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Center-Defined Unacceptable HLA Antigens Facilitate Transplants for Sensitized Patients in a Multi-Center Kidney Exchange Program

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Multi-center kidney paired donation (KPD) is an exciting new transplant option that has not yet approached its full potential. One barrier to progress is accurate virtual crossmatching for KPD waitlists with many highly sensitized patients. Virtual crossmatch results from a large multi-center consortium, the National Kidney Registry (NKR), were analyzed to determine the effectiveness of flexible center-specific criteria for virtual crossmatching. Approximately two-thirds of the patients on the NKR waitlist are highly sensitized (>80% CPRA). These patients have antibodies against HLA-A (63%), HLA-B (66%), HLA-C (41%), HLA-DRB1 (60%), HLA-DRB3/4/5 (18–22%), HLA-DQB1 (54%) and HLA-DPB1 (26%). With donors typed for these loci before activation, 91% of virtual crossmatches accurately predicted an acceptable cell-based donor crossmatch. Failed virtual crossmatches were attributed to equivocal virtual crossmatches (46%), changes in HLA antibodies (21%), antibodies against HLA-DQA (6%), transcription errors (6%), suspected non-HLA antibodies (5%), allele-specific antibodies (1%) and unknown causes (15%). Some failed crossmatches could be prevented by modifiable factors such as more frequent assessment of HLA antibodies, DQA1 typing of donors and auditing data entry. Importantly, when transplant centers have flexibility to define crossmatch criteria, it is currently feasible to use virtual crossmatching for highly sensitized patients to reliably predict acceptable cell-based crossmatches.

Keywords: HLA antibodies, kidney paired donation (KPD), virtual crossmatch

Abbreviations: CPRA, calculated panel reactive antibody; DSA, donor-specific antibody; KPD, kidney paired donation; MFI, mean fluorescence intensity; NKR, National Kidney Registry; OPTN, Organ Procurement and Transplantation Network

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Introduction

Kidney paired donation (KPD) offers new transplant opportunities for patients with a living donor who is willing and medically suitable but HLA or ABO incompatible (1). The usefulness of KPD has been demonstrated by large single-center KPD programs that have used this approach for up to 35% of their living donor transplants (2–4). Theoretically, multi-center KPD programs with larger pools of donors and recipients should result in more transplants than single-center programs (5–7). Several multi-center consortia (including an Organ Procurement and Transplantation Network [OPTN] program) have been created to facilitate multi-center KPD transplants, but the number of transplants has fallen far short of the predicted potential (5,8,9). In 2012, a multidisciplinary consensus conference on KPD identified several factors that hinder multi-center KPD (5). One of the major factors is virtual crossmatches that fail to predict an acceptable cell-based crossmatch.

Virtual crossmatching is particularly challenging in the KPD setting because the majority of waitlisted patients are highly sensitized to HLA (10,11) and the results for cell-based crossmatches are often difficult to predict (12–14). Strategies that have been developed to improve virtual crossmatch accuracy for this population include utilizing a core laboratory (15), specifying thresholds for assigning unacceptable HLA types (13,16) and allowing centers to enter two sets of antigens, one representing the center's criteria for automatic refusal and another that includes antibodies that are not an automatic contraindication but could be a problem, particularly when there are several weak donor-specific antibodies (DSAs) (17). However, these strategies have not resulted in transplantation of large numbers of highly sensitized patients, in part because use of conservative approaches to prevent unexpected

positive crossmatches can exclude donors that would have cell-based crossmatches that some transplant centers would consider acceptable for proceeding to transplant (16). Although accurate virtual crossmatches are critical for efficient KPD, the optimal approach for virtual crossmatching remains controversial.

The National Kidney Registry (NKR) has allowed centers to develop center-specific criteria for virtual crossmatches; conservative centers can avoid all higher-risk transplants while other centers can take advantage of innovative approaches for patients who are unlikely to be transplanted using traditional criteria (18,19). In this report, we characterize the results of virtual crossmatching in this large KPD registry where HLA compatibility criteria are at the discretion of each center and are sometimes tailored for individual patients.

Methods

Study population

Virtual crossmatches were studied for patients who were registered in the NKR and received a match offer between March 1, 2011 and December 20, 2012. Transplant centers (n = 64 on December 20, 2012) listed unacceptable donor HLA types based on their assessment of the recipient's antibody profile and history. The registry listed age, gender, ABO blood type and HLA type of each donor and recipient along with other factors that could influence a transplant center's acceptance of a donor kidney including vascular anatomy, relevant medical history and willingness of the donor to travel. Patients who were listed in the NKR on December 20, 2012 were studied to determine HLA sensitization and HLA antibody specificities. Study of data from the NKR registry is approved by the Institutional Review Board at Stanford University.

HLA typing

For donors, HLA-A, -B, -Bw4/6, -C, -DRB1, -DRB3/4/5, -DQB1 and -DPB1 types were required before the donor-recipient pair could be activated. Certain HLA types that are associated with a high frequency of allele-specific antibodies were resolved to higher resolution types corresponding to HLA molecules represented in commercial reagents for determining antibody specificity (e.g. HLA-DPB1*04 resolved to HLA-DPB1*04:01 and HLA-DPB1*04:02). For recipients, HLA-A, -B and -DRB1 typing were required.

Unacceptable antigens

Transplant centers in consultation with their HLA laboratories determined criteria for unacceptable donor antigens for each patient. For this study, all centers used at least one solid-phase assay to identify anti-HLA antibodies (predominantly single antigen reagents). Centers could list unacceptable antigens for HLA-A, -B, -C, -DRB1, -DR51, -DR52, -DR53, -DQB1 and -DPB1. Each transplant center set its own threshold for unacceptable antigens; criteria for listing unacceptable antigens varied considerably among transplant centers. For example, some centers routinely used a threshold of 1000 mean fluorescence intensity (MFI) for DSAs to exclude donors while others accepted DSAs >10 000 MFI but employed desensitization protocols (18,19). Additionally, centers were allowed to use patient-specific factors to determine unacceptable antigens, including relaxed criteria for very highly sensitized patients or more stringent criteria for patients who were likely to have several compatible donors.

Panel reactive antibodies

For the NKR, calculated panel reactive antibody ($CPRA^{NKR}$) was dynamically determined for each patient at the time of match offers using the unacceptable antigens listed for each candidate and the HLA types of the current NKR donor pool. The $CPRA^{NKR}$ was the percentage of donors that are excluded by virtual crossmatches that are automatically performed as part of the match run. For this study, $CPRA^{NKR}$ was determined for waitlisted patients using donor HLA types and unacceptable antigens that were listed in the registry on December 20, 2012. Patients with $CPRA^{NKR} \geq 80\%$ were considered to be highly sensitized. To compare the $CPRA^{NKR}$ with a national metric, an online calculator (http://optn.transplant.hrsa.gov/resources/professionalResources.asp?index=78) was used to determine CPRA using an algorithm developed by the OPTN ($CPRA^{OPTN}$). The $CPRA^{OPTN}$ calculation predicts the percentage of incompatible donors using haplotype frequencies (HLA-A, -B, DR and -DQ) determined from HLA types of OPTN donors (20).

Crossmatching

Computer-generated match offers were based on virtual crossmatches as described elsewhere (21). The virtual crossmatch was considered negative if a potential donor had none of the HLA types that were listed as an unacceptable antigen for the patient. The program used this information to identify potential chains of KPD transplants with negative virtual crossmatches. Transplant centers with patients in the selected chain had an opportunity to review the potential donor's medical record and HLA typing to consider factors which might preclude transplant including multiple weak HLA antibodies against the donor, allele-specific antibodies and recent changes in HLA antibodies. If the donor offer was accepted by the transplant center, cell-based crossmatches were planned and samples were sent to each center's HLA laboratory. The acceptance criteria for cell-based crossmatches were at the discretion of each transplant center. A virtual crossmatch was considered to be a failure if the reason for refusing the donor at this stage was the result of the cell-based crossmatch. Transplant centers self-reported the causes for failed virtual crossmatches. To identify approaches to prevent recurrent failures, unsuccessful virtual crossmatches were also periodically reviewed by a panel of experts from participating centers and laboratories. For example, HLA-DPB typing of donors became mandatory after several virtual crossmatch failures were attributed to antibodies against HLA-DPB.

Results

CPRA

Since the number and source of donor HLA types used for determining CPRA could influence the result, $CPRA^{NKR}$ that is based upon HLA types of a relatively small donor pool was compared with $CPRA^{OPTN}$ that is calculated using a large population of deceased donors in the United States (Figure 1). For most patients, the CPRAs determined by each method were similar. The exceptions were patients with antibodies against HLA-C and -DP. For these patients, if few donors are excluded by antibodies against HLA-A, -HLA-B, HLA-DR and HLA-DQ, the CPRA divergence can be large because the UNOS CPRA calculation did not yet consider HLA-C and -DP antibodies during the time interval for this study. When most donors are already excluded by antibodies that are not against HLA-C and/or -HLA-DP, the CPRAs are similarly high for patients with or without HLA-C and HLA-DP antibodies.

HLA antibodies

NKR candidates have antibodies against HLA-A (63%), HLA-B (66%), HLA-C (41%), HLA-DRB1 (60%), HLA-DRB3/

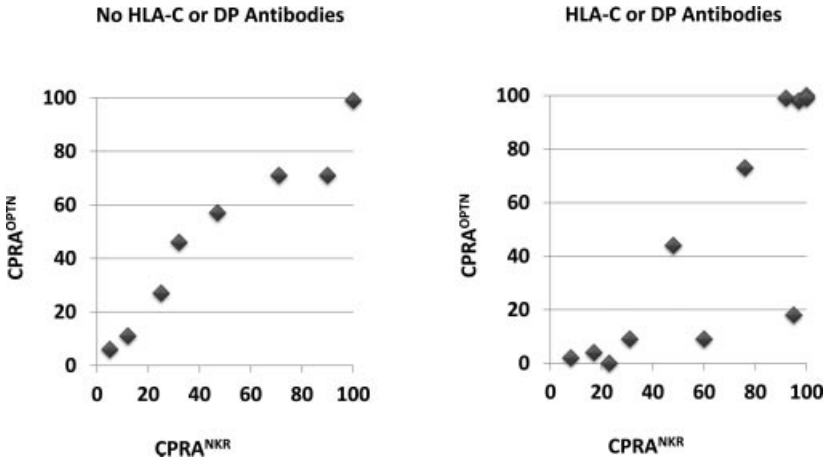

Figure 1: Comparison of $CPRA^{NKR}$ and $CPRA^{OPTN}$. CPRA values for patients without HLA-C and/or HLA-DP antibodies are shown in the left panel and those with HLA-C and/or HLA-DP antibodies are shown in the right panel. CPRA, calculated panel reactive antibody; NKR, National Kidney Registry; OPTN, Organ Procurement and Transplantation Network.

4/5 (18–22%), HLA-DQB1 (54%) and HLA-DPB1 (26%) (Figure 2). For the patients that were 100% $CPRA^{NKR}$ antibodies were almost always detected against HLA-A (97%) and -B (99%) and a high proportion of the patients also had antibodies against molecules encoded by all other HLA loci. Of note, many of these patients had HLA-C (70%) and HLA-DP (42%) antibodies. The majority of patients with $CPRA^{NKR}$ 80–99% had antibodies against HLA-A, -B, -DR and -DQ and for those with >95% $CPRA^{NKR}$ antibodies against HLA-C and -DP were also prevalent. For the small number of patients with <79% $CPRA^{NKR}$ antibodies were detected against HLA-A, -B, -C, -DR, -DQ and -DP.

Virtual crossmatches

Between March 1, 2011 and December 20, 2012, the NKR made 2450 match offers and 1682 of these were accepted based upon a virtual crossmatch. However, many acceptances did not proceed to cell-based crossmatches because chains were disrupted by donor refusals before the crossmatch could be performed. For the 709 crossmatch results that were reported, 67 (9%) involved an unacceptable cell-based crossmatch that was attributable to a failed virtual crossmatch. Refusals that were not attributed to an unacceptable cell-based crossmatch were caused by a variety of reasons including other unacceptable donor factors, recipient not ready, donor not available and data entry errors that did not involve HLA.

Unacceptable positive crossmatches were more likely to be observed for highly sensitized patients (Figure 3). Nearly half of the unacceptable crossmatches were attributed to equivocal virtual crossmatches caused by the cumulative effects of multiple weak DSAs or DSAs that were near the

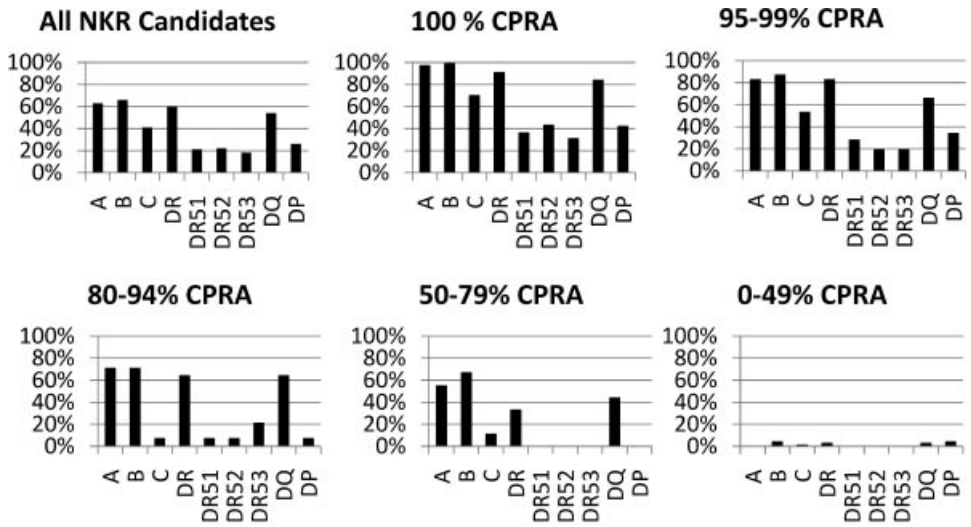

Figure 2: HLA antibody specificities. The percentage of candidates with antibodies against the products of each HLA locus are shown for the entire NKR waitlist and five CPRA ranges (100, 95–99, 80–94, 50–79 and <50%). Patients with 0% CPRA had no HLA antibodies and were included in the calculations for the entire waitlist. CPRA, calculated panel reactive antibody; NKR, National Kidney Registry.

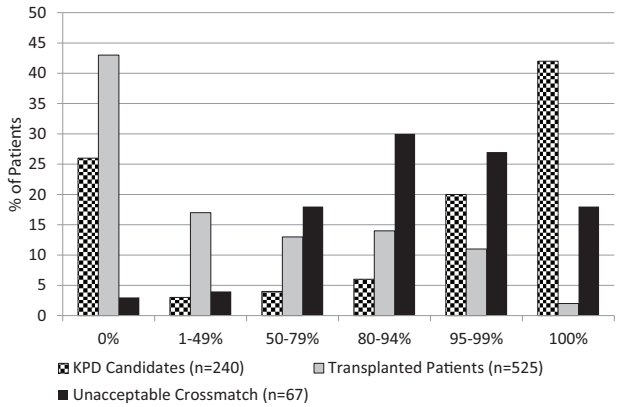

Figure 3: CPRA distribution for KPD candidates, transplanted patients and unacceptable crossmatches. The percentage of patients for each population is shown for six CPRA ranges (0, 1–49, 50–79, 80–94, 95–99 and 100%). CPRA, calculated panel reactive antibody; KPD, kidney paired donation.

threshold for an unacceptable crossmatch (Table 1). The second leading cause of failed virtual crossmatches (21%) was changes in the recipient's HLA antibodies. Limitations in donor typing caused five virtual crossmatch failures; four (6%) were attributed to antibodies against HLA-DQA and one (1%) was attributed to allele-specific antibodies. As a result of these virtual crossmatch failures, HLA-DQA typing of donors subsequently became a requirement for all NKR donors. Other factors were transcription errors (6%) and suspected non-HLA antibodies (5%). A cause was not reported for 15% of failed virtual crossmatches.

Transplants and waiting list

As of December 2012, the NKR had facilitated 525 transplants and 142 (27%) of the transplanted patients had ≥80% $CPRA^{NKR}$ including 10 patients with 100% CPRA. During the interval of this study, 307 transplants were performed and 96 (31%) of these had ≥80% $CPRA^{NKR}$ including 8 patients with 100% CPRA. Figure 3 shows that on December 20, 2012, 42% of the patients remaining on NKR waiting list were 100% CPRA and 68% were highly sensitized (>80% PRA^{NKR}).

Nine transplants performed during the period of this study failed, six were sensitized recipients including two with >80% CPRA. The causes of graft failure are listed in Table 2. For patients with functioning grafts, mean serum creatinine levels were 1.3 mg/dL at 6 months (n = 288; median 1.2; range 0.2–5.0) and 1 year (n = 269; median 1.2; range 0.3–5.1). Among the 96 highly sensitized patients, at 6 months the mean serum creatinine level was 1.3 (n = 92, median 1.2; range 0.6–2.2) and at 1 year again it was 1.3 (n = 83; median 1.2; range 0.5–2.5). Among the 54 patients with ≥95% CPR^{NKR}, at 6 months the mean serum creatinine level was 1.2 (n = 52, median 1.2; range 0.7–2.2) and at 12 months the mean serum creatinine level was 1.3 (n = 47; median 1.2; range 0.7–2.2). Delayed graft function was reported for 23 recipients, 16 of whom were sensitized. No biopsy or antibody-mediated rejection data were available.

Table 1: Causes of unacceptable final crossmatches (n = 67)

Number (%)	Cause
31 (46)	Equivocal virtual crossmatch
14 (21)	Change in antibodies
4 (6)	Antibodies against DQA
4 (6)	Transcription error
3 (4)	Suspected non-HLA antibodies
1 (1)	Allele-specific antibodies
10 (15)	Unexplained/unknown

Table 2: Causes of graft failures for patients transplanted during the study

Patient	CPRA (%)	Survival days	Cause of failure
1	90	353	BK nephropathy
2	75	499	Recurrent disease
3	74	82	Thrombosis
4	71	103	Death
5	65	152	Primary nonfunction
6	0	462	HCV/chronic rejection
7	0	191	Noncompliance
8	0	677	Acute/chronic rejection
9	98	383	Death

CPRA, calculated panel reactive antibody; HCV, hepatitis C virus.

Discussion

There is widespread agreement that accurate virtual crossmatches that do not eliminate acceptable donors are required for KPD to reach its full potential (5). However, considerable controversy remains regarding the best practices for accomplishing this goal (15–17,22,23). This report demonstrates that virtual crossmatches can be used to reliably predict acceptable cell-based crossmatches and a large number of transplants can be achieved by allowing each transplant center to establish criteria for assigning unacceptable antigens and acceptable crossmatches.

The NKR serves an extremely sensitized patient population; as of December 2012, 68% of patients had CPRA ≥80%. During the period of this investigation (between March 1, 2011 and December 20, 2012) the NKR facilitated 307 transplants including 96 (31%) to highly sensitized patients (≥80% $CPRA^{NKR}$). For comparison, the UNOS deceased donor waiting list in 2011 had 17% highly sensitized patients (>80% PRA^{OPTN}) and 5% of new listings in 2011 were highly sensitized (2011 HRSA:SRTR data report; http://srtr.transplant.hrsa.gov/annual_reports/2011/default.aspx). During 2011, 18% deceased donor recipients and 7% living donor recipients had $CPRA^{OPTN}$ >80%.

We believe that one of the factors contributing to the large number of NKR transplants involving highly sensitized patients was a 91% accuracy rate for virtual crossmatches, which was achieved by allowing participating centers to set individual thresholds that were appropriate for their criteria for an acceptable final crossmatch. Importantly, this high rate of accurate virtual crossmatches was achieved without conservative strategies that have been proposed by others, such as establishing common parameters for unacceptable antigens and acceptable crossmatches or employing a central laboratory (15,16).

Other approaches have achieved high success rates for virtual crossmatches for KPD but these conservative approaches can exclude acceptable donors (24). For example, the Australian National Exchange program used 2000 MFI to assign unacceptable antigens, but no compatible donors were identified in four quarterly match runs (16,22,23). The likelihood of a match was improved by increasing the threshold to 8000 MFI, but patients with even higher levels of DSAs can be successfully transplanted (18,19). It is likely that any standardized approach using MFI to define unacceptable antigens will prevent transplants that might be successful because this strategy does not consider differences in HLA antibodies that might affect rejection risk (e.g. different levels of HLA expression) or modified transplant protocols. The study reported here shows that transplant centers in consultation with their histocompatibility laboratories can develop center-specific criteria to achieve virtual crossmatches for reliably selecting donors that meet each center's criteria for transplantation.

Comprehensive HLA typing of donors is important for virtual crossmatching because sensitized patients have antibodies against the products of all HLA loci (Figure 2). During the interval of this study, donors were routinely typed for HLA-A, -B, -Bw4/6, -C, -DRB1, -DRB3/4/5, -DQB1 and -DPB1. In situations where antibodies frequently distinguished the subtypes, there were additional requirements for subtyping (e.g. DPB1 was subtyped into 04:01 and 04:02). Since 26% of NKR patients listed HLA-DP unacceptable antigens, HLA-DP typing of donors likely played an important role in accurate virtual crossmatching for this highly sensitized population. HLA-DQA1 typing and additional allele-level typing could have eliminated five of the unexpected crossmatches observed during this interval.

In June 2013, the NKR made HLA-DQA1 typing donors mandatory and this is expected to further increase virtual crossmatch accuracy. HLA-DQA1 typing offers two advantages: (1) automatic elimination of donors when the patient has antibodies that appear to be specific for HLA-DQA1 and (2) an opportunity to exclude donors based upon antibody epitopes formed by a particular combination of HLA-DQ alpha and beta chains. The ability to consider combinations of DQA and DQB chains is important because a high percentage of HLA-DQ antibodies are against epitopes created by a particular combination of DQA and DQB chains (25–27) and the component HLA-DQA and -DQB types would exclude compatible donors who have the same HLA-DQA and -DQB types but in different combinations that do not contain the relevant antibody epitopes. With HLA-DQA1 typing, specific combinations of DQA1 and DQB1 types can be individually considered before moving forward with cell-based crossmatching. Precise HLA-DQ typing is particularly important because many patients have HLA-DQ antibodies (53% of patients had HLA-DQB unacceptable antigens) and epitopes do not always correspond to the classic serological types.

There are additional modifiable factors that could further improve virtual crossmatch accuracy. Four virtual crossmatch failures (6% of failed virtual crossmatches) were attributed to errors in data entry. To prevent such errors, the NKR has recently implemented a requirement for laboratories to audit histocompatibility data. A major cause of virtual crossmatch failures was changes in HLA antibodies ($n = 14$, 21% of failed virtual crossmatches). At least some of these could be eliminated by more frequent antibody testing. A minimum of quarterly testing was recommended by a consensus conference, but this might be insufficient for highly sensitized patients who might experience changes in antibody levels from any inflammatory event, including infections (28). Another potentially modifiable factor is non-HLA antibodies that cause positive cell-based crossmatches but are not a contraindication to transplant. Autoantibodies are one example of this situation that could be addressed by performing autologous crossmatches, particularly for patients at high risk for autoantibodies such as those with autoimmune disease.

The major cause of unexpected positive cell-based crossmatches is equivocal virtual crossmatches caused by DSA levels that cannot be used to reliably predict the result of a cell-based crossmatch (MFI near the threshold for an unacceptable crossmatch or the cumulative effects of multiple weak DSAs that individually would be acceptable). Improved technology and more experience with virtual crossmatching are likely to diminish these somewhat, but virtual crossmatching is unlikely to reach 100% accuracy for predicting the results of cell-based crossmatching because there is technical variation for solid-phase antibody tests and cell-based crossmatches. Exclusion of donors-based upon equivocal virtual crossmatches is not recommended because this might eliminate the only option for transplant for some patients. KPD programs could take measures to diminish the impact of equivocal virtual crossmatches. For example, preliminary cell-based crossmatches could be performed when virtual crossmatches are equivocal. A progressive option, which was utilized by two of the most active centers in the NKR, is to utilize desensitization protocols designed for patients with positive cell-based crossmatches (18,19). It has been reported that using desensitization protocols for transplantation of highly sensitized patients with positive crossmatches improves

patient survival relative to those who are not transplanted (24). Longer follow-up of a large cohort is needed to determine if this advantage will also be realized by patients currently being transplanted through exchange programs.

To ensure that assessment of sensitization was not substantially influenced by the relatively small donor pool used to calculate $CPRA^{NKR}$, $CPRA^{OPTN}$ was also determined (20). CPRAs were remarkably similar when there were no antibodies against HLA-C and HLA-DP that are not considered in the OPTN calculation. This suggests that the size of the donor pool used for determining PRA is not very important for approximating the percentage of incompatible donors. This comparison also illustrates how the current limitations of the OPTN CPRA calculator can affect CPRA values, which in turn influence organ allocation. When the CPRA is extremely high, there are often many antibodies against HLA-A, -B, -DR and -DQ, which create a high CPRA independent of HLA-C and HLA-DP antibodies. However, when the CPRA is lower, the contributions from HLA-C and -DP antibodies can be substantial. Until this is remedied, these patients will be disadvantaged in the national allocation system.

There are limitations to use of registry data. The NKR database records unacceptable antigens, not DSA levels. Therefore, DSA levels could not be correlated with transplant outcomes. Although only a few grafts have failed (2.9%) and serum creatinine levels at 6 months and 1 year were generally acceptable, follow-up times are still relatively short and we were unable to evaluate rates of antibody-mediated rejection or pathological changes in kidneys transplanted to sensitized and highly sensitized patients. Only three failures were reported to be directly or indirectly due to immunological rejection and all occurred in recipients who were unsensitized at the time of transplant. Another limitation of this study is that it is too early to know if long-term outcomes for NKR patients will be acceptable.

The recommendations for histocompatibility testing for KPD (e.g. more HLA typing requirements, auditing data entry, more frequent testing for HLA antibodies and testing for non-HLA antibodies) can increase costs for managing listed patients. However, the costs of additional testing prevent wasting of other financial and human resources related to unexpected positive crossmatches and disrupted chains. Further, reducing chain failures should diminish frustration of staff, patients and donors that can discourage participation in KPD. In addition, accurate and efficient virtual crossmatching requires close communication between the lab and the transplant center. A dedicated and passionate KPD team is important for managing patients and ensuring close monitoring of HLA antibodies. KDP involves financial and professional investment, but for some patients, KPD is the best or only option for transplant and transplants made possible by KPD can improve their survival.

In summary, the NKR, which serves as a highly sensitized patient population, achieved a 91% accuracy rate for virtual crossmatches. Data presented here show that highly predictive virtual crossmatches, which are extremely important for efficient identification of chains of compatible donor-recipient pairings, can be achieved without using a standardized approach for assigning unacceptable antigens. By allowing centers to set their own thresholds, centers have the opportunity to transplant more sensitized patients based upon their risk tolerance, but long-term follow-up is still needed to establish the efficacy of higher-risk transplants. Analysis of virtual crossmatch failures can guide development of new policies that will further improve accuracy. Based upon the results reported here, the NKR has developed a donor preview function that allows centers to exclude donors if a patient has multiple DSAs that fall below the unacceptable threshold, but in combination, might be unacceptable. Analysis of NKR data also resulted in a new requirement for HLA-DQA1 typing for donors. Options to request additional HLA typing (for alleles) and an exploratory crossmatch prior to accepting a potential donor have been added for evaluating complex virtual crossmatches. These new developments should further improve virtual crossmatch accuracy, ultimately resulting in transplantation of more highly sensitized patients and reduced waiting time.

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Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Joe Sinacore is Director of Research & Education for the National Kidney Registry, which is a nonprofit organization that receives fees to facilitate paired exchange transplants and manage the related logistics process.

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