OPTN

Briefing to the OPTN Board of Directors on

Update Post-Transplant Histocompatibility Data

OPTN Histocompatibility Committee

Prepared by: Courtney Jett
UNOS Policy Department

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Update Post-Transplant Histocompatibility Data

Sponsoring Committee: *Histocompatibility*
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Executive Summary

Post-transplant histocompatibility data collection in the OPTN Computer System requires updating to accommodate current laboratory practices. Much of the current data collection incorporates testing methods which are no longer common practice, such as serologic human leukocyte antigen (HLA) typing. By 2013, 99.9% of all deceased donors were typed via molecular methods,[1] and in 2016 use of molecular methods for all deceased donor HLA typing became a requirement in OPTN policy.[2] In addition, while there is post-transplant data collection on physical crossmatching, there is no current data collection on virtual crossmatching. Crossmatching is a test performed by histocompatibility laboratories to determine the immunologic compatibility of a potential transplant recipient with a donor organ. Physical crossmatching involves the mixing of patient serum with donor cells, and virtual crossmatching involves assessment of immunologic compatibility based on candidate HLA antibody and donor HLA typing data. Previously, physical crossmatching was the primary way laboratories assessed immunologic compatibility, but studies have shown an increasing trend of virtual crossmatching use.[3]

The Committee reviewed all of the post-transplant histocompatibility data collection in the OPTN Computer System and identified the following areas requiring change:

- Update post-transplant histocompatibility data collection forms to be consistent with current histocompatibility testing methods
- Add data collection for virtual crossmatching to inform recipient treatment and evaluate impacts of the practice on recipient outcomes, graft outcomes, and cold ischemic time
- Generate Discrepant HLA Typings reports for all potential HLA critical discrepancies which will increase awareness of, allow for a system-wide perspective of, and better inform future policy updates related to critical HLA discrepancies

The Committee made the following post-public comment changes to proposed data collection, as recommended by the community:

- Added a definition for virtual crossmatching
- Removed the proposed data element for result of virtual crossmatch
- Added a data element for date of the most recent HLA antibody screening used for virtual crossmatching

[1] OPTN Histocompatibility Committee, *Expanding Candidate and Deceased Donor HLA Typing Requirements to Provide Greater Consistency Across Organ Types Board Briefing Paper*. (Richmond: Organ Procurement and Transplantation Network, 2014).
[2] "Expanding Candidate and Deceased Donor HLA Typing Requirements to Provide Greater Consistency Across Organ Types" was implemented on January 21, 2016.
[3] Puttarajappa CM, 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 Int. 2021 Sep;100(3):660-671. doi: 10.1016/j.kint.2021.04.020. 2021.

- Retained cytotoxicity as a data element for T-cell and B-cell crossmatch tests
- Removed proposed physical/virtual crossmatch concordance question
- Made minor clarifying language changes to some data elements and responses

Purpose

The Committee reviewed the post-transplant histocompatibility data collection within the OPTN Computer System and identified the following areas they are proposing to change:

- Update post-transplant histocompatibility data collection forms to be consistent with current histocompatibility testing methods
- Add data collection for virtual crossmatching to inform recipient treatment and evaluate impacts of the practice on recipient outcomes, graft outcomes, and cold ischemic time
- Generate Discrepant HLA Typings reports for all potential HLA critical discrepancies which will increase awareness of, allow for a system-wide perspective of, and better inform future policy updates related to critical HLA discrepancies

Background

There are three post-transplant histocompatibility data collection instruments in the OPTN Computer System that are required to be completed by histocompatibility laboratories within 60 days post-transplant. These instruments collect data on donor and recipient HLA typings, recipient antibody testing, crossmatching, and donor and recipient discrepant HLA typings. These instruments currently include data collection on outdated testing methods, and do not collect information on virtual crossmatching. Data collection on virtual crossmatching practices could be used to evaluate impacts of the practice on recipient and graft outcomes as well as cold ischemic time (and therefore allocation efficiency). In addition, this information is important to inform recipient treatment. The existing data collection related to serologic HLA typing may no longer be informative, as by 2013, 99.9% of all deceased donors were typed via molecular methods,[4] and as of 2016 all deceased donor HLA typing was required by OPTN policy to be performed via molecular methods.[5]

The Committee formed a subcommittee that met six times and performed a comprehensive review of the data elements within the Donor Histocompatibility Form (DHF), Recipient Histocompatibility Form (RHF), and Discrepant HLA Typings report, as well as the generation and branching logic included. These data collection instruments are completed within the Data System for the Organ Procurement and Transplantation Network post-transplant. These proposed data collection changes were presented to the Data Advisory Committee (DAC) prior to[6] and after the completion of the comprehensive review[7] and received endorsement from the DAC.

Proposal for Board Consideration

The Committee is proposing changes to all of the histocompatibility post-transplant data collection instruments within the OPTN Computer System. The majority of these changes are to update the data collection to reflect current testing methods. There is also proposed added data collection on virtual

[4] OPTN Histocompatibility Committee, *Expanding Candidate and Deceased Donor HLA Typing Requirements to Provide Greater Consistency Across Organ Types Board Briefing Paper*. (Richmond: Organ Procurement and Transplantation Network, 2014), 6.
[5] "Expanding Candidate and Deceased Donor HLA Typing Requirements to Provide Greater Consistency Across Organ Types" was implemented on January 21, 2016.
[6] https://optn.transplant.hrsa.gov/. OPTN Data Advisory Committee, 02/02/2023, Meeting Summary.
[7] https://optn.transplant.hrsa.gov/. OPTN Histocompatibility Committee, 12/13/2023, Meeting Summary.

crossmatching, as well as a proposed update to how the Discrepant HLA Typings report is generated. The proposed changes are outlined below grouped by each individual instrument.

Donor Histocompatibility Form

The Donor Histocompatibility Form is filled out within 60 days post-transplant by the laboratory that performed the original living or deceased donor HLA typing. All of the data collection on this form is related to the donor HLA typing. Proposed updates to this form are to remove a net of four data collection fields related to previous laboratory practices or testing methods.

The Committee is proposing to remove separate data collection fields for the date HLA typing is completed and the target cell source for Class I and Class II typing. Currently, these dates are separated, even though almost all labs are performing Class I and Class II typing simultaneously on samples processed together. They are replacing the date HLA typing was completed and target cell source with singular data collection fields, as both are still important and relevant data collection.

The Committee is also proposing to remove the data collection fields for typing method for Class I and Class II typing entirely. Currently the response options are “DNA” and “Serology”. Since all donor HLA typings are required by OPTN policy to be via molecular, or DNA-based, methods, the Committee felt that asking which typing method was performed is no longer necessary.

Recipient Histocompatibility Form

The Recipient Histocompatibility Form is filled out within 60 days post-transplant by the laboratory for each organ recipient. The data collection on this form is currently broken into five sections: test information, recipient HLA typing, HLA antibody screening, crossmatching, and donor retyping. The data collection changes being proposed to this form include removal of unnecessary data collection related to previously used test methods, clarification of existing data elements, and the addition of data collection on virtual crossmatching.

Test Information and Virtual Crossmatching

The “Test Information” section of the Recipient Histocompatibility Form drives which other sections are generated. All data collection fields within this section are required. The form is able to be marked complete if this section is completed and no HLA testing was completed for the recipient. The Committee is not proposing changes to this logic, as they feel the current logic reduces data collection burden on users, as they are only required to fill out data collection for the testing that was actually completed.

The Committee is recommending adding virtual crossmatching data to this section in order to measure the impacts of virtual crossmatching on recipient outcomes and cold ischemic time. In addition, this information is important to inform recipient treatment. The Committee is proposing one data collection field asking if a prospective virtual crossmatch was performed. The Committee felt that knowing prospective virtual crossmatching information was more important for measuring impact on allocation efficiency. During public comment the Committee had proposed including a result for the virtual crossmatch, with the response options of “Positive”, “Negative”, and “Indeterminate”. However, they had received some concerns in public comment about defining a positive virtual crossmatch and decided afterwards that it was best to remove this proposed data element. In addition, they received public

comment on the need for a definition of virtual crossmatch, and are proposing to add the following for clarity: “A virtual crossmatch is the final immunologic assessment used to proceed with transplantation, consistent with CLIA regulation and laboratory policies. It is prospective if it is completed prior to transplantation.” The Committee also received public comment recommending adding the most recent antibody testing date used to inform virtual crossmatch and propose adding “Date of most recent HLA antibody screening used for virtual crossmatch”.

While there is existing data collection on current donor-specific antibodies, this does not capture the necessary data on virtual crossmatching. While an assessment for pre-transplant donor-specific HLA antibodies is a part of a virtual crossmatch, a virtual crossmatch is an assessment of overall compatibility of the candidate and the donor organ. This includes additional factors, such as an analysis of the patient’s sensitization history, and levels of burden of the donor-specific antibodies and their epitopes or cross-reactive groups. In addition, a candidate may have low-level donor specific antibodies and may be positive for donor-specific antibodies, but considered negative for a virtual crossmatch as there may be a low immunologic risk for those antibodies overall. Therefore, the Committee felt it important to maintain both a question on donor-specific antibodies as well as a question on virtual crossmatching but decided not to include a question classifying the results of virtual crossmatching as positive or negative overall. Public comment supported the Committee’s position.

Recipient HLA Typing and Donor Retyping

The “Recipient HLA Typing” section of the form generates if the user selects that a recipient HLA typing was performed, and the “Donor Retyping” section generates if the user selects that the donor was retyped at the recipient’s transplant program’s request. These sections do not generate if the user selects that the respective testing was not completed.

For both the recipient HLA typing and the donor retyping sections of the form, the Committee is proposing the same data collection changes as those on the Donor Histocompatibility Form. The Committee is proposing removal of separate data collection fields for Class I and Class II typing dates and target cell source and replacing them with singular data collection fields for each. In addition, the Committee proposes removing the data collection fields for whether Class I and Class II typing methods were DNA-based or serologic-based entirely.

HLA Antibody Screening

The “HLA Antibody Screening” section of the form generates if a user selects that HLA antibody screening was completed in the “Test Information” section of the form. If the user selects that HLA antibody screening was not completed, this section does not generate.

General HLA antibody detection relates to any HLA antibodies a recipient may have, not just HLA antibodies to a donor’s HLA typing. Currently, there are two data collection fields for general HLA antibody detection, one for cytotoxicity and one for solid-phase testing. The Committee discussed whether they would like to just remove cytotoxicity as a response option, since it is no longer a common form of testing. However, they felt that the type of HLA antibody testing was less important than whether HLA antibodies were present. In addition, they wanted to clarify the timing of the HLA antibodies being detected. So ultimately, they determined that the data collection field would be “Were any HLA antibodies detected pre-transplant?”, with the response options of “Yes”, “No”, and “Not Done”.

There is currently a data collection field "Were there current donor specific HLA antibodies". The Committee felt that the timing of "current" is unclear and are proposing this data collection be rephrased to "Were there pre-transplant donor-specific HLA antibodies" for clarity.

The Committee is proposing removing a data collection field related to historical donor specific antibodies, as they felt these are not relevant to graft outcomes if not present at the time of transplantation.

There are two data collection fields related to a recipient's Calculated Panel Reactive Antibody (CPRA) on the form for heart and lung recipients, one for the most recent CPRA and one for the peak CPRA. The most recent CPRA and peak CPRA are displayed for kidney and pancreas recipients as read-only and calculated from unacceptable antigens in the OPTN Waiting List. The Committee felt that displaying the calculated CPRA as read-only from the OPTN Waiting List for the most recent CPRA would be most helpful option and is proposing to do so for all organ recipients. This will be displayed in the "Recipient Information" section of the form. In addition, the Committee is proposing that the recipient's peak CPRA data collection should be removed, as well as the read-only peak CPRA field for kidney and pancreas recipients. They felt that the timing of this data element was unclear and may be difficult to find for candidates who have been waiting for many years, as it is not a discrete field in most laboratory information systems (LISs). In addition, they felt that this is likely not clinically relevant to graft outcomes if this is not the recipient's sensitization level at the time of transplantation. There is currently the option to manually enter in CPRA for heart and lung candidates, and the data for the manual entry has previously been found to highly correlate with the calculated CPRA from the OPTN Waiting List.[8] As such, the Committee decided that this data collection did not provide additional value beyond the data collection on the OPTN Waiting List, and are proposing to remove the field to manually enter in CPRA for thoracic candidates.

Crossmatching

The "Crossmatch" section of the Recipient Histocompatibility Form generates if a user selects that a physical crossmatch was completed in the "Test Information" section of the form. If the user selects that a physical crossmatch was not completed, this section does not generate.

The Committee is proposing that the "Crossmatching" section of the form be renamed to "Physical Crossmatch", so that it is not confused with virtual crossmatching.

Current response options for T-cell and B-cell crossmatches being performed are reported as multi-select options and include "Cytotoxicity no AHG", "Cytotoxicity AHG", "Flow Cytometry", "Solid Phase", and "Not tested". Each option selection generates a single-select sub-response for "Positive" or "Negative", and they are proposing to add "Indeterminate" for the sub-response options, as some physical crossmatches can provide indeterminate results that are neither positive nor negative. The Committee had proposed to remove both response options that include cytotoxicity, as they felt this test is no longer in common use. However, they received feedback in public comment that some laboratories still utilize cytotoxicity as a testing method. Therefore, the Committee decided to keep one cytotoxicity data element, with no distinguishing between whether AHG was added to the test or not.

[8] Kelsi Lindblad, *Prevalence of Sensitization in Adult Heart Candidates* (Richmond: Organ Procurement and Transplantation Network, 2023), 4-7.

The Committee is also proposing to remove the data collection field for historical crossmatch results, as they felt that it is not clinically relevant to graft outcomes and the timing around how old historical results should be reported is unclear. Candidates who had been waiting for multiple years may have multiple historical crossmatches, and since they were performed for other donors where transplant did not proceed for that candidate, they are likely not impactful for clinical decision making and patient care.

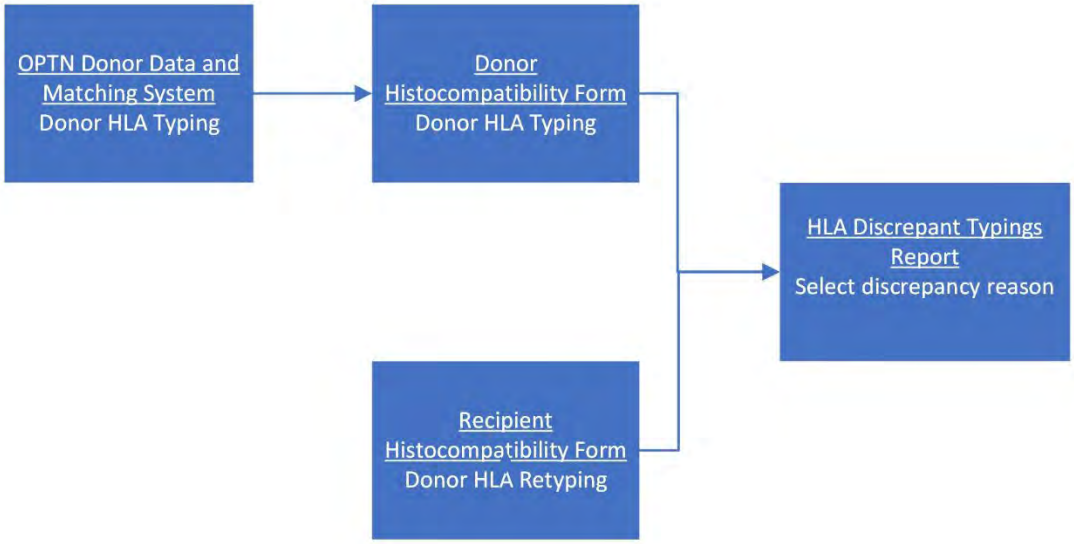
The Committee had proposed to add one data element in this section, "If virtual crossmatch done, was physical crossmatch considered concordant with virtual crossmatch?", with the response options of "Yes", "No", and "Not Done". However, they received concern during public comment about this proposed data element. The Committee chose to remove this proposed data element, as many factors can impact the concordance of virtual crossmatch with the physical crossmatch. In addition, they felt that the test types are not directly comparable in what they measure.

The Committee discussed at length whether there needed to be a definition of mean fluorescence intensity (MFI) cutoffs or other thresholds for concordance or unacceptable antigen selection. They had concerns that these are not standardized values, and have significant variability between testing methods, preparation procedures, and laboratories. While this was raised again in public comment, the Committee ultimately chose not to incorporate a data element related to MFI cutoffs or other thresholds.

Discrepant HLA Typings Report

The Discrepant HLA Typings Report compares HLA typings for donors and recipients from the OPTN Donor Data and Matching System, OPTN Waiting List, and the Donor and Recipient Histocompatibility Forms. When HLA typings provided by one or more labs are not equivalent by the HLA equivalency tables provided within OPTN *Policy 4.11: Reference Tables of HLA Antigen Values and Split Equivalences*, a report is generated for every lab which reported an HLA typing for that donor or recipient. For example, if the original donor HLA typing lab reported A*01:02 and a recipient typing lab re-typed the donor and reported A*01:01, a Discrepant HLA Typings Report would be generated as these values are not equivalent. However, if the original donor lab reported A1 and the recipient typing lab reported A*01:01, a report would not be generated, as these values are equivalent, even though they are at two different resolutions of HLA typing. See **Figure 1** for the current data flow for the HLA Discrepant Typings report. OPTN *Policy 4.4.B: Requirement to Resolve Critical Discrepant Donor and Recipient HLA Typing Results* requires labs to identify the correct HLA typing and report the reason for the discrepancy. Labs routinely review attached source documentation and contact other involved labs in order to resolve discrepancies.

Figure 1: Current Data Flow for HLA Discrepant Typings Report



Currently, the Discrepant HLA Typings Report generates discrepancies in the HLA-A, B, and DRB1 loci for kidney, pancreas, and kidney-pancreas donors and recipients. The Committee felt that it was important for providers to be aware of discrepancies regardless of the organ transplanted and regardless of the locus, as all organ types and all loci have the potential for patient safety implications. In addition, they felt it important for labs to resolve and report the reason for every discrepancy. The Committee is proposing that this report be generated for HLA critical discrepancies at all loci for all organ types. This report will only generate for non-equivalent values and will not generate for differences in typing resolution.

These proposed changes will increase required data collection for labs if they are involved in a critical HLA discrepancy. However, in 2022 there were only 70 deceased donor critical HLA discrepancies in the country[9] that the form would have been generated for with the proposed logic, with a median of one discrepancy across all labs with critical HLA discrepancies.[10] These reports generate for all labs involved in the discrepancy, which means there may be less than 150 reports in total across the entire country per year, as there are on average 1.05 retypings per donor.[11] These reports would then be spread across 139 total HLA lab members in the country.[12] In addition, some of these reports are already being generated based on the existing logic. Overall, most labs should not have a significantly increased number of Discrepant HLA Typings reports to fill out.

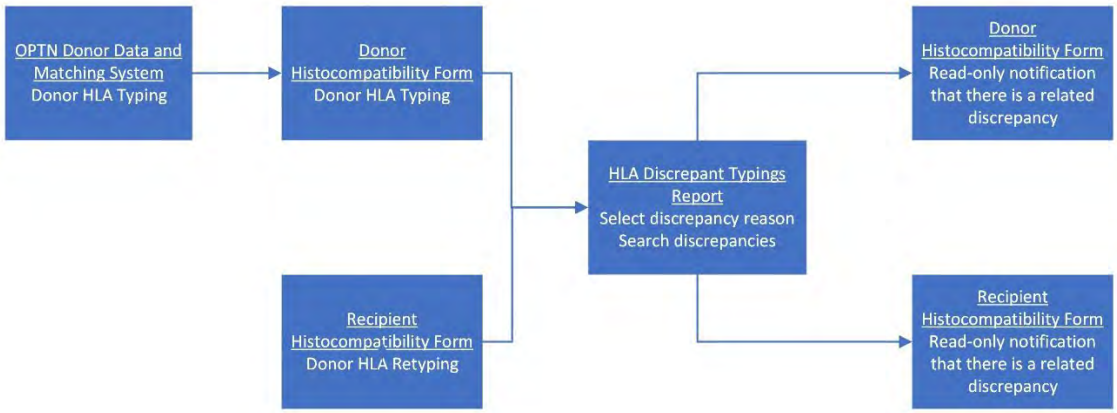
In addition, the Committee heard multiple concerns about insufficient data collection on critical HLA discrepancies during public comment for a previous proposal. During the proposal to "Require Confirmatory Human Leukocyte Antigen (HLA) Typing for Deceased Donors", multiple community members gave feedback during regional meetings and through individual written comments that there is insufficient information about the causes of critical HLA discrepancies. In addition, community

[9] https://optn.transplant.hrsa.gov/. OPTN Histocompatibility Committee, 06/13/2023, Meeting Summary.
[10] https://optn.transplant.hrsa.gov/. OPTN Histocompatibility Committee, 07/11/2023, Meeting Summary.
[11] Based on OPTN data for all organs between September 1, 2021 and August 31, 2022.
[12] Based on OPTN Membership data as of December 8, 2023.

members provided feedback that the current data collection on critical HLA discrepancies is incomplete.[13] The Committee agreed that more robust data collection was needed to better understand the reasons behind these critical discrepancies and ensure they are being resolved as required by OPTN policy. This was supported by public comment feedback received.

The Discrepant HLA Typings Reports are not currently viewable or searchable by the user once the resolved reason for the discrepancy is provided. The Committee is proposing that the data remain searchable to labs, and that a read-only notification is added on both the Donor and Recipient Histocompatibility Forms, as applicable if there is a discrepancy, so that labs are aware of all relevant information for recipient care when reviewing records. The proposed data flow for discrepant HLA typings is outlined in **Figure 2**.

Figure 2: Proposed HLA Discrepant Typings Data Flow



The Committee is also proposing to update the list of discrepancy reasons labs can provide, as many of the discrepancy reasons were related to serologic testing and are no longer applicable. The Committee is proposing revising the list to the reasons provided in **Table 1**.

Table 1: Proposed Discrepancy Reasons and Definitions

Discrepancy Reason	Definition
Ambiguous Assignment (with required free text box)	The HLA typing results were ambiguous. Requires additional explanation as to how the results were ambiguous.
Reagent/Assay Issue	There was a reagent or assay malfunction that caused the discrepancy. For example, a well in an assay did not react.
Parent Vs. Split	The HLA typing results are equivalent, as one HLA typing result is a parent antigen and the other is a split antigen of that parent.
Null Allele	A null allele was reported as non-null in the HLA typing.
P-group Equivalency	The HLA typing results are equivalent, as one HLA typing result is a P-group and the other is an allele within that P-group.

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

Incorrect Specimen	The specimen or HLA typing was for a different patient than it was reported for.
Transcription Error	There was an error in manual transcription of the HLA typing data.
Incorrect Split	The incorrect serologic split was reported from a broader parent antigen.
Incorrect Allele Assignment	The incorrect allele was reported from a list of multiple potential alleles.
This Typing Confirmed Correct	This HLA typing result has been confirmed to be the correct HLA typing for the patient.
Other, specify (with required free text box)	The reason for the discrepancy does not fit into any of the other reasons. Requires additional explanation as to the reason for the discrepancy.

"This Typing Confirmed Correct" is provided in the list of reasons because all labs involved in a discrepancy must provide a response, and at least one of the typing labs will likely have submitted the correct HLA typing information when originally entering HLA typing information into the OPTN Computer System. It is important for clinical care that the correct HLA typing information be known and clearly marked in order to allow for proper monitoring of donor-specific antibody development. "Confirmed Correct" is included in the reason, as the Committee wanted to ensure it was clear to labs that they must resolve the discrepancy and confirm that the typing was correct in some way, as required by OPTN *Policy 4.4.B*. This data element had previously been proposed as "Original Typing Confirmed Correct", however the Committee received concerns in public comment that this phrasing was confusing, and therefore they decided to rephrase it.

"P-group Equivalency" is provided in the list of reasons as there is not currently an equivalency table in OPTN Policy or the OPTN Computer System for P-groups that would separate them out as a difference in typing resolution instead of as a potential critical discrepancy. The Committee has discussed modifying the definition of critical HLA discrepancies for a future public comment,[14] so their inclusion within the definition and report is potentially subject to change in the future.

"Null Allele" is provided in the list of reasons as these results will appear discrepant in the OPTN Computer System, even if a null allele originally reported as non-null will not cause an immunologic reaction in a recipient. Many of the common null alleles are at the third field, with other third-field alleles in the same two-field allele or serologic antigen that are non-null. There is no way to distinguish from a serologic antigen or two-field allele HLA typing if the original result was reported incorrectly for another reason or because a null allele was present that was not distinguished at the time of reporting the HLA typing to the OPTN.

The Committee is proposing removing the data element on the report for "Discrepancy not resolvable". The Committee felt that every discrepancy should have a known resolution or cause. OPTN *Policy 4.4.B: Requirement to Resolve Critical Discrepant Donor and Recipient HLA Typing Results* requires labs to identify the correct HLA typing and report the reason for the discrepancy. Labs routinely review attached source documentation and contact other involved labs in order to resolve discrepancies.

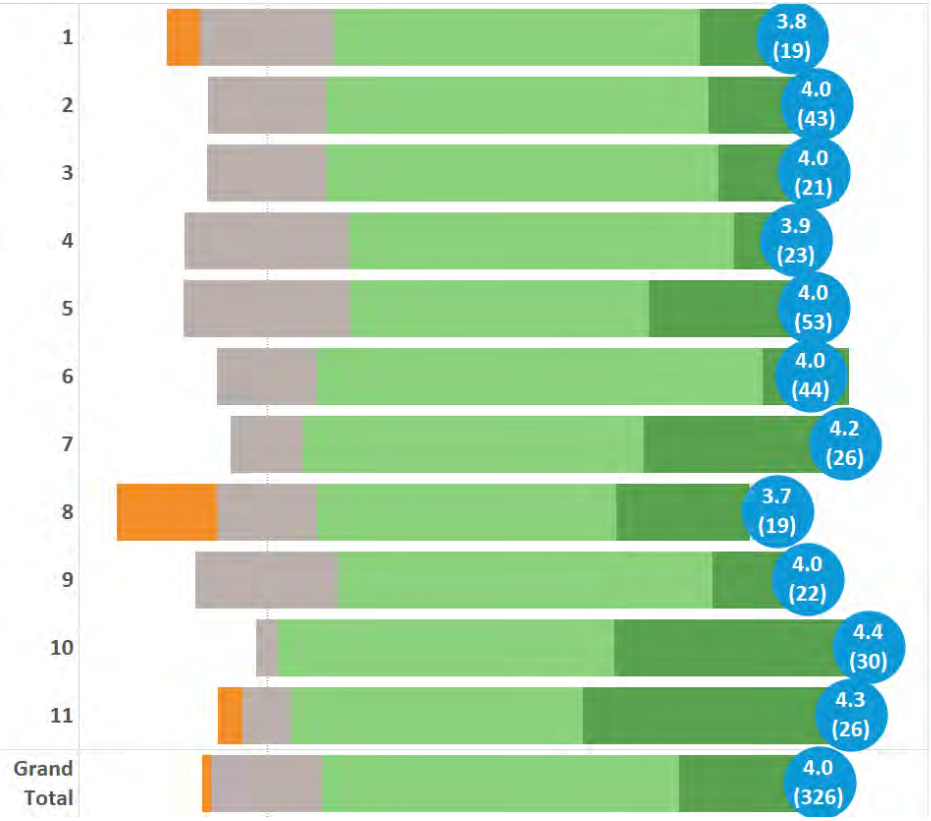
[14] https://optn.transplant.hrsa.gov/. OPTN Histocompatibility Committee, 09/27/2023, Meeting Summary.

Overall Sentiment from Public Comment

This proposal was distributed for public comment from January 23, 2024, to March 19, 2024 and the feedback is described below. The comments received included responses to a specific feedback question regarding whether the discrepancy reasons were comprehensive and clear.

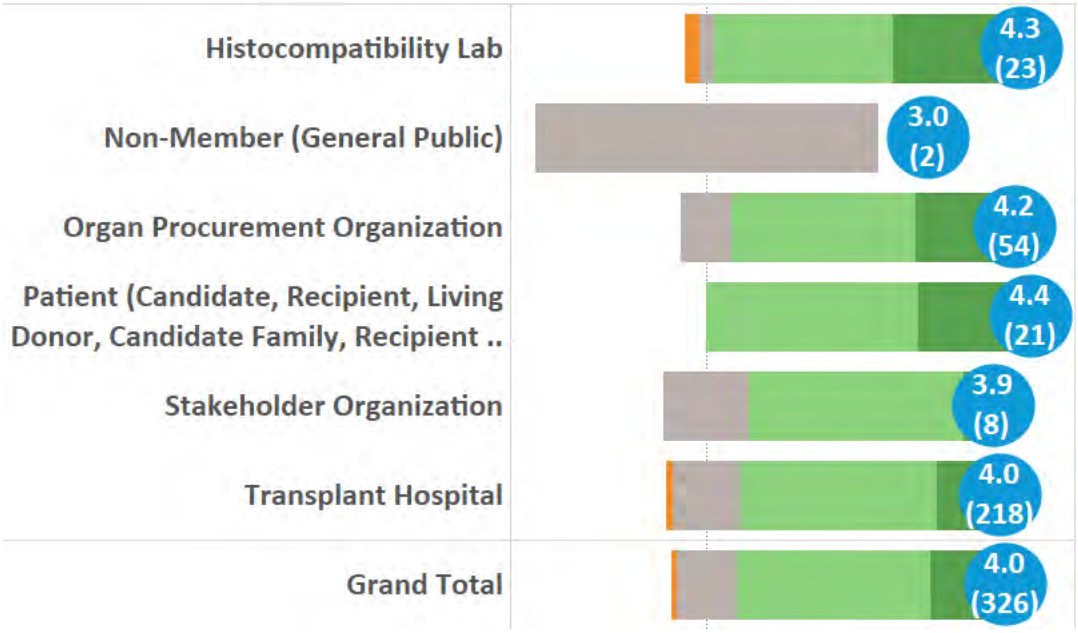
Sentiment is collected on public comment proposals and is measured on a 5-point Likert scale from strongly oppose to strongly support (1-5). Generally, public comment sentiment has been supportive of this proposal, as indicated by the total sentiment score of 4.0, with few pockets of concern. Below are graphics that illustrate the sentiment received through public comment. **Figure 3** shows sentiment received from all respondents (regional meeting, online, and email) by their OPTN region. Again, there was overall support for the concept, demonstrated by a sentiment score of 4.0.

Figure 3: Sentiment by Region, *Update Post-Transplant Histocompatibility Data*, 2024



Public Comment sentiment also indicated general support across all member types, as shown in **Figure 4**.

Figure 4: Sentiment by Member Type, *Update Post-Transplant Histocompatibility Data*, 2024



Public comments addressed several main topics, most notably support for data collection on virtual crossmatching, and request for a clearer definition on virtual crossmatching. There was also broad support for the general need for the proposed updates. A summary of the items that garnered comments as well as the Committee's responses are highlighted below. Final recommendations for all data elements can be found at the end of the proposal.

- *Virtual crossmatching data collection*- There was broad agreement that capturing data related to virtual crossmatching is important, including that "this would significantly impact post-transplant outcomes and morbidity", and that in the future this data should be correlated with "organ acceptance offers, recipient treatment, and transplant outcomes". Multiple commenters stated how this would impact post-transplant outcomes. A few commenters provided areas for consideration of additional virtual crossmatching data to collect, with two commenters recommending the serum date or date of last HLA antibody screening used to inform virtual crossmatching and one commenter asking about how current the serum should be. The Committee chose to incorporate the data element "Date of most recent HLA antibody screening used for Virtual Crossmatch".

- *Virtual crossmatching definition*- While commenters agreed on the need for virtual crossmatching data collection, five commenters mentioned a need for a definition of virtual crossmatching to accompany the proposal. Two commenters recommended leaving the definition of whether a virtual crossmatch is "positive" to the lab's clinical discretion. The Committee proposed to add the following definition to the prospective virtual crossmatch data element: "A virtual crossmatch is the final immunologic assessment used to proceed with transplantation, consistent with CLIA regulation and laboratory policies. It is prospective if it is

completed prior to transplantation." The Committee chose to remove the question on virtual crossmatch results.

- *HLA Discrepant Typings report*- One commenter stated that while there may be an increase in reporting requirements for some laboratories, "this information is critical to evaluating the scope of the matter and allow for future development of related policies". The American Society for Histocompatibility and Immunogenetics (ASHI) also commented that this information is critical to evaluating the scope of critical discrepancies and informing future policies. Commenters specifically commented on the discrepancy reason of "Original Typing Confirmed Correct", with three commenters stating that it was confusing, especially if the original typing is the incorrect typing. Two commenters proposed alternate language, and the Committee decided on the discrepancy reason wording of "This Typing Confirmed Correct".

- *Cytotoxicity antibody testing*: The American Society of Transplantation (AST) agreed with removal of Cytotoxicity for antibody detection.

- *Solid Phase Antibody Testing*: AST recommended adding the method for the collection of solid phase antibody test type. The Committee chose not to incorporate type of solid phase antibody testing performed at this time.

- *Cytotoxicity physical crossmatch*: AST recommended removing "Cytotoxicity AHG" and "Cytotoxicity no AHG" as separate response options but maintaining "Cytotoxicity crossmatch" as an option for physical crossmatching, as they state not all programs have abandoned it. The Committee chose to re-incorporate a data element for "Cytotoxicity" for both T-cell and B-cell crossmatch tests in response.

- *CPRA*: AST recommended a field for collection of pre-transplant CPRA, stating that the most recent CPRA on the OPTN Waiting List is not the same as the CPRA at the time of transplant. The Committee chose to maintain the most recent OPTN Waiting List CPRA as the data element for CPRA, as the laboratory has the option to update unacceptable antigens between the time of offer and the time of RHF submission if they should choose to do so.

- *Date of Antibody Screening for Virtual Crossmatching*: AST recommended adding a field for the date of HLA antibody screening used for virtual crossmatching to inform future optimization of virtual crossmatching strategies. Another commenter stated that serum date for virtual crossmatching would help with the prediction of physical crossmatching results. The Committee agreed with this suggestion and chose to incorporate the data element "Date of most recent HLA antibody screening used for Virtual Crossmatch".

- *Unacceptable Antigen Thresholds*: AST recommended adding a field for the threshold of an antibody used when determining which antibodies to avoid for purposes of CPRA. The Committee had discussed this prior to public comment and had declined to incorporate it due to the variability in Mean Florescence Intensities (MFI) between different testing methods and laboratories. The Committee reaffirmed their choice not to incorporate this data element.

- *Target Cell Source*: One commenter stated there is utility in maintaining the target cell source, and that "The addition of transfusion history would be helpful in deciding whether to request tissue rather than peripheral blood from donors. With the increase in donors and recipients that previously had stem cell transplants, the addition of buccal swab as a source would be useful." Another commenter stated that this data is no longer relevant with the use of molecular typing. The data element for target cell source is maintained within this proposal. In addition, transfusion history is captured within the OPTN Donor Data and Matching System as well as the Deceased Donor Record (DDR).

- *Virtual Crossmatching Concordance*: One commenter recommended omitting the question on virtual crossmatching concordance with the physical crossmatch, as the virtual crossmatch may be based on data from an old antibody screening. In addition, the donor typing resolution may change the virtual crossmatch results. Another commenter suggested the following language in lieu of the proposed question language for clarity: "Was physical crossmatch concordant with virtual crossmatch". The Committee chose to remove this proposed data element, as many factors can impact the concordance of virtual crossmatch with the physical crossmatch. In addition, they felt that the test types are not directly comparable in what they measure.

- *Donor Transfusion History*: One commenter suggested the addition of donor transfusion history and number of products received, as it "would be informative and may help explain reasons for requesting tissue rather than using peripheral blood sample for testing." Transfusion history is captured within the OPTN Donor Data and Matching System as well as the Deceased Donor Record (DDR). The OPTN Donor Data and Matching System, which is filled out in the organ evaluation and recovery process, contains a section for "Transfusions/Blood Products" which includes the number of transfusions during the terminal hospitalization as well as any other blood products received. The Deceased Donor Record, which is completed post-recovery, contains data fields on transfusions prior to or following ABO determination, with required data collection for the total volume of transfusions for each field. Given this, the Committee chose not to incorporate the suggested data elements.

- *Physical Crossmatch*: One commenter suggested further clarity whether the Committee was referring to a prospective or retrospective physical crossmatch in the section on physical crossmatching. This section refers to any physical crossmatch performed by the laboratory, and there is an existing question on timing of the crossmatch. The Committee did choose to make two small changes to this section for clarity—changing the data element for "Date of the most recent crossmatch serum" to "Date of the most recent recipient crossmatch serum" and changing "Cell source" to "Donor cell source".

- *Recommendations for future work*- AST recommended that the Committee develop an upper limit for serum age for virtual crossmatching in OPTN Policy. This was out of scope of the current proposal, but the Committee will consider it for future work.

Compliance Analysis

NOTA and OPTN Final Rule

The Committee submits this data collection proposal under the authority of the National Organ Transplant Act of 1984 (NOTA) and the OPTN Final Rule. NOTA requires the Organ Procurement and Transplantation Network (OPTN) to "collect, analyze, and publish data concerning organ donation and transplants,"[15] and the Final Rule requires the OPTN to receive and maintain records of all transplant recipients.[16] This proposal will update the collection of data concerning post-transplant histocompatibility of organ recipients as well as add data collection for virtual crossmatching to inform recipient treatment and evaluate impacts of the practice on recipient outcomes, graft outcomes, and cold ischemic time.

OPTN Strategic Plan

1. *Increase the number of transplants:*
   Evaluation of outcomes and efficiency data related to virtual crossmatching may allow for dissemination of best practices related to immunologic assessments. Increasing the efficiency of transplantation by increased usage of virtual crossmatching may lead to a lower non-utilization rate of kidneys through earlier assessments, reduced delays due to logistical barriers of shipping physical samples, and a reduction in cold ischemic time.
2. *Improve waitlisted patient, living donor, and transplant recipient outcomes:*
   Evaluation of outcomes data related to virtual crossmatching may allow for dissemination of best practices related to immunologic assessments. In addition, broader usage of virtual crossmatching may lead to a reduction in cold ischemic time, improving recipient outcomes.

OPTN Data Collection Principles

Institutional members must provide sufficient data to OPTN to allow it to:

a) Develop transplant, donation, and allocation policies

Data on both virtual crossmatching and HLA critical discrepancies will allow for the development of future related policies.

Implementation Considerations

Histocompatibility Laboratories

Operational Considerations

This proposal alters the post-transplant data collection required by histocompatibility laboratories. Labs will need to become familiar with the revised data collection requirements, including new data collection for virtual crossmatching. This proposal overall reduces the number of data collection elements required to be submitted for the Donor and Recipient Histocompatibility Forms by removing a net of four data elements from the DHF and eight from the RHF. It does, however, increase the number

[15] 42 USC §274(b)(2)(I).
[16] 42 CFR §121.11(a)(1)(i-iii).

of projected occurrences that the Discrepant HLA Typings Report will be generated for labs. However, in 2022 there were only 70 donor critical HLA discrepancies in the country[17] that the form would have been generated for with the proposed logic, with a median of one donor discrepancy across all labs with critical HLA discrepancies.[18] While these reports generate for all labs involved in the discrepancy, some of these reports are already being generated and most labs should not have a significantly increased number of Discrepant HLA Typings reports to fill out.

Fiscal Impact

There is a low expected fiscal impact on Histocompatibility Laboratories. Minor changes to staff training are anticipated.

Organ Procurement Organizations

Operational Considerations

This proposal is not expected to impact Organ Procurement Organization operations.

Fiscal Impact

This proposal is not anticipated to have any fiscal impact on Organ Procurement Organizations.

Transplant Hospitals

Operational Considerations

This proposal is not expected to impact transplant hospital operations.

Fiscal Impact

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

OPTN

Operational Considerations

This proposal will require technical implementation within the OPTN Computer System, for the Donor Histocompatibility Form, Recipient Histocompatibility Form, and Discrepant HLA Typings Report. This proposal requires the addition and removal of multiple data elements, as well as changes to field labels for clarity. It also requires changes to when the Discrepant HLA Typings Report generates and how the entered data is viewed after resolution and associated with donor and recipient records.

This proposal requires the submission of official OPTN data that are not presently collected by the OPTN. The OPTN contract requires that data collected pursuant to the OPTN's regulatory requirements in §121.11 of the OPTN Final Rule will be collected through OMB approved data collection forms. Therefore, after OPTN Board approval, the forms will be submitted for OMB approval under the

[17] https://optn.transplant.hrsa.gov/. OPTN Histocompatibility Committee, 06/13/2023, Meeting Summary.
[18] https://optn.transplant.hrsa.gov/. OPTN Histocompatibility Committee, 07/11/2023, Meeting Summary.

Paperwork Reduction Act of 1995. This will require a revision of the OMB-approved data collection instruments, which may impact the implementation timeline.

Resource Estimates

It is estimated that 4,185 hours would be needed to implement this proposal. Implementation would involve updates within the OPTN Computer System for the Donor Histocompatibility Form, Recipient Histocompatibility Form, and Discrepant HLA Typings Report. In addition, implementation would include educating histocompatibility laboratories on the revised data collection requirements. It is estimated that 70 hours would be needed for ongoing support. Ongoing support will involve the evaluation of incoming data to assess post-implementation performance and answering member questions.

Potential Impact on Select Patient Populations

One goal of adding data collection for virtual crossmatching is to inform future recipient treatment, with the hope that these data on recipient and graft outcomes will increase utilization of virtual crossmatching in the future. Candidates who have a harder time accessing the transplant hospital due to logistical barriers such as rural residence or incarceration may be more impacted by this proposal if it does increase the utilization of virtual crossmatching. Increased use of virtual crossmatching may reduce barriers in access by allowing a program to better assess immunologic compatibility prior to physical crossmatch sample receipt and candidate travel.

Post-implementation Monitoring

Member Compliance

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

Data Collection Monitoring

The following metrics, and any others subsequently requested by the Committee, will be evaluated as data become available to assess performance after the implementation of this data collection:

Crossmatch Practices

1. Count and percent of transplants with a prospective virtual crossmatch performed
2. For transplants with a prospective virtual crossmatch, distribution of time between most recent HLA antibody screening used for virtual crossmatch and date of transplant
3. Count and percent of transplants with a physical crossmatch performed
4. Count and percent of transplants with a physical crossmatch performed by whether it was prospective to transplant

Outcomes

1. Distribution of cold ischemic time
2. Count and Percent of transplants with delayed graft function
3. Post-transplant graft and patient survival rates

The above outcomes metrics will be stratified by virtual crossmatch status, as well as physical crossmatch results. Graft and patient survival will be reserved for the 1- and 2-year reports as enough data becomes available.

These metrics will be evaluated at approximately 6-months, 1-year and 2-years post-implementation.

Conclusion

After a comprehensive review of post-transplant histocompatibility data collection in the OPTN Computer System, the Committee is proposing the following changes:

- Update post-transplant histocompatibility data collection forms to be consistent with current histocompatibility testing methods
- Add data collection for virtual crossmatching to inform recipient treatment and evaluate impacts of the practice on recipient outcomes, graft outcomes, and cold ischemic time
- Generate Discrepant HLA Typings reports for all potential HLA critical discrepancies which will increase awareness of, allow for a system-wide perspective of, and better inform future policy updates related to critical HLA discrepancies

The Committee made the following post-public comment changes to proposed data collection, as recommended by the community:

- Added a definition for virtual crossmatching
- Removed the proposed data element for result of virtual crossmatch
- Added a data element for date of the most recent HLA antibody screening used for virtual crossmatching
- Re-added cytotoxicity as a data element for T-cell and B-cell crossmatch tests
- Removed proposed physical/virtual crossmatch concordance question
- Made minor clarifying language changes to some data elements and responses

Proposed Changes to Data Elements

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

Table 1: Data Modifications: OPTN Data System (Donor Histocompatibility)

Data Field	Form	Response Option Description
Date Typing Completed	Donor Histocompatibility Form	MM/DD/YYYY
~~Date Typing Completed Class I~~	Donor Histocompatibility Form	~~MM/DD/YYYY~~
Target Source	Donor Histocompatibility Form	Peripheral Blood, Lymph Nodes, Spleen, Buccal Swab or Other (Multi-select)
~~Target Source for Class I~~	Donor Histocompatibility Form	~~Peripheral Blood, Lymph Nodes, Spleen, Buccal Swab or Other (Multi-select)~~
~~Typing Method Class I~~	Donor Histocompatibility Form	~~Serology, DNA (Multi-select)~~
~~Date Typing Completed Class II~~	Donor Histocompatibility Form	~~MM/DD/YYYY~~
~~Typing Method Class II~~	Donor Histocompatibility Form	~~Serology, DNA (Multi-select)~~
~~Target Source for Class II~~	Donor Histocompatibility Form	~~Peripheral Blood, Lymph Nodes, Spleen, Buccal Swab or Other (Multi-select)~~

Table 2: Data Modifications: OPTN Data System (Recipient Histocompatibility)

Data Field	Form	Response Option Description
Most Recent CPRA	Recipient Histocompatibility Form: Recipient Information	Display calculated CPRA from Waitlist (Displays for kidney, pancreas, lung, heart, liver, intestine, and vascular composite allografts)
Prospective Virtual Crossmatch Performed	Recipient Histocompatibility Form: Test Information	Yes, No
~~Date HLA Typing Completed Class I~~	Recipient Histocompatibility Form: Section I-Recipient HLA Typing	~~MM/DD/YYYY~~
Date HLA Typing Completed	Recipient Histocompatibility Form: Section I-Recipient HLA Typing	MM/DD/YYYY
~~Typing Method Class I~~	Recipient Histocompatibility Form: Section I-Recipient HLA Typing	~~Serology, DNA (Multi-select)~~
~~Date HLA Typing Completed Class II~~	Recipient Histocompatibility Form: Section I-Recipient HLA Typing	~~MM/DD/YYYY~~
~~Typing Method Class II~~	Recipient Histocompatibility Form: Section I-Recipient HLA Typing	~~Serology, DNA (Multi-select)~~
Were any HLA antibodies detected ~~by:~~ pre-transplant?	Recipient Histocompatibility Form: Section II-HLA Antibody Screening	~~Cytotoxicity?~~ ~~Yes, No, Not Done~~ ~~Solid-phase?~~ ~~Yes, No, Not Done~~ Yes, No, Not Done
Were there ~~current~~ pre-transplant donor specific HLA antibodies?	Recipient Histocompatibility Form: Section II-HLA Antibody Screening	Yes, No, Unknown
~~Were there historical donor specific HLA antibodies?~~	Recipient Histocompatibility Form: Section II-HLA Antibody Screening	~~Yes, No, Unknown~~
~~CPRA (%) – Most Recent~~	Recipient Histocompatibility Form: Section II-HLA Antibody Screening	~~(Free text)~~
~~CPRA (%) – Peak~~	Recipient Histocompatibility Form: Section II-HLA Antibody Screening	~~(Free text)~~

Data Field	Form	Response Option Description
Date of most recent HLA antibody screening used for Virtual Crossmatch	Recipient Histocompatibility Form: Section III-Virtual Crossmatch	MM/DD/YYYY
Date of the most recent recipient crossmatch serum	Recipient Histocompatibility Form: Section ~~III~~ IV- Physical Crossmatch	MM/DD/YYYY
Donor ~~C~~cell source	Recipient Histocompatibility Form: Section ~~III~~ IV- Physical Crossmatch	Peripheral blood, lymph nodes, spleen, buccal swab or other
Which T-cell crossmatch tests were performed?	Recipient Histocompatibility Form: Section ~~III~~ IV- Physical Crossmatch	~~Cytotoxicity no AHG~~, ~~Cytotoxicity AHG~~, Cytotoxicity, Flow Cytometry, Solid Phase, Not tested (multi-select, each one triggers a sub-response for positive, negative, or indeterminate single select)
Which B-cell crossmatch tests were performed?	Recipient Histocompatibility Form: Section ~~III~~ IV- Physical Crossmatch	~~Cytotoxicity no AHG~~, ~~Cytotoxicity AHG~~, Cytotoxicity, Flow Cytometry, Solid Phase, Not tested (multi-select, each one triggers a sub-response for positive, negative, or indeterminate single select)
~~Which historical crossmatch tests were performed?~~	Recipient Histocompatibility Form: Section ~~III~~ IV- Physical Crossmatch	~~Cytotoxicity no AHG, Cytotoxicity AHG, Flow Cytometry, Solid Phase, Not tested (multi-select, each one triggers a sub-response for negative or positive single select)~~
~~Donor Retyped Class I~~	Recipient Histocompatibility Form: Section ~~IV~~ V - Donor Retyping	~~Yes, No, Unknown~~
~~Date Typing Completed Class I~~	Recipient Histocompatibility Form: Section ~~IV~~ V - Donor Retyping	~~MM/DD/YYYY~~
Date HLA Typing Completed	Recipient Histocompatibility Form: Section ~~IV~~ V - Donor Retyping	MM/DD/YYYY
~~Typing Method Class I~~	Recipient Histocompatibility Form: Section ~~IV~~ V - Donor Retyping	~~Serology, DNA (Multi-select)~~

Data Field	Form	Response Option Description
~~Donor Retyped Class II~~	Recipient Histocompatibility Form: Section ~~IV~~ V - Donor Retyping	~~Yes, No, Unknown~~
~~Date HLA Typing Completed Class II~~	Recipient Histocompatibility Form: Section ~~IV~~ V - Donor Retyping	~~MM/DD/YYYY~~
~~Typing Method Class II~~	Recipient Histocompatibility Form: Section ~~IV~~ V - Donor Retyping	~~Serology, DNA (Multi-select)~~

Table 3: Data Modifications: OPTN Data System (Discrepant HLA Typings)

Data Element	Form	Response Option Description
Resolved Reason for Discrepancy	Discrepant HLA Typings Report	~~Low Cell Numbers~~ ~~Poor Cell Viability~~ ~~Low Antigen Expression~~ ~~PBL Vs LN/Spleen~~ ~~Serology Vs Molecular Typing~~ Incorrect Assignment Parent Vs Split(s) Incorrect Split ~~Crossreactive Antigen~~ ~~Blank Antigen~~ ~~Unable to Type/Identify Antigens~~ Incorrect Specimen Transcription Error ~~Correct Typing~~ Other, specify (with free text box) Null Allele This Typing Confirmed Correct Reagent/Assay Issue Incorrect Allele Assignment P-group Equivalency Ambiguous Assignment (with free text box)
~~Discrepancy Not Resolvable~~	Discrepant HLA Typings Report	~~Check box~~

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Appendix A: Post-Public Comment Changes

New language that was proposed following public comment is underlined and highlighted (example); language that is proposed for removal following public comment is struck through and highlighted (~~example~~).

Table 2: Data Modifications: OPTN Data System (Recipient Histocompatibility)

Data Field	Form	Response Option Description
Prospective Virtual Crossmatch Performed*	Recipient Histocompatibility Form: Test Information	Yes, No ~~If yes, what was the result? Response: Positive, Negative, Indeterminate~~
Date of most recent HLA antibody screening used for Virtual Crossmatch	Recipient Histocompatibility Form: Section III-Virtual Crossmatch	MM/DD/YYYY
Date of the most recent recipient crossmatch serum	Recipient Histocompatibility Form: Section ~~III~~ IV- Physical Crossmatch	MM/DD/YYYY
Donor ~~C~~cell source	Recipient Histocompatibility Form: Section ~~III~~ IV- Physical Crossmatch	Peripheral blood, lymph nodes, spleen, buccal swab or other
Which T-cell crossmatch tests were performed?	Recipient Histocompatibility Form: Section ~~III~~ IV- Physical Crossmatch	~~Cytotoxicity no AHG~~, ~~Cytotoxicity AHG~~, Cytotoxicity, Flow Cytometry, Solid Phase, Not tested (multi-select, each one triggers a sub-response for negative, positive or indeterminate single select)
Which B-cell crossmatch tests were performed?	Recipient Histocompatibility Form: Section ~~III~~ IV- Physical Crossmatch	~~Cytotoxicity no AHG~~, ~~Cytotoxicity AHG~~, Cytotoxicity, Flow Cytometry, Solid Phase, Not tested (multi-select, each one triggers a sub-response for negative, positive or indeterminate single select)
~~If virtual crossmatch done, was physical crossmatch considered concordant with virtual crossmatch?~~	Recipient Histocompatibility Form: Section ~~III~~ IV- Physical Crossmatch	~~Yes, No~~

*Virtual Crossmatch Definition added post-public comment: A virtual crossmatch is the final immunologic assessment used to proceed with transplantation, consistent with CLIA regulation and laboratory policies. It is prospective if it is completed prior to transplantation.

Table 3: Data Modifications: OPTN Data System (Discrepant HLA Typings)

Data Element	Form	Response Option Description
Resolved Reason for Discrepancy	Discrepant HLA Typings Report	~~Low Cell Numbers~~ ~~Poor Cell Viability~~ ~~Low Antigen Expression~~ ~~PBL Vs LN/Spleen~~ ~~Serology Vs Molecular Typing~~ Incorrect Assignment Parent Vs Split(s) Incorrect Split ~~Crossreactive Antigen~~ ~~Blank Antigen~~ ~~Unable to Type/Identify Antigens~~ Incorrect Specimen Transcription Error ~~Correct Typing~~ Other, specify (with free text box) Null Allele ~~Original~~ This Typing Confirmed Correct Reagent/Assay Issue Incorrect Allele Assignment P-group Equivalency Ambiguous Assignment (with free text box)

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Appendix B: Data Definition

Prospective Virtual Crossmatch Performed: Select **Yes** if a prospective virtual crossmatch was performed. Select **No** if a prospective virtual crossmatch was not performed.

> **Definition:** A virtual crossmatch is the final immunologic assessment used to proceed with transplantation, consistent with CLIA regulation and laboratory policies. It is prospective if it is completed prior to transplantation.

Discrepancy Reason: Select the reason why there was a discrepancy (only one may be selected)

> **Ambiguous Assignment (with required free text box):** The HLA typing results were ambiguous. Requires additional explanation as to how the results were ambiguous.
>
> **Reagent/Assay Issue:** There was a reagent or assay malfunction that caused the discrepancy. For example, a well in an assay did not react.
>
> **Parent Vs. Split:** The HLA typing results are equivalent, as one HLA typing result is a parent antigen and the other is a split antigen of that parent.
>
> **Null Allele:** A null allele was reported as non-null in the HLA typing.
>
> **P-group Equivalency:** The HLA typing results are equivalent, as one HLA typing result is a P-group and the other is an allele within that P-group.
>
> **Incorrect Specimen:** The specimen or HLA typing was for a different patient than it was reported for.
>
> **Transcription Error:** There was an error in manual transcription of the HLA typing data.
>
> **Incorrect Split:** The incorrect serologic split was reported from a broader parent antigen.
>
> **Incorrect Allele Assignment:** The incorrect allele was reported from a list of multiple potential alleles.
>
> **This Typing Confirmed Correct:** This HLA typing result has been confirmed to be the correct HLA typing for the patient.
>
> **Other, Specify (with required free text box):** The reason for the discrepancy does not fit into any of the other reasons. Requires additional explanation as to the reason for the discrepancy.