POLICY STATEMENT

This policy outlines the HLA Typing requirements for patients and confirmatory HLA typing (HLA-CT) requirement for unrelated donors.

BUSINESS SECTION/DEPARTMENT

Specialized Services

PURPOSE

Sufficient high-resolution patient-donor HLA match is of primary importance in transplantation with unrelated donors. Patients and donors should be typed by sequencing-based methods at high-resolution HLA-A, -B, -C, -DRB1, and -DPB1 loci. Other loci (e.g., HLA-DQB1, -DRB3/4/5, -DQA1, -DPA1) are not required but may be typed to help in selecting donors and minimizing the potential risk of graft failure for HLA-sensitized patients. Accurate and adequate HLA typing on the patient before a formal search can ensure effective and timely donor selection; accurate and adequate HLA typing on the unrelated donor before work-up can ensure timely collection.

SCOPE

This policy applies to unrelated donor hematopoietic cell transplant facilitated by NMDP.

RELATED DOCUMENTS

Form 22 and Form 117: available on the Network Web Site

DEFINITIONS

- High-resolution typing is defined as the identification of HLA alleles that encode the same protein sequence within the antigen-binding site and excluding non-expressed alleles listed as Common and Infrequent (CI).
- CIWD HLA alleles: Common (>1 in 10,000), Infrequent (>1 in 100,000), WD (5 observations). The Common, Infrequent and Well-Documented HLA Alleles in World Populations: CIWD Version 3.0.0 is being prepared for submission to HLA Journals.
- HLA G assignments: Assignments that identify a set of alleles with the same nucleotide sequence in the exons that specify most of the antigen-binding site (i.e., exons 2 and 3 for HLA class I genes and exon 2 for HLA class II genes). A G-group may include both expressed and non-expressed alleles.
- Identity verification typing is defined as repeating HLA typing of transplant patient using a new sample such that the individual's HLA identity is verified before patient conditioning for transplant or before the administration of Filgrastim to the donor, whichever occurs first.

RESPONSIBILITIES

NMDP clinical HLA services: develop and manage policy.

REQUIREMENTS

Sample and Timing Requirements

- High resolution typing on the patient before formal search using sequencing-based methods is required to ensure an effective and efficient search.
- High-resolution HLA-CT on all primary donors requested for workup must be performed and reported to NMDP before patient conditioning for transplant or before the administration of Filgrastim to the donor, whichever occurs first.
- Patient identity verification typing using a new sample must be performed and reported to NMDP before patient conditioning for transplant or before the administration of Filgrastim to the donor, whichever occurs first.
- HLA antibody analysis on the patient before the formal search is highly recommended to ensure an effective search and minimize the potential risk of graft failure for HLA-sensitized patients.
- Using a buccal sample for HLA typing during the acute leukemic phase to avoid HLA haplotype/allele dropout due to potential chromosome abnormality.
- If a patient typing was performed more than two years before the search by a non-sequencing-based method, it must be repeated again to ensure accurate HLA assignments for donor selection.
- If a patient typing was performed by a methodology that did not include all required HLA genes and exons within the previous five years, it must be repeated to ensure accurate HLA assignments.

HLA Typing Requirements

- For patient and all primary donors requested for work-up: HLA-CT Typing of HLA loci using the sequencing-based method. Optimum: HLA-A, -B, -C, -DRB1, DRB3/4/5, -DQA1, -DQB1, -DPA1 and –DPB1; Minimum: HLA-A, -B, -C, -DRB1 and -DPB1.
- At a minimum, HLA alleles are defined at the first and second field according to WHO nomenclature.
- CI null allele, wherever the polymorphism is located, is excluded unless it can be demonstrated that an expressed antigen is present on the cells.
- Typing assignments obtained at the time of donor recruitment do not replace HLA-CT on a second independent sample.
- HLA G group allele assignment, excluding all null alleles on the CI listing (http://igdawg.org/cwd.html).
- Genotypes: the reported high-resolution HLA typing results must meet **one** of the following two criteria:
    1. Must contain only one unambiguously assigned genotype or
    2. May contain multiple alternative genotypes if one includes two CI alleles and the others do not include any alleles listed as CI. No distinction is made between common (C) and infrequent (I) in the policy.
- Exceptions must be submitted and approved by NMDP clinical HLA services. Timely submission will ensure prompt approval without delay in the search process.

Exceptions

The transplant center medical director is responsible for compliance with the NMDP CT typing requirements. The medical director may request an exception to the typing requirements by submitting a written request to the NMDP. Justification for the variance must be included in the request. Also, the program requesting such variance must have the conditions of the variance in its agreement with its histocompatibility laboratory.

Reporting results to NMDP

- High-resolution typing results must be reported on Form 22 (donor)/117 (patient).
- Form 22/117 should be electronically submitted. For TCs who are submitting the forms manually, NMDP will collaborate with TCs' testing lab to achieve electronic submission.
- The patient original and verification typing should be concordant, and the lab should only report the high-resolution type on the Form117.
- Typing ambiguities, the result of meeting minimum resolution requirement, need to be reported on Form 22 or Form 117 either spelling out or using NMDP codes.

Accreditation of testing laboratories

HLA laboratories must adhere to standards and policies associated with the corresponding accreditation agency for Unrelated Donors for Hematopoietic Cell Transplantation by the American Society for Histocompatibility and Immunogenetics (ASHI), the College of American Pathologists (CAP), or the European Federation for Immunogenetics (EFI).

REFERENCES

1. 2018 ASHI standard:
2. EFI 2017-07-18_Standard_version_7
3. CAP Accreditation Histocompatibility Checklists—2018 Edition
4. IMGT/HLA: https://www.ebi.ac.uk/ipd/imgt/hla/
5. Common and Well-Documented HLA Alleles: 2012 update to the CWD catalog. Mack SJ, et al. 2013. Tissue Antigens 81(4):194-203.
6. Nunes E, Heslop H, Fernandez-Vina M, et al. Definitions of histocompatibility typing terms. Blood. 2011;118(23):e180-183.
7. Spellman S, Bray R, Rosen-Bronson S, et al. The detection of donor-directed, HLA-specific alloantibodies in recipients of unrelated hematopoietic cell transplantation is predictive of graft failure. *Blood*. 2010;115(13):2704-2708.
8. Ciurea SO, Thall PF, Wang X, et al. Donor-specific anti-HLA Abs and graft failure in matched unrelated donor hematopoietic stem cell transplantation. *Blood*. 2011;118(22):5957-5964.
9. Palmer J, Chai X, Pidala J, et al. Predictors of survival, nonrelapse mortality, and failure-free survival in patients treated for chronic graft-versus-host disease. *Blood*. 2016;127(1):160-166.
10. Pidala J, Lee SJ, Ahn KW, et al. Nonpermissive HLA-DPB1 mismatch increases mortality after myeloablative unrelated allogeneic hematopoietic cell transplantation. *Blood*. 2014;124(16):2596-2606.
11. Dehn J, et al. Selection of Unrelated Donors and Cord Blood Units for Hematopoietic Cell Transplantation: Guidelines from the NMDP/CIBMTR *Blood*. 2019 Jul 10.
12. An electronic copy of this policy can be found at the NMDP Bioinformatics Website: http://bioinformatics.nmdp.org/Policies/Policies.aspx
13. HLA typing example for both optimum and minimum resolution:

Example of optimum gene coverage and resolution

A*	B*	C*	DRB1*	DRB345*	DQA1*	DQB1*	DPA1*	DPB1*
02:07	15:27	04:01	09:01	4*01:03	03:02	03:03	02:02	02:01
24:02	46:01	01:02	15:01	5*01:01	01:02	06:02		05:01

Example of minimum gene coverage and resolution

A*	B*	C*	DRB1*	DRB345*	DQA1*	DQB1*	DPA1*	DPB1*
02:07	15:27	04:01	09:01:02G					04:01:01G
24:02	46:01	01:02	15:01:01G					04:02:01G

REVISION HISTORY

Revision	Brief Description of Revision
P00079 rev. 1	Changed document type to policy and revised HLA typing requirements. Previously controlled as A00261.
P00079 rev. 2	DRAFT