Review

Paired exchange programmes can expand the live kidney donor pool

A. O. Mahendran and P. S. Veitch

Renal Transplantation Unit, Royal Free Hospital and University College London Medical School, Pond Street, London NW3 2QG, UK
Correspondence to: Mr. P. S. Veitch (e-mail: peter.veitch@royalfree.nhs.uk)

Background: **Kidney paired donation (KPD) is an exchange of organs between two live donors, who are otherwise ABO incompatible or cross-match positive, and their intended recipients. The outcome is the generation of compatible transplants conferring an improvement in quality of life and longevity.**
Methods: **Medline was searched for articles on KPD using a combination of keywords. Publications focusing on protocols and policy, mathematical modelling, ethical controversies, and legal and logistical barriers were identified.**
Results: **Many are precluded from transplantation because of incompatibilities with their intended donors. KPD has the potential to increase the rate of transplantation by facilitating exchange transplants between otherwise incompatible donor–recipient couples. Ethical controversies surrounding paired donation include confidentiality, conditionality of donation, synchronicity of operations and the possibility of disadvantaging blood group O recipients. Logistical barriers hampering KPD programmes involve the location of donor surgery and organ transport.**
Conclusion: **Paired donation may expand the living donor pool by providing an alternative successful strategy for incompatible donor–recipient couples. Its widespread implementation will depend on resolving ethical and logistical constraints.**

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Introduction

The rising number of patients requiring renal replacement therapy places a heavy burden on healthcare resources[1]. Although dialysis provides an intermediary step in the management of endstage renal failure (ESRF), renal transplantation remains the treatment of choice for most eligible individuals. Not only does it offer an improvement in quality of life, it also confers significant survival benefit[1,2]. There are strong demographic trends in trauma-related deaths and deaths from intracranial haemorrhage that continue to reduce the availability of cadaveric organs for transplantation[1,3,4]. Initiatives such as laparoscopic nephrectomy, aimed at reducing disincentives to live donation, have fostered an expansion of live donor programmes. In addition, advances in immunosuppression have improved graft survival, obviating some of the need for close human leucocyte antigen (HLA) matching[4,5]. This has encouraged transplantation from genetically unrelated individuals such as spouses, friends and altruistic donors.

In 1990, 9416 renal transplants were performed in the USA; 78 per cent were from cadaver donors and 22 per cent from living donors. In contrast, of the 15 128 transplants performed in 2003, 57 per cent were from cadaver donors and 43 per cent from living donors[6]. The advantages of a living donor transplant are well documented. They include improved long-term graft survival, a lower rate of delayed graft function, the possibility of pre-emptive transplantation and less time spent on dialysis[1,4,6]. The 5-year graft survival rate is 73 per cent for kidneys from unrelated living donors in the USA. This is similar to the 5-year graft survival rate of kidneys from non-HLA-identical genetically related donors (69 per cent) and better than that of transplants from cadaver donors (58 per cent)[7]. Transplantation is precluded between donor–recipient pairs when there is an ABO blood group incompatibility or a positive pretransplant cross-match due to antibodies to class 1 donor HLA antigen. It is predicted that in the USA alone between 10 and 20 per cent of potential donors are eliminated because of ABO incompatibility or cross-match positivity[8].

Other than paired exchange, the only strategies aimed at circumventing these problems involve desensitization techniques and various forms of live donor–cadaver donor list exchange[2,9]. The latter allows the potential recipient of an otherwise incompatible pairing to receive priority on the cadaver waiting list by providing a recipient on that list with a kidney from his or her intended donor. The main ethical issue posed by list exchange is that it disadvantages blood group O recipients who are likely to endure longer waiting times on the cadaver list[10–12]. Studies of blood type frequencies have shown a 35 per cent chance that any two unrelated individuals will be ABO incompatible[8]. In addition, 30 per cent of patients awaiting donation in the New England registry have been sensitized to HLA antigens, usually owing to previous transplants, pregnancies or blood transfusions[8].

Desensitization protocols aimed at sustained depletion of alloantibodies to HLA combine plasmapheresis, intravenous immunoglobulin and pharmacological B cell depletion or splenectomy[13–15]. However, their long-term efficacy has yet to be proven and they are resource intensive. In addition, some treatments are associated with an unpredictable rate of accelerated rejection and allograft loss[15]. Sustained depletion of naturally occurring antibodies to A or B blood groups, sufficient to attain successful transplantation across an ABO mismatch, has, however, been effective using similar strategies.

This article compares and contrasts the kidney paired donation (KPD) protocols and results published by various groups in the international transplantation community. It also explores the ethical controversies and logistical limitations to exchange programmes.

Methods

Literature on kidney paired exchanges was identified by searching Medline and PubMed databases. In particular, single-centre articles were searched to derive the protocols used and the results produced by national and regional KPD programmes. The following keywords were used in various combinations: paired exchanges, paired donation, protocols, ethical limitations, legal issues, logistical barriers, mathematical modelling, relay exchanges, novel approaches, ABO-incompatible transplants, expanding donor pool, solicitation of organs, and blood group O recipients. Common trends in procedure were identified, as were recurring ethical and logistical problems.

Paired exchange

Rapaport[5] formulated the principle of paired exchange in 1986, giving it the title 'kidney paired donation' (KPD). He envisaged a process involving two otherwise incompatible donor–recipient pairs, treated at separate transplant centres simultaneously, with an immediate exchange of two kidneys to produce two compatible pairs (*Fig. 1*). Within paired donation there are two forms of kidney exchange, conventional and unconventional donation. A conventional paired donation describes a situation in which two donor–recipient pairs who are blood type-incompatible exchange donors to produce compatible transplants (*Fig. 2a*). Conventional paired donations are limited to donors and recipients with blood types A and B[10]. An unconventional paired donation applies to donor–recipient pairs who are incompatible because of a positive cross-match. This permits donors and recipients with blood type O and AB to participate in the exchange[10] (*Fig. 2b*).

Paired exchange programmes are now operational on a regional basis in the USA and as a national donor exchange scheme in both the Netherlands and South Korea[2,17–21]. In the UK, following enabling legislation, the operation of a national scheme is currently under debate. Computer programs have been developed to facilitate pairings that account for ABO and HLA compatibility. In addition, paired donation is not limited to generating two-way exchanges alone[16,18]. In South Korea a similar programme has undergone substantial evolution producing an advanced relay of transplants and multiple exchanges.

Domino paired donation is a more recent concept, initially described by a team from Johns Hopkins Medical School[17], with the aim of maximizing the benefit of altruistic donation. Here a potential recipient who has a willing but incompatible living donor is matched with a compatible altruistic donor. The kidney from the

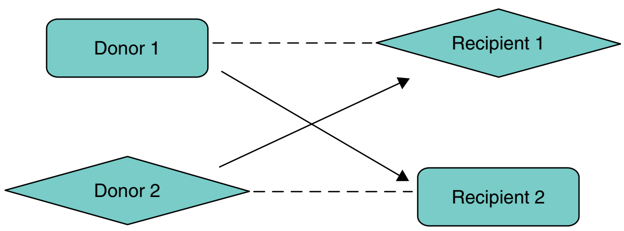

Fig. 1 Paired donor exchange between two recipients. The exchange involves donor 1 providing an ABO-compatible and cross-match-negative kidney to recipient 2, and donor 2 donating an ABO-compatible and cross-match-negative kidney to recipient 1. The exchange creates two ABO-compatible and cross-match-negative transplants[16]

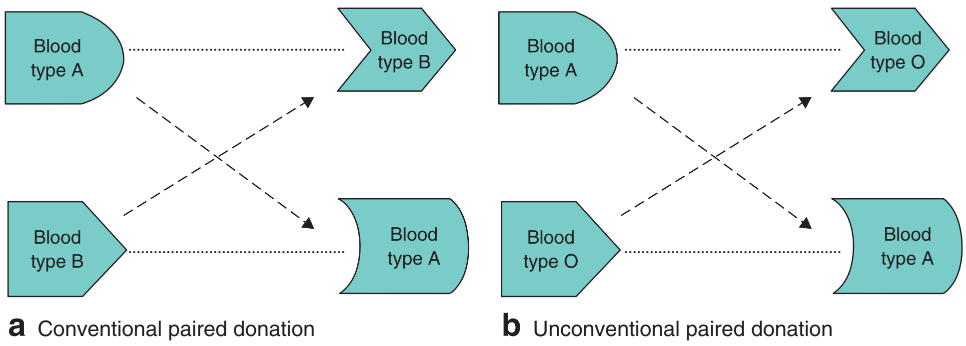

Fig. 2 Kidney paired donations. **a** In conventional paired donation, a blood type A and B donor–recipient pair is matched to a pair with the opposite incompatibility. The result is two compatible transplants. Conventional paired donations are limited to donors and recipients with blood types A and B. **b** In an unconventional paired donation donor–recipient pairs who are incompatible because of a positive cross-match are included. As a result, donors and recipients with blood types O and AB also are eligible, provided that their incompatibility is a positive cross-match. Recipients exchange donors such that both resulting transplants are blood type and cross-match compatible

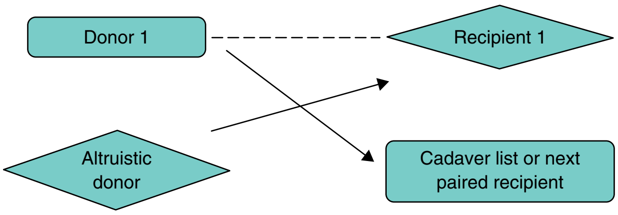

Fig. 3 Domino paired exchange. The exchange involves an altruistic donor providing an ABO-compatible and cross-match-negative kidney to recipient 1, and donor 1 donating an ABO-compatible and cross-match-negative kidney to the cadaver list or another pair. The exchange creates two ABO-compatible and cross-match-negative transplants

recipient's donor is then dominoed to the next compatible patient on the cadaver waiting list or is used to add another incompatible pair to the chain (*Fig. 3*).

The Dutch algorithm

The seven kidney transplant centres in the Netherlands have developed an allocation algorithm designed to match compatible donor–recipient pairs in a national scheme[18]. This ensures that even hard-to-match highly sensitized recipients have the best chance of finding a compatible donor. The allocation is facilitated by a computer program, which calculates the match probability (MP) of every potential recipient. This is derived from the peak panel reactive antibodies of the recipient, the HLA unacceptables of the recipient and the incidence within the paired donor population of compatible ABO blood groups. The patient with the lowest MP, reflecting the least chance of finding a compatible donor, is given priority. Then, in an iterative fashion of prioritization, the program ensures that as many donor–recipient pairs are matched as possible. Matching runs, followed by enrolment of new donor–recipient pairs, are conducted every 3 months. Of the first run of 53 participating incompatible pairs, 22 were found a compatible donor–recipient pair[18]. Potential conflicts were addressed as follows. If two recipients had the same MP, priority was determined by the time spent on dialysis and the date of the match. To minimize the potential disadvantage faced by blood type O recipients, the ABO blood group identicals were allocated first. Within these groups pairs were ranked according to the MP of each recipient. Where possible, O-type donors were preferentially chosen to provide kidneys for an O-type recipient rather than, for example, an A-type recipient. This ensured the maximum number of donors for type O recipients. The same principle was applied to AB blood types.

Korean relay transplantation

The Korean relay system expands the concept of single matched pairs to involve multiples up to a reported peak of seven pairs exchanging grafts over a period of time[22]. Such an outstretched relay may result in a would-be recipient waiting up to 1 year for transplantation. To start the process, a living anonymous donor makes the initial donation, and the next donor, related to the first recipient, makes the second. The third donor, related to the second recipient, makes the third and so on until the loop has been completed. In Korea, the rate of living kidney donation far exceeds the relatively low rate of cadaveric donation. From 1993 to 2002 relay kidney operations constituted 5 per cent of all living donor kidney transplants. Of the 410 procedures that took place, 282 were two-relay, 57 three-relay, 48 four-relay, ten five-relay, six were six-relay and seven seven-relay.

First-accept scheme *versus* mathematical modelling (USA)

In contrast to the Dutch allocation algorithm, a number of transplant centres in the USA currently use the first-accept matching scheme[2,8,16]. Here an incompatible donor–recipient pair is matched to the first compatible donor–recipient pair that meets certain acceptance criteria (*Table 1*). After matching, both pairs are removed from the database and so are no longer available for the generation of alternative combinations, even though this might yield better matches with other pairs.

In an alternative approach to a first-accept scheme, Montgomery and colleagues[16] investigated the potential of a mathematically optimized matching algorithm. By prioritizing pairings with the fewest HLA mismatches, the algorithm yielded more matches in addition to a lower HLA disparity. Priorities could also be customized to emphasize regional considerations. Their study found that most pairs preferred matches within their region, even if it was at the expense of an increase in the number of HLA mismatches. Priorities could also be assigned to disadvantaged groups, such as highly sensitized patients, in order to maximize donor availability. Using this optimized algorithm, every feasible donor–recipient combination could be considered, giving the best set of solutions to any given set of priorities. Of a pool of 1000 donor–recipient pairs, the first-accept method evaluated a single solution whereas the optimized algorithm considered approximately 10^{250} feasible solutions before assigning the best.

Table 1 First-accept matching scheme criteria[8]

All pairs	Blood type compatibility required
Pairs with unsensitized recipients	Only donors of the same age group or younger accepted
Pairs with sensitized recipients	Donors of any age accepted
Pairs unwilling to travel	Only considered for matches within the same region
Highly sensitized recipients	Only offered exchanges with 0 or 1 HLA antigen mismatches

HLA, human leucocyte antigen.

Combining paired donation with list exchange (USA)

In 2001, a paired exchange protocol was approved in New England[2]. Devised by Region 1 of the United Network for Organ Sharing, which included 14 New England transplant centres and two organ procurement organizations, it was designed to enable either a simultaneous paired exchange at the same or different centres, or a list exchange for recipients unable to be paired (*Table 2*). The crucial point in the handling of incompatible donor–recipient couples involved establishing the donors' willingness to provide a kidney to an unknown recipient and, conversely, the recipients' willingness to accept, whether as part of a paired donation or a list exchange. Centres were responsible for the necessary psychiatric and/or psychological evaluation. Priority was given by the precise date of notification if more than one pair was able to participate in a paired exchange. If no opportunity for a paired donation arose, a list exchange was considered.

Currently, centres allow a 1-month wait for a second incompatible donor–recipient pair to present before proceeding with a list exchange. However, it seems that this wait is not strictly regulated. The criteria for identifying suitable recipients are different for paired donation and for list exchange. For example, live donor transplantation may involve candidates who are yet to enter end-stage renal failure. Thus transplantation as a pre-emptive measure is possible with paired donation but would not be considered for list exchange.

Delmonico and co-workers[2] reported four live KPD exchanges and 17 list exchanges over a year. The interval between the live donor and the deceased donor transplants ranged from 5 days to more than 3 months. The authors noted a number of problems with their programme. At one point in the list exchange scheme, three candidates had an option on the next cadaver donor. It was decided to defer further list exchanges temporarily. Thereafter, the original policy was modified to allow only two exchange recipients to be listed simultaneously to avoid an unpredictable wait.

Table 2 Procedural steps of the Region 1 plan[2]

1 Live donor exchange preferable for identified incompatible donor–recipient pairs
2 If no live donor exchange feasible, live donor list exchange considered by the Oversight Board
3 List exchange recipient (unknown to the living donor) identified from the match run using the centre list. Recipient for whom the donor kidney was originally intended receives right of first refusal for the next ABO-identical (cross-match-negative) deceased donor kidney available within the region

The second issue concerned those recipients experiencing early graft failure following the receipt of a cadaver list exchange graft. It was agreed that affected individuals should be given priority for a second cadaver kidney. The third issue related to the inequalities faced by blood group O recipients is discussed below.

Regional *versus* national paired donation programmes

It is widely accepted that the true potential of paired donation remains unknown. In the USA, the number of paired donations performed annually is less than 10 per cent of all living donation[23], although it is postulated that as many as 3000 recipients a year could receive kidneys through a national donor exchange programme[3]. The limitations of paired donation have been ascribed to a number of issues, such as the need for the donor to travel or the kidney to be shipped, and the fact that single centres may have too few donor–recipient pairs to generate a significant number of matches[2,6]. Geographical barriers seem to present a significant problem for a number of reasons. Donors appear reluctant to travel long distances or may be concerned about a nephrectomy in unfamiliar surroundings. Alternatively, shipping a kidney lengthens the cold ischaemia time and may convert a routine daytime operation into one that is undertaken out of hours. In densely populated areas this is less of a problem as there are greater numbers of potential recipients and donors[2,10]. Gentry *et al.*[9] showed that the greatest number of matches could be achieved from a national paired donation programme utilizing a computer-driven algorithm to optimize matches. Their model demonstrated that, in smaller populations, patients were better served with list exchange rather than paired donation. Montgomery and colleagues[16] proposed from a simulated study that about 50 per cent of incompatible pairs could receive transplants within a national scheme and suggested that unmatched patients might be accommodated by desensitization programmes or a less restricted paired donation search. They suggested that a national programme would benefit highly sensitized individuals in particular. None of the paired donation programmes have had more than 20 donor–recipient pairs available for matching at any one time.

At present there is no evidence of high referral rates of ABO- and cross-match-incompatible pairs to any national scheme, with the possible exception of the Netherlands' programme[2]. Reasons cited are many and, apart from geographical considerations, include time constraints on transplant coordinators and physicians, and problems of identifying, educating, consenting and referring patients on to appropriate schemes. Woodle[23] has commented that, although no paired donation programme has more than 20 donor–recipient pairs available for matching at any one time, the number of potential matches is an exponential function of the number of donor–recipient pairs – the so-called 'critical mass' effect.

Clinical results of paired donation transplantation

There have been surprisingly few reports on the outcome of paired donation programmes. However, there is no obvious reason to believe that the clinical results from paired donation should be any different from those of live donor transplants between other unrelated individuals. Montgomery and co-workers[16] recently published the results of their single-institution study with 22 patients involved in ten paired donor transplants, two of which were triple exchanges. Six conventional and four unconventional transplants were performed at their centre between June 2001 and November 2004. The patient and graft survival rate was 100 and 96 per cent respectively at a median follow-up of 13 months. One-third of their recipients had undergone previous transplants and the rate of acute cellular rejection was 18 per cent. Delmonico and co-workers[2] documented eight paired exchanges and 17 list exchanges over a 1-year period. In the paired exchanges there was one accidental death with a functioning graft and one early failure; the remaining six patients were alive with excellent graft function.

The problem of blood group O recipients

The fate of potential recipients who are blood group O is a concern. These patients have always endured longer waiting times for transplantation[12]. Reasons include a relative shortage of group O cadaver kidneys, particularly when organ allocation prioritizes HLA over ABO matching and blood group incompatibility in living donor pairs. In fact most of the blood type incompatibilities that preclude transplantation occur when the donor is blood group A or B and the recipient is blood group O[24]. Even when a suitable group O donor is available transplantation may not be possible because of a positive cross-match. The impact of exchange programmes on group O recipients is as follows. In so-called conventional exchanges on a paired donation programme transplantation would normally occur between pairs who are blood groups A and B[25]. These individuals represent the minority of donor–recipient pairs, so these exchanges are of no benefit to group O recipients. Unconventional exchanges, where initial sensitization precluded transplantation from a blood group O donor, can to a degree mitigate against this effect and permit some exchanges to the benefit of group O recipients[25]. List exchange programmes also disadvantage blood group O recipients. Again this arises as most incompatible recipients are blood group O and so, when their non-O donor gives a kidney to the deceased donor pool shortening non-O waiting times, it conversely increases O waiting times[24–25].

The alternative for difficult-to-match O recipients is to find appropriate O donors as part of a paired exchange. At present, it is rare to find a blood group O donor taking part in an exchange programme. As universal donors they can donate to any ABO recipient. However, is it ethical to ask a blood group O donor to participate in a paired kidney exchange even though he or she could donate directly to their intended recipient[24,25]? Ross and Woodle[23] examined this scenario. They considered this as an unbalanced exchange in which one donor–recipient pair can participate in a direct donation but the second donor–recipient pair cannot. It is unbalanced because of the differences in the degrees of altruism required by the two donor–recipient pairs. So an already altruistic donor would be required to be more altruistic by relinquishing their ability to donate directly to their genetically or emotionally related recipient in order that two patients received transplants instead of one. Finally, in defending the use of paired donation, in spite of an early disadvantage for group O recipients, it could be argued that once regional or national programmes become established, allowing large numbers of A and B recipients to be removed from the waiting list, O recipients will ultimately benefit through shorter waiting times[23–25].

Other ethical concerns

The intimate and unique nature of relationships between family members can place potential donors under unacceptable pressure to donate. Previously, some reluctant donors who felt coerced or emotionally blackmailed into donating may have won a reprieve from surgery as a consequence of an ABO incompatibility or a positive cross-match. Paired donation, however, removes such barriers and may again place the burden of participation on an unwilling donor. This may require a more robust psychiatric or psychological evaluation than is commonly practised in standard living related and unrelated programmes. Although a paired exchange may appear fair, there may still be inequities. For example, one donor may provide a better-quality kidney by being younger or by exhibiting a better HLA match. Both parties, however, may find it a better compromise, particularly if it avoids ongoing dialysis or an unknown waiting time on the cadaver list[26,27].

Rapaport[5] originally proposed that the KPD operations should be conducted simultaneously, the idea being that both procedures could be aborted if a complication arose in one individual. Logically, the point of no return would be the division of the renal vessels. This approach would provide the best chance for both couples of a fair and just exchange of kidneys. In the event that one recipient could not receive the intended donor kidney owing to anaesthetic or operative complications beyond the point of no return, some centres have consented the would-be recipient for right of first refusal on the cadaver list[2,18–20]. However, there is still no consensus as to when synchronous procedures should be halted in the event of a donor complication. Furthermore, in the event of a recipient complication precluding transplantation, there is no consensus on how to allocate the non-transplanted kidney.

In the USA, the number of live donor transplants in some units has surpassed the number from cadaver donors. This has led to concern over public solicitation of organs[28]. A Boston-based website, MatchingDonors.com, was launched in February 2004, advertising itself as 'a venue where patients and potential donors can meet and communicate, and hopefully expedite a donor agreeing to give a patient a much needed organ'[28]. It claims to be a non-profit organization with all member fees going towards maintenance of the site. As of July 2005, it had paired 30 living recipient–donors with 12 subsequent kidney transplants taking place. Clearly such agreements between participating individuals would currently be viewed as outside of the normal organ allocation process but, in particular, it raises concern about conditionality. For example, a patient-driven web-based solution might well foster kidney allocation not just on the basis of ABO and cross-match compatibility but also on the basis of the participant's views on race, religion and ethnicity. Aware of the ethical problems posed by conditionality, most paired donation programmes have upheld the importance of anonymity, certainly up to the point of organ exchange. With the soaring demand for organs, however, such initiatives raise questions about the integrity of the organ allocation process and whether there should be specific policies to prevent individuals placing restrictions or conditions on paired organ donation. Some measures have been introduced, but none directed specifically at paired donation. The state of Florida has passed a law prohibiting patients and families from placing restrictions on donation following the case of a brain-dead Florida resident who agreed to donate his organs, but insisted that the recipient be white[29,30].

Discussion

A shortage of cadaver kidneys for transplantation remains in spite of many initiatives to expand the organ donor pool. These include public awareness campaigns, organ donor registers, required request, assumed consent and non-heart-beating donation. It has been postulated, however, that even if all potential deceased donors became actual donors, there would still be a shortage of organs[23,26]. The number of living donors has increased primarily because of a reduction in the importance of HLA matching with modern immunosuppression, the use of emotionally related donors (partners, wives and close friends) and a reduction in disincentives to donation such as laparoscopic approaches. However, it is the use of unrelated live donors that has the greatest potential for increasing the availability of kidneys.

The immediate benefit of paired donation is that patients can be transplanted, while those remaining on the waiting list have improved access, as they are not competing for the same deceased donor pool. Surgery can be performed in a timely fashion, possibly obviating the need for dialysis. Other advantages include graft survival rates that are similar to those of living related donor kidney transplants, transplants that can be scheduled at a medically convenient and safe time, and emotional benefits to both recipient and donor. The greatest advantage of paired donation is in ensuring the continued participation of a number of suitable, motivated living donors who would otherwise be lost to the live donation programme by virtue of an incompatibility with their intended recipient. Given the success of unrelated living donor transplants in general, paired exchanges should have excellent long-term outcomes. If the latter is to become widespread, however, a key area to be addressed is the potential trade-off between programmes designed to maximize transplant numbers (Dutch) and schemes that permit a degree of choice for individual pairs (USA). It is likely that exchange protocols will be moulded to an extent by the ethical issues concerning any particular transplant community[31].

Kidney exchange programmes were devised with the clear utilitarian aim of expanding the pool of compatible donors and so the rate of transplantation[32]. Although it may not generate the large numbers of additional organs needed to make a significant impact on the waiting list, KPD may still emerge as a significant and novel strategy in the drive to increase the overall number of recipients undergoing successful transplantation.

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