

Briefing to the OPTN Board of Directors on

Require Notification of Critical Human Leukocyte Antigen (HLA) Typing Changes

OPTN Histocompatibility Committee

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Require Notification of Critical 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
Board of Directors Date: June 14, 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 critical 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 defining what constitutes a critical HLA typing change and proposing mandatory notifications to transplant programs and OPOs when there is a candidate, recipient, or donor critical HLA typing change. The Histocompatibility Committee developed this proposal with collaboration from the Organ Procurement Organization (OPO), Operations and Safety, and Kidney Committees to ensure consideration for logistical implications and that no candidates are disadvantaged.

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, according to OPTN *Policy 4.4: Resolving Discrepant Donor and Recipient HLA Typing Results*. 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. Clinical interpretation, especially for HLA typings at lower resolutions, can lead to many of the non-critical discrepancies that the Committee identifies. 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.¹ 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.

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.

There have been 37 patient safety reports to the OPTN due to discrepant HLA typings between January 1, 2018 and April 1, 2021. Multiple reports specified that the transplant programs or OPOs were not contacted in a timely fashion, with delays of between three days and three months after the discovery event.²

Required double entry of HLA typing information in UNetSM was implemented on February 27, 2020³ to help address clerical errors causing discrepant HLA information. Clerical errors, however, accounted for 30 out of 48 critical HLA typing errors in 2019. While the Committee will monitor this 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.

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

¹ Based on OPTN HLA discrepancy data presented to the Committee for review quarterly. OPTN data includes donors recovered each quarter, their de-identified patient and laboratory numbers, and any change in HLA data between match runs, the Donor Histocompatibility Form (DHF) and Recipient Histocompatibility Form (RHF), or the assignment of broad antigen groups in any of these locations. This data includes HLA data at each locus, typing method, timing of match runs, and any reason for discrepancy reported by the involved Histocompatibility laboratories.

² Based on OPTN data reported through the UNetSM Improving Patient Safety Portal for incidents reported between January 1, 2018 and April 1, 2021.

³ https://optn.transplant.hrsa.gov/media/2791/histo_policynotice_201901.pdf.

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.

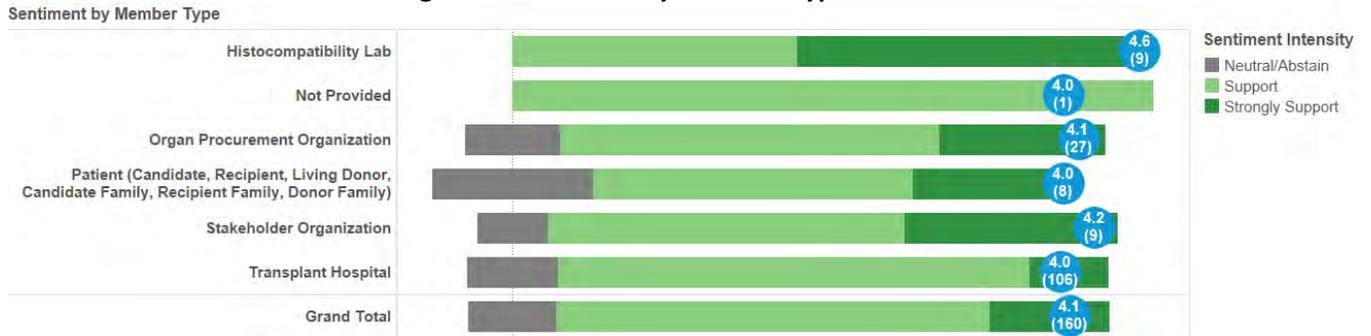
Sentiment from Public Comment

The proposal was released for public comment from January 21, 2021 to March 23, 2021. During that time, it received 175 responses, eleven of which also had a substantive written comment. Following are a summary of the overall sentiment for the proposal, as well as a summary of feedback on certain themes of the proposal. The major areas that the OPTN received feedback on were:

- Timing of notifications
- Re-execution of the match run
- Automated electronic notifications

The proposal was supported across all member types, with an average sentiment score of 4.1/5 on the Likert sentiment scale. *Figure 1* shows the sentiment by member type, with the highest support coming from histocompatibility laboratory members.

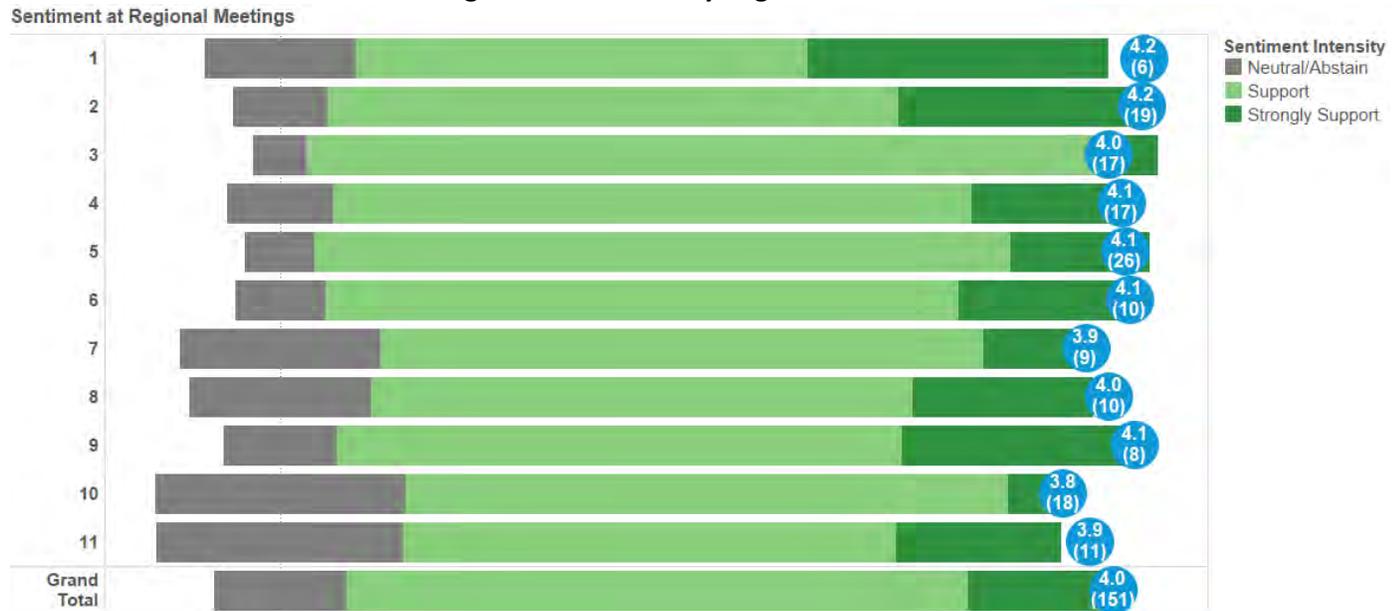
Figure 1: Sentiment by Member Type⁴



⁴ Sentiment is reported by the participant using a 5-point Likert scale (1-5 representing Strongly Oppose to Strongly Support). Sentiment by member type includes all comments regardless of source (regional meeting, committee meeting, online, fax, etc.) The circles after each bar indicate the average sentiment score and the number of participants is in the parentheses.

The next graphic, *Figure 2*, shows the sentiment by Region. This shows the sentiment received at regional meetings, which again was supportive overall.

Figure 2: Sentiment by Region⁵



This proposal was also presented to a number of OPTN committees, who provided comment without providing overall sentiment on the proposal. Those committees were the Organ Procurement Organization (OPO), Operations and Safety, Kidney Transplantation, and Transplant Coordinators. Their feedback is summarized alongside feedback received via regional meetings, from stakeholder organizations, and from individual submissions.

Timing of Notifications

Feedback on the proposed timing of the notifications was overall supportive. The OPTN Operations and Safety Committee, North American Transplant Coordinators Organization (NATCO), and an individual commenter all recommended changing the post-procurement reporting timeline for OPOs from 12 to 24 hours to parallel other post-procurement reporting timeframes for OPOs. Twelve hours was originally chosen to maintain consistency with pre-procurement reporting in the proposal, but the workgroup and committee agreed that a 24-hour timeframe would still allow for any necessary interventions to be initiated.^{6,7} Hyperacute rejection occurs within the first few hours of transplant, and the only current treatment is removal of the transplanted organ.⁸ Acute rejection or antibody-mediated rejection typically occurs days to weeks after transplant, so OPO notification to transplant programs within 24 hours would still allow for recipient clinical interventions prior to acute symptoms.⁹

⁵Sentiment is reported by the participant using a 5-point Likert scale (1-5 representing Strongly Oppose to Strongly Support). Sentiment for regional meetings only includes attendees at that regional meeting. Region 6 uses the average score for each institution. The circles after each bar indicate the average sentiment score and the number of participants is in the parentheses.

⁶ https://optn.transplant.hrsa.gov/media/4531/20210308_histo_discrepant_typings_subcom_meeting_summary.pdf

⁷ OPTN Histocompatibility Committee Meeting, April 13, 2021

⁸ Naik RH, Shawar SH. Renal Transplantation Rejection. [Updated 2020 Dec 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK553074/>

⁹ Id.

Re-execution of the Match Run

Feedback on whether or not a critical HLA discrepancy should require re-execution of the match run supported the committee's decision to exclude this requirement from the proposal. Many commenters agreed that if the original intended recipients of an organ are no longer able to accept an organ a match run should be re-executed if logistically possible, due to the possibility of sensitized patients being excluded from the original organ offer. If the transplant program determines that the organ is no longer acceptable for the original intended recipient, all commenters agreed that the OPO should maintain discretion as to whether to re-execute a match run or continue allocating using the previous match run in order to prevent excessive cold ischemic time and potentially organ discard.

During the development of the proposal, the committee and workgroup had discussed a potential requirement to re-execute a match run if there is a critical HLA discrepancy. They ultimately decided that the current policies surrounding organ offer acceptance and released organs sufficiently address these considerations, 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.

Automated Electronic Notifications

Many commenters agreed that an automated notification from histocompatibility labs to OPOs, and OPOs to transplant programs would be beneficial in quickly communicating critical information. In order to best implement potential electronic notifications, the committee will be discussing this issue further with various stakeholders and will consider it for a future enhancement.

Further Topics for Consideration

The American Society for Transplant Surgeons (ASTS) had multiple recommendations on how to further evaluate and prevent HLA typing errors. Their recommendations included universal barcoding for HLA specimens, and the committee further evaluating the root causes of discrepancies. The committee will be evaluating these recommendations for future consideration.

The Committee and workgroup had also discussed potential requirements for discrepancies discovered post-procurement yet still pre-transplant¹⁰, but there has been no evidence of discrepancies being discovered during that window within the past three 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 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 typed at a higher resolution.

¹⁰ https://optn.transplant.hrsa.gov/media/4262/2020_11_19_histo_hla-discrepant-typings_mtg-summary.pdf.

Proposal for Board Consideration

The proposal sets forth requirements for histocompatibility laboratories to notify OPOs and transplant hospitals, and OPOs to notify transplant hospitals, when there is a critical HLA typing discrepancy. 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. All notifications must be followed by documentation of the correct typing.

The principles of the proposal did not change following public comment. The committee proposes changing the donor notification timeframe for post-procurement from 12 to 24 hours, to mirror other post-procurement donor findings, such as post-procurement donor culture results or discovery of malignancy. In addition, the committee clarified that an OPO would still be required to report discrepancies to the transplant program if they were discovered independently instead of reported by the histocompatibility laboratory. Language defining the discovery of the discrepancy was clarified to state that the histocompatibility laboratory must determine the correct HLA typing prior to notification. Multiple commenters had expressed concern that discovery of a potential error may lead to re-typing, which could take hours, and that a laboratory would not have actionable information for the OPOs and transplant program until determination of the correct HLA typing.

Figure 3: Proposed Notification Requirements

When member...	Does...	For...	They must notify...	Within...
Histocompatibility laboratory	Determines correct typing	Donor	OPO	1 hour
		Candidate/Recipient	Transplant hospital	5 days
OPO	Receives documentation from laboratory, or discovers independently	Donor pre-procurement	Transplant hospital	12 hours, or pre-procurement
		Donor post-procurement	Transplant hospital	24 hours

Donor HLA Typings

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

After receiving the correct documentation from the histocompatibility laboratory, 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. If the critical discrepancy is discovered prior to procurement, the notification is required within 12 hours of being notified by the laboratory, or prior to procurement, whichever is sooner. If the discrepancy is discovered after procurement, the OPO will be required to notify transplant programs within 24 hours of being notified by the laboratory. 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 based on the updated information. If that occurs, the OPO can proceed with re-allocation according to the policies pertaining to that specific organ.

Candidate or Recipient HLA Typings

If a histocompatibility laboratory 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, such as the raw HLA typing information. The workgroup felt that these discrepancies did not have the same level of urgency, as they would primarily impact post-transplant donor-specific antibody monitoring. At this time the Committee does not evaluate potential discrepancies in unacceptable antigen assignment, as these can vary by clinical practice and due to changing candidate factors over time.

Discrepancy Reports

The histocompatibility laboratory is required to report the reason for the discrepancy in the HLA discrepancy report to the OPTN. 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 is extended from 30 to 60 days, in order to better align with the data submission requirement changes to the donor histocompatibility form (DHF) and recipient histocompatibility form (RHF) approved by the Board in December 2019.¹¹ Committee members and the American Society for Histocompatibility and Immunogenetics (ASHI) had supported the change in timing for submission of the DHF and RHF in 2019 in order to allow for re-typing and further clarification of typing data,¹² and Committee members felt that the increase in submission time for the discrepancy report within UNet is appropriate for the same reasons.¹³

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..."¹⁴ 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."¹⁵ 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. Early communication of HLA typing changes could allow for reallocation if necessary. Reallocation due to HLA typing changes

¹¹ <https://optn.transplant.hrsa.gov/media/3459/modify-data-submission-policies-policy-notice.pdf>.

¹² <https://optn.transplant.hrsa.gov/governance/public-comment/modify-data-submission-policies/>.

¹³ https://optn.transplant.hrsa.gov/media/4287/2020_12_04_histo_discrepant-hla-typings_mtg-summary.pdf.

¹⁴ 42 USC 274(b)(2)(A)(ii).

¹⁵ 42 CFR §121.4(a)(1).

would most affect sensitized patients, with 100% CPRA patients having over a fourteen times lower offer rate per patient year than unsensitized patients.¹⁶

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,”¹⁷ 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 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.”¹⁸ This proposal:

- **Is based on sound medical judgment**¹⁹ because it is an evidenced-based change relying on the following evidence:
 - Review of OPTN data to inform the Committee existing problem and identification of potential solutions, including HLA typing data submitted through DonorNet and TIEDI, as well as patient safety reports made over the last three years due to HLA typing discrepancies.
 - Peer-reviewed literature demonstrating that HLA incompatibility is the leading cause of hyperacute rejection,²⁰ which leads to graft failure.^{21,22} Timely reporting of discrepancies allows for programs to properly assess potential deceased donors for HLA compatibility with the intended recipient. Timely reporting could also allow for proper treatment and monitoring of recipients who have already been transplanted, in order to minimize risk of rejection.
 - The medical consensus of the committee based on collective experience with typing errors and treatment of post-transplant HLA mismatches
- **Is designed to avoid futile transplants**²³: This proposal seeks to increase communication of HLA typing changes, in order to avoid immunologically incompatible transplants which could result in graft failure. Timely reporting of discrepancies allows for programs to properly assess potential deceased donors for compatibility with the intended recipient ahead of transplant will permit the transplant program to make informed decisions as to whether to accept the organ given the updated information, and post-transplant notification will allow the transplant program to effectively treat the recipient to assist in avoiding graft failure due to HLA mismatch.

¹⁶ 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.

¹⁷ 42 CFR §121.4(a)(1).

¹⁸ 42 CFR §121.8(a)(1)-(8).

¹⁹ 42 CFR §121.8(a)(1).

²⁰ Suchitra Sumitran-Holgersson, HLA-specific alloantibodies and renal graft outcome, *Nephrology Dialysis Transplantation*, Volume 16, Issue 5, May 2001, Pages 897–904, <https://doi.org/10.1093/ndt/16.5.897>

²¹ Harmer, A. W., Koffman, C. G., Heads, A. J., & Vaughan, R. W. (1995). Sensitization to HLA antigens occurs in 95% of primary renal transplant rejections. *Transplantation proceedings*, 27(1), 666–667.

²² Lee, Po-Chang; Terasaki, Paul; Takemoto, Steven; Lee, Po-Huang; Hung, Chung-Jye; Chen, Yi-Lin; Tsai, Alen; Lei, Huan-Yao. All chronic rejection failures of kidney transplants were preceded by the development of HLA antibodies, *Transplantation*: October 27th, 2002 - Volume 74 - Issue 8 - p 1192-1194

²³ Id.

- **Is not based on a candidate’s place of residence or place of listing.**²⁴
- **Is designed to avoid wasting organs**²⁵ 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, as a discovery of the mismatch close to the scheduled transplant may otherwise prevent the OPO or transplant program from identifying a suitable alternate recipient for the organ.

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**²⁶ by ensuring organs are allocated and transplanted according to medical urgency.
- **Is designed to...promote patient access to transplantation**²⁷ by giving similarly situated candidates equitable opportunities to receive an organ offer.
- **Promotes the efficient management of organ placement**²⁸ 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.”²⁹ The correct information should be made available by the laboratories to the OPOs, who in turn will make the information available to the transplant programs, for effective 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 date of the revised policies no less favorably than they would have been treated under the previous policies.”³⁰ The Committee felt that the proposed policy changes would not treat any candidates less favorably than they are treated under the current policy, and does not recommend any particular transition procedures.³¹

Alignment with OPTN Strategic Plan³²

Promote living donor and transplant recipient safety

Proposed changes allow histocompatibility to be accurately assessed when considering donor acceptance. HLA incompatibility is the leading cause of hyperacute rejection,³³ which leads to graft

²⁴ 42 CFR §121.8(a)(8).

²⁵ 42 CFR §121.8(a)(5).

²⁶ 42 CFR §121.8(a)(2).

²⁷ Id.

²⁸ Id.

²⁹ 42 CFR §121.6(a).

³⁰ 42 CFR §121.8(d).

³¹ https://optn.transplant.hrsa.gov/media/4531/20210308_histo_discrepant_typings_subcom_meeting_summary.pdf.

³² For more information on the goals of the OPTN Strategic Plan, visit <https://optn.transplant.hrsa.gov/governance/strategic-plan/>.

³³ Suchitra Sumitran-Holgersson, HLA-specific alloantibodies and renal graft outcome, *Nephrology Dialysis Transplantation*, Volume 16, Issue 5, May 2001, Pages 897–904, <https://doi.org/10.1093/ndt/16.5.897>

failure.^{34, 35} Timely reporting of discrepancies allows for programs to properly assess potential deceased donors for HLA compatibility with the intended recipient. Timely reporting could also allow for proper treatment and monitoring of recipients who have already been transplanted, in order to minimize risk of rejection.

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, laboratory and OPO communication must occur quickly. Laboratories currently have systems to address critical values and alert value reporting.

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 laboratory may need to perform additional testing, such as prospective flow crossmatch or virtual crossmatch.

³⁴ Harmer, A. W., Koffman, C. G., Heads, A. J., & Vaughan, R. W. (1995). Sensitization to HLA antigens occurs in 95% of primary renal transplant rejections. *Transplantation proceedings*, 27(1), 666–667.

³⁵ Lee, Po-Chang; Terasaki, Paul; Takemoto, Steven; Lee, Po-Huang; Hung, Chung-Jye; Chen, Yi-Lin; Tsai, Alen; Lei, Huan-Yao. All chronic rejection failures of kidney transplants were preceded by the development of HLA antibodies, *Transplantation*: October 27th, 2002 - Volume 74 - Issue 8 - p 1192-1194

Cost savings include better patient safety and reduced risk of major discrepancy events.

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

Policy and Community Relations (PCR) hosted a workgroup to evaluate how to communicate discrepant HLA typings. PCR staff worked with cross-department UNOS staff to prepare the proposal for public comment, and incorporate changes to the proposal based on the Committee's decisions following public comment.

A small OPTN implementation effort, estimated at 185 hours, includes offerings from Professional Education and Communications with support from PCR and Member Quality to educate members about the policy changes. No IT implementation is required.

Research anticipates a very small effort in routine monitoring. Member Quality does not anticipate any change to their current monitoring.

Post-implementation Monitoring

Member Compliance

The Final Rule requires that allocation policies “include appropriate procedures to promote and review compliance including, to the extent appropriate, prospective and retrospective reviews of each transplant program's application of the policies to patients listed or proposed to be listed at the program.”³⁶

The proposed language will not change the current routine monitoring of OPTN members. Any data entered in UNetSM 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.”³⁷

³⁶ 42 CFR §121.8(a)(7).

³⁷ 42 CFR §121.8(a)(6).

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
- 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

The number of annual discrepancies is too low to show a statistical relationship between discrepancies and graft failures or rejection events. Instead, the evaluation will focus on the timing of discrepancy corrections and their resolution.

Conclusion

The OPTN Histocompatibility Committee 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.

This proposal establishes an OPTN requirement for histocompatibility laboratories to communicate critical human leukocyte antigen (HLA) typing changes to transplant programs or organ procurement organizations (OPOs). When transplant programs are not aware of critical HLA typing changes, patient safety may be adversely impacted. Serious adverse events such as hyperacute rejection, graft failure, and death can occur. This proposal was supported in public comment, and post-public comment changes were limited to clarifications of the proposed language and aligning the post-procurement reporting timeframe for OPOs with other post-procurement donor reporting timeframes. This proposal would require timely notification of critical HLA typing discrepancies for donors, candidates, and recipients in order to allow for proper assessment of potential donor compatibility, and proper treatment of recipients post-transplant.

Policy Language

1 **RESOLVED**, that the changes to *Policy 4.4: Resolving Discrepant Donor and Recipient HLA Typing Results*,
2 as well as the creation of *4.4.A: Requirement to Notify Transplant Programs and OPOs*, *4.4.A.i: Donor*
3 *HLA Critical Discrepancies*, *4.4.A.ii: Candidate and Recipient HLA Critical Discrepancies*, and *4.4.B:*
4 *Requirement to Resolve Critical Discrepant Donor and Recipient HLA Typing Results*, as set forth below,
5 are hereby approved, effective September 1, 2021.

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.

6 **4.4 Resolving Critical HLA Discrepant Discrepancies in Candidate,** 7 **Donor, and Recipient HLA Typing Results**

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

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

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

21 For the purposes of this policy, a human leukocyte antigen (HLA) critical discrepancy is a difference
22 among non-equivalent values, according to Policy 4.10: Reference Tables of HLA Antigen Values and Split
23 Equivalences, at one or more loci in a candidate's, donor's, or recipient's HLA typing.

24 **4.4.A Requirement to Notify Transplant Programs and OPOs**

25 **4.4.A.i: Donor HLA Critical Discrepancies**

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

30 Upon independent discovery or receipt of documentation of the discrepancy, the OPO must do
31 the following:

- 32 • If the discrepancy is discovered prior to procurement, the OPO must notify and provide
33 supporting documentation to all accepting transplant programs as soon as possible, but no
34 later than 12 hours following discovery of the discrepancy or prior to procurement,
35 whichever occurs first.
- 36 • If the discrepancy is discovered post-procurement, the OPO must notify and provide
37 supporting documentation to all accepting transplant programs within 24 hours following
38 the discovery.

39 **4.4.A.ii: Candidate and Recipient HLA Critical Discrepancies**

40 If a laboratory discovers a critical HLA discrepancy in a candidate’s or recipient’s HLA typing, the
41 laboratory must notify the listing transplant program and provide documentation of the
42 discrepancy as soon as possible, but within 5 days following determination of the correct HLA
43 typing.

44

45 **4.4.B: Requirement to Resolve Critical Discrepant Donor and Recipient HLA Typing**

46 **Results**

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

50

51 #