

# Donor choice

WBMT workshop

Hanoi 10-12 November 2011

# Donor choice

## Type of donor

### Related

- HLA identical sibling  
Bone marrow or cord blood
- Haploidentical family donor

### Unrelated

- Matched unrelated adult donor
- Mismatched unrelated cord blood donor

## Source of cells

- Bone Marrow
- G-CSF mobilized peripheral blood stem cells
- Cord blood

### Investigational

- T cell depleted PBSC
- Donor lymphocyte infusion (DLI)
- Mesenchymal stromal cells (MSC)

# HLA typing

- Related transplants

Type for HLA-A, B, DRB1 of both parents and all siblings low resolution should be enough to determine haplotypes

- Unrelated transplants

Allele typing for HLA-A,-C,-B,-DRB1, DQB1, DPB1

Look for a 10/10 or 9/10

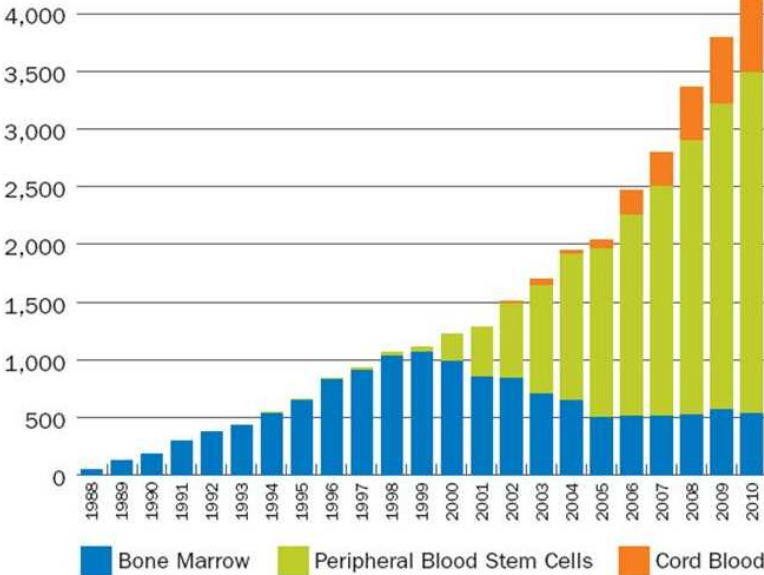
# Other factors to be considered

- **ABO** better if no major mismatch
- **CMV**
- **Hepatitis**
- **Sex** :avoid female donor immunized by previous pregnancies
- **Age**: younger donors

# Stem cell sources for allogeneic HSCT (US, 1988-2010)

## NMDP Transplants by Cell Source

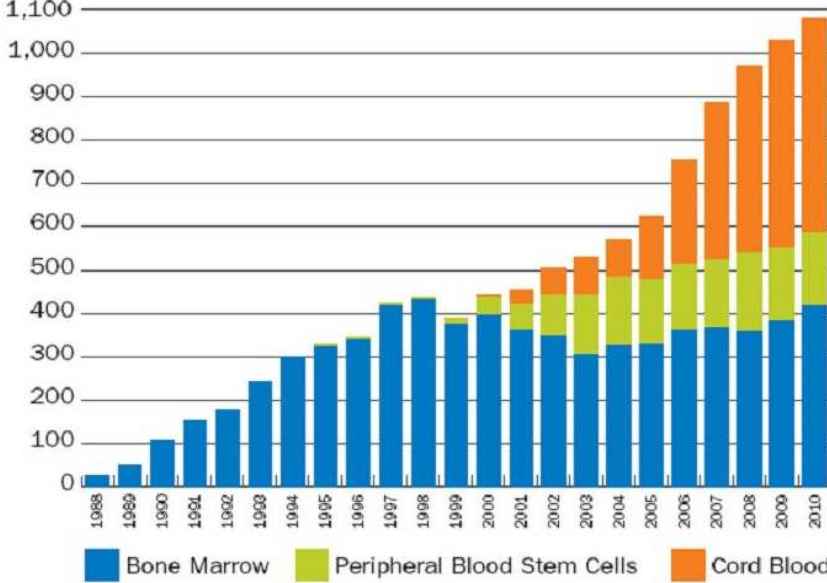
Adult Recipients (Age 18 Years and Older)



Source: National Marrow Donor Program FY 2010

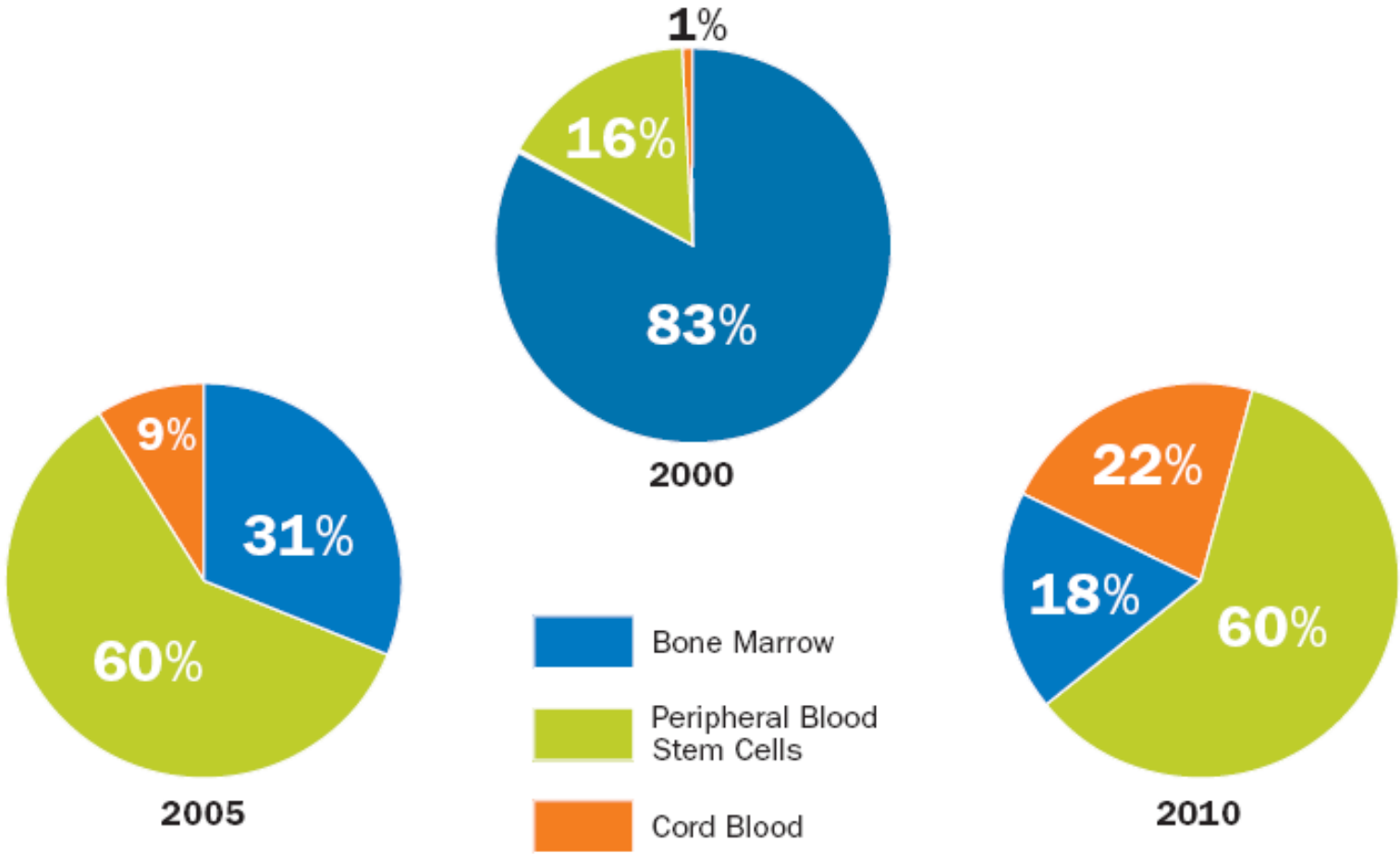
## NMDP Transplants by Cell Source

Pediatric Recipients (Age Younger Than 18 Years)



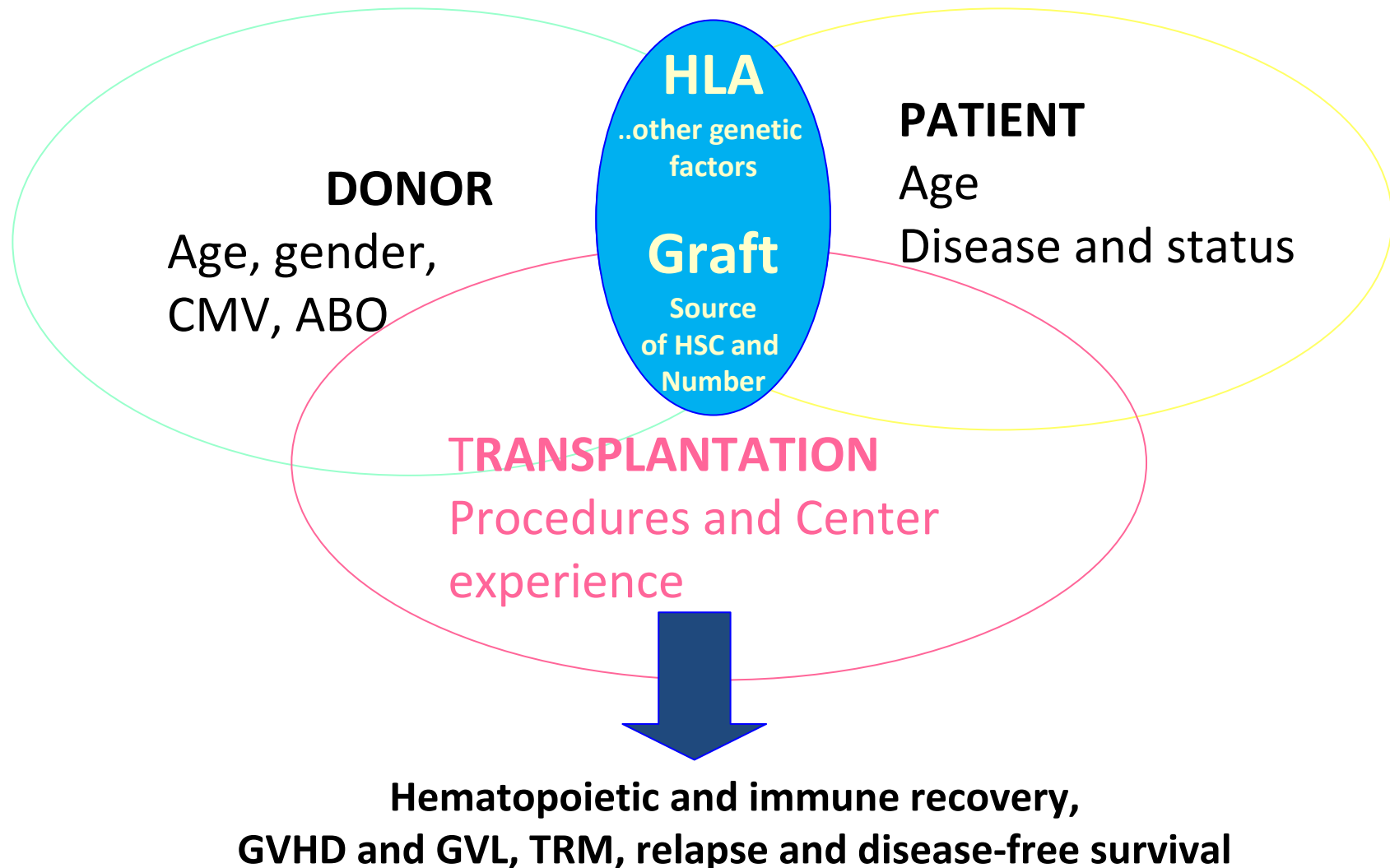
Source: National Marrow Donor Program FY 2010

# NMDP Transplants Distribution of Cell Source



Source: National Marrow Donor Program FY 2010

# Factors associated with outcomes after allogeneic HSCT



## 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



# Donor Selection – HLA Matching

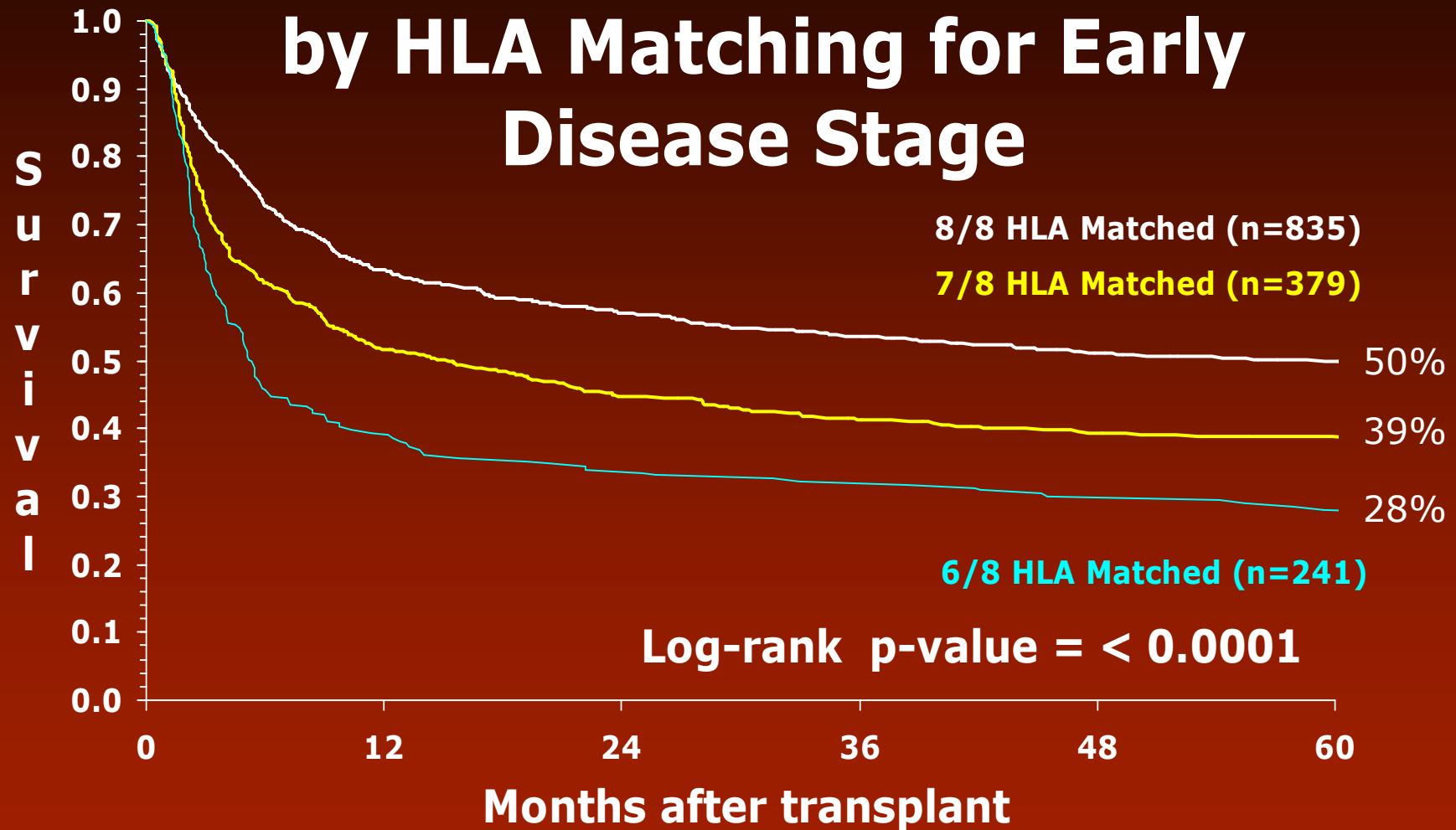
- ◆ General agreement that fully HLA-matched donor is the goal
- ◆ An 8 of 8 (HLA-A, B, C, DRB1)-sequence matched URD is not available for many patients who need a transplant
- ◆ Prior large studies suggest conflicting strategies for choosing the best partially matched donor
  - ◆ Antigens vs. alleles
  - ◆ Class I vs. class II
  - ◆ Specific loci

# Any Single Locus Mismatch

9/10 associated with worse survival, DFS, TRM, AGVHD

	n	RR (95% CI)	P-value
Survival	952	1.17 (1.06-1.329)	0.002
DFS	945	1.16 (1.05-1.28)	0.003
TRM	945	1.31 (1.16-1.47)	<0.0001
Relapse	945	0.90 (0.81-1.00)	0.04
Engraftment	956	0.90 (0.80-1.01)	0.06
Acute GVHD	957	1.35 (1.19-1.56)	<0.0001
Chronic GVHD	910	0.96 (0.91-1.03)	0.25

# Probability of Overall Survival by HLA Matching for Early Disease Stage



# Conclusions

- ◆ Single mismatches HLA-A or DRB1 appear more poorly tolerated than at HLA-B and HLA-C
- ◆ Each mismatch is associated with a 9-10% decrease in survival, and the absolute decrement in survival is most pronounced in the early stage patients

The HLA laboratory can help in providing a probability estimate to identify a 10/10 matched donor

## Probability to identify a 10/10 matched donor

high

>95%

priority to non-HLA factors (age, CMV, ...)

intermediate  $\approx 50\%$

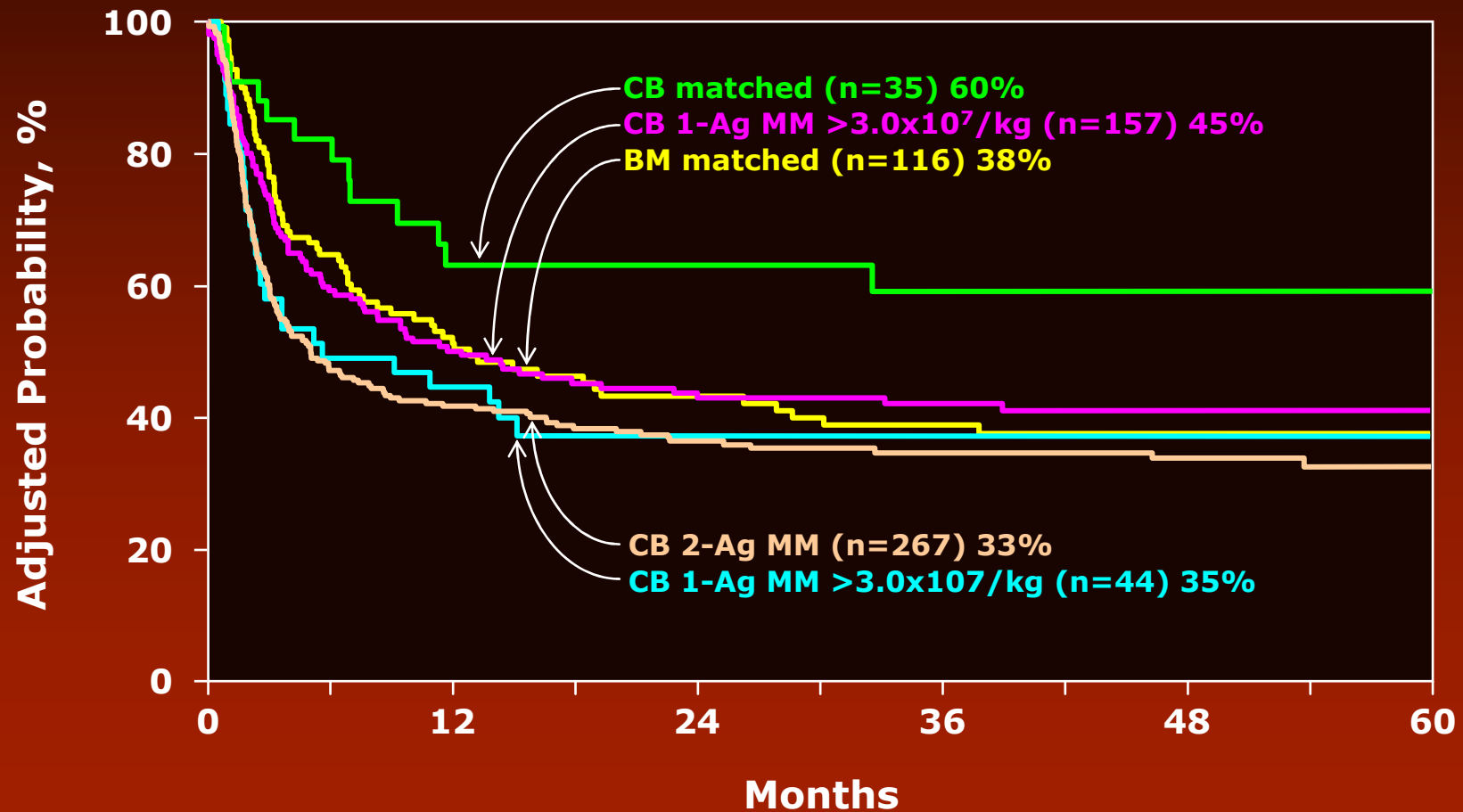
if no 10/10 match after testing  $\approx 5$  donors:  
consider a 9/10 match  
or go on if transplantation not urgent

low

<5%

consider rapidly a 9/10 match  
or alternative therapy (CB/haplo/autologous)

# Leukemia-free Survival in children with leukemia



## 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 > MUD 10/10 = UCB 5/6 > CB 4/6 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

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



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

High resolution HLA typing

↓  
To be considered Haplo T-depleted in experienced centres high CD34 cell dose

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

UBMT

UCBT

# 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

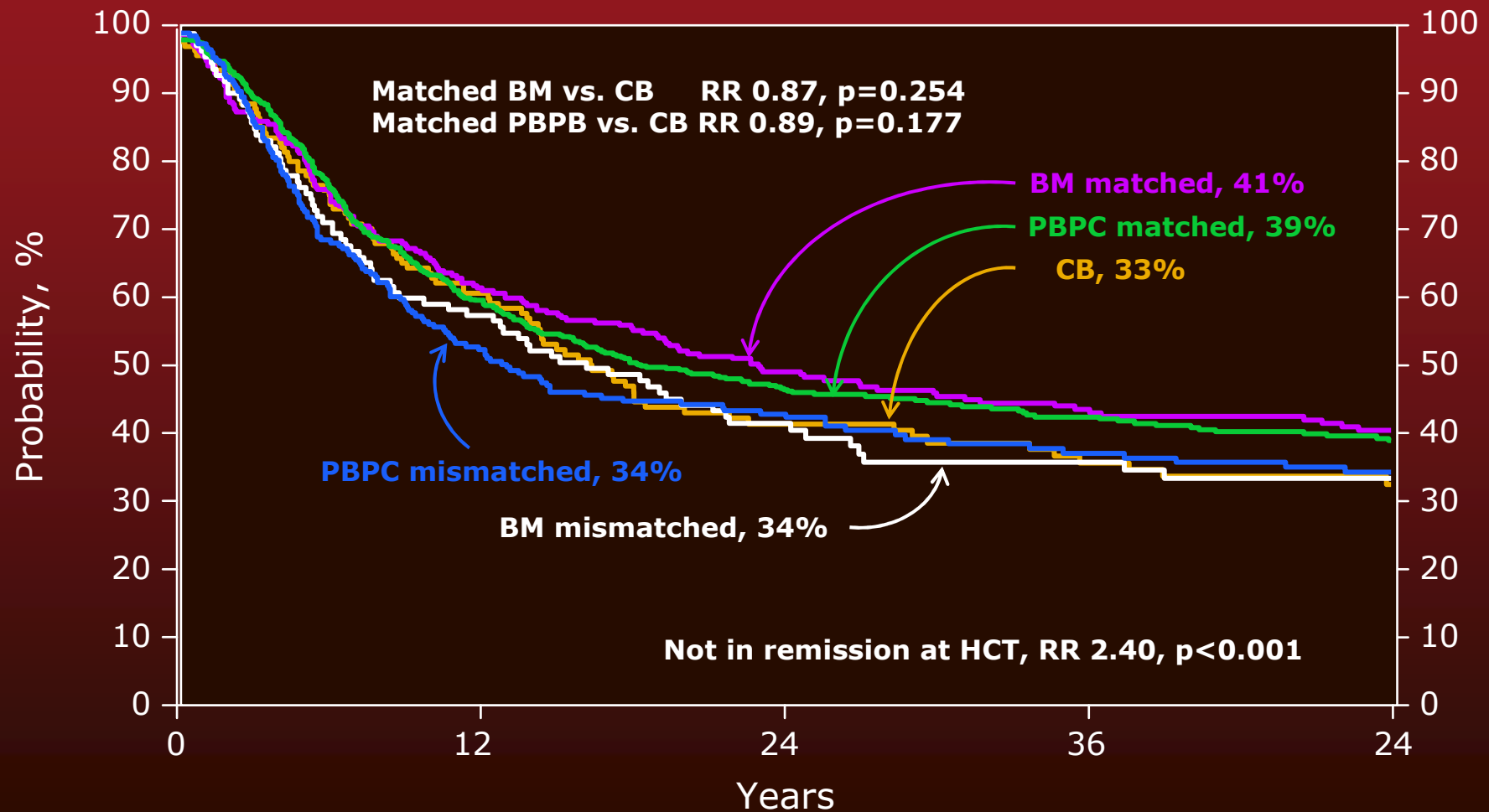
From the Center for International Blood and Marrow Transplant Research, Eurocord-ALWP-EBMT and New York Blood Center

M Eapen, V Rocha, G Sanz et al



# Leukemia-free Survival

-Adjusted for Disease Status at Transplantation-

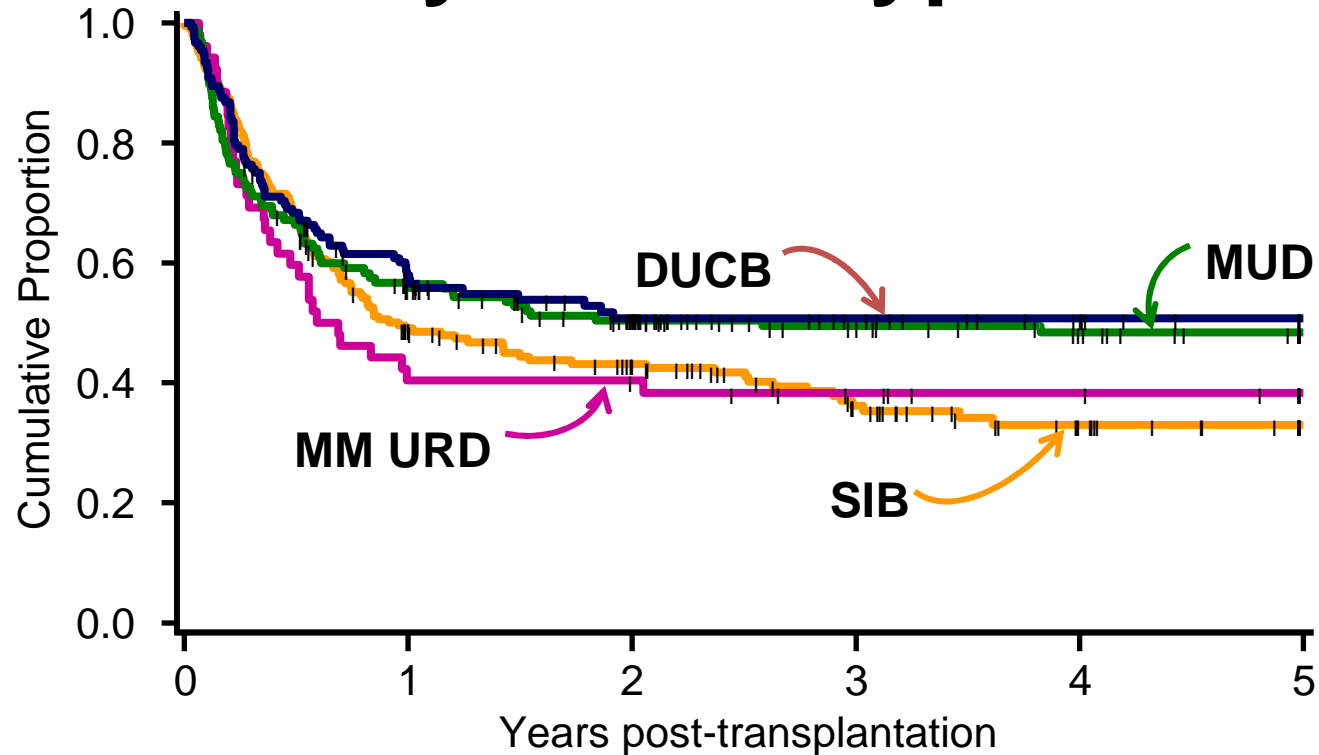


# Comparison between stem cell source

Minnesota and FHCRC Seattle

C Brunstein and C Delaney

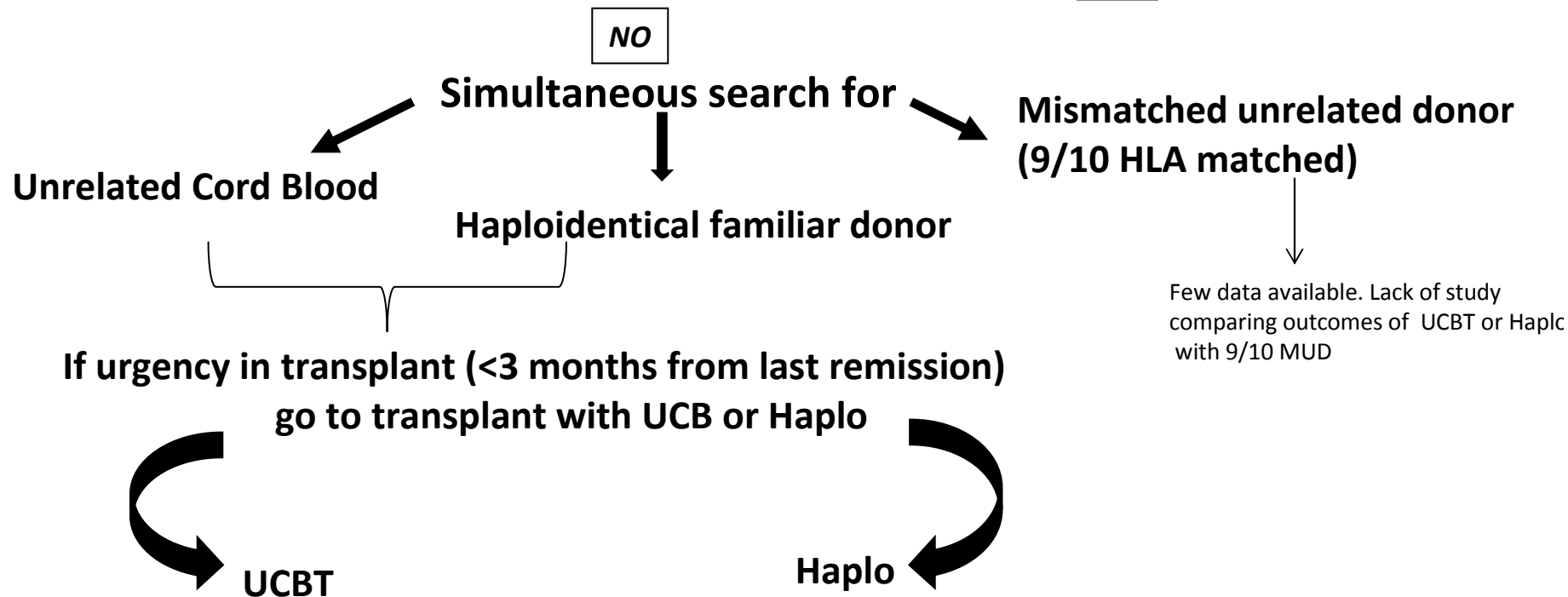
# Leukemia-Free Survival by Donor Type



<b>Matched Sibling*</b>	<b>1.0</b>	
<b>MUD</b>	<b>0.83 (0.62-1.11)</b>	<b>P=.20</b>
<b>MMUD</b>	<b>1.04 (0.70-1.53)</b>	<b>P=.85</b>
<b>DUCB</b>	<b>1.00 (0.73-1.37)</b>	<b>P=.99</b>

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

HLA identical sibling or HLA matched BM or PBSC donor (10/10) YES → Transplantation



- > 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