Chapter 2
Kidney Paired Donation Programs for Incompatible Living Kidney Donors and Recipients

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Rationale

About one-third of people who offer to donate a kidney will be either blood type incompatible or human leukocyte antigen (HLA) incompatible with their intended recipient. Kidney paired donation (KPD), or kidney exchange, circumvents the incompatibility between donor and intended recipient by redistributing organs among two or more donors before the transplants [1]. In the simplest type of KPD, two donors exchange kidneys so that their two candidates can each receive a compatible transplant (Fig. 2.1). The donor operations are usually started simultaneously, to prevent the situation in which one donor decides not to donate after that donor's intended recipient has already received a kidney.

Many extensions to this concept, such as three-way and larger exchanges, compatible paired donation, and use of nondirected (altruistic) donors, have allowed greater numbers of people to find matches. KPD is the fastest-growing modality of living donation in the U.S., growing from just a handful of transplants in 2000 to

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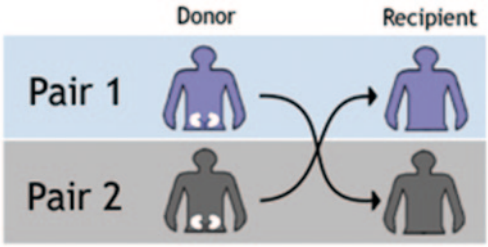

Fig. 2.1 A two-way kidney paired donation. The donor in *blue* is not compatible with his or her intended recipient, and the donor in *gray* is not compatible with his or her intended recipient, but, through KPD, both recipients can be transplanted

surpass 500 transplants per year in 2010 [2]. Kidney exchange accounted for nearly 10% of living kidney transplants in 2011.

History

KPD was first suggested in the literature by Rapaport in 1986 [3], but some observers argued that this modality would help only a small number of people [4]. The earliest functioning exchange programs may have been those in Korea that accomplished more than 100 transplants by 1997 [5]. In the U.S., single-center programs were performing KPD at a low rate until 2005, when a national consensus conference was held to discuss the possibility of larger registries that would combine incompatible pairs from many transplant centers to find more matches. Because the National Organ Transplantation Act of 1984 forbade acquiring or transferring a kidney for valuable consideration, members of the transplant community pressed the US Congress to pass the Charlie W. Norwood Living Organ Donation Act of 2007 clarifying that kidney exchange was legal. The current landscape for KPD in the U.S. includes several single-center programs [6], multicenter consortia [7–9], and a registry operated by the organization that administers deceased donation in the U.S., the United Network for Organ Sharing. Recently, a second consensus conference produced detailed recommendations for developing KPD in the U.S. [10].

Mathematical and Computational Considerations

Once a paired donation program exceeds about 10 or 20 pairs, it requires a nontrivial mathematical optimization to find the combination of matches that achieves the greatest number and the most optimal transplants. Two possible combinations of matches for the same ten pairs are shown in Figs. 2.2a and b. Each small numbered circle represents two people: a kidney transplant candidate and his incompatible donor. The lines that connect some of the circles show cases in which a paired exchange is possible; that is, if a line connects two circles, then the donor of each pair

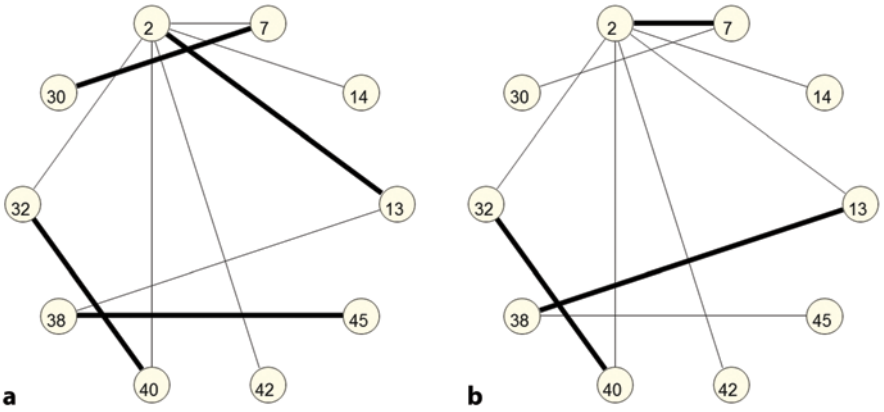

Fig. 2.2 **a** One possible combination of two-way KPD matches is shown with *dark lines*, representing eight transplants among ten incompatible pairs. Each small arbitrarily numbered *circle* represents two people: a kidney transplant candidate and his incompatible donor. The *lines* that connect some of the *circles* show which two-way KPD matches are possible. If a *line* connects two *circles*, then the donor of each pair is compatible with the recipient of the other pair. **b** A different combination of two-way KPD matches is shown in the *dark lines*, representing six transplants among the same ten incompatible pairs as in (**a**). There are no feasible KPD matches for the remaining four incompatible pairs

is compatible with the recipient of the other pair. Sophisticated mathematical algorithms are required, in general, to find the optimal matching in Fig. 2.2a, in which the dark lines show how four exchanges could result in transplantation for eight of these ten participants. All of the decisions in any paired exchange registry affect the opportunities for other pairs in the group. For instance, after performing the three exchanges shown in Fig. 2.2b, only six people out of these same ten have been transplanted, and there is no way to find compatible transplants for the remaining four.

Many considerations besides the absolute number of transplants are important in choosing which incompatible pairs should be matched with more optimal donors and candidates. Matches that involve pediatric candidates, highly sensitized candidates, or matches in the same transplant center are preferred, as are matches for the pairs that have been waiting the longest. KPD registries generally use optimization methods like integer programming to maximize the benefit afforded to all pairs in the registry.

These static optimization methods require all donors and recipients to wait for some period of time before any matches are made, or else the entire advantage will be lost. KPD registries that do not wait for 25–100 registrants to accumulate between matches are predicted to achieve about 10–20 % fewer transplants than would otherwise be possible [11]. Competition among multiple registries might predictably lead to just this outcome, in which the drive to make matches earlier means fewer matches overall. A more advanced mathematical technology called dynamic optimization could alleviate this trade-off, but these methods for KPD matching are still being developed [12, 13].

An expanded definition of KPD would include exchanges among three or more pairs. The donor of one pair gives the recipient of the next pair, whose donor gives to the recipient of the next pair, and so on, until the last pair's donor gives to the recipient of the first pair in the cycle. Moving to three-way or larger exchanges significantly increases the likelihood that any pair will find a match.

Desensitization protocols using high-dose intravenous immunoglobulin (IVIg) or plasmapheresis and low-dose IVIg have enabled successful transplants against either human leukocyte antigen (HLA) or blood type incompatibilities. Thus, desensitization might be viewed as an alternative to KPD. However, some incompatible pairs can only be transplanted through a combination of desensitization and KPD. This situation arises when a transplant candidate has very high donor-specific antibody levels against the intended donor, but the candidate has a lower level of donor-specific antibody for some other donor in the exchange pool. To offer one example, more than half of all KPD recipients in the Johns Hopkins Hospital Incompatible Kidney Transplant program have required desensitization.

One complicating factor in all paired donation registries is imperfect prior information about exactly which donors are compatible with which candidates. Even with proper histocompatibility testing, which includes donor and recipient HLA typing and recipient antibody testing to identify unacceptable antigens, unexpected positive crossmatches will occur. An unexpected positive crossmatch will cancel all of the transplants in a planned kidney exchange. These unexpected positive crossmatches are very disruptive to the operations of a KPD registry, causing delays and disappointment for enrolled incompatible pairs. Strict standards for histocompatibility laboratories might mitigate this difficulty. Histocompatibility experts play a vital role in managing KPD, especially for centers that combine KPD with desensitization.

Blood Type Distribution and the Role of Compatible Pairs

Because a selection bias skews blood types among incompatible pairs, the pairs who have overrepresented blood types will find it difficult to match to a complementary pair. For example, the population of incompatible pairs will be enriched for O blood type recipients because O recipients are blood type incompatible with all A, B, and AB donors. On the other hand, pairs with O blood type donors would only seek KPD in the comparatively rare circumstance that the donors were HLA incompatible with their intended recipients. The 28% of incompatible pair donors who have O blood type will not be sufficient to match the 59% of incompatible pair recipients who have O blood type [14]. Simulation studies suggest that O blood type recipients with non-O donors and all recipients with AB donors will wait longer and match at lower rates [15].

If donors who are compatible with their intended recipients also participated in KPD, the blood type imbalance could be corrected and twice as many incompatible pairs would find a match [16]. Compatible pairs might join a kidney exchange pool to find a donor who is a better size match, HLA match, or age match for the intended

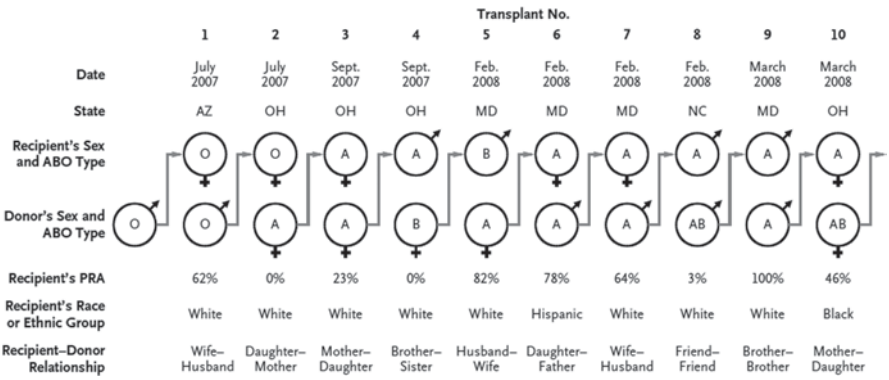

Fig. 2.3 A nonsimultaneous extended altruistic donor chain, initiated by a nondirected donor from Michigan. The recipients of transplants 6 and 9 required desensitization in conjunction with donor exchange. (From Rees et al. [19], Copyright © 2009, Massachusetts Medical Society. Reprinted with permission)

recipient; recent evidence supports this practice, particularly in the case of older living donors [17]. Compatible pairs also might offer to participate in kidney exchange out of an altruistic desire to help candidates with incompatible donors. The largest single-center KPD program in the U.S., at Methodist Specialty and Transplant Hospital in San Antonio, makes extensive use of compatible pairs and 35% of its transplant volume is paired donation [6].

Role of Nondirected Donors

Nondirected donors, or altruistic donors, are people who volunteer to donate a kidney without naming any intended recipient. After appropriate screening and counseling, a nondirected donor might give to a candidate on the deceased donor waiting list. Alternatively, a nondirected donor might give to the recipient of an incompatible pair, and the incompatible donor's kidney can go to another pair, and so on, thereby multiplying the gift of the nondirected donation. Figure 2.3 illustrates one such chain. A consensus conference recently urged that all nondirected donors be informed about KPD and their potential to trigger multiple transplants through these programs [10].

Nondirected donors are especially empowered to enable transplants for incompatible pairs. In many operating KPD programs, a majority of the transplants are accomplished in exchanges started by nondirected donors [18]. This is true both because of a favorable blood type distribution among nondirected donors, with 48% of nondirected donors having O blood type, and because nondirected donors relax the reciprocality requirement that otherwise constrains the last donor to match the intended recipient of an initiating pair. Further, kidney exchanges that start with a nondirected donor can relax the restriction of simultaneity.

At the end of a chain of transplants initiated by a nondirected donor, the donor of the last pair might donate a kidney to a candidate on the deceased donor waiting list, or might be asked to wait a few months as a bridge donor. The bridge donor delays his donation so that he or she can serve as the starting donor for another chain of transplants after new incompatible pairs join the program. A chain that is always continued with a bridge donor after a delay is called a nonsimultaneous extended altruistic donor (NEAD) chain [19]. A chain of donations started by a nondirected donor that ends with a donation to a deceased donor waiting list candidate is called a domino paired donation [20]. A simultaneous domino paired donation ends immediately with a donation to the waiting list; a nonsimultaneous domino paired donation incorporates one or more bridge donors who extend the domino through time until it ultimately ends with a donation to the waiting list.

When the donations are performed in succession starting with a nondirected donor, there is less risk associated with nonsimultaneous operations. Because none of the donor operations in the chain occurs before the intended recipient of that donor has received a transplant, there is no way for a candidate to remain untransplanted after his bargaining chip, his intended donor, has already given a kidney. If a bridge donor decides not to donate, then the incompatible pairs farther down the chain can be matched into a different KPD arrangement, because every candidate still has his incompatible donor. This observation holds only for operations performed in the natural sequence. At least one group has reported performing a successful out-of-sequence nonsimultaneous chain [21].

In theory, each nondirected donor could begin a very long NEAD chain of donations extending over time. In practice, the bridge donors become increasingly difficult to match to the next recipient. In fact, the reason someone is designated as a bridge donor is usually that he or she does not match any of the recipients presently in the incompatible pairs registry. Transplant 9 in Fig. 2.3, for example, required desensitization across a blood type barrier to use an AB blood type donor, and the sequence of transplants halted again at an AB blood type donor after transplant 10. It might be the case that bridge donors who are difficult to match and who have to wait longer are more likely never to donate in the long run. Every KPD registry using bridge donors that we are aware of has had at least one bridge donor who ultimately did not donate.

It is not entirely clear whether extending all NEAD chains indefinitely, or ending domino paired donations with the deceased donor waiting list, will yield a larger number of transplants [22, 23]. The preferred strategy depends on the precise characteristics of the incompatible pairs, the relative prevalence of nondirected donors, and the probability of bridge donor withdrawal. The usual practice in registries that use bridge donors is to ask the bridge donor to donate to someone on the deceased donor waiting list if no opportunity has been found for that donor to match an incompatible pair candidate within some reasonable span of time.

Ethical concerns about nondirected donors in KPD include fears of coercion for bridge donors who promise to donate later, and the permanent diversion of transplants from nondirected donors away from the deceased donor waiting list in NEAD chains [24].

Donor Travel Versus Living Donor Kidney Transport

Long-distance kidney exchanges between pairs who live hundreds or thousands of miles apart are becoming more frequent in the era of large multicenter paired donation registries. A recent study found that 44 % of matches involved transplant centers in different states [2]. In the earliest days, physicians worried about degrading the performance of living donor kidneys by delaying the transplants to allow transportation time. Thus, physicians would ask donors in a paired transplant to travel to the hospital where the other pair's candidate would receive his transplant.

However, a retrospective review of transplant registry data showed that moderately prolonged cold ischemia times had no impact on long-term outcomes for live donor kidney transplant [25]. In the first long-distance transport of a live donor kidney that we are aware of, surgeons transported a kidney by charter jet from San Francisco, California, to Baltimore, Maryland [26]. Later, a series of 56 transported live donor kidneys was reported with cold ischemia times up to 14.5 h, and with no incidence of delayed graft function [27]. Today, the majority of kidney exchanges among multiple transplant centers in the U.S. are accomplished by shipping the kidneys rather than by requiring donors to travel.

Donor Education and Other Considerations

All potential living donors should be advised of the possibility of KPD early in the counseling process, even before tests of compatibility are completed. Potential donors should have time to consider their preferences regarding donor exchange, to prevent feelings of coercion if KPD is only mentioned after a finding of incompatibility [10].

Donors considering KPD should receive the standard counseling offered to all living donors, but should additionally be informed of the unique aspects of multicenter KPD registries [10]. When joining a paired donation registry, donors and their intended recipients should know that delays in finding a paired exchange opportunity are common. If a provisional match for paired donation arises, there are many reasons that it might not culminate in an exchange transplant, including logistical, medical, or compatibility contraindications that could not have been anticipated. Each donor should know that details of his or her medical history and health status, but not his or her identity, likely need to be disclosed to potential matching candidates and those candidates' care providers.

The donor consent process for KPD should cover the risks of kidney transport, the possibility of last-minute cancellations, and the potential for redirecting the kidney to another recipient under rare circumstances.

In kidney exchanges, donor and recipient pairs are kept anonymous to the other people involved in the exchange, at least until the transplants are completed. After

that, donors and recipients often arrange to meet each other, or keep each other informed of their health status, by mutual consent. In some cases, donors involved in paired exchanges might never learn of the outcome for the person who received their organ. Alternatively, if exchange partners decide to share information and if any recipient in a kidney exchange has an unfavorable outcome, it could have an adverse psychological impact on donors.

Financing KPD

KPD, particularly between different transplant centers, presents novel challenges for administrators and payers [28]. Every exchange transplant necessitates individual financial negotiations and contracts, which might or might not align with the guidelines for recipient payers. Many prospective donors who require workups before they can be entered into KPD registries will not actually donate. There may be additional costs for organ transport or donor travel, as well as out-of-network pricing for the donor operations. There are also costs, which are not directly related to the number of transplants performed, for the administrative and logistical coordination of a multicenter paired donation registry. There is an effort under way to establish a national KPD standard acquisition charge (SAC), which would accumulate all costs associated with evaluating KPD donors and possibly donor-related professional fees [29].

International Programs

Many other countries have established KPD programs, which can vary substantially from the US-centric description of kidney exchange presented in this chapter. For instance, in Germany anonymous donation is strictly forbidden; therefore, the exchange donors always meet their paired recipients prior to the transplants [30]. In geographically compact Netherlands, rather than transporting the organs after recovery, as in the U.S., donors in a paired exchange always travel to the transplant center of their actual recipient [31]. In Canada, some regulatory difficulties have stalled the widespread use of live donor kidney transports.

Some of the earliest kidney exchanges occurred in Korean transplant programs, as well as the first known report of a donor hesitating to donate after his intended recipient had received a kidney transplant [5]. In those early days, researchers also had to address concerns that allografts from unrelated donors might not perform as well as those from related donors [32]. With local variations that derive from differing laws or differing transplant practices, KPD programs are flourishing in many countries: Canada, Korea, the UK, Romania, India, the Netherlands, and Australia. A kidney exchange between two countries has even been reported [33].

Conclusion

Paired donation offers many donors a path to helping a loved one receive a kidney transplant, and is the fastest-growing arena of living donation. As exciting as the numbers are, studies suggest that KPD has room to grow. There are still some transplant centers where kidney transplant candidates who present with an incompatible living donor do not have access to a KPD registry. At other centers, there may be transplant candidates who have been on the deceased donor waiting list for some time who know about a potential living incompatible donor, but have not been enrolled for KPD. If all US transplant centers were as active in promoting and pursuing kidney exchanges as the highest-performing centers, researchers estimate that an additional 1,000 kidney transplants could be achieved every year [34].

This modality is incredibly promising, and many groups working in KPD are at the forefront of clinical innovation to eliminate histocompatibility, transport, logistical, and mathematical barriers to performing more transplants. To reduce the number of provisional matches refused for compatibility or donor criteria, many registries have employed a preselection step for transplant centers to specify which of the potential donors are acceptable for each candidate. Coordination of HLA laboratories is also important, and was responsible for decreasing the unexpected positive crossmatch rate from 57 to 9% in one registry [8]. Cryobanking of preserved donor lymphocytes might enable prescreening of crossmatch compatibility for highly sensitized candidates.

There are a dozen or more different KPD registries operating in the U.S., and many incompatible pairs are enrolled in more than one of these registries. This can lead to disappointment if a pair starts to move forward with an exchange opportunity available through one program while another program tries to match that same pair to a conflicting arrangement. Further, the highest proportion of incompatible pairs find a transplant when exchanges are considered among the largest possible group of exchange partners [11]. That is, if the same 1,000 incompatible pairs are all enrolled in the same registry, then more transplants will be possible than if 500 pairs join one registry and the other 500 join a separate registry. As this emerging field matures, candidates with incompatible donors would gain the most benefit from a unified KPD registry in the U.S. [10].

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