Kidney Exchange and the Alliance for Paired Donation: Operations Research Changes the Way Kidneys Are Transplanted

Kidney Exchange and the Alliance for Paired Donation

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Abstract

Many end-stage renal disease sufferers who require a kidney transplant to prolong their lives have relatives or associates who have volunteered to donate a kidney to them, but whose kidney is incompatible with their intended recipient. This incompatibility can be sometimes overcome by exchanging kidneys with another incompatible donor pair. Such kidney exchanges have emerged as a standard mode of kidney transplantation in the United States. The Alliance for Paired Donation (APD) developed and implemented an innovative operations research based methodology of non-*simultaneous extended altruistic donor (NEAD) chains*, which, by allowing a previously binding constraint (of simultaneity) to be relaxed, allowed better optimized matching of potential donors to patients, which greatly increases the number of possible transplants. Since 2006, the APD has saved more than 220 lives through its kidney exchange program, with more than 75% of these achieved through long non-simultaneous chains. The technology and methods pioneered by APD have been adopted by other transplant exchanges, resulting in thousands of lives already saved, with the promise of increasing impact in coming years. The percentage of transplants from non-simultaneous chains has already reached more than 6% of the total number of transplants from live donors (including directed living donors) in the last year. We describe the long-term optimization and market design research that supports this innovation. We also describe how the team of physicians and operations researchers worked to overcome the skepticism and resistance of the medical community to the NEAD innovation.

Introduction

This paper describes how the Alliance for Paired Donation (APD) has used operations research methodology to make improved matches between kidney disease sufferers and potential kidney donors. To date, the APD has itself saved more than 220 lives through its development and implementation of so-called *non-simultaneous extended altruistic donor (NEAD) chains*. In

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addition, other kidney transplant institutions and kidney exchange programs have adopted the APD originated methodology, thereby saving more than a thousand lives to date and we can expect that in the future thousands of lives will be saved annually. The percentage of transplants from non-simultaneous chains has reached more than 6% of the total number of transplants from live donors (including directed living donors) in the last year. We estimate that the number of transplants conducted through kidney exchange programs has increased due to non-simultaneous chains by more than 10% and the percentage of very highly sensitized patients transplanted has increased by more than 50%.

The project involved a blend of operations research methods including optimization algorithms for finding larger number of matches between donors and recipients, and market design mechanisms to ensure collaboration across organizational boundaries by hospitals, institutions and surgeons who otherwise compete in the 50 Billion dollars end-stage renal disease (ESRD) industry.

Background: About 100,000 sufferers of end-stage renal disease (ESRD) are currently on the waiting list in the United States for a kidney transplant -- the preferred treatment for this severe disease. Sadly, about 4,000 of them will die this year before receiving a transplant and another 2,500 will be removed from the queue since they will have deteriorated so much that they are no longer viable transplant candidates. In addition there will be about 5000 transplants from directed living donors and about 10000 transplants from deceased donors this year. The problem is growing worse, as the queue increases by about 7,000 patients per year, making ESRD one of the most expensive problems of the US health care system.

The long waiting times for transplants of so many ESRD sufferers have two dominant causes. First, is the shortage of kidneys available for transplant – kidneys are available either from a deceased donor, or from live persons who are willing to donate one of their two healthy kidneys. The second cause is potential incompatibility between live donors and their intended recipients. The thrust of kidney exchange programs is to significantly increase the number of live donor kidney transplants by bringing together incompatible donors and recipients and conducting cross-transplants, essentially developing a ‘’market’’ for kidney exchanges, taking into account that a monetary market is forbidden by law. Specifically, kidney exchange allows potential living donors whose kidneys are incompatible with their intended recipients to nevertheless donate a kidney to another patient so that their own recipient receives a compatible kidney from another donor. This is done by exchange between two or more incompatible patient-donor pairs: each donor gives a compatible kidney to another donor’s intended recipient (see Figure 1a). Rapaport (1986) was first to suggest the idea of swapping donors between incompatible pairs, and the first such exchanges took place in Korea in the 1990’s (Park et al. (1999)). The first exchange in the United States was carried out in 2000 at the Rhode Island Hospital.

Originally, most kidney exchanges were conducted through simple cyclic exchanges, as, for example, in the two cycles depicted in Figure 1a. Out of fear of possible reneging, such cyclic exchanges have been conducted simultaneously, making the exchange process a significant logistical challenge: Four operating rooms and four surgical teams are required. For these reasons, cyclic exchanges with length more than three are rarely conducted. Another type of exchange took the form of a chain. Chains, initiated by altruistic donors (kidney donors who decide to donate without having an intended recipient), were also conducted at first simultaneously, thus involving only 2 or 3 transplants at a time ending with a transplant to a patient on the waiting list (see Figure 1b).

Contribution: At first the APD adopted the design and optimization methods for identifying short cycles and chains. It was, however, the introduction by APD of a new innovative, and in fact a highly controversial approach, based on long non-simultaneous (NEAD) chains that significantly increased the number of transplants that can be achieved through kidney exchange.

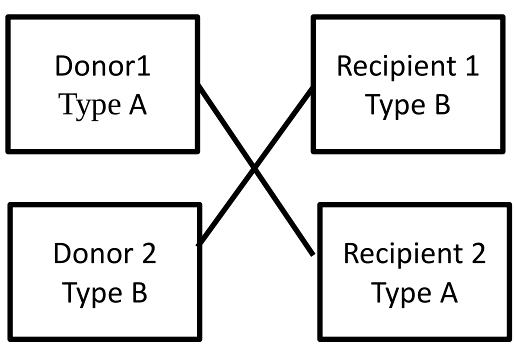

Figure 1a: A 2-way cyclic exchange between two blood type incompatible recipient-donor pairs, R1-D1 and R2-D2.

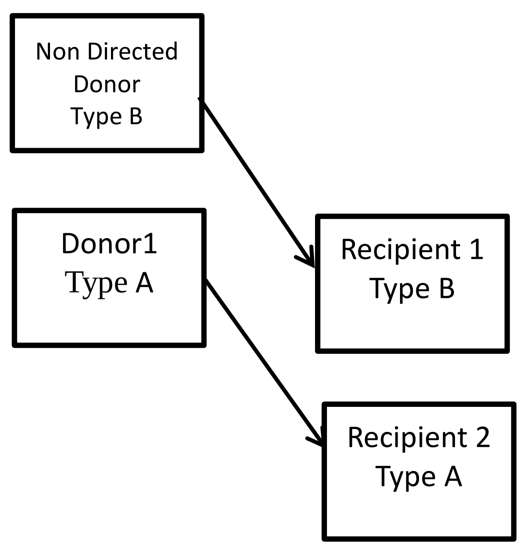

Figure 1b: A 2-way chain involving one non-directed donor, one blood type incompatible recipient -donor pair, R1-D1, and one sole recipient R2.

The added value derived from using NEAD chains is threefold. First, there is ample empirical evidence from current clinical practice, substantiated by conclusions drawn from mathematical models (see the body of the paper) that when exchanges are conducted in an optimal way, the bulk of the transplants (approximately 70%) are conducted via NEAD chains (with length at least

4). Thus NEAD chains are today responsible for the majority of successful kidney transplants conducted by the kidney exchange programs, both at APD and other exchange programs. By allowing only short (at most length three) chains the number of transplants would have been reduced by at least 12% and more than 30% of the recipients would have been transplanted after a longer waiting period. The number of very highly sensitized transplanted patients (further discussed below) would have been reduced by approximately 50%.

Second, unlike cyclic exchanges, chains can be conducted non-simultaneously while assuring that every patient in each patient-donor pair receives a kidney *before* the donor of the same pair donates the kidney. The lack of the simultaneity requirement thus significantly reduces the logistical overhead and makes long chains possible, which accomplish many transplants. The longest NEAD chain to date achieved 30 transplants, i.e. it involved 60 people, 30 donors and 30 patients (NY times, 2012).

Finally, NEAD chains can provide transplants for many hard to match patients. A patient receiving a donor's kidney needs to be both blood-type and tissue-type compatible (meaning that the patient does not have an antibody that would lead to the rejection of the donor's kidney). Chains offer particular hope to "highly sensitized" patients who are likely to be incompatible with the people who wish to donate a kidney for them. Highly sensitized patients typically wait unusually long before a compatible kidney from a deceased donor becomes available, if one ever does. For many such patients, while no cyclic exchanges could be identified, chains involving these patients and originating with altruistic donors were found and implemented, providing what turned out to be the only kidney transplant option for them.

Conducting kidney exchanges through cycles or chains introduces the challenge of finding a maximal set of compatible matches, a classical combinatorial optimization problem in operations research which we solve using integer programming techniques and insights from the theory of random graphs. Allowing chains to be long has significantly increased the size of the optimization models and with that has come computational challenges.

Moreover, because kidney exchange is decentralized-- there are over 200 transplant centers in the U.S. and innumerable dialysis clinics -- organizing kidney exchange is not just an optimization problem, but also a serious market design/coordination problem. A successful broad scale approach to designing kidney exchange clearinghouses and protocols needs to take into account the goals and interests of the hundreds of existing institutions in the $50Billion/year business of caring for patients with ESRD, since participating agents often have conflicting objectives. Thus, market design issues are central to this work.

In the body of the paper we describe both the optimization approach and the market design developed by the Alliance for Paired Donation (APD) for conducting kidney exchange. In addition to technical issues, we emphasize the cultural and political obstacles to implementation of long chains, and our multifaceted work to overcome them. We survey the steps, beginning in

2004 that led our team towards the current successful practices as conducted by the APD. We will detail its direct impacts through the APD, describe how other organizations have adopted non-simultaneous chains, and provide estimates of the overall impact of these innovations.

Operations research for Kidney exchange - market design and optimization

Early experience: exchanges with short simultaneous cycles and chains

In 2000 Michael Rees, the founder to be of the APD and his father, Alan, wrote the first computer program to heuristically identify all 2-way cyclic kidney exchanges possible within a pool of incompatible pairs This program applied a utility score to each exchange and produced a rank-ordered list of all possible exchanges. This program was modified in 2003 by Rees and Jonathan Kopke (at the University of Cincinnati) to be web-based and track participating patients and donors from registration through transplantation. The Ohio Solid Organ Transplantation Consortium (OSOTC) living donor kidney exchange program utilized this software from 2004 until 2006, when the OSOTC was disbanded.

Operations research methods for the first time were applied to kidney exchange when Roth, Sönmez and Ünver (Roth et al. 2004) proposed organizing kidney exchange on a large scale, including integrating exchange cycles and chains. They proposed an allocation mechanism that made it safe for participating patients and their surgeons to reveal relevant information (e.g. revealing their medical data and which donors in the pool are acceptable). That proposal involved algorithms that could generate large cycles and long chains. The mathematical treatment of those algorithms dates back to the “top trading cycle” algorithm introduced by Shapley and Scarf (1974), who attributed it to David Gale. Its dominant strategy incentive properties, which would be relevant in the kidney exchange context, were established by Roth (1982), and the algorithm was adapted to more general settings by Abdulkadiroglu and Sönmez (1999) who modeled the allocation of dormitory rooms in a way that later provided a natural bridge to models for allocating kidneys.

However, the surgical culture and infrastructure in 2004 permitted only pairwise simultaneous exchanges. To avoid the possibility that one pair would give a kidney and then not receive one (for example due to reneging), it was (and remains) the practice that all the surgeries in a cyclic exchange be conducted simultaneously. So even the simplest exchange between two patient-donor pairs, required four operating rooms and four surgical teams for the two nephrectomies and two transplants to be conducted simultaneously.

Responding to this limitation, Roth et al. (2005a) therefore stepped back and considered how to organize kidney exchange around only pairwise exchange. This constraint actually allowed the application of classic graph theory methods (such as Edmond's matching algorithm (Edmonds 1965), Gallai-Edmonds decomposition (Gallai 1964) and the fact that the sets of match-able nodes in a graph constitute a matroid). They were able to show how to achieve a maximal set of kidney transplants in a way that continued to give patients and surgeons incentives to reveal all relevant information (including, e.g. the number of willing donors associated with a patient in cases there was more than one). In contrast to the simple OSTOC rank-ordered program, the New England Program for Kidney Exchange (NEPKE), established in 2005, was the first multi-hospital kidney exchange program to optimize pairwise kidney exchanges (Roth et al. 2005b). While collaborating with NEPKE and gaining experience with pairwise exchanges, Saidman et al. (2006) and Roth et al. (2007) showed that efficiency gains could be achieved by incorporating chains (still short ones) and larger cyclic exchanges that would require only relatively modest additional surgical infrastructure. Ashlagi et al. (2013) have shown that 3-way cycles and 3-way chains would increase the number of transplants by more than 50% (see Ashlagi et al. 2013), and indeed 3-way cycles and short simultaneous chains fairly quickly began to be part of regular kidney exchange practice

These proposals were instrumental in stimulating the founding the Alliance for Paired Donation (APD) in 2006 under the direction of Dr. Michael Rees. While the APD's predecessor, the OSOTC identified all 2-way cycles and then greedily ranked them, and thus did not find the largest number of 2-way cycles, the APD adopted optimization software designed by Roth, Sönmez and Ünver that maximized the weighted number of transplants in existing pools. Weights are used in order to define and account for priorities between different matches. This algorithm found optimal solutions consisting of cycles and chains whose length was bounded by 3 or 4, depending on the circumstances. The algorithm was based on solving an integer program in which each feasible cycle and chain was assigned a decision variable. The cycles and chains were found first by simply searching the graph induced by the compatibilities between donors and patients. Until 2007 cycles and chains were implemented simultaneously, thus significantly limiting the length of these cycles and chains. For example a three-way exchange required six operating rooms and six surgical teams (for three nephrectomies and three transplants).

Relaxing the simultaneity constraints and the benefit of long chains.

In 2006 Roth, Sönmez and Ünver together with Drs. Frank Delmonico and Susan Saidman observed that the growing number of altruistic non-directed donors would allow the simultaneity constraint to be relaxed for transplant chains initiated by non-directed donors (Roth et al. 2006). When a chain is initiated by a non-directed donor, it can be organized so that the non-directed donor makes the initial donation, and no patient-donor pair has to donate a kidney before they receive one. By reducing the cost of a broken link, we open the door to the potential benefits of chains in which operations are conducted non-simultaneously. The benefit is that non-simultaneous chains can be *longer*, as more operating rooms and surgical teams can be assembled over a longer time frame.

But practitioners in the transplant community raised objections about the use of non-simultaneous chains. They were concerned that a broken chain or chains (due to reneging) would cause patients and the public to lose trust in the kidney exchange system. Dr. Rees disagreed and felt that the utilitarian gains outweighed the risk of equity losses. Therefore, after careful planning to minimize this danger, the APD was the first to implement a NEAD chain and began to carry out the first non-simultaneous, long chain of kidney transplants in July 2007. The incompatible donors of the recipients of the first two transplants were trusted to donate in the future after their intended recipient had already received a transplant. Neither donor reneged! Furthermore, as of now, while the scope of kidney exchanges based on non-simultaneous expanded greatly, the incidence of reneging is very low. Subsequently, APD makes the last donor of each identified segment of the chain be the *bridge donor* for future segments of the chain. They trusted bridge donors to "pay-it-forward" in the future. Segments of the first NEAD chain were actually identified dynamically as the process unfolded and transplants were sometimes separated by months and thousands of miles. By March 2008, this first NEAD chain included 10 transplants and 11 donors, ten of whom had donated kidneys to ten patients they didn't know. Rees et al. (2009) reported it in the New England Journal of Medicine (See Figure 2 for details).

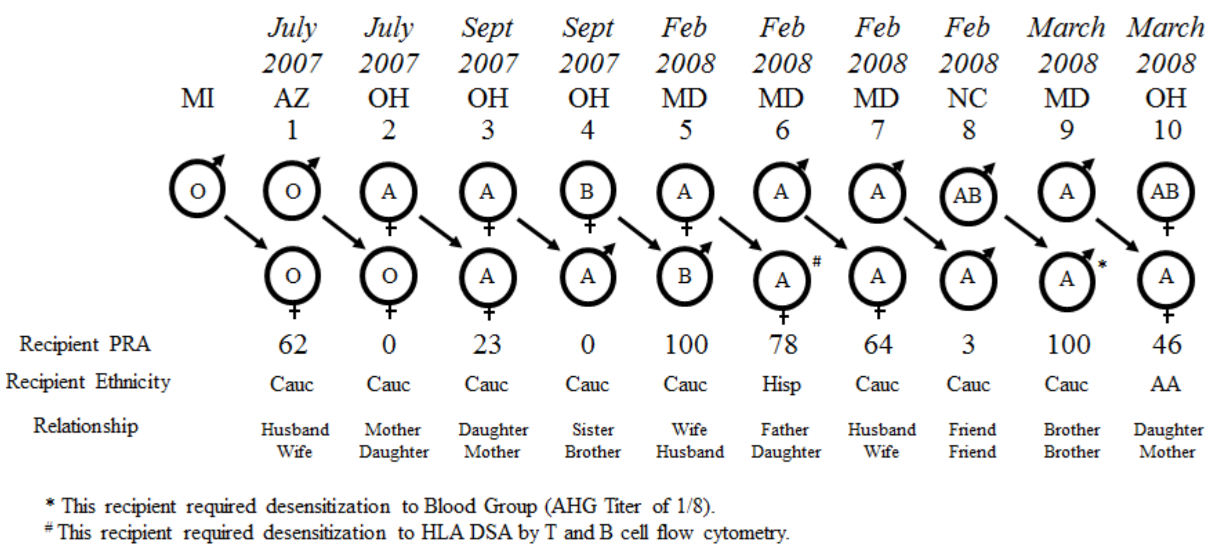

Figure 2, the first NEAD chain, reported in Rees et al. 2009

The end of the chain was the 11th donor, whose blood type was AB, and who was the last bridge donor at the time the paper was published. She eventually waited three years before she donated to continue the chain. (AB is the least frequent blood type in the population and most AB patients who join kidney exchange are highly sensitized, since AB patients are never blood- type incompatible with any donor, and so are only incompatible with their donor due to tissue type incompatibilities.)[2] That initial chain was eventually extended to 16 transplants, and only ended when the APD participated with UNOS in an exchange and they chose to end the chain

Since 2007, NEAD chains were adopted by several other Kidney exchange matching services for arranging kidney exchanges in the US. Most notably, the National Kidney Registry built their matching service around this approach and subsequently produced the longest NEAD chain so far reported, including 60 people, 30 transplants and thirty nephrectomies (NY Times, 2012). The NKR has so far conducted more than 900 transplants and more than 67% of them done through NEAD chains. While long chains may seem intuitively attractive, it was not initially clear whether they were actually advantageous. Long chains might not increase efficiency if they simply identify transplants that could otherwise have been done in multiple short cycles. In addition, as we remarked earlier many in the transplant community still continued to worry that non-simultaneous chains and trusting bridge donors to carry through on their promise to donate their kidney in the future to a stranger was fraught with the danger of eroding trust in the entire kidney exchange enterprise.

Allowing chains to be non-simultaneous and thus longer than 3, meant optimizing over a huge solution space. For example in a pool with 150 pairs with just one non-directed donor the number of chains bounded by length 3 can reach up to a few thousands while there can be more than one million chains if we permit them to be of length 6. (We will discuss further computational issues and algorithms in the Algorithms section).

Simultaneous or non-simultaneous chains? Criticism and objections.

Whether or not to proceed with NEAD chains or to just to continue with short simultaneous chains became a major debate in the (medical) kidney transplant community in 2009. An influential team from Johns Hopkins Hospital, argued, based on computer simulations, that non-simultaneous chains were a bad idea and should not be conducted, because even a modest risk of a broken chain implied that more transplants would be accomplished via short simultaneous chains (Gentry et al. 2009). They called these *Domino Paired Donation* (DPD) chains, which are short simultaneous chains including up to 2 incompatible pairs that end with a patient on the waiting list for deceased donors. Since the waiting list always contains many patients (today almost 100,000), it is always possible to find a compatible patient on the waiting list for the last kidney in a chain, and if this transplant is done simultaneously with the others, there is no bridge donor who might break the chain by failing to donate at a later date.

We engaged in the debate and our paper in the American Journal of Transplantation (Ashlagi et al. 2011) noted that the Hopkins team failed to capture some of the potential for NEAD chains to accomplish many transplants, because their model constrained NEAD chain to have 3 or fewer transplants in each round of optimization. We showed that their conclusions were reversed when

[2] Exchange progams no longer wait with an AB bridge donor to continue a chain within the kidney exchange pool, but rather close the chain with a donation of the AB donor to a patient on the (overloaded) waiting list for deceased donors.

long chain segments were allowed. Moreover, most of the additional transplanted patients arising from using long chains rather than shorter ones would be very highly sensitized patients. This debate within the medical academic community continued (see Gentry et al. (2011) and Ashlagi et al. 2011b), but did not prevent the continued adoption of long chains by APD and a few other transplant networks. As additional favorable clinical experience and data accumulated, the debate was settled in favor of NEAD chains.

A team from Carnegie Mellon University also conducted simulations that led them to conclude that while NEAD chains result in more transplants than DPDs, NEAD chain segments should be capped at 4 transplants (Dickerson et al. 2012). This constraint on chains has been adopted in the national UNOS pilot program.

However, as of the time of writing this paper, the accumulated clinical success of NEAD chains, including some very long ones, has become so apparent that early opponents (such as Johns Hopkins Hospital) have now adopted them (Baltimore Sun, 2013) making exchanges based on non-simultaneous, potentially long chains a standard practice.

The power of long chains. Mystery explained.

We now explain what makes long chains based kidney exchanges so potent, how it came to be realized, and how this has changed the practice of kidney exchange. In our results section we will detail the resulting substantial increase in the number of transplants, including the number of transplants to the hardest-to-match patients.

The key reason for why long chains actually increase the number of transplants is the high percentage of very highly sensitized patients in kidney exchange pools. Patient sensitivity is measured by the so-called Panel Reactive Antibody (PRA) which is the likelihood that the patient will be tissue type incompatible with a random donor. For example, if a patient has a PRA of 99%, then 99% of the blood-type compatible potential donors for that patient will not be tissue compatible. By simulating a pool using a statistical process based on empirical medical characteristics, less than 10% of the general population patients are expected to have expected to have at PRA level of at least 80. This is in fact the case in the general pool of ESRD patients. However, in general kidney exchange pools, and in particular in the APD pool, more than 40% of the patients have a PRA more of at least 80! In addition, more than 65% of the APD patients with PRA level of 80-100 actually have PRA greater than 95. Figure 3 plots the percentage of patients registered to the APD pool with a PRA of at least 95 (in addition, the percentages of patients with PRA>95 newly registered to the pool in 2010, 2011 and 2012 were 33, 33 and 30).

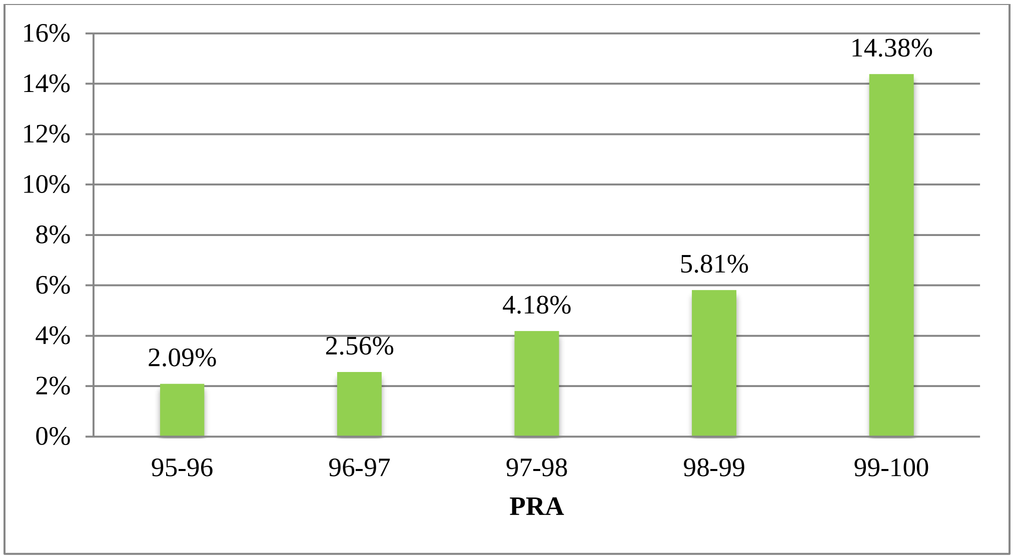

Figure 3: Percentage of patients in the APD pool with given Panel Reactive Antibody (PRA).

This means that the directed graph depicting the compatibilities between members of a kidney exchange pool is very sparse. There are several reasons why kidney exchange pools have such high PRAs – as contrasted to general patient population. As kidney exchange has grown, hospitals became strategic players. Hospitals (or directors of transplant centers) have bigger strategy sets than do individual surgeons or patients, since hospitals see multiple patient-donor pairs. Now that many major transplant centers have acquired experience with kidney exchange, hospitals often match their easy-to-match pairs internally (see Ashlagi et al. (2013)), and only refer their difficult-to-match pairs to the kidney exchange networks. This causes kidney exchange pools to contain a very large percentage of highly sensitized patients. The second reason is that most highly sensitized patients and hard-to-match pairs naturally accumulate over time in the pool (up to a "steady-state"). Pools consisting of primarily highly sensitized patients coupled with the shortage of non-directed donors lead to the need for exchanges based on long chains, because the resulting compatibility graphs become sparse, and as a result exchanges based only on short cycles and short chains are substantially suboptimal. Mathematically, the benefit of long chains in such pools can be illustrated by some classical facts from the theory of random graphs. In the so-called sparse Erdos-Renyi random graphs, the number of short cycles involving highly sensitized patients is very small. At the same time there exists with significant probability a long chain covering a substantial number of nodes in the graph. Ashlagi et al. (2013) analyze a random graph with a mixture of dense (corresponding to low PRA patients) and sparse (high PRA patients) parts. We show that in such graphs allowing for long chains amounts to first order of magnitude increase in the number of patients participating in the exchanges.

To illustrate further the typical properties of pools of patients encountered in practice, consider a snapshot of APD data depicted in Figure 4. This figure describes the compatibility graph induced by the subset of patient-donor pairs such that all patients and all donors have blood type A. In particular, there are no blood-type incompatibilities among these pairs. At the moment represented by this compatibility graph, there were 38 such pairs that have some compatibilities among themselves (there were also 18 such pairs that weren't compatible with any other of these pairs), each represented by a node of the graph. An arrow points from one node to another if the kidney from the donor in the first pair is compatible with the patient in the second pair. 30 of the 38 pairs contain patients with high PRAs and are depicted as white nodes. We see that these nodes have few incoming edges. The nodes containing the 8 low PRA patients have substantially more incoming edges, and are shaded in the figure. The dashed edges are parts of cycles. Note that there is ***no*** cycle that contains only high PRA patients, and only one cycle included one high PRA patient.

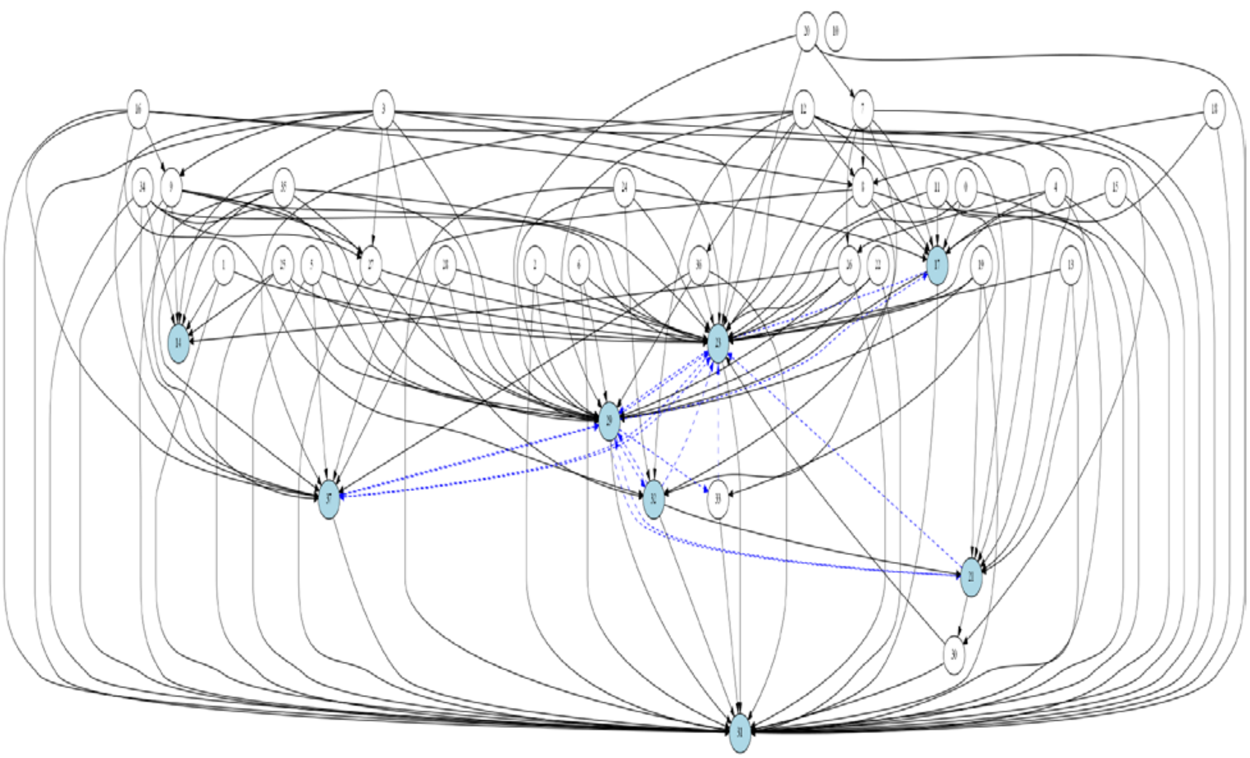

Figure 4: A compatibility graph of patient-donor pairs each with blood type A, from APD data. Most patients are highly sensitized, and cannot participate in cyclic exchanges, but can be reached via chains.

That is, because many patients are highly sensitized, they have few in-edges in the resulting compatibility graph, and are consequently included in very few short cycles. As mentioned above, Ashlagi et al. (2013b) have further explained analytically the importance of long chains.

NEAD chains have become the regular practice at the APD, which now uses an optimization algorithm in which the length of chains is not constrained (more on this below). This is now also the practice at the National Kidney Registry (NKR), the highest volume kidney exchange program today. Later in the paper we'll show the impact outside the APD by reviewing data from the NKR, and from the pilot federal program, run by the United Network for Organ Sharing—UNOS.

Benefits

Results at the APD

Before describing the impact, we discuss how the typical matching process works at the APD. There are currently more than 80 transplant centers registered with the APD.[3] Every weekday after new incompatible pairs are entered into the APD pool or a potential match is abandoned (for example when a pair does not accept a match offer), the APD conducts a "match-run" to find a maximum weighted number of matches allowing both cyclic and long non-simultaneous chain exchanges. The solution is based on the virtual compatibilities between patients and donors in the pool using their medical information. The APD pool contains approximately 200 patient-donor pairs at any given time. Finding a solution typically takes not more than 3 minutes (see Algorithms section for more details). The solution is determined according to virtual compatibilities using the medical information of patients and donors (actual blood tests should still be done before the transplant actually takes place). After an optimal solution is found by the software, crossmatch tests on the blood samples of the patients and donors are conducted in a central lab to detect whether each recipient in the solution is tissue type compatible with her intended donor. Then, the transplant center of each patient that is part of the solution is informed about their match (the details about their matched donor) in order to finally accept the donor. Centers/patients can refuse to accept offers. An exchange (chain or cycle) proceeds to the transplantation stage if no failure occurred during these stages.

Very significant benefits accrue directly to the transplanted recipients, who are freed from being tied to dialysis for many hours each week, regain their health and ability to work, and have their lives extended. However, there are also savings to the medical system and to the third party payers. Most ESRD patients receive dialysis treatments, which costs Medicare $87,272 per year (USRDS, 2013), and costs private insurers much more. Transplanting a single kidney failure patient, at a cost of $32,922 (averaged over five years), rather than having them remain on dialysis, saves Medicare $271,750 over five years. Note the average survival on dialysis is about 5 years.

Since 2007 the APD has conducted over 220 transplants through kidney exchange and more than 168 of these have been done through chains. So we can give some indication of the purely financial impact of these transplants. If each transplant saves $275,000 over five years, the 200+ transplants of the APD have produced savings in excess of $46 Million dollars for the US healthcare system. In a more conservative analysis of the savings from a single living donor kidney transplant (which takes into account that transplant patients live longer than dialysis

[3] Centers do not commit to enroll all their pairs or whether to accept matches.

patients and therefore incur medical costs over a longer period), Matas et al. estimated the savings at $94,579 (US dollars, 2002), and 3.5 quality-adjusted life years (QALYs) were gained. Adding the value of QALYs, a living unrelated donor transplant saved $269,319, assuming society values additional QALYs from transplantation at the rate paid per QALY while on dialysis. Using this analysis from 2004, 168+ living donor transplants has saved $16 Million and produced a value to society of $45Million.

Wolfe (NEJM, 1999) did an analysis that showed that the average patient who received a *deceased* donor kidney transplant lived 10 years longer than had the patient stayed on dialysis. So these 168+ patients have received at least 1600 extra life years through APD transplants. Those are conservative numbers, since the average living donor kidney lasts twice as long as the average deceased donor kidney.

Impact at the other transplant networks in US.

Overall in the United States there have been over 2,600 paired donation kidney transplants performed since the year 2000 when the first two KPD transplants were performed at Rhode Island Hospital (more than 2250 of them have been done since 2008). Demonstrating the impact of NEAD chains, in 2006, when exchanges were all still constrained to be simultaneous, there were 74 paired donation kidney transplants performed in the US and 68 non-directed living kidney donations. In 2012, more than 200 of the 528 paired donation transplants performed in the US resulted from NEAD chains.

According to UNOS, the number of transplants from kidney exchange in the US has reached 2658 (we believe this number is a lower bound, as many centers conduct internal exchanges that may not be reported, and the 2013 numbers are still subject to change as centers are still reporting their 4th quarter numbers). The progress by year is given in table 1:

Table 1: Transplants through kidney exchange since 2000.

2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
2	4	6	19	34	27	74	111	228	281	430	446	528	506

Two other important kidney exchange programs

The National Kidney Registry (NKR) and the UNOS KPD pilot program are both running multi-hospital exchange programs in the US. The NKR, a private organization, was founded around by Dr. Garet Hil in 2007 around the idea of recruiting non-directed donors and running NEAD chains. It is currently the highest volume clearinghouse in the US and has facilitated more than 900 transplants since it launched. The United Network for Organ Sharing (UNOS) is the federal contractor responsible for administering the waiting lists for deceased donor organs. (It therefore has working relations with every U.S. transplant center, and is a natural candidate to organize a federally sponsored kidney exchange that would unite all American transplant centers.) It launched a pilot Kidney Paired Donation (KPD) program in October 2010 that has yet to become a major producer of kidney exchange transplants, but has been making recent progress since moving to allow chains. Through 2013 it conducted 79 transplants (52 of them in 2013). Since launching, more than 1600 pairs have enrolled in the NKR and more than 1000 pairs have enrolled in UNOS (the arrival rate was very low in the first years). The pools of both programs seem to have stabilized around 220-250 pairs (UNOS reached this level around the beginning of 2013).[4]

Chains play a significant role in both programs. About 88% of the transplants facilitated by NKR have been achieved through chains (176 chains overall). More than 28% of the transplanted patients had PRA>80 and more than 15% had PRA>95 (in the past 2 years, this percentage increased to 20%). As of this writing (1/30/14) NKR had conducted 179 chains that accomplished 823 transplants, and 44 cyclic exchanges that accomplished 103 transplants. More than a quarter of these transplants were accounted for by the 16 chains involving more than 10 or more transplants, while the 96 chains involving three or fewer transplants only accounted for about 10% of these transplants. That is the long chains are rare (fewer than 10% of the chains), but they account for a disproportionate share of the transplants.

The lengths of all chains conducted by the NKR are given in Figure 4. Note the long tail: most chains are short, but the longest 3% of chains account for more than 10% of all transplants (and more than13% of all transplanted patients with PRA>= 97 have been transplanted through those chains. In addition, 73% of the transplanted patients with PRA>=97 transplanted through chains or cycles that have length at least 4, while only 67% of all transplanted patients have been transplanted through chains and cycles of length at least 4).

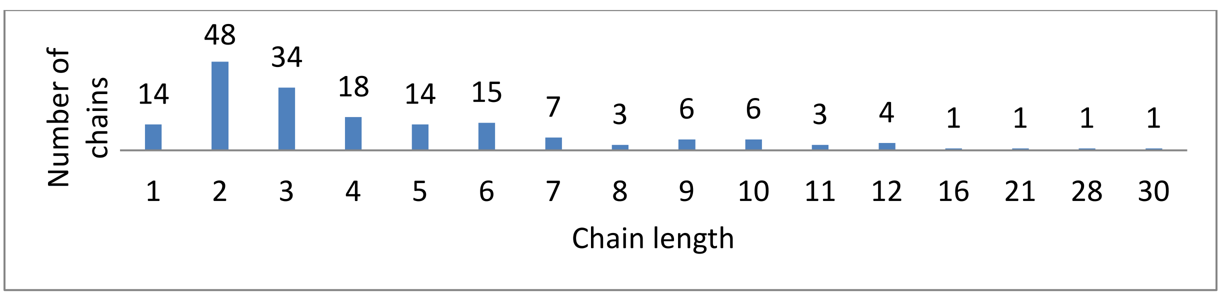

Figure 4: The number of chains and their lengths achieved in the in NKR.

The experience of the UNOS KPD pilot program is somewhat different. At first, UNOS searched only for 2-way exchanges, but in 2011 the UNOS algorithm was adapted to find chains unrestricted by length. Their very high failure rate after identifying matches (due to match offer

[4] Ashlagi, Rees and Roth are presently advisors to UNOS and members of the UNOS KPD Workgroup. Ashlagi and Roth and Rees have all advised NKR, and Ashlagi and Roth collaborated with NKR to develop and validate their current optimization algorithm (see NKR, 2014)

refusals and crossmatch failures) but prior to transplants led them to limit chain segments to 4 since October 2012 (such chains are also often conducted non-simultaneously). About 15% of the transplants UNOS has facilitated have been achieved through 2-way cycles, 40% through 3-way cycles and 45% through chains. That is, even with the restriction on chain length, most UNOS transplants have come from chains and 3-way cycles.

The UNOS Kidney exchange program and the NKR have different experiences that lead to slightly different policies, though in both programs NEAD chains are playing a major role in successful transplants. The National Kidney Registry is very successful in attracting non-directed donors. This success is largely due to providing incentives to transplant centers to share the non-directed donors that approach them (guaranteeing them to end a chain with a patient within their center). Not all chains need to be long when there are so many altruistic donors. Most of the chains the very short chains conducted by NKR (ending with a patient on the waiting list) are done because they include patient that is very highly sensitized, or because the quality of the match is very high or because the non-directed donor is an AB donor, in which case is very unlikely to match an AB patient within a pair.

The importance of matching the most highly sensitized patients through long chains cannot be overemphasized, since many of these patients have little or no prospect of receiving a deceased donor kidney. OPTN data for the whole United States shows that the median waiting time for patients with (peak) PRA $\geq$80 was 13.5 years for candidates listed in 1999-2000, and the median time for such patients who began waiting in 2003-04 cannot yet be computed because fewer than half of them have been transplanted. As we've seen, NEAD chains serve a disproportionate share of the most very highly sensitized patients, with PRA $\geq$ 95.

Finally, we note that the number of non-directed donors has significantly increased since the advent of NEAD chains—in part because of the added draw of being able to help more than one patient as a result of one's altruism.

Algorithms, optimization and implementation

The APD (as well as other kidney exchange programs) organizes transplants by regularly searching the compatibility graph generated by the current pool of patients and donors for the maximum weighted number of transplants that can be achieved through cycles and chains. It is convenient to think of the pool as a compatibility network described by a directed graph $G(V,E)$. In this graph each pair and each non-directed donor (NDD) is a node $v \in V$. There is an edge between two nodes v_1 and v_2 if the donor of node v_1 is compatible with the patient of node v_2. Edges are associated with weights to capture some priority (importance, urgency) for conducting the corresponding matches.

The optimization problem considered prior to the introduction of non-simultaneous chains had the following form:[5]

Maximize weighted number of matched pairs

*s.t. e*ach pair is matched at most on*ce via a cycle or chain*

cycle length at most 3

chain length at most 3

Existing pools typically contain about 200 pairs and up to 10 NDDs, some of which are bridge donors and some are altruistic donors. A bridge donor is part of an incompatible pair who is waiting to continue an existing chain (and donate a kidney) after his intended recipient already received a kidney. An altruistic donor initiates a new chain.

At first[6], kidney exchange programs considered algorithms searched for an optimal solution allowing up to 3--way cycles and up to 3-way chains as described in the formulation above. The problem is solved using integer programming technique by introducing a decision variable for every cycle with length at most three and every chain with length at most three. This formulation works very well for the pools experienced in practice.

Abraham et al. (2007) and earlier Michael Cheung and Michel Goemans (personal communication) have shown that solving the optimization problem above is an NP hard problem. In practice however computational issues haven't been a serious issue when both chains and cycles are bounded by a short length. Abraham et al. (2007) developed an algorithm based on column generation to solve such problems for very large pools. Their algorithm was briefly used in the APD and an extended version of it is now also used by UNOS allowing finding chains with segments of length less than 4, now that UNOS policy has been changed to allow them.

Allowing for longer chains (larger k) makes the formulation above hard to solve not only theoretically, but also in practice, as the potential number chains grows very fast as the allowed chain length grows (in an historical pool of 150 pairs, the number of chains of length 6 beginning with an O donor may easily typically reaches over 5 million).

[5] The OSOTC program did not optimize. The APD used optimization and unrestricted length of chains and cycles from the outset. Now we restrict the length of cycles to 4, but still allow chains to be of unrestricted length.
[6] The OSOTC program, and the initial NEPKE program, allowed only 2-way exchanges and not chains.

We describe next two algorithms we developed in order to solve the optimization problem when long chains are permitted. These algorithms scale very well on the existing pools and find optimal solutions in a short time in all encountered instances.

The Recursive algorithm

In this algorithm we solve an optimization problem using constraint generation without assigning a variable for every chain, but instead introducing flow conservation constraints. In the graph $G(V, E)$ we use a binary decision variable y_e that determines whether edge e (from a donor to a compatible recipient) will be chosen or not. Let in(v) be the set of edges that point to node v and let out(v) be the set of outgoing edges from node v. For each edge e, let w_e be the weight associated with edge e. We further add an edge from every node corresponding to an incompatible pair to every node corresponding to NDD. This is done so that every chain originating from an NDD can be extended to a cycle beginning and ending with an NDD. Our algorithm then uses the following formulation:

Recursive: *Maximize* $\sum w_e y_e$

$$s.t. \quad \sum_{e \in out(v)} y_e \leq \sum_{e \in in(v)} y_e$$

$$\sum_{e \in in(v)} y_e \leq 1$$

$$y_e \in \{0,1\}$$

This in fact an integer programming formulation which finds the largest disjoint cycle cover of a graph. As such this formulation ignores for now bounds on the length of the cycles and chains. Now in order to incorporate a bound on the length of the cycles (to be say at most 3) and at the same time allowing chains originating from NDD to be arbitrarily long, we run the algorithm recursively by eliminating long cycles one at a time. Specifically, our recursive algorithm works as follows: it first solves the formulation above. It then inspects the optimal solution. If the optimal solution outputs a cycle C of size more than 3 which does not include a NDD (and thus this is not a feasible cycle), we add a constraint to resolve the recursive formulation with an additional constraint that violates this cycle. This constraint has the following simple form:

$$\sum_{e \in C} y_e \leq |C| - 1,$$

where C is the identified cycle. The integer programming problem is then solved again with this additional constraint. The procedure is repeated until a solution is identified without cycles with length 4 or more. This algorithm works well in many instances (see the next section), however for many other instances the running time became substantial (exceeding 20 minutes). In order to solve the remaining instances we proposed an alternative integer programming formulation based on the Prize-Collecting Travelling Salesman Problem (PC-TSP). This formulation and the running times corresponding to both formulations are described below.

The PC-TSP based algorithm

Recall that in the Travelling Salesman Problem (TSP) one is given a graph and the goal is to find a route that visits each node exactly once at minimum cost. In the PC-TSP, the goal is to find a route in the directed graph that visits each node at most once while paying some penalty for each node that is not visited. Qualitatively the PC-TSP is similar to the optimization problem we are facing, in that one wants to find long paths in a graph without the need to visit every node. Our solution is presented in the Appendix and is very similar to the solution to PC-TSP. As in the PC-TSP case, the formulation has an exponential number of constraints that have a "cut" interpretation. The solution relaxes those constraints but more aggressively attempts to find violating constraints, using a technique called "cutting planes" (see more details in the Appendix).

Table 2 describes the running time of both algorithms on what we call ''difficult'' instances, namely instances involving at least 500 constraints of type (*) in the recursive algorithm and analogue "cut" constraints in the PC-TSP algorithm. These instances were generated while running each algorithm on real data from the APD and NKR programs.

Instance info			Running time (secs)	
NDDs	Pairs	Edges	Recursive	PC-TSP
3	202	4706	0.18	0.255
10	156	1109	4.425	1.069
6	263	8939	16.186	11.055
5	284	10126	28.063	16.03
6	324	13175	143.432	
6	328	13711	150.877	27.67
6	312	13045	1200*	1200*
10	152	1125	10.388	0.245
3	269	2642	13.896	0.056
10	257	2461	16.206	0.113
7	255	2390	16.7	0.108
6	215	6145	44.101	2.237
10	255	2550	103.112	0.136
1	310	4463	177.582	0.151
11	257	2502	201.154	0.154
6	261	8915	340.312	3.829
10	256	2411	347.791	0.119
6	330	13399	522.619	6.507
10	256	2347	683.949	0.121
7	291	3771	1200*	0.163
8	275	3158	1200*	0.306
4	289	3499	1200*	0.376
3	199	2581	1200*	1.943
7	198	4882	1200*	8.255
2	389	8346	1200*	16.076

Table 2: Performance of the Recursive and PC-TSP algorithms for "difficult" real instances (instances that generated at least 500 violating constraints). Instances for which the optimal solution was not found within 20 minutes are indicated by '*'. In instances above the midline, both algorithms have running time within the same order of magnitude, and for instances below the midline, the PC-TSP based algorithm was at least order of magnitude faster.

Anderson, Ashlagi, Gamarnik and Roth (Anderson et al. 2014) have developed software based on running both of the algorithms above concurrently and outputting the optimal solution produced by whichever algorithm manages to find it. This software is currently being launched at APD. Other exchange programs presently use our software include the Northwestern Medical Center, the Methodist Hospital in San Antonio and the Georgetown Medical Center. This software is also used to suggest kidney exchanges from merging the NKR, APD and the San Antonio pools. This essentially means that this software identifies matches in the largest combined pool in the US -- more than 600 pairs.

Conclusions

Kidney exchange has become a standard part of transplantation in the United States, and the innovative ideas of many researchers and practitioners have played an important role in this success. One distinct innovation that has had a very profound effect in increasing the number of transplants has been the introduction by the APD of long non-simultaneous chains. After non-simultaneous chains were introduced more than 75 percent of the more than 2600 transplants have been conducted through NEAD chains).The APD was the first to implement such chains, and the first to optimize matches that incorporated them, and the APD team has collaborated in assisting other centers and kidney exchange programs to adopt this methodology. Hence, over time other clearinghouses have adopted NEAD chains as well (notably, the NKR, which is presently the highest volume clearinghouse for kidney exchange, has facilitated more than 85% of its transplants through non-simultaneous chains). Early opponents of long non-simultaneous chains have adopted them, and there is no longer controversy about their effectiveness. Furthermore, early ethical concerns for choosing to give a non-directed donor's kidney to someone other than the top patient on the deceased donor waiting list have since then been trumped by the profound increase in the number of transplants due to NEAD chains.

It is perhaps the very highly sensitized patients who benefit the most from the use of long chains, because such chains are often the only way these patients can receive a transplant. But the nature of exchange is that it benefits all parties, and so the benefits flow not only to all participants in kidney exchange, but also to patients without a donor who are waiting for a deceased donor kidney. Some of those patients benefit directly when they receive the last donor kidney from a long chain. But even patients who will eventually receive a deceased donor kidney benefit from kidney exchange since every living donor transplant accomplished through kidney exchange potentially relieves the recipient from having to wait (longer) for a deceased donor kidney, since it delivers living donor kidneys to patients who are on the waiting list for deceased donor kidneys, and so shortens the wait for those who have no other option.

Non-simultaneous chains allow a patient to receive a kidney before waiting for her incompatible donor to find a match. While 2-way cycles may be simple to implement, they often will involve two relatively easy-to-match pairs, leaving less opportunity for the harder-to-match ones (since it is even harder to match ‘’hard to match’’ pairs to each other than it is to match them to ‘’easy to match’’ pairs). Studying how long chains should be implemented in practice will be even more important in the future as the kidney exchange market grows. Increases in the number of NDDs as well the increases in the number of incompatible pairs will impact the algorithmic challenges of implementing long chains. All successful clearinghouses use optimization and the new algorithms help to find optimal solutions including chains efficiently.

There remain important design issues that need to be understood and implemented in order for kidney exchange to continue to grow. One important issue is to provide more incentives for transplant centers to fully participate, i.e. to offer kidney exchange to their easy-to-match pairs as well as those that are difficult to match. Ashlagi and Roth (working paper) explore how “frequent flyer” programs could be developed to provide appropriate incentives for centers to enroll their easy-to-match pairs. Such programs that incentivize centers to enter their NDDs are already taking place in the NKR and the APD (a chain terminates with a patient that is associated with a center that entered an NDD). Already today most chains end with patients on the waiting list for deceased donors.

In closing, we would also like to note that when Operations Research began to emerge as a distinct discipline in the years following World War II, it was quite closely linked to Economics, but those links grew more tenuous over time. The development of kidney exchange and the field of market design more generally illustrates how close those links can still be. Market design draws on both optimization and game theory, to deal with both the operational aspects that constrain exchange and with the incentive constraints that may also have to be satisfied. In the case of kidney exchange, the operational constraints involve assembling the resources to coordinate and conduct complicated surgical procedures across many hospitals. The incentive constraints involve assembling the medical information that is held by patients, surgeons, and hospitals by making it safe for them to reveal this information (such as the number and characteristics of their willing donors). They also involve the incentives facing hospitals when it comes to enrolling not only their hard to match patients and donors, but easy to match pairs as well. Solving these problems is an evolving task that will need to continue to keep pace with evolving logistical capabilities and other concerns. But in the meantime, kidney exchange has made possible several thousand life-saving and life-enhancing surgeries, yielding millions of dollars in savings and many thousands of additional healthy years of life.

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Appendix

The PC-TSP based algorithm

We first present the algorithm for unbounded chain length and then describe the modifications in order to solve for any bounded chain length. To write down the formulation we need some notations. For each cycle C of length at most k, we introduce a variable z_C that indicates if we are using the cycle C. We use flow variables y_e for each edge e as in the recursive algorithm to indicate if we use the edge e. We define decision variables f_v^i and f_v^o to be the flow in and flow out of node v respectively. N and P are defined to be the set of NDDs and pairs in the graph respectively. Define $C_k(v)$ to be all the cycles of length at most k that include node v. We can now write the formulation:

$$\max \sum_e w_e y_e + w_C z_C$$

$s.t.\quad \sum_{e\in in(v)} y_e = f_v^i ,\quad v \in V$ (i)

$\sum_{e\in out(v)} y_e = f_v^o ,\quad v \in V$ (ii)

$f_v^o + \sum_{C\in C\_k(v)} z_C \leq f_v^i + \sum_{C\in C_{k(v)}} z_C \leq 1,\ \ v \in P$ (iii)

$f_v^o \leq 1,\quad v \in N$ (iv)

$\sum_{e\in out(S)} y_e \geq f_v^i ,\quad S \subseteq P, v \in S$ (v)

$y_e \in \{0,1\}, e \in E,\ \ z_C \in \{0,1\}, C \in C_k(v)$

Constraints (iii) say two things: first that the amount of flow out of pair v is at most the amount of flow that goes into pair v, and second that the sum of the amount of flow that goes into pair v and the number of cycles that pair v is assigned to at most 1. Constraints (iv) say that the amount of flow leaving every NDD is at most 1.

Constraints (v) is very similar to the cutset inequalities for the TSP as adapted to the PC-TSP (see e.g. Goemans 2009). Essentially they work as follows. Suppose a chain is reaching some node v, and as a result f_v^i equals 1. Now suppose that we "cut" the graph into two pieces such that the half containing v (which we denote as S) does not contain any of the NDD nodes from N. Since every chain begins at some NDD (and thus not in S), in order for the chain to reach $v \in S$, it must use an edge that begins not in S and ends in S. Thus the constraint requires that whenever there is flow into v, for every way that v can be cut off from the NDDs, there is at least this much flow over the cut.

As in the recursive algorithm, there are exponentially many constraints of type (v), and therefore we can use the same recursive heuristic as in the recursive algorithm. Instead, while we relax the constraints (v), we use the separation problem to identify violating constraints to add them sooner to the formulation. The separation problem for (v) can be solved by solving $O(P)$ network flow problems (Anderson et al. (2014)).

When chains are required to be bounded by length, we slightly modify the formulation as follows. For each non-directed donor n and each edge e we introduce auxiliary variables y_e^n and $f_v^{i,n}, f_v^{o,n}$ indicating flow that must begin at node n. We then add a few categories of constraints. First, we enforce that for each edge e, the flow on y_e must come from exactly one of the y_e^n. Second, we define the same relationship between $f_v^{i,n}$, $f_v^{o,n}$, and y_e^n as in constraints (i) and (ii) from the PC-TSP formulation. Third, we require that for each NDD n and each vertex v, we have $f_v^{o,n} \leq f_v^{i,n} \leq 1$. Finally, we add the maximum chain length constraint, saying that for each NDD n, we use a total number of edges y_e^n that is at most the maximum chain length.