OPTN Histocompatibility Committee
Meeting Summary
January 11, 2022
Conference Call

Peter Lalli, Ph.D, D(ABHI), Chair
John Lunz, Ph.D, D(ABHI), Vice Chair

Introduction

The OPTN Histocompatibility Committee met via Citrix GoToMeeting teleconference on 01/11/2022 to discuss the following agenda items:

1. Review CPRA and HLA equivalency tables used in CPRA Calculation proposal
2. Updated waitlist analysis
3. Update concerning regional meetings and CPRA Calculation presentation

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

1. Review CPRA and HLA equivalency tables used in CPRA Calculation proposal

The Committee was briefed on the process used by the HLA Equivalency Tables and CPRA subcommittees to identify discrepancies in the OPTN unacceptable antigen to IMGT/HLA two-field allele equivalency tables and the results of the group's efforts. The Committee members were asked for their feedback on the appropriateness of the process the group used.

Summary of discussion:

The Chair described the process used to validate the equivalency tables, and asked for the Committee members' feedback about the appropriateness of the process. Broadly, the process consisted of the following:

- Staff assigned IMGT/HLA allele equivalences to all UNet℠ unacceptable antigens based on expert-assigned equivalences. Committee members were asked to consider whether the assignments should include or exclude expert-assigned equivalences;
- Staff then assigned allele equivalences based on WHO-assigned equivalences, and re-assigned any that disagreed with the expert-assignment;
- Staff then assigned allele equivalences based on OPTN-UA screening tables, and re-assigned any that disagreed with the previous assignment;
- Manual review by staff and subcommittee members;
- Committee members were asked to comment on whether the null alleles should be removed from the IMGT/HLA equivalences, and also how the WHO unconfirmed alleles that have only been reported by a single lab should be addressed.

The Chair asked the Committee members if this was a reasonable process, and the members concurred. One member indicated that there might be some confusion involving what constitutes the "expert" assignment process, and also asked whether the neural network process had been considered. UNOS staff said that the neural network process had been considered; however, it was not included as part of the group's efforts because there were still some questions about it. Another member stated that if

using the neural network is a more appropriate option, then the Committee may need more education about what the neural network was based on, in order to know what it is using. The member continued that a similar education effort about what the expert assigned approach entails might also be needed. The Chair pointed out that the labs are not performing crystal structures on each allele, so the serologic assignment results are still approximations, but very good approximations, and the Committee can be comfortable using them.

Another member stated that what is most important is to have good criteria defining how the Committee made its decisions, such as how they selected the antigen, and how they selected the antigen equivalents to alleles. Another member concurred stating that as long as there is a clear, publishable process then it will be clear that there was more to the decision-making than just a Committee decision. The members' consensus was that the process used was appropriate. UNOS staff said that they will follow-up on the neural network versus expert assigned question and notify the Committee members about the answers. However, members confirmed that an answer is not necessary prior to the document being released for public comment.

UNOS staff asked if there were any concerns about including unconfirmed alleles that have only been reported to the WHO nomenclature committee by a single lab. Some of the Subcommittee members who reviewed the information had asked whether or not unconfirmed alleles should be included in the CPRA equivalency tables, or if the Committee should wait for confirmation. There were some questions, but the consensus was that the Committee should wait until those alleles are confirmed by WHO. As a result, it was agreed that the unconfirmed alleles will be removed, with the understanding that the Committee can always revisit the question in the future.

The Committee then reviewed the few discrepancies that had been identified. There were a total of 13 discrepancies. Of those, only one would have an effect on candidate CPRA within one-hundredth of a percent. The other 12 were determined to have even less of an effect on candidate CPRA.

Next steps:

The Committee moved forward with the identified process. UNOS staff would follow-up on the neural network versus expert assigned question and report back to the Committee.

2. Updated waitlist analysis

UNOS Research staff provided a presentation about the impacts of changes to NMDP CPRA. The Committee had originally received the presentation in October, 2021, but all of the figures and tables have been updated since then. The main findings are that the recalculated NMDP CPRA shows improvement over the previous metrics, and the majority of waiting list candidates will see little impact from the change. In terms of outstanding issues, some alleles still cannot be distinguished in the updated dataset, and also because donors are rarely types at the allele level, candidates can add allelic UAs for CPRA boost without screening many donors.

The Committee agreed that the proposal should be made available for public comment as it currently exists.

Summary of discussion:

UNOS Research staff stated that the presentation covered a subset of the full report, which had been provided to the Committee via the meeting materials and was an updated version of previous reports presented to the Committee. The updates reflect the re-calculated NMDP CPRA to the expected versus actual percent of kidney donors screened. The analysis also looked at the impact on the waiting list for

certain subgroups, as well as, metrics on expected offer and transplant rates for these different CPRA calculations.

The most recent analysis conducted in October 2021 found that the new NMDP CPRA improved on the previous proposed CPRA calculations as well as the current OPTN CPRA. Based on the updates to the CPRA equivalency tables, the answer remains the same. For purposes of this discussion, staff focused on the changes between the October 2021 proposed CPRA and current proposed CPRA calculation. Staff reported that there was very little change with regard to the equivalency table differences from what was presented in October, 2021 and that none of the conclusions about improvements over the current OPTN CPRA calculation have changed. In fact, the differences between the two proposed CPRA calculations are very slight. For example, as part of the updated analysis, the number of outliers has been reduced from four to three. Staff reminded the Committee that the equivalency tables used for the analysis were not designed against the current tables, but rather against the upcoming implementation of equivalency tables. The important takeaway is that the NMDP CPRA is still performing better than the current OPTN CPRA calculation in all metrics the Committee considered.

UNOS staff also detailed the impact on the waiting list for a variety of sub-groups. No differences were identified in the overall number of registrations that changed CPRA when comparing the revised version to the version provided in October.

When comparing the magnitude of the CPRA change, the results indicate that the updates to the equivalence tables for the NMDP CPRA generally shifted up the CPRA slightly. The previous version of the CPRA equivalences tended to be missing alleles resulting in an under-representation of the candidate's actual sensitization. Nonetheless, for the vast majority of candidates, it was a very small shift.

The next analysis focused on the number of candidate registrations with 100 percent CPRA. Again, because the October 2021 calculation provided an underestimation, the updated results reflect an increase. Overall, a total of 39 candidates on the kidney waiting list would have their CPRA increase to 100 percent. Additionally, when considering ethnicity, the results are consistently proportional to the percent of registrations for each ethnicity. The findings suggest that a total of 17 black registrations would increase to 100 percent CPRA. This does not reflect a substantial change; however. In general, the minimum change in CPRA for some of the groups became less negative following the re-calculation. Similarly, there were very few differences between the October results and the updated results when looking at CPRA by region.

UNOS staff next provided an overview of which metrics are considered most predictive of offer rates. And, here the currently proposed CPRA calculation performed the best (with the best meaning the lowest AIC, which represents highest predictive correlation). The metric comparing the CPRA calculation predictions of transplant rates was also reviewed, and the conclusion was roughly the same.

Overall, a large number of updates were made to the CPRA equivalency tables in this iteration, but the actual impact on the overall waiting list kidney CPRA calculation was quite small overall.

The Committee members did not have any questions or follow-up comments.

3. Update concerning regional meetings and CPRA calculation proposal

Summary of discussion:

The Committee members considered several questions. First, whether the proposal should be released for public comment as currently written, or whether the Committee should make additional changes and submit the proposal as part of a special public comment period? The Chair recommended releasing

the document for public comment without any additional changes, and the consensus of the Committee was to follow that path. One Committee member had earlier recommended the inclusion of a section on the criteria for determining OPTN unacceptable antigen equivalents to IMGT/HLA two-field alleles prior to publication.

Second, the OPTN website has limits on file size, so the Committee needs to identify what supplementary materials should also be provided as part of the public comment release under the limitations. For example, the full genotype frequency data set that the Committee might consider providing as supplemental material is so large, it cannot be added to the OPTN public comment website. The Committee was asked about sharing the overall waitlist analysis, the lung ethnic frequency data analysis, and CPRA equivalency tables. UNOS staff also inquired about what the Committee might want to do with the genotype dataset, because it is too large to be added to the OPTN website. Staff asked if it would be helpful to provide the waitlist unacceptable antigen options instead? The Committee members agreed that it would be helpful and that it was acceptable to add a note on the public comment page indicating that the full genotype dataset can be obtained by contacting UNOS staff.

And third, the Chair asked that if any of the members are interested in joining the CPRA subcommittee, that they let UNOS staff know.

Following the discussions, the Committee members were reminded about the upcoming OPTN regional meeting schedule, and which members are regional representatives and would be responsible for presenting the proposal if it were included on the Discussion Agenda. If the proposal is part of the Consent Agenda, there will not be a formal presentation to the regions. In that case, it is likely there would be targeted outreach to the appropriate entities.

UNOS staff let the members know that, in terms of the virtual cross-matching workgroup, it is likely another Committee meeting will occur before they are asked to form the workgroup. More information about the workgroup will be provided at the next Committee meeting. HRSA staff reminded the members that there is an ongoing need for clarification of the benefits of virtual cross-matching, as opposed to a physical crossmatch, and such clarification would be helpful to CMS staff as they make a determination about how to go forward in terms of coverage. HRSA staff added that providing the information in as clear and plain language as possible will be very helpful to CMS staff. UNOS staff responded that the Committee will be contacting CLIA regarding representation on the workgroup.

Next Steps:

Committee members were asked to contact UNOS staff if they would like to participate on the virtual cross-matching workgroup.

Upcoming Meetings

- February 8, 2022
- March 8, 2022

Attendance

- **Committee Members**
  - Peter Lalli, Chair
  - John Lunz, Vice Chair
  - Caroline Alquist
  - Valia Bravo-Egana
  - Amber Carriker
  - Yvette Chapman
  - Idoia Gimferrer
  - Bill Goggins
  - Reut Hod Dvorai
  - Evan Kransdorf
  - Gerald Morris
  - Omar Moussa
  - Cathi Murphey, Past Chair
  - Marcelo Pando-Rigal
  - Vikram Pattanayak
  - Jennifer Schiller
  - Karl Schillinger
  - Manu Varma
  - Eric Weimer
- **HRSA Representatives**
  - Jim Bowman
  - Marilyn Levi
- **SRTR Staff**
  - Katie Audette
- **UNOS Staff**
  - Amelia Devereaux
  - Betsy Gans
  - Courtney Jett
  - Kelsi Lindblad
  - Eric Messick
  - Sarah Scott
  - Susan Tlusty