Summer School 2015

Alloreattività e trapianti nell'uomo: le nuove metodiche di studio e i trapianti alternativi

LA SCELTA DEL DONATORE NEL TRAPIANTO EMOPOIETICO ALTERNATIVO

Raimondo Marceno

04 - 06 giugno 2015 Villaggio Cala la Luna Favignana (TP)

..... da oltre 50 anni

la storia dei trapianti e quella delle donazioni

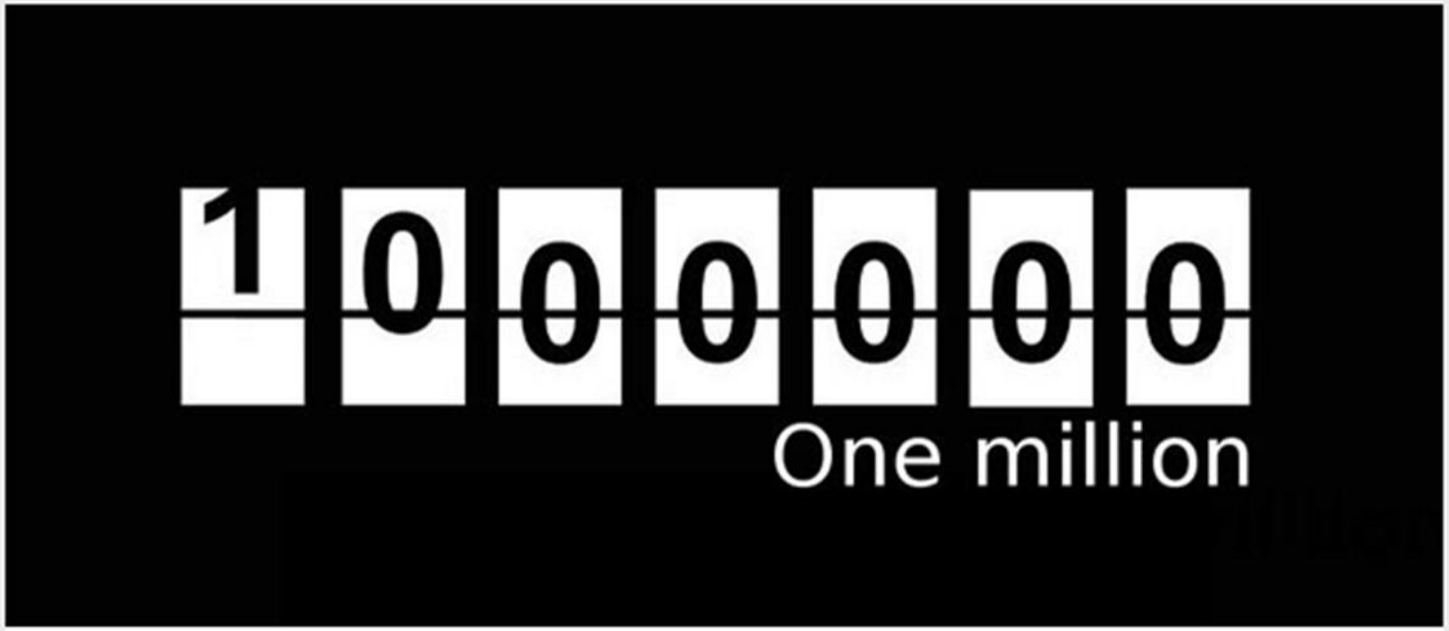
corrono insieme...

Leggi la versione online

9 aprile 2015 | numero 46

Trapianti in rete

Un progetto del Centro Nazionale Trapianti



Un milione di trapianti emopoietici nel mondo, ma c'è ancora molto da fare

2015, un milione di trapianti emopoietici e di donazioni : un bel traguardo !

Bone Marrow Donors Worldwide is celebrating a momentous milestone

2015

Bone Marrow Donors Worldwide is celebrating a momentous milestone: 25 million people are currently listed as potential marrow donors on worldwide donor registries: This record number of registry members gives greater hope to blood cancer patients, caregivers and healthcare professionals around the world

Quest'anno si celebra un altro traguardo storico : 25 milioni di donatori di midollo osseo !

La storia dei trapianti emopoietici è iniziata oltre 50 anni fa, ma negli ultimi quindici anni è rapidamente cambiato lo scenario complessivo, con un miglioramento senza precedenti dei risultati e delle possibili applicazioni cliniche.

Sono cambiati i trapianti allogenici, e sono parimenti cambiati i parametri di scelta dei donatori e delle fonti di Cellule Staminali Emopoietiche (CSE)

datata
2001

Principali variabili non-HLA influenzanti il trapianto allogenico

(nel tempo variamente valutate ed integrate)

Paziente

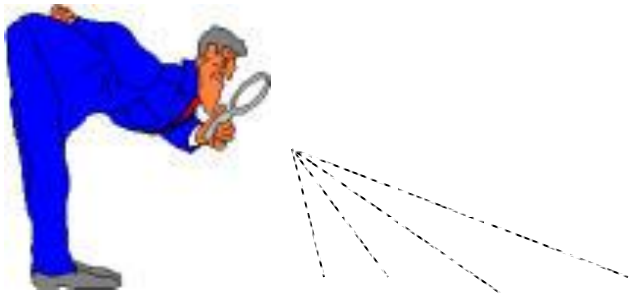
- età, sesso, peso, patologia
- patologie associate
- intervallo dalla diagnosi
- storia chemioterapica
- infezioni
- fonte e numero di cellule staminali
- numero e tipo di cellule immunocompetenti
- terapia immunosoppressiva
- gruppo sanguigno

Donatore

- età, sesso
- peso
- modalità di donazione
- CMV (ed altri virus)
- gruppo sanguigno
- eventuali patologie (nei correlati)

Generale Consensus agli inizi di questo secolo

……. trapianti emopoietici e la barriera HLA:
quello che si pensava 25 anni fa, è ancor vero ?



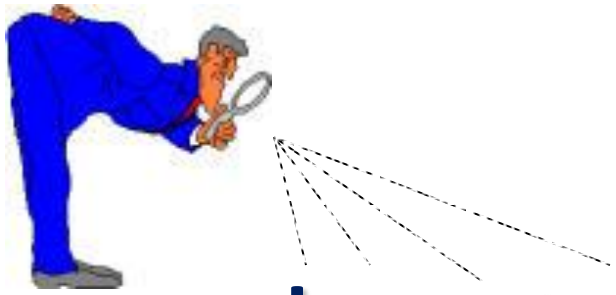
…….ma è certamente nel Sistema HLA

che va ricercata la variabile

che maggiormente influenza

la riuscita del trapianto allogenico

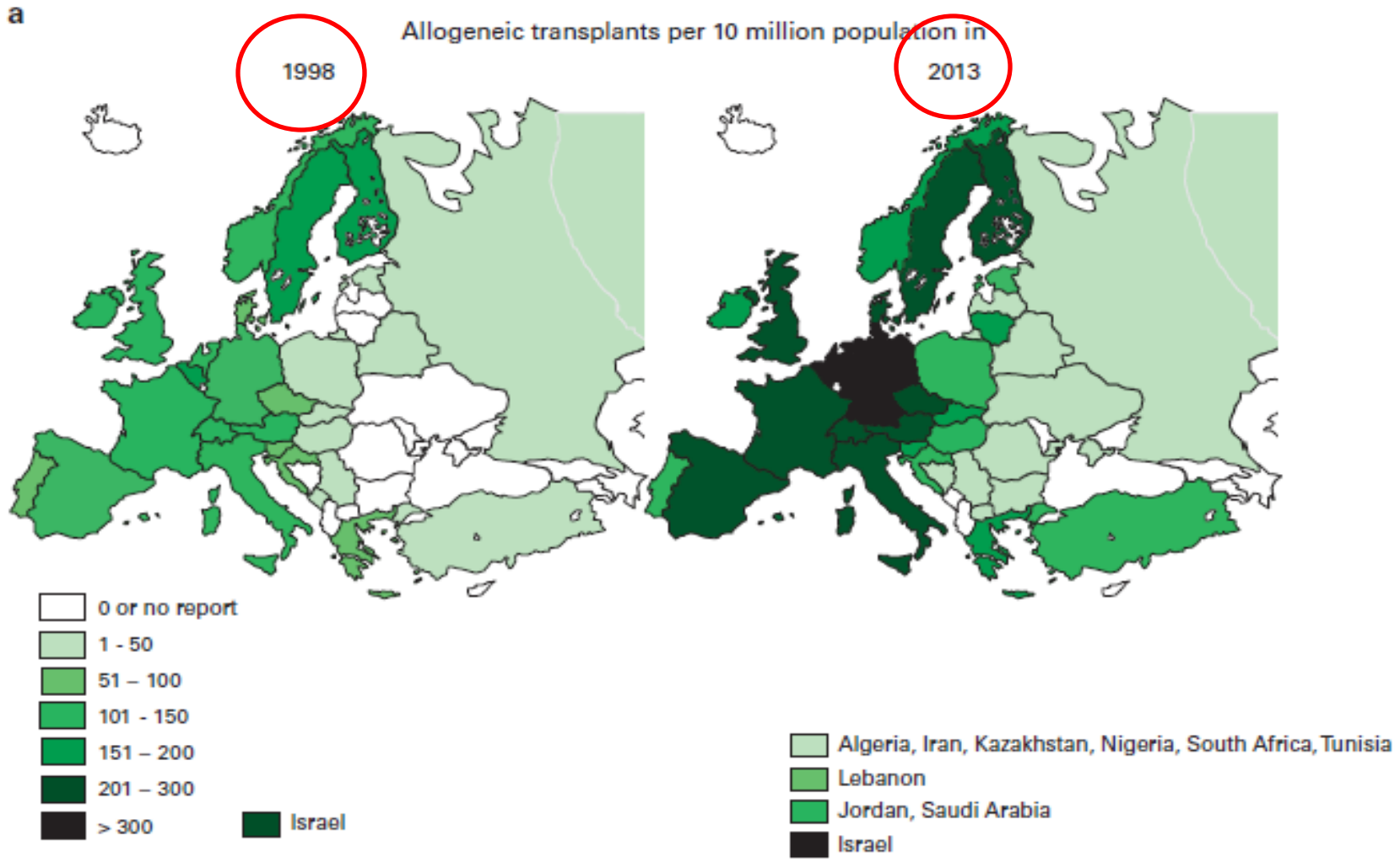
Anasetti C , N Engl J Med 1989



……. questo paradigma, per lungo tempo accettato, non è più considerato una barriera preminente, ma viene piuttosto valutato insieme a tutte le altre variabili cliniche

Wang M et al, Int J Hematol 2015

Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants



Passweg JR, BMT 2015

Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants

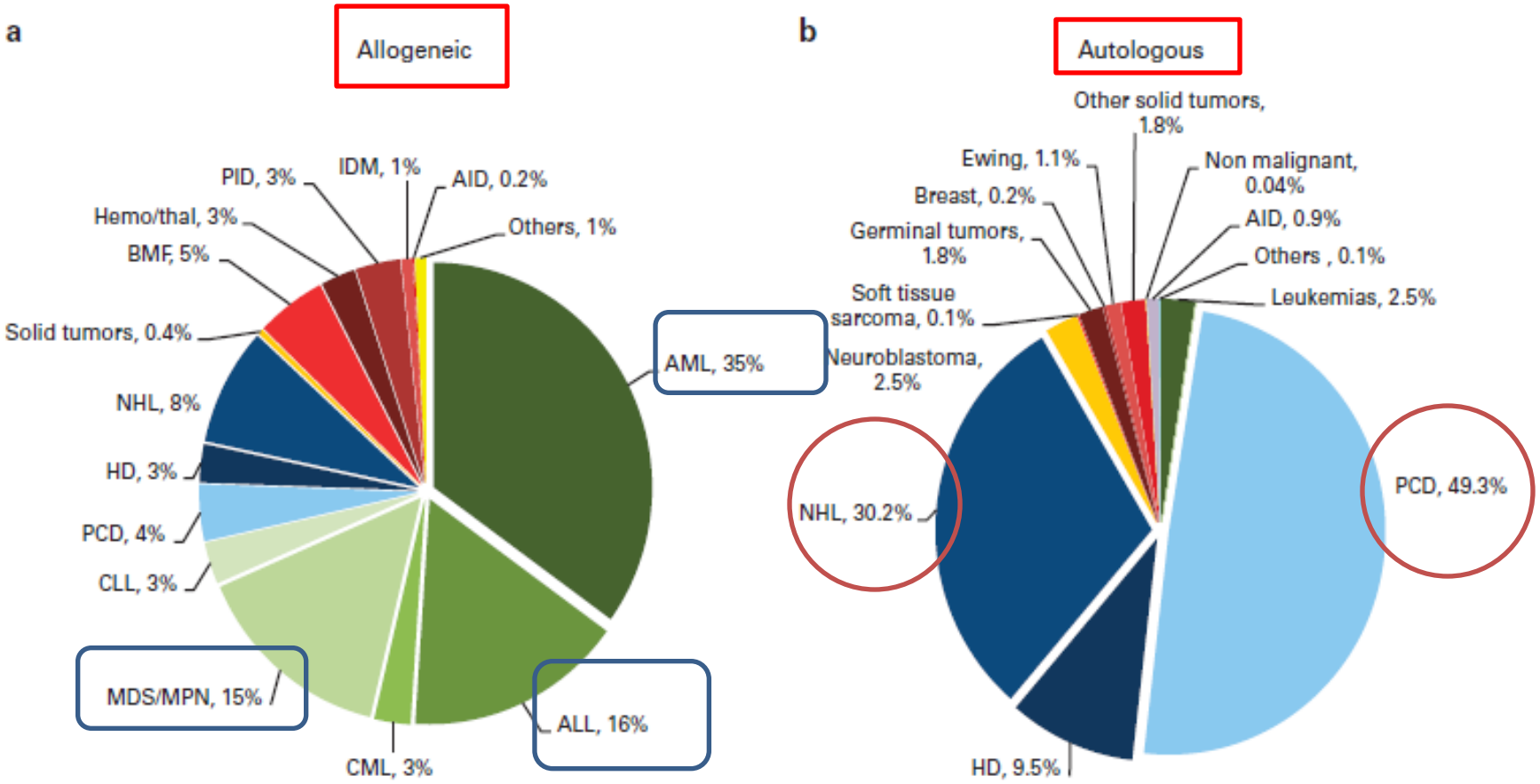
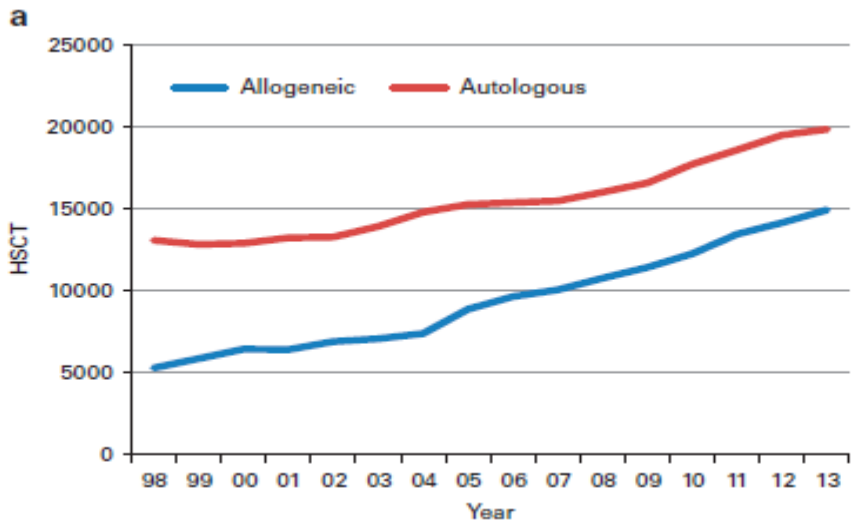


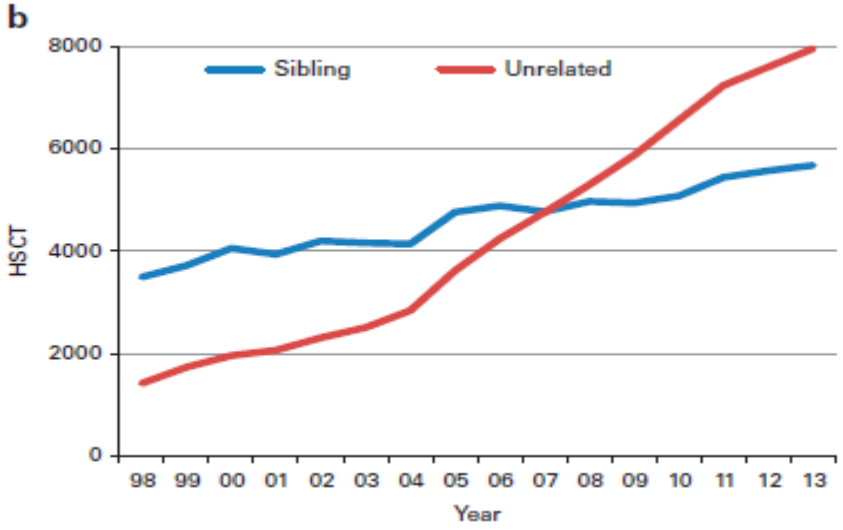
Figure 1. Relative proportions of indications for an HSCT in Europe in 2013. (**a**) Proportions of disease indications for an allogeneic HSCT in Europe in 2013. (**b**) Proportions of disease indications for an autologous HSCT in Europe in 2013.

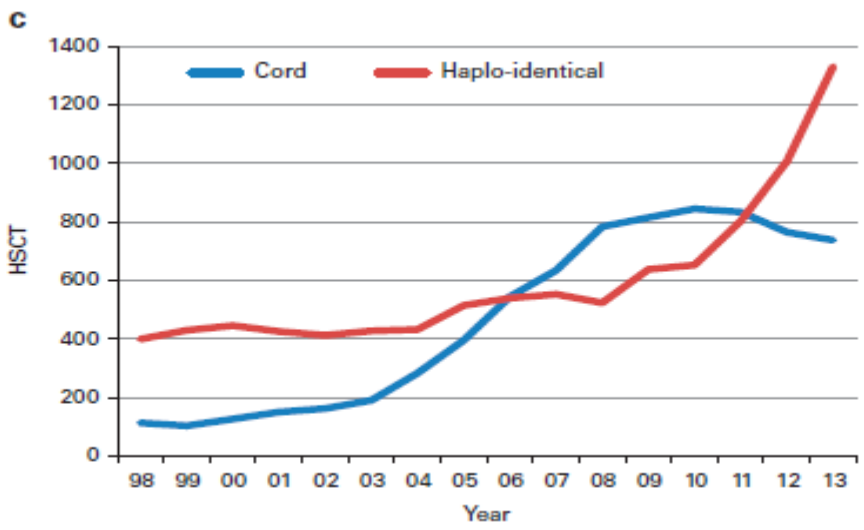
Passweg JR, BMT 2015

Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants

Passweg JR, BMT 2015







Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants

Cambiano le fonti, ma cambiano poco le indicazioni (ad es. HD)

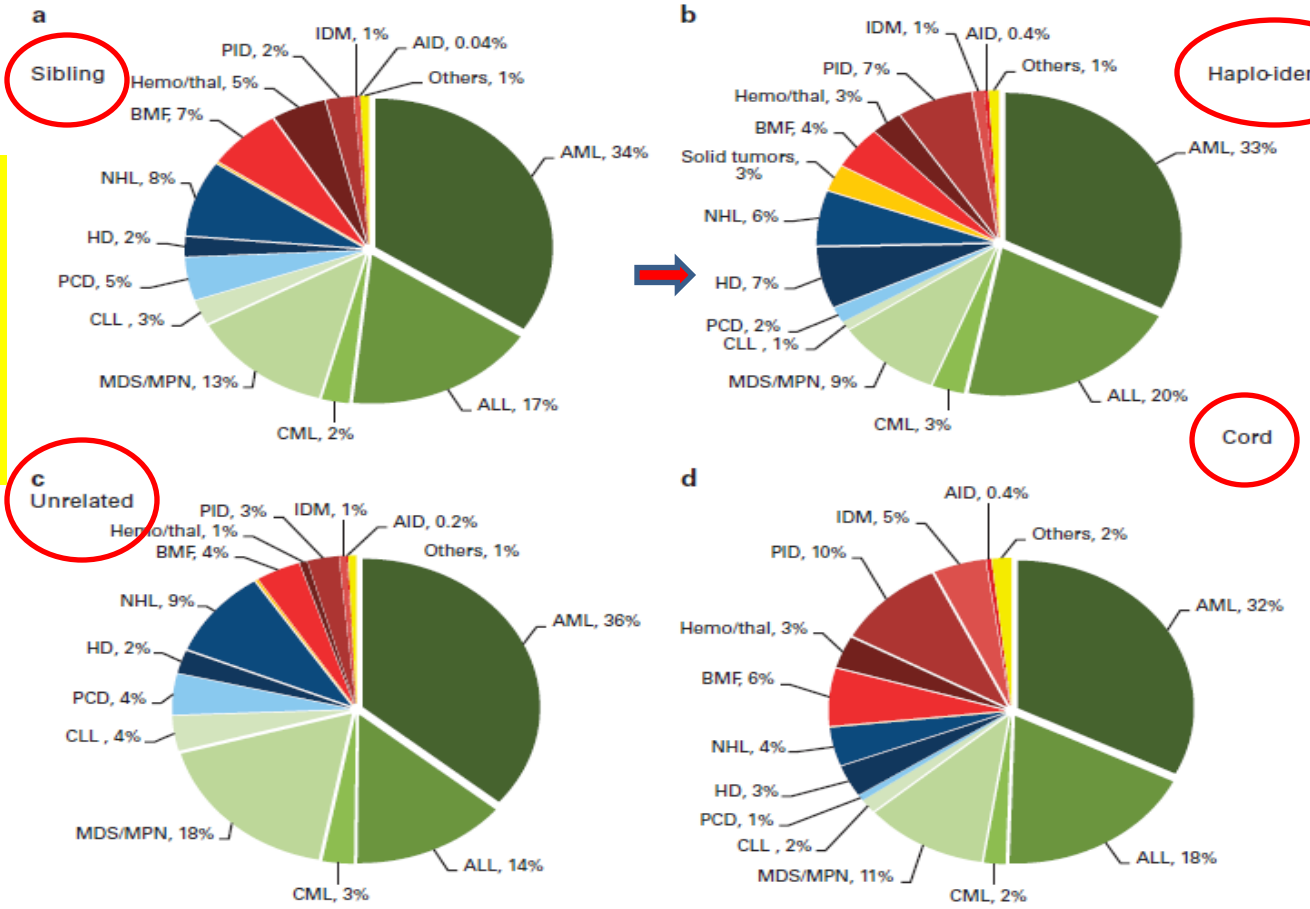
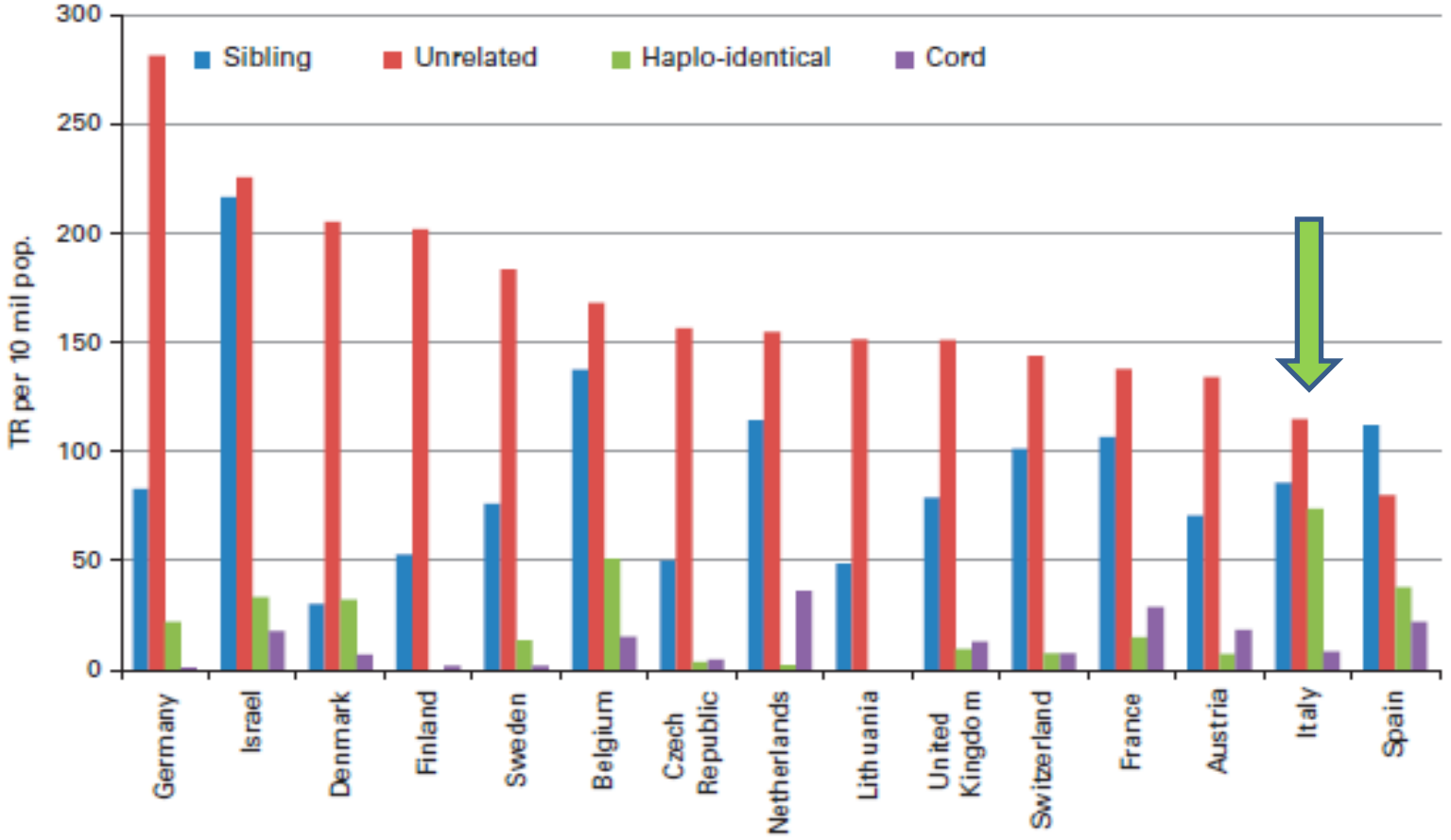


Figure 4. Disease indications by donor type in 2013. (**a**) Proportions of disease indications in 2013 for sibling donor HSCT. (**b**) Proportions of disease indications in 2013 for haplo-identical donor HSCT. (**c**) Proportions of disease indications in 2013 for unrelated donor HSCT. (**d**) Proportions of disease indications in 2013 for cord blood HSCT.

Passweg JR, BMT 2015

Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants



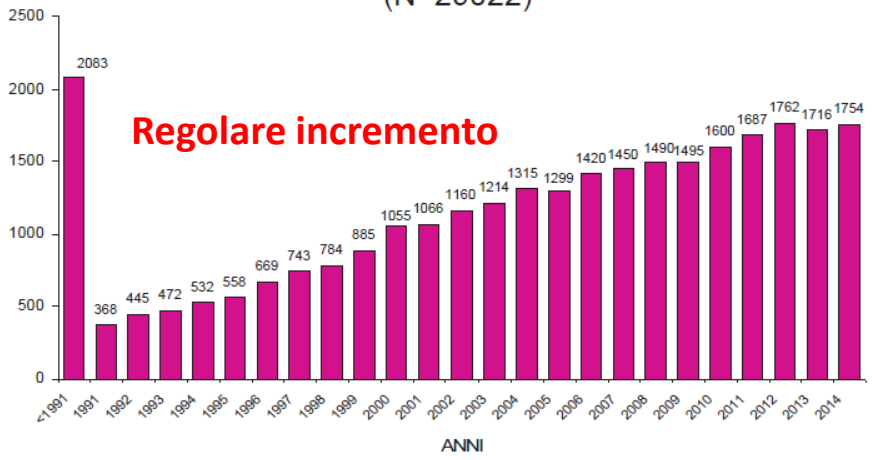
TR Allo	387	494	275	257	275	372	215	308	200	253	260	288	230	283	252

Spicca, in Italia, il numero di trapianti da donatore aploidentico

Passweg JR, BMT 2015

GITMO Trapianto Allogenico

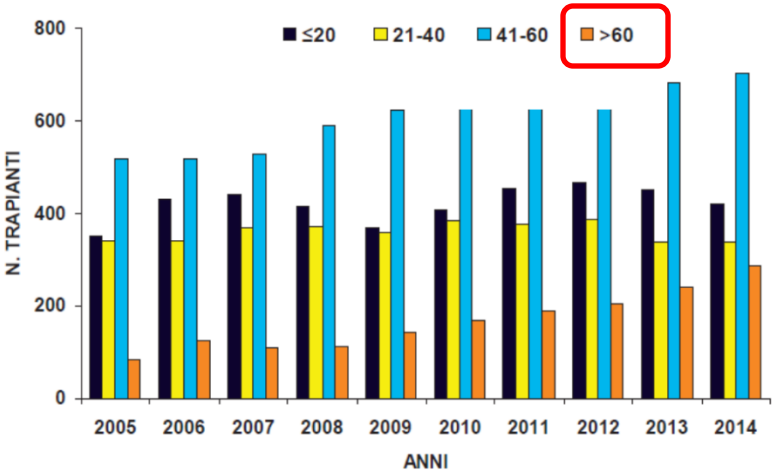
Allotrapianti registrati
(N=29022)



GITMO

GITMO Trapianto Allogenico

Età al trapianto



GITMO

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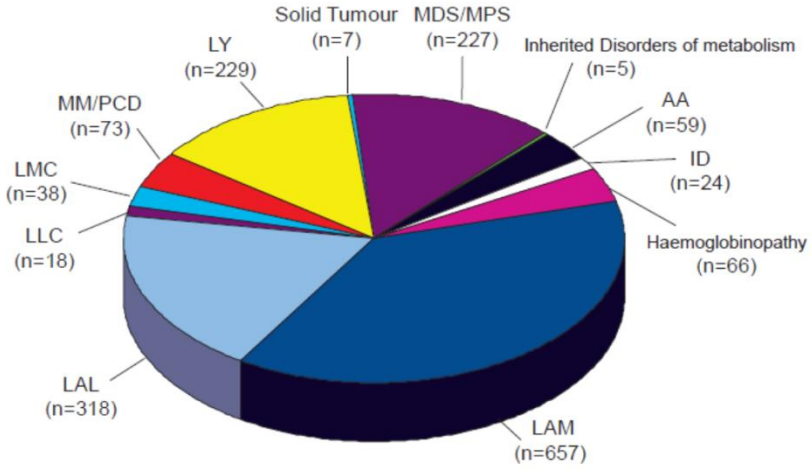
Numero Trapianti per principali Patologie
Attività 2014



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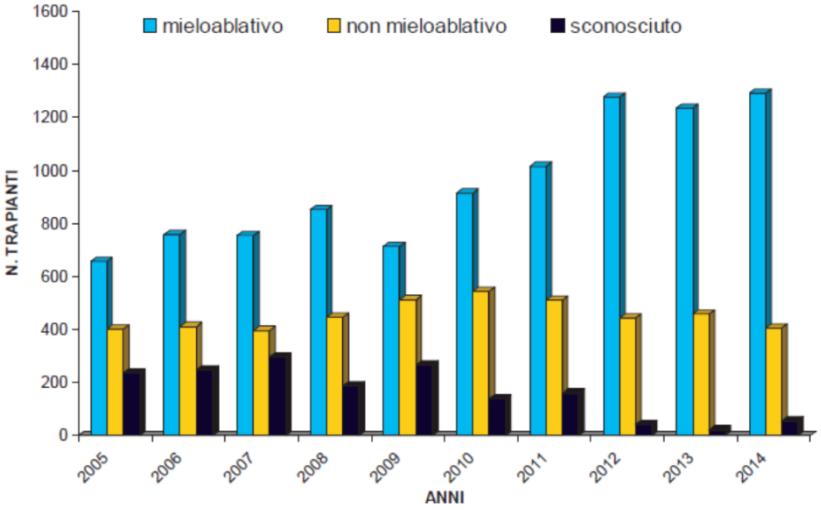
GITMO Trapianto Allogenico

Condizionamento nel trapianto Allogenico



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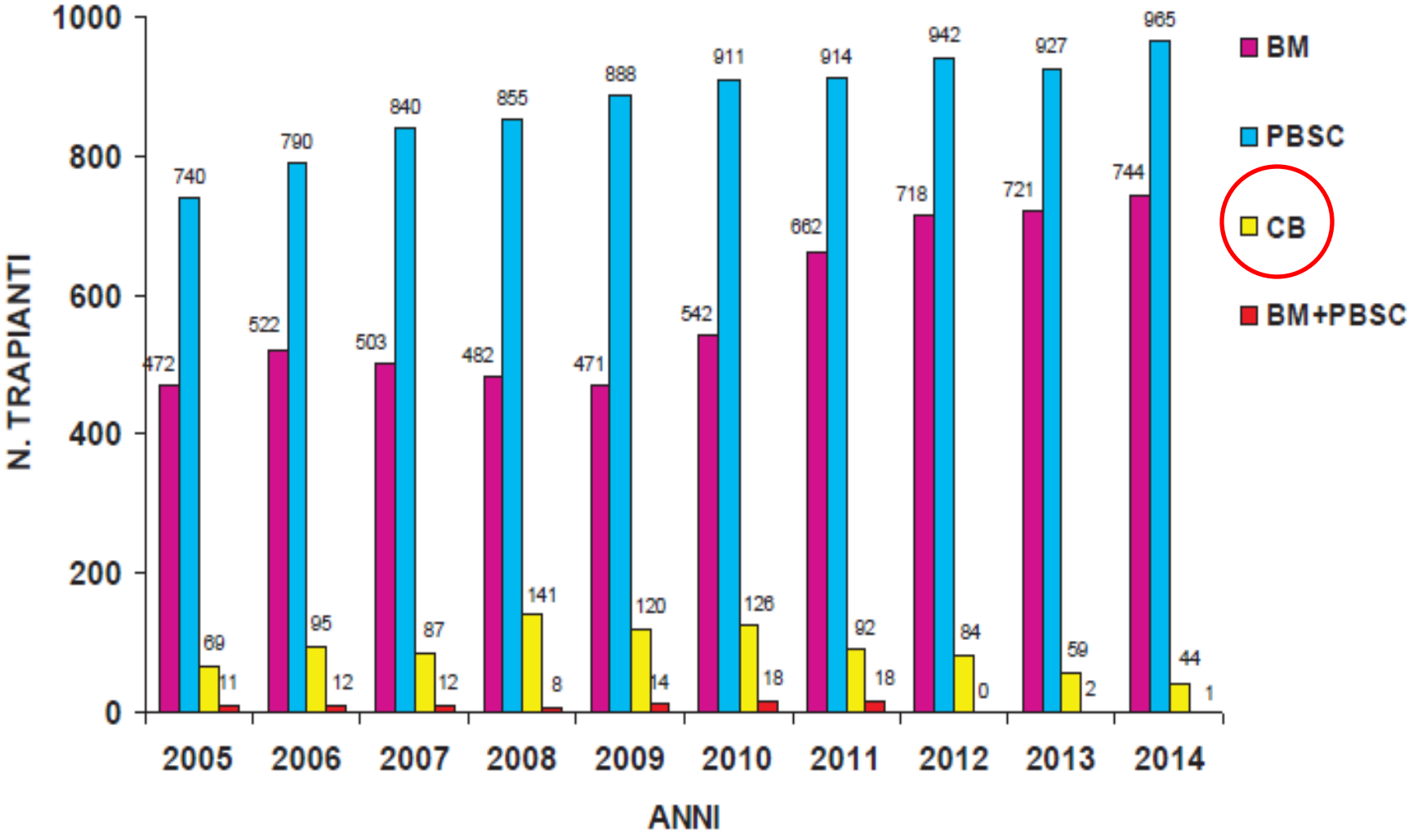
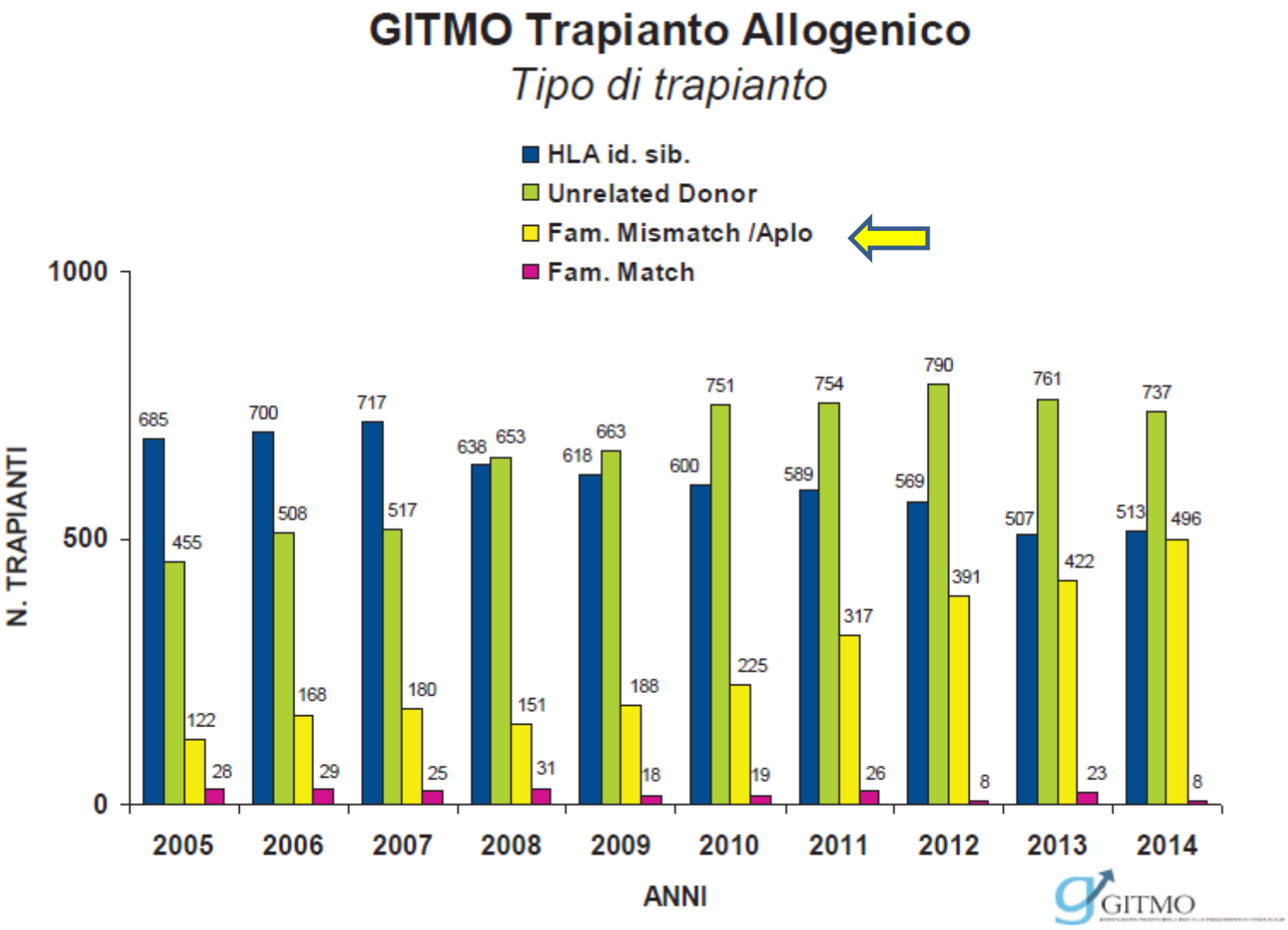
GITMO Trapianto Allogenico

Sorgente di CSE



Anche in Italia si registra un minor uso di Unità di Cord Blood

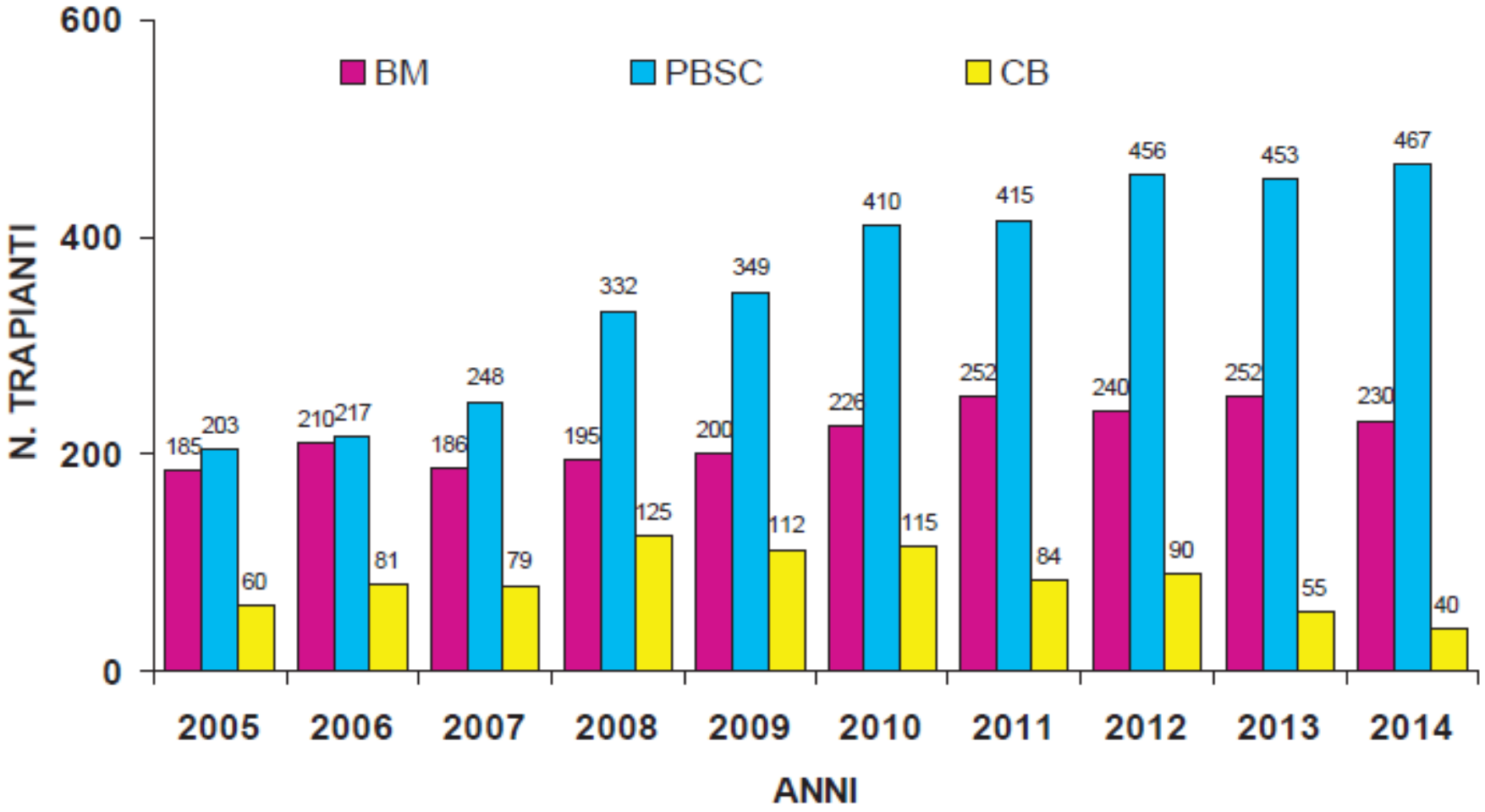
GITMO



Dal 2013 si riducono i trapianti da MUD, parallelamente all'aumento degli aploidentici (costante dal 2008)

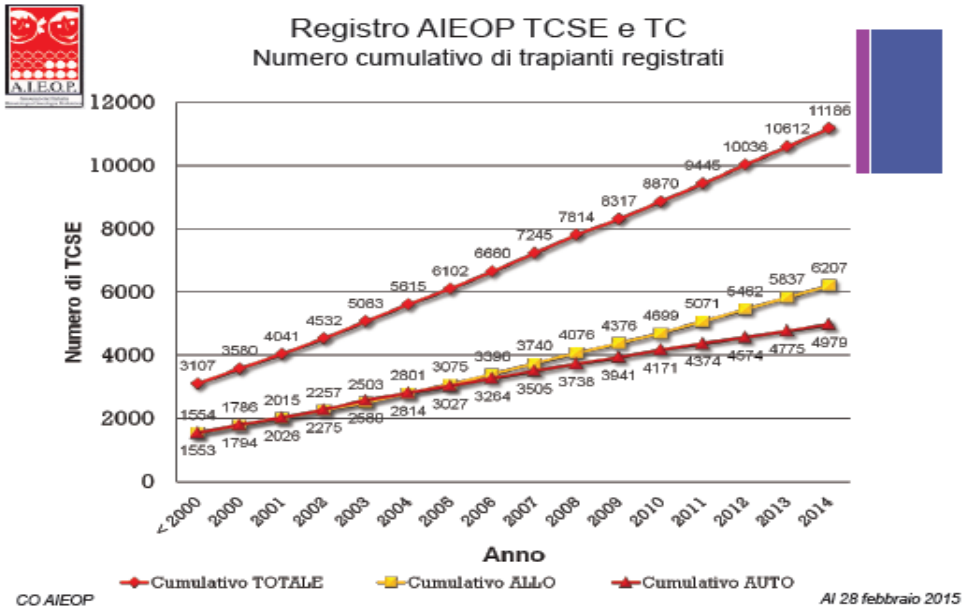
GITMO Trapianto Allogenico

Donatore non familiare e Sorgente CSE

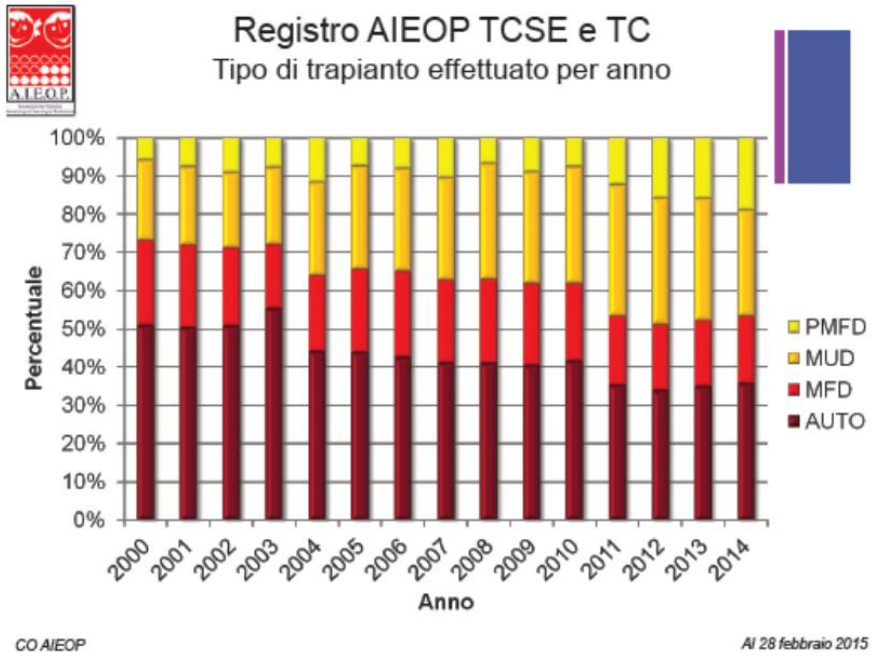


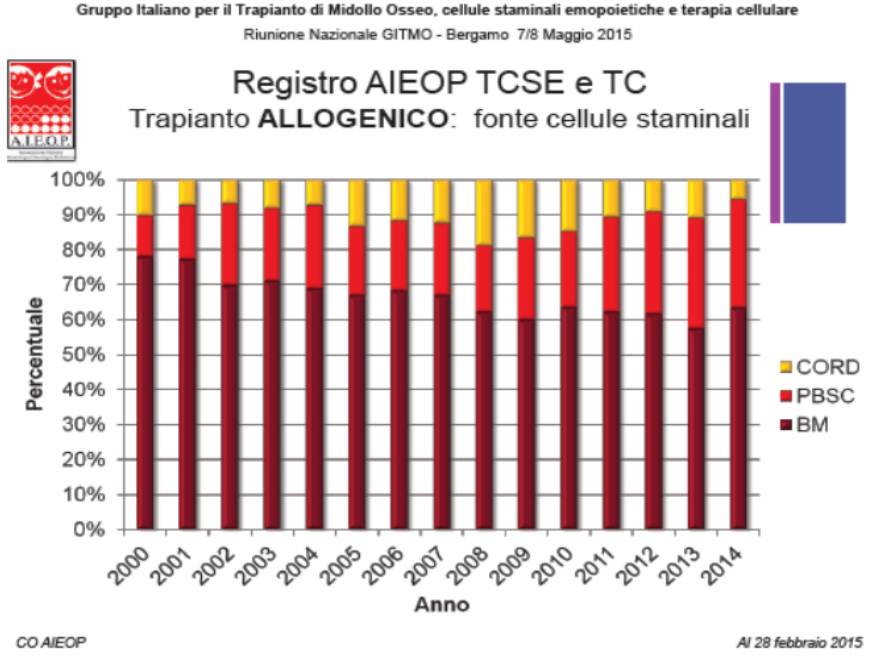
Le PBSC rimangono la fonte preminente

GITMO

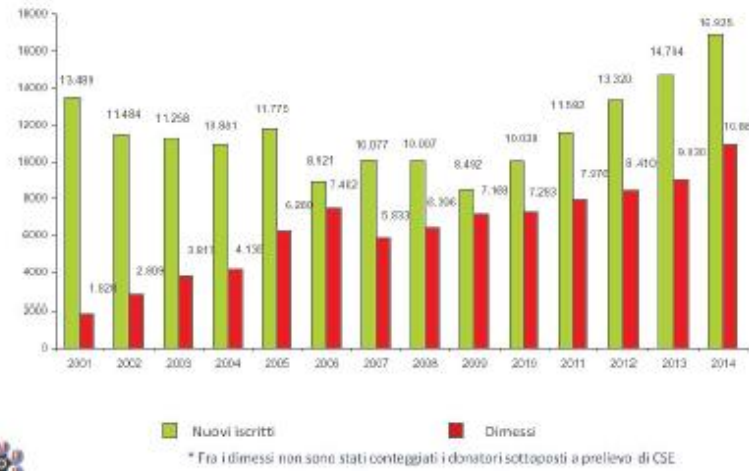


Anche in campo pediatrico si incrementano i trapianti allogenici e, soprattutto, quelli alternativi; continua a ridursi l'uso del cord blood quale fonte di CSE





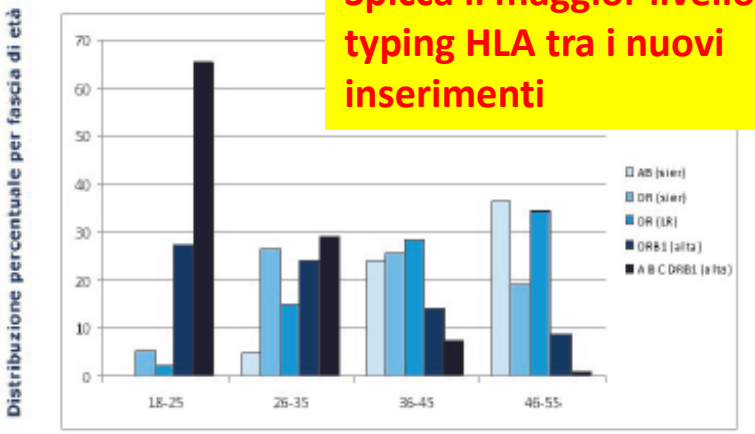
Donatori inseriti (con HLA) e dimessi 2014



* Fra i dimessi non sono stati conteggiati i donatori sottoposti a prelievo di CSE

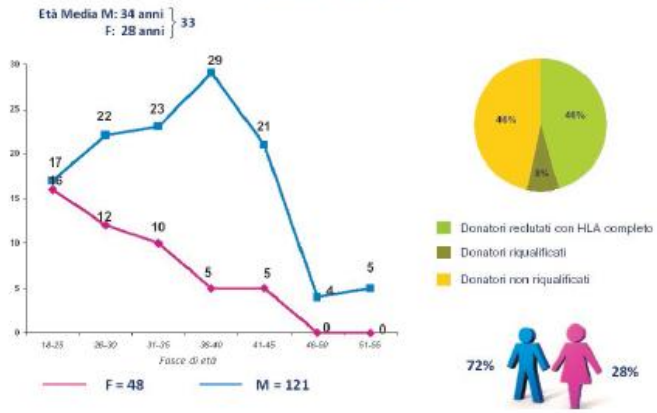
Potenziali donatori e livello di indagine genetica per età

Spicca il maggior livello di typing HLA tra i nuovi inserimenti



Età dei potenziali donatori IBMDR

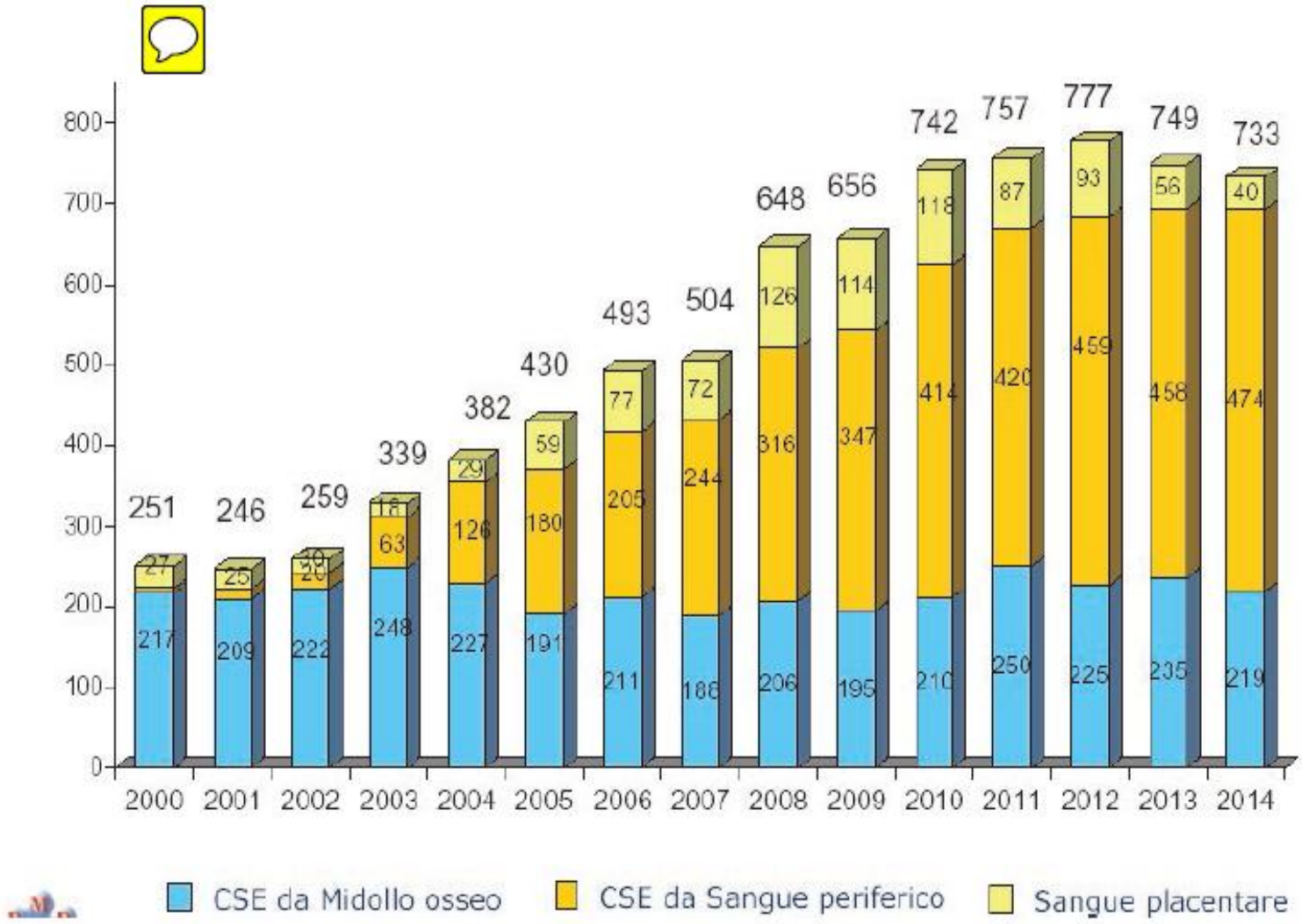
Caratteristiche dei soggetti IBMDR che hanno donato nel 2014



I donatori IBMDR giunti a donazione nel corso del 2014 sono prevalentemente maschi (72% vs 66% nel 2013) con un'età media pari a 33 anni (29 nel precedente anno).

MUD tipo: maschio, 30 anni circa; typing HLA-A,-B,-C,-DRB1 hr
tempo max di ricerca 3 mesi

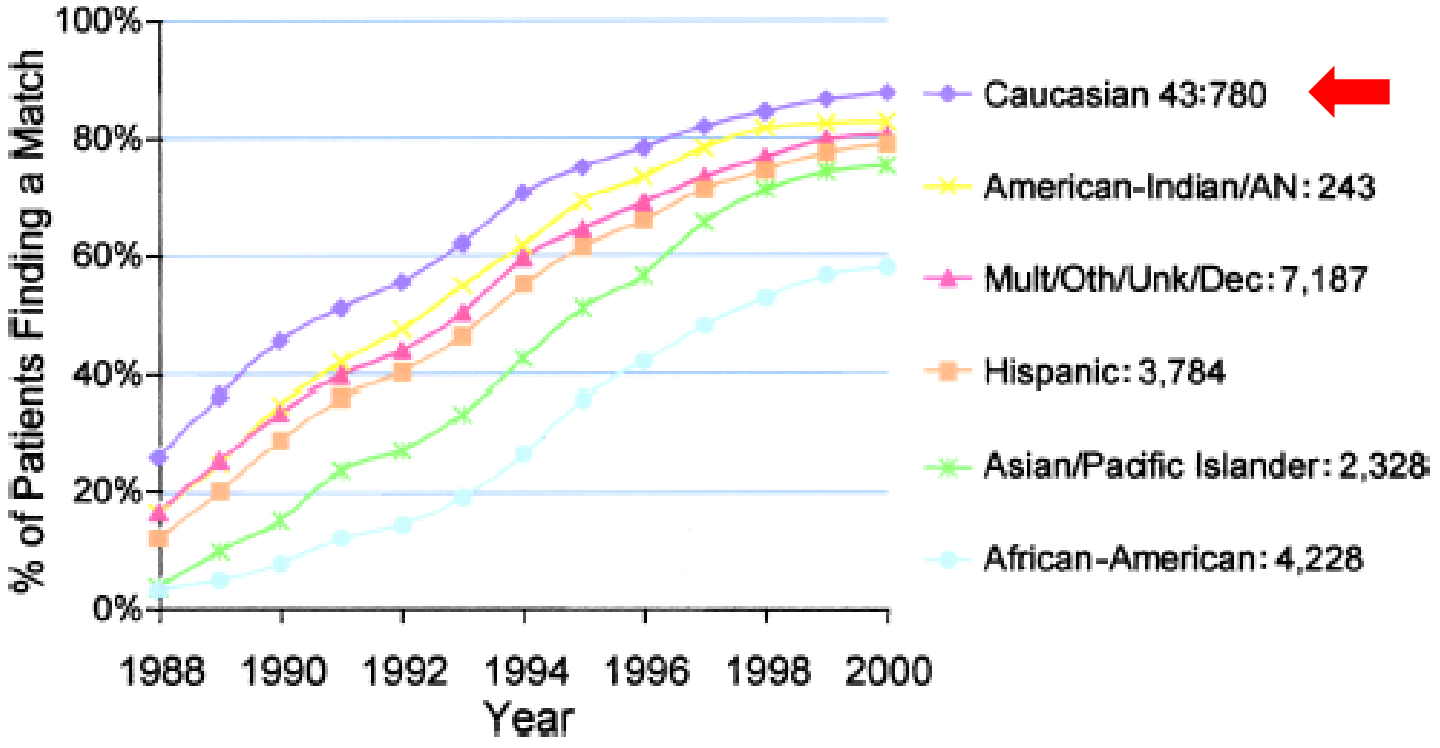
Trapianti di CSE da non consanguineo in Italia



Anche il numero totale di trapianti eseguiti in Italia con l'utilizzo di CSE è in diminuzione, ciò principalmente dovuto al minor utilizzo di unità di sangue cordonale e forse dall'avvio di numerosi programmi di trapianto da donatore familiare aploidentico.

Probability of finding a matched donor and impact of NMDP registry growth on the matching likelihood for each major racial/ethnic group

CK Hurley et al, Tissue Antigens 2003



Dal 2003 in poi , i Registri Donatori hanno offerto migliori possibilità a tutti i pazienti ?

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

Gragert L et al, NEJM, 2014

In assoluto sono aumentati gli inserimenti MUD (>25 milioni!),
ma si è accentuato l'iniziale sbilanciamento che favorisce l'etnia caucasica

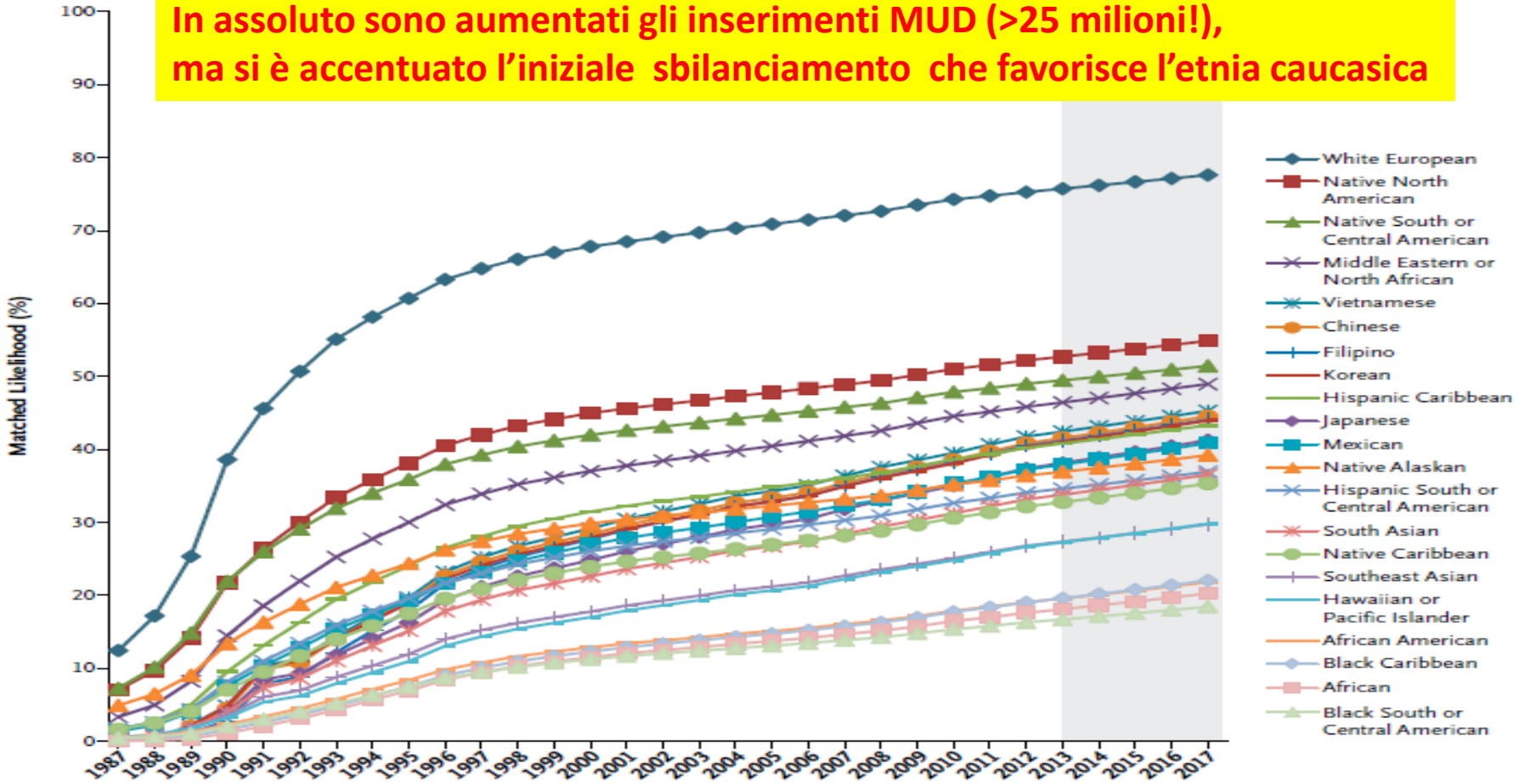


Figure 2. Likelihood of Finding an 8/8 HLA Match by Year End, Based on Current Donor Availability and with Recruitment Trends Extended to 2017.

Projected match likelihoods for 2013 through 2017 (shaded area) were calculated on the basis of anticipated recruitment growth of 9% cumulatively each year.

Nonostante 25 milioni di MUD, non sempre è possibile reperire un donatore entro 3 mesi (il fattore tempo è la prima variabile di rilievo nella ricerca del donatore)

Ciò, insieme all'insufficienza di donatori familiari HLA identici, ha indotto nel tempo verso i trapianti alternativi

Lo studio immunogenetico rappresenta ancora la base da cui partire per garantire il reperimento di un donatore alternativo

Il progresso delle conoscenze immunogenetiche, ha consentito di meglio aggirare la barriera tessutale e disegnare nuovi protocolli di trapianto alternativo.

L'HLA è pur sempre la base da cui partire !

Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome

Flomenberg N et al , Blood 2004

Table 3. Impact of HLA mismatching at specific loci on transplant-related outcomes: associations between HLA mismatch (high- or low-resolution) at specific loci and outcome after unrelated donor BMT

Mismatched		Engraftment			Grade III–IV acute GVHD			Chronic GVHD			Mortality		
locus	No.	OR	95% CI	P	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
HLA-A	374	0.88	(0.39, 1.22)	.20	*1.41*	*(1.16, 1.71)*	*.0005*	*1.35*	*(1.09, 1.66)*	*.006*	*1.33*	*(1.15, 1.54)*	*.0002*
HLA-B	477	1.07	(0.61, 1.88)	.82	1.24	(1.03, 1.50)	.03	1.04	(0.84, 1.30)	.71	*1.22*	*(1.06, 1.41)*	*.007*
HLA-C	749	0.54	(0.33, 0.89)	.02	1.19	(1.00, 1.41)	.05	1.01	(0.84, 1.21)	.92	*1.21*	*(1.06, 1.38)*	*.005*
HLA-DRB1	311	1.07	(0.57, 2.02)	.83	1.28	(1.01, 1.56)	.04	1.27	(0.98, 1.64)	.07	*1.23*	*(1.04, 1.45)*	*.01*
HLA-DQ	415	0.67	(0.39, 1.14)	.14	1.03	(0.85, 1.26)	.78	0.93	(0.74, 1.16)	.50	0.98	(0.84, 1.14)	.80
HLA-DP	1648	0.69	(0.38, 1.25)	.22	1.19	(0.98, 1.43)	.08	1.17	(0.98, 1.39)	.08	1.07	(0.88, 1.27)	.48

Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome

Flomenberg N et al , Blood 2004

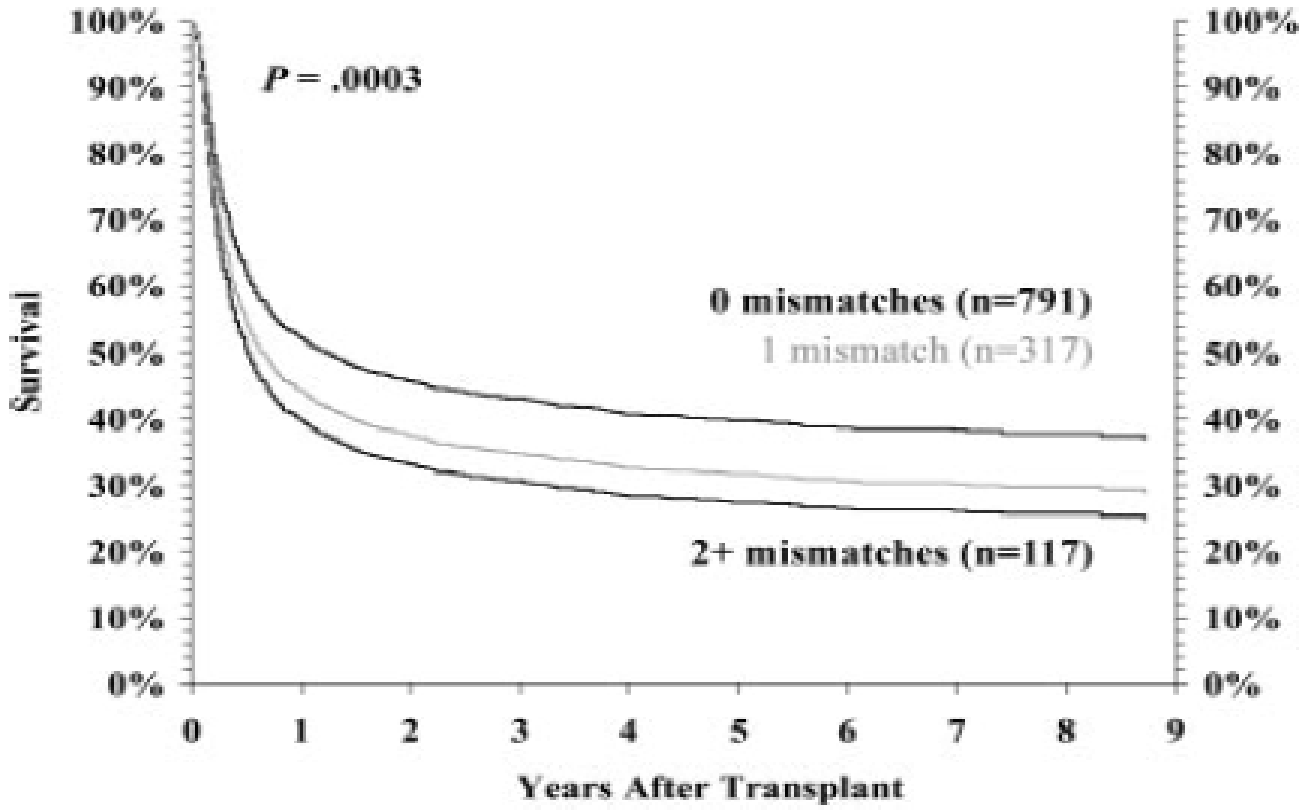


Figure 2. Risk-adjusted survival among HLA-A, -B serologic, and -DRB1 allele-matched pairs by number of mismatched class I loci. Survival after

Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome

Flomenberg N et al , Blood 2004

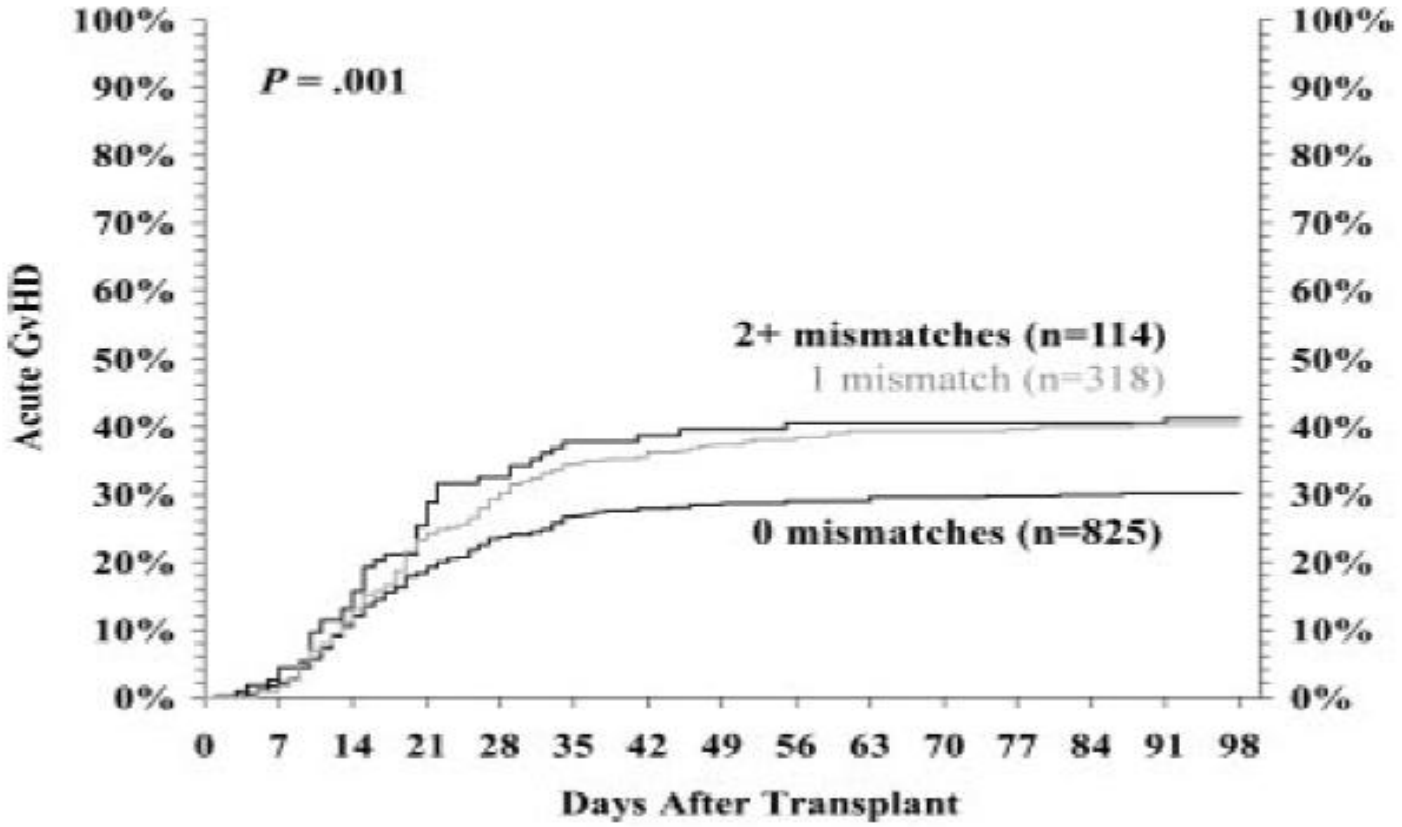
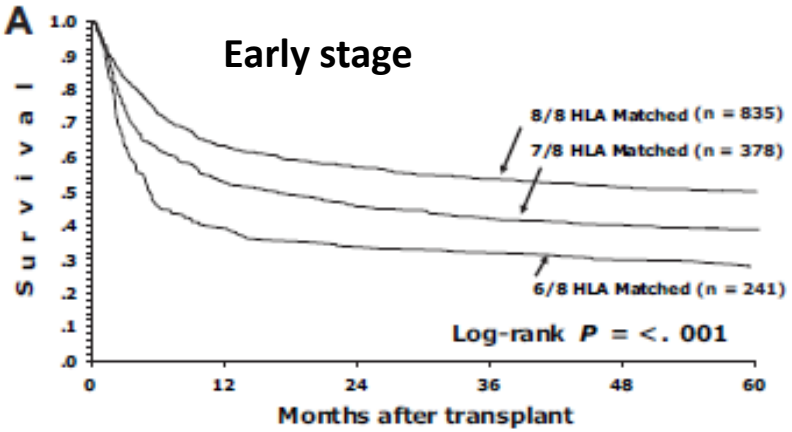
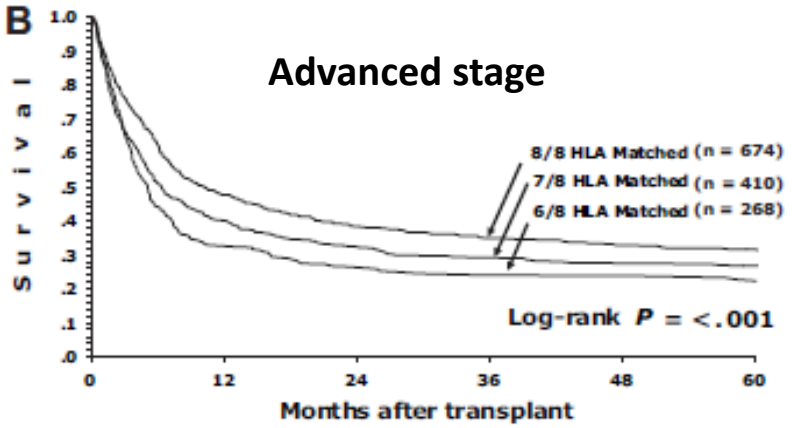


Figure 1. Grades III/IV acute GVHD among HLA-A, -B serologic, and -DRB1 allele-matched pairs by number of class I mismatched loci. The incidence of

High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation

S. J. Lee et al , Blood 2007





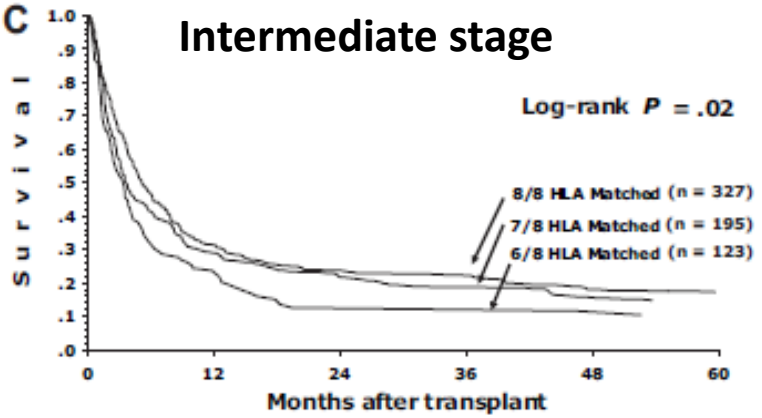


Figure 1. Survival of patients with early, intermediate, and advanced disease depending on degree of HLA matching (8/8, 7/8, and 6/8) for HLA-A, -B, -C, and -DRB1. (A) Early-stage disease for 8/8, 7/8, and 6/8, respectively: 1-year survival 63%, 52%, and 39%; 5-year survival 50%, 39%, and 28%. (B) Intermediate-stage disease for 8/8, 7/8, and 6/8, respectively: 1-year survival 48%, 40%, and 32%; 5-year survival 32%, 27%, and 22%. (C) Advanced-stage disease for 8/8, 7/8, and 6/8, respectively: 1-year survival 31%, 29%, and 24%; 5-year survival 17%, 15%, and 10%.

Il livello di HLA-matching nei trapianti da MUD, correla significativamente con la sopravvivenza globale, specialmente negli stadi precoci di malattia (casistica: AML, ALL, CML, MDS)

Multiple mismatches at the low expression HLA loci DP, DQ, and DRB3/4/5 associate with adverse outcomes in hematopoietic stem cell transplantation

Fernandez-Vina M A, Blood 2013

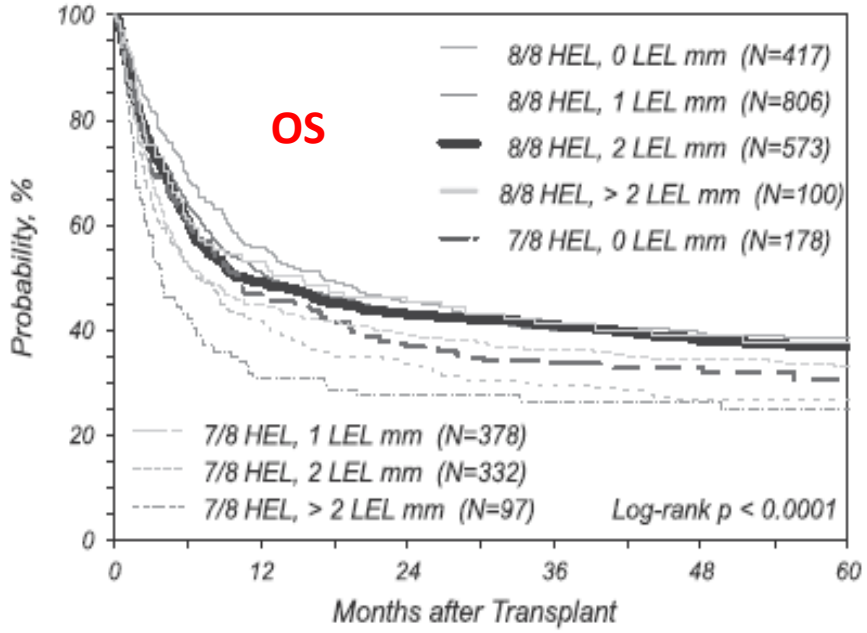


Figure 1. Kaplan Meier estimate of overall survival in patients presenting no mismatch (8/8) or one mismatch (7/8) in the GvH vector in the HEL (HLA-A, -B, -C, and -DRB1 loci) stratified according to the degree of mismatching at HLA-DRB3/4/5, DQ, and DP (LEL) loci.

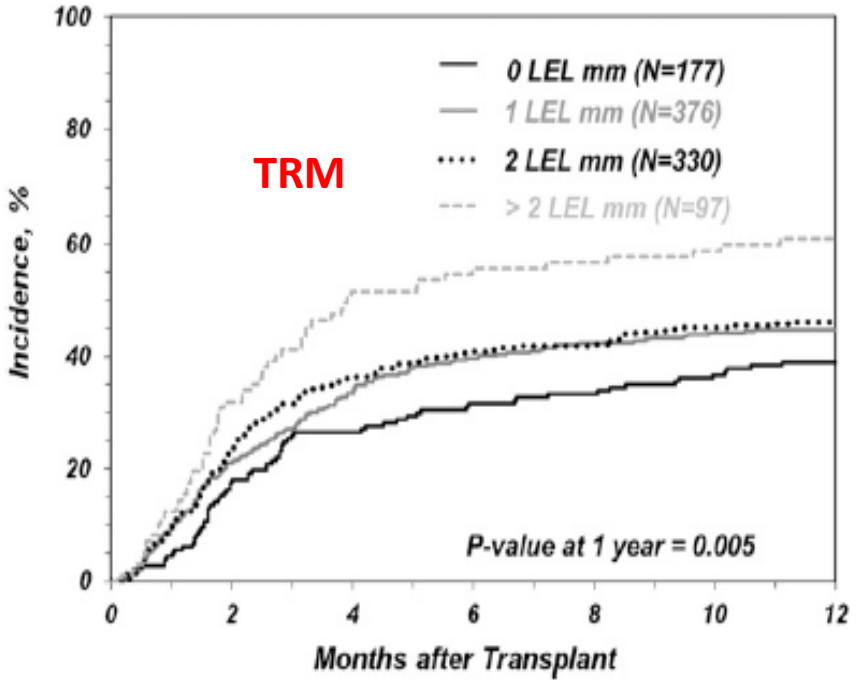
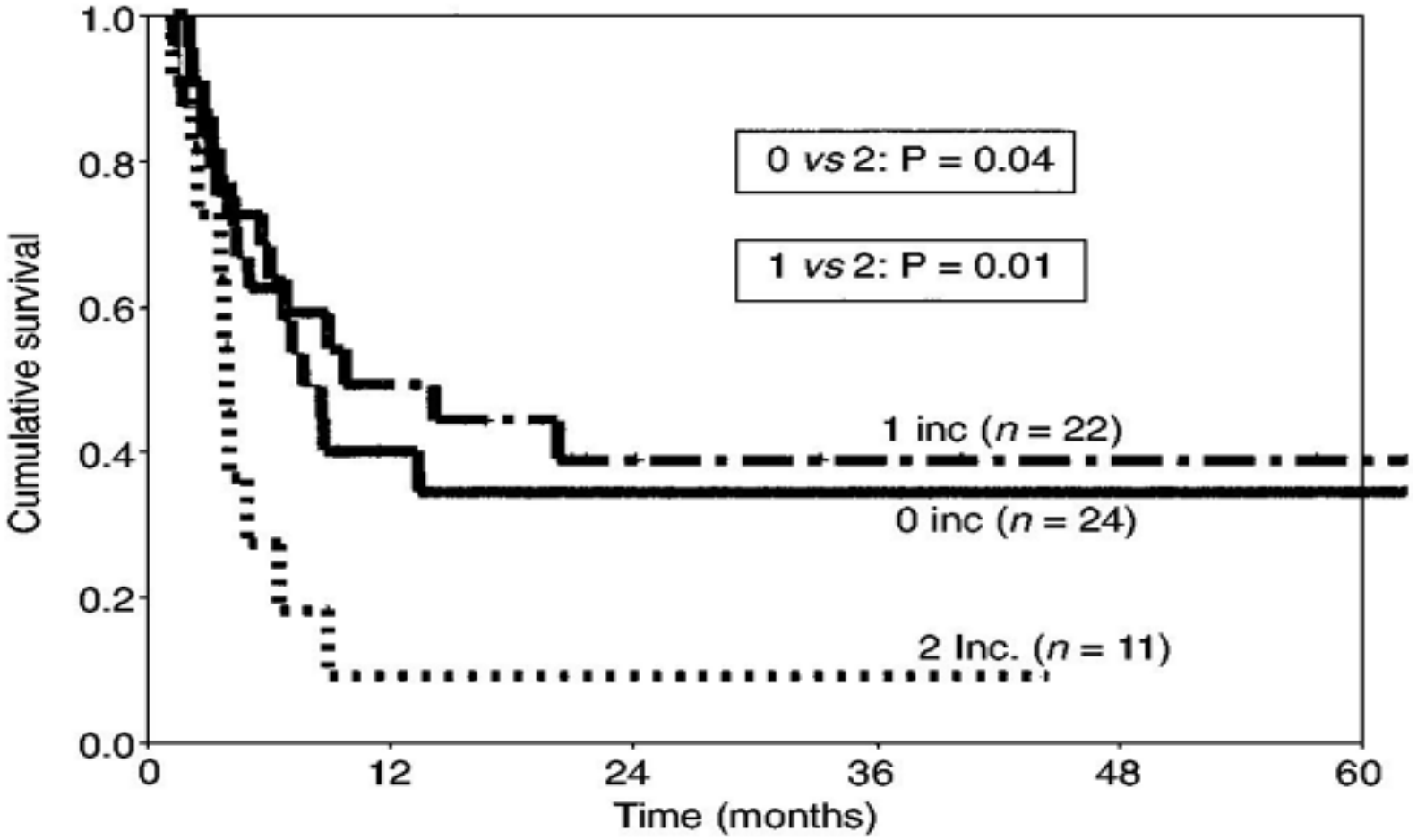


Figure 2. Incidence of TRM as a function of degree of mismatching at HLA-DRB3/4/5, DQ and DP (LEL) loci in transplants matched in 7/8 alleles of HLA HLA-A, -B, -C, and -DRB1 loci.

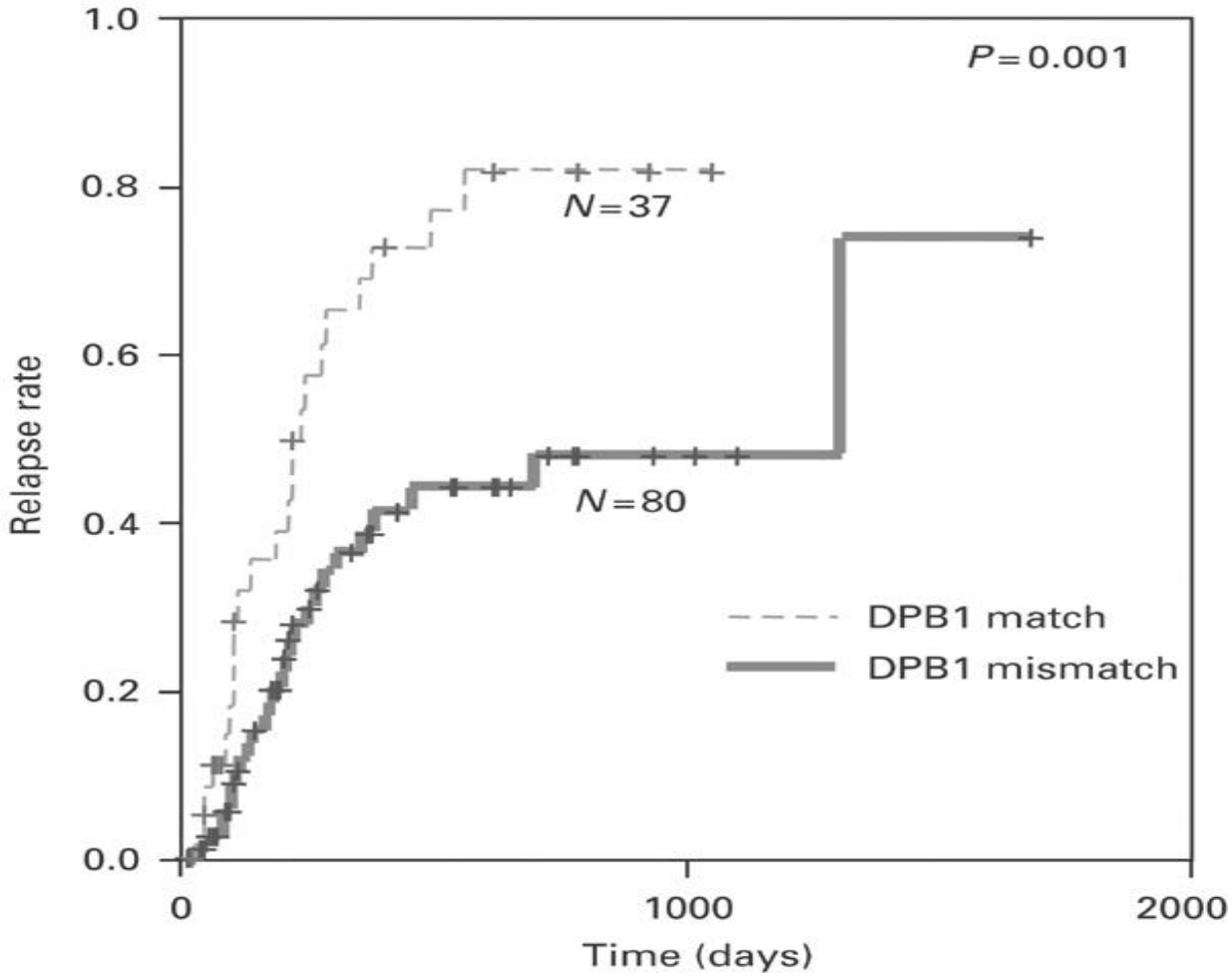
HEL: High Expression LOCI (HLA-A, -B, -C, -DRB1) Sono Loci ad alta espressione fenotipica e fortemente associati con l'andamento del trapianto, a conferma dello studio di Flomenberg

LEL: Low Expression LOCI (HLA-DRB3/4/5, -DQ, -DPB) Loci a bassa espressione fenotipica, diversamente associati con l'andamento del trapianto

Effect of DPB1 incompatibilities on survival in 57 MUD transplants identical for HLA-A, B, C, DRB, DQB1 alleles (Loiseau et al, BMT 2002)

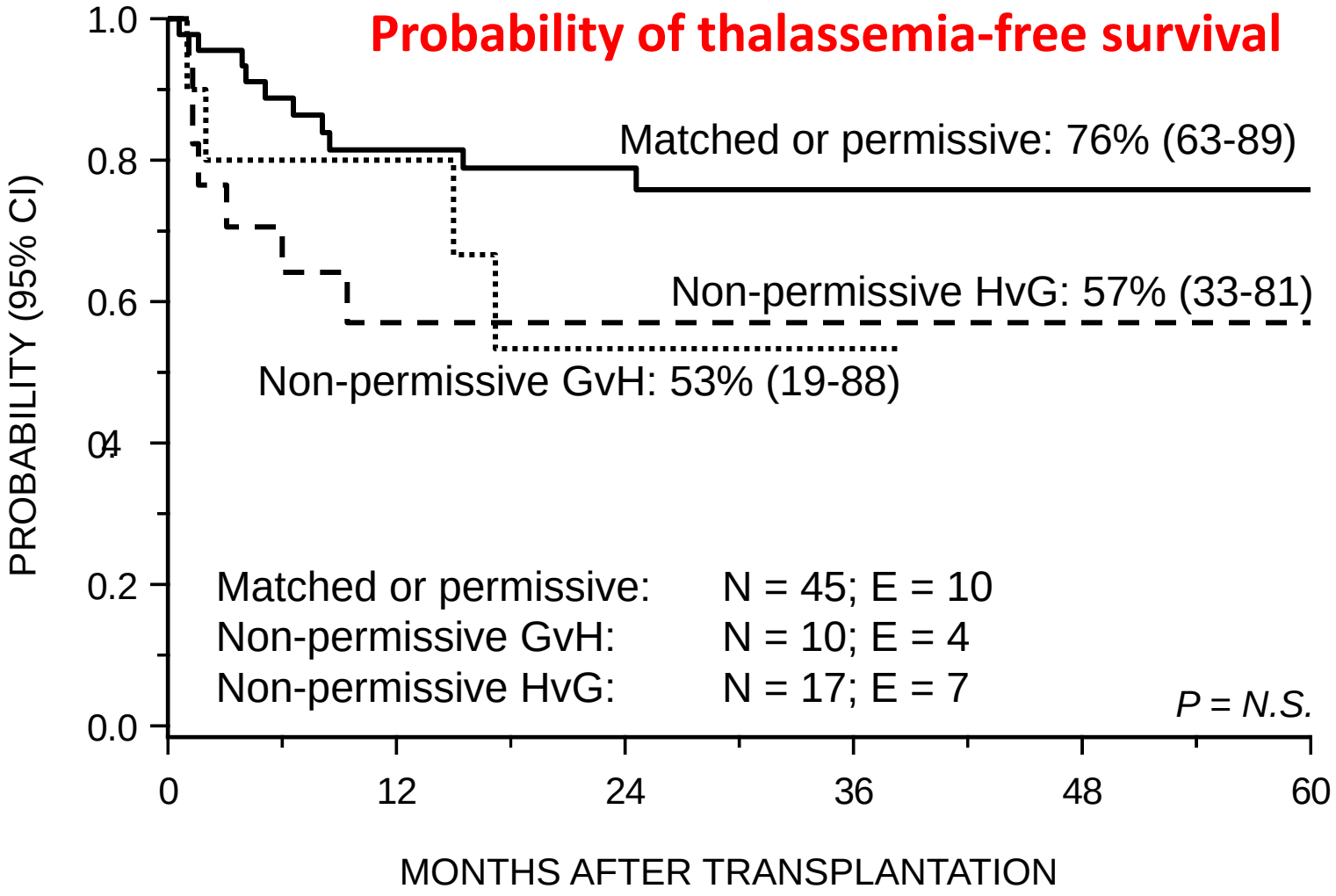


Disease relapse with or without DPB1 matching following 143 HSCT (BE Shaw et al MBT 2003)



Role of HLA-DPB1 mismatches on the clinical outcome in 72 unrelated HSCT for b-thalassemia

Fleishhauer et al. Blood 2006.

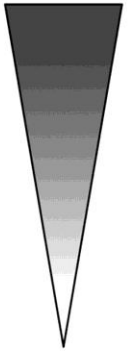


Previsione dell'alloreattività diretta mediata da linfociti T

Dati ottenuti in vitro di due cloni T-cellulari allo reattivi isolati da un ricevente di CSE in cui il rigetto del trapianto era dovuto al mismatch HLA-DPB1

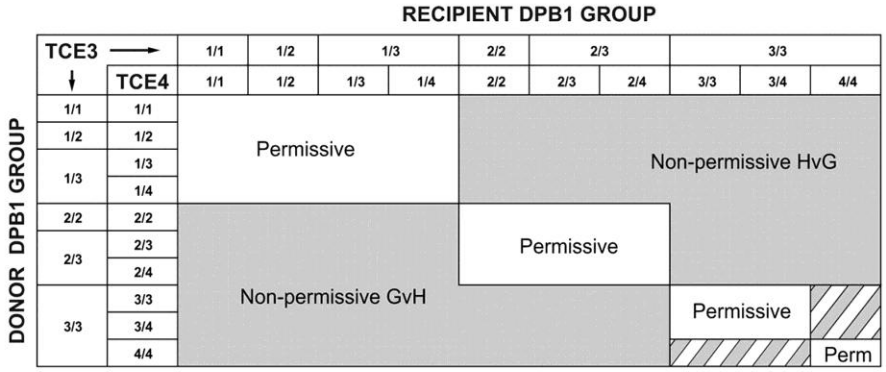
Cloni allo reattivi T cellulari riconoscono gli antigeni HLA-DPB1 in modo diretto

A

DPB1* alleles	TCE3 group	TCE4 group	Immunogenicity
0901 1001 1701	1	1	
0301 1401 4501	2	2	
0201 0202 0203	3	3	
Others		4	

Crocchiolo et al. Blood 2009

B



Permissive in TCE3 and TCE4 | Permissive in TCE3, but not in TCE4 | Non permissive in TCE3 and TCE4

Trapianti di CSE

Maggiore incidenza di GvHD, Rigetto Mortalità

Fleishauer et al. Lancet Oncology 2012

I nuovi concreti risultati :

Il miglioramento delle conoscenze sulla compatibilità tessutale,

e migliori programmi clinici di trapianto emopoietico,

hanno portato ad ottenere risultati comparabili

nel trapianto allogenico da familiare HLA identico rispetto a quelli alternativi:

Fam id = MUD = APLO

Matched unrelated donor allogeneic transplantation provides comparable long-term outcome to HLA-identical sibling transplantation in relapsed diffuse large B-cell lymphoma

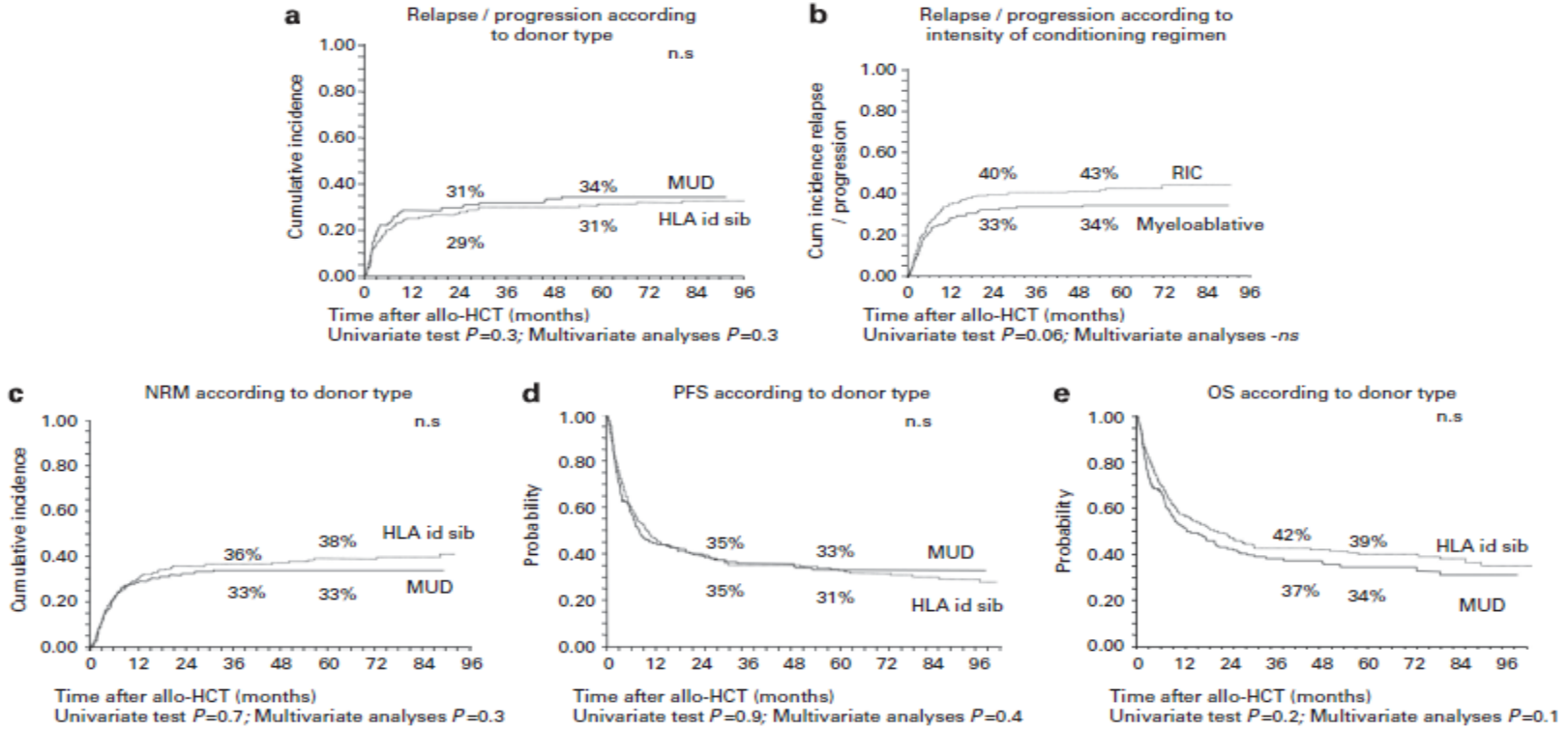


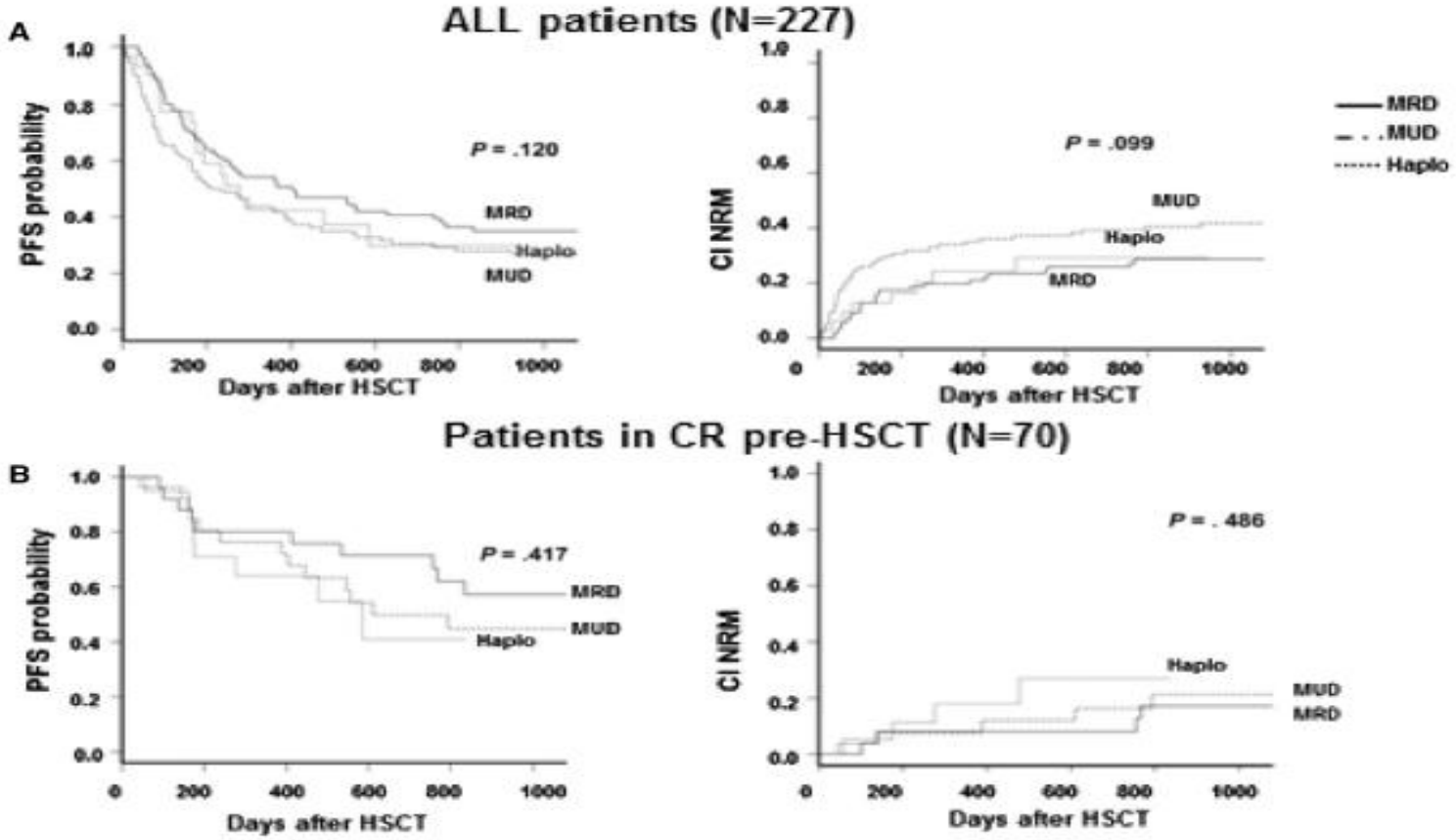
Figure 1. Transplant outcome according to donor type. (**a**) Relapse/progression according to donor type. (**b**) Relapse/progression according to intensity of conditioning regimen. (**c**) NRM according to donor type. (**d**) PFS according to donor type. (**e**) Overall survival according to donor type.

Andamento comparabile nei trapianti da familiare identico, rispetto al MUD

Avivi I et al BMT 2014

Similar Transplantation Outcomes for Acute Myeloid Leukemia and Myelodysplastic Syndrome Patients with Haploidentical versus 10/10 Human Leukocyte Antigen–Matched Unrelated and Related Donors

Di Stasi A et al , BBMT, 2014



Andamento simile nei trapianti da familiare identico, rispetto a MUD o ad aploidentico, in una casistica omogenea , considerando un matching 10/10

HLA Disparity is not crucial for the survival rate and severity of chronic health conditions in adult recipients following family donor hematopoietic stem cell transplantation

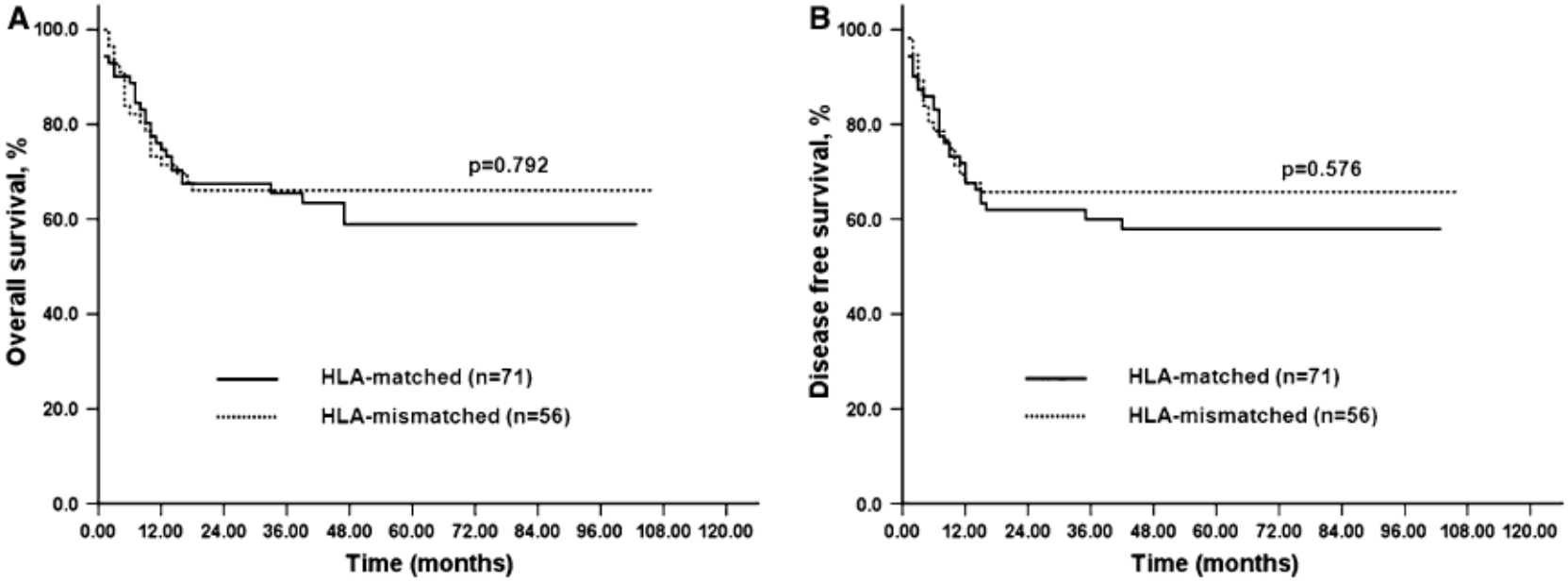


Fig. 1 OS and DFS after transplantation. There was no significant difference in the OS (a) and DFS (b) between HLA-matched and -mismatched transplant recipients ($p = 0.792$ and $p = 0.576$, respectively)

Analogo andamento dei trapianti da donatore familiare HLA-matched Rispetto a HLA-mismatched

Wang M et al, Int J Hematol 2015

HLA Disparity is not crucial for the survival rate and severity of chronic health conditions in adult recipients following family donor hematopoietic stem cell transplantation

Wang M et al, Int J Hematol 2015

Table 4 Risk factors related to chronic health conditions in 76 HSCT survivors

Risk factors	Univariate analysis	Multivariate analysis	
	p	*p*	Relative risk (95 % CI)
Age older than 40 years at HSCT	0.022	0.016	3.4 (1.3–9.3)
Sex (male)	0.391	–	–
HLA-matched	0.021	0.234	–
Advanced disease	0.555	–	–
Use of ATG	0.001	0.045	0.1 (0.003–0.9)
cGVHD	0.001	0.007	3.4 (1.4–8.4)
Grades II to IV aGVHD	0.366	–	–
CMV infection	0.191	–	–
EBV infection	0.222	–	–
Donor age (over 40 years)	0.383	–	–
Interval between HSCT and study >48 months	0.729	–	–

L'analisi multivariata (71 matched vs 56 mismatched don-fam) non evidenzia significative differenze nella sopravvivenza (OS, DFS). Età e cGVHD si confermano fattori di rischio indipendenti per eventi clinici cronici (CHCs). L'uso di ATG si rivela fattore protettivo.

Gli studi sui trapianti da cord blood confermano la correlazione tra livello di compatibilità tessutale e risultati, ma viene sottolineata la positiva correlazione con il numero dei mononucleati infusi

Combined effect of total nucleated cell dose and HLA match on transplantation outcome in 1061 cord blood recipients with hematologic malignancies

Juliet N. Barker,[1] Andromachi Scaradavou,[1] and Cladd E. Stevens[1]

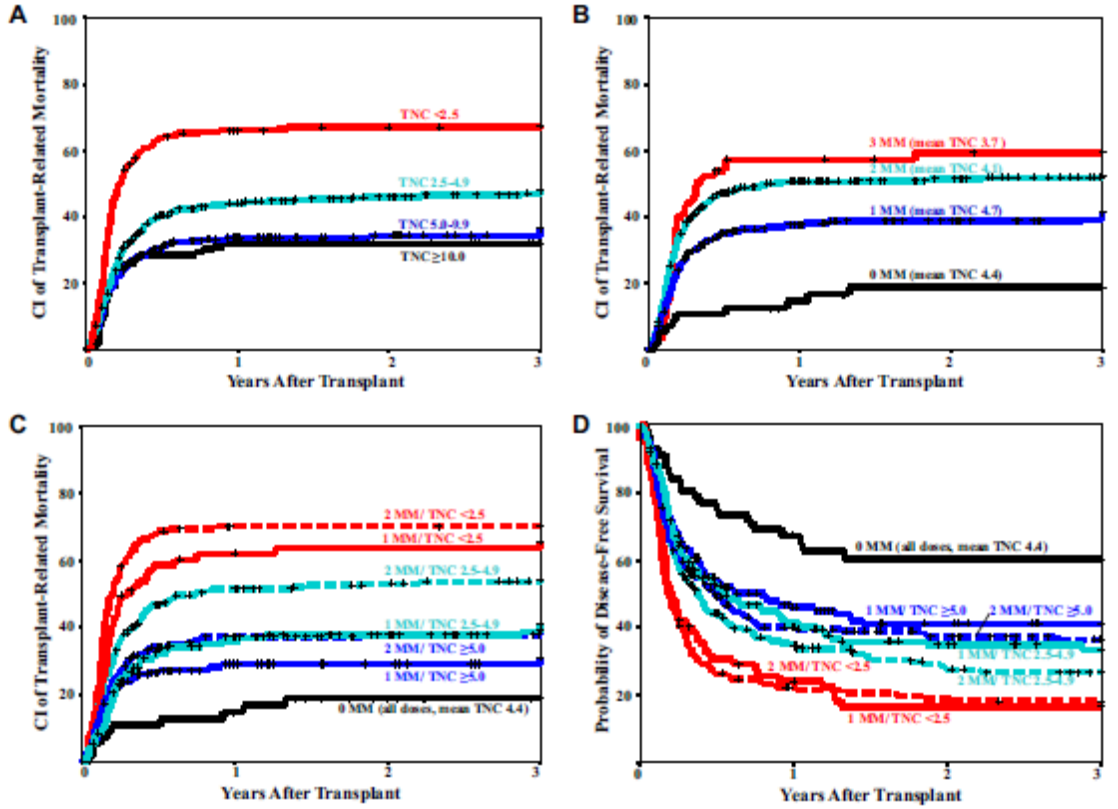


Figure 4. CI of 3-year TRM. Data are shown by TNC dose (A), HLA-mismatch (B), TNC dose and HLA-mismatch combined (C), and the Kaplan-Meier probability of disease-free survival (D). Recipients of units with either 1 or 2 mismatches were analyzed by separate TNC dose categories, whereas recipients of 0-MM units and 3-MM units were not.

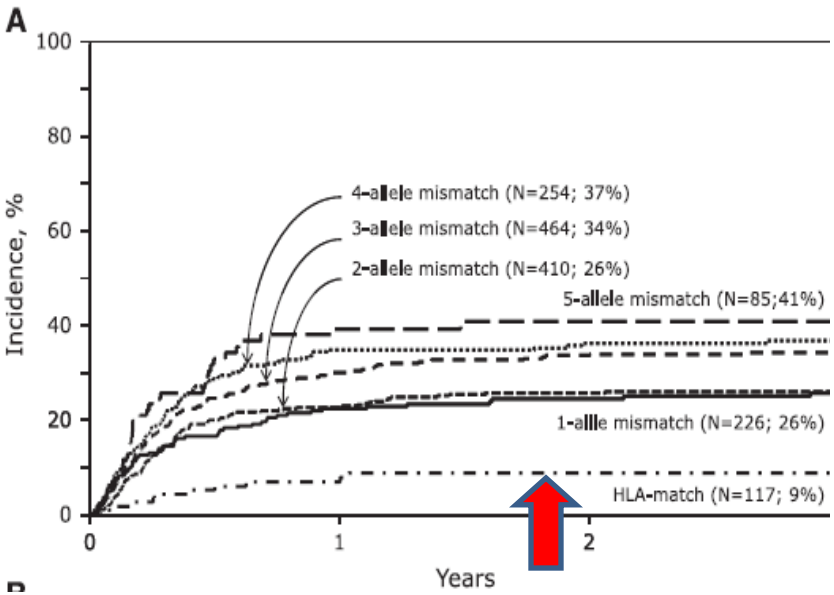
Sia il numero di cellule nucleate che il matching HLA influenzano l'esito del trapianto da sangue placentare

BLOOD, 4 MARCH 2010 • VOLUME 115, NUMBER 9

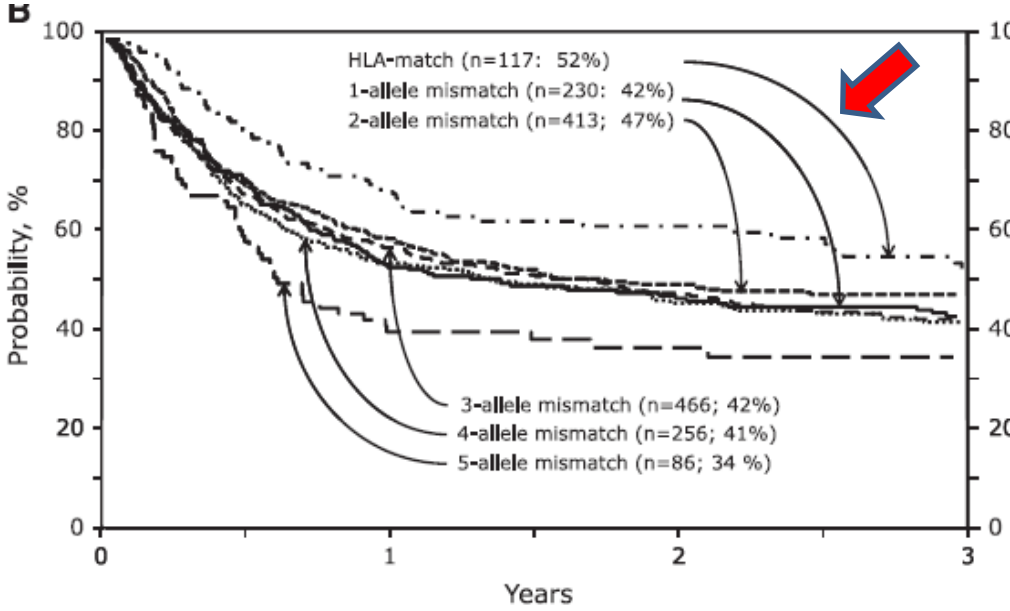
Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy

M. Eapen, Blood 2014

Non Relapse Mortality by HLA match



Overall Survival by HLA match

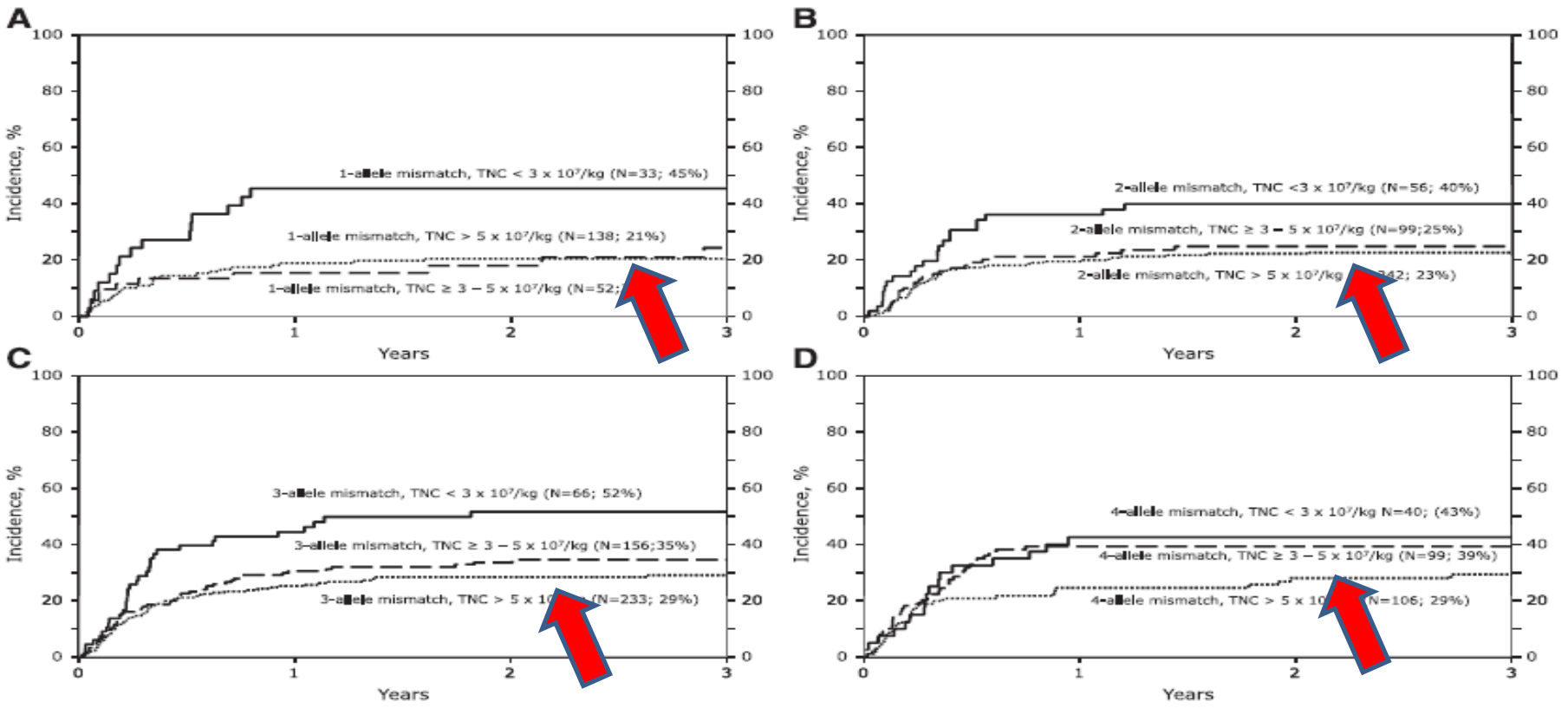


Il livello di matching allelico HLA , correla significativamente con l'andamento del trapianto di sangue placentare

Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy

M. Eapen, Blood 2014

Non Relapse Mortality by total nucleated cell dose



Il numero di mononucleati (>5 x10E7/Kg) correla significativamente con l'andamento del trapianto di sangue placentare

Mismatched Related and Unrelated Donors for Allogeneic Hematopoietic Cell Transplantation for Adults with Hematologic Malignancies

M. Eapen, BBMT 2014

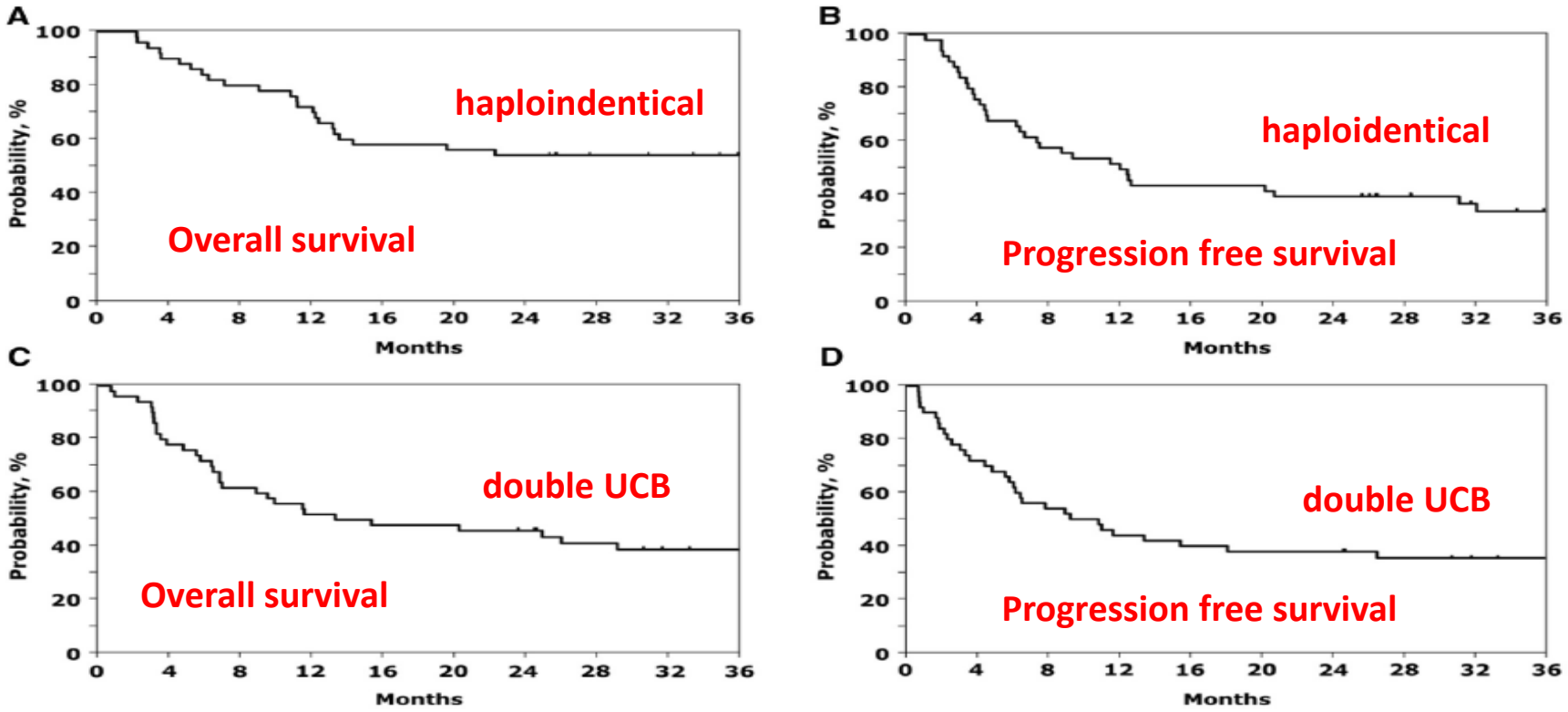


Figure 1. The 3-year probability of (A) overall survival after HLA-haploidentical bone marrow transplantation, (B) progression-free survival after HLA-haploidentical bone marrow transplantation, (C) overall survival after double UCB transplantation, and (D) progression-free survival after double UCB transplantation.

Risultati comparabili tra aploidentico vs doppia Unità Cord Blood

Emerge parimenti l'importanza del rilievo nel donatore di Anticorpi anti-HLA (DSA), diretti verso specifici Antigeni del ricevente.

Sono correlabili con la Graft-Failure, evento molto grave che si produce nell'1-6% dei casi

Anticorpi anti-HLA (alloreattività diretta)

Eventi alloimmunizanti:

- **Gravidanze**
- **Trasfusioni di sangue**
- **Trapianti allogenici**

→ **Produzione di anticorpi anti-HLA classe I e/o classe II**

Anticorpi anti-HLA donatore specifici (DSA)

Trapianti di organi solidi

Rigetto anticorpo mediato

Lefaucheur et al. Am J Transpl 2008

Trapianti di CSE

Graft Failure

Spellman et al. Blood 2010

Donor-specific HLA alloantibodies (DSA)

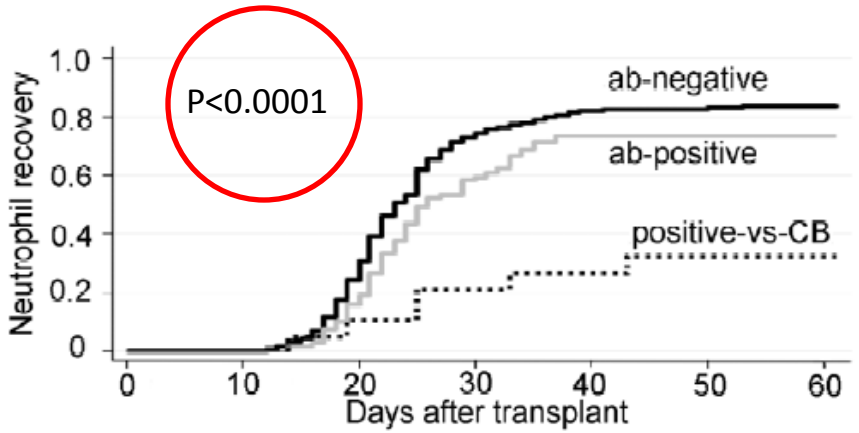
- **Graft failure in HLA-mm unrelated SCT** ***(Spellman, Blood 2009)***
- **Engraftment and survival in unrelated cord SCT** ***(Takanashi, Blood 2010)***

HLA-mismatched unrelated SCT

	Odds ratio	95% confidence interval	P
Class I DSA	11.34	1.49-∞	.017
Class II DSA	12.00	1.46-551.97	.014
Class I and/or II DSA	22.84	3.57-∞	< .001

>3-fold higher risk of graft failure

Unrelated Cord Blood SCT



I dati indicano una forte correlazione fra DSA e Graft Failure nei trapianti MUD HLA-mm e, soprattutto, nei trapianti UCB.
La determinazione dei DSA è auspicabile nella scelta del MUD

Previsione dell'alloreattività diretta mediata da linfociti T

Cytotoxic T Lymphocyte Precursor Assays (CTLp)

Poiché i vari antigeni HLA possono essere associati alle frequenze di CTLp, questi saggi sono utili per distinguere tra mismatch permissivi e non permissivi in vitro

Elevata frequenza di CTLp

Trapianti di organi solidi
Rigetto

Herzog et al. Transplantation1987

Trapianti di CSE
GvHD e Peggiore sopravvivenza

Affaticati et al. , BMT 2000
Jeras et al. , Transplant Immunology 2003

Metodica molto laboriosa, in uso in pochi laboratori

Ma non è solo il grado di compatibilità tessutale che riveste un ruolo strategico sull'andamento dei trapianti allogenici. Emergono, significativamente, anche altri fattori di rischio quali

età, sesso, CMV

High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation

S. J. Lee et al , Blood 2007

Table 6. Association between patient and donor characteristics and survival

Variable/category	No.	Hazard ratio	95% CI	*P*
HLA match				
8/8	1840	1.00	—	—
7/8	985	1.25	1.13-1.37	<.001
6/8	633	1.65	1.48-1.84	<.001
Disease diagnosis				
AML	969	1.00	—	—
ALL	834	1.07	0.95-1.20	.25
CML	1367	0.78	0.69-0.87	<.001
MDS	288	0.73	0.62-0.86	<.001
Disease status				
Early	1454	1.00	—	—
Intermediate	1352	1.38	1.25-1.53	<.001
Late	645	1.90	1.67-2.16	<.001
Patient age, y				
Younger than 31	1467	1.00	—	—
31 to 45	1263	1.51	1.36-1.67	<.001
Older than 45	728	1.79	1.59-2.02	<.001
Patient race				
White	3077	1.00	—	—
Black	132	1.53	1.26-1.87	<.001
Hispanic	170	1.05	0.87-1.27	.62
Other	78	0.68	0.51-0.92	.012
Donor/recipient, CMV				
−/−	1209	1.00	—	—
−/+	969	1.31	1.18-1.45	<.001
+/−	555	1.08	0.95-1.23	.23
+/+	623	1.36	1.20-1.54	<.001
Unknown	102	1.34	1.06-1.71	.016
Donor/recipient, sex match				
M/M	1246	1.00	—	—
M/F	824	1.00	0.90-1.11	.99
F/M	693	0.99	0.86-1.15	.89
F/F	695	1.03	0.90-1.19	.65
Donor parity				
Male or not parous	2615	1.00	—	—
Parous	814	1.10	0.96-1.27	.17
Donor age, y				
Younger than 31	887	1.00	—	—
31 to 45	1929	1.05	0.95-1.16	.38
Older than 45	642	1.06	0.93-1.20	.42

M indicates male; F, female; and —, not applicable.

In questo studio si evidenzia la significativa correlazione tra HLA, età del ricevente, CMV ed etnia, e la sopravvivenza globale dopo trapianto

The EBMT risk score (Gratwhol A, BMT 2012)

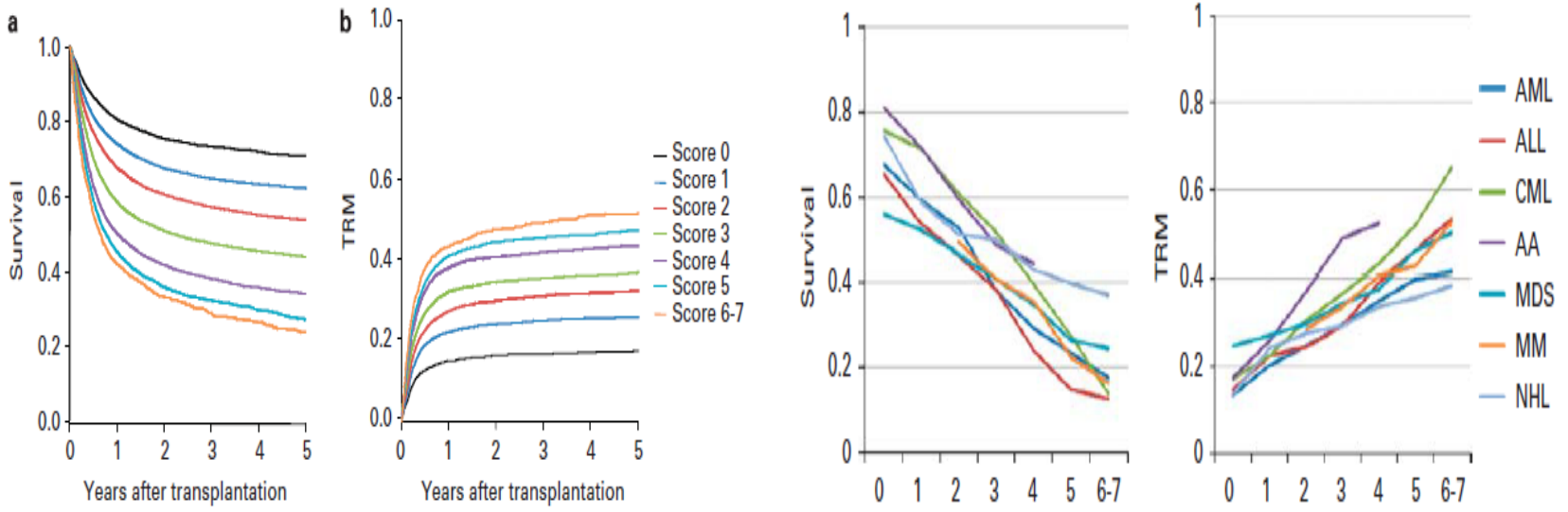
Table 1 EBMT risk score definition

Risk factor	*Score points*
Age of the patient, years	
<20	0
20–40	1
>40	2
Disease stage[a]	
Early	0
Intermediate	1
Late	2
Time interval from diagnosis to transplant, months[b]	
<12	0
>12	1
Donor type[c]	
HLA-identical sibling donor	0
Unrelated donor, other	1
Donor recipient sex combination[c]	
All other	0
Female donor, male recipient	1

[a]See text for definitions according to main disease category. Disease stage does not apply for aplastic anemia (score 0).
[b]Does not apply for patients transplanted in first CR (score 0).
[c]Does not apply for patients with autologous HSCT (score 0).

The EBMT risk score (Gratwhol A, BMT 2012)

Survival / TRM and diagnosis by risk score



Positiva correlazione tra risk score ed esiti del trapianto (sopravvivenza, mortalità correlata, diagnosi)

The EBMT risk score (Gratwhol A, BMT 2012)

Impatto relativo del rischio individuale rispetto alla diagnosi

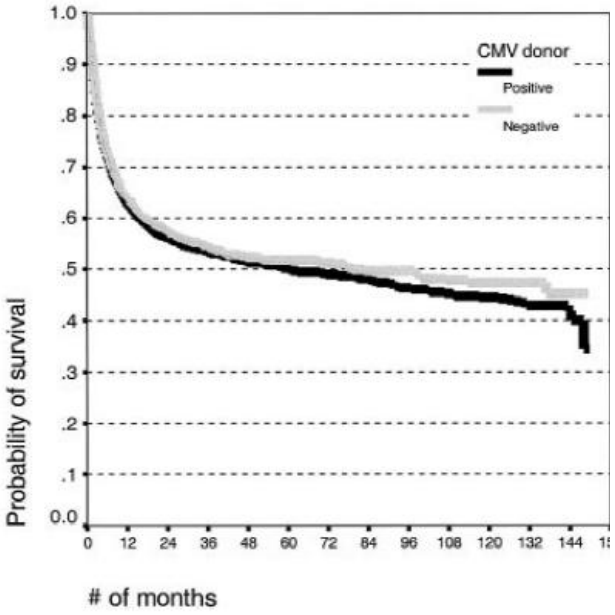
Table 2 Relative impact of the individual risk factors, depending on main disease category

Risk factors	*AML*	*ALL*	*CML*	*MDS*	*MM*	*NHL*	*AA*	*Combined*
Age, years								
<20	1	1	1	1	1	1.	1	1
20–40	1.20	1.44	1.18	1.43	1.14	1.02	1.45	1.34
>40	1.45	1.94	1.58	1.80	NA	1.03	2.90	1.67
Stage								
Early	1	1	1	1	1	1	1	1
Intermediate	1.47	1.48	1.75	1.22	1.59	1.64	1.45	1.52
Advanced	2.92	2.58	3.31	1.71	2.34	2.58	2.90	1.52
Time interval, months								
<12	1	1	1	1	1	1	1	1
>12	0.90	1.26	1.24	1.03	1.17	0.75	1.58	1.12
Donor type								
HLA-id sib	1	1	1	1	1	1	1	1
Other	1.30	1.27	1.39	1.32	1.46	1.28	2.09	1.35
Gender combination								
Other	1	1	1	1	1	1	1	1
RMDF[a]	1.07	1.04	1.22	1.05	1.15	1.16	1.10	1.10
Explanatory content[b]								
Cox	0.648	0.634	0.642	0.603	0.597	0.616	0.656	0.634
Score	0.630	0.616	0.634	0.600	0.591	0.577	0.633	0.621

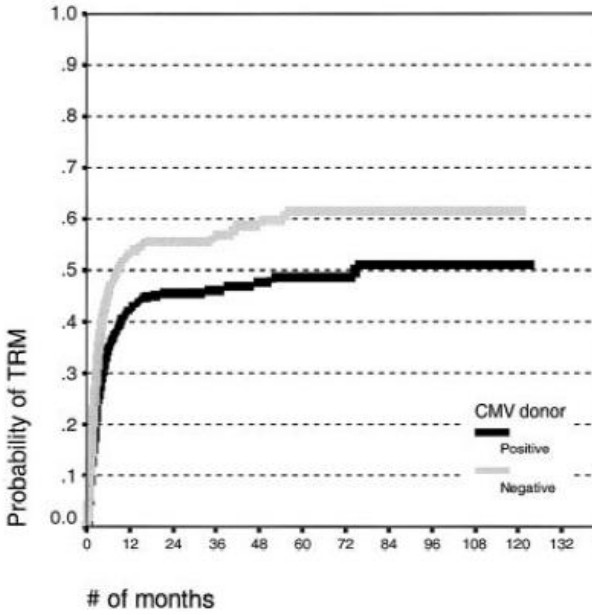
Abbreviation: AA = aplastic anemia; MDS = myelodysplastic syndrome; MM = multiple myeloma; NHL = non Hodgkin lymphoma.
[a]RMDF recipient male, donor female.

Donor CMV serologic status and outcome of CMV-seropositive recipients after unrelated donor stem cell transplantation: an EBMT megafile analysis

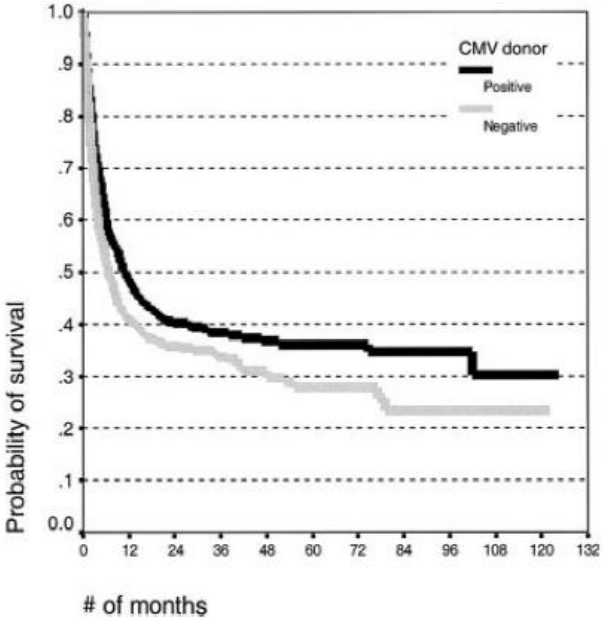
Ljungman P et al, Blood 2003



Survival
HLA identical sibling SCT
P ns



TRM
Unrelated donor SCT
P .001



Survival
Unrelated donor SCT
P .02

La positività per CMV si rivela fortemente correlata all'andamento del trapianto (mortalità correlata e sopravvivenza globale)

CMV serostatus still has an important prognostic impact in de novo acute leukemia patients after allogeneic stem cell transplantation: a report from the Acute Leukemia Working Party of EBMT

Schmidt-Hieber M, Blood 2013

Key Points

- Donor and/or recipient CMV seropositivity is still associated with an adverse prognosis in de novo acute leukemia patients after allo-SCT.

Table 2. Impact of CMV serostatus on LFS, RI, NRM, OS, chronic GVHD, and neutrophil engraftment

CMV serostatus	LFS	RI	NRM	OS	cGVHD	NEG
Total (n = 16 628)	45	32	22	51	45	97
D-CMV$^-$/R-CMV$^-$	49	31	20	56	45	97
D-CMV$^+$/R-CMV$^-$	44	34	22	49	47	96
D-CMV$^-$/R-CMV$^+$	43	31	25	49	44	96
D-CMV$^+$/R-CMV$^+$	45	33	23	51	44	96
P	< .001	.11	< .001	< .001	.63	< .001
D-CMV$^-$/R-CMV$^-$	49	31	20	56	45	97
Other combination	44	32	23	50	45	96
P	< .001	.08	< .001	< .001	.6	.08

CMV serostatus still has an important prognostic impact in de novo acute leukemia patients after allogeneic stem cell transplantation: a report from the Acute Leukemia Working Party of EBMT

Schmidt-Hieber M, Blood 2013

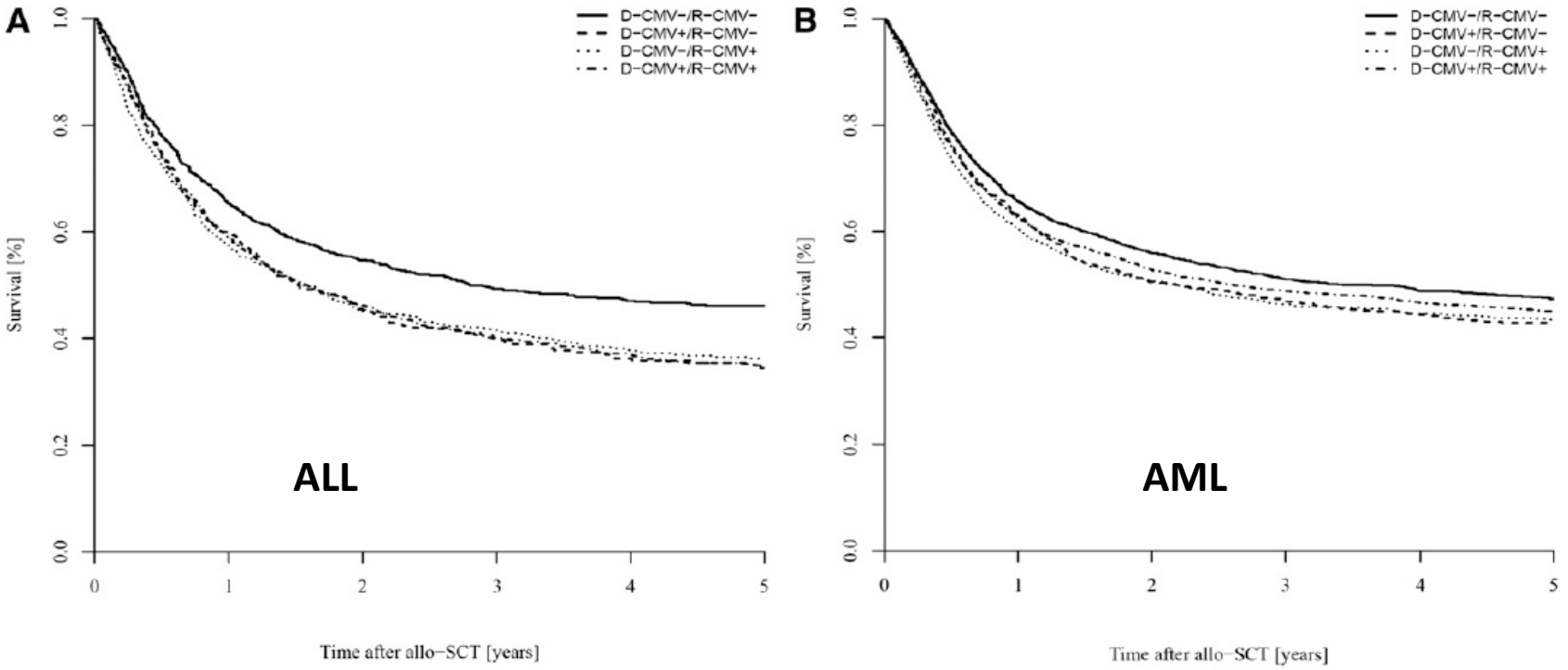


Figure 1. Impact of donor/recipient CMV serostatus on OS. Impact in (A) ALL vs (B) AML.

La negatività CMV del donatore si conferma fortemente correlata alla sopravvivenza globale (migliore combinazione : Don-/Rec-)

Risk-Factor Analysis of Poor Graft Function after Allogeneic Hematopoietic Stem Cell Transplantation

Xiao Y ET AL , Int J Med Sc 2014

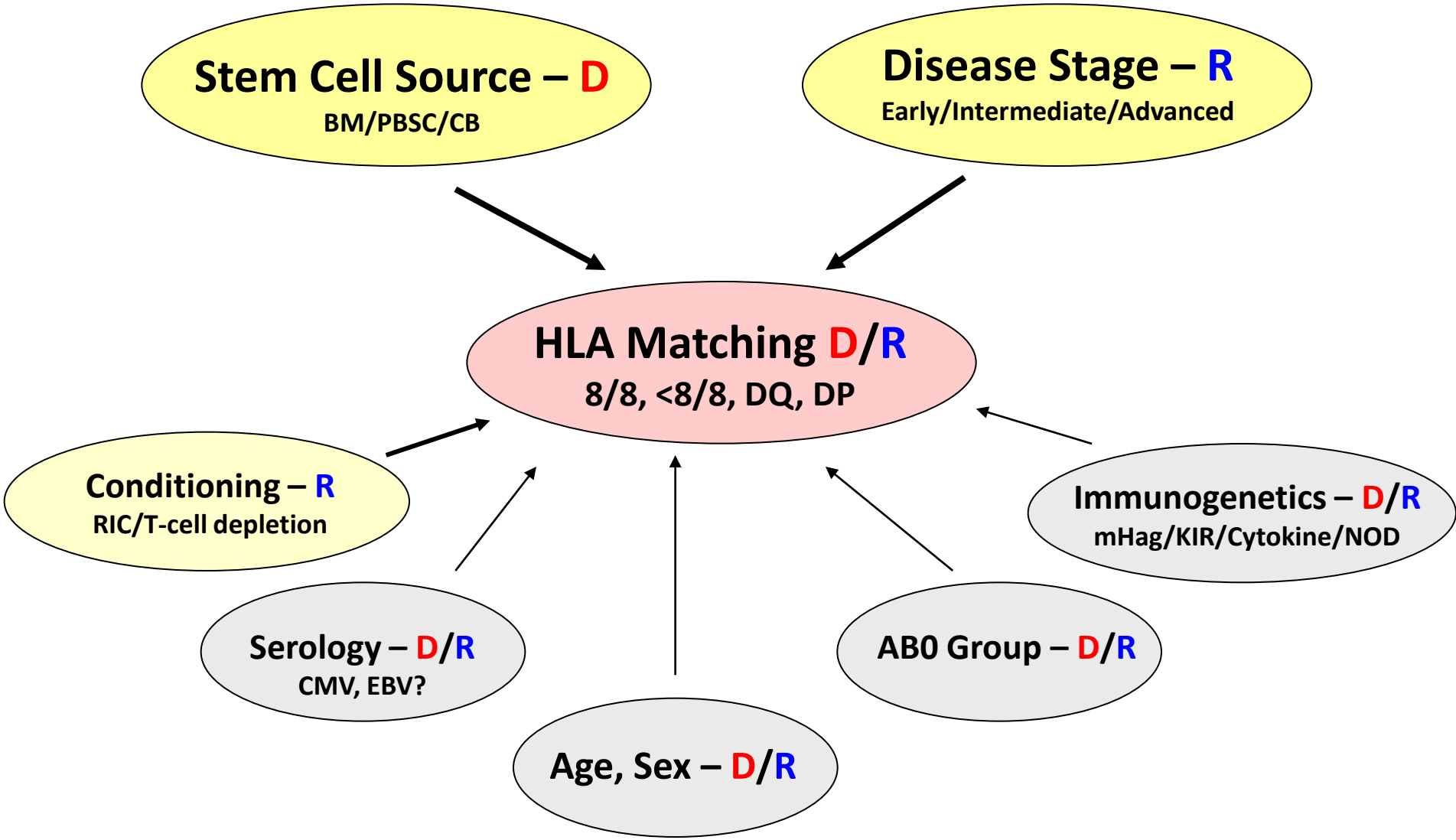
Age of patient, Blood mismatch and CMV infection are significant contributors to Poor Graft Function (PGF) in HSCT

Table 2. Multivariate logistic analysis for risk factors of PGF.

Risk factors	β	S_b	Wald value	*P* value	*OR* value	95% CI for *OR*	
						Lower limit	Upper limit
Age of patient	1.011	0.340	8.843	0.003*	2.747	1.411	5.347
Donor-recipient blood mismatch	1.399	0.635	4.561	0.033*	4.051	1.122	14.629
CMV infection	2.213	0.918	5.815	0.016*	9.146	1.513	55.276

*: P<0.05.

Factors influencing outcome of allo-SCT



Alternative donor transplant of benign primary hematologic disorders

Table 1. Alternative donor options: advantages and disadvantages

Graft source	*Advantages*	*Disadvantages*
Unrelated donor	Historical 'gold standard' Wealth of experience Well-published outcomes Reproducible quality of stem cell product Faster immune reconstitution Donor lymphocytes available	Availability (~50%, ⩽10% for minorities) Time delay More expensive
Umbilical cord blood	Availability (>95%) Speed to HSCT No risk to donor Extension of the donor pool Small cryopreserved volume with easy transportability Low risk of infectious disease transmission of latent viruses Decreased GVHD	Low cell number Single use/no DLI available Slower hematopoietic engraftment/immune reconstitution Infection Few large-size and high-quality units compared with URD More expensive Recommendation to have autologous product as back-up
HLA-haploidentical related donor	Availability Speed to HSCT Less expensive Maximize cell dose Faster immune reconstitution Donor lymphocytes available	Less experience Delayed immune reconstitution and expensive (T cell-depleted grafts)

Abbreviations: HSCT = hematopoietic SCT; URD = unrelated donor.

Tolar J, BMT 2015

Possibile algoritmo per la selezione di un donatore di CSE

M. Eapen, BBMT 2014

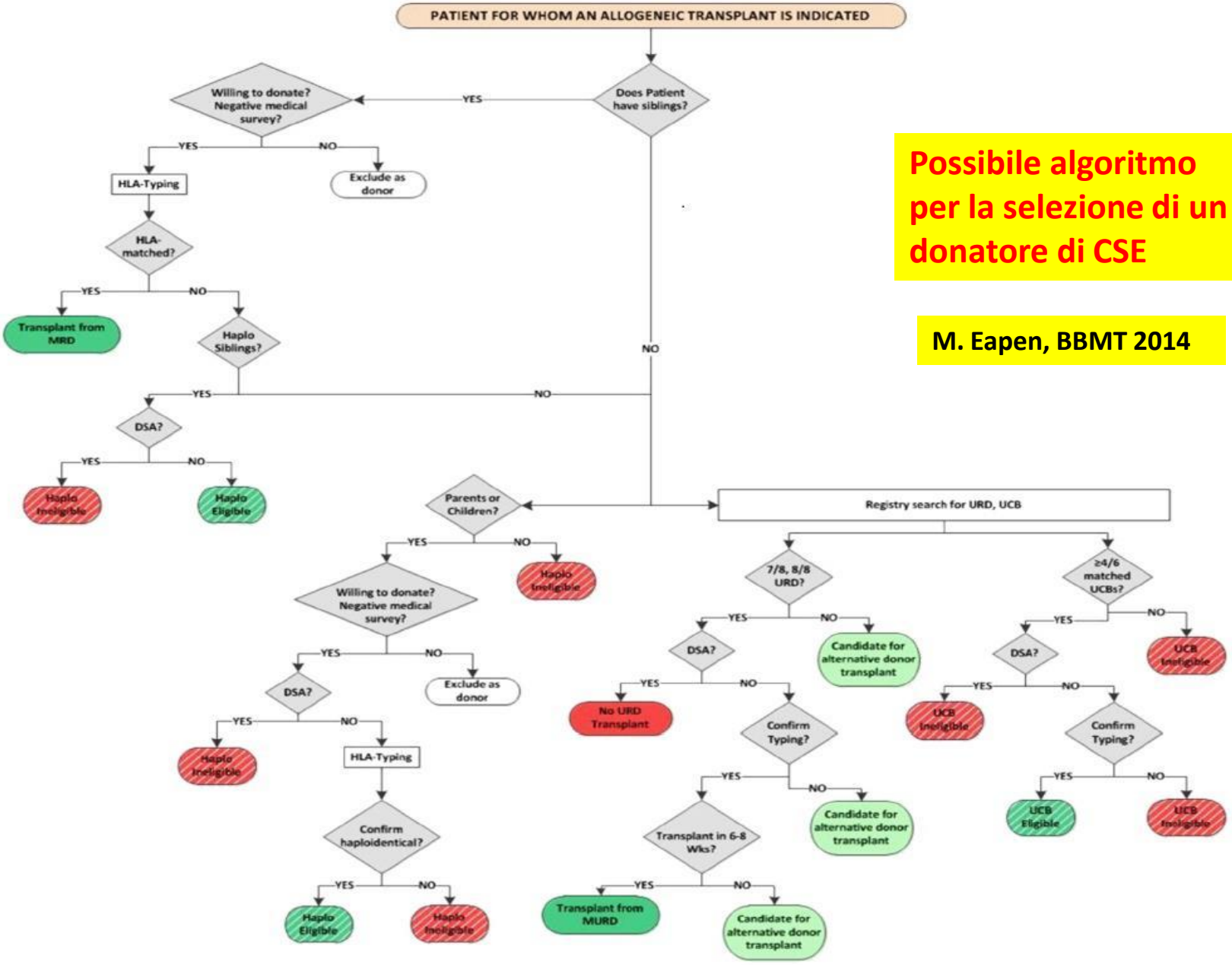


Figure 3. Donor selection algorithm. MRD indicates matched related donor; URD, unrelated donor; MURD, HLA-mismatched unrelated donor; DSA, donor-specific antibody.

La scelta del donatore (Take Home Messages 1)

- **Familiare HLA identico ? Si ⇨ trapianto**
- **Familiare HLA identico ? No ⇨ trapianto alternativo**
- **Donatore da Registro UCB/MUD entro 3 mesi ? ⇨ trapianto**
- **Non UCB/MUD entro 3 mesi ? ⇨ aploidentico**

Considerati gli stessi risultati FAM/MUD/APLO, comandano la scelta:

- **mediana tempo di ricerca donatore**
- **disponibilità clinica del donatore (età, sesso, CMV)**
- **frequenza genetica HLA**
- **immunoterapia post-trapianto**
- **trasmissibilità virosi**
- **scelta della fonte di CSE (ancora oggi fortemente Centro-dipendente)**

La scelta del donatore e del trapianto
Possibile prossimo futuro
(Take Home Messages 2)

HLA

↓

Età - SESSO - CMV (scelta donatore)

↓

Sibling id. MUD APLO (scelta tipo trapianto)

“La speranza è un sogno fatto da svegli”

Aristotele ***(Citazione da Diogene in Vite dei filosofi)***