

Providing Better-Matched Donors for HLA Mismatched Compatible Pairs Through Kidney Paired Donation

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Background. Participation of compatible pairs (CP) in kidney paired donation (KPD) could be attractive to CPs who have a high degree of HLA mismatch, if the CP recipient will gain a better HLA match. Because KPD programs were not designed to help CP, it is important to define allocation metrics that enable CP to receive a better-matched kidney, without disadvantage to incompatible pairs (ICP). **Methods.** Simulations using 46 ICPs and 11 fully HLA-mismatched CPs were undertaken using the Australian KPD matching algorithm. Allocations were preformed adding 1 CP at a time or all 11 CPs at once, and with and without exclusion of unacceptable antigens selected to give a virtual calculated panel-reactive antibody ranging 70% to 80% to improve HLA matching in CP recipients. **Results.** On average, most CP recipients could be matched and had a lower eplet mismatch (EpMM) with the matched donor (57 ± 15) than with their own donor (78 ± 19 , $P < 0.02$). However, only recipients who had an EpMM to own donor greater than 65 achieved a significant reduction in the EpMM with the matched donor. The gain in EpMM was larger when CPs were listed with unacceptable antigens. Furthermore, inclusion of 1 CP at a time increased matching in ICP by up to 33%, and inclusion of all 11 CPs at once increased ICP matching by 50%. **Conclusions.** Compatible pair participation in KPD can increase match rates in ICP and can provide a better immunological profile in CP recipients who have a high EpMM to their own donor when using allocation based on virtual crossmatch.

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The presence of an incompatible blood group (ABO) or of preexisting donor-specific antibodies (DSA) to HLA between a kidney transplant candidate and their intended donor are major barriers to live donor kidney transplantation, ruling out more than 50% of otherwise appropriate pairs.¹ Although the outcomes of ABO-incompatible kidney transplantation are equivalent to ABO-compatible transplants,^{2,3} preformed DSA are associated with worse graft and patient survivals, particularly in the presence of a positive CDC and to some extent flow cytometric crossmatch.⁴ Over the last decade, in many countries, kidney paired donation (KPD) has become an established practice to assist overcoming ABO and HLA incompatibility barriers.^{5–7} Kidney paired donation allows an exchange of kidneys when 2 or more donor-recipient pairs are HLA-incompatible or ABO-incompatible, provided the respective donors are compatible with the reciprocal recipients.^{7,8}

Despite the progressive refinements and expansion of KPD programs, not every incompatible pair (ICP) is able to find a suitable match within a KPD pool. In some programs, the shortage of blood group O donors limits the ability of unsensitized blood group O recipients to be matched. Because of the excellent outcomes with ABO-incompatible live donor kidney transplants, these pairs often opt for directed antibody-incompatible kidney transplantation.^{2,3} As a consequence, the proportion of HLA-incompatible ICP registered in some KPD programs is as high as 85%.⁸ Among these patients, those who are highly sensitized with calculated panel-reactive antibody (cPRA) 95% to 100% tend to accumulate and fail to find a suitable match after multiple match cycles.⁹

The probability of finding a suitable pair to undertake an exchange is greatly influenced by the pool size. Even in a successful large KPD program, only around 60% of ICPs find a match and are transplanted.^{8,10} An alternative strategy to

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increase the pool size is to promote inclusion of ABO-HLA compatible pairs (CP) who may benefit from receiving better HLA matching than with their original donor.^{11,12} Kidney paired donation can be attractive to otherwise CP who have a high degree of HLA mismatch, if the KPD allocation algorithm provides a better HLA match or a younger donor for the recipient in the CP.^{13,14} This could help overcome some of the ethical concerns that inclusion of CP in kidney exchange might raise.¹⁵

A national KPD program was established in Australia in August 2010, allocating compatible donors to recipients using a virtual crossmatch approach that ignores HLA matching between donor and recipient.^{10,16,17} Although a few CPs have been registered and successfully transplanted in this program, it is necessary to determine well-defined inclusion and matching criteria to allow widespread inclusion of CP in the Australian program. Thus, the aims of this CP modelling study were, first, to determine the allocation metrics that would ensure compatible donor-recipient pairs receive the benefit of a better-matched kidney, without disadvantage to ICP; and second, to evaluate gains that can be achieved when CPs are included as an alternative allocation strategy to help highly-sensitized ICP candidates in a KPD program.

MATERIALS AND METHODS

Donors and Recipients

In the Australian KPD program, on average, 45 to 55 ICPs are included in the quarterly match cycles.^{8,10} The pool of ICP from the August 2015 match cycle was used to model the matching outcome after inclusions of CP, this pool included 46 pairs ABO and/or HLA-ICPs. To determine the effect of including CP, we identified 11 pairs who had undergone directed live donor kidney transplantation. Pairs were selected if donors were fully mismatched at HLA-A, -B, and -DR to their recipient, because these are the HLA loci traditionally used in deceased organ donor allocation in Australia. Furthermore, these pairs were selected to have variations and combinations of HLA typing among donors and patients to be sufficiently representative of a broad range of

potential pairs. Compatible pair donors were further fully typed at HLA loci -A, -B, -Cw, -DRB1, -DPB1, -DQB1, -DQA1, -DRB3, -DRB4, and -DRB5 (4-digit HLA typing) to satisfy the requirements of the KPD allocation program.¹⁷ In addition, all CP recipients were also fully typed at all HLA loci. None of these recipients had DSA to the intended donor. For each CP, the eplet mismatch (EpMM) between donor and recipient was calculated for each recipient using the HLAMatchmaker program.¹⁸ The cumulative class I and II EpMM was used to estimate improved matching for recipients in CP added into the KPD run. A gain or loss of 10 EpMM was considered neutral, a gain greater than 10 EpMM was considered a disadvantage, and a loss greater than 10 EpMM, an advantage for the recipient in the CP.^{19,20} Because class II may be more important to match than class I, particularly from the point of view of preventing sensitization, further analysis comparing class I versus class II EpMM was also performed.

Enhancing Immunological Matching for CP Recipients

To enhance the chance of reducing the eplet load (ie, improve HLA matching), a series HLA molecules with greatest EpMM were selected as unacceptable antigens for each recipient to give a virtual cPRA in the range of 70% to 80% (Table 1) to use as an option to improve immunological matching. Additional computer simulations were performed using a virtual cPRA of 90%.

Computer Matching

The allocation was first performed using only the 46 ICP without inclusion of CP. Altruistic donors were not included in the modelling runs, even though 1 altruistic donor participated in the August match cycle. Thereafter, multiple match cycles were performed including 1 each of the selected CP or all CP at once. Match cycles were performed with and without authorization of unacceptable antigens in the Authorized Previous MisMatch row in the National Organ Matching System computer program.¹⁷ Unacceptable antigens in the Authorized Previous MisMatch row exclude recipients to be matched if they share the same antigen.

TABLE 1.

Characteristics of compatible pairs included in match simulation with 46 incompatible pairs of the Australian kidney paired donation Program

Pair-ID	Blood group		EpMM original donor			Unacceptable antigens for exclusion	Virtual cPRA
	Donor	Recipient	Class I	Class II	Total		
CP1	O	O	31	76	107	A1, A24, A36, A80, Cw17, DR53	75%
CP2	O	A	25	72	97	A1, DQA1*01	75%
CP3	AB	AB	28	68	96	DR51, DR52	78%
CP4	O	O	28	64	92	A1, DRw53, DQ2	68%
CP5	O	B	31	53	84	A2, A68, A69, DQA1*01	81%
CP6	O	O	13	66	79	DR53, DQA1*05, DQ7	80%
CP7	O	O	32	46	78	A2, DQA1*01	79%
CP8	AB	AB	20	45	65	A2, DQA1*05	80%
CP9	A	AB	16	41	57	B60, B81, DRw53, DQ2	71%
CP10	O	O	22	32	54	A1, A30, DQA1*05, DQ7	68%
CP11	A	AB	27	27	54	A2, DQA1*05, DQ2	82%

EpMM: number of eplet mismatches to the own donor. Match procedures were performed without and with the optional unacceptable antigens to ensure the compatible donor-recipient pair receives a better-matched kidney.

TABLE 2.**Number of matched pairs after inclusion of 11 CP in a kidney paired donation pool of 46 ICPs**

	No CP added	Virtual cPRA with exclusion of unacceptable antigens		
		No exclusion	70%	90%
Pairs in match cycle	46	57	57	57
Total matches	12	28	26	19
CP matched	—	10	10	5
ICP matched	12	18	16	14
cPRA				
Mean ± SD	70 ± 31	75 ± 30	74 ± 32	73 ± 33
Median (IQR)	77.3 (39-98.9)	79.5 (39-99)	82.4 (39-98.4)	77.3 (39-97)
No. patients ≥97%	1	4	3	2

Match procedures were performed with and without the exclusion of unacceptable antigens to ensure the compatible donor-recipient pair receives a better-matched kidney. IQR, interquartile range.

Data Analysis

The key questions were first, whether the inclusion of CP resulted in more ICP potentially being matched; second, whether the inclusion of CP facilitated matches among highly sensitized ICP (>97% cPRA); and third, whether recipients in CP gain an improved EpMM profile with the matched donor. Statistical analysis was performed with STATA 12.1 (StataCorp. 2011. STATA statistical software: Release 12; StataCorp LP, College Station, TX) Fisher exact test was used for categorical data. Wilcoxon signed-rank test was used for paired continuous data. All *P* values are 2-sided, and a *P* value of 0.05 or less was considered to be statistically significant.

RESULTS

Immunologic characteristics of CP included in the matching simulation studies are shown in Table 1. The number of EpMMs in recipients of CP ranged from 54 to 107. In ICP, donor blood group was 54% O, 35% A, 9% B and 2% AB, recipient blood group was 61% O, 28% A, 7% B and 4% AB. The median cPRA of registered ICP recipients was 98.3% (interquartile range, 39-100%); 61% of them had cPRA of 97% or greater and 35% had cPRA of 99% or greater.

Allocation Without Inclusion of CP

The allocation using ICP only and without inclusion of CP identified 12 possible matches arranged in two 2-way and two 4-way loops. The median cPRA of matched ICP recipients was 69.8% (interquartile range, 39-98.9%), and only 1 matched recipient had a cPRA of 97% or greater (Table 2).

Allocations Adding 1 CP at a Time to the KPD Pool

Of the individual CP entered in the simulation, 10 (91%) found a match when no unacceptable antigens were listed for recipients in the CP. One of these CPs added to the KPD pool of 46 ICP resulted in most instances in 1 to 4 additional matched ICP compared with the original KPD pool matching (Figure 1). When recipients were enlisted with unacceptable antigens corresponding to cPRA of up to 80%, only 9 (82%) found a match, but the inclusion of 1 CP with authorized unacceptable antigens resulted in up to 3 additional matched ICPs in only 45% of the cases. With an average of 1.4 ± 1.6 additional ICPs matched, it compares unfavorably to CP added without exclusions (average ICP match rate, 2.3 ± 1.2 ; $P < 0.005$).

There was no disadvantage to ICP when assigning a virtual cPRA to recipients in CP, with no reduction in the overall number of matches or matches among highly sensitized ICP. Inclusion of a single CP had limited ability to facilitate matches among highly sensitized ICP, with 1 extra ICP recipient with cPRA of 97% or greater being matched in 55% and 36% of cases, when CP were included without and with exclusion of unacceptable antigens, respectively (Figure 2).

Not all recipients in CP gained an improved EpMM profile with the matched donor (Figure 3). The difference in the average EpMM with the own donor (78 ± 19) was not different to the matched donor (69 ± 15 , $P = 0.21$) when CP were entered without unacceptable antigens (Figure 3) but was significantly lower (57 ± 15 , $P < 0.02$) when recipients in CP had unacceptable antigens entered for exclusion (Figure 3). A better EpMM with the matched donor was particularly noticeable for class II antigen (own donor vs matched donor: 54 ± 17 vs 44 ± 16 , $P < 0.21$ without unacceptable antigens and 54 ± 17 vs 31 ± 11 , $P < 0.001$ with unacceptable antigens).

The EpMM with the original donor was a good predictor of potentially improved immunological profile. Recipients whose EpMM to own donor was 65 or greater (CP1-CP8) significantly reduced the EpMM with the matched donor. When CP9-11 was excluded, EpMM to the matched donor was significantly lower without exclusion (69 ± 18 , $P < 0.01$) and with exclusion (55 ± 14 , $P < 0.0001$) of unacceptable

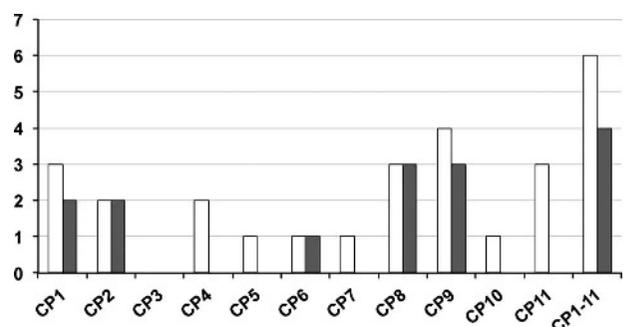


FIGURE 1. Number of new incompatible pairs matched when fully HLA mismatched CPs are included in a kidney paired donation match cycle. Simulations were done by adding 1 CP at a time or all CPs at once (CP1-11). CPs were added without (white bars) or with (solid bars) unacceptable antigens yielding a virtual cPRA of 70% to 80%.

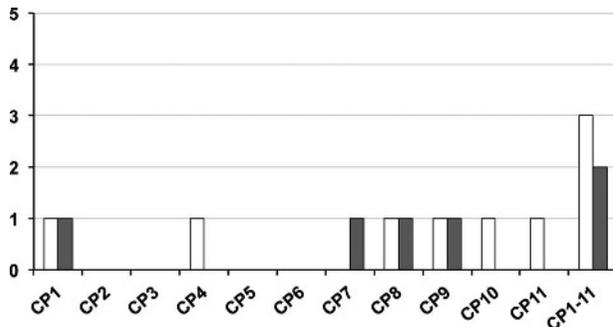


FIGURE 2. Number of new incompatible pairs with cPRA greater than 97% matched when fully HLA mismatched CPs are included in a kidney paired donation match cycle. Simulations were done by adding 1 CP at a time or all CP at once (CP1-11). CPs were added without (white bars) or with (solid bars) unacceptable antigens yielding a virtual cPRA of 70% to 80%.

antigens, compared with the EpMM with the own donor (87 ± 13).

Allocations Adding 11 CP at Once to the KPD Pool

The allocation using the 46 ICPs and 11 CPs identified between 19 and 28 matches, depending on the list of unacceptable antigens assigned to recipients in CP to improve immunological profile of a matched donor (Table 2). Of the CP entered in the simulation, 10 (91%) found a match, regardless whether they were entered without or with unacceptable antigens corresponding to cPRA of up to 80% (Table 2). These facilitated matching of 4 to 6 additional ICP (33-50% more matched ICP), including 2 to 3 additional pairs with a cPRA of 97% or greater (Figures 1 and 2). Increasing the number of unacceptable antigens to 90% resulted in a significantly lower number of matches for CP ($N = 5$), as well as a lower number of additional ICP matched ($N = 2$). On average, the EpMM with the matched donor was significantly better than with the own donor (own donor vs matched donor: 78 ± 19 vs 58 ± 10 , $P < 0.03$ without unacceptable antigens and 78 ± 19 vs 52 ± 17 , $P < 0.01$ with unacceptable antigens). The higher the EpMM to own donor, the greater was the gain in eplet load, and this correlation was strong with both unrestricted

($R^2 = 0.78137$, $P < 0.0001$) and restricted unacceptable antigens ($R^2 = 0.77604$, $P < 0.0001$). However, only recipients who had EpMM to own donor of 65 or greater (CP1-CP8) significantly reduced the EpMM with the matched donor (Figure 4).

A better EpMM with the matched donor was particularly noticeable for class II antigen (own donor vs matched donor: 54 ± 17 vs 38 ± 8 , $P < 0.05$ without unacceptable antigens and 54 ± 17 vs 22 ± 10 , $P < 0.005$ with unacceptable antigens).

Eight CP recipients gained better HLA matching with the matched donor compared to the own donor. Although CPs were fully mismatched at HLA-A, -B, -C, -DRB, -DQB, and -DQA to their recipient, the average match for HLA-A, -B, and -C was 1.2 ± 0.4 , and for HLA-DRB, -DQB, and -DQA, it was 2.1 ± 0.8 (Table 3).

DISCUSSION

This study shows that fully HLA mismatched CP can be included in a KPD program resulting in the majority of CP being able to find an immediate match, with some gaining a better immunological profile with the matched donor. This is not an insignificant number because many donors are genetically unrelated to their intended recipient, and in this instance, an immunological advantage could be important to prevent sensitization. The immunological advantage for CP is only apparent when the EpMM between donor and recipient in the CP is higher than 65. The benefit to ICP of inclusion of CP in a KPD program is the increased number of ICP being matched, which can be up to 30% when a single CP is added or up to 50% when multiple CP are included in a match cycle. Although we undertook what we estimated to be a realistic simulation for the Australian KPD program, where in each quarterly match run, 45 to 55 pairs (10-20 new entries) are included and CP participation may only have a small benefit for ICP, it has been mathematically demonstrated that with larger pools, the match rate increases and therefore the match probability for ICP using our strategy is likely to be higher in larger KPD cohort.

In KPD, the probability of finding a match from 2-way and 3-way loops is dependent on match cycle pool size.^{21,22} One strategy to increase KPD pair numbers is the inclusion of

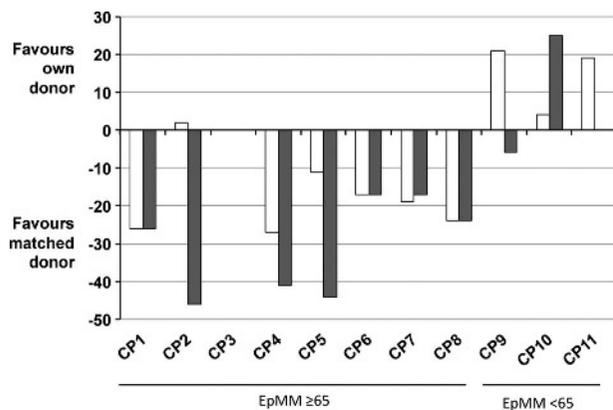


FIGURE 3. Change in the EpMM load in recipients of CP with a matched donor compared with the own donor when 1 CP at a time was included in the match cycle simulations. CPs were added without (white bars) or with (solid bars) unacceptable antigens yielding a virtual cPRA of 70-80%.

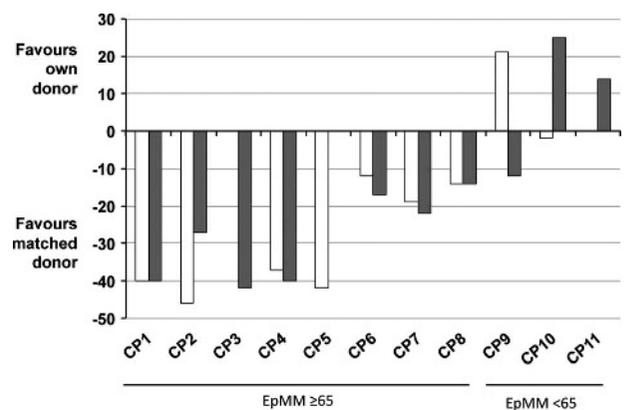


FIGURE 4. Change in the EpMM load in recipients of CP with a matched donor compared to the own donor when all CPs at once were included in the match cycle simulations. CPs were added without (white bars) or with (solid bars) unacceptable antigens yielding a virtual cPRA of 70% to 80%.

TABLE 3.**Number of HLA matches between recipients in compatible pairs and their matched donor, best of any simulation**

Pair-ID	Class I	Class II
	-A, -B, -C	-DRB, -DQB, -DQA
CP1	—	3
CP2	—	3
CP3	2	2
CP4	1	1
CP5	1	1
CP6	—	3
CP7	1	2
CP8	1	2
CP9	—	—
CP10	1	—
CP11	—	—

Compatible pair recipients were fully mismatched at HLA-A, -B, -C, -Dr, -DQB, and -DQA with their own donor.

ABO-HLA compatible, who may also benefit from receiving a transplant better suited for them.^{11,12} Inclusion of CP in KPD was first proposed as a possible solution to help blood group O recipients in a KPD program^{13,23,24}; 1 ABO-ICP is matched to another compatible but nonidentical pair optimizing the total number of living donor transplants. The numerical benefit of including CP in KPD has already been demonstrated by the San Antonio single-center experience.²⁵ However, CP participating in a KPD program may be disadvantaged by waiting for a match, delaying transplant surgery that may otherwise have proceeded, and thus, it is felt that the altruism of their participation should be balanced by benefit potential. Kidney paired donation can be attractive to otherwise CPs who have a high degree of HLA mismatch if the KPD allocation algorithm provides a better HLA match for the recipient in the CP.¹³ The selection of a better-matched donor may ultimately be important for those likely to require repeat transplantation, with lower potential for subsequent sensitization.²⁶

The first aim of this CP modelling study was to determine the allocation metrics that would ensure compatible donor-recipient pairs receive the benefit of a better-matched kidney, without disadvantage to ICP. Inclusion of 1 CP without exclusion of unacceptable antigens in the CP recipient can identify a match for 91% of CP. One pair could not be matched, probably owing to the low recipient match potential of the donor, because he could donate to less than 10% of recipients in the KPD pool, due to the donor's common HLA-A, -B, and -DR antigens. Although most CP pairs are likely to find a match in the first match cycle, not all recipients in CP gain an improved immunological profile with the matched donor, expressed as EpMM. The present findings indicate that the EpMM with the original donor is a good predictor of potentially improved immunological profile; if the recipient in the CP has a high class I+II EpMM of 65 or greater with their donor, they are more likely to gain some immunological advantage with the new match donor. A better immunological matching can be achieved by excluding unacceptable antigens in the CP recipient that would yield a cPRA of 70% to 80% without significantly affecting their match probability and can identify a match for 82% of CP.

However, increasing the number of unacceptable antigens to yield a cPRA of 90% significantly reduces the match probability of CP. The magnitude of the reduction in EpMM with the matched donor for class II antigen was up to 50%, and this is likely to be clinically relevant, as shown by the decreased incidence of transplant glomerulopathy achieved with minimization of HLA-DR and DQ EpMMs.²⁰ Interestingly, if the recipient in the CP has an EpMM less than 65 with their donor, they are likely to have an immunological disadvantage with the new matched donor, regardless of whether the matching is done with or without the inclusion of unacceptable antigens to force a better eplet matching. The study included 2 CP donors that were blood group AB and in general, the match rates for pairs with AB donors are exceedingly low. Because of acceptance of ABO incompatible donor matching for ICP pairs in the Australian program,²⁷ both CP with the AB donor could be matched, and it is therefore encouraging to show that there is no apparent disadvantage for CP with AB donors even in a relatively small pool of ICPs.

Another aim of this CP modeling study was to evaluate gains that can be achieved when CP are included as an alternative allocation strategy to help ICP candidates in a KPD program. Inclusion of 1 CP in a KPD allocation results in up to 33% additional ICP potentially being transplanted in 90% of cases if the CP recipient is allocated without exclusion of unacceptable antigens. However, increased match rate of additional ICP is less than 50%, if the CP recipient is allocated with exclusion of unacceptable antigens yielding a cPRA of 70% to 80%. A key question is whether ICPs are disadvantaged, when CPs are included, particularly when adding a virtual cPRA to recipients in CP. In these simulation studies, no reduction in matches among highly sensitized ICP resulted from the inclusion of CP.

One limitation of the present analysis is that it may be difficult to judge how applicable the outcomes from this study are to other registries, because only 46 ICPs were in the database, and only 11 different CPs were used, and therefore, it could be argued that this is not a representative population. On the other hand, other simulations have demonstrated that match probability increases with pool size,^{21,22} and thus it would be expected that in larger registries, the expected match rates would be even higher.

Although an incompatible donor-recipient pair has to participate in a KPD program to achieve transplantation if they are unable to circumvent their immunological incompatibility with desensitization, a compatible donor-recipient pair does not. Because a benefit is assured for the ICP as compared with the CP, if the compatible recipient does not gain a benefit in participating in KPD, this type of live donor kidney exchange is regarded as unbalanced.²³ Thus, an important aspect of CP participation in KPD includes providing a benefit to the compatible donor-recipient pair. One of the theoretical advantages of CP participation is that it allows the living organ donor to help someone in addition to the intended recipient. Another more tangible advantage is the possibility of the recipient in a CP to receive a better-quality kidney or a better-matched kidney; this approach has been described as risk mitigation.²⁸ The strategy of providing a benefit through a better-quality kidney (younger donor) was addressed Gentry et al¹⁴ by simulating the percentage of donor-recipient pairs who found matches, based

on total number of 539 ICP registered in the KPD program and adding 250 CP. Using simulated donors and recipients, they mathematically demonstrated that CP increased ICP match rates from 28% to 53% when CP were entered to gain a donor age benefit or 64% CP were entered altruistically with no benefit for the recipient.¹⁴ This would indicate that the requirement for risk mitigation does not substantially reduce match rates. These findings are in line with our current simulations showing that avoidance of selected unacceptable antigens allows most recipients in CP to gain improved immunological compatibility with the matched donor, without affecting match rates.

A few studies have explored attitudes of CP toward participation in KPD and demonstrated varying degrees of ambivalence in the willingness to participate in KPD,^{12,13} with only one third of Dutch donor-recipient pairs prepared to consider KPD.¹³ Interestingly, in a more recent study, Hendren et al²⁹ showed that over 90% of compatible donors and recipients were willing to participate in KPD. Compatible pairs were more likely to consider KPD if reimbursement for the costs of participation or an advantage to the recipient (younger donor or better HLA match) were provided. The support of the concept of CP participation in live donor kidney exchange in this study may reflect a growing confidence in a transplant option that has become more widespread and well established only in recent years.

An important factor decreasing the willingness to participate was delay in transplant surgery beyond 3 to 6 months and donor travel.^{12,29} Our simulations suggest that the majority of CP would find an immediate match; even when unacceptable antigens are assigned to the CP recipient to gain a better immunological match. Thus, these findings provide reassurance that a better-matched donor can be identified without excessively delaying the time of surgery.

In conclusion, the present data demonstrate that CP participation in KPD with the purpose to gain a greater HLA compatibility has a considerable potential for increasing KPD volumes while minimizing ethical concerns raised by asking CP to participate in KPD.¹⁵ Our data show that fully HLA-mismatched CP can be included in a KPD program, and the majority of these CP are able to find an immediate match. The immunological advantage for CP recipients is only apparent when the EpMM to the own donor is greater than 65. A better immunological matching can be achieved by excluding unacceptable antigens in the CP recipient that would give a virtual cPRA of 70% to 80%, without affecting CP match probability. The benefit to the pool of ICPs in the KPD program is that the inclusion of HLA-mismatched CP can increase the number of ICP being matched by up to 50%. Compared with 8% of matched ICP having cPRA of 97% or greater without inclusion of CP, the match rate of ICP with cPRA of 97% or greater can increase by up to 22%. Importantly, there is no disadvantage to ICP when assigning a virtual cPRA to CP recipients, with no reduction in matches among highly sensitized ICP.

In conclusion, the present findings help to further quantify the benefit of CPs in KPD programs, which informs not only KPD program development but also informed consent for potential pair participation. Further adoption of this strategy could lead to a significant increase of living donor transplants.

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