Kidney paired donation: state of the science and practice

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Purpose of review

The aim of this article is to review all publications regarding kidney paired donation published over the past 2 years and in doing so provide an evaluation of the current state of development of the field.

Recent findings

A few large multicenter paired donation consortia have been developed, and using computer-based matching algorithms have entered significant numbers of donor–recipient pairs (although no program to date has conducted computer match runs with over 75 donor–recipient pairs). In addition, significant progress has been made in developing innovative matching strategies and in modeling potential results of paired donation programs. Despite these advances, these programs have only scratched the surface of the estimated potential of paired donation programs to increase living kidney donation. The greatest effects on increasing volume can be made by increasing donor/recipient identification and enrolment.

Summary

Significant advances have been made in clinical experience and technological development of paired donation programs. Technical advances have occurred, however, at a more rapid pace than clinical advances in paired donation. Significant work with respect to ethical and educational foundations needs to be accomplished to close this gap.

Keywords

desensitisation, kidney exchange, paired donation

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Abbreviations

HLA	human leukocyte antigen
NAPDN	North American Paired Donation Network
OPTN	Organ Procurement and Transplantation Network
PRA	panel reactive antibody

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Introduction

A decade has lapsed since the first paired donation publication appeared in 1997, yet clinical paired donation programs have tapped only a small fraction of their potential for increasing living donor kidney transplantation [1–3,4••,5–7]. To our knowledge, paired donation is one of the few surgical innovations for which publication of ethical considerations preceded clinical trials. Moreover, the recent rapid growth in paired donation technologic research [8–17,18••,19•,20,21,22••,23•,24,25] has outstripped the development of ethical frameworks. The purpose of this publication is to review the state of the science and practice of paired donation with a focus on publications that have appeared in the preceding 2 years.

Clinical paired donation programs and networks

Three programs – a single center program, a multicenter consortia (the Dutch Living Donor Kidney Exchange Program), and a network of consortia (the North American Paired Donation Network) – have recently described significant clinical experiences with paired donation. The Dutch Living Donor Kidney Exchange program consists of seven kidney transplant centers in The Netherlands, with a yearly volume of 275 living donor transplants in 2005, and a population base of 16 000 000 [2,3,4••] (Table 1). The Dutch program conducted its first computer-based match run in January 2004 and has conducted 10 match runs to date. In the most recent publication of the Dutch experience, 146 donor–recipient pairs have been enrolled from seven transplant centers, and a total of 57 transplants have been conducted [2].

The North American Paired Donation Network has recently described development of a network of regional paired donation consortia and impediments to developing large scale paired donation programs [5–8]. Major barriers that were identified included effort required to establish paired donation programs, education and training of transplant professionals, patient education, interprogrammatic cooperation, and programmatic and patient care costs. In addition, issues related to new strategies were discussed.

In general, single-center paired donation programs have consisted of smaller experiences than those reported from consortia. One exception has been the Johns Hopkins program, in which 43 patients have been transplanted to date via paired donation [9]. In a recent report, the

Hopkins group described 22 patients who received living donor transplants in 10 paired donation procedures (eight two pair exchanges and two three-pair exchanges) [10]. Short-term [median follow-up 13 months (range 1–42 months)] results were good: patient survival 100% and renal allograft survival 95%.

In this report, the Hopkins group combined paired donation with partial desensitization in 13 of the 43 paired donation transplants. In these 13 paired donation transplants, recipients were 'partially' desensitized, as they had residually positive crossmatches at the time of transplantation. The approach of combining paired donation and partial desensitization has not been employed (to our knowledge) by other paired donation programs. The strategy of combining paired donation and partial desensitization is ethically and medically complex, as risks to the recipient are difficult to quantify.

Building and networking regionalized paired donation programs

The North American Paired Donation Network (NAPDN) recently reported results from the first two regional consortia (Mid-West/Mid-Atlantic region and New Jersey region) that were developed using NAPDN program development tools (web-based matching software, patient educational brochures, patient educational websites, informed consent forms, educational conferences) [7]. At the time of this report, the two regional paired donation consortia had entered a total of 119 donor–recipient pairs, conducted 17 computer-based match runs, and transplanted 14 patients. Comparison of demographic and immunologic data revealed that the recipients registered in the two consortia were similar with respect to sex, ABO blood group and panel reactive antibody (PRA) distributions. Racial differences were noted, however, with respect to proportions of Caucasians and other races, as New Jersey had more non-Caucasian recipients registered.

The NAPDN has also recently reported progress in creation of several large regional paired donation consortia in the United States [8]. Using the NAPDN program development package noted above, seven regions had initiated the several step process in forming paired donation consortia: seven regions had initial presentations, six had also held organizational meetings, four had voted to form regional paired donation consortia, and four had held transplant professional training conferences. These four regions include 77 Organ Procurement and Transplantation Network (OPTN)-certified kidney transplant programs in 18 states that served a population exceeding 163 000 000.

Comparison of experiences from large multicenter consortia can provide insight into factors that influence paired donation results and, therefore, lead to new approaches that can be modeled or evaluated in clinical programs. Tables 1 and 2 present the structure and results from the Dutch program and the North American Paired Donation Network.

Matching algorithms and simulation studies of paired donation programs

An important advance in the paired donation field has been the development of computer models that simulate paired donation programs. Segev and Gentry [9] from the Hopkins program have developed a sophisticated model for a nationalized paired donation program that has allowed important observations on the structure of paired donation programs and the effects of matching strategies. Using this model, Segev and Gentry [9] compared the 'first accept' approach (the most commonly used method for computer-based matching in the United States) with an 'optimized' algorithm. In the 'first accept' approach, all ABO and human leukocyte antigen (HLA)-compatible matches are determined using the given set of donor–recipient pairs. All feasible matches are then ranked

Table 1 Clinical results from paired donation consortia in Europe and the United States

	Dutch [2,3,4••]	Paired Donation Network [5–8,11–13]
Population base	16 000 000	>83 000 000
Number of living donor transplants/year[a]	275	>300
Number of centers enrolling patients	7	19
Date first patient entered	Jan 2004	Jan 2004
Date of first computer match run	Jan 2004	April 2004
Number of months enrolling/matching patients	30	39
Number of match runs performed	10	21
Number of donor–recipient pairs enrolled to date	147	156
Average number of patients enrolled per month	4.67	4.00
Number of patients enrolled/center (mean, median, range)	21, 20, (7–34)	13.8, (1–34)
Number of matches after computer-based immunologic screening (for ABO compatibility and unacceptable HLA antigens	1019	60
Positive crossmatch rate for each transplant in an immunologically screened match[b]	NR	21%
Number of transplants performed	57	18

NR, not reported.
[a] Performed in centers that enrolled patients in paired donation.
[b] Positive flow cytometric crossmatches are acceptable if due to non-HLA antibody.

Table 2 Protocol differences between the Dutch program and the Paired Donation Network

	Dutch National Program	North American Paired Donation Network
Donor/recipient eligibility	Either ABO or serologic crossmatch incompatibility	ABO or crossmatch (serologic or flow) incompatibility
Methods for identifying unacceptable HLA	Serologic CDC and ELISA on historic and current sera	HLA single antigen beads on historic and current sera, HLA from previously rejected allografts
Matching/allocation criteria	[a]Match probability, blood type, waiting time, and donor age	PRA, pediatric recipient, waiting time, donor–recipient age matching, donor–donor age matching
Transplants require negative serologic crossmatch	Yes	Yes
Transplants require negative flow cytometry crossmatch	No	Yes, unless due to non-HLA antibody
Donor travel versus kidney transport	Donor travel	Regional preference

CDC, complement-dependent cytotoxicity; ELISA, enzyme-linked immunosorbent assay; HLA, human leukocyte antigen; PRA, panel reactive antibody.
[a] Match probability takes into account ABO blood group frequency and frequency of acceptable HLAs for the recipient.

according to the quality of the matches (quality criteria are predetermined). Crossmatches are conducted, and those paired donations with negative crossmatches are performed in the order in which they are ranked. In contrast, the 'optimized' algorithm evaluates all of the feasible combinations of ABO and HLA-compatible paired donation transplants that may be performed. The optimized algorithm then selects the best combined results for several predetermined criteria (for example, total number of transplants, best HLA matching, smallest travel distances). This work also indicated that an optimized approach, if employed on a national level, would yield a greater proportion of recipients transplanted than the first accept approach (by approximately 11–14% in the scenarios that were modeled). 'Optimized' algorithms may also allow improved HLA matching and graft survival.

A practical problem with 'optimized' solutions is that the increase in the transplants requires that a complete set of transplants are performed. At present, however, crossmatching is performed after the match run is conducted, and therefore some transplants will be excluded because of positive crossmatches. The alternative of performing crossmatches prior to match runs creates the practical and financial problems of performing a large number of crossmatches for transplants that will never be conducted.

Improved HLA antibody screening may significantly reduce, but not eliminate this problem. Computer simulations indicate that the negative effect of unexpected positive crossmatches is diminished by including crossmatch positive pairs in successive match runs [9]. In addition, there is no reason *a piori* to assume that positive crossmatches will affect the 'first accept' approach more than the 'optimized' approach. The Hopkins group has performed initial evaluation of the effects of positive crossmatches, which supports this concept [9].

The Hopkins group also evaluated the need for regional versus national matching. While the optimized approach would provide benefits at the regional level, 'sensitized' recipients would receive substantial benefits at a national level, if national matching provided large numbers of donor–recipient pairs for matching. The benefits of national matching for sensitized patients warrant careful consideration as paired donation programs are developed.

Gentry and Segev used the same modeling approach to answer another question: under specified conditions, which approach (wait list paired donation, paired donation, or paired donation followed by wait list paired donation) allows the most patients to be transplanted [14]? Wait list paired donation is distinct from paired donation: list paired donation involves only one incompatible donor–recipient pair in which the donor is allowed to donate a kidney (that goes to an individual on the deceased donor wait list) and in return their intended recipient gets increased priority on the deceased donor wait list. Wait list paired donation, however, is complicated by ethical problems including the fact that a living donor kidney is exchanged in return for a deceased donor kidney of lesser quality [26].

In this study, the authors demonstrated that once the donor–recipient pool size exceeds 50 registrants, that paired donation results in as many transplants as wait list paired donation when each are applied exclusively. Moreover, if wait list paired donation is allowed following paired donation, the additive effect is minimal. This study demonstrated the minimal importance of creating an operational framework for wait list paired donation in the setting of regional and national paired donation programs.

Although modeling studies are important, a recent commentary has provided perspective on their interpretations and limitations [15]. This commentary pointed out several problems with modeling approaches including patient registration rates to date fall far short of their potential, crossmatch positivity rates are not static, but are rapidly changing due to introduction of newer testing methodologies, and the modeling studies have not evaluated the potential competitive effect of desensitization of incompatible recipients.

The Hopkins group has also modeled waiting times for paired donation [16]. This simulation of a national program assumed 85% enrollment of all expected eligible pairs (250 pairs per month). Although the likelihood of such numbers being achieved anytime in the near future is small, the studies indicated that median waiting times for unsensitized patients (PRA < 80%) of each blood group would be only a few months. These data indicate that paired donation for unsensitized patients in a highly efficient national program will be associated with waiting times much shorter than those currently experienced with deceased donor transplantation. It is likely, however, that highly sensitized patients will suffer long wait times for paired donation, although it is not clear how long these will be.

Developments in matching strategies and computer-based matching technologies for paired donation programs

Roth, Sonmez and Unver have also contributed to the rapidly expanding area of matching strategies by modeling 'higher order' paired donations (i.e., paired donations that involve three or more pairs) [18••]. In this study, two patient data sets were used for modeling: a small 'local' data set of 68 donor–recipient pairs, and a larger simulated data set based on OPTN/Scientific Registry of Transplant Recipients (SRTR) data. Results from both data sets were similar, and studies with the larger dataset revealed that paired donations involving two and three pairs provided an absolute increase in the proportion of patients matched from 49.8% to 59.8% with a donor–recipient pool size of 100 patients. Higher order exchanges involving four or more pairs, however, yielded only an increase to 60.4% of pairs matched. These studies by Roth and colleagues indicate that for large donor–recipient pool sizes of up to 100 donor–recipient pairs, optimized matching algorithms that include both 2 and 3-pair matching may allow higher transplant rates. It is unclear what the advantages of higher order matching will be on a larger scale. Moreover, optimized matching including higher order matches becomes computationally demanding when large numbers of pairs are present.

It is important to realize, however, that two pair matches require two negative crossmatches, whereas three pair matches require three negative crossmatches. With higher crossmatch rates, therefore, the effect of three-pair matching may be negated. As an example, current positive crossmatch rates for match pairs in the North American Paired Donation Network are 21% (Table 1). This finding means that that 38% (0.79^2) of all two pair matches (each two pair match requires a negative crossmatch for both of the transplants) will be excluded by crossmatching, but 51% (0.79^3) of all three pair matches will be excluded.

Roth and colleagues [19•] also evaluated the strategy of 'chain' paired donation programs. This strategy has been called 'chain paired kidney donations' [19•], which are also termed 'domino paired kidney donation' [20] or nondirected donor-facilitated paired donation [5]. 'Chain' paired donation occurs when a one pair, two pair, or higher order paired donation begins with a nondirected kidney donation that results in a cascade of transplants with the end result being a live donor kidney from the last donor–recipient pair being distributed to the deceased donor wait list. Using a small set of 34 paired donation intended recipients and a larger data set based on OPTN/SRTR data, Roth and colleagues [20] demonstrated that inclusion of nondirected donor kidneys in paired donation programs provides a means for inducing variable increases (depending on ABO blood groups involved, PRA) in the number of paired donation transplants that can be performed. It is important to note that this increase is on the order of 0.5–2.0 extra paired donation transplants for each nondirected donor. It is also important to note that a thorough consideration of the ethics and effects on blood group waiting times on the OPTN kidney wait list by nondirected donor-facilitated paired donation remains to be established. To date, published ethical considerations of 'chain' or 'domino' paired donation is limited to a cursory examination of the issues [20]. Clinically, five paired donation procedures utilizing nondirected donors in 'domino' paired donations have been performed in the Hopkins program [20].

Psychological barriers to paired donation in patients and transplant professionals

Despite the considerable attention that has been paid to technological aspects of matching strategies and modeling, the fact remains that the numbers of patients participating in paired donation programs has been very limited to date (165 patients in the United States as of end of 2006 (website: http://www.unos.org). Two recent studies have begun to examine the possibilities that patient or transplant professional willingness to participate in paired donation programs may represent substantial barriers to patient registration [21,22••]. In an important, ongoing research effort, Waterman and colleagues have examined donor willingness to participate in paired donation programs [22••]. The most important observation from this study is that donors are more willing to participate in paired donation than in wait list paired donation since their recipient is guaranteed an immediate kidney if the donor donates. This observation adds strongly to the arguments against wait list paired donation. Logistic regression also revealed that the following factors influenced donor willingness to participate in paired donation: donors with less formal education, and donors who had higher empathy and a closer relationship with the recipient.

Woodle and colleagues [21] have, in a similar manner, examined transplant professional attitudes toward living donation and paired donation. These studies have indicated a high level of awareness of paired donation amongst transplant professionals. They also revealed that transplant professionals are ambivalent about paired donation, and have a number of reservations regarding financial, ethical, and medical aspects of paired donation.

The wait list paired donation controversy

Considerable debate has continued regarding the ethics and acceptability of wait list paired donation [23•,24–28]. The New England (UNOS Region 1) group has remained the primary proponent of wait list paired donation [24], but a recent survey of minority patients demonstrated a lack of acceptability of wait list paired donation [23•]. In response, the New England group has countered that wait list paired donation should continue to be practiced until 'paired kidney exchange is a flourishing program' [24]. This stance may be a reasonable compromise given that Segev and Gentry have shown that until paired donation pools reach a size of 50–100 donor–recipient pairs, list paired exchange can provide more transplants [14]. If this approach is accepted, however, programs that perform wait list paired donation have a responsibility to be sure that their program does not preclude achievement of large sized pools of donor–recipient pairs. Patients will need to be required to wait an acceptable period of time in paired donation programs before being allowed access to wait list paired donation. In addition, if other paired donation programs exist where critical mass has been achieved, patients may be better served by joining these programs rather than undergoing wait list paired donation.

Conclusion

Paired donation remains a rapidly developing field as a result of ethical, scientific, and clinical innovations and development. Despite this growth, paired donation has not realized its potential; however, several paired donation programs in the US, Europe, and Asia are established and actively recruiting patients. Much remains to be learned about how to establish effective paired donation consortia that will maximize transplantation rates. It appears that we may be approaching the end of the beginning of paired donation in kidney transplantation.

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References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 433).

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