Chapter 8
New Sources in Living Kidney Donation

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History

The first successful living kidney transplantation occurred in 1954 when Ronald Herrick donated a kidney to his identical twin brother, Richard, at the Peter Bent Brigham Hospital in Boston, Massachusetts. There was no possibility of a rejection of the kidney because the brothers were genetically identical twins. Since then, however, the field of kidney transplantation has evolved so that genetic identity or matching is no longer a necessary criterion for success. Advances in immunosuppressive drugs (and changes in attitudes toward non-directed living donation) currently allow successful kidney transplantation between donors and recipients even with a complete human leukocyte antigen (HLA) mismatch. Despite these advances, the risk of hyperacute rejection has prohibited kidney donation and transplantation between ABO blood type incompatible donors and renal transplant candidates. Transplantation of a kidney to a candidate who has developed antibody reactive to donor-specific HLA (alloantibodies) incurs an even greater risk. Candidates develop antibodies when exposed to foreign HLA antigens as the result of pregnancy, blood transfusion, previous organ transplant, and occasionally autoimmune disorders. To avoid kidney rejection in candidates who are sensitized (have developed preformed alloantibodies), a crossmatch of donor and candidate blood is performed prior to transplant. A positive crossmatch predicts rejection of the transplanted kidney and the donation would not occur.

Approximately one-third of potential living donors are unable to donate to their intended candidates due to either ABO incompatibility or antigen incompatibility indicated by a positive crossmatch.[1] Previously either of these incompatibilities prevented donation and transplantation. Transplantation across the ABO barrier has a reasonable success rate if one utilizes protocols that remove natural isoagglutinin antibodies and recipients are closely monitored after transplantation.

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D.B. McKay, S.M. Steinberg (eds.), *Kidney Transplantation: A Guide to the Care of Kidney Transplant Recipients*, DOI 10.1007/978-1-4419-1690-7_8,

Desensitization protocols that remove donor preformed HLA alloantibodies reactive to the donor antigens are increasing in utilization; however, these protocols are technically demanding and expensive with long-term outcomes unknown at this time. Kidney paired donation (KPD) and kidney list donation (KLD) are alternative options for candidates with an incompatible living donor.

The concept of KPD was initially conceived by Rapport in 1986,[2] but it was not implemented until 1991 when the first KPD transplants were performed in South Korea.[3] The United States performed its first KPD transplant in 2000 at Rhode Island Hospital when two adult children who were incompatible with their mothers each donated a kidney to the other's mother.[4] The first KLD in New England occurred in 2001.

New England Implementation

In February 2001, Region 1 of the United Network for Organ Sharing (UNOS) initiated a system of kidney transplantation that would enable renal transplant candidates to participate in either KPD or KLD among the 14 transplant centers and 2 organ procurement organizations (OPO) in New England.[5] This laid the groundwork for the establishment of the New England Program for Kidney Exchange (NEPKE)[6] in 2004.

Kidney List Donation

Kidney list donation, also known as living donor/deceased donor list exchange, occurs when the donor in an incompatible pair donates to someone on the UNOS deceased donor waitlist. In exchange for donating a kidney to a candidate on the waitlist, their incompatible candidate is allocated a kidney from the deceased donor pool (Fig. 8.1). Regions must apply for a variance from UNOS in the allocation of kidneys from deceased donors to participate in kidney list donation.

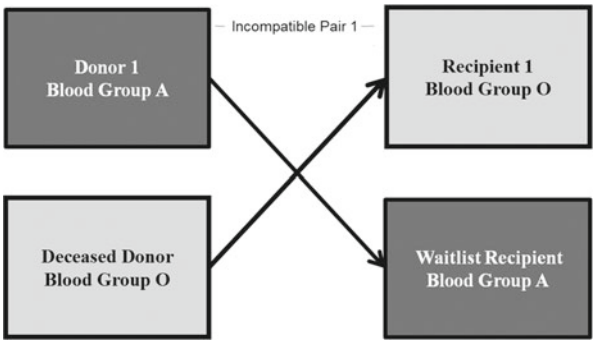

Fig. 8.1 Kidney list donation

Kidney Paired Donation

The NEPKE system identifies various types of KPDs, also known as kidney exchange. These include both cyclical exchanges and chains. Cyclical exchanges involve either two or three donor/recipient (D/R) pairs. Chains begin with an unpaired donor and/or end with a recipient on the UNOS deceased donor waitlist. The initial proposal for a computerized KPD system called for the consideration of large cycles and chains.[7] However, for logistical reasons, early exchanges were limited to two pairs, with the computer system adapted to find the optimal set of two-way matches.[8] Today two and three-pair exchanges as well as non-directed donor (NDD) chains are common.

Two-Pair Exchange: Two-pair exchanges begin when the donors in two D/R pairs are incompatible with their intended recipients. If the donors are both compatible with the recipient in the opposite pair, an exchange of kidneys can occur [8,9] (Fig. 8.2).

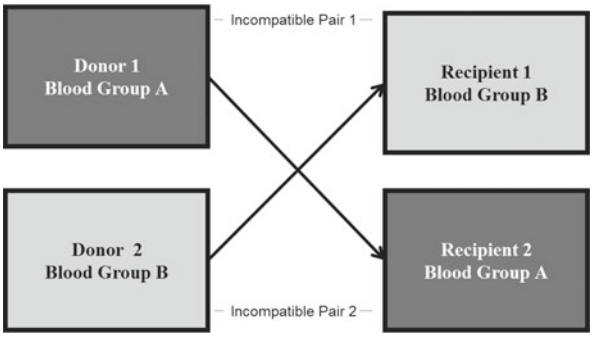

Fig. 8.2 Kidney paired donation: two-pair exchange

Three-Pair Exchange: As the name three-way exchange indicates, a third incompatible pair is added to the match. As shown in Fig. 8.3, pairs 1 and 2 are incompatible due to ABO, while pair 3 is incompatible due to positive crossmatch. In this exchange, paired donor 1 donates to recipient 2, while donor 2 donates to recipient 3 and donor 3 donates to recipient 1.[10]

Non-directed Donor Chain: A NDD, commonly referred to as a Good Samaritan or altruistic donor, does not know someone who needs a kidney transplant, he/she would like to donate to anyone in need. When a NDD enters a KPD program, they allow pairs to match who otherwise would not. As a result, two or three recipients undergo kidney transplantation following the gift of one NDD. Figure 8.4 illustrates how a NDD entering a KPD system donates to a recipient of an incompatible donor, that first donor donates to a recipient of a second incompatible pair and that pair's donor donates to someone on the UNOS waitlist. Traditionally, the NDD would donate directly to the waitlist, with only one person benefiting from transplantation. As incentive for transplant programs to enter NDDs into the NEPKE system, the

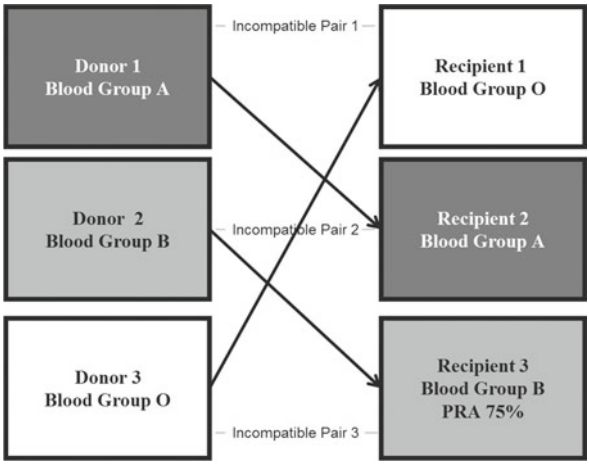

Fig. 8.3 Kidney paired donation: three-pair exchange

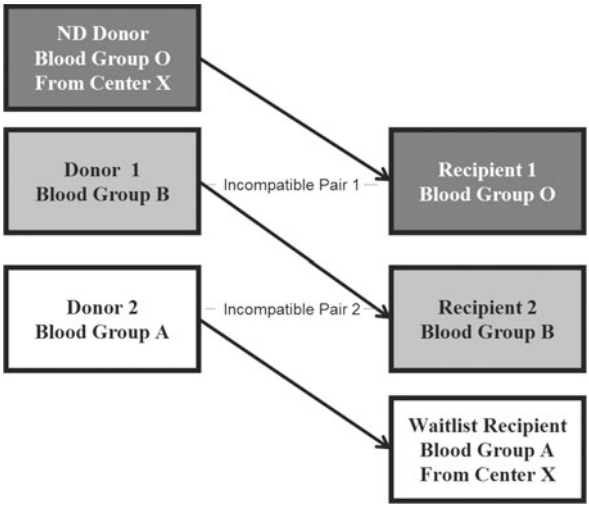

Fig. 8.4 Kidney paired donation: NDD chain

evaluating center receives the kidney at the end of the chain to transplant a candidate on their center's waitlist. In some KPD programs, rather than the third donor donating to the waitlist, they return to the KPD pool and become the next NDD to begin a new chain.[11]

List Exchange Chain: A list exchange chain combines KPD and KLD. A pair who meets criteria for a standard KLD enters the KPD system. This pair is matched with another pair, a recipient on the UNOS waitlist and a deceased donor. The initial KLD eligible donor provides a kidney to the recipient in another incompatible pair, the second donor donates to someone on the UNOS waitlist, and the initial KLD candidate is allocated a kidney from the deceased donor pool[11] (Fig. 8.5).

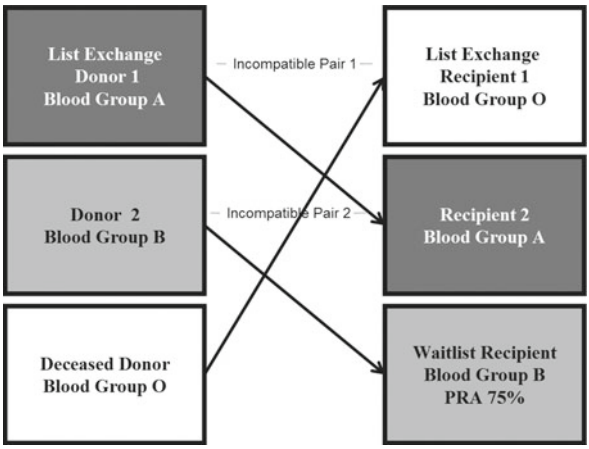

Fig. 8.5 Kidney paired donation: list exchange chain

Benefits of KPD

The recipient of a paired donation receives all the benefits of a living donor kidney transplant. Transplants from living kidney transplants, both related and unrelated, have greater graft survival than deceased donor transplants, benefiting the individual recipient. Graft survival for living unrelated is similar to living related kidney transplant, providing the recipients of paired donation the same benefits of directed living donation.[12,13] In addition to individual benefits, KPD and KLD increase the number of kidneys available for transplant, removing the intending recipient from the deceased donor list or pre-empting the need for placement on the list, benefiting all kidney transplant candidates.

Computer Optimization

Prior to computer optimization programs, exchanges involved matching of ABO incompatible pairs and two-way exchanges only. The development of a mechanism based on computer optimization algorithms, specifically designed for kidney matching, revolutionized KPD.[6] Initially algorithms were adapted to handle only two-pair exchanges in New England[6] and later elsewhere.[9] As logistical ability has improved, flexible integer programming formulations were developed that allow optimization to specify the maximum size cycles and chains that will be considered,[14] these too have been adopted elsewhere. Compatibility is based on ABO blood type, HLA typing, and predicted crossmatch results (based on candidate alloantibody screening). The first task of the computer is to generate a compatibility matrix, which searches for recipients who are ABO compatible with all registered donors. If a recipient has an identified unacceptable antigen to a donor's HLA, the computer eliminates the unacceptable match from further consideration. Optimization

techniques identify incompatible recipients who would potentially receive a transplant through KPD. Integer programming then determines maximal two- and three-way exchanges, NDD chains, and list exchange chains based on a set of priorities listed in Table 8.1.

Table 8.1 NEPKE matching priority

1. Candidate is a prior living donor
2. PRA ≥ 80% (Class I or II)
3. Maximum number of kidneys transplants
4. Candidate < 18 years old
5. PRA 50–79%
6. Collective wait time of matched pairs

For example, suppose there are eight patient–donor pairs registered to the database through the participating transplant centers. Further, suppose that all pairs have the same priority. Thus, we would like to find a set of exchanges that serves the largest number of pairs.[14] The computer defines the compatibility matrix as demonstrated in Table 8.2. The rows denote the recipients and columns denote the donors. D1 is the paired donor of recipient R1; D2 is the paired donor of recipient R2; and so on. NEPKE software finds the compatible and incompatible donors for each recipient and the reasons for incompatibility.

Table 8.2 Compatibility matrix for kidney paired donation

	D1	D2	D3	D4	D5	D6	D7	D8
R1	ABO	OK	OK	ABO	HLA	ABO	HLA	OK
R2	OK	HLA	ABO	OK	ABO	OK	HLA	ABO
R3	OK	HLA	ABO	HLA	ABO	OK	ABO	ABO
R4	ABO	OK	ABO	ABO	ABO	ABO	ABO	ABO
R5	ABO	OK	ABO	ABO	ABO	ABO	ABO	ABO
R6	ABO	HLA	HLA	ABO	OK	ABO	HLA	HLA
R7	ABO	HLA	HLA	ABO	HLA	ABO	HLA	OK
R8	ABO	HLA	ABO	ABO	ABO	ABO	ABO	ABO

The second task for the computer is to identify optimal exchanges using the information generated from the compatibility matrix. In this example, there are four possible exchanges (Fig. 8.6). Without using optimization, one can choose Exchange 1, but none of the other exchanges will be feasible due to the same pair involved in multiple matches. In this case, pair 1 and pair 2 donate and receive transplants. However, by using optimization the computer identifies a maximal two- and three-way match choosing Exchanges 3 and 4. Using optimization pairs 1, 2, 3, 5, and 6, all benefit from kidney exchange with an additional three transplants performed.[15] In this step the computer uses integer programming techniques to maximize the number of pairs matched under the given possible exchange cycles. Other objectives (as summarized in Table 8.1) are also utilized by these techniques.

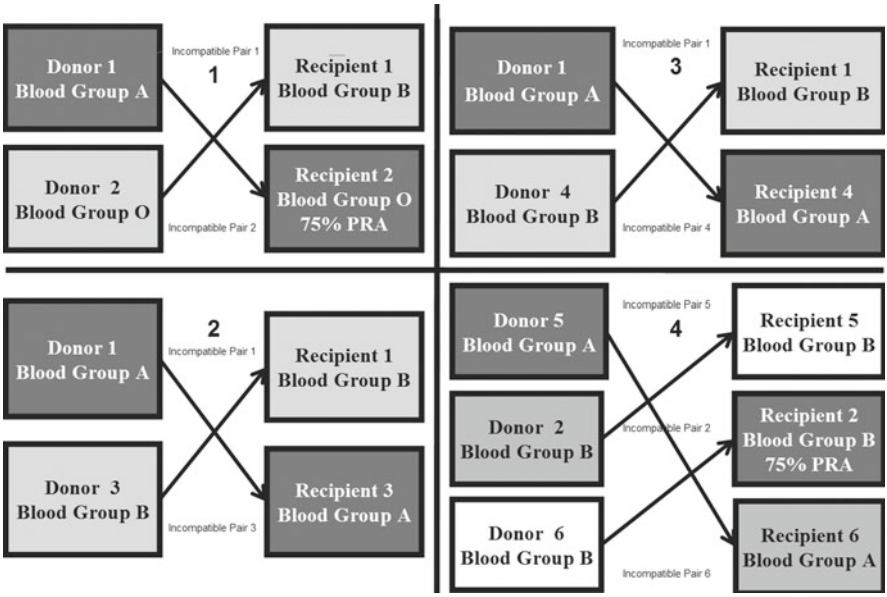

Fig. 8.6 Four possible exchanges generated. Using optimization, the computer software identifies matches 2 and 4 as providing the greatest number of transplants

Types of KPD Programs

There are several models of KPD programs currently in use in the United States. In a center-specific program, all pairs are registered at the same transplant center. The major advantage of a center-specific program is that the logistics of coordinating an exchange are less complicated and no travel is necessary for the donor or the kidney. In a multicenter regional program exchanges are determined between pairs registered at two or more transplant centers in same region. Advantages are short travel time for either the donor who will travel to their match center for surgery or reduced cold ischemic time if the kidney shipped to the match center after recovery. A cross-regional program involves the exchange between pairs at two or more transplant centers in different UNOS regions. The advantage of this type of program is an increase in the number of pairs entered in the system, which increases the number of potential matches and transplants. Finally, a national program would involve the exchange between pairs entered in a centralized national database in which any UNOS-affiliated transplant program has the ability to enter pairs.

Multiregional Application

The benefits of expanding the pool of D/R pairs in KPD programs are well established.[16,17] In an effort to increase the chance that NEPKE pairs would fine a

match, NEPKE works with individual transplant centers and other paired donation programs outside Region 1. In 2006 the Mid-Atlantic Paired Exchange Program (MAPEP), organized through the New Jersey Sharing Network, and their five affiliated transplant centers began entering incompatible D/R pairs into the NEPKE system. Combining NEPKE and MAPEP increases the number of pairs in both systems thereby increasing the number of potential matches and actual transplants. Although the matching process remains the same, MAPEP developed their own consent forms and policies on issues such as donor evaluation and antibody screening. These policies are consistent with NEPKE policies and have not posed an impediment to programs working together.

Candidacy for Kidney List Donation

Candidates for list donation must be eligible for a kidney transplant and have a medically suitable living donor who is incompatible by blood type. The candidate wishing to enter the KLD program must meet specific criteria prior to acceptance. Criteria include first deceased donor kidney transplant; currently treated with dialysis; unsensitized, defined as a PRA less than 10%; on the list of New England candidates awaiting a kidney transplant (with an established care relationship with a UNOS Region 1 center); and has waited 45 days to find a KPD match prior to moving to KLD[5] (Table 8.3).

Table 8.3 Region 1 candidate requirements for kidney list donation

- First deceased donor transplant
- Currently on dialysis
- Unsensitized (<10%)
- Has established care relationship with UNOS Region 1 center
- On New England Region 1 waiting list
- Has waited at least 45 days for a Kidney Paired Donation

Kidney List Donation Allocation

The UNOS Kidney Committee has sponsored an alternative allocation system for the original intended candidates of living donors. In this system for standard donors less than 35 years of age, the original intended candidate of a living donor comes after zero ABDR mismatches, local prior living organ donors, local highest scoring high PRA candidates, local pediatric candidates, and payback debts and credits. The local original intended candidates come right before the local candidates on the match run. For standard donors over 35 years of age, the original intended candidate of a living donor comes after zero ABDR mismatches, local prior living organ donors, and payback debts and credits but before local kidney alone candidates (this

Table 8.4 Region 1 allocation priority for standard criteria donors

1. Kidney + lifesaving extra-renal
2. Region 1 emergency kidney
3. Region 1 zero antigen MM K/P w/ PRA > 80%
4. National zero antigen MM K/P w/ PRA > 80%
5. Region 1 standard K/P top 12 unsensitized
6. Zero antigen MM (region and national)
7. Prior living donors
8. Region 1 KLD recipients
9. Region 1 highest scoring high-PRA recipients (category on donors ≤35)
10. Pediatric priority recipients (category on donors ≤35)
11. UNOS paybacks
12. Region 1 list

allocation does not have separate classifications for local highest scoring high PRA candidates and local pediatric candidates). Four regions have adopted the UNOS Kidney Committee allocation while Region 1 and others have adopted a slightly different allocation policy (Table 8.4).[18]

Candidacy for Kidney Paired Donation

As with KLD, the candidate for KPD must also be eligible to receive a kidney transplant; however, they may participate in KPD pre-emptive of the initiation of dialysis. The candidate may be incompatible to their intended donor by blood type and/or positive crossmatch. In addition, there is no limit to the number of previous kidney transplants from either living or deceased donors.

Donor Candidacy for KPD and KLD

Donors entered into NEPKE must meet one of the following criteria: the living donor must be willing but unable to donate a kidney to their intended candidate due to an incompatible blood type, positive crossmatch, and/or some other incompatibility or be a NDD. Donor medical and psychosocial suitability is determined by individual transplant center criteria with a recommendation of the following: the UNOS Guidance for the Development of Program-Specific Living Kidney Donor Medical Evaluation Protocols[19] and Guidelines for the psychosocial evaluation of living unrelated kidney donors in the United States.[20] To decrease the number of potential matches in which a donor is later found to be medically or psychosocially unsuitable for donation, a standard minimum donor evaluation for all NEPKE donors is required prior to entering the program.

Alloantibody Screening

Prior to registration in NEPKE antibody screening is required for all candidates with a PRA greater than 10%. Class I and II antibody screening can be performed by FlowPRA, Luminex, or ELISA. If screen is positive, solid phase specific/panel assay for Class I and/or II is performed. Report must include all HLA alloantibody specificities. If PRA is high and/or antibody specificities cannot be determined, single antigen solid phase assay is performed. Any additional routine screening by the transplant center is performed using the center's standardized tests. Additional testing does not need to be reported to NEPKE. The candidate, however, may benefit from additional solid phase screening if there is a significant decrease in PRA.

Consent for Participation

Once suitability for KPD is determined, donors and candidates are given the opportunity to make an informed decision regarding program participation. A transplant center representative reviews the components of NEPKE with each recipient and their donor(s) separately providing accurate and complete information regarding participation in the NEPKE. After review, each individual participant is asked to sign a separate consent form if he/she agrees to participate in KPD. The consent form outlines what KPD and NEPKE are; the KPD procedure; information that will be entered into the database and how it will be used; how confidentiality will be maintained; and the risks, benefits, and alternatives to participating in the program.

The transplant team provides a preliminary review of the general risks for kidney transplant and donor nephrectomy surgeries, including risk that surgery may not occur due to unforeseen events in the operating room such as hypotension, myocardial infarction, unexpected findings. The surgical team responsible for the operative procedure of each specific patient in the exchange reviews the risks and benefits of surgery and obtains informed consent.

Exchange Process

Once a potential match has been accepted by all involved centers, more detailed donor information is exchanged between centers and if this is acceptable, preliminary crossmatches are conducted between the candidate and their matched donor. Flow crossmatch is strongly recommended when appropriate. For candidates with high levels of alloantibodies ($\geq$80%), detailed analyses including autocrossmatch testing and testing of several historical serum samples are encouraged. Donor blood is generally sent to the histocompatibility laboratory of their matched candidate for crossmatch, that is, the crossmatch is performed at the potential recipient's histocompatibility laboratory. Transplant centers update donor medical and psychosocial evaluation as needed. The center that will actually perform the donor's surgery meets

that donor, reviews their medical history, obtains any new testing that is warranted, and obtains the legal surgical consent signature. Candidates are re-evaluated by their transplant center to determine current suitability for transplant. Transplant centers consider psychosocial issues specific to KPD and discuss with both the donor and recipient. Transplant centers and participants agree to date and time of simultaneous donor nephrectomies immediately followed by candidate kidney transplant. Final crossmatches between the candidate and their matched donors are conducted prior to surgery according to transplant center guidelines; flow crossmatch are recommended when appropriate.

A conference call is scheduled with involved transplant centers several days prior to the surgery date to discuss logistics of the donation and transplant, donor follow-up, and D/R correspondence/meeting. Donor surgeons speak to each other in the operating room prior to incision. If any donor nephrectomy is delayed, all donor nephrectomies are rescheduled to occur simultaneously.

Ethical and Legal Issues in Kidney Paired Donation and Kidney List Donation

Legal and ethical issues have arisen involving the practice of KPD and KLD in the United States. Ambiguity in the National Organ Transplant Act (NOTA) delayed the universal acceptance of these exchanges as standard practice. NOTA prohibits the buying and selling of human organs by making it unlawful to exchange "valuable consideration" for human organs for use in transplantation.[21]

Legal concerns raised under NOTA caused many transplant centers and the UNOS to hesitate implementation of KPD and KLD programs. The solution to legal ambiguities and threat of possible lawsuits required legislative clarification of valuable consideration as it relates to KPD and KLD.

In March 2007, Department of Justice, C. Kevin Marshall Deputy Assistant Attorney General in a memo to the Department of Health and Human Services concluded "that valuable consideration term as used in section 301 does not apply to KLD or KPD, because neither involves the buying or selling of a kidney or otherwise commercializes the transfer of kidneys."[22] It is important to note that in NOTA "The term 'valuable consideration does not include the reasonable payments associated with their removal, transportation, implantation, processing, preservation, quality control, and storage of a human organ or the expenses of travel, housing, and lost wages incurred by the donor of a human organ in connection with the donation of the organ.'[21] These exclusions address types of 'payments' and 'expenses' that may otherwise fall within the term 'valuable consideration' on the theory that they involve monetary benefits or at least a monetary transfer. Any benefits received in the KPD/KLD exchanges, on the other hand, are not monetary. The lack of comparable exclusion for non-monetary benefits may suggest that non-monetary KPD and KLD exchanges do not involve valuable consideration."[22]

The Charlie W. Norwood Living Organ Donation Act, signed into law in 2007, amends NOTA to clarify that valuable consideration and associated criminal penalties do not apply to KPD. Section 301 274e states that "it shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human organ for valuable consideration for use in human transplantation if the transfer affects interstate commerce." The Charlie W. Norwood Act added, "The preceding sentence does not apply with respect to human organ paired donation."[21] Although earlier versions of the bills addressed KLD, the final version does not.

National Pilot Program

The Charlie W. Norwood Living Organ Donation Act allows UNOS to move forward with a National Pilot KPD program. A national system will (1) allow centers not large enough to participate at the single center level access to KPD, (2) provide greater opportunity for difficult to match pairs to find an exchange, and (3) increase the total number of kidney donors, benefiting all candidates waiting.

In order for a national KPD program to be successful, it will require participation of a large number of transplant centers. In order to engage transplant centers, the national program will need to be flexible enough to satisfy the diverse needs of different transplant programs. Current optimization programs permit this flexibility, allowing a menu of clinical and logistical options that accommodate the varying needs of different transplant centers and their patients.[23] In June 2008, the OPTN/UNOS Board of Directors approved a proposal for a national KPD pilot program administered by the OPTN.[24] This proposal will accommodate the various needs of individual transplant programs and patients, providing the flexibility needed for participation.

Proposed Operational Guidelines

Optimization and Prioritization

The national optimization protocol will look at every possible matching from the list of potential D/R pairs (compatibility matrix similar to NEPKE).[25] The computer program will compare the possible matches using predetermined weights based on objectives established for the program. The program then selects the matches with the greatest number of points. Priority points assigned are listed in Table 8.5.

Options for Individual Patients and Transplant Programs

In the current plan for the national pilot program, transplant programs will be able to choose to participate in either two-way alone or two- and three-way matches.

Table 8.5 Priority points for national KPD pilot program

1. Zero antigen mismatch between donor and candidate
2. Highly sensitized candidate (PRA $\geq$ 80%)
3. Prior living donor status of the candidate
4. Pediatric candidate (age < 18 years)
5. Waiting time accumulated within the KPD program
6. Geographic proximity (transplant center, local, or regional)

Table 8.6 Transplant program choices in KPD

Donor	Candidate
Distance willing to travel	Distance willing to travel
Nephrectomy type (open/laparoscopy/either)	Acceptable donor age
Nephrectomy side	Acceptable donor BMI
Willing to participate in an open NDD chain	Donor blood pressure limits
Willing to participate in a close NDD chain	Donor CMV status
	Donor EBV status
	Donor history of cancer
	Willing to participate in an open NDD chain
	Willing to participate in a close NDD chain

This allows centers who are new to KPD to start with logistically easier matches if desired. Transplant programs as well as patients will have the opportunity to choose between lists of options regarding logistics and medical criteria (Table 8.6).

Crossmatching

As the number of pairs in a system increases, the accuracy of virtual crossmatching will become increasingly important. In the national pilot program donors and candidates will be typed for HLA – A, B, Bw4, Bw6, Cw, DQ, DR, Dr51, DR52, DR53, and DP. Centers will have the option to enter unacceptable antigens at levels of high and low stringency for each candidate in the program. High stringency is defined as all HLA antigens to which the candidate has antibodies and low stringency as only unacceptable antigen that are highly likely to cause a positive crossmatch. These options provide flexibility for each transplant program based on their individual center protocols and the individual needs of each candidate. Crossmatches usually take place at the histocompatibility laboratory affiliated with the matched candidate; however, some programs recommend that using a centralized tissue typing laboratory to perform preliminary crossmatches may be more efficient than exchanging blood among participating transplant centers. Until such a laboratory can be established, a national KPD program will need to utilize currently available resources.

Living Donor Evaluation

The potential living donor will need to undergo a medical evaluation similar to the NEPKE requirements with professional consultations by a nephrologist and local transplant or donor nephrectomy surgeon, as well as a psychosocial evaluation by a social worker or psychologist. The medical evaluation should adhere to the guidelines set forth in the Amsterdam Forum On the Care of the Live Kidney Donor[26] and consist of at least a history and physical examination; blood and urine testing; creatinine clearance; tissue typing, ABO blood typing; a duplex ultrasound of both native kidneys documenting size, presence of cysts, and/or other abnormalities; and age-appropriate cancer screening. Transplant programs will be required to use consent process outlined in "The Resource Document for Informed Consent for Living Donors"[27] developed by the UNOS Living Donor committee and approved by the Executive Committee. As the UNOS Board of Directors approves other resource documents, such as recommendation for the medical and psychosocial evaluation of living kidney donors, the Kidney Committee will work to incorporate these resource documents into the national KPD pilot program.

Program Evaluation

Monitoring participation of transplant programs in a national KPD program is vital to its success. The UNOS Kidney Committee will evaluate the national KPD program every 6 months for the first 3 years, recommending adjustments to the system as needed. Additional enhancements to the program will be considered on a regular basis, such as NDD chains involving altruistic living donors. Making enhancements and maintaining flexibility will enable a national KPD program to accommodate the diverse needs of individual transplant programs and their candidates, increasing the transplant opportunity for all participants.

Acknowledgments We thank Dr. Kenneth Andreoni, Chair of the OPTN/UNOS Kidney Paired Donation Work Group Committee, and Elizabeth F. Sleeman MHA, UNOS Policy Analyst, for their valuable assistance and insightful comments.

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