

**OPTN Histocompatibility Committee  
Meeting Summary  
March 8, 2022  
Conference Call**

**Peter Lalli, PhD, F(ACHI), Chair  
John Lunz, PhD, D(ABHI), Vice Chair**

## Introduction

The Histocompatibility Committee (the Committee) met via Citrix GoToMeeting teleconference on 03/08/2022 to discuss the following agenda items:

1. Public Comment Feedback: *Change Calculated Panel Reactive Antibody (CPRA) Calculation* proposal
2. Discrepant Typings Subcommittee Update
3. Specimen Storage Discussion
4. Follow-Up & Next Steps

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

### **1. Public Comment Feedback: *Change Calculated Panel Reactive Antibody (CPRA) Calculation* proposal**

The Committee received an overview of the feedback that was received during public comment on the *Change Calculated Panel Reactive Antibody (CPRA) Calculation* proposal. A full list of comments and analysis by theme was included in the Committee's meeting materials.

The following public comment feedback was presented to the Committee:

- Suggestions
  - Modify unacceptable antigen entry to make it easier to enter multiple specificities for high PRA patients
  - Increase transition time to longer than one week for kidney programs for CPRA>98% patients
    - Some programs say one week would be sufficient, many say it would not
    - Increase amount of data in transition report so programs are better able to assess impacts on full waitlist, not just highly sensitized candidates
- General feedback
  - Ensure that the criteria for unacceptable antigen entry is not overly stringent or limiting patient-provider choice
  - Increasing the size of the data set will increase accuracy
  - Support for increasing access of highly sensitized candidates
  - Support for having CPRA viewable for all candidates, not just kidney/pancreas/lung candidates
  - Potential for this to change program behavior for unacceptable antigen listing, recommendations to monitor changes
- Concerns

- This may decrease matching efficiency through the entry of unacceptable antigens for human leukocyte antigen (HLA)-DQA1, DPA1, and DPB1 and lead to a decrease in transplants
- DP alleles should not be used in CPRA calculation
  - Concern that DP antibodies require high relative MFIs to cause positive flow crossmatches, and belief that this means DP antibodies are clinically irrelevant
  - Concern that anti-DPB1 antibodies are common in highly sensitized candidates, and if centers list lower-level antibodies it may decrease access for other highly sensitized candidates due to an increase in national share numbers
  - Other comments suggested that DP allele incorporation in CPRA is overdue

Summary of discussion:

A member inquired about the discussion surrounding DP alleles being included in the CPRA calculation, since centers could list antibodies they don't think are clinically relevant, or are no risk to disadvantaging their patients because they would not list and would still be able to accept the organ offers from donors with the DP antigens their candidate may have antibodies to. The Chair stated that the Committee didn't have much discussion regarding the listing of DP antibodies because the Committee's stance was that they needed to allow programs clinical discretion in their practice of medicine. In addition, the Chair mentioned that he didn't think there was enough long-term data on the patient impact of DP antibodies, which would be needed to support excluding DP alleles from the calculation. In addition, he stated that the purpose of CPRA is to combat the barrier to access a sensitized candidate faces through not being able to accept organ offers due to antibodies, and that if the program is willing to accept the organ offers for a candidate in spite of antibodies the candidate does not have a lower access to organs and does not need prioritization. The CPRA contractor agreed that this is the purpose of CPRA, to show the percentage of donors a candidate cannot accept, and that its use in allocation should not advantage/disadvantage any candidates, but instead should counteract the candidate's biological disadvantage.

The Chair emphasized the importance of monitoring this proposal and mentioned that if, five years from now, candidates with DP antibodies included in their CPRA calculation have significantly higher or lower transplant rates, or data shows DP antibodies are irrelevant in transplant, then the Committee can revisit the inclusion of DP unacceptable antigens in CPRA at that point.

There was no further discussion.

**2. Discrepant Typings Subcommittee Update**

The Committee received the following information on the 2021 Discrepancies Update:

- Decrease in clerical errors since implementation of double entry
- Other technical/interpretative errors and sample integrity errors remain constant
- Cw3 split versus parent may no longer be relevant to evaluate, or that the committee may need to clarify how they expect C\*03:05 to be reported

Discrepancy	2021					Total
	Q1	Q2	Q3	Q4		
Sample Integrity Issue	3	0	0	0	0	3
Typing Errors (Clerical, Technical and Interpretive)						33
Bw4/Bw6 Issues	1	1	0	0	0	2
DRB345 Issues	2	0	0	1	1	3
DR53 Null Issues	1	0	0	0	0	1
DPB1 Errors	2	3	2	4	4	11
Other Typing Errors	9	3	2	2	2	16
Split vs. Parent						51
Cw3	16	10	14	4	4	44
DR3	0	0	0	1	1	1
DQ3	1	2	0	2	2	5
Other	0	1	0	0	0	1
Total Errors	35	20	18	14	14	87
Critical Errors	15	7	4	7	7	33
Total Donors	3245	3611	3463	3248	3248	13567
Percentages	1.08%	0.55%	0.52%	0.43%	0.43%	0.64%
Critical Error Percentage	0.46%	0.19%	0.12%	0.22%	0.22%	0.24%
Discrepancies	15	7	4	7	7	33
Match Rerun	9	3	1	6	6	19
Percentage	60.00%	42.86%	25.00%	85.71%	85.71%	57.58%
Average Time Between Match Runs	9.6	7.3	8	2	2	6.725

The Committee also reviewed recommendations from the Discrepant Typings Subcommittee in response to a memo that was sent to the Committee regarding concerns about the current lack of required redundancy for HLA typing, as compared to ABO typing, in spite of the fact that both typings are critical to determine candidate/donor compatibility. The concerns raised included that incorrect HLA typing in the match run may mean offers are given to patients highly sensitized against the donor, that virtual crossmatching or assessment of immunologic risk requires correct HLA typing to determine candidate/donor matches and DSA which affects acceptance/rejection of an organ offer and peri-transplant care for a recipient, and that crossmatches and confirmatory typings often occur after transplant for hearts and lungs which leaves the potential for hyperacute or accelerated rejection. The memo recommended an increase in safeguards to ensure correct donor HLA typing, with some redundancy in the system, including requiring confirmatory HLA typing in policy.

The Discrepant Typings Subcommittee provided the following recommendations:

- Deceased donors should have two HLA samples run, drawn at two separate times, similar to ABO
  - Possibly further discussion on best practices for different sample types or assays
  - Did not want to create requirements that would increase the time to allocation or burden on staff

- Both samples should be typed at a molecular level for all loci
- Require raw HLA typing data to be uploaded for both samples in DonorNet attachments

Summary of discussion:

*2021 Discrepancies Update*

A member inquired if the Discrepant Typings Subcommittee had looked at discrepancies that were not otherwise categorized. The member explained that their center has been flagged for reporting a C\*03:05 as a Cw3 during an ASHI inspection. The Chair explained that the Subcommittee started evaluating Cw3 discrepancies out of a concern that donors were being improperly screened from match runs due to C\*03:05 being listed in UNet as Cw3, even when it has different reactivity from the serotype and should be a separate allele. The incoming Vice Chair also clarified that often C\*03:05 is reported in a string of Cw3 alleles, and that either way the lab reports is incorrect, as the HLA typing is neither an unambiguous Cw3 or an unambiguous C\*03:05, and that often a lab cannot distinguish the two in the time constraints for deceased donor typing.

When discussing the issue of C\*03:05 reporting, the Vice Chair mentioned that there is a current study underway by the Stanford HLA lab to better map alleles to serotypes, and that the committee should develop their recommendations after this study and the work of the upcoming International Histocompatibility and Immunogenetics Workgroup 18 (IHIW18) HLA dictionary project are published. He also mentioned that the committee evaluation of serologic mapping may be better sequenced along with a proposal to update the HLA equivalency tables to World Health Organization (WHO) HLA nomenclature, and that trying to complete this as a project ahead of the other work in the broader community and committee would not be advisable.

*Memo Recommendations*

To open the discussion, the Chair posed the following questions:

- Do you agree with the subcommittee's recommendation? Do you have any concerns or additions?
- Does the HLA confirmatory typing need to be completed prior to match run, or transplant?
  - Could there be any timing concerns if it needs to be completed prior to match run, or can these samples be processed completely in parallel?
- Do we need a discrete data field that captures that two samples were tested?
  - Does this add any value beyond the raw HLA data uploaded in the attachments, or is this simply for compliance monitoring?
  - If yes, do we need a field that the testing was concordant?

The Committee agreed with the recommendations of the subcommittee. A member mentioned that they believe it is absolutely feasible to run confirmatory typings without a delay in match run execution, even if a lab only has one real-time PCR instrument they could still be completed within three hours running two plates back-to-back. The member also mentioned this is still within the timeframe of when infectious disease testing would be completed.

Another member stated that they already run confirmatory typings in their laboratory; however, they run one sample on two separate assays. The member stated this is feasible and their lab would just have to start using two samples instead of one. Another member stated that they have the same practice and agree that the change would be feasible.

A member inquired if labs are only billing organ procurement organizations (OPOs) once for typing the one sample and if others' behavior would change if it was required to type two samples. Three members

who report currently performing confirmatory typing state that they only bill once, since it's only one sample and it's for their peace of mind. One member stated that they would consider changing their itemized billing practices if it were required. Another member stated that they aren't really billing the OPOs, that everything is based on the laboratory contract and reimbursable through CMS as a part of the organ procurement cost report. He stated that he currently just has a single deceased donor typing fee, which includes on call availability, rather than itemizing the fee. Staff stated that, if the Committee were to propose this new policy, then it would need to be clarified that labs and OPOs may need to alter their agreements, and possibly propose items for OPOs and labs to consider.

One member stated that there should be a place in UNet to enter the confirmatory typing. Staff asked if there would need to be two separate fields for HLA typing entry, or if the guidance to the community would be to simply enter the highest resolution donor typing, out of concern that multiple typings could create difficulties with the logic for unacceptable antigen screening and HLA matching on the match run. Members stated that it seemed reasonable to just input the highest resolution typing in the discrete fields in DonorNet. The Vice Chair pointed out that adding additional data fields would have a technical implementation cost associated with the proposal, which may delay the proposal's approval or implementation due to scarce resources, especially if there is logic associated with two separate HLA typings. Another member stated that the additional data collection would really just be compliance monitoring, and that the necessary information would be in the existing data fields and raw typing uploads attached. The Chair stated that there should just be two date fields of when the two samples were typed and that may be less burdensome than requiring the entry of two full HLA typings but would still document the attestation that two typings were done and they were concordant.

There was no further discussion.

### **3. Specimen Storage Discussion**

The Committee reviewed OPTN Policy 4.8 regarding preservation of excess donor specimens for future histocompatibility testing and discussed recent questions that had arisen, including the intended purpose of the stored donor specimens, and what the exact specimens should be and how they should be stored.

The Vice Chair opened the discussion by asking the following questions:

- Do histocompatibility labs still need a donor sample to test for at least five years after transplant?
- Is there a specific sample type that may be required?
- Are there any type of educational materials that the Committee can create for the community for clarification of the requirement?

#### Summary of discussion:

One member stated that it would be helpful to be able to explain what labs should store, including the amount of isolated DNA and/or potentially viable cells, and that labs would appreciate the granularity. Another stated that clear guidance on those matters would definitely be appreciated, but that it's likely too granular for policy.

A member stated that one of the concerns is that some labs don't freeze cells for viability and there's a potential for adding on a little bit more burden for those labs who don't currently do so. The member stated that the question is whether it is meaningful for those labs to have those viable cells, which could be used for both crossmatching and repeat typing.

A member suggested that guidance should be updated to include frozen extracted deoxyribonucleic acid (DNA) since DNA is easier to freeze and work with, and that he's recovered DNA >8 years old that is still usable in spite of older storage methods being used.

Staff asked if only requiring DNA storage would cover all lab requirements for future donor testing. A member inquired if the policy language is intended as excess sample storage for the needs of the member lab/transplant program or for the greater good. Some labs may determine that they are never going to do a retrospective cross match with the stored samples, so they don't necessarily need to store viable cells. Staff explained that the intent of storage has not been clarified in policy or guidance.

A member stated that an easy solution to community questions and concerns would be to clarify that each lab should store whatever is needed for their own testing for the next five years, and that the individual lab would determine what samples meet their needs.

A member mentioned that that may be inadequate when it comes to living donors, whose recipients may move and change centers where they receive care. The member emphasized that labs that do work for the transplant center have to be responsible and have samples available for other people.

A member also mentioned that there may be differences in requirements between labs that perform deceased donor typings, labs that perform crossmatching, and labs that perform living donor typings, and that in general the policy and guidance could benefit from revision and clarification.

Members agreed with that distinction and mentioned that when updating guidance and policy the Committee needs to clarify labs performing typing and labs performing cross matching.

To summarize, staff stated that this topic should continue to be discussed as a potential project to revise both the Committee's 2017 guidance and some of the histocompatibility policies.

There was no further discussion.

#### **4. Follow-Up & Next Steps**

The Committee was asked to continue thinking about deceased donor specimen storage to discuss during their virtual, in-person meeting on April 5 from 11:00 AM to 3:00 PM ET.

#### **Upcoming Meetings**

- April 5, 2022 (teleconference)

## Attendance

- **Committee Members**
  - Peter Lalli
  - John Lunz
  - Amber Carriker
  - Bill Goggins
  - Eric Weimer
  - Gerald Morris
  - Idoia Gimferrer
  - Jennifer Schiller
  - Karl Schillinger
  - Marcelo Pando
  - Omar Moussa
  - Reut Hod Dvorai
  - Valia Bravo-Egana
  - Vikram Pattanayak
- **HRSA Representatives**
  - Jim Bowman
  - Marilyn Levi
  - Raelene Skerda
- **SRTR Staff**
  - Katherine Audette
- **UNOS Staff**
  - Courtney Jett
  - Amelia Devereaux
  - Sarah Scott
  - Susan Tlusty