TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

REVIEW

Allocation and matching in kidney exchange programs

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Keywords
allocation, kidney exchange, living donor kidney transplantation, transplantation across the blood-type barrier, unspecified donation.

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Conflicts of interest
The authors have declared no conflicts of interest.

Received: 4 June 2013
Revision requested: 21 July 2013
Accepted: 15 September 2013
Published online: 17 October 2013

doi:10.1111/tri.12202

Summary

Living donor kidney transplantation is the preferred treatment for patients suffering from end-stage renal disease. To alleviate the shortage of kidney donors, many advances have been made to improve the utilization of living donors deemed incompatible with their intended recipient. The most prominent of these advances is kidney paired donation (KPD), which matches incompatible patient–donor pairs to facilitate a kidney exchange. This review discusses the various approaches to matching and allocation in KPD. In particular, it focuses on the underlying principles of matching and allocation approaches, the combination of KPD with other strategies such as ABO incompatible transplantation, the organization of KPD, and important future challenges. As the transplant community strives to balance quantity and equity of transplants to achieve the best possible outcomes, determining the right long-term allocation strategy becomes increasingly important. In this light, challenges include making full use of the various modalities that are now available through integrated and optimized matching software, encouragement of transplant centers to fully participate, improving transplant rates by focusing on the expected long-run number of transplants, and selecting uniform allocation criteria to facilitate international pools.

Introduction

Living kidney donation is an obvious strategy to increase the number of kidney transplants [1–6]. Moreover, grafts taken from living donors generally function twice as long as grafts taken from deceased donors [7]. Clinical advances such as laparoscopic nephrectomy and vaginal extraction have helped increase the number of living donor kidney transplants over recent years [8]. In the Netherlands, for instance, more than half of the transplants now involve a living donor [9]. Nevertheless, the number of kidneys available for transplantation is still largely insufficient to meet demand: in Europe and the United States together, approximately 30 patients die each day while waiting for a kidney transplant [10,11]. A major part of the problem is that, even when a living donor is willing to donate, in over 30% of the cases, the donor is incompatible with his or her intended recipient due to blood-type or cross-match incompatibility [12].

Several strategies have emerged to improve the utilization of living donors by mitigating or overcoming the causes of incompatibility. Kidney paired donation (KPD) [13], alternatively known as kidney exchange [14], is a strategy that allows incompatible patient–donor pairs to be matched with other incompatible pairs in order to proceed with transplantation through an exchange procedure. Other strategies include patient desensitization, living donor-deceased donor list exchange, and altruistic (unspecified or nondirected) donation [15–17].

This review compares and discusses the various approaches to matching and allocation in KPD as published in the international transplant community. In particular, it focuses on the underlying principles of matching and allocation approaches, the combination of KPD with

other strategies such as ABO incompatible transplantation, the organization of KPD, and future challenges.

History of KPD

The concept of KPD was first proposed by Rapaport [13]. The initial idea was to facilitate exchange between pairs with reciprocal blood-type incompatibilities (A-B and B-A), but this would later be expanded to other blood-type combinations and cross-match incompatible pairs. The first actual exchange procedure was performed in South Korea in 1991 [18], followed by Europe in 1999 [19], and then, the United States in 2000 [20], the slow acceptance being mainly due to ethical and legal considerations [21,22]. After these first procedures, KPD has developed rapidly. In 2004, the Netherlands was first to launch a nationwide KPD program [23]. Various countries have since then begun to develop national KPD programs, including the United States [24], Australia [25], Canada [26], Romania [27], and the UK [28,29]. International exchanges, although on an ad hoc basis, have also been documented [30,31].

Transplant modalities

Two-way KPD

Since the inception of KPD, various transplant modalities have become available to incompatible pairs. The simplest modality is a pairwise exchange, or two-way KPD, between two pairs with reciprocal incompatibilities (see Fig. 1a). In this exchange, the donor of the first pair donates to the patient of the second pair and vice versa. Usually, transplants take place simultaneously so as to prevent donors from withdrawing consent after their intended recipient has received a transplant, but before they have donated themselves [18,23].

k-Way KPD

Exchange can also take place between more than two pairs by generalizing the above concept to a so-called *k*-way KPD (Fig. 1b). *k*-Way KPD—which involves *k* pairs—allows to capture more benefits of trade as reciprocal matching is no longer required [32,33]. In most cases, *k* is limited to 3 or 4 because of logistical reasons such as the simultaneous availability of operating rooms [25,28,32–36]. Although this limit is sufficient to provide full benefits of trade for blood-type incompatible pairs in the pool [32], highly sensitized patients could benefit if *k* were allowed to be larger [37].

Unspecified donor chains

Alternative to the cyclic exchange procedures described above, transplants can be organized in chain procedures. One option is to initiate a chain with an unspecified donor. Instead of donating to a patient on the deceased donor waitlist, as has been common in many countries [28,38], an unspecified donor donates to a patient of an incompatible pair [39,40]. Subsequently, the donor of that pair donates to a patient of another pair, and so forth, until the donor of the last pair in the chain donates to a patient on the deceased donor waitlist. This modality is referred to as domino-paired donation (DPD; Fig. 1c) [17]. As it is possible to arrange the transplants in a chain such that no donor–recipient pair needs to donate a kidney before having received one, donor withdrawal can do less harm in a chain than in a *k*-way KPD. Therefore, the requirement of simultaneous transplants could be relaxed in chains. Nonsimultaneous extended altruistic donor (NEAD) chains (Fig. 1d) do this by recruiting "bridge donors" who—instead of donating to the deceased donor waitlist like the last donor in a DPD chain—may continue the chain at a later moment in time [41]. The relaxation of simultaneity allows chain procedures to involve more incompatible pairs than *k*-way KPD (if there is no donor withdrawal), potentially benefitting highly sensitized patients [37]. There has been an ongoing debate on whether it is best to use DPD or NEAD chains [42–45]. A recent study shows that the answer depends on the composition of the KPD pool and that benefits of NEAD chains are limited in case of low numbers of highly sensitized patients and sufficient unspecified donors [46].

List exchange

Another option is to initiate a chain with a list exchange (Fig. 1e), in which the first patient in the chain does not directly receive a transplant, but instead receives priority on the deceased donor waitlist for a future deceased donor kidney, which is usually a blood type O kidney [14,47]. The last donor of the chain again facilitates a transplant to a patient on the waitlist. However, the procedure is controversial because the latter transplant usually involves a non-blood type O kidney. Therefore, list exchanges can produce disadvantages to blood-type O patients on the deceased donor waitlist [16]. List exchanges have only been used in several regions in the United States, where the procedure has been declared acceptable by the American Society of Transplantation [48].

Altruistically unbalanced exchange

All of the procedures described above can also take place with compatible pairs (Fig. 1f). This is known as "altruistically unbalanced exchange donation" [49,50]. It allows incompatible pairs a better chance of finding a match, while at the same time offering compatible pairs the opportunity

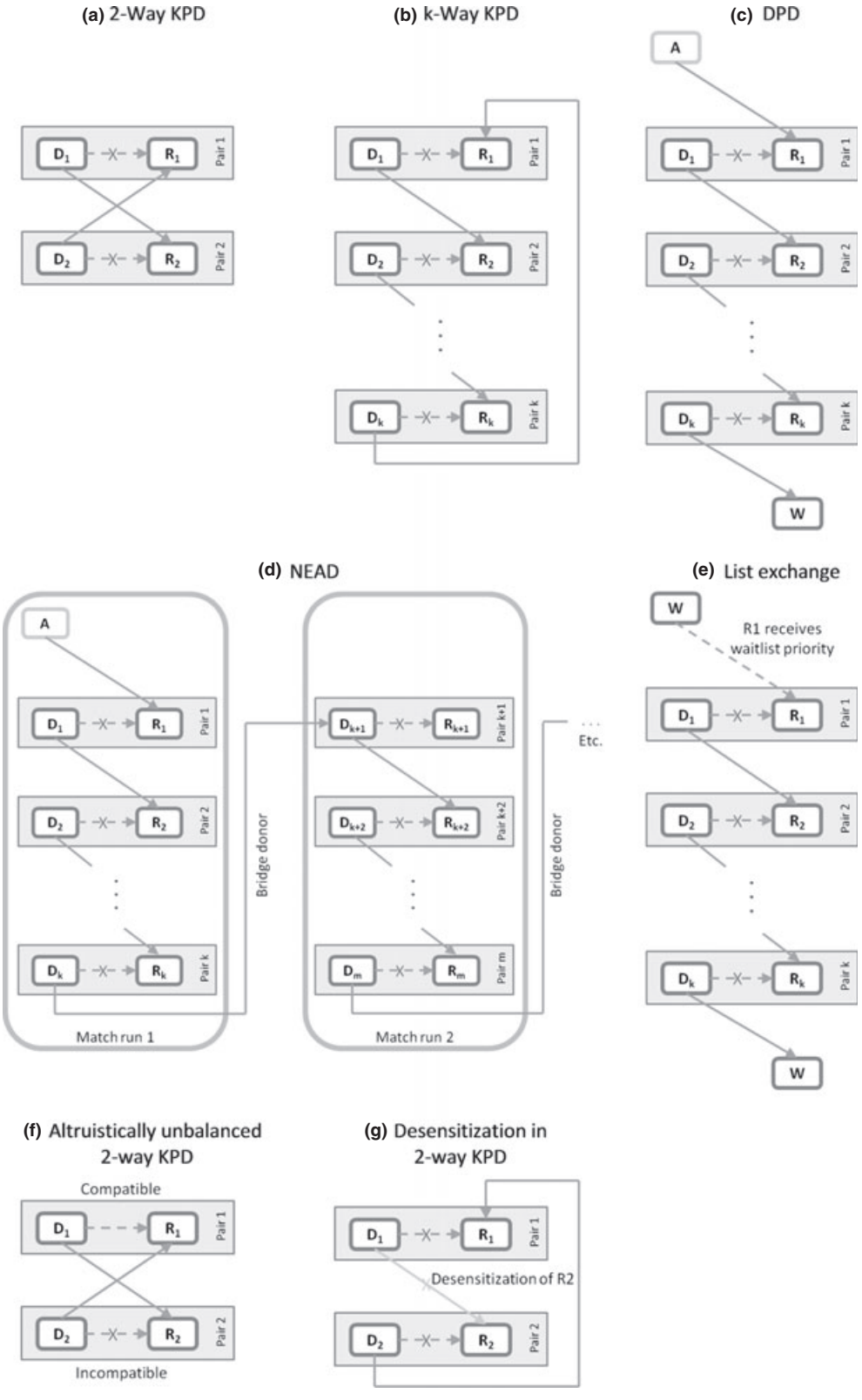

Figure 1 Transplant modalities. Solid arrows indicate matches between donors and recipients. D_i = donor i, R_i = recipient i, A = altruistic donor, W = waitlist.

of obtaining a better quality kidney [51–53]. Studies suggest that 45% of recipients in compatible pairs can obtain a kidney from a younger donor or a 0 mismatch kidney by participating in KPD [51] and that approximately one-third of compatible pairs would indeed be willing to do so [50]. Therefore, altruistically unbalanced exchanges could result in both a higher number of transplants and a higher quality of transplants. Nevertheless, this form of exchange is ethically complicated as it involves asking an otherwise suitable pairs to exchange kidneys with strangers [51].

Desensitization

Finally, there is the possibility of using desensitization techniques to overcome blood-type or tissue-type incompatibility. Although these techniques are costly and technically demanding, several programs have reported promising short-term and intermediate-term results and using such techniques has become an acceptable procedure in selected individuals [15,54–59]. In particular, desensitization for ABO incompatibility has been shown to provide good long-term graft survival, while still comparing favorably to dialysis in terms of costs [60–62]. Combining desensitization with KPD can provide transplant opportunities to patients that would otherwise have been deemed contraindicated and would have waited indefinitely for a suitable kidney [63–66]. This is particularly true if the modalities are not just offered separately to patients, but are coordinated such that hard-to-match patients can be desensitized after identifying a more favorable donor in a KPD [46,64].

Imbalance

Not all incompatible patient–donor pairs have equal chances of success through KPD [32,67–70]. This is primarily due to blood-type imbalance. Because most blood-type O donors can donate directly to their intended recipients, O donors will only need to enter a KPD pool if they have a positive cross-match with their recipient. This leads to a scarcity of blood type O kidneys in KPD pools. At the same time, almost all patients are compatible with O donors. Consequentially, there will be higher demand for O kidneys than A or B kidneys and, similarly, higher demand for A or B kidneys than AB kidneys. This leaves patient–donor pairs of types O-A, O-B, O-AB, A-AB, and B-AB at a disadvantage as they need a kidney that is in higher demand than the kidney they offer [32]. Table 1 provides a characterization of the pair types by blood type in terms of whether they are over-, under-, self-, or reciprocally demanded [71], and typical match results.

Another imbalance is due to patient sensitization. Highly sensitized patients are at a disadvantage because they can only accept a small fraction of kidneys, mostly from donors with few HLA types, which are in high demand. Patients who are both highly sensitized and have formed an under-demanded pair will be most difficult to match.

Success rates of KPD are further largely dependent on pool size and pool composition [28,32,48,70]. The number of potential matches increases considerably with pool size. However, even in large pools, typically only 50% of pairs can be matched through KPD alone [67] (see Table 1). In the Netherlands, under-demanded pairs comprise 40% of the national pool and they have a 19% chance of finding a match. Other pairs, which comprise 60% of the pool, have a 73% chance of finding a match. Because compatible pairs, altruistic and deceased donors typically represent the blood-type frequencies of the general population, allocating these donors to KPD programs permits better matching. Furthermore, because blood-type and tissue-type distributions may differ between countries, international exchanges

Table 1. Characterization of the position of patient–donor types in kidney paired donation (KPD) pools by blood type and their historical match results in the Dutch KPD program.

	Donor blood type (% in population)			
	O (47%)	A (42%)	B (8%)	AB (3%)
Patient blood type (% in population)				
O (47%)	Self-demanded	Under-demanded	Under-demanded	Under-demanded
	16% of pool	33% of pool	6% of pool	1% of pool
	65% success rate	20% success rate	15% success rate	0% success rate
A (42%)	Over-demanded	Self-demanded	Reciprocally demanded	Under-demanded
	8% of pool	13% of pool	8% of pool	1% of pool
	84% success rate	67% success rate	89% success rate	0% success rate
B (8%)	Over-demanded	Reciprocally demanded	Self-demanded	Under-demanded
	4% of pool	9% of pool	1% of pool	0% of pool
	71% success rate	74% success rate	33% success rate	N.A. success rate
AB (3%)	Over-demanded	Over-demanded	Over-demanded	Self-demanded
	1% of pool	1% of pool	0% of pool	0% of pool
	100% success rate	100% success rate	N.A. success rate	N.A. success rate

may provide benefits for selected patient–donor pairs [30,31]. For instance, in the Dutch KPD program, 17% of the patients has a % panel reactive antibodies (PRA) > 80 with respect to the KPD donor population, whereas in the program of the Alliance for Paired Donation in the United States, over 50% of the enrolled patients has a PRA > 80 [37]. Part of the reason for these differences may be the use of different techniques to detect unacceptable HLA specificities.

Allocation criteria

In KPD procedures, patient–donor pairs do not select the pairs with which they exchange kidneys. Instead, the allocation of donors to recipients is determined centrally. For this reason, the authority that oversees the KPD procedures must carefully consider the allocation criteria it will use. There can be many different perspectives as to what constitutes the best allocation.

European agreements governed in the convention on human rights and biomedicine [72] prescribe that allocation of organs should be both "optimal" and "fair," without stipulating precisely what is meant by those terms. Similarly, in the United States, the National Organ Transplantation Act states that donated organs should be allocated "equitably" among transplant patients [73]. The United Network for Organ Sharing (UNOS) defines "equitably" as a balance between utility and justice [74]. While "optimality" and maximum utility is generally interpreted as achieving the maximum number of transplants, defining "fairness" and justice is less straightforward, particularly in light of the imbalance described earlier.

Although initial KPD programs have matched patient–donor pairs on an *ad hoc* basis taking in account the above principles, most programs have now formulated precise guidelines for the allocation process [43,75–80]. In this regard, it is important to make a distinction between allocation requirements that limit the number of feasible allocations and thereby transplants (e.g., requiring donors to be in the same age category or have the same CMV-EBV serology as their recipients) and actual allocation criteria that determine the selection of an allocation from the set of feasible allocations (e.g., maximum number of transplants between donors and recipients of the same blood type).

Traditionally, deceased donor organs have been allocated to recipients in priority order. Several KPD programs have also specified a priority order for KPD allocation criteria. These include the programs operated in the Netherlands, Australia, Austria, and Korea [75–80]. Here, the criteria are hierarchical and include such factors as follows: maximizing the number of matched recipients, maximizing the number of blood-type identical matches (to maximize the likelihood of O patients receiving a kidney and to help overcome their disadvantage), prioritizing allocations based on the number of involved recipients with a low match probability, minimizing the length of the cycles and chains, and prioritizing allocations based on waiting time of the involved recipients. Simulations show that thanks to the inclusion of the above secondary criteria, the number of highly sensitized patients matched may increase by 10% [76].

Alternatively, criteria could also be weighted as is for example performed in the UNOS KPD pilot program and the program of the Alliance for Paired Donation in the United States [43,81]. These programs have specified weights for factors as waiting time, HLA match, PRA, prior cross-match history, pediatric status and preferences of the incompatible pairs and their transplant centers (e.g., the distance the pair is willing to travel and whether the transplant center would accept a shipped kidney) and select the allocation that has the largest total weight [43,81].

Other programs have formulated requirements and criteria with regard to age, travel distance, etc [35,79,82,83]. Two unconventional possibilities are worth mentioning. The first is the use of quality adjusted life years from transplant. Use of quality adjusted life years is commonly accepted as a prime decision criteria for many medical interventions, following the framework of Health Technology Assessment [84,85]. However, it may conflict with commonly accepted criteria such as maximizing the number of transplants [86,87]. Another possibility is to consider long-term instead of short-term criteria [88–90]. These two do not necessarily coincide. For example, to maximize the long-term number of matched patients, it may be necessary to allow for some match runs in which matches are postponed (e.g., to allow for a future three-way KPD to take place instead of a current two-way KPD).

After an allocation has been selected, it may not always find continuation. Proposed matches may fail due to negative cross-matches or patient or donor illness. In such cases, a new allocation can be determined based on the updated information, as is for instance performed in the Netherlands, but this requires appropriate organization of cross-matching (see under Organization). An alternative solution is to maintain the initial allocation as much as possible and only reallocate pairs that are part of procedures that are discontinued. For instance, a discontinued k-way KPD could still result in multiple two-way KPDs going forward (see Fig. 2). The KPD program in the UK utilizes a set of hierarchical allocation criteria that aim to maximize the number of transplants that can take place after such a continuation [80], by first maximizing the number of potential two-way KPDs (including "back-up" two-way KPDs) and as a secondary priority maximizing the total number of transplants [80].

It can happen that different allocations rank the same on all of the selected allocation criteria. To select an allocation

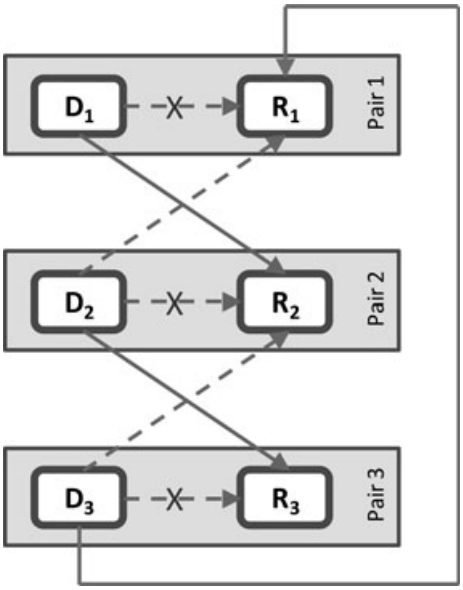

Figure 2 Match failure. Initially, a three-way kidney paired donation (KPD) is selected. If the match between donor 3 and recipient 1 fails, it is still possible to perform a two-way KPD, either between pair 1 and pair 2, or between pair 2 and pair 3.

then, most programs use a deterministic tie-breaking rule [75,80]. However, an interesting alternative for such cases is to use a stochastic rule, that is, a lottery which selects an allocation randomly [71]. A stochastic rule can provide several fairness properties, in particular because the probability of selecting a recipient need not be the same for all recipients and can be set in a way that alleviates the imbalance due to blood-type and tissue-type distributions [71].

Participation constraints

Kidney paired donation programs benefit from the participation of as many centers as possible to create a large pool. However, multicenter cooperation has brought about several difficulties. Firstly, it requires consensus between participating transplant centers on the allocation requirements and criteria. Secondly, centers may judge that it is not in the interest of (some of their) patients to participate and hence may prefer to not cooperate (fully). Thirdly, financial, scientific, or other incentives may exist, which cause cooperation to be potentially suboptimal. Thus, transplant centers may prefer to match some donors and patients locally instead of submitting them to the national pool [46,91] (see Fig. 3). One way to overcome such incentive issues is by implementing participation constraints which ensure that each transplant center can perform at least the same number of transplants in a national pool as that it can achieve on its own. Although such constraints limit the set of feasible allocations, it has been shown that they do not

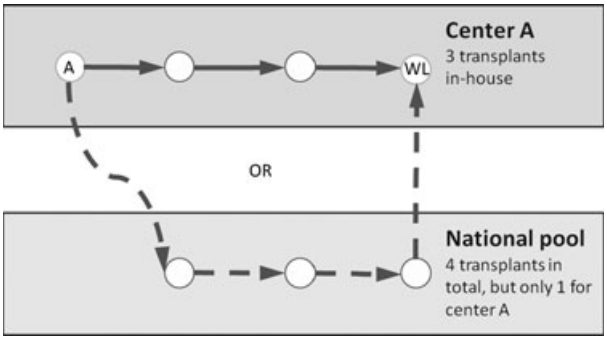

Figure 3 Potential participation problems. Center A can perform three transplants in house. If center A participates in the national pool, four transplants can be performed, but only 1 at center A.

negatively affect the long-term benefits of KPD programs [46,91].

Matching algorithms

Initially, most KPD programs manually selected the allocation that best fit their criteria. However, given that the number of possible allocations grows exponentially with the size of the KPD pool, manually evaluating all possible allocations is only feasible for very small pools. In the United States, the process of finding a match therefore originally followed a "first-accept" scheme, which involves matching an incompatible patient–donor pair to the first pair that meets the acceptance requirements, even though matching with another pair might yield a better outcome [92].

Most KPD programs today use computer software to identify the best allocation with respect to their criteria [43,75,77–80,93,94]. Such software typically compares all possible allocations and can perform virtual cross-matching based on known donor HLA types and patient unacceptable HLA mismatches. However, as KPD programs expand and start to be combined with other transplant modalities, the number of possible allocations becomes so large that even for computer programs, it becomes intractable to enumerate all feasible allocations. In these situations, mathematical optimization algorithms are required to guarantee the selection of the best possible allocation [76,80,95,96]. The best current algorithms use a technique known as "branch-and-price," which enables them to select an optimal allocation within minutes because they only need to consider a small subset of all possible allocations [76,95].

There are several aspects that provide challenges for the future. The first is that as KPD programs continue to evolve, highly sensitized and hard-to-match patients are likely to accumulate in the pool [37]. In such pools, the use of long chain procedures becomes essential to achieve the full benefits of exchange [37]. However, this renders the

process of computing an optimal allocation drastically more difficult. Fortunately, recently developed algorithms have been shown to perform well even when pools are large and sparse and long chains are required [76].

Another aspect is that taking into account the probability of match failure by maximizing the expected number of transplants (which is different from maximizing the number of matches) may become more important as this will eventually lead to more transplants going forward [97,98]. Although this still poses computational challenges, it may be an opportunity to significantly increase the success rates of KPD programs [98].

Similarly, considering dynamic—instead of static—optimization of kidney exchanges takes into account the timing of exchanges and the fact that patients and donors enter and leave the KPD pool over time, to optimize the desired allocation criteria in the long run [46,88–90,99]. Essentially, this better represents the real decision problem underlying KPD. As of yet, because of computational complexity, it is only possible to find approximate solutions to the dynamic problem, but even these are often significantly better than solutions achieved through static optimization. Figure 4 illustrates how dynamic optimization can provide benefits. Shifting focus from static to dynamic optimization—and thereby from short-term to long-term goals—raises questions as to what defines optimality and what is equity in a dynamic setting. Full answers to these questions await further research.

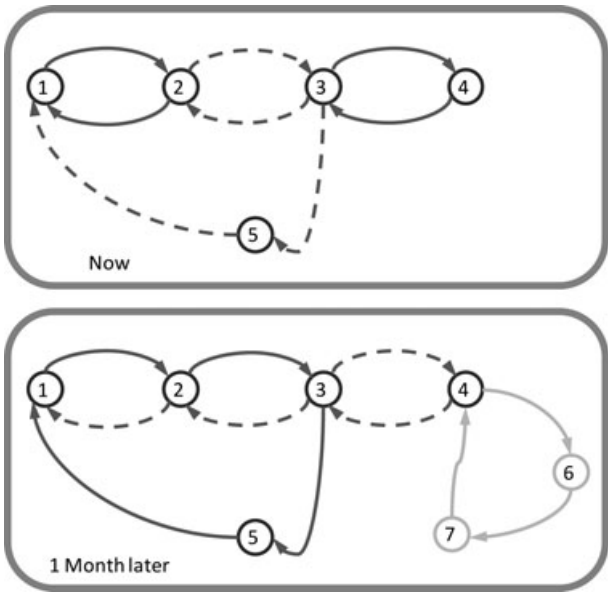

Figure 4 Dynamic optimization. There are five pairs in the current kidney paired donation (KPD) pool. Two two-way KPDs are performed involving pairs 1 and 2, and pairs 3 and 4. One month later pairs 6 and 7 enter the pool. In hindsight, it would now have been better to perform one four-way KPD between pairs 1, 2, 3, and 5, and one three-way KPD between pairs 4, 6, and 7. Dynamic optimization anticipates such situations and maximizes the expected number of transplants.

Organization

Several countries have now implemented or pursue a national KPD program. However, there are several differences in how these programs are organized. Primarily, this is because of geographical differences: for example, the United States has 244 kidney transplant centers spread out over a large area [100], while the Netherlands has eight kidney transplant centers that are relatively close together [23]. This has immediate implications for the coordination between transplant centers and donor travel. In the Netherlands, it is feasible to move donors to the center where the matched recipient will receive the transplant. This is preferable as the recipients' home institution can provide the recipient with continuity of care and follow-up and avoids long cold ischemic times. In the United States, the retrieval surgery typically takes place at the donor center and the kidneys are shipped to the recipient's center for transplantation. Even though this requires longer cold ischemic times and risks transportation delays, recent studies show comparable graft survival rates of shipped kidneys and nonshipped kidneys [36,41,101–103].

A major contributor to the success of the Dutch program in establishing consistent high match rates is its use of a national centralized tissues typing laboratory [48,104]. In this laboratory, potential donors and recipients are tested for HLA cross-match. Having a centralized laboratory substantially enhances coordination between centers as it removes dispute about cross-match outcomes by setting a uniform cross-match standard.

Finally, the frequency of match runs—and thereby the timing of exchanges—also is a differentiating element between KPD programs. Some programs perform match runs on demand—such as Korea—whereas others perform them once per month or once per 3 months—as in the Netherlands [43,46,48,79]. Although frequent performance of match runs may result in shorter waiting time for matched recipients, it risks removing only easy-to-match pairs as the pool may not always be saturated enough for the procedures involving hard-to-match pairs to take place. Deciding when to match is therefore an important decision for KPD programs [46]. New matching software is able to advice on the optimal timing based on the composition of the pool [88–90,99].

Outlook

Since its inception in 1986, KPD has greatly expanded and has become an accepted method of transplantation at transplant centers throughout the world. Many advances

have been made in terms of surgical technique, shipping donor kidneys and international exchanges. Nevertheless, many blood type O and highly sensitized patients still remain without a transplant. Important factors that have limited the success of KPD programs are logistic issues, basic trust between the various participants, and match failures. Innovative transplant modalities as altruistic donor chains and desensitization can help ameliorate the problem for critical patient groups. However, to achieve the best possible outcomes, these modalities should be coordinated jointly with KPD [46]. In this regard, this review has summarized different allocation and matching strategies. While there are many other issues that could be explored in the evolving field of KPD, matching is a key element in KPD, and by selecting the right matching strategy, many patients can benefit. Future opportunities and challenges include making full use of the various modalities that are now available through integrated and optimized matching software, encouragement of transplant centers to fully participate, improving transplant rates by focusing on the expected long-run number of transplants, and selecting uniform allocation criteria to facilitate international pools.

Funding

The authors have declared no funding.

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