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Article *in* Transplantation · June 2015
DOI: 10.1097/TP.0000000000000817 · Source: PubMed

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Commentary

Organ Transplantation: An Introduction to Game Theory

Anton I. Skaro, MD, PhD,[1] Gordon Hazen, DPhil,[2] Daniela Ladner, MD, MPH,[1] and Bruce Kaplan, MD[2]

The transplantation system serves as a shining example of ongoing quality assessment and performance improvement. This was facilitated by the creation of a federally mandated registry administered by the Organ Procurement and Transplantation Network.[1,2] Subsequently, these data are analyzed by a separate federal contractor, the Scientific Registry for Transplant Recipients, generating program specific reports assessing the performance of transplant programs across the United States, which at the time was unprecedented in any field of health care.[3] This infrastructure has provided a platform for the ongoing evaluation of the scientific and clinical status of organ transplantation. It has fostered transparency in risk communication and provided vital data used to inform patient, clinician, policy-maker, and payer decision making.[4] It is these features which have characterized the transplantation system as perhaps a successful example of an early iteration of the Learning Healthcare System which has only more recently garnered attention as part of the ongoing debate over health care reform.[5]

The national data that are reported to the Organ Procurement and Transplantation Network and analyzed by the Scientific Registry for Transplant Recipients truly are an asset of the transplant community. These data are integral to the development and reform of national organ allocation policy.[2] Moreover, registry data provide a foundation for the creation of transplant-specific quality metrics that are the focus of quality assurance program improvement initiatives, as well as fuel discussions surrounding refinement of value-based purchasing systems for the delivery of transplantation services. Although these aspects of transplantation have positively distinguished it from other areas of health care, there are issues which require attention if transplantation is to remain a leader.

First, the use of aggregate national data to inform quality metrics, such as waiting time or length of stay in the absence of the context provided by location-specific and more granular covariates, such as organ quality/availability, candidate disease severity, and transplant center or patient decision-making behavior is inaccurate and potentially hazardous.[6] For instance, current models make the flawed assumption that decision makers, including patients and transplant centers, act solely to maximize the societal benefit associated with organ transplantation rather than their own individual benefit. Within the organ allocation system, a patient reacts to an organ offer in anticipation of higher individual benefit; or if the decision is made by a transplant center, it should primarily benefit the patient(s) listed for transplantation at that center. For instance, a positive societal benefit would be incurred with greater utilization of high (>85%) kidney donor profile index kidneys and donation after circulatory death (DCD) livers realized through a reduction in the waitlist and candidate disease severity.[7-9] However, this might occur to the detriment of certain subpopulations of individual patients.[10,11]

The tools used throughout the organ allocation policy development and reform process are incapable of modeling complex behavioral responses to the environment created by allocation policy. Thus, unintended consequences of policy changes can and do occur. For instance, when the kidney allocation system was altered to include priority points for pediatric candidates to enhance their access to kidneys from deceased donors younger than 35 years, an abrupt decline in living donor transplants among pediatric recipients was observed.[12,13] Similarly, United Network for Organ Sharing implementation of the Model of End-stage Liver Disease has seen a dramatic increase in simultaneous liver and kidney transplants, making fewer kidneys available for kidney waitlist candidates.[14]

In addition, the Centers for Medicare and Medicaid services use of the program-specific reports to determine accreditation/reaccreditation for participation in the Medicare reimbursement program [15] might dramatically influence transplant center programmatic and patient-level decision making.[3] With a growing focus by funding (Patient-Centered Outcomes Research Institute) and regulatory (Food and Drug Administration) agencies toward patient-centered and personalized medicine,[16,17] transplantation regulators must increasingly consider the objectives and decision-making behavior of transplant centers and their patients.

For the aforementioned reasons, the discipline of transplantation should increasingly consider the complex behavioral aspects of decision-makers including patients and transplant centers. Interestingly, these are issues that game theory models are uniquely designed to accommodate. In fact, game theory more recently has been applied to justify the play calling during the final seconds of the controversial end of Super Bowl XLIX.[6] The remainder of this manuscript will broadly introduce game theory and discuss how it might be applied to the transplantation system.

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[1] Comprehensive Transplant Center, Northwestern University Feinberg School of Medicine. Chicago, IL.

[2] Comprehensive Transplant Center, University of Kansas, Kansas City, KS.

The authors declare no funding or conflicts of interest.

Correspondence: Anton I. Skaro, MD, PhD, Department of Surgery, Comprehensive Transplant Center, Northwestern University, Feinberg School of Medicine, Arkes Family Pavilion, Suite 19-087, 676 North St. Clair Street, Chicago, IL 60611-2923. (askaro@nm.org).

ISSN: 0041-1337/15/9907-1316

DOI: 10.1097/TP.0000000000000817

Game theory was first developed in 1944 by von Neumann and Morgenstern to better model economic systems.[18] They argued that economics does not adhere to mathematics designed to describe the "workings of a disinterested nature." Instead, they observed economics to behave like a game with players each using strategy, which considers that of their counterpart. Game theory is the study of strategic decision making. More formally, it is "the study of mathematical models of conflict and cooperation between intelligent rational decision-makers".[19] Game theory has found its major usage in economics and business for modeling competing behaviors of interacting agents. Applications include a wide range of economic phenomena, such as auctions, bargaining, oligopolies, mechanism design, and voting systems.[20] However, game theory has been broadly applied to health-related fields including neuroscience,[21] oncology,[22] surgery,[23] and kidney transplantation.[24]

According to game theory, games may be classified according to a number of parameters (Table 1). Most obviously, games can be categorized into 1-player, 2-player, or n-player (n greater than 2) games, each with distinguishing characteristics. Whether the large pool of wait list candidates and/or the numerous transplant centers are considered players, organ transplantation strictly satisfies the criterion of an n-player game. Solving for the organ transplantation game may however be cumbersome and computationally difficult given the large number of players. The organ allocation system is an example of a game with imperfect information since vital data are either false, incomplete, or missing altogether, in contrast to games based on perfect information, such as chess, where all players possess complete information at all times. Games may be further classified according to whether the objectives of the participants are in alignment or not. For instance, in constant-sum games, also known as zero-sum, if 1 player gains the other loses such that their objectives are in total conflict. Similarly, a donor organ whether it be a kidney, pancreas, liver, heart or lung, either is used in 1 transplant candidate or another leading most to believe that it is consistent with a zero-sum game. However, after deeper examination of the allocation system, it is apparent that the outcome or payoff of organ utilization in 1 candidate or another may be vastly different. Thus, the organ allocation system may more appropriately be classified as a variable-sum or non-zero-sum game, which is characterized by participants that can all gain or suffer together. The variable-sum category can be further subdivided into games that are cooperative, where players communicate toward developing binding agreements, and noncooperative, where players are unable to make enforceable contracts. Arguably, when organ offers are made little or no communication or binding agreements are made between candidates or their transplant centers such that the noncooperative designation seems appropriate. Finally, organ allocation is an example of a finite game with a finite albeit large number of players making finite choices to accept or reject an organ offer.

In noncooperative games, a crucial concept is called the Nash Equilibrium (NE).[25] The NE is a set of strategies in which each strategy is a best response to the strategy of others. Thus, no single participant has a unilateral incentive to deviate.[25] Stated simply, a group of players are in NE if each one is making their best decision while considering the decisions of the others in the game. Solving for the NE of a noncooperative game might therefore provide useful insights toward what unintended consequences may develop as a consequence of the milieu created by policy changes to the organ allocation system.

Game theory models that include a dynamic component are called stochastic games. Given the dynamic nature of the progression to end-stage organ failure and waxing and waning candidate disease severity, a stochastic approach is warranted. Stochastic games were first introduced by Shapley in 1953.[26] Shapley demonstrated the existence of value and optimal stationary strategies for zero-sum discounted stochastic games. A stochastic game is a dynamic game with probabilistic transitions played by one or more players. The game is played in a sequence of stages. At the beginning of each stage, the game is in some state. The players select actions and each player receives a payoff that depends on the current state and the chosen actions. The game then moves to a new random state whose distribution depends on the previous state and the actions chosen by the players. The procedure is repeated at the new state and play continues for a finite or infinite number of stages. The total payoff to a player is often taken to be the discounted sum of the stage payoffs. A stationary strategy is one in which the rule of choosing an action is the same in every stage. Note that this does not imply that the action chosen in each stage will be the same. Since that time, iterative developments have culminated in the description of average payoff non–zero-sum stochastic games with many states.[27] These refinements allow us to seek for equilibrium solutions for n-person

TABLE 1.

Game Theory Classification Scheme

No. Players (n)	1	2	n > 2
Level of information	Perfect	Imperfect	
Alignment of objective function	Constant-sum (zero-sum)	Variable-sum (non–zero-sum)	
		Cooperative	
		Noncooperative	
Options	Finite	Infinite	
Form	Extensive	Normal (strategic)	Characteristic-function

The games studied in game theory are well-defined mathematical objects which specify the following elements: the number of players, the information, the actions available to each player, and the payoffs for each outcome. These elements along with a solution concept are used to deduce a set of equilibrium strategies for each player such that, when these strategies are used, no player can profit by unilaterally deviating from their strategy. These equilibrium strategies determine an equilibrium to the game—a stable state in which either one outcome occurs or a set of outcomes occur with known probability. Cooperative games characterized by collusion among players are typically presented in the characteristic function form in which the payoff is shared and separate rewards are not given. Examples of noncooperative games include the extensive form with a time sequencing of moves that are played on trees, whereas normal/strategic forms are usually represented by a matrix which shows the players, strategies, and payoffs.

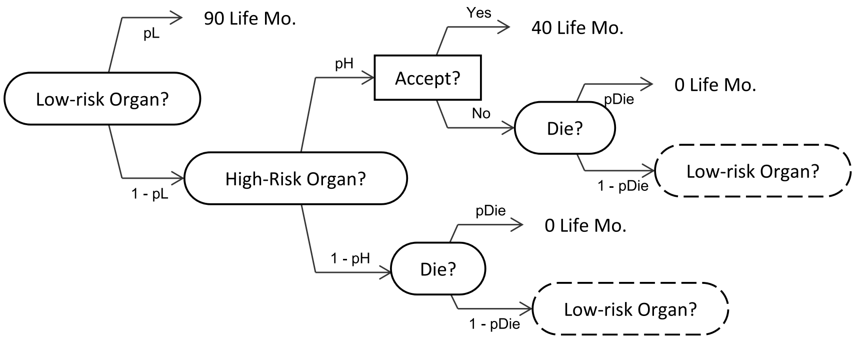

FIGURE 1. The extensive form of the sequential game depicting the decisions, risks and payoff in life months for a waitlisted patient when considering transplantation with low-risk and high-risk organs.

stochastic game models and provide the basis for their use to model complex systems such as organ allocation.[27]

For instance, organ scarcity has led Centers for Medicare and Medicaid services to encourage the use of DCD organs.[4] At first glance, it is straightforward that when more organs are provided, more patients can enjoy the benefit of transplantation leading to a shorter waitlist and distributive benefit. However, DCD livers are associated with higher complication rates, inferior survival, and higher costs[28-33] invoking a lower average post-transplant benefit. Moreover, increasing marginal organ offers leads to more choices for patients and their transplant centers leading to greater selectivity and a higher likelihood of organ discard. Thus, the societal impact of such a policy change is indeed indefinite and warrants evaluation using a stochastic game approach.

Consider a hypothetical transplant regime depicted in Figure 1, where a waitlisted patient anticipates an organ offer that may be of low risk or high risk. Here risk is characterized by the expected number of life months (quality adjusted) following transplant, 90 for a low-risk organ and 40 for a high-risk organ. The patient will accept a low-risk organ if it is offered, but may decline a high-risk offer. If there is no low-risk offer, and the patient declines or does not get a high-risk offer, then the patient may die. If the patient receives no transplant and survives, then the situation repeats. The probability *pL* of a low-risk offer and the probability *pH* of a high-risk offer depend on the behavior of other individuals on the waitlist, as summarized in Figure 2. As the proportion of the waitlist accepting high-risk organs increases, the probability an individual gets a low-risk offer increases because fewer candidates on the waitlist remain to compete for such offers. However, the probability an individual gets a high-risk offer decreases because other candidates are accepting these organs. It should be stressed that the numbers in Figure 2 are hypothetical inputs that in practice would need to be estimated from waitlist observations.

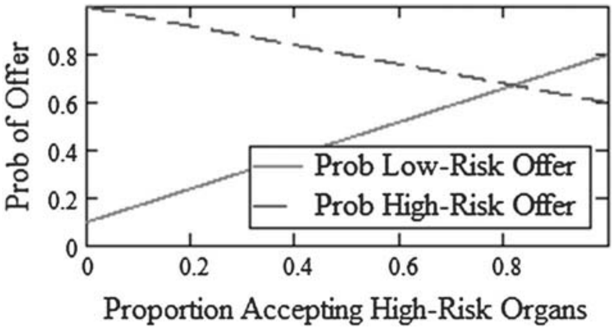

FIGURE 2. The probability a waitlist participant receives a low-risk (solid red line) or a high-risk (dashed blue line) organ offer depends on the proportion of the waitlist accepting high-risk organs.

Assuming individuals maximize their expected life months, how would they behave? Treating this situation as a stochastic game, we can calculate equilibrium behavior based on the Figure 2 inputs. Equilibria are determined as in Table 2, which shows how an individual's expected life months depend on the behavior of the rest of the waitlist, and whether or not the individual accepts high-risk organs (HRO). Consider, for instance when there are only 1200 high-risk organs offered per year (the top portion of the table). For waitlist HRO acceptance percent below the boldface level (30%), it is preferable in terms of life months for an individual to accept rather than decline an HRO. Therefore, individuals would have incentive to accept HROs if they were not already doing so. Above the boldface level, the reverse occurs—individuals would have incentive to decline HROs. It is only at the boldface level (30% accepting HROs) where accepting and declining HROs have equal expected life months, and individuals have no incentive to change behavior. The boldface 30% level of HRO acceptance is therefore the equilibrium acceptance level—the level which, if reached, would persist

TABLE 2.

In This Transplantation Game, the Payoff in Expected Life Months for an Individual Depends on the Percent of the Waitlist Accepting HRO, Which Itself Depends on High-Risk Organ Availability

1200 High-Risk Organs/y	**Percent of Waitlist Accepting High-Risk Organs**						
Life months	20%	22%	24%	26%	28%	**30%**	32%
Individual accepts HRO	52	53	53	54	55	**55**	56
Individual declines HRO	48	49	51	53	54	**55**	57
2000 high-risk organs/y	**Percent of waitlist accepting high-risk organs**						
Life months	20%	22%	**24%**	26%	28%	30%	32%
Individual accepts HRO	54	55	**56**	57	58	58	59
Individual declines HRO	52	54	**56**	58	59	61	62

The matrices depict distinct equilibria in life months between accepting and declining HRO when few (upper matrix) and many (lower matrix) HRO are available. It is only at the boldface equilibrium points that individuals have no incentive to change HRO acceptance behavior.

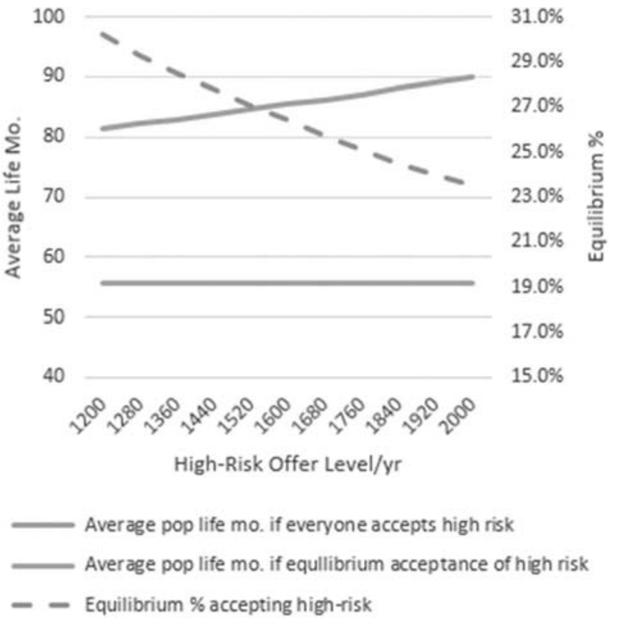

FIGURE 3. Results of increasing availability of high-risk organs. Solid lines depict population payoff in life months (left axis), and dashed line depicts equilibrium high-risk organ acceptance percentage (right axis).

over time due to lack of incentives to change. When there is a greater availability of HROs (2000/year—the second portion of Table 2), incentives are different and a different equilibrium level (24% accepting HROs) results.

The most striking feature of these results is that the equilibrium level of acceptance of high-risk organs is not 100%. In fact—and this is also interesting—this level decreases as high-risk organ availability increases, falling from 30% to 24% as available HROs increase from 1200/year to 2000/year. These results are shown in greater detail in Figure 3. Yet another interesting feature is that average population life months at equilibrium is considerably lower than it would be if there were 100% acceptance of high-risk organs. In fact, equilibrium life months do not change as high-risk organ availability increases. This is because the acceptance rate for high-risk organs declines. It occurs even though expected life months at 100% acceptance *does* increase with high-risk organ availability. The lesson here is that game-theoretic equilibrium analysis accounts for individual behavioral response to policy change, and so may give results that violate naïve expectations. In this simple example, increasing the level of high-risk organ availability does not benefit the waitlist population as one might expect, and only results in a lower acceptance level for high-risk organs.

In conclusion, although the discipline of transplantation has been a leader in health care by fostering evidenced-based practice, transparent outcome reporting, and development of quality metrics, there is room for improvement. In addition to the age old challenges of organ shortage and transplantation tolerance, the transplantation community should consider augmenting the data and analytics which have become the basis for increasing regulation. The unintended consequences of this and other policies might well be mitigated by the incorporation of stochastic game models to presently used modeling techniques for policy development and reform, and performance measurement and reporting.

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