OPTN

Public Comment Proposal

Require Human Leukocyte Antigen (HLA) Confirmatory Typing for Deceased Donors

OPTN Histocompatibility Committee

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Affected Policies: *4.3.A Deceased Donor HLA Typing*
Sponsoring Committee: *Histocompatibility*
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Executive Summary

Human Leukocyte Antigen (HLA) typing is a vital step for successful organ transplantation. An incorrect HLA typing can lead to hyperacute rejection, graft failure, and death. These errors can place the life of the recipient at risk, and can cause unnecessary organ non-utilization and prolonged waiting time for multiple candidates. Furthermore, any incorrect typing results have the potential to significantly delay the allocation process. The OPTN instituted a requirement for dual manual entry of HLA typings to reduce clerical discrepancies, implemented in 2020[1].

The OPTN Histocompatibility Committee, the Committee, proposes to create additional safety protocols for other causes of HLA discrepancies by requiring two HLA typings be performed on all deceased donors with samples drawn at two separate times. Requiring confirmatory HLA typing for deceased donors will help ensure a recipient is receiving a compatible organ that can function to improve their health and increase post-transplant survival. Highly sensitized candidates, female candidates, and black candidates are particularly vulnerable in cases of incorrect HLA typings, as these groups are more likely to have pre-formed antibodies that could cause an adverse immunologic reaction.

[1] Organ Procurement and Transplant Network (OPTN) *Policy 4.3: Requirements for Performing and Reporting HLA Typing* (effective: October 27, 2022).

Purpose

The purpose of this proposal is to ensure the accuracy of immunologic testing results used in allocation and reduce the chance of unintended HLA incompatibility within the transplant system. The Committee proposes requiring two HLA typings be performed from specimens drawn at two separate times for all deceased donors, similar to the existing requirement for blood group typing. Incorrect typings in either category have the same immunologic potential, and the Committee believes they should receive the same safeguards. In addition, an increased confidence in HLA typing result accuracy may increase utilization of virtual crossmatching, which could lead to a decrease in cold ischemic time, a decrease in late organ declines due to positive crossmatch, and an increase equity for highly sensitized candidates.

Background

The Committee has discussed and recommended confirmatory HLA typing previously. In 2006, the Committee recommended confirmatory HLA typing for all shared donors in a guidance document.[2] When developing a proposal to address HLA typing errors, the Committee had initially considered requiring confirmatory HLA typing. They ultimately only addressed clerical errors, as the Committee had felt that confirmatory typing could increase the cost of HLA typing for laboratories and would not address the clerical errors that were the primary source of HLA discrepancies prior to the implementation of that proposal.[3]

In February 2022, the Committee received written correspondence on the risk of running a single HLA typing from Johns Hopkins School of Medicine. The Director of the Immunogenetics Laboratory for the John Hopkins School of Medicine highlighted the critical need for HLA confirmatory typing for patient safety and the nationwide organ allocation system: "…even if an error in the deceased donor HLA typing is caught in time to prevent a catastrophic event, it will cause the nation-wide allocation system to be disrupted as organs that have already been shipped to transplant centers may not be used for the intended recipient."[4]

In 2020 the OPTN implemented a double data entry requirement for HLA typings to reduce clerical errors. This policy has been successful in reducing clerical errors but was not intended to address other discrepancy causes such as sample switches or laboratory reagent failures. While critical HLA typing errors currently occur in approximately 0.24% of deceased donor typings, the adverse events these errors can cause can include hyperacute rejection, graft failure, and recipient death.[5] An inaccurate HLA typing can also lead to organ non-utilization or unnecessarily extend cold ischemic time while an organ is re-allocated.

Data received from the OPTN Patient Safety Reporting Portal also indicates there is a need for confirmatory typing tests to occur. This data is not inclusive of all events that occurred, as reporting these discrepancies to the OPTN Patient Safety Reporting Portal is optional. OPTN policy only requires a laboratory to notify the host OPO regarding deceased donor HLA critical discrepancies.[6] Critical HLA

[2] OPTN Histocompatibility Committee. "Recommended Histocompatibility Guidelines". OPTN Guidance Document. December 2006.
[3] OPTN Histocompatibility Committee. "Addressing HLA Typing Errors". OPTN Public Comment Proposal. August 2018. 9.
[4] Maria P. Bettinotti, written letter to OPTN Histocompatibility Committee, February 2, 2022.
[5] https://optn.transplant.hrsa.gov/media/vgdjehtl/2022_03_02_histo-discrepant-typings-subcommittee_meeting-summary.pdf.
[6] OPTN *Policy 4.4.A: Requirement to Notify Transplant Programs and OPOs* (Implemented September 1, 2021).

discrepancies are those that are non-equivalent at one or more loci and have the potential to cause an adverse immunologic reaction.[7] From 2015 to 2021, there were 94 critical HLA discrepancies that have been voluntarily reported through the portal.[8] Only four of these events were identified and remedied prior to match run execution, and 41 additional events were caught prior to transplant of any organs. Out of the 94 events in total, 44 of these events have the primary reporting reason as being detected due to confirmatory HLA typing. While a significant portion of these events were due to clerical errors, 54 events occurred due to other errors, including 12 events that occurred due to samples being switched.[9]

There is also evidence that exists outside of OPTN reporting channels. In a 2022 research article was published by the Immunogenetics and Transplantation Laboratory Department of Surgery staff at the University of California San Francisco (UCSF), a laboratory whose internal protocols include HLA confirmatory typing. In this article, researchers examined four HLA critical discrepancies from within their lab between 2018 and 2021. The authors estimate "…over 30 deceased donors are erroneously typed per year in the USA, which in consequence can impact over 150 life-saving heart, lung, liver, pancreas, intestinal, and kidney transplantations per year in the USA."[10]

The OPTN Histocompatibility Committee also reviews HLA critical donor discrepancies quarterly. Donor HLA typings are compared from every match run executed, the Donor Histocompatibility Form (DHF), and Recipient Histocompatibility Form (RHF), and therefore will not include discrepancies identified and remedied prior to match run. Between 2015 and 2021, there were 471 critical HLA discrepancies. This review does not include a root cause of the discrepancy communicated by the laboratories involved, but 18 discrepancies involved more than half of the donor's HLA typing being critically discrepant. In total, 0.2% of HLA typings between 2015 and 2021 were critically discrepant.[11]

The OPTN has taken steps to reduce critical errors from occurring with donor blood typings. Yet, unlike ABO testing, HLA testing has no such safeguard in place. Some laboratories have taken it upon themselves to institute HLA confirmatory typing as an internal policy, but without OPTN policy requiring all laboratories to perform this testing, some candidates may be left unprotected. This is particularly concerning for those highly sensitized candidates that are difficult to match, who could either be transplanted with an incompatible organ or be eliminated from a match run for a compatible organ due to an incorrect typing.

Data has shown that as of 2018, approximately 18% of kidneys were transplanted with a virtual crossmatch and no prospective physical crossmatch.[12] Utilizing virtual immunologic assessments has the

[7] https://optn.transplant.hrsa.gov/media/4637/histo_require-notification-of-human-leukocyte-antigen-hla-typing-changes_june-2021_briefing-paper.pdf.
[8] Based on OPTN data as of March 2, 2022. https://optn.transplant.hrsa.gov/media/vgdjehtl/2022_03_02_histo-discrepant-typings-subcommittee_meeting-summary.pdf.
[9] https://optn.transplant.hrsa.gov/media/vgdjehtl/2022_03_02_histo-discrepant-typings-subcommittee_meeting-summary.pdf.
[10] Thea dela Cruz et al, 464.
[11] https://optn.transplant.hrsa.gov/media/vgdjehtl/2022_03_02_histo-discrepant-typings-subcommittee_meeting-summary.pdf.
[12] Puttarajappa et al. "Trends and impact on cold ischemia time and clinical outcomes using virtual crossmatch for deceased donor kidney transplantation in the United States." Kidney International, Vol. 100(3), 2021, 660-671. https://doi.org/10.1016/j.kint.2021.04.020.

potential to greatly reduce cold ischemic time,[13,14,15,16] especially in cases when crossmatching materials cannot be sent prior to organ transport due to logistical constraints. Virtual crossmatching also has the potential to increase equity for highly sensitized candidates while reducing the concern for underutilization, as it allows transplant teams to complete an immunologic assessment and accept organs from farther distances with greater assurance of organ compatibility.[17,18,19] In spite of the many benefits of virtual crossmatching in situations in which the transplant team deems it appropriate, transplanting a candidate without a physical crossmatch and with incorrect HLA typing results could lead to an incompatible transplant, resulting in hyperacute rejection and its consequences. In view of this increasingly common practice, it is more important than ever to ensure correct HLA typings. In addition, an increased confidence in HLA typing result accuracy may increase utilization of virtual crossmatching, which could lead to a decrease in cold ischemic time, a decrease in late organ declines due to positive crossmatch, and an increase equity for highly sensitized candidates.

Leadership from the Committee met with the OPTN Organ Procurement Organization Committee on October 6, 2022, and with members from the OPTN Membership and Professional Standards Committee on September 23, 2022, to discuss this proposal. Both committees raised questions regarding the costs for running an additional test and concerns around the time increase in running an additional test for each deceased donor.[20,21] The Histocompatibility Leadership responded to the questions by stating the tests could be run simultaneously to help reduce the time, and they confirmed there would be a cost increase. The Histocompatibility Committee discussed these concerns at length in two following committee meetings and determined the safety assurances that are gained by performing a confirmatory test outweigh any cost increase or potential time delays that could occur.[22,23]

Overview of Proposal

The Committee proposes requiring two HLA typing tests be performed for all deceased donors. The HLA tests may be performed simultaneously, but the tests must be performed on two separate samples that are drawn at two separate times. The laboratory performing the tests must provide both results as specified in their contract with the OPO. If discrepancies are discovered, the laboratory will follow current policy to resolve them and provide the correct results to the OPO. Laboratories are already required to determine the correct HLA typing, and provide notification and supporting documentation

[13] Puttarajappa et al, 9.
[14] Aslam et al. "The Impact of Virtual Crossmatch on Cold Ischemic Times and Outcomes Following Kidney Transplantation". The American Surgeon. Vol. 87(1). 2021. 109-113.
[15] Jaramillo et al. "Using the Virtual Crossmatch to Allow for Safer and More Efficient Kidney Transplantation of Highly Sensitized Patients". Transplantation. Vol. 104(6). June 2020. 1121-1122.
[16] Rohan et al. "Virtual Crossmatching in Kidney Transplantation: The Wait Is Over". Journal of the American College of Surgeons. Vol. 230(4). April 2020. 373-379.
[17] Jaramillo et al.
[18] Rohan et al.
[19] Roll et al. "A Virtual Crossmatch-based Strategy Facilitates Sharing of Deceased Donor Kidneys for Highly Sensitized Recipients". Transplantation. Vol. 104(6). June 2020. 1239-1245.
[20] OPTN Organ Procurement Organization Committee. Meeting Summary, October 2, 2022. Richmond, Virginia. 11-13. https://optn.transplant.hrsa.gov/media/bgri3s0t/20221006-opo-committee-meeting-summary.pdf.
[21] OPTN Membership and Professional Standards Committee (MPSC). Meeting Summary, September 23, 2022. https://optn.transplant.hrsa.gov/media/1eonebmf/20220923_mpsc_meeting_minutes_public.pdf.
[22] OPTN Histocompatibility Committee. Meeting Summary, October 7, 2022. Chicago, Illinois. 6-7. https://optn.transplant.hrsa.gov/media/cw3jhgii/20221007_histo-meeting-summary.pdf.
[23] OPTN Histocompatibility Committee. Meeting Summary, November 8, 2022. Virtual Meeting. https://optn.transplant.hrsa.gov/media/znbfznje/20221108_histo_meeting-summary.pdf

to the OPO within one hour of determination of the correct typing.[24] This proposal does not change the organs for which HLA typing is required, nor does it change the timing of required HLA typings.

NOTA and Final Rule Analysis

The Committee submits the following proposal under the authority of the National Organ Transplant Act (NOTA), which states, "The Organ Procurement and Transplantation Network shall— (E) adopt and use standards of quality for the acquisition and transportation of donated organs."[25] This proposal develops a standard of quality for deceased donor HLA typing by requiring confirmatory typing to ensure accuracy.

In addition, the OPTN Final Rule provides authority as it 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."[26] Confirmatory HLA typing will aid in determination of immunologic contraindications by ensuring accuracy to allow for additional confidence in donor acceptance.

Implementation Considerations

Member and OPTN Operations

Operations affecting Histocompatibility Laboratories

Histocompatibility laboratories will be required to perform two HLA typings for every deceased donor. Confirmatory typing may allow increased confidence in virtual crossmatching results, which may increase the number of virtual crossmatches a laboratory is asked to perform.

Operations affecting Organ Procurement Organizations

Organ Procurement Organizations will need to draw and send an additional sample to histocompatibility laboratories for all deceased donors. This second sample must be drawn at a second time. OPOs may also see an increase in time while awaiting test results if using histocompatibility laboratories that are unable to run tests in parallel.

Operations affecting Transplant Hospitals

This proposal is not anticipated to impact transplant hospitals because the confirmatory testing is only required for deceased donors.

Operations affecting the OPTN

This proposal will not involve technical implementation changes to OPTN data systems. Education and communication to members will be needed.

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[24] OPTN *Policy 4.4.A.i: Donor HLA Critical Discrepancies*. Implemented September 1, 2021. https://optn.transplant.hrsa.gov/media/4696/hla_typing_changes_june_2021_policy_notice.pdf.
[25] 42 USC §274 (b)(2)(E).
[26] 42 CFR §121.6 (a).

Potential Impact on Select Patient Populations

Highly sensitized candidates, female candidates, and black candidates are particularly vulnerable in cases of incorrect HLA typings, as these groups are more likely to have pre-formed antibodies that could cause an adverse immunologic reaction. While this proposal would reduce overall risk of HLA typing errors, it may have a greater impact on these candidates.

Projected Fiscal Impact

Projected Impact on Histocompatibility Laboratories

The cost of consumables for HLA typings will double per donor. There is not anticipated to be an increased cost for equipment. Updating and implementing lab procedures to resolve discrepancies will result in additional staff time. This includes an increase in the amount of testing materials a lab must keep on hand for HLA typing purposes, which could require additional processing and associated costs. Using two different assays could lead to an increase HLA typing cost.

Projected Impact on Organ Procurement Organizations

The proposal may increase allocation time if typings are not run in parallel. OPOs may be required to pay an increased fee for HLA typings due to the additional required time and supply costs from laboratories.

Projected Impact on Transplant Hospitals

The proposal may increase kidney organ acquisition costs since this will increase typing costs for each donor.

Projected Impact on the OPTN

The OPTN will need to update the relevant policies on the OPTN website, as well as communicate the proposed changes to the transplant community and monitor the changes after implementation.

Post-implementation Monitoring

Member Compliance

This proposal will not change the current routine monitoring of OPTN members. Any data entered into OPTN computer systems 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."[27]

[27] 42 CFR §121.8(a)(7).

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

In order to ensure organs are properly matched to recipients, a major goal of the Committee is to minimize critical HLA typing discrepancies. Performing confirmatory tests on all deceased donors will help ensure candidates are receiving compatible organs.

Considerations for the Community

The Histocompatibility Committee is seeking input from the community on this proposal.

- Would laboratories be able to run tests in parallel or would they anticipate an increase in the required time for HLA typing?
- Would a potential increase in turnaround time for initial HLA typing be worth the increased confidence in the results, and the ability to confidently use virtual crossmatching*?*
- Would potential increased costs for confirmatory typing of the deceased donor's HLA be prohibitive for labs or OPOs?
- Should the use of two different testing modalities be a requirement that is included in the new policy?

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.

4.3 Requirements for Performing and Reporting HLA Typing

Laboratories must ensure that all HLA typing is accurately determined and report HLA typing results to the OPO or Transplant Program according to the deadlines specified in the written agreement between the laboratory and the OPO or transplant program. Laboratories must report HLA typing results to the OPTN. HLA typing results that are entered manually must be verified by reporting each result twice.

4.3.A Deceased Donor HLA Typing

If the laboratory performs HLA typing on a deceased donor, the laboratory must perform molecular typing and report results at the level of serological splits to the OPO for all required HLA types on deceased donors according to *Table 4-1: Deceased Donor HLA Typing Requirements*. The laboratory must ensure that each deceased donor's HLA type is determined by testing at least two deceased donor samples.

The deceased donor samples must meet the following requirements:

1. Be obtained on two separate occasions,
2. Be submitted as separate samples.

Prior to reporting any deceased donor HLA typing results to the OPO, the laboratory must review both test results and determine that no critical discrepancies are present.

Table 4-1 below provides the requirements of HLA typing of HLA A, B, Bw4, Bw6, C, DR, DR51, DR52, DR53, DQA1, DQB1, DPA1 and DPB1 antigens.

Table 4-1: Deceased Donor HLA Typing Requirements

If a Laboratory Performs HLA Typing on a:	Then the Laboratory Must Report Results to the OPO at the Following Times:
Deceased Kidney, Kidney-Pancreas, Pancreas, or Pancreas Islet Donor	Prior to organ offers
Deceased Heart, Heart-Lung, or Lung Donors	Prior to final acceptance, if required by the transplant program
Deceased Liver Donors	Within the period specified by the transplant program

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