OPTN/UNOS Histocompatibility Committee
Report to the Board of Directors
November 14-15, 2011
Atlanta, GA

Summary

I. Action Items for Board Consideration

- None

II. Other Significant Items

- The Committee submitted a proposal for public comment in fall 2011 that would update the frequencies used to calculate CPRA. These updates include the HLA frequencies used to calculate CPRA and the addition of the HLA-C antigen frequencies to the calculation. (Item 1, pages 3-4)

- The Committee submitted a proposal for public comment in fall 2011 that updates the histocompatibility standards in OPTN policy and the UNOS and OPTN bylaws. (Item 2, pages 4-5)

- The Committee continues to monitor the use of the Calculated Panel Reactive Antibody (CPRA) within the transplant community. (Item 3, pages 5-6)

- The Committee approved the ballot of new laboratory and new laboratory directors for the Membership and Professional Standards Committee (MPSC) consideration for OPTN membership. It also continues to consider the question of the maximum number of laboratories that may be appropriate for one person to direct. (Item 4, page 6)

- The Committee continues to work with the Kidney Transplantation and Pancreas Transplantation Committees to award points for sensitization levels based on a sliding scale. (Item 4, page 6)

- The Committee reviewed the operation of HLA Discrepant Typing Report as it is now functioning in Tiedi®. This is done in conjunction with monitoring compliance with the requirement for molecular typing of deceased kidney, kidney –pancreas, and pancreas donors that was passed by the BOD in November 2010 and went into effect June 1, 2011. (Item 5, page 6)

- The Committee continues to work with the Pediatric Transplantation Committee to develop a plan for the regional sharing of kidneys for highly sensitized pediatric candidates. (Item 6, page 7)

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Nancy Reinsmoen, Ph.D., (ABHI), Chair
Lee Ann Baxter-Lowe, Ph.D., (ABHI), Vice Chair

The following report presents the OPTN/UNOS Histocompatibility Committee's deliberations and recommendations on matters considered during its July 11-12, 2011 meeting.

1. Proposal to Update the frequencies used to calculate CPRA**.** This proposal was distributed for public comment in fall, 2011 and is scheduled to be considered by the Board in June 2012. **(Exhibit A)**

   The proposal recommends that the HLA frequencies used by the CPRA calculator be updated to better reflect the current definition of HLA antigens and alleles in the donor pool. (No policy language is affected by this proposal; it will be a programming-only effort.) The suggested revisions include the addition of the antigen HLA-C to the calculation, updating the HLA frequencies used to calculate CPRA and the addition of a question to the waiting list to better interpret the 0% default CPRA value.

   - Addition of HLA-C. At the July 13-14, 2010 meeting, the Histocompatibility Committee voted to propose the inclusion of HLA-C frequencies into CPRA calculation. (16-Approve, 0-No, 0-Abstain)

     On February 28, 2011, there were 93,711 kidney registrations on the waiting list. Eleven percent (10,569) of these registrations had at least one unacceptable HLA-C antigen reported on the waiting list. These candidates are screened from match runs but receive no additional CPRA value. Among all kidney registrations with unacceptable HLA-C antigens, 7% (728) only had antibodies to HLA-C antigens. These candidates are screened from match runs but have a CPRA of zero (0).

     In addition, of the kidney candidates who have antibodies to HLA-C antigens, only 63% have a CPRA of 80% or higher, which makes them eligible for 4 additional sensitization points. Inclusion of HLA-C frequencies into CPRA calculation would result in a higher CPRA value for most of these registrations. For those listed with C antibodies, almost 644 registrations had a recalculated CPRA value of 80% or higher. Members of the Committee pointed out that it is likely that the number of candidates listed with C antibodies is grossly underestimated because many programs do not currently list C as an unacceptable because it is not part of the CPRA calculation and it has only recently been added to the requirements for deceased donors.

     Based on these observations, the inclusion of HLA-C frequencies into CPRA calculation would benefit a relatively large number of kidney registrations.

   - Update frequencies. At the July 2011 meeting, the Committee reviewed the data needed to support updating the HLA frequencies used to calculate CPRA. The HLA frequencies currently used for CPRA calculation (HLA-A, -B, -DR and -DQ) are based on the HLA phenotypes of deceased kidney donors recovered from January 1, 2003 through December 31, 2004. Ethnic

frequencies are based on deceased kidney donors recovered from January 1, 2006 through June 30, 2007.

The Committee reviewed data to assess whether using HLA frequencies based on a more recent cohort of donors would improve CPRA accuracy. CPRA was recalculated based on HLA and ethnic frequencies derived from a more recent cohort of deceased kidney donors (2007-2008). It was shown that if the recalculated CPRA were used for allocation of deceased donor kidneys, almost 500 kidney registrations with current CPRA of less than 80 would become eligible for 4 sensitization points. Committee members noted a large portion of this increase is due directly to the increased reporting of split HLA-DQ antigens in donors and more frequent reporting of subtypes rather than broad antigens.

Therefore, the Committee opined that these frequencies must be updated to a more recent period so that the CPRA truly reflects the probability of an incompatible match with the current donor pool. (16-Approve, 0-No, 0-Abstain)

Zero (0%) CPRA default. The main issue with the CPRA value defaulting to zero (0%) is that it does not differentiate the following situations:

- candidates who are truly unsensitized and have no donor specific antibodies,
- candidates who have some donor specific antibodies, but none who warrant the listing as unacceptable,
- candidates who have antibody to HLA-C and/or DP antigens, which are not part of the CPRA algorithm, and
- candidates who have had no data entered into the system.

Each one of the above scenarios describes a very different candidate, and one could not tell these differences from the current way CPRA is displayed. Therefore, when presented with a candidate with a CPRA of zero (0%), the transplant professionals cannot tell if the candidate is truly unsensitized, or sensitized. This is important information especially because of the increased use of a prospective virtual crossmatch.

Therefore, the Committee has requested that there be a way to distinguish these candidates on the waitlist. UNOS IT informed the Committee that the field on waitlist could not remain blank if untested, and must be filled with a numeric value. (00 is also not an option).

Consequently, the Committee proposes that a mandatory field be added to the waitlist form for all kidney, kidney/pancreas and pancreas candidates. They also requested that this field be added to other organ allocation systems, such as the thoracic waitlist form, if the Thoracic Committee decides to utilize CPRA within their system. This field would ask, "Was this candidate tested for anti HLA antibodies?" with the drop down box giving the following options: yes, antibodies detected, yes, no antibodies detected, or no, not tested. This information would distinguish among the various circumstances underlying a CPRA equal to zero (0%).

2. Revision of the UNOS bylaws, the OPTN Bylaws and the OPTN Policies that apply to HLA laboratories. UNOS staff has begun the process of consolidating, reorganizing, and simplifying the language of the OPTN Policies and OPTN and UNOS Bylaws. (These updates are not substantive in

nature; they are not intended to change the meaning of the policies and bylaws.) These changes to the language are scheduled to go out for public comment, the bylaws in the winter of 2012 and the policies in the summer of 2012.

The Histocompatibility Committee reviewed the documents from the Rewrite Project pertaining to histocompatibility (HLA) laboratories at their July 2011 meeting and identified several challenges. The Committee defined these areas as major defects that are not in line with current practice. Therefore, the Committees voted to make updates within the current UNOS Bylaws, the OPTN Bylaws and the OPTN Policies now in an effort to improve the review process that will happen later next year within the Rewrite Project.

The proposal to correct the most egregious defects went out for public comment in the fall of 2011. **(Exhibit B)**

The Committee said this would only be the first step in rewriting the existing histocompatibility standards. It was noted that the UNOS Bylaws, the OPTN Bylaws and the OPTN Policies that apply to HLA laboratories have become obsolete. Many of the required tests and methods are out of date or are no longer useful. The Committee stated that these requirements must be made to be more succinct and to reflect current lab practices. The Committee knows updating the standards will be a huge undertaking, but they look forward to beginning the process.

3. CPRA. The Committee continues to monitor the use of the Calculated Panel Reactive Antibody (CPRA) within the transplant community. A summary of the report follows:

- There was an increase in the number of unacceptable antigens that were reported on the waiting list and a substantial decrease in the number of kidney refusals due to the positive crossmatch.

- The percentage of non-sensitized registrations (0%/Not reported PRA/CPRA) increased and the percentage of low sensitized registrations (1-20% PRA/CPRA) decreased. The percentage of very broadly sensitized registrations (>95% PRA/CPRA) also increased.

- Only 30% of primary transplant registrations are sensitized to any degree (>0% CPRA) compared to 77% for registrations with a previous graft failure.

- There is a variation in CPRA distribution by center. There has been some criticism of CPRA within the transplant community because a given candidate may have a different CPRA at different centers. It was reported that for adult kidney alone patients actively waiting at two or more centers on 03/31/2011, 60% of patients have the same CPRA value at all centers and 19% of those listed with 0% CPRA at one center had >20% CPRA at a different center. A comparison was also made of the CPRA values at removal from the first center and at listing at the second center for adult kidney alone registrations transferred to a different center; 61% of registrations had the same CPRA value at both centers. Committee members opined that the difference in the reporting of unacceptables was center rather than technique driven.

- After an initial decline for non-sensitized, and an increase for broadly sensitized patients, transplant rates for these groups seem to return to pre policy implementation levels.

- For all ethnicity groups, the percentage of very broadly sensitized registrations (PRA/CPRA > 95%) increased. It was also illustrated that only 49% of female registrations are non-sensitized (0% CPRA) compared to 72% for males. In addition, that 25% of females are broadly sensitized

(80%+ CPRA) compared to 11% males. After CPRA implementation the percentage of very broadly sensitized registrations (>95% CPRA) increased for both genders.

- Only 30% of primary transplant registrations are sensitized to any degree (>0% CPRA) compared to 77% for registrations with a previous graft failure.

- 18 months after CPRA implementation the percentage of very broadly sensitized registrations (>95% CPRA) increased by 16 percentage points for those waiting for a re-transplant compared to 18 months prior.

- Transplant rates for low sensitized group (1-20% PRA/CPRA) significantly decreased after the policy implementation. Even after the decrease, transplant rates for this group were not significantly different from rates for other groups post policy implementation.

- Transplant rate for moderately sensitized candidates (21-79%) did not change significantly following the policy implementation.

The Committee said it was essential to note the types of transplant sensitized candidates were receiving (0MM vs. Non0MM). In addition, when reviewing the data, they said it is important that the Kidney Transplantation Committee be made aware that a large amount of the transplants that took place for the higher CPRA candidates were 0MM.

The Committee also discussed how a sliding scale for sensitization points would work within the new kidney allocation system. Members opined that sensitized candidates should be removed from any system that would limit their donor pool. They noted that all of the data reviewed so far have been based on exposure to 100% of the donor pool. Therefore, the Committee considered the question, at what point is a candidate "sensitized" enough to be removed from the proposed system? Members of the Committee also opined that these changes must be on a local level to adjust for geographical variation in the size of the donor pool. To ensure that the impact of sensitization is not underestimated in future analyses the Committee requested data on the median waiting and dialysis time and percent transplanted within several years of listing by sensitization group.

4. Report for the Membership and Professional Standards Committee (MPSC). The Committee approved new laboratory and new laboratory directors for the membership ballot at their July 2011 meeting. This ballot is prepared by the UNOS Membership Department. It summarizes the progress made in the approval process for applicant HLA laboratories and laboratory personnel. The summary is provided to the Committee by the two agencies that 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 reviewed this document and made recommendations to the MPSC as to whether the applicants should be approved for OPTN membership.

   The Committee then discussed the problem created when one individual directs multiple laboratories. The Committee is troubled 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 goal of developing recommendations to the full Committee.

5. Discrepant typing report**.** The Histocompatibility Committee annually reviews the 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 the donor HLA (A, B and DR) on kidney match runs is different from the donor HLA reported on donor and recipient histocompatibility forms. These data are used for reviewing and evaluating discrepancies found and determining if any actions should be taken.

At the July 2011 meeting, the Committee reviewed the data and asked to provide an annual update at their July 2012 meeting. The Committee felt that it was important to continue to monitor discrepancies within the transplant community given the increased use of a prospective virtual crossmatch. The Committee was also concerned that there were still many laboratories that were not aware of the existence of Appendix C to Policy 3 and of the report. In an effort to assure compliance with the policy, they asked letters be sent to member laboratories informing them of the number of their unresolved discrepancies compared to the national average. The Committee also asked that the discrepant typing report be added to the ASHI/CAP checklist for use in lab inspections.

6. Report from Pediatric Transplantation Committee. The Pediatric Transplantation Committee asked for guidance from the Histocompatibility Committee in a memo dated April 26, 2011. The memo explained how pediatric kidney transplantation candidates experience substantial long-term side effects due to dialysis, including growth and development delays, which are more pronounced in those candidates who experience barriers to transplant (e.g., due to sensitization). It went on to say that although the implementation of Share 35 in September 2005 resulted in an increase in the absolute number of all kidney transplants in children, highly sensitized pediatric candidates (especially teens and adolescents) have realized significantly less benefit when compared to other pediatric candidates.

   The Pediatric Transplantation Committee asked for volunteers from the Histocompatibility Committee to join a working group to discuss further the Histocompatibility Committee's opinions and recommendations. This working group, made up of members from the Histocompatibility, Pediatric and Kidney Transplantations Committees recently discussed the possibilities of regional sharing of kidneys to improve access to transplant for the highly sensitized pediatric kidney candidate. The group asked for modeling of this concept, including CPRA and other cohorts, to be reviewed at their next meeting.

Committee Member Attendance

NAME	COMMITTEE POSITION	07/11/2011
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
Robert Bray, PhD	Region 3 Rep.	
Cathi Murphy, 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
Sara Dionne, PhD	Region 8 Rep.	x
Rex Friedlander	Region 9 Rep.	x
A. Bradley Eisenbrey MD, PhD	Region 10 Rep.	x
David Kiger	Region 11 Rep.	x
Laine Krisiunas, BS,MBA	At Large	x
Luis Campos, MD	At Large	x
James Selby	At Large	x
Howard Gebel	SRTR Liaison	x
Bryn Thompson	SRTR Liaison	x
Lori Gore	Committee Liaison	x
Anna Kucheryavaya	Support Staff	x
Jory Parker	Support Staff	x
James Bowman	Ex officio (HRSA)	x