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Utilizing List Exchange and Nondirected Donation through 'Chain' Paired Kidney Donations

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In a list exchange (LE), the intended recipient in an incompatible pair receives priority on the deceased donor waitlist (DD-waitlist) after the paired incompatible donor donates a kidney to a DD-waitlist candidate. A nondirected donor's (ND-D) kidney is usually transplanted directly to a DD-waitlist candidate. These two established practices would help even more transplant candidates if they were integrated with kidney paired donation (KPD).

We consider a scenario in which the donor of an LE intended recipient (LE-IR) donates to a compatible KPD intended recipient (KPD-IR), and the KPD donor (KPD-D) donates to the waitlist (an LE-chain). We consider a similar scenario in which an ND-D donates to a KPD-IR and the KPD-D donates to the DD-waitlist (an ND-chain).

Using data derived from the New England Program for Kidney Exchange (NEPKE) and from OPTN/SRTR recipient-donor distributions, simulations are presented to evaluate the potential impact of chain exchanges coordinated with KPD. LE donors (LE-D) and ND-D who are ABO-O result in the highest number of additional transplants, while results for ABO-A and B donors are similar to each other. We recommend that both LE and ND donations be utilized through chain exchanges.

Key words: Kidney exchange, kidney transplantation, list exchange, non-directed donor, optimal matching, paired kidney donation

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Introduction

Live donors are an increasing source of kidney transplants. Usually live donations are directed, meaning there is a named intended recipient of a kidney donated by a relative, friend, or spouse. However, ABO blood incompatibility or a positive crossmatch prevents some of these intended transplants from being performed.

Recently, several kidney exchange or kidney paired donation (KPD) programs have been established (1–4). In a two-way KPD, two incompatible pairs exchange donor kidneys so one KPD-IR receives the kidney of the other KPD-D (5). Three-way exchanges, in which three pairs participate, can also be utilized. To expand the opportunity for KPD, optimal matching algorithms were designed to identify maximal sets of compatible donor/recipient pairs from a registry of incompatible pairs (6–8). These protocols are currently used in NEPKE, the regional exchange program in UNOS Region 1 (9).

To increase access to kidney transplantation for some candidates, the New England region conducts UNOS approved list exchanges (LE). In an LE, a living incompatible donor (LE-D) provides a kidney to a candidate on the DD-waitlist and in return the LE-IR receives a 'priority' on the DD-waitlist (10). Through April 2006, 24 have been performed. Participants in the LE in New England must be candidates for a first deceased donor (DD) kidney, be unsensitized (PRA <10%) and on dialysis (1).

There is a debate in the transplantation community about ethical issues concerning LE. The apparent adverse effect of LE on blood-type O recipients with no live donors is well analyzed (11). However, the full potential benefits of LE have not been investigated as thoroughly. We will demonstrate that integrating LE and KPD benefits additional candidates without any further adverse effect on O candidates on the DD-waitlist.

Another source of live-kidney donations is nondirected altruistic donors (ND-D) (12). The number of ND-Ds has been increasing (20 in 2000, 56 in 2002, 79 in 2005) according to OPTN data (retrieved from http://www.optn.org on 3/23/2006). In most cases, an ND-D kidney is transplanted to the highest priority appropriate candidate on the DD-waitlist, as described in a UNOS bioethics white paper

(Allocation of Organs From Nondirected Living Donors, at http://www.unos.org/resources/bioethics.asp?index=9).

In this article, we determine if integrating KPD with LE and ND-D can increase the number of individuals who receive a transplant, as suggested by Roth, Sönmez and Ünver (6). The potential gains are analyzed by doing simulations with anonymous data sets from New England, which include pairs on the NEPKE list, pairs who participated in LE, and an ND-D whose donation was integrated with NEPKE. The results from simulations using OPTN/SRTR data are also presented.

Methods

Definition of LE-chain and ND-chain exchanges

An LE-chain exchange involves at least two pairs, one willing to participate in LE and a second willing to participate in KPD. The LE-IR gets a priority on the DD-waitlist, the LE-D donates to the KPD-IR, and the KPD-D donates to the DD-waitlist. LE-chain exchanges in which more than one additional pair participates can also be considered (see Figure 1). Instead of only helping one candidate receive a transplant, i.e. the LE-IR in a traditional LE, an LE-chain exchange can help two or more candidates (the LE-IR, and at least one KPD-IR). We concentrate primarily on LE-chains of length no more than two, or no more than three, for the same logistical considerations that cause KPD to involve two or sometimes three pairs.

In an ND-chain exchange, the ND-D would donate to the KPD-IR instead of to a DD-waitlist candidate. In return the KPD-D would donate to a waitlist candidate. An ND-chain exchange is very similar to a LE-chain exchange, only the chain starts with an ND-D instead of a LE pair. There can be more than one pair in an ND-chain exchange (see Figure 2). This idea has been applied by Johns Hopkins in May 2005 (personal communication), by New-York Presbyterian hospital in May 2006 (press release) and by NEPKE in July 2006.

Simulations regarding ND-chains and LE-chains are very similar, so it is straightforward to draw conclusions using the same simulations for both ND-chains and LE-chains.

Simulations using local data sets

NEPKE data set: The NEPKE data set involved 34 distinct KPD-IRs and their incompatible live donors who registered for KPD through April 28, 2006. Anonymous data were provided by NEPKE and included ABO and HLA types, panel reactive antibody (PRA) and antibody specificity if present. One KPD-IR had three paired-donors, one had two, and the rest had one paired-donor each. These KPD-IRs and their donors registered over time and some withdrew from the list for various reasons, but all pairs were included in this study.

Five of the NEPKE pairs participated in LEs so they were considered only in the LE data set. Seven KPD-IRs did not have HLA class II antibody screen data available and were excluded, so the eventual NEPKE data set included 22 KPD-IRs. Eight (36.3%) were highly sensitized, with overall PRA greater than 70%. Six (27.3%) had PRA <10%, and the rest (8/22) were moderately sensitized. The high percentage of sensitized IRs can be attributed to the increased likelihood that such individuals have incompatible donors. Thirteen of 22 (59.1%) were ABO-O, six (27.3%) ABO-A and three (13.6%) ABO-B. Of the 25 donors, ten were (45.45%) ABO-O, seven (31.8%) ABO-B, seven (31.8%) ABO-A and one (4.5%) ABO-AB.

New England LE pairs and ND-Ds: The LE data consisted of 24 pairs who had received a kidney transplant using the LE. These included 15 pairs

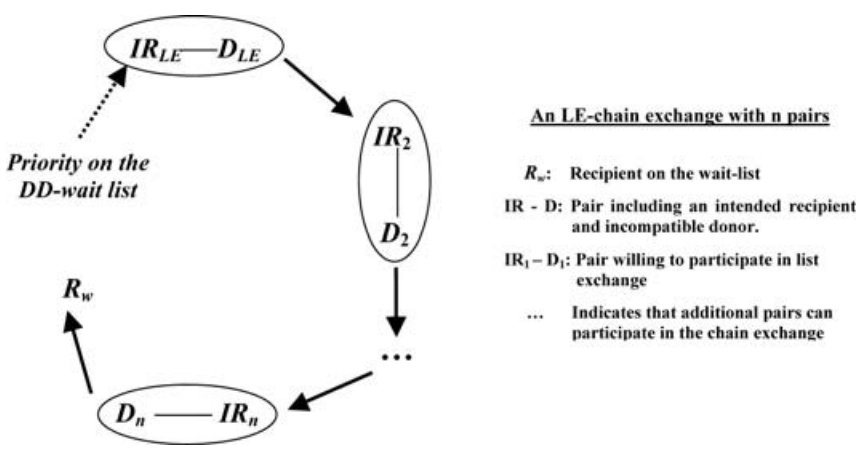

Figure 1: An LE-chain exchange with n pairs. *D* refers to a donor and *IR* refers to his/her intended recipient. Pairs are denoted in ellipses. IR_{LE}—D_{LE} is the incompatible pair who is willing to participate in the list exchange (LE). The other n-1 pairs come from the kidney paired donation (KPD) pool. R_w is a recipient on the deceased donor (DD)-waitlist. Arrows show the resulting transplants. Example: an ABO-A living donor cannot give to a relative who is ABO-O. In a list exchange, the A donor would give his kidney to an A candidate on the DD-waitlist, and in return his incompatible IR would receive the next suitable ABO-O DD kidney that becomes available in the region. An LE-chain exchange is another option designed to increase the number of transplants in the region. Instead of giving to a patient on the DD-waitlist, the ABO-A donor (D_{LE}) instead gives to an ABO-A candidate on the KPD waitlist (IR_2). If IR_2's incompatible donor (D_2) is ABO-B, then D_2 gives to an ABO-B patient on the DD-waitlist. D_{LE}'s incompatible recipient (IR_{LE}) would receive the next suitable DD kidney that becomes available in the region, resulting in a total of three transplants. Alternatively, D_2 could donate to another candidate on the KPD waitlist who is compatible and allow an even longer chain of transplants. In every case, the final donor in the chain gives a kidney to a patient on the DD-waitlist and IR_{LE} receives the next suitable DD kidney.

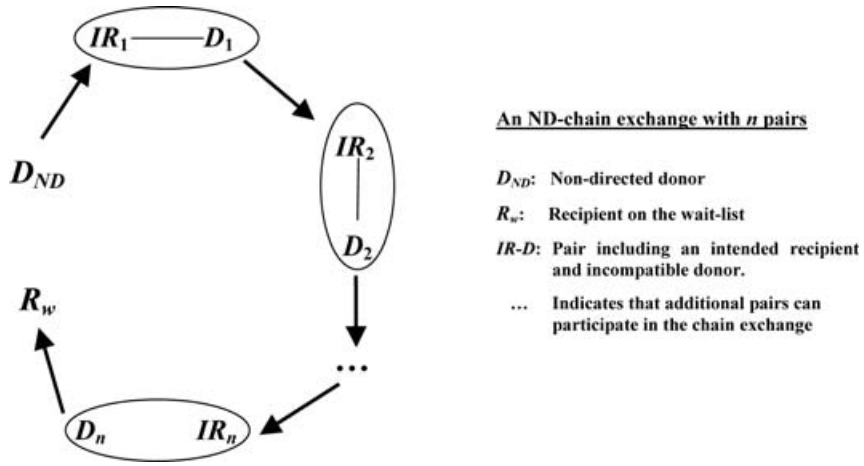

Figure 2: An ND-chain exchange with n pairs. All pairs come from the kidney paired donation (KPD) pool. R_w is a recipient on the deceased donor (DD)-waitlist and D_{ND} is a nondirected donor. Arrows show the resulting transplants. Example: If D_{ND} is ABO-O, he would donate to an ABO-O candidate on the KPD waitlist (IR_1). If IR_1's incompatible donor (D_1) is ABO-A, he would donate to an ABO-A patient on the DD-waitlist, allowing two transplants to occur. Alternatively, D_1 could donate a kidney to an ABO-A candidate on the KPD waitlist (IR_2), and IR_2's incompatible donor (D_2) would donate either to a candidate on the DD-waitlist, or to a compatible IR on the KPD waitlist, allowing an even longer chain of transplants. In every case, the final donor in the chain gives a kidney to a patient on the DD-waitlist. A D_{ND} of any blood type can potentially start an ND-chain and benefit additional patients.

with ABO-O IRs and ABO-A donors (O-A blood types), one pair with O-O, five pairs with O-B, two pairs with O-AB and one pair with A-B blood types. The O-O blood type pair is unusual in the LE since sensitized candidates are excluded, but this donor was unsuitable for reasons other than ABO or crossmatch.

In addition to the LE pairs, one ND-D (ABO-O) who was willing to donate a kidney as part of an ND-chain is included.

Local data simulations: *Integration of LE pairs and ND-D with NEPKE*. In the first set of simulations, the *compatibility matrix* (i.e. which IRs were compatible with which donors) was determined. Compatibility was based on ABO and predicted crossmatch results (13). IRs who would potentially be able to receive a transplant through KPD were identified using optimization techniques previously described (7,13,14). Integer programming was used to determine maximal unrestricted exchanges and maximal two-and-three-way exchanges, and Edmonds' algorithm (15) was used to determine maximal two-way exchanges, as previously explained (7,14).

To measure the marginal impact of an LE pair or the ND-D, they were introduced one at a time to the NEPKE pool. This means that environments where numbers of LE or ND-Ds are relatively small compared to the KPD pool are being simulated. Maximal exchanges in each of the three exchange regimens together with the potential LE-chain exchange were computed. For each regimen the marginal impact of each LE pair and the ND-D was calculated by finding how many additional IRs in the NEPKE pool were matched in the presence of an LE pair or the ND-D.

In summary, three computational experiments were simulated to answer the following questions:

What is the marginal impact of a LE-chain/ND-chain exchange on the NEPKE pool when

Experiment 1. Each exchange and chain can involve an unrestricted number of transplants?

Experiment 2. Each exchange and chain can involve two or three transplants?

Experiment 3. Each exchange or chain can involve only two transplants?

Integration of Random ND-Ds. In the second set of simulations, the number of additional transplants possible by introducing randomly generated ND-Ds (denoted only by blood type) in the NEPKE pool was evaluated. We simulated positive crossmatch probability using PRA levels of the KPD-IR as previously described (13). Monte Carlo simulations (which find averages and standard deviations by simulating the model with randomly generated samples) of 500 ND-D were run for each blood type. These simulations were also used to draw conclusions about the impact of randomly generated LE pairs on the NEPKE pool.

OPTN/SRTR data and simulating chain exchanges

Additional simulations were conducted based on data from the OPTN/SRTR 2003 Annual Report (retrieved from http://www.optn.org on 11/22/2004). These simulations were conducted to determine the potential benefits of integrating ND donations with KPDs in a more representative data set for the U.S. kidney transplant population, and in larger KPD pools. Conclusions about integrating LE pairs with KPD can also be drawn from these simulations.

Generation of simulated pairs: Distributions of (simulated) donor and IR blood types and gender, PRA distribution, and frequency of spousal donations were obtained from OPTN/SRTR data. (IR characteristics from the new waitlist registrations data, living donor relational type distribution from living donor transplants data).

Data generation assumptions were similar to simulations previously described (9,13). Pairs were randomly generated (assuming one donor per IR). Probability of a positive crossmatch was based on IR PRA data. A pair was included in the sample population if the IR and donor were incompatible by blood type or crossmatch. Incompatible pairs were generated until a sample pool size of n (n = 25, 50 or 100) was reached. Monte-Carlo simulation of 500 random populations was used for each sample pool size. Once

Table 1: The ABO distribution of kidney paired donation intended recipient (IR)-donor (D) pairs obtained in single donor simulations (n = 100)

IR-D blood types	ABO distribution (%)
O-O	11.36
O-A	30.71
O-B	13.09
O-AB	3.50
A-O	7.57
A-A	5.46
A-B	9.33
A-AB	2.43
B-O	3.34
B-A	9.28
B-B	1.03
B-AB	1.04
AB-O	0.92
AB-A	0.64
AB-B	0.25
AB-AB	0.066

the incompatible pairs were generated, the matching algorithms described for the NEPKE data simulations were used to determine maximal sets of exchanges in the same three experiments. ND-Ds with each of the four blood types were introduced to the pool one at a time to measure their marginal impact.

Two separate simulations were conducted using the same data generating assumptions as in Saidman et al. (13). For simplicity in the first simulation, IRs and their donors were assumed to be blood type unrelated (Table 1). In the second simulation, additional assumptions as in Zenios et al. (11) were used. Each IR was assumed to have zero or one spouse, zero, one or two parents, and zero or one siblings as suitable donors (leading to 12 different donor configurations). Each of the configurations could occur with equal probability. In both simulations, all characteristics of IRs and donors were independently drawn from their respective distributions.

Simulations integrating LE with KPD: To draw conclusions about the impact of integrating LE with KPD, the same set of simulations for ND-chain exchanges as described for NEPKE data were used. These simulations show the effects of integrating LE-chain exchanges for each LE-D blood type.

Distribution of LE-D and LE-IR ABO blood groups: Both ND-chains and LE-chains result in a different donor, possibly with a different blood group, being available for a DD-waitlist candidate instead of the original ND-D or LE-D. Here the donor blood group distribution when LE-chains are incorporated is analyzed. (Analysis is similar for ND-chains).

Simulations to estimate the distribution for LE-D (and LE-IR) blood groups were run using two methods. In the first, a hypothetical exchange program that made all LE pairs initially only available for two-way KPD was used. Each two-way KPD match run was conducted after 25 pairs entered the KPD pool. The pairs that remained unmatched became available for a second two-way match run when 25 more pairs were added to the pool. Third and fourth two-way KPD match runs were continued in a similar fashion. Pairs with unsensitized IR from the initial pool (with the initial 25 LE pairs) who remained unmatched after the fourth match run were only then considered eligible for LE. A Monte-Carlo simulation of 500 such groups gave the distribution of the LE-IR and LE-D blood groups.

In the second method, blood group distribution was generated using blood groups of the 24 New England LE pairs. These two distributions were generated for each of the two simulations described above, i.e. for IRs with single or with potentially multiple blood-related donors.

In simulations with potentially multiple donors for an IR, one of the donors was chosen to be sent to a DD-waitlist candidate (if that IR was the last person in an LE-chain exchange) either randomly or selectively. In the selective choice, an ABO-O donor was the first choice if available. Second choice was ABO-B, then ABO-A and finally an ABO-AB donor. The hierarchy in the selective choice was based first on the desire to maximize O donors, and then on the median waiting times of different blood type candidates on the DD-waitlist.

In summary, four distributions for the LE-IR and LE-D blood types were generated (Table 2). These were for (1) single donor simulations, (2) multiple donor simulations with randomly chosen LE-D (3), multiple donor simulations with selectively chosen LE-D, and (4) the New England LE data Using these distributions, the blood-types of donors sent to the DD-waitlist, average impact of an LE pair on helping other candidates when LE-chain exchanges are integrated with KPD, and the blood-types of the LE-IRs who receive priority on the DD-waitlist were estimated.

Table 2: The distribution of list exchange intended recipient (LE-IR) and list exchange donor (LE-D) blood types calculated according to the four distribution generation processes

		Single donor simulations (distribution 1) (%)	Multiple donor simulations—randomly chosen LE-D (distribution 2) (%)	Multiple donor simulations—selectively chosen LE-D (distribution 3) (%)	NE-LE pairs (distribution 4) (%)
LE-IR blood types	O	89.53	88.64	88.64	95.83
	A	6.64	5.89	5.89	4.17
	B	3.83	5.47	5.47	0.00
	AB	0.00	0.00	0.00	0.00
LE-D blood types	O	0.00	0.00	0.00	4.17
	A	57.27	64.40	59.73	62.50
	B	25.67	23.45	29.29	25.00
	AB	17.06	12.15	10.99	8.33

NE = New England; LE = list exchange.

Table 3: Number of additional transplants resulting from integrating LE-chain exchanges with paired exchanges using New England list exchange and NEPKE databases

Marginal impact of LE pairs					
			Additionally matched in the NEPKE pool due to a LE pair		
			Experiment 1	Experiment 2	Experiment 3
LE-IR blood type	LE-D blood type	Number of LE pairs of these types	When unrestricted number of transplants can occur in an exchange or chain	When at most three transplants are permitted in an exchange or chain	When at most two transplants are permitted in an exchange or chain
O	O	1	5	2	1
O	A	15	1	1	1
O	B	5	0	0	0
O	AB	2	0	0	0
A	B	1	0	0	0

The impact of integrating the O blood group nondirected donor is the same as that of the single O blood group LE-D shown in the first row.
NEPKE = New England Program for kidney exchange; LE = list exchange; LE-D = List exchange donor; LE-IR = List exchange intended recipient.

Results

New England data simulation

In the NEPKE dataset, six pairs out of 22 could be matched through maximal two-way exchanges, and also under maximal two-and-three-way exchanges or maximal unrestricted exchanges.

Table 3 shows how many additional pairs would benefit from integrating LE-chain exchange with KPD when each LE pair joins the NEPKE pool one by one. When the LE-D is ABO-A, 1 additional KPD-IR benefits in this limited population. But when the LE-D is ABO-O, as many as five additional KPD-IRs can receive transplants. Finally when the LE-D is ABO-B, no additional KPD-IR can receive a transplant. These numbers are in addition to one LE-IR who receives priority on the DD-waitlist, one waitlist candidate who receives transplant through the LE-chain and six KPD-IR who already can receive transplants through two-way exchanges.

Similar to integrating an ABO-O LE-D, integrating the ABO-O ND-D with NEPKE under the three experiments considered would benefit five, two and one additional pairs, respectively. This is in addition to the DD-waitlist candidate who always benefits from ND-chain exchanges.

In the second set of simulations, random simulated ND-Ds were introduced to the NEPKE pool one at a time (Table 4). When exchanges are unrestricted, an ABO-O ND-D would help on average 5.25 additional KPD-IRs to receive kidneys; an ABO-A donor would help 3.25; whereas a B or AB donor would not help any additional KPD-IRs. When exchanges (including ND-chain exchanges) are two-and-three way (Table 4, Experiment 2) or only two-way (Table 4, Experiment 3), maximum possible gains are obtained by an ABO-O ND-D facilitating two and one additional transplants, respectively. The number of additional transplants falls to 1.45 and 1, respectively, for an ABO-A ND-D.

The results can be generalized for simulated LE pairs. Table 4 results would still apply if random simulated LE pairs with ABO-O, A, B or AB donors were considered instead of ND-Ds.

The cost of LE in terms of missed KPD opportunities was also studied. All LE pairs were added to the NEPKE pool, resulting in 46 pairs. 8, 9 or 11 pairs could be matched through two-way, two and three-way, or unrestricted exchanges respectively. However, the additional benefit of KPD for LE-IRs was due entirely to the ABO-O LE-D. If this unusual pair was excluded from KPD, then only 6 of the remaining 45 pairs could be matched in any size exchanges. This is the same number matched through KPD in the original 22 pair pool. Only one of 23 LE pairs could participate in an exchange, and only at the expense of one of the NEPKE pairs who originally could have been matched.

Simulation with OPTN/SRTR data

Results of the OPTN/SRTR data simulations are in Tables 5–9. Tables 5 and 6 show results of simulations involving KPD-IRs with single unrelated donors and Tables 7 and 8 show results of simulations involving KPD-IRs with multiple donors. Results for single donor simulations are summarized here.

Table 5 shows the number of additional transplants from integrating ND-chain and KPD exchanges. For pool size n = 100, about 60 pairs are matched through unrestricted exchanges or two-and-three-way exchanges, and about 50

Table 4: Number of additional transplants resulting from integrating ND-chain exchanges with kidney paired donation (KPD) in the NEPKE database using random ND-D

	Additionally matched due to an O blood-type ND-D	*Additionally* matched due to an A blood-type ND-D	*Additionally* matched due to a B blood-type ND-D	*Additionally* matched due to an AB blood-type ND-D
Experiment 1				
When unrestricted number of transplants can occur in an exchange or chain				
Average	5.25	3.25	0	0
Std dev	0.87	2.49	0	0
Experiment 2				
When at most three transplants are permitted in an exchange or chain				
Average	2	1.45	0	0
Std dev	0	0.50	0	0
Experiment 3				
When at most two transplants are permitted in an exchange or chain				
Average	1	1	0	0
Std dev	0	0	0	0

In all three cases, only six intended recipients can be matched in the NEPKE database through KPD only.
NEPKE = New England Program for kidney exchange; ND-D = nondirected donor.

pairs are matched through two-way paired exchanges. If a single ABO-O ND-D is introduced to the exchange pool, approximately 2, 1.9, and 1 additional transplants could occur when exchange and chain size is unrestricted (Experiment 1), two-and-three-way (Experiment 2), and two-way (Experiment 3), respectively. Therefore, an ABO-O ND-D helps (almost) the maximum feasible number of additional IRs in experiments 2 and 3. Note that these numbers are *in addition* to a DD-waitlist candidate who receives a transplant through the ND-chain. If the ND-D is ABO-A, 0.96-1 additional pairs are matched. If the ND-D is ABO-B, 0.83–0.89 additional pairs are matched. Under all scenarios, ABO-AB ND-Ds rarely help any additional pairs receive transplants, since it is rare that a KPD-IR is ABO-AB and is incompatible with her own donor.

As the pair pool size decreases below 100, additional benefit of A and B blood-type donors slightly decreases for all experiments. However, as a percentage of the pool size, all ND-chain exchanges have higher marginal effect in smaller pools.

The results for ND-chain exchanges are used to draw conclusions regarding LE-chain exchanges. Table 6 summarizes the gains from LE-chain exchanges and distribution of the blood-type of the donor kidney sent to the DD-waitlist when LE-chain exchanges are integrated through KPD, as compared to when LE is conducted independently of KPD.

Integration of LE-chain exchanges with KPD benefits 0.77 to 1 additional pairs under the three experiments. But the donor kidney sent to the waitlist is more likely to be ABO-AB compared to ordinary LE. In two-way exchange (Experiment 3), ABO-AB donors are sent to the waitlist less frequently than in other experiments. Also in this experiment, occasional ABO-O donors are sent to the waitlist while none are sent under other experiments, and ABO-A and B donors are sent to the waitlist more frequently than in other experiments.

The effect of the LE alone on the blood type of the donor kidney sent to the waitlist is at the bottom of Table 6. The major difference between LE alone and LE-chain exchanges is that ABO-A donors are sent to the DD-waitlist less frequently under LE-chain exchanges (but instead AB blood type donors are sent), and occasional ABO-O kidneys can be sent under the LE-chain exchanges, while no O donors are sent under LE alone.

Table 7 shows the magnitudes of the additional benefits slightly increase for KPD-IRs with multiple donors for all experiments (except the marginal benefit of O blood-type ND-D under two-way exchanges). Table 8 gives the distributions of the blood types of donors sent to the waitlist when donors are chosen randomly. Choosing donors selectively results in slightly more O, A and B blood type donors and fewer AB blood type donors being sent to the DD-waitlist (data not shown).

The distribution of the blood type of the average LE-IR in the single donor simulations is shown in Table 9 for both LE and LE-chain exchanges (average with respect to distribution (1)). Mostly ABO-O IRs receive priority on the DD-waitlist under both LE and LE-chain exchanges as expected and predicted by previous studies (11). The blood type distributions of the LE-IRs in the multiple donor simulations are also shown (averages with respect to distributions (2) and (3)) and are similar to the single donor simulation results (i.e. most of the LE-IRs have O blood type).

Discussion

KPD is widely accepted as an ethical procedure (16,17). LE is more controversial, but is utilized in New England with

Table 5: Number of additional transplants resulting from integrating ND-chain exchanges with kidney paired donation (KPD) in UNOS/SRTR simulations when each intended recipient has a single unrelated donor

Experiment 1
When unrestricted number of transplants can occur in an exchange or chain

Number of pairs		Matched through only unrestricted KPD	*Additionally* matched due to an O blood-type ND-D	*Additionally* matched due to an A blood-type ND-D	*Additionally* matched due to a B blood-type ND-D	*Additionally* matched due to an AB blood-type ND-D
N = 25	Average	12.37	2.04	0.77	0.70	0.04
	Std dev	4.03	0.93	0.74	0.80	0.22
N = 50	Average	28.36	2.02	0.85	0.71	0.05
	Std dev	5.43	0.73	0.62	0.71	0.22
N = 100	Average	60.38	2.03	0.96	0.83	0.056
	Std dev	7.23	0.58	0.55	0.61	0.25

Experiment 2
When at most three transplants are permitted in an exchange or chain

Number of pairs		Matched through only 2&3-way KPD	*Additionally* matched due to an O blood-type ND-D	*Additionally* matched due to an A blood-type ND-D	*Additionally* matched due to a B blood-type ND-D	*Additionally* matched due to an AB blood-type ND-D
N = 25	Average	11.63	1.82	0.85	0.71	0.03
	Std dev	4.09	0.39	0.73	0.74	0.19
N = 50	Average	27.60	1.87	0.90	0.77	0.02
	Std dev	5.52	0.34	0.64	0.75	0.15
N = 100	Average	59.80	1.89	1.02	0.89	0.034
	Std dev	7.36	0.35	0.58	0.62	0.16

Experiment 3
When at most two transplants are permitted in an exchange or chain

Number of pairs		Matched through only 2-way KPD	*Additionally* matched due to an O blood-type ND-D	*Additionally* matched due to an A blood-type ND-D	*Additionally* matched due to a B blood-type ND-D	*Additionally* matched due to an AB blood-type ND-D
N = 25	Average	9.12	1	0.79	0.63	0.06
	Std dev	3.50	0	0.41	0.48	0.23
N = 50	Average	22.02	1	0.89	0.71	0.06
	Std dev	5.00	0	0.31	0.46	0.24
N = 100	Average	49.76	1	0.97	0.88	0.08
	Std dev	6.91	0	0.22	0.36	0.27

ND-D = nondirected donor; DD = deceased donor.

UNOS approval. ND-Ds are rare but numbers are increasing. In this article, we propose two ways of increasing the benefits of LE and ND-D through chain exchanges integrated with KPD.

A chain exchange involves at least one additional pair besides the original LE pair or ND-D. In a chain exchange, instead of the first donor (LE-D or ND-D) directly donating to a waitlist candidate, the kidney is donated to a KPD-IR and in return the KPD-D donates to the DD-waitlist. Longer chain exchanges involving more pairs can also be feasible. We conducted simulations using both local and OPTN/SRTR data to see the potential benefits of chain exchanges. The benefits of this integration with KPD are largest for ABO-O blood-type donors (ND-D or LE-D), but are also significant with ABO-A or B donors (although in the small local sample, an ABO-B or AB donor did not help any IRs).

However, LE and ND chain exchanges differ in their impact on the DD-waitlist due to the difference in the ABO blood type distributions of the ND-Ds and the LE-Ds. The blood types of the ND-Ds are the same as the blood type distribution of the general population. In contrast, the blood type distribution of the LE-Ds almost never includes ABO-O donors.

How donations from ND-D should be utilized is currently at the discretion of donors. In Region 1, ND-Ds are offered the

Table 6: Number of additional transplants resulting from integrating LE-chains with KPD in UNOS/SRTR simulations when each IR has a single unrelated donor (n = 100 pairs) : comparison of the blood type of donors

Experiment 1 (When unrestricted number of transplants can occur in an exchange or chain)						
		Additional pairs matched	Blood type of donor sent to the DD-waitlist			
			O (%)	A (%)	B (%)	AB (%)
LE-D blood type	O	2.03	0.00	4.00	5.20	90.80
	A	0.96	0.00	4.80	7.20	88.00
	B	0.83	0.00	2.20	6.80	91.00
	AB	0.056	0.00	0.80	2.80	96.40
Average using simulated LE distribution (1)		0.77	0.00	3.45	6.35	90.20
Average using NE LE pair distribution (4)		0.89	0.00	3.78	6.65	89.57
Experiment 2 (When at most three transplants are permitted in an exchange or chain)						
		Additional pairs matched	Blood type of donor sent to the DD-waitlist			
			O (%)	A (%)	B (%)	AB (%)
LE-D blood type	O	1.89	0.00	8.60	17.80	73.60
	A	1.02	0.00	6.20	8.00	85.80
	B	0.89	0.00	4.00	13.00	83.00
	AB	0.034	0.00	1.20	1.00	97.80
Average using simulated LE distribution (1)		0.82	0.00	4.78	8.09	87.13
Average using NE LE pair distribution (4)		0.94	0.00	5.33	9.08	85.59
Experiment 3 (When at most two transplants are permitted in an exchange or chain)						
		Additional pairs matched	Blood type of donor sent to the DD-waitlist			
			O (%)	A (%)	B (%)	AB (%)
LE-D blood type	O	1	1.20	61.40	29.40	8.00
	A	0.97	0.00	26.00	23.60	50.40
	B	0.88	0.40	31.00	34.60	34.00
	AB	0.08	0.00	2.20	3.20	94.60
Average using simulated LE distribution (1)		0.88	0.15	26.74	24.89	53.73
Average using NE LE pair distribution (4)		1	1.20	61.40	29.40	48.22
List exchange alone						
		Additional pairs matched	Blood type of donor sent to the DD-waitlist			
			O (%)	A (%)	B (%)	AB (%)
Average using simulated LE distribution (1)		0	0.00	57.27	25.67	17.06
Average using NE LE pair distribution (4)		0	4.17	62.50	25.00	8.33

LE-D = list exchange donor; DD = deceased donor; IR = intended recipient.
LE distribution (1) = Distributions for LE-IR and LE-D blood types for single donor simulations.
LE distribution (4) = Distributions for LE-IR and LE-D blood types for New England LE data.

option to either donate directly to a candidate on the DD-waitlist at a transplant center they choose, or to integrate their donation into NEPKE. Figure 3 shows how an ND-D was integrated with NEPKE paired donation candidates in an "ND-chain" of transplants conducted in July 2006. The ND-chain allowed an additional two transplants to occur, one of which was a highly sensitized recipient. Better utilization of their gift through ND-chain exchange may even result in an increased motivation for ND-Ds and thus more live donor kidneys may be donated to the DD-waitlist.

In an LE-chain exchange, the effect on the DD-waitlist will be similar to that of LE and will not affect the number of kidneys donated to the DD-waitlist. However, as currently happens in LE, mostly blood type O kidneys will be received from the DD-waitlist and fewer blood type O kidneys will be donated in return. So the distributional impact of an LE-chain to ABO-O recipients with no live donors is similar to that of an LE.

Ross and Zenios (18) suggested that restricting LE to ABO incompatible IR with ABO-A, B and AB bood types, and to recipients with an ABO-compatible but crossmatch incompatible living donor, would be fairer. Under this proposal, ABO-O DDs would not be diverted from ABO-O candidates. However, the authors acknowledge that such restrictions do not allow for the maximum number of possible transplants. They also require that sensitized recipients be allowed to participate in LE, which is currently not allowed in Region 1.

Table 7: Number of additional transplants resulting from integrating ND-chain exchanges with KPD in UNOS/SRTR simulations when *each IR can have multiple donors*: 12 scenarios are considered, one IR can have 0,1 or 2 parents; and 0 or 1 sibling; and 0 or 1 spouse with equal probability

When each KPD-IR can have multiple donors

Experiment 1

When unrestricted number of transplants can occur in an exchange or chain

Number of pairs		Matched through only unrestricted KPD	*Additionally* matched an O blood-type ND-D	*Additionally* matched due to an A blood-type ND-D	*Additionally* matched due to a B blood-type ND-D	*Additionally* matched due to an AB blood-type ND-D
N = 25	Average	13.35	2.32	0.86	0.81	0.04
	Std dev	3.99	1.14	0.85	0.99	0.23
N = 50	Average	31.69	2.09	0.91	0.84	0.07
	Std dev	5.30	0.77	0.66	0.72	0.26
N = 100	Average	67.31	2.02	0.98	0.94	0.12
	Std dev	7.31	0.52	0.50	0.54	0.35

Experiment 2

When at most three transplants are permitted in an exchange or chain

Number of pairs		Matched through only 2&3-way PE	*Additionally* matched due to an O blood-type ND-D	*Additionally* matched due to an A blood-type ND-D	*Additionally* matched due to a B blood-type ND-D	*Additionally* matched due to an AB blood-type ND-D
N = 25	Average	12.18	1.87	0.86	0.75	0.03
	Std dev	3.95	0.34	0.75	0.78	0.16
N = 50	Average	30.02	1.90	1.00	0.94	0.05
	Std dev	5.73	0.31	0.70	0.74	0.23
N = 100	Average	66.63	1.92	1.01	0.95	0.082
	Std dev	7.60	0.27	0.52	0.54	0.28

Experiment 3

When at most two transplants are permitted in an exchange or chain

Number of pairs		Matched through only 2-way PE	*Additionally* matched due to an O blood-type ND-D	*Additionally* matched due to an A blood-type ND-D	*Additionally* matched due to a B blood-type ND-D	*Additionally* matched due to an AB blood-type ND-D
N = 25	Average	9.28	1	0.75	0.58	0.04
	Std dev	3.20	0	0.43	0.49	0.20
N = 50	Average	23.26	1	0.90	0.77	0.07
	Std dev	5.02	0	0.31	0.42	0.25
N = 100	Average	54.19	1	0.94	0.90	0.10
	Std dev	7.60	0	0.22	0.29	0.31

Other ethical objections were reported by Ackerman et al. (19), who showed that 40% of minority candidates surveyed did not feel that LE was fair if ABO-O waitlist candidates had to wait any longer for a DD organ. However, Morrissey has argued in support of LE (20). He notes that Region 1 has acknowledged the disadvantage for ABO-O waitlist candidates, but suggests that the small disadvantage from the limited number of LE pairs presented in the region so far has been offset by the addition of live donors to the pool of candidates awaiting DD transplants. Simulations have shown that LE is the best way to increase living donation among small groups of recipients, but as incompatible population size increases to greater than 100 pairs, LE offered less benefit than KPD (21). However, the added beneficial effect of integrating LE and KPD was not fully considered in that study.

The utilization of LE-chains is likely to inherit the ethical concerns raised regarding LE (11). However, an LE donor will rarely be ABO-O, but in an LE-chain the blood type of the donor sent to the DD-waitlist may sometimes be ABO-O depending on the pairs participating. Therefore, in general the overall effect of an LE-chain exchange will not be worse than LE alone regarding any disadvantage to ABO-O candidates on the DD waitlist, and may sometimes be better. Also, the ethical concerns might be somewhat alleviated since unlike LE, an LE-chain benefits more than one transplant candidate. There will be few or no missed KPD opportunities due to pairs who opt for LE if no LE-chain exchanges are possible.

Moreover, while this is not the current practice in New England, it has been proposed that LE-chains might be utilized

Table 8: Number of additional transplants resulting from integrating LE-chain exchanges with KPD in UNOS/SRTR simulations when *each IR can have multiple donors* (for 100 pairs) : comparison of the blood type of the *donors* sent to the DD-waitlist if the donor is *randomly chosen*

Experiment 1						
(When unrestricted number of transplants can occur in an exchange or chain)						
		Additional pairs matched	Blood type of donor sent to the DD-waitlist			
			O (%)	A (%)	B (%)	AB (%)
LE-D blood type	O	2.02	0.00	5.40	2.00	92.60
	A	0.98	0.00	4.80	2.00	93.20
	B	0.94	0.00	4.00	4.20	91.80
	AB	0.12	0.00	0.20	0.80	99.00
Average using simulated LE distribution (2)		0.87	0.00	4.05	2.37	93.58
Average using NE LE pair distribution (4)		0.94	0.00	4.24	2.45	93.31
Experiment 2						
(When at most three transplants are permitted in an exchange or chain)						
		Additional pairs matched	Blood type of donor sent to the DD-waitlist			
			O (%)	A (%)	B (%)	AB (%)
LE-D blood type	O	1.92	0.00	6.80	9.80	83.40
	A	1.01	0.00	9.80	3.60	86.60
	B	0.95	0.00	5.60	10.40	84.00
	AB	0.082	0.00	1.60	0.40	98.00
Average using simulated LE distribution (2)		0.88	0.00	7.82	4.81	87.38
Average using NE LE pair distribution (4)		0.96	0.00	7.94	5.29	86.77
Experiment 3						
(When at most two transplants are permitted in an exchange or chain)						
		Additional pairs matched	Blood type of donor sent to the DD-waitlist			
			O (%)	A (%)	B (%)	AB (%)
LE-D blood type	O	1	1.00	69.00	22.20	7.80
	A	0.94	0.00	38.40	14.80	46.80
	B	0.90	0.20	37.40	21.20	41.20
	AB	0.10	0.00	2.60	1.20	96.20
Average using simulated LE distribution (2)		0.83	0.05	33.82	14.65	51.49
Average using NE LE pair distribution (4)		0.86	0.09	36.44	15.58	47.89
List exchange alone						
		Additional pairs matched	Blood type of donor sent to the DD waitlist			
			O (%)	A (%)	B (%)	AB (%)
Average using simulated LE distribution (2)		0	0.00	64.40	23.45	12.15
Average using NE LE pair distribution (4)		0	4.17	62.50	25.00	8.33

LE distribution (2) = Distributions for LE-IR and LE-D blood types for multiple donor simulations with randomly chosen LE-D.
LE distribution (4) = Distributions for LE-IR and LE-D blood types for New England LE data.

Table 9: Blood type distribution of the IRs who received priority on the DD-waitlist as result of LE or integration of LE-chain exchanges with KPD in the SRTR/OPTN simulations

	Blood type of *IR* who received priority on the DD-waitlist			
	O	A	B	AB
Average using simulated LE distribution (1) for simulation 1	89.53	6.64	3.83	0.00
Average using simulated LE distribution (2) and (3) for simulation 2	88.64	5.89	5.48	0.00
Average using NE LE pair distribution (4)	95.83	4.17	0.00	0.00

LE distribution (1) = Distributions for LE-IR and LE-D blood types for single donor simulations.
LE distribution (2) = Distributions for LE-IR and LE-D blood types for multiple donor simulations with randomly chosen LE-D.
LE distribution (3) = Distributions for LE-IR and LE-D blood types for multiple donor simulations with selectively chosen LE-D.
LE distribution (4) = Distributions for LE-IR and LE-D blood types for New England LE data.

selectively (6) to avoid any adverse affect on the ABO-O DD-waitlist by avoiding LE-chain exchanges where the net effect to the ABO-O DD-waitlist is negative. That would mean an ABO-O KPD-IR would receive priority at the DD-waitlist only if the donor whose kidney is donated to the DD-waitlist via the LE-chain exchange is of blood–type O. However, this may not allow for the maximum number of transplants to occur.

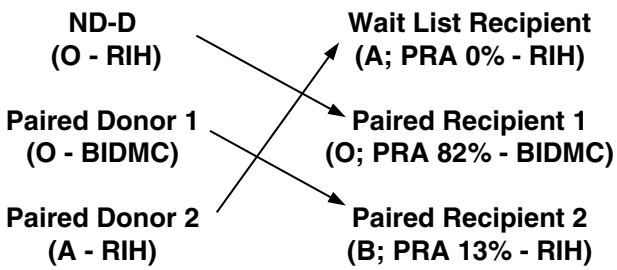

Figure 3: Example of an ND-chain exchange in New England. Transplants occurred on July 11, 2006 at two different centers — Rhode Island Hospital (RIH) in Providence and Beth Israel Deaconess Medical Center (BIDMC) in Boston. ABO types of donors and recipients, and PRA of the recipients are shown. The nondirected donor (ND-D) initially contacted RIH and then agreed to be integrated into the New England Program for Kidney Exchange (NEPKE) waitlist. The ND-D donation allowed two pairs on the NEPKE list to participate in an ND-chain exchange, for a total of three transplants. The ABO-O ND-D gave a kidney to a highly sensitized ABO-O recipient at BIDMC who had been on the NEPKE waitlist for 11 months (Paired Recipient 1). That recipient's paired donor (Paired Donor 1), who was also ABO-O but incompatible due to a positive crossmatch, gave a kidney to an ABO-B recipient (Paired Recipient 2) at RIH. The ABO-A incompatible donor of that pair (Paired Donor 2) gave a kidney to a candidate on the RIH deceased donor waitlist. All transplants occurred simultaneously at the transplant center of the recipients.

In the current practice of KPD, all transplants are conducted simultaneously, which makes larger exchanges logistically more demanding. Nevertheless the benefits of three-way exchange over two-way exchange are well documented (13,14). Similar limitations are required for LE-chain exchanges. In a two pair LE-chain exchange, the two transplants would normally be conducted simultaneously. As with KPD, it may be difficult to conduct a LE-chain involving more than three pairs.

But such a limitation in exchange sizes may not be required for ND-chain exchanges. It may not be necessary to conduct all exchanges simultaneously, since the first donation comes from an ND donor. If something goes wrong in subsequent transplants and the whole ND-chain cannot be completed, the worst outcome will be no donated kidney being sent to the waitlist and the ND donation would entirely benefit the KPD pool. This will likely be a subject of debate should ND-chain exchanges become more prevalent.

We recommend that both LE and ND-Ds be integrated with KPD. Our simulations clearly support this position. In New England, pairs who are eligible for LE under the strict criteria established by the region are required to remain in the NEPKE pool for at least 45 days (an arbitrarily chosen time requirement) before opting out for LE. This can facilitate new LE-chain exchange so additional IRs may be helped. Similarly ND-Ds are given the opportunity to have their donation utilized through NEPKE (if possible) with the understanding that their gift may then help even more individuals receive a kidney transplant.

There is growing consensus in the medical community on the need for a national KPD program in the US to coordinate paired exchanges. Benefits of larger pools for KPD are well established (8,13,14). There has also been discussion of enlarging the set of pairs eligible for exchange to include some compatible pairs (9,22). We propose that at least ND-chain exchanges should be incorporated in such a program to maximize the benefits of KPD. This would be an opportunity to help more transplant candidates in every region in the country. Interested regions (as in New England) could also integrate LE-chain exchanges with their current systems and transplant even more living donor kidneys.

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