The Causes of Racial Inequalities in Kidney Transplantation

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ABSTRACT. Large racial inequalities in kidney transplantation pose an empirical and theoretical puzzle. White transplant candidates are about twice as likely to obtain a kidney transplant as are black candidates. Yet all patients with end-stage renal disease are eligible for Medicare coverage, and racial discrimination does not appear to play a major role for patients on the kidney transplantation waitlist. Using data on all kidney donors and transplant recipients in the U.S. since 1987, results show that these inequalities result from a complex process combining residential stratification, blood type and other biological differences, and the probability of obtaining a living donor from one's family and friendship networks. Finally, future research using counterfactual microsimulation techniques is described.

Kidney transplantation is an important and understudied topic in demographic research on health. According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 11.5% of adults 20 and older showed symptoms of chronic kidney disease between 1999-2004, and more than 500,000 were receiving treatment for end-stage renal disease in 2007.[1] Furthermore, kidney and related diseases (such as diabetes and hypertension) are major sources of health disparities in the U.S.; diabetes, hypertension, and renal failure collectively account for 27.5% and 8.2% of racial and educational disparities in mortality rates, respectively (Wong et al. 2002).

Over the past 23 years, over 500,000 individuals in the U.S. have sought a kidney transplant, and many do not receive one before death, often waiting for years on dialysis (a medically inferior stopgap measure). As a result the axes of advantage in kidney transplantation system are extreme but familiar: for instance, African Americans in the United States are more than three times as likely to need a kidney transplants compared to whites, and nearly half as likely to get one (see Figure 1). Similarly, Latinos and members of other races are respectively 63 and 58% as likely to receive a transplant once in the transplantation system as are whites. Therefore well-known inequalities in cardiovascular disease and diabetes are magnified in the case of inequalities in kidney transplantation.

Organ transplantation is a case of inequalities where, naively, one would not expect to see them. By this I mean that popular explanations for inequality by race typically point toward one of two primary mechanisms: discrimination and resource inequality. Yet both of these factors are largely minimized in the organ allocation

[1] http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/. Viewed 9/15/2010.

system. Kidneys are either allocated algorithmically (in the case of deceased donor organs) or come from friends or family, and Medicare has covered all end-stage renal disease treatments since 1972. Furthermore in the last decade, in fact, the United Network for Organ Sharing (UNOS) has made significant changes to the kidney allocation system with the explicit goal of reducing demographic inequalities in outcomes. Yet, as predicted by the fundamental causes paradigm (Link and Phelan 1995) in social epidemiology and the structural conflict perspective (e.g., Bonilla-Silva 1997) they nonetheless persist.

This research contributes to demographic understanding of racial disparities in health by investigating how they are produced under this unique set of circumstances. Preliminary analyses (discussed in detail below) reveal that education, race/ethnicity, age, gender, and region are major markers of one's prospects for a kidney transplant once on the waitlist, and that while the distribution of cadaveric organs has become more equitable in the U.S. in the last decade, large inequalities persist in the living donor system (now about half of all transplants) and, for the best educated, in the cadaveric organ allocation system as well. The reasons for these inequalities, and the effect of policy settings in which they have taken hold, are the topics of this research.

This paper is organized as follows. First, some background information is presented on kidney transplantation in the U.S. Second, the dataset used is described. Third, descriptive analyses of racial disparities in kidney transplantation are presented, followed by an analysis of the likely causes thereof. Finally, a description of ongoing (but as-yet incomplete) research on the contribution of racial and ethnic differences to disparities in kidney transplantation is provided, and the paper is concluded.

Background

Between 1988 and 2007, more than 420,000 organ transplants were performed in the United States with high and steadily improving rates of success. However, in many senses organ transplantation is different from other medical treatments. To replace a diseased organ, one must first obtain a healthy one. Unlike drugs whose production can be scaled up in response to burgeoning demand, organ transplantation requires the willingness of those who are not afflicted with diseased organs to help those who are. This means that organ transplantation is something of a zero-sum game – every organ that an individual receives is an organ that another cannot. This poses a substantial difficulty because there are not enough donated organs for all who want them– as of January 29, 2010, 105,482 individuals are awaiting an organ transplant in the United States, and in most cases they will wait for years to receive one – if they survive that long. In recent years, more than 7,000 patients have died every year awaiting an organ which never came, a number which has increased as steadily as the waitlist.

Due to this shortage of needed organs, organ transplantation is an allocative (and therefore sociological) problem as well as surgical and altruistic one in which allocative choices must be made. In the case of living donors, the donor chooses the recipient, an allocative process about which there is little controversy. Since 1984, in the U.S. allocation of deceased donor kidneys has been entrusted to UNOS by the government, which has done so by dividing the task among 11 subsidiary administrative regions. Within these regions subsidiary organizations known as Organ Procurement Organizations (OPOs) collect and allocate organs for transplantation according to national rules, with local variations, a process which has for some time been implemented

by a computer system which maximizes some function of medical, biological, and geographic factors to make this decision.

The Organ Allocation Process

Figure 2 depicts the current (as of 9/15/09) UNOS standard (high quality) cadaveric kidney allocation procedure for organ donors age 35 and older. Similar procedures are used for younger donors. This allocation formula does not depict subnational variation in allocative procedures due to space limitations. "Expanded criteria" donor (ECD, kidneys donated by those who are older or less healthy than those typically accepted; see Danovitch and Cecka 2003 and Table A2 in Appendix A) organs are allocated on a similar basis, but without prioritization of pediatric patients or high-PRA patients. For more details on the kidney allocation process, see Appendix A.

Data

Since 1987, UNOS has collected detailed information on every organ transplant recipient, donor, and candidate in the U.S., containing information on the demographic, socioeconomic, medical status, laboratory, and medical treatment characteristics of each such person. Furthermore, these data are able to link donors to recipients, patients to transplant centers and OPO membership, and contain ZIP code information on transplant center locations. Finally, at 6 months and one year post-transplantation, and every year thereafter (until death or loss-to-follow-up), follow-up data is collected on transplant recipients and living donors, containing information on their medical status, medical treatment, demographic and socioeconomic characteristics, and, if deceased, their date and cause of death.

Additionally, UNOS maintains data files on all those to whom each organ which is offered, with information on whether it was accepted and reasons for refusal if not accepted. Unfortunately, this dataset does not contain information on pre-waitlist renal disease patients, so inequalities in the organ transplant system prior to waitlisting (e.g., Epstein et al. 2000) may be explored only crudely.[2] Finally, the data contain information only on living donors who actually donate, so key mechanisms of inequality in this process cannot be directly explored using these data.

Exploratory Results: Racial Disparities in Kidney Transplantation

Changes in the Kidney Transplantation System

In the last 30 years the key facts of kidney transplantation have changed dramatically. These major changes are shown in Table 1. First, the number of kidney (KI) transplants has increased at a steady rate. In 1988 nearly 9,000 KI transplants were performed; in 2007, the same figures were more than 16,500– an 87% increase. Furthermore, transplant outcomes have greatly improved – graft survival (how long the transplanted organs continue to function properly without rejection) has increased substantially from its already high rate, with 5-year survival rates increasing by 27% (see also Figure 3). However, waitlist mortality rates have increased with the length of the waitlist – between 1988 and 2000, the 3-year mortality rate nearly doubled from 6 to 12% (Figure 4).

These changes reflect a combination of rising demand and (to a lesser degree) rising supply. On the demand side, the number of patients with end-stage renal disease in

[2] This task could be better accomplished using Medicare data which includes information on all end-stage renal disease patients in the U.S., but there is an expense associated with acquiring it. Should this be deemed crucial to the project, I will seek grant money to acquire and use it.

the United States has exploded. For instance, from 1991 to 2001 the number more than doubled from 201,000 to 406,000 (Norris & Agodoa 2005); as of 2006 the prevalence figure was 506,256.[3] The primary causes of ESRD include, in roughly rank order, diabetes, hypertension, glomerularonephritis, pylenonephritis and reflux nephropathy, and cystic disease (Winearls & Mason 2001), so concomitant increases in the first two in the United States are likely driving this increase in prevalence.

On the supply side, the increasing number of kidney transplants reflects increases in both living and cadaveric donors. Evidence on the latter suggests that the increase in cadaveric kidney donors resulted from an increase in the 'conversion rate' (the percentage of suitable donors who donate a kidney) rather than an increase in the number of brain dead or otherwise suitable, deceased donors. Alongside this increase, increasing numbers of transplant candidates are obtaining living donor transplants, and since 1995 8-10% of all transplanted kidneys have come from expanded criteria donors. Finally, in recent years donors with non-beating hearts (Donation after Cardiac Death, or DCD) transplants have been found to be potentially viable, which has the potential to increase the supply of organs for transplantation further.

Inequalities by Race

Amidst all of these changes, however, one pernicious fact has remained – the outcome of this process has always served to disproportionately benefit white individuals compared to racial and ethnic minorities. The size of these inequalities is surprising. Consider Figure 1, which shows the distribution of major racial and ethnic groups in the general, transplant candidate, and transplant recipient populations in 2007 in the United

[3] http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/; accessed 6/7/2010.

States. The graph is crude but revealing – compared to whites, African Americans are greatly overrepresented in the transplant candidate population (crude odds ratio[4] = 3.14) and greatly underrepresented in the transplant recipient population (OR = 0.53). Together, these numbers demonstrate that African Americans are more likely to need a transplant and less likely to receive one *conditional on needing one* (ignoring pre-waitlist inequalities). Similar (but somewhat less severe) inequalities are observed for other racial and ethnic groups, as well as other measures of social status.

Figures 6 and 7 further illustrate the inequalities at work in the form of racial and ethnic differences in waitlist mortality rates per 1000 patient years. (Figure 5 shows average mortality rates from 1998-2007; Figure 6 shows change standardized by the 1998 rate.) As can be seen, the overall mortality rates have decreased slightly from 1998-2007, but racial and ethnic inequalities persist. What is surprising, given the information in Figure 1, is that whites have *higher* waitlist mortality rates than do racial minorities – indeed, whites' mortality rates are the only ones which are consistently higher than average over this time span. How can we make sense of this finding combined with the evidence that waitlisted whites are more likely to receive organ transplants?

The answer is that they wait far less time on average for an organ than do members of any other racial or ethnic group, as shown in Figures 7 and 8. (Again, Figure 7 shows the average of 25th percentile statistics from 1998-2007; Figure 8 shows change in this statistic standardized by the 1998 statistic.) Over the years, whites' 25th percentile waiting time is 64-72% that of the overall transplant candidate population. Therefore

[4] What I dub the 'crude odds ratio' is calculated as $(C_B/P_B)/(C_W/P_W)$, where C is the transplant candidate population percentage of the group in question, P is the population frequency percentage, B subscripts refer to African Americans, and W refers to whites. This is calculated similarly for the transplant recipient odds ratio calculation, except that transplant candidate frequencies are treated as the population at risk and transplant recipients are the outcome.

while white transplant candidates die at higher rates while awaiting a transplant, they generally have to wait for far shorter periods.

Hidden within these rates in transplantation, however, is a telling difference in transplantation types, especially in recent years: whites are much more likely to receive a living donor transplant (Figure 9), and less likely to get a standard cadaveric transplant (at least until very recently; see Figure 10) than are members of non-white racial and ethnic groups. However, these inequalities are not counterbalancing – especially since 2000, whites have enjoyed an advantage in overall transplantation rates (Figure 11). These inequalities by transplant type suggest that increasingly the source of white racial advantage in transplantation lies not primarily inside the standard cadaveric system, but without it. As waiting times have increased with excess transplant demand, living donor transplantation has become the transplant method of choice for whites. Since the 2000 waitlist cohort, among transplant recipients whites have been 113% as likely as would be expected at random to obtain a living donor transplant, whereas blacks have been only 66% as likely to do so.

So far these differences have mapped rates in eventual outcomes, not controlling for differential rates of other outcomes. What about differences in cadaveric transplant outcomes among those who do not obtain a living donor – do the white differences persist in this group? They do– as Figure 12 shows, whites in this subgroup are somewhat advantaged in their efforts to obtain a standard cadaveric (SCD) transplant. In fact, in recent years (since about 2003) a white advantage in the standard cadaveric system has grown compared to blacks and Asians. However, this recent difference could be due to differences in the timing of transplants, not the eventual outcomes. It can also

be seen in Figure 12 that Hispanics are consistently the most advantaged group in this system.

Explaining Inequalities

What could account for these observed demographic inequalities? A number of candidate explanations are available, and are addressed in turn: SES, discrimination, lifestyle, group-specific availability of kidney donors, differences in blood type and other genes used to match donors and candidates, medical condition (and thus mortality hazard), rates of living donor transplantation, and rates of transplant offer acceptance.

SES. First, these inequalities are not likely to be principally the result of income differences between racial groups for the majority of the population. By federal law, since 1973 all kidney-failure medical treatments have been covered by Medicare, including dialysis, transplantation, and subsequent immunosuppressant and other post-transplant treatment regimes. However, the large divide (not shown) between the highest educated and others in the standard cadaveric system suggests that socioeconomic resources do play a limited role even in this system.

Discrimination. Second, it is unlikely that these inequalities result principally from discrimination (again, in the interpersonal sense). The inequalities depicted above address principally inequalities which arise *after one is on the organ transplant waiting list*. There is some evidence (e.g., Epstein et al. 2000) that doctors are less likely to place their African American patients on the organ transplant waiting list, and to do so later in the disease progression, than their white patients. This suggests that the mechanism which disproportionately sorts African Americans into renal failure understates the true upstream inequalities in this process. However, once a patient is on the organ transplant

waiting list, cadaveric organ allocation decisions are made using a computer algorithm, and race itself is not a factor in this decision.

Lifestyle and Culture. The most common conclusion on the source of inequalities by race and ethnicity in rates of ESRD attribute them to diabetes (Norris & Agodoa 2005), hypertension (USRDS 2003, Klag et al 1997, Coresh et al 2001), and/or diet (Norris & Agodoa 2005). Furthermore, there is some evidence of differences in treatment preferences by race among those with ESRD: for instance, African Americans are three times less likely to be a registered organ donor (Boulware et al 2002), and are less likely to prefer kidney transplantation to dialysis as a treatment modality (Young & Gaston 2002). An ethnographic study of African American ESRD patients found that most patients feared that the donor would be harmed by donating their kidney, but that they might accept a living donor transplant if their prognosis became bad enough (Gordon 2001).

Donor Supply. Furthermore, allocative inequalities by race cannot be explained by crude differences in the distribution of organ donors in the U.S. The distribution of histocompatibility genes and blood types is imperfectly correlated with race, so one might suppose that, given that a transplant candidate is more likely to be a tissue match with a member of one's own ethnic group, differential rates of organ donation might be responsible for these inequalities. As shown in Figure 13, there is some evidence for this: among those who receive a transplant, there is racial variation in the degree of genetic matchup on HLA genes, to the disadvantage of African and Asian Americans.

HLA Polymorphism by Race. The HLA genes used to match donors to transplant candidates are the most polymorphic (variable) in the human genome (Hedrick 2004),

and the degree of polymorphism varies by race, presumably due to genetic bottlenecks associated with ancient human migration patterns. Further evidence is gained from an empirical probability analysis of the distribution of different HLA genes in each subpopulation, from which the probability of different match degrees with alters with different genetic relationships to ego who are of the same race are derived in Table 2. (See Appendix B for the details of these calculations.)

The most obvious lesson of this table is that parents, children, and siblings (who have genetic relationship r=.5) give one by far the highest probabilities of satisfactory HLA match degrees. Parents and children are guaranteed to share at least three of these six alleles (one at each locus), which the probability of sharing additional alleles structured by the distribution of these genes within the racial/ethnic subpopulation (assuming that parents do not assortatively mate with regard to these genes). However, although parents and children share the same average genetic relationship as do siblings, the latter should be expected to show a wider distribution of match degrees since their shared genes are less deterministic. Below this level of genetic relationship, probabilities of satisfactory HLA match degree drops sharply, such that the most probable match degree between a transplant candidate and an unrelated individual is only 1-3 HLA matches.

However, if one focuses on the probabilities of the most favorable (4 or more) HLA match degrees, strong differences by relationship degree and race may be seen, as shown in Table 3. Because of their wider distribution of HLA matches, siblings are the best prospective candidates for excellent matches, with 43-45% of siblings sharing at least this many HLA genes. Parents and children provide the next best prospects, and probabilities decrease non-linearly with declining genetic relationship degree. Furthermore,

conditional on genetic relationship, due to distributional differences in these genes (wherein whites are less polymorphic than those from other races) whites are more likely to have excellent matches than members of other race or ethnic groups for all genetic relationship degrees. Finally, these race differences become more exaggerated with declining genetic relationship degrees.

Medical Diagnosis. One's prognosis, as always, depends substantially on one's medical diagnosis, as seen in Figure 14, which depict cross-year means and change in waitlist mortality rates per 1,000 patient-days separately by primary medical diagnosis. By far the highest mortality rates are observed for patients whose renal failure is associated with diabetes (Diab.) or cancer (Neoplsms.). On the other side of the prospects scale, one's chances are significantly improved compared to other diagnoses if one needs a transplant due to polycystic kidneys (Poly. Ks.) or other congenital disorders (Congent.). Given the well-known demographic patterning of diabetes, for instance, these inequalities in mortality rates could serve to create racial disparities in outcome.

Blood Type Distributions. Furthermore, there are blood type differences by race which could be responsible for some degree of inequality in the organ allocation system because one can rarely cross the so-called ABO barrier when matching organs to transplant candidates. As shown in Table 4, whites are more likely than typical to be type A and less likely to be type B; blacks have the opposite pattern; Hispanics are more likely to be type O and less likely to be type B or AB; and Asians are more likely to be type AB or B and less likely to be types A or O. Because exact ABO matches result in somewhat better transplant outcomes and exact matches are prioritized in the allocation algorithm, these differences could result in some degree of inequality in kidney transplant rates and

outcomes thereafter. Indeed, at least one study (Lunsford et al. 2006) has found that this was a major mediator of racial differences in living donor transplantation rates.

However, while the differences between groups are noticeable, the key question for this purpose is to consider what proportion of the donor pool is ABO-compatible with transplant candidates of each type. (Recall that AB blood types are compatible with all other types, A can receive A or O, B can receive B or O, and O can receive only O.) As shown in Figure 15, there are only substantively minor differences by race in the proportion of the organ donor pool whose organs are ABO-compatible with their own. Table 5 shows similarly small within-group differences. While these differences could certainly mediate the race-transplant relationship, these are insufficient to account for the bulk of the differences in prospects.

However, when one breaks these differences down by race, blood type, and one's genetic relationship degree with potential living donor candidates, one finds some substantively moderate differences in the probability of being ABO-compatible with these network alters (Table 6). These figures, derived using standard probability calculations following Kanter & Hodge (1990) (detailed in Appendix B), show that there are race differences in one's potential to find an ABO compatible living donor within-group. These calculations account simultaneously for group differences in all blood type distributions and therefore present additional information beyond the previous two tables.

Furthermore, because alters' probabilities of ABO compatibility drop off precipitously with declining genetic relationship degrees, differences in 1st degree kinship networks are likely to be more consequential for differential rates of living donor transplantation than are differences in extended kinship and friendship networks – except

for those with AB blood types. Finally, the greatest group differences in the probability of ABO compatibility is found among unrelated alters. Therefore, one's combination of race and blood type becomes far more consequential if seeking a living donor among unrelated alters than among related ones.

Living Donors. Given the growing prevalence of living donor kidney transplants, inequalities therein could explain a large portion of overall transplantation inequality. Gore et al. (2009) found that 14% of the variance in living donor transplantation could be accounted for by the fact that older, African American, lower educated, and lower income patients have lower rates of living donor transplants.

Living donors are typically family members or close friends. However, even if one's potential living donor is biologically compatible they may not be sufficiently healthy to donate an organ. Therefore the structure of one's kinship and social network, as well as the health and genes of one's network alters, likely structure group differences in the likelihood of living donor transplants to a large degree.

Furthermore, there are significant social differences in the relationship one has with one's living donor. For instance, as shown in Table 7, compared to whites, blacks are more likely to have child, half-sibling, cousin or niece/nephew living donors and less likely to have non-relative family, friend, or parent living donors; and Hispanics are more likely to get parent, child, sibling, or niece/nephew living donors and less likely to have friend, non-relative family, or spouse living donors. More generally, non-whites are far less likely than whites to have friend or non-relative family living donors, and are typically more likely to have child, sibling, or extended relative living donors. These

differences could be due to differences in the number or strength of these relationships or due to different levels of genetic heterogeneity in the HLA genes by race.

Mortality and Graft Failure. Transplant candidates sometimes die while awaiting a transplant, and the distribution of mortality is far from random. For instance, Gordon and Caicedo (2009) found substantial variability in post-transplant mortality by race in the United States, with Asians and Hispanics experiencing the lowest mortality rates, followed by whites and African Americans.

Far more research has been conducted on the determinants of graft failure (i.e., kidney rejection) without differentiation by survival status. In particular attention has been paid to black-white differences therein (Feyssa et al. 2009; Young & Gaston 2002; Press et al. 2005). The differences are staggering – the half-life of kidney grafts for African Americans are only 30-40% that of whites on average. According to this literature, the primary causes of graft failure include acute rejection (usually because of an undetected presensitization to donor antigens),[5] patient 'noncompliance' with immunosuppressant regimes, graft damage during transplantation, and hypertension (Magee & Pascual 2004), so differences in these rates are likely responsible for group differences in graft failure.

Kidney Offer Acceptance Rates. For different reasons patients and/or doctors frequently refuse organs which are allocated to them (in which case the organ is then offered to the next person in the allocative ranking queue). This is the result of the large majority of organ offers (since July 2000, 98.8%) and occurs for a number of reasons. The most common reason has to do with the characteristics of the donor and their

[5] For definitions of these and other terms used in human immunology, as well as an overview of the organ rejection process, please see Appendix C.

biological compatibility with those of the transplant candidates – this is the result for 83% of all organ offers. Extremely poor patient health (3.8%), logistical hangups (2.4%), and insufficient information (2.1%) also account for the disposition of a significant minority of organ offers. Regardless, the likelihood of acceptance of offered organs represents a third potential mechanism of inequality which is not directly captured in the kidney allocation algorithm discussed above.

Indeed, there are large group differences in rates of organ offer acceptance rates. For instance, whites accept organ offers at higher rates than non-whites, less educated persons accept at higher rates than better educated, high PRA individuals accept at far lower rates than others, B blood type individuals accept at much higher (3.8%) rates, and children younger than 18 accept at relatively very high rates (5%). The most telling differences, however, are between UNOS administrative regions, where the acceptance rates range from 8.6% (Region 6, including Washington, Oregon, and Montana), to 0.9% (New York). Therefore organ acceptance rates are a potential mediating mechanism for inequalities of these sorts.

Results of Preliminary Empirical Models

The results of the models of waitlist and post-transplant events are presented in Figures 16-19, and the results of the model of kidney offer acceptance are presented in Table 8. These results are different from the planned analyses in two respects. First, the interaction of independent variables with time is estimated parametrically in quadratic form. As discussed above, this will be changed to interactions with indicator variables for time variable in future modeling. Second, not all desired independent variables are

included in these models. Many are omitted because of generally low rates of availability in the data. In the future I will correct for this problem by imputing missing values.

Figures 16-19 present the marginal hazard responses (using the recycled predictions method) associated with different races for living donor, waitlist mortality, post-transplant graft failure, and post-transplant mortality hazards respectively, calculated after 1, 3, 5, and 10 years on the waitlist or post-transplant. As can be seen, living donor transplant hazards assume a bathtub shape over one's time on the waitlist, with whites and Hispanics enjoying living donor advantages throughout. Similarly, whites' and Asians' waitlist mortality hazards are the lowest observed. However, post-transplantation whites are not so definitively advantaged. Their graft failure rates are among the lowest early on but are comparable to blacks' post-transplant. Finally, whites have the highest post-transplant mortality hazards of all racial groups.

In other words, the results of these models confirm the results of the descriptive analyses and the large level of inequality experienced in the kidney transplantation system. Table 8 presents additional results in tabular form, showing patterns of kidney offer acceptance according to candidate demographics (all columns), donor-candidate match degree (columns 2-4), candidate characteristics (columns 3-4), and donor characteristics (column 4).

The results by race show that there is a fair amount of racial heterogeneity in the probability of accepting a kidney offer, and that this heterogeneity is even larger when the donor-candidate biological match degree is controlled. Black and Asian patients, in particular, are 1.51 and 1.64 times as likely to accept an organ offer as are whites with a similar match degree. Therefore racial dispositions to accept a kidney offer are

potentially very relevant, but run in the opposite direction of the observed inequalities. (See Figure 12, which shows that these same groups are less likely to receive an SCD transplant than are whites.)

Finally, the associations of HLA and ABO match degree show that these are major predictors of organ acceptance, as well. Those with two allele matches on the DR or B HLA loci are 4 to 4.8 times as likely to accept an offer as those with no matches at these loci, while the similar effect for two allele matches at the A locus is 1.99 to 2.05 times higher. Finally, compared to ABO-identical pairings, those with merely equivalent or non-equivalent kidney offers are appreciably less likely to accept this offer.

To summarize, it does not appear that demographic variation in the probability of accepting an organ offer can explain inequalities in the cadaveric kidney transplantation system. While there is large heterogeneity in these dispositions, these typically run in the opposite direction of the inequalities observed. Therefore, these processes somewhat ameliorate, not exacerbate, the inequalities in this system which would otherwise be observed.

Ongoing Research Design

With the goal of explaining demographic and socioeconomic disparities in kidney transplantation rates, ongoing research (to be completed before the PAA annual meeting) seeks to more precisely quantify the contributions of allocation variables, candidate characteristics, and donor characteristics to racial disparities in kidney transplantation outcomes. The contributions of each of these factors will be evaluated using counterfactual microsimulation techniques which, using the observed timing and characteristics of U.S. organ donors and transplant candidates, redistributing the values of

each of these factors at random to eliminate group differences in each, then simulate the allocative process according to real-world allocation rules to evaluate the degree of inequality which would be observed under these conditions.

The Counterfactual Model of Causality

The primary task of this ongoing analysis is to explain group differences in transplant system exit outcomes from different causes in a counterfactual manner. In brief, the crucial intuition behind the counterfactual approach is to consider all observations as having two or more potential outcome states in response to an exogenous 'treatment,' as in an experiment. The *causal effect* in such a framework is the gap between the outcome state of an observed case under hypothetical treatment and control assignment statuses. Following Holland's (1986) exposition, the causal effect of interest in the dichotomous predictor case amounts to $Y_t - Y_c$, where Y_t is the observed outcome under the 'treatment' condition and Y_c is the observed outcome under the 'control' condition of the predictor variable of interest (say, an intervention). In the pithy phrase of the counterfactual tradition, therefore, there is "no causation without manipulation" (Holland 1986:959).

On the basis of this theoretical underpinning, methodologists have developed a whole suite of methods which attempt to replicate the ideal thought experiment in which one can observe the difference in outcome of the same unit of observation under two different conditions of interest – among them, fixed effects, first differences, instrumental variable regression, matching techniques, and the utilization of natural experiments.

Unfortunately, none of the existing counterfactual techniques (e.g., fixed effects, instrumental variable regression, matching techniques, and natural experiments) are

appropriate for the question at hand. This is because allocative inequality is fundamentally a population-level characteristic. Furthermore, one cannot treat organ transplant outcomes as independent due to the shortage of kidneys for transplantation – a kidney that person A receives is one that person B cannot, and there are not enough for everyone. In sum, a traditional counterfactual research design is uninformative for this research problem. Luckily, counterfactual thinking suggests a better approach for this problem - microsimulation.

Microsimulation as a Counterfactual Tool

Microsimulation[6] is a method of portraying differences observed in an outcome variable when the distribution of some variable is changed. In this study, this will be implemented by combining the results of a series of empirical competing risk hazard models with a simulation of the functioning of the UNOS cadaveric kidney allocation system. Empirical models will be used to simulate the hazards of mortality, graft failure, living donor transplantation, and cadaveric kidney offer acceptance based upon observed characteristics. Meanwhile, the UNOS kidney allocation system will be reproduced following published descriptions thereof. In this way, transplant candidates will be advanced over time onto the waitlist (where they may experience mortality, living donor transplantation, or cadaveric transplantation) and, conditional on undergoing a transplant, into post-transplant life (where they may experience mortality or graft failure and a return to the waitlist). The simulation proceeds over time as each observed individual enters the simulation (at the same time they did so in the observed data) and take their place on the waiting list even as organs become available (again, with timing dictated by the observed

[6] Those familiar with this method should note that the modeling strategy I describe shares some characteristics in common with both microsimulation and the closely related method of agent based modeling (Gilbert 2008).

data) and are allocated to the individual who maximizes the allocation ranking formula among all transplant candidates for that organ (or proceeds downward through the ranking when top-ranked individuals refuse that organ). Figure XX displays the simulation design graphically.

The method just described serves to reproduce the functioning of the observed kidney transplantation and inequalities therein. Next, the counterfactual effects of group differences in a large set of proximate determinants of kidney transplantation outcomes will be estimated. This is done by taking the observed distribution of a variable and reassigning these values completely at random, thereby equalizing the distribution of this characteristic among all social groups. Having equalized this distribution, the kidney transplantation system will be re-simulated using this counterfactual data. The counterfactual contribution of the equalized factor to racial disparities in kidney transplantation is then the difference between the level of racial inequality in the observed data simulation and the counterfactual data simulation.

The variables and parameters which will be equalized in these simulations are listed in Table 9. In the case of parameters (such as those obtained from models of non-cadaveric transplant waitlist events, described below), the vector of time- and outcome-specific hazards will be redistributed in this manner. Finally, in the case of probabilities of kidney offer acceptance, probabilities thereof will be equalized across all transplant candidates conditional on ABO and HLA match degree.

So, for instance, using this method in my research I can answer questions such as: How much racial inequality in transplant outcomes would there be if there were no residential segregation? Or genetic and blood type differences? Or probability of getting

a living donor? If appropriately done, the difference between the observed level of inequality and that simulated using this technique is the estimate of the causal effect of each of

One limitation of this modeling strategy is that, when the main counterfactual components of each variable are summed together, they may 'explain' more inequality than is present in the data. The solution is to estimate the independent effect of each equalization by comparing the level of inequality observed when all candidate processes and variables are redistributed against that when all but the factor of interest is equalized. In other words, if one is interested in the role of residential pattern differences by race in these inequalities, one can estimate the independent causal effect of this process first by equalizing all candidate factors, and then equalizing everything but geographic residential patterns, then run the simulation and compare the levels of inequality observed. The difference between the two observed inequalities will be the independent effect of residential stratification.

Conclusion

In summary, racial disparities in kidney transplantation are a very complicated phenomenon, arising as a function of geographic, social, family, biological, institutional, and medical factors. However, using the research methods just described (and currently being implemented), this problem becomes more tractable, and interpretable in a causally satisfying manner. By using novel research methods, this research will contribute to demographic understanding of racial disparities in kidney transplantation specifically, and in health outcomes generally.

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TABLES AND FIGURES

Table 1: Absolute and Percentage Change for Kidney Transplants

	Absolute Change	Percent Change
Kidney Waitlist Length, 1988-2008	76089-17930=58159	324.4% [b]
Transplants, 1988-2007	16634-8878=7756	87.4%
Cadaveric Transplant %	56.49-80.67=-24.17%	-30.0%
Living Donor Transplant %	33.59-19.29=14.30%	74.2%
Graft Survival Rates		
12 Month, 1988-2007	92.9-78.3=14.6	18.7%
36 Month, 1988-2006	83.6-66.9=16.6	24.9%
60 Month, 1988-2004	72.7-57.4=15.3	26.6%
Median Wait Times	2106-542=1564	288.6%[a]
Waitlist Mortality Cumulative Probability		
6 Month	1.8%-1.7%=0.1%	4.1%[b]
12 Month	3.1%-3.2%=-0.1%	-4.0%[b]
36 Month	9.3%-6.3%=3.0%	48.3%[c]
Waitlist Transplant Cumulative Probability		
6 Month	6.6%-30.2%=-23.6%	-78.3%[b]
12 Month	10.0%-43.3%=-33.3%	-77.0%[b]
36 Month	24.9%-59.8%=-34.9%	-58.3%[c]

[a]: 1988-1994; [b]: 1988-2008; [c]: 1988-2006. NOTE: Years compared vary based on data availability and case counts. Percent change is calculated as (Year2-Year1/Year1). Discrepancies in range calculation due to rounding. 1988 waitlist length calculated from author calculations; 2008 waitlist length from SRTR data, available at http://www.ustransplant.org/annual_reports/current/data_tables_section1.htm. Accessed 8/21/2010.

Table 2: Expected Percentage Distribution of HLA Match Degree by Relationship Type and Race

		P(0)	P(1)	P(2)	P(3)	P(4)	P(5)	P(6)
Parent-Child	**White**	0	0	0	25	45	26	4
	Black	0	0	0	32	45	20	3
	Hispanic	0	0	0	40	44	15	1
	Asian	0	0	0	32	46	20	3
	Other	0	0	0	44	42	13	1
r=.5	**White**	0	1	7	20	33	28	10
	Black	0	2	9	23	33	25	8
	Hispanic	0	3	11	25	32	22	6
	Asian	0	2	9	23	33	25	8
	Other	0	3	12	26	32	21	6
r=.25	**White**	1	8	21	31	26	11	2
	Black	2	11	25	31	22	8	1
	Hispanic	3	14	28	30	18	6	1
	Asian	2	10	25	32	22	8	1
	Other	3	16	30	29	16	5	1
r=.125	**White**	3	14	29	31	18	6	1
	Black	5	19	31	28	14	3	0
	Hispanic	7	24	33	24	9	2	0
	Asian	4	19	32	28	14	3	0
	Other	9	27	33	22	8	2	0
r=0	**White**	6	23	33	25	10	2	0
	Black	10	29	33	20	7	1	0
	Hispanic	16	35	31	14	3	0	0
	Asian	10	29	34	20	6	1	0
	Other	20	37	29	12	3	0	0

NOTE: 'W'=Whites, 'B'=Blacks, 'H'=Hispanics, 'A'=Asians, 'O'=Others (including multiracials). 'r' is the expected genetic relationship degree between the candidate and an alter with a specific relationship type: .5 includes siblings; .25 includes half-siblings, aunts/uncles, niece/nephews, and grandparents/grandchildren; .125 includes cousins and great aunts/uncles, etc; 0 includes all those not genetically related. Darker gray cells indicate more probable outcomes. Expected percentages calculated using distributional information on HLA genes by race and UNOS-supplied tables of serological equivalence between alleles for HLA-A, -B, and -DR.

Table 3: Expected Percentage of Alters with Excellent HLA Matches (≥4 Matches) by Relationship Type and Race

	Parent-Child		r=.5		r=.25		r=.125		r=0	
	%	OR	%	OR	%	OR	%	OR	%	OR
White	30	--	38	--	13	--	6	--	2	--
Black	23	0.76	33	0.86	9	0.72	4	0.62	1	0.50
Hispanic	16	0.54	28	0.74	6	0.49	2	0.34	0	0.19
Asian	23	0.76	33	0.86	9	0.71	4	0.60	1	0.46
Other	14	0.46	26	0.69	5	0.42	2	0.27	0	0.13

NOTE: Expected percentages calculated using distributional information on HLA genes by race.

Table 4: Race/Ethnicity-Specific Blood Type Distributions

	White	Black	Hispanic	Asian	Other
A	0.394	0.255	0.297	0.259	0.289
AB	0.037	0.041	0.022	0.067	0.029
B	0.111	0.203	0.098	0.279	0.132
O	0.459	0.502	0.583	0.395	0.550

NOTE: Dark gray cells indicate >110% of average of group-specific means. Light gray cells indicated <90% of average of group-specific means.

Table 5: Race/Ethnicity Average ABO-Identical and ABO-Compatible, Within-Group

	White	Black	Hispanic	Asian	Other
Identical	0.379	0.360	0.438	0.305	0.404
Compatible	0.646	0.628	0.690	0.581	0.664

Table 6: Probability of ABO Compatibility by Blood Type, Race, and Relationship Type

Parent-Child		White	Black	Hispanic	Asian	Other
A	(A+O)	0.852	0.757	0.880	0.654	0.839
AB	(All)	1.000	1.000	1.000	1.000	1.000
B	(B+O)	0.570	0.705	0.681	0.674	0.682
O	(O)	0.459	0.502	0.583	0.395	0.550
r=.5						
A	(A+O)	0.858	0.771	0.883	0.684	0.845
AB	(All)	1.000	1.000	1.000	1.000	1.000
B	(B+O)	0.616	0.727	0.707	0.700	0.708
O	(O)	0.532	0.564	0.627	0.487	0.601
r=.25						
A	(A+O)	0.789	0.665	0.827	0.541	0.771
AB	(All)	1.000	1.000	1.000	1.000	1.000
B	(B+O)	0.447	0.601	0.573	0.564	0.574
O	(O)	0.334	0.377	0.462	0.276	0.426
r=.125						
A	(A+O)	0.758	0.618	0.800	0.485	0.737
AB	(All)	1.000	1.000	1.000	1.000	1.000
B	(B+O)	0.386	0.549	0.518	0.509	0.520
O	(O)	0.272	0.315	0.401	0.216	0.364
r=0						
A	(A+O)	0.726	0.572	0.774	0.428	0.704
AB	(All)	1.000	1.000	1.000	1.000	1.000
B	(B+O)	0.325	0.497	0.464	0.454	0.466
O	(O)	0.210	0.252	0.340	0.156	0.303

NOTE: Dark gray cells indicate >110% of average of group-specific means. Light gray cells indicated <90% of average of group-specific means.

Table 7: Percentage Ratios of Living Donor Relationship Type by Race

BY RACE	Black	Hispanic	Asian	Other
Parent	83%	125%	98%	82%
Child	158%	123%	90%	120%
MZ Twin	75%	200%	250%	0%
Sibling	103%	120%	117%	113%
Half Sibling	178%	105%	79%	165%
Spouse	76%	88%	110%	77%
Cousin	115%	99%	104%	117%
Aunt/Uncle	101%	99%	64%	141%
Niece/Nephew	136%	129%	118%	146%
Oth. Biological	122%	84%	95%	149%
Friend	75%	51%	74%	74%
Non-Rel. Family	40%	70%	76%	55%
Other/Unk.	88%	62%	117%	111%

NOTE: Percentage ratios (PRs, equal to 100*(Odds Ratio)) computed relative to whites.

Dark gray cells are those with PR≥110. Light gray cells are those with OR≤90.

Table 8: Results of a Logistic Regression Analysis of Kidney Offer Acceptances

	(1)	(2)	(3)	(4)
	Demographics	+ Match	+ Cand. Health	+ Donor Chars.
Female	1.04	1.03	1.03	1.04
RACE				
White (Ref.)	--	--	--	--
Black	1.14	1.51	1.48	1.49
Hispanic	1.06	1.26	1.29	1.30
Asian	1.19	1.64	1.61	1.58
Other	1.07	1.38	1.42	1.39
INSURANCE				
Private (Ref.)	--	--	--	--
Medicaid	1.16	1.20	1.19	1.17
Medicare	1.11	1.12	1.09	1.09
Other Government	1.01	1.01	0.98	0.96
Self	0.93	0.92	0.94	0.94
Other	1.04	1.03	1.13	1.09
CITIZENSHIP				
US Citizen (Ref.)	--	--	--	--
Resident Alien	1.17	1.18	1.13	1.16
Non-Res. Alien	0.93	1.02	0.98	1.05
AGE				
0-17 (Ref.)	--	--	--	--
18-25	0.81	0.66	0.74	0.88
26-35	0.82	0.67	0.77	0.94
36-45	0.83	0.68	0.82	1.00
46-55	0.85	0.71	0.86	1.05
56-65	0.81	0.67	0.84	1.05
66-75	0.74	0.62	0.78	0.99
76+	0.67	0.56	0.65	0.89
EDUCATION				
None (Ref.)	--	--	--	--
Grade School	1.21	1.19	1.10	1.16
HS / GED	1.18	1.15	1.07	1.13
Some College	1.11	1.08	1.02	1.08
BA / Associates	1.09	1.07	1.01	1.07
Post-Bacc. Degree	0.99	0.97	0.92	0.96
Years on Waitlist	0.56	0.62	0.63	0.65
PRA	1.00	1.00	1.00	1.00
HLA MATCHES				

0 DR Matches (Ref.)		--	--	--
1 DR Match		1.87	1.88	1.79
2 DR Matches		4.80	4.80	4.32
0 B Matches (Ref.)		--	--	--
1 B Match		1.41	1.44	1.41
2 B Matches		4.62	4.41	4.02
0 A Matches (Ref.)		--	--	--
1 A Match		1.17	1.16	1.17
2 A Matches		2.06	1.99	2.05
BLOOD TYPE MATCH				
ABO Match (Ref.)		--	--	--
ABO Equivalent		0.64	0.64	0.66
ABO Not Equiv.		0.80	0.79	0.78
Cand. Diabetes?			0.86	0.85
CANDIDATES' CAUSE OF ESRD				
Glomerularnephritis (Ref.)			--	--
Congenital Diseases			1.02	1.00
Diabetes			0.93	0.94
Neoplasms			1.01	1.03
Hypertension			1.03	1.01
Graft Failure			0.57	0.56
Other			0.97	0.96
CANDIDATE HEALTH STATUS/HISTORY				
Previous KI Tx?			2.24	2.25
Cerebrovascular Disease			0.97	0.99
Peptic Ulcer			0.99	0.99
Treatment for Hypertension			0.97	0.98
Hospitalized at Registration			1.06	1.09
Peripheral Vascular Disease			0.89	0.88
Treatment for Chron. Obstruct. Pulmonary Disease			0.86	0.89
On Dialysis at Registration			1.11	1.07
BMI			1.00	1.00
FUNCTIONAL STATUS AT REGISTRATION				
Fully Disabled (Ref.)			--	--
Moderately Disabled			1.03	1.04
Not Disabled			0.91	0.90
DONOR CHARACTERISTICS				
Donor Creatinine				0.87
Vasodilators in Last 24 Hours				1.27
COD: Anoxia (Ref.)				--

COD: Cerebrovascular Disease				1.29
COD: Head Trauma				1.82
COD: Neoplasm				0.35
COD: Other				0.79
Donor Age				1.00
Protein in Urine				0.91
Cocaine Use				0.82
Cigarette Use				0.87
Other Drug Use				1.24
Liver Function (SGPT)				1.00
Organ Function (SGOT)				1.00
Venereal Diseases				0.60
Cold Ischemic Time				0.94
Diabetes				0.82
Hypertension				0.94
Cancer History				0.83
ECD Donor				0.75
Intercept	0.07	0.04	0.04	0.10
N	1,189,243	1,189,243	891,552	745,990
Log Pseudolikelihood	-162,199	-148,616	-111,577	-85,989
Pseudo R-Sq	0.1196	0.1933	0.1942	0.2349

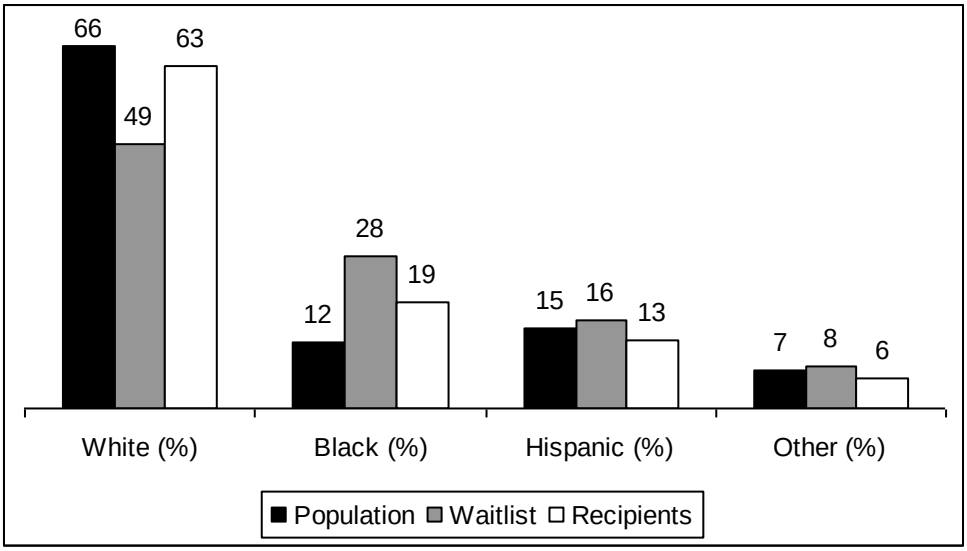
NOTE: N represents the number of candidate*offer observations available with complete information on the outcome and all covariates.

Table 9: Equalized Factors in Counterfactual Simulations

Equalized Factor	**Details**
HLA Antigens	Genotypes reallocated as a joint unit
ABO	ABO Antigens
ZIP Code	Primary place of residence
PRA	
Age	Pediatric/Adult
ECD Organ Acceptance	Predicted probability of ECD organ offer acceptance
SCD Organ Acceptance	Predicted probability of SCD organ offer acceptance
Living Donor Probability	Living transplantation hazard
Waitlist Mortality	Pre-transplant mortality hazard
Re-waitlisting	Time-specific hazards of waitlist reentry post-transplant
Multiple listings	Probability of multiple listing: region-specific; reallocated within regions only

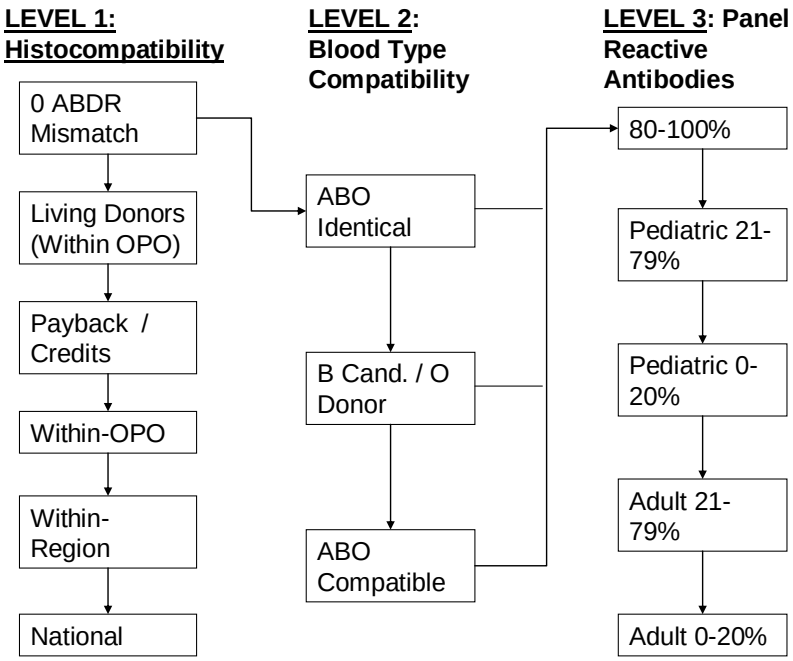
NOTE: Individual-specific, time-invariant variables (HLA, ABO, ZIP, PRA, Age) are redistributed at random between individuals. When equalized factor is a parameter (living donor probability, waitlist mortality hazard, rewaitlisting and multiple listing probability), the vector of time-specific hazards will be equalized. When the equalized factor is the probability of SCD or ECD organ acceptance, the probability of acceptance conditional on donor and donor-candidate match degree will be equalized.

Figure 1: Organ Donation and Receipt by Race



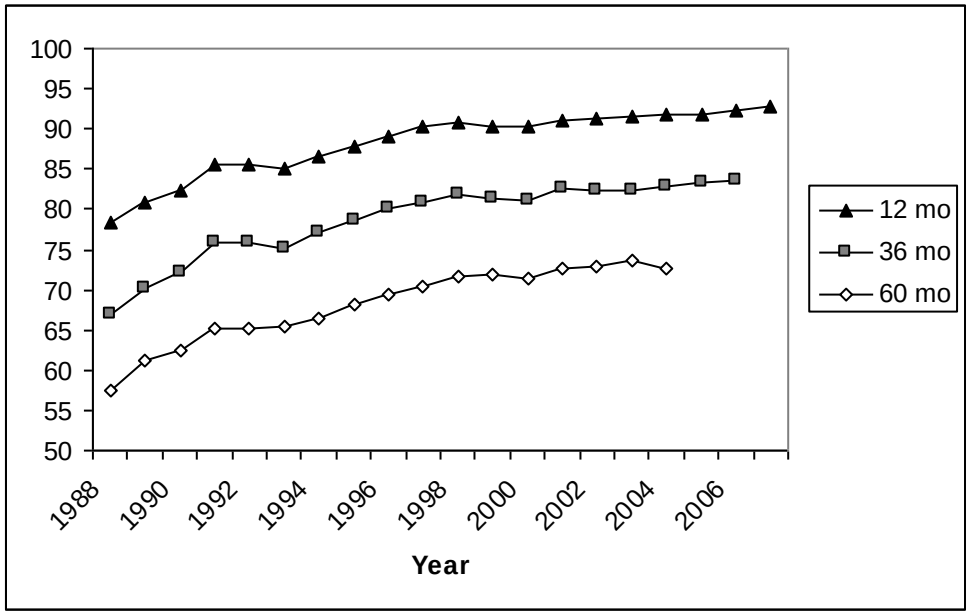
Sources: 2006/7 OPTN Data, 2005-2007 American Community Survey

Fig. 2: Current UNOS Kidney Allocation Rules, Standard Donors Age > 35



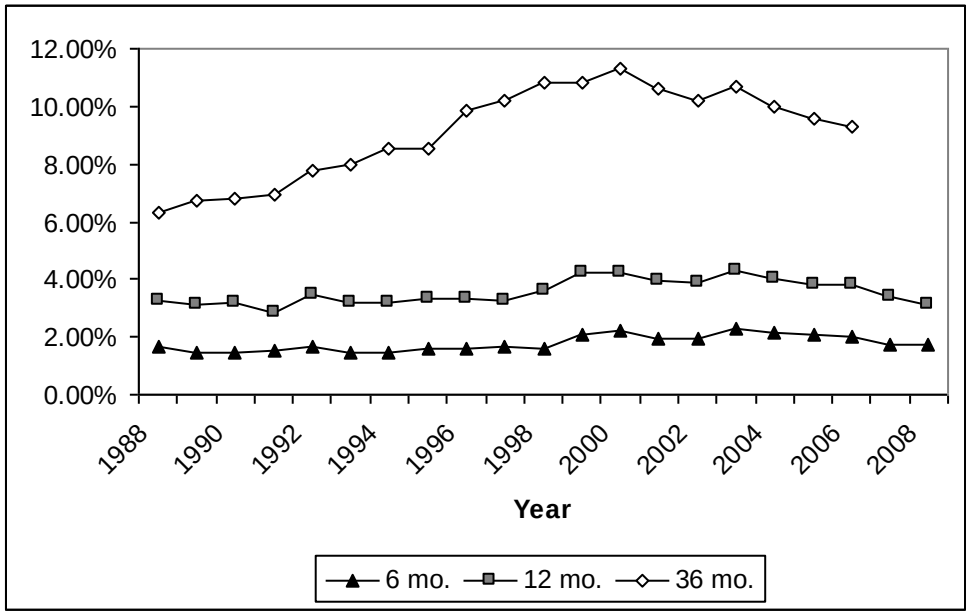
NOTE: ABDR is a measure of genetic histocompatibility. OPO means 'organ procurement organization,' a set of geographically-bound administrative subunits of UNOS. 'ABO Identical' indicates that two patients' blood types match exactly. 'ABO Compatible' means that their blood types are compatible in the sense that the potential recipient is capable of accepting the donor's blood type (e.g., O donors can donote to all blood types, but can receive organs only from other O donors). Panel Reactive Antibodies are a measure of immunological responsiveness which are measured in terms of their cumulative immunological sensitivity scores.

Figure 3: U.S. Kidney Transplant Graft Survival Rates by Year



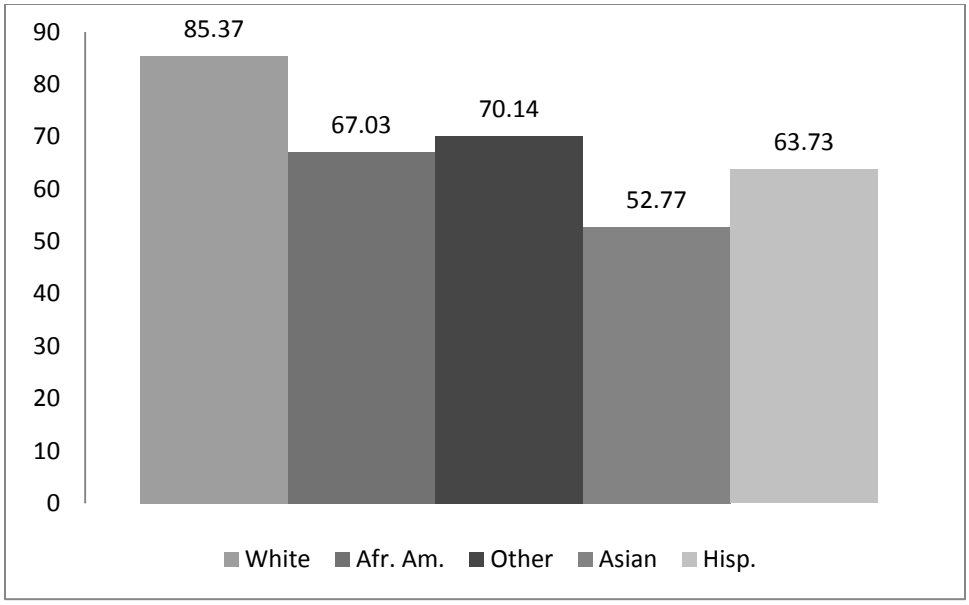
Source: 1988-2008 OPTN Data

Figure 4: U.S. Kidney Transplant Waitlist Death Rates, by Year



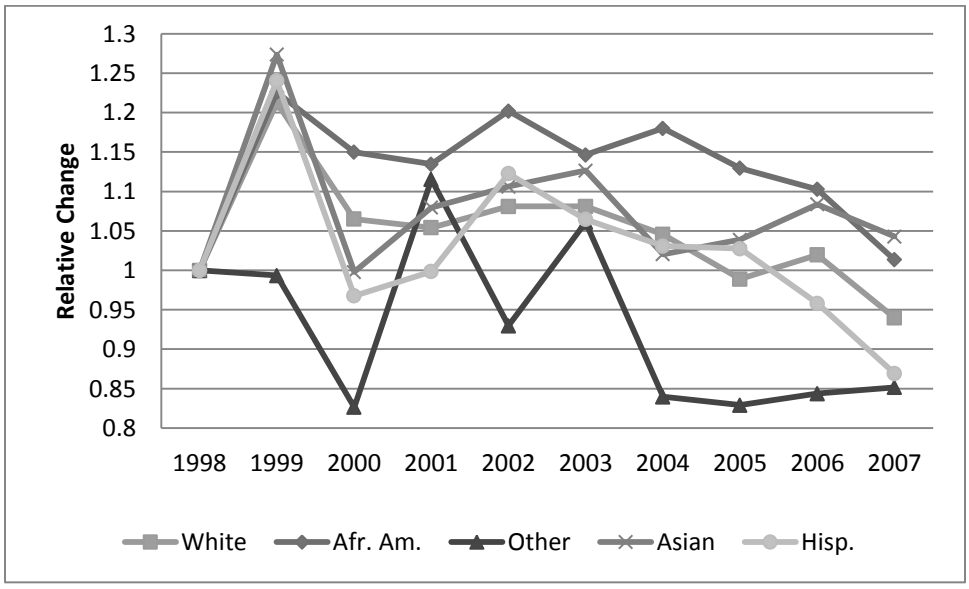
Source: 1988-2008 OPTN Data

Figure 5: U.S. Kidney Waitlist Death Rates, by Race



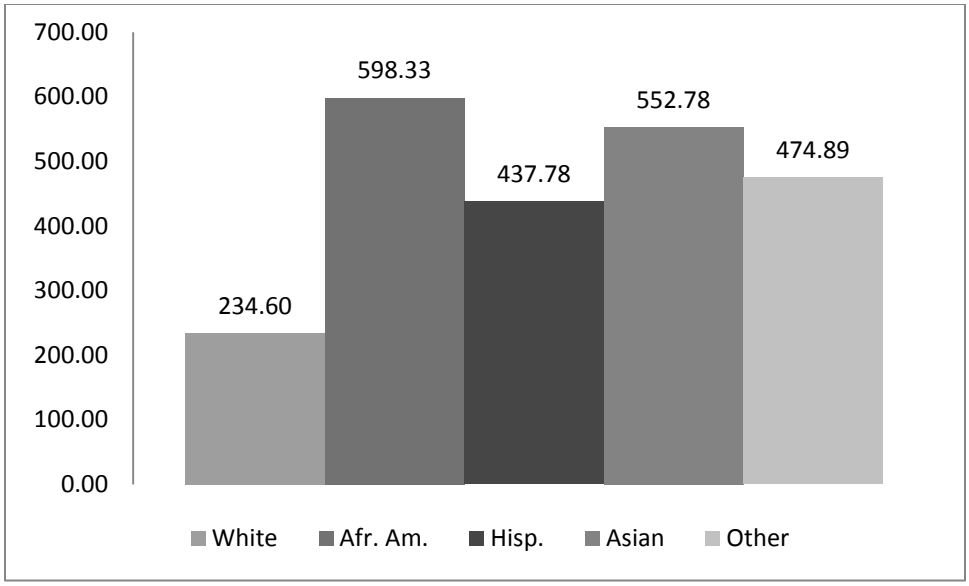
Source: 1998-2007 SRTR Data

Figure 6: U.S. Kidney Waitlist Relative Death Rates over Time, by Race



Source: 1998-2007 SRTR Data

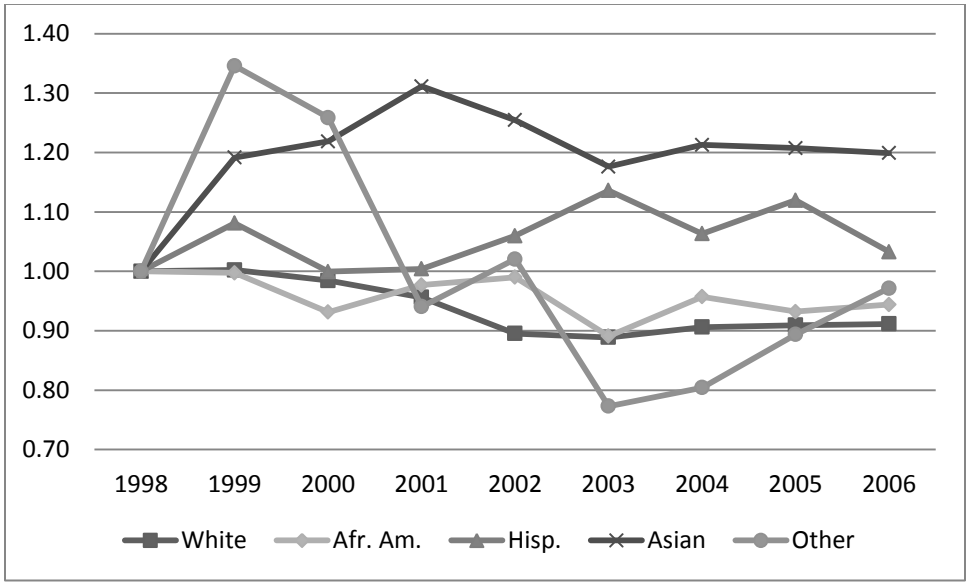
Figure 7: U.S. Kidney 25th Percentile Waitlist Times, by Race/Ethnicity



Source: 1998-2006 SRTR Data

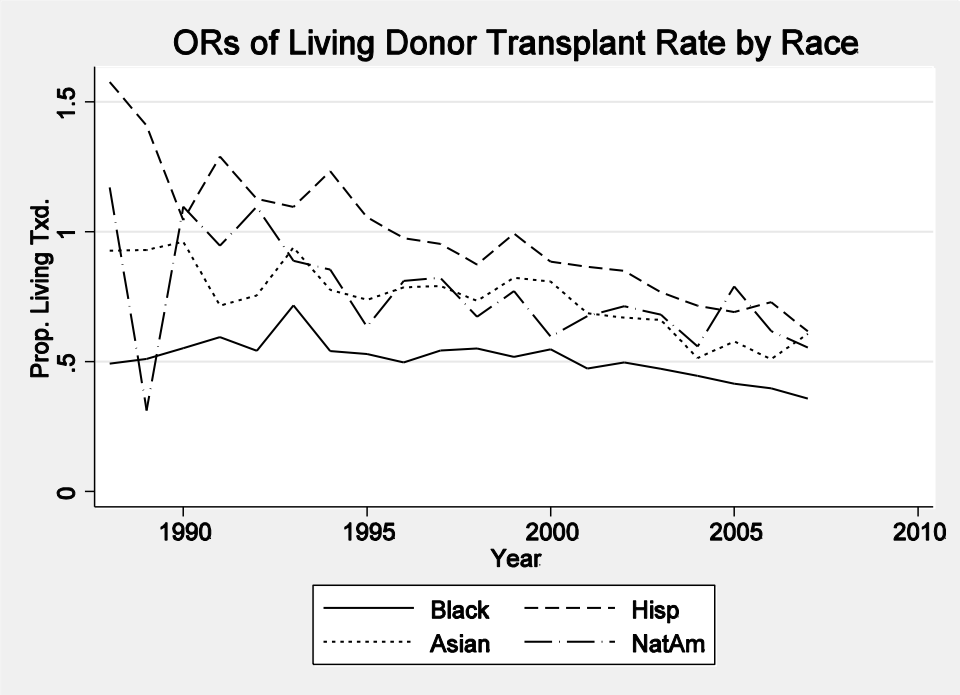
NOTE: 25th Percentile wait times are used because median and higher wait times were not always available for all groups due to small cell sizes.

Figure 8: U.S. Kidney 25th Percentile Waitlist Times over Time, by Race/Ethnicity



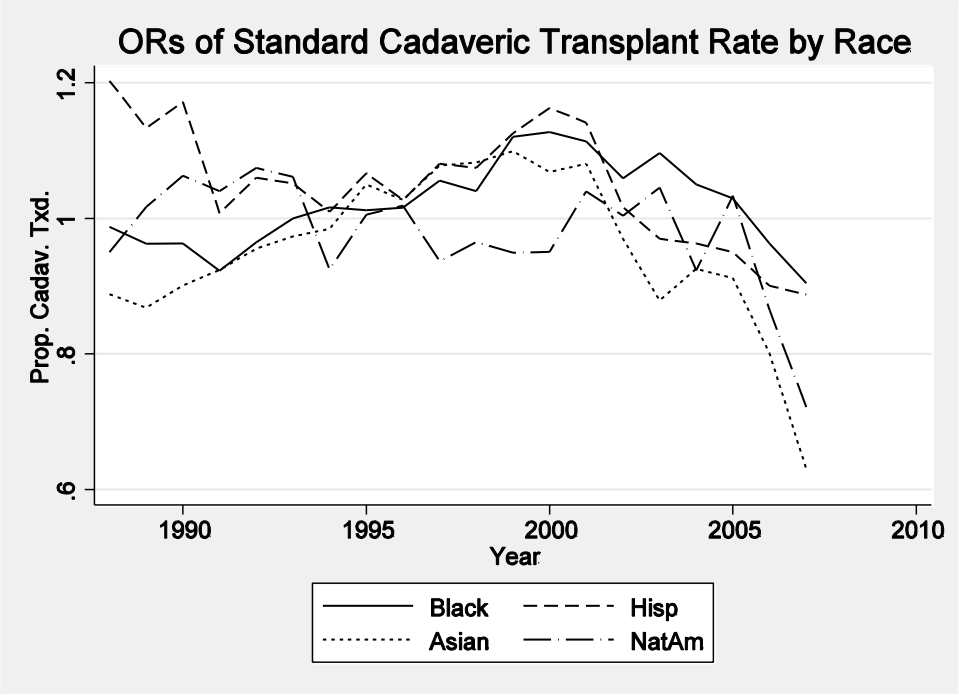
Source: 1998-2006 SRTR Data

Figure 9



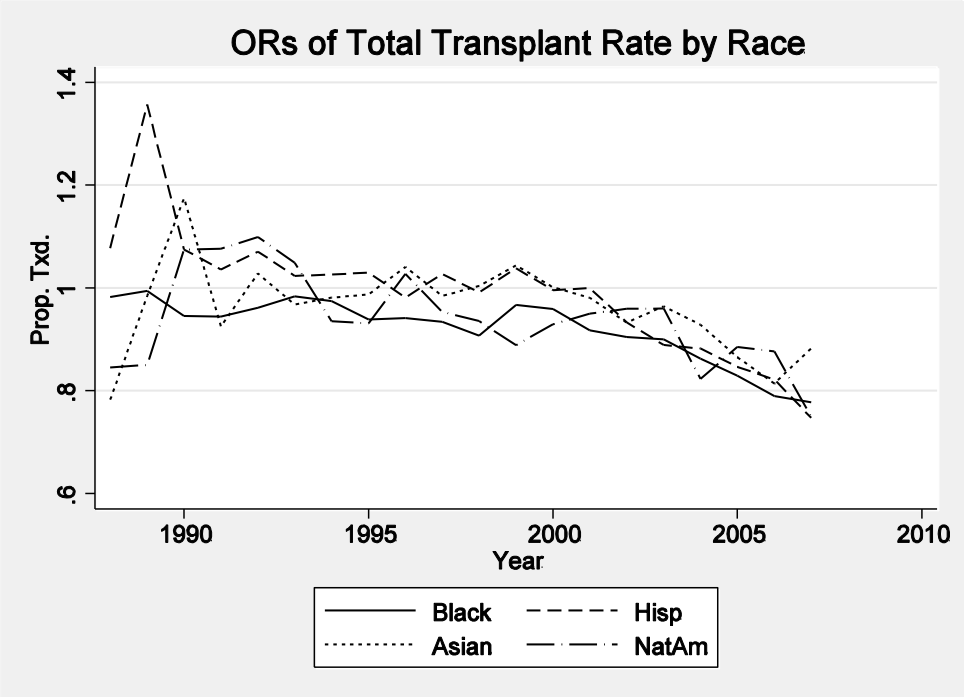
SOURCE: UNOS STAR Files 1988-2007

Figure 10



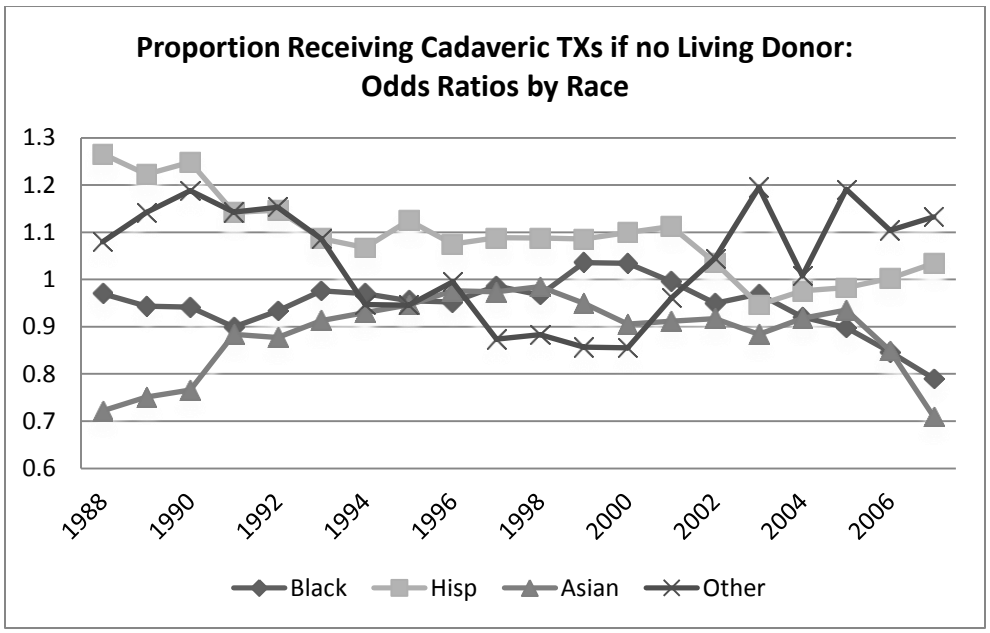
SOURCE: UNOS STAR Files 1988-2007

Figure 11



SOURCE: UNOS STAR Files 1988-2007

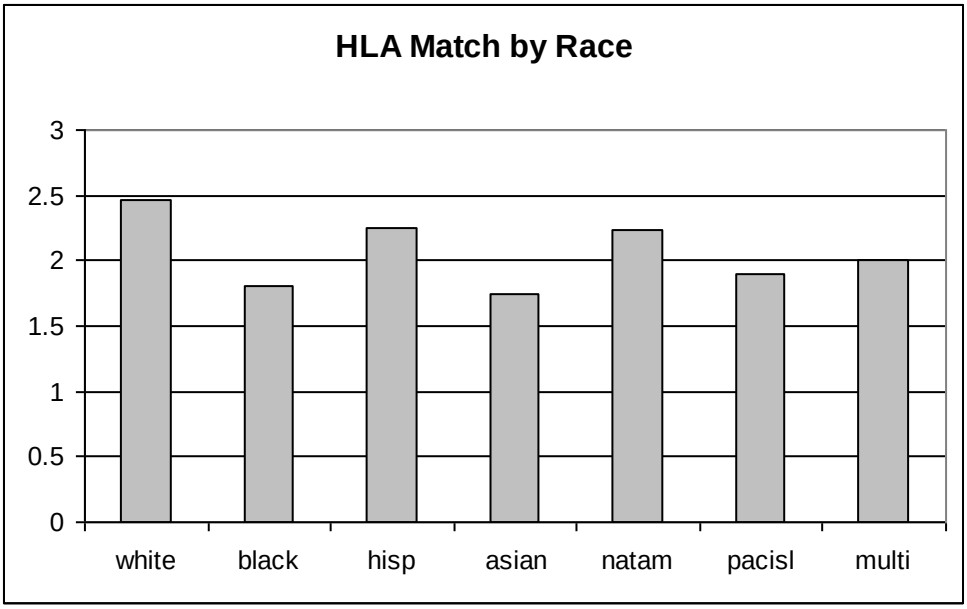
Figure 12



NOTE: Odds ratios calculated compared to whites.

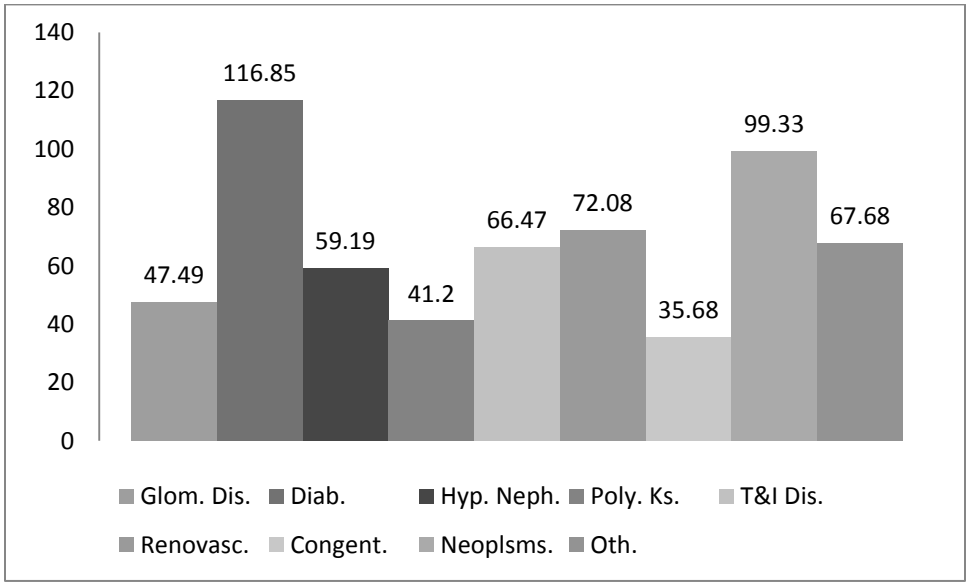
SOURCE: UNOS STAR Files 1988-2010

Figure 13



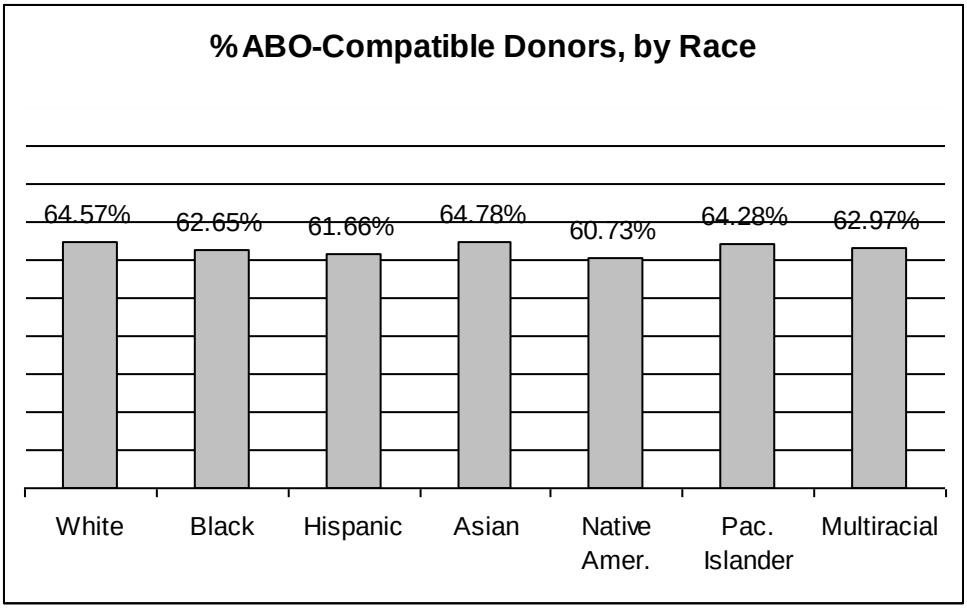
Source: UNOS STAR Files, 1988-2010

Figure 14: U.S. Kidney Waitlist Mortality Rates, by Diagnosis



Source: 1998-2007 SRTR Data

Figure 15



Source: UNOS STAR Files, 1988-2010

Figure 16

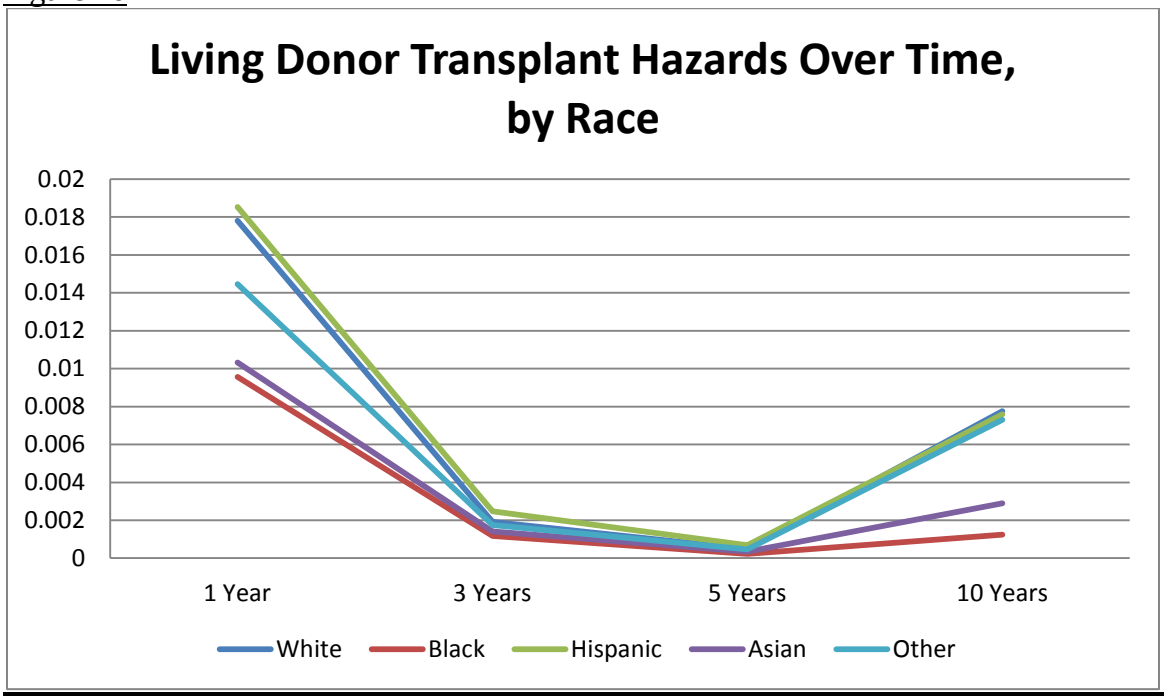


Figure 17

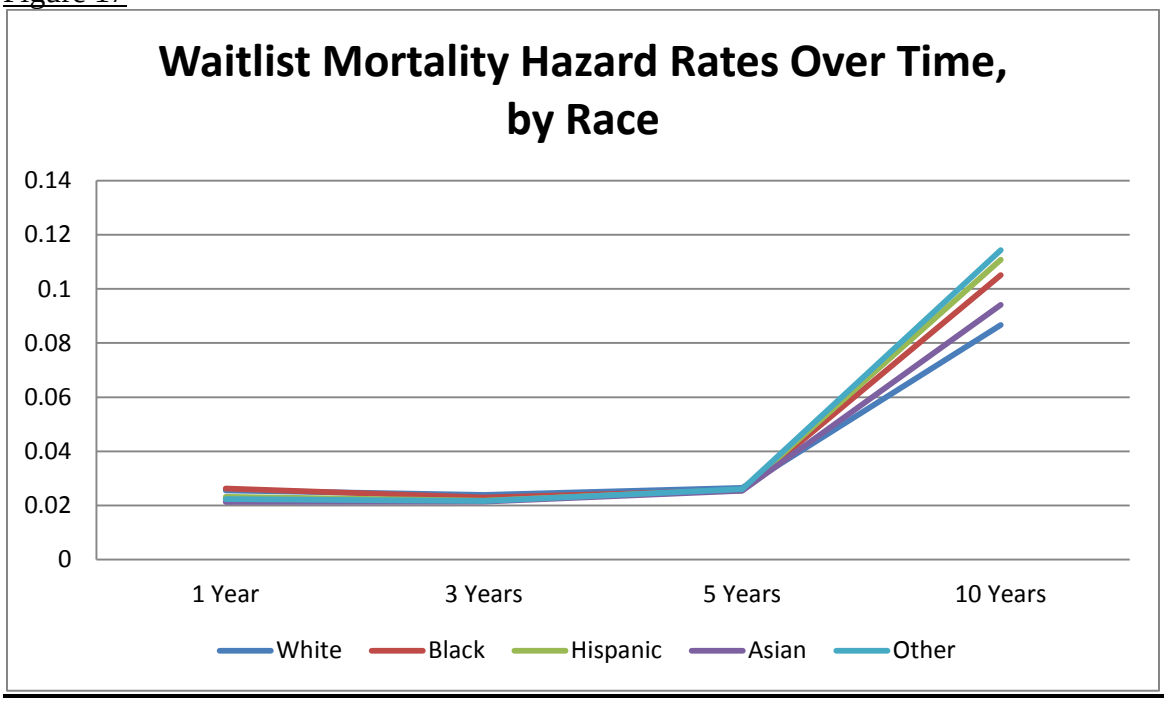


Figure 18

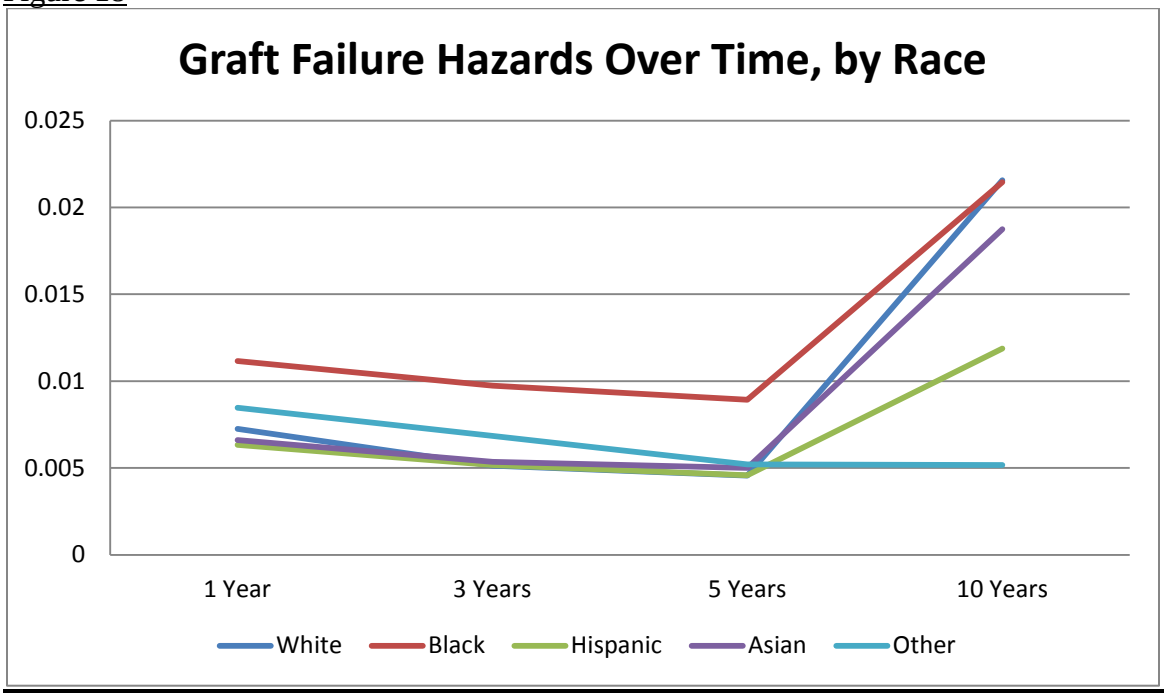
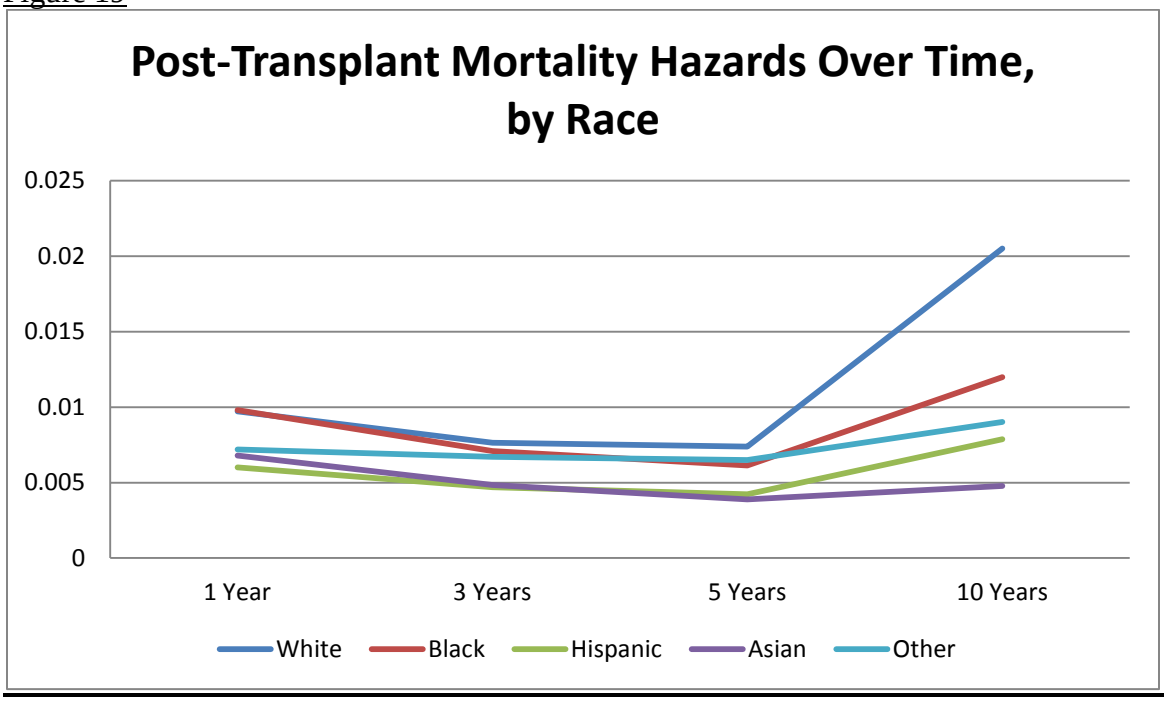


Figure 19


Post-Transplant Mortality Hazards Over Time, by Race
0.025
0.02
0.015
0.01
0.005
0
1 Year
3 Years
5 Years
10 Years
White
Black
Hispanic
Asian
Other

APPENDIX A: ORGAN ALLOCATION SYSTEM, IN DETAIL

Table A1: Allocation Points for Standard Cadaveric Kidneys

Variable	**Points, 1987-1995**	**Points, 1995-2003**	**Points, 2003-Present**
Waiting Time	0.5 per year	1 per year	1 per year
Waiting List Rank	(X/N), where X=waiting rank (inverse) N=total candidates on waiting list	(X/N), where X=waiting rank (inverse) N=total candidates on waiting list	(X/N), where X=waiting rank (inverse) N=total candidates on waiting list
HLA Antigen Mismatching:			∞ (national) for 0A/B/DR mismatch
0 A/B/DR mismatches	10	∞ (national)	
0 B/DR mismatches	7	7	2 if no DR
0 A/B mismatches	6	0	mismatches
1 B/DR mismatch	3	5	
2 B/DR mismatches	2	2	1 if 1 DR mismatch
3 B/DR mismatches	1	0	
Calculated Protein Reactive Antibody (CPRA) Score >80%	4	4	4
Pediatric Candidate			
If <11 years old	2	4	4
If 11-18 years old	1	3	3
Pediatric Candidate & Donor <35 years old			∞ If multiple candidates: - descending point sequence offers, -1 point if age <11
Previous Organ Donor			4 At local level only: - ∞ points - If multiple, waiting time order

Candidates are ranked and receive offers locally (by OPO), regionally, and nationally using this system.

Table A2: Definition of Extended Criteria Donors

Donor Condition	Donor Age<50	50-59	60-69
CVA+HTN+HCR		X	X
CVA+HTN		X	X
CVA+HCR		X	X
HTN+HCR		X	X
CVA			X
HTN			X
HCR			X
None of the Above			X

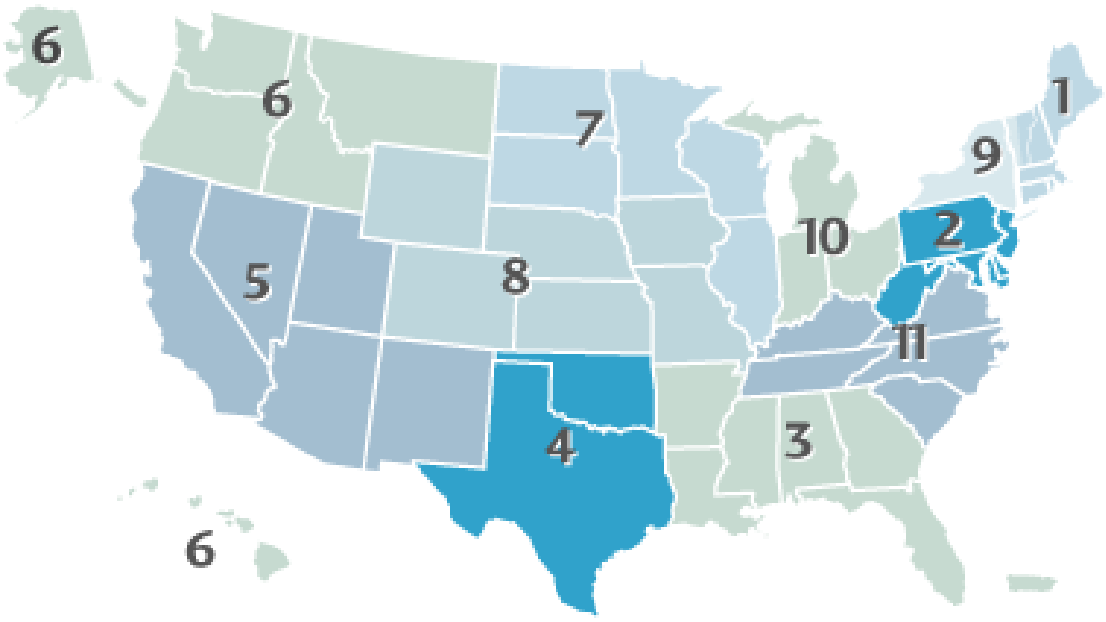
CVA: Cardiovascular cause of death

HTN: History of hypertension

HCR: Creatinine > (1.5 mg/dl) (an indicator of poor kidney function)

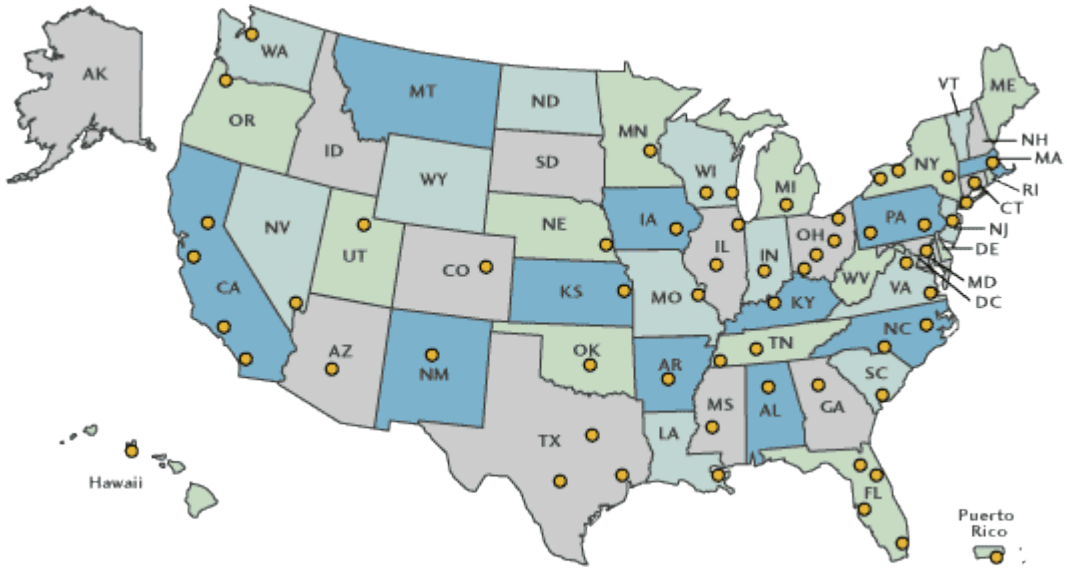
'X' indicates ECD donor

Figure A1: UNOS Regions



http://www.unos.org/whoWeAre/OPOs.asp, accessed 6/7/2010

Figure A2: UNOS OPO Boundaries



http://www.unos.org/whoWeAre/regions.asp, accessed 6/7/2010

Other Rules:

1) 0 HLA mismatch donor-candidate pairs are mandatorily shared nationally. Offers must be made to at least 10 such candidates if they exist. 0 mismatch candidates are those who have serologically equivalent alleles for all six HLA alleles and a compatible blood type. If multiple zero mismatch candidates, offers made in the following order:
    a. Local candidates
    b. >=80% PRA candidates:
        i. in payback OPOs
        ii. in same region
        iii. nationally
    c. <80% PRA candidates:
        i. <18 years old in payback OPOs
        ii. <18 years old in same region
        iii. <18 years old nationally
    d. 21-79% PRA candidates:
        i. in payback OPOs
        ii. in same region
        iii. nationally
2) Extended criteria donor (ECD) kidneys are allocated following the present point system for waiting time alone. Points are so awarded only to those who voluntarily agree to consider ECD organ offers and have a compatible blood type to the organ offered.
3) Sharing organs regionally or nationally (except for 0 mismatch shares) create a balance of accounts between OPOs, and this balance of accounts may not exceed 9 for all blood groups combined. Payback organs must be of the same blood type as those received.
4) ABO-O organs must be transplanted into ABO-O candidates and ABO-B organs must be transplanted into ABO-B candidates. Mandatory exceptions apply for zero mismatch pairings.
5) Multiorgan transplants:
    a. Combined kidney-pancreas transplants are the most common.
    b. Rules are complex and the scope is minor. Multiorgan transplant seekers will be treated as kidney seekers in present study.

APPENDIX B: CALCULATING PROBABILITIES OF HLA AND ABO MATCH BY GROUP

ABO Compatibility

On the assumption that individuals do not assortatively mate by blood type and that kinship and friendship networks are entirely racially homophilous, one may calculate the probability that ego-alter pairs in each racial and ethnic group are ABO-compatible with one another, stratified by genetic relationship type. These calculations are based on empirical distributions of blood type by group (measured by transplant candidate frequencies), basic probability theory, and ABO compatibility rules discussed in the main text.

Following Kanter & Hodge (1990), the probability that a member of one's own group is ABO-compatible with oneself is calculated as:

$$P(C_{ijk}) = T_{2ijk} + T_{1ijk}q_k + T_{0ijk}q_k^2$$

where i indexes ego, j indexes alter, and k indexes racial/ethnic group. T_{xijk} is defined as the probability of sharing x alleles due to common inheritance at the ABO locus for a dyad with the i-j pair's genetic relationship degree. Finally, q_k is defined as the percentage of the racial/ethnic group that has a compatible blood type with i's ABO phenotype. The distribution of blood types by race is shown in Table 4 in the main text; to obtain q_k for a blood type-race/ethnicity combination, one just adds together the percentages for all compatible blood types (A with O, B with O, and AB with all) within-group.

T_x is defined for all races/ethnicities as:

	T_2	T_1	T_0
MZ Twins	1	0	0
Child/Parent	0	1	0
Full Sibling	.25	.50	.25
Aunt/Grandparent/Niece/Half-Sibling	0	.50	.50
First Cousin	0	.125	.875
Unrelated	0	0	1

Therefore i-j pairs which are more distantly related increasingly rely upon the unconditional probability of ABO compatibility within group.

Combining these values of T with the values of q implied by Table 4 permitted the calculation of the values in Table 6, following the formula above. However, to the

degree that individuals assortatively mate within their own race/ethnicity according to blood type, these probabilities would be somewhat different. Also, lack of total homophily in mating, kinship, and friendship patterns limits the usefulness of these calculations, although the probability of being ABO compatible with members of another group is straightforwardly calculable using the above formula and T values, but using the alter's q values instead of one's own group's.

HLA Match Degree

HLA match degree distribution is similarly calculated as the ABO calculations, except that the probability of match degree at each locus is treated as an independent trial. This approach assumes that the alleles are independently inherited, that there is no assortative mating based on HLA, and that there are no compatibility patterns between alternative HLA alleles at the same locus. None of these assumptions are strictly true, and will be relaxed in future research.

While the assortative mating assumption is fairly benign for ABO compatibility – there is no reason to assume that people seek out mates with or without compatible blood types net of their tendency for demographic homophily – this assumption is more doubtful in the case of HLA match probabilities. Starting with Wedekind et al. (1995), a large number of studies have investigated humans' sexual preferences based upon HLA (dis)similarity. The usual (but not uniform) conclusion is that humans show a preference for mates with dissimilar HLA profiles than their own. The argument is that this preference helps ensure that entire genealogies are not susceptible to single strains of bacteria or parasites – a defense against immunological incest.

Furthermore, the calculations make an additional, erroneous assumption: that each of the HLA alleles are independently inherited from a subpopulation distribution. Because without assortative mating based on ABO genes there is no threat that this is so, this possibility was not considered above. However, since the HLA genes under consideration consist of three loci on the same chromosome and closely spaced together, certain combinations of HLA genes are more commonly observed than one would expect at random – a phenomenon known as linkage disequilibrium.

However, the calculations presented in Table 2 and 3 do account for one methodological challenge. As mentioned in the text, most HLA alleles at all loci have a list of other alleles which are indistinguishable in the bloodstream – i.e., serologically equivalent alleles. These patterns of equivalence have been accounted for in the calculations presented in Tables 12 and 13.