

Brief Communication

The Incorporation of an Advanced Donation Program Into Kidney Paired Exchange: Initial Experience of the National Kidney Registry

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The continued growth of kidney paired donation (KPD) to facilitate transplantation for otherwise incompatible or suboptimal living kidney donors and recipients has depended on a balance between the logistics required for patients and the collaborating transplant centers. The formation of chains for KPD and the shipping of kidneys have permitted networks such as the National Kidney Registry (NKR) to offer KPD to patients over a transcontinental area. However, over the last 3 years, we have encountered patient requests for a more flexible experience in KPD to meet their individual needs often due to rigid time constraints. To accommodate these requests, we have developed an Advanced Donation Program (ADP) in which the donor desires to donate by a specific date, but their paired recipient has not yet been matched to a specific donor or scheduled for surgery. After obtaining careful informed consent from both the donor and paired recipient, 10 KPD chains were constructed using an ADP donor. These 10 ADP donors have facilitated 47 transplants, and thus far eight of their paired recipients have received a kidney within a mean of 178 (range 10–562) days. The ADP is a viable method to support time limited donors in a KPD network.

Abbreviations: ADP, Advanced Donor Program; CMS, Centers for Medicare and Medicaid Services; cPRA, calculated percent reactive antibody; KPD, kidney

paired donation; NDD, nondirected donor; NKD, National Kidney Registry; UNOS, United Network for Organ Sharing

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Introduction

The continued growth of kidney paired donor (KPD) exchange has been accompanied by novel logistics, which are a departure from the early paradigms of same day two-way swaps. As originally envisioned, a donor–recipient pair would exchange kidneys with another donor–recipient pair at the same time in the same hospital (1). The demonstrated safety of shipping live donor kidneys from one center to another, and the emergence of chains driven by nondirected donors (NDDs), has permitted the wider application of KPD across much larger geographic areas (2). In addition, the formation of chains up to 30 transplants deep (3) has necessitated modifications to traditional KPD chains such as out of sequence donation (4,5). A further evolution of the development of KPD has been the Advanced Donation Program (ADP), whereby the surgery date for the paired recipient has not been identified at the time the paired donor donates their kidney.

This concept of ADP can be thought of as the inverse of a bridge donor. A bridge donor is defined as a paired donor who donates a day or more after their paired recipient has received a kidney transplant. An ADP donor desires to donate by a specific date, but their paired recipient has not yet been matched to a specific donor or scheduled for surgery. The need for such a logistical arrangement arises when the paired donor chooses to donate in advance due to time constraints or the desire to eliminate the wait for conventional paired exchange. In our experience, specific drivers for advanced donation have included absolute school deadlines, work return deadlines, military leave, intercurrent illness, a desire for completion of donor recovery to provide care for the recipient spouse or sibling, and a NDD with subsequent potential spousal need for a kidney transplant after his chain had been formed. The purpose of this report is to describe the initial experience of the first 10 ADP cases in a KPD network over a 3-year period.

Methods and Materials

The National Kidney Registry (NKR) is a voluntary network of 65 transplant centers in 28 states in the US that use novel computational algorithms to facilitate exchanges of live donor kidneys between centers. The matching algorithm is focused on the creation of chains with clusters that maximize the number of transplants facilitated within the current donor and recipient pool (6). The ADP was developed as a response to a growing number of kidney donor requests for a more flexible experience in KPD that met their individual needs. In this program, a donor for their paired recipient is not yet identified when the ADP donor undergoes nephrectomy. In advance, the ADP donor gives full informed consent and is educated regarding the waiting period required and uncertainty for completing the ADP paired exchange (Supplemental Digital Forms 1 and 2). Recipient factors such as ABO blood group and degree of HLA sensitization are the primary variables that determine the wait time for matching an ADP patient. However, additional recipient factors such as recovery from intercurrent illnesses or rehabilitation from surgical procedures may influence when the paired recipient is ready to be transplanted.

The goals for the ADP kidney swap remain the same as the conventional paired exchange program, with an ABO-compatible and lymphocyte crossmatch-negative transplant completed. The decision to use donors, for whom desensitization is required, can be selectively applied. As in the conventional paired exchange program, the transplant center and the paired recipient make the final decision to accept or decline future kidney offers. The role of the ADP donor to begin or sustain a chain of KPD transplants is optimized to facilitate the maximal number of transplants that can be done at the time the ADP donation occurs (Figure 1). Once the ADP donor donated and the paired recipient was activated, the paired recipient was placed into the NKR computer matching algorithm to end the next available chain, according to blood group and NKR Medical Board priorities for ending chains.

The following principles were involved in determining which centers within the NKR should participate in the ADP. (1) A center should not be at risk of closing their live donor kidney transplant program due to regulatory censure or other factors, allowing the ADP paired recipient the greatest opportunity

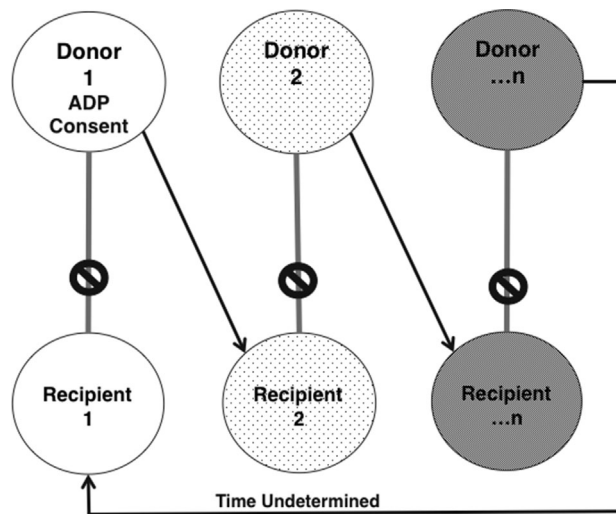


Figure 1: Advanced Donation Program: Time-limited donor undergoes nephrectomy before paired recipient has an established donor identified.

over time to receive a kidney. (2) A center should have a low probability of stopping participation in the NKR, allowing the ADP paired recipient the greatest opportunity over time to receive a kidney. (3) A center should not be in a deficit with regard to the number chains started and chains ended with the NKR to ensure fairness relative to other centers that have started chains through the NKR.

For this report describing the initial outcomes of the ADP within the NKR, the anonymous data collection and analysis was approved by the Cleveland Clinic IRB #15-297.

Results

The decision to enter and consent a donor for the ADP was based on particular donor circumstances and requests. These were at times straightforward and at times complex. An example of a straightforward request was a spouse who was the primary care giver to the paired kidney recipient and had limited access to additional family support. The goal was for the paired donor to complete the nephrectomy and recover prior to the paired recipient surgery in order to aid in recipient recovery.

There were several examples of more complex reasons to decouple the paired donor and paired recipient surgery from the conventional KPD process. Three examples are as follows:

1. A 62-year-old husband wanted to donate his kidney to his 60-year-old spouse, but was ABO-incompatible and entered paired exchange. During the husband's donor evaluation process, the wife received a deceased donor transplant (October 2010). Several months later, the donor requested that he become a NDD, completed his evaluation, enrolled as an NDD in the NKR (July 2011), and a chain was organized. After the chain was organized, the wife experienced problems with her 2010 transplant and the husband enrolled in the ADP so that his wife had an opportunity to receive a kidney if her current graft failed. The husband donated October 2011, starting a chain that facilitated 10 additional transplants, including five with cPRAs >95% (Table 1) (Case 1). The wife-recipient lost her graft and was activated as an ADP recipient in March of 2012. During her time waiting in the NKR, her cPRA increased to 96%, which was very hard to match given she was blood group O. She received several match offers that failed due to a positive crossmatch. She finally received a kidney from an NKR donor in October of 2013, which was 2 years after husband donated and 19 months after she was activated as an ADP recipient.
2. Rigid time restrictions: A 36-year-old son wanted to donate to his mother but had a short donation window due to his limited leave from the Navy in December 2012. He needed to complete his recovery in order to resume deployment. Using the ADP, the son was able to donate within his leave window before his

Table 1: Case 1: ADP interval 19 months

Center	Donor	Age (years)	ABO	Center	Recipient	Age (years)	ABO	cPRA	Date
1	D1 ADP	62	A	2	R2	78	A	25	10-18-2011
2	D2	47	A	3	R3	64	A	66	10-18-2011
3	D3	60	B	4	R4	70	B	0	10-19-2011
5	D4	30	O	5	R5	40	O	0	10-8-2013
6	D5	35	A	7	R6	52	A	96.3	10-8-2013
7	D6	51	O	8	R7	56	O	99	10-8-2013
8	D7	23	O	9	R8	65	O	0	10-8-2013
9	D8	36	A	7	R9	37	O	99.7	10-10-2013
7	D9	44	O	10	R10	49	O	98.3	10-10-2013
10	D10	46	O	1	R1	60	O	95.2	10-10-2013

R1 is the paired ADP recipient eventually transplanted.
ADP, Advanced Donor Program; cPRA, calculated percent reactive antibody.

mother-recipient was fully worked up and cleared for transplant. The mother (O blood group, cPRA 58%) was relatively easy to match but was involved in several failed swaps before she received a match from a 27-year-old donor and was transplanted 5 months after the ADP donor donated. Since the son was an O blood type, five subsequent transplants were facilitated, including one with a 99% cPRA. In addition, the mother had weak donor-specific antibodies (DSA) to one of the son’s antigens so this could be considered a quasi-compatible pair that received a better match (Table 2) (Case 2).

3. A 62-year-old female donor was working full-time and living with her 83-year-old mother and 56-year-old brother-recipient. The brother-recipient was bipolar and stable on medication. The donor requested that her nephrectomy be performed first, in order to help with her brother’s posttransplant recovery. The brother was ABO-incompatible but had 0% cPRA and was considered easy to match. The sister-donor proceeded with nephrectomy and recovered rapidly. However, shortly after her donation, the recipient suffered an unexpected bipolar manic episode and needed inpatient psychiatric care. His transplant was put on hold. The patient improved over the following year and was cleared by his psychiatrist for surgery. Once activated as an ADP recipient, he received a match offer immediately and ended a chain from a 47-year-old female 15 months after his ADP donor donated (Table 3) (Case 3).

Ten pairs participated in the Advanced Donation Program over the 3-year period spanning from August 2011 to

August 2014. The first 10 ADP donors facilitated 47 ABO-compatible or lymphocyte crossmatch–negative transplants. Eight of the ten ADP recipients were successfully matched and transplanted. One of the ten ADP intended recipients was deactivated in the system and the second is waiting for a transplant 5 months after activation. The reasons for the decision to enter the ADP are listed in Table 4.

The first of the untransplanted ADP intended recipients is a 69-year-old (blood group A, cPRA 98%) friend of the paired donor. The donor was a teacher at the time of her donation and requested a donation date to fit her work schedule. Within 1 month of activation (December 2013), the intended recipient received a biologically compatible match offer for a 37-year-old donor kidney but declined the offer due to her planned relocation to another state. The intended recipient has remained inactive since declining this offer. The second untransplanted intended recipient is a 77-year-old (blood group O, cPRA 90%) friend of the paired donor. The donor was also a teacher at the time of her donation and requested a donation date to fit her work schedule. This intended recipient has remained active in the system since August 2014.

The wait times for the eight ADP recipients who were transplanted have ranged from 2 weeks to 19 months. As a group, the ADP donors had a mean age of 49.3 (34–62) years; there were five males and five females; and the ABO blood groups were A=5, B=1, and O=4. The paired recipients for these ADP donors had a mean age of 63.1

Table 2: Case 2: ADP interval 5 months

Center	Donor	Age (years)	ABO	Center	Recipient	Age (years)	ABO	cPRA	Date
1	D1 ADP	36	O	2	R2	43	O	0	11-28-2012
2	D2	46	B	3	R3	38	B	99.4	11-28-2012
3	D3	46	O	4	R4	32	O	0	12-3-2012
4	D4	63	A	4	R5	60	A	0	12-27-2012
5	D5	27	O	1	R1	68	O	57.5	4-16-2013

R1 is the paired ADP recipient eventually transplanted.
ADP, Advanced Donor Program; cPRA, calculated percent reactive antibody.

Table 3: Case 3: ADP interval 15 months

Center	Donor	Age (years)	ABO	Center	Recipient	Age (years)	ABO	cPRA	Date
1	D1 ADP	62	A	2	R2	58	A	97.5	3-22-2013
3	D2	47	B	1	R1	57	B	0	6-20-2014

R1 is the paired ADP recipient eventually transplanted.

ADP, Advanced Donor Program; cPRA, calculated percent reactive antibody.

(42–76) years; there were five males and five females; and the ABO blood groups were A = 4, B = 1, and O = 5. The degree of HLA sensitization varied with five having a cPRA of 0%, and the others were 15, 58, 90, 96, and 98%, respectively. The relationship of the ADP donor to the paired recipient included six friends, two spouses, one child, and one sibling. All eight transplanted ADP recipients are alive with a functioning kidney at this time.

Discussion

The ADP within the NKR has developed as a flexible enhancement to conventional paired exchange in response to specific donor needs that support their decision to become a kidney donor. As one can observe from the various reasons that led to the decision to undergo nephrectomy prior to donor identification for their paired recipient, these reasons vary widely (Table 4). This is perhaps not surprising since each potential kidney donor has a unique set of motivations and method of processing risk and benefit that they use to solidify their decision to donate. For some potential donors, the prime factor in making their decision to undergo nephrectomy is timing. For these individuals, a specific window of time is essential in order for them to be comfortable with their decision to donate their kidney. As demonstrated in this report, having a system in place that accommodates these donor time constraints may be essential to allow a particular donor-recipient pair to go forward with KPD. The net benefit of such flexibility for the first 10 ADP donors can be seen by the 47 KPD transplants that were facilitated by the ADP.

An additional consideration for the use of ADP donors within a sizeable KPD network such as the NKR is their placement in various nodal points within the system (Table 4). An ADP donor can start a chain (Case 2); sustain a chain originating with an NDD (Case 10); or be part of a direct loop with another pair at another center at a later time, where the actual donor is bridging (Case 6). Most often, the recipient paired with the ADP donor is ultimately transplanted with a kidney that derives from a donor who is ending a chain that may be quite deep and may extend over several months. In this fashion, the debt paid by the ADP donor is paid back in kind from a future chain or loop. In addition to helping the specific recipient entered as a pair within KPD, it should not be understated that kidney donors register significant emotional support and good will from extending their gift to others in need

through the creation of chains (7). In fact, some ADP donors have expressed the desire to proceed with their nephrectomy at a set time in order not to disrupt a previously constructed chain. The use of these 10 ADP donors enabled several hard-to-match pairs to become unlocked with at least 17 recipients with a cPRA greater than 80% ultimately transplanted.

The creation of such an ADP should come under close scrutiny and oversight in order to protect the integrity of the KPD network, and the safety of the donors and recipients involved in the ultimate decision to proceed. For these reasons, the program was developed through the NKR Medical Board with careful consideration given to ensure appropriate informed consent for both donor and recipient. An early determination was made that both the ADP donor and paired recipient should be patients at the same transplant center, where the surgical procedures would be performed and detailed explanation of the process would be done by the same transplant team and independent donor advocate. In addition, the patients are clearly informed that participation in the ADP does not confer any benefit or penalty within the national deceased donor kidney allocation system. At this time, we do not advocate participation in ADP if either the donor or the paired recipient has reservations about the risks and benefits of the program, or is uncomfortable with the uncertainty that is inherent in the system.

Separate ADP donor and recipient consent forms were specifically developed for the ADP (Supplemental Digital Forms 1 and 2). These are signed in addition to the standard-of-care informed consent documents that each transplant center is required to utilize according to the United Network for Organ Sharing (UNOS) and Center for Medicare and Medicaid Services (CMS) guidelines (8). The ADP informed consent documents highlight the particular considerations that each donor and recipient are required to understand and affirm. Perhaps the most important consideration is that a time frame for identification of a suitable donor for the paired recipient cannot be predicted, and that due to logistical and medical concerns a future transplant through the ADP may never occur. The two recipients who remain untransplanted at this time highlight the importance of careful selection of candidates for this program. As one would predict, blood group O recipients and highly sensitized patients should expect the longest wait times. For these reasons, donors and recipients who contemplate entry into the ADP

Table 4: Characteristics of first ten ADP participants

Cases	ADP kidney donor				Paired recipient entered with ADP donor				
	Age (years)	Gender M/F	ABO group	Relationship	Age (years)	Gender M/F	ABO group	cPRA %	Interval (days)
1	34 ¹	F	B	friend	42	M	A	0	10
2	36 ²	M	O	son	68	F	O	58	138
3	52 ³	F	A	spouse	58	M	O	0	14
4	62 ³	F	A	sibling	57	M	B	0	448
5	62 ⁴	M	A	spouse	60	F	O	96	562
6	47 ⁵	M	A	friend	73	M	O	0	67
7	54 ¹	M	O	friend	67	F	A	98	pending
8	45 ⁵	M	A	friend	61	M	A	28	176
9	50 ¹	F	O	friend	76	F	O	90	pending
10	51 ¹	F	O	friend	69	F	A	15	15

Reasons given for entering the ADP:

¹Return to work, school, business.

²Military leave.

³Donor recovery to aid in care of recipient.

⁴Future need of paired recipient.

⁵Intercurrent recipient medical or surgical problem.

ADP, Advanced Donor Program; cPRA, calculated percent reactive antibody.

should be given a sufficient amount of time to make their decision to participate and offered the opportunity to reconsider their decision at any time before surgical procedures are performed.

At the current time, there is a large imbalance between the number of potential recipients in need of a kidney transplant and the total number of either deceased or live donors available to them. Properly and safely performed, live donor kidney transplantation represents a critical source of transplant kidneys (9). The emergence of KPD exchanges is expanding the pool of living donors, and has become an important way to find donors for even highly sensitized recipients (6,10). The ADP within the structure of an established KPD network further enhances the ability to deliver the gift of life to the target population in need.

Conclusions

The Advanced Donation Program is a viable method to support time limited donors in a KPD program. The use of ADP donors increases transplant opportunities and unlocks hard-to-match patients in chains that are down-stream from the ADP donor. Similar to an NDD, the ADP donor does not know the precise time when their paired recipient will receive a transplant. However, great care is needed to provide informed consent for the uncertainty of the process. Hard-to-match recipients, especially blood group O recipients with high cPRAs, remain a difficult to match and should be carefully considered in the ADP selection process.

Addendum

On March 26, 2015, patient 9 (Table 4) received a compatible kidney transplant; she had waited 174 days since activation.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. JS and GH are employees of the National Kidney Registry, Inc., Babylon, NY. The other authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplemental Digital Forms 1 and 2