

The National Kidney Registry Time to Buy In?

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In this issue of *CJASN*, Leeser *et al.* (1) describe patient and graft survival in patients who participated in the National Kidney Registry, a nonprofit, 501(c) organization founded in 2007 to facilitate living kidney donor exchange. Outcomes of recipients of paired kidneys in the National Kidney Registry ($n=2363$) were compared with outcomes in all living donor recipients from registry data ($n=54,497$), control unrelated living donor recipients ($n=25,900$), and control patients who received kidneys through non-National Kidney Registry paired donation ($n=4535$). Because of shipping of most kidneys, National Kidney Registry transplants had a notably greater cold ischemic time (9 hours versus 1 hour for the primary control group). This correlated with a higher risk of delayed graft function in National Kidney Registry recipients, with a 1.4 times risk (5% versus 3%; $P<0.001$) compared with other living donor recipients. However, at a median of 3.7 years of follow-up for National Kidney Registry recipients, death-censored graft survival and patient survival were similar compared with control living donor recipients as a whole.

In contrast to analysis of National Kidney Registry data, an Australian paired exchange cohort with a median follow-up of 6.6 years demonstrated that cold ischemic time was associated with outcomes in recipients of donors >50 years of age. Compared with cold ischemic time of 1–2 hours, cold ischemic time of 4–8 hours was associated with an increased odds of overall and death-censored graft failure with these older paired donors (hazard ratio, 1.93; 95% confidence interval, 1.21 to 3.09; $P=0.006$ and hazard ratio, 1.91; 95% confidence interval, 1.05 to 3.49; $P=0.04$, respectively (2). The follow-up in the current National Kidney Registry analysis is relatively short, and future studies with longer follow-up times are required to determine whether long-term survival is negatively affected by the greater cold ischemic time and delayed graft function in the National Kidney Registry cohort.

One surprising finding is that National Kidney Registry recipients appeared to have superior death-censored allograft survival compared with recipients of non-National Kidney Registry paired exchange kidneys. Compared with this control group, National Kidney Registry recipients were more likely to be black, with a higher percentage with prior transplantation, greater dialysis vintage, greater cold ischemic time, and a substantially higher rate of alloantibody sensitization

as measured by panel reactive antibody (PRA). Despite these risk factors, the National Kidney Registry recipients displayed superior death-censored graft survival. It is unclear what may have led to improved outcomes in the National Kidney Registry recipients. Recipients who participated in the National Kidney Registry may have been carefully selected with favorable resources, education, and adherence. National Kidney Registry recipients may also have had lower rates of donor-specific antibodies or need for desensitization, although such data were not available for the non-National Kidney Registry cohort. Rates of desensitization in the National Kidney Registry have dropped to $<5\%$ since 2018 (3). This illustrates a strength of the program, allowing for matching of compatible donors despite an over one fifth of recipients being highly sensitized with a $PRA>80\%$. Recipients with a $PRA\geq 98\%$ remained disadvantaged as expected in the National Kidney Registry (4). This risk can be mollified by matching with a paired donor with a lower titer cross-match compared with the intended pair.

Original concepts of paired donation envisioned single hospitals and simultaneous transplants between paired donors (5). However, the success of national exchange programs relies on the ability to separate transplants by geographic space and time, particularly when they involve longer transplant chains. One concern with delaying subsequent transplants is that chains may be broken, but a recent report from the National Kidney Registry found a low rate of broken chains of 5.8% (6). Primary reasons for chain breakage in that analysis included donor medical issues or donors backing out while serving as bridge donors (*i.e.*, donors who donate at least 1 day after their intended recipient has received a kidney).

One trend has been a shift away from bridge donors, and to greater participation in an advanced donation program. Advanced donation occurs before transplantation of the intended recipient, sometimes by months, and before an alternative donor being selected for their intended recipient. Preliminary data showed that advanced donation facilitated chains of transplants in National Kidney Registry, with approximately five transplants averaged for each advanced donation-associated chain (7). One advantage of advanced donation is that a prospective caregiver for the recipient may donate, recover from donor surgery, and later

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serve as a healthy support person for their intended recipient. Additionally, a donor who has a specific window of time for donation, related to work or travel, may donate at an earlier convenient time. A risk related to advanced donation is that the intended recipient may later encounter medical issues leading to deactivation from the transplant list, and this risk is emphasized in the consent of donor–recipient pairs for advanced donation in the National Kidney Registry (7).

Other innovation has led to the success of national registry programs, and such innovation has been spearheaded by the National Kidney Registry (3). As above, at the expense of longer cold ischemic time, shipping of kidneys has improved convenience and willingness of living donors to participate without the need to travel to recipient centers, which may be thousands of miles away (8). The National Kidney Registry utilizes global positioning system to track donor kidneys during transport, allowing for monitoring of displaced kidneys. The National Kidney Registry also implemented donor blood cryopreservation in 2015 allowing for cryopreserved donor cells to be shipped to recipient centers. This process improved the timeliness of crossmatches and eliminated the need for donors to provide repeat blood samples. Donor computerized tomography scans are shared on the National Kidney Registry website to avoid the need for shipping of hard copies of films. Finally, a concept of donation with “family vouchers” has been implemented (9). This process allows for living donation in exchange for nontransferrable “vouchers” for a number of intended recipients (up to five immediate family members in the National Kidney Registry, with cancellation of additional vouchers if one voucher is utilized). Such recipients do not yet (and may never) need or qualify for transplantation, thus blurring the lines between nondirected donation and donor exchange. Scenarios where the voucher program may be considered include older living donors with younger family members with progressive kidney disease, or family members with existing kidney transplants who may require retransplantation in future years. Outcomes with the voucher program will take years to assess, and donors under such a system must be counseled that the family vouchers may never be utilized.

Some have argued that the National Kidney Registry is expensive and punitive. Transplant programs pay the National Kidney Registry thousands of dollars per transplant, and there are costly penalties for centers that do not comply with monthly data entry and timely acceptance of matches. There is also a significant labor burden for transplant surgeons, with frequent input required on the complex National Kidney Registry website. Costs are used as an incentive, as they are waived for donor–recipient pairs who are compatible or for O donors. Another incentive provided by National Kidney Registry is the Center Liquidity Contribution (CLC) score. Centers that enter blood group O nondirected donors and ABO favorable pairs (blood group O donors with A, B, or AB recipients) receive CLC points which prioritize recipients at that center. As described in the National Kidney Registry website, a positive CLC score has the greatest effect on shortening wait times for pairs with unfavorable blood type combinations, such as O recipients with non-O donors. Because it incentivizes transplant programs to enter favorable pairs, the CLC point system may be

key in preventing an accumulation of hard to match recipients in the National Kidney Registry (10).

The expectation from the National Kidney Registry is that centers participating will have an “all in” policy and contribute all nondirected donors and incompatible paired donors to the registry. Some transplant centers may prefer internal swaps to maximize their own transplant numbers as well as avoiding costs and greater cold ischemic time associated with a national program. However, individual programs will still have difficulty in matching their most highly sensitized candidates, and may choose to enter such patients into a national registry. Such a registry will not succeed if only the most difficult patients to match are entered. A key component of the success of the National Kidney Registry is to have large buy in from multiple transplant programs, with the consistent addition of altruistic donors, particularly with blood group O, as well as compatible donor–recipient pairs. Compatible pairs who could otherwise proceed locally without exchange may be particularly helpful in facilitating transplant chains in the National Kidney Registry, especially if the donor is O with a non-O recipient, or the recipient is AB with a non-AB donor (V. Chipman, B. Lee, M. Cooper, M.C. Cuffy, M. Ronin, G. Hil, S. Flechner, A. Thomas, D.A. Mandelbrot, A.D. Waterman, C.E. Freise, G.R. Roll, unpublished data).

Ideally there will be greater unification and national participation in large donor exchange programs in the United States over time. If the early success of the National Kidney Registry is sustained, it may be the program of choice for national participation. The National Kidney Registry has led the way in technology and innovation, and outcomes demonstrate success for those classically disadvantaged for living donor transplant, including black recipients and those who are highly sensitized. The current report on 10 years of transplantation through the registry is encouraging, and may convince more transplant programs to “buy in” to the National Kidney Registry.

Disclosures

Dr. Augustine and Dr. Syed have nothing to disclose.

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