Department of Health & Social Care

Report of the ISOU Histocompatibility and Immunogenetics (H&I) Sub-Group

Shared with Implementation Steering Group for Organ Utilisation (ISOU)
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Contents

Publisher's note

This Histocompatibility and Immunogenetics (H&I) recommendations report was presented to Department of Health and Social Care (DHSC) Ministers following agreement of the report at the Implementation Steering Group for Organ Utilisation (ISOU) meeting in December 2024.

Since then, we have entered a period of significant change, following the announcement on 13 March that the Government will be abolishing NHS England and rolling its functions into DHSC.

DHSC's vision is to promote innovation and support the shift to roll out new technology. As such, we felt it was important to publish this report and these recommendations in their entirety to showcase the emerging technological innovations in the field of H&I which has the potential to improve outcomes for transplant patients in the UK and ultimately save lives.

We will consider how any next steps should be revisited, for example, who will take responsibility for the delivery of these recommendations going forward.

Acknowledgements

The Histocompatibility and Immunogenetics subgroup would like to acknowledge the input of the following experts consulted during the writing of these guidelines.

Dr Hatem Ali	Coventry UK
Prof Nithya Krishnan	Coventry UK
Prof David Briggs	Birmingham UK
Prof Peter Nickerson	Manitoba, Canada
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Dr Adrienne Seitz	Leeds, UK
Lisa Mumford	NHSBT, UK
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Dr Lloyd D’orsogna	Perth, Australia
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Jessica Jones	ISOU patient sub-group Co-chair
Dr Claire Fuller	ISOU patient sub-group Co-chair
Kirit Modi	Patient representative
Robert Burns	Patient representative

Abbreviations and Glossary

H&I Histocompatibility & Immunogenetics - the scientific discipline of transplant compatibility and study of the immune system

HLA Human Leucocyte Antigens - Proteins which should ideally be matched between transplant donor and recipient to ensure optimal outcome

HLA type Human Leucocyte Antigens type - the characterised properties of a patient or organ donors' HLA.

dd-cfDNA Donor derived cell free DNA - transplanted donor material which can be detected in the recipients' blood sample

DNA sequencing - a technique which can be used to determine a patient or donors HLA type

PROMs Patient reported Outcome Measures

Co-chair's Introduction

ISOU H&I sub-group Co-chair’s introduction

Recently available and emerging technological innovations in the field of Histocompatibility & Immunogenetics (H&I) have helped improve our understanding of compatibility of organs between organ donors and recipients. Leveraging the opportunities from such technologies will enable higher quality clinical decision making whilst matching organs between donors and recipients to both improve long term outcomes and reduce inequity for patients currently deemed ‘harder to match’.

The ISOU H&I sub-group approached its’ mandate by focusing on innovations expected to have measurable improvements to patient outcomes with the potential to be implemented in the NHS within the next 5-10 year time horizon. The group conducted its work by consulting widely and we are especially grateful for the selfless and transparent sharing of scientific and implementation experiences from our international colleagues spanning time zones from Australia to Canada.

As Co-Chairs we could not have asked for more engaged and active membership of expert colleagues from across the UK. All members generously gave their time and full attention, being open minded to give all points of view a fair hearing and contributed whole-heartedly from start to finish. The camaraderie, transparency and ability to debate fiercely but still be prepared to reach consensus made group working pleasurable and productive – best evidenced by the groups’ unanimous view this collaboration should continue in some way even after submission of the final draft of the recommendations. This is very relevant as the group acknowledged that both knowledge and technology is ever-changing in H&I and having a national forum to debate and, where relevant, help adopt such innovations at the earliest opportunity could maximise benefits for patients and the wider NHS.

Finally, none of this would have been possible without the active support of ISOU Co-Chairs William Vineal and John Forsythe and the excellent support from DHSC team including Helen McDaniel, Michael Hopkinson and Samantha West. On behalf of all members of the H&I sub-group, many thanks.

Rommel Ravanan & Richard Battle

Executive Summary

Histocompatibility and Immunogenetics (H&I) is the pathology discipline that evaluates and makes recommendations on how well donated organs match to potential transplant recipients. Broadly, better matched organs have lower risk of rejection and result in better patient outcomes.

The laboratory techniques used to assess such matching are continually improved, and the most contemporary techniques offer benefits in terms of cost-effectiveness and accuracy. Consequently, these techniques enable an understanding of the matching of proteins (also called Human Leucocyte Antigens or HLA molecules) on organ donors and recipients to a much higher resolution, and their application enables significant advantages in transplant compatibility assessments and transplant risk management.

In line with ISOU recommendation 9 (“evaluating and embracing innovation that could improve outcomes for patients”) the H&I sub-group was set up with the mandate to evaluate and make recommendations concerning new ways for HLA compatibility assessment and related technologies and how such innovations could be implemented within organ transplantation services in the UK.

To discharge its duties, the sub-group: (a) invited and heard from subject matter experts from across the world, including both technical aspects and implementation practicalities of new technologies/innovation in routine clinical practice; (b) consulted and incorporated input from the ISOU patient sub-group; (c) interacted with industry providers to review current and future innovations that are expected to come to market; (d) consulted statistics and IT infrastructure experts in NHSBT on practical aspects of incorporating any innovation within NHSBT processes.

The sub-group approached its’ mandate by exploring and making recommendations around three main themes.

Theme 1: performing and digital capture of high-resolution HLA typing data for organ donors and recipients.

Recommendation 1: Transplant services in the UK implement technologies which can routinely report rapid high-resolution HLA typing of potential organ transplant donors and recipients.

Recommendation 2: Digital infrastructure in transplant centres and NHSBT have the capability to send/receive, store and access high-resolution HLA typing data to enable improved pre- and post-transplant risk assessment for patients.

Theme 2: utilising high resolution HLA typing data to improve donor/recipient compatibility assessment and patient outcomes.

Recommendation 3: High resolution HLA typing data should be included within a national transplant dataset and used amongst the variables informing relevant organ offer/allocation algorithms.

Theme 3: other technologies/innovations to improve patient outcomes.

Recommendation 4: NHSBT should evaluate benefits, safety and acceptance to patients of incorporating Artificial Intelligence (AI) technologies in organ offering algorithm design and/or patient information provision.

Recommendation 5: National Institute for Clinical Evidence (NICE) should be invited to evaluate the clinical and cost effectiveness of donor derived cell-free DNA (dd-cfDNA) testing in solid organ transplantation settings.

Theme 1 - performing and digital capture of high-resolution HLA typing data for organ donors and recipients.

Recommendation 1:

Transplant services in the UK implement technologies which can routinely report rapid high-resolution HLA typing of potential organ transplant donors and recipients.

Specific detail for the above recommendation includes:

- Technologies which can produce a HLA type to the 2nd field (minimum) for HLA-A,B,C,DRB1/3/4/5, DQB1, DQA1, DPB1, DPA1 within acceptable (service specification) timeframes offer advantages in donor and recipient characterisation.

- Implementation within ISO15189:2022 compliant laboratories must be assured for technologies used to characterise transplant donors/recipients.

Serological (technology that uses antibodies present in blood) HLA typing techniques used in the 1980/90s were able to define an HLA type to low/medium resolution (at a HLA antigen level). Modern molecular technologies however can define the HLA type to higher resolution and are capable of identifying the specific HLA allele (specific genetic sequence in the individual) which encodes the HLA molecule.

NHS H&I laboratories have a strong track record of implementing and developing the latest available technology. Most recently, DNA sequencing HLA typing technology has been implemented across most H&I laboratories to support higher resolution typing. This enables better definition of HLA alleles and consequently an improved ability to determine the immunological risk associated with organ transplantation.

Current HLA sequencing technology has a test reporting time of 24-72 hours and therefore has been routinely applied only in situations that are not time critical e.g. living donor transplantation or stem cell transplantation. For deceased donor transplantation, rapid determination of donor HLA type is needed to enable timely retrieval and safe allocation of organs. Current service specifications require HLA typing of the deceased organ donor within 4 hours. This has resulted in reliance on traditional techniques that can only produce low/medium resolution HLA type within the 4 hours required, despite most H&I laboratories having the expertise and equipment to produce high resolution HLA reporting when there is less time pressure.

Emerging typing technologies, some recently released on the market, are able to generate a high resolution HLA type within a 4-5 hour time period that would therefore be

acceptable for a deceased donor HLA typing service. Utilizing the data generated from these assays will have a significant benefit in terms of pre-transplant risk assessment and enable higher quality organ matching/allocation decisions.

Implications for the NHS:

Impacted organisations: H&I laboratories/providers supporting NHS patients in England (and devolved equivalents) and NHSBT (and equivalents).

Cost implications: Minimal. Current service providers can transition to new HLA typing technologies as part of scheduled tenders /contract renewals.

Workforce implications: Current workforce has the required expertise to adopt and utilise the new HLA typing technologies. Sustainable delivery is dependent upon recruitment & retention of specialised H&I Healthcare Science workforce with appropriate expertise and HCPC registration.

Risks: No additional risk compared to current practice identified.

Benefits: Improved long-term outcomes for transplant recipients and improved access to transplantation for ethnic minorities and harder-to-match patients (see Benefits section of recommendation 3).

Recommendation 2:

Digital infrastructure in NHSBT and transplant centres should have the capability to send/receive, store and access high-resolution HLA typing data to enable improved pre-transplant risk assessment for patients.

Specific detail for the above recommendation includes:

- As a minimum, the available IT infrastructure should be capable of capturing HLA data to a 2nd field for both donor and recipient (This should apply to HLA typing and HLA antibody data recording for HLA-A,B,C,DRB1/3/4/5, DQB1, DQA1, DPB1, DPA1)

- The data capture should be future proofed by enabling data capture to the 4th field when available and include capability for data from antigen systems, other than HLA, whose relevance in the transplant setting is emerging (such as Human Neutrophil Antigen - HNA).

- World Health Organization HLA nomenclature formatting and universal Histocompatibility and Immunogenetics mark-up language requirements should be followed.

- Data should be capable of bi-direction electronic transfer in a secure format and have the capability for direct download into relevant secure patient records.

- Recording of HLA antibody defined unacceptable antigens/alleles should also be capable to 2nd field resolution for HLA-A, B, C, DRB1/3/4/5, DQB1, DQA1, DPB1, DPA1.

Alongside the ability to generate improved resolution data comes a requirement for additional data capture. While recent improvements in NHSBT H&I high resolution data capture have been made, particularly within the LivingPath digital transformation program and consequent improvements within the National Kidney Sharing Scheme digital workspace, this is not matched in deceased organ donor settings. Successful delivery of the Living Path digital transformation program confirms NHSBT has the required expertise and digital infrastructure to implement a similar program in the deceased donor setting but would require appropriate prioritisation of resources to enable this transformation. A similar challenge is beginning to be addressed by other countries in Europe, USA, Canada and Australia and it is imperative patients in the UK are not left behind from gaining maximum benefit from emerging technologies.

Availability of high-resolution HLA typing data will enable improved compatibility assessment between donor and recipient (see recommendation 3) and therefore better long term patient outcomes. Combining high resolution HLA typing data with available HLA antibody data (currently routinely evaluated at high resolution level) will enable better matched transplants for ethnic minorities and harder-to-match patients, who are currently dis-advantaged due to defaulting of rarer HLA types found in ethnic minorities to more common HLA types in a predominantly Caucasian organ donor pool. Establishing an IT infrastructure that captures both high resolution HLA type and HLA-antibody profile would progress clinical care in the NHS to the same level as leading countries in the world.

Implications for the NHS:

Impacted organisations: H&I laboratories/LIMS providers supporting NHS patients in England (and devolved equivalents) and NHSBT (and equivalents).

Cost implications: NHSBT to undertake discovery work to arrive at cost estimate and include in future negotiation with DHSC.

Workforce implications: Expertise recruitment +/- training of NHSBT IT team members

Risks: Minority of NHS laboratories may require time to onboard

Benefits: Improved long-term outcomes for transplant recipients and improved access to transplantation for ethnic minorities and harder-to-match patients (see Benefits section of recommendation 3).

Theme 2 - Utilising high resolution HLA typing data to improve donor/recipient compatibility assessment and patient outcomes.

Recommendation 3:

High resolution HLA typing data to be included within the existing national transplant dataset and used amongst the variables informing relevant organ allocation algorithms.

- Availability of high-resolution HLA typing data in the national organ transplantation dataset is essential to derive alternative organ allocation algorithms to improve long term patient outcomes and/or reduce inequity due to ethnicity or other demographic factors.

- High resolution HLA typing within the national dataset can be assessed in the context of reported 'molecular HLA matching' techniques (e.g. Amino acid mismatch score, EMS3D, risk epitopes) to improve donor-recipient compatibility assessment and immunological risk assessment and, hence, to improve long-term patient outcomes.

Currently the organ allocation systems in the UK are based on robust statistical analysis of available data reporting outcomes. However, the improved HLA typing and data collection (recommendations 1 and 2) will act as enablers to review and, where appropriate, introduce changes to organ allocation aimed at better matching to reduce the risk of rejection, improve organ longevity (e.g. fewer patients return to dialysis) and patient quality of life.

Importantly, availability of high-resolution HLA typing data and 'molecular HLA matching' techniques can improve organ compatibility assessment for ethnic minority groups who are currently dis-advantaged due to having less frequent HLA types compared to the UK population. High-resolution HLA typing combined with already available high resolution antibody data allows more accurate compatibility assessments and transplant allocation for 'difficult to match patients', such as ethnic minorities, women (sensitised due to pregnancy) and re-transplant patients.

High-resolution HLA data, in addition to other variables important to patients (e.g. PROMs), would derive improvements in organ matching algorithms to maximise organ utilisation and outcomes important to patients.

Implications for the NHS:

Impacted organisation/s: NHSBT.

Cost implications: Minimal / will be part of BAU

Workforce implications: Minimal / will be part of BAU

Risks: No additional risk compared to current practice identified.

Benefits: Improved long-term outcomes for transplant recipients and improved access to transplantation for ethnic minorities and harder-to-match patients (see Benefits section of recommendations 1 and 3).

Theme 3 - Other Technologies / Innovations

Theme 3: other technologies/innovations to improve patient outcomes.

Recommendation 4:

NHSBT should evaluate benefits, safety and acceptance to patients of incorporating Artificial Intelligence technologies in organ offering algorithm design and/or patient information platforms.

The incorporation of high-resolution HLA typing data amongst the variables informing relevant organ offer/allocation algorithms (recommendation 3), in conjunction with outcome measures important to patients, will provide NHSBT with one of the most comprehensive datasets within the solid organ transplant field.

Whilst currently utilised statistical approaches to determine optimal organ allocation remain the preferred methodology, advances within Artificial Intelligence (AI) technologies offer an opportunity to compare benefits-vs-risks of current versus AI based methods. Acceptability of incorporating AI in organ offering systems to both patients and clinicians will need to be explored. Access to AI technology enabled applications as patient information platforms will provide novel opportunities for patients to make informed choices regarding organ offers for transplantation.

Implications for the NHS:

Impacted organisation/s: NHSBT.

Cost implications: £250k (mainly pay and software costs, over a 2-year period)

Workforce implications: AI expertise recruitment +/- training of NHSBT Statistics team members in AI

Risks: No additional risk compared to current practice identified.

Benefits: Will need to be quantified as part of evaluation exercise. If established to be safe and acceptable for patients, likely improved patient experience from improved patient information.

Recommendation 5:

National Institute Health and Care Excellence (NICE) should be invited to evaluate the clinical and cost effectiveness of donor derived cell free DNA (dd-cfDNA) testing in solid organ transplantation settings.

There is currently a significant unmet clinical requirement for a non-invasive approach to monitoring transplant dysfunction. Current approaches to transplant graft monitoring vary according to the organ transplanted. In kidney transplant surveillance monitoring, a blood test (serum creatinine) is routinely used and is readily and widely available, cost effective, and results can be provided rapidly (in <2 hours). Other markers of kidney transplant function include assessment of urine and other blood tests from specialised laboratories (e.g. donor specific antibody). Despite these advantages, such blood and other body fluid biomarkers may not identify graft injury in an optimal timeframe or in all settings. Confirmatory proof of transplant health can only be assessed by an invasive kidney transplant biopsy with associated costs of hospital admission, management of uncommon but recognised complications, histology assessment etc. Further, in the paediatric setting biopsies may be distressing and require general anaesthesia.

Unlike kidney transplantation with a universally available, reasonable blood biomarker, most other solid organ transplants do not have a similar blood/body fluid biomarker. For example, routine surveillance of heart or lung transplants require hospital admission for invasive biopsies of the organ and associated costs of hospital admission, heart catheterisation laboratory for heart biopsy and bronchoscopy suite for lung biopsies, in addition to costly and time-consuming histology assessments.

The emerging technology of dd-cfDNA has potential as a non-invasive blood biomarker in organ transplantation to improve patient experience. Further, reduction in requirement for hospital admissions for invasive biopsy tests may prove cost effective for the NHS. Care pathways of specific populations such as paediatric patients, may have additional advantages by reducing risk associated with general anaesthetic procedures. Patient experience would be significantly improved if there was access to a reliable, non-invasive test.

A variety of test platforms to measure dd-cfDNA are emerging on the market, with some platforms using techniques that could fall within the expertise already held within H&I or genetic laboratories. If NICE assessment establishes clinical and cost effectiveness of such tests (in one or more specific organ transplant settings), implementation could reliably follow via established commissioning processes for NICE approved technologies.

Implications for the NHS:

Impacted organisation/s: NICE

Cost implications: N/A

Workforce implications: Not applicable at this stage. If NICE evaluation recommends utilisation, it is possible that testing can be delivered by NHS H&I laboratories.

Risks: No risks identified for NICE undertaking the review. Not undertaking robust NICE evaluation risks piece-meal introduction of testing without proof of clinical and cost effectiveness and un-warranted variation in access to such tests across the country.

Benefits: NICE evaluation may identify cost savings (reduced hospital admissions / hospital resource use) and improved patient experience.

Appendix

Appendix 1. Terms of Reference

Purpose

1. The purpose of the Histocompatibility & Immunogenetics (H&I) sub-group is to provide independent advice to DHSC Ministers and the Secretary of State for Health and Social Care on collaborative use of new technology and service provision related to H&I and solid organ transplantation.

   The sub-group will be tasked with producing recommendations to the Ministers on the H&I service for solid organ transplantation, including:

   - Stock-take of innovative methods and their utility and effectiveness;
   - Explore potential for improvements to patient benefit, optimal use of the precious donor resource, clinical team efficiency and cost-effectiveness to the service, wider NHS and UK economy;
   - Focus on innovations which can be implemented on a 5-10 year time scale;
   - Prepare proposals for best use of these new techniques.

Scope

2. It is acknowledged that while implementation of the Organ Utilisation Group's (OUG) recommendations by the Implementation Steering group for Organ Utilisation (ISOU) apply to England, there is significant engagement and buy-in from Devolved Governments. s Organ transplantation is organised across the UK and some patients cross borders to access services. Whilst ISOU's evaluation and any implementation of the H&I sub-group's recommendations in England may inform work in the home nations, any decisions regarding implementation of recommendations outside England will be made locally by the Devolved Governments.

Membership

3. The Co-Chairs of the sub-group will be nominated by the DHSC ISOU Co-Chairs. The sub-group membership will include (a) patient facing clinicians with H&I subject matter expertise (SME), (2) H&I laboratory SME, (3) Laboratory provider SME. All ISOU sub-groups would typically have lay/patient representation. Due to the highly technical nature of the H&I sub-group's remit, an alternative model of lay/patient engagement will be considered. This will be with the sub-group Co-Chairs ensuring regular engagement with relevant patient/lay panels (for example the ISOU Stakeholder

Forum or Patient Engagement sub-group) with this feedback embedded in the sub-group's work and final recommendations.

4. Representatives of Government and/or health commissioners from all four UK nations will be invited as observers. Policy leads from all four UK nations will also receive updates from the subgroup at the main ISOU meetings as well as from subgroup members that are based in their respective nations.

5. At the discretion of the sub-group Co-Chairs and ISOU Co-Chairs additional members may be co-opted for specific input as needed.

6. At the discretion of the sub-group Co-Chairs and ISOU Co-Chairs representatives from the commercial sector may be invited to speak to specific points related to their products/innovations. In this scenario, all possible providers of the product/innovation will be invited to prevent any undue commercial advantage to a specific provider. DHSC will provide any commercial advice required prior to inviting commercial representatives to H+I sub-group meetings.

7. Members will not be remunerated for their time, but reasonable travel and subsistence costs will be re-imbursed in line with DHSC expenses policy.

Meetings

8. The sub-group will conduct in-person and/or hybrid and/or virtual meetings at the discretion of the Co-Chairs. In-person or hybrid meetings where possible will be conducted at DHSC (or NHSBT) premises.

9. The sub-group will meet every 6-8 weeks over approximately 12 months. Additional meetings may be called at the discretion of the Co-Chairs. The sub-group will be disbanded on the completion of its' task.

10. The meeting will be considered quorate if attended by at least 3 patient facing SME and 3 H&I laboratory SME.

11. Members will have signed a declaration form to alert the secretariat to potential conflicts of interest or concerns and to agree to honour confidentiality in terms of information shared or the purposes of sub-group discussions.

Secretariat

12. DHSC will provide the Secretariat and administrative support for the sub-group, including the following activities:

    Secretariat:

- Working with the Co-Chairs, collate the agenda and papers
- Draft papers, to be cleared by Members and Co-Chairs as appropriate
- Drafting and or compiling reports to Ministers and others, but the responsibility for the content lies with the members and ultimately the Co-Chairs of the sub-group.
- Working under the instruction of the Co-Chairs, drive activity and progress between meetings

Administration:

- Setting dates and issuing invites
- Hosting virtual meetings
- Organising venues for in-person/hybrid meetings
- Taking notes, clearing notes with the Co-Chairs, circulating notes to delegates

Governance

13. The sub-group will report to ISOU. The final recommendations (as detailed in point 1 above) produced by the sub-group will be submitted to the DHSC ISOU Co-Chairs

14. At the request of the DHSC ISOU Co-Chairs the sub-group may be invited to consider additional aspects related to H&I, that have not already been identified or considered by the sub-group.

15. The Co-Chair or identified member of this sub-group who is also a member of ISOU will escalate to the DHSC ISOU Co-Chairs any requests for help or intervention that may be necessary to successfully discharge the duties of the sub-group.

16. The Co-Chair or identified member of this sub-group who is also a member of ISOU will provide regular updates at ISOU meetings.

Appendix 2.

Membership list:

1.	Rommel Ravanan	Clinical Co-chair (ISOU member)
2.	Richard Battle	Scientific Co-chair / Scotland Representative
3.	Sian Griffin	Physician / Welsh Representative
4.	Aisling Courtney	Physician / Northern Ireland Representative
5.	Sunil Daga	Physician
6.	Vasilis Kosmoliaptsis	Surgeon / Heart Transplantation Representative
7.	Tom Nieto	Surgeon
8.	Sarah Peacock	H&I lab lead / Provider Representative / Heart Transplantation Representative
9.	Delordoson Kallon	H&I lab lead / Heart Transplantation Representative
10.	Olivia Shaw	H&I lab lead / Paediatric Representative
11.	Katy Latham	H&I lab lead / NHSBT Representative
12.	Brendan Clark	H&I lab lead
13.	Vicky Chalker	NHS E /Genomics Representative
14.	JJ Kim	Paediatric Representative