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Innovative Applications of O.R.

Deciding kidney-offer admissibility dependent on patients' lifetime failure rate

Michael Bendersky [a,*], Israel David [b]

[a] Facualty of Technology Management, Holon Institute of Technology, Holon, Israel
[b] Department of Industrial Engineering and Management, Ben-Gurion University of the Negev, Beer-Sheva, Israel

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ABSTRACT

We use developments in full-information *optimal stopping* to decide kidney-offer admissibility depending on the patient's age in treatment, on his/her estimated lifetime probabilistic profile and his/her prospects on the waiting list. We allow for a broad family of lifetime distributions – the Gamma – thus enabling flexible modeling of patients survival under dialysis. We fully automate an appropriate recursive solution in a spreadsheet application. It yields the optimal *critical times* for acceptance of offers of different qualities, and the ensuing expected value-to-go as a function of time. The model may serve both the organizer of a donation program for planning purposes, and the particular surgeon in making the critical decision at the proper time. It may further serve the potential individual recipient, practicing present-day *patient-choice*. Numerical results and their discussion are included.

1. Introduction

The US UNOS (United Network for Organ Sharing), the ERBP (European Renal Best Practice) and the Eurotransplant organization outline policies by which kidneys of the deceased are allocated locally, regionally and nationally (Eurotransplant manual, 2014; ERBP, European Renal Best Practice; US HRSA/OPTN, 2008a). They emphasize that the final decision to accept a particular organ remains the prerogative of the transplant surgeon and/or physician responsible for the care of the candidate in parallel, a*patient choice* practice has developed in recent years. Often, the choice is relegated to the patient (See Ahn & Hornberger, 1996; Su & Zenios, 2004a; 2004b; 2006; US HRSA/OPTN, 2008a and references therein). Patient-choice, particularly with regard to transplantation, benefits from hired professional advice. Because minor-quality kidneys are repeatedly refused for transplantation by patients on the waiting list and by their surgeons, excessive organ wastage is generated. To cope with this problem UNOS issued the ECD (Expanded Criteria Donor) policy, so kidneys from marginal donors are reserved for patients who declare in advance their willingness to accept such organs (US HRSA/OPTN, 2008a). Recently, *shared decision making* in kidney transplantation has been advocated impressively by Gordon et al. (2013). The question to be asked is what scientific and fact-based decision aids exist to help the individual in making such a critical decision, or the organizer of a donation program in assessing the future outlook of a pool of individual patients. The lack of accurate aids is explained by the immense difficulty of the analysis of a regulated dual donor-recipient streams (see Boxma, David, Perry, & Stadje, 2011; Yuan, Feldhamer, Gafni, Fyfe, & Ludwin, 2002; Zenios, Cherow, & Wein, 2000). Consequently, alternative decision-analytic approaches are sought. Such directions are heuristics - but still more analytically sound than the extant *point system*. For example, Yuan et al. (2002) suggest a *fuzzy logic* approach. The authors show, by way of example, that the fuzzy logic based policy is closer to an expert's (a medical practitioner) opinion than the policy attained by the UNOS point system. The authors, Chun and Sumichrast (2006) suggest a "rank based" approach for a selection problem applied to kidney allocation. The model proposed in the present work provides an analytical tool to help bridge the said decision-aid analytical gap, accompanied by an easy to use Excel workbook. The model and the software should prove useful to the individual patient, the consultant, the physician, and the social planner. We focus on the prospects of the *individual* patient. Optimizing the case of the single candidate (see e.g. Hornberger & Ahn, 1997) applies directly to patient-choice. As we show, it may further serve as a building block in the analysis of the dual (donor-recipient) queueing system at large. We ask for the patient's optimal, time-dependent, acceptance-rejection policy for kidneys of various quality, as a function of his/her blood-type (ABO) and immunological tissue characteristics (HLA). This policy depends also on the individual's deteriorating lifetime distribution under dialysis, and we assume that this lifetime distribution is *Gamma*(α, θ) with the shape parameter α being some integer (*Erlang* distribution). We use the recent study by

* Corresponding author. Tel.: +97 2524588533.
E-mail address: michael.bendersky@gmail.com (M. Bendersky).

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Bendersky and David (2015) in full-information *optimal stopping* to suggest a computational scheme which determines the optimal policy for the patient in question, in terms of *critical times*. The *Gamma* has long been popular in survival analysis and in medical research, with practical examples dating back to the 1950's (Collett, 2003; Lawless, 2011; Lee & Wang, 2003). The two-parameter Gamma family furnishes enough agreement in fitting it to many relevant datasets (Gupta & Kunda, 1999), and it admits ordering in distribution and in hazard rate, with respect to the shape parameter. Yet, due to the fact that the Gamma has no closed form for its cumulative distribution function, researchers preferred sometimes the *Weibull* or the *generalized exponential*. Still, in our case we show that letting the shape parameter be a positive integer (the Gamma becoming Erlang) we can compute both the value functions and critical times while providing enough flexibly for the modeling of different profiles of deterioration.

Our model relies on the quantification of rewards from each candidate and kidney-donation matching, on the ABO and HLA distribution in the population to which donors belong, and on the donation rate μ. In fact, to pass from the realm of the single candidate to that of the competitive world, we propose, by way of approximation, to use a value of "effective μ" – an expected average rate of future offers which become available to the specific candidate in question. This figure is to be assessed via databases such as UNOS's or the ERA-EDTA's. The effective μ will also have to take into account the candidate's position in the queue. The present exposition is supported by real data regarding the above mentioned factors.

In Section 2 we briefly outline the determinants of successful transplantation. Section 3 provides basics of the needed temporal modeling. Section 4 outlines the analysis of the stopping problem for Gamma deterioration, and the single-candidate decision algorithm. Section 5, accompanied with the appendices to this paper, demonstrates the use of the Excel application with numerical examples. These examples are then followed by a discussion, and Section 6 concludes the paper. We emphasize at the outset that the random offer value X in our model may not be based on HLA (Human Leukocyte Antigens, see below) match levels, but rather on *any finite set of real values of kidney quality, as perceived by the decision-maker.* In particular, it may be based on subjective probabilities or on utilities as perceived by the client and/or his/her advisor within the praxis of patient choice. As the HLA remains a significant factor in the allocation of live kidneys worldwide, and because real-life data with respect to tissue matching are available, we base our presentation on this criterion.

2. Success in transplantation

We begin by discussing the major factors that influence the success in kidney transplantation. These factors function in most allocation systems in prioritizing the pool of waiting candidates vis-à-vis any pending donor kidney.

2.1. The HLA tissue matching

Human tissue cells contain antigens that vary from person to person and are immunologically relevant to the specific organ. The system of these antigens is known as the HLA system. It can be subdivided into two groups: Class I that contains A, B or C antigens, which are present in body cells that have a nucleus, and Class II that contains antigens of the types DP, DR and DQ which are present only in the membranes of the cells responsible for triggering the immune system. The A, B,...,DQ antigens are arranged in sites A, B,...,DQ respectively. Every HLA site contains two *alleles*. Since the 80's, from the entire HLA genetic complex, sites A, B and DR were considered transplant relevant antigens. If transplanted into another individual, they can cause an immune response that can lead to the rejection of the *graft*. Yet, different medical centers put different emphases on the three sites, so that the same match combination may score differently. Part of the question is whether the benefit from HLA matching is worth the economic and social costs, including the rationing of fewer donor organs to black recipients (see Held et al., 1994; Vereestraeten et al., 1999). Lefaucheur et al. (2010) is an example for recent years renewed emphasis on the HLA matching for graft survival. In this exposition, we assume that any A, B or DR donor antigens which do not match the recipient can trigger an immune response. The higher the total number of such antigens, the lower the chance of a successful transplant. So, seven possible match-levels are possible - zero (all 6 alleles, aranged in three sites, do match) to six mismatches (none match). In assessing the future prospects of a given candidate, the HLA gene-distribution in the relevant donor population is assumed to be known.

One comprehensive source concerning histocompatibility testing is Cecka and Reid (2005).

2.2. ABO blood type

The blood types of the donor and the recipient must also match. In allocation systems worldwide O donors go to O recipients exclusively, except for the case when there is a recipient with a zero antigen mismatch. (UNOS and Eurotransplant have a similar ABO-B rule for donors and recipients). The incorporation of the ABO match probability to the tissue match probability of a random donor to a given candidate is routine (see Barnes & Miettinen, 1972). In our model, this probability may simply multiply the relevant donor arrival rate to yield an effective μ. (Since a Poisson process with rate μ and a probability p of counting any arrival yields a Poisson process with rate μp. See also Section 3.2 below). One may assume statistical independence between tissue classification and blood type.

2.3. Preferred candidates: pediatric, long waiting and sensitized (PRA)

Pediatric patients are allocated extra score points. Also, each extra year on the waiting list credits the candidate with extra points. These two quantifying criteria may also be taken into account by an effective μ. There is an additional determinant factor in transplantation, called PRA (Panel Reactive Antibodies). It refers to a periodical immunological check of each candidate (Cecka & Reid, 2005; Eurotransplant manual, 2014). Although the PRA status is included in allocation systems, we choose not to include it in the present exposition.

2.4. x-*year graft survival, QALY, and discounted-QALY*

Let us denote the reward for a given candidate from a random offer by X, a discrete random variable. In this presentation X is a one-to-one function of I, the total number of mismatches in the HLA A, B and DR sites combined. Medical assessments as to how to translate the number of HLA-mismatches I to X vary, mainly because controversy surrounds the question of what gain needs to be measured. See Gold, Siegel, Russell, and Weinstein (1996) for the prevailing notions of *QALY* (quality-adjusted life-years), *QALE* (quality-adjusted life expectancy) and *discounted-QALY* (see also Evans, Tavakoli, & Crawford, 2004 for a critique). The present work adopts an alternative measure, that of (post-transplant) 3-*years graft-survival*. Table 1 below summarizes the distribution of X which is used for the numerical examples in Section 5. The sources of these data are indicated in Section 5.1 and in Appendix A.

3. Temporal modeling with gamma deterioration

Obviously, the deteriorating profile of lifetime under dialysis treatment must be reflected in any prescriptive model for acceptance-rejection of a kidney for transplant. David and Yechiali (1985) used dynamic programming to show that if the lifetime of

Table 1
Reward X (3-years graft survival rates) as a function of HLA mismatch.

Mismatch	Value x of X	$P(X = x)$	$P(X \le x) = F(x)$
$(I = 6)$	$x_7 = 0.750$	0.1642	0.1642
$(I = 5)$	$x_6 = 0.771$	0.3632	0.5273
$(I = 3)$	$x_5 = 0.786$	0.3103	0.8377
$(I = 3)$	$x_4 = 0.802$	0.1306	0.9683
$(I = 2)$	$x_3 = 0.818$	0.0285	0.9968
$(I = 1)$	$x_2 = 0.833$	0.0031	0.9999
$(I = 0)$	$x_1 = 0.850$	0.0001	1.0000

the candidate is *Increasing in Failure Rate* (IFR), which is certainly the case under kidney failure, then the optimal threshold function $\lambda(t)$ for accepting an offer is a continuous non-increasing function of time. Further progress is offered in the recent optimal-stopping study by Bendersky and David (2015), which provides an explicit form for $\lambda(t)$ in the case of any Erlang underlying deterioration and dicrerte random variable X of offer value.

3.1. The lifetime distribution

The *hazard-rate (failure-rate)* function of a lifetime is defined by $r(t) = \lim_{x\to 0} \frac{1}{x}\left(1 - \bar{G}(t+x)/\bar{G}(t)\right)$ where $\bar{G}(t) = 1 - G(t)$ is the survivor function and $G(t)$ is the lifetime *cdf*. For the *Erlang*(n, θ)

$$r(t) = \frac{1}{(n-1)!} \Big/ \sum_{k=0}^{n-1} \frac{\theta^{k-n} t^{k-n+1}}{k!}. \tag{1}$$

(See e.g. Lee & Wang, 2003, p. 152.) The distribution $\Gamma(\alpha, \theta)$ ($\alpha = n$ for the Erlang case as the shape parameter) is IFR for $\alpha \ge 1$ (Barlow & Proschan, 1975). From Eq. (1) it is straightforward that $\lim_{t\to\infty} r(t) = \theta$. Also, the presentation $[r(t)]^{-1} = \int_0^\infty \left(1 + \frac{u}{t}\right)^{\alpha-1} e^{-\theta u} du$ (see Barlow & Proschan, 1975 again) gives that if $X \sim \Gamma(\alpha_1, \theta_1)$, $Y \sim \Gamma(\alpha_2, \theta_2)$ and $\alpha_1 > \alpha_2 > 1$ then if $\theta_1 = \theta_2$, $r_X(t) < r_Y(t)$ for all $t > 0$. For integer α's it is intuitive that Y is more surviving than X by the interpretation of the Erlang-n as a sum of n memoryless shocks. This observation is useful in comparative interpretation of lifetimes, and in assigning them a Gamma distribution. It is worth noting that if X and Y have the same expectation and $\alpha_1 > \alpha_2 > 1$ then $\theta_1 > \theta_2$ and no hazard ordering applies (See Fig. 3 in Section 5.1 below).

3.2. Poisson donation

We assume that the decision maker faces a random Poisson stream of offers, with rate μ. In our examples, below, the original value of μ is modified to account for *scaling* of time. If an estimated proportion of the offers is discarded, e.g. because kidneys go to preferred candidates on the waiting list, an effective μ may be used, and the stream remains Poisson.

3.3. The type of optimal policies

In defining $V(t, x)$ — the optimal expected discounted reward from offer $X = x$ at time t and on, $V(t)$ — the optimal expected reward at time t just before a bid arrives, and $\lambda(t)$ the future expected reward if the offer is arbitrarily rejected at time t while an optimal strategy is applied thereafter, the basic dynamic-programming equation is

$$V(t) = E_X V(t, X) = E[\max(\lambda(t), X)].$$

X admits a finite number of values $x_1 > x_2 > \cdots > x_m$, with probabilities $p_1,\ p_2, \ldots, p_m$ respectively. In our case $m = 7$ as the number of possible mismatches. x_1 is the kidney value for $I = 0$ — zero HLA mismatches — down to x_7 which is the kidney value for $I = 6$ — maximum HLA mismatches. Let $t_i = \max\{0, \lambda^{-1}(x_i)\}$. If $\lambda(t) > x_i$ for all $t \ge 0$ set $t_i = \infty$. The t_i's are the *critical times*. $0 = t_1 \le t_2 \le \cdots \le t_m$ because λ is non-increasing in t for any IFR lifetime. A *region* is a period between two consecutive t_i's. Thus, for region i, $1 \le i \le m$, we have $x_{i+1} \le \lambda(t) \le x_i$ and $t_i \le t \le t_{i+1}$ (with $t_{m+1} \equiv \infty$). When in region i, only x_i and higher offers (x_j *s.t.* $j \le i$) are acceptable. ($i - 1$ and smaller numbers I of mismatches are acceptable). Some regions can be vacuous. Fig. 1 provides a schematic depiction of $\lambda(t)$.

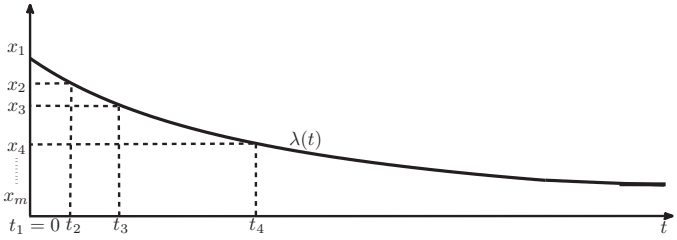

Fig. 1. The threshold value $\lambda(t)$ as a function of time.

4. The solution for any Erlang lifetime. An algorithm to decide critical times

In this Section we present needed material from Bendersky and David (2015), and move on to formulate a solution algorithm, applicable to the kidney application.

For the Erlang case we have that

$$\lambda(t) = \left(D_i e^{-A_i t} + \frac{B_i}{1 + A_i} \sum_{k=0}^{n-1} \left(1 - (-A_i)^{k-n}\right) \frac{t^k}{k!} \right) \Big/ \sum_{k=0}^{n-1} \frac{t^k}{k!} \tag{2}$$

for each region i, where A_i and B_i are constants depending only on the distribution function of X, $F_X(x)$. D_i is an integration coefficient. Each region i has its own A_i, B_i and D_i. The A_i's and the B_i's are calculated using the following result:

Proposition 4.1.

$$B_i = \begin{cases} -\mu q_1 x_1 & \text{if } i = 1 \\ -\mu\left[\sum_{j=1}^{i-1} q_j (x_j - x_{j+1}) + q_i x_i\right] & \text{if } i = 2, \ldots, m \end{cases}$$

$$A_i = -(1 + \mu q_i), \quad i = 1, \ldots, m \text{ where } q_i = \sum_{j=1}^{i} p_j, \quad i = 1, 2, \ldots, m.$$

Proofs for Eq. (2) and Proposition 4.1 are detailed by Bendersky and David (2015).

Having Proposition 4.1 we need to determine $i_{\max}$ - the last region attained by $\lambda(t)$. Since $\lambda(t)$ is bounded $\exists \lim_{t\to\infty} \lambda(t) = L$ and since $A_{i_{max}} < 0$, we have from (2) that $D_{i_{\max}} = 0$ (otherwise $\lambda(t)$ does not converge). In dividing the nominator and denominator of (2) by t^{n-1} it follows that

$$L = \frac{B_{i_{\max}}}{A_{i_{\max}}} \tag{3}$$

allowing for the determination of $i_{\max}$: by monotonicity of $\lambda(t)$ there exists exactly one region i for which the ratio in the R.H.S of (3) lies between x_{i+1} and x_i and this is the rightmost region (in t). $i_{max} = i$. (See Section 5 below for a numerical example how to obtain $i_{\max}$ and L). Now,

$$\lambda\left(t_{i_{\max}}\right) = x_{i_{\max}}. \tag{4}$$

$t_{i_{\max}}$ (the last critical time which is attained by $\lambda(t)$) can be found by (2), that is, by solving for t in:

$$x_{i_{\max}} = \frac{B_{i_{\max}}}{1 + A_{i_{\max}}} \cdot \sum_{k=0}^{n-1} \frac{t^k}{k!} \left(1 - \left(-A_{i_{\max}}\right)^{-(n-k)}\right) \Big/ \sum_{k=0}^{n-1} \frac{t^k}{k!}. \tag{5}$$

Having $t_{i_{\max}}$, the rest of the critical times t_i^*, and D_i's , $i \le i_{\max}$, are computed by an iterative procedure as explained in Section 4.1 below.

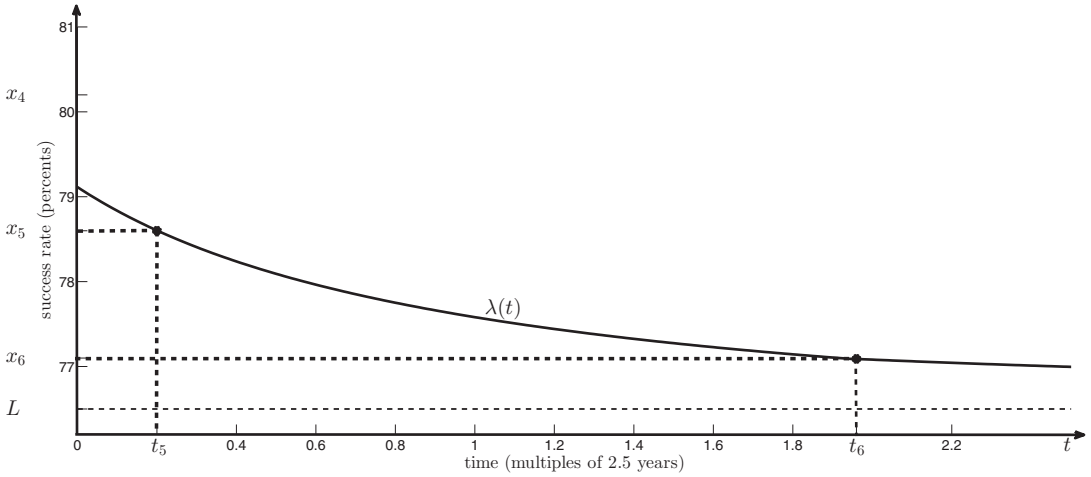

Fig. 2. The threshold function and the critical times in the $\alpha = 2$ example.

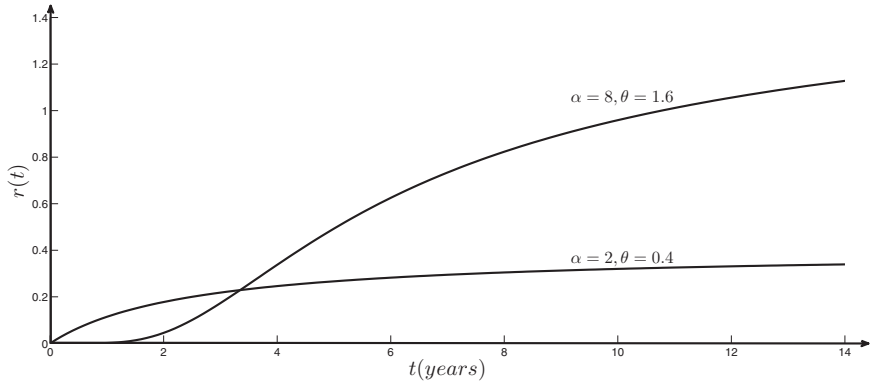

Fig. 3. The Gamma failure-rate for $\alpha = 2$, $\theta = 0.4$, and $\alpha = 8$, $\theta = 1.6$.

This procedure further gives an explicit expression for $\lambda(t)$ for all t (region dependent).

4.1. Algorithm to decide critical times

First, determine A_i, B_i using Proposition 4.1 and determine $i_{\max}$ and $t_{i_{\max}}$ by (3) and (5). Next, let $i = i_{\max}$, and specify D_{i-1} by:

$$D_{i-1} = \sum_{k=0}^{n-1} \frac{t_i^k e^{t_i} A_{i-1}}{k!} \left(x_i - \frac{B_{i-1}}{A_{i-1}+1} \left(1 - (-A_{i-1})^{-(n-k)}\right)\right). \tag{6}$$

t_{i-1} is extracted from solving the equation

$$x_{i-1} = \left(D_{i-1} e^{-tA_{i-1}} + \frac{B_{i-1}}{A_{i-1}+1} \sum_{k=0}^{n-1} \frac{t^k}{k!} \left(1 - (-A_{i-1})^{-(n-k)}\right)\right) \Big/ \sum_{k=0}^{n-1} \frac{t^k}{k!} \tag{7}$$

in t. Applying (6) and (7) repeatedly by letting $i := i-1$ we obtain all the lower critical times. When (7) admits no solution, the process stops. We let $i_{\min} = i$ and $t_1 = \ldots = t_{i_{min}-1} = 0$.

A pseudocode of this algorithm appears in Appendix B.

The optimal policy is determined as follows: when the waiting time t is between t_i and t_{i+1} the individual accepts only bid x_i and higher. Bids $x_1, \ldots, x_{i_{\min}-1}$ are always acceptable. Bids $x_{i_{\max}+1}, \ldots, x_m$ are never acceptable.

5. Numerical results, implications

Based on the results of Section 4 and on the solution algorithm, we present a few numerical examples. The two examples in Section 5.1 emphasize the significance of coping with the general Erlang case in modeling deterioration. It is shown that fitting the life distribution in changing the shape parameter n while maintaining a fixed life expectancy may affect considerably the optimal policy. In Section 5.2 we demonstrate the use of the application in research and planning, by studying the impact of *donation rate*. (Although numerical figures are presented in 4 decimal places in this paper, subsequent calculations are based on sufficient precision).

5.1. The effect of the shape parameter

We choose for the patient under discussion the following HLA antigens: # 2 and # 2 in site A (homozygous), #8 and #35 in site B, and #0 and #4 in site DR. The entire gene distributions for the three sites, for the US population, were taken from UNOS website (see Table A.5 in Appendix A below). For the quantification of the offer value X we use data regarding 3-year survival rate, taken from US HRSA/OPTN-SRTR (2008b). (See Table 5.10a: *Unadjusted Graft Survival, Deceased Donor non-ECD Kidney Transplants, Survival at 3 Months, 1 Year, 3 Years, and 5 Years*). The probabilities of the seven possible values of X $P(I = 0), \ldots, P(I = 6)$ are calculated by Eqs. (C.3)–(C.9) in Appendix C below. All combined, the data lead to Table 1, the distribution of kidney values X. The donation rate, as experienced by the decision-maker, is taken to be $\mu = 20$ annually. The candidate's life expectancy

Table 2
Values of A and B for Eq. (2).

Region index	Region in offer values	A	B	B/A
7	$0 \le \lambda(t) \le 0.75$	−51.0000	−38.8898	0.7625
6	$0.75 \le \lambda(t) \le 0.771$	−42.7916	−32.7336	0.7650
5	$0.771 \le \lambda(t) \le 0.786$	−24.6334	−18.7336	0.7605
4	$0.786 \le \lambda(t) \le 0.802$	− 9.1166	−6.5373	0.7171
3	$0.802 \le \lambda(t) \le 0.818$	− 2.5849	−1.2989	0.5025
2	$0.818 \le \lambda(t) \le 0.833$	− 1.1595	−0.1329	0.1147
1	$0.833 \le \lambda(t) \le 0.85$	− 1.0064	−0.0054	0.0054

Table 3
Optimal Policy for $\alpha = 2$ and $\alpha = 8$.

Optimal policy - time until rejection (years)		
Mismatch	$\alpha = 2$	$\alpha = 8$
$I = 0$	Always accept	Always accept
$I = 1$	Always accept	Always accept
$I = 2$	Always accept	Always accept
$I = 3$	Always accept	1.11
$I = 4$	0.53	2.23
$I = 5$	4.89	3.51
$I = 6$	Never accept	7.03

is taken to be 5 years. This figure relates to lifetime under dialysis which presently pertains to patients in the age group of 60–64 years. (European data, see European Renal Association & Registry, 2008 p. 79). In the first example we assume that $\alpha = 2$. Thus we may substitute $\theta = 1$ in the computations and $\mu = 20 \cdot 2.5 = 50$ (2.5 years is a new time unit which complies with a Gamma expectation $\alpha/\theta = 2$). Using Table 1 and Proposition 4.1 we arrive at Table 2, which specifies the required constants for the computations.

To demonstrate the algorithm and the iterative scheme, we solve this example manually. We start in identifying the maximal-index region in Table 2 which is attained by $\lambda(t)$. For $i_{\max} = 6$, $L \equiv \lim_{t\to\infty} \lambda(t) = B_{i_{\max}}/A_{i_{\max}} = 0.7650$. (Indeed, this value is between $x_7 = 0.75$ and $x_6 = 0.771$. See Eq. (3). This identification of i_{max} and L is easily automated, based on Table 2).

So, in $[t_6, \infty]$ Eq. (2) takes the simple form

$$\lambda(t) = \frac{b + at}{1 + t}, \tag{8}$$

where $b = \frac{B_6}{A_6}(1 - \frac{1}{A_6}) = 0.7828$ and $a = \frac{B_6}{A_6} = 0.7650$. (This is because $D_6 = 0$. Note that n is the Erlang parameter, $n = \alpha = 2$). The determination of t_i in this iteration is immediate by inverting (8), $t_6 = \lambda^{-1}(0.771) = 1.9560$, which is 4.89 years. Next, the determination of D in the following region (Region 5) is based on the continuity of $\lambda(t)$ and on the recent knowledge of the rightmost t in that region. $D_5 = 2.1458 \cdot 10^{-25}$ (substitute A_5, B_5, $t_6 = 1.9560$ and $x_6 = 0.771$ in the R.H.S. of Eq. (6)). The following step is the inversion $t_5 = \lambda^{-1}(0.786) = 0.2104$, which is 0.53 years. Here $\lambda(t) = (b + at + D_5 e^{-A_5 t})/(1 + t)$ where $b = (B_5/A_5)(1 - 1/A_5) = 0.7914$ and $a = B_5/A_5 = 0.7605$. For Region 4, $D_4 = 6.9913 \cdot 10^{-4}$ and we have $t_4 = 0$. The times $t_3 = 0, t_2 = 0, t_1 = 0$ are set to 0 as well, and we are done. See Fig. 2 and Table 3 for $\alpha = 2$.

As a second example, consider the case where $\alpha = 8$ while we keep the former life expectancy. Thus $\theta = 1.6$. The annual arrival remains the same as before, now translated to $\mu = 12.5$ with $\theta = 1$. Table 1 is still in effect (same recipient with same donor population as before). The obtained critical times are given in Table 3, column $\alpha = 8$. The calculations are performed using the Excel spreadsheet.

It can be seen that in the beginning the lifetime distribution with $\alpha = 2$, the more skewed, is better for the patient than the distribution with $\alpha = 8$. But this preference is reversed as time under dialysis goes by, an outcome might have been anticipated in examining the respective failure rates as functions of time. See Fig. 3.

Table 4
The impact of donation rate – reject-until figures (years).

I (# MM)	$\mu = 10$ (/yr.)	$\mu = 20$ (/yr.)	$\mu = 50$ (/yr.)	$\mu = 400$ (/yr.)	$\mu = 1000$ (/yr.)	$\mu = 10000$ (/yr.)
0	accept	accept	accept	accept	accept	accept
1	accept	accept	accept	accept	accept	0.14
2	accept	accept	accept	0.09	0.42	reject
3	accept	accept	0.12	5.67	reject	reject
4	0.08	0.53	2.48	reject	reject	reject
5	1.13	4.89	reject	reject	reject	reject
6	31.45	reject	reject	reject	reject	reject

5.2. The impact of donation rate

As is frequently the case with spreadsheet applications, various important sensitivity analyses may be easily performed. To illustrate, we check the sensitivity of the critical times to the*donation rate*. Table 4 below summarizes "reject until" results. They are obtained simply by adjusting the μ input-cell in the main sheet. We raise the value of μ from 10 to 20, 50, 400, 1000 and 10000. For each HLA match level (or, more generally, kidney-candidate matching reward which is distributed as X), the corresponding critical time is stated. As expected, the candidate becomes pickier as μ rises. Equivalently, the candidate becomes less picky with dimmer prospects of future offers, combined with deteriorating life expectancy upon dialysis. However, the exact figures are hardly predictable. For $\mu = 10$ a kidney with 3 mismatches is always accepted. If μ is 5 times bigger, the candidate only enjoys some 45 days (0.12 year) of rejecting such a kidney ($I = 2$ or $I = 1$ are still never rejected). For $\mu = 1000$ — only a fictional figure in the present state of affairs — a kidney with $I = 2$ will be rejected for about the first 5 months. However, no kidneys with lesser value will be accepted thereafter. Thus, even a candidate with top-priority should not reject a second-best kidney ($I = 1$), after some 2 months. A perfect match in unrelated donor transplantation is a golden opportunity.

5.3. Exponential lifetimes

The spreadsheet shows that if $\alpha = 1$, the results are always split between accept and reject. This is no surprise, because $\alpha = 1$ means an exponential, memoryless lifetime. Thus, the threshold function $\lambda(t)$ is constant over time, a horizontal line in Fig. 1. Temporal modeling in past research assumed the exponential, which proves now to be over-simplistic.

5.4. Alternative settings

It is evident that the $X - P$ entries (value, or utility, vs. probability) for the algorithm may be arbitrary. In the spreadsheet, one may overwrite the existing formulas for the HLA probabilities, and enter figures as one sees fit. For more than 7 X-values, some programming modification is required. For less than 7 values, the extra lines in the $X - P$ array may stand for dummy offers, in a straightforward manner. Recall that for applications such as patient choice (not necessarily in context of transplantation), the X distribution may even be tentative or subjective.

6. Conclusion

The large discrepancy between supply and demand in kidney transplantation, the high degree of waste of donated kidneys, and the

Table A.5
HLA- A,B,DR gene distribution in the US.

A Antigens	P	B Antigens	P	B Antigens	P	DR Antigens	P
0	0.100	0	0.075	53	0.032	0	0.123
1	0.111	5	0.002	54	0.001	1	0.072
2	0.215	7	0.079	55	0.012	2	0.040
3	0.101	8	0.099	56	0.005	3	0.097
9	0.002	12	0.001	57	0.028	4	0.172
10	0.002	13	0.018	58	0.019	5	0.012
11	0.047	14	0.022	59	0.000	6	0.030
19	0.003	15	0.002	60	0.043	7	0.082
23	0.040	16	0.001	61	0.012	8	0.043
24	0.082	17	0.007	62	0.052	9	0.021
25	0.013	18	0.048	63	0.010	10	0.010
26	0.032	21	0.001	64	0.001	11	0.072
28	0.039	22	0.002	65	0.009	12	0.020
29	0.031	27	0.031	67	0.000	13	0.069
69	0.002	45	0.017	81	0.001	99	0.000
74	0.007	46	0.002	99	0.000	103	0.000
80	0.001	47	0.003	4005	0.000	**Sum**	**1**
99	0.000	48	0.004	5102	0.000		
2403	0.000	49	0.021	7801	0.001		
Sum	**1**	50	0.014	8101	0.000		
		51	0.040	8201	0.000		
		52	0.012	**Sum**	**1**		

problematic equity issues involved in managing the waiting list, all call for carefully designed sharing rules, as well as for a means to predict the outcomes of the frequent changes in these rules. At the same time, increasing power has been placed in the hands of the individual kidney recipient. A mathematically based, user friendly tool is called for to aid individuals in making sound acceptance decisions. In this paper we suggest such a tool, based on continuous-time probabilistic dynamic programming. Its main advantage lies in its simplicity, portability and flexibility. Indeed, any researcher may implement changes in this tool as he/she sees fit, as well as any potential transplant recipient. The individual may use the model in an utterly subjective manner (independent of accepted classification of factors or their scoring by the centralized decision maker). We propose, presumably for the first time, a convenient vehicle for both computing the probabilities for a given candidate, and his/her prospective outlook in the time axis. Specifically, *critical times* are calculable for the compromise on any given kidney value as waiting time progresses. Output is dependent on the genetic statistics of the relevant, particular, population. The model we propose, and the computational tool, are not restricted to the kidney application, and they can be applied to any finite-valued, "*secretary*"-like problem of patient-choice under deterioration.

In numerical examples we exemplified the use of the model in studying the impact of donation rate, and the sensitivity of the optimal timing to the proper representation of the evolution of failure rate. Other workable sensitivity analyses might concern the dependence of the outcome on the population genetics statistics, on the estimation of utilities, and on the patient's personal attributes (HLA and ABO). All these options bear significance for debated issues in the field of transplantation, which now may be investigated given access to clinical databases. The spreadsheet decision-making tool is helpful because Excel is so easy in answering "what if" questions, and because the sensitivity of the critical times to μ is not dramatic: the accuracy of the reward figures (X) turns out to be the most influential.

Appendix A. UNOS's HLA gene statistics

The data in Table A.5 underline the computation which appears in the main text.

Appendix B. A pseudo-code for gamma deteriorating lifetimes

The following *pseudo-code* pertains to the material in Section 4 above.

1. Enter $x_1 > x_2 > \cdots > x_m$, $p_1,\ p_2, \ldots, p_m$ // Offer values and their respective probabilities.
2. Enter $n\,; E\,; \mu$ // Erlang shape parameter, Erlang expected lifetime (yr.), annual donation rate.
3. For $1 \le i \le m$ $\{q_i := \sum_{j=1}^{i} p_j\}$
4. $\mu := \mu \cdot E/n$; $x_{m+1} := 0$
5. For $1 \le i \le m$: {{If $\{i = 1\}$
   $B_i := -\mu q_1 x_1$
   else
   $B_i := -\mu[\sum_{j=1}^{i-1} q_j(x_j - x_{j+1}) + q_i x_i]\}$
   $A_i := -(1 + \mu q_i)$
   If $\{x_{i+1} \le B_i/A_i \le x_i\}$; $i_{\max} := i \quad D := 0\}$
6. $i := i_{\max}$
7. $\lambda_+ := x_i, \quad A := A_i, \quad B := B_i$
8. $t_- := \lambda^{-1}(\lambda_+)$ where $\lambda(t) = (De^{-tA} + \frac{B}{A+1}\sum_{k=0}^{n-1} \frac{t^k}{k!}$ $(1 - (-A)^{-(n-k)}))(\sum_{k=0}^{n-1} \frac{t^k}{k!})^{-1}$
9. {If {no positive value for t in the inversion (step 8)}
   {For $1 \le j \le i$ $t_j := 0$; Go to 10}
   else
   $t_i := t_-$; $D := \sum_{k=0}^{n-1} \frac{(t_-)^k e^{At_-}}{k!}(x_i - \frac{B}{A+1}$ $(1 - (-A)^{-(n-k)}))$;
   $i := i - 1$; Go to 7}
10. For $1 \le i \le i_{\max}$ $t_i := t_i \cdot E/n$ // Adjust the obtained t_i's for *years*. These are the required critical times.
11. End

Appendix C. HLA mismatch computation

For this presentation to be complete, we reproduce here some needed results from Alalouf, David, and Pliskin (2012). The Eqs. (C.1)–(C.9) below are embodied in the spreadsheet application, relative to the data in Appendix A.

The Distribution of I

Let $a_1, a_2, \ldots, a_n$ be the population of genes relevant to a given HLA site in humans, say HLA-A. Denote by f_m the probability (pertinent to the relevant society or country) to find gene a_m in the first allele (second allele) of a random person, recipient or donor, $m = 1, 2, \ldots, n$. Let a_i and a_j be the alleles possessed by the recipient at hand. Define

$$f_u = \begin{cases} f_i + f_j & if \quad i \neq j \\ f_i & if \quad i = j \end{cases} \tag{C.1}$$

the u notation is short for $u(i, j) = \{a_i \cup a_j\}$ and, thus, f_u is simply the probability for a random allele of the donor to be possessed by the recipient as well. (The case of $i \neq j$ in (C.1) is called*heterozygosity* and the case $i = j$ is called *homozygosity*). Define also

$$S(-u, f) = \begin{cases} \sum_m f_m^2 - f_i^2 - f_j^2 & if \quad i \neq j \\ \sum_m f_m^2 - f_i^2 & if \quad i = j \end{cases}. \tag{C.2}$$

This is the probability that the donor is homozygote, with a double allele, which is not possessed by the recipient.

Parallel to the notation for site A, define b_k and b_l (c_o and c_p) - alleles of recipient's site B (DR) and g_u and h_u the corresponding probabilities defined similarly to f_u. $S(-u, g)$ and $S(-u, h)$ are defined respectively. Finally let I be the total number of HLA mismatches in the three sites. The probability of perfect match is clearly

$$P(I = 0) = f_u^2 \cdot g_u^2 \cdot h_u^2. \tag{C.3}$$

Since $I = 0$ is comprised of the three disjoint events exactly one mismatch, and it occurs in A (or B or DR, respectively),

$$\begin{aligned} P(I = 1) = {} & [2f_u \cdot (1 - f_u) + S(-u, f)] \cdot g_u^2 \cdot h_u^2 \\ & + [2g_u \cdot (1 - g_u) + S(-u, g)] \cdot h_u^2 \cdot f_u^2 \\ & + [2h_u \cdot (1 - h_u) + S(-u, h)] \cdot f_u^2 \cdot g_u^2, \end{aligned} \tag{C.4}$$

where the terms in brackets signify exactly one mismatch in site A, B, or DR, respectively. Following similar reasoning (see Alalouf et al., 2012 for details)

$$\begin{aligned} P(I=2) = {} & [2f_u \cdot (1-f_u)+S(-u, f)] \cdot [2g_u \cdot (1 - g_u) + S(-u, g)] \cdot h_u^2 \\ & + [2f_u \cdot (1-f_u)+S(-u, f)] \cdot [2h_u \cdot (1-h_u)+S(-u, h)] \cdot g_u^2 \\ & + [2g_u \cdot (1-g_u)+S(-u, g)] \cdot [2h_u \cdot (1-h_u)+S(-u, h)] \cdot f_u^2 \\ & + \left[(1 - f_u)^2 - S(-u, f)\right] \cdot g_u^2 \cdot h_u^2 \\ & + \left[(1 - g_u)^2 - S(-u, g)\right] \cdot h_u^2 \cdot f_u^2 \\ & + \left[(1 - h_u)^2 - S(-u, h)\right] \cdot f_u^2 \cdot g_u^2 \end{aligned} \tag{C.5}$$

$$\begin{aligned} P(I = 3) = {} & [2f_u \cdot (1 - f_u) + S(-u, f)] \cdot [2g_u \cdot (1 - g_u) + S(-u, g)] \\ & \cdot [2h_u \cdot (1 - h_u) + S(-u, h)] \\ & + \left[(1-f_u)^2 - S(-u, f)\right] \cdot [2g_u \cdot (1 - g_u) + S(-u, g)] \cdot h_u^2 \\ & + \left[(1-f_u)^2 - S(-u, f)\right] \cdot [2h_u \cdot (1 - h_u) + S(-u, h)] \cdot g_u^2 \\ & + \left[(1-g_u)^2 - S(-u, g)\right] \cdot [2f_u \cdot (1 - f_u) + S(-u, f)] \cdot h_u^2 \\ & + \left[(1-g_u)^2 - S(-u, g)\right] \cdot [2h_u \cdot (1 - h_u) + S(-u, h)] \cdot f_u^2 \\ & + \left[(1-h_u)^2 - S(-u, h)\right] \cdot [2g_u \cdot (1 - g_u) + S(-u, g)] \cdot f_u^2 \\ & + \left[(1-h_u)^2 - S(-u, h)\right] \cdot [2f_u \cdot (1 - f_u) + S(-u, f)] \cdot g_u^2 \end{aligned} \tag{C.6}$$

$$\begin{aligned} P(I = 4) = {} & \left[(1 - f_u)^2 - S(-u, f)\right] \cdot [2g_u \cdot (1 - g_u) + S(-u, g)] \\ & \cdot [2h_u \cdot (1 - h_u) + S(-u, h)] \\ & + \left[(1 - f_u)^2 - S(-u, f)\right] \cdot \left[(1 - g_u)^2 - S(-u, g)\right] \cdot h_u^2 \\ & + \left[(1 - f_u)^2 - S(-u, f)\right] \cdot \left[(1 - h_u)^2 - S(-u, h)\right] \cdot g_u^2 \\ & + [2f_u \cdot (1 - f_u) + S(-u, f)] \cdot \left[(1 - g_u)^2 - S(-u, g)\right] \\ & \cdot [2h_u \cdot (1 - h_u) + S(-u, h] \\ & + \left[(1 - g_u)^2 - S(-u, g)\right] \cdot \left[(1 - h_u)^2 - S(-u, h)\right] \cdot f_u^2 \\ & + [2f_u \cdot (1-f_u)+S(-u, f)] \cdot [2g_u \cdot (1 - g_u)+S(-u, g)] \\ & \cdot \left[(1 - h_u)^2 - S(-u, h)\right] \end{aligned} \tag{C.7}$$

$$\begin{aligned} P(I = 5) = {} & \left[(1 - f_u)^2 - S(-u, f)\right] \cdot \left[(1 - g_u)^2 - S(-u, g)\right] \\ & \cdot [2h_u(1 - h_u) + S(-u, h)] \\ & + \left[(1 - f_u)^2 - S(-u, f)\right] \cdot \left[(1 - h_u)^2 - S(-u, h)\right] \\ & \cdot [2g_u \cdot (1 - g_u) + S(-u, g)] \\ & + \left[(1 - g_u)^2 - S(-u, g)\right] \cdot \left[(1 - h_u)^2 - S(-u, h)\right] \\ & \cdot [2f_u \cdot (1 - f_u) + S(-u, f)] \end{aligned} \tag{C.8}$$

$$\begin{aligned} P(I = 6) = {} & \left[(1 - f_u)^2 - S(-u, f)\right] \cdot \left[(1 - g_u)^2 - S(-u, g)\right] \\ & \cdot \left[(1 - h_u)^2 - S(-u, h)\right]. \end{aligned} \tag{C.9}$$

Obviously, variations in the HLA criteria lead to different distributions of the offer value, but the calculation of the probabilities is carried out along similar lines.

References

Ahn, J., & Hornberger, J. (1996). Involving patients in the cadaveric kidney transplant allocation process: a decision-theoretic perspective. *Management Science, 42*(5), 629–641.

Alalouf, A., David, I., & Pliskin, J. (2012). Computing the probabilities of hla-like matching. *Annals of Operations Research*, 1–13. doi:10.1007/s10479-011-1049-2.

Barlow, R. E., & Proschan, F. (1975). Statistical Theory of Reliability and Life Testing. *International Series in decision processes*. Holt, Rinehart and Winston.

Barnes, B. A., & Miettinen, O. S. (1972). The search for an hl-a and abo-compatible cadaver organ for transplantation. *Transplantation, 13*(6), 592–598.

Bendersky, M., & David, I. (2015). The full-information best-choice problem with uniform or gamma horizons. *Optimization*. doi:10.1080/02331934.2015.1080253.

Boxma, O. J., David, I., Perry, D., & Stadje, W. (2011). A new look at organ transplantation models and double matching queues. *Probability in the Engineering and Informational Sciences, 25*(02), 135–155.

Cecka, J. M., & Reid, E. F. (2005). Histocompatibility testing, crossmatching, and allocation of kidney transplants. In G. Danovitch (Ed.), *Handbook of kidney transplantation* (pp. 43–71). Lippincott Williams and Wilkins.

Chun, Y. H., & Sumichrast, R. T. (2006). A rank-based approach to the sequential selection and assignment problem. *European Journal of Operational Research, 174*(2), 1338–1344. doi:10.1016/j.ejor.2005.03.040.

Collett, D. (2003). Modelling Survival Data in Medical Research, Second Edition. *Chapman & Hall/CRC Texts in Statistical Science*. Taylor & Francis, London.

David, I., & Yechiali, U. (1985). A time dependent stopping problem with applications to live organ transplant. *Operations Research, 33*, 491–504.

Eurotransplant manual (2014). URL https://www.eurotransplant.org/cms/index.php?page=et_manual.

ERBP (European Renal Best Practice), ERBP Guideline on kidney donor and recipient evaluation and perioperative care, URL http://www.european-renal-best-practice.org/sites/default/files/Boekje%20niertransplantatie%20EN_0.pdf.

European Renal Association, E. D., & Registry, T. A. E.-E. (2008). *2006 Annual Report*. Amsterdam, The Netherlands: Academic Medical Center, Department of Medical Informatics.

Evans, C., Tavakoli, M., & Crawford, B. (2004). Use of quality adjusted life years and life years gained as benchmarks in economic evaluations: a critical appraisal. *Health Care Management Science, 7*, 43–49.

Gold, M. R., Siegel, J. E., Russell, B., & Weinstein, M. C. (1996). *Cost Effectiveness in Health and Medicine*. Oxford University Press, New York.

Gordon, E. J., Butt, Z., Jensen, S. E., Lehr, A. L.-M., Franklin, J., Becker, Y., … Abecassis, M. M. (2013). Opportunities for shared decision making in kidney transplantation. *American Journal of Transplantation, 13*, 1149–1158.

Gupta, R. D., & Kunda, D. (1999). Theory & methods: Generalized exponential distributions. *Australian & New Zealand Journal of Statistics, 41*(2), 173–188.

Held, P. J., Kahan, B. D., Hunsicker, L. G., Liska, D. D., Wolfe, R. A., Friedrich, P. K., … Krakauer, H. (1994). The impact of hla mismatches on the survival of first cadaveric kidney transplants. *New England Journal Medicine, 331*, 765–770.

Hornberger, J., & Ahn, J. (1997). Deciding eligibility for transplantation when a donor kidney becomes available. *Medical Decision Making, 17*, 160–170.

Lawless, J. F. (2011). Statistical Models and Methods for Lifetime Data. *Wiley Series in Probability and Statistics*. Wiley.

Lee, E. T., & Wang, J. (2003). Statistical Methods for Survival Data Analysis. *Wiley Series in Probability and Statistics*. Wiley.

Lefaucheur, C., Loupy, A., Hill, G. S., Andrade, J., Nochy, D., Antoine, C., … Suberbielle-Boissel, C. (2010). Preexisting donor-specific hla antibodies predict outcome in kidney transplantation. *Journal of the American Society of Nephrology, 21*(8), 1398–1406.

Su, X., & Zenios, S. (2004a). Incorporating recipient choice in kidney transplantation. *Journal of the American Society of Nephrology, 15*(6), 1656–1663.

Su, X., & Zenios, S. (2004b). Patient choice in kidney allocation: the role of the queueing discipline. *Manufacturing & Service Operations Management, 6*(4), 280–301.

Su, X., & Zenios, S. (2006). Recipient choice can address the efficiency-equity trade-off in kidney transplantation: a mechanism design model. *Management Science, 52*(11), 1647–1660.

US HRSA/OPTN, (2008a). (Organ Procurement and Transplantation Network) Policy 3.5, Organ distribution: allocation of deceased kidneys, OPTN/SRTR, 2006 Annual Report.

US HRSA/OPTN-SRTR, (2008b). (Organ Procurement and Transplantation Net-work and the Scientific Registry of Transplant Recipients), Optn/srtr, 2006 annual report.

Vereestraeten, P., Abramowicz, D., Andrien, M., Dupont, E., Depauw, L., & Kinnaert, P. (1999). Allocation of cadaver kidneys according to hla- dr matching alone would result in optimal graft outcome in most recipients. *Transplantation Proceedings, 31*, 739–741.

Yuan, Y., Feldhamer, S., Gafni, A., Fyfe, F., & Ludwin, D. (2002). The development and evaluation of a fuzzy logic expert system for renal transplantation assignment: is this a useful tool? *European Journal of Operational Research, 142*(1), 152–173.

Zenios, S. A., Cherow, G. M., & Wein, L. M. (2000). Dynamic allocation of kidneys to candidates on the transplant waiting list. *Operations Research, 48*(4), 549–569.