Interim Report
OPTN/UNOS HISTOCOMPATABILITY COMMITTEE

Teleconference
May 20, 2011
1:00-3:00 (EDT)

Welcome**.** Dr. Reinsmoen, chair of the Committee, called the meeting to order. She praised Anna Kucheryavaya, research liaison to the Committee, for a job well done at the recent ATC meeting. She said Ms. Kucheryavaya,,s presentation "The virtual crossmatch: National data show benefits of the change to Calculated PRA (CPRA) for sensitized patients after one year" was well received and mentioned in the "What's Hot" section of the program. (Dr. Reinsmoen and Dr. Cecka were coauthors on the abstract. Copies of the slides can be found on the Histocompatibility Committee SharePoint site under reference materials.)

Rewrite project. Lori Gore, liaison to the Committee, explained to the Committee that currently the UNOS Bylaws, the OPTN Bylaws and the OPTN Policies that govern HLA laboratories need revision. She said they are not in a central location, large portions are obsolete, several are contradictory, and the level of detail is inconsistent. These documents must become more succinct, and to reflect current laboratory practices.

She added the HLA laboratories are not accredited or monitored directly by UNOS, but through agencies that have deemed status with UNOS (American Society of Histocompatibility and Immunogenetics, ASHI and the College of American Pathologists, CAP). The contracts with these agencies require that a crosswalk be done biannually to make sure our standards and their standards are equivalent. Such a comparison has not been done since 2003, and Ms. Gore could not find a copy of it. A new cross walk that would reflect the current state of affairs cannot be initiated until our standards are in order.

She went on to say, the MPSC depends on the information given to it by ASHI and/or CAP to validate if histocompatibility standards are being met. For the first time in UNOS history, the MPSC is beginning to look into complaints pertaining to HLA laboratories. It must rely on the data supplied by these agencies to make their determinations. Therefore, the contracts with these agencies must be current

The UNOS Plain Language Rewrite Project-Phase I is currently reorganizing the laboratory requirements in the Bylaws and Policies. Ms. Gore shared with the Committee that UNOS has recently hired two individuals, Leigh Kades and James Alcorn to lead this effort. Ms. Gore introduced the pair to the Committee and asked that they say a few words.

Ms. Kades said she is focusing on rewriting and reorganizing OPTN/UNOS bylaws. Mr. Alcorn said that his focus will be on rewriting/reorganizing OPTN/UNOS policy. To enhanced clarity, the rewrite project will condense the Hiscompatibiblty standards found in the Bylaws into one document with more information presented in lists, tables and diagrams for easier reference. They also proposed that many standards currently found within the bylaws should actually be moved to UNOS policy. In addition to making Policy more clear, Mr. Alcorn would like the rewritten UNOS policy to have a central location for all definitions, a table of authorities for all policy cross references, tables and diagrams, and a new system to track policy changes.
Ms. Kades and Mr. Alcorn both stated they would appreciate help from the Committee. This is because neither is familiar with histocompatibility principles. They said they would appreciate

direction from the Committee and asked that the Committee look at their work to make sure it made sense.

Members of the Committee expressed concern because they said a reorganization of the standards could greatly affect the standards for CAP and ASHI. They went on to say that those standards have been are modeled from the CLIA standards and have a common a framework. Therefore, "reorganization" could be problematic. Ms. Gore reminded the Committee that we are at the very beginning of the process and we can keep that in mind as we move forward.

Ms. Kades and Mr. Alcorn were now looking for Committee members who could begin to examine the HLA lab content of the Bylaws and Policy to identify inaccuracies, inconsistencies and superfluous information. Ms. Gore mentioned that the changes up until now are not substantive changes. After these changes have been approved, the Committee can propose more substantive changes (phase 2) but that they would have to go out for public comment.

Dr. Reinsmoen said this all seemed vague and asked that UNOS staff have something put together by the July meeting to present to the Committee. Ms. Gore said she would work with Committee members to do that. Dr. Eisenbrey volunteered to work on this project along with Dr. Sullivan and Ms. Hubble (both are rolling off the Committee in July). Dr. Tyan also volunteered, but said her time would be limited. Dr. Eisenbrey asked that Don Constantino, an ASHI member be contacted to help. Dr. Bray, who will be joining the Committee in July was also thought to be a good resource.

Review of the Public Comment Proposals. The Committee reviewed the proposals currently out for public comment. They voted unanimously to support proposal # 9, the proposal that would Require Confirmatory Subtyping of Non-A1 and Non-A1B Donors (Operations and Safety Committee).

Appendix 3A. Ms. Gore gave the full Committee some background information on the implementation of the updates to Appendix 3A. She said these updates were approved by the OPTN/UNOS Board in November 2010. (Such modifications are made biannually and are made to reflect changes in HLA typing practice.) These updates are implemented in two phases:

- Phase 1 was implemented March 16, 2011, and is reflected in the updated tables found within Policy 3 Appendix A.
- Phase 2 will be implemented at a later date.

She reminded the Committee that this is the first time that these tables have been updated since the full implementation of CPRA. Because of this, there have been some unforeseen consequences to the CPRA of some kidney, kidney/pancreas, and pancreas candidates.

UNOS staff began to receive inquiries soon after the updates to the tables were made asking if the tables were working correctly. Most of the questions involved candidates that had a DQ antigen marked as unacceptable. For example, a candidate's CPRA with DQ 4, 6, 8, marked as unacceptable jumped from 45% to 78%.

Analysis established that the differences in CPRA values were resulting from changes in the HLA antigen equivalences made in the updated table that were not supported by the HLA frequencies used to calculate the CPRA. CPRA is currently calculated using frequencies that reflect the level of HLA typing performed in 2003-2004. At that time, broad antigen level assignments were being reported more frequently than that of the antigen splits. In some case, i.e. DQ5, the updates

to the tables within Appendix 3A added a broad antigen to a split antigen, making some CPRA values artificially elevated.

For example, in the previous version of Appendix 3A, DQ5 was equivalent only to DQ5. If the recipient had DQ5 marked as unacceptable, that person would be screened from all match runs where the donor had the antigen DQ5. When that person's CPRA was calculated it would use only the frequency of donors with DQ5. One of the suggested changes to the Appendix was to add DQ1 as an equivalent to DQ5. This is because the Committee wanted to make sure that if a candidate had DQ5 marked as an unacceptable; the candidate would be screened from match runs where the donor had DQ1 as an antigen. Now when that candidate's CPRA is calculated using the updated table, the frequencies for both DQ5 and DQ1 are used. The frequency reported for DQ1 was much higher in 2003-2004 than it is today. Therefore, because the CPRA will now be calculated using the frequencies of both DQ5 and DQ1 as they were reported in 2003-2004, the estimated probability of a positive crossmatch occurring may be incorrect.

The use of Appendix 3A will likely become obsolete with the implementation of the requirement of molecular typing of donors (which will go into effect in June 2011). After June 2011, no donors should be marked as DQ1. But in the meantime, the Committee asked what the magnitude of the problem is.

UNOS staff shared data that showed how the implementation of the updates to Appendix 3A affected candidates:

- A total of 32,162 kidney registration CPRA values changed
- 26,997 registrations had increasing CPRA values. Of these, 15,523 registrations had increases that were so small that they could not be recorded as a change in CPRA (Meaning that the increase was less than 1% point.)
- 9,563 registrations had increases in CPRA values of 1-10% points
- 1,471 registrations had increases in CPRA values of 11-20% points
- 407 registrations had increases in CPRA values of 21-30% points
- 32 registrations had increases in CPRA values of 31-40% points
- Only 1 registration had an increase of over 40% points in its CPRA value
- 5,165 registrations had decreasing CPRA values, but for almost all of these (5,141) the changes were less than 1% point
- Only 24 registrations had noticeably decreasing CPRA values (all changed by 1% point).

The Committee was concerned about how many of these candidates fell at the key threshold points of 20% and 80%. UNOS staff later reported to the subcommittee that:

- 251 kidney registrations going from less or equal to 20% to greater than 20%
- 679 kidney registrations going from less than 80% to greater than or equal to 80%
- 5 kidney/pancreas registrations going from less or equal to 20% to greater than 20%

- 15 kidney/pancreas registrations going from less than 80% to greater than or equal to 80%
- 7 pancreas registrations going from less or equal to 20% to greater than 20%
- 27 pancreas registrations going from less than 80% to greater than or equal to 80%

The Committee concluded that the impact of the new equivalences on CPRA values was minimal, noting that only a small number of disadvantaged sensitized candidates are affected in a way that may unfairly benefit them. Implementation of more recently derived HLA frequencies, which reflect significantly reduced entry of broad HLA antigens, would resolve this issue. However, the programming cannot be changed at this point and the frequencies cannot be updated before going out for public comment. The plan for the future is that a proposal will come from the Committee in fall 2011 to update CPRA. These updates will include updating the frequencies used to calculate CPRA and the addition of HLA-C to the calculation. If this proposal went out for public comment then, it would go to the BOD for approval in June 2012. The Committee noted we should also discuss how to approach Appendix 3A in the future and if we want to limit the use of broad antigens.

Several Committee members thought UNOS should provide a standard for the conversion of alleles to serologic types. Dr. Cecka mentioned a table that Ms. Hubbell had that may be useful as a starting point. (Ms. Hubbell has since sent the table to me and it is posted on our SharePoint site under reference materials.)

Memo from Pediatric Committee**.** The Pediatric Committee asked for guidance from the Histocompatibility Committee in a memo dated April 26, 2011, because pediatric kidney transplantation candidates experience substantial long-term side effects due to dialysis, including growth and development delays. These effects are more pronounced for pediatric candidates who experience barriers to transplant (e.g., due to sensitization).

This memo said that since the implementation of Share 35 in September 2005, there has been an increase in the absolute number of all kidney transplants in children; a general increase in the transplant rate per 1,000 active patient years for all blood groups and sensitivity cohorts; and a decrease in the total amount of time spent on the waiting list. Although these results are encouraging, those highly-sensitized pediatric candidates (especially teens and adolescents) have realized significantly less benefit when compared to all other pediatric candidates.

To improve highly-sensitized pediatric kidney candidates' access to transplant, the Pediatric and Kidney Committees have recently discussed the possibilities of regionally sharing kidneys for highly-sensitized pediatric candidates. Modeling regional kidney sharing for this group within the current kidney allocation algorithm indicates improved access for these pediatric candidates with minimal impact on adult kidney candidates.

The Pediatric Committee asked for volunteers from the Histocompatibility Committee to join a working group to discuss further the Histocompatibility Committee's opinions and recommendations.

Dr. Reinsmoen thought the Pediatric Committee needed some guidance because some of the suggestions contained in the memo seemed too stringent. She suggested that we could provide some guidelines, maybe based on the guidelines from the KPD program. Dr. Tyan, Dr. Monos, and Dr. Reinsmoen volunteered to take part in this work group.

Data Requests. Anna Kucheryavaya gave two presentations of data she gathered for the Subcommittee at their request. This data will be used in the proposal to update CPRA. The first set of data assessed whether HLA and ethnic frequencies used in CPRA calculation should be updated to better represent the deceased donor population.

- During the last conference call the subcommittee requested the following data to be presented to the full Committee:
- Current and recalculated CPRA values were compared for all kidney registrations on the waiting list on November 30, 2010 (N=93,070).
- All the results are based on the unacceptable antigen equivalences listed in Appendix A to OPTN Policy 3 as of December 24, 2010.

She reminded the Committee that the HLA frequencies currently used for CPRA calculation are based on the HLA phenotypes of deceased kidney donors recovered from January 1, 2003 through December 31, 2004 and the ethnic frequencies are based on deceased kidney donors recovered from January 1, 2006 through June 30, 2007. For the purpose of this presentation the updated HLA and ethnic frequencies were derived from deceased kidney donors recovered from January 1, 2007 through December 31, 2008.

Ms. Kucheryavaya said there are 1,891 registrations with absolute difference between Current and Recalculated CPRA > 5. For these registrations:

- 55% had antibodies to DQ7
- 86% had antibodies to DQ6 and/or DQ7
- 97% had antibodies to DQ 4, 5, 6, 7, 8 and/or 9.
- Reporting of these antigens for deceased kidney donors increased in the past decade. DQ 4, 5, 6, 7, 8 and/or 9 was reported for 61% of deceased kidney donors recovered in 2001 and for 90% of donors recovered in 2009.

She said that in current policy highly sensitized candidates (80%+ CPRA) during allocation of deceased donor kidneys are assigned 4 extra points. If recalculated CPRA was used for allocation:

- 498 (5 pediatric and 493 adult) registrations would become eligible for 4 extra points
- 28 registrations would lose 4 points

She also said that within current policy there is mandatory non-local sharing of zero antigen mismatched deceased donor kidneys for adult sensitized registrations with a CPRA greater than 20%. If the updated frequencies were used to calculate CPRA 93 adult registrations would become eligible for the sharing and 23 adult registrations would become not eligible for the sharing.

Ms. Kucheryavaya said it was important to point out that while most of the registrations have the same current and recalculated CPRA values:

- For 1,891 registrations Recalculated CPRA increased by more than 5% points.
- 498 registrations would become eligible for sensitization points if CPRA was based on updated frequencies.

- Ethnic distribution of deceased kidney donors is slowly changing. The percentage of White donors is decreasing and percentages of African American and Hispanic donors increasing.

Based on these observations it is thought that a large number of registrations would benefit from using CPRA based on updated frequencies.

The subcommittee also requested the data to support the Histocompatibility Committee's proposal to include HLA-C into CPRA calculation. Therefore the CPRA was calculated for kidney registrations on the waiting list with antibodies to HLA-C.

Ms. Kucheryavaya reported:

- Eleven percent of kidney registrations on the waiting list have antibodies to HLA-C antigens. Only 63% of these registrations have current CPRA of 80% or higher and are eligible for 4 additional sensitization points during allocation of deceased donor kidneys.
- More than 500 of kidney registrations with 50-79% current CPRA would be eligible for 4 extra sensitization points if CPRA was calculated based on a more recent set of HLA frequencies with inclusion of HLA-C.

Based on these observations it is thought that the inclusion of HLA-C frequencies into CPRA calculation would benefit a lot of kidney registrations with antibodies to HLA-C.

The Committee said that 524 out of 93,711 (total number of registrations on the kidney wait list on February 28, 2011) represented a small change but it would be very important to those 524 registrations. Especially if now have a CPRA of 0 (because C is not included in the calculation of CPRA.) It was pointed out that 11% of the kidney registrations have C listed as an unacceptable.

Dr. Baxter-Lowe said that this was enough for the POC (Policy Oversight Committee) to recommend that the Committee continue on this project. Dr. Reinsmoen mentioned that the reporting of C as an unacceptable may be low because currently candidates would receive no benefit. She said she thought the number of candidates who have C listed as an unacceptable may increase when it is included in the CPRA calculation.

Members of the committee rolling off in June. At this time Dr. Reinsmoen said a special thank you to the members of the Committee who would be rolling off in June. They include Karen Sullivan, Jerry Morrisey, Charlene Hubbell, John Schmitz, Douglas Keith, Bradley Kornfeld, Dawn Brims, and Mike Cecka. Thank you for a job well done and you will be sorely missed.

NAME	COMMITTEE POSITION	05/20/2011
J. Michael Cecka, PhD	Ex offi 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.	
Dolly Tyan, PhD	Region 5 Rep.	x
Paul Warner, PhD	Region 6 Rep.	x
David Maurer, PhD	Region 7 Rep.	
Sara Dionne, 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.	
Dawn Brims, B.S.N.,RN	At Large	
Douglas Keith, MD	At Large	
Brad Kornfeld	At Large	x
Howard Gebel	SRTR Liaison	x
Adrine Chung	SRTR Liaison	x
Lori Gore	Committee Liaison	x
Anna Kucheryavaya	Support Staff	x
Jory Parker	Support Staff	x
James Bowman	Ex officio (HRSA)	x