















# World Marrow Donor Association guidelines for the reporting of novel HLA alleles

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The guidelines for the implementation and reporting of HLA nomenclature for the World Marrow Donor Association have served as a reliable standard for communication of HLA data in the hematopoietic cell transplantation process. Wider use of next-generation sequencing made a special provision of the guidelines increasingly pertinent: how to communicate novel HLA alleles. Novel alleles need to be recognized by the WHO Nomenclature Committee for Factors of the HLA system to obtain official allele designations. Until then they have to be handled according to the specific rules. Leaving the actual rules basically unchanged we give some advice on how to communicate novel alleles to best facilitate the search process for cases where novel alleles are identified on donor or patient side.

## KEYWORDS

donor registry, HLA, new alleles, NGS typing, patient registry

Extensive communication regarding the HLA typing of the patient and potential donors takes place between registries worldwide to provide the best possible donor for patients in need of a hematopoietic cell

transplantation (HCT). One of the main applications of this data exchange is the use of HLA typing data as input for predictive search algorithms<sup>1–7</sup> to identify potentially matched donors. These algorithms rely on accurate HLA typing data in a standardized format. The WMDA guidelines for usage of HLA Nomenclature<sup>8,9</sup> provide a set of rules that define such a format. Section 1.3.2 of the supplement to the current WMDA guidelines<sup>9</sup> defines that new allele variants must be communicated using the special

**Abbreviations:** ARD, antigen recognition domain; HC, hematopoietic cell; HCT, hematopoietic cell transplantation; NGS, next-generation sequencing; VT, verification typing; WHO, World Health Organization; WMDA, World Marrow Donor Association.

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TABLE 1 Overview of recommended actions.

Region	Coding ARD	Coding non-ARD	Coding ARD	Coding non-ARD	Non-coding
Case	A	B	C	D	E
Variation type	Non-synonymous	Non-synonymous	Synonymous	Synonymous	Any
Action	Report NEW	Report G-group or NEW if no G-group exists	Report two-field name		
Example	<i>B*07:02:01</i> with a SNP variant → <i>B*NEW</i>	<i>B*07:02:01</i> with a SNP variant → <i>B*07:02:01G</i>	<i>B*07:02:01</i> with a SNP in one of these variants → <i>B*07:02</i>		

Note: Overview of recommended action based on variant type of novel allele. This is a precedence table, in case of a new allele that fits multiple categories, use the leftmost.

code NEW until the official designation has been assigned by the WHO Nomenclature Committee for factors of the HLA System.<sup>10,11</sup> For search algorithms, these new alleles are important special cases, as novel alleles, as long as represented by the special code NEW, do not match any other typing by definition. So, it is important that these findings of new allele variants are communicated following given rules.

According to section 1.3.2 of the supplement to the updated WMDA guidelines<sup>9</sup>:

*The special code NEW must be used temporarily for an allele that has not yet been given an official name as in section 2.5. To avoid confusion with multiple allele code definitions as in section 1.3.1, HLA assignments for potentially new alleles must not take the form B\*15:NEW, for example, but instead B\*NEW.*

For the communication of alleles with non-synonymous new variants in a coding region, that is, variants that lead to a different amino acid composition of the protein, that is part of the antigen recognition domain (ARD, i.e., the exons encoding the peptide binding domains: exon 2 and 3 for HLA class I and exon 2 for class II alleles), the above-mentioned special code NEW has to be used (see case A in Table 1). Here, the current rule is valid and remains unchanged.

If non-synonymous new variants are in a coding region outside the ARD using NEW would of course still be correct but might unnecessarily hinder the search process, especially if the novel allele is found on the patient side. When such new variants are reported in this way, they are always considered a mismatch, although according to the current WMDA and NMDP/CIBMTR standard, variants outside the ARD are not considered as matching relevant.<sup>12,13</sup> The recommendation of the WMDA Bioinformatics and Innovation Committee for the communication of new allele variants of that kind in the inter-registry communication is the appropriate G-code. G-codes group all alleles that share the identical

nucleotide sequence on the ARD. Thus, the use of the respective G-code would optimally support the search process. A full and up-to-date list of all G-codes can be found at:

HLA Nomenclature@hla.alleles.org.<sup>14</sup> If no appropriate G-code is available, then NEW must be used (see case B in Table 1).

Laboratories are also identifying an increasing number of new allele variants indicating either synonymous mutations within the coding region, either in or outside the ARD (cases C and D in Table 1) or variants in a non-coding region (case E in Table 1). While again, formally the communication of such new variants as NEW would be correct they face the same problem in respect of searchability as described in the previous section. The recommendation of the WMDA Bioinformatics and Innovation Committee for the communication of new allele variants of that kind in the inter-registry communication is the shortened two-field format of the known allele, with identical ARD information, for example, *B\*07:02* (+ new synonymous mutation) should be reported as *B\*07:02* in order to provide as much information to the search process as possible.

If a new allele variant fits into multiple categories in Table 1, then the leftmost category has to be applied. Such a pragmatic shortening in the communication of high-resolution novel alleles would support donor search optimally, suppress irrelevant information without sending inaccurate information and avoid the introduction of a new special code and the respective adaptations needed in existing search algorithms. As mentioned in section 1.3.2 of the supplement to the updated WMDA guidelines, the special code NEW is only to be used temporarily until a new allele designation is assigned by WHO. The same is true for the above suggested use of G-codes or two-field format to represent novel alleles with non-ARD relevant or synonymous variants. Here, the HLA typing information must be updated as soon as a new allele designation has officially been published. The IPD-IMGT/HLA Database, the reference

database, is updated quarterly in January, April, July, and October, and has to be checked accordingly.<sup>10</sup> In case the novel allele is known to be non-expressing, a so-called Null-Allele, the special code NEW might be best used, as a replacement with a respective G-code or two-field format would conceal the important expression information. If another replacement code is temporarily used for the novel allele, then it must be ensured that this code does not provide any false information with regard to its expression. In such cases, the update with the new allele designation is especially important. The same holds for typing results using other expression-level characters. This update should not only be done for donors, but is also recommended for patient typing.

The use of internationally accepted and clearly defined rulesets for the electronic communication of HLA typing results is an absolute necessity in a highly automated setting such as international search processes for unrelated HC donors. Therefore, it is important to highlight, that the current HLA Nomenclature Guidelines of the WMDA<sup>9</sup> can still be applied unchanged. The above-mentioned pragmatic solution for the communication of high-resolution novel alleles is an optional extension to the guidelines that helps to support the search process optimally by providing the highest level of detail despite facing a novel allele. Its use is suggested for inter-registry communication.

## AUTHOR CONTRIBUTIONS

Christine Urban and Jan A. Hofmann initiated the project. All authors contributed to discussions as well as writing and approved the final manuscript.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study

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