



Dear colleagues,

Eurotransplant is heading towards the introduction of virtual crossmatching to replace the physical donor center crossmatch. This will significantly reduce cold ischemia time, increase specificity, and make the serum exchange redundant. The introduction of the virtual crossmatch requires several conditions to be met and multiple steps to be taken. These will be discussed in the current newsletter.

Extension of vPRA panel

To be able to perform a crossmatch virtually, all unacceptable antigens for a given patient must be reported. This includes those at HLA-DQA, -DPB and -DPA, since antibodies directed against antigens encoded on these loci can result in a positive physical crossmatch. To make sure that the vPRA is representative of HLA immunisation including these loci, a new panel for vPRA calculation is required. Such panel on 11-loci unambiguous 2nd field HLA typing is not readily available for the Eurotransplant geographic area. Therefore, the ETRL is making an inventory through the individual TTAC representatives to determine how many actual ET donors have been typed at unambiguous 2nd field resolution at 11 loci (for example in case of DSA, or in study context). An additional source may be donors for living transplant procedures. Please contact your national TTAC representative in case your laboratory has donor HLA typing data that fulfills these requirements.

Unacceptable antigen definition

The virtual crossmatch will necessitate a more detailed listing of unacceptable antigens. The unacceptable antigen definition will be extended to include also HLA-DQA, -DPB and -DPA. Furthermore, the possibility to register unacceptable alleles will also be implemented, to solve the problem of registering transplant-relevant allele-specific antibodies.

Donor HLA typing

Upon allocation, there are two steps that need to be undertaken with regards to histocompatibility. The first is the virtual crossmatch, which requires HLA data on 11 loci, preferentially at the resolution at which unacceptable antigens can be defined, which is 2nd field resolution. While rapid HLA typing at 2nd field resolution is becoming more feasible with platforms such as nanopore sequencing, this is not a reality yet. Therefore, ambiguous intermediate resolution HLA typing is the best we can do at the moment to exclude certain

donors for immunized patients. Eurotransplant will collect second field, ambiguous donor HLA typing data for all 11 loci. The complexity of these data will be reduced by filtering for European CIWD alleles (Hurley et al, HLA 2020). If any of the remaining alleles is listed as an unacceptable antigen, this will be regarded as a positive virtual crossmatch.

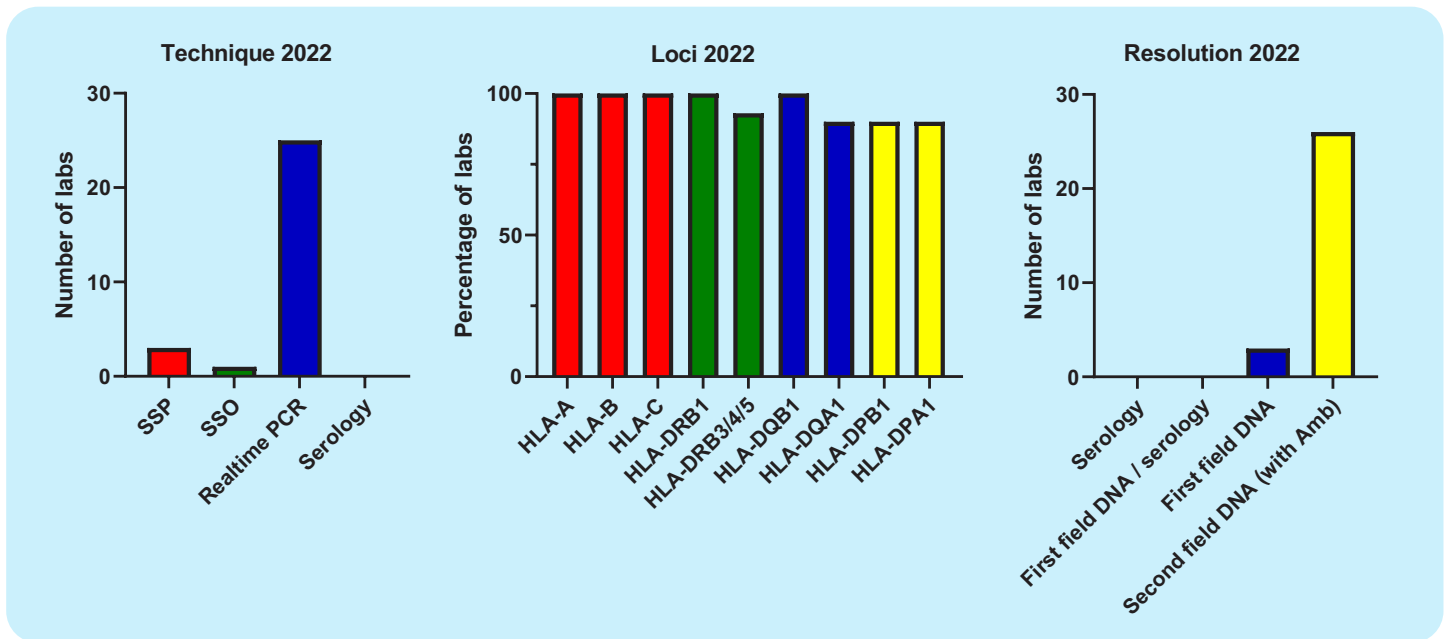
The second step in the allocation process is matching, which in principle remains unchanged, meaning broad serological antigen matching for HLA-A and -B, and split serological antigen matching for HLA-DR (match determinants). Within the Eurotransplant system, match determinants will automatically be assigned based on the CIWD filtered allele list.

Donor HLA reporting

The ETRL, together with the Eurotransplant office, and in close collaboration with Matchis and the DSO, is working hard to integrate Histoimmunogenetics Markup Language (HML) as the future HLA typing data standard within Eurotransplant. This development is necessary to transfer 11-loci ambiguous 2nd field HLA typing data to Eurotransplant in order to perform the virtual crossmatch. More detailed information on HML can be found here: <https://bioinformatics.bethematch-clinical.org/hla-resources/hml/>.

There is close contact with the vendors of intermediate resolution HLA typing kits to implement HML reporting in their software packages. The companies CareDx, BAG, One Lambda, Immucor and Inno-Train are already working on implementing HML reporting in their intermediate resolution typing software. Please contact the ETRL if HLA typing software is used in your lab for donor procedures is from a company not yet listed.

The plan is that HML files will be transferred to the Eurotransplant office through a web interface, negating the necessity for manual entry of data. In a later stage, the manufacturers of laboratory information systems will be involved in reporting through their systems. Once received by Eurotransplant, the Genotype List String (GL-string) will be distilled from the HML file and used for downstream processing.



Results ETRL Survey 2022. The left panel shows the main technique used in ET labs for deceased donor typing. The middle panel shows the loci that can be typed for during deceased donor procedures. The right panel shows the resolution that can be obtained during such procedures. Amb: ambiguities.

ETRL survey donor HLA typing

Recently, the ETRL held another survey to determine the status of donor HLA typing within Eurotransplant. We would like to thank all Eurotransplant affiliated donor labs for filling in the survey. The results from this survey can be found in the box above. Compared to previous surveys, it is clear that the vast majority of laboratories is using Realtime PCR for deceased donor HLA typing. Almost all centers are capable of reporting 11-loci HLA typing at the 2nd field level (with ambiguities).

Preliminary program Tissue Typer session at Annual Eurotransplant Meeting

The Eurotransplant Annual Meeting meeting will take place as hybrid meeting on Thursday September 22 and Friday September 23. The tissue typer session will be dedicated to the introduction of the virtual crossmatch. Please find below the preliminary program.

Sebastiaan Heidt (ETRL)

Introduction virtual crossmatch

Ben Matern (UMC Utrecht)

Data standards, focusing on HML and GL-string

Ben Furth (Eurotransplant)

Implementation of virtual crossmatch in ET