

Innovations in Kidney Paired Donation (KPD) Transplantation

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By expanding the donor pool and providing incompatible pairs an opportunity to receive a living donor kidney transplant, or enabling compatible pairs an opportunity to receive a better match, kidney paired donation (KPD) is a remarkable innovation in and of itself. As KPD becomes an increasingly common approach to kidney transplantation, advancements and innovations within KPD have furthered that growth by more than 200% from ten years ago (Figure 1).

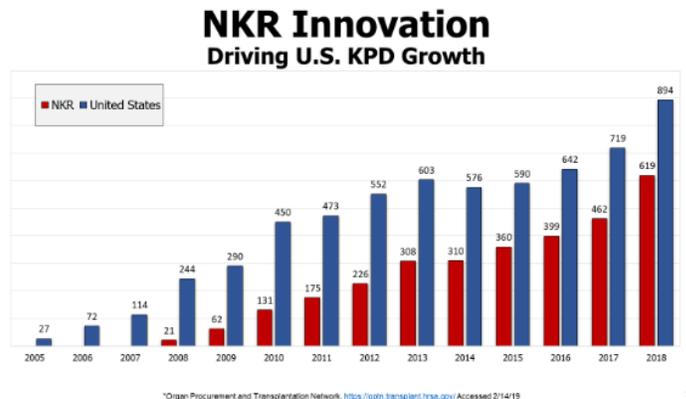


Figure 1

Shipping Living Donor Kidneys:

Perhaps the most significant of any advancement in KPD occurred on July 30th, 2008 when a living donor kidney was shipped across the United States unaccompanied on a commercial airline¹. Before this sentinel event, donors typically travelled to their KPD matched recipient's city for major surgery at an unfamiliar hospital, recovering apart from family and friends. The shipping of living donor kidneys eliminated this significant barrier to KPD participation, and resulted in a much larger pool of donor/recipient pairs. This innovation drastically increased the likelihood of recipients finding a match, and donors no longer were required to leave their preferred surroundings to participate in a kidney exchange. With research demonstrating no correlation between cold ischemic time and graft failure², the shipping of living donor kidneys has become the standard in the United States with nearly 3,000 living donor kidneys traversing the country to date³.

The increase in transporting living donor kidneys via commercial airlines introduced a potential risk of losing visibility to the whereabouts of these organs. To mitigate this risk, in 2010 the National Kidney Registry (NKR) began providing all donor centers with GPS devices to ship with the kidneys. On numerous occasions, the GPS has helped to identify instances where the kidney was not placed on the scheduled flight. In cases like these, the kidney can be quickly recovered, and the shipment expedited on a different flight to the recipient center.

¹ Butt FK, Gritsch HA, Schulam P, Danovitch GM, Wilkinson A, Del Pizzo J, Kapur S, Serur D, Katznelson S, Busque S, Melcher ML, McGuire S, Charlton M, Hil G, and Veale JL. (2009). "Asynchronous, Out-of-Sequence, Transcontinental Chain Kidney Transplantation: A Novel Concept. *American Journal of Transplantation*. 9:2180-2185.

² Treat, Eric; Chow, Eric K. H.; Peipert, John D.; Waterman, Amy; Kwan, Lorna; Massie; Thomas, Alvin G.; Bowring, Mary G; Leeser, David; Flechner Stuart; Melcher Marc; Kapur Sandip; Segev Dorry; Veale Jeffrey. (2018). "Shipping living donor kidneys and transplant recipient outcomes". *American Journal of Transplantation*. 18 (3): 632-641.

³ "Home Page - National Kidney Registry - Facilitating Living Donor Transplants". kidneyregistry.org

Consistent with a larger pool of incompatible donor/recipient pairs, better HLA matches are achieved with the avoidance of desensitization. As paired exchange volume has increased, the use of desensitization has decreased (Figure 2); and patients with a cPRA lower than 99% can generally find a clean match through the NKR in less than six months. Patients with a cPRA greater than 99%, who are unable to find a clean match after six months, often combine desensitization with KPD to reduce DSA conflicts and achieve better outcomes. In a recent report that reviewed the first 9 years of KPD transplants facilitated through the National Kidney Registry, there was a 27% lower 5-year graft failure rate when compared to traditional directed living donor transplants⁴ (Figure 3). NKR researchers attribute the better KPD transplant outcomes to superior antibody avoidance⁴.

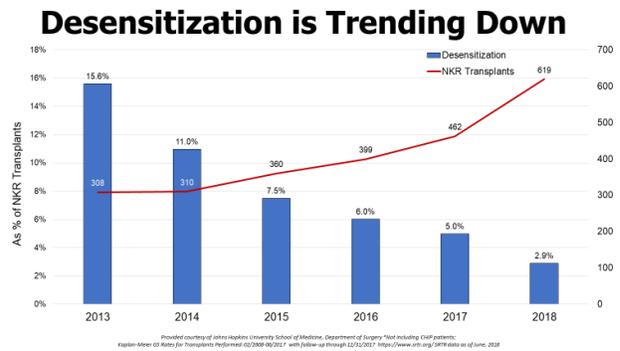


Figure 2

Innovation = Better Outcomes

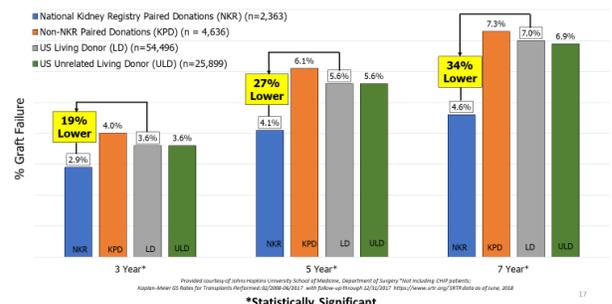


Figure 3

Laboratory:

Lab innovations have expanded outside of HLA matching and into process improvement initiatives for paired exchange, benefiting the transplant centers and donors alike. Among the process innovations is the use of exploratory cross matching to test for HLA compatibility in advance of initiating a swap.⁵ Although the use of exploratory cross matching helped a few highly sensitized patients get transplanted and reduced the rate of swap failures due to unacceptable cross match results, it was still difficult to obtain a fresh blood sample from a donor for what was not yet an actual match. It was not until 2015 when the NKR implemented multi-center donor blood cryopreservation that exploratory cross matching became fully utilized and yielded substantial results all while not inconveniencing the donor. This cryopreservation innovation enabled transplant centers to dramatically reduce the time to complete a cross match from 1–2 weeks to 1–2 days, facilitating more transplants for highly sensitized patients and reducing swap failures caused by unacceptable cross matches. Donor blood cryopreservation also reduces the number of times a donor needs to have blood drawn for cross matching, making paired exchange more convenient for donors.⁶

Mathematical and Logistical Optimization:

⁴ Source: Flechner, et al. (2018-04-30). "The first 9 years of kidney paired donation through the National Kidney Registry: Characteristics of donors and recipients compared with National Live Donor Transplant Registries". *American Journal of Transplantation*. 18 (11): 2730–2738.

⁵ Bingaman; Wright Jr.; Kapturczak; Shen; Vick; Murphey (1 Mar 2012). "Single-Center Kidney Paired Donation: The Methodist San Antonio Experience". *American Journal of Transplantation*. 12 (8): 2125–2132. doi:10.1111/j.1600-6143.2012.04070.x. PMID 22548839

⁶ "National Kidney Registry Initiates Donor Blood Cryo-Preservation" (Press release). National Kidney Registry. 2 Dec 2014.

The success of KPD goes beyond the surgical procedure or immunosuppressive medications and hinges on matching algorithms, computer software, and logistical optimization. In 2012, Dr. Lloyd Shapley (UCLA) and Dr. Alvin Roth (Harvard) won the Nobel Prize in part for applying the 'Gale-Shapley matching algorithm' to kidney exchanges. As KPD has continued to grow, more complex mathematical algorithms have been developed and real-time feedback can be provided to the transplant center based on their donor's matching potential, preference settings, and composition of the pool. A KPD pool of 100 incompatible donor/recipient pairs has the potential to be shuffled into trillions of possible chain combinations⁷. This requires the implementation of powerful software systems to perform this computation. One example of logistical optimization is the development of anatomical image sharing among member centers of the NKR. Previously, transplant coordinators were burdened by sharing the Computerized Tomography (CT) images of the donors' kidney anatomy with outside centers. Delays occurred as computer disks of the images were mailed across the country, and surgeons often had difficulty viewing the CT images as their computers required special viewing programs to be installed. Now images of the kidney anatomy from the donor hospital can be viewed by the recipient surgeon anywhere at any time with the click of the mouse through the NKR website.

The Voucher:

KPD was first completed in South Korea in the form of two-paired exchange (SWAP)⁸ and later with the addition of nondirected donors evolved into chains⁹. The next big evolution of KPD could be the 'voucher' where donors donate their kidney when convenient and their intended recipient receives a transplant when/if needed¹⁰. KPD dogma initially dictated that the donor operations should occur simultaneously, or that the paired original donor should only donate after their intended recipient (often family member) had received a kidney. However, by performing the donor procedure 'out-of-sequence' or 'in-advance' of the intended original recipient's transplantation enables operating rooms/surgeons the much needed flexibility, and at the same time more convenience for donors who often have donation time constraints^{1,11}. Vouchers take advanced donation one-step further, as the intended recipients (voucher holders) are not yet in need of a kidney transplant and may never need a kidney transplant. Additionally, voucher donors often function similar to nondirected donors and can trigger chains of transplants, as they do not have a paired recipient in the current chain (See Figure below).

Up to this point, donor/recipient pairs have only been considered incompatible by blood type or crossmatch, however donor/recipient pairs can also be incompatible by 'time' and the voucher

⁷ Veale, Jeffrey; Hil, Garet (2011). "The National Kidney Registry: 175 transplants in one year". *Clinical Transplants*: 255–278. ISSN 0890-9016. PMID 22755419

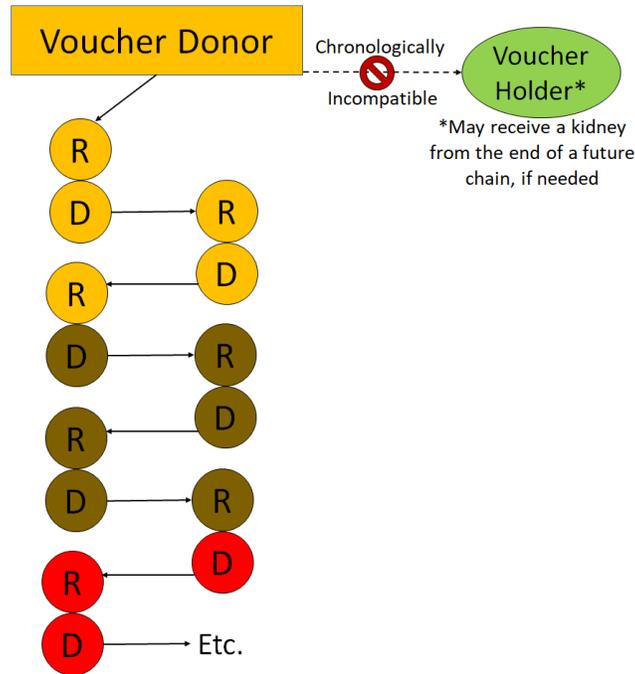
⁸ Kwak, J. Y.; Kwon, O. J.; Lee, K. S.; Kang, C. M.; Park, H. Y.; Kim, J. H. (1999). "Exchange-donor program in renal transplantation: a single-center experience". *Transplantation Proceedings*. 31 (1–2): 344–345. ISSN 0041-1345. PMID 10083136

⁹ Rees, Michael A.; Kopke, Jonathan E.; Pelletier, Ronald P.; Segev, Dorry L.; Rutter, Matthew E.; Fabrega, Alfredo J.; Rogers, Jeffrey; Pankewycz, Oleh G.; Hiller, Janet (2009-03-12). "A Nonsimultaneous, Extended, Altruistic-Donor Chain". *New England Journal of Medicine*. 360 (11): 1096–1101. doi:10.1056/NEJMoa0803645. ISSN 0028-4793. PMID 19279341

¹⁰ Veale, Jeffrey L.; Capron, Alexander M.; Nassiri, Nima; Danovitch, Gabriel; Gritsch, H. Albin; Waterman, Amy; Del Pizzo, Joseph; Hu, Jim C.; Pycia, Marek (09 2017). "Vouchers for Future Kidney Transplants to Overcome "Chronological Incompatibility" Between Living Donors and Recipients". *Transplantation*. 101 (9): 2115–2119. doi:10.1097/TP.0000000000001744. ISSN 1534-6080. PMID 28333861

¹¹ Flechner, S. M.; Leiser, D.; Pelletier, R.; Morgievlch, M.; Miller, K.; Thompson, L.; McGuire, S.; Sinacore, J.; Hil, G. (2015-10). "The Incorporation of an Advanced Donation Program Into Kidney Paired Exchange: Initial Experience of the National Kidney Registry". *American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 15 (10): 2712–2717. doi:10.1111/ajt.13339. ISSN 1600-6143. PMID 26012533

concept helps resolve this ‘chronological incompatibility’¹⁰. The natural next step in the voucher program is the ‘family-voucher’. As some potential altruistic donors may be reluctant to donate a kidney in case a healthy family member (child/spouse) would need it in the future. The family-voucher (which is being launched by the NKR in 2019), enables an altruistic donor to voucher up to five healthy family members and one voucher can be redeemed in the low likelihood one of the family members requires a kidney transplant in the future¹².



KPD is a relatively new field and the innovations it has spawned should continue to improve availability of high quality living donor organs, outcomes for recipients, convenience for donors, and better process management for KPD and traditional living kidney donation alike.

¹² https://kidneyregistry.org/pages/p500/Voucher_Brochure.php