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The optimal chain length for kidney paired exchanges: an analysis of the Dutch program

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Summary

Living donor kidney exchange programs offer incompatible donor–recipient pairs the opportunity to be transplanted. To increase the number of these transplants, we examined in our actual donor–recipient couples how to reach the maximum number of matches by using different chain lengths. We performed 20 match procedures in which we constructed four different chain lengths: two, up to three, up to four and unlimited. The actual inflow and outflow of donor–recipient couples for each run were taken into consideration in this analysis. The total number of matched pairs increased from 148 pairs for only two-way exchanges to 168 for three-way exchanges. When a chain length of 4 was allowed five extra couples could be matched over a period of 5 years. Unlimited chain length did not significantly affect the results. The optimal chain length for living donor kidney exchange programs is 3. Longer chains with their inherent logistic burden do not lead to significantly more transplants.

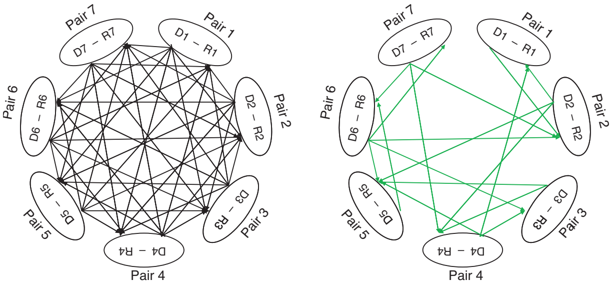
Introduction

Transplantation with a living donor has emerged as the best option for patients with end-stage renal disease. Unfortunately, some transplant candidates do not have a suitable donor because of ABO blood type incompatibility or a positive cross-match. Various solutions for these patients are possible, e.g. immunoadsorption or plasmapheresis to remove anti-HLA-antibodies or isoagglutinins. However, the best option is to participate in a living donor kidney exchange procedure that might also be triggered by altruistic donors. In Asia, United States and Europe kidney exchange programs were developed under different conditions and with different exchange algorithms [1–3]. In 2005, Segev *et al.* [4] reported their exploration to find the optimal number of new combinations based on the Edmonds algorithm theory. Interestingly, this theory was based on ancient Chinese calculations to minimize the lengths of routes walked by mail carriers [5]. The basic principle is that an algorithm considers every feasible solution, compares these solutions, and picks the one that best meets a set of individualized priorities. The group of Delmonico reported comparable studies with an algorithm based on the theory of Edmonds. Both algorithms were tested for efficacy using simulated but not actual donor–recipient combinations opting for a kidney exchange [6,7]. However, in Europe, Johnson *et al.* used an algorithm whereby all possible exchanges were selected based on a points scoring system. The criteria used in the scoring system are distance between the exchange centers, % PRA, the number of HLA-mismatches and donor age differences [8]. We wondered how to optimize the Dutch kidney exchange program with an algorithm that was flexible enough to create chains of unlimited length and used the data from the 312 couples that were enrolled in our program from January 2004 till December 2008.

Methods

Computerized matching

We embarked on a kidney exchange program in January 2004 [3]. Our National protocol was based on a consensus between the seven Dutch kidney transplant centers on registration, allocation and surgical procedures. Allocation was performed by an independent organization, the Dutch Transplant Foundation, according to a computerized algorithm. Surgical procedures were performed simultaneously while the donor traveled to recipient center and a strict anonymity between pairs was kept. All cross-matches between new matched donors and recipients were performed centrally by the National Reference Laboratory for Histocompatibility. By registration we collected data including name, date of birth, ABO blood type, gender and HLA typing of donor and recipient, the percentage panel reactivity antibody (PRA) and specificity of alloantibodies determined by standard complement dependent lymphocytotoxicity (CDC). Medically suitable donor–recipient pairs were registered four times a year in January, April, July and October. In January 2004, the computer program created on the basis of ABO compatibility and alloantibodies kidney exchanges between two couples, doublets. The highest possible number of doublets was manually selected from this list of possible exchanges while ensuring each enrolled couple would only be selected once. In 2005, the match program was changed making exchanges with two and three pairs possible. In October 2007, we changed the computer program algorithm once more to find even larger exchanges whereby a single exchange procedure consists of creating chains of couples whereby each donor donates to the recipient of the next couple and the donor of the last couple in the chain donates back to the first recipient in that chain. The program allowed unlimited chain size, although for practical reasons it was limited to a maximum of four. With the possibility of creating larger chains, the number of combinations made it impossible to manually select the exchanges to proceed with. Therefore, additional steps were added to the computer program. In the first step, the computer program searches for each donor in that particular match run to which recipients he can donate (Fig. 1). Thereafter these separate combinations (donor with new recipient) were used to make all possible chains with different sizes (Fig. 2). Then the computer program selected all possible groups of chain combinations without a couple appearing in more than one chain combination. As the program finds all possible chain combinations, the number of results explodes even further leading to a million possibilities when 50 couples are enrolled. This is why the program ranks all these possible groups according to a preset set of conditions (Fig. 3). We used six preset conditions for allocation, first the maximum number of matched pairs. Within the various groups with maximum number of pairs, the group with the highest number of blood type identical exchange pairs is selected. Thus, blood type O donors will preferentially donate to blood type O recipients, (iii) the next ranking criterion is the match probability (MP). The MP takes into account the prevalence of donors with compatible ABO blood types and acceptable HLA antigens for the recipient within each actual match procedure. MP is calculated by dividing the number of HLA and ABO compatible donors by the number of blood type compatible donors. The potential recipient with the lowest MP, which is the recipient with the smallest chance of finding a compatible donor in that match run, is ranked first. Thus, preferences are given to difficult to match highly sensitized patients, (iv) short chains are preferred above longer chains, for example rather two doublets than one quartet, to minimize the number of discontinuations resulting from one single positive crossmatch in a long chain, (v) recipients preferably spread over multiple centers instead of performing all surgical procedures in one center, and (vi) patients with the longest wait time on the deceased donor kidney wait list, calculated from the first day of dialysis. There is no further prioritization according to HLA-mismatches, serology of



All combinations	Possible new combinations
D1 → R2, R3, R4, R5, R6, R7	D1 → R2
D2 → R1, R3, R4, R5, R6, R7	D2 → R1, R4, R5
D3 → R1, R2, R4, R5, R6, R7	D3 → R4, R5
D4 → R1, R2, R3, R5, R6, R7	D4 → R1, R3, R5
D5 → R1, R2, R3, R4, R6, R7	D5 → R6
D6 → R1, R2, R3, R4, R5, R7	D6 → R2, R3, R5, R7
D7 → R1, R2, R3, R4, R5, R6	D7 → R2, R4, R6

Figure 1 Example of seven pairs in a match run: all donor–recipient combinations are analyzed resulting in possible new combinations based on blood type ABO compatibility and avoidance of unacceptable HLA antigens.

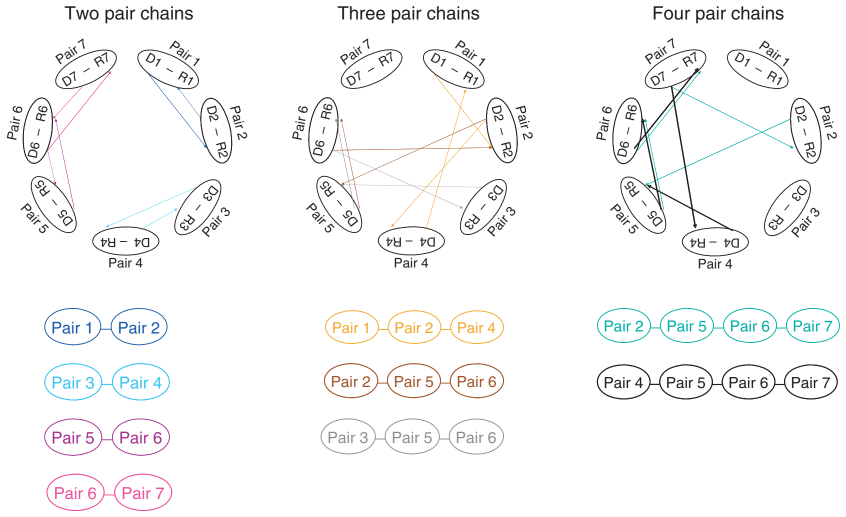


Figure 2 All possible chains with different sizes are constructed.

cytomegalovirus (CMV) or donor–recipient age differences. In case of impossibilities to continue with the selected group of exchange combinations, e.g. because of a positive cross-match or clinical contra indications, the next highest ranking group with the maximum number of participants is used. This is shown in (Fig. 3). When a positive cross-match is found between pair 1 and pair 2, solutions 1, 2, and 3 will not be possible and the highest ranking solution is number 4. Thus, there is no need to run a new computer match procedure.

Analysis

As our computer program has the flexibility to vary the maximum chain length, we have the opportunity to analyze the impact of the maximum chain length on the total number of newly created matches. We used data from the 312 actual couples that had participated in our program to compare the effect of four different maximum chain lengths: two, up to three, up to 4 and unlimited. From January 2004 till December 2008, we had performed 20 match runs with a median of 48 participants (range 16–85). The median input of new candidates per match run was 15 (range 7–22). The 312 enrolled donor–recipient pairs consisted of 169 blood type incompatible pairs and 143 positive cross-match pairs. The median PRA of the 143 recipients in the positive cross-match group was 50% (2–100%). Of the 312 enrolled pairs, we were able to construct 169 new matches that ultimately resulted in 131 successful transplants with an uncensored overall 5 years survival of 89%. In the present analysis we again performed 20 match procedures, but with four different maximum chain lengths and couples were enrolled in the same match run as in reality. When temporary medical contra indications prohibited couples to participate in one or more match procedures, they were also excluded for these specific runs for this analysis. A number of donor–recipient pairs definitely left the program because of an alternative kidney transplantation or because of recipient or donor related complications. All these factors were taken into account in the present analysis. For the recipients, an up to date screening dataset with unacceptable HLA antigens was available to exclude the occurrences positive cross-matches between recipients and their new donor.

Results

The match results of the four different procedures are shown in Table 1. The total proportion of matched pairs per process increased from 47% for two-ways exchanges to 56% for any size of exchanges. If only exchanges involving two donor–recipient pairs are allowed, a maximum of 148 pairs in the data set could exchange kidneys in 74 doublets. If the computer created matches up to three pairs, this resulted in a 14% (20/148) increase to 168 matches consisting of 27 doublets and 38 triplets. The procedure with a chain length up to 4 found for 173 recipients a match be made of 31 doublets, 13 triplets and 18 quartets. The increase from maximal three-ways to maximal four-ways is 3% (5/168). When unlimited exchanges were made possible the number of matched pairs was 175: 26 doublets, 15 triplets, 6 quartets, 5 quintets, 2 sextets, 1 septet and 1 chain with 10 pairs. This resulted in only two more exchanges compared with the maximal four-way exchanges. There were 143 donor–recipient s pairs who were matched in all the four different processes. Thus, five patients were only selected in the

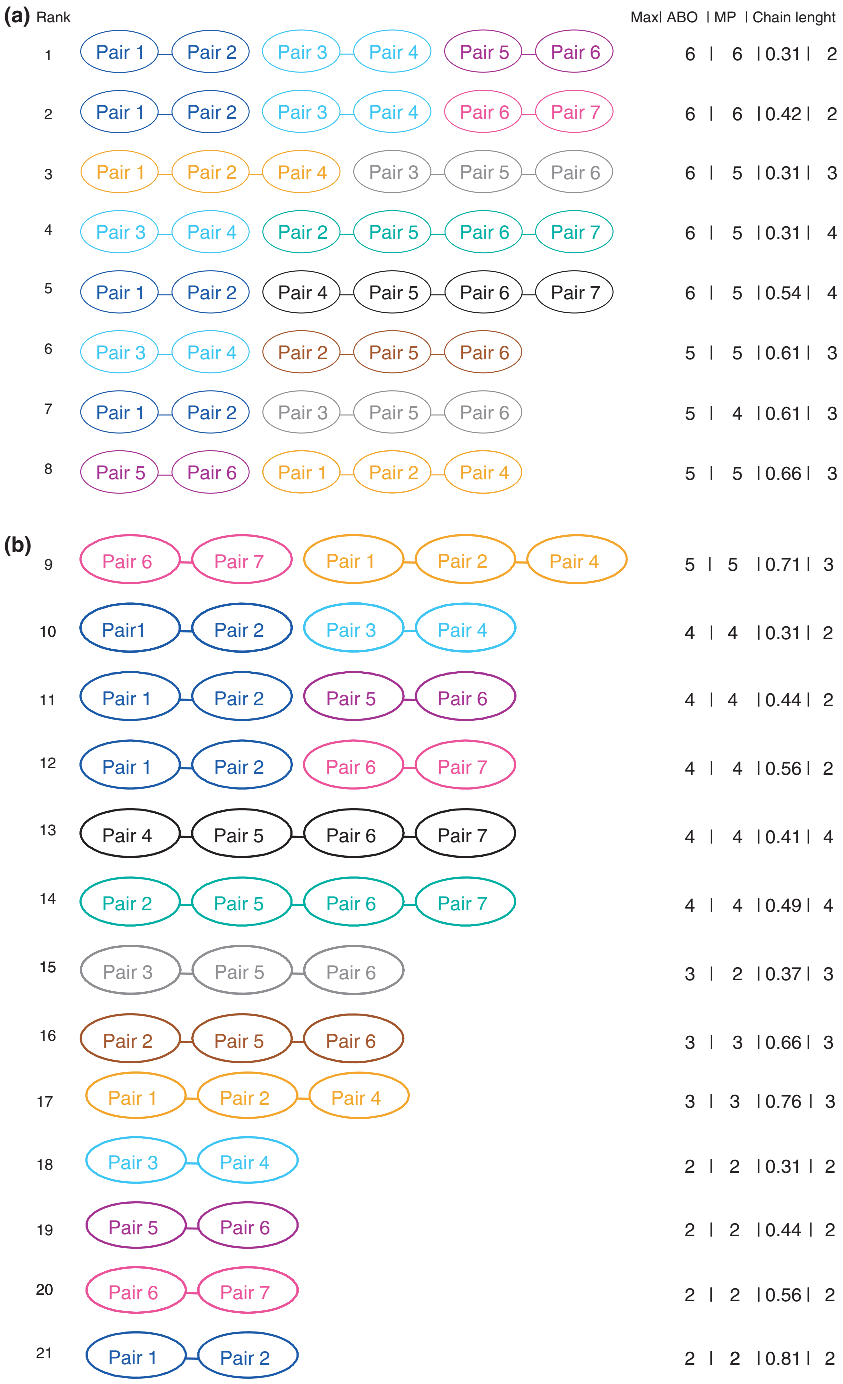


Figure 3 (a) Groups of possible chain combinations are ranked according to preset conditions including average MP. A pair can participate only once in each group. (b) Groups of possible chain combinations are ranked according to preset conditions including average MP. A pair can participate only once in each group.

two-ways procedure and not anymore when larger chains were created. On the other hand, longer chains made 25–27 alternative combinations possible, resulting in a total of 20–27 more new pairs compared with the two-way only system. In the total ABO blood type incompatible group, we observed a 14% increase in success rate when larger chains were allowed. In the subgroup with non-O recipients an optimal chain length of four pairs was found, while for the subgroup with O recipients the optimum was already reached with up to three-way exchanges Table 2a. In the total positive cross-match group, we found a 21% increase in success rate when larger chains were allowed. An increase was virtually restricted to the original O–O and A–A combinations Table 2b. If we looked for the median PRA for the matched sensitized patients in the positive cross-match group, there is a

Table 1. New solutions for ABO blood type incompatible pairs and positive cross-match pairs in various procedures.

Chain length	ABO blood type incompatible pairs (*n* = 169)	Positive cross-match pairs (*n* = 143)	Total (*n* = 312)
2	59 (35%)	89 (62%)	148 (47%)
Up to 3	63 (37%)	105 (73%)	168 (54%)
Up to 4	66 (39%)	107 (75%)	173 (55%)
Unlimited	67 (39.6%)	108 (75.5%)	175 (56%)

Table 2. (a) New solutions for the original blood type donor–recipient pairs in the ABO blood type incompatible group. (b) New solutions for the original blood type donor–recipient pairs in the positive cross-match group.

(a)

Blood types donor–recipient pairs (*n*)	Chain length			
	2	Up to 3	Up to 4	Unlimited
B–A, A–B, AB–A, AB–B (49)	34 (69%)	33 (67%)	37 (76%)	37 (76%)
B–O, A–O, AB–O (120)	25 (21%)	30 (25%)	29 (24%)	30 (25%)

(b)

Blood types donor–recipient pairs (*n*)	Chain length			
	2	Up to 3	Up to 4	Unlimited
O–A (27)	25	25	24	24
O–B (13)	8	8	9	9
O–AB (1)	1	1	1	1
O–O (55)	29	37	38	38
A–AB (3)	3	3	3	3
A–A (40)	23	31	32	33
B–B (4)	0	0	0	0

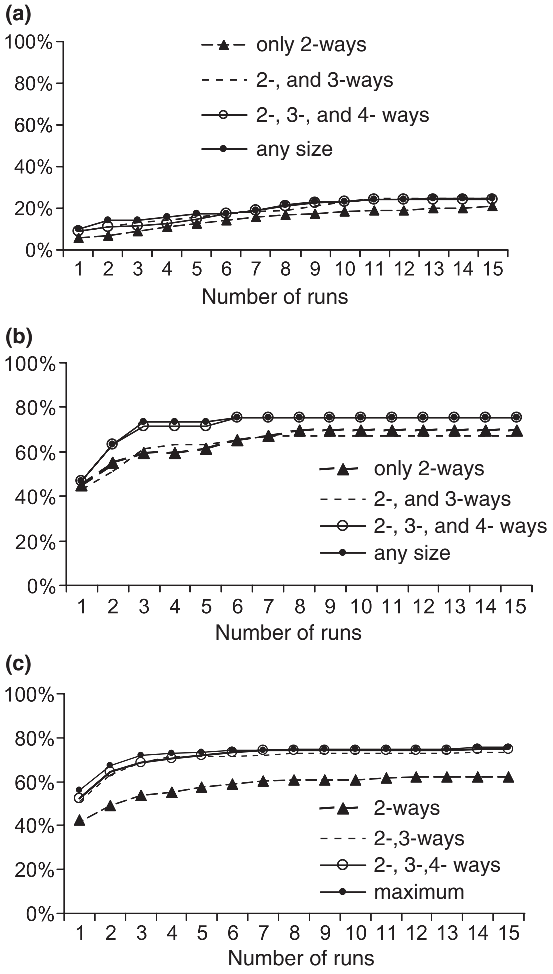


Figure 4 (a) The chance of finding a matching pair in relation to the number of attempts for O recipients in the ABO incompatible group in all procedures. (b) The chance of finding a matching pair in relation to the number of attempts for non-O recipients in the ABO incompatible group in all procedures. (c) The chance of finding a matching pair in relation to the number of attempts in the positive cross-match group in all procedures.

small effect of the different procedures, respectively 39%, 46%, 46% and 48%. Figure 4 shows in three different groups the chances for a couple to find a match in relation to the number of allocation procedures in which they participated. We observed that for the positive cross-match group and the non-O recipients in the ABO blood type incompatible group the chance to find a match did not increase after three or four attempts. The couples with an O recipient in the ABO blood type incompatible group showed a steadily but only slightly growing success rate.

Discussion

The present analysis shows that it is possible to increase the success rate of a kidney exchange program by constructing longer chain lengths. Our analysis is not based on computer simulations. We used actual donor–recipient data taken into account all the hurdles and barriers that were encountered in real life. Examples are comorbidity of the patient necessitating temporary or definitely leaving the program, withdrawal of consent by the donor, and alternative kidney transplants [9]. Our results are also based on the actual median input of 15 combinations every 3 months during a period of 5 years with a median of 48 enrolled couples in 20 match procedures compared with two-way exchanges only. We were able to find 18% more new combinations when chains of unlimited sizes were constructed while at the same time we even noted a 9% increase in median PRA of the matched patients. However, the biggest proportional increase both in numbers (14%) and PRA (7%) was already reached when three-way exchanges were allowed. Enlarging the potential chain length to 4 gained only 3% extra possibilities while unlimited chain length compared with up to 4 resulted in just 1% more new combinations. Thus, only a small number of couples may profit from unlimited chain lengths. This observation has to be balanced against the logistic burden of longer chains. In our analysis, the difference between three-way and four-way exchanges was only five extra couples over 5 years time, i.e. one extra couple a year. Therefore, we feel that the optimal maximal chain length for all practical purposes is 3, especially for newly starting exchange programs. Multiple simultaneous surgeries can stretch the capacities of several centers and requires a great deal of careful coordination. However, it should be noted that the results of this analysis are based on a Caucasian population, with a blood type distribution of 45% O, 40% A, 11% B and 4% AB. Another point for discussion is that not only chain length but also the preset conditions will affect the number of successful matches. Our main goal was to find the maximum number of exchanges, which then formed our leading preset condition. Thereafter blood type identity, difficult to match patients, logistics and wait time were taken into account. However, when other factors, e.g. differences in age between original and exchange donors, or between exchange donors and recipients, would be considered, the number of potential solutions would decrease. The number of HLA-mismatches and distance between donor and recipient center would likewise influence the success rate. These factors might be implemented for good medical reasons, but will result in less transplants, longer wait time on the deceased donor wait list and thus in higher morbidity in a patient group without alternative living donors. So limitation of allocation criteria is essential for the success of a kidney paired exchange program and is associated with excellent uncensored survival. Especially recipients with high PRA in the positive cross-match group profited from our program. However, we can not rule out that some cross-matches could have been positive despite our use of an up-to-date unacceptable HLA antigen dataset. The vast majority of the successful couples was already matched within three match runs. Thereafter their chances became small. For them domino-paired kidney transplantation triggered by Good Samaritan donors is the next alternative [10]. Thereafter desentization programs may function as last resort.

Authorship

MK: project coordinator, data collection and writing of article. WMD: designed the algorithm. MDW: performed laboratory tests. BJJMH-K: supervised allocation. FHJC and WW: project conception, design, article review and supervision.

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