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Motivations and outcomes of compatible living donor–recipient pairs in paired exchange

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Abstract

Increasing numbers of compatible pairs are choosing to enter paired exchange programs, but motivations, outcomes, and system-level effects of participation are not well described. Using a linkage of the Scientific Registry of Transplant Recipients and National Kidney Registry, we compared outcomes of traditional (originally incompatible) recipients to originally compatible recipients using the Kaplan–Meier method. We identified 154 compatible pairs. Most pairs sought to improve HLA matching. Compared to the original donor, actual donors were younger (39 vs. 50 years, $p < .001$), less often female (52% vs. 68%, $p < .01$), higher BMI (27 vs. 25 kg/m², $p = .03$), less frequently blood type O (36% vs. 80%, $p < .001$), and had higher eGFR (99 vs. 94 ml/min/1.73 m², $p = .02$), with a better LKDPI (median 7 vs. 22, $p < .001$). We observed no

differences in graft failure or mortality. Compatible pairs made 280 additional transplants possible, many in highly sensitized recipients with long wait times. Compatible pair recipients derived several benefits from paired exchange, including better donor quality. Living donor pairs should receive counseling regarding all options available, including kidney paired donation. As more compatible pairs choose to enter exchange programs, consideration should be given to optimizing compatible pair and hard-to-transplant recipient outcomes.

Keywords

clinical decision-making; clinical research/practice; donors and donation: paired exchange; health services and outcomes research; kidney transplantation/nephrology; kidney transplantation: living donor; patient education

1 | INTRODUCTION

Many incompatible donor–recipient pairs enter kidney paired exchange programs to overcome incompatibilities due to blood type, HLA mismatch, donor-specific antibodies, time, or other factors.^{1–4} Numerous innovations in the practice of paired kidney exchange have overcome logistic challenges, such as longer organ transportation times, with evidence of good long-term outcomes.^{5–8} As a result, compatible donor–recipient pairs have begun to enter paired exchange networks.^{9,10} While donor, recipient, and transplant center motivations may vary, the entry of compatible pairs into exchange programs can create system-wide benefits.

The entry of compatible pairs into paired exchange networks was discussed in the early days of paired donation. Using simulations and graph-theoretic optimization, Gentry et al. showed that compatible pairs could double the match rate within paired exchange networks.¹¹ However, these matches come with additional ethical considerations. Compatible pairs within the traditionally incompatible paired exchange are “altruistically unbalanced.”¹² To address this imbalance, compatible pairs should experience benefit, or at minimum equipoise, through participation in a paired donation. Donor–recipient pairs that receive satisfaction in an altruistic act may seek biological equipoise. Other donor–recipient pairs may seek donors of younger age, larger nephron mass, fewer HLA mismatches, or general donor quality measured by the living donor kidney profile index (LKDPI).^{13–17}

Using data from the largest paired exchange clearinghouse in the United States (US), the National Kidney Registry (NKR),¹⁸ we sought to examine the motivations and outcomes of compatible pairs that were transplanted through the system. We investigated potential motivations for participation including altruism, improved LKDPI, age match, and anatomical considerations (e.g., better size or avoidance of vascular anomalies). We also discuss the impact of these compatible pairs on the exchange.

2 | METHODS

2.1 | The National Kidney Registry

This study used data from the NKR, a nonprofit, 501(c) organization that facilitates kidney paired donations for members of its clinical network in the US.¹⁸ We identified 164 compatible donor–recipient pairs that received living donor kidney transplants (KTs) facilitated by the NKR between February 2008 and February 2019. The first known compatible pair transplant occurred in October 2013, so we limited the time period to October 2013 thru February 2019. All originally compatible donors were screened and approved for donation (a requirement for listing in the NKR). All compatible pairs entering the NKR are encouraged to select a reason (or goal) for entering paired exchange at the time of registration. The clinical and research activities of this study are consistent with the Declaration of Helsinki and Declaration of Istanbul. The NKR (based in New York) maintains approval from all participating centers to use data for research purposes; de-identified data for research purposes were exempt from ongoing review (IRB#18–26804).

2.2 | National registry data source linkage

This study used data from the Scientific Registry of Transplant Recipients (SRTR) external release made available in January 2021. The SRTR data system includes data on donors, waitlist candidates, and transplant recipients in the US, submitted by members of the Organ Procurement and Transplantation Network (OPTN).¹⁹ Data on kidney paired donation transplants facilitated by the NKR were linked to the SRTR using unique, encrypted person-level identifiers; they were cross-validated using redundantly captured characteristics (transplant center, transplant date, donor blood type, donor sex, recipient blood type, and recipient sex). Linked data were maintained and analyzed at Johns Hopkins University; this study was exempt from continuing review by the Johns Hopkins University IRB (NA_00042871). As a result of cross-validation, we linked outcomes for 160 (98%) transplants with the original compatible donor (called the “original donor”) and 154 (94%) transplants with the paired exchange matched donor (called the “actual donor”). To enable direct comparisons, we use 154 recipients and their original and actual donors in complete case analyses. We also identified 2115 originally incompatible donor–recipient pairs that were transplanted during the study period as a comparison group.

2.3 | Statistical analysis

Analyses were performed using Stata 15/MP for Linux (College Station, TX). Differences between original and actual donors were assessed using the χ^2 (categorical variables) and Mann–Whitney rank-sum (continuous variables) tests. To assess posttransplant outcomes, death-censored graft failure and mortality, we used Kaplan–Meier plots and compared groups using the log-rank test. We used a two-sided α of .05 to indicate a statistically significant difference.

3 | RESULTS

3.1 | Characteristics of donors

We compared 154 original donors (part of the compatible donor-recipient pair) to the actual living donors who underwent donor nephrectomy through the NKR (Table 1). The median wait time for these transplant procedures was 74 days. Compared to the original donor, actual donors were younger (median 39 vs. 50 years, $p < .001$), less often female (52% vs. 68%, $p < .01$), had higher BMI (median 27 vs. 25 kg/m², $p = .03$), less frequently blood type O (36% vs. 80%, $p < .001$), and had higher eGFR at time of donation (median 99 vs. 94 ml/min/1.73 m², $p = .02$). There were no statistically significant differences observed by African American race, Hispanic ethnicity, or anatomy. The LKDPI (range: -100, 100) measures donor quality for living donors and is set to the scale of the deceased donor kidney donor profile index (KDPI) (range: 0, 100). Actual donor kidneys had lower median LKDPI compared to original donors (7 vs. 21, $p < .001$), suggesting a higher quality organ for the recipient.

Looking at recipient-specific differences between original and actual donors, 107 transplants involved a younger donor (median 11 years younger, IQR: -22, 3), 87 transplants involved a larger donor (median 1 BMI unit larger, IQR: -3, 5), and 84 transplants involved a lower LKDPI kidney (median 7 units lower, IQR: -26, 14). Other reported advantages included better HLA match ($N = 79$) and avoiding low titer donor-specific antibodies ($N = 55$).

3.2 | Characteristics and outcomes of recipients

We compared 154 recipients who were part of a compatible donor-recipient pair to 2,115 recipients who entered the NKR as an incompatible donor-recipient pair (Table 2). Compared to originally incompatible (traditional) recipients, originally compatible recipients were less often female (33% vs. 47%, $p < .001$), younger (median 47 vs. 52 years, $p < .001$), had higher eGFR at time of transplant (median 9 vs. 8 ml/min/1.73 m², $p < .01$), more often preemptively seeking transplant (38% vs. 25%, $p < .001$), spent less time on dialysis (median 0.5 vs. 1.3 years, $p < .001$), and less often highly sensitized (PRA >80%, 5% vs. 20%, $p < .001$). There were no statistically significant differences observed by African American race ($p = .3$), Hispanic ethnicity ($p = .5$), college education ($p = .2$), or blood type ($p = .4$). Originally compatible recipients experienced less delayed graft function (1% vs. 6%, $p < .001$) compared to incompatible recipients. Over a median 3.6 (interquartile range (IQR): 2.6, 5.1) years of follow-up there were no differences in death-censored graft failure (Figure 1A, $p = .7$) or mortality (Figure 1B, $p = .1$).

3.3 | Reported motivations

Of the 154 compatible donor-recipient pairs, 104 reported a motivation/goal for entry. Of these, 28 (26.9%) sought a better HLA match, 19 (18.3%) younger donor, 16 (15.4%) larger donor/kidney, 15 (14.4%) to avoid low level DSA, 6 (5.8%) to avoid complex anatomy, and 6 (5.8%) reported other reasons. Importantly, the remaining 15 pairs (14.4%) reported the motivation was altruistic rather than based on recipient benefit.

3.4 | Observed benefits

We assessed HLA mismatches at the A, B, DR loci. Of the 154 compatible pairs, 90 received equivalent or better HLA matches with their actual (vs. original) donor. Of the 64 that had more A, B, or DR loci mismatches (range 1–4), 40 received a lower LKDPI kidney. For the remaining 24, 6 received younger donors, 12 received heavier donors, 3 received younger and heavier donors. The three remaining had an increase in LKDPI of 3, 8, and 9 points compared to their original donor. The absolute values of the LKDPI in those three were 4, –13, and 16, respectively.

3.5 | System-level effects

Chain lengths ranged from 1 to 10 recipients; a total of 280 transplants were completed in chains that utilized a compatible pair. Of these additional transplants, 13% were in recipients with PRA >80%, and 6% with PRA >95%. Among those receiving these compatible pair enabled transplants, the median wait time was 160 days. There were 23 recipients whose wait times exceeded 1 year prior to being matched through the exchange program, including one recipient who was listed in the NKR for 3.9 years.

4 | DISCUSSION

In this study of paired exchanges facilitated by the NKR, 154 compatible donor–recipient pairs were listed and transplanted through a paired exchange. The recipients in these pairs often received higher quality kidneys (median LKDPI 7 vs. 21) than they would have received from their original donor. Many recipients also experienced other advantages, including receiving younger or larger donors (measured by BMI). There were also profound system-wide benefits including the transplantation of very hard to match recipients. Of the 280 transplants that were facilitated by a compatible pair, 23 (8%) were very hard to match recipients with significant wait time in the NKR. Most compatible pairs joined paired exchange to seek a better match, but some (15/104) reported solely altruistic reasons. Over a median 3.6 years of follow-up, there were no differences in graft failure or mortality when comparing originally compatible recipients to originally incompatible (traditional) recipients.

The sizeable number of additional transplants may have been facilitated by the large number of originally compatible donors who were blood type O. An O donor (in an originally compatible pair) was replaced by a non-O donor (in the actual donation) in 60 cases; of those, 3 went directly to 100% cPRA and 2 to recipients with >90% cPRA. The interquartile range of LKDPI for originally compatible donors was 4–37. Thus, the entry of high-quality O donors enabled the rapid construction of short chains. These practices reflect the graph theory-based simulations presented by Gentry et al., but perhaps with a less dramatic increase in the match rate.¹¹ It is possible that logistical, ethical, or other factors contribute to this difference.

The entry of compatible pairs did not result in access disparities for African American or Hispanic patients in the NKR. Originally compatible recipients reflected the same distribution of traditional recipients and there were no race/ethnic differences between

original and actual donors. We did observe some associations that may suggest an access disparity by socioeconomic factors. Originally compatible recipients were more likely to be preemptively transplanted and not on public insurance. If similar findings are replicated in other paired exchange networks, then educational interventions may be warranted.

While many different motivations for entering paired exchange were mentioned, most compatible pair recipients received multiple advantages. The most common advantage was younger age (107/154), larger size (87/154), and better LKDPI (84/154). It may then be reasonable to assume that nearly all compatible pairs achieved benefit or equipoise regarding donor quality. While beyond the scope of this analysis, we observed that some donor-recipient pairs may have preferred certain advantages over others. For example, a compatible pair may seek a better size match even if the LKDPI is higher. These practices have been observed in other paired exchange networks,^{9,14} but it is unclear whether such advantages impact long term outcomes. There were three compatible pairs that did not receive a strictly better donor kidney as assessed by donor age, donor BMI, HLA mismatch number, or LKDPI. However, the absolute difference in LKDPI were small (less than 10 points), and the absolute value of LKDPI for the actual donor kidney were very low. The compatible pair and transplant centers involved considered this match to reach equipoise.

Many compatible pairs entered the system seeking a “better” HLA match; however, we were unable to systematically assess what qualifies as a better match in the eyes of NKR participants and centers. Given differences between participating centers laboratories, there is no common mean fluorescence intensity (MFI) threshold to designate low-level DSA. While we were able to analyze number of A, B, and DR mismatches, we do not have finer molecular details on this cohort. There are ongoing efforts to better understand HLA compatibility including the use of eplet mismatch load analysis or Molecular Mismatching.²⁰ For instance, recent work highlights the importance of HLA-DQ mismatches for the outcomes of DSA formation, rejection, and graft failure.²¹ NKR is currently employing high-resolution genotyping to improve molecular matching and blood typing (for A subtyping),²² and these efforts may be particularly important for compatible pairs entering paired exchange.

We have previously demonstrated that shipping living donor kidneys are not correlated with death-censored graft failure or mortality,^{5,6} but concerns remain. In the case of a compatible pair, very limited cold ischemia time (CIT) would have been likely for a locally completed transplant. Instead, originally compatible recipients received kidneys with a median CIT of 10 h. Despite the increased CIT, the risk of delayed graft function was low (1%) and there were no differences in outcomes comparing originally compatible recipients to traditional paired exchange recipients. We have previously shown that recipients transplanted through the NKR versus control living donor recipients have no difference in medium-term outcomes in unadjusted and adjusted models.⁷ Thus, the outcomes of originally compatible recipients meet the expectations of benefit or equipoise in outcomes.

Our study represents the largest cohort of compatible pair entries into a paired exchange network. With our robust linkage to the national transplant registry, we were able to study death-censored graft failure and mortality captured through multiple

mechanisms. In addition to measuring realized advantages (e.g., lower LKDPI), our study captured compatible donor-recipient motivations at the time of registration. However, we acknowledge several limitations. The definition of “compatible” was ultimately left to the center, with some adjudication by the NKR. Future studies of compatible pairs may consider definitions that exclude certain donor-specific antibody titers. While we were able to capture the motivations of most compatible pairs, nearly a third of pairs did not respond to this question. Moreover, this question did not allow complex responses. A qualitative study may be better suited to identify motivations for compatible pairs. We were also limited by the small sample size. While we identify several potential confounders that may affect the association between original compatibility status and posttransplant outcomes, we were unable to employ methods to properly account for these biases as well as potential selection bias. Finally, we do not have sufficient data to report on potential compatible pairs that were educated about paired donation but did not participate or were unable to find a suitable match. Such data will be critical for future efforts to build patient support decision tools.

Future studies should also consider how paired exchange networks can ensure equipoise for all compatible pairs. While NKR is the largest single network for paired exchange, other networks have reported use of compatible pairs with varying measures of match quality.^{9,13,14} Several investigators have suggested approaches to improve the ethical use of compatible pairs in paired exchange including a “reciprocity-based strategy.”²³ Gill et al. suggest prioritizing deceased donor allocation for paired exchange recipients who were originally part of a compatible pair; this would protect from graft failures over a 10-year horizon. Such a strategy would require modification to national allocation policy. Currently, all NKR participants, including compatible pairs, are protected from early graft failure (due to primary non-function) and offered a chain-end living donor kidney.⁸ In general, chain end organs work as well as other living donor kidneys.²⁴ Furthermore, NKR participants receive additional protections such as lost wage reimbursement, travel reimbursement, and disability and life insurance through the Donor Shield program (<https://www.donor-shield.org>).²⁵ Other networks should consider such protections to ensure equipoise for compatible pairs entering the paired exchange.

In conclusion, we identified 154 compatible pairs that entered and were transplanted in a large, paired exchange network. All compatible pairs accepted the transplant based on some perceived benefit (or equipoise), with most receiving kidneys from younger, larger, or better quality donors. These 154 compatible pairs, the majority of which included blood type O donors, allowed for 280 additional transplants to occur. Experience with compatible pairs is growing rapidly in the US. Paired exchange networks should continue to evaluate compatible pair entries carefully to ensure ethical balance.

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Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

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DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Dr. Cooper, Dr. Flechner, and Dr. Mandelbrot are on the Medical Board of the National Kidney Registry. Mr. Ronin and Mr. Hil are full-time employees of the National Kidney Registry. Dr. Segev reports that Johns Hopkins University receives institutional support from the National Kidney Registry to provide analytical support for general research activities. The other authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations:

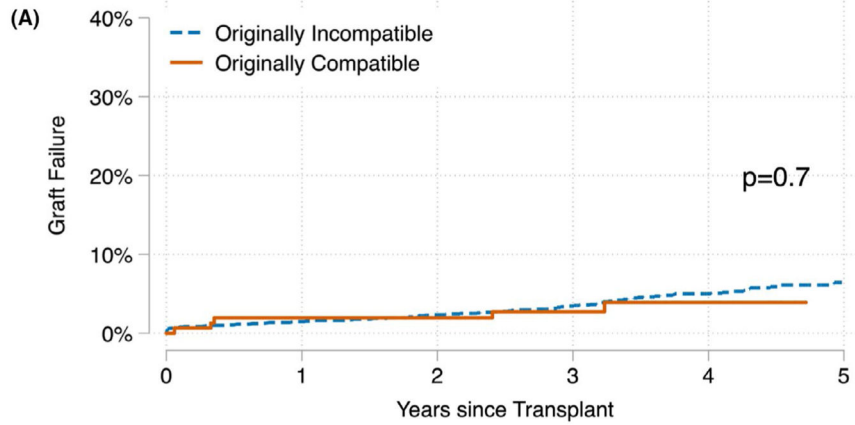
BMI	body mass index
CIT	cold ischemia time
DSA	donor specific antibody
eGFR	estimated glomerular filtration rate
HLA	human leukocyte antigen
KT	kidney transplant(ation)
LKDPI	living donor kidney donor profile index
NKR	National Kidney Registry
SRTR	Scientific Registry of Transplant Recipients

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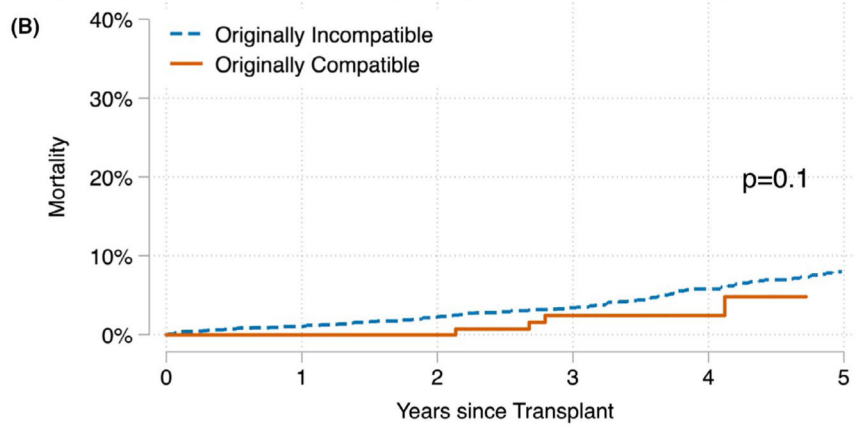
Originally Compatible vs. Originally Incompatible Recipients



Number at risk

Incompatible	2115	2065	1913	1353	938	603
Compatible	154	151	145	97	45	21

Originally Compatible vs. Originally Incompatible Recipients



Number at risk

Incompatible	2115	2093	1955	1398	985	648
Compatible	154	154	148	101	49	24

FIGURE 1. Posttransplant outcomes of graft failure (A) and mortality (B) comparing originally compatible recipients to originally incompatible (traditional) paired exchange recipients

TABLE 1

Characteristics of original and actual donors transplanted in the National Kidney Registry (October 2013–February 2019)

	Original donor	Actual donor	<i>p</i> value
N	154	154	
Female, %	67.5	51.9	<.01
African American, %	6.5	4.5	.5
Hispanic ethnicity, %	11.0	9.7	.7
Median (IQR) age, years	50.0 (42.0–58.0)	39.0 (31.0–47.0)	<.001
Median (IQR) BMI, kg/m ²	25.4 (23.0–28.3)	26.7 (24.2–29.2)	.03
Median (IQR) eGFR, ml/min/1.73 m ²	94.0 (82.0–104)	98.8 (85.9–113)	.02
Median (IQR) LKDPI	20.9 (4.6–37.7)	7.2 (–7.5–18.2)	<.001
Blood type			<.001
A, %	12.3	31.2	
A1, %	2.6	14.3	
A1B, %	0.0	0.6	
A2, %	1.9	1.9	
A2B, %	0.0	0.0	
AB, %	0.0	1.3	
B, %	3.2	14.9	
O, %	79.9	35.7	
Anatomy: renal veins			.1
1, %	93.5	96.1	
2, %	6.5	2.6	
3, %	0.0	0.0	
No data, %	0.0	1.3	
Anatomy: renal arteries			.06
1, %	75.3	85.1	
2, %	21.4	14.3	
3, %	3.2	0.6	
No data, %	0.0	0.0	
ABO incompatible, %	1.9	0.6	.3
Median (IQR) CIT, hours	9.8 (7.1–13.1)	9.5 (6.0–13.0)	.4

TABLE 2

Characteristics of recipients transplanted in the National Kidney Registry (October 2013–February 2019)

	Originally compatible recipient	Originally incompatible recipient	<i>p</i> value
N	154	2115	
Female, %	33.1	46.9	<.001
African American, %	15.6	18.7	.3
Hispanic ethnicity, %	12.3	10.6	.5
Median (IQR) age, years	47.0 (34.0–56.0)	52.0 (41.0–61.0)	<.001
Median (IQR) BMI, kg/m ²	27.2 (24.0–31.6)	26.7 (23.4–30.8)	.3
Median (IQR) eGFR, ml/min/1.73 m ²	8.9 (6.0–14.5)	7.9 (5.5–11.3)	<.01
Preemptive transplant, %	38.3	25.0	<.001
Median (IQR) years on dialysis	0.5 (0.0–1.7)	1.3 (0.0–3.0)	<.001
College education, %	72.0	67.1	.2
Public insurance, %	35.1	54.2	<.001
Diabetes, %	15.6	20.5	.1
Hypertension, %	9.1	16.2	.02
HCV, %	0.7	2.1	.2
Previous transplant, %	14.3	23.1	.01
PRA>80 at transplant, %	4.5	20.2	<.001
Blood type			.4
A, %	43.5	34.9	
A1, %	0.0	0.7	
A1B, %	0.0	0.0	
A2, %	0.0	0.1	
A2B, %	0.0	0.0	
AB, %	5.8	7.6	
B, %	14.3	18.0	
O, %	36.4	38.7	