Donor and stem cell source selection

21 November 2013

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EBMT Annual report, 2010

Figure 1: increase in the number of unrelated HSCT during the years 1990 and 2009

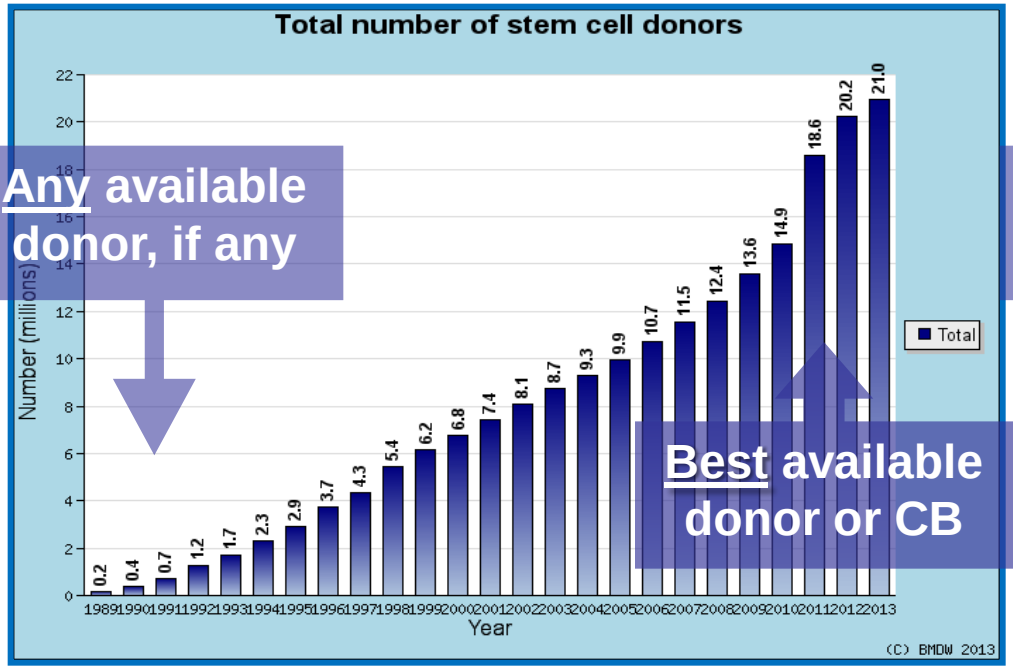
Hematopoietic stem cell transplantation (HSCT) has become an accepted therapy for many congenital or acquired disorders of the hematopoietic system and has seen major changes in indications and use of transplant techniques over the years.

Statement by the Worldwide Network for Blood & Marrow Transplantation (WBMT)

Up to end of December 2012:

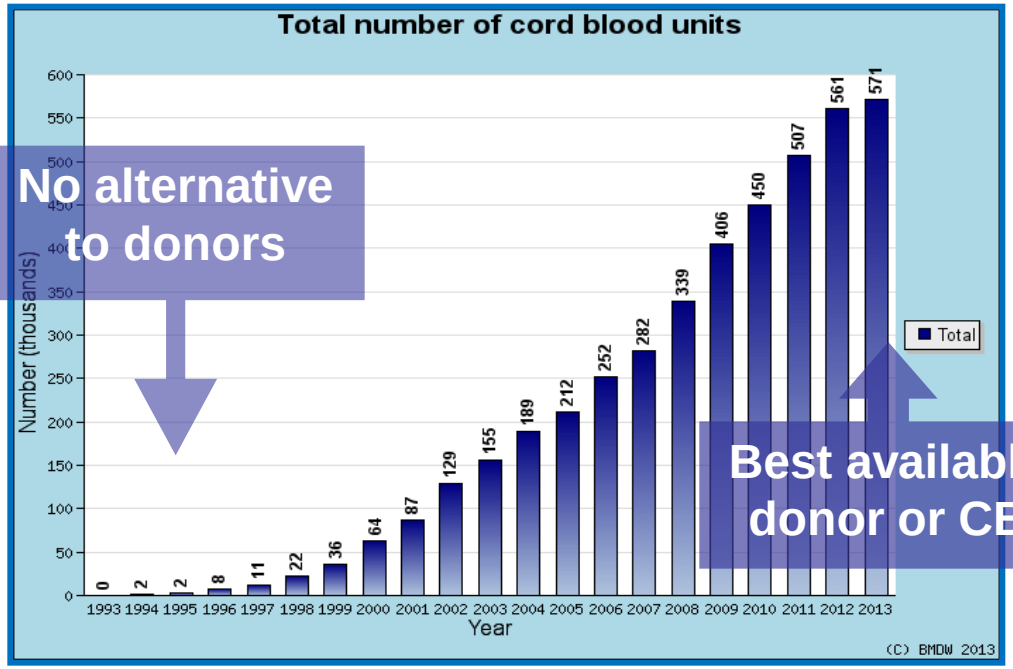
1 million HSCT have been performed worldwide

Number of stem cell donors and cord blood units worldwide



Any available donor, if any

Best available donor or CB



No alternative to donors

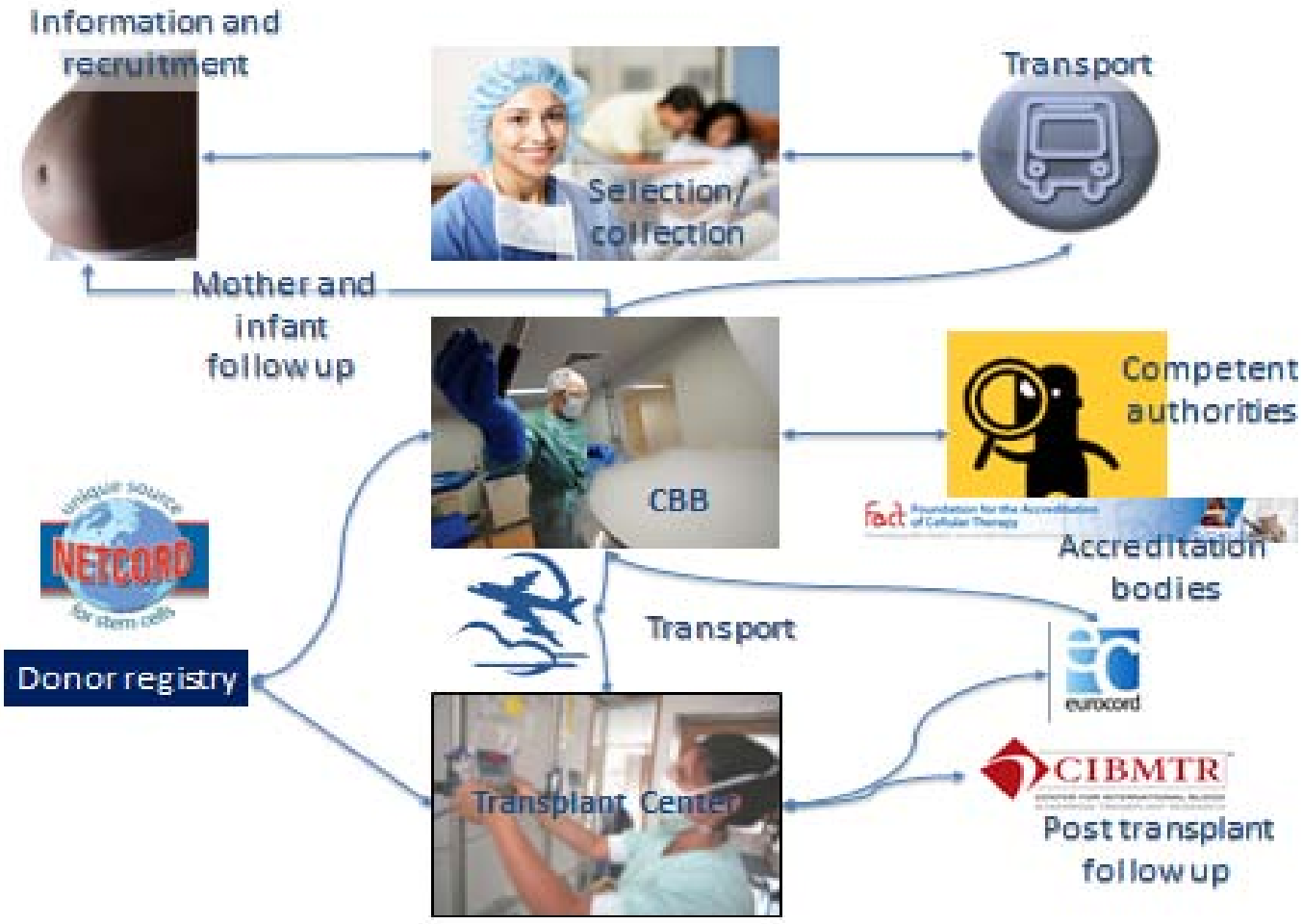
Best available donor or CB

≅ 22M stem cell donors

594,000 CBU's

Data from BMDW - Bone Marrow Donors Worldwide

Structure


Information and recruitment
Selection/ collection
Transport
Mother and infant follow up
CBB
Competent authorities
Accreditation bodies
Transport
Donor registry
Transplant Center
Post transplant follow up

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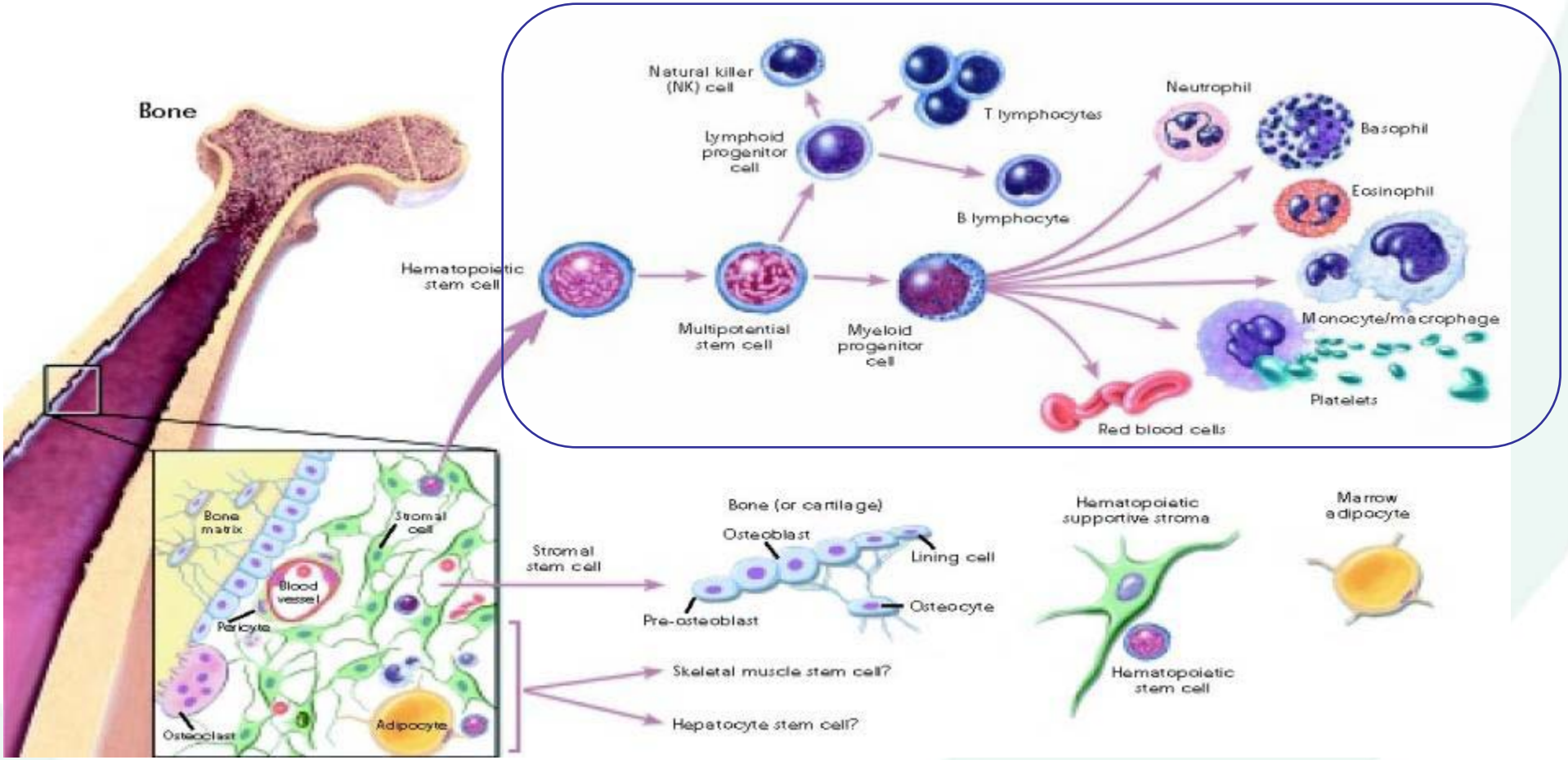
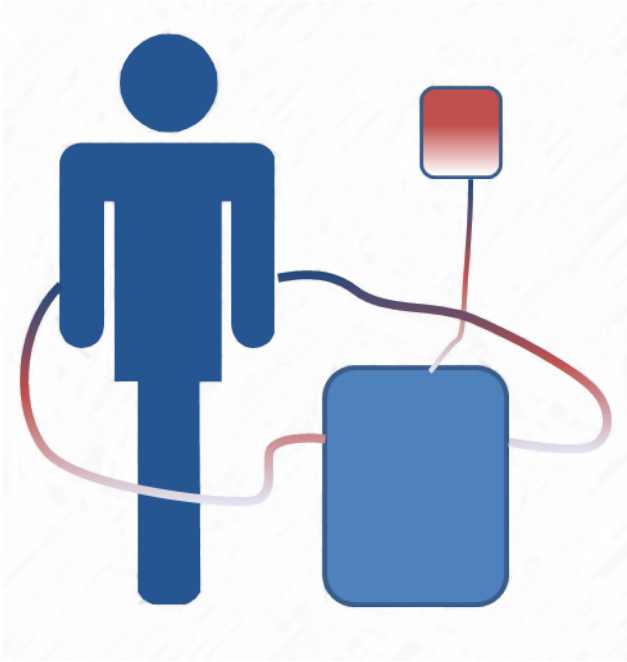
Bone marrow

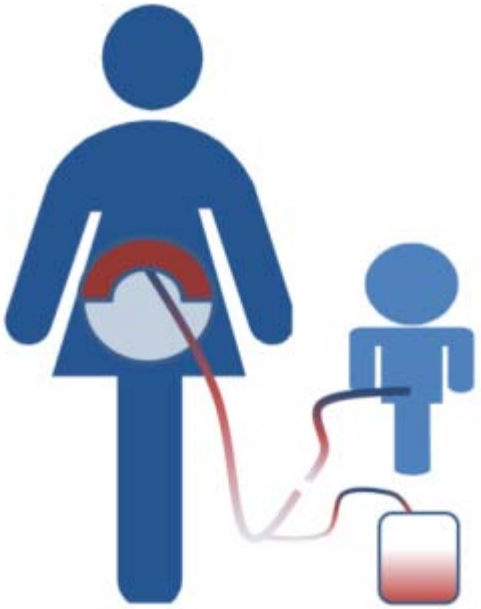

Bone
Natural killer (NK) cell
T lymphocytes
lymphoid progenitor cell
B lymphocyte
Neutrophil
Basophil
Eosinophil
Monocyte/macrophage
Platelets
Red blood cells
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Bone matrix
Stromal cell
Blood vessel
Pericyte
Osteoclast
Adipocyte
Stromal stem cell
Bone (or cartilage)
Osteoblast
Lining cell
Osteocyte
Pre-osteoblast
Skeletal muscle stem cell?
Hepatocyte stem cell?
Hematopoietic supportive stroma
Hematopoietic stem cell
Marrow adipocyte

Hematopoietic Stem Cell (HPC) sources

BM

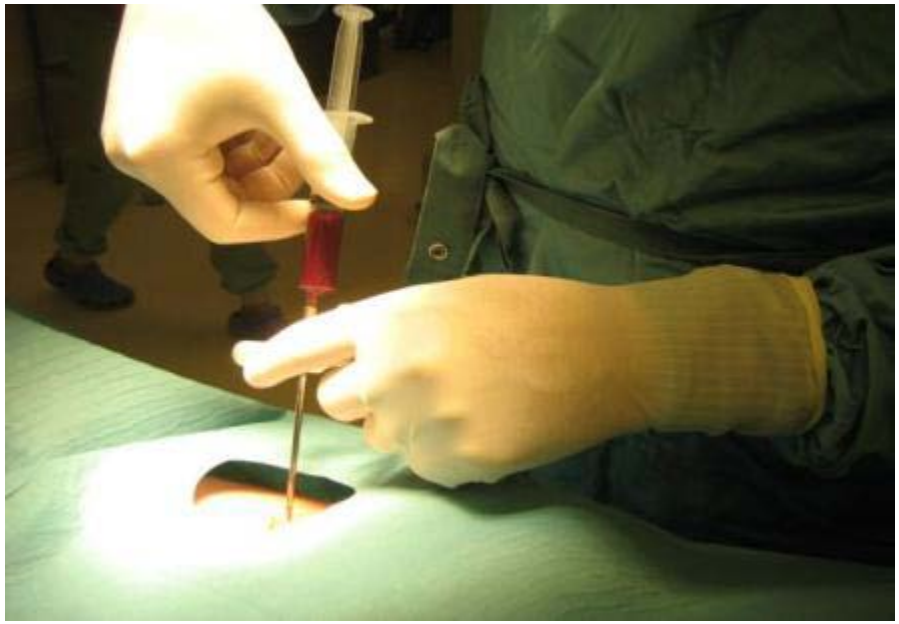


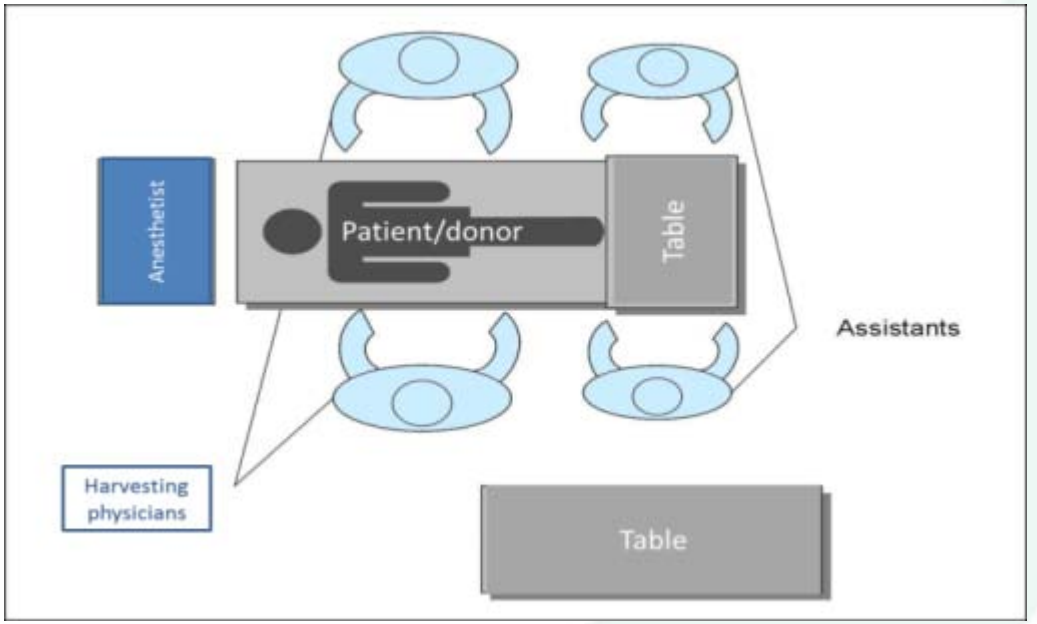
PBSC

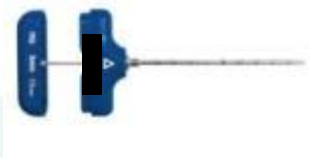


CB

Bone marrow collection





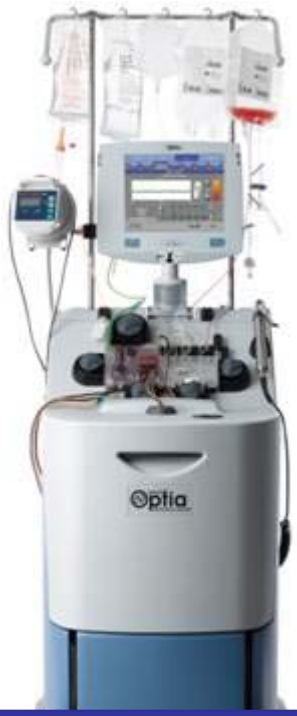


Anticoagulant type	Amount
Adenine Citrate Dextrose-A (ACD-A)	10-15mL/100 mL BM
Heparin	10U/mL BM

Target 3-4 x 10^8 NC/kg

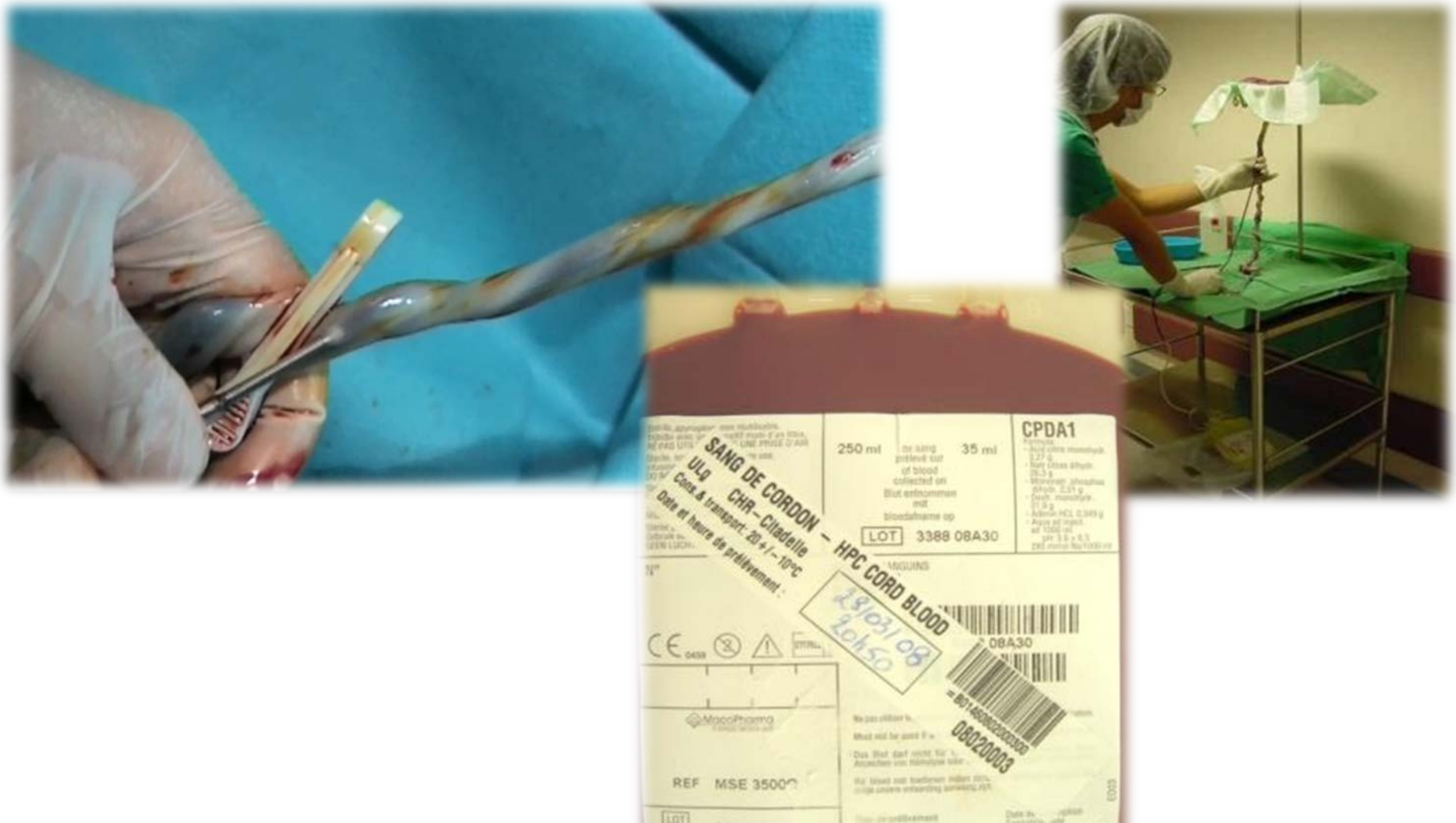
Peripheral stem cell collection

- Continuous flow cell separator
- Transportable equipment ➔ bedside collection allowed
- No general anesthesia
- Peripheral or central vein
- Disposable Kits disposables, closed circuit
- Flexible settings
- Quickly metabolised anticoagulant, low systemic effects
- Collection in adults and children
  10 ➔ 100+ Kg



		Ideal dose	Minimal dose	Remarks
HPC, Apheresis	Autologous	5 x 10^6 CD34/kg	2 x 10^6 CD34/kg	• x 2 if tandem autologous transplant foreseen • x 1.5 if processing is foreseen (selection, depletion) • CFU-GM useful (> 20 x 104/kg ?) if available cell dose low or multiple apheresis
	Allogeneic	Highest possible CD34/kg (> 5 x 10^6 CD34/kg)	2 x 10^6 CD34/kg	x 1.5 if processing is foreseen (selection, depletion)

Cord blood collection



DONOR TYPES

- Matched Sibling Donor
  - Usually HLA identical brother or sister (Sometimes as cord blood donor)
- Matched Unrelated Donor
- Unrelated CB Donor
- (Haploidentical Donor)

Donor/source of HPC

	Autologous	Allogeneic	
		Family	Unrelated
BM (HPC, M)	Patient	Sibling ➔	Donor registries
PBSC (HPC, A)	Patient	Sibling ➔	Donor registries
Cord Blood (HPC, CB)		Sibling ➔	CB Banks Donor registries

DONOR
Adult versus CB unrelated donor

	Adult volunteer	Cord blood
Engraftment	Rapid	Slow
Risk of GVHD	High	Low
HLA compatibility	8+ out of 8	4-5 out of 6
LIMITATION	**HLA**	**CELLULARITY**

DONOR
Adult versus CB unrelated donor

	Adult volunteer	Cord blood
Supply	10% loss/year	unlimited
Delay	6 months	Immediately available
Risk to donor	anesthesia (BM)	none
NC dose	OK	OK for children
Engraftment	Rapid	Slow
Risk of GVHD	High	Low
HLA compatibility	8+ out of 8	4-5 out of 6
Probability	65%	100%
LIMITATION	**HLA**	**CELLULARITY**

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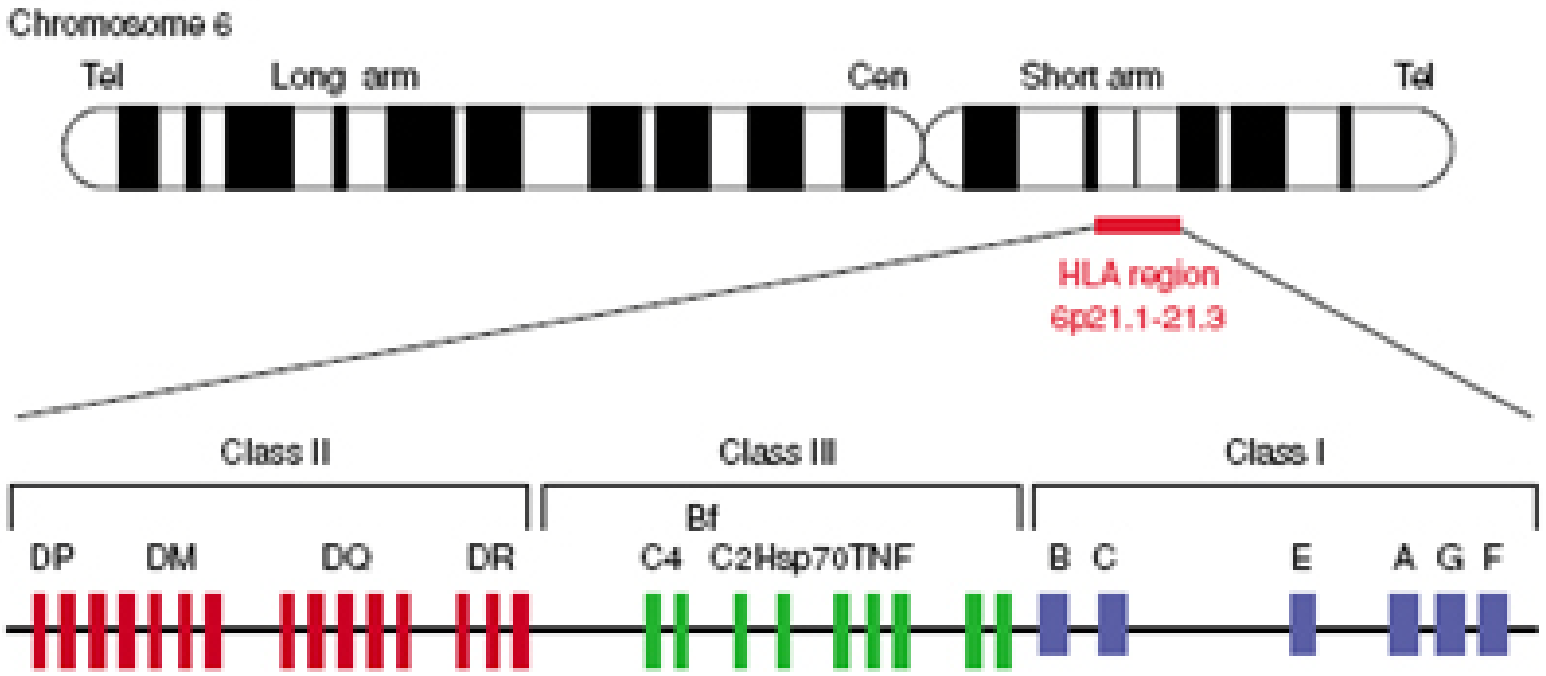
Human Leucocyte Antigen



DONOR
HLA system

- **12 genes on short arm of chromosome 6 :**
  - **3 HLA class 1 gene (A, B, C) : monomeric Ag (A, B, C)**
  - **9 HLA class 2 genes (DRA1, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1, DPB1)**
  - **DRB3, DRB4, DRB5 genes are mutually exclusive, are present only on certain haplotypes, in relation with particular DR Ag (DR52, DR53, DR51)**
- **Extreme polymorphism :**
  - **Antigenic level : A, B, C, DR, DQ antigens**
  - **Allelic level : A, B, C, DRA1, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1, DPB1 genes.**
    Number of identified alleles increases constantly

HLA alleles of importance for HSCT
Assigned April 2012

Locus	N Alleles
A	1884
B	2490
C	1384
DRB1	1194
DQB1	165

- **Range: 10^{23} genotypes**
- **Most frequent haplotype : A 01-B 08-DRB 0301 (6% of caucasians)**

DONOR
HLA incompatibility

- **Level of incompatibility :**
  - **Antigenic (2-digit) : A*02 vs A*03**
  - **Allelic (4-digit) : A*02:01 vs A*02:02**
- **Direction of incompatibility :**
  - **GVH direction**
  - **Rejection direction**
  - **Both directions (most frequent)**

DONOR
HLA typing

- Over 10^{23} genotypes
- Some alleles and some combinations of HLA alleles (haplotypes) are rare and others frequent

  Most frequent haplotype : A01-B08-DRB0301 (6% of caucasians)
- To make sure 2 siblings are genotypically identical, parental typing is necessary to identify haplotypes
- If one of the parents is homozygous at Ag level, low resolution typing does not allow verification of genotypic identity between donor and recipient

DONOR
HLA compatibility

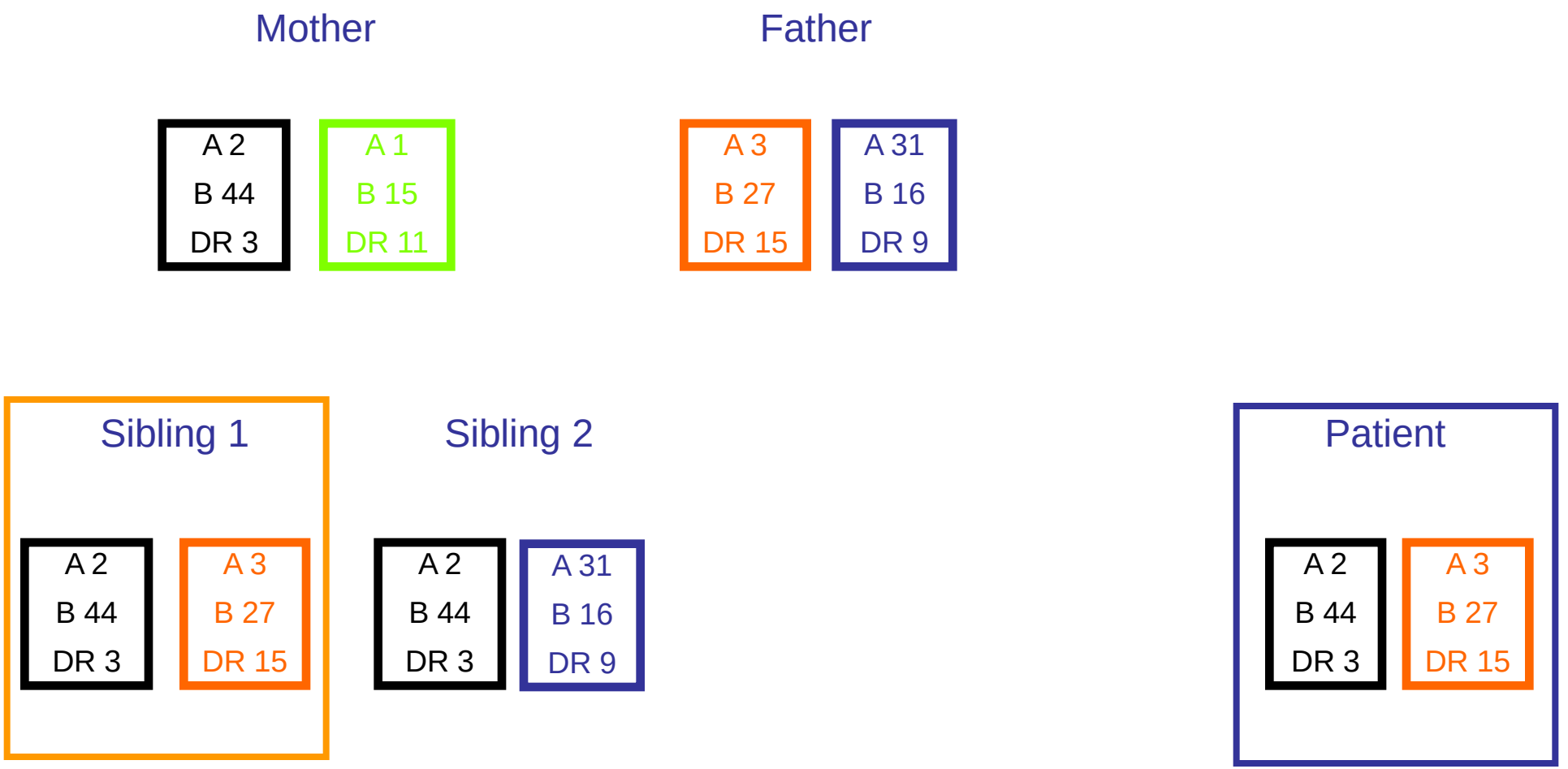
- **Degree of compatibility :**
  - **12/12 : A-B-C-DRB1-DQB1-DPB1 (not much used)**
  - **10/10 : A-B-C-DRB1-DQB1 (generally by high resolution typing)**
  - **8/8 : A-B-DRB1-DQB1 (not much used)**
  - **6/6 : A-B-DRB1 (generally by low resolution typing)**
- **Type of compatibility :**
  - **Genotypic : donor and recipient have received same 2 haplotypes from their parents (twins, siblings)**
  - **Phenotypic : donor and recipient have inherited one haplotype but not the other or are unrelated**

Donor		Donor	
A*	02:02	A*	02:02
B*	44:01	B*	35:01
C*	03:03	C*	04:03
DRB1*	01:01	DRB1*	08:02
DQB1*	02:03	DQB1*	04:03

Patient		Patient	
A*	02:02	A*	04:03
B*	44:01	B*	35:01
C*	03:03	C*	04:03
DRB1*	01:02	DRB1*	08:02
DQB1*	02:03	DQB1*	04:03

	Rejection		GVHD	
	Ag	Allele	Ag	Allele
A	0	0	1	0
B	0	0	0	0
C	0	0	0	0
DRB1	0	1	0	1
DQB1	0	0	0	0
Total	0	0.5	1	0.5
	9.5/10		8.5/10	

DONOR
HLA compatibility : genotypic



DONOR
Minimal and ideal compatibility

DONOR TYPE	MATCH LEVEL		REMARK
	IDEAL	MINIMUM	
Identical twin	By definition genotypically identical		
Brother/sister (sibling) or other family donor	6/6	5/6 IF one haplotype is genotypically identical. If not, see MUD	
Unrelated (MUD)	10/10	8/10 allelic*	
Cord blood	6/6	4/6 antigenic	Allelic match DRB1?
Haploidentical	1 haplotype identical Other haplotype: any		

(*) Minimum 8/10 allelic:	
• 1 antigenic MM (9/10)	• 1 allelic + 1 antigenic MM (8.5/10)
• 2 allelic MM (9/10)	• 1antigenic + 1 antigenic DQB1 (8/10)

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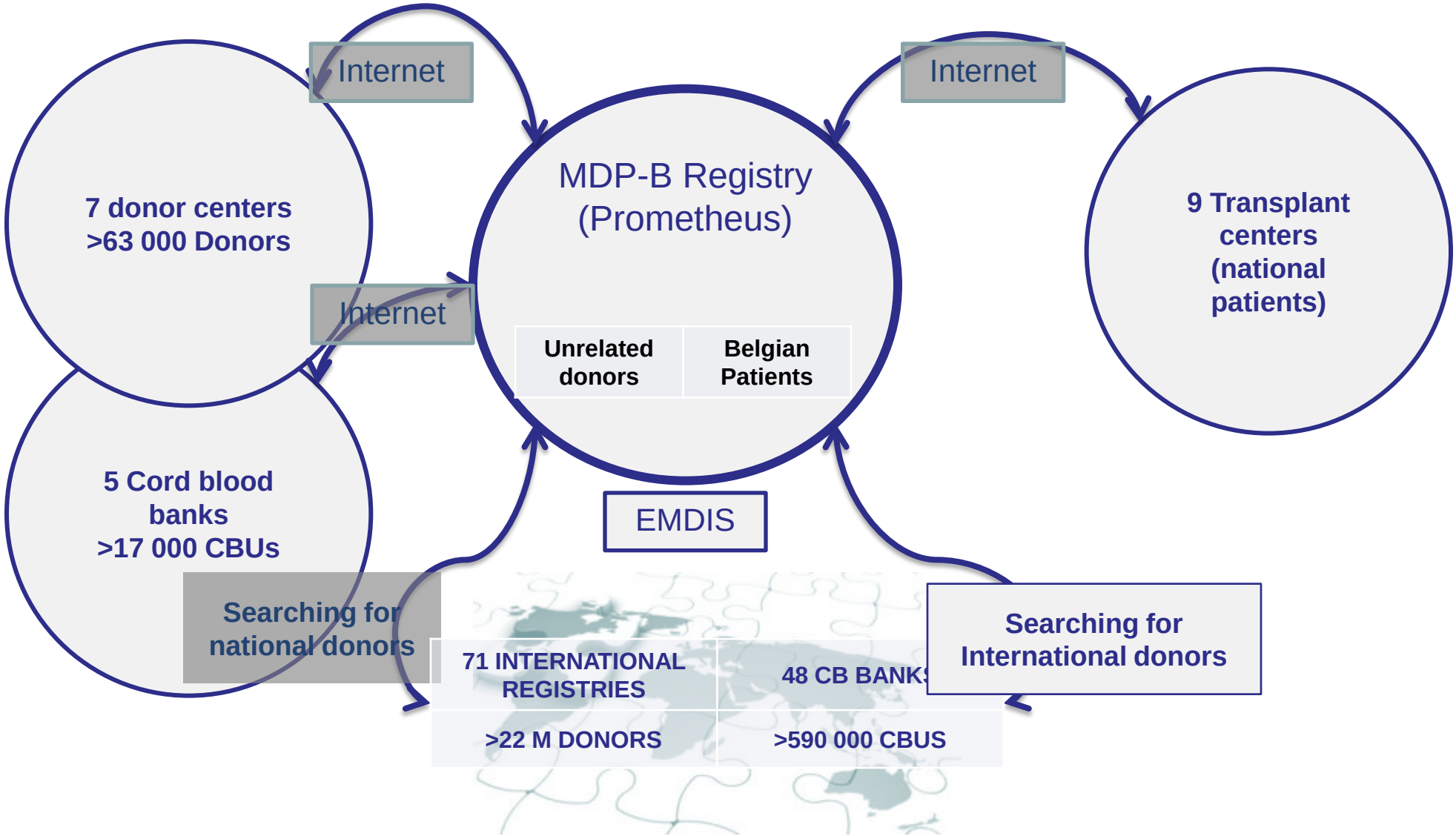
DONOR
Search for unrelated donors

- **Simultaneous VUD and CB search : based on type of HSCT (mini vs conventional) and donor selection criteria.**
- **BMDW (Bone Marrow Donor Worldwide) : all UD/CB listed by HLA compatibility with patient.**
- **MDP-B (Marrow Donor Program-Belgium) : Prometheus IT system and EMDIS network connecting with foreign registries including NMDP-USA.**
- **Netcord : CBB network, global search with NMDP-USA. Belgian hub is MDP-B.**
- **Confirmatory HLA typing (CT) in Liège on each donor before start of conditionning.**

MDPB-REGISTRY



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DONOR
Donor choice & eligibility

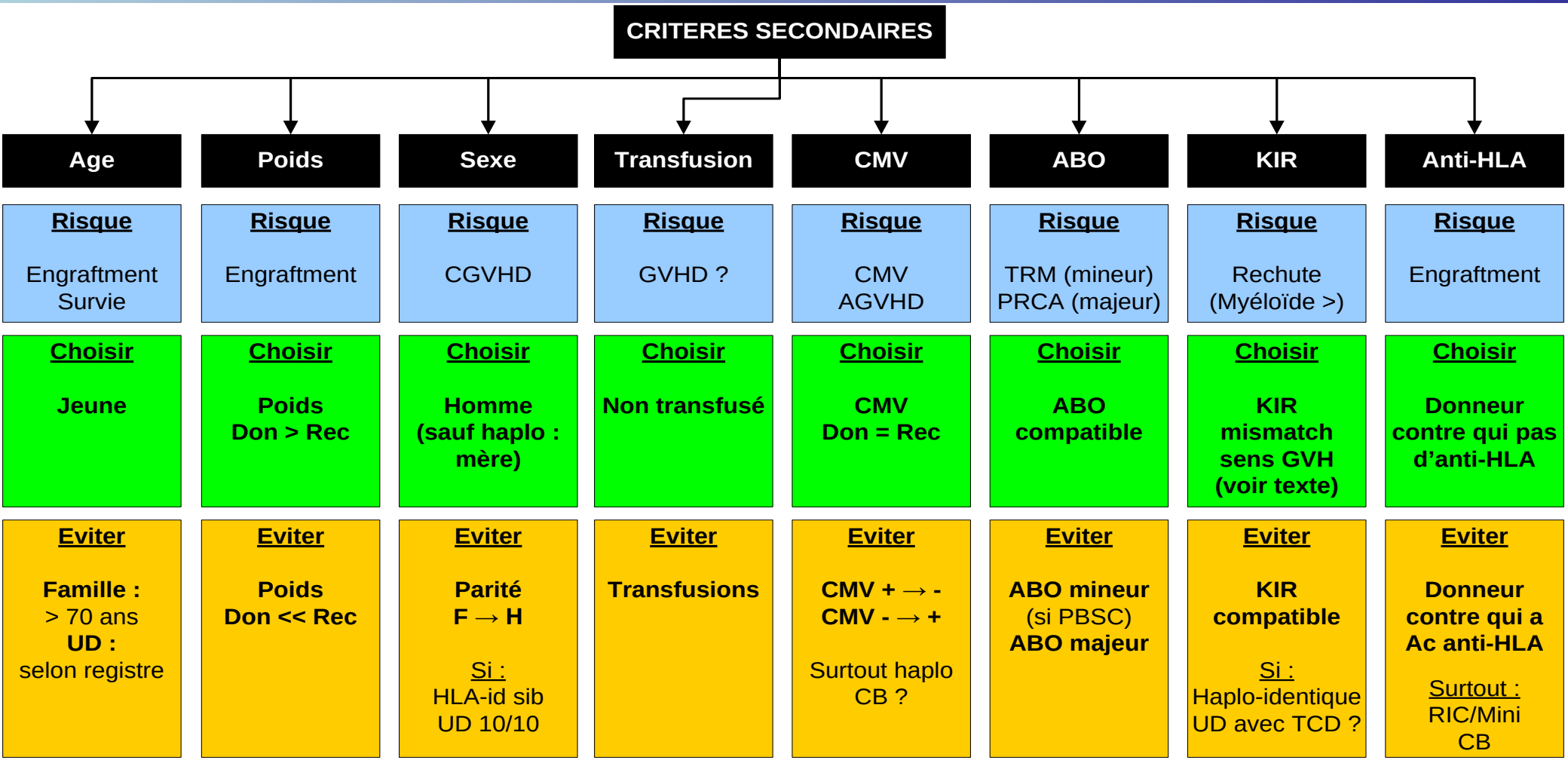
- **Choice: donor selection among a potential donors, based on:**
  - **HLA**
  - **Age, sex, CMV, ABO …**
  - **Donor preferences**
- Eligibility : donor acceptance, based on absence of contra-indication (non-conformity):
  - **Donor safety**
  - **Patient safety**

DONOR
Donor eligibility : non-conformity

- **Donor non conformity with any eligibility criteria may constitute:**
  - **Absolute contraindication to cell donation: dans ce cas, le besoin médical urgent (UMN, Urgent Medical Need) n'est pas possible.**
  - **Contre-indication relative au don de cellules : dans ce cas, le besoin médical urgent (UMN, Urgent Medical Need) est possible, moyennant décision du comité de greffe après éventuels avis spécialisés.**
  - **Précaution : le don de cellules est acceptable, mais des mesures complémentaires peuvent devoir être prises pendant le déroulement de la collecte et/ou de la greffe.**

Eligibility criteria

Criteria (examples)		Regarding donor safety	Regarding recipient safety
Pregancy		X	
Splenomegaly		X	
Autoimmune disease		X	X
Antocoagulant therapy		X	
Coronarian disease		X	
History of Cancer			X
Genetic disease			X
Vaccines			X
History of infection	Parasitic		X
	Microbial		X
	Viral		X
CJD/BSE risk evaluation			X
Blood and marrow disorders			X


CRITERES SECONDAIRES
Age
Poids
Sexe
Transfusion
CMV
ABO
KIR
Anti-HLA
Risque
Engraftment
Survie
Risque
Engraftment
Risque
CGVHD
Risque
GVHD ?
Risque
CMV
AGVHD
Risque
TRM (mineur)
PRCA (majeur)
Risque
Rechute
(Myéloïde >)
Risque
Engraftment
Choisir
Jeune
Choisir
Poids
Don > Rec
Choisir
Homme
(sauf haplo :
mère)
Choisir
Non transfusé
Choisir
CMV
Don = Rec
Choisir
ABO
compatible
Choisir
KIR
mismatch
sens GVH
(voir texte)
Choisir
Donneur
contre qui pas
d'anti-HLA
Eviter
Famille :
> 70 ans
UD :
selon registre
Eviter
Poids
Don << Rec
Eviter
Parité
F → H
Si :
HLA-id sib
UD 10/10
Eviter
Transfusions
Eviter
CMV + → -
CMV - → +
Surtout haplo
CB ?
Eviter
ABO mineur
(si PBSC)
ABO majeur
Eviter
KIR
compatible
Si :
Haplo-identique
UD avec TCD ?
Eviter
Donneur
contre qui a
Ac anti-HLA
Surtout :
RIC/Mini
CB

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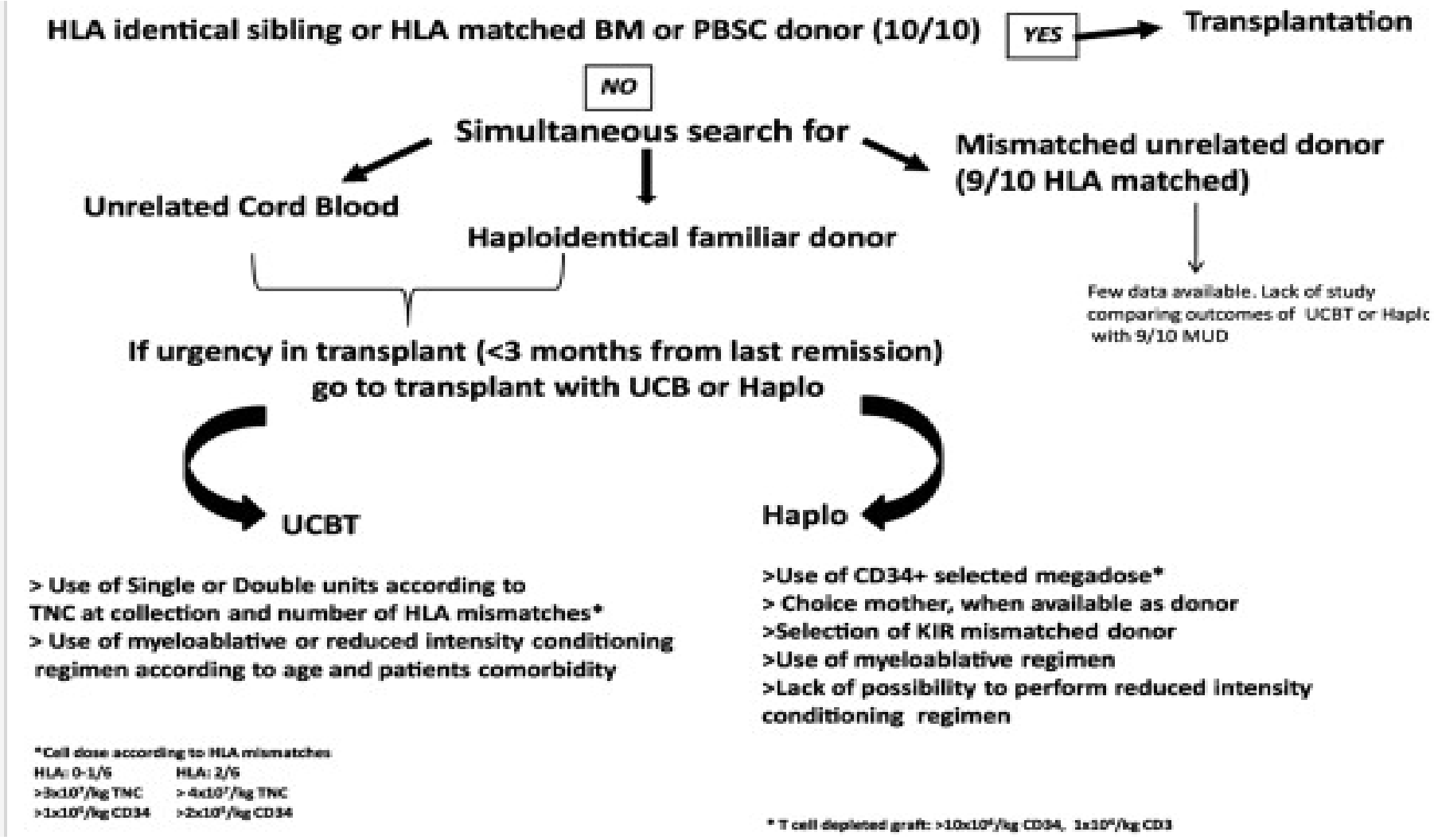
Strategy of alternative stem cell donor

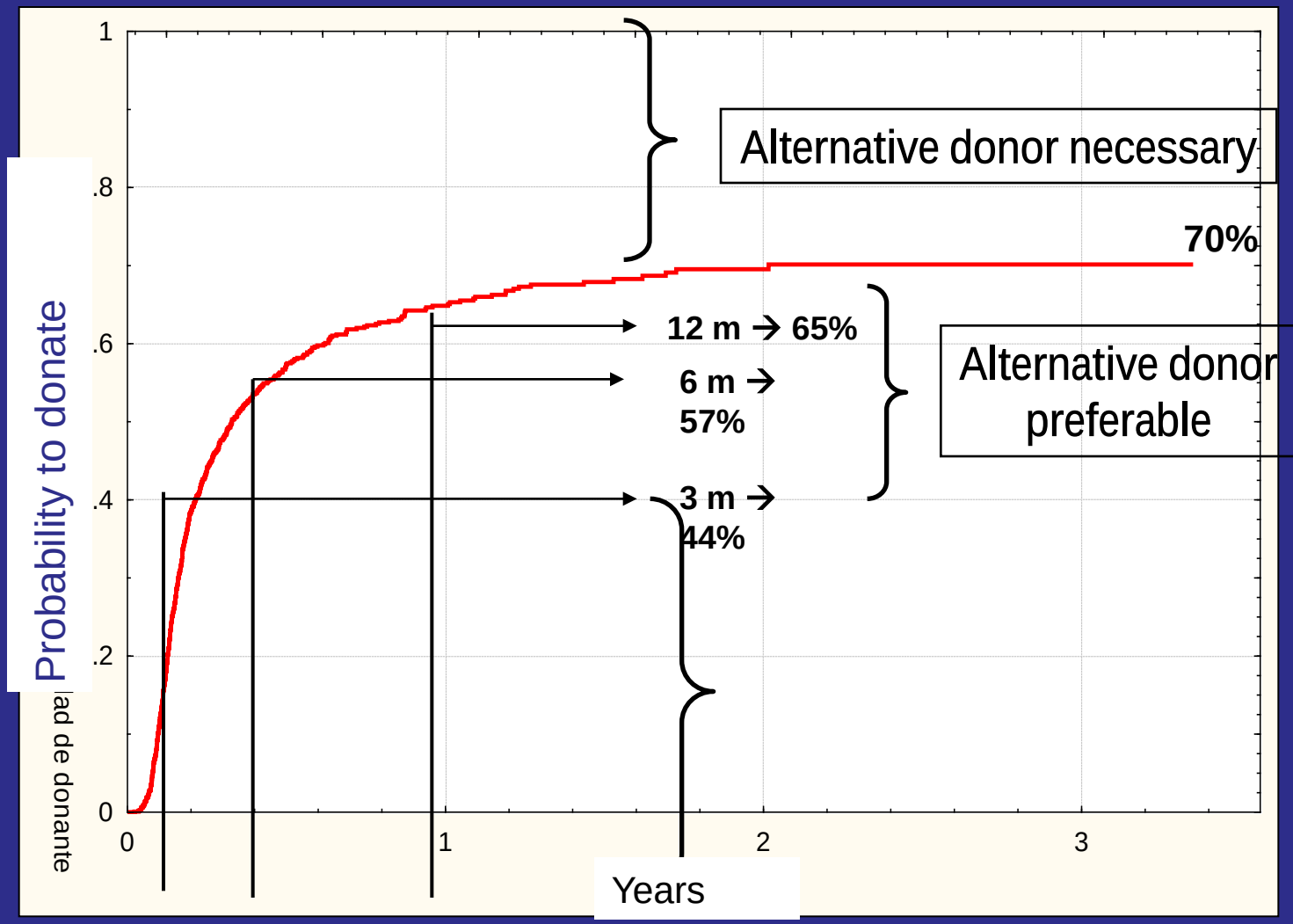


Finding a MUD

Search success rates and duration

- Search success rates
  (>20 million VUDs)
  - 8/8 match: 40 – 60%
  - 1 antigen mismatch: 60 – 90%
- Median search duration: 22 d – 2.5 mo
- Median time to transplant: 2 – 4 mo

Actuarial probability of finding a 7 / 8 or 8 / 8 MUD



in Spain (Memoria REDMO 2009)

Alternative donor allogeneic transplantation: criteria for choosing MUD vs. CBT vs. Haplo

	UBMT	*UCBT*	*Haplo-HSCT*
Information on A+B+DRB1 (DNA) typing (%)	16–56	~80	100
Median search time (months)	3–6	<1	Nil
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 the 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 to recipient	No	Yes	No
Risk for the donor	Very low	No	Very low
Main problems to be overcome	GvHD	Graft failure, delayed immune recovery	Delayed immune recovery, lack of T-cell-mediated GVL effect

Abbreviations: Haplo-HSCT=haploidentical hematopoietic stem cell transplantation; UBMT=unrelated donor BM transplantation; UCBT=umbilical cord blood transplantation.

[a] Modified from Grewal *et al.* [4]

Criteria of CB unit choice- EUROCORD

- **Patients screening for antibodies against HLA antigens**

→ **Look at the number of cells in MAC, RIC:**

- ✓ $\geq 2.5 \times 10^7$ NC/kg and or $\geq 1 \times 10^5$ CD34+/kg

→ **Look at HLA matches:**

- ✓ 0-1 mm better than 2 avoid 3-4 mm
- ✓ Prefer class I mismatches than class II
- ✓ Include HLA C typing, avoiding C mismatches
- ✓ Allele typing of HLA -A and –B (++ in case of 4/6 CBU)

→ **Then adapt to graft indication:**

- ✓ If the minimum number of cells for a single UCBT is not achieved, a double UCBT should be considered
- ✓ Malignant diseases: cell dose is the best prognostic factor because HLA differences reduce relapse (GVL)
- ✓ Non malignant diseases: increase cell dose (>4.0×10^7 NC/kg) and find the best HLA match
- ✓ → **Other considerations, if several CBU are available consider:**
- ✓ Cord Blood Bank accreditation status and location
- ✓ ABO compatibility
- ✓ NIMA and KIR status

blood
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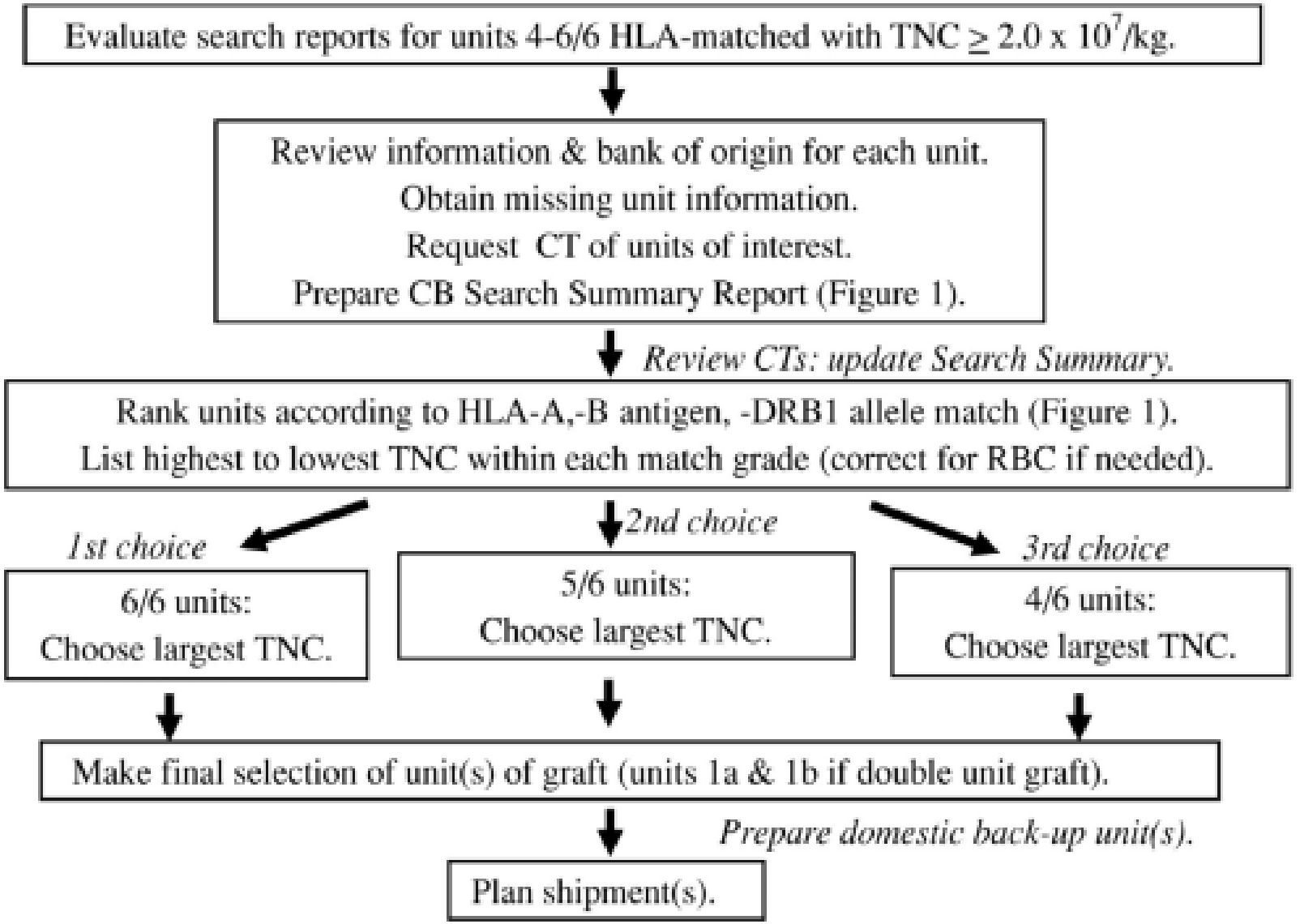
Schema of how we select CB units.



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- *Stevens C et al.*
  HLA mismatch direction in cord blood transplantation: impact on outcome and implications for cord blood unit selection
  Blood 2011 118: 3969-3978
- *Ponce DM et al*
  The Use of Back-up Units to Enhance the Safety of Unrelated Donor Cord Blood Transplantation
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  The EBMT Handbook, 6th Edition 2012 Chapters 6-7

Aknowledgements

- Y. Beguin, CHU Liège
- Annalisa Ruggeri, Eurocord
- M. Jagger and K. Richards, London UK