

## **OPTN Histocompatibility Committee**

### **Meeting Summary**

**November 9, 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 11/09/2021 to discuss the following agenda items:

1. DPB1 Frequencies in CPRA
2. Linkage Disequilibrium in CPRA
3. Rounding in CPRA
4. CPRA Language – Review and Vote
5. HLA Nomenclature Update Discussion

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

### **1. DPB1 Frequencies in CPRA**

The Committee focused this part of the meeting on discussing how some of the data available for typing frequencies for DPB1 only have typing information for groups. The Committee was asked if they preferred splitting the ambiguous alleles or combining them, as is already done for the DQA1.

#### Summary of discussion:

Loren Gragert led the discussion. It was stated that DPB1 is a unique locus in terms of policy because it contains unacceptable antigen categories that are based on antigen recognition domain equivalency. Therefore, there are sets of alleles that are identical in the antigen recognition domain. Adding it as the first allele in the list, it will result in blocking donors with any allele that is identical on the antigen recognition domain.

UNOS staff pointed out that, for the most part, the tables in policy use p-group equivalences for DPB1. There are only four instances in the DPB1 tables where there are single selector unacceptable antigens. And, that these would only screen off that one, single donor allele that is not within that p-group equivalence that are equivalent within exons two and three. What needs to be considered is that this would only be for four-specific alleles. Previously, the Committee had discussed combining everything that is undistinguishable in exons two and three. What is proposed is that the ambiguous alleles could be split using EM, and then take a direct count of the unambiguous type headings. Then split the frequency of ambiguous typings equally between every allele string. This approach might slightly overweight rare alleles, and slightly underweight more common alleles.

To demonstrate the different approaches, staff provided the CPRA of what it would be for the two separate methods. Staff provided an example showing that when splitting ambiguous alleles using EM, the allele DPB1\*104.01 has an individual CPRA value of 3.51. However, when combining all DPB1 alleles so they have the same frequency, then the CPRA weight is 16.88, because it would be combined with another allele, in this case 03.01. This occurs as a result of the donor recruitment typings. It was pointed

out that there is some asymmetry resulting, and whether or not that should be reflected in the CPRA calculator.

The question for the Committee was whether they would prefer to split the ambiguous alleles using EM, or would they prefer to combine the ambiguous alleles. For the Committee members' reference regarding the size of the impact on the population, UNOS staff provided the number of kidney candidates associated with each of the four single selector unacceptable antigens based on all kidney candidates identified in Waitlist from January 2018 through December 2020. A total of 342 kidney candidates were identified.

The Committee's consensus was to move forward with splitting the CPRA by DPB1.

## **2. Linkage Disequilibrium in CPRA**

The Committee then discussed how best to convey to the transplant community how the CPRA calculator is impacted by linkage disequilibrium. The CPRA calculation references a table of linked haplotypes to ensure that the unacceptable antigen frequencies are not over-represented with overlapping frequencies. If another unacceptable antigen is added, then the percentage is likely to go up, and it could be impactful. UNOS staff pointed out that for transparency purposes the OPTN has to explain how any changes might impact a candidate's allocation score, and also provide educational information about the changes to the transplantation community. The question for the Committee was, what is the best mechanism for sharing information about the changes?

A Committee member recommended having educational material available for candidates, physicians, and other stakeholders who may not be familiar with population genetics. Another member asked whether the expectation is that the information would be provided in a regional meeting forum or through some other method? The feedback was that this is probably not a discussion for a regional meeting, because there is so much information associated with it. UNOS staff suggested that inclusion of educational material on the OPTN website might be a more appropriate option.

The Committee's consensus was that they had no concerns about incorporating the information.

## **3. Rounding in CPRA**

For allocation calculations, a predetermined limit has to be established for rounding values. The number of numerals available for use in all calculations has to be limited for both allocation purposes and for display purposes. Such cutoffs should be considered within their clinical significance. UNOS staff stated that on an analysis of the number of deceased donors suggests that six decimal places would be clinically significant for CPRA. Based on the analysis, it is believed that six decimal places will probably produce more precision than necessary; however, six decimal places is also useful as a tiebreaker in allocation scoring. The Committee members had some discussion about the proposed rounding amount, and agreed that six decimal places is appropriate.

## **4. CPRA Language – Review and Vote**

UNOS staff provided an overview of each section of the proposed policy for Committee members' consideration. The members were largely supportive of the draft policy as written, and had questions about certain aspects of the proposal. The Committee approved the proposed policy language for distribution during the January-March, 2022 public comment period.

### Summary of discussion:

UNOS staff displayed and discussed each proposed change to the Committee members.

The proposal updates the definition of CPRA. CPRA will be derived from antigen allele epitope genotype frequencies from the different populations in proportion to those populations' representation. This is different than deriving CPRA from haplotype frequencies. The proposal also removes the introductory definition of CPRA from the Kidney and Pancreas policies. The Kidney and Pancreas allocation policies will still describe how CPRA works within those allocation systems, but it was determined that CPRA did not need to be defined again.

The primary proposed changes are found in *Policy 4.6: Calculated Panel Reactive Antibody (CPRA) Calculation*. It is proposed that the CPRA for candidates will be calculated automatically in the hospital for unacceptable antigens to the OPTN. The draft language recognizes that the Committee wanted CPRA to be calculated for every candidate, not just those candidates for whom it is used in allocation policy. As a result, the policy is open-ended so that CPRA won't only be calculated for kidney, pancreas, and lung candidates. This section of policy also includes the CPRA equation. Other additions include that the antigens in the equivalency tables have combined frequencies for CPRA calculation. The proposed policy also makes clear that the OPTN maintains the list of genotype frequencies and that the list will be provided on the OPTN website.

The proposed changes also update Policy 4.9 to focus on HLA Value Updates. The proposal removes duplicative language describing how HLA matching works. The proposal also clarifies that the Committee needs to review the HLA matching tables on an annual basis, but that Committee can recommend changes to the tables at any time. The proposal also specifies the tables the Committee will review to provide clarity for the community. This change will be beneficial because it will eliminate situations where the information has not been updated in a number of years, but the values have changed. The proposal will help the Committee ensure that the information in the tables stays more current. The proposed change has also been discussed with internal departments, and it should not be a large lift to remain current. The draft policy also states that future changes to the tables are eligible for the expedited action pathway.

As the members are aware, the Committee has a proposal being considered for approval at the December 2021 OPTN Board meeting. If approved by the Board in December, that language will be subsequently amended as part of the proposal before the Committee today by adding a description of how the CPRA calculation works.

The current proposal also removes the approximation tables for DR51, DR52, and DR53.

The members were supportive of the proposed changes. There was some discussion of whether the proposed changes will result in CPRA being calculated for all patients on the waitlist, regardless of the type or types of organ(s) being sought. The Committee members were told that is correct. The Committee members were interested in knowing because currently there is no requirement to report unacceptable antigens, and as a result, the amount of candidate information is incomplete and/or inconsistent across candidates. Members wondered about how this inconsistency will be addressed. For example, heart transplant programs are not required to enter unacceptable antigens on the waitlist forms. Such programs can instead directly enter a CPRA value into the adult heart justification forms, as opposed to having a value calculated. The Committee members identified the need for complete data to be entered consistently by the programs on behalf of their candidates as a very important issue. They also discussed that the matter is outside the scope of the current project, and agreed that it is appropriate for consideration for a potential future project.

Following the discussion, the members were asked if anyone was opposed to the proposed policy language, or whether anyone wished to abstain from voting on the proposal. There was no opposition,

nor were there any abstentions. The proposal was unanimously approved for submission to public comment in January-March 2022.

## **5. HLA Nomenclature Update Discussion**

Committee leadership provided an overview of the issues around HLA nomenclature, and stated that the matter would be discussed in more detail at the next Committee meeting.

### Summary of discussion:

The Chair reminded the members that the nomenclatures used by the OPTN and the World Health Organization (WHO) can and should be better aligned. The ARB, and likely CAP, have had to deal with the differences in managing how laboratories are reporting typing. In previous discussions, the Histocompatibility Committee members have recognized that they probably need to address the matter. For example, there is currently somewhat of a mix of molecular and serologic nomenclature in the HLA tables.

The Chair continued that the Committee will hold future discussions about the available options moving forward. First, is there a benefit to maintaining the serologic nomenclature or should the Committee try moving to a methodology where all molecular or at least molecular antigen groups are used instead of serology? Second, for other loci, such as DPB1, does the Committee want to consider alternatives outside of p-groups? The members briefly discussed some of the advantages and disadvantages of the different options, and decided to hold off on a deeper discussion of the matter until their next meeting, which is scheduled for December 14, 2021.

### **Upcoming Meetings**

- December 14, 2021

## Attendance

- **Committee Members**
  - Caroline Alquist
  - Amber Carriker
  - Reut Hod Dvorai
  - Idola Gimferrer
  - Bill Goggins
  - Evan Kransdorf
  - Peter Lalli, Chair
  - John Lunz, Vice Chair
  - Gerald Morris
  - Jennifer Schiller
  - Karl Schillinger
  - Marcelo Pando
  - Vikram Pattanayak
  - Phyllis Weech
  - Eric Weimar
- **HRSA Representatives**
  - Jim Bowman
  - Marilyn Levi
  - Raelene Skerda
- **SRTR Staff**
  - Katie Audette
- **UNOS Staff**
  - Betsy Gans
  - Courtney Jett
  - Eric Messick
  - Leah Slife
  - Susan Tlusty
- **Other Attendees**
  - Medhat Askar
  - Loren Gragert