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DEVELOPING A NATIONAL ALLOCATION MODEL FOR CADAVERIC KIDNEYS

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ABSTRACT

The UNOS Kidney Allocation Model (UKAM) is a software tool for the simulation and analysis of national cadaveric kidney and kidney-pancreas allocation policies for transplantation. UKAM is modular and is designed to enable easy updating of the various components as new data become available. UKAM's flexibility gives the user the ability to create and evaluate an almost infinite number of detailed allocation policies. This will enable the United Network for Organ Sharing (UNOS) to make decisions based on quantitative data when considering changes in organ allocation policies.

1 BACKGROUND AND PURPOSE OF UKAM

Renal transplantation is the treatment of choice for patients with end-stage renal (kidney) disease. Currently over 45,000 patients are waiting for a cadaveric kidney transplant (UNOS 2000). Although many patients with end-stage renal disease can live for years on dialysis, their quality of life is severely diminished. While on dialysis, patients must report for treatment 2-3 times a week and are at risk from many life-threatening illnesses (NIH 1998). In addition, waiting times are typically very long, with an overall median waiting time of 3 years (DHHS 1999), and may vary considerably depending on a patient's medical-demographic characteristics. In 1999 alone, over 3,000 people died while waiting for a kidney or combined kidney-pancreas transplant (UNOS 2000); thus, renal transplants are clearly life-saving. Unfortunately, only about 10,000 cadaveric kidneys were transplanted during all of 1999, due to the severe shortage of donated organs (UNOS 2000).

The United Network for Organ Sharing (UNOS), as the operator of the Organ Procurement and Transplantation Network (OPTN), is responsible for establishing fair and equitable organ allocation policies. In 1995, UNOS contracted with Pritsker Corporation (now Symix Systems) to develop the UNOS Liver Allocation Model (ULAM). For the first time, UNOS' committees and Board were able to estimate the effects of a proposed policy change prior to its implementation. With the success of ULAM has come a desire from the kidney transplant community for a similar tool to be used in the examination of kidney allocation policies. While the issues surrounding kidney allocation are very different from those in liver allocation, they are no less complex and may be more difficult to resolve.

The UNOS Kidney Allocation Model (UKAM) has been designed to meet this need. Its purpose is not to predict the future of transplantation under the current policy. Instead, UKAM allows UNOS to evaluate and compare quantitatively the results of different allocation methods. Using UKAM, UNOS can make policy changes with a better understanding of how the policy might affect the many different types of patients needing a kidney transplant.

2 STRUCTURE OF MODEL

Although the dynamics of kidney and kidney-pancreas allocation are more complex than for liver allocation, UKAM is very similar to ULAM in its basic structure. (Pritsker et al. 1995, Harper et al. 2000). The flow of events in UKAM is presented in Figure 1. The most vital components are described in Sections 2.2-2.6.

UKAM currently includes information on 256 transplant centers and 60 Organ Procurement Organizations (OPOs). For validation purposes, it was necessary to structure many components at the OPO and transplant center level. UKAM was not developed to examine the results of policies at these local levels, but rather to determine how a specific allocation policy will affect the nation as a whole.

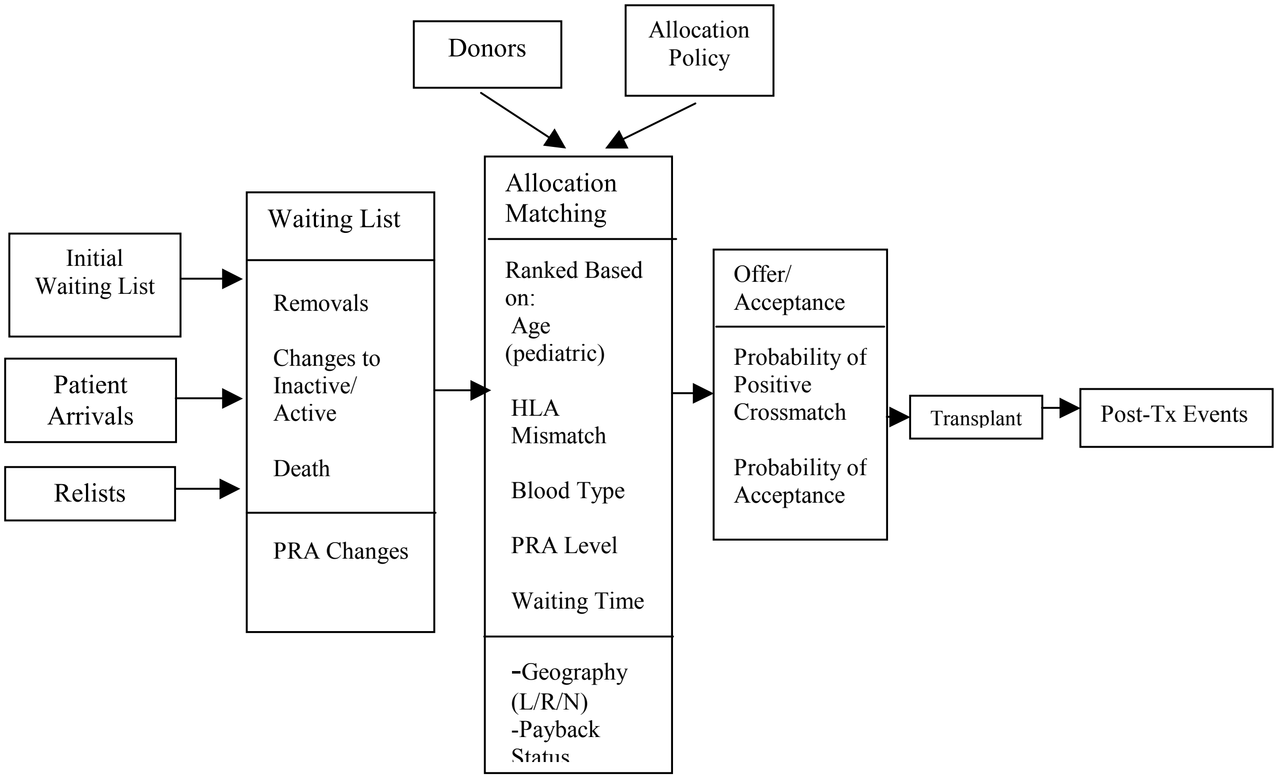

Figure 1: Flow of Events in UKAM

However, the center- and OPO-specific natures of some of UKAM's components provide more reliable estimates at the national level.

2.1 UKAM Software

UKAM was developed using AweSim! (Version 3). The model makes extensive use of the discrete event, sampling, animation, and statistics features of the package. Complex and custom organ allocation logic and data I/O for UKAM utilize MS C/C++ inserts available within AweSim (Pritsker and O'Reilly 1999). Visual Basic (VBA) macros within the UKAM (Excel) interface process UKAM data. They also allow UKAM to be executed from within the interface.

2.2 Patients Waiting for a Transplant

Starting from the left of Figure 1, the simulation begins with patients waiting for either a kidney or combined kidney-pancreas transplant. These patients come into the simulation in one of two ways. Either they are waiting at the beginning of the simulation (Initial Waiting List), or they are added to the waiting list for the first time as patient arrivals. Additionally, transplanted patients may come back onto the waiting list as relists through the post-transplant events model, described later.

Currently, the UKAM initial waiting list consists of actual patients who were waiting for a kidney or combined kidney-pancreas transplant as of January 1, 1996. Included is all of the information that is needed for donor-recipient matching, the ranking of patients on the waiting list, and determining the outcome of those transplanted. These data elements include the date the patient was listed, the center identifier, and various patient demographics. Some of the 15 patient demographics included are blood type, date of birth, race/ethnicity, gender, HLA information (i.e., the patient's antigens), type I diabetes status at listing (y/n), and dialysis status at listing (y/n).

UKAM can simulate transplantation scenarios using either historical patient arrivals or generated patients, the latter giving UNOS the option of comparing the outcomes of different allocation policies into the future. The historical patient stream is currently composed of actual patients who were added to the waiting list for transplant at specific transplant centers between January 1, 1996 and December 31, 1998. The flexibility of UKAM allows us to add additional years of historical arrivals, as the data become available. The same patient-specific information included on the initial waiting list is also provided for each historical patient arrival.

Generated patient arrivals are based on the historical patterns at each transplant center and are forecasted using linear regression. Patients arrive in the simulation according to a piece-wise homogeneous Poisson process (HPP), similar to the method used in ULAM (Harper et al. 2000). The patient characteristics are sampled with replacement ("bootstrapped") from the historical patient arrivals for 1996-1998 by transplant center. This ensures that the patients generated at each transplant center are similar to those historically listed at that center in terms of race/ethnicity, age, disease type, blood type, etc. These factors can make a significant difference in the waiting times and outcomes for a particular area's patients.

2.3 Waiting List Transitions

While on the waiting list, many events can take place. Patients can be transplanted, transition from an active to inactive status, die, or be removed from the waiting list for another reason (i.e. living donor transplant, too sick to transplant, etc.). A cadaveric transplant occurs through the allocation portion of the model, however the patient status change component accounts for the remaining waiting list events. First, this determines the probability that, on a given day, a patient will die. Then, listings for living patients are sampled for transition from active to inactive, or removal from the waiting list. The probabilities are estimated from historical waiting list data from 1996-1998. The probability for a given transition is calculated by counting the number of times that a specific transition occurred (e.g., active to inactive), and dividing by the total number of days required to make that transition. The kidney-only transition matrix is stratified by type I diabetes (yes/no) and whether the patient is on the initial snapshot or was listed during the simulation. The kidney-pancreas transition matrix is stratified by dialysis at listing (yes/no).

An important issue in donor-recipient matching for kidneys is the sensitization level of the patient. The percent Panel Reactive Antibody (PRA) value is a measure of the patient's sensitivity to donor antigens. The higher the PRA, the more sensitized a patient is to the general donor pool, and thus the more difficult it will be to find a suitable donor. A patient may become sensitized as a result of pregnancy, a blood transfusion, or a previous transplant. The PRA is recorded as a percent value between 0 (not sensitized) and 99 (extremely sensitized). A patient with a PRA of 20 will be sensitized to approximately 20% of donors. Patients with high PRA levels tend to wait much longer for a transplant since they require a closer antigen match to avoid organ rejection. For this reason, UKAM includes a component that allows the PRA level of patients to change while on the waiting list, as occurs in reality. To model transitions from one PRA category (0, 1-40, 41-79, 80+) to another, a Markov matrix was constructed using historical waiting list data from 1996-1998 and stratified by the time already spent on the waiting list (0-30 days, 31-300 days, 301+ days). Based on this transition matrix, each patient's PRA value is updated quarterly.

2.4 Cadaveric Donors

In order for the waiting patients to receive a transplant, a cadaveric donor must become available. As with the patient arrivals, UKAM can use either a historical or projected stream of donors.

The current historical stream of donors consists of all cadaveric donors from whom at least one kidney was recovered and transplanted between 1996 and 1998. The information necessary for donor-recipient matching and for determining the impact on recipient post-transplant outcome is included for each donor. These data elements include the date and time of recovery, the OPO where the donor was recovered, and various donor demographics. The donor demographics include, among others, the donor hospital, the donor blood type, age, number of kidneys recovered and transplanted, if the pancreas was recovered and transplanted, HLA (antigen) information, and other clinical information necessary in predicting post-transplant outcomes.

Generated donors are created in a manner similar to the generated patient arrivals. These donors arrive to the model according to a piece-wise homogeneous Poisson process (HPP) based on the historical patterns at each of the 60 OPOs currently in UKAM. The donor characteristics are sampled with replacement from the historical donors recovered at each OPO between 1996 and 1998. This is important, as it ensures us that the characteristics of the generated donors are similar to the actual donors at each OPO.

Once these donors arrive in the simulation, either from historical or generated data, another component determines if the donor is "marginal," or less than ideal. This component was created using actual data that indicated if the historical donor was refused for transplant for reasons of donor quality. Two logistic regression models were then created to determine the donor characteristics that predict marginal donors, one for donors with one available kidney and a second for those donors indicated to have two transplantable kidneys. Each model includes various factors related to the quality of the donor. These include whether a pancreas was recovered, the donor age, donor blood type, donor cause of death, and if the donor tested positive for hepatitis C. The models provide a probability, based on the specific characteristics of the donor, that the donor is marginal. A Monte Carlo selection process is used to make the final determination. The marginal status of the donor is used to determine offer/acceptance within UKAM.

2.5 Allocation

Once a donor becomes available a ranked list of the active patients waiting is created. The allocation system being modeled will determine the order of this list. The current system gives priority nationally for perfectly matched organs (i.e., all donor antigens are present in the recipient as well), and then allocates at the local OPO level, followed by UNOS region, and finally nationally. For less than perfect matches, points are assigned for other, high match levels. Extra points are also assigned for patients that are highly sensitized (PRA>80%), pediatric patients, and patients who have waited more than a year.

Once UKAM creates the ranked list of patients, the organs are offered to each patient in order. Determining whether the patient will accept the organ is currently a three-step process in UKAM. The likelihood of the patient rejecting the organ must first be determined. In practice, this is done with a test called a crossmatch, which, if positive, determines that the recipient's immune system would likely reject the donated organ. Originally, UKAM only modeled the "preliminary" crossmatch. However, during the validation process it was determined that in order to match historical data, it is necessary to perform both a preliminary and a final crossmatch, as is done in practice.

Two distinct methods of simulating the crossmatch process were evaluated. First, a logistic regression model was used in the creation of this component. The significant factors included the level of HLA matching and the PRA level of the patient. During validation it appeared that this method did not provide a high enough rate of positive crossmatch for the most highly sensitized patients. This may be due to a slight bias in the data used to develop the model. A simpler method was then tried: the patient's current PRA value was substituted for the probability of a positive crossmatch such that, if the patient has a current PRA of 90%, then the patient has a 90% chance of a positive crossmatch. Although much simpler than the logistic regression model, this method seems to provide better validation. It is likely that one of these two methods will be used in the final model.

If the preliminary crossmatch is positive, the next patient on the list is crossmatched. If the preliminary crossmatch is negative (and thus the organ is not likely to be rejected by the recipient), then the organ is offered to that patient via the offer/acceptance component of UKAM. This component was created using actual offer data on organs offered to patients between 1995 and 1999. For offers of kidney alone, the probability of accepting the organ is based on the degree of antigen mismatch between the donor and recipient, if the donor is marginal, and whether the kidney being offered was recovered at the patient's local OPO or elsewhere. A separate probability exists for each of the 60 OPOs in UKAM. This allows UKAM to account for differences in acceptance criteria in various areas of the country. For offers of both a kidney and a pancreas, the probability is based on the quality of the donor and whether the organs being offered were recovered at the patient's local OPO or elsewhere. A separate probability is calculated for each UNOS region.

If the patient refuses the organ, then the process begins again, with the next patient on the list being tested for a negative preliminary crossmatch. However, if the patient accepts the organ, a final crossmatch is performed. Currently this is done using the same process that was done for the preliminary crossmatch. This process appears to validate well; however, we plan to discuss our methodology with experts in the field of histocompatibility prior to final implementation. If the patient is determined to have a positive final crossmatch, the process begins again with a preliminary crossmatch for the next patient on the list. This continues until a patient accepts the kidney(s) offered and has a negative final crossmatch.

2.6 Post-Transplant Events

Due to the nature of kidney and combined kidney-pancreas transplantation, the post-transplant event component of UKAM is complex. Unlike liver transplantation, it is possible, and not uncommon, for a kidney recipient to continue to live long after their transplanted kidney, or "graft," has failed. The patient can resume dialysis and either relist and wait for another transplant, or decide not to seek a second transplant and continue to live with the aid of dialysis. UKAM uses two separate multinomial logistic regression models to predict the outcomes of kidney-alone, and combined kidney-pancreas transplants.

Due to the multiple options mentioned above, the events determined for kidney alone transplant recipients are:

1. Kidney fails, patient dies (but never relists).
2. Kidney fails, patient does not relist or die.
3. Kidney fails, patient relists.
4. No kidney failure or death, patient survives.
5. No kidney failure or death, patient "lost to follow-up" during simulation.

Some of the factors included in this model are: patient diagnosis at listing, patient on dialysis at listing (y/n), recipient race/ethnicity, recipient age, PRA level, previous transplant (y/n), HLA mismatch level, donor/recipient gender match, donor cause of death, donor race/ethnicity, and donor age.

The events determined for kidney-pancreas transplant recipients are:

1. Patient dies.
2. Pancreas fails, kidney still functions.
3. Kidney or kidney-pancreas combination fails, patient does not relist.
4. Kidney or kidney-pancreas combination fails, patient relists.
5. Both organs function throughout simulation.

The factors included in this model are recipient age, HLA mismatch level, donor/recipient gender match, donor age, and donor hypertension.

The two models, based on the various factors, produce a probability for each of the post-transplant events. If the chosen outcome includes failure, death, or relist, a time to each of these is assigned probabilistically, selecting from a historical distribution. If the chosen event includes relisting, the patient is placed back on the waiting list at the appropriate time.

3 USER INTERFACE

The UKAM user interface is a Microsoft Excel spreadsheet. The interface allows the user to make changes to the data inputs, probabilities, and policy parameters with relative ease. Nearly all the component models are contained in the interface to allow non-modelers to make changes and update key UKAM components.

As can be seen in Figure 2, the user interface is designed so that any end-user can create and simulate policies. Different point values can be assigned for pediatric patients with varying age categories, different types and levels of tissue matching can be specified, different points and point thresholds for sensitized patients, and different point assignments for time waiting. This allows the user to create and run virtually any type of policy without any modification to the underlying AweSim model. This is important as it gives the end-user the ability to produce results for a given allocation policy idea quickly and accurately.

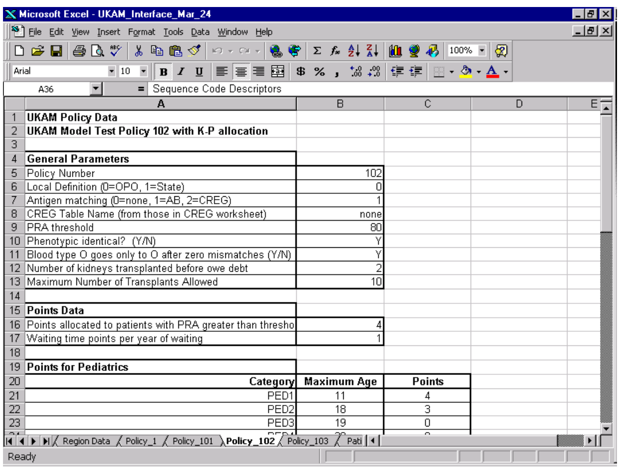

Figure 2: Portion of UKAM User Interface

4 OUTPUTS

There are many ways to measure the fairness of an allocation policy. UNOS is charged with balancing medical utility with patient justice. Since cadaveric kidneys are such a scarce resource, medical utility includes transplanting the largest number of patients with the fewest repeat transplants and the greatest graft and patient survival possible. On the other hand, a policy that favors medical utility may not take into consideration the justice issues of long waiting times for highly sensitized and African-American patients, as well as examining the special needs of pediatric patients with renal failure.

UKAM allows the user to output a record of information about each patient in the simulation. This allows the user to evaluate different policies in any number of ways. However, a specific list of the most commonly requested types of analyses is produced each time UKAM is run. These include:

- Number of primary/repeat transplants
- Transplant type (kidney/kidney-pancreas)
- Number/percent pediatric transplants
- Transplants by:
  - Race/Ethnicity
  - PRA
  - Blood type
  - HLA/CREG mismatch level
  - Share type
- Distance organ traveled
- Pre- and Post-transplant deaths
- Other waiting list removals
- Relists
- Median waiting times/percent transplanted at one year, by:
  - Race/ethnicity
  - PRA
  - Age
  - Organ type (kidney/kidney-pancreas)
- Patient/graft survival (12 and 36 months post-transplant).

5 ANIMATION

UKAM also includes an animation of the flow of patients and donor organs as they are allocated across the country. This feature was important in the broad acceptance of ULAM, and it is believed that it will be just as vital with UKAM. Its greatest use is in providing face validity to UKAM. With a few minutes of animation, policy-makers can verify that a specific allocation policy is distributing organs as they expect, based on the system chosen.

6 SUMMARY

UKAM employs many common modeling techniques in a very uncommon simulation model. The results of UKAM will likely be used in the creation of a new allocation policy for cadaveric kidney and kidney-pancreas combination transplants. These policy changes will affect the lives of thousands of patients across the United States. As long as the number of patients waiting for a kidney transplant far exceeds the number of cadaveric donors available, there will never be a "perfect" policy. However, UKAM allows UNOS to make more educated decisions in the quest for the best allocation policy possible.

We anticipate that UKAM, like ULAM, will evolve with time, in response to requests made by its many audiences. UNOS is confident that UKAM will be versatile enough to meet the challenges ahead, and will help the transplant community navigate through the ongoing debates surrounding renal allocation.

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REFERENCES

DHHS and UNOS. 1999. *1999 Annual Report of the U.S. Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network; Transplant Data 1989-1998.* U.S. Department of Health and Human Services, Health Resources Services Administration, Office of Special Programs, Division of Transplantation, Rockville, MD; UNOS, Richmond, VA.

Harper, A.M., S.E. Taranto, E.B. Edwards, and O.P. Daily. 2000. An update on a successful simulation project: the unos liver allocation model. To appear in *Proceedings of the 2000 Winter Simulation Conference.*

National Institutes of Health, NIDDK. 1998. *U.S. Renal Data System, USRDS 1998 Annual Data Report*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.

Pritsker, A.A.B, D.L. Martin, J. Reust, M.A. Wagner, J.R. Wilson, M.E. Kuhl, O.P. Daily, A.M. Harper, E.B. Edwards, L.E. Bennett, J.P. Roberts, M.D. Allen, and J.F. Burdick. 1995. Organ transplantation policy evaluation. In *Proceedings of the 1995 Winter Simulation Conference*, ed. C. Alexopoulos, K. Kang, W.R. Lilegdon, and D. Goldsman, 1314-1323. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers.

Pritsker, A.A.B and J.J. O'Reilly. 1999. *Simulation with Visual SLAM and AweSim* 2d ed. New York: John Wiley & Sons, Inc.

UNOS. 2000. United States renal transplant and waiting list data for 1999, as of March 24, 2000. UNOS, Richmond, VA.

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