OPTN/UNOS Histocompatibility Committee
Report to the Board of Directors
June 25-26, 2012
Richmond, Virginia

I. Action Items for Board Consideration

- The Board is asked to consider a proposal to include HLA-C in the CPRA calculation, update the HLA frequencies used to calculate CPRA and add a mandatory field to Waitlist[sm] for reporting of anti HLA antibodies (Item 1, Page 2).

- The Board is asked to consider proposed revisions to Appendix C (Membership Requirements for Histocompatibility Laboratories) (Item 2, Page 3).

II. Other Significant Items

- Histocompatibility Policy Rewrite (Item 3, Page 12).

- Update from the Kidney Transplantation Committee (Item 4, Page 13).

- Pediatric-Histocompatibility Subcommittee Update (Item 5, Page 16).

- HLA Typing Requirements for ECD Kidneys (Item 6, Page 16).

- Updates to Appendix 3A (Item 7, Page 17).

- Analysis of Transplant Program Size and Sensitization (Item 8, Page 17).

- Data Analysis Follow-up from July 2011 (Item 9, Page 19).

- Report from the Policy Oversight Committee (Item 10, Page 19).

- Request from the American Society of Histocompatibility and Immunogenetics (Item 11, Page 19).

- DonorNet[sm] Reporting of HLA-DP Typing (Item 12, Page 20).

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Nancy Reinsmoen, PhD, Chair
Lee Ann Baxter-Lowe, PhD, Vice Chair

This report details the discussions had and decisions made by the Histocompatibility Committee during its teleconference meetings on November 15, 2011, January 25, 2012, March 23, 2012, and May 2, 2012.

1. Proposal to Add HLA-C to Calculated Panel Reactive Antibody (CPRA) Calculation

The Committee finalized its proposal to update the frequencies and the antigens used to calculate CPRA to better reflect current laboratory practices as well as the current donor pool. These revisions include updating the HLA frequencies used to calculate CPRA, the addition of the antigen C to the calculation, and the addition of a question to the waiting list to better interpret 0% default CPRA value.

In November, Regional Representatives reported that most of the feedback received on the proposal to add HLA-C to the CPRA calculation was positive. David Maurer, PhD, reported that Region 7 questioned whether the clinical evidence supported the addition of HLA-C to the CPRA calculation at this time. The Committee determined that the evidence would not support mandatory reporting of C unacceptable antigens; however, this proposal allows individual centers to determine whether they will list HLA-C antigens as unacceptable. Currently, over 10,000 candidates have a HLA-C antigen listed as unacceptable. Because the reporting of HLA-C is now mandatory for all deceased donors, these candidates are screened from match runs but do not receive a compensatory increase in CPRA score. The Committee determined that centers who do not find HLA-C antibody to be relevant have the option to not list these as unacceptable. This practice will not disadvantage candidates from their center because only candidates who do have C listed as an unacceptable are screened from match runs.

In May, the Committee reviewed the post-public comment modifications to the proposal to update the CPRA calculation **(Exhibit A)**. The Committee advised that the compliance and monitoring plan should be supplemented with language to indicate that the histocompatibility laboratory must maintain records and supply these records to the OPTN Contractor upon request.

The Committee also reviewed a response to a comment from Region 1 and agreed to revise it with more precise data. The updated response will indicate that 63% of candidates are listed with a CPRA equal to 0%. This proposal does not contain any policy language modifications, therefore, the Board of Directors is asked to consider the following resolution, with complete details provided in the briefing paper **(Exhibit A)** and a resource and impact statement **(Exhibit B)**. The Committee approved the following resolution to be presented to the Board of Directors with a vote of 14 in favor, 0 opposed, and 0 abstaining:

> ****RESOLVED that the CPRA calculation and related fields in Waitlist[sm] shall be modified as set forth below, effective pending programming and notice to the membership:**
>
> **i. Update the HLA frequencies used to calculate CPRA;**
> **ii. Add HLA antigen C to the CPRA Algorithm; and**

iii. Add a mandatory field to Waitlist[sm] for all kidney, kidney/pancreas, and pancreas candidates to determine if a candidate has been tested for anti HLA antibodies and having this field display in reports and on match runs.

2. Revisions to Language Governing HLA Laboratories

The Committee then reviewed the post-public comment modifications to the Committee's proposal to revise the OPTN/UNOS bylaws and OPTN policies that govern HLA laboratories **(Exhibit C)**. The Committee asked that a statement be added to the Compliance and Monitoring Plan to make it clear that the OPTN Contractor will review any complaints related to these bylaws. The Committee reviewed and approved the modified language as presented below:

For the convenience of the reader, new policy language is underlined and revised language is ~~stricken through~~. Changes that have been made post public comment appear in double underlines.

C. Quality Assurance
C5.000 Proficiency Testing and Competency Evaluation
C5.300 The laboratory must test proficiency samples in the same manner ~~comparable~~ to that for testing clinical samples.
C9.000 Subcontracting
C9.100 A UNOS approved laboratory may engage another laboratory to perform testing by subcontracting the work to that laboratory. In that event, if histocompatibility and/or transplantation immunology testing is referred, the subcontracting laboratory must be CLIA certified~~/exempt~~ and either UNOS approved,~~ or~~ ASHI accredited, ~~/~~or CAP accredited for that testing…
F. Renal and Pancreas Organ Transplantation
F2.000 HLA Typing
~~F2.100 Prospective typing of donors and recipients for HLA-A, B, Bw4, Bw6, and DR antigens is mandatory.~~
~~F2.200 Prospective typing of donors and recipients for HLA-C, and DQ antigens and for DR51, DR52, DR53, is highly recommended.~~
F.2.100 Prospective typing of deceased donors for HLA-A, B, C, Bw4, and Bw6, and DR, DR51, DR52, DR53 and DQB antigens is mandatory.
F2.200 Prospective typing of candidates for~~of~~ HLA-A, B, Bw4, Bw6 and DR is mandatory, and the typing of C, DR51, DR52, DR53, and DQB is highly recommended.
F3.000 Antibody Screening
F3.100 Laboratories must have a policy in place to evaluate the extent of sensitization of each patient at the time of initial evaluation and following potentially sensitizing events, based on the antibody characteristics that are clinically relevant to each transplant center's protocols. ~~This information is provided to the laboratory by the transplant program.~~ The transplant program must provide this information to the laboratory.
This information must be~~is~~ provided to the laboratory by the transplant program.
F3.200 Laboratories must have a program to periodically screen serum samples from each patient for antibody to HLA antigens. The laboratory must have a documented policy establishing the frequency of screening serum samples and must have data to support this policy. ~~It is recommended that samples be collected monthly~~. Samples ~~will~~must be collected at time intervals outlined in the joint agreement between the laboratory and the transplant program.

I. ABO Blood Group Determination
I1.000 Laboratories performing ABO blood group determination~~s~~ must use ~~be performed by~~ techniques compliant with Federal regulations.

The Committee was asked to vote to approve two versions of the bylaws. These two versions are necessary because the Board meeting agenda had not yet been set and a more comprehensive revision to the entire set of OPTN Bylaws will also be considered during the meeting. One version of the histocompatibility bylaws was written in the current format and the second version was written in the revised format. By voting to approve both versions, the Committee allowed for flexibility at the Board meeting where Dr. Reinsmoen will be able to present the appropriate version for consideration.

During consideration of the below resolution, an amendment was proposed to retain the word "exempt" in the bylaw language since at least one OPTN member is a military hospital which is not required to maintain CLIA certification. The resolution was approved with a vote of three in support of the language as originally presented, nine in favor as amended, one opposed, and one abstaining. The proposed language below has been modified to reflect the amendment approved by the Committee.

****RESOLVED, that the following modifications to Appendix C (Membership Requirements for Histocompatibility Laboratories) are hereby approved pending notice to the membership:**

Current Bylaws:	**Rewrite Bylaws:**
C. Quality Assurance **C5.000 Proficiency Testing and Competency Evaluation** C5.300 The laboratory must test proficiency samples in <u>the same</u> manner ~~comparable~~ to that for testing clinical samples.	Appendix C: Membership Requirements for Histocompatibility Laboratories C.6 Histocompatibility Laboratory Testing Requirements **C. Testing Standards** Laboratories must meet requirements for testing accuracy and completeness as established by the OPTN Board of Directors through the OPTN Contractor policy development process. These standards are established to ensure accurate and dependable histocompatibility testing consistent with current technology and the availability of reagents. These testing standards establish minimal criteria that all Histocompatibility Laboratories must meet. The following testing standards have been prepared by the Histocompatibility Committee, and approved by the OPTN Board of Directors: 1. All procedures used in histocompatibility testing must conform to established protocols and be independently validated by the laboratory prior to use for clinical testing. 2. Each procedure must include quality assurance measures to monitor test performance. 3. Laboratories using its approval by the OPTN Contractor as proof of compliance to these standards must be current OPTN Members.

	The laboratory must perform at least twice a year a side-by-side comparison of any test results if it: 1. Performs the same test using different methods or instruments. 2. Performs the same test at multiple sites. The laboratory must verify or establish for each testing method the performance requirements for accuracy, precision, analytical sensitivity and specificity, and the acceptable range of test results. The laboratory must have appropriate controls for each test to evaluate test performance and accuracy. **Proficiency Testing and Competency Evaluation** The laboratory must participate in at least one external proficiency testing program, if available, for each analyte to assess the laboratory's ability to accurately perform testing. If an external proficiency program is not available, the laboratory must use other procedures that meet CLIA requirements to validate performance at least semi-annually for each analyte. The laboratory must test proficiency samples in ~~a~~ the same manner ~~comparable to~~ as that for testing clinical samples. The laboratory must determine and document the cause for each unsatisfactory proficiency test result. Unsatisfactory performance can be *either* of the following: ▪ Less than 80 percent correct for an entire year for a specific analyte or within a single survey. ▪ Two out of three consecutive surveys graded as unsatisfactory. If a laboratory's performance in an external proficiency testing program is unsatisfactory, the laboratory must participate in an enhanced proficiency testing program until given a satisfactory result.
C9.000 Subcontracting	Appendix C: Membership Requirements for Histocompatibility

C9.100 A UNOS approved laboratory may engage another laboratory to perform testing by subcontracting the work to that laboratory. In that event, if histocompatibility and/or transplantation immunology testing is referred, the subcontracting laboratory must be CLIA certified/exempt and either UNOS approved, ~~or~~ ASHI accredited, ~~/~~ or CAP accredited for that testing… .	Laboratories C.6 Histocompatibility Laboratory Testing Requirements **H. Subcontracting** A Histocompatibility Laboratory may use another laboratory as a subcontractor to perform testing. If a Histocompatibility Laboratory refers testing to another laboratory, the subcontracting laboratory must be *both*: 1. CLIA certified or exempt. 2. OPTN-approved, ~~or~~ ASHI accredited, or ~~/~~CAP accredited for that testing. For all testing performed by a subcontractor laboratory, the results must be returned to the referring laboratory and released only after the review and approval of the Director of the laboratory. The identity of the subcontracting laboratory and that portion of the testing for which it bears responsibility must be noted in the report of the Histocompatibility Laboratory. A copy of the testing laboratory's report must be kept on file by the laboratory receiving the results. Proficiency testing must not be referred to another laboratory.
F. Renal and Pancreas Organ Transplantation **F2.000 HLA Typing** ~~F2.100 Prospective typing of donors and recipients for HLA-A, B, Bw4, Bw6, and DR antigens is mandatory.~~ ~~F2.200 Prospective typing of donors and recipients for HLA-C, and DQ antigens and for DR51, DR52, DR53, is highly recommended.~~ F.2.100 Prospective typing of deceased donors for HLA-A, B, C, Bw4, and Bw6, and DR, DR51, DR52, DR53 and DQB antigens is mandatory. F2.200 Prospective typing of candidates for~~of~~ HLA-A, B, Bw4, Bw6 and DR is mandatory, and the typing of C, DR51, DR52, DR53, and DQB is highly recommended.	**Policy Appendix 3D:** Prospective typing of deceased donors for HLA-A, B, C, Bw4, and Bw6, and DR, DR51, DR52, DR53 and DQB antigens is mandatory. Prospective typing of candidates for ~~of~~ HLA-A, B, Bw4, Bw6 and DR is mandatory, and the typing of C, DR51, DR52, DR53, and DQB is highly recommended.

F3.000 Antibody Screening F3.100 Laboratories must have a policy in place to evaluate the extent of sensitization of each patient at the time of initial evaluation and following potentially sensitizing events, based on the antibody characteristics that are clinically relevant to each transplant center's protocols. ~~This information is provided to the laboratory by the transplant program.~~ The transplant program must provide this information to the laboratory. F3.200 Laboratories must have a program to periodically screen serum samples from each patient for antibody to HLA antigens. The laboratory must have a documented policy establishing the frequency of screening serum samples and must have data to support this policy. ~~It is recommended that samples be collected monthly~~. Samples ~~will~~must be collected at time intervals outlined in the joint agreement between the laboratory and the transplant program.	**Policy Appendix 3D:** Laboratories must have a policy in place to evaluate the extent of sensitization of each patient at the time of initial evaluation and following potentially sensitizing events, based on the antibody characteristics that are clinically relevant to each transplant center's protocols. ~~This information is provided to the laboratory by the transplant program.~~ The transplant program must provide this information to the laboratory. Laboratories must have a program to periodically screen serum samples from each patient for antibody to HLA antigens. The laboratory must have a documented policy establishing the frequency of screening serum samples and must have data to support this policy. ~~It is recommended that samples be collected monthly~~. Samples ~~will~~must be collected at time intervals outlined in the joint agreement between the laboratory and the transplant program.
I. ABO Blood Group Determination I1.000 Laboratories performing ABO blood group determination~~,~~ must use ~~be performed by~~ techniques compliant with Federal regulations.	**Policy Appendix 3D:** Laboratories performing ABO blood group determination~~,~~ must use ~~be performed by~~ techniques compliant with Federal regulations
Attachment IIB – UNOS Test Data Criteria for New HLA Laboratories and for the Addition of New Techniques **Data Submission** New laboratories are required to submit procedures and test validation data for all categories and methods of testing unless such work is performed, without exception, by another approved laboratory…	Appendix C: Membership Requirements for Histocompatibility Laboratories C.6 Histocompatibility Laboratory Testing Requirements **I. Submission Requirements for New Laboratories** A new Histocompatibility Laboratory is defined as one that has not yet been approved as an OPTN Histocompatibility Laboratory Member.

These materials are required to be submitted to an Agency with deemed status for the Accreditation of UNOS Laboratories~~, with a copy to the UNOS Histocompatibility Committee~~.	New laboratories are required to submit procedures and test validation data for all categories and methods of testing unless the testing is performed, without exception, by another approved laboratory. These materials must be submitted to an OPTN approved histocompatibility laboratory accrediting agency~~, with a copy to the OPTN Histocompatibility Committee~~.

The Committee then reviewed the items that were withdrawn from the proposal following public comment. The Committee agreed with all of the presented withdrawals as shown below.

Current Language	Revised Language	Rationale for Revision
UNOS BYLAWS **ATTACHMENT II TO APPENDIX B OF THE UNOS BYLAWS** **I. Key Personnel Qualifications** **A.1. Director Credentials** (i) The Director must be an MD, DO, or PhD in science, and must meet the qualifications of director of high complexity testing according to Federal CLIA requirements defined in 42CFR 493.1441. (ii) In addition to A1 (i), at least two of the years of the Director's training and/or experience must be in histocompatibility testing in a OPTN/UNOS approved training program or three years experience under a qualified OPTN/UNOS Histocompatibility Director.	**UNOS BYLAWS** **ATTACHMENT II TO APPENDIX B OF THE UNOS BYLAWS** **I. Key Personnel Qualifications** **A.1. Director Credentials** (i) The Director must be an MD, DO, or PhD in science, and must meet the qualifications of director of high complexity testing according to Federal CLIA requirements defined in 42CFR 493.1441. An M.D. or D.O. must also have a license to practice medicine in the state where the laboratory is located. (ii) In addition to A1 (i), ~~at least two of the years of the Director's training and/or experience must be in histocompatibility testing in a OPTN/UNOS an approved training program or Three years experience~~ if the candidate is also the technical supervisor of the laboratory, they must have completed two years general immunology plus two years histocompatibility experience under a qualified OPTN/UNOS Histocompatibility Director doing histocompatibility testing for solid organ transplantation.	These corrections must be made to be compliant with Federal CLIA requirements. It is also important to note that the OPTN does not approve training programs.

UNOS BYLAWS ATTACHMENT II TO APPENDIX B OF THE UNOS BYLAWS **I. Key Personnel Qualifications** **A2. Director Candidates** (ii) The director candidate must provide documentation of appropriate training and experience through submission of a portfolio of cases (see iii and iv, below) covered during the training in a OPTN/UNOS approved transplant center or must have certification by the American Board of Histocompatibility and Immunogenetics.	**UNOS BYLAWS ATTACHMENT II TO APPENDIX B OF THE UNOS BYLAWS** **I. Key Personnel Qualifications** **A2. Director Candidates** (ii) The director candidate must provide documentation of appropriate training and experience through submission of a portfolio of cases (see iii and iv, below) covered during the training in a OPTN/UNOS approved transplant center or must have certification by the American Board of Histocompatibility and Immunogenetics or other CMS approved board certification.…	It is now possible for a lab director to be qualified using other CMS approved certifications and there are currently several directors that do.
UNOS BYLAWS ATTACHMENT II TO APPENDIX B OF THE UNOS BYLAWS **I. Key Personnel Qualifications** **B.1. Responsibilities of a Director of a Histocompatibility Laboratory** (i) Ensure that the laboratory facilities are adequate and safe from physical, chemical, and biological hazards. (ii) Provide consultation to clients on test results. (iii) Must be accessible to the laboratory to provide onsite, telephone or electronic consultation, as needed. (iv) Ensure that an approved procedure manual is available to all technical personnel. (v) Ensure and monitor that all delegated duties are properly performed. (vi) Determine that a laboratory has a qualified general supervisor on-site for all routine testing. (vii) Ensure…….	**UNOS BYLAWS ATTACHMENT II TO APPENDIX B OF THE UNOS BYLAWS** **I. Key Personnel Qualifications** **B.1. Responsibilities of a Director of a Histocompatibility Laboratory** (i) Ensure that the laboratory facilities are adequate and safe from physical, chemical, and biological hazards. (ii) Provide consultation to clients on test results. (iii) Must be accessible to the laboratory to provide onsite, telephone or electronic consultation, as needed. (iv) Ensure that an approved procedure manual is available to all technical personnel. (v) Ensure and monitor that all delegated duties are properly performed. (vi) Determine that a laboratory has a qualified general supervisor. ~~is on-site for all routine testing.~~ (vii) Ensure…….	The Committee was concerned that this bylaw was unrealistic and that no laboratory requires that the general lab supervisor be on site 24 hours a day, seven days a week.

J Chimerism Analysis J1.000 Laboratories performing engraftment and chimerism testing using nucleic acid analysis must conform to all pertinent standards in Section K-Nucleic Acid Analysis. J2.000 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. J3.000 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. J4.000 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. **J5.000 Analysis and Reports** J5.100 Potential for preferential amplification of different sized alleles must be assessed and considered in the analysis. J5.200 If more than one locus is amplified in a single	~~**J Chimerism Analysis**~~ ~~J1.000 Laboratories performing engraftment and chimerism testing using nucleic acid analysis must conform to all pertinent standards in Section K-Nucleic Acid Analysis.~~ ~~J2.000 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.~~ ~~J3.000 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.~~ ~~J4.000 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.~~ ~~**J5.000 Analysis and Reports**~~ ~~J5.100 Potential for preferential amplification of different sized alleles must be assessed and considered in the analysis.~~ ~~J5.200 If more than one locus is amplified in a single~~	Chimerism testing is routinely used for blood and marrow transplantation. It is rarely used in solid organ transplantation (predominantly for suspected graft-versus-host disease, which is rare). Since it has never been routinely used for solid organ transplant, the Committee suggested removing it.

amplification (multiplex), the effects of such amplification on each system must be assessed and considered in the analysis. J5.300 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. J5.400 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. J5.500 When mixed chimerism is not detected, reports must state the sensitivity level of the assay.	~~amplification (multiplex), the effects of such amplification on each system must be assessed and considered in the analysis.~~ ~~J5.300 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.~~ ~~J5.400 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.~~ ~~J5.500 When mixed chimerism is not detected, reports must state the sensitivity level of the assay.~~	

Finally, the Committee reviewed its response to comment #48 (shown below) and agreed to make the following revisions to the briefing paper to answer all points made by the commenter. First, the inclusion of DQB will be clearly articulated in the response. Secondly, a reference to Policy Appendix 3D (which mandates an agreement between transplant programs and laboratories regarding sensitizing events) will be added. The comment will also be revised to indicate that the Committee intentionally did not assign responsibility for these actions to a specific individual in an attempt to not be overly prescriptive. Finally, the Committee pointed out that current policy requires laboratories to have a program to screen samples periodically and that any substantive change to that current requirement is outside of the scope of these revisions.

Comment 48:

vote: Support
Date Posted: 12/21/2011
Comments on the Proposed Revision to Histocompatibility Standards I. Key Personnel Qualifications The requirement for Technical Supervisor should be modified to require 2 years of human histocompatibility testing. F2.000 HLA Typing. The following clarification is needed. Is the requirement for DQ typing for DQB only or for both DQA and DQB. Typing of A, B, C, Bw4, Bw6, DRB1, DR51, DR52, DR53, and DQ should be mandatory for both donors and candidates. The rationale is that solid phase immunoassays have been known to yield apparent reactivity with a patient's own antigens as a result of reactivity with denatured antigens. In the absence of knowledge of the patients antigens, it would be possible to incorrectly identify an autologous antigen as unacceptable, potentially resulting in a missed opportunity for transplantation. References: El-Awar N, et al. Human Immunol. 70: 844, 2009 and Poli F, et al. Human Immunol. 2011 in epublication. F3.000 Antibody Screening F3.100 a clarification is needed as to what information is to be provided, information about sensitizing events or about antibody characteristics. Further, the histocompatibility laboratory may be considered part of the transplant program and therefore, it should be clarified that the information is to be provided by the transplant physician, coordinator, or nurse. F3.200. The responsibility for providing data to support the serum screening protocol should not be solely that of the laboratory. Federal Regulations require that protocols be established jointly by the laboratory and the clinical team. The laboratory can perform tests only as ordered by a qualified individual. Therefore, the responsibility for data supporting the protocol must be that of all individuals participating in establishing the protocol.

Committee Response:

Thank you, but due to the high volume of questions and concerns about this portion of the proposal, the Histocompatibility Committee has decided to withdraw some portion of the proposal and further address these requirements at a later date.

3. Histocompatibility Policy Rewrite Project

Current OPTN/UNOS policy includes a section detailing standards for member histocompatibility laboratories. Some of these standards have been found to be out of sync with practice and with other organizations that accredit histocompatibility laboratories (i.e., the American Society for Histocompatibility and Immunogenetics [ASHI] or the College of American Pathologists [CAP]). The Committee asked whether the OPTN/UNOS policies regarding histocompatibility standards could be removed and replaced with a reference to either the ASHI or CAP standards to eliminate incompatibility and redundancy between the different sets of standards. In November 2011, Lori Gore, UNOS liaison to the Histocompatibility Committee, explained that the process for OPTN policy development is different than that for ASHI or CAP. To simply adopt ASHI or CAP standards as OPTN policy would not provide the public or OPTN membership with an opportunity to comment on proposed changes.

In January 2012, Brian Shepard**,** Assistant Executive Director of Contract Operations, spoke to the Committee about how the rewritten OPTN Bylaws and the Policies that govern HLA laboratories should be structured. Committee members voiced the opinion that instead of starting from scratch, there should be a way to incorporate the ASHI and CAP standards into policy so that the OPTN policy development process could be utilized while maintaining better synchrony between the three sets of standards. Dr. Reinsmoen appointed a subcommittee to begin working on the project with a goal of reporting recommendations by February 29, 2012.

In March 2012, Ms. Gore provided an update on the bylaws rewrite project. The subcommittee met by teleconference with members of UNOS and HRSA to ask if the OPTN could require accreditation from an outside entity as condition of membership into the OPTN. The purpose of this accreditation would be to better ensure a certain level of proficiency. This idea was not well supported due to concerns that the OPTN would not be able to control the applied standards of an outside entity. As a compromise, the bylaws could require that a member meet the standards of ASHI or CAP as of a specified date. One method for demonstrating compliance with this requirement would be ASHI or CAP accreditation.

4. Update from the Kidney Transplantation Committee

In November 2011, Darren Stewart, UNOS research support for the Kidney Transplantation Committee (Kidney Committee), gave a presentation to the Histocompatibility Committee to update them on the continued discussion of the details of a potential new kidney allocation system. The Kidney Committee was focused on ensuring equitable access to transplantation for HLA sensitized candidates, either through giving regional or national priority to very highly sensitized candidates (e.g., >=95% CPRA) and/or using a scaled point system that would assign rank-ordering points on a graduated scale based on CPRA. The Kidney Committee recently asked for data to help answer specific questions, such as what threshold(s) should be used to start/end the CPRA sliding scale.

Mr. Stewart reported that nearly two-thirds of kidney registrations had CPRA of 0 at the end of 2009 and 2010. He said at the other end of the spectrum, about 11% of candidates had a CPRA of 95% or greater. Of those very highly sensitized candidates (>=95%), nearly half of them had CPRA=100%. He went on to say these distribution percentages did not vary remarkably from December 31, 2009 to December 31, 2010. The data showed that although candidates with a CPRA of 100% represented about 5% of the waitlist, less than 1% were actually ever transplanted.

He then reported on the demographics for the highly sensitized candidate; he said females were more likely than males to be very highly sensitized, or sensitized at all. However, the relationship of gender and CPRA appeared to be nonlinear. The ratio of percent female (68.6%) to percent male (31.4%) increased as CPRA increased, peaking around CPRA=95%. However, as CPRA increased from 95% to 100%, the ratio gradually decreased from 58.3% to 41.7%.

He also reported the African American candidates tended to disproportionately have very high CPRA scores (>=95%), whereas Hispanic candidates and Asian candidates tended not to be as highly sensitized. The relationship between sensitization and ethnicity appeared to be fairly weak, however.

Offer and transplant rates were also evaluated as a function of CPRA with results appearing similar to previous analyses. The transplant rate, defined as the number of transplants per 1,000 person-years, varied between 160 and 215 as CPRA increased from 0 to 69%. For the CPRA=70-79 group, the transplant rate dropped to 128.3. However, the transplant rate jumped to over 500 for the 80-84 group, then decreased as CPRA increased further, falling below 150 once CPRA reached 98%. The Committee was not surprised by the spike starting at CPRA=80-84, since candidates are currently defined as with CPRA scores>=80% are awarded four additional allocation points if CPRA. The decrease in transplant rates for the highly sensitized candidates was more pronounced by excluding zero-mismatches.

The Committee reviewed data which showed that unlike transplant rates, which showed very little trend prior to CPRA reaching 70%, offer rates decreased steadily as CPRA increased from 0% to 79%. As with transplant rates, offer rates showed an increase once CPRA reached 80%, then steadily decreased again, falling to 0.09 offers per patient year for CPRA=100% candidates. Though the offer rate increased when CPRA went from 75-79% to 80-84%, this 54% increase (3.88 to 5.99) was substantially lower than the

416% increase in transplant rates (128.3 to 534.4). Comparing non-sensitized candidates (CPRA=0%) with the opposite extreme (CPRA=100%), the offer rate for CPRA=0% candidates were 187 times more likely to receive an offer than CPRA=100% candidates; when zero-mismatches were excluded, the offer rate ratio exceeded 300.

The Committee thought an explanation for large disparity between offer rates – which showed a smooth, steady trend as a function of CPRA with an expected but moderate spike at 80%, and transplant rates, which revealed a more erratic pattern, may lie in the offer acceptance practices of individual transplant programs. As CPRA increases, transplant programs may become less selective and more willing to accept a lower quality kidney due to the concern that a sensitized candidate may not receive another suitable offer due to positive (virtual or prospective) crossmatch. The Committee opined that maybe this concern is even greater for candidates with CPRA>=80%, since this threshold has defines highly sensitized and thus may be a threshold perceived as indicating a smaller chance of another suitable offer being received.

The Committee was pleased to hear that the Kidney Committee would be asking for modeling that would start a sliding scale at a CPRA of 20% with a mandatory national share at 98%. The Kidney Committee will discuss the results of this model run in the near future.

In March 2012, Ciara Samana, UNOS liaison to the Kidney Committee Transplantation Committee, gave a review of the proposed kidney allocation system to the Committee which included:

- Longevity matching: Top 20% of donors (as defined by Kidney Donor Profile Index [KDPI]) to top 20% of candidates (as defined by Estimated Post Transplant Survival [EPTS])
- The CPRA sliding scale
- National priority for CPRA >=98% group, regional sharing for KDPI > 0.85 donors, and continued priority for pediatric candidates for kidneys with KDPI <=.35
- A definition of KPDI

Ms. Samana pointed out that if this proposed system were to be adopted, the majority of kidneys will be placed very similarly to the current rules. A member of the Committee asked why in the case where a donor has a KDPI of less than 20%, the ranking order of the proposed system put the regional top 20% below the local bottom 80%. If the Kidney Committee were trying to maximize longevity matching, sending a kidney with very long survival outside of the local area to reach a candidate who could realize that survival would make more sense. Ms. Samana explained that maintaining local priority was a compromise that the Committee felt was necessary at this time. Additionally, with kidney paybacks slated for elimination in the proposed system, there remains a concern within the transplant community about shipping large numbers of kidneys. Dr. Bowman, from HRSA, added that the intent of this new system was not to make a radical change in the local, regional, national order of allocation but to improve donor/recipient matching. Ms. Samana again emphasized that this new allocation system strongly resembles the current system and does not represent as major of a change as prior considered systems.

There was concern about the possibility of sensitized candidates (especially retransplant candidates) not falling within the top 20% EPTS kidney candidates, and that the proposed system was limiting their access to the entire donor pool. Ms. Samana said that was an excellent point and said the Kidney Committee should take a look to see if a relativity young person who had received a transplant with no diabetes could achieve a survival score high enough to be included within the top 20% EPTS kidney candidates. Anna Kucheryavaya, research liaison to the Committee, reminded members of data she presented to the Committee at the July 2011 meeting which showed that more than 40% of retransplant

patients have CPRA of greater than 95%. Ms. Samana indicated that the Kidney Committee would be very interested in these data if the Histocompatibility Committee would provide them.

Dr. Reinsmoen shared that the Kidney Committee is also discussing the possibility of allowing centers to list two separate pools of unacceptable antigens, one for local placement, which may not be as stringent, and one for imports that would be more robust. The purpose of the two lists would be so that a center could be very conservative when listing unacceptable antigens for an import offer to reduce the risk of an unexpected positive crossmatch. The same center, may decide not to list those antibodies or not include antibodies with a lower intensity for a local share because a center may be able to transplant across a weak positive cross match for a local offer.

Ms. Samana encouraged the Committee to provide its feedback to the Kidney Committee in a formal memo. The Committee continued the discussion with the Scientific Registry of Transplant Recipients (SRTR), and asked when the next phase of simulation modeling would be released. Adrine Chung, from the SRTR, answered simulation modeling should be available in the spring of 2012 (possibly May). Ms. Samana added that the earliest that the new kidney allocation proposal could go out for public comment would be in the fall of 2012 with it going to the BOD in the summer of 2013.

Members of the Committee wanted to make sure that the SRTR staff considered particular nuances of unacceptable antigens and CPRA for the simulation models. For instance, when a candidate with a high CPRA is listed, the candidate's risk of a positive crossmatch is underestimated because the current CPRA calculation does not take into account the antigens C, DP, and DQA. Many individuals who are listed with a CPRA of 80% or lower may actually have a higher chance of an incompatible donor than their CPRA value represents.

Members also wanted to confirm that the simulation modeling was using the unacceptable antigens listed and not just using the percent incompatible donors represented by the CPRA when doing their simulation. They asked if Policy Appendix 3A was being used. They also asked if they were also taking into account that when a candidate has C marked as an unacceptable, their CPRA value will not change but they will be screened from donor match runs. SRTR staff assured the Committee that all of these factors are a part of the simulation model. Members of the Committee asked if the simulation would indicate how often a kidney was not put into the intended recipient due to a positive crossmatch. Ajay Israni, MD, with the SRTR, commented that this is not currently possible since the modeling could not predict individual center behavior. He added that the next simulation would evaluate the number of transplants by CPRA for local/non local offers.

A member of the Committee asked how many candidates with high CPRA scores would never get an offer from a compatible donor unless it were a zero mismatch. Ms. Kucheryavaya offered to supply these to the Committee at its next face to face meeting in August 2012.

The Committee agreed to ask the Kidney Committee to analyze the effects on sensitized candidates of dividing the list into EPTS categories. In essence, the Histocompatibility Committee wants to understand how many sensitized candidates would miss out on an offer only because they are not in the top 20% EPTS category.

The discussion closed with Dr. Reinsmoen stating she would write a formal memo to the Kidney Committee that will be circulated to the full Committee to express these concerns.

5. Pediatric-Histocompatibility Subcommittee Update

In November 2011, Dr. Reinsmoen gave a brief summary of a conference call that took place between a subcommittee made up of Pediatric, Kidney Transplantation, and Histocompatibility Committee members. The subcommittee's charge was to design a system to better allocation kidneys for sensitized pediatric candidates.

The subcommittee developed a trial kidney allocation system, which would prioritize all highly-sensitized, pediatric kidney candidates that are located within the same region after the local prior living organ donors. This approach would add one new classification to the kidney allocation algorithm, and the general sequence would be as follows, with the new classification underlined:

All Current Zero Antigen Mismatch Classifications

Local Area Kidney, Prior Living Organ Donors

<u>Local Area and Regional Kidney, Highly Sensitized Pediatric</u>

Local Area Kidney, Highest Scoring High CPRA

Local Area Kidney, Pediatric

[no further changes]

This new category would include all candidates registered for a kidney transplant prior to their eighteenth birthday with a CPRA greater than or equal to 80%. The above sequence was being modeled with results expected during 2012.

6. HLA Typing Requirement for Expanded Criteria Donor (ECD) Kidneys

In January 2012, the Committee reviewed a discrepancy that had been discovered when programming the new policy to require deceased donor HLA typing to be performed by DNA methods. This policy was approved by the Board in November 2009 and was sponsored by the Histocompatibility Committee.

The approved policy requires that OPOs and their associated laboratories perform HLA typing of all deceased donors by DNA methods and identify the HLA-A, -B, -Bw4, Bw6, -C, -DR, -DR51, -DR52, -DR53 and -DQ antigens before making any kidney, kidney-pancreas, pancreas, or pancreas islet offers.

The Committee was asked if this policy should apply to all deceased donors, (i.e., standard criteria donors and expanded criteria donors). Currently, placement of ECD donors does not require HLA typing for placement. If the HLA is not provided at the time of the match, the sequence will close at zero and no offers can be made.

Data presented to the Committee showed of the 1457 ECD kidneys placed from January 1, 2010 to May 31, 2011, all but 7 were placed with the HLA information. Therefore, providing HLA information for ECD kidneys appears to be the standard of practice for the overwhelming majority of offers.

Based on the information, the Committee unanimously agreed to support the requirement for HLA for all deceased donors, including ECD, to be circulated for public comment by the Kidney Committee, as set forth below:

3.5.3.2 Computer Entry.

~~i.~~ Information regarding each and every deceased kidney donor must be entered into UNet[SM] prior to kidney allocation, to determine whether there is a zero antigen mismatch between the donor and any candidate on the Waiting List. Pre-procurement tissue typing is ~~expected~~ required in allocating expanded criteria donor kidneys. ~~In the absence of pre-procurement tissue typing, allocation of expanded criteria donor kidneys shall proceed pursuant to Policy 3.5.12 according to candidate waiting time. If pre-procurement tissue typing is not initiated, the Host OPO shall provide a written explanation of the reasons to the OPTN contractor.~~

7. Updates to Appendix 3A

In January 2012, the Committee started the process for updating Appendix 3A of Policy 3.0 since policy requires this task to be undertaken annually. The Committee unanimously agreed to start the process of updating the tables.

8. Analysis of Transplant Program Size and Sensitization

In March 2012, Anna Kucheryavaya from UNOS Research, presented data from a request made in July 2011, on the CPRA analyses for large adult kidney programs stratified by the percentage of broadly sensitized candidates (CPRA>=80%) **(Exhibit D)**. At the time of the request, the Committee reviewed an analysis of waiting list registrations during the 18 month period before and after CPRA implementation. At that time, it was found that at least some larger kidney transplant programs (defined here as programs with more than 100 adult kidney-alone registrations) had relatively small percentages of broadly sensitized registrations. To further investigate this finding further, the Committee asked for a comparison of candidate/recipient demographics, transplant, and offer data for larger transplant programs. Additionally, the Committee planned to compare these findings to what is presently observed throughout the kidney allocation system.

First, Ms. Kucheryavaya provided the distribution of the percentage of candidates with CPRA>=80% candidates for large centers included in this report. She said there were five big centers with less than 5% broadly sensitized candidates, 135 with 5-25% broadly sensitized candidates and 17 with more than 25% broadly sensitized candidates. Next she compared the percentages of re-transplant, female and minority candidates between the different groups of centers:

- The percentages of re-transplant and female candidates were similar in the centers with less than 5% broadly sensitized candidates and centers with 5-25%broadly sensitized candidates. But the percentages were significantly lower than in the centers with more than 25% broadly sensitized candidates. The centers with 5-25% broadly sensitized candidates had the lowest percentage of African Americans (34%). The percentage was significantly higher for less than 5% broadly sensitized candidates' centers (40%). Centers with greater than 25% of broadly sensitized registrations had the highest percentage of African Americans (43%).

The Committee commented that the demographics for the centers with less than 5% broadly sensitized candidates were not significantly different from the other groups. Therefore, those centers should have approximately the same number of sensitized candidates as the other groups.

Then the Committee examined the transplant rates for the different groups of centers by transplant type (zero antigen mismatch versus non zero antigen mismatch).

- Small number of transplants for centers with <5% broadly sensitized candidates resulted in wide confidence intervals for the group. None of the transplant rates for this center group was significantly different from rates for centers with 5-25% broadly sensitized candidates.
- With exception of the CPRA>=80% group, overall transplant rates for centers with greater than 25% broadly sensitized candidates were significantly higher than for centers with 5-25% broadly sensitized candidates. These differences were driven by non zero antigen mismatch transplants. Transplant rates for zero antigen mismatch transplants were similar for two groups of centers (5-25% and >25%).

Committee members said these data verified that the overall transplant rates between the three groups did not differ significantly. The Committee was pleased to see that those centers that listed unacceptable antigens (with >25 broadly sensitized candidates) had the highest rate of transplant for their highly sensitized candidates.

Next, the Committee compared the percentage of kidney offers refused due to the positive crossmatch by offer type (zero antigen versus non zero antigen mismatch), sensitization level, and center group:

- Not surprisingly, the centers with less than 5% broadly sensitized candidates had the highest percentage of offers refused due to positive crossmatches (1.5%). This was found to be significantly higher than the percentages for the centers with 5-25% broadly sensitized candidates (0.5%) and centers with >25% broadly sensitized candidates (0.6%).
- Due to the small number of zero antigen mismatch offers, all of the differences in the percentage of positive crossmatches reported as a reason for organ refusals were not statistically significant.

The Committee examined the number and percentage of kidney offers refused due to the positive crossmatch by offer type (local vs. non local), sensitization level and center group:

- For each group of centers the percentage of local offers refused due to positive crossmatches was significantly higher than for non local offers.
- For local offers, there was no significant difference in percentages for centers with less than 5% broadly sensitized candidates and centers with greater than 25% groups broadly sensitized candidates (1.9% vs. 2.4%). Both percentages were significantly higher than the percentage for centers with 5-25% broadly sensitized candidates (1.0%).
- For non local offers, there was no significant difference in percentages for centers with 5-25% broadly sensitized candidates and centers with greater than 25% groups broadly sensitized candidates (0.1% vs. 0.1%). Both percentages were significantly lower than the percentage for centers with less than 5% broadly sensitized candidates (1.3%).

The Committee stated that the data confirmed the hypothesis that the centers not listing unacceptable antigens are using the crossmatch as their screening mechanism. This practice not only disadvantages their candidates but also slows down the entire allocation system. The next set of data confirmed these assertions by showing the number and percentage of kidney offers accepted for transplant but not transplanted into the intended recipient.

The data showed the centers with less than 5% broadly sensitized candidates had the highest percentage of such offers (42.4%). The rate was significantly higher than the percentages for centers with 5-25% broadly sensitized candidates (9.6%) and centers with greater than 25% (2.7%) broadly sensitized candidates. The Committee asked that future analyses show the number of candidates affected by offers refused due to positive crossmatches and offers accepted but organs not transplanted into the intended recipient.

Ms. Kucheryavaya also shared data which showed the median positions of transplanted patients on the match run by sensitization level and center group. For all sensitization groups, recipients in the centers

that had less than 5% broadly sensitized candidates had by far the highest median position on the match run. Non sensitized recipients at centers with less than 5% broadly sensitized candidates had a median position of 83.5 versus a median position of three to seven for all other large centers.

The Committee recognized that there was no policy requiring the listing of all unacceptable antigens or a policy that requires an acceptable number or percentage of offers that can be declined due to positive crossmatches for shipped organs. The majority of the Committee said that these policies should be reviewed and proposals made to address these shortcomings. Several members suggested the place to begin the process was to decide what a reasonable rate of organs not being used within the intended recipient because of a positive cross match should be. This could be done by first establishing a national average. Ms. Gore reminded the Committee that there must be a written formal problem statement that could be presented to the BOD to begin the process of formulating these policies.

9. Data Analysis Follow Up from July 2011

In March 2012, Ms. Kucheryavaya asked for clarification on a research request that was submitted following the Committee's July 2011 meeting. As part of the request, the Committee asked for comparison of the CPRA of candidates who were multiply listed or had transferred to another center. While conducting this analysis, Ms. Kucheryavaya found that when a candidate moved to another center, the unacceptable antigens were not always entered right away. She asked the Committee for an estimate of a reasonable amount of time for centers to list unacceptable antigens after listing a new candidate. Members of the Committee advised a period of four to six weeks from time of listing. Ms. Kucheryavaya asked if there would be a danger of a kidney candidate having a sensitizing event during that time frame but members of the Committee felt that was highly unlikely.

Ms. Kucheryavaya then asked the Committee to compare the DPB drop down on various UNet^{sm} forms, particularly the Teidi (Donor and Recipient Histocompatibility forms), and Kidney Paired Donation (KPD) forms. She pointed out to the Committee that these two forms varied and asked which the Committee preferred for Donor and Recipient Histocompatibility forms. To make the DPB drop downs more consistent, the Committee decided to add two additional options, antigens 2 and 4, to the approved DPB drop down on Donor and Recipient Histocompatibility forms. The new DPB drop down was approved by the Committee during February 5, 2010 conference call.

10. Report from the Policy Oversight Committee (POC)

Lee Ann Baxter-Lowe, PhD, reported that the Policy Oversight Committee (POC) is providing oversight of all OPTN committee projects and helping with the prioritization of the implementation of those projects.

Additionally, the POC has created a task force to determine better methods for allocating organs to candidates who require more than one organ at a time. The HLA requirements for multi-organ candidates will need to be more stringent in these cases to reduce the chance of an unexpected positive crossmatch. Ms. Krisiunas and Dr. Reinsmoen agreed to develop some guidelines for review by the POC on this matter.

11. Request from the American Society of Histocompatibility and Immunogenetics (ASHI)

In March 2012, Ms. Gore shared a memo from ASHI which asked the Committee to consider making the typing of DPB mandatory for all donors. The Committee agreed with this request in theory agreed that the first step would be to have the field made available in UNet^{sm}. A few members volunteered to write a formal reply to ASHI on this matter to be reviewed by the full Committee.

12. DonorNet® Reporting of HLA-DP Typing.

Since the requirement to share HLA-DP (if requested) for thoracic donors was put into place, in November 2011, Ms. Gore shared with the Committee that she had received several calls from members who were frustrated with the lack of a field to post this information in DonorNet®. The Committee asked that a new project be created so that it could add fields for HLA-DP and HLA-DQ alpha. Ms. Gore agreed to write a problem statement for review by the Executive Committee on this matter.

Participation in the
Teleconferences
of the
Histocompatibility Committee

NAME	COMMITTEE POSITION	11/15/2011	1/25/2012	03/23/2012	05/02/2012
Nancy Reinsmoen, PhD	Chair	x	x	x	x
Lee Ann Baxter-Lowe, PhD	Vice chair	x	x	x	
Massimo Mangiola, PhD	Region 1 Rep.	x	x	x	
Dimitri Monos, PhD	Region 2 Rep.	x	x	x	x
Robert Bray, PhD	Region 3 Rep.	x	x	x	
Cathi Murphy, PhD	Region 4 Rep.			x	
Dolly Tyan, PhD	Region 5 Rep.	x	x	x	
Paul Warner, PhD	Region 6 Rep.	x	x	x	
David Maurer, PhD	Region 7 Rep.	x	x	x	x
Sara Dionne, PhD	Region 8 Rep.	x	x	x	x
Rex Friedlander	Region 9 Rep.	x			x
A. Bradley Eisenbrey MD, PhD	Region 10 Rep.	x	x	x	
David Kiger, CHS, CHT	Region 11 Rep.	x	x	x	x
Laine Krisiunas, BS, MBA	At Large	x	x	x	
Luis Campos, MD	At Large	x			
James Selby	At Large	x	x		
Howard Gebel	SRTR Liaison	x	x	x	
Bryn Thompson	SRTR Liaison				
Adrine Chung	SRTR Liaison				x
Lori Gore	Committee Liaison	x	x	x	
Elizabeth Sleeman	Committee Liaision				x
Ciara Samana	Committee Liaison				x
Gena Boyle	Committee Liaison				x
Anna Kucheryavaya	Support Staff	x	x	x	x
Jory Parker	Support Staff	x	x	x	
Cheryl Hall	Support Staff				x
James Bowman	Ex officio (HRSA)	x	x	x	x
Raelene Skerda, RPh, BPharm	Ex officio (HRSA)		x		