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Health Policy Analysis

The Health Value of Kidney Exchange and Altruistic Donation

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ABSTRACT

Objectives: Living donor kidney transplantation (LTx) is the preferred treatment for patients with end-stage renal disease. Kidney exchange programs (KEPs) promote LTx by facilitating exchange of donors among patients who are not compatible with their donors. We analyze and maximize the efficacy and effectiveness of KEPS from a health value perspective and the health value of altruistic donation in KEPs.

Methods: We developed a Markov model for the health outcomes of patients, which was embedded in a discrete event simulation model to assess the effectiveness of allocation policies in KEPs. A new allocation policy to maximize health value was developed on the basis of integer programing techniques. The evidence-based transition probabilities in the Markov model were based on data from the Dutch KEP using a variety of econometric models. Scenarios analysis was presented to improve robustness.

Results: The efficacy of the Dutch KEP without altruistic donation is reflected by the increase in expected discounted quality-adjusted life-years (QALYs) by 3.23 from 6.42 to 9.65. The present Dutch policy and the policy to maximize the number of transplants achieve 63% of the potential efficacy gain (2.11 discounted QALYs). The new policy achieves 69% of this gain (2.33 discounted QALYs). When systematically enrolling altruistic donors in the KEP, the new policy increased expected discounted QALYs by 4.05 to 10.27 and reduced inequities for patients with blood type O.

Conclusions: The Dutch KEP can increase health value for patients by more than half. An allocation policy that maximizes health outcomes and maximally allows altruistic donation can yield significant further improvements.

Keywords: allocation policies, altruistic donation, health value, kidney exchange.

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Introduction

The burden of disease attributed to chronic kidney disease has almost doubled since 1990, forming 1.64% of the global burden of disease in 2019.[1] Chronic kidney disease may progress over several stages toward end-stage renal disease (ESRD) and is the 11th most common cause of death globally.[1] An estimated 2.5 million patients were treated for ESRD worldwide in 2017, and an even larger number of patients lacked access to treatment.[2]

The most common treatment for ESRD is dialysis. The alternative of deceased donor transplantation (DTx) refers to the practice of harvesting organs for transplantation from deceased donors. The practice of transplanting 1 of the 2 kidneys from a living donor (LTx) has developed as a third alternative.

Transplantation is considered to be lifesaving because it offers a much better survival probability than dialysis.[3] It is more cost-effective because it also yields substantially lower burden of disease and costs.[4-8] For instance, annual average total healthcare cost of dialysis patients ranged between €77 566 and €105 833 in The Netherlands over the year 2012 to 2014. During the same period, the average total healthcare cost after transplant amounted €85.127 in the first year after transplant and €29 612 and €20 156 in the second and third years, respectively.[9]

LTx is the preferred treatment because it is more effective than DTx and has the lowest cost.[9-14] Globally, LTx forms 36% of the 95 479 kidney transplants annually.[15] Many countries only legally allow family members and close friends of patients to donate. Unfortunately, for more than 40% of the patients who find a living donor among family or friends, transplantation is not feasible because of blood type incompatibility, human leukocyte antigen (HLA) incompatibility, or both.[16] Blood type incompatibility refers to the infeasibility of donation depending on blood type (A, B, AB, and O) between the donor and recipient. HLA incompatibility refers to the presence of antibodies in the recipient against the intended alien donor kidney.[17]

A kidney exchange program (KEP) is a regulated mechanism to overcome these incompatibilities. It promotes living donor donation by matching patients with living donors of other patients. For instance, when the donor of a first patient is compatible with a second patient and the donor of the second patient is compatible with the first patient, these 2 patients can exchange donors pairwise.[18] In addition to pairwise exchanges, KEPs may use cycles

of 3 or more pairs and chains that are initiated by deceased or altruistic donors.[19]

Given that KEPs can facilitate access to a lifesaving and most cost-effective treatment, KEPs have arisen within medical centers, among medical centers, at the national level, and even transnationally.[16,20,21] Nevertheless, although more than 80 countries have reported to perform LTx, fewer countries have initiated KEPs with substantial volumes.[15] For instance, by 2017, only 10 European countries had national KEPs, which had realized 1300 transplants in total.[16] The contributions KEPs have made to reduce the burden and cost of ESRD are still modest, and there is little evidence on their efficacy and effectiveness.[16,22] This research considers the lower cost of LTx than DTx and dialysis as a given and aims to provide evidence on the value of KEPs in terms of efficacy and effectiveness. The efficacy and effectiveness are importantly determined by the allocation policies used that specify that patients receive a kidney and from which donor. This process typically takes the form of periodically executing a match run. A match run considers all patient donor pairs participating in the KEP and selects pairs from which patients and donors are matched. The primary objective of allocation policies in existing KEPs is to maximize the number of patients (pairs) matched in each match run.[16,20,21]

Allocation policies often take additional objectives and constraints into account to promote equity, fairness, and expected outcomes.[16,21] Although utility forms a leading measure in economic evaluation[23,24] of health services, none of the existing KEPs evaluate allocation decisions based on utility, for example, as the sum of the quality-adjusted life-years (QALYs) obtained for the patient population. This also applies to The Netherlands and the United Kingdom, countries with the longest standing national KEPs and which explicitly and formally incorporate cost-effectiveness assessment in health policy. Our first research question is to establish KEP efficacy. The second research question is to compare the effectiveness of existing allocation policies and a newly proposed policy to maximize expected discounted QALYs.[25-27]

Altruistic donation refers to living donation by an (altruistic) individual without a previous relationship to a specific patient. In countries that allow altruistic donation, it has become increasingly common to enroll altruists into the KEP. The donor paired to a patient receiving an altruistically donated organ can donate to another enrolled patient or to a patient on the DTx waitlist. The third research question is to establish the incremental health value offered by altruistic donation when incorporated into a KEP. We answer the research questions through a retrospective case study on the Dutch KEP, distinguishing relevant subpopulations to report on equity.

Methods

A Markov Model to Estimate QALY Effects From Kidney Exchange Policies

Markov models form a prime health technology assessment method[28] and have been applied in the assessment of transplantation in relation to dialysis as early as 1975.[29] Since then,[30] various authors have used Markov models to investigate cost-effectiveness of transplantation programs.[31-33] We extend this research toward the analysis of KEP effectiveness and develop a Markov model for health state transitions of patients with ESRD participating in a KEP.

The initial state for each of these patients is the state "ESRD," which they enter as soon as registering for the KEP together with a donor with whom they form a pair. The Markov model defines 6 states, consisting of the following 5 transient treatment states: (1) "ESRD," (2) "Renal Function Recovery," (3) "LTx Recovery," (4) "DTx Recovery," and (5) "KE Recovery" and 1 absorbing state, (6) "Death."

Many patients participating in KEPs also subscribe to the deceased donor transplant waiting list and may qualify for and accept a DTx. The state "DTx Recovery" refers to the state of a patient who has received a deceased donor transplant. Likewise, a patient may accept a transplant from a living donor outside of the program (eg, a family member), as modeled by the state "LTx Recovery." The state "KE Recovery" represents the situation in which the patient received a transplant through the KEP. The state "Renal Function Recovery" models the unlikely but possible state of recovered renal functioning and hence unsubscribing from the KEP. From each of the recovery states, it is possible for patients to return to the ESRD state. This can, for instance, happen because of graft failure after transplant. Figure 1 displays the state space and possible transitions.

The transition probabilities are functions of the patient and donor characteristics, blood type (O, A, B, AB), gender, age (16-44, 45-64, 65-74, and 75+ years), and panel reactive antibody (PRA) level. PRA level estimates the probability of the (body of a) patient to reject a transplant because of HLA mismatch. Distinguishing patient subpopulations based on these demographics enables a more refined and accurate model and to differentiate outcomes per subpopulations as needed to compare equity among allocations policies.

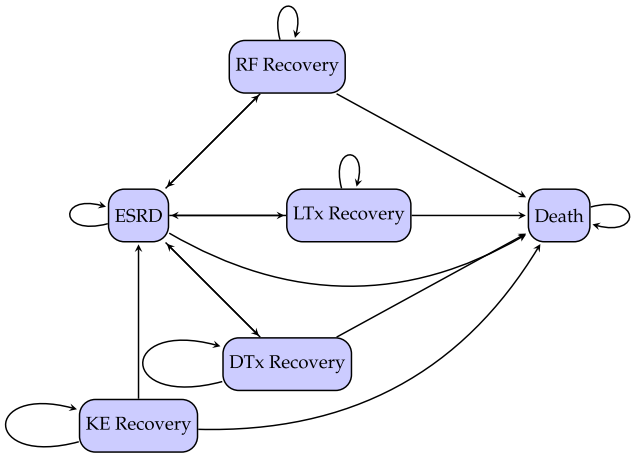
Let QoL(x, s) denote the quality of life of patient x when in state s. Let t = 1, 2, … denote the time periods between subsequent match runs, and s(x, t) the state of patient x at time t for a given sequence of transitions. Then, against per period discount rate δ, for each patient x, the discounted QALYs gained Q(x) can be calculated as

$$Q(x) = \sum_{t=0}^{\infty} \frac{Qol(x, s(x,t))}{(1+\delta)^t}.$$

Discrete Event Simulation and Monte Carlo Analysis

The presented Markov model, probabilities, and health values enable to estimate expected health outcomes for patients of pairs

Figure 1. Markov model with health states of patients participating in kidney exchange programs.



DTx indicates deceased donor transplantation; ESRD, end-stage renal disease; KE, kidney exchange; LTx, living donor transplantation; RF, renal failure.

arriving at the KEP and to conduct Monte Carlo simulations using historic (retrospective) probabilities. Such simulation models, however, do not include the actual matching of donors to recipients and cannot capture the effects of changes in allocation policies. Hence, we developed a discrete event simulation model that combines the Markov model with the arrival of pairs and donors into the KEP pool and subsequent events of leaving the pool. For this purpose, the discrete event simulation model advances stepwise from match run to match run. For each of these discrete time points, the simulation first probabilistically generates any transitions for patient in the KEP from the state "ESRD" to states other than "KE Recovery" (eg, a transition from state "ESRD" to state "DTx Recovery," simulating that a patient accepts a transplant through the deceased donor wait list). Second, it probabilistically generates the arrivals of new pairs and altruistic donors. Third, with the pairs and altruists that then form the KEP pool, a match run is held with the specified allocation policy, which determines the transitions to the state "KE Recovery." Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012 presents the integer programming models and methods to implement the allocation policies. Transitions beyond the stage "KE Recovery" are not simulated. For this state, the expected future health value is calculated using transition probabilities and discounted quality of life in expected future health states.

It may be noted that this approach is considerably more complex than traditional discrete event simulation approaches used in cost-effectiveness analysis of ESRD (see eg, Lee Chris et al[34]) because it involves repeatedly solving an allocation problem (eg, P1 or problem PQALY in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012) to determine transitions to state "KE Recovery." The allocations affect the expected discounted QALYs for the matched patients and for the unmatched patients who remain in the pool (in state "ESRD") until the next match run.

Comparative Analysis of Allocation Policies With and Without Altruistic Donors

The answer to the second research question is obtained by comparative analysis of the simulation results for the following 3 policies: (1) maximize the number of transplants (MaxTx), (2) policy presently practiced by Dutch KEP, and (3) maximize the total sum of discounted QALYs (Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012; PQALY). The probabilistic nature of the state transitions calls for Monte Carlo simulation to obtain robust estimates of policy performance and its variance. This robustness can be further enhanced by randomizing the arrival dates for pairs and altruistic donors. We generate 30 sets of arrival dates for patients and donors and run each of the 3 policies for each of the 30 sets. The expectation (and variance) of the sum of QALYs for each allocation policy is then estimated as the average (and variance) over 30 simulation runs. We calculate signs, means, and variances of the differences in outcomes among the policies for each of the 30 sets. The comparative analysis then consists of (1) testing whether the mean difference in outcomes between a pair of policies is significantly different from zero (Z test, 5% level) and (2) sign testing the difference in outcomes. Over 30 simulations, a positive (negative) sign test identifies a difference as significant at the 5% level if 20 or more simulations have strictly positive (negative) difference. The third research question is answered using the same methods and by comparing the results of the simulations with and without enrolling altruists into the KEP (Z test, 5% level).

Simulation of the Dutch KEP

The first matching round of the Dutch KEP was organized in early 2004. The evidence-based parameters for the simulation involve data from all 698 pairs enrolled until December 31, 2016, and 109 altruistic donors considered in the KEP for the period 2003 to 2011 who have given consent for their data to be used. In total, 399 altruistic donors have registered in The Netherlands from 2004 to 2016. The anonymized data were obtained from the Dutch Transplant Foundation (NTS) on approval by the NTS Research Committee and data from NTS annual reports from 2004 to 2017. Details on deriving evidence-based transition probabilities and QALYs per state for the Dutch KEP are presented in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012. The Dutch KEP conducts match runs every 3 months. The allocation policy of the Dutch KEP is based on a hierarchy of priorities[35,36]: (1) number of transplants, (2) number of blood type identical transplants, (3) match probabilities of matched patients (inverse ranking), (4) longest cycle and chain length (inverse ranking), (5) smallest spread per cycle and chain over transplant centers, and (6) longest wait time, and it selects the highest ranking allocation. See Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012 and the studies by Glorie Kristiaan et al[36,37] for modeling and previous related work.

Proposed matches may fail to go forward to transplantation because a final cross match test between the donor and the intended recipient is positive, because of desensitization failure, or because of patient or donor withdrawal for medical, psychological, or other reasons. Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012 describes the modeling of the match failure probabilities included in the simulation model. In case of match failure, the simulation model reruns the allocation policy with the updated compatibility information (following the standard procedures of the Dutch KEP). This process is repeated until a feasible matching is found.

The 30 problem instances are created for the period October 2003 to December 2016 from the provided data by sampling patient donor with replacement from the population of 698 pairs. For each sampled pair, an arrival date is drawn uniformly over the simulation period, corresponding to a Poisson arrival process. For the simulations with altruists, the Monte Carlo simulations uniformly sample 399 altruistic donor arrivals from the available altruistic donor data with replacement, again corresponding to a Poisson arrival process.

Given that the number of patients of blood types B and especially AB have been limited in the Dutch KEP, the (evidence-based) transition probability from stage ESRD to the stages LTX and DTx as estimated from historic data may be inaccurate. Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012 presents alternative transition probabilities derived from a more general data set, and Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012 presents simulation results for these alternative transition probabilities. The results below are for the case directly based on historic data from the Dutch KEP. The analysis considers 2 sets of evidence-based QALYs and discount rates, referred to as the "optimistic" and a "pessimistic" scenarios (see Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012). Finally, we have conducted analyses in which the parameter values for the annual changes in graft and patient survival rates are not based on evidence taken directly from the Dutch KEP, but instead are based on European averages in an overlapping time period as reported in Appendix 4 in

Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012, Section 4.4 onward. Together, these analyses address the sensitivity to using alternative evidence from relevant alternative sources, as considered in the discussion.

Results

Efficacy

The first research question regarding KEP efficacy is answered by (retrospectively) solving PQALY (see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012) to optimality and comparing the resulting total health value (column "QALYs in perfect KEP" in Table 1) with the total obtained for the same patient population without match runs (column "QALYs without KEP"). The results for the perfect KEP are in bold face when the average difference with results obtained without KEP over 30 simulation runs is significantly different from (above) zero and underlined when the 2-sided sign test result is significant. The last row depicts that the average number of matched pairs equals 436.57 of the 698 enrolled pairs, when perfectly maximizing discounted QALYs. Over the population of enrolled patients, the discounted QALY per patient increases by 4.41 from 6.45 to 10.86, an increase of almost 70%. The absolute increase is particularly large for the age groups 45 to 64 and 65 to 74, for the blood types A, B, and AB, and for the lowly sensitized patients (PRA 0-10). Patients with blood type O benefit less, likely because there are relatively fewer matching (type O) donors (see Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012). The relative increase is largest for the age groups 65-74, and 75+, although for the latter only the sign test is significant. Given that the discounted QALYs for recipients who remain unmatched in the perfect KEP are higher than without KEP, the perfect KEP prioritizes patients who would otherwise have less than average remaining discounted QALYs. Although there are differences, these general observations remain valid for the alternative transition probabilities and the pessimistic QALYS and discount rates (Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012).

Comparative Analysis of Policy Effectiveness

The results of the simulation runs to answer the second research question are presented in Table 2. Significance is again indicated by bold face and underlining. The second column presents the results of the commonly reported allocation policy to MaxTx. The third column displays the difference with the performance obtained when perfectly maximizing total health value. MaxTx delivers approximately 81% of the number of transplants of the perfect KEP and more than 83% of the total health value, closing approximately 58% of the gap between a perfect KEP and no KEP. The difference with the perfect policy is not significantly different from zero for the small populations of 75+-year-old patients or for the now different and larger population of unmatched patients.

Results for the currently practiced Dutch allocation policy (Dutch) in comparison with MaxTx are depicted in the fourth column. The differences are mostly small and nonsignificant, as might be expected because it prioritizes maximizing the number of matches. Interestingly, over the simulation period, the sign test indicates that it matches more patients than MaxTx.

The fifth column presents comparative results for the allocation policy that maximizes discounted QALYs (MaxQaly). MaxQaly delivers a significant increase of 0.19 discounted QALYs for the entire population and achieves 85% of the total health value of a perfect KEP. Interestingly, the sign test now suggests it may match fewer patients than MaxTx. It significantly improves health value for middle-aged patients, lowly sensitized patients, type O patients, and unmatched patients. These results are very similar for the scenarios with other transition probabilities and pessimistic QALYS and discount rates (Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012).

Table 1. Efficacy.

Population	Number of patients	QALYs in perfect KEP	QALYs without KEP
All patients	698	**10.86**	6.45
Age, y			
16-44	212	**12.61**	10.49
45-64	384	**10.74**	5.19
65-74	97	**7.69**	2.68
75+	5	4.16	0.77
Blood type O	401	**9.38**	6.16
Blood type A	201	**12.87**	6.93
Blood type B	86	**12.64**	6.54
Blood type AB	10	**12.98**	7.64
PRA level 0-10	521	**10.49**	5.40
PRA level 10-80	150	**11.88**	9.30
PRA level 80-95	18	**12.22**	9.96
PRA level 95+	9	**10.94**	8.85
Matched		13.32	-
Unmatched		6.77	6.45
Number matched in KEP		436.57	0

Note. Boldface is used when an average difference with results obtained without KEP over 30 simulation runs is significantly different. Underline is used when the 2-sided sign test result is significant.
KEP indicates kidney exchange program; PRA, panel reactive antibody; QALY, quality-adjusted life-year.

The Incremental Health Value From Altruistic Donation

The results of the simulation runs to answer the third research question are presented in Table 3. With altruists, the maximum transplant policy replicates the effectiveness of the perfect KEP without altruists. The altruists generate an effectiveness increase of 0.73 QALYs. Again, the Dutch policy achieves very comparable results. The MaxQaly policy increases discounted QALYs by 0.54 compared with MaxTx. The benefits are especially substantial for the age group 45 to 64 years, for type O patients, for lowly sensitized patients, and for unmatched patients.

Discussion and Conclusion

Kidney transplantation is often presented as lifesaving, and the emphasis of allocation policies in KEPs has correspondingly been on maximizing the number of transplants. This also applies to countries such as the United Kingdom and The Netherlands, where (cost)-effectiveness and specifically discounted QALYs play an important formal role in healthcare resource allocation. To our knowledge, this study is the first to propose allocation policies optimizing discounted QALYs and to evaluate KEPs and allocation policies on the basis of discounted QALYs. For this purpose, it presents a retrospective case study on the Dutch KEP and analyzes its efficacy and the effectiveness of allocation policies. Moreover, it

Table 2. Comparative analysis of allocation polices.

Population	MaxTx	PI—MaxTx	Dutch—MaxTx	MaxQ—MaxTx
All patients	9.02	**1.84**	−0.01	**0.19**
Age, y				
16-44	12.14	**0.46**	0.03	−0.10
45-64	8.23	**2.51**	−0.03	**0.37**
65-74	5.40	**2.30**	−0.01	0.13
75+	2.60	1.56	0.10	0.14
Blood type O	7.96	**1.42**	−0.01	**0.21**
Blood type A	10.45	**2.42**	0.03	0.15
Blood type B	10.28	**2.36**	−0.03	0.22
Blood type AB	10.82	**2.16**	−0.20	0.06
PRA level 0-10	8.39	**2.11**	−0.03	**0.29**
PRA level 10-80	10.75	**1.13**	0.08	−0.06
PRA level 80-95	11.12	**1.10**	−0.02	−0.11
PRA level 95+	9.79	**1.15**	−0.11	−0.10
Matched	11.37	**1.95**	0.04	0.12
Unmatched	6.63	0.14	−0.09	**0.33**
Total matched	352.37	**84.20**	2.6	−5.33

Note. Boldface is used when an average difference with results obtained without KEP over 30 simulation runs is significantly different. Underline is used when the 2-sided sign test result is significant.
MaxQ indicates policy to maximize discounted QALYs; MaxTx indicates policy to maximize the number of transplants; PI, clairvoyand perfect allocation policy; PRA, panel reactive antibody.

explicitly addresses the effects of enrolling altruistic donors in the KEP.

Even without altruistic donation, the efficacy of the Dutch KEP is substantial and significant. In expectation, a clairvoyant, perfect policy adds more than 4 healthy life years for enrolled patients, increasing discounted QALYs from 6.45 to 10.86. The straightforward policy of maximizing the number of transplants in each match run attains 58% of that efficacy increase, as is also the case for the current Dutch policy. It should be noted that the current Dutch policy also explicitly targets performance measures, which remain unconsidered in our study.[20]

Table 3. Comparative analysis of allocation polices with altruists.

Population	MaxTx	Dutch—MaxTx	MaxQ—MaxTx
All patients	10.86	0.01	**0.54**
Age, y			
0-44	13.47	0.00	**0.25**
45-64	10.23	0.04	**0.72**
65-74	7.68	−0.07	0.44
75+	5.45	−0.13	−0.01
Blood type O	10.61	0.09	**0.70**
Blood type A	11.21	−0.07	**0.37**
Blood type B	11.15	−0.15	0.23
Blood type AB	11.24	0.01	0.25
PRA level 0-10	10.55	0.03	**0.80**
PRA level 10-80	11.81	−0.03	−0.16
PRA level 80-95	11.77	0.00	−0.20
PRA level 95+	10.35	0.06	−0.21
Matched	11.43	−0.01	**0.35**
Unmatched	7.78	0.07	**1.69**
Total matched	590	2.83	−8.93

Note. Boldface is used when an average difference with results obtained without KEP over 30 simulation runs is significantly different. Underline is used when the 2-sided sign test result is significant.
MaxQ indicates policy to maximize discounted QALYs; MaxTx, policy to maximize the number of transplants; PRA, panel reactive antibody.

A policy that maximizes discounted QALYs closes 63% of the gap between a perfect KEP and no KEP, adding an expected 0.19 discounted QALYs compared with current practice or maximizing the number of transplants. The policy adds an expected 0.33 discounted QALYs to the life expectancy of the patients who remain unmatched. It also results in significant and substantial improvements for type O patients, reducing the disparities for this subpopulation without negatively affecting outcomes for any of the other blood types. Because the differences in the number of transplants among the policies are less than 1 transplant per year, the cost differences can be expected to be negligible.

Enrolling available altruists, the Dutch KEP would yield the same improvement in health value with the current policy or a policy maximizing the number of transplants as the perfect KEP achieves without altruists. We believe these improvements can be obtained without negatively affecting results from altruistic donation outside of the KEP given that the donors of patients receiving a transplant from an altruistic donor can now in turn donate to patients outside of the KEP (eg, to the deceased donor waitlist). Recalling that costs after (living) donation are the lowest, especially compared with those of dialysis,[9] our results provide evidence of substantial and equitable cost-effectiveness increases attainable by enrolling all altruistic donors in the Dutch national KEP.

While being cautious to generalize results of the Dutch KEP to other countries, this retrospective case study indicates that KEPs that include altruists can substantially improve healthy life expectancy for the growing global population of millions of patients with ESRD. The results confirm the urgency to develop and advance KEPs and effective allocation policies. Moreover, they

raise the question whether restricting legal and policy concerns justly outweigh improvements in cost, health, and life for individuals and populations. The relatively poor outcomes for type O patients are a concern and an area for further research. Such research needs to take the larger transplantation context captured in the Markov model into account because there are differences in the likelihood to receive a transplant outside of the KEP. More generally, research on disparities seems an important area for further research because the differences in health value obtained for patients of different blood types, ages, and levels of sensitization raise new questions about fairness of allocation. For instance, should patients whose lower expected health value increase, such as older patients, be considered less valuable to be matched? What are the fairness and equity requirements that need to be in place, when optimizing health value instead of the number of transplants?

The sensitivity analysis results for different model parameters provided in Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.012 confirm that the outcomes of the study are quite robust for the Dutch KEP. The QALYs obtained may vary in absolute terms (from a 0.7 decrease to a 0.25 increase). Nevertheless, the differences in effectiveness between the various policies are very comparable. This robustness strengthens the validity of the conclusions above for the Dutch context.

A first limitation of our study is that KEPs follow different legislations and regulations in different countries, calling for caution when generalizing specific findings from the Dutch case study, more so, because the evidence base of the Markov model is largely based on available retrospective Dutch data. Therefore, although we have presented several basic forms of one-way sensitivity analysis, studies that consider relevant future parameter values and further elaborate time dependency of parameters, for instance, regarding the likelihood of receiving a DTx, are an important direction to advance this research. Likewise, the anonymized data have necessitated us to consider each enrollee to represent a new patient, and therefore, we have not considered recurrence of transplants by the same patient (who might be increasingly sensitized). Caution is also justified when calculating and discounting health values further in the future, even when the hazard functions are evidence based. We hope these limitations are taken as encouragements for further research rather than barriers to advance the (cost)-effectiveness of KEPs.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2021.07.012.

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