OPTN/UNOS Histocompatibility Committee

Adding HLA DQA1 Unacceptable Antigen Equivalences Table

Prepared by:
Geoffrey P. Zindren
UNOS Policy Department

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Executive Summary

This proposal intends to bridge a gap between the science and practice of human leukocyte antigen (HLA) compatibility assessments and the realities of computer programming. Policy approved by the OPTN/UNOS Board of Directors in November 2014 requires HLA typing for HLA-DQA1 for deceased donors to be reported to the OPTN, and requires UNOS to change UNet^{SM} programming to allow transplant programs to report DQA1 as an unacceptable antigen. This proposal adds an HLA DQA1 equivalency table to policy that identifies the relationship between parent antigens and corresponding allelic subtypes. The addition of the table allows UNOS staff to program data entry for DQA1 unacceptable antigens/alleles, removing concerns about patient safety due to human error and incorrect data entry.

Adding HLA DQA1 Unacceptable Antigen Equivalences Table

Affected Policies: 4.11 Reference Tables of HLA Antigen Values and Split Equivalences

Sponsoring Committee: Histocompatibility Committee

Public Comment Period: January 25 – March 25, 2016

What problem will this proposal solve?

In November 2014, the OPTN/UNOS Board of Directors approved a policy modification to expand OPTN HLA typing requirements to include DQA1 and DPB1 as part of the allocation process.[1] During the implementation phase of this project, the Histocompatibility Committee noticed an incongruity between the unacceptable antigen relationships within the DQA1 locus and how UNOS programmed DQA1 unacceptable antigen data entry. Because the policy approved by the Board in November 2014 did not include an equivalency table for DQA1, UNOS programmed a one-to-one exclusionary relationship for unacceptable antigens. In the one-to-one relationship, candidates are only excluded from donors when there is an exact match between donor type entered and the unacceptable antigen/allele entered for candidates. For example, a donor whose phenotype is recorded as DQA1*03:01 will NOT be excluded from a candidate when a center marks the DQA1*03 allele as unacceptable for that candidate. The DQA1*03:01 donor type will only be excluded if a transplant center also marked DQA1*03:01 as unacceptable.

However, within HLA there are broad categories of DQA1 types and specific subtypes that belong to each category. The broad category is a simple way to represent all the subtypes as unacceptable antigens without having to enter each one. It is critical that when the broad category is entered as unacceptable, no donor with one of the subtypes is ever offered to the candidate. Hence, the current system, with its one-to-one exclusionary relationship, creates a potential problem since it does not exclude the subtypes of the broad category automatically, and relies on members to enter the broad antigen (DQA1*03) and all of the corresponding subtypes (DQA1*03:01, 03:02, and 03:03) in order to exclude donors with that broad antigen from the match run.

Members of the Histocompatibility Committee find that the current system creates potential patient safety issues. Ideally, if a member wants to exclude donors with DQA1*03, the system should automatically exclude donors with the corresponding subtypes. Under the current input method, it is possible for candidates who cannot accept broad categories of antigens to match with donors who have a subtype of the parent if the transplant program has not manually selected to exclude each subtype.

By adding a DQA1 equivalency table, UNOS staff can program UNet to recognize the relationships between parent antigens and subtypes, and which subtypes to automatically exclude if a broad antigen is chosen.

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[1] Alcorn, James. Policy Notice: Expanding HLA Typing Requirements. December 12, 2014. http://optn.transplant.hrsa.gov/media/1140/policy_notice_12-2014.pdf (last visited January 6, 2016).

Why should you support this proposal?

Adding a DQA1 equivalency table will help alleviate some of the data entry burden on OPTN/UNOS members, reduce risks to patient safety, and decrease the likelihood of inappropriate organ allocation. This proposal will help reduce the burden on members in two ways. First, it will minimize human error by simplifying entry of unacceptable antigens for DQA1. Second, adding the equivalency table allows UNOS to program DQA1 unacceptable antigen entry in the same manner as other HLA loci. Uniformity across HLA data entry screens will help eliminate errors due to members having to remember special rules for DQA1 entry.

By relieving the burden of data entry on members, there is a corresponding reduction in risks to patient safety. Including subtypes as unacceptable antigens automatically when parent antigens are selected as unacceptable antigens reduces the risk of graft rejection due to the presence of incompatible DQA1 subtype antigens. Additionally, this proposal has the potential to reduce cold ischemia time and organ discard caused by scenarios when a transplant program accepts an organ offer under the assumption that a donor's and candidate's HLA is compatible, only to find that the physical crossmatch is positive and the organ cannot be transplanted into the intended candidate.

How was this proposal developed?

The Committee developed this proposal in response to the implementation of previously approved policies. The Committee noticed that selection of broad DQA1 antigens did not exclude candidates from matching with donors that had a subtype of that antigen. UNOS staff developed a solution to avoid immediate patient safety issues and to implement the DQA1 typing requirements as planned by posting explanatory text in the DQA1 selection field. However, programing cannot be changed to automatically associate DQA1 parent alleles with the corresponding subtypes until an equivalency table is created. Therefore, the Committee quickly created a DQA1 equivalency table based on the ImMunoGeneTics HLA database maintained by the European Bioinformatics Institute[2]. The table defines the convention to use for the relationship between the broad antigens and their corresponding subtypes. The Committee then voted to submit the table for public comment.

How well does this proposal address the problem statement?

By creating a DQA1 equivalency table, UNOS staff can program UNet to recognize the relationship between DQA1 parent alleles and corresponding subtypes, and directly solve the problem related to DQA1 unacceptable matching. Currently, data on how often incompatible matches occur between broad antigen and corresponding subtype are not collected for DQA1. The Committee recognized the patient safety issue prior to the UNet update on January 21, 2016. Nonetheless, the presence of the potential patient safety issue is real and one that the Committee wants to proactively address.

Which populations are impacted by this proposal?

Sensitized candidates will be positively impacted by this proposal, especially those who have antibodies against subtype antigens of DQA1. Adding the DQA1 equivalency table will reduce the likelihood that candidates will receive an incompatible donor offer based on failure to select all subtype antigens associated with a broad DQA1 allele, relieving potential safety issues associated with DQA1 unacceptable antigen entry. This proposal also relieves the burden on member labs, transplant programs, and OPOs by reducing data entry requirements in UNet where human error can affect patient safety,

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[2] http://www.ebi.ac.uk/ipd/imgt/hla/

allocation, and cold ischemia time. The proposal also alleviates any confusion among members by creating a uniform method of entering unacceptable antigens in UNet among all HLA loci.

How does this proposal support the OPTN Strategic Plan?

1. *Increase the number of transplants:* This proposal increases the number of transplants by avoiding incompatible donors and decreasing prolonged cold ischemia time or discard of the donor organ.
2. *Improve equity in access to transplants:* The proposal will allow sensitized candidates to receive more offers from compatible donors.
3. *Improve waitlisted patient, living donor, and transplant recipient outcomes:* This proposal will improve recipient outcomes by automatically preventing recipients that are sensitized to a broad antigen from receiving a donor organ with a subtype of that antigen.
4. *Promote living donor and transplant recipient safety:* This proposal promotes transplant recipient safety by avoiding matches between donors and candidates that could result in acute rejection, prolonged cold ischemia time, or discard of the donor organ. This is the primary goal of this proposal.
5. *Promote the efficient management of the OPTN:* This proposal promotes efficient management of the OPTN by aligning the entry for DQA1 with other HLA loci already in policy. Users will be relieved of following special rules for data entry regarding one locus.

How will the sponsoring Committee evaluate whether this proposal was successful post implementation?

This policy will be evaluated approximately 1 and 2 years post-implementation to determine whether the number of organs refused due to a positive crossmatch has decreased.

How will the OPTN implement this proposal?

This proposal will require a small programming effort in UNet^{SM}. This project is expected to be implemented in conjunction with other HLA projects scheduled in 2016. Additionally, the addition of the DQA1 equivalency table could be included in a KPD programming effort also scheduled for 2016.

The OPTN/UNOS will notify members in advance of any changes to the system. To communicate these changes, the OPTN/UNOS will use standard communication vehicles such as system notices, member e-newsletters, Transplant Pro articles and Tech News articles.

Corresponding instructional programming will depend on the development and implementation plan for the proposal.

How will members implement this proposal?

Members will need to be aware when the changes to the system occur and change how they enter unacceptable antigens for DQA1.

Will this proposal require members to submit additional data?

Members will not need to submit additional data.

How will members be evaluated for compliance with this proposal?

The proposed language does not change any member compliance requirements, so there will be no need to evaluate member compliance with the proposal.

Policy or Bylaw Language

Proposed new language is underlined (example) and language that is proposed for removal is struck through (~~example~~)

4.11 Reference Tables of HLA Antigen Values and Split Equivalences

Tables 4-3, 4-4, and *4-5* show patient-donor antigen combination and whether they are mismatches. For each candidate antigen, the donor antigens that are not mismatched are listed below. All other combinations are considered mismatches. Antigens with an * indicate an allele that may not have a World Health Organization (WHO)-approved serologic specificity. Antigens given **99 means the patient locus was not tested.

Table 4-3: HLA A Matching Antigen Equivalences

Patient A Locus Antigen	*Equivalent Donor Antigens*
1	1
2	2, 203
3	3
9	9
10	10
11	11
19	19
23	23
24	24, 2403
25	25
26	26
28	28

Patient A Locus Antigen	*Equivalent Donor Antigens*
29	29
30	30
31	31
32	32
33	33
34	34
36	36
43	43
66	66, *6601, *6602
68	68
69	69

Patient A Locus Antigen	*Equivalent Donor Antigens*
74	74
80	80
203	203, 2
210	210, 2
2403	2403, 24
*6601	*6601, 66
*6602	*6602, 66
** 99	(No equivalent)

Table 4-4: HLA B Matching Antigen Equivalences

Patient B Locus Antigen	Equivalent Donor Antigens
5	5
7	7, 703
8	8
12	12
13	13
14	14, 64, 65
15	15
16	16
17	17
18	18
21	21
22	22
27	27
35	35
37	37
38	38

Patient B Locus Antigen	Equivalent Donor Antigens
39	39, 3901, 3902, *3905
40	40, 61
41	41
42	42
44	44
45	45
46	46
47	47
48	48
49	49
50	50, 4005
51	51, 5102, 5103
52	52
53	53
54	54

Patient B Locus Antigen	Equivalent Donor Antigens
55	55
56	56
57	57
58	58
59	59
60	60
61	61
62	62
63	63
64	64
65	65
67	67
70	70, 71, 72
71	71, 70
72	72, 70
73	73
75	75, 15

Patient B Locus Antigen	Equivalent Donor Antigens
76	76, 15
77	77, 15
78	78
81	81
82	82, *8201
703	703, 7
*0804	*0804, 8

Patient B Locus Antigen	Equivalent Donor Antigens
*1304	*1304, 15, 21, 49, 50
2708	2708, 27
3901	3901, 39
3902	3902, 39
*3905	*3905, 39
4005	4005, 50

Patient B Locus Antigen	Equivalent Donor Antigens
5102	5102, 51, 53
5103	5103, 51
7801	7801
*8201	*8201, 82
** 99	(No equivalent)

Table 4-5: HLA DR Matching Antigen Equivalences

Patient DR Locus Antigen	*Equivalent Donor Antigens*
1	1, 103
2	2
3	3
4	4
5	5
6	6
7	7
8	8

Patient DR Locus Antigen	*Equivalent Donor Antigens*
9	9
10	10
11	11
12	12
13	13
14	14, 1403, 1404
15	15

Patient DR Locus Antigen	*Equivalent Donor Antigens*
16	16
17	17
18	18
103	103, 1
1403	1403, 14, 6
1404	1404, 14, 6
** 99	(No equivalent)

*** Indicates an allele; may not have a WHO-approved serologic specificity**

**** Code 99 means not tested**

Examples of how "Matching Antigen Equivalences" works:

If patient has B70: Donors with B70, B71, and B72 are considered not mismatched.

If patient has B71: Donors with B71 and B70 are considered not mismatched. Donors with B72 are considered mismatched.

Table 4-6: HLA A Unacceptable Antigen Equivalences

Patient's Unacceptable A Locus Antigen	*Donor Equivalent Antigens*
1	1
2	2, 203, 210
3	3
9	9, 23, 24, 2403
10	10, 25, 26, 34, 66, *6601, *6602, 43
11	11
19	19, 29, 30, 31, 32, 33, 74
23	23
24	24
25	25
26	26
28	28, 68, 69
29	29
30	30
31	31
32	32
33	33
34	34
36	36
43	43
66	66, *6601, *6602
68	68
69	69
74	74
80	80
203	203
210	210
2403	2403
*6601	*6601
*6602	*6602

Table 4-7: HLA B Unacceptable Antigen Equivalences

Patient's Unacceptable B Locus Antigen	*Donor Equivalent Antigens*
5	5, 51, 5103, 52,78
7	7, 703
8	8
12	12, 44, 45
13	13
14	14, 64, 65
15	15, 62, 63, 75, 76, 77
16	16, 38, 39
17	17, 57, 58
18	18
21	21, 49, 50, 4005
22	22, 54, 55, 56
27	27
35	35
37	37
38	38
39	39, 3901, 3902, *3905
40	40, 60, 61
41	41
42	42
44	44
45	45
46	46
47	47
48	48
49	49
50	50, 4005
51	51, 5103
52	52
53	53
54	54
55	55
56	56
57	57
58	58
59	59
60	60
61	61
62	62
63	63
64	64
65	65
67	67
70	70, 71, 72
71	71
72	72
73	73
75	75
76	76
77	77
78	78
81	81
82	82, *8201
703	703
*0804	*0804
*1304	*1304
2708	2708
3901	3901
3902	3902
*3905	*3905
4005	4005, 50
5102	5102
5103	5103
7801	7801, 78
*8201	*8201, 82
Bw4	Bw4, 5, 13, 17, 27, 37, 38, 44, 47,49, 51, 52, 53, 57, 58, 59, 63, 77
Bw6	Bw6, 7, 8, 14, 18, 22, 2708, 35, 39, 40, 41, 42, 45, 48, 50, *4005, 54, 55, 56, 60, 61, 62, 64, 65, 67, 70, 71, 72, 75, 76, 78, 81, 82

Table 4-8: HLA C Unacceptable Antigen Equivalences

Patient's Unacceptable C Locus Antigen	*Donor Equivalent Antigens*
w1	w1
w2	w2
w3	w3, w9, w10
w4	w4
w5	w5
w6	w6
w7	w7
w8	w8
w9	w9
w10	w10
*12	*12
*14	*14
*15	*15
*16	*16
*17	*17
*18	*18

Table 4-9: HLA DR Unacceptable Antigen Equivalences

Patient's Unacceptable DR Locus Antigen	*Donor Equivalent Antigens*
1	1
2	2, 15, 16
3	3, 17, 18
4	4
5	5, 11, 12
6	6, 13, 14, 1403, 1404
7	7
8	8
9	9
10	10
11	11
12	12
13	13
14	14, 1403, 1404
15	15
16	16
17	17
18	18
103	103
1403	1403
1404	1404
51*	51
52*	52
53*	53

Table 4-10: HLA DQ Unacceptable Antigen Equivalences

Patient's Unacceptable DQ Locus Antigen	*Donor Equivalent Antigens*
1	1, 5, 6
2	2
3	3, 7, 8, 9
4	4
5	5, 1
6	6, 1
7	7, 3
8	8, 3
9	9, 3

Table 4-11: HLA DQA1 Unacceptable Antigen Equivalences

Patient's Unacceptable DQA1 Locus Antigen	*Donor Equivalent Antigens*
01	01, 01:01, 01:02, 01:03, 01:04, 01:05, 01:06, 01:07, 01:08, 01:09, 01:10, 01:11, 01:12
01:01	01:01
01:02	01:02
01:03	01:03
01:04	01:04
01:05	01:05
01:06	01:06
01:07	01:07
01:08	01:08
01:09	01:09
01:10	01:10
01:11	01:11
01:12	01:12
02	02, 02:01
02:01	02:01
03	03, 03:01, 03:02, 03:03
03:01	03:01
03:02	03:02
03:03	03:03
04	04, 04:01, 04:02, 04:04
04:01	04:01
04:02	04:02
04:03N	04:03N
04:04	04:04
05	05, 05:01, 05:02, 05:03, 05:04, 05:05, 05:06, 05:07, 05:08, 05:09, 05:10, 05:11
05:01	05:01
05:02	05:02
05:03	05:03
05:04	05:04

Patient's Unacceptable DQA1 Locus Antigen	*Donor Equivalent Antigens*
05:05	05:05
05:06	05:06
05:07	05:07
05:08	05:08
05:09	05:09
05:10	05:10
05:11	05:11
06	06, 06:01, 06:02
06:01	06:01
06:02	06:02

***Indicates an allele; may not have a WHO-approved serologic specificity**

*****Please refer to the end of this section for information**

Examples of how "Unacceptable Antigen Equivalences" works:

If a patient has B70 listed as an "unacceptable antigen": Donors typed as B70, B71, and B72 are considered unacceptable. Donors typed as B73 and B75 are considered acceptable.

Additional Unacceptable Antigen Equivalences to be used in the Calculated PRA Only:
DR51 should also include DR2, DR15, and DR16.
DR52 should also include DR3, DR5, DR6, DR11, DR12, DR13, DR14, DR17, and DR18.
DR53 should also include DR4, DR7, and DR9.

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