OPTN

Notice of OPTN Policy Changes

Change Calculated Panel Reactive Antibody (CPRA) Calculation

Sponsoring Committee:	**OPTN Histocompatibility Committee**
Policies Affected:	***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
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	11.1: Calculated Panel Reactive Antibody (CPRA)
Public Comment:	**January 27, 2022—March 23, 2022**
Board Approved:	**June 27, 2022**
Effective Date:	**Pending implementation and notice to OPTN members**

Purpose of Policy Changes

This proposal was developed 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 Human Leukocyte Antigen (HLA) typing and reporting capabilities increase. Updating the Calculated Panel Reactive Antibody (CPRA) calculation to more accurately reflect sensitization is intended to increase access for highly sensitized candidates who have unacceptable antigens at HLA loci and alleles not factored in the current CPRA calculation.

Proposal History

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 by location based on testing methods.[1] 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.[2] CPRA was

[1] 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.
[2] Ibid.

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.[3] In 2011, the HLA-C was added to the algorithm and the HLA and ethnic frequency cohort was updated to January 1, 2007-December 31, 2008.[4]

The OPTN Board of Directors approved changes to the CPRA calculation at the June 2022 meeting.

Summary of Changes

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[5] to a genotype-based algorithm to more accurately and efficiently calculate candidates' sensitization through direct observation of frequencies of alleles within the population.

Implementation

Histocompatibility laboratories and 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 laboratory director's and transplant physician's or surgeon's signed approval of the listed unacceptable antigens prior to receiving additional allocation priority.[6] 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.

OPTN implementation will involve updates to the CPRA calculation due to the December 2021 *Update Human Leukocyte Antigen (HLA) Equivalency Tables* proposal, and updates to OPTN Computer Systems including the Application Programming Interfaces (APIs) and OPTN Waiting List and Kidney Paired Donor Pilot Program (KPDPP). Implementation will also include member communications, training, and education.

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[3] Ibid.

[4] *Proposal to Update the Calculated PRA (CPRA).* OPTN Histocompatibility Committee Report to the Board of Directors. 14 November 2011.

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

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

At the time of implementation, all candidates' CPRA values will be updated to the new calculation. 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 Kidney Allocation Score (KAS) changes, including candidates who will have a CPRA of 99-100% upon implementation a minimum of one month prior to implementation.

Affected Policy Language

New language is underlined (example) and language that is deleted is struck through (~~example~~).

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.

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 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~~

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.~~

~~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)*.~~