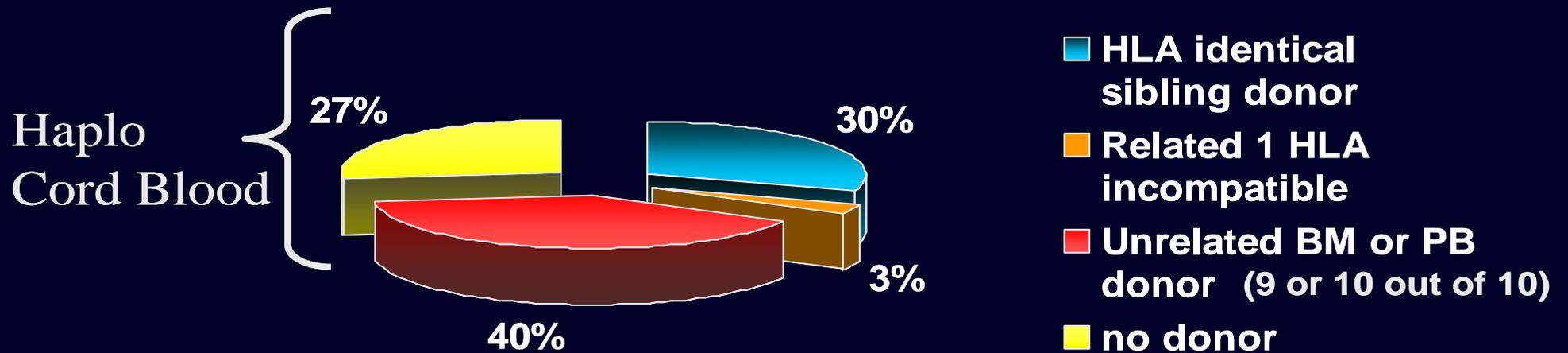


# Graft source and donor Algorithm

**V Rocha, MD, PhD**

**Professor of Haematology – Oxford University  
Medical Director of British Blood and Marrow Donor  
Registry and Cord Blood Banks- NHS-BT  
Scientific Director of Eurocord**

# Estimate number of patients with an indication of an allogeneic hematopoietic stem cell transplants



Conditional probability of finding an 10 of 10 allele level matched unrelated adult donor in the Swiss registry for a Caucasian was found in 69% of the patients ( high probability), but in only 11% of the patients with a low-probability estimate ( $P < 0.00001$ ) ( Tiercy JM et al, BMT 2007)

Conditional probability of finding an 8 of 8 allele level matched unrelated adult donor is

51% for Caucasians

30% for Hispanics (certainly lower in LA)

20% for Asians

17% for African Americans

( NMDP data)



# Searching and identifying an alternative stem cell donor

## Main criteria to be considered

	UBMT	UCBT	Haplo-HSCT
Information on A + B + DRB1 typing (%)	16 – 56	~ 80	100
Median search time (months)	3 – 6	< 1	immediate
Donors identified but not available (%)	20 – 30	~ 1	None
Rare haplotypes represented (%)	2 – 10	20	Not applicable
Main limiting factor to graft acquisition	HLA identity	Cell dose (?)	Poor mobilization
Ease of rearranging date of cell infusion	Difficult	Easy	Easy
Potential for immunotherapy	Yes	No (?)	Yes (limited)
Potential for viral transmission to recipient	Yes	No	Yes
Potential for congenital disease transmission	No	Yes	No
Risk for the donor	Low	No	Low
Main problems to be overcome	GvHD	Graft failure, delayed immune recovery	Delayed immune recovery, lack of T-cell mediated GVL effect

Grewal et al, Blood 2003 – Rocha V and Locatelli F, BMT 2008



# Age and Disease Adapted Donor Choice

Children or Adults ?

Non-malignant or Malignant disorders ?

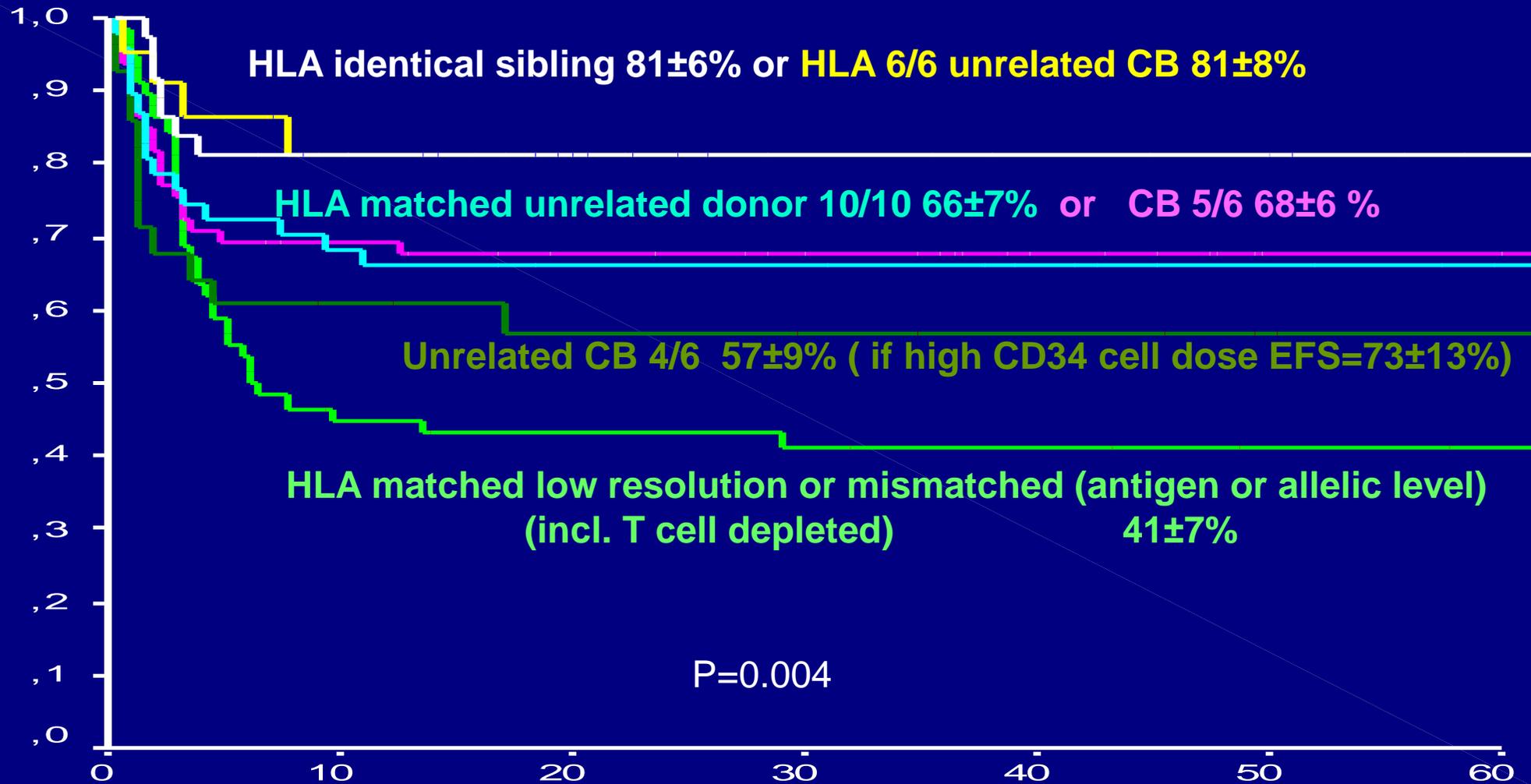
# Age and Disease adapted donor choice

Children

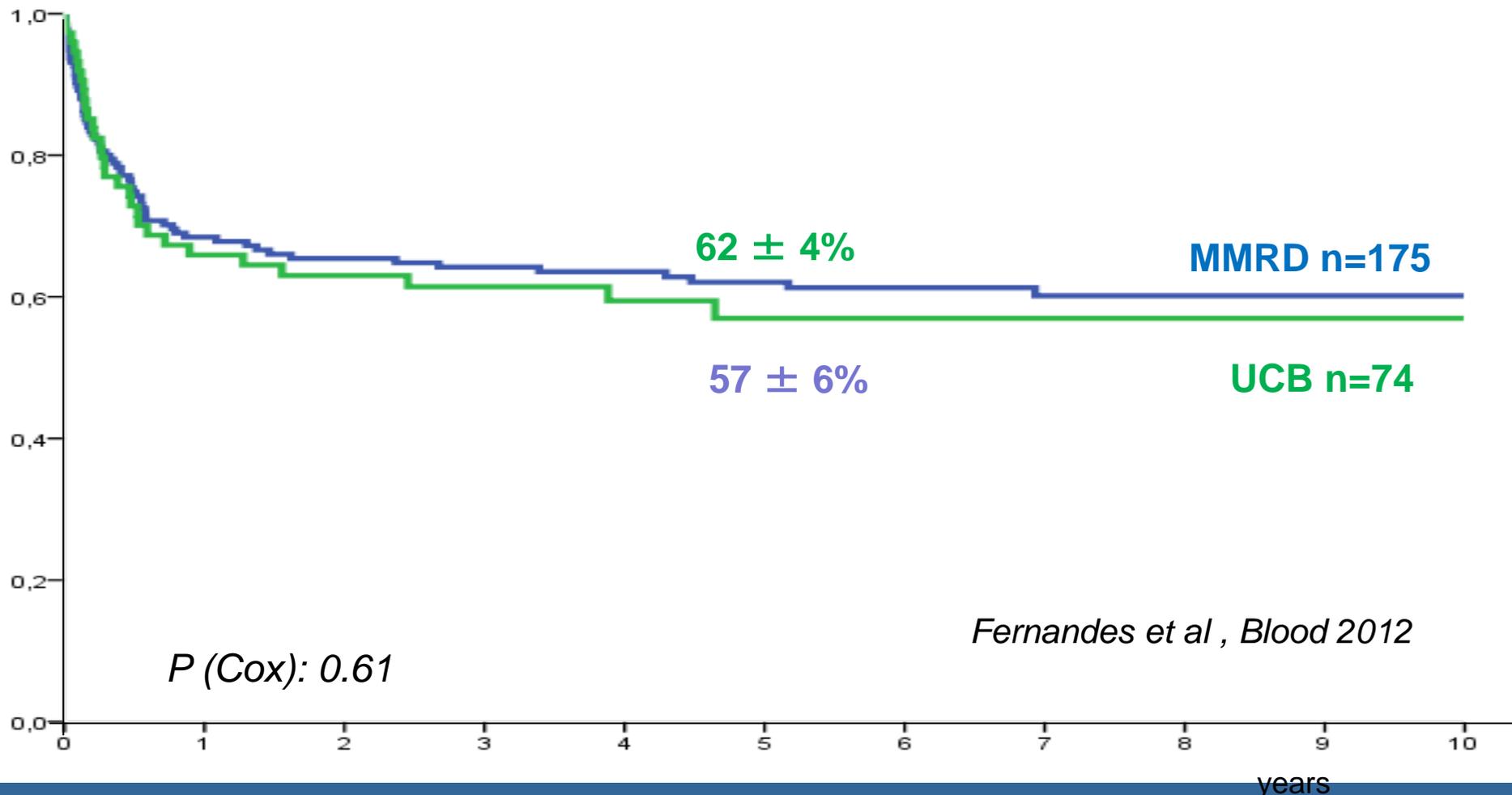
Non malignant disorders

# Children with Hurler disease

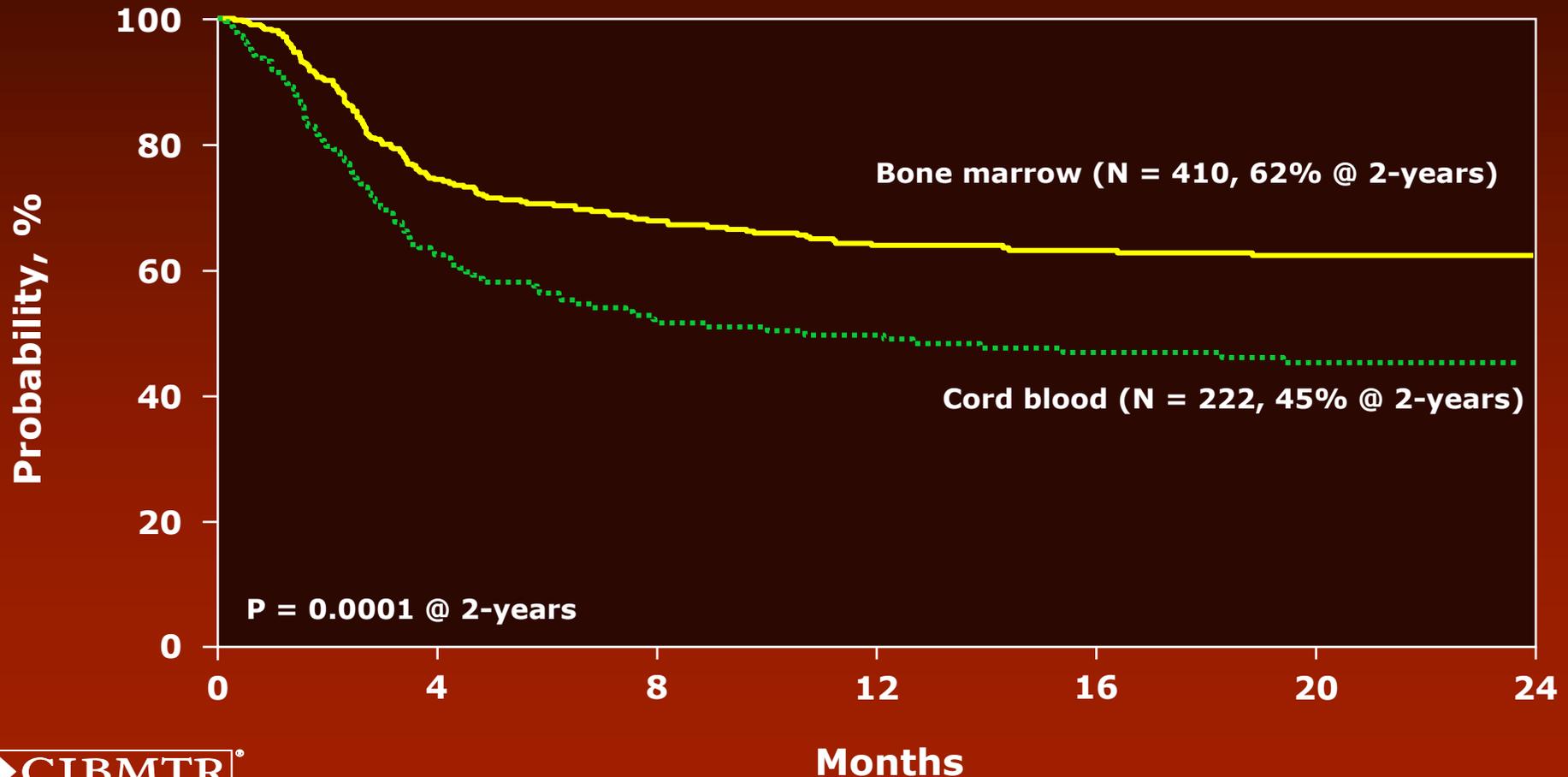
## Disease Free Survival by type of donor and HLA



# Overall Survival after Unrelated Cord Blood or HLA Mismatched Family donor for patients with SCID



# Overall Survival after Unrelated Transplants for aplastic anemia and Other Inherited Bone Marrow Failure Disease, Age $\leq 16$ , 1996-2006 - by Graft Type -



# Strategy of alternative stem cell donor in children with non malignant disorders

**Metabolic Disorders ( better results in early ages)**

**HLA identical= Unrelated 6/6 CB> MUD10/10=UCB5/6>CB4/6 high cell dose**

**Primary Immunodeficiencies ( Urgent situations)**

**HLA identical > UCB=HLA mismatched Donor= MUD (10/10) (rare)**

**Aplastic Anemia ( congenital or acquired)**

**HLA identical>MUD 10/10>MUD 9/10 >> CB (6/6 or 5/6 cell dose  $>4.5 \times 10^7/\text{Kg}$ )**

**Haplo HSCT under investigation**

**Hemoglobinopathies**

**HLA identical, other alternative donors under investigation**

**In cases of unrelated donors always ask for BM cells**

**Do not forget to search for antibodies against HLA in cases of HLA mismatched HSCT**

# Age and Disease adapted donor choice

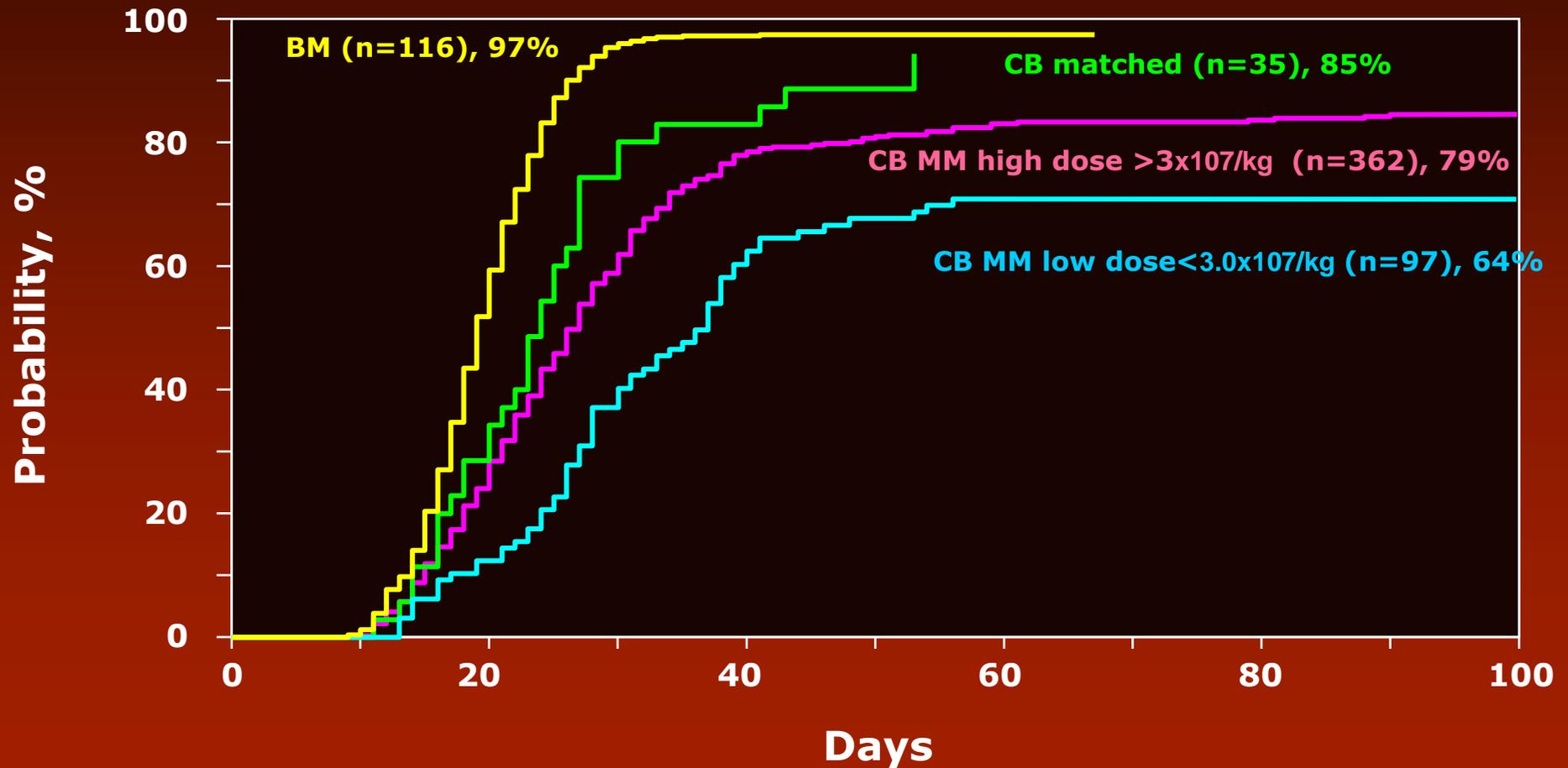
Children

Malignant disorders

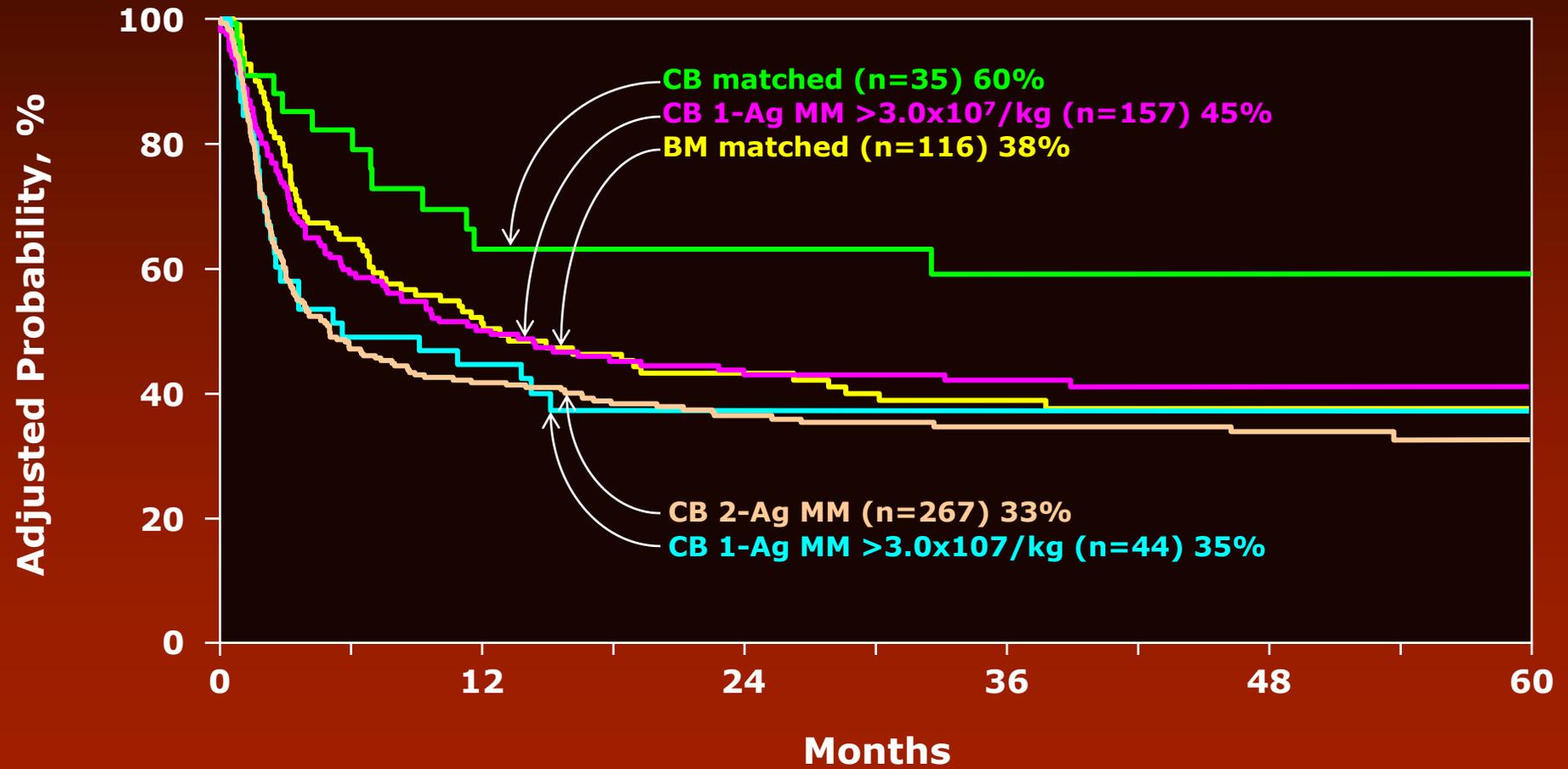
# **Unrelated Cord Blood versus allele typing Unrelated Bone Marrow Transplants in Children with Acute Leukemia**

**M Eapen et al , Lancet 2007**

# Neutrophil Recovery



# Leukemia-free Survival



# Strategy of alternative stem cell donor in children with malignant disorders

High resolution HLA typing

To be considered Haplo T-depleted in experienced centres.. Cy after??

Simultaneous search

Cord Blood Banks

Bone Marrow donor registries

NC dose collected to be increased with number of mismatches (single or double)

**>2.5x10<sup>7</sup>/kg NC**

**>1x10<sup>5</sup>/kg CD34**

**HLA: 0-1/6**

**> 3.5x10<sup>7</sup>/kg NC**

**>2x10<sup>5</sup>/kg CD34**

**HLA: 2/6**

<8/8 or >3 mths delay for AL)

HLA 8/8 or 9/10 or 10/10

**UCBT**

**UBMT**

# Age, Disease and disease status adapted donor choice

Adults

Malignant disorders:

Acute Leukemias (AML, ALL)

MDS

Lymphoid malignancies

**In remission or not**

(Myeloablative or reduced intensity)

# Comparative studies between UCBT and UBMT in adults (V Rocha NEJM 2004, M Laughlin 2004 , S Takahashi Blood 2004)

**Cord Blood vs Unrelated Bone Marrow**  
**6/6**



# A Meta-Analysis of Unrelated Donor Umbilical CBT versus Unrelated Donor BMT in Adult Patients

- 316 adults undergoing UCBT (mostly 1 or 2 antigen-mismatched), and 996 adults undergoing UBMT (almost entirely fully matched with the recipient), were analyzed.
- T-cell-depleted UBMT was excluded; where data were available, only fully matched UBMT was used in the analysis.

## RESULTS

- For adults, **transplantation-related mortality** (pooled estimate, 1.04; 95% CI = 0.52-2.08; P = .91) and **disease-free survival (DFS)** (pooled estimate, 0.59; 95% CI = 0.18-1.96; P = .39) were not statistically different.

# **Effect of Stem Cell Source on Transplant Outcomes in Adults with Acute Leukemia**

**A Comparison of Unrelated Bone Marrow, Peripheral Blood Progenitor Cells and Single Cord Blood**

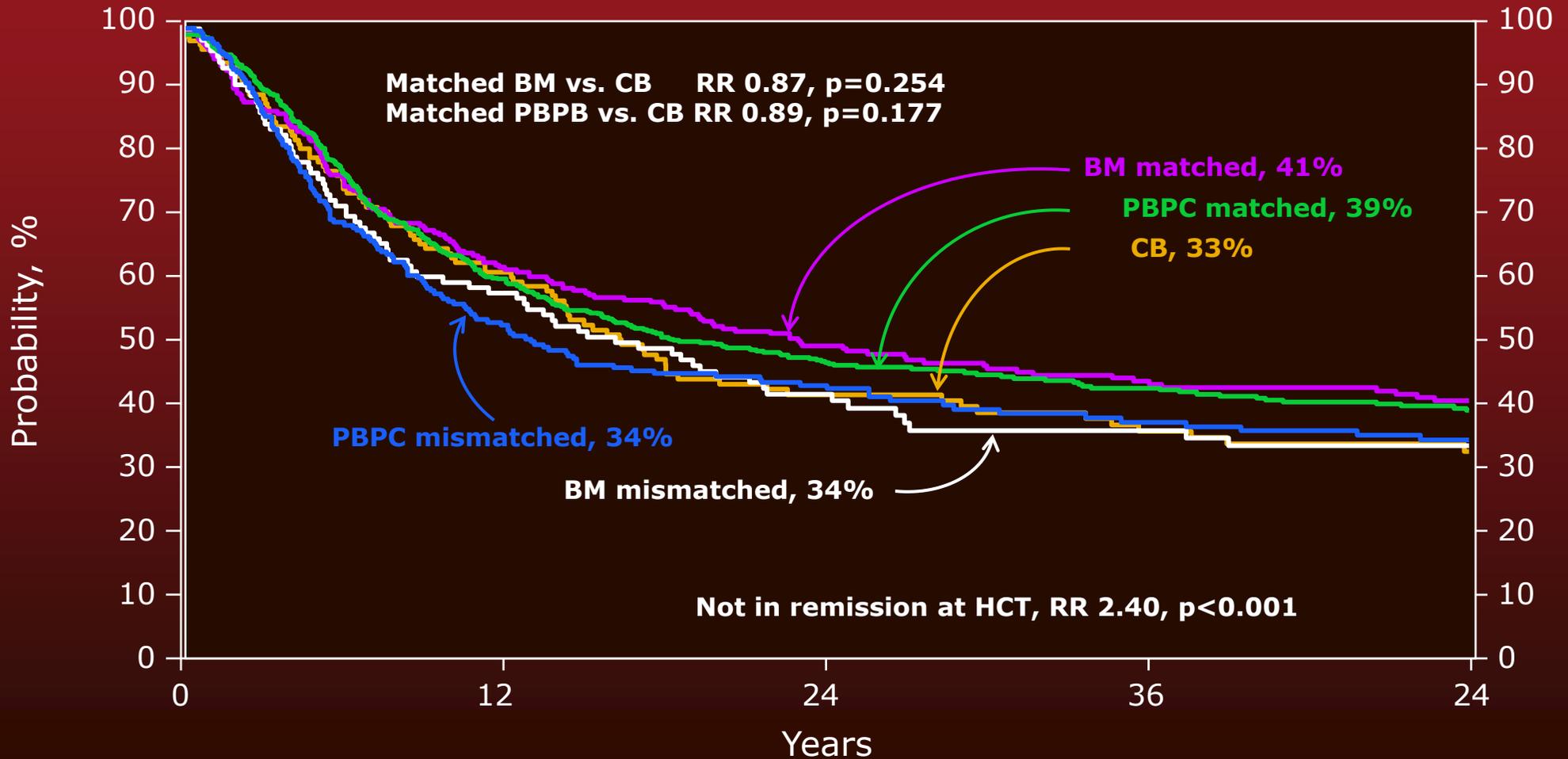
**From the Center for International Blood and Marrow Transplant Research, Eurocord-ALWP-EBMT and New York Blood Center**

**M Eapen, V Rocha Lancet Oncology 2010**



# Leukemia-free Survival

-Adjusted for Disease Status at Transplantation-



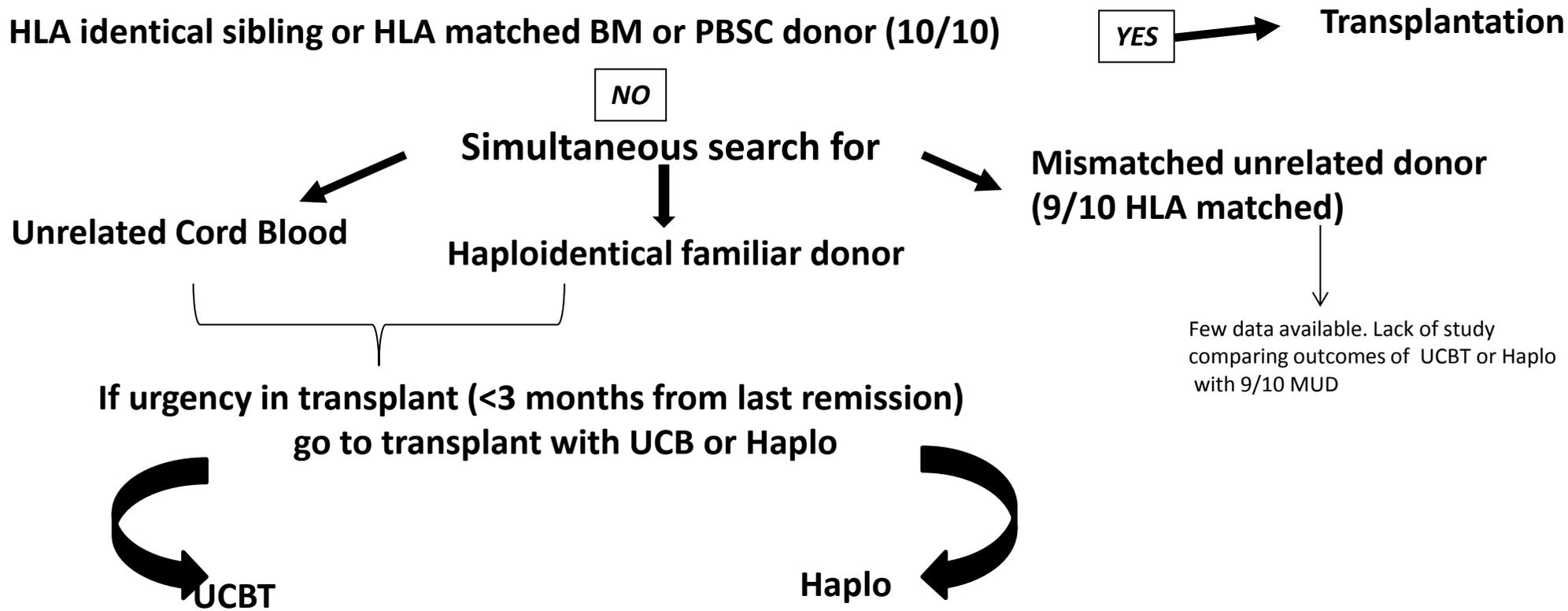
# Haplo Transplants

To be considered....

IMPACT OF KIR MATCHING (IN AML  
PATIENTS), CD34 CELL DOSE,  
MOTHER AS A DONOR  
AND  
CENTRE EXPERIENCE

New developments of Haplo-HSCT  
GSCF Primed BM transplants, T cell replete with increased  
immunosuppression in vivo ( Chinese approach and post CY)  
Immunotherapy

# Possible algorithm of donor choice in adults with high risk AL with an indication for allogeneic transplantation (Ruggeri A and Rocha V, 2010)



- > Use of Single or Double units according to TNC at collection and number of HLA mismatches\*
- > Use of myeloablative or reduced intensity conditioning regimen according to age and patients comorbidity

- > Use of CD34+ selected megadose\*
- > Choice mother, when available as donor
- > Selection of KIR mismatched donor
- > Use of myeloablative regimen
- > Lack of possibility to perform reduced intensity conditioning regimen

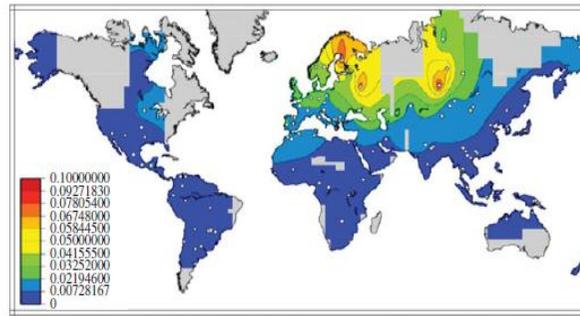
\*Cell dose according to HLA mismatches

HLA: 0-1/6	HLA: 2/6
>3x10 <sup>7</sup> /kg TNC	> 4x10 <sup>7</sup> /kg TNC
>1x10 <sup>5</sup> /kg CD34	>2x10 <sup>5</sup> /kg CD34

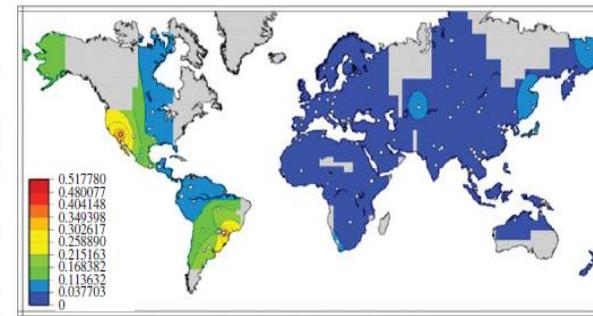
\* T cell depleted graft: >10x10<sup>6</sup>/kg CD34, 1x10<sup>4</sup>/kg CD3

# HLA diversity in LA

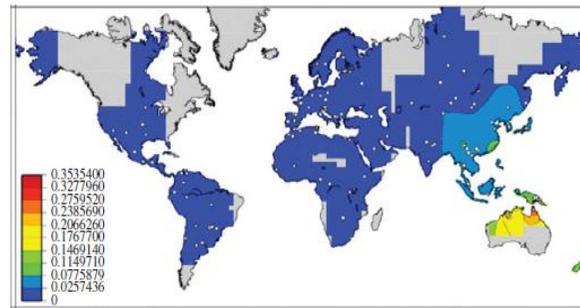
DRB1\*0801



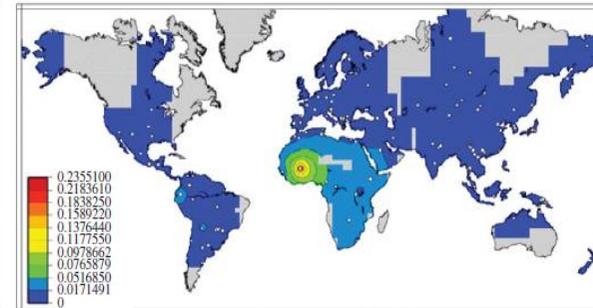
DRB1\*0802



DRB1\*0803



DRB1\*0804



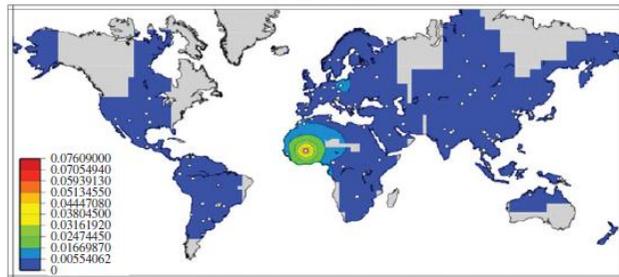
## Tracking human migrations by the analysis of the distribution of HLA alleles, lineages and haplotypes in closed and open populations

Marcelo A. Fernandez Vina, Jill A. Hollenbach, Kirsten E. Lyke, Marcelo B. Sztein, Martin Maiers, William Klitz, Pedro Cano, Steven Mack, Richard Single, Chaim Brautbar, Shoshahna Israel, Eduardo Raimondi, Evelyne Khoriaty, Adlette Inati, Marco Andreani, Manuela Testi, Maria Elisa Moraes, Glenys Thomson, Peter Stastny and Kai Cao

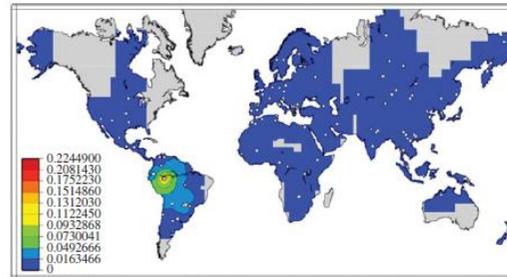
*Phil. Trans. R. Soc. B* 2012 **367**, doi: 10.1098/rstb.2011.0320, published 6 February 2012

(c)

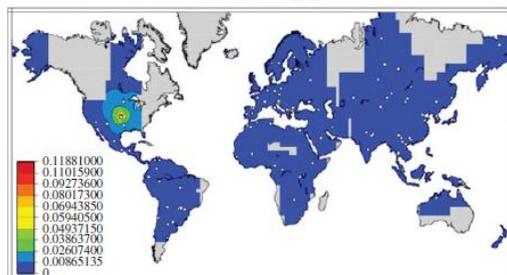
DRB1\*0806



DRB1\*0807

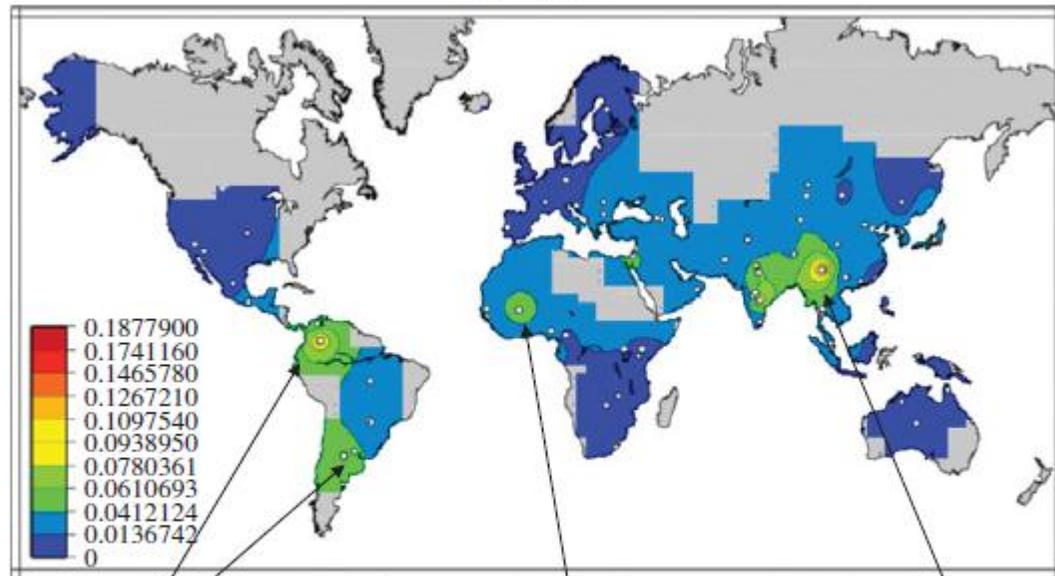


DRB1\*0811



(b)

B\*5201



B\*52:01:02-C\*03:03:01

B\*52:01:02-C\*16:01

B\*52:01:01-C\*12:02:02

Is the algorithm of graft source and donor the same in different LA countries ?

- ***Brazil***

HLA identical siblings>HLA 10/10 or 9/10>Cord Blood>Haplo

- ***Chile***

HLA identical siblings>CBU>Haplo

- ***Mexico***

HLA identical siblings>HLA 10/10 or 9/10>Cord Blood>Haplo

# Donor Registries and CBB listed in BMDW

Registry	Registry Code	Total	ABDR	%ABDR Typed	DNA Class I	DNA Class II	Date Last File
Argentina	AR	34,979	30,887	88.3	34,979	30,886	2013-09-24
Argentina CORD	ARCB	1,973	1,970	99.8	1,973	1,970	2012-04-17
Brazil	BR	3,065,249	3,057,726	99.8	2,931,816	3,052,113	2013-06-10
Chile Cord Blood Bank	SACB	634	634	100.0	634	634	2013-08-06
Mexico	MX	12,349	12,349	100.0	0	12,342	2013-05-23
Mexico CORD	MXCB	303	303	100.0	0	303	2013-05-23
Uruguay	UY	521	521	100.0	521	521	2013-09-19

# Discussion on alternative donors in LA

## Centers with expertise in Unrelated, CB and Haplo HSCT

- Establishment of Donor Registries/ costs
  - (Brazil, Argentina, Mexico, CBB Chile and Uruguay)
  - Cord blood banks/ costs and costs of CBU and transplants ( delay engraftment and viral infections)
  - Haplo transplants
- + and - selection (expertise and costs, problems, relapse, viral infections)
- CY after: still short follow up (interesting approach)