OPTN Histocompatibility Committee
Meeting Summary
September 27, 2023
Detroit, Michigan

John Lunz, Ph.D., F(ACHI), Chair
Gerald Morris, MD, Ph.D., Vice Chair

Introduction

The Histocompatibility Committee (the Committee) met in person in Detroit, Michigan on 09/27/2023 to discuss the following agenda items:

1. Welcome and Updates
2. OPTN Task Force on Efficiency in Allocation
3. Guidance for HLA Critical Discrepancies
4. Critical Discrepancy Reporting Policy Changes
5. Recommended Data Collection Changes from the TIEDI Forms Subcommittee
6. Remove Calculated Panel Reactive Antibody (CPRA) 99-100% Form for Highly Sensitized Kidney Candidates
7. Update HLA Equivalency Tables, 2023
8. Organ Donation After Transplant

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

1. Welcome and Updates

The Chair welcomed the Committee and thanked the members for traveling to Detroit, Michigan for the in-person meeting.

An update was given regarding the upcoming release of a typing API for deceased donors and waitlist candidates, which would automate data transfer, potentially reducing transcription errors. Individual vendors were expected to integrate this functionality into their systems.

The Chair also touched on the topic of lung continuous distribution. The update pertains to the Lung Continuous Distribution system, where lower-than-expected transplant rates were observed for blood group O lung candidates. This issue resulted from the original modeling not considering blood group incompatibility when assessing organ offers. To address equity concerns, the Lung Committee evaluated revised modeling and submitted a proposal to adjust blood group weighting for special public comment, which was completed on September 7, 2023. This proposal has been implemented today.

The Lung Committee is also conducting a project to improve allocation efficiency, particularly by considering the need for HLA typing before the match run. They have requested data on the number of lung donors lacking HLA typing and the number of sensitized lung donors. The data and recommendations from the Lung Committee will be reviewed in an upcoming meeting of the Histocompatibility Committee.

2. OPTN Task Force on Efficiency in Allocation

OPTN contractor staff provided additional details about the OPTN Taskforce on Efficiency and presented on attaining efficiency in allocation.

Presentation summary:

- There is a lack of efficiency in allocation which is leading to an unacceptable level of organ non-use, and the problem is getting worse
- Current trends show that even though the rate of kidneys has risen, the organ non-use rate also continues to increase
- Taskforce key responsibilities:
    - Evaluate existing data and recommendation regarding system challenges and improvements
    - Engage directly and frequently with the community to obtain data, feedback, and suggestions
    - Prioritize which issues to address, and recommend both short-term improvements and long-term strategies to address larger challenges
    - Frequently update the Executive Committee and Board of Directors
- Kidney and Pancreas continuous distribution will proceed on a slower timeline to provide the time needed to further develop and incorporate the efficiency considerations of the taskforce
- Goal is for the committees to work within its scope and support the task force through review of relevant policy and data collection projects and providing input and suggestions to the task force as needed

Summary of discussion:

The Committee discussed the need for histocompatibility representation within the task force. The Chair emphasized the importance of having representatives from the histocompatibility community actively participate in the task force rather than solely relying on input from Committee members in an external capacity. The goal is to ensure that histocompatibility representatives are actively engaged in voicing the views of the broader compatibility community. It was noted that task force work would continue to be discussed in future meetings, and participants were urged to stay informed about the task force's objectives and goals. The hope was to facilitate greater efficiency and knowledge-sharing within the histocompatibility community for the benefit of the broader transplant community.

A member suggested advocating for the inclusion of anti-HLA antibodies in continuous distribution biology scoring, especially concerning the heart. The participants recognized the challenge of allocating hearts efficiently compared to kidneys, emphasizing the need for incentivizing the use of filters.

Participants discussed how virtual cross-matching could significantly improve the efficiency of the transplant system and how gaining CMS (Centers for Medicare and Medicaid Services) approval would be beneficial. Using the task force to advocate on behalf of the Committee could influence CMS to rule on the formal use of virtual crossmatching.

The conversation continued with concerns about the burden on laboratory personnel due to excessive virtual crossmatch requests for unsensitized and 0% CPRA patients. This was suggested as a potential area of improvement. A participant suggested creating a flag for laboratories that would notify and pre-approve these patients who are unsensitized and have a CPRA of 0%. This option could be made available in a guidance document that would state the best practice in these cases is to pre-screen for patients that may be immunologically eligible.

A member also highlighted the need for guidelines and policy to address the inefficiencies in the testing process across different centers. For example, some labs may do antibody screening more or less than others. Those who screen less may cause a delay in the system considering they often require or request a more recent antibody screening.

Next steps:

The Committee will evaluate current and future Histocompatibility Committee projects to ensure that their work aligns with the efficiency goals of the task force.

3. Guidance for Human Leukocyte Antigen (HLA) Discrepancies

The Committee considered the content to be included in a guidance document that would provide best practices that minimize HLA typing discrepancies. The Committee split into four groups to discuss the four different stages of HLA typing (pre-analytical, analytical, reporting, confirmatory).

Summary of discussion:

Pre-analytical group discussion:

The pre-analytical group acknowledged that there was a need for better practices in maintaining the integrity of blood samples throughout the testing process. The Chair discussed the common concerns surrounding pre-analytical issues, particularly sample labeling, and fidelity.

The group highlighted a specific concern where samples could be collected before obtaining a unique identifier, potentially leading to labeling errors. As a recommendation, the group suggested that laboratories establish practices to maintain sample fidelity throughout the testing process, even if the identifier changes at some point. They also emphasized the importance of maintaining a unique identifier throughout.

It was acknowledged that certain situations might require deviations, but the need for proper documentation and communication was crucial. The group also discussed the challenges of maintaining sample fidelity when handling multiple donors simultaneously. An example was shared where a near miss occurred due to mislabeling, highlighting the need for improved practices in such cases. A suggestion was made to establish a process where two donors on the same system would require a double verification process to minimize errors.

Analytical group discussion:

The analytical group suggested that an overview of the available technologies be provided within the guidance document. The group discussed the technical aspects, specifically the ability to drill down into technology, considering failures and software issues associated with different types of testing. The member also suggested they should look at how laboratories effectively notify relevant parties about critical failures beyond merely alerting transplant groups. The group acknowledged that these failures are currently identified within the system, but they explored the possibility of streamlining notifications into a single efficient process.

Reporting group discussion:

The Committee discussed the implementation of an API for reporting and ways to reduce critical discrepancies. The participants also explored the possibility of adding notes to reports, especially when there are minor ambiguities or issues to highlight. There was a focus on ensuring that the level of resolution in reporting aligns with the technical method used for typing, considering various typing methods and their resolutions. The importance of having raw data uploads for transparency and the ability to verify typing calls was emphasized. The discussion concluded with a consensus on the significance of reviewing raw data for compatibility assessment.

Confirmatory group discussion:

The Committee's discussion began with the acknowledgment that confirmatory typing encompassed two aspects: either a second sample or a second method at the time of initial reporting. The primary objective was to address issues concerning the quality and reliability of confirmatory typing.

The participants identified three critical questions that underlie the issue of confirmatory typing. First, it is essential to rule out errors, whether they result from sample swaps, reagent failures, software glitches, or other sources. Second, they emphasized the need to investigate non-resolvable or low confidence typings that might have a serologic or clinical impact. Lastly, there was a consideration of the challenge posed by the increased information derived from low-resolution typings and the potential need for additional tests.

It was noted that most labs currently perform some form of low-resolution typing for donors due to cost-efficiency, but high-resolution typing is not yet widespread. An additional point raised was the potential for discrepancy between serological antigen typing and molecular typing, which was clarified, emphasizing the importance of improving the process of providing feedback and notifying when issues arise.

General discussion:

The Committee discussed the potential implementation of double typing, particularly with respect to the associated costs and practicality. A Committee member emphasized that costs should not be considered in these cases. He stressed that the prevention of typing discrepancies should be the primary focus, urging the committee to be proactive in addressing this issue. His argument was that the minor additional costs of double typing pale in comparison to the significance of ensuring accurate typing results for patients. A different member responded and said that while the cost of reagents may not be prohibitive, the expenses related to technologists having to perform the testing twice should be taken into consideration.

Another participant highlighted the significance of correct typing, particularly for cross-matching, and proposed using two different vendor reagents, which might be a simpler approach. The member strongly encouraged the committee to communicate the importance of monitoring discrepancies, arguing that addressing discrepancies is critical, even if it incurs extra costs.

Further discussions revolved around practicality and the possibility of conducting parallel typing. The idea was that it might be feasible to perform two typings concurrently and manage the process efficiently, with one machine running in real-time and the other on a regular machine.

Next steps:

OPTN contractor staff, alongside Committee members, will take the discussions provided and will explore how these suggestions may be worked into a guidance document.

4. Critical Discrepancy Reporting Policy Changes

The Committee discussed potential policy changes to critical discrepancy reporting.

Presentation summary:

- Current OPTN policy requires reporting of critical HLA discrepancies to OPOs/Transplant Hospitals and resolution with other HLA labs
    - Need policy around reporting to OPTN
- Critical discrepancy definition reviewed by DHF/RHF workgroup and may require revision

- Received comments in multiple Public Comment proposals around need for review of critical discrepancies/data, and confusion over critical discrepancy definition
- Discrepancies subcommittee recommended adding language that the p-group should be considered equivalent to the alleles within the p-group
- Subcommittee recommended required reporting to the OPTN
- Reporting critical discrepancies to the OPTN was supported by public comments on the confirmatory HLA typing proposal from January 2023 Public Comment
- Subcommittee recommended reporting via the patient safety portal and on the discrepancies form in TIEDI
    - However, we are unable to collect root cause analysis data in TIEDI- that will need to be submitted via the patient safety portal
- The root cause analyses would still be able to be collected via the patient safety portal, and aggregate results would still be able to be shared with the Histocompatibility Committee
- The TIEDI discrepancies form could still be a tool to help identify critical HLA discrepancies for reporting, and to report basic discrepancy reasons

Summary of discussion:

When asked about the need for p-groups to be equivalent to alleles within the same p-group, a member of the Committee stated that it made a difference with the use of high-resolution typing. More specifically, with a better resolution donor typing laboratories are going to get high-resolution that does not fall within serological antigen level typing. This may not fully represent or predict the reactivity of a donor or recipient. The p-group change is intended to be the bridge for the transition to high-resolution typing. A member stated that they would support p-groups being in the non-critical discrepancy category. The rest of the group did not oppose p-groups being in this category.

When discussing whether required reporting of critical discrepancies should be made mandatory, a member emphasized the need for a well-defined documentation process. They stressed the necessity of providing a brief yet comprehensive explanation for these discrepancies, as it helps laboratories further understand their critical discrepancies. Furthermore, the mention of including comments as a part of this process is highlighted, as it can enhance clarity and prevent misunderstandings. Ultimately, the participants agreed on the importance of clarity in defining and reporting discrepancies.

The group delved deeper into the logistics of mandatory reporting. Specifically, the Committee considered whether it was logical to mandate reporting to the OPTN simultaneously with the report to the Organ Procurement Organization (OPO) or transplant hospital, which is to be done within one hour of identification, or if it would be more practical to establish a 24-hour window for reporting to the OPTN. Members proposed that a 24-hour timeframe would be suitable for reporting these issues. Given that action and review from the OPTN would take place later in the process, the 24-hour reporting window appeared to be the more fitting choice.

Next steps:

OPTN contractor staff will take the recommendations of the Committee to draft policy language for review at a future meeting, for a future public comment cycle. In addition, the Vice Chair of the Committee will present the project to the Policy Oversight Committee for the approval of changes.

5. Recommended Data Collection Changes from the TIEDI Forms Subcommittee

The Committee reviewed the recommended data collection changes to the Donor Histocompatibility Form, the Recipient Histocompatibility Form, and the Discrepant HLA Typings Form.

Presentation summary:

- Donor and Recipient Histocompatibility Forms Revision Workgroup has been meeting monthly since March 2023
- Developed data collection recommendations for the Donor Histocompatibility Form, Recipient Histocompatibility Form, and Discrepant HLA Typings tool

Summary of discussion:

Donor Histocompatibility Form:

Upon reviewing the recommended changes to the Donor Histocompatibility Form, the Committee had no questions or concerns about the proposed revisions.

Recipient Histocompatibility Form:

The Committee decided to add a new question to the Data Element section of the Recipient Histocompatibility Form which proposes the following:

Prospective Virtual Crossmatch Performed

- Response: Yes, No (Triggers Section III: Crossmatch)
- If yes, what was the result?
    - Response: Positive, Negative, Indeterminate

The Committee believed that adding this question was meaningful because there are situations in which a form is required to determine whether the virtual crossmatch was positive, negative, or indeterminate. Another member adds that there are instances in liver transplants where they are required to do retrospective liver transplants. Therefore, he agreed that the addition of this question would be valuable for livers as well. While "indeterminate" had not originally been included as an option, the group thought adding it would cover situations in which there's missing information.

The Committee shared a few concerns regarding reporting donor-specific antibodies (DSA) and MFI in Section II: HLA Antibody Screening of the Recipient Histocompatibility Form. One individual expressed discomfort with required MFI reporting, noting that the form is completed by a technologist who may not be the appropriate person to record that information. The participant acknowledged the usefulness of the information but felt uneasy about the process. The discussion then shifted towards the universal applicability of the reporting system and how Donor Specific Serology (DSS) was interpreted, which varies among different laboratories. Concerns were raised regarding the consistency of MFI data and its potential utility.

The participants contemplated the need for a clear algorithm for reporting and the challenge of making the data consistent across various labs. It was noted that the diversity in MFI among laboratories might limit the usefulness of the data.

Members also touched upon the difficulties of making data consistent without imposing strict practices or making labs uncomfortable. The idea of a pilot project involving 5-10 labs was raised, but the practicality of such an initiative was debated.

The Committee discussed the possibility of classifying DSA as low, medium, or high risk rather than specifying numeric values. A participant stressed the importance of collecting DSA and MFI data, emphasizing that it was not additional work but rather an essential step that had been missing in data collection. A few members agreed about the importance of collecting DSA and MFI data, and they mention that not collecting any of that information may be harmful to future analyses.

The participants discussed the complexity of the data and the potential risks associated with collecting variable DSA and MFI data. More specifically, there were concerns about the interpretation of this data and the potential for false conclusions to be drawn from it. Some participants suggested that including an optional section for labs that wished to provide the information could be a compromise.

In Section II of the Recipient Histocompatibility Form, the Committee decided to display Calculated Panel Reactive Antibody (CPRA) from the OPTN Waiting List, and not include a free text option for the question "CPRA (%) – Most Recent."

The Committee voted on the inclusion of the question regarding reporting DSA and MFI in Section II: HLA Antibody Screening in the Recipient Histocompatibility Form. The question is:

(If DSA is yes) At which locus did you detect donor specific HLA antibodies?

- Response options: Free text the particular DSA, multiple entry option
    - (If yes for each DSA entered) What is the MFI?
        - Response options: Whole number free text

Vote: Yes (5), No (8), Abstain (4)

Discrepant HLA Typings Form:

A member commented and mentioned that there may be scenarios involving incorrect allele assignments and ambiguity in the data. It was noted that situations could arise where the assignment of alleles might be ambiguous, making it difficult to definitively classify the situation as incorrect. The idea of introducing a new category to acknowledge this ambiguity without labeling it as incorrect was brought up.

The option "ambiguous assignment" was proposed, and it was discussed whether a free-text option should be made available for additional information in such cases. Members agreed that a free text option would be suitable to provide further context for the ambiguous classification and situation.

Vote to send changes to public comment:

Vote: Yes (18), No (0), Abstain (0)

Next steps:

These changes will be sent to January public comment.

6. Remove CPRA 99-100% Form for Highly Sensitized Kidney Candidates

The Chair of the Committee reviewed the public comment feedback of their previous *Remove CPRA 99-100% Form for Highly Sensitized Kidney Candidates* proposal. In addition, the group reviewed the changes to policy language, and voted to approve the proposed changes.

Presentation summary:

Purpose and Proposal:

- Increase candidate equity for highly sensitized kidney candidates
- Remove additional documentation for CPRA 99-100% kidney candidates

    - Histocompatibility lab director and transplant physician or surgeon signatures must currently be documented on OPTN Waiting List in order for these candidates to receive higher allocation priority

Feedback Themes:

- Need to remove this barrier for highly sensitized patients as quickly as possible (re-iterated by many commenters)
- Recommendations for some form of periodic audit/other way to monitor proper assignment of unacceptable antigens
    - Others recommended that source documentation and existing requirement for labs to review HLA data in the OPTN Waiting List is sufficient
- Recommendation to evaluate listing time for highly sensitized patients after policy implementation as compared to before
- No written comments unsupportive of the proposal

Summary of discussion:

The Committee did not share or discuss any concerns.

Vote to send proposal to Board for approval in December 2023:

Vote: Yes (18), No (0), Abstain (0)

Next steps:

OPTN contractor staff will submit this proposal to the Board for their approval in December 2023.

7. Update HLA Equivalency Tables, 2023

The Chair of the Committee reviewed the public comment feedback regarding the *Update HLA Equivalency Tables, 2023* proposal. In addition, the group reviewed the proposed changes to the HLA Equivalency Tables.

Presentation summary:

Purpose and Proposal:

- Add all Immuno Polymorphism Database-International ImMunoGeneTics (IPD-IMGT) HLA P-groups that contain more than a single two-field allele for HLA typings for all loci
    - Allows for more precise immunologic screening of potential donors
- Update HLA matching equivalences to more equitably incorporate higher resolution HLA typings by making all HLA typings within a serologic antigen group match each other
- Update HLA-DPB1 tables to IPD-IMGT/HLA version 3.52.0
    - Ensures that the unacceptable antigen screening for candidates will appropriately exclude incompatible donors based on current P-group equivalences and epitopes
- Does not change requirements for candidate, donor, or recipient HLA typing
- Updates the equivalency tables via the expedited updates pathway

Feedback Themes:

- Support for impact on safety, equity, and outcomes
- Concern about discrepancy potential with p-group reporting and confusion about p-groups
    - There was concern this will create confusion; for example, one can select both A*01:01 or A*01:01P—why not just use the P group.

- Recommendation to remove older nomenclature from tables, recommendation to move to IMGT/HLA molecular nomenclature
- A*32:04 is listed as matched equivalent to A3. Yet, this allele bears sequences (eplets 76ESI, 81ALR) not present in A3 but present in other A32 and A25, etc.

Summary of discussion:

Some members expressed concern over listing typings where serology is not well defined, and cases where people might over interpret p-groups for the certainty of the typing assignment. However, they agreed that something needs to be done to create a pathway for high-resolution typing. The Chair stated that the use of p-groups is the first step to overcoming some of the limitations in current nomenclature. In addition, the p-groups will also give individuals the flexibility to be able to report alleles.

Upon reviewing updates made to the HLA Equivalency Tables, a Committee member questioned why A*01:01P is unacceptable if you call A*01:01. The group recognized this and agreed that in this case you should not list A*01:01P as unacceptable. Considering that these changes would require a considerable amount of time to execute, OPTN contractor staff decided to restructure these edits and bring it back to a future meeting.

Next steps:

OPTN contractor staff will restructure these changes and will bring them back to a future meeting.

8. Organ Donation After Transplantation

The Chair of the Committee discussed the complexities of immunology in cases where organ donation takes place after transplantation.

Presentation summary:

Background:

- Concerns raised about donors who were previous recipients donating received organ
- Inability to denote two HLA typings in OPTN Computer System when applicable
- No discrete field to identify previous SOT or HSCT recipients
- Considering that transplant rates have increased over the years, cases of organ donation after transplantation (ODAT) has also increased
- Between 1985 and 2014, 67 previously transplanted organs were utilized for a second recipient

Problems to Solve:

- Safety concerns about:
    - Not knowing/preserving both HLA typings in system, not knowing which typing applies to which recipient for future care
    - Chimerism and unacceptable antigens
    - Crossmatching samples being inadequate if from peripheral blood for an ODAT donor

Summary of discussion:

A member questioned if the Committee had any data regarding how many of the 67 ODAT cases had information on their typing and the original typing. Even though the Committee does not have that data, the Chair mentioned that most ODAT cases happen quickly after the original surgery. These cases are not usually taking place two-years following the original transplant.

A member proposed the idea of prioritizing ODAT donors for specific recipient groups. One participant suggested the idea of allocating organ donors only to recipients with a 0% CPRA to avoid complications.

The discussion continued with the suggestion to limit donor organs to AB recipients only. The concept behind this approach was that organ recipients and their donated organs might not have an exact antigen match due to the complexities of stem cell and other cell interactions within the organ.

The participants acknowledged that when an organ is transplanted into a person, stem cells and other cells might populate the organ, making it a mix of different cell types. This complexity can pose challenges when typing the organ. The discussion also touched on the difficulty of determining the proportion of donor cells that homed into the recipient long term.

The meeting participants recognized that the problem had three main components. The first component was the lack of a requirement to know specific details. The second was the lack of clarity on how to handle such situations, and the third component pertained to the complex biology involved in these cases.

While one member brought up the concern of extensive cold ischemia time (CIT) on these organs, a few members determined that this was a topic that was outside of the purview of the Committee. Other individuals also mentioned that this may be an opportunity to work with the OPO Committee to determine if policy or guidance is needed to address what to do in cases similar to this in which they typing is unclear. An individual questioned whether these cases could be flagged in the OPTN Donor Data and Matching System to notify and alert organizations to look more closely at these situations.

Considering that the creation of a system flag in the OPTN Donor Data and Matching System would be considered a system enhancement, it wouldn't require a policy change and may be a viable option. The Chair also suggested that being transparent with OPOs and alerting them to the existence of such situations may be a helpful first step. In addition, providing them with a few tips and guidance of how to proceed in these cases could be beneficial.

Through conversation, the Committee agreed that the lack of direction surrounding ODAT was a concern. Often laboratories may be confused about which data to enter and who that data should come from. A member argued whether this should really be a priority of the Committee if this only affects upwards of 60 donors. He stated that since the Histocompatibility Committee is larger, maybe there might be other concerns they should be prioritizing. A member responded and said that maybe the group does not know the full extent of this issue considering that data has only been collected up to 2014. He stated that they need to look at the scope of the problem before deciding to pursue this as a project.

The Chair clarified that the goal would be to provide guidance and best practices compared to a redesign of the allocation system. If guidance is provided, laboratories should be able to understand how to proceed in these cases. A different member argued that more needs to be done other than providing guidance. He stated that there needs to be additional data collection to understand the problem. Members clarified that the main goal is to understand whether a donor has had a previous transplant or a previous stem cell transplant, and they suggested that the group not get too deep in the weeds of the topic. In addition, an individual added that if a policy is put in place for these situations, there is the potential to see an increase in ODAT transplants.

The group suggested that the next steps involve focusing on transparency with OPOs, guidance, and system updates. In addition, the Committee agreed that it would be beneficial to submit a data request that would provide a more accurate outlook on the scope of problems associated with ODAT.

The Histocompatibility Committee took a vote to determine if they wanted to pursue any of the proposed options. These options include doing further research, working with the OPO Committee, providing guidance, and proposing system enhancements.

Vote to continue pursuing proposed options as they relate to ODAT:

Vote: Yes (18), No (0), Abstain (0)

Next steps:

The Committee will further evaluate and pursue the different ODAT options that were proposed within the discussion.

Upcoming Meeting

- October 10, 2023, 12PM EST

Attendance

- **Committee Members**
  - John Lunz
  - Gerald Morris
  - Roshini Abraham
  - Caroline Alquist
  - Laurine Bow
  - Manish Gandhi
  - Lenore Hicks
  - Julie Houp
  - Andres Jaramillo
  - Helene McMurray
  - Omar Moussa
  - Darryl Nethercot
  - Stephanie Osier
  - Hermant Parekh
  - Jerome Saltarrelli
  - Crystal Usenko
  - Qingyong Xu
  - Hua Zhu
- **HRSA Representatives**
  - James Bowman
  - Marilyn Levi
- **SRTR Staff**
  - Rajalingam Raja
  - Katherine Audette
- **UNOS Staff**
  - Courtney Jett
  - Susan Tlusty
  - Jenna Reformina
  - Stryker-Ann Vosteen
  - Thomas Dolan
  - Betsy Gans
  - Krissy Laurie
  - Kelsi Lindblad
  - Jon Miller
  - Laura Schmitt