



Beaumont Hospital
Dublin

**THE NATIONAL HISTOCOMPATIBILITY
AND IMMUNOGENETICS SERVICE FOR
SOLID ORGAN TRANSPLANTATION
(NHISSOT)**

USERS' GUIDE

A Guide to the Services provided by the

*Department of Histocompatibility
and Immunogenetics*

7th Edition - January 2009

Disclaimer

No part of this booklet may be produced or transmitted in any form by any means without the prior consent of the Department of Histocompatibility and Immunogenetics, Beaumont hospital. The information provided in this user guide is correct at the time of going to press, however, as Histocompatibility and Immunogenetics is a rapidly developing speciality, techniques and details of investigations may change.

Feedback

The Department welcomes any feedback on all aspects of the service. The Consultant Immunologist and staff of the H&I department are always happy to discuss the service and individual patients in more detail.

Any correspondence including comments, corrections and suggestions, should be addressed to the Chief Medical Scientist.

Updates of users' guide

The H&I users' manual is available on the Beaumont Hospital website at: www.beaumont.ie in pdf format.

It is planned to produce a new print version of the guide every 2 years, or as required.

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Content

1. How to contact the H&I Department and National Transplant Coordinators
2. Introduction
3. HLA antigens
4. Graft rejection
5. How to order tests
6. Transportation of specimens to the laboratory
7. Specimen requirements
8. Tests available
9. HLA typing of patients for solid organ transplantation
10. Antibody screening
 - 10.1 General screening
 - 10.2 Specific screening
 - 10.3 Antibody analysis and identification
 - 10.4 Specimen requirements for antibody screening and crossmatching
 - 10.4.1 Cytotoxic antibody samples required from renal/pancreatic patients who are on the transplant waiting list
 - 10.4.2 Cytotoxic antibody samples required from renal/pancreatic patients who are ***not*** on the transplant waiting list
 - 10.4.3 Cardiothoracic patients on either the lung or heart waiting list
11. Solid organ transplant pools work-up
 - 11.1 Renal/Pancreatic patients
 - 11.2 Cardiothoracic patients
 - 11.3 Liver patients
12. Deceased donor work-up and potential recipient list generation
13. Living donor work-up
14. Crossmatching for solid organ transplantation
 - 14.1 Standard NIH (National Institute of Health) microcytotoxicity crossmatch
 - 14.2 Flow cytometry crossmatching
 - 14.3 The interpretation of crossmatch results

- 14.4 IgM positive crossmatches
- 15. Autocrossmatching
- 16. Post-transplant monitoring
 - 16.1 Renal/Pancreatic patients
 - 16.2 Cardiothoracic patients
 - 16.3 Liver patients
- 17. Desensitisation programme
- 18. Acceptable mismatch programme
- 19. Patients for Disease Association
- 20. Patients for HLA-B57 typing
- 21. HLA typing for partners of recipients
- 22. ABO blood group typing
- 23. Matchability scores
- 24. PRA and Pgen
- 25. Out-of-hours services (on-call)
- 26. Data protection act and freedom of information act
- 27. Reports and expected Turn Around Times (TAT)
- 28. Abbreviations used on H&I reports and printouts

1. How to contact the H&I Department and national Transplant Co-ordinators

The postal address of the department is:

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Beaumont Hospital
PO Box 1297
Beaumont Road
Dublin 9
Tel No: (01) 809 2650 or (01) 809 2651
Fax No: (01) 809 2106

Telephone Numbers:

Departmental Secretary (01) 809 3377

Mr Derek O'Neill (01) 809 2661

Chief Medical Scientist

E-mail: derekoneill@beaumont.ie

Laboratory	Serology	(01) 809 2650/2549
	Molecular	(01) 809 3997/3955
	Scientists Office	(01) 809 3238/2960/2100
	Reporting Room	(01) 809 2651/3139/2849
	Antibody Screening	(01) 809 2338/2653

Dr Mary Keogan (01) 809 2652 (Secretary)

Consultant Immunologist

E-mail: marykeogan@beaumont.ie

To contact Dr Keogan out-of-hours please ring the switch at Beaumont Hospital

Tel No: (01) 809 3000/ 837 7755

Chute System to the H&I terminal: 2650

Routine and Urgent service

Laboratory hours are from 8.30am to 4.30pm Monday to Friday.
The laboratory is closed on Saturday, Sunday and Bank Holidays.

On-Call

The Department provides an out-of-hours service 365 days a year and has a mobile phone for contacting the Medical Scientist on duty:

On-call mobile number: 087 2615 112

To speed dial the mobile phone from within Beaumont hospital:

Speed Dial: 70128

Urgent Requests

An urgent service is available. See section 25.

Renal/Pancreatic Transplant Co-ordinators- Beaumont Hospital

Office: (01) 809 2759

Fax: (01) 837 2802

E-mail: transplantcoordinators@beaumont.ie

Ms Phyllis Cunningham

Ms Aileen Coughlan

Ms Andrea Fitzmaurice

Ms Laura Brannigan

Ms Regina Reynolds

To contact the co-ordinators urgently please ring the switch at Beaumont Hospital
Tel No: (01) 809 3000/ 837 7755

Cardiothoracic Transplant Co-ordinators – Mater Hospital

Office: (01) 803 4274

Fax: (01) 803 2985

To contact the co-ordinators urgently please ring the switch at the Mater Misericordiae University Hospital. Tel No: (01) 803 2000

Liver Transplant Co-ordinators – St Vincent’s Hospital

Office: (01) 209 4131

Fax: (01) 221 3407

E-mail: liver.transplant@st-vincent.s.ie

To contact the co-ordinators urgently please ring the switch at St. Vincent’s University Hospital. Tel No: (01) 277 4000

2. Introduction

The National Histocompatibility and Immunogenetics Service for Solid Organ Transplantation (NHISSOT) was set up to provide a nationwide transplant immunology service for solid organ transplantation, including HLA typing and crossmatching donors and recipients for solid organ transplants.

The H&I Department is accredited by CPA (Clinical Pathology Accreditation) UK Ltd, and aims to gain accreditation by EFI (European Federation for Immunogenetics) in the near future.

The H&I Department is committed to providing and maintaining a service of the highest quality by strictly adhering to policies and procedures that are in place to ensure standards are being maintained.

We actively participate in well established external and internal quality control programmes to ensure best practice is being followed and we are continuously implementing ways to improve the service.

We continually assess and validate new assays and techniques to provide the best level of service for our patients and we also have an active training and educational programme.

This Users' guide is intended as a guide to the services and tests available in the H&I Department. It provides details of the tests available, their specimen requirements, as well as appropriate background information.

3. HLA antigens

HLA (Human Leucocyte Antigen) typing refers to the techniques for identifying the 'tissue type' of a patient. A person's tissue type is defined by the presence or absence of different antigens or 'markers' on their cell surfaces. In solid organ transplantation the major HLA antigens involved are HLA-A, HLA-B, HLA-DR and HLA-DQ. However, HLA-C and HLA-DP may also be relevant.

HLA-A, HLA-B and HLA-C (Class I) antigens are found on all nucleated cells in the body including all the tissues in the kidney, heart, lung and liver and on platelets.

The HLA-DR, HLA-DP and HLA-DQ (Class II) antigens are normally present on a more restricted range of cells in the body. These cells include B cells, macrophages, activated T Cells and endothelium. HLA class II expression can be induced on cells, which do not normally express these molecules during infections and episodes of inflammation including during organ reperfusion.

The mismatches between the donor tissue type and the recipient tissue type are a major stimulus leading to the patient's immune system recognising the 'foreign tissue' and rejecting the transplanted organ. While HLA mismatches provoke a very strong immune stimulus, other differences between donor and recipient can also stimulate a clinically relevant immune response.

One such clinically relevant non-HLA system is the MICA antigen (MHC class I related chain A), which is expressed on epithelial cells in response to stress. MICA is recognised by specific antibodies in sera of transplanted patients and this suggests the MICA may be a target molecule in rejection. It may be involved in allograft rejection by activating both the antibody-mediated and cellular mechanisms.

Following a blood transfusion, pregnancy or a failed graft, patients can develop antibodies to HLA antigens. If patients receive an organ bearing HLA antigens to which they have preformed antibodies, they will lose

the organ due to hyperacute rejection. These antibodies complicate finding a suitable organ for the recipient and hence a major focus of the H&I department is active antibody screening and identification.

The H&I Department tissue types all patients and donors to provide information about how closely matched donor organs and recipients are. More importantly this allows us to ensure that recipients do not receive an organ to which they have made antibodies.

4. Graft rejection

Transplant rejection occurs when the recipient's immune system attacks the transplanted organ. This is because the immune system can recognise the transplant as foreign and attempts to destroy it. The immune response during rejection is mediated through T cell mediated and humoral immune (antibodies) mechanisms. There are four categories of rejection: Hyperacute, acute humoral rejection, acute cellular rejection and chronic allograft dysfunction (or chronic allograft nephropathy in the case of renal transplantation). Chronic allograft dysfunction may result from both immunological and non-immunological insults to the transplanted organ.

Hyperacute rejection is a rapid process which occurs immediately following transplant. It is mediated by pre-formed antibodies that react with many different antigens expressed on the transplanted organ. The result of hyperacute rejection is rapid destruction of the transplanted organ which must be removed immediately to prevent a severe inflammatory response.

Acute humoral rejection (AHR) typically occurs in the sensitised patient and its onset is usually a few days to 4 weeks after transplant. Occasionally AHR can result in delayed graft function. AHR may be seen in non-sensitised patients due to *de novo* production of donor specific antibodies post transplant. In this case the onset is usually later (3 to 6 weeks) and the rise in creatinine (in renal transplants) is less dramatic than that seen in sensitised patients. Early diagnosis is essential as aggressive treatment with plasma exchange to remove donor specific antibodies can salvage the graft in >80% of cases, although long term graft outcome is usually significantly compromised.

Acute cellular rejection can occur at almost any time, usually from 1 week to 6 months post transplant. With the development of powerful immunosuppressive drugs the incidence of acute rejection has been greatly reduced. This form of rejection is usually readily reversed with a

steroid boost, although occasionally steroid resistant rejection requires more intensive immunosuppression.

Chronic allograft dysfunction can occur from 6 months to many years post transplant. In renal transplantation it is characterised by progressive deterioration of graft function, proteinuria and specific histological appearances. Recent data has shown that post transplant production of donor specific antibodies is associated with an earlier onset of chronic allograft dysfunction. Demonstration of complement deposition in these grafts indicates that antibodies are involved in damaging the graft, at least in a large proportion of patients. Unfortunately there are no effective treatments for this form of graft injury, which is the commonest cause of graft failure seen in patients who require a second renal transplant.

5. How to order tests

The department offers a national service. As renal patients can move between different dialysis centres around the country, accurate labelling of patients' samples is very important. **The standard required by the H&I department is name and date of birth on all specimens received and date the sample was taken.**

1. For patients to be HLA typed and HLA antibody screened a request form **must** accompany the specimens. Specimens **can only be processed if both specimen and form are identified with the patient's name and date of birth.** These details must be legible on both request form and bottle, and must correspond with each other. For Beaumont Hospital patients, the information is automatically generated on the specimen label by the Beaumont Hospital Information System (BHIS) but a request form **must** accompany the specimens.

The request form must be fully completed including all patient's details, sample date, blood transfusion history, pregnancies and the Consultant's name and hospital to which the report should be returned.

For renal patients, the request forms must be signed by the patient and the medical person ordering the test.

It is the responsibility of the requesting clinician to ensure that the patient has read and understood the permission statement on the request form and that this is initialled by the patient. For more information on the permission statement please contact the laboratory.

Request forms for HLA typing and HLA antibody screening are available from the department and can be supplied to dialysis centres around the country.

2. Patients for antibody screening only (Cytotoxic antibodies) must meet the same standards of identification.

Note: For virology testing the referring hospital/consultant must organise samples to be taken and sent for virology testing with the NHISSOT renal transplant virology work-up request form. The H&I Department no longer send samples for virology testing

6. Transportation of specimens to the laboratory

It is essential that all specimens are transported to the laboratory under conditions which:

- Comply with the Hospital Safety Statement, as well as relevant National Postal, Health and Safety legislation and IATA regulations.
- Protect postal workers, couriers, porters and laboratory staff.
- Ensure the integrity of the sample to be processed.

Specimens where the external surface is contaminated with blood or other body fluids should not be submitted – another specimen should be collected. If a specimen arrives in a condition which places staff at risk, it will not be processed and the relevant unit will be notified for a repeat sample to be taken.

Within the hospital

- All specimens for H&I must be individually bagged in biohazard bags.
- Request forms must be kept separate to the samples but placed in the pouch on the outside of the biohazard bag.
- Specimens may be sent via the Chute System to the H&I terminal (2650).

From outside the hospital

- All samples being sent to the H&I Department must be placed in mailing containers. The mailing containers must then be placed into biohazard bags. These are then placed in special mailing boxes. These mailing boxes must comply with current regulations with regard to transportation. Request forms must not be placed inside the biohazard bag but placed in the pouch on the outside of the bag.
- Mailing containers, biohazard bags and mailing boxes are all available from the department on request.
- Samples should be addressed to the laboratory and show the senders address.

Please note: Glass specimen tubes are not acceptable due to Health and Safety regulations. Please contact the laboratory for correct specimen tubes to be used.

7. Specimen requirements

Paediatric patients:

HLA Typing	5ml citrated blood
HLA antibody screening	3ml clotted blood

Adult patients:

Test	Specimen required	BHIS ordering code (Beaumont Hospital only)
HLA Typing	20ml citrated blood	HLA
HLA antibody screening	10ml clotted blood	CYTO
Urgent requests De-sens, AMR	10ml clotted blood	PTXAB
HLA-B27	10ml citrated blood	B27
HLA-B57	10ml citrated blood	B57HR
Other disease association work	10ml citrated blood	HLAEXT + letter detailing request
Transplant Processing	10ml citrated blood 10ml clotted blood	TX

8. Tests available

- HLA typing of patients for solid organ transplantation
- Cytotoxic antibody screening
- ELISA/Luminex antibody screening
- Antibody analysis and identification
- Solid organ transplant pool work-up
- Deceased donor work-up
- Potential recipient list
- Living donor work-up
- Crossmatching for solid organ transplants
- Autocrossmatching
- Post transplant monitoring
- Patients for disease association- Beaumont Hospital patients only and GPs in our catchment area
- HLA-B57 typing for antiretroviral treatment – Beaumont Hospital patients only
- HLA typing for partners of recipients
- ABO blood grouping – For patients for solid organ transplantation and potential donors. Blood grouping is carried out in the blood transfusion department

9. HLA typing of patients for solid organ transplantation

All potential recipients are routinely typed by serology and by low resolution molecular techniques for HLA-A, HLA-B, HLA-DR, and HLA-DQ. These techniques use commercial sera and probes and primer sets selected according to the current standards of EFI.

Note 1: Specimens for HLA typing received into the H&I Department are separated and the DNA stored. The patient is blood grouped and a Specimen Received Report is then issued to the referring unit/consultant. When the transplant evaluation pack for a patient is received in the Transplant Office, HLA typing will be carried out on that patient and a report issued before the patient's appointment at the Transplant Clinic. Additional examinations may be requested at anytime once the DNA is stored.

Exceptions to this protocol are paediatric patients, cardiothoracic patients and liver patients.

1. Serological (Complement dependent cytotoxicity) typing

Patient's lymphocytes are isolated from citrated blood by using commercial immunomagnetic beads for HLA typing by serology. The lymphocytes can then be 'tissue typed' using commercial tissue typing trays.

2. Molecular (DNA) typing

The development of PCR (Polymerase chain reaction) has led to a higher resolution of HLA typing. Patient's DNA is isolated from citrated blood and typed by molecular means using two techniques:

- i. PCR-SSP (sequence specific primers) – these SSP primers consist of allele and group specific

primers that are designed to anneal to specific sequences characteristic of a given allele or group of alleles. If SSP anneal to each of the complementary strands of a target DNA sample, PCR amplification can occur. Amplified products of DNA are visualised by gel electrophoresis

- ii. PCR-SSO (sequence specific oligonucleotides)
 - After PCR amplification the amplicons are denatured to form single stranded DNA which are added to a nylon membrane containing specific SSO probes. The amplicons then hybridise to those probes that contain a complementary target sequence. The amplicon-probe complex is then visualised using a colourmetric reaction and analysed.

HLA-C typing

HLA-C locus typing is performed on all living donors and their potential recipient and deceased donors. In the near future, HLA-C locus typing will be performed on all recipients, but currently this is only performed on recipients by specific request.

HLA-DP typing

HLA-DP locus typing is performed on all living donors and their potential recipient and deceased donors. In the near future, HLA-DP locus typing will be performed on all recipients, but currently, this is only performed on patients by specific request

Anomalous results by molecular techniques are referred for DNA sequencing etc. to the National Histocompatibility and Immunogenetics Reference Laboratory (NHIRL), Irish Blood Transfusion Service (IBTS), National Blood Centre, James's Street, Dublin 8.

Note 2: Patients are HLA typed on two separate occasions to ensure there are no discrepancies between samples.

Note 3: Molecular techniques are generally regarded as being more accurate than serological techniques. However, one limitation is that molecular techniques may not distinguish between null alleles (alleles which are not expressed) and expressed alleles of some HLA antigens. If molecular techniques were used exclusively to type donors, this could result in a patient with an antibody to a HLA antigen not being considered, even when the donor only carried a non-expressed allele. Hence, molecular and serological typing are complementary.

- **Specimen requirements:** 20ml citrated sample

10. Antibody screening

The antibody screening and sample request policies are consistent with the current standards issued by EFI.

All patients for solid organ transplantation are screened for HLA antibodies using various screening techniques.

Note 1: Specimens for Antibody Screening for the transplant pool work-up are separated and the serum stored. A Specimen Received Report is then issued to the referring unit/consultant. When the transplant evaluation pack for a patient is received in the Transplant Office, antibody screening will be scheduled for the patient and a report issued before the patient's appointment at the Transplant Clinic. Additional examinations may be requested at anytime once the serum is stored.

Exceptions to this protocol are cardiothoracic patients and patients already on the waiting list.

10.1 General Screening

All patients are screened by Luminex screen. Luminex screening is a bead-based immunoassay used to qualitatively detect HLA antibodies. Beads coated with HLA antigens are incubated with patient serum, washed, and incubated with detection antibody. Stained beads are analysed on a Luminex machine, which is a modified flow cytometer. The signal intensity from each bead is compared to the signal intensity of each negative control bead to determine if the bead is positive or negative for bound antibody. This technique does not identify specificities.

10.2 Specific Screening

Luminex Single Antigen and ID: These techniques use microbeads coated with purified HLA antigens for antibody detection. Up to 100 different coloured beads may be combined in one suspension for a single test. Following incubation of the serum with the beads, bound antibodies are labelled with a fluorescent conjugate. The Luminex flow analyser detects the fluorescent emission from the beads, and the amount of fluorescence indicates the amount of antibody present.

Lambda Antigen Tray High Definition (LAT-HD) and Class II: These ELISA based assays are used to detect HLA specific Class I and Class II antibodies. The LAT assay presents a series of monospecific HLA Class I and Class II antigens permitting the evaluation of %PRA and antibody specificity of the test sample. The specific binding of antibody from the test sample is detected by spectrophotometry following addition of appropriate enzyme substrate for the development of colour. Qualitative assessment of antibody specificity is performed by analysis of the LAT-HD and Class II reactivity pattern.

Lambda Cell Tray™ (LCT): These commercial trays are used to detect the presence of HLA antibodies by CDC (complement dependent cytotoxicity). Each well on the tray contains HLA typed cells that have been frozen. Patient's serum is incubated with the cells and on addition of complement any antibody present will cause the cells to break down (lysis). Any antibody present can then be characterised.

CDC Screening: This screening technique uses a 30-40 cell T lymphocyte panel by CDC. Reaction patterns can be analysed and any antibody present can then be determined. The PRA (panel reactive antibody level - %) is then calculated. These screens also have a panel of CLL (chronic lymphocytic leukaemia) cells to identify Class II antibodies and autoantibodies.

10.3 Antibody analysis and identification

Once the results from the antibody screens are available, the antibody profile of each patient is then analysed and any unacceptable antibodies are identified.

These unacceptable antibodies are entered onto the patient's transplant pool screening card and into their computer files.

These unacceptable antibodies are entered into our 'unacceptable antigen' computer programme. On creating a potential recipient list, any potential recipient that has an antibody to the transplant organ will be rejected. This reduces a patient's disappointment on being called for transplant and then being rejected due to a positive crossmatch.

Comment:

CDC screening using the cell panel or LCT trays is insensitive and only detects complement fixing antibodies. When present, these antibodies will cause hyperacute rejection if directed against the donor. However, a variety of non-HLA specific antibodies can interfere with these assays giving false positive results.

ELISA and Luminex techniques are more sensitive and detect both complement fixing and non-complement fixing antibodies. It is now well established that donor specific antibodies detected by these techniques indicate a significant risk of acute humoral rejection often resistant to therapy.

10.4 Specimen requirements for antibody screening and crossmatching

10.4.1 Cytotoxic antibody samples required from renal/pancreatic patients who are on the transplant waiting list:

- Patients on the transplant waiting list are screened for HLA antibodies routinely every 3 months
- The department requires a cytotoxic antibody specimen from these patients every December, March, June and September
- CAPD and pre-emptive patients can have the samples taken by their local GP and send them directly to the department by post-see Section 6 for transport requirements
- All patients post transfusion require a clotted sample 14 days post transfusion or as soon as possible thereafter. It is **vital** we receive these samples

Note: The routine 3 monthly samples are essential for screening and crossmatching patients on the waiting list. If we do not have a sample less than 93 days old, the patient will be temporarily suspended until one is received – status ‘TS’ on the monthly waiting lists with a comment ‘Awaiting CYTO’. A 2 week ‘grace period’ is allowed in each of the screening months to allow for specimens in transit to the laboratory.

10.4.2 Cytotoxic antibody samples required from renal/pancreatic patients who are not on the transplant waiting list:

- All patients **not** on the waiting list should have one sample taken annually These will be stored indefinitely when/if these patients are being considered for transplantation
- All patients post transfusion require a clotted sample 14 days post transfusion or as soon as possible thereafter. It is **vital** we receive these samples

10.4.3 Cardiothoracic patients on either the lung or heart waiting list

- Patients identified as positive for HLA antibodies – **Monthly sample**
- Patients with no identified HLA antibodies – **Annual sample**

Post transfusion samples from Cardiothoracic patients on the waiting lists

Because time constraints in cardiothoracic transplants often preclude getting a day of transplant sample, the following schedule applies to ensure that a sample within an acceptable time frame is available for crossmatch

- **Weeks 1 – 4** following transfusion we require a weekly sample
- **Weeks 5 – 16** (4 months) we require a sample every 2 weeks
- Then monthly if antibody positive or annually if antibody negative

Cardiothoracic patients on LVADs/BiVADs or Novalungs

- Weekly samples required unless otherwise notified

Specimen requirements: 10ml clotted sample

11. Solid organ transplant pools work-up

11.1 Renal/Pancreatic patients

Once a patient has been seen at the clinic by the Consultant Surgeon, a transplant pool request authorisation card will be completed by the transplant co-ordinators with all the patient's details and signed by the Surgeon. These forms are then sent to the H&I Department and the patient is put on the transplant waiting list.

On receiving a transplant pool request authorisation card, all the patient's details and relevant information including tissue typing report forms, blood group and antibody screening results are placed in the patient's transplant folder. A transplant pool card will also be completed for each patient. All patients on the waiting list have their own transplant folder and transplant pool card. All information regarding the patient is contained in these folders and cards.

Once a transplant pool request authorisation card has been received into the H&I Department the patient's status will be changed to 'temporarily suspended' until all relevant work is completed. At this time patients will appear on the 'TS' list with a comment 'H&I workup' against their names.

Patients are then 'activated' when all the paper work has been completed and checked and all the appropriate technical work has been completed and checked.

For patients to be activated they must satisfy the following criteria:

- All relevant information must be available including information on pregnancies, transfusions, previous transplants and transplants performed overseas.
- HLA typed twice by serological and molecular techniques.
- Blood group typed twice.

- All relevant archived sera samples and current samples on patient are screened by CDC, ELISA and Luminex (as appropriate).
- Virology results must be up to date i.e. within 12 months of being activated on the waiting list.

Note: When all the immunological work has been completed the patient and their consultant nephrologist will receive a letter from the H&I department informing them that they are active on the transplant list.

11.2 Cardiothoracic patients.

The Cardiothoracic Transplant Co-ordinators in the Mater Hospital inform the H&I Department of patients going on the cardiothoracic transplant waiting lists. Once a week a Medical Scientist and /or the Consultant Immunologist attend the cardiothoracic meeting at the Mater Hospital and specific patients are discussed.

Assessment proceeds over several weeks. During this time the patient is HLA typed twice by serology and molecular techniques and screened for antibodies using ELISA on one specimen and Luminex on another. If positive by either technique, an LCT is performed. A report is issued indicating whether the patient will need a prospective crossmatch or not, if listed.

All the patient's details and relevant information including tissue typing report forms, blood group and antibody screening results are placed in the patient's transplant folder. A transplant pool card will also be completed for each patient. All patients on the waiting list have their own transplant folder and transplant pool card.

11.3 Liver patients

Patients awaiting liver transplantation are HLA typed. Once transplanted a report is issued indicating the risk of GVHD (Graft Versus Host Disease), which is influenced by the matchgrade. This report is faxed to the Transplant Co-ordinators usually within 24 hours of the transplant taking place.

12. Deceased donor work-up and potential recipient list generation

The Transplant Co-ordinator contacts the H&I Department about a potential donor and organise bloods to be taken and sent to the laboratory.

On receiving bloods, the Medical Scientist on duty will:

- HLA type the potential donor by serological and molecular techniques.
- Send a sample to the blood transfusion department for ABO blood grouping.
- Run a match programme and printout suitable recipients.
- A potential recipient list is prepared according to agreed criteria, to include clinically urgent patients, paediatric patients, acceptable mismatched patients, significantly sensitised patients, best HLA-matched patients, potentially suitable patients with rare tissue types (low matchability) and patients waiting for the longest period.
- Review all antibody screening results for each recipient on the potential recipient list.
- Once the Medical Scientist is satisfied that all the potential recipients on the list are suitable, the list is sent to the Transplant Co-ordinator on duty.

13. Living donor work-up

The number of people suffering from end stage renal failure (ESRF) is rapidly rising and a kidney transplant is the treatment of choice for many patients. Approximately 150 renal transplants are performed in Ireland each year, the majority of which are from deceased donors. Deceased donors are those who have been declared brain stem dead.

The Living donor programme was recently re-established in Beaumont Hospital. A kidney from a living donor is the optimal form of transplant. The kidney usually starts working immediately after the operation and the graft survival for a kidney from a living donor is superior to that from a deceased donor. Since family members have a similar genetic makeup the chance of a recipient receiving a well matched kidney is increased. This offers a particular advantage to children and patients who have made HLA antibodies.

What is living donation?

Living donation takes place when a living person donates an organ (or part of an organ) for transplantation to another person. Donation of an organ or part of an organ is only considered after thorough evaluation when the donor is healthy, where the loss of the organ or part of an organ is not deemed to place their longterm health at undue risk, and where the donor understands the process and freely consents to donation.

What organs can come from living donors?

The organ most commonly given by a living donor is the kidney. People usually have two kidneys, and one healthy kidney is sufficient to maintain longterm health. Although not routine in this country, donation of a lobe of a lung, or a lobe of the liver is technically feasible.

What makes a donor suitable?

- **Compatible blood group**

The donor and recipient blood groups must be compatible.

- **Compatible tissue type**

HLA antigens determine a person's tissue type. Half of these are inherited from the mother and half from the father therefore; blood relatives are more likely to have a similar tissue type. A brother and sister have a one in four chance of having an identical type.

We look at six different HLA antigens for matching (HLA-A, -B, -C, -DR, -DQ, -DP) and the best compatibility between donor and recipient is a six loci match.

- **Antibody screening**

All potential recipients for living donation are screened for antibodies so any unacceptable antigens that are on the potential kidney are identified and the potential donors can be eliminated at the first stage of living donor work-up, if these antibodies pose a risk to the graft.

- **Negative crossmatch**

A crossmatch is carried out to ensure that the recipient has no antibodies directed against the potential donor kidney. Cells, obtained from a blood sample from the potential donor, are incubated with recipient's serum and if there are any antibodies directed against any antigen on the kidney they will cause a positive crossmatch rendering the organ unsuitable for transplant.

If the crossmatch is negative, there are no antibodies present against the donor kidney and the donor is considered immunologically suitable for that recipient. However many other factors are also considered in determining the potential suitability of the donor.

- **Virology**

To ensure the potential donor does not have any viruses that may be harmful to the recipient, virology screening is carried out at an early stage in the process.

The potential donor's blood will be screened for the presence of antibodies to viruses including the following; Hepatitis B, Hepatitis C and HIV. If any of these viruses are detected the transplant cannot proceed.

Summary of stages for Living Donor work-up

Note: Families willing to donate **must** contact the Transplant Co-ordinators to arrange a suitable time for samples to be taken. Any samples received into the laboratory **will not be processed** without prior contact with the Transplant Co-ordinators.

- **First live donor work-up**

We require 20ml citrated sample from the potential donors for blood group and tissue typing.

If the blood group and tissue type prove to be compatible it is possible to proceed to the second live donor work-up.

- **Second live donor work-up**

We require 60ml citrated sample, 20ml clotted sample and a signed virology consent form for virology screening from the potential donor. A repeat blood group and tissue type is carried out and a crossmatch using the potential donor's cells and recipient's sera. If the crossmatch is negative it is possible to proceed to the third and final work-up.

- **Third and final live donor work-up**

We require 60ml citrated sample, 20ml clotted sample and a re-signed virology consent form for virology screening from the potential donor. A repeat blood group, tissue type and a final crossmatch is carried out.

Reporting

Reports for the first and second work-up are issued to the Transplant Co-ordinator and the final work-up sent to the Consultant Surgeon and Transplant Co-ordinator.

Note: Results cannot be transmitted directly to the potential recipient's Nephrologists or dialysis centre.

14. Crossmatching for solid organ transplantation

The purpose of the crossmatch assay is to detect any recipient antibody which is reactive against the HLA antigens of a potential donor. Lymphocytes (white blood cells), extracted from donor lymph nodes/spleen are used for these assays. In the case of living donors peripheral blood lymphocytes are used.

The crossmatch assays are generally performed prior to the transplantation in order to ensure that there is no detectable antibody mediated sensitisation of the recipient to the donor. Multiple sera of a potential recipient including a recent serum and several 'historic' samples (usually with raised PRA) are normally tested. Because there are multiple methods which can be used and each has its unique clinical application, we provide a narrative interpretation of the assays for the clinician. The Consultant Immunologist and the Medical Scientist on duty are available on a 24 hour basis for telephone consultation.

14.1 Standard NIH (National Institute of Health) microcytotoxicity crossmatch

This is the standard crossmatch, based on complement-mediated cytotoxicity (cell death). The basic crossmatch is performed using a mixed lymphocyte preparation extracted from donor lymph nodes. In addition, crossmatches using donor B cells and donor T cells are also performed to detect recipient class I and/or class II antibodies directed against the donor antigens. In this assay patients' sera is incubated with donor cells. Complement is then added and any antibody present in the patient's serum directed against the donor HLA antigens will cause lysis (break down) of the cells resulting in a positive crossmatch. No antibodies present against the donor antigens, the cells remain intact and the crossmatch is negative.

In order to categorise the immunoglobulin class of any antibody reacting with the donor cells the serum is treated with DTT

(Dithiothreitol) to destroy all IgM antibodies rendering crossmatches negative if IgM is the only specific antibody present.

14.2 Flow cytometry crossmatching

The flow crossmatch is a more sensitive technique than cytotoxic crossmatch assays. It can detect HLA class I and /or class II donor specific IgG antibodies. It can also detect non-complement fixing antibodies, which can go undetected in the cytotoxic crossmatch, and very low titre (strength) antibodies. In this assay patient's serum is incubated with donor lymphocytes. The cells are then stained with fluorescent dyes that detect human IgG antibodies, T cells and B cells. The cells are then analysed by a fluorescence activated cell sorter for the presence of anti-donor antibodies.

Flow cytometry crossmatching is poorly standardised between laboratories and great care must be used when interpreting published data. In Beaumont, we have clinically validated our technique and cut-offs and, in our hands, a positive flow cytometry cut-off indicates a 90% positive predictive value for acute humoral rejection.

14.3 The interpretation of crossmatch results

Transplanting an organ into a patient who has circulating complement-fixing antibodies to donor HLA antigens would result in hyperacute rejection and immediate loss of the organ.

Transplantation where donor specific non-complement-fixing antibodies are present is associated with acute humoral rejection and a high risk of graft loss. The crossmatch prior to transplantation will detect any anti-donor antibodies and thus prevent hyperacute rejection, and greatly reduce acute humoral rejection.

The standard cell preparations used for crossmatching are as follows:

- Mixed T&B cell preparations.
- T cell preparation.
- B cell preparation.

The antigens found on the different cell types are as follows:

- T cells - HLA Class I antigens, autoantigens and various T cell markers.
- B cells – HLA Class I and HLA Class II antigens, autoantigens and various B cell markers.

Therefore, HLA Class I antibodies should be T and B cell positive and HLA Class II antibodies should be B cell positive only.

B cells are also positive for HLA class I antigens and indeed express class I antigens more strongly than T cells. Hence they are more sensitive than T cells in detecting low levels of HLA Class I antibodies. This can complicate interpretation of B cell positive crossmatches.

The crossmatch uses a selection of both current and historical sera in the crossmatch for the following reasons:

- Historical antibodies are important because they indicate sensitisation (exposure) of the patient to the donor antigens and hence the presence of memory T and B cells which can lead to rapid immunological responses in a patient if challenged with the same antigen again.
- Current antibodies are important because if they are directed against HLA antigens present on the graft they will cause hyperacute rejection of the organ, or an acute humoral rejection.

Please note:

- **It must be stressed that all crossmatch interpretation should be done in consultation with the H&I staff and the Consultant Immunologist.**
- **All positive crossmatches are discussed by the Medical Scientist on duty with the Consultant Immunologist.**
- **For positive crossmatches, the Consultant Immunologist may advise that from an immunological point of view, it is reasonable to proceed with the transplant, taking the sensitisation history and antibody screening profile of the patient into account, and/or may request additional screening/crossmatching before proceeding with the transplant**
- **Occasionally, particularly in cardiothoracic transplantation, in discussion with the Surgeon, it may be appropriate to transplant with a borderline or weakly positive crossmatch using antibody removal techniques or other forms of augmented immunosuppression.**

14.4 IgM positive crossmatches

These are particularly complicated given that autoreactive antibodies, sensitisation episodes and medical history are all involved in their interpretation. These IgM antibodies are often not a contraindication to successful transplantation. An interpretive report will be issued verbally and in writing

indicating whether these antibodies are deemed clinically relevant or not.

15. Autocrossmatching

This assay involves a crossmatch of the recipient's lymphocytes with autologous (own) serum, and is done to identify any self-reactive antibodies which may have developed due to an autoimmune disorder, viral infection, SLE, connective tissue diseases and/or certain medications.

There are a number of variants on the autocrossmatch assay which can help determine the nature of the antibody. Knowledge of the presence and type of autoantibody can be extremely helpful in interpreting positive crossmatches and ensuring that patients do not miss out on potentially suitable organs due to false positive crossmatches.

Specimen requirements: 10ml clotted sample
10ml citrated sample for CDC
autocrossmatch only
60ml citrated samples for flow
autocrossmatch

16. Post-transplant monitoring

16.1 Renal/Pancreatic patients

The Department requires a clotted sample for antibody screening weekly for four weeks following transplant from all patients and twice weekly from highly sensitised patients. A clotted sample should also be sent routinely when any post-transplant patient is admitted to hospital for investigations. This enables us to detect any antibodies that develop during rejection episodes and is essential for evaluation and crossmatching should the patient require another graft at some time in the future.

Samples should be taken monthly until three months post transplant, then quarterly up to one year, then annually.

Specimen requirements:

- Clotted sample weekly for 4 weeks post transplant.
- Clotted sample twice weekly for 4 weeks post transplant for highly sensitised patients.
- Clotted sample monthly until 3 months post transplant.
- Clotted sample quarterly up to one year post transplant.
- Clotted sample once a year post transplant.
- Clotted sample taken routinely on admission to hospital.

Note: At present we do not have sufficient staff to process these samples however we hope to address this when our service plan is considered by the HSE. However in patients who require re-transplant, availability of these specimens is essential to fully evaluate them. Where antibody mediated rejection is suspected clinically, the patient should be discussed with the Consultant Immunologist and samples ordered using the mnemonic PTXAB, or if outside Beaumont Hospital the term URGENT should be used.

16.2 Cardiothoracic patients

- A clotted sample should be taken at any time when a biopsy is being performed (both protocol biopsies and biopsies performed to assess possible rejection). Thereafter a clotted sample is desirable when the patient routinely presents at clinic (every few months in the first year and yearly thereafter).
- Antibody screening is performed on all post transplant sera taken at one month and as close as possible to three months, or at known rejection episodes.

The Consultant Immunologist is notified immediately of any new or increased positivity and a post transplant antibody report is sent to the Cardiothoracic Consultant.

- **Specimen requirements:** 10ml clotted sample.

16.3 Liver patients

When white blood cells from the donor liver react to the recipient's tissues, they may destroy them. This is known as graft versus host disease (GVHD) and can pose significant risks to liver transplant patients. Donors homozygous at all HLA loci carry a higher risk for GVHD. Diagnosis of patients with suspected GVHD can be confirmed by the demonstration of substantial donor lymphocyte chimerism. HLA typing by PCR-SSP on recipient peripheral blood can detect donor HLA antigens. If GVHD is suspected the Consultant Immunologist should be contacted immediately.

- **Specimen requirements:** 10ml citrated sample.

17. Desensitisation programme

The number of transplants for patients with high levels of HLA antibodies (PRA >80%) is low due to the difficulty in finding a kidney with a negative crossmatch. Kidneys transplanted across a positive crossmatch have very poor graft survival and increased risk of hyperacute rejection.

Desensitisation programmes have been set up in a number of transplant units world wide to reduce and/or eliminate donor specific antibodies (DSA) so the risk of rejection post transplant is decreased.

A programme was initiated on a compassionate basis in 2003 using plasmapheresis, intravenous immunoglobulin and an immunosuppressant to remove circulating antibodies and suppress antibody production.

Despite excellent early results (100% one year graft survival) the medium term results are disappointing. At present a full review is being undertaken to determine the future role, if any, of this approach.

It is essential that patients who have undergone desensitisation continue to have regular post transplant monitoring samples sent, no less frequently than three monthly.

- **Specimen requirements:** 10ml clotted sample.

18. Acceptable mismatch programme

An acceptable mismatch programme is currently being developed. This exploits Single Antigen technology to define 'windows' or HLA antigens to which patients are **not** sensitised. Patients with a Pgen > 95% and waiting > 3 years will be evaluated for windows, and when a donor organ becomes available which is suitable, they will receive additional priority on the potential recipient list. In time the 3 year period will be reduced and finally removed totally as historic (stored) samples are evaluated by single antigen technology.

No separate referral is needed, as patients fulfilling criteria will be automatically selected.

No change in immunosuppression is required.

19. Patients for Disease Association

Some patients suffer from diseases which have been known to be associated with certain HLA antigens.

We HLA type patients for disease association, in particular B27, from Beaumont Hospital patients only and for GP patients in our catchment area. All disease association typing from outside hospitals is carried out in the NHIRL, IBTS, National Blood Centre, James's Street, Dublin 8.

- **Specimen requirements:** 10ml citrated blood.

20. Patients for HLA-B57 typing

Patients who express a specific allele of HLA-B57 (HLA-B*5701) are at risk of a life-threatening reaction if exposed to abacavir, a useful antiretroviral drug. We HLA type patients who are on or will require antiretroviral treatment for HLA-B57 only. Patients who do not express HLA-B57 are reported as negative. Patients found to be HLA-B57 on low resolution typing have a blood sample referred to the NHIRL for high resolution HLA-B57 typing. In these patients HLA-B57 type is reported at the allelic level.

This test is available for Beaumont Hospital patients only.

- **Specimen requirements:** 10ml citrated blood.

21. HLA typing for partners of recipients

A baby has HLA antigens of which half come from the mother and half from the father. During pregnancy or birth the baby's cells can cross the placenta into the mother's blood and expose the mother to the father's HLA antigens.

Occasionally this can induce an immune response and the mother subsequently can develop HLA antibodies. These antibodies do not harm the baby or the mother, and only become clinically relevant if the mother subsequently requires a transplant.

HLA typing the partner is helpful to identify the antigens the mother has been exposed to or those which may develop in time. This can aid antibody identification and help to build up an antibody profile on a patient.

- **Specimen requirements:** 10ml citrated sample.

22. ABO blood group typing

The Beaumont Hospital Blood Transfusion Department checks all donor and recipient blood groups and issues a printed report to the H&I Department. The technique used by the Transfusion Department is a gel system which utilises the patient's/donor's red cells and serum.

- **Specimen requirements:** 10ml clotted sample.

23. Matchability scores

The H&I Department has a database of over 1,000 HLA types of previous deceased donors from our population. We use this database of donor HLA types to calculate the chance of a patient getting a good match from our donor population.

This data is expressed as a percentage of the population and is made available to the referring clinicians and the Department of Transplantation on the monthly transplant waiting lists. It can be used to accurately discuss the likelihood of a patient getting a very good match, or how unlikely this is, depending on the patient's HLA type.

The scores from over 2,500 patients analysed to date range from below 0.01 to 16% i.e. ranging from 1 in every 10,000 donors to 16 in every 100 donors being a close genetic HLA match. To use the matchability score, you need to know the patient's blood group. If the blood group is B or AB, there are very few donors of these blood groups, and therefore, waiting for a close match is inadvisable.

The UKT (United Kingdom Transplant Service) define a favourable match as:

- 000, 100, 200, 010, 110, 210 (HLA -A, -B, -DR) – Figures represent donor mismatched antigens
- These grafts show a definite survival advantage in most large studies. Additionally, for patients likely to require another transplant in the future, the degree of sensitisation after a well matched graft is usually less than that seen after a poorly matched graft.
- Any DR mismatch negates any advantage of matching at the A or B locus.
- We still list up to 1 DR mismatch as 'reasonably matched' in an effort to reduce future sensitisation.

Defining Matchability

For patients of blood groups A and O:

Score	Reported
5% or under	Low
5.1-7.9%	Medium
8% and over	High

24. PRA and Pgen

PRA - Panel Reactive Antibody

PRA is based on the CDC assay of a panel of lymphocytes and is expressed as a percentage of positive reactions against those lymphocytes.

Reaction against unseparated lymphocytes (mainly T cells) is reported as PRA 1.

Reaction against a panel of CLL cells (mainly B cells) is reported as PRA 2.

Because of changes in technology, and the limitations of PRA as a measure of transplantability, the term PRA as determined above is falling into disuse.

Pgen - Generated or calculated PRA

The CDC assay is very insensitive in detecting all HLA antibodies and does not detect non-complement fixing antibodies. With the introduction of new assays such as ELISA and particularly Luminex, more significant antibodies are now being detected by these techniques.

Some patients appeared almost unsensitised from their anti-HLA antibodies based on CDC assays but often were incompatible with 90% of potential donors.

Using our database of donor HLA types, it was possible to calculate how many of these previous donors were unsuitable and we refer to this as generated PRA – Pgen.

The Pgen value is not used to guide immunosuppressive therapy but as an indicator of how difficult it is to find a compatible graft. A

calculated PRA is increasingly being used internationally, and in publications in the transplant literature.

How do we use Pgen?

For renal patients our matching programme is set to list acceptable mismatched patients and significantly sensitised patients with a PRA1, 2 or Pgen of greater than 50% so patients with non-complement fixing antibodies are not disadvantaged.

25. Out of hours services (on-call)

The H&I Department provides an out-of-hours service for solid organ transplantation.

This service is available at all times including nights, weekends, Christmas, etc.

The services available are:

- Tissue typing and crossmatching all potential donors for solid organ transplantation.
- Urgent antibody screening for cardiothoracic patients.
- Urgent antibody screening for post transplant rejection episodes.

Note:

- **All requests for urgent antibody screening out-of-hours must be done in consultation with the Consultant Immunologist/Chief Medical Scientist.**
- During normal working hours urgent requests must be discussed with the Chief Medical Scientist and may also require discussion with the Consultant Immunologist. It is helpful if requests for urgent samples can be made by telephone as early as possible in the day before all members of staff embark on their routine assays.

26. Data protection act and freedom of information act

The H&I Department keeps patient data on its computer system and on a back-up paper system. All data is stored in compliance with data protection legislation to protect patients' confidentiality.

The data held can include some or all of the following, where relevant:

- Name.
- Hospital chart numbers.
- Date of birth.
- Address.
- Phone number(s).
- Email address
- Dates of dialysis.
- Type of dialysis.
- Dates of transfusions.
- Dates of sera samples received.
- Antibody screening information and results.
- HLA type.
- Molecular DNA typing information.
- Blood group.
- Number of pregnancies.
- Virology results on potential recipients.
- Related donor information, where patients have been transplanted.
- Related family information, where a family study has been performed.
- Partner's HLA type where applicable.

27. Reports and Turn Around Times

The following reports are issued regularly by the department:

1. HLA typing report.

2. H&I transplant pool work-up report.

This includes the HLA type, blood group, antibody screening and virology results. Issued to the Transplant Co-ordinators and the referring Nephrologist.

3. Cardiothoracic patient reports.

This includes the HLA type, blood group, antibody screening results, generated PRA and crossmatch recommendations. Generated and issued to the Transplant Co-ordinators. Post transplant antibody screening reports are issued routinely to the Post Transplant Co-ordinators following receipt of screening samples.

4. Potential recipient listing.

Issued to the Transplant Co-ordinators and/or Surgical Consultant/registrar following work-up on a donor. The report categorises the potential recipients as *ABO/SPK/PTX, paediatric patients, acceptable mismatched patients, significantly sensitised patients, favourable matched/best HLA matched patients, low matchability scoring patients, and longest waiting patients.*

5. Renal/pancreatic crossmatch report.

Issued to the Consultant Surgeon following donor/recipient crossmatch.

6. Cardiothoracic crossmatch report.

Issued to the Consultant Surgeon following donor/recipient crossmatch.

7. Post transplant matching reports for liver recipients.

This includes the recipient's HLA type, blood group and donor details including HLA type, mismatch and risk of GVHD. Issued to the Liver Transplant Co-ordinators following transplantation.

8. Living donor reports for renal transplantation.

- 1st workup - all family members HLA typed and blood group. Potential donors identified.
- 2nd workup - Immunological compatibility confirmed.
- 3rd work-up - Final crossmatch report.

Issued to the Transplant Co-ordinators only.

9. Renal/pancreatic transplant pool(s).

- Active list.
- Suspended list.
- Imminent temporary suspended list.
- Temporary suspended list

10. Transplant pool listings generated monthly:

- Full listing of all patients.
- Centre specific or combined (on request).
- Consultant specific.

11. Donor reports

Issued to UKT (United Kingdom Transplant) and the Irish Renal Registry for data analysis and statistical reasons.

12. Renal/pancreatic transplant service statistics

Generated and issued monthly.

13. Antibody analysis and matchability report

Issued to all centres and the Transplant Co-ordinators on request

14. Requests for antibody screening samples

Issued weekly for:

- Renal/pancreatic patients.
- Cardiothoracic patients.

Turn around times

TESTS	TURN AROUND TIMES
HLA typing for solid organ transplants	3 weeks - <i>Urgent service available</i>
HLA antibody screening	2 – 4 weeks - <i>Urgent service available</i>
<i>HLA antibody screening and HLA typing requests for emergency transplantation</i>	<i>Same day service</i>
Transplant pool work-up	2 – 6 weeks
Deceased donor work-up	Immediately
Potential recipient list	Immediately
Crossmatching for solid organ transplants	Immediately
Living donor work-up	1 - 4 weeks Same day service for final work-up
Autocrossmatching	2-3 days
Post transplant monitoring	2 days (on request)
<i>Post transplant monitoring – Urgent antibody screening request for query graft rejection</i>	<i>Same day service</i>
HLA typing for disease association	3 weeks
HLA typing for B57	3 weeks
HLA typing for partners	3 weeks
ABO blood grouping	2-3 hours

28. Abbreviations used on H&I reports and printouts

Centres

AM	Antrim Area Hospital
BE	Beacon Clinic, Dublin
BF	Belfast City Hospital
BH	Beaumont Hospital, Dublin
CA	Cavan General Hospital
CB	Mayo General Hospital, Castlebar
CO	Cork University Hospital
CR	Our Lady's Hospital for Sick Children, Crumlin, Dublin
EU	Patients dialysing in hospitals overseas within the EU
GA	Merlin Park Hospital, Galway
GW	Wellstone Clinic, Galway
JA	St. James's Hospital, Dublin
KK	Wellstone Clinic, Kilkenny
LE	Letterkenny General Hospital
LI	Midwestern Regional Hospital, Limerick
MA	Mater Misericordiae University Hospital, Dublin
NC	Northern Cross Clinic, Dublin
NE	Daisy Hill Hospital, Newry
OS	Patients dialysing overseas – outside the EU zone
SL	Sligo General Hospital
SV	St. Vincent's University Hospital, Dublin
TA	Tallaght Hospital (AMANCH), Dublin
TE	Children's University Hospital, Temple Street, Dublin
TR	Tralee General Hospital
TU	Tullamore General Hospital
UK	Patients dialysing in hospitals within the United Kingdom
WA	Waterford Regional Hospital

Patient category abbreviations for Renal/Pancreatic Lists

ABO	First available crossmatch negative ABO compatible kidney (highest urgency)
HX	Patients awaiting a combined heart and kidney transplant
LX	Patients awaiting a combined liver and kidney transplant
PED	Paediatric patients
PTX	Patients awaiting a pancreas transplant only
RO	Routine
SPK	Patients awaiting a simultaneous pancreas and kidney transplant
NX	Retrospective crossmatch required

Renal/Pancreatic transplant pool printout abbreviations

AGE	Age in years
CAT	Patient category: (see separate listing above)
CMV	Known positive CMV (Cytomegalovirus) patients indicated by a '+'
CTR	Dialysis centre (see separate listing)
DIAL	Dialysis type: P = CAPD/CCPD H = Haemodialysis
EL Pos or Neg	ELISA/Luminex antibody screening results i.e.
FAV	Matchability score
GRP	Blood Group

HCV	Known positive HCV (Hepatitis C virus) patients indicated by a '+'
KG	Weight in kilos
PGEN	Generated PRA
PRA 1	Peak Class I panel reactive antibody level
PRA 2	Peak Class I and Class II panel reactive antibody levels
TX	Previous transplant(s): Number is printed
WAIT	Length of time on transplant pool in months

Crossmatch codes

DoTx	Day of transplant sample required
Std	Standard – sample(s) available in the laboratory and suitable for crossmatch
NX	Retrospective crossmatch

Virology/ Disease screening codes

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency virus
CMV	Cytomegalovirus
EBV	Epstein Barr virus
HSV	Herpes Simplex virus
VZV	Varicella Zoster virus
HTLV	Human T Lymphocyte virus
TOX	Toxoplasmosis
SYPH	Syphilis