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Advances in the Selection of HLA-Compatible Donors: Refinements in HLA Typing and Matching over the First 20 Years of the National Marrow Donor Program Registry

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INTRODUCTION

Over the past 20 years the understanding of human leukocyte antigen (HLA) diversity and the impact of HLA matching on unrelated donor hematopoietic stem cell transplantation (HSCT) outcomes have evolved greatly. The National Marrow Donor Program (NMDP) has been intimately involved in monitoring, developing, and applying new methodologies for HLA testing, data capture techniques, and data representation methods to ensure that HLA typing of newly registered potential volunteer HSC donors and donors identified as potential matches is of the highest quality and accuracy for the benefit of searching patients. The following commentary provides an overview of the evolution of HLA typing for the NMDP Registry over the 20-year history of the organization. Of special note are the methodologic changes and the development of high-quality HLA data capture, interpretation, and storage systems that have made significant enhancements to the NMDP search algorithm, yielding more efficient and accurate unrelated donor and cord blood unit (CBU) searches. In addition, the application of these strategies to the NMDP Research Sample Repository of donor-recipient pairs has allowed the completion of several critical retrospective analyses of HLA match and outcome.

MEASURING COMPATIBILITY: FROM CELLULAR ASSAYS TO DNA-BASED TECHNIQUES

During the first 9 years of the NMDP Registry, the minimum level of HLA typing required to list a newly registered volunteer HSC donor was serologically defined HLA-A and -B typing, with the majority of the testing performed by laboratories that were selected by the donor center network staff. HLA-DR typing was not routinely performed because of its difficulty and expense. Serologic typing utilizes human alloantisera to identify proteins (antigens) on the surface of lymphocytes. This typing method is known to have many limitations, including the requirement for viable cells, the lack of appropriate sera to type antigens more commonly found in minority populations, and relatively high discrepancy rates [1]. Because alloantisera were typically derived from a specific racial/ethnic population, the methodology was less than optimal for testing a racially/ethnically diverse population targeted for inclusion on a volunteer donor registry. In addition to serologic matching, donor/recipient compatibility for HLA class II types was typically assessed using the mixed lymphocyte culture (MLC) assay. This cellular assay was time consuming, required large volumes of blood, and was influenced by the health of the recipient and the viability of donor cells often

shipped from long distances [2]. Taken together, these recognized limitations of serologic and MLC typing methods led many within the HLA community to seek more robust reproducible methodologies to more accurately assess the compatibility of donor/recipient pairs and to ensure high-quality testing results that could stand the test of time on a registry of volunteer HSC donors.

The International Histocompatibility Workshops (IHWS) of the mid-1980s through the mid-1990s expended significant energy to refine DNA-based HLA typing methods. A major leap forward in DNA-based HLA typing technology came with the introduction of the polymerase chain reaction (PCR) [3] and studies demonstrating the feasibility of HLA typing via PCR and sequence-specific oligonucleotide probes (SSOP) [4,5]. This assay employed gene amplification and identification of oligotypes by the hybridization of single-stranded DNA probes to sites of DNA sequence variation (i.e., polymorphisms). The 11th workshop evaluated the ability to assign HLA alleles using PCR-SSOP DNA-based methods [6]. In addition, other DNA-based methodologies including sequence-specific primers (SSP), PCR heteroduplex formation, and direct sequencing assays were described, adding to the diverse repertoire of techniques. The development of DNA methods for class II typing allowed HLA laboratories to eliminate the MLC as a means of evaluating donor/recipient compatibility for class II loci.

During the development of HLA typing methodologies, an improvement in DNA sequencing methodologies resulted in the identification of new HLA alleles. Eighty-seven new HLA alleles were described by the 11th workshop and published in the report on Nomenclature for Factors of the HLA System, 1991 [7]. Since that time, the number of new alleles identified has continued to increase, so that today almost 2000 HLA alleles have been identified at the HLA-A, -B, and -DRB1 loci. To address the continuous increase in HLA diversity, robust sequencing strategies were developed within NMDP research studies and applied to patients and their potential donors to provide matching at high resolution and to develop matching guidelines to improve outcome.

TRANSITIONING TO DNA-BASED TYPING FOR NMDP REGISTRY VOLUNTEERS

The inadequacies of serologic typing and the benefits of DNA-based typing were demonstrated in several large studies spearheaded by the NMDP and the C.W. Bill Young Department of Defense Marrow Donor Program, Naval Medical Research Institute (Center since 1998) (Navy) during the early to late 1990s following feasibility studies by the Navy. The first studies were directed toward development of a reliable DNA-based typing system to discern HLA-DRB1/3/5 and -DQB1 oligotypes (groups of alleles defined by a hybridization pattern with a panel of SSOP). As the importance of DRB1 matching was demonstrated through outcome studies [7], the traditional methods for class II compatibility proved unreliable [2], and as DNA-based typing for DRB1 became more routine and cost effective, typing strategies changed to include DRB1. In 1992, the NMDP initiated a Navy-supported prospective DNA testing program for DRB1 and, working with a team of HLA typing laboratories, optimized approaches for large-volume testing. The results of the effort were presented in 2 separate reports from Ng et al. [8,9].

The first report detailed the initial 7 months of typing activity utilizing SSOP techniques to test volunteer donor samples [8]. Seven laboratories participated in the project, with many employing the primers and probes described in the 11th IHWS and others using locally developed primer and probe sets. Laboratories received shipments of volunteer donor samples intermingled with identically labeled "blind" quality control samples (samples previously typed by the Navy/NMDP). The group assessed the sensitivity of the assay (probability of testing positive if the type was present) and specificity (probability of testing negative if the type was not present). The study found correct assignment of DRB1/3/4 and DQB1 oligotypes in 99% and 98%, respectively, from a cohort of 1652 blind quality control samples. The results were very impressive, especially because the quality control samples were intermingled with over 9000 volunteer donor samples and were not given any special attention during the testing process. This analysis was the first definitive demonstration that PCR/SSOP HLA typing was feasible on a large scale and was highly specific, accurate, and reliable.

The follow-up analysis detailed the results of the second year of the project [9]. The 7 participating laboratories completed an additional 62,216 HLA-DRB1/3/4 and -DQB1 typings (57,580 donors samples and 4636 blind quality control samples). The average percent of correctly classified HLA oligotypes based on 9244 DRB1 and 7244 DQB1 assignments was 99.8% (range 99.4%-100%) and 99.8% (range 99.6%-100%), respectively. The results were again remarkable considering the increased typing volume from the first phase of the project and an increase in the overall resolution of the typing, that is, additional oligonucleotide probes added to the typing kit.

Following up on the success of the implementation of class II typing by DNA-based methods, the NMDP helped lead an effort to develop a testing system for HLA-A and -B. The application of DNA-based HLA typing for HLA-A and -B was further assessed for accuracy, and validated in 2 large-scale analyses by Hurley et al. [10] and Noreen et al. [1]. The Hurley

study evaluated accuracy and reliability of the class I DNA-based typing by assessing the quality control testing rates from July 1997 to June 1998 of an NMDP typing project in a manner similar to the approach used for class II testing assessment [10]. A total of 64,180 volunteer donor samples and over 11,400 quality control samples were tested. The authors observed an error rate of 1.1% and 1.9% for HLA-A and -B, respectively, demonstrating that the SSP and PCR/SSOP techniques employed in the testing were robust.

Noreen et al. [1] went on to validate the accuracy of the techniques through assessment of volunteer donors tested in parallel with serologic techniques. Serologic typing was performed between 1993 and 1997 on 42,160 volunteer donors of which 99.9% were from U.S. minority population groups. The analysis was conducted in 2 phases. In phase I, DNA-based typing was performed without knowledge of the previous serologic assignments. The authors found discrepancies between the serologic and DNA-based assignments in 24% of the volunteer donor samples. In phase II, a random sampling strategy was used to select a statistically significant number of individuals for repeat DNA typing from each of the categorized discrepant groups. The repeat DNA-based testing was correct for approximately 99% of HLA-A assignments, over 98% for HLA-B and >97% for HLA-A and -B combined. This analysis provided a comprehensive validation of the ability of DNA-based typing to define all known low-resolution types and supported transition of registry typing protocols to DNA-based approaches.

In January 2000, the NMDP merged the separate class I and II typing programs based on the results of a Health Resources and Service Administration and Office of Naval Research sponsored study completed in 1999 by Kollman et al. [11]. This study concluded that recruiting new volunteers and typing them for only HLA-A and -B was not a cost-effective strategy. Although initially less expensive per volunteer, a regression model estimated that a searching patient with a matched volunteer was nearly 5 times more likely to proceed to transplantation if their match was already fully typed in the Registry. These data, combined with cost efficiencies that could be achieved by the contract laboratories and repositories by shipping the sample only once, extracting DNA once, and reporting once for each new donor, supported the decision.

The development of the NMDP registry typing programs relied on key contributions from the Navy, NMDP Histocompatibility Committee, the participating laboratory principal investigators, and reagent/typing system manufacturers. Periodic meetings were held with the principal investigators to review the functionality of the typing methodologies and to discuss modifications to the reagent set or processing protocols to improve resolution or robustness of the system. Significant effort was placed on evaluating the typing reagents to produce robust results and increased resolution aimed at distinguishing among common HLA alleles [12]. Reagents that gave weak or inconsistent signals were redesigned either in-house (at 1 of the HLA typing laboratories) or by the vendor to improve the accuracy of testing. The NMDP continues to follow this collaborative model to ensure that the registry typing program continues to generate the most accurate and highest resolution results possible.

IMPROVING ACCURACY, QUALITY, PRICE, AND RESOLUTION OF HLA ASSIGNMENTS

The impact of the change from serologic to DNA-based testing is best illustrated by the increasing accuracy when the initial HLA typing of a volunteer is compared to the HLA typing obtained when that donor is retested as a potential HSC donor for a searching patient. Figure 1 shows the change in the number of samples discrepant at the time of confirmatory typing with the typing obtained at recruitment [13]. Although it is not possible to distinguish discrepancies because of errors in recruitment typing from other sources of errors, that is, changes in nomenclature or higher resolution reagents, it is clear that the discrepancies are clearly decreasing over time for all 3 HLA loci evaluated. The increased accuracy of the DNA typing has had a significant positive impact on the patient search process. In minority race donors recruited from 1991 to 1996, the rate of discrepancy from recruitment typing to CT typing was approximately 10%. For minority donors recruited and typed in the years of 1997 to 2001, the rate of uncovering any type of HLA-A, -B, or -DRB1 discrepancy with CT typing dropped to 3.5%.

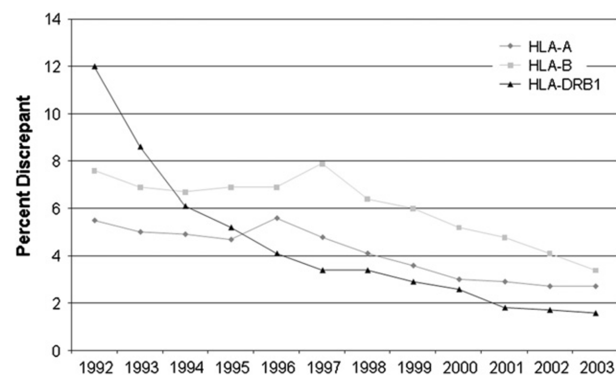

Figure 1. The percent of confirmatory typing results that were inconsistent with the volunteer donor's HLA typing on the NMDP file by year of recruitment. In most cases, the typing in the file was obtained at the time of recruitment. It is not possible to attribute the source of error to the recruitment typing versus other sources of errors.

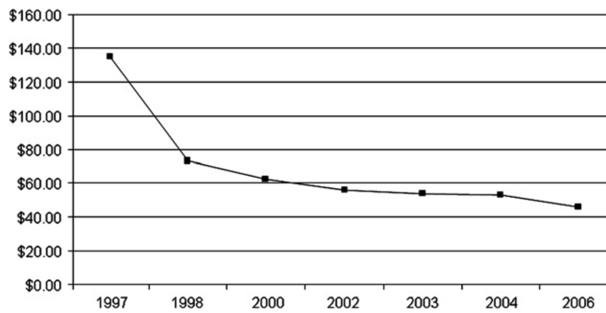

Figure 2. Declining Price of Registry HLA-A, B, DRB1 typing. The change in HLA-A, -B, -DRB1 recruitment typing cost for the NMDP registry over the past 10 years.

The decrease in HLA-A, -B, and -DRB1 recruitment typing costs over the past 10 years is illustrated in Figure 2. A major reason for the large decline in the late 1990s was the transition from separate class I and II typing programs to a combined program that utilized a single sample for the testing. Additionally, the introduction of new typing systems, that is, bead-based SSOP, decreased the labor-intensive nature of the testing and was amenable to automation.

Concomitant to the reduction in pricing, significant increases in resolution for HLA-A, -B, and -DRB1 were achieved over the 10-year time frame. Initially, in 1999, DNA-based typing resolution was similar to the level achieved by serologic typing (e.g., A*01XX = A*0101, 0102, 0103, 0104, 0105 equivalent to A1). By the end of 2006, the resolution was at “high/intermediate,” where the laboratories reported at either the allele level (e.g., A*0104) or utilized oligotypes with reduced combinations of alleles (e.g., A*01AF = A*0101 and A*0104). Within the same time frame the number of alleles that had to be considered (and the resulting increase in potential alternative allele combinations that needed to be tested for and resolved) in the typing strategy for class I grew from 430 to 1180 and for DRB1 from 226 to 511.

The higher level of resolution in the HLA assignments allows transplant centers to more rapidly narrow the search and identify the best potentially allele matched HSC donors. The high accuracy rate and the decreased cost per sample demonstrate the accomplishment of optimizing DNA typing technology for high-volume testing. In addition, testing initially required up to 60 days, and now the majority of testing is complete in 14 days or less. The shortened testing time frames help to ensure that new donors, particularly those recruited through patient-focused drives, are registered quickly. The decreased cost positively impacts the ability to add higher numbers of new donors to the Registry, therefore increasing the probability of searching patients finding suitably matched unrelated donors.

CHANGING SAMPLE REQUIREMENTS AND CENTRALIZED REPOSITORIES

The transition from serologic to DNA-based methods for HLA testing had profound effects on the NMDP’s volunteer donor sample collection and distribution network. The need for fresh viable leukocytes for serologic testing necessitated the direct shipment of samples to typing laboratories to ensure the highest sample quality possible. The introduction of DNA-based testing made feasible the archiving of volunteer donor samples in centralized repositories to standardize processing, labeling, and distribution, and to facilitate long-term storage for repeat testing or step-wise testing upgrades. The NMDP established 2 frozen blood sample repositories to handle the large volume of donor recruitment samples. Later, processing and storage was centralized at an NMDP-operated donor sample repository in Minneapolis.

Sample collection and storage procedures were constantly evaluated to ensure that the stored samples were the most cost-effective possible. In the late 1990s, the NMDP began to explore the potential to begin a transition to collecting, storing, and HLA testing potential HSC donor blood samples dried on filter paper cards to eliminate the need for frozen blood storage. The groundwork for the effort was developed from earlier studies evaluating the technical aspects of the sample collection process, long-term sample stability, and the accuracy and precision of DNA-based HLA typing protocols utilizing 2 uniquely different filter paper cards [14]. In August 2002, the NMDP recruitment network was transitioned to collect small quantities of blood by finger stick with the expectation that phlebotomists would not be required, and therefore, a significant cost savings could be achieved. When these cost savings were not realized because of requirements in many states that all blood samples be collected by licensed phlebotomists, another method, collection of donor DNA by buccal swabs, was evaluated and implemented in May 2006. These swabs can be more easily shipped and can be stored at room temperature, further reducing cost.

DEVELOPING ELECTRONIC HLA DATA REPORTING, INTERPRETATION, AND CURATION SYSTEMS

It was recognized at the inception of DNA-based HLA typing that the optimal approach to avoid the complexities created by the addition of new HLA alleles over time would be to record and utilize the probe and primer hybridization data (i.e., DNA nucleotide sequence polymorphisms) in addition to the interpreted HLA type (i.e., HLA oligotype) [15]. Recording the HLA typing data (i.e., primary data) on new donors as polymorphisms present, absent, or not tested would eliminate outdating of oligotypes and facilitate selection of donors who may be possible matches for further

testing. To most efficiently utilize all information resulting from donor typings, the NMDP had to develop information technology and communication systems capable of accepting and managing the typing data at a subnomenclature representation. With funding support and guidance from the Navy, computer infrastructure to manage primary typing data reported by laboratories in addition to the interpreted HLA oligotypes used on search reports was developed and implemented.

The utility of this approach was demonstrated in a study led by Maiers et al. [12], where the authors evaluated DNA-based HLA-DRB1 assignments reported from 371,187 donors. All typing results and probe hybridization patterns were electronically reported to the NMDP. The hybridization patterns were reinterpreted using a computer program and compared to the original results. There was a high correlation between the typing assignments between the computer system and the submitting laboratory. The stored data was later reinterpreted using an allele list defined approximately a year after the typings were submitted and the authors found that 74% of the interpretations of primary data leading to HLA-DRB1 assignments would have been altered by newly described alleles. The findings of the analysis clearly demonstrated the utility of storing polymorphic DNA sequences present or absent rather than interpreted typing results.

The original systems developed by the NMDP required consistency in message formatting and reagent sets. In more recent years, the systems were enhanced to accept primary data from multiple types of methodologies including SSOP, SSP, and sequence-based typing (SBT) from kits developed by multiple vendors. The NMDP established confidentiality agreements with all participating reagent vendors to allow the population of a database with their proprietary nucleotide sequences of the probes and primers, which in turn, allowed on-site reinterpretation of the primary data into HLA oligotypes. This acted as an additional measure of quality control and allowed for the eventual integration of these data into the enhanced matching algorithm, HapLogic^{SM} (described below).

INTEGRATING SEROLOGIC AND DNA TYPING ASSIGNMENTS FOR MATCHING

Today, 58.9% of volunteer donors on the NMDP Registry have HLA assignments determined by DNA-based methodologies, 23.3% have a mixture of serologic and DNA assignments, and 17.8% have only serologic assignments. To include both the serologically typed volunteers and the more recently DNA-typed volunteers in the search for a specific patient, NMDP has had to develop a strategy to compare results obtained with various typing methodologies to identify matched donors. These efforts led to an international collaboration to collect and correlate serologic assignments with DNA oligotypes and individual alleles. Initial efforts employed the use of the Expectation Maximization (EM) algorithm to evaluate NMDP volunteers who had both DNA and corresponding serologic HLA assignments. This innovative application of the EM algorithm to predict the most likely serologic association, along with information from the UCLA International Cell Exchange and results from individual HLA typing laboratories, resulted in a serology to DNA "dictionary" that was first published in 1997. This dictionary has become a reference work and is updated every few years [16-19].

In 2003, the NMDP enhanced the dictionary by developing a neural network strategy to predict the serologic assignments of HLA alleles lacking this information. This study by Maiers et al. [20] used the protein sequences of the many HLA antigens and their known serologic associations in the prediction. This bioinformatics strategy has been incorporated into the latest serology-DNA dictionary. These studies provide the information needed to populate tables used by HapLogic to select potentially matched donors for searching patients. It is also used by foreign registries for their search algorithms. Most importantly, it is used as a resource by transplant centers worldwide in the search for potentially matched HSC donors.

THE NMDP MATCH ALGORITHM: HAPLOGIC

The transition to DNA-based HLA typing and the development of sophisticated data processing systems and serologic interpretation tables have all contributed to the recent enhancements to the NMDP match algorithm, HapLogic. Prior to the introduction of HapLogic, to provide a consistent evaluation of all donors regardless of typing method the serologic and DNA-based results were converted to serologic equivalents [21]. HapLogic employs the reverse strategy, converting serologic typings to lists of possible DNA genotypes based on serology-DNA equivalency tables. This strategy permits all of the data within the NMDP registry to be converted to genotype lists for use in donor and CBU searches. It allows reinterpretation of the genotype data to include newly described alleles, and fully permits evaluation of which alleles appear in a genotype pair together when stored primary data is available, which are distinct advantages over the previously employed serologic equivalent matching logic [22].

HapLogic also utilizes allele level haplotype frequency data calculated from a donor data set representing the primary U.S. racial/ethnic groups. The haplotype data are used to predict a probability score, indicating the likelihood that a potentially matched HSC donor or CBU will result in an allele match for

the searching patient. The initial release of HapLogic in February 2006 provided predictions on a scale of 0% to 99% for an HLA-A, -B, and -DRB1 allele match at each locus and an overall prediction for a 6 of 6, 5 of 6, and 4 of 6 allele level match. The January 2008 release incorporated prediction scores for HLA-C and -DQB1 to support donor and CBU selection for additional loci important for transplant outcome. Since the introduction of HapLogic, the NMDP has noted a 30% reduction in the number of donors requested for confirmatory typing, reflecting the utility of the predictions to rapidly identify donors or CBUs with the highest probability of matching the searching patient.

However, even with the advances in the matching algorithm, the increasing complexity of HLA assignments and matching requirements requires that transplant centers either acquire in-house HLA expertise or rely on external support. The NMDP has developed services that assist transplant centers with complex adult volunteer HSC donor or CBU searches. In particular, the HLA Search Strategy Advice program uses external and internal HLA experts to provide search strategy recommendations to help identify the best potentially matched stem cell source for a patient. In addition to providing search strategy advice, the core group of internal NMDP HLA experts rigorously check quality control and validate enhancements to HapLogic to help ensure the accuracy and utility of all modifications. The NMDP is committed to further enhancing HapLogic to simplify donor selection, but for difficult searches HLA expertise will be required for development of effective worldwide search strategies.

GUIDING OPTIMAL DONOR SELECTION

In 1994, the NMDP initiated a Navy supported research project aimed at retrospectively identifying the HLA alleles carried by donor/recipient pairs banked in the NMDP Research Sample Repository. The Repository was begun in 1987, and today contains biologic samples from over 14,000 HSCT recipients and their respective donors. The goals of the study were to develop robust high-resolution typing methods for HLA alleles and to determine the impact of HLA matching for specific loci (HLA-A, B, C, DRB1/3/4/5, DQA1, DQB1, DPA1, and DPB1) on transplant outcome. The project was the first extensive application of sequence-based typing to the HLA class I alleles. The initial samples sets were typed blindly in 2 different laboratories to evaluate the reliability and reproducibility of the results. During the testing of the first 2800 pairs, typing discrepancies dropped dramatically as the testing strategies became more robust.

In the evaluation of HLA disparities between donor and recipient in an initial 1775 pairs, 29% of 6 of 6 antigen matched transplant pairs were observed to carry allele mismatches at HLA-A, -B, and/or -DRB1, and 92% carried at least 1 allele mismatch at 1 of the 8 HLA loci tested [23]. The typing methodologies developed through this research study were adopted by the HLA laboratories supporting transplant programs. The refinements in high-resolution HLA typing have enhanced the ability of transplant centers to more completely characterize patient alleles for a more effective HSC donor search.

The donor-recipient HLA data were used in an outcome study by Flomenberg et al. [24] to demonstrate the importance of HLA-C matching. Based on this information, the NMDP published guidelines for matching in unrelated donor HSCT in 2003 [25]. Most recently, Lee et al. [26] evaluated an extended dataset (N = 3857 pairs) and showed that a single mismatch, antigen, or allele, at HLA- A, -B, -C, or -DRB1 conferred an increased relative risk for mortality of 1.25 (confidence interval [CI] 1.13-2.38, $P < .0001$) and a 9% decrease in patient survival at 1 year. Single mismatches at HLA-DP or -DQ were not associated with increased mortality in both studies. The guidelines incorporating these new results are updated in this supplement (Bray R., Hurley C, Kamani N, et al. National Marrow Donor Program HLA matching guidelines for unrelated adult hematopoietic cell transplants.) The donor/recipient HLA database also allows the evaluation of permissive mismatching strategies. One study by Wade et al. [27] determined that selection of a CREG matched donor had no impact on outcome, allowing wider latitude in mismatched donor selection.

Although the donor/recipient HLA database currently includes over 11,000 pairs and the Repository over 14,000 pairs, the population still yields limited statistical power for the evaluation of HLA matching in particular transplant situations. Therefore, the database will need to continue to accrue pairs for the assessment of HLA matching requirements for different stem cell sources (marrow versus peripheral blood versus umbilical cord blood), for different patient populations (e.g., adult versus pediatric; malignant versus nonmalignant disease; minorities) and evolving treatment strategies (e.g., reduced intensity conditioning [RIC]). The database is now routinely used as the definitive source of HLA match assignments for all research studies conducted through the NMDP and the Center for International Blood and Marrow Transplant Research.

OPTIMIZING COMPATIBILITY ASSESSMENT AND OUTCOME: WHAT DOES THE FUTURE HOLD?

Over time, the operational systems in the laboratories, in the repositories and at the NMDP have been

enhanced for accuracy, flexibility, speed, and cost efficiency. This has resulted in the development of cutting edge information and data management systems, implementation of laboratory robotic systems, and refined repository storage systems. HLA typing resolution continues to improve, resulting in near allele level typing for HLA-A, -B, and -DRB1 at donor registration. Increased efficiencies in testing may allow the typing of additional HLA loci at recruitment or more rapid typing for urgent cases.

Many research laboratories are developing new competing approaches to DNA testing methods. Most of this DNA research is focused on developing whole genome testing, and these approaches are being applied to identifying other histocompatibility loci. The methods are likely to lower the cost of DNA analysis, making it practical to determine whether additional genetic matches or mismatches may cause additional transplant risks across a potentially large number of genes. As information on the importance of other polymorphic genes in HSCT becomes available, testing strategies can be readily implemented by the NMDP through its contract laboratory network.

One drawback to current high resolution typing methods is the limitations in unambiguously identifying patient and donor genotypes. Even Sanger-based DNA sequencing produces data for both pairs of homologous chromosome sequences (e.g., HLA sequences from both the maternal and paternal genes) in each test run unless the genes are separated either physically or by allele specific amplification as part of the laboratory test. Because of the high number of HLA alleles that share sequence polymorphisms, most tests result in multiple possible alternative genotypes. The resolution of these alternative genotypes requires additional laboratory tests that can be complex, costly, and time consuming. DNA sequencing methods currently being developed analyze loci from single chromosomes independently and, if cost effective, will eliminate ambiguous typing results.

The potential advantage is low-cost unambiguous allele level typing for all newly registered volunteers and rapid allele level typing for all patients seeking HSC donors. Physicians searching for a donor for their patient will be able to identify the precise type and closeness of match almost immediately from a computer-based analysis of possible donors. Of course, the donor must be approached to assure their availability and to obtain a second sample to confirm identity. Strategies to identify the HLA alleles present in recipient and donor have resulted in better matching and the ability to develop risk-adapted therapies for mismatched transplantations, thus increasing transplant as an option for more patients. The database of donor/recipient HLA assignments and clinical outcome will continue to support research studies aimed at optimizing outcome.

The complexity involved in optimal HLA matching continues to drive the need for growth in the genetic diversity on adult volunteer HSC donor and CBU registries to supply appropriately matched stem cell sources to searching patients. The logistic and analytic methods required to rapidly identify the best potential match from worldwide sources will continue to evolve, and the NMDP will continue to develop resources necessary to facilitate the process.

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