OPTN

Public Comment Proposal

Require Reporting of HLA Critical Discrepancies and Crossmatching Events to the OPTN

OPTN Histocompatibility Committee

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Require Reporting of HLA Critical Discrepancies and Crossmatching Events to the OPTN

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Sponsoring Committee:	*Histocompatibility*
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Executive Summary

Human Leukocyte Antigen (HLA) typing is a vital step for ensuring donor-recipient compatibility leading to successful organ transplantation. OPTN Policy defines HLA critical discrepancies as a "difference among non-equivalent values, according to *Policy 4.11: Reference Tables of HLA Antigen Values and Split Equivalences*, at one or more loci in a candidate's, donor's, or recipient's HLA typing." Currently, histocompatibility laboratories must report critical discrepancies to the transplant hospital, as well as the organ procurement organization (OPO), however, they are not required to report these events to the OPTN. Critical discrepancies reflect instances of incompatibility between the potential recipient and donor wherein a severe, potentially fatal, immunologic reaction is possible if the organ were to be transplanted. Due to patient safety concerns, as well as increasing transparency through data collection, the OPTN Histocompatibility Committee (Committee) proposes required reporting of these events to the OPTN within 24 hours of discovery through the OPTN Patient Safety Reporting Portal. Furthermore, this proposal modifies the definition of a critical discrepancy to no longer encompass discrepancies within the same split antigen group. The proposal would also require reports through the OPTN Patient Safety Reporting Portal when an incorrect sample is used for a physical crossmatch, and when an incorrect donor HLA typing or incorrect candidate HLA antibody test is analyzed for a virtual crossmatch.

Considerations for the Community

- Do you agree that the discovering lab should be responsible for reporting critical HLA discrepancies to the OPTN?
- Does the patient, living donor, and donor family community agree that this proposal adequately addresses this issue?
- Is 24 hours an appropriate time frame for the initial report of a critical HLA discrepancy to the OPTN?
- Do you agree with the modified definition of a critical HLA discrepancy?
- Should incorrect donor or recipient samples used for crossmatch be included in required reports?

- Should incorrect donor HLA typings or incorrect candidate HLA antibody test be used for virtual crossmatch be included in required reports?

Purpose

This proposal is intended to require reporting of critical discrepancies in HLA typing to the OPTN to gain insight into the root cause and then reduce the total number of HLA critical discrepancies. When caught before transplant, these discrepancies may require re-allocation, which can impact system efficiency and impact organ quality through increased cold ischemic time. When caught after transplant, they are a patient safety concern due to their potential to have an immunologic reaction in the recipient(s). Reducing HLA critical discrepancies would increase patient safety and increase system efficiency.

Background

HLA critical discrepancies are errors in HLA typings that can potentially cause an immunologic reaction. If not detected prior to transplant, some reactions may be serious enough that they lead to graft loss or mortality.[1] The OPTN Histocompatibility Committee (Committee) reviews retrospective, aggregate donor and recipient HLA critical discrepancies through a data quality report utilizing data entered in the OPTN Computer System. This data is reviewed quarterly with about 60-70 total cases of HLA critical discrepancies identified every year.[2] Since OPTN policy does not require reporting critical discrepancies and the Committee reviews them retrospectively and in a deidentified manner, there is a lack of meaningful data on recipient outcomes and no avenue for targeted OPTN intervention for recurrences. While current OPTN policy requires reporting of HLA critical discrepancies to organ procurement organizations (OPOs) and transplant hospitals, reporting of critical discrepancies to the OPTN is voluntary.

Between January 1, 2015, and March 1, 2023, there was a total of 95 submissions to the OPTN for HLA-related events. 35 of these were a data entry error, 23 were a verification error, 14 were an interpretation error, 11 were sample switches, 10 were equipment malfunctions, 8 were a laboratory IT/technical issue, 7 were a typing method error, and one cause was pending at the time of this report.[3] There were 95 submissions to the OPTN, with some submissions having more than one cause reported.

During the Winter 2023 OPTN Public Comment cycle, the Committee sought feedback on their proposal *Requiring HLA Confirmatory Typing for Deceased Donors.*[4] While this proposal ultimately did not move forward for consideration from the OPTN Board of Directors, the feedback obtained was instrumental in gaining a better understanding of community concerns and determining the appropriate avenue to address critical discrepancies, which aims to prevent critical discrepancies that could lead to graft loss. Many in the community supported reporting these HLA critical discrepancies to the OPTN, with commenters noting the scarcity of data on HLA critical discrepancies and subsequent recipient outcomes due to the current voluntary reporting process. The Committee heard the community's

[1] Shi, X., Lv, J., Han, W. *et al.* What is the impact of human leukocyte antigen mismatching on graft survival and mortality in renal transplantation? A meta-analysis of 23 cohort studies involving 486,608 recipients. *BMC Nephrol* **19**, 116 (2018). https://doi.org/10.1186/s12882-018-0908-3.

[2] Based on OPTN Critical HLA Discrepancy Data as of June 24, 2024.

[3] https://optn.transplant.hrsa.gov/. OPTN Histocompatibility Committee, May 9, 2023. Meeting Summary.

[4] https://optn.transplant.hrsa.gov/policies-bylaws/public-comment/require-human-leukocyte-antigen-hla-confirmatory-typing-for-deceased-donors/.

concerns and agreed that additional data was needed on critical HLA discrepancies and their causes.[5,6] It was determined that more data was needed to help inform this policy.

Following this public comment cycle, the Committee evaluated additional data to understand critical discrepancies. In a report provided to the OPTN Board of Directors regarding the *Requiring HLA Confirmatory Typing for Deceased Donors* proposal, alternative solutions were identified, including revision of the OPTN Computer System existing discrepancy reports and collection of additional data on discrepancies.[7] The Committee noted that it would be premature to make a final decision on the method used for reducing HLA critical discrepancies before evaluating additional data related to the root causes of the discrepancies. With this, the Committee continued to work towards the goal of reducing critical discrepancies and opted to review additional OPTN Data surrounding critical discrepancies.

Overview of Proposal

This proposal has multiple components, focusing on reporting critical HLA discrepancies, modifying the definition of HLA critical discrepancy, and reporting incorrect specimens or typings used for crossmatching. Although they vary slightly, each modification is integral for increasing transplant recipient safety. Each section below details the changes to OPTN policy and what is expected from histocompatibility labs.

Reporting Critical HLA Discrepancies to the OPTN

Currently, the OPTN Patient Safety Reporting Portal only requires submission for certain safety events, none of which are required by histocompatibility labs. **The Committee suspects not all critical discrepancies are reported to the OPTN**. As part of inquiries into reported events, members often provide a Root Cause Analysis (RCA) to better understand what went wrong for this issue to occur. If the member identifies a gap in their training or a misunderstanding of policy requirements through the RCA, commonly members will submit a Corrective Action Plan (CAP) which details how they will prevent this error from recurring. Subsequently, the OPTN Membership and Professional Standards Committee (MPSC) will review each case and its supporting documentation, as part of a confidential medical peer review, and determine if any further actions or interventions are appropriate per the OPTN Bylaws.[8]

Current policy requires laboratories to notify the host organ procurement organizations (OPOs) of critical discrepancies as soon as possible, but no later than one hour following determination of the correct HLA typing. Upon independent discovery or receipt of documentation of the discrepancy, the OPO must notify and provide supporting documentation to all accepting transplant programs no later than 12 hours (if the discrepancy is discovered prior to procurements) or 24 hours (if the discrepancy is discovered post-procurement).[9] In review of current policy, the Committee reasoned that since action and review from the OPTN takes place later in the process, a 24-hour reporting window would be appropriate.[10] The Committee is requesting feedback on the proposed 24-hour reporting timeframe.

[5] https://optn.transplant.hrsa.gov/. OPTN Histocompatibility Committee, April 11, 2023, Meeting Summary.
[6] https://optn.transplant.hrsa.gov/. OPTN Histocompatibility Committee, September 27, 2023, Meeting Summary.
[7] Histocompatibility - Require Human Leukocyte Antigen (HLA) Confirmatory Typing for Deceased Donors.pdf
[8] OPTN Bylaws, Appendix L: Reviews and Actions. https://optn.transplant.hrsa.gov/media/lgbbmahi/optn_bylaws.pdf.
[9] OPTN Policy 4.4.A.i: Donor HLA Critical Discrepancies as of July 24, 2023.
[10] https://optn.transplant.hrsa.gov/. OPTN Histocompatibility Committee, September 27, 2023, Meeting Summary.

This proposal would require that histocompatibility laboratories report an HLA critical discrepancy to the OPTN via the OPTN Patient Safety Reporting Portal within 24 hours of discovery. This initial report to the OPTN Patient Safety Reporting Portal does not require an RCA or CAP, nor does it require the correct typing to be identified. While any information the member has available at that time is helpful, the initial report only requires that a discrepancy has been discovered and reported. RCAs and CAPs may be requested as part of the inquiry into the event and the Committee believes that engaging in these quality improvement efforts will improve the overall processes and safety standards for histocompatibility laboratories.

In line with protections of confidential medical peer review, these events will only be reviewed in an identified and individualistic manner by the MPSC and the MPSC Histocompatibility Subcommittee in closed session. Through systematic monitoring, the MPSC will be able to identify and refer any recurring themes or issues to the Histocompatibility Committee to pursue a policy or guidance project as appropriate. The Histocompatibility Committee will also review the deidentified, aggregate information on a regular cadence. This aggregate information will be used to inform community-wide education and ongoing updates to policy and guidance.

Modifying the Definition of a Critical HLA Discrepancy

Currently, the definition of a critical HLA discrepancy is a difference among non-equivalent values, according to OPTN *Policy 4.11 Reference Tables of HLA Antigen Values and Split Equivalences*, at one or more loci in a candidate's, donor's, or recipient's HLA typing. The Committee is proposing changing the definition of a critical HLA discrepancy to

> " a human leukocyte antigen (HLA) critical discrepancy is a difference among non-equivalent values, at one or more loci in a candidate's, donor's, or recipient's HLA typing. Values within the same serologic split antigen group or provided as equivalent for the purposes of unacceptable antigen screening within *Policy 4.11 Reference Tables of HLA Antigen Values and Split Equivalences* are considered equivalent."

This change is being made to focus required reporting of what is most immunologically significant and align with the required HLA typing resolution. For example, A*01:01 is currently critically discrepant from A*01:02, however with this proposal, it will no longer be considered critically discrepant because it will be within the same split antigen group. This means that certain antigen pairs with no immunologic significance will not be required to be reported with the revised definition.

Reporting Incorrect Specimens or Typings Used for Crossmatching

When receiving a presentation on the histocompatibility-related reports submitted through the OPTN Patient Safety Reporting Portal, the Committee discussed the potential for incorrect donor or recipient samples to be used in a physical crossmatch.[11] The Committee agreed that this is a patient safety concern because it could cause a potential immunologic reaction between the recipient and potential donor to go undetected and therefore should be a required report. Similarly, the Committee felt that analyzing the incorrect donor HLA typing or incorrect candidate HLA antibody test for a virtual crossmatch should be a required report for the same reasons. Therefore, the Committee is proposing that both of these events be included in the required reports.

[11] https://optn.transplant.hrsa.gov/. OPTN Histocompatibility Committee, May 14, 2024, Meeting Summary.

NOTA and Final Rule Analysis

This project is authorized under the authority of the National Organ Transplant Act of 1984 (NOTA), which states, "The Organ Procurement and Transplantation Network Shall… (A) establish… (ii) a national system… to match organs and individuals included in the list, especially individuals whose immune system makes it difficult for them to receive organs…".[12] HLA discrepant typings may disproportionately negatively impact highly sensitized recipients, as they are more likely to have developed antibodies towards the HLA typing and are at higher risk for rejection events. In addition, the Committee submits the proposal for consideration under the authority of NOTA, which requires the OPTN to "adopt and use standards of quality for the acquisition and transportation of donated organs"[13] and the OPTN Final Rule, which states that "An OPTN member procuring an organ shall assure that laboratory tests and clinical examinations of potential organ donors are performed to determine any contraindications for donor acceptance".[14] This proposal is intended to increase the quality standard for laboratory testing that is used to evaluate the immunologic risk of deceased donor organs for a given candidate by increasing laboratory accountability and oversight.

Implementation Considerations

Member and OPTN Operations

This proposal would impact histocompatibility laboratories and the OPTN but would not impact transplant hospitals or organ procurement organizations.

Operations affecting Histocompatibility Laboratories

This proposal would require histocompatibility laboratories to report critical discrepancies and crossmatching events to the OPTN within 24 hours of discovery. Upon review of the reported incident, this may involve performing root cause analyses to determine the cause of the HLA critical discrepancy and implementing corrective action plans as needed. This would total about 40-50 additional reports per year,[15] spread across all 138 active histocompatibility laboratories nationally.[16]

Operations affecting Organ Procurement Organizations

No anticipated impact.

Operations affecting Transplant Hospitals

No anticipated impact.

[12] 42 USC §274 (b).
[13] 42 USC §274(b)(2)(E).
[14] 42 CFR §121.6(a).
[15] Based on OPTN Critical HLA Discrepancy Data as of June 24, 2024, assuming the current rate of 20 cases per year reported through the OPTN Improving Patient Safety Portal.
[16] Based on OPTN Membership Data as of May 28, 2024.

Operations affecting the OPTN

The OPTN will receive approximately 40-50 additional reports to the OPTN Patient Safety Reporting Portal per year, increasing the quantity of patient safety cases the OPTN and MPSC reviews. The OPTN will use the information submitted in the OPTN Patient Safety Report Portal as the basis for their inquiry to the member. Based on historical information, it is possible that additional MPSC engagement and monitoring could arise from the findings of the review. This includes any component of monitoring or member action outlined in the OPTN Bylaws *Appendix L: Reviews and Actions.*[17]

Potential Impact on Select Patient Populations

HLA critical discrepancies can impact any recipient of any organ if the recipient is unknowingly transplanted with an organ they have preexisting donor-specific antibodies towards. However, these scenarios may greatly impact highly sensitized candidates, as they have more pre-formed antibodies and would be more likely to have pre-formed antibodies toward the donor as well. If a recipient is unknowingly transplanted with an organ they have a high level of preexisting donor-specific antibodies toward, they are at risk for hyperacute rejection and graft failure. Since highly sensitized patients, certain minority groups, and women are more likely to have pre-formed antibodies, HLA critical discrepancies may disproportionately impact them. As previously stated, this proposal will provide information related to the root causes of the discrepancies that will assist the Committee in assessing how to reduce HLA critical discrepancies and increase patient safety.

Projected Fiscal Impact

Overall Projected Fiscal Impact

The Fiscal Impact Advisory Group, comprised of representatives from histocompatibility laboratories, organ procurement organizations, and transplant hospitals, reviewed this proposal and completed a survey to estimate anticipated costs. They rated this project as low, medium, or high based on the estimated staffing and/or training, overtime, equipment, or IT support needed in the implementation of this proposal.

This proposal was determined to have low impact on histocompatibility labs. No fiscal impact was recorded for transplant hospitals and organ procurement organizations.

Projected Impact on Histocompatibility Laboratories

This proposal is anticipated to have a low fiscal impact on histocompatibility laboratories as staff will be required to submit reports of HLA discrepancies to the OPTN in addition to the submissions already being made to transplant centers and organ procurement organizations. Though there will be an increase in submission requirements, the burden on staff is estimated to be low as it does not deviate significantly from standard operating procedures.

Projected Impact on Organ Procurement Organizations

This proposal is not anticipated to have any impact on OPOs.

[17] OPTN Bylaws, Appendix L: Reviews and Actions. https://optn.transplant.hrsa.gov/media/lgbbmahi/optn_bylaws.pdf.

Projected Impact on Transplant Hospitals

This proposal is not anticipated to have any impact on transplant hospitals.

Projected Impact on the OPTN

It is estimated that 383 hours ($25,059) would be needed to implement this proposal. Implementation would involve review of all current processes, documents, templates, and guidance to account for new types of required cases and updates to all reporting templates and processes. In addition, implementation would include reviewing and preparing implementation communications and educational materials and creation of new education courses. It is estimated that 761 hours ($49,850) will be needed for ongoing support. Ongoing support includes investigation of critical discrepancy cases, compilation, documentation, and posting of cases for MPSC review, and monthly reporting. In addition, ongoing hours will include consulting on member questions, evaluation and monitoring of data, and follow-up.

Post-implementation Monitoring

Member Compliance

OPTN Contractor staff will continue to send inquiries on behalf of the MPSC to OPTN members who report these patient safety events and will request information about the program/safety event, such as:

- Procedures and protocols
- Quality review processes
- Plans for improvement

The MPSC will continue to review the information submitted by the histocompatibility laboratory and may request that the member submit additional information about certain aspects of the program or submit a plan for quality improvement. The MPSC may also request that a member participate in additional engagement with the MPSC, such as an informal discussion or a peer visit. In rare circumstances where the MPSC identifies a potential ongoing risk to patient health or public safety, the MPSC may request that a member inactivate the histocompatibility laboratory to mitigate the risk.

Policy Evaluation

The Final Rule requires that allocation policies "be reviewed periodically and revised as appropriate".[18] The Committee actively monitors the prevalence of HLA discrepancies per their charge in the Bylaws through HLA quarterly discrepancy reports. For this policy, the Committee will continue to monitor the prevalence of HLA discrepancies through these quarterly HLA discrepancy reports, with no additional monitoring unless other subsequent metrics are requested by the Committee.

Conclusion

This proposal, which has an overarching goal of increasing patient safety, is multifaceted. It aims to require reporting of HLA critical discrepancies to the OPTN within 24 hours of discovery, modifying the

[18] 42 CFR §121.8(a)(6).

definition of an HLA critical discrepancy, and require reporting incorrect specimens or typings used for crossmatching. By reporting critical discrepancies to the OPTN, labs can benefit from the evaluation of HLA critical discrepancy events which can increase patient safety, prioritize efficiency, and positively impact the transplant system as a whole. Modifying the definition of an HLA critical discrepancy is intended to reduce required reports to only the most immunologically significant and align with the required HLA typing resolution. Through the information and knowledge gained through reporting and quality improvement reviews, such as RCAs and CAPs, more systemic data can be used to help identify where education or policy may be needed to prevent future occurrences of critical discrepancies. Finally, requiring the reporting of incorrect specimens or typings used for crossmatching is intended to increase patient safety by mitigating potential future immunologic reactions between the recipient and potential donor. The required reporting and subsequent examination of the event will yield information to improve patient safety and maintain system integrity. This new qualitative information on the causes of HLA critical discrepancies could be utilized to refine policies further and create guidance to reduce future discrepancies and increase overall system efficiency.

Considerations for the Community

- Do you agree that the discovering lab should be responsible for reporting critical HLA discrepancies to the OPTN?
- Does the patient, living donor, and family community agree that this proposal adequately addresses this issue?
- Is 24 hours an appropriate time frame for the initial report of a critical HLA discrepancy to the OPTN?
- Do you agree with the modified definition of a critical HLA discrepancy?
- Should incorrect donor or recipient samples used for crossmatch be included in required reports?
- Should incorrect donor HLA typings or incorrect candidate HLA antibody test be used for virtual crossmatch be included in required reports?

Policy Language

Proposed new language is underlined (example) and language that is proposed for removal is struck through (~~example~~). Heading numbers, table and figure captions, and cross-references affected by the numbering of these policies will be updated as necessary.

Policy 4.4: Critical HLA Discrepancies in Candidate, Donor, and Recipient HLA Typing Results

~~For the purposes of this policy, a~~ A human leukocyte antigen (HLA) critical discrepancy is a difference among non-equivalent values~~, according to *Policy 4.10: Reference Tables of HLA Antigen Values and Split Equivalences,*~~ at one or more loci in a candidate's, donor's, or recipient's HLA typing. Values within the same serologic split antigen group or provided as equivalent for the purposes of unacceptable antigen screening within *Policy 4.11*: *Reference Tables of HLA Antigen Values and Split Equivalences* are considered equivalent.

[…]

4.4.B: Requirement to Resolve and Report to the OPTN Critical Discrepant Donor and Recipient HLA Typing Results

The laboratory director of each laboratory involved in ~~the~~ a candidate, donor, or recipient critical HLA typing discrepancy, or their designee, must identify the correct HLA typing. The laboratory director of the laboratory who discovers the critical HLA typing discrepancy, or their designee, must report the critical HLA typing discrepancy to the OPTN via the OPTN Improving Patient Safety Portal within 24 hours of discovery of the discrepancy. Each laboratory director involved in the critical HLA typing discrepancy, or their designee, must ~~and~~ report the reason for the discrepancy to the OPTN within 60 days of ~~discovery of the discrepancy~~ the initial report.

4.11.B: HLA Unacceptable Antigen Equivalences

At the time of the match run, if an antigen or epitope is entered as unacceptable for a candidate, then the candidate will not appear on the match run for donors reported with any of the equivalent antigens described in *Tables 4-7, 4-8, 4-9, 4-10, 4-11, 4-12, 4-13, 4-14, 4-15, 4-16, 4-17, and 4-18* below.

CPRA calculations include all donor alleles equivalent to a candidate's reported unacceptable antigens, alleles, and epitopes.

~~HLA values listed below as equivalent for the purposes of unacceptable antigen screening are also equivalent for the purposes of reporting HLA typing, with the exception of epitope-based unacceptable antigen assignments in the Table 4-18.~~

18.5.D: Required Reporting by Histocompatibility Laboratories

Histocompatibility laboratories must report the following events to the OPTN according to *Table 18-6* below.

Table 18-6: Required Reporting by Histocompatibility Laboratories

Discovering Laboratories must report if:	**To the:**	**Within 24 hours after:**
A donor, candidate, or recipient HLA typing critical discrepancy occurs, as defined by OPTN *Policy 4.4: Critical HLA Discrepancies in Candidate, Donor, and Recipient HLA Typing Results*	OPTN Patient Safety Reporting Portal	The laboratory becomes aware
An incorrect donor or candidate sample was used for a physical crossmatch	OPTN Patient Safety Reporting Portal	The laboratory becomes aware
An incorrect donor HLA typing or incorrect candidate HLA antibody test was analyzed for a virtual crossmatch	OPTN Patient Safety Reporting Portal	The laboratory becomes aware

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