AJKD
Narrative Review

Kidney Paired Donation: Fundamentals, Limitations, and Expansions

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Incompatibility between the candidate recipient and the prospective donor is a major obstacle to living donor kidney transplant. Kidney paired donation (KPD) can circumvent the incompatibility by matching them to another candidate and living donor for an exchange of transplants such that both transplants are compatible. KPD has faced legal, logistical, and ethical challenges since its inception in the 1980s. Although the full potential of this modality for facilitating transplant for individuals with incompatible donors is unrealized, great strides have been made. In this review article, we detail how several impediments to KPD have been overcome to the benefit of ever greater numbers of patients. Limitations and questions that have been addressed include blood group type O imbalance, reciprocal match requirements, simultaneous donor nephrectomy requirements, combining KPD with desensitization, the role of list-paired donation, geographic barriers, legal barriers, concerns regarding living donor safety, fragmented registries, and inefficient matching algorithms.
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INDEX WORDS: Kidney exchange; paired donation; incompatible; matching; altruistic donor; good Samaritan donor; nondirected donor; nonsimultaneous extended altruistic donor chain; bridge donor; list-paired donation.

Candidates for kidney transplant often face years of waiting for an organ from a deceased donor. Many candidates have family members or friends who want to donate one of their own kidneys, but about one-third of such offers must be declined because of blood group type or crossmatch incompatibility. Kidney paired donation (KPD), also referred to as kidney exchange or live donor paired exchange, circumvents the incompatibility by allowing a living donor to direct the donated organ to a different compatible recipient, with the intent that another donor will donate to the first donor's designated recipient.[1]

In the most elementary scenario, a type A donor with a type B intended recipient gives instead to a type A recipient who has a type B donor, and vice versa. Additionally, donors who are blood-type compatible but have a positive crossmatch or HLA antigen incompatibility with their intended recipients could benefit from KPD. The pairs participating in KPD need not be strictly incompatible. A pair consisting of a kidney transplant candidate and compatible intended living donor might participate in an exchange for medical or altruistic reasons. Potential medical benefits include finding a younger donor, finding a better size match (for example, a large muscular male transplant candidate with a compatible but small female donor might seek a donor with more "nephron mass"), or finding a better immunologic match (such as avoiding a repeated HLA antigen mismatch or finding a perfectly HLA antigen–matched donor). The compatible pair alternatively could be motivated by altruism to help incompatible pairs who otherwise could not find a match. About half of all compatible pairs could be matched in KPD for some medical benefit, whereas an additional 10% of compatible pairs could benefit others by participating in KPD.[2] All variants of KPD discussed in this article are listed in Box 1 and illustrated in Fig 1.

In reasonably sized registries, match rates for incompatible pairs can be as high as 50%.[3] For incompatible pairs, the highest match rates generally are for crossmatch-positive pairs with low to moderate candidate sensitization and also pairs with a type A donor and a type B candidate, or vice versa.[4]

Because there is no systematic registry for incompatible pairs in the United States, simulation has had a key role in KPD research in this country.[5,6] Simulation is a method by which computers randomly construct virtual databases for which observed data do not exist (ie, incompatible donor/candidate pairs) from observed distributions of blood group types, sensitization, and other characteristics.[7] Using these virtual

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Box 1. Kidney Paired Donation Types and Alternative Terminology

- *2-Way kidney paired donation*: Paired exchange, kidney exchange, kidney swap, 2-way cycles
- *3-Way kidney paired donation*: Paired exchange, kidney exchange, kidney swap, 3-way cycles
- *Compatible kidney paired donation*: Altruistically unbalanced exchange, voluntary compatible paired donation
- *Domino paired donation*: Chain, daisy chain, w-chain
- *Open chain*: NEAD, never-ending chain
- *Closed chain*: NEAD chain ending in the waitlist, domino paired donation
- *List paired donation*: Living/deceased donor paired exchange, waiting list paired donation

Note: Figure 1 illustrates which donors give to which recipients in each arrangement.

Abbreviation: NEAD, nonsimultaneous extended altruistic donor.

databases, researchers can test hypotheses about matching algorithms and patient decisions. Simulation and computational trials might be more appropriate than clinical trials because the efficiency of matching algorithms will affect the earliest KPD registrants and the time to accrue observed cohorts would be prohibitive. Also, because KPD has not yet become the standard of care, the sparse data available for actual donors and candidates might not reflect the broad population to which this modality applies. Both clinical and simulation data are cited throughout this article.

The idea of KPD was described first in 1986,[8] and as recently as 1998, some have argued that it could benefit only a very small proportion of recipients with incompatible donors.[9] Since then, both researchers and clinicians have greatly expanded the concept and thereby the reach of KPD. As a result, many hundreds of transplants have resulted from this modality, and KPD programs are active in many countries: the Netherlands,[10] Korea,[11] Canada, the United Kingdom,[12] and Romania.[13] In the United States, KPD transplants have grown from only a handful before 2003[14] to more than 300 in 2009,[15] performed at many institutions and through several different registries.[16-18] In parallel, the United Network for Organ Sharing (UNOS) is piloting a nationwide registry to unite these efforts. This article reviews the evolution of the field of KPD from concept to general practice. The tremendous unrealized potential of KPD will be achieved only when all barriers to an efficient system of KPD are eliminated.

BLOOD GROUP TYPE O IMBALANCE

Of potential living donors and their intended recipients, relatively few type O donors will be found incompatible with their intended recipients, but every non–type O donor will be incompatible with a type O recipient, so type O donors will be under-represented in incompatible pairs. This blood type skewing is one of the biggest limitations of KPD. In typical KPD pools, >50% of pairs have type O recipients, whereas only about 30% of pairs have type O donors.[19] In traditional KPD pools of incompatible pairs, match rates for type O recipients with non–type O donors are ~15%, whereas rates for other pairs with donors of other blood group types are ~50%.[4] With this type O imbalance, there will never be enough type O donors in incompatible pairs to allow all pairs to match. Table 1 lists the distributions of blood group types in incompatible pairs.

Compatible pairs could greatly alleviate the type O imbalance in incompatible pools because of the compatible living donor/recipient pairs, ~65% have type O donors and only 45% have type O recipients. Simulations show that if compatible pairs participate in KPD, even if only when they gain a tangible medical benefit, the 15% match rate for type O recipients with non–type O donors would climb to 75% and nearly twice as many incompatible pairs could be

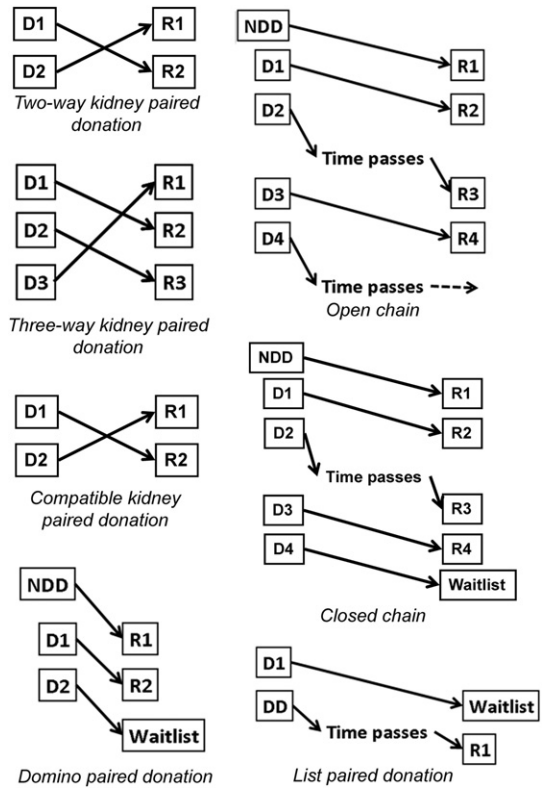

Figure 1. Illustration of the combination of transplants involved in various kidney paired donation arrangements. Refer to Box 1 for alternative terms. In the diagrams, donors (D) and their intended recipients (R) are shown in numbered pairs. Arrows show the actual recipient of each donor's kidney. In diagrams in which time passes, time is in months. Abbreviations: DD, deceased donor; NDD, nondirected donor.

Table 1. Distribution of Blood Group Types in Incompatible Donors and Candidates

	Donor O	Donor A	Donor B	Donor AB	Total
Candidate O	18	30	10	1	59
Candidate A	7	12	5	3	27
Candidate B	2	5	3	2	12
Candidate AB	0	1	0	0	2
Total	28	47	18	7	

Note: Values are shown as percentage. Some rows and columns do not sum to total because of rounding.

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matched.[2] Table 2 lists distributions of blood group types in compatible pairs.[20]

RECIPROCAL MATCH REQUIREMENTS

The KPD matches discussed thus far require reciprocal compatibility; not only must the donor of the first pair be compatible with the recipient of the second pair, but the donor of the second pair also must be compatible with the recipient of the first pair. In cases with no 2-way reciprocal compatibility, there still may be cycles of 3 or more incompatible pairs from which each pair's donor can give to the next pair's recipient, with the final pair's donor completing the cycle by giving to the first recipient.[21] Allowing 3-way matches increases the proportion of incompatible pairs that could find a compatible donor in any pool of incompatible pairs from ~54% matched to 66% matched in one simulation study.[22] Very large cycles can be problematic because a large number of simultaneous operations might be required and every additional pair involved increases the risk of scuttling the proposed transplant for unpredicted positive crossmatch or donor or recipient medical factors. The largest reported simultaneous KPD involved 6 donors and 6 recipients at Johns Hopkins in 2008.

Nondirected donors, also known as altruistic donors, good Samaritan donors, anonymous donors, or stranger donors, are donors who want to give a kidney, but do not have an intended recipient. A KPD sequence could be initiated by a nondirected donor rather than an incompatible pair. This greatly eases the restrictiveness of reciprocal compatibility because the last donor gives to a recipient from the larger deceased donor waiting list, rather than necessarily to the recipient of the first incompatible pair. These domino paired donations, or chains, greatly expand the opportunity for paired donation.[23,24] For example, if all 302 nondirected donors in the United States between 1998 and 2005 had participated in 2-way domino KPDs, 583 transplants might have been performed.[23] A nondirected donor can give to a difficult-to-match recipient without placing a reciprocal requirement that the recipient's donor has to match a particular recipient. Instead, the paired donor at the end of a domino paired donation gives to a compatible recipient from the deceased donor waiting list. This is particularly beneficial for pairs with difficult-to-match donors, as well as difficult-to-match recipients. In this way, each nondirected donor can enable 2 or more transplants with 1 donation.

When nondirected donors participate in KPD, they also mitigate the type O imbalance in incompatible pairs. Nondirected donors are most similar to the general population and therefore 48% of nondirected donors are expected to have blood type O, whereas only about 25% of donors in incompatible pairs are blood type O.[25]

SIMULTANEOUS DONOR NEPHRECTOMY REQUIREMENTS

When possible, all donor operations in a KPD arrangement are started simultaneously. Starting donor operations simultaneously ensures that each donor has the autonomy to withdraw at any time until undergoing anesthesia, without the worry that some intended recipient in the KPD will be left unfairly without a donor. In a handful of instances, donors in nonsimultaneous KPD arrangements have withdrawn consent after their intended recipients underwent transplant.[11,26] However, in some circumstances, the simultaneity restriction has been relaxed. In the Korean experience, donor nephrectomies are not always simultaneous, with some operations subsequently occurring on the same day or in the space of a few days.[26] In one report, some donors donated before the nondirected donor at the nominal head of the chain to accommodate participants' life circumstances.[27] Finally, an extreme example is the nonsimultaneous extended altruistic donor (NEAD) chain, in which a KPD that begins with a nondirected donor is extended over months. The longest reported NEAD chain spanned 10 transplants during 8 months.[18]

Table 2. Distribution of Blood Group Types in Directed Living Kidney Donors and Their Recipients

	Donor O	Donor A	Donor B	Donor AB	Total
Recipient O	45	0	0	0	45
Recipient A	14	24	0	0	38
Recipient B	6	0	7	0	13
Recipient AB	1	1	1	1	4
Total	65	26	8	1	

Note: Values are shown as percentage. Some rows and columns do not sum to total because of rounding.

Data from United Network for Organ Sharing.[20]

In an NEAD chain, a donor for whom there is no compatible recipient available is asked to delay donating until days to months after his or her intended recipient gets a transplant in hopes that during the intervening period, either a new pair with a suitable recipient will have registered with the program or a pair already matched to that donor will become logistically available (in terms of either their life circumstances, medical circumstances, or operating room availability). These waiting donors are referred to as bridge donors. Bridge donors will almost never have blood group type O, unlike the nondirected donors who start NEAD chains.[25] Simulations show that bridge donors often are difficult to match (eg, this group becomes enriched with individuals with type AB) and might compete with opportunities for simultaneous KPD arrangements in incompatible pairs.[25] However, the genuine enthusiasm for this modality springs from the following: (1) the notion that 1 nondirected donor can begin a long cascade of other transplants, and (2) the greater flexibility at both the patient and center level afforded by relaxing the simultaneity requirement. If priority is given to chains, both practice[18] and simulations[25] show that chains will be longer and traditional simultaneous KPD will be used less. NEAD chains also shift the benefit of nondirected donors away from recipients on the deceased donor waiting list in favor of recipients with living donors. If during a long waiting period some of these bridge donors withdraw or become medically ineligible to donate, the bridge donor's potential contribution will be lost. If no bridge donor is ever lost, NEAD chains enable ~3% more transplants than simultaneous domino paired donations that end with a living donor giving to a recipient on the deceased donor waiting list.[24]

COMBINING KPD WITH DESENSITIZATION

The donor in a KPD match need not be strictly compatible with the patient who ultimately receives the kidney.[28] Many recipients are so broadly sensitized that compatible donors will almost never be found for them in any pool of incompatible pairs. Desensitization techniques make it possible to cross both blood group type and/or crossmatch incompatibility barriers in favorable pairings if the recipient cannot find a fully compatible donor.[29,30] Combining desensitization with KPD allows a recipient to find a donor to whom he or she can be more easily desensitized than the intended donor.

To facilitate these matches, centers must characterize the candidate's level of sensitivity to various HLA antigens. One possible way to handle this situation is to have the paired donation registry track at least 2 categories of candidate sensitivities: completely unacceptable antigens, which rule out a match, and somewhat undesirable antigens, which result in a positive crossmatch, but to which the candidate might be desensitized. A small priority point deduction for somewhat undesirable antigens can ensure that compatible matches are prioritized above these desensitization-requiring matches.

LIST PAIRED DONATION

Another variant of KPD is list paired donation, also called living/deceased donor paired exchange, in which a donor who is incompatible with an intended recipient donates to a person on the deceased donor waiting list. In recompense, the intended recipient receives priority for the next available compatible deceased donor kidney.[31] List paired donation rearranges the usual allocation order for deceased donor organs and thus in the United States requires a local allocation variance from UNOS. List paired donation is nonsimultaneous because the living donor donates prospectively. In practice, only unsensitized candidates have been accepted, with the justification that a sensitized candidate might wait for an extended period after the paired donor's gift before a compatible deceased donor organ becomes available.

Unrestricted list paired donation would disproportionately harm type O recipients on the waiting list because donations to the waiting list usually are from non–type O donors. This is particularly controversial because type O recipients already have the longest waiting times. In a report from New England, 16 of 17 list paired donations matched a non–type O living donor with a type O deceased donor; in other words, deceased donor organs that in a traditional manner would have been donated to the type O waiting list were "lost" to list paired donation, and instead, 16 patients from non–type O waiting lists received living donor organs.[31] Some have proposed restricting list paired donation to non–type O recipients to eliminate this ethical concern.[32,33] However, type O recipients are the only group for which the drawbacks of list paired donation are outweighed by a greater probability of transplant. If list paired donation is restricted to non–type O recipients and KPD from a living donor is preferred when both options are available, only ~4% of incompatible pairs will be candidates for list paired donation.[7]

GEOGRAPHIC BARRIERS

KPD is a modality that demands scale and thus is influenced by geography. It has been reported that match rates for incompatible pairs increase with the size of the population in a KPD registry.[5,6,12,22] The very smallest pools of fewer than 15 incompatible pairs frequently contain no matching pairs at all,

whereas a nationwide pool in the United States is predicted to afford a 47% match rate.[5]

Two early examples of countries with broadly successful KPD registries are South Korea, where donor exchanges began in 1991,[11] and the Netherlands, which established a national registry in 2003. These countries have nearly identical population densities of about 1,270 people per square mile,[34] and donor travel to the actual recipient's transplant center has not been described as a significant impediment in either country.[19]

In the United States, which has a large population, but a much lower average population density of 88 people per square mile, increasing the number of KPD transplants requires searching for matching pairs across a significant geographic range. Of the 186 KPD transplants in the United States through April 2007, a total of 44% involved a match between pairs from different states and 31% involved a match between pairs from different UNOS regions.[14] Canada has twice the population of the Netherlands, but fewer than 10 people per square mile; thus, many matches in its new (2009) Living Donor Paired Exchange registry will be made across long distances.[35]

In the earliest paired donations involving more than 1 transplant center, each donor travelled to the center at which his or her kidney would be transplanted. In a large country like the United States, travel imposes financial and personal burdens on the donor, separates the donor (who often is a relative, spouse, or close friend) from the recipient by possibly thousands of miles, and may be a major hindrance to otherwise beneficial matches. In 2007, a retrospective cohort study showed that recipients of live donor kidney transplants with 2-8 hours of cold ischemia time did not have worse transplant function, decreased transplant survival, or increased rates of acute rejection compared with transplants with less than 2 hours of cold ischemia time.[36] Shortly thereafter, in the setting of a KPD, the first living donor kidney transplant with cross-country organ transport was performed.[37] A rare compatible donor for a very highly sensitized recipient at Johns Hopkins had been identified in the pairs registered for KPD at California Pacific Medical Center as part of a 3-way transplant involving 2 California-based pairs and the Hopkins pair. However, the key pair in California preferred a different match that did not require the donor to travel. Rather than give up the opportunity of a transplant, the Hopkins recipient accepted an arrangement in which the transplant was recovered in California, flown to Hopkins, and transplanted with 8 hours of cold ischemia time. Transplant function was immediate and results were excellent. Since then, other transplant centers have begun to transport kidneys to the recipient centers instead of requiring donor travel. More than 50 kidney transplants have been performed using transported living donor transplants.[38]

LEGAL BARRIERS

Legal barriers to KPD exist in many countries, particularly when the legislation surrounding living donation predates awareness of the possibility of this modality. In the United Kingdom, living donation had been permissible only if the donor was genetically related to or had a strong emotional relationship with the recipient. By 2006, the United Kingdom had legalized both paired donation and nondirected donation.[12]

Initially, legal barriers also significantly delayed implementation of a unified national KPD program in the United States, even as several independent paired donation registries began operation in the country. The National Organ Transplantation Act of 1984 (NOTA) states that it is illegal to transfer a human organ for "valuable consideration."[39] Cautiously, UNOS shelved its 2004 proposal[40] to create a national KPD registry. Uncertainty about whether KPD constituted valuable consideration persisted until the US Congress passed legislation explicitly exempting KPD from NOTA in 2007.[41] At present, UNOS is piloting its national KPD program with the support and participation of many of the active regional programs in the country.

LIVING DONOR SAFETY

KPD programs aim to increase living donation by removing the impediment of incompatibility. Concerns about the safety of living donation might deter potential participants, but accumulating evidence suggests the short- and long-term safety of living donation. A recent study of more than 80,000 living kidney donors between 1994 and 2009 identified matched controls who were not living donors to eliminate confounders, such as the general good health of acceptable donors. This study showed no increased mortality in donors after the perioperative period.[42] Other research has suggested that living kidney donors do not have an increased risk of end-stage renal disease or hypertension.[43]

FRAGMENTED REGISTRIES

Despite inventive work by clinicians and researchers, KPD remains greatly underused in the United States. For example, the Dutch national KPD program facilitated 128 transplants in its first 5 years from a small population.[19] Scaling that success to the United States would predict nearly 3,000 transplants, but only a few hundred have occurred.[14] The small and fragmented

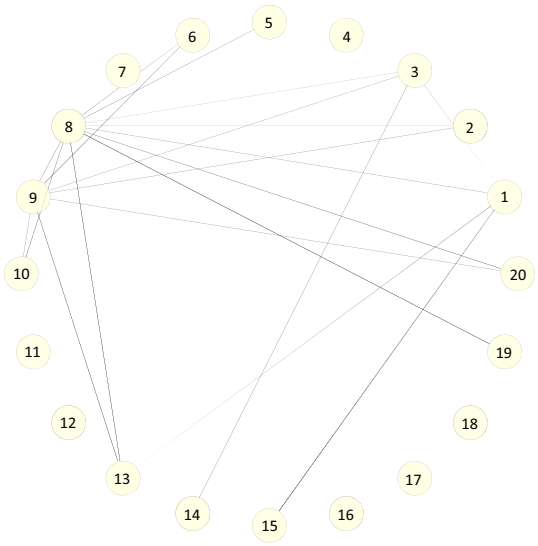

Figure 2. Schematic of incompatible pairs and reciprocal compatibility shows 2-way paired donation possibilities. Each numbered circle represents a transplant candidate/incompatible donor pair. A connecting line is shown if the donor from each pair can donate to the candidate of the other pair.

registries that exist have done important formative work and established a record of successful paired donations, but broad participation in a nationwide registry would result in a higher matching rate and more transplants. A national registry under the aegis of UNOS is well underway. After approval by the UNOS board, 4 coordinating centers were chosen to participate in this pilot phase, and the registry created its first matches in October 2010.

A number of transplant centers in the United States maintain KPD registries. However, the success or stagnation of a registry depends on match opportunities, which are related to the volume of incompatible pairs; the more pairs available, the greater the proportion of pairs that will find a match.[5] The Alliance for Paired Donation (Toledo, OH), the New England Program for Kidney Exchange (Boston, MA), the Johns Hopkins Incompatible Kidney Program (Baltimore, MD), the National Kidney Registry (New York, NY), and the Paired Donation Network (Covington, KY) are examples of consortia that pool incompatible pairs from various transplant centers to enable more pairs to find match opportunities. Greater public awareness of this modality also should translate to greater numbers of pairs registered and therefore greater benefits to all participants because most donors who are incompatible with their intended recipients are willing to participate in KPD.[44]

MATCHING ALGORITHMS

Generating a set of KPD matches from a list of recipients and their incompatible donors requires an algorithm for deciding among conflicting potential matches. The best algorithms, known as optimization algorithms, guarantee that no better set of matches could have been found.[5] Figure 2 shows a pool of incompatible pairs appearing as numbered circles, with potential 2-way KPDs shown as lines connecting them, and Fig 3 shows a selection of matches with lines in bold type that maximizes the number of transplants. Depending on the priorities of the program, a better set of matches might be one in which more recipients underwent transplant or, alternatively, one in which the same number of recipients were matched, but with more highly sensitized recipients. Correct optimization algorithms for KPD are mathematically intricate, usually involving either graph theoretical or integer programming techniques. Intuitively appealing simple algorithms, such as choosing transplants in order of some desirability score, are not optimization algorithms and are provably inferior.

Varied as the arrangements can be, from domino paired donations to list exchanges to 3-way paired donations requiring desensitization, it is essential that an optimization algorithm consider all these variants simultaneously to find the best set of matches.[24] Every decision in a KPD pool potentially interacts with every other decision; thus, making decisions in a sequence instead of using a comprehensive process might yield a suboptimal outcome. Fewer transplants might be possible if, for example, one first chooses a set of matches among incompatible pairs and then

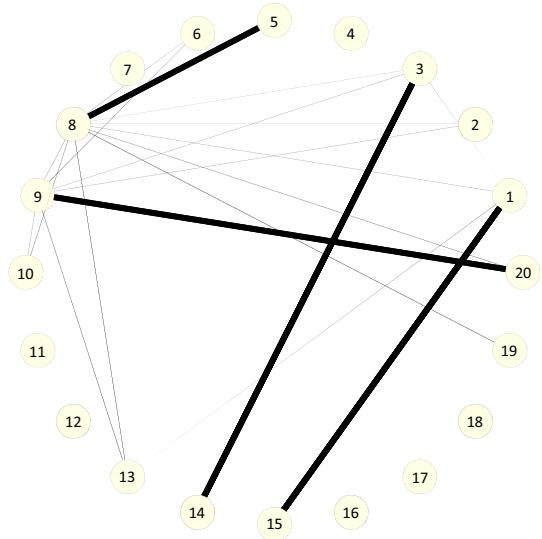

Figure 3. Optimal matching. The bold lines denote optimal matching of incompatible pairs for 2-way paired donations; for example, pair 1 matches with pair 15. Using an appropriate mathematical algorithm guarantees that the largest number of transplants or best set of transplants using some other criterion will be chosen. For instance, if incompatible pair 1 and incompatible pair 3 were matched for paired donation, neither pair 14 nor pair 15 could undergo transplant.

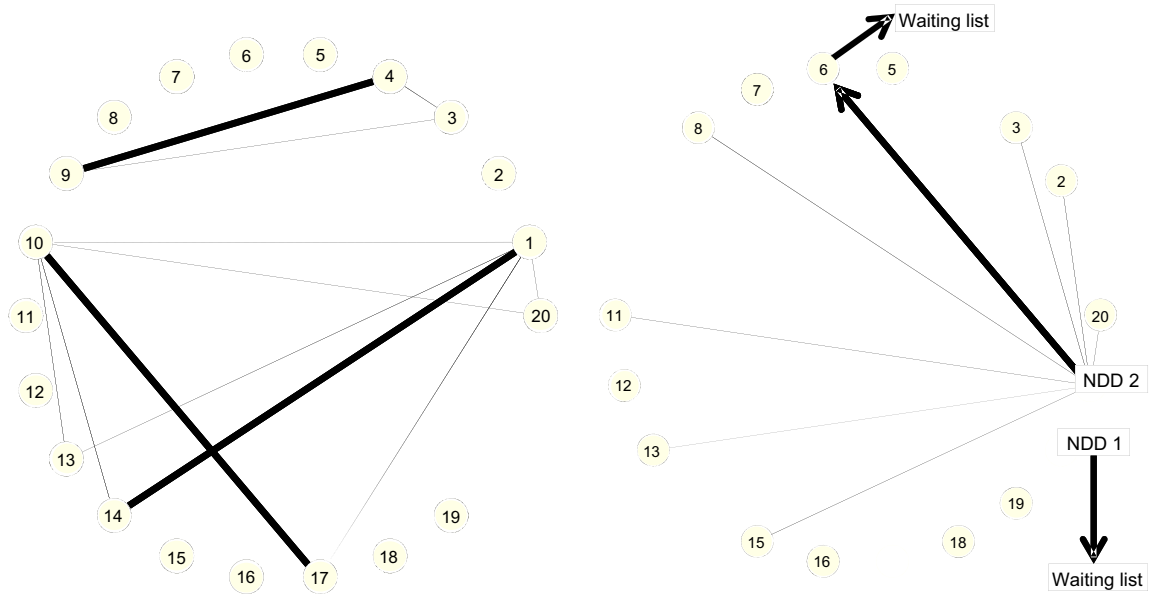

Figure 4. (Left) Optimized 2-way kidney paired donation followed by (right) domino paired donation yields only 9 transplants (bold lines), with 6 transplants from paired donation and 3 transplants from domino paired donation. Note that living nondirected donor (NDD) 1 could have participated in a domino paired donation with either pair 4 or pair 9 (see Fig 5), but cannot participate because pairs 4 and 9 were matched for paired donation before domino paired donations were considered.

considers the remaining pairs for domino paired donation (Fig 4), compared with the comprehensive alternative of finding the best set of matches including all nondirected donors and all incompatible pairs (Fig 5).

SUMMARY

Many restrictions that appeared to limit the usefulness of KPD have been resolved by innovations that extend geographic reach, include more types of participants, relax reciprocity and simultaneity requirements, and use improved matching algorithms. This exciting modality promises to significantly increase living kidney donation as patients and physicians become more familiar with it and institutions such as UNOS establish comprehensive paired donation registries. KPD empowers people who want to become living donors by circumventing incompatibilities that might otherwise prevent them from donating.

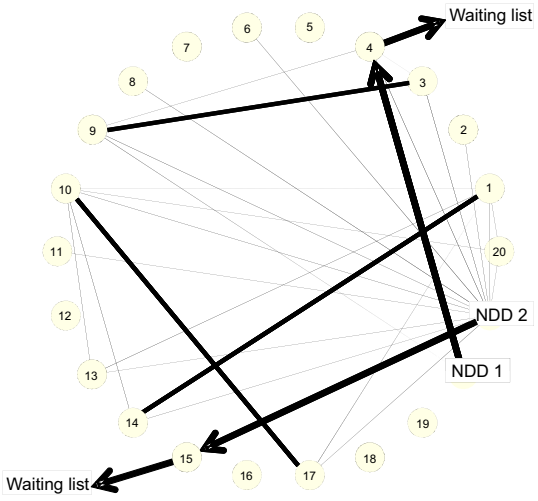

Figure 5. Optimized domino paired donation, in which all pairs (circles) and living nondirected donors (NDDs; squares) are considered simultaneously, yields 6 transplants from paired donation and 4 transplants from domino paired donation for a total of 10 transplants.

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