

Interpretation of HLA Typing Results for Entry into UNetsm Implications for the OPTN/UNOS HLA Matching Algorithm

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The definition of HLA antigens began with the discovery that white cells from different individuals can be discriminated from each other by antibodies made by people exposed to allogeneic cells through pregnancy or transfusion (1). Today, using molecular methods, we are able to define hundreds of different HLA alleles that differ by one or more nucleotides and, in most cases, one or more amino acids (2). Even single amino acid differences can result in immunologic responses against donor antigens (3,4). Allelic level differences in HLA antigens have been shown to affect graft survival, with the best kidney allograft survival occurring in individuals matched at the allele level (5). Nonetheless, for cadaveric kidney transplantation, matching at the allele level would be impractical and cost-prohibitive. Therefore, matching at the “antigen” level is still considered the standard method by which donor kidneys are allocated through UNOS. Zero antigen mismatched kidneys still have significantly better outcomes than all other transplants. (6)

UNOS provides a list of antigens that may be entered through UNetsm; this list forms the basis of the HLA matching algorithm for cadaveric kidney and pancreas allocation (7). The intent of the algorithm is to match antigens as closely as possible, taking into account uncommon or poorly defined antigens that may be misidentified as other, usually more common, antigens. The algorithm allows each antigen to match itself and, in some instances, other related antigens. In some cases, one way matching of rare antigens with a closely related common antigen may be permitted due to the relative disadvantage to the patient with rare antigens in receiving a well-matched kidney. The list of antigens and criteria are reviewed annually. All antigens recognized by the World Health Organization (WHO) Nomenclature Committee are on the list; in addition, the list includes some 4-digit names representing alleles that may be readily identified by low resolution molecular testing and represent unique antigens, not yet recognized by the WHO serologic nomenclature.

Because the criteria have changed over the years and also because the identification of antigens has improved over time, there is some confusion as to how the match algorithm works (7). The greatest confusion involves “splits” – i.e., division of a single antigen into subtypes based on previously unrecognized differences. Serological identification of some splits can be difficult, especially when one of the splits occurs at low frequency and/or when appropriate serological reagents are difficult to find. In recognition of the problems associated with the identification of rare splits, the Histocompatibility Committee has defined criteria that determine which splits (antigen subtypes) match only themselves and which match the parent antigen as well. (See examples below.) These criteria incorporate the consensus typings for antigens reported by several proficiency testing (PT) and cell exchange programs, as well as data from molecular typing kits. They are based on the premise that antigens identified consistently by participating laboratories should be readily definable during routine cadaver donor testing.

Unfortunately, an obvious consequence of this system is that non-equivalence in matching may occur when one split is commonly identified and the other split is not well defined. When typing potential organ recipients, the laboratory has the time to do additional testing to clear up any ambiguities before the recipient is placed on the waiting list. However,

the rapid typing of cadaver donors does not always allow time to resolve these ambiguities. Therefore, a misinterpretation of data is more likely to occur for difficult-to-assign antigens with a donor than for the recipient type. This is becoming less of a problem as more labs use molecular typing for donor testing. Nonetheless, the Histocompatibility Committee recognizes the problems inherent in the typing of donors and has tried to address them in the structure of the matching criteria. The criteria used take into account the desire to match donor and recipient as closely as possible, considering those situations where there may be a high degree of difficulty in identifying the correct antigen. The criteria differ somewhat for Class I and II antigens, so they are discussed separately below.

MATCHING FOR HLA DR

Compared to HLA A and B, the rules for DR are fairly simple. Some splits of DR match other splits and some do not. This has been based on the following: Antigens that reach 90% consensus on Proficiency testing are considered equivalent to themselves, the parent or broad antigen, if applicable, and any reportable alleles of the antigen that have not reached 90% consensus. This is best shown by example:

Ex. A donor is entered as a DR15. The donor will match a recipient with DR15 or the parent antigen, DR2. It will not match DR16 (the other split of DR2), because typing for DR15 has achieved >90% consensus in proficiency testing.

Ex. A donor is entered as DR16. The donor will match a recipient with DR2, 15 or 16. Since DR16 has not yet reached 90% consensus, it will match itself, the parent antigen, and the other split.

Ex. A donor is entered as DR14. This donor will match DR14, the parent antigen DR6, and DR1403 or 1404. It will not match DR13 (the other split of DR6), since both DR13 and 14 have reached >90% consensus. DR1403 and 1404 have not reached consensus; nonetheless, some labs have the capability of reporting these antigens, and may do so if they are unequivocally identified.

Despite the fact that some DR splits match other splits of the same broad DR antigen, it is highly recommended that ALL identified splits be entered into UNetsm for both donors and recipients. In most cases, this is routinely done. The frequency of reporting recipients as the parent DR antigen between 1995 and 2000 was less than 5% for all parent antigens except DR3. For DR3, 44% of all typings were reported as DR3 and not DR17 or 18. This number is, in part, due to reporting of molecular typings as DR3 instead of DR17 or 18. Most likely due to the decision of the WHO to name all DR3 alleles using the broad antigen designation DRB1*03, rather than DRB1*17 or DRB1*18 as was done for the splits of DR2, 5, and 6. However, it is possible to differentiate DR17 from DR 18 using molecular testing. To do this, DRB1*0301 must be differentiated from DRB1*0302/*0303. If this is done, then those strings of alleles including DRB1*0301 should be listed as DR17, NOT DR3, no matter how many alleles are included. This is because the frequency of DRB1*0301 is so high compared to any other DRB1*03 allele. This can be seen in the HLA Dictionary report (2) of the number of alleles randomly typed for NMDP and found to be DRB1*03. Of those typings, 12,867 were identified as DRB1*0301, 377 were DRB1*0302/*0303, and only 12 other cells were typed with other DRB1*03 alleles. As can be seen from this data, despite the number of alleles that may be included in a string containing DRB1*0301, the overwhelming probability is that the serologic

type is DR17, due to the high frequency of DRB1*0301. While matching will occur between broad antigens and their splits, it is of importance to the integrity of the UNOS data that whenever DR split antigens can be identified with confidence, they should be reported as splits. Having accurate, specific data available in the UNOS computer will allow the best possible analysis of matching as it relates to transplant outcomes.

UNetsm has also been updated to allow entry of data for DR51, 52, 53, and DQ. DR51, 52, 53 and DQ can all be entered as unacceptable antigens if appropriate. While it is not required that labs enter this information, it can be of significant value, not only for ruling out unacceptable antigens but also in providing information on these loci for data analysis. Whenever this information is available, it should be entered, on both cadaver typings and follow-up forms for UNET.

MATCHING FOR CLASS I, HLA A AND B

For Class I (HLA-A and -B), the rules are more complex because of the greater number of splits and hybrid types, especially at the B locus. For broad (parent) antigens, the broad antigen will only match splits that do not consistently reach 90% consensus on PT. Because of this, antigens should be reported as splits whenever possible. In some cases, antigens or alleles that are not true splits may be assigned to a broad antigen if it is likely that the broad antigen will be assigned when this antigen or allele is present.

- Ex. Donors with A2403 or A24 will match A2403 or A24, but not A23 or 9.
- Ex. Donors with B7 will match either B7, 703, 2708 or 81 recipients, but recipients with B7 will only be matched with B7 and 703 donors.
- Ex. Donors with B15 will only match B15, 75, 76, 77, *1304. Donors with each of these equivalents will match B15 recipients as well as themselves, but not each other. B15 will not match B62 or B63.

Antigen splits that can be routinely typed by most laboratories are considered equivalent to themselves, but not the parent antigen or other splits of the parent.

- Ex. Donors with B55 will match only B55 and the rare antigen *8201, not the parent B22 or the splits B54 or 56.
- Ex. Donors with A32 will only match A32, not the parent antigen A19 or other splits of 19 (A29, 30, 31, 32, 33, 74).
- Ex. Donors with B51 will match only B51 and B5102 and B5103, the less well-defined splits of B51. It will not match the parent antigen B5 or the other split, B52.

Only a few 4 digit antigens or alleles are included in the list of antigens that can be entered into the UNOS computer. If typing is performed by molecular methods and an allele found on the UNOS antigen list is identified, it should be entered as that allele, without conversion to a serologic type. Some of these alleles are not considered to be splits of other antigens, but nonetheless are commonly misidentified as those antigens.

Ex. Donors with B15, 21, 49 and 50 are considered equivalent to recipients with B*1304, and a donor with B*1304 is considered a match for 15 and 21 as well *1304 recipients. This allele has been reported to type as B21x15 and is Bw4 associated.

Ex. Donors with B*8201 will match B45, 22, 54, 55, 56, as well as itself.

Like for Class II, UNetsm has also been updated to allow entry of data for Cw, even though it is not required that labs enter this information. This can be of significant value, both in terms of ruling out unacceptable antigens and in providing information on these loci in the database. The low resolution equivalent of all Cw locus antigens and allele groups may be entered as unacceptable antigens, if warranted. Whenever Cw typing is available, it should be entered, on both cadaver typings and follow-up forms for UNetsm.

CONVERSION OF MOLECULAR TYPES FOR UNOS MATCHING PURPOSES

Despite the maintenance of antigen level typing as the OPTN/UNOS allocation standard, laboratories have been changing to molecular typing procedures for both Class I and Class II HLA typing for transplant candidates and donors. These typing methods, particularly SSP, have permitted rapid HLA typing that does not rely on viable cells, significant numbers of lymphocytes, or adequate antigen expression on different cell types. Thus, testing can be performed using small samples of blood or other tissue that would be inadequate for serologic typing, and provides a highly reliable, reproducible method of HLA typing. This has been particularly useful for Class II typing. Molecular Class I typing, while reproducible, has created new problems when the issue of defining equivalent “antigens” arises.

When allelic nomenclature was initiated, it was designed to reflect the existing serological nomenclature. Thus, the letter designates the locus (A, B, C, etc.), the first two digits correspond to the presumed serological grouping (A*01 = A1), and the subsequent digits reflect the individual alleles that encode the same serologically equivalent products (A*0101, 0102, 0103, etc. all encode the serological product A1). However, as new alleles were discovered in cells never tested by serology, names of alleles were derived based on amino acid sequence similarities that did not always result in similar serology. For example, the allele B*4005 has several sequence similarities with other B*40 alleles, but types serologically as a “short” B50 and has even been given a unique serologic designation, B4005. In several other cases, the molecular nomenclature cannot be directly equated to the corresponding serologic designation.

To make matters more complex, in most instances related sequences have been grouped and named according to “split” serologic designations, but in some other cases, according to the broad antigen group. The most complex of these is the broad HLA B*15 group that includes all of the B15 and B70 “splits”. The use of the B15 (or other) broad antigen designation, whether derived serologically or by molecular methods, can cause incorrect donor-recipient “matching” and can actually render molecular typing less specific, and for these purposes, less accurate, than serologic typing. This is not due to inaccurate typing by molecular methods, but is due to inappropriate interpretation of the serologic equivalent.

Because of these complexities, questions have been raised as to how molecular Class I typing results should be entered into UNetsm and what level of resolution is required. These questions have been extensively discussed at meetings of the Histocompatibility Committee and in many other venues. An “official” list of UNOS Molecular Equivalents has been discussed, but at the current time, the Histocompatibility Committee is of the opinion that it is not

logistically feasible to assign antigen equivalents for every allele and keep the list current. Thus, it is up to each laboratory to determine which antigen from those available for entry into the UNOS computer should be used for a particular allele or group of alleles. Recommendations have been provided in a previous report (8) and have been expanded upon here as guidance for UNOS-member HLA laboratories.

The first principle to consider is based on UNOS Standard E1.100: "**The level of resolution of HLA typing must be appropriate for the clinical application**" (9). (The corresponding ASHI standard has been sent for approval by CMS.) Allocation is currently based on types that can be defined by "readily available reagents" [Standard E2.110 (9)]. Transplant centers are expected to type for identified antigen "splits" when there has been a national consensus regarding the definition of those "splits". The OPTN/UNOS matching algorithm is based on matching of splits whenever possible. This is not likely to change in the near future since patients' unacceptable antigens and crossmatch test results are defined by serological reactions. Standard E1.100 is therefore taken to mean that if molecular typing is used, the resolution must allow serologic equivalent types to be assigned at a level appropriate for organ allocation. That is, molecular typing must be able to assign all splits clearly identifiable by serology. For most types, low resolution (2-digit) Class I molecular typing provides the appropriate serological equivalent. However, for the low resolution molecular types B*15 and B*40, as well as numerous other examples, this is NOT true (see table). For alleles whose serology does not correspond to the low resolution type, the most probable serologic equivalent should be used. This standard requires laboratories to report the correct serological equivalents for the UNOS application in order to assure the most appropriate allocation and to allow screening for unacceptable antigens. Some examples of conversion of groups of alleles to the appropriate serologic type are provided here, along with examples of the consequences of inappropriate conversion.

Example #1: Donor HLA-B = B*1501101/01102N/013/04/07/26N/27/30/32-35/38/45/50/58/60/63 -

Correct Entry: Enter B62

Match result: B62 would be a "zero mismatch" for B62 recipients only. The alleles B*1501, *1504, *1507, *1527, *1530, *1532, *1535, *1538, and *1545 have been defined in the HLA "Dictionary" (2) as B62. The remaining (rare) alleles type as B15, are null, or are undefined. Based on frequencies of these alleles, B62 is the most likely serologic equivalent for the above type and should be entered into UNET.

Incorrect Entry: B15

Match result: B15 matches recipients with B15, B75, B76, B77 and B*1304 (note the latter two are Bw4 associated, while the possible donor types all have Bw6). B15 does not match B62, B*1501, or other alleles with B62 serology equivalents. Many potential recipients would inappropriately be left out of consideration for a zero antigen mismatch, while those recipients selected as zero mismatches would actually be mismatched at the split level with the donor. B15 should never be entered into UNetsm with a low resolution typing containing a B*1501 allele.

Example #2 - Donor HLA-B = B*40011/012/07/14/22N/25/30/31/33/34/42

Correct Entry: Enter B60.

Match result: B60 would match B60, but not 40 or 61. The B60-defined alleles include B*4001, *4007, *4010, *4031, and *4034 (3). B60 should be entered into UNET.

Incorrect Entry: Enter B40

Match result: B40 matches recipients with B40 and B61, but not B60. As above, many potential recipients would inappropriately be left out of consideration for a zero antigen mismatch, while those selected would not actually receive a zero mismatched kidney. B40 should never be entered into UNetsm with a low resolution typing containing a B*4001 allele.

Two alleles that formerly were misidentified by molecular type were B*1522 and 1559, which serologically typed as B35. These allele designations have been deleted by WHO and the alleles have been renamed B*3543 and 3544 to more accurately reflect their serologic type (11). Therefore, any patient currently listed in UNetsm as B*1522 should be changed to B35.

An appropriate strategy for Class I molecular typing for UNOS laboratories should at least include generic level typing for all HLA-A and -B types, typing for Bw4 and Bw6 epitopes, and typing for allelic subgroups of B*15 and B*40 that can distinguish the common alleles defining the serological splits. For many years, the National Marrow Donor Program (NMDP) has required that typing laboratories using molecular methods at least be able to distinguish the serologically distinct subgroups of B*15 and B*40. As a result, primers and probes that distinguish the major serologic splits are readily available from commercial sources. Although these reagents may not perfectly discriminate *all* the B*15 or B*40 types, they will be able to distinguish an allele group that includes the common allele B*1501 (B62), from groups that include B*1502 (B75), B*1516/17 (B63) or B*1503 (B72). *Neither recipients nor donors should be entered into UNOS as B15 or B40 unless there is no other appropriate alternative.* For other types, when only low resolution typing is used, the laboratory may consider the most likely alternative allele(s) and not require high resolution testing to enter the type into UNET. For example, although it is known that A*3204 corresponds serologically to A3 rather than A32 (see table), that allele is less common than the other A*32 alleles (2). If the typing identifies only the A*3204 allele, then it should be listed as A3. However, since this is a low frequency event, an individual generically typed as A*32 and including A*3204 may be entered as A32 without any requirement for further testing. In summary, “if the primer or probe pattern identifies a group of alleles that include one or more common alleles with the same known serologic equivalents and other less common alleles with or without serologic equivalents, the common serologic equivalent should be reported”(10).

An important consideration is that typing for the Bw4 and Bw6 epitopes is now *required by UNOS*. Bw4 or Bw6 should be entered based on the presence of the epitope on a B locus antigen and not A locus antigens with the Bw4 or Bw6 sequence. Reporting the Bw4/w6 type provides important additional information to allow the appropriate match to be made. There are several low resolution types that include alleles with aberrant Bw4 or Bw6 sequences, such as B*0802/03 and B*4409 (see Table1) or variable Bw4/Bw6 sequences, as for B*15. Consideration of those reactions should allow the most appropriate choice for UNOS data entry. For those examples of alleles (mostly rare) that retain their conventional serological equivalent specificity, but have a non-conventional Bw4 vs. Bw6 epitope, such as B*0802 and *0803, entering the donor as B8 and also entering Bw4 would be the appropriate action to match the donor and recipient and correctly rule out potential recipients with donor-specific antibodies. Another example, B*5607, types serologically as B56, Bw4 and should be entered as such. In the case of the Bw6 positive allele B*4409, it should be entered into UNOS as B45, Bw6, since

it is reported by serology labs as B45. The importance of the new UNOS requirement for entry of Bw4 and Bw6 types for donors is especially evident in these circumstances, which collectively are not rare. As long as donor Bw4 and Bw6 types are entered appropriately, kidneys will not be shipped to patients who have known antibodies to Bw4 or Bw6, even when the donor antigen has an unusual Bw4/Bw6 association.

Still another complication involves the molecular detection of serologically null alleles. The "null" variant of DRB4 (DR53) is common in individuals with the DR7, DQ9 haplotype (12). Although the updated UNetsm software now allows laboratories to assign DR53 as present ("P") or absent ("N"), no laboratory should assign DR53 as present if the associated DR type is DR7 in conjunction with DQ9 and molecular typing for DRB4 has only been at low resolution, since low resolution typing usually assigns the null allele as present. The inappropriate assignment of DRB4 (DR53) could unfairly rule out patients with DR53 listed as an unacceptable antigen. This could even occur in a patient with the DR7 type and a "zero mismatched" donor if a DR53 antibody was identified as unacceptable. Null variants of many of the HLA-A and B locus types are also seen at a low frequency, especially for HLA-A24 (13). Therefore, discrepancies such as the detection of a molecular type and the absence of its serological equivalent require further investigation and testing for the potential recipient. A patient with the null variant of A24 could make an antibody to A24. A donor with A24 should not be considered to be a zero mismatch for a recipient with a A24 null allele. For donor typing, if only molecular methods are used and a string of alleles includes a null allele, it would be acceptable to err on the side of calling the antigen present (except for DRB4), if further investigation was not possible within the time frame available for allocation. Ideally, null alleles should be identified either by use of parallel serologic typing or the use of molecular kits that identify null alleles. All confirmed null alleles should be entered as blanks.

For laboratories performing high resolution Class I typing, the problem of choosing the best serologic equivalent for UNOS is more straightforward. For reference, the HLA Dictionary (2) provides a list of the WHO assigned serologic designations and the actual serology test results for many alleles. For most of these alleles, the serologic types are known to correspond to the first two digits of the molecular type. For those molecular types (e.g., A*0227) for which no WHO assignment or serologic typing results are available, the lab may assume that the serologic type corresponds to the first two digits of the molecular type (e.g., A2 for this example). The Table below lists many of the alleles with serologic equivalences that are discrepant from the expected serology type (first 2 digits) or that have unusual Bw4/Bw6 associations. For each of these alleles, multiple samples were tested by both serologic and molecular methods in the UCLA cell exchanges, by NMDP Transplant Center HLA Laboratories, or by other laboratories, as referenced in (2). For other alleles, if no data are available, it is appropriate to use the 2-digit low resolution type for conversion.

Most of the time molecular typing gives clear results that can readily be interpreted, even when serologic typing is ambiguous. In those instances when the molecular typing results are not clear, parallel serologic typing may be helpful in determining the type to be entered into the UNOS computer. It is important to pay attention to the information provided by both tests, when available, in the final interpretation of the donor typing.

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TABLE I
SUGGESTED UNOS SEROLOGY EQUIVALENTS FOR MOLECULAR TYPES

Molecular Type(s)	Suggested UNOS Equivalent*
A*3204	A3
B*0802, 0803	B8 (Bw4)
B*1401	B64 (Bw6)
B*1402	B65 (Bw6)
B*1501, 1504, 1505, 1506, 1507, 1515, 1520, 1524, 1525, 1527, 1530, 1535, 1538, 1539, 1545	B62 (Bw6)
B*1502, 1508, 1511, 1521,	B75 (Bw6)
B*1503	B72 (Bw6)
B*1509, 1529, 1537, 1551	B70 (Bw6)
B*1510, 1518	B71 (Bw6)
B*1512, 1514, 1519	B76 (Bw6)
B*1513	B77 (Bw4)
B*1516, 1517	B63 (Bw4)
B*1522 renamed B*3543, B*1559 renamed B*3544 (13)	B35 (Bw6)
B*1523	B51 (Bw4)
B*1536	B13 (Bw4)
B*1546	B50 (Bw6)
B*2708	B2708 (Bw6)
B*4001, 4007, 4010, 4031, 4034	B60 (Bw6)
B*4002, 4003, 4004, 4006, 4008, 4009, 4011, 4016, 4018, 4020	B61 (Bw6)
B*4005	B4005 (Bw6)
B*4012	B48 (Bw6)
B*4019	B47 (Bw4)
B*4409	B45 (Bw6)
B*4416	B47 (Bw4)
B*4702	B60 (Bw6)
B*5002	B45 (Bw6)
B*5605	B7 (Bw6)
B*5606	B78 (Bw6)
B*5607	B56 (Bw4)

*The UNOS equivalent antigen suggested here is the consensus serology type from the HLA Dictionary (2) or, in the absence of a clear consensus (e.g., B*1515 or B*1523), the alternative type most reasonable to use for UNOS allocation purposes. UNetsm is already programmed for certain alleles (e.g., B*3905), so that no further conversion is needed.

General guidelines for entering antigens into the UNOS computer.

- 1) For serologic typing, enter all identified splits.
- 2) For both serologic and molecular typing, enter Bw4 and Bw6 for all B locus antigens. Do not enter Bw4 or Bw6 for A locus antigens that bear those epitopes.
- 3) For molecular typing, if an allele is identified, and the WHO has designated a serologic type for an allele, enter that type.
- 4) For a group of alleles, the serologic equivalent (according to the HLA Dictionary) of the most common allele(s) should be entered into the UNOS computer.
- 5) For specific alleles, if there is no WHO designation, but there are data available in the HLA dictionary or other valid reference, the likely serologic type from the available data should be used.
- 6) For specific alleles, if there is no serologic WHO designation for an allele, and there are data in the HLA dictionary that indicate the type is within a broad antigen grouping but no clear split is identified, the allele should usually be listed as the broad antigen.
- 7) For specific alleles, if there is no WHO designation, and the serologic data are absent or inconclusive (but consistent with the 2-digit type), then the 2-digit allele designation should be used (Ex. A*0219, B*0813). For alleles whose 2-digit type is a broad antigen (Ex. B*15), conversion to the 2-digit type should be carefully considered due to the consequences. For example, B*1542 would be converted to B15 because there are no good data available about the likely type, but B*1538, which has data in the dictionary that 75% of labs typed it as a B62, should be listed as a B62)
- 8) Confirmed null alleles should be entered as a blank
- 9) When low resolution molecular typings on donors give the type DRB1*07, DQB1*03 (DQ9), DRB4 positive, DR53 **should not** be entered as present based only on low resolution molecular typing for DRB4.