Received: 18 April 2022 | Revised: 29 August 2022 | Accepted: 15 September 2022 | Published on: 26 October 2022

DOI: 10.1002/nav.22083

RESEARCH ARTICLE

WILEY

Predicting older-donor kidneys' post-transplant renal function using pre-transplant data

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Funding information
Agency for Healthcare Research and Quality, Grant/Award Number: R03-HS27671-01; U.S. Department of Health and Human Services; University of Texas at Austin.

Abstract

This paper provides a methodology for predicting post-transplant kidney function, that is, the 1-year post-transplant estimated Glomerular Filtration Rate (eGFR-1) for each donor-candidate pair. We apply customized machine-learning algorithms to pre-transplant donor and recipient data to determine the probability of achieving an eGFR-1 of at least 30 ml/min. This threshold was chosen because there is insufficient survival benefit if the kidney fails to generate an eGFR-1 $\geq$ 30 ml/min. For some donor-candidate pairs, the developed algorithm provides highly accurate predictions. For others, limitations of previous transplants' data results in noisier predictions. However, because the same kidney is offered to many candidates, we identify those pairs for whom the predictions are highly accurate. Out of 6977 discarded older-donor kidneys that were a match with at least one transplanted kidney, 5282 had one or more identified candidate, who were offered that kidney, did not accept any other offer, and would have had $\geq$80% chance of achieving eGFR-1 $\geq$ 30 ml/min, had the kidney been transplanted. We also show that transplants with $\geq$80% chance of achieving eGFR-1 $\geq$ 30 ml/min and that survive 1 year have higher 10-year death-censored graft survival probabilities than all older-donor transplants that survive 1 year (73.61% vs. 70.48%, respectively).

KEYWORDS
machine-learning, older-donor kidneys, post-transplant renal function

1 | INTRODUCTION

In the US, the demand for transplantable kidneys outstrips the supply. As of January 30, 2022, 97 796 people were registered on the national kidney transplant waitlist, but only 18 699 received a deceased-donor kidney transplant in 2021 (OPTN, 2022). Additionally, some of the 500 000+ people currently on dialysis could benefit from access to transplants (USRDS, 2021). The Organ Procurement and Transplantation Network's (OPTN's[1]) metric of transplant success is that the recipient should be alive and off dialysis at the 1-year transplant anniversary (SRTR, 2020). This confounds two outcomes: recipient survival and freedom from dialysis. While the latter cannot exist without the former, factors that affect recipient's death, such as strokes, heart attacks, tumors, and infections, are often not related to those that affect freedom from dialysis, that is, the renal function, measured by the estimated Glomerular Filtration Rate (eGFR) (ml/min/1.73 m^2). Because younger-donor kidneys have higher chances of achieving the OPTN success metric, Transplant Programs (TxPs) prefer younger donors and recipients with fewer comorbidities. Conversely, TxPs are more risk-averse when deciding whether to transplant *older-donor* (55+ years of age) kidneys because they provide lesser renal function.

[1]A list of abbreviations used throughout this paper is available in Online Appendix A.

TxPs receive prodigious amounts of data on each donor and, per OPTN policy, they have 1 h in which to make an accept or decline decision on behalf of their candidates. To help TxPs, OPTN has provided several composite measures of donor quality over time, such as Standard versus Expanded Criteria Donor—see Rao et al. (2009) for an explanation and shortcoming of this dichotomy. The current measure of donor quality utilized by the transplant community is the Kidney Donor Risk Index (KDRI) (Rao et al., 2009), and its normalized version, the Kidney Donor Profile Index (KDPI) (UNOS, 2020), which captures the relative risk of graft failure. The *survival benefit*, that is, the 1–5 year post-transplant patient and graft survival probabilities, are correlated with KDPI. Older-donor kidneys have higher KDPI and therefore lower aggregate survival benefit. However, kidneys that survive 1 year and have similar values of KDPI often result in different kidney function. Consequently, a natural progression in helping TxPs quantify the risk and benefit of performing a transplant is based on the amount of renal function that is provided by the transplant (Gill et al., 2003; Kasiske et al., 2011).

This paper develops a methodology for predicting the 1-year post-transplant renal function (assessed by eGFR-1) for surviving transplanted kidneys. Reasons for focusing on older donors are: (i) they present the greatest opportunity to increase kidney supply (Klassen et al., 2016), (ii) they have higher discard rates (40.8% vs. 12% among younger donors), and (iii) long-term outcomes are worse for older-donor transplants (5 and 10-year graft survival probabilities among older vs. younger-donor transplants are 80.4%, 65.5% vs. 86.8%, 75.7%, respectively). Similarly, reasons for focusing on 1-year renal function are: (i) Kasiske et al. (2011) have demonstrated that long-term kidney survival correlates well with eGFR-1, and (ii) Gill et al. (2003) have observed that many patients who survived 6 months after transplant had either no consequent change or improvement in eGFR. Neither study provides a methodology to predict eGFR-1, nor do they focus on older donors. Our approach consists of predicting the probability that a donor-recipient pair will achieve a specified minimum eGFR-1 using their pre-transplant data. It is independent of the selected eGFR-1 threshold. However, because only 15% of the transplants come from older donors and the average eGFR-1 among this cohort is less than 50 ml/min, prediction reliability suffers upon choosing a minimum eGFR-1 threshold >30 ml/min. We therefore focus on 30 ml/min. This specific threshold is clinically significant because it is one of the six eGFR stages (KDIGO, 2012) of Chronic Kidney Disease (CKD), it is familiar to practitioners, and Pruett et al. (2021) showed that there was no transplant benefit relative to remaining on dialysis if the kidney achieved an eGFR-1 < 30 ml/min.

Our probabilistic prediction is referred to as the *Transplant Risk and Benefit* (TRB) score. While the benefit component is denoted by b, the risk is 1 minus the TRB score. In this paper, we only consider the TRB score associated with a minimum eGFR-1 level of $b = 30$. We label a transplant as *viable* only if the risk of not achieving the benefit level is sufficiently low (≤ 0.2). If a donor-candidate pair does not meet the viability threshold, then our methodology for classifying transplants may not provide useful additional information to clinicians. This is a limitation of the data, which contains relatively few older-donor transplants. Although we are not able to reliably quantify the risk of every potential transplant, we can identify several candidates for each older-donor kidney for whom the TRB score would have been sufficiently high had the transplant been performed. We apply this approach to discarded older-donor kidneys and their matched candidates to identify the number of viable transplants.

We found that 5282 older-donor discarded kidneys had TRB ≥ 0.8 for at least one candidate. Had these kidneys been transplanted, they would have achieved average 1 and 10-year[2] death-censored graft survival probabilities of 94.69% and 73.61%, respectively, which are higher than the realized survival probabilities of 92.57% and 70.48%, respectively, among older-donor transplants in the data. Moreover, based on the findings in Gill et al. (2003), it is expected that most of these candidates would have maintained a similar level of renal function 5 years post-transplant. Given an estimated annual cost of $90 602 per dialysis candidate (USRDS, 2019), a better utilization of discarded kidneys could result in significant savings for US taxpayers.

1.1 | Contribution

Although some older-donor kidneys (mostly high-KDPI kidneys) can provide significant survival benefit (Massie et al., 2015; Merion et al., 2005), they are often discarded because TxPs find it difficult to identify which recipients could have ex-ante benefited from which kidneys. Our approach uses innovative data processing, feature selection, predictive algorithms, and simulated match-runs to associate pre-transplant data with probabilistic prediction of post-transplant renal function, which helps identify transplants with a high probability of achieving eGFR-1 of at least 30 ml/min.

1.2 | Potential implementation and impact

If our approach were to be implemented, OPTN would provide the TRB score to TxPs for each older-donor and candidate pair, adding one field to the DonorNet.[3] To prevent accumulation of Cold Ischemia Time (CIT), the OPTN may ask TxPs to pre-specify the maximum level of risk (1-TRB)

[2]The 10-year graft survival probabilities are conditional on the patient and the graft surviving 1 year.

[3]DonorNet is a web-based tool that allows Organ Procurement Organizations (OPOs) to launch match runs and make organ offers to TxPs, https://unos.org/technology/unet/.

they are willing to accept from older-donor kidneys, similar to how they currently specify whether they will consider high-KDPI (>85%) kidneys. The magnitude of the benefit of our approach would depend on two factors: the acceptable level of risk associated with eGFR-1, and the degree to which TxPs adopt algorithmic risk-assessment based utilization of kidneys. For some levels of risk tolerance (e.g., ≥ 0.3), our approach could potentially have both life-saving (more transplants) and life-improving (higher eGFR-1) impacts. For stricter requirements (e.g., ≤ 0.2), it is likely that our approach will be even more life-improving, but may lead to fewer transplants. A detailed evaluation of the trade-off between the risk and benefit of transplantation and the availability of kidneys is outside the scope of this paper.

2 | LITERATURE REVIEW

A consensus report by the National Academies of Sciences, Engineering and Medicine, (Kizer et al., 2022, Chapter 2), provides a detailed overview of the US Organ Transplantation System. Many papers in the Operations Research/Management literature deal with the distribution and allocation of organs, modeling of recipients' accept-decline decisions, and mitigating geographical disparities—see for example, Arkan et al. (2018), Ata et al. (2017), Barah and Mehrotra (2021), and Bertsimas et al. (2013). Recent surveys are available in Ersoy et al. (2021) and Ata et al. (2018). There is also significant biomedical literature on all aspects of kidney transplantation. We do not discuss these streams of literature because they are not directly related to our work. Instead, we focus on studies that predict survival and renal function using machine-learning methods and that aim to reduce organ waste.

Mark et al. (2019) use an ensemble of statistical methods to predict kidney transplant survival and identify important predictive variables. Yoo et al. (2017) expand the set of variables used to predict graft survival to include immunological factors. They apply ensemble-learning algorithms to predict graft survival, compare their predictions with those of straw-man algorithms like decision trees and Cox regression (Cox, 1972), and establish the superiority of using ensemble methods. Barah and Mehrotra (2021) use machine-learning techniques to predict whether a kidney will be discarded. They find that Random Forest performs the best, with an Area Under the ROC Curve (AUC) of 0.888. However, they find that the AUC decreases to 0.814 when the Random Forest algorithm is applied to kidneys with KDPI > 85%, the majority of which come from older donors. In another study, Topuz et al. (2018) address the problem of selecting important features to predict graft survival at the 1, 3, 5, 7, and 9 year cutoff points. They use a combination of machine-learning methods and achieve an average accuracy of 0.684. Similar to ours, these papers utilize machine-learning tools to predict the outcome of kidney transplants. However, our approach is different because we predict eGFR-1 (not graft survival or kidney discards), we focus specifically on older-donor kidneys, for which prediction is more challenging due to limited data availability, and we apply our prediction model to a carefully selected set of discarded kidneys to estimate the potential impact of using the TRB score.

Lasserre et al. (2012) is the only paper that applies machine-learning techniques to pre-transplant data from 707 Eurotransplant donor and recipient characteristics to predict eGFR-1. They do not focus specifically on older-donor transplants, although they noted that age of the donor is the strongest factor for allograft function. Additionally, our algorithms maximize the positive predictive value (PPV) of renal function of older-donor transplants because our goal is to maximize the reliability of prediction when the algorithms are applied to discarded kidneys.

Some recent papers, summarized in Table 1, share our motivation of reducing organ waste. These papers use myriads of analytical/empirical techniques. Our perspective is different because we focus on predicting the transplant outcome using pre-transplant data and demonstrate how this could help increase the utilization of some discarded kidneys. In addition to these papers, Dai et al. (2020) analyze the welfare consequences of introducing a donor-priority rule, which grants registered donors priority in receiving organs if they need transplants in the future. Although not focused on reducing organ waste, its aim is to increase organ supply via increased registrations, for which family authorization is not necessary. The authors also propose a priority-freeze rule that guarantees an improvement in social welfare.

3 | DATA: DESCRIPTIVE STATISTICS

Two sets of de-identified data from January 1, 2000 through December 31, 2018 were obtained from OPTN: (i) the national Standard Transplant Analysis and Research (STAR) file, containing information on deceased older donors, waitlisted candidates, transplants, and outcomes, and (ii) the match-run data, comprised of transplanted and discarded kidney offers. Because 1-year post-transplant data were needed to calculate outcomes, only transplants performed up to December 31, 2017 were considered. After performing data processing steps (see Section 4.1 for details), we obtained our study cohort of 11 527 older-donor transplants. The descriptive statistics of donors in the study cohort and their recipients are shown in Table 2. This table also includes characteristics of donors of 6977 discarded kidneys (for which there are no recipients) that were similar to kidneys in the study cohort.

We calculated eGFR-1 from recipients' 1-year serum creatinine (S_{cr}) using the CKD_EPI equation (Levey & Stevens, 2010), which is

TABLE 1 Summary of articles focusing on reducing kidney waste

Article	Objective	Key results
Arora and Subramanian (2019)	Identify possible misalignments in the objectives of the social planner, the Organ Procurement Organization (OPO), and the donor hospital to improve quality-adjusted life-years (QALYs) from recovered organs (reduce waste) and possible mechanisms to alleviate such misalignments.	There exists thresholds of donor hospitals operating room utilization that determine when donors of different quality (in terms of QALYs) should be prioritized for authorization and recovery.
Ata et al. (2021)	Identify candidate ranking policies, based on donor and candidate characteristics, that achieve optimal efficiency-equity tradeoff among all such policies.	The set of affine policies in patient waiting times contains an optimal policy. Total QALYs can be increased substantially by allowing patient rankings to depend on the kidney quality.[a]
Wang et al. (2022)	To estimate the amount by which the existence or introduction of an airline route between two airports affect the number of kidney transplants between donors and recipients connected by those airports.	The introduction of a new airline route increases the number of shared kidneys by 7.3%, with a concomitant net increase in the total number of kidney transplants and a decrease in the organ discard rate. Furthermore, the post-transplant survival rate remains largely unchanged.
Tunç et al. (2022)	Self-interested individuals utilize fewer kidneys than what would be socially optimal, in part because of the cost of returning to the retransplantation queue. The authors study the effect of a mechanism for compensating individuals when they return to the transplant queue on organ utilization and social welfare.	Following the use of the proposed incentive, the discard rate may change, ranging from a low of 6.2% (strong population response) to 15.1% (weak response), which may lead to between 1630, and 338 more transplants per year, respectively. The 1-year post-transplant survival and the quality of transplants deteriorate by a small amount.

[a] From a managerial perspective, our results are consistent with this study, that is, matching older-donor kidneys with specific candidates can reduce kidney waste while maintaining similar outcomes.

TABLE 2 Descriptive statistics of key variables (IQR = interquartile range)

	Transplanted kidneys similar to discarded	Discarded kidneys similar to transplanted
Sample size (*n*)	11 527	6977
Donor characteristics		
Median (IQR), mean age (years)	60 (57–64), 60.79	62 (58–67), 62.76
Median (IQR), mean weight (kg)	77.6 (67.5–89), 78.95	77.11 (67–89.81), 79
Median (IQR), mean creatinine (mg/dl)	0.9 (0.7–1.17), 0.99	1 (0.8–1.3), 1.09
Median (IQR), mean KDPI	0.84 (0.75–0.91), 0.82	0.9 (0.82–0.95), 0.88
% Female	51.09	52.26
% Caucasian	79.74	78.96
% African-American or Black	4.75	6.49
% Hispanic	11.83	9.60
% Asian	3.13	3.1
% Other races	0.55	1.85
% Death due to stroke	70.51	74.34
% Biopsy performed	86.81	90.6
Recipient characteristics		
Median (IQR), mean age (years)	61 (53–67), 59.44	NA
Median (IQR), mean weight (kg)	80.1 (68.6–93), 81.51	NA
Median (IQR), mean creatinine (mg/dl)	7.4 (5.57–9.66), 7.85	NA
% Female	38.46	NA
% Caucasian	44.98	NA
% African-American or Black	30.42	NA
% Hispanic	14.63	NA
% Asian	7.69	NA
% Other races	2.28	NA

Note: Row-wise comparison shows that the categorical variables of the matched transplanted and discarded kidneys are similar to each other, while for the continuous variables, matched discarded donors tend to be slightly older, have higher creatinine and higher KDPI than the similar transplanted donors.

$$\text{eGFR} - 1 = \begin{cases} 141 \times \min\left\{\frac{S_{cr}}{0.7}, 1\right\}^{-0.329} \times \max\left\{\frac{S_{cr}}{0.7}, 1\right\}^{-1.209} \\ \quad \times 0.993^{\text{Age}} \times 1.018 \times 1.159 \quad \text{[if Black]} \\ \qquad\qquad\qquad\qquad\qquad\qquad \text{if female,} \\ 141 \times \min\left\{\frac{S_{cr}}{0.9}, 1\right\}^{-0.411} \times \max\left\{\frac{S_{cr}}{0.9}, 1\right\}^{-1.209} \\ \quad \times 0.993^{\text{Age}} \times 1.159 \quad \text{[if Black]} \\ \qquad\qquad\qquad\qquad\qquad\qquad \text{if male,} \end{cases} \tag{1}$$

Although alternate methods for calculating eGFR exist, for example, the Cockroft-Gault formula, CKD_EPI equation is a widely accepted method and it is more accurate over a broad range of eGFR values (NIDDK, 2020). There have been recent attempts to eliminate race as a variable in calculating eGFR-1, because race is not a biological construct (NKF and ASN, 2021). If the equation for calculating eGFR-1 were to change, then our analysis would have to be repeated. However, this would not affect the methodology proposed in this paper.

Next, we present two key observations that motivate this study. We focus on eGFR categories of CKD stages (KDIGO, 2012) instead of continuous eGFR because they are familiar to candidates.

Observation 1 CKD stages of eGFR-1 better stratify death-censored 1–10 year graft survival than KDPI strata.

To compare eGFR-1 and KDPI, we found how many kidneys achieved each CKD stage and the corresponding KDPI threshold that resulted in the same number of transplants. There were 1635 (14.2%) transplants with eGFR-1 of 0–29 (corresponding KDPI of 0.95–1.0), 3752 (32.5%) with 30–44 (KDPI of 0.85–0.95), 3563 (30.9%) with 45–59 (KDPI of 0.73–0.85) and 2577 (22.4%) with 60+ (KDPI $\leq$ 0.73). Figure 1 shows the Kaplan–Meier (KM) 1–10 year survival curves and 95% confidence intervals (CIs) by eGFR-1 ranges and KDPI groups. The survival probabilities are censored either by death, or by the end of observation period. A death-censored survival analysis is performed because it estimates kidney quality/outcomes after removing the effect of recipient comorbidities correlated with death. Table 3 reports the average and 95% CI 10-year graft survival probabilities of transplants achieving various eGFR-1 and KDPI levels.

Figure 1 and Table 3 show that transplants with eGFR-1 < 30 are undesirable. Moreover, the range of 10-year graft survival from best (orange dashed line) to worst (blue solid line) is 44.2% for eGFR-1 and 17.8% for KDPI, further supporting our argument that KDPI does a poor job of stratifying transplant durability, whereas the amount of eGFR at 1 year is much more discriminatory. The survival difference highlights the importance of predicting the amount of function at the 1-year transplant anniversary, rather than just whether the recipient is alive and off dialysis. Our next observation shows that KDPI strata do not predict CKD levels, justifying the need to augment KDPI with the TRB score.

Observation 2 KDPI strata do not correlate well with CKD levels for older-donor transplants.

To assert Observation 2, we tested whether kidneys belonging to different KDPI strata belong to different CKD levels. We created 5 subsets $k = 1, \ldots, 5$ of KDPI, each containing 20% of the data. For each k, let p_{ke} denote the proportion of transplants that achieved CKD level $e \in \{1,2,3,4\}$, where $e = 1$ means CKD 4/5, 2 means 3b, 3 means 3a, and 4 means 2/1, with $\sum_e p_{ke} = 1, \forall k$. Let

$$s_k = \frac{(|p_{k1} - p_{k2}| + |p_{k1} - p_{k3}| + |p_{k1} - p_{k4}| + |p_{k2} - p_{k3}| + |p_{k2} - p_{k4}| + |p_{k3} - p_{k4}|)}{3}, \tag{2}$$

be a stratification measure that captures how well KDPI level k indicates which CKD level to expect. The numerator of s_k

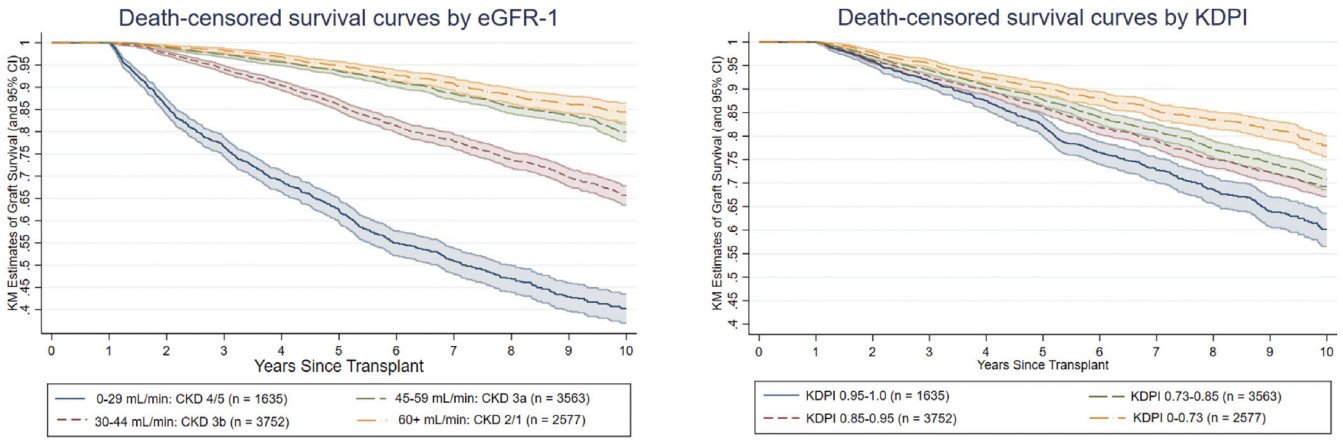

FIGURE 1 Death-censored 1–10 year graft survival curves by eGFR-1 and KDPI. The survival curves based on KDPI stratification tend to be less splayed (overlapping CIs in the middle range) than the ones based on eGFR-1. Clearly, KDPI does not stratify long-term survival as well as eGFR-1 does

TABLE 3 Average and 95% CI 10-year graft survival probabilities by eGFR-1 and KDPI ranges

eGFR-1 range (ml/min)	Average (95% CI) 10-year graft survival	KDPI range	Average (95% CI) 10-year graft survival
0–29 (CKD 4/5)	0.402 (0.367 – 0.435)	0.95–1	0.601 (0.564 – 0.635)
30–44 (CKD 3b)	0.657 (0.635 – 0.679)	0.85–0.95	0.691 (0.669 – 0.712)
45–59 (CKD 3a)	0.799 (0.779 – 0.817)	0.73–0.85	0.711 (0.689 – 0.731)
60+ (CKD 2/1)	0.844 (0.813 – 0.864)	0–0.73	0.779 (0.756 – 0.801)

Note: Stratification by eGFR-1 results in distinct 95% CIs, except for CKD 3a and 2/1, while the 95% CIs are not as far apart when stratified by KDPI.

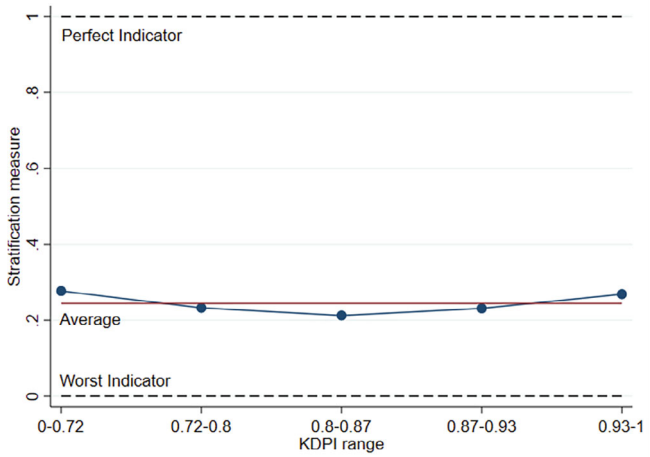

FIGURE 2 Stratification measure s_k versus KDPI. The value of the stratification measure s_k is low and constant across different ranges of KDPI

captures the magnitude of the differences in the proportions, and the denominator is used for scaling purposes. By construct, if KDPI were perfectly correlated with a particular CKD level, then $s_k = 1$, implying that for a range of KDPI, only one CKD level would be possible. If KDPI were the worst indicator, then each CKD level would occur with equal probability and therefore $s_k = 0$. The closer s_k is to 1, the better the ability to stratify CKD levels. Figure 2 shows the stratification measure s_k and the average over the five subsets of KDPI.

We find that s_k hovers slightly above 0.2 across different ranges of KDPI, thus implying that different levels of KDPI are not correlated with distinct CKD levels for older-donor transplanted kidneys that are similar to discards. This is the case even for very high KDPI values for which one would expect very high proportion of CKD 4/5.

4 | METHODS

We developed a methodology to: (1) calculate the TRB score using pre-transplant data, and (2) identify older-donor discarded kidneys that could achieve high TRB scores. The methodology can be adapted to various thresholds of eGFR-1, different sets of matched transplanted and discarded kidneys, and different age cutoffs for identifying older donors. Figure 3 depicts our approach.

4.1 | Data processing

4.1.1 | Donor study cohort

We identified a study cohort of 11 527 (≈56% of transplants) older-donor adult, single-kidney, first-time transplants that survived 1-year and did not have data entry errors or missing values of key variables. In addition, we identified 6977 discarded kidneys (≈35% of discards) whose discard reason was not a specified reason for non-use (e.g., "organ trauma," or "anatomical abnormalities"). Details of data cleaning steps are presented in Figure 4 and in Online Appendix B. Because TxPs carefully select older-donor kidneys to transplant, not all transplanted kidneys are similar to discarded ones. This selection bias was mitigated by matching the study cohorts of transplanted and discarded kidneys on 13 variables available prior to acceptance. Ten of these variables (age, cause of death, creatinine, diabetes status, whether the donation was after cardiac death, ethnicity, height, Hepatitis C status, history of hypertension and weight) were selected because they are used to calculate the KDRI. Three additional variables (gender, whether a biopsy was performed and ranges of glomerulosclerosis) were added because they are relevant for kidney acceptance decisions (Stewart et al., 2017). We considered a discarded kidney to be similar to a transplanted one if the values of its categorical variables were identical, and the values of continuous variables were within 10% of the difference between the 1st and the 99th percentile of that continuous variable to ensure that the 10% range would be reasonably small. Note that these matching criteria are stricter than aggregate-score based criteria, such as propensity score matching (Dehejia & Wahba, 2002), because each individual attribute must match. It is possible that more older kidneys in the transplanted and discarded groups were similar. However, matching by KDRI variables, biopsy outcomes, and known candidate characteristics was necessary to ensure reliable prediction of renal function on the discards.

4.1.2 | Candidate study cohort

Following the rationale behind matching donors of transplanted and discarded kidneys, recipients of the 11 527 transplanted kidneys were matched based on 6 key variables (age, diagnosis, ethnicity, gender, weight, and whether the candidate was on dialysis) with candidates who were offered the 6977 discarded kidneys. These variables were chosen because they are recorded in the STAR file for nearly every candidate at the time of registration on the national

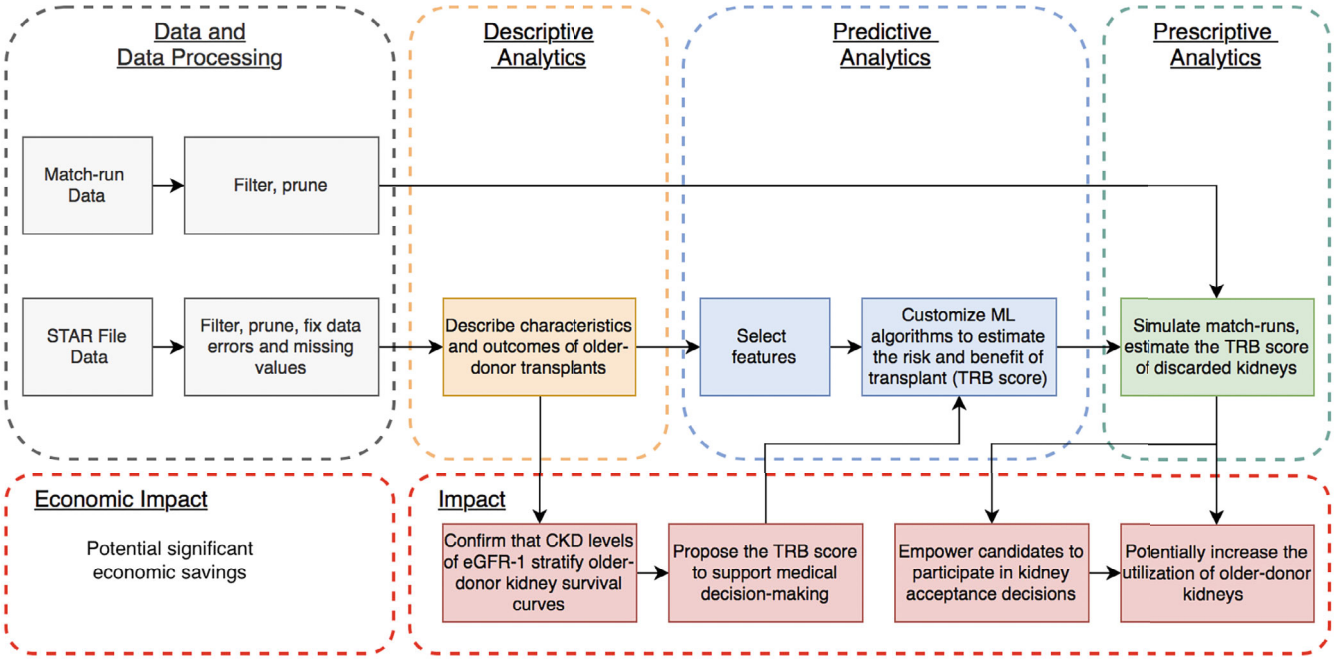

FIGURE 3 A schematic of our approach

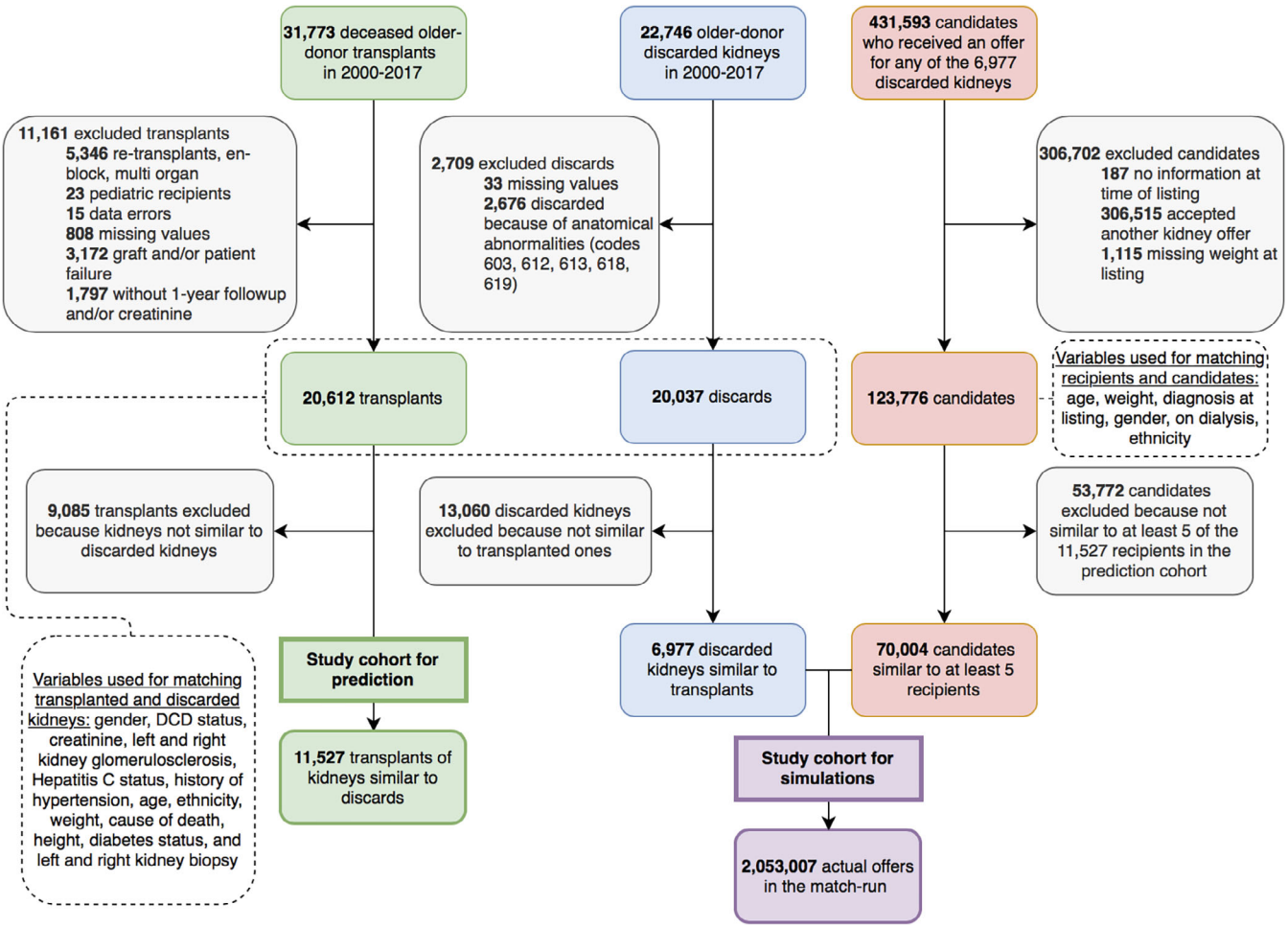

FIGURE 4 Data processing steps

waitlist. A candidate was considered similar to a recipient if the values of the categorical variables were identical and the values of the continuous variables were within 10% of the difference between the 1st and the 99th percentile of that variable. Additionally, because the STAR file does not contain full information on candidates' characteristics at the time of offer, missing data elements were imputed by matching each candidate to at least 5 other recipients for whom data were available. For each candidate and for each variable that needed to be imputed, one out of the set of 5 similar recipients was randomly selected and the value of that similar recipient's variable of interest at time of transplantation was assigned to the candidate at the time of offer. Because each candidate was matched with at least 5 recipients, this avoided creating candidates that would be clones of each other in the simulated match-runs. This procedure resulted in a final candidate cohort of 70 004. The simulated match-runs contained 2 053 007 actual offers.

From the transplanted-kidney data, all variables relevant to renal function and known at the pre-transplant stage were considered. We created binary dummy features to represent categorical variables, and some new variables—for example, the proportion of older-donor transplants performed by each TxP, which accounted for TxP-specific effects. The final data set had 916 features.

4.2 | Prediction of eGFR-1

Because the only unknown variable in the CKD_EPI equation for eGFR-1 is creatinine at 1 year, the TRB score was calculated by first predicting the creatinine value at the 1-year follow-up visit. We created multiple 70%/30% random splits of data (70% for training and cross validation, and 30% for testing) from the cohort of 11 527 older-donor transplants for feature selection and prediction algorithms.

4.2.1 | Feature selection

We used Elasticnet, which by default finds the optimal weights placed on LASSO and Ridge regressions, and the optimal penalty placed on larger coefficients through 10-fold cross-validation (Hastie et al., 2009), to determine which of the 916 features to include in the prediction model. To avoid overfitting, Elasticnet was applied to 30 random splits of training data and at each split, the intersection set of important features (those with non-zero weight) was selected. As a robustness check, we also implemented Adaptive LASSO on the 30 random splits of data and compared the selected features with those of Elasticnet.

4.2.2 | Prediction models and the TRB score

We customized and applied three prediction algorithms, namely Ordinary Least Squares (OLS), Random Forest (RF), and AdaBoost (BOOST) (Hastie et al., 2001), to the first 10 splits of training and test data to predict 1-year creatinine. We then calculated the TRB score (i.e., the probability that eGFR-1 $\geq b$) for each donor-candidate pair using the CKD_EPI equation. Proposition 1 shows how to calculate the TRB score (proof in Online Appendix C).

Proposition 1 *The TRB score can be calculated for every donor-candidate pair as*

$$\mathrm{TRB} = \Phi\left(\frac{\min\left\{\gamma, \left(\frac{b\gamma^{\alpha}}{A}\right)^{1/\alpha}\right\} - \mu_c}{\sigma_c}\right) + \left[\Phi\left(\frac{\left(\frac{b\gamma^{-1.209}}{A}\right)^{\frac{-1}{1.209}} - \mu_c}{\sigma_c}\right) - \Phi\left(\frac{\gamma - \mu_c}{\sigma_c}\right)\right]^{+}, \quad (3)$$

where, Φ *is the Standard Normal Cumulative Distribution Function*, $(\cdot)^{+} = \max\{0, \cdot\}$, μ_c *and* σ_c *denote the predicted mean and standard deviation of the forecast of 1-year creatinine*, $A \doteq 141 \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if Black}]$, $\gamma = 0.7$ *and* $\alpha = -0.329$ *if female and* $\gamma = 0.9$ *and* $\alpha = -0.411$ *if male*.

To improve the prediction accuracy, we used cross-validation to create cubic splines (with 5 knots) for donors' age, recipients' age, creatinine, and weight, and proportion of older-donor transplants by TxP. The quantiles corresponding to each knot were chosen according to the recommended values in Harrell (2015, p. 27). Table 2 in Online Appendix D shows the 5 knots for each of these continuous variables.

The goodness of the prediction algorithms was compared based on the confidence that our recommendation would be accurate, rather than on balancing false positive and false negative classifications. This was done to mitigate the selection bias introduced by TxPs that tend to transplant older-donor kidneys into older recipients because the latter are less likely to outlive the transplant. Using r to denote the risk that b will NOT be achieved, we calculate the positive predictive value (PPV) for every (b, r) combination as:

$$\mathrm{PPV} = \frac{\text{Number of transplants with TRB} \geq 1 - r \text{ and actual eGFR} - 1 \geq b}{\text{Number of transplants with TRB} \geq 1 - r}. \quad (4)$$

The most reliable algorithm is the one that provides the highest PPV. To further increase this reliability, an Ensemble (ENS) method was utilized in which a transplant was labeled as viable only if this was predicted by the two algorithms (among OLS, BOOST, RF) with the highest PPV.

4.3 | Evaluation of discarded kidneys and matched candidates

In simulated match-runs, the TRB score was calculated for each of the 2 053 007 offers in the simulation cohort. To

ensure that all matching criteria (e.g., the number of HLA mismatches) and allocation order remained intact, simulated match-runs preserved the order in which offers were made in reality. In addition, we identified the number of viable transplants among the discarded kidneys and their matched candidates. We also compared the characteristics of actual recipients and of matched candidates, and analyzed the reasons for declination by matched candidates.

5 | RESULTS

In what follows, we present the results of the prediction models and simulated match-runs.

5.1 | Prediction of eGFR-1

The intersection set of important features stabilized after 17 splits, resulting in 33 features. Table 4 shows the important variables, which are fewer than the number of features because categorical variables were converted into multiple binary features. Although clinically important, CIT was not included as a predictor because it is typically not available at the time of offer. Adaptive LASSO yielded a similar set of important variables—see Table 3 in Online Appendix E. Although either methodology could be used to select features, we selected ElasticNet as an example in this paper in part because those variables were vetted by a transplant surgeon. Table 4 in Online Appendix F provides the coefficients and significance levels of each feature obtained by OLS.

Next, we calculated the TRB score for each prediction algorithm. Patient and graft survival is affected by various peri- and post-transplant events, some of which are not captured in our data. Examples include cardiac events and strokes, antibody rejections, post-transplant lymphoproliferative disorder, and non-adherence to drug regimens. The prediction reliability must be studied by comparing predicted and actual levels of eGFR-1, which is only possible if there are sufficient transplants within each stratum of risk level. Keeping these limitations in mind, Figure 5 plots the distribution of predicted TRB for the 11 527 older-donor transplants. There are very few actual transplants with TRB > 0.9 (equivalently, $r < 0.1$) and most transplants have TRB > 0.6. For this reason, we tested $r \in \{0.3,0.2,0.1\}$.

Table 5 compares the weighted sum of 10 splits (based on number of observations) of out-of-sample (30% of data set aside for testing) PPV for OLS, RF, BOOST, and ENS for $b = 30$ and $r \in \{0.3,0.2,0.1\}$. It also includes the standard deviations (SD) and sample sizes n, that is, the number of transplants with TRB $\geq (1 - r)$.

Table 5 shows that the PPV increases as r decreases and that OLS and BOOST result in higher PPV than RF. For this reason, they were selected for the ENS method, which resulted in further improvement in the PPV and was therefore used for the remainder of the analysis.

5.2 | Clinical relevance

Table 6 shows the number of transplants with TRB $\geq (1 - r)$ and the average eGFR-1 of transplants with TRB $\geq (1 - r)$. The average realized eGFR-1 decreases as the risk level increases and it stabilizes for risk level ≥0.3. By limiting risk to be less than 0.1, a high average eGFR-1 of 58 ml/min is possible, but very few transplants (438) meet that requirement. Table 6 demonstrates the effect of selection bias in the

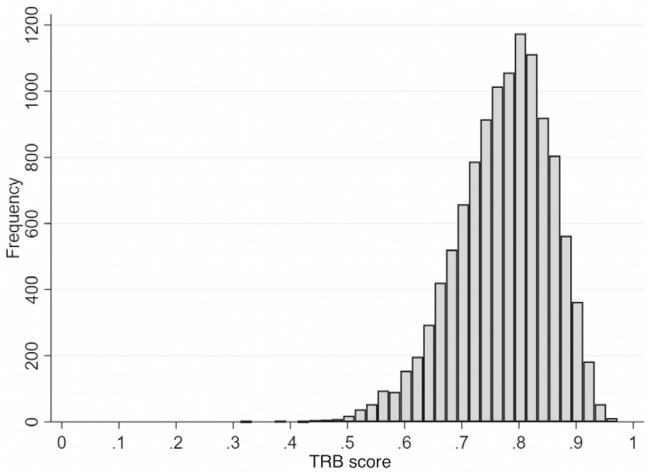

FIGURE 5 Frequency distribution of older-donor transplants with predicted TRB

TABLE 4 Important variables

Donor related	Recipient related	Others
Age	Age	Allocation (local, regional, national)
Controlled non-heart beating	Creatinine at transplant	TxP specific: Proportion of 55+ transplants
Death mechanism	Ethnicity	
Ethnicity	Height	
Expanded criteria donor	Previous pregnancies	
Height	Weight	
Hypertension duration		
Hypertension method of control: diet		
Region		

TABLE 5 Weighted PPV associated with predicted TRB scores meeting various r thresholds

	Study groups		
	$b = 30$ $r = 0.3$	$b = 30$ $r = 0.2$	$b = 30$ $r = 0.1$
OLS			
PPV, mean (SD)	0.878 (0.002)	0.911 (0.002)	0.951 (0.003)
n	22 772	13 542	1183
RF			
PPV, mean (SD)	0.873 (0.002)	0.888 (0.002)	0.914 (0.002)
n	29 337	19 839	6325
BOOST			
PPV, mean (SD)	0.875 (0.003)	0.904 (0.003)	0.937 (0.002)
n	29 195	15 960	2161
ENS			
PPV, mean (SD)	0.880 (0.002)	0.912 (0.002)	0.951 (0.003)
n	26 762	12 192	1020

Note: The ENS method (based on OLS and Boost) consistently resulted in the highest PPV.

TABLE 6 Number of transplants (txs) with TRB $\geq (1 - r)$ and average eGFR-1 of txs with TRB $\geq (1 - r)$

Risk level r	No. of txs with TRB $\geq (1 - r)$	Average eGFR-1 of txs with TRB $\geq (1 - r)$
1	11 527	48.08
0.9	11 527	48.08
0.8	11 527	48.08
0.7	11 527	48.08
0.6	11 524	48.09
0.5	11 490	48.13
0.4	11 151	48.43
0.3	9394	49.56
0.2	4732	52.80
0.1	438	58.49

Note: The average eGFR-1 and number of transplants are stable for risk levels greater than 0.3, but vary significantly for risk levels 0.3, 0.2, and 0.1. Lower risk levels result in higher average eGFR-1, but fewer transplants meet those risk thresholds.

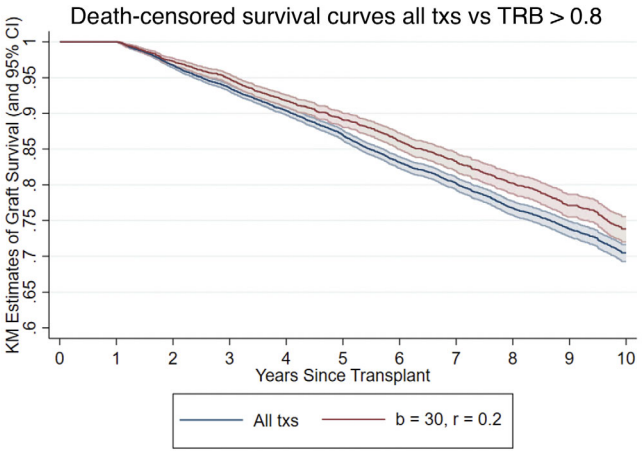

FIGURE 6 Death-censored 1–10 year graft survival curves for the study cohort, and $b = 30$, $r = 0.2$ (TRB ≥ 0.8). Transplants with TRB ≥ 0.8 have significantly higher 1–10 year graft survival than those in the study cohort

national data. Clinicians carefully select transplants such that most have a risk level less than 0.3. While this is good for recipients, it limits the choice of risk levels in ensuing analysis. Figure 6 shows that the 1–10 year death-censored graft survival of kidneys in the subset with $b = 30$ and $r = 0.2$ ($n = 4732$) is greater than that of the study cohort ($n = 11{,}527$), although the number of transplants with TRB ≥ 0.8 is smaller than those in the study cohort.

The higher the b (or lower the r), the smaller the number of transplants meeting those requirements, and the greater the survival probability. Different candidates may arrive at a different balance between kidney availability and function/durability. Some may desire increased access even if the transplant does not provide durable freedom from dialysis with high probability, whereas others may want high probability of long-term function irrespective of the wait. We also find that the 1-year graft survival probability of kidneys with TRB ≥ 0.8 is higher than that among all older-donor transplants (94.69% vs. 92.57%), demonstrating that our choice of b and r also identifies transplants with high probability of 1-year survival.

5.3 | Evaluation of discarded kidneys and matched candidates

The distribution of the TRB score for each of the 2 053 007 discarded kidney-candidate matches is shown in Figure 1 of Online Appendix G. Of the 6977 discarded but matched kidneys in the simulation study cohort, 5971, 5282, and 1500 had at least one matched candidate with risk level $r \in \{0.3,0.2,0.1\}$, respectively. As expected, the number of discarded kidneys that provide sufficient benefit decreases as r decreases. Still, with $r = 0.2$, over 75% (5282) of the 6977 discarded kidneys under consideration had at least one candidate who could have received significant long-term benefit.

TABLE 7 Comparison of key characteristics of actual recipients and identified candidates

	Actual recipients	Identified candidates
Sample size (*n*)	11 527	5282
Characteristics		
Median (IQR), mean age (years)	61 (53–67), 57.05	62 (55–67), 60.74
% Male	61.5	70.20
% Caucasian	44.98	36.9
% African-American or Black	30.42	35.82
% Hispanic	14.63	21.81
% Other races	9.97	5.47
% History of diabetes	43.8	64.4

Note: Identified candidates are slightly older, more likely to be males, Black and Hispanic and to have diabetes than actual recipients.

There are some differences in the characteristics at time of listing of the actual recipients of the 11 527 kidneys and the 5282 candidates with TRB ≥ 0.8 identified in the simulations—see Table 7. Compared to actual recipients, the identified candidates were slightly older (60.74 vs. 57.05 years), more likely to be males (70.2% vs. 61.5%), more likely to be Black and Hispanic (35.8% and 21.8% vs. 30.4% and 14.6%), and more likely to have diabetes (64.4% vs. 43.8%). These results are consistent and reinforce the findings in Tullius and Rabb (2018) and Concepcion et al. (2016) that older candidates with diabetes may be the ones that benefit from currently discarded organs.

The most commonly-stated reason (72.81%) why TxPs declined the 5282 discarded kidneys was donor age or quality. We conjecture that the uncertainty associated with the assessment of older-donor kidney quality is a primary reason why TxPs reject older-donor kidneys because otherwise a more specific reason would have been provided, for example, kidney anatomy or glomerulosclerosis. The second most common reason (12.91%) was organ preservation, which is related to logistics/transportation/CIT. The algorithm we propose can identify which candidates could benefit from such kidneys, and provide a rationale for a bypass mechanism that would avoid long CIT.

6 | CONCLUDING REMARKS

We present a versatile tool that can be used by the OPTN to more judiciously utilize older-donor kidneys. Using customized machine-learning techniques and data available at the time of offer, we illustrate how to estimate the risks and benefits of transplantation for each donor-candidate pair. Additionally, as a proof-in-concept of the value of our approach, we performed simulation experiments to quantify the number of older-donor discarded kidneys that could have provided sufficient benefit to at least one matched candidate. Some of the discarded kidneys could have been used with better outcomes compared to transplanted kidneys if TRB and $r = 0.2$ were used to select which transplants to perform. The analysis so far has been restricted to data included in the STAR file, leaving out clinically-relevant data elements that are available to clinicians at the time of kidney offer, for example, the size and mass of the kidney. Finally, anticipated transportation delays are likely to play a role in organ acceptance decisions. Such issues are not included in the current model and present an opportunity for further improving the methodology.

ACKNOWLEDGMENTS

This project was funded, in part, under grant number R03 HS27671-01 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services (HHS). This work was supported in part by Health Resources and Services Administration contract HHSH250-2019-00001C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. Additional funding was provided by the McCombs School of Business, University of Texas at Austin via a Research Excellence Grant to Diwakar Gupta. The authors are solely responsible for this document's contents, findings, and conclusions, which do not necessarily represent the views of AHRQ. Readers should not interpret any statement in this report as an official position of AHRQ or of HHS.

CONFLICT OF INTEREST

None of the authors has any affiliation or financial involvement that conflicts with the material presented in this report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Health Research and Services Administration. Restrictions apply to the availability of these data, which were used under license for this study. Data may be obtained directly from the United Network for Organ Sharing after obtaining permission from the Health Research and Services Administration. The authors of this study are not permitted to share the data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Martin, P., Gupta, D., & Pruett, T. (2023). Predicting older-donor kidneys' post-transplant renal function using pre-transplant data. *Naval Research Logistics (NRL)*, *70*(1), 21–33. https://doi.org/10.1002/nav.22083