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INVITED COMMENTARY

When a zero mismatch is no longer superior

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In kidney paired donation (KPD), a medically approved donor–recipient pair exchanges kidneys with one or more other pairs so that all recipients receive a compatible kidney from a stranger [1,2]. In most cases, KPD is performed because of blood group ABO incompatibility or because of the presence of a positive cross-match as a result of circulating donor-specific HLA-antibodies (DSA). Recently, KPD has also been proposed as a means to find a better-quality kidney for an otherwise compatible pair in so-called altruistically unbalanced exchange donation [3]. KPD has proven to be a successful strategy to increase kidney transplantation rates and since the first KPD programme was established in South Korea, many other countries have started their own local, regional or national KPD programmes [1,2,4,5].

A key ingredient of any KPD programme is the matching algorithm that is used to select the donor–recipient pairs from the pool [1]. Most algorithms will select pairs that are blood group compatible, as well as DSA or cross-match negative but important differences exist between the various programmes with regard to the consideration of additional factors for allocation. Such allocation criteria may include the number of HLA mismatches, the distance between the transplant centres of the donor–recipient pairs, the age difference of the donor and recipient, and EBV or CMV serostatus [1].

The Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) Kidney Paired Donation Pilot Program (KPDPP) was implemented in the United States in 2010, and since the first match run was conducted in October 2010, 88 patients have received a kidney through this nationwide programme as of March 2014 [6]. At present, 138 of the total of 228 active U.S. living donor programmes participate in the KPDPP [6]. The OPTN/UNOS KPDPP allocates priority to potential donor/recipient pairs with zero mismatches at HLA-A, HLA-B and HLA-DR [7]. Additional prioritization points are awarded to those matches of which the intended kidney transplant recipient has a calculated PRA ≥80%, is a prior living organ donor, or was younger than 18 years at the time of registration in the KPDPP [7]. The reason for prioritizing donor–recipient pairs with zero mismatches at the traditional six major histocompatibility antigens is the fact that survival of zero-mismatched grafts from deceased, as well as living-related donors is superior to that of comparable transplants that are matched less well [8–11]. In

KPD, however, kidneys are exchanged between living-unrelated donors and it has not been established whether optimal HLA matching provides a graft survival benefit in this setting.

In this edition of *Transplant International*, Casey *et al.* [12] report the results of their study on the effect of the degree of HLA matching on graft survival after living-unrelated donor kidney transplantation. Using data from the OPTN Scientific Registry of Transplant Recipients, 109 987 recipients of a living donor kidney transplanted in the USA between 1 October 1987 and 4 September 2012 were identified. Among these, 32 654 patients received a kidney from a living-unrelated donor, whereas 75 848 received a kidney from a living-related donor. The study group consisted of the 83 patients who received a zero-HLA mismatched kidney from a living-unrelated donor. These patients were matched retrospectively (for donor age and transplantation year) in a 1:1-5 ratio to 407 patients who received a >0 HLA mismatched kidney from a living-unrelated donor [12].

Among recipients of a living-unrelated donor kidney, death-censored graft survival was not different between the zero-HLA mismatched and >0 HLA mismatched groups and equalled 78% and 80%, respectively, 10 years after transplantation. A zero-HLA mismatch was also not associated with higher death-censored graft survival using multivariate Cox regression modelling (hazard ratio 1.46; 95%-CI 0.78 to 2.73; $P = 0.24$). In contrast, among recipients of a living-related donor kidney, the survival of the 9544 zero-HLA mismatched kidneys was better compared with the 63 632 >0 HLA mismatched kidneys and equalled 83% and 70%, respectively, 10 years after transplantation. Among all zero-HLA mismatched living donor transplants, a significant benefit in death-censored graft survival was seen in related (83%) over unrelated (78%) living donor transplant recipients. Finally, zero-HLA mismatching was not associated with improved patient survival after living-unrelated kidney transplantation [12].

The findings of Casey *et al.* suggest that graft and patient survival do not benefit from zero-HLA mismatching in the living-unrelated donor setting. This may seem counterintuitive, and the results may have been affected by the actual low number of zero-HLA mismatched unrelated-donor kidney recipients ($n = 83$). Nonetheless, a large national registry was analysed and a possible explanation may be that in the living-related donor setting, zero-HLA mismatches at the 6 major histocompatibility antigens serves as a marker for full haplotype matching. In the unrelated-living donor setting, zero-HLA mismatches at these three loci may not necessarily mean identity at other nontraditional major and minor histocompatibility antigens.

These findings have important implications for the US KPDPP. Allocation of organs in a KPD programme should be done 'equitably' among transplant recipients, which may be interpreted as striving to achieve the maximum number of transplants in a donor–recipient pool [1,2]. When using additional allocation criteria such as in the KPDPP, two things need to be considered. First, although such additional restraints may result in a preferred transplant for certain recipients, these putative individual benefits may well be outweighed by prolonged waiting time on dialysis [13]. Second, prioritization criteria should not negatively influence the access to transplantation of other donor–recipient pairs in the pool. Each KPD programme should balance the advantages of selecting low immunologic risk donor–recipient pairs with overall transplant numbers, equity and access to transplantation [1,2]. Although finding such a balance may be more a question of philosophy than science, the findings of Casey *et al.*, do provide evidence that there is no longer a justification for allocating priority to zero-HLA mismatched kidneys among living-unrelated donors.

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