UK NEQAS Histocompatibility & Immunogenetics

UK NEQAS H&I

Annual Participant's Meeting 2023-24

@UKneqasHI

@UK_NEQAS

@UKNEQAS

Welcome and Introduction

Dr Helena Lee

Chair of UK NEQAS for H&I Steering Committee

Key Data from the Schemes

Amy De'Ath
UK NEQAS for H&I Manager

GIG CYMRU NHS WALES | Ymddiriedolaeth GIG Prifysgol Felindre | Velindre University NHS Trust

Welsh Blood Service

Meet The Team!

Director: Deborah Pritchard

Manager: Amy De'Ath

Deputy Manager: Melanie Bartley

Healthcare Scientist Practitioner: Geraint Clarke

QA Technical Officer: Jack Jefferies

MLA: Sue Davies

UKNEQASHandI@Wales.NHS.UK

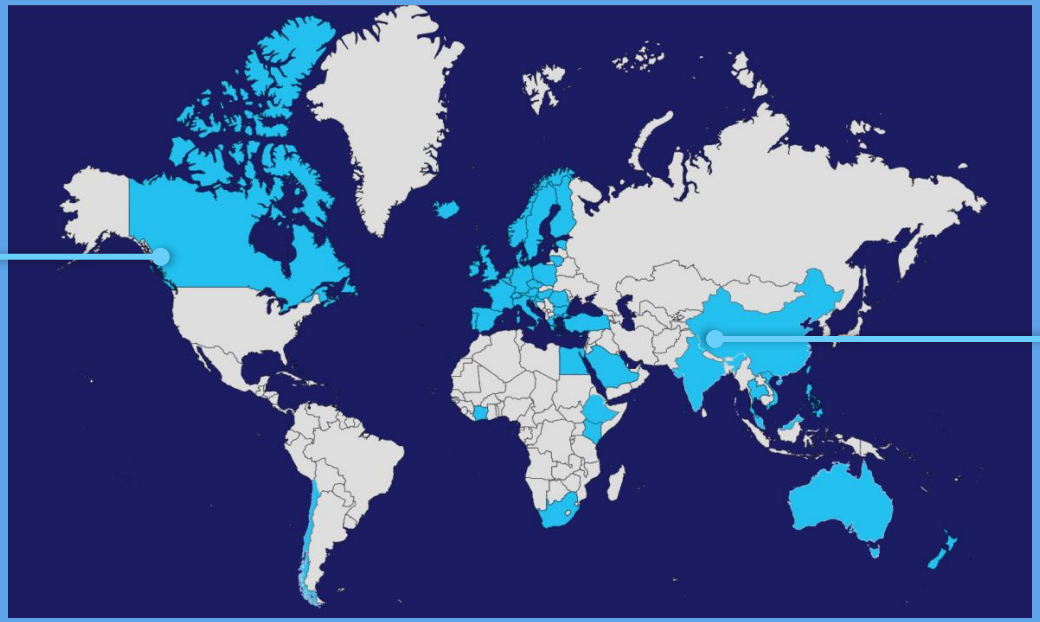
UK NEQAS for H&I Steering Committee 2023-24

Helena Lee (Chair)
Arthi Anand
Katy Derbyshire
Sylvia McConnell
Katherine Mounsey
Anthony Calvert
Sunil Daga (Clinical Representative)
Elizabeth Wroe (BSHI Representative to UK NQAAP)

Rhys Goodhead (Expert Advisor Scheme 5B)
Barbara McNamara (Expert Advisor Scheme 5B)
Tim Clench (Expert Advisor Scheme 5B)

UK NEQAS for H&I: An Overview

>320 participants



>50 countries

Things To Note...

Presentation Focus...

Performance, key trends, discussion points and 2024 changes

Further Details...

The presentation will be available to view on our website.

Lab Locations...

Generally:
1-100 = UK & Ireland.
101+ = Rest of the world

Scheme Assessments

- Most Schemes assessed on a consensus basis using a 75% consensus level i.e. 75% of reports must agree on a result for it to be assessed.
- Reference typing results are used for typing/disease schemes if consensus not reached plus educational schemes where required:

  - *e.g. Scheme 8: HLA Genotyping for Coeliac and Other HLA Associated Diseases*

- Equivocal result only accepted for Scheme 2B.
- All Not Tested (NT) results excluded from assessment.
- Labs that fail to return results or do not a provide valid reason for NT are assessed as unacceptable.

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 analysis and CAPA form.

Changes for 2024-25

Director

Deborah Pritchard

Webinars

iED feedback continuing

Scheme Changes: Antibody Schemes

Scheme 3 – Result Entry Improvements

Scheme 11 – Select Specific HPA

Scheme Changes: Molecular Schemes

Scheme 4A2 – 3rd Field: clarified reporting of cis/trans ambiguities

Scheme 8 – Pharmacogenetic reactions: addition of HLA-A2 detection for Tebentafusp

https://ukneqashandi.org.uk/scheme-4a2-results-submission-help/

Feedback from the Participant Survey

- Survey sent in October 2023:

Needs Improvement	Good	Great	Excellent
• Courier service • Visibility of Steering committee	• Portal • Website • Finance	• Service provision • Communication • Participant manual • Participant engagement • Sample quality • Scheme design	• Reports • Educational schemes

Expansion - 20% interested in HNA scheme, 14% interested in a dd-cfDNA scheme

Scheme 2A

Cytotoxic Crossmatching

Scheme 2A – Cytotoxic Crossmatch

Purpose

Assess participants ability to determine cell/serum cytotoxicity crossmatch status

Consensus

At least 75% agreement on pos/neg result

Satisfactory Performance

85% of reports agree with consensus in distribution year for each cell/DTT type

10 blood samples, 40 serum samples over 5 distributions

Scheme 2A: Performance

All cells with and without DTT	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	75 (19)	71 (18)	71 (22)	66 (16)	63 (15)	59 (15)	47 (10)
Number with Unsatisfactory Performance (< 85%) (UK&I)	16 (6)	16 (7)	5 (1)	7 (0)	4 (0)	6 (3)	2 (2)
% Unsatisfactory Performance (UK&I)	21.3% (31.6%)	22.5% (38.8%)	7.0% (4.5%)	10.6% (0)	6.3% (0)	10.2% (20%)	4.2% (20%)

2023: 2 Unsatisfactory Performers (2 UK & Ireland)

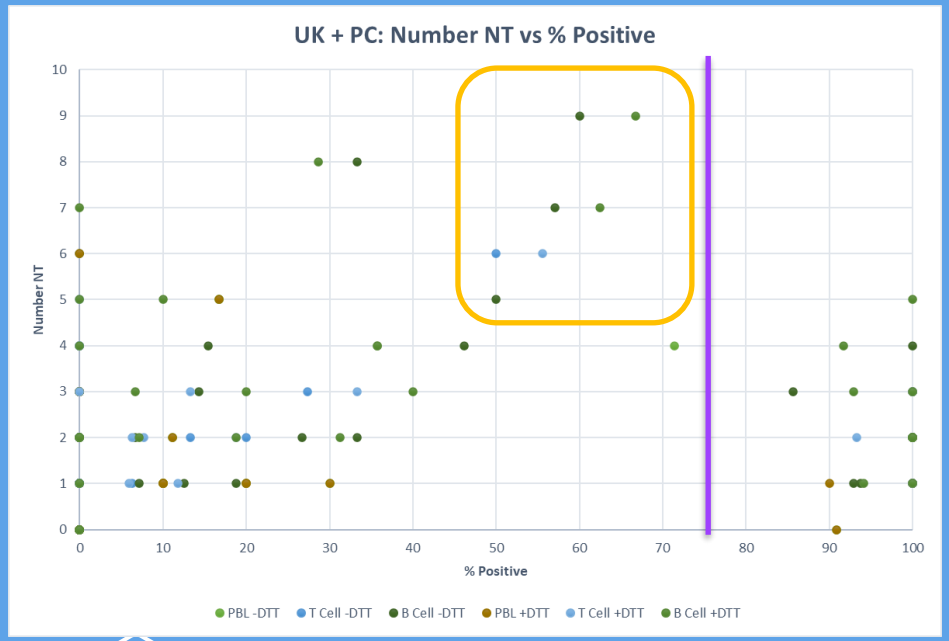
Scheme 2A: Performance by category

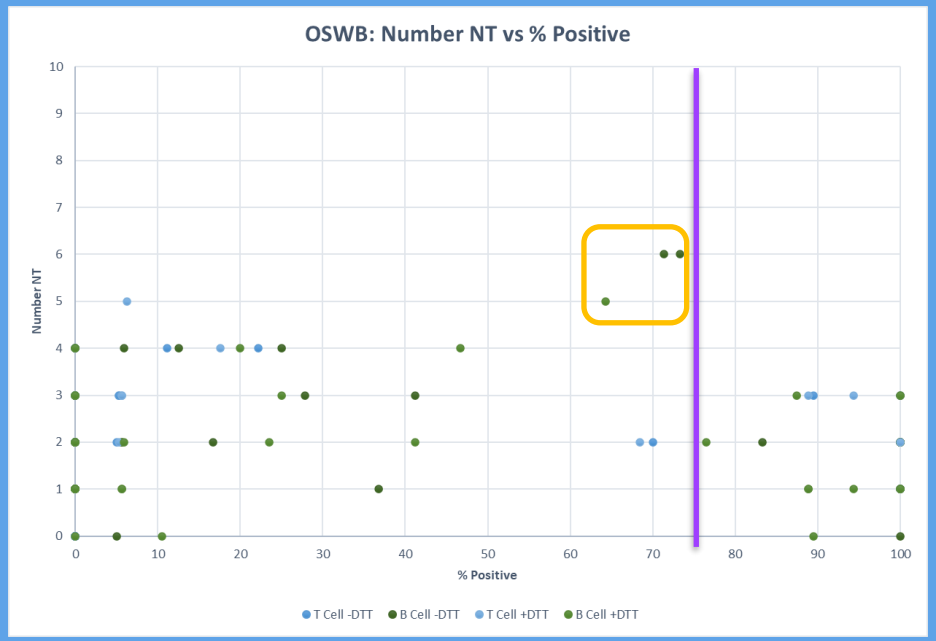
	PBL	PBL +DTT	T Cell	T Cell +DTT	B Cell	B Cell +DTT
Crossmatches assessed (n=40) (UK&I)	35 (35)	35 (35)	39 (38)	39 (38)	35 (27)	37 (27)
NT – Assessed samples only	15.6%	15.3%	9.3%	10.1%	13.2%	13.6%
% incorrect assignments	3.5%	3.6%	1.3%	1.6%	3.1%	4.0%
False Positive	3.2%	3.0%	1.1%	1.3%	2.4%	2.4%
False Negative	0.3%	0.6%	0.1%	0.3%	0.7%	1.6%

Scheme 2A: Unacceptable Performers 2023

Lab ID	PBL -DTT	T -DTT	B -DTT	PBL + DTT	T + DTT	B + DTT	Lab Identified Error
15					81%		False pos/high sensitivity
45			64%				Awaiting response

Scheme 2A: Reporting of Not Testing





Scheme 2A: Discussion

- Not all Scheme 2A results will reach consensus (that's ok!)
- B-cells are difficult (transport, non-specific binding)
- CDC assays are not quantitative so reliant on subjective assessment
- Only partially emulates clinical practice
- 2A is a technical assessment of cytotoxic crossmatching and should not be 'interpreted'
- Lab's need to ensure that all test parameters and acceptance criteria are met prior to reporting NEQAS samples

Scheme 2B

Crossmatching by Flow Cytometry

Scheme 2B: Crossmatching by Flow Cytometry

Purpose
Assess participants ability to determine cell/serum flow crossmatch status

Consensus
At least 75% agreement on pos/neg or equivocal result

Satisfactory Performance
85% reports agree with consensus in distribution year for each cell type

10 blood samples, 40 serum samples over 5 distributions

Scheme 2B: Performance

	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	85 (22)	83 (22)	84 (23)	80 (21)	80 (22)	84 (19)	83 (21)
Number with Unsatisfactory Performance (< 85%) (UK&I)	8 (1)	15 (2)	12 (1)	11 (0)	5 (0)	6 (2)	10 (0)
% Unsatisfactory Performance (UK&I)	8.7% (4.5%)	18.1% (9.1%)	14.2% (4.3%)	13.8% (0)	6.3% (0)	7.1% (10.5%)	12% (0)

2023: 10 Unsatisfactory Performers (0 UK & Ireland)

Scheme 2B: Performance by Category

	T Cells			B Cells		
	UK&I	RoW PC	RoW WB	UK&I	RoW PC	RoW WB
Number of participants	21	27	33	21	27	31
Number of XM assessed (>75% consensus)	33/40 (82.5%)	36/40 (90%)	33/40 (82.5%)	36/40 (90%)	32/40 (80%)	32/40 (80%)
Number of Positive XM	26 (79%)	22 (61%)	25 (75%)	27 (75%)	24 (75%)	25 (78%)
Number of Negative XM	7 (21%)	14 (39%)	8 (25%)	9 (25%)	8 (25%)	7 (22%)
Number of incorrect assignments	16	54	17	28	49	29
Number of False Pos	4	25	5	15	20	26
Number of False Neg	12	21	12	13	29	3
Number of equivocal assignments	1	0	2	1	5	4
Number of samples NT	41	111	98	50	78	100

UK&I and RoW receive different blood samples

Scheme 2B: Unacceptable Performers 2023

Lab	T Cell	No. of results submitted	B Cell	No. of results submitted	Issue
117	81%	36/40	86%	35/40	Procedural error
118	94%	40/40	81%	40/40	False pos/sensitivity issues
122	90%	32/40	80%	32/40	Delivery delays-poor sample prep/sensitivity issues
139	97%	40/40	73%	40/40	No response
145	83%	40/40	94%	40/40	False negs reported after repeat testing
149	75%	40/40	84%	40/40	Technical/neg control issues
191	91%	40/40	81%	40/40	False neg/pos
283	82%	32/40	66%	32/40	Multiple issues, delivery delays, poor preps
1409	94%	40/40	84%	38/40	False negs/sensitivity issues
1420	57%	8/32	57%	8/32	No response

10 labs with UP (<85%)

Scheme 6

HLA Antibody Detection

Scheme 6: HLA Antibody Detection

Purpose

Assess participants ability to determine **presence or absence** of HLA antibodies

Consensus

At least 75% agreement on presence/absence of HLA antibodies

Satisfactory Performance

80% reports agree with consensus in distribution year

12 serum samples over 3 distributions

Scheme 6: Performance

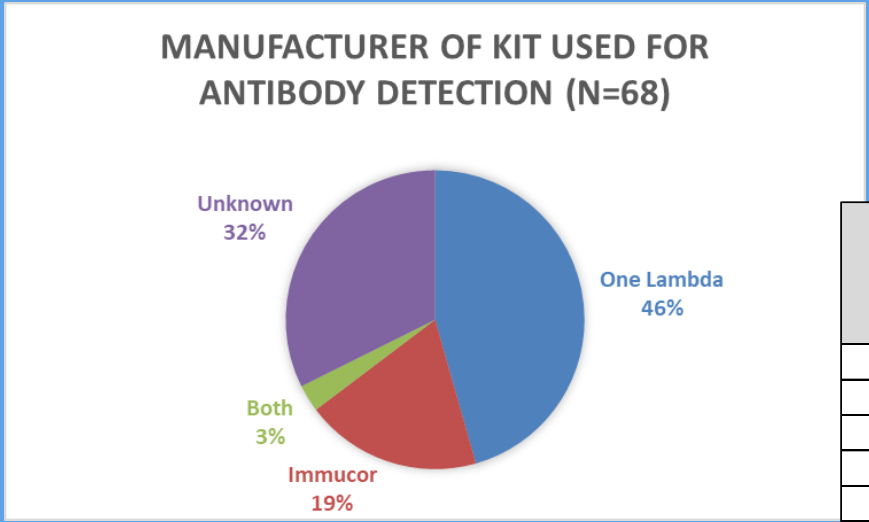
3 Unsatisfactory Performers (0 UK&I)

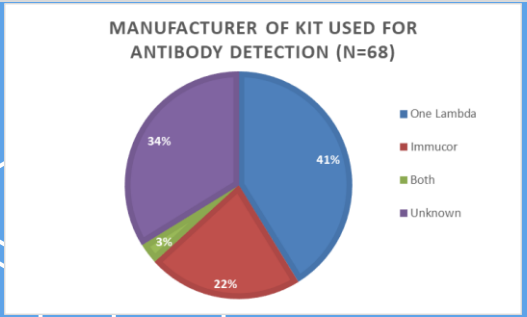
	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	101 (24)	88 (25)	82 (25)	74 (25)	71 (23)	68 (23)	68 (23)
Number with Unsatisfactory Performance (< 80%) (UK&I)	21 (0)	5 (0)	8 (0)	2 (0)	0 (0)	4 (0)	3 (0)
% Unsatisfactory Performance	20.8% (0%)	5.7% (0%)	9.7% (0%)	2.7% (0%)	0% (0%)	5.0% (0%)	4.4% (0%)

Scheme 6: Unacceptable Performers 2023

Lab	Performance (<80%)	Issue
1418	72.7%	Kit issues
1420	62.5%	No response
189	66.7%	Transcription Error

Scheme 6: Kit Use and Performance





2023	Class I				Class II			
	One Lambda (n=31)	%	Immucor (n=13)	%	One Lambda (n=31)	%	Immucor (n=13)	%
601	Positive	71	Negative	100	Negative	94	Negative	100
602	Positive	100	Positive	100	Positive	100	Positive	100
603	Positive	100	Positive	100	Positive	100	Positive	100
604	Negative	87	Negative	77	Negative	97	Negative	77
605	Positive	100	Positive	100	Positive	100	Positive	100
606	Positive	97	Positive	100	Negative	63	Negative	100
607	Negative	94	Negative	92	Negative	94	Negative	100
608	Positive	100	Positive	100	Positive	100	Positive	100
609	Positive	100	Positive	100	Positive	97	Positive	92
610	Positive	100	Positive	100	Positive	100	Positive	92
611	Positive	84	Positive	92	Positive	100	Positive	92
612	Negative	100	Negative	100	Negative	97	Negative	92

Scheme 3

HLA Antibody Specificity Analysis

Scheme 3: HLA Antibody Specificity Analysis

Purpose

Assess participants ability to determine **specificity** of HLA antibodies

Consensus

At least 75% agreement on presence of HLA antibodies, 95% agreement on absense.

Satisfactory Performance

75% reports agree with consensus in distribution year

10 serum samples over 3 distributions

Scheme 3: Performance

Class I		2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)		72 (24)	73 (25)	70 (25)	64 (24)	65 (24)	65 (24)	64 (24)
Number with Unsatisfactory Performance (UK&I)	Presence	10 (0)	15 (1)	3 (0)	1 (0)	1 (0)	1 (0)	4 (0)
	Absence	3 (0)	5 (0)	2 (0)	1 (0)	1 (0)	1 (0)	1 (0)
% Unsatisfactory Performance	Presence	13.8%	20.5%	4.2%	1.6%	1.5%	1.5%	6.3%
	Absence	4.2%	6.8%	2.6%	1.6%	1.5%	1.5%	1.5%

Overall 5 labs with UP (0 UK&I)

Class II		2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)		72 (24)	75 (25)	69 (25)	63 (24)	64 (24)	64 (24)	64 (24)
Number with Unsatisfactory Performance (UK&I)	Presence	5 (0)	12 (0)	5 (0)	2 (0)	3 (0)	1 (0)	4 (0)
	Absence	2 (0)	3 (0)	2 (0)	1 (0)	1 (0)	1 (0)	1 (0)
% Unsatisfactory Performance	Presence	6.9%	16.0%	7.2%	3.2%	4.7%	1.6%	6.3%
	Absence	2.8%	4.0 %	2.8%	1.6%	1.6%	1.6%	1.6%

Scheme 3: Unacceptable Performers 2023

5 labs (0 UK&I) with UP (<75%)

	Class I		Class II		CAPA	Kit
Lab	Presence	Absence	Presence	Absence		
112	69%	100%	89%	100%	No reply	Werfen (Immucor)
211	51%	98%	85%	83%	No reply	Werfen (Immucor)
302	80%	33%	43%	63%	No reply	Werfen (Immucor)
1411	65%	100%	87%	95%	False negs/sample issues	Werfen (Immucor)
1418	71%	100%	80%	94%	Interpretation/assignment issues	One Lambda

Scheme 3: Class I Assessment

	Number of HLA Class I Specificities (n=62)										
	301	302	303	304	305	306	307	308	309	310	Total
Present (≥75%)	5	5	2	15	25	12	6	25	21	30	146
Absent (<5%)	20	9	9	22	32	20	44	15	23	27	221
Negative 0%	52	68	73	34	11	53	37	41	31	19	419
Not Assessed (5-74%)	13	7	5	18	20	5	1	8	14	13	104

417 (absent 0% not included in analysis) specificities reported over 10 samples

31.0% reached consensus presence

46.9% reached consensus absence

22.1% specificities were not assessed

Scheme 3: Class II Assessment

(DPB included in assessment from 2021)

	Number of HLA Class II Specificities (DR, DQ, DP) (n=62)										
	301	302	303	304	305	306	307	308	309	310	Total
Present (≥75%)	23	4	18	0	2	15	14	10	14	16	116
Absent (<5%)	9	10	14	11	8	6	1	1	5	0	65
Negative 0%	9	25	8	32	34	14	28	34	19	27	230
Not Assessed (5-74%)	5	7	6	3	2	11	3	1	8	2	48

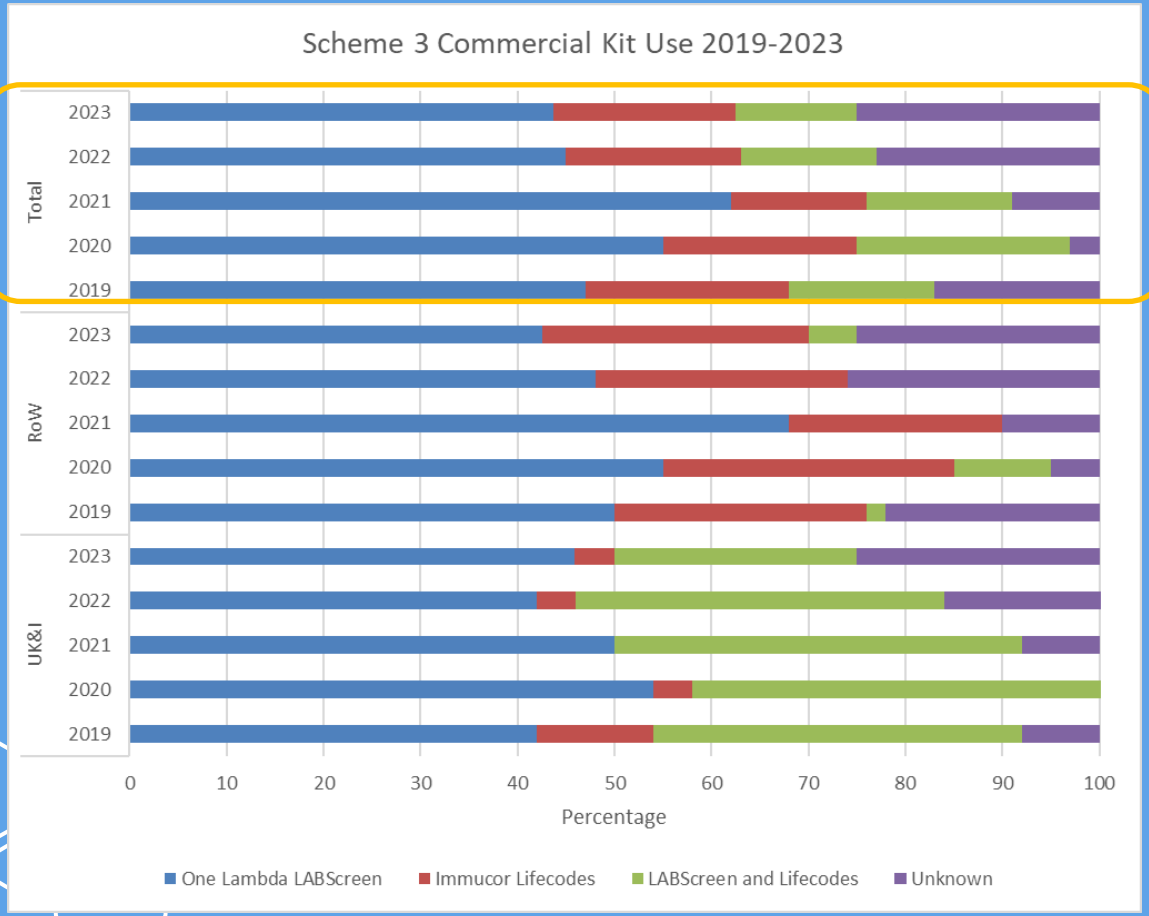
229 specificities (absent 0% not included in analysis) reported over 10 samples

50.6% reached consensus presence

28.4% reached consensus absence

21.0% specificities were not assessed

Scheme 3: Kit Use 2019-2023

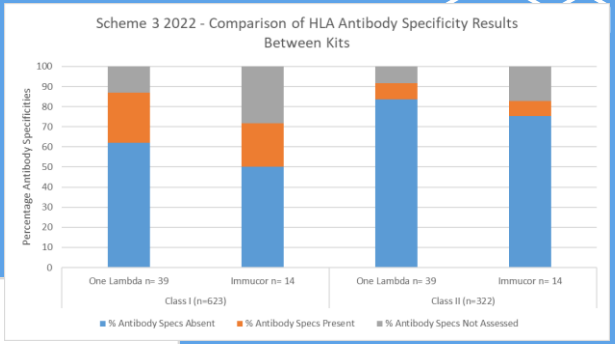


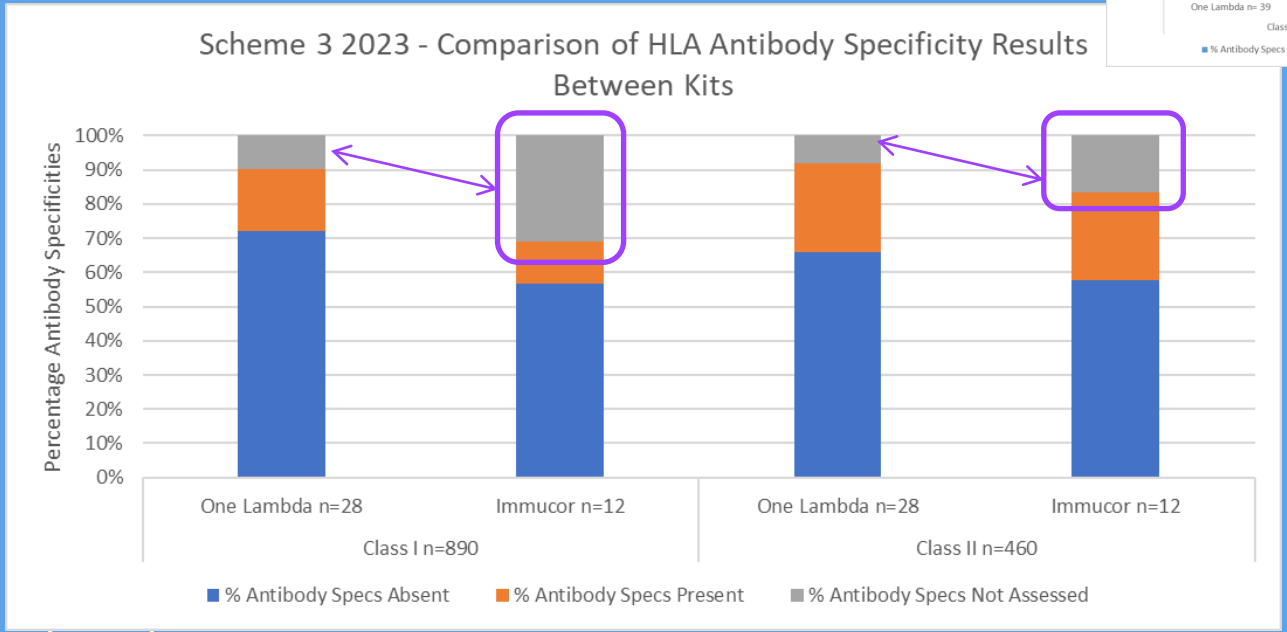
Overall OL kits are the most widely used

UK&I labs are more likely to use a combination of kits

Immucor only kit use more prevalent in RoW labs

Scheme 3: Results by Kit Use





Similar percentage of antibodies reach consensus present (orange) in both kits

Less concordance in 'absent' antibodies

Greater percentage of Class I antibodies classed as not assessed

Scheme 3: Kit Use and Performance

2023-24

Average Performance	Class I		Class II	
	OL	Imm	OL	Imm
Presence	96.9% ↑	86.2%	95.8% ↑	88.2%
Absence	98.8% ↔	93.7%	98.6% ↔	94.1%

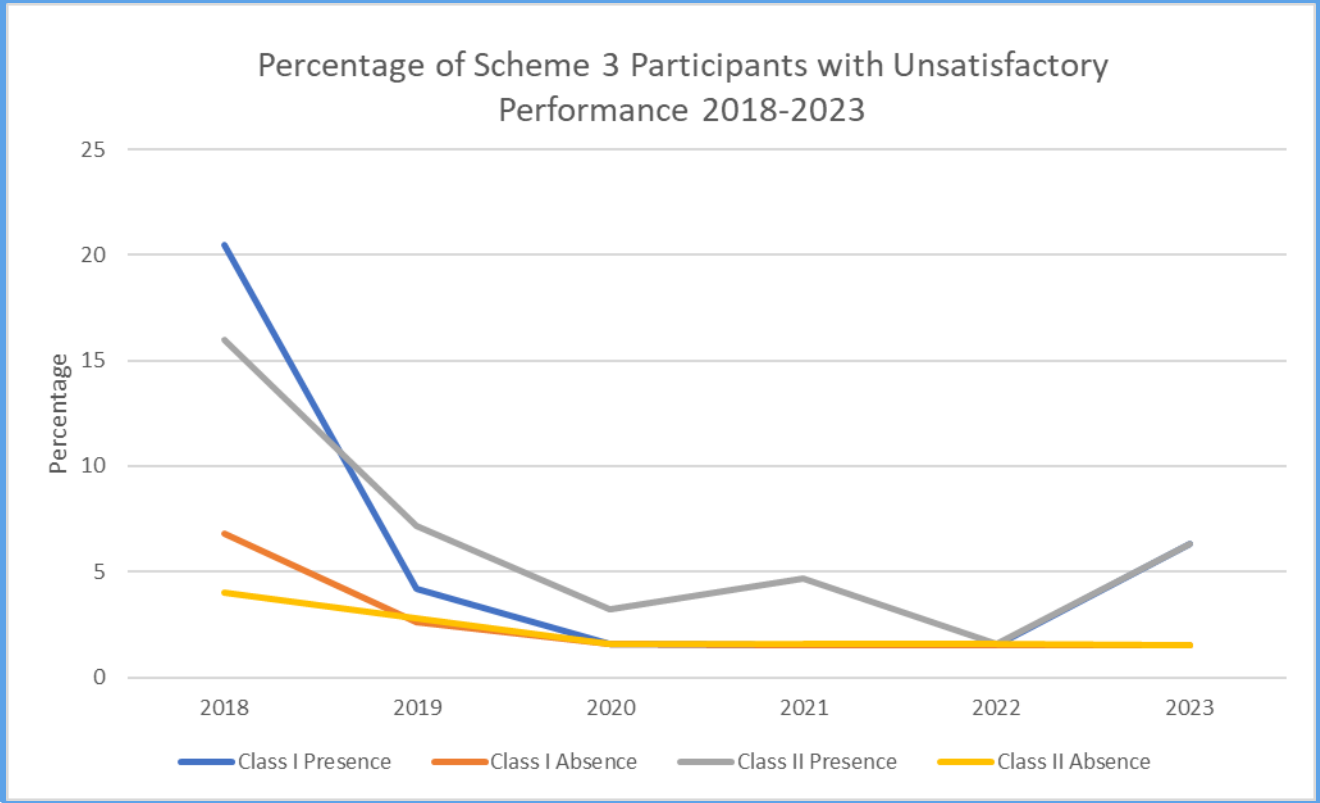
2022-23

Average Performance	Class I		Class II	
	OL	Imm	OL	Imm
Presence	97.4%	86.9%	96.1%	89.0%
Absence	98.5%	95.4%	98.4%	95.6%

Average overall performance for detecting the 'presence' of antibodies it was marginally higher for users of OL kits.

For the confirmation of 'absence' of antibodies the difference in overall performance was also comparable between kit users.

Scheme 3: Overall Performance

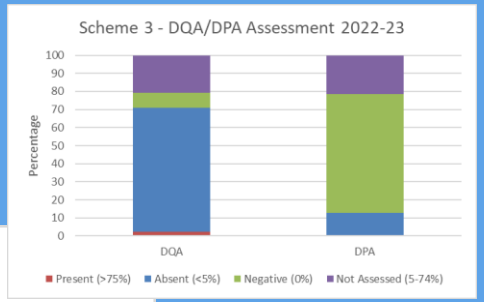


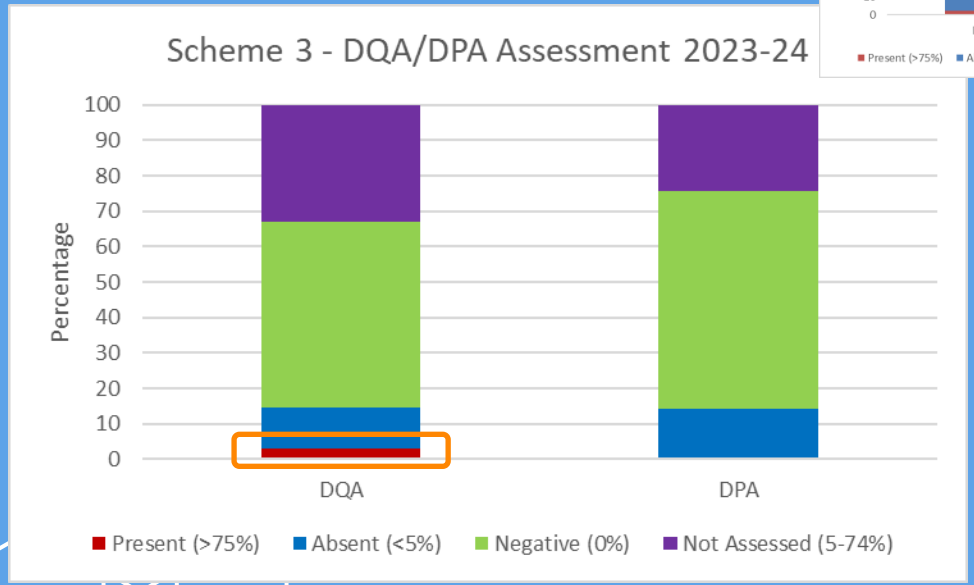
Scheme 3: DQA/DPA Antibody Reporting

Reporting of antibodies to HLA-DQA and –DPA is optional and not assessed.

Overall 38/66 (58%) report DQA, 33/66 (50%) report DPA

UK&I 13/24 (54%) report DQA, 13/24 (54%) report DPA





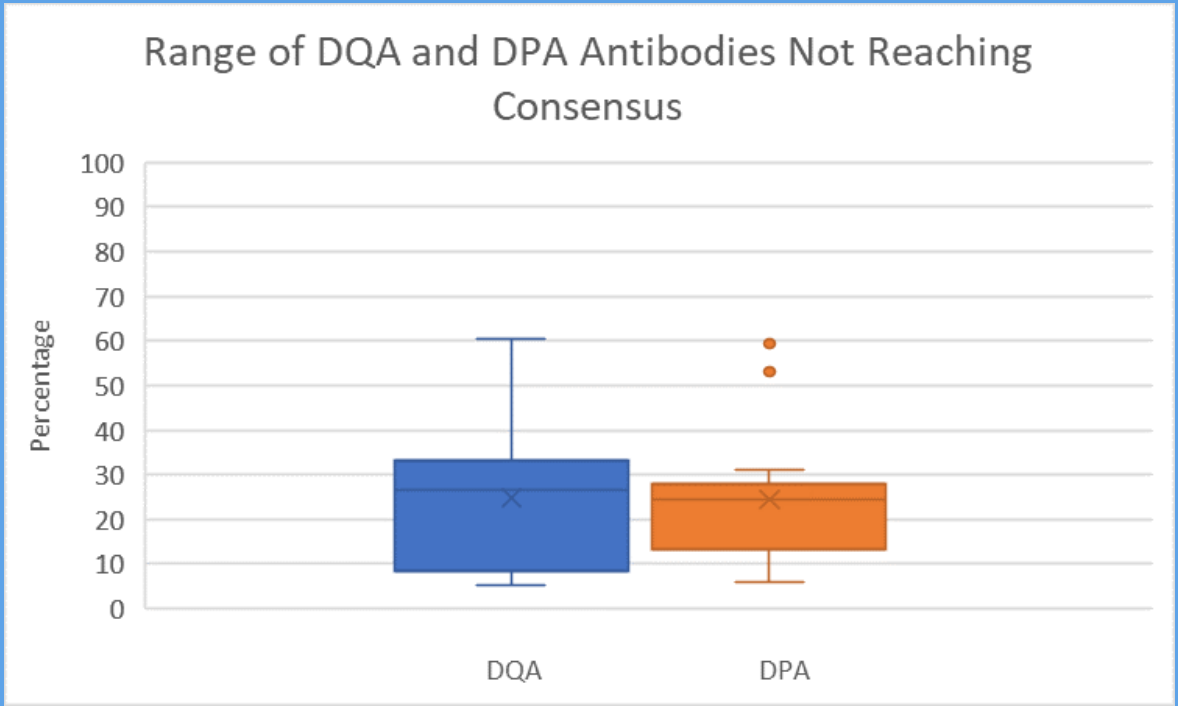
An analysis of the data submitted for DQA and DPA antibodies in 2023-24 and 2022-23 was performed.

Large proportion of samples are negative or consensus absent.

Very few positives.

Approx 25-30% not assessed.

Scheme 3: DQA and DPA Antibody Reporting



Scheme 11

HPA Antibody Detection/Specification

Scheme 11: HPA Antibody Detection/Specification

Purpose

Assess participants ability to correctly determine pesence and specificty of HPA antibodies.

Satisfactory Performance

At least 75% of specificities in agreement with the consensus result in a distribution year.

Consensus

Presence of specificity determined by at least 75% agreement and absence determined by at least 95% agreement.

8 serum/plasma samples over 2 distributions

Scheme 11: Performance

- 2 Unsatisfactory Performers (0 UK&I)

	2017 Pilot	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	13 (3)	35 (4)	39 (5)	42 (4)	43 (4)	43 (4)	43 (4)
Number with Unsatisfactory Performance (< 75%) (UK&I)	N/A	1 (0)	1 (0)	3 (0)	6 (0)	2 (0)	9 (0)
% Unsatisfactory Performance	N/A	2.9%	2.6%	7.1%	13.9%	4.5%	20.9%

Scheme 11: HPA Antibody Detection/Specification

2023 Sample	HPA Detection	HLA Detection	Expected Result	HPA Antibody ID	
				Presence	Absence
1	97.6% Neg	100% Neg	HPA neg, HLA pos	N/A	HPA-5b 98%
2	100% Pos	97.7% Pos	HPA-5b	HPA-5b 100%	N/A
3	100% Neg	97.7% Pos	HPA neg, HLA pos	N/A	N/A
4	86.0% Pos	88.4% Neg	HPA-1a	HPA-1a 86%	HPA-3a 98%, 4b 95.3%, GPIIb/IIIa 97.7%
5	90.5% Pos	100% Pos	HPA-1b + 3b + 5b	HPA-1b 83.3%, 3b 76.2%, 5b 90.5%	HPA-1a, 3a, 4b, CD109 97.6%, 15b 95.2%
6	100% Neg	100% Pos	HPA neg, HLA pos	N/A	N/A
7	97.7% Neg	61.9% Pos	HPA neg, HLA pos	N/A	HPA-15a 97.7%
8	93.0% Pos	83.3% Neg	HPA-1a + 5b	HPA-1a, 5b 93%	HPA-1b, 3b, 4b 97.7%, 3a 95.3%

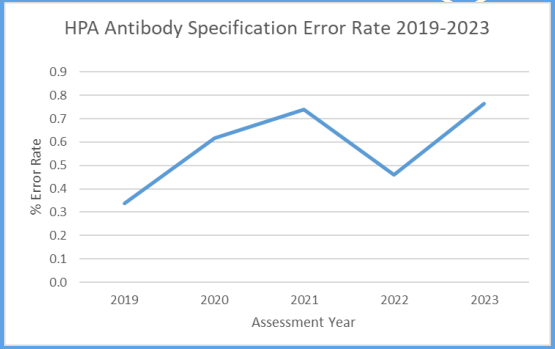
Scheme 11: Unacceptable Performers 2023

Lab	HPA Presence	HPA Absence	Samples reported	Method	Error
130	71%	100%	8/8	N/A	Kit/interpretation issues
163	57%	100%	8/8	MAIPA	Technical/procedural issues
267	43%	73%	8/8	PAK Plus	Clerical/reporting errors
309	71%	100%	8/8	Immucor PakLx	Results entry error
386	71%	100%	8/8	MAIPA In house	Sensitivity/interpretation
388	57%	100%	8/8	PAK Plus	No response
390	57%	100%	8/8	MAIPA ApDia	Multiple issues
1345	43%	93%	8/8	MAIPA ApDia	No response
1383	14%	73%	8/8	ELISA	No response

Scheme 11: Analysis of Errors 2019-2023

- Error rate extremely low (overall 0.59%) but errors often at clinically relevant polymorphisms.

- Most errors found at HPA-1a (n=31, error rate 1.85%), 1b (n=27, error rate 1.61%), 5b (n=27, error rate 1.61%).



Errors 2019-2023	HPA-1a	HPA-1b	HPA-2a	HPA-2b	HPA-3a	HPA-3b	HPA-4a	HPA-4b	HPA-5a	HPA-5b	HPA-6a	HPA-6b	HPA-15a	HPA-15b	GP IIb/IIIa	GP Ia/IIa	GP Ib	GP Iv	CD109	Total
False Pos	5	4	2	1	10	6	5	14	6	5	0	0	2	7	7	4	7	3	7	95
False Neg	26	23	0	0	12	10	0	0	0	22	0	0	0	0	0	0	0	0	0	93
Total Errors	31	27	2	1	22	16	5	14	6	27	0	0	2	7	7	4	7	3	7	188
% Error Rate	1.85	1.61	0.12	0.06	1.31	0.95	0.30	0.83	0.36	1.61	0.00	0.00	0.12	0.42	0.42	0.24	0.42	0.18	0.42	0.59
Total Tested	1680	1680	1680	1680	1680	1680	1680	1680	1680	1680	1680	1680	1680	1680	1680	1680	1680	1680	1680	31920

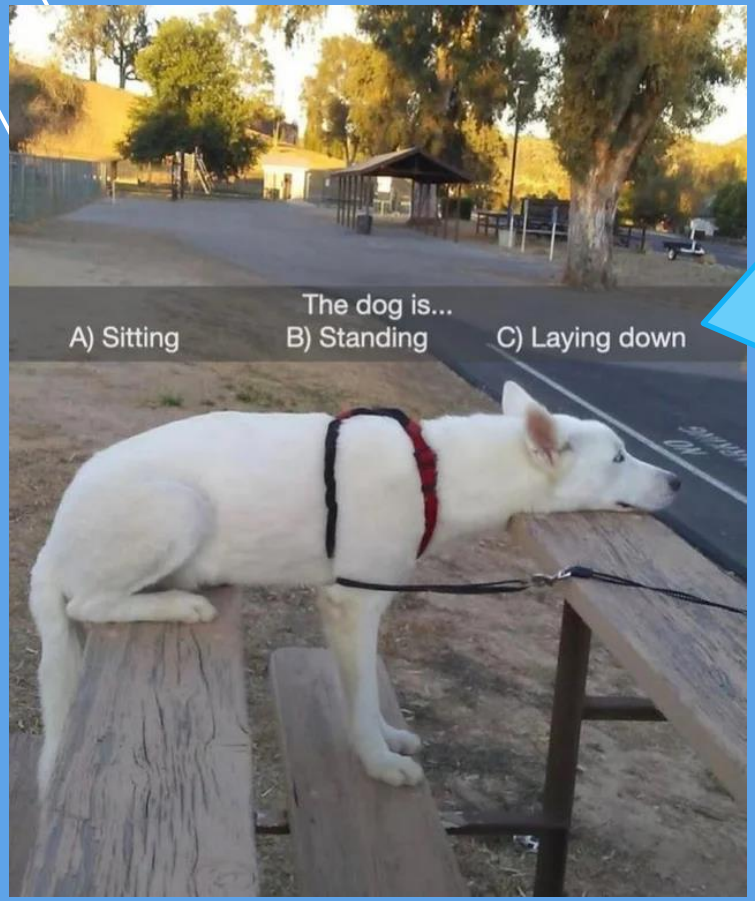
- Even split of false positive (n=95) and false negative (n=93) errors.

- In the last 5 years: most labs had only 1 or 2 errors but some have multiple

Number of Errors	Number of Labs
1	9
2	9
3	4
4	4
5	2
6-10	10
>11	1

Scheme 11: Factors Affecting Performance

- Limitations of commercial kits
- Scheme Design
  - lack of genotype
- Sample quality
  - volume of sample was increasing to 1.5ml in 2022-23
  - complexity of sera e.g. multiple HPA ab or HLA & HPA
- Individual testing strategy
  - ability to detect certain antibodies e.g. HPA-15



New for 2024:
Labs can select which HPA antibodies they want to be assessed for

Do you have any questions?

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Key Data from the Schemes

Deborah Pritchard
UK NEQAS for H&I Director

Scheme 1A

HLA Phenotyping

Scheme 1A: HLA Phenotyping

Purpose

Assess participants ability to use serological and supplementary methods to correctly identify HLA phenotype

Consensus

At least 75% agreement on each specificity.

Satisfactory Performance

9 or more complete HLA phenotypes in agreement with consensus per distribution year.

10 blood samples over 5 distributions

Scheme 1A: Performance

- 2 labs with unsatisfactory performance (0 UK&I).

	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	38 (6)	38 (6)	38 (5)	34 (4)	33 (2)	28 (1)	23 (0)
Number with Unsatisfactory Performance (< 90%) (UK&I)	1 (0)	6 (1)	8 (1)	3 (1)	2 (0)	2 (0)	2 (0)
% Unsatisfactory Performance	2.6%	15.8%	21.1%	8.8%	6.1%	7.1%	8.7%

Scheme 1A: 2023 Incorrect Assignments

<u>11/230 (4.8%) incorrect HLA types in 2023 reported by 5 labs:</u>

- 4 reports that contained broad not split specificity (e.g. B40 v B60)
- 2 reports that contained an incorrect split specificity (e.g. B64 not B65)
- 0 reports with molecular based nomenclature (e.g. A01 v A1)
- 2 reports with incorrect specificity
- 2 reports of missed or homozygous assignments
- 1 clerical/typo error

0/2 labs with unsatisfactory performance completed CAPA

Scheme 1A: 2022 Incorrect Assignments Resulting in UPs

Sample	ID	Consensus	Report
1A 03	159	A11, A31; B7, B18	A11, A31; B7, B -
1A 04	159	A1, A1; B8, B53	A1, A36; B8, B53
1A 07	159	A29, A30; B7, B41	A29, A30; B7, B7
1A 09	159 + 1420	A26, A33; B51, B65	A26, A33; B51, B14
1A10	1420	A2, A25, B18, B35; DR7, DR15; DQ6, DQ9	A2, A25, B18, B35; DR7, DR15; DQ6, DQ8

Scheme 4A1

DNA Typing at 1st Field Resolution

Scheme 4A1: DNA Typing at 1st Field Resolution

Purpose

Assess participants ability to correctly determine HLA genotypes at the 1st field resolution.

Satisfactory Performance

9 or more full HLA types in agreement with consensus/reference result in a distribution year.

Consensus

At least 75% agreement on each allele. When consensus is not met, a reference result is used. Reference result is always used for DPB1 assessment

10 blood samples over 3 distributions

Scheme 4A1: Performance

- 11 labs with unsatisfactory performance (1 UK&I)

	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	106 (28)	105 (28)	100 (28)	88 (26)	82 (25)	81 (25)	81 (25)
Number with Unsatisfactory Performance (< 90%) (UK&I)	11 (1)	15 (1)	4 (1)	8 (0)	6 (1)	7 (0)	11 (1)
% Unsatisfactory Performance	10.4% (3.6%)	14.3% (3.6%)	4% (3.6%)	9.1% (0%)	7.3% (4%)	8.4% (0%)	13.6% (4%)

Scheme 4A1: 2023-24 Incorrect Assignments

74/11240 (0.66%) errors reported by 25 different labs (6 UK&I) – last year 0.7%

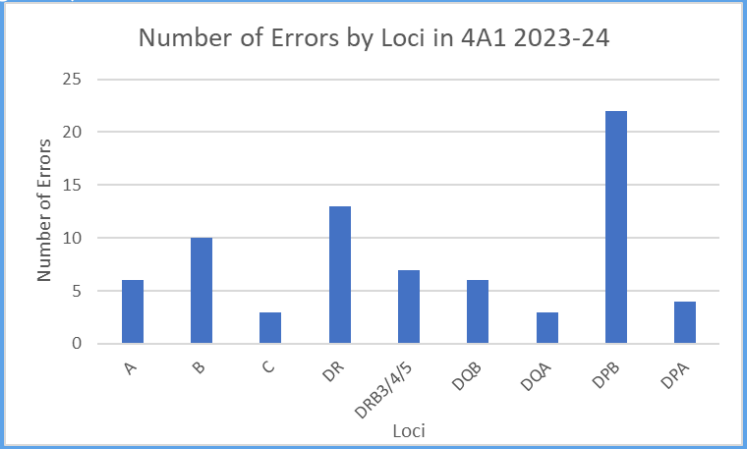
15 (60%) labs made 1 error
9 (36%) labs made 2-4 errors
1 (4%) lab made 5 errors

45 samples contained an error:

- 22 samples with incorrect assignments *e.g. DPB1*03:01 instead of DPB1*104:01 (4 UK&I)*
- 8 samples with additional assignment (reported heterozygous when homozygous)
- 7 missed assignment (reported homozygous when heterozygous)
- 3 samples where HLA types were not reported
- 2 samples with ambiguities *e.g. B*07 or 42*
- 2 HLA types completely incorrect (1 UK&I)
- 1 sample with incorrect uses of nomenclature

*e.g. DQB1*07 instead of DQB1*03:01 (1 UK&I)*

37 (82%) HLA types with one error
8 (18%) HLA types with multiple errors



Scheme 4A1: Unacceptable Performers 2023

Lab	Sample	Error	CAPA Response
62	02+03	Potential sample mixup	Procedural error
128	01+02	Incorrect DPB1* types	Human error & interpretation error
260	01-03	DQA1* missed assignments	No reply
1352	01+03+04+07	Incorrect A* and DPB1* types	No reply
1379	01+02+08-10	Incorrect DRB1* types	Multiple issues
309	01+05+08	Multiple reporting errors	Staff error
1394	01+09	Incorrect DRB1* and DPB1* types	No reply
318	03+08	Incorrect A* and DRB1* types	No reply
1372	04+06+07	Ambiguous B* types	No reply
155	08-10	No results returned	No reply

Scheme 4A1i

Interpretive HLA Genotype

Scheme 4A1: Interpretive HLA Genotype

Purpose

Assess participants ability to correctly interpret their 4A1 genotype result to the 'split' specificity level.

Satisfactory Performance

9 or more full HLA types in agreement with consensus/reference result in a distribution year.

Consensus

At least 75% agreement on each specificity. When consensus is not met, a reference result is used.

10 HLA genotypes from Scheme 4A1

Scheme 4A1i: Performance

- 1 lab with unsatisfactory performance (0 UK&I)

	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	36 (20)	40 (21)	44 (22)	44 (22)	42 (21)	40 (21)	40 (21)
Number with Unsatisfactory Performance (< 90%) (UK&I)	6 (1)	6 (0)	8 (1)	6 (2)	5 (1)	2 (0)	1 (0)
% Unsatisfactory Performance	16.7%	15.0%	18.1%	13.6%	11.9%	5.0%	2.5%

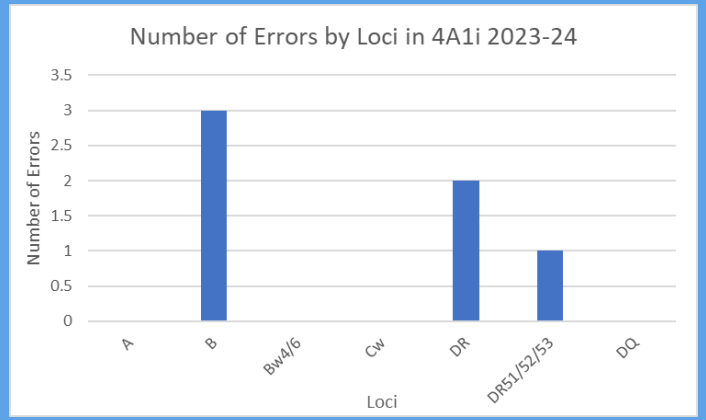
Scheme 4A1i: 2023-24 Incorrect Assignments

- 6/5611 (0.11%) incorrect results reported by 2 different labs (1 UK&I) – last year 0.28%

1 (50%) lab made 1 error
1 (50%) lab made 3 errors

- 4 samples contained an error:
  - 2 samples with additional assignment (reported heterozygous when homozygous)
  - 2 reporting at broad not split specificity level (1 UK&I)

2 (50%) HLA types with single errors
2 (50%) HLA type with multiple errors



Scheme 4A1i: Unacceptable Performers 2023

Lab	Sample	Error	CAPA Response
1418	04-06	Multiple reporting/assigning errors	Staff training/knowledge

Scheme 4A2

DNA Typing to 2nd or 3rd Field Resolution

Scheme 4A2: DNA Typing to 2nd or 3rd Field Resolution

Purpose

Assess participants ability to correctly determine HLA type to 2nd or 3rd field.

Consensus

At least 75% agreement on each allele. If consensus is not met, a reference result is used.

Satisfactory Performance

9 or more full HLA types in agreement with consensus/reference genotype in a distribution year.

10 blood samples over 3 distributions

Scheme 4A2: Performance

- 45/65 participants registered for 2nd field
- 22/65 participants registered for 3rd field

- 9 labs with unsatisfactory performance (2 UK&I)

8/9 labs with unsatisfactory performance completed CAPA

	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	66 (21)	63 (20)	62 (20)	64 (20)	63 (22)	61 (23)	65 (23)
Number with Unsatisfactory Performance (< 90%) (UK&I)	4 (0)	9 (2)	9 (1)	7 (0)	6 (0)	4 (0)	9 (2)
% Unsatisfactory Performance	6.1%	14.3%	14.5%	11.0%	11.1%	6.5%	13.8% (8.7%)

Scheme 4A2: Incorrect Assignments: 2nd Field

45/8236 (0.55%) incorrect HLA alleles reported by 11 labs (3 UK&I) – last year (0.15%)

- 9 reports of errors at the 2nd field *e.g. DRB1*14:01 rather than DRB1*14:54 (1 UK&I)*
- 6 samples with alleles in a string that should have been resolved

*e.g. DRB1*15:01/04 (1 UK&I)*

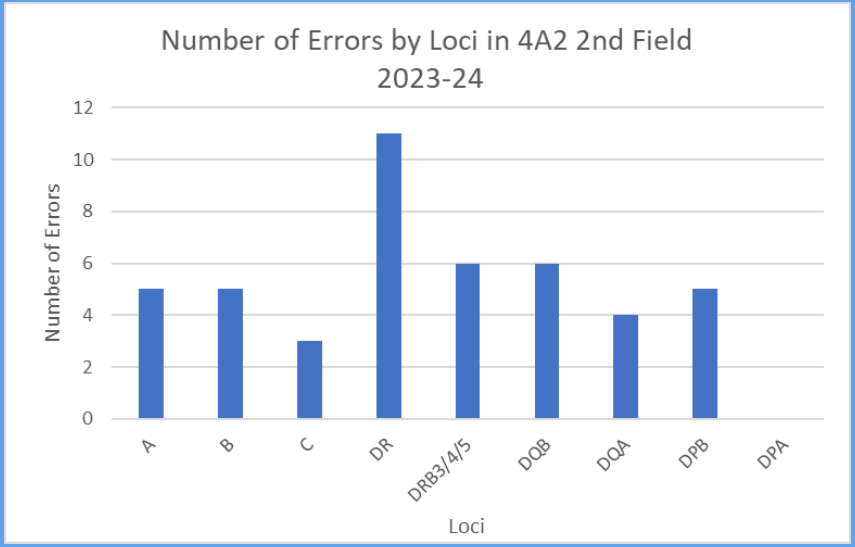
- 2 reports of the wrong HLA type
- 1 report of incorrect assignment

*e.g. reported DRB3*01:03 rather than DRB4*01:03 (1 UK&I)*

- 1 report of missing a null allele

*e.g. reported DRB4*01:01 instead of DRB4*01:03N*

6 (55%) labs made 1 error
2 (18%) labs made 2 errors
3 (27%) labs made 3 errors



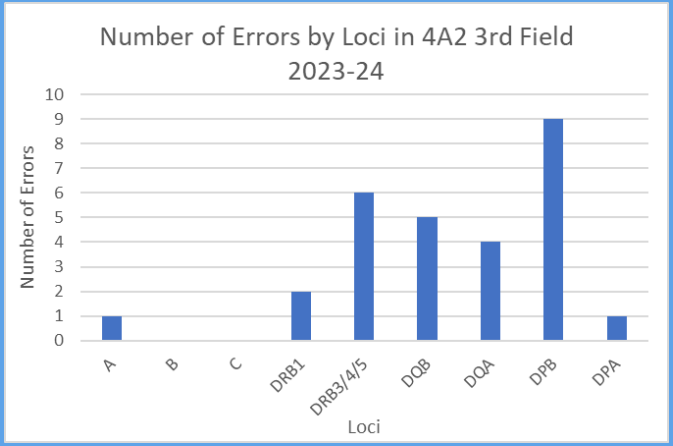
5 HLA types with multiple errors
14 HLA types with a single error

Scheme 4A2: Incorrect Assignments: 3rd Field

28/3452 (0.81%) incorrect HLA alleles reported by 7 labs (1 UK&I) – last year (0.39%)

- 5 reports of unresolved ambiguities e.g. DPB1*04:01:01/105:01:01
- 3 only reporting to 2nd field
- 2 errors at 2nd field e.g. DQB1*06:01:01 rather than 06:02:01
- 2 incorrect assignments e.g. A*03:01:01 rather than A*01:01:01
- 1 nomenclature issue e.g. DQB1*02/01/01 rather than DQB1*02:01:01

3 (43%) labs made 1 error
2 (29%) labs made 2 errors
2 (29%) labs made 3+ errors

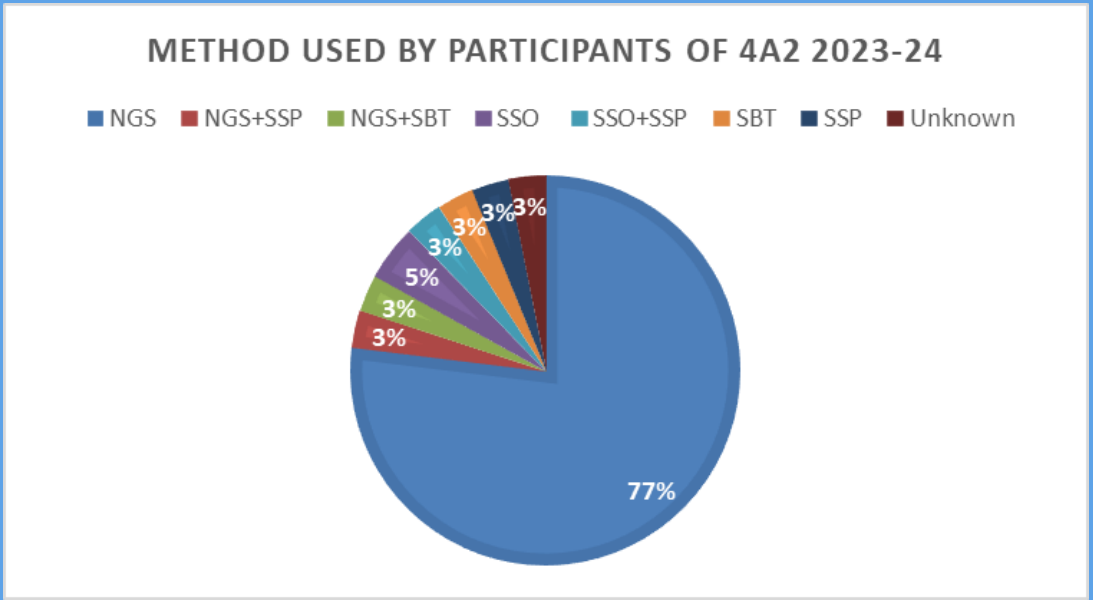


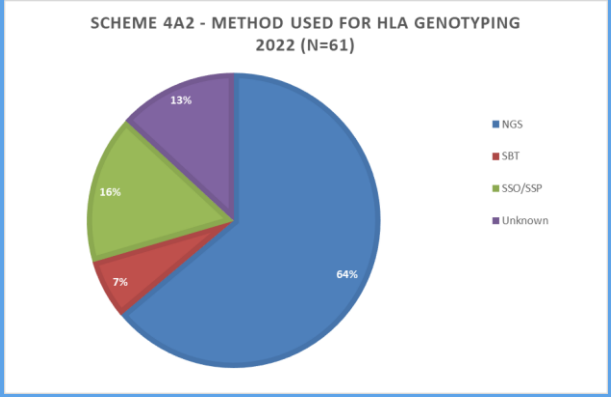
7 HLA types with multiple errors
6 HLA types with a single error

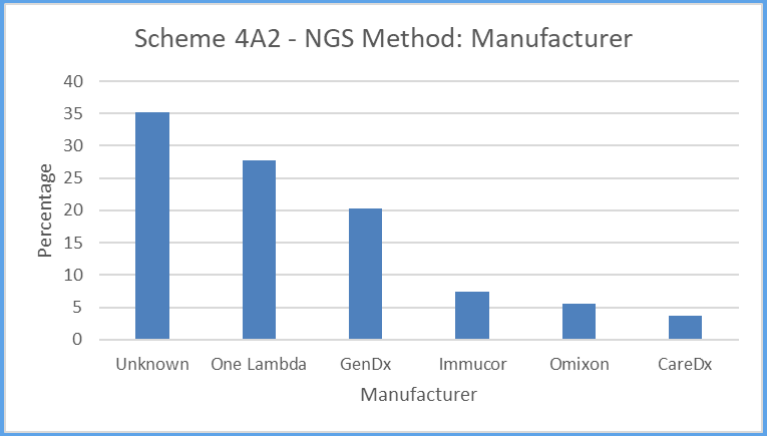
Scheme 4A2: Unacceptable Performers 2023

Lab	Sample	Error	Field	CAPA Response
9	02+03	Reported DPB1*04:02/1346 for both samples	2nd	Incorrect nomenclature/manual error
276	02+03	Probable sample mix up	2nd	No response
309	01+02+06	4A2 01/2023: Incorrect nomenclature (/ instead of :), reporting DPB1* ambiguity 4A2 02/2023: Reported A*03:01:01, consensus 01:01:01; reported DQA1*02:04:01, consensus 01:04:01 4A2 06/2023: Reported DRB1* 09:01:01, 15:01:01, consensus 03:01:01, 07:01:01	3rd	Wrong format/staff error/results mixup
134	01+05+06+07+10	4A2 01/2023: Reported DRB1*03:01:02, consensus 03:01:01, reported DRB3*03:01:02, consensus 01:01:02 4A2 05+06/2023: Reported ambiguities for DRB3/4/5* and DPB1* 4A2 07/2023: Reported ambiguities for DRB3/4/5* 4A2 10/2023: Reported DRB3* to 2nd field only	3rd	Interpretation issue/results entry
145	05+06	4A2 05+06/2023: Reported DPB1* G groups	3rd	Kit interpretation issues
361	02+04+05	4A2 02/2023: Reported DRB1*14:01, consensus 14:54; Reported unacceptable ambiguity DRB1*15:04 4A2 04/2023: Reported unacceptable ambiguity DRB1*15:04 4A2 05/2023: Reported unacceptable ambiguity A*24:07 and DRB1*15:04	2nd	Unacceptable ambiguities
374	02+04+10	4A2 02/2023: Reported DRB1*14:01, consensus 14:54 4A2 04/2023: Reported C*08:01, consensus 08:02 4A2 10/2023: Reported DRB1*12:02, consensus DRB1*12:01	2nd	Interpretation/reporting errors
45	10	4A2 10/2023: Reported DQA1* to 2nd field only	3rd	Incorrect registration for CII loci
286	08+09	4A2 08/2023: Reported DRB4*01:01, 01:01; consensus DRB4*01:01, 01:03N 4A2 09/2023: Reported DRB4*01:01; consensus DRB4*01:03	2nd	Reporting/incomplete errors

Scheme 4A2: Testing Methods







Scheme 4A2 Sample 08/23: New Allele

HLA-A*02:01:01, A*24:02:01; B*07:02:01, B*44:03:01; C*07:02:01, C*16:01:01; DRB1*07:01:01, DRB1*-; DRB4*01:01:01, DRB4*01:03:01N; DQA1*02:01:01, DQA1*-; DQB1*02:02:01, DQB1*03:03:02; DPA1*02:01:01, DPA1*-; DPB1*NEW, DPB1*NEW

At 2nd Field (n=45)

- 76% of labs did not indicate that any new allele were present in the assessment fields
- 62% of labs did report or made a comment that a novel allele was present at DPB1
  - 21% reported a new allele at DPB1*11
  - 32% reported a new allele at DPB1*13
  - 46% reported a new allele but couldn't determine if this was related to DPB1*11 or 13
- 33% of labs made no indication of new allele

At 3rd Field (n=14)

- 50% of labs did not indicate that any new allele were present in the assessment fields
- 71% of labs did report or made a comment that a novel allele was present at DPB1
  - 10% reported a new allele at DPB1*11
  - 30% reported a new allele at DPB1*13
  - 60% reported a new allele but couldn't determine if this was related to DPB1*11 or 13
- 27% of labs made no indication of new allele

Most common responses stated that no amino acid change was noted (ACG to ACA: Threonine) in Exon 4 at Position 199

Scheme 9

KIR Genotyping

Scheme 9: KIR Genotyping

Purpose

Assess participants ability to correctly determine the presence or absence of specific KIR genes.

Satisfactory Performance

9 or more full KIR genotypes in agreement with consensus/reference genotype in a distribution year.

Consensus

At least 75% agreement on the presence/abesence of each gene. Reference type used where consensus is not met

10 blood samples over 2 distributions

Scheme 9: 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

Scheme 9: Performance

- 2 labs with unsatisfactory performance

	2016 (Pilot)	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	11 (2)	8 (3)	9 (1)	12 (1)	12 (1)	15 (1)	15 (1)	15 (1)
Number with Unsatisfactory Performance (UK&I)	N/A	0 (0)	1 (0)	3 (0)	0 (0)	1 (0)	0 (0)	1 (0)
% Unsatisfactory Performance	N/A	0%	11.1%	25%	0%	6.7%	0%	6.7%

Scheme 9: Unacceptable Performers 2023

Lab	Polymorphism	Error	CAPA Response
1428	KIR-2DS2	False Neg	Interpretation of results

Scheme 10

HPA Genotyping

Scheme 10: HPA Genotyping

Purpose

Assess participants ability to correctly determine HPA polymorphisms.

Satisfactory Performance

9 or more full HPA types in agreement with consensus/reference genotype in a distribution year.

Consensus

At least 75% agreement on the presence/abesence of each allele. Reference type used where consensus is not met

10 blood samples over 2 distributions

Scheme 10: HPA Genotyping

- Participants able to report any of the following: *HPA-1, HPA-2, HPA-3, HPA-4, HPA-5, HPA-6, HPA-15*

  - 34/39 reported HPA-1, 2 , 3, 4, 5 and 15

  - 30/39 labs reported HPA-6

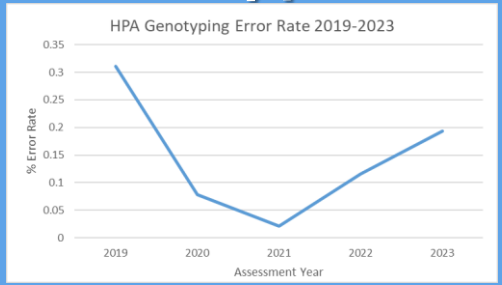
- Also able to report any other HPA polymorphisms detected, *for information*

Scheme 10: HPA Genotyping

- 2 errors (? Sample mix up)
- 1 lab with unsatisfactory performance

	2016 Pilot	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	12 (4)	15 (5)	37 (6)	38 (6)	40 (0)	38 (6)	39 (6)	39 (6)
Number with Unsatisfactory Performance (< 100%) (UK&I)	N/A	1 (0)	1 (0)	3 (0)	0 (0)	0 (0)	1 (0)	1 (0)
% Unsatisfactory Performance	N/A	6.7%	2.7%	7.9%	0%	0%	2.6%	2.6%

Scheme 10: Errors in HPA Genotypes 2019-2023



- Error rate extremely low 0.14% but errors often at clinically relevant polymorphisms.
- Most errors found at HPA-15b (n=8, error rate 0.42%), HPA-15a (n=7, 0.39%) HPA-3b (n=5, 0.26%), HPA-5b (n=5, 0.26%), HPA-1b (n=3, 0.16%) and HPA-2b (n=3, 0.16%)

Errors 2019-23	HPA-1 a	HPA-1 b	HPA-2 a	HPA-2 b	HPA-3 a	HPA-3 b	HPA-4 a	HPA-4 b	HPA-5 a	HPA-5 b	HPA-6 a	HPA-6 b	HPA-15 a	HPA-15 b	Total
False Neg	1	2	0	1	1	3	0	0	0	1	1	0	4	3	17
False Pos	0	1	0	2	0	2	0	1	0	4	0	1	3	5	19
Total Errors	**1**	**3**	**0**	**3**	**1**	**5**	**0**	**1**	**0**	**5**	**1**	**1**	**7**	**8**	**36**
% Error	**0.05**	**0.16**	**0.00**	**0.16**	**0.05**	**0.26**	**0.00**	**0.06**	**0.00**	**0.26**	**0.07**	**0.07**	**0.39**	**0.42**	**0.14**
Total Tested	1935	1935	1905	1905	1905	1905	1615	1615	1935	1935	1385	1385	1805	1905	25070

- Fairly even split of false positive (n=19) and false negative (n=17) errors.
- HPA-5b and 15b more likely to be reported as false pos
- Most labs only have 1 or 2 errors:
  Not related to method

Number of Errors	Number of Labs
1	2
2	4
3	1
4	1

Scheme 1B

HLA-B27 Testing

Scheme 1B: HLA-B27 Testing

Purpose

Assess participants ability to correctly determine HLA-B27/2708/B*27 status.

Satisfactory Performance

Making 10/10 reports that are in agreement with consensus in a distribution year.

Consensus

At least 75% agreement on B27 status. Reference type used where consensus is not met

10 blood samples sent over 5 distributions

Scheme 1B: Performance

- 11 labs with unsatisfactory performance (3 UK&I)

	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	127 (52)	133 (54)	133 (53)	141 (52)	141 (50)	139 (49)	134 (50)
Number with Unsatisfactory Performance (< 100%) (UK&I)	7 (2)	10 (3)	4 (1)	12 (2)	3 (0)	8 (0)	11 (3)
% Unsatisfactory Performance (UK&I)	5.5% (3.8%)	7.5% (5.5%)	3.0% (1.9%)	8.5% (3.8%)	2.1%	5.7%	8.2% (6%)

Scheme 1B: 2023 Incorrect Assignments

Sample	Result	Lab Number	Technique	HLA Type	Lab Identified Cause
1B 01+02	No results submitted	28 334 1335 1364 1417	Molecular Not known Serological Not known Not known	B8 B27 B27 B56	Delivery delay/registration pending No results submitted No results submitted No results submitted No results submitted
1B 01	False neg	1392 1405	Molecular Molecular	B8 B27	Lab reporting error Procedural error/staff competency
1B 03	False neg	1392	Molecular	B8 B27	Technical error/poor DNA
1B 03+04	No results submitted	65 256 1335 1364	Serological Serological Serological Not known	B8 B27 B14 B40	No results submitted Sample delays/did not test Registration pending Registration pending
1B 07+08	False neg & false pos	101	Molecular	B7 B44 B27 B53	Potential sample mix up

- 5/10 samples distributed were HLA-B27 positive
- 5 errors: 4 false neg, 1 false pos
- 4/11 errors involved serological technique
- 1 sample mix up

7/11 labs with unsatisfactory performance completed CAPA

Scheme 5A

HFE Typing

Scheme 5A: HFE Testing

Purpose

Assess participants ability to correctly determine HFE mutations.

3 mutations assessed:

- Codon 63: Histidine63Aspartic acid (H63D)
- Codon 282: cysteine282tyrosine (C282Y)
- Codon 65: Serine63Cysteine (S65C)

Satisfactory Performance

10 reports in agreement with consensus/reference result in a distribution year.

Consensus

At least 75% agreement on each HFE mutation. Reference type used where consensus is not met

10 donor samples sent over 3 distributions

Scheme 5A: Performance

- 1 lab with unsatisfactory performance (1 UK&I)

	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	56 (42)	58 (44)	51 (38)	49 (36)	45 (32)	37 (27)	38 (26)
Number with Unsatisfactory Performance (< 100%) (UK&I)	3 (2)	0 (0)	2 (1)	1 (1)	1 (1)	4 (3)	1 (1)
% Unsatisfactory Performance	5.3% (4.8%)	0%	3.9% (2.6%)	2.0% (2.8%)	2.2% (3.1%)	10.8% (11.1%)	2.6% (3.8%)

CAPA response

- Sample/labelling mix up

Scheme 5B

Interpretive HFE genotype and Hereditary Haemochromatosis

Scheme 5B: Interpretive HFE genotype and Hereditary Haemochromatosis

Purpose

Assess participants ability to produce an accurate, clear and concise clinical report. HFE genotype and various clinical information provided

Satisfactory Performance

Must have <50% of available penalty points available to be considered acceptable.

Assessment

Reports must be identical in format to those typically produced by lab. Penalty points awarded for failure to cover interpretive criteria identified and agreed by the expert assessors.

Twice a year, 2 clinical scenarios

Scheme 5B: Performance

- 0 labs with unsatisfactory performance (0 UK&I)

	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	20	21 (18)	21 (17)	19 (15)	16 (12)	15 (11)	12 (10)
Number with Unsatisfactory Performance (UK&I)	0	1 (1)	3 (1)	1 (0)	0 (0)	2 (1)	0 (0)
% Unsatisfactory Performance	0%	4.8%	14%	5.3%	0%	13%	0%

Scheme 5B: Performance

- 2023 – All 4 scenarios:

  maximum 6 penalty points per scenario, 24 in total.

4	labs got	0-1 penalty points
2	got	1.5-2 penalty points
3	got	2.5-3 penalty point
2	got	3.5-4 penalty points
1	got	4.5-5 penalty points
0	got	>12 penalty points

Scheme 7

HLA-B*57:01 Typing for Drug Hypersensitivity

Scheme 7: HLA-B*57:01 Typing for Drug Hypersensitivity.

Purpose

Assess participants ability to correctly determine HLA-B*57:01 status

Satisfactory Performance

Making 10 sample reports in agreement with the consensus/reference result in a distribution year.

Consensus

At least 75% agreement on the status of HLA-B*57:01. Reference result used when consensus not met.

10 blood samples over 3 distributions

Scheme 7: Performance

- 5/10 samples distributed were HLA-B*57:01 positive
- 2 labs with unacceptable performance

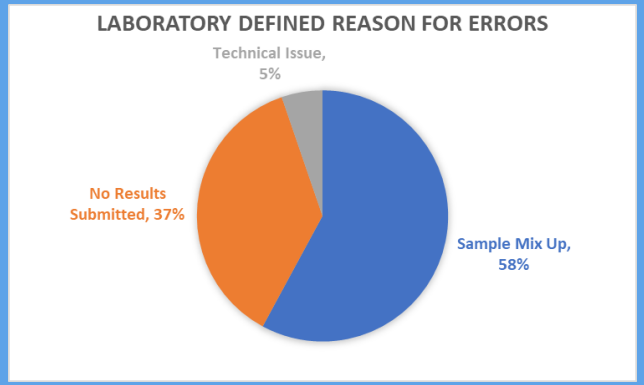
	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	64 (26)	67 (27)	67 (27)	67 (27)	64 (25)	52 (18)	50 (18)
Number with Unacceptable Performance (< 100%) (UK&I)	4 (1)	2 (0)	0 (0)	2 (0)	1 (1)	3 (0)	2 (0)
% Unsatisfactory Performance	6.3%	3.0%	0.0%	3.1%	1.6%	5.8%	4.0%

Scheme 7: Unacceptable Performers 2023

Lab	Sample	Error	CAPA Response
413	02+03 06+07	False neg/pos	Potential sample mix up
142	08+09	False pos/neg	Potential sample mix up

Scheme 7: Error Rate 2019-2023

- In scheme 7 from 2019-2023 19/2977 errors were made – error rate 0.6%
- 7 laboratories made errors: 2 made one error, 3 made 2 errors, 2 made >3 errors (1 lab did not submit results)
- 7 false negative, 5 false positive, 7 results not submitted
- Laboratory reported reasons for errors:
  - 58% due to sample mix ups
  - 37% due to not submitting results (without justification)
  - 5% due to a technical issue



- Performance in HLA pharmacogenetic schemes over the last 5 years is encouraging, with 99.4% results reported correctly.
- Future combined scheme for HLA typing and pharmacogenetics including Allopurinol, Carbamazepine and Phenytoin hypersensitivity plus further options e.g., development of Tumour-Necrosis Factor antibodies (DQA1*05), Flucloxacillin hypersensitivity (B*57:01) and Tebentafusp efficacy (A*02:01)

Scheme 8

HLA Genotyping for Coeliac and other HLA Associated Disease

Scheme 8: HLA Genotyping for Coeliac and other HLA Associated Disease.

Purpose

Assess participants ability to correctly determine HLA type associated with various diseases e.g. coeliac disease, narcolepsy.

Satisfactory Performance

Making 10 sample reports in agreement with the reference genotype in a distribution year.

Assessment

Lab results reported in format identical to clinical report. Reference HLA result used for assesment.

10 blood samples over 3 distributions

Scheme 8: Performance

- 18 Unsatisfactory Performers (2 UK&I)

	2017	2018	2019	2020	2021	2022	2023
Number of Participants (UK&I)	45 (9)	52 (10)	50 (11)	55 (12)	55 (10)	54 (11)	57 (11)
Number with Unsatisfactory Performance (< 100%) (UK&I)	15 (2)	14 (4)	13 (2)	17 (5)	12 (2)	25 (5)	18 (2)
% Unsatisfactory Performance	33% (22%)	27% (40%)	26% (18%)	31% (42%)	22% (20%)	46.3% (45%)	31.6% (18%)

CAPA responses

- Transcription errors
- Kit interpretation error
- Reporting error

11/18 labs with unsatisfactory performance completed CAPA

Scheme 8: Unacceptable Performance by Disease

Disease	HLA Association	Number of Participants	No. of Participants with Unacceptable Performance
Coeliac	DQ2.5, DQ8, DQ2.2	56	16 (29%)
Narcolepsy	DQB1*06:02	26	2 (8%)
Actinic Prurigo	DRB1*04:07	4	0
Birdshot Retinopathy	A*29	13	0
Behçet's	B*51	19	0
Rheumatoid Arthritis	DRB1*04	7	0
Diabetes	DR3, DR4	9	1 (11%)
Psoriasis	C*06	5	0
Allopurinol Hypersensitivity	B*58	6	0
Carbamazepine	A*31:01	5	3 (60%)
Phenytoin	B*15:02	1	0

Scheme 8: Coeliac Disease – Interesting Sample

Reference Genotype: **DRB1*07:01, DRB1*11:02; DQA1*02:01, DQA1*05:05; DQB1*02:02, DQB1*03:19 (DQ7).**

- Performance:

  8/56 unacceptable performers

- Unusual HLA type

  DQB1*03:19 = DQ7

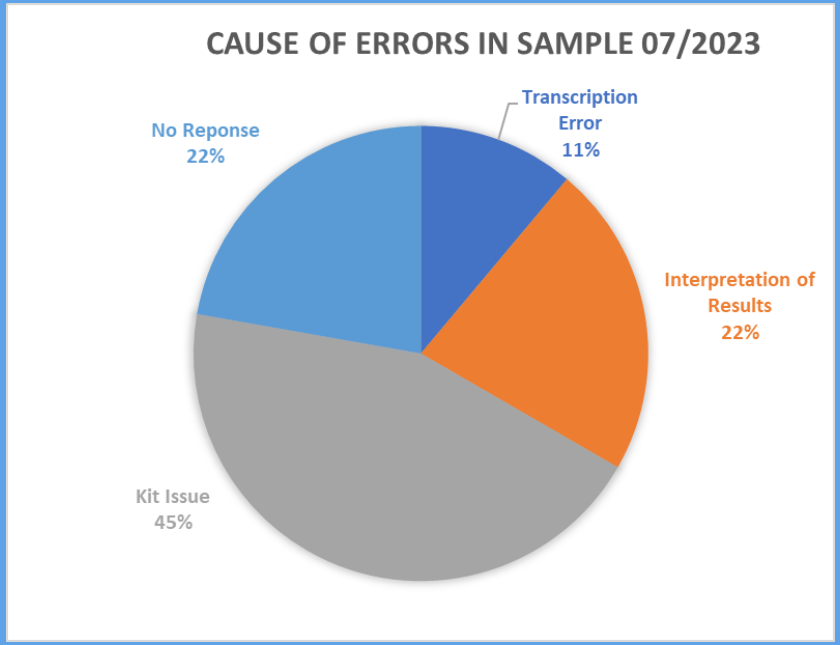
  Prevalence <1% population

- Issues

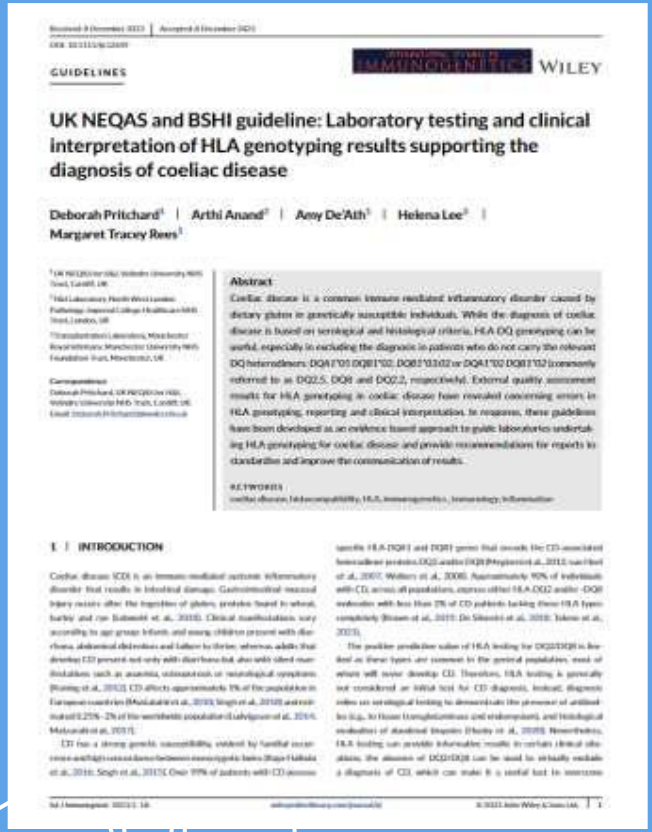
  Difference in detection capabilities

  Some commercial kits cannot detect DQB1*03:19

  Labs did not interpret DQB1*03:19 as DQ7



Scheme 8: Coeliac Disease – Guidelines



GUIDELINES

WILEY

UK NEQAS and BSHI guideline: Laboratory testing and clinical interpretation of HLA genotyping results supporting the diagnosis of coeliac disease

Deborah Pritchard[1] | Arthi Anand[2] | Amy De'Ath[3] | Helena Lee[3] | Margaret Tracey Rees[1]

Abstract

Coeliac disease is a common immune mediated inflammatory disorder caused by dietary gluten in genetically susceptible individuals. While the diagnosis of coeliac disease is based on serological and histological criteria, HLA DQ genotyping can be useful, especially in excluding the diagnosis in patients who do not carry the relevant DQ heterodimers: DQA1*05 DQB1*02, DQB1*03:02 or DQA1*02 DQB1*02 (commonly referred to as DQ2.5, DQ8 and DQ2.2, respectively). External quality assessment results for HLA genotyping in coeliac disease have revealed concerning errors in HLA genotyping, reporting and clinical interpretation. In response, these guidelines have been developed as an evidence based approach to guide laboratories undertaking HLA genotyping for coeliac disease and provide recommendations for reports to standardise and improve the communication of results.

1 | INTRODUCTION

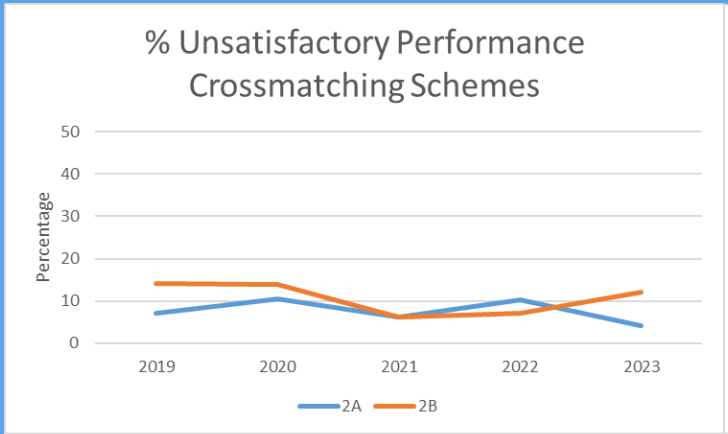
These guidelines were developed by UK NEQAS for H&I in response to the error rate noted in reporting of HLA typing results in relation to the diagnosis of Coeliac Disease. The hope is that these guidelines provide an evidence-based approach to guide laboratories undertaking HLA genotyping for Coeliac Disease and provide recommendations for reports to standardise and improve the communication of patient results to Clinicians.

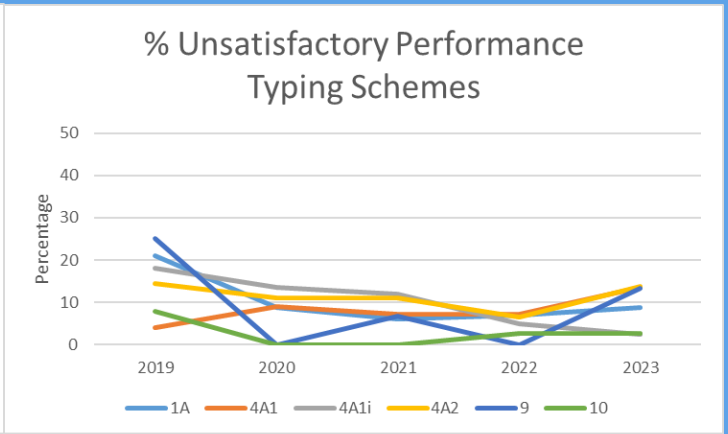
Pritchard D, Anand A, De'Ath A, Lee H, Rees MT. UK NEQAS and BSHI guideline: Laboratory testing and clinical interpretation of HLA genotyping results supporting the diagnosis of coeliac disease. Int J Immunogenet. 2024 Jan;51 Suppl 1:3-20. doi: 10.1111/iji.12649. Epub 2023 Dec 28. PMID: 38153308.

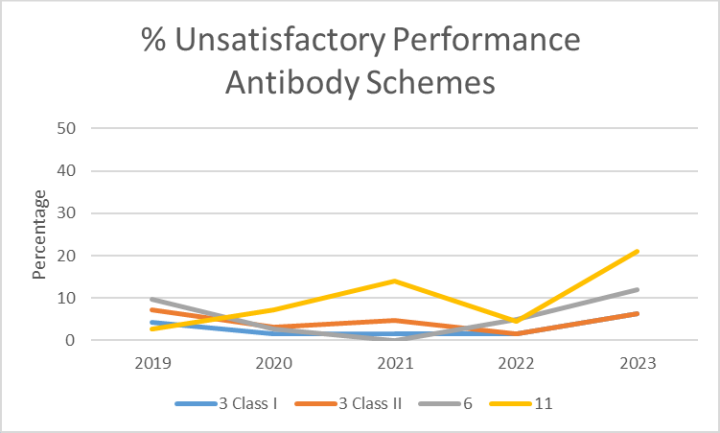
Scheme Summary

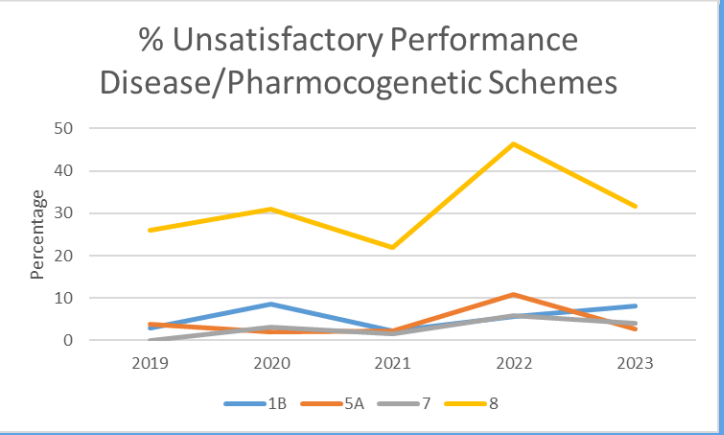
Performance Summary for all Schemes

5 Year Trends in Unsatisfactory Performance









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UK NEQAS for H&I

Educational Crossmatch Scenario (EDXM)

Amy De'Ath

UK NEQAS for H&I Manager

UK NEQAS
Histocompatibility
& Immunogenetics

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

Whole Process ‘EQA’

Assessed Schemes

- 1A, 4A1, 4A2 – HLA Typing
- 6 – HLA Antibody Detection
- 3 – HLA Antibody Specification
- 2A, 2B – Crossmatching

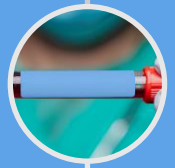
Educational Schemes

- Interpretative Educational Scenarios
- Educational Crossmatch Scheme
  - 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 (repertoires, cut-offs)

Educational Scheme Distribution

Educational Scheme Distribution

'Donor' Sample

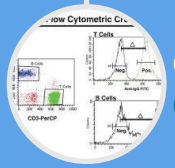


'Patient' Samples

3 x Serum Samples

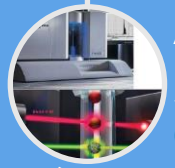
HLA Typing

(Schemes 4A1 & 4A2)



Crossmatching

(Schemes 2A & 2B)



Antibody Detection / Specification

(Schemes 3 & 6)

Clinical Interpretation
Transplant Risk Stratification

2023 Submissions

- 37 participants submitted results
- Not all labs reported results for all tests

- HLA genotype:

Consensus HLA Type	A*	B*	C*	DRB1*	DRB3*	DRB5*	DQA1*	DQB1*	DPA1*	DPB1*
	02	08	05	03 (17)	01	01	01	02	01	04:01
	25	44	07	15			05	06	01	06:01
Number of reports	37	37	37	37	24	24	34	37	25	30
% Labs in consensus	95%	95%	95%	95%	100%	100%	94%	95%	92%	93%

- Number of errors noted.
- 2 participants reported the wrong HLA type – this related to NEQAS Scheme ED01/2023 suggesting a sample mix up.
- Results from these 2 participants were removed from the crossmatching analysis.

01 Serum 1

Results

Serum 1 Results

	Result	% Consensus	Comments
HLA Class I Antibodies	Positive	100% (35/35)	
HLA Class II Antibodies	Positive	97% (34/35 Pos)	Multiple high DR DSA at >10,000. Discrepancy in some reporting of DP antibodies (detected between 5,000 – 9,999 MFI)
DSA	Present	100% (35/35)	Multiple CI and CII DSA. Huge range in MFI e.g. A2 reported by 100% with MFI range of 4,300-23,836
CDC XM	PBL Positive T cell No Consensus B cell Positive	100% (4/4) 64% Pos (7/11) 89% (8/9)	CDC Positive FCXM Positive
FCXM T Cell	Positive	100% (32/32)	
FCXM B Cell	Positive	91% (29/32)	
Transplant Risk	Contraindication	80% (28/35)	20% stated High Risk
Immunological Advice	Not suitable for direct transplantation. High levels of IgG DSA. High risk of hyperacute rejection.		
Recommendations	Seek alternative donor. Consider de-sensitisation such as Imlifidase. Monitor antibodies over time to consider de-listing.		

02

Serum 2

Results

Serum 2 Results

	Result	% Consensus	Comments
HLA Class I Antibodies	No Consensus	69% Neg (24/35)	
HLA Class II Antibodies	Positive	94% (33/35)	
DSA	Present	91% (32/35)	91% DR antibodies reported at 2-5,000 6% DP antibody 970-2,250 20% DQ6 antibody 2,000-13,000
CDC XM	PBL Negative T cell Negative B cell Negative	100% (4/4) 100% (11/11) 89% (8/9)	CDCXM Negative FCXM T cell Negative
FCXM T Cell	Negative	100% (32/32)	
FCXM B Cell	No Consensus	59% Pos (19/32)	
Transplant Risk	Medium/Standard	48% (17/35)	26% stated High risk, 9% a contraindication, 17% stated low risk
Immunological Advice	Not suitable for direct transplantation. High risk of AMR. If transplant proceeds use enhanced immunosuppression and post-transplant monitoring. Test for non-HLA and autologous antibodies.		
Recommendations	Seek alternative donor. Consider de-sensitisation. Monitor antibodies over time to consider de-listing.		

03

Serum 3

Results

Serum 3 Results

	Result	% Consensus	Comments
HLA Class I Antibodies	Positive	97% (34/35)	
HLA Class II Antibodies	Positive	94% (33/35)	DQ antibodies >10,000
DSA	Present	97% (32/33)	97% reported DQ6 antibody between 2-16,000 MFI 94% reported A2 antibody between 1-6,000 MFI
CDC XM	PBL Negative T cell Negative B cell Negative	100% (4/4) 100% (11/11) 100% (9/9)	CDCXM Negative FCXM No Consensus (? Positive)
FCXM T Cell	No Consensus	66% Pos (21/32)	
FCXM B Cell	No Consensus	72% Pos (23/32)	
Transplant Risk	High Risk	50% (17/34)	26% Contraindication, 24% Medium/standard Risk.
Immunological Advice	Not suitable for direct transplantation. Risk of AMR. Consider de-sensitisation. If transplant proceeds use enhanced immunosuppression and post-transplant monitoring. Test for non-HLA and autologous antibodies.		
Recommendations	Seek alternative donor. Consider de-sensitisation. Monitor antibodies over time to consider de-listing.		

UK NEQAS for H&I Comments

The same sample was used for both Serum 1 and Serum 2.

The sample was provided at neat for Serum 1 and at a dilution of 1:16 for Serum 2.

We thought it would be interesting to see how the dilution affected the detection of antibodies across different laboratories.

Most antibodies reduced but one antibody had increased MFI at 1:16 dilution.

Summary of Crossmatch and DSA Detection Results

2023 Results		Serum 1 NEAT		Serum 2 1:16		Serum 3	
DSA Defined by Luminex		Class I	Class II	Class I	Class II	Class I	Class II
MFI >10,000		A2 (100%)	DR15 (100%) DR51 (80%)	N/A	N/A	N/A	DQ6 (97%)
MFI 5,001-9,999		N/A	DP6 (77%)	N/A	DQ6 (20%)	A2 (94%)	N/A
MFI 2,501-5,000		N/A	DQ6 (6%)	N/A	DR15 (91%) DR51 (71%)	N/A	DQA1*01 (6%)
MFI <2,500		B44 (14%)	DR52 (6%) DP4 (3%) DQ2 (3%)	A2 (9%)	DP6 (60%)	N/A	DP6 (49%) DR51 (11%)
CDCXM B CELL	No DTT	Positive		Negative		Negative	
	DTT	Positive		Negative		Negative	
FCXM	T Cell	Positive		Negative		No Consensus (66% Pos)	
	B Cell	Positive		No Consensus (59% Pos)		No Consensus (72% Pos)	
Risk		Contraindication (80%) High (20%)		Medium (48%) High/Contraindication (35%) Low (20%)		High (50%) Contraindication (26%) Medium (24%)	

The table shows the percentage of participants identifying a DSA and the most common MFI range it was reported in.

Benefits

Benchmarking

Monitor performance of multiple techniques
Make clinical interpretations on own results
Compare local policies for clinical assessment

Education

Monitor concordances
Review variations
Staff training

Competency

Laboratory staff
Clinical staff

Future Considerations

Formal Assessment

Basis of future scheme design

Complexity

How to assess the correct clinical interpretation

Workload

Participants
NEQAS team

Competency

Individual competency assessment

Any ideas?

Do you have any questions?

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