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REVIEW

Evidence-based development of liver allocation: a review

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Summary

Liver transplantation has undergone a rapid evolution from a high-risk experimental procedure to a mainstream therapy for thousands of patients with a wide range of hepatic diseases. Its increasing success has been accompanied by progressive imbalance between organ donor supply and the patients who might benefit. Where demand outstrips supply in transplantation, a system of organ allocation is inevitably required to make the wisest use of the available, but scarce, organs. Early attempts to rationally allocate donor livers were particularly hampered by lack of available and suitable data, leading to imperfect solutions that created or exacerbated inequities in the system. The advent and maturation of evidence-based predictors of waiting list mortality risk led to more objective criteria for liver allocation, aided by the increasing availability of data on large numbers of patients. Until now, the vast majority of allocation systems for liver transplantation have relied on estimation of waiting list mortality. Evidence-based allocation systems that incorporate measures of post-transplant outcomes are conceptually attractive and these transplant benefit-based allocation systems have been developed, modeled, and subjected to computer simulation. Future implementations of benefit-based liver allocation await continued refinement and additional debate in the transplant community.

Introduction and historical perspective

Between Starzl's initial demonstration of the feasibility of human liver transplantation (LT) in the 1960s and the initial clinical use of cyclosporine in 1978, LT was considered an experimental procedure [1]. Liver procurement and allocation were initially conducted within single transplant hospitals and decisions to use donated liver grafts were made for locally managed patients, without much consideration for broader need at a regional or national level. The standardization of brain death criteria allowed donor organs to be physiologically maintained after declaration of death, making them available to transplant candidates outside of the immediate donor hospital environment [1]. This led to the need to prioritize LT candidates and create a systematic organ distribution system.

Ad hoc systems and the rise of waiting time as a primary allocation criterion

Until the National Organ Transplant Act (NOTA) was enacted in 1984 in the United States (US), there were no formal guidelines for determining priority on the LT waiting list [2]. LT prioritization schemes followed the example set in renal transplantation, offering transplants to those who had been waiting longest [1,3]. Individual transplant programs evaluated patients and applied non-standardized transplant eligibility criteria. Passage of NOTA ushered in the era of governmental oversight and

regulation of transplantation through the creation of an Organ Procurement and Transplantation Network (OPTN), charged with creating national policies for organ allocation and distribution. These fledgling policies continued to emphasize waiting time, but a vocal minority of clinicians advocated a system that ordered patients by disease severity. The resulting medical urgency status system led to more acutely ill patients being given higher priority categorizations for donor liver eligibility, even for donors beyond the local area [1,3,4]. Status designations were based first on whether the patient required emergent transplant (Status 1) and nonemergent patients were further categorized based on the location of their medical management, as a presumed surrogate for disease severity: intensive care unit (ICU) (Status 2), non-ICU hospital inpatient (Status 3) or outpatient (Status 4) [1,4]. These status categories comprised extremely broad ranges of disease severity and waiting time remained the primary means to rank patients within each status designation. The location-based status designation system was susceptible to subtle and sometimes overt manipulation by transplant providers [1].

Incorporation of the Child-Turcotte-Pugh score into allocation policy

The allocation system was subsequently amended and new policies evolved from 1996 to 1999 [3]. The status-based system was preserved, along with priority for patients with acute liver failure and primary LT nonfunction. However, the arbitrary nature of the location-based designations for candidates with chronic liver disease was altered to incorporate levels of the more objective Child-Turcotte-Pugh (CTP) score [3,4], a well-established arbiter of mortality risk for cirrhotic patients undergoing surgical procedures [5] (Table 1).

Despite using CTP score as the main criterion for status designation (Table 2), waiting time dominated allocation sequence, because it was retained as the main ordering tool for candidates of the same blood type within each status level. As a result of geographical differences in donor availability, organ procurement organization (OPO) performance, and waiting list practices, waiting time to transplant for patients with similar CTP scores became increasingly divergent across the country [1–3,6,7] and perception persisted that the liver allocation system was ineffective and inequitable [1,2,7].

Ultimately, the US Department of Health and Human Services promulgated regulations in a Final Rule in the late 1990s and for the first time required organ allocation rules based on objective medical criteria, ideally based on continuous measures of medical urgency [1–3,7]. The Final Rule clearly advocated for a system that would promote equity by reducing disparities in waiting list outcomes. This process ultimately moved the LT community away from a waiting time-based system by using evidence-based analyses to define medical urgency.

Table 1. Child-Turcotte-Pugh scoring system for liver disease severity.

	Points		
Criteria	1	2	3
Serum albumin (g/dl)	>3.5	2.8–3.5	<2.8
Total bilirubin (mg/dl)	<2.0	2.0–3.0	>3.0
International normalized ratio	<1.7	1.71–2.24	>2.25
Ascites	None	Medically controlled	Poorly controlled
Hepatic encephalopathy	None	Medically controlled	Poorly controlled

Adapted from Freeman [1].

Table 2. U.S. liver allocation system for adult patients by disease severity, 1998.

Status designation	Description
Status 1	Fulminant hepatic failure with life expectancy <7 days Primary graft nonfunction <7 days after liver transplantation Hepatic artery thrombosis <7 days after liver transplantation Acute decompensated Wilson's disease
Status 2A	Chronic hepatic failure, hospitalized in intensive care unit with life expectancy <7 days; CTP score ≥10; and (at least one of): • Acute unrelenting variceal hemorrhage • Hepatorenal syndrome • Refractory ascites or hepatic hydrothorax • Stage 3 or 4 (poorly controlled) hepatic encephalopathy
Status 2B	Chronic hepatic failure, requiring continuous inpatient medical care; CTP score ≥10; or CTP ≥7 and (at least one of): • Acute unrelenting variceal hemorrhage • Hepatorenal syndrome • Spontaneous bacterial peritonitis • Refractory ascites or hepatic hydrothorax
Status 3	Chronic hepatic failure; CTP score ≥7, but not meeting criteria for Status 2B
Status 7	Temporarily inactive on the waiting list

Adapted from Institute of Medicine [3].
CTP, Child-Turcotte-Pugh.

Development and evolution of MELD-based liver allocation policy

A more granular metric for medical urgency was required to displace waiting time as the de facto allocation criterion.

The Model for End-stage Liver Disease (MELD) was originally developed at the Mayo Clinic as a predictor of 3-month mortality risk after transjugular intrahepatic portosystemic shunt for variceal bleeding or refractory ascites from a cohort of 231 patients [8]. Serum creatinine, bilirubin, international normalized ratio (INR) of prothrombin time and etiology of the liver disease were found to be significant and independent predictors of death. The MELD score, subsequently employed for LT allocation policy, utilizes the regression coefficients from the three laboratory values and is calculated as MELD = $10 \times (0.957 \log_e$ creatinine + $0.378 \log_e$ bilirubin + $1.12 \log_e$ INR + 0.643). Note that the final term is a constant and does not depend on disease etiology, which was felt to be too subjective and controversial for inclusion.

The MELD score, validated in other patient datasets, performed well as measured by the c-statistic, a goodness of fit for Cox regression model analogous to the area under the receiver operating characteristic curve of a logistic regression model [6,9,10]. MELD predicted 3-month mortality in hospitalized patients (c-statistic 0.87) and ambulatory patients with noncholestatic (c-statistic 0.80) and cholestatic diseases (c-statistics 0.87) [10]. In a study of 3437 transplant candidates with chronic liver disease, MELD at the time of listing was superior to CTP in predicting waiting list mortality [6].

The MELD was developed for chronic liver disease patients and is not suitable as an allocation criterion for patients with conditions such as inborn errors of metabolism, malignancy in the absence of cirrhosis, and other unusual diagnoses. Hepatocellular carcinoma (HCC) is a special case discussed below and other conditions have been recently reviewed [11], but are not further discussed here.

MELD-based liver allocation in the US

The MELD score was adopted on February 28, 2002 as the liver allocation tool for chronic liver disease candidates. Priority for Status 1 candidates was maintained. However, additional arbitrary changes not based on mortality risk evidence were incorporated into the form of MELD used to administer the allocation policy [6,12]. The lower bound of bilirubin and creatinine were set at 1.0 mg/dl to avoid negative MELD scores, without any particular objective rationale. The upper bound of serum creatinine was set at 4 mg/dl, ostensibly to limit the access advantage afforded to patients with renal insufficiency. Candidates receiving renal replacement therapy (RRT) in the previous week were also given an arbitrary serum creatinine of 4 mg/dl for calculating their MELD score [13]. Lastly, MELD scores were capped at 40, despite data showing that patients with MELD >40 had higher waiting list mortality than patients with MELD of exactly 40 [6,12,14]. A Pediatric End-Stage Liver Disease (PELD) score was developed for children. PELD components include age, albumin, INR and growth failure, and although based on a completely different regression equation, the MELD and PELD scores were commingled for allocation purposes [12].

Introduction of MELD in the US was associated with 12% reduction in waiting list registrations (particularly among those with MELD <10), 3.5% reduction in waiting list mortality, and an increase in transplantation rates distributed across all demographic and epidemiologic strata [15]. Early patient and graft survival after deceased donor LT remains unchanged despite sicker patients receiving a higher proportion of donor livers [15].

MELD and HCC

In the early 1990s, Mazzaferro *et al.* prospectively studied patients transplanted for small HCC, defined as a single lesion <5 cm in diameter or three lesions <3 cm diameter each (Milan criteria). The 4-year recurrence-free survival rate was 83%, with a recurrence rate of 8% [16]. Based on these encouraging results for patients previously shown to have dismal outcomes, and the expectation that patients with HCC would not have MELD scores high enough to gain access to donor organs, the Milan criteria were incorporated into an exception system to the MELD-based allocation system [13]. Initially, progression beyond the Milan criteria was equated with unsuitability for transplant, which was presumed to lead quickly to death.

Based upon extrapolated tumor doubling times, it was estimated that HCC candidates with stage T1 (1 lesion <2 cm) and stage T2 (1 lesion 2–5 cm or 2–3 nodules all <3 cm) tumors would have a risk of progression and waiting list dropout of 15% (equivalent to MELD 24) and 30% (equivalent to MELD 29) respectively [13,17]. Furthermore, candidates who remained untransplanted but within the Milan criteria were assigned a MELD score equivalent to an additional 10% increase in mortality risk every 3 months [13]. No clinical data from actual transplant candidates were used to make these decisions.

Not surprisingly, the rate of deceased donor LT for HCC significantly increased in the MELD era compared with the pre-MELD era [18]. There was a corresponding decrease in the waiting time to transplantation and 5-month dropout from the waiting list [18]. Single center data revealed that the 1-year waiting list dropout rate for patients with stage T1 lesions was <10%, but >50% for stage T2 lesions [19]. However, the cumulative proportion of transplanted HCC candidates was significantly

higher than the corresponding proportion of candidates without HCC at similar MELD scores [20]. The excessive priority for HCC candidates has progressively reduced through a series of empiric policy actions. Currently, HCC candidates with stage T1 HCC do not get additional MELD priority and those with stage T2 HCC receive a MELD score of 22 [13].

Allocation versus distribution

As a practical matter, organ allocation policy in the US is actually a candidate-ordering system (allocation rules) nested within a system of geographic tiers (distribution rules) where the allocation rules are sequentially applied. Distribution is accomplished via local OPOs. OPOs serve donor hospitals and transplant programs within a defined service area. They were created as a patchwork without regard to equity or efficiency considerations and their boundaries persist largely unchanged today. In addition, regional aggregates of OPOs have been created, also without any scientific rationale.

Initially, donor livers were offered to all candidates in the local OPO service areas, in descending order of MELD score. It was common to have candidates in adjacent OPO service areas with higher MELD scores than the local recipient. This represented an apparent distortion of the MELD-based system's intent to offer donor livers to those at highest risk of waiting list death. Additional data showed that LT provided a smaller incremental survival benefit to patients with lower MELD than those with higher MELD (and in some cases worse survival with transplant than without) [14]. Subsequently, a modification of the MELD-based system [21] was investigated using the Liver Simulated Allocation Model [22] developed by Arbor Research Collaborative for Health as the contractor for the Scientific Registry of Transplant Recipients. As a result of these analyses, distribution was altered to offer organs to regional candidates with MELD >15 before offering them to local candidates with MELD <15 [14]. This important policy modification became known as the ''Share-15'' rule.

MELD and renal function

In examining the MELD equation, serum creatinine has the greatest impact on the overall score. It reflects the influence of kidney dysfunction on survival in liver disease [23,24] and is influenced by treatment. Although various combinations of creatinine, bilirubin, and INR values produce the same score, MELD is unable to discriminate between candidates with severe synthetic hepatic dysfunction and well-preserved renal function versus those with serious renal disease in the setting of well-preserved liver function. As a result, a significantly higher proportion of candidates with creatinine ≥2.0 mg/dl have undergone transplant in the MELD era compared with pre-MELD era. Moreover, the proportion of candidates on RRT at the time of LT has also increased significantly in MELD era [24]. The rate of combined liver and kidney transplant doubled (2.6% in 2001 vs. 5.2% in 2005) in the pre-MELD era [21].

We have recently shown that serum creatinine is over weighted in the MELD formula. An updated MELD, derived from a cohort of 38 899 candidates awaiting LT using a time-dependent Cox regression model with MELD components as predictors of waiting list mortality, assigns a lower weight to creatinine and INR and a higher weight to bilirubin [23]. Updated MELD (c-statistic 0.68) performed better than existing MELD (c-statistic 0.64) in predicting overall waiting list mortality. Moreover, this study also showed that among candidates with the same MELD score, those with lower serum creatinine have significantly higher waiting list mortality risk compared with their counterparts with high serum creatinine [23]. Adoption of the more accurately weighted updated MELD formula is predicted to be associated with reduced waiting list mortality by reordering the offers of organs to those at higher risk of waiting list death. To date, however, the formula has not been updated for allocation use.

Liver allocation in the future

Liver transplantation is generally the best option for chronic end-stage liver disease patient survival. Merion *et al.* found that post-transplant mortality (covariate-adjusted) was approximately one-fifth that on the waiting list [14]. Were there enough organs, it appears that most patients would opt for LT. However, there is a wide gap between patients awaiting LT and available donor organs, necessitating the prioritization of patients for each available deceased donor liver.

It is now well-established that the comparison between post-LT and waiting list survival depends strongly on patient characteristics. When Merion *et al.* compared liver waiting list and post-transplant death rates by MELD score, the authors found that at higher MELD scores, the difference between pre- and post-transplant mortality was greater. Specifically, the covariate-adjusted hazard ratio (HR) was estimated at HR = 0.04 ($P < 0.001$), indicating that, all else equal, patients with MELD 40 have a 96% reduction in mortality post-transplant, relative to not being transplanted. For patients at lower MELD scores (e.g., MELD < 15), the HR > 1.0 ($P < 0.001$), indicating that waiting list mortality was significantly lower than post-transplant mortality; i.e. because of the relatively low

death rates at low MELD scores and a maximum of 1 year post-transplant follow-up available when the article was written.

A study by Merion *et al.* (as alluded to in the preceding paragraph) was based on a limited amount of post-transplant follow-up. It is well-known that post-transplant death rates are initially very high, owing to operative and peri-operative mortality; as described in detail by Wolfe *et al.* for kidney transplantation [25]. Conversely, waiting list mortality rates demonstrate no such phenomenon. Therefore, considering two studies of the same LT patients, the study with longer post-transplant follow-up should have the lower (average) post-transplant mortality rate. Merion *et al.* anticipated that future studies (presumably with longer follow-up) comparing pre- and post-LT mortality would yield more favorable results for LT given the same MELD scores, and this was indeed later demonstrated. Studies by Schaubel *et al.*, Lucey *et al.*, and Englesbe *et al.* [26–29] each revealed lower MELD category-specific post-transplant/waiting list HRs than Merion *et al.*, indicating greater improvement in mortality with (versus without) a deceased donor LT.

The degree to which the population as a whole gains from a valuable, yet scarce resource depends heavily on the resource allocation method. This widely accepted notion applies to the allocation of deceased donor livers. Patient survival is not uniform across LT recipients, there are recipient characteristics that affect graft survival [28]. Therefore, a transplant candidate's anticipated post-transplant prognosis should play a role in their prioritization for transplantation. Conversely, the candidate's prognosis in the absence of transplantation should also be considered. It appears that there are two valid yet competing criteria for prioritizing waiting list patients. It would be undesirable to give high priority to patients with poor post-transplant prognosis; it would be perhaps equally undesirable to assign high priority to patients for whom good outcomes are anticipated in the absence of transplantation. The concept of transplant survival benefit is intended to combine criteria for waiting list and post-transplant outcomes into a single score for ranking waiting list candidates.

Principles of organ allocation

Specification of the goal of an allocation system by the transplant community and society at large is the first step in the development of evidence-based allocation methodologies. In some countries, including Switzerland and the United Kingdom, the allocation system has moved beyond exclusive consideration of the risk of death on the waiting list. Post-transplant outcome or benefit is integrated into these systems, although they have mainly evolved in an informal manner applied by individual transplant programs.

Types of organ allocation schemes generally fall into one of three categories: utility, urgency, and benefit. Suppose a donor organ is to be allocated to one of three patients on the waiting list. In Table 3, we list the most important characteristics of the three wait-listed patients: how long each is predicted to live if they receive the transplant (labeled TX); if they do not receive a transplant (labeled WL), and predicted survival benefit derived from the transplant (B = TX − WL). A utility-based allocation system would rank candidates in decreasing order of predicted post-transplant survival, in which case patient 1 would receive the organ. An urgency-based system would offer the organ to the patient with the worst prognosis on the waiting list, i.e. patient 2 in our example. A benefit-based system would allocate to the patient with the greatest difference in post-transplant and waiting list outcomes, namely patient 3.

The patients in Table 3 illustrate the weaknesses of the utility- and urgency-based allocation systems. Utility-based systems identify patients with the best post-transplant prognosis; these patients may also be expected to do well in the absence of transplant. By contrast, urgency-based systems give top priority to patients expected to die most quickly on the waiting list, at the risk of selecting patients who (because of their deteriorated condition) are doomed with or without a transplant. Transplant benefit-based allocation assigns priority in order of how much additional lifetime the patient is projected to receive, incorporating their predicted survival time both with and without a transplant.

Table 3. Organ allocation schemes: application of utility-, urgency- and benefit-based allocation.

Patient	Predicted lifetime		Predicted transplant survival benefit (B) B = TX − WL	Additional survival time gained by population
	Post-transplant (TX)	Waiting list (WL)		
1	10	7	3	17 = 10 + 2 + 5 = 3 + (7 + 2 + 5)
2	3	2	1	15 = 7 + 3 + 5 = 1 + (7 + 2 + 5)
3	9	5	4	18 = 7 + 2 + 9 = 4 + (7 + 2 + 5)

If the goal of an allocation system is to make the biggest difference to the patient population, then one would prefer to allocate by transplant survival benefit, evident in the last column of Table 3. Before the organ is allocated, the total future lifetime (across all waitlisted patients) equals the sum of the WL column; this calculation is unaffected by whether or not the organ is actually transplanted. The only patient affected by the available donor organ is the patient who receives the transplant; this patient is expected to receive *B* additional years of life as a result of the transplant. Therefore, to maximize the additional lifetime gained by the patient population as a whole, each transplant should be assigned to the patients with the greatest difference in predicted number of future years lived (with the transplant, versus without).

The primary strength of benefit-based allocation is that, for any fixed pool of donor organs, the number of additional patient-years gained through transplantation will be maximized. Granted, the setting we consider is very simple; but, the essential ideas carry over to much more complicated scenarios. More complicated data structures would imply more complex computations to predict TX, WL, and hence, *B*; but our discussion thus far is agnostic as to how exactly TX, WL and *B* are predicted.

Development of a liver benefit score for allocation

There has been considerable work to develop a LT survival benefit score and an excellent summary of progress to date has been recently published [28]. In its current form, the benefit score is computed as the difference between 5-year predicted post-transplant lifetime and 5-year predicted future waiting list lifetime (i.e., survival time in the absence of LT). Higher scores indicate greater benefit, i.e., a greater difference between a candidate's survival prospects with the transplant versus without.

The score is donor- and recipient-specific. For each deceased donor liver to be allocated, active waiting list candidates would be ranked in decreasing order of the benefit score, accounting for the effect of the specific donor's characteristics as well as the characteristics of the intended recipient. Thus, the benefit score would replace MELD as the central criterion for prioritization of LT candidates.

Figure 1 illustrates the survival benefit score. Consider a LT candidate active on the waiting list. Given the patient's characteristics and the characteristics of the donor, we can project a predicted post-transplant survival curve to represent the patient's survival if (s)he receives that organ; this is the upper curve in Fig. 1. Note that the curve is projected out to 5 years. The area under the post-transplant survival curve equals the predicted number of years that patient would live, out of the next 5 years, with this donor liver. Given the waiting list candidate's characteristics, we can also predict survival (from the date of offer) in the absence of LT. Predicted waiting list survival is given by the lower curve in Fig. 1, the area under which equals the predicted number of years the patient will live in the absence of LT, out of the next 5 years. The survival benefit score is the area between the predicted post-transplant and waiting list survival curves.

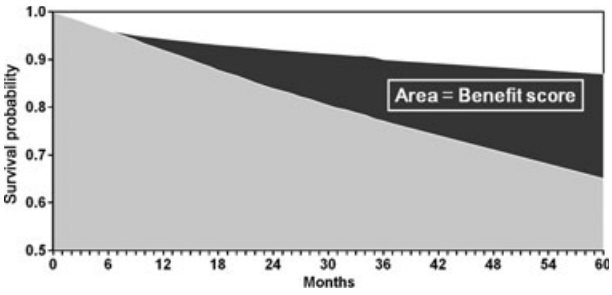

Figure 1 Liver transplant survival benefit is calculated by measuring the difference between the area under the waiting list survival curve (light shading) and the area under the post-transplant survival curve (dark shading) over a 5-year interval.

Liver allocation was originally based on waiting time. The Status-based system represented a major step forward, especially as CTP score was incorporated as an objective measure. The MELD system represents another incremental step forward, but remains an urgency-based allocation system that is suboptimal for organ stewardship. The components of the MELD score are incorrectly weighted, as noted above, and many patient characteristics aside from MELD and its components have proven to be significant predictors of waiting list survival. Considering survival benefit, MELD is, unfortunately, an inaccurate predictor of post-transplant survival. For these reasons, the ordering of

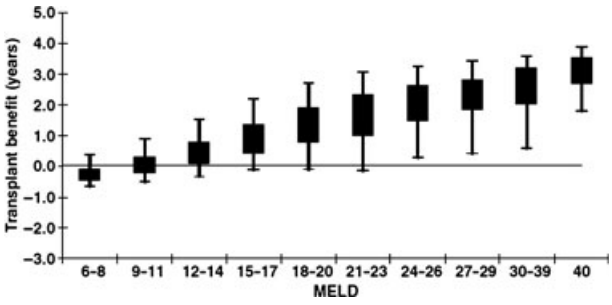

Figure 2 Calculated transplant benefit varies considerably by Model for End-stage Liver Disease (MELD) score and there is marked heterogeneity of calculated benefit within MELD score categories. As a result of the extensive overlap in benefit across MELD scores, candidates would be re-ordered if transplant benefit were utilized for allocation instead of MELD. Adapted from Schaubel DE *et al. Am J Transplant* 2009; **9**: 970.

waitlisted patients would change substantially under a benefit-based allocation system. Two patients with identical MELD scores may have dramatically different waiting list survival and/or post-transplant survival and hence, very different benefit scores (Fig. 2). A patient with a MELD 30 could have a benefit score that is less than a patient with a MELD 20. The rank correlation between the benefit and MELD scores is estimated at 0.67 (perfect correlation would equal 1) which is very low considering the two measures being compared are intended to serve the same function (i.e., allocation score). We anticipate that switching from MELD to benefit-based allocation would have immediate substantial effects. Liver Simulated Allocation Model results predicted that, based on one calendar year of experience, benefit-based allocation would result in at least 100 fewer deaths [28]. More importantly, switching from MELD- to benefit-based allocation was predicted to produce more than 2000 additional life-years saved, considering only the first 5 years of follow-up. If maximizing additional survival time gained via LT is the overall objective, it appears that the next logical step is toward survival benefit-based allocation.

Conclusions

Evidence-based development of liver allocation has progressed dramatically over the past 25 years. Early *ad hoc* arrangements between donor hospitals and transplant programs have led to increasingly sophisticated metrics designed to assess the risk of death of waiting candidates in the absence of a transplant. In recent years, the MELD system has become the standard for evidence-based liver allocation in the US, as well as several countries in Europe and South America. The future of liver allocation appears poised to incorporate more objective measures of post-transplant outcome into allocation systems, to gauge the incremental lifetime afforded to waiting patients and to ensure that society makes the wisest decisions as stewards of the scarce supply of donor organs.

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