Chapter 10

Histocompatibility Testing

Change record

Date	Author	Version	Change reference
24-04-2023	C.S.M. Kramer	5.2	§10.2.2: added HML without DQA and/or DP are accepted. §10.3.1: changed CDC screening cell requirements to representation of ET donor population §10.4: updated according to vXM as of April 24th 2023 §10.5.1: added information on DQA and/or DP unacceptable antigens for AM program inclusion §10.6.1: added EPT typing must be performed as donor HLA typing on 11 loci
16-03-2023	C.S.M. Kramer	5.1	§ 10.3.3: clarified information unacceptable HLA antigens for ETHAS patients §10.4.1: added information on CIWD genotype and generated/adjusted full phenotype for virtual crossmatch §10.5 textual corrections
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15-10-2020	S. Heidt	4.7	§ 10.4: mandatory reporting of crossmatch results § 10.5.1: HLA typing of child(ren) and/or father of children for female AM program candidate
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20-11-2018	S. Heidt	4.5	§10.4: typo CSDc corrected to CDC §10.5.1: details on AM program inclusion further clarified, and future changes highlighted.
19-09-2017	S. Heidt	4.4	§10.3.1: Clarified information on when autologous crossmatches must be performed §10.4.1: Clarified information on the use of the B cell crossmatch at donor centers §10.5.1: details on AM program inclusion clarified
20-06-2017	S. Heidt	4.3	§10.3.3: Updated information on how unacceptable antigens should be entered (split or broad)

02-05-2017	S. Heidt	4.2	§10.2.1: HLA typing after stem cell transplantation for patients awaiting a solid organ §10.2.2: 'Patients with uncommon HLA type' added §10.3: annual screening patients awaiting non-renal organ §10.4.7: preference for barcodes added §10.5.3: corrected 'blood group compatible' to 'ET blood group compatible'. Description of use of minimal match criteria in AM program updated
16-11-2016	J. de Boer	4.1	Erratum outdated screening (§10.3)
04-08-2016	S. Heidt	4.1	Paragraph 10.4.5: 'retyping of the donor must be performed' changed into 'should be performed'
21-06-2016	S. Heidt	4.0	Major textual adjustments, §10.2.2 and 10.6.5 added
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10-03-2012	I. Doxiadis	1.0	

The Eurotransplant Manual contains the rules and regulations for the implementation and specification of national legislation and national guidelines for waiting list management, organ procurement and allocation. It has been prepared with the best of knowledge and the utmost care. In case of discrepancies between the content of this manual and national binding provisions, the following applies:

- Insofar provisions about the acceptance of organ recipients to the waiting list are concerned, this manual has only an informative character. Only the national provisions which are applicable for the transplant centers are relevant and legally binding.
- For the allocation of organs only the national provisions are legally binding. The display of the allocation provisions in this Manual are based on these legally binding national provisions. As far as necessary, they have been specified by Eurotransplant in this Manual. Deviations from such specifying Eurotransplant provisions cannot be considered as a breach of the national provisions as long as the latter are not violated. Eurotransplant cannot be held liable for a potentially wrongful description in this Manual of procedures, in connection with the organ allocation, as long as the actual allocation follows national provisions.

Chapter 10 – Histocompatibility Testing Table of Contents

10.1. General

All Tissue Typing Centers (TTC) providing and/or handling histocompatibility data and participating in the framework of Eurotransplant (ET) must have a valid accreditation of the European Federation for Immunogenetics (EFI) or the American Society for Histocompatibility and Immunogenetics (ASHI) and participate in the External Proficiency Testing scheme of Eurotransplant without any sample selection.

The Standards for Histocompatibility Testing of EFI in their latest valid version apply for all described procedures unless stated otherwise in the present manual.

The recommendations released by ET regarding histocompatibility testing, screening, and crossmatching must be followed after approval by the respective national authorities.
Within ET the official WHO HLA nomenclature is used, as indicated in the latest nomenclature report. For allocation purposes "matching determinants" are generated by the different ET matching algorithms from the reported HLA typing data of recipients and donors according to the Eurotransplant HLA tables published on the ETRL website (https://etrl.eurotransplant.org/resources/new-hla-tables/).

The TTC is responsible for the accuracy, reliability, and consistency of all relevant histocompatibility data of their recipients and donors reported to ET. They must follow the written and valid Standard Operation Procedures (SOP) released by the laboratory to meet the requirements of the ET Manual and the EFI Standards.

The Eurotransplant Reference Laboratory (ETRL) is an integral part of ET with the following duties and responsibilities:

- Organize and oversee all ET EPT exercises and release of an annual report and annual certificates.
- Provide expertise and practical aid in the area of histocompatibility testing to ET-affiliated TTC including a 24 hours / 7 days a week on call service for immunological questions regarding organ allocation in general and allocation of organs through the Acceptable Mismatch (AM) program in particular.
- Help ET-affiliated TTC in defining acceptable mismatches for recipients awaiting a renal transplant and review every application for recipients to enter the AM Program. Decide on whether a patient is eligible to participate in the AM program based on transparent and uniform criteria.
- Visit TTC and help in solving histocompatibility related problems.
- Organize the annual ET Tissue Typers Meeting and other meetings relevant to the Tissue Typers community within ET.
- Provide chair and secretary to ET Tissue Typing Advisory Committee (TTAC).

10.1.1 Registration of transplant recipients

Relevant histocompatibility and immunological data of all potential organ recipients are registered centrally in the Eurotransplant Network Information System (ENISNext).

To avoid clerical errors, only trained personnel are authorized to report the results of HLA typing and screening to ENISNext, preferably via the TTC of the recipient and preferably by electronic communication. The local TTC is responsible for correct transmission of the results of HLA typing and antibody screening.

10.1.2 Material for histocompatibility testing

Prior to entering a recipient on the waiting list for organ transplantation, HLA typing and a screening for HLA-specific antibodies must be performed for kidney, pancreas, combined kidney/pancreas, intestine, heart, lung and should be done for liver. Every potential transplant recipient should be HLA typed on two separate occasions using two different samples.
The TTC affiliated to the transplant center should have standard policies on the requirements of samples for performing HLA typing and antibody screening and on the tests to be performed for a recipient before entering the waiting list.
In general, all required material must be sent to the TTC affiliated to the transplant center where a recipient is registered. The samples must be labeled according to the EFI Standards. The samples must be accompanied by the necessary administrative information (immunizing events: transfusions, pregnancies, previous transplants). An up-to-date listing of the TTC affiliated to ET is available at the ET office.

Typing for organ donors and physical crossmatching must follow the SOP released by the TTC, following the recommendations of ET and EFI. All immunologically relevant data (i.e., HLA typing, crossmatch and screening data) reported to ET must be controlled for clerical errors. Every mistake or inconsistency must be reported immediately for correction to ET.

10.2. Typing for HLA

10.2.1 Minimum requirements for HLA typing of recipients

Every recipient must be typed for HLA-A, -B, -C, -DR, and -DQ using DNA based typing. Preferentially, every recipient should be typed for 11 loci (HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, -DPA1) by DNA typing. The HLA typing of recipient must be registered in ENISNext. For patients with allele-specific antibodies, second field unambiguous typing for the respective locus/loci is preferred.

In case of suspected homozygosity, a family typing or molecular typing must be performed to confirm homozygosity. Extended DNA typing is also accepted for the definition of homozygosity. In case of confirmed homozygosity, the homozygous antigen must be entered in duplicate.

The minimum requirement for HLA typing for recipients to be communicated to ET is at the ET match determinant level, as described in HLA tables (10.7 addendum). HLA alleles, as determined by DNA typing, can also be reported to ET, as long as the alleles are present in the Eurotransplant HLA Tables. In cases where there are no serological equivalents defined, the most probable serological equivalent of a DNA typing result should be given (e.g., C*12 is translated to Cw12). For HLA-DQA, -DPB, -DPA the conversion of HLA alleles to ET match determinants are based on serotypes as described by Osoegawa *et al.* HLA 2022;100(3):193-231. Entering of Bw4/Bw6 must be done on basis of HLA-B antigens only.

The HLA typing provided is translated to “matching determinants” by the different ET matching algorithms for allocation purposes.

In case of stem cell transplantation before organ transplantation, a new HLA typing and AB0 blood group typing should be performed.

10.2.2 Minimum requirements for HLA typing of donors

Every donor must be DNA typed for HLA-A, -B, -C, -DRB1/3/4/5, -DQB1, -DQA1,-DPB1 and -DPA1 at intermediate resolution (minimum second field level with ambiguities). HLA typing data of the donor must be reported directly to ET by uploading an HML (histoimmunogenetics markup language) file to the ET immunology service.

Providing ET with this level of HLA typing is required for the virtual crossmatch. In rare cases no HML can be uploaded, or rejection of the HML file by the immunology service, the full HLA typing (match determinants) of donors must be entered manually which will be used for the virtual crossmatch. In exceptional cases HLA-DQA1, -DPB1, and/or -DPA1 are not present in HML file due to technical reasons. The immunology service validation will accept files lacking information on the loci.

The donor HLA typing provided is translated to "matching determinants" by the different ET matching algorithms for allocation purposes.

10.2.3 HLA retyping of donor samples

From EPT data, it is known that the error rate in HLA typing is around 1.5% (period 2018-2022). To prevent an organ to be transplanted on the basis of erroneous HLA data, retyping of all donors by the recipient center is recommended. In case of a discrepant HLA typing, the recipient center must report to ET, upon which the donor center and recipient center are notified and have to come to a consensus HLA type. If no consensus between the two labs is reached, the ETRL is issued to perform the reference typing.

10.3. HLA antibody Screening

Sera from all potential organ recipients should be screened for HLA-specific antibodies at regular time intervals. For potential kidney recipients on the waiting list a screening must be performed every three months, accompanied by a critical review of the unacceptable antigens listed. The screening of sera from potential kidney recipients on the waiting list must be carried out in time to prevent outdated screening (i.e., >180 days in between two antibody screenings), leading to exclusion of the recipient from the allocation list.
For other organs than kidneys, according to the national legislations, recipients should be screened for HLA specific antibodies prior to entering the waiting list, as well as on an annual basis. In addition, further screenings are required after every immunizing event.

A screening for HLA-specific antibodies for all potential organ recipients should be performed at 2 and 4 weeks after every immunizing event, e.g., blood transfusion, transplantation, pregnancy and graft removal. The screening policies must follow the recommendations of the National Bodies, ET, EFI, and the transplant center.

The TTC must check the waiting list with respect to histocompatibility related aspects. The screening is performed by the TTC affiliated to the transplant center where the recipient is registered. The information must be recorded in the recipient file and reported to ENISNext.

The TTC must use solid phase screening methods for the definition of antibodies against HLA class I and HLA class II. A complement dependent cytotoxicity (CDC) screening for HLA specific antibodies must be done at least once a year. For HLA antibody positive sera, the HLA specificities should be reported, and in case these are deemed unacceptable, these unacceptable HLA antigens must be reported. The degree of sensitization will only be determined on basis of the unacceptable antigens registered in ENISNext.

10.3.1 Screening for HLA specific antibodies

The CDC screening for determining the presence of complement fixing antibodies must be done using a panel of HLA typed cells that is representative of the ET donor population. Solid phase screening methods must be used for the definition of antibodies against HLA class I and HLA class II. Unacceptable antigens must be defined, ideally on basis of both CDC screening and solid phase screening data. Upon registering the unacceptable antigens in ENISNext the virtual PRA (vPRA) will be calculated automatically based on these unacceptable antigens, and included in the ENISNext data file. The vPRA is the only parameter to indicate that a patient is sensitized.

In case the patient has unacceptable antigens and has known CDC reactive antibodies at time of registration, or develops these in a subsequent serum sample, an auto-crossmatch should be performed to exclude that CDC reactivity is based on autoantibodies.
The recipient's TTC must update the HLA antibody and unacceptable antigen status of the recipients on the waiting list after every screening and check whether recipients have an outdated screening.

10.3.2 Autoantibodies

The identification of autoantibodies or transplantation irrelevant antibodies must be performed by the TTC. Such antibodies can lead to false positive crossmatches. Therefore, the screening and the auto-crossmatch using the recipient's own cells must be done with and without dithiothreitol (DTT) at least once.

10.3.3 Unacceptable HLA antigens

Unacceptable HLA antigens are HLA antigens that are forbidden as donor HLA mismatches. HLA antigens, towards which the recipient has formed alloantibodies defined with CDC in the current serum must be reported as unacceptable HLA antigens and entered into ENISNext. Both HLA class I and HLA class II specificities can be entered as unacceptable antigens. Depending on the policy of the transplant center, additional specificities can be entered into the unacceptable HLA antigen field. These can be based on historical antibodies against mismatched HLA antigens of the previous organ donor, repeat mismatches, or spousal HLA antigens in case the recipient has been pregnant.

Not all HLA antibody specificities detected by solid phase assays only (CDC negative) are necessarily unacceptable antigens. All plausible antibody specificities detected with solid phase techniques only should be considered a risk factor and can be entered as unacceptable antigens according to the policy of the transplant center (center or patient dependent). A direct link from defined HLA antibody specificities to unacceptable antigens is neither desirable nor possible. Unacceptable antigens should be entered at the split antigen level or on the allele level in case of allele specific HLA antibodies. In case all split antigens from a broad antigen are unacceptable, the broad antigen should be entered as unacceptable. The responsible TTC must confirm every unacceptable HLA antigen separately. From the list of unacceptable antigens, the vPRA value will be automatically calculated within ENISNext.

This value appears in the immunological report of the recipient. The definition of unacceptable HLA antigens must be discussed by the transplant center and the TTC.

For allocation through ETKAS, ESP, or EPAS , no offer will be made if an organ donor expresses unacceptable HLA antigens on allelic or split/broad level (all 11 loci) of a given patient as those patients will be excluded from the match (a synonym of virtual crossmatch positive). For allocation through ETHAS (HE and HELU), patients will be filtered out if an organ donor expresses unacceptable HLA antigens on the split/broad level (all 11 loci) of a given patient. In case an unacceptable antigen is registered at allele level for a thoracic patient, this will be translated back to split/broad level according to the HLA table and as such used in ETHAS (HE and HELU) match. Therefore, it is strongly recommended to register the unacceptable HLA antigens of these patients at split/broad level[1]. For ETHAS (LU) this policy is not yet implemented. This policy is not applicable to allocation through ELAS.

Based on the unacceptable antigens and ABO blood group of a patient, the chance to receive an offer of an ABO identical or -compatible renal transplant can be calculated. There are three calculators based on the blood group; ABO identical, ABO compatible and ABO ET compatible. These Donor Frequency Calculators have been developed by the ETRL (https://etrl.org/) and are also implemented into ENISNext.

10.4. Crossmatch

The crossmatch is an integral step in the decision-making process for organ allocation and transplantation. Both virtual and physical crossmatches are performed. The prerequisite for the virtual crossmatch is the definition of HLA antibody specificities that are deemed to be unacceptable HLA antigens and are to be avoided in the donor's HLA-type.
The physical decisive crossmatch using the recipient serum and lymphocytes or splenocytes of the prospective donor is usually done with the CDC technique. All physical crossmatch results must be communicated to the ET allocation office.

HLA antibody status	Unacceptable antigens defined	vPRA	Decisive crossmatch
No HLA antibodies or only non-complement fixing HLA antibodies	No	0%	Yes (may be retrospective)
	Yes	>0%	Yes
Complement fixing HLA antibodies	Yes	>0%	Yes

Table 10.4. Overview of physical crossmatch rules

[1] In case the donor HLA type is not known at time of the ESP, EPAS, or ETHAS (HE or HELU) match it may be possible that an organ offer is made which harbors antigens that are listed as unacceptable for this patient.

10.4.1 The "allocation" crossmatch: virtual crossmatch

No allocation will be done to a recipient, whose immunological profile shows unacceptable HLA antigens that are present in the HLA phenotype of the donor (positive virtual crossmatch). From the donor typing HML file, the GL-string will be extracted, from which the alleles present in the HLA tables (https://etrl.eurotransplant.org/resources/new-hla-tables/) will be selected (CWID genotype). The CIWD genotype alleles will be compared to unacceptable antigens on allele level, and the generated/adjusted full phenotype match determinants will be compared to unacceptable antigens on split/broad level of the respective recipient. In case a donor allele, or split / broad antigen containing the donor allele is present in the unacceptable antigen profile of the recipient, the virtual crossmatch is deemed positive, and the organ offer will not be made. Currently, virtual crossmatch will not yet be implemented for ETHAS and AM match.

10.4.2 The "transplantation" or "decisive" crossmatch"

The "transplantation" or "decisive" crossmatch with and without DTT is performed in the TTC where the recipient is registered, or the TTC cooperating with the recipient's transplant center according to Table 10.4. Either unseparated, T cells and/or B cells may be used as targets. The evaluation of the decisive crossmatch prior to transplantation follows the SOP established by the TTC and follows the recommendations of the National Bodies, the transplant center, ET and EFI. It is the responsibility of the TTC to adhere to these recommendations. The recipient's transplant center decides upon acceptance or denial of the offer. Transplantation can only be performed in case of a negative decisive crossmatch, unless otherwise decided by the local transplant center. The reasons must be reported to ET before transplantation.

For kidney and combined kidney/pancreas transplantation of a recipient with a vPRA>0% a decisive crossmatch must be performed before transplantation using current sera as specified by the recipient transplant center and TTC unless otherwise decided by the National Bodies. In addition, historical (peak) sera should be included. In case a prospective crossmatch is not performed, the reason, final decision, and outcome of the possible transplantation must be documented at the TTC, following the EFI standards. In addition, the crossmatch with the pre-transplant serum must be performed and documented retrospectively.

For organs other than kidney, at least a retrospective crossmatch should be done for recipients who either harbor HLA-specific alloantibodies, or have had an allo-immunizing event such as pregnancy, blood transfusion, or previous transplantation. Unless otherwise decided by the transplant center, for recipients waiting for heart, lung, pancreas, and small bowel or a combination of those organs and being allo-immunized, a crossmatch must be performed. Recipients with cytotoxic antibodies may require a prospective crossmatch.

10.4.3 Shipment of cell material for crossmatching

Anti-coagulated (citrate or heparin) peripheral blood, a piece of spleen and / or lymph nodes in phosphate buffered saline or equivalent must be included in the designated container. A sufficient number (if available) of isolated lymphocytes can also be sent. Labeling of every vial and all information included must include the Eurotransplant donor number and must follow the EFI Standards. In case of reshipment of the organ to a second recipient center, all material for histocompatibility testing must be placed back in the organ box.

10.4.4 Donor TTC

The donor TTC must perform HLA typing of post-mortal organ donors. In Germany, the donor TTC is named regional TTC.

The donor TTC must apply policies allowing quick and reliable results avoiding any unnecessary prolongation of the cold ischemia period and delay in allocation process.

10.4.5 Recipient TTC

Besides recipient HLA typing and screening for HLA specific antibodies, the recipient TTC (in Germany the respective regional TTC) must perform the decisive crossmatch for transplantation of the selected recipient and potential back-up of local/regional recipients selected by the ET allocation office. In addition, retyping of the donor should be performed. The decisive crossmatch can be performed retrospectively (see 10.4.2).

The recipient TTC and transplant center are responsible for the decision on the histocompatibility of the transplant.

Germany only: The sera of all potential recipients of a pancreas transplant must be sent to all German TTC.

Sera for immunized recipients for heart, liver, lungs, intestine **must** still be sent to the donor centers. All serum samples you receive for heart, liver, lungs, intestine patients **must** be stored. For these patients a crossmatch request can be sent to you in case of an offer or acceptance of the organ. Sera older than one calendar year should be discarded.

10.5. Acceptable Mismatch (AM) Program

The AM program has been established to increase the chance of highly sensitized kidney transplant candidates to receive a crossmatch negative offer. The program is open for all potential kidney transplant recipients of ET affiliated countries. The organ offer is mandatory. For the procedure of application AM status: see the ETRL website.

10.5.1 Eligibility of a recipient for the AM Program

The potential AM recipient must be on the ETKAS waiting list for at least two years in total, as defined by the date of first dialysis (both adult and pediatric). Patients must have status T(ransplantable) and must be typed for HLA-A, -B, -C, -DR and -DQ at the split antigen level to be eligible for acceptance in the AM program. Preferentially, every recipient to be included in the AM program should be typed for 11 loci (HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, -DPA1) by DNA typing. In case of HLA-DQA1, -DP unacceptable antigens the recipient must be typed for HLA-DQA1 and/or -DP. Panel reactive cytotoxic HLA antibodies resulting in a vPRA value of ≥85% must be detectable in the serum of two different bleeding dates of the recipient. In addition to CDC reactivity, those antibodies solely detected by solid phase assays will only contribute to the AM status when the specificities can be explained by earlier transplantation, e.g., HLA mismatches of the previous donor(s), or a specific sensitization of the recipient, e.g., HLA antigens of the partner or children in women. In case of a female with suspected immunization due to pregnancy, HLA typing of child(ren) and/or father of children is

required for eligibility check. Unacceptable antigens for HLA-DQA, -DPB, and -DPA will be taken into consideration for AM program acceptance in case of clear antibody reactivity according to the following rules. There are no changes in the prerequisite that CDC reactivity directed at HLA class I and/or class II must be present.

HLA-DQA-specific antibodies

- DQA typing from immunizing event(s) is known.
- In case the DQA typing from the immunizing event(s) is unknown, it can be derived from the DRB1-DQB1 typing based on linkage.
- In case of several DQA antibody specificities, these can be taken into consideration provided that they share an antibody verified eplet with immunizing DQA allele(s) and clear antibody reactivity is present in the serum against all alleles that share this eplet.

HLA-DP specific antibodies

- DP typing of immunizing event(s) is known and can be taken into consideration.
- In case of several DP antibody specificities, these can be taken into consideration provided that they share an antibody verified eplet with the immunizing DP allele(s) and clear antibody reactivity is present in the serum against all alleles that share this eplet.
- DP typing of immunizing event(s) is unknown. In this case the DP antibody which has the highest MFI value is considered to be the immunizing event and antibody verified eplets are taken into consideration in the same way as described above.

Preferentially, acceptable HLA-C and HLA-DQ antigens should also be defined. Current and historical sensitization are regarded equally important. Unacceptable antigens for HLA-A, -B, -C, -DR, -DQ, -DP contributing to the AM status need to be confirmed by screening of a peak serum by the ETRL. For the time being, for AM recipients it is strongly advised to list unacceptable antigens on serological level.

Recipients are not eligible for the AM program if:

- No unacceptable antigens are reported.
- The recipient possesses solely solid phase defined HLA antibodies not detectable in CDC.

In case a recipient center removes unacceptable HLA antigens, the ETRL will re-evaluate whether the recipient still fulfills the criteria for the AM waiting list. For AM recipients returning to the waiting list after failure of the previous graft a new serum needs to be send to ETRL for re-evaluation of the unacceptable and acceptable HLA antigens.

10.5.2 Exceptions

Patients listed for both a liver and kidney transplant can be entered into the AM program but will not receive priority in case of a combined liver/kidney transplant, since in this situation ranking will be done on basis of the MELD score. The AM priority in this setting will only apply to patients (fulfilling the criteria mentioned above) who receive a kidney after liver transplant.

10.5.3 Selection of recipients upon availability of a donor organ

The AM program runs for every organ donor, and recipients are selected on the basis of the ET modified blood group compatibility and HLA compatibility of the donor with the recipient's own HLA type in combination with the acceptable antigens. The AM allocation overrides the center profile with regards to local minimal match criteria. One must bear in mind that acceptable mismatches are truly acceptable and should not be a reason to decline an organ offer.

The HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, and -DPA1 DNA typing of the deceased organ donor is entered into immunology service. Potential recipients will be selected on the basis of their own HLA-A, -B and -DR antigens in combination with the HLA-A, -B and -DR acceptable antigens on the split antigen level. These acceptable antigens are regarded as recipient's own HLA antigens. Full compatibility between donor and recipient including the acceptable antigens is a prerequisite for allocation of kidneys via the AM program. Matching is based on "split" HLA class I antigens and "split" HLA-DR antigens. In principle, minimal match criteria of sharing of one HLA-B antigen and one HLA-DR antigen, or two HLA-DR antigens on the split antigen level with the patient's own HLA antigens are adhered to.

For every patient on the AM waiting list, the ETRL calculates the chance that a suitable donor becomes available in the ET donor population based on the patient's blood group, own HLA type and acceptable HLA antigens and the minimal match criteria. Upon calculation of the chance that a suitable donor becomes available, the recipients are divided into two categories:

Low chance of receiving a donor kidney: donor frequency ≤ 0.1%
High chance of receiving a donor kidney: donor frequency > 0.1%

A donor frequency of 0.1% represents a chance of 1- 2 organ donors per year (based on immunological grounds only). For recipients with a low chance of receiving a donor kidney as defined above, or urgency status HU, the minimal match criteria are reduced to one HLA-DR match at the broad antigen level.

The ETRL immunologist on duty is informed about every potential offer for a recipient included in the AM program. In case of a potential offer through the AM program, the ETRL immunologist on duty checks the HLA typing of the organ donor, the HLA typing of the recipient, the acceptable and unacceptable antigens, the chance of receiving a kidney through the AM program, and the reported HLA specific antibodies.

After approval by the ETRL immunologist on duty, the respective transplant center is informed, and if accepted by the transplant center, the kidney must immediately be dispatched. The crossmatch must be performed in the recipient TTC. In case of a negative crossmatch, the transplantation can be performed. Repeat HLA mismatches for broad and split HLA-A, -B, -DR antigens are regarded as a contraindication for transplantation, unless otherwise reported. HLA-C and HLA-DQ specificities reported as unacceptable antigens are taken into consideration The ETRL immunologist on duty will deny an offer if unacceptable antigens are reported in the donor HLA typing, or if the minimal match criteria are not met (when applicable).

The order in which the kidneys will be offered in case of multiple potential AM recipients is based on the calculated chance to receive an organ within the AM program as provided by the ETRL (Donor Frequency calculator Acceptable Mismatch Program). Recipients with the lowest chance get the highest priority. In case of identical chance, the patient with the longest waiting time within the AM program gets prioritized.

10.6. ET proficiency testing (EPT)

ET being an organ exchange organization relies on the work of the affiliated TTC. An essential step in maintaining the high standards of histocompatibility related matters within ET is the fulfillment of the ETRL External Proficiency Testing exercises. This is the only EPT scheme where a center to center comparison within ET is possible. Therefore, all ET affiliated laboratories entering data into ENISNext or immunology service must participate in all EPT exercises without any sample selection, and must fulfill the requirements of EFI. The ETRL has established the EPT scheme in order to assess, maintain, and improve the quality of HLA typing, screening for HLA specific antibodies and crossmatching of TTC affiliated to ET. The participants are informed at the end of each calendar year how the EPT scheme of the following year will be organized, and what data are required for the analysis and certificates. The results of the EPT form the basis for future decisions of bodies such as the Tissue Typing Advisory Committee or the Kidney Advisory Committee of ET. The participants must use the local SOP for the EPT. The Standards released by the External Proficiency Testing Committee, and approved by the Executive Committee of EFI, form an essential basis for the Histocompatibility quality control and assurance within ET. Modification of any of those Standards is done if deemed necessary.

All results must be communicated to the ETRL through the EPT website (https://www.etrl.org/), with the exception of the patient-based cases. These results can be returned by email to aetrl@eurotransplant.org. In general, the participants can download the analysis of the results from the EPT website within four weeks after the deadline. When analyzed, results are published on the website and participants will be notified by e-mail. Every participant receives these results in an open way (i.e., disclosing the identity of the laboratory) with the center code as provided by ET. The participants receive the analysis of the results via the EPT website. Every participant receives by December 31 of every calendar year latest a certificate of performance, which states whether the TTC fulfills the criteria for the particular EPT exercise. In case of irregularities, changes in the certificate can be made within two months of issuing. When a TTC is not fulfilling the requirements, it will be supported by the ETRL with respect to corrective actions. A summary of the EPT results is included in the Annual Report of ET.

The actual schemes include EPT exercises for: HLA typing, crossmatching, screening detection and identification and patient-based cases. In addition, a serum crossmatching EPT is designed in case of postal or customs problems. At the beginning of each new cycle, the TTC receives information from the ETRL regarding the EPT schemes. This information is published on the EPT website.

10.6.1 EPT on HLA typing

This EPT is performed 4 times per year and consists of a shipment of peripheral blood from healthy blood donors for HLA typing. The TTC are divided into two groups for logistical reasons: 1) TTC performing deceased donor HLA typing, in addition to recipient typing and screening for HLA specific antibodies (donor TTC) and 2) TTC performing recipient typing and screening for HLA specific antibodies (recipient TTC) and TTC not affiliated to ET.

EPT typing must be performed as a donor HLA typing on 11 loci, as described in section 10.2.2, and must be reported at the ET match determinant level as described in HLA table (10.7 addendum), which is the minimum requirement for HLA typing to be communicated to ET.

Homozygosity rules as described in section 10.2.1 apply. All TTC submitting transplantation relevant HLA typing results to ET must participate without any selection of samples. When the typing is not in consensus, the typing result of the organizer is regarded the correct typing. In case a participant disapproves with the results, the secretary of the TTAC must be informed by e-mail. The issue will then be discussed in the following TTAC meeting.

10.6.2 EPT on crossmatching

This EPT is performed 4 times per year using each time the 3 peripheral blood samples distributed for the EPT on typing and 3 selected sera only used for crossmatching . All TTC performing physical crossmatches for deceased donors must participate. The TTC must perform all crossmatches with and without DTT. The TTC must use unseparated lymphocytes, and/or separated T cells, and may use B cells for the crossmatch according to the local SOP

10.6.3 EPT on screening

This EPT is performed once per year and consists of a shipment of 12 sera of transplant recipients or multiparous women, different from those sera sent for crossmatching. All TTC reporting screening data to ENISNext must participate in the EPT on screening. The TTC must report the presence or absence of CDC reactive antibodies with and without DTT, the existence of HLA class I and/or HLA class II antibodies, and the specificity (-ies). Methods reported in the local SOP must be used. All ET affiliated TTC must report screening identification results tested with CDC. Next to this at least one solid phase test must be used to define HLA class I and class II antibodies. The use of additional methods is allowed. The analysis of this EPT will be performed as stated in the respective information published on the ETRL website and reported to the participants.

10.6.4 EPT on serum crossmatch

This EPT is designed for TTC not having received the samples for crossmatch EPT in time, because of postal or customs problems. This EPT is only available for selected TTC and for a short period of time. A set of defined sera is sent to the TTC where selected HLA typed suspensions must be used. The results must be reported immediately to the ETRL. The standards of the External Proficiency Testing Committee of EFI apply.

10.6.5 EPT on patient-based cases

The ETRL will publish 3 patient-based cases each EPT year. The deadline is two weeks after publication. Various data about a patient will be provided, so that is possible for the participant to make a decision whether the transplant can proceed on an immunological basis. Participation is mandatory for ET affiliated TTC.

10.7. Addendum HLA Tables

The Eurotransplant HLA tables are published on the ETRL website: https://etrl.eurotransplant.org/resources/new-hla-tables/.