Addressing US National Geographic Disparity in Kidney Transplantation By Creating Sharing Partnerships

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Abbreviations: DSA: Donor Service Area, ESRD: End Stage Renal Disease, KDRI: Kidney Donor Risk Index, OPTN: Organ Procurement and Transplant Network, PRA: Panel Reactive Antibody, UNOS: United Network for Organ Sharing

Abstract

Background: The national shortage of kidney organs has led to divergent waiting times for patients seeking transplantation in different regions of the country. Policy-makers wish to promote greater equity, but only with minimal disruption to current patients.

Objective: KSHARE2 is a proposal to ameliorate geographic disparity with modest changes to an already complex allocation system. The model identifies a national and regional partner for each Donation Service Area (DSA) and redirects a pre-specified proportion of organs to localities with greater need.

Methods: We model each DSA as a $M/M/1/\infty +M$ queue and identify 3 performance measures: waiting time to transplantation, transplantation rate, and mortality. Using Efficiency-Driven heavy traffic approximations, we deduce relationships among the performance measures while simultaneously solving a deterministic mixed-integer linear program to determine the optimal sharing partners for each DSA. To incorporate stochasticity, we initialize a more accurate simulation model of the allocation system with the deterministic solution and then employ a heuristic to find better partnerships. The long-run behavior of the proposed policy is then analyzed using heavy traffic approximations.

Results: When 40% of available kidney organs are redirected, the national range of average transplant rates, mean waiting times, and mortalities decreased by approximately 29%, 39%, and 29%, respectively - indicating significantly less disparity than the current allocation system. Smaller proportions of redirected kidneys yield lesser reductions.

Conclusions: Promoting greater fairness in patients' transplantation experiences and outcomes is critical and discovering practicable solutions for complex applications requires several methodologies.

Introduction

End Stage Renal Disease (ESRD) currently affects over 700,000 people in the United States (US) (1). ESRD patients receive treatment in the form of dialysis or kidney transplantation. Compared to dialysis, kidney transplantation provides increased quality of life, decreased morbidity and mortality, and is more cost-effective (2-11). Unfortunately the national organ shortage has continued to worsen over time. While over 94,000 patients are currently listed for kidney transplantation, only 17,000 kidney transplants took place in 2012 (12, 13). The equitable distribution of this scarce organ supply is therefore paramount.

The United Network for Organ Sharing (UNOS) is responsible for establishing organ allocation policies. Since kidney organs must be allocated efficiently to avoid the harmful effect of cold ischemic time (CIT), UNOS segmented the country to prioritize localized allocation (14, 15). First, the country is divided into eleven UNOS regions, which are groupings of neighboring states. Each of these regions is further subdivided into Donor Service Areas (DSAs) with 58 DSAs in total in the US. Each DSA has a designated Organ Procurement Organization (OPO) that is responsible for facilitating the donation and allocation of all locally procured kidney organs. When a kidney is donated, the organ is first offered to patients in the DSA of procurement. If local allocation is not successful, then the organ is offered to patients listed in the UNOS region of procurement and ultimately nationally until a recipient is found (15).

A patient's ability to receive a kidney transplant depends on where they seek transplantation. Moreover, mortality rates and waiting times have continued to diverge across regions over time (16, 17). In 1998, the Department of Health and Human Services (HHS) released the "Final Rule," stating that organ allocation should be geographically equitable (18). Since this ruling though, no changes have been implement explicitly regarding the geographic distribution of kidney organs, and by 2009, median waiting times to kidney transplantation ranged across DSAs from 0.61 to 4.57 years (19). UNOS has recently shown a renewed interest in reducing geographic disparities, tasking each organ-specific allocation committee to develop geographic fairness metrics by June 30, 2013 (20). While there is yet no established consensus for measuring geographic disparity for kidney allocation, three performance measures have been proposed and analyzed: transplantation rate, waiting time to transplantation and pre-transplant mortality (16).

Other attempts have been made to resolve the geographic inequalities (21-23). This past research has focused on redesigning the configuration of all UNOS regions for the purposes of reducing geographic disparity. While this will not change the fundamental design of the geographic kidney allocation policy, it still imposes some barriers to beneficial implementation. First, UNOS policy changes are discussed at the regional level, with each UNOS region represented on the national UNOS kidney committee (24). In changing the UNOS region configurations, UNOS boards will also need to be reformed, which may be difficult for transplant community acceptance. Second, UNOS regions have traditionally been compact, consisting of neighboring states. If newly configured regions are not compact and/or cover a large geographic area, it would be practically difficult for OPOs to habitually share biological materials over longer distances to ensure there is a negative crossmatch, or a suitable match for a distant transplant recipient. Finally, there is no current evidence that such a system change would prove beneficial.

Fortunately, there is evidence however that a Statewide Sharing Local Allocation Variance can be beneficial in reducing geographic disparities in the states where it was implemented (25). With statewide sharing variance, a donated kidney is still offered first to patients in the DSA of procurement. If this allocation is unsuccessful, the kidney is offered to patients listed in other DSAs in the same US state prior to regional and national kidney offers (25). This variance is limited though in its potential national impact since sharing partnerships have historically been limited to DSAs in the same state. This empirical result is the foundation of our proposal: by identifying select partners for each DSA and having an intermediate allocation prior to regional allocation, we can help mitigate disparity without preempting local allocation. A regional and national partner for each DSA would help ameliorate the regional and national inequalities respectively. There is however a limitation on the number of such partnerships. Our discussions with clinicians revealed skepticism in allowing for more than one non-regional partnership, and therefore we focus our analysis on the case where each DSA is paired with one regional and one national partner.

The remainder of this paper is organized as follows. In Section 2, we discuss a stylized queueing network adaptation of the kidney transplantation system and fluid approximations for selected performance measures in the long-run. In Section 3, we detail an alternative kidney allocation strategy: KSHARE2, and in

Section 4 we formulate a deterministic mixed-integer linear optimization model in accordance with this new strategy that is aimed to improve disparity by identifying an optimal regional- and national- sharing partner for each DSA. Section 5 extends the deterministic model with a more realistic discrete-event simulation, and then discusses the proposed kidney sharing strategy and its impact on national geographic disparity. In Section 6, we again employ the heavy-traffic approximations to discuss how using the new allocation strategy will impact the system prospectively. We conclude in Section 7 by summarizing out findings and outlining the need for future research.

2. Kidney Transplantation Queueing Network and Long-Run Fluid Approximations of System Behaviors

At the system level, the national kidney transplantation network consists of 58 individual DSA waitlists. Since patients mainly receive blood type-compatible (ABO) kidneys for transplantation, each DSA waitlist decomposes by patient blood type. Thus, in essence there are four separate kidney transplantation systems by blood type. Each DSA blood type patient waitlist operates separately and they are connected together by the national organ allocation process.

2.1. The Kidney Transplantation Network

For a single DSA, patients of a specific blood type b arrive to their DSA i's corresponding blood type waitlist according to interarrival rate distribution $\lambda_{ib}(t)$ in year t. As established by Davis et. al., this patient interarrival rate distribution follows an exponential distribution with increasing mean interarrival rates over time (26). Once a patient has joined the list, they are primarily prioritized by their time in the system.

Patients are removed from the waitlist for one of two reasons. First, a patient may survive long enough on the list to reach the front of the waitlist and find a suitable match for transplantation. Patients are "serviced" from the list according to the interarrival time between organs of a specific blood type b arriving for transplant in DSA i in time period t, $\mu_{ib}(t)$ – also established to be exponentially distributed (26). Unlike patient interarrival rates, the interarrival rate of kidneys for transplantation is not significantly changing over time. This transplant "service" time depends on the national kidney allocation policy and kidney procurement rates for each DSA. Let $s_{ib}(t)$ represent the interarrival rate of kidneys of blood type b being donated for transplantation

in DSA i in time period t. This interarrival rate is exponentially distributed and time-varying (26). In accordance with a given kidney allocation policy, the likelihood that a kidney procured in DSA i will be shared with another DSA j in time period t can be estimated from past allocation data, $p_{ijb}(t)$. The transplant service rate, $\mu_{ib}(t)$, is then determined by the linear combination of kidney procurement rates from each DSA.

$$\mu_{ib}(t) = \sum_{j \in OPOs} p_{ijb}(t) * s_{jb}(t)$$

Patients can also be removed from the transplant system because they are too sick to transplant and/or die. This happens because ESRD patients can only sustain their life on dialysis for a limited amount of time.. The individual mean abandonment time from a DSA i's waitlist of a patient with blood type b in year t can be represented by the mean total dialysis time of an ESRD patient, $\gamma_{ib}^{-1}(t)$. Then, $\gamma_{ib}(t)$ represents the individual patient abandonment rate from DSA i's waitlist. Davis et. al. also showed that the individual abandonment time distribution is exponentially distributed (26).

Finally, because of the national organ shortage, each DSA blood type waitlist "queue" is overloaded with a traffic intensity, $\rho_{ib}(t) = \frac{\lambda_{ib}(t)}{\mu_{ib}(t)} \gg 1$. Given this information and the exponential properties of each DSA's waitlist, each DSA waitlist may be modeled as a heavy-traffic M/M/1/r+M queueing system, with all DSA waitlist queues connected by the national organ allocation policy.

2.2. Fluid Approximations of Long Run Waitlist Behaviors

Changing the national kidney allocation policy involves multiple steps and many hurdles. First, the UNOS Kidney Committee, consisting of membership from all eleven UNOS regions, develops a new policy given the latest data and requests from the general community for change. Next, the proposed policy is released for Public Comment, whereby advocate groups, current patients, and the general public can provide feedback. If the policy is received favorably in the Public Comment period, the proposed policy proceeds for review by the UNOS General Board who certifies or denies the proposal (27).

Because of this multi-level process, complex changes to the kidney transplantation system are difficult to pass to implementation. For example, in 2009 the UNOS Kidney Committee attempted to change how patients were prioritized for transplant using a Life Years from Transplant (LYFT) score (28). This ranking

score was too complex for patients to understand their placement in the system and advocacy groups worried how it would negatively impact older patient subgroups. When the LYFT policy failed, the American Society of Transplant Surgeons (ASTS) urged that future proposed policies be presented through frequent communication with members of the general public, be easily comprehendible, and provide a stepwise implementation structure to phase in a new policy over time (29). Therefore, our goal is to eliminate geographic disparity in long-run DSA waitlist behaviors across all DSAs using small, incremental changes over time. We will now construct the long-run fluid approximations of transplant system outputs for each queue.

In Section 2.1, the DSA kidney waitlists were defined and discussed as heavy-traffic M/M/1/r+M queueing systems, connected together via the national kidney allocation policy. Previous work by Whitt et al. (2004) defines fluid approximations for long run queue behaviors for M/M/s/r+M queueing networks (30). In the Appendix, these long run queue behaviors are shown to extend to our transplant system queueing network setting. We will now motivate why each long run queue behavior is important to discuss geographic disparity in the transplant system setting.

Long-Run Transplant Rate: Upon joining any DSA's waitlist, a patient should have the same likelihood of receiving a kidney transplant over time. In 1999, the Institute of Medicine supported the use of transplant rate as a measure of geographic disparity (31). In the long-run, steady state of the system, this likelihood of a patient listed in DSA i of blood type b receiving a transplantation over time, $TR_{ib}(t)$ is approximated by the relationship between $\lambda_{ib}(t)$ and $\mu_{ib}(t)$:

$$TR_{ib}(t) = \frac{\mu_{ib}(t)}{\lambda_{ib}(t)}, \quad \forall\, i \in OPOs, b \in Blood\ Type, t \in Years$$

Long-Run Waitlist Mortality Rate: Upon joining any DSA's waitlist, a patient should have the same likelihood of becoming too sick and/or dying on the waitlist prior to transplantation. A goal in society is to minimize this probability as much as possible across all DSAs. In the long-run, steady-state of the system, the waitlist mortality rate for patients listed in DSA i of blood type b, $MR_{ib}(t)$ is approximated by the following relationship between $\lambda_{ib}(t)$ and $\mu_{ib}(t)$:

$$MR_{ib}(t) = \frac{\lambda_{ib}(t) - \mu_{ib}(t)}{\lambda_{ib}(t)}, \quad \forall\, i \in OPOs, b \in Blood\ Type, t \in Years$$

Long-Run Mean Waiting Time to Transplantation: Patients are currently prioritized on the kidney transplant waitlist primarily according to their waiting time in the system (15). Therefore, in the long-run, steady-state transplant system, we would like all patients to wait the same amount of time for transplantation. The mean long-run waiting time for patients in DSA i of blood type b, $WT_{ib}(t)$, can be approximated by the following relationship between $\lambda_{ib}(t)$, $\mu_{ib}(t)$, and $\gamma_{ib}(t)$:

$$WT_{ib}(t) = \left(\frac{1}{\gamma_{ib}(t)}\right) * \ln\left(\frac{\lambda_{ib}(t)}{\mu_{ib}(t)}\right), \quad \forall\, i \in OPOs, b \in Blood\ Type, t \in Years$$

Each of these measures need to be stabilized as much as possible via changes to the national organ allocation policy, and subsequently $\mu_{ib}(t)$. Creating an optimization model to determine alternative values of $\mu_{ib}(t)$ would result in the creation of highly complex, multi-objective non-linear optimization models. Therefore, let us revisit these three fluid approximations. As shown below, each fluid approximation can be represented by a monotone function of transplant rate. One minor assumption must be made to achieve this simplification is that the abandonment rates at each DSA i for blood-type b at time t is the national average; namely $\gamma_{ib}(t) \approx \bar{\gamma}_{ib}(t)$. The assumption implies that all patients can survive on average the same amount of time pre-transplantation and ignoring the regional differences in dialysis quality. Thus, we can rewrite the three performance metrics as the following:

$$TR_{ib}(t) = \frac{\mu_{ib}(t)}{\lambda_{ib}(t)}, \quad \forall\, i \in OPOs, b \in Blood\ Type, t \in Years$$

$$MR_{ib}(t) = 1 - \frac{\mu_{ib}(t)}{\lambda_{ib}(t)} = 1 - TR_{ib}(t), \quad \forall\, i \in OPOs, b \in Blood\ Type, t \in Years$$

$$WT_{ib}(t) = \left(\frac{1}{\gamma_{ib}(t)}\right) * \ln\left(\frac{\lambda_{ib}(t)}{\mu_{ib}(t)}\right) \approx \left(\frac{1}{\bar{\gamma}_{ib}(t)}\right) * \ln\left(\frac{1}{TR_{ib}(t)}\right), \quad \forall\, i \in OPOs, b \in Blood\ Type, t \in Years$$

Given the approximation, geographic disparity with respect to all long-run system outputs can best be reduced by focusing on the reduction in transplant rate disparity. We will now move forward to discuss an alternative kidney sharing strategy that aims to reduce national long run kidney transplant rate disparity as much as possible.

3. KSHARE2 Kidney Sharing Strategy

Previous analysis has shown that the statewide sharing local allocation variance has improved geographic disparity in the states where it was implemented (32). By this variance, if a procured kidney cannot be allocated locally, the organ is offered to patients listed in other DSAs in the same state prior to regional and national kidney offerings (25). While this strategy functions well for reducing statewide geographic disparity, implementing statewide sharing in all states will still not eliminate national geographic disparity as disparity will still remain between states.

A past analysis focused on testing a statewide sharing-based kidney sharing strategy, which allows sharing partnerships to be formed between DSAs in different states but still within a feasible distance for habitual sharing, known as KSHARE (36). This analysis showed that outside-of-state sharing partnerships that are within 600 miles from the DSA of sharing can reduce national disparity. This strategy fails however to be potentially implementable since to date, no organ allocation policy or local allocation variance has allowed for habitual sharing between DSAs in different UNOS regions (25). Further, changing the retention of kidney organs locally, regionally or nationally will be a politically difficult challenge to garner transplant community support (37). We will now develop a new alternative kidney sharing strategy KSHARE2 that takes these new concerns into consideration.

In KSHARE2, each DSA will have one regional DSA sharing partner and one national DSA sharing partner. Following the KSHARE2 policy, when a kidney is not allocated locally, the kidney will be offered to the DSA's regional sharing partner prior to full regional kidney sharing. Then, if regional allocation is not possible, the kidney will be offered to the DSA's national sharing partner prior to full national kidney sharing. KSHARE2 therefore adds two minor prioritizations to the current kidney allocation system. The best regional and national sharing partner for each DSA is determined so as to best reduce national geographic disparity in long-run DSA transplant rates. The feasible set of regional sharing partners for each DSA depends on the UNOS region of the DSA, ranging from 1 to 9. The feasible set of national sharing partners for each DSA depends also on the UNOS region of the DSA, ranging from 48 to 56.

There are advantages and disadvantages to the KSHARE2 strategy. First, KSHARE2 presents a small change to the current UNOS kidney allocation policy and does not impact the retention of local, regional, and national kidney organs. Instead, the most disparate regional and national DSA are given priority for all kidneys not used locally in order to improve their system outputs. Also, by explicitly identifying each DSA's regional and national partner and establishing a formal relationship, individual DSAs can better manage logistics than if they had multiple, unspecified partners. A possible drawback to the KSHARE2 kidney sharing strategy is that not all DSAs will be on the receiving end of any DSA sharing partnerships and will see a slight reduction in their annual transplant volume. To reduce geographic disparity, however, changes to the flow of kidneys for allocation must be achieved. In maintaining locally procured kidney levels and portions of their regional and national kidney allocation levels, each DSA will not incur a large organ deficit.

4. Multi-Objective Optimization of Organ Flow to Improve Fluid Approximated Geographic Disparity

We will now discuss the formulation of the KSHARE2 optimization model.

4.1. Objective Function

As discussed in Section 2, the kidney transplantation system can be considered as the culmination of four DSA waitlist queuing networks with one for each blood type. In addition, geographic disparity reduction will have to be represented by blood type. We therefore aim to best reduce long run geographic disparity separately for each blood type while only establishing one consistent regional and national kidney sharing partnership for each DSA independent of blood type. To calculate the overall geographic disparity, a weight set must be established to determine how each blood type's geographic disparity contribution will be weighted in the multi-objective function. One option would be to equally weight each blood type's contribution. This may not be preferable however since the number of patients seeking transplantation is not the same across all blood types. Instead, we may take the perspective that geographic disparity should be reduced the most for the blood types with the most patients. The proportion of new registrations each year having each specific blood type varies over time. In Table 1 below, we show the distribution of patient registrations by blood type for 2000 through 2009. Instead of using the mean blood type distribution weights, we can minimize geographic disparity

for the worst case blood type distribution scenario. The optimal sharing partnerships will then be optimally robust against fluctuations to changes to the transplantation system.

Table 1: Distribution of New Patient Arrival Blood Types (2000-2009)

Year	Proportion of New Patients (%)			
	A	AB	B	O
2000	35.17	2.43	15.16	47.24
2001	33.34	6.45	12.68	47.53
2002	30.05	4.29	14.99	50.67
2003	31.37	3.05	17.13	48.46
2004	32.42	4.10	13.88	49.60
2005	34.25	5.43	11.79	48.53
2006	31.21	3.22	14.67	50.91
2007	33.73	4.06	12.60	49.61
2008	34.77	1.74	14.26	49.23
2009	30.82	3.02	15.02	51.14

4.2. KSHARE2 Model Assumptions

The KSHARE2 optimization model makes four assumptions about the present kidney transplantation system. First, waitlisted patient growth and annual kidney procurement per DSA for each year is assumed to be the same as that in actual retrospective data. Second, KSHARE2 ignores the stochastic and time-varying nature of the system, when in reality, we do not know the effect our change in policy will have on waitlisting and procurement rates. Third, the model treats all patients equally and does not focus on racial, age, and other patient subgroups individually, but in stabilizing the overall DSA kidney transplant rate we intend to stabilize the rate across all patient groups. Fourth, KSHARE2 assumes that if a kidney is offered to a DSA, then a patient in that DSA will accept the kidney. We will examine the impact of the optimal KSHARE2 policy when these model assumptions are relaxed via simulation and sensitivity analyses.

4.3. KSHARE2 Formulation

KSHARE2 is formulated as follows.

Parameters: Let Set I represent the set of all DSAs in the US. For each DSA i, let set J_i represent the set of all DSAs in the same UNOS region as DSA i and let set N_i represent the set of all DSAs that are not in the same UNOS region as DSA i. Let B represent the set of all possible blood types (A, AB, B, and O). Let T

represent the last year of the phase-in period. Let w_b represent a weight for blood type b from the weight set shown in Table 1. Let s_{ikb} and z_{ikb} represent the α% of regionally and nationally allocated kidneys, respectively, that are procured in DSA i of blood type b in year k that are eligible for redistribution by KSHARE2. KSHARE2 will be solved and discussed for various values of α. Let o_{ikb} represent the remaining kidneys transplanted in DSA i of blood type b in year k that were allocated via current kidney allocation policy. Let f_{ib} represent the number of patients of blood type b on DSA i's waitlist at the beginning of the phase-in process. Let l_{ikb} represent the number of new patient arrivals to DSA i's waitlist in year k of blood type b, and let r_{ikb} represent the number of patient removals from DSA i's waitlist in year k of blood type b. Let a_{ib} represent the total number of patient arrivals to DSA i of blood type b by the end of year T.

Variables: Let P_{ijb} represent the percentage of kidneys of blood type b shared from DSA i to a regional DSA sharing partner j each year according to KSHARE2. Let X_{inb} represent the percentage of kidneys of blood type b shared from DSA i to a national DSA sharing partner n each year according to KSHARE2. Let D_{ikb} represent the number of patients of blood type b on DSA i's waitlist at the start of year k. Let T_{ikb} represent the total number of transplants of blood type b in DSA i in year k. Let Y_{ij} be a binary variable that is set equal to 1 if DSA i establishes a regional sharing partnership with DSA j. Let Z_{in} be a binary variable that is set equal to 1 if DSA i establishes a national sharing partnership with DSA n. Let TR_{ib} represent the probability of transplantation for blood type b patients in DSA i, and let $minTR_b$ represent the minimum DSA probability of transplantation for blood type b.

Formulation: In Objective (1), we aim to minimize the worst-case weighted sum of blood type specific probability of transplantation geographic disparity – hereafter referred as the worst-case blood type weighted transplant rate disparity score. In Constraint (2), we set the initial waitlist size in DSA i for all blood types b. In Constraint (3), each DSA i's waitlist of blood type b patients is updated annually based on the growth of patients, removals from the waitlist, annual transplants, and waitlist size from the previous year. In Constraint (4), we set the number of transplants in DSA i of blood type b based on kidneys allocated to the DSA via KSHARE2 and current kidney allocation policy. Constraint (5) ensures that all kidneys from DSA i of blood type b that are eligible for alternative regional sharing are allocated. Constraint (6) confirms that sharing

between regional DSAs can only occur if a regional sharing partnership is formed between DSA i and j.

Constraint (7) makes sure that each DSA only has one regional sharing partner. Similarly, Constraint (8) ensures that all kidneys from DSA i of blood type b that are eligible for sharing between national DSAs can only occur if a national sharing partnership is formed between DSAs i and n. In Constraint (9), we confirm that sharing can only occur between national DSAs if a sharing partnership is formed between DSA i and DSA n.

Each DSA can only have one national sharing partner as restrained in Constraint (10). In Constraint (11), we calculate the probability of transplantation for each DSA i and blood type b at the end of the phase-in process. Constraint (12) determines the minimum DSA probability for transplantation for blood type b. Finally, Constraints (13) and (14) establish non-negativity and binary restrictions for all variables.

$$\max_{w_b} \min_{Y_{ij}, Z_{in}} \sum_{b \in B} \sum_{i \in I} w_b * (TR_{ib} - minTR_b) \tag{1}$$

s.t.

$$D_{i0b} = f_{ib} \, , \qquad\qquad\qquad \forall\, i \in I, b \in B \tag{2}$$

$$D_{ikb} = D_{ik-1b} + l_{ikb} - r_{ikb} - T_{ikb} \, , \qquad \forall\, i \in I, k = 1, \dots, T, b \in B \tag{3}$$

$$T_{ikb} = \sum_{j \in J_i} P_{jib} * s_{ikb} + \sum_{n \in N_i} X_{nib} * z_{ikb} + o_{ikb} \, , \qquad \forall\, i \in I, k = 0, \dots, T, b \in B \tag{4}$$

$$\sum_{j \in J_i} P_{ijb} = 1 \, , \qquad\qquad\qquad \forall\, i \in I, b \in B \tag{5}$$

$$P_{ijb} \leq Y_{ij} \, , \qquad\qquad\qquad \forall\, i \in I, j \in J_i, b \in B \tag{6}$$

$$\sum_{j \in J_i} Y_{ij} = 1 \, , \qquad\qquad\qquad \forall\, i \in I \tag{7}$$

$$\sum_{n \in N_i} X_{inb} = 1 \, , \qquad\qquad\qquad \forall\, i \in I, b \in B \tag{8}$$

$$X_{inb} \leq Z_{in} \, , \qquad\qquad\qquad \forall\, i \in I, n \in N_i, b \in B \tag{9}$$

$$\sum_{n \in N_i} Z_{in} = 1 \, , \qquad\qquad\qquad \forall\, i \in I \tag{10}$$

$$TR_{ib} * a_{ib} = \sum_{k=0}^{T} T_{ikb} \, , \qquad\qquad \forall\, i \in I, b \in B \tag{11}$$

$$MinTR_b \leq TR_{ib} \, , \qquad\qquad\qquad \forall\, i \in I, b \in B \tag{12}$$

$$D_{ikb}, P_{ijb}, X_{inb}, T_{ikb}, TR_{ib}, minTR_b \geq 0 \qquad \forall\, i \in I, j \in J_i, n \in N_i, k = 0, \dots, T, b \in B \tag{13}$$

$$Y_{ij} \in \{0,1\}, Z_{in} \in \{0,1\}, \qquad\qquad \forall\, i \in I, j \in J_i, n \in N_i \tag{14}$$

Solving the KSHARE2 optimization model provides the best, deterministic regional and national sharing partnership per DSA. However, when using these sharing partnerships in actual kidney allocation, slightly different DSA sharing partnerships may provide additional improvement. In Davis et al., 2013, we

developed a discrete even simulation model of the kidney transplantation system, called KSIM2, to evaluate alternative kidney sharing strategies at the system level (38). KSIM2 incorporates uncertainty in patient and organ arrival distributions when simulating the impact of an alternative kidney allocation policy and provides system outcomes at the DSA level for various patient demographics.

Using KSIM2, we study the stochastic impact of using an alternative kidney sharing strategy on national geographic disparity by DSA and patient demographic. Since simulation optimization methodologies are not yet advanced enough to optimize the stochastic flows of kidneys for this highly complex and constrained queueing network, we need to employ a heuristic technique. This heuristic technique searches for a sharing partnership swap for each DSA to improve upon the current reduction in geographic disparity. The DSA sharing partnership swap heuristic is repeated if an improvement is found. The heuristic search concludes once no improving sharing partnership swap is found for any DSA.

5. Optimal KSHARE2 Kidney Sharing Strategy

Optimal KSHARE2 DSA sharing partnerships were determined using CPLEX optimization solver (39). KSIM2 with the inclusion of the heuristic described in Section 5 was used, running 100 replications of ten years of the transplantation system (2000-2009) for each possible sharing configuration possible. Each replication of KSIM2 requires 52 minutes, 11.8 seconds CPU time. While the heuristic in Section 4 was used, the deterministic sharing partnership configuration could not be improved upon. We will now outline the optimal DSA sharing configuration and its ability to reduce geographic disparity after implementation over ten years.

5.1. Optimal KSHARE2 DSA Sharing Configuration

According to KSHARE2, each DSA has one regional and one national DSA sharing partner. In Figure 2, we can see that each DSA tends to share with the most disparate regional DSA and with one of the nationally most disparate DSAs. In doing so, we increase the efficient access to shared kidneys for these worst-off DSAs.

Figure 2: DSA Sharing Partnership Configuration for KSHARE2 with Blood Type
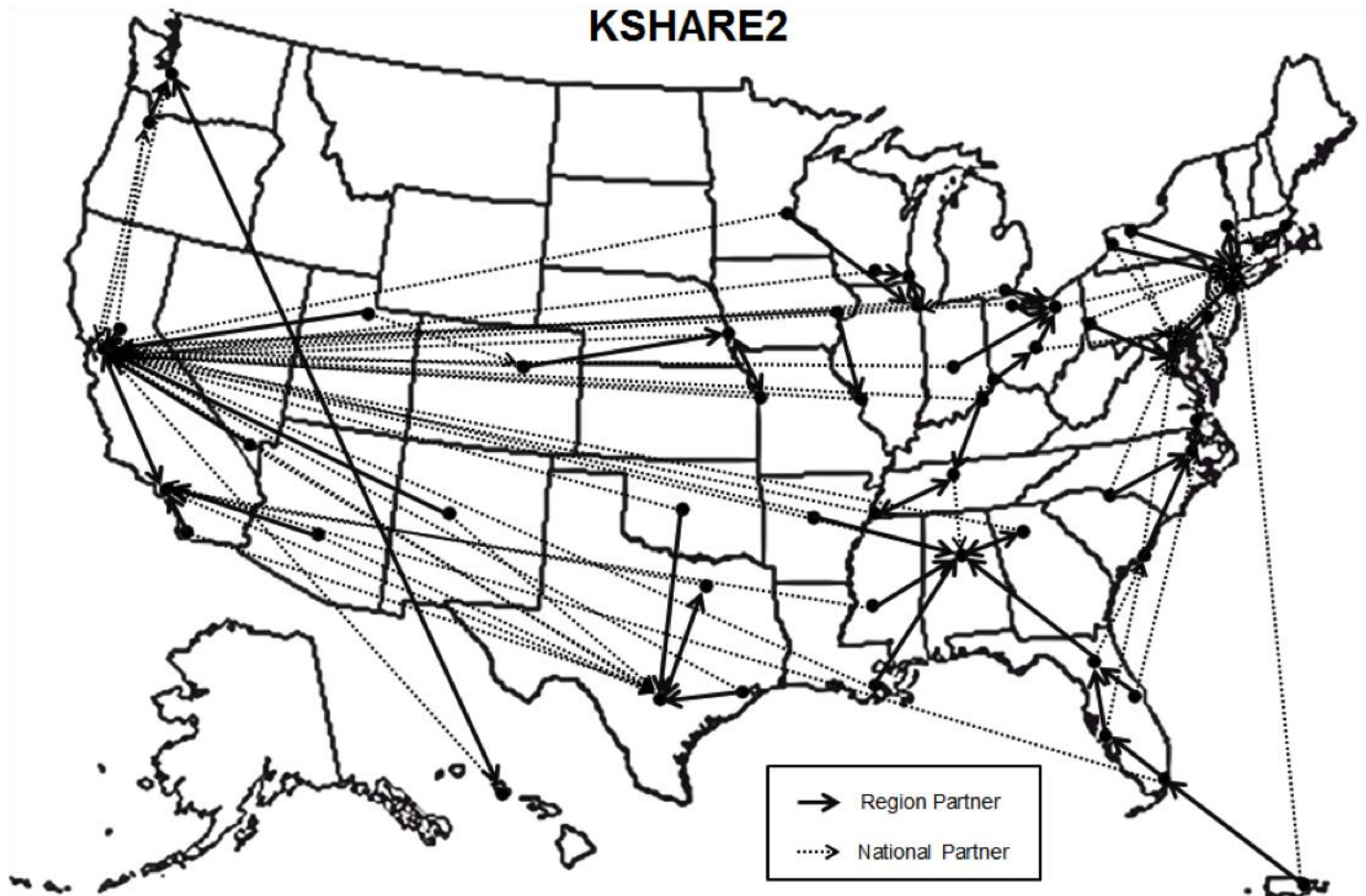

Optimal DSA sharing partnerships when 40% of regionally and nationally shared kidneys are eligible for KSHARE2 allocation.

5.2. Impact of DSA Sharing Levels on KSHARE2 Effectiveness

The impact of KSHARE2 on reducing long-run transplant rate geographic disparity depends on the value of α used to dictate the percentage (α) of non-locally allocated kidneys that are eligible for allocation following KSHARE2. We will now compare the worst-case blood type weighted transplant rate disparity score for various values of α, relative to the actual disparity score in 2009. If α =10%, then the disparity is only reduced by 17.5% (from 5.20 to 4.29). If α =50%, then the disparity is reduced by 43.7% (from 5.20 to 2.93). At its highest usage when α =100%, the disparity is reduced by 48.9% (from 5.20 to 2.66). Figure 3 shows the worst-case weighted disparity score for KSHARE2 stratified by α.

Figure 3: Comparison of Worst-Case Disparity Scores in 2009 versus KSHARE2 for various sharing levels
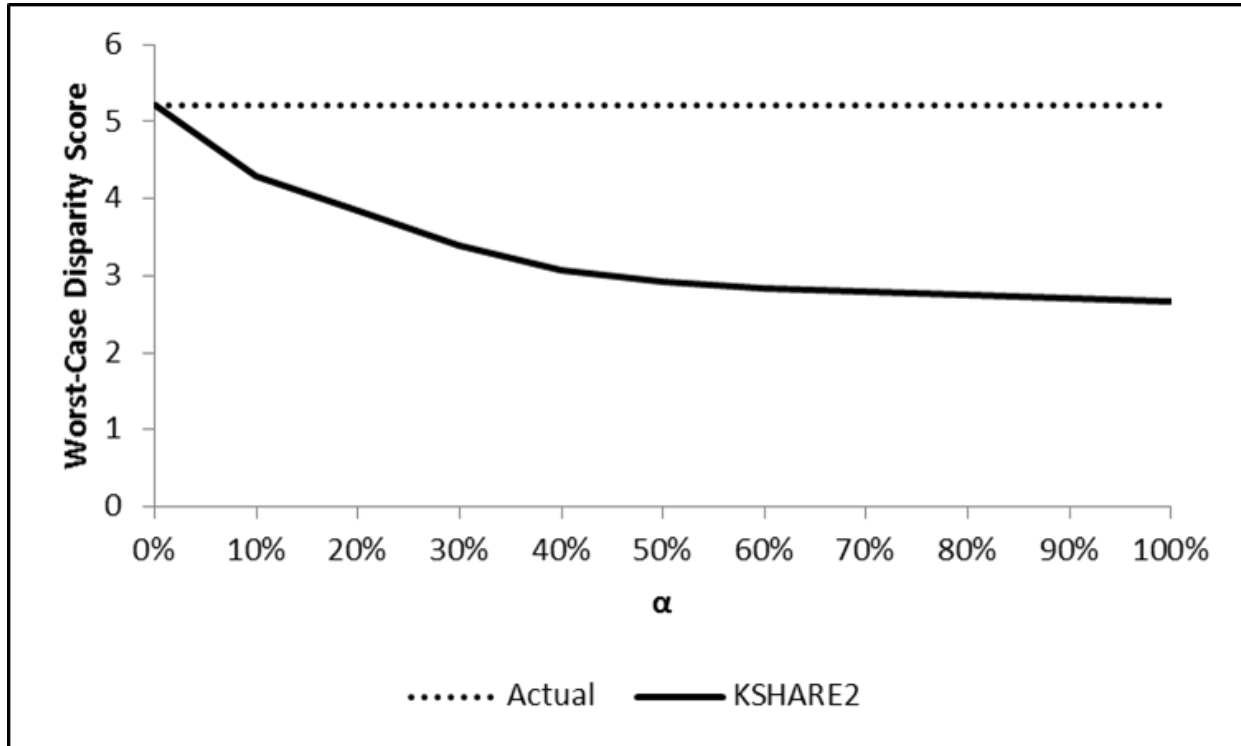
Worst-Case Disparity Score – The worst-case blood type distribution weighted summation of DSA transplant rate disparity.

$$\max_{w_b} \min_{Y_{ij}, P_{ijb}} \sum_{b \in B} \sum_{i \in I} w_b * (TR_{ib} - minTR_b)$$

α: The percentage of kidneys currently allocated regionally or nationally that are assumed to be eligible for reallocation via KSHARE2

Figure 3 shows that the worst-case disparity score is not significantly reduced when the percentage of regionally and nationally allocated kidneys for reallocation via KSHARE2 increases from 40% to 100%. Therefore, KSHARE2 can be effective without requiring significant DSA buy-in to the alternative sharing technique. When 40% of regionally and nationally allocated kidneys are reallocated according to KSHARE2's optimal sharing partnerships, only 7% of all kidneys procured for transplantation are reallocated each year. The remaining 93% of procured kidneys are allocated according to current policy.

We will now discuss the 40% sharing level KSHARE2 results in further detail.

5.3. KSIM2 Simulated Impact of KSHARE2

Using KSIM2, we modeled the effect of KSHARE2 on mean waiting time to transplantation, waitlist mortalities, and kidney transplant acceptance behaviors. Table 2 summarizes the impact of KSHARE2 on mean waiting time to transplantation and waitlist mortalities by patient subpopulation of interest.

Table 2: KSIM2 Simulated Geographic Disparity when using KSHARE2 versus Current Allocation Policy in 2009

Patient Population of Interest	KSHARE 2		Actual	
	Mean Waiting Time Disparity**	Number of DSA Waitlist Deaths	Mean Waiting Time Disparity**	Number of DSA Waitlist Deaths
Blood Type A				
All Patients	2.97	1,161	4.30	1,377
< 18	3.35	110	3.79	168
18-65	2.16	790	2.80	925
> 65	2.62	261	2.82	284
Non-Hispanic White	2.08	672	2.37	762
Non-Hispanic Black	3.75	271	4.51	347
Hispanic	3.51	158	3.95	194
Asian	2.30	45	4.49	53
Blood Type AB				
All Patients	2.53	132	4.10	140
< 18	1.89	15	3.68	17
18-65	1.60	94	2.64	99
> 65	3.20	23	4.34	24
Non-Hispanic White	1.65	56	2.63	59
Non-Hispanic Black	2.92	58	4.58	60
Hispanic	1.51	2	3.42	3
Asian	3.66	15	6.28	16
Blood Type B				
All Patients	4.70	688	6.40	719
< 18	4.85	83	5.12	92
18-65	4.44	462	4.80	482
> 65	2.63	142	3.81	145
Non-Hispanic White	4.14	239	5.43	246
Non-Hispanic Black	4.63	334	5.97	344
Hispanic	2.65	61	4.46	66
Asian	3.43	51	6.67	55
Blood Type O				
All Patients	3.48	2,296	4.80	2,450
< 18	3.99	267	4.52	312
18-65	3.28	1,525	3.51	1,620
> 65	2.68	504	3.57	518
Non-Hispanic White	3.24	1,025	4.22	1,080
Non-Hispanic Black	4.38	750	7.49	788
Hispanic	3.18	397	4.45	435
Asian	3.35	69	6.73	79

**Disparity represented as the difference between the maximum and minimum Donor Service Area (DSA) waiting time.

5.3.1. Mean Waiting Time to Transplantation

By 2009, the range in mean waiting times to kidney transplantation fell significantly for each blood type when following KSHARE2. For blood type A patients, the range in DSA mean waiting times to transplantation fell from 4.30 years (0.78 – 5.08 years) in 2000 to 2.97 years (1.02 – 3.99 years) in 2009, representing a 30.9% reduction. For blood type AB patients, the range in DSA mean waiting times to transplantation fell from 4.07 years (0.47 – 4.54 years) in 2000 to 2.53 years (0.67 – 3.21 years) in 2009, representing a 37.8% reduction. For blood type B patients, the range in DSA mean waiting times to transplantation fell from 6.41 years (1.12 – 7.53 years) in 2000 to 4.70 years (1.34 – 6.03 years) in 2009, representing a 27.0% reduction. Finally, for blood type O patients, the range in DSA mean waiting times to transplantation fell from 4.76 years (1.38 – 6.15 years) in 2000 to 3.48 years (1.42 – 4.90 years) in 2009, representing a 26.9% reduction.

The range in DSA mean waiting times to kidney transplantation fell significantly for all age subpopulations in this analysis. For the patient population less than 18 years of age, the range in DSA mean waiting times fell from 3.82 years in 2000 to 2.35 years in 2009 for blood type A patients, 4.58 years in 2000 to 1.89 years in 2009 for blood type AB patients, 5.45 years in 2000 to 4.85 years in 2009 for blood type B patients, and 5.11 years in 2000 to 3.99 years in 2009 for blood type O patients, representing 12.3%, 58.8%, 11.0%, and 21.9% reductions, respectively. For the patient population between 18 and 65 years of age, the range in DSA mean waiting times fell from 2.87 years in 2000 to 2.16 years in 2009 for blood type A patients, 4.18 years in 2000 to 1.60 years in 2009 for blood type AB patients, 5.19 years in 2000 to 4.44 years in 2009 for blood type B patients, and 3.64 years in 2000 to 3.28 years in 2009 for blood type O patients, representing 24.6%, 61.6%, 14.5%, and 9.9% reductions, respectively. For the patient population older than 65 years of age, the range in DSA mean waiting times fell from 3.02 years in 2000 to 2.62 years in 2009 for blood type A patients, 3.93 years in 2000 to 3.20 years in 2009 for blood type AB patients, 3.40 years in 2000 to 2.63 years in 2009 for blood type B patients, and 3.95 years in 2000 to 2.68 years in 2009 for blood type O patients, representing 13.1%, 18.7%, 22.7%, and 32.1% reductions, respectively.

The range in DSA mean waiting times to kidney transplantation fell significantly for all race subpopulations in this analysis. For the non-Hispanic White patient population, the range in DSA mean waiting

times fell from 2.31 years in 2000 to 2.08 years in 2009 for blood type A patients, 2.81 years in 2000 to 1.65 years in 2009 for blood type AB patients, 4.96 years in 2000 to 4.14 years in 2009 for blood type B patients, and 4.12 years in 2000 to 3.24 years in 2009 for blood type O patients, representing 10.0%, 41.3%, 16.5%, and 21.5% reductions, respectively. For the non-Hispanic Black patient population, the range in DSA mean waiting times fell from 4.59 years in 2000 to 3.75 years in 2009 for blood type A patients, 3.63 years in 2000 to 2.92 years in 2009 for blood type AB patients, 5.35 years in 2000 to 4.63 years in 2009 for blood type B patients, and 6.93 years in 2000 to 4.38 years in 2009 for blood type O patients, representing 18.2%, 19.6%, 13.6%, and 36.7% reductions, respectively. For the Hispanic patient population, the range in DSA mean waiting times fell from 5.04 years in 2000 to 3.51 years in 2009 for blood type A patients, 2.72 years in 2000 to 1.51 years in 2009 for blood type AB patients, 5.20 years in 2000 to 2.65 years in 2009 for blood type B patients, and 5.83 years in 2000 to 3.18 years in 2009 for blood type O patients, representing 30.5%, 44.3%, 48.9%, and 45.4% reductions, respectively. For the Asian patient population, the range in DSA mean waiting times fell from 4.82 years in 2000 to 2.30 years in 2009 for blood type A patients, 5.40 years in 2000 to 3.67 years in 2009 for blood type AB patients, 6.04 years in 2000 to 3.43 years in 2009 for blood type B patients, and 4.33 years in 2000 to 3.35 years in 2009 for blood type O patients, representing 52.2%, 32.2%, 43.3%, and 22.6% reductions, respectively.

5.3.2. Waitlist Mortalities

KSIM2 provides information with regards to the number of waitlist mortalities per DSA and year. From this information, we can compare the total number of waitlist mortalities during 2000-2009 using current allocation policy compared to KSHARE2. For blood type A, the number of total waitlist mortalities fell by an average of 216 patients per year, representing an 11.1% reduction. For blood type AB, the number of total waitlist mortalities fell by 8 patients on average per year, representing a 6.6% reduction. For blood type B, the number of total waitlist mortalities fell by an average of 31 patients per year, representing a 4.7% reduction. For blood type O, the number of total waitlist mortalities fell by 154 patients on average per year, representing an 8.2% reduction.

We will now compare the total number of waitlist mortalities during the study period (2000-2009) following current allocation policy versus KSHARE2 for each age subpopulation. For blood type A patients, the number of waitlist mortalities fell by an average of 57.7 patients per year for patients less than 18 years old, 134.9 patients per year for patients between 18 and 65 years old, and 23.4 patients per year for patients over 65 years old, representing 27.5%, 15.0%, and 10.1% reductions, respectively. For blood type AB patients, the number of waitlist mortalities fell by an average of 2.1 patients per year for patients less than 18 years old, 5.1 patients per year for patients between 18 and 65 years old, and 0.8 patients per year for patients over 65 years old, representing 12.3%, 5.7%, and 4.6% reductions, respectively. For blood type B patients, the number of waitlist mortalities fell by an average of 8.7 patients per year for patients less than 18 years old, 19.6 patients per year for patients between 18 and 65 years old, and 2.7 patients per year for patients over 65 years old, representing 7.7%, 3.6%, and 2.3% reductions, respectively. For blood type O patients, the number of waitlist mortalities fell by an average of 45.0 patients per year for patients less than 18 years old, 95.0 patients per year for patients between 18 and 65 years old, and 14.0 patients per year for patients over 65 years old, representing 12.5%, 5.7%, and 3.5% reductions, respectively.

We will now compare the total number of waitlist mortalities during the study period (2000-2009) following current allocation policy versus KSHARE2 for each race subpopulation. For blood type A patients, the number of waitlist mortalities fell by an average of 90.4 patients per year for non-Hispanic White patients, 76.0 patients per year for non-Hispanic Black patients, 35.6 patients per year for Hispanic patients, and 7.7 patients per year for Asian patients, representing 11.7%, 22.0%, 23.3%, and 18.1% reductions respectively. For blood type AB patients, the number of waitlist mortalities fell by an average of 2.9 patients per year for non-Hispanic White patients, 2.2 patients per year for non-Hispanic Black patients, 1.2 patients per year for Hispanic patients, and 1.0 patients per year for Asian patients, representing 5.1%, 4.4%, 16.1%, and 13.6% reductions respectively. For blood type B patients, the number of waitlist mortalities fell by an average of 7.4 patients per year for non-Hispanic White patients, 10.1 patients per year for non-Hispanic Black patients, 5.4 patients per year for Hispanic patients, and 4.5 patients per year for Asian patients, representing 2.6%, 2.8%, 8.3%, and 8.6% reductions respectively. For blood type O patients, the number of waitlist mortalities fell by an

average of 54.6 patients per year for non-Hispanic White patients, 37.7 patients per year for non-Hispanic Black patients, 38.4 patients per year for Hispanic patients, and 9.6 patients per year for Asian patients, representing 4.9%, 4.7%, 10.9%, and 13.1% reductions respectively.

5.3.3. Kidney Acceptance Behavior

As discussed in Section 3, KSIM2 assumes that each DSA will transplant the optimal percentage of shared kidneys allocated by KSHARE2, regardless of their actual kidney acceptance behavior. KSIM2 also provides us with the kidney acceptance behavior necessary for KSHARE2 to be effective. In comparing the actual with KSHARE2 kidney acceptance distributions for each DSA using a Chi-Squared test, 5 of the 58 national DSAs have a significant shift in acceptance distribution ($p < 0.05$). Thus, while 5 DSAs will have to shift their behavior, the 53 remaining DSAs will not have to change their kidney acceptance behavior to achieve the benefits provided by KSHARE2.

6. Impact of KSHARE2 Kidney Sharing on Long-Run Transplantation System Behaviors

The results shown in Section 5 depict the impact of KSHARE2 on transplant system outcomes and behaviors when implemented for ten years. The goal of this analysis was also to create a strategy that best reduces long-run transplant system disparity. In Table 3, we provide the M/M/1/r+M fluid approximations of long-run transplant system national disparity by patient blood type for KSHARE2 versus actual allocation policy.

Table 3: Fluid Approximations of Long-Run Transplant System Disparity following KSHARE2 and Current Allocation Policy

	KSHARE 2			Actual		
Blood Type	Transplant Rate Disparity[**]	Mean Waiting Time Disparity[**]	Mortality Rate Disparity[**]	Transplant Rate Disparity[**]	Mean Waiting Time Disparity[**]	Mortality Rate Disparity[**]
A	43%	5.2	43%	67%	9.1	67%
AB	38%	3.8	38%	64%	7.1	64%
B	46%	6.9	46%	82%	12.1	82%
O	41%	6.0	41%	52%	9.2	52%

[**]Disparity represented as the difference between the maximum and minimum Donor Service Area (DSA) waiting time.

Long-Run Transplant Rate Disparity: In the long-run, the probability of receiving a transplant following current policy varies across DSAs from 20% to 87% for blood type A patients, from 18% to 82% for blood type AB patients, from 6% to 88% for blood type B patients, and from 12% to 64% for blood type O patients. Comparatively, the long-run probability of receiving a transplant following KSHARE2 varies across DSAs from 39% to 82% for blood type A patients, from 51% to 89% for blood type AB patients, from 27% to 73% for blood type B patients, and from 30% to 71% for blood type O patients, representing 36%, 41%, 44%, and 21% reductions, respectively.

Long-Run Mean Waiting Time to Transplantation Disparity: In the long-run, the mean waiting time to transplantation following current policy varies across DSAs from 0.2 to 9.3 years for blood type A patients, from 0.2 to 7.3 years for blood type AB patients, from 0.2 to 12.3 years for blood type B patients, and from 0.3 to 9.5 years for blood type O patients. Comparatively, the long-run mean waiting time to transplantation following KSHARE2 varies across DSAs from 1.4 years to 6.6 years for blood type A patients, from 0.84 years to 4.67 years for blood type AB patients, from 2.18 years to 9.05 years for blood type B patients, and from 2.41 years to 8.43 years for blood type O patients, representing 43%, 46%, 43%, and 35% reductions, respectively.

Long-Run Mortality Rate Disparity: Following from the fluid approximations, percentage reductions in long-run disparities mortality rates should be similar to those of the transplant rates. the long-run, the probability of dying on the waitlist following current allocation policy varies across DSAs from 13% to 80% for blood type A patients, from 18% to 82% for blood type AB patients, from 12% to 94% for blood type B patients, and from 36% to 88% for blood type O patients. Comparatively, the long-run probability of dying on the waitlist following KSHARE2 varies across DSAs from 18% to 61% for blood type A patients, from 11% to 49% for blood type AB patients, from 27% to 73% for blood type B patients, and from 29% to 70% for blood type O patients, representing 36%, 41%, 44%, and 21% reductions, respectively.

7. Conclusions

Geographic disparity continues to grow over time in kidney transplantation, in direct conflict with federal mandate. As a result, patients who must seek transplantation close to home are disadvantaged in the

system, and at a higher risk of dying of end stage renal disease prior to transplantation. While current efforts are focused on replacing the current kidney allocation policy at the patient level, system-level changes are necessary to reduce national geographic disparity(40). UNOS has recognized this important change (20), but has yet to define and test alternative strategies.

In this analysis, we have suggested a potential path to increased geographic equity via a sharing strategy that does not greatly impact current kidney allocation practices. KSHARE2 was motivated according to published beliefs of the transplant community (29, 41) and designed to build upon past, successful allocation policy variances (i.e. statewide sharing) (32).

By KSHARE2, a procured kidney is offered first locally, then to a regional sharing partner, then to the reminder of the UNOS region, then to a national sharing partner, and ultimately nationally. The strategy therefore does not change overall local, regional or national transplant volumes. Instead, a proportion of kidneys allocated regionally will be reallocated to optimally fix regional disparity while a proportion of kidneys allocated nationally will be reallocated to optimally fix national disparity. Further, this strategy only requires two sharing partnerships (one regional, one national) to be formed. As such, this will be easier to implement at the policy level then if a DSA has numerous sharing partners to manage. Finally, KSHARE2 provides the most reduction in geographic disparity compared to all other strategies without requiring immense change in kidney acceptance behavior for the majority of national DSAs.

Our simulated results show that KSHARE2 will incrementally reduce geographic disparity over time. Implementing KSHARE2 for the ten-year period from 2000 through 2009 would have reduced geographic disparity in DSA mean waiting times significantly (Table 2) for multiple patient subgroups. In addition, an average of 409 less waitlist deaths would have occurred annually, as patients would have received a transplant prior to becoming too sick to transplant. Finally, long-run transplant system outcomes due to the sustained use of KSHARE2 over time could dramatically decrease geographic disparity in kidney transplantation (Table 3). This benefit is mirrored across various age groups and racial demographics of interest.

The results from KSHARE2 occur under the assumption that the transplant community is willing to change two important transplant behaviors. First, KSHARE2 assumes that the transplant community would be

willing to share 40% of regionally and nationally offered kidneys to optimal KSHARE2 sharing partners prior to regional and national kidney offerings. This would redirect the allocation process for approximately 7% of procured kidneys for transplantation each year. Second, five DSAs would need to significantly change their acceptance behavior towards transplanting lower quality kidneys. This may be a difficult proposition for these areas as they must meet mandated transplant recipient outcomes to remain accredited programs, but following KSHARE2, kidneys may potentially be allocated to these areas more efficiently. As a result, low quality kidneys will sustain less cold ischemic time (CIT), potentially making them more attractive for transplantation.

This study has some limitations. First, KSHARE2 results are based solely on simulation results. Ideally, we would recommend for UNOS to conduct appropriate case studies within the current transplant system to test the impact of KSHARE2 implementation. Second, transplant system retrospective data was only available for this study through 2009. Over time, the simulated impact of KSHARE2 should be updated to reflect the most current transplant system behaviors.

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9. Appendix - Fluid Approximation Validation

The validity of the M/M/s/r+M fluid approximations established by Whitt et al., 2004 is now examined for this transplantation system adaptation. Fluid approximations of the transplant system assume a known and stable value of $\lambda, \gamma,$ and μ (Whitt, 2004). The most recent (2009) estimates of $\lambda, \gamma,$ and μ shown in Davis et al., 2013 will be used to determine long-run system approximations. Since patient inter-arrival rates seeking transplantation are likely to increase in the future (REF), it is within reason to assume that the fluid approximation values discussed here will represent a lower bound on the actual long-run transplant system outputs.

KSIM2 was used to simulate 50 years of the transplantation system from 2010 to 2060, with 100 replications of KSIM2 for each blood type. We calculated 95% confidence intervals for mean KSIM2 estimates of mean probabilities of waitlist mortality and transplantation, mean waiting time to transplantation, and mean waitlist length. Each fluid approximation value was compared with the mean simulated value from the final five years of the simulation for each blood type. Chi-Squared tests were used to test for significant differences between the simulated and approximated system values, with all p-values less than 0.05 considered significant.

The long-run estimates across all DSAs are now compared according to the simulated and approximated values. In Figure A1, the resulting values are compared for each blood type. No significant differences were found when comparing simulated and approximated system values for all comparisons ($p > 0.05$), implying that fluid approximations for the M/M/s/r+M system are appropriate for the transplant system adaptation.

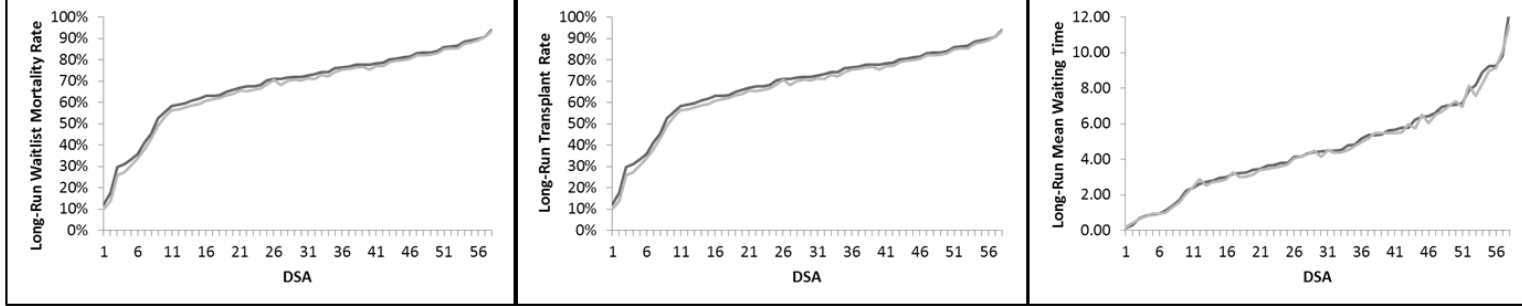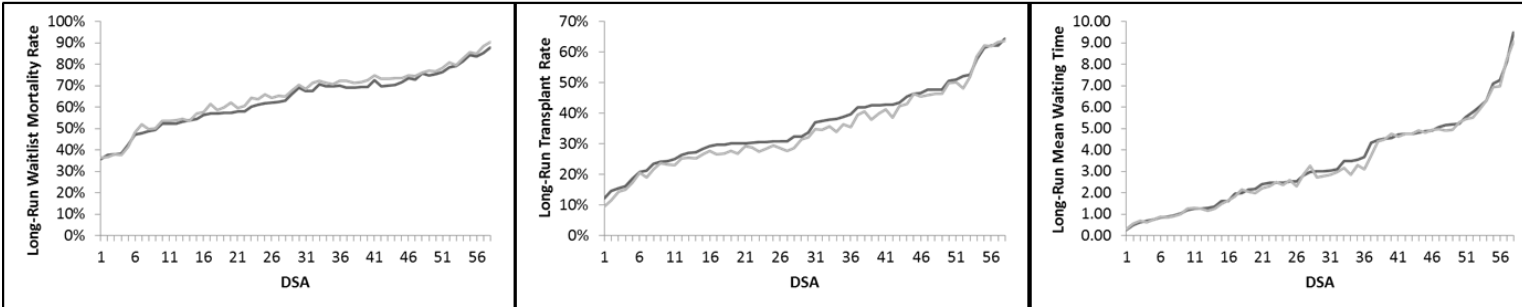# Figure A1: Long-Run System Output Estimates by Blood Type

A Blood Type
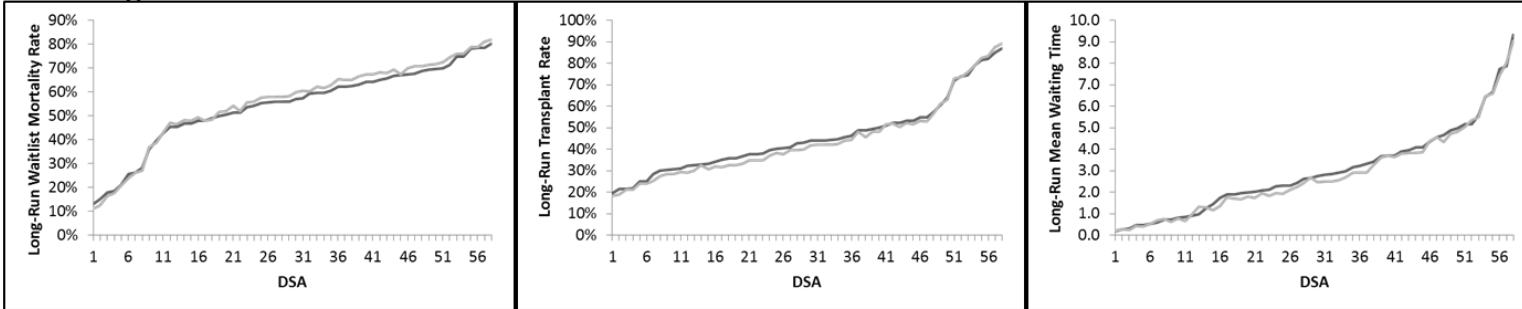
AB Blood Type
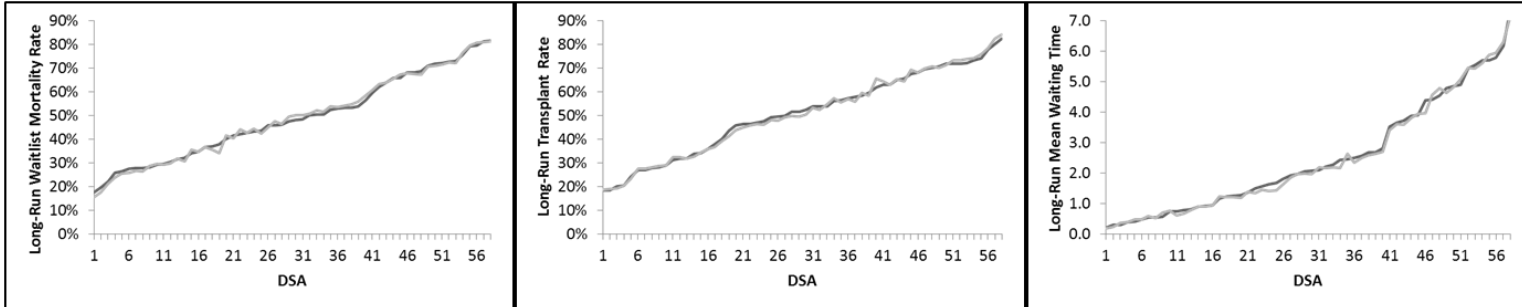
B Blood Type

O Blood Type

KSIM₂ ——— FLUID