OPTN

Guidance Document

Guidance Document for OPTN Histocompatibility Laboratory Bylaws and Policies

OPTN Histocompatibility Committee

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Contents

Summary

The OPTN Histocompatibility Committee created this guidance document in order to provide additional information or clarification for the OPTN bylaws and policies[1]. This document is designed to provide guidance for operationalization of OPTN 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 developed during the histocompatibility bylaws and policies rewrite. During that time the Committee decided that several sections of bylaws and policies were better suited as a guidance document. 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 The Committee reviewed those sections, and decided to omit certain sections that referenced out of date components of histocompatibility testing, or because they related to testing standards better governed by lab accrediting agencies like the American Society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).

In 2025[2], the Committee requested to update language in section C.2.C #9: Frequency of periodic sample collection to align with updated Center for Medicare and Medicaid Services standards that were released in December 2024[3]. The guidance language update was approved by the OPTN Board of Directors on May 15th, 2025.

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.

OPTN Membership and Management Policies Appendix C: Membership Requirements for Histocompatibility

C.2 Facilities and Resources

C.2.C: Written Agreements

Membership and Management Policy C.2.C: Transplant Program Affiliation lists the different components required in the agreements between histocompatibility labs and the transplant programs they support.

[1] https://optn.transplant.hrsa.gov/media/hziblkem/20220405_histocompatibility_meeting-summary.pdf
[2] https://optn.transplant.hrsa.gov/media/c0hda2qn/20250114-histo-meeting-summary.pdf
[3] https://www.cms.gov/files/document/qso-25-10-clia.pdf

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 Membership and Management Policy 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.
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.~~

It is recommended that laboratories have monthly serum samples for candidates and use these samples

to develop an antibody history and facilitate final crossmatches. Determination of the specific schedule for sample collection, storage, and testing is ultimately determined by the transplant programs and laboratories.

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:

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 it is recommended that the laboratory perform the physical crossmatch concurrently with the transplant or retrospectively to guide post-transplant care.
2. 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.

OPTN Policy 4: Histocompatibility

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.