UK NEQAS
International Quality Expertise

Histocompatibility and Immunogenetics

Participants Meeting 2017

WiFi password: Chinese2018

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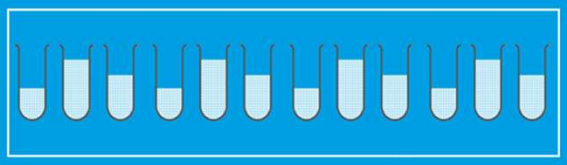
Histocompatibility and Immunogenetics

Welcome and Introduction

Judith Worthington

Chair of UK NEQAS for H&I Steering Committee



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2017 Steering Committee

- Judith Worthington (Chair)
- Arthi Anand
- Patrick Flynn
- James Kelleher
- Anthony Poles
- Ruhena Sergeant
- John Smith
- Helena Lee (BSHI Representative to UK NQAAP)
- Edwin Massey (Clinical Representative)

- Alan Balfe (Expert Advisor Scheme 5B)
- Carol Hardy (Lead Expert Advisor Scheme 5B)
- Gavin Willis (Expert Advisor Scheme 5B)

Notes

- Presentation focus on performance, interesting trends, discussion points, changes for 2018
- Handout contains full scheme analysis
- Labs 1-99 are from the UK and Ireland (UK&I)
- Labs 100 + are from the rest of the world (RoW)
- Please ask questions!

Scheme Assessment

- All Schemes (except 5B – Interpretative HFE, educational and pilots) assessed on a consensus basis
- All use 75% consensus level i.e. 75% of reports must agree on a result for it to be assessed
- Not tested (NT) and equivocal results excluded from assessment
- Labs that fail to return results, or provide valid reason for NT are assessed as unacceptable

	Summary of Results			
Total tested	21	21	21	21
Positive	20	14	13	1
Negative	1	7	8	20
Not Tested	2	2	2	2
% Positive	95.2%	66.7%	61.9%	4.8%
% Negative	4.8%	33.3%	38.1%	95.2%
Consensus	**Positive**	**Not Assessed**	**Not Assessed**	**Negative**
HLA Antibody (Defined By CDC)	A3, B7, B27, B22	B12, B21	A9, B57+	B18+
	Without DTT			
Lab No.	Serum 1	Serum 2	Serum 3	Serum 4
9	Positive	Negative	Negative	Negative
11	Positive	Positive	Positive	Negative
12	Positive	Negative	Positive	Negative
14	Positive	Positive	Positive	Positive
15	Positive	Positive	Positive	Negative
19	Positive	Positive	Negative	Negative
20	Positive	Negative	Negative	Negative
23	Negative	Negative	Negative	Negative
24	NT	NT	NT	NT
25	Positive	Negative	Negative	Negative
28	Positive	Negative	Negative	Negative
34	Positive	Positive	Positive	Negative
35	Positive	Positive	Positive	Negative
38	Positive	Positive	Negative	Negative
39	Positive	Positive	Positive	Negative
41	Positive	Positive	Negative	Negative
42	Positive	Positive	Weak Positive	Negative
45	Positive	Negative	Positive	Negative
48	NT	NT	NT	NT
51	Positive	Positive	Positive	Negative
54	Positive	Positive	Positive	Negative
58	Positive	Positive	Positive	Negative
62	Positive	Positive	Positive	Negative

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Unsatisfactory Performance (UP)

- Each scheme has minimum annual performance criteria
  - HLA Typing schemes 90%
  - Crossmatching 85%
  - Disease Association Schemes 100%
  - Antibody Specificity 75%
  - Antibody Detection 80%
- Participants that do not meet the minimum criteria are classed as unsatisfactory performers
- Must complete a root cause and CAPA form

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Changes for 2018

- Steering Committee - Kathryn Robson (Expert Advisor Scheme 5B)
- NEQAS Operations Manager to cover maternity leave
- Financial year operation by 2019
- Reference typing results for typing/disease schemes if consensus not reached
  - Scheme 8 & DPB1 assessment in Scheme 4A1 will always use reference result
- No longer offering Scheme 4B (ABO genotyping)
- IT system for online data entry

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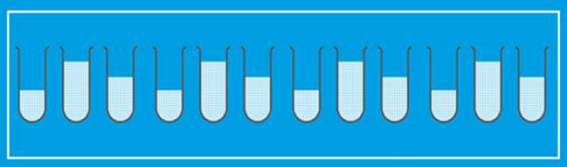
Scheme 1B
HLA-B27 Testing



Ruhena Sergeant

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2017 Incorrect Assignments

Sample	Result	Lab Number	Technique	HLA Type	Root Cause
1B02	False Pos	137	Flow	B7, B37	Antibody cross reactivity
1B03	False Pos	21	Flow	B7, B44	Sample mix-up
1B04	False Neg	21	Flow	B27, B62	
1B07	False Neg	326	Flow	B27, B57	No response
1B09	False Neg	46, 104 129, 142	Flow Molecular	B27, B18	Interpretation error Sent to referral lab – incorrect result EQA material different to clinical material No response
1B10	False Pos	137	Flow	B8 B13	Antibody cross reactivity

4 HLA-B27 positive samples distributed

9 errors: 6 False Neg, 3 False Pos

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Performance 2017

- 7 Unsatisfactory Performers (2 UK & Ireland)

	2013	2014	2015	2016	2017
Number of Participants (UK&I)	96 (47)	107 (51)	115 (54)	123 (54)	127 (52)
Number with Unsatisfactory Performance (< 100%) (UK&I)	4 (1)	4 (2)	8 (4)	15(6)	7 (2)
% Unsatisfactory Performance (UK&I)	4.2% (2.1%)	3.7% (3.9%)	6.9% (7.4%)	12.2% (11.1%)	5.5% (3.8%)

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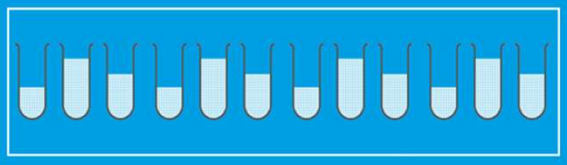
Scheme 5A
HFE Typing



Ruhena Sergeant

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Scheme 5A Performance

- H63D (56 participants)
- C282Y (56 participants
- S65C (24 participants)
- 5 errors (3 labs)

5A Incorrect Assignments					
Sample	**Codon**	**Report**	**Consensus**	**Lab Number**	**Root Cause**
5A03	63	HH	HD	85	Transcription error
5A09	282	YY	CC	99 150	Transcription error Sample mix-up
5A10	282	CC	YY	99 150	Transcription error Sample mix-up

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Scheme 5A Performance

	2013	2014	2015	2016	2017
Number of Participants (UK&I)	58 (10)	59 (50)	60 (49)	58(49)	56 (42)
Number with Unsatisfactory Performance (< 100%) (UK&I)	2 (2)	2 (2)	0 (0)	3 (2)	3 (2)
% Unsatisfactory Performance	3.9%	3.4%	0%	5.2%	5.3%

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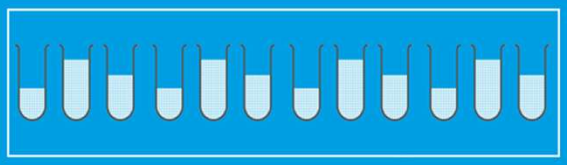
Scheme 5B

Interpretative HFE genotype and hereditary haemochromatosis



Carol Hardy

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Scheme 5B

- Twice a year, 2 clinical scenarios
- HFE genotype provided, together with various pieces of clinical information; fictitious cases based on real or typical experience
- Reports must be identical in format to that used for routine clinical reporting in participants' laboratories
- For each scenario, interpretative criteria expected to be covered by the report were identified and agreed by the expert assessors
  - Penalty points awarded

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Performance

2017 – all 4 scenarios

5 penalty points per scenario, 20 in total

1	lab got	0 penalty points
6	labs got	1 penalty point
7	labs got	2 penalty points
2	labs got	3 penalty points
1	labs got	4 penalty points
2	labs got	5 penalty points
1	lab got	6 penalty points

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Scheme 5B Performance

	2012	2013	2014	2015	2016	2017
Number of Participants	21	19	20	18	19	20
Number with Unsatisfactory Performance	3	3	5	0	0	0
% Unsatisfactory Performance	14.3%	15.8%	25.0%	0%	0%	0%

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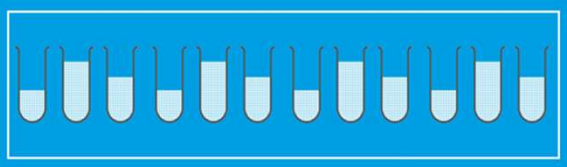
Scheme 7

HLA-B*57:01 Typing for Drug Hypersensitivity



Ruhena Sergeant

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2017 Incorrect Assignments

Sample	Result	Lab Number	Root Cause
701	False Neg	190 245	No response
703	False Pos	190	No response
704	False Pos	190	
705	False Neg	190	No response
706	False Neg	126	Borderline result
708	False Neg	11	Transcription error

7 HLA B*57:01 samples distributed in 2017

7 errors in 2017 made by 4 labs (5 false neg, 2 false pos)

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Scheme 7 Performance

- 4 labs with unacceptable performance

	2013	2014	2015	2016	2017
Number of Participants (UK&I)	47 (23)	56 (24)	62 (26)	62 (25)	64 (26)
Number with Unacceptable Performance (< 100%) (UK&I)	0 (0)	1 (0)	0 (0)	1 (1)	4 (1)
% Unsatisfactory Performance	0.0%	1.8%	0.0%	1.6%	6.3%

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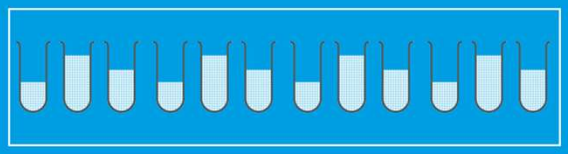
Scheme 8

HLA and Disease Typing for
HLA-DR/DQ/DP Only



Deborah Pritchard

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Reporting

RESULTS OF PARTICIPATING LABORATORIES

DESPATCHED ON 26/01/2016

SAMPLE 801/2016

CONSENSUS TYPE FROM SCHEME 4A2 SAMPLE:

Class I	A*	A*	B*	B*	C*	C*
	03:01	29:02	27:05	44:03	02:02	16:01

Class II	DRB1 04:01	DRB1 07:01	DRB4* 01:01	DRB4* 01:03	DQA1 02:01	DQA1* 03:03	DQB1 02:02	DQB1 03:02	DPA1	DPA1	DPB1 06:01	DPB1 10:01

Lab No.	DRB1	DRB1	DRB4*	DRB4*	DQA1	DQA1*	DQB1*	DQB1	DPA1	DPA1	DPB1	DPB1	Comments
14	04	07	01		02	03	02	03:02	01	02	06	10	
24	04	07			02:01	03	02:02	03:02					DQB1*: string of alleles
25	04	07	01		02:01	03:01/02/0	02:02	03:02	01:03	02:01	06:01	10:01	
86	04	07			02:01	03:01	02:02	03:02					
113	04:01	07			02:01	03	02	03:02					
124	04	07					02:02	03:02					
126					02	03	02	03:02					
127	04	07	01:01		02	03	02	03					
129	04:01				02:01	03	02	03:02					
154	04	07			02:01	03:03	02:02	03:02					
185	04	07			02	03	02:02	03:02					
225	04	07											
245	04:01	07			02	03	02	03:02					
274	04	07			02	03	02	03:02					
276	04	07	01		02	03	02	03	01	02			
295													
307					02:01	03:03	02	03:02					
319						03:01	02	03:02					
342					02	03	02	03:02					

HLA Type

PRESENCE/ABSENCE RESULTS OF PARTICIPATING LABORATORIES

DESPATCHED ON 26/01/2016

SAMPLE 802/2016

CONSENSUS TYPE FROM SCHEME 4A2 SAMPLE:

DRB1* 07:01	DRB1* 11:01	DRB3* 02:02	DRB4* 01:03N	DQA1* 02:01	DQA1* 05:05	DQB1* 03:01	DQB1* 03:03	DPA1*	DPA1*	DPB1* 04:02	DPB1* 04:02/blank

Lab No.	DQB1*	Present	DQB1*	Present	DQB1*	Present	DQB1*	Present	DQB1*	Present	DQB1*	Present	DQB1*	Present	DQB1*	Present	DQB1*	Present
11	02	No									03:02	No					06:02	No
16			02:01	No	02:02	No					03:02	No					06:02	No
17			02:01	No							03:02	No					06:02	No
124	02	No									03:02	No			03:05	No	03:10	No	06:02	No
126	02	No									03:02	No						
129	02	No									03:02	No						
173	02	No									03:02	No	03:03	Yes				
201	02	No									03:02	No						
223	02	No									03:02	No					06:02	No
225	02	No									03:02	No					06:02	No
263	02	No									03:02	No						
269	02	No					02/03:02	No										
276	02	No									03:02	No					06:02	No
278	02	No					02/03:02	No										
279			02:01	No	02:02	No					03:01	Yes	03:02	No				
285			02:01	No	02:02	No					03:01	Yes	03:02	No				
317	02	No					02/03:02	No										
319	02	No											03:02	No				
329	02	No											03:02	No				
333	02	No									03:01	Yes	03:02	Yes				
338			02:01	No	02:02	No					03:01	Yes	03:02	No				
343	02	No											03:02	No				

Presence/absence of specific alleles (disease association kits)

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2017 Incorrect Assignments

Sample	Lab	Result	HLA Type	Root Cause
801	185	DQB1*02:01	DQB1*02:02	Ambiguous kit result
	255	DQB1*02 Neg		Reporting error
	355			Kit limitations
802	276	DRB1*15	DRB1*16	Reporting error
803	127	DQB1*03:02 Neg	DQB1*03:02	Reporting error
	255	DQB1*02 Neg	DQB1*02:02	Reporting error
805	17	DQA1*03 Neg	DQA1*03:03	Reporting error
	129	DRB1*04 Neg	DRB1*04:01	Reporting error
806	113	DRB1*04:05	DRB1*04:08	Reported more frequent allele
	127	DQA1*03 Neg	DQA1*03:03	Reporting error
	127, 142	DQA1*03:02/03:03 Neg	DQA1*03:03	Reporting error
	295	DRB1*04 Neg DQA1*03 Neg	DRB1*04:08 DQA1*03:03	Technical error – machine at incorrect temperature

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2017 Incorrect Assignments

Sample	Lab Number	Result	HLA Type	Root Cause
807	127, 142	DQB1*02/03:02 Neg	DQB1*02:01	Reporting error
808	109	DQB1*02 Neg	DQB1*02:02	Reporting error
	129, 142	DQB1*02/03:02 Neg		Reporting error
	331	DQB1*03:02	DQB1*03:03	Reporting error
	333	DQB1*03:02 Pos		No response
809	307	DQA1*05 Pos	DQA1*01:01, 01:02	Reporting error
810	78	DQA1*06 DQB1*01	DQA1*01:02 DQB1*06:02	Reporting error

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Scheme 8 Performance

- 24 incorrect assignments in 2017 (2 UK&I – reporting errors)

	2013	2014	2015	2016	2017
Number of Participants (UK&I)	19 (8)	21 (9)	30 (8)	39 (8)	45 (9)
Number with Unsatisfactory Performance (< 100%) (UK&I)	2 (1)	3 (2)	8 (0)	8 (3)	15 (2)
% Unsatisfactory Performance	10.5%	14.3%	26.7%	20.5%	33.3%

10/15 UP due to reporting errors

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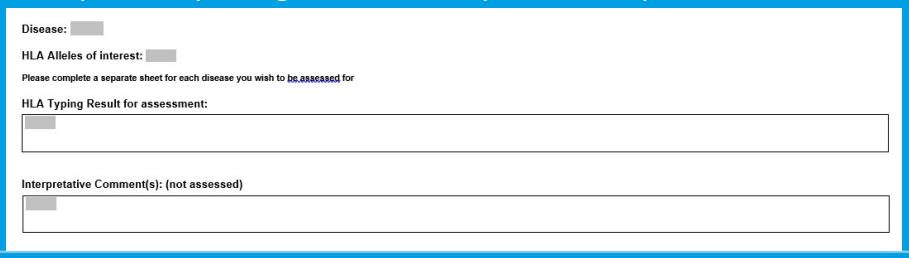
Changes for 2018

- Scheme 8 – "HLA genotyping for coeliac and other HLA associated diseases"
- Includes all Class I and Class II HLA associated diseases (not B27)
- 10 blood samples (no longer DNA). Reference typing result.
- Participants register for diseases
- For each disease a report must be made as per clinical report – simplified reporting format, with optional interpretative comments


Disease:

HLA Alleles of interest:

Please complete a separate sheet for each disease you wish to be assessed for

HLA Typing Result for assessment:

Interpretative Comment(s): (not assessed)

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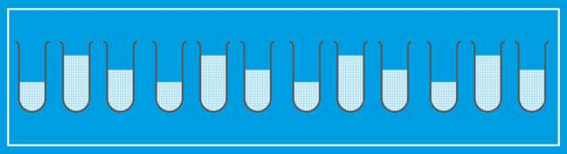
Schemes 1B, 5A, 5B, 7, 8

Discussion



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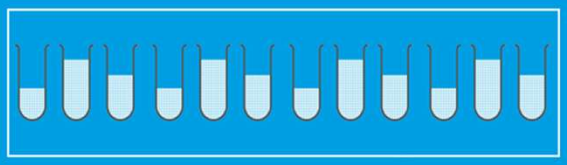
Scheme 2B

Crossmatching by Flow Cytometry



James Kelleher

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Scheme 2B Summary

	T Cells			B Cells	
	UK&I	RoW		UK&I	RoW
Number of participants	22	57-63		22	57-63
Number of XM assessed (>75% consensus)	36/40	34/40		31/40	29/40
Number of Positive XM	17	9		23	12
Number of Negative XM	19	25		8	17
Number of incorrect assignments	23 (2.6%)	97 (4.0%)		11 (1.6%)	82 (3.6%)
Number of False Pos	11	45		7	28
Number of False Neg	12	52		4	54
Number of equivocal assignments	44 (5.0%)	86 (3.6%)		41 (5.9%)	115 (5.0%)
Number of NT assignments	20 (2.3%)	294 (12.2%)		45 (6.4%)	355 (15.5%)

UK&I and RoW receive different blood samples

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Unacceptable Performers 2017

- 8 labs with UP (<85%)

Lab	T	No. of results submitted	B	No. of results submitted
23	83.3%	32	91.3%	32
133	79.4%	38	86.2%	39
206	89.7%	35	80.0%	34
218	87.5%	8	57.1%	8
252	79.4%	40	93.3%	40
260	88.2%	40	80.6%	40
276	92.9%	32	76.0%	32
302	66.7%	8	50.0%	8

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Scheme 2B Performance

Scheme 2B	2015	2016	2017
Number of Participants (UK&I)	73 (23)	76 (23)	85 (22)
Number with Unsatisfactory Performance (< 85%) (UK&I)	13 (3)	13 (1)	8 (1)
% Unsatisfactory Performance	17.8%	17.1%	8.7%

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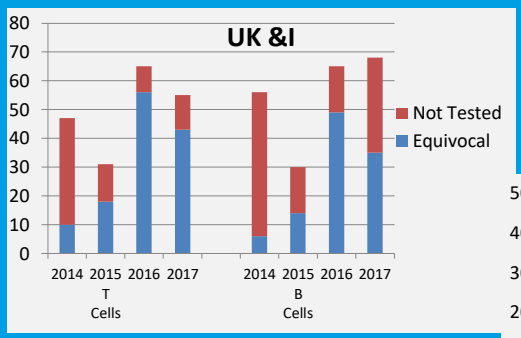
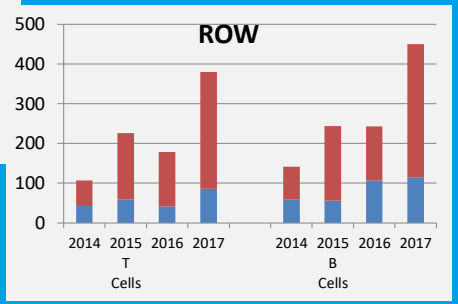
Increase in Equivocal Reports





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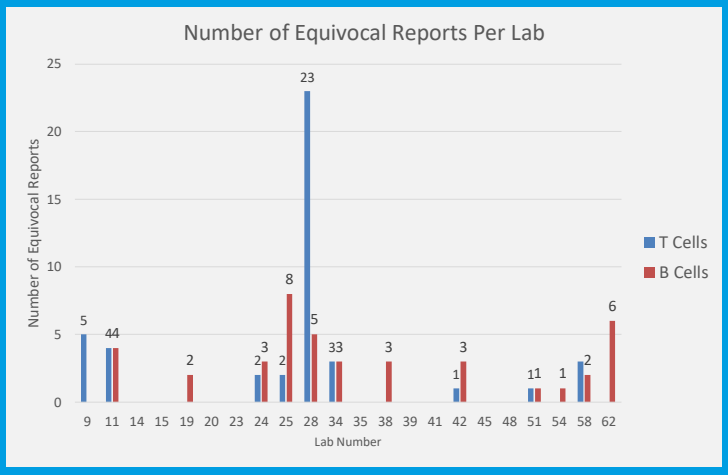
Equivocal Reports Per Lab



- 13/22 labs reported ≥1 equivocal result

Equivocal Issues

Prior to 2018, equivocal reports were excluded from assessment

But – they can impact on the consensus

e.g. sample 2B10/2016 T cell result

- Reported positive by 75% (12/16)
- Reported equivocal by 30.4% (7/23)
- Not assessed due to high number of equivocal reports

Total tested	16
Positive	12
Negative	4
NT/Equivocal	7
% Positive	75.0%
% Negative	25.0%
Consensus	**Not Assessed***
HLA Antibody Specificity (Defined By CDC)	B12
Lab No.	Serum 1
9	Positive
11	Positive
12	Negative
14	Negative
15	Positive
19	Positive
20	Positive
23	Positive
24	Equivocal
25	Positive
28	Equivocal
34	Equivocal
35	Equivocal
38	Positive
39	Negative
41	Positive
42	Positive
45	Positive
48	Negative
51	Equivocal
54	Positive
58	Equivocal
62	Equivocal

Equivocal Result Options

1. Include equivocal results in assessment (positive/negative/equivocal)
2. Not allow equivocal results (only positive/negative) and introduce minimum number of results required
3. No change - continue to exclude equivocal results from assessment

Which would you choose?

Debate

- Should Equivocal Results be assessed in Scheme 2B?
- 'No' – Judith Worthington
- 'Yes' – John Smith

Define Equivocal

- Open to more than one interpretation
  - Vague, indeterminate, imprecise, inexact, blurry, hazy
- Uncertain or questionable in nature

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Equivocal and Clinical Reporting

- Extract from Cardiology Handbook re: myocardial perfusion imaging
  - *"Many reports fall short on being clear and informative by using words such as "suggestive of" "of unknown significance" and "equivocal". These words are NOT useful to the referring physician"*

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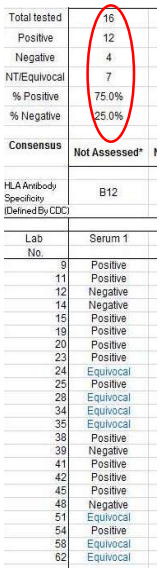
Equivocal and EQA

The crossmatch status of each sample is determined by at least 75% of labs agreeing on the positivity or negativity of each test

- 23 laboratories returned results but we are only using the results of 16 to assess!

- Why the rise of the Equivocal?
  - ISO15189 and MoU
  - Results forms!



Total tested	16
Positive	12
Negative	4
NT/Equivocal	7
% Positive	75.0%
% Negative	25.0%
Consensus	**Not Assessed***
HLA Antibody Specificity (Defined By CDC)	B12

Lab No.	Serum 1
9	Positive
11	Positive
12	Negative
14	Negative
15	Positive
19	Positive
20	Positive
23	Positive
24	Equivocal
25	Positive
28	Equivocal
34	Equivocal
35	Equivocal
38	Positive
39	Negative
41	Positive
42	Positive
45	Positive
48	Negative
51	Equivocal
54	Positive
58	Equivocal
62	Equivocal

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The Problem with Including Equivocal in the Scoring

- This is a purely technical scheme – pos or neg
- Consensus scoring with 3 possible results
  - Less results will be assessed
  - Only strong positive / negative
  - If consensus is equivocal we will be penalising labs who have an actual result
- Reduce the benefit of the scheme
- Disadvantage labs who do not use equivocal

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Debate

- Should Equivocal Results be assessed in Scheme 2B?
- 'No' – Judith Worthington
- 'Yes' – John Smith

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Scheme 2B

To assess participants' ability to correctly determine cell/serum flow cytometry crossmatch status.

Note that the scheme is a technical assessment of flow cytometry crossmatching, and results should not be 'interpreted' before reporting.

So no single antigens, no sensitisation histories, no antibody specificity to influence borderline results and reporting

Because that is then an interpretive scheme

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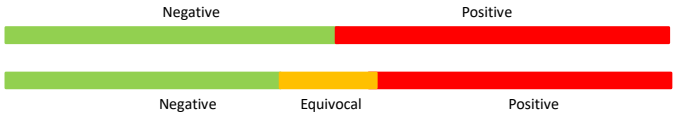
Equivocal Result Options

1. Include equivocal results in assessment (positive/negative/equivocal)
2. Not allow equivocal results (only positive/negative) and introduce minimum number of results required
3. No change - continue to exclude equivocal results from assessment

Is 'equivocal' a valid result?

13/22 labs reported ≥1 equivocal result – so maybe?



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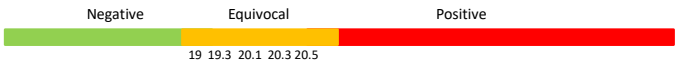
Hypothetical example

Repeat test 5 times (each one in triplicate) and get these mean shift values
3 are POSITIVE and 2 are NEGATIVE
Is this result Positive or Negative?

The mean of these 5 tests is 19.84 - NEGATIVE



<u>Labscreen mixed assay</u>
We all set our ratio cut-offs to have 3 regions
1. Definite negative
2. Definite positive
3. An area where there may or may not be antibodies – for further investigation

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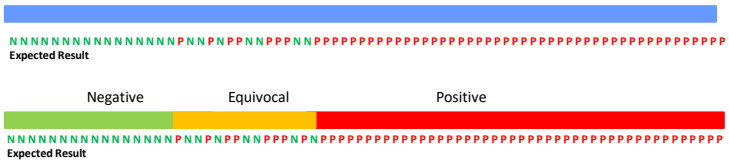
Flow crossmatch validation
Tested over 100 different cell:sera combinations.
Each combination had an 'expected' result based on antibody reactivity and cell HLA type
Analysed channel shift by ROC curve analysis



There is a range of channel shifts where the result can be positive or negative depending on a variety of factors including
Antibody specificity
Antigen expression
Non-specific binding

Hopefully, you'll agree that 'equivocal' is a valid result in the flow crossmatch

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Issues

1. Some labs use 'equivocal' result and some don't.
   I would urge all labs who have a straight pos/neg cut-off to go back and investigate

2. In the short term there may be an increase in the number of 'not assessed' reports

3. Need to make sure these are reported only when the assay has worked and the result is truly 'equivocal'.

4. Mustn't be used for assays where something went wrong and we're not sure what it was.

EQUIVOCAL IS A VALID RESULT AND SHOULD BE ASSESSED

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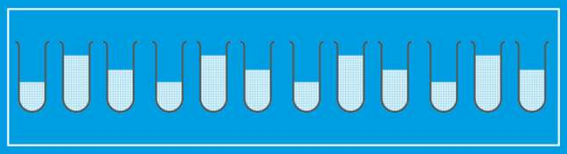
Equivocal

Discussion



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Equivocal Result Options

1. Include equivocal results in assessment (positive/negative/equivocal)
2. Not allow equivocal results (only positive/negative) and introduce minimum number of results required
3. No change - continue to exclude equivocal results from assessment

Which would you choose now?

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Equivocal Modelling

- Based on samples 1-8/2017 (32 xm results)
- UK&I: 2 additional T-cell and 2 B-cell results would be 'not assessed'
- RoW: 3 additional T-cell and 1 B-cell result would be 'not assessed'

Number of labs with UP would
- Remain at 13 labs for T-cells
- For B cells increase from 6 to 13

	2B08 T Cell UK&I	
	Exclude Equivocal	Include Equivocal
Pos (n=16)	80.0%	72.7%
Neg (n=4)	20.0%	18.2%
Equivocal (n=2)	N/A	9.1%
Consensus Result	Positive	Not Assessed

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Changes for 2018

- Equivocal results will be assessed
  - i.e if 75% or more of participants report positive/negative, any laboratories reporting 'equivocal' will be assessed as 'unacceptable'
  - If a 75% consensus result is not reached when including the equivocal reports, the sample will not be assessed.
- Technical issues and invalid results (e.g control failures, replicate issues, sample quality issues) should be reported as 'Not Tested' with the reason stated.
- Please report your technical result

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Discussion

"The EQA crossmatch results do not correlate with HLA antibody results"

- 22/40 FCXM results from UK&I in 2017

Consensus Result	No of results	DSA			
		> 5000	2-5000	<2000	No DSA
T+ B+	7	7	0	0	0
T- B-	6	1 (A1 & B18)	2 (A29, B60)	1 (Cw4)	2
T NA B NA	2	1 (A1 & A3)	0	0	1
T+ B NA	2	2 (A3 & A26 & Cw6, Cw6)	0	0	0
T- B NA	4	2 (B44, B35)	1 (B18, B27, Cw12)	0	1
T NA B +	1	1 (B8)	0	0	0

NA = Not assessed

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Discussion

- Scheme is a technical exercise
  - Report the reactivity you see, not interpretation
- Discrepancies between SA bead testing and FCXM results will occur (sensitivity, non-HLA antibodies etc)
- Not all Scheme 2B results will reach consensus (that's ok!)
- B-cells are difficult (transport, non-specific binding)
- Should UK NEQAS provide results of SA bead testing for Scheme 2B?

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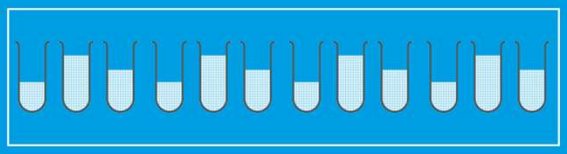
Scheme 2B

Discussion



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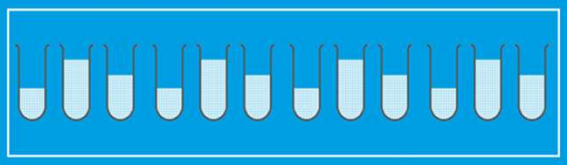
Scheme 2A
Cytotoxic Crossmatching



Patrick Flynn

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UK&I Performance

	PBL	PBL +DTT	T Cell	T Cell +DTT	B Cell	B Cell +DTT
Crossmatches assessed (n=36)*	28	30	32	33	27	29
% NT/Equivocal	10.3%	13.9%	7.4%	6.1%	19.9%	25.8%
NT	20	20	28	20	110 [a]	139 [a]
Equivocal	6	15	16	14	16	15
% incorrect assignments	3.5%	4.1%	1.8%	2.3%	5.1%	5.4%
FP/FN	7/1	8/1	9/1	11/1	16/10	19/5

*Excludes sample 2A 02/2017 which was not assessed due to poor sample quality

[a] Higher number of B cell results not tested due to dynabead product recall

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Scheme 2A Performance

(PBL/T cells & B Cells)	Without DTT		With DTT	
	2015	2016	2015	2016
Number of Participants (UK&I)	77 (21)	77 (21)	64 (18)	64 (18)
Number with Unsatisfactory Performance (< 85%) (UK&I)	16 (2)	14 (3)	9 (0)	13 (6)
% Unsatisfactory Performance (UK&I)	20.8% (9.5%)	18.2% (14.3%)	14.0% (0%)	20.3% (33.3%)

All cells with and without DTT	2017
Number of Participants (UK&I)	75 (19)
Number with Unsatisfactory Performance (< 85%) (UK&I)	16 (6)
% Unsatisfactory Performance (UK&I)	21.3% (31.6%)

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Unacceptable Performers 2017

- 16 labs with UP
- Majority due to B cells – Dynabead product recall
- Fewer B cell test results submitted

For T cells 72.9% labs reported ≥ 36 results compared to 37.7% for B cells

	PBL	T	B	PBL + DTT	T + DTT	B + DTT
9	84.2%			81.0%		
11			83.3%			
12						76.9%
20			75.0%			
38			81.0%			
39			81.3%			
116			75.0%			84.2%
145			80.8%			
157			71.0%			68.2%
189				84.4%		
205	71.4%		50.0%	66.7%		63.6%
212			66.7%			82.8%
216				84.6%		
239		84.4%	83.9%			78.1%
262						78.1%
351		68.8%	66.7%			66.7%

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Changes for 2018

- No longer accept equivocal reports

	PBL	PBL +DTT	T Cell	T Cell +DTT	B Cell	B Cell +DTT
No. Equivocal results	6	15	16	14	16	15

- Technical issues and invalid results (e.g control failures, replicate issues, sample quality issues) should be reported as 'Not Tested' with the reason stated
- The Steering Committee feel that there are no circumstances where a result is undetermined or equivocal for cytotoxic crossmatching

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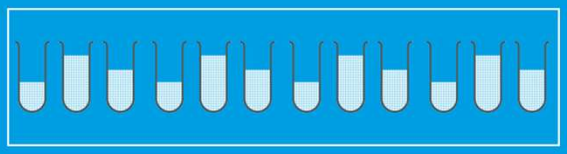
Scheme 2A

Discussion



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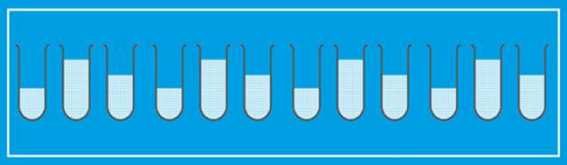
Scheme 6

HLA Antibody Detection



John Smith

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Not Assessed Samples

Sample	Class I All Labs (n=98)	Class I UK&I (n=24)		Class II All Labs (95)	Class II UK&I (n=24)
601	97.9%	100%		90.4%	100%
602	97.9%	100%		55.4%	62.5%
603	97.9%	95.8%		95.7%	100%
604	91.8%	100%		88.3%	100%
605	70.1%	95.8%		95.7%	100%
606	84.4%	100%		70.7%	91.7%
607	96.9%	100%		93.7%	100%
608	63.5%	79.2%		93.7%	100%
609	100%	100%		100%	100%
610	91.8%	91.7%		88.3%	91.3%
611	84.5%	100%		85.1%	91.7%
612	80.4%	91.7%		70.2%	87.5%

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Kit Differences?

Sample	All Labs (n=98)	One Lambda (n=52)	Lifecodes (n=31)
602 Class II	55.4% (Neg)	60.4% (Pos)	75.9% (Neg)
605 Class I	70.1% (Pos)	96.3% (Pos)	66.7% (Neg)
606 Class II	70.7% (Neg)	94.3% (Neg)	64.5% (Pos)
608 Class I	63.5% (Pos)	88.9% (Neg)	80.0% (Pos)
612 Class II	70.2% (Neg)	87.7% (Neg)	69.0% (Pos)

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Mixed v Single Antigen

- Mixed kits have an 'undetermined' region
- Scheme requires 'positive' or 'negative' result
  - Test using additional kits
- Known sensitivity difference between mixed and SA beads
- Could account for not-assessed results
  - 20 labs reported testing using single antigen beads
- Result interpretation

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Scheme 6 2017

Serum 602/2017

	Class I	Class II
602/2017	Positive	Not assessed (55.5% Neg)

Bead	Rxn	Raw	Normal	Cnt	Specificity	Allele Specificity	
010	4	1757.38	1614.86	106	DR4	DRB1*04:04	
030	4	1526.19	1314.67	115	DR16	DRB1*16:01	
007	4	1478.11	1278.59	111	DR18	DRB1*03:02	
067	4	1254.76	1027.24	97	DP1		DPA1*01:03, DPB1*01:01
078	1	1050.28	891.76	131	DP6		DPA1*01:03, DPB1*06:01
031	1	1011.64	838.12	94	DR16	DRB1*16:02	

One Lambda have previously reported elevated background observed with DR4 and DR16 antigens (especially bead #10, DRB1*04:04).

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Scheme 6 Errors

139/1820 (7.6%) results out of consensus (9 UK&I)

More false positive results

Error	UK&I	RoW
Class I only	4	54
Class II only	3	46
Class I & II	1	15

	Class I		Class II	
	False Pos	False Neg	False Pos	False Neg
UK&I	5	0	2	2
RoW	65	4	49	12

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Scheme 6 Performance

	2015	2016	2017
Number of Participants (UK&I)	97 (24)	98 (24)	101 (24)
Number with Unsatisfactory Performance (< 80%) (UK&I)	6 (3)	18 (4)	21 (0)
% Unsatisfactory Performance	6.2%	18.4%	20.8%

The 21 labs with unacceptable performance:

- 4 used One Lambda kits only (3 mixed, 1 Single Antigen)
- 13 used Immucor kits only (10 mixed, 1 ID kits, 1 Single Antigen)
- 4 gave no information as to kit usage

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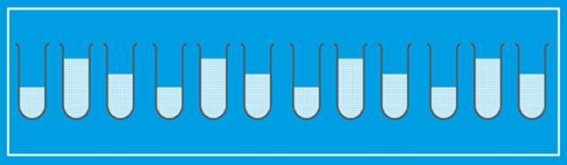
Scheme 3

HLA Antibody Specificity Analysis



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Class I Assessment

	Number of HLA Class I Specificities (n=72)										
	301	302	303	304	305	306	307	308	309	310	Total
Present (≥75%)	11	5	25	2	30	2	8	5	0	0	57
Absent (<5%)	8	13	24	55	31	40	42	27	41	26	307
Absent 0%	64	54	22	16	15	26	28	50	42	52	368
Not Assessed (5-74%)	6	17	18	16	13	21	11	7	6	11	127

491 specificities reported over 10 samples

11.6% reached consensus presence

62.5% reached consensus absence

25.8% specificities were not assessed

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Class II Assessment

	Number of HLA Class II Specificities (DR, DQ) (n=72)										
	301	302	303	304	305	306	307	308	309	310	Total
Present (≥75%)	4	1	7	5	17	8	5	4	0	0	51
Absent (<5%)	8	16	16	13	5	10	17	8	3	13	109
Absent 0%	5	1	3	2	2	2	2	6	22	13	58
Not Assessed (5-74%)	10	9	1	7	3	7	3	9	2	1	52

212 specificities reported over 10 samples
- 24.1% reached consensus presence
- 51.4% reached consensus absence
- 24.5% specificities were not assessed

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Unacceptable Performers 2017

- 13 labs with UP (<75%)

	Class I		Class II		Kit
Lab	Presence	Absence	Presence	Absence	
133	72.4%	99.7%	88.2%	99.1%	Lifecodes SA
165	83.9%	42.3%	62.7%	53.2%	No Info
197	41.4%	95.4%	52.9%	89.9%	No Info
214	19.5%	100.0%	86.3%	100.0%	Lifecodes SA
216	5.7%	96.1%	82.4%	97.2%	Lifecodes ID
222	67.8%	49.2%	82.4%	78.9%	No Info
239	40.2%	95.8%	78.4%	98.2%	Lifecodes ID
252	17.2%	99.0%	60.8%	96.3%	Lifecodes ID
267	73.6%	100.0%	86.3%	99.1%	Lifecodes SA
293	83.9%	100.0%	70.6%	94.5%	One Lambda SA
302	20.7%	97.7%	60.8%	89.0%	Lifecodes ID
351	100.0%	65.8%	100.0%	54.1%	One Lambda SA
361	73.6%	100.0%	96.1%	98.2%	Lifecodes SA

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Scheme 3 Performance

Class I		2015	2016	2017
Number of Participants (UK&I)		81 (24)	85 (24)	72 (24)
Number with Unsatisfactory Performance (UK&I)	**Presence**	9 (1)	8 (0)	10 (0)
	Absence	2 (0)	3 (0)	3 (0)
% Unsatisfactory Performance	**Presence**	11.1%	9.4%	13.8%
	Absence	2.5%	3.5%	4.2%

Class II		2015	2016	2017
Number of Participants (UK&I)		81 (24)	85 (24)	72 (24)
Number with Unsatisfactory Performance (UK&I)	**Presence**	4 (0)	5 (0)	5 (0)
	Absence	3 (0)	4 (0)	2 (0)
% Unsatisfactory Performance Presence/ Absence	**Presence**	4.9%	5.9%	6.9%
	Absence	3.7%	4.7%	2.8%

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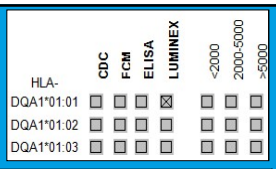
DPB



	Number of HLA DPB Specificities (n=60)										
	301	302	303	304	305	306	307	308	309	310	Total
Present (≥75%)	10	0	0	0	0	13	0	0	0	0	23
Absent (<5%)	7	0	1	2	2	1	13	2	5	0	33
Absent 0%	0	18	15	16	1	3	6	16	14	19	108
Not Assessed (5-74%)	2	1	3	2	16	2	0	1	0	0	27

60/72 labs reported DPB1 results
2 samples had DPB1 specificities that reached consensus

83 specificities reported over 10 samples
- 27.7% reached consensus presence
- 39.8% reached consensus absence
- 32.5% specificities were not assessed

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DPB Assessment

Assessment modelling carried out on 60 labs that reported DPB results

- Assessment 'presence' results changed for 2 labs when including DPB with DR and DQ assessment

Lab No.	Presence Assessment	Presence Assessment + DPB
165	62.7%	60.7%
268	76.5%	71.6%
293	70.6%	79.7%
302	62.3%	60.8%

- Fewer labs reported DQA (n=48) and DPA (n=44)

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Changes for 2018

- DPB will be assessed as part of Class II registration
- Labs should report DPB specificities detected in samples
- Continue to report DQA and DPA, but these will not be assessed in 2018

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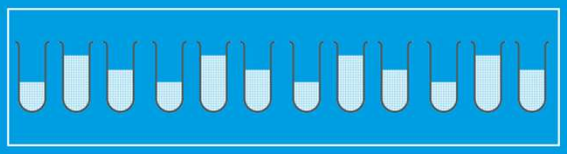
Schemes 3, 6

Discussion



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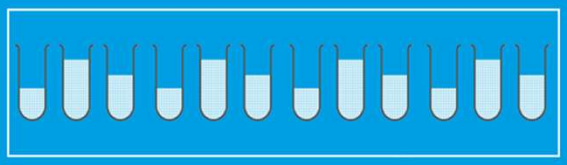
Maria Cheadle

Welsh Blood Service

Quality Improvement Management



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Gwasanaeth Gwaed Cymru
Welsh Blood Service

Incident Investigation, Root Cause Analysis & Effective Prevention

Maria Cheadle
Quality Improvement Manager
Welsh Blood Service

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Learning Objectives

Gwasanaeth Gwaed Cymru
Welsh Blood Service

- Define the term 'incident' and acknowledge why incidents happen
- Define RCA and its purpose
- Recognise when an RCA investigation is required
- Identify how to determine the effectiveness of corrective and preventive actions
- Recognise the need to adopt an holistic approach to investigation
- Acknowledge that human error is NOT always the root cause

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What is an incident?

- **Incident -** an event that **actually occurred**, causing a **loss** of some kind (e.g. equipment breakage, loss of results etc.)
- **Accident -** an unplanned, unwanted event that caused an injury (e.g. slip causing fall, injury to arm etc.)
- **Near Miss -** any event that if it were not for skilful management would in all probability have become an accident or incident, i.e. any accident or incident that was avoided

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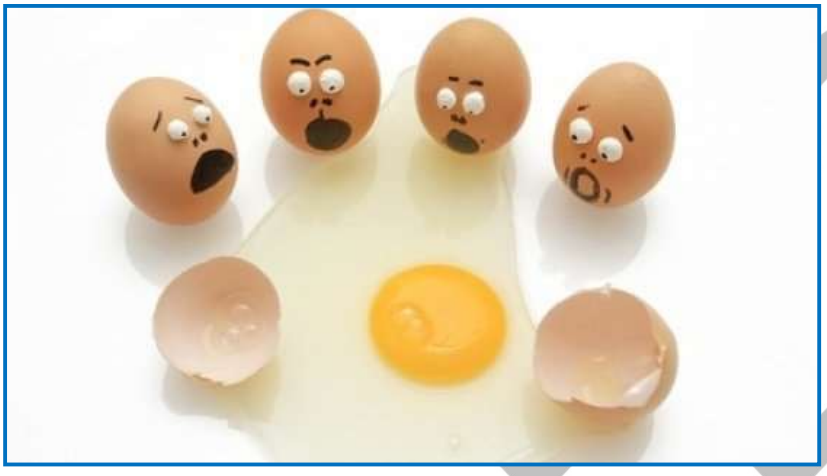
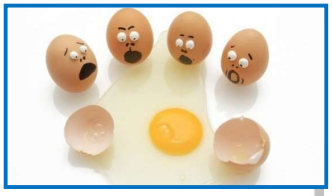
Why do incidents happen?



80

How do you prevent them?



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Prevention, better than cure...

- **Effective** risk control measures that address the **immediate**, **underlying** and **root** causes

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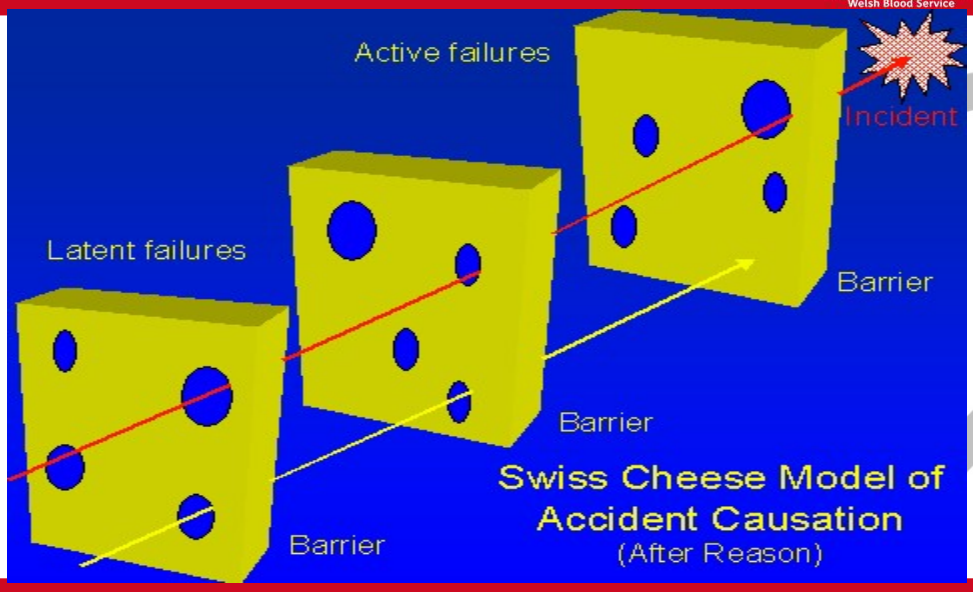
Why do incidents happen?



James Reason (1990) Defences, Barriers & Safeguards

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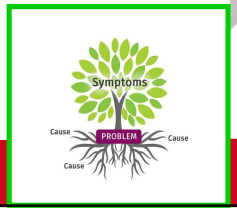
How do you know what to fix?

Root cause(s):

The failure from which all other failings grow

- often remote in time and space from the adverse event



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Investigation and RCA?

Gwasanaeth Gwaed Cymru
Welsh Blood Service

What happened?

*Identify **exactly** what happened*

Why did it happen?

*Use problem solving tools to identify the **real problem***

What to do to stop it happening again

*Iidentify **changes** that need to be made **to prevent recurrence***

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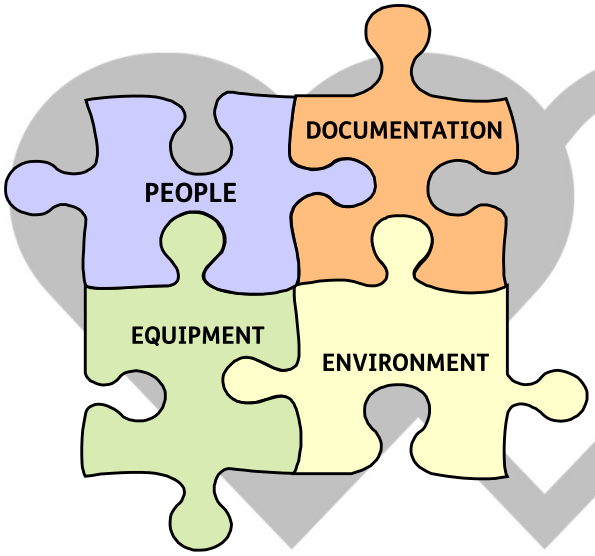
Investigation

Gwasanaeth Gwaed Cymru
Welsh Blood Service

What happened?

How did it happen?



86

Analysis

Why did it happen?

- Chronology of events – tabular timeline
- Analyse changes – what should have happened vs. what actually happened

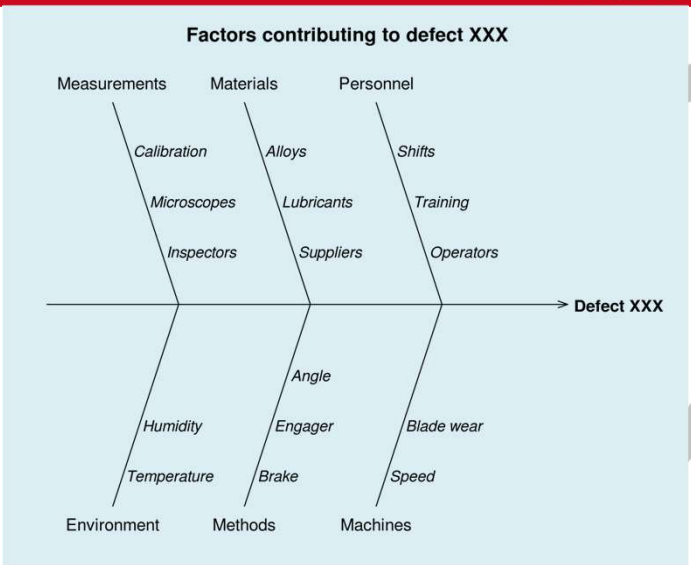
Tools:

- Brain storming, Change Analysis, 5 Whys, Fishbone diagram

87

Analysis – Contributory Factors

Why did it happen?



88

Corrective & Preventive Action (CAPA)

Gwasanaeth Gwaed Cymru
Welsh Blood Service

What to do to stop it happening again

- Identify system and process errors
- Barrier analysis – are current barriers effective?
- Simple solutions - look for preventable causes
- Involve staff/users in developing fixes

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A real life investigation….

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Welsh Blood Service

A laboratory porter was taking the post (including lab results) from the Pathology building to the main hospital. He was carrying the mail in his hand and chatting to a colleague as he walked.

The wind was very strong that day and caught some of the mail; it blew off into the field behind the Pathology building….

The porter didn't realise that this had happened.

A member of lab staff saw the post blowing across the field, out of the upstairs window, and raised their concerns

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Consider:

What happened?

How did it happen?

Why did it happen?

- What would be your immediate action?
- Who would you want to interview?
- What do you think the root cause is?

91

Identifying Root Cause

Why did it happen?

When an incident occurs how quickly do you judge what you think the problem/root cause is?

What are the dangers of having a pre-formed opinion?

Footer

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Identifying Root Cause

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Welsh Blood Service

Using 5 Whys

Think about the importance of asking the right questions:

1. Some of the lab post wasn't delivered to the main hospital as expected. *Why?*

2. Items of post were lost on the way. *Why?*

3. The post was caught by the wind and blew across the field without the porter noticing. *Why?*

4. It was a really windy day. *Why?*

5. It's Winter, we've been having a lot of bad weather lately!

Is bad weather really the root cause?

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Identifying Root Cause

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Using 5 Whys

Ensure the problem is correctly defined:

1. **Hard copies of laboratory results/patient information have potentially been lost (or are irretrievable).** Why?

2. Several items of post were not delivered to the main hospital as expected. *Why?*

3. These items were caught by the wind and blew away. *Why?*

4. The porter was carrying the post by hand. *Why?*

5. There is no requirement for the porter to use a carrier. *Why?*

It's not part of the procedure

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Identifying Root Cause

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Why did it happen?

Contributory factors?

Solution Development

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Identifying Root Cause

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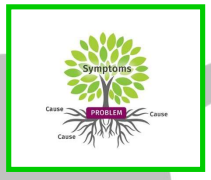
Solution Development

Re-write the SOP
Give the Pathology porters carriers



Redefine the problem:

1. There is no requirement for the porter to use a carrier. *Why?*
2. It's not part of the procedure. *Why?*

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Identifying Root Cause

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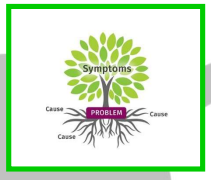
Solution Development



Actual root cause:

The Information Governance process has not been fully considered, i.e. potential loss of postal items during transport was not recognised and there was no mitigating action to reduce this risk across the WHOLE organisation.

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Preventive Action

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Welsh Blood Service

1. Discuss with the porter?
2. Stop porter(s) from carrying the post?
3. Remind porter(s) to be more vigilant when windy?
4. Add more quality checks?
5. Rewrite the SOP – add the need to use a carrier?
6. Retrain the porter(s)?

Or:

Risk assess information governance issues for all postal items, across all disciplines, and mitigate accordingly

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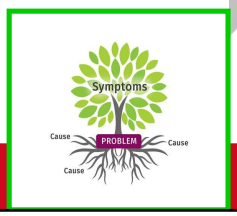
Remember…

'To get rid of weeds you must dig up the root, if you only cut off the foliage, the weed will grow again.' HSE



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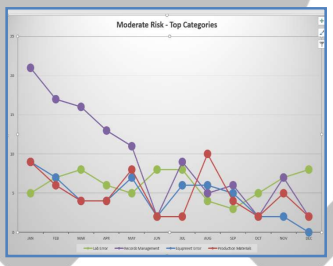
Look for trends

- Has this happened before?
- How many times?
- Is there a pattern? *day, time, person*

- What did you do last time?
  - *Update SOP?*
  - *Retrain?*
  - *Send out a memo?*



100

CAPA – a reminder

- **Corrective action** – what you need to do in response to a deviation to make things safe (ISO 15189 refers to this as 'remedial' action)
- **Preventive action** - what you put in place to stop it happening again (ISO 15189 refers to this as corrective action; preventive action is action taken to eliminate the cause)

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Preventive (?) actions

Will these actions <u>really</u> prevent a recurrence?

1. Discussion with the individual
2. Stop individuals from carrying out certain tasks
3. Remind people to be vigilant
4. Retrain staff
5. Rewrite the SOP – add more barriers
6. Add more quality checks

7. Fully examine systems and processes

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Reasons CAPA not robust

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Welsh Blood Service

- **The problem is not well defined**
- **The root cause is not determined/identified properly**
- **It's not really CAPA**
  State the problem and determine root cause first, otherwise it's just a project
- **We over-think it**
  Doesn't need to be labour intensive
  Major processes need not be applied to minor problems
- **It's considered not important**
  Living with an ongoing problem is the path of least resistance
  People develop 'workarounds'

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Monitoring Effectiveness

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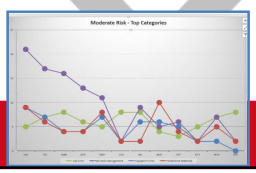
Welsh Blood Service

Allow **less time** after implementing the solution when:

- Higher opportunity for occurrence / observation
- Higher probability of detection
- Engineered solution
- Fewer observations needed for high degree of confidence

Allow **more time** when:

- Lower opportunity for occurrence/ observation
- Lower probability of detection
- Behavioural/ training solution
- More observations needed for high degree of confidence



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Monitoring Effectiveness

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Audit

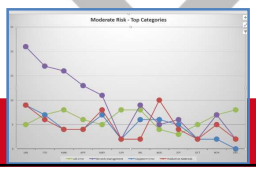
- Use when the solution involves changes to a system
- Determines whether changes are in-place procedurally and in-use behaviourally

Spot Check

- Random observations/review of records
- Provides immediate, but limited feedback

Monitoring

- Use for real-time observations over a defined period
- Verifies that changes were implemented



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Monitoring Effectiveness

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Trend Analysis

- Retrospective review of data to verify that expected results were achieved

Periodic Review

- Retrospective, at least annually, of trends of multiple parameters to confirm the state of control

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Thank you for participating

Welsh Blood Service

Any questions?

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Participants Meeting 2017

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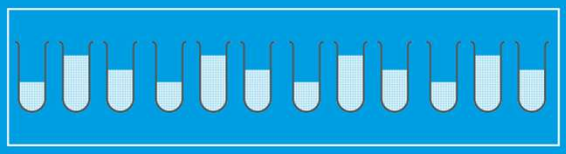
Scheme 1A

HLA Phenotyping



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2017 Incorrect Assignments

Sample	Lab Number	Consensus	Report
1A 02	279	Cw1, Cw12	Cw1, -
	292	DR13	DR17
1A 04	142	A31	A30
	268	DQ5	DQ8
1A 08	227, 323	B65	B14
1A 09	223	B62	B15
	193	DR15 DQ6, DQ8	DR2 DQ1, DQ3
1A 10	20	Cw7, Cw14	Cw7, -
	193	DQ6	DQ1

10/380 (2.6%) incorrect HLA types in 2017 reported by 9 labs;
- 5 reports of broad, not split specificity
- 3 reports of wrong specificity (e.g. DR13 not DR17)
- 2 reports of missed specificity (i.e. reported blank)

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1A Performance 2017

- 1 lab with Unsatisfactory Performance

	2012	2013	2014	2015	2016	2017
Number of Participants (UK&I)	22 (10)	30 (10)	42 (9)	45 (9)	41 (7)	38 (6)
Number with Unsatisfactory Performance (< 90%) (UK&I)	1 (0)	0 (0)	8 (0)	4 (0)	3 (0)	1 (0)
% Unsatisfactory Performance	4.5%	0.0%	19.0%	8.9%	7.3%	2.6%

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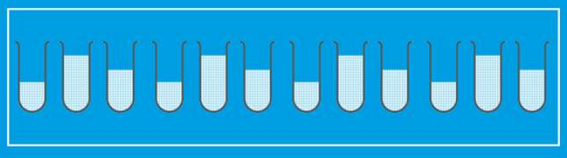
Histocompatibility and Immunogenetics

Scheme 4A1

DNA Typing at 1st Field Resolution



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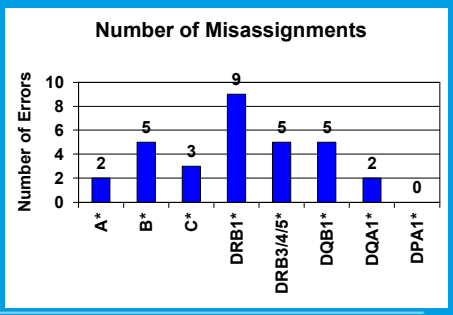
Incorrect Assignments

- 40/1010 (4.0%) incorrect HLA types reported by 20 labs (3 UK&I)
  - 11 incorrect assignments (e.g. B*42 instead of B*08)
  - 9 complete type errors – sample mix-up (3 samples by 1 UK&I lab)
  - 8 missed assignments (e.g. reported homozygous/blank) – (1 UK&I)
  - 7 extra assignments (e.g. reported heterozygous when homozygous)
  - 5 other errors e.g. DQB1* 05 or 06, DRB3/4/5 presence/absence errors (1 UK&I)

Methods for labs with errors

- 6 labs used SSP only
- 9 used Luminex only
- 4 used a combination (e.g.SSP&Luminex)
- 1 no info



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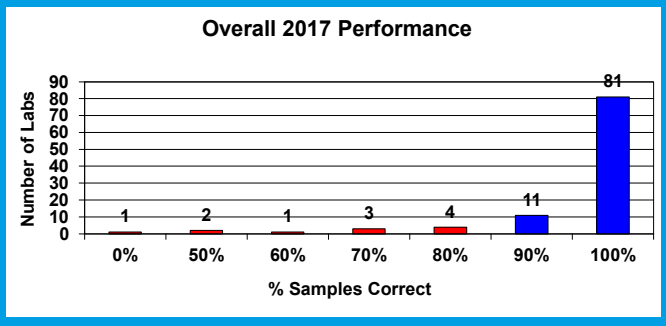
4A1 Performance 2017



	2013	2014	2015	2016	2017
Number of Participants (UK&I)	96 (30)	96 (30)	100 (29)	102 (28)	106 (28)
Number with Unsatisfactory Performance (< 90%) (UK&I)	5 (0)	9 (0)	7 (1)	21 (4)	11 (1)
% Unsatisfactory Performance	5.2%	9.4%	7.0%	20.6%	10.4%

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Changes for 2018

- Participants can register for DPB1 assessment at low/medium resolution (i.e. SSP/SSO results)
- Assessed against a reference type
- Report DPB1 alleles at the resolution applicable to clinical need
- Strings of alleles not penalised if reference allele is present

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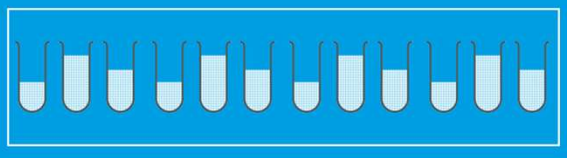
Scheme 4A1i

Interpretive HLA Genotype



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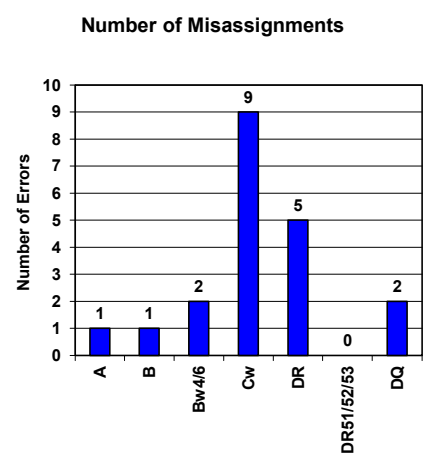
Interpreted DNA Results

- 20/355 (5.6%) incorrect HLA types reported by 8 labs (1 UK&I)
  - 14 reports of broad, not split specificity (e.g. Cw3 not Cw9)
  - 1 missed assignments (e.g. reported homozygous/blank)
  - 5 antigen mis-assignments (e.g. Bw4 instead of Bw6) (1 UK&I reported Cw10 not Cw9)



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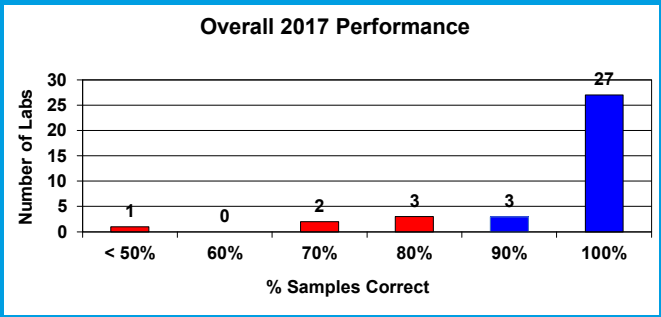
4A1i Performance 2017



	2017
Number of Participants (UK&I)	36 (20)
Number with Unsatisfactory Performance (< 90%) (UK&I)	6 (1)
% Unsatisfactory Performance	16.7%

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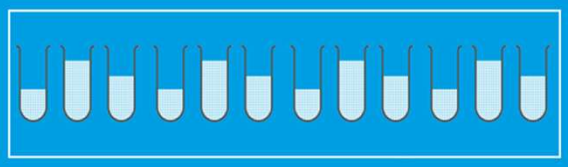
Scheme 4A2

DNA Typing to 2nd Field Resolution



Arthi Anand

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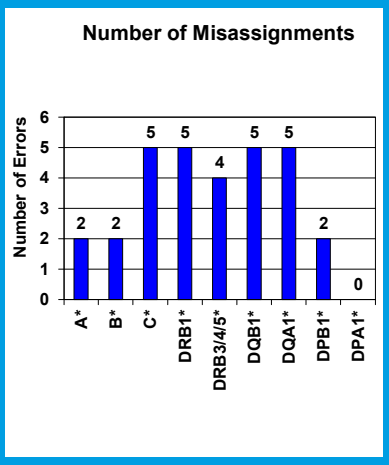
2017 Incorrect Assignments

- 23/629 (3.7%) incorrect samples reported by 16 labs (3 UK&I)
  - 17 reports of alleles in a string that differ from the consensus allele in exons 2/2&3 (e.g. B*08:01/159) (2 UK&I)
  - 13 reports of incorrect allele (e.g. A*26:02 not A*26:01) (1 UK&I)



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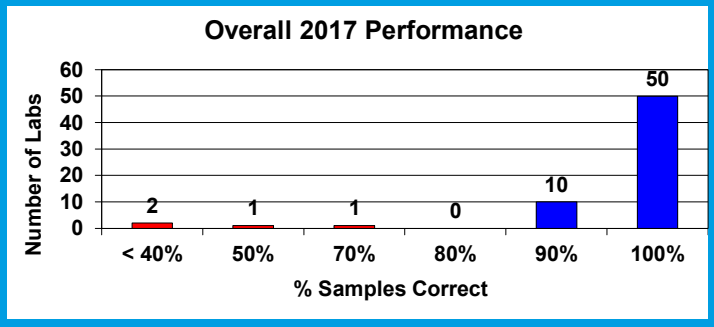
4A2 Performance 2017



	2014	2015	2016	2017
Number of Participants (UK&I)	59 (21)	59 (20)	63 (21)	66 (21)
Number with Unsatisfactory Performance (< 90%) (UK&I)	5 (1)	7(1)	8 (2)	4 (0)
% Unsatisfactory Performance	8.5%	11.9%	12.7%	6.1%

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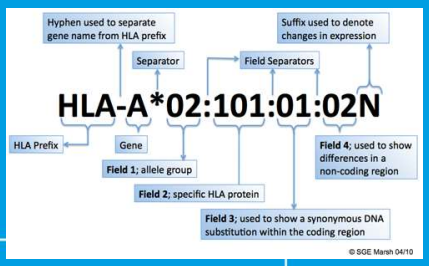
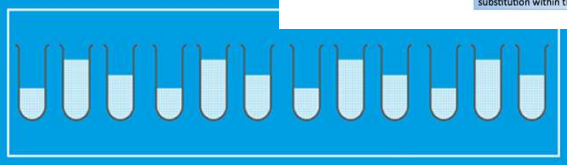
Histocompatibility and Immunogenetics

Pilot Allelic HLA Typing Scheme

DNA Typing above the 2nd Field Resolution





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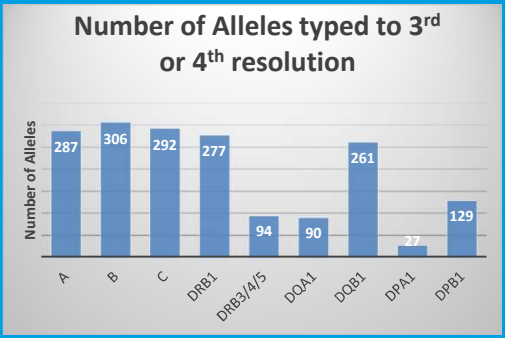
Results

- 17 labs reported results at 3rd or 4th field resolution
- Total of 1763 alleles

- 1017 (57.7%) alleles reported as unambiguous 3rd field result (e.g. B*07:02:01
- 639 (36.2%) reported as unambiguous 4th field result (e.g. B*07:02:01:01)
- 107 (6.1%) contained 3rd or 4th field ambiguities (e.g. B*40:01:02:01/04)



123

Discordant results

- 6 alleles with discordant 3rd or 4th field results:

4A2 02/2017	No. of results
C*04:01:01	3
C*04:01:79	7
C*04:01:01:06	1
C*04:01:NEW	2

4A2 03/2017	No. of results
DRB1*04:01:01	11
DRB1*04:01:01:01	2
DRB1*04:01:01:02	3

4A2 03/2017	No. of results
DPB1*04:01:01	7
DPB1*04:01:01:01	1
DPB1*04:01:01:02	1
DPB1*04:01:01:NEW	1

4A2 07/2017	No. of results
C*14:02:01	6
C*14:02:01:01	5
C*14:02:01:04	3

4A2 06/2017	No. of results
DRB1*15:01:01	8
DRB1*15:01:01:01	1
DRB1*15:01:01:02	1

4A2 06/2017	No. of results
DPB1*04:01:01, -	4
DPB1*04:01:01:01, -	1
DPB1*04:01:01:01, 04:01:01:06	1

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New for 2018

- Participants can register for assessment of 3rd field results in Scheme 4A2
- Results at the 4th field can be reported, but will not be assessed

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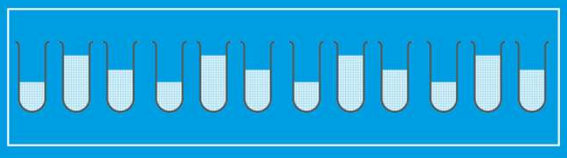
Histocompatibility and Immunogenetics

Schemes 1A, 4A1, 4A1i, 4A2

Discussion



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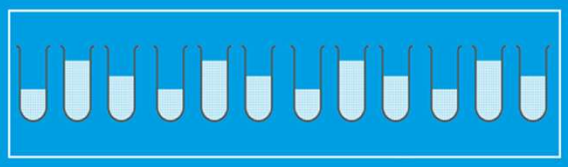
Histocompatibility and Immunogenetics

Scheme 9

KIR Genotyping



Anthony Poles

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KIR Genotyping

- Participants able to report any of the following: KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5, KIR3DL1, KIR3DL2, KIR3DL3, KIR3DS1, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR2DP1, KIR3DP1.
- Also able to report any other KIR polymorphisms they detected for information
- Participants can also report an 'A' or 'B' haplotype for each sample based on the gene content of the sample

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Performance 2017

- 0 Errors
- 0 Unsatisfactory Performers

	2015 Pilot	2016 Pilot	2017
Number of Participants (UK&I)	7 (1)	11 (2)	8 (3)
Number with Unsatisfactory Performance (< 100%) (UK&I)	N/A	N/A	0
% Unsatisfactory Performance (UK&I)	N/A	N/A	0%

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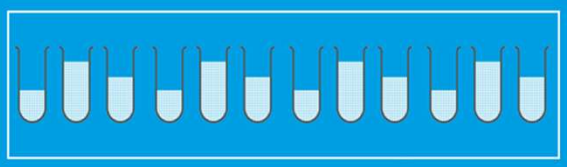
International Quality Expertise

Histocompatibility and Immunogenetics

Scheme 10

HPA Genotyping



Anthony Poles

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HPA Genotyping

- Participants able to report any of the following: HPA-1, HPA-2, HPA-3, HPA-4, HPA-5, HPA-6, HPA-15
  - All labs reported HPA-1, 2 , 3, 4, 5 and 15
  - 10 labs reported HPA-6
- Also able to report any other HPA polymorphisms detected, for information
  - 1 lab also reported HPA-9
- All results reported in line with consensus

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Performance 2017

Sample	Lab Number	Result	HPA Type	Root Cause
10 02	267	1b Neg	1a 1b	Test undergoing validation- not yet used clinically
10 03	267	1b Neg 3b Neg	1a 1b 3a 3b	
10 04	267	3a Pos	3b 3b	
10 05	267	5b no result	5a 5a	
10 09	267	2a Neg 3a Neg	2a 2b 3a 3a	

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Performance 2017

- 7 Errors (1 lab)
- 1 Unsatisfactory Performer

	2015 Pilot	2016 Pilot	2017
Number of Participants (UK&I)	14 (3)	12 (4)	15 (5)
Number with Unsatisfactory Performance (< 100%) (UK&I)	N/A	N/A	1 (0)
% Unsatisfactory Performance (UK&I)	N/A	N/A	0%

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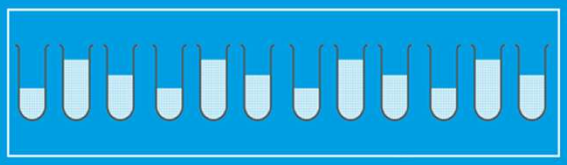
HPA Antibody Detection/Specification Pilot



Deborah Pritchard

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2017 Results

- 13 labs
  - 3 UK&I
- 3/8 samples contained HPA antibodies
  - Anti HPA-1a
  - Anti HPA-5b x2
- Lab 267 reported GP Ia/IIa (consensus HPA-5b)

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Changes for 2018

- Scheme 11 – HPA antibody detection/specification
- Fully assessed in 2018
- NIBSC no longer offering platelet genotyping or antibody schemes
- NIBSC participants offered to transfer to UK NEQAS for H&I

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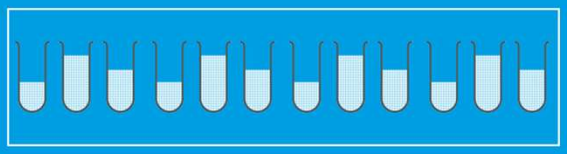
Histocompatibility and Immunogenetics

Schemes 9,10, 11

Discussion



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Scheme Performance – UK&I

	2013	2014	2015	2016	2017
Scheme 1A	0	0	0	0	0
Scheme 1B	1	2	4	6	2
Scheme 2A Without DTT Scheme 2A With DTT	2 N/A	6 N/A	2 0	3 6	6
Scheme 2B	0	2	3	1	1
Scheme 3 Class I Scheme 3 Class II	1 0	0 0	1 0	0 0	0 0
Scheme 4A1	0	0	1	4	1
Scheme 4A1i	N/A	N/A	N/A	N/A	0
Scheme 4A2	2	1	1	2	0
Scheme 5A	2	2	0	2	2
Scheme 6	0	1	3	4	0
Scheme 7	0	0	0	1	1
Scheme 8	1	2	0	3	2
Scheme 9	N/A	N/A	N/A	N/A	0
Scheme 10	N/A	N/A	N/A	N/A	0
Total	**9**	**16**	**15**	**32**	**15**

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ing 2017

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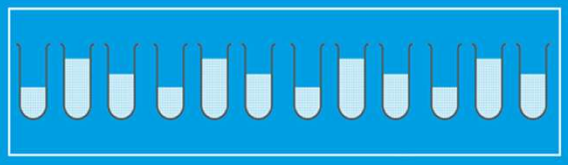
Histocompatibility and Immunogenetics

Steering Committee
Q&A Session



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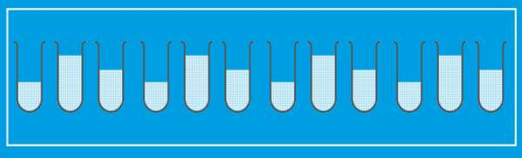
EDXM Scheme

Incorporating Crossmatching, HLA Typing and Antibody Detection/Specification



Tracey Rees

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'Whole Process' EQA

- UK NEQAS for H&I
  - Scheme 1A, 4A1, 4A2 – HLA Typing
  - Scheme 6 – HLA Antibody Detection
  - Scheme 3 – HLA Antibody Specification
  - Schemes 2A and 2B – Crossmatching
  - Solid Organ Interpretive Scenarios (Paper based)

"Schemes should relate more closely to clinical scenarios rather than testing individual test assays."

- Clinical decision making based on results from multiple assays
- Each assay only gives part of the picture
- Results from one assay can influence the interpretation of another
- Variation between centres
  - Sensitivity/cut offs
  - Assay repertoires

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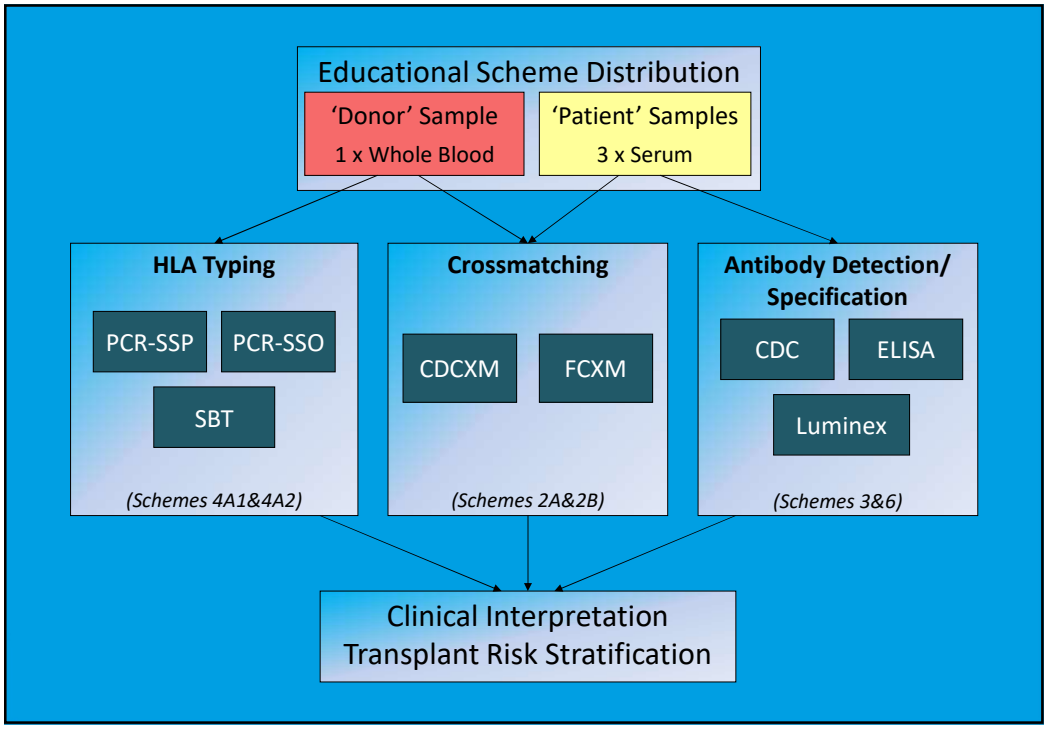

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2017 Results

- 35 Participants
- 100% agreement on HLA type

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Serum 1 Results

	Result	% Consensus	Comments
HLA Class I Antibodies	Positive	100%	
HLA Class II Antibodies	Positive	100%	
DSA	No	97% (34/35)	Lab 181 reported A32 DSA MFI 480 (low risk tx)
CDC XM	Negative	95.5% (21/22)	Lab 149 reported a positive PBL crossmatch with & w/o DTT
FCXM T Cell	Negative	96.1% (25/26)	Lab 159 reported positive
FCXM B Cell	Negative	95.8% (23/24)	Lab 20 reported positive
Transplant Risk	Low	75.8% (25/33)	8 labs reported medium risk (28, 48, 114, 122, 142, 147, 149, 238)

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Serum 2 Results

	Result	% Consensus	Comments
HLA Class I Antibodies	Negative	97.1% (33/34)	Lab 20 detected A31 and A80 <1500 MFI
HLA Class II Antibodies	Negative	85.3% (29/34)	5 labs detected DQB/A antibody <1500 MFI (42, 54, 58, 142, 194)
DSA	No	100%	
CDC XM	Negative	90.9% (20/22)	Lab 147 & 149 reported a positive PBL crossmatch with & w/o DTT
FCXM T Cell	Negative	100%	
FCXM B Cell	Negative	100%	
Transplant Risk	Low	96.7% (32/33)	Lab 149 reported medium risk (no FCXM)

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Serum 3 Results

	Result	% Consensus	Comments
HLA Class I Antibodies	Positive	72.7% (24/33)	Multiple A, B, C specs reported up to 9999 MFI (but none reached 75% consensus level)
HLA Class II Antibodies	Positive	100%	
DSA	Yes	100%	DSA included DQ2, B8, A3, B7, DR17, DQA, A32
CDC XM with DTT PBL T cell B Cell	 Negative Negative Positive	 75.0% (6/8) 93.3% (14/15) 71.4% (10/14)	 Labs 9 & 149 reported positive PBL xm with DTT Lab 45 reported positive T-cell xm with DTT Labs 20, 41, 194, 260 reported B cell negative xm
FCXM T Cell	Negative	76.9% (20/26)	6 labs reported positive (11, 25, 41, 45, 54, 58)
FCXM B Cell	Positive	77.3% (17/22)	5 labs reported negative (15, 23, 34, 48, 260)
Transplant Risk	Contraindication /High risk	75.8% (25/33)	7 labs reported a medium risk (15, 23, 34, 39, 149, 194, 260)

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Lab	DSA	Interpretation based on results	Assigned risk
12	A3 (1183), B8 (2974), B7 (908), DQ2 (17889), DR17 (915)	This patient is highly sensitised (cRF 96%). This patient has HLA class I and II donor specific antibodies (DSA): high level HLA-DQ2 (MFI:17,889); intermediate level HLA-B8(MFI:2,974); low level HLA-A3(MFI:1,183) and -B7(MFI:908). The IgG B cell lymphocytotoxic crossmatch result was positive, likely caused by high level HLA-DQ DSA.	High
15	DQ2 (8437), DQA5 (8480)	The flow cytometry crossmatch is negative but there are donor specific HLA-DQ antibodies which have caused a shift in the result. Our advice would be to look for an alternate donor (see answer to number 4) however if no other source of donor available this result would NOT be a contraindication to transplant.	Medium
23	A3 (2150), B7 (1528) *(No DQ2 DSA despite reporting presence of DQ2 in sample)*	Compatible - Progress to transplantation. Risk for accelerated acute rejection.	Medium
34	B8 (1842), DQ2 (11163), DQA1*05:01 (11163)	Although the Flow and CDC crossmatches for this pair are negative, high resolution antibody detection methodology (Sag) has shown the presence of B8 low MFI, DQ2 and DQA1*05:01 high MFI DSAs.	Medium
38	B8 (1078), DQ2 (14295)	HLA antibody testing on serum 3 detected HLA-B8 and DQ2 donor-directed antibodies. The negative T-cell and positive B-cell flow cytometry crossmatch results reflect the MFI values of the donor-directed antibodies; low level class I antibodies, present by Luminex testing but not causing a positive crossmatch, and high level class II antibodies, causing a positive crossmatch. A CDC crossmatch was not performed due to insufficient lymphocyte numbers isolated from the 'donor' blood sample, and this would be needed to complete the risk assessment. We would report the antibody results, the FC XM results and state the we would require further blood so as to be able to carry out a CDC XM.	
39	DQ2 (12668)	Positive B cell crossmatch due to donor specific antibodies. (No CDC XM performed)	Medium
149	DQ2 (2000)	Presence of DSA detected with Luminex assay and CDC crossmatch (Positive PBL CDC xm)	Medium
194	DQ2 (8180), B8 (1211), A3 (898), DR17 (683)	Donor-specific HLA class II and weak class I antibodies; positive B cell flow cytometry crossmatch; weak positive B cell CDC crossmatch but negative with DTT	Medium
260	DQ02	Patient who gave serum3 suitable for transplantation despite the presence of anti HLA DQ*02 antibody. Because there were no donor reactivity by the cross-match tests.	Medium

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Benefits

- Participants able to:
  - Monitor performance of multiple techniques within a single scheme
  - Make clinical interpretations based on their own results
  - Compare local policies for clinical assessment
- Educational
  - Monitor concordances
  - Review variations
  - Trainees
- Competency
  - Laboratory staff
  - Consultants

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Future Considerations

- Could the scheme form the basis of future formal EQA scheme design?
- Workload
  - Participants
  - UK NEQAS
- Assessment complexity
  - Consensus?
  - Incorrect result, correct interpretation?

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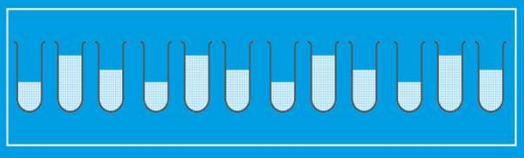
Interpretive Educational Schemes



Tracey Rees

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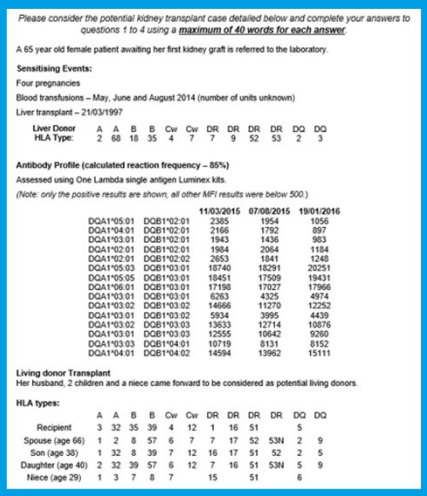
Interpretive Educational Scheme

- 3 Clinical Scenarios a year
  - Solid Organ, HSCT, Platelet/transfusion
- Based on patient cases
  - Provide relevant clinical details and test results
  - Questions on interpretation of results and clinical advice
- Not Assessed
- Provided free of charge



*Please consider the potential kidney transplant case detailed below and complete your answers to questions 1 to 4 using a **maximum of 40 words for each answer**.*

A 65 year old female patient awaiting her first kidney graft is referred to the laboratory.

Sensitising Events:

Four pregnancies

Blood transfusions – May, June and August 2014 (number of units unknown)

Liver transplant – 21/03/1997

	A	A	B	B	Cw	Cw	DR	DR	DR	DR	DQ	DQ
Liver Donor HLA Type:	2	68	18	35	4	7	7	9	52	53	2	3

Antibody Profile (calculated reaction frequency – 85%)

Assessed using One Lambda single antigen Luminex kits.

(Note: only the positive results are shown, all other MFI results were below 500.)

		11/03/2015	07/08/2015	19/01/2016
DQA1*05:01	DQB1*02:01	2385	1954	1056
DQA1*04:01	DQB1*02:01	2166	1792	897
DQA1*03:01	DQB1*02:01	1943	1436	983
DQA1*02:01	DQB1*02:01	1984	2064	1184
DQA1*02:01	DQB1*02:02	2653	1841	1248
DQA1*05:03	DQB1*03:01	18740	18291	20251
DQA1*05:05	DQB1*03:01	18451	17509	19431
DQA1*06:01	DQB1*03:01	17198	17027	17966
DQA1*03:01	DQB1*03:01	6263	4325	4974
DQA1*03:02	DQB1*03:02	14666	11270	12252
DQA1*03:01	DQB1*03:02	5934	3995	4439
DQA1*03:02	DQB1*03:03	13633	12714	10876
DQA1*03:01	DQB1*03:03	12555	10642	9260
DQA1*03:03	DQB1*04:01	10719	8131	8152
DQA1*04:01	DQB1*04:02	14594	13962	15111

Living donor Transplant

Her husband, 2 children and a niece came forward to be considered as potential living donors.

HLA types:

	A	A	B	B	Cw	Cw	DR	DR	DR	DR	DQ	DQ
Recipient	3	32	35	39	4	12	1	16	51		5	
Spouse (age 66)	1	2	8	57	6	7	7	17	52	53N	2	9
Son (age 38)	1	32	8	39	7	12	16	17	51	52	2	5
Daughter (age 40)	2	32	39	57	6	12	7	16	51	53N	5	9
Niece (age 29)	1	3	7	8	7		15		51		6	

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Scenarios

	Solid Organ	HSCT	Platelet/ transfusion
2013	Live kidney transplant	Matched unrelated donor selection	N/A
2014	Deceased kidney transplant	Mismatched unrelated donor selection	N/A
2015	Cardiothoracic transplant	Paediatric cord blood donor selection	Platelet refractory
2016	Deceased donor virtual XM	Donor search for patient with unusual HLA type	Platelet refractory
2017	Cardiothoracic transplant	Haploidentical donor selection	TRALI

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Scenario 1- Cardiac Transplant Case

Offer of cardiac transplant to your centre and selection of recipients

Provided

- Donor HLA type and ABO (O)
- Luminex results for 7 potential recipients
- Information on potential recent sensitising events
- Crossmatching results

- 46 returns (20 UK&I)

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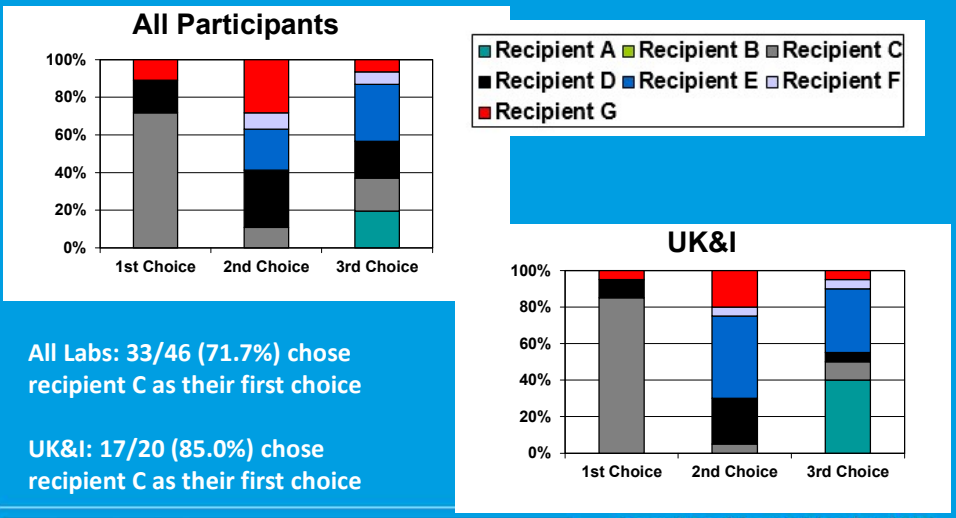
Rank the 3 most suitable recipients



All Labs: 33/46 (71.7%) chose recipient C as their first choice

UK&I: 17/20 (85.0%) chose recipient C as their first choice

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Reasons for Selection

Donor HLA type: A1, A24; B8, B60; Cw7, Cw10; DR4, DR13; DR52, DR53; DQ6, DQ7
ABO: O Offer date 22/08/17

No Selected (UK&I)	ID	Blood group	Antibody specificities (MFI in brackets)	Date of last sample	Comments
0,0,9 (0,0,8)	A	A POS	Cw7 (3,000)	13/07/2017	Cw7 DSA
0,0,0 (0,0,0)	B	O NEG	A1 (2,400), B8 (3,500)	14/07/2017	A1 & B8 DSA
33,5,8 (17,1,2)	C	O POS	Negative	15/08/2017	
8,14,9 (2,5,1)	D	O POS	A2 (12,000), A29 (9,400), A43 (7,600), A68 (10,000), A69 (8,500), B44 (3,600), DP4 (5,400)	03/06/2017	DP type of donor unknown
0,10,14 (0,9,7)	E	O POS	A23 (1,300), A24 (1,800), B35 (8,000), B51 (6,500), B53 (4,600), B78 (4,800)	29/07/2017	A24 DSA
0,4,3 (0,1,1)	F	A NEG	Negative	01/12/2016	No Recent sample
5,13,3 (1,4,1)	G	O POS	A2 (1,600), A68 (1,400), Bw4 (6,500)	22/07/2017	Bw4 DSA (A24)

6 UK&I participants chose recipient G. ? Not consider Bw4 epitope on A specificities

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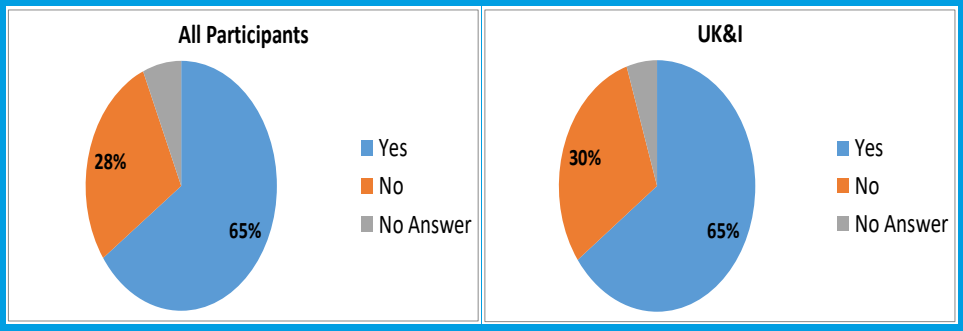
Patient A and C received VADs & multiple blood transfusions in past 2 weeks

- Does this change your recipient selection?



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- Patient D now added to ‘super urgent’ waiting list
- Further testing reveals that the antibodies to HLA A29 and A43 are directed against denatured HLA antigens on single antigen Luminex beads.
- Select immunological risk for 5 blood group compatible donors considered for VXM

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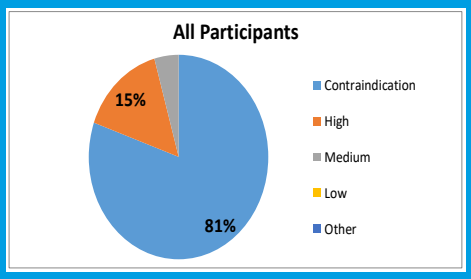
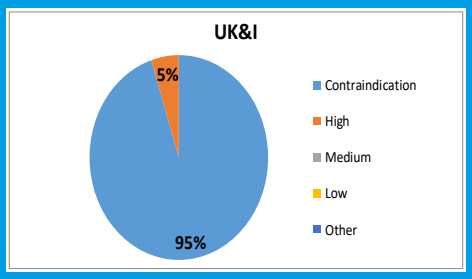
Select immunological risk for VXM – Donor 1

HLA Antibodies: A2 (12,000), *A29 (9,400), A43 (7,600),* A68 (10,000), A69 (8,500), B44 (3,600), DP4 (5,400)

1	A1, A2, B7, B44, Cw5, Cw7 DR4 DR17 DR52 DR53 DQ2, DQ7, DP2, DP4





Contraindication/High risk – Cumulative DSA >20,000MFI

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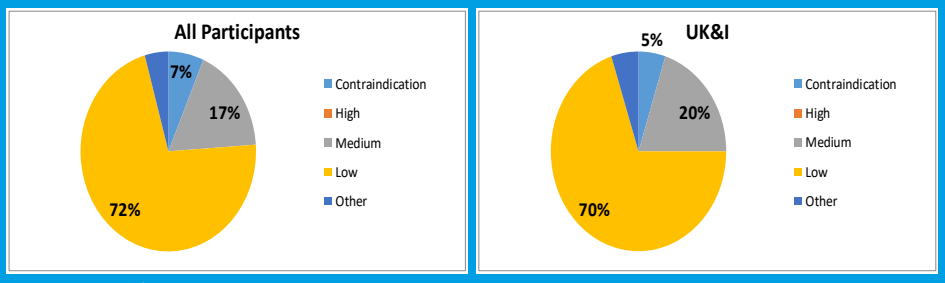
Select immunological risk for VXM – Donor 2

HLA Antibodies: A2 (12,000), *A29 (9,400), A43 (7,600),* A68 (10,000), A69 (8,500), B44 (3,600), DP4 (5,400)

2 A1, A29, B7, B35 Cw4 Cw7 DR13, DR15 DR51 DR52 DQ6 DP1 DP2



Medium/Low risk – Denatured A29 unlikely to be clinically relevant
Contraindication – Denatured A29 still considered DSA

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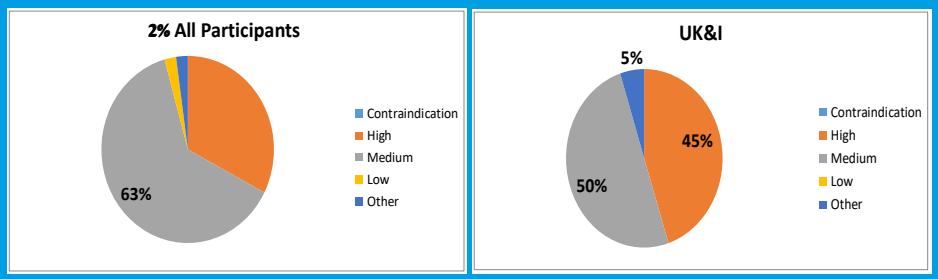
Select immunological risk for VXM – Donor 3

HLA Antibodies: A2 (12,000), *A29 (9,400), A43 (7,600),* A68 (10,000), A69 (8,500), B44 (3,600), DP4 (5,400)

3 A3, A11 B44, B55 Cw9 Cw5 DR7 DR11 DR52 DR53 DQ2 DQ7 DP1 DP5



Medium risk – B44 DSA < 5000 MFI – acceptable risk for super urgent patient
High risk – CTAG risk level III

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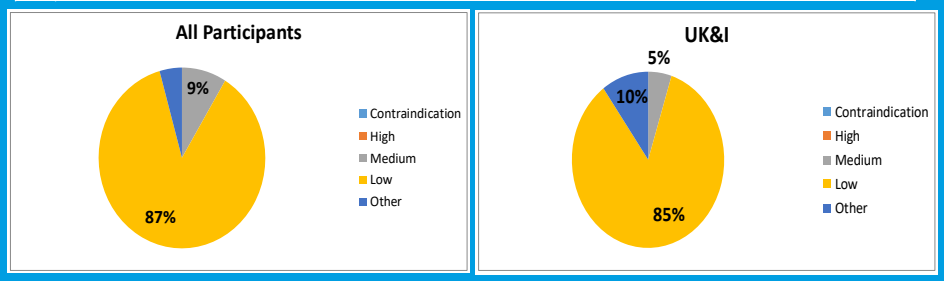
Select immunological risk for VXM – Donor 4

HLA Antibodies: A2 (12,000), *A29 (9,400), A43 (7,600),* A68 (10,000), A69 (8,500), B44 (3,600), DP4 (5,400)

4 A25 A32 B45 B57 Cw6 DR1 DR15 DR51 DQ5 DQ6 DP2



Low risk – No DSA
Medium risk – high number of mismatches, cross reaction with B45 possible

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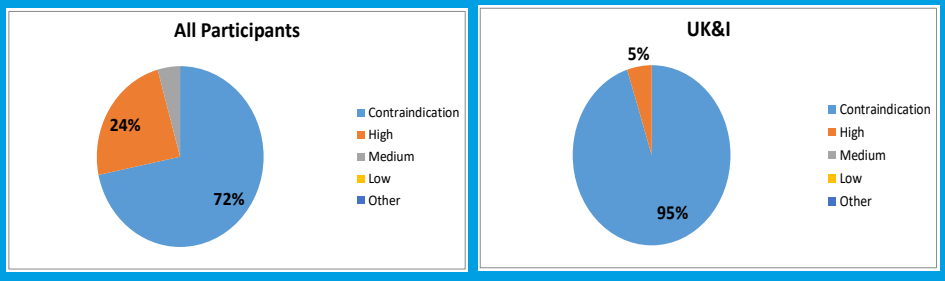
Select immunological risk for VXM – Donor 5

HLA Antibodies: A2 (12,000), *A29 (9,400), A43 (7,600),* A68 (10,000), A69 (8,500), B44 (3,600), DP4 (5,400)

5 A2 A32 B44 Cw5 DR7 DR53 DQ2 DP4



Contraindication/High Risk – Cumulative DSA >5000 MFI

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Scenario 2 – HSCT Scenario

- 63 year old female with AML
- Blood group: O Rh Pos
- CMV status: Positive

A*02:02, A*23:01; B*14:01, B*42:01; C*08:02, C*17:01;
DRB1*07:01, -; DQB1*02:02, -; DPB1*01:01, DPB1*105:01

Unrelated donor search

- 49 responses received (19 UK&I)

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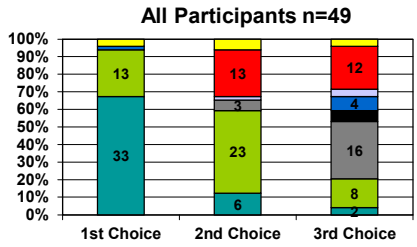
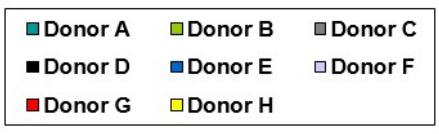
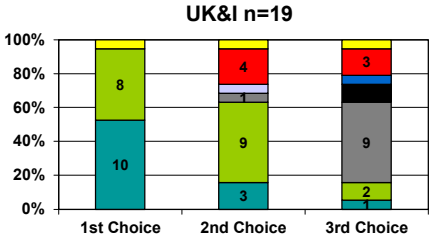
Which 3 unrelated donors would you select?







All Labs: Donor A most popular 1st choice (33/41). Donor B selected by 44/49 participants overall

UK&I: Donor A most popular 1st choice (10/19). Donor B selected by 19/19 participants overall

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Donor Selection Reasons

No. labs (UK&I)	Donor ID	Registry	A*	B*	C*	DRB1*	DQB1*	DPB1*	Blood group	Age	CMV	Sex	Reasons for selection
	Patient Type		02:02 23:01	14:01 42:01	08:02 17:01	07:01	02:02	01:01 105:01	O Rh Pos	63	Positive	F	
13,23,8 (8,9,2)	B	NMDP	23 30	14:01 42:01	08:02 17	07:01	02		Unknown	29	Unk	M	Male, young, potential 9/10, A MM, reliable registry
33,6,2 (10,3,1)	A	Brazil	02 23	14:01 42		07:01			Unknown		Unk		Potential 10/10
0,3,15 (0,1,9)	C	NMDP	2	64 42		07:01			A Rh Pos	38	Neg 1996	M	Male, potential 9/10, A MM
0,13,12 (0,4,3)	G	Germany	02 23	14:01 41:01	08 17	07	02		O Rh Pos	40	Unk	F	Potential 9/10, ABO, reliable registry
2,3,2 (1,1,1)	H	Israel	02 23	14:01 42	08:02 17	07:01 11:01			Unknown	24	Positive	M	Young, male, CMV, potential 9/10 match
0,0,3 (0,0,2)	D	NMDP	80 23	64 42		07			Unknown	59	Unk	F	Potential 9/10, A MM
1,0,4 (0,0,1)	E	Germany	02 23	14:01 41:02		07			Unknown	40	Unk	F	Potential 9/10, B MM, reliable registry
0,1,2 (0,1,0)	F	France	02 23	14 42		07 03:02			Unknown	20	Unk	M	Potential 7/8 match, young, male

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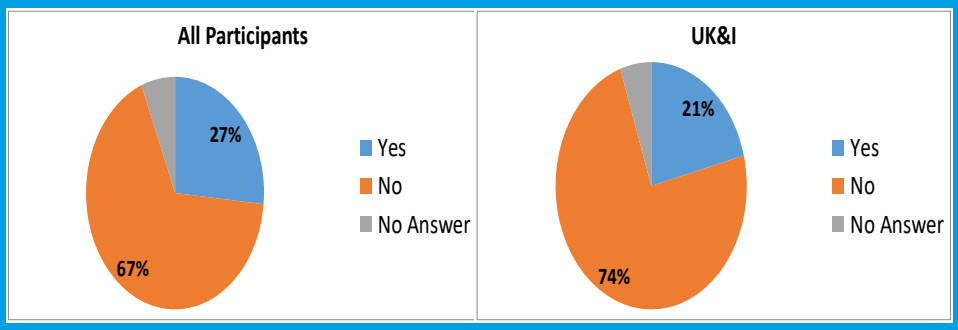
One 9/10 donor, (DRB1 mismatch) and CMV mismatch. Would you recommend using this donor?



33/49 would not recommend using this donor (UK&I 14/19)

- Avoid HLA & CMV mismatch combinations
- Explore alternative options
- DRB1 mismatch unacceptable
- Unlikely to find better match
- Urgency of transplant

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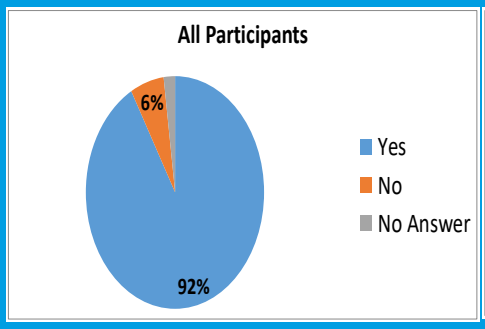
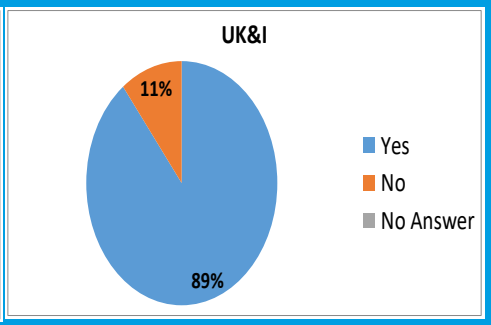
Would you investigate alternative transplant options for this patient?





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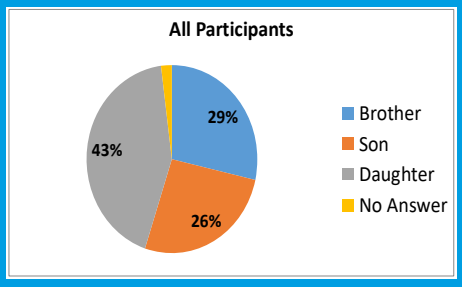
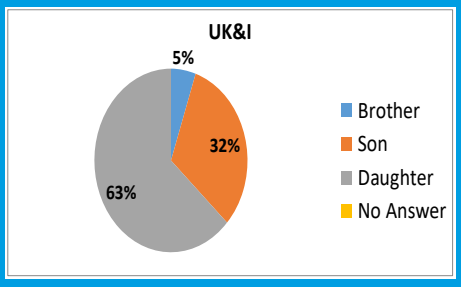
Which haploidentical donor would you select?





Donor ID	A*	B*	C*	DRB1*	DQB1*	DPB1*	Age	CMV	Sex	DSA (MF)	Donor KIR B-Content Calculator	Reasons for selection
Patient Type	02:02 23:01	14:01 42:01	08:02 17:01	07:01	02:02	01:01 105:01	63	Pos	F			
Brother	23:01 29:02	42:01 45:01	16:01 17:01	03:01 07:01	02:01 02:02	01:01 18:01	64	Neg	M	None	Neutral	No DSA, Male
Son	23:01 68:01	42:01 58:01	06:02 17:01	07:01 12:01	02:02 05:01	01:01 17:01	30	Pos	M	A68 (3517)	Neutral	Young, CMV match, male, low MFI DSA
Daughter	02:02 74:01	14:01 15:03	02:10 08:02	07:01 13:02	02:02	04:02 105:01	33	Pos	F	DPB1*04:02 (9015)	Better	Young, CMV match, DP DSA no concern, better KIR score

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Scenario 3 – Transfusion Related Acute Lung Injury (TRALI)

- 29 year old male patient with AML and suspected TRALI after transfusion of red cells and platelets

- Provided transfused unit details
- HLA and HNA type of patient
- Luminex Class I and II results &
- Granulocyte antibody results of 3 donors

- 27 responses received (12 UK&I)
  - 9 provide a full or partial TRALI service
  - 14 no TRALI service

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Provide a summary of antibody results for each donor in relation to TRALI diagnosis

- Donor 1:
  - Low MFI patient specific HLA antibodies A*03 (878 MFI), B*44 (991 MFI), unlikely to be clinically significant
  - Potential HNA-1a antibody present in donor's serum as seen in GIFT IgG/GCLT but not relevant in this case as the patient does not possess the cognate antigen.
  - Duration between transfusion and clinical events too long for TRALI (>6 hours)
- Donor 2:
  - No HLA or granulocyte specific antibodies detected
- Donor 3
  - HLA-A3 patient specific antibody (6027)
  - No granulocyte antibodies detected.
  - Onset of symptoms within 6 hours after the transfusion

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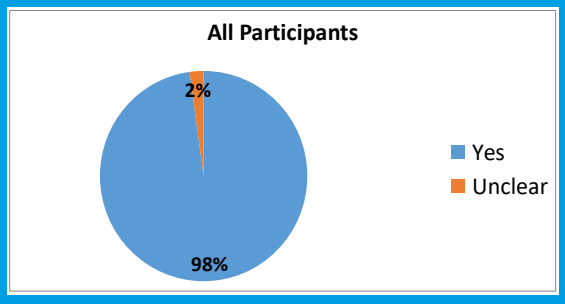
Do the results support the diagnosis of TRALI?



26/27 'Yes' (12/12 UK&I)

HLA-A*03 antibody detectable in Donor 3 is relevant as the patient possesses cognate HLA-A*03. Transfusion within 6 hours of the reaction so donor 3 is the potential cause of antibody mediated TRALI.

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What advice with regards to future blood component use would you provide?

- Donor 1:
  - Resign donor from donating any product / therapeutic donations
  - Use for red cell products only / no plasma containing products
- Donor 2:
  - No restrictions, donor can continue to donate
- Donor 3:
  - Resign donor from donating any product / therapeutic donations
  - Use for red cell products only / no plasma containing products

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iED Discussion

- Questions / comments ?
  - Ideas for cases
  - Result feedback
  - Format of cases
  - Complexity level
  - Educational benefit
  - Number of questions

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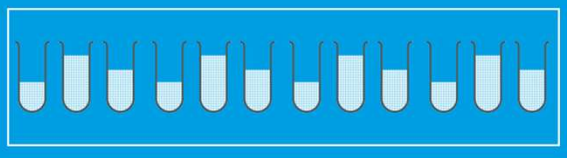
Discussion



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