Matched Unrelated Donor Hematopoietic Cell Transplantation

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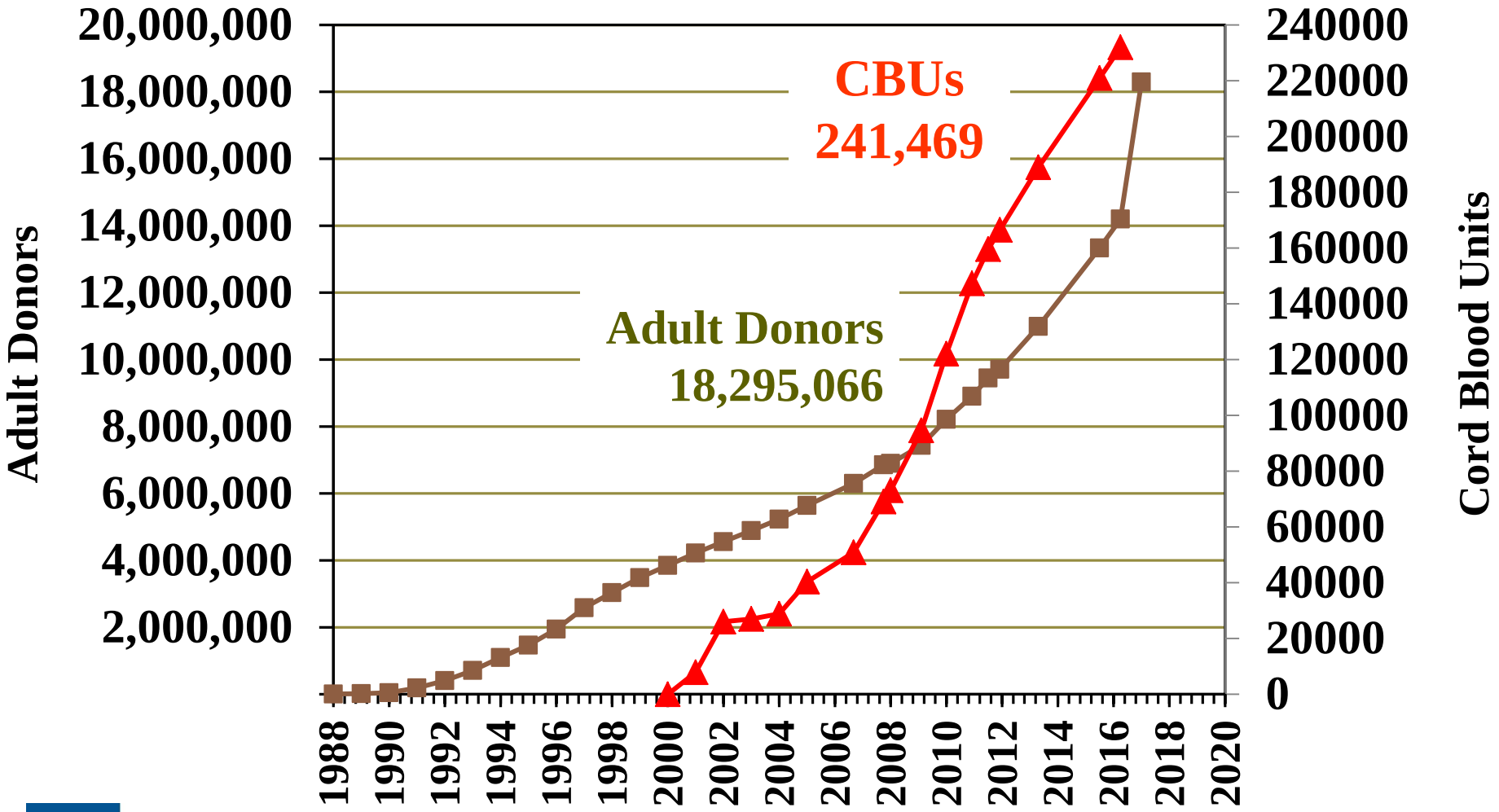
Three Sources for HLA-Matched and Partially Matched Unrelated Donor HCT

- Unrelated adult donor bone marrow, HPC(M)
- Unrelated adult donor peripheral blood stem cells, HPC(A)
- Unrelated umbilical cord blood, HPC(CB)

Donors for Unrelated Donor Transplantation

- >29 million adult donors and 720,000 CBU are listed in registries and CBU banks worldwide
- 98 Registries and 92 cord blood banks in 54 countries
- NMDP / Be The Match has the intent to put as much inventory as possible in its primary search file
  - >18 million adult donors
  - > 240,000 CBU
  - Mirroring cord blood inventory with several cord blood registries

National Marrow Donor Program Adult Donors & Cord Blood Units – January 9, 2017



A Comprehensive Model for Registry Match Rates

The NEW ENGLAND JOURNAL of MEDICINE

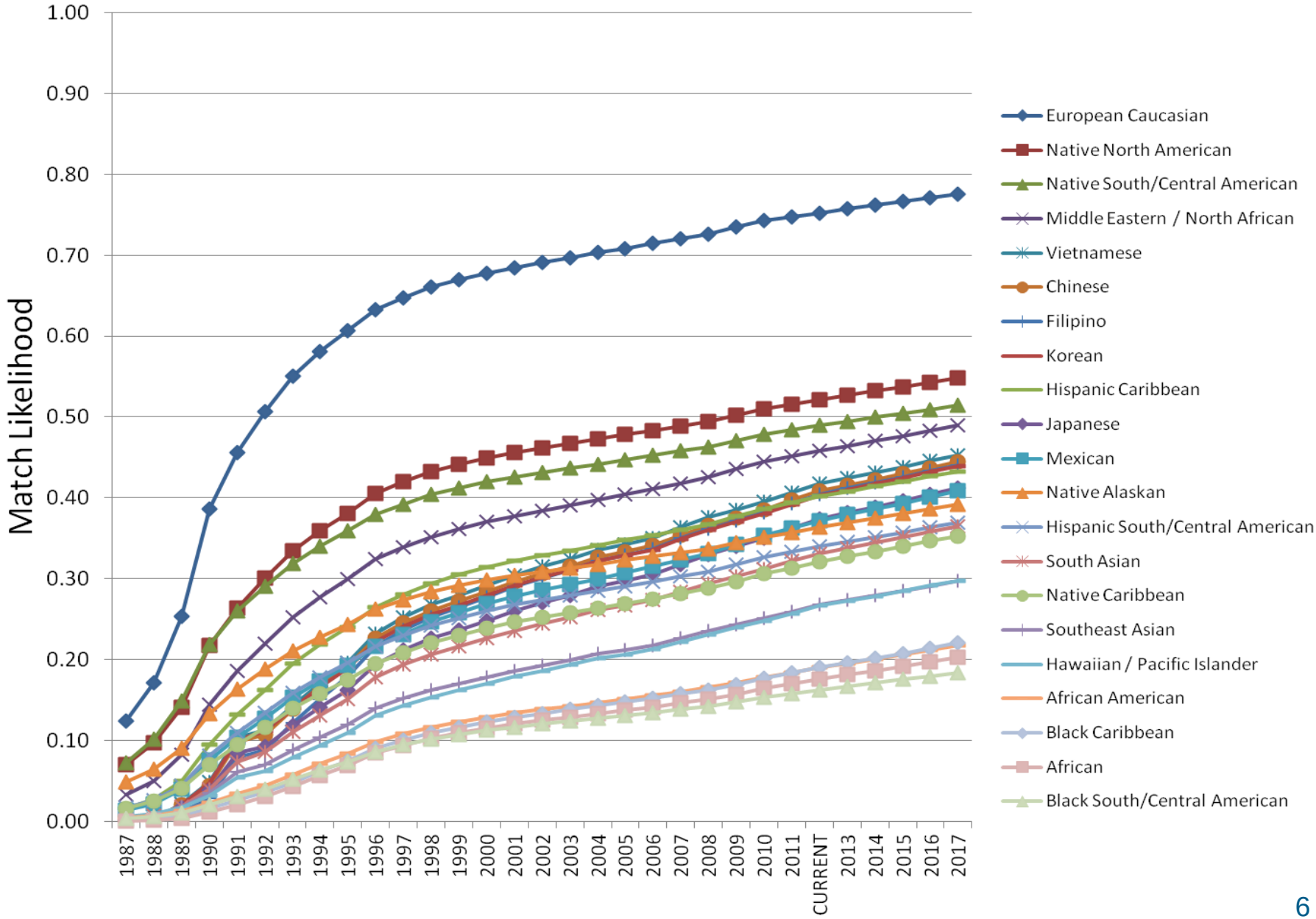
SPECIAL ARTICLE

HLA Match Likelihoods for Hematopoietic Stem-Cell Grafts in the U.S. Registry

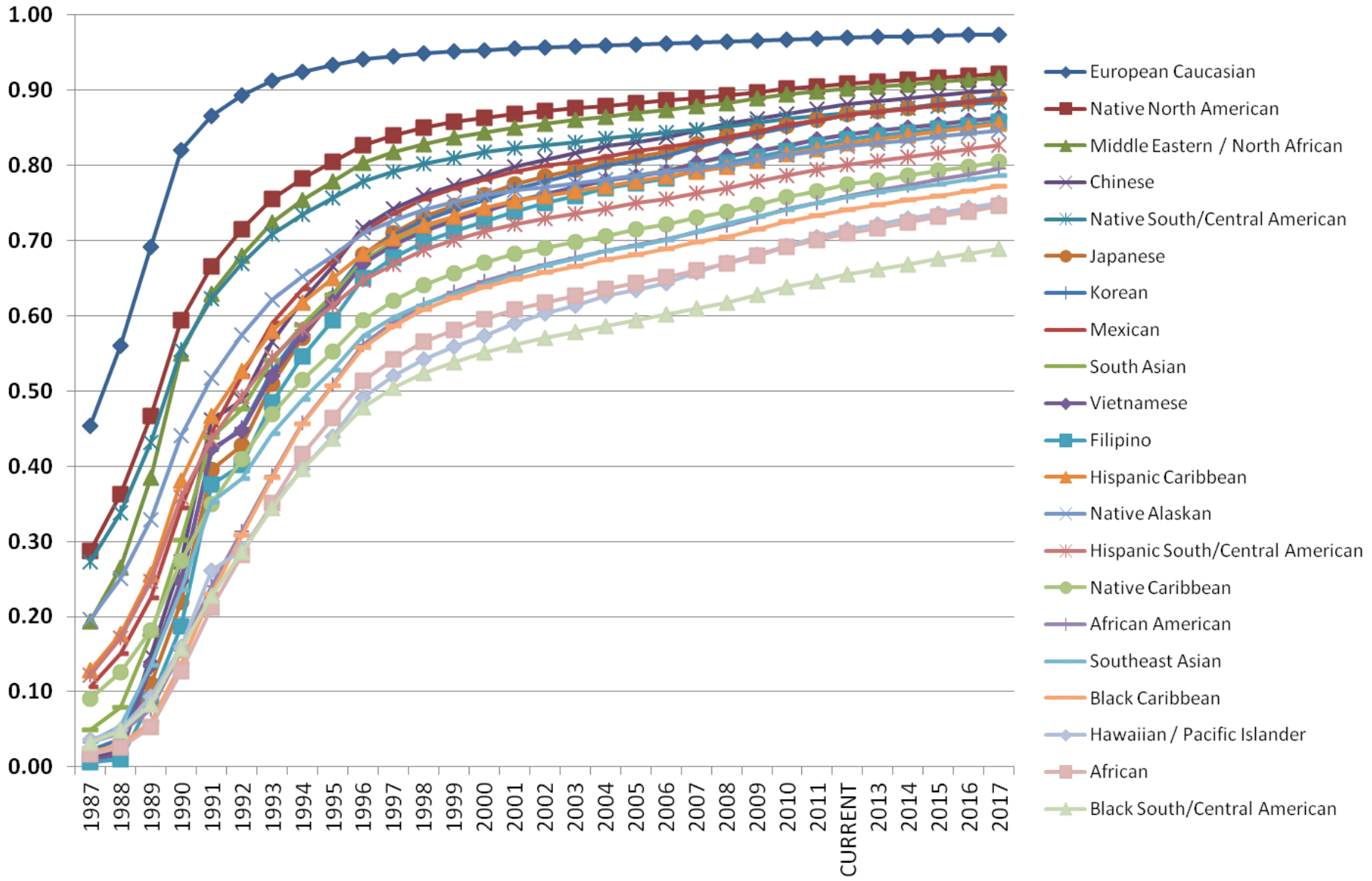
Loren Gragert, B.S., B.A., Mary Eapen, M.B., B.S., Eric Williams, Ph.D., John Freeman, B.S., Stephen Spellman, M.B.S., Robert Baitty, M.P.P., Robert Hartzman, M.D., J. Douglas Rizzo, M.D., Mary Horowitz, M.D., Dennis Confer, M.D., and Martin Maiers, B.A.

N Engl J Med 2014;371:339-48

8/8 match likelihoods by year-end using current donor availability, extending recruitment trends to 2017



7/8 or 8/8 match rates by year using current donor availability, extended recruitment trends to 2017



BMT CTN Protocol 0201
Results of a Phase III Randomized Multicenter Trial of HLA compatible Unrelated Donor Transplantation:

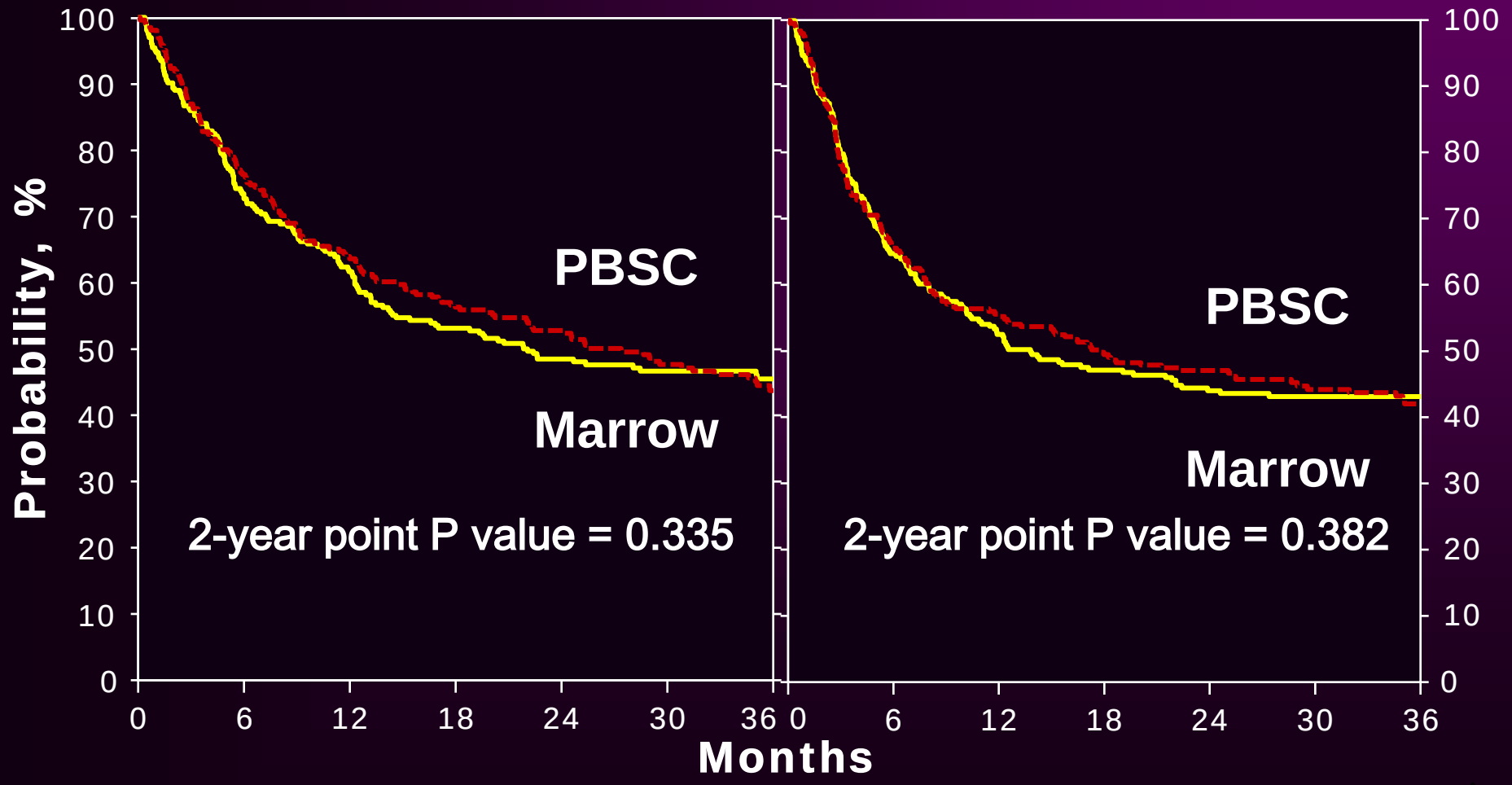
G-CSF Mobilized Peripheral Blood Stem Cells (PBSC)
Versus
Bone Marrow

Study Characteristics

- ***Design:*** Randomized, multicenter trial
- ***Primary endpoint:*** Two-year survival
- ***Randomization:*** PBSC *vs.* marrow, 1:1
- ***Accrual:*** 550 donor-recipient pairs
- ***Enrollment:*** March, 2004 to September, 2009
- ***Median follow-up:*** 36 months

Analysis after Transplantation

Overall Survival Disease-free Survival

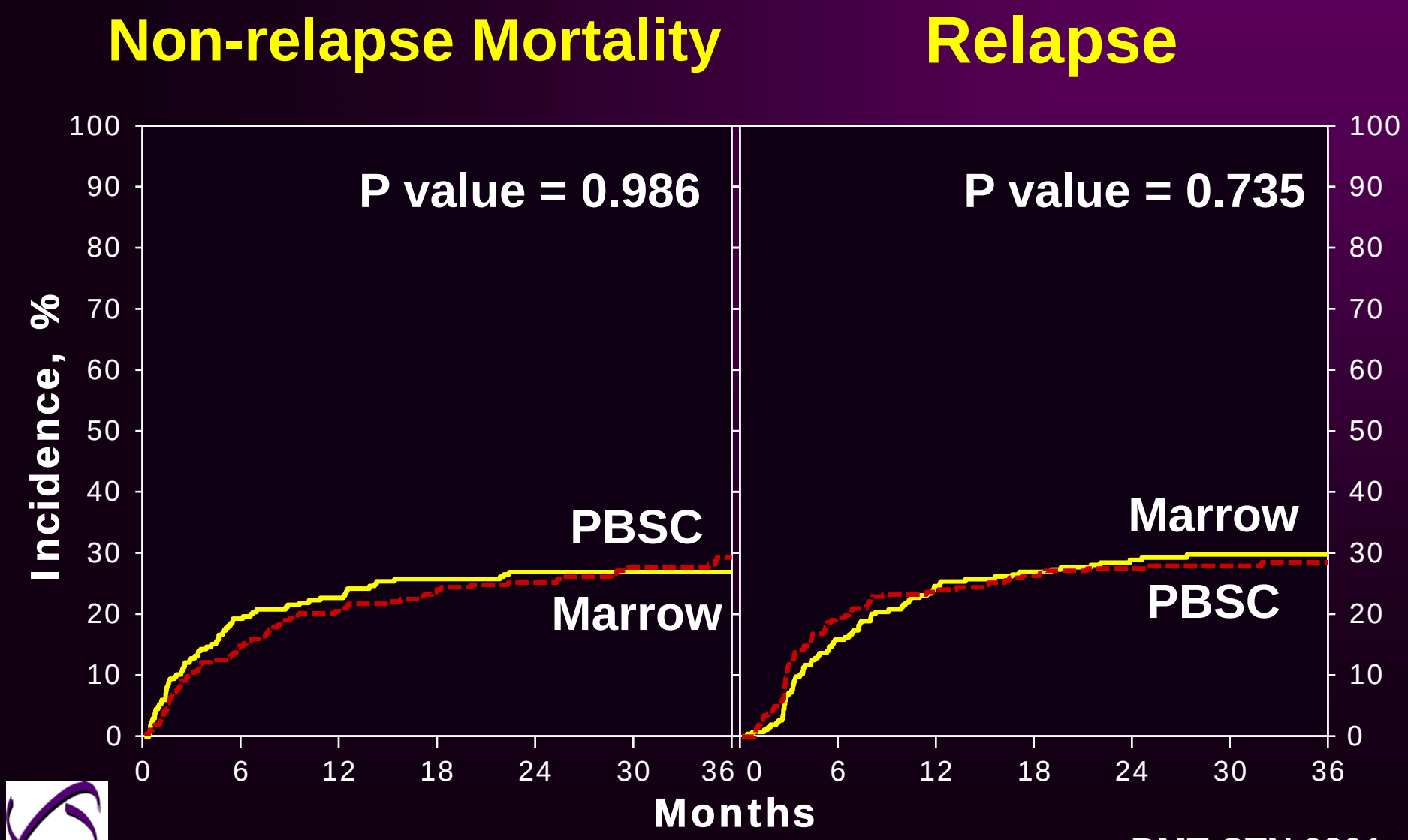


Preplanned subset analyses did not find study arm interaction with:

- -Disease Risk
- -Donor HLA matching
- -Patient Age

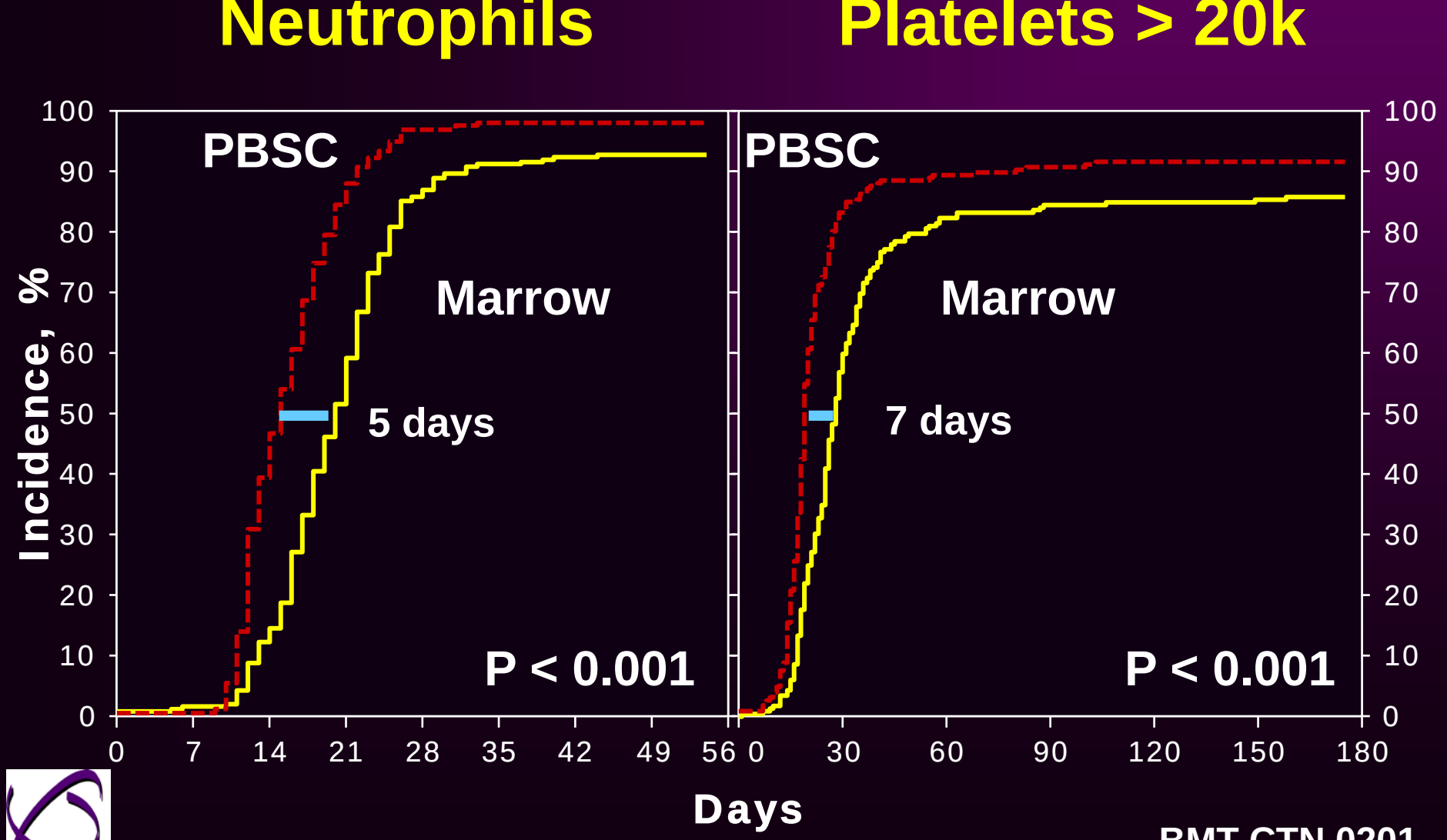
BMT CTN 0201

Analysis after Transplantation



BMT CTN 0201

Engraftment after Transplantation



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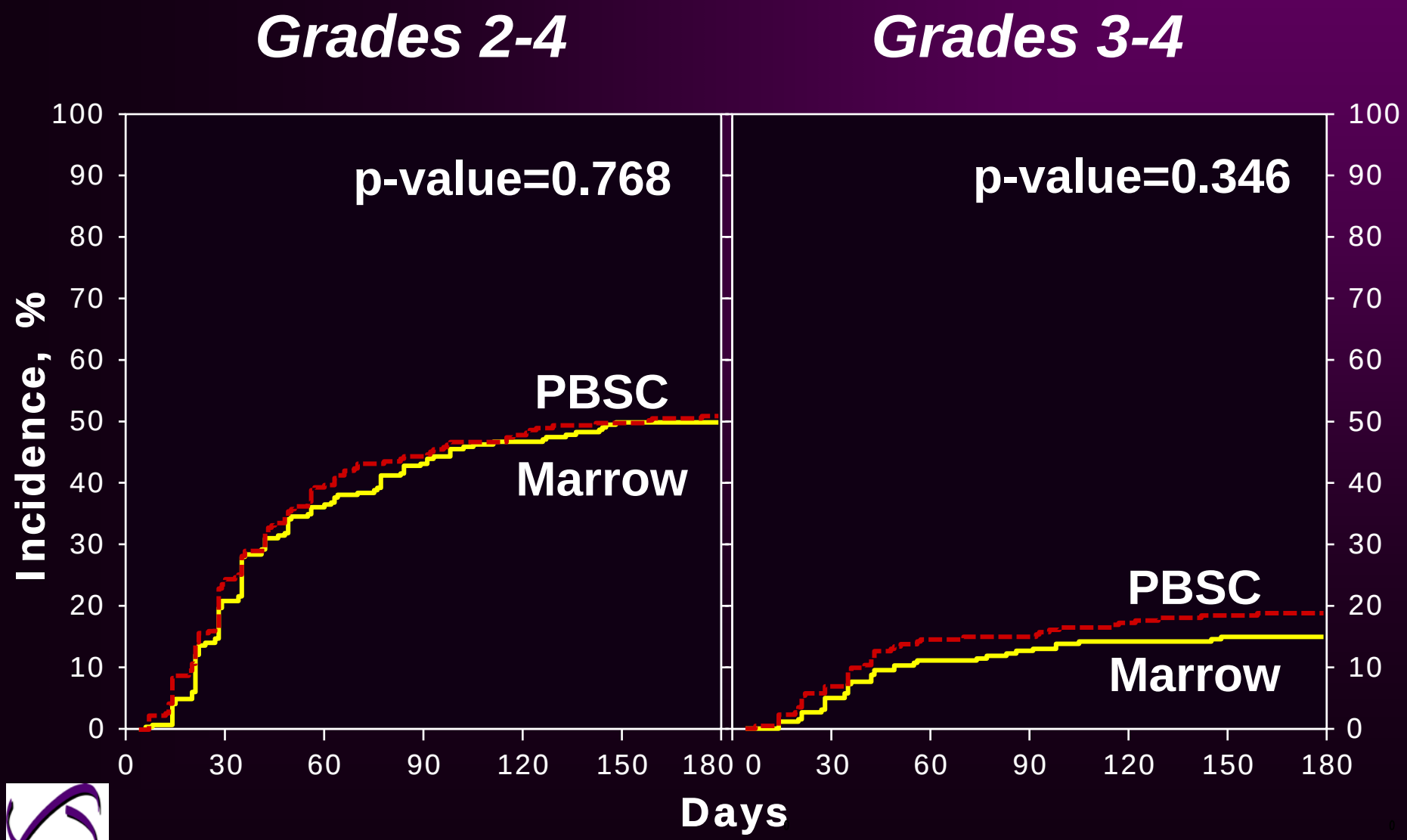
Acute Graft-versus-Host Disease (GVHD)



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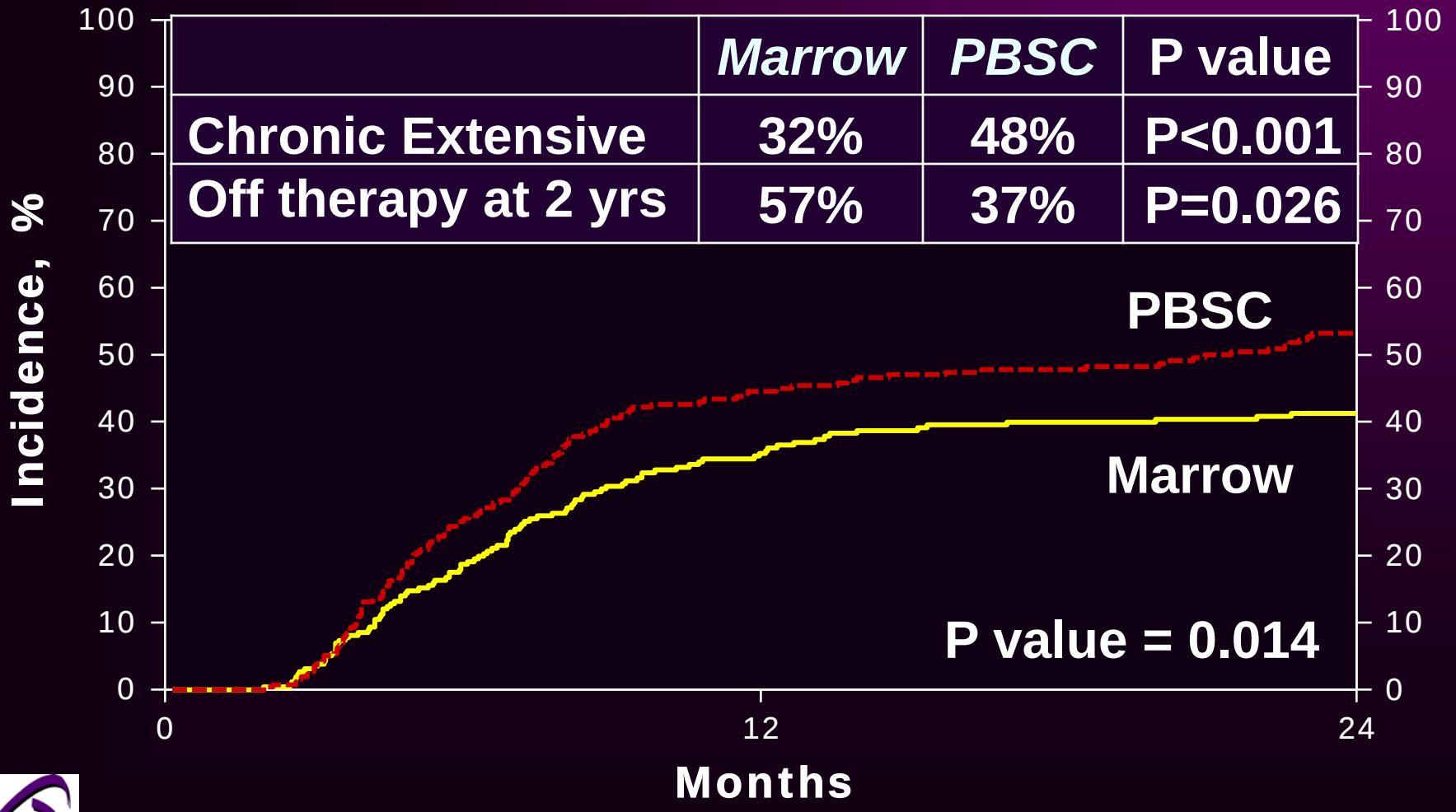
Overall Chronic GVHD

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



BMT CTN 0201

Summary Marrow vs. PBSC

- There is no difference in survival, disease-free survival or acute graft-versus-host disease
- PBSC HCT has more rapid engraftment of neutrophils and platelets
- PBSC is associated with a higher incidence and severity of chronic GVHD
- In 5-year follow-up by Lee, et al*, the negative impact of PBSC cGVHD continues
  - Higher symptom burden
  - Worse quality of life
  - 50% less likely to return to work

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*JAMA Oncol 2016; 2:1583

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 the infant donor
  - Allows more HLA-mismatch with lower risk of GVHD, yet retains a graft-vs-tumor effect
- Disadvantages:
  - Low cell numbers - inadequate cell dose for many adults
  - Slow hematopoietic recovery and higher risk of graft failure

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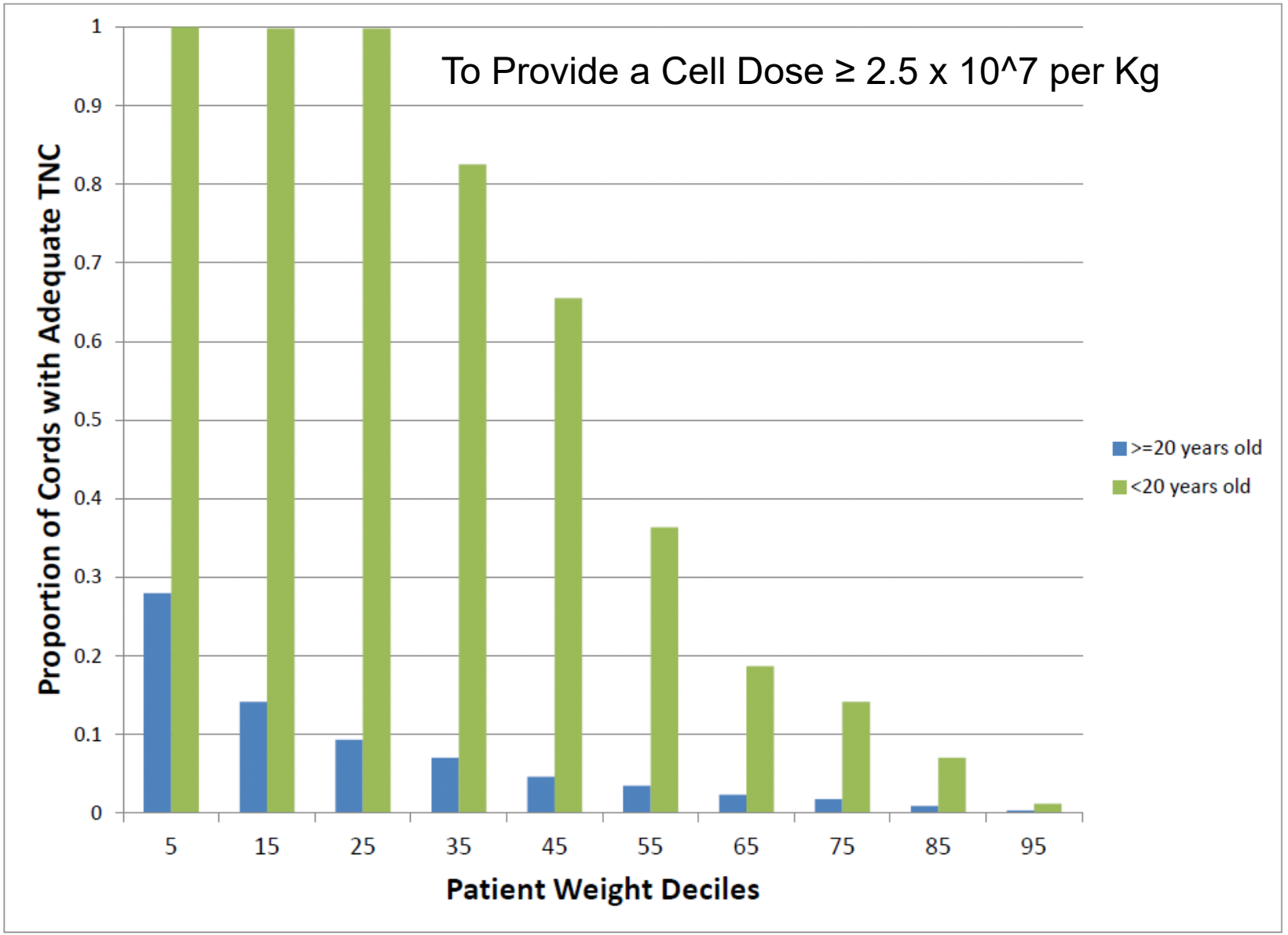
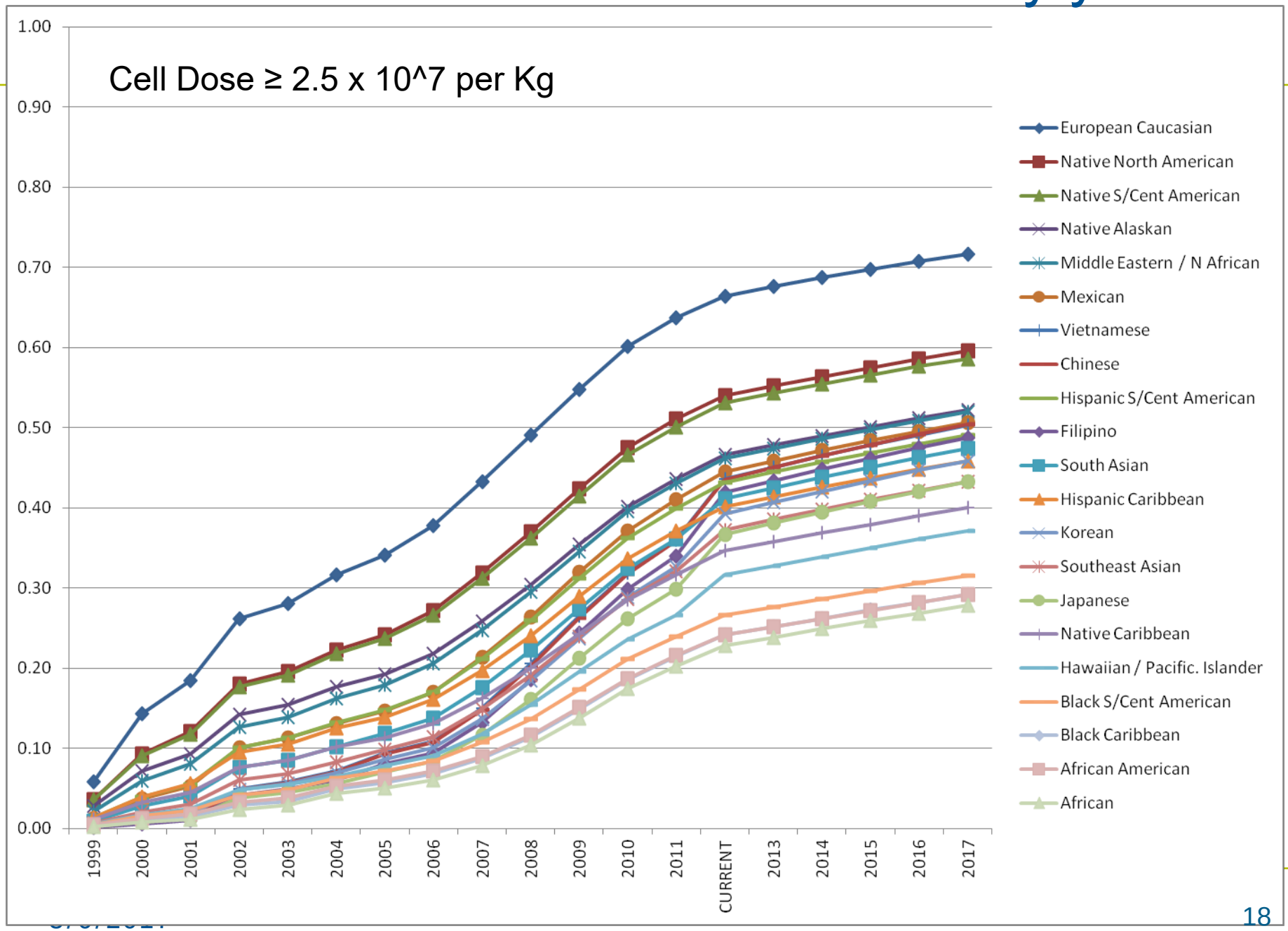
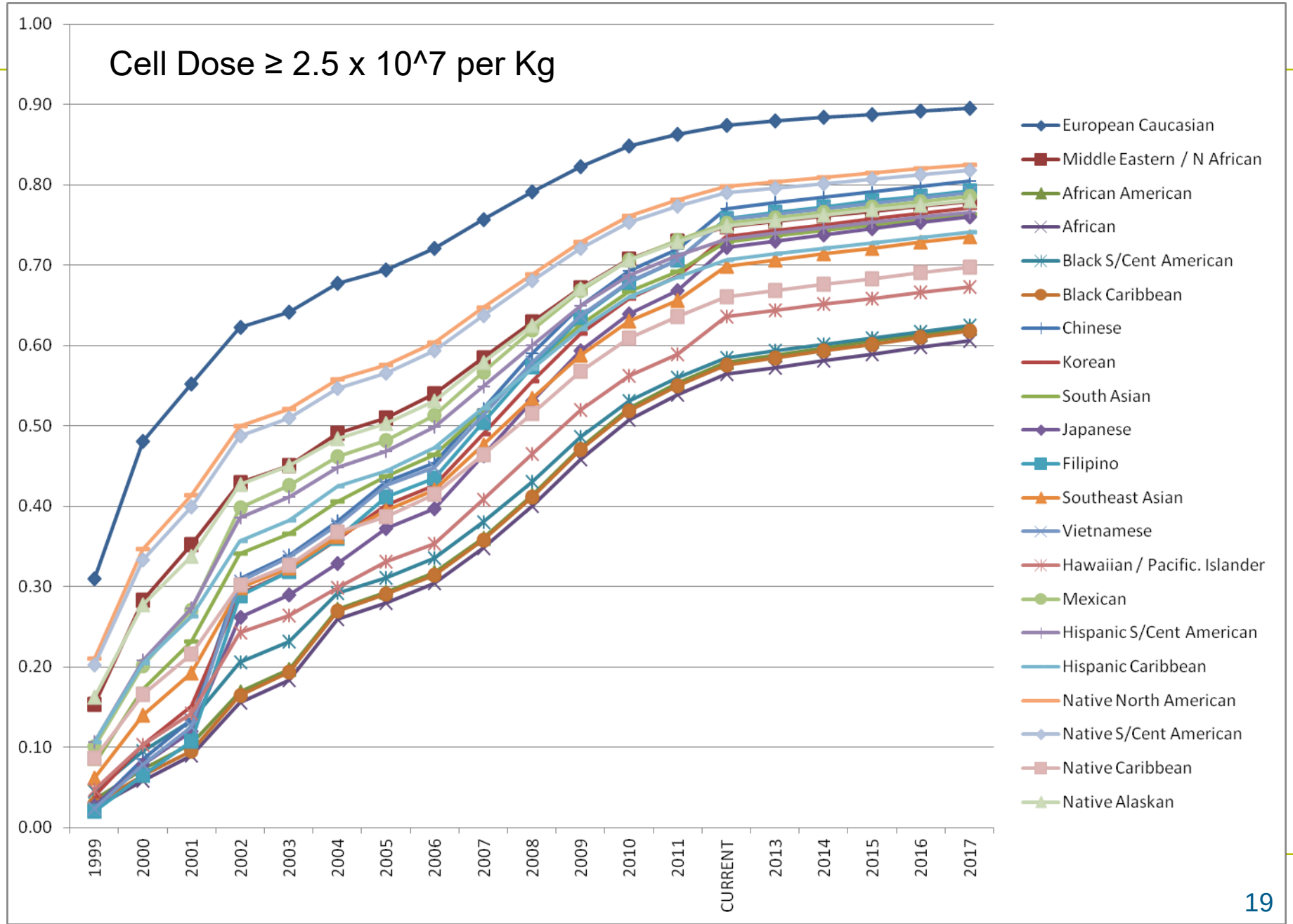
Effective Cord Inventory Adjustments Based on Patient Age and Weight



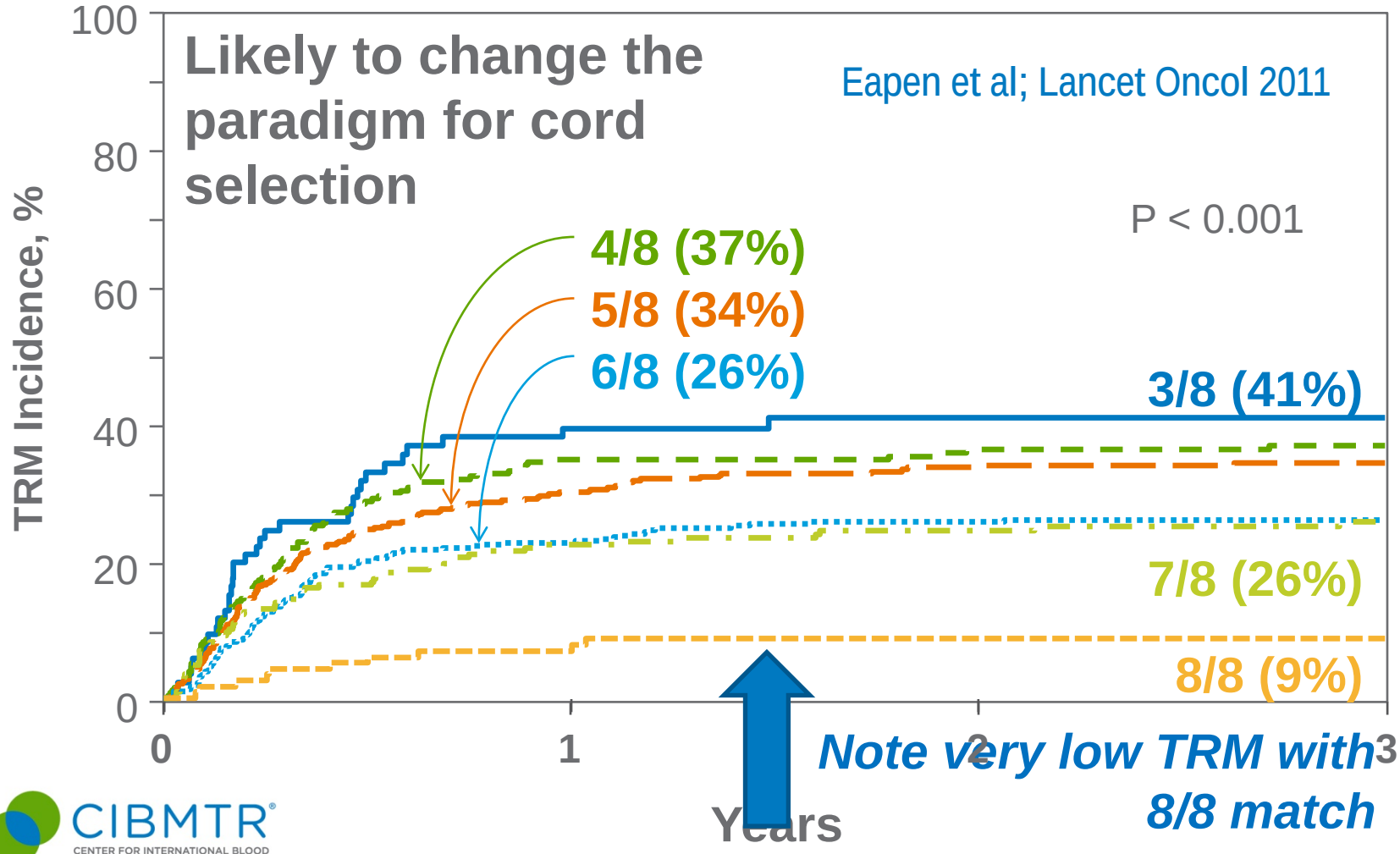
≥ 5/6 CBU match rates for adults by year



≥ 5/6 CBU match rates for children by year



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



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eurocord

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%**

HLA-Matched and Partially Matched Unrelated Graft Sources: Summary

- Allele-level typing at HLA-A, -B, -C and –DRB1 is necessary for matching all unrelated sources
- The standard for HPC(A) and HPC(M) is 8 of 8 or 7 of 8 alleles matched
- The standard for HPC(CB) is an adequate cell dose and matching as many alleles as possible, preferably ≥6 of 8
- Acute and chronic GVHD remain serious problems
- Even with millions of unrelated graft sources world-wide, many people will lack a suitable unrelated graft
- New strategies for haploidentical related donor HCT may solve this problem

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