OPTN

Public Comment Proposal

Require Notification of Human Leukocyte Antigen (HLA) Typing Changes

OPTN Histocompatibility Committee

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Require Notification of Human Leukocyte Antigen (HLA) Typing Changes

Affected Policies: *4.4: Resolving Discrepant Donor and Recipient HLA Typing Results*
Sponsoring Committee: *Histocompatibility*
Public Comment Period: *January 21, 2021 – March 23, 2021*

Executive Summary

There is no current OPTN requirement for histocompatibility laboratories to communicate human leukocyte antigen (HLA) typing changes to transplant programs or organ procurement organizations (OPOs). Histocompatibility laboratories are required to submit the Donor Histocompatibility Form (DHF) within 30 days after procurement, but there is no requirement for direct notification to transplant programs when HLA typing differs either before or after transplant. When transplant programs are not aware of HLA typing changes, patient safety may be adversely impacted. Serious adverse events such as hyperacute rejection, graft failure, and death can occur.

Due to patient safety concerns, the OPTN Histocompatibility Committee is proposing mandatory notifications to transplant programs and OPOs when there is a critical candidate, recipient, or donor HLA typing change. The Histocompatibility Committee is working with the Organ Procurement Organization (OPO), Operations and Safety, and Kidney Committees to ensure the policy is developed with consideration for logistical implications and making sure that no candidates are disadvantaged.

The OPTN is seeking the following feedback:

- Should an automated electronic notification be included as part of this implementation?
- Should there be a policy requirement for post-procurement and pre-transplant?
- Should there be a requirement to re-execute a match run if there is a critical HLA discrepancy?
- Are the proposed notification timelines reasonable?

Background

HLA compatibility between a donor organ and a potential candidate affect how the immune system reacts to the donor organ. If an organ is transplanted into a candidate who has HLA antibodies to it, there is the potential for hyperacute rejection, graft failure, and death. OPOs and transplant programs need to know the correct HLA typing for a given candidate and donor in order to protect against adverse patient outcomes. If these discrepancies are known prior to transplant, programs can avoid potential patient safety issues. If these discrepancies are known post-transplant, programs can appropriately monitor donor-specific antibodies and adjust immunosuppressive medication as needed.

The OPTN Histocompatibility Committee reviews discrepant HLA typings at least every three months. The Committee formed a workgroup with representation from the OPO, Operations and Safety, and Kidney Committees in order to evaluate the discrepant typings reports and evaluate how communication of discrepancies should occur.

The discrepant HLA typings report includes organ donors with differing HLA information between DonorNet® and the Donor Histocompatibility Form (DHF) or when broad antigen groups are assigned due to HLA typing ambiguities. In 2019, there were 11,702 organ donors with HLA typing information in both DonorNet and the DHF, and 48 critical discrepancies in HLA typing. The Committee defines critical discrepancies as ones that are non-equivalent at one or more loci. These are discrepancies that have the potential to cause adverse patient safety events.

There have been 27 patient safety reports to the OPTN due to discrepant HLA typings between January 1, 2018 and September 1, 2020. Multiple reports specified that the transplant programs or OPOs were not contacted in a timely fashion, with a delay of between three days and three months after the discovery event.

Required double entry of HLA typing information in UNet℠ was implemented on February 27, 2020[1], and the Histocompatibility Committee developed the proposal to help address clerical errors causing discrepant HLA information. Clerical errors, however, only accounted for 30 out of 48 critical HLA typing errors in 2019. While the Committee will monitor the newly implemented policy and expects to see a reduction in discrepant HLA values due to clerical errors, there are still other causes of discrepancies that have the potential to cause hyperacute rejection, graft failure, and death in affected recipients.

The Committee and workgroup also discussed a potential requirement to re-execute a match run if there is a critical HLA discrepancy. They ultimately decided that the current policies for released organs sufficiently encompass this requirement, as they wanted OPOs to continue to manage match runs and organ offers with critical data changes during allocation. The workgroup was concerned that not all situations would require match run re-execution, and that requiring re-execution may increase cold ischemic time and other potential factors that could lead to increased organ discards.

The Committee and workgroup discussed potential requirements for discrepancies discovered post-procurement yet still pre-transplant, but there has been no evidence of discrepancies being discovered during that window within the past two years. They were hesitant to create a requirement for such an infrequent occurrence, especially as an OPO would be unlikely to know when transplant of an organ into

[1] https://optn.transplant.hrsa.gov/media/2791/histo_policynotice_201901.pdf

the recipient occurred in real time. As such, the committee and workgroup did not feel that it was practical to make a policy requirement for this situation. The Committee and workgroup also discussed whether to require notification for any HLA typing change or just for critical discrepancies. They felt that the notification requirement would not be necessary for further refinement of HLA typings, where a value would still be equivalent but would be typed at a higher resolution.

Purpose

The OPTN Histocompatibility is submitting this proposal to protect patient safety by identifying and reporting HLA discrepancies as early as possible. This proposal may affect allocation, as candidate and donor HLA typings are used for matching purposes in kidney and pancreas allocation. In addition, donor HLA typings are used to screen incompatible candidates from a match for all organs. The OPTN has the authority to propose this per the Final Rule, which states that "The OPTN Board of Directors shall be responsible for developing…policies for the equitable allocation for cadaveric organs."[2] In addition, the OPTN Final Rule states "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, in accordance with policies established by the OPTN."[3] The correct information should be available for evaluation of donor and potential recipient compatibility.

Overview of Proposal

The proposal sets forth requirements for notification of critical HLA typing discrepancies. These notifications would be required any time an HLA typing is changed to a non-equivalent value at one or more loci, regardless of the cause of the change. Any form of notification that requires acknowledgment would be acceptable, including a phone call. Notification must be followed by documentation of the correct typing.

Donor HLA Typings

If a histocompatibility lab becomes aware of a discrepancy in a donor's HLA typing from what is entered in UNet, they would be required to notify the OPO within one hour of determining the correct typing and provide documentation of the corrected typing. This documentation could include the raw HLA typing information.

After receiving the correct documentation from the histocompatibility lab, the OPO would then be required to notify all accepting transplant programs and provide documentation. This notification and documentation would be required as soon as possible, but within 12 hours. If the discrepancy is discovered prior to procurement, the OPO would also be required to notify transplant programs before procurement. The transplant program has the ability to release the organ according to *OPTN Policy 5.9: Released Organs* if it is no longer suitable for the intended candidate. If that occurs, the OPO can proceed with re-allocation according to the policies pertaining to that specific organ.

[2] 42 CFR §121.8(a).
[3] 42 CFR §121.6(a).

Candidate or Recipient HLA Typings

If a histocompatibility lab becomes aware of a discrepancy in a candidate or recipient's HLA typing from what is entered in UNet, then proposed OPTN *Policy 4.4.A.ii: Candidate and Recipient Critical HLA Discrepancies* would require them to notify the transplant program within five days of determining the correct typing and provide documentation of the corrected typing. This documentation could include the raw HLA typing information. The workgroup felt that these discrepancies did not have the same level of urgency, as they would impact post-transplant donor-specific antibody monitoring, but would not lead to rejection events.

Discrepancy Reports

The histocompatibility laboratory is required to report the reason for the discrepancy in the HLA discrepancy report within UNet. This is a current requirement under *OPTN Policy 4.4: Resolving Discrepant Donor and Recipient HLA Typing Results* and will continue to be required under this policy. This discrepancy report allows the Histocompatibility Committee to know which typing is correct, as well as the reason for the error. The error reason helps inform the Committee as they create and monitor applicable policies in an effort to minimize typing discrepancies. The timeline for discrepancy reporting to the OPTN has been extended from 30 to 60 days, in order to better align with the data submission requirement changes approved by the Board in December 2019.[4]

NOTA and Final Rule Analysis

The Committee submits the following proposal for the Board consideration under the authority of the National Organ Transplantation Act, 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…"[5] Early communication of HLA typing changes could allow for reallocation if necessary. Reallocation due to HLA typing changes would most affect sensitized patients, with 100% CPRA patients having over a fourteen times lower offer rate per patient year than unsensitized patients.[6] The Committee also submits the following proposal for the Board consideration under the authority of the OPTN Final Rule, which states "The OPTN Board of Directors shall be responsible for developing…policies for the equitable allocation for cadaveric organs."[7] This proposal may affect allocation, as candidate and donor HLA typings are used for matching purposes in kidney and pancreas allocation. In addition, donor HLA typings are used to screen incompatible candidates from a match.

The Final Rule requires that when developing policies for the equitable allocation of cadaveric organs, such policies must be developed "in accordance with §121.8," which requires that allocation policies "(1) Shall be based on sound medical judgment; (2) Shall seek to achieve the best use of donated organs; (3) Shall preserve the ability of a transplant program to decline an offer of an organ or not to use the organ for the potential recipient in accordance with §121.7(b)(4)(d) and (e); (4) Shall be specific for each organ type or combination of organ types to be transplanted into a transplant candidate; (5) Shall be

[4] https://optn.transplant.hrsa.gov/media/3459/modify-data-submission-policies-policy-notice.pdf
[5] 42 USC 274(b)(2)(A)(ii).
[6] Wilk, Amber R, John Beck, and Anna Y Kucheryavaya. Two Year Evaluation of the New, National Kidney Allocation System (KAS). Richmond, VA: Organ Procurement and Transplantation Network, 2017.
[7] 42 CFR §121.8(a).

designed to avoid wasting organs, to avoid futile transplants, to promote patient access to transplantation, and to promote the efficient management of organ placement;…(8) Shall not be based on the candidate's place of residence or place of listing, except to the extent required by paragraphs (a)(1)-(5) of this section." This proposal:

- **Is based on sound medical judgment**[8] because it is an evidenced-based change relying on the following evidence:
    - HLA incompatibility is the leading cause of hyperacute rejection, which leads to graft failure. Timely reporting of discrepancies allows for programs to properly assess potential deceased donors for compatibility with the intended recipient. Timely reporting also allows for proper treatment and monitoring of recipients who have already been transplanted, in order to minimize risk of rejection.
- **Is designed to avoid futile transplants**[9]**:** This proposal seeks to increase communication of HLA typing changes, in order to avoid immunologically incompatible transplants. Timely reporting of discrepancies allows for programs to properly assess potential deceased donors for compatibility with the intended recipient.
- **Is not based on a candidate's place of residence or place of listing except to the extent required by other regulatory requirements.**[10]
- **Is designed to avoid wasting organs**[11] **by** decreasing the number of organs recovered but not transplanted.
    - Early communication of HLA typing changes could allow for reallocation if necessary, so that the transplant recipient and organ are compatible.

Although the proposal outlined in this briefing paper addresses certain aspects of the Final Rule listed above, the Committee does not expect impacts on the following aspects of the Final Rule:

- **Seeks to achieve the best use of donated organs**[12] **by** ensuring organs are allocated and transplanted according to medical urgency.
- **Is designed to…promote patient access to transplantation**[13] **by** giving similarly situated candidates equitable opportunities to receive an organ offer.
- **Promotes the efficient management of organ placement**[14] **by** taking into account factors including the costs and logistics of procuring and transplanting organs.

The OPTN Final Rule also states "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, in accordance with policies established by the OPTN."[15] The correct information should be available for evaluation of donor and potential recipient compatibility.

The OPTN Final Rule also requires the OPTN to consider **"whether to adopt transition procedures that would treat people on the waiting list and awaiting transplantation prior to the adoption or effective**

[8] 42 CFR §121.8(a)(1).
[9] Id.
[10] 42 CFR §121.8(a)(8).
[11] 42 CFR §121.8(a)(5).
[12] 42 CFR §121.8(a)(2).
[13] Id.
[14] Id.
[15] 42 CFR §121.6(a).

date of the revised policies no less favorably than they would have been treated under the previous policies."[16] It is not evident that patients would be treated less favorably under the new policy, and therefore a transition plan is unlikely to be necessary. However, the committee welcomes feedback on this issue.

Alignment with OPTN Strategic Plan[17]

Promote living donor and transplant recipient safety
Proposed changes allow histocompatibility to be accurately assessed when considering donor acceptance.

Implementation Considerations

Member and OPTN Operations

Operations affecting Histocompatibility Laboratories

Histocompatibility laboratories will need to train and ensure key personnel complete data entry for the HLA discrepancy reports. Completing the report is already a requirement under current OPTN policy.

Operations affecting Organ Procurement Organizations

OPOs will need to train staff on the requirement to notify and provide documentation to all accepting transplant programs.

Operations affecting Transplant Hospitals

Transplant hospitals will need to provide staff training on the new requirements regarding the expected notification and HLA information that will be received for reported discrepancies.

Operations affecting the OPTN

The OPTN will create educational materials to support members with the new requirements established in this proposal.

Projected Fiscal Impact

Projected Impact on Histocompatibility Laboratories

According to recent data reviews, a minimal number (<30) of match runs per year occurred nationwide that required a significant change to HLA typing and a new match run. When an event occurs, lab and OPO communication must occur quickly. Labs currently have systems to address critical values and alert value reporting.

[16] 42 CFR §121.8(d).
[17] For more information on the goals of the OPTN Strategic Plan, visit https://optn.transplant.hrsa.gov/governance/strategic-plan/.

Since these are rare events, the new requirement should not have significant effect on staffing or hours. In the rare case that allocation must be re-run due to a significant HLA discrepancy, the accepting transplant center or lab may need to perform additional testing, such as prospective flow crossmatch or virtual crossmatch.

Cost savings include better patient safety and reduced risk of major discrepancy events. Implementation time is minimal, as system programming and alert messaging will be performed the OPTN.

Projected Impact on Organ Procurement Organizations

While typing change events occur in relatively small numbers, the proposed required notification could result in significant staff time and effort to notify multiple transplant centers and OPOs per case. This could also require additional staff time for reporting and verification purposes if reported post-transplant. Additionally, when a significant error is reported during allocation, there may be a need to close the match runs and reallocate which is a current practice for many OPOs.

Projected Impact on Transplant Hospitals

There is no or minimal expected impact for transplant hospitals. This proposal strives to ensure that recipients receive compatible organs and are able to be appropriately monitored post-transplant. While this would affect a small number of recipients a year, this could save significant resources on each affected patient.

Projected Impact on the OPTN

There is minimal expected impact for the OPTN, as this proposal does not require programming efforts.

Post-implementation Monitoring

Member Compliance

The proposed language will not change the current routine monitoring of OPTN members. Any data entered in UNet℠ may be reviewed by the OPTN, and members are required to provide documentation as requested.

Policy Evaluation

The Final Rule requires that allocation policies "be reviewed periodically and revised as appropriate."[18]

This proposal will be formally evaluated at approximately 1, 2, and 3 years post- implementation. The following metrics, and any subsequently requested by the Committee, will be evaluated as data become available (appropriate lags will be applied, per typical UNOS conventions, to account for time delay in institutions reporting data to UNet) and compared pre- and post-implementation:

- The number of donor and recipient discrepancies reported in UNet

[18] 42 CFR §121.8(a)(6).

- The source of these discrepancies (Donor Histocompatibility Form, Recipient Histocompatibility form, Waitlist, etc.)
- The count and percent of these discrepancies marked resolved after three months
- The reported reasons for those discrepancies that have been resolved

Conclusion

This proposal is intended to protect patient safety through required communication and documentation of discrepant HLA typing results. This proposed policy applies to candidate, recipient, and donor HLA typings. The Histocompatibility Committee and community have taken steps to minimize HLA typing discrepancies, and they need to be communicated quickly when they do occur to reduce the chance of an adverse event.

The OPTN is seeking the following feedback:

- Should an automated electronic notification be included as part of this implementation?
- Should there be a policy requirement for post-procurement and pre-transplant?
- Should there be a requirement to re-execute a match run if there is a critical HLA discrepancy?
- Are the proposed notification timelines reasonable?

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.

4.4 ~~Resolving~~ Critical HLA ~~Discrepant~~ Discrepancies in Candidate, Donor, and Recipient HLA Typing Results

~~Laboratories must submit donor and recipient histocompatibility forms to the OPTN after transplant according to Policy 18: Data Submission Requirements. After laboratories submit donor and recipient HLA typing results to the OPTN, the OPTN will provide a report to the laboratories including any discrepant HLA typing results.~~

~~Laboratories must resolve discrepancies within 30 days of notification of discrepant HLA typing results. The Laboratory Director or designated staff must contact the other Laboratory Director or designated staff to resolve the discrepancies. Each laboratory involved in the HLA typing discrepancy must identify and report the reason for the discrepancy to the OPTN.~~

~~The OPTN will remove all discrepant flags from HLA typing results that have been resolved. Discrepancies that have not been resolved will remain flagged. The Histocompatibility Committee will review, at least every three months, any outstanding discrepant typing recorded since the last review. The committee will use the results of these reviews to determine whether policy modifications are required.~~

For the purposes of this policy, 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.

4.4.A Requirement to Notify Transplant Programs and OPOs

4.4.A.i: Donor HLA Critical Discrepancies

If a laboratory becomes aware of a critical discrepancy in a donor's HLA typing, the laboratory must notify the host OPO of the discrepancy. Notification and supporting documentation must be provided as soon as possible, but no later than one hour following the discovery of the discrepancy.

Upon receipt of documentation of the discrepancy, the OPO must do the following:

- If the discrepancy is discovered prior to procurement, the OPO must notify and provide supporting documentation to all accepting transplant programs as soon as possible, but no later than 12 hours following discovery of the discrepancy or prior to procurement, whichever occurs first.
- If the discrepancy is discovered post-procurement, the OPO must notify and provide supporting documentation to all accepting transplant programs within 12 hours following the discovery.

4.4.A.ii: Candidate and Recipient HLA Critical Discrepancies

If a laboratory discovers a critical HLA discrepancy in a candidate's or recipient's HLA typing, the laboratory must notify the listing transplant program and provide documentation of the discrepancy as soon as possible, but within 5 days following discovery of the discrepancy.

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

The laboratory director of ~~each~~ laboratory involved in the HLA typing discrepancy, or their designee, must identify the correct HLA typing and report the reason for the discrepancy to the OPTN within 60 days of discovery of the discrepancy.