OPTN/UNOS Histocompatibility Committee
Meeting Minutes
October 16, 2018
Chicago, IL

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Introduction

The OPTN/UNOS Histocompatibility Committee met in person in Chicago, Illinois on 10/16/2018 to discuss the following agenda items:

1. Addressing HLA Typing Errors
2. Change CPRA Calculation Project Update
3. Memo to Thoracic Committee re: Heart Allocation Data
4. Kidney Allocation Update
5. Operations and Safety Committee: Guidance on Effective Practices
6. CMS Virtual Crossmatching Discussion
7. Project Portfolio Review
8. Other Discussion

The following is a summary of the Committee's discussions.

1. Addressing HLA Typing Errors

Summary of discussion:

UNOS staff reported 29 comments on the public comment website on this Committee sponsored proposal that was out for public comment this fall. The Living Donor, Patient Affairs, and Organ Procurement Committees all supported the proposal after hearing a presentation of the proposal. Overwhelming support in each region and among the major professional organizations is reported. There were a few comments on the public comment website opposing the proposal, but there was no indication as to why.

The Chair said there were many comments expressing a desire for automatic download. This would take time, energy, and expense but may be considered as a future proposal. The Chair also commented that it seems that not everyone understands the double-entry HLA system. Copy and paste for double entry is not permitted.

A Committee member commented that some opposition was from smaller labs that feel it will be an undue burden to complete double entry.

A Committee member commented there was a concern about double entry for the second antigen. It should be evident that this can be left blank. This is a programming change that will not be addressed by policy, but will be brought back to UNOS IT for a potential system enhancement. There may be confusion among coordinators about this, so there should be education.

No changes are needed to policy language post public comment.

The Committee voted unanimously (17 yes, 0 no, 0 abstain) to approve the policy language, as written.

The proposal will be implemented one year from the Board Meeting Date, and the exact timeline of that will be determined when staff reviews and determines timelines for all approved Board

proposals after the December Board meeting. Staff will continue to share updates with the Committee.

A Committee member asked if it can it be mandatory for labs to upload the raw results sooner than the double entry component of the proposal. Staff said it can be announced right after the Board meeting, in the Policy Notice, for labs to start uploading raw results. Verifying this will be part of the site survey.

A Committee member asked if labs would be referred to the Membership and Professional Standards Committee (MPSC) if they were not complying with this. Some education from UNOS should be created in conjunction with this implementation effort so members have more information about these changes. The MPSC will be monitoring the written agreement between labs and OPOs.

UNOS staff have begun to consider what the data portal will look like with discrepant typing. The Committee will receive an update on this in the future.

A process for referring discrepancies has also been discussed, such as referring labs to the MPSC. Staff said letters were sent in the past, but labs continue to make these discrepancy errors. Providing members with more up to date reports will allow labs to review their discrepancies sooner. Errors have reduced in the most recent two quarters of 2018. Q1 reported 11 errors and Q2 reported 14 errors.

Committee members also expressed that there should be more transparency between labs and the centers they serve about discrepancy rates. Additionally, the idea of piloting automatic downloads with some of the larger labs was discussed at a recent OPTN Board meeting.

Next steps:

The proposal will go to the Board of Directors at the December 2018 meeting.

2. Change CPRA Calculation Project Update

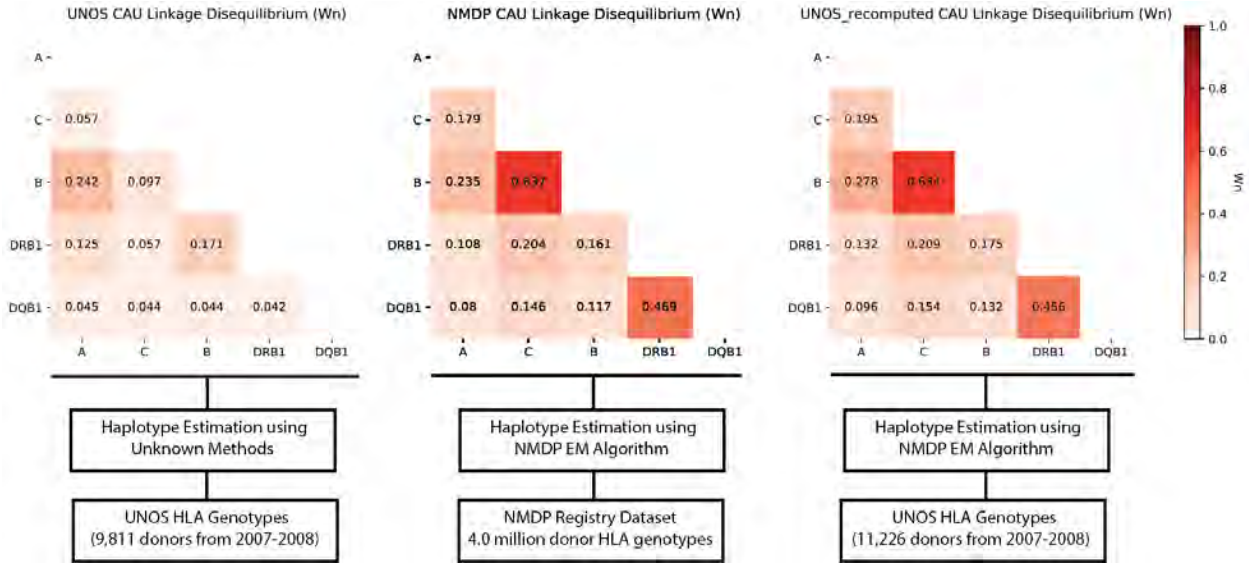
The Committee will discuss the project status, including the data status, timeline, proposed solutions, and next steps.

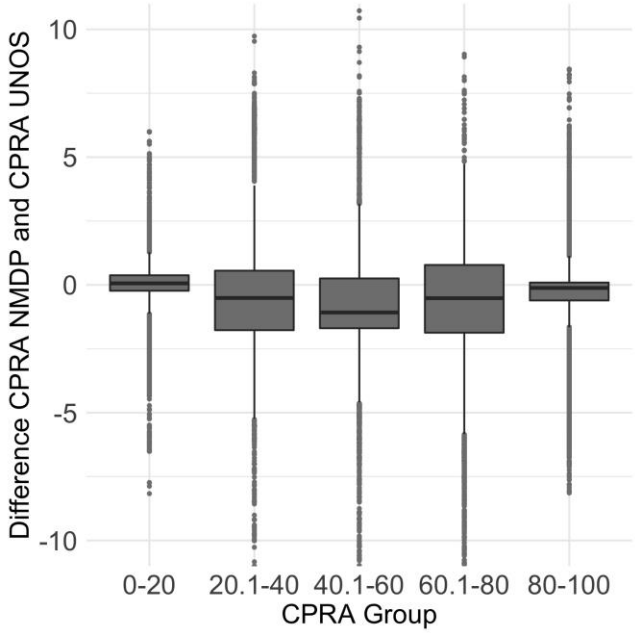
Data summary:

Project researchers presented the current status of the ongoing Change Calculated Panel Reactive Antibodies (CPRA) Calculation Project. The presenters have been researching the feasibility of using human lymphocyte antigens (HLA) frequencies from the National Marrow Donor Program (NMDP) stem cell registry for CPRA. Their analysis revealed:

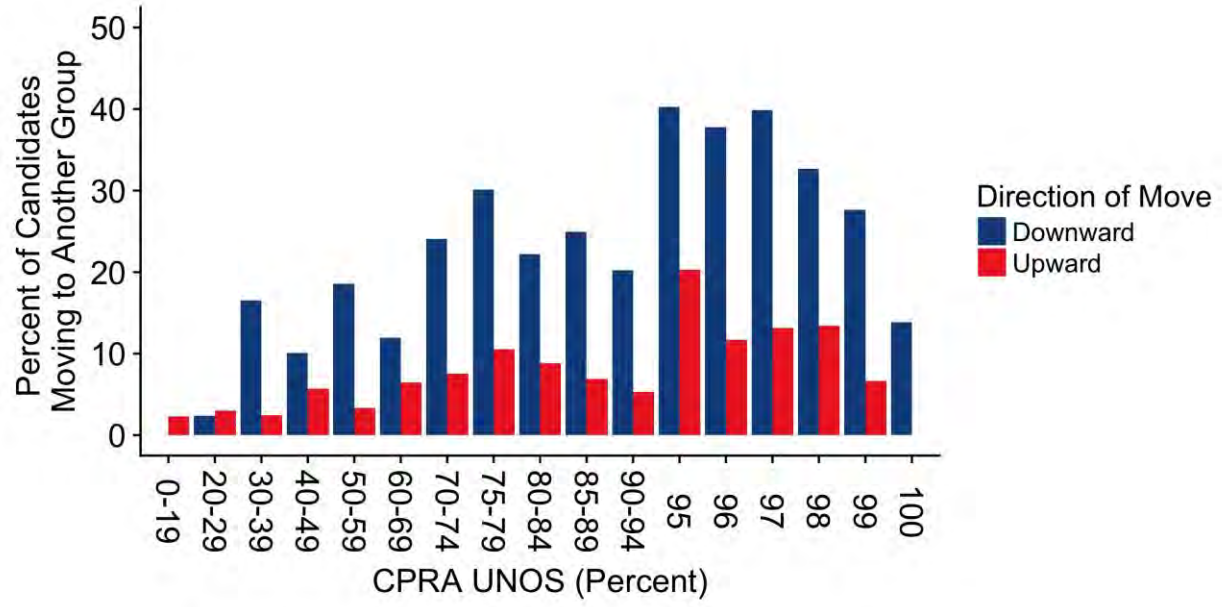
- They found the allele frequencies between UNOS and NMDP reference panels are very similar. However, there is very little similarity for 5-locus haplotypes.
- 2-locus haplotypes that include HLA-C and DQ antigens are very disparate.
- The most common haplotype in NMDP is different from what is in UNOS database, which indicates an issue with multi-locus haplotypes in UNOS data.

Validated Flaws in UNOS CPRA Haplotype Estimation





- If NMDP data is used, it could have a significant effect on the reassignment in CPRA groups and allocation.



Summary of discussion:

The Committee discussed the different types of data sets and how they were used for analysis. There were concerns over the discrepancies in the original data (9,811 donors) and the newly recomputed data (11,226 donors). UNOS staff indicated they are researching how the original data was calculated and will report their findings to the Committee soon.

Some oddities were discovered in the UNOS STAR dataset where HLA DQ and DP unacceptable antigens have been converted into time format (ex. “15:01”, ”3:01PM”). The issue has been communicated to UNOS Research staff.

The Committee discussed how to potentially move forward with the future data discoveries. The researchers have begun conversations with UNOS IT staff.

Next steps:

The group will continue their research in the following areas:

- Using pre-Kidney Allocation System (KAS) data, the researcher’s initial models showed that using NMDP CPRA was a better predictor of time-to-transplant than UNOS CPRA. The analysis is being redone now with post-KAS data.
- Kidney-pancreas simulated allocation modeling (KPSAM) to project impact of alternative CPRA measures on equity
- Analyzing how much of the disparity in access to transplant would be explained by 9-locus NMDP CPRA.

3. Memo to Thoracic Committee re: Heart Allocation Data

The Histocompatibility Committee is in the process of drafting a memo requesting that the Thoracic Committee review and consider changing the risk stratification data fields that were implemented as part of the new heart allocation system on September 18, 2018. The three data fields that the committee suggests be changed include CPRA, PRA typing method and the MFI threshold.

Summary of discussion:

Specific feedback was asked from Committee members about the form and the fields that were included in the memo to be changed.

Committee members said that they did not get to review the form prior to its release. There have been multiple questions from committee members' centers regarding how data should be inputted into the forms. There was general concern amongst committee members that HLA-related materials appearing in UNet^{SM} and other UNOS-related software is not being assessed by the Histocompatibility Committee prior to implementation or release. The Committee members felt strongly that by approving all histocompatibility materials prior to their implementation in software or medical forms that this could lead to greater accuracy and efficiency for the OPTN.

There was overall agreement by Committee members that the fields in the forms need to be changed. However, the Committee members questioned the purpose of collecting the data, because without the purpose they are unable to give specific details into what data should be included on the form. Clarification was given that since 2005, HLA data has been collected for heart allocation. However, the effort now is to clean the data in order to make it more meaningful (an example such as what is the effect on CPRA patients twenty-five or above).

One Committee member commented that the data they have been collecting is currently not being entered on the form created by the Thoracic Committee. Another Committee member explained that certain data such as unacceptable antigens are not being collected at their facility, which could contribute to inaccuracies in the data analysis. Committee members stated that the transplant centers should be asked what their "unacceptable" criteria would be that would cause them not cross for their patients.

Another point of discussion was that there was no easy way to capture CPRA for thoracic patients in the past.

The Committee desires to get in touch with the Thoracic Committee in order to learn more about what that specific committee wants to capture in their data. The Committee is unsure of how best to help the Thoracic Committee capture their data without further inquiries. It was mentioned that the Thoracic Committee wants to capture specific data to help in heart allocation.

Next steps:

Committee leadership will be in conversation with the Thoracic Committee leadership to learn more about what they need for their outputs or outcomes in order to tailor the data collection tool. The Histocompatibility Committee would then like to have a conference call with the Thoracic Committee for clarification.

4. Kidney Allocation Update

Summary of discussion:

The Committee heard a brief update on the most recent Kidney Committee meeting where they discussed potential new allocation models. The Kidney Committee is awaiting modeling reports from the Scientific Registry of Transplant Recipients (SRTR) before making a decision on their preferred allocation model. Committee members expressed concerns over cost, equity, and discard rates with any potential allocation change and if those factors are included in the modeling.

Next steps:

The Committee will await further updates from the Kidney Committee.

5. Operations and Safety Committee: Guidance on Effective Practices

The UNOS/OPTN Operations and Safety Committee (OSC) Vice-Chair and two OSC members joined the Histocompatibility Committee meeting via teleconference.

Background:

The OSC is creating an effective practices guidance document with the intent to identify effective practices and shared lessons learned in light of the geography issues that are coming up. Ad hoc Geography advised the OSC to develop guidance with the goal to maximize efficiencies and avoid known issues in logistics planning (like transportation) and offer, recovery, and transplant processes. There are six topics that are in the guidance document. The committee was specifically looking for input from the Histocompatibility Committee on specimen sharing and cross matching (using virtual cross matching, managing prospective specimen sharing needs, and cross mitigation).

Discussion Summary:

The Vice Chair of the OSC wanted the discussion to be focused on the process and operational issues surrounding the ability to be more efficient than how, with broader sharing, will be offering organs to places far away in greater number than it has been done in the past. The focus is to learn from other places that have adopted practices that have made this process more efficient. The OSC voiced an interested in getting feedback/insight from the Histo Committee on the following:

- Are some best practices that either labs have with each other or with their local OPOs/transplant centers that have addressed how to get organs placed faster and more efficiently?

- Virtual cross matching always comes up and there is a lot of discussion about centers practices around that, but are there avenues that can be pushed forward in the guidance document?

- What is it that the Histo committee are doing, thinking, or would like to see?

Histo Committee Members voiced the difficulty in standardizing effective practices overall because it is a center-specific policy. It will come down to the joint agreement between the transplant center and the HLA lab. Transplant centers (depending on the joint agreements between the HLA labs, their transplant centers, and the clinicians) are not all set up for any kind of risk. There are centers that may be willing to take on low level DSA and there are other centers that will take low level DSA, but not moderate DSA; it defines units of their own practice what they'll accept and what they won't.

It was agreed by both the Histo Committee and OSC that there is great variability in practices done from one area to another. The focus should instead be on the following:

- It does not need to be one size fits all
- Don't want to be prescriptive in this document; Don't want to say "this is what you need to do"
- Want to get transplant programs/OPOs/lab thinking about how do we put systems in place to be as efficient as possible in the cross matching, virtual cross matching, and HLA process to enable our patients to have the best opportunities to receive the transplant

The OSC was asked of any big barriers that they were seeing and it was discussed that again, OPOs have a lot of variability in their cross matching and allocation processes. Due to this great variation, it was discussed that the guidance document should include the encouragement of OPOs to share specimen when possible to avoid bypassing patients that are listed needing cross matches and becoming more efficient when sending out offers so that the process is not delayed. The process is taking much longer than it used to and there should be discussion on ways to minimize the process time so that opportunities are not lost.

In focusing on the content for the effective practices guidance document, the OSC Vice-Chair asked the Histo Committee to start thinking about those systems that could be put into place in the transplant programs, OPOs and HLA labs to support the idea that the number of import offers coming in from outside of local areas were going to increase, and the number of organ offers the OPOs are going to be making to transplant centers outside of their areas is also going to increase – often without the benefit of early notice to move specimen and get cross matches done in a timely manner.

The Histo Committee agreed that the following should be mentioned/included in the guidance document:

- **Consideration to listing unacceptables (especially in thoracic), so that it will help move the allocation along**
    - There may be some reservations about based on the differences in clinical practices. It could be managed by deciding to use certain parameters to list as unacceptable. For example, if there is an antibody of MFI at 15,000, why not put that in there?
    - A suggestion like this should be included in the guidance document to get the idea going of creating systems and process to be more efficient but also want to keep in mind of not depriving a transplant center the opportunity to retrieve an organ if they would consider it.
    - Right now for heart and lung, even though you're putting in unacceptables, there can still be offers on donor typing for which an unacceptable has been entered, because the match run are being ran before the typing is in there.
    - Can encourage OPOs to learn heart and lung lists with the HLA in there so that it makes their allocation more efficient.

- **Putting HLA type in for running**
    - Most of the time, there is the time to wait until you have HLA to run the list, but there are those circumstances where you've got to go quicker than you would like to because you still want to be able to put out the offers if you're under a time crunch.
    - In the normal case where there is time, it can be made into a suggestion in the guidance document without being so prescriptive that we're mandating that OPOs and transplant centers and HLA labs do certain things.

- **Scarcity of donor material**
    - Making a point that there's an infinite pool of material that can be distributed. There is a restricted amount for donor stability, for efficiency that can be distributed and it has to be in a meaningful fashion.

- **Recommendation that centers enter the unacceptable antigen**
    - Reservations on using the term “recommendation”. A recommendation like this would need to come from the Histo Committee. The guidance document is making a suggestion.
        - If this is a recommendation/suggestion that the Histo committee agrees on, this could be incorporated into the document stating so.

Timeline:

- Going out for public comment in January
- Wanting to move forward with input from the stakeholder groups.
- The Histo Committee has agreed to provide feedback once the draft is ready to be reviewed

Additional Discussion:

The Committee discussed a variety of situations that can occur with virtual crossmatching but decided to focus the guidance document on the standard cases.

The Committee also emphasized that the scarcity of donor material, limited donor matches, and necessity for effective distribution are key motivating factors for virtual crossmatching. The presenter from the Operation and Safety (Ops and Safety) Committee wanted to make it clear that the guidance document would serve as helpful suggestions rather than recommendations or prescriptive directives.

The following are topics for the Ops and Safety guidance document for effective practices, which may overlap with the subject material of virtual crossmatching:

- Building Relationships to Optimize Operations
- Organ Allocation Procedures
- Staffing
- Streamlining Communication
- Setting or Time
- Specimen sharing & crossmatching

The Ops and Safety will send over a draft of their guidance document regarding effective practices to the Histocompatibility Committee so the two guidance documents can present a cohesive message. The Committee will draft a response memo about virtual crossmatching to the OPO Committee.

6. CMS Virtual Crossmatching Discussion

The Committee discussed a 2017 Request for Information from the Organ Procurement Organization (OPO) Committee seeking input from the Committee regarding the future of virtual cross matching in kidney transplantation and reducing the need for blood samples shipments. The Committee also discussed a recent Request for Information from CMS regarding, among other things, virtual crossmatching.

<u>Summary of discussion:</u>

The Committee was in consensus of providing a guidance memo to the OPO Committee in regards to crossmatching. Several committee members expressed concern regarding opposition to virtual crossmatching from some members of the OPO community, most notably a 2017 paper supported by over a dozen OPOs.

The Committee was in agreement that virtual crossmatching was an appropriate and helpful tool for certain patients and support generating a guidance memo. The Committee discussed the variation of processes that exist regarding effective virtual crossmatching. Different OPOs choose to have different policies regarding virtual crossmatching. Virtual crossmatching may not be effective for all transplant candidates, however it can help programs more efficiently screen organ offers. Some programs do not have strong confidence in virtual crossmatching and will avoid doing it all together, including skipping over patients who require crossmatching. Some programs choose to do crossmatching before an offer for an organ is even extended.

7. Project Portfolio Review

An overview of the Active Committee Projects for the Histocompatibility Committee was discussed as follows:

- **Review of HLA Tables**
  - Pending implementation.
    - Equivalency table update is including DPB1 unacceptable antigen equivalency
  - Will be going live the first week in December

- **Addressing HLA Typing Errors Project**
  - Going to the board in December

- **Change CPRA Calculation Project (this project will be taking priority)**
  - Evidence gathering stage
  - Will be the bulk of the committees time now

8. Other Discussion: Discussion of Potential Committee Projects

The Histocompatibility Committee agreed that there will be a great deal of dedication to the CPRA project, but wanted to review projects that have been in the idea phase that have been previously brought up. The floor was open for members to discuss any potential projects to think about in the future. Some suggestions were as follows:

- **CPRA for thoracic organs:** A member suggested that while working on the CPRA project, it would be good to think about including the CPRA for thoracic organs as well as the DPA equivalencies for that. It was agreed by members that although these topics would fall under the same topic, the focus should be on the CPRA due to the amount of resources needed to complete such a large project. It was agreed that when the committee speaks with thoracic leadership about the stratification fields, they can possibly start to develop the CPRA for thoracic, making it into a joint project with the thoracic committee.

- **HLA Discrepant typing data –** As the histocompatibility committee is always tasked with reviewing the HLA discrepant typing data, the committee should not lose focus on developing a type of electronic or automatic download from their information systems into UNOS and should be an ongoing project.

- **0-ABDR mismatch discussion –** From previous data, the 0-ABDR mismatch was shown to have dropped from about 8% to about 4.5% of the total transplants and the distribution is clearly to one ethnic group and work is starting to be redone on the

analysis that was done back in 2004 (by John Robertson publication). A member suggested that this should open up a discussion in regards to the following questions:

- What's the value of keeping the 0-ABDR mismatch as an allocation criteria for everybody (with the exception of pediatrics)?
- Is there really an outcome benefit when we know it's only going to one particular ethnic group?

A member suggested that getting rid of the 0-ABDR mismatch for all the other categories, except for the pediatrics is probably reasonable, and could see some of that data redone to support that.

- **Guidance Document: Key Personnel:** Currently, when there is a change of a director (in a lab), it is required to list all the personnel and requalify everyone in the laboratory again even if the lab had just been inspected six months ago. The Committee has agreed that a guidance document would be most appropriate in addressing this issue and could potentially be a smaller project for the committee to work on.

The topic revised guidelines with CAP was brought up by a committee member. The discussion was focused on the proper protocol regarding the release of deceased donor information to the patient's (recipient) chart. This conversation was brought up in a previous histocompatibility meeting where the question was posed to CMS and the answer being that the deceased donor was not considered a patient. It was interpreted to mean that the PHI rule does not necessarily apply in that context to a deceased donor.

Does this violate HIPPA? It was clarified by a HRSA representative that they have eliminated everything that has been done with the donor's identity – there is only a UNOS identifier. It was believed to be documentation from UNOS that could provide some guidance regarding informed consent of deceased donors and OPO exemptions from HIPPA that could be referred to. The committee member would be engaging in this discussion with CAP, but believes that this question may come back in a future meeting.