OPTN Histocompatibility Committee
Discrepant HLA Typings Subcommittee
Meeting Summary
March 2, 2022
Conference Call

Peter Lalli, Ph.D, D(ABHI), Chair
John Lunz, Ph.D, D(ABHI), Vice Chair
Eric Weimer, Ph.D., D(ABHI), Subcommittee Chair

Introduction

The Discrepant HLA Typings Subcommittee of the OPTN Histocompatibility Committee met via Citrix GoToMeeting teleconference on 03/02/2022 to discuss the following agenda items:

1. 2021 Discrepancy Reports
2. 2015-2021 Patient Safety Portal Reports
3. Memo to the Committee

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

1. 2021 Discrepancy Reports

The Committee Chair introduced Eric Weimer as the new Subcommittee Chair. The Subcommittee reviewed the most recent discrepancy reports and considered potential trends.

Summary of discussion:

The Subcommittee members reviewed information about discrepant typings as provided by UNOS Research staff. The information categorized to permit comparisons of like items, as well as to permit comparisons across time. Some of the classifications used include "Sample Integrity Issues" which can represent the incorrect use of a sample, while other classifications reflect what are generally described as technical or transcription errors.

Another category included on the reports involves "Split vs. Parent." Whether the Subcommittee should continue including this as a category was put before the Subcommittee members. It was argued that the bulk of the identified issues involved Cw3, and that for the most part they were reported as Cw3 for CO305, which in the IMGT HLA dictionary does define their serology equivalent as an 03. However, the neural network or expert assignment identifies it as a ten. The community is at a point where they should probably define how to report 03 and 05, or just accept reporting Cw3 as Cw3.

The Chair identified the critical error percentage as the most important information for the Subcommittee to consider. The information indicated that during the last few months the critical error percentage has been hovering between 0.1% and 0.3%, as a total of all donors. The Chair pointed out that this represents a substantial decrease from previous time periods. When looking at critical HLA discrepancies on an annual basis from 2015 through 2021, the largest categories of typing errors occurred as clerical errors/technical/interpretative errors. According to the data provided, DPB1 continues to be somewhat of an issue, but that is partly related to the complexity of DP typing generally. It was also noted that following the implementation of double-entry in early 2020, the percentages are trending in a positive manner. Nonetheless, double-entry has not solved the problem altogether, but

can be associated with positively impacting getting the correct donor information used for organ allocation. There were no questions from the Committee members about the information shared.

2. 2015 – 2021 Patient Safety Portal Reports

The Subcommittee reviewed information that has been submitted to the Patient Safety Portal regarding incorrect HLA typings that have been used for allocation and what, if any, potential impact such typings have had on transplant recipients. Key takeaways include that about half of the reported events were caught prior to transplant and they were caught due to confirmatory typing either by the original typing lab or the import lab.

Summary of discussion:

As part of the background for discussing the OPTN patient safety portal, UNOS staff pointed out that because the patient safety portal is based on voluntary reporting, it will reflect fewer cases than appeared in the previous analysis. In addition, because matters reported to the portal include patient-specific information, the details represent protected health information and are also protected by the medical peer review requirements established by the OPTN's Membership and Professional Standards Committee (MPSC). The information being shared today with the Histocompatibility Committee will be reported in an aggregated form.

While there are limits to sharing portal information, there are also some benefits, such as details about the root causes of issues, when a matter was discovered and/or communicated, and patient outcomes. This level of detail is not available when considering the de-identified information related to HLA typings. The patient safety portal information reflects the period from 2015 through 2021 and was categorized using the previously discussed classifications. Adverse patient events being shared with the Committee represent graft failures or patient deaths that have a potential immunological origin. Due to limitations in the data, some events were excluded including recurrence after transplant, diagnosis, malignancy, or infection. The events that were included: chronic and acute rejection, primary non-function or primary failure (which may or may not be related but could potentially be related). Classification of the timing was based on information provided in the case reports, as well as the HLA audit log for whether or not these were communicated prior to transplant, post-transplant, or prior to match run, post-match run.

Based on the reported data, there were 94 total events from 2015 through 2021 that were HLA-related. Of the events that could be aggregated and reported, 12 were due to incorrect samples, one related to Bw4 or Bw6 issues, two due to DRB345 issues, four associated with DR52 Null issues, and nine related to DPB1 errors. In addition, there were 40 clerical errors and another 26 errors associated with other technical/interpretative typing.

Examining the timing of reported events, four of the 94 events were caught prior to match run. An additional 41 events were caught prior to organ transplant, but following the match run. Of these 45 events (4 + 41), there was no potential patient harm. Finally, 44 events have the reporting reason as detected due to confirmatory typing. The confirmatory typing may have been performed by the original histocompatibility lab or an import lab, but the reason for the detection was the confirmatory typing process. Of the 94 events, it was determined that only three patients potentially had adverse events of an immunological origin. UNOS staff reminded the Committee members that it is not possible to determine the exact cause due to the data reporting limitations. Finally, staff explained that ten of the technical/interpretative errors were reported as the root cause due to assay or software issues.

3. Memo to the Committee

The Subcommittee discussed a memo that was submitted to the full Histocompatibility Committee regarding issues involving duplicate typing, and considerations to ensure correct typing occurs.

Summary of discussion:

The Subcommittee Chair began the discussion by referencing the memo that was sent to the Histocompatibility Committee from the Director of the Immunogenetics Laboratory at the Johns Hopkins School of Medicine regarding confirmatory HLA typing. In summary the concern presented to the Committee involves the lack of redundancy for HLA typing as compared to ABO typing. More specifically, the memo highlighted that the inclusion of the incorrect HLA typing can impact who receives an offer, particularly in the case of a highly sensitized patient. In light of the increasing reliance on virtual cross-matching, having the wrong typing will impact how labs assess those matches. Cross-matching and confirmatory typing for hearts and lungs occur after transplant so there are greater implications with those organs. The Subcommittee Chair stated that the Subcommittee needs to consider how they might mitigate the potential for patient safety risks identified in the memo. The Subcommittee members were asked for feedback regarding ways to address the small, but important patient safety risks going forward?

A member stated that the Committee might want to consider treating this like ABO. The member said that their institution requires OPOs to get two antibody tests for their donors when thoracic organs are involved because the institution has become so dependent on virtual crossmatching. Basically, the institution is already treating the HLA typings like ABO blood typing. Another member said their institution is performing two assays for every donor.

The Subcommittee members recommended that a way to mitigate the described risk would be to implement a requirement that two separate blood samples be analyzed and that those results have to be dual entered. The consensus was that two separate blood samples would adequately address the concerns. It was pointed out that using two separate samples is beneficial because it can be implemented as a requirement more quickly, and it permits labs to continue using their current method of analysis, as opposed to requiring a lab to implement a new process that might require the hiring of additional staff to specifically perform those analyses because the lab is unfamiliar with them.

The Subcommittee considered the impact that such a requirement might have on labs, and whether it would be onerous. The members raised the issue that two separate blood samples will increase the costs incurred by the organ procurement organizations (OPO). It was mentioned that performing the second analysis could cost OPOs approximately $250 to $350, which can quickly add up. A member stated that the trade-off for that amount is that it will result in a much lower risk of death among transplant recipients as a result of incorrect typing. The Subcommittee also identified lab tech staff as potentially being negatively impacted by the additional time required to do the testing. Some of the members mentioned that there might be opportunities to perform the testing at the same time, thereby reducing the additional time needed.

A question was raised about whether the Subcommittee should require a second entry or some type of verification? Or, if the second value is in-line with the first value, then only require the HLA to be entered once and just have both raw typings uploaded? A Subcommittee member responded that doing it once would be ideal, from an implementation standpoint. However, an option to consider could be having one place for reporting the HLA data, and on the screen where the information is entered, have two data fields added that are labelled something like “initial specimen – date and time, and confirmatory specimen – date and time.

Next Steps:

The Subcommittee will share today's discussion with the full Histocompatibility Committee membership, and will continue discussing the matter in the future. At some point, when there is great resolution the Committee will reach out to the OPTN Operations and Safety Committee and the MPSC for additional discussions.

Upcoming Meetings

- TBD

Attendance

- **Subcommittee Members**
  - Peter Lalli, Chair
  - John Lunz, Vice Chair
  - Reut Hod Dvorai
  - Idoia Gimferrer
  - Gerald Morris
  - Marcelo Pando
  - Jennifer Schiller
  - Karl Schillinger
  - Eric Weimer
- **HRSA Representatives**
  - Jim Bowman
  - Marilyn Levi
- **UNOS Staff**
  - Courtney Jett
  - Amelia Devereaux
  - Betsy Gans
  - Kelsi Linblad
  - Eric Messick
  - Sarah Scott
  - Leah Slife