

## REVIEW

# Paired kidney exchange transplantation – pushing the boundaries

Vijay Kher  & Pranaw Kumar Jha 

Department of Nephrology & Transplant Medicine, Medanta – The Medicity, Gurgaon, Haryana, India

## Correspondence

Vijay Kher, Medanta Kidney and Urology Institute, Division of Nephrology and Kidney Transplant Medicine Medanta, The Medicity Gurugram, Haryana, India.  
Tel.: 91-1244141414;  
fax: 911-2448341111;  
e-mails: vijay.kher@medanta.org;  
vijaykher51@yahoo.com

## SUMMARY

The scarcity of living organ donors makes it imperative to develop newer innovations to optimize and maximize the utilization of the available pool. ABO and HLA sensitization are important immunological barriers in renal transplant and can potentially lead to rejection of almost one-third of the willing living donors. Paired kidney exchange (PKE) is a rapidly growing method used to overcome these barriers and has grown in popularity over the last three decades since its introduction in 1986. Evolution of the matching strategies and use of complex algorithms has led to increase in the number of possible matches thereby benefiting multiple recipients. The use of altruistic donors and compatible pairs has also helped in increasing the possible exchanges. This review provides an in-depth analysis of the evolution, the present global scenario, and the future of PKE. It also discusses the recent trends of advanced donation, trans-organ paired exchange and global kidney exchange and the associated ethical concerns.

*Transplant International* 2020; 33: 975–984

## Key words

domino kidney paired donation, kidney paired donation, paired kidney exchange, renal transplant

Received: 24 June 2019; Revision requested: 2 August 2019; Accepted: 1 July 2020; Published online: 2 August 2020

## Introduction

Kidney transplantation is the best form of renal replacement therapy for patients with end-stage kidney disease [1] but there is a huge demand and supply gap. The waitlist for kidney transplantation is increasing by every passing year. In view of the increasing backlog and the limited available donor pool, innovative solutions are required to meet the ever-increasing demand.

Living donor transplant outcomes such as graft survival and biopsy-proven acute rejection rates have been shown to be better than those of deceased donor transplants [2]. But unfortunately, almost one in three potential kidney donors are deemed incompatible due to the immunological barriers of blood group incompatibility or human leukocyte antigen (HLA) sensitization [3]. A

recipient–donor pair is said to be compatible if their blood groups match and the crossmatch is negative. Blood group compatibility means that the A and B blood group recipients can receive kidney from the same blood group or O blood group donors. O blood group can receive kidney from only O blood group donors while AB blood group recipients can receive kidney from donor of any blood group. Although it is possible to do incompatible transplants after desensitization, such transplants are expensive and fraught with high risk of rejections, infections, and poor graft survival [4–6].

## What is paired kidney exchange?

Paired kidney exchange (PKE) is a process whereby kidneys are exchanged between two or more

HLA-incompatible or ABO-incompatible living donor kidney pairs and recipients receive better compatible kidneys. Desensitization is a complex procedure which requires sophisticated immunological tests, plasmapheresis or immunoadsorption, rituximab, etc. – leading to increased expense, hospitalization, immunosuppression and greater infections, rejection, and graft loss. Medically a simple procedure PKE is less expensive than the incompatible transplants with reduced risk of infections because of lesser immunosuppressive burden [4,6]. Although unlike regular directed donations, there are logistic issues in PKE. The logistics involved in doing multiple transplants at the same time can be challenging. Last moment problems with any one of the swap members can lead to postponement or cancellation of the transplant. There is also risk of donor renegeing. Because of these reasons, paired kidney exchanges can be difficult to execute.

### Paired kidney exchange – the evolution

Rappaport first proposed the paired kidney exchange in 1986 [7] but it was not until 1991 when the first PKE was done in South Korea [8]. This was an in-center match and done manually. First PKE of Europe was done in 1999 in Switzerland while that of USA was done in 2000 [9,10]. Initial swaps were single center experiences but soon it was realized that to maximize the numbers in such two-way, three-way, or multi-way transplants, larger number of pairs were needed. First national PKE was established in the Netherlands when eight transplant centers in collaboration with the Dutch Transplant Foundation (NTS) started a crossover exchange program [11]. Various countries have established national level programs since then including Canada, Australia-New Zealand, UK, Spain, and other European countries [12–15].

In the USA, various multicenter programs operating at the national level have evolved. The Alliance for paired kidney donation started in 2006 and The National Kidney Registry (NKR) was established in 2007 [16]. Later on United Network for Organ Sharing (UNOS) organized its first PKE in 2010 [10]. There are other PKE registries which includes the New England Kidney Exchange program [17], the John Hopkins Hospital incompatible kidney transplant program [18], and the Methodist Hospital PKE program [19].

National kidney registry is a nonprofit organization in USA that was established in 2007 by the Hil family after the hurdles they faced while searching for a compatible kidney donor for their daughter who had lost

her kidney. The parents as well as elder sister were ruled out as a suitable donor due to blood group and HLA incompatibility. Despite having multiple PKE programs, they could not get a suitable match and finally she received the kidney from her compatible cousin. Since its inception, it has been one of the most successful nongovernment multicenter nationwide PKE programs [20]. It has used many innovative solutions such as advanced donation program, voucher system, family voucher system, and remote donation to maximize the number of possible PKE. The outcomes have been at par with the other living transplants and in few instances even better than that [13,21,22]

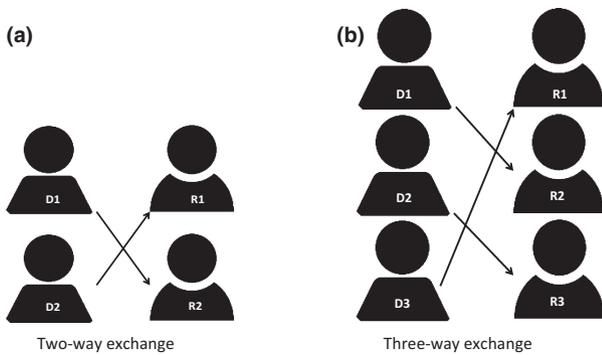
Further expansion of the PKE has led to international exchanges and evolution of global kidney exchange between low- and middle-income countries (LMIC) and high-income countries (HIC) [23,24]. Small countries with smaller donor pools have started cross-border kidney exchanges, and various international cooperation programs have been initiated [15,25]. European Network for Collaboration on Kidney Exchange Programmes (ENCKEP) is a collaboration project of European countries which was started in 2016 with the aim of developing and testing a prototype for transnational PKEs apart from its other functions [15].

### Paired kidney exchange – the matching strategies

Initially, PKE started in its simplest form of a two-way exchange where two incompatible pairs (either ABO or HLA) came together to exchange the kidneys [7]. Later on, three and more pairs were utilized to perform multiple exchanges thereby benefiting many patients [26,27]. Although, this required simultaneous performance of multiple surgeries thereby making it technically challenging [26,28] (Fig. 1).

### Domino paired kidney exchange

This concept incorporates a nondirected altruistic donor (NDAD) who donates a kidney but does not have an intended recipient. This kidney is matched to a recipient with incompatible donor whose living donor donates to another incompatible recipient starting a domino that terminates with a donation to a recipient on deceased donor wait list [29–31] (Fig. 2a). This requires surgeries to be performed in different centers and time zones in a multicenter or national program. Performing such surgeries simultaneously is difficult and hence nonsimultaneous exchanges came into being and shipping of living

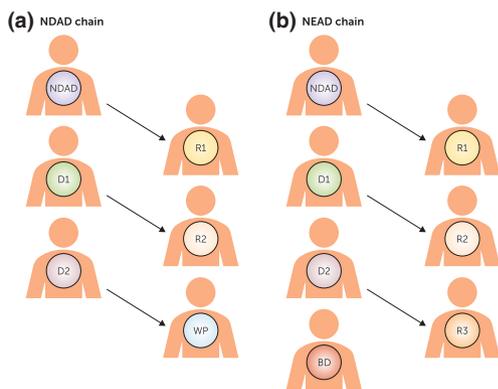


**Figure 1** Different types of simple paired kidney exchanges. (a) Two-way exchange, (b) multi (n)-way exchange between multiple pairs.

donor kidneys started [32]. The increase in cold ischemia time with shipping of PKE kidneys has been documented to have no impact on outcomes of PKE transplant [33,34]

Another modification of such NDAD initiated chain is a nonsimultaneous extended altruistic donor (NEAD) chain where the final donor instead of donating to a wait-listed patient waits till a suitable match is found with a new incompatible pair and becomes a bridge donor to start another cluster [32,35] (Fig. 2b). Although appealing, such approach has disadvantages as well. Such chain may sometime end up with a difficult to match donor who may have to wait long to donate. Ultimately, such donors might decide not to donate. The chance of bridge donor renegeing increases significantly and has been reported to be up to 7% in one of the studies [35].

In a national level or multi-center exchange programs, the match process involves complex computer algorithms to get the best match depending upon the blood group and



**Figure 2** Matching strategies with non-directed anonymous donors (NDAD) – (a) NDAD starting chain ending up with the final kidney donation to a recipient on the waiting list (WP); (b) non simultaneous extended altruistic donor (NEAD) chain ending up as a bridge donor (BD) who can start a new chain.

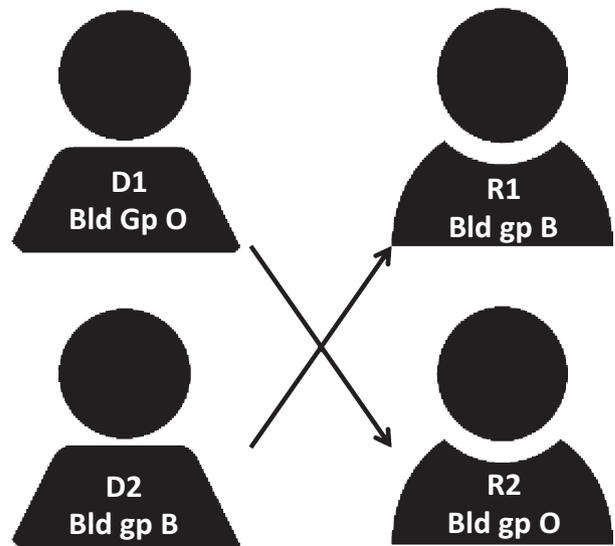
the sensitization status of the recipients [3]. Alvin Roth & Lloyd Shapley received 2012 Nobel prize in economics for developing the algorithm utilized to match large number of donors and recipients in PKE program [36].

### Paired kidney exchange with compatible pair participation

Participation of ABO and HLA compatible pairs can further increase the number of successful paired exchanges. The compatible pair participating in the PKE may benefit from such exchange in the form of a better HLA and size-matched kidney or a younger donor [37]. This type of exchange, which used to be known as the unbalanced paired kidney exchange, has been renamed as compatible pair participation (CPP; Fig. 3). Addition of such pairs improves the scope and success of PKE and needs better acceptability among all stakeholders.

### Paired kidney exchange with desensitization – two-way solution to a complex problem

Desensitization has been used to successfully transplant recipients with donor-specific antibodies and also those who are ABO incompatible. Complexity of the desensitization protocol depends upon the strength of these antibodies. By combining PKE program with desensitization protocols, such recipients may get more suitable donor against whom they have a lower level of sensitization. Thus, combining PKE with desensitization may allow better compatible donors for these patients. This



**Figure 3** An altruistic unbalanced paired kidney exchange (PKE) or compatible pair participation PKE using blood group and crossmatch compatible pairs.

**Table 1.** Prominent national and multicenter paired kidney exchange program with nationwide reach.

Program	Country	Remarks
Dutch PKE program [11,59–62]	The Netherlands	<ul style="list-style-type: none"> <li>• Started in 2004 by 8 transplant centers in collaboration with the Dutch Transplant Foundation</li> <li>• Donors travel to the recipient's center</li> <li>• Has a central histocompatibility laboratory</li> <li>• From 2004 till 2014 – 685 pairs registered – 529 (77%) transplanted</li> <li>• 90 patients transplanted through the domino paired donation</li> </ul>
UK living kidney sharing scheme [14,15,63]	UK	<ul style="list-style-type: none"> <li>• Started in 2007</li> <li>• The largest European PKE program</li> <li>• 1000th PKE done in 2019</li> <li>• Accepts ABOi matches in exchange</li> </ul>
Spanish PKE program [15,64]	Spain	<ul style="list-style-type: none"> <li>• First exchange performed in 2009</li> <li>• Till 2016 performed 142 PKE</li> <li>• Accepts ABOi matches in exchange</li> </ul>
Canadian kidney paired donation program [12,65]	Canada	<ul style="list-style-type: none"> <li>• Started in 2009</li> <li>• Total 742 transplants done till 1st of May 2020</li> <li>• Donors travel to the recipient's center</li> </ul>
Australian and New Zealand paired kidney exchange (ANZKX) [42,66]	Australia and New Zealand	<ul style="list-style-type: none"> <li>• Started as PKE program in 2010 in Australia. Later joined by New Zealand</li> <li>• High transplant rate as ABO-incompatible matching accepted</li> </ul>
National kidney registry [16,21,22]	USA	<ul style="list-style-type: none"> <li>• Started in 2007</li> <li>• More than 4000 transplants done till May 2020</li> <li>• Better outcomes compared to other US living donor transplants</li> <li>• Uses ADP, voucher program</li> </ul>
Alliance for paired kidney donation [35,52,67,68]	USA	<ul style="list-style-type: none"> <li>• Started in 2001 as Ohio Solid Organ Transplantation Consortium – reorganized in 2006</li> <li>• Performed world's first nonsimultaneous altruistic donor chain in 2007</li> <li>• Has on demand in-house crossmatch facility</li> <li>• Performed first global kidney exchange to overcome financial barrier</li> <li>• During 6-year period 65% of registered 1121 patient transplanted – 37% by PKE</li> </ul>
UNOS [10]	USA	<ul style="list-style-type: none"> <li>• Performed first match in 2010</li> <li>• Administers as an Organ Procurement and Transplantation Network contractor</li> <li>• Around 35% matching rate</li> </ul>

ABOi, ABO incompatible; ADP, advanced donation program; OPTN, Organ Procurement and Transplantation Network; PKE, paired kidney exchange; UK, United Kingdom; UNOS, United Network for Organ Sharing; USA, United States of America.

has been successfully utilized by Montgomery and his colleagues at John Hopkins Institute [38,39].

### Multicenter and national paired kidney exchange programs

With increasing awareness of the fact that an increase in the number of registered pairs leads to a proportionate increase in the number of successful exchanges, various multicenter and national level programs have come into existence. In these PKE programs, a match run is conducted once a sizeable number of incompatible pairs accumulate. This could be done every few days, weeks, or

months depending upon how rapidly the pairs accumulate. Match cycle ends when all the identified matches are transplanted or cannot proceed any longer. Swapping may either be done by transporting the donor kidney or by moving the donor to the recipient center. While moving the donors at local city level is feasible it is difficult to do it at a national level and moving the kidney is a far more efficient way to create larger chains. The study by Nassiri et al showed that prolonged cold ischemia time involved in transporting such kidneys does not affect the graft outcome [20].

Table 1 shows prominent multicenter and national PKE programs.

### Paired kidney exchange – the outcome

Outcome of PKE has been encouraging. This explains its increasing popularity in developed as well as developing countries. Due to the living nature of donation, the outcomes are better than deceased donation. Table 2 shows the PKE patient and graft outcome in various studies. A PubMed search was performed for PKE studies and those reporting on the outcomes of graft and/or patient survival were included.

### Paired kidney exchange – the limitations

Although PKE is a boon for the incompatible pairs who have no other alternative than undergoing expensive desensitization preconditioning with considerably much more immunosuppressive burden, it has few problems of its own as outlined below.

- It may not be always possible to match all the pairs, especially in single center programs with few pairs. Increasing the number of registered pairs can increase the number of successful matches. Bingaman et al showed a strong correlation between the number of successful PKE transplantations performed and addition of new pairs to the pool and suggested that a sharp rise occurs once pool size increases to 100 recipients [40]. Use of compatible pairs and accepting ABO-incompatible matches with low titer can increase the overall numbers.
- Blood group O donors are universal donors. Therefore, O group recipients are disadvantaged and accumulate on the list [41]. Similarly, AB donors also accumulate on the list. One solution to counter this problem is to register more pairs who have O donor or AB recipient but are crossmatch positive A multi-way exchange helps to achieve better matching rates in this situation. The use of both blood group and HLA compatible pair participation can also help disadvantaged O group recipients [37]. A compatible pair can benefit by receiving younger kidney, overcoming low-level donor-specific antibody, getting a better HLA match, and avoiding complex donor kidney anatomy. This strategy has been used successfully in the NKR program [22]. Another innovative way of tackling this problem is by using blood group incompatible donor matching. The Australian program uses this strategy for patients with anti-blood group antibody titers <64. This has resulted in enhanced transplant rates [42].
- PKE is fraught with the risk of donor backing out after the recipient has received the kidney from another pair. To prevent this, two-way, three-way, and domino

chain donations are performed simultaneously despite the logistic difficulties involved. But in a NEAD chain, as discussed above, the bridge donor renegeing is potentially higher. Although it has been argued that despite this potential risk it is justified by the overall better utility provided by the NEAD chain. Also, this could be avoided by counseling the donors in advance about the probable long waiting time for donation as a bridge donor.

- Few argue that by its nature PKE donors are at greater pressure to donate as the “escape” route of incompatibility as an excuse is not available anymore. In the NEAD chain, this pressure is even higher as more number of patients are involved and the recipient of the intended bridge donor has already received the transplant [43]. Hence, a thorough predonation psychological assessment and education of the donor is a must.
- There is a tendency for the pairs to match the “quality” of the kidney they are going to receive. The one receiving lower GFR kidney might remain dissatisfied.
- In a national level or multicenter PKE program, kidneys are transported from one center to the other, as donors are not comfortable traveling to the other center for donation. Donors prefer to undergo surgery near their home where they can get the necessary support of family members. This transportation of kidney raises the concern of prolonging of cold ischemia time. However, Segev et al in their study have shown that if the cold ischemia time is less than 14 h the live kidney performs well [44]. There have been similarly reports of acceptable cold ischemia time from <8 to 24 h [33,45–47].

### Newer trends in paired kidney exchange

#### Trans-organ paired exchange

This is a new concept wherein those donors who are ruled out for donating one organ due to some reason are still able to donate other organ for exchange. For example, if a donor from pair 1 is ruled out from donating his/her kidney due to any reason specific to the kidney can still donate his/her liver to another pair 2 whose recipient needs a liver transplant and the donor of the pair 2 who has been rejected for liver donation donates his/her kidney to pair 1. First such case has been published by Torres et al. [48] (Fig. 4).

Although this is an attractive proposition, there are few things to be kept in mind. The surgical risk of donation is different for different organs. For example, the mortality risk of kidney donation is 1 in 3000 whereas for liver donation is 1 in 500 surgeries. Consent

**Table 2.** Outcomes of various paired kidney exchange studies.

Author and year	Sample	Outcome	Remarks
Leeser et al. 2020 [16] (2008–2017) <i>NKR, USA</i>	2363 NKR PKE compared to control kidney transplant recipients ( $n = 54,497$ )	Median follow-up 3.7 years Similar graft failure and mortality	NKR registry was relatively high risk – more likely to be black, women, older, >80% PRA, previous transplant and longer time on dialysis
Flechner et al. 2018 [22] <i>NKR, USA</i>	2037 NKR PKE txp (2008–2017) vs. 1. Living donor related txp (49610) (UNOS) 2. Living unrelated txp no. 23310 3. UNOS non-NKR PKE no. 4236	One and 3 year comparable graft survival outcomes and better 5 years graft survival in PKE transplant	
Allen et al. 2018 [69] <i>Australia</i>	First 100 transplants in Australian PKE program	37 exchanges mean operating time $115 \pm 44$ min. CIT for nonshipped kidneys $2.6 \pm 0.6$ h vs. $6.8 \pm 2.8$ for shipped kidneys two DGFs. One year allograft survival 97%	Shipping kidneys rather than donor
Kute et al. 2017 [70] (2000–2016) <i>India</i>	300 of total 3616 LDKT and 561 DDKT; mean follow-up $3 \pm 3$ years	Patient survival 96%, death censored graft survival 83%; Mean serum creatinine 1.3 mg/dl	124 two-way, 14 three-way, 1 four-way and 1 six-way transplant
Jha et al. 2015 [71] (2010–2013) <i>India</i>	26 PKE vs. 716 non-PKE Follow-up 20 months	Serum creatinine at 1 month and last follow-up better in PKE Similar graft and patient survival and BPAR	All two-way exchanges; reason for exchange – blood group incompatibility
Malik et al. 2014 [12] (2009–2013) <i>Canada</i>	235 PKE	1-year patient survival 100%, graft survival 98% and BPAR 8%	
Tuncer et al. 2012 [72] (2008–2011) <i>Turkey</i>	57 PKE vs. 1081 living related txp	Similar first and second year GFR, AR, graft loss, pt. loss	PKE pts had higher HLA mismatch and age
Leeser et al. 2012 [73] (2007–2011) <i>NKR, USA</i>	44 pair leading to 50 txp.	DGF – 6%; 1 year rejection rate – 9.1%; 1 year pt. and graft survival 98% and 94%	Blood type incompatibility – 54.4%; sensitization – 43.2%
Bingaman et al. 2012 [19] (3 years) <i>Methodist San Antonio, USA</i>	134 (117 incompatible and 17 compatible pairs)	3 episodes of rejection, no graft lost due to rejection	5 desensitization combined with PKE 44% with PRA >80%
Klerk et al. 2011 [74] (2004–2011) <i>Dutch PKE program</i>	187 transplants – 83 blood group incompatible and 104 positive crossmatch pairs	5-year uncensored survival – 85%; death censored graft survival – 89%	40% of the registered patients got transplanted
Montgomery et al. 2005 [18] (2001–2004) <i>Johns Hopkins, USA</i>	22; median follow-up 13 months	Patient survival 100%; graft survival 95.5%; 6 months creatinine – 1.2 mg/dl; ACR – 18%; no AMRs	Two triple exchanges; 5 patients were highly sensitized

ACR, acute cellular rejection; AMR, antibody-mediated rejection; AR, acute rejection; BPAR, biopsy-proven acute rejection; CIT, cold ischemia time; DDKT, deceased donor kidney transplantation; DGF, delayed graft function; GFR, glomerular filtration rate; LDKT, living donor kidney transplantation; NKR, National Kidney Registry; PKE, paired kidney exchange, PRA, panel reactive antibodies, PRA, panel reactive antibody, UNOS, United Network for Organ Sharing.

needs to be modified accordingly [49]. Critics also feel that this system might create additional pressure on the donor.

### Advanced donation program

The advanced donation program (ADP) is a novel method of PKE to overcome “chronological incompatibility.” Here, the donor chose to donate kidney at a time as per his convenience while the recipient undergoes transplantation at a later date. This may happen because of future commitments of the donor such as a deadline to return to the work when he may not be available for the donation. Hence, this is a preplanned nonsequential exchange, and ultimately, the recipient receives the kidney from the intended donor. The national kidney registry in USA has been providing such ADP services since 2011.

Another modification of ADP is a voucher system. Here, the donor donates the kidney like a nondirected donor to initiate a chain and the recipient gets a voucher. The recipient is not yet in need of transplant and can get the voucher redeemed at a later date when he needs one. This is helpful in circumstances when the donor may become too old to donate by the time the recipient is in actual need of transplant kidney. For example, a grandfather may want to donate to his grandchild who is not in need of the kidney at present but might need it twenty years later when the grandfather will be too old to donate [50]. The donor donating the kidney to a chain can benefit multiple patients at present and will ultimately benefit the intended recipient as well in the future. Sometimes there may be

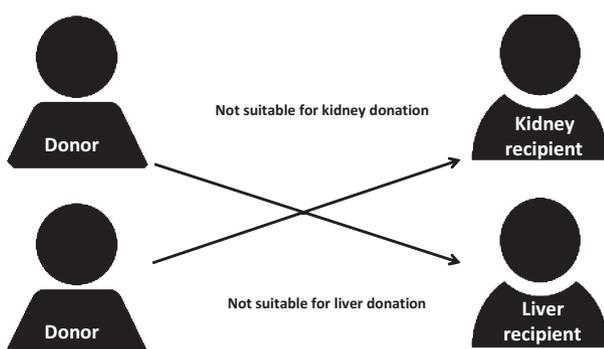
multiple willing donors for the same intended recipients who can thereby initiate multiple chains thereby benefiting multiple patients. Not all vouchers may need redemption in the future, as the intended recipients might not require transplantation ever due to nonprogression of the kidney disease or death due to other cause. Although attractive, there are few concerns. Both the donor and recipient need to be informed that there is no guarantee that the recipient will receive a kidney when the voucher is redeemed. Also, as is well known with other paired kidney programs, the O blood group as well as highly sensitized recipients are at disadvantage.

The NKR launched a family voucher program in 2019. The standard voucher program discussed above requires the voucher donor to name a voucher holder who has some form of kidney impairment. In the family voucher program, a voucher donor can provide up to five vouchers for healthy family members and it can be redeemed should they need a kidney transplant in the future. Only one voucher can be redeemed for each family voucher donor [51].

### Global kidney exchange

Global kidney exchange is a new strategy, which has been proposed to increase renal transplantation through PKE. It involves PKE between a pair from high-income countries (HICs) with another pair in low- and middle-income countries (LMICs). The pair from LMICs is compatible biologically but financially incompatible due to poor socioeconomic status while the pair from HICs is biologically incompatible. The cost of dialysis saved for patient from HIC is used to fund the transplant-related expense of the pair from LMICs and also for post-transplant care (including medications) for five years. Rees et al. first published an experience of GKE in 2017 where a pair from Philippines initiated the exchange benefiting multiple recipients in USA [52].

The proponents of GKE claim that it is beneficial for both the HIC and LMICs [52,53]. Although appealing, it is fraught with multiple ethical and legal challenges. Firstly, the advantage is skewed toward HIC as they are going to benefit much more in terms of number of transplants that can be done with one single pair entering the chain and also in terms of economic advantage sustained thereby. It does not guarantee post-transplant care of recipient–donor pair from LMIC once they return home. Therefore, it can be said that it is an exploitation of vulnerable LMIC pairs. Secondly, it has been viewed as a way of organ trafficking, as the pair



**Figure 4** Trans-organ paired exchange. The initially intended donor of prospective kidney recipient is not fit for renal donation but can donate his liver to a prospective liver recipient from the second pair whose own intended liver donor is not fit for liver donation. His initially intended liver donor instead donates his kidney to the former pair.

from LMIC is not donating kidney out of goodwill to help the other pair. Rather the donor here is donating his kidney in exchange for incentive of post-transplant care and cost of transplantation for the LMIC pair. Hence, the LMIC pair is being exploited due to their financial and socioeconomic status. It has been seen as an impediment to the development of national kidney pair exchange program in LMICs by diverting the pair to HIC [53,54].

### Paired kidney exchange – the way forward

Paired kidney exchange is a promising innovation in the field of renal transplantation. No wonder its popularity has increased over the last two decades. PKE program has grown exponentially and still continues to be a field of exciting opportunities. Few of the newer trends as well as issues to address while moving forward in the field of PKE are as follows:

- Use of artificial intelligence to provide failure and fairness aware dynamic exchange models, which will also take into account other complex parameters that remains hitherto untouched during manual matching. This can lead to twice as many successful transplants and lessens the match failure rate for highly sensitized recipients by up to 45% [55].
- Formation of national exchange program as the numbers of registered pairs will increase so will the chances of getting a suitable match.
- Use of compatible and sensitized pairs in the exchange process to leverage maximum benefits for these patients. Centers may be incentivized for adding favorable blood types. National Kidney Registry has Center Liquidity Contribution (CLC) program, which provides scores for member centers based on their contribution to the pool liquidity. Points are awarded to the center if (i) they contribute NDD to start chain (ii) favorable blood type compatible pairs have been matched/transplanted (iii) favorable incompatible pairs with recipient calculated panel reactive antibody (cPRA) <100 matched/transplanted (iv) hard to match donors accepted as a chain end. Points are deducted if (i) unfavorable blood type pairs have been matched/transplanted (ii) patients with cPRA >90% have been matched/transplanted (iii) surgical unavailability declines CLC targeted pairs (iv) preselect reversal declines for CLC targeted pairs [56].
- Highest level of ethics and consenting along with more emphasis on donor and patient education to increase the trust in healthcare system [57].

- International exchange, that is, PKE exchanges between different countries [23].
- Cryobanking of preserved donor lymphocytes and use of virtual crossmatch to help in prescreening crossmatch compatibility of highly sensitized candidate [58].
- Unification of multiple registries in any particular country to maximize the number of matches.
- Adoption of newer trends such as voucher system and trans-organ paired exchange while addressing the issues associated as discussed above.
- Efforts to eliminate disincentives associated with living donation. Initiatives such as Donor Shield Programs should be promoted under which the donor gets lost wage reimbursement as well as reimbursement for travel, lodging, mileage. Donors are also provided with life insurance, disability insurance, legal support, and coverage for donor complications costs [56].

### Conclusion

Paired donation is a ray of hope for the patients with an immunologically incompatible donor. It has come a long way since its inception and the growth in this field of transplantation has been phenomenal with new innovations. There are quite a few advantages of PKE when compared to desensitization such as less intensive immunosuppression requirement, better graft outcome, lower infection risk, cost saving, and benefiting multiple recipients. Registration of more pairs increases the number of successful matches. Involvement of altruistic donors and compatible pairs increases the number of feasible matches and should be promoted.

Paired kidney exchange should be offered to all the prospective transplant recipient and donor pairs if they are willing as this can significantly increase the transplant numbers and circumvent the problem of O blood group recipient, AB group donor, and highly sensitized recipients.

Use of artificial intelligence and complex algorithms helps in maximizing the number of matches by providing a failure aware matching system. Newer methods such as advanced paired donation and trans-organ paired exchange have opened up new possibilities and should be utilized to maximize the number of exchanges. Although there are few concerns such as renegeing, chances of coercion and inability to match all the pairs, PKE provides a significant way forward to increase the living donor pool and maximize the numbers of feasible transplantation.

## Funding

The authors have declared no funding.

## Conflicts of interest

The authors have declared no conflicts of interest.

## REFERENCES

1. Watson CJ, Dark JH. Organ transplantation: historical perspective and current practice. *Br J Anaesth* 2012; **108**(Suppl 1): i29.
2. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. *N Engl J Med* 1995; **333**: 333.
3. Segev DL, Gentry SE, Warren DS, Reeb B, Montgomery RA. Kidney paired donation and optimizing the use of live donor organs. *JAMA* 2005; **293**: 1883.
4. de Weerd AE, Betjes MGH. ABO-incompatible kidney transplant outcomes: a meta-analysis. *Clin J Am Soc Nephrol* 2018; **13**: 1234.
5. Marfo K, Lu A, Ling M, Akalin E. Desensitization protocols and their outcome. *Clin J Am Soc Nephrol* 2011; **6**: 922.
6. Axelrod D, Lentine KL, Schnitzler MA, et al. The incremental cost of incompatible living donor kidney transplantation: a national cohort analysis. *Am J Transplant* 2017; **17**: 3123.
7. Rapaport FT. The case for a living emotionally related international kidney donor exchange registry. *Transplant Proc* 1986; **18** (Suppl. 2): 5.
8. Kwak JY, Kwon OJ, Lee KS, Kang CM, Park HY, Kim JH. Exchange-donor program in renal transplantation: a single-center experience. *Transplant Proc* 1999; **31**: 344.
9. Thiel G, Vogelbach P, Gürke L, et al. Crossover renal transplantation: hurdles to be cleared!. *Transplant Proc* 2001; **33**: 811.
10. Wallis CB, Samy KP, Roth AE, Rees MA. Kidney paired donation. *Nephrol Dial Transplant* 2011; **26**: 2091.
11. de Klerk M, Keizer KM, Claas FH, Witvliet M, Haase-Kromwijk BJ, Weimar W. The Dutch national living donor kidney exchange program. *Am J Transplant* 2005; **5**: 2302.
12. Malik S, Cole E. Foundations and principles of the Canadian living donor paired exchange program. *Can J Kidney Health Dis* 2014; **1**: 6.
13. Ferrari P, Weimar W, Johnson RJ, Lim WH, Tinckam KJ. Kidney paired donation: principles, protocols and programs. *Nephrol Dial Transplant* 2015; **30**: 1276.
14. Johnson RJ, Allen JE, Fuggle SV, Bradley JA, Rudge C, Kidney Advisory Group UKTN. Early experience of paired living kidney donation in the United Kingdom. *Transplantation* 2008; **86**: 1672.
15. Biró P, Haase-Kromwijk B, Andersson T, et al. Building kidney exchange programmes in Europe-an overview of exchange practice and activities. *Transplantation* 2019; **103**: 1514.
16. Leeser DB, Thomas AG, Shaffer AA, et al. Patient and kidney allograft survival with national kidney paired donation. *Clin J Am Soc Nephrol* 2020; **15**: 228.
17. Hanto RL, Reitsma W, Delmonico FL. The development of a successful multiregional kidney paired donation program. *Transplantation* 2008; **86**: 1744.
18. Montgomery RA, Zachary AA, Ratner LE, et al. Clinical results from transplanting incompatible live kidney donor/recipient pairs using kidney paired donation. *JAMA* 2005; **294**: 1655.
19. Bingaman AW, Wright FH Jr, Kapturczak M, Shen L, Vick S, Murphey CL. Single-center kidney paired donation: the Methodist San Antonio experience. *Am J Transplant* 2012; **12**: 2125.
20. Nassiri N, Kwan L, Bolagani A, et al. The "oldest and coldest" shipped living donor kidneys transplanted through kidney paired donation. *Am J Transplant* 2020; **20**: 137.
21. Flechner SM, Leeser D, Pelletier R, et al. The incorporation of an advanced donation program into kidney paired exchange: initial experience of the national kidney registry. *Am J Transplant* 2015; **15**: 2712.
22. Flechner SM, Thomas AG, Ronin M, et al. The first 9 years of kidney paired donation through the National Kidney Registry: characteristics of donors and recipients compared with National Live Donor Transplant Registries. *Am J Transplant* 2018; **18**: 2730.
23. Tuncer M, Tekin S, Yuksel Y, et al. First international paired exchange kidney transplantations of Turkey. *Transplant Proc* 2015; **47**: 1294.
24. Rees MA, Paloyo SR, Roth AE, et al. Global kidney exchange: financially incompatible pairs are not transplantable compatible pairs. *Am J Transplant* 2017; **17**: 2743.
25. Böhmig GA, Fronek J, Slavcev A, Fischer GF, Berlakovich G, Viklicky O. Czech-Austrian kidney paired donation: first European cross-border living donor kidney exchange. *Transpl Int* 2017; **30**: 638.
26. Saidman SL, Roth AE, Sonmez T, Unver MU, Delmonico FL. Increasing the opportunity of live kidney donation by matching for two- and three-way exchanges. *Transplantation* 2006; **81**: 773.
27. Keizer KM, de Klerk M, Haase-Kromwijk BJ, Weimar W. The Dutch algorithm for allocation in living donor kidney exchange. *Transplant Proc* 2005; **37**: 589.
28. Roth AE, Sonmez T, Unver U. Efficient kidney exchange: coincidence of wants in markets with compatibility-based preferences. *Am Econ Rev* 2007; **97**: 828.
29. Montgomery RA, Gentry SE, Marks WH, et al. Domino paired kidney donation: a strategy to make best use of live non-directed donation. *Lancet* 2006; **368**: 419.
30. Roodnat JJ, Zuidema W, van de Wetering J, et al. Altruistic donor triggered domino-paired kidney donation for unsuccessful couples from the kidney-exchange program. *Am J Transplant* 2010; **10**: 821.
31. Roth AE, Sonmez T, Unver MU, Delmonico FL, Saidman SL. Utilizing list exchange and nondirected donation through 'chain' paired kidney donations. *Am J Transplant* 2006; **6**: 2694.
32. Rees MA, Kopke JE, Pelletier RP, et al. A nonsimultaneous, extended, altruistic-donor chain. *N Engl J Med* 2009; **360**: 1096.
33. Treat E, Chow EKH, Peipert JD, et al. Shipping living donor kidneys and transplant recipient outcomes. *Am J Transplant* 2018; **18**: 632.
34. Gill J, Rose C, Joffres Y, Kadatz M, Gill J. Cold ischemia time up to 16 hours has little impact on living donor kidney transplant outcomes in the era of kidney paired donation. *Kidney Int* 2017; **92**: 490.
35. Ashlagi I, Gilchrist DS, Roth AE, Rees MA. Nonsimultaneous chains and dominos in kidney-paired donation-revisited. *Am J Transplant* 2011; **11**: 984.

36. Krudy, E *Nobel Winner Roth Helped Spark Kidney Donor Revolution* [Press Release]. New York, NY: Reuters, 2012.
37. Cuffy MC, Ratner LE, Siegler M, Woodle ES. Equipoise: ethical, scientific, and clinical trial design considerations for compatible pair participation in kidney exchange programs. *Am J Transplant* 2015; **15**: 1484.
38. Montgomery RA, Lonze BE, Jackson AM. Using donor exchange paradigms with desensitization to enhance transplant rates among highly sensitized patients. *Curr Opin Organ Transplant* 2011; **16**: 439.
39. Montgomery RA. Renal transplantation across HLA and ABO antibody barriers: integrating paired donation into desensitization protocols. *Am J Transplant* 2010; **10**: 449.
40. Bingaman AW, Wright FH, Murphey CL. Kidney paired donation in live-donor kidney transplantation. *N Engl J Med* 2010; **363**: 1091.
41. Gentry SE, Montgomery RA, Segev DL. Kidney paired donation: fundamentals, limitations, and expansions. *Am J Kidney Dis* 2011; **57**: 144.
42. Ferrari P, Hughes PD, Cohney SJ, Woodroffe C, Fidler S, D'Orsogna L. ABO-incompatible matching significantly enhances transplant rates in kidney paired donation. *Transplantation* 2013; **96**: 821.
43. Ross LF, Rubin DT, Siegler M, Josephson MA, Thistlethwaite JR Jr, Woodle ES. Ethics of a paired-kidney-exchange program. *N Engl J Med* 1997; **336**: 1752.
44. Segev DL, Veale JL, Berger JC, et al. Transporting live donor kidneys for kidney paired donation: initial national results. *Am J Transplant* 2011; **11**: 356.
45. Montgomery RA, Katznelson S, Bry WI, et al. Successful three-way kidney paired donation with cross-country live donor allograft transport. *Am J Transplant* 2008; **8**: 2163.
46. Butt FK, Gritsch HA, Schulam P, et al. Asynchronous, out-of-sequence, transcontinental chain kidney transplantation: a novel concept. *Am J Transplant* 2009; **9**: 2180.
47. Rees MA, Schnitzler MA, Zavala EY, et al. Call to develop a standard acquisition charge model for kidney paired donation. *Am J Transplant* 2012; **12**: 1392.
48. Torres AM, Wong F, Pearson S, et al. Bi-organ paired exchange-sentinel case of a liver-kidney swap. *Am J Transplant* 2019; **19**: 2646.
49. Samstein B, de Melo-Martin I, Kapur S, Ratner L, Emond J. A liver for a kidney: ethics of trans-organ paired exchange. *Am J Transplant* 2018; **18**: 1077.
50. Veale JL, Capron AM, Nassiri N, et al. Vouchers for future kidney transplants to overcome "chronological incompatibility" between living donors and recipients. *Transplantation* 2017; **101**: 2115.
51. Pullen LC. Family voucher program helps patients meet the challenge of rare diseases. *Am J Transplant* 2020; **20**: 623.
52. Rees MA, Dunn TB, Kuhr CS, et al. Kidney exchange to overcome financial barriers to kidney transplantation. *Am J Transplant* 2017; **17**: 782.
53. Pullen LC. Global kidney exchange: overcoming the barrier of poverty. *Am J Transplant* 2017; **17**: 2499.
54. Delmonico FL, Ascher NL. Opposition to irresponsible global kidney exchange. *Am J Transplant* 2017; **17**: 2745.
55. Dickerson JP, Procaccia AD, Sandholm T. Failure-aware kidney exchange. *Manage Sci* 2019; **65**: 1768.
56. Info for Centers. Available from: [https://www.kidneyregistry.org/transplant\\_center.php#](https://www.kidneyregistry.org/transplant_center.php#) [cited 2019 1 September].
57. Rodrigue JR, Leishman R, Vishnevsky T, Evenson A, Mandelbrot DA. Concerns of ABO incompatible and crossmatch-positive potential donors and recipients about participating in kidney exchanges. *Clin Transplant* 2015; **29**: 233.
58. Piazza A, Ozzella G, Poggi E, Caputo D, Manfreda A, Adorno D. Virtual crossmatch in kidney transplantation. *Transplant Proc* 2014; **46**: 2195.
59. The Dutch living donor kidney exchange. Available from: <http://vbhcprize.com/the-dutch-living-donor-kidney-exchange/> [cited 2019 14 June].
60. De Klerk M, Van Der Deijl WM, Witvliet MD, Haase-Kromwijk BJ, Claas FH, Weimar W. The optimal chain length for kidney paired exchanges: an analysis of the Dutch program. *Transpl Int* 2010; **23**: 1120.
61. de Klerk M, Witvliet MD, Haase-Kromwijk BJ, Weimar W, Claas FH. A flexible national living donor kidney exchange program taking advantage of a central histocompatibility laboratory: the Dutch model. In: Cecka JM & Terasaki PI, eds. *Clinical Transplants*. Los Angeles: Terasaki Foundation Laboratory, 2008: 69–73. ISBN 1-880318-17-2.
62. de Klerk M, Witvliet MD, Haase-Kromwijk BJ, Claas FH, Weimar W. Hurdles, barriers, and successes of a national living donor kidney exchange program. *Transplantation* 2008; **86**: 1749.
63. UK's living kidney sharing scheme to hit 1000th transplants milestone this week. Available from: <https://www.organdonation.nhs.uk/get-involved/news/uk-s-living-kidney-sharing-scheme-to-hit-1000th-transplants-milestone-this-week/> [cited 2019 14 June].
64. Valentin M, Mahillo BB, Martinez II, et al. Living kidney donation in Spain, a global strategy to increase this modality of transplantation. *Transplantation* 2018; **102**: S133.
65. Kidney Paired Donation (KPD) Program. Available from: <https://professionaleducation.blood.ca/en/organs-and-tissues/programs-and-services/kidney-paired-donation-kpd-program> [cited 2020 8 June].
66. Cantwell L, Woodroffe C, Holdsworth R, Ferrari P. Four years of experience with the Australian kidney paired donation programme. *Nephrology* 2015; **20**: 124.
67. Stepkowski SM, Mierzejewska B, Fumo D, et al. The 6-year clinical outcomes for patients registered in a multiregional United States kidney paired donation program – a retrospective study. *Transpl Int* 2019; **32**: 839.
68. Bozek DN, Dunn TB, Kuhr CS, et al. Complete chain of the first global kidney exchange transplant and 3-yr follow-up. *Eur Urol Focus* 2018; **4**: 190.
69. Allen RDM, Pleass HCC, Woodroffe C, Clayton PA, Ferrari P. Challenges of kidney paired donation transplants involving multiple donor and recipient surgeons across Australia. *ANZ J Surg* 2018; **88**: 167.
70. Kute VB, Patel HV, Shah PR, et al. Impact of single centre kidney paired donation transplantation to increase donor pool in India: a cohort study. *Transpl Int* 2017; **30**: 679.
71. Jha PK, Sethi S, Bansal SB, et al. Paired kidney exchange transplantation: Maximizing the donor pool. *Indian J Nephrol* 2015; **25**: 349.
72. Tuncer M, Tekin S, Yucetin L, Sengul A, Demirbas A. Comparison of paired exchange kidney transplantations with living related kidney transplantations. *Transplant Proc* 2012; **44**: 1626.
73. Leiser DB, Aull MJ, Afaneh C, et al. Living donor kidney paired donation transplantation: experience as a founding member center of the National Kidney Registry. *Clin Transplant* 2012; **26**: E213.
74. de Klerk M, Kal-van Gestel JA, Haase-Kromwijk BJ, Claas FH, & Weimar W. Eight years of outcomes of the Dutch Living Donor Kidney Exchange Program. In: Cecka JM & Terasaki PI, eds. *Clinical Transplants*. Los Angeles: Terasaki Foundation Laboratory, 2011; 287–290.