A kidney offer acceptance decision tool to inform the decision to accept an offer or wait for a better kidney

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We developed a kidney offer acceptance decision tool to predict the probability of graft survival and patient survival for first-time kidney-alone candidates after an offer is accepted or declined, and we characterized the effect of restricting the donor pool with a maximum acceptable kidney donor profile index (KDPI). For accepted offers, Cox proportional hazards models estimated these probabilities using transplanted kidneys. For declined offers, these probabilities were estimated by considering the experience of similar candidates who declined offers and the probability that declining would lead to these outcomes. We randomly selected 5000 declined offers and estimated these probabilities 3 years post-offer had the offers been accepted or declined. Predicted outcomes for declined offers were well calibrated (<3% error) with good predictive accuracy (area under the curve: graft survival, 0.69; patient survival, 0.69). Had the offers been accepted, the probabilities of graft survival and patient survival were typically higher. However, these advantages attenuated or disappeared with higher KDPI, candidate priority, and local donor supply. Donor pool restrictions were associated with worse 3-year outcomes, especially for candidates with high allocation priority. The kidney offer acceptance decision tool could inform offer acceptance by characterizing the potential risk–benefit trade-off associated with accepting or declining an offer.

**KEYWORDS**
clinical decision-making, donors and donation, health services and outcomes research, kidney (allograft) function/dysfunction, kidney transplantation/nephrology, organ acceptance, organ procurement and allocation

**1 | INTRODUCTION**

The kidney donor risk index (KDRI) was originally proposed to quantify donor risk and help in decision-making regarding offers of deceased donor kidneys by assessing potential posttransplant outcomes. The kidney donor profile index (KDPI), which corresponds to percentiles of the KDRI for recovered kidneys, has since been implemented for use in allocation of deceased donor kidneys. High KDRI and KDPI correspond to higher deceased donor kidney risk with worse posttransplant outcomes; these are common reasons for declining an offer of a deceased donor kidney. However, the decision to decline an offer based on the expectation of being offered a better kidney is questionable because less than 50% of wait-listed candidates undergo a first deceased donor transplant within 5 years. Rather than base the acceptance decision solely on expected posttransplant outcomes, the decision to accept or decline a deceased donor kidney should depend on the candidate’s expected outcome if the offer is accepted versus if it is declined and the candidate remains on the waiting list.

**Abbreviations:** AUC, area under the curve; CIF, cumulative incidence function; CIT, cold ischemia time; DSA, donation service area; GFR, glomerular filtration rate; KDPI, kidney donor profile index; KDRI, kidney donor risk index; OPTN, Organ Procurement and Transplantation Network; SRTR, Scientific Registry of Transplant Recipients.
 Previous research has shown that receiving a high-KDPI kidney is associated with better long-term patient survival than remaining on the waiting list for a lower-KDPI kidney despite a higher risk of delayed graft function. Yet over 50% of kidneys with KDPI above 85% were discarded in 2015. Despite the long-term benefits of high-KDPI kidneys, there are at least two potential reasons for declining such offers:

1. The candidate has high priority in the kidney allocation system, eg, received an offer early in the match run. Previous research did not explicitly consider allocation priority, and a candidate with high priority may more quickly be offered a kidney from a high-quality donor. Thus, declining high-KDPI kidneys could potentially lead to better outcomes.

2. The candidate is listed in a donation service area (DSA) with a relatively high supply of donor kidneys. Previous research did not directly account for variability in donor supply, which may determine whether a candidate is more likely to receive a high-quality offer and thereby have better outcomes by declining a high-KDPI kidney.

Both of these reasons are based on the concept that the candidate is more likely to quickly receive a better offer than the typical candidate. However, it is not clear that candidates with high priority or those listed in high-supply DSAs are more likely to undergo transplant or that the increased likelihood of transplant offsets the higher rates of morbidity and mortality associated with longer dialysis durations.

We developed a kidney offer acceptance decision tool that directly models the trade-off between accepting an offered kidney versus declining it and remaining on the waiting list. Specifically, given donor and candidate characteristics, the tool estimates the probability of a functioning graft and patient survival over three years after the offer is accepted or declined. We accounted for allocation priority and local supply by considering the wait-list experiences of candidates with similar clinical characteristics who also declined offers, DSA supply, and priority in the kidney allocation system. Thus, if the offered kidney maximizes graft and patient survival, it should be accepted. Otherwise, the offer should be declined.

2 | METHODS

2.1 | Data

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system has been previously described. It includes data on all donors, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight of the activities of the OPTN and SRTR contractors.

2.2 | Offer acceptance decision tool

The probability of graft survival or patient survival 1-3 years post-offer was estimated separately for accepted and declined offers. For accepted offers, the probability of these outcomes was derived, respectively, from estimated posttransplant graft and patient survival curves. For declined offers, the estimation depended on the candidate’s expected wait-list experience after the offer. Specifically, the probability of graft survival corresponded to the probability of the candidate receiving a living or deceased donor kidney that still functioned 1-3 years after the offer. The probability of patient mortality (not surviving) was the sum of dying: (1) on the waiting list, (2) after a deceased donor transplant, (3) after a living donor transplant, and (4) after being removed from the waiting list for reasons other than transplant or death. Figure 1 illustrates the calculation of the probability of graft survival and patient mortality for declined offers, and the Supplementary Materials provide further technical details.

2.3 | Survival models

Posttransplant graft and patient survival were estimated with a Cox proportional hazards model for first-time kidney-alone recipients who underwent transplant between May 1, 2007, and June 30, 2015. A separate model was estimated for living versus deceased donor recipients, and the effects of continuous variables were estimated with penalized splines. Both living and deceased donor models adjusted for candidate characteristics: sex, race, ethnicity, blood type, education, public insurance, age at transplant, body mass index (BMI), diabetes

![FIGURE 1](image-url) An illustration of the process for estimating graft survival and patient mortality with the offer acceptance decision tool. For example, after an offer is declined, we consider the likelihood of deceased donor transplant, living donor transplant, death, and removal from the list for other reasons. We combine the likelihood of being removed from the waiting list with the likelihood that the corresponding removal results in graft survival or patient mortality. Patient survival is equal to 1 minus patient mortality. DD, deceased donor; GS, graft survival; LD, living donor; PM, patient mortality; PS, patient survival.
status, and dialysis duration at transplant. BMI was trimmed to the first and 99th quantiles to reduce the influence of extremely small or large values. The deceased donor model also adjusted for KDRI and cold ischemia time (CIT; hours) at transplant. Other candidate and donor risk factors could have been included, but we assumed a parsimonious offer acceptance decision tool would improve accessibility and, ultimately, clinical utilization.

A Cox proportional hazards model estimated patient survival after removal from the waiting list for reasons other than transplant or death, and adjusted for the effects of ethnicity, education level, age at removal, diabetes status, and dialysis duration at removal. The model was estimated with first-time kidney-alone candidates who declined an offer between January 1, 2013, and March 31, 2013, and were subsequently removed from the waiting list for reasons other than transplant, transfer to a different program, or death.

### 2.4 Probability of wait-list removal

Cumulative incidence functions (CIFs) estimated the probability of wait-list removal from the time of offer while accounting for the competing risks of deceased or living donor transplant, death on the waiting list, and removal for reasons other than transplant or death.9 Candidates removed from the waiting list due to undergoing transplant elsewhere or transfer to a different program were censored at removal date. “Local” estimation of the CIFs accounted for the effects of candidate characteristics, wait-list priority, and local donor supply.10 Specifically, we selected declined offers from a similar point in the match run (ie, the metric of candidate priority) for candidates with the same blood type, calculated panel-reactive antibodies (cPRA), diabetes status, and similar age at offer. We accounted for local donor supply by further subdividing declined offers for candidates listed in the 19 DSAs with the most similar probability of transplant 3 years after an offer was declined. To ensure a sufficient sample size for estimating the CIFs, the age at offer cutoff was adaptively chosen to ensure at least 100 offers. For donor pool restrictions, deceased donor transplants were censored if the CIT at transplant or the KDPI was above the specified limits. The Supplementary Materials provide further details on the estimation of the CIFs.

The time scale of the CIFs was set to the number of years after the offer. We adjusted for repeated offers to the same candidate by weighting each offer by 1 divided by the number of offers the corresponding candidate received within the given subset. Zero-HLA mismatch offers were excluded from the estimation of CIFs due to their rare occurrence and heightened priority in kidney allocation. The cohort of declined offers was derived from first-time kidney-alone candidates listed at their first program from match runs that ended in acceptance between January 1, 2013, and March 31, 2013.

### 2.5 Assessment of predictions for declined offers

The offer acceptance decision tool is based on statistical predictions and should be evaluated for predictive accuracy. The predicted error of posttransplant survival models and, therefore, the outcomes of accepted offers is well-established.1,11,12 Thus, we evaluated the predicted error and calibration for estimating graft survival and patient survival for declined offers. We randomly selected 5000 candidates with declined offers between April 1, 2013, and April 30, 2013, and, for each candidate, one declined offer with at least one HLA mismatch was randomly selected. We specifically avoided evaluating offers used in the offer acceptance decision tool due to potential underestimation of the predicted error, although the cohort likely included candidates in the cohort for the offer acceptance decision tool. For each randomly selected offer, the estimated 3-year probabilities of graft survival and patient survival were compared with the observed outcomes 3 years after the offer. The calibration was assessed by the observed minus predicted graft survival and patient survival, and the predicted error was assessed by the area under the receiver operating characteristic curve (AUC).

The calibration and predicted error across offer number, which is the point in the match run at which a candidate receives an offer and approximates candidate priority, was assessed with a two-step estimation approach: each metric was first estimated within 5% quantile bins of offer number and the estimate for each bin was then smoothed with a spline, similar to a previously used approach.13

### 2.6 Evaluation of risk–benefit trade-off

The offer acceptance decision tool was applied to the 5000 randomly selected declined offers to characterize the risk–benefit trade-off of accepting an offer compared with declining it and remaining on the waiting list. The probability of graft survival and patient survival after acceptance was estimated with the donor’s KDPI and an assumed 20 hours of expected CIT, which was unknown for declined offers. After stratifying by donor KDPI, the difference in the probability of graft survival and patient survival after accepting versus declining an offer was investigated across offer number (ie, candidate priority) and local donor supply. To identify potential non-linearity, splines estimated the effect of offer number. Donor supply was defined as listing in a low-, medium-, or high-donor-supply DSA with cut points based on the 1/3 and 2/3 quantiles of the probability of transplant within 3 years after declining an offer.

The impact of donor pool restrictions was evaluated by taking the difference between the predicted probabilities of graft survival and patient survival for a declined offer with and without restrictions. Three donor pool restrictions were considered: donors with less than 30 hours of CIT at transplant and KDPI less than 70%, 80%, and 90%. The impact of restricting the donor pool was evaluated across offer number, and the effect was estimated by splines to identify potential non-linear effects.

### 2.7 Statistical analyses

All analyses were completed in R v3.2.2.14 The survival package estimated each survival model and the cumulative incidence functions. The mgcv package estimated the splines for the analysis of declined offers.
3 | RESULTS

3.1 | Calibration and predicted error for declined offers

Predicted graft survival and patient survival 3 years after a declined offer were well calibrated (<3% overall difference between observed and predicted outcomes), with relatively good AUC (0.69 and 0.69 for graft survival and patient survival, respectively) (Figure 2). The offer acceptance decision tool slightly overestimated the probability of subsequent graft survival (~3%) after declined offers, and the variability in the calibration increased with higher offer numbers. The average difference between observed and predicted patient survival was 0 and did not show obvious trends across offer number. The average AUC for graft survival was lower early in the match run but increased with higher offer numbers. The average AUC for patient survival slightly decreased with higher offer numbers.

3.2 | Analysis of declined offers

For low- and medium-KDPI kidneys (KDPI <85%), accepting the offer was associated with a significantly higher probability of graft survival and a higher probability of patient survival than declining the offer (Figure 3 and Table 1). The advantages of acceptance dramatically attenuated for lower offer numbers, with the likelihood of graft survival nearly identical for candidates at the top of the waiting list. For high-KDPI kidneys, acceptance was typically associated with a higher probability of graft survival, and the advantage attenuated for candidates with high priority. Acceptance of high-KDPI kidneys for high-priority candidates did not typically confer significant increases in patient survival. Similar advantages and acceptance trends occurred across local donor supply with attenuation for candidates listed in high-supply DSAs, especially for patient survival and high-KDPI kidneys. The analysis was robust to the assumed hours of CIT for the deceased donor offers (see Figures S1 and S2).

3.3 | Impact of restricted donor pools

Donor pool restrictions were associated with lower probabilities of graft survival and patient survival (Figure 4). As the potential donor pool became more restricted, the probabilities of graft survival and patient survival decreased. The level of donor pool restrictions also interacted with offer number. Specifically, the effect of restricting the donor pool at KDPI 90% was relatively constant across offer number. However, when the donor pool was restricted at KDPI 70%, low offer numbers (i.e., high-priority candidates) were associated with a larger decrease in the probabilities of graft survival and patient survival than higher offer numbers.

3.4 | Illustration of the offer acceptance decision tool

The offer acceptance decision tool (Figures 5 and 6) was illustrated with characteristics similar to those of a randomly selected

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**FIGURE 2** The calibration and estimated predicted error for the approach used to estimate the probability of graft survival and patient survival 3 y after declined offers. Each circle represents the estimate within a 5% quantile bin of offer number. The solid lines correspond to penalized splines of the estimated effects within each bin [Color figure can be viewed at wileyonlinelibrary.com]
**Figure 3** The estimated differences in predicted graft survival and patient survival between accepting versus declining an offer, 3 y after the offer. The dashed lines represent the 95% confidence intervals for the mean difference across offer number. The evaluated offers were 5000 randomly selected declined offers. Estimated differences above the dotted horizontal line indicated that acceptance led to better predicted outcomes than declining the offer. KDPI, kidney donor profile index; GS, graft survival; PS, patient survival [Color figure can be viewed at wileyonlinelibrary.com]

**Table 1** Estimated difference in predicted graft survival and patient survival after 3 years for accepting versus declining a given offer across different levels of local donor supply

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Local donor supply in DSA</th>
<th>Overall, %</th>
<th>KDPI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0-34  35-84  85-100</td>
</tr>
<tr>
<td>Graft survival</td>
<td>Low</td>
<td>56</td>
<td>60  57  48</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>44</td>
<td>45  46  36</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>36</td>
<td>38  38  28</td>
</tr>
<tr>
<td>Patient survival</td>
<td>Low</td>
<td>7</td>
<td>7   7   5</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>5</td>
<td>7   6   3</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>4</td>
<td>5   5   3</td>
</tr>
</tbody>
</table>

DSA, donation service area; KDPI, kidney donor profile index.
declined offer to a candidate in a slightly below average donor supply organ procurement organization. The candidate was a 59-year-old non-Hispanic white man, blood type A, half-year of dialysis, no diabetes, BMI of 30 kg/m², high-school education, and 0 cPRA. The candidate received a non-local offer, offer number 500, for a KDPI 90 kidney; we assumed 20 hours of expected CIT. Figure 5 illustrates that acceptance led to an 85% probability of graft survival 3 years after the offer, compared with a 46% probability if the offer was declined. Figure 6 illustrates that restricting the donor pool with a maximum KDPI of 85% and CIT of 20 hours deceased the probability of graft survival to 33% 3 years after the offer was declined.

4 | DISCUSSION

The kidney offer acceptance decision tool was developed to characterize the risk–benefit trade-off after 3 years between accepting an offer, eg, for a high-KDPI kidney, compared with declining the offer and remaining on the waiting list. The tool suggested that declined offers could have provided better candidate outcomes, although the advantages disappeared for candidates at the beginning of match runs (ie, high-priority candidates) who received offers of high-KDPI kidneys. These results confirm previous findings indicating that transplanting high-KDPI kidneys can benefit wait-listed candidates, and extend the findings by explicitly incorporating the candidate’s relative

FIGURE 4 The estimated differences in predicted graft survival and patient survival 3 y after an offer with and without restrictions on the donor pool. The restrictions consist of KDPI cutoffs of 70%, 80% and 90% with a maximum CIT of 30 h. The dashed lines represent the 95% confidence intervals for the mean difference across offer number. The evaluated offers were 5000 randomly selected declined offers. Estimated differences below the dotted horizontal line indicated that the donor pool restrictions reduced the probability of graft survival and patient survival. CIT, cold ischemia time; KDPI, kidney donor profile index; GS, graft survival; PS, patient survival [Color figure can be viewed at wileyonlinelibrary.com]
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priority and available donor supply. Additionally, the offer acceptance decision tool can incorporate the effect of restricting the donor pool and provides interpretable summary measures of the potential outcomes. Thus, the tool may help inform the decision to accept or decline an offer of a deceased donor kidney.

We found that potential benefits of high-KDPI kidneys were nuanced, especially for candidates with high allocation priority. Specifically, acceptance of high-KDPI offers for high-priority candidates was associated with similar, or better, expected probability of graft survival at 3 years, but potentially worse patient survival. The patient survival result extends previous research in which high-KDPI kidneys had a negligible survival benefit for candidates from DSAs with shorter waiting times. Yet, certain candidates may tolerate higher mortality for the better quality of life associated with a functioning kidney transplant. However, this requires kidney transplant programs and candidates to develop a mutual understanding of the trade-off between graft survival, patient survival, and donor KDPI. The offer acceptance decision tool may help programs and candidates better understand this trade-off for a given offer.

Kidney transplant programs are required to obtain informed consent from candidates before transplanting high-KDPI kidneys (KDPI ≥ 85%). The offer acceptance decision tool could help

**FIGURE 5** Offer acceptance decision tool screenshot showing that acceptance led to an 85% probability of graft survival 3 y after the offer, compared with a 46% probability if the offer was declined [Color figure can be viewed at wileyonlinelibrary.com]
demonstrate the potential advantages of accepting high-KDPI kidneys versus remaining on the waiting list. However, the expected wait-list experience of candidates at the time of listing or informed consent likely differs from the experience of candidates who actively receive offers. Thus, the offer acceptance decision tool may be inappropriate for informing patients of the risk–benefit trade-off of high-KDPI kidneys at the time of listing. An alternative approach could instead evaluate potential outcomes of similar wait-listed candidates who were willing versus unwilling to accept high-KDPI kidneys. This deserves further investigation as a potential tool to help inform kidney transplant candidates of the advantages of high-KDPI kidneys at the time of listing.

FIGURE 6 Offer acceptance decision tool screenshot showing that restricting the donor pool with a maximum kidney donor profile index of 85% and cold ischemia time of 20 h deceased the probability of graft survival to 33% 3 y after the offer was declined [Color figure can be viewed at wileyonlinelibrary.com]

Donor pool restrictions had the largest impact on high-priority candidates despite higher likelihood of being offered a low-KDPI kidney. This counterintuitive result suggests that these candidates received kidneys with KDPI above 70% despite their high priority. Additionally, since high-priority candidates typically had the best probability of graft survival and patient survival, donor pool restrictions had the largest absolute impact due to lower likelihood of receiving a deceased donor kidney, which is the main path to graft survival for high-priority candidates (see Figure S3). However, young candidates may continue to have better long-term outcomes by waiting for higher-quality kidneys to minimize the likelihood of re-transplant, which would likely occur...
later than the evaluated 3-year outcomes. Regardless, a strict KDPI cutoff was not associated with better 3-year outcomes for most waitlisted candidates, especially high-priority candidates.

The offer acceptance decision tool may depend heavily on the estimated CIFs, which would likely change over time due to modifications in the kidney allocation system and/or variability in the supply and demand of transplantable kidneys. For example, the offer acceptance decision tool overestimated the likelihood of graft survival 1 year post-offer for offers declined after implementation of the new kidney allocation system (see Figure S4). Thus, the cohort of declined offers the tool uses should be continually updated. As an additional challenge, the cohort of declined offers requires sufficient lag to ensure adequate follow-up for estimating these probabilities 3 years after an offer. This is particularly important as the long-term benefits of declining an offer could take years to manifest due to the potentially long delay required to receive a better offer. In fact, longer-term outcomes, eg, 5 years after an offer is declined, could be relevant to offer decisions. Additionally, the offer acceptance decision tool currently focuses on first-time kidney-alone candidates. Wait-list experiences of candidates seeking re-transplant likely differ from those of first-time candidates, and expected outcomes may also differ. Re-transplant candidates are difficult to integrate because the tool currently uses a non-parametric (ie, model-free) estimator for the CIFs. An alternative approach could estimate the CIFs within a model-based framework using several years of declined offers. This approach could potentially account for candidate characteristics including first-time versus re-transplant candidates and for temporal trends in wait-list experiences.

The glomerular filtration rate (GFR) is an important component of posttransplant kidney function, and high-KDPI kidneys are associated with worse posttransplant GFR. A potential approach to the offer acceptance decision process could attempt to maximize recipients’ GFR. In this case, lower-KDPI kidneys would likely lead to better posttransplant GFR than high-KDPI kidneys. This approach incorrectly assumes that candidates who decline offers of high-KDPI kidneys would subsequently undergo transplant with a lower-KDPI kidney. A more appropriate approach would instead compare the expected GFR after accepting a high-KDPI kidney with the GFR after declining an offer regardless of eventual transplant status. The GFRs of candidates who do not undergo transplant would be set to zero. A methodology similar to the approach described here could then estimate the expected GFR for candidates who decline offers. However, estimating posttransplant GFR requires a fundamentally different approach that accounts for the interval data collection and potentially missing data. This would be an interesting area for further research.

A Markov decision process model has been previously investigated for acceptance decisions in liver transplantation. It estimated optimal decision rules that maximized candidate survival based on the likelihood of receiving an offer in the future and the corresponding patient survival. The Markov model implicitly assumed that future offer acceptance decisions would be optimally determined. In contrast, the offer acceptance decision tool estimated the expected graft survival and patient survival of declined offers under the assumption that future offer acceptance and organ utilization behavior would be similar to historical behavior. Yet historical behavior may not correspond to the optimal acceptance decisions that maximize candidate outcomes. It is therefore possible that an optimal decision rule for kidney offer acceptance could provide conclusions different from those based on the approach we took. The potential differences between these two approaches deserve further investigation.

The offer acceptance decision tool has several limitations. First, the survival models and cumulative incidence functions exclude predictors of survival and likelihood of transplant. For example, candidates could have unmeasured cardiovascular risk factors beyond pretransplant dialysis duration. For declined offers, unmeasured cardiovascular risk factors could increase the likelihood of wait-list mortality and reduce the likelihood of deceased donor transplant and, alternatively, increase the likelihood of graft failure and patient mortality after accepted offers. Additionally, while the offer acceptance decision tool considers the likelihood of living donor transplant, a candidate with a potential living donor actively undergoing evaluation may be more likely to undergo living donor transplant than other candidates who declined deceased donor offers. The offer acceptance decision tool cannot incorporate this information and the likelihood of graft survival, and patient survival after declining the offer may be higher than estimated. Second, KDPI is only one metric of donor quality and likely fails to identify the entire range of donor quality, eg, time-to-death for donation after circulatory death donors. The offer acceptance decision tool could be improved by considering a wider range of donor and candidate predictors at the cost of parsimony, eg, candidates seeking re-transplant. Third, the likelihood of graft survival and patient survival after accepting an offer were estimated with transplanted kidneys. Discarded kidneys likely have additional risk factors beyond KDPI that may lower the probability of graft survival and patient survival. However, the current offer acceptance decision tool likely provides a reasonable baseline for offer acceptance decisions. For example, if acceptance of a high-KDPI kidney was associated with 39% higher probability of graft survival (see Figure 5), then the risk factors not identified by KDPI would have to confer an additional 39% lower 3-year graft survival rate to offset the risk associated with declining the offer. Lastly, despite attempts to impose a minimum amount of information, the offer acceptance decision tool does not assess the variability in the estimate, which obscures the strength of evidence associated with the estimated probabilities of graft survival and patient survival.

Previously declined offers may have benefited wait-listed candidates. Thus, the offer acceptance decision tool may help inform the offer acceptance decision by providing clinicians and patients with clinically relevant summary measures of the risks and benefits of accepting a given offer versus declining it and remaining on the waiting list.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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