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Asynchronous, Out-of-Sequence, Transcontinental Chain Kidney Transplantation: A Novel Concept

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The organ donor shortage has been the most important hindrance in getting listed patients transplanted. Living kidney donors who are incompatible with their intended recipients are an untapped resource for expanding the donor pool through participation in transplant exchanges. Chain transplantation takes this concept further, with the potential to benefit even more recipients. We describe the first asynchronous, out of sequence transplant chain that was initiated by transcontinental shipment of an altruistic donor kidney 1 week after that recipient's incompatible donor had already donated his kidney to the next recipient in the chain. The altruistic donor kidney was transported from New York to Los Angeles and functioned immediately after transplantation. Our modified-sequence asynchronous transplant chain (MATCH) enabled eight recipients, at four different institutions, to benefit from the generosity of one altruistic donor and warrants further exploration as a promising step toward addressing the organ donor shortage.

Key words: ABO incompatibility, altruistic donation, anonymous donation, shortage of donor organs, living donor transplantation, cold ischemia, donor exchange, renal transplantation, organ procurement/non-directed living kidney donation, living donor exchange, long-distance transportation

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Introduction

According to the United Network for Organ Sharing (UNOS), over 70 000 people are currently listed, awaiting kidney transplantation nationwide, but only 13 148 living and deceased kidney donors were available in 2008 (1). One possible solution is to develop a national living donor kidney exchange program (2–5). Patients with willing, incompatible living donors would receive a compatible kidney through a 'donor exchange' with another incompatible pair. Successful programs utilizing paired exchanges exist in the Netherlands (2) and Korea (5,6). An estimated additional 2000 kidney transplants could be performed annually if a similar program were implemented in the United States (7,8). Most exchanges could take place locally, but donors or organs may occasionally be required to travel.

The first US paired kidney exchange ('SWAP') was performed in 2000 at Rhode Island Hospital (9). The two donor/recipient pairs were ABO-incompatible with each other, but compatible with a member of the other pair. This procedure provided an alternative for candidates with incompatible living donors and served to facilitate additional donor exchanges (10). As transplantation has evolved to include altruistic donors, new strategies for exchanging living donor kidneys have developed, including 'domino' and 'chain' transplantation (11,12).

'SWAP' donation entails simultaneous donor operations to prevent either donor from backing out after his/her incompatible recipient has received a kidney from the other donor (Figure 1). Similarly, in chain transplantation, each successive donor donates his/her kidney to the next recipient after their own incompatible recipient has received a kidney from the preceding donor in the chain. This stepwise donation ensures that recipients do not lose their 'bargaining power' (i.e. their incompatible donor with a kidney to donate) if the chain is unexpectedly broken due to illness or other unforeseen circumstances.

Approximately one-third of patients who have willing, living donors will be incompatible due to either ABO-blood type or HLA incompatibility (3) and will end up listed for a deceased donor kidney transplant. A national program

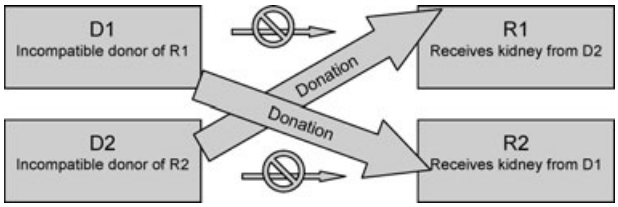

Figure 1: Paired SWAP donation involves anesthetizing both donors simultaneously, to prevent either one from backing out after their recipient has received a kidney from the other donor.

offering these donors the opportunity to provide a kidney for another recipient, in exchange for a kidney for their incompatible recipient, could result in the most significant expansion of the donor pool since the Uniform Determination of Death Act was established in 1981.

We describe the first modified-sequence asynchronous transplant chain (MATCH) performed in the United States (Figure 2), where the first recipient in the chain, R1, received her kidney from an altruistic donor 1 week after her incompatible donor, D1, had already donated his kidney to the subsequent recipient, R2.

Materials and Methods

This chain involved several transplant centers, including New York-Presbyterian Hospital/Weill Cornell Medical Center, Stanford University Medical Center, California Pacific Medical Center and University of California, Los Angeles (UCLA) Medical Center. Three transcontinental shipments of living donor kidneys were performed, utilizing local organ procurement organizations (OPOs) and commercial airlines. Participating donors underwent laparoscopic donor nephrectomies at their hometown institutions. A compatible altruistic donor for R1 was found in New York City (NYC) through the National Kidney Registry (NKR). The pairs transplanted in Los Angeles (LA) were matched through the paired kidney exchange program at UCLA. The remaining transplant pairs were matched through NKR.

Information regarding the donor/recipient pairs is summarized in Table 1.

Results

We report a living donor kidney transplant chain involving eight incompatible donor/recipient pairs, initiated by an altruistic donor in NYC whose kidney was transported by commercial airline to LA for transplantation. The chain was conducted out of sequence, involved four different transplant centers and has resulted in eight transplants to date. One intrastate and three transcontinental shipments of unaccompanied live donor kidneys were transplanted with 8, 14, 12 and 11 h of cold ischemia, respectively. The kidneys were transported and transplanted without incident. All recipients remain off dialysis.

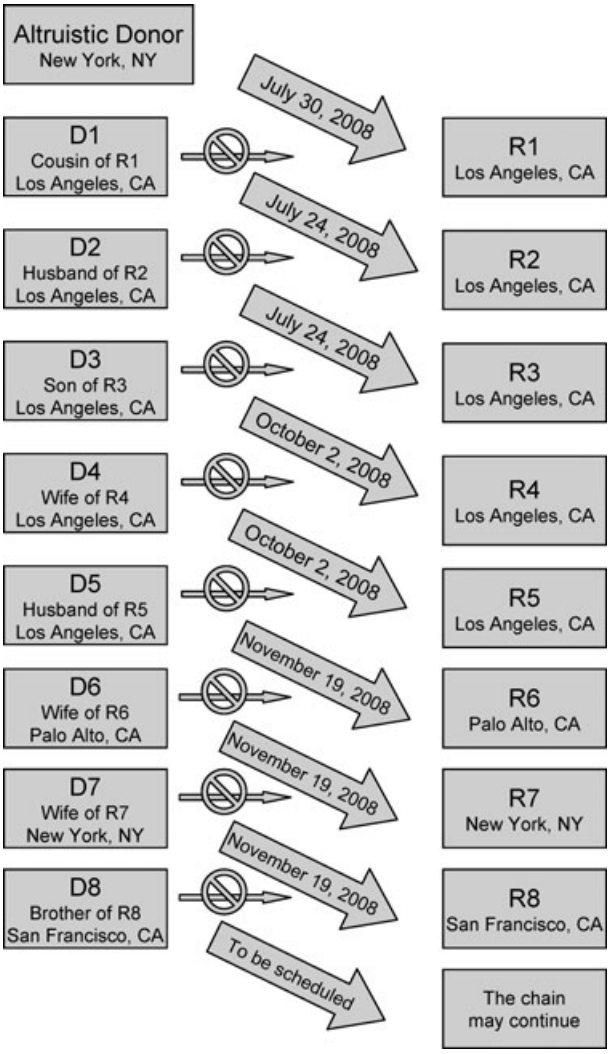

Figure 2: Modified-sequence asynchronous transplant chain (MATCH) conducted with initial altruistic donor kidney flown from New York to Los Angeles. Note that D1 donated his kidney 1 week before R1 received hers. Donor nephrectomies were performed at the same hospital as their incompatible recipients' transplants. Kidneys from the altruistic donor, D5, D6 and D7 were all transported, unaccompanied, by commercial flight to the next recipient's hospital.

The logistics of our transplant chain are outlined in Figure 2. The results are detailed in Table 2.

Discussion

The concept of chain donation was first proposed by Michael Rees, a urologist at Ohio's University of Toledo Medical Center, who launched the first kidney transplant chain in the United States in 2007, involving 10 recipients (13,14). The chain presented here is the fourth performed in the United States and the first chain conducted out of sequence.

Table 1: Demographics of donors and recipients, including incompatibility data and presence of donor-specific antibody

Donor/ Recipient	Age	Sex	Race	Blood type	Incompatibility data	Recipient diagnosis	Dialysis (years)
D1	51	Male	Caucasian	O+	T-cell crossmatch	Polycystic kidney	
R1	52	Female	Caucasian	A+	A2, B60	disease	0
D2	44	Male	Hispanic	A+		Chronic	
R2	36	Female	Hispanic	B+	ABO-incompatible	glomerulonephritis	1
D3	30	Male	Hispanic	O+	T & B-cell crossmatch	Systemic Lupus	
R3	52	Female	Asian	A+	A2, B44, DR13	erythematosus	1.5
D4	56	Female	Caucasian	B+			
R4	57	Male	Caucasian	O+	ABO-incompatible	Diabetes mellitus	1
D5	54	Male	Caucasian	A+			
R5	55	Female	Caucasian	B+	ABO-incompatible	Takayasu's arteritis	3
D6	39	Female	Asian	B+			
R6	44	Male	Asian	A+	ABO-incompatible	IgA nephropathy	0.42
D7	59	Female	Caucasian	A+		Focal segmental	
R7	60	Male	Caucasian	B+	ABO-incompatible	Glomerulosclerosis	0
D8	38	Male	Asian	AB+			
R8	31	Male	Asian	A+	ABO-incompatible	Hypertension	6

The altruistic donor for R1 was located through NKR. Founder, Garet Hil created the Registry to facilitate the matching process for incompatible donor/recipient pairs (15). The altruistic donor is a 40-year-old female who had several personal experiences with kidney transplantation, including witnessing a coworker's death on the waiting list and a friend's significantly improved quality of life following kidney transplantation. There is a recent trend to change the terminology and call these donors 'nondirected donors', as they have no designated recipients. We felt that this was truly an altruistic donor, as she requested complete anonymity, foregoing any recognition. The generosity that originally began with the altruistic donor was passed on through successive donors and recipients, resulting in our transcontinental, multicentered transplant chain.

This chain has involved 16 separate surgical procedures thus far, 10 of which occurred at one institution, and there are possibly more to come. The number of operating rooms and staff required to perform these procedures simultaneously would have been prohibitive. In order to accommodate all participants' individual life schedules, the transplant chain was conducted out of sequence, which is a departure from standard practice. The first recipient, R1, received her kidney transplant 1 week after her cousin had already donated his kidney to recipient R2. This donation meant that R1 had lost her 'bargaining power', since her incompatible donor no longer had a kidney to offer to another recipient, should the chain be unexpectedly broken. She had to trust that she would receive the kidney from the altruistic donor as planned, relying on that donor's generosity, a person she had never met.

Critics may argue that conducting the chain out of sequence could allow a preceding donor to withdraw. When prospective donors are being assessed, they undergo an extensive psychosocial evaluation; the time between evaluation and donation should be sufficient to allow donors the opportunity to reconsider and even change their minds (16,17). The sheer desire to be a donor for a complete stranger is a testament to that person's remarkable generosity and capacity to act in 'good faith'.

Table 2: Results with dates of transplants, cold ischemia times and recipient creatinine at times specified. Note follow-up for R1 and R2 is 6 months, R5 is 4 months and the remainder is 3 months

			Recipient serum creatinine			
Donor–recipient pairs (D–R)	Transplant date	Cold ischemia time (hours)	Pre-op	Post-op Day# 1	Discharge (Post-op day)	Follow-up (months)
D1-R2	7/24/2008	1	10.9	3.1	1.1 (4)	1.0 (6)
D2-R3	7/24/2008	1	5.5	3	1.1 (5)	1.0 (3)
AD-R1	7/30/2008	14	5.1	2.2	1 (6)	1.2 (6)
D3-R4	10/2/2008	1	4.5	2.7	0.7 (5)	1.0 (3)
D4-R5	10/2/2008	1	7.4	2.7	0.8 (8)	1.0 (4)
D5-R6	11/19/2008	8	7.3	6.1	9 (6)	1.5 (3)
D6-R7	11/19/2008	12	4.5	3.7	1.9 (4)	1.3 (3)
D7-R8	11/19/2008	11	8.7	6.9	1.9 (4)	1.7 (3)

AD = altruistic donor.

The altruistic donor may be considered to have a high likelihood of backing out, as she had nothing to gain by her donation, but she was actually the least likely to withdraw her participation. Her motivation was driven by her own personal experiences with transplantation, not by a loved one receiving a kidney. She was remarkably well-informed going into this process and her resolve only strengthened as she continued. In this case, the risk of the altruistic donor backing out was extremely small and the benefits were extraordinary, as eight people were transplanted and another eight patients improved their position on the waiting list. If the altruistic donor had backed out, R1 would remain listed for a deceased donor kidney and could wait for another altruistic donor to come forward. Nevertheless, the remaining seven recipients in the chain would have benefitted from D1's donation.

The possibility of other donors backing out in a multicentered chain such as this one must be addressed. No one involved in this chain was required to sign a contract. Live organ donation is strictly voluntary; donors always retain the right to change their minds and must never feel coerced by signed contracts. We relied on donors' honesty and good will to follow through as planned. We maintain that the basic principle of organ donation is based upon selfless generosity and faith in the human spirit, rather than contractual obligations. We would discourage future participants from becoming mired in legal arguments and lengthy debates that would only cause interminable delays.

D3 and D5 may be regarded as high risk for withdrawing their involvement, as these donations occurred several weeks after their incompatible recipients had received their transplants. Although a valid concern, D3 stated that his participation was one of the most meaningful experiences of his entire life. He was motivated to significantly modify his lifestyle because he was so grateful that his mother no longer required dialysis. He lost weight and decreased his alcohol intake to be in the best shape possible for donating his kidney to a complete stranger. D5 has specifically stated that he would have remained committed to donate at anytime, even if an appropriate recipient for his kidney was found several years later, as he was profoundly grateful that his wife had received a transplant after being on dialysis for 3 years. He now looks forward to realizing his dream of traveling to Europe with her. Nevertheless, if a donor chooses to withdraw, there are no significant repercussions for the next recipient when the chain is performed in sequence, despite being staggered. The recipient retains 'bargaining power' with his/her incompatible donor intact and could participate in a different chain. Other potential altruistic donors could step forward, continuing the chain. The recipient would also remain listed for a deceased donor kidney.

Donors and recipients were not encouraged to meet each other, unless both parties asked to do so and were agreeable; then it was arranged. The altruistic donor remains anonymous, as she requested. The donor/recipient pairs from LA expressed a desire to meet each other after their operations. They share a special bond, having participated in this remarkable experience together and some continue to keep in touch regularly.

What if an adverse outcome had occurred in one of the recipients or donors? The risks are fully discussed with all participants, just as with standard living donor transplants. The chain does not guarantee a successful outcome; it simply offers an opportunity to expediently receive a quality living donor transplant, rather than remain listed for a deceased donor kidney indefinitely. All donors eagerly embraced the opportunity to participate in this chain, once informed that their loved one could receive a transplant promptly with their participation. Although no formal psychiatric assessment was performed after donation, the donors in this chain have all stated that they felt a great sense of satisfaction by helping people outside of their own families. We expect results similar to the national experience, where the 1-year graft survival of living donor renal transplants is 96%, as detailed in the Scientific Registry of Transplant Recipients (SRTR). Similar to any other living donor kidney transplant, should one of these kidneys fail, the recipient will experience disappointment and grief and will be relisted for a deceased donor kidney. The possibility for another living donor, even an altruistic donor, to come forward will be explored.

Traditionally, donors have traveled to the recipient's hospital. Occasionally, donors participating in a kidney exchange program may be reluctant to leave the surgical team with whom they have developed a rapport, preferring to stay at their own center, rather than undergoing surgery at the recipient's location with an unfamiliar team (7). The altruistic donor preferred to have her surgery in NYC, where she could enjoy the support of friends and family as she recovered. In order to accommodate the altruistic donor's wishes, she underwent a laparoscopic donor nephrectomy in NYC and the unaccompanied kidney was transported on ice, by commercial flight, to LA. In April 2007, a living donor kidney was transported from San Francisco to Baltimore for transplantation after 8 h of cold ischemia (7) without any adverse effects. That case utilized a private jet and a GPS tracking device, which resulted in additional expense. As a successful system exists for the transportation of deceased donor kidneys on commercial flights, we felt that we could confidently utilize this established system.

The kidney that was transplanted into R1 had 14 h of cold ischemia and produced urine immediately after reperfusion. Although this is not surprising based on the US deceased donor experience, the shipment of live donor kidneys does challenge traditional dogma. Waki and Terasaki (18) have proposed instituting a national kidney exchange program, supported by the shipment of live donor kidneys. Their study concluded that live donor kidneys could be transported without adversely affecting graft function. To

date, transplant centers have been reluctant to transport live donor kidneys long distances. This reluctance may stem from a belief that a short cold ischemia time (CIT) is essential to ensuring immediate function. The advantages of living donation may correlate more with the quality of the organs, which are recovered from a living, anesthetized donor, rather than the CIT involved (7,18,19). This chain involved long-distance transportation of four living donor kidneys with CITs ranging from 8 to 14 h and there were no appreciable adverse effects on the transplanted organs. Transportation of live donor kidneys can be performed cost-efficiently, utilizing commercial jets and local OPO involvement, with the additional benefit of not requiring the donor to travel. Deceased donor kidneys are routinely transported across the United States without hesitation and with this publication, it is our hope that transplant programs will feel comfortable transporting living donor kidneys as well.

Chain transplantation could substantially increase the donor pool with high- quality donor organs, in contrast to utilizing organs of uncertain caliber from extended criteria donors (ECD) and donation after cardiac death (DCD) donors. As stated by Bromberg and Halloran (20) in a recent issue of the American Journal of Transplantation, 'transplant societies [need to] realize that we are mired in old paradigms and that resource allocation and attitudinal changes must take place to truly increase donation of high-quality living and deceased organs to make an impact on the mortality rate of those waiting for organs. The gains [thus far] are at the expense of worse outcomes and higher costs through the use of ever more marginal organs.'

We would like to encourage an attitude of cooperation, rather than competition, between various transplant centers. This transplant chain was successful because the institutions involved were able to work together toward the common goal of getting the patients transplanted. Transplant programs may differ with regards to immunosuppression protocols and post-transplant care, but we can expect that comparable standards exist for the donor nephrectomy. Programs should not fear that the kidney they receive from another center, with that center's surgeons performing the recovery, would be inferior to their own. Individual egos need to be put aside and transplant centers should trust one another with regards to participation in a chain such as the one presented here. The results could benefit all programs, by getting their patients transplanted with quality living donor kidneys in a timely fashion, rather than having them endure long waits for a deceased donor kidney.

Conclusion

Prolonged dialysis while awaiting renal transplantation is associated with increased costs, increased mortality rates and worse posttransplant outcomes. Chain transplantation has the potential to significantly expand the donor pool with quality living donor kidneys and facilitate renal transplantation. Traditionally, donors travel to the recipients' location and transplant chains are conducted in sequence. When donors wish to recover at their own institution near friends and family, transplant centers should not hesitate to accept a transported living donor kidney. Extended cold ischemia times, secondary to transportation, do not appear to adversely affect living donor renal allograft function. When logistics such as patient life events, or operating room schedules, prohibit the chain from occurring sequentially, then the chain should be performed as a MATCH, with modification of the sequence and asynchronous completion. The benefits of releasing numerous patients from the constraints of dialysis, which include an improved quality of life and significantly increased survival, outweigh the risk of breaking the chain. Although the MATCH is a concept still in need of further validation, we believe this will come from the use of this technique by multiple other groups. We propose that a national program should exist to facilitate chains such as this one.

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