

Kidney Paired Donation and Optimizing the Use of Live Donor Organs

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RENAL TRANSPLANTATION HAS emerged as the treatment of choice for medically suitable patients with end-stage renal disease.¹ More than 60 000 patients await kidney transplantation and are listed on the United Network for Organ Sharing (UNOS) recipient registry.² Live donor renal transplantation represents the most promising solution for closing the gap between organ supply and demand.

Unfortunately, many patients with willing live donors will be excluded from live donor renal transplantation because of blood type incompatibility or positive donor-specific crossmatch. Based on blood type frequencies in the United States, there is a 35% chance that any 2 individuals will be ABO incompatible. Furthermore, 30% of the patients awaiting donation from the UNOS recipient registry are sensitized to allo-HLA due to previous transplants, pregnancies, or blood transfusions. While successful desensitization techniques have been developed to overcome incompatibilities, these have been limited to specialized programs and are very resource intensive.³⁻¹⁰

Kidney paired donation (KPD) offers an incompatible donor/recipient pair the opportunity to match with another donor and recipient in a similar situation.¹¹ In the United States, these transplantations are currently performed at few institutions, with matches identified through local or regional pa-

Context Blood type and crossmatch incompatibility will exclude at least one third of patients in need from receiving a live donor kidney transplant. Kidney paired donation (KPD) offers incompatible donor/recipient pairs the opportunity to match for compatible transplants. Despite its increasing popularity, very few transplants have resulted from KPD.

Objective To determine the potential impact of improved matching schemes on the number and quality of transplants achievable with KPD.

Design, Setting, and Population We developed a model that simulates pools of incompatible donor/recipient pairs. We designed a mathematically verifiable optimized matching algorithm and compared it with the scheme currently used in some centers and regions. Simulated patients from the general community with characteristics drawn from distributions describing end-stage renal disease patients eligible for renal transplantation and their willing and eligible live donors.

Main Outcome Measures Number of kidneys matched, HLA mismatch of matched kidneys, and number of grafts surviving 5 years after transplantation.

Results A national optimized matching algorithm would result in more transplants (47.7% vs 42.0%, $P < .001$), better HLA concordance (3.0 vs 4.5 mismatched antigens; $P < .001$), more grafts surviving at 5 years (34.9% vs 28.7%; $P < .001$), and a reduction in the number of pairs required to travel (2.9% vs 18.4%; $P < .001$) when compared with an extension of the currently used first-accept scheme to a national level. Furthermore, highly sensitized patients would benefit 6-fold from a national optimized scheme (2.3% vs 14.1% successfully matched; $P < .001$). Even if only 7% of patients awaiting kidney transplantation participated in an optimized national KPD program, the health care system could save as much as \$750 million.

Conclusions The combination of a national KPD program and a mathematically optimized matching algorithm yields more matches with lower HLA disparity. Optimized matching affords patients the flexibility of customizing their matching priorities and the security of knowing that the greatest number of high-quality matches will be found and distributed equitably.

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tient databases.^{2,4,12} However, even with the increasing popularity of KPD, only 51 patients have received transplants via paired donation, with nearly half of them performed at Johns Hopkins University.² UNOS has recently proposed a national live donor KPD program through the Organ Procurement and Transplantation Network, but regulatory obstacles to a national program still exist (including the question of “valuable consideration”); therefore, no data exist regarding the impact of national vs regional programs.^{12,13} Because it is

critical to find the most effective method of matching patients and donors at the outset, before any national strategy is implemented, we investigated virtual paired donation programs on simulated patient populations.

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Table 1. Blood Type Characteristics of Simulated Donor/Recipient Pairs*

Blood Type	Patients, %			
	Donor O	Donor A	Donor B	Donor AB
Recipient O	14.0	37.8	12.0	2.0
Recipient A	6.3	6.8	5.1	2.8
Recipient B	2.4	6.1	1.2	2.1
Recipient AB	0.5	0.5	0.2	0.1

*Based on the Zenios model.¹⁵**Box 1. Characteristics of Simulated Donor/Recipient Pairs****Region and Percentages of Patients*†**

- 1 (3.6%): Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island
- 2 (15.0%): Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, West Virginia
- 3 (12.3%): Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, Puerto Rico
- 4 (7.2%): Oklahoma, Texas
- 5 (23.1%): Arizona, California, Nevada, New Mexico, Utah
- 6 (2.3%): Alaska, Hawaii, Idaho, Montana, Oregon, Washington
- 7 (8.8%): Illinois, Minnesota, North Dakota, South Dakota, Wisconsin
- 8 (3.9%): Colorado, Iowa, Kansas, Missouri, Nebraska, Wyoming
- 9 (8.5%): New York, Vermont
- 10 (6.7%): Indiana, Michigan, Ohio
- 11 (8.6%): Kentucky, North Carolina, South Carolina, Tennessee, Virginia

Race‡

Recipient: conditioned on ABO type

Donor: race is identical to recipient race with 90% probability; otherwise donor race distributed according to UNOS waiting list

HLA§

Race-specific distribution of HLA antigens among recipients in the UNOS registry

Sensitization¶

14% highly sensitized

Donor age, y||

18-34: 36.8%

35-49: 45.4%

50-64: 16.8%

≥65: 1.0%

Abbreviation: UNOS, United Network for Organ Sharing.

*Detail of regional boundaries acquired from UNOS Web site.

†Based on UNOS waiting list.²‡Based on UNOS waiting list² and assumption.§Based on Leffell et al.¹⁴||Based on UNOS living donors.²

We believe that KPD is a cost-effective and underused method of providing transplants to the large number of patients with incompatible donors. Centers that perform KPD currently use

a “first-accept” matching scheme. Using local/regional databases, an incompatible donor/recipient pair is matched with the first compatible pair identified, the individuals’ listings are re-

moved from the pool, and they are provided with transplants. The pairing identified and removed from the pool might not be the best solution for either the 2 pairs involved or the other pairs in the KPD program pool. Inefficient matching algorithms are likely limiting the number and quality of matches that can be identified.

We developed a model that uses simulated pools of incompatible donor/recipient pairs to determine if alternative matching algorithms might increase the number and quality of matches that can be found in a small (regional) or large (national) pool.

METHODS**Simulated Sample Size**

Since there are no direct data regarding the incompatible donor/recipient pool that would enter a national KPD program, we simulated patient pools using probability models and UNOS data (TABLE 1) (BOX 1). According to a model reported by Zenios, at least 884 new incompatible donor/recipient pairings will occur yearly.^{15,16} This model incorporates the genetic linkage of potential related pairs, the social network of unrelated pairs, blood type distributions, blood type compatibility, and predicted rates of positive cross-match. Assuming 15% of incompatible pairs will seek transplantation by other modalities, approximately 750 patients could enter a KPD program yearly. Assuming the average waiting times for identifying an appropriate deceased donor, there are approximately 4000 recipients with incompatible donors listed on the UNOS recipient registry who could enter a KPD program initially and then 750 each subsequent year.²

Simulated Patient Characteristics

Recipients were simulated by blood type, race, and region according to the model reported by Zenios¹⁵ and distribution of data from the UNOS deceased donor kidney waiting list.² Two HLA-A, B, and DR antigens were assigned to each recipient based on the race-specific distribution among recipi-

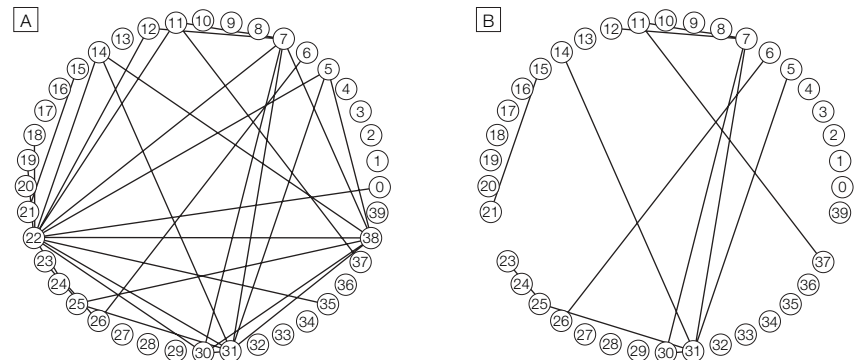
ents in the UNOS registry.¹⁴ Finally, consistent with the incidence of highly sensitized patients (panel reactive antibodies $\geq 80\%$) on the current UNOS waiting list, 14% of recipients were marked as highly sensitized.²

Donors were similarly assigned with blood type determined by the Zenios model.¹⁵ For the analyses described here, we assumed each donor and recipient were from the same region and that 90% of donors were of the same race as the recipient. This is consistent with our institutional experience of live donor renal transplantation. The remaining donors (10%) were assigned other races based on blood-type specific distribution of race in the UNOS registry of live kidney donors.² Donors were given an age grouping based on age distributions from the UNOS registry, and HLA antigens were assigned based on the race-specific distribution among donors in the UNOS registry, as determined by Leffell et al.¹⁴

Matching Algorithms

An optimized algorithm based on the Edmonds algorithm from graph theory^{17,18} (FIGURE 1) was implemented using a personal computer and compared with the current first-accept method of kidney matching.¹² In brief, the first-accept scheme scans a database of donor/recipient pairs and identifies 1 feasible solution (BOX 2). An optimized algorithm considers every feasible solution from the donor/recipient pool, compares these solutions, and picks the one that best meets a set of individualized optimization priorities, modified by a predefined optimization bonus. For example, with a pool of 1000 donor/recipient pairs, the currently used first-accept method evaluates only 1 solution, while the optimized algorithm considers approximately 10^{250} feasible solutions before it picks the best one. The optimized algorithm used in this study has been mathematically proven to yield the best possible solution for any given sets of priorities.^{17,18} (For additional information and a demonstration, see <http://www.optimizedmatch.com>)

Figure 1. Graph Theory Model of Donor/Recipient Nodes, With Links Indicating Compatible Matches



Each node represents an incompatible donor/recipient pair. A, The most links (13) are seen by pair 22, a blood type A recipient and a blood type O donor who are both willing to travel. Pairs 31 and 38 have the same donor and recipient types as pair 22, but see only 7 links each because these pairs are unwilling to travel outside of their region. Pair 5 sees 3 links with a type O recipient (who is restricted to only type O donors) and a type A donor. Pairs 6 and 35 also have the same blood type configuration as pair 5, but see only 1 link each because pair 6 is unwilling to trade with older donors and pair 35 is unwilling to travel. B, By matching the strategically wrong pairs without first considering all possible combinations of matches, many future possibilities are lost. The same nodes and links from panel A are shown here after matching pair 22 with pair 38.

Crossmatch Handling

Although many groups have tried, predicting crossmatch outcomes is difficult.¹⁹⁻²² The published probability of a positive crossmatch between 2 strangers is 11%.¹⁶ Unsensitized patients in this model were given an 11% chance of a positive crossmatch with any random donor; highly sensitized patients are much more likely to have a positive crossmatch and were considered only if there were 0 or 1 HLA mismatches with the proposed donor.

Since a paired donation is not ultimately plausible unless a crossmatch is performed, and since this information is not available before a KPD algorithm is run, we report on a method for incorporating the results of those crossmatches into the algorithm in real-time (Box 2).

Statistics

For every experiment, unless otherwise indicated, we generated random databases of 4000 donor/recipient pairs, based on the simulated patient characteristics described previously. Each experiment was executed 30 times, each time using a different simulated patient database. Statistical significance between

numbers of pairs matched and numbers of surviving grafts was calculated using the Wilcoxon paired sign-rank test. Because HLA mismatches are nonnormal, statistical significance between HLA mismatches was calculated using the Wilcoxon rank-sum test. Statistical significance was defined as $P < .05$.

A sensitivity analysis was performed to assess the impact of altered patient characteristics on our projections. The simulated patient characteristics were varied and the effect on differences between optimized and first-accept matches was analyzed. We varied the incidence of highly sensitized patients (5%-20%), the racial makeup of the pool, the percentage of donors who were of the same race as their recipients (60%-100%), and the regional distribution. Finally, the effect of donor and recipient blood types was analyzed by applying 4 normal (mean, 1; SD, 0.25) perturbations to the Zenios model.¹⁵

RESULTS

Comparison of Match Algorithms

We compared performance of the first-accept and optimized algorithms using a wide range of static database sizes, ranging from 100 to 5000 pairs

Box 2. Definitions and Descriptions of Matching Algorithms

Feasible Solution

A set of matches within a given pool of donor/recipient pairs, with patient-specified acceptance criteria and the obvious restriction that no pair can be involved in more than 1 match.

Acceptance Criteria

Criteria required for a match between 2 donor/recipient pairs to be plausible. These can be selected by each donor/recipient pair. For the experiments in this report:

- (1) For all pairs, blood type compatibility would be required.
- (2) For pairs with unsensitized recipients, donors would be accepted only of the same age donor group or younger, while for pairs with sensitized recipients, donors of any age would be accepted.
- (3) Pairs unwilling to travel would only be considered for matches within the same region.
- (4) Highly sensitized recipients would only accept exchanges with 0 or 1 HLA antigen mismatch.

In some experiments certain criteria, such as willingness to travel, were individualized based on different estimates of patient preference.

Optimization Priorities

When the optimized match algorithm searched for the best feasible solution, the highest priority was given to paired matches with the fewest HLA mismatches. These priorities could be customized to the wishes of each individual donor/recipient pair. For example, in some experiments the priority was modified to emphasize regional considerations. In these experiments, simulated pairs preferred matches within their region even if the number of HLA mismatches increased.

Optimization Bonus

Bonus points could be awarded in the optimized algorithm to any disadvantaged group. For example, a bonus would be given in some experiments to highly sensitized patients to maximize donor availability for hard-to-match patients.

First-Accept Match

This is the matching scheme that has been used by transplant centers currently performing kidney paired donation. A first-accept match starts with the first incompatible donor/recipient pair on the list. The database is searched for any donor/recipient pair that meets acceptance criteria as defined above. Both pairs involved in the first acceptable match are then removed from the database and transplantation is arranged. Notably, these pairs are no longer available for consideration in other combinations, even though they might have yielded better matches to other pairs. The next incompatible pair is then matched and removed from the pool. This process is repeated until all identified matches are performed and no match opportunities remain in the database. Optimization priorities and optimization bonuses are not applicable to a first-accept match.

Optimized Match

In our optimized algorithm, all possible combinations from the entire data set are considered at once. Each match in a particular feasible solution is given a score based on the optimization priorities of the donor/recipient pairs and any optimization bonuses. The scores for the entire combination of matches are summed. This process is repeated for every different feasible solution (every different combination of matches possible) for the pool of donor/recipient pairs. The combination of matches that yields the highest summed score is chosen, these matches are removed from the database, and the transplants are arranged.

Crossmatch Handling

An optimized match is used to identify the combination of matches with the highest number and quality. Crossmatch tests are performed on all identified matches. Negative crossmatch matches are removed from the database and transplantation is arranged. The optimized match is run again on the pairs remaining in the database after adding back any positive crossmatch pairings. This is repeated until all possible matches have been tested and crossmatched.

(FIGURE 2). Optimization afforded a statistically significant advantage with regard to the number of matches recognized for all database sizes ($P < .001$). We also studied the recognized matches in terms of HLA antigen mismatch, which has been shown in multiple studies to correlate with crossmatch likelihood and

allograft outcomes.^{2,21,23-26} Matches identified by the optimized algorithm had significantly fewer HLA mismatches when compared with first-accept ($P < .001$).

Furthermore, we calculated the number of transplanted kidneys predicted to survive 5 years following KPD using HLA mismatch–based live donor transplan-

tation data from Opelz.²³ Although HLA mismatch is not the only predictor of 5-year graft survival, it is the only predictor that can be improved by better matching algorithms. A significantly higher number of recipients matched through the optimized algorithm were predicted to have functioning kidneys at

5 years when compared with first-accept (34.9% vs 28.7%; $P < .001$).

With a national database of 5000 pairs, a mean of 2394 pairings were possible using mathematical optimization with an average of 3 mismatches, whereas only 2110 pairs with an average of 4.5 mismatches resulted from the currently used first-accept scheme ($P < .001$). At 5 years, this would result in 1666 predicted transplants surviving with optimized algorithm vs 1414 from first-accept ($P < .001$). The improvement in overall quality is highlighted by a 10-fold increase in 0 mismatch (423 vs 41) transplants identified.

Initial and Yearly Benefit

We estimated that at least 4000 donor/recipient pairs would initially participate in a KPD, as calculated by waiting times for patients modeled by Zenios.¹⁵ We calculated the benefit of using an optimized algorithm for the initial accrued pool, with a significantly greater predicted number of grafts surviving at 5 years (1150 vs 1397; $P < .001$).

According to the Zenios model, we estimated that at least 750 new donor/recipient pairs would participate in KPD per year, or 250 every 4 months. To calculate the recurring advantage afforded by an optimized algorithm, we first eliminated the maximum number of kidneys that could be matched from the initial pool. Every 4 months, 5% of the pool was assumed to seek transplantation by means other than KPD and 250 new pairs were added to the pool. Optimized and first-accept algorithms were compared over a 5-year period, ie, 15 iterations of dropouts and new pairs. The optimized algorithm again outperformed first-accept with significantly more matches ($P = .02$), better HLA concordance ($P < .001$), and more grafts predicted to survive at 5 years ($P < .001$).

National vs Regional Matching

Local and regional KPD programs are already in practice at a limited number of centers. A larger national pool offers the possibility of a greater number and quality of matches. However, this would require that the donor or re-

Figure 2. Potential Matches Using Mathematical Optimization Compared With the Currently Used Practice of First-Accept Matching

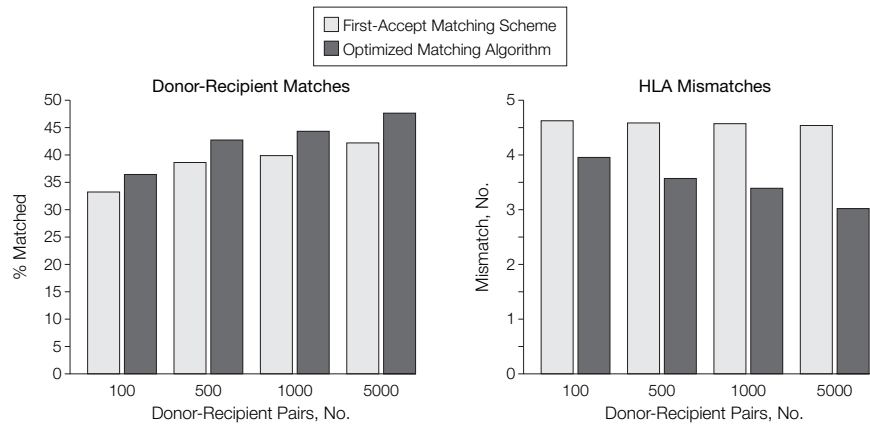


Table 2. Patients Required to Travel for Potential Matches Using a National Matching Scheme, Based on the Number of Patients Willing to Travel

Willing to Travel, %	First-Accept Patients, %		Optimized Patients, %	
	Matched	Required to Travel	Matched	Required to Travel
None	38.4		42.7	
Sensitized	39.9	1.0	45.1	1.4
Sensitized +10	40.2	5.9	46.5	2.4
Sensitized +25	40.7	11.0	47.0	2.7
Sensitized +50	41.4	16.1	47.5	2.8
Sensitized +75	41.8	18.0	47.4	2.8
All	42.0	18.4	47.7	2.9

ipient of each incompatible pair receive the transplant at the same hospital as the matched partner or that kidneys get transported between institutions. Local/regional programs would reduce the distance that patients or organs would have to travel. Transporting kidneys may reduce some of the benefits of live donor transplantation by increasing cold ischemia time. Currently, no data are available on the trade off between a larger national pool and the requirement of a greater travel distance for patients or organs.

To identify the number of patients who could benefit if matching were performed using a national database, we varied the number of pairs willing to travel outside of their region between 0% and 100% (TABLE 2). A simulation with no patients willing to travel represented a strictly regional KPD program. Patients who were willing to travel were considered for all paired donations, but matches

within the region were preferred for all patients. The patients required to travel might be unmatchable within their regions or might receive an advantage in HLA matching quality.

More pairs would be matched if some were willing to travel ($P < .001$). This was observed with both strategies, but the difference was more pronounced with the optimized algorithm (mean, 1712 regional vs 1891 national; a gain of 179) when compared with first-accept (mean, 1544 regional vs 1673 national; a gain of 129). The improvement derived by mathematical optimization when compared with the current first-accept scheme was statistically significant with regard to number of pairs matched, HLA mismatch, and predicted number of grafts surviving at 5 years, no matter how many pairs were willing to travel ($P < .001$). In fact, the role of optimization was important enough that greater benefit would be

Table 3. Per-Patient Analysis of Transplant Costs and Desensitization While Awaiting Donation From the Deceased Donor List vs Kidney Paired Donation (KPD)

Recipient Type	Years on Waitlist*	Cost of Dialysis†	Cost of Desensitization‡	Cost of KPD§
Highly sensitized	6.73	\$485 038	\$233 717	\$204 738
Blood type O	4.85	\$374 605	\$201 544	\$172 565
Blood type A	2.97	\$264 172	\$169 372	\$140 393
Blood type B	5.48	\$411 309	\$212 237	\$183 258
Blood type AB	1.63	\$185 453	\$146 439	\$117 460

*Average years awaiting deceased donor donation are based on UNOS data.²

†Average per-patient cost of dialysis calculated according to Medicare payments of \$58 758/year for dialysis, for the number of years the average patient awaits a donation from the deceased donor waitlist, plus \$89 508 for the cost of transplantation and the first year of postoperative care.²⁷

‡Average per-patient cost of desensitization calculated according to Medicare payments of \$28 979 for desensitization, \$89 508 for transplantation and the first year of postoperative care, and \$17 118/year of immunosuppression for the number of years the patient would have awaited a donation from the deceased donor waitlist.²⁷

§Average per-patient cost of a patient successfully matched through a KPD calculated according to Medicare payments of \$89 508 for the cost of transplantation and the first year of postoperative care, and \$17 118/year of immunosuppression for the number of years the patient would have awaited donation from the deceased donor waitlist.²⁷

derived from a regional optimized algorithm than a national first-accept scheme ($P = .002$).

Travel Advantage

The benefit to the overall pool of patients of a national KPD program was clearly shown. However, concerns regarding feasibility of a national KPD program focus in part on the willingness of donors and/or recipients to travel outside of their regions.

To evaluate the potential individual benefit of traveling to the unsensitized patient, we compared match likelihood and quality between unsensitized pairs willing to travel and those unwilling to travel outside of their region. No matter what fraction of pairs was willing to travel, the optimized solution always found more and better matches for those willing to travel ($P < .05$).

Furthermore, the optimized solution could profoundly reduce the subset of pairs that are actually required to travel when compared with a first-accept scheme (Table 2). Even if 100% of pairs were willing to travel, only 2.9% of the pool would actually need to travel in order to achieve the maximum benefit from an optimized algorithm, as compared with 18.4% of the pool required to travel in a first-accept scheme ($P < .001$). In all cases, mathematical optimization would yield more and better matches than first-accept but require fewer pairs to travel ($P < .001$).

Highly Sensitized Patients

The most challenging recipients are the 14% of UNOS registrants who have become highly sensitized. Because these patients harbor anti-HLA antibody, they are harder to match, resulting in a median waiting time of 6.73 years for the highly sensitized patient (panel reactive antibodies $\geq 80\%$).² This group of patients would arguably derive the greatest benefit from KPD due to the increased chance of finding a negative crossmatch donor. The cost of implementing a transplant in 1 highly sensitized patient after 6.73 years of waiting and undergoing dialysis until a negative crossmatch deceased donor organ can be obtained is approximately \$485 038. Alternatively, immediate transplantation with KPD followed by 6.73 years of immunosuppression costs only \$204 738 (TABLE 3). Maximizing matches for these patients would produce the greatest benefit to the individual patient and reduce the burden to the health care system. We tested 2 modalities for improving matches for this subgroup.

First, the effects of the method of matching and willingness to travel were evaluated with regards to highly sensitized patients. In the current system of first-accept regional matches, only 2.3% of highly sensitized patients received transplants in our simulation. However, if highly sensitized patients were willing to travel nationally and mathematical optimization was used, 14.1%

of highly sensitized patients would be successfully matched, a 6-fold increase ($P < .001$). This increase in pairs matched was lost with national first-accept (8.4%) or regional optimized searches (5.3%).

Second, the effect of giving an optimization bonus to highly sensitized patients was evaluated. This type of optimization is not possible using the first-accept scheme. Using a national optimized search as previously described, 90 highly sensitized patients found matches. This number rose to 132 when highly sensitized patients were favored with a bonus in the optimized algorithm ($P < .001$). No statistical difference was seen in the number of unsensitized or overall matches found. These findings demonstrate that highly sensitized patients can benefit from prioritization without a negative impact on the overall pool.

Crossmatch Handling

Another criticism of KPD relates to feasibility of crossmatching a national pool of patients while executing a matching algorithm. We evaluated our optimized crossmatch handling algorithm with regards to number of matches identified, the quality of these matches, as well as the predicted number of crossmatch and iterations required. No reduction was seen in the number of transplants performed or HLA mismatch when crossmatch was taken into consideration. Furthermore, only 1.23 crossmatch tests were required for every transplant performed, and an average of 6 (range, 5-8) iterations were required to complete the algorithm. This shows that optimization is still logistically plausible in the context of real-world crossmatch testing.

Sensitivity Analysis

For all of the variations in input data described in the "Methods" section, the difference between number of matches, HLA quality, and number of transplanted kidneys predicted to survive 5 years following KPD was significantly better using the optimized algorithm when compared with a first-accept scheme ($P < .001$).

Cost Analysis

When compared with dialysis while awaiting a transplant from the deceased donor transplantation list, a live donor kidney transplant offered through a KPD provides a cost advantage as well as an improvement in graft and patient survival. We have shown that KPD is less expensive than dialysis or desensitization for each type of recipient with a willing incompatible live donor (Table 3). The costs of various treatment options for a pool of simulated incompatible donor/recipient pairs were calculated for only the patients matched using KPD (TABLE 4) and for the entire pool (TABLE 5). A mathematically optimized algorithm not only increases the number of potential matches, but also saves nearly \$48 million over the currently utilized first-accept schemes.

For a pool of 4000 potential recipients (<7% of the current UNOS registry), nearly \$750 million would be saved by KPD compared with the cost of dialysis and deceased donor transplantation. The greatest cost savings would be realized by a national system that offered optimized KPD and desensitization of all unmatched recipients.

COMMENT

Kidney paired donation is no longer just a concept. The ethical and legal concerns that once dominated the discussion of KPD have given way to administrative and logistical challenges inherent in organizing complex cooperative programs between transplant centers.^{11,28,29}

Local, state, and regional programs are being introduced around the United States. Despite this, only a relatively small number of patients have benefited from KPD to date. It is critical to the success and public perception of KPD that careful consideration be given to what impact a local/regional vs national scheme will have on the ability to make transplants available to the greatest number of patients both equitably and cost-efficiently. Determining optimal allocation priorities and algorithms is absolutely crucial to the smart proliferation of KPD in the United States and the prevention of a haphazard system that di-

Table 4. Cost Benefit to Patients Matched Using Kidney Paired Donation (KPD) From a Pool of 4000 Incompatible Pairs

	No. of Patients Matched	Years on Waitlist*	Cost of Dialysis†	Cost of Desensitization‡	Cost of KPD§
First-accept KPD	1673	4.22	\$564 423 428	\$319 036 693	\$270 554 826
Savings with first-accept KPD			\$293 868 601	\$48 481 867	
Optimized KPD	1891	4.34	\$651 661 462	\$364 597 305	\$309 798 016
Savings with optimized KPD			\$341 863 446	\$54 799 289	
Extra savings with optimized KPD			\$47 994 845	\$6 317 422	

*Years on waitlist are based on type-specific data (Table 3), weighted by the sensitization and blood type distribution of patients entered into the KPD algorithm who would have successfully matched through this algorithm.

†Total cost of dialysis calculated for the number of patients who would have matched through KPD, according to Medicare payments of \$58 758 per year for dialysis, for the number of years that the patients who would have matched through KPD would have to await donation from the deceased donor waitlist, plus \$89 508 for transplantation and the first year of postoperative care.²⁷

‡Total cost of desensitization calculated for the number of patients who would have matched through KPD, according to Medicare payments of \$28 979 for desensitization, \$89 508 for transplantation and the first year of postoperative care, and \$17 118 per year of immunosuppression for the number of years that the patients who would have matched through KPD will have to await donation from the deceased donor waitlist.²⁷

§Total cost of KPD calculated for the number of patients who matched through KPD, according to Medicare payments of \$89 508 for transplantation and the first year of postoperative care, and \$17 118 per year of immunosuppression for the number of years that the matched patients would have awaited donation from the deceased donor waitlist.²⁷

Table 5. Cost Benefit to a Pool of 4000 Incompatible Pairs Using Optimized Kidney Paired Donation (KPD)*

Treatment Scheme (Matched Patients, Unmatched Patients)	Cost of Treating Patients Who Could Be Matched With Optimized KPD	Cost of Treating Patients Who Remain Unmatched After Optimized KPD	Total Cost of Treating Entire 4000-Patient Pool	Savings of Choosing Optimized KPD vs Dialysis
Dialysis for both†	\$651 661 462	\$822 390 179	\$1 474 051 641	
KPD, dialysis‡	\$309 798 016	\$822 390 179	\$1 132 188 195	\$341 863 446
Desensitization for both§	\$364 597 305	\$434 481 302	\$799 078 607	\$674 973 034
KPD, desensitization	\$309 798 016	\$434 481 302	\$744 279 318	\$729 772 323

*All amounts are rounded to the nearest dollar.

†Cost of dialysis for 1891 patients who would have matched using optimized KPD for an average of 4.34 years (based on the average distribution of patients entered into our optimized KPD algorithm who are successfully matched through this algorithm) and 2109 patients who would have remained unmatched after optimized KPD for an average of 5.11 years (based on the average distribution of patients entered into our optimized KPD algorithm who go unmatched). All patients eventually undergo transplantation and costs include the 1-year perioperative period, as calculated in Table 3.

‡One-year perioperative transplantation costs and 4.34 years of immunosuppression for 1891 patients matched using KPD, with cost of 5.11 years of dialysis and 1-year perioperative transplantation costs for 2109 people who would have remained unmatched after optimized KPD.

§Cost of desensitization, 1-year perioperative transplantation costs, and 4.34 years of immunosuppression for 1891 patients who would have matched using KPD, and cost of desensitization, 1-year perioperative transplantation costs, and 5.11 years of immunosuppression for 2109 patients who would have remained unmatched after KPD.

||One-year perioperative transplantation costs and 4.34 years of immunosuppression for 1891 patients matched using KPD, with 1-year perioperative transplantation costs, cost of desensitization, and cost of 5.11 years immunosuppression for 2109 people who would have remained unmatched after optimized KPD.

minishes the impact of this promising approach to the organ shortage.

To study the effects of algorithmic decisions and priorities on both local/regional and national matching outcomes, we created a computer program to simulate databases of recipients and their donors. First, the data show that a national KPD program would provide a greater number and quality of matches than local/regional schemes. Even more significantly, these simulations have shown that mathematically verifiable optimization would further

increase the number and quality of matches identified in any KPD cohort. In fact, greater benefit would be derived from adopting an optimized algorithm on a regional basis than expanding the currently used first-accept algorithm to a national level. In terms of outcome and cost, it is critical to optimize matching for KPD.

We have also shown that an optimized national KPD scheme would result in significant rewards for those who are willing to travel, as well as for the remaining pool of patients. Fur-

thermore, only 2.9% of the donor/recipient pairs would actually need to travel to achieve the maximum benefit from an optimized algorithm. This finding discredits one of the most widely perceived barriers to implementation of a national KPD program and greatly reduces the need to transport patients or organs between regions.

The advantages of optimization are not in quantity and quality alone. Resistance to KPD is a patient-specific issue, and includes concerns such as reluctance to travel, worries about donor age and quality and concerns that others will benefit most from the scheme. Optimization can be individualized on a patient-by-patient basis, with priorities regarding travel, HLA matching, donor age, transport of donor kidneys, and other parameters left in the hands of the patient and the transplant center entering the data. Adding an optimization bonus allows the flexibility to maximize transplantation of highly sensitized patients or other disadvantaged groups without hampering the overall outcome of the match.

We believe that KPD should be the preferred treatment for patients who have incompatibilities with their intended donors who wish to participate, as KPD is less expensive than desensitization and requires less immunosuppression. Our simulations suggest that approximately 47% of incompatible pairs could be matched through an optimized national KPD program. Those who do not match can either await the next round of matching or undergo desensitization with their cross-match-positive and/or ABO-incompatible intended donor. Some patients will favor desensitization because of timing issues, travel concerns, and desire to receive a kidney from a loved one. Furthermore, due to the breadth of their HLA reactivity, only a modest percentage of the highly sensitized patients will find an ABO-compatible donor with whom they have a negative cross-match. Patients who are difficult to match can be paired with donors that do not completely eliminate incompatibility but provide better immunologic con-

ditions for desensitization. We have combined KPD with desensitization at our institution: patients not eligible for antibody reduction protocols due to high donor-specific antigen titers can be matched with a donor with whom their donor-specific antigen titer is lower and thus amenable to desensitization.³⁰

Public perception is critical to the future success of KPD. If a national system does not use an algorithm that yields the best matches for a given pool, taking into account the priorities of individual patients, the public will be uneasy about paired donation. Concerns about equity are best addressed within an optimized framework where priority can be assigned to matches that help vulnerable populations. We believe that a national optimized match would best utilize this new source of live donor organs.

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Study concept and design: Segev, Gentry, Montgomery.

Acquisition of data: Segev, Gentry, Reeb.

Analysis and interpretation of data: Segev, Gentry, Warren, Montgomery.

Drafting of the manuscript: Segev, Gentry.

Critical revision of the manuscript for important intellectual content: Segev, Gentry, Warren, Reeb, Montgomery.

Statistical analysis: Segev, Gentry.

Administrative, technical, or material support: Warren, Reeb.

Study supervision: Montgomery.

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REFERENCES

1. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med.* 1999;341:1725-1730.
2. UNOS organ procurement and transplantation network data. United Network for Organ Sharing Web site. Available at: <http://www.unos.org/>. Accessed Sept 17, 2004.
3. Montgomery RA, Zachary AA, Racusen LC, et al. Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. *Transplantation.* 2000;70:887-895.
4. Montgomery RA, Cooper M, Kraus E, et al. Renal transplantation at the Johns Hopkins Comprehensive Transplant Center. *Clin Transpl.* 2003;199-213.
5. Takemoto SK, Zeevi A, Feng S, et al. National conference to assess antibody-mediated rejection in solid organ transplantation. *Am J Transplant.* 2004;4:1033-1041.
6. Jordan SC, Vo AA, Nast CC, Tyan D. Use of high-dose human intravenous immunoglobulin therapy in sen-

sitized patients awaiting transplantation: the Cedars-Sinai experience. *Clin Transpl.* 2003;193-198.

7. Sonnenday CJ, Warren DS, Cooper M, et al. Plasmapheresis, CMV hyperimmune globulin, and anti-CD20 allow ABO-incompatible renal transplantation without splenectomy. *Am J Transplant.* 2004;4:1315-1322.

8. Stegall MD, Dean PG, Gloor JM. ABO-incompatible kidney transplantation. *Transplantation.* 2004;78:635-640.

9. Warren DS, Zachary AA, Sonnenday CJ, et al. Successful renal transplantation across simultaneous ABO incompatible and positive crossmatch barriers. *Am J Transplant.* 2004;4:561-568.

10. Zachary AA, Montgomery RA, Ratner LE, et al. Specific and durable elimination of antibody to donor HLA antigens in renal-transplant patients. *Transplantation.* 2003;76:1519-1525.

11. Ross LF, Rubin DT, Siegler M, et al. Ethics of a paired-kidney-exchange program. *N Engl J Med.* 1997;336:1752-1755.

12. Delmonico FL, Morrissey PE, Lipkowitz GS, et al. Donor kidney exchanges. *Am J Transplant.* 2004;4:1628-1634.

13. UNOS. Concept Proposal for a National Live Donor Paired Kidney Exchange Program through the Organ Procurement & Transplantation Network/United Network for Organ Sharing. Presented August 20, 2004, for consideration by the UNOS Board.

14. Leffell MS, Steinberg AG, Bias WB, et al. The distribution of HLA antigens and phenotypes among donors and patients in the UNOS registry. *Transplantation.* 1994;58:1119-1130.

15. Zenios SA. Optimal control of a paired-kidney-exchange program. *Manage Sci.* 2002;48:328-342.

16. Zenios SA, Woodle ES, Ross LF. Primum non nocere: avoiding harm to vulnerable wait list candidates in an indirect kidney exchange. *Transplantation.* 2001;72:648-654.

17. Edmonds J. Paths, trees, and flowers. *Can J Math.* 1965;17:449.

18. Lovász L, Plummer MD. *Matching Theory.* New York, NY: Elsevier; 1986:369-375.

19. Doxiadis II, Smits JM, Schreuder GM, et al. Association between specific HLA combinations and probability of kidney allograft loss: the taboo concept. *Lancet.* 1996;348:850-853.

20. Doxiadis II, Smits JM, Stobbe I, et al. Taboo HLA mismatches in cadaveric renal transplantation. *Transplant Proc.* 1996;28:224.

21. Duquesnoy RJ. HLA Matchmaker: a molecularly based algorithm for histocompatibility determination. *Hum Immunol.* 2002;63:339-352.

22. Thompson JS, Thacker L, Byrne J. Prospective trial of a predictive algorithm to transplant cadaver kidneys into highly sensitized patients. *Transplantation.* 2002;73:1274-1280.

23. Opelz G. Impact of HLA compatibility on survival of kidney transplants from unrelated live donors. *Transplantation.* 1997;64:1473-1475.

24. Gjertson DW, Terasaki PI, Takemoto S, Mickey MR. National allocation of cadaveric kidneys by HLA matching. Projected effect on outcome and costs. *N Engl J Med.* 1991;324:1032-1036.

25. Takemoto SK, Terasaki PI, Gjertson DW, Cecka JM. Twelve years' experience with national sharing of HLA-matched cadaveric kidneys for transplantation. *N Engl J Med.* 2000;343:1078-1084.

26. Martin S, Connolly J, Jos V. Importance of HLA matching in highly sensitized renal transplant recipients with high transplant survival rates. *Transplant Proc.* 1993;25:265-266.

27. United States Renal Data System Annual Data Report 2003. Available at: http://www.usrds.org/adr_2003.htm. Accessed March 24, 2005.

28. Ross LF, Woodle ES. Ethical issues in increasing living kidney donations by expanding kidney paired exchange programs. *Transplantation.* 2000;69:1539-1543.

29. Roth AE, Sönmez T, Ünver MU. Kidney exchange. *Q J Economics.* May 2004;457-488.

30. Montgomery RA. ABO incompatible transplantation. *Am J Transplant.* 2004;4:1011-1012.