American Journal of Transplantation 2015; 15: 2636–2645
Wiley Periodicals Inc.

doi: 10.1111/ajt.13413

Planning for Uncertainty and Fallbacks Can Increase the Number of Transplants in a Kidney-Paired Donation Program

M. Bray[1,2,*], W. Wang[1,2], P. X.-K. Song[1,2], A. B. Leichtman[2,3], M. A. Rees[4,5], V. B. Ashby[1,2], R. Eikstadt[1,2], A. Goulding[6] and J. D. Kalbfleisch[1,2]

[1]*Department of Biostatistics, University of Michigan, Ann Arbor, MI*
[2]*Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor, MI*
[3]*Arbor Research Collaborative for Health, Ann Arbor, MI*
[4]*Department of Urology, University of Toledo Medical Center, Toledo, OH*
[5]*Alliance for Paired Donation, Inc., Maumee, OH*
[6]*School of Information, University of Michigan, Ann Arbor, MI*
[*]*Corresponding author: Mathieu Bray, braymath@umich.edu*

A kidney-paired donation (KPD) pool consists of transplant candidates and their incompatible donors, along with nondirected donors (NDDs). In a match run, exchanges are arranged among pairs in the pool via cycles, as well as chains created from NDDs. A problem of importance is how to arrange cycles and chains to optimize the number of transplants. We outline and examine, through example and by simulation, four schemes for selecting potential matches in a realistic model of a KPD system; proposed schemes take account of probabilities that chosen transplants may not be completed as well as allowing for contingency plans when the optimal solution fails. Using data on candidate/donor pairs and NDDs from the Alliance for Paired Donation, the simulations extend over 8 match runs, with 30 pairs and 1 NDD added between each run. Schemes that incorporate uncertainties and fallbacks into the selection process yield substantially more transplants on average, increasing the number of transplants by as much as 40% compared to a standard selection scheme. The gain depends on the degree of uncertainty in the system. The proposed approaches can be easily implemented and provide substantial advantages over current KPD matching algorithms.

Abbreviations: APD, Alliance for Paired Donation; DPD, domino-paired donation; HLA, human leukocyte antigen; KPD, kidney-paired donation; MFR, match failure rate; NDD, nondirected donor; NEAD, nonsimultaneous extended altruistic donor; PFR, pair failure rate; PRA, panel reactive antibodies

Received 10 December 2014, revised 05 April 2015 and accepted for publication 23 April 2015

Introduction

In a kidney-paired donation (KPD) pool, pairs consisting of kidney transplant candidates and intended but incompatible donors are matched with other complementary pairs in an attempt to find combinations such that enrolled candidates can obtain a transplant (1–4). An exchange cycle (or simply ''cycle'') involves a sequence of matches where the donor of one pair donates to the candidate in the next pair along the cycle. The cycle is completed when the donor in the last pair gives a kidney to the candidate in the first pair (5). The cycle is defined so that the candidate in each pair is matched with a donor who is expected to be immunologically compatible based upon the candidate's pattern of donor-specific antibodies. The initial assessment is referred to as a virtual crossmatch, which needs to be confirmed by a laboratory crossmatch. Nondirected donors (NDDs), also referred to as altruistic donors, can initiate chains of transplants in the KPD pool that end by transplanting a candidate on the deceased donor waiting list, called domino-paired donation (DPD) (6–8). Alternatively, a nonsimultaneous extended altruistic donor (NEAD) chain segment can be identified in each match run, where the donor corresponding to the candidate at the end of the segment, referred to as a bridge donor (9,10), can continue the chain in a new segment chosen at a later time.

Traditionally, a KPD pool is managed through a sequence of match runs, whereby at regular intervals, the pool is assessed and a solution consisting of cycles and chains is determined such that no pair is simultaneously involved in more than one cycle or chain. In larger pools, there are many cycles and/or chains and consequently many possible solutions. The preferred selection would ideally be determined by prespecified objective standards (11), such as maximizing the total number of potential transplants (12). Optimization schemes assign a value to each potential transplant, based upon candidate and/or donor characteristics. These values are termed utilities and potential transplants assigned a higher utility receive precedence

in the optimization. The solution that yields the maximum total utility of potential transplants is, therefore, the optimal solution (13). Note that assigning an equal utility of 1 to all potential transplants results in a solution that maximizes the number of potential transplants.

In cycles, there is a practical limitation that all transplants should be performed simultaneously in order to avoid the possibility of a scheduled donor opting to leave the pool prior to donation. Without this restriction, the possibility exists that a donor will donate a kidney without the associated candidate obtaining a transplant. For this reason, if any one of the transplants in a proposed cycle cannot be completed, none of the selected transplants in the cycle can proceed. On the other hand, if one of the transplants in a proposed chain segment cannot be completed, transplants prior to the point of failure can still proceed since the issue of an untransplanted candidate with no donor does not arise (6,7,10). Failure to proceed with a proposed transplant can occur for a number of reasons, including a positive laboratory crossmatch, a candidate or physician declining an assigned donor, or donors or candidates having to leave the pool due to illness or other reasons (14).

Recent studies suggest that optimization schemes that take into account the probability that selected transplants fail to proceed to actual transplantation can improve upon schemes that ignore this uncertainty. These approaches aim to maximize expected utility and on average increase the total utility from completed transplants within each match run (13–15). In addition, one can plan for fallback options should the optimal solution fail to proceed. Strategies that include fallback options for each cycle and chain under evaluation consider all possible sub-cycles and sub-chains that could be taken as alternatives in the event that the main cycle or chain fails to proceed (13). With fallbacks, the expected utility should take into account the individual expected utilities of each sub-cycle or sub-chain. An example is given in Figure 1, which displays a three-way cycle with a possible fallback to a two-way cycle. This three-way cycle with the fallback has higher expected utility and would be preferred to a three-way cycle with no fallback.

It is also possible to extend the idea of fallback options to more general subsets of pairs and NDD chain segments, where each subset may have possibilities for cycles and chains within it. The more cycles and chains that exist within a subset, the more useful it will be in arranging fallback options. In our implementation, we consider subsets of four or fewer pairs and/or NDDs, and seek a selection of such subsets that maximize the expected utility, taking account of the fallback options. An example of such a subset is given in Figure 2.

In these simulations, we evaluate several optimization schemes with respect to numbers and characteristics of transplants over the course of several match runs in a realistic model of KPD program similar to that outlined in Ashlagi et al (9).

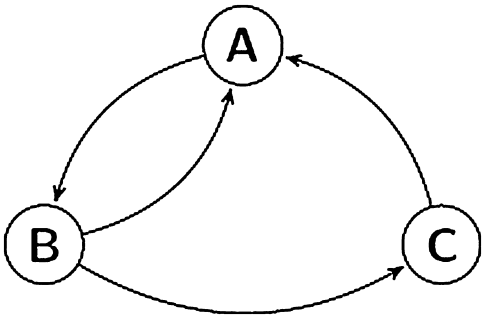

Figure 1: Example of a three-way cycle with a fallback to a two-way cycle. Pairs are represented by circles and denoted A, B, and C. An arrow from one pair to a second pair denotes a potential transplant from the donor in the former to the candidate in the latter, based on a virtual crossmatch. Should C be unavailable for transplantation, or either of the potential transplants involving C be deemed unviable, one could proceed with the transplant between pairs A and B as a fallback option.

Methods

Data

We used deidentified data on 538 candidate/donor pairs and 55 NDDs (including bridge donors) from the Alliance for Paired Donation (APD). The data set includes donor and candidate blood type, major human leukocyte antigen (HLA) information for the donors, and candidate donor-specific antibody information and panel reactive antibody (PRA) values. Using this information on donors and candidates, a virtual crossmatch was performed for every possible transplant between donor and candidate by assessing

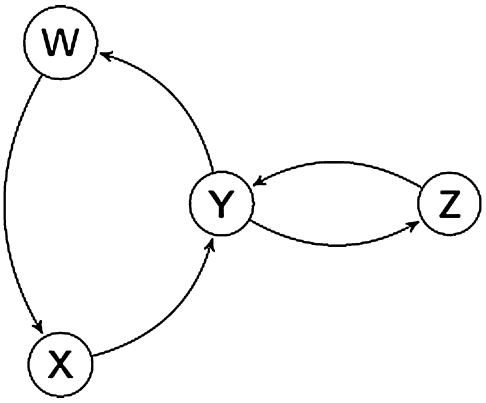

Figure 2: Example of a subset of four pairs, with multiple fallback options. Pairs are represented by circles and denoted W, X, Y, Z. An arrow from one pair to a second pair denotes a potential transplant from the donor in the former to the candidate in the latter, based on a virtual crossmatch. This subset contains a three-way cycle between W, X, and Y, and a two-way cycle between Y and Z. Depending on availability and viability of pairs and matches, one would proceed with the best available option.

ABO blood type and HLA antigen-antibody compatibility (at HLA-A, B, Bw, Cw, DR, DRw, and DQ).

Uncertainties

For each potential transplant, we assign a probability, based on the PRA of the candidate, that the transplant will be prohibited. These baseline probabilities, given in Table 1, are taken from Ashlagi et al (9), who remark that they are empirically determined crossmatch failure rates. Additional failure rates of 10% and 20% are added to these baseline values in a sensitivity analysis to reflect potentially higher probabilities of match failure due to candidate, donor, or physician preferences. We refer to these probabilities, all of which are summarized in Table 1, as match failure rates (MFRs). We also consider the probability that each selected pair would be unable to proceed to transplant, which we took to be 0%, 10%, and 20% in our simulations; we refer to these probabilities as pair failure rates (PFRs). In total, we consider nine probability settings with three levels of PFRs for each of three levels of MFRs.

Optimization schemes

We consider four general optimization schemes that are defined in Table 2. Calculations are based on those described in Li et al (13). The simplest scheme, denoted *Utility*, involves maximizing the utility, defined as the number of potential transplants of the selected cycles and chains. This is equivalent to the approach considered by Ashlagi et al (9), and forms the basis of matching in some existing KPD systems. The second scheme, denoted *Expected Utility*, takes both MFR and PFR into account to find the solution with the largest expected utility. Two additional optimization schemes, denoted *Fallbacks* and *Extended Fallbacks*, incorporate the idea of contingency planning. The former selects nonoverlapping cycles and chain and restricts fallbacks to those within the chosen cycles and chains, whereas the latter considers general subsets of pairs and NDDs and takes account of fallbacks to sub-cycles and sub-chains within the chosen subsets.

Match run example

These optimization schemes are illustrated in a relatively simple example in the Supporting Information that accompanies this article, and the interested reader is referred there for more detail. To further illustrate the methodology here, we include a brief example of the solution envisaged in the *Extended Fallbacks* scheme; for this example, a comparison to the *Fallbacks* scheme is given in the Supporting Information. The example illustrates a match run on data from April 2014, for 44 pairs and a single NDD in the University of Michigan KPD pool. The recommendation based on *Extended Fallbacks* with subsets of size 4 or less is displayed in Figure 3A. The scheme has chosen disjoint subsets of four or fewer pairs (and/or NDDs) which include as many fallback options as possible. Given the solution presented in Figure 3A, we would check the viability of each potential match, as well as the availability of each pair. It is common at this stage that some potential transplants and/or pairs/NDDs will fail to proceed to transplant for various reasons including donor or candidate preferences, sickness, or positive lab crossmatch. Figure 3B shows the potential transplants remaining after a (hypothetical) assessment of the proposed transplants. We proceed to carry out those transplants that result in the largest number of candidates receiving a kidney. In this example, pair 683 was unavailable for the match run, and several other potential transplants were ruled out. Remaining are the single transplant from NDD 693 to pair 702, and the two-way cycle between pairs 701 and 642, as well as between 676 and 700.

Table 1: MFR considered in simulations

	MFR		
PRA level	Baseline[1]	Baseline + 10%	Baseline + 20%
75–100	50%	60%	70%
50–74	35%	45%	55%
25–49	20%	30%	40%
0–24	5%	15%	25%

MFR, match failure rates; PRA, panel reactive antibodies.
[1]Baseline values are taken from Ashlagi et al (9).

Table 2: Description of optimization schemes used in simulations

Utility	The optimal solution is the selection of disjoint cycles and chains with the highest total utility. Note that, by setting the utility value for all potential transplants to 1, we obtain the selection with the largest number of transplants. This scheme is equivalently used by Ashlagi et al (9).
Expected Utility	The optimal solution is the selection of disjoint cycles and chains that yields the largest expected utility, taking account of the probabilities that potential transplants will be confirmed by laboratory crossmatches and be viable at the time of transplantation, and the probabilities that pairs involved in these transplants will be available at the time of transplantation.
Fallbacks	The optimal solution is the selection of disjoint cycles and chains that yields the maximum total expected utility, taking into account the fallback options offered by all sub-cycles and sub-chains within the selected cycles and chains.
Extended Fallbacks	The optimal solution is the selection of disjoint subsets of pairs/NDDs that yield the maximum total expected utility, taking into account the fallback options offered by all sub-cycles and sub-chains within the subsets. The calculations of expected utility for each subset proceed analogously to those used in the *Fallbacks* scheme (13,20).

NDDs, nondirected donors.

Simulation description

Simulation parameters and conditions follow those in Ashlagi et al (9), although we also note the simulations by Gentry et al (8,16) suggesting that simultaneous DPD chains are preferable to longer NEAD chain segments in certain situations. We consider DPD chains with a maximum length of 2 (with implicit final donation to the deceased donor list), as well as NEAD chain segments with maximum allowable chain segment lengths of 3, 4, and 5 (denoted NEAD3, NEAD4, and NEAD5). Two hundred simulations of evolving KPD pools over eight match runs are performed. Each simulation implements each of the different optimization schemes (*Utility, Expected Utility, Fallbacks, and Extended Fallbacks*) and chain criteria (DPD, NEAD3, NEAD4, NEAD5). At the beginning of each simulation, 30 incompatible pairs and 1 NDD for each of the 8 match runs is obtained by sampling with

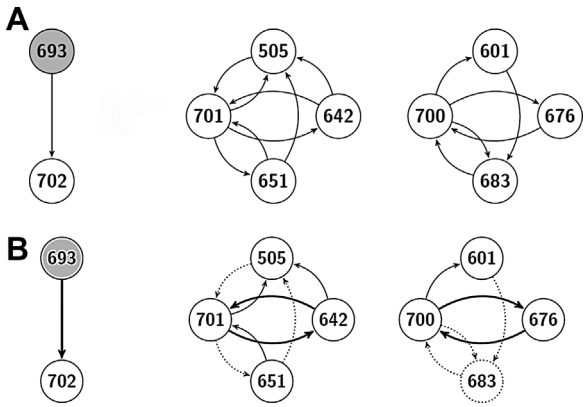

Figure 3: (A) Solution for the example match run using *Extended Fallbacks*. The solution displays three disjoint subsets of pairs, represented by white circles, and a single NDD (693) represented by a gray circle. An arrow from one pair/NDD to another represents a potential transplant from the donor in the former to the candidate in the latter, based on a virtual crossmatch. (B) Hypothetical reduced solution for the *Extended Fallbacks* scheme after assessing compatibility and determining availability of pairs. The dotted circle indicates the unavailability of pair 683 for this match run, and dotted arrows represent potential transplants that were deemed unviable, or otherwise removed from consideration. Bolded arrows represent a choice of transplants resulting from this reduced solution. In this example, remaining are the single transplant from NDD 693 to pair 702, and the two-way cycles between pairs 701 and 642, as well as between 676 and 700. NDD, nondirected donor.

replacement from the data, so that each optimization scheme is applied to the same data.

The simulations described here aim to maximize the number of transplants. At each match run, the optimal solution is determined based on the optimization scheme and the chain criterion. After selection, proposed transplants can fail to proceed, either due to failure on the match (positive lab crossmatch or donor/candidate preferences) based on MFR, or if one of the pairs involved is unable to proceed to transplant, based on PFR.

NEAD chain segments follow the same procedure as in Ashlagi et al (9). Bridge donors have a renege rate of 1%, representing the rate at which bridge donors refuse to continue the chain after their associated recipient receives their transplant. DPD chains end with a final donation to the deceased donor list, which is included among realized transplants (i.e. transplants successfully occurring within the simulation) in our results. As in Ashlagi et al (9), chains which would leave bridge donors with blood type AB are not allowed. Following completion of each match run, each pair in the pool has a 2% chance of permanently leaving the pool prior to the next match run. NDDs and bridge donors remaining at the end of the eighth match run are recorded as giving rise to one additional transplant, reflecting their potential to provide further transplants in future match runs, and to obtain results that are comparable to those of DPD chains. Specific aspects of the simulation are summarized in Table 3.

The procedure is repeated for each optimization scheme, each chain criterion, and each of the nine combinations of MFR/PFR. We collect the number of transplants realized and the characteristics of the associated recipients (in terms of blood type and PRA) for each policy. We also summarize the extent to which transplants are accomplished through the use of cycles or chains. Note that, due to computational complexity, the optimization scheme denoted *Fallbacks* has only been simulated for NEAD chain segments of up to length 4 on each match run (with only 100 iterations performed for the NEAD4 criterion). *Extended Fallbacks* considers subsets of size 3 or less, restricting to DPD chain segments (of length 2), and alternatively, subsets of size 4 or less, restricting to NEAD chain segments of up to length 3. Simulations were written in C++, and optimal solutions were selected using the linear programming software Gurobi 5.6.3 (17).

Table 3: Steps in the simulation procedure for each match run

1	30 pairs and 1 NDD are selected at random with replacement, and added to the pool.
2	The optimal solution of cycles, chain segments, or subsets of pairs/NDDs (based on the current optimization scheme) is obtained using two-way and three-way cycles, and either DPD chains or NEAD chain segments.
3	Failure or success of each potential transplant and selected pair is determined by simulation. Failed matches are removed from future match runs. Failed pairs return to the pool for the next match run.
4	For *Utility* and *Expected Utility*, if failure occurs anywhere in a cycle, none of the selected transplants proceed. If failure occurs in a chain, all the candidates prior to the point of failure are transplanted. Once viability of transplants and pairs is determined, the *Fallbacks* and *Extended Fallbacks* schemes may still contain cycles/chains/subsets with multiple possible transplant choices. For each of these, a (much simpler) *Utility* optimization is applied to select the transplants within the cycle/chain/subset to implement.
5	Realized transplants are recorded and corresponding donors and candidates are removed from the pool.
6	Pairs and bridge donors are removed from the pool based on attrition and renege rates respectively.

NDD, nondirected donor; DPD, domino-paired donation; NEAD, nonsimultaneous extended altruistic donor.

Results

Transplants and ratio to DPD-Utility

Tables 4 and 5 show, respectively, the number of transplants achieved and the ratio of the number of transplants achieved compared to the DPD-*Utility* simulation for each optimization scheme and chain length. Figure 4 also shows a selection of the plots corresponding to Table 5 in our high and low failure rate simulations. Note that in comparing *Extended Fallbacks* to other schemes, subsets of size 3 are compared to DPD chains, and subsets of size 4 are compared to NEAD chain segments with a maximum length of 3.

Evaluation of the *Utility* simulations demonstrates that maximizing the number of transplants without taking into account probabilities of failure delivers diminishing returns

Table 4: Averages of realized transplants for each combination of match failure rate (MFR) and pair failure rate (PFR)

		Pair failure rate (%)											
		0				10				20			
Match failure rate		Utility	Expected Utility	Fallbacks	Extended Fallbacks	Utility	Expected Utility	Fallbacks	Extended Fallbacks	Utility	Expected Utility	Fallbacks	Extended Fallbacks
Baseline	DPD	75.27	73.77	76.79	77.09	70.40	70.80	73.35	74.02	64.33	65.94	69.38	70.34
	NEAD3	78.96	78.89	80.55	84.33	74.20	75.40	77.49	81.02	68.02	70.81	73.83	77.37
	NEAD4	81.60	80.00	82.45		76.66	76.33	79.76		70.13	71.41	75.72	
	NEAD5	82.16	80.65			77.40	76.59			69.28	71.63		
Baseline +10%	DPD	66.23	66.23	69.54	69.95	61.62	63.19	66.67	67.06	55.12	59.02	62.63	63.98
	NEAD3	70.70	71.66	74.25	77.52	65.38	67.95	70.84	74.94	58.54	63.67	67.33	71.13
	NEAD4	72.75	72.52	75.60		67.06	69.25	72.43		60.98	64.48	69.08	
	NEAD5	73.15	72.75			67.56	68.82			60.94	64.50		
Baseline +20%	DPD	55.88	57.96	61.36	62.52	50.16	55.50	58.45	59.67	45.07	51.51	55.79	56.62
	NEAD3	59.72	63.59	66.67	70.36	54.89	60.74	63.85	67.70	49.34	56.00	60.35	64.95
	NEAD4	61.30	64.48	67.77		56.52	61.39	64.97		50.22	56.34	62.18	
	NEAD5	61.97	64.95			56.74	61.39			50.88	57.00		

DPD, domino-paired donation; NEAD, nonsimultaneous extended altruistic donor.

Table 5: Ratio to DPD-*Utility* for each combination of match failure rate (MFR) and pair failure rate (PFR)

		Pair failure rate (%)											
		0				10				20			
Match failure rate		Utility	Expected Utility	Fallbacks	Extended Fallbacks	Utility	Expected Utility	Fallbacks	Extended Fallbacks	Utility	Expected Utility	Fallbacks	Extended Fallbacks
Baseline	DPD	1.000	0.980	1.020	1.024	1.000	1.006	1.042	1.051	1.000	1.025	1.079	1.093
	NEAD3	1.049	1.048	1.070	1.120	1.054	1.071	1.101	1.151	1.057	1.101	1.148	1.203
	NEAD4	1.084	1.063	1.095		1.089	1.084	1.137		1.090	1.110	1.182	
	NEAD5	1.091	1.071			1.099	1.088			1.077	1.113		
Baseline +10%	DPD	1.000	1.000	1.050	1.056	1.000	1.025	1.082	1.088	1.000	1.071	1.136	1.161
	NEAD3	1.067	1.082	1.121	1.170	1.061	1.103	1.150	1.216	1.062	1.155	1.222	1.290
	NEAD4	1.098	1.095	1.138		1.088	1.124	1.176		1.106	1.170	1.256	
	NEAD5	1.104	1.098			1.096	1.117			1.106	1.170		
Baseline +20%	DPD	1.000	1.037	1.098	1.119	1.000	1.106	1.165	1.190	1.000	1.143	1.238	1.256
	NEAD3	1.069	1.138	1.193	1.259	1.094	1.211	1.273	1.350	1.095	1.242	1.339	1.441
	NEAD4	1.097	1.154	1.217		1.127	1.224	1.296		1.114	1.250	1.376	
	NEAD5	1.109	1.162			1.131	1.224			1.129	1.265		

DPD, domino-paired donation; NEAD, nonsimultaneous extended altruistic donor.

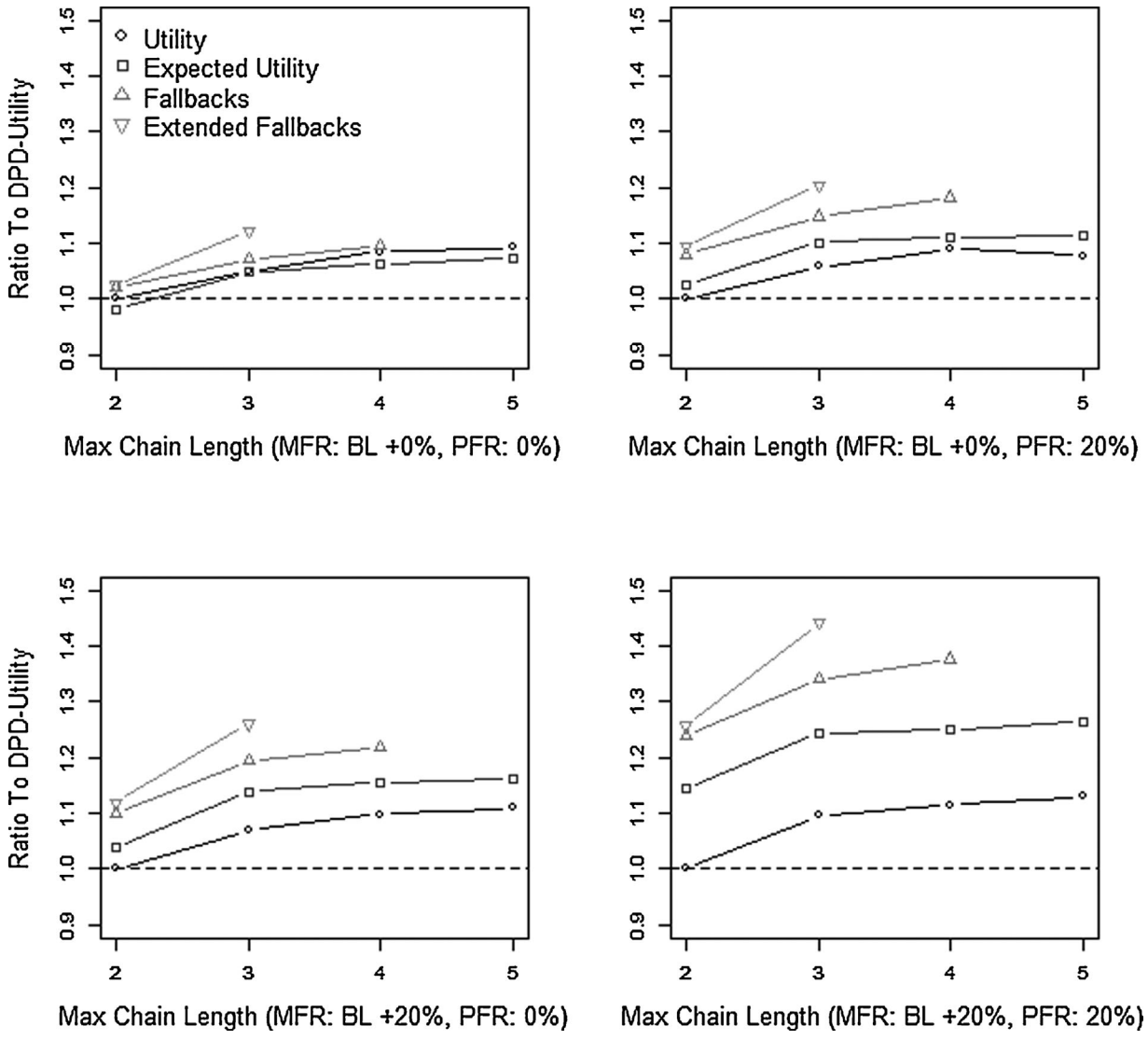

Figure 4: Ratio of number of transplants for each scheme compared to the DPD *Utility* scheme. Maximum chain length of two corresponds to the DPD strategy applied to each optimization scheme. Parenthetical remarks under each panel indicate the values of MFR and PFR, where ''MFR: BL+0%'' refers to Baseline MFR, and ''MFR: BL + 20%'' refers to Baseline + 20% MFR (see Table 1). DPD, domino-paired donation; MFR, match failure rate; PFR, pair failure rate.

as chain segment length increases past 4. Results for *Utility* are qualitatively similar to those reported in Ashlagi et al (9).

As compared to DPD-Utility, we obtain between 2% and 44% more transplants by using the *Extended Fallbacks* scheme. In general, the advantage of *Fallbacks* and *Extended Fallbacks* over *Utility* increases as the failure rates increase. *Extended Fallbacks* outperformed all other schemes for all maximum chain lengths considered, and this strategy provided the largest number of transplants in all simulations.

Transplant distribution

Figure 5 illustrates the distributions of achieved transplants over the course of our high and low failure rate simulations. For *Utility*, the proportion of transplants completed via chains increases as chain segment length increases. *Expected Utility* shows relatively little change in transplant distribution as maximum chain segment length ranges from 3 to 5, especially as the probabilities of failure (MFR and PFR) increase. The analogous result for *Fallbacks* and *Extended Fallbacks* is not clear since to date, time and memory resources have restricted simulations for the longer chain segment lengths in these cases.

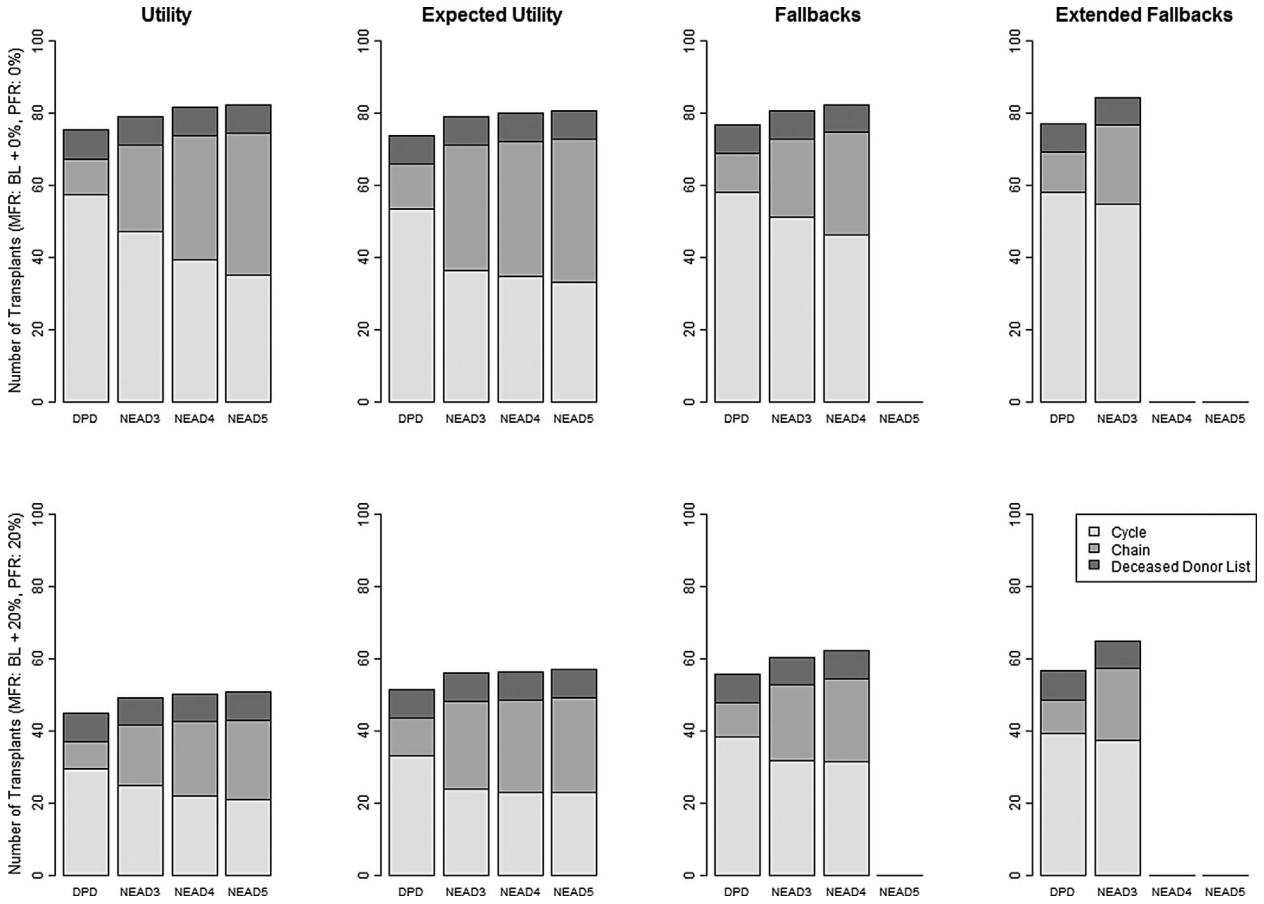

Figure 5: Transplant distribution charts for each optimization scheme indicating average number of transplants achieved via cycles, chains, and donations to the waiting list. The top (bottom) panel corresponds to simulations with Baseline (Baseline + 20%) MFR and 0% (20%) PFR. MFR, match failure rate; PFR, pair failure rate.

Blood type and PRA distributions

The distribution of blood type among transplant recipients is similar for all schemes and failure rates. Similarly, we do not observe any differences between schemes in the proportion of candidates of each blood type receiving a transplant over the course of the match runs.

Figure 6 displays the proportion of patients within each PRA grouping that receive a transplant. We find that a higher proportion of the *Utility* transplants are of candidates with high PRA compared to *Expected Utility* simulations with no fallbacks; this is as expected since the *Expected Utility* approach introduces bias against higher PRA candidates for whom selected transplants are less likely to be completed. When contingency plans are taken into account at the optimization stage as in *Fallbacks* and *Extended Fallbacks*, however, these biases are reduced. This is an empirical result that is not easily explained on intuitive grounds. It appears, however, that incorporating fallback options in the allocations tends to include more candidates with high PRA in the chosen sets since the penalty for their inclusion is reduced by the presence of fallbacks.

Discussion

In the *Utility* approach, where no account is taken of potential failures, long chain segments tend to be selected as opposed to smaller cycles or chain segments. When the probability of failure is substantial, long chain segments will tend to end early resulting in fewer transplants than one would have obtained with a selection that takes these probabilities into account. In Figure 5, we see that the proportion of transplants from chains increases markedly with chain segment length under the *Utility* scheme. Although less dramatic, this increase is also seen in the other schemes considered.

The primary finding of this work is that there is substantial advantage for KPD programs from taking into account possible fallback options at the optimization stage, as in the *Fallbacks* and *Extended Fallbacks* schemes. This confirms and extends the results of previous studies (13,14,18). An *ad hoc* approach would be to select cycles and chains simply by maximizing utility, but then to look for fallback options within that selection. We have also simulated this

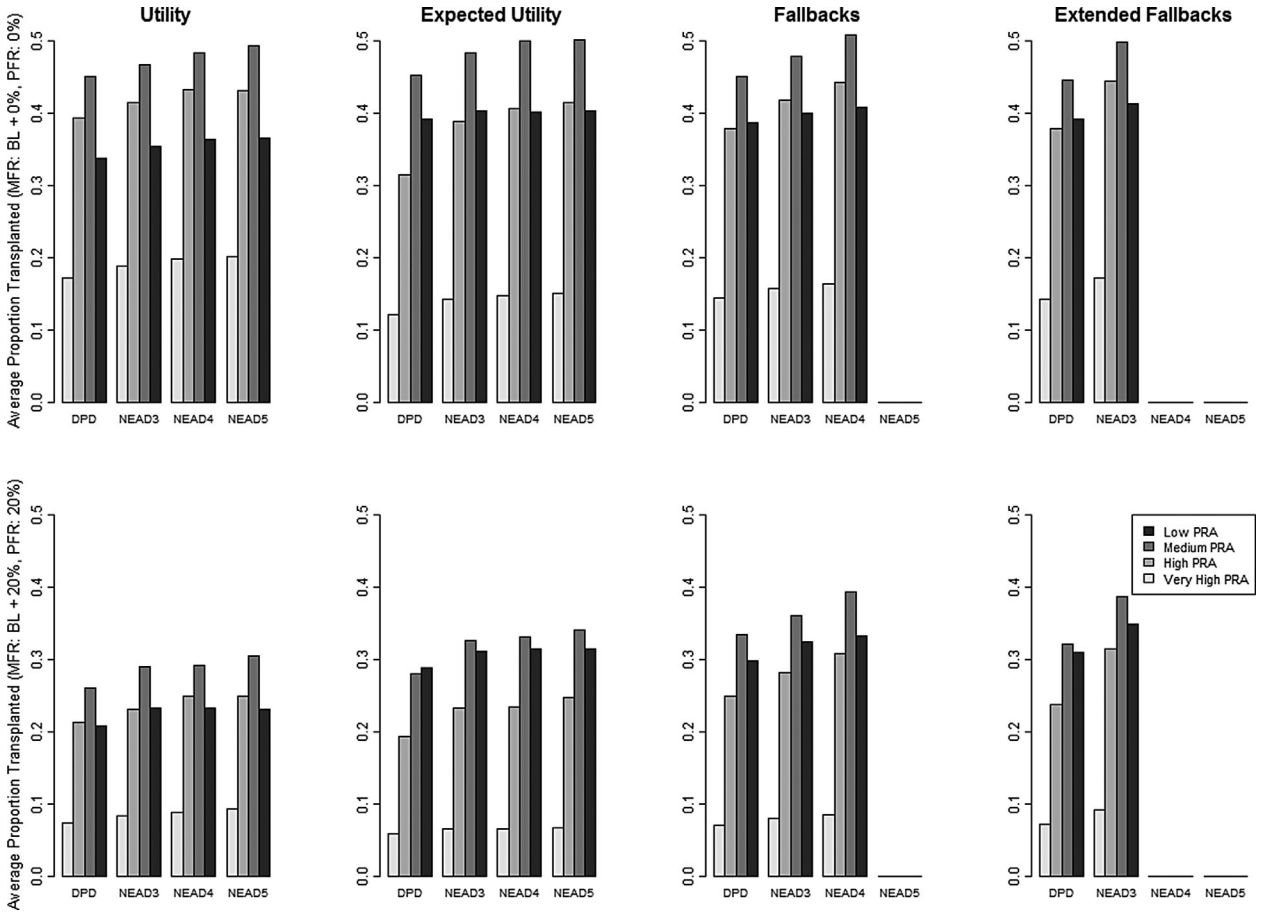

Figure 6: Distributions of the proportion of candidates of each PRA level transplanted over the course of the match runs in each scheme. The top (bottom) panel corresponds to simulations with Baseline (Baseline + 20%) MFR and 0% (20%) PFR. PRA, panel reactive antibodies; MFR, match failure rate; PFR, pair failure rate.

approach; although this offers improvement over a *Utility* scheme alone, there remains a substantial advantage to taking account of contingency or fallback options at the planning stage.

The probabilities assigned are meant to encompass all possible failures within a KPD: the MFR represents all match-specific failures, including the willingness to accept a proposed match, and the PFR represents the potential unavailability of a pair. We have modeled a range of probabilities of failure for the match and the pair in what might be viewed as a sensitivity study. Ideally, these probabilities on the match and the pair would be empirically determined based on experience in KPDs. In the absence of such data, however, it is still useful to incorporate an overall level of uncertainty that is more or less reflective of experience. The values for the MFRs and PFRs we specify are perhaps low given experience at the APD and the Michigan KPD programs. If more precise values for the failure rates were available from data, they could be incorporated without difficulty. Ignoring uncertainties, as is done in traditional schemes, is equivalent to assuming that the failure rates are null and is certainly suboptimal; including even approximate uncertainties and introducing fallbacks would be expected to achieve more transplants.

Optimization schemes that take account of the probability of failure may introduce bias toward potential transplants that are most likely to move ahead to completion. Thus, one might expect biases against high PRA candidates and in favor of lower PRA candidates where the success probability for the match is higher. Figure 6 examines the issue of PRA for the optimization schemes considered. There may be advantage to proactively giving preference to highly sensitized candidates by assigning additional utility to a potential transplant when the candidate is highly sensitized. Evaluating such schemes is an area under current investigation. All of these methods can be generalized to allow utility assignments to potential transplants which assign extra value, for example, to high PRA candidates, O to O transplants or candidates with long waiting times. Alternatively, one could use utilities that reflect the likely outcome of the proposed transplant, such as the probability of 5-year graft survival. We are

investigating such utility schemes in further research, but the general conclusions that taking uncertainties and fallbacks into account increases the number of realized transplants seem to hold for all such utility assignments.

Compatible pairs can also be included into KPD programs, especially when there is potential advantage to the candidate in the compatible pair (19). Our simulations do not include such pairs, although their inclusion would not fundamentally change modeling strategies. In the APD and University of Michigan KPD experience, compatible pairs tend to be less likely to participate in an exchange, which would correspond to a higher MFR, and it is likely that such pairs would tend to leave the pool early if no suitable match is obtained. Additional complexities arise in multi-program setups, where pairs are enrolled and can potentially participate in several programs. These methods may still be valuable in a given program, even with interference from other programs; the interference would tend to increase the uncertainties as represented by MFR and PFR, but more work would need to be done to estimate probabilities under these circumstances. Several assumptions in our simulations may not hold for all KPD programs, depending on protocols. For example, some KPD programs may turn down entire selected chains that cannot be completed, instead of allowing them to proceed until a point of failure. We would expect such a protocol to increase the desirability of shorter chain segments of only 2 or 3 in a given match run.

We believe the match runs as described provide an orderly approach that alleviate the logistical issues associated with re-selecting and then reconstituting the pool whenever an exchange is found to fail. Although questions of length of chain are not completely settled, especially for *Extended Fallbacks*, it appears from our results that there may be little advantage in considering chain segments longer than 3. It should be emphasized, however, that long NEAD chains are still valuable as they build up through a series of shorter segments determined in a strategic manner over several match runs. In our *Extended Fallbacks* simulation with NEAD-3, the first NDD gives rise to a chain of average length roughly 5.5 (Baseline MFR, 0% PFR) to 4.5 (Baseline + 20% MFR, 20% PFR) by the end of the 8th match run, even though each match run segment is of size 3 or less (75th percentile ranged from 6 to 7 depending on MFR/PFR; maximum length ranged from 10 [for 20% PFR, Baseline + 10%, and Baseline + 20% MFR] to 15 [for Baseline + 10% MFR, 0% PFR])..

The algorithms discussed in this article require extensive computation, especially for optimization using fallback options. This might become a problem for large nationwide pools, where the pool size could be on the order of thousands (14), as opposed to a few hundred maximum in these simulations. It should be noted, however, that implementing these strategies for a single match run, as opposed to simulations with hundreds of replicates, is a much simpler problem and feasible for fairly large pools.

Acknowledgments

This work was supported in part by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) through grant number 1R01-DK093513, and by the Natural Sciences and Engineering Research Council of Canada (NSERC), in the form of a Post-Graduate Scholarship (Master's) PGS M award to M.B. M.R. was supported in part by National Institute of Allergy and Infectious Diseases (NIAID) grants R21 AI-111579 and R01-AI090244. M.R. and A.L. were supported in part by Agency for Healthcare Research and Quality (AHRQ) grant R18 HS-020610. The authors thank Jonathan Kopke of the APD for preparing data that formed the basis of the simulations and Dr. Edward Cole for helpful comments on this work. Finally, the authors acknowledge Dr. Itai Ashlagi for his guidance in describing earlier simulations and in placing this work in context. We also wish to thank the editors and referees for their helpful comments and suggestions that led to a much improved exposition of this work.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Dr. Rees reports receiving grant support for the Alliance for Paired Donation from Novartis, Genzyme, Astellas, Roche, Wyeth, and Pfizer Pharmaceuticals.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplemental Methods

Appendix: Illustration of optimization schemes, match run example revisited.

Table S1: Number of transplants and expected number of transplants for cycles and chains in the example of Figure S1, both without and with fallbacks.

Table S2: Optimization schemes and their expected utilities taking account of fallbacks where appropriate.

Figure S1: An example of a small KPD pool to illustrate the optimization schemes used. Pairs 1 through 5 are denoted by white circles; NDD 6 is represented by a gray circle. An arrow from one pair/NDD to a second pair denotes a potential transplant from the former to the latter.

Figure S2: Illustration of the results of the optimization schemes applied to the KPD pool in Figure S1. The panels (i), (ii), (iii), and (iv) correspond, respectively, to the solutions obtained under the *Utility, Expected Utility*, *Fallbacks*, and *Extended Fallbacks* schemes.

Figure S3: (A) Solution for the example match run from the main paper using the *Fallbacks* scheme. The solution contains two three-way cycles and a chain of length 1, consisting of pairs, represented by white circles, and a single NDD (693) represented by a gray circle. An arrow from one pair/NDD to another represents a potential transplant from the donor in the former to the candidate in the latter, based on a virtual crossmatch. (B) Hypothetical reduced solution for the *Fallbacks* scheme after assessing compatibility and determining availability of pairs. The dotted circle indicates the unavailability of pair 683 for this match run, and dotted arrows represent potential transplants deemed unviable, or otherwise removed from consideration. Bolded arrows represent a choice of transplants resulting from this reduced solution. In this example, remaining are the single transplant from NDD 693 to pair 702, and the two-way cycle between pairs 701 and 642; no transplants result from the final (right-most) selected cycle.