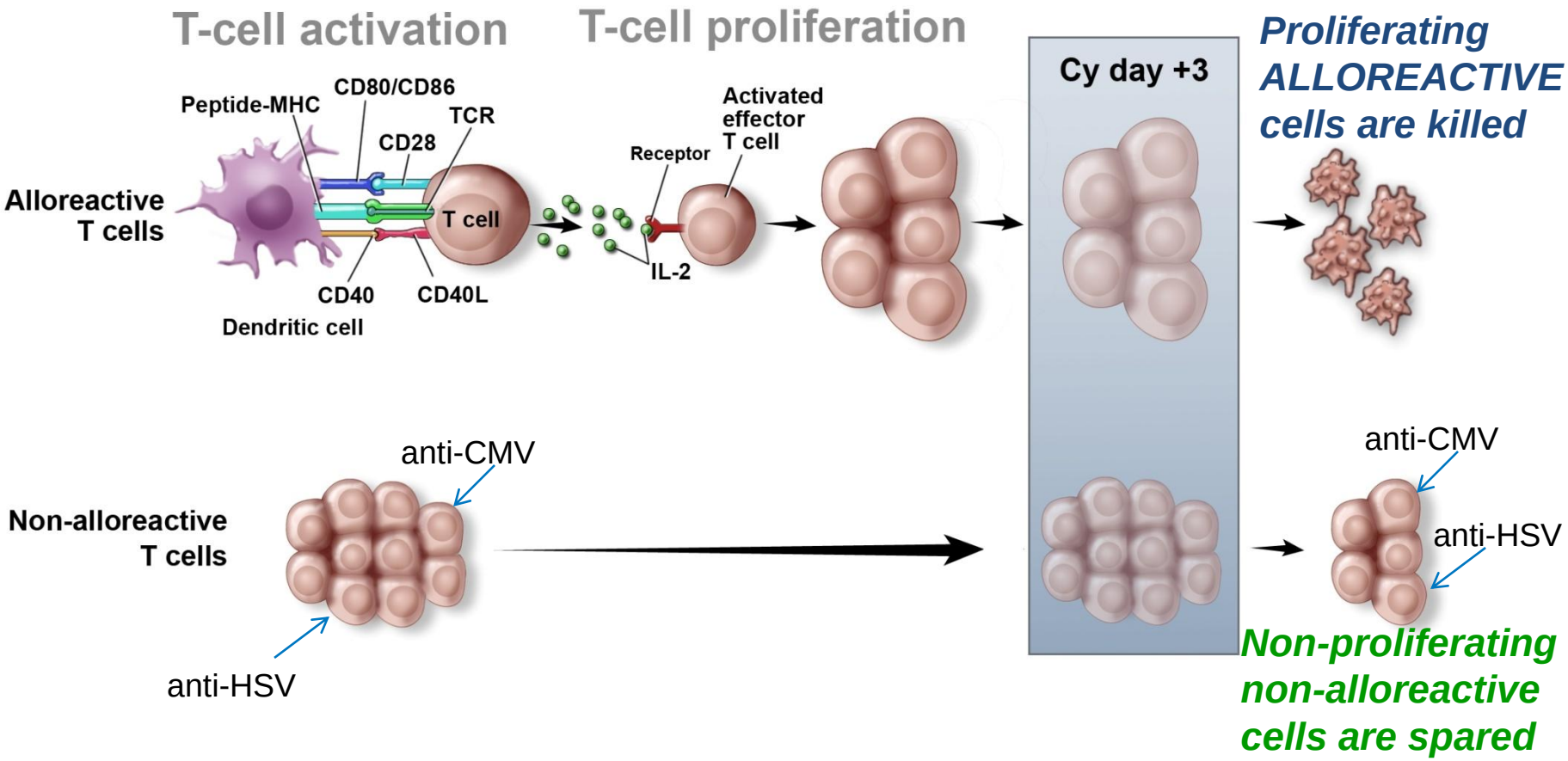
Cumulative incidence of transplant-related deaths at 2 years for patients with acute lymphoblastic leukemia (ALL; A) or acute myeloid leukemia (AML; B) who were in either hematologic remission (solid lines) or relapse (dotted lines) at transplantation.



Aversa F et al. JCO 2005;23:3447-3454

JOURNAL OF CLINICAL ONCOLOGY ASCO

Cyclophosphamide-induced tolerance



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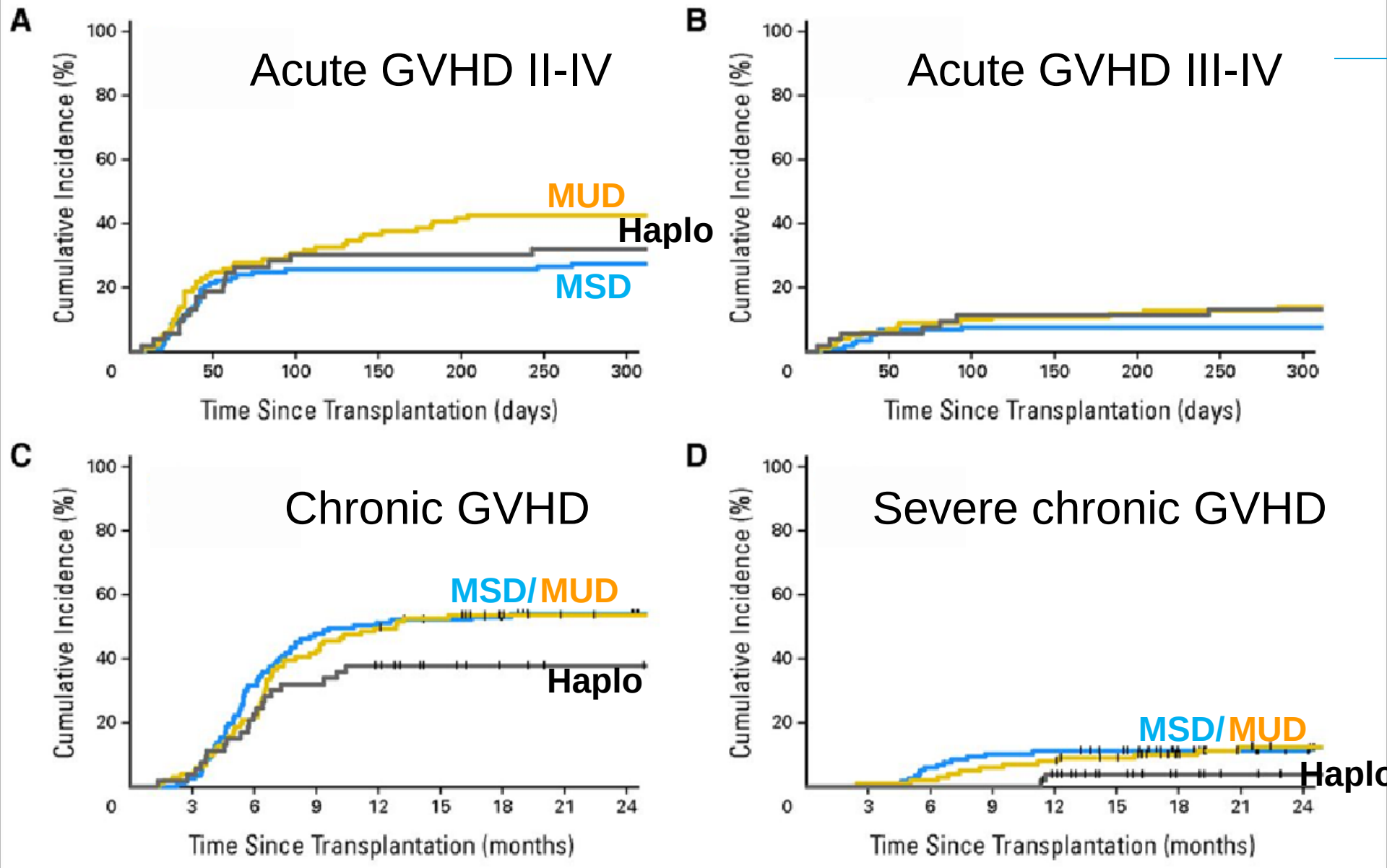
PT/Cy decreases GVHD after haploidentical HCT

Only recipients of haplo grafts got PT/Cy



A Bashey et al. J Clin Oncol 31:1310, 2013

Haploidentical versus double cord HCT after reduced intensity conditioning

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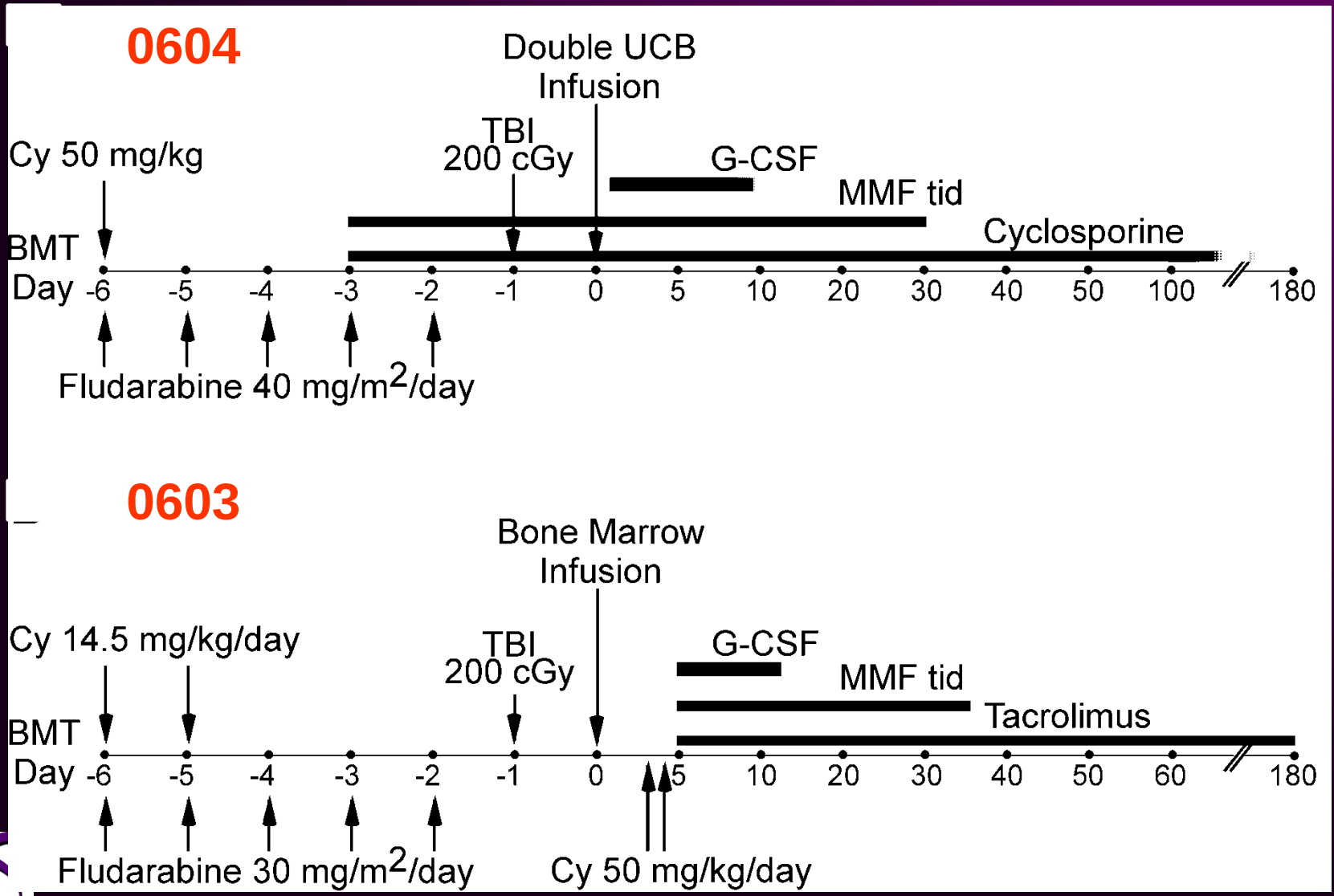
BMT CTN 0603 (haplo) and BMT CTN 0604 (double cord)

- Parallel phase II trials (n=50/trial) of alternative donor stem cell transplantation after fludarabine/200 cGy TBI-based conditioning
- Acute leukemia in CR, lymphoma
- Hypothesis: Survival at six months is >60% (CIBMTR benchmark for unrelated HCT)
- Trials conducted at 16 or 17 centers each, completed within 18 months

Patient Characteristics

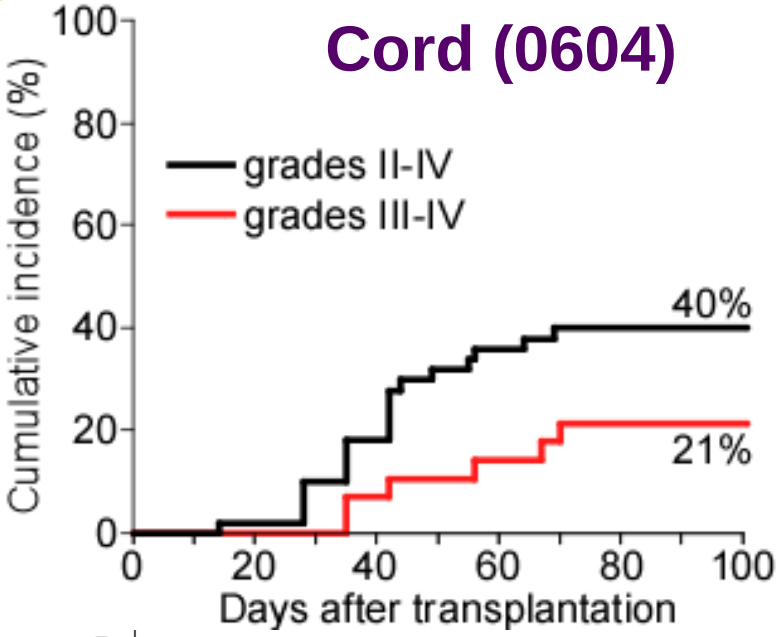
	CTN 0604 dUCB (N=50)	CTN 0603 HaploBM (N=50)
Median age (range)	58 (16-69)	48 (17-70)
Primary disease		
ALL	12%	12%
AML	58%	44%
Other leukemia	2%	6%
Lymphoma	28%	38%

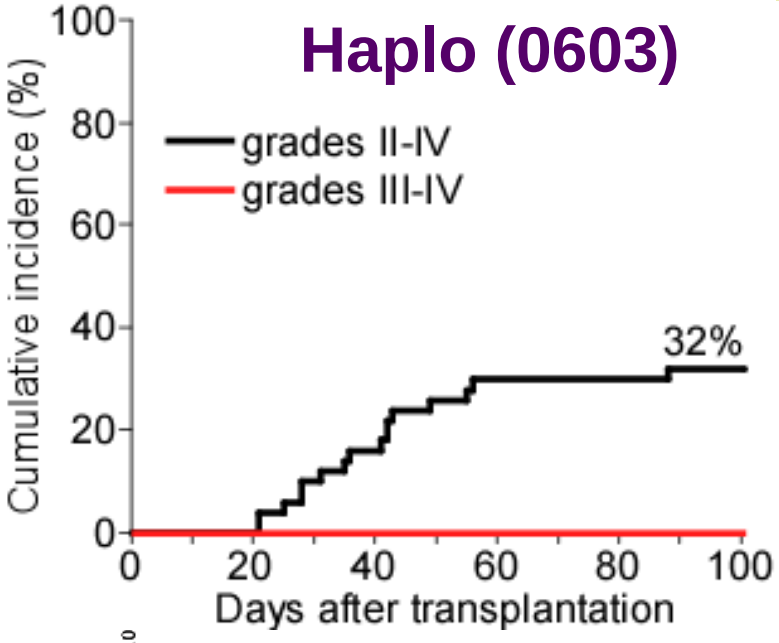
Treatment Regimens



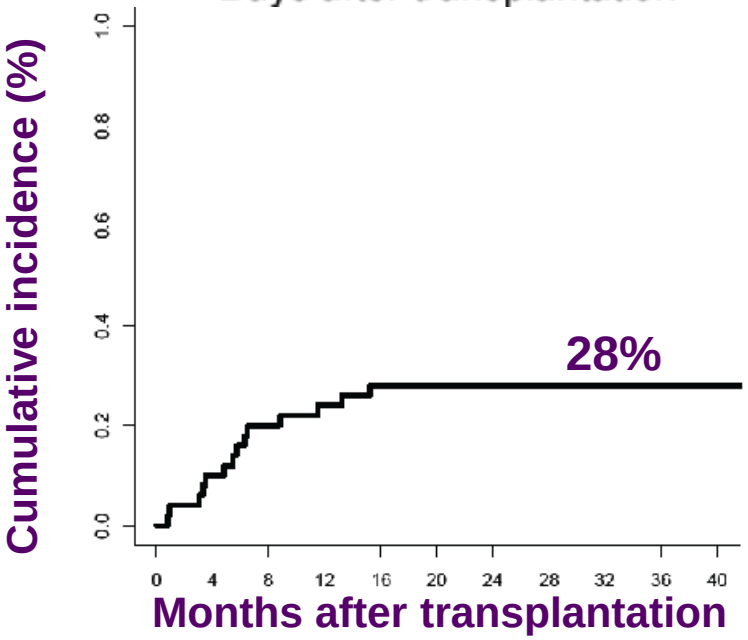
Graft-versus-host disease

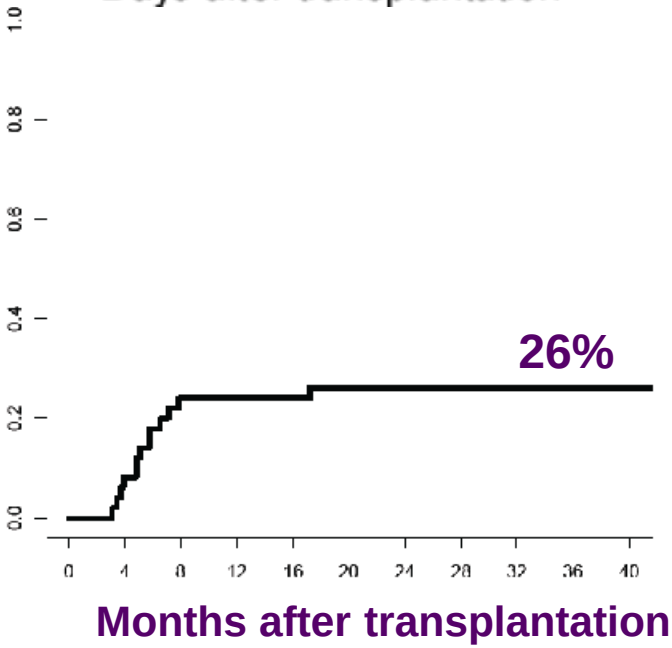
Acute GVHD



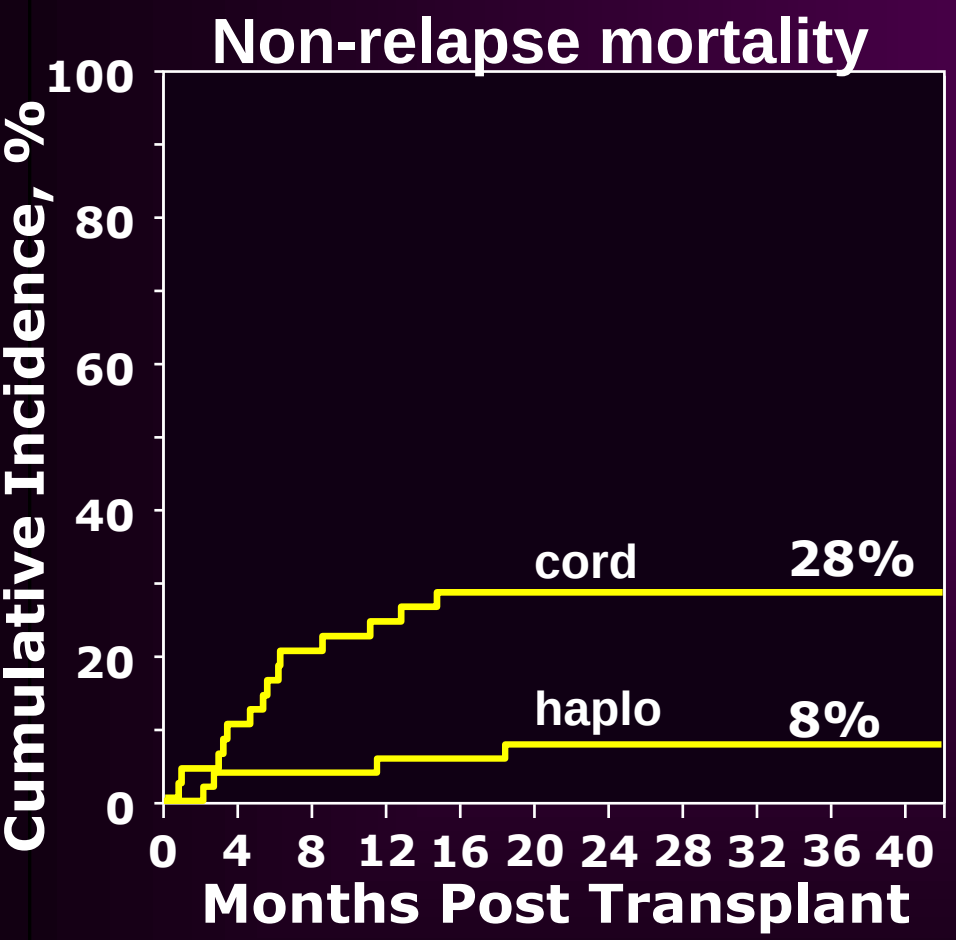


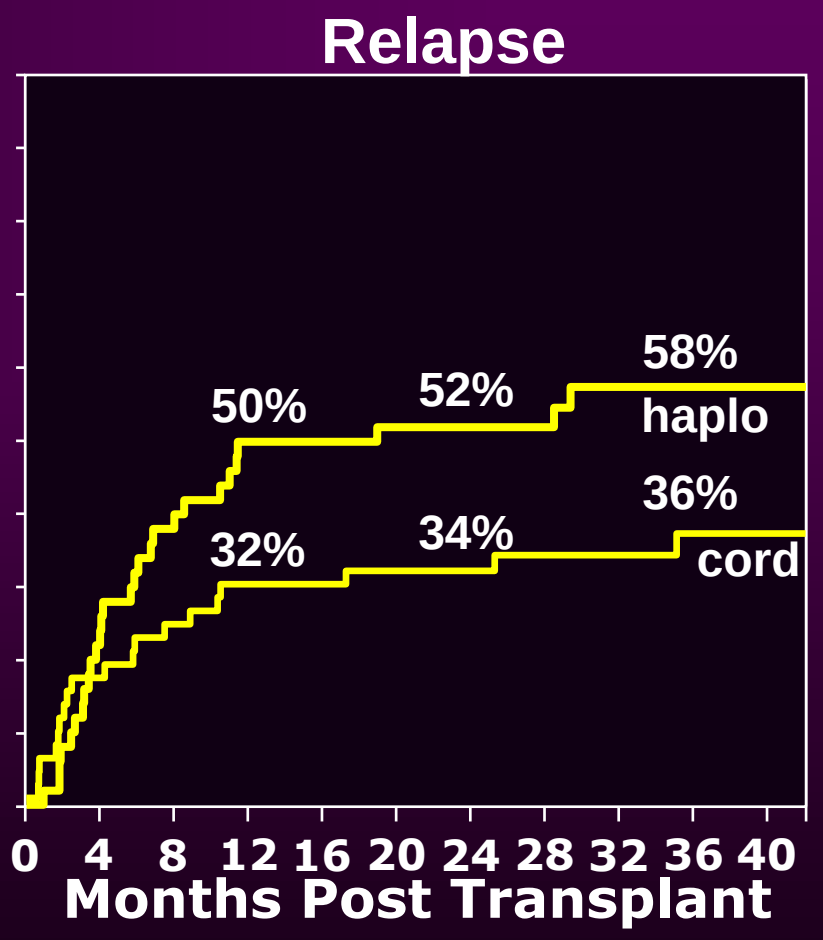
Chronic GVHD



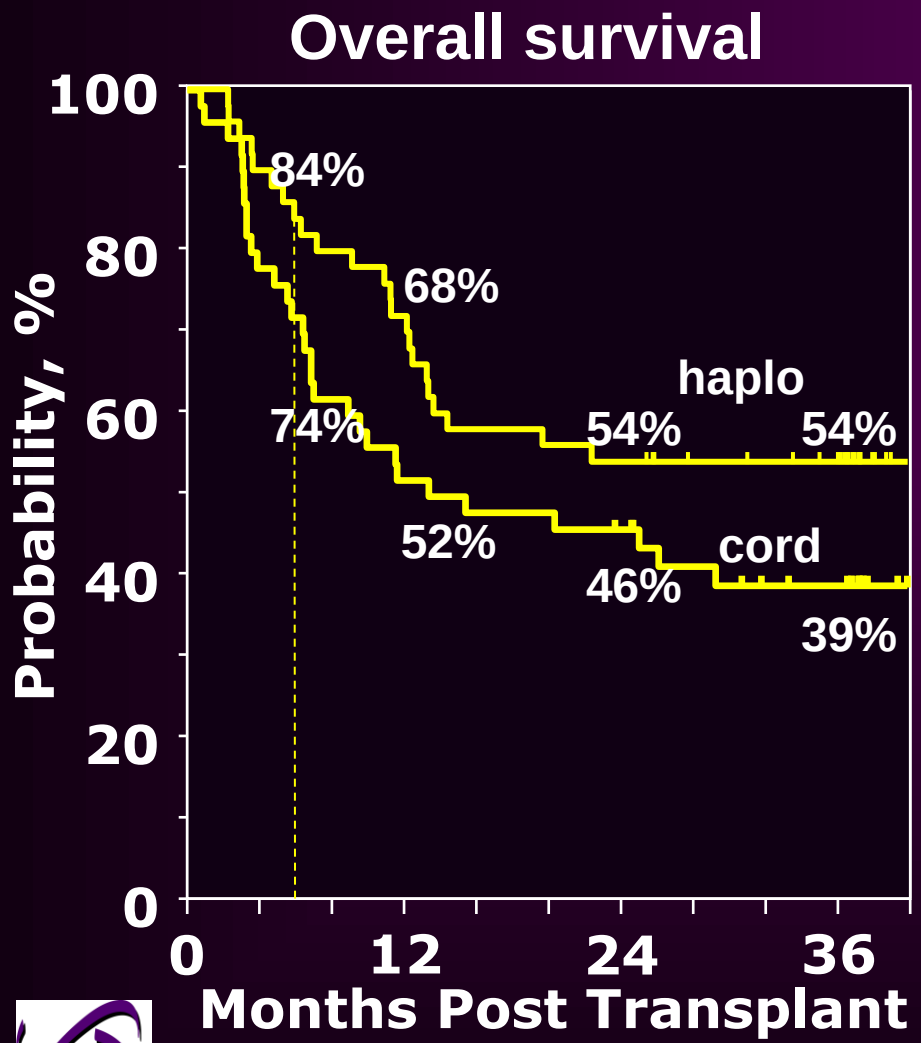


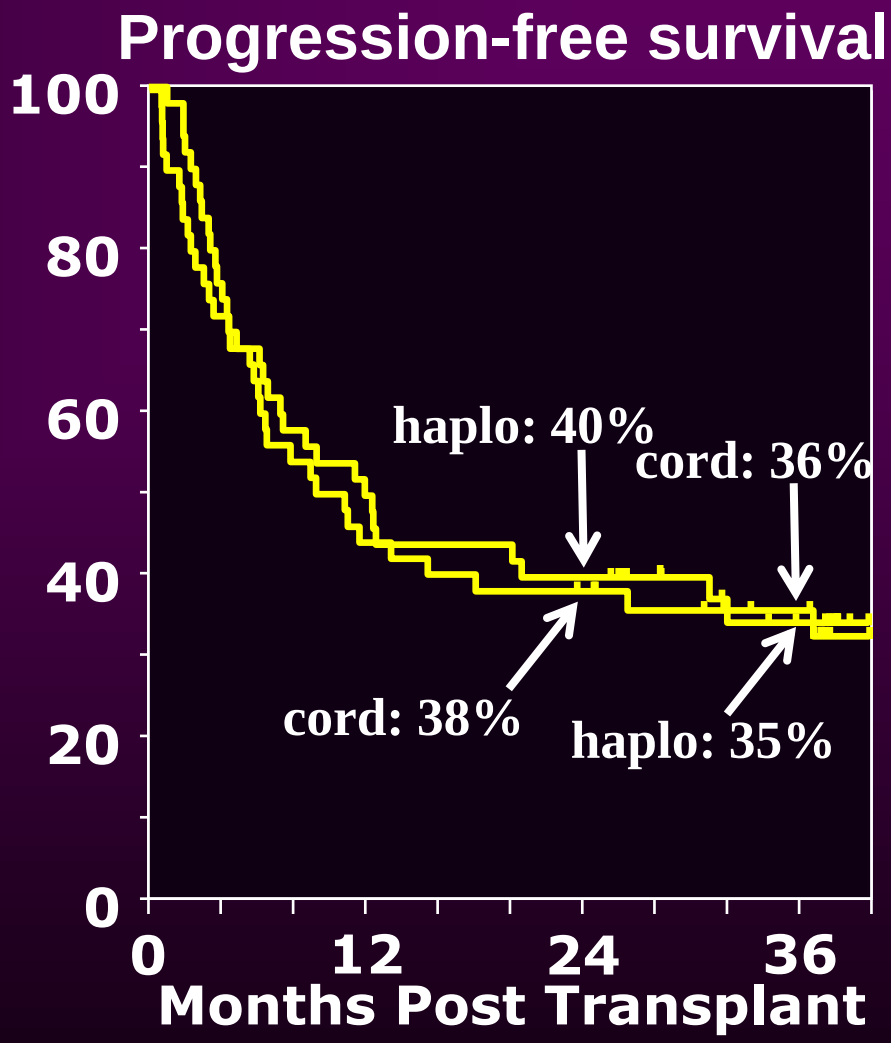
BMT CTN 0603/0604
Non-relapse mortality and relapse





BMT CTN 0603/0604:
Survival





The results of BMT CTN 0603 and 0604 establish which of the following?

A. Non-relapse mortality is higher after cord blood than after haplo HCT
B. Relapse is higher after haplo than after cord blood HCT
C. Progression-free survival after cord blood or haploHCT is not significantly different
D. All of the above
E. None of the above

Answer: "E" (none of the above). Results from parallel phase II trials cannot be compared statistically

The results of BMT CTN 0603 and 0604 provide equipoise for a randomized phase III clinical trial with progression-free survival as the primary endpoint

BMT CTN 1101 Hypothesis: Two year PFS is similar after related haplo-BM donor transplantation or after dUCB transplantation.

BMT CTN 1101: Study Endpoints

Primary

- Progression-free survival at 2 yrs

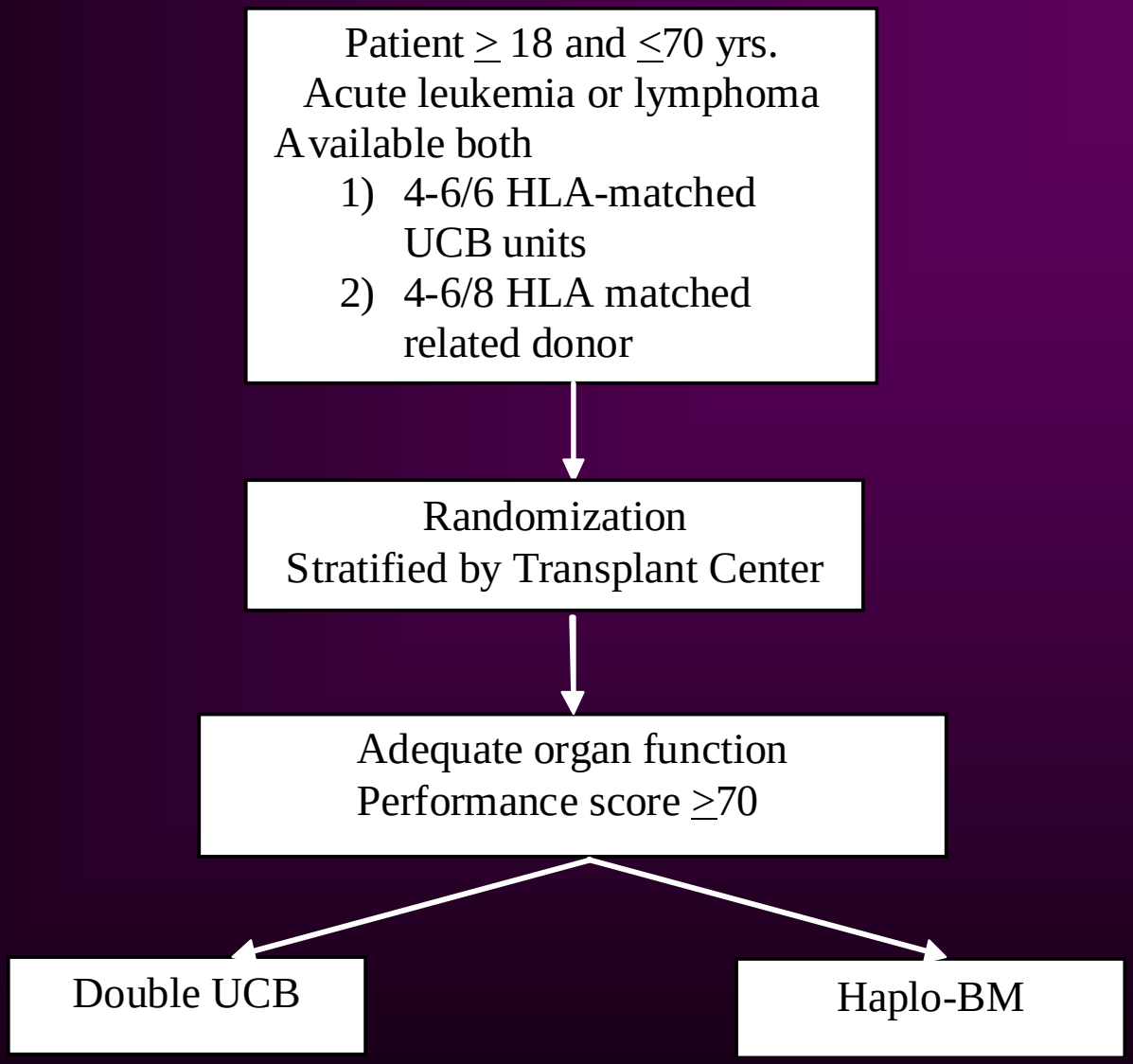
Secondary

- Engraftment
- GVHD
- Relapse
- TRM
- Quality of Life
- Cost Effectiveness
- Immune reconstitution (planned)

Sample size: n=410 patients over 4 years
(approximately 8/month)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1101 Schema



BMT CTN 1101
Ancillary and co-accruing studies

- **Cost-effectiveness analysis (R01-HL116291, PI: Scott Ramsey)**
- **Easy to read informed consent (ETRIC; BMT CTN 1205)**
- **PBMCs collected (pre-BMT, d28, d56, d180, d365) and stored for analysis of immune reconstitution**

BMT CTN 1101
Eligibility

- Age 18-70
- Diagnoses:
  - Acute leukemia, not good risk, in CR
  - Relapsed, chemosensitive Hodgkin, large cell, or mantle cell lymphoma (not eligible for autoSCT)
  - Follicular or marginal zone lymphoma, relapsed after at least two prior regimens
- No matched sibs and BOTH GRAFT SOURCES AVAILABLE

BMT CTN 1101: Accrual (as of 9/14/14)

- Trial opened June 19, 2012
- 35 centers activated
- 5 centers pending activation
- German cooperative group DKMS joining in early 2015
- 114 patients accrued; total target is 410

1101 Will Not Answer All Questions

- Restricted to reduced intensity conditioning in adults
- Diverse diseases with little power to discern disease-specific efficacy differences
- Comparison only to double cord transplants

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GS14-01 Comparison of Haplo and HLA-Matched Unrelated Donor HCT in AML

- 1982 MUDs; 192 haplos
- AML, all stages
- Age 21-70 years
- 2008-2012, US and a single Italian center
- Post-tx Cy for GVHD prophylaxis in haplos
- Variety of GVHD prophylaxis regimens in unrelated donor HCTs
- Primary outcome: 2 year survival (all surviving patients censored at 2 years)

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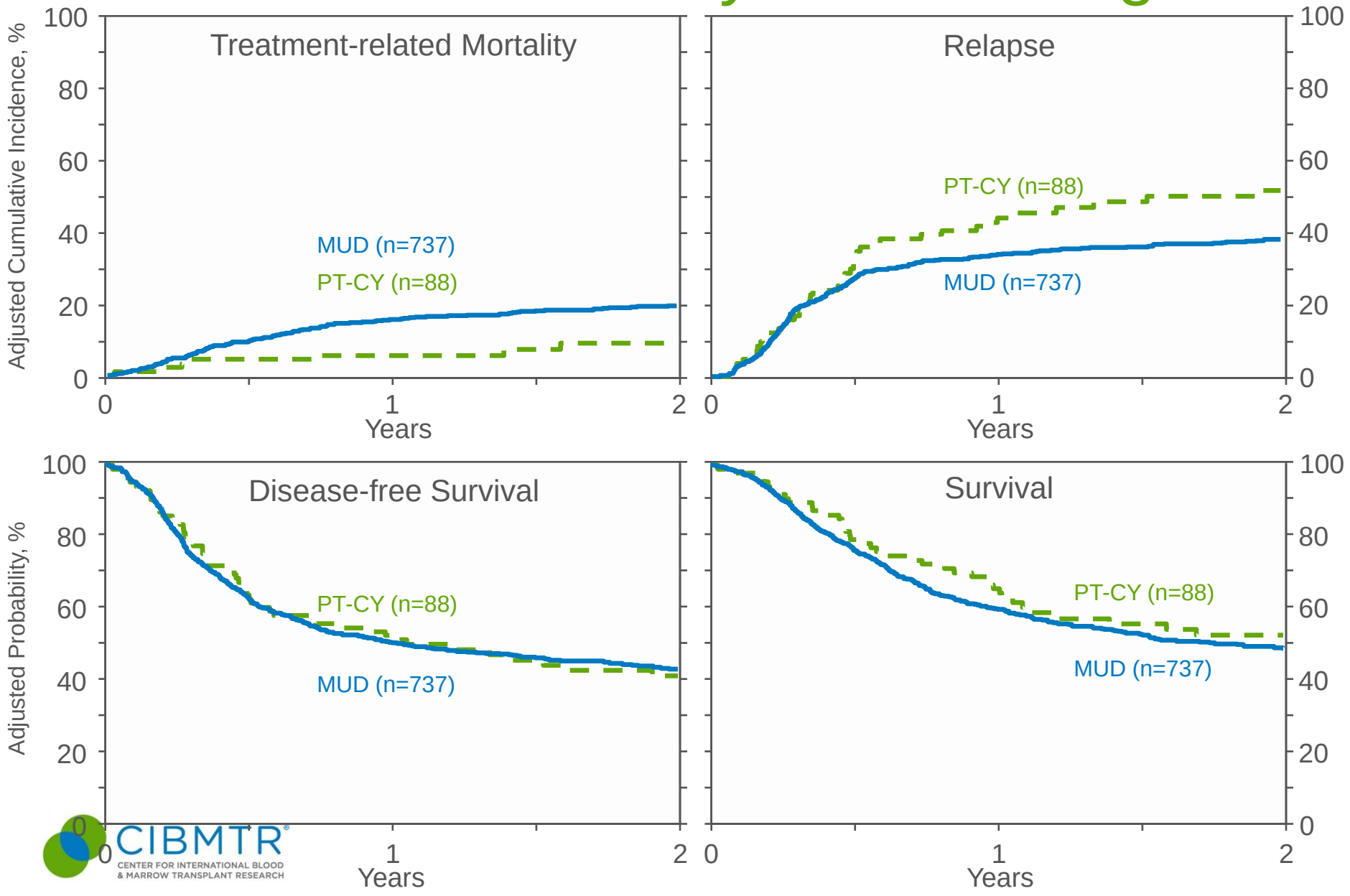
Patient Characteristics - Myeloablative

	Haplo (N=104)	Unrelated (N=1245)	
Centers	7	101	
Median age	47 y	47 y	NS
Sorror Index			<.001
0	33%	32%	
1	24%	23%	
2	11%	23%	
3	4%	22%	
Unknown	29%	<1%	
Disease status			NS
CR1	46%	55%	
CR2+	20%	20%	
Not in CR	34%	25%	
Year of HCT			<.001
2009	11%	23%	
2010	13%	24%	
2011	35%	29%	
2012	41%	25%	

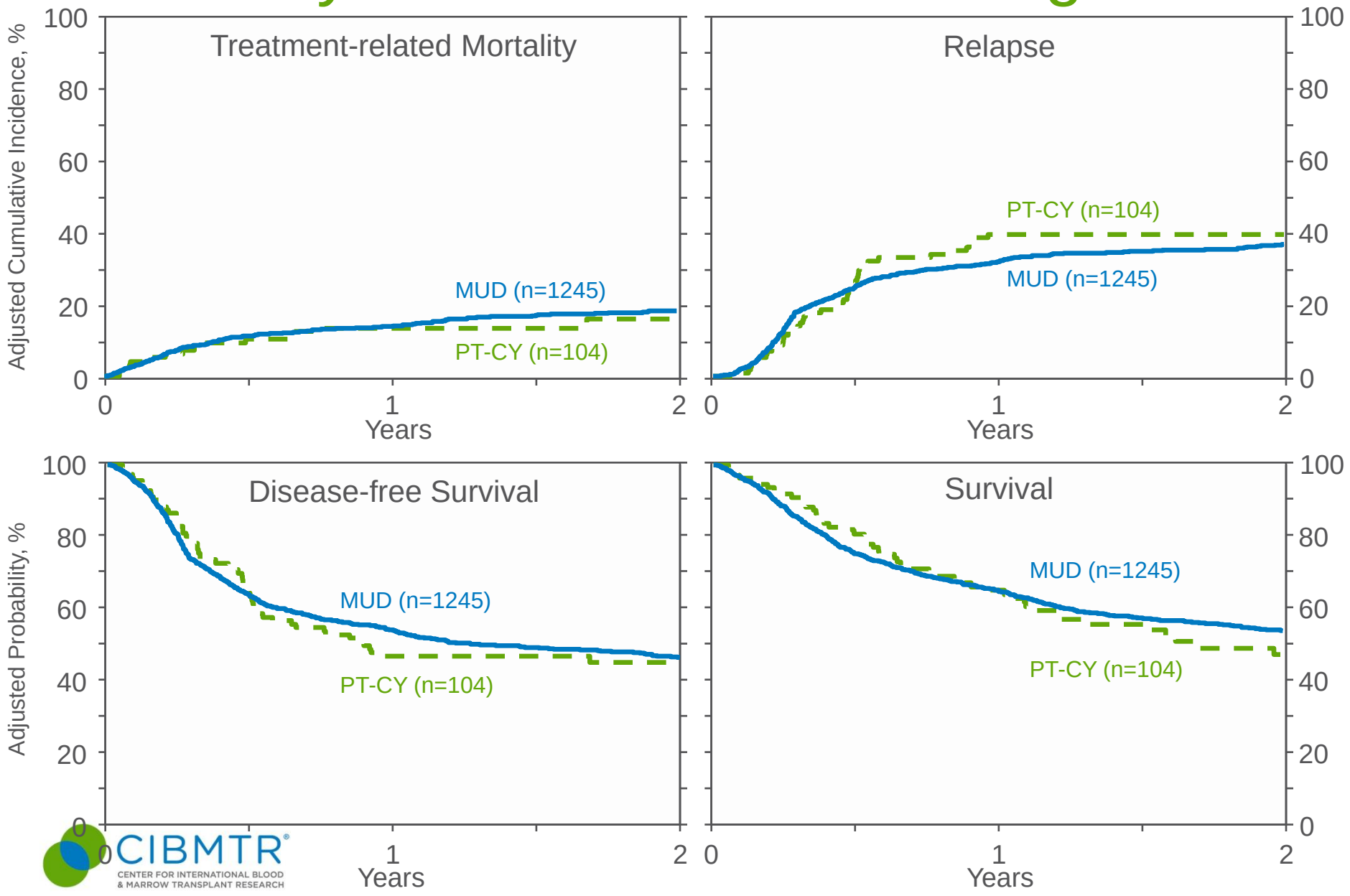
Patient Characteristics – Reduced Intensity

	Haplo (N=104)	Unrelated (N=1245)	
Centers	17	82	
Median age	55 y	62 y	<.001
Sorror Index			<NS
0	27%	30%	
1	25%	23%	
2	17%	21%	
3	31%	27%	
Disease status			NS
CR1	49%	61%	
CR2+	35%	17%	
Not in CR	16%	22%	
Year of HCT			NS
2008	13%	16%	
2009	20%	18%	
2010	22%	21%	
2011	20%	23%	
2012	25%	22%	

Reduced–intensity Conditioning



Myeloablative Conditioning



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What Do We Know?

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

What Don't We Know?

- The long-term outcome of haploidentical HCT, particularly long-term disease control
- Differences in efficacy by specific blood cancer
- Outcomes in children or non-malignant disease
- Optimal graft type (PB or BM) or preparative regimen
- Relative efficacy compared to other donor sources (all studies to date underpowered to detect 10-15% differences in outcome)

Conclusions

- Haploidentical HCT is a valid option in patients without an HLA-identical adult donors but there are insufficient data to recommend it over umbilical cord blood or HLA-mismatched unrelated donor HCTs
- Given the level of uncertainty regarding the optimal “alternative donor”, participation in clinical trials in should be encouraged

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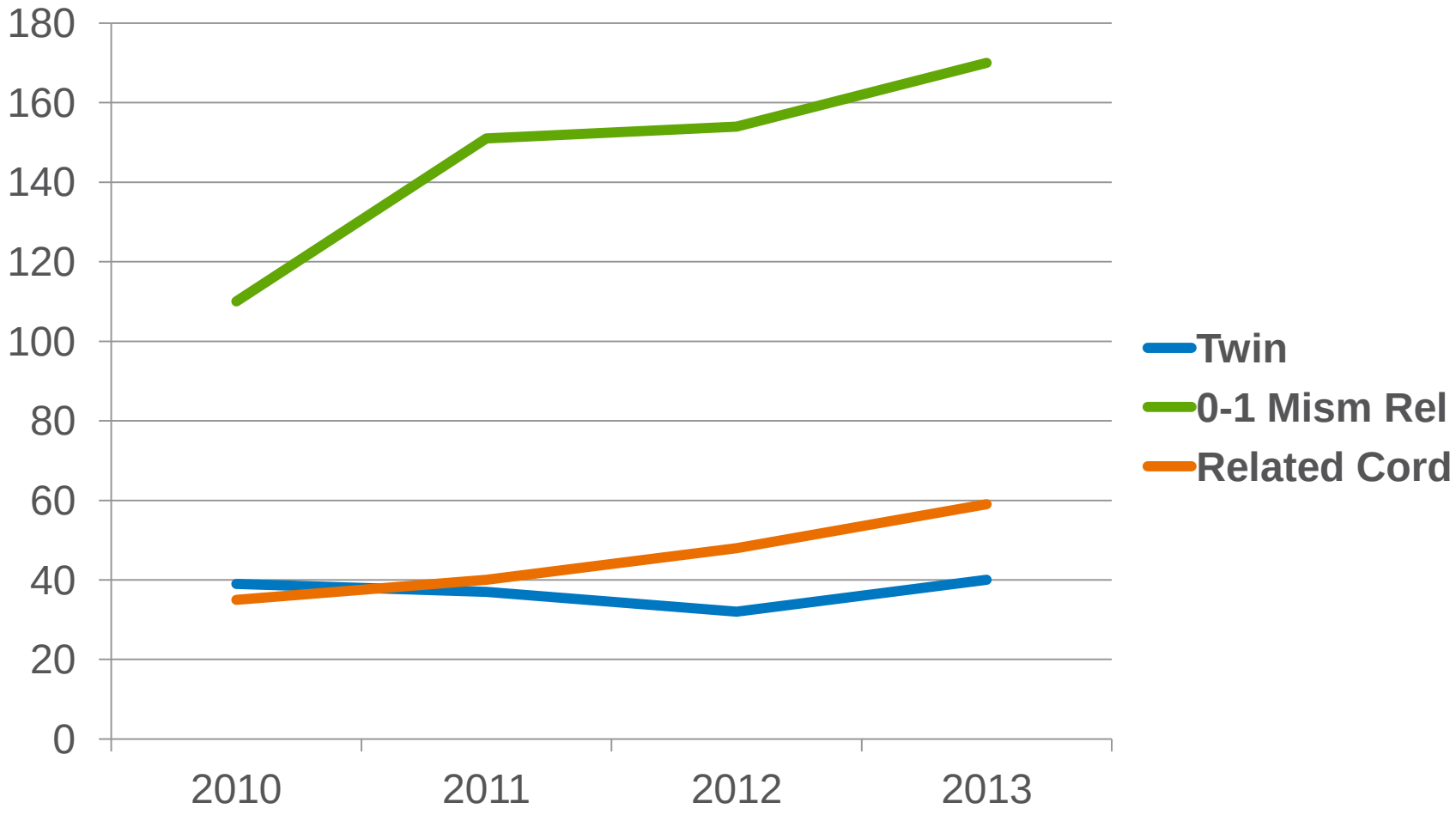
What's Missing? Other Types of Donors



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