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Optimizing Live Kidney Donor Workup: A Decision Analysis Approach

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Background. Screening potential live kidney donors is an intense process for both candidates and the healthcare system. It is conventionally implemented using a standard generic protocol. Efficiencies in this process could potentially be achieved using personalized protocols that are optimized for a given candidate. Aim: To create personalized protocols (by age, sex, and paired exchange status) and evaluate them relative to the standard generic protocol. **Methods.** Two personalized protocols were created. One sequenced tests according to probability (high to low) of excluding a given candidate. The other sequenced tests according to the expected cost (low to high) per exclusion. Test costs and exclusion probabilities were extracted predominantly from Australian sources. These were integrated into a decision analysis incorporating Markov processes. This estimated the expected financial cost and expected number of tests performed to exclude an ineligible candidate in the standard generic and personalized protocols. **Results.** The standard generic protocol consistently ranked poorest in terms of expected costs and expected tests per exclusion across all ages, sexes, and paired exchange status. Compared with the most efficient personalized protocol, the standard generic protocol was on average A\$1767.49 more expensive and required 3.53 more tests. **Conclusions.** Personalized protocols enhance the ability of a kidney transplant unit to effectively exclude live kidney donor candidates more quickly and cost effectively compared with the conventional standard generic protocol.

(*Transplantation Direct* 2018;4: e340; doi: 10.1097/TXD.0000000000000777. Published online 5 April, 2018.)

Received 10 January 2018. Revision requested 15 March 2018.

Accepted 27 January 2018.

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The authors declare no funding or conflicts of interest.

J.Y.C. participated in data extraction, model design, and prepared the article. A.M. participated in model design and prepared the article. G.R. participated in data extraction. B.A.C. provided oversight of research.

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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.transplantationdirect.com).

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000000777

Workup of live kidney donors is an arduous and expensive process. For the potential donor, these costs include opportunity costs to visit medical appointments, exposure to harm, and emotional burden. For the healthcare system, the costs are both monetary (for example, tissue typing A\$3988.54) as well as in manpower and resources. Minimizing both number of tests performed and healthcare cost are therefore important in live donor workup.

Currently, across most Australian hospitals, donor candidates follow a fixed algorithm (SDC, Protocols <http://links.lww.com/TXD/A77>) to guide the order of medical investigations. There is no standard in order or number of investigations, although principles for Australian transplanting hospitals have been laid out.¹ Although simple, this does not consider the circumstances of the individual candidate. As a result, inefficiencies are inevitable. For instance, an older candidate is more likely to have accumulated comorbidities, such as diabetes, obesity, and hypertension.² Therefore, it may be more efficient to evaluate for this earlier. By contrast, younger patients generally have fewer comorbidities; therefore, tissue typing to exclude these donors early may be of higher yield. We propose personalizing a protocol for each donor based on demographics.

Further, donors undergo several tests (as part of each stage) before they are reassessed. At our center, first stage investigations include basic blood tests, urine analysis, chest

x-ray, electrocardiography, and a psychiatric evaluation. Results are only delivered at the end of each stage rather than after each test. Consequently, there may be an increased number of redundant tests. This exposes candidates to additional costs and risks, for example, acute kidney injury and radiation exposure due to a computed tomography (CT) renal angiogram. False positives also occur, triggering otherwise unnecessary referrals to relevant specialists and emotional concern.³ Costs accumulate for the healthcare system by association. Our proposed solution is therefore to reassess donor suitability after each test.

In contrast to the current 3 stage standard protocol, our 10 stage personalized protocol sequences tests according to demographic parameters (in this article, age, sex, and if the candidate is willing to undergo paired kidney exchange). This has the potential advantage of minimizing the number of tests needing to be performed. The basis of a “probability based protocol” (PBP) sequences tests from most likely to least likely to exclude candidates. Another approach is to prioritize cost efficiency: a “cost-effectiveness-based protocol” (CBP) where tests are sequenced from most cost effective (ie, cheapest cost per donor exclusion) to least cost effective (most expensive cost per donor exclusion).

Decision analysis is a strategy used to evaluate complex alternatives accounting for uncertainty.⁴ In this case, it is used to determine which protocol performs optimally—minimizing number and cost of tests performed. A decision tree is created by mapping all of a clinical problem's possible pathways, relationships (probabilities of passing or failing each stage), and outcomes.⁵ To our knowledge, decision analysis has not been applied to optimize the workup of candidates in its entirety.⁶

AIMS

To create and compare 2 personalized protocols (probability based and cost effectiveness based) to the current local 3-stage protocol with regard to mean cost and tests per patient in live kidney donor candidates aged 25 to 64 years.

MATERIALS AND METHODS

The current screening protocol was disassembled into 10 testing stages. These stages were sequenced to form 1 of 2 new types of screening strategy tailored to age group (25-34 years, 35-44 years, 45-54 years, 55-64 years), sex, and willingness to participate in paired kidney exchange. The 2 new types of screening strategy sequenced the test stages (from low to high) in terms of either: (1) the probability of passing a test stage or (2) the average cost per screen-fail (eg, a A\$250 test that had a 20% probability of eliminating a candidate has an average cost per screen-fail of A\$1250). These strategies were respectively labeled the “probability-based protocol” and the “cost-effectiveness-based protocol.” The cost for each test was obtained from the Medicare Benefits Scheme in 2017 Australian dollars.⁷

We assumed that the probability of successfully passing a testing stage depended only on age and sex and not the order in which the test stage arose. The probability estimates used were informed by the results of a systematic literature search. MEDLINE inclusion criteria included adults, large studies (preferably $n > 1000$), and a significant proportion of whites (to reflect Australian demographics). Data from Australian cohorts or specifically pertaining to live kidney donors were

favoured. Parameters of study included were deemed to be core in donor suitability.⁸⁻¹⁰ They included obesity, history of gestational diabetes, uncontrolled hypertension, affective disorders, hematuria, albuminuria, proteinuria, left ventricular hypertrophy, valvular heart disease, hepatitis B, hepatitis C, human immunodeficiency virus, estimated glomerular filtration rate less than 80 mL/min per 1.73 m², diabetes, tissue typing, sestamibi abnormalities, anatomical renal tract abnormalities; or significant electrocardiogram (ECG), chest x-ray, electrolyte, liver function or full blood count abnormalities precluding surgery. Red Cross Australia data were collected for probability of positive complement dependent cytotoxic cross-match; and blood group data. Further details of the chosen studies can be found in **SDC, Data Sources** (<http://links.lww.com/TXD/A77>). Where multiple studies were appropriate, 2 examiners agreed on the chosen study.

The exact sequence of tests in the PBP and CBP are age- and sex-dependent; nevertheless, some general characteristics can be described.

With the PBP, history and physical examination was the leading cause of exclusion of donor candidates regardless of age or sex. In younger age groups (25-44 years), anatomical factors (CT renal angiogram and surgical consultation) and tissue typing were the second and third causes of exclusion, whereas in older age groups (45-64 years), blood tests were the second most common cause of candidate exclusion. Chest x-ray was the least likely or second least likely test to exclude donors, irrespective of age and sex.

With the CBP, history and physical examination was the first or second most cost-effective test per donor exclusion regardless of age or sex. Electrocardiogram was generally highly ranked earlier in the sequence with the CBP than with the PBP. Further, tissue typing was the least cost-effective test in excluding potential donors in both sexes. Anatomical factors were also less favored than the PBP.

The three screening strategies (PBP, CBP, and current standard) were arranged in a decision tree with each strategy appearing as a branch emanating from an initial decision node. The branches led to a Markov process that represented the sequence through the testing stages (ie, the stage transitions) prescribed by the relevant screening strategy. The basic structure of the decision tree is illustrated in Figure 1. The probability of passing through a given test stage was used as the corresponding transition probability in the Markov processes. The transition probabilities are presented in **SDC, Data Sources** (<http://links.lww.com/TXD/A77>). The analysis was performed in TreeAge Pro 2016.¹¹

The uncertainty surrounding each transition probability (p_i) in the model was accounted for by defining each as a random variable with a beta distribution with mean μ_i and variance σ_i^2 . Each μ_i represented what we believed to be the best estimate of p_i , and each σ_i^2 was chosen such that 95% of the probability density fell approximately within what was considered a clinically plausible range given the uncertainty about p_i . Three levels of uncertainty were specified—low, medium, and high. Transition probabilities were assigned a σ^2 based on a coefficient of variation 5%, 10%, or 20% reflecting either low, medium, or high uncertainty. Ninety-five percent of the density of each resultant distribution fell approximately within $\pm 10\%$, 20% , and 40% of the specified μ_i . For example, the probability that a 25- to 34-year-old man would fail screening on nephrologist review was estimated to

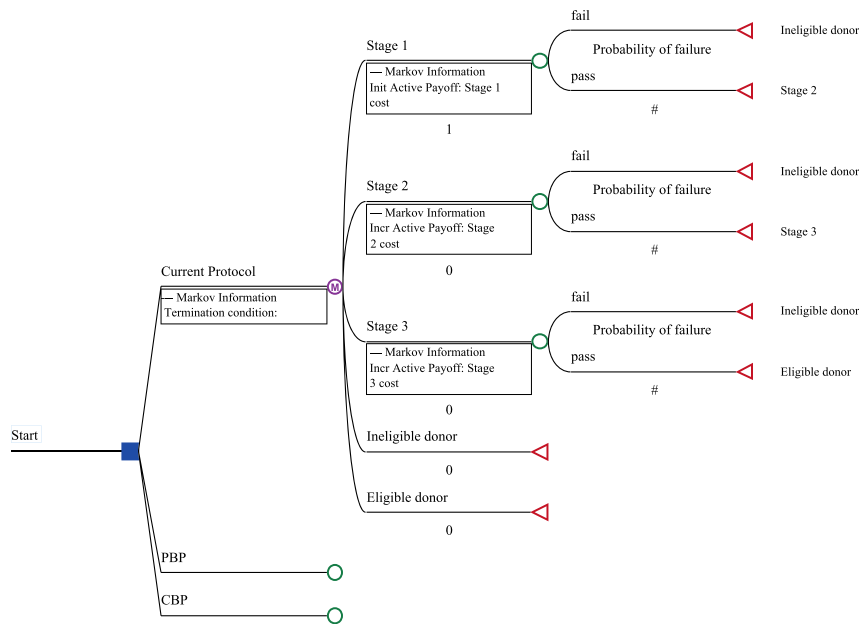


FIGURE 1. Markov model schematic.

be 0.228 with a medium level of uncertainty and thus assigned a coefficient of variation of 10%. In the decision analysis, this parameter was consequently specified as a beta distribution with $\mu = 0.228$ and $\sigma^2 = 0.0228$. Ninety-five percent of this probability distribution lies within 0.185 to 0.274, that is, a range that is approximately $\pm 20\%$ of 0.228. The cost of each test stage was assumed to be estimated with no uncertainty.

The average cost, and the average number of test stages, associated with screening a candidate under each strategy was calculated by deriving the expected values of these quantities for hypothetical cohorts. Fifty thousand candidates were run separately through each strata: by age groups, 25 to 34 years, 35 to 44 years, 45 to 54 years, 55 to 64 years; sex; and pairing status. Paired kidney exchange increases the likelihood for transplantation for eligible patients who have a willing but incompatible living donor (a “pair”). A database searches for other pairs with the hope that the opposing pair’s donor is compatible. Applying the concept to our model, a paired cohort assumed that all donors therefore pass the compatibility transition probability.

Strategies with lower expected values are recommended over those with higher expected values.

RESULTS

The current standard protocol was the least preferred strategy overall. This was consistent across all strata (defined by age grouping, sex, and participation in paired kidney exchange), as it was associated with the greatest expected costs and greatest number of tests. The CBP had the lowest expected cost at A\$2245.51 (95% credibility interval [CI], A\$1968.66-2528.96) per candidate compared with the current protocol of A\$3992.85 (95% CI, A\$3601.65-4370.14). The PBP was associated with the lowest expected number of tests at 4.43 (95% CI, 3.95-4.92) tests compared with 7.95 (95% CI, 7.61-8.27) for the current protocol.

Figure 2 provides estimates by sex and age grouping. Estimates for male and women were similar across the age groups. Overall, expected costs and expected number of tests

decreased with age across all protocols. This is to be expected because an older candidate is more likely to have pathology and therefore excluded earlier. In the unpaired younger (25-44 years) groups, there was a small difference in cost between the PBP and CBP. On average, this was A\$787.16 (95% CI, A\$98.05-1463.33). This effect was attenuated by age. This may be due to older candidates accumulating more comorbidities. This resulted in less differences observed between protocols.

Participants in paired kidney exchange (ie, ignoring exclusion by tissue typing) exerted differing effects on PBP, current and CBPs. In the PBP, it decreased the average cost of exclusion. In males aged 35 to 44 years for instance, cost was A\$2821.56 (95% CI, A\$2521.92-3121.92) compared with A\$3606.84 (95% CI, A\$3249.01-3957.65) unpaired. This is explained by tissue typing (the most expensive stage) being relegated as the final stage in the PBP in paired candidates (due to 0% chance of failure). Therefore, less candidates reached this stage. As a result, there was an associated trend of increased number of tests from 4.96 (95% CI, 4.51-5.4) tests unpaired to 5.44 (95% CI, 4.93-5.93) paired. Again, this effect was attenuated with increased age. By contrast, the effect of pairing on the current protocol was minimal. Similar to the PBP, there was a trend to an increasing number of tests performed. Dissimilarly, there was a trend to an increase in cost. This is because this 0% failure probability nonetheless accumulated the cost of tissue typing. Unlike the PBP, tissue typing remained as part of the protocol’s stage 2. Completion of this stage finishes 90% of individual tests. Pairing had no effect on the CBP’s outcomes. This is because tissue typing consistently ranked as this protocol’s final stage.

DISCUSSION

The implication of this research suggests the need to move toward a personalized workup of kidney donors. As far as the authors are aware, this is the first quantitative research exploring the impact of a personalized donor screening pathway for live kidney donation. Although the authors recognize

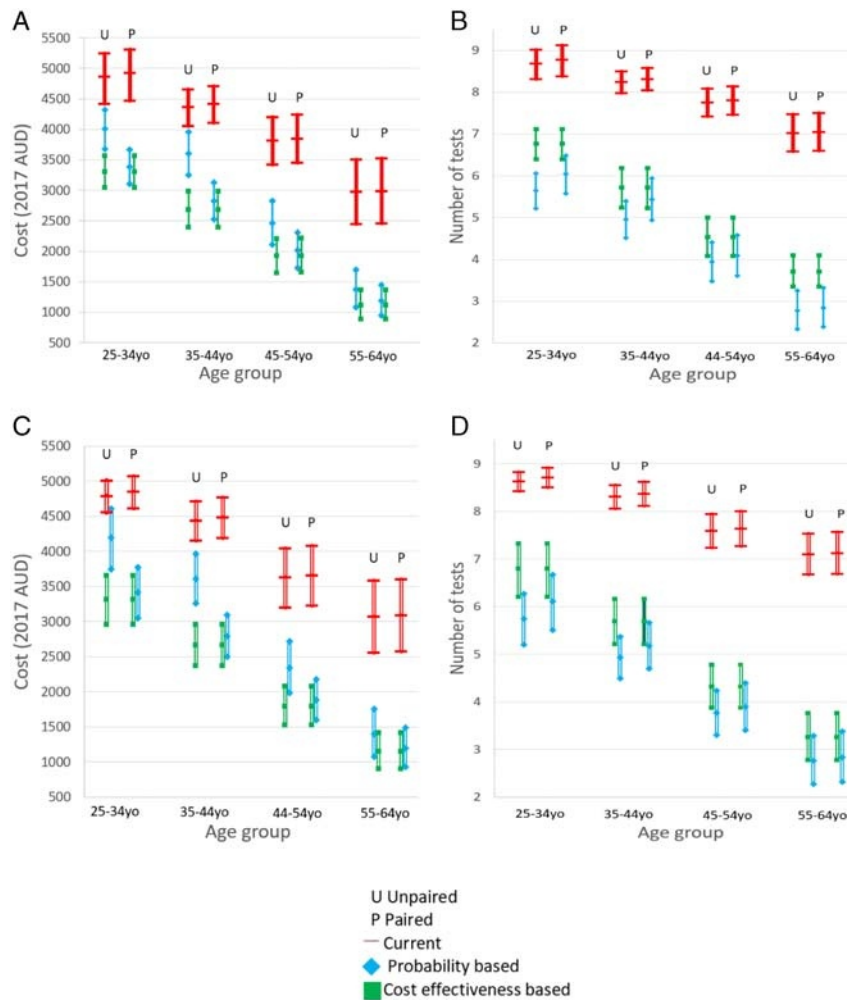


FIGURE 2. A, Mean cost (male). B, Mean number of tests (male). C, Mean cost (female). D, Mean number of tests (female).

standardized protocols exist to promote consistency,¹² this research adds weight to favoring specific protocols targeting individuals on a case-by-case basis.¹³

Although the personalized protocols are superior to the current protocol, there was no clear superior protocol in comparing PBP and CBP. Clinician judgment is important in choosing the strategy chosen. For example, PBP favors CT renal angiogram in the first half of the workup, whereas CBP defers this test. In a young patient, the clinician may therefore opt to choose the CBP to attempt to postpone radiation exposure.

Key assumptions in this study are (a) external validity of data (b) real world applicability.

Concerning external validity, this study is limited by the use of multiple data sources. This involves heterogenous populations (including ethnicity and year of study). This selection bias may compromise our estimates. However, to the authors' knowledge, there is no single body of data available from which all parameters could be drawn from. Collinearity is also likely an issue. For example, it is likely that those with hypertension are also more likely to have obesity and diabetes. These parameters were treated separately within our protocol. Therefore, we used a certainty-probability matrix to create compensatory standard deviations. Together with the probabilistic sensitivity analysis, this minimized the impact of uncertainty

on our results. Further variables can also be built into future models, including candidates excluded due to cancer.

Regarding real world application, practicality needs to be considered. Personalized protocols have more stages with less individual tests per stage. Given more stages each comprising less tests, it may be argued this will lead to more phone calls to receive results. On the other hand, the current protocol has less stages comprising more tests per stage. Because of this testing in bulk, it may be countered that just as many (if not more) phone calls may be required to receive results. Take for example a male candidate aged 55 to 64 years. By the current protocol, on average, he would get blood, urine analysis, a chest x-ray, ECG, see a psychiatrist, have echocardiography, a sestamibi, tissue typing, and nephrologist review (Figure 2B; **SDC, Protocols** <http://links.lww.com/TXD/A77>). Although he only requires—on average—7 tests to be excluded, the staged nature of the current protocol means 9 tests are performed. In our local district, this would require at least 5 visits (if bloods, urine, chest x-ray, and ECG were done on the same visit; psychiatry; echocardiography; sestamibi; tissue typing done with a nephrologist visit), and tracking of 9 test results. This contrasts with the same candidate undergoing the PBP. On average, he would see a nephrologist, undergo baseline blood tests, then sometimes an echocardiogram before being excluded (Figure 2b; **SDC,**

Protocols <http://links.lww.com/TXD/A77>). This would require the donor candidate to present 3 times, and the coordinator tracking down 3 results. This is 6 less test results to pursue on average in this example. Therefore, personalized protocols may decrease the amount of work required to pursue results.

Hypothetically, if increased manpower was required, however, personalized protocols would still be justified. The authors' district is staffed by a 0.5 full time equivalent renal transplant nurse. This costs approximately A\$1000 per week.¹⁴ Approximately 40 donor candidates have entered the authors' workup process in the full year of 2017. This represents less than 1 new candidate per week. If the role was to be expanded to 1 full time equivalent, this would increase the transplant unit's expenses by approximately A\$50 000 per year. Assuming a steady flow of 40 new candidates per year, this would increase cost by approximately A\$1250 per candidate. This is still more cost effective than the current protocol for any age group or sex in the CBP (and for most of those in the PBPs).

Another unmeasured offset we have not quantified in this study is the minimization of opportunity cost to the economy. As donor candidates undergo multiple rounds of testing, they incur time and monetary expense travelling to and from healthcare settings. As in the above example of the 55- to 64-year-old men (generally in the prime of earning capacity), the PBP decreases the required visits to hospital from 5 to 3. This means less opportunity cost to the economy by minimizing productivity loss.

Ultimately personalized protocols need to be trialed empirically to assess impact on manpower. It may decrease the manpower required. However, even if more is needed, it will likely still be cost effective. Other economic benefits have not been studied in this preclinical project.

CONCLUSIONS

Personalized protocols optimize live kidney donor workup by targeting patient demographics and reevaluating donor progress earlier. Across compared protocols, the PBP demonstrated minimization in number of tests performed compared

with the current protocol. The CBP demonstrated minimization of cost. This was consistently present across all subgroups—age, sex, and participation in paired exchange. Principles of this research are relevant for real-world translation across kidney transplant, as well as the wider world of live organ donor workup.

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