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Brief Communication

Broken Chains and Reneging: A Review of 1748 Kidney Paired Donation Transplants

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Concerns regarding the potential for broken chains and "reneges" within kidney paired donation (KPD) and its effect on chain length have been raised previously. Although these concerns have been tested in simulation studies, real-world data have yet to be evaluated. The purpose of this study was to evaluate the actual rate and causes of broken chains within a large KPD program. All patients undergoing renal transplantation through the National Kidney Registry from 2008 through May 2016 were included for analysis. Broken chains and loops were identified. A total of 344 chains and 78 loops were completed during the study period, yielding a total of 1748 transplants. Twenty broken chains and one broken loop were identified. The mean chain length (number of transplants) within broken chains was 4.8 compared with 4.6 of completed chains (p = 0.78). The most common causes of a broken chain were donor medical issues incurred while acting as a bridge donor (n = 8), donors electing not to proceed (n = 6), and kidneys being declined by the recipient surgeon (n = 4). All recipients involved in a broken chain subsequently received a transplant. Based on the results, broken chains are infrequent, are rarely due to lack of donor motivation, and have no significant impact on chain length.

Abbreviations: cPRA, calculated panel reactive antibody; CT, computed tomography; DPD, domino paired donation; KPD, kidney paired donation; NDD, nondirected donor; NEAD, nonsimultaneous extended altruistic donor; NKR, National Kidney Registry

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Introduction

Kidney paired donation (KPD) affords the opportunity for patients with chronic kidney disease and an incompatible donor a means to obtain the benefits of living donor transplantation while avoiding costly desensitization regimens. Since its inception in 1986, many barriers to KPD have been overcome, including the development of national registries, shipping kidneys via commercial flights, and incorporation of nondirected donors (NDDs) into chains (1–4). One of the first suggested barriers to overcome was the risk of a donor deciding against donation, initially referred to as "reneging," once their intended (but incompatible) recipient had received a kidney transplant (5). To mitigate this risk, the collaborators in the first successful kidney exchange recommended that all donor operations be performed simultaneously (5). Although this approach was possible with the simplest forms of KPD, increasingly complex strategies evolved utilizing nonsimultaneous donor operations. This furthered concerns regarding the potential consequences of a donor withdrawing their intent to donate after initiation of a chain sequence (3).

We sought to determine the specific causes of broken chains in a modern KPD cohort and the prevalence of donors who elected not to donate (i.e., reneged) after their intended recipient had received a transplant. To study the impact of donors backing out on KPD outcomes, early reports relied on computer simulations requiring hypothetical data points because little real-world data were available (6,7). These hypothetical simulation data were highly variable and had significant influence on simulated chain lengths. In an effort to clarify the actual rate of donors deciding against donation and to determine the real-world effect on number of transplants facilitated, our study reviewed outcomes from the United States's largest national KPD program. Furthermore, we aimed to evaluate the rates of broken chains as well as the effect of broken chains on the number of transplants facilitated.

Materials and Methods

A retrospective review was performed of all patients who underwent renal transplantation via KPD facilitated through the National Kidney Registry (NKR). The NKR is a 501(c)(3) nonprofit organization composed of 77 participating transplant programs throughout the United States. A description of the National Kidney Registry's method of pair enrollment, evaluation, and chain creation has been discussed in detail previously (8,9).

Chains are initiated by NDDs (sometimes referred to as *altruistic* donors) and are composed of multiple clusters of transplants that are linked together by a bridge donor (Figure 1A). As such, a single chain may require multiple bridge donors before it is completed. A *bridge donor* is defined as any patient who donates their kidney >1 day after their intended but incompatible recipient has received a kidney. Although any donor whose surgery is performed after their intended recipient has received a kidney has the ability to then decline donation, bridge donors have been the focus of previous studies because of their potential for prolonged wait times and perceived increase risk of backing out on donation. Depending on the preference of the bridge donor, he or she may donate to the waitlist and finish the chain or wait until a compatible recipient is found in a new cluster to continue the chain. Unlike chains, loops do not utilize an NDD, and the final donor in the sequence donates to the recipient of the first incompatible pair (Figure 1B). After a chain or loop is created by the computer software, it is offered to participating centers. Pending approval by all involved centers, a crossmatch is performed and, if appropriate, the cases are scheduled.

A *broken chain* was defined as an ongoing sequence of transplants initiated by an NDD and subsequently canceled because of donor, recipient, or surgeon issues. Broken chains and loops were identified and the causes of the break were obtained via review of NKR records and communication with involved centers. Particular attention was paid to broken chains in which the donor did not undergo donor nephrectomy despite the intended recipient having received a kidney (Figure 1C). Donors who elected not to proceed and who provided no persuasive medical rationale for withdrawal were used to calculate a "renege rate." A subset of broken chains termed *real-time swap failures* were also identified. Real-time swap failures were defined as a chain that was broken on the day of the planned surgery (Figure 1D). Real-time swap failures were evaluated separately because they require quick and resourceful efforts to fix. Centers at which a broken chain or loop has occurred are requested to submit an explanation of the event either by email or in a telephone discussion with the NKR.

All patients who underwent renal transplantation from 2008 through May 2016 within the NKR were included in the analysis, and no patients were excluded. Details regarding chain and loop length as well as bridge donor utilization were reviewed. All data reported in this study were collected in a centralized database maintained by the NKR and deidentified prior to review. Descriptive statistical analysis was performed. The study was approved by the UCLA institutional review board.

Results

A total of 344 chains and 78 loops were initiated during the study period, yielding a total of 1748 transplants (Table 1). Chains (completed and broken) resulted in 1568 transplants with a mean chain length of 4.6 (SD ±3.71) transplants including active chains that had not yet been completed. Chain lengths ranged from one to 35 transplants facilitated, with two being the most common chain length (Table 2). Loops yielded 180 transplants with a mean length of 2.3 transplants (SD ±0.63). Loop lengths ranged from two to five transplants facilitated, with two being the most common loop length (Table 2). A total of 407 bridge donors were utilized over the study period, and the use of bridge donors decreased over time (Table 3). Overall, 36% of chains utilized bridge donors over the study period. Broken chains were identified in 20 cases (5.8% of chains), and a single instance of a broken loop was documented (1.2% of loops). The mean length of broken chains was 4.8 (SD ±4.46) compared with a mean length of 4.6 (SD ±3.96) for unbroken chains. No statistically significant difference in mean chain length was identified when comparing broken versus unbroken chains ($p = 0.78$). Within this cohort of patients, 28% had a calculated panel reactive antibody (cPRA) >80%, and approximately 40% of patients were unsensitized (cPRA 0%) (10). Data for 2016 revealed that approximately 3500 match offers resulted in 399 transplants via 87 chains and 10 loops. This required ≈1200 crossmatch commencements (11).

Table 4 lists the reasons provided for a broken chain or loop. The most common causes of a broken chain were donor medical issues incurred while acting as a bridge donor (n = 8), donors electing not to proceed (n = 6), and kidneys being declined by the recipient surgeon (n = 4). Chains broken because of donors electing not to proceed represented 1.7% of all chains. The six donors who elected not to proceed represented 1.5% of the 407 bridge donors and 0.3% of all donors over the study period.

Real-time swap failures as a subset of broken chains were identified in seven cases and as a subset of broken loops in one case (Table 4). Of interest, a single case of real-time swap failure occurred that was "repaired" the same day and facilitated an additional seven transplants. In this case, the kidney was declined by the recipient surgeon. The center performing the donor nephrectomy was able to utilize this kidney for a recipient of another incompatible pair that had been enrolled within the NKR, and the chain was able to continue.

Discussion

The National Kidney Registry is the United States's largest national KPD registry and helped facilitate almost two-thirds of all KPD transplants performed in 2015 within the United States (10,12). In this review of 1748 transplants facilitated by the NKR, we found that broken chains are uncommon (5.8%) and have no significant effect on overall chain length. Within this cohort, the etiology of broken chains was most frequently due to a donor medical issue incurred while bridging. In six cases, a chain was broken because the bridge donor elected not to proceed. Based on these results, other KPD programs can be reassured that the risk of chains breaking

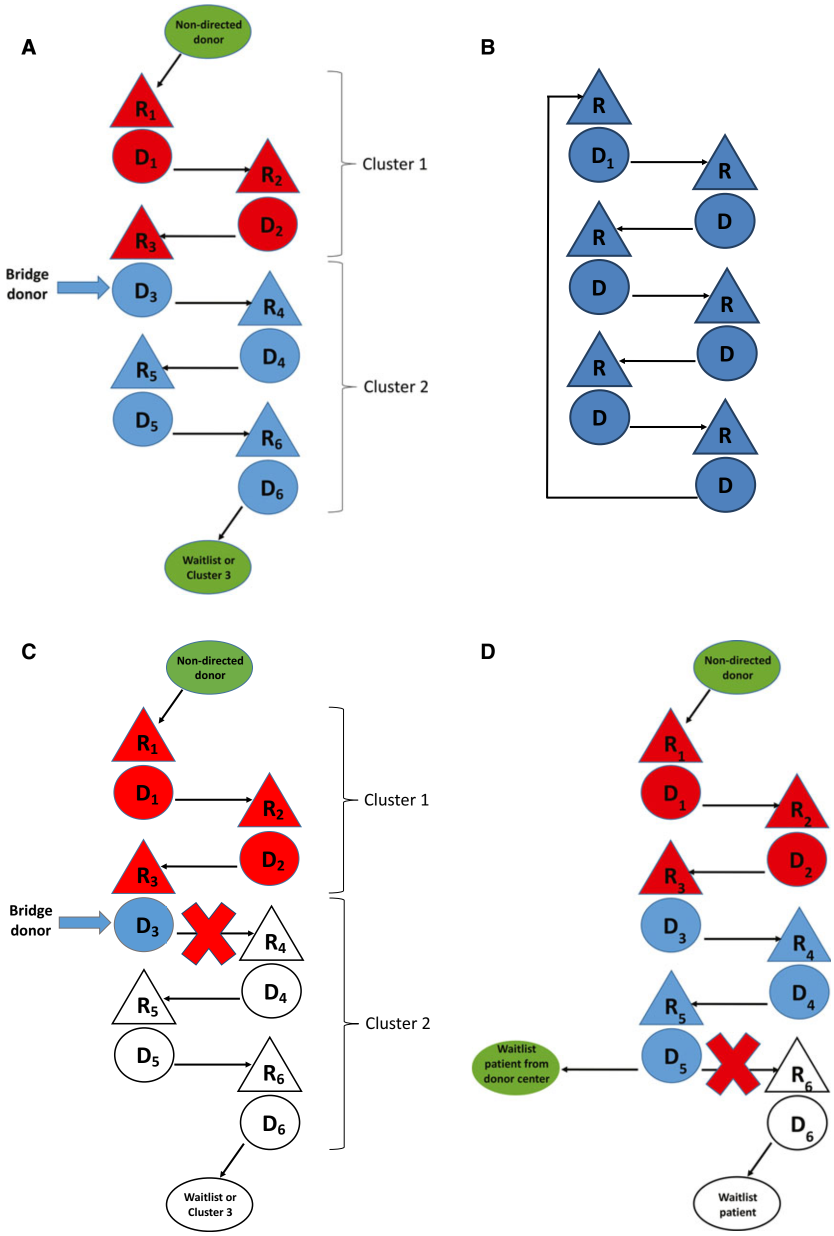

Figure 1: (A) Completed chain. A chain is composed of clusters and is initiated by a nondirected donor. The clusters of transplants may be separated in time by days or weeks. A "bridge donor" (heavy arrow) links these clusters together and, by definition, is a patient who donates a kidney >1 day after the intended but incompatible recipient (R3) has received a kidney. The final donor in a cluster (D6) can be made into a new bridge donor and link to a future cluster or end the chain by donating to a patient on the waitlist. (B) Completed loop. A loop is a sequence of transplants that is not initiated by a nondirected donor and terminates with the last donor donating to the initial recipient of the incompatible pair. No bridge donors are created in this sequence, and the donors will typically all donate on the same day. (C) Broken chain due to a bridge donor. In this sequence of transplants, the bridge donor (D3) failed to undergo donor nephrectomy despite their intended recipient (R3) having already received a kidney. (D) Real-time swap failure. A real-time swap failure is a chain that breaks on the day of planned surgery. Depicted is a case in which a recipient center surgeon (patient R6) has declined the kidney from a donor who has already undergone donor nephrectomy (D5). In this scenario, the donor center is able to utilize the kidney (D5) for a local waitlist patient who was identified as a backup prior to initiation of the chain.

is low and that the policy of simultaneous anesthesia for donors can be discontinued to improve logistics and to minimize donor disincentives.

Within the United States, one-third of end-stage renal disease patients with a potential living donor will be incompatible based on either blood type or HLA

Table 1: Chain and loop details

Category	Count	Mean length	Transplants
Active/ended	324	4.5	1472
Broken	20	4.8	96
Chain total	344	4.6	1568
Loops	78	2.3	178

Table 3: Utilization trend of bridge donors each year since the beginning of the National Kidney Registry

Year	Bridge donors, n	Chains, n	Bridge donors per chain
2008	9	4	2.3
2009	29	9	3.2
2010	61	28	2.2
2011	75	36	2.1
2012	54	46	1.2
2013	37	69	0.5
2014	49	59	0.8
2015	53	72	0.7

antibodies (13). In its original form, first reported by Park et al, multiple incompatible pairs would simultaneously undergo donor nephrectomy and subsequent renal transplantation to avoid the risk of a donor backing out (referred to as a "renege") (5). Over the following decade, KPD evolved to incorporate NDDs through domino paired donation (DPD), and the practice of simultaneous donor operations continued (14). With development of nonsimultaneous extended altruistic donor (NEAD) chains in 2009, new concerns were raised that bridge donors created through this strategy might introduce even greater risk for donor reneging as a result of increased donor wait times (3,6,7).

Review of the limited previous literature involving donor reneging offers insight into perceptions of the issue. In their 2009 simulation analysis comparing two different chain strategies (DPD and NEAD), Gentry et al estimated a bridge donor renege rate of 5% per month for NEAD chains. The simulation was then run over 24 mo and resulted in 35% (17 of 48) of chains broken by donor reneging, significantly higher than our finding of 1.7% (six of 344). In our study, we identified six cases of donors electing not to proceed among a group of >400 bridge donors, yielding a real-world bridge donor renege rate of 1.5%, also much lower than previous estimates. In addition, although bridge donors have been the focus of prior studies based on a perceived increased renege risk given their need to delay donation, any donor has the potential to decline to donate if he or she does not donate simultaneously with other donors in a chain. As previously noted in a report by Kute et al, this means that a donor whose surgery is scheduled to begin even a few minutes or hours after the intended recipient has received a kidney retains the ability to back out and disrupt the sequence of planned transplants (15). This would suggest that our bridge donor renege rate of 1.5% is actually an overestimate of the "at risk" population for this potential problem.

The impact of donor renege rates on further evolution of KPD is significant. Unlike traditional two- or three-way

Table 2: Number of transplants facilitated by each chain/loop length

Chain length (number of transplants per chain)	Number of chains (n = 344)	Total number of transplants (n = 1568)	Loop length (number of transplants per loop)	Number of loops (n = 78)	Total number of transplants (n = 180)
1	21	21	1	0	0
2	93	186	2	60	120
3	74	222	3	13	39
4	38	152	4	4	16
5	29	145	5	1	5
6	24	144	–	–	–
7	13	91	–	–	–
8	13	104	–	–	–
9	11	99	–	–	–
10	7	70	–	–	–
11	5	55	–	–	–
12	6	72	–	–	–
13	2	26	–	–	–
16	3	48	–	–	–
19	1	19	–	–	–
21	1	21	–	–	–
28	1	28	–	–	–
30	1	30	–	–	–
35	1	35	–	–	–

Table 4: Causes of broken chains and loops

#	Details regarding broken chain	Year	Real time swap failure
1	**Donor incurred significant career and personal changes during prolonged period of bridging and many failed crossmatches**	2008	–
2	**Donor elected not to proceed**	2008	–
3	**Donor was lost to follow-up after intended recipient received kidney**	2008	–
4	**Donor sick at time of original surgery date, then later elected not to proceed**	2009	✓
5	**Donor elected not to proceed**	2009	–
6	Donor declined by center after suffering rotator cuff injury requiring chronic pain medication	2010	–
7	Donor declined by the National Kidney Registry after second nuclear GFR test <80 (79 down from 82)	2010	–
8	Donor declined by center after becoming pregnant	2012	–
9	**Donor elected not to proceed after change in unspecified lab values and spousal pressure, although remained a candidate per donor center protocols**	2012	–
10	Donor declined by center after reevaluation of computed tomography urogram, which revealed Bosniak 2F cyst	2012	–
11	Aborted donor surgery due to intraoperative donor complication	2012	–
12	Aborted donor surgery due to intraoperative donor instability while establishing pneumoperitoneum	2013	✓
13	Kidney declined by recipient surgeon	2013	✓
14	Recipient medical issue	2013	✓
15	Kidney declined by recipient surgeon	2014	✓
16	Donor developed significant tinnitus	2014	–
17	Recipient medical issue (loop)	2014	✓
18	Donor declined by center for newly diagnosed prostate cancer	2014	–
19	Donor declined by center for decline in renal function	2014	–
20	Kidney declined by recipient surgeon	2015	✓
21	Kidney declined by recipient surgeon	2016	✓

Cases in bold were considered as donor reneges.

exchanges, use of an NDD in both DPD an NEAD mitigates the risk of donor reneges for participating pairs, as these strategies perform the transplants in sequence. A donor backing out in either of these strategies would not irreparably harm incompatible pairs further down the chain, as their "bargaining chip" (their incompatible donor) is maintained. The potential consequences for participants in chain transplants performed out of sequence, first reported by Butt et al in 2009, are more severe (2). It is imperative that all patients who are considering KPD undergo thorough counseling regarding these potential risks and benefits and provide informed consent prior to enrollment.

KPD policies that recognize the potential for harm and are designed to facilitate rapid correction when it occurs are essential. The National Kidney Registry, for example, has a detailed policy that prioritizes how future chains will end such that mending broken chains is prioritized second only to prior NDDs in need of a transplant (9). This policy permits utilization of the entire donor pool to drive the creation of chains that quickly repair the harm incurred by the participants. More specifically, when a broken chain occurs and a recipient is left without a donor, the NKR prioritizes the creation of a new chain for which the final donor in the sequence would terminate with the "orphaned" recipient. This holds true even if that chain generates fewer transplants than an alternative sequence would allow. Within the NKR, all recipients involved in a broken chain have subsequently received a transplant, typically with a wait time <6 mo from reactivation within with the NKR. Furthermore, a strength of independent organizations such as the NKR is that they are able to implement policy that rapidly adapts to new challenges as KPD continues to evolve.

Our finding of a real-world renege rate of 1.5% also has implications for interpretation of these previous simulation studies' average chain length. Gentry el al concluded that, using their base case scenario variables (bridge donor renege rate of 5% per month), an NDD-initiated chain would on average result in only 1.9 transplants. We found a mean chain length of 4.8 in broken chains and 4.6 in completed chains. Interestingly, despite previous studies' focus on donor reneging as a significant cause of broken chains, we found that medical issues incurred by donors while bridging were actually the major contributor to broken chains. These medical issues were varied and often could not be anticipated by the transplant centers or the NKR. They included pregnancy, trauma, significant tinnitus, and rising prostate-specific antigen resulting in a new diagnosis of prostate cancer. Conversely, donor medical issues such as an interval decline in GFR and a Bosniak 2F cyst could potentially be anticipated and have resulted in revision of NKR policy. Donor computed tomography (CT) scans must now be uploaded for recipient centers to review, and a nuclear renal scan is required for donors with creatinine clearance ≤85 mL/min by 24-hour urine collection. Bridge donor medical issues accounted for 40% of broken chains, whereas donors electing not to proceed accounted for 25% of all broken chains. Interestingly, 20% of broken chains resulted from the kidney being declined by the recipient surgeon. In all cases in which the kidney was declined by the recipient surgeon, the kidneys were able to be utilized by the originating center that performed the donor nephrectomy.

Real-time swap failures as a subset of broken chains occurred in 35% of cases. NKR protocols are in place to rapidly address such cases, and in one instance, a real-time swap failure was mended in a manner such that an additional seven transplants were facilitated. These protocols include attempting to cancel or reschedule the remaining chain as soon as a real-time swap failure is identified. If any of the donor surgeries cannot be aborted, the NKR works to immediately identify a bridge or NDD to end a chain to the recipient who did not receive a kidney. NKR policy also mandates that both donor and recipient institutions assign local waitlist backup so that no kidney is discarded should there be an issue on either side of the exchange. Furthermore, the recipient center is held financially responsible for shipping and logistics in the case where a kidney is shipped back to the donor center and utilized after being declined by the recipient center surgeon. The idea of real-time swap failures was not included in prior simulation analyses and highlights a significant limitation of such studies (6,7). Simulation analyses can only be as good as the variables that are used in the model, and concepts such as donor motivation to follow through with a promise are difficult to estimate in simulation studies.

Numerous factors have contributed to the low rate of broken chains within this cohort. As noted, donor motivation to follow through with surgery is a major contributor to the success of KPD. If this element were lacking, then KPD almost certainly would not exist in the form it does today. Patients are only enrolled into the program once they have completed a thorough evaluation including medical, surgical, and psychiatric evaluations in addition to laboratory work, age-appropriate screening tests, and a CT scan. This likely selects for individuals more motivated to donate. Cryopreservation of donor blood has also minimized donor disincentives by decreasing laboratory visits for blood draws when new chains are constructed and may have prevented the first renege incurred by the NKR. Furthermore, the NKR strategy has evolved over time to focus on chain frequency rather than chain length. Longer chains (and loops) are logistically more complicated and thus are prone to breaking. In fact, >80% of chains during the study period were chains lengths of six transplants or fewer, and 77% of loops resulted in only two transplants.

Decreasing the utilization of bridge donors and minimizing bridge donor wait time has also become a priority. This is reflected in a median bridge donor wait time of only 13 days in 2015 compared with 59 days in 2008 and 41 days in 2009 (10). These changes were undertaken in an effort to simplify logistics and minimize the impact on bridge donors and have coincided with a decreased rate of donors electing not to proceed. Five of the six donor reneges in this study occurred during the first 4 years of the NKR when, on average, more than two bridge donors per chain were being utilized (Table 3). In the subsequent 4 years, less than one bridge donor was used per chain (on average), and only one donor renege occurred. Although wait times of bridge donors have been described as being as long as 1 year in the NKR and 2 years in the Alliance for Paired Donation, every effort should be made to reduce the time a bridge donor waits so that the impact on his or her life is minimized. Attempting to define a "maximum duration" for bridge donation thus omits the fact that each potential bridge donor has a unique set of life circumstances that may make him or her suitable for short-term bridging, long-term bridging, or avoidance of bridging altogether. This decision is best left to donors and their KPD providers to determine on a case-by-case basis.

The findings within this study are a testament to the generosity and commitment of all living donors and should be considered in future KPD policy development. Although our study confirms that the risk of donors electing not to proceed is low, it is imperative that all of those involved in supporting KPD continue to maintain the autonomy of donors to change their mind until the moment they undergo anesthesia. Furthermore, although previous studies have used the term *renege* to describe the potential risk, our feeling is that this term can imply nefarious intentions by the donor when in fact more complex considerations may be involved that force the donor to decline to donate. We believe our results refute donor reneging as a significant concern within modern-day KPD such that the term *renege* should be retired from the KPD lexicon.

Our study is not without limitations. Selection bias is a concern in any retrospective analysis, and our cohort represents only a sample of the KPD transplants performed in the United States. An additional limitation of the study is that reporting of the cause of a broken chain was voluntary. Although every effort was made to determine whether a bridge donor had a justifiable cause for failing to donate, it is reasonable to consider that the provided explanations were a means to avoid following through with donation. If we include all bridge donors who failed to donate except for those declined by donor centers or recipient surgeons, the rate increases from 1.5% to 1.7%, yet remains lower than prior hypothetical rates.

In conclusion, our results demonstrate that the risk of a donor electing not to proceed once involved with a KPD chain is low and an infrequent cause of broken chains, with an estimated renege rate of 1.5%. In the rare instance in which a donor declines to proceed with donation, there is no significant effect on chain length, as has been speculated previously by simulation studies. In addition, all recipients involved in a broken chain subsequently received a transplant.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Jeffrey Veale is a member of the National Kidney Registry (NKR) medical board. Joe Sinacore is paid by the NKR in his role as the director of education and development. The NKR receives fees from participating centers to facilitate paired exchange transplants and to manage the logistics process. The other authors have no conflicts of interest to disclose.

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