

Allocating Deceased Donor Kidneys to Candidates with High Panel-Reactive Antibodies

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Abstract

Background and objectives In December of 2014, the Organ Procurement and Transplant Network implemented a new Kidney Allocation System (KAS) for deceased donor transplant, with increased priority for highly sensitized candidates (calculated panel-reactive antibody [cPRA] >99%). We used a modified version of the new KAS to address issues of access and equity for these candidates.

Design, setting, participants, & measurements In a simulation, 10,988 deceased donor kidneys transplanted into waitlisted recipients in 2010 were instead allocated to candidates with cPRA ≥80% ($n=18,004$). Each candidate's unacceptable donor HLA antigens had been entered into the allocation system by the transplant center. In simulated match runs, kidneys were allocated sequentially to adult ABO identical or permissible candidates with cPRA 100%, 99%, 98%, etc. to 80%. Allocations were restricted to donor/recipient pairs with negative virtual crossmatches.

Results The simulation indicated that 2111 of 10,988 kidneys (19.2%) would have been allocated to patients with cPRA 100% versus 74 of 10,988 (0.7%) that were actually transplanted. Of cPRA 100% candidates, 74% were predicted to be compatible with an average of six deceased donors; the remaining 26% seemed to be incompatible with every deceased donor organ that entered the system. Of kidneys actually allocated to cPRA 100% candidates in 2010, 66% (49 of 74) were six-antigen HLA matched/zero-antigen mismatched (HLA-A, -B, and -DR) with their recipients versus only 11% (237 of 2111) in the simulation. The simulation predicted that 10,356 of 14,433 (72%) candidates with cPRA 90%–100% could be allocated an organ compared with 7.3% who actually underwent transplant.

Conclusions Data in this simulation are consistent with early results of the new KAS; specifically, nearly 20% of deceased donor kidneys were (virtually) compatible with cPRA 100% candidates. Although most of these candidates were predicted to be compatible with multiple donors, approximately one-quarter are unlikely to receive a single offer.

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Introduction

Historically, the degree of sensitization to HLA antigens among candidates waiting for a kidney transplant was referred to as panel-reactive antibody (PRA) activity and ranged from 0% to 100%. However, patients never have 100% PRA (because they do not have antibodies against self-HLA antigens) but could appear to on the basis of composition of the HLA-typed panel cells used to assign the PRA value. Typically, PRA activity was assessed using a panel of lymphocyte targets from 30 to 60 HLA-typed individuals (1). On the basis of their increased mortality and difficulty finding compatible donors, the US National Kidney Allocation System (KAS) mandated that sensitized candidates be given priority for allocation of HLA-A, -B, and -DR matched/zero antigen-mismatched deceased donor (DD) kidneys (2,3). Additionally, candidates with PRA >80% were awarded four extra priority points toward organ allocation (4). Transplant

centers were allowed to assign PRA values for their patients and select which HLA antigens would be unacceptable. Recognition that PRA values varied with the composition of the HLA-typed panel cells (1) led to calculating PRA values (calculated panel-reactive antibody [cPRA]) on the basis of candidates' unacceptable antigens (5). Briefly, the unacceptable HLA antigens are entered into a software program (the cPRA calculator), a database of >12,000 HLA-A, -B, -C, -DRB1, and -DQB1 typed DDs maintained by the United Network for Organ Sharing (5). The cPRA calculator determines the percentage of donors expressing one or more unacceptable antigens. The resulting value is the candidate's cPRA. The cPRA calculator is used to assign a cPRA for every sensitized candidate awaiting a DD kidney in the United States. In 2009, the Organ Procurement and Transplantation Network (OPTN) modified the KAS policy, such that four additional allocation points were awarded only when

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the candidate's unacceptable antigens corresponded to a cPRA value $>80\%$ (6,7). Coupled with implementation of newly developed solid-phase antibody detection technology (8) and improved ability to predict negative physical crossmatches between donors and recipients, the amended KAS policy served two purposes: (1) uniformity in reporting candidate sensitization and (2) improved efficiency and logistics of kidney allocation (9,10).

Nonetheless, the gap widened between supply of and demand for DD kidneys. Candidates with the highest cPRAs (98%–100%) were shown to be the most disadvantaged of an already disadvantaged group (11,12).

A new KAS, implemented on December 4, 2014 (13), prioritized local, regional, and national allocation of DD kidneys to compatible candidates with cPRA 98%, 99%, and 100%, respectively. Early data showed that the new policy was beneficial to those highly sensitized candidates. Specifically, from January to November of 2014 (preimplementation), 2.4% of DD kidneys were transplanted into cPRA 99%–100% candidates. Remarkably, between December of 2014 and May of 2015 (postimplementation), 15.5% of DD kidneys were allocated to and transplanted into such candidates, some of whom had been waiting for >15 years (14). These data led to numerous questions regarding allocation to cPRA 100% candidates. Were all such candidates equally likely to be offered a compatible kidney? Might these candidates be compatible with more than one donor? If so, how many?

In the United States, the mandatory allocation of HLA-matched/zero antigen-mismatched kidneys to highly sensitized candidates (2,3) in the previous KAS fueled a long-held perception that well matched organs were the best opportunity for these candidates to undergo transplant. It was logical to anticipate that most kidneys allocated to cPRA 100% candidates in the new KAS would come from six HLA antigen-matched/zero antigen-mismatched donors. However, an informal survey revealed that this was untrue. Almost all cPRA 100% candidates were allocated DD kidneys with which they were compatible but not perfectly matched (W. Bry, personal communication; O. Moussa, personal communication; and C. Murphey, personal communication).

In this study, we explored whether waiting time for highly sensitized candidates (cPRA $\geq 80\%$ in the previous KAS) was prolonged because of an extensive HLA antibody repertoire or the United States allocation process.

Materials and Methods

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States submitted by the members of the OPTN and has been described elsewhere (15). The Health Resources and Services Administration, US Department of Health and Human Services provides oversight of the activities of the OPTN and SRTR contractors.

Modeling Approach

We conducted simulations using a modified version of the kidney-pancreas simulated allocation model (KPSAM) software used to evaluate new policy proposals for the

OPTN committees (16). The original and modified versions both used 2010 data, but the modified version did not include all donor organs ($n=13,621$), only those that were transplanted ($n=10,988$). By eliminating allocation of historically discarded organs, we consider our approach to be a more realistic estimate of organ acceptability. The modified KPSAM simulated the arrival of donated organs and new candidates on the waiting list over a 1-year period, checked compatibility of organs with candidates on the waiting list at the time that an organ became available, and created ordered lists of compatible candidates. Candidates had to have a negative virtual crossmatch with their donors to receive organ offers. Every candidate remained alive and active on the waiting list until a successful kidney allocation occurred. All organ offers were accepted. After allocated, an organ was not offered to any other candidate.

Patients

Only adult candidates (age ≥ 18 years old at the time of listing) on the kidney-alone waiting list for at least 1 day between January 1 and December 31, 2010, with cPRA $\geq 80\%$ were included and listed as active ($n=18,004$). The last cPRA value entered between the listing date and December 31, 2010, was selected. Candidates with cPRA $\geq 80\%$ but no recorded unacceptable antigens ($n=54$) were excluded.

Unacceptable Antigens

The unacceptable HLA-A, -B, -C, -DRB1, and -DQB1 antigens submitted by the transplant centers were used.

Organs

All kidneys recovered from 6141 DDs and transplanted in 2010 ($n=10,988$) were included in the simulation.

Allocation Scheme

To focus on highly sensitized candidates, the modified KPSAM allocated DD kidneys exclusively to cPRA $\geq 80\%$ candidates. Recipients were ABO identical or compatible with the kidney, and their virtual crossmatches (HLA-A, -B, -C, -DRB1, and -DQB1 only) were negative. Kidneys were offered sequentially to candidates with cPRA 100%, 99%, 98%, *etc.* to 80%. An organ was offered to a lower cPRA tier only if no candidate in the higher tier was compatible with it. Within each cPRA level, candidates were sorted by kidney points. Blood type compatibility was assessed per current OPTN policy, which allows the transplant of ABO:A2 and ABO:A2B organs into authorized ABO:B candidates. Because the necessary data were not collected in 2010, a random subset (20%) of blood type A or AB white, black, or Hispanic donors was assigned a blood type of A2 or A2B, respectively, and a random subset (70%) of candidates with blood type B was assigned low anti-A antibody titers and could accept kidneys from donors with an A2 or A2B blood type. In data not shown, we found that the prevalence of B candidates with acceptable anti-A antibody titers did not vary with cPRA.

Results

Waitlist Demographics

Figure 1 shows the racial distribution of candidates on the 2010 OPTN kidney waiting list stratified by cPRA. Of

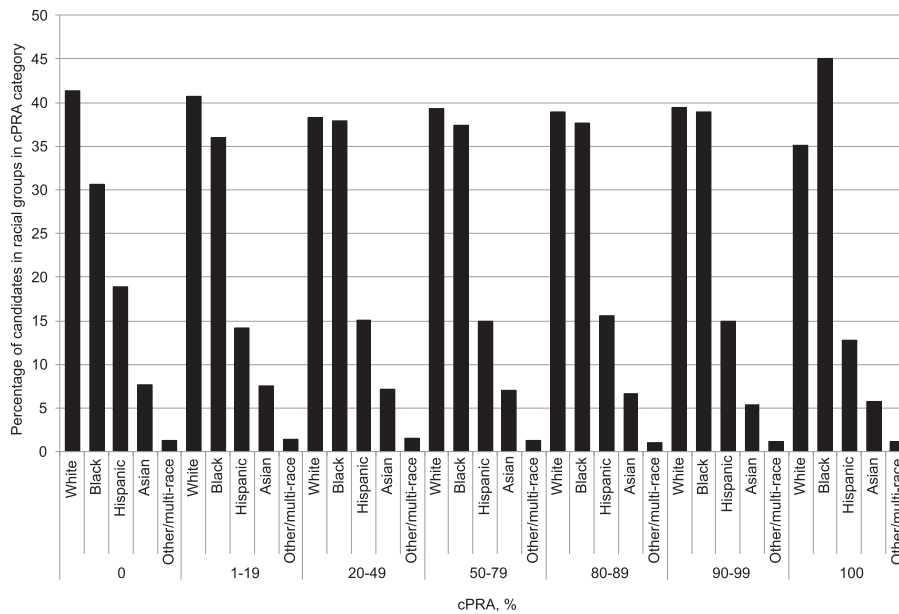


Figure 1. | Graphic representation of 2010 adult kidney-alone waitlisted candidates according to race and calculated panel-reactive antibody (cPRA) percentages. The distribution of candidate race within cPRA category is shown on the x axis, and the percentage of candidates by race within cPRA group is shown on the y axis; the total in each cPRA group equals 100%.

117,278 adult kidney-alone candidates, 40.5% were white, 33.5% were black, 17.4% were Hispanic, 7.3% were Asian, and 1.3% were of other or unknown race. Racial distribution and primary or regrant status differed by PRA level. Of patients with cPRA 0% ($n=75,391$), 94% were awaiting a first transplant, 41.4% were white, and 30.7% were black. By comparison, of candidates with cPRA 100% ($n=5381$), 35.1% were white, 45.1% were black, and only 34% were awaiting a first transplant. Black women made up the largest group of cPRA 100% candidates (27%), more than one half (54%) of whom were awaiting a first transplant.

Allocation Reconfiguration

In 2010, 10,988 DD kidneys were allocated to and transplanted into candidates according to the OPTN kidney allocation policy then in effect. Blood group-matched donor kidneys were offered first to HLA-compatible $cPRA \geq 20\%$ candidates only if they were six-antigen HLA matches/zero-antigen HLA mismatches (HLA-A, -B, and -DR), and then, they were offered according to ranking on local, regional, and national OPTN waiting lists, respectively. In our simulation, kidney allocation was restricted to cPRA 80%–100% candidates. Kidneys were allocated to candidates who were both ABO and HLA compatible (*i.e.*, with no HLA-A, -B, -C, -DRB1, or -DQB1 antibodies to unacceptable antigens listed by the transplant center). These allocation processes are compared in Table 1. In 2010, 74 of 10,988 kidneys (0.7%) were transplanted into cPRA 100% candidates, and only 1.4% of cPRA 100% candidates (74 of 5381) underwent transplant. In the simulation, 39.2% of cPRA 100% candidates (2111 of 5381) were allocated kidneys, corresponding to 19.2% of kidneys (2111 of 10,988). Strikingly, 91.1% of cPRA 90%–99% candidates were allocated kidneys in the simulation compared with only 8.1% of recipients in 2010 who actually underwent transplant (8245 of 9052 versus 730 of 9052).

Additional analysis revealed that 57% of highly sensitized black candidates and 63% of highly sensitized white candidates were allocated kidneys in the simulation compared with 7% and 10%, respectively, who actually underwent transplant. Highly sensitized black and white candidates benefitted similarly in the simulation. For example, 34.5% of waitlisted black and 43.1% of waitlisted white candidates with cPRA 100% were offered kidneys in the simulation compared with <1% of each who actually underwent transplant.

Highly Sensitized Recipients Are Compatible with Multiple Donors

To evaluate the number of cPRA 80%–100% candidates who were HLA incompatible with all 6141 donors, we

Table 1. Transplants performed in high calculated panel-reactive antibody candidates in reality in 2010 and in simulation

cPRA, %	Waiting List, <i>n</i>	Transplants, <i>n</i> (%)	
		2010	Simulation
80–84	1677	369 (22.0)	88 (5.2)
85–89	1894	310 (16.4)	401 (21.2)
90–94	2525	318 (12.6)	2183 (86.5)
95	655	69 (10.5)	638 (97.4)
96	848	83 (9.8)	818 (96.5)
97	989	79 (8.0)	968 (97.9)
98	1443	88 (6.1)	1378 (95.5)
99	2592	93 (3.6)	2260 (87.2)
100	5381	74 (1.4)	2111 (39.2)

cPRA, calculated panel-reactive antibody.

calculated the exchange between every donor and every candidate (Figure 2). Of 18,004 waitlisted cPRA 80%–100% candidates, 16,603 (92%) were ABO and HLA compatible with at least one donor. The median number of compatible donors for 74% of cPRA 100% candidates ($n=3983$ of 5381) compatible with at least one donor was six. Remarkably, the average number of compatible donors for each of these candidates was 17. Not surprisingly, of 1401 candidates in the simulation without a single compatible donor in 2010, nearly all ($n=1398$) had cPRA 100%, and the remaining three had cPRA 99%. Higher percentages of black, Hispanic, Asian, and Native American candidates were incompatible with all donors who entered the system compared with white candidates (Figure 3).

Compatibility Versus Perfect HLA Matching for Highly Sensitized Candidates

Of 1483 transplants in 2010 in patients with cPRA 80%–100%, 269 (18.1%) were HLA-A, -B, or -DR six-antigen matched or zero-antigen mismatched (Figure 4). In contrast, only 308 of 10,845 kidneys (2.8%) allocated to these highly sensitized recipients in our simulation were six-antigen matched or zero-antigen mismatched.

Discussion

In 2010, 10,988 kidneys from 6141 DDs were transplanted into renal allograft candidates (4). For most transplants, kidneys were allocated according to a point-based ranking system. Under the previous KAS, points were awarded for waiting time (one point per year), HLA-DR donor/recipient matching (one point for a single HLA-DR match and two points for a two HLA-DR match), and cPRA \geq 80% (four points) (17). Typically, the highest ranked ABO and HLA compatible candidates were selected for transplant. Waiting time was the most significant factor in rising to the top of the list. The exceptions

were cPRA \geq 20% candidates who were six-antigen matched/zero-antigen mismatched (HLA-A, -B, and -DR) with a DD. Such candidates were given higher priority for those donor kidneys than candidates with more points.

Of 1483 kidneys transplanted into cPRA \geq 80% candidates in 2010, 269 (18.1%) were from six antigen HLA-matched/zero antigen HLA-mismatched donors. Notably, 66% (49 of 74) of recipients with cPRA 100% received kidneys from six antigen-matched/zero antigen-mismatched donors (Figure 4). These demographics help explain the perception during the previous KAS that transplants among highly sensitized candidates (cPRA \geq 80%) in the United States were highly dependent on allocation of perfectly matched HLA donor kidneys. It was logical to conclude that most compatible donors for cPRA 100% candidates would be perfect matches in the new KAS. However, our simulation data and early data after implementation of the new KAS (14) indicate that the need for perfect matching of donors with highly sensitized candidates is more perceived than real. The collective data in Figure 4 and Table 1 show that six antigen-matched/zero antigen-mismatched kidneys were not the only compatible kidneys for cPRA 100% candidates. These data illustrate that cPRA 100% is a misnomer and should not be interpreted to mean that these candidates are incompatible with every potential donor. Rather, a cPRA of 100% is assigned when candidates react with \geq 99.5% of donors. A candidate with cPRA 99.5% is predicted to be compatible with 50 of 10,000 donors; a candidate with an actual cPRA of 99.99% is predicted to be compatible with 1 of 10,000 donors. The simulation data show that an astonishing 99% of DD kidneys could have been allocated to cPRA \geq 80% candidates, with the preponderance to cPRA \geq 90% candidates. Candidates with cPRA 80%–84% were allocated only 5.2% of the organs in the simulation and 22% in 2010, because organs compatible with these candidates

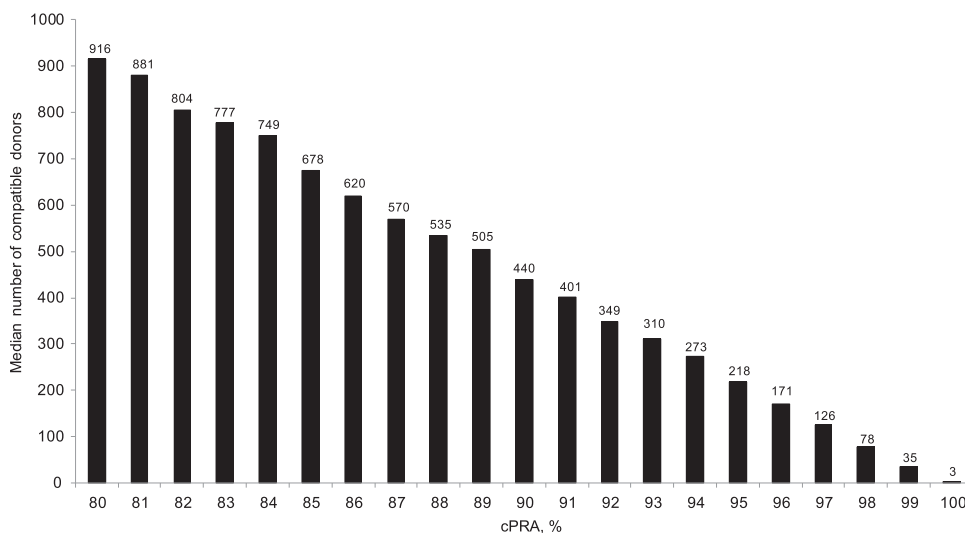


Figure 2. | Median compatible donors by broad calculated panel-reactive antibody (cPRA) category among adult kidney-alone waitlisted candidates in 2010. Each donor ($n=6141$) was assessed for compatibility with each candidate ($n=18,004$) with cPRA \geq 80%. The median number of donors compatible with candidates at specific cPRA levels is displayed at the top of each bar.

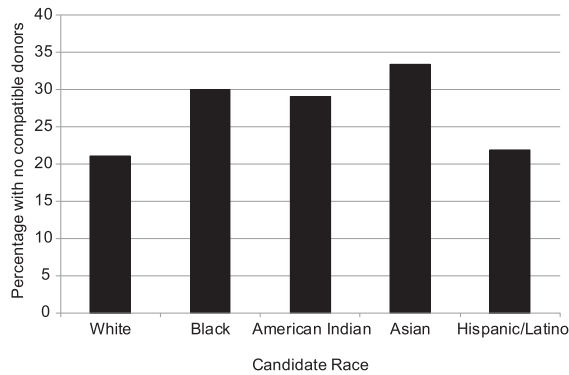


Figure 3. | Racial distribution of candidates with calculated panel-reactive antibody 100% (n=1398) who were incompatible with every deceased donor kidney transplanted in 2010. Higher percentages of black, Hispanic, Asian, and Native American candidates than of white candidates were incompatible with all donors.

had already been allocated to candidates with higher cPRA levels in the simulation. Our data reveal that, although most cPRA 100% candidates underwent transplant with perfectly matched kidneys in 2010, this was not because those kidneys represented their only possibility for transplant. Rather, it is likely that these were the organs to which these candidates had priority access. Our simulation data support the studies by Duquesnoy (18), Duquesnoy *et al.* (19), and Claas *et al.* (20) that reported that compatible donors for highly sensitized recipients in Europe need not be HLA identical if appropriate strategies were applied to identify those donors.

Despite 99% (10,845 of 10,988) of kidneys being successfully allocated to cPRA ≥80% candidates in our simulation, not all candidates would have proceeded to transplant. This is a limitation of this study. Models assess policy

implications but cannot accurately predict clinical practice. Thus, despite all of the kidneys included in this simulation being actually transplanted in 2010, it may not have transpired in this simulation. Depending on transplant center philosophy, transplant surgeons and/or clinicians may be reluctant to accept organs for highly sensitized candidates (*i.e.*, cPRA >98%) that, although acceptable on the basis of a negative virtual crossmatch, do not account for organ quality, size, anatomy, ischemia time, or the candidate’s health at the time of the offer. These factors would reduce the number of transplants that our simulation predicted. Another consideration is that, in 2010 (and currently), HLA-A, -B, -C, -DRB1, and -DQB1 were the only antigens that could be entered as unacceptable, even if antibodies to HLA-DQA and -DP were identified. Despite kidneys in the simulation being allocated only to candidates with negative virtual crossmatches, those virtual crossmatches did not account for donor-specific HLA-DQA or -DP antibodies. Presence of such antibodies could reduce the number of predicted transplants. Recent studies show that >60% of cPRA 99%–100% candidates have antibodies to HLA-DQA or -DP (21,22). Because these candidates now receive regional and national priority for DD kidneys (13), more than one-half of the kidneys allocated to highly sensitized candidates are to candidates with HLA class 2 antibodies not accounted for in the OPTN’s current data system. A recent study by Tambur *et al.* (23) revealed that 320 of 2948 (11%) flow cytometric B cell crossmatches among waitlisted candidates and their prospective donors were positive solely because of HLA-DP donor specific antibodies. A positive crossmatch may halt the anticipated transplant and require a local backup substitute or returning the organ for reallocation. Consequently, organs allocated to cPRA 99%–100% candidates may incur prolonged ischemia time and additional costs (*e.g.*, shipping and crossmatching). Recognizing these issues, the OPTN Board of Directors mandated that DD kidneys be prospectively

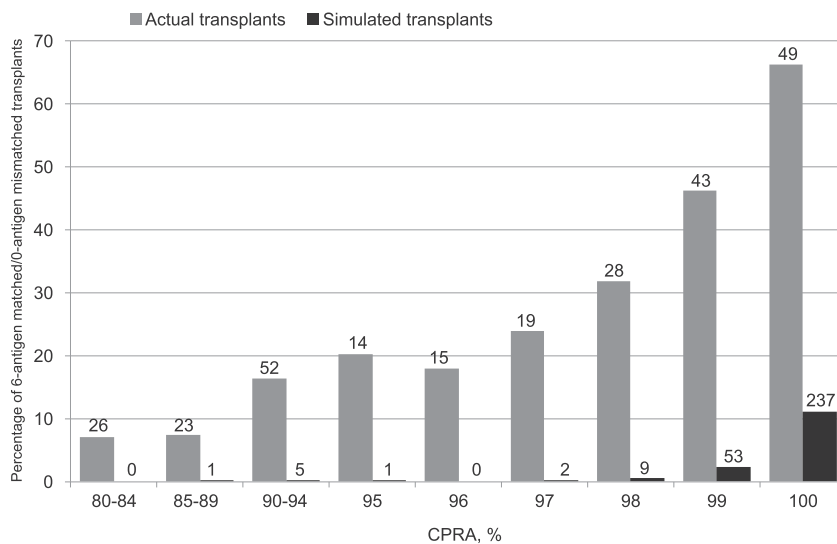


Figure 4. | Percentage of six antigen-matched/zero antigen-mismatched kidneys allocated to patients by incremental calculated panel-reactive antibody (cPRA) levels that were actually transplanted in 2010 and as simulated, respectively. Total six antigen HLA-matched/zero antigen-mismatched transplants: actual, 269; simulated, 308.

HLA-DQA and -DP typed and that the OPTN develop the capability to list those antigens as unacceptable (24). These changes have not yet been implemented.

With implementation of the new KAS, the United States has begun to adopt the European concept of acceptable mismatching that has been in place since 1988 (25,26). Most simply, acceptable mismatches are HLA antigens to which the recipient has no corresponding HLA antibodies. In Eurotransplant, DD kidneys are mandatorily directed to PRA>85% candidates with no donor-directed antibodies. Until now, the United States allocation policy took the opposite approach; the policy prevented allocation of kidneys to highly sensitized candidates with antibodies to donor HLA antigens. Conceptually, Eurotransplant pulled compatible kidneys in, whereas the United States pushed incompatible kidneys away (27). Before implementation of acceptable mismatching, most Eurotransplant renal candidates with PRA>85% waited 10–15 years for a transplant. Currently, approximately 60% of these highly sensitized candidates undergo transplant within 2 years (28) and represent only about 2% of the waiting list. The data in Table 1 show that almost all cPRA>90% candidates have compatible donors (at least with regard to HLA-A, -B, -C, -DRB1, and -DQB1). Although our simulation indicated that only 5.2% of cPRA 80%–84% candidates were allocated kidneys, this was because of limited donor supply and not incompatibility (*i.e.*, most organs were successfully allocated to candidates with higher cPRA).

Collectively, the data suggest that reconfiguration of the allocation system could allow almost all highly sensitized candidates to undergo transplant within a relatively short time. However, approximately 25% of candidates with cPRA 100% (about 1400 candidates) were not compatible with even one donor in our simulation. These candidates will likely require additional attention, such as increasing the threshold (mean fluorescence intensity level) of HLA antibodies before considering the corresponding antigens unacceptable or desensitization therapy (29–32) coupled with paired donor exchange (33,34). Some may not be candidates for transplant. Identifying who these candidates are will be an important facet of organ allocation, even with the new KAS. Knowing that a candidate has access to one or multiple donors can influence whether the transplant center accepts an offer for candidates who have waited without receiving even one offer.

In conclusion, our data reveal that compatible donors are available for almost all highly sensitized candidates. Our simulation predicts that, in a single year, >75% of candidates with cPRA 100% will be compatible with multiple donors. This is important new information that can provide insight into the decision regarding whether to accept offers for these highly sensitized candidates. Additionally, our study reveals that prioritization and not an extensive repertoire of HLA antibodies is the primary barrier to transplant for highly sensitized candidates.

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Disclosures

None.

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