

**OPTN/UNOS Histocompatibility Committee
Report to the Board of Directors
June 23-24, 2014
Richmond, Virginia**

**Lee Ann Baxter-Lowe, PhD, Chair
Dolly Tyan, PhD, Vice Chair**

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This report reflects the work of the OPTN/UNOS Histocompatibility Committee from October 1, 2013 - April 28, 2014.

Action Items

1. Histocompatibility Policy Rewrite Proposal

Public Comment: September 6 - December 6, 2013

This proposal reflects recommendations from the Histocompatibility Committee (“the Committee”) following a comprehensive review of the OPTN policies governing histocompatibility testing. The Committee is proposing to eliminate numerous sections of the current policies because they are outdated or adequately addressed in the standards required by histocompatibility accrediting agencies (ASHI and CAP). Several changes are intended to address requests from UNOS staff to resolve issues with policies identified as difficult to monitor. Finally, the Committee is proposing several new policies pertaining to HLA typing accuracy, crossmatching requirements for kidney transplantation, and preservation of excess specimens. In recognition of the fact that testing methods and technology continue to evolve and clinical practice for histocompatibility testing often varies among patients, the Committee intends to move most of the sections proposed for elimination from policy into a guidance document that will be developed at the conclusion of this process.

The Committee reviewed and discussed public comment feedback on a March 19, 2014 teleconference. After much consideration, the Committee voted 10-Yes, 0-No, 0-Abstentions to recommend the Board of Directors approve the following new and modified policies:

RESOLVED, that Policies 4.1 through 4.15 are stricken in their entirety and replaced with new Policies 4.1 (HLA Typing), 4.2 (Resolving Discrepant Donor and Recipient HLA Typing Results), 4.3 (Antibody Screening and Reporting), 4.4 (Crossmatching), 4.5 (Blood Type Determination), 4.6 (Preservation of Excess Specimens), and 4.7 (HLA Antigen Values and Split Antigen Equivalences); and that modifications to Policies 2.8.C (Required Information for Deceased Heart Donors), 2.8.D (Required Information for Deceased Lung Donors), and 4.16 (Reference Tables of HLA Antigen Values and Split Equivalences), as set forth in Exhibit A, are hereby approved, effective September 1, 2014 and effective pending programming and notice to the OPTN membership.

Committee Projects

2. Expanding HLA Typing Requirements

*Public Comment: Spring, 2014
Board Consideration: November 2014 (Estimated)*

In 2012, the Committee began conducting a comprehensive rewrite of the OPTN policies governing histocompatibility testing. As part of this effort, the Committee organized all the HLA typing requirements into two tables, one for deceased donors and one for candidates.

The Committee identified several problems with the current HLA typing requirements:

- It is critical for all transplant physicians to have complete HLA information when making decisions about donor acceptance and performing post-transplant monitoring. However, there are several inconsistencies in the list of HLA types required to be reported for deceased donors across organ types.
- Recent research suggests that antibodies to HLA-DQA and HLA-DPB are frequently observed in sensitized transplant candidates. If donors with the relevant types are not avoided, these antibodies can contribute to adverse graft outcomes. However, these HLA types are not required to be reported on deceased donors. HLA-DPB is currently only required if requested for heart or lung offers and the OPO's laboratory performs this testing. Even if an OPO's histocompatibility laboratory types the donor for HLA-DQA or HLA-DPB prior to allocation, the only way to currently communicate this information is through an attachment function in DonorNet®, which can sometimes be overlooked.
- Publications suggest anti-HLA antibodies may contribute to negative outcomes in pancreas islet transplants and negatively impact the ability of islet recipients to undergo further islet, pancreas, or kidney transplantation. HLA typing could be crucial for evaluating risk from pre-transplant and de novo HLA antibodies. However, there are currently no HLA typing requirements for deceased pancreas islet donors or candidates.
- It is critical for heart and lung transplant programs to have deceased donor HLA typing information prior to transplant. However, HLA typing is only required on deceased heart, heart-lung, and lung donors if requested by the candidate's transplant program.
- There is increasing evidence of antibody mediated rejection (AMR) in liver transplantation. However, there is currently no requirement for HLA typing to be performed on a deceased liver donor if the candidate's transplant program requests it.
- Deceased donor HLA typing performed using molecular methods provides superior accuracy and advantages for transplant candidates. However, laboratories are currently required to perform molecular typing on deceased kidney, kidney-pancreas, and pancreas donors only.

Early in the process, the Committee identified a list of solutions to address these problems:

- Make consistent the list of HLA loci required to be reported across organ type.
- Add HLA-DQA and HLA-DPB to the list of HLA loci required to be reported for deceased donors.
- Align requirements for deceased pancreas islet donors and candidates with those of deceased pancreas donors and candidates.
- Require HLA typing be performed and reported for deceased thoracic donors (not merely if requested), either pre-transplant or within a certain period of time after transplant.
- Require HLA typing to be performed for deceased liver donors if requested by the candidate's transplant program.

- Require molecular typing to be performed on all deceased donors (both when OPTN policy requires the typing to be performed and when it is required only if requested by a candidate's physician).

The Committee then presented these solutions to the following groups for feedback:

- Organ Procurement Organization (OPO) Committee
- Thoracic Organ Transplantation Committee
- Kidney Transplantation Committee
- Pancreas Transplantation Committee
- Liver and Intestine Transplantation Committee
- American Society of Histocompatibility and Immunogenetics (ASHI) Board of Directors
- College of American Pathologists (CAP) Histocompatibility Committee and accreditation staff

In December 2013, the Committee held a conference call to review feedback from the OPO and organ specific committees. After discussing the feedback, the Committee unanimously agreed to distribute this proposal for public comment. This proposal is currently out for public comment. Public comment has been favorable thus far, with 100% of individuals commenting supporting the proposal, along with two OPTN Regions and the Pancreas Transplantation and Minority Affairs Committees.

3. Histocompatibility Bylaws Rewrite: Phase 2

Public Comment: Fall, 2014 (Estimated)

Board Consideration: June 2015 (Estimated)

In November 2013, the Board approved several new changes to the OPTN Bylaws governing histocompatibility laboratories. The Committee is now in the second phase of the comprehensive review of the Bylaws. This second phase will clean up sections pertaining to the education and experience required for approval as key laboratory personnel, along with performance indicators for testing performed and results reported to the OPTN. The Committee is collaborating with the American Society for Histocompatibility and Immunogenetics (ASHI) and the College for American Pathologists (CAP) on this project.

The Bylaws Rewrite subcommittee has held regular meetings since November 2013 and has made the following recommendations thus far:

- The Committee is proposing to clarify the two education pathways for approval for OPTN histocompatibility laboratory directors--M.D./D.O. or PhD. For each, the subcommittee has drafted new language that would specify the education, experience, and licensing requirements. The subcommittee hopes to specify that foreign equivalent education and experience is permissible (there is currently no pathway for foreign equivalent education and experience in the Bylaws for laboratory directors).
- The Committee is proposing to simplify requirements for the technical supervisor, general supervisor, and clinical consultant by only requiring that these individuals meet the requirements in the federal Clinical Laboratory Improvement Amendments (CLIA).
- The Committee is proposing to eliminate references to the histocompatibility technologist. The Bylaws do not have requirements for this group of personnel.

- The Committee is proposing a number of changes in the section that lists criteria for mandatory performance reviews of histocompatibility laboratories, including but not limited to new criteria around HLA typing errors that result in an incompatible transplant or the reallocation of an organ.
- The Committee is proposing to delete a number of these sections that are out of date or are more appropriately monitored by ASHI or CAP.

4. Addressing HLA Typing Errors

Public Comment: Spring, 2015 (Estimated)

Board Consideration: November 2015 (Estimated)

The Committee continues to focus on the problem that the OPTN does not currently have a policy or system for timely reporting or oversight of HLA typing errors (discrepancies are flagged on the donor and recipient histocompatibility forms completed after transplant, but there is currently no timely mechanism for detecting errors used for the match run).

The Committee overwhelmingly supports changes in policy that would provide accountability for laboratories that make HLA typing errors--especially for the MPSC to take disciplinary action in cases of serious errors. The Discrepant HLA Typing Subcommittee recently discussed defining a serious HLA typing error as a wrong antigen assignment where the HLA type reported for a deceased donor was used for the match run and the result was that an organ was allocated incorrectly, either to a recipient who was transplanted with an incompatible organ or where the organ had to be re-allocated upon realization of the error.

In these cases, the Committee has discussed requiring the laboratory to report the error to the transplant program(s) and/or OPO(s) who received incorrect HLA typing and to UNOS through the patient safety portal. UNOS staff (DEQ) and the MPSC would then review the error to determine whether there was a policy violation or significant patient safety concern. These new requirements will likely be proposed in the rewrite of the Histocompatibility Bylaws.

The Discrepant HLA Typing Subcommittee plans to meet in the summer of 2014 to discuss the following policy changes intended to prevent HLA typing errors from occurring prior to allocation or to detect them prior to transplant:

Require second person confirmation for reporting HLA

The Committee has generally been in favor of this solution if the policy language specifies that one of the reviewers must be from the histocompatibility laboratory. This is intended to address reporting errors that may be occurring because the persons entering the data (OPO or transplant hospital staff) are not HLA experts. One committee member also pointed out that ASHI currently requires a second party verification on analysis of DNA based typing, but recognized that not all OPTN laboratories are accredited by ASHI.

Require recipient laboratories to retype deceased donors

The committee is still somewhat divided on this idea. Data show less than 50% of deceased kidney, kidney-pancreas, and pancreas donors are retyped by the recipient laboratory and, therefore, it is difficult to have a complete understanding of the scope of HLA typing discrepancies. Several members suggested that the Committee review data

on the frequency of retyping by laboratory in order to understand how many laboratories retype deceased donors currently.

Several members of the Committee are in favor of this new requirement, arguing that donor retyping is essential in order to confirm that the organ received is the one accepted for the intended recipient. Others added this requirement is important due to increased use of virtual crossmatching.

However, some members have expressed concern that this would possibly be an expensive burden on laboratories and suggest instead that the Committee focused on finding solutions that prevent HLA typing errors prior to allocation (this retyping would occur after the organ has already been allocated). Several members of the Committee have argued that the majority of typing errors are clerical or due to interpretation issues and requiring recipient laboratories to retype will not solve this problem.

The Committee is currently collaborating with the Operations and Safety Committee to obtain data on the number and types of HLA errors being reported through the Improving Patient Safety Portal. The Committee also plans to present this proposed policy change to ASHI, CAP, and the OPO and organ specific committees for feedback.

5. Enhancing Prioritization for DR Matching in Deceased Kidney Donor Allocation

Public Comment: Spring, 2016 (Estimated)

Board Consideration: November 2016 (Estimated)

The Enhancing Priority for DR Matching Subcommittee met in September and November 2013 to review data on long term graft survival of deceased donor kidney transplants by DR and DQB mismatch.

The data show the following:

- 22% of transplants were zero DR mismatches and 23% were zero DQB mismatches.
- 60% of transplants had the same level of DR and DQB mismatch. This percentage was higher for 0 and 1 DR mismatch levels compared to 2 DR mismatch (67% and 67% vs. 48%).
- Recipients with lower levels of DR mismatch had significantly higher survival within 8 and 12 years post transplant.
- Recipients with a zero DQB mismatch transplant had significantly better survival within 8 and 12 years compared to those with higher DQB mismatch levels. Survival rates for 1 and 2 DQB mismatch level transplants were similar.
- Better survival rates for zero DQB mismatch transplant recipients was probably affected by a high percentage of zero DQB mismatch transplants that also had a zero DR mismatch level (67%).
- Within each DR mismatch level, survival was similar by DQB mismatch level.
- 0/0 DR/DQB recipients had significantly better survival rates comparing to all other groups with DR mismatch levels higher than 0. Differences between 0/0 vs. 0/1 and 0/0 vs. 0/2 groups were not significant.

The subcommittee reached the following conclusions:

- Recipients with lower levels of DR MM had significantly better long term (within 8 and 12 years) survival.
- There is some indication that better DQB matching leads to better long term survival (0MM vs. 1MM and 0MM vs. 2MM)
- Survival doesn't seem to be improved by DQB matching in addition to DR matching or better DQB matching within the same level of ABDR mismatch

Currently, the subcommittee is focused on the question of whether more prioritization points are needed for transplants with lower levels of DR mismatches. The subcommittee will soon review simulation modeling performed during the development of the new kidney allocation system (KAS) to determine whether the changes are likely to increase or decrease the number of zero-DR mismatch transplants.

6. Changes to KAS: CPRA and Priority for Candidates Undergoing Desensitization

Public Comment: *Fall, 2015 (Estimated)*

Board Consideration: *June, 2016 (Estimated)*

The Committee continues to discuss CPRA prioritization points for kidney candidates undergoing desensitization. Under the kidney allocation system, highly sensitized kidney candidates who undergo desensitization lose allocation points associated with their CPRA score, reducing their opportunity for kidney offers. In January, a workgroup comprised of members of the Histocompatibility, Kidney Transplantation, and Minority Affairs Committees held an introductory call on this project and discussed barriers to getting data on how many patients would benefit from a policy change.

The workgroup decided that the most effective step for moving forward is to conduct a survey of kidney transplant programs to learn whether more programs would utilize desensitization for highly sensitized candidates if these candidates could keep the prioritization associated with their CPRA score for a period of time. The workgroup also requested data to determine whether there is a level of sensitization (indicated by CPRA score) where patients would most benefit from desensitization, whether this change would benefit minority populations in particular, and whether the modeling previously provided on the new Kidney Allocation System (KAS) showed increased or decreased access for certain categories of sensitized patients that the workgroup should focus on.

7. Histocompatibility Testing Guidance Document

Public Comment: *N/A*

Board Consideration: *June 2015 (Estimated)*

In recognition of the fact that testing methods and technology continue to evolve and clinical practice for histocompatibility testing often varies among patients, the Committee is proposing to move a number of existing OPTN histocompatibility policies into a guidance document. The Committee will begin work on this project in the summer of 2014 if the Board approves the Histocompatibility Policy Rewrite proposal.

Committee Projects Pending Implementation

8. Update to the HLA Equivalency Tables

Public Comment: Spring, 2013
Board Approval: November 2013
Projected Implementation: By the end of 2014.

Current OPTN Policy requires the Histocompatibility Committee to recommend updates, on an annual basis, to the HLA Equivalency tables. This project will implement the following changes to the HLA Equivalency tables:

- 8 broad antigens will be eliminated in the 'Matching Antigen Equivalences' tables.
- 4 equivalences will be added and 57 deleted in the 'Unacceptable Antigen Equivalences' tables.
- The Cw13 antigen will be removed from the system completely.

Implemented Committee Projects

9. Update to CPRA

Public Comment Fall 2011
Board Approval: June 2012
Implementation: December 5, 2013 (part 1) and March 20, 2014 (part 2)

In June 2012, the OPTN Board of Directors approved updating the HLA and ethnic frequencies used to calculate CPRA for kidney, kidney-pancreas, and pancreas registrations on the waiting list and adding HLA-C into the calculation. These changes were implemented on December 5, 2013. During a December 2, 2013 conference call, the Committee discussed monitoring the effects of this policy change. The Committee requested data on changes in CPRA values immediately after implementation of the policy to evaluate the impact on the waiting list.

The Committee requested to compare CPRA values before and after the implementation for kidney, kidney-pancreas, and pancreas registrations waiting on December 5, 2013, overall and by:

- Age group (adult vs. pediatric registrations)
- Gender
- Ethnicity
- Registration type (primary vs. retransplant)

The Committee also requested the number and percentage of candidates that moved to a different CPRA group:

- 0% vs. >0%
- <80% vs. 80%+
- ≤20% vs. >20% (for adult registrations)
- <98%, 98%, 99% vs. 100%

The Committee was also interested in the number and percentage of registrations with CPRA increasing from 0% to >0% and from <80% to 80%+ because of unacceptable HLA-C antigens. All results were provided by organ.

On the March 19th conference call, the committee reviewed the requested data:

- Changes to CPRA calculation implemented on December 5, 2013 resulted in CPRA value changes for 20% of kidney, 21% of kidney-pancreas and 22% of pancreas registrations. For registrations with unacceptable antigens reported on the waiting list, CPRA changed for approximately half of registrations.
- For those with CPRA changes, the value increased for about two thirds of registrations and over half of registrations experienced only a small change (1% point increase or decrease).
- Out of 1,271 registrations with 5% points or more CPRA decrease, 1,270 (99.9%) registrations had unacceptable DQ 1, 3, 5, 6, 7, 8 and/or 9 antigens reported on the waiting list. Note that in the currently programmed HLA equivalency tables, unacceptable DQ5 and 6 antigens are equivalent to themselves and donor's DQ1 antigen and DQ7, 8 and 9 are equivalent to themselves and donor's DQ3 antigen. Reporting of broad donor antigens (including DQ1 and DQ3) decreased in recent years, which was reflected in changes in HLA frequencies.
- For registrations with unacceptable C antigens reported, adding HLA-C frequencies into calculation resulted in CPRA change for approximately 60% of registrations and a 10% points or more increase for approximately 20% of registrations (N=2,473).
- CPRA increased from 0% to >0% for 1,222 registrations (1,200 were kidney registrations). This increase was caused by addition of HLA-C into calculation. No registrations experienced a decrease in CPRA value from >0% to 0%.
- CPRA increased from <80% to 80%+ for 763 registrations (740 were kidney registrations) and decreased from 80%+ to <80% for 128 registrations (125 were kidney registrations).
- Almost all registrations with old CPRA = 100% (5,915 out of 6,039) have new CPRA=100%. The remaining ones have new CPRA value=99%. For 1,212 registrations with old CPRA value below 100%, CPRA increased to 100% (85% of those had old CPRA=99%).
- For registrations with old CPRA=99%, 55% remained in 99% group, 39% now have CPRA value of 100% and for remaining registrations CPRA value decreased to 80-98%.

Conclusion

- The reporting of broad donor antigens decreased through the years, resulting in a decrease in corresponding HLA frequencies and CPRA values after implementation for some registrations (8% of kidney, kidney-pancreas, and pancreas waiting list). Registrations who get screened from offers for donors with DQ1 or DQ3 experienced the most noticeable decrease in CPRA value.
- At the same time, CPRA values increased for 12% of kidney, kidney-pancreas, and pancreas registrations due to updated HLA and ethnic frequencies and the addition of HLA-C.
- Changes in CPRA values reflect a decreased reporting of broad HLA antigens and changes in ethnic distribution of deceased donors. Addition of HLA-C to the CPRA calculation ensured that candidates who are sensitized to HLA-C are considered for

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allocation priority similar to those candidates who are sensitized to HLA-A, -B, -DR and -DQB antigens.

In a second release on March 20, 2014, a required question, “Was the candidate tested for anti-HLA antibodies?” was added to the waiting list for kidney, kidney-pancreas, and pancreas candidates. The question was added to help transplant teams better interpret a 0% CPRA score when making decisions about organ acceptance.

Other Committee Work

10. Histocompatibility Membership Advisory Subcommittee

Several members of the Committee serve on a joint working group with members of the Membership and Professional Standards Committee (MPSC). This workgroup serves in an advisory capacity to assist the MPSC in reviewing applications for new histocompatibility laboratories and changes in key laboratory personnel.

From October 2013 - April 2014, the Committee met twice via conference call. The workgroup reviewed and recommended approval of the following to the MPSC:

- 5 new labs – 3 of which were reclassifications (i.e. moved from hospital based to independent or the reverse)
- 9 changes in key personnel.

Meeting Summaries

The Committee held meetings on the following dates:

- September 23, 2013
- December 2, 2013
- March 19, 2014

Meetings summaries for this Committee are available on the OPTN website at: <http://optn.transplant.hrsa.gov/members/committeesDetail.asp?ID=7>.

Histocompatibility Policy Rewrite Proposal

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Title: Comprehensive Histocompatibility Policy Rewrite Proposal**Sponsoring Committee: Histocompatibility Committee****Summary and Goals of the Proposal:**

This proposal reflects recommendations from the Histocompatibility Committee (the “Committee”) following a comprehensive review of the OPTN policies governing histocompatibility testing. The Committee is proposing to eliminate numerous sections of the current policies because they are outdated or adequately addressed in the standards required by histocompatibility accrediting agencies (the American Society for Histocompatibility and Immunogenetics (ASHI) or the College of American Pathologists (CAP)). Several changes are intended to address requests from UNOS staff to resolve issues with policies identified as difficult to monitor. Finally, the Committee is proposing several new policies pertaining to HLA typing accuracy, crossmatching requirements for kidney transplantation, and preservation of excess specimens. In recognition of the fact that testing methods and technology continue to evolve and clinical practice for histocompatibility testing often varies among patients, the Committee intends to move most of the sections proposed for elimination from policy into a guidance document that will be developed at the conclusion of this process.

The Committee hopes to achieve the following goals with this proposal:

- promote transplant safety by requiring histocompatibility laboratories to accurately determine and report HLA typing, resolve HLA typing discrepancies in a timely manner, and preserve excess specimens when performing histocompatibility testing that results in transplantation of a deceased donor organ
- promote the efficient management of the OPTN by simplifying policies governing histocompatibility testing for solid organ transplantation and eliminating policies that are outdated or adequately addressed in the standards required by histocompatibility accrediting agencies (ASHI and CAP)

Background and Significance of the Proposal:

In 2012, the OPTN/UNOS Policy Oversight Committee released a ‘plain language’ rewrite of all OPTN policies. This ‘plain language’ rewrite included a major re-organization of the OPTN policies governing histocompatibility laboratories. With this re-organization, UNOS staff flagged numerous histocompatibility policies that were difficult to monitor and asked the Histocompatibility Committee to conduct a comprehensive review of the OPTN policies for histocompatibility testing. The American Society of Histocompatibility and Immunogenetics (ASHI) also offered feedback on the ‘plain language’ rewrite and this feedback was referred to the Committee to consider when writing this proposal.

The Committee conducted this comprehensive policy review and rewrite from 2012-2013. The Committee concluded from the review that the current policies governing histocompatibility testing are outdated and many do not reflect current clinical practice. In an effort to update the policies, address issues identified by UNOS staff, and respond to comments submitted by ASHI, the Committee is proposing numerous changes to Policy 4.

One of the biggest changes being proposed is the elimination of numerous sections of policy that the committee determined were difficult for UNOS to monitor, more appropriate for guidance, or covered by existing standards required by histocompatibility accrediting agencies (ASHI or CAP). The sections included in this category are as follows:

- 4.1 Guidelines for Written Contracts between Histocompatibility Laboratories and Transplant Programs
- 4.1.A Recommended Elements for Histocompatibility Contracts
- 4.1.B Sensitization History
- Table 4-1: Determining Sensitization
- 4.1.C Detection of Antibodies
- Table 4-2 Assays to Identify Antibody to HLA: Screening, Specificity, or Crossmatching
- 4.1.D Periodic Sample Collection
- 4.1.E Crossmatching Strategies
- Table 4-3: Recommended Elements for Crossmatching Strategies
- 4.2 HLA Typing
- 4.2.A Typing Assignment
- 4.2.B Reagent Validation
- 4.2.C HLA Typing by Nucleic Acid Analysis
- 4.2.D Typing by Sequenced Based Typing (SBT)
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- 4.13.D CPRA Determination
- 4.13.E Histocompatibility Typing
- 4.14 Chimerism Analysis
- 4.14.A Analysis and Reports

The Committee intends will transition many of these sections into a guidance document that will be developed at the conclusion of this process.

Sections 4.6.A *Personnel Requirements* and 4.1 *Guidelines for Written Contracts Between Histocompatibility Laboratories and Transplant Programs* were previously moved Appendix C of the OPTN Bylaws through a Board of Directors action in November 2013.

The policy sections remaining are incorporated either in part or altogether into the draft for the proposed policy and the below new requirements are being proposed:

1. Laboratories must ensure that HLA typing is accurately determined and reported according to the turnaround time specified in the written agreement between the laboratory and the transplant program or OPO (4.1.A *Requirements for Performing and Reporting HLA Typing*).
2. Laboratories must resolve HLA typing discrepancies within 30 days of notification of discrepant HLA typing results and the Histocompatibility Committee must review outstanding discrepant HLA typing reports at least every three months (4.2 *Resolving Discrepant Donor and Recipient HLA Typing Results*). Notice of HLA typing discrepancies are currently displayed in TIEDI®.
3. When performing an antibody screening, laboratories must use at least one solid phase immunoassay using purified HLA molecules (4.3 *Antibody Screening and Reporting*).
4. When performing histocompatibility testing for kidney transplantation, laboratories must perform a final crossmatch and report the results to the transplant program prior to transplant (4.4 *Crossmatching*).
5. When performing testing for blood type determination, laboratories must follow manufacturer's directions for materials and equipment used (D.5 *Blood Type Determination*).
6. If the laboratory performs testing to determine histocompatibility between a donor and recipient, the laboratory must preserve enough specimen from the deceased donor to

perform subsequent testing for at least five years after the transplant (4.6 *Preservation of Excess Specimens*).

7. The Histocompatibility Committee must review and recommend any needed changes to the HLA Equivalency Tables by June 1 of each year (D.6 *Preservation of Excess Specimens*).

Crosswalk for the proposal

The following tables provide a crosswalk for this proposal. The first table provides recommendations by current policy sections, along with the reason for the committee’s recommendation. The second table provides a reference to current policy sections incorporated, a list of any proposed new requirements, and the reason for any new requirements added.

Table 1: Changes to Current Policy

Section	Policy Title	Recommendation	Reason
4.1	Guidelines for Written Contracts between Histocompatibility Laboratories and Transplant Programs	Rewritten and moved to Appendix C of OPTN Bylaws with Board action in November 2013	This subject matter is more appropriate for the Bylaws
4.1.A	Recommended Elements for Histocompatibility Contracts	Rewritten and moved to Appendix C of OPTN Bylaws with Board action in November 2013	This subject matter is more appropriate for the Bylaws
4.1.B	Sensitization History	Move to guidance document	This section is outdated and merely conveys guidance.
Table 4-1	Determining Sensitization	Move to guidance document	This section is outdated and merely conveys guidance.
4.1.C	Detection of Antibodies	Move to guidance document	This section merely conveys guidance.
Table 4-2	Assays to Identify Antibody to HLA: Screening, Specificity, or Crossmatching	Move to guidance document	This section merely conveys guidance.
4.1.D	Periodic Sample Collection	Move to guidance document	This section merely conveys guidance.
4.1.E	Crossmatching Strategies	Move to guidance document	This section merely conveys guidance.
Table 4-3	Recommended Elements for Crossmatching Strategies	Move to guidance document	This section merely conveys guidance.

Section	Policy Title	Recommendation	Reason
4.2	HLA Typing	The list of HLA types required to be reported by organ type has been converted into a table (Table 4.1 in new policy). The language pertaining to reporting splits has been moved to guidance document.	The Committee is converting HLA typing requirements into a table in order to clearly convey what types laboratories are required to report by organ types. The language pertaining to splits is merely written as guidance.
Table 4-4	Requirements for HLA Typing	Move rows 2-4 in the table to guidance document. Move requirement in row 1 to new policy 4.1 <i>HLA Typing</i>	Rows 2-3 are outdated or merely guidance. Row 1 contains requirement for laboratories to perform molecular typing for deceased kidney, kidney-pancreas, and pancreas donors.
4.2.A	Typing Assignment	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.2.B	Reagent Validation	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.2.C	HLA Typing by Nucleic Acid Analysis	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.2.D	Typing by Sequenced Based Typing (SBT)	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.3	HLA Antigen Values and Split Equivalences	Move to new policy 4.7	This reorganization will place the policy next to the HLA Equivalency Tables.
4.4	Resolving Discrepant Donor and Recipient HLA Typing Results	Move to new policy 4.2	This reorganization will place the policy after the HLA typing requirements.
4.5	Antibody Screening	Move to guidance document	This section merely conveys guidance.
Table 4-5	Requirements for Antibody Screening	Delete	This table makes reference to policies that are being moved to the guidance document.

Section	Policy Title	Recommendation	Reason
4.5.A	Techniques	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.5.B	Sera	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.5.C	Panel and Target Selection	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.6.A	Personnel Requirements	Moved to Appendix C in OPTN Bylaws with November 2013 Board action	This subject matter (personnel coverage) is more appropriate for the Bylaws
4.6.B	HLA Typing	Incorporate the requirements in this section in Tables 4.1 and 4.2. Move language suggesting typing on candidates to guidance document	This better clarifies the HLA types required to be reported by organ type.
4.6.C	Antibody Screening	Move to guidance document	This section was determined to be vague and difficult to monitor. The majority of the language conveys guidance.
4.6.D	Crossmatching	Move #1 to new policy 4.4 #2 was incorporated into Appendix C of the OPTN Bylaws with a November 2013 Board action	#1 is an important requirement specific to testing for solid organ transplantation. #2 contained a subject matter more appropriate for the OPTN Bylaws
4.6.E	Techniques	Move #1 in this section to new policy 4.4 Delete the remainder of this section	#1 is an important requirement specific to testing for solid organ transplantation. The remainder of the section was determined to be difficult to monitor or more appropriately monitored by histocompatibility accrediting agencies.

Section	Policy Title	Recommendation	Reason
4.6.F	Samples	<p>Move #1 to guidance document</p> <p>#2 was incorporated into Appendix C of the OPTN Bylaws with November 2013 Board action</p>	<p>#1 merely conveys guidance.</p> <p>#2 has a subject matter that is more appropriate for the Bylaws.</p>
4.7	Other Organ and Islet Cell Transplantation	<p>#1 and #4 were incorporated into Appendix C of the OPTN Bylaws with November 2013 Board action</p> <p>Move #2 to new policy 4.1.</p> <p>Move #3 to new policy 4.4</p> <p>Move #5 to guidance document</p> <p>Move # 6 to new policy 4.3</p>	<p>#1 and #4 were pertaining to a subject matter more appropriate for the Bylaws.</p> <p>#2, 3, and 6 were reorganized under the appropriate subject matter (antibody screenings, crossmatching, HLA typing)</p> <p>#5 was determined to be vague and difficult to monitor</p>
4.8	Cytotoxicity Methods	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.8.A	Percentage of Cell Killed	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.8.B	Controls	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.8.C	Target Cells	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.

Section	Policy Title	Recommendation	Reason
4.8.D	Complement	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.9	Blood Type Determination	Incorporate into new policy 4.5	
4.10	Nucleic Acid Analysis	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.10.A	Nucleic Acid Extraction	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.10.B	Electrophoresis	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.10.C	Analysis	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.10.D	Template Amplification	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.10.D.i	Facilities and Equipment	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.10.D.ii	Reagents	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.10.E	Primers	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.

Section	Policy Title	Recommendation	Reason
4.10.F	Amplification Templates	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.10.G	Contamination	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.10.H	Controls and Quality Assurance	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.10.I	Technique-Specific Standards	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.10.I.i	Oligonucleotide Probe Assays	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.10.J	Other Techniques	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.11	Flow Cytometry	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.11.A	Instrument Standardization and Calibration	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.11.B	Flow Cytometric Crossmatch Technique	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.

Section	Policy Title	Recommendation	Reason
4.11.C	Controls	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.11.D	Interpretation	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.11.E	Immunophenotyping By Flow Cytometry	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.11.F	Cell Preparation	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.11.G	Quality Control	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.11.H	Reagents	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.12	ELISA	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.12.A	The ELISA Reader	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.12.B	ELISA Technique	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.

Section	Policy Title	Recommendation	Reason
4.13	Solid Phase Multi-channel Arrays	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.13.A	Instrument Standardization/Calibration	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.13.B	Reagents	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.13.C	Techniques	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.13.D	CPRA Determination	Delete	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.13.E	Histocompatibility Typing	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.14	Preservation of Zero Mismatch Tissue Typing Materials	Incorporated into new policy 4.6	The Committee members agreed that it was important to maintain this requirement and to make it apply to the storage of all deceased donor specimens across organ types.
4.14.A	Analysis and Reports	Move to guidance document	This section contains requirements that are more appropriately monitored by the histocompatibility laboratory accrediting agencies.
4.15	Reference Tables of HLA Antigen Values and Split Equivalences	Moved to new policy 4.8 with no changes	N/A

Table 2: Proposed Policy with Current Policy References

Section	Policy Title	Changes	Reason	Policies Incorporated
4.1.A	Requirements for Performing and Reporting HLA Typing	Laboratories must ensure that HLA typing is accurately determined and report results to the OPO or Transplant Program according to the turnaround time specified in written agreements.	The committee's comprehensive review revealed that current OPTN policy does not require that HLA typing be accurately determined and reported. The committee modeled this new policy after the OPTN requirement for accuracy in determining and reporting donor and candidate blood type.	Table 4.4 4.6.B 4.7
Table 4.1	HLA Typing Requirements for Deceased Donors	Current HLA typing requirements for deceased donors have been incorporated into this table	The committee determined that the OPTN needed to simplify the way it conveys HLA typing requirements and include the types to be reported by organ in one place. The committee noted that there are inconsistencies in the typing requirements and plans to collaborate with the transplant community about making these requirements consistent.	2.8.A 2.8.C 2.8.D 2.8.E 4.6.B
Table 4.2	HLA Typing Requirements for Candidates	Current HLA typing requirements for candidates have been incorporated into this table	The committee determined that the OPTN needed to simplify the way it conveys HLA typing requirements and include the types to be reported by organ in one place.	4.6.B

Section	Policy Title	Changes	Reason	Policies Incorporated
4.2	Resolving Discrepant Donor and Recipient HLA Typing Results	<p>Laboratories must resolve HLA typing discrepancies within 30 days of being notified of discrepant HLA typing results.</p> <p>The Histocompatibility Committee must review, at least every three months, any outstanding discrepant typing recorded since the last review.</p>	<p>Current policy does not provide a deadline for resolving discrepancies. This allows discrepancies to remain unresolved for long periods of time (even years). The committee determined that laboratories need to resolve discrepancies within <u>30</u> days of notification in order to determine if a discrepancy will impact post-transplant care.</p> <p>The committee will review the discrepancies more frequently (currently policy requires the committee to review discrepant reports annually) to determine if policy changes are needed.</p>	4.4
4.3	Antibody Screening and Reporting	<p>When performing an antibody screening, the laboratory must use at least one solid phase immunoassay using purified HLA molecules.</p>	<p>The requirement for this particular type of assay to be used for determining unacceptable antigens currently only applies to kidney transplantation, where unacceptable antigens are used for calculating CPRA. The committee determined that this requirement is important for antibody testing for all solid organ transplantation, not exclusively for kidneys.</p>	9.1 (in part)

Section	Policy Title	Changes	Reason	Policies Incorporated
4.4	Crossmatching	Laboratories performing histocompatibility testing for kidney transplants or multi-organ transplants in which a kidney is being transplanted must perform a final crossmatch and report the results to the transplant program before transplant.	Federal regulation CFR §493.1278 requires that the results of the final crossmatch be available prior to kidney transplantation (including when a kidney is to be transplanted with other organs). The committee determined it was important to include this requirement in OPTN policy because the current policy is silent on these requirements.	4.6.D 4.6.E
4.5	Blood Type Determination	If a laboratory performs blood type testing, the laboratory must follow manufacturer's directions for materials and equipment used in testing.	The committee determined this is an important requirement to add for blood type determination.	4.9
4.6	Preservation of Excess Specimens	If a laboratory performs testing to determine donor and recipient histocompatibility, then the laboratory must preserve enough specimen from the deceased donor for at least five years.	The current policy requires preserving excess tissue typing materials from kidney donors and recipients. The committee determined that preserving excess specimens from a donor and recipient is important for <u>all</u> transplants (not exclusive to kidney) for purposes of subsequent testing.	4.14

Section	Policy Title	Changes	Reason	Policies Incorporated
4.7	HLA Antigen Values and Split Equivalences	The Histocompatibility must review and recommend any changes needed to the tables on or before June 1 of each year.	The committee determined that a deadline should be set for when the committee’s review and recommended changes for the HLA Equivalency Tables is due. Specifying a date has the effect of this becoming an annual committee project that does not need to be reviewed/approved by the OPTN/UNOS Policy Oversight Committee.	4.3
4.8	Reference Tables of HLA Antigen Values and Split Equivalences	No changes.		4.15

Expected Impact on Living Donors or Living Donation:

Not applicable

Expected Impact on Specific Patient Populations:

Histocompatibility testing is important for all organ transplant candidates. To the extent that this proposal improves accuracy in HLA typing, it will be especially important for sensitized candidates.

Expected Impact on OPTN Key Goals and Adherence to OPTN Final Rule:

This proposal furthers the following OPTN strategic goals:

- promote transplant safety by requiring histocompatibility laboratories to accurately determine and report HLA typing, resolve HLA typing discrepancies in a timely manner, and preserve excess specimens when performing histocompatibility testing that results in transplantation of a deceased donor organ
- promote the efficient management of the OPTN by simplifying policies governing histocompatibility testing for solid organ transplantation and eliminating policies that are outdated or adequately addressed in the standards required by histocompatibility accrediting agencies (ASHI and CAP)

Plan for Evaluating the Proposal:

The Committee will review donor and recipient HLA discrepancies more frequently and will monitor types of discrepancies and reported reasons pre- and post-policy implementation.

Additional Data Collection:

No additional data collection will be required as a result of these policy changes.

Expected Implementation Plan:

If approved by the OPTN Board of Directors, this proposal will become effective September 1, 2014, with the exception of the new deadline for HLA typing discrepancies, which will become effective pending programming and notice to the membership.

After a laboratory submits donor and recipient histocompatibility forms post-transplant, the laboratory will receive a report in TIEDI if any HLA typing discrepancies are flagged by UNOS that involve the individual laboratory. Laboratories will have 30 days from the date of notification to resolve these discrepancies. The current method for resolving a discrepancy is to indicate in the system a reason for the discrepancy. The Committee has requested programming for a field to display the number of days remaining to resolve the discrepancy.

Communication and Education Plan:

Not applicable

Compliance Monitoring:

UNOS will establish a contract agreement with ASHI and CAP to review histocompatibility laboratories' compliance with OPTN policies. Identified noncompliance will be reported to the Membership and Professional Standards Committee for further review.

Policy or Bylaw Proposal:

RESOLVED, that Policies 4.1 through 4.15 are stricken in their entirety and replaced with new Policies 4.1 (HLA Typing), Table 4.1 (HLA Typing Requirements for Deceased Donors), Table 4.2 (HLA Typing Requirements for Candidates), 4.2 (Resolving Discrepant Donor and Recipient HLA Typing Results), 4.3 (Antibody Screening and Reporting), 4.4 (Crossmatching), 4.5 (Blood Type Determination), 4.6 (Preservation of Excess Specimens), and 4.7 (HLA Antigen Values and Split Antigen Equivalences); and that modifications to Policies 2.8.C (Required Information for Deceased Heart Donors), 2.8.D (Required Information for Deceased Lung Donors), and 4.16 (Reference Tables of HLA Antigen Values and Split Equivalences), as set forth in Exhibit A, are hereby approved, effective September 1, 2014.

2.8.C Required Information for Deceased Heart Donors

The host OPO must provide all the following additional information for all deceased donor heart offers:

1. Height
2. Weight
3. Vital signs, including blood pressure, heart rate, and temperature
4. History of treatment in hospital including vasopressors and hydration
5. Cardiopulmonary, social, and drug activity histories
6. Details of any documented cardiac arrest or hypotensive episodes
7. 12-lead interpreted electrocardiogram
8. Arterial blood gas results and ventilator settings
9. Cardiology consult or echocardiogram, if the hospital has the facilities
10. Human leukocyte antigen (HLA) typing if requested by the transplant hospital, including A, B, Bw4, Bw6, C, DR, DR51, DR52, DR53, and DQB antigens

For heart deceased donors, if a transplant hospital requires donor HLA typing prior to submitting a final organ acceptance, it must communicate this request to the OPO and document the request. ~~†The transplant hospital OPO must provide the HLA information required in the table list above and document this request that the information was provided to the transplant program.~~ The transplant hospital may request HLA-DPB typing, but the OPO need only provide it if its affiliated laboratory performs related testing. ~~The OPO must document HLA typing provided to the requesting transplant hospital.~~

2.8.D Required Information for Deceased Lung Donors

The host OPO must provide all the following additional information for all deceased lung donor offers:

1. Height
2. Weight
3. Vital signs, including blood pressure, heart rate, and temperature
4. History of medical treatment in hospital including vasopressors and hydration
5. Smoking history
6. Cardiopulmonary, social, and drug activity histories
7. Arterial blood gases and ventilator settings on 5 cm/H2O/PEEP including PO2/FiO2 ratio and preferably 100% FiO2, within 2 hours prior to the offer
8. Bronchoscopy results
9. Chest x-ray interpreted by a radiologist or qualified physician within 3 hours prior to the offer
10. Details of any documented cardiac arrest or hypotensive episodes
11. Sputum gram stain, with description of sputum
12. Electrocardiogram
13. Echocardiogram, if the OPO has the facilities

- HLA typing if requested by the transplant hospital, including A, B, Bw4, Bw6, C, DR, DR51, DR52, DR53, and DQB antigens

If the host OPO cannot perform a bronchoscopy, it must document that it is unable to provide bronchoscopy results and the receiving transplant hospital may perform it. The lung recovery team may perform a confirmatory bronchoscopy provided unreasonable delays are avoided and deceased donor stability and the time limitations in Policy 5.5.B: Time Limit for Acceptance are maintained.

For lung deceased donors, if a transplant hospital requires donor HLA typing prior to submitting a final organ acceptance, it must communicate this request to the OPO and document the request. The transplant hospital OPO must provide the HLA information required in the table list above and document this request that the information was provided to the transplant program. The transplant hospital may request HLA-DPB typing, but the OPO need only provide it if its affiliated laboratory performs related testing. The OPO must document HLA typing provided to the requesting transplant hospital.

Policy 4: Histocompatibility

4.1 HLA Typing

4.1.A Requirements for Performing and Reporting HLA Typing

Laboratories must do *all* of the following:

- Perform HLA typing on all potential transplant recipients and donors when requested by a physician or other authorized individuals.
- Ensure that all HLA typing is accurately determined and report HLA typing results to the OPO or Transplant Program according to the turnaround time specified in the written agreement between the laboratory and any affiliated OPO or transplant program.
- Report serological split level and molecular typing results to the OPO for all required HLA types according to Table 4.1 *HLA Typing Requirements for Deceased Donors*, whenever the lab performs HLA typing on deceased kidney, kidney-pancreas, and pancreas donors.
- Report HLA typing results to the Transplant Program for all required HLA types, according to Table 4.2 *HLA Typing Requirements for Candidates*, whenever the laboratory performs HLA typing on candidates.

Table 4.1 shows HLA types required to be reported for deceased donors.

Table 4.1 HLA Typing Requirements for Deceased Donors

<u>Organ</u>	<u>A</u>	<u>B</u>	<u>Bw4</u>	<u>Bw6</u>	<u>C</u>	<u>DR</u>	<u>DR51</u>	<u>DR52</u>	<u>DR53</u>	<u>DPB</u>	<u>DQB</u>
<u>Kidney</u>	● —	● —	● —	● —	● —	● —	● —	● —	● —		● —
<u>Pancreas</u>	● —	● —	● —	● —	● —	● —	● —	● —	● —		● —
<u>Kidney-Pancreas</u>	● —	● —	● —	● —	● —	● —	● —	● —	● —		● —

<u>Organ</u>	<u>A</u>	<u>B</u>	<u>Bw4</u>	<u>Bw6</u>	<u>C</u>	<u>DR</u>	<u>DR51</u>	<u>DR52</u>	<u>DR53</u>	<u>DPB</u>	<u>DQB</u>
<u>Heart*</u>	● —	● —	● —	● —	● —	● —	● —	● —	● —	● —	● —
<u>Lung*</u>	● —	● —	● —	● —	● —	● —	● —	● —	● —	● —	● —

* For deceased heart and lung donors, if a transplant hospital requires donor HLA typing prior to submitting a final organ acceptance, it must communicate this request to the OPO and document this request. The OPO must provide the HLA information required in the table above and document that the information was provided to the transplant program. The transplant hospital may request HLA-DPB typing, but the OPO need only provide it if its affiliated laboratory performs related testing.

Table 4.2 shows HLA types required to be reported for candidates.

Table 4.2: HLA Typing Requirements for Candidates

<u>Organ</u>	<u>A</u>	<u>B</u>	<u>Bw4</u>	<u>Bw6</u>	<u>DR</u>
<u>Kidney alone</u>	● —	● —	● —	● —	● —
<u>Pancreas alone</u>	● —	● —	● —	● —	● —
<u>Kidney-Pancreas</u>	● —	● —	● —	● —	● —

4.2 Resolving Discrepant Donor and Recipient HLA Typing Results

Laboratories must submit donor and recipient histocompatibility forms to the OPTN Contractor after transplant according to Policy 18.0 Data Submission Requirements. After laboratories submit donor and recipient HLA typing results to the OPTN Contractor, the OPTN Contractor will provide a report to the laboratories including any discrepant HLA typing results.

The report includes all of the following donor information:

1. Donor id
2. HLA typing results
3. Date of tests
4. Test methods
5. Laboratory Identifiers
6. OPO Identifier (if applicable)

The report includes all of the following recipient information:

1. SSN
2. HLA typing results
3. Date of tests
4. Test methods
5. Laboratory identifier

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

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

4.3 Antibody Screening and Reporting

The laboratory must screen a patient for the presence of anti-HLA antibodies if requested by a physician or other authorized individuals.

Whenever a laboratory is performing an antibody screening, the laboratory must do *all* of the following:

- Report anti-HLA antibodies identified to the candidate's requesting provider
- Use at least one solid phase immunoassay using purified HLA molecules

4.4 Crossmatching

D.4 (A) Crossmatching for Kidney Transplants

Laboratories performing histocompatibility testing for kidney transplants or multi-organ transplants in which a kidney is to be transplanted must perform a final crossmatch and report the results to the Transplant Program before transplant.

D.4 (B) General Crossmatching Requirements

Whenever a laboratory is performing a crossmatch, the laboratory must do *all* of the following:

1. Perform a crossmatch according to the terms specified in the written agreement between the laboratory and the OPO or transplant program if a physician or other authorized individual requests it.
2. Perform crossmatches with potential donor T lymphocytes to identify class I anti-HLA antibodies.
3. Perform crossmatches with potential donor B lymphocytes to identify class I and class II anti-HLA antibodies using a method that distinguishes between reactions with T and B lymphocytes.
4. Use a crossmatching technique with increased sensitivity.

4.5 Blood Type Determination

If a laboratory performs blood type testing, the laboratory must:

1. Follow manufacturer's directions for materials and equipment used in testing.

2. Perform testing in compliance with federal regulations.

4.6 Preservation of Excess Specimens

If a laboratory performs testing to determine histocompatibility between a donor and recipient, then the laboratory must preserve enough specimen from the deceased donor to perform subsequent testing for at least five years after the transplant.

4.7 HLA Antigen Values and Split Equivalences

HLA matching of A, B, and DR locus antigens is based on the antigens which are listed in Policy 4.8 Reference Tables of HLA Antigen Values and Split Equivalences. The Histocompatibility Committee must review and recommend any changes needed to the tables on or before June 1 of each year. For matching purposes, split antigens not on this list will be indicated on the waiting list as the parent antigens and will match only with the corresponding parent antigens.

4.8 Reference Tables of HLA Antigen Values and Split Equivalences

Tables 4-63, 4-74, and 4-85 show patient-donor antigen combination and whether they are mismatches. For each candidate antigen, the donor antigens that are not mismatched are listed below. All other combinations are considered mismatches. Antigens with an * indicate an allele that may not have a World Health Organization (WHO)-approved serologic specificity. Antigens given **99 means the patient locus was not tested.

Table 4-63: HLA A Matching Antigen Equivalences

<i>Patient A Locus Antigen</i>	<i>Equivalent Donor Antigens</i>	<i>Patient A Locus Antigen</i>	<i>Equivalent Donor Antigens</i>	<i>Patient A Locus Antigen</i>	<i>Equivalent Donor Antigens</i>
1	1	28	28	68	68
2	2, 203	29	29	69	69
3	3	30	30	74	74
9	9	31	31	80	80
10	10	32	32	203	203, 2
11	11	33	33	210	210, 2
19	19	34	34	2403	2403, 24
23	23	36	36	*6601	*6601, 66
24	24, 2403	43	43	*6602	*6602, 66
25	25	66	66, *6601, *6602	** 99	(No equivalent)
26	26				

Table 4-74: HLA B Matching Antigen Equivalences

Patient B Locus Antigen	Equivalent Donor Antigens
5	5
7	7, 703
8	8
12	12
13	13
14	14, 64, 65
15	15
16	16
17	17
18	18
21	21
22	22
27	27
35	35
37	37
38	38
39	39, 3901, 3902, *3905
40	40, 61
41	41
42	42
44	44
45	45
46	46

Patient B Locus Antigen	Equivalent Donor Antigens
47	47
48	48
49	49
50	50, 4005
51	51, 5102, 5103
52	52
53	53
54	54
55	55
56	56
57	57
58	58
59	59
60	60
61	61
62	62
63	63
64	64
65	65
67	67
70	70, 71, 72
71	71, 70
72	72, 70

Patient B Locus Antigen	Equivalent Donor Antigens
73	73
75	75, 15
76	76, 15
77	77, 15
78	78
81	81
82	82, *8201
703	703, 7
*0804	*0804, 8
*1304	*1304, 15, 21, 49, 50
2708	2708, 27
3901	3901, 39
3902	3902, 39
*3905	*3905, 39
4005	4005, 50
5102	5102, 51, 53
5103	5103, 51
7801	7801
*8201	*8201, 82
** 99	(No equivalent)

Table 4-8: HLA DR Matching Antigen Equivalences

<i>Patient DR Locus Antigen</i>	<i>Equivalent Donor Antigens</i>	<i>Patient DR Locus Antigen</i>	<i>Equivalent Donor Antigens</i>	<i>Patient DR Locus Antigen</i>	<i>Equivalent Donor Antigens</i>
1	1, 103	9	9	16	16
2	2	10	10	17	17
3	3	11	11	18	18
4	4	12	12	103	103, 1
5	5	13	13	1403	1403, 14, 6
6	6	14	14, 1403, 1404	1404	1404, 14, 6
7	7	15	15	** 99	(No equivalent)
8	8				

* Indicates an allele; may not have a WHO-approved serologic specificity

** Code 99 means not tested

Examples of how “Matching Antigen Equivalences” works:

If patient has B70: Donors with B70, B71, and B72 are considered not mismatched.

If patient has B71: Donors with B71 and B70 are considered not mismatched. Donors with B72 are considered mismatched.

Table 4-95: HLA A Unacceptable Antigen Equivalences

<i>Patient's Unacceptable A Locus Antigen</i>	<i>Donor Equivalent Antigens</i>	<i>Patient's Unacceptable A Locus Antigen</i>	<i>Donor Equivalent Antigens</i>	<i>Patient's Unacceptable A Locus Antigen</i>	<i>Donor Equivalent Antigens</i>
1	1	10	10, 25, 26, 34, 66, *6601, *6602, 43	24	24
2	2, 203, 210	11	11	25	25
3	3	19	19, 29, 30, 31, 32, 33, 74	26	26
9	9, 23, 24, 2403	23	23	28	28, 68, 69
				29	29
				30	30

<i>Patient's Unacceptable A Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
31	31
32	32
33	33
34	34
36	36
43	43

<i>Patient's Unacceptable A Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
66	66, *6601, *6602
68	68
69	69
74	74
80	80

<i>Patient's Unacceptable A Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
203	203
210	210
2403	2403
*6601	*6601
*6602	*6602

Table 4-406: HLA B Unacceptable Antigen Equivalences

<i>Patient's Unacceptable B Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
5	5, 51, 5103, 52,78
7	7, 703
8	8
12	12, 44, 45
13	13
14	14, 64, 65
15	15, 62, 63, 75, 76, 77
16	16, 38, 39
17	17, 57, 58
18	18
21	21, 49, 50, 4005

<i>Patient's Unacceptable B Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
22	22, 54, 55, 56
27	27
35	35
37	37
38	38
39	39, 3901, 3902, *3905
40	40, 60, 61
41	41
42	42
44	44
45	45
46	46
47	47

<i>Patient's Unacceptable B Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
48	48
49	49
50	50, 4005
51	51, 5103
52	52
53	53
54	54
55	55
56	56
57	57
58	58
59	59
60	60
61	61

<i>Patient's Unacceptable B Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
62	62
63	63
64	64
65	65
67	67
70	70, 71, 72
71	71
72	72
73	73
75	75
76	76
77	77
78	78

<i>Patient's Unacceptable B Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
81	81
82	82, *8201
703	703
*0804	*0804
*1304	*1304
2708	2708
3901	3901
3902	3902
*3905	*3905
4005	4005, 50
5102	5102
5103	5103
7801	7801, 78

<i>Patient's Unacceptable B Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
*8201	*8201, 82
Bw4	Bw4, 5, 13, 17, 27, 37, 38, 44, 47, 49, 51, 52, 53, 57, 58, 59, 63, 77
Bw6	Bw6, 7, 8, 14, 18, 22, 2708, 35, 39, 40, 41, 42, 45, 48, 50, *4005, 54, 55, 56, 60, 61, 62, 64, 65, 67, 70, 71, 72, 75, 76, 78, 81, 82

Table 4-447: HLA C Unacceptable Antigen Equivalences

<i>Patient's Unacceptable C Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
w1	w1
w2	w2
w3	w3, w9, w10
w4	w4
w5	w5

<i>Patient's Unacceptable C Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
w6	w6
w7	w7
w8	w8
w9	w9
w10	w10
*12	*12

<i>Patient's Unacceptable C Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
*14	*14
*15	*15
*16	*16
*17	*17
*18	*18

Table 4-428: HLA DR Unacceptable Antigen Equivalences

<i>Patient's Unacceptable DR Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
1	1
2	2, 15, 16
3	3, 17, 18
4	4
5	5, 11, 12
6	6, 13, 14, 1403, 1404
7	7
8	8

<i>Patient's Unacceptable DR Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
9	9
10	10
11	11
12	12
13	13
14	14, 1403, 1404, 6
15	15
16	16

<i>Patient's Unacceptable DR Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
17	17
18	18
103	103
1403	1403
1404	1404
51*	51
52*	52
53*	53

Table 4-139: HLA DQ Unacceptable Antigen Equivalences

<i>Patient's Unacceptable DQ Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
1	1, 5, 6
2	2
3	3, 7, 8, 9

<i>Patient's Unacceptable DQ Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
4	4
5	5, 1
6	6, 1

<i>Patient's Unacceptable DQ Locus Antigen</i>	<i>Donor Equivalent Antigen</i>
7	7, 3
8	8, 3
9	9, 3

*** Indicates an allele; may not have a WHO-approved serologic specificity**

***** Please refer to the end of this section for information**

Examples of how “Unacceptable Antigen Equivalences” works:

If a patient has B70 listed as an “unacceptable antigen”: Donors typed as B70, B71, and B72 are considered unacceptable. Donors typed as B73 and B75 are considered acceptable.

Additional Unacceptable Antigen Equivalences to be used in the Calculated PRA Only:

DR51 should also include DR2, DR15, DR16.

DR52 should also include DR3, DR5, DR6, DR11, DR12, DR13, DR14, DR17, DR18.

DR53 should also include DR4, DR7, DR9.

History

Appendix 3A: HLA Antigen Values and Split Equivalence: 9/17/2007; 11/9/2010

Appendix 3D: Guidelines for the Development of Joint Written Agreements between Histocompatibility Laboratories and Transplant Programs: 11/17/2008; 6/26/2012

Policy 4: Histocompatibility:

Notes

- ~~For donor crossmatching requirements, see *Policy 2.3: Evaluating and Screening Potential Deceased Donors*.~~
- For heart donor HLA requirements, see *Policy 6: Allocation of Hearts and Heart-Lungs*.
- For candidate HLA requirements, see *Policy 3: Candidate Registrations, Modifications, and Removals*.
- For KPD histocompatibility requirements, see *Policy 13: Kidney Paired Donation (KPD)*.
- For histocompatibility reporting requirements see *Policy 18: Data Submission Requirements*.
- For the release of HLA information, see Policies *19.11: Release of Human Leukocyte Antigen (HLA) Type of a Recipient's Prior Donor* and *19.12: Release of HLA Type of Donors and Recipients with Laboratory Name and Identifier*.

Policy 4: Histocompatibility

4.1 Guidelines for Written Contracts between Histocompatibility Laboratories and Transplant Programs

Histocompatibility laboratories must have written contracts with each transplant program they serve. These guidelines summarize the recommended elements to be included in these agreements.

4.1.A Recommended Elements for Histocompatibility Contracts

Written agreements between histocompatibility laboratories and transplant programs should include *all* of the following elements:

1. A process to obtain accurate and current sensitization history for each patient.
2. The assay format that will be used for antibody screening and for crossmatching.
3. The frequency of periodic sample collection.
4. The frequency of antibody screenings.
5. The criteria and a process for establishing a risk category for each patient and the crossmatching strategy for each established risk category.
6. The criteria and a process for determining unacceptable antigens or acceptable antigens used during organ allocation.
7. A process for monitoring recipients post-transplant, or for monitoring desensitization protocols.
8. A process for blood type verification according to *Policy 3.3: Candidate Blood Type Determination and Reporting before Waiting List Registration*, if the laboratory registers candidates for the transplant program.

4.1.B Sensitization History

Laboratories should evaluate the data in *Table 4-1* below when determining sensitization history.

Table 4-1: Determining Sensitization

If this event occurred:	Then the laboratory should evaluate:	And note:
Previous graft of solid organ, bone or tendon	Date of transplant and organs transplanted	
	Date of graft loss	Dates of graft removal, re-transplant, and return to dialysis.
	Cause of graft loss	
	HLA typing of donors	Used to identify potential unacceptable antigens.
	Rejection history, history of delayed function, history of non-compliance, or reduced immune-suppression due to infection	
Pregnancy	Number, year of each occurrence	Gravida/para-

If this event occurred:	Then the laboratory should evaluate:	And note:
Transfusions	Number, type of product, month and year of each occurrence	
Assist device placement	Type of device, date of placement, duration of treatment	Primarily for thoracic transplantation.
Disease	Identification of diseases causing end-stage organ failure	Auto-immunity may invalidate some laboratory assays.
Acute infections	Viral infection or bacterial infection requiring antibiotics	If the infection occurred since last antibody screening test. Induction of cells or antibodies with specificity for HLA or non-specific activation of memory.
Chronic infections	Viral infection	Response to tolerance induction protocols.
Vaccinations	Type, date of each occurrence	Time passed since last antibody screening test.

4.1.C — Detection of Antibodies

An antibody history is used in the antibody screening and crossmatching of donors and recipients. Laboratories may use the tests in *Table 4-2* below to create an antibody history and assess sensitization in transplant candidates.

Table 4-2: Assays to Identify Antibody to HLA: Screening, Specificity, or Crossmatching

This assay:	Is used:
Standard complement-dependent lymphocytotoxicity (CDC)	To detect IgG antibodies known to cause hyperacute rejection <i>and</i> for panel measurements or crossmatch

This assay:	Is used:
Anti-human Globulin-enhanced cytotoxicity (AHG-CDC)	To improve detection of weak or low level antibodies and for panel measurements or crossmatch
Enzyme-Linked Immune Sorbent Assay (ELISA)-based assays: <ul style="list-style-type: none"> • Mixed antigens • Cell equivalents • Single antigens • Solubilized cells 	To provide a more sensitive test that does not depend on complement fixation: <ul style="list-style-type: none"> • For monitoring • To measure specificity • To measure specificity • For crossmatch
Flow cytometry-based assays: <ul style="list-style-type: none"> • Cell-based • Microparticle-based soluble antigens • Microparticle-based single HLA-antigen beads 	The most sensitive test for antibody: <ul style="list-style-type: none"> • For crossmatch or panel measurements • For panel measurements without background from cell membranes • For high resolution antibody identification
Determine isotype of antibody: <ul style="list-style-type: none"> • IgG or IgM • Complement-fixing IgG? 	For panel measurements or crossmatches
Rule out contribution by autoantibody: <ul style="list-style-type: none"> • Treatment of serum • Autologous cells 	For panel measurements or crossmatches

Assays should be used to:

1. Identify whether a patient has circulating antibodies to HLA class I and class II antigens:
 - Initial serial screening should include cytotoxicity and more sensitive tests to identify patients with antibodies.
 - Several sera should be evaluated to establish a baseline.
2. Determine antibody specificity in patients with detectable circulating antibodies using some combination of:
 - A panel of representative cells for cytotoxicity.
 - ELISA tests for specificity.
 - Antigen-coated microparticles.
3. Monitor patients who do not currently have antibodies for the development of antibodies using:
 - Periodic screening of unsensitized patients to detect appearance of anti-HLA antibodies.
 - Characterization of antibody specificity.

4.1.D — Periodic Sample Collection

Laboratories should collect monthly serum samples for candidates and maintain the samples to develop an antibody history and to facilitate final crossmatches.

4.1.E — Crossmatching Strategies

The Histocompatibility Laboratory and the Transplant Program should collaborate to develop specific strategies for evaluating the relative risk of a rejection. When developing these strategies,

the following should also be considered:

1. In thoracic transplantation, prospective crossmatches are not commonly used for patients with no detectable HLA antibodies.
2. In kidney transplantation, there may be exceptional cases when it is better to proceed with the transplant before a crossmatch can be completed. If after careful consideration a pre-transplant crossmatch is not completed, then the laboratory should perform a peri-transplant or retrospective crossmatch to guide post-transplant care.

Table 4-3 below lists elements that laboratories should include in developing crossmatching strategies. Strategies should be tailored to the level of risk.

Table 4-3: Recommended Elements for Crossmatching Strategies

Element:	Options:
Selection of technique(s)	Refer to <i>Table 4-2: Assays to Identify Antibody to HLA: Screening, Specificity, or Crossmatching</i> .
Selection of serum	Stability of a candidate's antibody response incorporated into choice of time between serum collection and transplant. Use of historic serum.
Timing	Prior to transplant (number of hours or days). Peri-transplant or retrospective (number of hours or days). Timed to limit cold ischemia.

4.2 HLA Typing

Table 4-4 below provides the requirements of HLA typing of HLA A, B, Bw4, Bw6, C, DR, DR51, DR52, DR53, and DQB Antigens. Laboratories should report splits for all loci shown in *Policy 4.16: Reference Tables of HLA Antigen Values and Split Equivalences*.

Table 4-4: Requirements for HLA Typing

If a Laboratory:	Then the Laboratory Must:
Performs deceased donor typing for kidney, kidney-pancreas, pancreas, or pancreas islet allocation	Report serological split level and molecular typing results for all required antigens prior to organ offers.
Uses cytotoxicity techniques to perform HLA typing	Conform to all relevant standards in <i>Policy 4.8: Cytotoxicity Methods</i> .
Uses nucleic acid analysis, to perform HLA typing	Conform to all relevant standards in <i>Policy 4.10: Nucleic Acid Analysis</i> .
Uses alternative methods for HLA typing	Define the procedures, validate the procedures, and include sufficient controls to ensure accurate assignment of HLA types. The laboratory must conform to all relevant standards from the above sections.

4.2.A Typing Assignment

Laboratories must do *all* of the following:

1. Define each HLA antigen by a sufficient number of reagents to clearly define each antigen or allele group for which the laboratory tests.
2. Use a level of resolution of HLA typing that is appropriate for the clinical application.

- ~~3. Document the method of assignment of HLA phenotypes for each technique used.~~
- ~~4. Establish and adhere to a written policy that defines when antigen redefinition and retyping are required.~~
- ~~5. Maintain a list of antigens and alleles defined by each test used in the laboratory.~~

4.2.B — Reagent Validation

Laboratories must do *all* of the following:

- ~~1. Have cell or deoxyribonucleic acid (DNA) panels of known HLA class I and class II phenotype available to validate new typing reagents.~~
- ~~2. Document and confirm, by external or internal quality control testing, the specificity of typing reagents obtained locally or from other sources and used for preparation of local trays.~~
- ~~3. Establish and employ detailed policies and procedures for evaluations of new commercial reagents.~~
- ~~4. Evaluate each lot and shipment of new commercial reagents.~~
- ~~5. Validate techniques used to define HLA class I antigens, class II antigens, and alleles.~~

4.2.C — HLA Typing by Nucleic Acid Analysis

Laboratories must do *all* of the following:

- ~~1. Define the HLA alleles detected by each primer, probe, or template primer combination.~~
- ~~2. Test primers and probes with all alleles recognized by the World Health Organization's (WHO) *Nomenclature Committee for Factors of the HLA System*, if nucleotide sequences and reference DNA are readily available.~~
- ~~3. Have a process to recognize and document ambiguous combinations of alleles for each template, primer, or probe combination.~~

4.2.D — Typing by Sequenced Based Typing (SBT)

Laboratories must do *all* of the following:

- ~~1. Have sufficient specificity for a locus or allele to provide primary sequencing data for analysis.~~
- ~~2. Compare each unknown sequence with the sequences of all alleles recognized by the WHO *Nomenclature Committee for Factors of the HLA System* if the nucleotide sequences are readily available.~~
- ~~3. Maintain records that define the sequence database used to interpret the primary data. Laboratories must update this database at least annually. If a determined sequence has more than one possible interpretation of available data, then the report must indicate all possible allele combinations.~~

4.3 — HLA Antigen Values and Split Equivalences

~~HLA matching of A, B, and DR locus antigens is based on the antigens which are listed in *Policy 4.16: Reference Tables of HLA Antigen Values and Split Equivalences*. These tables will be updated annually by the Histocompatibility Committee. For matching purposes, split antigens not on this list will be indicated on the waiting list as the parent antigens and will match only with the corresponding parent antigens. Laboratories are encouraged to assign all splits.~~

~~Refer to *Tables 4-6, 4-7, 4-8, 4-9, 4-10, 4-11, 4-12, and 4-13* in this Policy to determine the candidate-donor antigen combinations reported and whether they are mismatched.~~

~~4.4 Resolving Discrepant Donor and Recipient HLA Typing Results~~

~~After laboratories report donor and recipient HLA typing results to the OPTN Contractor, the OPTN Contractor will provide a report to the laboratories including any discrepant HLA typing results. Laboratories must try to resolve these discrepancies.~~

~~The report includes all of the following donor information:~~

- ~~1. Donor ID~~
- ~~2. HLA typing result~~
- ~~3. Date of test~~
- ~~4. Test method~~
- ~~5. Laboratory Identifier~~
- ~~6. OPO Identifier (if applicable)~~

~~The report includes all of the following recipient information:~~

- ~~1. SSN~~
- ~~2. HLA typing result~~
- ~~3. Date of test~~
- ~~4. Test method~~
- ~~5. Laboratory identifier~~

~~The laboratory director or designated staff must contact the other laboratory director or designated staff to resolve the discrepancies. If a resolution is reached, the laboratory with the corrected typing results should report the corrected HLA typing to the OPTN Contractor as resolved. The laboratory must also identify the specific reason for the discrepant typing.~~

~~The OPTN Contractor will remove all discrepant flags from HLA typing results that have been resolved. Discrepancies that have not been resolved will remain flagged, and will be reviewed by the Histocompatibility Committee. The Histocompatibility Committee will review, at least annually, any outstanding discrepant typings recorded during the previous 12 months.~~

~~4.5 Antibody Screening~~

~~Table 4-5 below summarizes the requirements of antibody screening.~~

Table 4-5: Requirements for Antibody Screening

Laboratories performing assays using:	Must conform to standards in:
Cytotoxicity	<i>Policy 4.8: Cytotoxicity Methods</i>
Flow cytometry	<i>Policy 4.11.A: Instrument Standardization and Calibration and Policy 4.11.B: Flow Cytometric Crossmatch Technique</i>
ELISA techniques	<i>Policy 4.12: ELISA</i>
Solid phase multichannel arrays	<i>Policy 4.13: Solid Phase Multi-channel Arrays</i>

4.5.A — Techniques

Laboratories must do *all* of the following:

1. Determine the antibody specificities that can be identified by the techniques used.
2. Use a technique appropriate for the clinical application.
3. Use a method to detect antibodies to HLA class II antigens that distinguishes them from antibodies to HLA class I antigens.
4. Have a procedure in place to monitor and adjust for non-specific binding of antibody.
5. Use appropriate methods or controls to assess the impact of xenogeneic and monoclonal therapeutic antibodies.

4.5.B — Sera Testing

Laboratories must do *all* of the following:

1. Test sera at concentrations determined to be optimal for detection of antibodies to HLA antigens.
2. Document the dilutions in the test records.
3. Include an appropriate positive and negative control.

4.5.C — Panel and Target Selection

Laboratories must do *all* of the following:

1. Use a sufficient number of antigen panels that are in phenotypic distribution with respect to individual antigens or cross-reactive groups (CREGs) for the population served and for the intended use of the test results.
2. Maintain documentation of the HLA class I or class II phenotypes of the panel.
3. Have appropriate target cells or purified HLA molecules for all assays intended to provide information on HLA antibody specificity.
4. Have sufficient concentration, condition, and phenotype of target cells or purified HLA molecules to ensure that the antibodies being tested for (either HLA class I or class II) can be detected.

4.6 — Kidney and Pancreas Organ Transplantation

4.6.A — Personnel Requirements

If deceased donor transplants are performed, then the laboratory must have personnel for the required histocompatibility testing available 24 hours a day, seven days a week.

4.6.B — HLA Typing

Laboratories must perform prospective typing of donors and candidates for HLA-A, B, Bw4, Bw6, and DR antigens. In addition, laboratories must perform prospective typing of donors for HLA-DR51, DR52, DR53, C, and DQB antigens. Laboratories should perform prospective typing of candidates for HLA-C and DQB antigens and for DR51, DR52, DR53.

4.6.C — Antibody Screening

Laboratories must have *all* of the following:

1. A protocol in place to evaluate the extent of sensitization of each candidate at the time of initial evaluation and following potentially sensitizing events, based on the antibody characteristics that are clinically relevant to each Transplant Hospital's protocols.

2. ~~A program to periodically screen serum samples from each candidate for antibody to HLA antigens.~~
3. ~~A written protocol establishing the frequency of screening serum samples and data to support this policy.~~

Laboratories should do *all* of the following:

1. ~~Collect serum samples monthly.~~
2. ~~Test serum samples for antibody to HLA antigens.~~
3. ~~Consider information about antibody specificity when evaluating the patient for transplant.~~
4. ~~Use serum samples having defined class I or class II specificities in crossmatch testings.~~
5. ~~Identify, report, and distinguish from antibodies to non-HLA antigens, the HLA class I and class II specificity of antibodies.~~

4.6.D — Crossmatching

Laboratories must do *both*:

1. ~~Perform a prospective crossmatch when requested to by a physician or other authorized individuals, except when clinical circumstances prevent a prospective crossmatch.~~
2. ~~Have a joint written protocol with their transplant programs on transplant candidate crossmatching strategies. This protocol must also identify the clinical circumstances when a prospective crossmatch may be omitted.~~

4.6.E — Techniques

~~If a laboratory is determining donor-recipient compatibility, then the laboratory must use a crossmatching technique with increased sensitivity. Laboratories may also use the basic complement-dependent microlymphocytotoxicity test in addition to the crossmatching technique.~~

Laboratories must also:

1. ~~Perform crossmatches with potential donor T lymphocytes. Laboratories should also perform crossmatches with B lymphocytes using a method that distinguishes between reactions with T and reactions with B lymphocytes.~~
2. ~~Establish and follow a written protocol determining the serum used in the final crossmatch that is supported by published data or data generated in the laboratory. The protocol must consider or include historic and current sensitizing events.~~

4.6.F — Samples

Laboratories must do *both*:

1. ~~Test sera at a dilution that is optimal for each assay.~~
2. ~~Establish a policy for the storage and maintenance of recipient sera that defines the samples to be retained and the duration of storage.~~

4.7 — Other Organ and Islet Cell Transplantation

Laboratories must do *all* of the following:

1. ~~Establish a written protocol with their transplant programs on transplant candidate antibody screening, antibody identification, and crossmatching strategies.~~
2. ~~HLA type all potential transplant recipients and donors if a physician or other authorized individual requests it.~~

3. ~~Perform a prospective crossmatch when requested by a physician or other authorized individuals, except when clinical circumstances prevent a prospective crossmatch.~~
4. ~~Have a joint written policy with their transplant programs on transplant candidate crossmatching strategies. This protocol must also identify the clinical circumstances when a prospective crossmatch may be omitted.~~
5. ~~Use techniques with increased sensitivity in comparison with the National Institute of Health's (NIH) complement dependent microlymphocytotoxicity.~~
6. ~~Screen any patient for the presence of anti-HLA antibodies at initial evaluation and following sensitizing events if a physician or other authorized individual requests it and should also identify any unacceptable antigens.~~

4.8 Cytotoxicity Methods

4.8.A Percentage of Cell Killed

Laboratories must do *both*:

1. ~~Record the results for each cell-serum combination in a manner that indicates the approximate percent of cells killed.~~
2. ~~Have a written policy that assigns positive or negative results based on percentage of cells killed.~~

4.8.B Controls

Laboratories must include in each tray *both* of the following:

1. ~~At least one positive control serum that reacts with all cells expressing the class of antigens being tested.~~
2. ~~At least one negative control serum documented to be non-reactive under the specified test conditions.~~

~~Cell viability in the negative control well at the end of incubation must be sufficient to ensure accurate interpretation of results.~~

~~Laboratories must use appropriate methods or controls to assess the impact of xenogeneic or monoclonal therapeutic antibodies in patient samples on the cytotoxicity assay.~~

4.8.C Target Cells

~~If a laboratory is testing enriched cell populations, then the level of purity must be sufficient to ensure accurate interpretation of results.~~

4.8.D Complement

Laboratories must do *all* of the following:

1. ~~Test each lot and shipment of complement to determine that it mediates cytotoxicity in the presence of specific antibody, but is not cytotoxic in the absence of specific antibody.~~
2. ~~Establish and document optimal performance.~~
3. ~~Test complement separately for use with each type of target cell and with each test method used, since a different dilution or preparation may be required for optimal performance.~~

4.9 Blood Type Determination

~~If a histocompatibility laboratory performs blood type testing, the testing must be performed in compliance~~

with federal regulations.

If testing for the A₁ subgroup of type A blood is performed, the extract of *Dolichos biflorus* must be used at a dilution and with a technique documented not to agglutinate A₂ cells. Each assay or batch test run must include known A₁ and A₂ cells as controls.

If titration of anti-ABO antibodies is performed, the procedure and criteria for interpretation must be established and validated by the laboratory.

Laboratories using molecular techniques for blood type testing must conform to all pertinent standards in *Policy 4.10: Nucleic Acid Analysis*.

4.10 Nucleic Acid Analysis

4.10.A Nucleic Acid Extraction

Laboratories must do *all* of the following:

1. Purify nucleic acids by standard methods that have been validated in the laboratory.
2. Have written guidelines specifying the minimum acceptable sample.
3. Conform to established protocols and independently validate all testing procedures, if a laboratory performs tests without prior purification of nucleic acids.
4. Store samples under conditions that preserve their integrity if a laboratory does not use nucleic acids immediately after purification.
5. Use nucleic acids of sufficient quality to ensure reliable test results.

4.10.B Electrophoresis

Laboratories must include in each electrophoretic run negative and positive controls that are processed with each assay to verify adequate and appropriate polymerase chain reaction (PCR) amplification of target DNA.

If size of the resulting nucleic acid fragment is a critical factor in the analysis of the data, then the laboratory must do *all* of the following:

1. Load an amount of DNA in each lane that is within a range that ensures equivalent migration of DNA in all samples, including size markers.
2. Include in each gel size markers that produce discrete electrophoretic bands spanning and flanking the entire range of expected fragment sizes.

The laboratory must establish criteria for accepting validity of each gel and of each lane of the gel and determine and validate acceptable electrophoretic conditions for each assay.

4.10.C Analysis

Laboratories must do *all* of the following:

1. Specify acceptable limits of signal intensity for positive and negative results. If these are not achieved, corrective action is required.
2. Use two independent interpretations of primary data.
3. Validate automated systems and computer programs prior to use.
4. Test automated systems and computer programs routinely for accuracy and reproducibility of manipulations.

4.10.D—Template Amplification

4.10.D.i—Facilities and Equipment

Laboratories performing amplification of nucleic acids must do *all* of the following:

1. Establish and employ protocols to prevent DNA contamination using physical or biochemical barriers.
2. Perform pre-amplification procedures in a work area that excludes amplified nucleic acid that has the potential to serve as a template in any amplification assays performed in the laboratory.
3. Use dedicated equipment and reagents as well as physical and biochemical barriers to prevent nucleic acid contamination (carry-over).
4. Perform procedures to remove carry-over contamination from work areas used for manipulation of pre-amplification reagents or samples.
5. Add the template for subsequent amplifications in an area isolated by physical or chemical barriers from both the pre-amplification work area and post-amplification work areas, when using methods that utilize two consecutive steps of amplification.
6. Have dedicated pipettors for each work area. Positive displacement pipettes or filter barrier tips are recommended for pre-amplification and secondary amplification work areas.
7. Use thermal cycling instruments that precisely and reproducibly maintain the appropriate temperature of samples.
8. Verify the accuracy of temperature control for samples at least every 6 months.
9. Monitor incubators and water baths for accurate temperature maintenance every time the assay is performed.

4.10.D.ii—Reagents

All reagents used in the amplification assay must:

1. Be dispensed in aliquots for single use or be dispensed in aliquots for multiple uses if documented to be free of contamination at each use.
2. Not expose reagents used for initial amplification to post-amplification work areas.
3. Store reagents used for secondary amplification in an area that prevents carry-over contamination.

4.10.E—Primers

Primers must be stored under conditions that maintain specificity and sensitivity. Conditions that influence the specificity or quantity of amplified product must be demonstrated to be satisfactory for each set of primers.

Laboratories must also do *all* of the following:

1. Have a policy for quality control of each lot and shipment of primers using reference or well-characterized material.
2. Validate the specificity and robustness of the detection method for labeled primers.
3. Confirm periodically the performance of reagents stored for extended periods.

4.10.F—Amplification Templates

Samples containing nucleic acids that will be amplified must be stored under conditions that do not result in artifacts, inhibition of the amplification reaction, and exposure to post-amplification

~~work areas or any other sources of carry-over contamination. The acceptable range for the amount of target must be specified and validated.~~

4.10.G — Contamination

~~Nucleic acid contamination must be monitored for the most common amplification products that are produced in the laboratory. Routine wipe tests of pre-amplification work areas must be performed. Monitoring must be performed using a method that is at least as sensitive as routine test methods. If amplified product is detected, the area must be cleaned to eliminate the contamination and retested. Corrective measures must be taken to prevent future contamination.~~

~~At least one negative control (no nucleic acid) must be included in each amplification assay. Testing of open tubes in the work area is recommended.~~

4.10.H — Controls and Quality Assurance

~~Laboratories must also do *all* of the following:~~

- ~~1. Monitor the quantity of specific amplification products.~~
- ~~2. Specify criteria for accepting or rejecting an amplification assay.~~
- ~~3. Include controls to detect amplification in every amplification mixture, if presence of an amplified product is used as the end result.~~
- ~~4. Monitor amplification specificity on a periodic basis, if presence of an amplified product is used as the end result.~~
- ~~5. Monitor the variation in the amount of amplified product (e.g., hybridization with a consensus probe or gel electrophoresis), if an amplified product is used as a nucleic acid target.~~
- ~~6. Specify the acceptable range for the amount of test DNA, if an amplified product is used as a nucleic acid target.~~

4.10.I — Technique-Specific Standards

4.10.I.i — Oligonucleotide Probe Assays

~~Laboratories must also do *all* of the following:~~

- ~~1. Define the specificity and target sequence of oligonucleotide probes.~~
- ~~2. Store oligonucleotide probes under conditions that maintain specificity and sensitivity.~~
- ~~3. Use oligonucleotide probes under empirically determined conditions that achieve the defined specificity.~~
- ~~4. Perform quality control testing to confirm specificity for each lot and shipment of probe. Use reference material for quality control whenever possible.~~
- ~~5. Establish and document that oligonucleotide probe specificity and detection method sensitivity is reproducible before results are reported.~~
- ~~6. Perform hybridization under empirically determined conditions that achieve the defined specificity.~~
- ~~7. Validate a procedure for reuse of nucleic acids (probes or targets) bound to solid supports or in solution.~~
- ~~8. Use controls to ensure sensitivity and specificity of the assays are unaltered.~~

4.10.I.ii — Sequence Specific Amplification

~~Each amplification reaction must include internal controls to detect technical failures, such as additional primers or templates that produce a product that can be distinguished from the typing product.~~

4.10.J — Other Techniques

Appropriate controls must be included for each component of the test.

4.11 Flow Cytometry

4.11.A — Instrument Standardization and Calibration

Laboratories must also do *all* of the following:

1. Run an optical standard, consisting of latex beads or other uniform particles, to ensure proper focusing and alignment of all lenses in the path for both the exciting light source and signal (light scatter or fluorescence, etc.) detectors.
2. Run standards for each fluorochrome used to ensure adequate amplification of the fluorescent signals. These fluorescent standards may be incorporated in the beads or other particles used for optical standardization, or may be a separate bead or fixed cell preparation.
3. Run both the optical and fluorescent standards each time the instrument is turned on and at any time maintenance, adjustments, or problems have occurred during operation that could potentially affect instrument function.
4. Record the results of optical focusing and alignment in a daily quality control log.
5. Establish threshold values for acceptable optical and fluorescent standardization results for all relevant signals for each instrument used.
6. Have a written protocol detailing the corrective action required if a particular threshold value cannot be attained.
7. Use an appropriate procedure to compensate for overlap in emission spectra if performing analyses that require the simultaneous use of two or more fluorochromes.
8. Record laser power output and current input, in amplitudes, daily for each instrument.
9. Document acceptable thresholds and corrective action protocols.

4.11.B — Flow Cytometric Crossmatch Technique

Laboratories must also do *all* of the following:

1. Ensure the appropriate definition and purity of cell populations by the use of either a multi-color technique or other documented method.
2. Assess the binding of human immunoglobulin using a fluorochrome labeled reagent such as either an F(ab')₂ anti-human IgG that is specific for the Fc region of the heavy chain or other documented method.
3. Base crossmatch results for a specific cell population on the use of a monoclonal antibody that detects an appropriate cluster designated antigen.
4. Establish and document the optimum serum to cell ratio.

4.11.C — Controls

The negative control must be human serum documented to be non-reactive against the crossmatch target cells.

The positive control must be human antibody of the appropriate isotype for the assays and specific for the antigens that are targeted in the crossmatch. Positive controls must be used at a dilution appropriate for the assay, and must react with appropriate target cells from all humans.

The anti-human immunoglobulin reagent must be titered to determine the dilution with optimal activity (signal to noise ratio). If a multicolor technique is employed, the reagent must not demonstrate cross reactivity with the other immunoglobulin reagents used to label the cells.

Regardless of the method used for reporting raw data (mean, median, mode channel shifts, or quantitative fluorescence measurements), each laboratory must establish its own threshold for discriminating positive reactions. Any significant change in protocol, reagents, or instrumentation requires repeat determination of the positive threshold.

4.11.D— Interpretation

Laboratories must also do *both*:

1. Define the criteria used to define positive and negative crossmatches.
2. Use appropriate methods or controls to assess the impact of xenogeneic and monoclonal therapeutic antibodies on flow crossmatches.

4.11.E— Immunophenotyping By Flow Cytometry

Terminology used must conform to the most recent publication of the International Workshop of Differentiation Antigens of Human Leucocytes or other appropriate scientific organizations.

4.11.F— Cell Preparation

The method used for cell preparation must yield enough viable cells to ensure accurate test results. For internal labeling, the method used to allow fluorochrome labeled antibodies to penetrate the cell membrane must be documented to be effective.

4.11.G— Quality Control

Specificity controls, consisting of appropriate cell types known to be positive for selected standard antibodies must be run often enough to assure the proper performance of reagents.

A negative reagent control or controls must be identified for each test cell preparation. It is recommended that this control consist of monoclonal antibodies of the same species and subclass and be prepared and purified in the same way as the monoclonal used for phenotyping. For indirect labeling, it is recommended that the negative control reagent be an irrelevant primary antibody and the same secondary antibodies be conjugated with the same fluorochromes used. For direct labeling, it is recommended that the negative control reagent be an irrelevant antibody conjugated with the same fluorochrome and at the same fluorochrome: protein ratio used in all relevant test combinations.

Laboratories must also do *all* of the following:

1. Define acceptable time periods between processing, labeling and analysis of samples. Treat control samples alike.
2. Use gating strategies to assure that the population of interest is being selected without significant contamination.
3. Draw conclusions about abnormal proportions or abnormal numbers of cells bearing particular internal or cell surface markers only in comparison with local control data obtained with the same instrument, reagents and techniques.
4. Take into consideration the determination of percent positives of the negative control reagent.

4.11.H— Reagents

Laboratories must also do *all* of the following:

1. Have a policy to validate the specificity of monoclonal antibodies, either by using appropriate controls or by testing in parallel with previous lots.
2. Determine the quantities of reagents used for each test sample by the manufacturer's

~~recommendations or from published data, and whenever possible, that are verified by the laboratory using titration.~~

- ~~3. Process monoclonal antibodies, that have been reconstituted from lyophilized powder form for storage at 4°C, according to the manufacturer's instructions or locally documented procedures, to remove microaggregates prior to use in preparation of working stains.~~

4.12 ELISA

4.12.A The ELISA Reader

Laboratories must also do *all* of the following:

- ~~1. Have a reader with a light source and filter that produces the intensity and wavelength of light required for the test system.~~
- ~~2. Perform and document calibration and verification of plate alignment and instrument linearity according to the manufacturer's instructions or at least once every 6 months and must be documented.~~
- ~~3. Check and document monthly the performance of the microplate washer, if used.~~

4.12.B ELISA Technique

~~Each assay must contain positive, negative, and reagent controls that are appropriate for the intended use of the assay and the test results. The dilution of reagents and test specimens must be documented. For an assay to be valid, all controls must meet or exceed established thresholds as specified in the assay procedure, and this must be documented.~~

~~Sample identity and proper plate orientation must be maintained throughout the procedure.~~

4.13 Solid Phase Multi-channel Arrays

4.13.A Instrument Standardization/Calibration

~~Instruments must be standardized or calibrated as described *Policy 4.11.A: Instrument Standardization and Calibration*. Calibration and verification of plate alignment and instrument linearity must be performed according to the manufacturer's instructions or at least once every 6 months. The precise movement of the tray and plate must be documented.~~

~~If used, the microplate washer performance must be checked and its acceptable performance documented monthly.~~

4.13.B Reagents

~~Assays must use positive, negative, and reagent controls that are appropriate for the intended use of the assay and the test results. Document any dilution or optimization of reagents or test specimens.~~

~~For an assay to be valid it must meet or exceed established thresholds specified in the assay procedure, and this must be documented.~~

4.13.C Technique

~~Sample identity and proper plate orientation must be maintained throughout the procedure.~~

4.13.D CPRA Determination

~~The quality control of the new system's reagents must adhere to the standards described in~~

~~Policy 4.10.D.ii: Reagents.~~

~~4.13.E — Histocompatibility Typing~~

~~If the typing system is probe based, all standards relating to SSO procedures are applicable and must be adhered to as outlined in Policy 4.10.I.i: Oligonucleotide Probe Assays.~~

~~4.14 Chimerism Analysis~~

~~Laboratories performing engraftment and chimerism testing using nucleic acid analysis must conform to all pertinent standards in Policy 4.10: Nucleic Acid Analysis.~~

~~The specificity and sequence of primers must be defined. The genetic designation (e.g., locus) of the target amplified by each set of primers must be defined and documented. For each locus analyzed, the laboratory must have documentation that includes the chromosome location, the approximate number of known alleles, and the distinguishing characteristics (e.g., sizes, sequences) of the alleles that are amplified.~~

~~If sample processing involves the isolation of cell subsets or specific hematopoietic cell lineages, the laboratory should document the purity obtained whenever possible. If purity is not documented for a given sample, then this information must be provided on the patient report.~~

~~For each locus tested, patient and donor samples collected pre-transplant, and/or control samples demonstrated to have similar performance characteristics (e.g., sensitivity, competition in PCR) must be amplified and analyzed concurrently with patient samples collected post-transplant.~~

~~4.14.A — Analysis and Reports~~

~~Potential for preferential amplification of different sized alleles must be assessed and considered in the analysis.~~

~~If more than one locus is amplified in a single amplification (multiplex), the effects of such amplification on each system must be assessed and considered in the analysis.~~

~~Reports must identify the genetic loci analyzed according to standard nomenclature or published reference. For RFLP testing, the restriction endonuclease used and the fragment size must be identified.~~

~~If results are reported in a quantitative or semi-quantitative manner, criteria for evaluating the relative amounts of recipient and donor in a mixed chimeric sample must be established.~~

~~When mixed chimerism is not detected, reports must state the sensitivity level of the assay.~~

~~4.15 Preservation of Zero Mismatch Tissue Typing Materials~~

~~For future studies of HLA identification, tissues suitable for the isolation of DNA or purified DNA itself, from both the organ donor and recipient, should be preserved for each 0 mismatched cadaveric kidney transplant. If tissue is preserved it should be preserved by the recipient transplant hospital's HLA laboratory, under conditions which maintain the integrity of the DNA, for at least 5 years. This rule is applicable only when biologic specimens available are in excess of that necessary for the performance of required biologic tests.~~

Public Comment Responses

1. Public Comment Distribution

Date of distribution: September 08, 2013

Public comment end date: December 06, 2013

Public Comment Response Tally					
Type of Response	Response Total	In Favor	In Favor as Amended	Opposed	No Vote/ No Comment/ Did Not Consider
Individual	38	30 (78.95%)	0 (0%)	8 (21.05%)	0
Regional	11	9 (81.82%)	2 (18.18%)	0 (0%)	0
Committee	19	0 (0%)	0 (0%)	0 (0%)	19

2. Primary Public Comment Concerns/Questions

Many individuals commented on the new crossmatching requirement for kidney transplantation, specifically that the Committee's stated intent was that the OPTN would allow a virtual crossmatch alone to be sufficient for kidney transplantation. Because this new requirement was based on a federal regulation, individuals inquired as to whether the Committee had obtained official guidance from CMS on whether or not the interpretation of the federal regulation includes the use of a virtual crossmatch alone for kidney transplantation. Some individuals commented that virtual crossmatches should *not* be considered sufficient in lieu of a physical crossmatch, especially since the OPTN does not require HLA-DQA or HLA-DPB to be reported on deceased donors.

There were also concerns expressed about the original language for preserving excess specimens. Several individuals were concerned that requiring 'any' excess specimens was too broad and would be burdensome for laboratory storage. Some individuals also commented that it would be financially burdensome for laboratories to store excess specimens for five years.

3. Regional Public Comment Responses

Region	Meeting Date	Regional Votes	Approved as Amended (see below)	Meeting Format
1	9/30/2013	17 yes, 1 no, 0 abstentions		In person
2	10/25/2013	30 yes, 0 no, 0 abstentions		
3	12/6/2013	17 yes, 0 no, 0 abstentions		In person
4	12/6/2013	19 yes, 0 no, 1 abstention		
5	12/12/2013	20 yes, 0 no, 0 abstentions		In person

6	10/04/2013	62 yes, 0 no, 0 abstentions	In person
7	11/22/2013		21 yes, 0 no, 1 abstention In person
8	12/06/2013	21 yes, 0 no, 0 abstentions	In person
9	10/23/2013	19 yes, 0 no, 1 abstention	In person
10	10/18/2013		17 yes, 0 no, 0 abstentions
11	12/6/2013	18 yes, 2 no, 0 abstentions	

Region 1:

The region approved the proposal with the following comments:

- Policy D.4 (A) should be amended to include that the final crossmatch can be a physical or virtual crossmatch.
- The region discussed the policy language pertaining to discrepant HLA typing results. Several members of the region think that the discrepancies should be resolved pre-transplant and that the committee should move toward the identification of discrepant results in real time.

Committee Response:

Thank you for your comment. The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

The Committee also shares the region's concern that discrepant HLA typing results should be resolved prior to transplant. Unfortunately, at this time, UNetSM is programmed to only flag discrepancies on the Donor and Recipient Histocompatibility forms generated after transplant. In addition, there is currently no policy requiring recipient laboratories to perform confirmatory HLA typing on donors, so there often isn't a second HLA typing to compare to the first. The Committee has been discussing a number of policy changes to prevent HLA typing discrepancies prior to transplant and address discrepancies once they do occur. However, those changes will need to be released in a separate policy proposal.

Region 2:

The region unanimously approved the proposal with the comment that policy language should specify what types of typing materials need to be saved for 5 years.

Committee Response:

The Committee discussed this issue, but decided that there should be flexibility in the types of materials preserved.

Region 4:

The region approved the proposal with the following modifications:

- Section D.6, strike the word “any”, otherwise the laboratory will be responsible for preserving all specimens received.

D.6 Preservation of Excess Specimens

If a laboratory performs testing to determine histocompatibility between a donor and recipient, then the laboratory must preserve ~~any~~ excess specimens from the deceased donor for at least five years.

- Section D.6, retain previous language that required the laboratory to preserve specimens under conditions which maintain the integrity of the DNA.

D.6 Preservation of Excess Specimens

If a laboratory performs testing to determine histocompatibility between a donor and recipient, then the laboratory must preserve ~~any~~ excess specimens from the deceased donor for at least five years under conditions which maintain the integrity of the DNA.

Committee Response:

The Committee voted to remove the word ‘any’ from the policy language. The Committee considered the recommendation to use the phrase ‘under conditions which maintain the integrity of the DNA’ but decided that specifying DNA is restrictive and members wanted to make allowances for other tests.

Region 7:

Regional Amendment: The region request that the committee add verbiage stating that both a VIRTUAL and a PHYSICAL crossmatch are acceptable methods. The region is aware that there is language in the proposal that addresses this, but wanted it added to the policy language to ensure that there is not later re-interpretation of the language.

Regional Comments: The region would ask that the committee readdress the proficiency Issue. Several regional programs were concerned that there is not enough emphasize on the fact that centers use this information to make important clinical decisions. They felt that there should be an expectation of a high level of accuracy for this type of testing.

Committee Response:

The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate’s physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently

informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

The Committee shares the regions concern about accuracy in HLA typing. This proposal would require HLA typing to be performed and reported accurately, which was not previously specified. In addition, the Committee is going to review HLA typing discrepancies more frequently (every 3 months) in order to look for patterns and identify serious patient safety issues that may need to be reviewed by UNOS staff and the Membership and Professional Standards Committee (MPSC). The Committee is also working on developing proposed performance metrics for histocompatibility laboratories with regard to accuracy in HLA typing.

Region 10:

- The region requested an amendment to the proposal to add the words virtual and physical crossmatch as acceptable methods.
- The region did express concern that it is not standard practice for multi-organ transplants (liver/kidney) for a crossmatch to be done prior to transplant. In most cases crossmatch occurs post transplant and will mean a change in practice. The region did not feel that there was any clinical reason that for liver-kidney that this should be a requirement.

Committee Response:

The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

The requirement to perform a final crossmatch for multi-organ transplants involving a kidney is based on federal regulation CFR §493.1278. Under this federal regulation, histocompatibility laboratories are required to perform a crossmatch prior to transplant for multi-organ transplants involving a kidney.

Region 11:

The region approved the proposal with the following questions:

- Can the committee clarify what is meant by “any excess specimens” in Section-D.6 Preservation of Excess Specimens? Should this be all excess specimens?

Committee Response:

The Committee voted to remove the word ‘any’ from the policy language. The Committee amended the language to clarify that the laboratory must ‘preserve enough specimen for subsequent testing.’

4. Committee Public Comment Responses**Liver and Intestinal Organ Transplantation Committee:**

During the November 21, 2013 call, the Committee received an overview of the proposed changes, as well as changes that will specifically apply to liver transplantation. The proposed policy would apply to liver transplantation in cases where the laboratory performs a crossmatch at the physician’s request and there are excess donor specimens. The laboratory that performs the crossmatch would be required to keep any excess donor specimens. A Committee member asked if the cost of this requirement had been analyzed; it was estimated to be trivial, as most laboratories are already doing this. The Committee did not express any other concerns.

Committee Response:

Thank you for your comment. The Committee did approve amended language that specifies that the laboratory must preserve enough excess specimen to perform subsequent testing’ (removing the word ‘any’). This limits the amount of specimens that would need to be stored. The Committee did weigh additional cost as a consideration, but ultimately decided that having specimens available for testing post-transplant is often vital to patient safety and graft survival.

Minority Affairs Committee:

The committee discussed the timing of the final crossmatch with regard to multi-organ transplants. The committee inquired whether the final crossmatch needs to be completed or reported before implantation of a specific organ.

The committee determined that there was no inherent minority impact resulting from the proposal; however, it forwarded a request for clarification on the timing of the crossmatch to the Histocompatibility Committee for follow-up.

Committee Response:

Under the proposed policy, the crossmatch is required to be performed prior to transplant. This is already a requirement under federal regulation CFR §493.1278.

Thoracic Organ Transplantation Committee:

The Committee did not voice concerns or questions about the proposed policy, and voted in favor of it: 20-supported; 0-opposed; and 0-abstained.

Committee Response:

Thank you for your review of the policy proposal.

5. Individual Public Comment Responses**Comment 1:**

vote: Oppose

Date Posted: 12/06/2013

1. I do not support the use of a virtual crossmatch in lieu of an actual cellular crossmatch. The virtual crossmatch is simply a prediction based on available (and often limited) data, not a true test. Many of us have witnessed instances in which the virtual cross-match prediction was not borne out by the actual cellular crossmatch. 2. I believe that the requirement to preserve specimens for 5 years would place an undue burden on laboratories as it would incur the need for increased storage space, equipment, and expense, while adding little to improve patient care. 3. I suggest that HLA typing of DQ-alpha and DP-beta should be included in required testing for deceased donor organs, as this will provide additional valuable information that will improve organ allocation and transplant outcomes.

Committee Response:

1. The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.
 2. The Committee did weigh additional cost as a consideration, but ultimately decided that having specimens available for testing post-transplant is often vital to patient safety and graft survival.
 3. The Committee agrees that HLA-DQA and HLA-DPB should be included in the information required to be reported on deceased donors. However, that change is out of scope for this proposal. The Committee has proposed this change in a recent proposal released for public comment in March 2014.
-

Comment 2:

vote: Oppose

Date Posted: 10/25/2013

For D.4, first of all, it is necessary to obtain confirmation from CMS that virtual crossmatch is permissible under the intent of CFR 493.1278(f)(2) and that virtual crossmatch can be used to substitute a physical crossmatch for renal-associated transplants. Secondly, for live-saving

transplants (e.g. heart, lung and liver) that are also associated with kidneys, prospective crossmatch may not always be feasible depending on the recipients medical circumstances. Would this policy allow for a final crossmatch not being performed before the transplant? For D.5, I agree with these new requirements but would highly recommend their incorporation into the existing policy 3.2.4 governing ABO grouping and subgrouping. It is confusing to find relevant requirements in different policies. For D.6, while I support the intent of this requirement, it is necessary to establish some kind of measurable minimum on the quantity of excess donor materials to be preserved. For me, any equates to all. For OPO laboratories like us where donor materials are provided to the laboratory almost always in a huge surplus for the purpose of crossmatch, it will be an extreme burden for us to preserve ALL the donor materials we received on every donor we crossmatched. For your reference, our current policy dictates the cryopreservation of up to four aliquots of lymphocytes for every donor transplanted. Thank you.

Committee Response:

The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

The Committee did approve amended language that specifies that the laboratory must preserve enough excess specimen to perform subsequent testing' (removing the word 'any'). This limits the amount of specimens that would need to be stored.

Comment 3:

vote: Oppose

Date Posted: 12/05/2013

Generally the "Proposed Histocompatibility Policy Rewrite" is supported but there are serious problems which need to be opposed, eliminated or rewritten. 1. Re: Section D.1 HLA Typing, We should have equivalency between our solid phase specificity analysis and what we type for in the donors. Therefore, all of the DQalpha and DPbeta should be the least that are included in the mandatory typing. Our experience with failed crossmatches that break NKR chains or DSAs that result in rejection strongly suggests that these loci alleles identified in solid phase need to be typed in the donor. Furthermore, if we expect to transplant 100% cPRA patients these loci alleles need to be identified in the donors. 2. Re: Section D.4 Crossmatching. Initially, the use of virtual crossmatching as a substitute or even replacement is appealing. However, virtual crossmatching without cellular crossmatching should be opposed. As transplant professionals we know there is a high degree of equivalency with virtual and cell crossmatching but we also have seen the circumstance where strong positive solid phase results have no correlation to a cellular crossmatch result. Virtual crossmatch prediction must take into account cross reaction of antibody to the presumed epitopes found on cells versus those on beads. That is, conformational

changes may result in significant differences between cell and solid phase results. Additionally, there are differences in the cell surface expression, and/or HLA bound to beads that make the use of only the virtual crossmatch technique incorrect. Therefore, we need to rely on both cell and solid phase to make a correct interpretation of risk or absence of risk. Currently, we need both tests in real time and this should be stated explicitly.

Committee Response:

The Committee agrees that HLA-DQA and HLA-DPB should be included in the information required to be reported on deceased donors. However, that change is out of scope for this proposal. The Committee has proposed this change in a recent proposal released for public comment in March 2014.

The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

Comment 4:

vote: Oppose

Date Posted: 12/06/2013

I may have already submitted comments for this proposal but I'm not sure so I am submitting them now just in case. I am opposing this proposal because there is no check box to "support only if amended". The amendments I suggest are, first, for new section D.6 which should be amended to eliminate the word "any" which implies that ALL available excess specimens need to be preserved and to add the phrase "under conditions that maintain DNA integrity"(as worded in the deleted Policy D.3) because I'm sure that is the intention of the revised policy but unless it is so stated that might not happen. I would also propose adding the word "Pancreas" to new section D.4 (A) (Crossmatching) (as required by ASHI at least and probably also CMS)and to specify that "Virtual" crossmatches are only permissible under "emergency situations, to be justified by the Transplant Program, since we all know that current solid phase antibody identification techniques, although much better than previously available techniques, are fraught with errors due to missing specificities, IgM antibodies blocking IgG antibody detection, artifactual antigen presentation due to the "bead" manufacturing processes, etc. and Programs should not lightly switch completely to virtual crossmatching just because it appears that the OPTN/UNOS is now allowing that.

Committee Response:

The Committee did approve amended language that specifies that the laboratory must preserve enough excess specimen to perform subsequent testing' (removing the word 'any'). This limits the amount of specimens that would need to be stored. The Committee considered the recommendation to use the phrase 'under conditions which maintain the integrity of the DNA' but

decided that specifying DNA is restrictive and members wanted to make allowances for other tests.

The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

Comment 5:

vote: Oppose

Date Posted: 12/06/2013

I support much of the Histocompatibility Committees UNOS Policy rewrite; however, I have concerns regarding several of the proposed changes: Appendix 3D: D.1.A.3: Reporting serological equivalents should be acceptable for all Deceased Donor typing. There is no reason why specifically molecular typing results need be reported to the OPO, except when there is no serologically equivalent antigen. Reporting only molecular results could lead to confusion for the OPOs that enter typing results into UNOS, and is unnecessary where serological equivalents are sufficient. Table D.1: DRB3, 4, and 5 results should be reported for heart donors. Additionally, DPB1 and DQA1 results should be reported for all Deceased Donors to be congruent with current solid phase antibody assays. Also, allowing OPOs the option of not reporting DPB and DQA antigens based on the typing offered by their associated laboratory does not make sense. The typing should either be required or not. D.2: The laboratory with the incorrect results should be submitting the corrected typing. D.6: Storage of Deceased Donor specimens for 5 years is excessive. Laboratories may store samples for 5 years if they wish, but this time period should not be required by UNOS. It is appropriate for the storage time period to be determined by agreement with the laboratorys transplant center(s); however, if it is necessary for UNOS to require a specific time frame, I believe it should not exceed 2 years. D.4: The Crosswalk table for the proposal makes the following statement: It is important to note that the committee intends for either a virtual or physical crossmatch to be permissible to meet this standard and that this policy will apply to both deceased and living kidney donation. This statement is inappropriate and unacceptable for several reasons. 1. Without broad standardization of solid-phase testing, virtual crossmatching cannot be consistently applied to all patients. There will be variation based on test type performed, vendor used, etc. Therefore, donors may be accepted with a negative virtual crossmatch, based on where the positive antibody determining cutoff is placed, in cases where a physical crossmatch would have been positive. This represents a significant risk to the patient in terms of antibody mediated rejection, the possibility of which could not be determined without a physical crossmatch until after the transplant. This would result in improper utilization of Deceased Donor organs, as the possibility of acute rejection increases. 2. Virtual crossmatching is predictive, but is not a test in and of its self. There is no virtual crossmatch test defined by CLIA, nor is there any mention of using predictions as final results. As such, it should only be

used as guidance, but never as the final arbiter of transplant acceptability. Additionally, to my knowledge there is no system for obtaining compensation for a virtual crossmatch as a billable test or consultation. 3. Without complete Deceased Donor typing for all HLA-relevant antigens appearing in the solid-phase assays performed by the laboratory, any virtual crossmatch is incomplete and therefore not predictive of transplant acceptability. For example, DPB typing is not currently required by UNOS for Kidney, Pancreas and KP donors; and based on the proposed revisions DPB typing will continue to be optional. However, most laboratories performing Class II solid phase assays will have access to a patient's DPB antibody profile. This creates a situation where the predictive value of the virtual crossmatch is significantly diminished. Additionally, a laboratory's screening algorithm may not require testing for all patient HLA antibody at a frequency that allows for accurate virtual crossmatching. It has been demonstrated that the virtual crossmatch has significant predictive value. However, as discussed above, it is not appropriate for UNOS to comment on the acceptability of the virtual crossmatch as a final crossmatch. There are situations where a virtual crossmatch may be warranted, such as: for non-sensitized patients, emergent situations due to logistical concerns or organ ischemia, etc. However, all virtual crossmatches must be followed by a physical crossmatch as the test to determine transplant acceptability. The same criteria apply in the case of living donor transplantation; however, there would not typically be a situation where a physical crossmatch could not be performed. Therefore, it is logical to require a physical crossmatch for all living donors. Thank you for your attention.

Committee Response:

Thank you for your comments. It's important to note that reporting molecular typing results (at the level of serological splits) is already required for deceased kidney, kidney-pancreas, and pancreas donors under the current policy 4.2 *HLA Typing*. This proposal merely reorganizes the current requirement in a different section. The two tables showing HLA typing requirements are also merely a restatement of the current policy and changes to this after public comment are out of scope for this proposal. The Committee is proposing the changes referenced in a proposal that was released for public comment in March 2014.

The Committee did clarify that each laboratory involved in an HLA typing discrepancy must report the reason to UNOS, because the current system is programmed to require this reporting. This also allows for an assessment of which laboratory was determined to be in error.

The Committee did discuss whether or to decrease the length of time specimens are required to be stored, but ultimately decided that having specimens available for testing post-transplant for five years is often vital to patient safety and graft survival.

The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

Comment 6:*vote: Oppose**Date Posted: 10/10/2013*

My concern is in regards to section D.4 Crossmatching both as written and in theory. The problem with the way this section is written is that D.4(A) does not explicitly state that both virtual or physical crossmatches are acceptable. Section D.4(B) then goes on to state general crossmatching requirements which begins with "Whenever a laboratory is performing a crossmatch, the laboratory must do all of the following" and goes on to identify 3 physical attributes of a crossmatch(2,3 & 4). If you must do all of the following when performing a crossmatch, this precludes a "virtual" crossmatch, and furthermore, requires both T & B-cell crossmatches be performed. In regards to the concept of a virtual crossmatch, I agree with its utility but question the committee's authority to provide an interpretation on Federal regulation CFR 493.1278 which requires that the results of the final crossmatch be available prior to kidney transplantation (including when a kidney is to be transplanted with other organs). I have not seen anything from CMS regarding an opinion on a virtual crossmatch being an acceptable final crossmatch. Furthermore, I am not assured that the community is ready to go primetime with a virtual crossmatch on any population of transplant candidates other than those with no preformed anti-HLA antibodies. I have several concerns including a lack of standardization with these relatively new solid phase assays used to provide unacceptable antigens for virtual crossmatch, presence of denatured antigen on some beads and a center's ability to understand and deal with them, a lack of consensus on which antibodies are clinically relevant and the potential for some candidates to be disadvantaged because these issues.

Committee Response:

The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

Comment 7:*vote: Oppose**Date Posted: 12/06/2013*

Overall the Proposed Histocompatibility Policy Rewrite is supported; however, there are couple of issues which I feel need to be addressed. 1. Regarding Section D.1 HLA Typing, I feel that the required HLA typing for deceased donors is not adequate. We should have equivalency between our solid phase specificity analysis and what is being typed in the donors. Therefore, HLA-DQA and HLA-DPB should be required in the mandatory typing. With that said, the ability to list DPB and DQA as Unacceptable Antigen is much needed to help reduce the number of positive

crossmatches that are seen in both Deceased Donors as well as kidney paired exchange programs. The ultimate efficiency and success in transplant 100% cPRA patients are dependent upon accurate donor HLA typing and identification of patient antibodies which include both DQA and DPB. 2. Regarding Section D.4 Crossmatching, I feel virtual crossmatching without a physical cellular crossmatching should be opposed. As transplant professionals we have seen many broken NKR chains due to failed virtual crossmatches. Lack of adequate donors HLA typing (DQA & DPB), reaction of a patients antibodies to the actual donor cells versus to that of the beads in the solid phase assay as well as the cell surface expressions on donor cells versus the HLA antigens bound to beads are just some of the potential reasons why a negative prediction in a virtual crossmatch can result in a positive physical cellular crossmatch. Currently, I feel we need to rely on actually physical crossmatch in real time to accurately interpret the risk or absence of risk. I strongly oppose permitting the use of a virtual crossmatch in the absence of a physical final crossmatch.

Committee Response:

The Committee agrees that HLA-DQA and HLA-DPB should be included in the information required to be reported on deceased donors. However, that change is out of scope for this proposal. The Committee has proposed this change in a recent proposal released for public comment in March 2014.

The Committee discussed at length whether to allow virtual crossmatches to be permissible for kidney transplantation. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, since the Committee was recently informed that CMS interpretive guidelines do not allow virtual crossmatches alone to be sufficient under the federal regulation (the issue is currently under review by CMS staff), the Committee decided to leave the language as proposed. The Committee is concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that virtual crossmatches are permissible under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

Comment 8:

vote: Oppose

Date Posted: 12/03/2013

Point 1 - Unless the rules regarding frequency of serum collection and screening for HLA antibodies are changed as well, the new rules allowing the "final crossmatch" to be either physical OR virtual is a really bad idea. Serum collection and screening frequency requirements were previously relaxed using the logic that most people have relatively little short-term change in antibody profile, and a (real) final crossmatch would catch the exceptions. Predicting crossmatch compatibility based on a thorough evaluation of known antibody specificity relative to donor mismatches (i.e. virtual crossmatching) is a reasonable approach ONLY if the available antibody specificity data is complete and accurate. With many patients (especially those initially determined to be 0% PRA at activation) now receiving very little subsequent monitoring, many virtual crossmatches will be interpreted based on data that is 6 months to a year old. Our lab monitors monthly, and in supporting over 300 renal transplants a year, there are always one or two "surprise" positive crossmatches due to a recent increase in HLA antibody. This is usually

due to unreported transfusions (and no matter how hard one tries to improve communication on this subject, when dealing with several hospitals, dozens of dialysis units and twice as many physicians, most will be unreported) since the last sample. Bottom line: allowing BOTH a virtual final crossmatch AND infrequent antibody monitoring is unwise. Point 2 The requirement for labs to preserve any excess specimens from deceased donors for at least five years is far too broad. It should be stated that specimens refers only to serum/plasma (primarily for additional infectious disease testing if needed) and lymphocytes (primarily for additional typing and crossmatching if needed), and any should be changed to indicate the minimum volumes and numbers that must be saved (if available).

Committee Response:

The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

Comment 9:*vote: Support**Date Posted: 11/07/2013*

American Society for Histocompatibility & Immunogenetics (ASHI) Response to UNOS Proposed Policies - December 2013 #2: Proposed Histocompatibility Policy Rewrite (Histocompatibility Committee) Response: ASHI appreciates the amount of work that has been done by the committee to update and streamline the OPTN policies governing histocompatibility testing. In general, we are in support of the proposed changes and feel that oversight of the laboratories will be better carried out with these policies in place. However, we believe that some of the changes need clarification, as indicated below. In addition, we have a few specific comments: Will laboratories be required to adhere to the sections that are moved to a guidance document and will the guidance document be subject to public comment? For section D.4 Crossmatching, ASHI urges caution in permitting either a virtual or physical crossmatch under this standard. CMS has not yet ruled whether virtual crossmatching is permissible under the intent of CFR 493.1278. If the UNOS policies specifically allow either a virtual or physical crossmatch, and CMS eventually rules that virtual crossmatch cannot replace physical crossmatch, then the UNOS and CMS policies will conflict, and laboratories will not be in compliance with CMS regulations. Thus, it may be premature for UNOS to make this allowance. In addition, in these difficult economic times, permitting only a virtual crossmatch might cause transplant program administrations to force the abandonment of physical crossmatches as a perceived cost-saving measure, even if the laboratory and transplant physicians or surgeons do not support this change. For section D.5 Blood Type Determination, we are in agreement with this new requirement and feel that it protects the laboratory. If a laboratory modifies the manufacturer's directions, the laboratory will not have

a defense in the case of an accidental ABO mismatch. For section D.6 Preservation of Excess Specimens, the use of any implies that all excess specimens must be saved for 5 years. This will create an undue burden for laboratories, especially those that perform testing on numerous deceased donors each year. While we do support the intent of this requirement and agree that some material should be saved on all donors, we feel that the language should be changed to reflect that only a portion or a representative sample of the donor material must be saved. We are in agreement with the new requirements in sections D.1.A Requirements for Performing and Reporting HLA Typing, D.2 Resolving Discrepant Donor and Recipient HLA Typing Results, and D.7 HLA Antigen Values and Split Equivalences. We appreciate the opportunity to comment on these proposals.

Committee Response:

Laboratories will not be required to adhere to sections moved to a guidance document. Guidance documents are not enforceable, but merely a compilation of suggested best practices. Guidance documents are not typically released for public comment, but the Committee will ensure that all professional transplant societies are given the opportunity for input as the document is developed.

The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

The Committee did approve amended language that specifies that the laboratory must preserve enough excess specimen to perform subsequent testing' (removing the word 'any'). This limits the amount of specimens that would need to be stored.

Comment 10:

vote: Support

Date Posted: 12/05/2013

I generally support the Proposed Histocompatibility Policy Rewrite proposal. However, I have some reservations and comments regarding some of the proposed changes. Regarding Section D.1 HLA Typing, I feel that the required HLA typing for deceased donors is inadequate. I feel that typing of HLA-DQA and HLA-DPB should be required in order to better facilitate the allocation of deceased donor organs. The widespread use of single-antigen beads to screen recipient anti-HLA antibodies has greatly increased the ability to detect antibodies against DQA and DPB, and data demonstrating the clinical significance of these antibodies has been steadily accumulating. The ability to list unacceptable DQA and DPB antigens will help reduce the number of positive crossmatches (as has been demonstrated in kidney paired exchange programs), and this is reliant upon the availability of donor DQA and DPB typing. Additionally, the approval of the proposed revisions to deceased donor kidney allocation presages national allocation of deceased donor

kidneys to recipients with 100% CPRA. The ultimate efficiency of this process will be dependent on accurate comparison between patient antibodies and donor antigens, including DQA and DPB. Regarding Section D.4 Crossmatching, I do not support permitting the use of a virtual crossmatch in the absence of a physical final crossmatch. Although the predictive value of a virtual crossmatch has increased with the enhancement of antibody detection and typing methods, the actual accuracy as performed is dependent on the specific methods used and how they are applied. Solid phase assays to determine antibody specificities vary in their resolution and their inclusion of screened antigens. Even presuming accurate determination of recipient antibodies, inadequate typing of the donor's HLA (e.g. lacking DQA and DPB typing) invalidates a virtual crossmatch. The experience of the NKR with regard to failed virtual crossmatches is a perfect example of such a circumstance. I support the sections D.2, D.3, D.5, D.6, and D.7 as proposed.

Committee Response:

The Committee agrees that HLA-DQA and HLA-DPB should be included in the information required to be reported on deceased donors. However, that change is out of scope for this proposal. The Committee has proposed this change in a recent proposal released for public comment in March 2014.

The Committee discussed at length whether to allow virtual crossmatches to be permissible for kidney transplantation. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, since the Committee was recently informed that CMS interpretive guidelines do not allow virtual crossmatches alone to be sufficient under the federal regulation (the issue is currently under review by CMS staff), the Committee decided to leave the language as proposed. The Committee is concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that virtual crossmatches are permissible under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

Comment 11:

vote: Support

Date Posted: 10/07/2013

In general, these proposals define ambiguous or out of date recommendations for the Histocompatibility testing community. However, the recommendation in section D.4, enabling use of either cellular or virtual crossmatch to fulfill the requirement for pre-transplant testing falls short of the goal of ensuring immunologic compatibility. Considerable variation exists in laboratory methodology for identification of alloantibodies, and there is continuing debate as to the clinical relevance of antibodies identified exclusively by solid phase immunoassay (regardless of methodology). There is sufficient data in the literature illustrating the clinical relevance of cellular crossmatch testing and outcomes, as well as demonstrating discordant cellular and virtual crossmatch results, to warrant a continued requirement for pre-transplant cellular crossmatch testing to evaluate immunologic compatibility for kidney transplant recipients.

Committee Response:

The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice

decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

Comment 12:*vote: Support**Date Posted: 12/04/2013*

Point 1 - Unless the rules regarding frequency of serum collection and screening for HLA antibodies are changed as well, the new rules allowing the "final crossmatch" to be either physical OR virtual is a really bad idea. Serum collection and screening frequency requirements were previously relaxed using the logic that most people have relatively little short-term change in antibody profile, and a (real) final crossmatch would catch the exceptions. Predicting crossmatch compatibility based on a thorough evaluation of known antibody specificity relative to donor mismatches (i.e. virtual crossmatching) is a reasonable approach ONLY if the available antibody specificity data is complete and accurate. With many patients (especially those initially determined to be 0% PRA at activation) now receiving very little subsequent monitoring, many virtual crossmatches will be interpreted based on data that is 6 months to a year old. Our lab monitors monthly, and in supporting over 300 renal transplants a year, there are always one or two "surprise" positive crossmatches due to a recent increase in HLA antibody. This is usually due to unreported transfusions (and no matter how hard one tries to improve communication on this subject, when dealing with several hospitals, dozens of dialysis units and twice as many physicians, most will be unreported) since the last sample. Bottom line: allowing BOTH a virtual final crossmatch AND infrequent antibody monitoring is unwise. Point 2 The requirement for labs to preserve any excess specimens from deceased donors for at least five years is far too broad. It should be stated that specimens refers only to serum/plasma (primarily for additional infectious disease testing if needed) and lymphocytes (primarily for additional typing and crossmatching if needed), and any should be changed to indicate the minimum volumes and numbers that must be saved (if available).

Committee Response:

The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The

Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

The Committee did approve amended language that specifies that the laboratory must preserve enough excess specimen to perform subsequent testing' (removing the word 'any'). This limits the amount of specimens that would need to be stored.

Comment 13:*vote: Support**Date Posted: 11/30/2013*

The American Nephrology Nurses Association supports this proposal without revisions.

Committee Response:

Thank you for your support of this proposal.

Comment 14:*vote: Support**Date Posted: 10/11/2013*

This proposal is a significant improvement over the last proposal and in general I support the effort. I have 2 comments. First regarding the requirement to preserve donor material for 5 years. While I basically support this, my lab does store cryopreserved donor material, but our space is limited to 3-4 years. To increase to 5 years would require significant capital investment by the hospital. I imagine that it would be an even larger issue for labs that do not currently store material. If implemented, it would be fair to provide longer time for labs to comply. Second, I support the inclusion of using a VIRTUAL crossmatch. However, be aware that currently there is NO provision for such a "test" under CMS. ASHI ARB is in discussion with CMS regarding the issue, but currently not permitted under existing CLIA law.

Committee Response:

The Committee did discuss whether or to decrease the length of time specimens are required to be stored, but ultimately decided that having specimens available for testing post-transplant for five years is often vital to patient safety and graft survival.

The Committee discussed at length whether to amend the policy language to clarify that the final crossmatch for kidney transplantation can be either physical or virtual. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, the Committee members were recently informed that CMS interpretive guidelines do not allow virtual crossmatches performed prior to transplant to meet the requirement of the federal regulation (the issue is currently under review by CMS staff). The Committee members were concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that a virtual crossmatch in lieu of a physical crossmatch is permissible prior to transplant under the federal regulation, putting laboratories at risk of being cited during federal inspections. The Committee recommended that the policy language remain broad at this time, in order to provide for flexibility in the future should CMS change the federal interpretive guidelines.

Post Public Comment Consideration:

The Committee met via conference call on March 19th, 2014 to review public comments received on the proposal and final recommendations from the Histocompatibility Policy Rewrite Subcommittee. The Committee decided that the new requirement to preserve ‘any’ excess specimens was too broad. The Committee discuss whether or to decrease the length of time specimens are required to be stored, but ultimately decided that having specimens available for testing post-transplant for five years is often vital to patient safety and graft survival. The Committee adopted the following language (strike through indicates language deleted post-public comment and underlines indicate language added post-public comment):

If a laboratory performs testing to determine histocompatibility between a donor and recipient, then the laboratory must preserve ~~any~~ enough ~~excess~~ specimens from the deceased donor to perform subsequent testing for at least five years after the transplant.

The Committee also adopted updated language that better reflects the way the TIEDI system is programmed to account for resolutions in HLA typing discrepancies. The Committee adopted the following language (strike through indicates language deleted post-public comment and underlines indicate language added post-public comment):

Laboratories must resolve discrepancies within 30 days of notification of discrepant typing results. The Laboratory Director or designated staff must contact the other Laboratory Director or designated staff to resolve the discrepancies. Each laboratory involved in the HLA typing discrepancy must identify and report the specific reason for the discrepancy to the OPTN Contractor. ~~If a resolution is reached, the laboratory with the correct typing results must submit the corrected HLA typing to the OPTN Contractor as resolved. The laboratory must also identify the specific reason for the discrepant typing.~~

In addition, the proposal includes a post-public comment change to clarify existing policy regarding the reporting of HLA typing requirements for deceased heart and lung donors (strike through indicates language deleted post-public comment and underlines indicate language added post-public comment):

For heart deceased donors, if a transplant hospital requires donor HLA typing prior to submitting a final organ acceptance, it must communicate this request to the OPO and document the request. ~~†The transplant hospital OPO must provide the HLA information required in the table list above and document this request that the information was provided to the transplant program.~~ The transplant hospital may request HLA-DPB typing, but the OPO need only provide it if its affiliated laboratory performs related testing. ~~The OPO must document HLA typing provided to the requesting transplant hospital.~~

For lung deceased donors, if a transplant hospital requires donor HLA typing prior to submitting a final organ acceptance, it must communicate this request to the OPO and document the request. ~~†The transplant hospital OPO must provide the HLA information required in the table list above and document this request that the information was provided to the transplant program.~~ The transplant hospital may request HLA-DPB typing, but the OPO need only provide it if its affiliated laboratory performs related testing. ~~The OPO must document HLA typing provided to the requesting transplant hospital.~~

During the post-public comment period, the Committee discussed at length whether or not to amend the proposal to specify that a virtual or physical crossmatch is sufficient for kidney

transplants and multi-organ transplants involving a kidney. The majority of the Committee members believe that the method of the crossmatch is a clinical and medical practice decision that should be made by the candidate's physician in consultation with the histocompatibility laboratory staff in each case. However, since the Committee was recently informed that CMS interpretive guidelines do not allow virtual crossmatches alone to be sufficient under the federal regulation (the issue is currently under review by CMS staff), the Committee decided to leave the language as proposed in order to provide for flexibility in the future should CMS change the federal interpretive guidelines. The Committee is concerned that amending the language at this time could give OPTN histocompatibility laboratories and transplant programs the impression that virtual crossmatches are permissible under the federal regulation, putting laboratories at risk of being cited during federal inspections.