UK NEQAS
International Quality Expertise

Histocompatibility
& Immunogenetics

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Interpretive Educational Scheme (iED)
Clinical Scenario 1/2022 – Renal Transplantation

Dispatched on 31st May 2022

Summary of Results

A total of 39 responses were received, 17 from UK & Ireland (UK&I) based laboratories and 22 from Rest of the World (RoW) based laboratories.

Background Information
Samples from a 26 year old male, with IgA nephropathy, were received in the laboratory.

Patient HLA type:
A*02, A*23; B*07, B*15:01+; C*03:04+, C*07, -; DRB1*11, DRB1*13; DRB3*02; DQB1*03:01+, DQB1*06; DPB1*04:01, -

Patient blood group:
B Positive

The patient was clinically well and had not yet started dialysis, with an eGFR of 11, weight 110kg. The patient had previous transfusions four years ago.

The recipient was tested using One Lambda LABScreen Mixed kits which had consistently given a negative result for HLA antibody Class I antibodies. The HLA Class II result was positive and the patient was tested used a One Lambda LABScreen Single Antigen Bead Class II kit. The results for the patient's latest samples are displayed in Table 1.

Table 1: One Lambda LABScreen Single Antigen Bead Class II Kit Results (note all other beads <500 MFI).

Bead Specificity	Sample 1	Sample 2
DRB1*04:01	1290	1132
DRB1*04:02	113	552
DRB1*04:04	1286	1198
DRB1*04:05	1307	1275
DRB1*07:01	1451	1358
DRB1*04:03	999	1054

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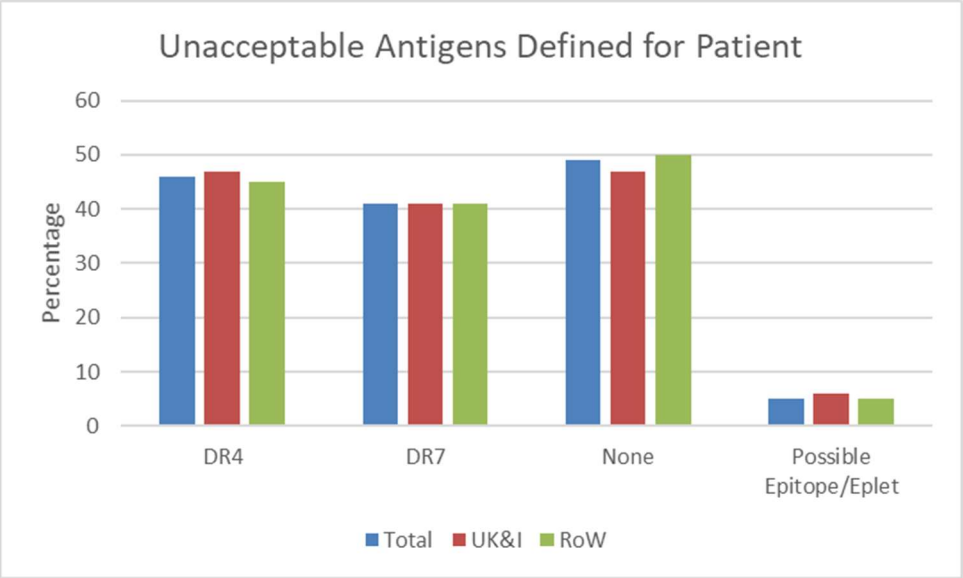
Q1) What unacceptable antigens would you define, if any, when registering this patient on the deceased donor register?

Unacceptable Antigen	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
DR4	18	46%	8	47%	10	45%
DR7	16	41%	7	41%	9	41%
None	19	49%	8	47%	11	50%
Possible Epitope/Eplet	2	5%	1	6%	1	5%



Whilst waiting for an offer on the deceased donor register a potential living donor, donor AA, comes forward. The potential donor is a 26 year old unrelated friend.

Donor AA - Unrelated potential donor HLA type:
A*02, -; B*15:01+, B*40:01+; C*03:03+, C*03:04+; DRB1*04, DRB1*09; DRB4*01; DQB1*03:01+, DQB1*03:03+; DPB1*04:01, DPB1*06:01

Donor AA blood group:
O Negative

HLA mismatch 012

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Q2) Comment on the immunological compatibility of Donor AA for the patient?

Immunological Compatibility	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Potential Donor Specific Antibody	27	69%	12	71%	15	68%
ABO Compatible	12	31%	5	29%	7	32%
Additional HLA Mismatches	8	21%	4	24%	4	18%
Low Level MFI	6	15%	3	18%	3	14%
Perform Prospective Crossmatch	6	15%	4	24%	2	9%
Standard Risk	5	13%	5	29%	0	0%
High Resolution HLA Genotyping	5	13%	3	18%	2	9%
Virtual XM Negative	4	10%	4	24%	0	0%
Use Kidney Exchange Scheme/Seek Alternative Donor	4	10%	2	12%	2	9%
Suitable for Direct Donation	3	8%	1	6%	2	9%
High Risk	2	5%	1	6%	1	5%
Discuss with MDT	2	5%	0	0%	2	9%
SAB Testing	2	5%	1	6%	1	5%
Virtual XM Positive	1	3%	1	6%	0	0%
Increased Risk of Rejection	1	3%	0	0%	1	5%
Intermediate Risk	1	3%	0	0%	1	5%
Avoid 2 DR Mismatch	1	3%	1	6%	0	0%
Potential Memory Immune Response	1	3%	1	6%	0	0%
Age Match	1	3%	1	6%	0	0%

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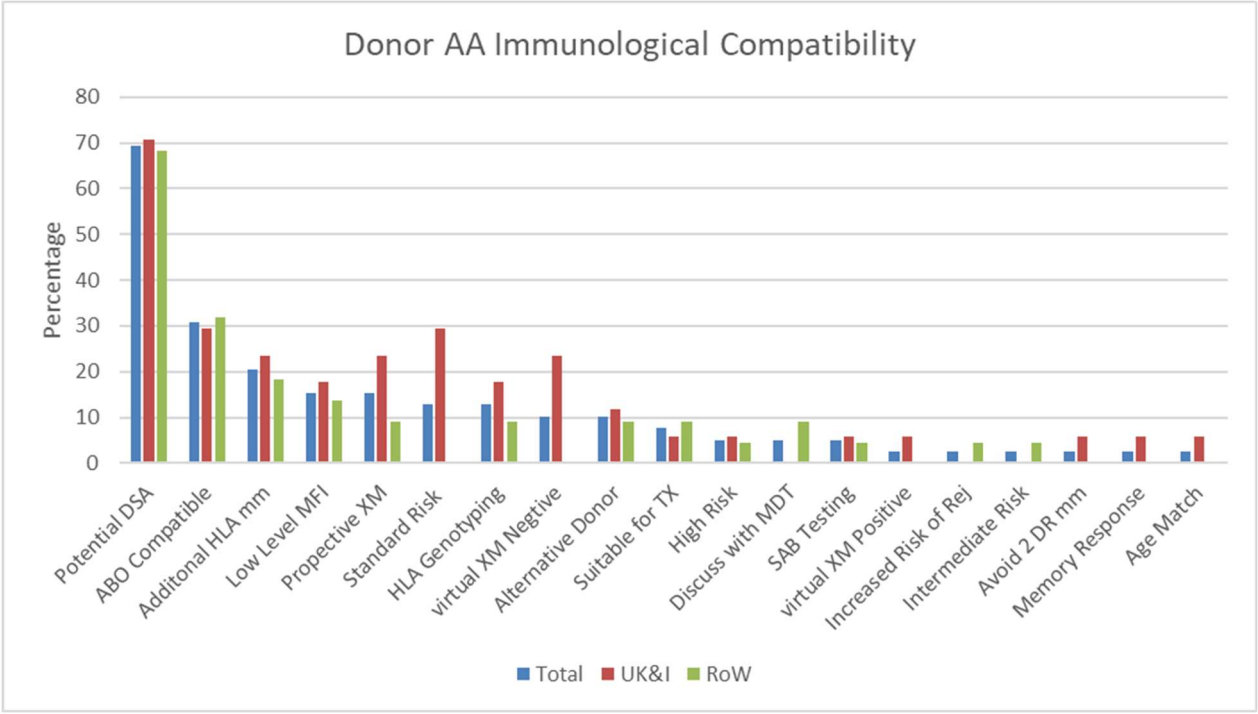

The case was discussed at the multi-disciplinary team meeting (MDT) and the decision was made to enter the patient and donor AA in the UK Living Kidney Sharing Scheme (UKLKSS).

Q3) Would you carry out any further lab work prior to entering the patient in the kidney sharing scheme?

Further Work	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Single Antigen Bead Testing	22	56%	10	59%	12	55%
HLA Genotyping - Patient	21	54%	11	65%	10	45%
HLA Genotyping - Donor	21	54%	11	65%	10	45%
Alternative Method of Antibody Testing	17	44%	12	71%	5	23%
Crossmatch	14	36%	6	35%	8	36%
Epitope Analysis	3	8%	2	12%	1	5%
Virtual Crossmatch	2	5%	1	6%	1	5%
3rd Party Crossmatch	2	5%	1	6%	1	5%
Autologous Crossmatch	2	5%	2	12%	0	0%
Anti-A Titre	2	5%	0	0%	2	9%

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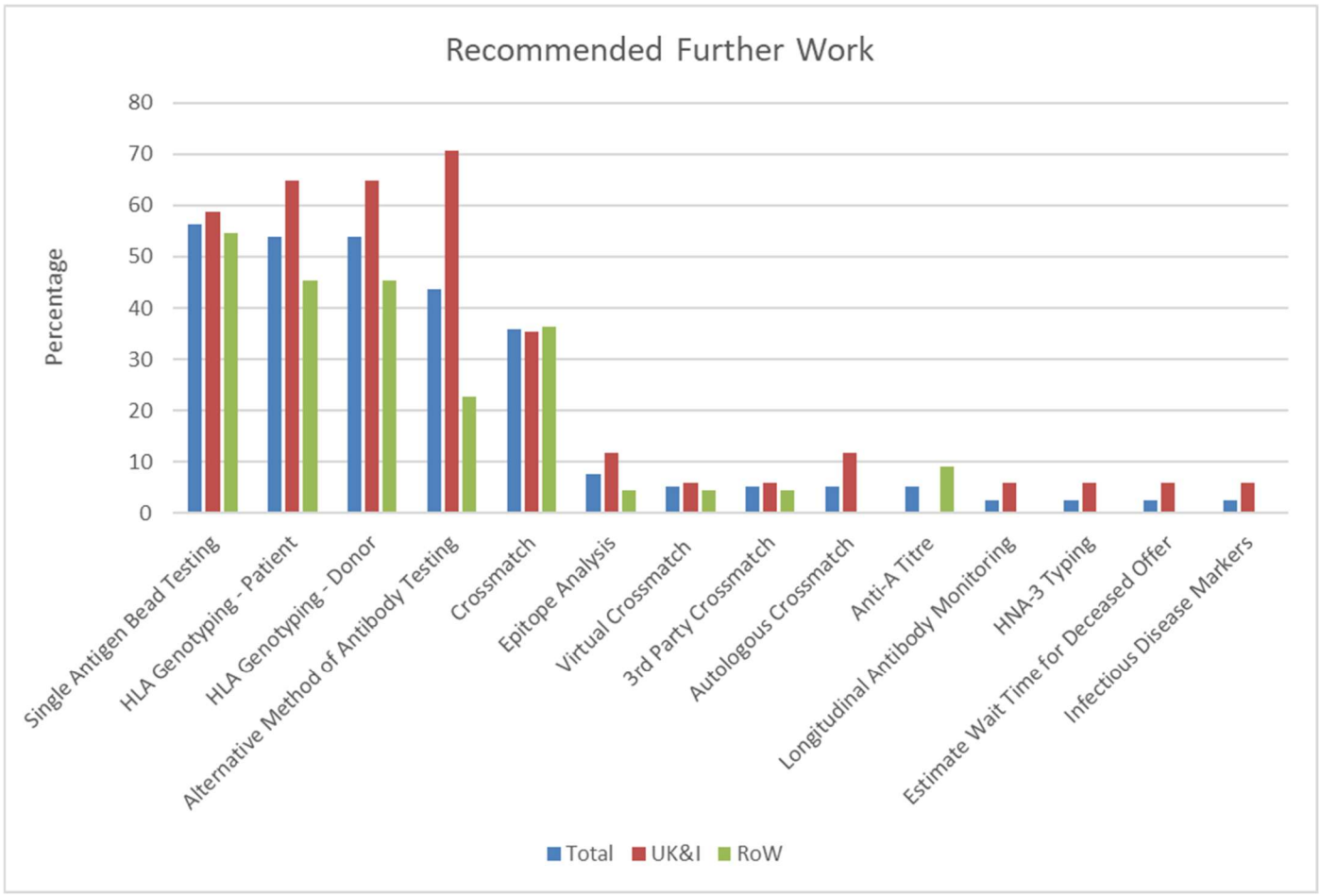

Q4a) Would you alter your current listing of unacceptable antigens to enter the pair in the kidney sharing scheme?

Alter UA for KSS	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Yes	11	28%	2	12%	9	41%
No	23	59%	14	82%	9	41%
Not Sure	5	13%	1	6%	4	18%

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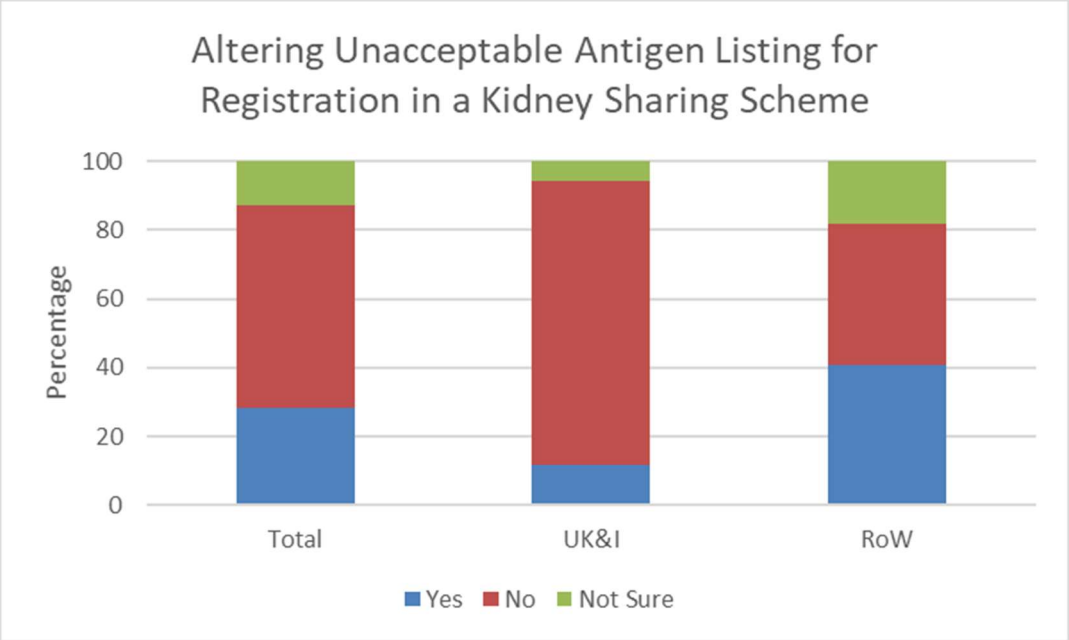

Q4b) Please provide a reason for your answer.

Option	Reasons	Total		UK&I		RoW	
		Number	%	Number	%	Number	%
Yes	Antibodies do not meet local listing criteria/low MFI	2	5%	0	0%	2	9%
	Avoid donors with DR4 and DR7	6	15%	2	12%	4	18%
	Require more information/further testing	1	3%	0	0%	1	5%
	Get patient a better HLA match	1	3%	0	0%	1	5%
	Patient factors: young, fit, pre-dialysis	2	5%	1	6%	1	5%
	Reduce risk	2	5%	0	0%	2	9%
	No new antibodies detected	1	3%	0	0%	1	5%
No	Antibodies do not meet local listing criteria/low MFI	9	23%	7	41%	2	9%
	Avoid donors with DR4 and DR7	1	3%	1	6%	0	0%
	Require more information/further testing	3	8%	1	6%	2	9%
	Get patient a better HLA match	2	5%	1	6%	1	5%
	Patient factors: young, fit, pre-dialysis	2	5%	1	6%	1	5%
	Reduce risk	1	3%	0	0%	1	5%
	MDT decision	2	5%	1	6%	1	5%
	Secondary immune response	1	3%	1	6%	0	0%
	No new antibodies detected	2	5%	1	6%	1	5%

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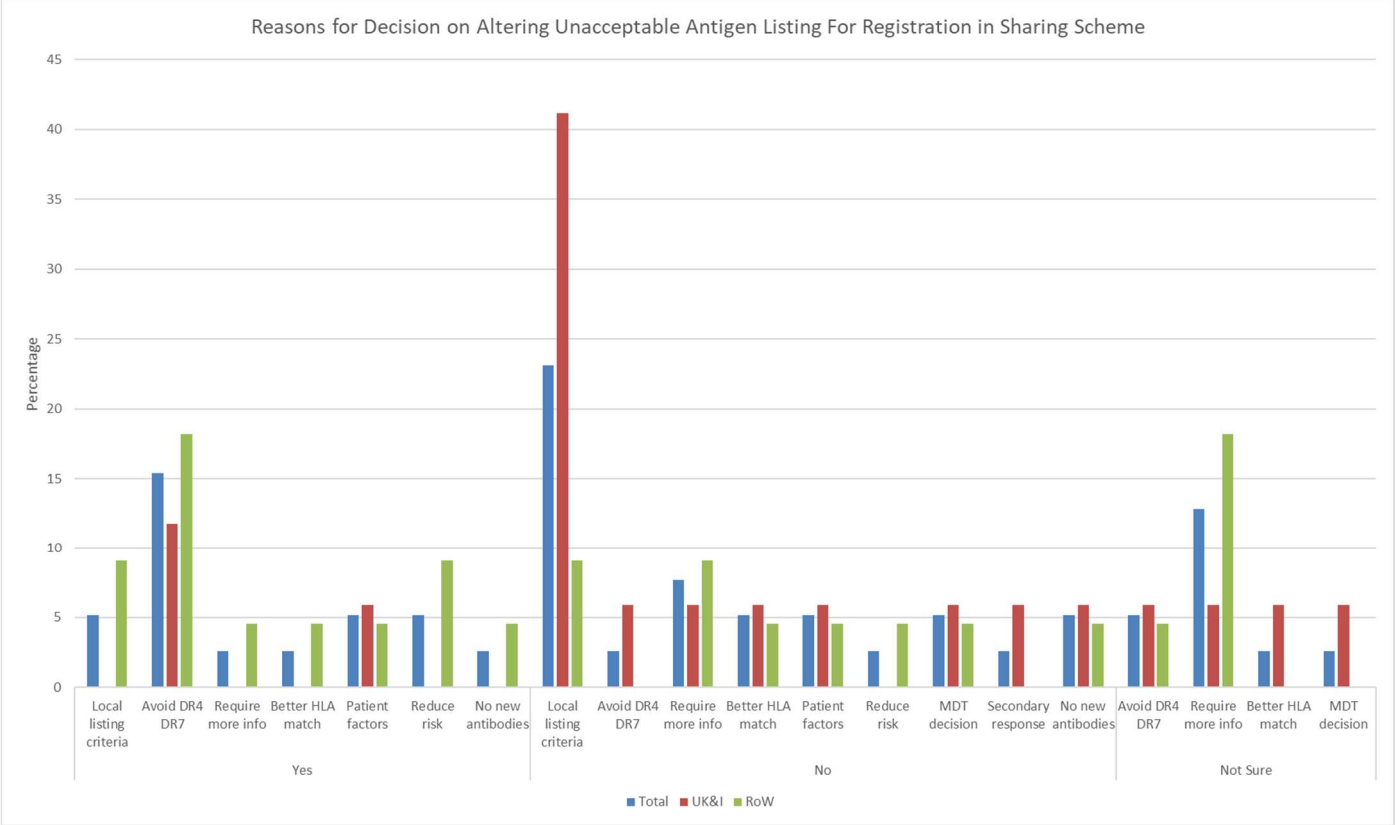
Not Sure	**Avoid donors with DR4 and DR7**	2	**5%**	1	**6%**	1	**5%**
	Require more information/further testing	5	**13%**	1	**6%**	4	**18%**
	Get patient a better HLA match	1	**3%**	1	**6%**	0	**0%**
	MDT decision	1	**3%**	1	**6%**	0	**0%**



The pair are entered into the kidney sharing scheme. Two potential matches for the patient were identified, details provided below:

Donor ID	Donor gender	Donor age	Donor HLA type	NHSBT-ODT mismatch grade
1	Male	57	A2; B13, B60(40); Bw4, Bw6; Cw10(3), Cw6; DR11(5), DR7; DR52; DR53; DQ2, DQ7(3); DPB1*03:01, DPB1*17:01	021
2	Female	42	A3, A24(9); B64(14), B63(15); Bw4, Bw6; Cw7, Cw8; DR13(6), DR7; DR52; DR53; DQ6(1), DQ2; DPB1*03:01, DPB1*04:02	111

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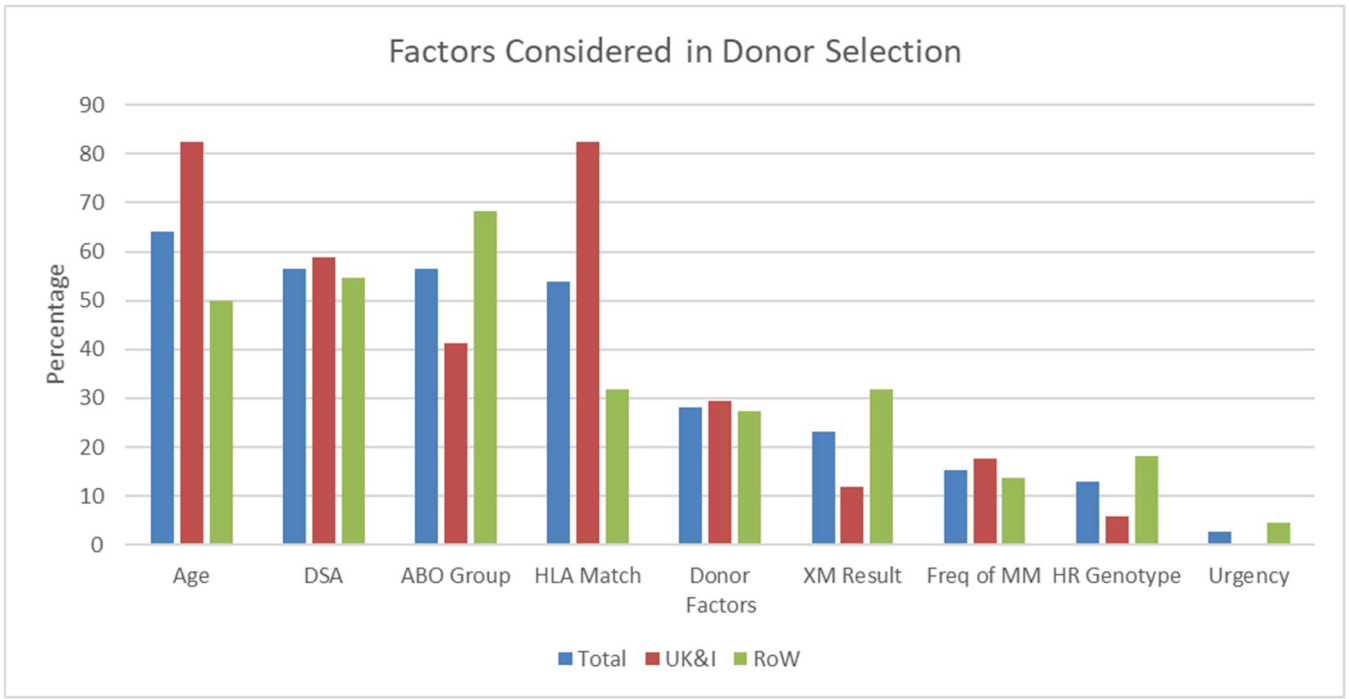
Q5a) What factors would you consider in the decision to progress with one of these donors?

Factors Considered in Donor Selection	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Age	25	64%	14	82%	11	50%
Donor Specific Antibodies	22	56%	10	59%	12	55%
Blood Group	22	56%	7	41%	15	68%
HLA Match Grade	21	54%	14	82%	7	32%
Donor Size / Health	11	28%	5	29%	6	27%
Crossmatch Result	9	23%	2	12%	7	32%
Frequency of Mismatch/Epitope Load	6	15%	3	18%	3	14%
High Resolution Genotype	5	13%	1	6%	4	18%
Clinical Urgency	1	3%	0	0%	1	5%



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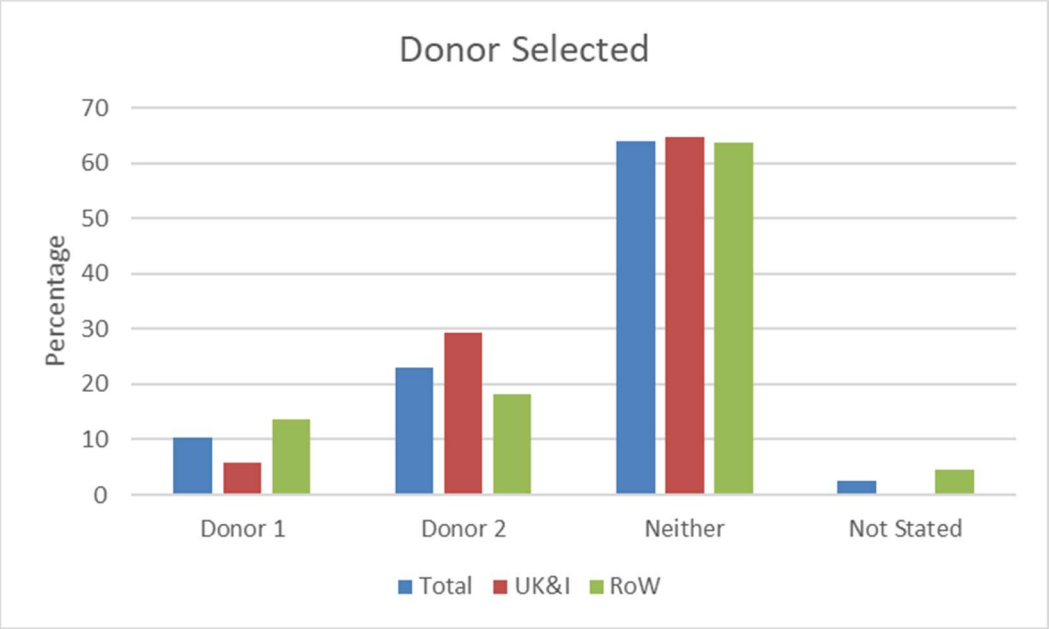
Q5b) Which donor would you select?

Reasons	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Donor 1	4	10%	1	6%	3	14%
Donor 2	9	23%	5	29%	4	18%
Neither	25	64%	11	65%	14	64%
Not Stated	1	3%	0	0%	1	5%



Q5c) Please provide a reason for your answer.

Option	Reasons	Total		UK&I		RoW	
		Number	%	Number	%	Number	%
Donor 1	Better HLA Match	3	8%	1	6%	2	9%
	Reduced Sensitisation for Re-Transplant	2	5%	1	6%	1	5%
	Age	1	3%	0	0%	1	5%
	B leader mm/DP permissive/C mm	1	3%	0	0%	1	5%

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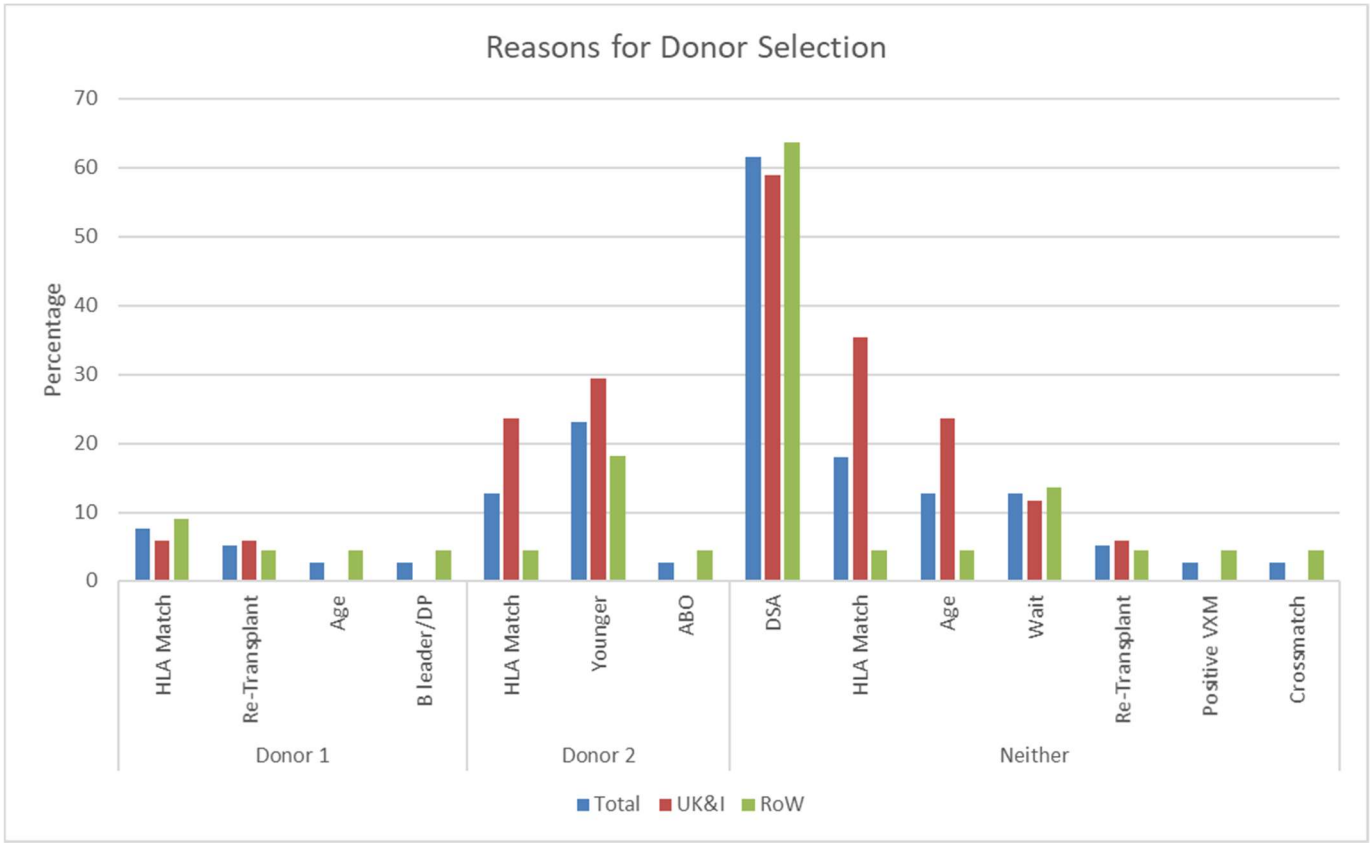
Donor 2	**Better HLA Match**	5	**13%**	4	**24%**	1	**5%**
	Younger	9	**23%**	5	**29%**	4	**18%**
	ABO compatible	1	**3%**	0	**0%**	1	**5%**
Neither	**Donor Specific Antibodies**	24	**62%**	10	**59%**	14	**64%**
	HLA Match Grade	7	**18%**	6	**35%**	1	**5%**
	Age	5	**13%**	4	**24%**	1	**5%**
	Wait for Better Donor	5	**13%**	2	**12%**	3	**14%**
	Sensitisation for Re-Transplant	2	**5%**	1	**6%**	1	**5%**
	Positive Virtual Crossmatch	1	**3%**	0	**0%**	1	**5%**
	Perform Crossmatch	1	**3%**	0	**0%**	1	**5%**



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The transplant does not proceed.

In a subsequent kidney sharing scheme matching run the patient is matched to another potential donor:

Donor 3 - 39 year old male:
HLA-A2, A24; B44, B18; Bw4, Bw6; Cw5, -; DR17, DR12; DR52; DQ2, DQ7; DPB1*02:01, DPB1*04:01

Blood group:
O Positive

Q6) Comment on the immunological suitability of Donor 3 for this patient?

Comments on Suitability	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
HLA Match	26	67%	15	88%	11	50
No DSA	26	67%	11	65%	15	68
ABO Compatible	18	46%	8	47%	10	45
Low/Standard Risk	8	21%	5	29%	3	14
Future Sensitisation	3	8%	2	12%	1	5
Negative Virtual Crossmatch	2	5%	2	12%	0	0
Additional Testing Required	2	5%	0	0%	2	9
Crossmatch Required	1	3%	1	6%	0	0
Re-enter Kidney Sharing Scheme	1	3%	0	0%	1	5
B Leader Mismatch / DP Permissive	1	3%	0	0%	1	5

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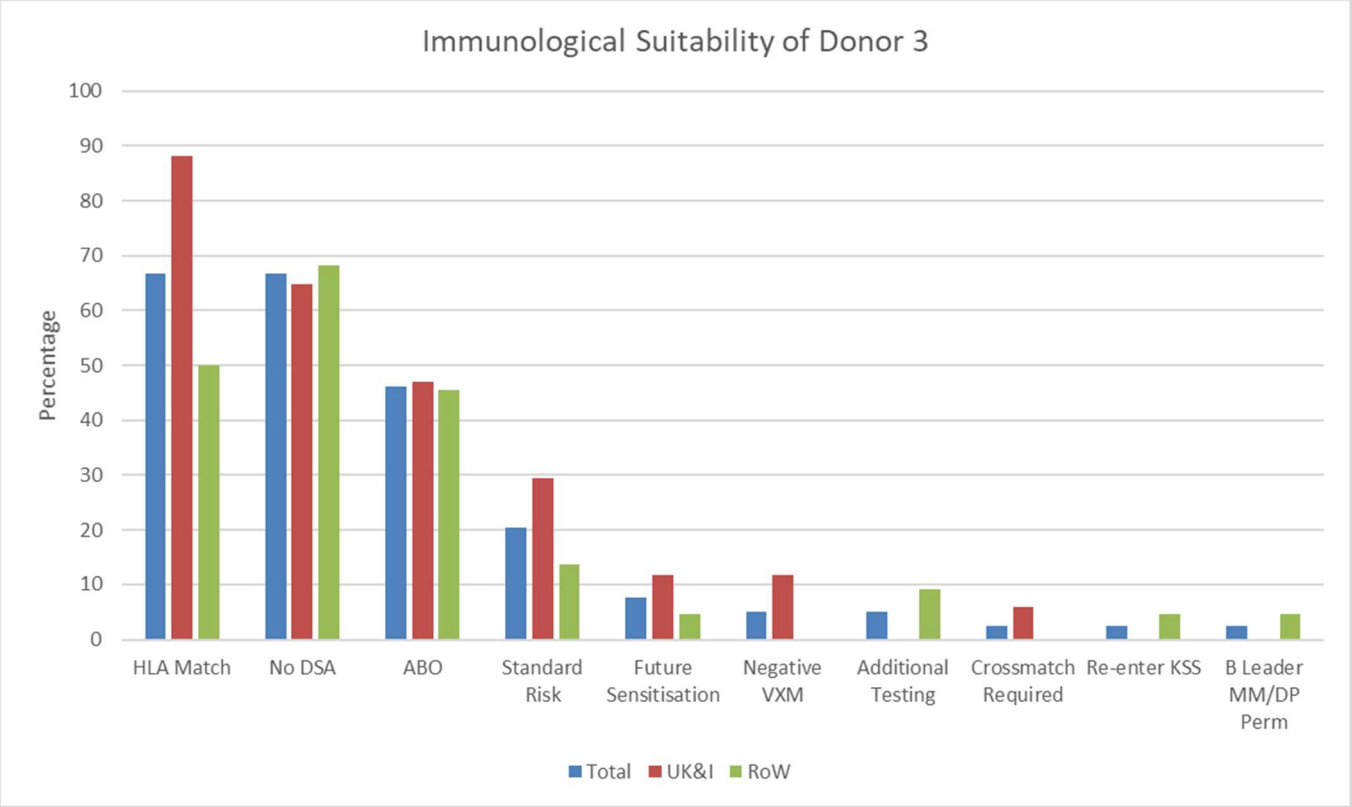

Q7a) Based on the information provided, how would you advise your clinical team to proceed?

Reasons	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Donor AA	5	13%	3	18%	2	9%
Donor 3	27	69%	12	71%	15	68%
Neither	7	18%	2	12%	5	23%

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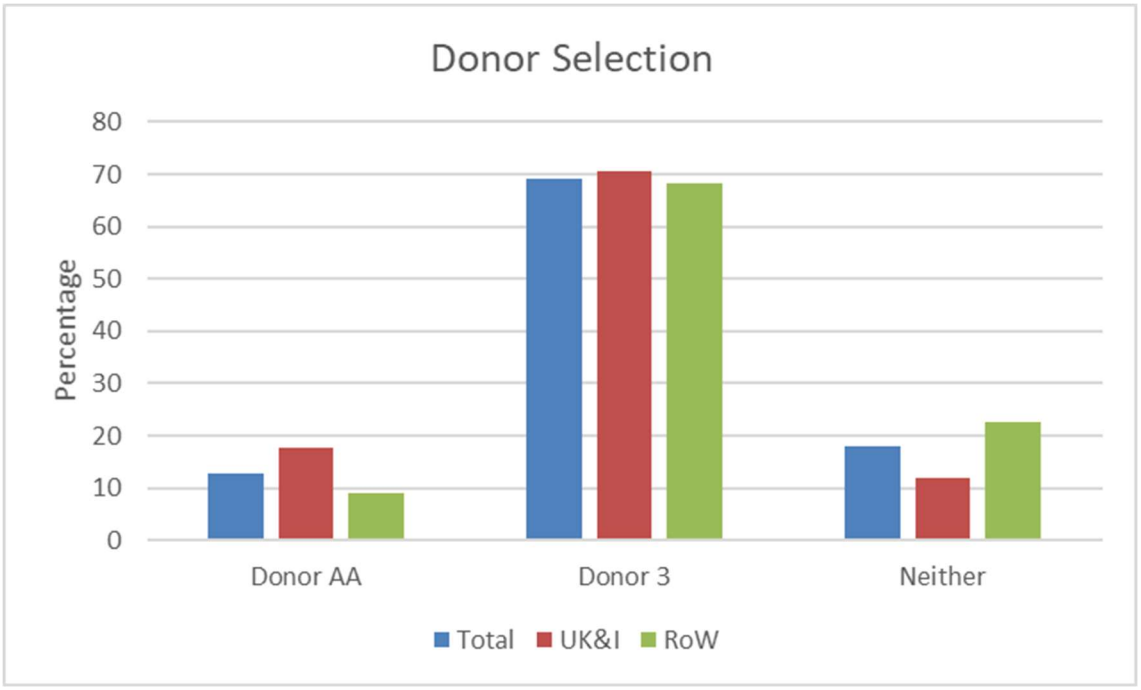

Q7b) Please provide a reason for your answer.

Option	Reason	Total		UK&I		RoW	
		Number	%	Number	%	Number	%
Donor AA	Age - younger donor	4	10%	3	18%	1	5%
	HLA match / Sensitisation	4	10%	3	18%	1	5%
	Standard risk	3	8%	2	12%	1	5%
Donor 3	No Donor Specific Antibodies	22	56%	11	65%	11	50%
	Age - younger donor	10	26%	5	29%	5	23%
	ABO compatible	6	15%	3	18%	3	14%
	HLA match	6	15%	2	12%	4	18%
	Perform crossmatch / SAB analysis	5	13%	3	18%	2	9%
	Standard risk	3	8%	3	18%	0	0%
	Negative virtual crossmatch	4	10%	1	6%	3	14%
	Male	2	5%	1	6%	1	5%
Neither	Wait for alternative donor	3	8%	2	12%	1	5%
	Insufficient info / further test required	3	8%	0	0%	3	14%
	HLA match	3	8%	1	6%	2	9%
	Donor specific antibodies	1	3%	0	0%	1	5%

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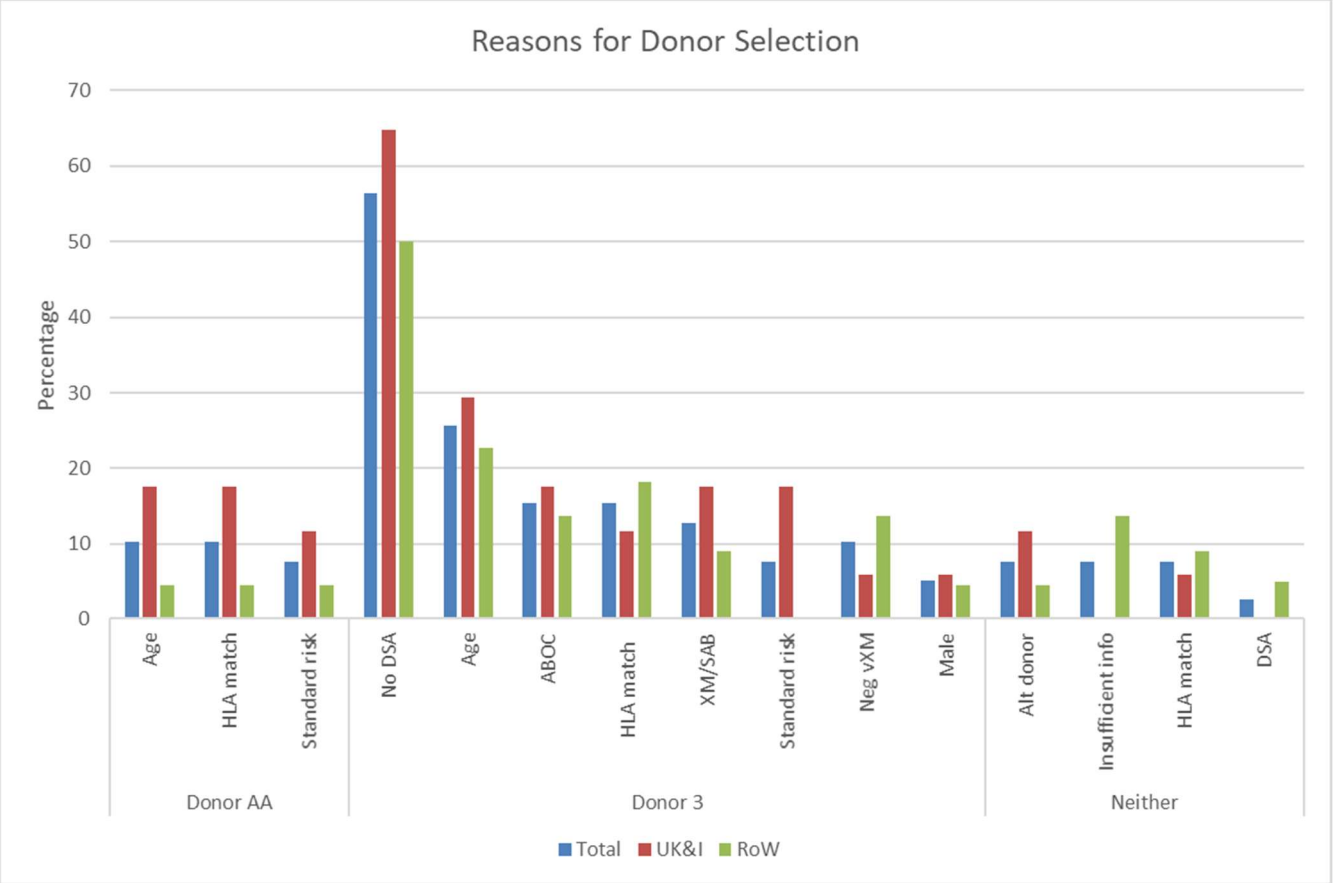

At this point a change in laboratory policy meant that the latest recipient sample (Sample 2) was tested using single antigen bead kits for Class I in addition to the Class II testing already performed. Results are shown in Table 2.

Table 2: One Lambda LABScreen Single Antigen Bead Class I Kit Results (note all other beads <500 MFI) for Sample 2.

Mixed screen	One Lambda SAB Class I	MFI
Negative	B*44:02	2432
	B*44:03	3785
	C*01:02	1978
	C*02:02	1859
	C*05:01	4652

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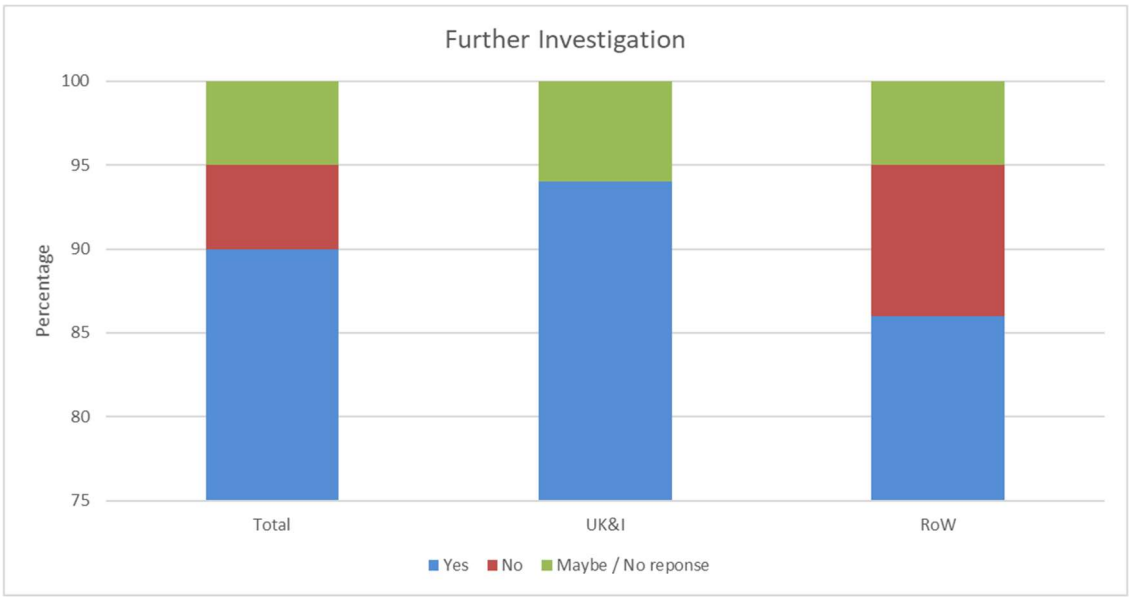
Q8a) Would you investigate this result further?

Option	Reason(s)	Total		UK&I		RoW	
		Number	%	Number	%	Number	%
Yes	Re-test SAB	35	90%	16	94%	19	86%
	Use alternative antibody detection method e.g. EDTA, Dilutions, PRA, Immucor, HistoSpot, C1q						
	Longitudinal antibody monitoring						
	High resolution HLA genotyping						
	Crossmatch						
	3rd party crossmatch						
	Request sensitising information						
No	Result is not unexpected	2	5%	0	0%	2	9%
Maybe / No response	May test historic samples	2	5%	1	6%	1	5%



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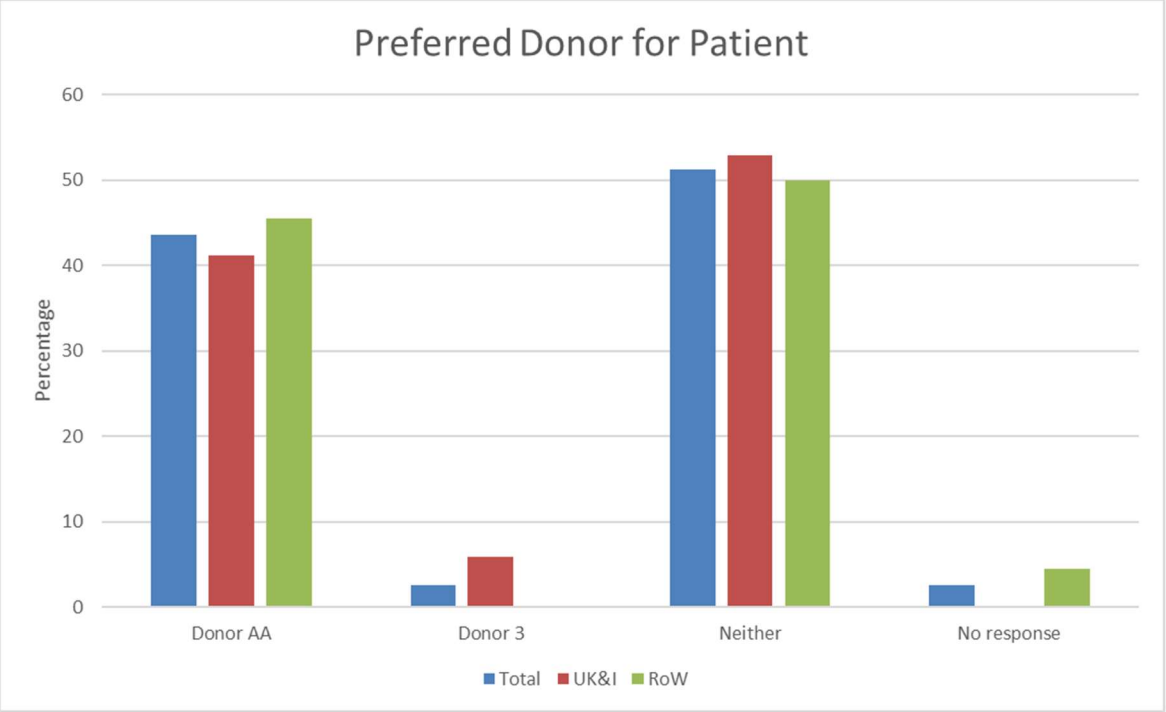
Q8b) Has this information altered your decision - what is your preferred donor for this patient?

Reasons	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Donor AA	17	44%	7	41%	10	45%
Donor 3	1	3%	1	6%	0	0%
Neither	20	51%	9	53%	11	50%
No response	1	3%	0	0%	1	5%



Q8c) Please provide a reason for your answer.

Option	Reason	Total		UK&I		RoW	
		Number	%	Number	%	Number	%
Donor AA	Lower level DSA	13	33%	6	35%	7	32%
	Better HLA match	6	15%	3	18%	3	14%
	Younger	4	10%	4	24%	0	0%
	Likely negative crossmatch	2	5%	2	12%	0	0%
	Use desensitisation protocol	1	3%	0	0%	1	5%

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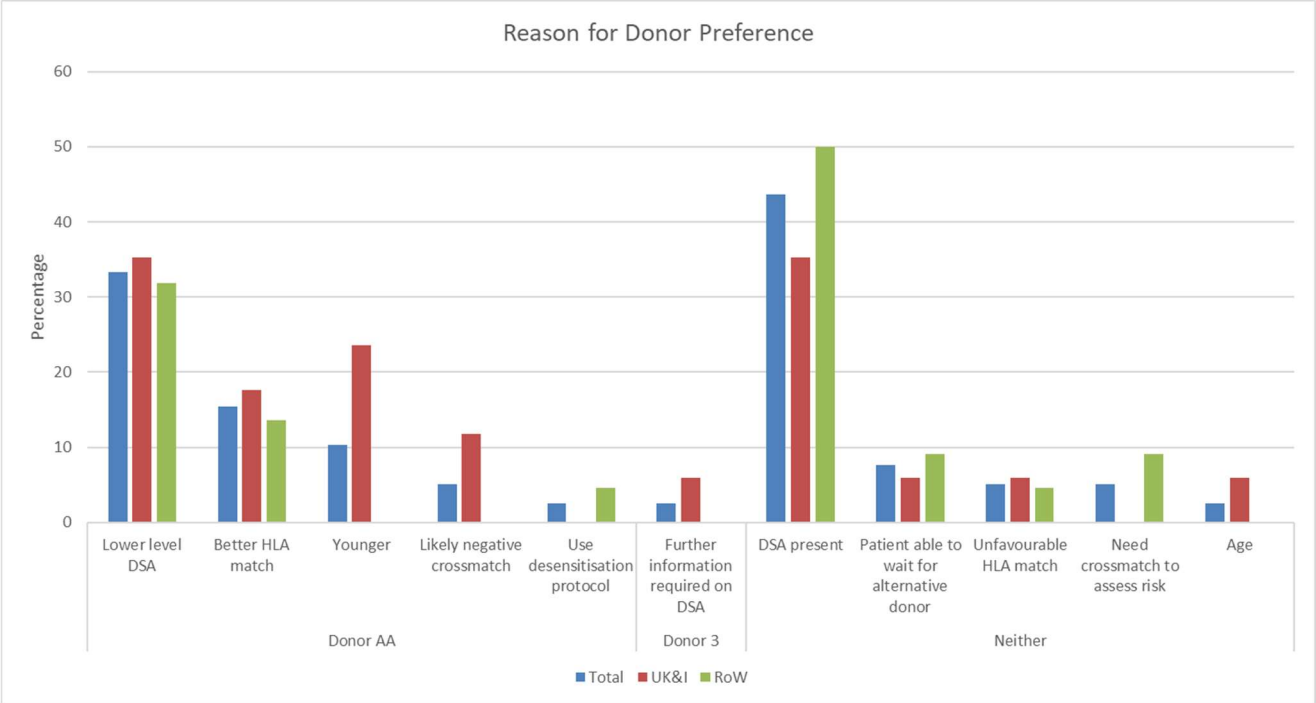
Donor 3	**Further information required on DSA**	1	**3%**	1	**6%**	0	**0%**
Neither	**DSA present**	17	**44%**	6	**35%**	11	**50%**
	Patient able to wait for alternative donor	3	**8%**	1	**6%**	2	**9%**
	Unfavourable HLA match	2	**5%**	1	**6%**	1	**5%**
	Need crossmatch to assess risk	2	**5%**	0	**0%**	2	**9%**
	Age	1	**3%**	1	**6%**	0	**0%**



Q8d) What would you recommend to increase the chances of a successful transplantation for this patient?

Reason	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Regular DSA monitoring	14	**36%**	6	**35%**	8	**36%**
Modified induction therapy	12	**31%**	5	**29%**	7	**32%**
Desensitisation	10	**26%**	3	**18%**	7	**32%**
Alternative donor options	9	**23%**	5	**29%**	4	**18%**
Register for deceased donor	7	**18%**	3	**18%**	4	**18%**

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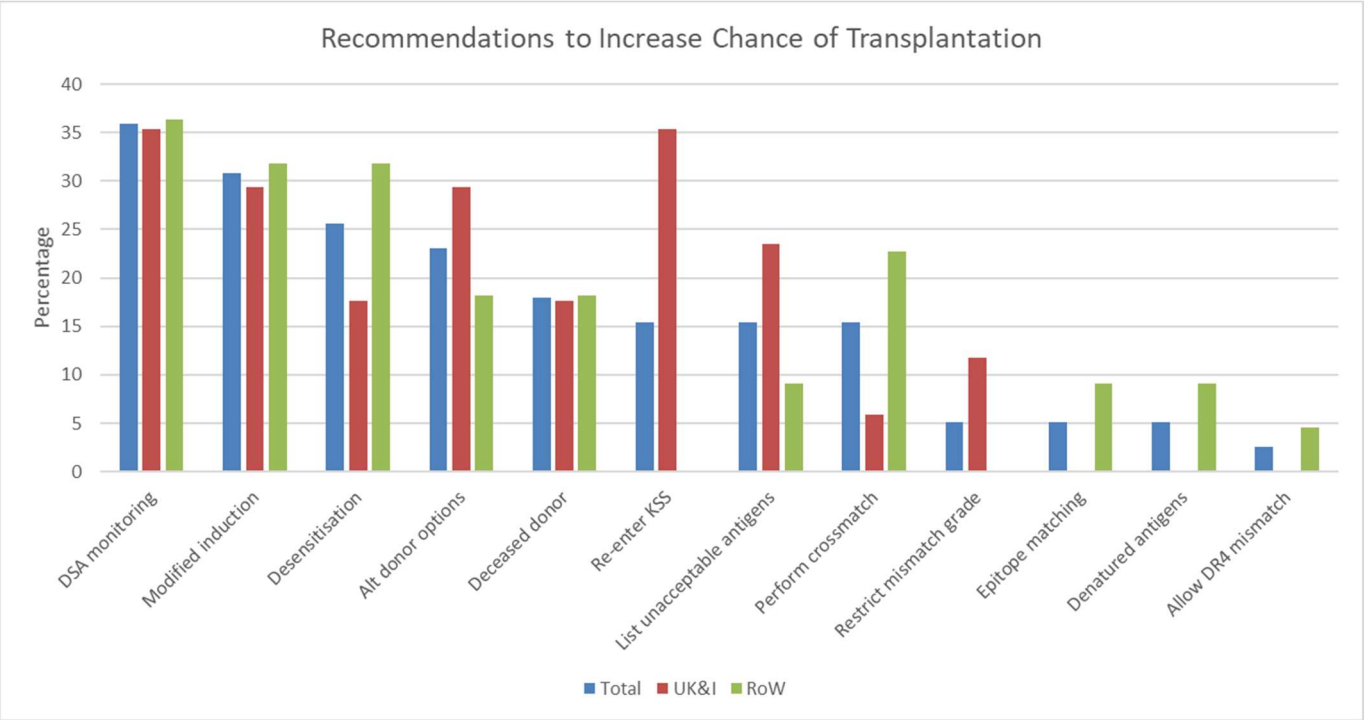
Re-enter kidney sharing scheme	6	**15%**	6	**35%**	0	**0%**
List unacceptable antigens	6	**15%**	4	**24%**	2	**9%**
Perform crossmatch	6	**15%**	1	**6%**	5	**23%**
Restrict mismatch grade to 2 DR	2	**5%**	2	**12%**	0	**0%**
Epitope matching	2	**5%**	0	**0%**	2	**9%**
Check for reactivity to denatured antigens	2	**5%**	0	**0%**	2	**9%**
Allow DR4 mismatch	1	**3%**	0	**0%**	1	**5%**



Q9a) Does your laboratory support testing for renal transplantation?

Reasons	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Yes	35	**90%**	14	**82%**	21	**95%**
No	4	**10%**	3	**18%**	1	**5%**

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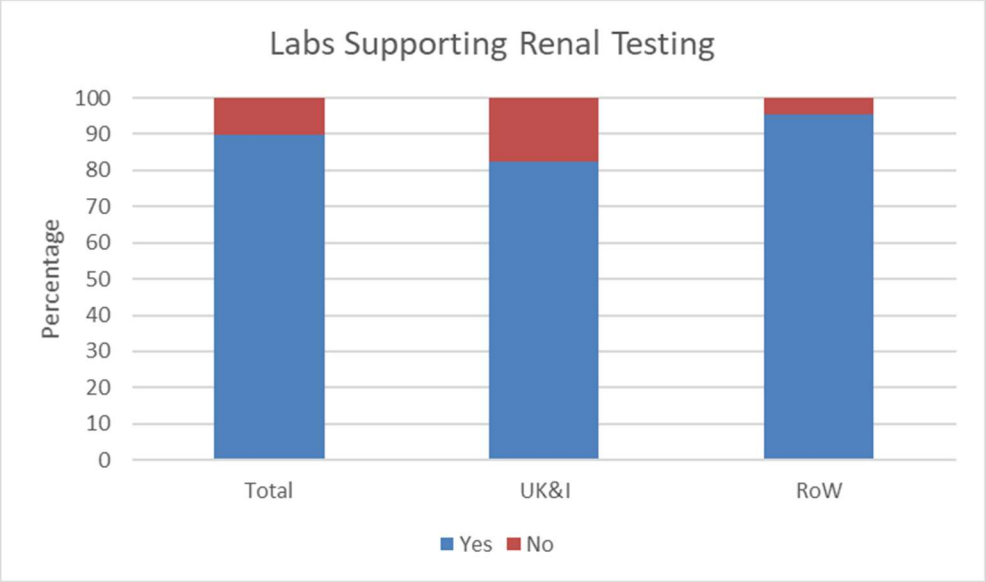
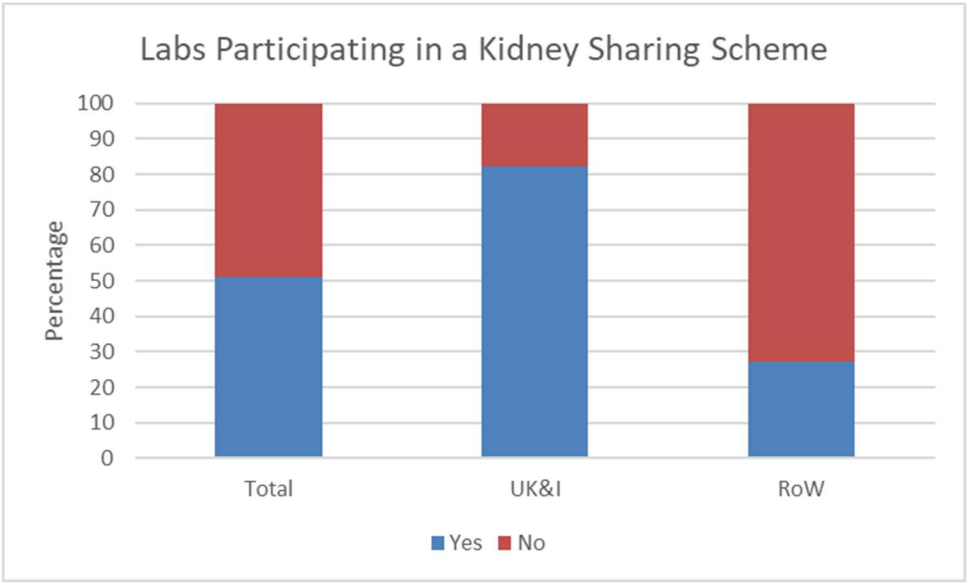


Q9b) Do you routinely enter patients in to a kidney sharing scheme?

Reasons	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Yes	20	51%	14	82%	6	27%
No	19	49%	3	18%	16	73%



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Q10) Any further comments on the scenario?

- A good NEQAS iED scenario.
- Not enough information provided to fully answer questions.
- Results of any crossmatches performed would have been useful to see.
- Please include the method of HLA typing for the patient and the potential donors. Thank you.
- High res typing of the potential donors would have been beneficial. Antibody screening data using alternative test.
- Close monitoring of the patient's HLA antibody profile using SAB as per BSHI/BTS guidelines. Consider any other living donor options. Enter into another UKLKSS run.
- We would not normally have the option of two donors when reviewing matching runs from the sharing scheme, each patient has one donor assigned. Our MFI cut-off is 1000 so we generally would not be offered a donor with DSA unless there was DQA1 HLA antibodies which we currently do not list with ODT. We would normally always do a PRA1/2 or SA1/2 if PRA positive for all patients being activated on the transplant waiting list.
- Given the apparent health of the patient and the fact that he had not yet started dialysis the unit were very keen to transplant. An eGFR of 11; it would be really useful to know either the units or the normal range.
- There would be a potentially lower CIT with a direct living donor.
- Class I antibody testing at higher resolution would likely have been performed considerably earlier in the W/U prior to registration in the sharing scheme, particularly in view of the transfusion history and knowledge that Mixed screening kit less sensitive than SAB. Data from alternative screening panels would also be useful to confirm specificities prior to listing as UAg. This scenario highlights differences in centre protocols as it is unlikely that offering sharing scheme over direct transplantation would have been considered for this patient at our centre unless the preference for a lower mismatch was decided by Clinical Team prior to registration. Significantly more information would be required to make decisions being asked in this scenario - knowledge of the clinical protocols around mismatching for example, along with information regarding the timeframe to transplant, the willingness and availability of the donor to enter multiple sharing rounds to achieve a better donor match. This doesn't really reflect a real life situation where ongoing conversations with the clinical team and input from the donor and recipient would be needed to make the decisions being asked.
- In these cases, we like to use the ODT calculator to determine possible cRF for patient should they become sensitised to all mismatches in a specific donor.
- If flow cross matches for first donor AA were negative, we would not have entered this patient into the sharing scheme at all. In our center we have the policy to always perform Luminex SA class I and class II with the first serum sample available from the patient to

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have information about antibodies present in this technique. Whole case seems to our opinion not really realistic case.

- Before transplantation single antigens are recommended despite of negative screening to avoid false negative screening.
- Further discussion with clinical team is paramount. We would recommend to explore further options before proceeding with donor AA. If time permits, extensive search for a live donor is suggested. Consider the use of different commercial kits and physical crossmatch i.e. CDC and Flow cytometry.
- Useful to assess the recent sensitization state with a new sample. Assessment for recurrence of disease (Ig A nephropathy) needs particular careful workup after transplantation.

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

Question 1 – definition of UA

We would recommend that all laboratories perform their own evaluations to develop an understanding of what local MFI ranges may result in a positive flow crossmatch. These evaluations should incorporate clinical outcome data and be regularly reviewed to ensure optimum patient outcome without unnecessarily limiting access to transplantation.

Question 2 – immunological compatibility with Donor AA

The patient may have a donor specific antibody to HLA-DR4 that requires further investigation.
The patient is young and clinically stable so we would recommend entering the patient and Donor AA in to a kidney exchange scheme. This may provide a more favourable donor, avoiding any potential donor specific antibodies, improve on the 012 HLA match (Donor AA) and limit future sensitisation of the patient.

Question 3 – further lab work prior to entry to KSS

It would be prudent to re-test the patient for HLA antibodies prior to entry in to a kidney sharing scheme, perhaps incorporating extended testing using kits from alternate manufacturers if available. It may also be useful to perform crossmatching using cells expressing HLA-DR4 to determine the clinical relevance of the potential antibody detected by the One Lambda single antigen bead kit. Likewise, epitope analysis might be useful to explain reactivity patterns.
If your local kidney sharing scheme allows it, we would also recommend adding limits on the maximum mismatch grade. This would ensure that any offers the patient received were a better HLA match than Donor AA.

Question 4 – listing UA prior to entry into KSS

If the patient was entered into a kidney sharing scheme and your laboratory believed the DR4 and DR7 antibody reactivity to be clinically relevant it would be useful to list both DR4 and DR7 as unacceptable antigens. This would prevent HLA-DR4 and DR7 positive donors being offered to the patient which, if declined, could break a donor chain.

Question 5 – suitability of donors 1 and 2

Factors to consider when assessing the suitability of Donor 1 and 2 include the HLA match, the antigen frequency of any HLA mismatches and the age of donors. It is also wise to consider the presence of any unlisted donor directed HLA antibodies the patient may have e.g. DR7.
We feel that neither Donor 1 nor 2 present an optimum match for this patient. The donors both possess high frequency HLA mismatches (e.g. HLA-DQ2) and generate an increased potential percentage calculated reaction frequency compared to Donor AA (https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/calculators/ - Donor AA cRF = 50%, Donor 1 cRF = 60%, Donor 2 cRF = 71%).

Question 6 – immunological suitability of donor 3

The patient has no potential donor specific antibodies to this donor. We would anticipate a negative virtual crossmatch and a standard risk transplant. However, when matching at the 'broad' level the HLA mismatch grade is 021, at 'split' level specificity the mismatch would be 122. The HLA mismatched antigens have a potential for generating 69% calculated reaction frequency (https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/calculators/) which is a cause for concern given the patient is young and will likely need re-transplantation in the future.
Laboratories may want to consider programmes such as HLA matchmaker to assess donor and patient compatibility at an epitope level.

Question 7 – advice to a clinician

We would advise declining the offer from Donor 3. Donor 3 is younger than Donor 1 and 2. The patient has no donor specific antibodies and is ABO compatible. This would represent a standard risk transplant.

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However, the HLA mismatch is not optimal for clinical outcome and the risk of sensitising the patient to common antigens could affect the patient's ability to be re-transplanted successfully.

Question 8 – Investigations after further ab testing

We would advise using additional testing such as an antibody kit from alternative manufacturer e.g. Immucor to gauge the clinical relevance of the Class I antibodies defined. It may also be useful to perform 3rd party or surrogate crossmatching.

Our preferred donor of those represented for this patient would be Donor AA. This is due to the potential donor directed HLA-B44 and Cw5 antibodies to Donor 3. Donor AA is also younger and a better HLA match. Although there are potential DSA to DR4, these antibodies were detected at low level. A crossmatch should be performed to fully assess immunological risk.

To increase the chances of successful transplantation it may be useful to consider augmented immunosuppression and regular post-transplant monitoring.

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.