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Kidney paired donation

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Abstract

Kidney paired donation (KPD) was first suggested in 1986, but it was not until 2000 when the first paired donation transplant was performed in the USA. In the past decade, KPD has become the fastest growing source of transplantable kidneys, overcoming the barrier faced by living donors deemed incompatible with their intended recipients. This review provides a basic overview of the concepts and challenges faced by KPD as we prepare for a national pilot program with the United Network for Organ Sharing. Several different algorithms have been creatively implemented in the USA and elsewhere to transplant paired donors, each method uniquely contributing to the success of KPD. As the paired donor pool grows, the problem of determining allocation strategies that maximize equity and utility will become increasingly important as the transplant community seeks to balance quality and quantity in choosing the best matches. Financing for paired donation is a major issue, as philanthropy alone cannot support the emerging national system. We also discuss the advent of altruistic or non-directed donors in KPD, and the important role of chains in addition to exchanges. This review is designed to provide insight into the challenges that face the emerging national KPD system in the USA, now 5 years into its development.

Keywords: allocation; incompatible kidney transplantation; paired kidney exchange; transplantation policy; transplant finances

Introduction

Kidney transplantation has been established as the best treatment for patients suffering from end stage renal dis-

ease (ESRD). Patients fortunate enough to receive a kidney transplant, on average, live 10 years longer than those who remain on dialysis [1], and it is now clear that a living donor kidney transplant is better than a kidney from a deceased donor. The average deceased donor kidney transplant will function for 8.6 years, while a living donor kidney provides an average of >16 years of dialysis-free survival [2]. Sadly, the demand for a kidney transplant far exceeds the supply that can be met by deceased donors, so much so that roughly 19 patients die each day in the USA, while waiting for a kidney donation [3]. Unfortunately, all too often, a willing living donor is deemed incompatible due to blood type or unacceptable donor-specific antibodies. Kidney paired donation (KPD) provides a solution to this dilemma by pairing two incompatible pairs together to facilitate an exchange between the willing donors' kidneys.

KPD was first suggested by Felix Rapaport in 1986 [4] (See Figure 1) and in 1991, the first kidney exchange was performed in South Korea [5]. Several years later, in 1999, the first paired exchange in Europe took place at University Hospital in Basel, Switzerland [6]. The next year, the first KPD transplants were performed in the USA in 2000, first in New England then followed by the Johns Hopkins team [Ratner L. (personal communication)] [7]. KPD has grown rapidly since then, utilizing advanced matching algorithms that identify both simple exchanges and more complex chains of transplants to increase the number of transplants achieved. As of the third quarter of 2010, >1000 KPD transplants have been performed in the USA (see Figure 2) [3].

There are still many obstacles in most countries, including the USA, preventing widespread and national implementation. The Netherlands, however, set a precedent in 2004 by successfully launching the first national KPD program in the world [8]. New approaches incorporating

History of KPD

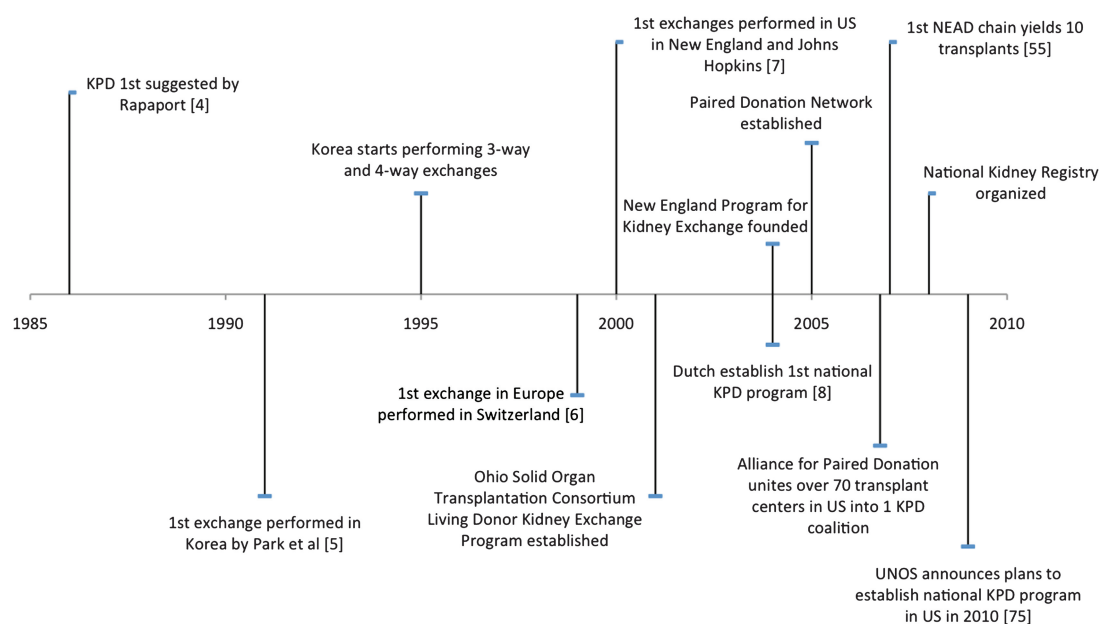


Fig. 1. A history of kidney paired donation from its original proposal by Felix Rapaport to the present day.

KPD and NDD Transplants in U.S. 1998 - 2010

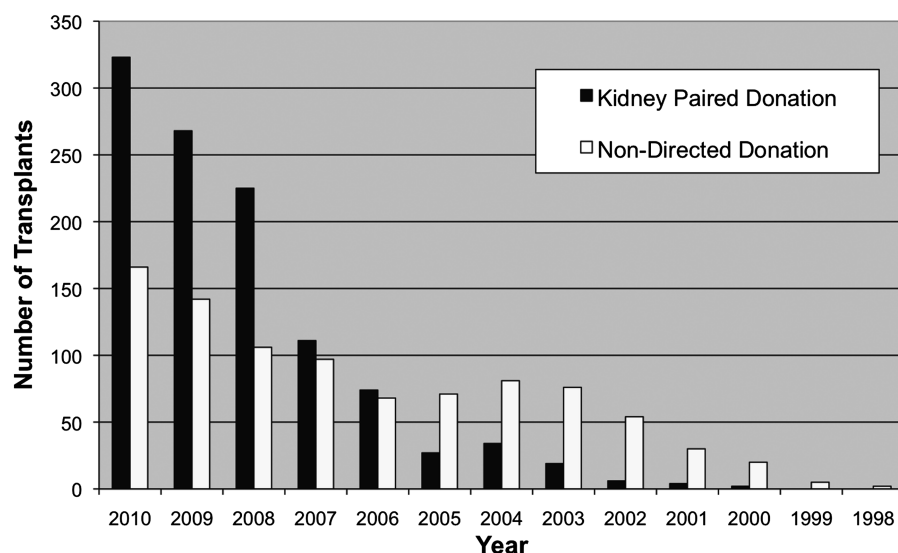


Fig. 2. KPD and nondirected donation (NDD) transplants per year since 1998 [3].

altruistic donors (or nondirected donors) allow KPD to multiply the good that results from the donor's gift. This review discusses different KPD-matching algorithms, the balance between quality and quantity, the challenges of developing a national program and the financial and ethical hurdles inherent in this new approach to living kidney donation.

Matching algorithms

Strategies of matching incompatible pairs to maximize transplants have evolved dramatically since Rapaport [4] first suggested the concept in 1986. At first, it seemed that only blood type A and B pairs would participate since pairs with universal O donors or AB recipients would not

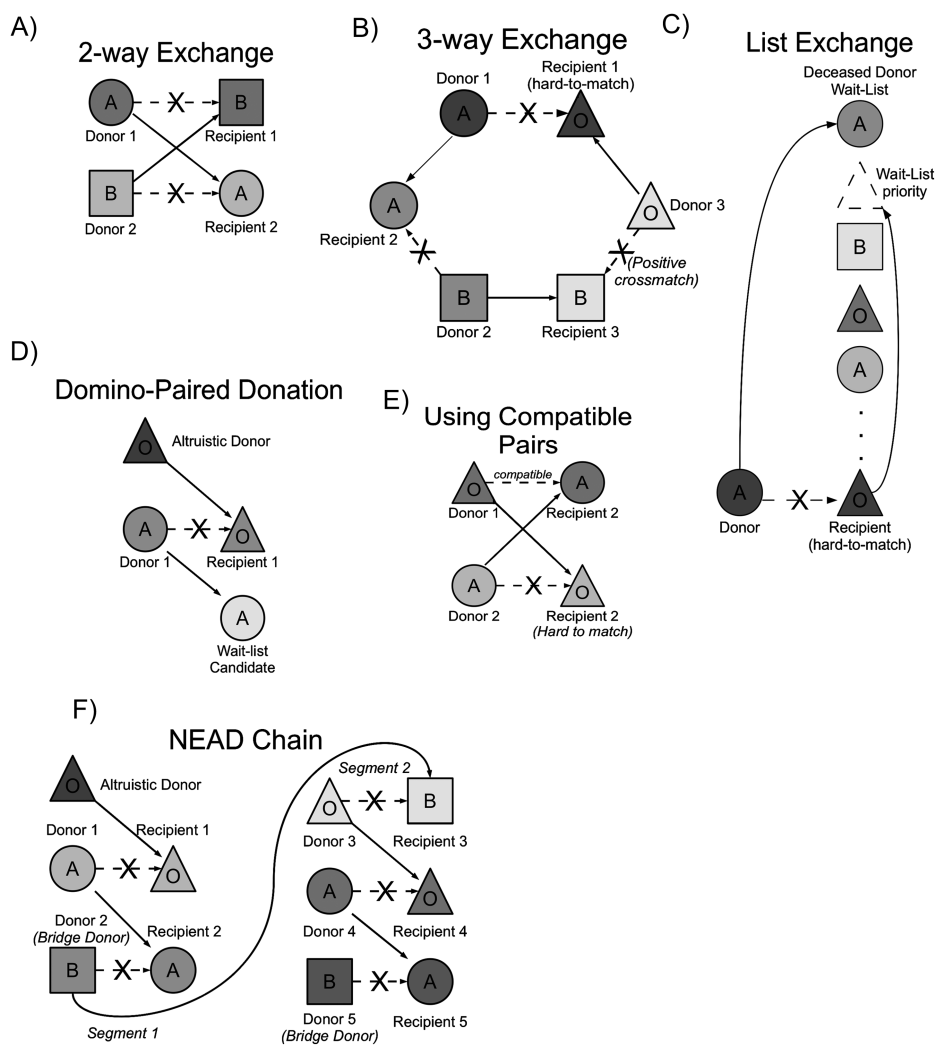


Fig. 3. A history of KPD from its original proposal by Felix Rapaport to the present day. (A) Two incompatible pairs swap kidneys in a two-way exchange. (B) A three-way exchange with no reciprocal exchanges so hard-to-match pairs are better matched. (C) In a list exchange, an incompatible donor donates to a wait-list candidate in exchange for wait-list priority for the recipient. (D) DPD pairs an altruistic donor with an incompatible recipient. The donor then continues the chain or donates to a wait-list candidate. (E) A compatible pair can join an exchange helping hard-to-match pairs. (F) NEAD chains are like domino chains except the last donor becomes a bridge donor and awaits more pairs to perpetuate the chain at a later time.

participate, leaving hapless pairs with O recipients or AB donors unmatched. Since the most prevalent ABO incompatibility is a blood type O recipient with an A donor, early predictions estimated match rates at under 3% [9]. Fortunately, incorporation of pairs that are incompatible due to donor-specific antibodies, referred to as a positive cross-match, introduced O donors and AB recipients into the KPD pools [10].

The most basic exchange between incompatible pairs is through a two-way exchange, where two incompatible pairs with reciprocal incompatibilities are paired up and kidneys are swapped (see Figure 3A). In this model, the donor from the first pair donates to the recipient of the second pair and the donor from the second pair donates to the recipient of the first pair. Thus, both recipients benefit from a live donation indirectly through their willing but incompatible donor. This strategy has been successfully implemented by a number of institutions around the world

[5,8,11–19]. Three-way exchanges build upon the foundation of two-way exchanges by including an additional incompatible pair (see Figure 3B). This approach not only increases the number of transplants possible but also facilitates better outcomes for hard-to-match pairs by not requiring reciprocal matching [20–22]. For example, in a two-way exchange, an O recipient has difficulty not just in finding a compatible donor but in also finding a compatible donor whose incompatible recipient can receive a kidney from the O recipient's incompatible donor. A three-way exchange eases this burden by including another incompatible pair that overcomes this need for reciprocity. The advantage of three-way exchanges can be expanded further to include more incompatible pairs, however, the logistics of coordinating exchanges with more than three pairs becomes challenging [21–23].

While early strategies limited exchanges to involve only incompatible pairs, more recent approaches have incorpo-

rated additional resources. In a list exchange (see Figure 3C), an incompatible living donor donates to a candidate waiting for a deceased donor kidney, and in exchange, the recipient from the incompatible pair acquires priority on the wait-list for a future deceased donor organ [12,24]. This model is successful in its ability to facilitate an additional transplant through the generosity of the willing donor, while at the same time awarding a much shorter waiting time for the incompatible recipient [12,25]. However, many fear list exchanges promote an unacceptable disadvantage to blood type O candidates on the wait-list since the most common list exchange would involve non-blood type O donor kidneys being exchanged for blood type O deceased donor kidneys [26]. Additionally, by including compatible pairs in KPD match runs, O recipients and pairs with AB donors can gain access to the elusive O donors and AB recipients they require for a match (see Figure 3E) [26–31]. However, using compatible pairs is ethically complicated since it involves inviting an otherwise suitable pair to exchange kidneys with strangers, but many feel compatible pairs may either derive benefit from the arrangement through a better match or they may be motivated to participate through sincere altruism [28,29].

Another protocol combines the advancing technique of desensitization with KPD matching to enable transplantation of patients who are highly sensitized. Desensitization in and of itself has been labeled as risky, technically demanding and costly [8,15,32], but several programs have reported acceptable short-term results from utilizing such practices to help highly sensitized patients [14,33–38]. While desensitization for ABO incompatibility appears to have good long-term graft survival, recent data suggest that, for highly sensitized patients, there are limitations to this approach [39–41]. Even so, new strategies combine KPD with desensitization by allocating incompatible pairs who fail to match in standard KPD match runs to a separate pool to first evaluate whether the incompatible pair is suitable for desensitization with each other. If the pair is not suitable for desensitization they enter another match run, this time to find alternative pairs whose donor could provide a kidney to a highly sensitized recipient via desensitization [42].

Altruistic donation (or nondirected donation) provides another option by which incompatible pairs can be transplanted. While many programs choose to allocate altruistic donor kidneys to the deceased donor list [43–45], others seek to multiply the gift of an altruistic donor by matching them with incompatible pairs to initiate a chain of transplants. So far, two methods have been established. In the first, called a domino-paired donation (DPD) chain (see Figure 3D), an altruistic donor gives to the recipient of an incompatible pair. In return, the donor of the incompatible pair either extends the chain by donating to another recipient of an incompatible pair or terminates the chain by donating to a wait-list candidate. DPD chains are established on one match run, generally involve four or less pairs and are performed simultaneously [24,46–48]. The second method is called a nonsimultaneous extended altruistic donor (NEAD) chain (see Figure 3F). A NEAD chain is similar to a DPD chain in that it involves an altruistic donor initiating a chain but differs in that transplants are not per-

formed simultaneously [49]. Instead, the last donor—who would have donated to a candidate on the deceased donor waiting list in a DPD chain—becomes a ‘bridge donor’ and waits for another segment of exchanges. This approach risks renegeing by the bridge donor, thus, requiring careful evaluation and management to ensure the selection of appropriate donors [47–51]. New approaches combine these two concepts, so that nonsimultaneous chains end with a donation to the waiting list. Of course, many of the approaches detailed above could be combined as was done in a recently reported 13-way exchange involving altruistic donor chains and desensitization [52].

Allocation in paired donation

Two driving factors have fueled KPD innovation over the years: maximizing the number of incompatible pairs that can be served and finding the best possible matches between participants. Maximizing the quantity of KPD exchanges is a straightforward concept: larger pool sizes and successful matching equals more transplants. Determining the quality of matches is more complex as it requires allocation decisions that, until the advent of paired donation, are typically limited to the realm of deceased donor kidneys. In KPD, living donors do not choose their recipients; the matching algorithm must do this. For this reason, the entity that controls allocation of KPD kidneys must carefully consider allocation principles as there are many different perspectives as to what defines the best match. According to the National Organ Transplant Act, donated organs are to be allocated equitably among transplant patients [53]. The United Network for Organ Sharing (UNOS) defines ‘equitable’ as a balance between utility and justice [54]. KPD fosters utility by creating viable transplants out of a pool of donors who are unable to give their loved one a kidney. Justice is less intuitive. Justice requires balancing the perspectives of recipients, donors, transplant centers and society as a whole, which tend to vary greatly, in terms of the proper allocation of living organs [46,55]. The recent inability of UNOS to gain consensus on life years from transplant (LYFT) as a new strategy for allocating deceased donor organs emphasizes the controversial nature of determining quality in organ allocation [56].

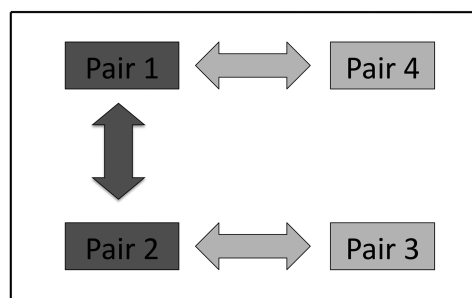


Fig. 4. If an exchange between Pair 1 and Pair 2 is performed at one center, only two transplants occur; however, in the larger pool, Pair 1 can exchange with Pair 4 and Pair 2 can exchange with Pair 3 allowing four transplants instead of two.

Whereas living donor kidneys historically have been allocated by the living donor themselves, or in the case of nondirected donors by the local transplant center, a paradigm shift is required if KPD is to expand between many centers on a regional or national scale. Not only does KPD require consensus regarding the allocation of living donor kidneys but the new allocation system will also need to consider the desire of local transplant programs to maximize the number of transplants for patients at their center. Take the following example: one transplant center has two pairs that can simply participate in a two-way exchange. However, if these two pairs are put into a national pool, they may get matched to two other pairs from other transplant centers, so that a child and a highly sensitized patient are transplanted, allowing four people to be transplanted instead of two (Figure 4) [57]. The risk for the center enrolling these two pairs into the national system is that only one patient of their two might get matched, while their other patient is left untransplanted. In this sense, they are not advocating the best for 'their' two patients. Thus, as more transplant centers are drawn into cooperation with one another, it is likely that effective matching protocols will have to give centers appropriate incentives to submit all of their incompatible patient-donor pairs to the kidney exchange pool, and not just those for whom they cannot arrange exchanges internally [57]. If centers are doing some internal exchanges without making those pairs available to the national pool, that means those exchanges, *de facto*, had higher priority than, for example, children at other centers. One can imagine, based on the stark differences between these competing allocation philosophies, how challenging it will be to achieve a national consensus on how to quantify quality so that transplant programs will accept the allocation approach and agree to put all their pairs into a single pool, thus offering all patients the best opportunity through KPD.

While it may appear that efforts to increase the quality of transplants would do so at the expense of higher quantity matches and vice versa, there are many strategies that seek to improve both. The simplest way quantity and quality of KPD matching is improved is through increasing pool size. In simulations of paired donation pools and calculations of outcomes, the number of potential matches will exponentially increase as the paired donor pool increases [21,44,47,58]. While there has been no determination of a 'critical mass' or a volume of enrolled incompatible pairs that would begin a cascade of transplants, some have suggested that a pool size of at least 100 pairs is necessary for sustainable matching [59]. Naturally, as more incompatible pairs are added to a KPD registry, more transplants are made possible and the likelihood that hard-to-match and highly sensitized pairs will find suitable donors increases, as illustrated in the previous example [58]. This fundamental concept has inspired programs to create national pools in spite of substantial logistical obstacles that invariably stand in the way [10,21,22,60]. Other methods to improve quality and quantity involve utilizing specific computer algorithms and allocation protocols. Originally, the process of finding a match among a pool of incompatible pairs followed a 'first-accept' scheme, which entails matching pairs without considering the impact of that choice on all the other possible choices. This algorithm would remove easy-to-match pairs,

hurting the remaining hard-to-match pairs by concentrating them in the pool [61]. Most programs today have adopted an 'optimization' algorithm, which searches for every possible match in the available pool and then analyzes which option will generate both the highest quantity of matches and the best quality of matches [8,14,60,62,63]. Match quality is ensured by establishing a list of specific allocation criteria that helps guide the computer in coordinating its match run. This set of criteria goes beyond blood type compatibility and human leukocyte antigen (HLA) sensitization to include factors such as age, travel distance, wait-time on dialysis and any number of additional parameters that facilitate the best possible outcomes.

Although specific-allocation criteria may differ, most programs agree that there is a delicate balance between assigning too few criteria, which leads to poor matching and outcomes and assigning too complex criteria, which can limit matching, particularly in smaller pools [47]. The most successful programs are able to straddle this line and therefore maximize KPD outcomes. Our program, the Alliance for Paired Donation (APD), is overseen by a Scientific Operations Committee (SOC) composed of representatives from each participating transplant program and led by an executive committee from 10 of these programs. Our SOC regularly reevaluates the matching algorithm to ensure that the optimized matches reflect desired priorities. The upcoming UNOS KPD pilot program has likewise sought to achieve a consensus on allocation—a process that has taken >5 years to develop. Experience and careful study of the different allocation approaches currently in practice should yield critical insights to create an optimal algorithm for increasing the quantity and quality of paired donation transplants achieved [64].

As stated previously, a three-way exchange not only enables more transplants than a two-way but also allows higher quality matching since pairs no longer require a reciprocal match [20–22,62,63]. Altruistic donors provide a similar advantage. By initiating chains with an altruistic donor, both DPD and NEAD chains, like three-way exchanges, bypass the need for reciprocal matching, providing higher quality matches to participants and allowing more pairs to profit [49–51]. Additionally, DPD and NEAD chains permit better matching just by including altruistic donors alone, which typically represent the blood type frequencies of the general population. This means that there is a high probability that any given altruistic donor will be blood type O and will therefore be able to match with a hard-to-match O recipient to initiate a chain. All of these advantages give altruistic donor chains an unmistakable edge in the effort to maximize quality and quantity.

Financial considerations

One of the many perks of KPD is the substantial savings that performing a live kidney transplant generates as opposed to prolonged dialysis treatment [14,23,61,65,66]. Several authors estimate that a national KPD program in the USA would save at least \$750 million annually [66]. Nonetheless, one of the largest logistical obstacles to the implementation of successful KPD programs is funding

[51,62,67,68]. Even though kidney transplantation is proven to be the most cost-effective therapy for ESRD, insurance companies are reluctant to pay for the workup of a potential KPD donor if he or she will not provide an organ to a patient covered by that insurance company. The reality is that, while KPD programs are successful at producing transplants from pools of incompatible pairs, not all of these pairs will inevitably find a match and lead to transplantation. Private payers therefore cannot justify paying for the evaluation of a potential donor if there is uncertainty as to whether that donor will ever provide a transplant. Even if eventual transplantation could be guaranteed, no payer would pay the costs for evaluation or transplantation if the recipient were a client of another insurance provider. Because of these limitations, transplant programs utilizing KPD must fund incompatible donor evaluations at their own peril, not to mention the administrative costs of the KPD-matching programs. To date, such matching programs have relied primarily on philanthropic support.

One proposed way of circumventing this obstacle is by following the example of deceased organ procurement in the USA. The inability to pay for a donor's evaluation and organ recovery prior to identifying the recipient of those organs used to limit the allocation of deceased donor organs to a single transplant center until the concept of a financial intermediary was proposed. Now Organ Procurement Organizations (OPO) serve as the financial intermediary, paying all of the expenses for donor workup and procurement up front, then allocating the costs back to the appropriate payer once a compatible donor-recipient pair is identified. Thus, the cost of evaluating and recovering potential deceased donors for transplantation is paid by a third party, independent of the payers and transplant hospitals. This organization is then able to recover their expenses via a Standard Acquisition Charge (SAC), approved by the Center for Medicare & Medicaid Services (CMS). This SAC fee represents the fraction of the OPO's total cost of evaluating and procuring organs over the last year divided by the number of transplants. By keeping track of past costs, OPOs budget for their expected expenses, and if transplantations are short one year then CMS will reimburse them for the balance. Thus, the challenge of paying for deceased donors before knowing the identity of the recipient is taken out of the equation. This system of transplant financing has allowed deceased donor kidney transplantation to flourish in the USA for the last 25 years. If KPD programs were able to establish a similar system then many of the funding pressures currently limiting the adoption of a national program would be overcome [51].

Altruistic donors add an additional layer of complexity to this issue since they also require special interviewing and psychological evaluations to ensure proper intentions in the kidney donation process [45,62]. However, it is the sharing of altruistic donors that presents the most challenging financial dilemma. Since, by definition, an altruistic donor does not have an intended recipient, it is often the case that once matched, the donor must travel to another transplant center to initiate a chain or donate to a wait-list candidate. While in a traditional KPD exchange the traveling donor would leave a recipient to receive a kidney from

the other pair's donor, the altruistic donor has no recipient staying behind, so the transplant center responsible for the workup does not benefit from a transplant. This presents a financial disadvantage to the transplant center responsible for evaluating the altruistic donor, since they do not benefit if the altruistic donor's kidney is not allocated to a recipient at their hospital. Therefore, the tendency of many institutions in the USA is to allocate altruistic donor kidneys to candidates at their own transplant center and to refuse to evaluate altruistic donors if the paying center is not allowed to control the allocation of such kidneys. This policy thus limits the potential impact of altruistic donors since cooperation among multiple facilities is required to create the best chains of KPD transplants [51].

Obstacles to a national system

Since larger pools promote better matching outcomes, the impetus for KPD programs around the world is to nationalize their registries to maximize pool size [10,21,22,58,60,67]. Although a national program may be the end goal for the KPD movement, there are many logistical issues that hinder its progress. As discussed above, developing consensus on allocation and determining the best approach for funding are some of the challenges currently preventing a national program in the USA [51,62,67,68]. Another challenge is the coordination required between transplant centers [51,61,62,67,69,70]. This task is easier in smaller countries like The Netherlands, where distances are short and there are only seven transplant centers and one payer [8]. However, coordination will prove much more complicated in the USA, where there are 244 kidney transplant centers spread out over a vast area and a myriad of insurance providers [3]. One way in which collaboration may be enhanced, while also minimizing match failure, is through a national tissue typing laboratory where potential donor/recipient pairs are tested for HLA crossmatch [62,70]. The Dutch program attributes much of its success in establishing consistent high match rates to its national centralized tissue typing laboratory [70].

Another question for a national KPD system is how to facilitate exchanges across large geographic areas. The recipient's transplant procedure is preferably carried out by their home institution for various reasons including continuity of care, follow-up, travel limitations, stress reduction and reimbursement for the transplant workup and procedure. Therefore, it was thought that in an exchange, each donor would travel to the transplant facility of his or her newly matched recipient. The shipping of kidneys between centers was thought to be detrimental due to prolonged cold-ischemia times (CIT) and risks of transportation delays [45]. However, there have been several reports lately of successful exchanges and chains that utilized shipped kidneys, most with a CIT <8 h, some up to 24 h, with comparable graft survival rates of exchanges where donors traveled to the recipients' facility [20,49,50,71–74]. This data has helped kidney shipping become more acceptable, especially since it lowers travel costs and allows donors to be with their families and in familiar hospital surroundings [71,74].

Ethical issues in paired donation

As with any new approach in transplantation, there have been ethical concerns since the beginning of KPD. A new issue arising with paired donation is the involvement of separate unrelated patients participating in an exchange; this raises the question of maintaining anonymity between exchanging pairs [6]. While some KPD programs allow full contact between participating pairs, others prevent contact until after the procedure and still others discourage meeting altogether [12,16,23,43,50,62,65,68,69,75,76]. Those that support anonymity argue that there is a risk of anger or frustration with poor transplant outcomes [16,76], that it might affect the decision to participate in the exchange, or that loss of anonymity might promote unethical or unlawful interactions such as coercion or bartering [23]. In our experience with the APD, anonymity has been the decision of the participating transplant centers. At the authors' home transplant center, patients are offered the choice and only 1 pair in 25 has chosen to remain anonymous. All the other recipients and donors met prior to the transplant procedure and in every case, the meetings have been a positive experience. Others have also allowed donor–recipient pairs to meet with positive responses [23,43], whereas many of the arguments supporting anonymity have been based on speculation and do not correlate with studies evaluating patient desires [77]. Thus, anonymity between KPD participants is an area that requires data to help guide future policy development.

Until recently, KPD transplants were performed simultaneously in order to prevent donor reneging [11,43,62,69,75,78]. Domino chain donations are also done simultaneously for the same reasons [32,79]. A NEAD chain, on the other hand, has the potential for 'bridge' donor reneging, but this controversial risk of inequity has been justified by a belief that nonsimultaneous chains would provide better utility [49,62,64,77–79]. Experience will need to determine whether risking donor reneging by nonsimultaneous chains results in utility gains and sufficiently low renege rates in order to continue its practice.

Coercion has been a concern for living donation since its beginning, and some argue that KPD places donors under even greater pressure to donate because it eliminates incompatibility as an excuse to avoid donation [6,76]. In addition, since NEAD chains create a situation where bridge donors' incompatible recipients have already received transplants, some argue that this inappropriately limits the donor's ability to withdraw and by its very nature is coercive [80]. Further ethical concerns include privacy, confidentiality, exploitation and commercialization [80]. Danovitch *et al.* [81] argue that the benefits of NEAD chains outweigh the hypothetical concerns about the unintended consequences of such a policy. Again, experience will distill those concerns with merit and clarify the best way forward.

Discussion

While there are many other issues that could be explored in the evolving field of KPD, this review has summarized dif-

ferent matching strategies and some of the barriers to developing a national program in the USA. It is therefore worth noting that UNOS initiated a KPD pilot program in the fall of 2010 [67]. In this pilot, four coordinating centers have been chosen: the APD, the Johns Hopkins Program, the New England Program for Kidney Exchange and a UCLA-led consortium. Through these coordinating centers, >75 transplant programs will participate in a pilot that has been under development for >5 years. However, the limitations of the pilot emphasize the challenges—highlighted in this review—that hinder movement from the UNOS pilot to a national program. The initial UNOS pilot does not allow for chains, but is limited to two- and three-way exchanges. There is no strategy in place to pay for incompatible donor evaluations, the expenses of the coordination centers, or for donor or kidney shipping. There is no web-based data entry portal and there is no provision for a centralized laboratory to perform screening cross-matches. Another limitation is that the matching algorithm does not provide assurances to transplant centers that encourage them to enroll all of their pairs instead of performing internal exchanges utilizing their easy-to-match pairs.

This list of deficiencies is not meant as a criticism but as an example of the difficulty of building consensus. UNOS as an organization is dependent on achieving consensus. As such, it is less able to innovate and this review makes clear that KPD remains a rapidly evolving field. Furthermore, while a contractor for the federal government, UNOS does not control the allocation of federal funding that is required to support a national KPD program. For these reasons, KPD is likely to remain in the hands of smaller regional programs that have the advantage of driving innovation, but the disadvantage of limited pool size that by definition will not provide the greatest number of opportunities for patients with incompatible, but willing living donors. Nonetheless, the UNOS KPD Pilot Program represents the nascent beginning of a national KPD program in the USA that promises hope to the growing number of patients suffering from ESRD.

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Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation: a European Renal Best Practice (ERBP) position statement

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Abstract

KDIGO (Kidney Disease: Improving Global Outcomes) is an international independent body aiming to 'improve the care and outcomes of kidney disease patients worldwide, through the development and implementation of clinical

practice guidelines'. Recently, the KDIGO work group has produced comprehensive clinical practice guidelines for the care of kidney transplant recipients (KTRs). The guideline makes recommendations for immunosuppression, graft monitoring, as well as prevention and treatment