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International Quality Expertise

Histocompatibility & Immunogenetics

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Interpretive Educational Scheme (iED)
Clinical Scenario 2/2022 – Haematopoietic Stem Cell Transplantation

Dispatched on 30th August 2022

Summary of Results

A total of 39 responses were received, 14 from UK & Ireland (UK&I) based laboratories and 25 from Rest of the World (RoW) based laboratories.

Background Information

Patient KW is 47-year-old male who has been diagnosed with Myelodysplastic Syndrome (MDS). His HLA type is given below:

Patient HLA Type		
HLA-A	A*01:01	A*26:01
HLA-B	B*07:02	B*38:01
HLA-C	C*07:02	C*12:03
HLA-DRB1	DRB1*11:01	DRB1*15:01
HLA-DQB1	DQB1*03:01	DQB1*06:02
HLA-DPB1	DPB1*04:01	-

Patient KW: Blood group O+, CMV+

The patient has 2 siblings who have been HLA typed. The results are shown below:

Sibling 1 - Sister 49 years				**Sibling 2** - Brother 52 years		
HLA-A	A*01:01	A*02:01		HLA-A	A*01:01	A*02:01
HLA-B	B*07:02	B*44:02		HLA-B	B*08:01	B*44:02
HLA-C	C*05:01	C*07:02		HLA-C	C*05:01	C*07:01
HLA-DRB1	DRB1*01:01	DRB1*11:01		HLA-DRB1	DRB1*01:01	DRB1*04:01
HLA-DQB1	DQB1*03:01	DQB1*05:01		HLA-DQB1	DQB1*03:01	DQB1*05:01
HLA-DPB1	DPB1*04:01	-		HLA-DPB1	DPB1*03:01	DPB1*04:01

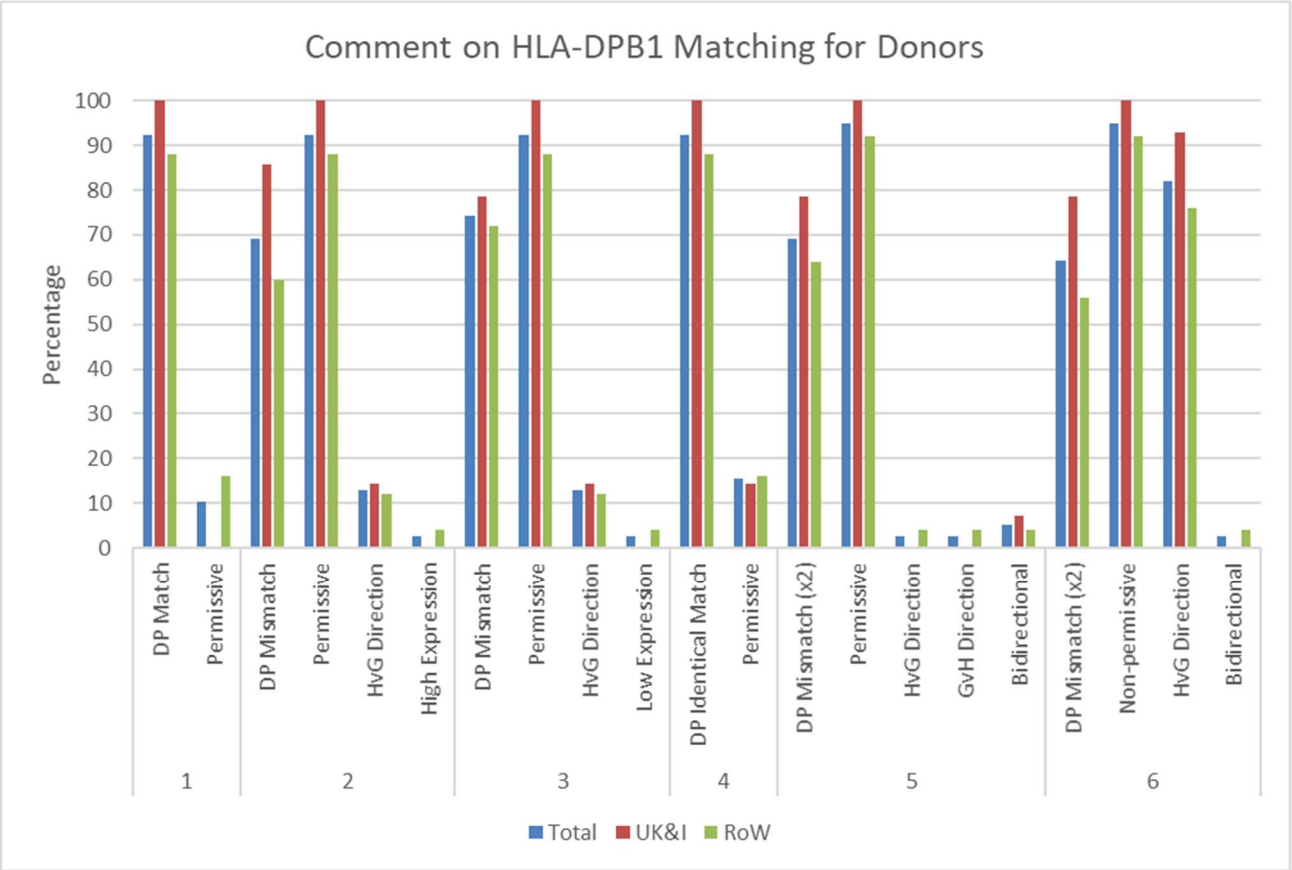
**Mismatches have been highlighted in red*

An search for an unrelated donor was also carried out and confirmatory samples were requested from the following donors:

Donor Number and Registry	Sex	Age	Blood group	CMV	HLA-A	HLA-B	HLA-C	HLA-DRB1	HLA-DQB1	HLA-DPB1
Patient	***M***	***47***	***O+***	***Pos***	***01:01 26:01***	***07:02 38:01***	***07:02 12:03***	***11:01 15:01***	***03:01 06:02***	***04:01***
Donor 1 Germany	M	23	A+	neg	01:01 26:01	07:02 38:01	07:02 12:03	11:01 15:01	03:01 06:02	04:01
Donor 2 Germany	M	27	A+	pos	01:01 26:01	07:02 38:01	07:02 12:03	11:01 15:01	03:01 06:02	01:01 04:01
Donor 3 Austria	M	23	B+	pos	01:01 26:01	07:02 38:01	07:02 12:03	11:01 15:01	03:01 06:02	02:01 04:01
Donor 4 UK	F	23	O+	pos	01:01 26:01	07:02 38:01	07:02 12:03	11:01 15:01	03:01 06:02	04:01
Donor 5 UK	M	47	O+	pos	01:01 26:01	07:02 38:01	07:02 12:03	11:01 15:01	03:01 06:02	01:01 02:01
Donor 6 Germany	M	33	O+	pos	01:01 26:01	07:02 38:01	07:02 12:03	11:01 15:01	03:01 06:02	03:01 09:01

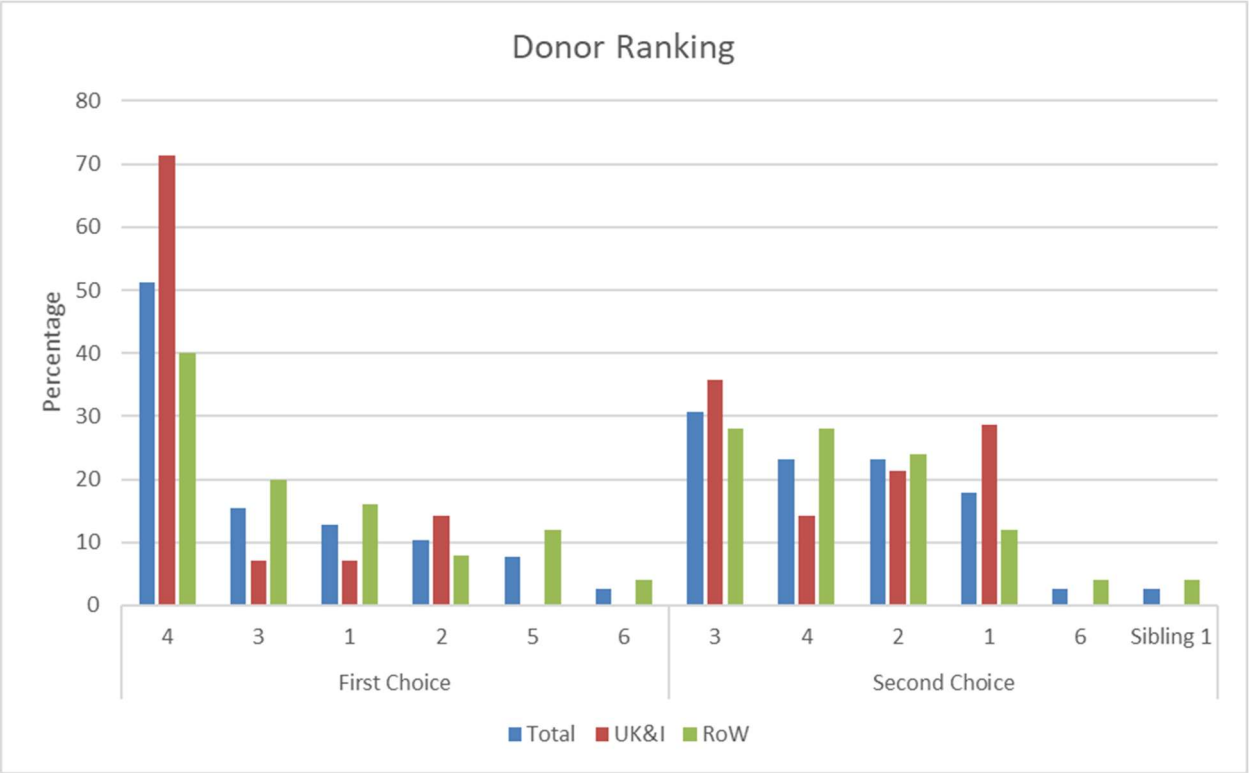
1.1 Comment on the HLA-DPB1 matching for each unrelated donor:

Donor ID	Comment on DP Matching	Total		UK&I		RoW	
		Number	%	Number	%	Number	%
1	**DP Identical Match**	36	**92**	14	**100**	22	**88**
	Permissive	4	**10**	0	**0**	4	**16**
2	**DP Mismatch**	27	**69**	12	**86**	15	**60**
	Permissive	36	**92**	14	**100**	22	**88**
	HvG Direction	5	**13**	2	**14**	3	**12**
	High Expression	1	**3**	0	**0**	1	**4**
3	**DP Mismatch**	29	**74**	11	**79**	18	**72**
	Permissive	36	**92**	14	**100**	22	**88**
	HvG Direction	5	**13**	2	**14**	3	**12**
	Low Expression	1	**3**	0	**0**	1	**4**
4	**DP Identical Match**	36	**92**	14	**100**	22	**88**
	Permissive	6	**15**	2	**14**	4	**16**
5	**DP Mismatch (x2)**	27	**69**	11	**79**	16	**64**
	Permissive	37	**95**	14	**100**	23	**92**
	HvG Direction	1	**3**	0	**0**	1	**4**
	GvH Direction	1	**3**	0	**0**	1	**4**
	Bidirectional	2	**5**	1	**7**	1	**4**
6	**DP Mismatch (x2)**	25	**64**	11	**79**	14	**56**
	Non-permissive	37	**95**	14	**100**	23	**92**
	HvG Direction	32	**82**	13	**93**	19	**76**
	Bidirectional	1	**3**	0	**0**	1	**4**



1.2 Based on the information provided please rank the top two donors, from the related and unrelated donors available, in order of preference and outline your reasons.

Priority	Donor ID	Total		UK&I		RoW	
		Number	%	Number	%	Number	%
First Choice	4	20	51	10	71	10	40
	3	6	15	1	7	5	20
	1	5	13	1	7	4	16
	2	4	10	2	14	2	8
	5	3	8	0	0	3	12
	6	1	3	0	0	1	4
Second Choice	3	12	31	5	36	7	28
	4	9	23	2	14	7	28
	2	9	23	3	21	6	24
	1	7	18	4	29	3	12
	6	1	3	0	0	1	4
	Sibling 1	1	3	0	0	1	4



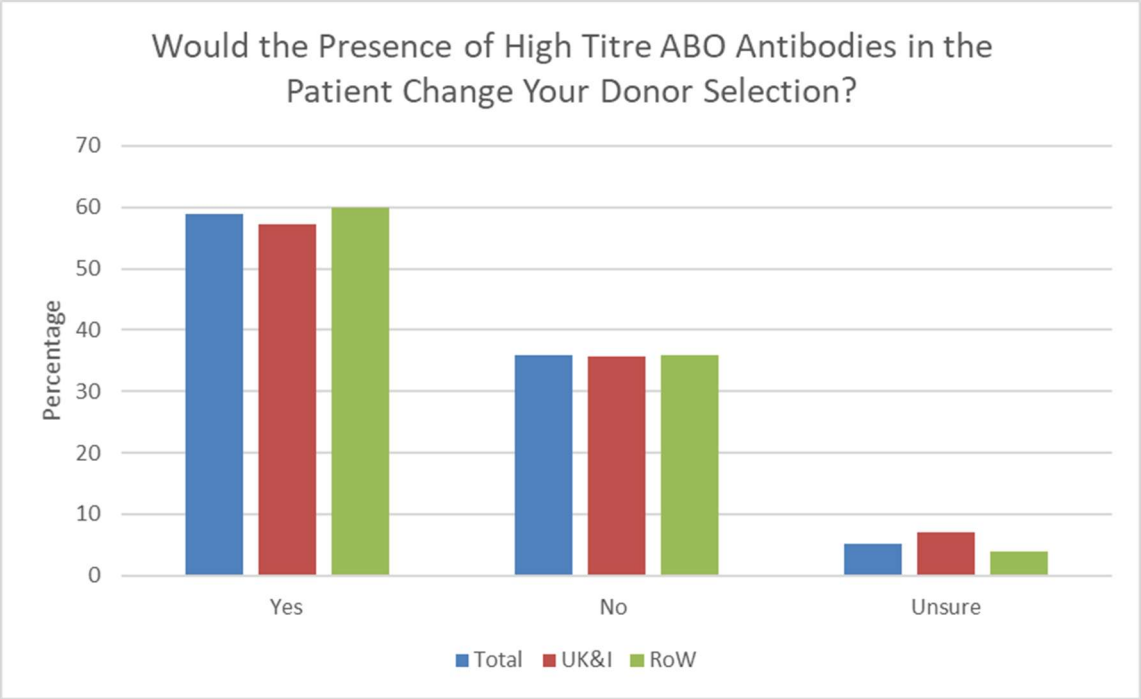
Donor ID	Reasons for Selection									
	12/12 Match	11/12 Match	10/10 Match	Permissive DP	ABO Match	CMV Match	Young	Male	Haploidentical	Reliable Registry
Donor 1	✓			✓		✓	✓	✓		✓
Donor 2		✓	✓	✓		✓	✓	✓		✓
Donor 3		✓	✓	✓		✓	✓	✓		
Donor 4	✓				✓	✓	✓			✓
Donor 5				✓	✓	✓		✓		
Donor 6					✓	✓	✓	✓		
Sibling 1									✓	

The clinical team inform you that the patient has high titre anti-A and anti-B antibodies:

Antibody	Titre End Point
Anti A	1 in 2048
Anti B	1 in 1024

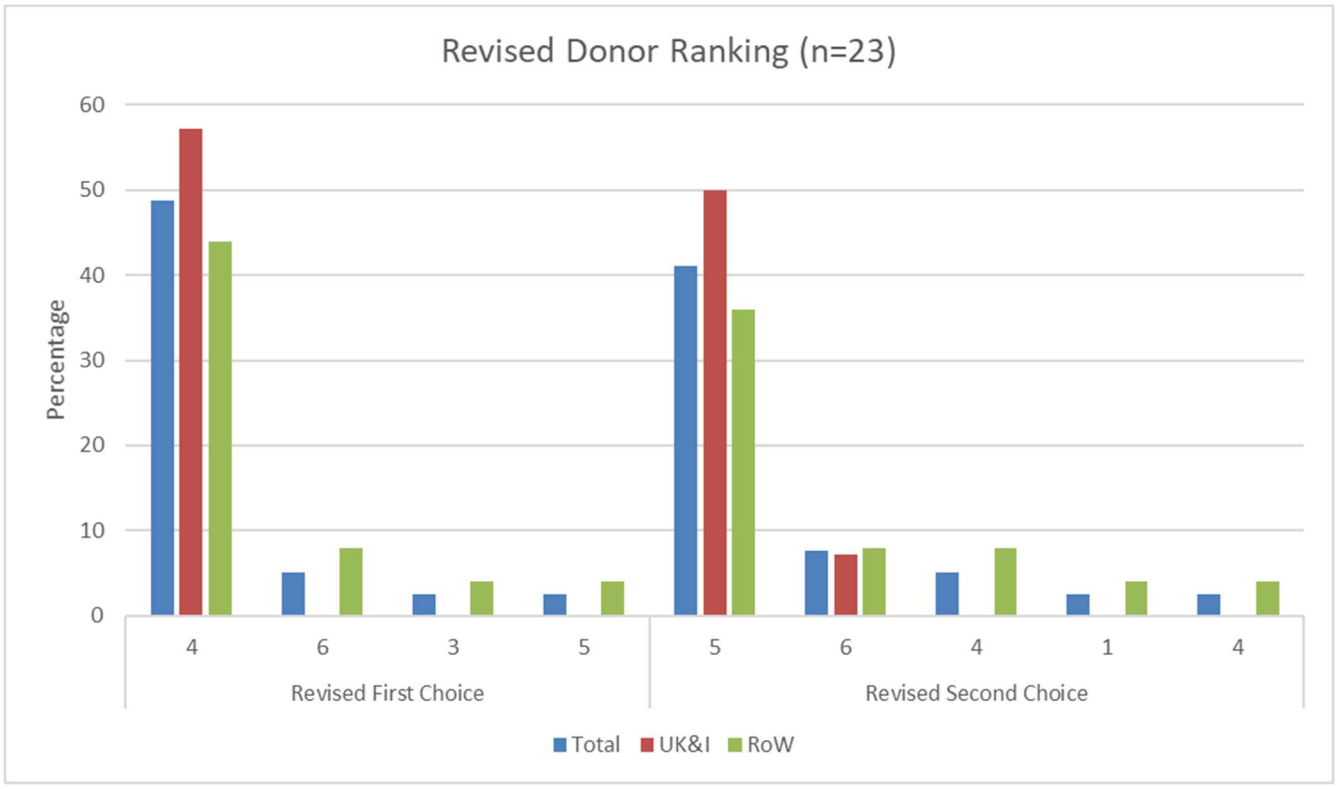
1.3 Would this change the donors you selected?

	Total		UK&I		RoW	
Option	**Number**	**%**	**Number**	**%**	**Number**	**%**
Yes	23	**59**	8	**57**	15	**60**
No	14	**36**	5	**36**	9	**36**
Unsure	2	**5**	1	**7**	1	**4**



1.4 If yes, then please re-rank the top two donors in order of preference and outline your reasons.

59% Changed Selection	Donor ID	Total		UK&I		RoW	
		Number	**%**	**Number**	**%**	**Number**	**%**
Revised First Choice	**4**	19	**49**	8	**57**	11	**44**
	6	2	**5**	0	**0**	2	**8**
	3	1	**3**	0	**0**	1	**4**
	5	1	**3**	0	**0**	1	**4**
Revised Second Choice	**5**	16	**41**	7	**50**	9	**36**
	6	3	**8**	1	**7**	2	**8**
	4	2	**5**	0	**0**	2	**8**
	1	1	**3**	0	**0**	1	**4**
	4	1	**3**	0	**0**	1	**4**



Donor ID	Reasons for Revised Donor Selection								
	12/12 Match	10/12 Match	Permissive DP	Non-Permissive DP (HvG)	ABO Match	CMV Match	Young	Male	Titre Anti-A Antibodies
Donor 1									✓
Donor 2									✓
Donor 3			✓			✓	✓	✓	
Donor 4	✓				✓	✓	✓		
Donor 5		✓	✓		✓	✓			
Donor 6		✓		✓	✓	✓	✓	✓	

You are then given the results of further infectious disease marker testing for both the patient and the unrelated donors:

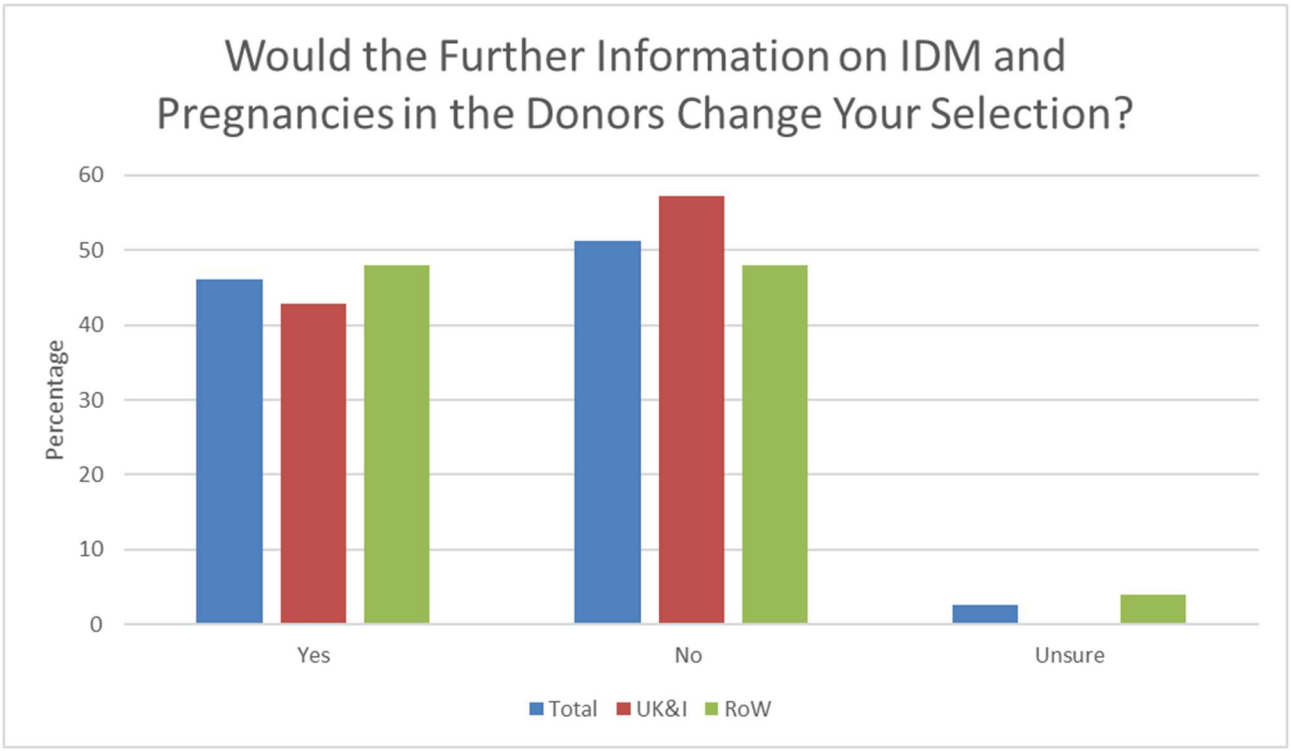
Patient KW: Blood group O+, CMV+, EBV+, HSV+

Donor Number and Registry	Sex	Age	Blood group	Cytomegalo-virus (CMV)	Hepatitis B Surface Antigen (HBsAg) Screen	Epstein-Barr Virus (EBV)	Human Immuno-deficiency Virus (HIV)	Herpes Simplex Virus (HSV)
Donor 1 Germany	M	23	A+	negative	negative	positive	negative	positive
Donor 2 Germany	M	27	A+	positive	negative	negative	negative	positive
Donor 3 Austria	M	23	B+	positive	negative	positive	negative	positive
Donor 4 UK	F	23	O+	positive	negative	positive	negative	negative
Donor 5 UK	M	47	O+	positive	negative	positive	negative	positive
Donor 6 Germany	M	33	O+	positive	negative	positive	negative	positive

You are also told that Donor 4 has had two pregnancies.

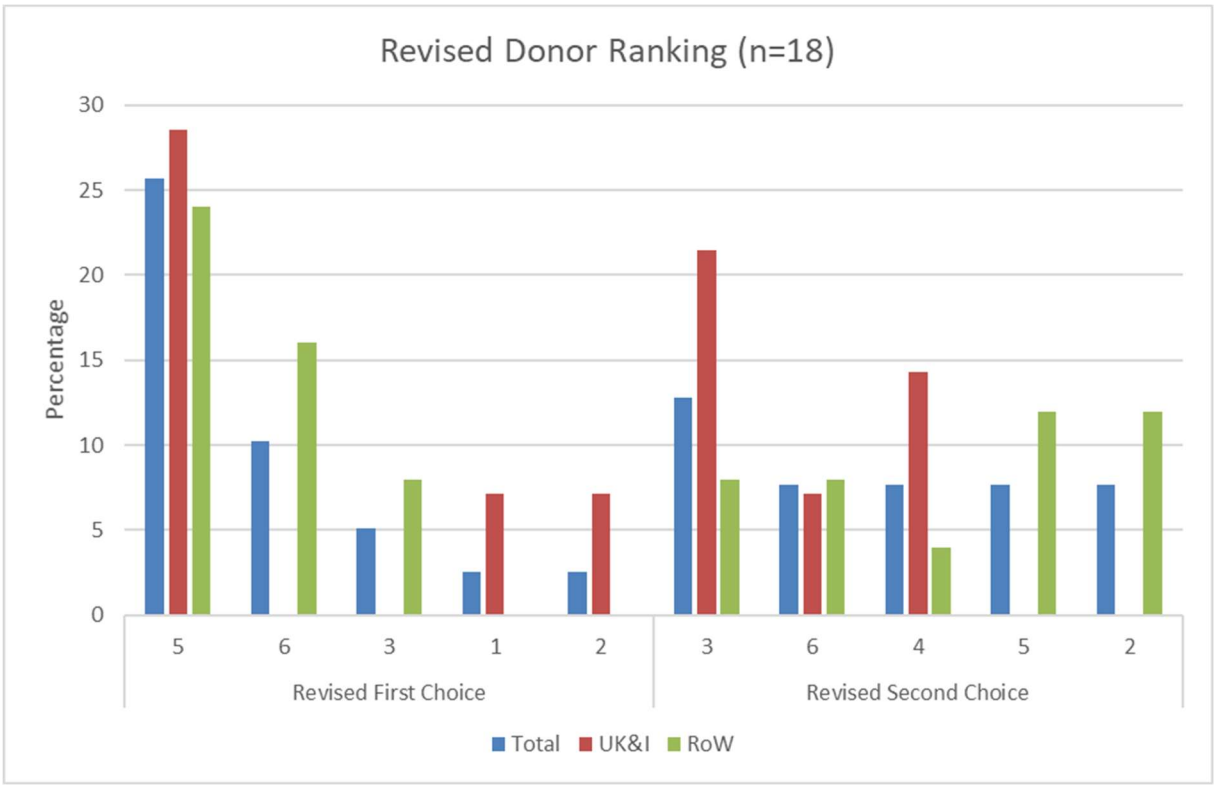
2.1 Would this change your answer given above (in either 1.2 or 1.4)?

	Total		UK&I		RoW	
Option	**Number**	**%**	**Number**	**%**	**Number**	**%**
Yes	18	**46**	6	**43**	12	**48**
No	20	**51**	8	**57**	12	**48**
Unsure	1	**3**	0	**0**	1	**4**



2.2 If yes, then please re-rank the top two donors in order of preference and outline your reasons.

46% Changed Selection	Donor ID	Total		UK&I		RoW	
		Number	%	Number	%	Number	%
Revised First Choice	5	10	26	4	29	6	24
	6	4	10	0	0	4	16
	3	2	5	0	0	2	8
	1	1	3	1	7	0	0
	2	1	3	1	7	0	0
Revised Second Choice	3	5	13	3	21	2	8
	6	3	8	1	7	2	8
	4	3	8	2	14	1	4
	5	3	8	0	0	3	12
	2	3	8	0	0	3	12



Donor ID	Reasons for Revised Donor Selection												
	12/12 Match	11/12 Match	10/12 Match	Permissive DP	Non-Permissive DP (HvG)	ABO Match	CMV Match	Young	Male	EBV Matched	HSV Matched	Titre Anti-A Antibodies	Comments
Donor 1	✓							✓	✓				
Donor 2		✓		✓			✓	✓	✓				Increased risk of EBV reactivation but as we T cell deplete we would closely monitor and treat prophylactically.
Donor 3		✓		✓				✓	✓	✓	✓	✓	Use plasma exchange to reduce anti-B titre. Use Letermovir for CMV prophylaxis.
Donor 4	✓					✓	✓	✓			✓		HSV mm so be mindful of reactivation, treat with prophylaxis Two previous pregnancies.
Donor 5			✓	✓		✓				✓	✓		
Donor 6			✓		✓	✓	✓			✓	✓		

Patient KM was transplanted with an unrelated donor on 22/03/2021. Post-transplant the patient has had some problems with persistent infections which have required readmission.

The lab has been receiving regular samples for chimerism testing. The results of peripheral blood percentage donor chimerism are shown in the table below:

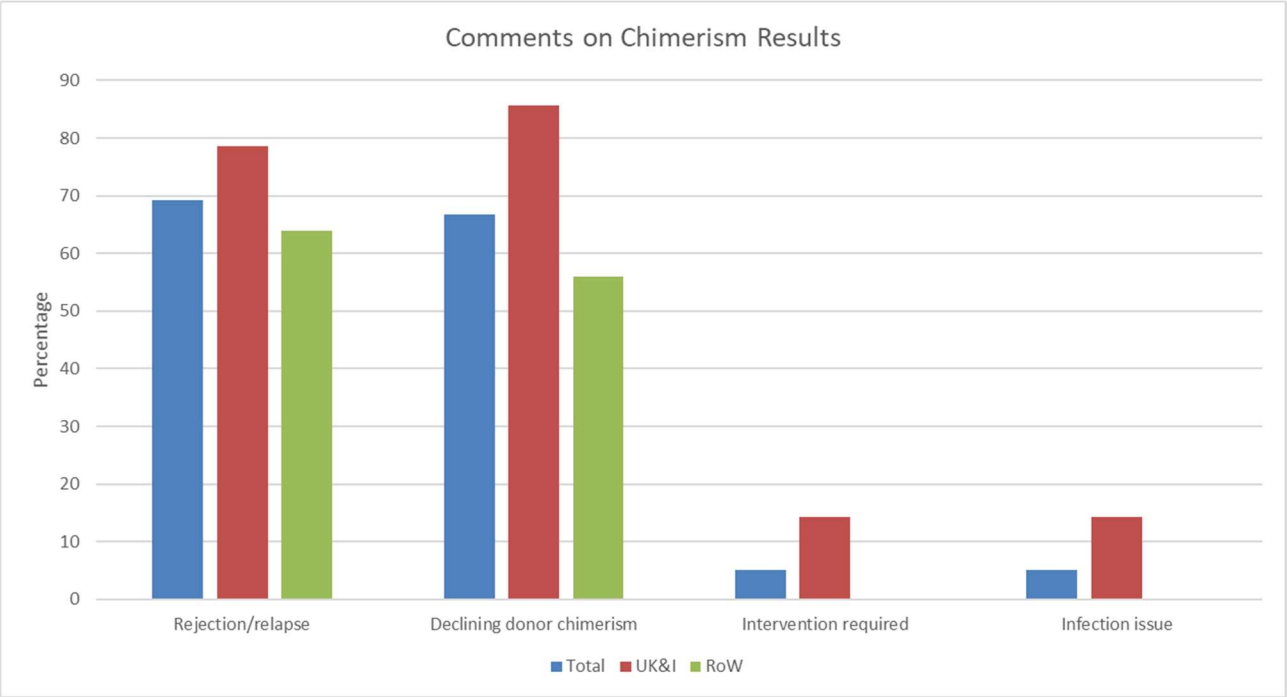
Date Taken	Whole Blood	T Cells	Myeloid	B cells
21/04/2021	92%	79%	96%	90%
04/05/2021	98%	NT*	NT*	NT*
10/05/2021	94%	79%	94%	99%
06/06/2021	63%	62%	70%	94%
04/07/2021	35%	52%	40%	74%

**Not tested – cell linage separation could not be done due to insufficient cells*

3.1 Please comment on these results.

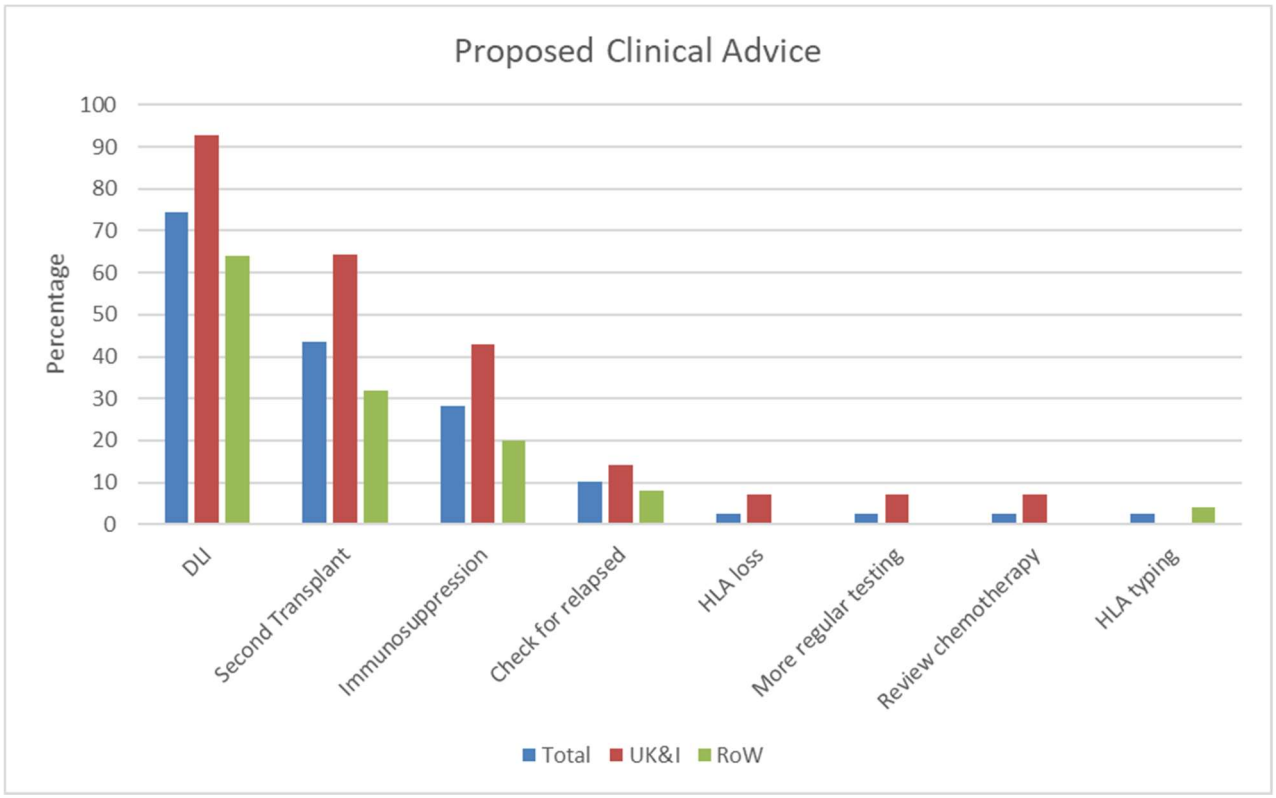
Comment on Chimerism Testing	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Rejection/relapse	27	**69**	11	**79**	16	**64**
Declining donor chimerism	26	**67**	12	**86**	14	**56**
Intervention required	2	**5**	2	**14**	0	**0**

Infection issue	2	**5**	2	**14**	0	**0**



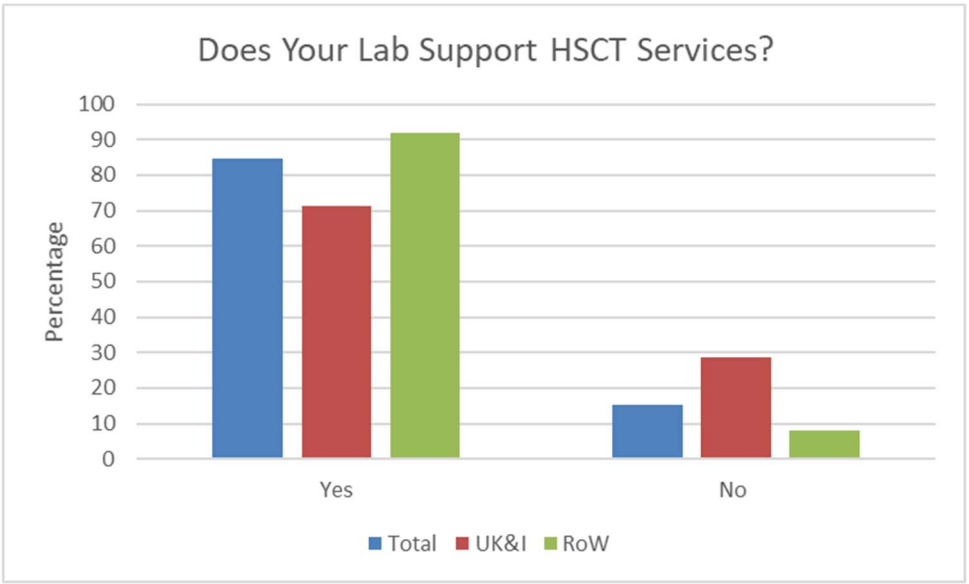
3.2 What clinical advice you would offer?

Clinical Advice	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Donor Lymphocyte Infusion	29	**74**	13	**93**	16	**64**
Second Transplant	17	**44**	9	**64**	8	**32**
Decrease Immunosuppression	11	**28**	6	**43**	5	**20**
Check if MDS has relapsed or transformed	4	**10**	2	**14**	2	**8**
HLA loss	1	**3**	1	**7**	0	**0**
More regular testing	1	**3**	1	**7**	0	**0**
Review chemotherapy	1	**3**	1	**7**	0	**0**
Perform verification HLA typing	1	**3**	0	**0**	1	**4**



4.0 Does your service support HSCT?

	Total		UK&I		RoW	
Option	**Number**	**%**	**Number**	**%**	**Number**	**%**
Yes	33	**85**	10	**71**	23	**92**
No	6	**15**	4	**29**	2	**8**



5.0 Any further comments on the scenario?

- Providing more information such as other laboratory results will be very helpful specially when giving clinical advice.
- Patient weight – it will help in donor selection to include or exclude potential female donors. Patient HLA antibody profile – it will help in donor selection in case of selecting HLA mismatched donor.
- Thought provoking scenario creating some good discussion about donor selection.
- It is interesting to see the selection of IDMs highlighted in the current IED. It would be interesting to note how many labs would use all these IDM results in the selection of the optimal unrelated donor option. Also, it would have been useful to know the stem cell source to be used for transplant as this would increase or decrease the importance of ABO matching. Major ABO incompatibility is not a contraindication for HSCT at our local Transplant Centre, even in the presence of high titres.
- Priority is given to donors who are CMV matched over DPB1 match or permissive mismatch. Young males donors also preferred. Donor selection is often completed before an extended virology report is received. Transplant Centre would not change donor choice based on this information. The only exception is for patients where EBV is relevant to the primary disease.
- Our Laboratory does not perform chimerism testing or interpretation.
- 1.4) Reference to anti-A and anti-B Ab titres in EBMT handbook. We would not automatically have access to anti-A and anti-B Ab titre information for HPCT donor selection in this lab, although we consider blood group matching and avoiding major ABO mismatch where possible as per the BSHI guidelines for HPCT donor selection.
  2.2) As a lab, we follow BSHI guidelines for HLA matching and donor selection of HPCT, with no reference to virology for selection other than CMV. We excluded the CMV negative donor (donor 1) on this basis. We are aware of the risk of EBV related PTLD post HPCT and that the risk of EBV-PTLD is related to the degree of T cell depletion and selection of suitable donors but this is not routine practice in our laboratory and is a clinical decision.
- Our approach is constantly evolving. For example, due to experience of post-transplant complications attributed to infectious disease, our strategy is becoming increasingly focused on matching according to virology in addition to HLA and other factor.
- The sibling haplo-identical donors were not considered in the top ranking donors as our centre will not consider these if a 12/12 or 10/10 DP permissive unrelated donor is available for both adult and paediatric patients.
- Donor 4 was considered as a second choice as ordinarily using a multiparous donor poses the risk of increased GvHD.
- In a real life situation additional information - such as accredited registry status, weight/size of donors, availability of donors, HLA Abs/potential DSA in recipient - would be available and useful.
- Good Scenario. Some elements of the patient's treatment, which may impact donor selection, would be within the remit of the clinical team rather than H&I lab, e.g. donor/recipient virological mismatching for HSV.
- Many of these decisions would be made through discussions with our Transplant Centres as they have preferences with regards to the level of risk they are willing to take in relation to ABO mismatching, HSV/EBV mismatching and use of multiparous donors.
- The limitations of our laboratory are that we are not directly involved in managing the patients and cannot monitor the other laboratory investigations which are performed at their respective hospitals.
- For the choice of donor we would also take into account the HLA antibody status of the patient, this information was missing in the case. It is possible that antibodies are present in the patient directed against the mismatched HLA-DPB1 molecule of the donor. Furthermore the CMV status and the blood group of sibling 1 was missing, this information is relevant for the donor selection. For question 1.3 we filled in 'unsure' because we do not perform this test ourselves and therefore we cannot interpret the data.
- We use supplementary selection criteria to choose between MUD who are otherwise equal (meaning equally matched in HLA-A*/B*/C*/DRB1*/DQB1* loci, have no DSAs, similar age (donors younger than 32 are preferred over donors between 33 and 49, who are preferred over donors above 50 years of age)and have fewest number of HLA-DRB3*/4*/5*).
  The secondary selection criteria pertains to CMV-status (patient and donor of same CMV-status are preferred), gender (male donors are the preferred choice for male patients, male donors or female donors who have not been pregnant previously are the preferred choice for female patients) and ABO compatibility (identity or minor incompatibility are preferred).
- As you ask for post-transplant advice you should mention if a blood group A donor was selected.
- The choice of the unrelated donors depends on the type of malignancies (necessity to have a strong GvL effect or not?), the urgency of the graft, the evolution of the anti-viral treatments, the rate of anti-A and B

antibodies… Indeed, the advent of new therapeutics against CMV has recently changed the criteria of donor choice : is the CMV compatibility still more important than ABO group ? Is the DP compatibility more important than CMV and ABO group ? The proportion of each criteria during the donor choice procedure is still not clear and vary from one center to another.

- Current patient data and counts would be useful. Additional results.
- Patient and donor weights would also be considered, also patient co-morbidities. ABO incompatibility does not seem to have great weight for most of the transplant centers we work with, CMV is the larger problem as many treatments lead to fragile grafts.
- The answers to this case are based on the NMDP guidelines published in 2019 (Dehn et al., Blood 2019). The most important criteria for selection between 8/8 donors are age and permissive DP mismatch (which may decrease the risk of relapse compared to fully DP matched donors, see Fleishhauer, Lancet Oncology 2012)). ABO incompatibility and CMV status are not associated with overall survival in large cohorts. High titers of anti-A and anti-B in the recipient may be managed with plasmapheresis.
- More information is needed regarding the HLA matching of the donor and recipient and infectious markers.
- Does the clinical urgency of the case permit the reduction of the titer of incompatible recipient isoheamagglutinins? Monitor ABO antibody titre post graft. The ethnic origin of the patient was not mentioned.

Comments and suggested responses from the UK H&I experts providing this scenario*

Question 1

This scenario presented you with a number of HLA matched donors. The strategy of selecting donors within this scenario will depend on how laboratories prioritise secondary characteristics such as DP match, ABO, CMV, age and gender. For example, some labs may select a DP matched CMV mismatched donor and give the patient Letermovir prophylaxis for CMV.
This patient has MDS which may affect responses i.e. transplant centres not requiring a GvL effect.

The majority of participants selected Donor 4 (12/12 match, CMV and ABO match, young, female and from a reliable registry) as the first choice donor whilst the second choice donor was much more split. There is also the option of a haplo-identical sibling donor to consider, but only one participant would select this sibling as a donor option.

Once the scenario introduces that the patient has high titre ABO antibodies the majority of participants would alter their donor selection as they felt the high titre Anti-A and -B antibodies ruled out donors 1-3. Donor 4 is still the predominant first choice but now participants are more likely to select Donor 5 (10/12, permissive DP mismatch, ABO and CMV match, older male) as a second choice option.

High titre ABO antibodies have been reported as causing issues such as haemolysis post-transplant. It can also be difficult to remove these antibodies through desensitisation. Most labs seemed to prefer blood group matched donors (Donor 4, 5 and 6). However, not all transplant centres test for ABO titres as standard.

Question 2

After the inclusion of further information regarding testing for infectious diseases and some information regarding pregnancies for Donor 4 a split decision was noted regarding whether participants would change their donor selection. Those that would alter their donor selection favoured Donor 5 as first choice, but again, decisions on second choice were split. Many participants commented that donors 1-4 were now excluded due to high titre anti-A/B antibodies, virology results (and the associated risk of post-transplant lymphoproliferative disease (PTLD)) or prior pregnancies (and increased risk of GvHD). Donor 5 offers a 10/12 permissable DP match older donor which participants generally favoured over Donor 6 which was younger but had a non-permissive DP mismatch.

Donor ID	Matching Criteria										
	12/12 Match	10/12 Match	Permissive DP	ABO Identical	<35 years	Male	Previous Pregnancies	CMV Match	EBV Matched	HSV Matched	Anti-ABO Antibodies Present
Donor 1	✓				✓	✓			✓	✓	✓
Donor 2			✓		✓	✓		✓		✓	✓
Donor 3			✓		✓	✓		✓	✓	✓	✓
Donor 4	✓			✓	✓		✓	✓	✓		
Donor 5		✓	✓	✓		✓		✓	✓	✓	
Donor 6		✓		✓	✓	✓		✓	✓	✓	

Question 3

The patient has a falling percentage of donor chimerism which could be due to a persistent infection in the patient (if there is a large T cell expansion in response to an infection there may be a decrease in percentage donor chimerism).
We would advise a clinician to be watchful for signs of disease relapse and consider a Donor Lymphocyte Infusion in the first instance.

Please note:
These comments have been have been compiled by subject matter experts from the NEQAS Steering Committee in accordance with current guidelines. We accept that guidelines are not always explicit for every situation and therefore the responses may be aligned with the clinical practices of an individual transplant centre and may not be directly applicable across all settings. NEQAS are not necessarily endorsing these responses as the only correct action, just one possible view which, we acknowledge, may be biased towards UK practice.

Further reading:

Carreras E, Dufour C, Mohty M, Kröger N, editors. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies [Internet]. 7th ed. Cham (CH): Springer; 2019. PMID: 32091673.

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