OPTN Histocompatibility Committee
Meeting Summary
October 7, 2022
In-person meeting

John Lunz, PhD, D(ABHI), Chair
Gerald Morris, MD, PhD, Vice Chair

Introduction

The OPTN Histocompatibility Committee (the Committee) met in Chicago, IL, on 10/7/2022 to discuss the following agenda items:

1. Welcome, Introductions, Round Robin
2. 12-Month Post Implementation Monitoring Report: HLA Tables Update 2021
3. Kidney Removal of DSA/Region 12-month monitoring report
4. Continuous Distribution Update
    - Role of the Histocompatibility Committee
5. NASEM Report Update
6. Project Updates
    - HLA Policies and Guidance
    - HLA Confirmatory Typing
7. CPRA Update
8. Grouping Unacceptable Antigens for Allocation
    - Updated serologic groups
    - P-groups
    - Molecular antigen groups
9. Project ideas/prioritization
10. Meeting Adjourns

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

1. Welcome, Introductions, Round Robin

The Chair welcomed Committee members and asked everyone about their first car as an icebreaker.

Summary of discussion:

The Committee members shared their first car and introduced themselves.

2. 12-Month Post Implementation Monitoring Report: HLA Tables Update 2021

United Network for Organ Sharing (UNOS) staff presented the 12-month post implementation monitoring data on the Update Human Leukocyte Antigen (HLA) Equivalency Tables implemented changes. These updates were implemented on June 17, 2021. The cohort includes candidate data consisting of kidney candidates ever waiting on the OPTN Waiting List one-year post-policy implementation (6/17/21-6/16/22) and donor data including all deceased kidney donors recovered in the post-policy era.

The updates included changes in references for certain HLA-B and DR matching equivalencies and changes in references for certain HLA-B, C, DR, DQB1, and DPB1 unacceptable antigen assignments. The update added epitope-based unacceptable allele assignments for HLA-DPB1 and added reference of DPB1 alleles. UNOS staff explained the focus of the monitoring report is on the changes with DPB1 unacceptable antigen assignments and DPB1 epitope-based assignments.

Data Summary:

Changes to candidate data included the reporting of DPB1 unacceptable antigens. Of 126,000 reports, approximately 7% reported DPB1. 293 candidates in post policy era had one epitope selected as an unacceptable antigen the two most used epitopes were 84DEAV and 55DED. The least used epitope was 55AAE.

Donor data included new DPB1 values that could be entered as typings. UNOS staff noted the full table of frequencies can be found in Table 4 of the report. When examining the different typings for deceased donors between the match run and the histocompatibility form, 35 out of 12,900 donors had changes in typings (.271%). UNOS staff explained this information can be found in Table 5 of the report.

The report concluded that 7.395% of all kidney candidates ever waiting in the post-policy era reported DPB1 as an unacceptable antigen and the new epitope-based option of assigning DPB1 unacceptable antigens is being utilized. Additionally, relatively few of the new typings for DPB1 added in this update are being utilized and there were a minimal number of changes seen in typings between the match run and the Donor Histocompatibility Form.

Summary of discussion:

The Chair stated it is interesting to see the percentage of candidates that have DPB1 listed as unacceptable. This allows the Committee see which labs are calling DPB1 unacceptable. He mentioned the sizable percentage listed is notable. However, he commented that the number of labs reporting epitopes is such a low percentage, but he is glad to see that at least some labs are doing so since this shows a start for utilization of that methodology. The Chair explained that this lays the groundwork if the community wants to use epitope-based reporting for other loci.

The Ex-officio asked if the changes in DPB1 from match run to donor histocompatibility for include changes that stayed within G or P groups. UNOS staff responded that those were included, and all that was excluded were changes with syntax errors.

The Chair stated that for DPB1, the guidance previously is these can only be identified at a P group, and are listed as a P group instead of at a higher group. A member stated if an epitope of DQ is in there for a patient, there is a DSA on those patients. He asked if in terms of DP, if D7 is entered as unacceptable, will this be automatically excluded. The Chair responded yes and stated there is a crosswalk that includes this. A member asked if there is more granular data on this and UNOS staff responded this data reflects kidney candidates and if a donor is pediatric. Another member asked if these are mostly retransplants. UNOS staff will investigate this.

The Chair noted this data helps the OPTN assess if the objective of the policy is being met. The Ex-officio noted including race and ethnicity in this report would be helpful. Members asked to include how many centers are using this strategy in the report and remind centers this an advantageous approach. The Chair explained that listing an epitope avoids listing individual alleles and provides simplicity.

3. Kidney Removal of DSA/Region 12-month monitoring report

UNOS staff explained that this policy was implemented March 15, 2021, when Donation Service Area (DSA) and region was replaced with 250 nautical mile (NM) circles. Proximity points were assigned based on distance between the donor and transplant hospital.

UNOS staff noted the cohort used for this report came from March 15, 2020-March 14, 2021 (pre-policy) and March 15, 2021-March 14, 2022 (post-policy).

Data Summary:

UNOS staff noted transplant rates increased overall and for all subpopulations. This went from 31 to 37 transplants per 100 active patient years. Transplants increased throughout all age groups, but the largest change was for pediatric patients (11–17-year-olds). Additionally, it increased for all racial and ethnic groups, and increased by dialysis time at listing for those who were on dialysis for a longer period (a 51% increase). Rates increased most notably for patients with a Calculated Panel Reactive Antibodies (CPRA) of 80-97 and across all bloody types.

There was no change in transplants by HLA mismatch level and the distance from donor hospital increased from 68 to 121 NM. The data shows that kidneys are traveling further, and few are going outside of 250 NM, while cold ischemic time (CIT) has increased from 17 to 19 hours median hours. Delayed graft function rates increased slightly while discard rates increased overall and across all KDPI groups (most significantly for 35-85% KDPI). Offer rates increased for all CPRA groups while acceptance rates decreased for all CPRA groups.

UNOS staff noted refusals stemmed from positive crossmatch for kidney matches by CPRA and candidates with CPRA 98-100% were most likely to refuse organs with a refusal rate of 18 to 12 percent post-policy. There was no change in six-month post-transplant graft survival overall or within CPRA or within 0 ABDR.

Equity in access to transplant can be seen by increased transplant rates overall and for pediatric candidates, minority candidates, candidates with CPRA values at 80-97%, and candidates with long dialysis time. Efficient allocation can be evaluated by deceased donor kidneys traveling farther and increased CIT, rate of delayed graft function, and discard rates.

Next steps:

The OPTN Kidney Transplantation Committee and the OPTN Pancreas Transplantation Committee will continue to monitor policy impacts and committees will consider impact as part of the development of a continuous distribution framework.

Summary of discussion:

The Vice Chair asked if it is possible to dive deeper into the increasing discard rate and see whether this is due to kidneys that need to be rehomed. UNOS staff stated a manuscript is being drafted regarding discard rates and that is a possibility. The Chair asked why the six-month monitoring report showed a decrease in discards, but the one-year report did not. UNOS staff stated this is unknown.

A member asked if there will be a change in how organ procurement organizations (OPOs) handle kidneys since reallocating from center to center is difficult and does not allow for open offers. UNOS staff noted open offers are not a part of policy. Members asked if refusal due to positive crossmatch is based on physical or virtual crossmatching and members responded that virtual crossmatch has recently been added as a refusal code but was not previously separated from physical.

The Chair noted the frequency of transplant in candidates with an 80-97% CPRA would be beneficial to examine to indicate whether rates are stable or going down. UNOS staff stated this will be examined in the two-year monitoring report. A member asked if transplant rate increasing came from more organs supplied and UNOS staff noted this possibility and stated it could also be attributed to less waiting time. The member asked how to separate what is due to increased organ supply and transplant rate. UNOS staff responded a time series analysis is done and that a more involved analysis could reflect this. The Ex-officio asked what defines a discard and whether OPOs not attempting to place an organ is counted as a discard. UNOS staff explained this is defined as the number of deceased donor kidneys recovered for intent of transplant, and if OPOs try to allocate prior to recovery that will not count.

4. Continuous Distribution Update

- Role of the Histocompatibility Committee

UNOS staff presented on the background of continuous distribution. He explained that the current system places candidates into rank-ordered classifications review in sequence and the new framework ranks all candidates using a composite allocation score, without categorizing into classifications. The composite score is determined by multiple factors, called "attributes," that are weighted against each other during the calculation. The composite allocation score will ensure each attribute will have a specific weight relative to the entire formula, some attributes will have more effect than others on the total score, no one attribute will decide an organ match, and the total score will determine a candidate's position on the OPTN Waiting List. The more points a candidate receives in their composite allocation score, the higher they will be on a match run for an organ offer.

UNOS staff noted the rating scale of an attribute determines how points are assigned for that attribute and the weight of an attribute determines how important that attribute is relative to other attributes. Examples of attributes used in this score could include medical urgency, post-transplant survival, candidate biology, patient access, and placement efficiency.

He explained that currently, kidney allocation and candidate prioritization differ depending on the donor kidney's Kidney Donor Profile Index (KDPI). Weight modifiers can replicate this, and mathematically modify the relative importance of each attribute based on KDPI.

UNOS staff updated the Committee on the current progress to date of each organ. He noted that lung continuous distribution is the implementation phase, kidney and pancreas are in the modeling and analyses phase, and liver and intestine and heart are in the identifying attributes phase.

Summary of discussion:

The Ex-officio voiced concern regarding the weight of CPRA. He asked that if a component is only weighted 25% but a candidate has an 100% CPRA, how will these candidates be ranked above other. UNOS staff acknowledged this was a popular concern and that modeling has helped identify appropriate weighting, which has shown that 100% CPRA and pediatric candidates should be in the top tier. The Ex-officio agreed that tiered grouping is beneficial, and the histocompatibility community will be happy to see equations that reflect these candidates receiving the same access after continuous distribution implementation.

UNOS staff and the Ex-officio discussed that extreme modeling was conducted to caution the community before release. The Vice Chair commented that a steeper curve would be more beneficial since 80-90% PRA had the largest benefit because of an increase in the donor pool.

The Chair asked how amendable attributes are for each organ. UNOS staff explains that this depends, but changes to weights are easy to make. A member asked about the difference in weighting between

KDPI and CPRA for kidney. He asked if a patient with high CPRA and high KDPI would be excluded from the OPTN Waiting List. UNOS staff responded that donor weight modifiers only impact where you are on the OPTN Waiting List but will not screen you off it. He explained that the longevity of matching differently between KDPI and EPST scores was studied. The differences were used to create a linear line, which differs greatly from the current system. He explained that CPRA and blood type will be large factors and will help indicate which percentage of the donor pool a candidate will match based on candidate characteristics. He noted there will be a larger number of points for blood type than there will be for CPRA. This will help remove the disadvantage currently faced by candidate biology.

5. NASEM Report

UNOS staff gave an overview of the National Academies of Sciences, Engineering, and Medicine (NASEM) Report, stating, the NASEM Ad Hoc Committee on A Fairer and More Equitable, Cost-Effective, and Transparent System of Donor Organ Procurement, Allocation, and Distribution issued a report "Realizing the Promise of Equity in the Organ Transplantation System" in February 2022. The OPTN Board of Directors responded to the NASEM report in April 2022, and the NASEM committee leadership presented the report's recommendations to the Board in June 2022.

The recommendations fell into the categories of improving equity, using more donated organs, and improving the system and system performance. UNOS staff explained how the OPTN has worked to incorporate these recommendations

Improving equity:

- Kidney
    - Implemented policy requiring use of race-neutral eGFR calculations in July 2022
    - KDPI and EPTS mapping tables updated annually
- Liver
    - Approved changes to MELD to address sex-based disparity in June 2022
    - MMaT updated quarterly
- Lung
    - Implemented updates to prediction models in 2021
- Heart
    - Updating adult status qualifications
- All organs: Ongoing Social Determinants of Health Special Study Projects
- Multi-organ: Approved changes to balance access between kidney-alone and multi-organ transplant (MOT) candidates in June 2022

Use more donated organs:

- Improve use of organs
    - Donation after cardiac death (DCD) Collaborative increased recovery and transplant of DCD organs
    - Ethical considerations of normothermic regional perfusion (NRP) in DCD
- Make it easier for transplant centers to say "yes" to organ offers
    - Kidney Offer Filters – national rollout Jan '22; concept paper on optimizing use out for PC
    - Redefining Provisional Yes and the Approach to Organ Offer and Acceptance concept paper out for PC
    - OPTN predictive analytics pilot project
    - Approved Standardize Kidney Biopsy Requirements and Reporting in June 2022

    - Enhancements to OPTN Donor Data Collection out for PC
    - Deceased Donor HIV Positive Test Result Clarification - new project

Improve the system and system performance:

- Standardized metrics to track performance – new MPSC metrics approved
    - Pre-transplant mortality rate ratio
    - Offer acceptance rate ratio
    - 90-day graft survival hazard ratio
    - 1-year conditional graft survival hazard ratio
- Embed continuous quality improvement efforts in system
    - OPTN Individual Member Focused Improvement – IMFI
    - OPTN Collaborative Improvement Projects
- Improve the OPTN policy-making process
    - Pursuing resources from the National Quality Forum

Summary of discussion:

The Chair noted that patients rely on the transplant community to get them the best care and the NASEM report recommendations are focused on improving this. He suggested the Committee focus policy efforts that allow us to work on these recommendations. The Ex-officio stated that these recommendations are needed because the Committees are hindered by the government and its regulations. UNOS staff explained we are all here to constantly improve our system and that the Committee's contributions are valued and appreciated.

6. Project Updates

- HLA Policies and Guidance

The Chair announced that this project will move to August 2023 public comment to align with new CMS updates on virtual crossmatching.

- HLA Confirmatory Typing

The Chair gave an overview of the timeline of this proposal. The OPTN Membership and Professional Standards Committee (MPSC) heard the proposal in September 2022. The OPTN OPO Committee gave feedback in July and October 2022. He explained the proposal is set to go to January 2023 public comment and then to the OPTN Board of Directors in June 2023. The proposal is awaiting blind data for details on discrepancies. The policy will require two typings on deceased donor samples to determine HLA type. The samples must be collectede on two separate occasions and be submitted as separate samples.

The Chair discussed feedback from other committees. The MPSC and OPO committees asked what would happen when a discrepancy occurs. The Chair suggested the lab would follow internal policy and report the discrepancy, but this may lead to issues regarding non-standardized policy. The MPSC asked if testing could be performed with lymph nodes and blood samples, and the Chair stated this is possible. The OPO committee vocalized concern regarding the cost for additional testing and time delays for testing at labs incapable of performing simultaneous testing. The OPO committee explained this may cause donor families to back out due to this delay, but this could positively impact increased use of virtual crossmatching.

Data Summary:

The Chair gave an overview of the reduction in discrepancies after the implementation of dual entry of HLA data into the OPTN Computer System. He explained that there is little change to discrepancies after implementation. There is a large amount of three sample integrity errors. Parent vs. split issues are still present and affect patient care.

Summary of discussion:

The Vice Chair noted the community will lean more toward virtual crossmatching after the implementation of this proposal. A committee member stated it is important to differentiate wrong samples from samples that were perhaps compromised. She noted this fix may not solve that. She asked for actual incidence of wrong samples typed. She vocalized concern about increased cold ischemia time and increased crossmatching. She stated asking labs to do this will likely get the same result. She explained that assays are imperfect and NGS strategies are coming, which may put the community at a different place in terms of accuracy.

The Ex-officio asked how many members' labs already conduct two typings. Four members stated their labs do this already. The Ex-officio noted that a fair number of labs have the capability to do this and that initially there will be issues. A member responded they would be in support of the proposal if it required two different assays. She stated it takes ten minutes to run an ABO typing and it is much cheaper. She explained a lot of discrepancies are due to differences in methodology. She suggested the issue is the different interpretations and different platforms used to type. The Chair responded that mandating two different assays would only work for labs that can do SSO. He agreed this is best practice, but that the Committee needs to recognize the limitations of labs.

Another member vocalized concern regarding the language around what should be done when typings are discrepant. The Vice Chair and the Chair explained that policy 4.4.B requires labs to resolve discrepancies and produce accurate typings. A member explained that discrepancies that are unresolved in blood typing are reported as an AB donor, and most of the errors in typing are clerical errors. He asked how many of the 33 discrepant typings are due to wrong typings. The Ex-officio explained that cannot be analyzed. He explained that high resolution typing from low resolution typing based on haplotype data already exists. He stated future projects could help us gather better data and analysis on typings. He explained that when a sample is typed incorrectly and then a second sample is conducted, another typing would be able to catch those types of errors. The likelihood the sample would be incorrect twice is unlikely. A member suggested if cost is the issue and a lab is doing SSO it may be best to check ABDR, but the Ex-officio stated this would not help resolve issues with C.

Members stated it is hard to support this without the level of granularity that reflect these discrepancies. Another member noted cost will be an issue and asked when high resolution typing that all labs can perform will be available. The Chair responded this is more than five years out. A member stated the second typing should be from a different test, and the Chair explained this is best practice, but labs may struggle to bring this on board if they only use SSO. The Ex-officio explained this aligns with NASEM report recommendations because it improves the system and allows for more accurate data, while improving patient safety.

Multiple members supported mandating two different assays and asking the OPO committee for feedback on this, and another member stated mandating more than two tests would be overstepping.

7. CPRA Update

UNOS staff explained that the Change to the CPRA calculation will be implemented on November 30, 2022.

Summary of discussion:

UNOS staff agreed to share the draft report with the Committee leadership the week of October 24, 2022. She explained that transplant centers will still need to go into the OPTN Waiting List to add a signature for a candidate if this was never populated before. This will show up on the critical dashboard. The Committee confirmed they know how to get into the data services portal. UNOS staff explained CPRA will be rounded to six decimal places, and the Chair stated leadership will give an update at the ASHI conference. He explained this calculation will include weighting for alleles DP, DPA, and DQA, which will be the most accurate depiction of a candidate's sensitization.

8. Grouping Unacceptable Antigens for Allocation

The Chair asked the Committee to think about translations and how to achieve the best use of typing data available. He suggested the Committee consider what current methodologies are used and what solutions will bridge the community to unambiguous two field typing.

- Updated serologic groups

The Chair explained that this method is currently based on molecular methods and the goal is to create an unambiguous two-field HLA type.

- P-groups

The Chair explained this would involve using multiple P-groups for a given serologic equivalency.

- Molecular antigen groups

The Chair explained this would include using first field equivalency with known exceptions.

Summary of discussion:

- Updated serologic groups

The Vice Chair stated this is currently in silico and is solving a problem not necessarily in organ allocation. He asked what should be done when there is no serologic equivalent. He emphasized this must be vetted in vivo first with a hands-on test. A member stated that in the future epitopes will be used universally and converting everything to serology may be a waste. The Chair explained that is what the Committee is interested in- whether the committee will use epitope matching or allele specificities and where the community will be with antibody testing.

The Vice Chair stated a method is needed that incorporates the element of reduction. Epitopes are a great idea but are a complex set of interactions, as opposed to reducing that complexity down to P groups or G groups. He noted that guidance on how the community will deal with DP as a complexity is essential.

A member stated that converting everything to serology may be best now, but when a donor is narrowed down to certain alleles, donor specific antibodies will have to be found. He stated this helps identify when physical crossmatching is needed, which is still essential.

- P-groups

The Chair stated we need to think about the greater use of P groups and molecular groups, since serologic groups are the standard today. The Vice Chair noted that testing a protein is limited by the inability to generate an infinite amount of sequence. A member asked how complicated it will be to incorporate these P groups into current process. The Chair responded a crosswalk is available for DP, but it will be difficult to do so in complicated differentiation situations. The Vice Chair stated it is best to lean

on manufacturers to resolve allele specific antibodies. The Chair agreed asking the vendors to limit down to a single P group is reasonable. A member noted P groups work very well for bone marrow transplantation as well.

The Vice Chair asked how difficult this will be to integrate into the OPTN Computer System when going from partial P group use to total P group use. The Chair responded that if there is a locus that can guide this and map it out that will be helpful. He encouraged the Committee to think of ideas moving forward.

9. Project Ideas/Prioritization

The Chair asked for project ideas and ran through previous ideas formulated for the Committee.

Summary of discussion:

The Ex-officio suggested removing the requirement of signatures for CPRA. The Committee members agreed and stated it could harm patients to require these signatures.

The Chair suggested a CPRA match run requirement for all organs except liver. A member stated he believes As should be added to BW4. Members agreed and suggested updating the equivalency tables and keeping AW4 separate. The member responded that AW4 has been neglected.

The Chair and Vice Chair emphasized a need for better data communication for prior transplant recipients. A member noted the Donor Risk Assessment Interview indicates a lot of this information. The form asks if previous transplant or medical procedures were conducted that involved tissues, live cells, organs, etc. The Vice Chair suggested a policy that requires the HLA typing of any organ that is allocated and requires crossmatch with the appropriate materials.

A member suggested that once the virtual crossmatching regulations come from CMS this information is collected. The Chair noted this will go through the policy process and then to Office of Management and Budget (OMB).

Members suggested adding unacceptable antigen (UA) “avoids” in the OPTN Waiting List. Members argued that this is the centers’ job, not the OPTN’s. This would require the OPTN to pay for validating and maintaining this information.

The Ex-officio explained the amount of time coordinators spend trying to match a difficult to match kidney delays allocation. He stated providing the tools to reduce this time would reduce discard as well. The Vice Chair argued that empowering OPOs or coordinators to make decisions on immunologic compatibility is risky and the lab will still likely get calls from the OPO to provide expertise.

The Committee agreed that the HLA tables will need to be updated to add DPs and make minor modifications. The Vice Chair suggested removing the many drop-down options and use DP as a test case.

The Committee discussed ABO molecular genotyping. A member stated there is the ability to translate from genotype to serotype, but there is a significant requirement to look at serologic equivalencies. The Vice Chair noted we have the expertise of this Committee to examine this. He stated ABO genotyping is very different from ABO typing. He requested policy and guidance on non-A1s and massive transfusions.

A member noted that molecular testing is still not FDA approved and American Society for Histocompatibility and Immunogenetics (ASHI) still requires the lectin test. She noted this is not the time for this proposal since the regulatory bodies are not ready. The Vice Chair argued if this is pushed forward the regulatory bodies will push forward as well. He stated that blood type for allocation cannot solely be based on this, but blood type discrepancies need to have policy and guidance on this. If policy is provided on how to use this, assay allocation will be more efficient and equitable. Members agreed

and stated that this is currently inequitable to the African American population. The Vice Chair suggested conducting ABO molecular for practical issues and blood type testing for serology. If non-A1 organs are allocated, a policy must be in place with a second method requirement.

Members stated this may delay allocation if the second method requirement causes the genotyping to be outsourced. The Vice Chair argued it would take an extra hour and can be run simultaneously to typing. He agreed that centers may have a hard time wrapping procedurally around this. A member stated that non-A1 has many different flavors and there is a lot more to this than putting it in a machine and getting a result. The community is not ready for a molecular assay requirement. The Chair agreed he would like to see it more established in papers and literature. The Vice Chair suggested forming a workgroup to make a compelling argument for a policy update or make sure everyone is performing the lectin test the same way.

10. Meeting adjourns

The Chair thanked the committee members for joining and thanked UNOS staff for conducting the meeting.

Summary of discussion:

There was no further discussion by the Committee.

Upcoming Meetings

- November 8, 2022, teleconference, 12pm EST

Attendance

Committee members:

- Amber Carriker
- Andres Jaramillo
- Caroline Alquist
- Gerald Morris
- Hua Zhu
- John Lunz
- Kelley Hitchman
- Lenore Hicks
- Laurine Bow
- Marcelo Pando
- Omar Moussa
- Peter Lalli
- Qingyoung Xu
- Reut Hod Dvorai

SRTR Staff

- Katherine Audette

HRSA Representatives

- Jim Bowman
- Marilyn Levi
- Megan Hayden

UNOS Staff

- Amelia Devereaux
- Alex Carmack
- Keighly Bradbook
- James Alcorn
- Courtney Jett
- Susan Tlusty
- Taylor Livelli
- Thomas Dolan