Interim Report

OPTN/UNOS Histocompatibility Committee Meeting
O'Hare Airport Hilton Hotel, Chicago, IL
July 13-14, 2010

Nancy Reinsmoen, Ph.D. opened the meeting by introducing herself as the new chair of the Committee and Lee Ann Baxter-Lowe, Ph.D. as the new vice chair. Lori Gore, Committee Liaison, then gave a brief orientation on the Committee roles and responsibilities.

Orientation from the SRTR. Dr. Alan Leichtman gave an overview of the Scientific Registry of Transplant Recipients (SRTR).

Summary of the Meeting of the Board of Directors. Ms. Gore provided the Committee with a brief update of relevant actions from the June 2010 meeting of the OPTN/UNOS Board of Directors (BOD) in Richmond, Virginia. The Committee's primary interests were an update on the Kidney Paired Donation (KPD) Pilot Program and the BOD approval for the use of the Kidney Donor Profile Index (KDPI) as an informational reference to assess kidney donor quality.

OPTN/UNOS Strategic Planning. Ms. Gore updated the Committee on the development and identification of the OPTN/UNOS strategic planning goals for the Committee. The Top 2010 goals for the Histocompatibility Committee are as follows:

- Develop a fair and effective sliding allocation point scale for sensitized patients based on CPRA. (Preliminary proposal submitted for modeling)
- Develop strategy to preserve waitlist rank for patients undergoing desensitization
- Develop guidelines and mechanisms to utilize the HLA discrepant typing reports and HLA typing data from the match run and from the donor and recipient histocompatibility to improve accuracy of listing.

The Committee was informed that these annual goals were developed by the incoming and outgoing president with staff input. The Committee was informed that the goals should continue to form the primary basis of Committee activity over the next year.

Request from UNOS. -Currently there is a work order in UNOS to add a warning message to the Waitlist Lab Data - Import Unacceptable Antigen Data process when a 'parent' antigen is listed as an unacceptable antigen and the candidate is typed for a 'split' of the unacceptable parent antigen. The Committee was asked to review this request.

The Committee approved of the warning but felt the language was too vague and that most coordinators would click right through it because they did not know what it meant. The Committee thought the message should be scarier and the actual language simpler.

The Committee suggested the pop up message be accompanied with a big red X and to have the text say "STOP. You have entered an antigen as an unacceptable that would prevent this candidate from ever receiving a 0MM offer. It is strongly recommended that you check with you HLA laboratory director before proceeding. Click OK to save the form click as is or Cancel to return to the page."

Membership Issues and Report from the Membership and Professional Standards Committee (MPSC). The Committee approved a new format for the membership ballot in February 2009. This ballot is a document prepared by Sally Aungier, Administer from the UNOS Membership Department. In it, she summarizes information concerning progress made in the approval process for applicant HLA laboratories and laboratory personnel. This information is provided to her by the agencies which have deemed status with UNOS to accredit laboratories; the American Society of Histocompatibility and Immunogenetics (ASHI) and the College of American Pathologists (CAP). The Committee reviews this document periodically and then makes recommendations to the MPSC as to whether these changes should be approved for UNOS membership. The Histocompatibility Membership Subcommittee requested a new format for this ballot because they said the Committee needed more information about the impending approval to make a decision. The Subcommittee was particularly concerned with the significant amount of time required for some laboratories to gain final approval and the number of laboratories one person could direct.

The Committee reviewed key personnel changes within histocompatibility laboratories and made recommendations to be presented to the Membership and Professional Standards Committee at its July 27, 2010 meeting. The Committee discussed the evaluation of directors with multiple laboratories and concluded (again) that this is an enormously complex issue best left to the accrediting agencies unless there are complaints or incidents that would require action by UNOS.

However, Committee members noted that many of the new fields that were requested in 2009 were not provided in the documentation provided by the accrediting agencies, therefore; the Committee tabled several lab director approvals till a time that those fields were filled out. The Committee members were especially interested in the individual coverage plans that were provided to the accrediting agency. Ms. Gore said she will contact the accrediting agencies and ask for the documentation.

The Committee then discussed the problem created when one individual directs many laboratories. The Committee is dismayed by the lack of standards in both the accrediting agencies and UNOS. They discussed what matrix could be used to form a standard, but soon concluded that the problem was too complex to solve at this meeting. A subcommittee was formed to discuss the matter further, with the hope they could make recommendations to the full Committee soon. Dolly Tyan PhD, Brad Eisenbrey MD, Phd, John Schmitz, PhD, and David Mauer, PhD volunteered to serve on this subcommittee.

One of the options offered in Committee discussion was the development of a "check list" that must accompany the application of a new lab director. This check list could provide information about how the new director plans to supervise the lab. Ms. Gore mentioned that the contract with ASHI and CAP is currently being updated. She said such a checklist could be added to the revisions.

Ms. Gore will arrange for the subcommittee to meet by teleconference to discuss these and other options with the goal of reporting back to the full Committee on their fall conference call.

Review of the Proposals from the Committee. The Committee then reviewed the responses to the two proposals from the Committee that are currently out for public comment. Two subcommittees were formed, one for each proposal. Char Hubbell, MT, and Dr. Maurer agreed to go over the comments for the "Updates of Appendix 3A." Dimitri Monos, PhD, Massimo Mangiola, PhD, and Drs. Eisenbrey and Reinsmoen agreed to go over the comments for the "Requirement for Molecular Typing."

Ms. Gore will arrange for the subcommittees to meet by teleconference to reply to the comments with the goal of reporting back to the full Committee on their fall conference call.

OMB forms. The Committee discussed the recent revisions to the OMB forms particularly the Recipient Histocompatibility form and the Donor Histocompatibility form. These forms may be reviewed as Exhibit A. After much discussion, the Committee recommended the following changes:

Donor Form:

1. For Target Cell Source Class I and II – add "Buccal swab or other"
2. Rename "DQ" to "DQb" and "DP" to "DPb" – drop down menu stays the same
3. Add two fields for "DQa" and two fields for "DPa" – dropdown menu needed

Dr. Baxter-Lowe agreed to write the rational that must be provided to make these changes.

Recipient Form:

1. First page. Recipient Information section. – The Committee recommended adding Most Recent and Peak CPRA fields for kidney, kidney-pancreas and pancreas recipients and unacceptable antigens for all recipients. Unacceptable antigens will be the ones listed at the time of removal. These requested fields will be display only (i.e. prefilled). –
2. Section I. Recipient HLA information - Rename "DQ" to "DQb" and "DP" to "DPb" – drop down menu stays the same Add two fields for "DQa" and "DPa" (total of 4 fields) – dropdown menu needed
3. Section II. HLA Antibody Screening – for thoracic candidates add Most recent CPRA and Peak CPRA with corresponding status fields (so if there is no CPRA then a lab can choose Missing, Unknown, N/A, Not Done)
4. Section IV. - Rename "DQ" to "DQb" and "DP" to "DPb". Add two fields for "DQa" and "DPa" (total of 4 fields).

Dr. Tyan volunteered to provide the rational for asking for a peak as well as the most recent CPRA on these forms. Dr. Baxter-Lowe will provide rationales for proposed changes and new dropdown menus for DQa and DPa.

All changes proposed by the Committee at May and July meetings will be sent to Policy Oversight Committee (POC) for final review and decision. If they are approved by the POC; they will be reviewed by the Board of Directors in November.

After lengthy discussion, the Committee decided that they would like to reopen the decision to continue listing PRA on the Recipient Histocompatibility forms. The Committee did recommend replacing PRA with CPRA on these forms, but the POC did not agree with this recommendation based on opposition from the Thoracic Committee. The Committee feels strongly that PRA is an outdated and erroneous representation of sensitization, and remains strongly opposed to its continued use.

J. Michael Cecka, PhD, reported to the Committee that the Thoracic Committee had two major concerns with the elimination of PRA from the forms. First, the Thoracic Committee said that PRA must be included as a risk factor in calculating their Center-Specific Reports. They could not use CPRA to do this because CPRA is not currently calculated for thoracic candidates. Second, they were apprehensive about the lack of standardization in the solid-phase tests required to list unacceptable antigens that are used for the CPRA calculation. The Committee opined that both concerns could be addressed. Dr. Cecka volunteered to write a letter to the Thoracic Committee that he will present at their next meeting in an effort to eliminate PRA from the Histo forms.

All the additional proposed changes to Histo forms are scheduled to go to Policy Oversight Committee (POC) this September.

Calculated Panel Reactive Antibody (CPRA Update). The Histocompatibility Committee is charged by the BOD to monitor the second phase of CPRA as it was implemented in UNet^{SM} on October 1, 2009. On the February 5, 2010 call, the Committee discussed a monitoring and evaluation plan for the CPRA policy and requested data to be presented during their meeting in July 2010. Anna Y. Kucheryavaya, research liaison to the Committee gave a report to the Committee about the first 6 months of CPRA implementation.

She said overall the implementation of CPRA led to an increase of unacceptable antigens reported on the waiting list and a dramatic decrease of kidney offers refused because of the positive crossmatch. She also said the absolute number of low sensitized candidates on the waiting list decreased and number of very highly sensitized (97 %+) candidates went up.

The Committee was pleased with the findings of the report. They said implementing CPRA clearly increased the efficiency of organ allocation by reducing the number positive crossmatches. It also showed that sensitized patients benefitted from CPRA. The percentages of sensitized patients who were transplanted increased and more than doubled from 7% to nearly 16% among those candidates with 80+% CPRA.

Request from the Thoracic Organ Transplantation Committee. The Thoracic Committee asked the Histocompatibility Committee to cosponsor a proposal to require HLA typing of deceased donors prior to a thoracic match run. The Committee supports this proposal and agreed to work jointly with the Thoracic Committee toward that end.

The OPO Committee had expressed opposition to any proposal to include HLA with thoracic offers. For the most part, the OPO Committee has said that obtaining HLA typing for thoracic donors before performing a match-run could be burdensome operationally to many OPOs.

Dr. Cecka represented the Histocompatibility Committee, along with Maryl Johnson, M.D., Chair of the Thoracic Committee at the April 20, 2010 OPO Committee meeting in an effort to gain a better understanding of the OPO Committee's concerns.

The issue, Dr. Cecka reported according to the OPO Committee, was how to permit allocation when the HLA could not be completed. They recognized the goal of HLA typing of thoracic donors was to facilitate sharing for sensitized patients, but they said many thoracic candidates are not sensitized and sometimes procurement must be done urgently. They were fearful that if HLA typing became a requirement, thoracic organs may be needlessly discarded.

The group discussed, that there is at this time, limited knowledge of what HLA data OPOs could or could not readily provide for thoracic donors. It was agreed that UNOS staff would prepare a survey that would be sent to all OPOs and laboratories that serve those OPOs to better understand the national practice of obtaining HLA typing on deceased thoracic organ donors.

The Histocompatibility Committee discussed the raw data from this survey at this meeting. The Thoracic Committee actually sent out two surveys; one geared toward OPOs and the other to Histocompatibility laboratories.

The Committee discussed the results from HLA laboratories. Seventy six laboratories responded to the survey. Dr. Cecka was concerned because in the survey only 80% said they provided donor typing using peripheral blood, meaning the remaining 20% still used lymph nodes. He was concerned this may be why the typing for thoracic donors is delayed because he thought nodes could only be taken from donors at the time of the procurement. However, several committee members said that nodes could be taken before procurement. The Committee noted the wide time frame indicated for HLA typing (2.5 hour to 72 hours). Committee members thought this may be because the question was misinterpreted to be asking the time from receiving the sample to the time of actually reporting the results. Dr. Cecka was also concerned that many laboratories indicated they treated donors who had received many transfusions, differently from those who had not. Dr. Cecka said this was not necessary and opined that some education from the committee may be necessary.

Discrepancy report. The Histocompatibility Committee annually reviews data from the Discrepant HLA Typings Reports in UNet^{SM}, as referenced in Appendix C to Policy 3. The Committee also receives annual updates on how often donor HLA (A, B and DR) on the kidney match run is different from donor HLA reported on Donor and Recipient Histocompatibility forms.

At the July 2010 meeting the Committee reviewed data on discrepancies in the Donor and Recipient Discrepant HLA Typings Reports in UNet^{SM}.

The Committee expressed concern that once the discrepancy is resolved, it is no longer shown in the report. They felt that it is important for laboratories to know how many HLA discrepancies they had during the most recent 12 months and how they compare to other laboratories. The Committee asked that a letter to be sent to all laboratories stating what the particular lab's discrepancy rate is and how it compare to the national average.

The Committee felt that sending letters will educate laboratories about the Discrepant HLA Typings Reports in UNet^{SM}. They also stated that laboratories with higher number of discrepancies might change their practices and report fewer discrepant HLA typings in the future.

Review of the New Kidney Allocation Proposal. Ciara Samara, UNOS liaison to the Kidney Transplantation Committee gave a review of the proposed kidney allocation system to the Committee as it exists currently. First she emphasized that this was not a full proposal but a high level overview of what the Kidney Committee had developed so far. She cautioned the Committee that this overview did not include the intricacies that may interest the Committee such as sensitization points. She said those decisions have yet to be made and will be partially based on the recommendations from the Committee.

She said that the proposed allocation system would begin with the characteristics of the kidney donor or with the Kidney Donor Profile Index (KPDI.) The KDPI summarizes the risk of graft failure for a particular kidney following transplant by combining a variety of donor factors into a single number. Unlike the current system which classifies a kidney as either Standard Criteria donor (SCD) or Expanded Criteria Donor (ECD), the KDPI would provide a continuous score. The BOD approved the use the KDPI as an informational reference to assess kidney donor quality the June 2010 meeting.

She went on to say that the KPDI score is calculated based on the donor information only. If the KDPI score is less than 20% (kidneys with the predicted longest function), the donor's kidneys will first be offered to local candidates who have longest estimated post-transplant survival, before being offered to all other candidates. If the KDPI score is greater than 20%, the kidney is first offered to candidates who are between 15 years older and 15 years younger than the donor before being offered to all other candidates.

At this point, several members of the Committee asked her why the decision was made to represent the kidneys with the predicted longest function with the lower numbers. Members of the Committee said the public may find this confusing and recommended that it be switched; the kidneys with the longer predicted survival be given the higher score. Ms. Samara said she would bring this suggestion back to the Kidney Committee.

The Committee than discussed two new proposals they would like to be included within the new kidney allocation proposal.

The first is a sliding scale for awarding sensitization points to candidates with a CPRA. Current policy grants four points to those kidney candidates with a CPRA of 80% or higher. Policy does not grant any points to those candidates with a CPRA level of 79% and lower. The members of the Histocompatibility Committee, as well as those from the Kidney Transplantation Committee, have expressed a concern that this policy was not fair because all sensitized candidates are disadvantaged to some degree.

The four allocation points awarded to those with a CPRA of 80% or above improve access to transplantation to highly sensitized candidates. However candidates with 79% CPRA or less, currently receive no sensitization points even though they are similarly disadvantaged in proportion to their level of sensitization. Since the implementation of CPRA, sensitized patients receive fewer offers than unsensitized patients in direct proportion to their CPRA value. To compensate for this biological disadvantage, the Committee discussed using a linear scale for moderately to highly sensitized candidates up to a certain CPRA value and then giving an absolute priority to all candidates with CPRA above a certain value. To finalize the proposal, the Committee requested data on transplant rates, offer rates and distribution of kidney registrations on the waiting list by CPRA group to be presented at their October 2010 conference call. It is hoped that this data would identify patterns of transplant rates for sensitized individuals and that this information could be extrapolated into the new kidney allocation system. Drs. Reinsmoen, Tyan and Baxter-Lowe agreed to work with the kidney Committee along those lines.

The second issue that the Committee would like to bring to the Kidney Committee is an unintended consequence of CPRA. Sensitized candidates who undergo desensitization have been disadvantaged since the implementation of CPRA on October 1, 2009. CPRA and the allocation points awarded to sensitized patients (80+% CPRA) are directly linked to the unacceptable antigens listed. When a candidate undergoes desensitization, unacceptable antigens may become acceptable when the corresponding antibodies are reduced or eliminated by the desensitization protocol. When these antigens are removed, the CPRA may fall below 80% and the patient's waitlist rank may also fall. Prior to October 1, 2009, programs could remove unacceptable antigens without a change in PRA, sensitization status or waitlist rank.

The committee emphasized that patients should not be disadvantaged by the implementation of CPRA .Dr. Tyan added that currently the transplant rate for candidates with a CPRA of 80% or more is 2.5% per year; their chance of dying is between 5-7%. Therefore, their rate of dying is double that of being transplanted. The Committee feels very strongly that we should not further disadvantage this already disadvantaged group.

Dr. Reinsmoen stated this should be simple fix; there must be a way to permit a desensitized patient's CPRA to remain at pre-desensitization levels until an immunologically acceptable donor is identified even though unacceptable antigens may be removed.

The question of "gaming" or cheating the system has been raised as a concern of this proposal The Committee has tried to answer those concerns. It should be noted that this proposal does not give a patient with greater than 80% CPRA any donor access advantage, unless desensitization works and UAs are removed.

Ms. Samara asked the Committee to build a case for this proposal that could go out for public comment. To do this, the Committee must provide additional information such as how many candidates are currently going through desensitization protocols, and how many have CPRA that are close enough to 80% to be in danger of losing their sensitivity points. Douglas Keith, MD, and Drs. Tyan and Reinsmoen agreed to serve on a subcommittee to research these and other questions.

In the mean time a working alternative may be a local rather than a national fix. The Committee discussed if local priority agreements might prevent a loss of rank or give priority for patients undergoing desensitization with specific limits and conditions set by the transplant centers within a (donor service area)DSA whose patients would be affected (as long as few patients are affected.) UNOS would have to agree to allow some out-of-sequence transplants for such patients undergoing desensitization. The committee said it will be important to accommodate these

patients in the new kidney allocation system especially as we gain broader experience with desensitization.

The addition of Cw to CPRA. CPRA was fully implemented in October 2009 with HLA frequencies generated by M. Sue Leffell, Ph.D from Johns Hopkins University in Maryland. The CPRA frequencies used were based on deceased donors entered into OPTN registry from January 1, 2003 through December 31, 2004. The calculation itself included frequencies for A, B, Dr and DQ. The HLA antigen Cw was considered at that time, but ultimately not included because there was not enough data on the frequency of Cw in donors. That has since changed; updated frequencies using data from January 1, 2007 through December 31, 2008 contain enough data to generate the Cw frequencies. The Committee said this should be done as soon as possible because candidates who are sensitized to the HLA antigen Cw are not addressed by CPRA.

Currently close to 10,000 kidney candidates are listed with at least one Cw antigen as an unacceptable. These candidates are screened from lists but receive no CPRA value for their increased potential of a positive crossmatch because Cw is not part of the CPRA calculation. Also, currently candidates can be sensitized to the antigen Cw and look to the UNet system as being completely unsensitized because their CPRA would be 0. Adding Cw to the CPRA calculation would mark these candidates as sensitized, and could possibly raise the candidate's CPRA to over 80% and thus receive 4 points.

The Histo Committee voted unanimously that Cw should be part of the CPRA algorithm. Ms. Gore told the Committee she was uncertain how to proceed. She said she did not know if this request should go out for public comment or if this would be considered an upgrade to the existing system. Ms. Gore said she would take this request back to UNOS and would let the Committee know the path forward at their next meeting.

Committee Attendance:

NAME	COMMITTEE POSITION	
J. Michael Cecka, PhD	ex officio (past chair)	x
Nancy Reinsmoen, PhD	Chair	x
Lee Ann Baxter-Lowe, PhD	Vice chair	x
Massimo Mangiola, PhD	Region 1 Rep.	x
Dimitri Monos, PhD	Region 2 Rep.	x
Karen Sullivan, PhD	Region 3 Rep.	x
Jerry Morrisey, PhD	Region 4 Rep.	x
Dolly Tyan, PhD	Region 5 Rep.	x
Paul Warner, PhD	Region 6 Rep.	x
David Maurer, PhD	Region 7 Rep.	x
Steve Geier, PhD	Region 8 Rep.	x
Char Hubbell, M.T.	Region 9 Rep.	x
A. Bradley Eisenbrey MD, PhD	Region 10 Rep.	x
John Schmitz, PhD	Region 11 Rep.	x
Dawn Brims, B.S.N.,RN	At Large	By phone
Douglas Keith, MD	At Large	x
Brad Kornfeld	At Large	-
Emily Messersmith	SRTR Liaison	x
Alan Leichtman, MD	SRTR Liaison	x
Lori Gore	Committee Liaison	x
Anna Kucheryavaya	Support Staff	x
Jory Parker	Support Staff	By phone