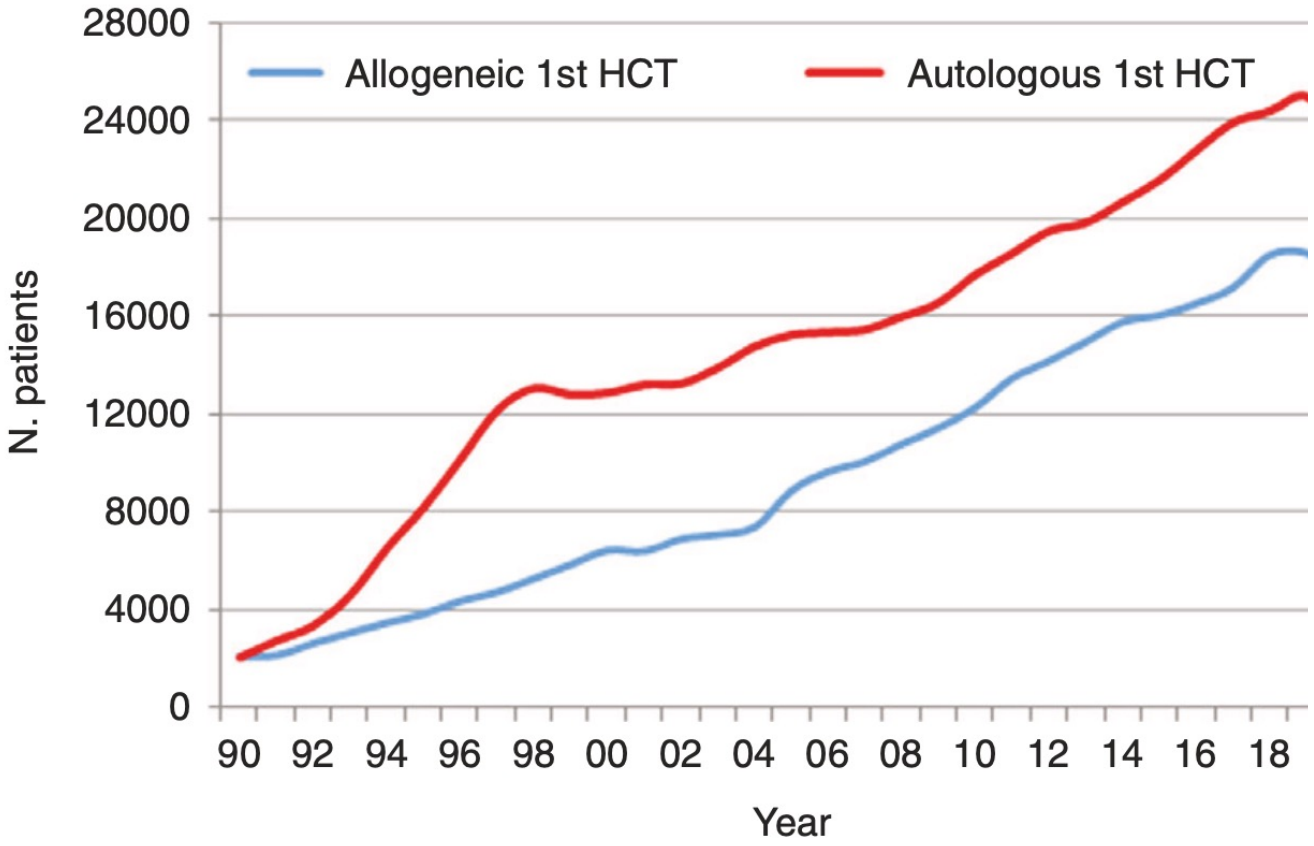
Stem Cell Transplantation: Indications and Donor Selection

Ann De Becker

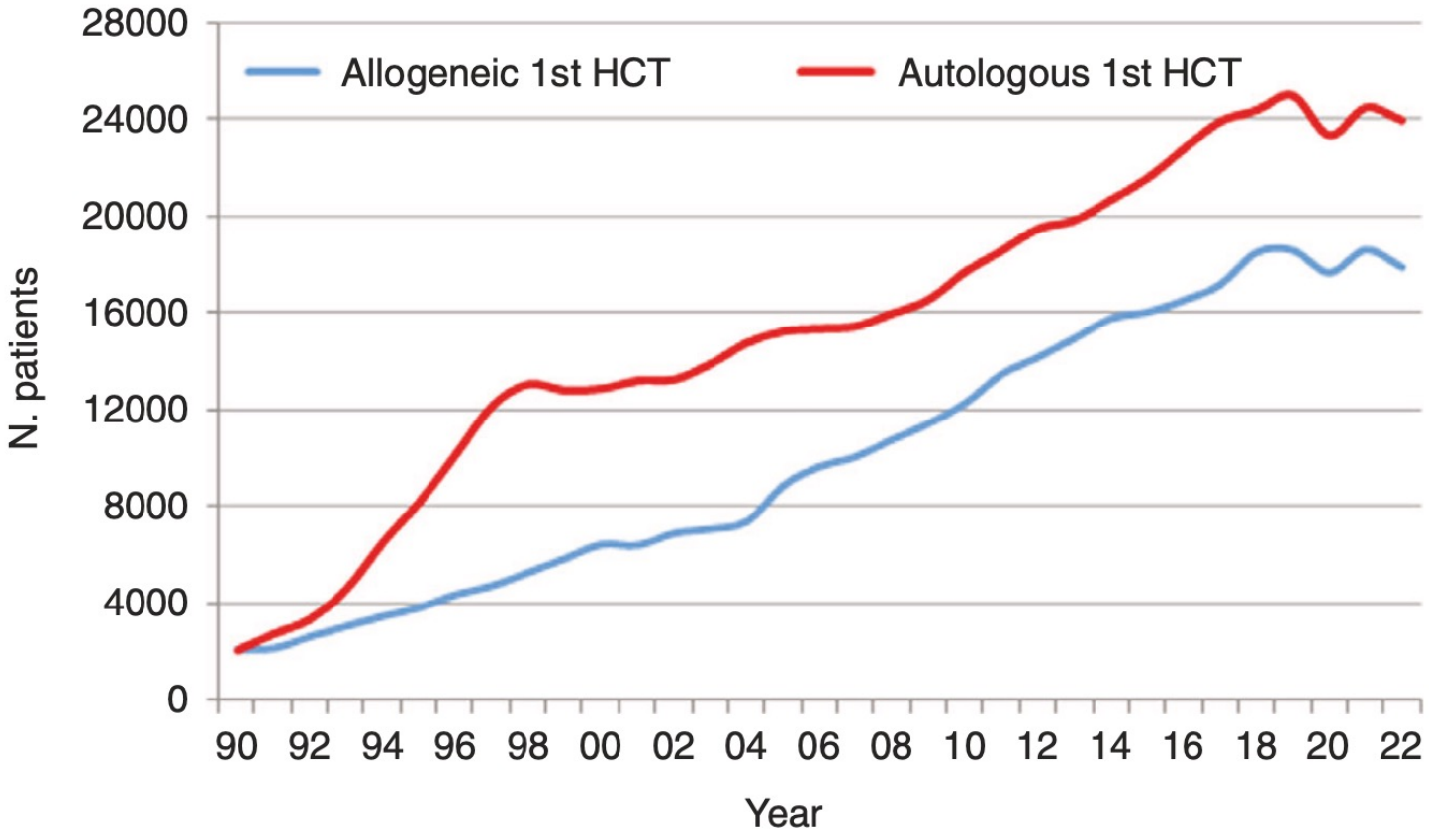
16/03/2024

EBMT activity report 2022



Passweg JR et al, BMT 2024

EBMT activity report 2022



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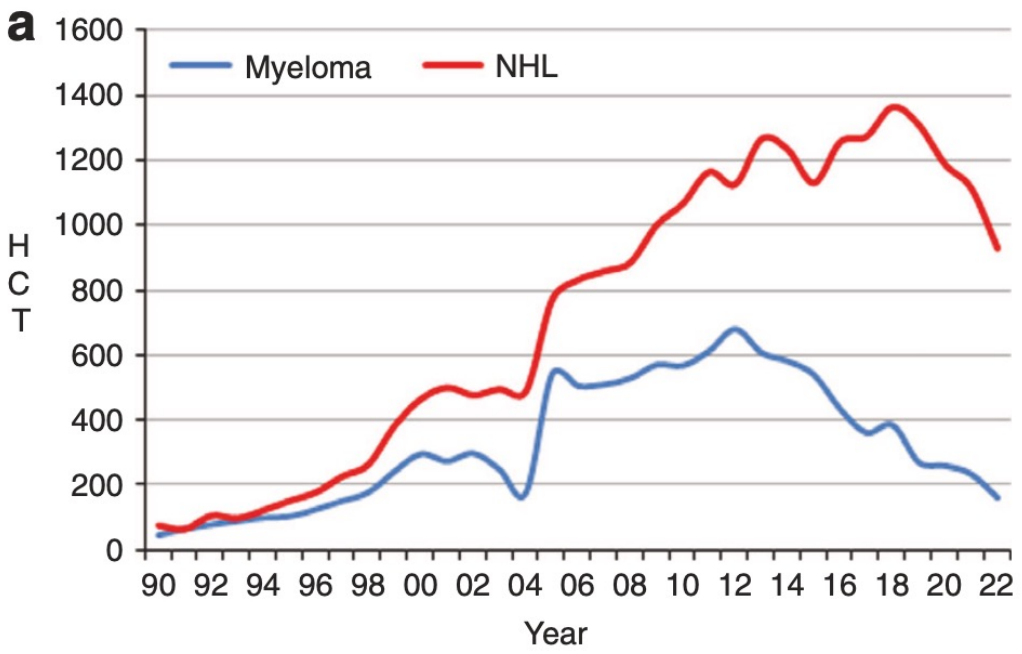
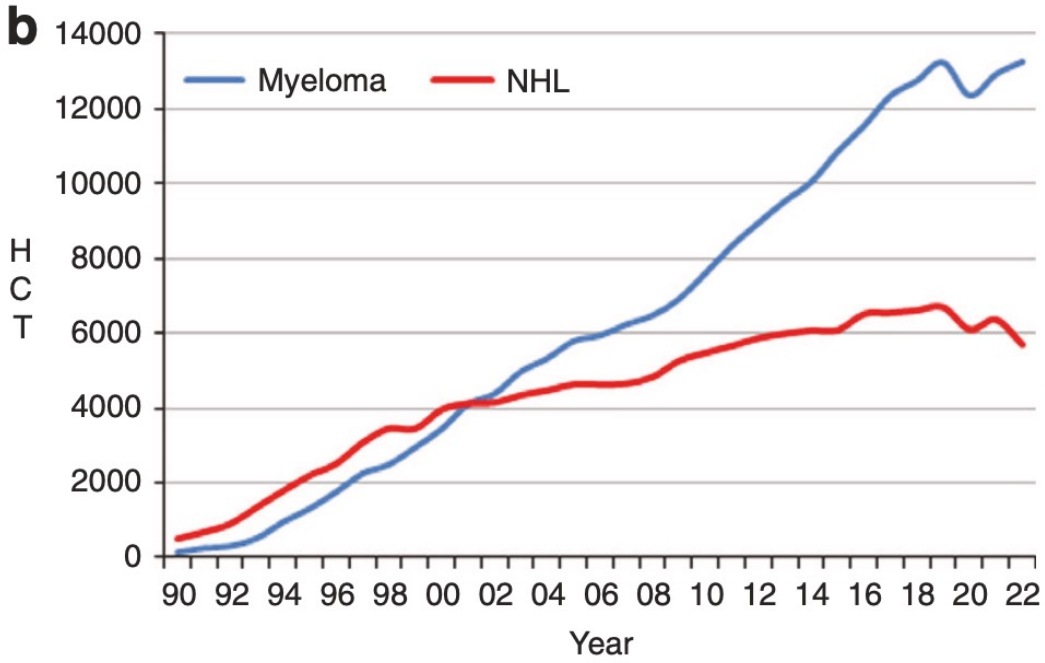
EBMT activity report 2022

Allogeneic transplants

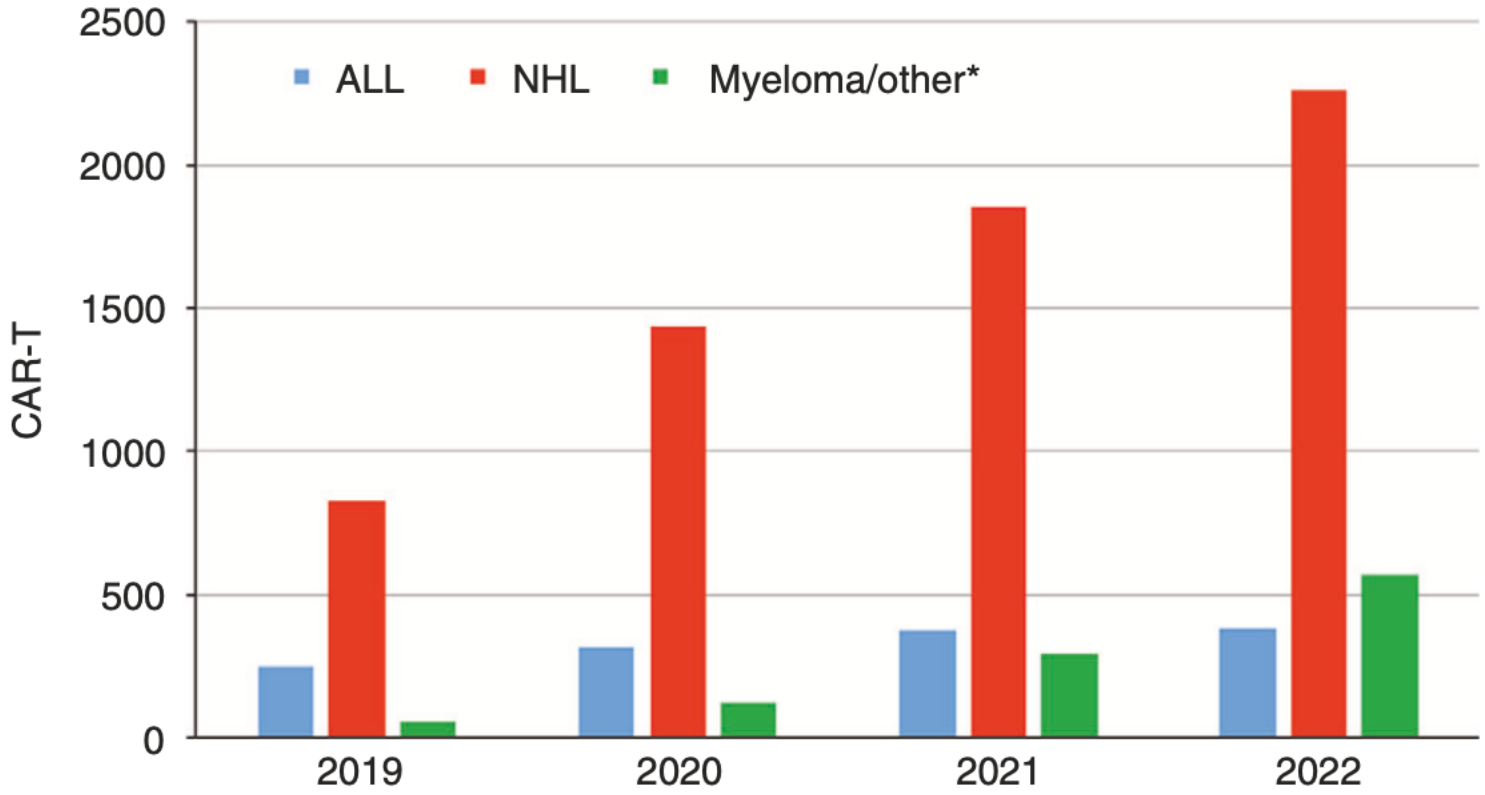


Autologous transplants



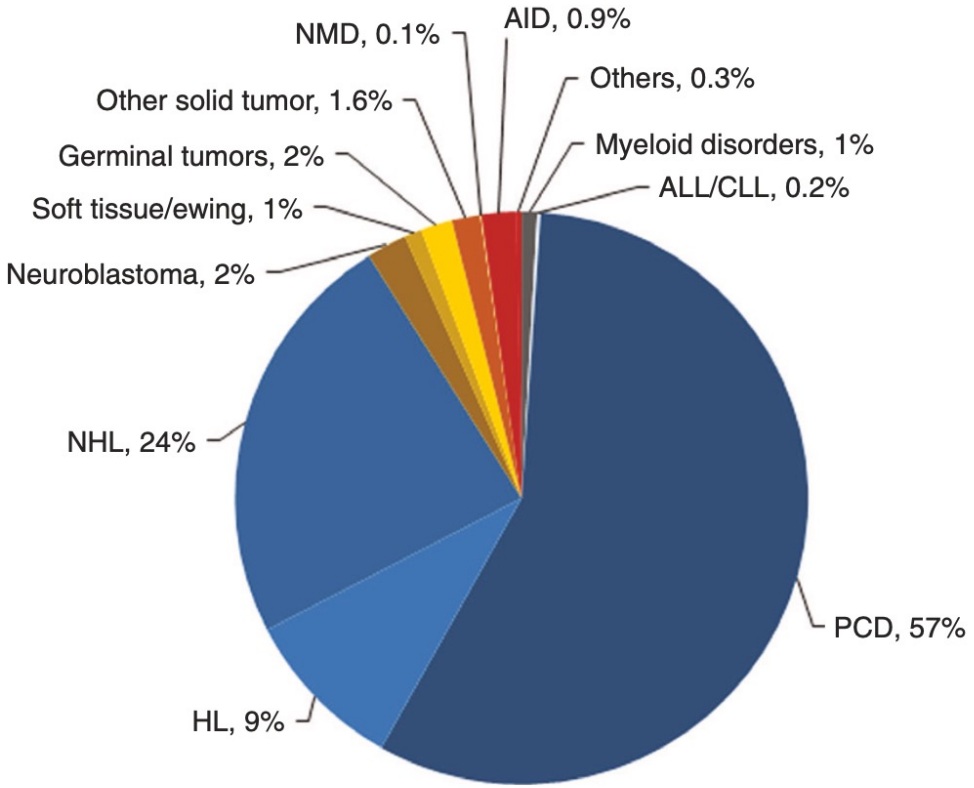
Passweg JR et al, BMT 2024

EBMT activity report 2022: rise of the CAR T



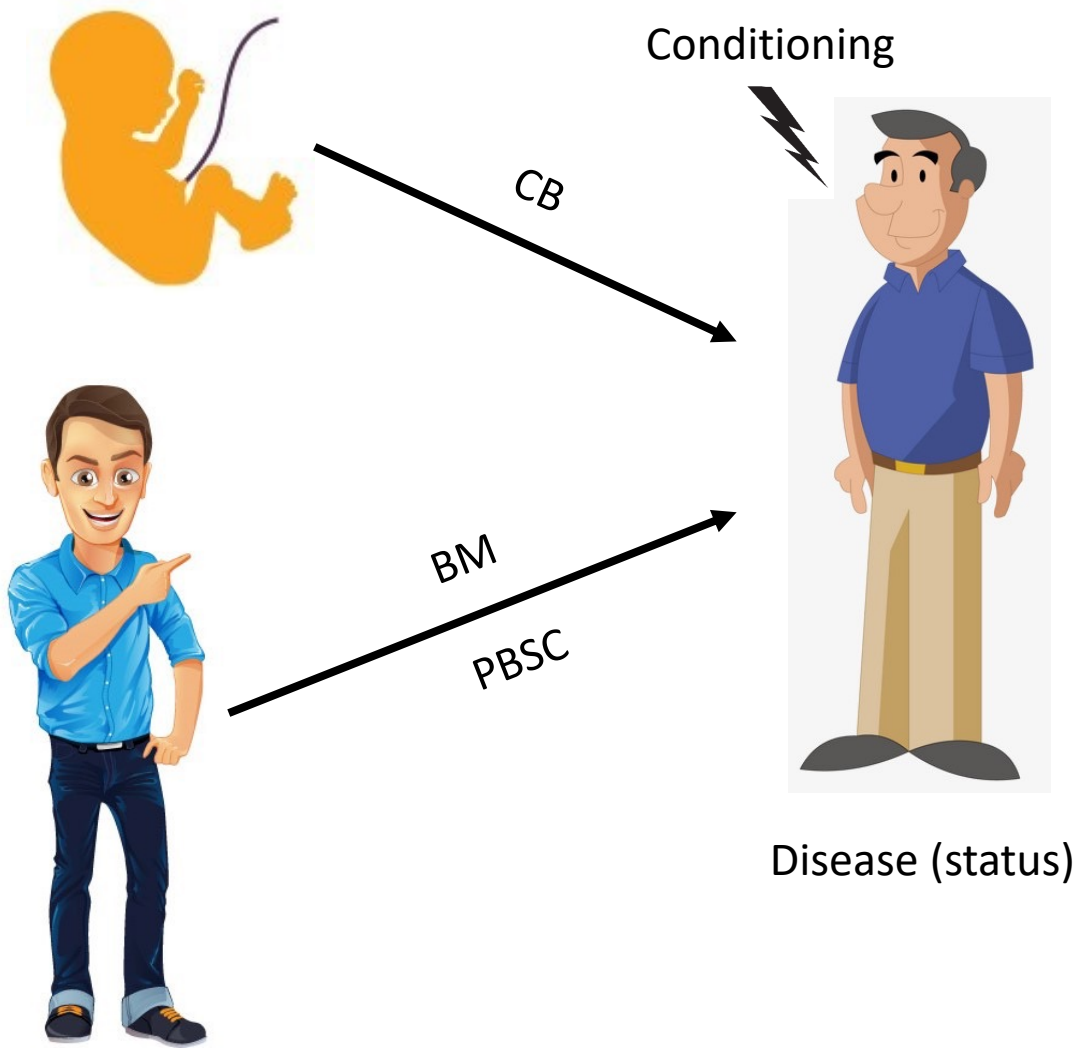
Passweg JR et al, BMT 2024

Indications for autologous SCT in Europe in 2022

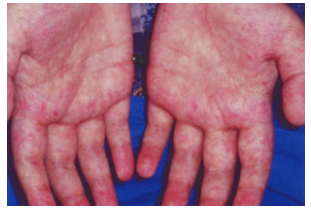
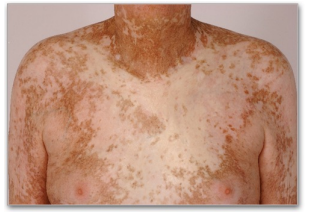
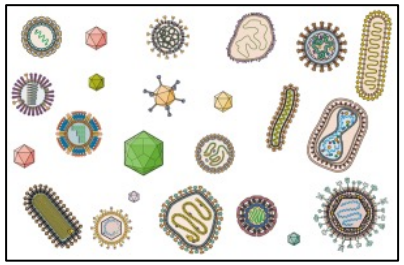
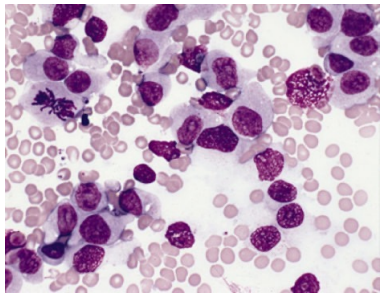


Passweg JR et al, BMT 2024

Allogeneic stem cell transplantation



Survivorship

Should we offer transplant to a patient?

Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022

John A. Snowden[1✉], Isabel Sánchez-Ortega[2], Selim Corbacioglu[3], Grzegorz W. Basak[4], Christian Chabannon[5], Rafael de la Camara[6], Harry Dolstra[7], Rafael F. Duarte[8], Bertram Glass[9], Raffaella Greco[10], Arjan C. Lankester[11], Mohamad Mohty[12], Bénédicte Neven[13], Régis Peffault de Latour[14], Paolo Pedrazzoli[15], Zinaida Peric[16], Ibrahim Yakoub-Agha[17], Anna Sureda[18], Nicolaus Kröger[19] for the European Society for Blood and Marrow Transplantation (EBMT)

Cases

Mary Jane	Miranda	Daniel
25 years old AML CR1 	64 years old MDS-IB2 	53 years old Relapsed mantle cell lymphoma Prior autologous SCT 

EBMT Indications for SCT

- Indication according to:
  - Disease
  - Disease status
  - Donor type

- Not in the list but also important:
  - Co-morbidities
  - Patient age

EBMT Indications for SCT: categories

Standard of care (S)	Hard data from trials
Clinical option (CO)	Small patient cohorts show efficacy, confirmatory randomised trials lacking
Developmental (D)	Limited experience, additional research needed, best in clinical trial
Generally not recommended (GNR)	

Cases: should we offer allo transplant?

Mary Jane

25 years old
AML CR1

MRD+

2 HLA id siblings:
1 brother
1 sister
1 haplo id brother

Disease	Disease status	MSD allo	MUD allo	MMAD allo	Auto	CAR-T
Haematological malignancies						
AML[a]	CR1 (favourable risk and MRD–)[b]	GNR/II	GNR/II	GNR/II	CO/I	
	CR1 (favourable risk and MRD+)[b]	S/II	CO/II	CO/II	GNR/II	
	CR1 (intermediate risk)[b]	S/II	CO/II	CO/II	CO/I	
	CR1 (adverse risk)[b]	S/II	S/II	S/II	GNR/I	
	CR2	S/II	S/II	S/II	CO/II	
	APL Molecular CR2	S/II	CO/II	GNR/III	S/II	
	Relapse or refractory	CO/II	CO/II	CO/II	GNR/III	

Cases: should we offer allo transplant?

Miranda

64 years old
MDS-IB2

IPSS-R high

1 sibling - unfit
No MUD available
2 children

Disease	Disease status	MSD allo	MUD allo	MMAD allo	Auto	CAR-T
MDS	Very low and low-risk (IPSS-R)	CO/II	CO/II	CO/II	GNR/III	
	Intermediate-risk without additional factors[c] (IPSS-R)	CO/II	CO/II	CO/II	CO/II	
	Intermediate-risk with additional factors[c] (IPSS-R)	S/II	S/II	S/II	GNR/III	
	High-, very high-risk (IPSS-R)	S/II	S/II	S/II		
	sAML in CR1 or CR2	S/II	S/II			

Cases: should we offer allo transplant 2019

Daniel

53 years old
Relapsed mantle cell lymphoma
Prior autologous SCT

1 sibling – no match
MUD available
1 child (son)

Disease	Disease status	MSD Allo	MUD Allo	MMAD Allo	Auto
Lymphoid malignancies					
DLBCL	CR1 (Intermediate/high IPI at dx)	GNR/III	GNR/III	GNR/III	CO/I
	Chemosensitive relapse, ≥CR2	CO/II	CO/II	D/III	S/I
	Chemosensitive relapse after auto-HSCT failure	S/II	S/II	CO/III	GNR/III
	Refractory disease	CO/II	CO/II	CO/III	CO/II
	Primary CNS lymphoma	GNR/III	GNR/III	GNR/III	S/I
FL	CR1, untransformed	GNR/III	GNR/III	GNR/III	GNR/II
	CR1, transformed to high-grade lymphoma	GNR/III	GNR/III	GNR/III	CO/III
	Chemosensitive relapse, ≥CR2	CO/III	CO/III	GNR/III	S/II
	≥CR2 after auto-HSCT failure	S/II	S/II	D/III	GNR/III
	Refractory	CO/II	CO/II	CO/III	GNR/III
MCL	CR1	GNR/III	GNR/III	GNR/III	S/I
	CR/PR > 1, no prior auto-HSCT	CO/III	CO/III	D/III	S/II
	CR/PR > 1, after prior auto-HSCT	S/II	S/II	CO/III	GNR/II
	Refractory	CO/II	CO/II	D/III	GNR/II

Cases: should we offer allo transplant 2022

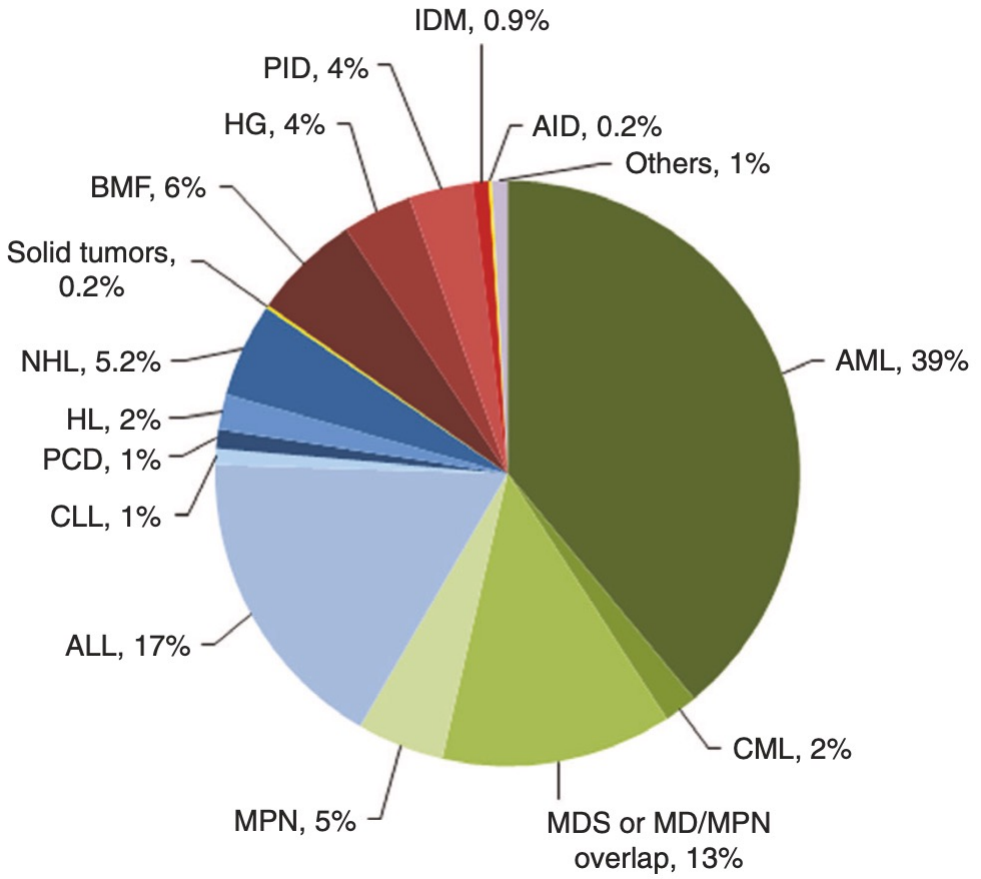
Daniel

53 years old
Relapsed mantle cell lymphoma
Prior autologous SCT

1 sibling – no match
MUD available
1 child (son)

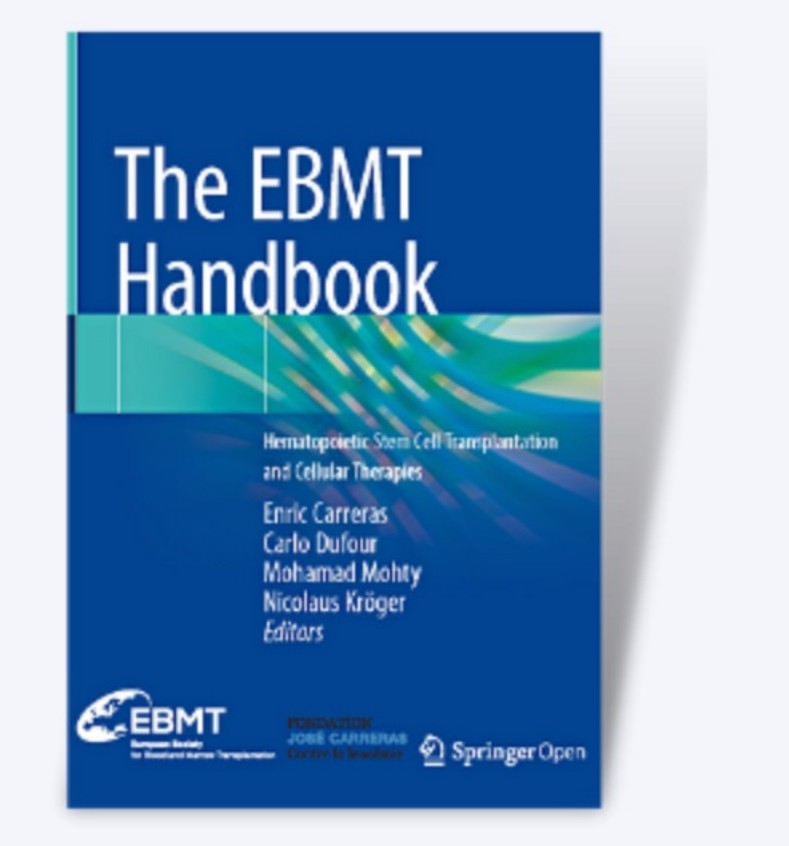
Disease	Disease status	MSD allo	MUD allo	MMAD allo	Auto	CAR-T
MCL	CR1	GNR/III	GNR/III	GNR/III	S/I	GNR/III
	CR/PR >1, no prior auto-HCT	CO/III	CO/III	D/III	CO/II	S/II
	CR/PR >1, after prior auto-HCT	CO/II	CO/II	CO/III	GNR/II	S/II
	Refractory	CO/II	CO/II	CO/III	GNR/II	S/II

Allogeneic SCT in Europe 2022



Passweg JR et al, BMT 2024

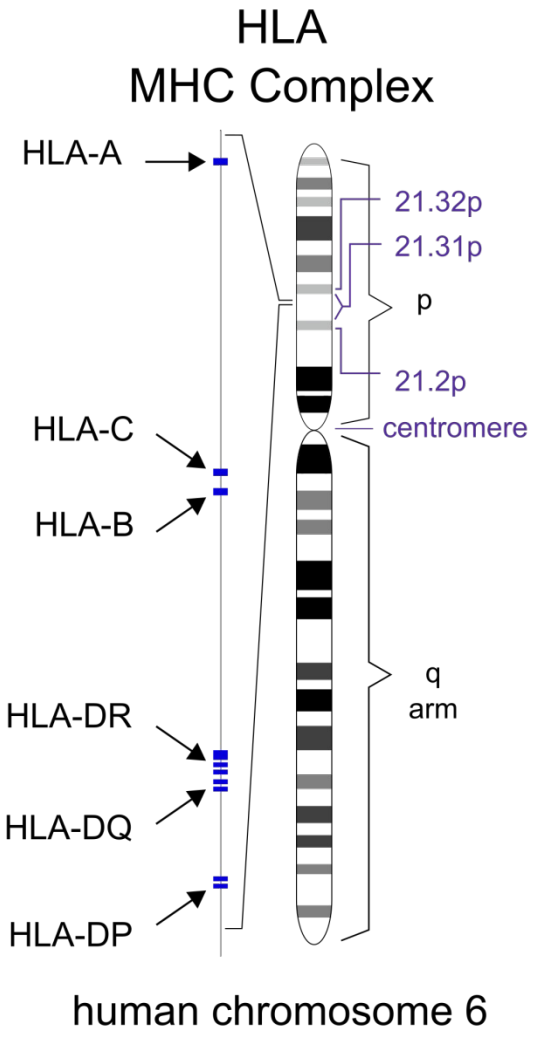
Donor Selection



- Donor selection: chapter 12

Donor choice: definition of donor types

- HLA-identical donor: 10/10
  - Sibling
  - Matched unrelated donor
- Mismatched donor
  - <10/10
- Haplo-identical donor
  - 3/6
  - Parent/child/sibling
- Cord blood
  - ≥ 4/6



Donor choice: definition of donor types

- HLA-identical donor: 10/10
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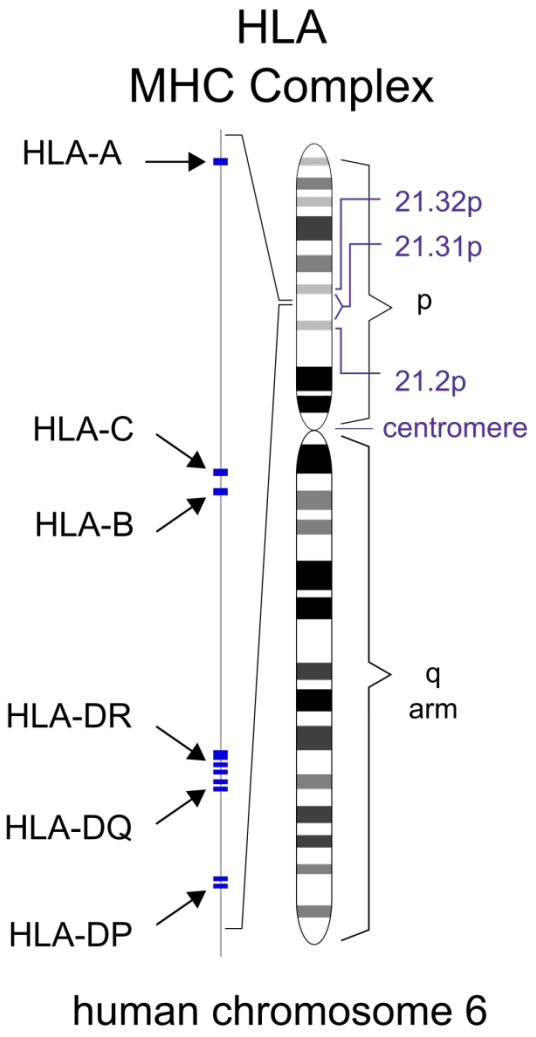
Mismatched alternative donors (MMAD)



Chances of obtaining a matched donor

- HLA-identical sibling donor: **30%**
- Matched unrelated donor:

	10/10	9/10	8/8*	≥ 7/8*
European	50%	20-30%		
African			18%	71%
Middle-East/ North-Africa			46%	90%
Asian			27-42%	76-88%
Hispanic			34%	80%

*8/8: HLA A/B/C/DR

Haematologica 2016; 101(6):680-687

Donor characteristics and outcome

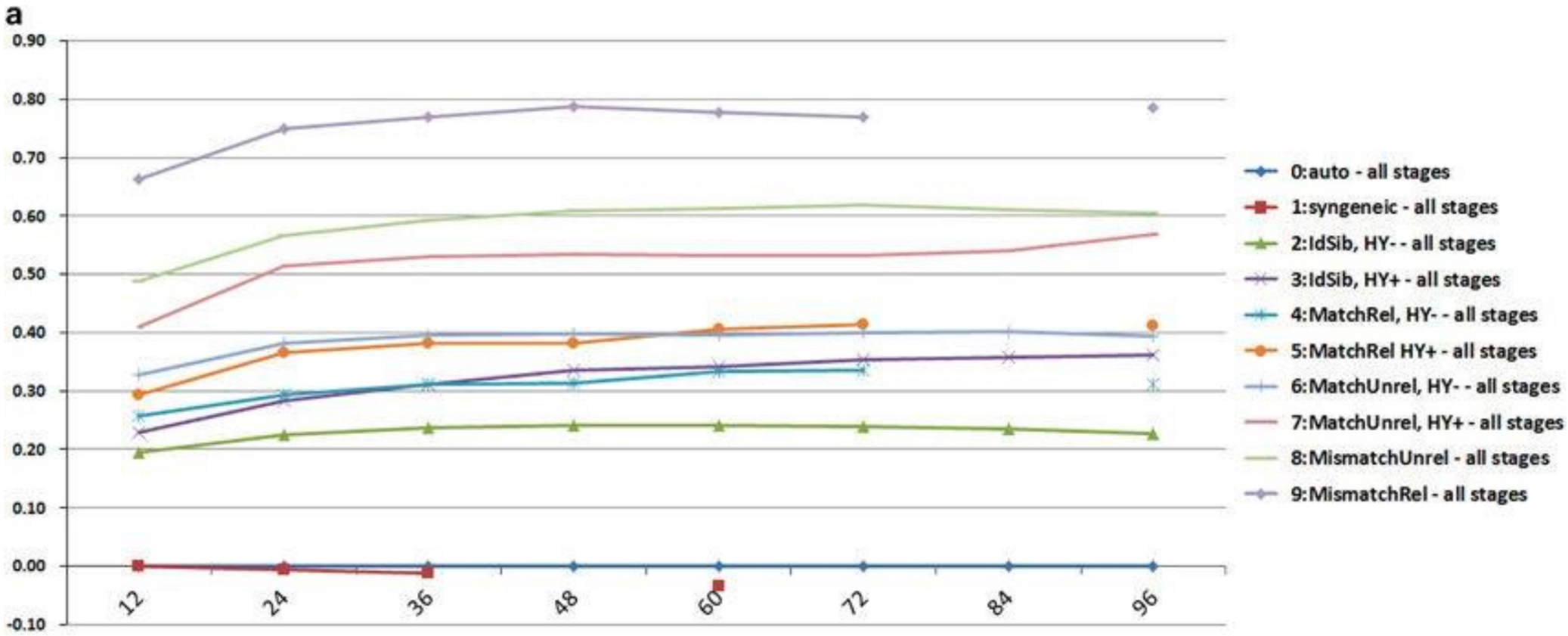
- Non genetic factors:
  - Age
  - Sex
  - Parity
  - CMV serostatus
  - Presence of donor specific antibodies in the host
  - Donor availability
  - Stem cell dose
  - Germline predisposition

- Other HLA factors:
  - DPB1

- Non HLA genetic factors:
  - KIR
  - ABO type

Dehn et al, Blood 2019 // Holtan et al JCO 2021

Donor selection: HLA disparity and NRM



Gratwohl A et al, Leukemia 2017

Donor selection: female to male

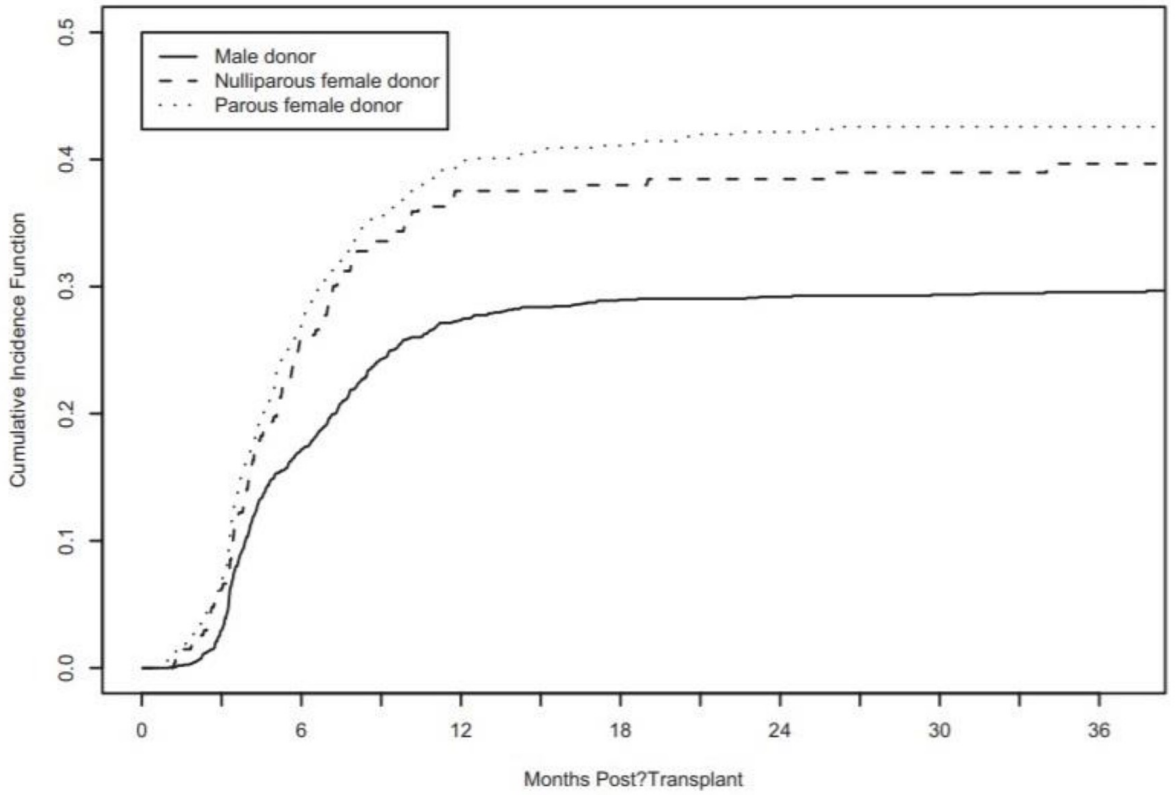
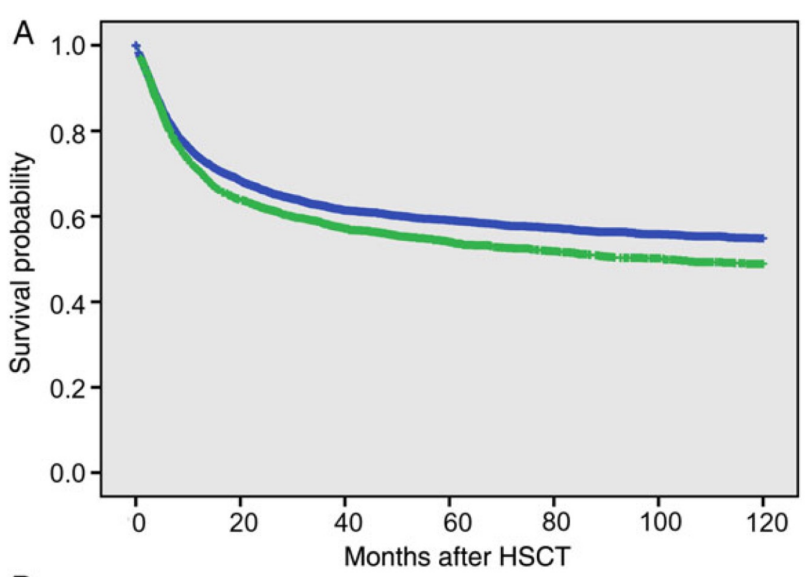


Figure 2. Cumulative incidence of chronic GVHD by donor sex/parity.

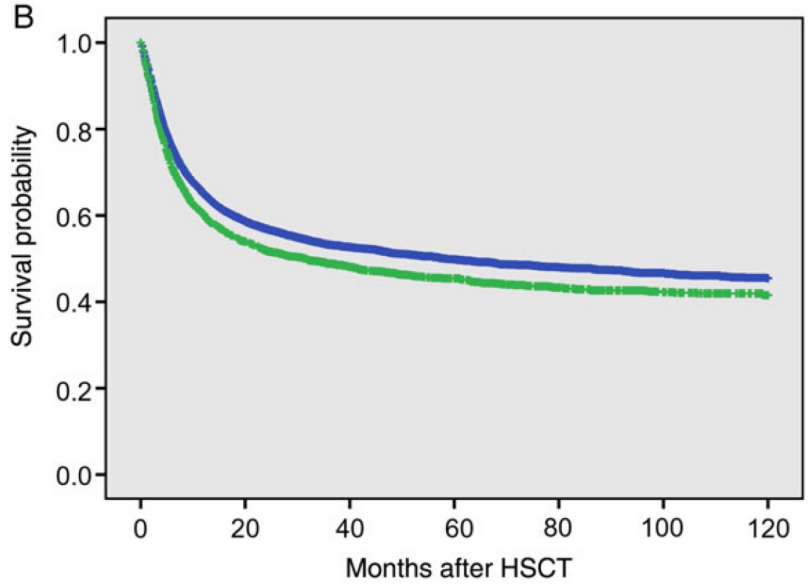
Loren A et al, BBMT 2006

Donor selection: CMV serostatus

CMV seronegative patients undergoing SCT with a CMV **seropositive** or **seronegative** donor



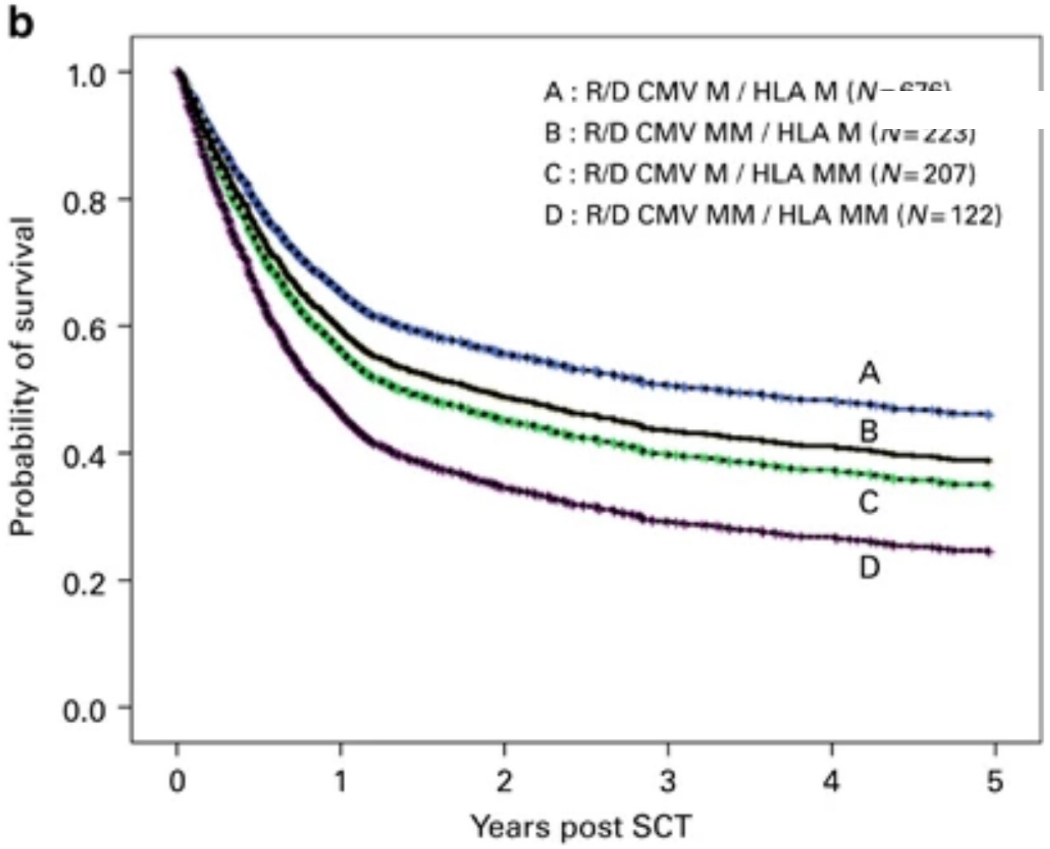
Sibling donor
p = 0,06



Unrelated donor
p = <0,0001

Ljungman et al, Clin Infect Dis 2014

Donor selection: CMV serostatus



Shaw et al, BMT 2017

Donor selection: ABO mismatch

Mismatch Type	ABO Blood Type		Potential Clinical Consequence	Etiology	Potential Interventions
	Recipient	Donor			
Major	O	A, B, AB	• Acute hemolytic episode • Delayed RBC engraftment	• Transfusion of incompatible red blood cells • Recipient anti-donor isohemagglutinins	• Red blood cell reduction of stem cell product • Therapeutic plasma exchange in recipient to reduce isohemagglutinins before transplantation (uncommon in United States) • Promote donor erythropoiesis via erythropoietin administration
Major	A	AB	• Pure red blood cell aplasia	• Loss of immature stem cells from processing with ABO antigens expressed on granulocytes and platelets	
Major	B	AB	• Delayed granulocyte and platelet engraftment		
Minor	A	O	• Acute hemolytic episode • Delayed hemolysis secondary to passenger lymphocyte syndrome	• Donor plasma with elevated isohemagglutinin titers/small blood volume recipient • Passenger lymphocytes producing isohemagglutinins	• Plasma reduction • Continual clinical monitoring between days +5 and 15 for signs/symptoms of hemolysis (including laboratory monitoring with LDH, bilirubin, CBC, DAT)
Minor	B	O			
Minor	AB	O, A, B			
Bidirectional	A	B	• Combination of major and minor consequences	• Combination of major and minor etiologies	• Combination of major and minor interventions
Bidirectional	B	A			

LDH indicates lactate dehydrogenase; DAT, direct antiglobulin test.

Booth GS et al, BBMT 2013 // Little AM JD et al, Immunogenetics 2020

Donor selection: impact of ABO mismatch?

Effect of ABO Incompatibility on Recipient Survival and Incidence of Graft-versus-Host Disease

Study Authors	Year	Survival after ABO-Incompatible HCT Transplantation			Risk of Graft-versus-Host Disease
		Major	Minor	Bidirectional	
Kimura et al. [3]	2008	Decreased	Decreased	No difference	Increased with minor or major ABO mismatch
Helming et al. [13]	2007	No difference*	No difference*	No difference*	No difference*
Erker et al. [15]	2005	No difference	Decreased	Decreased	No difference
Kim JG et al. [12]	2005	No difference	No difference	No difference	No difference
Stussi et al. [14]	2002	Decreased	No difference	No difference	Increased with minor ABO mismatch
Benjamin et al. [18]	1999	Decreased†	Decreased†	No difference	No difference with minor or major mismatch
Bacigalupo et al. [19]	1988	—	—	—	Increased with minor ABO mismatch
Benisnger et al. [41]	1982	No difference	—	—	No difference with major ABO mismatch
Buckner et al. [17]	1978	—	No difference	—	No difference with minor ABO mismatch

Booth GS et al, BBMT 2013

Donor selection

Table 2. Univariate analyses of recipient and donor factors on OS and NRM and relapse

	N	*Survival at 5 years (%) (95% CI)*	P-*value*	N	*NRM at 1 year (%) (95% CI)*	P-*value*	N	*Relapse at 5 years (%) (95% CI)*	P-*value*
Overall	1271	40.6 (38–44)	–	1236	26.5 (24–29)	–	1236	42.1 (39–45)	
HLA-match status									
10/10	933	43.1 (40–47)		905	20.3 (27–23)		905	42.1 (39–46)	
1 mismatch	254	35.6 (30–42)	0.001	247	26.1 (21–32)	0.007	247	41.5 (36–48)	0.96
>1 mismatch	84	28.4 (20–40)		84	33.4 (24–45)		84	44.1 (34–57)	
Donor age (years)									
<30	388	45.3 (40–51)	0.01	376	19.2 (16–27)	0.075	376	39.5 (35–45)	0.18
⩾30	869	38.6 (35–42)		846	27.9 (24–32)		846	43.6 (40–47)	
Recipient age (years)									
<20	248	45.7 (39–52)		248	21.1 (17–27)		248	40.2 (34–47)	
20–39	370	44.9 (40–50)	0.005	370	20.9 (17–26)	0.41	370	44.0 (39–50)	0.07
40–59	524	38.5 (34–43)		524	22.5 (19–27)		524	43.6 (39–48)	
⩾60	129	23.5 (16–33)		129	29.2 (22–39)		129	34.5 (26–45)	
Recipient/donor CMV									
Matched	883	44.1 (41–48)	<0.001	861	19.1 (17–22)	<0.001	861	42.5 (39–46)	0.61
Mismatched	345	32.2 (28–38)		332	30.4 (26–36)		332	41.9 (37–48)	
Donor sex									
Male	1022	41.1 (38–45)	0.26	989	20.9 (19–24)	0.011	989	42.0 (39–45)	0.91
Female	249	38.3 (32–45)		247	28.2 (23–35)		247	42.3 (36–49)	
Recipient/donor sex									
Other combination	1138	41.3 (38–44)	0.11	1103	21.4 (19–24)	0.018	1103	42.1 (39–45)	0.94
Male/female	133	34.8 (27–44)		133	30.4 (23–39)		133	42.2 (24–52)	
Stem cell source									
BM	580	38.9 (35–43)	0.078	561	25.0 (22–29)	0.027	561	45.2 (41–50)	0.024
PBSC	682	42.2 (38–47)		666	20.4 (18–24)		666	38.7 (35–43)	
R/D ABO matching									
Match	557	40.9 (37–46)		537	20.0 (17–23)		537	42.0 (38–47)	
Minor mismatch	310	46.5 (41–53)	0.011	303	20.5 (16–26)	0.040	303	39.8 (34–46)	0.69
Major mismatch	283	33.9 (29–40)		277	29.1 (24–35)		277	42.1 (36–49)	
Bidirectional	78	36.8 (27–50)		76	22.8 (15–35)		76	46.4 (36–60)	

Shaw et al, BMT 2017

Donor selection

Table 3. Multivariate analysis of survival and NRM

	Overall survival			*Non-relapse mortality*		
	N	*RR (95% CI)*	P-*value*	N	*RR (95% CI)*	P-*value*
HLA match						
10/10 match	878	1.00		871	1.00	
1 mismatch	239	1.21 (1.1–1.5)	0.042	239	1.24 (0.9–1.6)	0.14
>1 mismatch	77	1.43 (1.1–1.9)	0.016	83	1.59 (1.1–2.4)	0.028
Recipient/donor CMV						
Match	863	1.00		861	1.00	
Mismatch	331	1.40 (1.2–1.6)	< 0.001	332	1.63 (1.3–2.1)	< 0.001
Recipient age (years)						
< 20	221	1.00				
20–39	351	1.07 (0.8–1.4)	0.57			
40–59	497	1.26 (1.0–1.6)	0.047			
⩾60	125	1.71 (1.3–2.3)	0.001			
Previous autos						
0	1014	1.00				
>0	180	1.42 (1.2–1.8)	0.001			
Donor age, years						
< 30	372	1.00				
>30	822	1.17 (0.98–1.4)	0.078			
Era						
1996–1999	142	1.00		143	1.00	
2000–2003	421	0.84 (0.7–1.1)	0.18	418	0.57 (0.4–0.8)	0.002
2004–2007	345	0.76 (0.6–1.0)	0.049	343	0.54 (0.4–0.9)	0.002
2008–2011	286	0.77 (0.6–1.1)	0.078	289	0.60 (0.3–0.7)	0.001
Disease risk—EBMT						
Good	557	1.00				
Intermediate	444	1.37 (1.2–1.6)	< 0.001			
Poor	193	1.33 (1.1–1.7)	0.013			
Recipient/donor sex						
Other combination				1061	1.00	
Male/female				132	1.38 (0.99–1.9)	0.063

Shaw et al,
BMT 2017

Donor selection score?

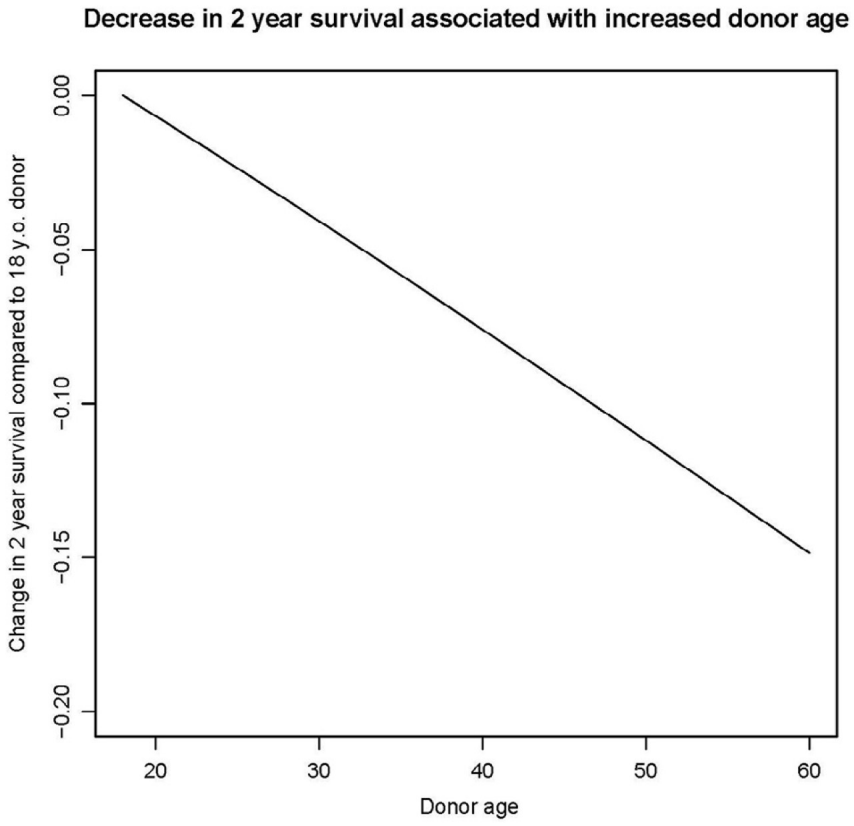
- CIBMTR analysis of **10462** 8/8 MUD transplants to identify a *Donor Selection Score:*
  - 1999-2011: 5952
  - 2012-2014: 4510
- Donor characteristics implemented:

Age	Sex
HLA DBP1	HLA DBQ1
CMV	ABO
Parity	Ethnicity

Shaw B et al, BBMT 2018

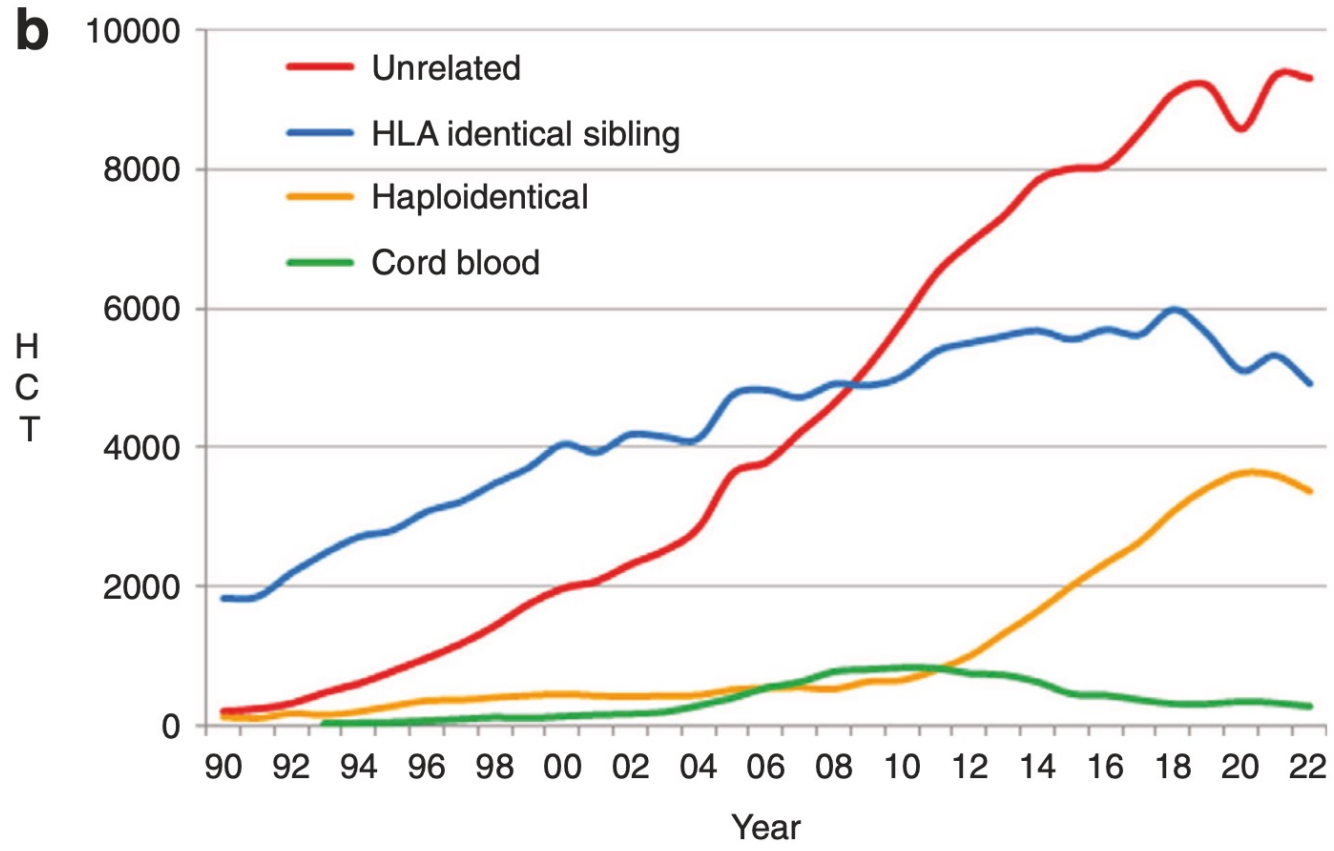
Donor selection score?

- Results first cohort (1999-2011)*:*
  - 3 donor factors correlate negatively with outcome
    - HLA DBP1 matching
    - Older age
    - CMV mismatching for CMV+ recipients
- Results second cohort (2012-2014):
  - Only age has a negative impact on outcome



Shaw B et al, BBMT 2018

Donor selection: EBMT activity 2022



Passweg JR et al, BMT 2024

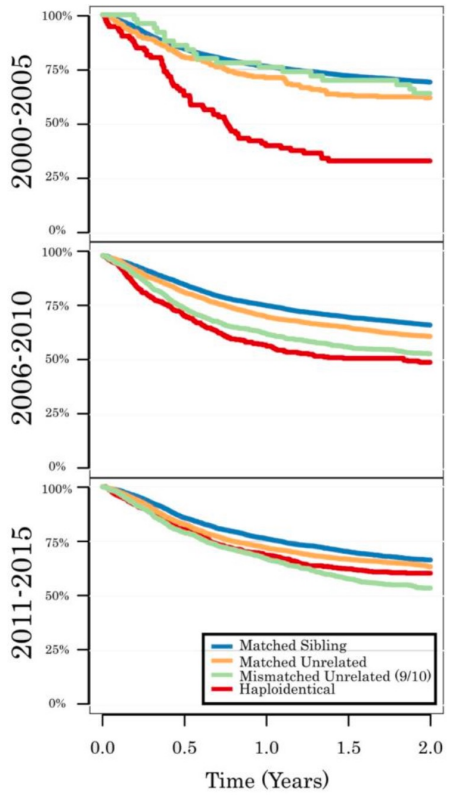
Donor selection: haplo

- EBMT-ALWP analyzed transplantation outcome by **Disease Risk** and **Donor Type** over **Time**
- **>100000** allogeneic stem cell transplants included
- 2000-2015:
  - 2000-2005: 25%
  - 2006-2010: 33%
  - 2011-2015: 42%
- Reference: low risk disease transplanted in 2011-2015
- Cord blood transplants were excluded

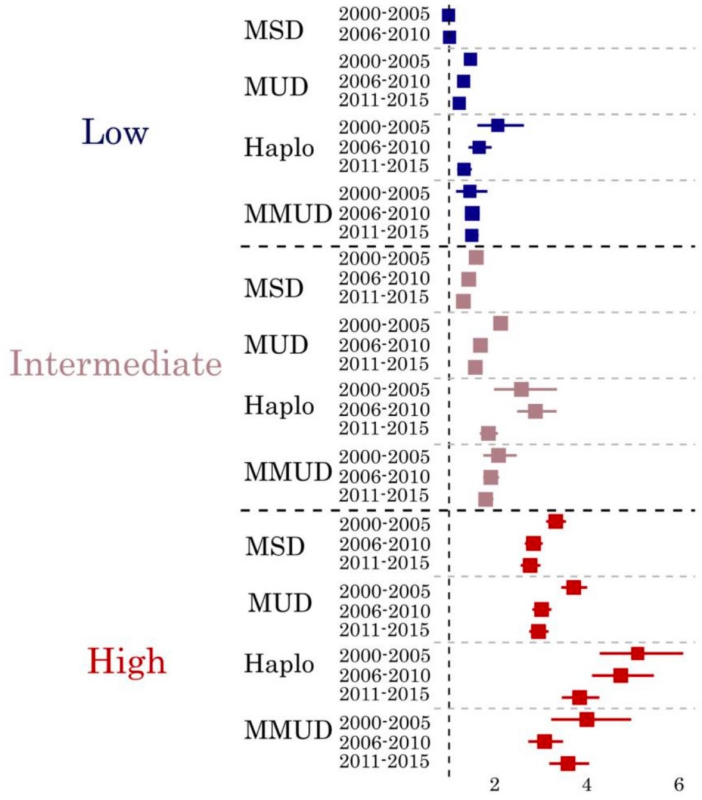
Shouval R et al, Lancet Haem 2019

Donor Type

Probability for overall survival of low risk disease



Hazard ratio for overall survival



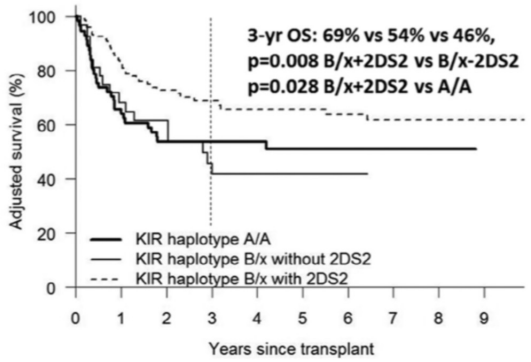
Shouval R et al, Lancet Haem 2019

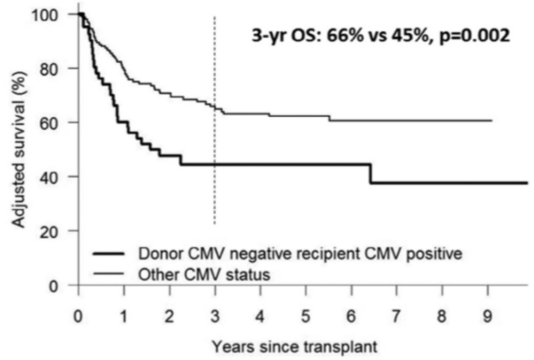
Haplo donors: do the same rules apply?

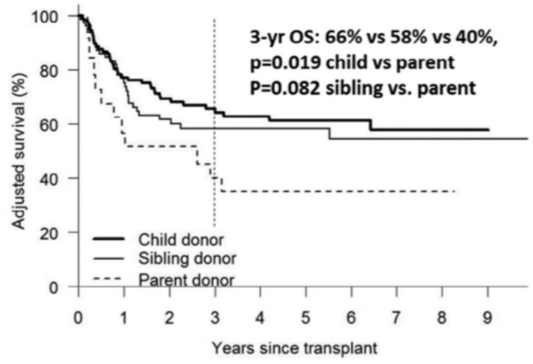
- Single center analysis
- 208 haplo transplants
- Donor variables analyzed:
  - Age
  - Sex
  - Relationship
  - CMV status
  - ABO compatibility
  - HLA disparity
  - KIR mismatch

Solomon R et al, BBMT 2018

Haplo donors: do the same rules apply?







Solomon R et al, BBMT 2018

Haplo donors: donor selection score

Table 4
Proposed Scoring System for Donor Selection

DonorVariable		OS		DFS		Relapse	
		β	Score	β	Score	β	Score
Relation	Child	−1.12	3	−1.23	3	−1.31	3.25
	Sibling	−.81	2	−.84	2	−.98	2.5
CMV serostatus	D CMV+ or R CMV−	−.93	2.5	−.91	2.5	−.71	1.75
HLA ×/10 mismatch (GVH)	≥4 mismatch	−.05	0	−.51	1.5	−1.23	3
HLA-DR (GVH)	Mismatch GVH	−1.00	2.5	−.58	1.5	.06	0
HLA-DP	Nonpermissive mismatch	−.63	1.5	−.82	2	−1.33	3.25
KIR R-L	Mismatch	−.47	1	−.56	1.5	−.89	2.25
KIR Haplotype	B/× with 2DS2	−.92	2.5	−.87	2	−.84	2
	A/A	−.08	0	−.08	0	−.45	1

β, regression coefficient (e^{β} = HR), indicates the relative risk of each donor variable on a certain outcome. For each variable a score (approximately 2.5 × [-β]) is determined and indicates proportional protective effect between various donor variables. To pick the best donor to optimize survival or relapse reduction, respectively, add up points and choose donor with highest score.

Solomon R et al, BBMT 2018

EBMT Haplo donor selection consensus criteria

T cell depleted haploidentical transplants	T cell replete haploidentical transplants
-No DSAs (MFI < 1000)	-No DSAs (MFI < 1000)
-NK cell alloreactive donor	-Younger donor over older donor
-Younger donor over older donor	-Male donor for a male recipient
-Male donor for a male recipient	-Sibling or offspring donor over parent donor
-First degree relative over second degree HLA half-matched donor	-Between parent donors, father is preferred over mother donor
-Between parent donors, mother is preferred over father	-ABO matched is preferred to minor ABO mismatch to major ABO mismatched donor
-ABO matched donor	-Donor with KIR ligand match for a recipient of HHCT[a]
-CMV seropositive donor for CMV seropositive recipients	-First degree relative over second degree HLA half-matched donor[a]
	-Donor with NIMA mismatch over NIPA mismatch for a recipient of HHCT[a]

DSA donor-specific anti-HLA antibodies, *NK* natural killer cells, *HHCT* haploidentical hematopoietic cell transplantation, *NIMA* non-inherited maternal antigens, *ABO* blood group

[a]Conclusive data available for the TCR Haploidentical transplants with GCSF-primed bone marrow and enhanced GVHD prophylaxis (Beijing protocol)

Ciura et al, BMT 2020

Donor selection in practice

- Related donor: transplant center
- Unrelated donor registries:
  - Marrow Donor Program Belgium (MDP-B)
  - World Marrow Donor Association (WMDA)
- Quality assurance:
  - MDP-B – JACIE – WMDA
  - SAE reporting
- Standards for donor suitability evaluation:
  - Primum non nocere!

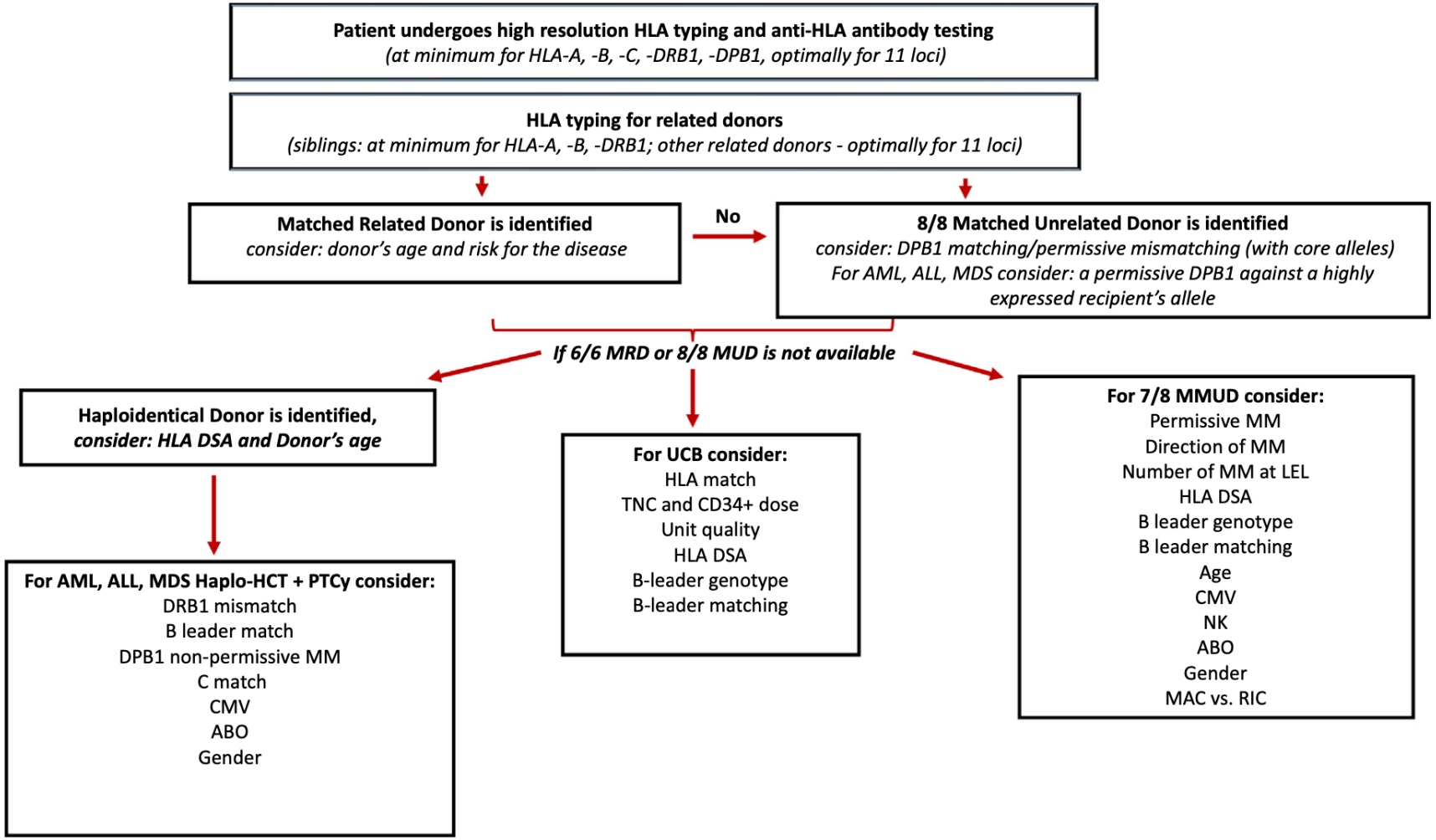
Donor suitability

- Donor risk:
  - Minimise any avoidable risk
  - Stem cell collection requires treatment of a healthy individual:
    - G-CSF and apheresis if peripheral blood stem cell collection
    - General anesthesia if bone marrow stem cell collection
  - Screen for medical conditions that increase donor risk
  - Related donor:
    - Donor advocate!
    - Evaluation by team independent of transplant team
  - Donor follow-up: MDP-B, JACIE, EBMT, WMDA

Donor suitability

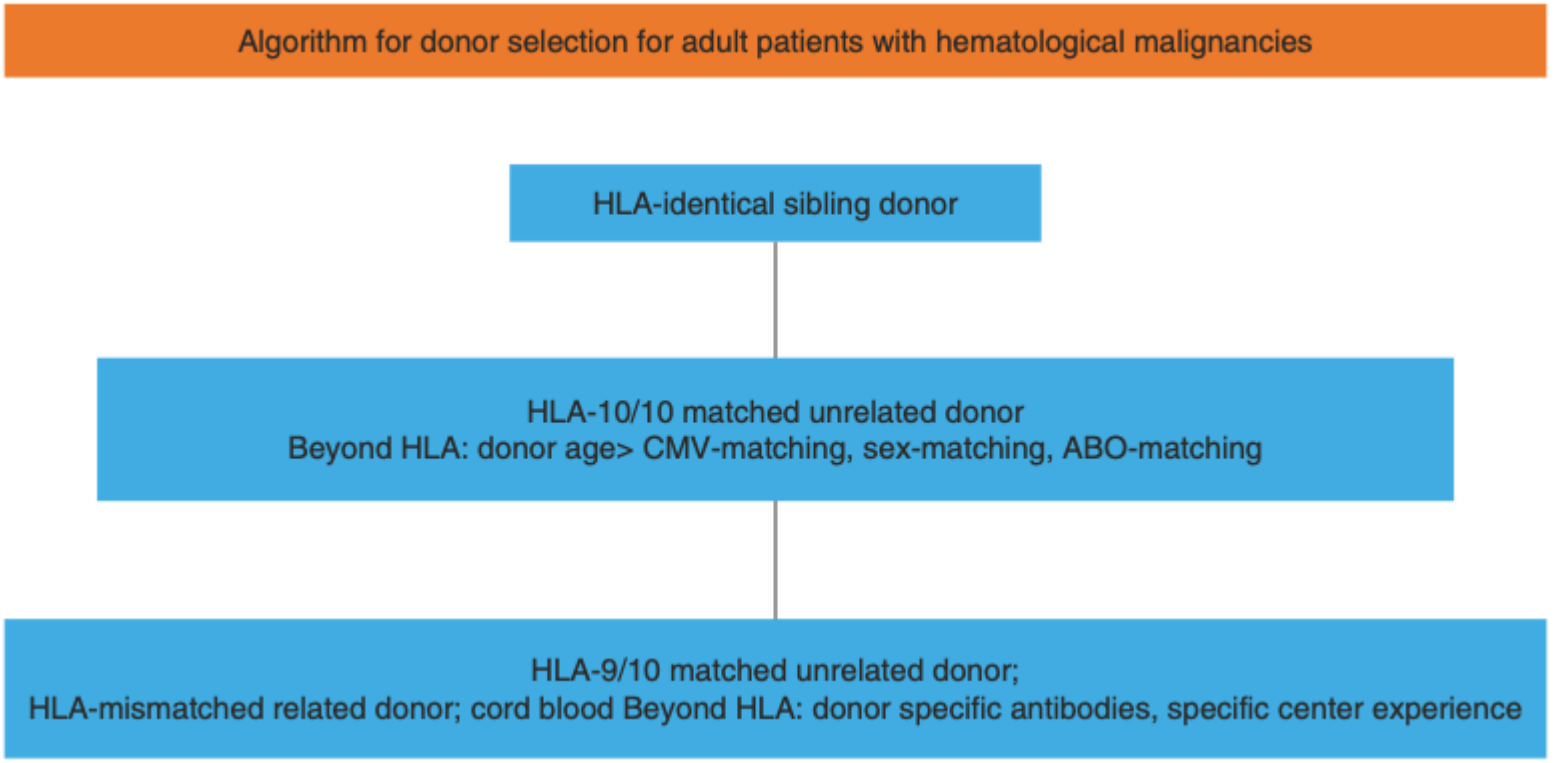
- Recipient risk:
  - alloSCT is often only possibility for cure/long term remission
  - Informed risk-benefit judgement
  - Screen donor for transmissible agents:
    - Infectious:
      - viral: HIV, hepatitis, HTLV
      - prion diseases
    - Auto-reactive lymphocytes:
      - Systemic lupus erythematosus
      - Multiple sclerosis
      - Inflammatory bowel disease

Donor selection flow chart



Timofeeva O et al, Human Immunology 2022

Donor selection flow chart



Back to the cases

Mary Jane	Miranda	Daniel
25 years old AML CR1 MRD+	64 years old MDS-IB2	53 years old Relapsed mantle cell lymphoma Prior autologous SCT
		
2 HLA id siblings: *1 brother (23y)* *1 sister (35y)* *1 haplo id brother*	*1 sibling - unfit* *No MUD available* *2 children*	*1 sib[illegible] match* CAR T Or MUD

Conclusion

- Main indication for autoSCT is myeloma 1st line
- Main indication for alloSCT is acute leukemia
- Indication for transplant depends on:
  - Disease characteristics
  - Donor type available
  - Patient characteristics
- Donor choice main factors:
  - HLA matching
  - Donor age
  - CMV mismatch?
  - ABO matching?