OPTN

Briefing to the OPTN Board of Directors on

Change Calculated Panel Reactive Antibody (CPRA) Calculation

OPTN Histocompatibility Committee

Prepared by: Courtney Jett
UNOS Policy and Community Relations Department

Contents

Change Calculated Panel Reactive Antibody (CPRA) Calculation

Affected Policies:	*1.2: Definitions* *4.6: Calculated Panel Reactive Antibody (CPRA) Calculation* *4.9: HLA Antigen Values and Split Equivalences* *4.10.B: HLA Unacceptable Antigen Equivalences* *5.3.A: Reporting Unacceptable Antigens for Calculated Panel Reactive Antibody (CPRA)* *8.1: Calculated Panel Reactive Antibody (CPRA)* *11.1: Calculated Panel Reactive Antibody (CPRA)*
Sponsoring Committee:	*Histocompatibility*
Public Comment Period:	*January 27, 2022 – March 23, 2022*
Board of Directors Meeting:	*June 27, 2022*

Executive Summary

Calculated Panel Reactive Antibody (CPRA) is an algorithm used to determine what proportion of deceased donors a potential candidate may be immunologically incompatible with and therefore unable to accept organs from; in other words, how "sensitized" a candidate is. A high level of sensitization means that a candidate has fewer potentially compatible donors. CPRA has a high impact on kidney and pancreas candidate access to transplant because CPRA prioritizes candidates' allocation in proportion to the deceased donor offers a candidate is unable to accept. Our current calculation is not fully reflective of a candidate's sensitization, as it only captures five of the eleven classic human leukocyte antigen (HLA) loci a candidate may be sensitized against, with approximations used for three additional loci. In addition, the current CPRA does not account for allele-level (high resolution) unacceptable antigens. Inclusion of additional HLA loci and allele-level unacceptable antigens would provide a more accurate proportion of deceased donors a candidate may be incompatible with which may affect a highly sensitized patients' access to transplant. In order to properly assess a candidate's sensitization and assign appropriate allocation priority, the OPTN Histocompatibility Committee (the Committee) is proposing a new algorithm, using an HLA frequency data set derived from the National Marrow Donor Program (NMDP) potential hematopoietic stem cell (HSC)[1] donor population.

[1] Hematopoietic stem cell (HSC) transplant is sometimes called "bone marrow transplant". These transplants often occur in cases of blood cancer, such as leukemia, as the HSCs create white and red blood cells. The NMDP holds the HRSA contract to maintain the United States registry of HSC potential donors.

Purpose

The Committee is submitting this proposal to more precisely calculate candidates' sensitization for use in allocation, as well as build a calculation that would be more efficient to update as high-resolution HLA typing and reporting capabilities increase. Updating the CPRA calculation to more accurately reflect sensitization would increase access for highly sensitized candidates who have unacceptable antigens at HLA loci and alleles not factored in CPRA. The Committee identified the following needed areas of change in the current calculation:

1. Use of an alternative data set as a source of HLA typing due to limitations in the number and resolution of HLA typings in the OPTN data set. The Committee selected the National Marrow Donor Program (NMDP) data set, which contains both more data and data at a higher resolution than the OPTN data set.
2. Addition of antibodies in the CPRA algorithm. Addition of HLA-DQA1, DPA1, and DPB1 loci, as well as allele-level antibody values. This allows candidates who are sensitized to these HLA to be appropriately prioritized in allocation.
3. Change in the proportions used to better approximate the HLA frequencies in the deceased donor population. Expansion of the ethnic groups utilized in approximating the deceased donor population, as well as change from a kidney-based deceased donor population to a deceased donor population inclusive of all organs. These changes more accurately and inclusively represent potential deceased donors when determining HLA frequencies.
4. Change from a haplotype[2] to a genotype-based algorithm to more accurately and efficiently calculate candidates' sensitization through direct observation of frequencies of alleles within the population.

Background

CPRA is an allocation calculator used in kidney and pancreas allocation, designed to measure patients' access to deceased donor transplant based on their immunologic sensitization (the likelihood that their immune system will reject a transplanted organ).[3] A higher CPRA indicates a greater sensitization, with a candidate's CPRA value being the expected percent of deceased donors they would be unable to accept.[4] Its purpose is to prioritize candidates for the offers that they are able to receive based on their level of sensitization, as a candidate with a CPRA of 99% would be expected to be compatible with only 1 in 100 deceased donors.[5]

Prior to the development of CPRA, the Panel Reactive Antibody (PRA), a laboratory-based method using a panel of local blood donors to represent the potential HLA composition of the area, was used in the allocation of kidneys and pancreata. The original algorithm used to calculate CPRA was implemented in October 2009 to standardize the way in which sensitization is calculated, as PRA values could vary widely

[2] A haplotype is the combination of multiple genes that are inherited together.

[3] *Proposed Modification to UNOS Policy 3.5.11.3 (Panel Reactive Antibody). Replacement of Panel Reactive Antibody with CPRA, the calculated frequency of incompatible donors having one or more unacceptable antigens.* OPTN Histocompatibility Committee Report to the Board of Directors, 14 December 2006.

[4] Ibid.

[5] Ibid.

by location based on testing methods.[6] CPRA standardizes the calculation by using unacceptable antigens entered for a candidate and HLA frequency data in different ethnic groups and the proportion of their representation in the national deceased donor population in order to determine how likely a candidate is to be unable to accept an organ offer based on their unacceptable antigens.[7] CPRA was originally implemented using serologic antigen-level frequency data from the OPTN deceased donor kidney cohort from January 1, 2003-December 31, 2004 for HLA-A, B, DR, DQB1, and an approximation for DR51/52/53.[8] In 2011, the Committee added HLA-C to the algorithm and updated the HLA and ethnic frequency cohort to January 1, 2007-December 31, 2008.[9]

While the current CPRA is relatively predictive of access to transplant, it lacks a measure of sensitization at the HLA-DQA1, DPB1, or DPA1 loci, as well as for allele-specific antigens.[10] Therefore, candidates sensitized to these loci or specific alleles are not appropriately prioritized for allocation, in spite of being unable to accept organ offers from donors with these HLA. African American patients may be particularly disadvantaged by these exclusions, as they have been shown to be more likely to have unacceptable antigens to HLA-DQA1 and DPB1.[11] In addition, some rare unacceptable antigen combinations actually decrease a candidate's CPRA in the current calculation due in part to the way current haplotype frequencies were calculated,[12] in spite of increasing the number of deceased donors a candidate would be unable to accept. Using HLA frequency data from the OPTN dataset for CPRA also does not allow for iterative updates as HLA typing and unacceptable antigen values within the OPTN Computer System are added. A multi-year delay would be needed to collect sufficient data to incorporate new HLA frequencies after the implementation of the additional values within the OPTN Computer System.

The current CPRA calculation utilizes a haplotype-based method, where it uses the frequencies of HLA values inherited as a group. This method allows for the estimation of how genes may be inherited together in individuals, which can be especially useful when inferring larger trends from smaller data sets using Hardy-Weinberg Equilibrium.[13,14] The current algorithm is as follows:

$$CPRA = \sum_i [1-(1-S1+S2-S3+S4-S5)^2] \times D_i$$

[6] OPTN Policy 3.5.11.3: Calculated Panel Reactive Antibody (CPRA) was implemented on October 1, 2009. This policy was approved by the OPTN Board of Directors in December 2006.
[7] Ibid.
[8] Ibid.
[9] *Proposal to Update the Calculated PRA (CPRA).* OPTN Histocompatibility Committee Report to the Board of Directors. 14 November 2011.
[10] Tinckam, K. J., R. Liwski, D. Pochinco, M. Mousseau, A. Grattan, P. Nickerson, and P. Campbell. "CPRA Increases With DQA, DPA, and DPB Unacceptable Antigens in the Canadian CPRA Calculator." *American Journal of Transplantation* 15, no. 12 (2015): 3194–3201. https://doi.org/10.1111/ajt.13355.
[11] https://optn.transplant.hrsa.gov/media/3353/20191016_histo_meeting-minutes.pdf. Based on OPTN Waiting List candidates as of December 2018.
[12] Selecting HLA A*24 and C*12 as unacceptable antigens both decrease a candidate's CPRA within OPTN computer systems.
[13] Hardy-Weinberg Equilibrium is a population genetics principle that states that allele and genotype frequencies will remain constant without external influences. The formula that is the basis of Hardy-Weinberg Equilibrium can be used to calculate the probability of genes being inherited together and fill in missing data based on the most likely inheritance patterns of the genes.
[14] Kransdorf, Evan; Pando, Marcelo; Gragert, Loren; Kaplan, Bruce. HLA Population Genetics in Solid Organ Transplantation, Transplantation: September 2017. Volume 101, Issue 9. p 1971-1976. doi: 10.1097/TP.0000000000001830.

Figure 1: Variables Used in Current CPRA Calculation

Where…	Is defined as…
i	The racial or ethnic base population, as reported to the OPTN for deceased donors
S1	Sum of all 1 locus haplotype frequencies within each ethnic group (HLA A, B, DR, DQB1, C; five calculations)
S2	Sum of all 2 locus haplotype frequencies within each ethnic group (HLA A-B, A-DR, A-DQB1, A-C, B-DR, B-DQB1, B-C, DR-DQB1, DR-C, DQB1-C; ten calculations)
S3	Sum of all 3 locus haplotype frequencies within each ethnic group (HLA A-B-DR, A-B-DQB1, A-B-C, A-DR-DQB1, A-DR-C, A-DQ-C, B-DR-DQB1, B-DR-C, B-DQB1-C, DR-DQB1-C; ten calculations)
S4	Sum of all 4 locus haplotype frequencies within each ethnic group (HLA A-B-DR-DQB1, A-B-DR-C, A-B-DQB1-C, A-DR-DQB1-C, B-DR-DQB1-C; five calculations)
S5	Sum of all 5 locus haplotype frequencies within each ethnic group (HLA A-B-DR-DQB1-C; one calculation)
$\mathbf{D}_i$	The proportion of donors in each specific race or ethnicity *i* in the OPTN deceased donor population

Each ethnic group used in the calculation uses 31 calculations per unacceptable antigen per locus, see **Figure 1**, with a total of four ethnic groups incorporated for a total of 134 calculations per unacceptable antigen per locus.[15]

The current CPRA algorithm does not use a haplotype calculation for HLA-DR51/52/53 due to the small sample size of the current OPTN data set, and instead approximates the proportions of DR51/52/53 by the haplotype frequencies of equivalent DR-locus antigens. The equivalences used for approximation are available within **Figure 2**, below.

Figure 2: HLA-DR antigen equivalences used to approximate HLA-DR51/52/53 for CPRA[16]

Locus	Patient Unacceptable Antigen	Unacceptable DR antigen equivalences used for CPRA calculation
DR51	51	2, 15, 16
DR52	52	3, 5, 6, 11, 12, 13, 14, 17, 18
DR53	53	4, 7, 9

The current CPRA calculation uses HLA haplotype frequencies derived from the HLA entered into the OPTN Computer System for deceased kidney donors recovered from January 1, 2007 through December

[15] *Proposed Modification to UNOS Policy 3.5.11.3 (Panel Reactive Antibody). Replacement of Panel Reactive Antibody with CPRA, the calculated frequency of incompatible donors having one or more unacceptable antigens.* OPTN Public Comment Proposal, August 2006.

[16] OPTN *Policy 4.10: Reference Tables of HLA Antigen Values and Split Equivalences*, *Table 4-17: Additional Unacceptable Antigen Equivalences to be used in the Calculated Panel Reactive Antibody (CPRA) Only*.

31, 2008.[17] The ethnic frequencies for the current CPRA calculation are derived from deceased kidney donors recovered during the same time period, and can be found in **Figure 3**.

Figure 3: Ethnic Frequencies Used in Current Calculation[18]

Ethnicity	Proportion
White	0.687
African American	0.147
Hispanic	0.143
Asian/Pacific Islander	0.023
Total	1.000

Race and ethnicity are used in CPRA calculation due to differences in HLA haplotype and genotype frequencies between races, with alleles that are common in certain populations being uncommon in others.[19] In order to more accurately reflect the actual United States deceased donor population, the OPTN calculation multiplies the frequencies of the unacceptable antigens in each race or ethnicity by the proportion of that race or ethnicity in the deceased donor population.[20]

In summary, the current CPRA calculation utilized by the OPTN does predict transplant candidates' likelihood of compatibility with potential deceased donors, but could be more accurate.

Proposal for Board Consideration

Access to Transplant in the OPTN Waiting List Population

The proposed changes to CPRA are expected to have no impact on non-sensitized candidates within the waiting list population, but potentially significant impact for candidates who are immunologically sensitized. The most significant impacts will be for candidates with unacceptable antigens (UA) that are not accounted for in the current CPRA calculation. As a candidate's CPRA increases, they are less likely to be able to receive an offer unless it is potentially compatible based on their entered unacceptable antigens. **Figure 4** shows a graphic of modeled candidate CPRA change with the proposed calculation, and **Figure 5** shows the range, median, and mean of the expected changes. The vast majority of candidates would have little to no change in their CPRA, with greater changes in CPRA for candidates with unacceptable antigens that are not currently accounted for. The inclusion of HLA-DQA1 and DPB1 may have a larger impact on African American candidates, as they have been shown to be more likely to have unacceptable antigens at these loci.[21] The proposed changes to the CPRA calculation have also been shown to increase access for women.[22] Decrease in CPRA for this modeling is due to the inclusion

[17] *Proposal to Update the Calculated PRA (CPRA).* OPTN Histocompatibility Committee Report to the Board of Directors. 14 November 2011.
[18] Derived from deceased kidney donors recovered from January 1, 2007 to December 31, 2008.
[19] Hurley, Carolyn K., Jane Kempenich, Kim Wadsworth, Jürgen Sauter, Jan A. Hofmann, Daniel Schefzyk, Alexander H. Schmidt, et al. "Common, Intermediate and Well-Documented HLA Alleles in World Populations: CIWD Version 3.0.0." *HLA* 95, no. 6 (2020): 516–31.
[20] *Proposal to Update the Calculated PRA (CPRA).* OPTN Histocompatibility Committee Report to the Board of Directors. 14 November 2011.
[21] https://optn.transplant.hrsa.gov/media/3353/20191016_histo_meeting-minutes.pdf. Based on OPTN Waiting List candidates as of December 2018.
[22] Kransdorf EP, Pando MJ, Stewart D, Lindblad K, Bray R, Murphey C, Kaur N, Patel JK, Kim I, Zhang X, Maiers M, Kobashigawa JA, Gragert L. *Stem cell donor HLA typing improves CPRA in kidney allocation*. Am J Transplant. 2021 Jan;21(1):138-147. doi: 10.1111/ajt.16156. Epub 2020 Jul 13. PMID: 32558252.

of changes from the concurrent proposal to update the HLA equivalency tables, which removed multiple broad antigen equivalents from allelic unacceptable antigens.

Figure 4: Change in CPRA for Candidates with Unacceptable Antigens Without Frequencies in the Current OPTN CPRA Calculation[23]

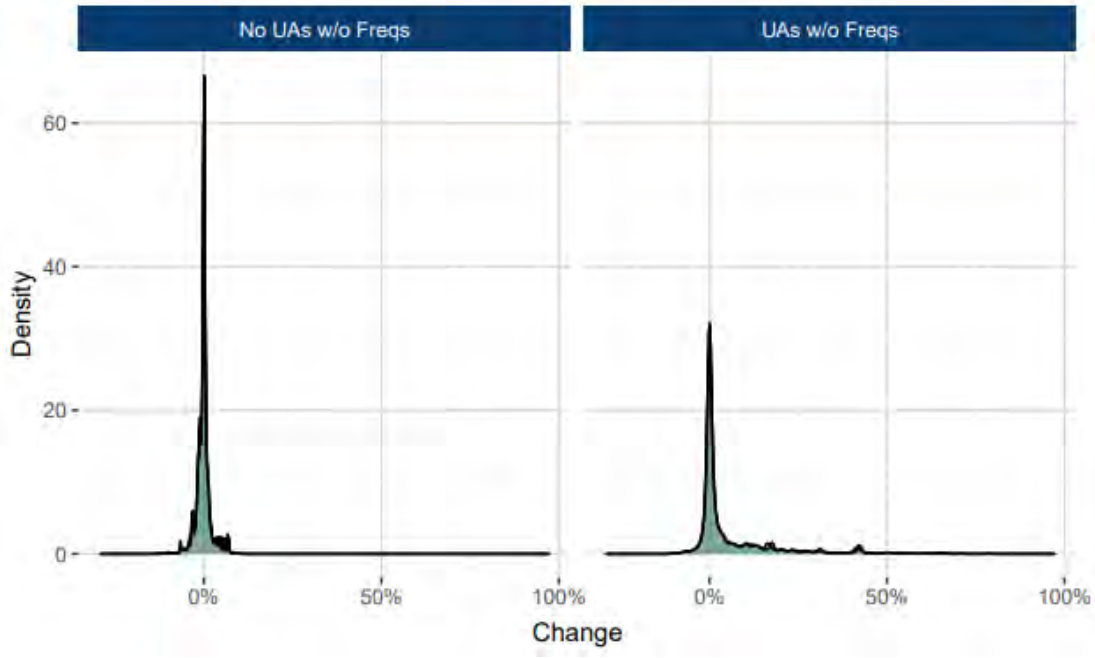


Figure 5: Change in CPRA for Candidates with Unacceptable Antigens (UAs) Without Frequencies in the Current OPTN CPRA Calculation[24,25]

Frequency Status	Calculation	N	Min	25th Percentile	Mean	Median	75th Percentile	Max
No UAs w/o Freqs	4 Groups	21112	-15.47%	-0.95%	-0.09%	-0.06%	0.43%	11.36%
	7 Groups		-15.41%	-0.91%	-0.13%	-0.01%	0.45%	11.48%
UAs w/o Freqs	4 Groups	20768	-14.44%	-0.04%	5.74%	0.27%	5.45%	97.12%
	7 Groups		-29.02%	-0.02%	5.75%	0.37%	6.32%	94.31%

Use of National Marrow Donor Program (NMDP) Data to Determine Human Leukocyte Antigen (HLA) Allele Frequencies

The OPTN data set has multiple limitations including the number of typings available, typing resolution, and lack of data collection at certain loci in the past. The Committee selected the NMDP donor registry

[23] Lindblad, Kelsi. "Impact of Changing the CPRA Calculation to a Genotype-Based, Stem Cell Donor-Derived Metric". Report to the OPTN Histocompatibility Committee, January 2022.
[24] Ibid.
[25] Throughout these analyses, "4 groups" refers to the ethnic groups in the current CPRA calculation (White, African American, Hispanic, Asian/Pacific Islander). "7 groups" refers to the ethnic groups for the proposed CPRA calculation (White, African American, Hispanic, Asian, American Indian/Alaskan Native, Pacific Islander, Multiracial).

data set as the ideal alternative to the OPTN deceased donor data set.[26] This data set has more donors than the OPTN data set which more accurately represents HLA frequencies in the US population, is at a higher resolution, and collects all 11 classic HLA loci. The NMDP data set of potential stem cell donors used to develop HLA frequencies contains over 2 million potential stem cell donors typed from 2015 onward.[27,28]

Hematopoetic stem cell transplant (HSCT) donors are typed at a higher resolution than solid organ transplant (SOT) donors. This is in part due to the risk of graft vs. host disease (GVHD) in HSCT,[29] and in part due to the much shorter turnaround for typing for SOT donors due to deceased donor management and allocation requirements.[30] Typing at NMDP recruitment centers from 2015 onward occurred via Next Generation Sequencing (NGS), with Class I typings including Exons 1-8[31] and Class II typings including Exons 2-3.[32] Due to the lower resolution of HLA typing for deceased donors, the OPTN does not have sufficient data to implement allelic CPRA values using solely OPTN data until the majority of deceased SOT donors are typed at a high resolution. The use of the NMDP data allows for potential recipients with allelic antibodies to be prioritized for allocation according to CPRA, which eliminates the need for programs to select serologic antigen equivalents as unacceptable antigens for candidates to receive allocation priority. If serologic antigen equivalents are substituted for allelic antibodies, this may potentially screen off compatible organ offers for donors typed at a lower resolution.

The use of NMDP data would also allow for iterative calculation updates as allelic values are added for unacceptable antigen selection, as the OPTN cannot implement frequency data to be used in CPRA using solely OPTN deceased donor data if the frequencies have not been previously collected. Using an outside data source with a closely related population to the SOT deceased donor population allows for the implementation of these frequencies as they are added as unacceptable antigen options, which also allows for the accurate prioritization of sensitized candidates.

Originally, the NMDP data set used contained HLA typings from potential stem cell donors from 2005 onwards, but these typings had a much higher level of ambiguity and it was not possible to assign individual frequencies to 37 alleles that are equivalent within the antigen recognition domain (ARD) but that are currently available to report as individual unacceptable antigens. These antigens are only equivalent to themselves within OPTN policy, and this discrepancy would have affected over 5% of the kidney waiting list.[33] In some cases, this discrepancy incorrectly skewed candidate CPRA up to 44 points. The new data set has nine DQA1 alleles that cannot be assigned individual frequencies due to an identical sequence in Exons 2/3. These alleles can be found below in **Figure 6.**

[26] https://optn.transplant.hrsa.gov/media/2447/20180213_histo_meetingsummary.pdf.
[27] https://optn.transplant.hrsa.gov/media/pvfhxt2r/20210810_histo_committee_meeting_summary.pdf.
[28] While the NMDP does have an international component, the frequencies used in the proposed calculation were limited to US residents.
[29] Ibid.
[30] Giralt, Sergio, and Michael R Bishop. "Principles and overview of allogeneic hematopoietic stem cell transplantation." *Cancer treatment and research* vol. 144 (2009): 1-21. doi:10.1007/978-0-387-78580-6_1
[31] Major Histocompatibility Complex (MHC) genes have 8 exons, which are separate segments of DNA coding the HLA protein. The HLA protein crosses the cellular membrane, with the immune system reacting to the extracellular portion of the protein. Exons 2 and 3 contain the full extracellular portion of the classic HLA being considered, with only a few exceptions.
[32] https://optn.transplant.hrsa.gov/media/pvfhxt2r/20210810_histo_committee_meeting_summary.pdf.
[33] Lindblad, Kelsi. "Frequencies of DQA1 Unacceptable Antigens for Kidney Registrations". Analysis for the OPTN Histocompatibility Committee. 7/15/2021.

Figure 6: Alleles Selectable Separately as Unacceptable Antigens, Unable to be Distinguished from NMDP Data Set[34, 35]

Combined Weight Unacceptable Antigens	CPRA
DQA1*01:01, DQA1*01:04, DQA1*01:05	26.0180%
DQA1*01:02, DQA1*01:11	35.7192%
DQA1*03:02, DQA1*03:03	13.7879%
DQA1*05:01, DQA1*05:05, DQA1*05:09, DQA1*05:11	41.2462%
DQA1*05:03, DQA1*05:07	1.3690%

The Committee discussed whether these alleles should be incorporated into the CPRA calculation with their combined weights due to their inability to be distinguished in the frequency data set or whether these alleles should be excluded entirely from the calculation. The Committee ultimately decided that since the exclusion could increase inequity most for women, minorities, and other patients with increased sensitization. Due to increased sensitization for those groups, and increased sensitization at the DQA1 locus for African American candidates, [36] that it would be preferable to incorporate them. The Committee will monitor their usage with quarterly reports to ensure that members are continuing to enter the appropriate alleles for their candidates. Additional information on the committee's monitoring plan can be found in the *Post-Implementation Monitoring* section below.

The NMDP data set was compared to other published data sets, with the results reviewed by the Committee for quality assurance purposes. There was a high level of concordance to published haplotypes for DRB1~DQA1~DQB1 and DPA1~DPB1.[37] This data set was also compared to data published from the 17th International Histocompatibility and Immunogenetics Workshop (IHIW 17). Both Caucasian and African American populations showed a high level of concordance, with the slightly lower concordance in African American populations likely being attributable to the smaller numbers in the IHIW 17 study, with 376-394 typings per locus, as compared to 2362-2423 typings in the Caucasian population. With fewer than 50 haplotypes from Asian donors and less than 60 from Hispanic donors, there was insufficient information to make a reasonable comparison for these groups. There was no data available for Native American/Alaskan Native, Hawaiian/Pacific Islander, or multiracial populations for comparison.

[34] This is the CPRA of the unacceptable antigens by themselves and does not account for linkage disequilibrium based on other potential unacceptable antigens.
[35] The value for the combined weight unacceptable antigens for DQA1*05:03, DQA1*05:07 was originally written as "13.6901%" and has been corrected to "1.3690%" to reflect the accurate CPRA.
[36] Ibid.
[37] https://optn.transplant.hrsa.gov/media/eo0f3m3u/20211014_optn_histocompatibility_meeting_summary.pdf.

Figure 7: Comparison to IHIW 17 by Locus and Concordance for Caucasian Populations

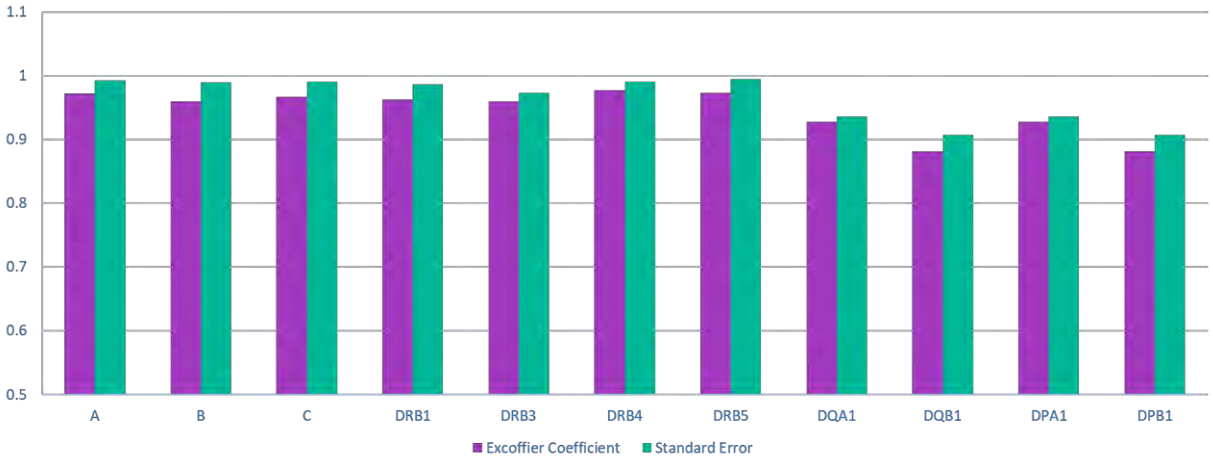
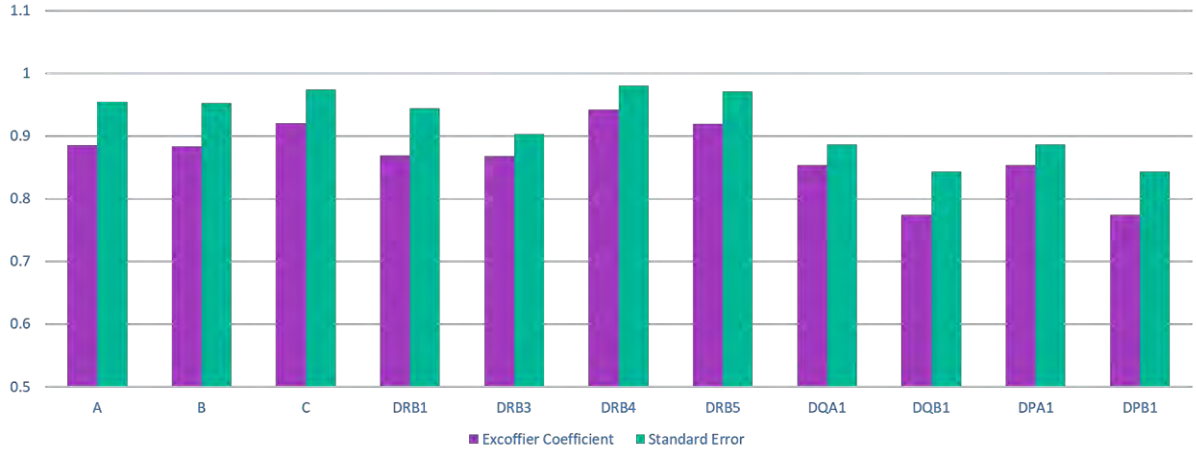


Figure 8: Comparison to IHIW 17 by Locus and Concordance for African American Populations



There was low concordance between the NMDP data set and *Common, Intermediate and Well-Documented HLA Alleles in World Populations: CIWD Version 3.0.0*.[38] The Committee agreed that this is likely due to the CIWD's utilization of direct counts of HLA alleles at the typing resolution submitted by the participating labs, with a large variability in typing methods including two-field, three-field, and four-field resolution, P-groups, G-groups, and multiple allele codes.[39]

The original NMDP data set of potential stem cell donors was also compared to the OPTN data set of deceased kidney donors currently used in CPRA calculation.[40] The level of concordance for racial and ethnic groups was 0.974 for white, 0.925 for Asian/Pacific Islander, and 0.896 for Hispanic,[41] which shows that the populations for both data sets are extremely similar. Of the four ethnic populations for which the OPTN currently has haplotypes used in CPRA, the least concordant result was I_f=0.873 for

[38] Hurley, Carolyn K., Jane Kempenich, Kim Wadsworth, Jürgen Sauter, Jan A. Hofmann, Daniel Schefzyk, Alexander H. Schmidt, et al. "Common, Intermediate and Well-Documented HLA Alleles in World Populations: CIWD Version 3.0.0." *HLA* 95, no. 6 (2020): 516–31.

[39] https://optn.transplant.hrsa.gov/media/eo0f3m3u/20211014_optn_histocompatibility_meeting_summary.pdf.

[40] Excoffier L, Slatkin M. *Maximum-likelihood estimation of molecular haplotype frequencies in a diploid population*. Mol Biol Evol. 1995 Sep;12(5):921-7. doi: 10.1093/oxfordjournals.molbev.a040269. PMID: 7476138.

[41] Ibid.

African American candidates.[42] The limited sample size in the OPTN data set may contribute to this lack of concordance.[43] Overall, the NMDP and OPTN population groups are highly concordant, with differences that are possibly attributable to differences in sampling sizes.

The NMDP genotype data set was also evaluated using an HLA typing resolution score metric[44] to evaluate the precision of the data used in the calculation. This was calculated with an unphased metric, as alpha-beta heterodimers[45] are not incorporated in the CPRA calculation at this time. The Committee reviewed and discussed the typing score resolution and agreed that the data set is far more complete than other available data sets, including the OPTN data set.[46] They also had consensus that the lower resolution of the DQA1 and DPA1 data was likely due to a smaller number of typings at those loci, and that the slightly lower DPB1 resolution is likely due to the P-group allele reporting structure, which the OPTN also utilizes. They agreed that excluding intermediate resolution typings which decreased the typing resolution score would likely lead to a decrease in calculation accuracy due to the decrease in sample size, which would most disadvantage highly sensitized candidates and minorities. In addition, the NMDP is working to actively increase the number of DQA1 and DPA1 typings in the registry through a data quality project. In the future, the Committee may be able to update the cohort with additional genotype data.[47]

Addition of DQA1, DPA1, and DPB1 Loci and Allele-Level Antibody Values to Calculation

Entry of HLA-DQA1 and DPB1 are currently required for deceased kidney and pancreas donors prior to match run execution, and the OPTN would have sufficient information on serologic antigens at these loci to incorporate them into a revised CPRA data set. While the requirement for HLA-DPA1 typing was approved but not yet implemented for deceased donors,[48] these data are already entered in the Donor Histocompatibility Form (DHF) in the Data System for the Organ Procurement and Transplantation Network for over 80% of all deceased donors.[49]

A previous study performed showed that when the CPRA calculation incorporated these additional loci, even just at antigen level, the allocation categories for many candidates on the waiting list significantly changed.[50] This would increase access to transplant for sensitized candidates, and unsensitized candidates would have no change in their allocation category. This suggests that the current CPRA

[42] Kransdorf EP, Pando MJ, Stewart D, Lindblad K, Bray R, Murphey C, Kaur N, Patel JK, Kim I, Zhang X, Maiers M, Kobashigawa JA, Gragert L. *Stem cell donor HLA typing improves CPRA in kidney allocation*. Am J Transplant. 2021 Jan;21(1):138-147. doi: 10.1111/ajt.16156. Epub 2020 Jul 13. PMID: 32558252.
[43] N=2,101, based on black deceased kidney donors from January 1, 2007-December 31, 2008.
[44] Vanja Paunić, Loren Gragert, Joel Schneider, Carlheinz Müller, Martin Maiers. *Charting improvements in US registry HLA typing ambiguity using a typing resolution score*. Human Immunology. 2016. Volume 77, Issue 7. https://doi.org/10.1016/j.humimm.2016.05.002.
[45] Class II HLA antigens are made of two parts, the alpha and the beta chain. These form heterodimers, which is the full antigen structure on the cell surface that the patient's antibody reacts to. The OPTN captures the typings for these antigens separately, for example with DPA1 and DPB1 instead of as DPA1~DPB1 heterodimers.
[46] https://optn.transplant.hrsa.gov/media/hziblkem/20220405_histocompatibility_meeting-summary.pdf
[47] https://optn.transplant.hrsa.gov/media/hziblkem/20220405_histocompatibility_meeting-summary.pdf
[48] *Update Human Leukocyte Antigen (HLA) Equivalency Tables.* OPTN Histocompatibility Committee Report to the Board of Directors. 6 December 2021. Requirement effective pending implementation and notice to members.
[49] Based on OPTN deceased donors procured in 2020.
[50] Data presented to the OPTN Histocompatibility Committee on October 16, 2019 in Chicago, IL by Evan Kransdorf, Loren Gragert, and Kelsi Lindblad.

underestimates candidates' level of sensitization and that the addition of DQA1, DPA1, and DPB1 would better reflect candidate's sensitization than their current CPRA would suggest.

The current OPTN data set used in the calculation for CPRA has insufficient information on allelic (higher resolution) HLA in the deceased donor population to incorporate allelic antibodies due to the lower resolution of HLA typing used for most deceased donors. About 15% of patients may have allele-specific antibodies,[51] and patients with allele-specific antibodies currently do not receive any allocation benefit in the way of CPRA points unless the low resolution serologic equivalent is entered, potentially excluding donors with compatible alleles. Use of the NMDP data allows for the incorporation of allelic values in CPRA due to the high resolution of candidate and donor HLA typing in HSCT.

Using a snapshot of the kidney waiting list on December 31, 2020, 21,112 registrations had unacceptable antigens that are not accounted for in the current CPRA algorithm, which was 22% of all kidney registrations.[52] This includes allelic unacceptable antigens and unacceptable antigens to HLA-DQA1, DPA1, and DPB1. This means almost a quarter of all kidney candidates are currently receiving no allocation priority for these unacceptable antigens, in spite of the inability to accept deceased donors with these HLA antigens.

Change in Racial and Ethnic Calculations

Neither the OPTN deceased donor population[53] nor the NMDP potential donor population[54] share the exact racial and ethnic makeup of the United States as a whole, see **Figure 9**. In order to more accurately reflect a candidate's likelihood of receiving a deceased donor organ offer, both the current and proposed CPRA calculations multiply the frequency these antigens appear within a racial or ethnic group by the proportion of that racial or ethnic group within the OPTN deceased donor population.

[51] Zavyalova, D., Abraha, J., Rao, P., & Morris, G. P. (2021). Incidence and impact of allele-specific anti-HLA antibodies and high-resolution HLA genotyping on assessing immunologic compatibility. *Human immunology*, *82*(3), 147–154. https://doi.org/10.1016/j.humimm.2021.01.002.

[52] Based on the OPTN Waiting List population on December 31, 2020.

[53] Public Information Office. "2010 Census Shows America's Diversity." *Census.gov.* March 24, 2011. Available at: https://www.census.gov/newsroom/releases/archives/2010_census/cb11-cn125.html.

[54] Fingrut, Warren. "The Need for Ethnically Diverse Stem Cell Donors." *The University of British Columbia Medical Journal* 7, no. 1 (2015): 44–47.

Figure 9: Number of Donors in Each Racial or Ethnic Group in the OPTN and NMDP Donor Populations[55]

Ethnicity	NMDP Donor Numbers	NMDP Donor Proportions	OPTN Deceased Donor Proportions
White	1778352	0.6401	0.6550
African American	153606	0.0553	0.1565
Hispanic	345991	0.1245	0.1456
Asian	181631	0.0654	0.0252
American Indian/Alaskan Native	20277	0.0073	0.0061
Pacific Islander	3055	0.0011	0.0028
Multiracial	295311	0.1063	0.0088
Total	2778223	1.000	1.000

The current OPTN data set used to calculate the ethnic proportions of deceased donors is based solely on kidney donors, as CPRA has historically only been used in kidney and pancreas allocation. As the OPTN Board has approved a proposal to include CPRA as 5% of the lung Composite Allocation Score (CAS),[56] this proposal includes an expansion to the ethnic proportions of all deceased donors to better approximate deceased donors for all organs, instead of just deceased kidney donors. This will provide frequencies in the calculation that are able to applied more broadly to all organs, instead of having separate frequencies for each organ. The Histocompatibility and Lung Transplantation Committees felt that the use of multiple different frequencies may be confusing, especially for multi-organ candidates.[57] In addition, the median difference between CPRA calculations using the two separate weights was 0.05%, and the maximum difference was 1.55%.[58]

The current CPRA calculation only incorporates White, African American, Hispanic, and Asian/Pacific Islander donor ethnicities. The current OPTN data set used in the calculation for CPRA has insufficient information on American Indian/Alaskan Native, Native Hawaiian/other Pacific Islander, and multiracial groups in order to accurately calculate HLA haplotype or genotype frequencies, with less than 70 individual deceased donors in each respective population.[59] The extremely low numbers of donors would likely lead to inaccurate frequencies of HLA genotypes, simply due to the small sample. Due to the acquisition of the NMDP data set, the Committee is now able to include these three additional ethnic groups in the CPRA calculation. While there is not a significant difference in the CPRA with these groups included or excluded, see **Figure 9**, with a range of +/- 0.4% and the majority of candidates having no difference at all,[60] the addition allows for inclusion of smaller donor ethnic groups.

[55] The value for the OPTN Deceased Donor Proportions for white donors was originally written as “0.6650” and has been corrected to “0.6550” to reflect the accurate proportion.
[56] *Establish Continuous Distribution of Lungs.* OPTN Lung Transplantation Committee Report to the Board of Directors. 6 December 2021.Requirement effective pending implementation and notice to members.
[57] https://optn.transplant.hrsa.gov/media/4647/20210505_lung-meeting-summary_final.pdf.
[58] Lindblad, Kelsi. “Comparing CPRA with Lung-Specific Weights vs. All Deceased Donor Ethnic Weights”. Analysis for the OPTN Lung Committee. 12/16/2021.
[59] Based on OPTN deceased donors who donated at least one organ from January 1, 2007-December 31, 2008, the timeframe for the current OPTN HLA frequency data cohort.
[60] Lindblad, Kelsi. “Impact of Changing the CPRA Calculation to a Genotype-Based, Stem Cell Donor-Derived Metric”. Report to the OPTN Histocompatibility Committee, January 2022.

Figure 10: Change in Candidate CPRA using 4 vs. 7 Donor Ethnicities in the Calculation[61]

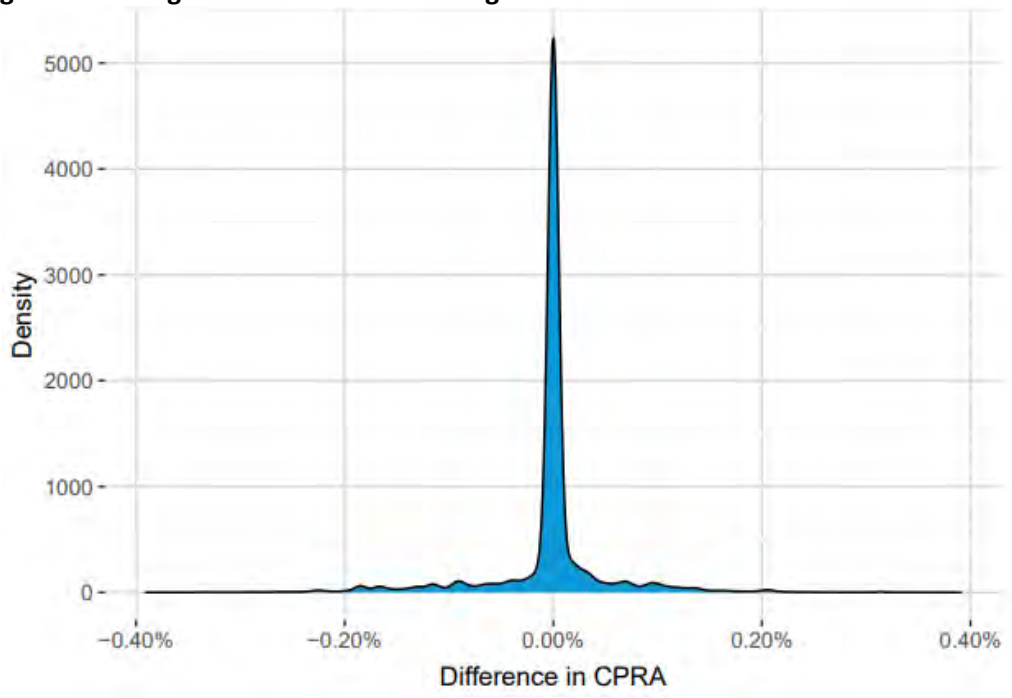


Figure 10 shows how the change from 4 to 7 ethnicities included in CPRA would affect candidates of each ethnic group, using the current CPRA calculation as the base for no change.[62] The CPRA was calculated using unacceptable antigens entered for all candidates on the OPTN Waiting List as of December 31, 2020. The difference in the median change between including 4 and 7 ethnicities in the CPRA calculation would be less than 0.01% in any given ethnic group.

Proposed CPRA Calculation

The proposed CPRA algorithm is genotype-based and relies on the frequencies of individual alleles observed within the NMDP cohort. The frequencies observed in the NMDP cohort are then correlated to the OPTN population using the proportion of each ethnicity present within the deceased donor population.

The algorithm is as follows:

$$\text{CPRA} = \sum_i \left[G_F \times D_i \right]$$

[61] Ibid.

Figure 11: Variables Used in Proposed CPRA Calculation

Where…	Is defined as…
i	The racial or ethnic base population, as reported to the OPTN for deceased donors
G_F	The frequency of HLA genotypes in each specific racial or ethnic population i equivalent to the unacceptable HLA antigens, alleles, and epitopes reported on the waiting list
D_i	The proportion of donors in each specific race or ethnicity i in the OPTN deceased donor population

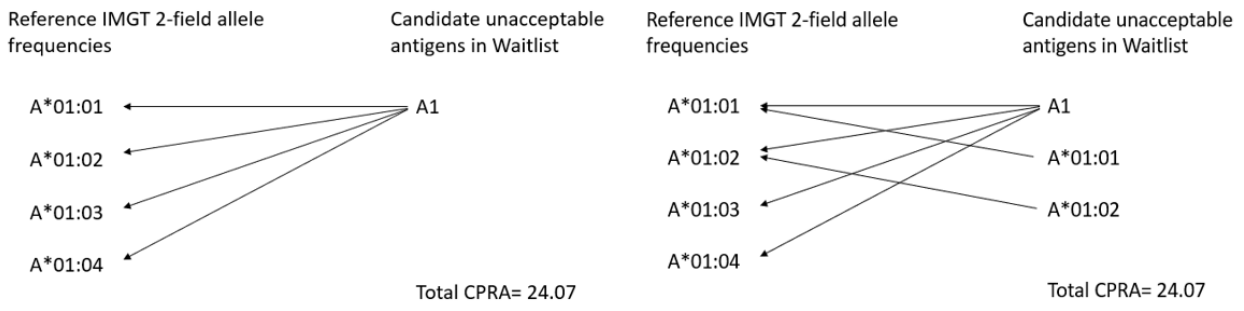
The proposed D_i, or donor ethnic weight, is based on all deceased donors from January 1, 2018 to December 31, 2020 and available in **Figure 12**. The OPTN will update the deceased donor racial and ethnic frequencies when updating the HLA equivalency tables.

Figure 12: Ethnic Frequencies for proposed D_i[63]

Ethnicity	Proportion
White	0.6650
African American	0.1565
Hispanic	0.1456
Asian	0.0252
American Indian/Alaskan Native	0.0061
Pacific Islander	0.0028
Multiracial	0.0088
Total	1.000

The CPRA frequencies are determined based on the IMGT 2-field alleles equivalent to a candidate's unacceptable antigens listed on the waiting list. Each 2-field allele can only be counted once towards a candidate's CPRA, ensuring that priority is based on the percentage of the population that a candidate cannot accept, not how many equivalent unacceptable antigens a transplant program lists. An example of this principle is available in **Figure 13**.

Figure 13: CPRA Frequency References



[63] Based on OPTN data from January 1, 2018-December 31, 2020.

These frequencies are taken from a direct count of genotypes in order to incorporate linkage disequilibrium. Linkage disequilibrium is the likelihood of genes to be inherited in patterns that put certain genes together more or less often than would be expected if the loci were completely independent. If linkage disequilibrium was not incorporated into the calculation, a candidate could theoretically have a CPRA of greater than 100%, since donors would be "double counted" as screened from the match run for all loci (A, B, C, DR, DR51/52/53, DQA1, DQB1, DPA1, and DPB1), and twice due to heterozygosity. In order to not "double count" donors, the calculation will only add each haplotype frequency to the calculation once, regardless of whether or not a candidate has multiple unacceptable antigens in the donor haplotype.

The genotypes in the data set in the calculation uses IMGT/HLA two-field alleles.[64] The equivalences to OPTN unacceptable antigen values were derived from the IMGT/HLA unambiguous serologies. Any allele without an unambiguous serology was assigned its assumed serology based on published IMGT/HLA data, as the majority of alleles named after 2008 do not have an unambiguous serology. Alleles were then reassigned as needed based on deceased donor screening criteria based on the HLA unacceptable antigen equivalency tables in OPTN *Policy 4.10: Reference Tables of HLA Antigen Values and Split Equivalences*, to ensure that the percentages in CPRA are based on actual deceased donors a candidate is unable to accept.

The CPRA calculation will be rounded to six decimal places. A CPRA of 0.999999, or 99.9999%, which indicates that a candidate would be expected to be compatible with only a single deceased donor in 50 years based on a donation rate of 20,000 deceased donors a year.[65]

Alternative Approach Considered: Haplotype Calculation

Haplotypes are useful in estimating heritable patterns when insufficient data exists to directly observe the frequency of alleles within a population.[66] Haplotypes look at how often an entire HLA group (A-B-C-DR-DR51/52/53-DQB1-DQA1-DPA1-DPB1) is inherited together, to make an inference of how often they appear within the population. A genotype-based calculation looks at every combination of haplotypes to directly observe how often they appear within the population.

Construction of HLA haplotypes using the ARELQUIN Expectation-Maximization software, such as the OPTN data set currently uses, has been shown to be incorrect for reconstructing loci with more than one recombination hotspot[67] between them in 38-57% of samples.[68] These inaccuracies may account for some of the observed discrepancies with the current OPTN calculation in which the addition of unacceptable antigens may decrease a candidate's CPRA, in spite of increasing the number of potential donors a candidate would be unable to accept. While the Committee reviewed a new algorithm that could increase accuracy of haplotype calculations using intermediate and high-resolution HLA typing,[69]

[64] https://www.ebi.ac.uk/ipd/imgt/hla/.
[65] https://optn.transplant.hrsa.gov/media/guhkhneh/2021_11_09_histo-committee-meeting-summary.pdf.
[66] Kransdorf, Evan; Pando, Marcelo; Gragert, Loren; Kaplan, Bruce. HLA Population Genetics in Solid Organ Transplantation, Transplantation: September 2017. Volume 101, Issue 9. p 1971-1976. doi: 10.1097/TP.0000000000001830.
[67] Recombination hotspots in genes have a higher level of genetic rearrangement, than most DNA regions. MHC genes, those that encode HLA proteins, have high levels of genetic recombination.
[68] Castelli, E C et al. "Evaluation of computational methods for the reconstruction of HLA haplotypes." *Tissue antigens* vol. 76,6 (2010): 459-66. doi:10.1111/j.1399-0039.2010.01539.x
[69] Craig Kollman, Martin Maiers, Loren Gragert, Carlheinz Müller, Michelle Setterholm, Machteld Oudshoorn, Carolyn Katovich

they felt that the genotype approach using direct observation would be more accurate and more easily implemented with epitope-level selection of unacceptable antigens.[70]

With the original implementation of the OPTN CPRA calculator, the data set used was too small to accurately implement a genotype calculation. However, with a one-hundred-fold larger cohort using the NMDP data set of over 2 million potential HSC donors, allele frequencies are able to be observed instead of estimated.

The alternate calculation considered but not selected by the Committee is as follows:

$$CPRA = \sum_i [[1-(1-S1+S2-S3+S4-S5+S6-S7+S8-S9)^2] \times D_i]$$

Figure 14: Variables for a Haplotype-Based CPRA Calculation

Where…	Includes…
i	The racial or ethnic base population, as reported to the OPTN for deceased donors
S1	Sum of all 1 locus haplotype frequencies within each ethnic group (HLA A, B, C, DR, DR51/52/53, DQB1, DQA1, DPA1, DPB1; nine calculations)
S2	Sum of all 2 locus haplotype frequencies within each ethnic group (36 calculations)
S3	Sum of all 3 locus haplotype frequencies within each ethnic group (84 calculations)
S4	Sum of all 4 locus haplotype frequencies within each ethnic group (126 calculations)
S5	Sum of all 5 locus haplotype frequencies within each ethnic group (126 calculations)
S6	Sum of all 6 locus haplotype frequencies within each ethnic group (84 calculations)
S7	Sum of all 7 locus haplotype frequencies within each ethnic group (36 calculations)
S8	Sum of all 8 locus haplotype frequencies within each ethnic group (Nine calculations)
S9	Sum of all 9 locus haplotype frequencies within each ethnic group (HLA A-B-C-DR-DR51/52/53-DQB1-DQA1-DPA1-DPB1, one calculation)
$\mathbf{D_i}$	The proportion of donors in each specific race or ethnicity *i* in the OPTN deceased donor population

Using a haplotype-based CPRA, there would be 511 calculations per ethnic group included for each combination of unacceptable antigens entered. Using the current 4 group CPRA, that would be 2,044 calculations, and expanding to the 7 group CPRA that would be 3,577 calculations. For a candidate who has two unacceptable antigens at the same locus, that calculation would be doubled, ad infinitum for every added unacceptable antigen per locus. The inefficiencies of haplotype-based calculations compound quickly when expanding the loci and ethnic groups used in the calculation.

Not only is the haplotype-based calculation inefficient when expanded to additional loci and ethnic groups, it is also less accurate due to assumptions of Hardy-Weinberg Equilibrium in the calculation. These assumptions include that there is no mutation, no migration, that alleles are inherited independently, and that their frequencies do not change between generations.[71] Using a large cohort

Hurley. "Estimation of HLA-A, -B, -DRB1 Haplotype Frequencies Using Mixed Resolution Data from a National Registry with Selective Retyping of Volunteers". *Human Immunology*, Volume 68, Issue 12, 2007, Pages 950-958, https://doi.org/10.1016/j.humimm.2007.10.009.

[70] https://optn.transplant.hrsa.gov/media/3465/20191205_histo_cpra-subcomm_meeting-summary.pdf.

[71] Ibid.

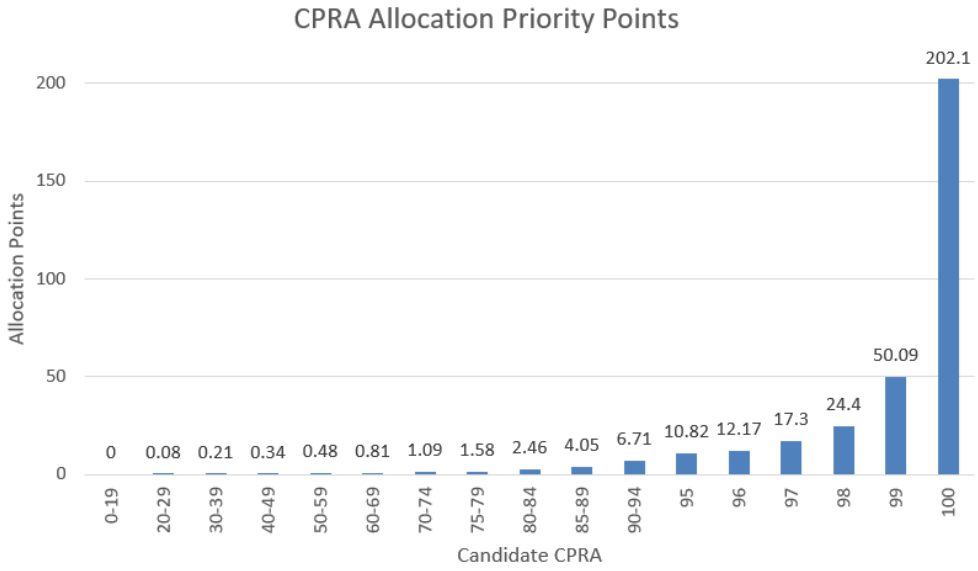
and a genotype-based calculation allows for more direct observation of frequencies of alleles within the population.

Effects on Kidney Allocation

Current Use in Allocation Policy

Kidney allocation currently has a sliding scale of allocation points assigned based on CPRA,[72] as demonstrated in **Figure 15**. In addition, candidates with a CPRA of >20% are prioritized in allocation classifications for all deceased donor Kidney Donor Profile Index (KDPI) classifications.[73]

Figure 15: Current CPRA Allocation Priority Points[74]



Impacts on Allocation

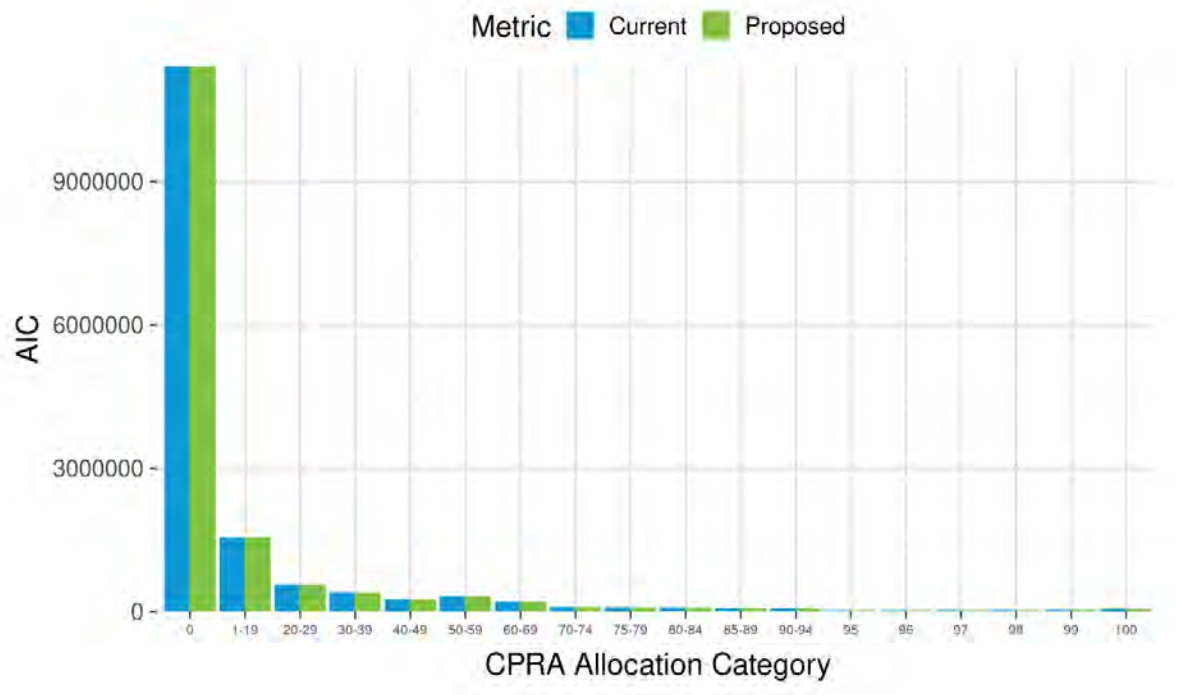
The proposed updates to CPRA would affect the allocation priority of 12% of kidney registrations on the waiting list as of December 31, 2020. The proposed updates would also change allocation priority for 44% of candidates with unacceptable antigens currently unaccounted for in CPRA.[75]

Kidney offer rates for candidates with any active time from January 1, 2018- December 31, 2020 were evaluated for the potential impact of changing the CPRA calculation. Offer rate analysis compares the anticipated to actual offers based on the proportions of deceased donors a candidate would be unable to accept based on unacceptable antigens. Models predicting number of offers based on candidate CPRA were constructed for both CPRA metrics and compared using the Aikake information criterion

[72] OPTN *Policy 8.3: Kidney Allocation Score*.
[73] OPTN *Policy 8.5.H: Allocation of Kidneys from Deceased Donors with KDPI Scores less than or equal to 20%*; OPTN *Policy 5.5.I: Allocation of Kidneys from Deceased Donors with KDPI Scores Greater than 20% but Less than 35%*; OPTN *Policy 8.5.J: Allocation of Kidneys from Deceased Donors with KDPI Scores Greater than or Equal to 35% but Less than or Equal to 85%*; OPTN *Policy 8.5.K: Allocation of Kidneys from Deceased Donors with KDPI Scores Greater than 85%*.
[74] Ibid.
[75] Lindblad, Kelsi. "Impact of Changing the CPRA Calculation to a Genotype-Based, Stem Cell Donor-Derived Metric". Report to the OPTN Histocompatibility Committee, January 2022.

(AIC)[76], where a lower AIC indicates a better model. The proposed CPRA is slightly more predictive of offer rate than the current CPRA in all allocation categories except 100%, as shown in **Figure 16**. For candidates with unacceptable antigens not currently accounted for, the proposed CPRA is again more predictive of offer rate than the current CPRA for all allocation categories except 100%, but to a greater degree than when considering all candidates. The proposed CPRA therefore better characterizes the number of deceased donors a candidate would be unable to accept for the majority of CPRA allocation categories. This makes the proposed CPRA more appropriate to use in allocation than the current CPRA, as the number of allocation points awarded for higher CPRAs must be calibrated to offset the decrease in offer rate as sensitization increases, and the proposed CPRA reflects that decrease more accurately.

Figure 16: Offer Rate Model fit by CPRA and Allocation Category[77]



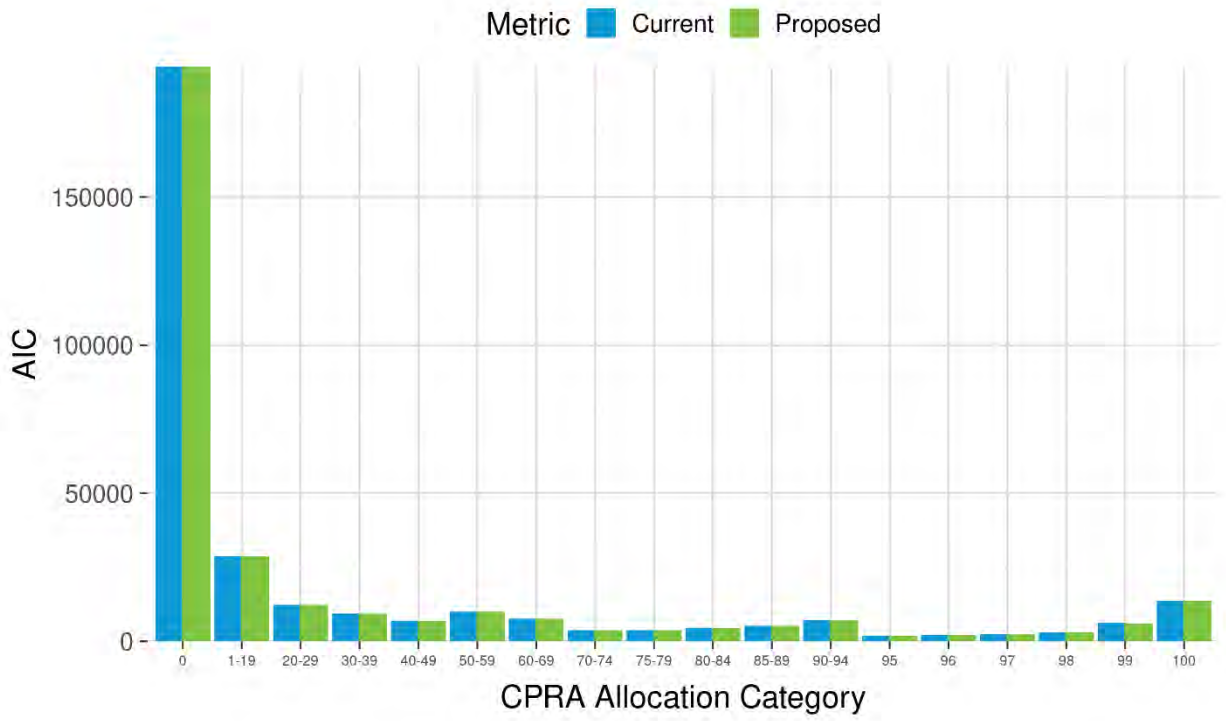
Similarly, transplant rates for kidney candidates with any active time from January 1, 2018- December 31, 2020 were evaluated for the potential impact of changing the CPRA calculation. While analyzing offer rates provides an estimate of a candidates' access to donors, studying transplant rates provides a measure of access that takes into account the fact that a candidates' likelihood of accepting an offer also depends on their level of sensitization. For example, highly-sensitized candidates are more likely than candidates with lower sensitization to turn down an offer due to a positive crossmatch.[78] The proposed CPRA was found to be more predictive of transplant rate in all allocation categories except 20-29%, 30-39%, 40-49%, and 100%, shown in **Figure 17**. The proposed CPRA was therefore better characterized access to transplant in the majority of CPRA categories.

[76] AIC is a statistical measure that compares different models to determine which one best fits the data. The lower the number, the better the data fits the proposed model. In this case, the model is the CPRA calculation used and the data is the candidate offer and transplant rates.

[77] Ibid.

[78] Douglas Keith and Gayle Vranic. "Approach to the Highly Sensitized Kidney Transplant Candidate." *Clinical journal of the American Society of Nephrology : CJASN* vol. 11,4 (2016): 684-93. doi:10.2215/CJN.05930615

Figure 17: Transplant Rate Model fit by CPRA and Allocation Category[79]



Overall Sentiment from Public Comment

This proposal was released for public comment from January 27, 2022 to March 23, 2022. This proposal received 237 comments, 34 of which contained a written comment in addition to sentiment.
Figure 18 shows the overall sentiment by member type for the public comment proposal. It was broadly supported across all member types.

[79] Ibid.

Figure 18: Sentiment by Member Type

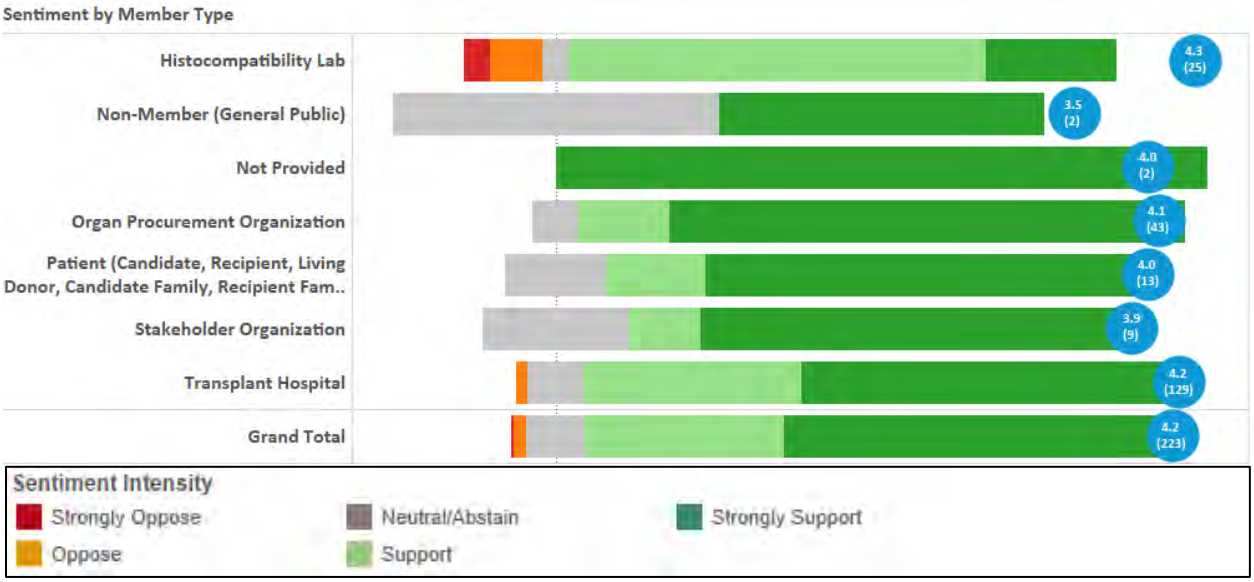
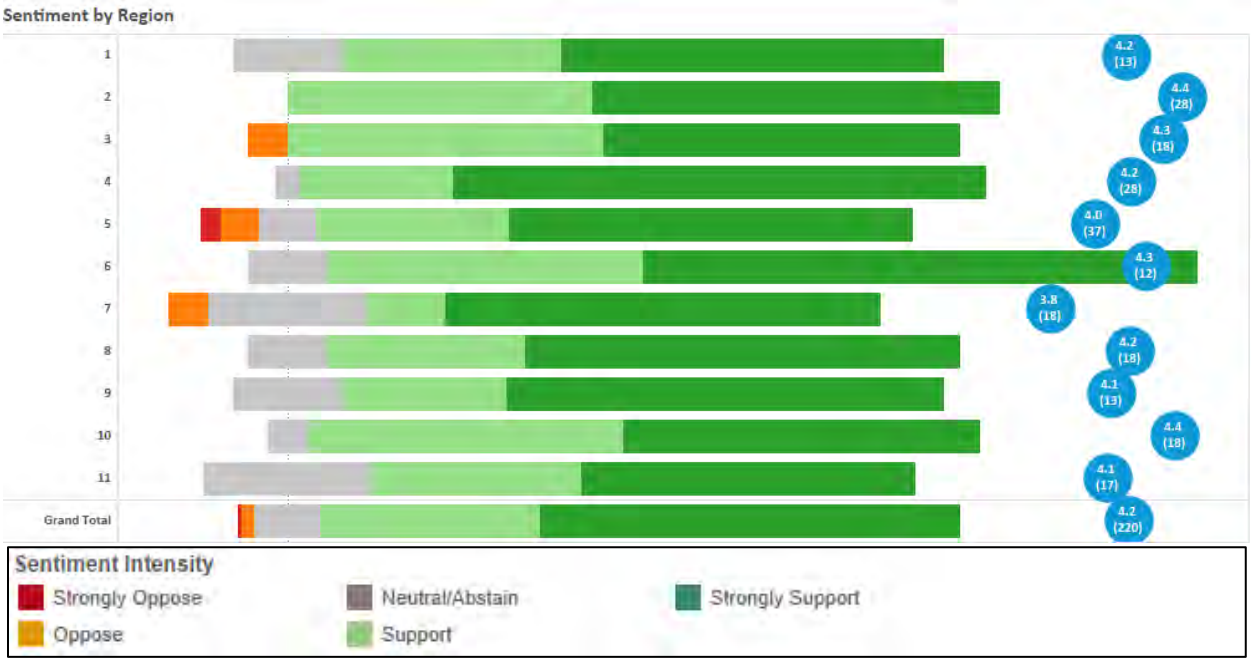


Figure 19 shows sentiment received by region. The majority of this sentiment was received from regional meetings, with 207 comments submitted through this process. This proposal was on the consent agenda in all 11 regions, but participants did have the option of submitting additional comments via a polling application. Of the other comments, 5 were from other OPTN Committees and 25 were submitted via the web.

Figure 19: Sentiment by Region



Substantive stakeholder organization feedback was received from American Society for Histocompatibility and Immunogenetics (ASHI), the American Society of Transplantation (AST), and the North American Transplant Coordinators Organization (NATCO). All three stakeholders supported the

proposal overall. They specifically commented in support of the inclusion of additional HLA values in the calculation and the increased precision in candidate sensitization evaluation. In addition, these stakeholder groups recommended an increased transition period time.

Commenters covered many different topics, along a few main themes:

- Candidate Access
- Transition Procedures
- HLA Loci and Resolution Included in Calculation
- Waiting List Management

Candidate Access

Multiple members expressed that these changes will be more predictive of potential organ compatibility and will benefit candidate access to transplant.

Transition Procedures

Multiple members stated that the transition time of one week for CPRA transition would be difficult or inadequate, especially for large kidney transplant programs. One member suggested that if the OPTN were to provide additional resources or tools to assist programs with the transition, the proposed week timeline may be acceptable. Proposed alternate transition timeframes ranges from two weeks to two months. In response, the Committee is proposing to increase the transition timeframe from one week to a minimum of one month, as well as providing a more comprehensive report for programs that would include both the CPRA change and Kidney Allocation Score (KAS) change for all kidney candidates on the OPTN Waiting List.

HLA Loci and Resolution Included in Calculation

One commenter noted that at their center, they had more Caucasian patients than African American patients with HLA DP antibodies, but mentioned that may be due to their patient population.

Of the four comments in opposition to the proposal, two were from a lab and its associated transplant hospital related to the addition of DP antibodies and whether or not they were clinically important in transplant. Eight other members commented specifically in support of adding DP antibodies to the CPRA calculation, and no other members expressed concern about the addition of these antibodies. The Committee discussed the inclusion of DP antibodies in the CPRA calculation, and was in consensus that they would continue to allow discretion in the selection of unacceptable antigens, and that the intent of the calculation in allocation is to combat the biological disadvantage a candidate experiences when they are unable to accept donor organs. If the program is willing to accept those organs on behalf of the candidate, they are not experiencing a biological disadvantage and do not need additional prioritization in allocation.[80, 81]

One member expressed concerns about the inclusion of allele-level antibodies in the CPRA calculation, stating concern that allelic antibodies do not severely disadvantage a large number of transplant candidates and that there is potential for abuse of this practice due to the current resolution of donor

[80] https://optn.transplant.hrsa.gov/media/vnndtcl1/20220308_histocompatibility_meeting-summary.pdf.
[81] https://optn.transplant.hrsa.gov/media/hziblkem/20220405_histocompatibility_meeting-summary.pdf

typing. The member suggested that programs should be required to apply to include allelic antibodies for a particular patient, with stringent criteria for approval and a robust review of accepted offers for these patients. Four other members commented specifically in support of adding allele-level antibodies to the CPRA calculation, and no other members expressed concern about the addition of allele-level antibodies. The Committee had previously discussed the issue of monitoring allele-specific antibody use, and had decided to monitor their usage with quarterly reports to ensure that members are continuing to enter the appropriate alleles for their candidates.[82, 83] Additional information on the committee's monitoring plan can be found in the *Post-Implementation Monitoring* section below. When the Committee discussed the concern after public comment, they had consensus that the proposed monitoring plan was sufficient to address the concern without placing additional data submission or application burdens on members.[84]

One member commented that the HLA DQ antibodies need to be listed as the alpha/beta heterodimers. The member commented that not listing the antibodies as heterodimers may disadvantage patients by not providing them with proportional allocation points, or by having to block compatible donors. The Committee discussed this issue and agreed that it could have potential for a future project, but was out of scope for the current proposal, as the proposed change would require altering the structure of HLA typing and unacceptable antigens data in the OPTN Waiting List and Donor Data and Matching System.[85]

Waiting List Management

Multiple commenters stated that the CPRA should be viewable for all organs after implementation and that it is useful in OPTN Waiting List management. One member commented that while it may not influence organ acceptance practices, it can still help the teams modify immunosuppression practices. In addition, one pediatric heart program commented that sensitization does play a large role in transplant eligibility and decision-making regarding desensitization. The Committee determined that they would like CPRA viewable for all candidates on the OPTN Waiting List, not just the candidates of organs that use CPRA in their allocation.[86]

Compliance Analysis

NOTA and OPTN Final Rule

The Committee submits the following proposal for the Board consideration under the authority of the National Organ Transplantation Act, which states, "The Organ Procurement and Transplantation Network shall… (A) establish… (ii) a national system… to match organs and individuals included in the list, especially individuals whose immune system makes it difficult for them to receive organs…"[87] Including data from the NMDP dataset in the OPTN's CPRA calculation will result in better characterization for sensitized candidates, due to inclusion of additional loci and two-field allele values incorporated.

[82] https://optn.transplant.hrsa.gov/media/ce2cvuvy/20211012_optn_histocompatibility_meeting_summary.pdf.
[83] https://optn.transplant.hrsa.gov/media/eo0f3m3u/20211014_optn_histocompatibility_meeting_summary.pdf.
[84] https://optn.transplant.hrsa.gov/media/hziblkem/20220405_histocompatibility_meeting-summary.pdf
[85] https://optn.transplant.hrsa.gov/media/hziblkem/20220405_histocompatibility_meeting-summary.pdf
[86] https://optn.transplant.hrsa.gov/media/hziblkem/20220405_histocompatibility_meeting-summary.pdf
[87] 42 USC §274(b)(2)(A)(ii).

The Committee also submits this proposal under the authority of the OPTN Final Rule, which states "The OPTN Board of Directors shall be responsible for developing…policies for the equitable allocation for cadaveric organs."[88] This proposal may affect allocation, as CPRA is a calculated value used in determining allocation priority in kidney and pancreas allocation, and the OPTN Board of Directors (Board) has approved its use in lung allocation.[89]

The Final Rule requires that when developing policies for the equitable allocation of cadaveric organs, such policies must be developed "in accordance with §121.8," which requires that allocation policies "(1) Shall be based on sound medical judgment; (2) Shall seek to achieve the best use of donated organs; (3) Shall preserve the ability of a transplant program to decline an offer of an organ or not to use the organ for the potential recipient in accordance with §121.7(b)(4)(d) and (e); (4) Shall be specific for each organ type or combination of organ types to be transplanted into a transplant candidate; (5) Shall be designed to avoid wasting organs, to avoid futile transplants, to promote patient access to transplantation, and to promote the efficient management of organ placement;…(8) Shall not be based on the candidate's place of residence or place of listing, except to the extent required by paragraphs (a)(1)-(5) of this section."[90] This proposal:

- **Is based on sound medical judgment**[91] because it is an evidenced-based change relying on the following evidence:
    - OPTN data, NMDP data, analysis, and literature that demonstrates these changes are more accurate than current calculations and are likely to lead in an increase in access to transplant for sensitized candidates, especially highly sensitized candidates and candidates from minority ethnic and racial groups.[92,93,94,95]
- **Is designed to…promote patient access to transplantation**[96] **by** giving similarly situated candidates equitable opportunities to receive an organ offer.
    - Sensitized candidates will have more equitable opportunities to receive an organ offer, as their sensitization will be appropriately accounted for by CPRA. [97]
- **Seeks to achieve the best use of donated organs**[98]
    - The proposed calculation is more predictive of potential organ compatibility, allowing histocompatibility labs to better assess a candidate's likelihood of positive crossmatch. [99]

[88] 42 C.F.R. §121.4(a)(1)

[89] *Establish Continuous Distribution of Lungs.* OPTN Lung Transplantation Committee Report to the Board of Directors. 6 December 2021. Requirement effective pending implementation and notice to members.

[90] 42 CFR §121.8(a)

[91] 42 CFR §121.8(a)(1).

[92] Lindblad, Kelsi. "Impact of Changing the CPRA Calculation to a Genotype-Based, Stem Cell Donor-Derived Metric". Report to the OPTN Histocompatibility Committee, January 2022.

[93] Kransdorf EP, Pando MJ, Stewart D, Lindblad K, Bray R, Murphey C, Kaur N, Patel JK, Kim I, Zhang X, Maiers M, Kobashigawa JA, Gragert L. *Stem cell donor HLA typing improves CPRA in kidney allocation*. Am J Transplant. 2021 Jan;21(1):138-147. doi: 10.1111/ajt.16156. Epub 2020 Jul 13. PMID: 32558252.

[94] Tinckam, K. J., R. Liwski, D. Pochinco, M. Mousseau, A. Grattan, P. Nickerson, and P. Campbell. "CPRA Increases with DQA, DPA, and DPB Unacceptable Antigens in the Canadian CPRA Calculator." *American Journal of Transplantation* 15, no. 12 (2015): 3194–3201. https://doi.org/10.1111/ajt.13355.

[95] https://optn.transplant.hrsa.gov/media/2140/histo_meetingsummary_20170321.pdf.

[96] 42 CFR §121.8(a)(5).

[97] Ibid.

[98] 42 CFR §121.8(a)(2).

[99] Douglas Keith and Gayle Vranic. "Approach to the Highly Sensitized Kidney Transplant Candidate." *Clinical journal of the American Society of Nephrology : CJASN* vol. 11,4 (2016): 684-93. doi:10.2215/CJN.05930615

- **Is designed to avoid futile transplants**[100]
    - Proposed changes increase the accuracy of measuring candidate sensitization, which allows programs to better assess potential immunologic incompatibility of a donor organ with a potential candidate. This helps to avoid the risk of worse post-transplant outcomes.
- **Is designed to avoid wasting organs**[101]
    - Proposed changes allow programs to better assess potential immunologic incompatibility of a donor organ with a potential candidate, allowing histocompatibility labs to better assess a candidate's likelihood of positive crossmatch. [102] Late turndowns of donor organs due to unexpected positive crossmatch can lead to organ discard.[103]
- **Promotes the efficient management of organ placement**[104]
    - Proposed changes allow programs to better assess potential immunologic incompatibility of a donor organ with a potential candidate, allowing histocompatibility labs to better assess a candidate's likelihood of positive crossmatch. [105] Late turndowns of donor organs due to unexpected positive crossmatch are likely to increase time to allocate an organ and potentially cold ischemic time.[106]
- This proposal **is not based on the candidate's place of residence or place of listing**.[107]

This proposal also preserves the ability of a transplant program to decline an offer or not use the organ for a potential recipient,[108] and it is specific to each organ type for which HLA reporting for donors and candidates is applicable.[109]

OPTN Strategic Plan

Improve equity in access to transplants

This proposal is intended to improve equity in access to transplants for highly sensitized candidates, whose sensitization may be underrepresented by the current CPRA. This is likely especially true for African American candidates, who proportionally have increased sensitization at the DQA1 and DPB1 loci, which are not accounted for in the current CPRA calculation.[110]

[100] Ibid.
[101] 42 CFR §121.8(a)(5).
[102] Douglas Keith and Gayle Vranic. "Approach to the Highly Sensitized Kidney Transplant Candidate." *Clinical journal of the American Society of Nephrology : CJASN* vol. 11,4 (2016): 684-93. doi:10.2215/CJN.05930615
[103] Cohen, J B et al. "Kidney allograft offers: Predictors of turndown and the impact of late organ acceptance on allograft survival." *American Journal of Transplantation.* 18,2 (2018): 391-401. doi:10.1111/ajt.14449
[104] Ibid.
[105] Douglas Keith and Gayle Vranic. "Approach to the Highly Sensitized Kidney Transplant Candidate." *Clinical journal of the American Society of Nephrology : CJASN* vol. 11,4 (2016): 684-93. doi:10.2215/CJN.05930615
[106] Ibid.
[107] 42 CFR §121.8(a)(8).
[108] 42 CFR §121.8(a)(3).
[109] 42 CFR §121.8(a)(4).
[110] Ibid.

Implementation Considerations

Operations affecting Histocompatibility Laboratories

Histocompatibility laboratories will need to assess whether any of their candidates should have additional unacceptable antigens entered prior to implementation, as per their transplant hospital agreements. Any kidney candidate who will have a CPRA of 99-100% upon implementation will need a laboratory director's signed approval of the listed unacceptable antigens prior to receiving additional allocation priority.[111] The OPTN will provide a blank updated version of the *Candidate CPRA Greater Than 98% Written Approval Form* prior to implementation, so that lab directors are able to provide written approval of unacceptable antigens for the affected candidates. A copy of this form must be available to the OPTN upon request.

Operations affecting Transplant Hospitals

Transplant hospitals will need to assess whether any of their candidates should have additional unacceptable antigens entered prior to implementation. Any kidney candidate who will have a CPRA of 99-100% upon implementation will need a transplant physician or surgeon's signed approval of the listed unacceptable antigens prior to receiving additional allocation priority. The OPTN will provide a blank updated version of the *Candidate CPRA Greater Than 98% Written Approval Form* prior to implementation, so that members are able to provide written approval of unacceptable antigens for the affected candidates. A copy of this form must be available to the OPTN upon request.

Operations affecting the OPTN

The OPTN will provide transplant hospitals and histocompatibility laboratories the ability to enter HLA-DPA1 unacceptable antigens a minimum of two months prior to implementation of the transition to the new CPRA calculator. In addition, the OPTN will provide programs with a report of kidney candidate CPRA and KAS changes, including candidates who will have a CPRA of 99-100% upon implementation a minimum of one month prior to implementation. The OPTN will update the deceased donor racial and ethnic frequencies when updating the HLA equivalency tables. The OPTN Histocompatibility Committee will periodically evaluate the accuracy of the CPRA calculation and whether additional HLA typings need to be incorporated into the frequency data set from the NMDP.

Operations affecting Organ Procurement Organizations

This proposal is not anticipated to affect the operations of Organ Procurement Organizations.

Projected Fiscal Impact

This proposal is projected to have a fiscal impact on the OPTN, but it is not anticipated to have any fiscal impact on histocompatibility laboratories, organ procurement organizations, or transplant hospitals.

Projected Impact on the OPTN

The OPTN Contractor estimates 3,210 hours for implementation. Implementation will involve updates to the CPRA calculation due to the HLA 2021 Equivalency table updates, updates to the Application Programming Interfaces (APIs) and OPTN KPDPP, member communication, news articles, member

[111] OPTN *Policy 8.5.F: Highly Sensitized Candidates*.

training, and education. The OPTN Contractor estimates 220 hours for ongoing support. Ongoing support will involve answering member questions and creating monitoring reports at one and two years post-implementation.

Post-implementation Monitoring

Member Compliance

The Final Rule requires that allocation policies "include appropriate procedures to promote and review compliance including, to the extent appropriate, prospective and retrospective reviews of each transplant program's application of the policies to patients listed or proposed to be listed at the program."[112] This proposal will not change the current routine monitoring of OPTN members. Any data entered into OPTN computer systems may be reviewed by the OPTN, and members are required to provide documentation as requested.

Policy Evaluation

The Final Rule requires that allocation policies "be reviewed periodically and revised as appropriate."[113]

The Histocompatibility Committee will evaluate the effect of this proposal at approximately six and eighteen months post-implementation.

The following metrics, and any others subsequently requested by the Committee, will be evaluated as data become available to compare performance before and after the implementation of this policy:

1. Change in CPRA values for kidney, kidney-pancreas and pancreas registrations on the day of implementation:
    - Distribution of the difference in pre- and post-implementation CPRA
    - The number of registrations for which the change in post-implementation CPRA values resulted in a change in the number of allocation points received
    - The net change in the number of registrations in each CPRA allocation category post-implementation
2. Difference between calculated CPRA and proportion of incompatible deceased kidney donors recovered in the two years before implementation for both pre- and post-implementation CPRA.
3. Count and percent of kidney, kidney-pancreas, and pancreas registrations with unacceptable antigens against loci not included in the current CPRA pre- and post-implementation.
4. Count and percent of kidney, kidney-pancreas, and pancreas registrations with allele-level unacceptable antigens pre- and post-implementation
    - Overall
    - For registrations with unacceptable antigens among the DQA1 alleles that will not be distinguished in the proposed calculator (**Figure 6**)
    - For registrations with an allele-level unacceptable antigen that do not also list the equivalent antigen-level antibody
    - The above metrics stratified by histocompatibility lab and listing center

[112] 42 CFR §121.8(a)(7).
[113] 42 CFR §121.8(a)(6).

5. Cases where a donor with antigen-level typing had a kidney, kidney-pancreas, or pancreas transplanted into a recipient with an allele-specific unacceptable antigen with the donor's antigen as its parent for the Committee to review

The Committee expects to see a change in CPRA for almost all registrations with unacceptable antigens, and particularly large changes in CPRA for registrations with unacceptable antigens without frequencies under the current CPRA. They expect that the proposed CPRA calculation will better reflect the actual proportion of incompatible donors for kidney candidates. They expect that there may be an increase in the utilization of unacceptable antigens against alleles and loci not included in the current CPRA, but this is not a major goal of the project.

The Committee expects to see little increase in the use of allele-level unacceptable antigens shortly after implementation and few cases of transplants where the donor had an antigen-level parent to the recipient's allele-level unacceptable antigen. The Committee will use this data to determine if more comprehensive monitoring or specific criteria in policy for allele-specific unacceptable antigen use are needed.

Conclusion

CPRA has a high impact on kidney and pancreas candidate access to transplant, but the current calculation does not properly assess a candidate's sensitization. The current CPRA calculation used in allocation only captures five of the eleven classic human leukocyte antigen (HLA) loci, with an approximation used for three other loci. In addition, the current CPRA does not account for high resolution (allele-level) unacceptable antigens. In order to properly assess a candidate's sensitization and assign appropriate allocation priority, the Committee is proposing a new algorithm, using an HLA frequency data set derived from the NMDP HSC donor population. This new algorithm will also use genotype data and expand the ethnic categories for donors, increasing both accuracy and inclusiveness.

Policy Language

Proposed new language is underlined (example) and language that is proposed for removal is struck through (~~example~~). Heading numbers, table and figure captions, and cross-references affected by the numbering of these policies will be updated as necessary.

1.2 Definitions

Calculated Panel Reactive Antibody (CPRA)

The percentage of deceased donors expected to have one or more of the unacceptable antigens indicated on the waiting list for the candidate. The CPRA is derived from HLA antigen~~/allele~~, allele, and epitope ~~group and haplotype~~ genotype frequencies for the different ~~ethnic groups~~ populations in proportion to their representation in the national deceased donor population.

5.3.A Reporting Unacceptable Antigens for Calculated Panel Reactive Antibody (CPRA)

In order to list an unacceptable antigen for a candidate on the waiting list, the transplant program must do at least one of the following:

1. Define the criteria for unacceptable antigens that are considered as contraindications for transplant. This may include clarification of unacceptable antigens based on solid phase testing, consideration of prior donor antigens or non-self antigens involved in pregnancies, prior blood transfusion, and unexpected positive crossmatches.
2. Base unacceptable antigens on laboratory detection of human leukocyte antigen (HLA) specific antibodies using at least one solid phase immunoassay with purified HLA molecules.

Transplant programs may establish criteria for additional unacceptable antigens including, but not limited to, multiple unexpected positive crossmatches. ~~CPRA will be derived from HLA antigen/allele group and haplotype frequencies for the different racial and ethnic groups in proportion to their representation in the national deceased donor population. CPRA values will be rounded to the nearest one hundredth percentage.~~

4.6 Calculated Panel Reactive Antibody (CPRA) Calculation

CPRA for a candidate will be calculated automatically when a transplant hospital reports unacceptable antigens to the OPTN.

The equation for CPRA calculation is

$$\text{CPRA} = \sum_i [G_F \times D_i]$$

Table 4-2: CPRA Calculation Values

Where…	Is defined as…
i	The racial or ethnic base population, as reported to the OPTN for deceased donors
G_F	The frequency of HLA genotypes in each specific racial or ethnic population i equivalent to the

Where…	Is defined as…
	unacceptable HLA antigens, alleles, and epitopes reported on the waiting list
D_i	The proportion of donors in each specific racial or ethnic population i in the OPTN deceased donor population

The CPRA derived from this calculation will be rounded to the sixth decimal place. The maximum CPRA is 100%.

The determination of the HLA genotype frequencies G_F used in the CPRA calculation includes all donor alleles equivalent to a candidate's reported unacceptable antigens, alleles, or epitopes according to *Policy 4.10: Reference Tables of HLA Antigen Values and Split Equivalences*. The antigens in *Table 4-3* will have combined frequencies for the purpose of CPRA calculation.

Table 4-3: Unacceptable Antigens with Combined Frequencies for CPRA Calculation

Locus	Antigens with combined frequencies for CPRA calculation
DQA1	01:01, 01:04, 01:05
DQA1	01:02, 01:11
DQA1	03:02, 03:03
DQA1	05:01, 05:05, 05:09, 05:11
DQA1	05:03, 05:07

The OPTN maintains a list of genotype frequencies (G_F) for each reportable unacceptable antigen, allele, and epitope.

4.9 HLA ~~Antigen Values and Split Equivalences~~ Value Updates

~~HLA matching of antigens is based on the antigens which are listed in *Policy 4.10: Reference Tables of HLA Antigen Values and Split Equivalences*.~~ The Histocompatibility Committee must review ~~and recommend any changes needed to~~ the HLA matching and unacceptable antigen equivalency tables and the proportions of donors (D_i) used in CPRA calculation on an annual basis. Changes to the equivalency tables in *Policy 4.10* and proportions of donors (D_i) are eligible for future expedited updates pursuant to OPTN *Bylaw 11.8: Expedited Actions*. ~~For matching purposes, split antigens not on this list will be indicated on the waiting list as the parent antigens and will match only with the corresponding parent antigens.~~

4.10.B: HLA Unacceptable Antigen Equivalences

At the time of the match run, if an antigen or epitope is entered as unacceptable for a candidate, then the candidate will not appear on the match run for donors reported with any of the equivalent antigens described in *Tables 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 4-11, 4-12, 4-13, 4-14, 4-15*, and *4-16* below.

CPRA calculations include all donor alleles equivalent to a candidate's reported unacceptable antigens, alleles, and epitopes.

HLA values listed below as equivalent for the purposes of unacceptable antigen screening are also equivalent for the purposes of reporting HLA typing, with the exception of epitope-based unacceptable antigen assignments in *Table 4-15*.

~~**Table 4-17: Additional Unacceptable Antigen Equivalences to be used in the Calculated Panel Reactive Antibody (CPRA) Only**~~

~~Locus~~	~~Patient Unacceptable Antigen~~	~~Unacceptable DR antigen equivalences used for CPRA calculation~~
~~**DR51**~~	~~51~~	~~2, 15, 16~~
~~**DR52**~~	~~52~~	~~3, 5, 6, 11, 12, 13, 14, 17, 18~~
~~**DR53**~~	~~53~~	~~4, 7, 9~~

~~8.1 Calculated Panel Reactive Antibody (CPRA)~~

~~CPRA is the percentage of donors expected to have one or more of a candidate's indicated unacceptable antigens. CPRA will be calculated automatically when a transplant hospital reports unacceptable antigens to the OPTN according to *Policy 5.3.A: Reporting Unacceptable Antigens for Calculated Panel Reactive Antibody (CPRA)*.~~

~~11.1 Calculated Panel Reactive Antibody (CPRA)~~

~~Pancreas and kidney-pancreas candidates will receive a calculated panel reactive antibody (CPRA) value according to *Policy 8.1 Calculated Panel Reactive Antibody (CPRA)*.~~

#