POLICY

POLICY STATEMENT

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

BUSINESS SECTION/DEPARTMENT

Provider Services

PURPOSE

A sufficient high-resolution patient-donor HLA match is of primary importance in transplantation with unrelated donors. Patients and donors must 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 transplants facilitated by the National Marrow Donor Program® (NMDP) / Be The Match®.

RELATED DOCUMENTS

F00775, *High-Resolution Recipient HLA Typing* (Form 117)

F00777, *Donor Confirmatory HLA typing (HLA-CT)* (Form 22)

DEFINITIONS

- High-Resolution Typing: The identification of HLA alleles that encode the same protein sequence within the antigen-binding site and excluding non-expressed alleles listed as CIWD. Refer to CIWD Null Allele Exclusion Requirement Table below for more information.
- CIWD HLA Alleles: Common (>1 in 10,000), Intermediate (>1 in 100,000), Well-Documented (WD) (5 or more observations). The Common, Intermediate, and Well-Documented HLA Alleles in World Populations: CIWD Version 3.0.0 is published open access in HLA. Refer to the References section of this policy for the Common, Intermediate and Well-Documented HLA Alleles in World Populations hyperlink.

- 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.
- HLA P Assignments: Assignments that identify a set of alleles with nucleotide sequences that encode the same protein sequence for the peptide binding domains (exon 2 and 3 for HLA class I and exon 2 only for HLA class II alleles). It follows the 2-field allele designation of the lowest numbered allele in the group.
- Identity Verification Typing: Repeating HLA typing of transplant patients using a new sample such that the individual's HLA identity is verified before patient conditioning for transplant, before donor marrow harvesting, or before the administration of filgrastim to the donor, whichever occurs first.

RESPONSIBILITIES

NMDP clinical HLA services develop and manage this policy.

REQUIREMENTS

Sample and Timing Requirements

- High-resolution typing on the patient before formal search using sequencing-based methods are required to ensure an effective and efficient search.
- High-resolution HLA-CT on all primary donors requested for workup must be performed, concordance verified/documented with the TC's NMDP case manager before patient conditioning for transplant, before donor marrow harvesting, or before the administration of filgrastim to the donor, whichever occurs first.
- Patient identity verification typing using a new sample must be performed, concordance verified/documented with TC's NMDP case manager before patient conditioning for transplant, before donor marrow harvesting, 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.
- A buccal swab should be used for HLA typing during the acute leukemic phase to avoid HLA haplotype/allele dropout due to potential chromosome abnormality.
- If patient typing was performed more than two years before the search by a non-sequencing-based method, it must be repeated to ensure accurate HLA assignments for donor selection.
- If 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

- Typing of HLA loci for patient and all primary donors requested for work-up must use a 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 by the first and second field according to WHO nomenclature.
- CIWD null alleles, regardless of where the polymorphism is located, must be 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 is acceptable if all CIWD null alleles are excluded. Documentation of the exclusion on Form 117 or Form 22 e-submission and on the lab report is required.
- HLA P group allele assignment is acceptable.
- 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 Common or Intermediate alleles, and the other genotypes do not include any alleles listed as Common or Intermediate or any CIWD null alleles. No distinction is made between common and Intermediate in the policy.
- When referencing CIWD 3.0.0 table, the cutoffs are based on the designation under the Total column and alleles at 2 fields only.
- Exceptions must be submitted via the transplant center's (TC) assigned NMDP case manager(s) and approved by NMDP clinical HLA services. Timely submission will ensure prompt approval without delay in the search process. Please provide the needed approval timeline in the submission.

Exceptions

- The TC 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)/Form 117 (patient). Do not re-submit patient identity verification typing on Form 117 electronically or manually.
- Form 22/Form 117 should be electronically submitted. For TCs who are submitting the forms manually, NMDP will collaborate with TCs' testing lab to achieve electronic submission.
- All manual form submission will require the submission of the HLA lab report simultaneously. No need to fill out HLA typing information on manual Form 117/Form 22 submission.
- The patient original and verification typing should be concordant and verified/documented before patient conditioning for transplant, before donor marrow harvesting, or before the administration of filgrastim to the donor,

whichever occurs first. The lab should only report the high-resolution type on Form 117.

- Reporting HLA typing, both Form 22/Form 117 electronic submission and the lab report, must follow ASHI standard D.5.2.2.15 and D.6.2.2.12 for ambiguity resolution and documentation.

Accreditation of Testing Laboratories

- All US 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. Common, Intermediate and Well-Documented HLA Alleles in World Populations: CIWD Version 3.0.0 https://onlinelibrary.wiley.com/doi/abs/10.1111/tan.13811
2. 2019 ASHI standard
3. EFI 2017-07-18_Standard_version_7
4. CAP Accreditation Histocompatibility Checklists—2018 Edition
5. IMGT/HLA: https://www.ebi.ac.uk/ipd/imgt/hla/
6. Common and Well-Documented HLA Alleles: 2012 update to the CWD catalog. Mack SJ, et al. 2013. Tissue Antigens 81(4):194-203.
7. Nunes E, Heslop H, Fernandez-Vina M, et al. Definitions of histocompatibility typing terms. Blood. 2011;118(23):e180-183.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. An electronic copy of this policy can be found at the NMDP Bioinformatics website: http://bioinformatics.nmdp.org/Policies/Policies.aspx

14. 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

15. CIWD Null Allele Exclusion Requirement Table:

HLA Confirmatory Typing Requirements for Unrelated Adult Donors and HLA Typing Requirement for Patients
Null allele exclusion requiment based on 3.0.0 CIWD

HLA-A		HLA-B		HLA-C		HLA-DRB1		HLA-DRB345		HLA-DQB1		HLA-DPB1	
A*01:04N*	WD	B*07:67N	WD	C*02:38N	WD	DRB1*07:10N	WD	**DRB4*01:03:01:02N***	WD	DQB1*02:18N	WD	DPB1*61:01N	WD
A*01:15N	WD	B*07:181N	WD	C*02:92N	WD	DRB1*07:26N	WD	DRB4*01:16N	WD	DQB1*02:20N	WD	DPB1*64:01N	WD
A*01:16N	WD	B*14:07N	WD	**C*04:09N***	I	DRB1*12:24N	WD	DRB4*02:01N	WD	DQB1*03:118N	WD	DPB1*120:01N	WD
A*01:57N	WD	**B*15:01:01:02N***	WD	C*04:93N	WD			DRB4*03:01N	WD	DQB1*06:26N	WD	DPB1*154:01N	WD
A*01:123N	WD	B*15:79N	WD	C*04:95N	WD			**DRB5*01:08N***	WD	DQB1*06:75N	WD	DPB1*161:01N	WD
A*02:53N	WD	B*15:181N	WD	C*05:07N	I			DRB5*01:10N	WD	DQB1*06:77N	WD	DPB1*218:01N	WD
A*02:83N*	WD	B*15:190N	WD	C*05:99N	WD					DQB1*06:144N	WD	DPB1*357:01N	WD
A*02:94N	WD	B*35:165N	WD	C*06:16N	WD							DPB1*570:01N	WD
A*02:113N	WD	B*37:03N	WD	C*06:79N	WD								
A*02:125N	WD	B*37:42N	WD	C*07:32N	WD								
A*02:227N	WD	B*39:40N	WD	C*07:33N	WD								
A*02:514N	WD	B*40:22N	WD	C*07:55N	WD								
A*03:21N*	WD	B*40:142N	WD	C*07:61N	WD								
A*11:21N*	WD	**B*40:155N***	WD	C*07:104N	WD								
A*11:109N	WD	B*44:23N	WD	C*07:198N	WD								
A*23:11N	WD	**B*51:11N***	WD	C*07:227N	WD								
A*23:19N	WD			C*07:452N	WD								
A*24:09N*	WD			C*08:127N	WD								
A*24:11N*	WD			C*15:122N	WD								
A*24:36N	WD			C*16:30N	WD								
A*24:84N	WD												
A*24:90N	WD												
A*24:252N	WD												
A*25:12N	WD												
A*30:70N	WD												
A*30:78N	WD												
A*31:14N*	WD												
A*31:60N	WD												
A*32:27N	WD												
A*32:45N	WD												
A*34:10N	WD												
A*68:18N	WD												

Table
1: C=Common; I=Intermediate; WD=Well-Documented
2: Null alleles listed were observed at least five times in the total population group of the most current dataset (CIWD 3.0.0). The table does not list all non-expressed alleles from IPD-IMGT/HLA version 3.31.0.
3: The highlighted alleles* are CIWD null alleles within the G group. When reporting G level resolution, exclusion of these null alleles are required. Documentation of the exclusion on form 117/22 e-submission and on the lab report is required.

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	Updated to reflect these key changes: • Require sequencing-based typing for patient & unrelated donor CT • Emphasize the timing of the HLA testing to improve search accuracy and reduce time to transplant • CIWD 3.0.0 update • Request electronic submission of Form 22/Form 117 • Require the HLA lab report for manual submission of Form 22/Form 117 • New ambiguity resolution and reporting requirement

ADDENDA

Not applicable