OPTN Histocompatibility Committee
Meeting Summary
April 13, 2021
Conference Call

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

Introduction

The Histocompatibility Committee met via Citrix GoToMeeting teleconference on 04/13/2021 to discuss the following agenda items:

1. Continuous Distribution Update
2. POC Report-Out
3. Require Notification of Critical HLA Typing Changes
4. HLA Tables Update Strategy
5. CPRA Transition Procedures

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

1. Continuous Distribution Update

UNOS Senior Policy Strategist presented on the current status of lung and kidney/pancreas continuous distribution. He also demonstrated the tradeoff curves tool, showing how changes in weighting for different attributes change candidate priorities on match runs.

Summary of discussion:

Committee members were strongly supportive of the proposed structure of continuous distribution and ability for modifications as needed. Committee members were also interested in how CPRA could fit into continuous distribution for non-renal organs.

Question for the committee: With Continuous Distribution, will policy need to require HLA typing prior to liver, intestine, heart, and lung match runs? Will this change how multi-organ allocation occurs?

- Committee members were strongly supportive of requiring HLA typing before match runs
- UNOS staff brought up that this may be an operational shift for OPOs, who often execute extrarenal match runs prior to receiving HLA typing information
- Multiple members postulated that this policy was likely in place due to previous limitations on the speed of HLA typing, but that a delay of 2-6 hours for HLA typing would likely be outweighed by the efficiency gained by the ability to utilize unacceptable antigens
- In addition, one member brought up that this would make for a fairer implementation of CPRA in lung as well, so that programs aren't entering unacceptable antigens simply for CPRA points but not being screened from match runs due to not requiring HLA typing

Next steps:

UNOS staff and committee leadership will take this feedback to the cross-committee workgroup.

2. POC Report-Out

Committee Vice Chair presented on the current work of the Policy Oversight Committee.

Summary of discussion:

Committee members had no questions or concerns.

3. Require Notification of Critical HLA Typing Changes

UNOS staff presented on the public comment sentiment, feedback, and post-public comment policy language changes to the Committee's proposal.

Public comment recommendations:

- Notifications of changes should also be sent to all HLA labs involved
- OPO post-procurement timeline to be 24 hours instead of 12, to be consistent with post-procurement culture reporting
- The committee should consider further assessment of root causes of HLA discrepancies
- Incorporation of an automated electronic notification

Summary of discussion:

The committee discussed application of the proposal to deceased or living donors. The language does not broaden from current policy. Living donor typings only get entered in KPD and through the TIEDI histocompatibility form post-transplant. Staff asked about A, B, and DR matching in the unacceptable equivalence tables versus the matching tables. The report reviewed by the Histocompatibility Committee does not account for equivalences but is based on the matching tables. The tables are being used to drive algorithms within the new CPRA calculator. If the use of the tables is expanding the original intent, does the Committee need to redefine how it uses the tables in the future? It was noted that the timing of typing is important. Policy language may not be fully defined in terms of timing, but clarification may need to be part of a future project instead of included without adequate review in this project.

In the last review of the tables, the Committee sought to ensure uniformity between matching and unacceptable tables. As part of the current review, the Committee discussed whether all equivalences need clearer definition to determine if it reflects a critical discrepancy in the OPTN tables. The Committee feels confident they've put into policy what they need for reporting critical discrepancies. If additional clarification or discussion is needed later, could do so at that point.

The Committee voted 14 yes, 0 no, 0 abstained to send the proposal to the Board of Directors.

Next Steps

The Board of Directors will review the proposed changes at their June Board meeting.

4. HLA Tables Update Strategy

Committee Vice Chair presented on the current discussions of the HLA Equivalency Tables Update Subcommittee and requested full Committee input on the two differing strategies discussed.

Data summary:

The presenter reviewed two options for the Committee to consider: updating the tables to expand to all common or common/intermediate alleles as defined by CIWD 3.0 (option 1) or just continue to review year by year and do not expand alleles beyond what is available in SAB testing (option 2). Pros discussed for option 1 would be to allow UNet to be more current with available testing and allow performance of

high resolution typing for reporting. Overall option 1 would allow the system to be more up to date and comprehensive. Option 1 could however lead to misunderstanding about high resolution typing if a test is used that isn't actually high resolution, like an RT-PCR. The community would need education or guidance so the right testing is used for high resolution typing. The Committee could consider additional data requests to look at donors with allele-level typing entered in DonorNet, or data showing if labs are truly performing high resolution typing, but the presenter noted the limitations of the data and that guidance would be preferable to a data request because of the data limitations.

Option 2 represents a continuation of the Committee's efforts to review HLA tables annually and update according to current policy, but this would still require piecemeal additions with delays in implementation. KPD is increasingly high resolution, and high resolution typing may not be able to enter unavailable alleles on donor/recipient histocompatibility forms. If the alleles are not expanded, it may become more difficult over time to use the tables in policy for all living and deceased donors.

In indicating support for this proposal, the DAC also specified that unacceptable antigens would be beneficial in allowing centers to auto-screen off those donors if they choose to. There should be uniform typing for candidate, living and deceased donors. Automation opportunities would reduce errors that come forward with typing from various places.

Summary of discussion:

The Committee discussed how this would impact update design of the CPRA calculator. In the reference data set, there will effectively be expansion of allele-specific categories. The data set reflects frequencies for alleles now even if not way to list the allele specific antigens that correspond to alleles. Should the values for allele specific unacceptables reflect frequency of allele in the donor population, or impact allele-specific unacceptable on decreasing offer rate? It is difficult to measure the impact of allele-specific unacceptables on decreasing offer rate, even adjusting for offers refused for manual vetting of the allele specific unacceptable and where the donor listed as parental antigen. The CPRA calculator would be expected to accurately reflect the chances of finding a donor who didn't have that specific allele or antigen.

A potential new CPRA metric is offer rate. When CPRA values of unacceptable are based on frequency of alleles in the population, CPRA is increasing but offer rate is decreasing. It may be difficult to interpret those sort of analyses where correlating CPRA values with offer rate and making a judgment as to what CPRA metric is more accurate. Question is whether we want CPRA to increase when offer rate doesn't increase? The impetus then is on manual vetting to have more offers refused to fill that gap between CPRA and offer rate. It's difficult to analyze the offer acceptance because of a lot of other reasons for offers to be refused other than immunology. It could be difficult to extract data because of refusal codes in which a donor is coded out for quality not immunology. The CPRA calculator thus will be reflective of the frequency of alleles in the deceased donor pool and the associated impact of that. The operating analysis will have some caveats.

In discussion of whether to update the HLA tables to be more reflective of the common or common/intermediate alleles, there was support for expanding the tables as much as possible. The Committee discussed that a very comprehensive review would set up for the future a robust system that can be more easily updated. To script out the tables, would need to define principles from the IMGT allele list and CIWD allele list. The Committee also considered that the CPRA calculator is going to have many more alleles available than previously. Scripting out could avoid inconsistent behaviors and errors. Committee members noted the need for a dictionary for alleles to match to serology. The Committee discussed utilizing a resource like IMGT but needing to define precisely what is being used and creating definitions to enter into policy. Committee members noted the benefit of option 1 to avoid playing

"catch up" every year. At the same time, this may be a significant effort to send to public comment in August on the current timeline. The other factor the Committee considered is compatibility with the CPRA calculator; if the more robust update isn't performed, would the CPRA calculator work well with the current tables? It would still be effective even with the current tables but may not reflect offer rates. After manual vetting for compatibility the fit for access that the patient would have based on antibody profile would fit pretty close.

The Committee overall preferred option 1 to option 2, but did not make any final decisions for this year's update to the tables to consider the effort to choose option 1 for this year versus waiting. Committee leadership and staff will follow up about feasibility of pursuing the change this year rather than next. Either way this is a significant priority for the Committee.

Next steps:

The HLA Typing Subcommittee will discuss these options further with an end to making a decision for the 2021 tables update.

5. CPRA Transition Procedures

The Committee considered whether a transition plan is needed for application of the new CPRA calculator, and additional outstanding questions related to the new CPRA calculator.

Factors affecting transition:

The Committee reviewed several factors affecting transition including:

- Programming of DPA1 and CIWD 3.0 alleles into UNet
    - Addition of new loci to CPRA that may not currently have unacceptables entered for them, and one completely new locus to Waitlist
    - Programs could also be entering additional unacceptables that don't currently add to a candidate's CPRA
- Will this require additional candidate or donor testing?
- Data entry time for candidates
    - Kidney program size range 0-4756 patients, median 267, mean 425
- How long will this transition take?
- Should transition include a new calculation, so members can see how unacceptable input affects a candidate's CPRA?

The Committee considered the following CPRA outstanding questions:

- How do we incorporate alleles if donors aren't typed at a high resolution? Do we need to evaluate the resolution of current DonorNet typing?
- How do we incorporate allele-level unacceptables with broad antigen equivalents within our tables? Do we include the frequencies of that board equivalent antigen? Do we include the frequencies of every antigen equivalent to that broad antigen?

Summary of discussion:

The Committee agreed that the new calculator should not require any additional candidate or donor testing. The Committee considered whether the changes of data entry was a reasonable timeframe. A member suggested a month as a transition; if candidates are already listed with unacceptable antigens, that will feed into the cPRA. The Committee discussed that programs could have 3-4 months from the the change to enter patient information ahead of information (since most places test quarterly). Another member noted that DP will be a big difference which will change a lot of patient CPRA for DP

antibodies. Could look at DQA1 versus DQB1 antibodies with heterodimers to see how many cases we may expect antibodies to be entered. Members discussed that a transition period may not be necessary but would not be a problem to include. The Committee agreed that a two-month transition period would be more than adequate. The Committee agreed that including the old and new calculation would be helpful, especially with changes in allocation for programs to get an idea of what the new list might look like.

The Committee also discussed instances in which a donor's DQ typing is incompatible with a patient's antibody. The list of these instances will be reviewed by the HLA Equivalency Tables Review Subcommittee to determine whether these are truly unacceptable or whether the broad equivalent antigens should be included. The Committee discussed how this could lead to falsely elevating a patient's CPRA. CPRA should be a reflection of the actual ability of a patient to be compatible with a donor. The unacceptables table is for practical use in differentiating the resolution of donor typing. Actual offer rate and donor compatibility should be separate. For example, you might get DQ3 with associations, but a negative crossmatch, and CPRA should reflect reality.

Next steps:

The HLA Equivalency Tables Review Subcommittee is meeting May 4th and will discuss the feedback from the Committee further.

Upcoming Meetings

- May 11, 2021

Attendance

- **Committee Members**
  - Amber Carriker
  - Bill Goggins
  - Cathi Murphey
  - Idoia Gimferrer
  - Jennifer Schiller
  - Jerry Morris
  - John Lunz
  - Manu Varma
  - Marcelo Pando
  - Pete Lalli
  - Reut Hod Dvorai
  - Tracy McRacken
  - Valia Bravo-Egana
  - Vikram Pattanayak
- **HRSA Representatives**
  - Jim Bowman
  - Marilyn Levi
- **SRTR Staff**
  - Katie Audette
  - Nick Salkowski
- **UNOS Staff**
  - Abby Fox
  - Adel Husayni
  - Betsy Gans
  - Bonnie Felice
  - Courtney Jett
  - James Alcorn
  - Kelsi Lindblad
  - Leah Slife
  - Nicole Benjamin
  - Rebecca Murdock
  - Ruthanne Leishman
  - Susan Tlusty
- **Other Attendees**
  - Loren Gragert
  - Medhat Askar
  - William Hildebrand