A Practical Approach to Reporting HLA to the CIBMTR

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Outline

- Introduction to HLA
- Overview of HLA nomenclature
- Form 2005: Confirmation of HLA
- Typing Laboratory report interpretation
- Form 2400: Pre-Transplant Essential Data
The Function of HLA Molecules

- Allows the immune system to detect foreign agents (bacteria, virus, etc.) by presenting fragments of these invaders to specific immune system cells and provoke a response.

- In transplantation, the differences in the HLA molecules between recipient and donor can provoke an immune response (GvHD or rejection).
HLA-matching For Adult Donors

- 8/8 Allele level matched at HLA-A, -B, -C, and DRB1 is associated with the best survival

- If a mismatch is unavoidable, a 7/8 single locus mismatched donor (at -A, -B, -C, or -DRB1) can be used with acceptable mortality risk

- HLA-DQ does not appear to be important for survival, TRM or acute GvHD
HLA-matching For Umbilical Cord Blood

- 8/8 Antigen level matched at HLA-A, -B, -C, and allele level matched at DRB1 is associated with the best survival

- Transplants mismatched at HLA-C are associated with higher non-relapse mortality when:
  - Matched at HLA-A, -B and -DRB1
  - When paired with a single mismatch at HLA-A, -B or -DRB1
  - Highest mortality risk when the mismatch occurred at HLA-C and -DRB1

Eapen M, Lancet Oncol 2011
HLA Typing Methods

- **Serology**
  Identifies HLA molecules on the cell surface using antigen specific anti-sera

- **DNA**
  Identifies HLA molecules by defining the DNA code in the cell nucleus
Examples of Serological Typing Nomenclature

A2 → B35 → DR15

Gene

Order of Antigen Discovery
Examples of DNA Typing Nomenclature

A*02:10 B*35:02 DRB1*15:04

gene

"*" DNA methodology

order of allele discovery

allele group
• structure
• serologic
NMDP Allele Codes

- Shorthand notation for reporting multiple alleles (intermediate/high resolution)
- Provides maximum information on the persons typing
- NMDP Bioinformatics Web site contains look-up Web tool:
  www.bioinformatics.nmdp.org
NMDP Allele Codes for Multiple Allele Designation

AB = 01/02

- A*02:01 or *02:02 = A*02:AB
- B*4001 or *4002 = B*40:AB
- DRB1*1501 or *1502 = DRB1*15:AB
New G codes

HLA alleles that have identical nucleotide sequences across the exons encoding the peptide binding domains (exon 2 and 3 for HLA class I and exon 2 only for HLA class II alleles) will be designated by an upper case ‘G’ which follows the allele designation of the lowest numbered allele in the group.

A*02:01:01G =

A*02:01:01:01/02:01:01:02L/02:01:01:03/02:01:08/02:01:11/02:01:14/02:01:15/02:01:21/02:09/02:43N/02:66/02:75/02:83N/02:89/02:97/02:132/02:134/02:140
New P codes

HLA alleles having nucleotide sequences that encode the same protein sequence for the peptide binding domains will be designated by an upper case ‘P’

A*02:01P=

A*02:01:01:01/02:01:01:02L/02:01:01:03/02:01:02/02:01:03/02:01:04/02:01:05/02:01:06/02:01:07/02:01:08/02:01:09/02:01:10/02:01:11/02:01:12/02:01:13/02:01:14/02:01:15/02:01:17/02:01:18/02:01:19/02:01:21/02:01:22/02:09/02:66/02:75/02:89/02:97/02:132/02:134/02:140
CIBMTR Confirmation of HLA Typing form (Form 2005)
Form 2005: Confirmation of HLA Typing

The Confirmation of HLA Typing form is completed for:

- Non-NMDP allogeneic or syngeneic donors
- Non-NMDP recipients
- Non-NMDP cord blood units

Complete a separate copy of this form for each donor, recipient*, or cord blood unit

*If a patient receives two CBUs, 1 unit is from the NMDP and the 2nd unit is not, only the non-NMDP CBU will need a form 2005. The HLA for the patient and the NMDP-CBU will come from the NMDP.

**Not required on NMDP facilitated transplants!**
Are you submitting a laboratory report?

☑ Add laboratory reports to Log of Appended Documents

If you have any questions about how to interpret a lab report, please contact:

Maria Brown, 612-627-8186 (mbrown2@nmdp.org)
# DNA in FormsNet

## Class I

<table>
<thead>
<tr>
<th>6</th>
<th>First A*</th>
<th>100 characters allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Second A*</td>
<td>100 characters allowed</td>
</tr>
<tr>
<td></td>
<td>not tested</td>
<td></td>
</tr>
</tbody>
</table>

## Class II

<table>
<thead>
<tr>
<th>9</th>
<th>First DRB1*</th>
<th>100 characters allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Second DRB1*</td>
<td>100 characters allowed</td>
</tr>
<tr>
<td></td>
<td>not tested</td>
<td></td>
</tr>
</tbody>
</table>
Serology in FormsNet

Drop down selection menu

Yes/No buttons

CIBMTR
Laboratory Reports
"/" ",," and "-"

The HLA field in FormsNet supports up to 100 characters

- A "/" is used to separate alleles (example A*02:01/01L or B*07:02/51)

- A ",," is used to separate alleles (example A*02:01, 01L, 02, 03)

- A "-" may be used to indicate a range of alleles (example 01:01-01:03 equals 01:01/01:02/01:03)
Which Typing do I use?

<table>
<thead>
<tr>
<th>Name</th>
<th>Relation</th>
<th>A^-</th>
<th>B^-</th>
<th>C^-</th>
<th>DRB1^-</th>
</tr>
</thead>
<tbody>
<tr>
<td>097140032, BLS</td>
<td>Patient</td>
<td>01:01</td>
<td>08:01</td>
<td>07:01</td>
<td>03:01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31:01</td>
<td>39:01</td>
<td>12:03</td>
<td>13:01</td>
</tr>
<tr>
<td>097140032</td>
<td>Unrelated</td>
<td>01:01</td>
<td>08:01</td>
<td>07:01</td>
<td>03:01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31:01</td>
<td>39:01</td>
<td>12:03</td>
<td>13:01</td>
</tr>
<tr>
<td>082087511, BLS</td>
<td>Unrelated</td>
<td>01:01</td>
<td>08:01</td>
<td>07:01</td>
<td>03:01</td>
</tr>
<tr>
<td>082087511</td>
<td></td>
<td>31:01</td>
<td>39:01</td>
<td>12:03</td>
<td>13:01</td>
</tr>
</tbody>
</table>

Mismatches:

<table>
<thead>
<tr>
<th>Name</th>
<th>Relation</th>
<th>A^-</th>
<th>B^-</th>
<th>C^-</th>
<th>DRB1^-</th>
</tr>
</thead>
<tbody>
<tr>
<td>097140032, BLS</td>
<td>Unrelated</td>
<td>01:01</td>
<td>08:01</td>
<td>07:01</td>
<td>03:01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31:01</td>
<td>39:01</td>
<td>12:03</td>
<td>13:01</td>
</tr>
<tr>
<td>082087511, BLS</td>
<td>Unrelated</td>
<td>01:01</td>
<td>08:01</td>
<td>07:01</td>
<td>03:01</td>
</tr>
<tr>
<td>082087511</td>
<td></td>
<td>31:01</td>
<td>39:01</td>
<td>12:03</td>
<td>13:01</td>
</tr>
</tbody>
</table>

Comments:

- 8/17/12 BLS 097140032 AMBIGUOUS WITH DRB1*03:08N, 13:105/117
- 8/17/12 BLS 082087511 AMBIGUOUS WITH DRB1*03:08N, 13:105/117

- Remember to check the comments or footnotes on your laboratory report.
- There is often further clarification of the HLA typing.
### What About Symbols @#$&%!

#### Laboratory Report

<table>
<thead>
<tr>
<th>A #1</th>
<th>A #2</th>
<th>B #1</th>
<th>B #2</th>
<th>Bw#1</th>
<th>Bw#2</th>
<th>DR#1</th>
<th>DR#2</th>
<th>C #1</th>
<th>C #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>*02:01</td>
<td>*32:01</td>
<td>*07:02</td>
<td>*08:01</td>
<td></td>
<td></td>
<td>*03:01</td>
<td>*11:01</td>
<td>07@</td>
<td>07:02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DQ #1</th>
<th>DQ #2</th>
<th>DRB345 #1</th>
<th>DRB345 #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>*02:01</td>
<td>03:01</td>
<td>NT</td>
<td></td>
</tr>
</tbody>
</table>

@ = C*0701/0706/0718  
NT = Not Tested

- ✔ Enter the alpha/numeric data from the footnote on the forms and/or into FormsNet.
- ✔ Please note that without the key we cannot decipher your symbols.
# Reporting NMDP Allele Codes

## HLA Typing Results

<table>
<thead>
<tr>
<th>Name / Lab ID</th>
<th>Relation</th>
<th>Hap A⁺</th>
<th>B⁺</th>
<th>C⁺</th>
<th>DRB1⁺</th>
<th>DRB3⁺</th>
<th>DRB4⁺</th>
<th>DRB5⁺</th>
<th>DQB1⁺</th>
<th>Sample Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
<td>26:01</td>
<td>40:01</td>
<td>03:04</td>
<td>04:04</td>
<td>01:01:01G</td>
<td>01:01:01G</td>
<td>03:02</td>
<td>08/19/12</td>
<td></td>
</tr>
<tr>
<td>673570</td>
<td>Unrelated</td>
<td>26:KDTG</td>
<td>40:KEHT</td>
<td>03:RCUS</td>
<td>04:04</td>
<td>01:01:01G</td>
<td>02:02</td>
<td>10/16/12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HLA typing was performed by one or more of the following molecular methods: SSOP, SBT, SSP. Some alleles may have been assigned based on their frequency (>1000 more likely than the alternative).

An allele reported with the suffix "G" is the most likely of multiple alternative genotypes that encode identical protein sequences in the antigen recognition site (ARS). The current list of HLA alleles that encode identical protein sequences in the ARS are available at IMGT HLA database (http://www.ebi.ac.uk/imgt/hla/ambig.html).

### Class I

- **26:KDTG**
- **29:KDTP**

Directly transcribe allele codes into FormsNet.
## Reporting G & P Codes

<table>
<thead>
<tr>
<th>Relation</th>
<th>RBC</th>
<th>Ha</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>DRB1</th>
<th>DRB3</th>
<th>DRB4</th>
<th>DRB5</th>
<th>DQB1</th>
<th>DPB1</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>A Pos</td>
<td>a</td>
<td>03:01:01G</td>
<td>35:01:01</td>
<td>04:01:01G</td>
<td>01:01:01</td>
<td></td>
<td></td>
<td>05:01:01</td>
<td>04:01P</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>c</td>
<td>02:01:01</td>
<td>18:01:01</td>
<td>05:01:01</td>
<td>11:01P</td>
<td>02:02P</td>
<td></td>
<td>03:01:01</td>
<td>02:01:02</td>
<td></td>
</tr>
</tbody>
</table>

An allele reported with the suffix "G" is the most likely of multiple alternative genotypes that encode identical protein sequences in the antigen recognition site (ARS). The current list of HLA alleles that encode identical protein sequences in the ARS are available at IMGT HLA database (http://www.ebi.ac.uk/imgt/hla/ambig.html).

### Class I

- First A*:
  - 03:01:01G
- Second A*:
  - 02:01:01

- not tested

### Class II

- First DRB1*:
  - 01:01:01
- Second DRB1*:
  - 11:01P

- not tested
What to do with Positives??

- Enter “positive” or “pos”
- Please do not use “+” or “-”

HLA Typing Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Relation</th>
<th>Hap</th>
<th>A*</th>
<th>B*</th>
<th>C*</th>
<th>DRB1*</th>
<th>DRB3*</th>
<th>DRB4*</th>
<th>DRB5*</th>
<th>DQB1*</th>
</tr>
</thead>
<tbody>
<tr>
<td>a 0101</td>
<td>Patient</td>
<td>0101</td>
<td>5201</td>
<td>1202</td>
<td>1502</td>
<td>NEG</td>
<td>NEG</td>
<td>POS</td>
<td>068VAH</td>
<td></td>
</tr>
<tr>
<td>c 0101</td>
<td>Patient</td>
<td>0101</td>
<td>5201</td>
<td>1202</td>
<td>1502</td>
<td>NEG</td>
<td>NEG</td>
<td>POS</td>
<td>068VAH</td>
<td></td>
</tr>
<tr>
<td>Unrelated</td>
<td>01BUYK</td>
<td>52/FYM</td>
<td>1202</td>
<td>1502</td>
<td>NEG</td>
<td>NEG</td>
<td>POS</td>
<td>068VAH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a 01BUYK</td>
<td>Brother</td>
<td>03BUYV</td>
<td>52/FYM</td>
<td>1202</td>
<td>1SSTK</td>
<td>POS</td>
<td>NEG</td>
<td>POS</td>
<td>068VAX</td>
<td></td>
</tr>
<tr>
<td>b 06EJUB</td>
<td>50AD</td>
<td>068UZJ</td>
<td>01PB</td>
<td>NEG</td>
<td>NEG</td>
<td>POS</td>
<td>068VAX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e 01BUYK</td>
<td>Brother</td>
<td>03BUYV</td>
<td>52/FYM</td>
<td>1202</td>
<td>1SSTK</td>
<td>POS</td>
<td>NEG</td>
<td>POS</td>
<td>068VAX</td>
<td></td>
</tr>
</tbody>
</table>

HLA Class I
- A*03:XXS, 31:01
- B*35:TDs, 40:01
- Bw6, 6
- C*03:04, 04:01

HLA Class II
- DRB1:01:01, 04:04
- DRB2*,-
- DRB4:01:03,-
- DRB5*,-
- DQB1:03:02, 05:01

HLA allele interpretation based on IMGT/HLA database version 3.3

**Code Translation**
- TDS 01/42
- XKS 03:01/03:01N

**SBT Exons Tested**
- A* 2, 3, 4
- B* 2, 3, 4
- C* 2, 3, 4, 5, 7
- DQB1* 2, 3
- DRB3* tested using SSP
- DRB4* tested using SSP
- DRB5* tested using SSP

Bw6/6 were determined using DNA sequence specific probes
- DRB3 was tested and found to be negative
- DRB5 was tested and found to be negative
Form 2005 Summary

☑ Form 2005 required on Non-NMDP donors/CBUs and recipients
  - Multiple donors = multiple forms

☑ Transcribe data directly as reported on laboratory report
  - Remember to watch for footnotes

☑ Include all possible alleles for DNA-based typing
Pre-Transplant Essential Data form (Form 2400)
Form 2400: Pre-TED

<table>
<thead>
<tr>
<th>Field</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>HLA-A locus</td>
</tr>
<tr>
<td>28</td>
<td>HLA-B locus</td>
</tr>
<tr>
<td>29</td>
<td>HLA-C locus</td>
</tr>
<tr>
<td>30</td>
<td>HLA-DRB1 locus</td>
</tr>
<tr>
<td>31</td>
<td>0 = matched, 1 = one mismatch, 2 = 2 mismatches, ND = not done</td>
</tr>
<tr>
<td>32</td>
<td>HLA-DRB1 locus</td>
</tr>
<tr>
<td>33</td>
<td>HLA Allelic 4 digits (A locus)</td>
</tr>
<tr>
<td>34</td>
<td>HLA-B locus</td>
</tr>
<tr>
<td>35</td>
<td>HLA-C locus</td>
</tr>
<tr>
<td>36</td>
<td>HLA-DRB1 locus</td>
</tr>
</tbody>
</table>
### 1st Pre-Ted Example

#### Antigenic Match

- A: 0 = matched
- B: 0 = matched
- C: ND = not done
- DRB1: ND = not done
- DQB1: 0 = matched

#### Allelic Match

- A: ND = not done
- B: ND = not done
- C: 0 = matched
- DRB1: 0 = matched
- DQB1: ND = not done
# 2nd Pre-Ted Example

<table>
<thead>
<tr>
<th>Donor id:</th>
<th>Patient:</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA typing:</td>
<td>HLA typing:</td>
</tr>
<tr>
<td>B: [*07:06]</td>
<td>B: [*07:02] [*35:01]</td>
</tr>
<tr>
<td>Cw: [*04:01]</td>
<td>Cw: [*04:01] [*15:05]</td>
</tr>
<tr>
<td>DQB1: [*03:19]</td>
<td>DQB1: [*03:19] [*06:09]</td>
</tr>
</tbody>
</table>

**Antigenic Match**
- A: 1 = mismatch
- B: ND = not done
- C: ND = not done
- DRB1: 1 = mismatch
- DQB1: ND = not done

**Allelic Match**
- A: ND = not done
- B: 1 = mismatch
- C: 0 = matched
- DRB1: ND = not done
- DQB1: 1 = mismatch

[CIBMTR Logo]
3rd Pre-Ted Example

Patient:
A*0101/01N, 2601
B*0801, 5801
Cw*0302, 0701/06/18
DRB1*0301, 0301/68
DQB1*0201, 0201

Donor:
A*0101/01N, 2601
B*0801, 5801
Cw*0302, 0701/06/18
DRB1*0301, 0301/68
DQB1*0201, 0201
Form 2400 Summary

☑ Default to the lowest resolution

☑ 1 Result (0, 1 or 2) per Locus
   - either antigenic or allelic matching
     - Remaining field (antigenic or allelic) should be marked “ND”

☑ Antigenic Match
   - Serology typing results
   - Allele string reported
   - Allele codes reported
   - The first 2 digits for allele strings or allele codes determine the match

☑ Allelic Match
   - 4 digits = allele level typing
   - Ignore silent mutations
Please remember:

*If you have any questions, contact: Maria Brown, 612-627-8186 mbrown2@nmdp.org*