Interpretive Educational Scheme (iED)
Clinical Scenario 2/2024 – Haematopoietic Stem Cell Transplant Case

Dispatched on 27th August 2024

Summary of Results

There were 43 responses received. 13 from laboratories based in the UK and Ireland (UK&I) and 30 from laboratories based in the rest of the World (RoW).

The patient is a 1-year-old girl recently diagnosed with Juvenile Myelomonocytic Leukaemia (JMML). The patient was referred to your laboratory in May 2024. The patient has one sister who has been HLA typed at HLA-DRB1 at medium resolution. The patient's sister was found to be HLA-DRB1 mismatched with the patient.

Table 1: Patient Details

Age	1 year
Gender	Female
Blood Group	O Pos
CMV Status	CMV Neg (Tested 09.05.24)
Weight	9 kg
Patient HLA Type	A*01:01:01, A*02:01:01; B*35:01:01, B*40:01:02; C*03:04:01, C*04:01:01; DRB1*04:04:01, DRB1*13:01:01; DRB3*02:02, DRB4*01:124; DQA1*01:03, DQA1*03:01; DQB1*03:02:01, DQB1*06:03:01; DPA1*01:03, -; DPB1*02:01:02, DPB1*04:01:01

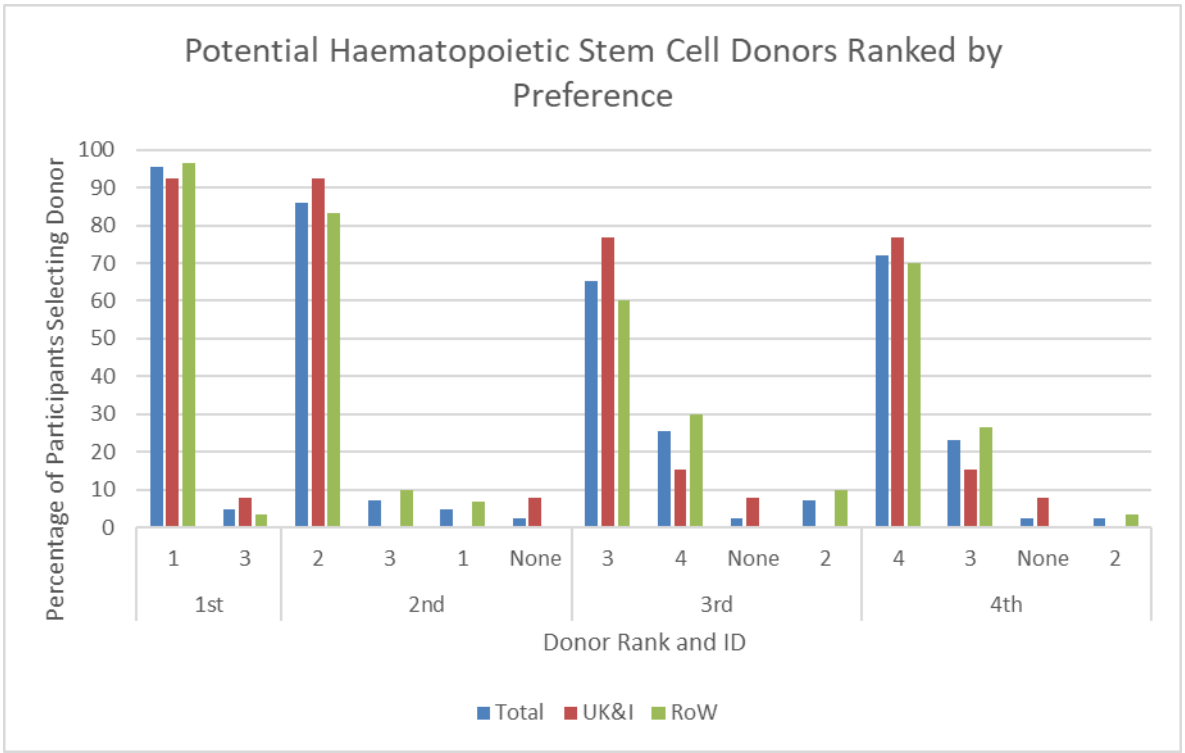
The transplant centre asks you to carry out an unrelated donor search. A summary of the search results is presented in Table 2.

Table 2: Unrelated Donor Search Results (Performed May 2024)

Donor Details	Gender	Age	ABO	CMV Status	Donor HLA Genotype					
Patient Details	***F***	***1***	***O+***	***Negative***	***A*01:01:01 A*02:01:01***	***B*35:01:01 B*40:01:02***	***C*03:04:01 C*04:01:01***	***DRB1*04:04:01 DRB1*13:01:01***	***DQB1*03:02:01 DQB1*06:03:01***	***DPB1*02:01:02 DPB1*04:01:01***
Donor 1 Germany	F	25	O+	Negative	A*01:01 A*02:01	B*35:01 B*40:01	C*03:04 C*04:01	DRB1*04:04 DRB1*13:01	DQB1*03:02 DQB1*06:03	DPB1*02:01 DPB1*06:01
Donor 2 USA	F	28	A+	Negative	A*01:01 A*02:01	B*35:01 B*40:01	C*03:04 C*04:01	DRB1*04:04 DRB1*13:01	DQB1*03:02 DQB1*06:03	DPB1*06:01 DPB1*14:01
Donor 3 Germany	F	46	A+	Positive	A*01:01 A*02:01	B*35:01 B*40:01	C*03:04 C*04:01	DRB1*04:04 DRB1*13:01	DQB1*03:02 DQB1*06:03	DPB1*04:01 DPB1*04:01
Donor 4 Germany	M	54	O+	Positive	A*01:01 A*02:01	B*35:01 B*40:01	C*03:04 C*04:01	DRB1*04:04 DRB1*13:01	DQB1*03:02 DQB1*06:03	DPB1*04:01 DPB1*06:01

Q 1a) Please rank the donors in order of preference and give reasons for your selection

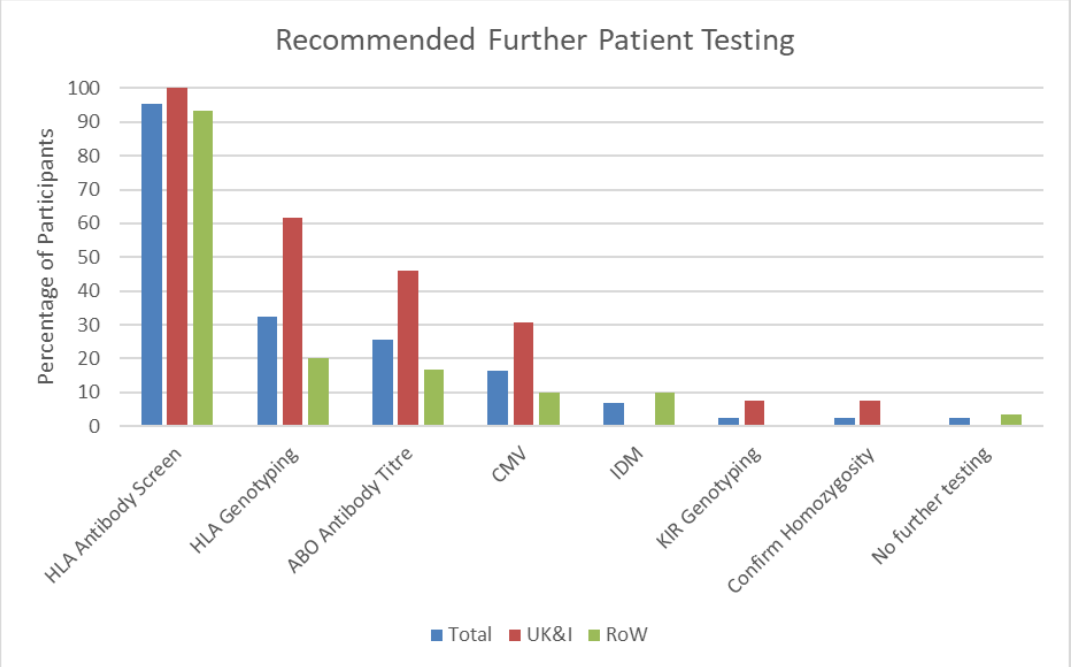
Donor Choice	Donor ID	Total (n=43)		UK&I (n=13)		RoW (n=30)	
		Count	%	Count	%	Count	%
1st	1	41	**95**	12	**92**	29	**97**
	3	2	**5**	1	**8**	1	**3**
2nd	2	37	**86**	12	**92**	25	**83**
	3	3	**7**	0	**0**	3	**10**
	1	2	**5**	0	**0**	2	**7**
	None	1	**2**	1	**8**	0	**0**
3rd	3	28	**65**	10	**77**	18	**60**
	4	11	**26**	2	**15**	9	**30**
	None	1	**2**	1	**8**	0	**0**
	2	3	**7**	0	**0**	3	**10**
4th	4	31	**72**	10	**77**	21	**70**
	3	10	**23**	2	**15**	8	**27**
	None	1	**2**	1	**8**	0	**0**
	2	1	**2**	0	**0**	1	**3**



Donor ID	Reasons Given for Donor Selection															
	Age	Male	Female	CMV match	ABO compatible	Trusted Registry	Permissive DP mismatch	Non-Permissive DP mismatch	HvG Direction	GvH Direction	HR Typing	10/10	10/12	11/12	12/12	Low PIRCHE Score
1	✓	□	✓	✓	✓	✓	□	✓	✓	□	✓	✓	□	✓	□	✓
2	✓		✓	✓		✓	□	✓	✓	□	✓	✓	✓			
3			✓			✓	✓		✓	✓	✓	✓		✓	✓	
4		✓				✓		✓	✓		✓	✓		✓	✓	

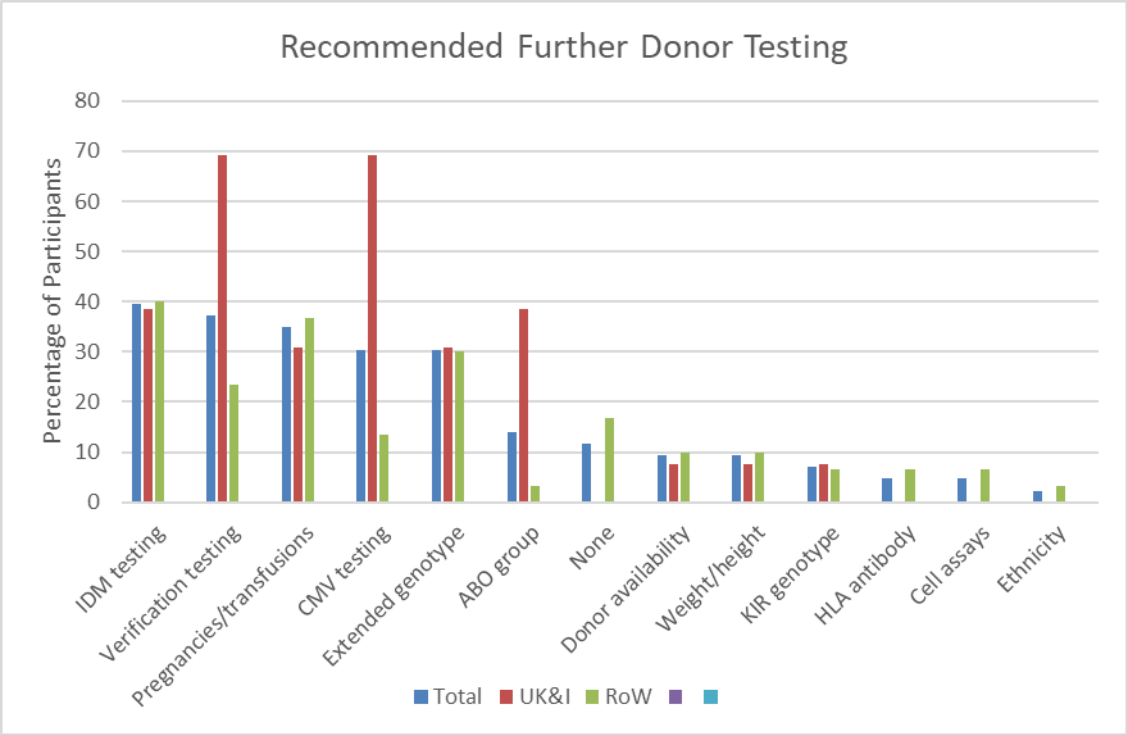
Q 1b) Is there any further testing you would request on the patient?

Further Patient Testing	Total (n=43)		UK&I (n=13)		RoW (n=30)	
	Count	%	Count	%	Count	%
HLA Antibody Screen	41	**95**	13	**100**	28	**93**
HLA Genotyping	14	**33**	8	**62**	6	**20**
ABO Antibody Titre	11	**26**	6	**46**	5	**17**
CMV	7	**16**	4	**31**	3	**10**
IDM	3	**7**	0	**0**	3	**10**
KIR Genotyping	1	**2**	1	**8**	0	**0**
Confirm Homozygosity (HLA Genotype Parents)	1	**2**	1	**8**	0	**0**
No further testing	1	**2**	0	**0**	1	**3**



Q 1c) Is there any further testing you would request on the potential donors listed in Table 2?

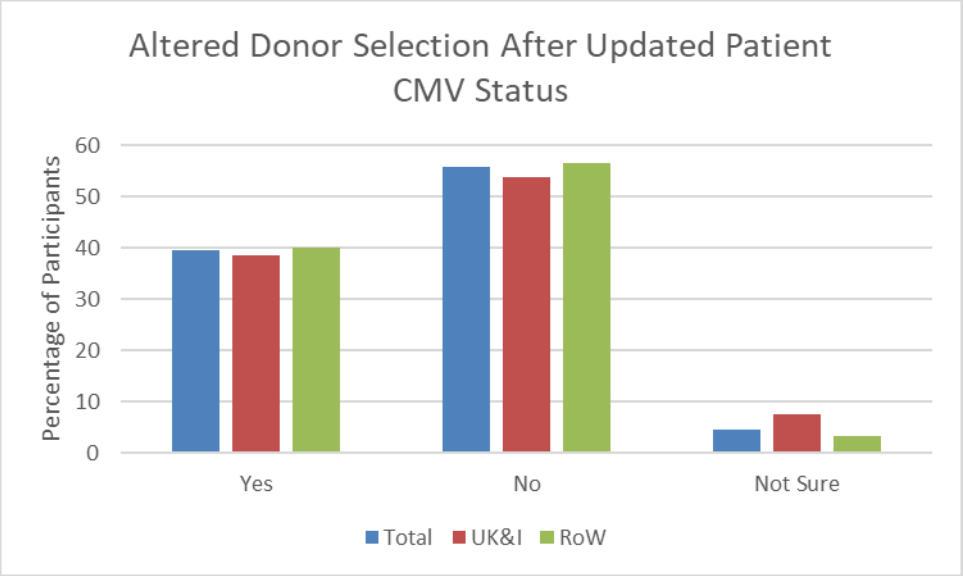
Further Donor Testing	Total (n=43)		UK&I (n=13)		RoW (n=30)	
	Count	%	Count	%	Count	%
Infectious disease marker testing	17	**40**	5	**38**	12	**40**
Verification testing	16	**37**	9	**69**	7	**23**
Previous pregnancies/transfusions	15	**35**	4	**31**	11	**37**
Updated CMV testing	13	**30**	9	**69**	4	**13**
Extended genotype e.g. DRB3/4/5	13	**30**	4	**31**	9	**30**
ABO group	6	**14**	5	**38**	1	**3**
None	5	**12**	0	**0**	5	**17**
Donor availability	4	**9**	1	**8**	3	**10**
Weight/height	4	**9**	1	**8**	3	**10**
KIR genotype	3	**7**	1	**8**	2	**7**
HLA antibody testing	2	**5**	0	**0**	2	**7**
Cell assays e.g. CDCXM, FCXM	2	**5**	0	**0**	2	**7**
Ethnicity	1	**2**	0	**0**	1	**3**



You then receive a phone call from your clinical colleagues to say that the patient has now switched to CMV equivocal. Further testing a week later confirms that the patient is now CMV positive.

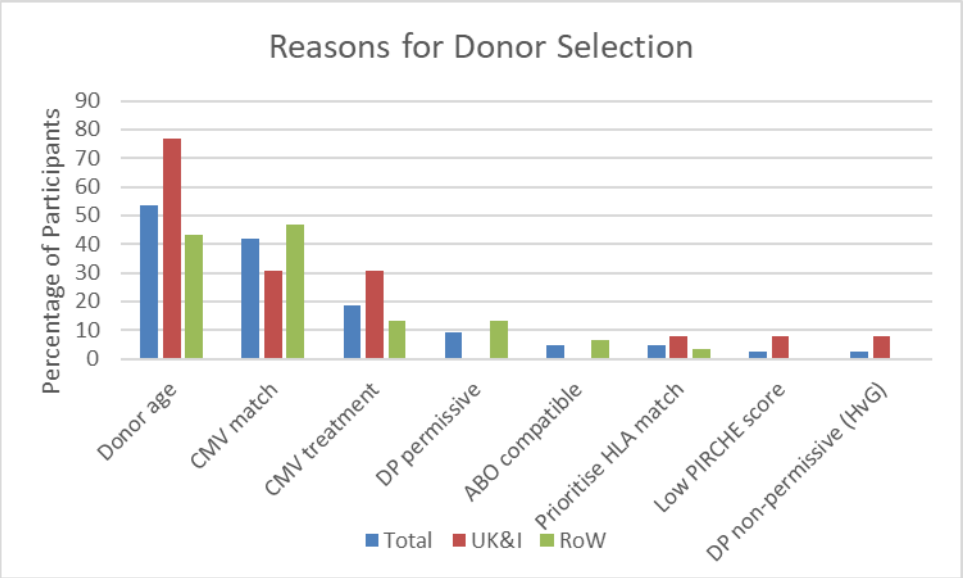
Q 2a) Would the change in patient CMV status alter your donor selection?

Response	Total (n=43)		UK&I (n=13)		RoW (n=30)	
	Count	%	Count	%	Count	%
Yes	17	**40**	5	**38**	12	**40**
No	24	**56**	7	**54**	17	**57**
Not Sure	2	**5**	1	**8**	1	**3**



Q 2b) Please give reasons for your response.

Donor Selection	Total (n=43)		UK&I (n=13)		RoW (n=30)	
	Count	%	Count	%	Count	%
Donor age	23	**53**	10	**77**	13	**43**
CMV match	18	**42**	4	**31**	14	**47**
Give patient CMV treatment e.g. Letermovir	8	**19**	4	**31**	4	**13**
DP permissive	4	**9**	0	**0**	4	**13**
ABO compatible	2	**5**	0	**0**	2	**7**
Prioritise HLA match	2	**5**	1	**8**	1	**3**
Low PIRCHE score	1	**2**	1	**8**	0	**0**
DP non-permissive (HvG)	1	**2**	1	**8**	0	**0**



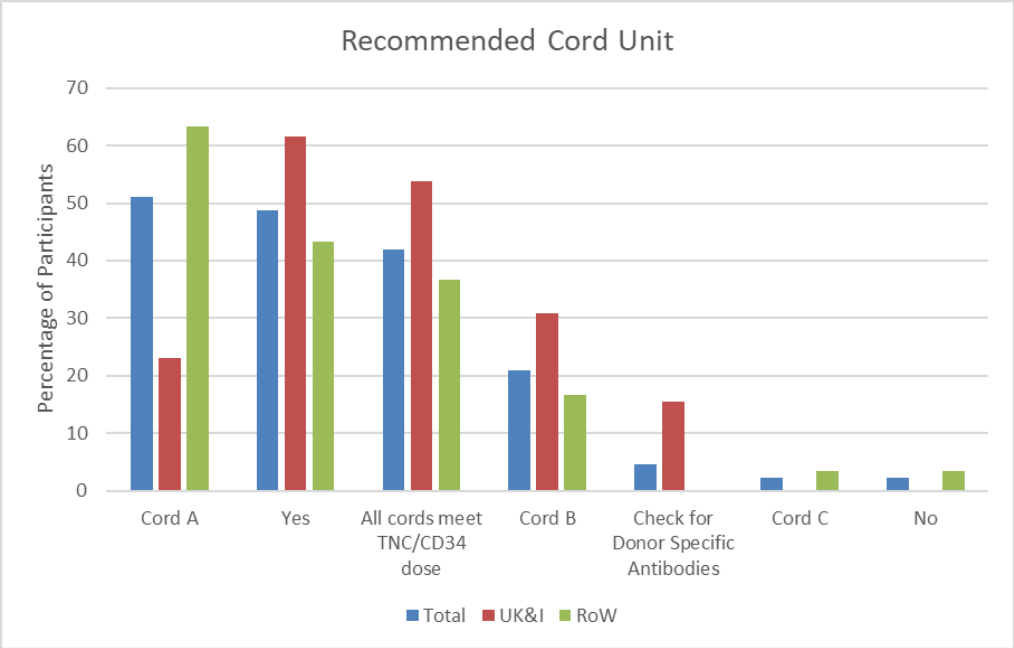
In addition, the clinical team ask you to carry out a cord blood unit search as they would like to proceed to transplant quickly. A summary of the search results is presented in Table 3.

Table 3: Cord Blood Unit Search Results (Performed June 2024)

Cord ID	HLA-A	HLA-B	HLA-C	HLA-DRB1	HLA-DQB1	HLA-DPB1	Registry	Gender	Year banked	Blood Group	TNC (x10^7)	CD34+ (x10^5)	Viability
Patient Details	***01:01 02:01***	***35:01 40:01***	***03:04 04:01***	***04:04 13:01***	***03:02 06:03***	***02:01 04:01***							
A	02:01	35:01 40:01	03:04 04:01	04:04 13:01	03:02 06:03	NT	Belgium	M	2013	A+	170	70	95%
B	02:01 31:01	35:01 40:01	03:04 04:01	04:04 13:01	03:02 06:03	03:01 06:01	Malaga	F	2010	O+	161	64	96%
C	02:01 31:01	35:01 40:01	03:04 04:01	04:04 13:01	03:02 06:03	04:01 06:01	Malaga	M	2011	A+	119	48	92%

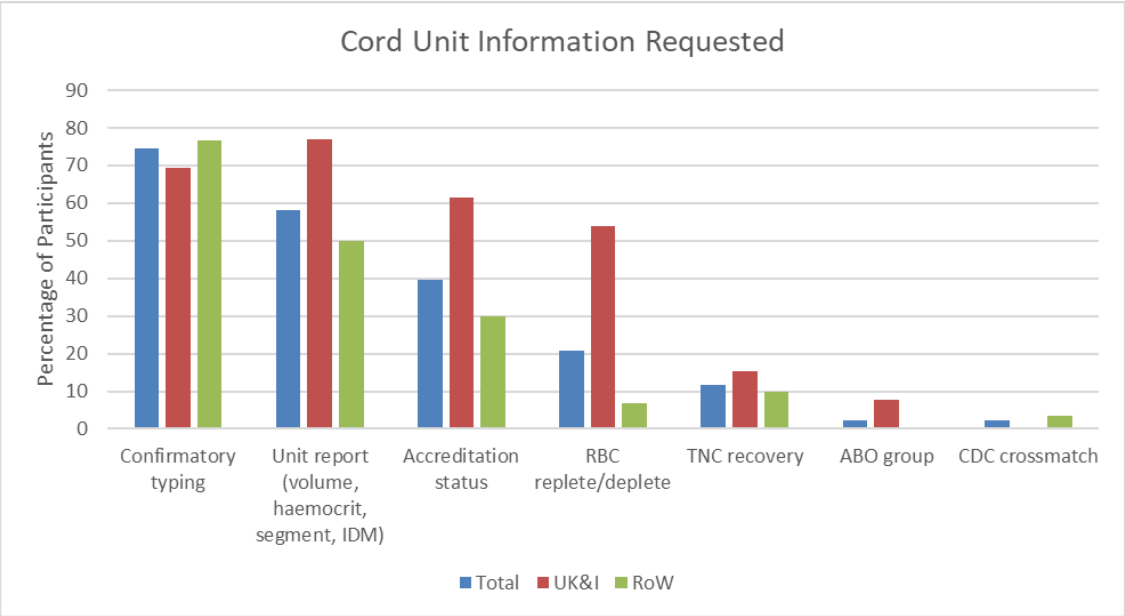
Q 3a) Would you recommend any of the cord units above for the patient?

Recommended Cord Units	Total (n=43)		UK&I (n=13)		RoW (n=30)	
	Count	%	Count	%	Count	%
Cord A	22	**51**	3	**23**	19	**63**
Yes	21	**49**	8	**62**	13	**43**
All cords meet TNC/CD34 dose	18	**42**	7	**54**	11	**37**
Cord B	9	**21**	4	**31**	5	**17**
Check for Donor Specific Antibodies	2	**5**	2	**15**	0	**0**
Cord C	1	**2**	0	**0**	1	**3**
No	1	**2**	0	**0**	1	**3**



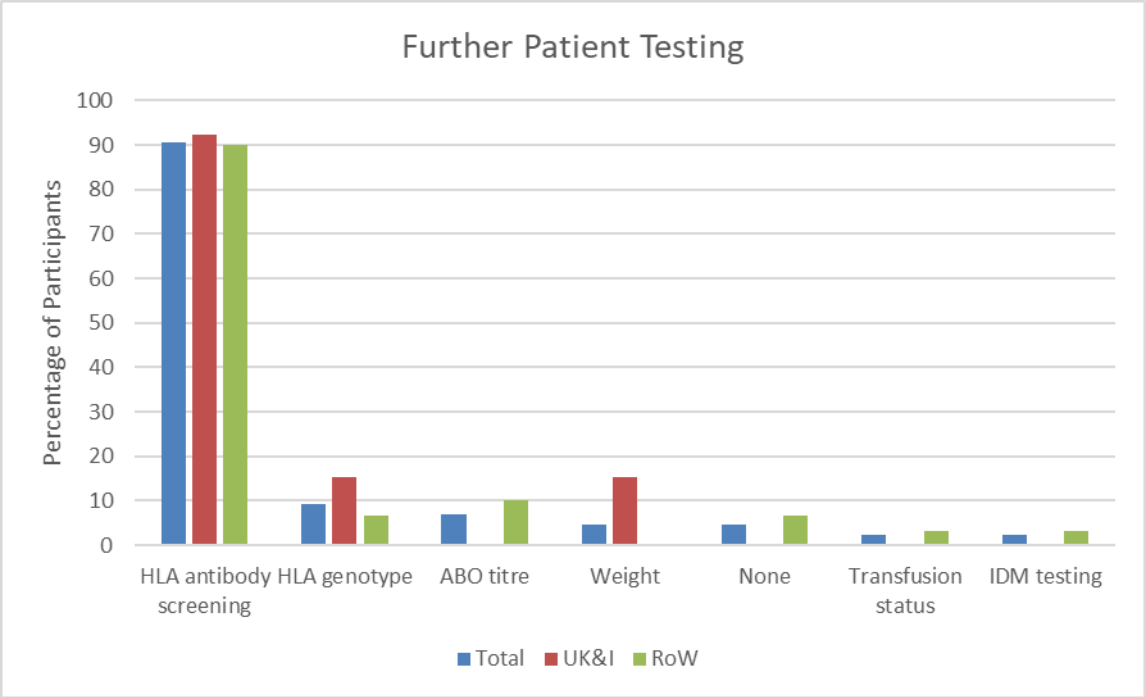
Q 3b) Is there any other information you would request on the cord units listed above?

Information Requested	Total (n=43)		UK&I (n=13)		RoW (n=30)	
	Count	%	Count	%	Count	%
Confirmatory typing	32	**74**	9	**69**	23	**77**
Unit report (volume, haemocrit, segment, IDM)	25	**58**	10	**77**	15	**50**
Accreditation status	17	**40**	8	**62**	9	**30**
RBC replete/deplete	9	**21**	7	**54**	2	**7**
TNC recovery	5	**12**	2	**15**	3	**10**
ABO group	1	**2**	1	**8**	0	**0**
CDC crossmatch	1	**2**	0	**0**	1	**3**



Q 3c) Is there any further testing you would carry out on the patient?

Information on units	Total (n=43)		UK&I (n=13)		RoW (n=30)	
	Count	%	Count	%	Count	%
HLA antibody screening	39	**91**	12	**92**	27	**90**
HLA genotype	4	**9**	2	**15**	2	**7**
ABO titre	3	**7**	0	**0**	3	**10**
Weight	2	**5**	2	**15**	0	**0**
None	2	**5**	0	**0**	2	**7**
Transfusion status	1	**2**	0	**0**	1	**3**
IDM testing	1	**2**	0	**0**	1	**3**



A serum sample from the patient is tested by One Lambda single antigen bead test in June 2024. A summary of potential donor specific antibodies is presented in Table 4.

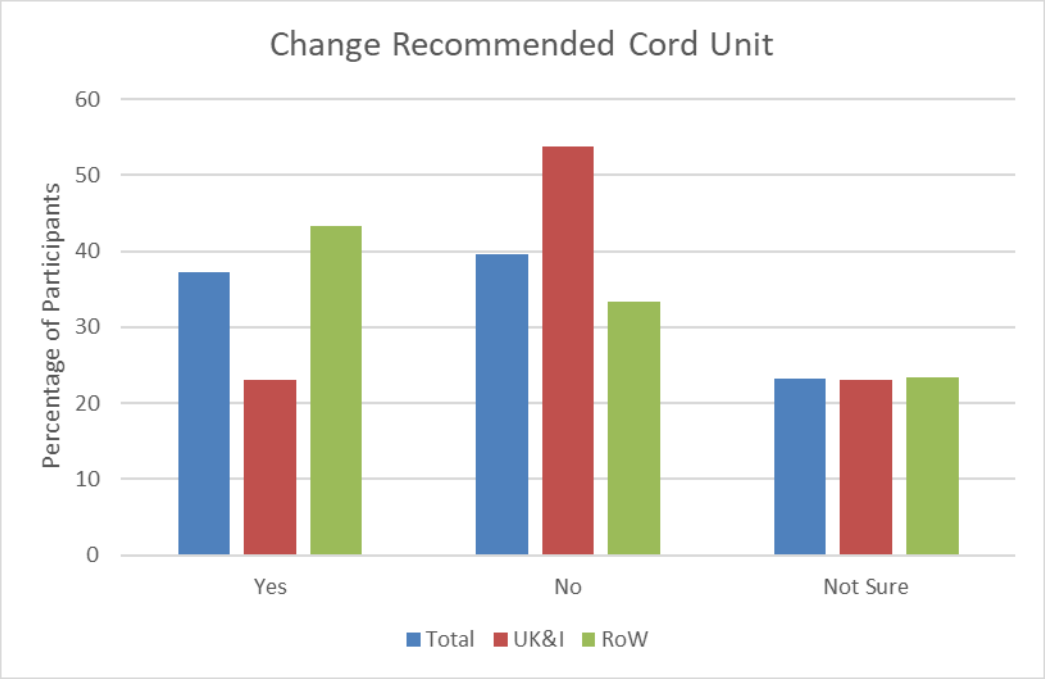
Table 4: Summary of Potential Donor Specific Antibodies from Single Antigen Bead Testing

Specificity	Normalised MFI*
A31	0
DRB3*01:01	1012
DP3	1288
DP6	1627
DP14	1243

** The highest Median Fluorescent Intensity (MFI) for each specificity is given.*

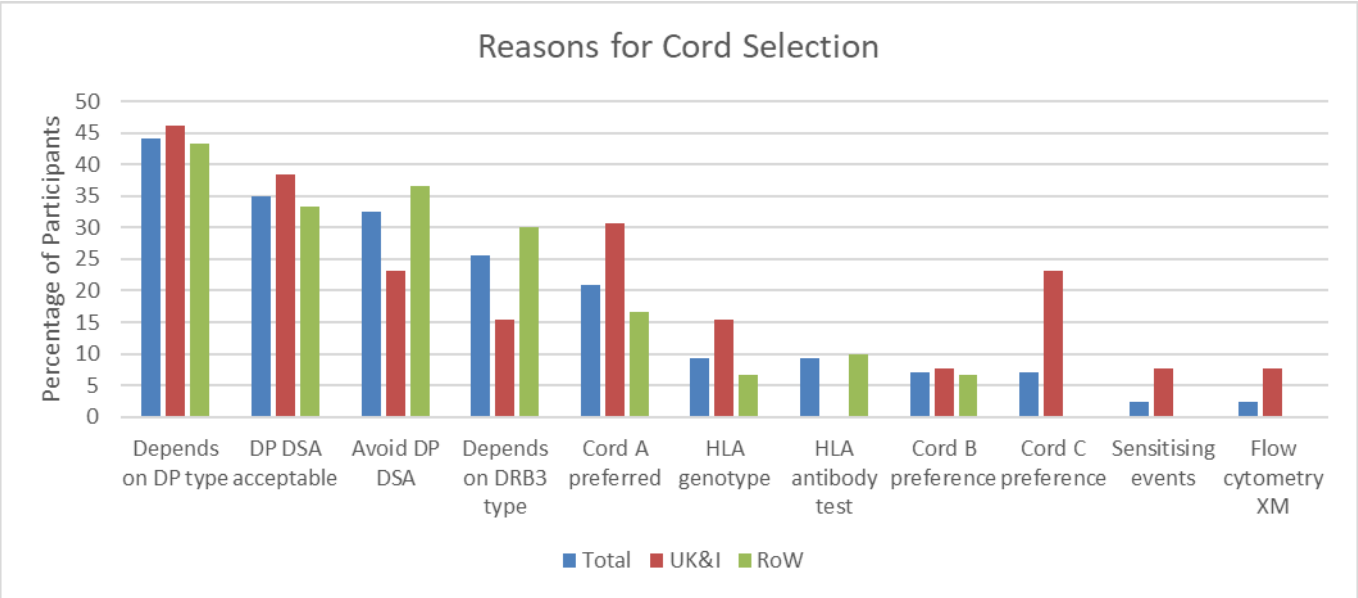
Q 4a) Would these results change the cord unit you recommend?

Response	Total (n=43)		UK&I (n=13)		RoW (n=30)	
	Count	%	Count	%	Count	%
Yes	16	**37**	3	**23**	13	**43**
No	17	**40**	7	**54**	10	**33**
Not Sure	10	**23**	3	**23**	7	**23**



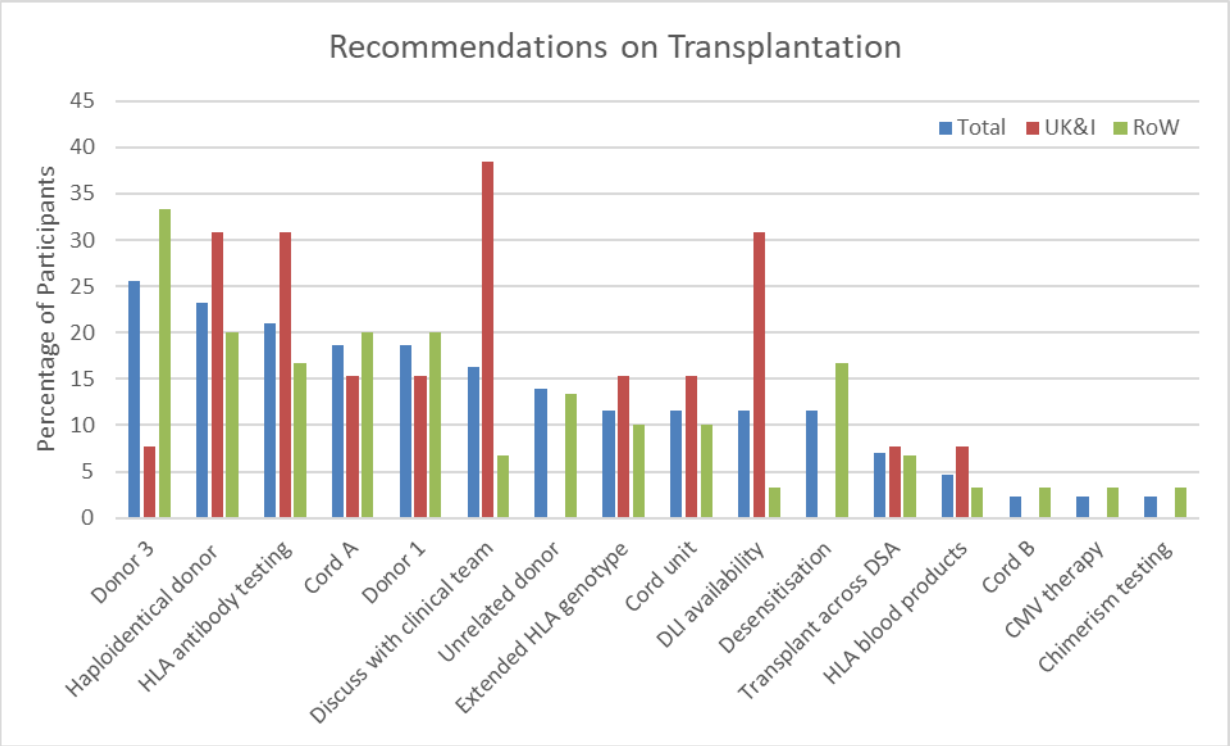
Q 4b) Please give reasons for your response.

Reasons for decision	Total (n=43)		UK&I (n=13)		RoW (n=30)	
	Count	%	Count	%	Count	%
Depends on DP type of Unit A	19	**44**	6	**46**	13	**43**
Low level DP DSA acceptable risk	15	**35**	5	**38**	10	**33**
Avoid low level DP DSA	14	**33**	3	**23**	11	**37**
Depends on DRB3 type	11	**26**	2	**15**	9	**30**
Cord A preferred	9	**21**	4	**31**	5	**17**
Extended HLA genotype	4	**9**	2	**15**	2	**7**
HLA antibody screening/alternate kit	4	**9**	1	**0**	3	**10**
Cord B preference	3	**7**	1	**8**	2	**7**
Cord C preference	3	**7**	3	**23**	0	**0**
Potential sensitising events	1	**2**	1	**8**	0	**0**
Flow cytometry crossmatch	1	**2**	1	**8**	0	**0**



Q 4c) How would you proceed with this patient? What would you recommend to your transplant centre?

Transplant Recommendation	Total (n=43)		UK&I (n=13)		RoW (n=30)	
	Count	%	Count	%	Count	%
Donor 3	11	**26**	1	**8**	10	**33**
Explore haploidentical donor e.g. parents	10	**23**	4	**31**	6	**20**
Regular HLA antibody testing	9	**21**	4	**31**	5	**17**
Cord A	8	**19**	2	**15**	6	**20**
Donor 1	8	**19**	2	**15**	6	**20**
Discuss with clinical team	7	**16**	5	**38**	2	**7**
Preference for unrelated donor	6	**14**	2	**0**	4	**13**
Extended HLA genotype/DRB3 compatibility	5	**12**	2	**15**	3	**10**
Preference for cord unit	5	**12**	2	**15**	3	**10**
DLI availability	5	**12**	4	**31**	1	**3**
Desensitisation	5	**12**	0	**0**	5	**17**
Transplant in presence of DSA	3	**7**	1	**8**	2	**7**
HLA matched blood products	2	**5**	1	**8**	1	**3**
Cord B	1	**2**	0	**0**	1	**3**
CMV therapy	1	**2**	0	**0**	1	**3**
Chimerism testing	1	**2**	0	**0**	1	**3**



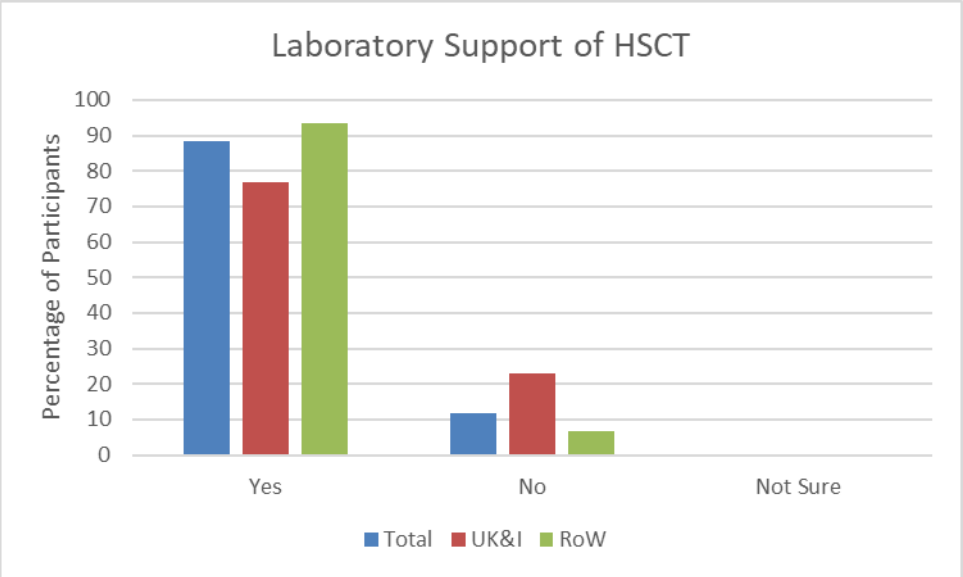
Q 5) Would you like to make any further comments on this case?

- Test with another screening kit to determining whether DP3 and DP6 are real antibodies. Patient's type is not uncommon but the donor results are poor.
- Decisions on ranking of donors is made following discussion with the clinical team and is determined on a case by case basis. The paediatric transplant program has only recently been introduced, with minimal experience of cord transplantation therefore the centre seeks guidance from the national cord selection advisory service in such cases.
- We would avoid relatives if disease due to genetic mutation.
- IMGT DPB1 T-Cell Epitope Algorithm v2.0 database used for HLA-DPB1 matching status.
- Given the age of the patient, it would be useful to HLA type the parents (particularly the mother). Potentially to consider a haploidentical transplant. But also to consider the non-inherited maternal antigens (NIMA) and whether mismatching at the antigens would offer additional potential donor options.
- Our policy would be to investigate matched unrelated donors and cord blood units simultaneously. We would perform sequential HLA single antigen bead screening to monitor potential donor directed antibodies over time along with post-transplant chimerism monitoring.
- Our laboratory supports several UK Transplant Centres, only one of which transplants paediatric patients. The paediatric transplant centre would definitely consider CBUs for a patient like this. However, our other Transplant Centres rarely perform CBU searches for their patients and would prefer to use a related haplo donor instead.
- Our laboratory supports hematopoietic stem cell transplantation for adult patients but not for paediatric patients. Therefore, this scenario does not fully align with our expertise, and we are unable to provide a final recommendation for donor selection.
- Ask for HLA typing DPB1 of cord Belgium.
- Missing information, with some details as the parents, weights of the donors, and emergency of the situation.
- Why not consider parents for donation?
- Repeat donor search.

- We would to know what kind of HSC (PBSC or BM) was wanted by physician and if donor were willing to donate only one or both collection method.
- Not familiar with paediatric cases.
- Other technology to test antibody profile, possible C1q testing on patient. Donor 3 most suitable – No DSA and DP permissive. Family members investigated for potential haplo?
- In JMML, cord blood transplants can sometimes be associated with delayed engraftment, so maximizing TNC and CD34+ cell doses is critical to ensure prompt recovery.
- The BMT should be performed at the earliest. A standby donor should be kept.
- The post-thaw segment potency must be evaluated in this case in order to know the percentage cell viability. In few instances, in cases of malignancies, very well matched HLA typing must be avoided in order to reduce risk of relapse.
- Ultimately it is the transplant team that would select between a cord unit and an unrelated adult donor based on the clinical requirements of the patient.

Q 6) Does your laboratory support haematopoietic stem cell transplant?

Response	Total (n=43)		UK&I (n=13)		RoW (n=30)	
	Count	%	Count	%	Count	%
Yes	38	**88**	10	**77**	28	**93**
No	5	**12**	3	**23**	2	**7**
Not Sure	0	**0**	0	**0**	0	**0**



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

Question 1

The ranking of unrelated donors will depend on the selection criteria and local guidelines followed by individual transplant centres. The importance placed on HLA match and donor age is well established but factors such as donor CMV status and sex will influence donor preference.

In terms of further testing of the patient confirming the HLA genotype, perhaps performing extended genotyping for DRB3/4/5 and testing for the presence of HLA antibodies could be recommended. Some centres may opt to look at DPB1 expression levels and, as the patient is ABO group O, it might be useful to test the patient for anti-A and anti-B titres.

When considering further information on potential donors testing for infectious disease markers (IDM), confirming HLA genotypes, sensitising events and requesting updated CMV testing on negative donors seems prudent. Patient clinical urgency and budgetary considerations will impact how many donors are selected for further investigation. Some transplant centres may also request HLA antibody screening on donors (especially female donors), consider KIR genotyping or use tools such as PIRCHE to inform donor selection.

Question 2

The change in CMV status of the patient from negative to positive may impact donor selection. Some transplant centres may proceed with a younger CMV negative donor and offer the patient therapeutic treatment such as Letermovir. Other centres may prefer to select a CMV matched donor accepting the potential impact of selecting an older donor.

Question 3

The ranking of cord units will depend on individual transplant centres selection criteria.

In terms of further information that may be useful in cord unit selection a unit report and post-thaw testing may be informative. Extended HLA genotyping and recent HLA antibody testing on the patient may also be useful.

Question 4 - would ab results change cord unit selected and reasons, how would you proceed with patient

The impact of the HLA antibody results will depend on the perceived clinical impact of these antibodies in terms of loci and MFI level. For example, some transplant centres may have a higher positive threshold for DP antibodies.

The overall recommendation on how to proceed with this young patient should be made in conjunction with a multidisciplinary team taking into consideration clinical urgency and balancing immunological risk when selecting an appropriate donor.

Please note:

These comments have been compiled by subject matter experts from the UK NEQAS for H&I 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. UK 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.