

# Kidney Transplant Chains Amplify Benefit of Nondirected Donors

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**Importance:** Despite the potential for altruistic nondirected donors (NDDs) to trigger multiple transplants through nonsimultaneous transplant chains, concerns exist that these chains siphon NDDs from the deceased donor wait list and that donors within chains might not donate after their partner receives a transplant.

**Objective:** To determine the number of transplantations NDDs trigger through chains.

**Design:** Retrospective review of large, multicenter living donor–recipient database.

**Setting:** Fifty-seven US transplant centers contributing donor–recipient pairs to the database.

**Participants:** The NDDs initiating chain transplantation.

**Main Outcomes Measure:** Number of transplants per NDD.

**Results:** Seventy-seven NDDs enabled 373 transplantations during 46 months starting February 2008. Mean

chain length initiated by NDDs was 4.8 transplants (median, 3; range, 1-30). The 40 blood type O NDDs triggered a mean chain length of 6.0 (median, 4; range, 2-30). During the interval, 66 of 77 chains were closed to the wait list, 4 of 77 were ongoing, and 7 of 77 were broken because bridge donors became unavailable. No chains were broken in the last 15 months, and every recipient whose incompatible donor donated received a kidney. One hundred thirty-three blood type O recipients were transplanted.

**Conclusion and Relevance:** This large series demonstrates that NDDs trigger almost 5 transplants on average, more if the NDD is blood type O. There were more blood type O recipients than blood type O NDDs participating. The benefits of transplanting 373 patients and enabling others without living donors to advance outweigh the risk of broken chains that is decreasing with experience. Even 66 patients on the wait list without living donors underwent transplantation with living-donor grafts at the end of these chains.

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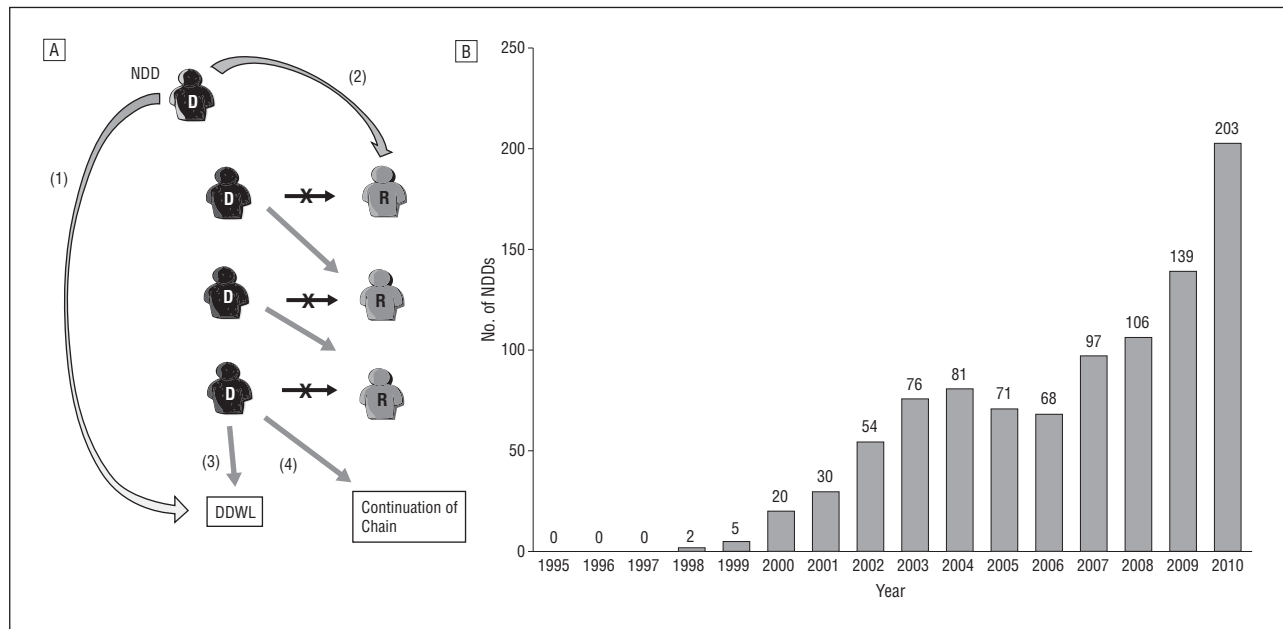
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**W**ITH MORE THAN 90 000 candidates waiting for kidney transplantation as of January 1, 2012, and fewer than 11 000 deceased donor transplantations performed each year, there is clearly a supply-and-demand mismatch.<sup>1</sup> Not only is living-donor kidney transplantation a strategy to address the high demand for kidney transplantation, but it also offers patients multiple additional advantages. For example, transplantation can be scheduled when it is convenient for the donor and the recipient and even prior to initiating dialysis. Outcomes are superior to deceased donor transplantation, and the surgery is elective. However, approximately one-third of patients who have healthy and willing po-

tential living donors are unable to receive a transplant from that donor because they may be blood type-incompatible or crossmatch positive.<sup>2</sup>

Kidney-paired donation (KPD) is a strategy to help patients with incompatible donors.<sup>3-7</sup> With KPD, 2 or more incompatible pairs are matched with other incompatible pairs such that multiple compatible transplantations can be performed. Kidney-paired donation, also known as closed-loop kidney swaps, can occur with any number of pairs participating with 2-, 3-, or multiway swaps being possible. Variations of KPD incorporate nondirected donors (NDDs) to start a chain of compatible transplantations.<sup>8</sup> The NDDs are willing to donate a kidney without the expectation that someone they know will receive a kidney in return. When



**Figure 1.** Chain donation. A, A nondirected donor (NDD) can either give directly to the deceased donor wait list (DDWL) (1) or to a chain of incompatible donor-recipient pairs (2). The last donor of the chain can donate to the DDWL (3) or continue the chain by donating to additional incompatible donor-recipient pairs (4). D indicates donor; R, recipient. B, Estimation of the use of NDDs in the United States. Estimation based on the assumption that most donors labeled as “nonbiological, unrelated, anonymous” living donors are in fact NDDs.

the NDDs start chains resulting in multiple transplantations occurring simultaneously and the chain is ended to the deceased donor wait list (DDWL), these are called domino-paired donor exchanges. When the “bridge donor,” the last donor of a cluster of simultaneous transplantations who is still waiting to donate, is used to initiate another cluster of transplantations, these linked clusters are considered to be part of a nonsimultaneous extended altruistic donor chain.<sup>9</sup> Since 1988, an estimated 953 NDDs (385 blood type O, 386 blood type A, 140 blood type B, and 42 blood type AB) have donated, and the numbers have increased significantly during the past decade<sup>1</sup> (**Figure 1**).

Theoretical advantages of chain transplantation go beyond the NDDs’ contribution of additional living-donor grafts to the system. Chains offer a mathematical advantage over paired-kidney donor exchanges because the donor of the second pair can donate to any other compatible patient in the database and does not require reciprocal matching back to the recipient of the first pair.<sup>10,11</sup> It has been the experience of those engaged in chain transplantation that many more incompatible pairs can be unlocked compared with traditional KPD as a result of the mathematical advantage afforded in this approach.<sup>12</sup> In addition, because NDDs are more likely to be blood type O compared with the incompatible donors brought to a pool of incompatible donor-recipient pairs, the blood type O patients participating in chains are advantaged compared with blood type O patients in traditional KPD who do not have access to these blood type O NDDs.<sup>2</sup>

However, NDDs have traditionally been a source of living-donor grafts for those waiting on the DDWL. Typically, an NDD would present to a transplant center wanting to altruistically donate a kidney to a compatible patient at the top of the DDWL who did not have the benefit of a living do-

nor. Although chain transplantation has been developed to maximize the benefit of an NDD by using his or her generous donation to trigger several transplantations before transplanting someone on the wait list, some have expressed concern that the use of NDDs in chain donation disadvantages the blood type O patients on the DDWL and even permanently diverts NDD kidneys from the DDWL if a bridge donor backs out and breaks a chain.<sup>8,13,14</sup> There is also disagreement as to the ideal length of chains and to the most appropriate way to end chains based on the mathematical modeling of KPD and chain logistics.<sup>15-17</sup>

In this study, we publish data from the multicenter registry that has facilitated the most chain transplants. We hypothesized that entering NDDs into donor chains maximizes the benefit of NDDs not only for patients with healthy and willing but incompatible donors, but also for patients awaiting transplantation on the DDWL. To test this hypothesis, we retrospectively reviewed the transplantations facilitated through the National Kidney Registry (NKR) to determine the number and type of transplantations that could be facilitated by NDDs.

## METHODS

Chains initiated and completed through the NKR from February 14, 2008, through December 31, 2011, were reviewed as approved by a Stanford University institutional review board, Stanford, California. The 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 a kidney transplant exchange into a single database.<sup>12</sup>

The NDDs enter into the database through 2 sources. Most have come through the NKR website that directs potential NDDs to a registration page. Once they have registered, the potential NDD is asked to obtain a medical certification from his or her

**Table. Blood Types of Recipients Broken Down by the Blood Type of the Nondirected Donor Initiating Chains**

ABO	No.	Age, Mean (Range), y	Chain Length, Mean (Median) [Range]	No. of Recipient ABOs
O	40	43 (21-65)	6.0 (4) [2-30]	O: 112 A: 71 B: 39 AB: 19
A	29	47 (21-67)	3.7 (2) [1-12]	O: 17 A: 55 B: 22 AB: 11
B	7	34 (20-51)	3.4 (2) [1-11]	O: 4 A: 9 B: 10 AB: 3
AB	1	54 (54)	1.0 (1) [1]	O: 0 A: 0 B: 0 AB: 1
<b>Total</b>	<b>77</b>	<b>44 (20-67)</b>	<b>4.8 (3) [1-30]</b>	O: 133 A: 135 B: 71 AB: 34

primary care physician declaring that the potential NDD “is of healthy mind and body, and to my knowledge, has no physical or mental health reasons that should limit his/her ability to donate a kidney” ([http://www.kidneyregistry.org/lib/pdf/MRF\\_and\\_health\\_certification.pdf](http://www.kidneyregistry.org/lib/pdf/MRF_and_health_certification.pdf)). Basic laboratory studies (complete blood cell count, complete metabolic panel, urinalysis, 24-hour urine collection for protein and creatinine clearance, glycosylated hemoglobin level, human immunodeficiency virus test result, and a hepatitis panel) are screened by the NKR medical director. If none of these results are a contraindication to donation, the person is referred to a participating transplant center on the basis of donor preference. Other potential NDDs can refer themselves directly to transplant centers. In either case, the transplant center then uses its policies and procedures to evaluate whether the person is an appropriate NDD.

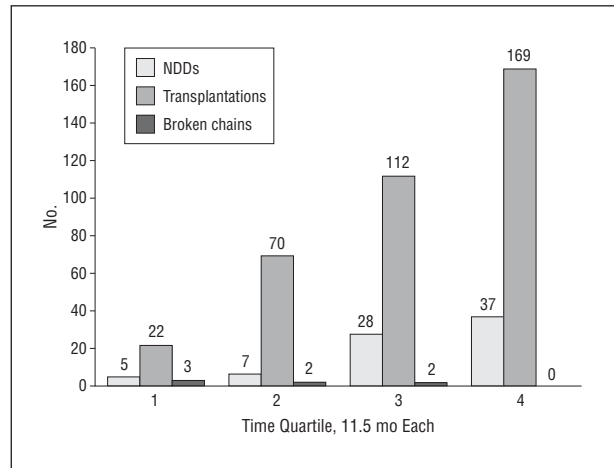
A comprehensive psychosocial and medical workup, including a computed tomographic angiogram, is required for the NDD to be activated and potentially matched to recipient pairs. Chains are preferentially ended to the DDWL of programs that have contributed NDDs so that programs are not disincentivized to enroll them in the NKR. The financial reimbursements are as described elsewhere.<sup>18</sup>

Data about completed transplantations are collected in a Health Insurance Portability and Accountability Act compliant database. Centers are responsible for following their own internal standard protocols and policies and for reporting their outcomes per United Network for Organ Sharing guidelines.

We applied the rank sum statistic of the Mann-Whitney-Wilcoxon test, using Wilcoxon scores in the linear rank statistics for 2-sample data, to compare chain length between blood type O and non-O NDDs. A 2-sided  $P < .05$  was statistically significant. Statistical analyses were conducted using the SAS system for Windows, version 9.2 (SAS Institute).

## RESULTS

Between February 14, 2008, and December 31, 2011, seventy-seven NDDs initiated chains resulting in 373 chain transplantations during these 46 months. The mean age of



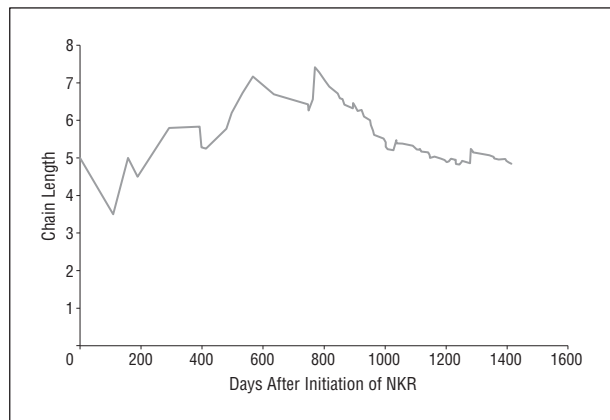
**Figure 2.** Number of transplantations, nondirected donors (NDDs), and broken chains during the study period categorized by quartiles.

the NDDs was 44 years (age range, 20-67 years) (**Table**). Of these 77 NDDs, 44 (57%) were female, 40 (52%) were blood type O, 29 (38%) were blood type A, 7 (9%) were blood type B, and 1 (1%) was blood type AB.

Of the 77 NDD-initiated chains, 4 chains, 10, 2, 1, and 2 transplants long at the close of the study period, remained open and had 1 blood type B, 1 blood type AB, 1 blood type O, and 1 blood type O bridge donors, respectively, still willing to donate their kidney to further extend their chains. These open chains were initiated by 3 blood type A and 1 blood type O NDDs. Sixty-six of the completed chains were closed to the DDWL despite 7 chains being broken when a bridge donor became unavailable to donate. All recipients whose incompatible donor donated received a kidney. The number of NDDs and transplantations increased, while the number of broken chains decreased over time (**Figure 2**). No chains were broken during the final 15 months of the study period.

The 77 NDD-initiated chains led to 373 transplantations for a mean chain length of 4.8 (median, 3; range, 1-30). **Figure 3** illustrates how the chain length cumulative moving average has changed as the program has matured. The distribution of chain lengths broken down by NDD blood type is illustrated in **Figure 4**. Eight chains were only 1 transplant long due to time constraints by NDDs. These transplantations were initiated by 5 blood type A, 2 blood type B, and 1 blood type AB NDDs. The chains that were only 1 transplant long were effectively donations directly to the DDWL, and if these were excluded from our analysis, the mean chain length would be 5.3 (median, 4; range, 2-30).

The mean chain length was 6.0 (median, 4; range, 2-30) per blood type O NDD, a mean of 3.7 per blood type A NDD (median, 2; range, 1-12), a mean of 3.4 per blood type B NDD (median, 2; range, 1-11), and 1 for the single blood type AB NDD (**Table**). A total of 133 blood type O, 135 blood type A, 71 blood type B, and 34 blood type AB recipients were transplanted in chains initiated by 40 blood type O, 29 blood type A, 7 blood type B, and 1 blood type AB NDDs, respectively. Blood type O NDDs led to significantly more chain transplants than non-O NDDs ( $P = .02$ ). The age of the NDDs did not seem to influ-



**Figure 3.** Cumulative moving average of chain lengths as each chain is ended to the deceased donor wait list or broken by a bridge donor withdrawing. NKR indicates National Kidney Registry.

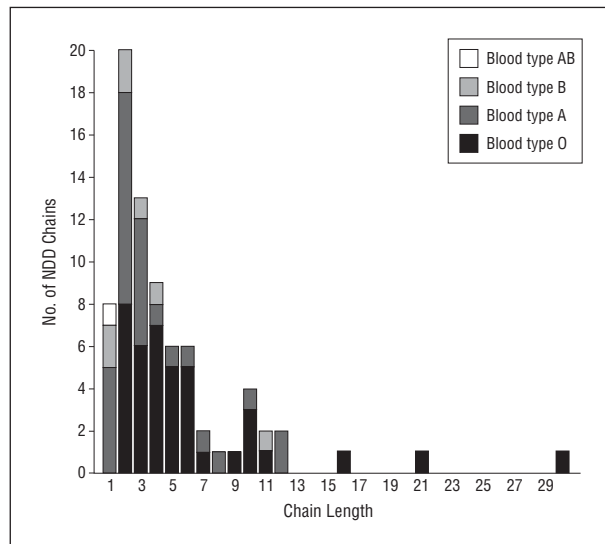
ence the length of chains. The Table also illustrates that 133 blood type O patients were transplanted using 77 NDDs, only 40 of whom were blood type O.

### COMMENT

An earlier analysis of the NKR database showed that highly sensitized patients could be transplanted with excellent outcomes without disadvantaging minorities using the chain donation strategy.<sup>12</sup> This article focuses on analyzing the advantages and disadvantages of using NDDs in chains compared with having them donate directly to the wait list. The NKR experience includes 77 chains resulting in 373 transplantations during a 46-month period. Therefore, on average, each NDD led to 4.8 transplantations (median, 3; range, 1-30). This extends the trend downward that we saw in our previous analysis of this database on an earlier set of chains<sup>12</sup> (Figure 3). Blood type O NDDs were the most powerful because they initiated chains a mean of 6.0 transplants long (median, 4; range, 1-30) (Table).

However, although NDDs can trigger multiple transplantations through chains, these grafts are directed to patients with incompatible living donors who are usually already on the DDWL but not necessarily at the top. Some physicians argue that this strategy is unfair to patients at the top of the DDWL who miss out on these acts of generosity.<sup>13</sup> One would predict that blood type O patients high on the wait list would be the most disadvantaged, because transplant chains are seldom ended to the wait list with a blood type O donor because, as the “universal donors,” O donors can often extend the chain farther. Blood type AB donors, however, are not in high demand in a database of incompatible donor-recipient pairs because blood type AB recipients can receive a kidney from donors of any blood type.

Therefore, we determined how many blood type O patients were receiving transplantations when NDDs were being directed to chains and performed a multivariate analysis on NDD characteristics to determine which donor characteristic correlated with the greatest influence on blood type O patients. The NKR experience suggests that enabling the blood type O NDDs to start chains leads



**Figure 4.** Distribution of chain lengths by blood type of nondirected donor (NDD). Bars subdivided to indicate how many of nondirected donors of each blood type initiated each chain.

to significantly more blood type O patients receiving transplantations than if these blood type O NDDs had donated directly to blood type O patients on the waiting list. Specifically, 40 blood type O NDDs facilitated transplantations in 112 blood type O recipients (Table). Therefore, chain transplantation benefits blood type O patients without living donors on the waiting list by clearing the list of other blood type O competing patients fortunate enough to have willing, although incompatible, living donors. While these patients were not at the top of the wait list, they would have risen to the top during the ensuing years. Even blood types A and B NDDs led to additional blood type O patients receiving transplantations and presumably being removed from the DDWL. In addition, patients without living donors on the DDWL benefited directly because 67 chains were successfully closed to the deceased list.

These benefits were obtained despite the fact that 7 chains broke prematurely because a bridge donor became unavailable. As reported previously, 3 donors became unavailable for medical reasons, 2 for personal decisions, 1 for a change in employment status, and 1 donor moved away.<sup>12</sup> The relative frequency of broken chains has declined (Figure 2) possibly because the NKR has been following strategies previously identified, including<sup>12</sup> (1) the potential donor’s psychosocial assessment, medical evaluation, imaging studies, and education should be complete prior to activation in the NKR and (2) ending chains to the DDWL earlier. More research needs to be done to identify factors predicting whether bridge donors will back out because the onus should be on transplant centers to only enroll donors who are likely to move forward to donation.

Another concern of participating centers is that they might not benefit if they refer NDDs to a multicenter registry. To alleviate these concerns, the NKR has a policy to end chains at centers that have contributed NDDs such that an equal number of patients from their DDWL receive transplantations.



In conclusion, these 77 NDDs led to 373 transplantations, 296 more than they would have had they donated directly to the DDWL. While blood type O NDDs are in the highest demand by patients on the DDWL, they also have the greatest influence both on the number of transplantations and the number of blood type O recipients in chains. Ultimately, NDDs deserve to understand the options available to them. They should have the choice of donating to a patient at the top of the DDWL or to participate in a donor chain program that may trigger several transplantations in people with willing but incompatible donors, understanding that more transplantations may be possible in larger databases maintained by multicenter programs. Even in the experience described in this article, some NDDs with very specific time constraints were given the option to donate directly to patients on the waiting list without potential living donors. The NDDs should be well informed and allowed to choose how their gift is used.

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**Conflict of Interest Disclosures:** Mr Hil is the founder of a nonprofit organization, the National Kidney Registry (NKR), which facilitates chain transplantation. NKR receives fees to facilitate paired exchange transplants and manage the related logistics process. Drs Melcher, Veale, Davis, and Milner are uncompensated members of the NKR Medical Board.

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**Additional Contributions:** Joe Sinacore, AAS, from the National Kidney Registry managed the database.

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