

SORT 38 (1) January-June 2014, 53-72

Decision making in kidney paired donation programs with altruistic donors

Yijiang Li¹, Peter X.-K. Song², Alan B. Leichtman³, Michael A. Rees⁴
and John D. Kalbfleisch⁵

Abstract

In recent years, kidney paired donation has been extended to include living non-directed or altruistic donors, in which an altruistic donor donates to the candidate of an incompatible donor-candidate pair with the understanding that the donor in that pair will further donate to the candidate of a second pair, and so on; such a process continues and thus forms an altruistic donor-initiated chain. In this paper, we propose a novel strategy to sequentially allocate the altruistic donor (or bridge donor) so as to maximize the expected utility; analogous to the way a computer plays chess, the idea is to evaluate different allocations for each altruistic donor (or bridge donor) by looking several moves ahead in a derived look-ahead search tree. Simulation studies are provided to illustrate and evaluate our proposed method.

MSC: 62-Statistics; 90-Operations Research, Mathematical Programming.

Keywords: Altruistic donors, decision analysis, kidney paired donation, look-ahead search tree.

1. Introduction

For patients with end stage renal disease (ESRD), kidney transplantation is a preferred treatment as compared with dialysis for it provides not only a longer survival but also a better quality of life (Evans et al., 1985; Russell et al., 1992; Wolfe et al., 1999). Accord-

¹ Statistician at Google Inc., Mountain View, CA 94043, USA (Email: yijiang1121@gmail.com).

² Professor, Department of Biostatistics, University of Michigan, Ann Arbor, MI 48109, USA (Email: pxsong@umich.edu).

³ Professor, Department of Internal Medicine, University of Michigan, Ann Arbor, MI 48109, USA (Email: leicht@med.umich.edu).

⁴ Professor, Department of Urology, University of Toledo Medical Center, Toledo, Ohio 43614, USA (Email: michael.rees2@utoledo.edu).

⁵ Professor, Department of Biostatistics, University of Michigan, Ann Arbor, MI 48109, USA (Email: jdkalbf@umich.edu).

Received: April 2013

Accepted: December 2013

ing to the Organ Procurement and Transplantation Network (OPTN), about 16,760 kidney transplants were performed per year from 2009 to 2012 in the U.S., while during that same period of time the yearly average number of patients added to the waiting list for kidney transplant surpassed 34,100. Part of this gap between supply and demand can be attributed to the unfortunate fact that many patients with kidney failure recruit willing organ donors who, upon evaluation, prove to be ABO blood type and/or Human Leukocyte Antigens (HLA) incompatible. With regard to blood type compatibility, A and B donors can donate to candidates of the same blood type or of type AB; AB donors can donate only to AB candidates; and O donors, known as universal donors, can donate to candidates of any blood type. The HLA incompatibility, on the other hand, is due to the candidate having antibodies against the HLA antigens of a potential donor resulting from prior exposure to donor antigens through pregnancy, transfusion or previous transplant. Both forms of incompatibility can lead to a rapid rejection of the transplanted organ and thus prohibit transplantation.

An evolving strategy, known as kidney paired donation (KPD) (Rapaport, 1986) matches one donor-candidate pair to another pair with a complementary incompatibility, such that the donor of the first pair donates to the candidate of the second, and vice versa; see Figure 1-A and Figure 1-B for illustrations of a two-way exchange and a three-way exchange. Although three-way or higher exchange cycles increase the chance of identifying compatible matches, most KPD programs restrict exchanges to at most three ways for two primary reasons. First, all surgical operations in a cycle must be performed simultaneously to avoid the possibility that one of the donors may renege. This requirement creates substantial logistical difficulties of scheduling, for example, eight surgeons and eight operating rooms at the same time for a four-way exchange. Second, the greater the length of an exchange cycle, the less likely the potential transplants involved will actually occur, for the whole exchange cycle collapses if any of the proposed transplants cannot proceed.

A fundamental problem in managing KPD programs lies in selecting the “optimal” set of kidney exchanges from among the many possible alternatives. This problem has been modeled and analyzed by economists using a game-theoretic approach (Roth et al., 2004). More general approaches have been developed to tackle such a problem via an integer programming (IP) formulation, first proposed by Roth et al. (2007); In this, each

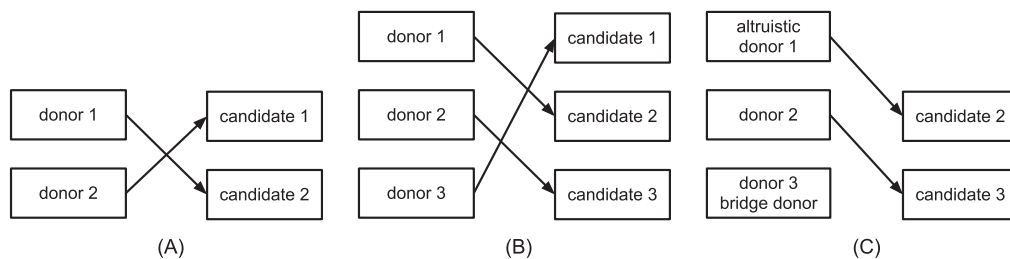


Figure 1: (A): A two-way exchange; (B): A three-way exchange; (C): A NEAD chain.

potential transplant was assigned equal weight, resulting in an allocation strategy that enables the greatest number of transplants to be potentially implemented. Abraham et al. (2007) adopted a more flexible weight assignment in this IP-based formulation and further developed an algorithm to reduce the computational complexity of managing large KPD programs. Li et al. (2013) considered a general utility-based evaluation of potential kidney transplants. Moreover, they explicitly took into account inherent uncertainties in managing KPD programs and exploited possible fall-back or contingent exchanges when the originally planned allocation cannot be fully executed. In a data-driven simulation system, they demonstrate that taking such additional elements into consideration would yield improved allocation strategies.

In recent years, KPD has also been extended to include living non-directed donors (LNDs), or altruistic donors; these are donors who have no designated candidates and decide to donate voluntarily to a stranger. In this context, an altruistic donor may donate to the candidate of an incompatible pair with the understanding that the donor of that pair will become a bridge donor, and further donate to the candidate of a second pair, and so on; such a process continues and thus forms an LND-initiated chain. One advantage to such chains as compared to two-way or higher order exchange cycles is that transplants along the chain do not need to be performed simultaneously (Montgomery et al., 2006; Roth et al., 2006). As a consequence, the donor whose incompatible candidate has received another donor's kidney but has yet to donate could donate later to another candidate; such donors are hence called "bridge donors". For this reason, this LND-initiated chain is sometimes called a non-simultaneous extended altruistic donor (NEAD) chain (Rees et al., 2009). Figure 1-C illustrates a NEAD chain. Kidneys from altruistic donors used to be designated to patients with no living donors and who have therefore been placed on a deceased-donor waiting list. A NEAD chain, however, allows for passing the altruism beyond saving just one patient, to potentially benefitting several patients in the chain; the final donor in an NEAD chain could still donate to the deceased-donor waiting list. The advantage of such chains has already been demonstrated via simulation studies by Gentry et al. (2009) and Ashlagi et al. (2011). In clinical practice, the standard way of incorporating LND and bridge donors into the optimization of a KPD is to consider chains up to a given length along with cycles in the optimization for each match run. Thus, at regular intervals, the KPD pool is examined and a set of chains segments and/or a set of cycles are chosen using the integer programming approach, and those chosen are implemented if possible.

In this paper, we consider a different strategy for developing a NEAD chain under uncertainties in a KPD program with one altruistic donor. We also discuss in general some possible extensions of this strategy to incorporate multiple altruistic donors. Analogous to the way a computer plays chess, we propose an approach to sequentially allocating an altruistic donor (or a bridge donor) so as to maximize the expected utility over a certain given number of moves. The idea is to evaluate different allocation options available for each altruistic donor (or bridge donor) by looking several moves ahead along a derived look-ahead search tree. With these options in mind, we proceed with the

next allocation of the altruistic or bridge donor that has the highest evaluation. This is the first step in developing an approach that would alternate between optimizing the use of LND and bridge donors and assigning cycles, each in an optimum way. This approach would then be compared with the standard simultaneous maximization over chains and cycles as described above.

The rest of the paper is organized as follows: in Section 2, we introduce a graph representation for a KPD program with altruistic donors. With this representation, we define the *optimal policy* in the context of managing a KPD program with one altruistic donor. This optimal policy can be obtained in general by following a standard decision-tree analysis, which we briefly illustrate in Section 3. The computation associated with this decision-tree based approach, however, is very expensive for large KPD programs. To address this issue, we propose, in Section 4, a more efficient and practical approach which sequentially extends a NEAD chain according to the utility calculated along a look-ahead search tree. Section 5 provides simulation studies to illustrate and evaluate our proposed strategy. In Section 6, we conclude with some discussion on possible extensions to incorporate multiple altruistic donors.

2. Problem formulation

In this section, we describe a graph representation for KPD programs that includes incompatible pairs as well as altruistic donors. We then define the optimal policy in the management of a KPD program with a single altruistic donor.

2.1. Graph representation

We represent a KPD program as a *directed graph*, $\mathcal{G} = (\mathcal{V}, \mathcal{E})$, where the *vertex set*, $\mathcal{V} \equiv \mathcal{V}(\mathcal{G}) = \{1, 2, \dots, m, m+1, \dots, n\}$, consists of m altruistic donors and $n - m$ incompatible donor-candidate pairs, where $m \leq n$. We denote by, $\mathcal{V}_a \equiv \mathcal{V}_a(\mathcal{G}) = \{1, 2, \dots, m\}$, the collection of altruistic donors, and $\mathcal{V}_p \equiv \mathcal{V}_p(\mathcal{G}) = \mathcal{V} \setminus \mathcal{V}_a$, the set of incompatible pairs. The *edge set*, $\mathcal{E} \equiv \mathcal{E}(\mathcal{G})$, is a *binary relation* on \mathcal{V} , consisting of ordered pairs of vertices in \mathcal{V} . An edge from i to j , denoted as (i, j) , implies that the donor in pair i (or the altruistic donor i) is predicted to be compatible with the candidate in pair j . Such a prediction is based on a *virtual crossmatch* test, which involves computer cross-checking for blood type compatibility as well as comparing preexisting candidate antibodies against donor HLA antigens. Before a predicted compatible transplant can be further considered for an actual surgical operation, the compatibility must be confirmed by a more labour-intensive *laboratory crossmatch* test to assure histocompatibility; this involves incubating the serum of a candidate with the white blood cells of a prospective donor. Figure 2 illustrates a graph representation for a two-way exchange, a three-way exchange, and a NEAD chain, corresponding respectively to scenarios (A)-(C) in Figure 1.

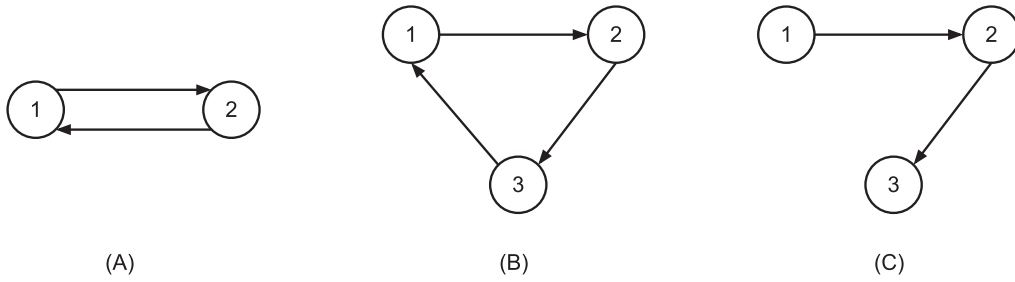


Figure 2: (A): A graph representation of a KPD program with a two-way exchange cycle, where $\mathcal{V}_p = \{1, 2\}$ and $\mathcal{E} = \{(1, 2), (2, 1)\}$; (B): A graph representation of a KPD program with a three-way exchange cycle, where $\mathcal{V}_p = \{1, 2, 3\}$ and $\mathcal{E} = \{(1, 2), (2, 3), (3, 1)\}$; (C): A graph representation of a NEAD chain, where $\mathcal{V}_a = \{1\}$, $\mathcal{V}_p = \{2, 3\}$ and $\mathcal{E} = \{(1, 2), (2, 3)\}$; donor 3 at the end of the chain becomes a bridge donor.

The virtual crossmatch test is necessary because in practice the laboratory crossmatch test cannot be undertaken on all possibly compatible donors and candidates due to labour and resource limitations. Further, even if the laboratory crossmatch result is negative (non-reactive), an actual transplant operation may not occur due to other friction including, for example, refusal or illness or death of the candidate or the donor. To incorporate such stochastic features, we associate with each edge, $e = (i, j)$, a probability (denoted as p_e or p_{ij}) that e , if chosen, could result in an actual transplant operation (Li et al., 2013). Throughout the rest of the paper, we use the term “*is viable*” to indicate that an edge could lead to an actual transplant.

In addition, we associate with each edge (or potential transplant) a general utility (Li et al., 2013). Such utilities are often rule-based and determined by various attributes such as degree of sensitization of the candidate against the potential donor pool, or time since enrolment in the KPD. These utilities could also be based on predicted medical outcomes such as the estimated graft or patient survival, or the incremental years of recipient life that would accrue with a kidney transplant as opposed to a candidate’s remaining on dialysis; see Wolfe et al. (2008). For each potential transplant $e = (i, j)$, we denote such an assigned utility as u_e or u_{ij} .

In this paper, our attention is not on the estimation of edge utilities and probabilities. It is worth noting though that research along this line is important and needed in the practical management of a KPD program; see more discussion on this aspect in Wolfe et al. (2008), Schaubel et al. (2009), and Li et al. (2013).

2.2. The optimal policy

One difficulty with selecting a long NEAD chain and then arranging transplants accordingly is that in practice this long chain can rarely be fully implemented. This is because the chain would break as soon as one transplant cannot proceed as planned. In this paper,

we propose to extend a NEAD chain sequentially in a near optimal way by selecting one potential transplant recipient at a time. In subsequent discussion, we note how this can be used as the basis of more general approaches.

Consider a KPD program with only one altruistic donor, i.e. $m = 1$ and $\mathcal{V}_a = \{1\}$. This naturally implies $(i, 1) \notin \mathcal{E}$ for all $i \in \mathcal{V}$, as altruistic donors don't have designated candidates. For $j \in \mathcal{V}$ such that $j = 1$ or $(1, j) \in \mathcal{E}$, let $\mathcal{G}(j) \equiv (\mathcal{V}_j, \mathcal{E}_j)$ be a *subgraph* of $\mathcal{G} = (\mathcal{V}, \mathcal{E})$, where

$$\begin{aligned}\mathcal{V}_j &= \{v \in \mathcal{V} : v \text{ is accessible from } j\}, \\ \mathcal{E}_j &= \{(v_1, v_2) \in \mathcal{E} : v_1 \in \mathcal{V}_j, v_2 \in \mathcal{V}_j, v_2 \neq j\}.\end{aligned}$$

In this paper, a vertex j is said to be *accessible* from a vertex i if $i = j$ or if there exists a set of edges in \mathcal{E} , denoted as $\{(i_k, i_{k+1}), k = 0, 1, \dots, n\}$ such that $i_0 = i$ and $i_{n+1} = j$. In general terms, $\mathcal{G}(j)$ represents the resulting KPD graph if the transplant according to $(1, j) \in \mathcal{E}$ is arranged and j becomes a bridge donor.

Managing a KPD program with one altruistic donor could then be viewed as a sequential decision problem, in which we start with $U = 0$ and $\mathcal{G} = \mathcal{G}(1)$, and then repeat the following steps until $|\mathcal{V}(\mathcal{G})| = 1$:

1. choose one edge from $A \equiv \{(1, j) : (1, j) \in \mathcal{E}\}$, say $(1, b)$.
2. if $(1, b)$ is viable, update

$$\begin{aligned}U &\leftarrow U + u_{1b}, \\ \mathcal{G} &\leftarrow \mathcal{G}(b), \\ 1 &\leftarrow b;\end{aligned}$$

if $(1, b)$ is not viable, update the KPD pool

$$\mathcal{G} \leftarrow \mathcal{G}_{-b}(1), \text{ where } \mathcal{G}_{-b} = (\mathcal{V}, \mathcal{E} \setminus \{(1, b)\}).$$

Step (i) is carried out to implement a *policy* that would be used to manage the KPD program by specifying what action from A to take at each loop; two sample policies are,

$$\begin{aligned}b &= \operatorname{argmax}_{j:(1,j) \in A} u_{1j} \\ b &= \operatorname{argmax}_{j:(1,j) \in A} u_{1j} p_{1j}.\end{aligned}$$

These correspond to greedy algorithms that look at the next step only and manage to optimize the utility or the expected utility of that step. They may, of course, be very poor strategies since they ignore any subsequent implications of possible next steps.

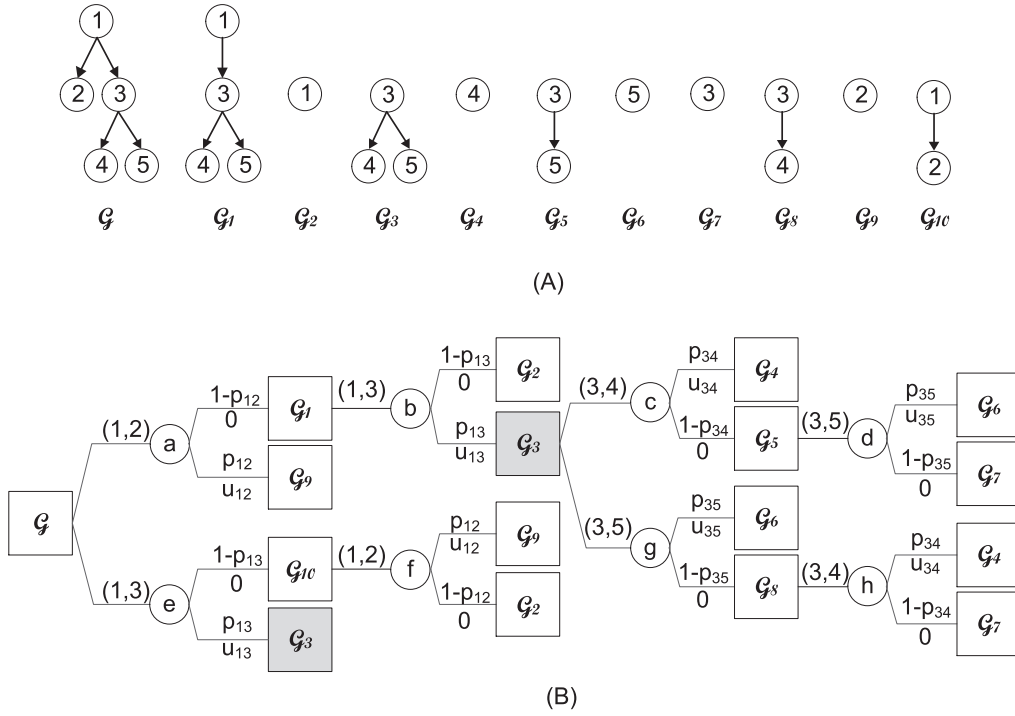


Figure 3: (A): A KPD program \mathcal{G} with one altruistic donor and four incompatible pairs as well as various subgraphs of \mathcal{G} ; (B): A standard decision tree analysis for a KPD program \mathcal{G} as in (A), with squares representing decision nodes and circles indicating chance nodes; the decision node \mathcal{G}_3 (which is shaded) appears twice in the tree and hence is only drawn once.

For any given policy on $\mathcal{G} = (\mathcal{V}, \mathcal{E})$, the value of U after the algorithm terminates can be interpreted as the cumulative claimed utility. This value, which we denote by U_∞ , is random; and its expectation could be used to evaluate the policy from which it arose. Among all policies defined in the above way, the *optimal policy* refers to the one that attains the highest value of $E(U_\infty)$. This way of defining the optimal policy provides a formal framework that will prove convenient in later discussions, even though in general one can rarely follow this optimal policy through until the iterative procedure ends. This is an important issue, arising due to various practical concerns, that we will revisit in Section 4.2.

Figure 3-A provides an illustrative example, where \mathcal{G} represents a KPD program with four incompatible pairs (vertices 2, 3, 4 and 5) and one altruistic donor (vertex 1). Starting from \mathcal{G} , the action space is $A = \{(1, 2), (1, 3)\}$ and suppose we proceed by selecting (1, 2). If it is viable, this would lead to $\mathcal{G}(2)$, denoted as \mathcal{G}_9 in Figure 3-A, and the resulting value of U_∞ is u_{12} ; if (1, 2) is not viable, we end up with \mathcal{G}_1 , at which the updated action space becomes $A = \{(1, 3)\}$. We then continue by selecting (1, 3), and if it is not viable, we stop at \mathcal{G}_2 ; if (1, 3) is viable, we then proceed to \mathcal{G}_3 , at which the updated action space becomes $A = \{(3, 4), (3, 5)\}$; and we continue this process by

selecting one allocation from A . In this paper, we assume that edges in a KPD graph have an independence relationship. Though this assumption can be relaxed, it is a reasonable one when pair withdrawal (due to factors such as pregnancy, illness, or death) does not occur frequently; see Li et al. (2013) for related discussion.

3. Decision tree analysis for KPD

The optimal policy introduced in the previous section can be obtained by conducting a standard decision tree analysis, which we briefly illustrate below using a small example. The computation associated with such an analysis, however, can be rather complicated for large problems. We will return to this computational issue in Section 4, and present an alternative and more efficient approach to analyzing policies and optimizing the allocations. Note that a general mathematical framework derived from theories of Markov decision processes (MDPs) can be used to rigorously formulate the problem of managing KPD programs with altruistic donors (Li, 2012). However, solving for the optimal policy is computationally difficult for large or even moderate KPD problems, which poses a serious impediment to the development of practical algorithms based on this MDP framework. We briefly describe the MDP formulation in this section by using a particular example. In Section 4, we describe an alternative and more efficient way of analyzing the KPD that takes account of the fall-back options.

The structure of \mathcal{G} in Figure 3-A cannot be used directly for a standard decision tree analysis due to the existence of various fall-back options; for example, if edge $(1,3)$ is selected but not viable, we could fall back to $(1,2)$. The complete analysis is instead provided by a derived decision tree (oriented from left to right) as shown in Figure 3-B, where squares represent *decision nodes* and circles indicate *chance nodes*. Each decision node is followed in this tree by a fixed number of chance nodes associated with all actions available at that decision node. Each chance node is then followed by two decision nodes corresponding to the two possible outcomes of choosing that chance node: one outcome is that the chosen transplant $e \in \mathcal{E}$ is viable, resulting in a utility of u_e , whereas the other is that e is not viable, for which zero utility is generated. These two utilities are associated with the edges from the chance node to the two corresponding decision nodes. For example, in Figure 3-B, starting from the decision node \mathcal{G} , two actions are available, either arrange a transplant according to edge $(1,2)$ leading to chance node a or according to edge $(1,3)$ leading to chance node e . In the case where $(1,2)$ is chosen, associated with the chance node a are two possible outcomes, \mathcal{G}_1 and \mathcal{G}_9 , which occur with probabilities $1 - p_{12}$ and p_{12} respectively. If \mathcal{G}_9 occurs, we claim a utility of u_{12} , and zero utility is generated if \mathcal{G}_1 occurs, for which we continue on this analysis from chance node b .

The *expected value* (EV) associated with a chance node or a decision node is calculated alternately in a backward direction along the tree from the right to the left. Precisely, (i) the EV at a leaf decision node is 0 (this could be set to some non-zero

number to represent the potential value associated with the corresponding bridge donor; see more discussion on this in Section 6); (ii) the EV at a chance node is computed by taking a weighted average of the sums of the utilities along the edges originating at this chance node and the EVs at the corresponding successor decision nodes; (iii) the EV at a non-leaf decision node is calculated by taking the maximum of the EVs of its children nodes.

For example, in Figure 3-B, the EVs at decision nodes \mathcal{G}_5 and \mathcal{G}_8 are $EV[\mathcal{G}_5] = EV[d] = p_{35}u_{35}$ and $EV[\mathcal{G}_8] = EV[h] = p_{34}u_{34}$ respectively. The EVs at chance nodes c and g are $EV[c] = p_{34}u_{34} + (1 - p_{34})EV[\mathcal{G}_5]$ and $EV[g] = p_{35}u_{35} + (1 - p_{35})EV[\mathcal{G}_8]$ respectively. This indicates that $EV[c] \geq EV[g]$ if and only if $u_{34} \geq u_{35}$, and the action taken at \mathcal{G}_3 is therefore (3, 4) or (3, 5) depending on which one has the larger edge utility. The EV at node \mathcal{G}_3 is then calculated as

$$\begin{aligned} EV[\mathcal{G}_3] &= \max\{EV[c], EV[g]\} \\ &= \max\{p_{34}u_{34} + (1 - p_{34})p_{35}u_{35}, p_{35}u_{35} + (1 - p_{35})p_{34}u_{34}\}. \end{aligned} \quad (1)$$

After computing EVs associated with all decision and chance nodes in this way, the optimal policy at each decision node is to adopt the action associated with the chance node that has the maximum EV. This procedure starts from the root decision node, that is from the altruistic donor.

4. A look-ahead search tree-based strategy

The structure of the derived decision tree in Figure 3-B is much more complicated than the structure of \mathcal{G} itself in Figure 3-A. As a result, the standard decision tree analysis as introduced in Section 3 results in substantial computational difficulties when the KPD graph is large. In this section, we address this issue by presenting a more efficient and practical approach that relies on evaluating different allocations for each altruistic donor (or bridge donor) according to a derived look-ahead search tree.

4.1. Identifying the optimal policy via a search tree

Consider first a KPD program, $\mathcal{G} = (\mathcal{V}, \mathcal{E})$, where $\mathcal{V}_a = \{1\}$, $\mathcal{V}_p = \{2, 3, \dots, n\}$, and $\mathcal{E} = \{(1, i) : i = 2, 3, \dots, n\}$. Without loss of generality, assume $u_{12} \geq u_{13} \geq \dots \geq u_{1n}$. For this specific KPD program, the optimal policy to follow at \mathcal{G} is to try transplant (1, 2), and if it fails then try (1, 3), then (1, 4) and so forth. The associated EV of this policy is

$$EV[\mathcal{G}] = \sum_{k=2}^n \left\{ u_{1k} p_{1k} \prod_{i=2}^{k-1} (1 - p_{1i}) \right\}. \quad (2)$$

Based on this fact, we could then select the optimal action to take from \mathcal{G} directly and hence avoid explicitly constructing a decision tree and calculating the EV associated with each node of the tree, as would be required for the standard decision analysis in Section 3. This observation is very useful as we can see, for example, by applying formula (2) at the decision node \mathcal{G}_3 in Figure 3-B. This would lead to the optimal action of taking (3,4) or (3,5) depending on which one has the larger utility; and the EV at \mathcal{G}_3 is therefore computed as

$$EV[\mathcal{G}_3] = 1_{[u_{34} \geq u_{35}]} \{p_{34}u_{34} + (1 - p_{34})p_{35}u_{35}\} + 1_{[u_{34} < u_{35}]} \{p_{35}u_{35} + (1 - p_{35})p_{34}u_{34}\}. \quad (3)$$

Note that formula (3) is exactly equal to the one calculated via a standard decision analysis as in formula (1), but this latter approach requires calculating EVs at additional nodes \mathcal{G}_5 and \mathcal{G}_8 .

Consider now a KPD program, $\mathcal{G} = (\mathcal{V}, \mathcal{E})$, where $\mathcal{V}_a = \{1\}$, let $A \equiv \{(1, j) : (1, j) \in \mathcal{E}\}$ and $u_{1j}^* \equiv u_{1j} + EV[\mathcal{G}(j)]$, for all $(1, j) \in A$. Without loss of generality, we assume $A = \{(1, j) : j = 2, 3, \dots, l\}$ and $u_{12}^* \geq u_{13}^* \geq \dots \geq u_{1l}^*$. Then the optimal decision to take at \mathcal{G} is to attempt transplant (1, 2); and if it fails, try (1, 3) and then (1, 4), and so on; the associated EV is

$$EV[\mathcal{G}] = \sum_{k=2}^l \left\{ p_{1k} u_{1k}^* \prod_{i=2}^{k-1} (1 - p_{1i}) \right\}. \quad (4)$$

Based on this result, we could evaluate various choices in A by u_{1j}^* and then proceed with the one having the largest value. We repeatedly apply this procedure from terminal nodes up to sequentially form a NEAD chain, with formula (4) evaluating the expected utility in this process.

To identify the optimal action to take at \mathcal{G} , we recursively apply formula (4), which in fact does not require calculating EVs associated with all decision nodes and chance nodes, but only a fraction of them. These required nodes can then be organized according to their dependence relationship as in (4) to form a *search tree*. In this tree, the node on the left hand side of (4) is the *parent* while the nodes on the right hand side denote *children*; and edges connecting them represent the corresponding actions. The structure of this tree therefore allows us to compute EVs associated with its nodes recursively in a backward manner from the leaf nodes to the root.

Figure 4 provides an example of a search tree and illustrates calculating EVs associated with its nodes; the search tree in this figure only involves 5 nodes, much less than that of the decision tree in Figure 3-B. The optimal action to take at \mathcal{G} in this example is edge (1, 3) if $u_{12}^* = u_{12}$ is smaller than $u_{13}^* = u_{13} + EV[\mathcal{G}_3]$ or edge (1, 2) otherwise; the EV at \mathcal{G} is therefore computed as

$$EV[\mathcal{G}] = 1_{[u_{13}^* \geq u_{12}^*]} \{p_{13}u_{13}^* + (1 - p_{13})p_{12}u_{12}^*\} + 1_{[u_{13}^* < u_{12}^*]} \{p_{12}u_{12}^* + (1 - p_{12})p_{13}u_{13}^*\}.$$

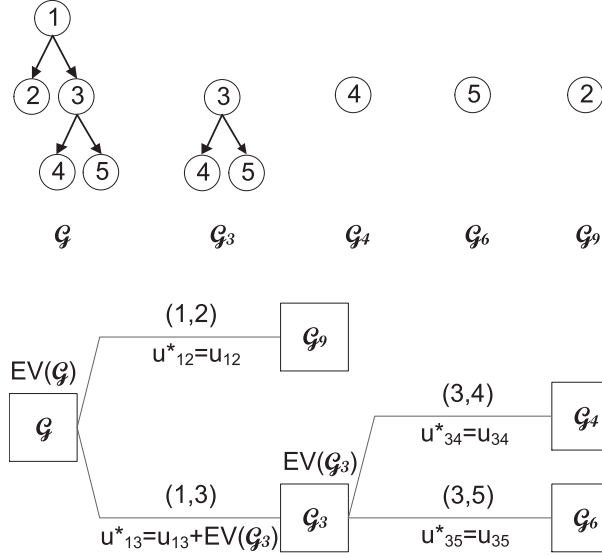


Figure 4: A search tree-based analysis for a KPD program \mathcal{G} .

Clearly, the decision analysis of this search tree is much simpler than that from a standard decision tree as in Figure 3-B, although both lead to the same result.

In general, the search tree associated with a KPD program can be constructed by an algorithm based on the classic depth-first search (DFS). We developed such an algorithm that also computes the EVs while performing a DFS on the KPD graph. The optimal policy is then determined by the following iterative algorithm:

1. for $\mathcal{G} = (\mathcal{V}, \mathcal{E})$, construct the corresponding search tree by following a DFS-based algorithm, and compute the EV associated with each node of this search tree; this is done recursively from the terminal nodes up to the root node.
2. update the current action space $A \equiv \{(1, j) : (1, j) \in \mathcal{E}(\mathcal{G})\}$, and calculate $u_{1j}^* = u_{1j} + EV[\mathcal{G}(j)]$ for $(1, j) \in A$.
3. choose $(1, b) \in A$ with $b = \operatorname{argmax}_{j:(1,j) \in A} u_{1j}^*$.
4. if $(1, b)$ is viable, update

$\mathcal{G} \leftarrow \mathcal{G}(b)$, i.e. update the KPD graph,

$1 \leftarrow b$, i.e. set the bridge donor b as the new altruistic donor;

if $(1, b)$ is not viable, update the KPD pool

$\mathcal{G} \leftarrow \mathcal{G}_{-b}(1)$, where $\mathcal{G}_{-b} = (\mathcal{V}, \mathcal{E} \setminus \{(1, b)\})$.

5. go back to (ii) until $|\mathcal{V}(\mathcal{G})| = 1$.

For completeness, we also briefly describe here a slightly more complicated example in which the KPD itself is not a tree (as it is in Figure 3-A above). The KPD in this example is obtained by adding edges (2,4) and (4,3) to the KPD graph \mathcal{G} in Figure 3-A. Note that vertex 4 can be reached in two distinct ways and gives rise to two distinct subgraphs. Specifically, if (1,3) and (3,4) are transplanted, $\mathcal{G}(4)$ only has vertex 4; if (1,2) and (2,4) are transplanted, $\mathcal{G}(4)$ has vertices 4 and 3 and also contains edge (4,3).

4.2. A depth- k search tree

Although the search tree-based approach allows for a much more efficient analysis than does a standard decision tree analysis, constructing such a search tree is computationally very expensive for a general large KPD graph; in fact, the computation is extensive even without the effort entailed in computing EVs associated with nodes along that tree. This unfortunate fact poses a substantial difficulty in identifying the optimal policy when the KPD program is large.

Further, a more important issue is that the optimal policy (even if it could be computed) would most likely not be implementable in practice. This is mainly because the practical process of initiating and extending a NEAD chain would require a relatively long period of time, during which the KPD pool would constantly be updated and evolve as new pairs arrive and/or existing pairs withdraw or candidates die; in addition, candidates in the pool may also be transplanted via exchanges among incompatible pairs or deceased donor kidneys from the waiting list, since these would typically be arranged in parallel with the NEAD chain mechanism. Thus, assessing strategies by looking a long way down the tree from the root node is often not that useful in practice.

To address such problems, we propose to proceed by first deriving a subtree, which we call a *depth- k search tree*, from the original search tree. Such a subtree can be readily obtained by the same DFS-based algorithm as introduced in Section 4.1, by simply restricting the depth of the search from the root node to k . We then follow the recursive relationship as in formula (4) to calculate the EVs associated with corresponding nodes in the subtree, beginning this calculation from the leaf nodes at depth k and working up through the tree to the root node. The EV of a leaf node is set to zero or some reasonable measurement of the value of the corresponding bridge donor (see Section 6 for more discussion). At this stage the iterative procedure presented in Section 4.1 can be applied, but with one modification that –if the chosen action $(1,b)$ is viable, we regenerate a depth- k search tree rooted at $\mathcal{G}(b)$ and compute EVs associated with the nodes of this new tree.

Instead of the optimality that exists only in a rather idealized scenario, the policy obtained from the depth- k search tree provides a more practical evaluation of potential bridge donors and a greatly reduced computational complexity. Further, our simulation results (see Section 5) suggest that the allocation strategy derived from a search tree performs reasonably well for a moderate depth of, say, 3 or 4. It is useful to note that

this strategy is feasible in the context of the search tree approach of this section, but would still be very complicated to implement using the standard decision tree analysis; for example, the depth-1 search tree constructed according to formula (2) provides the same analysis as the one via a standard decision tree of depth $2n + 1$.

5. Simulation studies

So far in this paper, we have explored a look-ahead search tree-based approach to manage a KPD program with one altruistic donor. This approach sequentially extends a NEAD chain by selecting one potential bridge donor at a time, taking into consideration the operational uncertainties and the long-term consequences associated with various possible selections. In this section, we provide simulation results of applying such an allocation strategy to manage a simulated KPD program.

5.1. Simulating incompatible pairs and altruistic donors

We simulate incompatible pairs and altruistic donors as in Li et al. (2013). For an incompatible pair, we simulate its candidate and donor separately from their own population distributions. Candidates are sampled at random (with replacement) from a database of incompatible pairs, which is derived from the University of Michigan KPD program. This database currently consists of 115 transplant candidates, each having at least one willing but incompatible donor. We are in the process of incorporating additional databases from other KPD programs for the purpose of reflecting a broader candidate variation. On the other hand, donors are simulated by sampling their blood types and HLA haplotypes respectively. Blood type is drawn from its U.S. population distribution: O, 44%; A, 42%; B, 10%; and AB, 4% (Stanford Blood Center, 2010), and HLA haplotypes are sampled according to a population frequency table derived from a public database on potential bone marrow donors (Maiers et al., 2007).

We consider a simulated donor-candidate pair as an incompatible pair, and hence include it in the KPD pool, if either their blood types mismatch or the donor's HLA haplotypes overlap with some of the candidate's antibody specificities. Finally, an altruistic donor is generated in the same way as we have described above for generating a donor in an incompatible pair.

5.2. Simulation setup

In Section 2.1, each potential transplant (which is predicted to be compatible by a virtual crossmatch test) is assigned a probability to reflect the inherent uncertainty in the system and a general utility to quantify the rule-based or outcome-based evaluation

of that potential transplant. As we have mentioned, estimation of these probabilities and utilities is an important aspect in the practical management of a KPD program. This also forms an independent line of research in parallel with the work of developing KPD allocation strategies. For illustrative purpose, our approach here is to obtain these utilities and probabilities according to certain simplified probability distributions, and then use them to study the method proposed in Section 4.2.

We perform a total of 3,000 simulations. In all simulations, edge probabilities are generated from a uniform distribution, $U(0.1, 0.5)$, which suggests an average success rate of 30% for a predicted compatible (by virtual crossmatch test) transplant. This rate is in line with the early experience at the University of Michigan KPD program and the Alliance for Paired Donation, though current success rate are somewhat higher. For edge utilities, we fix them at 1 for 1,000 simulations, draw them from uniform $U(10, 20)$ and $U(10, 30)$ respectively for the remaining 2,000 simulations (with 1,000 each). For each simulation, we execute an allocation strategy based on a depth- k search tree for k equal to 1, 2, 3, 4, and 5 respectively. We then record important performance measures such as cumulative claimed utilities and cumulative number of transplants. Note that when k is equal to 1, the allocation strategy simply corresponds to selecting, among all possible choices available for the altruistic donor, the one that has the largest edge utility.

5.3. Simulation results

First, we report on the cumulative number of transplants achieved in simulated KPD programs with one altruistic donor and 100 incompatible donor-candidate pairs. We compare the average number of transplants across different values of k and under the three utility generating distributions. Table 1 provides summary comparison, in which we observe a consistent pattern where the number of transplants performed increases with k . This is true regardless of which distribution is used to generate edge utilities.

Table 1: Summary of the average number of transplants performed (denoted by N) and the average cumulative utilities claimed (denoted by U_∞), by implementing a depth- k search tree-based allocation strategy on a simulated KPD program with one altruistic donor and 100 incompatible pairs. Edge utilities are generated from $U(1, 1)$, $U(10, 20)$, and $U(10, 30)$; and edge probabilities are generated from $U(0.1, 0.5)$. The summary is calculated over 3,000 rounds of simulations, with 1,000 simulations for each utility generating distribution. Note that for the choice $U(1, 1)$, the claimed utility equals the number of completed transplants.

depth- k	$u_e = 1$	$u_e \sim U(10, 20)$		$u_e \sim U(10, 30)$	
	mean N	mean N	mean U_∞	mean N	mean U_∞
$k = 1$	3.16	3.18	55.99	3.18	80.22
$k = 2$	8.17	6.65	112.21	6.19	149.58
$k = 3$	8.70	7.87	128.93	7.63	176.78
$k = 4$	8.74	8.26	133.54	7.99	181.92
$k = 5$	8.89	8.41	134.45	8.29	185.43

Table 2: Three correlation matrices for the total number of transplants performed in a depth- k search tree-based allocation strategy across different values of k . The entry at the i th row and the j th column represents the correlation between the total number of transplants when $k = i$ and that when $k = j$ when managing the same simulated KPD program (with one altruistic donor and 100 incompatible pairs). Matrix on the left: $u_e = 1$; matrix in the middle: $u_e \sim U(10, 20)$; matrix on the right: $u_e \sim U(10, 30)$.

1	.34	.34	.33	.31	1	.27	.29	.26	.29	1	.29	.27	.29	.29
–	1	.67	.67	.66	–	1	.50	.51	.48	–	1	.46	.48	.48
–	–	1	.79	.73	–	–	1	.66	.58	–	–	1	.58	.57
–	–	–	1	.81	–	–	–	1	.72	–	–	–	1	.72
–	–	–	–	1	–	–	–	–	1	–	–	–	–	1

Another observation is that the extra benefit in the number of transplants through increasing k is diminishing as k gets large. For example, when edge utilities are generated from $U(10, 20)$, increasing the value of k from 1 to 4 would almost triple the total number of transplants (on average from 3.18 to 8.26); however, further increasing k (from 4 to 5) appears to have very limited effects.

In terms of comparing the cumulative claimed utility, Table 1 also demonstrates similar patterns to those observed above for comparing the number of transplants. These results suggest that $k = 3$ or 4 would provide a satisfactory solution in practice. Further investigation, however, with data from more KPD programs would be useful. Notice that when edge utilities are fixed at 1, the cumulative claimed utility is the same as the cumulative number of transplants.

Finally, we take a look at the correlation matrix among five variables; each variable represents the number of transplants performed when k is equal to each one of the five values. We anticipate that the correlation between variable 4 (the number of transplants achieved when $k = 4$) and variable 5 would be higher than the correlation between variable 1 and variable 5. Table 2 exactly unveils such a pattern in three correlation matrices (with each one corresponding to one utility generating distribution). Similar observations are also noted in the correlation matrices for the cumulative claimed utility.

6. Concluding remarks

In this paper, we have studied the problem of managing a KPD program with one altruistic donor. One important yet challenging part of this problem is to recognize various friction (as discussed in Section 2.1) inherent in the system and to guide the decision-making process by taking into account these uncertainties. Realizing the fact that a long pre-specified NEAD chain in practice can almost never be implemented as planned, we propose to initiate and extend such a chain in a sequential way by selecting potential transplant recipients one at a time. Each selection is made keeping in mind the associated long-term consequences so as to maximize the expected gain over a certain given number of moves. In order to do this efficiently and practically, we

construct a depth- k search tree for a KPD graph using a DFS-based algorithm. We then evaluate various choices available for each altruistic donor (or bridge donor) according to the calculation performed along that search tree, and recommend the choice with the greatest expected utility.

In the process of extending a NEAD chain, the bridge donor at the end of the current chain might be incompatible with a majority of the candidate population, which would significantly prolong the waiting time for that bridge donor to be matched with a present or future candidate. Furthermore, this long waiting time for the hard-to-match bridge donor may make him/her more likely to withdraw from the KPD pool and so terminate the NEAD chain. To partially avoid this unfortunate circumstance, some KPD programs have not allowed a blood type AB donor to become a bridge donor. Actually, this issue can be partially addressed in our proposed sequential allocation strategy, which incorporates the long-term consequences associated with each pair choice, and would in general tend to avoid choices that could lead to a hard-to-match bridge donor. As we have briefly mentioned in Section 3 and Section 4.2, one way to further address this issue is to assign each possible bridge donor a reasonable *base utility*. This base utility represents the potential “contribution” from a bridge donor; a hard-to-match bridge donor would be assigned a small base utility and an easy-to-match one would be given a larger value.

Although this paper has focused on managing a KPD program with one altruistic donor, the proposed approach can be generalized to incorporate multiple altruistic donors. One way to achieve this is to construct a depth- k search tree for each altruistic donor and use this tree to evaluate various allocations options available for that altruistic donor according to the method in Section 4.2. Among all allocations possible for these altruistic donors, we select a disjoint collection such that the overall expected utility can be maximized. More specifically, let $\mathcal{V}_a \equiv \{1, 2, \dots, m\}$ be m altruistic donors in a general KPD program. We denote by $\mathcal{A} \equiv \cup_{i=1}^m \{(i, j) \in \mathcal{E}\}$ the possible allocations available for these m altruistic donors. Each potential transplant, $(i, j) \in \mathcal{A}$, can be evaluated by its expected utility, which is calculated as $u_{ij}^* = u_{ij} + EV[\mathcal{G}_{[i]}(j)]$, where $\mathcal{G}_{[i]} \equiv \mathcal{G}(i)$. We then select from \mathcal{A} a disjoint collection of edges (or transplants), in the sense that no two edges can share a common vertex, so as to maximize the sum of expected utilities. For those selected transplants, viable ones would result in actual operations and generate new bridge donors, and altruistic donors and incompatible pairs involved in non-viable transplants are recycled back to the KPD pool.

The above way of allocating multiple altruistic donors can be arranged in parallel with the selection of exchange sets (or cycles) among incompatible pairs. Let \mathcal{S}_r be the collection of all exchange sets of size up to r among $(n - m)$ incompatible pairs (Li et al., 2013). Typically, in clinical KPD programs, one chooses $r = 3$, although larger exchanges could be considered as well. For each $S \in \mathcal{S}_r$, let EU_S represent its expected utility and let Y_S be a decision variable equal to 1 if S is selected and 0 if not; for each $(i, j) \in \mathcal{A}$, Z_{ij} is another decision variable whose value is 1 if (i, j) is chosen for a transplant and 0 otherwise; the expected utility of this potential transplant (i, j) is given

by u_{ij}^* as discussed above. By adopting a formulation that is similar to the one proposed in Li et al. (2013), we then manage such a KPD program by solving the following IP problem:

$$\max_{\{Y_S\}, \{Z_{ij}\}} \left\{ \sum_{S \in \mathcal{S}_r} Y_S EU_S + \sum_{(i,j) \in \mathcal{A}} Z_{ij} u_{ij}^* \right\}, \quad (5)$$

$$\text{subject to } \sum_{S \in \mathcal{S}_r(l)} Y_S + \sum_{(i,j) \in \mathcal{A}(l)} Z_{ij} \leq 1, \forall l \in \mathcal{V}, \quad (6)$$

where, in (6), $\mathcal{S}_r(l)$ represents the exchange sets in \mathcal{S}_r that contain l and $\mathcal{A}(l)$ similarly denotes a subset of transplants in \mathcal{A} that involve l . Various extensions of this approach would be possible to allow fall back options for the exchanges and for the assignment of the altruistic donors. Such approaches are discussed in Li et al. (2013). This approach, and extensions of it, provide an alternative to the simultaneous selection of chains and cycles as is traditionally done in the match runs of a KPD; see for example, Roth et al. (2006), Gentry et al. (2009), and Ashlagi et al. (2011).

The mechanism of a NEAD chain allows the altruism from a single altruistic donor to benefit a potentially large number of patients, but it does so exclusively for patients recruiting a willing but incompatible living donor. This mechanism excludes patients without a designated living donor and who are therefore placed on a deceased-donor waiting list. Among those patients who would benefit from this NEAD chain, approximately 73% of them are white; whereas those who would not benefit from this mechanism form a 52% non-white population (Segev et al., 2008). On the other hand, not all altruistic (or bridge) donors are well suited for initiating and extending chains among a pool of incompatible pairs. For example, consider a KPD pool in which an altruistic donor may not be in a good position (because of either incompatibility or poor utility) to be matched up with any candidate. In this case, rather than placing this altruistic donor in a waiting “mode” for a potentially long time, redirecting him/her to a deceased-donor waiting list, where a compatible patient with potentially good transplant outcomes might be identified rather easily, appears a more suitable alternative.

To decide whether an altruistic donor is better off initiating a NEAD chain or donating directly to someone on a deceased-donor waiting list, we could evaluate an altruistic donor by the utility expected to be achieved if this donor is chosen to initiate a chain. To be precise, we may first perform the calculation according to formula (4) as in Section 4.1 to evaluate the expected utility for each altruistic donor, i.e. $\{EV[\mathcal{G}(i)] : i \in \mathcal{V}_a\}$. The result from this evaluation could then be used to assess the suitability of assigning each altruistic donor to a deceased-donor waiting list; a relatively high value of $EV[\mathcal{G}(i)]$ would recommend reserving altruistic donor i for extending a NEAD chain while a comparatively low value of $EV[\mathcal{G}(i)]$ would indicate a transplant to someone waiting for a deceased-donor kidney. It is worth noting that different ways of assigning edge utilities and probabilities could be adopted in calculating $\{EV[\mathcal{G}(i)]\}$

: $i \in \mathcal{V}_a$. This would provide extra benefit in allowing more control over what kidneys in general are distributed to a deceased-donor waiting list. For example, if each edge is assigned an equal utility while the edge probability remains representing the likelihood of that edge being viable, then altruistic (or bridge) donors who are less compatible with candidates in the current KPD pool would be more likely to be directed to a deceased-donor waiting list. In addition to evaluating an altruistic donor against the current KPD pool, it is often rational in practice to perform the evaluation against the deceased-donor waiting list. For example, Blood Type O or B candidates frequently wait a year or more longer on the deceased-donor waiting list before receiving a kidney transplant than do Blood Type A or AB candidates. Therefore a Blood Type O or B altruistic or bridge donor might be argued to have higher utility. So might someone who matches to a pediatric candidate. Similarly an altruistic or bridge donor that might match to a sensitized wait-listed candidate might have a higher utility, but a lower probability of progressing to transplant.

Acknowledgements

This work was supported in part by a grant from the National Institutes of Health (NIH) CTSA at the University of Michigan 2UL1TR000433-06 and by the NIH grant 1R01-DK093513. The authors thank the support from the Michigan Institute for Clinical and Health Research (MICHHR), Michigan School of Public Health, Scientific Registry of Transplant Recipients, and National Institute of General Medical Sciences (NIGMS). Last but not least, the authors would like to thank the editor and referees whose comments helped to improve this manuscript.

References

- Abraham, D. J., Blum, A. and Sandholm, T. (2007). Clearing algorithms for barter exchange markets: Enabling nationwide kidney exchanges. *Ec'07: Proceedings of the Eighth Annual Conference on Electronic Commerce*, 295–304.
- Ashlagi, I., Gilchrist, D. S., Roth, A. E. and Rees, M. A. (2011). Nonsimultaneous chains and dominos in kidney-paired donation-revisited. *American Journal of Transplantation*, 11(5): 984–994.
- Evans, R. W., Manninen, D. L., Garrison, L. P., Hart, L. G., Blagg, C. R., Gutman, R. A., Hull, A. R. and Lowrie, E. G. (1985). The quality of life of patients with end-stage renal disease. *New England Journal of Medicine*, 312(9): 553–559.
- Gentry, S. E., Montgomery, R. A., Swihart, B. J. and Segev, D. L. (2009). The roles of dominos and nonsimultaneous chains in kidney paired donation. *American Journal of Transplantation*, 9(6): 1330–1336.
- Li, Y. (2012). Optimization and simulation of kidney paired donation programs (doctoral dissertation). *University of Michigan, Ann Arbor*.
- Li, Y., Kalbfleisch, J. D., Song, P. X.-K., Zhou, Y., Leichtman, A. B. and Rees, M. A. (2013). Optimal decisions for organ exchanges in a kidney paired donation program. *Statistics in Biosciences*, 6(1), 85–104.

- Maiers, M., Gragert, L. and Klitz, W. (2007). High-resolution hla alleles and haplotypes in the united states population. *Human Immunology*, 68(9): 779–788.
- Montgomery, R. A., Gentry, S. E., Marks, W. H., Warren, D. S., Hiller, J., Houp, J., Zachary, A. A., Melancon, J. K., Maley, W. R., Rabb, H., Simpkins, C. and Segev, D. L. (2006). Domino paired kidney donation: a strategy to make best use of live non-directed donation. *The Lancet*, 368(9533): 419–421.
- Rapaport, F. T. (1986). The case for a living emotionally related international kidney donor exchange registry. *Transplantation Proceedings*, 18: 5–9.
- Rees, M. A., Kopke, J. E., Pelletier, R. P., Segev, D. L., Rutter, M. E., Fabrega, A. J., Rogers, J., Pankewycz, O. G., Hiller, J., Roth, A. E., Sandholm, T., Ünver, M. U. and Montgomery, R. A. (2009). A nonsimultaneous, extended, altruistic-donor chain. *New England Journal of Medicine*, 360(11): 1096–1101.
- Roth, A. E., Sönmez, T. and Ünver, M. U. (2004). Kidney exchange. *Quarterly Journal of Economics*, 119(2): 457–488.
- Roth, A. E., Sönmez, T. and Ünver, M. U. (2007). Efficient kidney exchange: Coincidence of wants in markets with compatibility-based preferences. *American Economic Review*, 97(3): 828–851.
- Roth, A. E., Sönmez, T., Ünver, M. U., Delmonico, F. L. and Saidman, S. L. (2006). Utilizing list exchange and nondirected donation through ‘chain’ paired kidney donations. *American Journal of Transplantation*, 6(11): 2694–2705.
- Russell, J. D., Beecroft, M. L., Ludwin, D. and Churchill, D. N. (1992). The quality of life in renal transplantation—a prospective study. *Transplantation*, 54(4): 656–660.
- Schaubel, D. E., Wolfe, R. A., Sima, C. S. and Merion, R. M. (2009). Estimating the effect of a time-dependent treatment by levels of an internal time-dependent covariate: Application to the contrast between liver wait-list and posttransplant mortality. *Journal of the American Statistical Association*, 104(485): 49–59.
- Segev, D. L., Kucirka, L. M., Gentry, S. E. and Montgomery, R. A. (2008). Utilization and outcomes of kidney paired donation in the united states. *Transplantation*, 86(4): 502–510.
- Wolfe, R. A., Ashby, V. B., Milford, E. L., Ojo, A. O., Ettenger, R. E., Agodoa, L. Y. C., Held, P. J. and Port, F. K. (1999). Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *New England Journal of Medicine*, 341(23): 1725–1730.
- Wolfe, R. A., McCullough, K. P., Schaubel, D. E., Kalbfleisch, J. D., Murray, S., Stegall, M. D. and Leichtman, A. B. (2008). Calculating life years from transplant (lyft): Methods for kidney and kidney-pancreas candidates. *American Journal of Transplantation*, 8(4p2): 997–1011.

