OPTN Histocompatibility Committee
Meeting Summary
October 14, 2021
Conference Call

Peter N. Lalli, MD, Chair
John G. Lunz, MD, Vice Chair

Introduction

The Histocompatibility Committee (the Committee) met via Citrix GoToMeeting teleconference on 10/14/2021 to discuss the following agenda items:

1. Vice Chair Selection Process
2. Discussion: Monitoring the Use of Allele-Specific Unacceptable Antigens in CPRA
3. Review Public Comment Feedback and Vote: Update to the HLA Equivalency Tables
4. Change to the CPRA Calculation: Updated Waitlist Modeling
5. Change to the CPRA Calculation: Frequency Data Set Comparison to Published Sources
6. Other Business, New Project Ideas, Discussion

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

1.   Vice Chair Selection Process

Within the Vice Chair selection process, the Committee had mentioned a desire for the nomination to be less leadership driven, with more transparency given to the Committee itself. UNOS staff gave a brief rundown of the current selection process, which included who was eligible and the requirements for application. This was not an attempt to change the process; rather, it was an open invitation anyone on the Committee to apply with complete information.

2.   Discussion: Monitoring the Use of Allele-Specific Unacceptable Antigens in CPRA

Following up on the committee meeting from 10/12, UNOS staff summarized the sentiment from that meeting that it was most important to monitor the changes as they progress. This process will include one, two, and three month reports which will notably follow the specific metric "organs accepted when a candidate has allele-level unacceptable antigens (UAs) and the donor has equivalence at the antigen level". This will help identify any potentially concerning trends that may be evolving as a consequence of this policy change. If further intervention is needed, the Committee can discuss involving histocompatibility accrediting organizations to assist in auditing listing practices.

3.   Review Public Comment Feedback and Vote: Update to the HLA Equivalency Tables

The public comment sentiment on the proposed changes was "overall, very favorable". All votes fell within strongly support, support, or neutral/abstain, with the large majority of those favoring support and strongly support.

Specific feedback first and foremost indicated support from a number of societies on the requirement of DPA1 typing. In addition, some of those comments suggested an increased ability to transmit data between lab informatics systems and the UNet^{SM} applications. While these changes would not be within the scope of this proposal, the Vice Chair suggested these could be considered for future API development. Finally, there was a request for the Calculated Percent Reactive Antibodies (CPRA)

calculator to be updated to include all classic loci. As this feedback ties in to projects that the Committee is currently drafting, there was no discussion regarding this specifically.

The Committee then moved to review the proposed policy language, and upon Committee consensus, to vote on whether to send it to the Board of Directors' 2021 December meeting. The major areas of the proposed changes address:

- Requirement of DPA1 typing for deceased kidney, pancreas, and kidney-pancreas donors, and other organs if requested
- Require DPA1 typing for OPTN KPD living donors
- Addition of a DPA1 equivalency table
- Update of DPB1 equivalences and reportable values
- Remove broad antigens equivalent to allelic antibodies
- Alignment of HLA donor and transplant candidate data collection across UNet^{SM}

There were no comments from the Committee on the proposed language changes, and they unanimously voted to send it to the Board of Directors (15 yes, 0 abstain, 0 no).

4. **Change to CPRA Calculation: Updated Waitlist Modeling**

UNOS staff presented on their proposed changes to CPRA modeling. During this, they explained the limitations of the previous NMDP (National Marrow Donor Program?) data set – notably, the difficulty in distinguishing between some alleles that can be entered as unacceptable antigens, which caused high CPRA for some rare alleles. The most recent dataset that the calculator is operating off of allows for separate frequencies for many alleles that were previously an issue; some, however, still cannot be distinguished. A full report is not available at present, but will be distributed once finalized. A summary of the presented data is below:

During the data presentation, it was noted that the previous calculator for CPRA consistently underestimated the actual percent of incompatible donors. However, when broken down into allele-level typing, the current model overestimates the actual percent of incompatible donors because few donors are typed at the allele level. Therefore, the proposed changes will be slightly adjusted to account for the overestimation of CPRA with allele-level typing, as well as incorporate the most recent NMDP data set.

The following slide indicated which alleles were distinguished by their own frequency in the new dataset in comparison to the old. This supported the next slide, which showed the percentage of candidates experiencing a change to CPRA, broken down between all candidates and those registrations with unacceptable antigens. The presenter expected little change to occur to the large majority of candidate's CPRA scores.

When viewing the median change broken down by ethnicity, there was not significant change. No ethnic group saw a change larger than .28%, with all but one other ethnic groups seeing change of less than .06%. The presenter stated that, while .28% may seem like a large amount in comparison to the other changes, all of these values are still significantly less than one percent.

A Committee member clarified on the following slides, which presented the metrics in comparison with one another in accuracy of predicting transplant rate, that the very slight difference between the models was not the correct way to read the graph. The member clarified, saying "what we're seeing here is just so much noise at the low CPRA's that we wouldn't see [any sizeable change in the greater-than-zero CPRA groups]". UNOS staff confirmed this was an accurate assessment of the data, while also

contributing that the displayed graph addressed how well the metrics predicted transplant, rather than how CPRA was being equitably redistributed.

In conclusion, the recalculated NMDP CPRA shows improvement over previous metric. This analysis is based off of the fact that metric is closer to the actual percent of donors screened and more predictive of offer and transplant rates. Similarly, there will not be a large impact to most candidates, though some will see adjustments based on the updated CPRA calculations.

This change to CPRA was presented to the Committee for comments and approval. The Committee was supportive of the proposed changes, though one member did question whether the unacceptable antigen group that had the least amount of specificity could be ruled out of allele level typing. This, again, followed the logic of preventing programs from listing candidates with unacceptable antigens that do not screen any donors off, therefore gaining CPRA points at no cost. The Committee responded, noting that if there becomes a need to weight different alleles, "we can always talk about whether or not we want to assign CPRA points for these alleles that can't be distinguished [in the future]". There was also concern amongst members that asymmetrically ruling out allele-level typing for some antigen groups could unintentionally disadvantage or advantage some candidates.

5.   Change to CPRA Calculation: Frequency Data Set Comparison to Published Sources

UNOS staff introduced the next topic for discussion, the comparison of the NMDP-based calculator against other potential datasets. The first was the Common, Intermediate and Well-Documented (CIWD) catalogue. It was noted by the Committee that this paper utilized direct counts of alleles as they were reported by labs, each with different resolutions. This presented a problem when attempting to compare it to the current calculator, as there was a comparison across frequencies with different resolutions. Furthermore, a member contributed that, "over half of the [CIWD] typings are at a lower resolution than the reference panel [for NMDP]. However, it was noted in the paper that this calculation was not intended to be used for frequency data, but instead to develop a reasonable clinical typing standard.

The Committee went on to review the Klitz 2003 paper examining DR-DQA1-DQB1 haplotypes. This paper did review data at the same resolution as the NMDP data set. However, this data set was significantly smaller, as it examined 1,899 unrelated European American donors, in contrast to the NMDP set, which contained 5,789,830 Caucasian donors. Additionally, alleles documented after 2003, such as those included in IMGT HLA, would either not be included or rolled into others. Even with these confounding factors, there was a large amount of concurrence with the current model, with prediction similarity above seventy percent.

The following paper was Hollenbach 2012, which examined the European American DPA1-DPB1 Haplotypes. This paper used a larger data set, 5,944 donors, in contrast to the Klitz 2003. This, in combination with the updated allele catalogue, contributed to similarities being between greater, at approximately 94 to 96 percent concurrence between the two data sets. However, the comparison did only compare to donors in the NMDP reported after 2015, which a Committee member said was because "before 2015, it wasn't able to get good estimates for the extended DP haplotypes. All the other loci were in good agreement, but DP was off". However, the member did note that finding this concordance between the data set after 2015 and the current one was "surprising" and could be useful later on.

Finally, the Committee moved to review the IHIW 17 set, the most recent and concordant of the three with the NMDP set. This was in part because it had the largest sample size, while also examining loci at the same resolution across similar frequencies. The data was demonstrated on the graph with two lines, one indicating the excoffier coefficient, and the other, the higher of the two, indicating the same data

adjusted for standard error. Within the Caucasian population, the data was the most accurate, as there were the most samples per locus, but across all ethnic groups, the data was above 80% - "really highly concordant" the presenter noted. Additionally, though the comparisons were drawn across the entire NMDP data set, a member confirmed that if you used the NMDP cut off at 2015, the concordance was even higher.

6. **Other Business, New Project Ideas, Discussion**

The Committee also reviewed the six month monitoring report for the implementation: Remove DSA from Kidney and Pancreas Allocation. The full monitoring report can be found [on OPTN](#). UNOS staff briefly summarized some of the transplant data, noting that they were going to primarily focus on data affecting histocompatibility laboratories. The Chair expressed interest in seeing the rate of refusal due to unacceptable antigens before and after the policy change. The Committee discussed whether the rate of transplant in the areas that had seen increases would approach equilibrium with other areas that had remained unchanged or decreased, noting that this policy is "stopgap" and would change again, once Continuous Distribution was effected. However, a number of members did share that, anecdotally, they felt like more candidates were getting transplanted.

As the Committee approached the end of the CPRA project, a number of new project ideas were hypothesized for the next policy cycle. These are bulleted below:

- The Addition of an "Avoid" Feature in Waitlist – this project would add an area to list low-level antibodies that would require director approval on match runs, similar to Kidney Paired Donation (KPD). This would not screen a candidate from a match run or add to CPRA, but would ensure proper oversight is given to potentially reactive antibodies. Additionally, it would allow laboratories to preempt a number of calls or concern from transplant programs about a candidate's antibodies. There was concern from a member that this would ultimately be less useful, as virtual crossmatching would still need to be done even with this added information. The Chair clarified that this would be a supplement to the virtual crossmatch, as an indicator for what is expected out of the crossmatching. A second member voiced support, saying this is something they already do with their laboratories, and that they would appreciate having a place in UNet^{SM} to place this information. A third member requested information on how useful this feature has been for KPD, where it is currently implemented; the Chair replied that, in theory, yes that information could be pulled, but the amount of information contained would not in any way be significant. Ultimately, the Committee agreed this idea requires further discussion.
- Align HLA Tables with World Health Organization (WHO) Nomenclatures – Current tables are a mix of serologic and molecular nomenclature. A small number of programs and accrediting organizations have brought this forward as a point of concern, suggesting that unifying into a cohesive system would improve data accessibility. The Committee agreed this was a high priority project, but it would need further discussion to identify the endpoints of the project; specifically, should WHO nomenclature be used? Is there a hybrid use of serologic and molecular typing that provides similar usability? Are there other options? However, there was unanimous agreement that this project should be examined
- Update Recipient Histocompatibility Forms – The recipient histocompatibility forms have not been updated in a number of years and contain extraneous fields and are lacking necessary additions. Currently, they contain no information on virtual crossmatching. Laboratories are instructed to leave the 'physical crossmatching' section blank if they completed a virtual crossmatch.

- Revise TIEDI Discrepancy Report – The TIEDI discrepancy report at present only reports kidney/pancreas donor and recipient discrepancies. In addition, this is limited only to HLA-A, B, and DR. In addition, there is no logic calculating equivalencies, so a report is generated even when the HLA is equivalent.
- Allow Ambiguous Molecular Typing Data to Be Collected – this was proposed to the Committee with no comments
- Increase Decimal Specificity in UNet^{SM} to Five Digits – UNOS staff noted that this is already included in the update to CPRA, and the system will calculate CPRA to seven digits.
- Using Epitope-Based HLA Matching – This project would more accurately determine HLA matching across donors and candidates, and it would be a massive undertaking for the Committee. It was noted that some of the data from epitope-based matching has not been published yet, and the Committee felt that, before committing to a project of this magnitude, they would like to see the data results. The Chair noted that this would require allele-level typing to be entered for Donors, as well as the implementation of an API to help manage this data exchange between laboratories, facilities, and UNOS.

The Committee agreed that, in terms of sequencing the ideas, the idea to align the HLA data collection with WHO nomenclature should come first, to ensure that the data is being correctly collected. The second in line would be to update data collection through forms and fields in TIEDI. Finally, the last in line would be to add the "avoid" functionality to UNet^{SM}. The Committee also agreed that there may be overlap between the first two proposals, and if necessary, they could discuss incorporating the two.

Upcoming Meetings

- November 9, 2021
- November 29, 2021

Attendance

- **Committee Members**
  - Peter Lalli
  - John Lunz
  - Caroline Alquist
  - Valia Bravo-Egana
  - Reut Hod Dvorai
  - William Goggins
  - Idoia Gimferrer
  - Evan Kransdorf
  - Gerald Morris
  - Omar Moussa
  - Vikram Pattanayak
  - Karl Schillinger
  - Jennifer Schiller
  - Manu Varma
  - Marcelo Pando
  - Phyllis Weech
- **HRSA Representatives**
  - Jim Bowman
  - Raelene Skerda
- **SRTR Staff**
  - Bryn Thompson
- **UNOS Staff**
  - Nicole Benjamin
  - Amelia Devereaux
  - Courtney Jett
  - Emily Kneipp
  - Kelsi Lindblad
  - Eric Messick
  - Susan Tlusty
  - Dean Wilson
- **Other Attendees**
  - Cathi Murphey
  - Loren Gragert
  - Medhat Askar