

OPTN Histocompatibility Committee

Meeting Summary

July 19, 2021

Conference Call

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Introduction

The Histocompatibility Committee met via Citrix GoToMeeting teleconference on 07/19/2021 to discuss the following agenda items:

1. CPRA Data Discrepancies
2. CPRA Proposed Analyses
3. CPRA Timeline/Next Steps

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

1. CPRA Data Discrepancies

Committee leadership and staff presented on the discovered discrepancies in the proposed CPRA calculator.

Data summary:

Current CPRA data set combines intermediate-level typing with g-group allele strings with high-resolution typing. The alleles within this data set are rolled into antigen-recognition domain (ARD) groups, and there are 37 HLA-C, DQA1, and DQB1 locus alleles currently recognized within the OPTN policies and UNetSM systems that don't have individual frequencies, as well as additional DPB1 locus alleles. Below is a table of the combined alleles and the proposed CPRA points assigned to all alleles within group using the currently proposed CPRA data set.

G-group first allele	All alleles combined	CPRA points
C*02:02	C*02:02, *02:10	9.6
C*07:01	C*07:01, *07:06, *07:18	27
C*17:01	C*17:01, *17:03	3.8
C*18:01	C*18:01, *18:02	1.1
DQA1*01:01	DQA1*01:01, *01:04, *01:05, *01:12	26
DQA1*01:02	DQA1*01:02, *01:08, *01:09, *01:11	37
DQA1*03:01	DQA1*03:01, *03:02, *03:03	29
DQA1*04:01	DQA1*04:01, *04:02, *04:04	9.0
DQA1*05:01	DQA1*05:01, *05:03, *05:05, *05:06, *05:07, *05:08, *05:09, *05:11	44
DQA1*06:01	DQA1*06:01, *06:02	0.51
DQB1*02:01	DQB1*02:01, *02:02	37
DQB1*03:01	DQB1*03:01, *03:19	35

This is expected to impact at least 4.2% of the kidney waiting list who has at least one two-field allele entered as an unacceptable antigen for HLA-DQA1. Based on the counts of unacceptable antigens entered in Waitlist, it is apparent that unacceptable antigens within the same ARD are being listed at different frequencies. This could increase candidate CPRA up to 30-40 points in some cases, which the data does not support as the actual proportion of incompatible donors. The table below shows the number of candidates that would be affected by each ARD group combination in the proposed CPRA calculator. This analysis did not distinguish between candidates listed with an unacceptable antigen for only one or more than one allele within the ARD. It is based on all kidney candidates on Waitlist as of June 30, 2021.

G-group first allele	CPRA points	Kidney Waitlist Candidates with at least one allele within the group
DQA1*01:01	26	453
DQA1*01:02	37	443
DQA1*03:01	29	3485
DQA1*04:01	9.0	1190
DQA1*05:01	44	5848
DQA1*06:01	0.51	1497

An analysis on calculated vs. observed CPRA based on the number of actual incompatible kidney donors was shown, with and without the ARD groups included. The exclusion of the ARD groups showed a much higher level of concordance between actual and expected incompatible kidney donors, with the Root Mean Square Error (RMSE) a more than halved standard deviation with the exclusion of the ARD groups.

2. CPRA Proposed Analyses

Committee leadership and staff presented the following as the proposed next steps for the data set and analyses to increase accuracy of the proposed calculation and requested the committee’s feedback.

- Breakdown of intermediate vs. two-field high-resolution typing in the NMDP database
 - Number and percent of data being used as intermediate vs. high-res
 - Analysis based on resolution (intermediate vs. high) of racial concordance with OPTN deceased donors
- Breakdown of high-resolution typing for the alleles unable to be distinguished at intermediate resolution
 - Including analysis of racial concordance with OPTN deceased donors

Staff proposed the following as a potential alternate solution to the discrepancies, if the above ask was not possible:

- Could use the allelic proportions from CIWD 3.0 for HLA-C and DQB1 discrepancies
 - Ethnic and racial categorization does not line up 1:1 with OPTN categorization
 - No haplotype data to inform an analysis on population similarity
- No information on HLA-DQA1
 - Half of ARD discrepant DQA1 alleles were not studied in CWD 2.0

Summary of discussion:

Committee members were supportive of the proposed data set changes and analyses. CPRA contractor explained that there likely won’t be as significant of haplotype data, but a committee member posed

that the committee wants to move forward with a genotype calculation, so that isn't a significant limitation.

One committee member asked what the next steps would be if the high-resolution data wouldn't be able to separate the alleles. Staff responded that it would depend on the committee members' medical judgment, so long as they are transparent about what frequencies are included in CPRA and discuss where or not there is a biological justification for their reasoning. One member stated that there can be antibodies formed to specific two-field alleles within ARD-groups, and that there is literature to support it in some cases.

Another member asked how to present these concerns at regional meetings. A different member posed that it's a good question for community input, and if there is concerns about not being able to distinguish alleles it would be beneficial to have that feedback during public comment.

One member brought up concerns that even though including allele-level antibodies increases equity and allows for a better measure of true sensitization, it won't actually screen off donors when most are typed at a serologic antigen equivalent. Members discussed the possibility of monitoring to determine if this is being abused, as well as creating policy around how unacceptable antigens must be assigned. Members discussed the possibility of monitoring the assignment of unacceptable antigens through the Membership and Professional Standards Committee (MPSC) and Member Quality staff or ASHI/CAP site surveys.

Next steps:

Staff will discuss the concerns around unacceptable antigens with MPSC/MQ and bring potential monitoring options to the committee at a future meeting.

3. CPRA Timeline/Next Steps

Committee leadership and UNOS staff presented the option of withdrawing the proposal for public comment for August 2021, with the potential of public comment by or before January 2022 and maintaining the proposed implementation timeline for Fall 2022. Committee chair recommended a vote to withdraw the proposal from public comment consideration at this time rather than have it repealed by the Policy Oversight Committee, Executive Committee, or HRSA.

Summary of discussion:

The committee discussed whether a special public comment or January public comment would be more appropriate. As regular public comment would allow for increased community involvement through regional meetings, especially with kidney transplant programs, the committee felt that would be the better option. Staff pointed out that it's not a decision necessary to be made now, and that the only decisions needed for this meeting are the proposed analyses and whether or not to withdraw the proposal from August 2021 public comment. Committee members agreed that the implementation timeframe is what is the priority, and asked for ways to solicit additional feedback ahead of January public comment to try to ensure there wouldn't be unexpected concerns that would need to be addressed and delay the proposal from the target implementation in Fall 2022.

Committee chair called for a vote to withdraw *Change the Calculated Panel Reactive Antibody Calculation* from public comment consideration for August 2021: 12 yes, 0 abstain, 0 no.

Next steps:

CPRA contractor will work with staff to provide the requested alterations to the data set and re-run the previous analyses.

Upcoming Meetings

- August 10, 2021, 12 PM EDT, Teleconference
- September 14, 2021, 12 PM EDT, Teleconference
- October 12, 2021, 12 PM EDT, Teleconference

Attendance

- **Committee Members**
 - Amber Carriker
 - Bill Goggins
 - Gerald Morris
 - Idoia Gimferrer
 - Jennifer Schiller
 - John Lunz
 - Karl Schillinger
 - Omar Moussa
 - Peter Lalli
 - Reut Hod Dvorai
 - Valia Bravo-Egana
 - Vikram Pattanayak
- **HRSA Representatives**
 - Marilyn Levi
 - Raelene Skerda
- **SRTR Staff**
 - Katie Audette
 - Nick Salkowski
- **UNOS Staff**
 - Abby Fox
 - Betsy Gans
 - Bonnie Felice
 - Courtney Jett
 - Emily Kniepp
 - Kelsi Lindblad
 - Lauren Mauk
 - Leah Slife
 - Samantha Weiss
 - Susan Tlusty
- **Other Attendees**
 - Cathi Murphey
 - Loren Gragert