OPTN | UNOS

Briefing Paper

Guidance Document for OPTN/UNOS Histocompatibility Laboratory Bylaws and Policies

OPTN/UNOS Histocompatibility Committee

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Guidance Document for OPTN/UNOS Histocompatibility Laboratory Bylaws and Policies

Affected Policies:	*N/A*
Sponsoring Committee:	*Histocompatibility*
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Executive Summary

The OPTN/UNOS Histocompatibility Committee (the Committee) created this guidance document in order to provide additional information or clarification for the OPTN/UNOS bylaws and policies. This guidance document is designed to assist members with interpreting the bylaws and policies governing histocompatibility laboratories and histocompatibility testing of donors and candidates.

This guidance document is intended only to provide guidance for labs on certain aspects of histocompatibility testing and written agreements. The guidance given for testing is not intended to overrule the clinical needs of a patient. Additionally, the scope and content of written agreements should reflect collaboration between laboratories and transplant programs, taking into consideration their needs and laboratory best practices.

This project was initiated during the histocompatibility bylaws and policies rewrite in 2014. During that time the Committee decided that several sections of bylaws and policies were better suited as a guidance document, as they provided recommendations for histocompatibility laboratory performance rather than requirements. In total, 28 sections of policy fell into this category. The Committee reviewed those sections, and decided to omit certain sections that referenced out of date components of histocompatibility testing, or because they related to testing standards better governed by lab accrediting agencies like the American Society for Histocompatibility and Immunogenetics (ASHI) and the College of American Pathologists (CAP).

The remainder of the document focuses on the written agreements between histocompatibility labs and transplant programs, cross matching, blood typing, and preservation and storage of excess specimens. These topics were chosen for inclusion in this guidance document based on two factors. First, they are what remains of the original 28 sections of policy flagged for inclusion that are not out of date or reflective of testing standards governed by the accrediting agencies. Second, they are representative of questions received by UNOS from members of the transplant community.

What problem will this proposal solve?

This project was initiated during the histocompatibility bylaws and policies rewrite in 2014. During that time the Committee decided that several sections of bylaws and policies were better suited as a guidance document, as they provided recommendations for histocompatibility laboratory performance rather than requirements. The guidance document also clarifies certain current histocompatibility bylaws and policies. The guidance document will help to solve problems related to misinterpretation of the current OPTN/UNOS policies and bylaws, and provide a template for best practices.

Why should you support this proposal?

The guidance document will be a useful resource for histocompatibility labs to reference when seeking clarification on OPTN/UNOS policies and bylaws.

The guidance document aims to provide clarity to areas of OPTN/UNOS histocompatibility policies and bylaws identified as vague or benefitting from further information. With careful review, the Committee created a document to help histocompatibility lab personnel make better informed decisions. The committee finely edited the guidance document to provide suggested methods for laboratories to use and include in the written agreements between laboratories and transplant programs. By supporting this proposal, members will be provided with an additional tool to help with decision making.

How was this proposal developed?

As part of the histocompatibility comprehensive policy rewrite in 2014, the Board of Directors voted to move 28 sections of policy out of policy and potentially into a guidance document. These sections were:

- D.1 History of Allosensitization
- D.1 Detection of Alloantibody: Creating an Antibody History
- D.1 Periodic Sample Collection
- D.1 Crossmatching Strategies
- Table 1. Documenting allosensitization
- Table 2. Assays to identify alloantibody (antibody screening or crossmatching)
- Table 3. Recommended elements for crossmatching strategies.
- D2.000 Typing Assignment
- D3.000 Reagent Validation
- D4.000 HLA Typing Nucleic Acid Analysis
- D4.300 Typing by Sequence Based Typing (SBT)
- E. Antibody Screening
- E2.000 Techniques
- E3.000 Sera
- E4.000 Panel and Target Selection
- F3.000 Antibody Screening
- F4.200 Techniques
- F4.300 Samples
- H1.000 Cytoxicity Methods
- H2.000 Controls
- H3.000 Target Cells
- H4.000 Complement
- J. Chimerism Analysis
- J5.000 Analysis and Reports
- K. Nucleic Acid Analysis
- L. Flow Cytometry
- M. Enzyme Linked Immuno Sorbent Assay (ELISA)
- N. Solid Phase Multi-channel Arrays

These sections were identified by the Committee to be difficult for UNOS to monitor, better suited as guidance than policy, or already standards required by ASHI or CAP.

The Committee formed a Guidance Document Subcommittee (the Subcommittee) to decide which of the identified sections were important to include in the document and create a first draft. Along with the Committee's earlier considerations, the Subcommittee reviewed the sections individually and discussed whether they were out of date and consequently no longer relevant or redundant to other existing policies.

After reviewing and paring down the original recommended sections, the Subcommittee drafted a guidance document with the remaining sections. The Subcommittee also created guidance for sections of the histocompatibility policies and bylaws identified by the Committee to be vague and that could benefit from clarification.

Through several comprehensive edits, the Committee and Subcommittee continued to refine the document, ensuring that it was current and provided thoroughly considered suggestions for best practice.

Table 1: Changes to Policy below shows the seven sections the Committee chose from the original 28 sections for inclusion in the guidance document. The remaining sections were not moved into the guidance document because they were identified as out of date, already monitored by ASHI or CAP, or redundant to other policies. Other sections included in the guidance document were not part of the initial guidance document considerations, but give guidance to members on certain areas of policy that could benefit from clarification.

Table 1: Changes to Policy

Original Policy Section	Recommendation	Reason and Changes
4.1.B: Sensitization History	Move to guidance document	This section is outdated and merely conveys guidance. Changes made to soften language and clarify that the following table is meant as a resource. Changed from "Laboratories should evaluate the data in *Table 4-1* below when determining sensitization history" to "For items to consider when assessing sensitization history, see *Table 1: Sensitization History for Bylaw C.2.C Compliance* below."
Table 4-1: Determining Sensitization	Move to guidance document	This section is outdated and merely conveys guidance. Changed title to "Table 1: Sensitization History for Bylaw C.2.C Compliance." Changes made to headers to soften language and make table more of a resource than suggested practices. First header changed from "If this event occurred" to "Events"; second header changed from "Then the laboratory should evaluate" to "Considerations." Other small edits made for updating and clarification purposes.
4.1.C: Detection of Antibodies	Move to guidance document	This section merely conveys guidance. Original language unchanged. Note added: "a solid phase method must be used to support the listing of unacceptable antigens in UNet^{SM} per *Policy 4.5: Antibody Screening and Reporting*"
Table 4-2: Assays to Identify Antibody to HLA: Screening, Specificity, or Crossmatching	Move to guidance document	This section merely conveys guidance. Title number changed to match guidance document table numbering (now Table 3). Small updates made to language, including adding "solid phase" to certain assays to maintain consistency throughout the guidance document.
4.1.D: Periodic Sample Collection	Move to guidance document	This section merely conveys guidance. Edited to soften language. "Laboratories should" changed to "It is recommended that laboratories." Language about collecting serum samples updated from "monthly" to "at regular intervals" to leave the timetable at the discretion of the written agreement participants.
4.1.E: Crossmatching Strategies	Move to guidance document	This section merely conveys guidance. Updated for clarification; Changed any occurrence of "crossmatch" to "physical crossmatch." Other non-substantive edits made for clarification or to soften the language (changed "peri-transplant" to "concurrently with the transplant").
Table 4-3: Recommended Elements for Crossmatching Strategies	Move to guidance document	This section merely conveys guidance. Title changed to "Table 2: Elements for Crossmatching Strategies." No substantive changes made. Only updated the numbering for a referenced table within the text and changed "peri-transplant" to "during the time of transplant."

Was this proposal changed in response to public comment?

The Committee choose to make several minor changes to the guidance document after public comment. Most changes were one word clarifications. Throughout the development of this guidance document, the Committee carefully considered the language as to not be too prescriptive or imply that recommendations should be considered for policy changes in the future. The Committee continued to consider word choice as they incorporated post public comment changes.

The proposal received overwhelming support from each region. The American Society of Transplantation (AST) supported the information included in the guidance document, but wanted to be sure that the guidance document is used as guidelines and not regulations. The Committee created the guidance document to provide the community with suggested practices, and supports AST's comments that the guidance document should only serve as guidelines and is not intended to be a regulatory document. The American Society of Transplant Surgeons (ASTS) supported the proposal as written.

Comments received from ASHI were considered in detail by the Committee. Some of ASHI's suggested changes were mentioned in other public comments as well; the Committee made changes to several sections that were addressed in multiple public comments. The Committee chose to exclude some suggested revisions that were too content specific or would require frequent updates in the future. Other clarifications were made in response to ASHI's comments, which are documented in more detail below.

The Committee considered all comments and chose to make the following clarifications:

Table 1: Sensitization History for Bylaw C.2.C Compliance:

The Committee softened one of the column titles from "Consideration" to "Consideration, <u>if available.</u>" Concern that the considerations listed would imply that the information would be available for every patient caused the Committee to clarify that this information should be considered only if available for the individual patient.

In response to one public comment, the Committee decided to add "composite tissue allografts" to the list of possible previous grafts. This addition will make the list of possible previous grafts more comprehensive.

C.2.C #11: The criteria for crossmatching

The Committee considered the recommendation from one public comment and reworded the language under the first point of this section, removing "should" and putting "it is recommended that" before the statement about when to perform a physical crossmatch if it cannot be completed before the transplant:

1. In kidney transplantation, there may be cases when it is better to proceed with the transplant before a physical crossmatch can be completed. If, after careful consideration, a pre-transplant physical crossmatch cannot be completed, then <u>it is recommended that</u> the laboratory ~~should~~ perform the physical crossmatch concurrently with the transplant or retrospectively to guide post-transplant care.

Table 3: Assays to Identify Antibody to HLA: Screening, Specificity, or Crossmatching

The Committee clarified that Enzyme-Linked Immuno Sorbent Assay (ELISA) is a solid phase assay. After consideration about the sensitivity of listed tests, the Committee removed "more sensitive" from one of the sections.

C.2.C #12: The assay format that will be used for antibody screening and for crossmatching

The Committee changed the wording in this section from "several sera" to "multiple sera" to clarify that the number of sera could be two or more instead of three or more.

Virtual Crossmatching

The Committee softened the language under the second point in this section by replacing “should” with “it is recommended.”

1.7 Blood Type Determination

The Committee added to this section in order to clarify that it referred to laboratories that perform ABO subtyping.

1.8 Preservation of Excess Specimens

In order to emphasize that this document is meant for guidance, the Committee softened language in this section to replace “it would be appropriate” with “it would be beneficial.” The Committee also changed “donor tissue” to “donor material” to broaden the recommendation.

Which populations are impacted by this proposal?

In general, this proposal does not directly impact any specific patient populations. The guidance document is to be used as a reference and general resource for the 152 approved histocompatibility labs.

How does this proposal impact the OPTN Strategic Plan?

Increase the number of transplants: There is no expected impact on this goal.

Improve equity in access to transplants: There is no expected impact on this goal.

Improve waitlisted patient, living donor, and transplant recipient outcomes: Better understanding of histocompatibility testing practices will improve recipient outcomes.

Promote living donor and transplant recipient safety: This document will primarily impact recipient safety by helping labs assure they are engaging in high quality HLA testing and lab practices.

Promote the efficient management of the OPTN: This document will supplement histocompatibility policies and bylaws, which will assist the community by providing necessary information to make informed decisions relating to histocompatibility.

How will the OPTN implement this proposal?

As this is a guidance document and not a policy or bylaw change, this proposal will not require implementation by the OPTN. This proposal will not require programming in UNet^{SM}. At this time there is no instructional effort needed. The guidance will be posted on the OPTN’s website and will be available to the histocompatibility laboratories and the public.

How will members implement this proposal?

Members will not be required to use the guidance document, but may choose to use it as a reference for their laboratories. The guidance document is not meant to be a list of regulations; instead, the guidance document is meant to provide members with suggested best practices to consider if feasible.

The Fiscal Impact Advisory Group reviewed the proposal and provided feedback for laboratories and hospitals:

Laboratories:

- Most labs are likely already following the protocols outlined in the guidance, causing minimal fiscal impact.
- If members are not already following the guidelines, implementation and ongoing costs can be substantial. An additional storage freezer can cost up to $20,000. Supplies, including freezing medium, liquid nitrogen, reagents, allele typing kits, tubes, tube holders, and additional utilities

can total to up to $50,000 annually, depending on testing volume. Minimal staff hours are required for training. If additional costs are not reimbursable or able to be absorbed by facility, labs can raise charges or create new charges to offset costs.

- Overall, additional costs vary widely, dependent on donor and waitlist testing volume and facility resources. Hospital labs may have access to additional shared resources, such as storage, while independent labs may have no shared resources.

Hospitals:

- Additional joint lab and hospital staff time in developing virtual crossmatching criteria and recording sensitizing events for candidate is an implementation impact.

How will members be evaluated for compliance with this proposal?

The proposed language does not change any member obligations, so there will be no need to evaluate member compliance with the proposal.

Guidance Document

RESOLVED, that the guidance document entitled *Guidance Document for OPTN/UNOS Histocompatibility Laboratory Bylaws and Policies*, as set forth below, is hereby approved, effective June 6, 2017.

Guidance Document for OPTN/UNOS Histocompatibility Laboratory Bylaws and Policies

Summary

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This guidance document is intended only to provide guidance for labs on certain aspects of histocompatibility testing and written agreements. The guidance given for testing is not intended to overrule the clinical needs of a patient. Additionally, the scope and content of written agreements should reflect collaboration between laboratories and transplant programs, taking into consideration their needs and laboratory best practices.

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OPTN/UNOS Bylaws Appendix C: Membership Requirements for Histocompatibility

C.2 Facilities and Resources

C.2.C: Written Agreements

Bylaw C.2.C: Transplant Program Affiliation lists the different components required in the agreements between histocompatibility labs and the transplant programs they support. Guidance on several elements of these agreements is given below.

C.2.C #8: A process to obtain sensitization history for each patient

For items to consider when assessing sensitization history, see *Table 1: Sensitization History* below.

Table 1: Sensitization History for Bylaw C.2.C Compliance

Events:	Considerations, if available:	And note:
Previous graft of solid organ, bone, tendon, or composite tissue allografts	1. Date of transplant and organs or tissue transplanted 2. Date of graft loss 3. Cause of graft loss 4. HLA typing of donors 5. Rejection history, history of delayed function, history of non-compliance, or reduced immuno-suppression due to infection	For #2: Dates of graft removal, re-transplant, and return to dialysis. For #4: Potential unacceptable antigens that can be identified.

Events:	Considerations, if available:	And note:
Pregnancy	Number and year of each occurrence	Gravida/para (GP)
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	Etiology of disease causing end-stage organ failure	That auto-immunity may invalidate some laboratory assays.
Acute/chronic infections	Viral infection or bacterial infection requiring antibiotics	If the infection occurred since last antibody screening test. Induction of antibodies with specificity for HLA.
Administration of immunomodulatory treatment.	Type, date, and duration of treatment	Induction of antibodies with specificity for HLA.
Vaccinations	Type, date of each occurrence	Time passed since last antibody screening test.

C.2.C #9: The frequency of periodic sample collection

It is recommended that laboratories collect serum samples, at regular intervals, for candidates and use these samples to develop an antibody history and facilitate final crossmatches.

C.2.C #11: The criteria for crossmatching

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:

2. In kidney transplantation, there may be cases when it is better to proceed with the transplant before a physical crossmatch can be completed. If, after careful consideration, a pre-transplant physical crossmatch cannot be completed, then it is recommended that the laboratory perform the physical crossmatch concurrently with the transplant or retrospectively to guide post-transplant care.
3. In thoracic transplantation, prospective physical crossmatches are not commonly used for patients with no detectable donor-specific HLA antibodies.

Table 2 below lists elements that laboratories should include in developing crossmatching strategies. Strategies should be tailored to the level of risk.

Table 2: Elements for Crossmatching Strategies

Element:	Options:
Selection of techniques	Refer to *Table 3: Assays to Identify Antibody to HLA: Screening, Specificity, or Crossmatching* below.
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). • During the time of transplant or retrospectively (number of hours or days). • Timed to limit cold ischemia.

C.2.C #12: The assay format that will be used for antibody screening and for crossmatching

An antibody history is used in the antibody screening and crossmatching of donors and recipients. Laboratories may use the tests in *Table 3: Assays to Identify Antibody to HLA: Screening, Specificity, or Crossmatching* below to create an antibody history and assess sensitization in transplant candidates. NOTE: a solid phase method must be used to support the listing of unacceptable antigens in UNet^{SM} per *Policy 4.5: Antibody Screening and Reporting.*

Table 3: 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 *and* for PRA or crossmatch
Anti-human Globulin - enhanced cytotoxicity (AHG-CDC)	To improve detection of weak or low level antibodies and for PRA or crossmatch
Enzyme-Linked Immuno Sorbent Assay (ELISA)-based assays (solid phase): • **Mixed antigens** • **Cell equivalents** • **Single antigens** • **Solubilized cells**	To provide a test that does not depend on complement fixation: • For monitoring • To measure specificity • To measure specificity • For crossmatch
Flow cytometry-based assays: • **Cell-based** • **Microparticle-based multi-antigen beads (solid phase)** • **Microparticle-based single HLA-antigen beads (solid phase)**	As the most sensitive test for antibody: • For crossmatch or PRA • For PRA without background from cell membranes • For high resolution antibody identification
To determine isotype of antibody: • **IgG or IgM** • **Complement-fixing IgG**	For PRA or crossmatches
To rule out contribution by auto-antibody: • **Treatment of serum** • **Autologous cells**	For PRA 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 could include cytotoxicity or more sensitive tests to identify patients with antibodies.
   - Multiple sera should be evaluated to establish a baseline.
2. Determine antibody specificity in patients with detectable circulating antibodies using at least one solid-phase detection system.
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.

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4.4 Resolving Discrepant Donor and Recipient HLA Typing Results

Laboratories should have a written protocol in place to resolve discrepant HLA typing results between laboratories within 30 days of OPTN Contractor notification.

4.6 Crossmatching

4.6.A Crossmatching for Kidney Transplants

The written agreement between the laboratory and the OPO or each transplant program it serves should document criteria for and procedures to use in assessing prospective compatibility (i.e., physical versus virtual crossmatch).

Physical Crossmatching

For deceased donor crossmatching, lymph nodes or spleen are preferable if available for increased cell purity and viability.

Virtual Crossmatching

When a laboratory assesses the immunologic compatibility based on a recipient's alloantibody profile compared to a donor's HLA antigen typing, the written agreement with the OPO or transplant program it serves should define:

1. Patient eligibility criteria based on their current and historic sensitization status.
2. Criteria for evaluating and documenting sensitizing events.
3. A schedule for sample collection and solid phase methods for antibody testing to be used for virtual crossmatch.
4. Cutoffs and thresholds for antibody data interpretation based on correlation with physical crossmatch data.
5. Criteria when physical crossmatch is required pre-transplant. For example, high CPRA

patients where DSAs cannot be clearly identified.

6. Criteria when physical crossmatch will be performed post-transplant to confirm the virtual crossmatch findings. If the two results do not concur, define criteria for immediate notification of the ordering physician and/or authorizing individual. Such notification should be documented in the patient's results.

Also note:

1. Additional molecular typing for DPA1 or allele level typing may be needed for any locus/allele against which the patient has documented antibody reactivity.
2. When a virtual crossmatch is used for selection of the actual donor/recipient pair to be transplanted, it is recommended that the data be interpreted by a technical supervisor, clinical consultant, or an individual with experience equivalent to the above. The consultation may be performed off site.

4.7 Blood Type Determination

For ABO subtyping, it is recommended that the laboratory should have a process for obtaining the RBC transfusion status of the donor blood samples being considered for subtype testing. See *Policy 2.6*: *Deceased Donor Blood Type Determination and Reporting* for more information.

4.8 Preservation of Excess Specimens

It would be beneficial for the laboratory to preserve donor material (e.g., spleen or lymph node) for future testing, whenever possible.

The type and amount of donor specimens preserved should correspond to any potential testing that may be requested by the clinicians for the purpose of patient care (e.g. crossmatch, additional HLA typing, and other genotyping).

The laboratory should maintain records of the type and amount of specimens preserved for each donor, and ensure these specimens are readily available for testing.

The handling and storage methods of preserved specimens should ensure that specimen integrity can be appropriately maintained for generating reliable test results for that type of specimen.

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