

## Letter to the Editor

# The Honeymoon Phase and Studies of Nonsimultaneous Chains in Kidney-Paired Donation

To the Editor:

Kidney-paired donation programs have been successfully incorporating nondirected donors into nonsimultaneous extended (NEAD) chains (1). Including nondirected donors in either NEAD chains or domino-paired donations (DPDs, chains that end in the waiting list rather than a bridge donor) increases match opportunities for incompatible pairs. When interpreting the performance of NEAD chain programs, though, we must recognize that the honeymoon phase (where many transplants are facilitated by a single donor) may not last forever. After the initial months or years of operation, bridge donors will accumulate, competing for scarce matches or dropping out altogether after long waits. Clinical experience in the longest-running registries also shows that many chains do not operate indefinitely, but dissipate as hard-to-match bridge donors languish.

A recent report of Ashlagi et al. (2) highlights the need to recognize the honeymoon phase, as the data demonstrate that inferences from the early stages can be overturned and reversed as registries operate over longer periods of time. Ashlagi et al. reproduced our computational findings (3) that NEADs would not facilitate more transplants than DPDs over 24 periods, or months, of operation. Then, using 8-period simulations with longer segments (our simulation limited concurrent segments to three pairs without limiting overall chain length), Ashlagi et al. argued that NEADs with longer segments facilitate more transplants than DPDs. However, comparing Figure 2 with Figure 3 of their manuscript illustrates that the ostensibly minor detail of switching from a 24-period simulation to an 8-period simulation was actually the decisive factor in reversing the predicted benefit of DPDs over NEAD chains, not the longer segments.

Our simulations showed that after 24 periods in mature registries, NEAD is not superior to DPD when segment lengths are limited to three. Figure 2 of Ashlagi et al. reproduces this result, with the endpoint of the NEAD-3 line below 1 (near 0.98). Figure 3 shows the opposite result for the exact same experiment when simulating only the first eight periods (the honeymoon phase): the endpoint of the NEAD-3 line in Figure 3 is above 1 (near 1.015). That is, NEAD chains seem superior to DPDs in Figure 3 but not in Figure 2, where the only difference is the number of periods simulated.

Contrary to their honeymoon phase results, the data that Ashlagi et al. present actually prove that in mature reg-

istries, the advantage of DPD over NEAD is larger with chains that allow longer concurrent segments. Figure 2 compares DPD with NEAD for segments of length 4 and shows that for all renege rates, DPD gives an equal or greater number of transplants than NEAD. Figures 3–10 show valid data for honeymoon phase inferences, but cannot elucidate what will happen as NEAD chains deteriorate over time.

Matching algorithms are also susceptible to the honeymoon phase problem. Ashlagi et al. limited their studies to only 8-period simulations because, as they stated, optimizing matches for later periods using longer segments was computationally prohibitive. This raises a question: how will optimized matches with longer segments be computed for real clinical registries beyond 8 periods? Of course, longer segments can also be logistically prohibitive because the concurrent segments become harder to manage, so the advantage of nonsimultaneity (one of the strongest arguments supporting NEAD chains) is lost. In practice, no concurrent segments of a NEAD chain longer than three pairs have been reported. Considering these challenges, limiting concurrent segments to three pairs seems reasonable and may even be necessary.

We maintain that NEAD chains do not, in the long run, create more transplants than DPD because bridge donors accumulate in the system and compete against other potential matches. In the later stages of our simulations, most bridge donors did not find matches and some dropped out as their waiting time lengthened. We urge the transplant community to recognize the changing composition of kidney-paired donation registries over time, beyond the honeymoon phase, and prepare to meet the new challenges that early success may bring.

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## Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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