

The Roles of Dominos and Nonsimultaneous Chains in Kidney Paired Donation

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Efforts to expand kidney paired donation have included matching nondirected donors (NDDs) to incompatible pairs. In domino paired donation (DPD), an NDD gives to the recipient of an incompatible pair, beginning a string of simultaneous transplants that ends with a living donor giving to a recipient on the deceased donor waitlist. Recently, nonsimultaneous extended altruistic donor (NEAD) chains were introduced. In a NEAD chain, the last donor of the string of transplants initiated by an NDD is reserved to donate at a later time. Our aim was to project the impact of each of these strategies over 2 years of operation for paired donation programs that also allocate a given number of NDDs. Each NDD facilitated an average of 1.99 transplants using DPD versus 1.90 transplants using NEAD chains ($p = 0.3$), or 1.0 transplants donating directly to the waitlist ($p < 0.001$). NEAD chains did not yield more transplants compared with simultaneous DPD. Both DPD and NEAD chains relax reciprocity requirements and rebalance the blood-type distribution of donors. Because traditional paired donation will leave many incompatible pairs unmatched, novel approaches like DPD and NEAD chains must be explored if paired donation programs are to help a greater number of people.

Key words: Blood-type incompatibility, donor exchange, incompatible donors, live donor kidney transplantation, nondirected donors, nonsimultaneous extended altruistic donor chains, paired kidney exchange

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Introduction

Kidney paired donation (KPD) is an expanding modality for transplanting patients with incompatible living donors by matching them to other patient–donor pairs (1–4). KPD allows donors and recipients who are otherwise excluded to participate in live donor transplantation. However, any

pool of incompatible pairs is enriched for blood-type O recipients and depleted of blood-type O donors. Because of this blood-type imbalance, only about half of incompatible pairs find matches to other incompatible pairs (5).

Matching nondirected donors (NDDs) to incompatible pairs versus allocating them to recipients on the deceased donor waitlist (Figure 1A), increases the match rate for incompatible pairs and multiplies each NDD's gift to facilitate transplants for two or more people (6,7). In a domino paired donation (DPD), an NDD gives to a recipient of an incompatible pair, and simultaneously the donor of the pair gives to another recipient. There may be one or two incompatible pairs involved, but the donor of the last pair gives to a recipient on the waitlist (Figure 1B).

A variant of DPD that was recently implemented is the nonsimultaneous extended altruistic donor (NEAD) chain (8). A NEAD chain (Figure 1C) consists of segments; each segment is like a DPD, except that the donor of the last pair is held in reserve and asked to donate later. The reserved donor is called a bridge donor.

The use of the word 'chain' for various transplant modalities has not been consistent in the literature. One paper referred to both NEAD chains and DPD as ND-D chains (7), but reported a quantitative model of just the DPD variant. List paired exchanges have also been described as w-chains (9). We use the word chain only for NEAD chains.

Both DPD and NEAD chains offer two advantages. First, they expand the blood-type distribution of donors that are matched in KPD, because NDDs are drawn from a population-based blood-type distribution rich in blood-type O people, while incompatible pairs are nearly devoid of blood-type O donors. Second, they relax the reciprocity requirement of KPD, so pairs need only find a donor who can give to the pair's recipient, rather than matching both the donor and recipient of another pair.

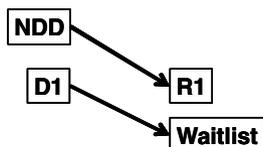
NEAD chains add another potential advantage. The simultaneity requirement of KPD or DPD is relaxed, so 'longer' chains that might not have been feasible simultaneously can occur over time. However, NEAD chains sequester the benefits of NDDs to recipients who have a living donor available, run the risk of a bridge donor reneging, and add logistical complexity in that programs must maintain contact with bridge donors after a chain segment is completed.

A NDDs give to recipients on deceased donor waitlist

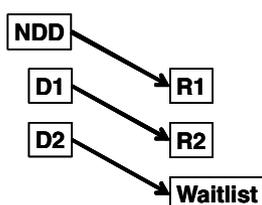


B NDDs participate in DPD

Two-way domino



Three-way domino



C NDDs participate in NEAD chains

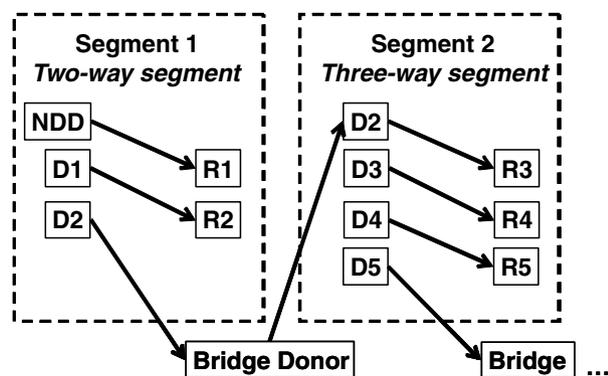


Figure 1: Strategies for matching nondirected donors (NDDs) to recipients. (A) NDDs are not incorporated into kidney paired donation (KPD); they give to recipients on the deceased donor waitlist. (B) Domino paired donation. (C) Nonsimultaneous extended altruistic donor chains.

The goal of our simulation study was to analyze the impact of NEAD chains on KPD, compared to the alternatives of DPD or allocating NDDs directly to recipients on the waitlist.

Methods

Simulated patients

The United Network of Organ Sharing (UNOS) does not currently collect data about patients' incompatible live kidney donors. We simulated pools of donor/recipient pairs according to a clinically detailed model that we have previously described (5,10). In brief, recipients and their social networks of potential donors are created, with blood types, ethnicity, and HLA profiles drawn from UNOS data, population averages and inheritance for related individuals (11). Recipients with a PRA of greater than 80 require a 0- or 1- mismatched donor. A virtual workup eliminates unwilling or medically unsuitable donors. If no donor can be found for a particular recipient or if a compatible donor is found, the recipient is censored. Otherwise, the recipient and one of his incompatible donors comprise an incompatible pair.

Table 1: Demographic assumptions for nondirected donors

Race of nondirected donors	
Caucasian	97.2%
African-American	1.7%
Hispanic	1.1%
HLA-A,-B,-DR	by race
Blood type	
O	47.6%
A	36.0%
B	12.4%
AB	4.0%

NDDs are simulated, with blood type and ethnicity distributions similar to those of NDDs in UNOS data. HLA profiles are drawn from ethnicity-specific population averages. Table 1 details demographic assumptions for NDDs.

Base case simulation

Each longitudinal simulation spans 24 months. In our base case, 30 incompatible recipient/donor pairs and two NDDs join the pool per month. We chose incompatible pair and NDD pool sizes based on reports from US KPD registries (12,13). NDDs primarily donate at a small number of high-volume centers, and this group of centers likely overlaps with centers offering paired donation (14). Each month, a match run identifies the best combination of paired donations, sometimes including DPDs or NEAD chain segments.

Incompatible pairs may leave the pool because the recipients get transplanted by another mechanism or become too sick for transplant, or because the donors become ineligible or reconsider participating. At the end of each month, simulated attrition removes 2% of the incompatible pairs in the pool. A bridge donor whose intended recipient has already received a transplant may renege if he decides not to donate or becomes ineligible. At the end of each month, simulated renege removes 5% of the bridge donors. Table 2 summarizes the evolution of the pool.

Table 2: Longitudinal composition of the paired donation pool

Month 1	Initial cohort of incompatible recipient/donor pairs arrive. Initial cohort of NDDs arrives. Optimized matching—first round. Crossmatch tests disqualify some matches. Optimized matching—second round. Crossmatch tests disqualify some matches. Some incompatible recipient/donor pairs leave pool. Some bridge donors renege.
Month 2	Additional cohort of incompatible recipient/donor pairs arrive. Additional cohort of NDDs arrives. Optimized matching—first round. Crossmatch tests disqualify some matches. Optimized matching—second round. Crossmatch tests disqualify some matches. Some incompatible recipient/donor pairs leave pool. Some bridge donors renege.
Month 3	Additional cohort of incompatible recipient/donor pairs arrive. Additional cohort of NDDs arrives. <i>et cetera...</i>
Month 24	Remaining bridge donors donate to waiting list.

Sensitivity analysis

Some factors influencing paired donation outcomes are simply unknown; others are predictable with some degree of certainty. By conducting repeated simulations while varying these uncertain factors, we can assess whether our inferences hold if the actual system departs from our assumptions. In our sensitivity analysis, we varied the number of incompatible pairs arriving each month. We also varied the number of NDDs arriving each month. We varied the renege rate of bridge donors whose recipients had already received a transplant. Finally, we tuned the optimization algorithm in an attempt to make NEAD chains more successful at increasing transplants.

Optimization

For a fixed pool of incompatible pairs and NDDs, an optimization algorithm determines which pairs should be matched to achieve the largest number of transplants. For NEAD chains, it is not possible to directly optimize the number of pairs that will eventually match, since the future composition of the pool is uncertain. In our basic simulation, we optimize only the number of pairs that match in the current month, neglecting all effects of the current matching choices on future pools. However, in our sensitivity analysis, we consider heuristic approaches that ostensibly enhance the performance of NEAD chains: disallowing AB donors as bridge donors, penalizing the choice of an AB donor as a bridge donor, prioritizing longer segments of NEAD chains and giving priority to NEAD chains over traditional paired donation.

Statistical analysis

For each experiment, we report results averaged over 30 Monte Carlo simulations. Every simulation was replicated under three different conditions: one in which NDDs gave directly to recipients on the waiting list and only incompatible donor/recipient pairs were considered for KPD, one in which NDDs were considered for simultaneous DPDs and one in which NDDs began NEAD chains. We calculated the total number of recipients transplanted in each scenario, from both the pool of incompatible pairs and the waitlist. In the NEAD chains case, bridge donors who were not yet matched for donation remained in the pool at the end of the simulation. In this case, we added the number of remaining bridge donors to the number of people transplanted, on the assumption that each remaining bridge donor could donate directly to the waitlist. We compared the number of transplants in each scenario by calculating a ratio. These ratios are reported in our figures, including 95% confidence intervals of mean ± 2 *(standard error).

Results

Number of transplants achieved

In all scenarios we tested, using NDDs in DPD or NEAD chains yielded more transplants than allocating NDDs to the deceased donor waitlist. DPD would increase the number of transplants by about 20%, depending on the size of the pool, as shown in Figure 2. NEAD chains yield similar results, when compared with direct donation to the waitlist.

However, NEAD chains did not significantly increase the number of transplants performed when compared with DPD. Figure 3 compares NEAD chains to DPD for varying numbers of incompatible pairs in the pools. In some cases DPD yields significantly more transplants at a 95% confidence level. Even where NEAD chains are strongest in Figure 3, there is no significant difference between the number of transplants using NEAD chains and using DPD.

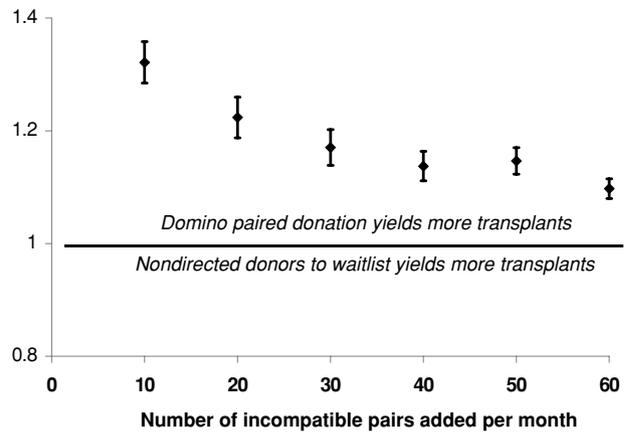


Figure 2: Ratio of the number of transplants achieved using nondirected donors (NDDs) in domino paired donation (DPD) to the number of transplants achieved when NDDs give to recipients on the deceased donor waitlist, as the number of incompatible pairs per month varies.

DPD enables more transplants because in a DPD, the donation to the waitlist is captured immediately. In NEAD chains, a bridge donor may wait many months to find a suitable recipient, as risks of that bridge donor changing his mind or becoming ineligible accumulate. There is no trend indicating that the situation improves with larger pools of pairs, as might be expected in a national registry; the largest pools do not match bridge donors quickly enough that NEAD chains would be superior to DPD.

If NEAD chains are used instead of DPD, paired donation arrangements will shift away from the straightforward

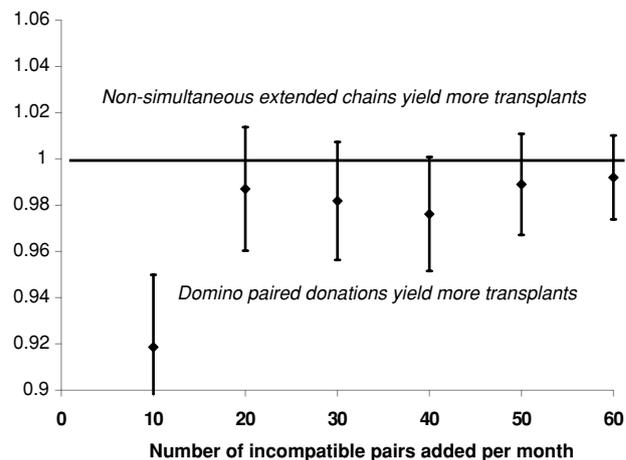


Figure 3: Ratio of the number of transplants achieved using nondirected donors (NDDs) in nonsimultaneous extended altruistic donor chains to the number of transplants achieved using NDDs in domino paired donation, as the number of incompatible pairs added per month varies.

Table 3: Average number of recipients in each category who receive transplants over 2 years, with 30 incompatible pairs and 2 NDDs joining each month, under three different strategies for allocating NDDs

	Waitlist	KPD	DPD	NEAD	Total
NDDs to waitlist	48	232.2	0	0	280.2
NDDs to DPD	48	203.9	76	0	327.9
NDDs to NEAD chains	29.4	181.9	0	112.2	323.4

The numbers in the DPD column do not include the recipients from the waitlist who are at the end of each exchange; waitlist recipients are instead listed in the first column. At the end of the simulation, remaining bridge donors are tallied as if they had donated directly to recipients on the waitlist.

matches among incompatible pairs and toward the more logistically complex NEAD chains, without increasing the numbers of transplants achieved. Table 3 shows the number of people transplanted in each paired donation type, across the strategies being tested. Using DPD, 73% of the matched pairs were in standard arrangements and 27% were in domino matches. Using NEAD chains, 62% of the pairs matched in standard arrangements and 38% were transplanted in chain segments. NEAD chains do slightly increase the match rate for incompatible pairs, from 40% to 41% in our simulations, but eliminate an equivalent or larger number of transplants for recipients on the waitlist.

NEAD chains become inactive

We call a NEAD chain active during a month if an NDD or bridge donor from that chain donates to a recipient during that month. Following an active month for a NEAD chain, a new bridge donor is generated from the end of that chain segment.

The mode of the number of active months for a NEAD chain in our simulations is one. That is, the most likely outcome for a NEAD chain is that an NDD will be used for an initial segment, and that the bridge donor will not be matched to anyone else for the duration of the simulation. The average number of active months for a NEAD chain is 1.28, and the average number of transplants achieved by a NEAD chain is 2.34. Still, a few chains in each simulation grow long, with an average of 7.4 transplants in the longest chain. The arrival, utilization, and eventual fate of each of the 48 NEAD chains over the 2 years of a typical simulation appears in Figure 4 (15).

It might be argued that NEAD chain matches should be prioritized above traditional KPD, to ensure bridge donors do not have to wait long periods before finding a suitable recipient. We tried giving NEAD chain matches an advantage in the optimization scheme. This did have the proximate effect of increasing usage of bridge donors, so that the average number of active months for a chain was 2.52 and the average number of transplants per chain was 3.68. How-

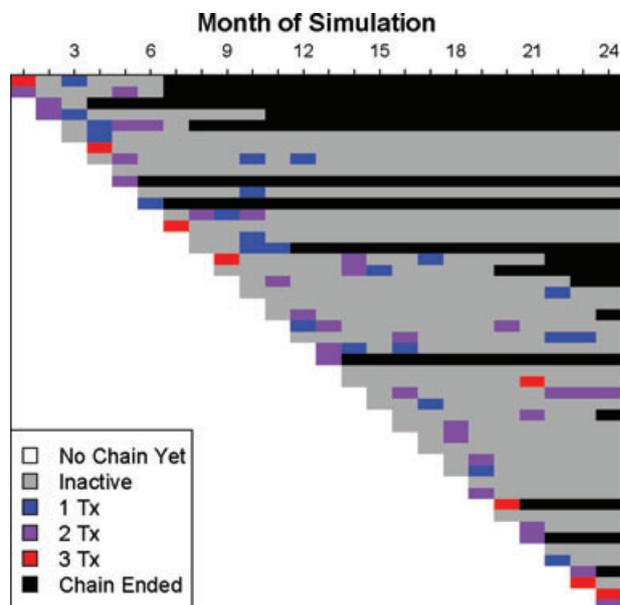


Figure 4: Each of the 48 rows of the figure depicts the arrival, utilization and eventual fate of one nonsimultaneous extended altruistic donor (NEAD) chain. The lower triangular region is white because NEAD chains arrive at a rate of two per month over a 2-year period. Rows that end in black show NEAD chains that have ended due to a bridge donor reneging. Inactive months are shown in gray, while active months are colored to represent the number of transplants in that segment.

ever, the overall number of transplants was the same as in the base case, because NEAD chains competed with traditional KPD opportunities. Prioritizing NEAD chains meant that about 60% of all paired donations were chain segments, as compared with 40% of paired donations in the base case.

Impact of differing numbers of NDDs

When large numbers of NDDs are available, NEAD chains become less attractive compared to DPD, as shown in Figure 5. NDDs and bridge donors compete with each other and with incompatible pairs for matches, so the bridge donors become idle over many months rather than immediately donating as they would in DPD.

This suggests that NEAD chains are most beneficial compared with DPD when few NDDs are available. We tested the scenario where only one NDD entered the program at the first month, and no more NDDs joined. We found that if the NDD had blood-type O, the NEAD chain transplanted an average of 10 people in about five segments over the 2 years. This simulation was consistent with the success of the single reported NEAD chain, which has transplanted 10 people over 1 year and required several patients to undergo desensitization to enable the continuation of the chain (8). However, in our simulation there was no difference between the total number of people transplanted

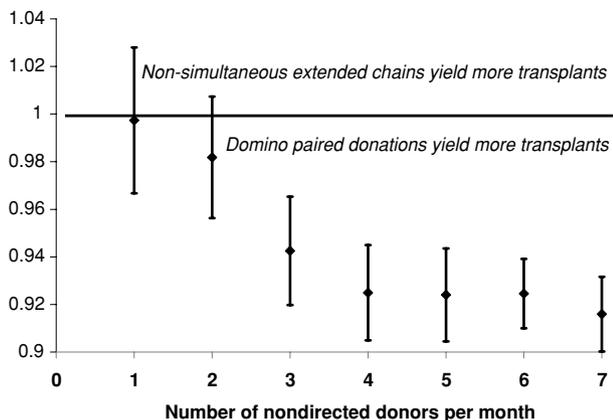


Figure 5: Ratio of the number of transplants achieved using nondirected donors (NDDs) in nonsimultaneous extended altruistic donor (NEAD) chains to the number of transplants achieved using NDDs in simultaneous domino paired donation (DPD), as the number of NDDs available per month varies.

when a solitary NDD began a NEAD chain versus when the solitary donor began a DPD. Rather, some matches that would otherwise have been made using incompatible pairs in traditional KPD were instead made with the NEAD chain.

Blood types of NDDs, bridge donors and paired donors

One reason that NDDs are so valuable to KPD is that their blood types are like those of the U.S. population, unlike incompatible pairs, among which blood-type O donors are scarce. Unfortunately, the desirable blood-type distribution of NDDs will be lost after the first segment of the NEAD chain. Figure 6 illustrates that bridge donors will almost never have blood-type O and that about 45% of bridge donors will have blood-type AB.

One may hypothesize that NEAD chains would function better if AB donors were proscribed, or at least disfavored, as bridge donors. We tried penalizing AB bridge donors in the matching algorithm, so that we always chose transplants where there was any alternative to choosing an AB bridge donor. Neither the percentage of bridge donors that are AB, nor the total number of transplants, differed from the base case (325.7 vs. 323.4, and 42% vs. 47%, respectively, $p = 0.3$). This suggests that alternative transplant arrangements that avoid choosing an AB bridge donor are almost never possible. When AB donors were disallowed as bridge donors, the total number of transplants was significantly lower than when AB bridge donors were allowed (302.0 vs. 323.4, $p < 0.01$); the restriction meant that many otherwise allowable matches were not made.

Allocating NDDs to DPD will certainly change the blood-type profile of the kidneys offered from living donors to recipients on the waitlist. Using DPD means that blood-

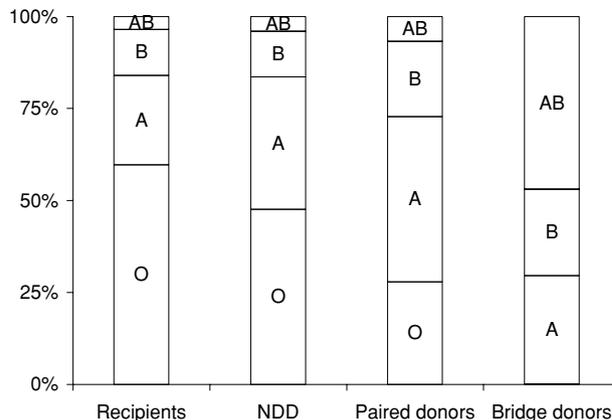


Figure 6: Blood-type distributions of: recipients with incompatible donors, nondirected donors, donors with incompatible recipients and bridge donors. Bridge donors are the connections between segments of a nonsimultaneous extended altruistic donor (NEAD) chain.

type O NDDs will rarely benefit the type O waitlist. However, using DPD does mean that every NDD will result in one donation to the waitlist. In comparison, NEAD donor chains will result in zero donations of any blood type to recipients on the waitlist. Table 3 includes a number of kidneys donated to waitlist recipients in the NEAD chains case, but this only reflects our study design, which specifies that bridge donors who have not matched during the study duration should donate to someone.

Impact of bridge donor renege rate

There are no data on which to base an estimate of the bridge donor renege rate. We detail the results of our sensitivity analysis in Figure 7. If the renege rate is

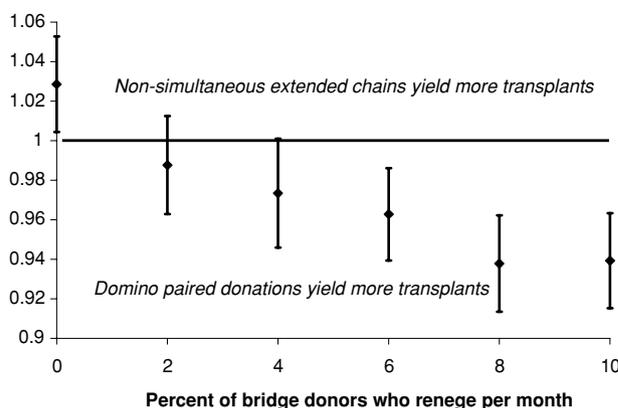


Figure 7: Ratio of the number of transplants using nondirected donors (NDDs) in nonsimultaneous extended altruistic donor (NEAD) chains to the number of transplants using NDDs in domino paired donation (DPD), as the bridge donor renege rate per month varies.

exactly zero, then NEAD chains will enable slightly more transplants than DPD. However, if the renege rate is 2%, then the two strategies enable about the same number of transplants, and if the renege rate is higher than 5%, then NEAD chains will yield fewer transplants than DPD.

Donor renegeing broke a NEAD chain at Johns Hopkins. In this instance there was a long interval between the intended recipient's transplant from an NDD and the request for the bridge donor to participate in the next transplant. We are not aware of any other chains that have been broken by an unwilling or ineligible bridge donor. However, only short-term implementation data are available, and long waits between the time one's intended recipient gets a kidney and the time one is asked to donate seem certain to increase the risk of renegeing. During a wait of several months, the donor's life circumstances may change or the intended recipient may die or lose his allograft and this could affect the donor's willingness to proceed.

Discussion

NDDs would facilitate more transplants by contributing to KPD programs than by donating directly to recipients on the deceased donor waitlist. DPD matches NDDs to incompatible pairs for a simultaneous exchange that would end in one donation to a recipient on the waitlist. In contrast, NEAD chains end in one donor becoming a bridge donor, waiting to give to another incompatible pair at a later time.

NEAD chains seem a boon to paired donation: one NDD creates a chain reaction by donating a kidney to a stranger, and every recipient of such kindness has a person in his life who donates a kidney to the next stranger. However, the actual advantages of NEAD chains over DPD are mostly illusory. Both NEAD chains and DPDs make use of the favorable blood-type distribution among NDDs, but in both cases the advantage disappears after the first transplant in the chain. Bridge donors do not share the favorable blood group profile of the original NDDs, so they might have to wait for long stretches of time before they are matched for their donations, increasing the risk that they will reconsider their donations.

Relaxing reciprocity in DPD allows the hard-to-match donor to find a match in the vast waiting list, while in NEAD chains the hard-to-match bridge donor can wait for months in the smaller incompatible pool and may remain unmatched. As for relaxing simultaneity to allow longer exchanges, it has been shown that very few additional transplants would result from allowing any-length exchanges versus three-way exchanges (16), and so it is unlikely that NEAD chains will increase the number of transplants performed. A long wait between a donor's intended recipient getting a transplant and the donor's future nephrectomy could be a disadvantage if there is even a small chance

that the donor will withdraw consent or become ineligible for health reasons. Additionally, it may be viewed as coercive to ask a donor's consent for his own nephrectomy many months after his intended recipient has been transplanted, especially if the recipient has had a poor outcome.

We acknowledge the following limitations of our study. All donor and recipient data are simulated, because no broad-based US registry has yet collected the characteristics of a generalizable pool of incompatible pairs. However, our incompatible pair demographics and match rate predictions are consistent with the Netherlands' national registry experience (1,17). Our prediction of the absolute number of transplants achieved is sensitive to changes in the modeling of PRA and recipient sensitization, and sensitive to the renege rate among bridge donors in NEAD chains.

We predict that in a program that uses NEAD chains, many people will receive transplants through this modality; however, our findings suggest that the same number could have been transplanted using DPDs and traditional paired donations. In every scenario tested save for one (where the renege rate is identically zero), NEAD chains offered no advantage over DPD in the number of transplants performed.

NEAD chains would shift the benefits of NDDs toward the pool of recipients with incompatible donors and away from recipients on the deceased donor list. As such, NEAD will likely impact the ethnic distribution of the beneficiaries of nondirected donation, by removing one source of transplants for the 52% nonwhite population of the waitlist and devoting it entirely to the population of recipients in KPD programs, who are 73.1% white (12).

A 2001 consensus conference on living NDDs recommended that NDD kidneys be allocated to patients with the highest priority on the UNOS waiting list (18). Balancing utility and justice was the goal of the organ allocation system adopted for deceased donation in the United States, and the consensus opinion mirrored these ethical tenets. However, the recommendations predated the inclusion of NDDs in DPD or NEAD chains. There remains no broadly accepted allocation system for NDDs. In addition to DPD and NEAD chains, several other allocation philosophies are currently in clinical practice at centers doing large numbers of NDD transplants. We previously described these allocation strategies and argued that DPDs best balanced the principles of utility and justice (6). Unlike DPDs, NEAD chains do not directly add kidneys to the deceased donor pool where they can be allocated by current UNOS policies and achieve the current standard of justice. Instead, NDD kidneys are allocated exclusively to incompatible pairs. It was thought that the utility of the greater number of transplants enabled by NEAD chains might offset concerns about justice. The results presented here suggest that no such windfall of transplants will result

from NEAD chains in comparison to DPDs. Under these circumstances, it could be argued that DPD provides a superior balance of equity and justice.

KPD programs face enormous hurdles in finding suitable matches for incompatible pairs. Exploring new ideas for getting incompatible pairs to transplantation can only help the individual patients and the wider transplant community. Importantly, this study shows that neither DPD nor NEAD chain matching approaches is clearly superior in terms of the number of transplants achieved. Both approaches allow NDDs to more fully realize their altruism by enabling more transplants than direct donation to the waiting list. Due to the inherent limitations of simulations we welcome demonstration trials using both strategies. It will only be through multicenter studies uncovering the real life behavior of bridge donors and the capability of programs to implement DPDs that the true effectiveness of these approaches will be discovered.

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