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Chain Transplantation: Initial Experience of a Large Multicenter Program

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We report the results of a large series of chain transplantations that were facilitated by a multicenter US database in which 57 centers pooled incompatible donor/recipient pairs. Chains, initiated by nondirected donors, were identified using a computer algorithm incorporating virtual cross-matches and potential to extend chains. The first 54 chains facilitated 272 kidney transplants (mean chain length = 5.0). Seven chains ended because potential donors became unavailable to donate after their recipient received a kidney; however, every recipient whose intended donor donated was transplanted. The remaining 47 chains were eventually closed by having the last donor donate to the waiting list. Of the 272 chain recipients 46% were ethnic minorities and 63% of grafts were shipped from other centers. The number of blood type O-patients receiving a transplant (n = 90) was greater than the number of blood type O-non-directed donors (n = 32) initiating chains. We have 1-year follow up on the first 100 transplants. The mean 1-year creatinine of the first 100 transplants from this series was 1.3 mg/dL. Chain transplantation enables many recipients with immunologically incompatible donors to be transplanted with high quality grafts.

Key words: kidney exchanges, kidney transplantation, living donor transplantation, organ exchanges

Abbreviations: DGF, delayed graft function; NDD, nondirected donor; NKR, National Kidney Registry; OPO, organ procurement organization; UNOS, United Network for Organ Sharing.

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Introduction

The demand for renal allografts is greater than ever before (1). Approximately 30% of patients with a willing living donor have traditionally been unable to receive a kidney from that donor due to blood type or cross-match incompatibility (2,3). ABO incompatible and desensitization protocols have been developed to address these obstacles with variable success. These require pretransplant treatment procedures that may include expensive and potentially hazardous interventions such as intravenous immunoglobulin, plasmapheresis, rituximab and/or splenectomy (4–9).

With the gradual acceptance of nondirected donors (NDDs), novel approaches such as traditional paired exchanges have evolved into chains of transplantations (10–12). Chains are initiated when an NDD donates a kidney to a patient who has a willing but incompatible donor. This incompatible donor, in turn, donates to another recipient who also has a willing but incompatible donor. The next donor of the chain can give their kidney to a recipient on the deceased donor waitlist (closed chain) or extend the open chain by giving their kidney to another recipient who also has an incompatible donor (12). "Closed chains" have also been called "domino transplants" especially when they occur simultaneously (10,13).

Chains offer theoretical advantages over traditional paired-exchanges. Foremost, matching algorithms for paired-exchanges are limited by the reciprocal matching requirement. When the first incompatible pair's donor is matched to a second incompatible pair's recipient, the second incompatible pair's donor must then reciprocally match back to the first pair's recipient. While this constraint becomes less limiting as paired-exchanges include multiple recipient/donor pairs, with chain transplantations the next pair's donor can potentially match any other pair's recipient in the database. This lack of reciprocity requirement is the driving force behind chains having superior matching performance; this allows for improved matching quality and increased quantity of transplantations performed (11). Additionally, if a donor withdraws from a chain, the next pair's recipient suffers no irreparable harm as they have not lost their original donor, thus enabling centers and their operating room staff the flexibility to perform the chain surgeries nonsimultaneously. This contrasts with traditional paired-exchanges that are performed simultaneously to reduce the chance of a donor backing out after their loved one receives a kidney.

Although chain transplantations have the potential to significantly increase the donor pool, concerns have been raised about utilizing NDDs, donors reneging, multicenter finances (14), shipment of living donor organs and the potential to disadvantage blood type O candidates or minorities (15). Simulations from the United States and reports from Korea and the Netherlands have not fully addressed these concerns (3,16,17). We report the experience of the first 54 chains involving 272 kidney transplants that were orchestrated by a multicenter registry using an exhaustive search algorithm to identify potential matches.

Methods

The National Kidney Registry (NKR) is a coalition of 57 transplant programs in the United States that pool their self-referred NDDs, incompatible pairs and even compatible pairs willing to enter an exchange into a single database. To register, member centers currently pay $4950 for training/start-up costs and $2500/year for membership. For database management, technologic support and logistics centers pay $3000 per facilitated transplant and $100/month on the list. Therefore, the estimated cost-per-transplant ranges from $4000 to $6000 dollars. The NKR is a 501(c)3 nonprofit organization guided by a medical board including surgeons, nephrologist, laboratory directors, transplant coordinators and public members.

Recipient and donor data entered in the registry include age, sex, ABO-blood type, HLA-antigens and HLA antibodies based on solid phase assays including single antigen beads. Centers entered recipient avoids based on their own mean fluorescence intensity cutoffs. Center preferences included: acceptable donor age range, acceptable donor vascular anatomy, willingness of recipients to accept shipped kidneys and donors to travel. To improve the accuracy of the virtual cross-matches, the required HLA-antigens included: A, B, C, DRB1, DRB3/4/5, DQ and DP. Bw4/6 determinations were also included since some patients have antibodies to these (public) epitopes widely shared by B locus (and some A locus) molecules. Personal health information is not kept in the database. Centers maintain the key to the encoded alias for their own patients.

Potential living donors are expected to be evaluated and consented based on guidelines put forth by the Amsterdam Forum (18) and UNOS (19). Imaging of donor anatomy was originally optional prior to being considered for a match offer; however, this policy has evolved and imaging is now required.

The selection of potential chains begins using a computer algorithm that performs an exhaustive combinatorial search of potential clusters of transplants. Clusters are a group of transplants, usually occurring temporally close together. Chains are composed of a series of clusters. The first cluster of a chain begins with an NDD. Subsequent clusters are linked together using "bridge" donors. The term "bridge donor", as defined by Woodle et al. (15), is a donor who "agrees not to donate his/her kidney at the same time as their loved one receives a kidney, but rather at a later date". A "renege" occurs if a "bridge donor" becomes unavailable to donate for any reason, including: health issues and changing their mind. "Closed" chains were ended to the wait list, and "open" chains were continued indefinitely (13). Originally the algorithm identified every potential cluster from 1 to 3 pairs long. However, the most recent version of the software can identify all potential clusters up to 20 pairs long.

The list of potential clusters is pared down by removing clusters that (1) include inactive donors, (2) include matches that violate center or donor preferences such as donor age and weight, or (3) include matches where O donors donate to non-O recipients. The resulting list is then prioritized by cluster length, the conservation of O donors, the difficulty of matching a potential recipient, the availability of an O bridge donor and the quality of the HLA match. The conservation of O donors is maximized by increasing ratio of O recipients to O donors within a cluster. The overall difficulty of matching potential recipients in a cluster is determined by the percentage of donors in the database who are blood type and HLA incompatible with each recipient. The HLA match quality is determined by giving 10 points for an A antigen match, 15 points for a B antigen match and 25 points for a DR match. Finally, in situations where the clusters are otherwise equally prioritized, age compatibility and logistical complexity are taken into account. For example, a cluster that includes several exchanges within the same institution may be favored over a cluster that requires several kidneys to be shipped to other institutions. The relative values of these priorities are actively managed with the guidance of the NKR medical board.

Match runs were typically performed on a daily basis to assess liquidity in the pool. Once a cluster was offered the involved patients were removed from the pool. Recipient centers had full authority to reject match offers based on their own criteria that could include: age, graft anatomy and immunological risk. Once an offer was accepted by all centers, the flow cross-matches were performed at the recipient hospitals. If all cross-matches were acceptable, appropriate donor imaging was completed, medical records were exchanged and surgery dates were scheduled. Logistical details, such as timing, organ transportation and contact information were coordinated through at least one conference call between the involved centers. Often match offers that fell through could be salvaged by recombining orphaned segments of clusters with other clusters to lengthen previously initiated chains. Since all the matches within the orphaned segments had been previously accepted already, these new combinations were formed rapidly. Throughout this process, centers were encouraged to stick to a tight time line and were usually given 1-3 days to accept or reject a potential offer and 7 to 10 days to perform flow cross-matches.

For logistical reasons, which include organ shipping constraints and the realities of surgeon and operating room availability, clusters of transplants were often performed over several days (nonsimultaneously). If the donor was located at a different center than the matched recipient, either the donor traveled or the kidney was shipped to the recipient's center. When possible, these living donor kidneys were shipped via commercial airlines using standard organ procurement organization (OPO) protocols for deceased donor organs (20). Participating surgeons were encouraged to communicate directly before and immediately following the donor nephrectomy to discuss donor anatomy and technical aspects of the case.

Participating centers agree to the NKR financial guidelines published online (21). The origin of these guidelines are as described previously (14).

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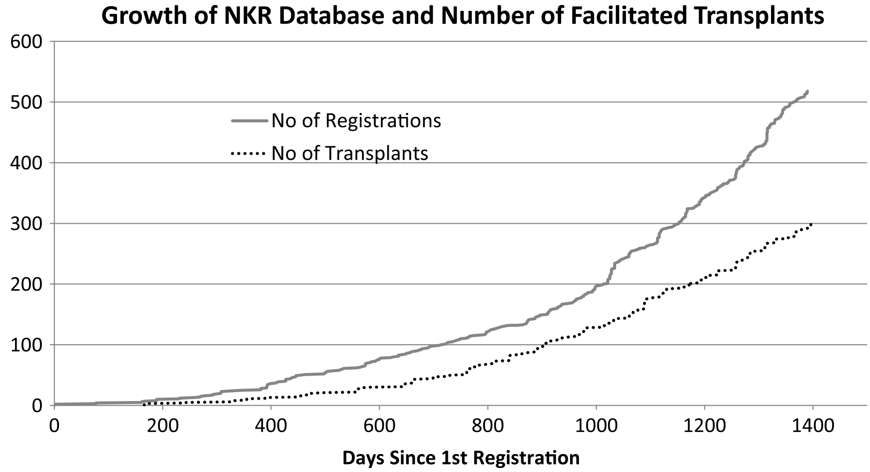

Figure 1: Plot comparing the growth of the NKR database to the growth of the number of transplants. This includes the 272 transplants facilitated by the first 54 chains as well as 18 patients from newly initiated, chronologically overlapping chains and 10 patients from traditional paired exchange.

Outcomes data collected in a centralized database include: chain lengths, reneges (defined as bridge donor who is no longer able to donate), shipment of kidneys, patient survival, graft survival and graft function.

Results

Characteristics of database

At the time of the 272nd chain transplant 519 recipient/donor pairs were registered in the NKR database (Figure 1). The proportion of registered patients who were white, black, Hispanic and Asian was 54%, 19%, 13% and 8%, respectively (Table 1). A total of 37% were blood type O, 38% were blood type A, 19% blood type B and 6% blood type AB (Table 1). Moreover, 51% of the pool was male.

Characteristics of the 54 chains

The first 54 chains facilitated 272 transplantations between February 14, 2008 and June 29, 2011. During this same time period 10 traditional paired exchange transplants were performed and were excluded from this analysis. The chains ranged from 1 to 21 transplants long (Figure 2). The moving cumulative mean chain length peaked at 7.1 after 85 transplants but came down to 5 after 272 transplants (median = 4). Thirty-two (59%) of the NDDs were blood type O, 16 (30%) were A, 5(9%) were B and 1 (2%) was AB. A total of 43% of the NDDs were female. Ninety (33%) of the recipients were blood type O, 105 (39%) were A, 60 (22%) were B and 17 (6%) were AB (Figure 3). A total of 53% of the recipients were male, and of the 267 patients whose ethnicities were disclosed, only 52% were white (Table 1). A total of 63% of the grafts were shipped from one institution to another, 56% (n = 151) by air and 7% (n = 19) by ground.

Forty-seven chains were ended to the deceased donor list resulting in the transplantation of 3(6%) O, 23(49%) A, 8(17%) B and 13(28%) AB patients. Seven chains ended because "bridge donors" became unavailable to donate. The reported reasons include: newly diagnosed medical conditions (3 people), personal decisions (2 people), a change in employment and a relocation.

For logistical reasons, some donors donated a day or more prior to their intended recipients' scheduled transplants. One such donor, unexpectedly, decided not to proceed. Per the NKR guidelines, the untransplanted recipient, whose donor had already donated to the next recipient in the chain, received an NDD graft two months later.

One-year outcomes of transplants

One-year follow up on the first 100 recipients was collected. At the time of the 100th transplant, 72 recipients remained unmatched in the pool. Table 2 compares the cPRA of those registered in the NKR to those who were transplanted from this pool (22). A total of 51% of these

Table 1: Demographics

Characteristics	Registered patients (n = 519)	Chain recipients (n = 272)
Gender (%)		
Male	51	53
Female	49	47
Blood types (%)		
A	38	39
B	19	22
AB	6	6
O	37	33
Ethnicity (%)		
White	53.9	52.2
Black	18.9	19.1
Hispanic	12.5	14.0
Asian	8.3	8.8
Mid-East	0.2	0.7
Pacific Islander	0.4	0.7
Other	2.7	2.6
Not disclosed	3.0	1.9

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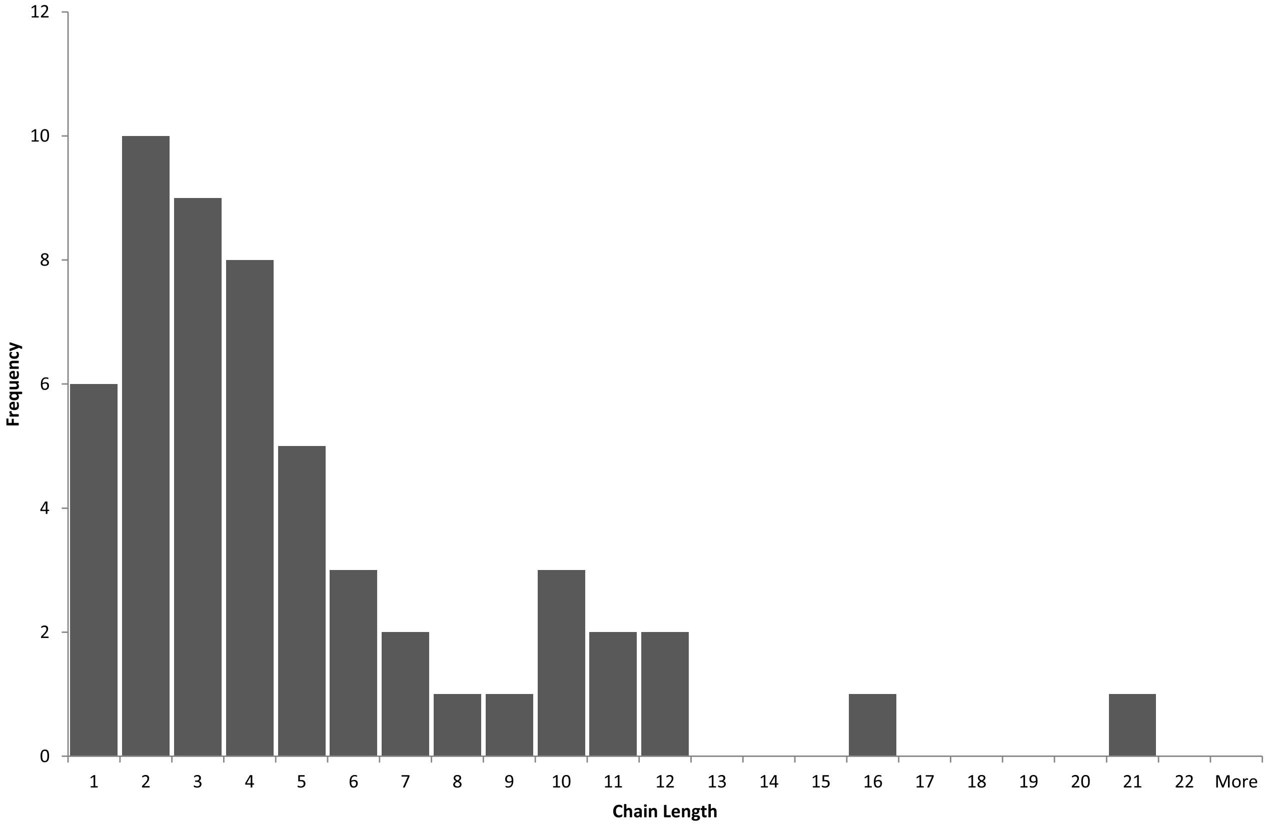

Figure 2: Distribution of the initial 54 chains facilitated through the NKR.

patients were ABO incompatible with their original donor, and 47% were cross-match positive with their original donor. Two donor/recipient pairs were compatible but participated to receive a younger and/or better matched kidney.

There was one known graft loss 8 months after transplant secondary to rejection in a 21-year-old man who discontinued his immunosuppression. One patient died from pneumonia within the first year posttransplantation. The median creatinine at 1 week was 1.5 mg/dL, ranging from 0.2 to 7.5 mg/dL. The mean creatinine for the 96 of the 98 patients with surviving grafts at 1 year was 1.3 mg/dL, ranging from 0.4 to 3.0 (median = 1.2 mg/dL).

A total of 47 of these 100 recipients with 1-year follow up received a shipped graft (Figure 4). Fourteen of these kidneys traveled "coast-to-coast" across the United States with an average cold ischemia time of 12 hours (range 7–17 hours). There was no delayed graft dysfunction (DGF) reported, and the median 1-week creatinine of grafts shipped coast-to-coast (1.6 mg/dL) was similar to those not shipped (1.5 mg/dL).

There were no donor deaths, conversions to open operations or reoperations.

Discussion

These first 272 transplants were completed in 40 months and were part of 54 chains that averaged 5.0 transplants long. This average chain length is longer than the 1.9 to 3.8 transplants predicted by various simulations (3). Factors that may contribute to this difference include: (1) the algorithms have different priorities. For example, the NKR algorithm focused on cluster length, rather than the total number of transplants, to maximize the benefit of the NDD rather than the overall number of transplants. Even within the NKR the relative value given to different matching priorities has evolved over time to favor "closed" chains over "open" chains that are at risk of breaking. As a result, while the average overall chain length peaked at 7.1, it has decreased to 5 at the end of this series. (2) Simulations may have difficulty predicting the rate of reneges without real-life data on the behavior of bridge donors. In the NKR experience many bridge donors remained motivated and donated months after their intended recipients' transplantation. One bridge donor even donated more than 1-year afterwards.

Our experience also differs greatly from that of South Korea and the Netherlands. The South Korean and Dutch groups have reported only domino chains that had no

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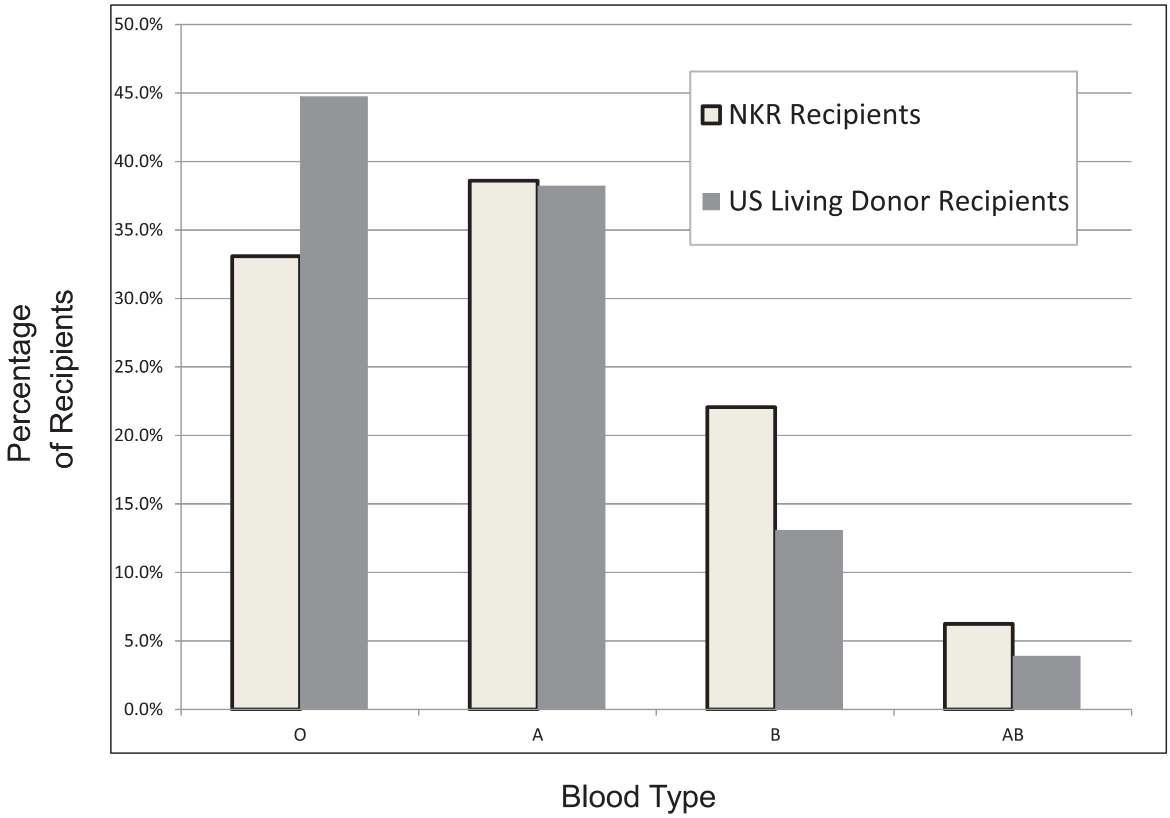

Figure 3: The blood types of the 272 chain transplant NKR recipients as compared to living donor recipients transplanted in the United States during 2008 (unos.org).

bridge donors and were designed to be kept short to avoid potential reneges. Additionally, their donors traveled to the recipients centers rather than the grafts being shipped (16,23).

To calculate the added benefit of chain transplantation, we conservatively assume that the 54 NDDs would have been willing to donate directly to the deceased donor list and that the two compatible pairs would have gone forward on their own. Therefore, through chain transplantation an additional 217 living donor transplants were performed. All 272 recipients were listed or in the process of being listed for a deceased donor transplant. Removal of these patients from the wait list reduces competition for deceased donor organs. The longest chain involved 21 recipients and 21 donors. Six chains included in this study were only 1-transplant long due to time constraints for donation dictated by the NDDs.

Table 2: Comparison of cPRA between registered patients and recipients

cPRA	Total pool (n = 172)	Transplanted (n = 100)	Nontransplanted (n = 72)
0–9%	55%	69%	36%
10–79%	17%	17%	18%
80–100%	27%	14%	46%

The total pool included all patients that had been registered in the NKR database at the time of the 100th transplant. cPRA calculated using the OPTN online calculator (22).

There were seven broken chains due to bridge donors becoming unavailable. Unlike traditional paired donation where the consequences of a donor ‘backing-out’ are devastating, in chain transplantation, the next recipient does not suffer ‘irreparable harm’ as they have not lost their willing incompatible donor and can participate in a new exchange when the transplants are carried out sequentially. For logistical reasons, some donors underwent a nephrectomy significantly before their intended recipient received a kidney. This has been previously described as “MATCH-transplantations” (20). In one case the subsequent donor backed out of the chain. This left a recipient, whose donor had already donated without a potential donor. Fortunately, this potentially asymmetric outcome was anticipated by NKR guidelines, and the infrastructure was already in place to use an NDD to replace the donor that backed out and mend the chain (21).

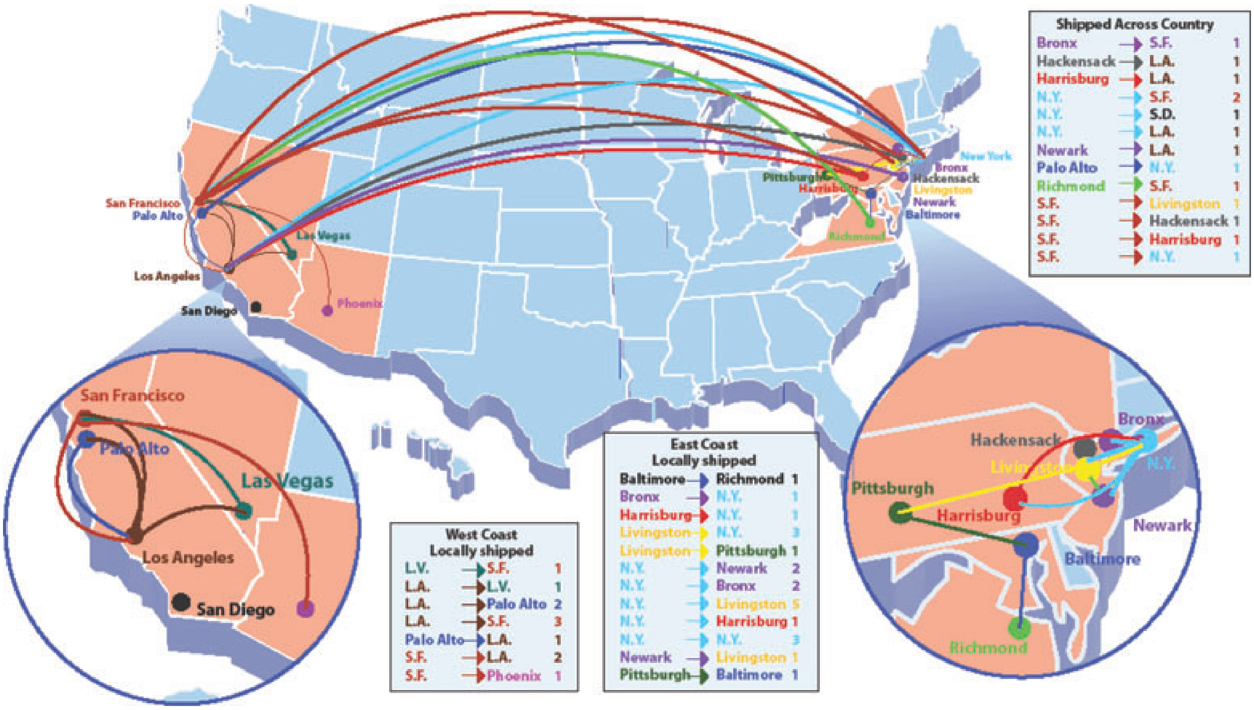

Figure 4: Illustration of kidneys with 1-year follow up shipped from one transplant center to another as part of the first 100 chain transplantations in the NKR database.

Although 'bridge donors' would not have been considered as potential donors were it not for the availability of an exchange program, the community has expressed concerns about a process in which these donors are able to back out (15). Clearly bridge donors are at risk of backing out, and when they do, there is disruption of an ongoing chain and at least one less living donor transplant. However, it is important to note that all chains will eventually break as they are extended unless they are terminated by having the last donor donate to the wait list.

The patients most harmed by reneges may be those at the top of the waiting list who would have benefited from a living donor had the chain eventually been closed to the list. Therefore, centers should feel an obligation to enter only donors into the database whom they feel have a high likelihood of going through with donation. Serendipitously, the recently imposed prematch-offer imaging requirement may help select committed donors who are willing to take this concrete step towards donation. To further minimize the number of broken chains the NKR now ends chains with bridge donors who are difficult-to-match or who may not tolerate a long waiting time by donating their kidney to a candidate on the waiting list.

Another concern is that chains will disadvantage blood type O candidates by having NDDs donate to a chain rather than the waiting list (15). In this series, 32 NDDs were blood type O and only 3 chains were ended to O patients on the waiting list; however, a total of 90 chain recipients were blood type O. Therefore, chain transplantation liberated an additional 58 O donors. These additional 58 O donors would likely not have been utilized as they were incompatible with their intended recipients. Therefore, allocating O NDDs into chains may actually benefit O candidates on the waiting list for two reasons (24). First, the O living donor pool is enlarged by utilizing previously unusable incompatible donors of sensitized recipients. Secondly, successful transplantation of these O candidates allows them to be removed from the waiting list and 'reduces the competition for deceased donors for those remaining on the waiting list' (24). Only O recipients without potential living donors near the top of the deceased donor list are unlikely to benefit directly from an NDD in this system.

It has previously been reported that 73% of pairs who participate in exchanges are white (25); however, in our series only 52% of recipients were white (Table 1). This difference may be a result of large urban centers with more ethnic diversity actively participating in chain transplantations. Notably, the ethnic composition of the chain recipients was similar to the ethnic composition of the database pool (Table 1).

As demonstrated in Table 2, the untransplanted pool contains 64% sensitized patients (cPRA $\geq$ 10%) while the transplanted pool has only 31% sensitized patients.

Strategies to transplant these sensitized patients may include recruiting compatible donor/recipients pairs into the pool and combining desensitization protocols with paired-exchange. Although not a part of the NKR algorithm, some might argue that O donors could also be directed to highly sensitized non-O recipients in the future.

Cost has been a major concern for kidney exchange registries in this country as CMS has not covered the costs of listing incompatible pairs in private exchange programs. The current cost to centers collaborating with the NKR ranged from $4000 to $6000 per kidney transplant. UNOS has also recognized that exchange programs require a financial investment for sustainability. Therefore, the UNOS board approved an increase of the registration fee for all new patients from $585 to $603 partially to cover new expenses of the UNOS Kidney Paired Donations pilot program (26). However, these fees still compare favorably to the costs of other strategies of transplanting incompatible pairs including desensitization and waiting for a deceased donor kidney (2). For example, there was excellent graft survival among the 100 patients with 1-year follow up data. A total of 31% of these recipients were sensitized and 14% had PRAs greater than 90%. To be transplanted otherwise, many of these recipients would have cost their centers tens of thousands of dollars to desensitize. Therefore, it may be appropriate for CMS to cover these expenses in the future.

Protocols instituted by the NKR that include chain planning conference calls, preoperation and postoperation surgeon communication, and development of shipment contingency plans have overcome many of the logistics of shipping kidneys. While the first few NKR chain transplants were completed within one city, transplant programs have now become comfortable shipping living donor kidneys. Thus, transplanting highly sensitized O patients can now be prioritized over patients within the same geographical region. In this series 63% of recipients received a shipped kidney. Some of these kidneys were included in a previously published article describing the U.S. experience of shipping living donor kidneys (27). The prolonged cold ischemia time appears to have no short-term deleterious effects on the function of the shipped kidneys. The shipment of living donor kidneys enables donors to recover alongside their intended recipients rather than being separated from family while they donate in unfamiliar surroundings. Local OPO s have the expertise to arrange the shipment of living donor kidneys by utilizing the same policies and procedures that are well established for the shipment of deceased donor organs (20). Should a kidney be lost in shipment, the intended recipient may be harmed since their donor may have donated already. While such asymmetric outcomes potentially can be ameliorated using an NDD or a bridge donor to repair the chain, transplant centers should include the possibility of such outcomes specific to chain transplantation in their consent process.

Conclusion

Chain transplantation enables multiple patients with immunologically incompatible donors to be transplanted with high quality grafts. This expansion of the donor pool does not appear to disadvantage minority or blood type O- patients. The successful transplantation of these recipients with living donor grafts was made possible by use of nondirected donors, cooperation between multiple transplant centers, willingness to ship donor kidneys across the country and a computer algorithm to identify chains of transplants using high-resolution HLA typing. There has been significant focus on these matching algorithms in the literature; however, our experience indicates that active management of the exchange process and overcoming logistical barriers were equally important for transplanting these 272 patients within 40 months. While, as feared, a few bridge donors became unavailable to continue a chain, careful guidelines prevented any chain recipients from being irreparably harmed.

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Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Garet Hil is the founder of a nonprofit organization, NKR, which facilitates chain transplantation. NKR receives fees to facilitate paired exchange transplants and manage the related logistics process.

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