

**OPTN Histocompatibility Committee
Meeting Summary
September 14, 2021
Conference Call**

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

Introduction

The Histocompatibility Committee met via Citrix GoToMeeting teleconference on 09/14/2021 to discuss the following agenda items:

1. Public Comment presentation: Update on OPTN Regional Review Project
2. Simultaneous Heart-Kidney and Liver-Kidney Transplants and Immunologic Risk: Discussion
3. Discrepancies Between OPTN and NMDP Two-field Allele Data

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

1. Public Comment presentation: Update on OPTN Regional Review Project

UNOS staff presented information about the Regional Review project, and asked for Committee feedback.

Summary of discussion:

UNOS staff provided Committee members with a presentation regarding the Executive Committee's Regional Review Project. The Project's objective is to re-evaluate the effectiveness of the existing regional structure in light of the current and future needs of the transplantation community. The current regional structure has been in place since the late 1980s. During this time, there have been substantial changes in the OPTN's donor and transplantation community, and in the OPTN's organ allocation policies. Last summer, the Executive Committee issued an initial request for community input about the regional review that resulted in varied opinions concerning next steps. Following that request for feedback, the consulting firm EY (formerly, Ernst and Young) was hired to manage the project going forward. EY reviewed community feedback and performed its own research and analysis to develop initial recommendations for the OPTN Board of Directors. Today's presentation represents EY's recommendations. Based on the community feedback concerning EY's recommendations, the OPTN Board of Directors will consider whether to propose changing the existing regional structure. If they do, then a public comment proposal would be developed sometime in the future.

EY identified three potential models for consideration. The models are: Communities of Common Interest, Repurposed Regions, and Hybrid Cohorts. The Communities of Common Interest model eliminates the geographic regions and instead organizes OPTN members into like-interested communities. For example, a community could be grouped by member type and interest. Such communities would operate similarly to how the regions function today, in that they would continue considering and debating policy. One difference from today's regional approach, communities would elect counselors to the Board, instead of regional counselors.

The Repurposed Region model would maintain the concept of geographical regions, but consider re-sizing or re-drawing the regions based on different factors that might include population size, or the

number of transplant programs, or other forms of geographic proximity. In this model, the regions would elect individuals to serve on a regional advisory committee. Individuals on the regional advisory committee would not be part of the OPTN Board of Directors, but would advise the Board on regional considerations and policy development, and provide a more national perspective.

The Hybrid Cohorts model would organize members based on geographic proximity, particularly community members that work together operationally, such as organ procurement organizations, histocompatibility labs, and transplant programs. In addition, stakeholder groups would be established to represent other groups, like patients.

Members of the Histocompatibility Committee were asked to provide feedback regarding the broader concepts identified with the models (as opposed to picking one of the three models). For instance, in terms of communicating with each other, should members be grouped by geographic proximity, existing working relationships, common roles or professions, or some other option? If regions are maintained, what changes should be considered? Should they be re-sized based on the number of transplant programs, transplant candidates, overall population, or another metric? Furthermore, what functions should any redefined groups have?

The Committee Chair indicated interest in the Communities of Common Interest model because of the potential impact a national group of histocompatibility members might have. The Chair also expressed a concern with the model about how histocompatibility labs that are associated with a transplant hospital (non-independent labs) would be represented under the Communities model.

Another Committee member asked about how shifting population dynamics would be accounted for in the models. UNOS staff responded that different metrics for capturing regions or populations have been considered and will continue to be considered as the project continues moving forward. For instance, the project has explored the use of different U.S. Census data, including data based on relationship mapping.

Another Committee member supported the regional structure because it creates a very multi-disciplinary approach that produces policy that is aligned and streamlined. The member also stated that while its impact has been reduced, geography remains a factor in allocation, and therefore, entirely disregarding geography is not appropriate. Perhaps what is needed is to rethink what the size or scope of the regions. The Committee Chair agreed with the sentiment about the importance and benefit of the cross-disciplinary discussions that occur as part of the regional meetings. Under the Community of Common Interest approach there is a potential for groups with similar interests to focus on their issues to the exclusion of other ideas.

Regarding the Hybrid Cohorts model, a member suggested that factors that might be most appropriate for developing policy might not be the same factors that are most appropriate for other OPTN functions. As a result, the question was raised about which functions might give greater priority to geography as a model versus the functions that might give greater priority to the Community of Common Interest.

UNOS staff also asked Committee members to comment on opportunities to best engage the patient population as part of the existing regional meeting process, or as part of the recommended models. The Committee Vice-chair acknowledged that discussion of issues involving histocompatibility can be very technical, and suggested that perhaps a layman's summary of the Committee's work could be created and reviewed with patient liaisons for feedback on readability.

The Committee members were encouraged to submit comments on the OPTN's public comment webpage, and to complete the separate feedback form that can also be found on the webpage. Members were also told they could contact UNOS staff with any specific questions.

Next steps:

UNOS Staff will draft a public comment response on behalf of the Committee and share it with leadership for review.

2. Simultaneous Heart-Kidney and Liver-Kidney Transplants and Immunologic Risk: Discussion

The Committee was provided with an overview of the Ad Hoc Multi-Organ Transplantation Committee's purpose and efforts to date. Committee members were also asked to provide clinical feedback about the potential immunologic risks associated with Heart-Kidney and Lung-Kidney transplants, and whether those risks are similar to or different from the immunologic risks associated with Liver-Kidney transplantation.

Summary of discussion:

The Ad Hoc Multi-Organ Transplantation (MOT) Committee was established by the Executive Committee in April 2021, and charged with developing allocation policies that address multiple organ groups and multiple organ allocation policy. The Committee is comprised of members of the organ-specific committees and the stakeholder committees. This broad membership is intended to produce a more comprehensive approach to how multi-organ allocation is developed and to ensure consistency with other policies. The MOT Committee is considering any potential changes in light of the Final Rule, as well as the current efforts involving continuous distribution. The project is expected to take place over the course of the next four years, and is aligned with the timelines established for moving all organs to continuous distribution allocation. As organs transition to continuous distribution allocation frameworks, the multi-organ combinations can be addressed as well.

Currently, specific allocation policies exist for some multi-organ combinations, but not all. Liver-Kidney policy, for example, was developed as part of a collaborative effort between the two committees. The MOT Committee's initial efforts are focused on addressing eligibility criteria and safety net criteria for Heart-Kidney and Lung-Kidney transplants. Eligibility criteria represent the requirements that must be met in order to be eligible for both organs. For instance, the eligibility criteria established for Simultaneous Liver-Kidney policy require that a candidate must be diagnosed with Chronic Kidney Disease, Sustained Acute Kidney Injury, or Metabolic Disease. While the term "Safety Net" is not used in policy, the concept involves providing priority to a candidate who received a single organ, and then within a certain timeframe, needs another type of organ. Safety Net candidates do not get the highest priority for the second/other organ, but they do get extra preference in the allocation sequences.

Establishing eligibility criteria and safety net criteria is part of a bigger first step towards defining the criteria that will be used to identify a multi-organ candidate for the purposes of allocation. Laying the groundwork now will assist in the future when committees are considering how to prioritize between multi-organ and sing-organ candidates.

In June 2021, the OPTN Board of Directors approved updates to Heart-Kidney and Lung-Kidney policy identifying the circumstances when a Kidney must be offered along with a Heart or a Lung(s). The circumstances are based solely on the severity of the candidate's Heart or Lung disease, and do not account for the severity of the candidate's Kidney disease. To address the disparity, the MOT Committee has been developing eligibility and safety net criteria for Heart-Kidney and Lung-Kidney that is largely consistent with the criteria in existing Liver-Kidney policy. The MOT Committee chose to keep the policies consistent, in part, because of a lack of data justifying the use of different criteria related to the Kidney functions of Heart and Lung candidates.

As a result, UNOS staff asked the Committee members whether there are immunologic differences between Livers, Hearts, and Lungs that would justify using a different approach for Heart-Kidney and Lung-Kidney, than what is in place for Liver-Kidney?

A member said that there are certain immunologic differences with the Liver versus say, a Heart-Kidney, but added that the differences may not justify changing the allocation scheme. The member wondered if there is a way to factor in the etiology of the underlying kidney disease, but thought it would be a more appropriate question for the nephrologists and the cardiologist. UNOS staff shared with the Committee that the members of the Heart Committee believe Heart-Kidney candidates should have more lenient eligibility criteria because Heart disease and Kidney disease share a lot of risk factors, and as a result, they exacerbate each other. UNOS staff said that unfortunately, there is not a lot of mortality data available to compare candidates waiting for simultaneous Heart-Kidney transplants and those waiting for Kidney-alone transplants.

Another member stated that getting two organs from the same donor would be advantageous for patients. According to the member there is an immunologic advantage for getting the two organs from the same donor in the case of Heart-Kidney and Lung-Kidney versus Liver-Kidney. The Committee Chair said there are advantages for both sides, although the types of advantages are slightly different.

Next steps:

The Committee members were encouraged to email any questions to UNOS staff supporting the MOT project or the Histocompatibility Committee.

3. Discrepancies Between OPTN and NMDP Two-field Allele Data

The Histocompatibility Committee members were told that a portion of the CPRA calculation will include frequency data that overestimates certain alleles within the DPB1 locus. The data available for analysis is unable to distinguish the alleles in question, and there is no alternative dataset available for analysis. Including the alleles may result in some candidate populations receiving additional priority that is most likely greater than the weight of the alleles' frequencies in the donor population. Conversely, excluding the alleles may result in the candidates being disadvantaged by not having their sensitization count towards allocation priority. The Committee was asked to discuss the potential advantages and disadvantages that vulnerable groups might experience based on the tradeoffs described. The Committee's discussion of the options is important because the Final Rule requires that decisions regarding allocation policy need to be based on sound medical judgment.

Summary of discussion:

UNOS staff reminded the Committee that decisions about allocation policies need to be based on sound medical judgment. Ideally, sound medical judgment would include the results of data analysis or clinical literature. In the absence of those, sound medical judgment can include the Committee members' combined clinical practice experience and judgments, as long as the Committee has a robust discussion of the options and the reasons associated with any decisions.

Committee members were told that, currently, for the antigen recognition domain version of the CPRA calculator, no matter which unacceptable is used, it will give the same CPRA value for that allele-specific antigen for all the alleles that have the same sequence in exons 2 and 3 of class two. This would result in overestimates. The Committee members were asked to consider whether it is appropriate to provide additional priority to certain vulnerable populations based on the available information, and what the advantages and disadvantages of prioritizing such groups would be for the allocation system as a whole.

Based on the available data, there is not an alternative for the frequencies being considered, that would include the frequency data for the alleles in question that have the combined weight. As a result, the Committee was asked to consider the trade-offs between a slight increase in some candidates' CPRA that may not necessarily be as accurate as the Committee would like, versus excluding priority for these alleles resulting in a slight decrease for the candidates' sensitization, and therefore a decrease in their overall CPRA. The Committee was asked to focus their discussion on how the differences would impact vulnerable populations. For instance, are there any indications for allele-specific antibodies that may be more impactful for women, or previous transplant recipients, based on what we've seen in clinical practice? And what are the advantages and disadvantages of each decision?

The Committee Vice-chair said that vulnerable populations include women, transplant recipients, and African-Americans, who are known to have higher PRAs. With increased PRA, the chances would be elevated that these populations would actually have an allele specific antibody. Eliminating the groups of alleles might reduce the points that the candidate populations might receive. As a result, the groups might be adversely impacted by not allowing them to have the allele-specific antibodies represented or any antibodies represented. Another member concurred with this sentiment, and added that excluding priority would probably be more detrimental to more populations, especially highly sensitized candidates and candidates with allele-specific antibodies who could be minority populations with rarer self alleles.

The Committee Chair stated support for keeping them combined. Doing so simplifies the situation a great deal. Additionally, if it is believed that a candidate has an antibody against the more rare allele, but not the more common allele, then it would be a very minimal number of candidates who would experience this circumstance. More than likely, if a candidate has an antibody against one, he or she is going to have an antibody against the other. It will be pretty hard to find a circumstance where they would be different, especially using the A or the exon 2 and 3 typing information. The Chair said that the second option presented is less practical than the first option.

UNOS Staff reminded members that the OPTN data does not include high resolution frequency data for DR and DP. The data is not sufficiently distinguished within the OPTN's deceased donor population because it does not go to the same level of resolution. Additionally, the NMDP data does not really distinguish the differences either, since there is a limit to the coverage of the genes being analyzed. The current recruitment typing strategy only uses exons 2 and 3, not exon 1.

UNOS staff clarified that the Committee's consensus appears to be that the frequency weights should be included because it could potentially more strongly impact sensitized patients, as well as potentially vulnerable populations. Several Committee members concurred with the clarification as stated.

Next steps:

The Committee's decision will be included in the CPRA calculation.

Upcoming Meetings

- October 12, 2021, 12:00 PM ET, Teleconference
- October 14, 2021, 11:00 AM ET, Teleconference

Attendance

- **Committee Members**
 - Peter Lalli, Chair
 - John Lunz, Vice-Chair
 - Caroline Alquist
 - Amber Carriker
 - Yvette Chapman
 - Idoia Gimferrer
 - William Goggins
 - Reut Hod Dvorai
 - Gerald Morris
 - Omar Moussa
 - Marcelo Pando
 - Vikram Pattanayak
 - Jennifer Schiller
 - Karl Schillinger
 - Manu Varma
 - Eric Weimer
- **HRSA Representatives**
 - Raelene Skerda
- **SRTR Staff**
 - Katie Audette
- **UNOS Staff**
 - Amelia Deveraux
 - Betsy Gans
 - Courtney Jett
 - Kaitlin Swanner
 - Kelsi Linblad
 - Leah Slife
 - Susan Tlusty
- **Other Attendees**
 - Loren Gragert
 - Cathi Murphey