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Deceased donors as nondirected donors in kidney paired donation

Wen Wang[1,2] | Michael A. Rees[4] | Alan B. Leichtman[2,3] | Peter X.-K. Song[1,2] | Mathieu Bray[5] | Valarie B. Ashby[1,2] | Tempie Shearon[1,2] | Andrew Whiteman[1] | John D. Kalbfleisch[1,2]

[1]Department of Biostatistics, University of Michigan, Ann Arbor, Michigan

[2]Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor, Michigan

[3]Department of Medicine, University of Michigan, Ann Arbor, Michigan

[4]Department of Urology, University of Toledo Medical Center, Toledo, Ohio

[5]GSK, Research Statistics, Collegeville, , Philadelphia, Pennsylvania

Correspondence
John D. Kalbfleisch
Email: jdkalbfl@umich.edu

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As proof of concept, we simulate a revised kidney allocation system that includes deceased donor (DD) kidneys as chain-initiating kidneys (DD-CIK) in a kidney paired donation pool (KPDP), and estimate potential increases in number of transplants. We consider chains of length 2 in which the DD-CIK gives to a candidate in the KPDP, and that candidate's incompatible donor donates to theDD waitlist. In simulations, we vary initial pool size, arrival rates of candidate/donor pairs and (living) nondirected donors (NDDs), and delay time from entry to the KPDP until a candidate is eligible to receive a DD-CIK. Using data on candidate/donor pairs and NDDs from the Alliance for Paired Kidney Donation, and the actual DDs from the Scientific Registry of Transplant Recipients (SRTR) data, simulations extend over 2 years. With an initial pool of 400, respective candidate and NDD arrival rates of 2 per day and 3 per month, and delay times for access to DD-CIK of 6 months or less, including DD-CIKs increases the number of transplants by at least 447 over 2 years, and greatly reduces waiting times of KPDP candidates. Potential effects on waitlist candidates are discussed as are policy and ethical issues.

KEYWORDS
donors and donation: deceased, donors and donation: paired exchange, health services and outcomes research, kidney transplantation/ nephrology, simulation, statistics

1 | INTRODUCTION

A kidney paired donation pool (KPDP) comprises pairs consisting of kidney transplant candidates and their intended but incompatible donors as well as nondirected donors (NDDs) who are willing to donate a kidney to a candidate in the pool. A virtual crossmatch, based on donor HLA antigens and candidate sensitivities, blood types, and possibly other candidate or donor criteria, provides a tentative set of potential transplants, specifying which candidates are possibly compatible with which donors.[1-4] Transplants proceed through cycles or via chains initiated by an NDD. In a cycle of length k, the donor of the first pair donates to the candidate in the next pair, which is completed when the donor in the kth pair gives a kidney to the candidate in the first pair.[5] A chain of length k is initiated by an NDD, who gives to a candidate in the first pair, the donor of whom gives to the candidate in the second pair. The final donor in the kth pair can either

Abbreviations: 0MM, zero mismatch; APKD, Alliance for Paired Kidney Donation; BD, bridge donor; CPRA, computed panel reactive antibodies; DD, deceased donor; DD-CIK, deceased donor chain-initiating kidneys; DSA, donation service area; HLA, human leukocyte antigen; KDPI, Kidney Donor Profile Index; KPDP, kidney paired donation pool; LD, living donor; NDD, nondirected donor; NEAD, nonsimultaneous extended altruistic donor; SRTR, Scientific Registry of Transplant Recipients.

donate to the deceased donor waitlist, yielding a domino paired donation chain,[6-8] or can stay in the pool as a bridge donor (BD) and act as an NDD in the future, creating a nonsimultaneous extended altruistic donor (NEAD) chain.[9-12]

A KPDP is usually managed through a sequence of match runs, leading to the selection of disjoint cycles and chains for transplant.[13,14] Once a set of transplants is selected, there is a chance that they cannot be implemented for various reasons. For example, the confirmatory laboratory crossmatch may be positive, the patient or donor may be ill or unavailable, or the proposed transplant may be refused. In some instances, there may be fallbacks available when a cycle or chain fails. Fallbacks lead to a wide variety of possible optimization algorithms that can result in substantial improvements in the number of transplants achieved, especially if the time between match runs is large.[15-18] If the withdrawal rates from the KPDP are relatively large, recent work[19] has shown that frequent match runs are most efficient, and in this case, fallback strategies may be less advantageous.

Various authors have suggested using deceased donor kidneys to initiate chains of transplants within a KPDP, where the donor of the last candidate transplanted would give back to the waitlist. Utilizing deceased donor chain-initiating kidneys (DD-CIK) has the potential advantage of leveraging additional transplants resulting from a DD kidney.[20-24] In the simplest case, a DD-CIK is donated to a KPD candidate, whose paired donor, by prior agreement, subsequently donates to the waitlist, thus generating 2 transplants instead of one.

As a proof of concept, we simulate assigning selected DD kidneys to a KPDP by altering the current allocation sequence. For a DD kidney with a Kidney Donor Profile Index (KDPI) number between 21 and 35, we consider offering at most 1 kidney to the KPDP just prior to the allocation of the kidney to the local donation service area (DSA) (see the Appendix S1 for more detail). We report on the simplest case where the donor associated with the KPD candidate receiving the DD-CIK would donate to the waitlist within a few days, if possible, replacing the kidney that was diverted in the allocation scheme. We believe this is of particular interest because it would be logistically a relatively simple way to incorporate DD-CIKs.

Previous articles have discussed ethical and policy issues that can arise from such a proposal. We have included comments on some of these in the Discussion.

2 | METHODS

2.1 | Data

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all deceased donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors. The study also used data on candidates and donors from the Alliance for Paired Kidney Donation (APKD) comprising 2068 pairs and 156 NDDs. Virtual crossmatches for every possible transplant between donors and candidates were assessed based on ABO blood type and HLA antigen-antibody compatibility at HLA-A, B, Bw4, Bw6, Cw, DQB, DR, DRw51, DRw52, and DRw53.

2.2 | Simulating an initial mature KPDP

Each simulation begins with the creation of a "mature" KPDP of size 400 or 800 pairs/NDDs. To achieve this, we consider arrivals of pairs and NDDs at average rates of 30/mo and 1/mo, respectively. We simulate a match run every 30 days, selecting cycles and chain segments of size 3 or less. The probability that a chosen transplant is not completed is the same as in the main simulation described later. If a chosen cycle or chain fails, then we make use of any available fallbacks that might be present. BDs are carried forward to the next match run as in a NEAD approach. We continue this process until the total number of pairs, NDDs, and BDs following a match run is at least 400 (800). This mature pool is intended to mimic KPD pools currently in operation with a large proportion of candidates with high computed panel reactive antibodies (CPRA) and/or of blood type O.

2.3 | The main simulation

1. SRTR data were used to obtain the actual sequence of deceased donors for the calendar years 2016-2017. One kidney obtained from an individual DD with a KDPI between 21% and 35% is eligible to be a DD-CIK unless:
   a. It has been discarded, or transplanted as a medical emergency, or transplanted "en bloc," or simultaneously with another organ (eg, pancreas or liver).
   b. It was donated before being made available to the local DSA as per classification 42 in Table 8-6 of [25]. That is, the kidney was allocated to a zero mismatch (0MM) candidate, a candidate with a CPRA ≥ 98%, a candidate in the same organ procurement organization who is a previous living donor (LD), or a candidate under age 18.
2. Candidates along with 1 or more associated donors and NDDs are drawn at random and with replacement from the APKD database. Events within the KPDP are as follows:
   a. A match run is carried out every 10 days seeking cycles or chain segments of length 3 or less. Chain segments emanate from an NDD or BD. At the end of a chain segment is a BD who is carried forward to the next match run as an NDD.
   b. Each pair or NDD/BD in a selected transplant is unavailable with probability 0.1. In addition, the proposed transplant is unacceptable or yields a positive lab crossmatch with probability 0.1 plus an additional probability depending on the CPRA of the candidate[9] (see Table 1).

TABLE 1 Match failure probability considered in the simulations. These include a baseline probability or rate that depends on calculated panel reactive antibodies (CPRA) plus an additional baseline (BL) amount that is constant across CPRA values

	Match failure probability		
CPRA level	Baseline (BL)[a]	Living donor transplant (BL+ 0.1)	DD-CIK transplant[b] (BL+ 0.2)
75-100	0.50	0.60	0.70
50-74	0.35	0.45	0.55
25-49	0.20	0.30	0.40
0-24	0.05	0.15	0.25

Abbreviation: DD-CIK, deceased donor kidneys as chain-initiating kidneys.

[a]Baseline values are taken from Ashlagi et al.[9]

[b]Exception: BL+ 0.5 for an A candidate with CPRA ≤ 85% and an O donor.

c. In a match run, pairs and NDDs identified for possible transplants are considered "inactive, awaiting transplant" for 9 days, after which untransplanted pairs and NDDs return to the pool. Fallbacks are used if available to salvage matches from failed cycles or chains.
d. Untransplanted pairs depart the KPDP with a probability of 0.0005 each day. This is a relatively low withdrawal rate that corresponds to about a 5% attrition in a 100-day period. We also considered a higher rate of 0.0015 as a sensitivity analysis and the results were similar in character (see Appendix S1).
e. If not transplanted for 90 days (9 match runs), NDDs and BDs leave the pool and potentially donate to the DD waitlist.

3. Deceased donor-initiated chain: One organ is selected from each eligible DD with 1 or 2 eligible kidneys (see #1) and offered to the KPDP just before it would be offered in the allocation sequence to adults in the local DSA. The transplant from a DD-CIK to a pair fails or is refused with a probability of 0.2 plus an additional probability based on the candidate's CPRA (see Table 1, which also describes 1 exception). The organ donated back to the waitlist from the KPDP replaces the diverted DD organ and is offered at the DSA of the originating DD-CIK.

A DD-CIK is allocated to the KPDP as follows:

1. A DD-CIK is given only to a candidate of the same blood type.
2. Candidates with a negative virtual crossmatch are ordered corresponding to the blood types of their donors with precedence O, B, A, AB, and ties are broken by the point score[25] used in the DD waitlist. If the highest-ranked KPDP pair for a given DD-CIK is found to be nonviable, we offer the kidney to the next highest-ranked pair and so on.
3. DD-CIK organs are not allocated to candidates in the KPDP with CPRA >= 98%. Such candidates are already prioritized above the local level in the kidney allocation sequence.[25] These candidates, however, are eligible for transplant in KPDP match runs.

The following factors are varied in the simulation:

1. KPD only vs DD&KPD. In the former, match runs occur only within the KPDP whereas, in the latter, we incorporate DD-CIKs as discussed previously.
2. Number of pairs/NDDs in the initial mature KPDP (400, 800)
3. Number of incompatible pairs entering the KPDP per year (365, 730)
4. Number of NDDs entering the KPDP per year (12, 36, 60)
5. Delay time (months) before a candidate entering the KPDP is eligible for a DD-CIK (0, 1, 3, 6, 12). (This does not affect KPD-only results.)

We performed 6 simulations of 2-year duration for each of the 240 combinations. Table 2 describes the steps in the simulation for the KPD&DD and KPD-only strategies. Simulations were programmed in C++ and carried out on a Linux cluster maintained by the Department of Biostatistics, University of Michigan.

3 | RESULTS

The initial KPDP is generated so as to have characteristics of a mature pool like those currently in existence, thus O blood type and high CPRA are overrepresented in the candidates as shown in

TABLE 2 Summary of the sequence of steps carried out in order each day for each kidney paired donors and deceased donors (KPD&DD) simulation. All steps except step 3 are also carried out in each KPD-only simulation

After the initial pool is created, each simulated day for the KPD&DD consists of the following steps

1. Each active pair exits the kidney paired donation pool (KPDP) with probability 0.0005
2. Arriving pairs/nondirected donors (NDDs) are added to the pool.
3. [a]Deceased donor kidneys as chain-initiating kidneys (DD-CIKs) arriving that day are allocated to the pool if possible. The living donor (LD) associated with the candidate receiving the DD-CIK donates to the DD waitlist (within a few days).
4. At the end of every 10th day a match run maximizing the expected numbers of transplant is carried out, chains and cycles are selected and marked by a transplant due date of 9 days after the current time, associated pairs and NDDs are removed from the pool and made inactive/awaiting transplant for 9 d.
5. Nine days after a match run,
   a. The viability of all transplants in selected chains and cycles is determined.
   b. Transplants are carried out as possible.
   c. Untransplanted pairs and NDDs return to the pool and matches are updated.
6. NDDs/bridge donors (BDs) who are untransplanted for 90 d donate to the DD waitlist.

[a]This step is omitted in a KPD-only simulation.

Table 3. The average time to generate the initial pools of size 400 and 800 was 650 and 1465 days, respectively.

For an untransplanted pair departure rate of 0.0005 per day and various arrival rates and delay times, Tables 4 and 5 summarizes the average number of transplants achieved over 2 years and associated standard errors with an initial pool size of 400 (800) pairs/NDDs, for the KPD&DD and KPD-only strategies. Similar tables for a pair departure rate of 0.0015 per day are presented in the Appendix S1. The final column of each table gives the average number of additional transplants in the KPDP achieved through KPD&DD as compared to KPD only. Over 2 years, these gains vary from 233 to 637 additional transplants across the cases considered. In contrast to the effect on KPD alone, increasing the number of NDDs has only a relatively small effect on the total number of transplants achieved in the KPD&DD strategy but increasing the number of NDDs reduces the number of DD-CIKs used. As the delay time increases, the total number of transplants achieved in the KPD&DD strategy decreases because of a large decrease in the number of DD-CIK transplants offset in part by a smaller increase in LD transplants.

It is important to note that both strategies, KPD&DD and KPD only, result in approximately the same number of organs being offered to the DD waitlist. However, for a kidney identified as DD-CIK, the kidney donated to the waitlist is from an LD under the KPD&DD strategy and from a DD in the KPD-only strategy. In the KPD&DD strategy, the DD-CIKs are replaced with LDs that typically score well compared to the DDs in the KDPI scale.[23] Thus, the gains seen in Tables 4 and 5 reflect the overall gain in numbers of transplants through implementing the KPD&DD strategy. Note that, the gains in number of transplants do not include the LD chain-ending kidneys that are returned immediately to waitlist candidates or any additional transplants from the NDDs or associated BDs who donate to the DD waitlist.

Table 6 summarizes the distribution of blood types of the DD-CIKs and the corresponding LDs who give to the DD waitlist for various delay times and an initial pool size of 400 averaged over all simulations. For example, in the first panel of Table 6, on average 531 of the DD-CIKs are blood type O donating to a blood type O KPD candidate, and 133 blood type O LD kidneys are donated to blood type O candidates on the DD waitlist, thus generating a net total of 664 blood type O recipients transplanted. Most candidates in a KPDP are also on the DD waitlist, so there would be a net increase on average of 133 blood type O waitlist candidates transplanted with KPD&DD compared to KPD only. Donation of 531 DD-CIKs of blood type O to the KPDP generates 115, 81, 305, and 29 blood type O, B, A, and AB LD donations to the waitlist. The average number of O transplants per DD-CIK of blood type O is 664/531 = 1.25 for a delay time of 0, and 1.21, 1.18, and 1.15 for delay times of 3, 6, and 12 months. Note that, the results in Table 6 are averaged over the levels of all variables not controlled in the table.

For various inputs, Figures 1 and 2, respectively, exhibit the distribution of CPRA and candidate blood type in the KPDP for the KPD&DD and KPD-only strategies for an initial pool size of 400. Additional results for pool size 800 are given in the Appendix S1. In all of these results, the pairs with CPRA ≥ 98 have been removed because their allocation priority precedes the allocation of the DD at the local level. Table S4 summarizes some simulation results on CPRA ≥ 98 candidates. In the KPDP&DD strategy, the pool size rapidly decreases for 150-250 days and then is stable with 100 to 200 pairs in statistical equilibrium with input and output in balance. In the KPD-only strategy, the pool continues to increase steadily with time.

Figure 3 shows the average accumulated number of DD-CIK transplants, LD transplants from chains, and LD transplants from cycles in the KPDP over the 2 years for arrival rates of 365 and 730 pairs per year and 36 vs 60 NDDs per year. Results are averaged over other variables. In the KPD&DD strategy, the overall number of transplants does not depend much on the arrival rate of NDDs although this does affect the distribution of transplants between chains and cycles. The cumulative plot for DD-CIK transplants shows that an equilibrium is reached after 150 days when the plot becomes linear; in equilibrium, the KPD&DD strategies would divert on average approximately 160-275 DD-CIKs on an annual basis. In the KPD-only strategy, the number of transplants increases with the arrival rate of NDDs.

For specific inputs, Figure 4 presents average Kaplan-Meier curves for the waiting time for transplant of patients in the KPDP depending on patient blood types and CPRA in the KPD&DD vs KPD-only strategies. Table 7 presents medium waiting times for a transplant as well as the percentage transplanted by 200 days for blood type and CPRA groups. As can be seen, waiting times tend to be shorter for the KPD&DD strategy and much shorter for blood type O candidates in particular.

4 | DISCUSSION

In this article, we considered the simplest of possible chains created by the DD-CIK, where the donation to a candidate in the KPDP is

TABLE 3 Average distribution of candidates' blood type and CPRA in an initial mature pool of size 400 and APKD database

KPDP candidate population	Candidate blood type distribution (%)				Candidate CPRA distribution (%)			
	O	B	A	AB	0-30	31-85	86-97	98-100
Initial mature pool	67.3	11.9	18.5	2.3	34.7	18.3	17.3	29.7
APKD database	61.3	13.2	23.5	2.0	43.1	22.9	15.3	18.7

Abbreviations: APKD, Alliance for Paired Kidney Donation; CPRA, calculated panel reactive antibodies; KPDP, kidney paired donation pool.

TABLE 4 Number of transplanted KPDP candidates over 2 y for KPD&DD and KPD-only strategies for an initial pool size of 400 and untransplanted pair/NDD departure rate of 0.0005 per day

Pair arrivals per year	NDD arrivals per year	Delay (mo)	Strategy				Transplants gained
			KPD&DD			KPD-only	
			LD	DD	Total	Total	
365	12	0	77.3 (4.7)	694.2 (13.2)	771.5 (16.5)	329.0 (14.7)	442.5 (4.5)
		1	223.5 (11.8)	532.8 (6.0)	756.3 (15.2)	329.0 (14.7)	427.3 (4.5)
		3	265.0 (8.5)	465.2 (9.8)	730.2 (15.2)	329.0 (14.7)	401.2 (4.6)
		6	286.2 (14.5)	398.8 (3.7)	685.0 (14.5)	329.0 (14.7)	356.0 (5.5)
		12	309.8 (12.7)	292.5 (6.6)	602.3 (14.9)	329.0 (14.7)	273.3 (2.5)
	36	0	114.0 (7.7)	664.2 (10.9)	778.2 (16.8)	369.0 (18.0)	409.2 (3.4)
		1	268.8 (12.9)	497.2 (3.8)	766.0 (14.0)	369.0 (18.0)	397.0 (5.4)
		3	307.8 (15.9)	424.3 (6.3)	732.2 (14.6)	369.0 (18.0)	363.2 (4.8)
		6	327.3 (14.1)	363.8 (4.1)	691.2 (14.2)	369.0 (18.0)	322.2 (5.5)
		12	345.7 (14.9)	269.2 (6.6)	614.8 (14.6)	369.0 (18.0)	245.8 (6.4)
	60	0	137.3 (6.5)	649.5 (16.7)	786.8 (20.1)	388.8 (14.5)	398.0 (6.5)
		1	294.2 (12.6)	466.5 (5.3)	760.7 (15.9)	388.8 (14.5)	371.8 (3.6)
		3	324.7 (12.3)	408.7 (8.6)	733.3 (19.6)	388.8 (14.5)	344.5 (6.1)
		6	349.2 (15.0)	341.5 (3.3)	690.7 (17.5)	388.8 (14.5)	301.8 (3.7)
		12	371.0 (14.1)	250.8 (7.9)	621.8 (18.7)	388.8 (14.5)	233.0 (5.0)

Numbers in parentheses are standard errors. The final column represents the 2-y gain in the number of transplants in the KPD&DD group. Note that both strategies transplant the same number of candidates on the DD waitlist.

Abbreviations: KPD&DD, kidney paired donors and deceased donors; KPDP, kidney paired donation pool; LD, living donor; NDD, nondirected donor.

TABLE 5 Number of transplanted KPDP candidates over 2 y for KPD&DD and KPD-only strategies for an initial pool size of 400 and untransplanted pair/NDD departure rate of 0.0005 per day

Pair arrivals per year	NDD arrivals per year	Delay (mo)	Strategy				Transplants gained
			KPD&DD			KPD-only	
			LD	DD	Total	Total	
730	12	0	166.0 (10.0)	1125.8 (11.0)	1291.8 (16.1)	655.2 (12.1)	636.7 (8.9)
		1	483.0 (12.2)	797.7 (5.0)	1280.7 (15.1)	655.2 (12.1)	625.5 (7.9)
		3	558.2 (16.4)	666.0 (10.0)	1224.2 (15.9)	655.2 (12.1)	569.0 (8.7)
		6	601.8 (12.1)	541.0 (4.5)	1142.8 (13.6)	655.2 (12.1)	487.7 (5.2)
		12	640.0 (11.9)	361.7 (8.3)	1001.7 (16.4)	655.2 (12.1)	346.5 (9.9)
	36	0	239.7 (6.2)	1053.2 (13.2)	1292.8 (14.9)	701.3 (13.1)	591.5 (12.6)
		1	530.3 (10.4)	745.0 (5.4)	1275.3 (12.4)	701.3 (13.1)	574.0 (10.1)
		3	607.7 (9.2)	619.3 (13.2)	1227.0 (17.9)	701.3 (13.1)	525.7 (13.5)
		6	636.5 (12.5)	512.0 (4.5)	1148.5 (14.8)	701.3 (13.1)	447.2 (4.6)
		12	672.2 (12.2)	345.2 (9.1)	1017.3 (16.9)	701.3 (13.1)	316.0 (14.1)
	60	0	279.0 (6.4)	1028.7 (18.1)	1307.7 (19.7)	727.8 (12.2)	579.8 (14.3)
		1	571.5 (9.4)	719.0 (6.7)	1290.5 (11.9)	727.8 (12.2)	562.7 (5.4)
		3	631.2 (13.5)	604.3 (13.4)	1235.5 (18.9)	727.8 (12.2)	507.7 (13.2)
		6	673.5 (10.1)	490.3 (2.4)	1163.8 (10.5)	727.8 (12.2)	436.0 (3.6)
		12	699.2 (11.0)	324.8 (11.1)	1024.0 (17.5)	727.8 (12.2)	296.2 (10.4)

Note: Numbers in parentheses are standard errors. The final column represents the 2-y gain in the number of transplants because of the KPD&DD strategy. Note that both strategies transplant the same number of candidates on the DD waitlist.

Abbreviations: KPD&DD, kidney paired donors and deceased donors; KPDP, kidney paired donation pool; LD, living donor; NDD, nondirected donor.

TABLE 6 Blood types of DD-CIKs directed to KPDP and of the corresponding LD donating to the DSA tabulated by the delay time (the time from entry of a pair to the KPDP until the candidate is eligible for DD-CIK transplant)

Delay (mo)	Deceased donor blood type	Living donor blood type				
		O	B	A	AB	Total
1	O	115.4	81.3	305.2	28.9	530.8
	B	7.8	9.5	13.5	11.5	42.3
	A	8.6	4.3	20.7	14.9	48.5
	AB	1.1	0.6	1.4	1.7	4.7
	Total	132.8	95.8	340.8	57.0	626.4
3	O	84.9	67.9	281.0	27.7	461.6
	B	4.6	7.1	8.4	10.2	30.5
	A	5.4	2.2	15.6	12.9	36.1
	AB	0.4	0.4	1.0	1.4	3.2
	Total	95.4	77.6	306.1	52.2	531.3
6	O	62.4	56.1	244.1	25.0	387.8
	B	2.9	5.6	6.2	9.3	24.2
	A	3.0	1.5	11.9	10.5	26.9
	AB	0.3	0.2	0.8	1.2	2.4
	Total	68.7	63.5	263.1	46.0	441.2
12	O	37.9	37.1	180.2	19.6	274.8
	B	1.4	3.4	3.3	7.0	15.1
	A	1.5	0.7	6.4	7.2	15.7
	AB	0.2	0.1	0.6	0.8	1.8
	Total	41.0	41.4	190.4	34.6	307.4

Note: Results are for an initial pool size of 400 and untransplanted departure rate of 0.0005 per day; and are averaged across simulations including pair arrival rates of 365 or 730 per year and NDD arrival rates of 12, 36, or 60 per year.

Abbreviations: DD-CIK, deceased donor kidneys as chain-initiating kidneys; DSA, donor service area; KPD&DD, kidney paired donors and deceased donors; KPDP, kidney paired donation pool; LD, living donor; NDD, nondirected donor.

followed by a donation by that candidate's LD to the DD waitlist. There would be possibilities of longer chains,[20-22] and we are investigating these, but this simplest case is of interest in its own right because each transaction involving a DD-CIK is typically concluded in a few days. In addition, we have demonstrated that this approach results in a substantial increase in the number of transplants achieved. Even in the environment of several KPD programs as in the United States, this approach would be relatively simple to implement, perhaps with some rules to accommodate allocating DD-CIKs to the different pools.

There are many variations that could be considered that involve different selections of DD-CIKs or different ways of handling DD-CIK donations.[21,22,24] For example, one could divert a smaller proportion of organs over a wider KDPI range (21-85 say, instead of 21-35 as modeled here); it would then be important to build into the simulation acceptance probabilities depending on KDPI of the DD-CIK, in addition to CPRA of the KPD candidate, and perhaps other variables.

Candidates with CPRA ≥ 98% are currently given priority in the OPTN allocation system.[25] It would be possible to prioritize in the allocation sequence, CPRA ≥ 98% candidates in the KPDP over CPRA ≥ 98% candidates generally. This could be done with the prearranged agreement that the incompatible donors of the high CPRA candidates would correspondingly donate to the waitlist. Currently such candidates could receive a DD transplant given the priorities in the allocation sequence, but there would be no expectation that the associated LD would donate to the waitlist. Note that 0MM could be treated in a similar manner, as could donations of DDs with KDPI ≤ 20%.

The role of NDDs in the KPD&DD strategy is particularly interesting. Overall, increasing the number of NDDs does not appreciably increase the number of transplants in the KPD&DD strategy although it does in the KPD-only strategy. In the KPD&DD strategy, however, increasing the number of NDDs results in a similar decrease in the number of DD-CIKs required. In the simulations, each NDD or BD arising from an NDD initiated chain donates to the DD waitlist after 90 days with no match. So, even in the KPD&DD strategy, NDDs increase transplants overall, just not in the KPDP.

Similarly, increasing the delay time results in a decrease in the number of transplants gained offset by a substantial decrease in the number of DD-CIKs used (Table 4). It may seem important to have a period of time before a new arrival to the KPDP is eligible for a

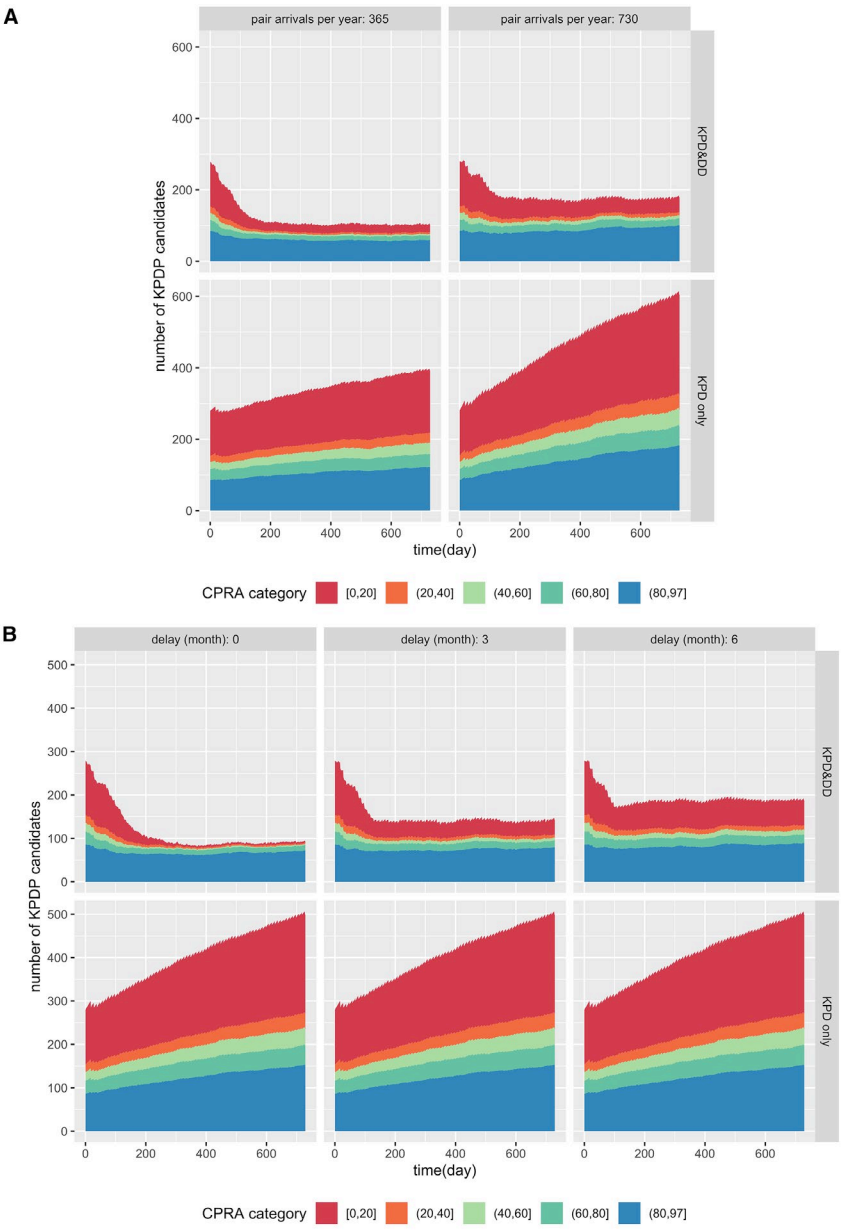

FIGURE 1 Distribution of calculated panel reactive antibodies (CPRA) in the kidney paired donation pool (KPDP) over time is presented for kidney paired donors and deceased donors (KPD&DD) and KPD-only strategies. Candidates whose CPRA is ≥98% are excluded from this figure. (On average there are about 119 candidates with CPRA ≥ 98% in the initial mature pool.) Results are for an initial pool size of 400 and an untransplanted departure rate of 0.0005 per day. In (A) results are averaged across simulations including nondirected donor (NDD) arrival rates of 12, 36, or 60 per year and delay times of 0, 3, or 6 mo. In (B) results are averaged across all simulations including pair arrival rates of 365 or 730 per year and NDD arrival rates of 12, 36, or 60 per year

DD-CIK transplant, so the delay time of 0, which is optimum in terms of the number of transplants achieved, may not be acceptable. A delay time of 3 months or possibly 6 months may be a reasonable compromise.

This use of DD-CIKs gives a new category of candidate, namely one with a willing but incompatible donor, a high priority in the allocation sequence, which is similar to that given to 0MM candidates or patients with CPRA ≥ 98%. In 2016, there were 609 and 1427 DD organs allocated to 0MM and CPRA ≥ 98%, respectively, and in total 955 of these were blood type O. In contrast, this proposal would have diverted a much smaller number of DDs. For example, in an initial pool of 400 and 730 pair arrivals per year with a 3-month delay, an average of 315 DD-CIKs would have been diverted over each of the 2 years (Table 5). Furthermore, unlike priority to 0 MM and CPRA ≥ 98%, a priority for DD-CIK would increase the total number of transplants achieved.

Patients with LDs tend to be from a higher socioeconomic group and so priority to DD-CIKs could be seen as further disadvantaging underrepresented minorities. This priority, however, would maintain the same number of transplants offered to the waitlist, so there is no overall disadvantage to patients who do not have a LD. In fact, the overall average waiting time on the waitlist would be decreased by the policy (because KPD candidates are also waitlist candidates) and the policy would reduce the demand for DDs generally. On the other hand, the use of DD-CIKs in this way might negatively affect some candidates, especially O candidates with high PRA near the top of the waitlist.[20,21,24] If, however, a DD is compatible with such a candidate in the local DSA and that donor has 2 kidneys to offer at the local level, one would be a DD-CIK whereas the other could still transplant the local candidate.

One concern about the use of DDs as NDDs is that the LD returning to the waitlist may be of poorer quality than the DD-CIK (eg,

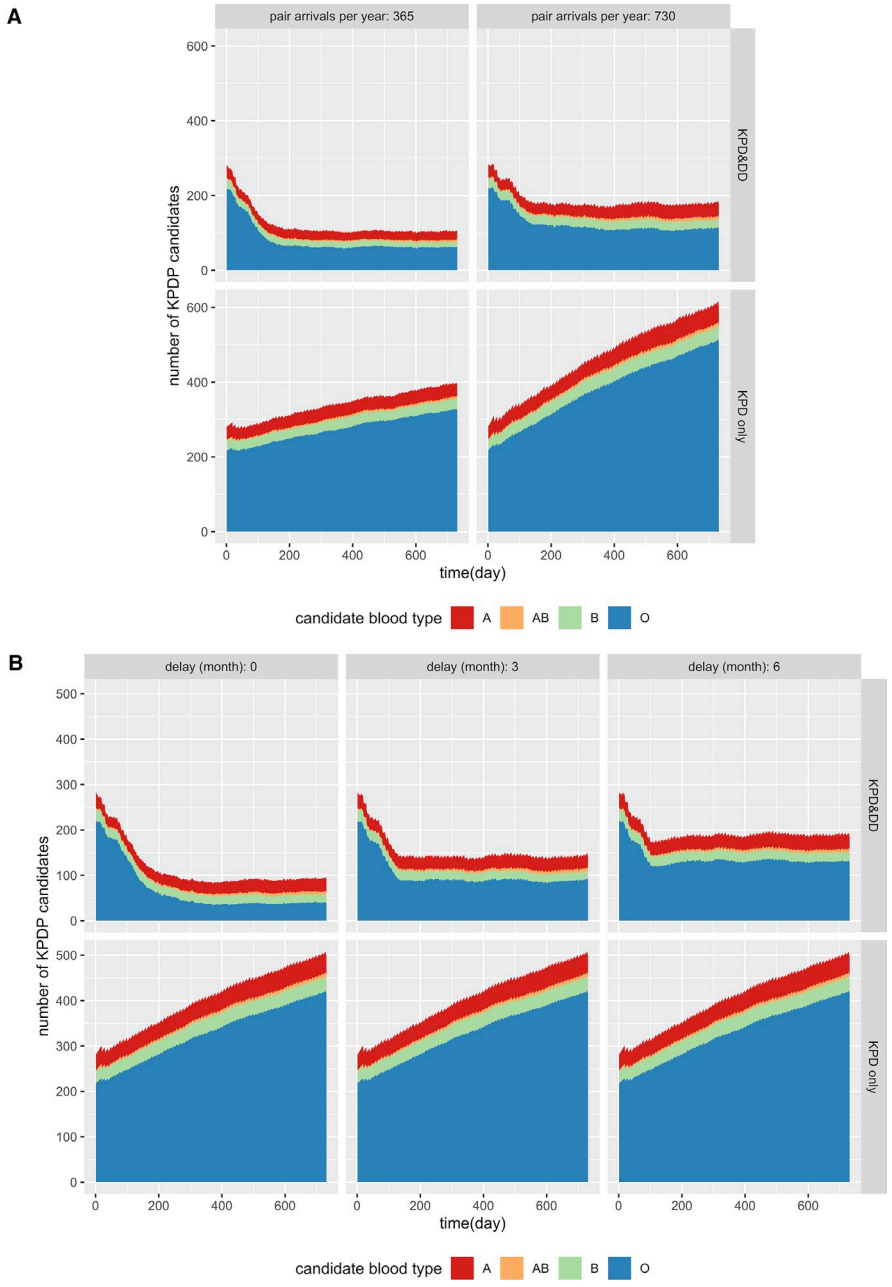

FIGURE 2 Distribution of blood type in the kidney paired donation pool (KPDP) over time is presented for kidney paired donors and deceased donors (KPD&DD) and KPD-only strategies. Candidates whose calculated panel reactive antibodies (CPRA) is larger than 97 are excluded from this figure. (On average there are about 119 candidates with CPRA ≥ 98% in the initial mature pool.) Results are for an initial pool size of 400 and an untransplanted pair departure rate of 0.0005 per day. In (A) results are averaged across simulations including nondirected donor (NDD) arrival rates of 12, 36, or 60 per year and delay times of 0, 3, or 6 mo. In (B) results are averaged across all simulations including pair arrival rates of 365 or 730 per year and NDD arrival rates of 12, 26, or 60 per year

20-22, 24). In our simulation, the KPDI of the LD[23] is less than the KDPI of the corresponding DD-CIK in 85% of the cases. Figure S5 also shows that the average KPDI of the LD is substantially less than that of the DD-CIK, which assures that the waitlist benefits in respect to the average quality of donations. It would be possible to constrain the simulation so that the LD KDPI is always less than or equal to the KDPI of the DD-CIK or to put in other limitations. Such constraints should be balanced against the consequent loss in number of transplants achieved.

We have placed the DD-CIK priority after allocation to multiorgan, highly sensitized, and zero mismatch candidates, but just above the allocation to adults in the local DSA as proposed in [20]. If this priority were to be added to the allocation sequence like other allocations above the local level, then as for 0MM transplants, there would be no adult in the local DSA from whom this organ has been "taken."[20]

We have not incorporated a renege rate for the LD corresponding to the DD-CIK. Based on published estimates of renege rates in,[26] we would expect the renege rate to be relatively small, especially because the donation to the waitlist is intended to be completed within days. If there were a renege rate of 2%, say, then the number of additional transplants in Table 4 would be reduced by about 2% of the DD-CIK transplants. Such reneges could be balanced by early allocation of a bridge donor or NDD to the waitlist.

The OPTN article[21] outlines 3 approaches to deceased donor-initiated chains. In a Candidate-Driven KPD Chain, the candidate donor pair agree to participate and the candidate is given high priority on the waitlist. After the candidate is transplanted, the donor enters the KPDP match runs and begins a chain ending with a donation to the waitlist. In a List Exchange KPD Chain, a candidate's LD first initiates a chain and then the candidate is entered into the waitlist with high

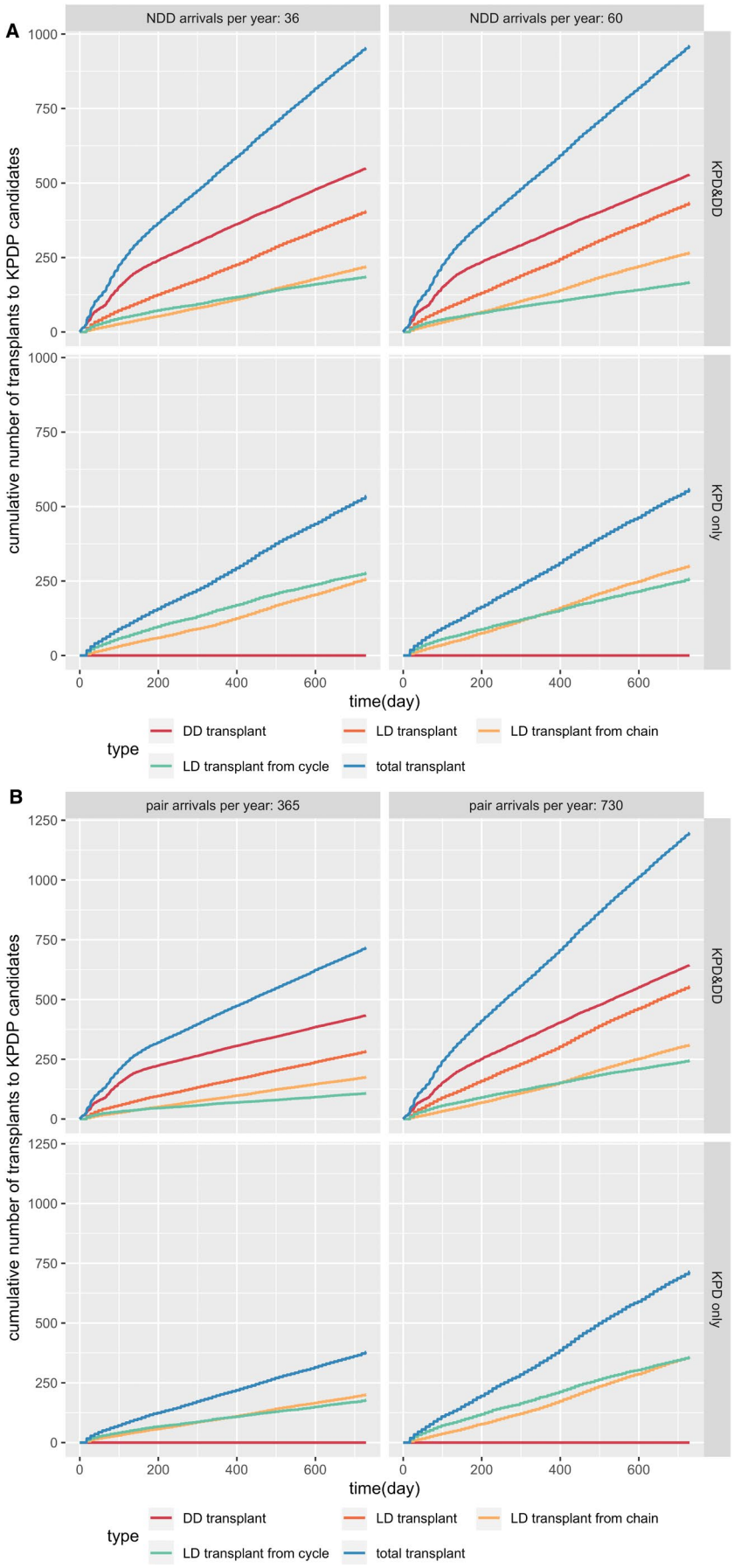

FIGURE 3 Average cumulative numbers of transplants to kidney paired donation pool (KPDP) candidates by living donors (LDs), deceased donors (DDs), chains and cycles over time for kidney paired donors and deceased donors (KPD&DD) and KPD-only strategies with an initial pool size of 400 and untransplanted pair departure rate of 0.0005 per day. In (A) results are averaged across simulations including 365 or 730 pair arrivals per year and delay times of 0, 1, 3, 6, or 12 mo. In (B) results are averaged across all simulations including 36 or 60 nondirected donor (NDDs) per year and delay times of 0, 1, 3, 6, or 12 mo [Color figure can be viewed at wileyonlinelibrary.com]

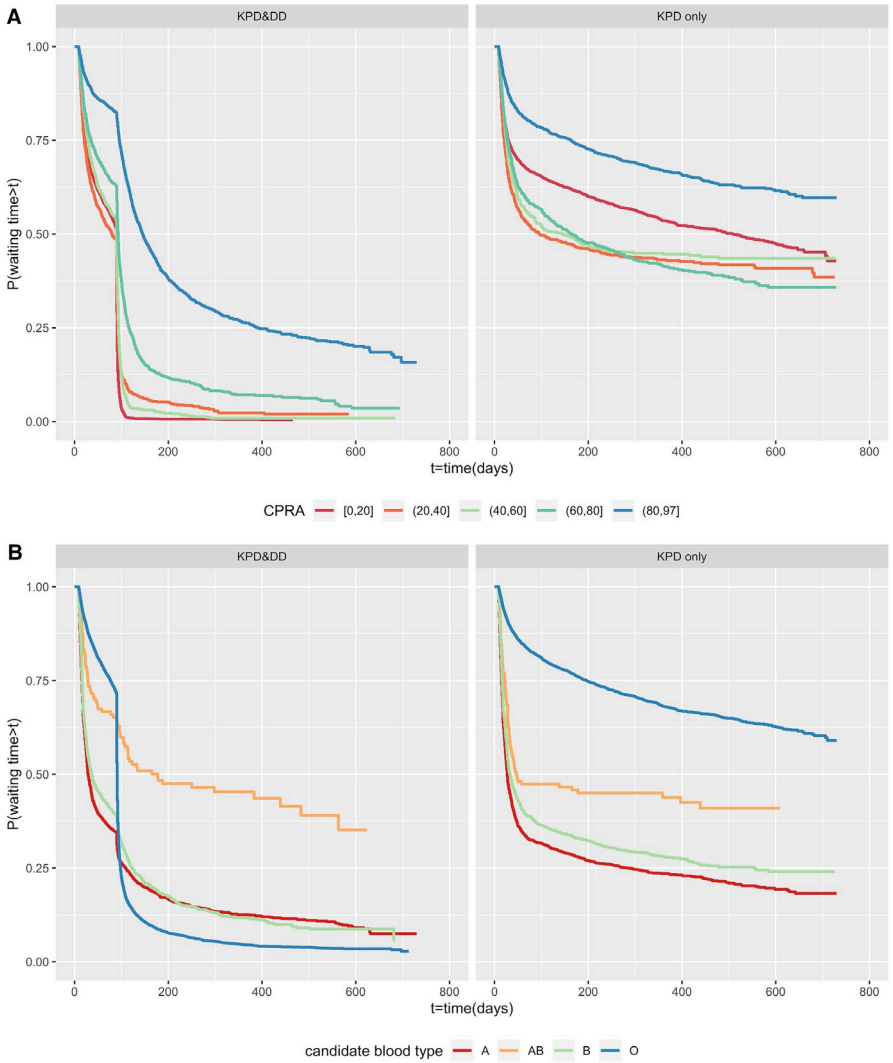

FIGURE 4 Average Kaplan-Meier estimates for kidney paired donation pool (KPDP) candidate wait times categorized by calculated panel reactive antibodies (CPRA) (A) and candidate blood type (B) for kidney paired donors and deceased donors (KPD&DD) and KPD-only strategies. Results are for an initial pool size of 400, an untransplanted departure rate of 0.0005 per day, pair arrival rate of 365 per year and a delay time of 3 mo. Results are averaged over nondirected donor (NDD) arrival rates of 12, 36, or 60 per year

TABLE 7 Median waiting time in days (MWT) and percent transplanted at 200 d (%Tx) in the KPDP for initial pool size of 400 and withdrawal rate of 0.0005 per day, 365 arrivals per year, delay time of 3 mo, and averaged over other variables

		Candidate blood type				Candidate CPRA				
Type	Method	O	B	A	AB	0-20	21-40	41-60	61-80	81-97
MWT	KPD-only	>730	33.0	27.0	48.0	511.0	96.0	147.0	164.0	>730
	KPD&DD	91.0	37.0	29.0	177.0	90.0	80.0	90.0	93.0	145.0
%Tx	KPD-only	25%	68%	73%	55%	40%	54%	53%	52%	27%
	KPD&DD	92%	83%	83%	52%	99%	95%	98%	88%	62%

Abbreviations: CPRA, calculated panel reactive antibodies; KPD&DD, kidney paired donors and deceased donors; KPDP, kidney paired donation pool.

priority. The approach we have taken is closest to the Donor-Driven KPD chain whereby a candidate agrees to a DD-CIK transplant after which the candidate's LD begins a chain ending in a donation to the waitlist.

In summary, we have shown that strategies that would divert some DD kidneys to serve as DD-CIKs in a KPDP have the potential to substantially increase the number of transplants achieved in the KPDP and overall logistical issues with implementing a strategy such as this are of course crucial and these would need to be worked through in order to implement a real-world approach.

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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 Michael Rees has an ownership interest in Rejuvenate Healthcare, LLC, and is the noncompensated CEO of the Alliance for Paired Kidney Donation. Dr Mathieu Bray contributed to this project while he was a PhD student at the University of Michigan. He is now employed as a statistical scientist at GlaxoSmithKline, SLC.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Scientific Registry of Transplant Recipients and the Alliance for Paired Kidney Donation. Restrictions apply to the availability of these data, which were used under data use agreements for this study.

ORCID

John D. Kalbfleisch https://orcid.org/0000-0001-9198-9667

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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