OPTN/UNOS Histocompatibility Committee
Report to the Board of Directors
November 12-13, 2012
St. Louis, Missouri

Summary

I. Action Items for Board Consideration

- None

II. Other Significant Items

- Updates from the Kidney Transplantation Committee (Item 1, Page 2).
- Evaluation of Modification to OPTN Policy of Using CPRA for Deceased Donor Kidney Allocation: 30 Month Data (Item 2, Page 3).
- CPRA Analysis for Larger Kidney Programs (Item 3, Page 4).
- Evaluation of the Molecular Typing Requirement (Item 4, Page 4).
- Reviewing Discrepancies in HLA Typing Reports (Item 5, Page 5).
- Plain Language Policy Rewrite (Item 6, Page 7).
- Update from the Kidney Paired Donation (KPD) Workgroup (Item 7, Page 8).
- Substantive Bylaws/Rewrite Subcommittee (Item 8, Page 9).
- Upcoming Public Comment Proposals (Item 9, Page 9)
- HLA DR/DQ Mismatching of Kidney Donors and Potential Transplant Recipients (Item 10, Page 9)

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Lee Ann Baxter-Lowe, PhD, Chair
Dolly Tyan, PhD, Vice Chair

This report details the discussions had and decisions made by the Histocompatibility Committee during its meetings on May 25, 2012, August 6, 2012 and August 7, 2012.

1. Updates from the Kidney Transplantation Committee

The Committee is actively monitoring the new kidney allocation proposal.

In May, the Committee met by conference call to view presentations from SRTR on the results from updated Kidney Pancreas Simulated Allocation Model (KPSAM) runs and to offer feedback to the Kidney Transplantation Committee (Kidney Committee) on issues specific to histocompatibility.

Committee members inquired about the data on the average kidney and kidney/pancreas transplants per run, wondering why there was variation in the data for each run. SRTR staff explained that the simulation models do not perfectly replicate reality. The results of each run are actually averages of 10 iterations. In each iteration, the kidneys become available in a different order, thereby affecting which candidates receive offers at certain points in time.

The Committee discussed at length data on kidney transplants by recipient age and members expressed concern over allocation changes that could result in a decrease in transplants for candidates over the age of 50. Staff from the Kidney Committee explained that the latest run results in a very small decrease in the number of transplants for this population and reminded the Committee that KPSAM does not take into account changes in acceptance behavior resulting from policy changes. SRTR staff added that the modeling software used does not account for changes in behavior but suggested that it may be helpful for future software to do so.

After viewing simulation modeling on prioritization by CPRA and the sliding scale proposal, Committee members noted the importance of ensuring that the new allocation model did not decrease transplants for highly sensitized patients.

After viewing modeling of kidney transplants by recipients with CPRA values between 95-100%, members of the Committee were concerned that, although the new N4 model seemed to increase the number of transplants for candidates with a CPRA of 99% and 100%, there was a disadvantage for candidates with a CPRA of 98%. According to several committee members, this disadvantage was largely due to the fact that the new model did not allow for regional sharing for candidates with a 98% CPRA.

Several members of the Committee voiced concern about potential unintended consequences of greater national sharing for highly sensitized patients and urged the Kidney Committee to consider increasing accountability in the system. The Committee noted that a prior data request revealed that a small population of centers had failed to transplant more than 40% of accepted kidneys into the intended recipient.

The Committee largely agreed that the new results from N4 were encouraging. The chair explained that the Histocompatibility Committee did not need to vote on the proposal, but instead the Committee should make some recommendations to the Kidney Committee. The Committee decided to offer support for the most recent proposal and to recommend that the Kidney Committee include the following: 1) regional sharing for candidates with a 98% CPRA; and 2) policy language that ensures more accountability for centers who misuse broader national sharing.

In August, the Chair of the Kidney Transplantation Committee (Kidney Committee) presented the Committee with an overview and modeling simulation results on the future kidney allocation system proposal. In this presentation, 2010 data were compared to N1 (simulation of the current allocation system) and N4 (simulation of the allocation system that the Kidney Committee currently plans to propose).

The data showed a slight decrease in the percentage of zero HLA mismatched kidney transplants.

Several committee members inquired whether the change in percentage of zero HLA mismatched transplants was more substantial for certain groups of patients. The committee requested data on zero HLA mismatched kidney transplants stratified by age group, recipient's sensitization level and re-transplant status. Prior transplant is one of the factors in estimated post transplant survival (EPTS). Re-transplant candidates are generally more highly sensitized than candidates waiting for their first transplant. The committee questioned how many sensitized candidates will be included in the top 20% EPTS category. SRTR staff will be developing a research presentation to the Committee to follow up on these data requests.

2. Evaluation of Modification to OPTN Policy on Using CPRA for Deceased Donor Kidney Allocation: 30 Month Data

In August, staff from the UNOS Research Department analyzed 30 months of data on the use of CPRA in the transplant community before and after CPRA was implemented. The results are as follows:

In the first 15 months after the change to CPRA,

- The percentage of kidney alone registrations and the median number of unacceptable antigens reported for sensitized registrations significantly increased.
- The number of offers refused due to a positive crossmatch decreased by 65%. The percentage decreased from 1.8% to 0.7%.
- The percentage of non-sensitized (0%) and very broadly sensitized (96%+) registrations significantly increased, while the percentage of low sensitized (1-21%) decreased.
- Compared to 15 months prior, transplant rates significantly decreased for non and low sensitized groups (0-21%) and for very broadly sensitized patients (96%+). Rates significantly increased for 21-79%, 80-89%, and 90-95% groups.

In the second 15 months after the change,

- The percentage of registrations with unacceptable antigens continued to increase, while the median number of unacceptable antigens remained stable.

- Compared to the first 15 months after implementation, the number and percentage of offers refused due to a positive crossmatch decreased by 9%. The percentage significantly decreased from 0.7% to 0.5%.
- The percentage of very broadly sensitized registrations continued to increase.
- Very broadly sensitized registrations (96%+) had significantly higher 25th percentile of waiting and ESRD time compared to groups with PRA below 90%. This group accumulated significantly more waiting time than any other sensitization group waiting for a kidney on July 13, 2012.

During discussion, several members of the Committee were concerned about data showing PRA/CPRA scores for individuals for primary transplant versus repeat transplants, noting that a significant number of repeat transplant candidates were highly sensitized (96%+). Committee members requested further data analysis to look at ethnicity and re-transplant status (primary vs. re-transplant) of waiting list registrations.

The Committee also requested an update to be presented at their Summer 2013 meeting in Chicago. To better monitor CPRA implementation, the committee requested some additional analyses on cold ischemia time, discard rates, rejection rates and graft survival rates.

3. CPRA Analysis of Larger Kidney Programs

In August, OPTN/UNOS staff presented data on larger kidney programs (defined as programs with more than 100 kidney candidates) stratified by the percentage of broadly sensitized candidates (80%+). These analyses (for July 2010 – June 2011) were first presented to the committee at the March 23, 2012 conference call.

During discussion, several committee members were concerned that some centers with a very low percentage of broadly sensitized registrations (<5%) didn't report a proportionate number of unacceptable antigens for their registrations. The committee requested an update of the results based on the most recent 12 months to be presented during their Fall 2012 meeting. Committee members requested updated data on the number and percentage of kidney offers accepted for transplant but not transplanted into the intended recipient and analysis of what ultimately happened with these kidneys (organ transplanted in a different recipient or discarded).

4. Reporting of Broad Antigens on Match Runs 10 Months Before and After Molecular Typing Requirement

In August, UNOS research staff presented data on the effects of the molecular typing requirement that was implemented on June 1, 2011 (Exhibit B). Specifically, the Committee requested data on the number and percentage of deceased donors with broad antigens reported on kidney, kidney-pancreas and pancreas match-runs, overall and stratified by encrypted laboratory.

The following conclusions were drawn from the data:

- After the policy change, the percentage of donors with broad antigens significantly decreased from 10.0% to 4.1%. The number of those donors decreased by 57%, from 619 to 265.

- The percentage of donors with broad antigens varies substantially among 104 laboratories.
- C3 was the most commonly reported broad antigen.
- DQ3, DQ1, and B14 were also frequently reported.

While the Committee was encouraged by the decreasing number and percentage of donors with broad antigens on the match run, many members were concerned that the level of reporting of broad antigens remains too high. Members were concerned that the levels of broad antigens reported (and the reporting of certain broad antigens in particular) suggest that some laboratories are still using serology, despite the OPTN's molecular typing requirement. The Committee discussed possible solutions to this problem, such as establishing certain thresholds and timelines for violations to refer to the MPSC. Ultimately, the Committee decided to request further data analysis to compare the most recent 6 months data with the previous six months to be presented at the Fall 2012 meeting. The Committee members hope to discern whether additional implementation time has allowed more centers to comply with the requirement.

5. Review and Evaluation of HLA Typing Discrepancies

In August, the Committee began its annual review of discrepant HLA typing reports in UNet. The Committee also heard a presentation on how frequently donor HLA (A, B, and DR) on kidney match runs is different from donor HLA reported on donor and recipient histocompatibility forms. At the July 2011 meeting, the Committee requested to review data before and after the molecular typing requirement went into effect. UNOS research staff presented this data to the Committee.

The *Discrepant Donor HLA Typings* report compares deceased donor HLA typings (for kidney, kidney-pancreas and pancreas donors) reported on the donor histocompatibility forms against donor HLA typings reported on recipient histocompatibility forms (kidney, kidney-pancreas, and pancreas donors). *Discrepant Recipient HLA Typings* report compares recipient HLA reported on the waiting list at the time of removal against recipient HLA reported on recipient histocompatibility forms (for deceased donor kidney, kidney-pancreas, and pancreas recipients). The following conclusions were drawn from data on discrepant HLA reports:

- During the 10 months after the molecular typing change (July 1, 2011-March 31, 2012), the percentage of donors and recipients with discrepant HLA typing was similar to 10 months prior.
- For both donors and recipients, the percentage of resolved discrepancies is significantly lower after the change compared to the 10 months prior. This may indicate that laboratories need additional time to resolve discrepancies.
- For both donors and recipients, the percentage of Bw4/Bw6 discrepancies didn't change significantly.
- There were 100 laboratories that had one or more discrepant donor typing. There were 78 laboratories that had one or more discrepant recipient typing.
- Smaller laboratories had fewer discrepancies for both donors and recipients.
- During the 10 months prior to the policy change, 7 laboratories were involved in more than 5 donor discrepancies. After the change, the number of laboratories involved decreased to 5.
- During the 10 months prior to the policy change, 9 laboratories were involved in more than 5 recipient discrepancies. After the change, the number of laboratories involved decreased to 5.

- In both eras, 'correct typing' was the most common reason reported by *donor* laboratories.
- 'Correct typing' and 'transcription error' were commonly reported by *recipient* laboratories.
- After the policy change, parent v. split(s) and serology v. molecular typing reasons are selected less frequently for both donor and recipient discrepant typing.

The following conclusions were drawn from data on deceased donors with kidney match run v. *donor* histocompatibility form HLA discrepancies:

- After the policy change, the percentage of donors with discrepancies significantly decreased from 1.2% to 0.6%.
- In the recent era, the number of donors with discrepancies decreased from 61 to 34.
- Types of discrepancies were similar in both eras.
- In the earlier era, two laboratories had a high number of discrepancies (8 and 10). Each of them had only one discrepancy in the most recent era. The maximum number in the most recent era was four.
- In each era, most laboratories have only one or two discrepancies.
- 33 laboratories had at least one discrepancy in the earlier era, 25 had discrepancies in the most recent era and 11 had discrepancies in both eras.

The following conclusions were drawn from data on deceased donors with kidney match run vs. *recipient* histocompatibility form HLA discrepancies:

- After the change, the percentage of retyped donors with HLA discrepancies significantly decreased from 5.7% to 4.0%.
- In the recent era, the number of donors with discrepancies significantly decreased by 30%, 142 to 99.
- Types of discrepancies were similar in both areas.
- The maximum number of discrepancies per laboratory was 9 in the earlier era and 6 in the most recent era.
- In each era most laboratories had 3 or less discrepancies.
- 62 donor laboratories had at least one discrepancy in the earlier era, 48 had discrepancies in the most recent era and 38 had discrepancies in both eras.

The Committee discussed the need to see the actual discrepancies (not aggregate data) to determine the seriousness of each discrepancy. The Committee asked for the data analysis to focus on the discrepancies recorded on the match run (due to the fact that the discrepant typing was used for allocating an organ); ones where 'correct typing' was reported as the reason for the discrepancy by both the donor and recipient laboratories; and those with transcription errors to determine whether or not these are frequently occurring in the same centers.

There was unanimous agreement among the Committee that accuracy of HLA typing is a serious issue and that molecular typing should not result in the number of discrepancies seen. The data presented suggest that there is a problem that should concern the OPTN. The Committee asked to form a subcommittee to look at a number of issues related to the accuracy of HLA typing and to make recommendations to the full Committee, including:

- Programming that will allow for more timely notification to laboratories when an HLA typing discrepancy has occurred, particularly when the discrepancy appears on the match run.
- Requiring the Histocompatibility Committee to annually review discrepant HLA typing reports and forward any unresolved, unexplained discrepancies to the MPSC with recommendations for disciplinary action.
- Requiring recipient laboratories to retype a donor prior to transplant. The subcommittee will also look at variations of such a policy (only requiring when unacceptable antigens are listed, only requiring for virtual crossmatches, and only requiring for candidates with an 80%+ CPRA).
- Request further research analysis to determine the extent of certain problems related to accuracy in HLA typing. This research will include information on laboratories that have not converted to molecular typing of donors and whether a policy change is needed to refer such laboratories to the MPSC for recommended disciplinary action.
- Developing future policy proposals.

The Discrepant Typing subcommittee will request additional research and communicate any policy development proposals to the Policy Rewrite Subcommittee.

6. Plain Language Policy Rewrite

In August, UNOS staff gave a presentation on the plain language rewrite of all OPTN/UNOS policies. One of the changes of significance to the Histocompatibility Committee is that several sections of language currently found in the UNOS bylaws are moving to policy. Once the plain language rewrite is approved by the Board, Policy 4 will contain all policies specific to Histocompatibility Laboratories. However, there will still be language in the OPTN/UNOS bylaws pertaining to membership standards for histocompatibility laboratories.

Members of the Histocompatibility Committee were assigned sections to review in the new Policy 4 and many offered feedback prior to the August 6 & 7 meeting. One committee member commented that the standard word for ABO is ‘blood group’, not ‘blood types’. Another member commented that certain terms, such as ‘periodic’ and ‘validate’ still exist and are too vague for labs to know how to comply. UNOS staff responded that these terms have been flagged to be addressed in the substantive bylaws/policy rewrite.

7. Update from the Kidney Paired Donation (KPD) Workgroup

In August, UNOS staff presented a policy proposal regarding the Kidney Paired Donation (KPD) program. The new KPD policy proposal received a substantial number of public comments related to histocompatibility. Details of the proposal are as follows:

- The candidate's Transplant Hospital is responsible for performing HLA-A, -B, -Bw4,Bw6, and, -DR antigen typing on the candidate. If the candidate has antibodies against HLA-DQA or -DPA or –DPB, the candidate's Transplant Hospital is responsible for performing HLA-DQA, -DPA, or –DPB antigen typing on the candidate.
- The potential donor's Transplant Hospital is responsible for performing HLA-A, -B, -Bw4, -Bw6, -C, -DR, -DR51, -DR52, -DR53, and, -DQ antigen typing on the potential donor.
- HLA typing must be performed at the level of split resolution. The primary HLA typing method must be molecular.

The KPD workgroup formed a Histocompatibility Advisory Committee to make recommendations on the policy proposal. The Advisory Committee made the following recommendations:

- Add Cw, DR51, DR52, DR53, DQA, DQB, and DPB to the required antigen typing on candidates.
- Add DQA and DP antigen typing on donors and specify that DQ is DQB.
- Mandate that transplant hospitals screen candidates for unacceptable antibodies and specify any unacceptable antigens it will not accept for its candidates.
- Require the candidate's hospital to retest the candidate for unacceptable antibodies at least quarterly and when a known sensitizing event has occurred. Changes must be entered in KPD database.
- Require a candidate's transplant hospital to analyze candidate's unacceptable antibodies when an unexpected positive crossmatch has occurred against a matched donor.
- Require donor antigens and candidate unacceptable antigens be entered and verified by two individuals, one of whom must be a histocompatibility expert working in the laboratory.
- When a match offer is declined due to positive crossmatch or unacceptable antigens prior to crossmatch, require the laboratory and/or transplant center declining the offer to submit in writing a detailed explanation of the positive crossmatch or decline of offer within 7 business days. A corrective action plan for preventing similar positive crossmatches or declines in the future, or an explanation of why the situation could not have been prevented, must also be provided.

Staff from the OPTN/UNOS KPD workgroup asked the Histocompatibility Committee members for feedback on these recommendations and whether there were any further recommendations. The Committee overwhelmingly supported these recommendations but made three additional recommendations:

- Require that materials for autoantibody screening be available.
- Require confirmatory donor typing at the time of final crossmatch.
- Require a histocompatibility laboratory director to review all prospective crossmatches.

8. Substantive Histocompatibility Bylaws and Policy Rewrite

In October, the Committee will meet by conference call to discuss substantive changes needed in the OPTN bylaws and policies governing histocompatibility laboratories. These efforts have been divided into 2 subcommittees.

The Histocompatibility Bylaws Rewrite Subcommittee will be reviewing the requirements for Histocompatibility Laboratories seeking membership in the OPTN. Among the amendments considered will be requirements for changes in key personnel, Laboratory Director availability, and performance indicators that prompt a review.

The Policy Rewrite Subcommittee will be reviewing OPTN policies for histocompatibility testing. Among the amendments that will be considered are those addressing significant HLA typing discrepancies, requiring certain elements for agreements between Histocompatibility Laboratories and Transplant Programs, and clarifying vague and unenforceable terms that currently exist.

9. Upcoming Public Comment Proposals

In addition to the Bylaws and Policy Rewrite Subcommittees, the Committee has formed two subcommittees to develop additional public comment proposals for Spring 2013. One proposal will be updating the equivalency tables used to calculate CPRA. The other will propose to add optional fields in WaitList and DonorNet to record HLA DQA and DPB.

10. HLA DR/DQ Mismatching of Kidney Donors and Potential Transplant Recipients

In August, the Committee discussed OPTN Policy 3.5.11.2. Under that policy, potential recipients are given 2 additional points during deceased donor kidney allocation if there are no mismatches between donor's and potential recipient's HLA-DR. One additional point is given if there is 1 DR mismatch and no points are given if there are 2 DR mismatches.

Committee members noted that in the original change that deleted points for A and B, mismatching for any DR made the adverse impact of A and B mismatching significant, whereas when DR was completely matched, A and B mismatches were no longer significant. There are also several recent studies suggesting that HLA-DQ matching between donor and recipient may be more beneficial than DR matching.

To evaluate the effect of the current policy on graft outcome to determine if any policy changes are needed, the committee requested data on graft survival by the level of DR/DQ mismatch and including the impact of A and B mismatching when DR was mismatched. The committee decided to form a subcommittee tasked with reviewing the data and providing recommendations to the full committee.

Participation in the
Meetings
of the
Histocompatibility Committee

NAME	COMMITTEE POSITION	08/06/2012 08/07/2012
Lee Ann Baxter-Lowe, PhD	Chair	X
Dolly Tyan, PhD	Vice Chair	X
Nancy Reinsmoen, PhD	Ex officio (Past Chair)	X
Neng Yu, MD	Region 1 Rep.	X
Julie Houp	Region 2 Rep.	X
Robert Bray, PhD	Region 3 Rep.	X
Cathi Murphy, PhD	Region 4 Rep.	X
Dolly Tyan, PhD	Region 5 Rep.	X
Ellen Klohe, PhD	Region 6 Rep.	X
Manish Gandhi, MD	Region 7 Rep.	X
Sara Dionne, PhD	Region 8 Rep.	
Rex Friedlander	Region 9 Rep.	X
A. Bradley Eisenbrey MD, PhD	Region 10 Rep.	X
David Kiger, CHS, CHT	Region 11 Rep.	X
Laine Krisiunas, BS, MBA	At Large	X
Luis Campos, MD	At Large	X
James Selby	At Large	
James Bowman	HRSA	X
Raelene Skerda	HRSA	X
Gena Boyle	Policy Liaison	X
Anna Kucheryavaya	Research Liaison	X
Cheryl Hall	Business Analyst	X
Tina Rhoades	RN Case Investigator	X
Howard Gebel, PhD	SRTR	X
Adrine Chung	SRTR	
Nick Salkowski	SRTR	X
Bryn Thompson	SRTR	
Sally Gustafson	SRTR	
Ken Lamb	SRTR	
Ajay Israni, MD	SRTR	