

OPTN/UNOS HISTOCOMPATIBILITY COMMITTEE REPORT SUMMARY

I Organ Availability Issues:

Action Items for Board Consideration:

- None

Other Significant Items:

- None

II Patient Access Issues:

Action Items for Board Consideration:

- None

Other Significant Items:

- The Committee noted that the number of 0-antigen mismatched deceased donor kidney transplants in minorities would increase if a less restrictive equivalence table was used. The Committee is reviewing more data to help it decide whether or not to recommend to the Board that a less restrictive equivalence table should be used to determine the level of HLA match (Item 8, page 5).
- The Committee continues to review the data on the crossmatch predictive value of new laboratory technologies. Accurate prediction of crossmatch results would allow broader sharing of deceased donor kidney transplants, and this would benefit sensitized patients (Item 10, page 5).

III Other Issues:

Action Items for Board Consideration:

- The Board is asked to approve modifications to UNOS Bylaws Appendix B Attachment 1 (Standards for Histocompatibility Testing) Standard H3.100 (Note: There is no corresponding OPTN Bylaw), proposed new policies 3.5.17 (Prospective Crossmatching) (for kidney transplantation) and 3.8.8 (Prospective Crossmatching) (for pancreas transplantation), and proposed new Appendix D to Policy 3 (Item 2, page 1).
- The Board is asked to approve a proposed new Policy 3.7.17 (Crossmatching for Thoracic Organs) which provides that a transplant program and its histocompatibility laboratory must have a joint written policy that states when a crossmatch is necessary (Item 3, page 2).
- The Board is asked to approve modifications to Policy 3.5.9 (Minimum Information/Tissue for Kidney Offer) which requires that the host OPO provide the HLA-A, B, Bw4, Bw6, and DR information to the potential recipient center with each kidney offer (Item 4, page 2).
- The Board is asked to approve modifications to policy 3.5.3.3 (Mandatory Sharing) and 3.5.11.3 (Panel Reactive Antibody) that would allow 4 points to be awarded to all high PRA candidates (Item 5, page 3).

Other Significant Items:

- At the request of the Membership and Professional Standards Committee, the Committee continues its work on defining criteria for the evaluation of Histocompatibility Laboratory Directors (Item 7, page 4).
- The Committee continues to monitor the new deceased donor kidney allocation policy. It noted that since implementation of the policy, more minorities have been transplanted, and more poorly HLA matched transplants were performed (Item 9, page 5).
- The Committee continues to discuss the utility of models to predict the probability of receiving a 0-antigen mismatched kidney. It has been suggested that the use of such models would be beneficial to both patients and physicians (Item 11, page 6).
- The Committee continues its dialog with the CAP regarding its request for deemed status to inspect and accredit laboratories (Item 12, page 6).

**REPORT OF THE
OPTN/UNOS HISTOCOMPATIBILITY COMMITTEE
TO THE
BOARD OF DIRECTORS**

**Minneapolis, MN
June 24-25, 2004**

**Susan L. Saidman, Ph.D., Chair
Geoffrey A. Land, Ph.D., Vice Chair**

1. **Membership Issues.** During the January 20-21, 2004, meeting and the May 4, 2004, conference call, the Committee reviewed key personnel changes and changes in laboratory status and made recommendations to the Membership and Professional Standards Committee.
2. **Proposed Modifications to UNOS Bylaws Appendix B Attachment 1 (Standards for Histocompatibility Testing) Standard H3.100 and Proposed New Policies for Kidney Transplantation - 3.5.17 (Prospective Crossmatching), and for Pancreas Transplantation - 3.8.8 (Prospective Crossmatching), and Proposed Appendix D to Policy 3.** At its June 2003 meeting, the Board of Directors approved modifications to standard H3.100 of Bylaws Appendix B Attachment 1 (Standards for Histocompatibility Testing), which was recommended for approval by the Kidney and Pancreas Transplantation Committee. Subsequently, the Histocompatibility Committee determined that this standard dictated clinical practice and felt that this was inappropriate since the Bylaws are standards that are pertinent only to laboratory practice. At its July 2003 meeting, the Committee approved a modification of standard H3.100 to “the laboratory must be capable of performing a prospective crossmatch and must do so when requested by a physician or other authorized individuals. Histocompatibility laboratories must have a joint written policy with their transplant program(s) on transplant candidate crossmatching strategies.” This proposed modification was sent out for public comment in August 2003. Although the majority of the comments supported the proposed modifications, some responses from the public, the Kidney and Pancreas Transplantation Committee, Patient Affairs Committee, and the Regions opined that there should be more specific language on the circumstances when a crossmatch (either prospective or retrospective) is required, particularly for sensitized patients. In response to these comments the Committee voted to not present to the Board its proposed modifications to standard H3.100. Instead, the Committee agreed that it would work with the Kidney and Pancreas Transplantation Committee to develop a laboratory standard regarding crossmatching that will reside in the Bylaws, and, at the same time, develop a clinical practice policy on crossmatch requirements that will reside in the OPTN/UNOS Policies section. In addition, guidelines for the development of a joint written agreement between laboratories and their transplant program(s) on crossmatch strategy would be developed.

At its January 2004, meeting, the Committee discussed and approved the language for the laboratory standard, the clinical practice policy regarding prospective crossmatching for kidney and for pancreas transplantation, and the guidelines. The Committee agreed that the current Bylaw dictates clinical practice and that it should be changed to address only laboratory practice. Therefore, the Committee unanimously approved (Committee vote: 15 For, 0 Against, 0 Abstentions) that modifications to Bylaws Appendix B Attachment 1 (Standards for Histocompatibility Testing), a proposed new policy for kidney transplantation, Policy 3.5.17 (Prospective Crossmatching), a proposed new policy for pancreas transplantation, Policy 3.8.8 (Prospective Crossmatching), Appendix D to Policy 3 (Guidelines for the Development of Joint Written Agreements Between Histocompatibility Laboratories and Transplant Programs), should be distributed for public comment.

At its May 4, 2004, meeting, the Committee reviewed comments from the public, the regions, and other committees. It noted that of the 39 responses that expressed an opinion, 36 (92.3%) supported the proposal and 3 (7.7%) opposed the proposal. The Patients Affairs and the Transplant Coordinators Committees both unanimously supported the proposal. All Regions that had met (except Region 2) voted to approve the proposal. One comment which was received from the public suggested that there should be a line in Table 2

of Appendix D that addresses the isotype (IgG Vs IgM) of the antibody. A member of the Committee felt that a distinction should be made between acute and chronic infections in Table 1. The Committee agreed to make these modifications to the tables, and with these modifications, the Committee voted to recommend to the Board that the following resolution be approved:

***** RESOLVED, that the modifications to UNOS Bylaws Appendix B Attachment 1 (Standards for Histocompatibility Testing) Standard H3.100 and new Policies for kidney transplantation, Policy 3.5.17 (Prospective Crossmatching), and for pancreas transplantation, Policy 3.8.8 (Prospective Crossmatching), and Appendix D to Policy 3, as set forth in Exhibit A (changes from the proposal as distributed for public comment are noted by double underlined text), be approved and implemented on January 1, 2005.**

Note: There is no corresponding OPTN Bylaw

Committee vote: 14 For, 0 Against, 0 Abstentions

The Committee approved an implementation date of January 1, 2005, as this would allow the laboratories and their transplant programs time to develop the joint written policy and will give ASHI (which has deemed status to inspect laboratories for UNOS) time to modify its inspection checklist and to allow its inspectors to inspect laboratories for the new standard and policy.

3. **Proposed New Policy 3.7.17 (Crossmatching for Thoracic Organs).** At its November 2003 meeting, the Board of Directors approved the Histocompatibility Committee's recommendation that standard I3.100 of the Bylaws Appendix B Attachment 1 - Standards for Histocompatibility Testing, which affects non-renal non-pancreas transplantation, be modified to state "the laboratory must be capable of performing a prospective crossmatch and must do so when requested by a physician or other authorized individuals. Histocompatibility laboratories must have a joint written policy with their transplant program(s) on transplant candidate crossmatching strategies." However, the Bylaws pertain only to laboratory practice and not to the clinical practice of transplant programs. Therefore, the Committee has proposed a new policy that applies to transplant programs. The intent of this proposed policy is essentially the same as the laboratory practice standard which was approved by the Board in November 2003. Therefore, the Committee approved (Committee vote: 15 For, 1 Against, 0 Abstentions) that that a new Policy 3.7.17 (Crossmatching for Thoracic Organs) be distributed for public comment.

At its May 4, 2004, meeting, the Committee reviewed comments from the public, the regions, and other committees. It noted that of the 37 responses that expressed an opinion, 35 (94.6%) supported the proposal and 2 (5.4%) opposed the proposal. The Patients Affairs and the Transplant Coordinators Committees both unanimously supported the proposal. All Regions that had met (except Region 2) voted to approve the proposal. One comment which was received from the public suggested that there should be a line in Table 2 of Appendix D that addresses the isotype (IgG Vs IgM) of the antibody. A member of the Committee felt that a distinction should be made between acute and chronic infections in Table 1. The Committee agreed to make these modifications to the tables, and with these modifications, the Committee voted to recommend to the Board that the following resolution be approved:

***** RESOLVED, that the following Policy 3.7.17 (Crossmatching for Thoracic Organs), shall be approved as set forth below and shall be implemented on January 1, 2005:**

3.7.17 Crossmatching for Thoracic Organs. The transplant program and its histocompatibility laboratory must have a joint written policy that states when a crossmatch is necessary. Guidelines for policy development, including assigning risk and timing of crossmatch testing, are set out in Appendix D of Policy 3.

Committee vote: 14 For, 0 Against, 0 Abstentions

4. **Mandatory HLA-A, B, Bw4/6, and DR typing of Kidney and Pancreas Transplant Candidates and Donors.** At the request of the Committee at its October 2003 conference call, Dr. Ting sent a memo to

histocompatibility laboratory directors and supervisors, and the Organ Center asking them to enter the complete HLA type and/or remind their OPO to enter the complete HLA type of all deceased donors. This request was in reference to standard H4.100 of Bylaws Appendix B Attachment 1 (Standards for Histocompatibility Testing) which states "Prospective typing of donors and recipients for HLA-A, B, Bw4, Bw6, and DR antigens is mandatory." However, the Bylaws pertain only to laboratories and do not apply to transplant programs and OPO's. Policy 3.5.9 (Minimum Information/Tissue for Kidney Offer) states that the host OPO must provide "(v) HLA typing" data to the potential recipient center with each kidney offer; but does not define the extent of "HLA typing." Therefore, the Committee recommends that the Board approve the following resolution:

***** RESOLVED, that the following modification to Policy 3.5.9 (Minimum Information/Tissue for Kidney Offer) be approved, and implemented on June 25, 2004.**

3.5.9 Minimum Information/Tissue for Kidney Offer. The host OPO must provide the following information to the potential recipient center with each kidney offer:

- (i) – (iv) [No changes]
- (v) HLA typing—A, B, Bw4, Bw6, and DR antigens
- (vi) – (xx) [No changes]

Committee vote: 15 For, 0 Against, 0 Abstentions.

The Committee requested that compliance for entry of HLA-A, B, DR, and Bw4/6 antigens into UNetsm for deceased kidney and pancreas donors and patients be obtained from UNOS and reviewed at its July 2004 meeting. The format of the report would be the same as that presented during the October 2003 meeting of the Committee by conference call.

5. PRA Points in the Deceased Donor Kidney Allocation Policy. Current policy states that 4 points shall be awarded to patients with high PRA (80+%) and a negative preliminary crossmatch. However, programming on the UNOS computer awards all high PRA patients 4 points regardless of crossmatch result. The Committee discussed the difference between policy and programming on the UNOS computer and agreed that not all laboratories entered preliminary crossmatch results into UNetsm prior to performing a match run, because they do not have the appropriate utility; do not always have the preliminary crossmatch results prior to a match run; and/or do not have the time to manually enter the preliminary crossmatch results prior to a match run. Therefore, the Committee felt that 4 points should be awarded to all high PRA patients regardless of crossmatch result. The Committee noted that this change would not affect the offers since those candidates who do have a positive crossmatch will not be offered the organ. The Committee voted to recommend that the Board approve the following resolution.

***** RESOLVED, that the following modifications to policy 3.5.3.3 (Mandatory Sharing) and 3.5.11.3 (Panel Reactive Antibody) be approved, and implemented on June 25, 2004.**

3.5.3.3 Mandatory Sharing. With the exception of deceased kidneys procured for simultaneous kidney and non-renal organ transplantation as described in Policy 3.5.3.4, if there is any patient on the UNOS Patient Waiting List for whom there is a zero antigen mismatch with a standard donor, the kidney(s) from that donor shall be offered to the appropriate UNOS member for the patient with the zero antigen mismatch subject to time limitations for such organ offers set forth in Policy 3.5.3.5. With the exception of deceased kidneys procured for simultaneous kidney and non-renal organ transplantation as described in Policy 3.5.3.4, if there is any patient on the UNOS Patient Waiting List who has agreed to receive expanded criteria donor kidneys for whom there is a zero antigen mismatch with an expanded criteria donor, the kidney(s) from that donor shall be offered to the appropriate UNOS member for the patient with the zero antigen mismatch who has agreed to be transplanted with expanded criteria donor kidneys subject to time limitations for such organ offers set forth in Policy 3.5.3.5. If both donor kidneys are transplantable, the recipient center that was offered the kidney for a patient with a zero antigen mismatch does not have the implicit right to choose between the two kidneys. The final decision as to which of the two kidneys is to be shared rests with the Host OPO. ~~In lieu of the four additional points for a patient with a PRA of 80% or~~

~~higher and a preliminary negative crossmatch (Policy 3.5.11.3) f~~Four additional points will be added to all patients for whom there is a zero antigen mismatch with a standard donor and whose PRA is 80% or higher ~~regardless of preliminary crossmatch results~~. When multiple zero antigen mismatches are found for a single donor, the allocation will be in the following sequence:

3.5.11.3 Panel Reactive Antibody. A patient will be assigned 4 points if he or she has panel reactive antibody (PRA) level of 80% or greater based upon historical or current serum samples, as used for crossmatch to determine suitability for transplant, ~~and there is a negative preliminary crossmatch between the donor and that patient~~. For geographic allocation units with UNOS approved renal allocation variances that assign points for PRA level, PRA points will also be assigned based on the historic or current serum sample as used for crossmatch to determine crossmatch suitability.

Committee vote: 12 For, 2 Against, 0 Abstentions

6. The Committee's Response to Proposals from Other Committees Distributed for Public Comment on March 15, 2004. The Committee reviewed the proposals from the other committees voted on the following proposals.

Proposal # 2: Proposed Modifications to OPTN/UNOS Policies 3.5.3.3 (Mandatory Sharing) and 3.5.5 (Payback Requirements) ("Exemption of Kidneys Recovered from Donation after Cardiac Death (DCD) Donors from Sharing Requirements for Zero Antigen Mismatched Kidneys or Payback).

Support. However, the Committee made the following comment: "That the number of Donation after Cardiac Death (DCD) donors be monitored at least annually, and if the numbers become substantial, that the policy would be re-evaluated." The Committee requested that UNOS provide the number of DCD donors by OPO to the Committee at all of its face-to-face committee meetings, beginning in July 2004.

Committee vote: 14 For, 0 Against, 0 Abstentions

Proposal # 5: Proposed Modifications to OPTN/UNOS Policies 3.5.5.1 (Payback Requirements) and 3.11.5.1 (Pediatric Kidney Transplant Candidates Not Transplanted within Time Goals).

Support.

Committee vote: 14 For, 0 Against, 0 Abstentions

Proposal # 6: Proposed Modifications to OPTN/UNOS Policy 3.5.11.2 (Quality of Antigen Mismatch).

Support.

Committee vote: 14 For, 0 Against, 0 Abstentions

Proposal # 8: Proposed Modifications to OPTN/UNOS Policy 3.8.1.6 (Mandatory Sharing of Zero Antigen Mismatch Pancreata).

Support.

Committee vote: 14 For, 0 Against, 0 Abstentions

Proposal # 21: Proposed Modifications to OPTN/UNOS Policy 3.1.4 (Patient Waiting List).

Support.

Committee vote: 14 For, 0 Against, 0 Abstentions

The Committee did not have opinions on the other proposals that were submitted for public comment.

7. Evaluation of Histocompatibility Laboratory Directors. At its January 2004, Committee meeting, Dr. Susan Saidman briefed the Committee on the original objective and formation of Joint ASHI/UNOS Task Force on Director Responsibilities. The original request came from the Membership and Professional Standards Committee (MPSC) for guidance when assessing the suitability of directors directing multiple laboratories.

The Task Force felt that it was not possible to come up with guidelines since there were so many factors involved, such as size and workload of laboratories, geographic distance between laboratories, other commitments of the director, etc. Instead, the Task Force developed a report describing the responsibilities of directors. The Report was sent out by ASHI for public comments, and was presented at the Directors' and Technologists' Forums at the ASHI Annual Meeting in October 2003. About 40 comments had been received, both from directors (the majority) and technologists. Most of the technologist comments were positive. However, a number of the comments were critical of the report. Based on this Report the Histocompatibility Committee's Membership Issues Subcommittee developed documents with proposed changes to Key Personnel Qualifications (OPTN Charter & Bylaws), and to Personnel Qualifications in Appendix B Attachment 1 - Standards for Histocompatibility Testing (UNOS Bylaws). At its May 4 conference call, the Committee discussed these documents. The majority of the members supported the documents as written, however, some members felt that there should be more detail about qualification, training, and education requirements for the laboratory director and other key personnel. The Committee agreed that OPTN/UNOS must have its own requirements for key personnel, and could not rely solely on ASHI's recommendations, based on its standards. The Committee continues with its discussion on this important issue. It hopes to be able to present a final document to the MPSC at its July 2004 meeting, for consideration. If approved, the document would be submitted for public comment in August 2004.

8. Zero-Antigen Mismatched Kidney Transplants Matched With and Without the Equivalence Table. At its January 2004 Committee meeting, in response to a Committee data request, Josh McGowan (SRTR) presented data which showed that among 0-antigen mismatched deceased donor kidney transplants an exact match (i.e., matched without using the equivalence table) did not show a better graft outcome than an equivalence match (ie, matched using the current equivalence table) except for highly sensitized patients (Exhibit B). The Committee was interested in reanalyzing the data using "broader" equivalences, and requested the SRTR to perform these analyses. At its May 4, 2004 conference call, the Committee reviewed this additional data. The analyses by the SRTR showed that using a less restrictive equivalence table resulted in an additional 10% 0-antigen mismatched transplants without affecting the overall graft survival (Exhibit C). The data also showed that the transplant rate in African-Americans increased by 16%. Dr. Arnold, his subcommittee, and the SRTR would prepare a manuscript. The full data analyses would be presented to the Committee at its July 2004 meeting. A discussion point will be to decide whether a recommendation should be made to the Board to modify the current equivalence table to make it less restrictive. The data would also be presented to the Kidney and Pancreas Transplantation Committee and the Minority Affairs Committee at their July 2004 meetings.
9. Monitoring the New Kidney Allocation Policy. The deceased donor kidney allocation policy was changed on May 7, 2003, to give 2 points for 0 DR mismatches and 1 point for 1 DR mismatch. The previous policy awarded 7, 5, and 2 points for 0, 1, and 2 B, DR mismatches, respectively. The intent of the new policy was to transplant more minority patients with minimal impact on graft survival overall. The Committee requested data to monitor the effect of the new policy on the race/ethnicity of the recipients being transplanted as well as the HLA mismatch levels of these transplants. Data were presented by Dr. Wida Cherikh (UNOS), which compared various factors of transplants performed six months after implementation of the new policy with transplants performed six months prior to the change (Exhibit D). The data showed that with the change in policy:
 - More minorities (Blacks and Asians) received a transplant.
 - More transplants were performed with a greater number of HLA mismatches.
 - More transplants were performed in patients who had waited longer.

Concern was expressed about the high proportion of transplants mismatched at DR, and whether the number of points assigned is sufficient. However, the data are from the first six months, and it may take some time for the system to reach "equilibrium." The Committee requested similar analyses to be performed with two sequential six-month post-policy cohorts, and to be presented to the Committee at its July 2004 meeting.

10. Broader Sharing of Deceased Donor Kidneys Through Accurate Prediction of Crossmatch Results. There is considerable interest in broader sharing of kidneys for highly sensitized patients. However, the main obstacle to overcome is to be able to accurately predict a crossmatch result. A number of studies were presented by Committee members that address the issue of accurately defining acceptable and unacceptable

mismatches. Three different approaches were discussed at the meeting.

- A. Use HLA Matchmaker to quantify the number of triplet mismatches between donor and recipient in the database for sensitized recipients. UNOS is working with Dr. Rene Duquesnoy.
- B. Investigate whether complete identification of HLA antibodies in patients' sera would predict the results of the crossmatch more accurately. Dr. Karen Nelson showed a better prediction of crossmatch result when antibody specificities were identified by single antigen beads technique.
- C. Dr. Afzal Nikaein presented her approach, which is to identify the polymorphic amino acids of the HLA molecules which patients' sera recognize. This is performed by absorption of sera with various HLA antigen and extensive analysis using the HLA sequence database. This analysis is a long term study and requires a sophisticated computer program. Perhaps a combination of HLA Matchmaker and sequence database would provide the best results.

The Committee continues its discussion on this important topic. Although single-antigen bead technology has the potential of accurately identifying "unacceptable" antigens (and therefore, "acceptable" antigens) only about 50% of the laboratories are using this technology. Until all laboratories are able to reliably identify "unacceptable" and "acceptable" antigens, broader sharing of deceased donor kidneys will not be possible.

11. Predicting the Probability of Receiving a 0-Antigen Mismatch Offer. The Committee invited Dr. Lee Ann Baxter-Lowe (University of California, San Francisco) to give a presentation on "Managing the Waiting List for Deceased Donor Kidneys: Prioritization Based upon Likelihood of an Offer for a 0-Antigen Mismatched Kidney." She and her team have developed a model to predict the likelihood of receiving a 0-antigen mismatch offer based on the blood group and HLA phenotype for patients at their center. Their center has a very large waiting list, and they find it impossible to get all their patients medically ready in case of a 0-antigen mismatch offer. They now work up candidates that have a 20% chance of receiving a 0-antigen mismatch offer within a year based on their model. The Committee feels that this model could be extremely useful to both physicians and patients on a national level, and is working with Dr. Baxter-Lowe towards this end.

Dr. Nancy Goeken produced a table which showed the common HLA phenotypes in blood group O and A candidates who had received a 0-antigen mismatched kidney transplant, their mean waiting time in days, and the number of transplants (Exhibit E).

12. Accreditation of Histocompatibility Laboratories by the College of American Pathologists (CAP). The Committee continues its discussion with the CAP regarding its request for deemed status to inspect and accredit histocompatibility laboratories for UNOS.

OPTN/UNOS HISTOCOMPATIBILITY COMMITTEE MEETING
O'Hare Hilton Airport Hotel
Chicago, IL
January 20-21, 2004

Members Present

Susan L. Saidman, Ph.D., dip ABHI
Geoffrey A. Land, Ph.D., HCLD
Laurine Bow, Ph.D.
Malek Kamoun, M.D., Ph.D.
Dod Stewart, CHS
Afzal Nikaein, Ph.D., HCLD
Michael Cecka, Ph.D., dip ABHI
Karen A. Nelson, Ph.D., dip ABHI
Bozena Labuda, MT, CHS
Nancy E. Goeken, Ph.D.
Charlene Hubbell, MT(ASCP), SBB
Dorothy Levis, MT, CHS
Angelo N. Arnold, Ph.D.
Robert A. Montgomery, M.D., Ph.D.
James A. Cutler, CPTC
Roger D. Wright, EDS, EDD

Chair
Vice Chair
Region 1
Region 2
Region 3
Region 4
Region 5
Region 6
Region 7
Region 8
Region 9
Region 10
Region 11
At Large
At Large
At Large

UNOS

Alan Ting, Ph.D.
Wida S. Cherikh, Ph.D.

Staff Liaison
Data Liaison

SRTR

Joshua McGowan, M.S.
Fritz Port, M.D.

OPTN/UNOS HISTOCOMPATIBILITY COMMITTEE MEETING
By Teleconference
May 4, 2004

Members Present

Susan L. Saidman, Ph.D., dip ABHI	Chair
Geoffrey A. Land, Ph.D., HCLD	Vice Chair
Laurine Bow, Ph.D.	Region 1
Malek Kamoun, M.D., Ph.D.	Region 2
Dod Stewart, CHS	Region 3
Afzal Nikaein, Ph.D., HCLD	Region 4
Michael Cecka, Ph.D., dip ABHI	Region 5
Karen A. Nelson, Ph.D., dip ABHI	Region 6
Bozena Labuda, MT, CHS	Region 7
Nancy E. Goeken, Ph.D.	Region 8
Charlene Hubbell, MT(ASCP), SBB	Region 9
Dorothy Levis, MT, CHS	Region 10
Angelo N. Arnold, Ph.D.	Region 11
James A. Cutler, CPTC	At Large
Roger D. Wright, EDS, EDD	At Large

Members Unable to Attend

Robert A. Montgomery, M.D., Ph.D.	At Large
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UNOS

Alan Ting, Ph.D.	Staff Liaison
Wida S. Cherikh, Ph.D.	Data Liaison

SRTR

Joshua McGowan, M.S.
Fritz Port, M.D.

Proposed Modifications to UNOS Bylaws Appendix B Attachment 1 (Standards for Histocompatibility Testing) Standard H3.100 and Proposed New Policies for Kidney Transplantation - 3.5.17 (Prospective Crossmatching), and for Pancreas Transplantation - 3.8.8 (Prospective Crossmatching), and Proposed Appendix D to Policy 3.

UNOS Bylaws Appendix B Attachment 1 (Standards for Histocompatibility Testing)

Section H - Renal and Pancreas Organ Transplantation

H3.000 Crossmatching

~~H3.100 Crossmatches are not mandatory for all kidney and pancreas transplant candidates. For example, patients documented as historically unsensitized, and who have no intervening sensitizing events, may be transplanted without a final crossmatch. However, laboratories must perform a prospective crossmatch if so requested by the transplant center and dictated by clinical circumstances. The laboratory must be capable of performing a prospective crossmatch and must do so when requested by a physician or other authorized individuals. Histocompatibility laboratories must have a joint written policy with their transplant program(s) on transplant candidate crossmatching strategies.~~

Policies

3.5.17 Prospective Crossmatching. A prospective crossmatch is mandatory for all patients, except where clinical circumstances support its omission. The transplant program and its histocompatibility laboratory must have a joint written policy that states when the prospective crossmatch may be omitted. Guidelines for policy development, including assigning risk and timing of crossmatch testing, are set out in Appendix D to Policy 3.

3.8.8 Prospective Crossmatching. A prospective crossmatch is mandatory for all patients, except where clinical circumstances support its omission. The transplant program and its histocompatibility laboratory must have a joint written policy that states when the prospective crossmatch may be omitted. Guidelines for policy development, including assigning risk and timing of crossmatch testing, are set out in Appendix D to Policy 3.

Appendix D to Policy 3

GUIDELINES FOR THE DEVELOPMENT OF JOINT WRITTEN AGREEMENTS BETWEEN HISTOCOMPATIBILITY LABORATORIES AND TRANSPLANT PROGRAMS

Histocompatibility testing provides clinicians with data to evaluate the immunological risk of proceeding to transplant. The timing and number of tests may vary depending upon specific needs of the program, waiting times, sensitizing events in individual patients or other considerations. These should be established to best suit the needs and concerns of each transplant program drawing upon the expertise of the histocompatibility laboratory. These guidelines summarize the recommended elements to be included in the joint agreements and provide background and discussion to support the recommendations. Data cited in reviews of histocompatibility testing for renal (1) and thoracic (2) transplantation formed the basis for these recommendations.

The following elements should be included in agreements developed between histocompatibility laboratories and transplant programs:

- A process to obtain accurate and timely history of allosensitization for each patient
- Selection of assay format for antibody screening and for crossmatching
- Selection of timing for periodic sample collection
- Selection of timing for performing antibody screening
- Criteria and a process for establishing a risk category for each patient and crossmatching strategy for each category
- Criteria and a process for use of Unacceptable Antigens or Acceptable Antigens for organ allocation
- Process for monitoring post-transplant or for monitoring desensitization protocols

History of Allosensitization

It is important to recognize 2 major sources of sensitization:

1. Graft failure – nearly all patients who survive graft failure produce anti-HLA antibodies against mismatched HLA antigens on the failed graft.
2. Previous pregnancies – up to 25% of women who have had children produce antibodies against mismatched paternal HLA antigens. This appears to increase with the number of live births.

Either of these factors raises the strong possibility that a patient has been immunized. Other factors may stimulate antibody production as well (particularly among patients with prior graft failure or pregnancy) including blood transfusions, vaccinations, certain infections and surgeries. Patients with autoimmune diseases (SLE, Age nephropathy) may have autoantibodies that will complicate evaluation as these produce false positive reactions in certain tests. Patients who have any of these risk factors are at high risk of rapidly developing an antibody response on exposure to alloantigens, so it is also important to determine whether any potential sensitizing events have occurred since the patient’s antibody status was last tested. Table 1 provides more detail of data to be evaluated in determining sensitization history.

Detection of Alloantibody: Creating an Alloantibody History

Current technologies for antibody measurement offer sophisticated means to detect circulating antibodies, which when evaluated in the context of the patient’s sensitization history should provide an estimate of a patient’s risk of producing antibody on re-exposure to the specific allogeneic HLA antigens of the donor at the time of transplant.

The major technologies are listed in Table 2. These tests (and others) can be used to assess sensitization in transplant candidates. The strategies should include:

1. Identification of patients who do or do not have circulating alloantibodies to HLA class I and class II antigens.
 - a. Initial serial screening should include cytotoxicity and more sensitive tests to identify patients with antibodies.
 - b. Several sera should be evaluated to establish a baseline.
2. Characterization of antibody specificity in patients with detectable circulating antibodies using some combination of:
 - a. A panel of representative cells for cytotoxicity
 - b. ELISA tests for specificity
 - c. Antigen-coated microparticles
3. Monitoring patients who do not have antibodies for their development.
 - a. Periodic screening of unsensitized patients is important to detect appearance of anti-HLA antibodies.
 - b. Characterization of antibody specificity.

The challenge in assessing sensitization status is in evaluating the risk of new patients, previously sensitized patients and patients with low levels of antibodies that are detected only by more sensitive tests (enhanced cytotoxicity tests using anti-human globulin (AHG) or flow cytometry) rather than lymphocytotoxicity. Estimating the risk for patients who have evidence of anti-HLA antibodies that are not detected by cytotoxicity must be accomplished by considering the patient’s sensitization history. Antibody titers rise after alloantigen exposure and fall over time when the antigen stimulus is removed, often leaving memory B-cells capable of rapidly expanding and secreting antibodies. The danger is that even the most potent immunosuppressive agents are not effective against a memory response which can increase anti-HLA antibody levels within days after re-exposure to HLA antigens on the graft. Although these antibodies rarely cause hyperacute rejection, they carry a high risk for accelerated acute rejections. Because patients are first encountered and evaluated at different stages of their overall immunological experience, the absence of detectable antibodies does not necessarily mean absence of sensitization. Although obtaining a detailed history of sensitizing events is often difficult, particularly for patients who are geographically distant, clinical transplant programs and histocompatibility laboratories should work together to optimize obtaining this information on a timely basis

Periodic Sample Collection

Monthly serum samples for waiting patients should be collected and maintained by the histocompatibility laboratory to develop an alloantibody history and to facilitate final crossmatches.

Crossmatching Strategies

During the mid-1960's, Terasaki (3) and Kissmeyer-Nielsen (4) independently discovered that preformed anti-donor lymphocytotoxic antibodies caused hyperacute rejection of kidney allografts. Patel and Terasaki reported that 24 (80%) of 30 patients transplanted with a positive crossmatch experienced hyperacute rejection and another 3 lost their grafts within 3 months. Since then a prospective crossmatch has been performed before every kidney transplant with few exceptions and, as a result, hyperacute rejections are rare.

The crossmatch test is a direct test for antibodies against the HLA antigens of a specific donor. Obviously a patient with no history of testing for anti-HLA antibodies cannot be considered to be unsensitized. A patient with broadly reacting circulating lymphocytotoxic antibodies would pose an extremely high risk for a positive crossmatch with a prospective donor. On the other hand, a patient who, after repeated tests against panels of potential donor cells or HLA antigen-coated microparticles or other solid supports, has no detectable circulating anti-HLA antibodies is unlikely to have a positive crossmatch test, assuming that testing was performed against a comprehensive panel of HLA antigens and there have been no intervening allosensitizing events. In the Patel and Terasaki study, only 4 hyperacute rejections occurred among 168 patients who tested negative against a panel of potential donor cells using a relatively insensitive test. The specific strategies for evaluating the relative risk of an antibody-mediated rejection must be developed through a joint collaboration between the histocompatibility laboratory and transplant program. In thoracic transplantation, prospective crossmatches are not commonly utilized for patients with no detectable HLA antibodies. In renal transplantation, there may be exceptional cases when it would be advantageous to proceed with transplantation before a pre-transplant crossmatch can be completed. However, such cases must be approached with caution to avoid the consequences of unrecognized antibodies (and the underlying immunity they represent) directed against the donor's HLA antigens. In all cases where a pre-transplant crossmatch is waived, a peri-transplant or retrospective crossmatch is recommended to guide post-transplant management. Table 3 lists elements to be included in crossmatching strategies.

References

1. Gebel HM, Bray RA, Nickerson P. Pre-transplant assessment of donor-reactive, HLA-specific antibodies in renal transplantation: contraindication vs. risk. Am J Transplant. 2003 Dec;3(12):1488-500.
2. Reinsmoen N, Zeevi A, Nelson K. Anti-HLA antibody analysis and crossmatching in heart and lung transplantation. Transplant Immunol, 2004 (in press).
3. Patel R, Terasaki PI. Significance of the positive crossmatch test in kidney transplantation. N Engl J Med 1969; 280:735-739.
4. Bergentz SE, Olander R, Kissmeyer-Nielsen F, Olsen TS, Hood B. Hyperacute rejection of a kidney allograft. Scand J Urol Nephrol. 1970;4(2):143-8.

Table 1. Documenting allosensitization

Event	Data	Notes
<u>Previous graft</u> (includes all solid organs and bone or tendon allografts)	<u>Date of transplant, organ(s)</u>	
	<u>Date of graft loss</u>	<u>Dates of graft removal, retransplant, return to dialysis</u>
	<u>Cause of graft loss</u>	
	<u>HLA typing of donor(s)</u>	<u>To aid in interpreting relevance of alloantibody and to identify potential Unacceptable Antigens</u>
	<u>Rejection history, history of delayed function, history of non-compliance or reduced immunosuppression due to infection</u>	
<u>Pregnancy</u>	<u>Number, years of occurrence</u>	<u>Gravida and para</u>
<u>Transfusions</u>	<u>Number, type of product, month and year of occurrence</u>	
<u>Assist device placement</u>	<u>Type of device, date of placement, duration of treatment</u>	<u>Primarily for thoracic transplantation</u>
<u>Disease</u>	<u>Identification of disease(s) causing end-stage organ failure</u>	<u>Autoimmunity may invalidate some laboratory assays</u>
<u>Acute infections</u>	<u>Viral infection or bacterial infection requiring antibiotics</u>	<u>Most important if occurred since last antibody screening test. Induction of cells or antibodies with specificity for HLA, non-specific activation of memory</u>
<u>Chronic infections</u>	<u>Viral infection e.g. HCV</u>	<u>May effect response to tolerance induction protocols</u>
<u>Vaccinations</u>	<u>Type, date of occurrence</u>	<u>Most important for time period since last antibody screening test.</u>

Table 2. Assays to identify alloantibody (antibody screening or crossmatching)

Assay	Description and Use
<u>Standard complement-dependent lymphocytotoxicity (CDC)</u>	<u>to detect IgG antibodies known to cause hyperacute rejection</u> <u>for panel measurements or crossmatch</u>
<u>Anti-human Globulin - enhanced cytotoxicity (AHG-CDC)</u>	<u>to improve detection of weak or low level antibodies</u> <u>for panel measurements or crossmatch</u>
<u>ELISA-based assays</u>	<u>to provide a more sensitive test that does not depend on complement fixation</u>
	<u>Mixed antigens</u> <u>for monitoring</u>
	<u>Cell equivalents</u> <u>to measure specificity</u>
	<u>Single antigens</u> <u>to measure specificity</u>
	<u>Solubilized cells</u> <u>for crossmatch</u>
<u>Flow cytometry-based assays</u>	<u>the most sensitive test for antibody</u>
	<u>Cell-based</u> <u>for crossmatch or panel measurements</u>
	<u>Microparticle-based soluble antigens</u> <u>for panel measurements without background from cell membranes</u>
	<u>Microparticle-based single HLA-antigen beads</u> <u>for high resolution antibody identification</u>
<u>Determine isotype of antibody</u>	<u>for panel measurements or crossmatches</u>
	<u>IgG or IgM</u>
	<u>Complement-fixing IgG?</u>
<u>Rule out contribution by autoantibody</u>	<u>for panel measurements or crossmatches</u>
	<u>Treatment of serum</u>
	<u>Autologous cells</u>

Table 3. Recommended elements for crossmatching strategies. Strategies should be tailored to level of risk.

Element	Options
<u>Selection of technique(s)</u>	<u>See Table 2. Level of sensitivity</u>
<u>Selection of serum</u>	<u>Stability of a patient's antibody response incorporated into choice of time interval between serum collection and transplant.</u> <u>Use of historic serum.</u>
<u>Timing</u>	<u>Prior to transplant (number of hours or days)</u> <u>Peri-transplant or retrospective (number of hours or days)</u> <u>Timed to limit cold ischemia</u>

Investigating Graft Outcomes by Exact HLA Matching vs. Matching Through Equivalency Tables

**Prepared by the Scientific Registry of
Transplant Recipients**

for Histocompatibility Committee

January 20, 2004

Study Purpose (1)

- Analyze graft survival by peak PRA using HLA equivalency tables (vs. an exact A, B, DR match)

Methods

- **Study Population:** Recipients of a first, kidney-only, zero mismatch transplant from a deceased donor.
- **Study Period:** Patients transplanted between 3/6/1995 and 12/31/2002. Follow-up occurred through 6/30/2003.
- **Adjustment variables:**
 - Donor: age, sex, race, ethnicity, history of hypertension, serum creatinine level
 - Recipient: age, sex, race, ethnicity, cause of ESRD, cold ischemia time, year of transplant, PRA, waiting time and zero mismatch status

Analysis

- Descriptive statistics by 0 MM type and % peak PRA
- Cox Proportional Hazards Regression model
- Current HLA equivalency tables used (rather than equivalency tables at the time of transplant)
- Deaths are counted as graft failure

Frequency of Receiving a 0 MM Transplant, by Type of Match and Peak PRA*

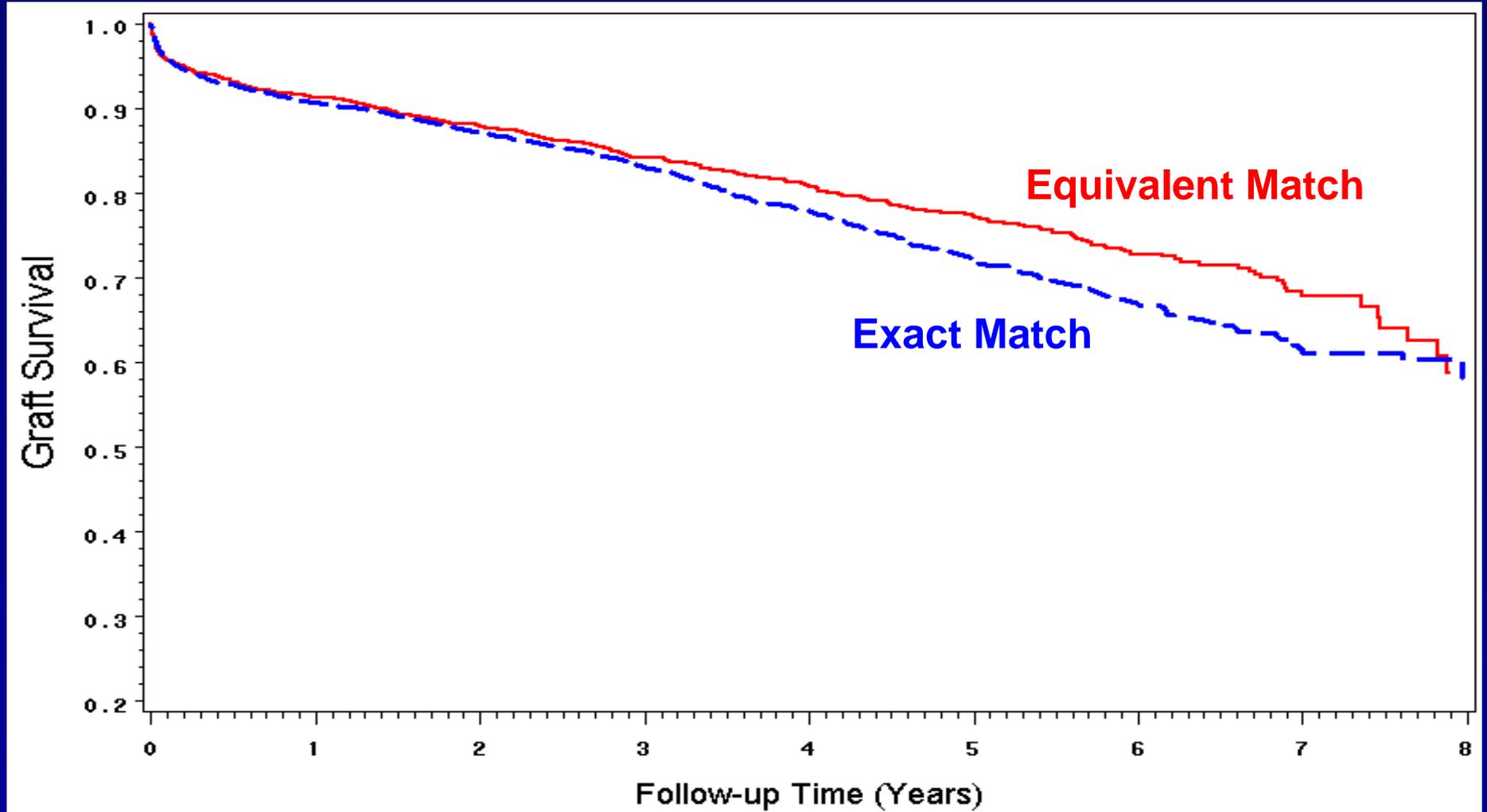
Characteristic	Peak PRA < 20%		Peak PRA 20-79%		Peak PRA 80+%	
	n (patients)	n (graft failures)	n (patients)	n (graft failures)	n (patients)	n (graft failures)
Exact Match	3809	818	501	119	403	102
Equivalent Match - A only	101	14	19	0	12	4
Equivalent Match - B only	91	11	12	5	11	2
Equivalent Match - DR only	1397	300	185	34	154	51
Equivalent Match - other	82	13	13	1	10	5

*n=6,800 patients; 1,479 graft failures

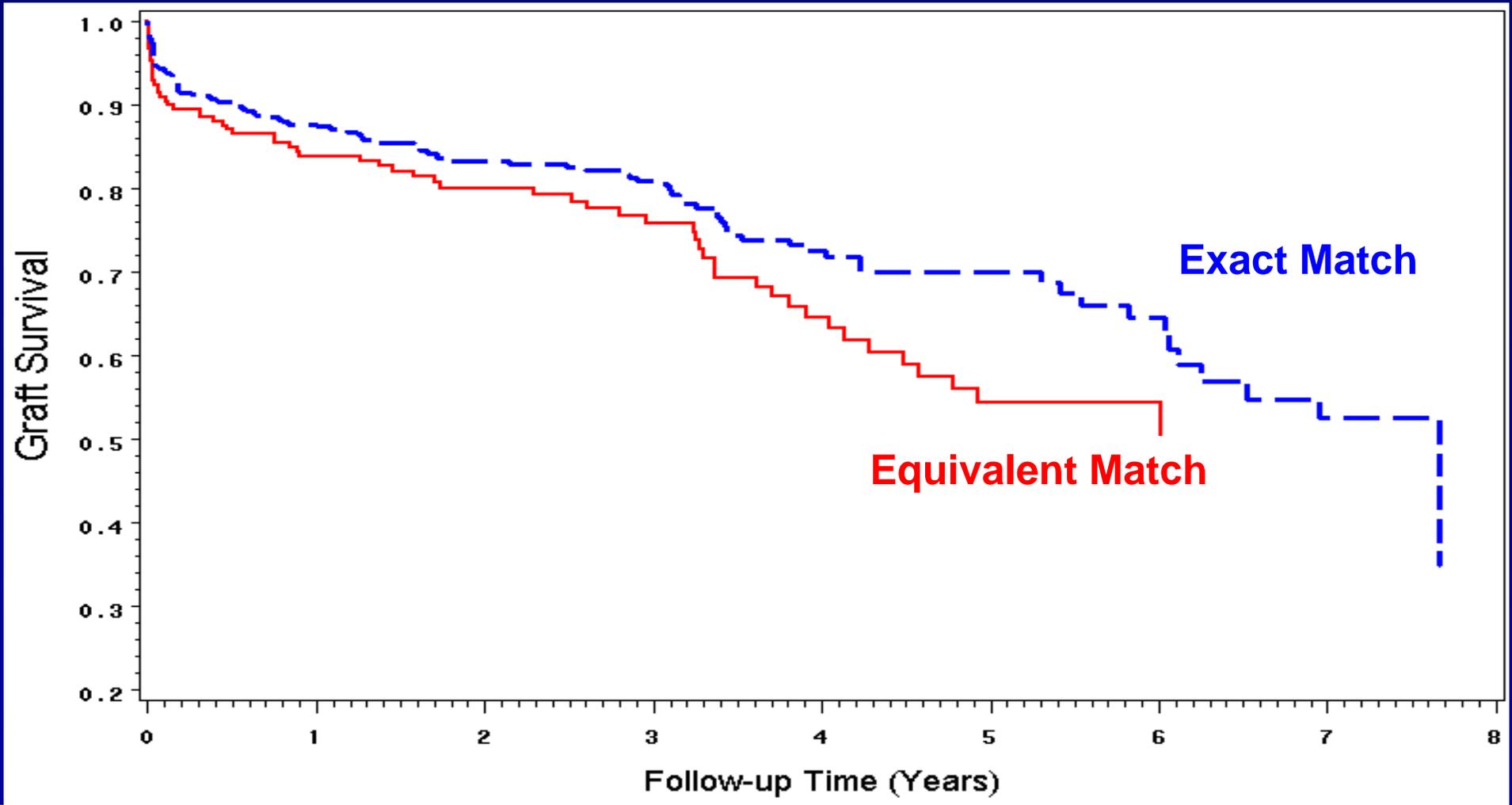
Relative Risk of Graft Failure Among 0 MM Recipients Due to Use of Equivalency Table

Measure	RR	p-value
Equivalent (vs. Exact Match)	0.90	0.07
Equivalent (vs. Exact Match) in:		
PRA < 80%	0.86	0.01
PRA 80% +	1.29	0.12

Adjusted Graft Survival Among 0 MM Recipients (Exact vs. Equivalent Match) – Peak PRA < 80%



Adjusted Graft Survival Among 0 MM Recipients (Exact vs. Equivalent Match) – Peak PRA 80% +



Summary

- **Among zero mismatch patients, an exact match transplant does not show a better outcome than an equivalent match, except for patients with peak PRA > 80%.**

Study Purpose (2)

- Investigate differences in graft survival between zero mismatch transplants when specifying split antigens (defined by the Committee) matched only with themselves versus all other zero mismatch transplants

Frequency of Patients Receiving a 0 MM Transplant, by Type of Match and % Peak PRA*

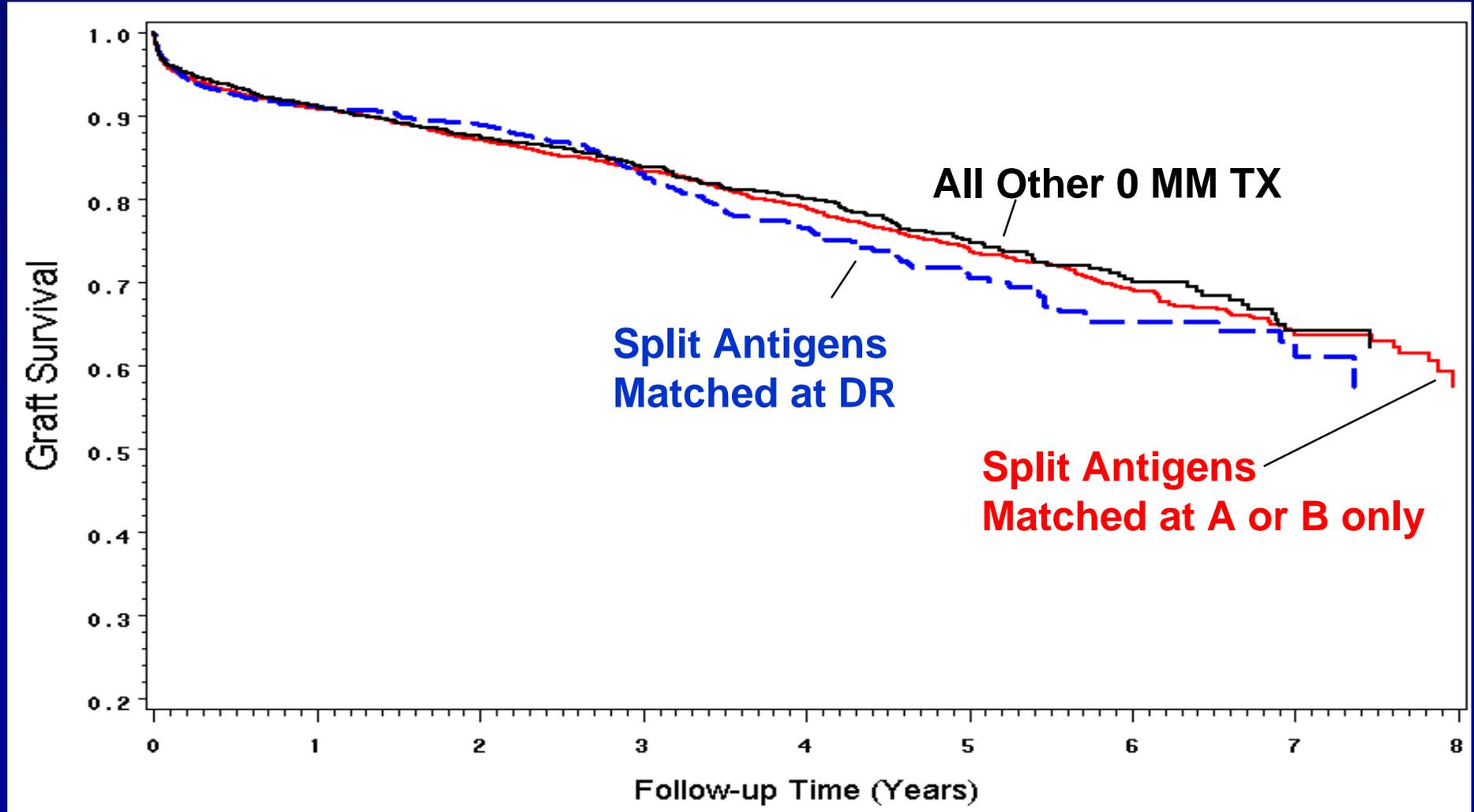
Characteristic	Peak PRA <80%		Peak PRA 80%+	
	n	n	n	n
	(patients)	(graft failures)	(patients)	(graft failures)
Split Antigens Matched Exact (A or B)	4082	862	318	95
Split Antigens Matched Exact (DR)	958	198	107	26
All Other 0 MM Transplants	1170	255	165	43

*n=6,800 zero MM patients; 1,479 Graft Failures; Only 173 of 5,465 patients were matched with split antigens at all 3 loci

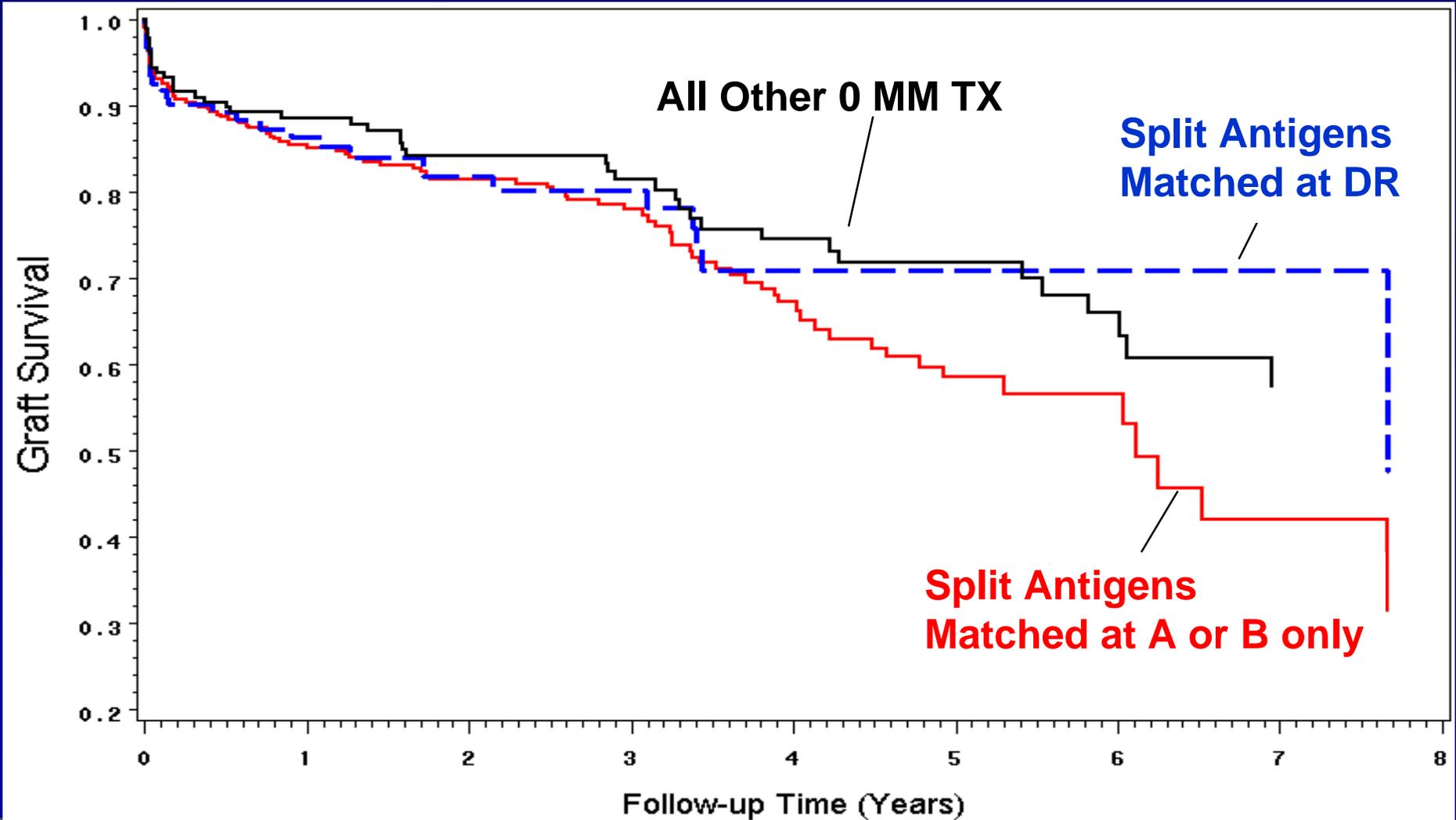
Relative Risk of Graft Failure Among 0 MM Recipients with Split Antigens Matched

Measure	RR	p-value
Peak PRA < 80%		
Split Antigens Matched Exact (A or B)*	1.04	0.54
Split Antigens Matched Exact (DR)*	1.10	0.31
All Other 0 MM Transplants	1.00	Ref.
Peak PRA 80% +		
Split Antigens Matched Exact (A or B)*	1.39	0.07
Split Antigens Matched Exact (DR)*	1.13	0.63
All Other 0 MM Transplants	1.00	Ref.

Adjusted Graft Survival Among 0 MM Recipients with Split Antigens Matched - Peak PRA < 80%



Adjusted Graft Survival Among 0 MM Recipients with Split Antigens Matched - Peak PRA 80% +



Relative Risk of Graft Failure Among 0 MM Recipients with Split Antigens Matched

Measure	RR	p-value
Peak PRA < 20%		
Split Antigens Matched Exact (A or B)*	1.04	0.63
Split Antigens Matched Exact (DR)*	1.04	0.72
All Other 0 MM Transplants	1.00	Ref.
Peak PRA 20% +		
Split Antigens Matched Exact (A or B)*	1.16	0.30
Split Antigens Matched Exact (DR)*	1.32	0.11
All Other 0 MM Transplants	1.00	Ref.

Summary

- **Exact matching of split antigens does not yield better graft survival than all other zero mismatch recipients.**
- **A worse outcome may exist for high PRA patients (>80%) at 5 years with exact matching at HLA A or B (interaction, $p=0.16$).**

Final Report for Data Request from the Histocompatibility Committee Meeting of January 20-21, 2004

Prepared by Fritz Port, M.D., M.S., Joshua McGowan, M.S., and Jennifer Bragg-Gresham, M.S., of the Scientific Registry of Transplant Recipients

This Final Report is submitted by the Scientific Registry of Transplant Recipients (SRTR) in response to the data request from the Histocompatibility Committee, dated February 26, 2004.

Purpose: To investigate whether or not a less restrictive split equivalence table would impact graft survival and if changes to the current table can be recommended by the Committee. In addition, to determine whether or not current data support mandatory sharing of zero mismatched kidneys.

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Data Request Routing Information and Analysis Timeline:

Histocompatibility Committee meeting date: January 20-21, 2004
 Histocompatibility Subcommittee request made: February 26, 2004
 Request Received by SRTR: March 2, 2004
 Analysis plan submitted: March 16, 2004
 Draft Report to be submitted to Full Committee: April 6, 2004
 Final Report to be submitted to Full Committee: April 20, 2004
 Next Full Committee Meeting Date: May 4, 2004

Data Request Overview

Analysis Requested

Inferential Statistical requests (responsibility of URREA as the SRTR contractor):

An analysis of all first, kidney-only, deceased-donor transplants performed from 3/1995 to 6/2003. Expanded criteria and non-heart beating donors should be excluded. Define zero mismatches by the current equivalence table (RUN 1) and the attached less-restrictive equivalence table (RUN 2). Break down the number and percent of patients that fall into the zero mismatch group by ethnicity for RUN 1 and 2. Using only peak PRA data, look at PRA <80% vs. 80%+ and <20% and 20%+. Compare equivalence and exact match. The transplants defined as Zero antigen mismatch in RUN 2 should consist of the Zero antigen mismatch in RUN 1 and split-mismatched organs that were not shared. Compare these two groups for survival. Provide the RR, p-values, and survival curves.

For comparison purposes, the Committee requests survival curves for the first, kidney-only, deceased-donor transplants performed from 3/1995 to 6/2003 that were not defined as zero mismatch transplants. We need to, once again, present current data showing that mandatory sharing of zero mismatched organs impacts outcome. One might argue, that a one or two antigen mismatch, that is not shipped, does as well as a zero mismatch that is shared. I expect that a reviewer of the paper will ask this question. An analysis looking at zero-mismatch, 1-2, 3-4, and 5-6 antigen mismatch should address this. We should also look at zero-mismatch vs. 0, 1, and 2 DR mismatch.

Purpose:

1. A priori, a less restrictive equivalence table will increase the number of mandatory share offers. Does a less restrictive equivalence table impact graft survival?
2. In RUN 2 the number of equivalence TXs should be higher than RUN 1. Do we still see the PRA effect? Is it statistically significant in both groups?
3. Can we recommend changes to the current split equivalence table?
4. Do the data still justify the mandatory sharing of zero mismatched kidneys? Is this true for high PRA? Should a high PRA patient get the zero mismatch only when exact matches are used?

[Quoted from request]

Analysis Plan

Background

Previous analysis has shown a trend for better survival through equivalence matching in recipients with PRA <80% and through exact-matched transplants in highly sensitized recipients (PRA 80%+). Also, improvements in HLA typing have reduced the number of equivalent antigens found in the current HLA Equivalence table. The Committee has developed an unpublished, alternative (i.e., less restrictive) equivalence table that equates closely related antigens in order to examine graft outcomes in recipients that would be considered a 1 or 2 antigen mismatch using the current table. These analyses will compare outcomes of exact and equivalent matched transplants using

both tables to determine if prior trends still hold. In addition, these analyses will examine mandatory sharing of zero-mismatch kidneys, especially for high PRA recipients that would be considered a zero-mismatch using the alternative equivalence table.

Study Population

These analyses will include recipients of a first, kidney-only transplant during the period 3/6/1995-6/30/2002. Kidney transplant recipients from an expanded criteria or non-heart beating donor will now be excluded from the study cohort (these recipients were not excluded in prior analyses). In addition, follow-up will occur until 6/30/2003.

Analytical Approach

The first analysis will compare the outcomes of an equivalent zero mismatch transplant using a less restrictive equivalence table defined by the Committee vs. an exact zero ABDR mismatch. In addition, we will perform a separate analysis that compares the outcomes of the additional zero mismatch recipients from the less restrictive table to those zero mismatch recipients defined under the current UNOS rule. A Cox proportional hazards regression model will be used to compare adjusted graft failure rates. The model will take into account the possible differences in the effect of equivalence vs. exact matching by % peak PRA. Due to the small number of highly sensitized zero-mismatch recipients (% PRA \geq 80), we will include patients with a peak PRA of 20-79% in the sensitized group for this analysis. The model will include donor age, sex, race, history of hypertension, s. creatinine, and an indicator for a shared organ. Recipient factors include age, sex, race, ethnicity, cause of ESRD, cold ischemia time, and year of transplant. Graft survival times will be calculated as the time from transplantation until death or graft failure, censoring at the earliest of last expected follow-up date, last date for recipient follow-up, date of re-transplant, or 6/30/2003. Adjusted graft survival curves and 5-year graft survival rates will be provided.

Results

Table 1.1: Frequency of Recipients in Study Cohort, by HLA Match and % Peak PRA (n=40,141)*

	Peak PRA < 20%	Peak PRA 20% +
1) Exact 0 ABDR MM	3,032	711
2) Equivalent 0 ABDR MM (current table)	1,384	356
3) Equivalent 0 ABDR MM (alternative table)**	449	109
4) 0 DR MM (excluding 0 ABDR recipients)	7,489	1,343
5) 1 DR MM (excluding 0 ABDR recipients)	13,511	2,820
6) 2 DR MM (excluding 0 ABDR recipients)	7,063	1,712

* n=162 recipients with Peak PRA or DR MM missing

** Additional zero MM recipients obtained through the less-restrictive equivalence table (adds approximately 10% to current 0 MM rule)

Table 1.2: Additional 0 MM Transplant Recipients Using Less Restrictive HLA Equivalence Table Compared to Current Rule (by Race), 3/6/95-6/30/2002

Recipient Race	Zero-MM Recipients Using Current HLA Table (Row 1 + Row 2)*	Additional 0 MM Recipients Using Less-Restrictive HLA Table (Row 3)*	Percent Increase (%)
White	4,633	406	8.7
Black	675	110	16.3
Asian	93	28	30.1
Other/Unknown/Missing	82	14	17.1
Total	5,483	558	10.2

* Rows per Table 1.1

Table 1.3: Relative Risk of Graft Failure Among 0 MM Transplant Recipients*

Measure	RR	p-value
Current Table (Row 2)**		
Equivalent 0 ABDR MM (vs. Exact 0 ABDR MM)	0.89	0.077
Peak PRA \geq 20% (vs. Peak PRA < 20%)	1.21	<0.001
Alternative Table (Rows 2 & 3)**		
Equivalent 0 ABDR MM (vs. Exact 0 MM)	0.91	0.111
Peak PRA \geq 20% (vs. Peak PRA < 20%)	1.21	<0.001

* Excludes kidney transplant recipients from an expanded criteria or non-heart beating donor

** Rows per Table 1.1

Table 1.3 shows the results comparing an Equivalent vs. Exact zero mismatch transplant using the current HLA table, as well as the alternative (less-restrictive) HLA table. In this analysis, the number of Equivalent 0 MM transplant recipients defined by the alternative table (n=2,298) includes those recipients defined by the current table (n=1,740). In both models, there is no evidence to suggest that graft failure rates differ for Exact vs. Equivalent zero mismatch transplants (p=0.077, 0.111 respectively). In addition, both models showed a 21% increase in the rate of graft failure for highly sensitized recipients (peak PRA \geq 20%; p < 0.001). However, unlike previous results, the interaction between Equivalent 0 MM transplants and % Peak PRA was not found to be statistically significant and was removed from the model. Therefore, the results do not indicate an additional risk of graft failure for highly sensitized 0 MM recipients matched using the HLA equivalence table compared with an Exact zero MM.

Table 1.4: Relative Risk of Graft Failure Among Transplant Recipients, by Mismatch Type*

Measure	RR	p-value
1) Exact 0 ABDR MM (n=3,743)	1.00	Ref.
2) Equivalent 0 ABDR MM (current table; n=1,740)	0.89	0.076
3) Equivalent 0 ABDR MM (alternative table; n=558)	0.97	0.760
4) 0 DR MM (excluding 0 ABDR MM; n=8,832)	1.12	0.016
5) 1 DR MM (excluding 0 ABDR MM; n=16,331)	1.26	<0.001
6) 2 DR MM (excluding 0 ABDR MM; n=8,775)	1.40	<0.001

* Excludes kidney transplant recipients from an expanded criteria or non-heart beating donor

The results in Table 1.4 are from a second analysis that examined the outcome of the additional zero mismatch recipients obtained through the use of the less-restrictive HLA equivalence table. These results suggest that the graft failure rate does not differ for the additional Equivalent zero mismatch recipients compared to an Exact zero mismatch (RR=0.97, p=0.760).

Table 1.5: Relative Risk of Graft Failure for the Additional Zero MM Transplants Using the Alternative HLA Equivalence Table (Row 3)*

Measure	RR	p-value
Equivalent 0 ABDR MM (alternative table) vs. Equivalent 0 ABDR MM (current table) Row 3 vs. Row 2**	1.09	0.417
Equivalent 0 ABDR MM (alternative table) vs. 0 DR MM (alternative table) Row 3 vs. Row 4**	0.87	0.141

* Excludes kidney transplant recipients from an expanded criteria or non-heart beating donor

** Rows per Table 1.4

Additional results, shown in Table 1.5, also indicate that the graft failure rate for the additional zero MM recipients defined by the less-restrictive table is not statistically different from either the Equivalent 0 MM recipients defined by the current HLA table (higher RR) or 0 DR MM recipients (lower RR). Again, the interaction between Equivalent 0 MM transplants and % Peak PRA was investigated and the effect was not found to be significant. The model also examined the effect of mandatory sharing of 0 MM transplants on graft failure. Shared organs had a 5% increase in the adjusted rate of graft failure (RR=1.05), but the result was not found to be statistically significant (p=0.085). In addition, the interaction between Equivalent 0 MM transplants and shared organs and was not statistically significant. Therefore, the results do not indicate an additional risk of graft failure for zero MM recipients of a shared organ matched using the HLA equivalence table compared with an Exact zero MM..

Figure 1: Adjusted 5-Year Graft Survival Rates Among Transplant Recipients, by Mismatch Type

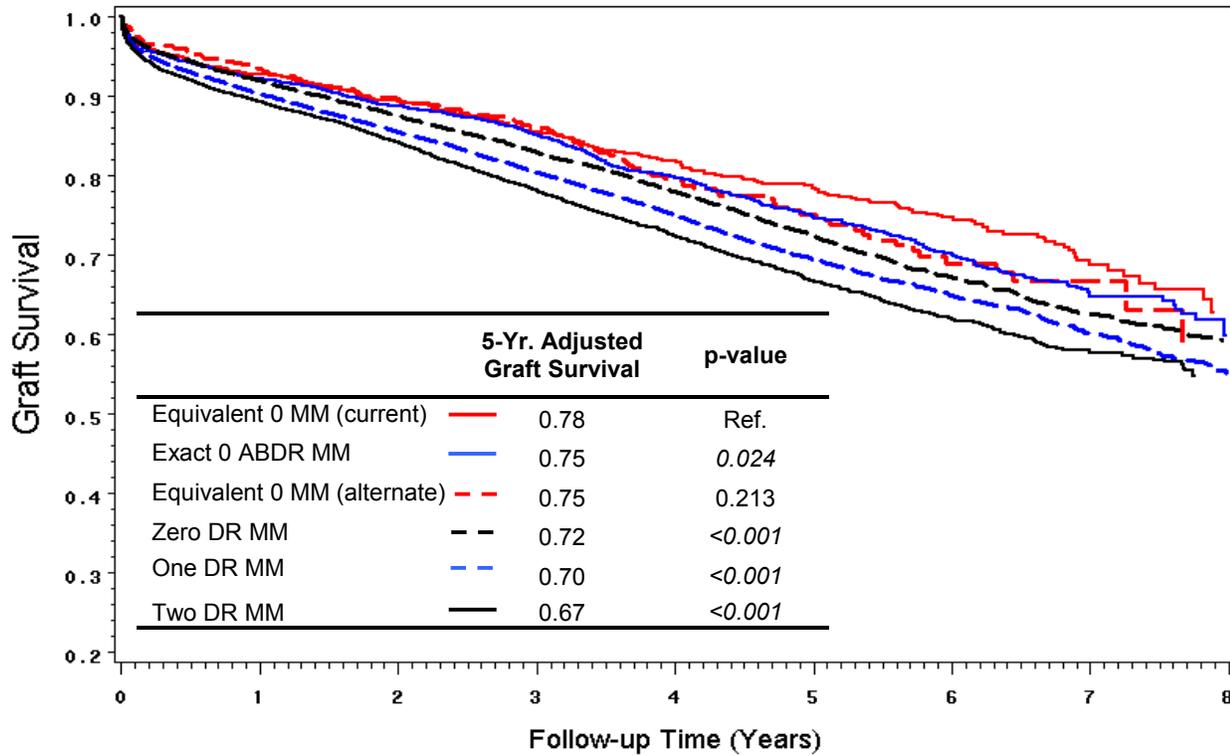


Figure 1 shows the 5-year adjusted graft survival rates according to type of mismatch. The 5-year adjusted rate for the Equivalent 0 MM transplants using the less-restrictive HLA table was not statistically different from the Equivalent 0 MM transplants matched using the current table (lower survival; p=0.213) or from 0 DR MM transplants (higher survival; p=0.241).

**OPTN/UNOS *Histocompatibility* Committee
Descriptive Data Request**

*Evaluation of New Kidney Allocation Policy
After the Elimination of Points for HLA-B Mismatch*

Prepared for:
Histocompatibility Committee Meeting
January 20-21, 2004

By:
Wida Cherikh, Ph.D. and Timothy Baker, B.S.
Research Department
United Network for Organ Sharing

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Committee Request

On May 7, 2003, the kidney allocation system has been modified so that points are no longer given for HLA-B mismatches, but 2 points are given for zero HLA-DR mismatches and 1 point for one HLA-DR mismatched. The Histocompatibility Task Force on Kidney Allocation has requested some descriptive data with regard to minority and ABO allocation to compare the first full 6 months after the points are modified with the last full 6 months of allocation using previous system.

Background/Purpose

Monitor performance of new HLA point system after 6 months of implementation with regard to minority allocation and local distribution of HLA-DR matched transplants.

Data and Methods

To assess the impact of the new HLA point system, the report was broken out into two periods, the pre-policy period, which covered the first full 6 months prior to the implementation of the policy (11/6/02-5/6/03), and the post-policy period, which covered the first full 6 months after the policy was implemented (5/7/03-11/7/03).

Since there are variations of the standard kidney allocation algorithm, we included only 18 OPOs that ran the same standard kidney allocation algorithm during the entire study period. This would ensure a cleaner comparison of the data between the pre- and post-policy periods.

I. Transplant Data

For reporting the transplant data, we included recipients of deceased donor kidney alone transplants performed at these 18 OPOs between 11/6/02 and 11/7/03. Pediatric recipients and recipients of expanded criteria donor (ECD) donor kidneys were excluded from the analysis.

The following data were provided for the first full 6 months (11/6/02-5/6/03) and the last 6 months (5/7/03-11/7/03):

1. Numbers and percentages of non-zero antigen mismatched transplants by ethnicity (white, black, Asian, Hispanic, other)
2. Numbers and percentages of non-zero antigen mismatched transplants by blood group
3. Numbers and percentages of non-zero antigen mismatched transplants by HLA-ABDR mismatch level, HLA-BDR mismatch level, HLA-DR mismatch level, and waiting time (0-6, 7-12, 13-18, 19-24, 25-36, 37-48, >48 months)
4. Number and percentages of 0-antigen mismatch mandatory shares stratified by ethnicity and blood group

II. Match Run Data

We looked at all the match runs for all the donors at these 18 OPOs during the study period. Potential candidates in the top 10% of the local list were included, and the ethnic composition of these candidates was compared between the two periods (11/6/02-5/6/03 vs. 5/7/03-11/7/03).

All information provided in this report is based on OPTN data as of January 2, 2004.

Results

There were 1,394 deceased donor kidney transplants included in the analysis (697 transplants in each period). The proportion of the zero-antigen mismatched transplants was 15.06% (105/697) in the pre-policy period, and 14.92% (104/697) in the post-policy period.

Table 1 summarizes the data for non-zero HLA mismatched transplants during the study period (pre- vs. post-policy period) by recipient ethnicity, ABO blood group, HLA-ABDR, BDR and DR mismatch levels, and wait time to transplant (in months) for all 18 OPOs combined.

Some of the data highlights from Table 1 are as follows:

- While the percentage of White recipients went down from 49.3% in the pre-policy period to 41.5% in the post-policy period, the percentage of Black recipients went up by 3.4 percentage points from 34.5% to 37.9%. The percentage of Asian recipients also went up by 3.9 percentage points from 3.55% to 7.42%. The percentage of Hispanic recipients and recipients of other ethnic group stayed pretty much the same at about 11% and 2%, respectively.
- The percentage of recipients with B blood group went up by 2 percentage points from 10% in the pre-policy period to 12% in the post-policy period, while the percentage of O recipients went down by 2 percentage points from 48% to 46%. The percentage of A and AB recipients stayed pretty much the same at about 37% and 6%, respectively.
- The percentage of transplants with 2- and 3-ABDR mismatches went down from 13% and 28% in the pre-policy period to 5% and 13% in the post-policy period, respectively. While the percentage of transplants with 4- and 6-ABDR mismatches only went up by about 2 percentage points, the percentage of transplants with 5-ABDR mismatches went up dramatically from 15% in the pre-policy period to 39% in the post-policy period.
- The percentage of transplants with 1- and 2-BDR mismatches went down from 22% and 38% in the pre-policy period to 5% and 22% in the post-policy period, respectively. In contrast, the percentage of transplants with 3- and 4-BDR mismatches went up from 20% and 19% in the pre-policy period to 44% and 29% in the post-policy period, respectively.
- The percentage of transplants with 0-DR mismatch went down from 23% in the pre-policy period to 14% in the post-policy period. In contrast, the percentage of transplants with 2-DR mismatches went up from 24% in the pre-policy period to 35% in the post-policy period. The percentage of transplants with 1-DR mismatch went down only by 1 percentage point from 53% to 52%.
- As compared to the pre-policy period, the percentage of transplant recipients who waited less than 24 months seemed to go down, while the percentage of transplant recipients who waited for more than 24 months increased during the post-policy period.

Table 2 summarizes the distribution of the zero-antigen mismatched transplants in the pre- and post-policy periods by recipient ethnicity and ABO blood group. Some of the data highlights from Table 2 include the following:

- While the percentage of White recipients with zero-mismatched transplants went down from 77% in the pre-policy period to 71% in the post-policy period, the proportion of Black recipients went up from 10.5% to 14.4%. The percentage of Hispanic and recipients went down a little bit from 10% to 9%. Although there was essentially no change in the percentage of Asian recipients, the proportion of recipients with other ethnic group went up from 1% to 4%.
- The proportion of O recipients went down from 51% in the pre-policy period to 40% in the post-policy period, while the proportion of recipients with A, AB and B blood type went up by 8, 1 and 2 percentage points, respectively.

Table 3 summarizes the ethnic distribution of the potential candidates in the top 10% of the local list for match runs performed in the pre- and post-policy periods at the 18 OPOs. As seen in Table 3, the proportion of White candidates that appeared in the top 10% of the local list went down from 42% to 38%, while the proportion of Black and Asian candidates went up from 39.8% and 3.6% in the pre-policy to 41.6% and 4.8% in the post-policy period. The percentage of Hispanic candidates and candidates of other ethnic group only went up very slightly from 12.1% and 2.4% to 12.4% and 2.8%, respectively.

In summary,

- More minority recipients (Black and Asian, in particular) received a non-zero mismatched transplants during the post-policy period
- There were more transplants with worse mismatches during the post-policy period
- There were more transplants for patients with longer waiting times during the post-policy period
- Although the proportion of zero-mismatched transplants was similar in the pre- and post-policy periods (about 15%), there were less White and more Black recipients who received a zero-mismatched transplant in the post-policy period.
- There was a trend for more minority candidates to appear more often in the top 10% of the local list for the match runs performed during the post-policy period.

Table 1. Non-Zero HLA Mismatched Transplants During 11/06/02 - 11/07/03

	TRANSPLANT PERIOD			
	Pre-Policy (11/6/02-5/6/03)		Post-Policy (5/7/03-11/7/03)	
	N	%	N	%
RECIPIENT ETHNICITY CATEGORY				
White	292	49.3	246	41.5
Black	204	34.5	225	37.9
Hispanic	63	10.6	66	11.1
Asian	21	3.55	44	7.42
Other Ethnic Group	12	2.03	12	2.02
RECIPIENT ABO BLOOD GROUP				
A	218	36.8	217	36.6
AB	33	5.57	36	6.07
B	60	10.1	69	11.6
O	281	47.5	271	45.7
HLA-ABDR Mismatch Level				
1	23	3.89	5	0.84
2	78	13.2	28	4.72
3	167	28.2	75	12.6
4	168	28.4	180	30.4
5	90	15.2	231	39.0
6	66	11.1	74	12.5
HLA-BDR Mismatch Level				
0	9	1.52	0	0.00
1	127	21.5	31	5.23
2	224	37.8	128	21.6
3	121	20.4	263	44.4
4	111	18.8	171	28.8
HLA-DR Mismatch Level				
0	136	23.0	80	13.5
1	314	53.0	307	51.8
2	142	24.0	206	34.7

	TRANSPLANT PERIOD			
	Pre-Policy (11/6/02-5/6/03)		Post-Policy (5/7/03-11/7/03)	
	N	%	N	%
Months on Waiting List				
0-6	114	19.3	96	16.2
7-12	87	14.7	74	12.5
13-18	80	13.5	87	14.7
19-24	75	12.7	68	11.5
25-36	113	19.1	122	20.6
37-48	66	11.1	79	13.3
> 48	57	9.63	67	11.3
All	592	100	593	100

Table 2. Zero HLA Mismatched Transplants During 11/06/02 - 11/07/03

	TRANSPLANT PERIOD			
	Pre-Policy (11/6/02-5/6/03)		Post-Policy (5/7/03-11/7/03)	
	N	%	N	%
RECIPIENT ETHNICITY CATEGORY				
White	81	77.1	74	71.2
Black	11	10.5	15	14.4
Hispanic	10	9.52	9	8.65
Asian	2	1.90	2	1.92
Other Ethnic Group	1	0.95	4	3.85
RECIPIENT ABO BLOOD GROUP				
A	38	36.2	46	44.2
AB	1	0.95	2	1.92
B	12	11.4	14	13.5
O	54	51.4	42	40.4
All	105	100	104	100

Table 3. Distribution of Candidate Ethnicity in the Top 10% of the Local List Match Runs During 11/6/02-11/7/03

	Top 10% of Local List					
	Donors	Candidate Ethnicity				
		White	Black	Hispanic	Asian	Other Ethnic Group
N	%	%	%	%	%	
Time Period						
Pre-Policy (11/6/02-5/6/03)	451	42.07	39.81	12.08	3.64	2.40
Post-Policy (5/7/03-11/7/03)	470	38.44	41.57	12.37	4.82	2.80

COMMON PHENOTYPES RANKED BY WAITING TIME IN BLOOD
GROUP A AND O CANDIDATES

Ranking of Phenotypes in Blood Group A Candidates

Mean Waiting Time (Days)	# Txs	A1	A2	B1	B2	DR1	DR2
62	5	2	3	7	44	2	4
102	5	3	29	7	44	2	7
158	6	2	3	7	62	2	4
171	8	1	29	8	44	3	7
225	7	1	2	8	44	3	4
231	5	1	2	8	57	3	7
235	22	1	3	7	8	2	3
361	4	1	2	8	60	3	13
410	6	1	2	7	8	2	3
416	5	1	3	7	8	1	3
419	21	1	2	8	62	3	4
491	5	1	3	8	35	1	3
510	4	1	23	8	44	3	7
753	4	0	1	0	8	0	3

Ranking of Phenotypes in Blood Group O Candidates

Mean Waiting Time (Days)	# Txs	A1	A2	B1	B2	DR1	DR2
62	5	2	3	7	44	2	4
79	4	2	3	7	62	2	4
102	5	3	29	7	44	2	7
158	6	2	3	7	62	2	4
171	8	1	29	8	44	3	7
225	7	1	2	8	44	3	4
231	5	1	2	8	57	3	7
235	22	1	3	7	8	2	3
361	4	1	2	8	60	3	13
364	4	2	24	35	61	4	8
410	6	1	2	7	8	2	3
416	5	1	3	7	8	1	3
419	21	1	2	8	62	3	4
441	4	1	24	8	60	4	7
467	4	1	2	8	60	13	17
491	5	1	3	8	35	1	3
510	4	1	23	8	44	3	7
550	4	1	31	8	60	3	4
753	4	0	1	0	8	0	3

Note: HLA phenotypes in italics are unique to Blood Group O