Modeling the Benefits and Costs of Integrating an Acceptable HLA Mismatch Allocation Model for Highly Sensitized Patients

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Background. The Eurotransplant acceptable mismatch program has improved transplantation access for highly sensitized recipients. However, the benefits and costs of implementing such a program remain unknown.
Methods. Using decision analytical modeling, we compared the average waiting time for transplantation, overall survival gains (in life-years and quality-adjusted life-years gained), and costs of integrating an acceptable mismatch allocation model compared with the current deceased-donor kidney allocation model in Australia.
Results. Acceptable mismatches were identified in 12 of 28 (43%) highly sensitized recipients using HLAMatchmaker. Inclusion of acceptable mismatches in the current allocation model improved the transplantation access for four (14%) highly sensitized recipients, with an average reduction in waiting time of 34 months (from 86 to 52 months). Compared with the current allocation model, incorporating an acceptable mismatch allocation model achieved an overall lifetime gain of 0.034 quality-adjusted life-years and savings of over $4,000 per highly sensitized patient, with a small consequential loss of 0.005 quality-adjusted life-years and extra costs of $800 for every reallocated patient.
Conclusions. Despite modest overall health gains, application of an acceptable mismatch allocation model is an equitable approach to improve transplantation access for highly sensitized transplant candidates without compromising the overall health benefits among the other patients on the deceased-donor waitlist in Australia.

Keywords: Cost-effectiveness analysis, Acceptable mismatch, HLAMatchmaker, Highly sensitized, Kidney transplantation.

(*Transplantation* 2014;97: 769–774)

Optimal human leukocyte antigen (HLA) matching at HLA-A, HLA-B, and HLA-DR loci between donor and recipient is a key paradigm in the allocation of transplant kidneys because greater HLA mismatch is associated with a heightened risk of graft rejection and failure (*1*). The average waiting time for a deceased-donor kidney in Australia is

The authors declare no funding or conflicts of interest.

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H.D.N. participated in designing and performing the research, analyzing the data, and writing the article. H.D.N. was supported by the Jacquot Research Entry Scholarship (administered by the Royal Australian College of Physicians) and the National Health and Medical Research Council Postgraduate Medical Scholarship for stipend. G.W. participated in designing and supervising the research, analyzing the data, and writing the article. K.H. participated in designing the research, analyzing the data, and writing the article. F.H.J.C. participated in writing the article. J.C.C. participated in designing the research and writing the article. S.F. participated in collecting patient clinical data. L.D. participated in writing the article. J.R.C. participated in designing the research and writing the article. A.I. participated in collecting patient clinical data. P.F. participated in writing the article. F.T.C. participated in designing the research and writing the article. W.H.L. participated in designing and supervising the research, and writing the article.
Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).
Received 5 August 2013. Revision requested 26 August 2013.
Accepted 10 October 2013.

ISSN: 0041-1337/14/9707-769
DOI: 10.1097/01.TP.0000438639.36838.ac

approximately 3.9 years (*2*), but can be longer depending on HLA genotype and sensitization status.

Despite prioritization for highly sensitized candidates, their waiting time remains twice that of unsensitized candidates (*2, 3*). The annual mortality rate of patients on the waitlist is at least 2-fold greater than patients who have undergone transplantation (*4*). One of the major barriers precluding transplantation for highly sensitized transplant candidates is the high likelihood of having positive complement-dependent-cytotoxicity (CDC) crossmatches against multiple donors, often attributed to the presence of anti-HLA donor-specific antibodies (DSA) known to be associated with a greater risk of rejection and graft loss (*5–9*).

An alternative approach to broad antigen HLA matching is utilization of acceptable HLA mismatches in the deceased-donor allocation algorithm (*10*). Acceptable HLA mismatches are mismatched HLA at the broad antigen level between donor and recipient that comprises structurally and functionally compatible epitopes at the structural level. Since the introduction of the acceptable mismatch program in Eurotransplant, the transplant waiting time among the highly sensitized patients has reduced by at least 50% while achieving short-term and long-term graft survival similar to that of non-sensitized patients (*10, 11*). However, no previous studies have evaluated the overall costs and health benefits of incorporating acceptable mismatches in deceased-donor kidney allocation. Using decision analytical modeling, we aimed to determine the effects on transplant waiting time and health benefits and costs of including acceptable mismatches compared to the current deceased-donor kidney allocation model in Australia. Decision analytical modeling is increasingly being conducted to assess the allocation of limited reserves between competing health care interventions or programs. It utilizes time-dependent probabilities to model the progression of chronic diseases over time and to calculate the long-term costs and health outcomes for a particular disease or healthcare intervention (*12*).

RESULTS

Baseline Characteristics of Highly Sensitized Kidney Transplant Recipients

There were 38 highly sensitized renal transplant recipients identified. Ten were excluded because of incomplete crossmatch histories, leaving 28 recipients (103 donor-recipient pairs) in our analysis (Table 1). The average waiting time of these recipients was 64 (SD=46) months. The average numbers of class I and class II HLA mismatches were 2.76 (SD=0.95) and 1.30 (SD=0.64), respectively, corresponding to 18.7 (SD=8.88) and 11.8 (SD=7.14) class I and II eplet mismatches, respectively.

The Prevalence of Recipients With Acceptable Mismatches

Acceptable mismatches were identified in 12 (43%) highly sensitized recipients. Over 80% were located in the class I loci. A total of 16 unique acceptable mismatches were identified among 25 donor-recipient pairs (12 of 28 recipients).

Inclusion of Acceptable Mismatches in the Current Deceased-Donor Allocation Model

The outcomes of the acceptable mismatch allocation model are shown in Table S1 (see **SDC,** http://links.lww.com/TP/A909). Compared with the current allocation model, inclusion of acceptable mismatches reduced the average waiting time for transplantation by 34 months (86–52 months, SD=22, P=0.056) in four (14%) highly sensitized recipients. Although acceptable mismatches were identified in eight other recipients, these recipients did not attain sufficient additional points to improve their ranking to have received a kidney offer. The immunologic profiles of the 12 reallocated recipients (three reallocated recipients for each of the four highly sensitized recipients) are shown in Table S1 (see **SDC,** http://links.lww.com/TP/A909). Of these 12, eight (67%) had PRA less than 10% and one (8%) had PRA greater than 80%.

TABLE 1. Patient characteristics

Patients (n)	28
Recipient-donor pairs (n)	103
Historically matched kidneys (n)[a]	3.7
Male (n, %)	9 (32%)
Waiting time (mo)	64 [46]
Antigen mismatch (n)[b]	
A	1.16
B	1.61
DR	1.30
Total ABDR	4.07
Eplet mismatch (n)[b]	
A	8.94
B	9.72
DR	11.75
Total ABDR	30.41

[a] Data expressed as mean per patient [standard deviation].
[b] Data expressed as mean per donor and recipient pair.

Compared with current allocation, the acceptable mismatch model increased the average transplant waiting time among the reallocated recipients by an average of 12 months (44–66 months, SD=8.9, P=0.001). The average waiting time of the reallocated recipients with PRA less than 10% remained less than the waiting time of highly sensitized recipients (44 vs. 52 months; P=0.715). The average number of HLA mismatches within the acceptable mismatch and the current allocation models was similar (3.6 vs. 3.9 HLA-ABDR mismatches, P=0.305).

Outcomes of the Decision Analytical Modeling

The incremental costs and benefits of the acceptable mismatch allocation model compared to the current allocation model are shown in Table 2. At a population level, the average incremental health gain of an acceptable mismatch model was 0.004 LYS (1.3 days) or 0.005 QALYs (1.8 quality-adjusted days), with savings of $622 for each highly sensitized recipient. Among all other patients on the waitlist, there was an average loss of 0.0003 life-years (0.1 days) or 0.0004 QALYs (0.15 quality-adjusted days) with $66 additional cost per patient.

If only the highly sensitized patients benefiting from acceptable mismatches were considered, the incremental gain in health benefits would be 0.027 LYS (10 days) or 0.034 QALYs (13 quality-adjusted days), with savings of $4,355 for each highly sensitized recipient. Considering only those who have been reallocated, there was an average loss of 0.0035 life-years (1 day of life) or 0.0052 QALYs (2 quality-adjusted days of life), with $805 additional cost per reallocated patient.

TABLE 2. Total and incremental cost and health benefit per patient associated with an acceptable mismatch allocation model for highly sensitized recipients compared to the current allocation model for deceased-donor kidney transplants

		Total			Population level			Individual level		
		Benefit		Cost	Incremental benefit		Incremental cost	Incremental benefit		Incremental cost
Recipients	Strategy	LYS	QALY gained	($AUD)	LYS	QALY gained	($AUD)	LYS	QALY gained	($AUD)
Highly sensitized	Acceptable mismatch	12.240	8.094	457,907	0.004	0.005	−622	0.027	0.034	−4,355
	Current	12.236	8.089	458,529						
Reallocated	Acceptable mismatch	13.169	9.267	311,613	−0.0003	−0.0004	66	−0.0035	−0.0052	805
	Current	13.169	9.267	311,547						

Sensitivity Analyses

The probability of transplantation and the proportion of highly sensitized recipients who benefit from the acceptable mismatch allocation model were the two most influential variables. The extent of the variability in incremental net health benefits for highly sensitized and non-highly sensitized transplant recipients associated with the different inputted variables are shown in Figure 1. Assuming the waiting time for transplantation was reduced by 50% for the highly sensitized recipients, there was an incremental gain of 0.006 QALYs with savings of $800 per highly sensitized recipient. Varying the proportion of highly sensitized patients benefiting from the acceptable mismatch allocation model between 10% and 50% increased the incremental health gains from 0.003 to 0.017 QALYs (1.3 to 6.2 quality-adjusted days) per highly sensitized recipient, with savings ranging from $400 to $2,000. On the contrary, varying the percentage increase in the overall waiting time for transplantation among the reallocated recipients from 10% to 50% resulted in a reduction of 0.0012 to 0.0001 QALYs gained.

DISCUSSION

Findings from our modeled analyses suggest that the integration of an acceptable mismatch allocation model into the current deceased-donor allocation is cost-saving attributable to a reduction in the waiting time for transplantation, resulting

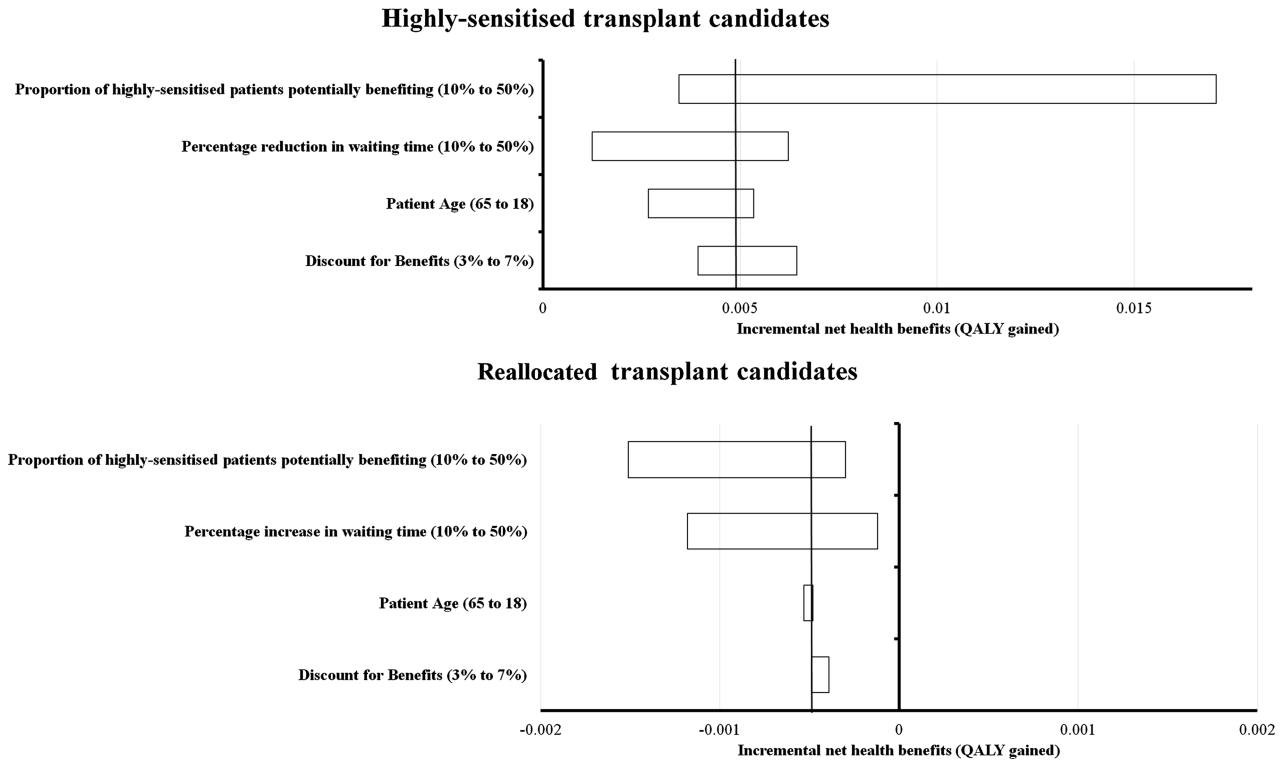

FIGURE 1. One-way sensitivity analyses indicating the potential variation in the net benefit estimates by altering certain inputted variables for the highly sensitized and reallocated kidney transplant recipients.

in dialysis avoidance and improved the overall longevity and quality of life for a proportion of highly sensitized transplant candidates without incurring a significant loss in life-years among the non-highly sensitized transplant candidates on the waitlist. It achieved an overall gain of 0.027 LYS (10 days) or 0.034 QALYs (13 quality-adjusted days) and savings over $4,000 per highly sensitized patient, with a small consequential loss of 0.0035 life-years (1 day) or 0.0052 QALYs (2 quality-adjusted days) and additional costs of $800 per reallocated patient.

We reported a comparable reduction in the average overall waiting time for transplantation among the highly sensitized transplant candidates as in the Eurotransplant program if acceptable mismatches were included in the current deceased-donor allocation algorithm in Australia. However, benefits were restricted to a smaller proportion of highly sensitized recipients, and therefore only modest overall lifetime gains in survival were seen. There are a number of potential reasons for the observed differences between the two regions. The size and characteristics of the donor pool in Australia are different compared to Eurotransplant (*3, 13*). Australia has a lower overall donation rate compared to Eurotransplant (14 vs. 18 per million population) (*13, 14*). Also, over 30% of the waitlisted potential transplant candidates originated from non-Caucasian ethnic background, but over 95% of deceased donors were from Caucasian Australians (Australia and New Zealand Organ Donation Registry, unpublished data). Given the differences in HLA genotypes between racial groups, the likelihood of finding acceptable mismatches between a potential donor-recipient pair of diverse ethnic background is likely to be lower than those from a homogenous ethnic group such as Spain or the Netherlands. Third, our allocation model was based upon integration of acceptable mismatches into the current system of scoring, which differs from that of the Eurotransplant Acceptable Mismatch program whereby all highly sensitized patients would receive the highest priority for any given compatible donor kidneys with no consideration of allocation scores. Lastly, we have only evaluated the donor pool from the Western Australian population and not the entire Australian cohort, which may mean we have underestimated the proportion of highly sensitized recipients who could have potentially benefited from the acceptable mismatch allocation model.

HLAMatchmaker identifies mismatched epitopes between donor and recipient and is effective in predicting the immunogenicity of specific broad HLA mismatches. Previous studies have shown that the number and nature of triplet mismatches for a given HLA genotype correlates with the risk of humoral sensitization (or development of anti-HLA antibody known to adversely affect graft survival). Even the presence of a single triplet amino acid mismatch is often sufficient to invoke a strong antibody response, leading to a 25-fold increased risk of antibody-mediated rejection (*5, 15*). Favorable outcomes from the Eurotransplant acceptable mismatch program were observed among the highly sensitized patients, with an overall 2-year and 10-year graft survival of 87% and 70%, respectively (*10, 11*). Potential reasons for the observed benefits include improved immunological profiling and reduction in the overall waiting time on dialysis (*16*). Furthermore, an analysis of two large multicenter databases of kidney transplant conducted by Duquesnoy et al. (*17*) reported an inverse relationship between the number of triplet mismatches and the 5-year renal allograft survival. In HLA-DR-matched renal transplant recipients, those with three or more triplet mismatches have lower 5-year graft survival compared to recipients with 0–2 triplet mismatches at the HLA-AB loci (72% vs. 84%). This observation has therefore led to the acceptance that 0-2 triplet mismatches is considered an acceptable mismatch. To better define epitope mismatch, the recently refined HLAMatchmaker program uses eplets rather than triplets, which may offer greater additional epitope discrimination and immunogenicity (*18*). Previous studies have also shown that the number of triplet and eplet mismatches correlates closely with both the development and strength of an alloantibody response (*15, 19*), suggesting that it is likely that a similar association exists for eplet mismatches and graft outcomes.

This is the first study to provide an economic evaluation of an acceptable mismatch allocation model. It is also the first to investigate the impact on transplant waiting time of an acceptable mismatch allocation model outside of Europe. Using the NOMS, we have accurately ascertained individual patient data from all highly sensitized transplant recipients in Western Australian since 2000.

However, our study has important limitations. Our analysis considered only transplant recipients and not candidates who were not transplanted as a result of repeated donor incompatibilities and death on the waitlist. Inclusion of these patients could potentially have increased the proportion of highly sensitized patients benefiting translating to overall greater benefits. Whereas the Eurotransplant acceptable mismatch program defines acceptable mismatches using a combination of structural matching through HLAMatchmaker and the absence of antibody reactivity using single HLA cell lines, we have used the former alone, which is likely to be as effective as the two combined (*11*). In addition, we estimated the number of eplet mismatches following conversion of two-digit HLA typing to four-digit typing based on the most frequently occurring alleles. Given the HLAMatchmaker conversion program was derived from a European population, the applicability of this method in the Australian population has not been validated. Also, as complete typing of class II HLA were unavailable, it is likely that we underestimated the numbers of acceptable mismatches. Given the lack of outcomes data associated with eplet-based acceptable mismatches, we have assumed that the clinical outcomes (risk of rejection, graft failure, and death) of patients with acceptable mismatches are similar to those with equivalent broad HLA mismatches.

Although we have shown potential benefit of integrating an acceptable mismatch program in Western Australia, similar analyses using the larger national cohort with consideration of both national exchange and local state allocation policies are underway. In addition, the association between the number of eplet mismatches and graft outcomes will need to be established to determine whether the current definition of acceptable mismatch using the threshold of 0–2 eplet mismatches is most appropriate, which will be crucial in determining whether an acceptable mismatch program should be adopted in Australia.

Highly sensitized potential transplant candidates are often disadvantaged in transplant allocation because of their

unusual HLA phenotypes or the presence of anti-HLA antibodies, or both, against common HLA as a result of previous sensitization. Although representing a small proportion of the transplant waitlist, they often have prolonged waiting times and are at greater risk of dying on the waitlist compared with unsensitized candidates. While our study shows the benefits in terms of overall lifetime health gains in survival and quality-adjusted survival of integrating an acceptable mismatch allocation model in Australia are relatively modest, inclusion of an acceptable mismatch allocation model may improve access to transplantation for a proportion of immunologically complex, highly sensitized transplant recipients without significantly disadvantaging non-highly sensitized recipients.

MATERIALS AND METHODS

Study Population

We included all highly sensitized (PRA >80%) kidney transplant recipients from January 2000 to December 2011 from Western Australia who had been historically matched with one or more donors via the state allocation. Recipients and their respective organ-matching histories were identified using the National Organ Matching System (NOMS). De-identified data including baseline demographics and the two-digit HLA typing of recipients and donors were collected.

Definition of Acceptable HLA Mismatches

In Eurotransplant, acceptable mismatches are tested using CDC crossmatches with single antigen-expressing cell lines. Acceptable mismatches can now be effectively identified using HLAMatchmaker, a computer program that compares functional epitopes of donor-recipient HLA antigens by matching surface-exposed sequences of amino acids known as triplets (three continuous amino acids) or eplets (clusters of non-continuous amino acid sequences) that form the binding sites for antigen-antibody interaction (*11*). We used the HLAMatchmaker computer program to define acceptable mismatches for donor-recipient pairs by converting two-digit HLA typing into four-digit typing based on the most common alleles (version 2.1) (available from: www.hlamatchmaker.net). For any set of recipient HLA alleles, HLAMatchmaker calculated the total number of eplet mismatches for each donor-recipient pair. Acceptable mismatches were defined as those HLA antigen mismatches with 0–2 eplet mismatches, a criteria based on Eurotransplant acceptable mismatch program (*17*). Eplet HLA-A-B-C and DR-DQ-DP matching models were used for HLA-A and HLA-B (class I) and HLA-DR (Class II) matching, respectively. Complete typings for HLA-C, DP, and DQ were not available in our cohort.

Inclusion of Acceptable HLA Mismatches in the Deceased-Donor Kidney Allocation Model

In Australia, deceased-donor kidney allocation occurs through a national interstate exchange and a state-based program. The program is based on a calculated scoring system which considers mismatched HLA antigens at the HLA-A, HLA-B, and HLA-DR loci and duration of dialysis (see **Tables S2** and **S3, SDC,** http://links.lww.com/TP/A909). Approximately 20% of donor kidneys are allocated through a national allocation for the highly sensitized potential recipients and among those with zero, one, or two HLA mismatches against the donor. Highly sensitized transplant candidates with PRA greater than 80% are given bonus points to improve their transplant potential. The remaining 80% are transplanted in the same state where the organs originated according to the state's individual allocation formula. Kidneys are offered to candidates with a negative T-cell CDC crossmatch and with no reported pretransplant class I DSA greater than 2,000 mean fluorescence intensity (MFI). In Western Australia, antibody profiling for all patients on the waiting list are performed thrice monthly. In this study, we have considered only kidneys allocated through the Western Australian state allocation.

The allocation score of each potential donor-recipient pair (with negative T-cell CDC crossmatch) was recalculated with consideration of acceptable mismatch (i.e., reduction in the number of HLA mismatches) using the era-specific allocation scoring system. Improvement in transplant potential was defined as reduction in waiting time if the recipient received a kidney at an earlier time point. We envisaged improvement in the transplant potential of a highly sensitized transplant recipient would result in reallocation of the donor kidney from its original intended recipient for that particular kidney, thus increasing the waiting time for this reallocated recipient (Fig. 2). We estimated the additional waiting time for the first and two subsequent reallocated recipients (the extra waitlist time until the availability of the next suitable deceased-donor kidney).

Statistical Analyses

Statistical analyses were performed using SPSS version 20. Data were expressed as proportion or as mean and standard deviation. Student *t* test was used to compare mean waiting time and mean HLA mismatches between recipients of the two allocation models. A *P* value less than 0.05 was considered as statistically significant.

Decision Analytical Modeling

Structure of the Model

Using a third-party payer perspective, two deterministic decision analytical models were constructed to compare the health benefits and costs of an acceptable mismatch allocation model with the current deceased-donor

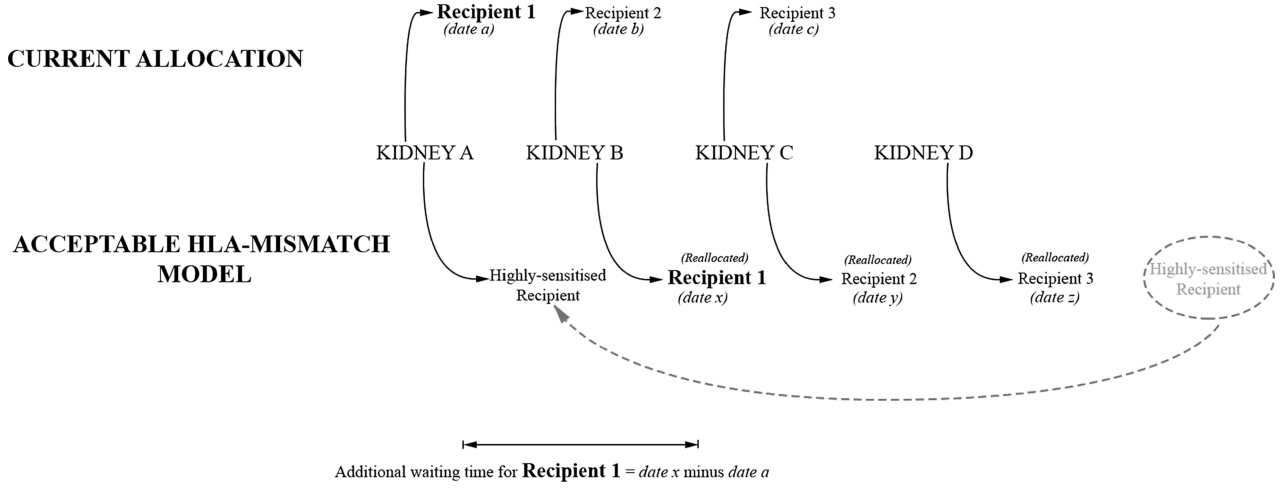

FIGURE 2. The process of reallocating displaced intended transplant recipients on the waiting list with inclusion of an acceptable mismatch allocation model in the allocation of deceased-donor kidneys.

allocation model for highly sensitized and non-highly sensitized patients on the transplant waitlist (n=10,000; start age=18). A simplified structure outlining the health states for the Markov model is shown in Figure S1 (see **SDC,** http://links.lww.com/TP/A909). The progression of an individual through each health state was dependent on age-specific transition probabilities. The models assumed that all transplant recipients were transplanted once and returned to dialysis following graft failure. The entire lifetime of an individual was modeled, whereby each transplant recipient was at risk of allograft failure and subsequent return to dialysis at the end of each annual cycle until all patients were deceased.

Input Parameters for the Model

Clinical data including the age-specific probability of receiving a deceased-donor kidney transplant and the mortality rates for patients on the transplant waitlist and following transplantation were sourced from the Australia and New Zealand Dialysis and Transplant registry and NOMS. The probability of transplantation using the acceptable mismatch allocation model was based upon the percentage reduction in waiting time demonstrated by our modeled simulations (i.e., 40% reduction in the waiting time equated to a 40% increase in the probability of receiving a transplant). Health state utilities for the estimation of quality-adjusted life-years were obtained from published literature (*20*).

Cost data were sourced from the 2008 NSW Dialysis Costing Study and the 2006 Kidney Health Australia Report on the Economic Impact of End-Stage Kidney Disease in Australia, the Medicare Benefits Schedule (December 2012), and the Schedule of Pharmaceutical Benefits (January 2013) (*21–24*). All costs were converted to the 2011 Australian dollar using the Australian Institute of Health and Welfare Total Health Price Index (*25*).

Sensitivity Analyses

Assumptions were tested over a range of plausible values to assess the robustness of the uncertainties in the model's input parameter estimates. We identified the most influential variables within the model using one-way sensitivity analyses.

Model Outcomes

Model outcomes included average and incremental costs and health benefits (in life-years saved [LYS] and quality-adjusted life-years [QALYs] gained) for highly sensitized and non-highly sensitized kidney transplant recipients between the current and acceptable mismatch allocation models. The average incremental benefits and costs were calculated for the entire population as well as for only individuals who benefited from acceptable mismatches. The former was calculated by distributing the total benefits and costs amongst all patients in the respective groups, while the latter calculated in those benefiting from the acceptable mismatch model. Future costs and benefits were discounted using a rate of 5% per annum and half-cycle corrections were used. We used TreeAge Pro Suite 2013 (TreeAge Software, Williamstown, MA, USA) (*26*) and Microsoft Excel to develop and analyze the model.

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