

## Personal Viewpoint

# Reciprocity to Increase Participation of Compatible Living Donor and Recipient Pairs in Kidney Paired Donation

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**Inclusion of compatible living donor and recipient pairs (CPs) in kidney paired donation (KPD) programs could increase living donor transplantation. We introduce the concept of a reciprocity-based strategy in which the recipient of a CP who participates in KPD receives priority for a repeat deceased donor transplant in the event their primary living donor KPD transplant fails, and then we review the practical and ethical considerations of this strategy. The strategy limits prioritization to CPs already committed to living donation, minimizing the risk of unduly influencing donor behavior. The provision of a tangible benefit independent of the CP's actual KPD match avoids many of the practical and ethical challenges with strategies that rely on finding the CP recipient a better-matched kidney that might provide the CP recipient a future benefit to increase KPD participation. Specifically, the strategy avoids the potential to misrepresent the degree of future benefit of a better-matched kidney to the CP recipient and minimizes**

**delays in transplantation related to finding a better-matched kidney. Preliminary estimates suggest the strategy has significant potential to increase the number of living donor transplants. Further evaluation of the acceptance of this strategy by CPs and by waitlisted patients is warranted.**

**Abbreviations: CP, compatible living donor and recipient pair; DCGL, death-censored graft loss; KPD, kidney paired donation; LD, living donor; NOTA, National Organ Transplant Act; OPTN, Organ Procurement and Transplantation Network; SRTR, Scientific Registry of Transplant Recipients**

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## Introduction

Kidney paired donation (KPD) has emerged as an important strategy to increase living donor (LD) kidney transplantation, but this strategy has not reached its full potential and novel strategies to increase transplantation through the KPD mechanism are needed (1,2). KPD has mostly been used for recipients with preformed antibodies against their potential LD's ABO blood group or HLA (also known as incompatible pairs). Recently, there has been interest in expanding KPD to include ABO- and HLA-compatible LD and recipient pairs to improve their matching on other factors that may limit long-term kidney transplant survival (3,4). For example, an ABO blood group- and HLA-compatible pair (CP) in which the LD is significantly older than the recipient would be considered quasi-compatible based on the donor and recipient age discrepancy (4). In theory, the inclusion of quasi-compatible pairs in KPD has dual potential benefits: Quasi-compatible pairs may find a better match, leading to a potential improvement in long-term transplant survival, and the inclusion of quasi-compatible pairs may increase the chances of matching for incompatible pairs. Surveys have shown that ABO and HLA compatible LDs may be willing to participate in KPD (5–7).

There are important challenges to including quasi-compatible pairs in KPD: Avoiding delays in transplantation is an issue of paramount importance when the

quasi-compatible pair is trying to achieve a preemptive transplantation. However, quasi-compatible pairs are also probably unwilling to significantly delay transplantation when the recipient is requiring dialysis treatment (5,6). Accurately quantifying the potential benefits of a KPD match to a quasi-compatible pair is also challenging (8). For example, it may be difficult to quantify the potential long-term benefits of accepting a younger KPD donor kidney compared with proceeding with a direct LD transplantation to a quasi-compatible pair that is better matched on HLA but mismatched on age.

To avoid these challenges, a reciprocity-based strategy that prioritizes the recipient in an ABO blood group and HLA antigen CP for a repeat deceased donor transplant in the event their first LD KPD transplant fails avoids these challenges. In this strategy, the priority for repeat deceased donor transplantation is a tangible benefit that can be guaranteed in exchange for the CP's participation in KPD before knowledge of the actual match facilitated by the CP.

Despite recommendations that all LDs be advised of their potential to participate in KPD (9), there have been few dedicated strategies to increase the participation of ABO- and HLA-compatible pairs in KPD. The objectives of this study are to introduce the concept of a reciprocity-based strategy, to discuss the practical and ethical considerations with this strategy, and to provide preliminary estimates of the potential impact of a reciprocity-based strategy to increase the participation of ABO blood group- and HLA-compatible pairs in KPD.

## Methods

This study was approved by the University of British Columbia, St. Paul's Hospital ethical review board.

### **Estimation of the potential impact of a reciprocity-based strategy to increase LD transplantation**

We first determined the increase in LD transplantation based on estimates published by Gentry and colleagues of the impact of ABO and HLA CP participation on the match rate for incompatible pairs in KPD in the United States (10). These simulations were based on the following assumptions: a single KPD program operating once per month for a period of 1 year with 250 incompatible pairs and 539 compatible pairs (based on current LD transplant volumes) per month. We then subtracted the number of CP recipients who would require prioritization for a repeat deceased donor transplant by calculating the 10-year incidence of death-censored allograft failure by using the Kaplan–Meier method and data from the Scientific Registry of Transplant recipients (SRTR) to determine the net impact on kidney transplantation. Additional sensitivity analyses of the need for repeat deceased donor transplantation excluded patients who were  $\geq 70$  years at the time of death-censored allograft failure and patients who died within 1 year of returning to dialysis after allograft failure. The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources

and Services Administration and the US Department of Health and Human Services provide oversight to the activities of the OPTN and SRTR.

The net impact on kidney transplantation was determined under two scenarios: (1) CPs were matched in KPD regardless of a matching benefit to the compatible pair or (2) CPs were matched only if there was a matching benefit to the CP. For the purposes of this analysis, two types of benefit were considered: receipt of a younger donor KPD kidney or avoidance of a child or spousal donation for female CP recipients.

## Results

If the KPD program included only incompatible pairs, 37% of pairs ( $n = 1123$ ) would be matched (Table 1). If the KPD program included matches for CPs who would match to a younger donor as well as pairs in which a female recipient avoided transplantation from a spousal or child donor, 69% ( $n = 2071$ ) of incompatible pairs would be matched and 948 CPs (15%) would be matched in the KPD. Including all CPs who matched regardless of whether the CP derived a benefit would result in 75% ( $n = 2263$ ) of incompatible pairs and 1140 CPs (18%) being matched in KPD (Table 1).

Table 2 shows the number of CP recipients who would require prioritization for repeat deceased donor transplant during a 10-year time horizon, assuming a calculated incidence of death-censored graft failure of 19% after 10 years (based on Kaplan–Meier method analysis of LD recipients who underwent transplantation in 2005 and were captured in the SRTR). The number requiring prioritization was calculated with and without the exclusion of CP recipients who were  $\geq 70$  years of age at the time of death-censored graft failure and CP recipients who died within 1 year of returning to dialysis after transplant failure. The number requiring prioritization was shown using three scenarios: only CPs who benefitted from a match were used in KPD, all CPs who matched were used in KPD, and all CPs who agreed to participate in KPD, regardless of whether they matched, were included in KPD.

**Table 1:** Number of incompatible pair and CP transplantations completed with inclusion of CPs in a KPD program<sup>1</sup>

Types of pairs included in KPD	Number of incompatible pair transplants		Number of CP transplants	
Incompatible pairs only	1123	37%	0	0%
CPs who benefit	2071	69%	948	15%
All CPs who match with/without benefit	2263	75%	1140	18%

CP, compatible living donor and recipient pair; KPD, kidney paired donation.

<sup>1</sup>From Gentry et al.<sup>10</sup>

**Table 2:** Number of CP recipients who would require prioritization for a repeat deceased donor transplantation during a 10-year time horizon using different eligibility criteria to receive the prioritization benefit

Eligibility criteria to receive for prioritization for repeat deceased donor transplantation	Number of CP recipients involved in KPD	Proportion of CP recipients with DCGL	Number of CP recipients with DCGL	Number with DCGL and age <70 years at time of DCGL and survival >1 year after DCGL
CPs who matched in KPD and benefitted <sup>1</sup>	948	19%	180	157
All CPs who matched in KPD	1140	19%	217	188
All CPs who participated regardless of whether they matched in KPD	6468	19%	1229	630

CP, compatible living donor and recipient pair; KPD, kidney paired donation.

<sup>1</sup>Benefit defined by receipt of a younger donor kidney or avoidance of a spousal or child donation among women recipients.

Table 3 summarizes the net impact of a 1-year reciprocity-based strategy to increase KPD on transplantation during a 10-year time horizon. The first two columns show the increase in LD transplantation with the use of CPs in KPD. In the base case, where only incompatible pairs participated in KPD, there would be 7591 total LD transplants including 1123 transplants among incompatible pairs in KPD and 6468 direct donor transplants between CPs. This total number of transplants would increase to 8539 if CPs who matched and benefitted were included in KPD, and 8731 transplants would be completed if any CP who matched was included in KPD. The middle three columns show the number of CP recipients who would require prioritization during a 10-year time horizon under different eligibility criteria to receive priority for repeat deceased donor transplant. The number varied from  $n = 36$ , if only CP recipients who matched but did not receive a benefit at the time of the KPD match were prioritized, to  $n = 1229$  if the recipient in every CP who participated in KPD was prioritized regardless of whether he or she matched in KPD. The last two columns show the net potential increase in LD transplantation with the inclusion of CPs in KPD in scenarios with different eligibility criteria to receive priority for repeat deceased donor transplantation, with and without the exclusion of CP recipients who were  $\geq 70$  years at the time of death-censored graft loss or who died within 1 year of returning to dialysis after transplant failure. All strategies involving CPs in KPD produced a large net increase in LD transplantation with the exception of a strategy that provided the repeat transplantation priority to all CP recipients who participated in KPD regardless of whether the pair matched (Table 3).

## Discussion

### **Ethical and legal considerations of a reciprocity-based study**

A fundamental consideration with any incentive-based strategy to increase transplantation is whether the incentive could unduly influence the potential donor's decision to donate. Unlike reciprocity-based strategies in

deceased donation where the incentive is intended to motivate donation (11), a reciprocity-based strategy targets compatible LD and recipient pairs who have already made a decision to proceed with living kidney donation, reducing the possibility that the reward would influence the donor's initial decision to donate a kidney. Nonetheless, prioritization of CP recipients for repeat deceased donor transplantation may be considered a valuable consideration under the National Organ Transplant Act (NOTA) (12). Although NOTA was originally intended to prevent pecuniary payments for organs, an amendment was required (The Charlie Norwood Act) to place KPD on firm legal ground (13). It is noteworthy that reciprocity has long been a fixture of living kidney donation, with priority for deceased donor transplantation provided to living kidney donors who develop end-stage renal disease in the United States since September 1996 (14). This history, together with fact that the proposed incentive is nonpecuniary and is unlikely to exacerbate inequities in access to transplantation, suggests that a reciprocity strategy might be permissible.

A frequently raised ethical consideration regarding the participation of ABO blood group- and HLA-compatible pairs in KPD is an imbalance in benefit for CPs compared with incompatible pairs, leading some authors to conclude that the participation of compatible pairs requires a higher degree of altruism (15). There is little empirical information about the psychological benefits of anonymous donations within or outside of KPD programs (16). Participation of CPs in KPD could also alter the gift relationship and weaken the emotional link between the donor and the recipient (8). Alternatively, participation in KPD might benefit some recipients by making it easier to manage the sense of indebtedness to their donor (8). The possibility of providing a biological benefit to the CP recipient by improved matching on factors beyond ABO blood group and HLA compatibility has been advanced as the main strategy to address this imbalance (4,10). However, the long-term benefit of matching on such factors may be difficult to reliably quantify and cannot be guaranteed in individual patients. For example, some investigators have shown that LD age < 65 years has little impact

**Table 3:** Net increase in transplantation over 10 years with a reciprocity-based system operating during the first year

KPD inclusion criteria	Increase in transplantation		Number of CP recipients requiring priority for a repeat deceased donor transplant under different eligibility criteria			Net increase in transplantation		
	Increase in living donor transplantations	Total number of LD transplantations	Given to	Number of CP recipients eligible for priority	Number of CP recipients who fail and need priority	No age or survival limits for CP recipients to receive priority	Only CP recipients <70 years and survival >1 year after DCGL receive priority	
Incompatible pairs only	0	7591	No one	0	0	0	0	
CPs who match and benefit	948	8539	CPs who match and benefit	948	180	768	791	
CPs who match	1140	8731	CPs who match	1140	217	923	951	
CPs who match	1140	8731	CPs who match but do not benefit	192	36	1104	1109	
CPs who match	1140	8731	All CPs who participate in KPD	6468	1229	-189	71	

CP, compatible living donor and recipient pair; DCGL, death-censored graft loss; KPD, kidney paired donation; LD, living donor.

on long-term transplant outcome (17,18). In contrast, a reciprocity-based strategy directly addresses this imbalance by providing a tangible benefit (i.e. priority for repeat deceased donor transplantation in the event of primary LD transplant failure) that is independent of the actual matching of the CP. The provision of a tangible benefit may also be easier to explain to CPs and minimizes the risk of misrepresenting future benefits of a better-matched kidney that may or may not be achieved in individual patients.

Importantly, a reciprocity-based strategy that is universally applied to all CPs and is independent of the actual matching of the CP minimizes the possibility to unduly influence or commodify CPs who may be more likely to facilitate the transplantation of incompatible pairs in KPD (i.e. compatible pairs with ABO blood group O donors). Transplant programs have an inherent conflict in advancing the participation of CPs in KPD that may contribute to a reluctance to discuss KPD participation with CPs (19,20). The provision of a tangible benefit to the CP may be useful in mitigating this issue and promoting the dissemination of standardized information to CPs regardless of their potential to facilitate transplantation for incompatible pairs.

An ethical concern with KPD in general is that participation in KPD removes ABO blood group or HLA incompatibility as a reason for potential donors to withdraw from living donation and, therefore, may compromise the donor decision-making process (8). Similarly, for CPs involving pediatric recipients who may require more than one transplant in their lifetime, a reciprocity-based strategy weakens the rationale to take advantage of the recipient's pediatric priority for deceased donor transplantation and reserve the potential LD's kidney for future donation after the loss of the recipient's pediatric priority. This may be viewed as beneficial by some donors but also may put pressure on some donors who would rather defer donation. Although these are relevant considerations, contemporary transplant programs have adopted alternative strategies to protect the autonomy of potential donors who decide not to proceed with donor nephrectomy (21).

**Practical advantages of a reciprocity-based strategy**

The fact that a reciprocity-based strategy is independent of the actual matching of the CP should help minimize delays in transplantation related to finding a match that might provide the CP recipient with some arbitrary minimum amount of a biological benefit. The *a priori* provision of a priority for repeat deceased donor transplantation would permit transplantation to proceed as soon as a match was found that provided the CP recipient with a kidney that was as least as good as that of their donor's rather than waiting to find a match that might provide better long-term survival than that donated by their donor. Similarly, the amount of priority provided to the

CP recipient for repeat transplantation could be varied based on the actual duration of death-censored allograft survival of the KPD transplant. A reciprocity-based strategy would also mitigate against the rare, but real, risk of early LD transplant failure and may be useful in reassuring CP recipients in the event of early complications such as delayed graft function that may or may not be related to the donor kidney or the fact that the transplant involved KPD.

A reciprocity-based strategy does not preclude efforts to identify a theoretically better-matched kidney for CP recipients in KPD. At a minimum, we believe the CP recipient should receive a donor kidney that is equivalent in quality to that donated by his or her donor. A reciprocity-based strategy could be combined with a strategy to match the CP recipient with a better-matched kidney, or CPs could even be given a choice of benefits (i.e. priority for repeat deceased donor transplantation, a better-matched kidney, or some weighted combination of the these two benefits based on the actual match identified for the CP). Based on our limited experience with CPs in the Canadian KPD program (22), the inability to provide CPs with a tangible benefit before knowledge of the actual match and uncertainty about whether an individual CP recipient will actually derive the projected benefits of a better-matched KPD kidney are significant practical and ethical challenges with a strategy that relies solely on finding CP recipients a better-matched donor that could be avoided by using a reciprocity-based strategy. However, because our estimates demonstrate only a relatively modest increase in transplantation when a benefit to the CP recipient is not required in the KPD, we could envision a strategy that attempts to find a better match for the CP recipient for a limited period of time but then reverts to a simpler matching algorithm that only requires the CP recipient to receive a kidney that is equivalent to that contributed by the donor. Such a system would not prorate the reciprocity benefit based on the degree of projected matching benefit (which is difficult to predict for individual recipients) but could weight the degree of prioritization for repeat deceased donor transplantation awarded to the CP recipient based on the actual duration of allograft function before the outcome of death-censored allograft failure.

#### **Potential impact of a reciprocity-based strategy on LD**

Although the preliminary estimates provided in this study show that a reciprocity-based strategy may significantly increase LD transplantation, these estimates are only intended to illustrate the mechanics and potential impact of this strategy and should not be considered precise estimates. It would be both premature and impractical to attempt to provide precise estimates of the impact of this strategy, because acceptance of the strategy by CPs is uncertain and because large data sets with information about the actual impact of CP in

contemporary KPD programs are not publically available (i.e. the SRTR does not contain information regarding CP transplants in KPD). Our estimates based on simulations by Gentry and colleagues may overestimate or underestimate the number of transplantations facilitated by CP participation in KPD: Underestimation may result from the fact that the simulations did not include consideration of longer-chain KPD transplantations achieved in contemporary KPD practice and the fact that some CP recipients who have allograft failure may receive a repeat LD transplant and not use their priority for repeat deceased donor transplantation, while overestimation may result from the fact that simulations did not consider the accumulation of difficult-to-match ABO- and HLA-incompatible pairs in KPD programs that occurs over time.

The estimates are conservative because we simply subtracted any transplant ending in death-censored allograft failure from the increase in transplantation facilitated by participation of CPs in KPD. It is important to recognize that an LD transplant immediately removes a patient from the deceased donor waitlist, increasing the opportunity for transplantation for patients without an LD who remain waitlisted. Therefore, even the most liberal strategy evaluated in this study that prioritized all CP recipients who participate in KPD for repeat deceased donor transplantation regardless of whether they matched in KPD would produce an increase in transplantation if the years of allograft function before death-censored allograft failure were not set to zero in our calculations. Similarly, the study estimates do not include the many potential variations in matching criteria, eligibility for prioritization for repeat deceased donor transplantation, or the amount of prioritization that could be incorporated into a reciprocity-based strategy to increase CP participation in KPD. Although future simulation studies to derive such estimates are planned, providing this information is beyond the scope of the current study.

In summary, a reciprocity-based strategy may be more successful in expanding the use of ABO blood group- and HLA-compatible CPs in KPD compared with strategies that rely solely on finding a better match for the CP recipient. We plan future studies to understand acceptance of a reciprocity-based strategy by the transplant community, y compatible donors and recipients, and by waitlisted deceased donor transplant candidates, as well as stakeholder engagement activities, to define an optimal implementation strategy in Canada.

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## Disclaimer

The data reported here have been supplied by the Minneapolis Medical Research Foundation (MMRF) as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation of the SRTR.

## Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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