# CPRA Calculation with Proposed Additions

## Addition of C, and the use of additional HLA frequencies,

## Public comment  Fall 2011

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# Synopsis

- **This proposal updates HLA frequencies used by the CPRA calculator to better reflect the current definition of HLA antigens and alleles in the donor pool**

- **No policy language will be affected; this will be a programming only effort**

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# These revisions include:

- **Addition of HLA-C frequencies to the calculation**

- **Addition of HLA frequencies for certain antigens and alleles that are better defined than previously**

  - **This applies, in particular to HLA-DQ, in the previous donor pool used for CPRA, the DQ frequencies were largely for "broad" antigens**

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# Frequencies

**Current CPRA is calculated based on the data:**

- HLA frequencies derived from the HLA phenotypes of deceased kidney donors recovered from January 1, 2003 through December 31, 2004

- Ethnic frequencies derived from deceased kidney donors recovered from January 1, 2006 through June 30, 2007

**Proposed CPRA will be calculated based on the data:**

- HLA frequencies derived from the HLA phenotypes of deceased kidney donors recovered from January 1, 2007 through December 31, 2008

- Ethnic frequencies derived from deceased kidney donors recovered from January 1, 2007 through December 31, 2008

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# CPRA and Ethnic Frequencies

- **Proposed frequencies are based on the same methodology as the current ones**
  - **Allele group frequencies were derived by gene counting of the broad and split antigens**
  - **Two, three, four, and five locus haplotype frequencies were estimated by the expectation maximization algorithm using Arlequin computer program (1)**

**1. Leffell MS, Cherikh WS, Land GA, Zachary AA. Improved definition of HLA frequencies among minorities and applicability to estimates of transplant compatibility. Transplantation 2007; 83:964-972**

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# Ethnic Frequencies (Four Major Groups)

- **CPRA is also based on ethnic frequencies for four major groups (White, African American, Hispanic and Asian ethnicities)**

- **Ethnic frequencies were derived based on deceased kidney donors:**

| | Current Frequencies – Donors recovered 01/01/2006-06/30/2007* | | Proposed Frequencies – Donors recovered 01/01/2007-12/31/2008** | |
|---|---|---|---|---|
| | Number | Proportion | Number | Proportion |
| White | 7,337 | 0.689 | 9,811 | 0.687 |
| African American | 1,558 | 0.146 | 2,101 | 0.147 |
| Hispanic | 1,507 | 0.142 | 2,037 | 0.143 |
| Asian | 242 | 0.023 | 333 | 0.023 |
| Total | 10,644 | 1.000 | 14,282 | 1.000 |

**Donors of other ancestry comprised about 1% of total number of deceased kidney donors during each time period. These groups were not included.**

**OPTN** * Based on OPTN data as of September 21, 2007
** Based on OPTN data as of August 19, 2011

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# Proposed CPRA Calculation

1. **Get a list of all unacceptable antigens including equivalences listed in Appendix 3A\* for <u>all</u> unacceptable antigens <u>(including HLA-C)</u>**

**Example:**

- **A kidney candidate is listed with antibodies to A1, B35, DR11, DQ7 <u>and C7</u>**

- **DQ7 is equivalent to DQ7 and DQ3**

- **A1, B35, DR11 <u>and C7</u> are only equivalent to themselves**

- **CPRA calculation will use A1, B35, DR11, DQ3, DQ7 <u>and C7</u> frequencies**

**\* The current version of Appendix 3A can be found on OPTN site at <u>http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_14.pdf</u>**

**OPTN** **Note: Proposed changes to CPRA algorithm are underlined**

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# Proposed CPRA Calculation (cont'd)

**2.** **For each ethnicity separately:**

■ **S1 - Sum all the 1 locus haplotype frequencies (A, B, DR, DQ, _C_)**

■ **S2 - Sum all the 2 locus haplotype frequencies (AB, ADR, ADQ, _AC_, BDR, BDQ, _BC_, DRDQ, _DRC_, _DQC_)**

■ **S3 - Sum all the 3 locus haplotype frequencies (ABDR, ABDQ, _ABC_, ADRDQ, _ADRC_, _ADQC_, BDRDQ, _BDRC_, _BDQC_, _DRDQC_)**

■ **S4 - Sum all 4 locus haplotype frequencies (ABDRDQ, _ABDRC_, _ABDQC_, _ADRDQC_, _BDRDQC_)**

■ **_S5 – Sum all 5 locus haplotype frequencies (ABDRDQC)_**

■ **CPRA for the ethnicity is:**

**probability of a positive crossmatch =**

**1 – probability of a negative crossmatch =**

$$1 - (1 - S1 + S2 - S3 + S4 - S5)^2$$

**OPTN** **Note: Proposed changes to CPRA algorithm are underlined**

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# Proposed CPRA Calculation (cont'd)

- **Since all allele groups weren't observed within all ethnic groups, some locus haplotypes don't have frequencies**

- **DR51, DR52, DR53, Bw4 and Bw6 frequencies are based on the approved equivalences listed in Appendix 3A**

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# Example*

**CPRA based on A1, B35, DR11, DQ3, DQ7 <u>and C7</u>**

**S1 - Sum all the allele (1 locus) frequencies (A, B, DR, DQ, <u>C</u>)**

| | White | African American | Hispanic | Asian |
|---|---|---|---|---|
| **A1** | 0.160000 | 0.053058 | 0.058164 | 0.040948 |
| **B35** | 0.084667 | 0.078837 | 0.160827 | 0.071121 |
| **DR11** | 0.093667 | 0.130396 | 0.091801 | 0.056034 |
| **DQ3** | 0.037833 | 0.024880 | 0.044849 | 0.040948 |
| **DQ7** | 0.177167 | 0.169365 | 0.205326 | 0.150862 |
| **C7** | 0.306000 | 0.211930 | 0.264891 | 0.230603 |
| **Total (S1)** | 0.859334 | 0.668466 | 0.825858 | 0.590516 |

**OPTN**  * **Example is based on the proposed changes and frequencies**

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# Example (cont'd)

CPRA based on A1, B35, DR11, DQ3, DQ7 <u>and C7</u>

- S2 - Sum all the 2 locus haplotype frequencies (AB, ADR, ADQ, <u>AC</u>, BDR, BDQ, <u>BC</u>, DRDQ, <u>DRC</u>, <u>DQC</u>)

| | White | African American | Hispanic | Asian |
|---|---|---|---|---|
| A1; B35 | 0.007427 | 0.002652 | 0.005049 | 0.002155 |
| A1; DR11 | 0.011515 | 0.005535 | 0.006820 | 0.001811 |
| A1; DQ3 | 0.006492 | 0.003281 | 0.002688 | 0.004310 |
| A1; DQ7 | 0.030450 | 0.007929 | 0.008359 | 0.000000 |
| A1; C7 | 0.050117 | 0.025592 | 0.025514 | 0.006022 |
| B35; DR11 | 0.011619 | 0.008921 | 0.019039 | 0.007035 |
| B35; DQ3 | 0.004596 | 0.003118 | 0.008489 | 0 |
| B35; DQ7 | 0.014156 | 0.013501 | 0.041636 | 0.031182 |
| B35; C7 | 0.026219 | 0.006426 | 0.008343 | 0 |
| DR11; DQ3 | 0.003480 | 0.007386 | 0.003162 | 0.000000 |
| DR11; DQ7 | 0.016587 | 0.068527 | 0.081298 | 0.045259 |
| DR11; C7 | 0.029763 | 0.030564 | 0.021730 | 0.021623 |
| DQ3; C7 | 0.014242 | 0.004900 | 0.013913 | 0.003641 |
| DQ7; C7 | 0.057504 | 0.028939 | 0.055567 | 0.022250 |
| Total (S2) | 0.284167 | 0.217271 | 0.301607 | 0.145288 |

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# Example (cont'd)

**CPRA based on A1, B35, DR11, DQ3, DQ7 <u>and C7</u>**

**S3 - Sum all the 3 locus haplotype frequencies (ABDR, ABDQ, <u>ABC</u>, ADRDQ, <u>ADRC</u>, <u>ADQC</u>, BDRDQ, <u>BDRC</u>, <u>BDQC</u>, <u>DRDQC</u>)**

|  | White | African American | Hispanic | Asian |
|---|---|---|---|---|
| A1; B35;DR11 | 0.002966 | 0 | 0.001269 | 0 |
| A1; B35; DQ3 | 0.000712 | 0 | 0.000295 | 0 |
| A1; B35; DQ7 | 0.002400 | 0 | 0.000968 | 0 |
| A1; B35; C7 | 0.001297 | 0 | 0 | 0 |
| A1; DR11; DQ3 | 0.000493 | 0.000459 | 0 | 0 |
| A1; DR11; DQ7 | 0.003938 | 0.001976 | 0.005868 | 0 |
| A1; DR11; C7 | 0.004109 | 0.001304 | 0 | 0 |
| A1; DQ3; C7 | 0.002324 | 0 | 0.000814 | 0.002155 |
| A1; DQ7; C7 | 0.010799 | 0.006607 | 0.000687 | 0 |
| B35; DR11; DQ3 | 0.001121 | 0.001199 | 0.000550 | 0 |
| B35; DR11; DQ7 | 0.002750 | 0.006424 | 0.015761 | 0.007008 |
| B35; DR11; C7 | 0.005739 | 0.000825 | 0.000594 | 0.002272 |
| B35; DQ3; C7 | 0.000811 | 0.000607 | 0.000971 | 0 |
| B35; DQ7; C7 | 0.004432 | 0.000651 | 0.001273 | 0.002621 |
| DR11; DQ3; C7 | 0.001388 | 0.001156 | 0.000476 | 0 |
| DR11; DQ7; C7 | 0.004488 | 0.020741 | 0.022217 | 0.01315 |
| **Total (S3)** | **0.049767** | **0.041949** | **0.051743** | **0.027206** |

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# Example (cont'd)

**CPRA based on A1, B35, DR11, DQ3, DQ7 <u>and C7</u>**
**S4 - Sum all 4 locus haplotype frequencies (ABDRDQ, <u>ABDRC</u>,**
**<u>ABDQC</u>, <u>ADRDQC</u>, <u>BDRDQC</u>)**

| | White | African American | Hispanic | Asian |
|---|---|---|---|---|
| **A1; B35; DR11; DQ3** | 0 | 0 | 0 | 0 |
| **A1; B35; DR11; DQ7** | 0.001540 | 0 | 0.001014 | 0 |
| **A1; B35; DR11; C7** | 0.000992 | 0 | 0 | 0 |
| **A1; B35; DQ3; C7** | 0 | 0 | 0.000350 | 0 |
| **A1; B35; DQ7; C7** | 0.000600 | 0 | 0 | 0 |
| **A1; DR11; DQ3; C7** | 0 | 0 | 0 | 0 |
| **A1; DR11; DQ7; C7** | 0.0014900 | 0.001703 | 0 | 0 |
| **B35; DR11; DQ3; C7** | 0 | 0 | 0 | 0 |
| **B35; DR11; DQ7; C7** | 0.00068 | 0.000321 | 0.000467 | 0.002272 |
| **Total (S4)** | **0.005302** | **0.002024** | **0.001831** | **0.002272** |

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# Example (cont'd)

CPRA based on A1, B35, DR11, DQ3, DQ7 <u>and C7</u>

<u>S5 – Sum all 5 locus haplotype frequencies (ABDRDQC)</u>

|  | White | African American | Hispanic | Asian |
|---|---|---|---|---|
| A1; B35; DR11; DQ3; C7 | 0 | 0 | 0 | 0 |
| A1; B35; DR11; DQ7; C7 | 0.000167 | 0 | 0 | 0 |
| Total (S4) | 0.000167 | 0 | 0 | 0 |

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# Example (cont'd)

**CPRA based on A1, B35, DR11, DQ3, DQ7 <u>and C7</u>**

- CPRA for the ethnicity is: 1 - probability of negative crossmatch $= 1 - (1 - S1 + S2 - S3 + S4 \underline{- S5})^2$

| | White | African American | Hispanic | Asian |
|---|---|---|---|---|
| | | | | |
| S1 | 0.859334 | 0.668466 | 0.825858 | 0.590516 |
| S2 | 0.284167 | 0.217271 | 0.301607 | 0.145288 |
| S3 | 0.049767 | 0.041949 | 0.051743 | 0.027206 |
| S4 | 0.005302 | 0.002024 | 0.001831 | 0.002272 |
| S5 | 0.000167 | 0 | 0 | 0 |
| Probability of a negative crossmatch | 0.144553 | 0.258959 | 0.181337 | 0.280728 |
| Probability of a positive crossmatch | 0.855447 | 0.741041 | 0.818663 | 0.719272 |

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# Proposed CPRA Calculation

3. **Get the final CPRA by applying ethnic weights:**

■ **For each ethnicity multiply CPRA for that ethnicity by ethnic weight**

■ **Sum all the values to get the final CPRA**

**Example:**

|  | White | African American | Hispanic | Asian |
|---|---|---|---|---|
| **CPRA for ethnicity** | 0.855447 | 0.741041 | 0.818663 | 0.719272 |
| **Ethnic weight** | 0.687 | 0.147 | 0.143 | 0.023 |

**CPRA = 0.855447 x 0.687 + 0.741041 x 0.147 + 0.818663 x 0.143 + 0.719272 x 0.023 = 0.83024 or 83%**

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# See the attached spreadsheet for proposed HLA Frequencies

## With the addition of HLA C

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