2021
A History of UK NEQAS for H&I

UK NEQAS Histocompatibility & Immunogenetics

A History of UK NEQAS for H&I

From its informal beginnings in the 1970s with some 30 UK based laboratories participating in two schemes, UK NEQAS for H&I has continue to grow and develop into the professional dedicated service for external quality assessment. UK NEQAS for H&I now provides 18 EQA schemes to over 330 laboratories in over 50 countries worldwide. It has maintained its core values of operating on a not-for-profit basis, and ensuring laboratory testing quality through continual improvement and education, for the benefit of patients.

Table 1: A timeline of major developments to the Service

Year	Event	Scheme
1975	UK Transplant in Bristol introduced a quality control exercise to standardise HLA phenotyping and crossmatching.	Scheme 1A Scheme 2A
1988	A scheme for HLA antibody specification was introduced	Scheme 3
1989	Schemes recognised as UK NEQAS	
1990	HLA-B27 scheme introduced	Scheme 1B
1992	HLA Class II DNA typing scheme introduced	Scheme 4A1
1994	The first non-UK based participants joined the service	
1996	Flow cytometry crossmatching scheme introduced 'high' and 'low' resolution HLA typing assessment started in Scheme 4	Scheme 2B
1998	An HFE testing scheme was introduced Class I HLA DNA typing assessment introduced	Scheme 5A
1998	Susan Corbin becomes a founding member of the EFI External Proficiency Testing Committee	
2000	Service relocated to Welsh Blood Service, Cardiff	
2001	A scheme for HLA antibody detection introduced	Scheme 6

2002	An educational HLA typing scheme introduced	Educational HLA typing
2003	A DNA based ABO typing scheme introduced	Scheme 4B
2008	HLA-B*57 typing scheme for drug hypersensitivity introduced	Scheme 7
2009	An interpretative scheme for HFE and hereditary haemochromatosis introduced	Scheme 5B
2011	'high' resolution HLA typing scheme splits from 'low' resolution typing A scheme to cover Class II HLA associated diseases introduced	Scheme 4A2 Scheme 8
2014	Interpretive educational schemes introduced for solid organ and haematopoietic stem cell transplantation Introduction of formal CAPA forms for unsatisfactory performance	iED
2015	Introduction of CDC crossmatch assessment with and without DTT	
2016	HPA typing, KIR typing and MICA typing schemes introduced Educational crossmatching scheme introduced Introduction of 'Google Forms' to allow some online data entry by participants	Scheme 9 Scheme 10 EDXM
2017	Pilot MICA scheme suspended due to lack of participants. Inclusion of '3rd' and '4th' field results in Scheme 4A2 for next generation sequence typing results Introduction of interpretative element from genotype to phenotype for scheme 4A1 Separation of PBL/T cell assessment in CDC crossmatch scheme	 Scheme 4A1i
2018	Transfer of HPA antibody scheme from NIBSC to UK NEQAS for H&I Scheme 4B discontinued due to low participant numbers Introduction of 'Participant's Portal' for full online management of EQA scheme Move to use of reference result for genotyping and disease association schemes if reference result not met. Introduction of Class I HLA associated diseases into Scheme 8 assessment	Scheme 11

2019	Scheme operation moves from calendar to financial year operations (April-March)
2020	First virtual Participant Meeting and webinars held

1970's

The origin of the UK NEQAS for H&I schemes can be traced back to 1975, when the National Tissue Typing and Reference Laboratory in Bristol initiated a quality control scheme for HLA typing and crossmatching to help laboratories in the UK and Ireland compare results. This organisation developed into UK Transplant and today is known as NHSBT-ODT.

The first documented evidence that exists from these initial schemes were in the 1976-77 annual report (Figure 1).

Figure 1: Extract from UK Transplant Annual Report 1976-77

UK Transplant annual report of 1 July 1976 to 30 June 1977

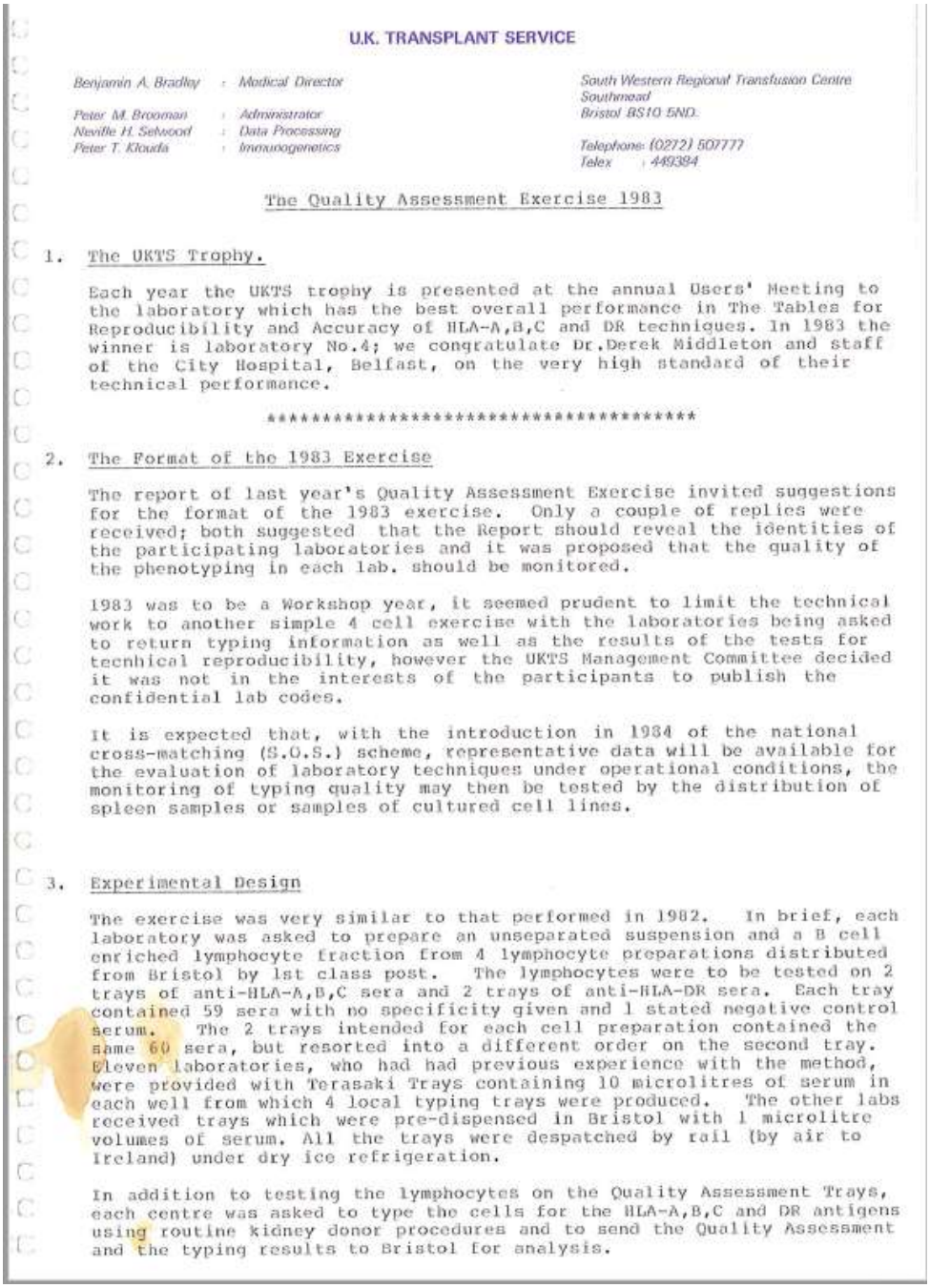
Dr Colin Entwistle, Deputy Director reports that they distributed selected sera and cells to 33 UK laboratories as part of the second "cross match" exercise to assess serological accuracy of laboratories concerned with transplantation and the screening of antisera. He also reports that the exercise confirms the two stage (NIH) procedure to be more sensitive than the 1 stage procedure

These initial schemes founded the basis of Scheme 1A – HLA phenotyping and Scheme 2A – CDC Crossmatching, but the exercises also included technical comparisons around comparing batches of complement and the sensitivity of different techniques.

1980's

In 1988 the first 'new' scheme was introduced, Scheme 3 – HLA antibody specification. The earliest Quality Assessment annual report in the archive is from 1983 (Figure 2). It is interesting to note that a 'UKTS Trophy' was awarded each year to the laboratory that had the best overall quality assessment performance, with Belfast being awarded the trophy in 1983.

Figure 2: **Scanned first page of the 1983 Annual Report, complete with coffee stain**



U.K. TRANSPLANT SERVICE

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The Quality Assessment Exercise 1983

1. The UKTS Trophy.

Each year the UKTS trophy is presented at the annual Users' Meeting to the laboratory which has the best overall performance in The Tables for Reproducibility and Accuracy of HLA-A,B,C and DR techniques. In 1983 the winner is laboratory No.4; we congratulate Dr.Derek Middleton and staff of the City Hospital, Belfast, on the very high standard of their technical performance.

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2. The Format of the 1983 Exercise

The report of last year's Quality Assessment Exercise invited suggestions for the format of the 1983 exercise. Only a couple of replies were received; both suggested that the Report should reveal the identities of the participating laboratories and it was proposed that the quality of the phenotyping in each lab. should be monitored.

1983 was to be a Workshop year, it seemed prudent to limit the technical work to another simple 4 cell exercise with the laboratories being asked to return typing information as well as the results of the tests for tecnhical reproducibility, however the UKTS Management Committee decided it was not in the interests of the participants to publish the confidential lab codes.

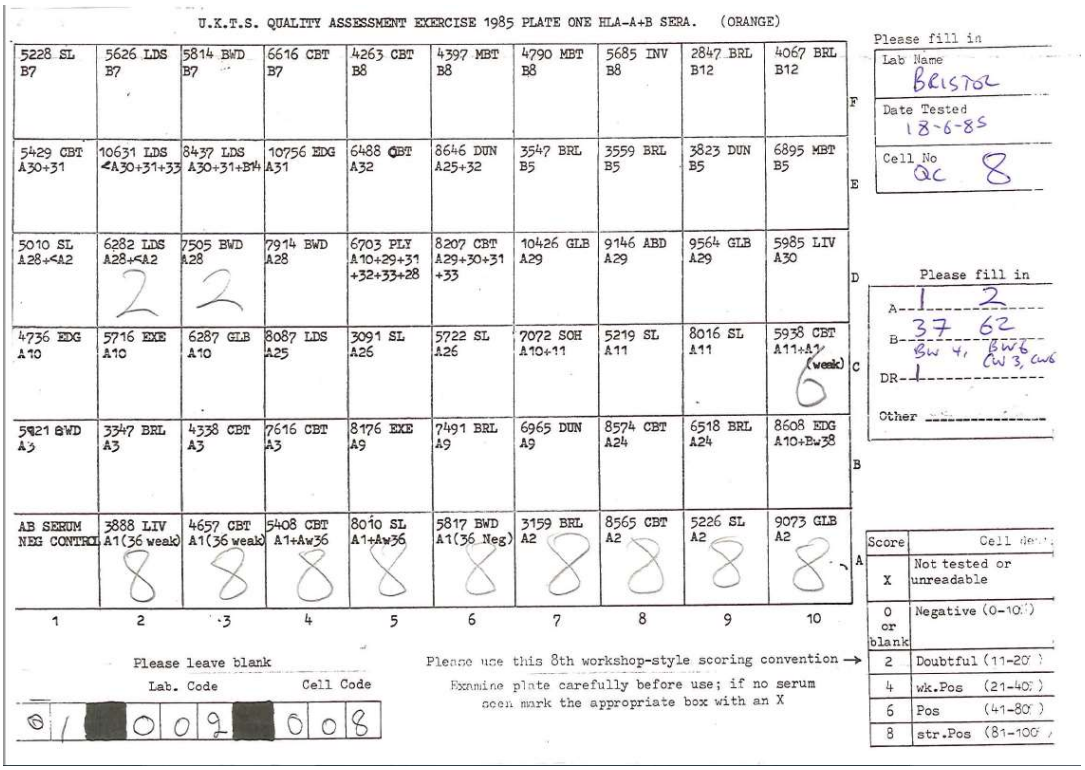
It is expected that, with the introduction in 1984 of the national cross-matching (S.O.S.) scheme, representative data will be available for the evaluation of laboratory techniques under operational conditions, the monitoring of typing quality may then be tested by the distribution of spleen samples or samples of cultured cell lines.

3. Experimental Design

The exercise was very similar to that performed in 1982. In brief, each laboratory was asked to prepare an unseparated suspension and a B cell enriched lymphocyte fraction from 4 lymphocyte preparations distributed from Bristol by 1st class post. The lymphocytes were to be tested on 2 trays of anti-HLA-A,B,C sera and 2 trays of anti-HLA-DR sera. Each tray contained 59 sera with no specificity given and 1 stated negative control serum. The 2 trays intended for each cell preparation contained the same 60 sera, but resorted into a different order on the second tray. Eleven laboratories, who had had previous experience with the method, were provided with Terasaki Trays containing 10 microlitres of serum in each well from which 4 local typing trays were produced. The other labs received trays which were pre-dispensed in Bristol with 1 microlitre volumes of serum. All the trays were despatched by rail (by air to Ireland) under dry ice refrigeration.

In addition to testing the lymphocytes on the Quality Assessment Trays, each centre was asked to type the cells for the HLA-A,B,C and DR antigens using routine kidney donor procedures and to send the Quality Assessment and the typing results to Bristol for analysis.

Figure 3: Example result form for HLA Phenotyping Scheme 1985



U.K.T.S. QUALITY ASSESSMENT EXERCISE 1985 PLATE ONE HLA-A+B SERA. (ORANGE)

1	2	3	4	5	6	7	8	9	10	
5228 SL B7	5626 LDS B7	5814 BWD B7	6616 CBT B7	4263 CBT B8	4397 MBT B8	4790 MBT B8	5685 INV B8	2847 BRL B12	4067 BRL B12	F
5429 CBT A30+31	10631 LDS <A30+31+33	8437 LDS A30+31+B14	10756 EDG A31	6488 CBT A32	8646 DUN A25+32	3547 BRL B5	3559 BRL B5	3823 DUN B5	6895 MBT B5	E
5010 SL A28+<A2	6282 LDS A28+<A2 2	7505 BWD A28 2	7914 BWD A28	6703 PLY A10+29+31 +32+33+28	8207 CBT A29+30+31 +33	10426 GLB A29	9146 ABD A29	9564 GLB A29	5985 LIV A30	D
4736 EDG A10	5716 EXE A10	6287 GLB A10	8087 LDS A25	3091 SL A26	5722 SL A26	7072 SOH A10+11	5219 SL A11	8016 SL A11	5938 CBT A11+A? (weak) 6	C
5921 BWD A3	3347 BRL A3	4338 CBT A3	7616 CBT A3	8176 EXE A9	7491 BRL A9	6965 DUN A9	8574 CBT A24	6518 BRL A24	8608 EDG A10+Bw38	B
AB SERUM NEG CONTROL	3888 LIV A1(36 weak) 8	4657 CBT A1(36 weak) 8	5408 CBT A1+Aw36 8	8010 SL A1+Aw36 8	5817 BWD A1(36 Neg) 8	3159 BRL A2 8	8565 CBT A2 8	5226 SL A2 8	9073 GLB A2 8	A

Please fill in
Lab Name BRISTOL
Date Tested 18-6-85
Cell No QC 8

Please fill in
A- 1 2
B- 37 62 Bw 4, Bw6 Cw 3, Cw6
DR- 1
Other

Please leave blank
Lab. Code 0092 Cell Code 08

Please use this 8th workshop-style scoring convention →
Examine plate carefully before use; if no serum seen mark the appropriate box with an X

Score	Cell density
X	Not tested or unreadable
0 or blank	Negative (0-10%)
2	Doubtful (11-20%)
4	wk.Pos (21-40%)
6	Pos (41-80%)
8	str.Pos (81-100%)

The premise of an annual participant meeting was introduced in these early days for laboratories to come together, discuss results of the quality control exercises and exchange ideas. It was from one of these Participant meetings in 1989 that the idea of a UK professional society for 'tissue typers' was formed, and the British Society for Histocompatibility and Immunogenetics was created that year.

1989 was also a significant year, as the schemes become part of the 'UK NEQAS' brand, a not for profit consortium of external quality assessment providers created in 1969.

1990's

In 1990 Scheme 1B – HLA B27 testing started and the first DNA based HLA typing scheme (4A) was introduced in 1992, initially just for Class II HLA typing, but later included Class I typing. As higher resolution HLA typing techniques were introduced by laboratories, this were initially also included in Scheme 4A, before 'high' and 'low' resolution DNA typing were separated in 2000.

1991 also saw Susan Corbin take over from Terry Ray as Scheme Manager. In 1994, Dr Chris Darke became Director and the first non-UK participants joined UK NEQAS for H&I. The 1990s also saw the creation of Scheme 2B – flow cytometry crossmatching and Scheme 5 – HFE typing and the service gained CPA (EQA) accreditation. In 1998 Susan Corbin became a founding member of the European Federation of Immunogenetics (EFI) External Proficiency Testing (EPT) committee, with the aim to harmonise and promote quality assessment schemes across Europe.

Figure 4a: Results from the first DNA based HLA Typing scheme in 1992.

HLA NEQAS SCHEME 4 (DNA TYPING)

INTERPRETATION OF PARTICIPATING LABORATORIES

Sample No. 6/92
Despatched: 8 September 1992 Report prepared: 1 December 1992

Lab. No.	DR	DR	DQ	DQ	
3					Inadq. hybridisation
6	4	13	7	6	DRB1*1302
11	4	13	3	6	DR6, (13(19))
12	4	13	7	1	DRB1*1302
16	4	13	7	6	DRB1*1302, DRB1*0407
17	4	13	7	6	DRB13a3
18					Inadq. hybridisation
25	4	?	1	3	
27	4	13	7	6	DR3/6
28	4	13	7	5	DR13a3
29	4	3/6	3	1	DQ Assoc. suggests DRB 4, 13a3
33	4	13	7	6	DR13a3
36	4	13	7	6	DR13a3
37	4	13	7	6	DR13a3
38					No results received
42					Technical failure
43	4	13	7	6	DRB1*1302, DRB1*0401/11
46					Postal delay-Poor yield
47	4	13	7	5	DR13a3
48					Routine DNA not typed
49					Still estab. method
52					Still estab. method

Summary

Concensus type : DR4, DR13 ;DQ7, DQ6

Detected by 13/14 reporting laboratories

Figure 4b: Laboratory methods from the first DNA based HLA Typing scheme in 1992.

HLA NEQAS SCHEME 4 (DNA TYPING)

INTERPRETATION OF PARTICIPATING LABORATORIES

Samples 1-4/92 despatched: 7 April 1992 Report prepared: 4 June 1992

Lab. No.	DNA extr. method	oligo/RFLP other	no. of probes	radio/non-radio labelling
3	salting-out	RFLP	3	radioactive
6	to follow			
11	to follow			
12	salting-out	oligo	53(WS)	non-radioactive
16	salting-out	oligo/RFLP	24(WS/BSHI)	radioactive
17	salting-out	RFLP	3	radioactive
18	not available			
25	not available			
27	salting-out	oligo/RFLP	4(WS)	non-radioactive
28	salting-out	RFLP		radioactive
29	satlting-out	RFLP		radioactive
33	phenol mini	RFLP		radioactive
36	salting-out	RFLP		radioactive
37	salting-out	RFLP		radioactive
38	not available			
42	salting-out	RFLP/PCR		radioactive
43	salting-out	RFLP		non-radioactive
46	salting-out	RFLP/other		radioactive
47	to follow			
48	not available			
49	not available			
52	salting-out	RFLP		non-radioactive
54	salting-out	RFLP/PCR		radioactive

All four samples were from "laboratory use" blood bags which were

virology negative. The units were taken into CPDA and were not diluted

2000's

The new millennium necessitated a new home for UK NEQAS for H&I, as the laboratories at UK Transplant were closed and became purely an administration site. The Service was relocated from Bristol to its current home at the Welsh Blood Service, just outside of Cardiff. The 2000's brought a period of expansion, with new schemes for HLA antibody detection (scheme 6), B57 testing (scheme 7) and an interpretative scheme for hemochromatosis (scheme 5B), to reflect the changing testing requirements of histocompatibility and immunogenetics laboratories. The first educational schemes were also introduced with unusual or 'rare' HLA types being distributed.

Figure 5: Repot of the first educational HLA typing scheme in 2002, with samples containing HLA-A3 null allele and 'low frequency' HLA-DRB1*04:09 allele.

UK NEQAS FOR H&I EDUCATIONAL SCHEME

HLA PHENOTYPING RESULTS OF SAMPLES ED01&02/02

DESPATCHED ON 5TH MARCH 2002

Sample ED01/02 probable HLA phenotype

HLA-A*03, A*3201 ; B*07, B*40 ;Cw*0702, Cw*1502 ;
DRB1*15, DRB1*0401 ;DRB4*0103 ;DRB5*0101 ;DQB1*0602, DQB1*0301

Sent as an example of an HLA-A 'null'. HLA-A*03 null allele - not A*0303N – preliminary data indicates A*03011 with a substitution in exon 3 which produces a premature stop codon.

Sample ED02/02 probable HLA phenotype

HLA-A*0101, A*0201 ;B*08, B*4402 ;Cw*0501, Cw*0701 ;
DRB1*04, DRB1*04 ; DRB4*01 ; DQB1*0301 ; DQB1*0302

Sent as an example of a 'low frequency' HLA-DRB1*04 allele (DRB1*0409). In combination with a 'common' DRB1*04 allele (DRB1*0404).

IMPORTANT REQUEST

Please use the correct nomenclature when reporting results. Please consult the 2002 Prospectus for full information on reporting criteria.

PLEASE NOTE THE NEXT DESPATCH DATE IS: TUESDAY 24TH SEPTEMBER 2002

Picture 1: L-R Dr Tracey Rees, Susan Corbin, Deborah Pritchard. EFI Conference Dinner Barcelona 2007.

2010's

2011 saw the introduction of a standalone 2nd field DNA HLA typing scheme (scheme 4A2, previously 'low' and 'high' resolution typing had been performed under the same scheme), which was further extended in 2018 to include 3rd and 4th field results for next generation sequencing assessment. This decade also saw the introduction of a further HLA disease association testing scheme (Scheme 8), HPA genotyping (scheme 10) and KIR typing (Scheme 9). A Scheme for MICA typing was also introduced but discontinued after a few years due to lack of participants.

Existing schemes were also modified in line with clinical practice;

- Scheme 2A - CDC crossmatching was assessed both with and with DTT
- Scheme 3 – HA antibody detection was expanded to include DPB and collect information for DQA/DPA, in recognition of the move to Luminex Single Antigen Bead testing by laboratories.
- Scheme 4A1 – DNA HLA typing at 1st field had an additional interpretative element added (scheme 4A1i) to ensure laboratories maintained expertise in converting molecular nomenclature to serological nomenclature.

In 2018, the UK HPA antibody scheme, previously run by NIBSC transferred to UK NEQAS for H&I (Scheme 11). Educational schemes were increased, with the introduction of Interpretative educational scenarios covering solid organ, haematopoietic stem cell transplantation and platelet/transfusion immunology, as well as the educational crossmatching scheme.

There were also significant staffing changes during this period; 2013 saw the retirement of Susan Corbin after 23 years as Scheme Manager, followed by Chris Darke in 2016 after 22 years as Director. They were succeeded by Deborah Pritchard as Manager, and Dr Tracey Rees as Director. There were also two interim Managers of the Service, Felicity May and Amy De'Ath, who covered a year each due to maternity leave.

In 2016 the service successfully transitioned from CPA (EQA) to ISO 17043 accreditation. 2018 also saw the modernisation of the result entry and reporting system, with the introduction of bespoke computer software, the 'Participant's Portal'.

Picture 2: L-R Susan Corbin, Dr Tracey Rees, Deborah Pritchard. EFI Conference Dinner. Maastricht 2013.

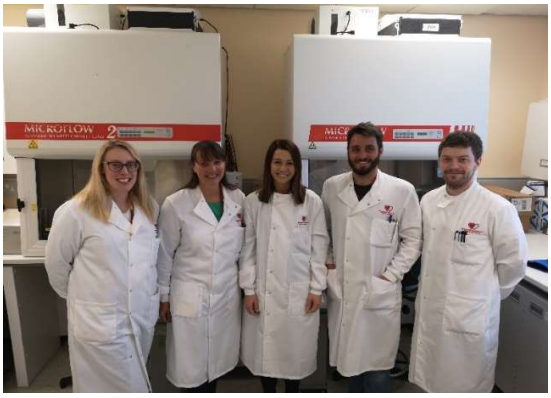
Picture 3: **EQA DNA preparation, Welsh Blood Service Laboratories 2013. L-R Luke Gardner, Geraint Clarke.**

Picture 4: **The UK NEQAS for H&I team out for a Christmas Meal, 2013. L-R (back) Geraint Clarke, Luke Gardner (front) Deborah Pritchard, Susan Corbin, Melanie Bartley.**

Picture 5: **UK NEQAS for H&I Team, May 2017, Welsh Blood Service Laboratories. L-R Melanie Bartley, Luke Gardner, Deborah Pritchard, Jemma Cornish Geraint Clarke.**

Picture 6: **Dispending EQA sera, Welsh Blood Services Laboratories, 2019. L-R Lucy Palmer, Luke Gardner.**

Picture 7: **UK NEQAS for H&I Team, 2019, Welsh Blood Service Laboratories. L-R Amy De'Ath, Melanie Bartley, Lucy Palmer, Geraint Clarke, Luke Gardner.**



2020's

Picture 8: **UK NEQAS for H&I Team, 2020, Welsh Blood Service Laboratories. L-R Luke Gardner, Geraint Clarke, Melanie Bartley, Amy De'Ath, Deborah Pritchard.**

The management structure of UK NEQAS for H&I was altered in 2020, with Amy De'Ath returning as Operations Manager and Deborah Pritchard moving to Deputy Director role. Due to the COVID-19 pandemic, UK NEQAS for H&I help its first 'virtual' participant meeting, and first webinars covering the interpretative scenarios.

UK NEQAS for H&I Directors

Dr Peter Klouda 1989-1994
D Chris Darke 1994-2016
Dr Tracey Rees 2015-currrent

UK NEQAS for H&I Deputy Directors

Deborah Pritchard 2020-current

UK NEQAS for H&I Managers

Terry Ray 1980-1991
Susan Corbin 1991-2013
Deborah Pritchard 2013-2020
Amy De'Ath 2020- current

UK NEQAS for H&I Steering Committee Chairs

Dr Ken Walsh 1993 -2001
Dr Deborah Sage 2002-2014
Dr Judith Worthington 2015-2021
Dr Helena Lee 2022-current

Picture 9: EQA blood preparation during the COVID-19 pandemic, Welsh Blood Service Laboratories, 2020. L-R Luke Gardner, Geraint Clarke.