

# Controversies in Kidney Paired Donation

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Kidney paired donation represented 10% of living kidney donation in the United States in 2011. National registries around the world and several separate registries in the United States arrange paired donations, although with significant variations in their practices. Concerns about ethical considerations, clinical advisability, and the quantitative effectiveness of these approaches in paired donation result in these variations. For instance, although donor travel can be burdensome and might discourage paired donation, it was nearly universal until convincing analysis showed that living donor kidneys can sustain many hours of cold ischemia time without adverse consequences. Opinions also differ about whether the last donor in a chain of paired donation transplants initiated by a nondirected donor should donate immediately to someone on the deceased donor wait-list (a domino or closed chain) or should be asked to wait some length of time and donate to start another sequence of paired donations later (an open chain); some argue that asking the donor to donate later may be coercive, and others focus on balancing the probability that the waiting donor withdraws versus the number of additional transplants if the chain can be continued. Other controversies in paired donation include simultaneous versus nonsimultaneous donor operations, whether to enroll compatible pairs, and interactions with desensitization protocols. Efforts to expand public awareness of and participation in paired donation are needed to generate more transplant opportunities.

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Many kidney transplant candidates who have identified incompatible living donors can find opportunities to exchange donors and obtain compatible transplants through kidney paired donation (KPD).<sup>1</sup> KPD has enabled thousands of kidney transplants internationally, including more than 2000 in the United States according to data from the Organ Procurement and Transplantation Network. In 2011, KPD accounted for nearly 10% of all living donor kidney transplants.<sup>2</sup> Certain categories of pairs, such as candidates with blood group O donors or unsensitized candidates with blood group incompatible donors, are more likely than others to be matched in KPD.<sup>3</sup> Based on Organ Procurement and Transplantation Network data, fewer KPD recipients are blood group O (39% vs 45%) and more are blood group B (20% vs 13%), compared with recipients of other live donor kidneys.

The United States has a government-organized registry run by the United Network for Organ Sharing (UNOS), and also a number of other single-center and multi-center KPD registries. The Alliance for Paired Donation,<sup>4</sup> the National Kidney Registry,<sup>5</sup> the New England Paired Kidney Exchange,<sup>6</sup> and the Johns Hopkins Hospital consortium are a few of the multicenter registries; the Methodist Hospital in San Antonio<sup>7</sup> runs a single-center registry. The Netherlands,<sup>8</sup> Canada, the United Kingdom,<sup>9</sup> and South Korea,<sup>10</sup> each have a unified KPD registry operating.

Among these many KPD registries, some approaches have been common to all, but some aspects of KPD have been handled differently in different systems. In this article, we describe a handful of these controversies or divergences within KPD: In matches involving two or more hospitals, should kidneys be transported or should donors (and/or recipients) travel? Must all transplants (or at least donor nephrectomies) in a KPD exchange occur simultaneously? What characteristics

should be prioritized in determining matches? What matching approaches best facilitate KPDs? Should nondirected (altruistic) donor chains be arranged as closed chains (ending with a donation to a candidate on the deceased donor waiting list) or open chains (ending with a bridge donor who waits some length of time before being asked to donate)?

## Transporting Kidneys Versus Donor Travel

When a KPD involves two or more different transplant centers, then either the donor must travel to the hospital of his/her matched recipient, or the recipient must travel to the hospital of his/her matched donor, or kidneys may be transported after being recovered at the donor's home center. Donor travel imposes both financial and personal burdens. The donor will undergo an operation by an unfamiliar surgical team and might either have to travel for follow-up care or be followed up by a different team. Multiple visits to the out-of-town transplant center might be required. In the United States, travel costs can be covered by the National Living Donor Assistance Center if they would constitute undue hardship. The donor might be separated from his intended recipient, and possibly his family and friends, at the time of the operations. The primary motivation of donor travel is minimizing

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cold ischemia time (CIT) and keeping the recovery and transplantation of the organ within the same center. In the Netherlands, where no two transplant centers are more than a few hours journey apart, donors always travel to the recipient center.<sup>8</sup>

The benefits of transporting organs rather than patients include continuity of donor care and minimizing the costs and disruption to the donor. Although longer CIT impacts outcomes of deceased-donor transplants, a 2007 retrospective study showed that in live-donor kidney transplants, CIT up to 8 hours was not associated with any adverse outcomes.<sup>11</sup> In April 2007, a kidney was transported from San Francisco to Baltimore because the transport was the only way to facilitate a transplant for a difficult-to-match candidate with a 96% PRA.<sup>12</sup> Since then, many more centers have transported donor organs, and the first national report of 56 live-donor kidneys transported between 30 centers with median CIT of 7.2 hours showed excellent early function with no instances of delayed graft function.<sup>13</sup>

## Desensitization and KPD

Desensitization is one alternative modality for candidates who have a living incompatible donor. Candidates with low-titer antibodies (<8 AHG CDC cytotoxic cross-match)<sup>14</sup> or ABO incompatibility<sup>15</sup> can often undergo successful desensitization and receive an incompatible directed donation. As such, transplant center that performs both desensitization and KPD could conceivably use one or the other approach to getting the candidate transplanted. Although these seem like competing modalities, in fact each modality is better suited to pairs of certain phenotypes, and some pairs even benefit from a combined approach.

Each incompatible pair can be characterized as either easy or hard to match: a pair is easy to match, for example, if the donor is O or the candidate is AB and is not broadly sensitized; a pair is hard to match if the donor is non-O and the candidate is O, or if the candidate is broadly sensitized (represented by a high PRA). Likewise, each incompatible pair can be characterized as either easy or hard to desensitize: a pair is easy to desensitize if they only require crossing an ABO barrier<sup>16,17</sup> or if the candidate has only low-titer donor-specific HLA antibody.<sup>14</sup> If a pair is easy to desensitize and hard to match, then the desensitization route makes more sense than extended waiting (and risk on dialysis) for a compatible

exchange. If a pair is hard to desensitize but easy to match, then that pair should wait until a suitable KPD opportunity arises, rather than undergoing a transplant with worse predicted outcomes.

For incompatible pairs that are both hard to match and hard to desensitize, combining the two approaches is likely the best path to a transplant<sup>18</sup>; these pairs seek, through KPD, not a perfectly compatible donor, but rather a donor against whom the candidate can be more easily desensitized.<sup>19</sup> This approach was first reported in 2005<sup>20</sup> and is now a common practice. Some question whether too many unexpected positive crossmatches will result at centers choosing this approach. In traditional KPD, sensitized patients report all *unacceptable antigens*, that is, antigens to which the candidate would be expected to mount an antibody-mediated response; when identifying matches, potential donors expressing these unacceptable antigens will not be matched to the candidate. However, when combining KPD with desensitization,

some of these unacceptable antigens (particularly those to which the candidate expresses only low-strength antibody) are purposefully not reported, with the anticipation that the candidate could be successfully desensitized against these antigens. Concerns have been expressed that including candidates with planned desensitization routes will increase the number of scuttled matches if the desensitization is not successful or if too many low-titer antibodies must be simultaneously overcome,<sup>21</sup> al-

though it is likely that centers with experience in characterizing antibodies and predicting antibody response will be much less at risk for these problems. Certainly, in our center, where the incompatible pool awaiting KPD is dominated by highly sensitized, hard-to-match pairs, the combination of KPD and desensitization has been the mainstay of successful transplantation for our patients.

## Compatible Pairs

Among incompatible pairs, about 30% of the donors are blood type O, whereas more than 60% of the candidates are blood type O.<sup>22</sup> This imbalance means that many incompatible pairs will never match in a KPD pool that includes only incompatible pairs and seeks compatible transplants. Including compatible pairs in a KPD pool would have a huge impact on this blood group O

### CLINICAL SUMMARY

- Kidney paired donation has increased living donor kidney transplantation and has the potential to facilitate even greater numbers of transplants.
- Transporting live donor kidneys for paired donation has become routine, with no reported adverse consequences from the resulting cold ischemia time.
- Including compatible pairs, and allowing some candidates to match to an incompatible donor against whom the candidate can be desensitized, will increase paired donation opportunities.
- Chains of transplants initiated by a nondirected donor can be extended, but not indefinitely, and so should end with donation to the deceased donor waiting list when further paired transplants are unlikely.

shortage and increase the match rate for pairs with O candidates and non-O donors from 27% to 71%.<sup>22</sup> In a single-center program that encourages compatible pair participation, more than one-third of the center's living kidney transplants are KPD transplants, a success rate that would imply more than 2000 KPDs annually if adopted nationwide.<sup>7</sup>

Although compatible pairs might participate in KPD out of purely altruistic motives, they are also quite likely to obtain a better kidney through this process. Compatible pairs might find a zero-HLA-mismatch donor (which would be very rare), might avoid repeat mismatches, or—most frequently—might find a substantially younger donor. Ethical concerns of asking compatible pairs to participate in KPD have been raised because the process might cause unnecessary delays, worry, or complexity for the compatible pair. Although there is clear evidence for the superiority of younger living donors compared with donors aged >70 years,<sup>23</sup> there is often no clinical rationale for preferring one donor over another when the age difference between the donors is less than a decade.

### Simultaneous Versus Nonsimultaneous Exchanges

Simultaneously performing all the donor operations of a KPD guarantees that no donor will change his/her mind about donating a kidney after other components of the exchange have occurred.<sup>24</sup> Conversely, in a nonsimultaneous exchange, if a donor withdraws consent after an exchange among incompatible pairs has begun, then one candidate will be left without a transplant after his/her donor has donated. This disastrous event did occur at least once in the Korean experience.<sup>10</sup> Simultaneous donor operations also protect donors from feeling coerced to donate because an exchange is already underway.

The drawbacks of simultaneous donor operations are primarily logistical. If multiple donor organs are being recovered in one center, then simultaneous donor operations might present logistical hurdles when surgeons or operating rooms are in short supply. In another instance, the imperative of accommodating donor time preference resulted in out-of-sequence and nonsimultaneous operations.<sup>25</sup>

Some argue that for chain KPDs, those that begin with a nondirected donor and continue with a chain of incompatible pairs, simultaneity is not strictly required to protect the participants. If the chain transplant operations are performed in sequence beginning with the nondirected donor, no irreversible harm occurs to any of the participating recipients if the donor of one of the pairs decides not to proceed with donation<sup>26</sup>: the donors of the incompatible pairs after the broken link in the chain will not yet have donated and these pairs can be matched later. However, fewer transplants will result if a donor reneges, and

the transplant that would have ultimately gone to a patient from the deceased donor waiting list (who does not have a live incompatible donor but happens to be at the top of the waiting list) will be lost.

### Closed Chains Versus Open Chains

Nondirected donors have traditionally been allocated by centers to candidates on the deceased donor wait-list. Matching nondirected donors for KPD can multiply a nondirected donor's gift by enabling others to donate, so that transplantation is facilitated for two or three or more people because of the initial donor's gift. At the end of a sequence of transplants initiated by a nondirected donor, the intended donor of the last recipient could donate immediately to a candidate on the deceased donor wait-list (a closed chain or domino transplant<sup>27</sup>), or could instead wait for some length of time until he/she can begin a new sequence of transplants (an open chain<sup>26</sup>). A donor of an incompatible pair who waits for a later donation date has been referred to as a *bridge donor*. An open chain may consist of many of these simultaneous (or at least simultaneously identified) chain segments, with a few months or more between them. One open chain has been extended over time to include 30 pairs.<sup>28</sup>

In closed chains, the donors whose kidneys are ultimately allocated to the deceased donor waiting list are obviously unlikely to be O donors because O donors are in such high demand among incompatible pairs that a chain would inevitably be propagated by an O donor. This highlights a concern that some have raised—O candidates on the deceased donor wait-list are disadvantaged by the inclusion of nondirected donors in KPD, because the nondirected O donors will be diverted from the wait-list. This concern is magnified for open chains because they represent a permanent diversion of all nondirected donors away from the deceased donor wait-list.<sup>29</sup> Also, bridge donors are asked to donate later, perhaps many months after their intended recipients have been transplanted. Asking people to pledge to become donors in the future may be unacceptably coercive.<sup>29</sup>

Beyond the ethical concerns, there has been debate about whether the open chain or closed chain strategy results in more transplants. Although the idea of an open chain multiplying one nondirected donation indefinitely into the future is appealing, in practice, chains are eventually closed. Bridge donors, unlike nondirected donors, tend to have difficult-to-match blood and tissue types and often wait a long time before being matched to a suitable paired candidate.<sup>30</sup> There have been several instances of bridge donors deciding not to donate once they are matched, and anecdotally the likelihood of withdrawing consent increases with increasing wait time between the recipient's operation and the donor's match.<sup>31,32</sup> Thus, the bridge donor is more likely to

donate if he/she donates in a closed chain to the deceased donor wait-list, from which a suitable candidate is always available. In practice, the majority of chains today are designed to end with a donation to the waiting list (closed chains, or nonsimultaneous dominos) rather than trying to propagate endlessly.

Two simulation studies have come to opposite conclusions about whether open chains increase the number of transplants possible through KPD with nondirected donors, as compared with closed chains. Our group reported that, with chain segments limited to three incompatible pairs, if bridge donor withdrawal occurs at a rate of  $\geq 2\%$  per month, then there is no numerical advantage of open chains over closed chains.<sup>30</sup> This conclusion was sensitive to the rate of bridge donor withdrawal, which is thus far unknown; however, numerous anecdotes of bridge donor withdrawal have been reported, so the rate is clearly greater than zero. Open chains involve competition between various chains for the same, infrequent donors to perpetuate the chains, and risk bridge donors withdrawing while they wait for a suitable match. A different group argued that if chain segments include 4, 5, or 6 incompatible pairs, then a system using open chains will result in more transplants.<sup>32</sup> There were other differences between the studies, including the span of time over which the 2 strategies were compared and the approach to simulating unexpected positive crossmatches, and so the debate has continued in the literature.<sup>33-35</sup> In practice, even among the strongest advocates for purely open chains, multiple reneges have motivated a practice of always closing a chain when the probability of perpetuation is low.

## Conclusion

The growth of KPD is great news for any kidney transplant candidate. Organizations around the world are working to make matches, although groups continue to diverge over specific practices in paired donation. Transporting the organs after recovery has become standard in the United States, whereas Canada and the Netherlands have maintained donor travel. Some registries have encouraged matches with compatible pairs or combined KPD with desensitization protocols, whereas others have not. In the United States, a high proportion of KPD transplants are actually domino or chain transplants facilitated by nondirected donors, and that fact might be either the cause or the consequence of the decision to allow nonsimultaneous donations. Controversies over the merits of open chains versus closed chains seem to fade as registries recognize that, while open chains can extend the sequence of transplants for some period of time, no chain can be extended indefinitely.

KPD has substantially increased living donor kidney transplantation and has the potential to facilitate even greater numbers of transplants. At a national consensus

conference held recently, the allocation team recommended a single registry for the United States, arguing that match rates for all participants, and especially for sensitized recipients, would be higher if pairs were in one large registry rather than being partitioned into smaller registries.<sup>36</sup> More broadly, efforts to expand public awareness of and participation in paired donation are critical to generate more transplant opportunities.

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