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KPDGUI: An interactive application for optimization and management of a virtual kidney paired donation program

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ABSTRACT

Background and objectives: The aim in kidney paired donation (KPD) is typically to maximize the number of transplants achieved through the exchange of donors in a pool comprising incompatible donor-candidate pairs and non-directed (or altruistic) donors. With many possible options in a KPD pool at any given time, the most appropriate set of exchanges cannot be determined by simple inspection. In practice, computer algorithms are used to determine the optimal set of exchanges to pursue. Here, we present our software application, KPDGUI (Kidney Paired Donation Graphical User Interface), for management and optimization of KPD programs.

Methods: While proprietary software platforms for managing KPD programs exist to provide solutions to the standard KPD problem, our application implements newly investigated optimization criteria that account for uncertainty regarding the viability of selected transplants and arrange for fallback options in cases where potential exchanges cannot proceed, with intuitive resources for visualizing alternative optimization solutions.

Results: We illustrate the advantage of accounting for uncertainty and arranging for fallback options in KPD using our application through a case study involving real data from a paired donation program, comparing solutions produced under different optimization criteria and algorithmic priorities.

Conclusions: KPDGUI is a flexible and powerful tool for offering decision support to clinicians and researchers on possible KPD transplant options to pursue under different user-specified optimization schemes.

1. Introduction

Currently, with 95,000 patients waitlisted for deceased donor kidney transplantation, and between 30,000–40,000 patients waitlisted annually, only about 15,000 patients receive a kidney transplant each year [1]. Kidney paired donation (KPD) provides an avenue for kidney transplant candidates with willing but incompatible donors to find alternative transplant opportunities [2,3]. KPD pools are comprised of kidney transplant candidates, each paired with one or more willing but incompatible donor(s), as well as non-directed (or altruistic) donors (NDD). The goal is to find suitable exchanges of donors to facilitate transplants for the candidates. KPD is feasible due to favorable outcomes for living donors, as well as increased quality of life and cost-savings for candidates compared to continuing dialysis [4–6]. According to the Organ Procurement and Transplantation Network (OPTN), 500–700 transplants have been facilitated by KPD programs yearly in the United States since 2012, and successful expansion of KPD programs has the potential to greatly increase the number of transplant recipients, alleviating pressure on the deceased donor waiting list [1].

Exchanges in a KPD program can proceed either via cycles, where the donor from one pair donates to the candidate in the next pair along the cycle with the final donor donating to the original candidate, or chains originating from NDDs (see Figs. 1 and 2) [7–10]. Potential transplants, or matches, between donors and candidates are determined based on the compatibility of their blood types and the sensitization of the candidate to human leukocyte antigens (HLA) of the donor, resulting from transfusion, pregnancy, or previous transplantation, and which increases the risk of antibody-mediated rejection of the

Abbreviations: KPD, Kidney Paired Donation; NDD, non-directed donor; HLA, human leukocyte antigens

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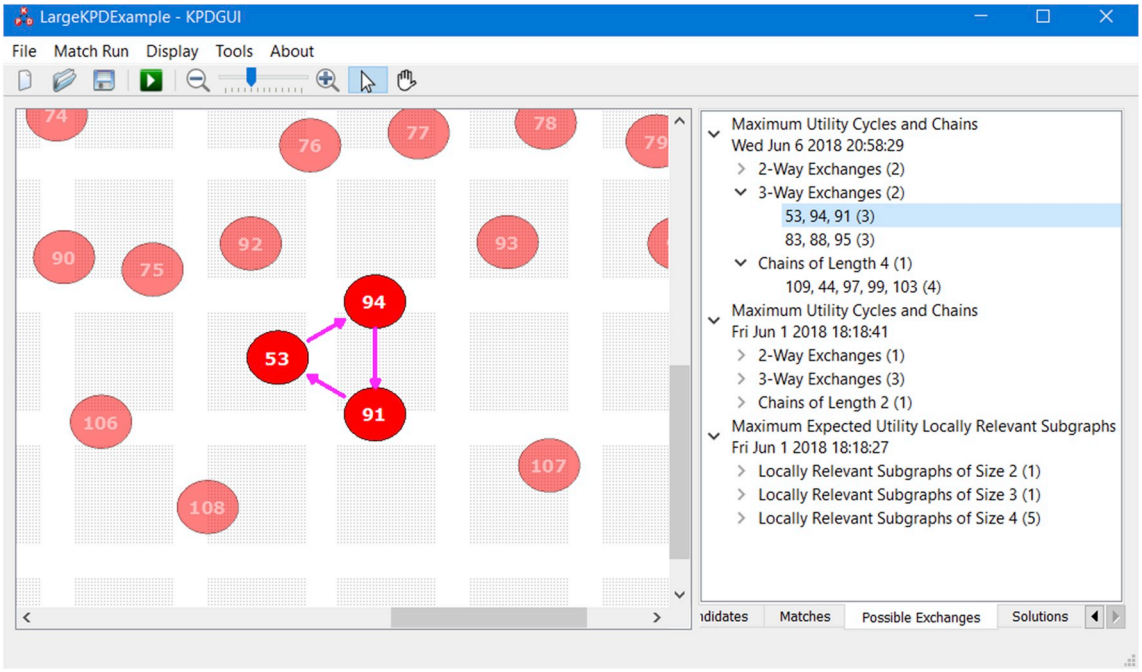

Fig. 1. An exchange cycle within a KPD program, where each node represents a donor-candidate pair. The cycle here has the donor of pair 91 donating to the candidate of pair 53, and the donor of pair 53 donating to the candidate of pair 94, whose donor closes the cycle by donating to the candidate of pair 91.

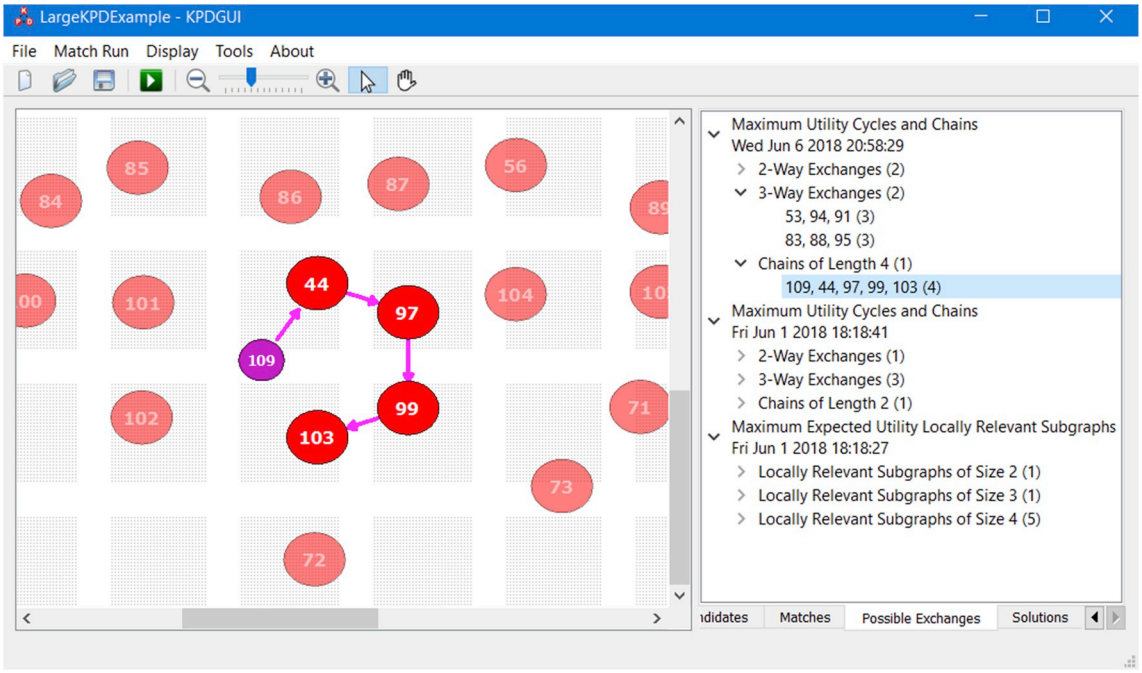

Fig. 2. A chain within a KPD program, where larger red nodes represent donor-candidate pairs and the smaller purple node represents an NDD. The chain begins with a transplant from NDD 109 to the candidate of pair 44, followed by a transplant from the donor of pair 44 to the candidate of pair 97, and so on through pairs 99 and 103. The donor from pair 103 that remains can then either donate to a candidate on the deceased donor waiting list or remain in the program as an NDD to initiate a future KPD chain. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

transplanted organ. Preferences of the donor, candidate and transplant center may also be included in KPD matching criteria [11]. We refer to this preliminary assessment of compatibility between a donor and a candidate as a virtual crossmatch.

One of the principal goals in KPD is to maximize the number of transplants achieved via cycles and chains among the pairs and NDDs in the pool [12]. Alternatively, a score value, which we refer to as the utility, can be assigned to each potential transplant within the pool, with the aim to maximize the total achieved utility [13]. With many possible options in a KPD pool at any given time, the most appropriate set of exchanges cannot be determined by simple inspection. In practice, computer algorithms are used to determine the optimal selections of exchanges to pursue. The problem of selecting optimal exchanges in a KPD program is NP-hard, though computational approaches are available that work well in practice for pools of modest size [14].

Prior to transplantation, matches that are expected to be

immunologically compatible based on previously identified candidate sensitivities must be confirmed through a laboratory crossmatch, where antibodies against a specific donor are detected by incubating candidate serum with donor lymphocytes. Hence, matches that were expected to be immunologically compatible may be found to be unviable after selection [15–17]. Failure to proceed with an exchange may also occur for other reasons, such as candidates or transplant centers declining a proposed transplant in the cycle or chain, or participants having to withdraw due to illness or unavailability [18]. Thus, one can realistically expect only a fraction of patients among the selected exchanges to progress to transplantation.

For a KPD cycle, the entire set of transplants cannot proceed if any of the selected exchanges is non-viable, as that would require a donor to donate without their paired candidate receiving their promised transplant. In contrast, although the entire original selection of transplants may not be completed, KPD chains can be carried out up to the point of failure, as no donor will have donated without their candidate first receiving a transplant [19,20].

In the cases of non-viability of transplants after selection, there might be opportunity for immediate recourse to alternative transplant options, for example to viable sub-cycles or sub-chains of the original cycles or chains in the optimization solution [17].

Previous research suggests including, along with the utilities, probabilities that selected exchanges might eventually be found to be non-viable, whereby the KPD solution consists of exchanges that maximize the expected utility [17,18,21–23]. Optimization can be further extended beyond selection of simple cycles or chains to encompass fallback options in case of non-viability [24–26]. We have previously investigated the incorporation of these considerations into KPD optimization through simulation, where formidable gains in realized utility were observed [27,28].

We present here our software application, KPDGUI (Kidney Paired Donation Graphical User Interface), for optimization and management of KPD programs. KPDGUI offers the user an interactive environment through which the pool of incompatible donor-candidate pairs and non-directed donors, as well as the exchanges suggested by optimization criteria, can be visualized. While proprietary software platforms for managing KPD programs exist to provide solutions to the standard KPD problem, we have implemented our previously developed optimization schemes that account for uncertainty regarding the viability of selected transplants and arrange for fallback options in cases where potential exchanges cannot proceed, with intuitive resources for visualizing alternative optimization solutions. We illustrate the advantage of accounting for uncertainty and arranging for fallback options in KPD using our application.

2. Methods

2.1. Mathematical formulation

A KPD pool can be modeled as a directed network $G = (V, E)$, with $V = V^p \cup V^a$ representing the set of pairs (V^p) and NDDs (V^a) in the KPD, and $E = \{(i, j): i \in V,\ j \in V^p,\ i \neq j,$ *donor of* i *matches with candidate of* $j\}$, the set of matches between donors and candidates. As noted earlier, matches are determined by virtual crossmatch, assessing the presumed biological compatibility of the donor and candidate, as well as incorporating expressed candidate, donor, or transplant center preferences. Other policy options may also play a role in determining acceptable matches in KPD. For example, a blood type O candidate can only receive a compatible transplant from a blood type O donor, while O donors can donate to candidates of any blood type. As such, to preserve options for O candidates, matches from O donors to non-O candidates in KPD are often discouraged [29].

Associated with each edge $e = (i, j) \in E$ is the utility, $u_e \equiv u_{ij} \in [0, \infty)$, indicating the relative value of the potential transplant. It is common to assume a default utility of 1 for all matches, such that all transplants are equally valuable. In this case, optimization is effectively defined in terms of the number of transplants. Alternatively, some KPD programs assign a score to each match, depending on factors such as age, distance between the donor and candidate institutions, waiting time of the candidate, and degree of sensitivity of the candidate to donor antigens, along with a priority for pediatric patients. We have also investigated utilities defined by the estimated 5- or 10-year graft survival of the transplant, based on certain donor and candidate characteristics and combinations thereof [30].

As remarked upon earlier, there is an element of uncertainty in a KPD program in that a selected match may not lead to a completed transplant due to the unavailability of the candidate or donor, or because expected compatibility is overturned by a laboratory crossmatch. We assign to each match, $e = (i, j) \in E$, a probability of viability, $p_e \equiv p_{ij} \in [0,1]$. Similarly, we can assign to each pair (or NDD), $i = V$, a probability, $q_i \in [0,1]$, that the donor and candidate, or simply the donor in the case of the NDD, remain available for transplantation after selection. Separate probabilities for the candidate and each donor can be assigned in cases where candidates join with more than one incompatible donor. We have proposed to steer selection toward exchanges we believe can lead to successful transplantation, while also affording the clinician the ability to take advantage of fallback options should donors, candidates, or matches prove to be non-viable.

2.2. Selection strategies

The most common strategy in KPD is to restrict attention to cycles and chains, capped at specified lengths. For example, we might consider all chains consisting of four or fewer transplants and all cycles involving three or fewer pairs. As noted earlier, the traditional method of selecting exchanges to pursue in a KPD program selects the set of disjoint chains and cycles that maximizes the number of transplants or utility achieved, assuming all selected transplants will be viable. This has the obvious disadvantage that it does not take account of the uncertainty associated with each potential transplant, and the possibility that selected cycles and chains may have to be abandoned or shortened in cases of non-viability. With the expectation that certain matches will be found non-viable after selection, we can attempt to select exchanges that allow for various fallbacks that can be pursued depending on which selected matches remain viable.

As a first step, we can select cycles and chains that offer fallbacks to sub-cycles and sub-chains that can be implemented when some of the proposed transplants are not viable. After accounting for donor, candidate, and match viability within each cycle and chain between the time of selection and the time of transplantation, one would proceed with the best remaining set of sub-cycles and sub-chains within each of the original cycles and chains [17].

In fact, however, we can do even better by extending the concept of cycles and chains to more general subsets of pairs and NDDs within our KPD network. For specified caps on cycle size and chain length, we identify subsets of pairs and NDDs in the KPD wherein each pair and NDD can be included in a cycle or chain of appropriate size or length within the subset. We refer to these as Locally Relevant Subgraphs (LRS), size-restricted sets of overlapping sub-cycles and sub-chains representing fallback options that can be taken in cases of non-viability after selection. More formally, an LRS is a subgraph of the original KPD network connected in such a way that any partition into two non-empty parts will result in the loss of at least one sub-cycle or sub-chain.

The idea behind the LRS is that it is easier to evaluate many smaller KPD subgraphs in a divide-and-conquer manner than evaluating the single large network as a whole, each representing transplant possibilities that can be easily assessed individually (Fig. 3). Similar ideas have been investigated by Klimentova et al. [24] and Alvelos et al. [25], where “subset-recourse” or “external recourse” referred to the idea of facilitating fallback options outside of a selected cycle or chain. The size

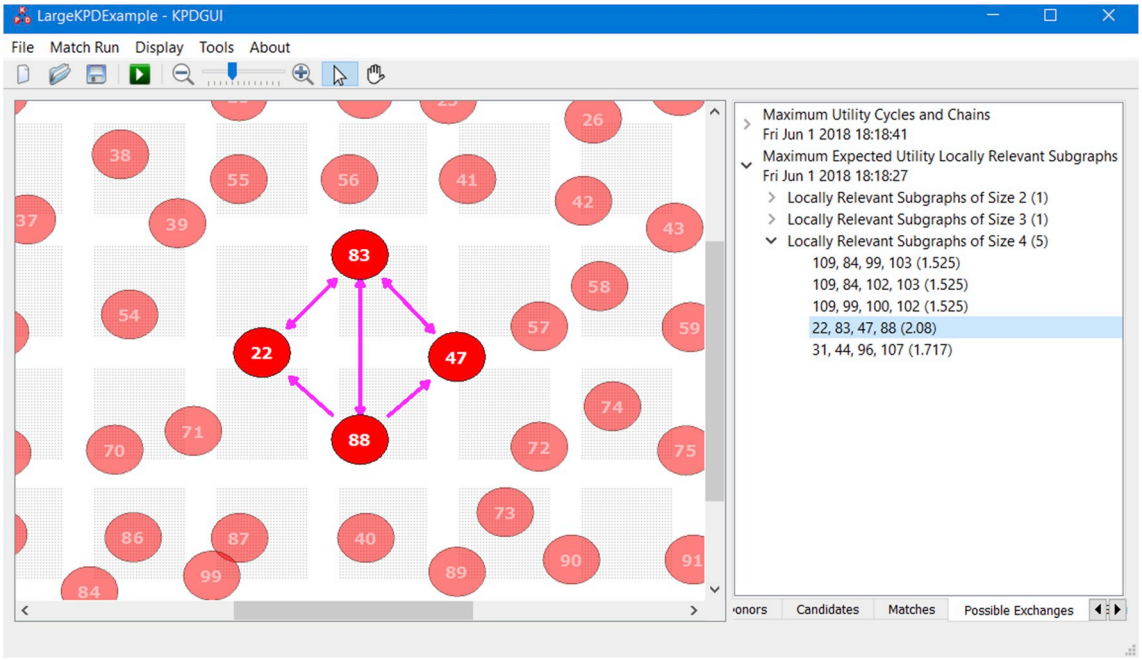

Fig. 3. An LRS within a KPD program. This LRS is a 4-node subgraph of the original KPD network, consisting of pairs 22, 47, 83, and 88, admitting two sub-cycles of size 3 (between pairs 88, 22, and 83, and between pairs 88, 47, and 83), and three sub-cycles of size 2 (between pairs 22 and 83, 47 and 83, and 83 and 88). After selection, the viability of the matches and the availability of the donors and candidates in the LRS are determined. If either of the size-3 sub-cycles remain viable, we proceed to transplantation with that sub-cycle. If both remain viable, we proceed with the sub-cycle that admits the higher utility. If neither of the size 3 sub-cycles is viable, then we proceed with the best size-2 sub-cycle that remains. It is also possible that none of the sub-cycles will remain viable (say, if pair 83 were unavailable).

of the sets of interest in previous studies are limited, with no explicit consideration for NDDs. The sets of interest here are formally defined and more thoroughly examined in Wang et al. [26], where methods of enumeration are also developed. Again, after accounting for donor, candidate, and match viability within each LRS, one proceeds with the best remaining set of sub-cycles and sub-chains within each subgraph.

2.3. Optimization

For the traditional model, let $\mathscr{C}$ represent the set of cycles and chains under consideration, capped at specified lengths. We denote a cycle or chain by $C = (V_C, E_C) \in \mathscr{C}$, where V_C represents the set of pairs/NDD and E_C represents the matches involved in C respectively. Each cycle and chain is assigned a value, U_C, which in this case is simply the sum of the individual utilities of the matches involved. The aim is therefore to select the set of cycles and chains that maximize the total utility.

We can use the same formulation for optimization in terms of LRSs. We denote the LRS by $S = (V_S, E_S)$, where V_S and E_S represent respectively the set of pairs/NDDs and matches involved in S. We also let LRS represent the class of all LRSs under consideration. Given our probability model, we can determine the expected utility associated with S, taking account of the fallbacks that are possible when certain matches are not viable or pairs or NDDs are no longer available. Here we let EU_S denote the expected utility, which can be computed for all $S \in LRS$. Our aim is to select disjoint LRSs so as to maximize the total expected utility. Note that expected utilities can also be calculated for a cycle or chain C, taking account of possible fallback options by extending E_C to include other matches between the pairs/NDD in V_C.

Selection of an optimal set of exchanges can be formulated as an integer programming problem. As noted earlier, the problem is NP-hard, and so optimization results are approximations based on heuristic algorithms, though the solutions produced tend to be accurate for KPD pools of modest size. Algorithms that have been traditionally employed to address the so-called "clearing problem" in KPD notably include the branch-and-price algorithm developed by Abraham, Blum and Sandholm [31]. Alternatively, optimization solutions can be obtained as the output of specialized optimization software, such as CPLEX or Gurobi [32].

For each $i \in V$, let $\mathscr{C}_{(i)}$ denote the cycles and chains under consideration in $\mathscr{C}$ that involve pair/NDD i, ie. $\mathscr{C}_{(i)} = \{C \in \mathscr{C}: i \in V\}$. For each $C \in \mathscr{C}$, let $Y_C = 1$ if C is selected, with $Y_C = 0$ otherwise. The optimization problem is then formulated as: $max_{\{Y_C\}} \sum_{C \in \mathscr{C}} Y_C U_C \; s.t. \; \sum_{C \in \mathscr{C}_{(i)}} Y_C \leq 1, \; \forall i \in V$. The formulation is similar for LRSs, with LRS replacing $\mathscr{C}$, S replacing C, and EU_S replacing U_C. Note that the restriction guarantees that no pair or NDD can appear in more than one selected exchange [7,12].

In recent work we have shown considerable advantage of the approach based on LRSs as compared to the simple selection of cycles and chains. Over time, schemes that utilize LRSs, accounting for the uncertainty and the possibility to pursue fallback options within a failed exchange, yield higher numbers of realized transplants in KPD micro-simulation models than schemes that only consider simple cycles and chains, with gains of roughly 40% when compared to the simplest settings [27,28].

2.4. Software implementation

2.4.1. Description

KPDGUI is written in C++, with the graphical user interface rendered using the Qt framework [33]. Approximate solutions to the optimization problem described in the previous section are obtained using Gurobi 6.5.0, an optimization software suite which is freely available under an academic license [32]. The application, code, example files and video tutorials can be accessed at https://github.com/mathieubray/KPDGUI. A more complete set of specifications can also be found at that site.

The main screen is divided into two panels. On the left, the application visualizes the underlying network representation of the KPD. On the right are a number of tabs which contain information about the KPD. The first tab holds a running history of the commands used during

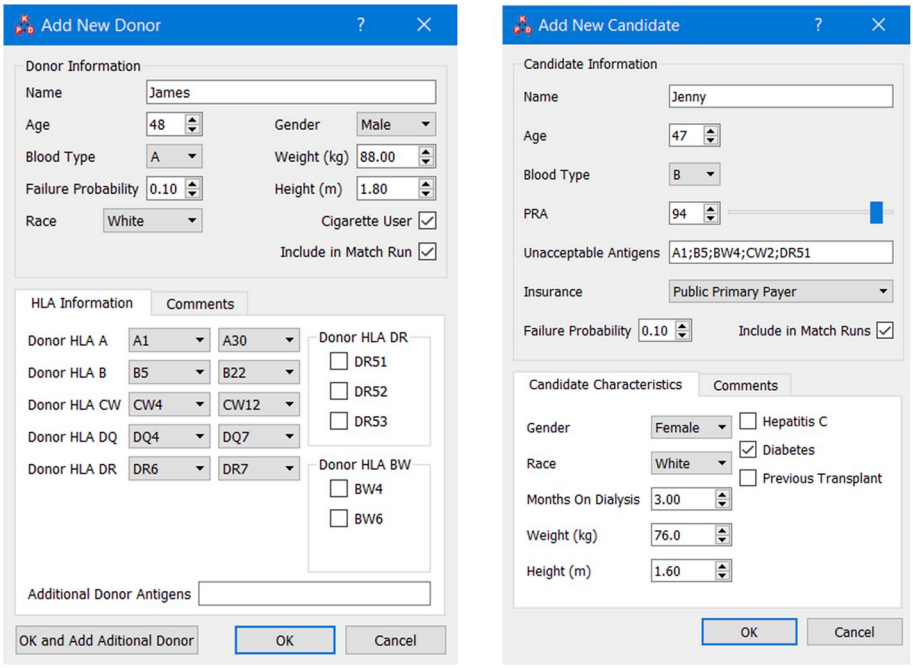

Fig. 4. Prompts for donor (left) and candidate (right) characteristics.

a session. The remaining tabs contain information on pairs and NDDs, individual donors and candidates, matches, and previously found solutions, as well as individual cycles, chains, and/or LRSs.

2.4.2. Adding pairs and NDDs

One can add pairs or NDDs and their characteristics individually to populate the virtual KPD program (see Fig. 4). Such characteristics include age, and blood type of the donor and candidate, and histological information, namely HLA information for donors and sensitivities against HLA for candidates. The user can specify clinical characteristics relevant for the estimation of graft survival probabilities, which include sex, Hepatitis C status for candidates, and cigarette smoking status for donors, among others. One can further specify failure probabilities for the donors and candidates for calculation in optimization schemes involving fallback options. Alternatively, one can load an entire set of pairs and NDDs from a structured file that contains the required information for each pair and NDD. Note that more than one donor can be associated with each candidate.

Once added, pairs and NDDs are displayed as colored nodes in the network. Nodes representing pairs are displayed in red, while NDDs are displayed in purple. If the candidate joins with more than one donor, each donor is represented by a smaller blue node, grouped together with the candidate. Right-clicking an individual donor or candidate node in the visual panel gives the option to edit the donor or candidate characteristics. In particular, the donor or candidate can be designated as excluded from future optimizations.

Matches are automatically generated for new pairs and NDDs based on virtual crossmatches against all other pairs and NDDs already in the pool. Matches are represented by arrows, originating from the donor and pointing to the matching candidate. If the virtual crossmatch between a donor and candidate fails, no arrow is included. The user can assign a custom transplant score to any match in the system, as well as change the failure probability for calculation in optimization schemes involving fallback options. Matches can also be designated as excluded from future optimizations.

2.4.3. Running optimizations

At any time, one can assess the pool in order to find the optimal selection of cycles and chains or LRSs, commonly referred to as a match run. Before the optimization, the user must specify certain parameters, the most important of which is the optimization scheme to employ. The schemes implemented in KPDGUI are as follows:

1. Cycles and Chains: The optimal solution is the set of disjoint cycles and chains that maximizes the total utility. The total utility is obtained by simply adding the individual utility values of each selected cycle and chain, without consideration of donor, candidate or match failure probabilities, or fallback options in the case of such failure. This is the optimization model most commonly used by KPD programs.
2. Cycles and Chains with Fallbacks: The optimal solution is the set of disjoint cycles and chains that maximizes the total expected utility. As described in Section 2.3, the expected utility accounts for possible donor, candidate, and match failures, and considers fallbacks to sub-cycles and/or sub-chains where possible. This is a straightforward extension of the first scheme and can be used as a comparison to solutions produced by the final scheme below.
3. Locally Relevant Subgraphs: The optimal solution is the set of disjoint LRSs that maximizes the total expected utility. Again, the expected utility accounts for failures and allows for fallbacks to sub-cycles and/or sub-chains. This scheme represents contributions from our previous studies, and based on our investigations, is the preferred optimization strategy.

For each of these options, the user must provide an upper bound to the size of the cycles and chains to be considered. An upper bound to the size of the LRSs must also be specified for the Locally Relevant Subgraphs setting, in which case the caps for cycles and chains refer to the sub-cycles and sub-chains within the LRS. For more details on the calculations involved for each of these schemes, we refer the readers to our recent investigations and additional related work [18,24,34].

The user also specifies the utility to assign to each individual match. The default is a value of 1 for each match, representing the single potential transplant it represents. Alternatively, the utility assigned can also be the estimated 5- or 10- year survival probability of the transplant, based on clinical characteristics of the donor, candidate, and combination thereof provided by the user, or the user-specified score supplied manually to each match. Other parameters include the number

of unique solutions to provide, and whether to estimate or calculate the expected utility exactly. Note that while certain cycles, chains or LRSs may appear in more than one solution, the combination will be different for each unique solution produced. Estimation is based on Monte Carlo sampling procedures outlined in our previous studies [28]. If estimating, the user also specifies the number of sampling iterations to apply in the estimation procedure.

After a match run, each individual solution is added to the "solutions" tab, and a summary of all found exchanges within these solutions are also added to the "possible exchanges" tab. Selecting any of these will highlight the relevant exchanges in the visual representation of the network, and double-clicking will bring up information about the optimization settings used to generate the results. The user can cluster and isolate any selected exchange set, which will also highlight the matches comprising the relevant exchanges.

3. Results

Here we illustrate an example of the use of KPDGUI, applied to a synthetic KPD program, obtained by sampling deidentified historical data from the Alliance for Paired Donation (APD). Our virtual program consists of 107 donor-candidate pairs (including 5 candidates with 2 incompatible donors, and 1 candidate with 3 such donors), and 11 NDDs.

We compare the results obtained by running each of the three optimization schemes: Cycles and Chains, Cycles and Chains with Fallbacks, and Locally Relevant Subgraphs. A utility value of 1 is assumed for each match, and a 0.1 probability of non-viability is assumed for each donor, candidate, and match involved. We allow a maximum size (in terms of number of transplants involved) of 3 for cycles and 4 for chains. For LRSs, the maximum size, which we cap at 5, is determined by the number of pairs and NDDs involved. The maximum sizes of sub-cycles and sub-chains for the LRSs are 3 and 4 respectively.

Fig. 5 illustrates a representative solution under each optimization scheme. The solution for the Cycles and Chains optimization is shown in Fig. 5a, with cycles of size 2 and 3 and chains of length 1 and 3 for a total of 9 transplants. Note that there are several possible solutions that admit 9 transplants. Secondary considerations can be employed when choosing among tied solutions, such as combined user-provided utility values of the potential transplants involved. Paired donation programs are primarily concerned with obtaining solutions as would be produced by a Cycles and Chains optimization. The APD currently employs their own scoring system for matches, and their optimization outputs solutions that maximize the number of transplants, followed by the corresponding solutions that maximize the total score.

While 9 transplants represent the best-case scenario, it is likely that donors or candidates will drop out before proceeding to transplantation, or presumed matches will be overturned upon a more definitive laboratory crossmatch, in which case cycles and chains would have to be abandoned or shortened, respectively. Thus, blind to possible fallback options other than immediate sub-chains up to the point of failure, would ultimately expect roughly 4.5 transplants to be realized from the Cycles and Chains solution. The Cycles and Chains with Fallbacks optimization attempts to correct for these situations, accounting for the probabilities and allowing for fallback options within each cycle and chain. The solution is displayed in Fig. 5b, with the expected utility calculation suggesting that one should expect 5.127 transplants. Here the chain from NDD 84 to pairs 103, 110, and 107 figures prominently, with an expected 1.815 transplants after accounting for the possibility of falling back to a sub-chain from NDD 84 to pairs 103 and 107, as well as the potential sub-cycle between pairs 103 and 110, in cases of non-viability.

The Locally Relevant Subgraphs optimization provides additional options for transplantation. This solution groups pair 70 into the chain discussed above, which provides another option for a sub-chain, increasing the expected number of transplants to 1.97. Another tightly connected subgraph, involving pairs 46, 67, 106, 114, and 117, admits an expected 2.143 transplants through the high number of sub-cycles within. The optimal LRS solution produces an expected 6.426 transplants. One may notice that, for example, while we have seen in the Cycles and Chains with Fallbacks solution that pair 115 forms a cycle with pairs 114 and 106, this option is not included within an LRS in our optimization due to the size constraints imposed. The transplant center can either include these situations in an ad hoc manner, or rerun the optimization allowing for larger LRSs. In either case, one should be aware that solutions will become increasingly complex as the size of the

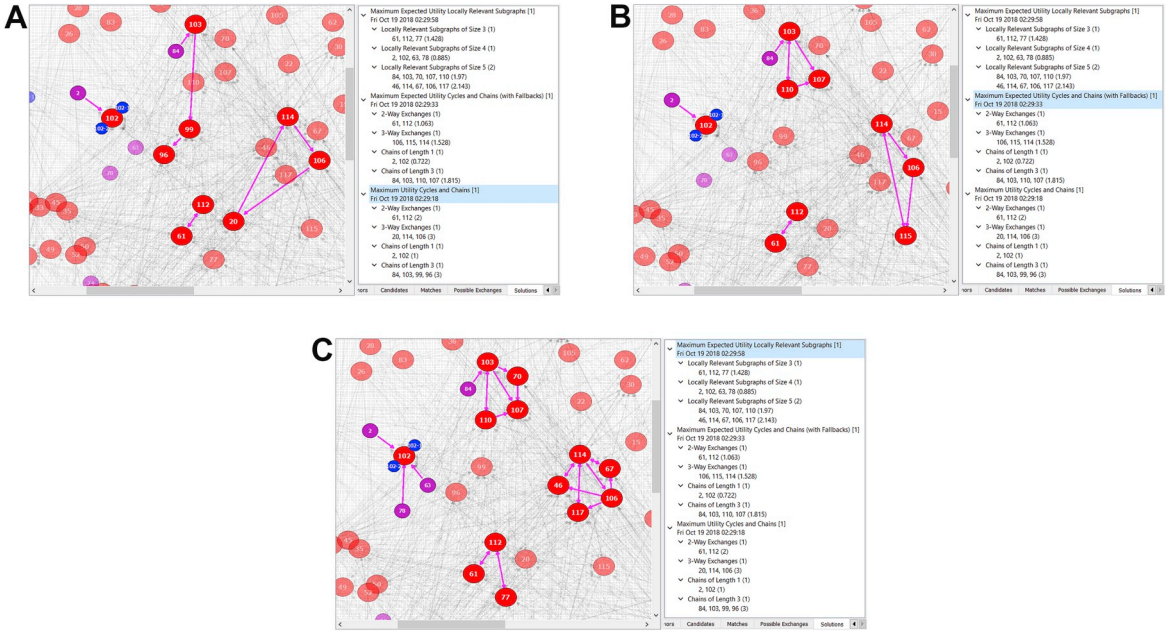

Fig. 5. KPDGUI solutions produced for a virtual KPD program under three optimization schemes: (a) Cycles and Chains, (b) Cycles and Chains with Fallbacks, (c) Locally Relevant Subgraphs.

KPD pool or the limits on cycle or chain size increase. It should be noted that the APD is currently investigating the use of the KPDGUI software and the potential of incorporating explicit considerations of uncertainty and fallback options.

4. Discussion

There are several policy considerations currently being explored in KPD that we would be interested in incorporating into subsequent versions of KPDGUI. Areas of future study in KPD generally focus on expanding the donor pool, addressing barriers to donation, and improving outcomes for patients.

It has been proposed to initiate chains in KPD by including deceased donor organs as if they were donated by NDDs. Such chains would end with a donation to the deceased donor waiting list [35]. In practice, a deceased donor kidney is offered to patients on the deceased donor waitlist according to a specified order of precedence. Under this proposal, instead of donating directly to the waitlist, a deceased donor organ satisfying certain criteria would be diverted to a KPD pool, effectively multiplying the life-saving potential of the deceased donor kidney, with a living-donor organ being returned to the waitlist.

Ethical issues arise under such a proposal, namely the lower number of expected blood type O transplants to the waitlist, candidates with lower precedence receiving transplants at the expense of candidates with higher precedence, and the possibility of living donors in KPD programs reneging on their commitment. As deceased donor organs are generally perceived to be of poorer quality than those of living donors, their use as NDDs would need to be agreed upon by KPD participants. Such chains would also need to be mobilized in a more urgent manner than those solely involving living donors [36]. Implementation of such a system in KPDGUI could illuminate the consequences of diverting deceased donor organs through KPD pools, in particular the effects on the distribution of characteristics of organs being returned to the waiting list.

Expansion of KPD pools can be achieved through the inclusion of compatible donor-candidate pairs, who can elect to join such a program despite their ability to proceed directly to transplantation [37]. Including compatible pairs in KPD expands the pool to reveal additional transplant options. They also may offset the deficiency of blood type O donors typical in KPD programs. Since the universal donor blood type is O, donors with this blood type are more commonly compatible with their intended recipient, and would thus only typically join KPD as a compatible pair.

Convincing compatible pairs to participate in KPD represents a major barrier to widespread adoption of this practice [38]. While compatible pairs may decide to join a KPD program out of a desire to help others, they may also seek a more advantageous match for the candidate, for example from a younger donor or one with fewer HLA mismatches [38–41]. Programs would need to assure that any match involving a candidate with an already compatible donor yields some incremental benefit to the candidate. Graft survival estimations can play an important role in informing compatible pairs about advantages or disadvantages of participating in KPD. Estimated 5- or 10-year graft survival, based on a number of donor, candidate, and match characteristics, is offered as a utility option in our application, and compatible pairs can be included in KPDGUI, with the option to produce solutions either involving or not involving compatible pairs [30].

It has become increasingly possible for certain transplants involving incompatible donors and candidates to cross blood type or HLA barriers through a process referred to as desensitization [29], which aims to eliminate or reduce HLA antibody levels in transplant candidates to the point where a successful laboratory crossmatch can be obtained [42]. Employing desensitization techniques in the KPD context can result in an increase in the number of exchange opportunities [43,44]. However, as these procedures represent higher risk to patients, possibly requiring aggressive or costly therapies, and are resource-intensive, desensitization is typically reserved for only the most difficult-to-match cases [44]. The ability to contrast proposed solutions with and without recourse to desensitization among certain donors and candidates can be incorporated as a consideration into KPDGUI.

Some countries operate a single national KPD registry, though the United States does not. Instead, several multi-center and single-center KPD programs operate concurrently, and pairs can join more than one KPD program, with the aim of increasing chances of finding a compatible transplant [45]. However, this multi-network arrangement leads to a number of issues, as each program seeks to optimize its own transplant decisions [46]. In particular, individual programs may be incentivized to withhold their easy-to-match pairs or NDDs, matching them internally such that the number of their own patients who receive a kidney is maximized, with only the more difficult-to-match pairs revealed to the larger multi-center collectives [47–50].

These practices also lead programs to evaluate pools more frequently to quickly discover any pair that might be transplantable. As there is a trade-off between the amount of time a KPD program waits before performing a match run and the number of pairs and matches within the pool, more frequent match runs has the potential shortfall of not allowing time to increase pool size, which may lead to fewer overall transplants [51]. While it had been thought that waiting for more pairs to accumulate in the pool before identifying potential exchanges is preferable, recent work has put this practice into question due competing costs associated with increasing waiting time for pairs [52–54]. We plan to incorporate these environmental aspects into KPDGUI, potentially allowing for pairs and NDDs to be associated with several KPD programs. The ability to compare solutions within and across programs may help collaborating and independent programs better coordinate their decisions to the advantage of patients.

We intend to include more streamlined uploading capabilities and further customization and interactivity, based largely on feedback from clinical collaborators. We are also investigating more efficient algorithms for identification and enumeration of relevant exchanges, and for calculation of expected utilities of exchange sets of interest.

5. Conclusion

In this investigation, we have presented our software application for visualizing and managing KPD pools and performing optimizations to compare choices for transplant exchanges. This application is a flexible and powerful tool for offering decision support to clinicians and researchers on possible KPD transplant options to pursue under different user-specified optimization schemes, accounting for the possibility of non-viability of identified exchanges, and the recourse to fallback options in such cases. We anticipate that the use of KPDGUI can help expand the adoption and utilization of KPD across the United States and internationally.

Contributors

M Bray wrote the software, performed the case studies, and prepared the manuscript. W Wang and VB Ashby also provided support in the development of the software and collection of data. MA Rees and AB Leichtman aided in the conception of the software and provided clinical expertise. PXK Song and JD Kalbfleisch oversaw the project and helped draft and revise the manuscript. All authors acknowledge their contributions and approve of the article.

Conflict of interest statement

MA Rees is the founder and CEO of the Alliance for Paired Donation. The authors have no other conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2019.03.013.

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