

February 28, 2018

Lt. Cdr. Brian Andrews-Shigaki
Office Warfighter Performance S&T Dept
875 N. Randolph St.
Arlington, VA 22203-1995

Subject: Final Technical Report with SF298 by the National Marrow Donor Program®

Reference: Grant N00014-16-1-2020 between the Office of Naval Research and the National Marrow Donor Program

Dear Lt. Cdr. Andrews-Shigaki,

In accordance with the requirements of the Referenced Office of Naval Research Grant, the National Marrow Donor Program (NMDP) hereby submits the required Final Technical Report for the period of December 01, 2015, through November 30, 2017.

Should you have any questions regarding the performance activity of under this Grant, you may contact our Chief Medical Officer – Dennis Confer, MD directly at 763-406-3425.

Please direct any contractual questions pertaining to the Grant to my attention at 763-406-3401 or npoland@nmdp.org.

Sincerely,

Nancy R. Poland

Nancy R. Poland, M.A.
Contracts and Compliance Manager

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14. ABSTRACT The main objective of this grant is to develop, test and mature the ability of the National Marrow Donor Program® (NMDP) to address contingency events wherein civilian or military personnel are exposed to marrow toxic agents, primarily ionizing radiation or chemical weapons containing nitrogen mustard. An accident, a military incident, or terrorist act in which a number of individuals are exposed to marrow toxic agents will result in injuries from mild to lethal. Casualties will be triaged by first responders, and those with major marrow injuries who may ultimately be candidates for hematopoietic cell transplantation (HCT) will need to be identified. HCT donor identification activities will be initiated for all potential HCT candidates. NMDP-approved transplant centers will provide a uniform and consistent clinical foundation for receiving, evaluating and caring for casualties. NMDP coordinating center will orchestrate the process to rapidly identify the best available donor or cord blood unit for each patient utilizing its state-of-the-art communication infrastructure, sample repository, laboratory network, and human leukocyte antigen (HLA) expertise. NMDP's on-going immunobiologic and clinical research activities promote studies to advance the science and technology of HCT to improve outcomes and quality of life for the patients.					
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National Marrow Donor Program N00014-16-1-2020

**DEVELOPMENT OF MEDICAL TECHNOLOGY
FOR CONTINGENCY RESPONSE TO MARROW TOXIC
AGENTS**

FINAL BENEFITS REPORT

December 1, 2015 – November 30, 2017



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I. Heading

PI: Dennis L. Confer, M.D.

National Marrow Donor Program

N00014-16-1-2020

Development of Medical Technology for Contingency Response to Marrow Toxic Agents

II. Scientific and Technical Objectives

The main objective of this grant is to develop, test and mature the ability of the National Marrow Donor Program® (NMDP) to address contingency events wherein civilian or military personnel are exposed to marrow toxic agents, primarily ionizing radiation or chemical weapons containing nitrogen mustard. An accident, a military incident, or terrorist act in which a number of individuals are exposed to marrow toxic agents will result in injuries from mild to lethal. Casualties will be triaged by first responders, and those with major marrow injuries who may ultimately be candidates for hematopoietic cell transplantation (HCT) will need to be identified. HCT donor identification activities will be initiated for all potential HCT candidates. NMDP-approved transplant centers will provide a uniform and consistent clinical foundation for receiving, evaluating and caring for casualties. NMDP coordinating center will orchestrate the process to rapidly identify the best available donor or cord blood unit for each patient utilizing its state-of-the-art communication infrastructure, sample repository, laboratory network, and human leukocyte antigen (HLA) expertise. NMDP's on-going immunobiologic and clinical research activities promote studies to advance the science and technology of HCT to improve outcomes and quality of life for the patients.

III. Approach

A. Contingency Preparedness

HCT teams are uniquely positioned to care for the casualties of marrow toxic injuries. The NMDP manages a network of centers that work in concert to facilitate unrelated HCT. The Radiation Injury Treatment Network (RITN), comprised of a subset of NMDP's network centers, is dedicated to radiological disaster preparedness activities and develops procedures for response to marrow toxic mass casualty incidents.

B. Development of Science and Technology for Rapid Identification of Matched Donors

Disease stage at the time of transplantation is a significant predictor of survival, decreasing the time to identify the best matched donor is critical. Methods are under development to rapidly provide the best matched donor for HCT.

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C. Immunogenetic Studies in Transplantation

Improving strategies to avoid and manage complications due to graft alloreactivity is essential to improve the outcomes of HCT. Research efforts are focused on strategies to maximize disease control while minimizing the toxicity related to alloreactivity in HCT.

D. Clinical Research in Transplantation

Clinical research creates a platform that facilitates multi-center collaboration and data management to address issues important for managing radiation exposure casualties. Advancing the already robust research capabilities of the NMDP network will facilitate a coordinated and effective contingency response.

IV. Concise Accomplishments

- a. Contingency Preparedness
 - i. Executed 2 full scale exercises (City of Hope and Emory University), 2 functional exercises (Spectrum Health and Mayo Clinic) and 3 regional table top exercises (City of Hope, Medical University of South Carolina and Roger Williams Medical Center).
 - ii. Conducted training sessions and tracked training activities at RITN centers.
 - iii. Updated the Operational Continuity Plan to include the new NMDP Coordinating Center.
- b. Development of Science and Technology for Rapid Identification of Matched Donors
 - i. Supported the high resolution HLA typing of 140,660 new culturally diverse (48.5% minority) donors added to the NMDP registry
 - ii. Published the Search Prognosis Genotype Frequency study and development of a prototype online tool that provides search prognosis results (good, fair and poor).
 - iii. Completed the Proactive Info Session Phase 1 and 2 studies demonstrating a substantial improvement of donor availability at confirmatory typing or workup versus normal donor availability.
- c. Immunogenetic Studies in Transplantation
 - i. Presented results on full HLA gene matching in unrelated donor transplant pairs at the ASHI annual meeting and received a best abstract award.
 - ii. Published a manuscript in PLoS One describing KIR haplotype associations in a diverse population of more than 10,000 individuals.
- d. Clinical Research in Transplantation
 - i. Published 142 peer reviewed manuscripts and presented 87 abstracts at national/international meetings.

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- ii. Initiated 35 new study protocols for the 2016-17 academic year.
- iii. Completed the cord blood release criteria analysis and presented results to the NMDP Cord Blood Advisory Group.
- iv. Released the RITN data collection forms in the CIBMTR FormsNet application.
- v. Implemented Medidata Rave for clinical trials management and data collection.

V. Expanded Accomplishments

Contingency Preparedness

Maintain the Radiation Injury Treatment Network (RITN) to prepare for the care of patients resulting from a hematopoietic toxic event.

Hospitals are eligible to join RITN if they participate in both the NMDP Network of treatment centers and the NDMS. The NDMS is comprised of over 1,800 accredited hospitals across the nation that have agreed to receive trauma casualties following a disaster. The program is managed by the Department of Health and Human Services. RITN conducts targeted recruitment on an annual basis with a goal of expanding the network. During the grant period, one new transplant centers joined RITN; resulting in a total composition of: 66 transplant centers, 5 donor centers, and 6 cord blood banks (Figure 1). The new centers that joined RITN were:

1. University of Virginia (VA)

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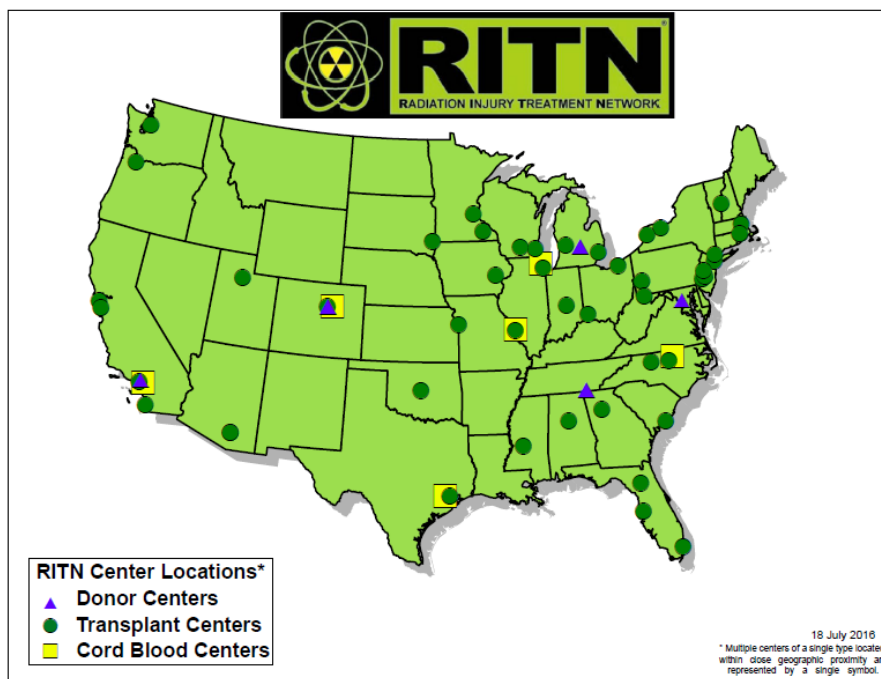


Figure 1. Location of RITN Centers

RITN Preparedness Activities

RITN centers were asked to continue to develop their level of preparedness during 2016. Tasks included communications drills, updating of standard operating procedures, outreach to local public health and emergency management contacts, a tabletop exercise and training of staff.

During 2016, 100% of active RITN centers completed all of their required annual tasks (Figure 2), which is consistent with the performance during previous years.

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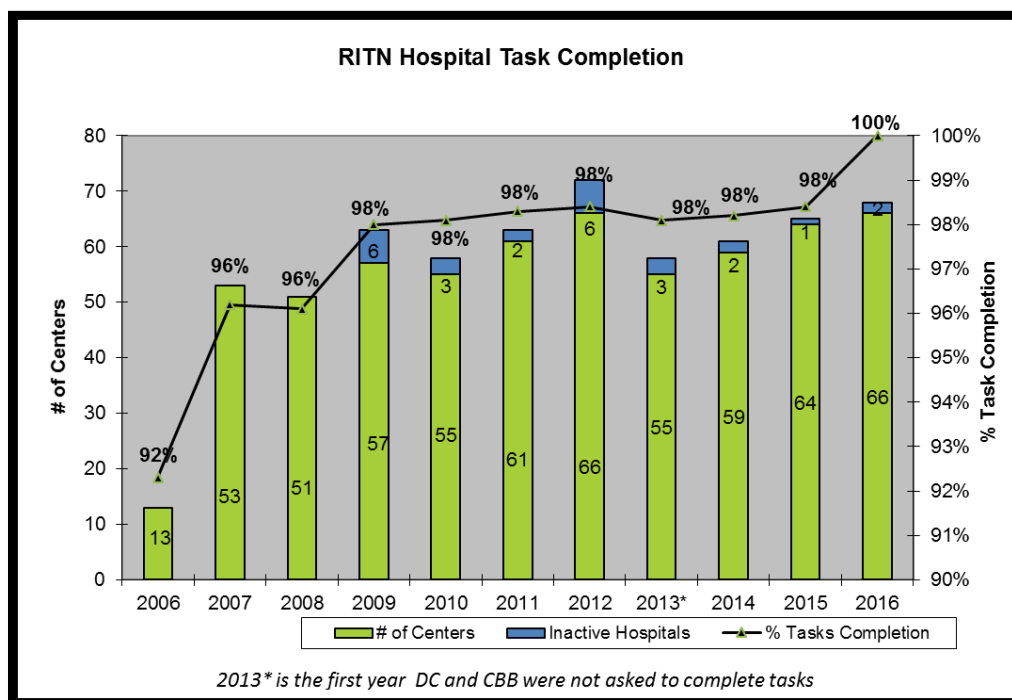


Figure 2. RITN annual training task completion rates by year

- **RITN Exercise Program:** RITN coordinates or provides support for many radiological exercises each year; these include full-scale, functional, regional tabletop and tabletop exercises (the intensity and effort required decreases accordingly from full-scale to tabletop). RITN has facilitated more than 580 exercises since 2006 (see Figure 5 for breakdown by type). During 2016 multiple radiological disaster exercises were supported across the nation. RITN coordinated and funded the following radiological disaster exercises:
 - Regional tabletop exercises in:
 - Los Angeles, CA (City of Hope National Medical Center)
 - Charleston, SC (Medical University of South Carolina)
 - Providence, RI (Roger Williams Medical College)
 - Full-scale exercises in:
 - Los Angeles, CA (City of Hope National Medical Center)
 - Atlanta, GA (Emory University Hospital)
 - Functional exercises in:
 - Rochester, MN (Mayo Hospital Clinic)
 - Grand Rapids, MI (Spectrum Health Medical Center)
 - Three special full scale exercises were funded through a partnership with the State of Illinois; these were conducted with key hospitals surrounding

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the Chicago metro that would be involved in the immediate response to a radiological disaster including:

- Order of Saint Francis-Saint Anthony Medical Center
- Riverside Medical Center
- Morrison Community Hospital
- Annual RITN tabletop exercise conducted by 64 hospitals
 - 40 hospitals participated in one of six web based tabletop exercises that were facilitated by RITN
 - 20 hospitals facilitated the RITN exercise on their own
- After Action Reports are posted on RITN.net

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Figure 3: Images from the City of Hope National Medical Center exercise August 2016.

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Figure 4: Images from the Emory University Hospital exercise September 2016

These exercises involved many external partners necessary for the response including:

- American Medical Response
- American Red Cross
- Blood Center Olmsted County
- California Department of Public Health / Emergency Medical Services Agency
- Care Ambulance
- Charleston County
- Charleston Office of Emergency Management
- City of Rochester
- City of Rochester Emergency Management
- Columbia Federal Coordinating Center
- Department of Public Social Services (LA County)
- Disaster Management Systems
- Health and Human Services /Assistant Secretary for Preparedness and Response
- Hospital Association of Rhode Island
- Kent County Emergency Management
- Kent County Health Dept.
- LA County Department of Public Health
- LA County Department of Homeland Security/Emergency Medical Services
- Long Beach Health Department
- Mayo Clinic Health System
- MCG, Inc
- Memorial Blood Center
- Michigan Blood

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- Michigan Department of Health and Human Services
- National Disaster Medical System and VA
- Pomona Valley Hospital Medical Center
- Providence Veteran's Administration Medical Center
- Region 6 Health Care Coalition
- Rhode Island Blood Center
- Rhode Island Department of Environmental Management
- Rhode Island Department of Health
- Rhode Island Emergency Management Agency
- Roger Williams Medical Center
- Roper St. Francis Hospital
- SC Department of Health and Environmental Control
- SC Hospital Association
- Schaefer Ambulance
- Southeast Minnesota Healthcare Coalition Partners
- The Salvation Army
- University of California – Los Angeles
- Veterans Administration Boston
- Veterans Administration Greater Los Angeles Healthcare System

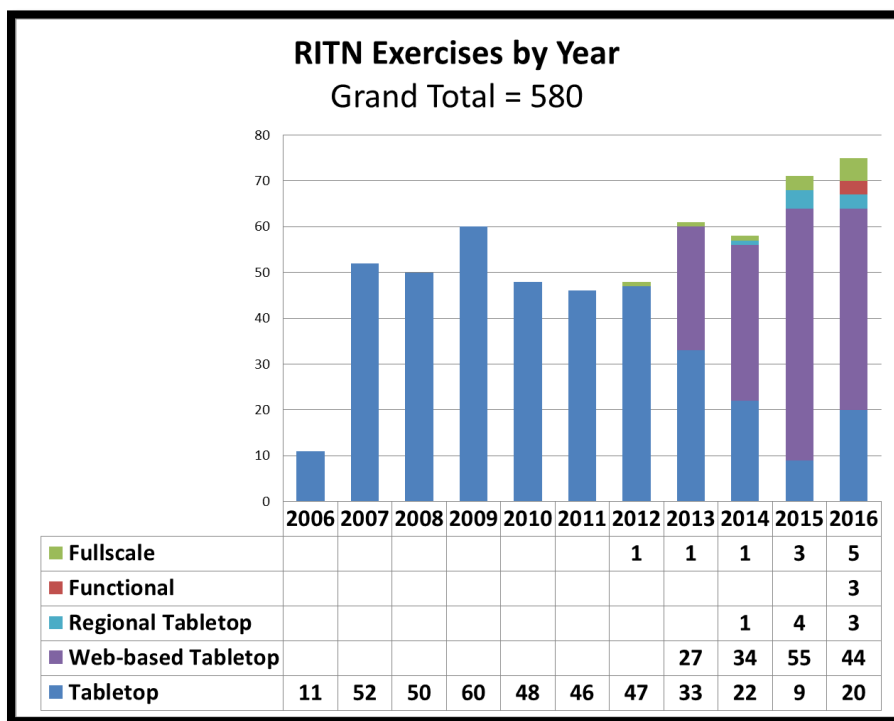


Figure 5. Number of RITN centers participating in exercises by year.

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Tabletop exercises

The 2016 tabletop exercise presented a scenario where a 1 kT improvised nuclear device was detonated in a metropolitan area, each hospital was asked specific questions about their Family Information Center planning to reconnect patients with their families. The number of RITN centers participating in tabletop exercises annually is summarized in Figure 5. A summary of RITN tabletop exercises conducted to date is provided in Table 1.

Table 1. Summary of annual RITN tabletop exercise scenarios and level of patient surge.

Summary of RITN Tabletop Exercise Scenarios		
Year	Scenario	Max Victims
2006	Radiological Exposure Device (RED) placed on public train system	650 identified as having some level of ARS. 50 patients to each center
2007	Train derailment spills multiple chemicals, produces vapor cloud which exposes a crowd of 15,000	5,000 (mostly children and senior citizens)
2008	IND was detonated and 300,000 victims were triaged	5,000 victims required RITN assistance
2009	10-kiloton nuclear device detonated in a major metropolitan center	12,000 patients with high radiation dose in the 200-600 rad range. 300 patients to each center
2010	Detonation of a surface burst 10-kiloton nuclear device in major metropolitan center	20,000 patients with high radiation dose in the 200-600 rad range. 500 patients to each center
2011	National Disaster Medical System (NDMS) flow and integration	Not specified
2012	1 KT IND detonated 500 miles away from RITN center, 20 patients to prioritize using provided casualty cards	20 casualty cards w/ limited bed availability provided
2013 w/ Webinar Option	Radiological exposure devices placed on mass transit vehicles in multiple US cities	4,500 casualties nationwide; 300 patients and 140 family members are sent to each RITN center
2014 Primarily Webinar	Detonation of a 1KT IND	100 patients from a large metropolitan area 500 miles away
2015	Four Radiological Exposure Devices (RED) planted on a university campus	20 adult and 20 pediatric patients with detailed patient profiles and required medical evaluation
2016	1 kiloton improvised nuclear device (IND) detonated in a metropolitan area 500 miles away	30 patients (adult or pediatric depending on the hospitals focus) with special emphasis on Family Information Centers to connect patients with their families

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RITN Sponsored Regional Tabletop Exercises

During 2016 three regional tabletop exercises were conducted across the nation (Los Angeles, CA – City of Hope National Medical Center; Charleston, SC – Medical University of South Carolina; Providence, RI – Roger Williams Medical College). Regional tabletop exercises were developed by RITN to fill a gap in planning efforts. Communities prepare for disasters that effect their community or their region; but few had considered the surge of casualties from a distant radiological incident. We brought together leaders in public health, emergency management, law enforcement, healthcare, federal agencies and non-governmental agencies that support disaster response. Then we presented a scenario where a radiological disaster occurred more than 1,000 miles away and asked how they would prepare to receive a surge of medical casualties in 7-10 days (per the RITN concept of operations).

RITN Sponsored Full-Scale and Functional Exercises

During 2016 two full scale exercises and two functional exercises were sponsored by RITN. The full scale exercises were held at City of Hope National Medical Center and Emory University. The functional exercises were held at Mayo Hospital Clinic and Spectrum Health Medical Center. Each year RITN solicits hospitals from RITN to submit proposals to conduct full-scale or functional exercises. A full scale exercise is significantly larger in scope than a functional exercise. Functional exercises test one specific area such as public communications, emergency operations center activation or patient tracking. Full scale exercises include all aspects of the response. Those given awards receive funding to help conduct the exercise; in exchange for the funding RITN receives copies of all materials which are posted online to help other organizations plan for and conduct their own radiological disaster exercises.

Training tasks

RITN centers are asked to conduct training with the intent to educate and increase the awareness of RITN and its efforts to the appropriate response community. Training options continue to be accessible online at no cost to anyone who is interested. In addition, the in person training option has expanded to include an Advanced HAZMAT Life Support (AHLS) for Radiological Incidents course. As shown in Figure 12 the training options continue to grow, centers can now choose between conducting Basic Radiation Training, having a physician or Advanced Practitioner complete the REAC/TS training, hosting an AHLS course, conducting an Acute Radiation Syndrome Medical Grand rounds session, and having a site assessment conducted. In addition, centers can conduct community outreach and education using the RITN Overview Presentation. All of these materials, with the exception of the REAC/TS training, are available unrestricted, through the RITN website. The RITN web based training catalog includes:

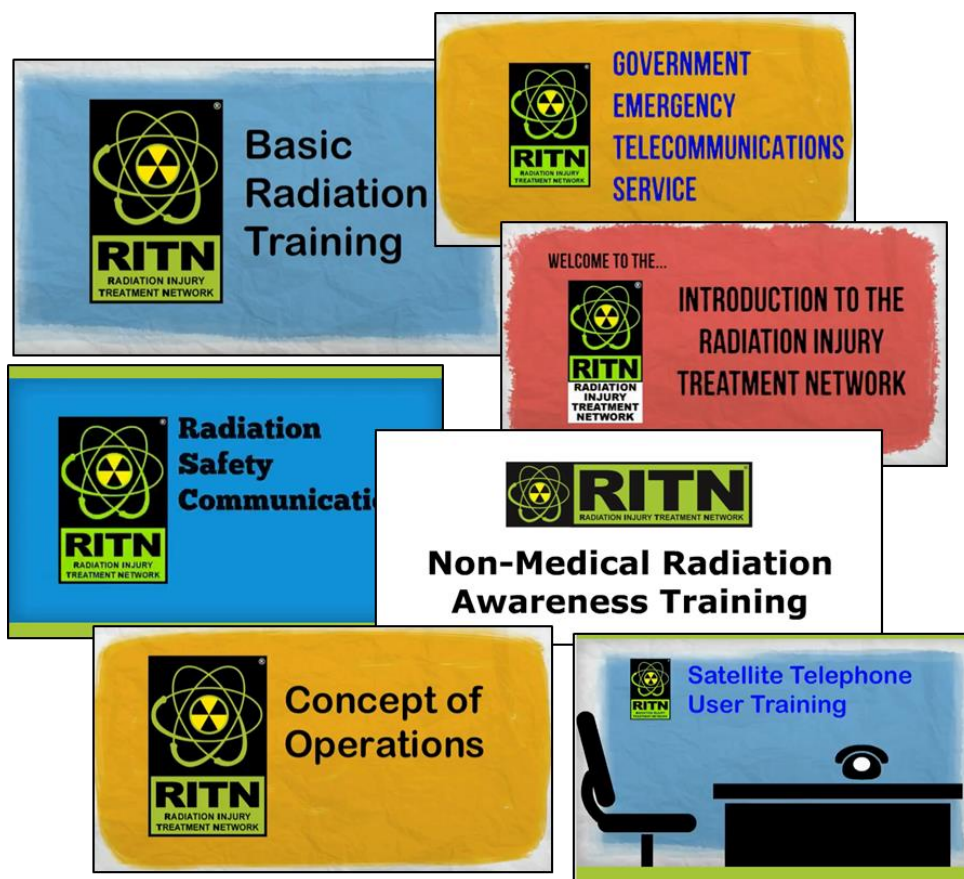
1. Introduction to RITN
2. RITN Concept of Operations
3. GETS 101
4. Satellite telephone 101

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5. Basic Radiation Training
6. Non-medical Radiation Awareness Training
7. Radiation Safety Communication Course

The online learning management system allows RITN center staff to complete the full course at their own pace and receive an electronic certificate of completion after meeting all the course objectives and knowledge assessments. Since 2006, RITN has had a hand in the disaster response training or education of over 13,500 medical staff affiliated with RITN hospitals.



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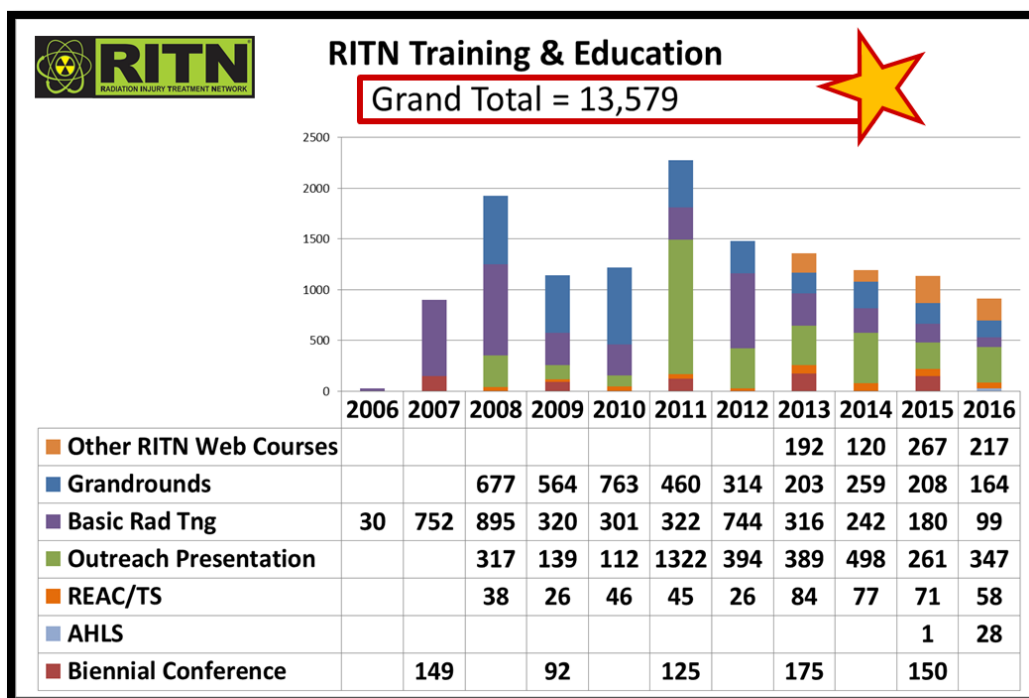


Figure 6. RITN center staff training accomplished by year.

In 2011, RITN initiated the Site Assessment program. RITN Control Cell staff members review existing documentation at RITN transplant centers using a standardized checklist to assess overall preparedness. Areas evaluated include Casualty Processing, Outpatient Treatment of Casualties, Inpatient Treatment of Casualties, Coordination with City, State and Regional Assets, and Documentation.

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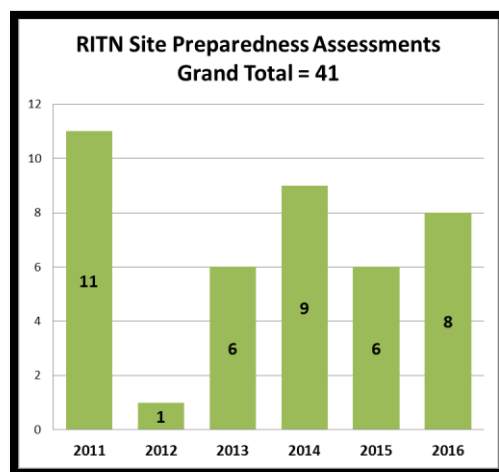


Figure 7. RITN center site assessments by year.

The Site Assessment Checklist formed the basis for revisions to the standard operating procedure (SOP) template that all centers used to update their local SOPs. The RITN site preparedness assessment activity since 2011 is summarized in Figure 7.

The RITN continuously seeks to formalize and develop further partnerships with federal agencies and organizations.

Memoranda of Understanding (MOU) have been established with the following groups to collaborate on preparedness efforts:

- ASBMT since 2006
- Department of Health and Human Services – Office of the Assistant Secretary for Preparedness and Response (HHS-ASPR) since 2007
- AABB-Disasters Task Force since 2008
- European Group for Blood and Marrow Transplantation - Nuclear Accident Committee (EBMT-NAC) since 2011

Additionally, the RITN maintains informal relationships to increase awareness about RITN worldwide through close interaction with:

- Biomedical Advanced Research and Development Authority (BARDA)
- Health Resources and Services Administration (HRSA)
- World Health Organization - Radiation Emergency Medical Preparedness and Assistance Network (WHO-REMPAN)
- Radiation Emergency Assistance Center and Training Site (REAC/TS)
- Armed Forces Radiobiology Research Institute (AFRRI)
- National Institute of Allergy and Infectious Diseases (NIAID)

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- National Institutes of Health (NIH) - National Library of Medicine (NLM) - Radiation Emergency Medical Management (REMM)
- American Hospital Association (AHA)
- Association of State and Territorial Health Officials (ASTHO)
- National Association of City and County Health Officials (NACCHO)
- Veteran's Administration Health System
- Centers for Medical Countermeasures Against Radiation (CMCR)
- National Security Council staff
- National Alliance for Radiation Readiness (NARR)



RITN uses Health Care Standard® (HCS®) software to consolidate participating hospitals Capability Reports and to communicate situation status updates to the network through a web based interface. Annual tests are conducted to ensure that users are familiar with the system and that it is capable of receiving and consolidating submitted data. This system allowed RITN to collect the bed availability and on-hand G-CSF quantities throughout the network during a prior grant period.



The Assistant Secretary for Preparedness and Response from the Department of Health and Human Services has been a partner since the foundation of RITN. This partnership is formalized through an MOU and is prominently displayed on the Department of Health and Human Services website for Public Health Emergencies on the Chemical, Biological, Radiological, Nuclear and Explosive Branch page, (<http://www.PHE.gov/about/oem/cbrne>, and Figure 8):

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Figure 8. Chemical, Biological, Radiological, Nuclear and Explosive Branch webpage noting the partnership with RITN.

NMDP's critical functions must remain operational during contingency situations that directly affect the Coordinating Center.

During the last grant period, the NMDP updated the majority of associated documentation to be in alignment with the new Coordinating Center location in downtown Minneapolis. The Operational Continuity Steering Committee reviewed changes and additions to the plan at the annual meeting. The committee is chaired by the Chief Medical Officer and seated by the Chief Information Officer; Chief Financial Officer; Chief Legal Officer; Chief Operating Officer; and Chief Human Resources Officer.

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Development of Science and Technology for Rapid Identification of Matched Donors

Increasing the resolution and quality of the HLA testing of volunteers on the Registry will speed donor selection.

Increased diversity of newly recruited donors

In NMDP FY16 (Oct. 2015-Sept. 2016), NMDP donor centers (including Department of Defense (DoD)) and recruitment groups recruited 157,699 minority race and 169,171 Caucasian donors, for a total of 326,870 U.S. donors added to the registry. Navy funding supported the HLA typing of 140,660 donors (excluding DoD) of this culturally diverse group (48% minority).

Advancing technology improved performance and pricing

The NMDP typing strategy maximizes the use of funds by utilizing new typing methodologies that deliver a higher resolution of results at a lower cost than previous methods. The overall goal is to ensure that new donors are listed on the registry with the best possible resolution and number of loci tested. This is particularly critical during times of a contingency where well HLA-characterized adult donors must be readily matched to patients in need of HCT for ARS.

- Since April 2014, all new donors are typed at minimum of HLA-A, B, C, DRB1, DQB1, and DPB1.
- Beginning April 2015, all donors were typed by an exon-based NGS approach that delivered G-group resolution or better.

Enhancing Non-HLA data for selected donors

Transplant centers utilize donor CMV status and blood type (ABO/Rh) as non-HLA selection factors when multiple equally well matched donors are available. Historically, the only process to obtain this information is to request the potential donor on behalf of the patient, obtain a fresh blood sample, and perform IDM tests that include the donor blood type and presence/absence of circulating antibodies to CMV.

ABO/Rh at Recruitment by DNA-based testing

Due to recent advances in testing methodology (primarily due to NGS), it became feasible to explore adding ABO/RhD as another locus that could be tested from the same sample at the same time as recruitment HLA testing. The NMDP made sets of 1000 blind samples available to two

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laboratories for validation testing. A high degree of concordance between genetic ABO/RhD result and known serological ABO/Rh was seen for both sets (>97% concordance). DNA-based ABO/RhD testing on a portion of recruitment samples began in August, 2014. As of October 01, 2014, all recruitment samples receive ABO/RhD testing along with HLA testing as noted above.

Additional Projects to Ensure Quality of HLA Data

Following the success of the review of rare allele typing and the identification of alleles which were incorrectly typed, this project has evolved to evaluate many aspects of uncommon alleles reported in the Be The Match Registry. Two scenarios evaluated in this time period were the review of HLA results of imputed non-CWD alleles due to the reporting of novel haplotypes and incorrect reporting of alleles around the time when a similar, population specific, allele was described. These typings were identified as suspicious and thought to have been incorrectly reported due to the following reasons:

- Typing methodologies used to report the allele were problematic
- Allele reporting of the allele in question were more prevalent prior to 2006
- Presence of two less common alleles in a donor typing
- Primary data interpretation does not support the reported typing
- Allele reported in a race/ethnic group different from the reference cell in the IMGT/HLA database

Samples were identified using the above rules and retyped by SSOP technology. A total of 1780 samples were typed through the project under this grant.

Table 2 shows the results of the retyping of 1421 non-CWD or uncommon reported allele calls many of which initially had supporting primary data. The low confirmation rate demonstrates that the primary data reporting had inaccurate results for the actual rare/uncommon allele calls.

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Table 2. Results of the re-typing of 1421 non-CWD allelic results reported to the Registry.

	# typed	corrected	% corrected
HLA-A	185	128	69%
HLA-B	291	143	49%
HLA-C	8	8	100%
DRB1	898	346	39%
DRB3/5	365	217	59%
DQB1	33	25	76%

Another group of samples were identified with typing from the 1990's when reporting requirements were different. These samples were reported with typing results which are no longer acceptable for reporting of HLA alleles. As a results, these donor samples may be excluded from international partners as is the case with 'X' serologic designations or require manipulation of the results to make them compatible with international partner reporting requirements, as is the case when DNA is reported using broad serologic designations such as DRB1*06:XX. Samples were identified and retyped by Sequence Specific Oligonucleotide Probes (SSOP) or Sequence Based Typing (SBT) technology. .

Table 3 shows the results of the retyping of 359 non-Common Well Documented (CWD) allele calls or outdated serology and DNA based typing results. Over 50% of the results were corrected. In the case with the imputed C corrected category, identifying the actual HLA-C in the rare haplotype provides further information to correctly inform the EM on rare HLA haplotypes. Improvement of these data will allow for more accurate prediction of rare haplotypes in future EM iterations. In addition, updating HLA type to current standards will allow more donors to be properly displayed on international partner sites for worldwide view of donors.

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Table 3: Results of retyping non-Common Well Documented allele calls or outdated serology and DNA-based typing results on the Be The Match registry.

Outcome of retyping efforts	Counts
Confirmed	141
Corrected	153
Imputed C corrected	65
Grand Total	359

Proactive Info Session Phase 1

Research suggests that stem cell transplantation that performed in the early disease stage results in more successful patient outcomes (Lee et al., 2007). However, time to transplant for a patient can be delayed due to waiting for confirmation of donor availability, completion of donor HLA typing, and evaluation of non-HLA factors, such as age, ABO, and CMV status. The aim of this project was to provide transplant centers with a pool of pre-screened, fully-matched donors that are able to go immediately to workup if a patient's search is urgent, and which are optimized for the patient's non-HLA factors. Prospective donors were contacted to confirm availability, underwent additional testing to upgrade non-HLA information, and were given a proactive information session to further educate and prepare them should they be asked to donate for a patient.

Ninety patients from U. S. transplant centers have been enrolled in this project. To date, 39% of those cases that received donor recommendations from the pre-screened pool subsequently activate one of those donors. Additionally, transplant centers that formalize donors before any recommendations can be provided are identifying these pre-screened donors themselves.

Overall, 36 of 105 donors that completed this process have been requested for confirmatory typing with some donors activated for multiple patients. To date, 13 enrolled donors have been selected for workup, and 5 have proceeded to or are scheduled to donate. Additionally, availability at confirmatory typing (CT) or workup for these enrolled donors was 85%, compared to 50% availability for similar donors that did not complete this process. Upgrading the availability, HLA, and non-HLA information displayed to transplant centers allows them to optimize their donor selections, as well as move quickly if a patient's search is urgent.

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Proactive Info Session Phase 2

Thirty nine patients from U. S. transplant centers were enrolled in this project. To date, 21% of those cases that received donor recommendations from the pre-screened pool subsequently activate one of those donors. Additionally, transplant centers that formalize donors before any recommendations can be provided are identifying these pre-screened donors themselves.

Overall, 18 of 61 donors that completed this process were activated, with some donors activated for multiple patients. To date, 6 enrolled donors have been selected for workup, and 3 have proceeded to or are scheduled to donate. Additionally, availability at confirmatory typing (CT) or workup for these enrolled donors was 83% which compares to typical donor availability around 50%.

Primary DNA typing data can be used within the Registry to improve the quality and resolution of volunteer donor HLA assignments.

An HLA assignment obtained by SSOP, DNA-based testing methods is derived from the positive and negative hybridizations of oligonucleotide reagents that define the presence of specific nucleotide sequences. Using this information and a list of known HLA alleles with their primary sequences, the typing laboratory interprets the hybridization results into possible allele combinations (interpreted data). The information for which polymorphic nucleotide sequences are present or absent is termed “primary data.” Similar primary data are available from other DNA-based methods, sequence specific primers (SSP) and sequence-based typing (SBT).

Several informatics challenges face the NMDP in regard to DNA-based HLA typing:

- New HLA alleles are described at a rate of approximately five per week.
- The low/intermediate resolution typing of newly recruited donors is reported as groups of potential alleles within families and assignments become outdated as new alleles are discovered within these families.
- Almost every low/intermediate resolution HLA assignment will be outdated within a single year unless a mechanism is developed to retrospectively incorporate newer alleles into previously reported results.

Searches are difficult for patients who carry new alleles, as matching must consider the donors tested before the new alleles were described.

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Because the low/intermediate resolution of the HLA typing usually includes strings of possible alleles, the laboratory must condense down the assignments into single reportable combinations that separate the possibilities for each chromosome at that locus. For example, A*02:01/02:02 and A*03:02/03:03 will be reported in the condensed format A*02:AB, 03:BC. Through this reporting process, new allele genotypes are implied which did not exist when the two chromosomes were actually tested together.

Example:

1st chromosome	2nd chromosome	
A*02:01	A*03:03	Actual genotype pair 1
A*02:02	A*03:02	Actual genotype pair 2
A*02:01	A*03:02	Did not exist
A*02:02	A*03:03	Did not exist

In this example, A*02:01, 03:03 or A*02:02, 03:02 were the actual interpreted possible types for a donor. The condensation into codes creates the additional potential types of A*02:01, 03:02 and A*02:02, 03:03 which did not exist at the time the laboratory performed the testing. This situation is termed “phase mismatching.” To further complicate the search process, due to the low/intermediate resolution donor typing, a patient with a less common allele might appear to have many potential donors, but the majority of these donors will not carry the patient’s assignment when tested at a higher level of resolution.

HLA typings based on nomenclature become outdated and diminish in value over time. This objective sets a new standard for managing HLA data by developing standards, methods, data formats and tools that allow the raw DNA information to be used.

Data Standards Hackathon

A Data Standards Hackathon (DaSH) meetings was held Feb 12-13, 2016 in Minneapolis. We had over 40 attendees with broad representation from hardware and software vendors, registries and academia. There was a strong presence from Europe to ensure any decisions are acceptable to the international community. The feature-service (<http://feature.nmdp-bioinformatics.org/doc/>) was a cornerstone of the event. All HLA and KIR variants are stored in this database and the tooling is now in place to offer fully automated accessioning of new variants at any region

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(intron, exon, UTR) of any HLA or KIR gene. This system will form the basis for reporting of novel variants for the 17th IHIW.

Over the course of the meeting we worked on the following additional efforts:

- Standardized reporting using GL string
- Converting to and from VCF and to and from PED formats
- Addressing issues about how to represent phase in consensus sequences
- A tool for applying coordinate systems to consensus sequence
- Predicting known splice errors/variants for HLA, and providing annotation
- Graph based assembly (FASTG, GA4GH)

Histo-immunogenetic Markup Language Gateway

We have implemented a new “HML Gateway” which increases our data processing capabilities utilizing cloud-based computing, and enhances the stability and security of information transmitted to the registry. The HML message format allows for the acquisition of genetic data that will be used for matching donors and recipients typed by Next Generation Sequencing technologies. Transplant Centers and other network partners depend upon the data accepted by the HML Gateway system for this purpose and will benefit by higher resolution and additional gene families.

MAC and FHIR HL7 Terminology Service

HL7 FHIR makes extensive use of defined vocabularies and terminologies to ensure structured reporting as unambiguous as possible. These include Code Systems and Value Sets, and Terminology Services to support these (see <https://hl7.org/fhir/terminology-service.html>). To use FHIR resources effectively, FHIR terminology services for histoinmunogenetics need to be developed. For example, a HL7 FHIR Terminology Service API has been developed for a set of code systems that could potentially be used by the NMDP for nomenclature-level HLA data. This service has been implemented as an API gateway to the Multiple-Allele Code (MAC) service.

The service operates mainly on three HLA code systems, labeled here as hla-multiple-allele-code, hla-amino-acid-allele, and hla-genomic-allele. Conceptually, the three code systems are non-overlapping: hla-multiple-allele-code includes only multiple-allele codes, hla-amino-acid-

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allele includes only 2-field short allele names and short names where an expression suffix has been transposed, and hla-genomic-allele includes only full-length IMGT/HLA genomic allele names. While it is possible for seemingly equivalent codes to be defined in both the hla-amino-acid-allele and hla-genomic-allele code systems, the exact meaning of such a code may differ depending on which code system (and version) defines it.

Source code for the prototype "MAC and FHIR" terminology service is on Github:

<https://github.com/nmdp-bioinformatics/nmdp-fhir/tree/master/nmdp-fhir-mac-gateway-parent>

HL7 FHIR Connectathon

HL7 hosts a FHIR Connectathon immediately prior to its Working Group Meeting, which is held three times a year. This is an opportunity for FHIR implementers to road test developing resources and profiles with different use cases.

The FHIR resources and profiles developed by the CGWG were tested during two recent HL7 FHIR Connectathons, held Jan 9-10, 2016 in Orlando, FL (http://wiki.hl7.org/index.php?title=FHIR_Connectathon_11), and May 7-9, 2016 in Montreal Canada (http://wiki.hl7.org/index.php?title=FHIR_Connectathon_12). NMDP sent two staff members to these connectathons (Bob Milius & Joel Schneider) to participate in the Clinical Genomics track with the goal of developing and exchanging HLA typing reports using existing FHIR resources and profiles. From these experiences, it became clear that enthusiasm for FHIR has not diminished and tools for exchanging HLA and KIR typing data are being developed, although further development of these resources and profiles are needed. During these connectathons, we were able to construct a transaction bundle that included Patient, Specimen, Sequence, and Observation Resources for a limited HLA typing report which was received without errors to a development FHIR server hosted by Cerner (<http://cerner-genomics.herokuapp.com/baseDstu3>). This was particularly exciting to see how an emerging FHIR specification can be implemented by different organizations including vendors to receive HLA typing data including genetic sequences.

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Manuscripts:

- Monos D, Maier MJ. Progressing towards the complete and thorough characterization of the HLA genes by NGS (or single-molecule DNA sequencing): Consequences, opportunities and challenges. *Hum Immunol.* 2015 Dec; 76(12):883-6. doi: 10.1016/j.humimm.2015.10.003.
- Milius RP, Heuer M, George M, et al. The GL service: Web service to exchange GL string encoded HLA & KIR genotypes with complete and accurate allele and genotype ambiguity. *Hum Immunol.* 2015 Nov 24. pii: S0198-8859(15)00578-9. doi: 10.1016/j.humimm.2015.11.017.
- Mack SJ, Milius RP, Gifford BD et al. Minimum information for reporting next generation sequence genotyping (MIRING): Guidelines for reporting HLA and KIR genotyping via next generation sequencing. *Hum Immunol.* 2015 Dec; 76(12):954-62. doi: 10.1016/j.humimm.2015.09.011.
- Milius RP, Heuer M, Valiga D, et al. Histoimmunogenetics Markup Language 1.0: Reporting next generation sequencing-based HLA and KIR genotyping. *Hum Immunol.* 2015 Dec; 76(12):963-74. pii: S0198-8859(15)00434-6. doi: 10.1016/j.humimm.2015.08.001.

In the past year we developed the HLA 1.0 data standard and the HML Gateway, a cloud based message processing pipeline for validating HML 1.0 messages. The focus of this aim in the next year is on development of a system for downstream storage and analysis of genomic data.

NGS technologies have brought about a shift in the focus of HLA testing from targeted sequencing of 1 or 2 exons to methods that target the full genes – in some cases spanning between untranslated regions (UTRs). As of IMGT/HLA Release 3.24.0, less than 7% of the named classical HLA alleles have curated full-length gene sequences or sequences outside the antigen recognition domain (ARD).

The first step in characterizing full-gene HLA sequence data is to investigate genetic variants, polymorphism, SNPs and linkage disequilibrium (LD) within the entire gene region for the classical HLA. Using pilot full-gene HLA data in the previous year of this grant, we performed multiple sequence alignment on full-length HLA Class I alleles (HLA-A, -B, -C) and partial-length (from intron 1 through intron 3) Class II alleles (HLA-DQB1, -DRB1) for 15,865 subjects followed by gene annotation. An automated gene annotation pipeline was developed that uses a number of open-source Bioinformatics tools (Clustal-Omega, ExonFinder, UniqueSeq) to parse consensus sequences from HML messages, perform alignment to references, predict exon-intron structures, and remove duplicates.

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Sequence weight distribution indicated good alignment coverage especially in exon regions (Figure 9). Uniqueness analysis revealed thousands of full-length HLA variants that are potential novel alleles. In consideration of unique CDS and protein products, ~50% of the variation was found in exons, resulting in 20% - 25% non-synonymous changes in class I HLA genes. Further analyses showed that exons 2 and 3 have significant high variability ($p < 0.0001$), enabling flexibility of the ARS. Introns 2, 3, and 5 of class I HLA genes have high variability also at a significance level of 0.001.

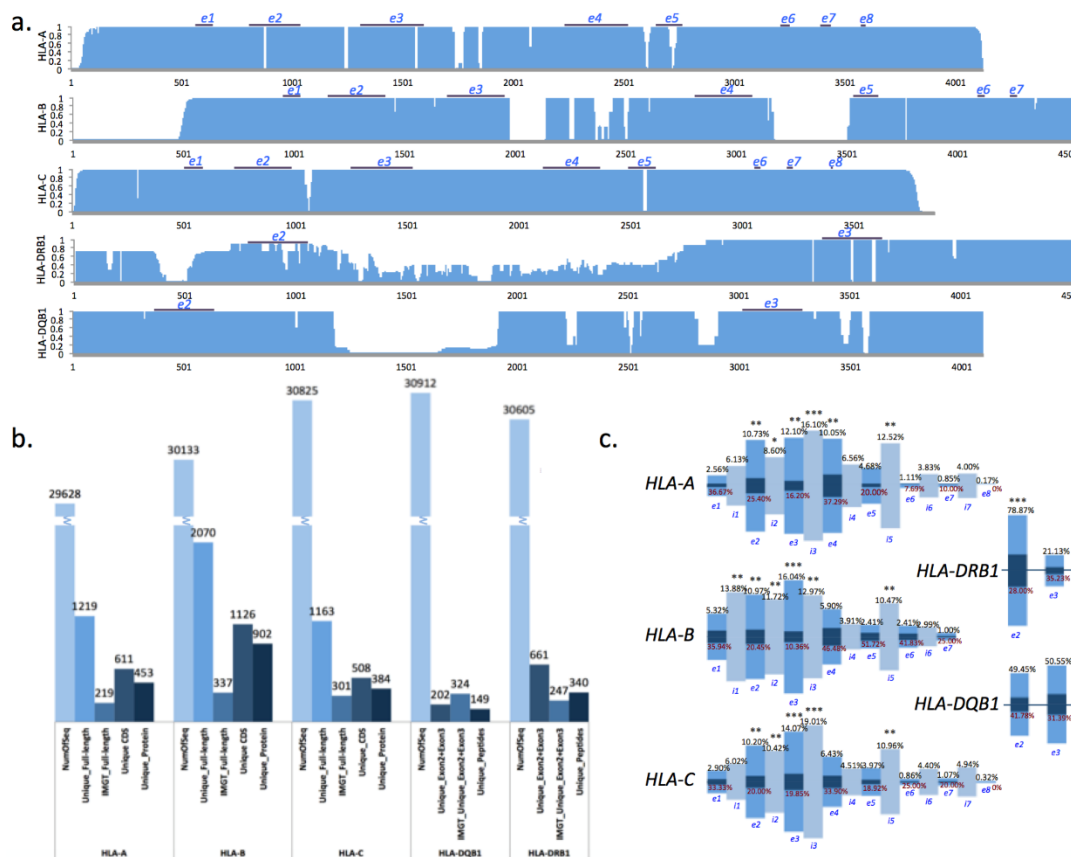


Figure 9: Genetic variation of HLA. (a). Alignment weight distributions. (b). Uniqueness analyses. (c). Proportion of variations. Dark blue indicates the non-synonymous variations.

We analyzed the Shannon's entropy of each nucleotide site and mutual information within each of the five loci. Conditional asymmetric linkage disequilibrium (ALD) measures were employed

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to characterize the LD between multiallelic SNPs within a locus. We found high levels of variation in untranslated regions of the HLA Class I alleles. Additionally, highly variable sites (entropy>0.01) appear most in the noncoding regions (intron 4 in HLA-A; introns 1 and 4 in HLA-B; introns 2 and 4 in HLA-C). Among non-ARS coding regions, exons 5 and 6 show high variation. However, considering the ambiguous gaps introduced by multiple sequence alignment, the distribution of variable sites was different after removing sites with at least one alignment gap. For noncoding regions, introns 1, 5 and 6 in HLA-A, intron 1 in HLA-B and intron 4 in HLA-C show the highest entropy variation; whereas for coding regions, exons 2 and 3 show the highest entropy variation across all five loci. The ALD measures indicate that highly associated polymorphic sites mostly reside within exons 2, 3 and 4 (exons 2/3 for class II). Some of these associations also showed high heterogeneity.

In order to address the nomenclature challenges posed by NGS-based full-gene HLA we have developed the “feature service”, a free, public web-service that accepts the submission of pre-curated sequences for individual features of HLA and KIR genes. The feature service (<http://feature.nmdp-bioinformatics.org>), allows full or partial HLA and KIR consensus sequence to be processed, accessioned and persisted so that each unique sequence for a particular locus, term (exon, intron, UTR, etc.) and rank (2,3,4, etc.) is assigned a unique identifier for analysis. Rank distinguishes features identified with the same term. For example, HLA-A exon 1 is defined as locus=HLA-A, term=exon, rank=1; HLA-A exon 2 uses the same locus and term identifiers, but is assigned rank=2; HLA-A intron 2, uses the same locus and rank, but is assigned term=intron, etc. The service uses JSON POST and GET operations to allow rapid, automated sequence data submission and retrieval, and any Gene Ontology term can be submitted as a feature service term. The service has been populated with 47,253 unique exon, intron and UTR feature sequences for the 14,473 alleles in IMGT/HLA Database version 3.24.0 and 8,192 unique feature sequences for the 753 alleles in IPD-KIR Database version 2.6.1. Features representing full-gene NGS HLA genotyping for 25,000 samples generated by two independent laboratories have been submitted as well. By identifying the locus, term, rank and accession number for the gene feature sequences of each allele, the gene sequences of known and novel alleles can be accurately described in the absence of HLA nomenclature. By sharing HLA and KIR gene sequences in this way, they can be applied for clinical and research purposes prior to curation by the IPD databases.

Presented 3 abstracts at the 2016 ASHI annual meeting in St. Louis, MO in September 2016.

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- Huang H, Wang W, Bolon Y, et al. Information theory-based analysis of classical HLA genes
- Wang W, Bolon Y, Huang H, et al. A method for large-scale analysis of HLA genetic variation
- Maiers M, Pearson E, Bashyal P, et al. The feature service: a community resource for automated annotation of HLA & KIR sequence variants

Registry data on HLA allele and haplotype frequencies and on the nuances of HLA typing can be used to design computer algorithms to predict the best matched donor or cord blood unit.

HLA allele and haplotype frequencies are central to matching and the selection process as well as for more strategic tasks such as modeling registry growth or estimating match rates beyond the typing resolution of the donors in the registry.

Manuscripts:

- Magalon J, Maiers M, Kurtzberg J, et al. Banking or Bankrupting: Strategies for Sustaining the Economic Future of Public Cord Blood Banks. PLoS One. 2015 Dec 1;10(12):e0143440. doi: 10.1371/journal.pone.0143440.
- Dunn PP, Lamb G, Selwyn C, et al. Diversity in exon 5 of HLA-C(*)04:01:01G is significant in anthropological studies. Hum Immunol. 2016 May;77(5):426-8. doi: 10.1016/j.humimm.2016.03.007. Epub 2016 Mar 24
- Torikai H, Mi T, Gragert L, et al. Genetic editing of HLA expression in hematopoietic stem cells to broaden their human application. Sci Rep. 2016 Feb 23;6:21757. doi: 10.1038/srep21757.
- Sivasankaran A, Cherkassky V, Albrecht M, et al. Donor Selection for Hematopoietic Stem Cell Transplant Using Cost-Sensitive SVM. 2015 IEEE 14th International Conference on Machine Learning and Applications (ICMLA) 9-11 Dec. 2015 pp: 831-836 doi:10.1109/ICMLA.2015.166
- Buck K, Wadsworth K, Setterholm M, et al. High resolution match rate of 7/8 and 9/10 or Better for the Be The Match® Unrelated Donor Registry. Biol Blood Marrow Transplant. 2015 Dec 24. pii: S1083-8791(15)01879-0. doi: 10.1016/j.bbmt.2015.12.012. [Epub ahead of print]
- Kollman C, Spellman SR, Zhang MJ, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. Blood. 2015 Nov 2. pii: blood-2015-08-663823. [Epub ahead of print]

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Oral Conference Presentations:

EFI 11-14 May 2016, Kos, Greece

- Maiers M, Louzoun Y. Bias in human offspring MHC due to selection for HLA genotypes that share KIR ligands.
- Halagan MS, Gragert L, Hurley CK, et al Imputation of DPB1 Permissibility for Donor Selection.
- Maiers M. Educational Session: MIRING of FHIR: Bioinformatics tools for improving the interoperability of HLA and KIR for improved Science and Health.

HLA-DP matching service

We implemented an open-source (<https://github.com/nmdp-bioinformatics/service-epitope>) REST microservice that assigns TCE group to HLA-DPB1 alleles and computes TCE-based permissibility categories for a given patient/donor pair. This service has been operationalized and is now use regularly by Transplant Centers via the Traxis user interface and HapLogic matching algorithm.

9-locus haplotype frequencies and HLA-DP prediction

Extension of recruitment HLA typing to additional loci in recent years has allowed us to complete an analysis of 9-locus A~C~B~DRB3/4/5~DRB1~DQA1~DQB1~DPA1~DPB1 haplotype frequencies. This data is being prepared for publication. We have also developed a system to use this data to predict DPB1 matching as defined by T-Cell epitope reactivity (TCE) groups and more recently (Petersdorf 2015) in terms of non-permissive DPB1 mismatch based on DPB1 expression variants. We compared the predicted TCE and expression permissibility for each pair to their true TCE and expression permissibility using the receiver operator characteristic (ROC). The ROC area under the curve (AUC) was greater than 0.90 for most populations. The average AUC observed was 0.92 with a standard deviation of 0.02 between populations. Imputation of DPB1 permissibility can be performed with strong predictive power for every major population when using A~C~B~DRB1~DQB1~DPB1 haplotype frequencies.

RSSA KIR

We developed several version of R-Shiny Search Application (RSSA) include one version specifically focused on KIR use in donor selection (Figures 10 and 11).

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The screenshot displays the RSSA-KIR application interface. On the left is a dark sidebar with navigation links: Home, Donors, Summary, Search List, and Cords. The main content area is divided into several sections:

- Data Pull Information:** Includes a 'Fetch Search' button, a 'Select data retrieval method' dropdown set to 'Smart Pull', and a note about the Smart Pull method.
- Patient Information:** A table showing patient details for ID 9272634, including Race (EURWRC), Sex (M), Weight (10 Kg), Age (74), Blood Type (A+), and CMV (U). It also lists HLA antigens A, B, C, DRB1, DQB1, DPB1, DRB3, DRB4, DRB5, and DQA1.
- Donor CT Budget and Estimation Parameters:** A green button.
- Donor CT Budget and Estimation Tables:** A blue button.
- Donor Search Results:** A red header section showing 'Smart method was used. 737 of the 31568 are available. Portion(s) loaded: 10/10'. It displays a table of donor results with columns for Donor ID, Status, Last HHQ, Age, Sex, Population, DPB1 Permissivity, CMV, Blood Type, KIR Available, MCat, P10/10, P9/10, P8/10, P8/8, P7/8, P6/8, A, and T.

Donor ID	Status	Last HHQ	Age	Sex	Population	DPB1 Permissivity	CMV	Blood Type	KIR Available	MCat	P10/10	P9/10	P8/10	P8/8	P7/8	P6/8	A	T
167414705	AV		20	F	NAMER	Not Available	U	A		10	98	99	99	99	99	99	P P 99	
125970905	AV	2015-12-22	28	F	NAMER	Not Available	U	O		10	98	99	99	99	99	99	P P 99	
183017318	AV		22	F	CAU	Not Available	U	B		10	98	99	99	99	99	99	P P 99	
182661215	AV		20	M	CAU	Not Available	U	A		10	98	99	99	99	99	99	P P 99	
182594796	AV		20	F	NAMER	Not Available	U	B		10	98	99	99	99	99	99	P P 99	

Figure 10. Screen shot of the RSSA KIR application

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KIR Typing for Donor: 511589152

Donor Score₁: Best

Donor Genotype: BB/AB

What would you like the table to include?

☒ Presence/Absence/CNV₂ ☒ Alleles ☒ Ligand₃

	CEN Genes				CEN or TEL Genes				TEL Genes				Framework Genes			
Haplogroup	A				B				A							
KIR Locus	2DP1	2DL3	2DL1	2DS2	2DL2	2DL5	2DS3	2DS5	3DS1	2DS1	3DL1	2DS4	3DL3	3DP1	2DL4	3DL2
Typing	N	N	N	P	P	P	P	N	P	P	P	P	P	P	P	P
Allele																
KIR Ligands		C1 ₃ C2 ₃	C2 ₃		C1 ₃ C2 ₃				Bw4 ₄			C1 ₃ C2 ₃ A11 ₅				A3 ₆ A11 ₆

Key: U = Untested P = Present N = Absent # = Copy Number Red = Activating Blue = Inhibitory

References:

1. S. Cooley *et al.* Blood 2010
2. W. Jian *et al.* Genome Res 2012
3. S. Cooley *et al.* J. Immunol. 2014
4. JE Gumperz *et al.* J Immunol. 1997
5. T Graef *et al.* J Exp Med. 2009
6. D Pende D. *et al.* J Exp Med. 1996

Figure 11. Screen shot of RSSA KIR application donor KIR haplotype assessment summary

The R-Shiny Search Application (RSSA) was re-platformed and re-designed in the past year under the project name “ignite” (Figure 12). This platform (Angular.js) is more scalable and high-performance providing noticeably fast response to the user and the ability to deploy to many current users. The key design principle of flexibility about new matching features and markers has been preserved so that as new features are developed and implemented as web-services these features can be incorporated rapidly into the user interface for immediate feedback from users.

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Summary Counts: Donors Cords

Display: 50 100 200

Results: 4,135 Donor ID Find Donor ID

2601311 / Last Name, First Name

Local ID: 1234567 Weight (kg): 0 Sex: F Race (Eth): NAM (UNK) ABO/Rh: -- --
Center: 501 Age: 0 CMV: -- Disease: AML

Status: A: B: C: DRB1: DQB1: DRB3: DRB4: DRB5: DPB1:
TX2 02:01 52:01 03:03 13:01 06:03 06:04 04:01
03:01 15:01 12:02 13:02 06:04 04:01

Add	Status	ID	Race (Eth)	Age	Sex	Contact Date	CMV	ABO/Rh	Prev Don	DPB1 TCE	Weight	Rep Sample	Avail Date	Reg Date	Ctr	M Cat	Pr(n) of 10 (%)
1	AV	288701737	CAU (UNK)	21	M	--	Untested	O+	--	--	0	--	10/10	9/10=99	8/10=99		10/10=99
2	AV	259133847	CAU (UNK)	26	F	--	Untested	--	--	--	0	--	10/10	9/10=99	8/10=99		10/10=99
3	AV	025167333	CAU (NHIS)	56	F	--	Untested	--	--	--	0	--	10/10	9/10=88	8/10=99		10/10=35
4	AV	706336085	CAU (UNK)	49	F	--	Untested	--	--	--	0	--	10/10	9/10=50	8/10=86		10/10=20
5	AV	063819307	CAU (UNK)	49	F	--	Untested	--	--	--	0	--	10/10	9/10=49	8/10=85		10/10=16
6	AV	006552018	CAU (UNK)	33	M	--	Untested	--	--	--	0	--	10/10	9/10=36	8/10=88		10/10=8
7	AV	008247605	CAU (NHIS)	59	F	--	Positive	A+	--	--	0	--	10/10	9/10=19	8/10=76		10/10=76

ignite-test.nmdp-bioinformatics.org/ignite/

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Figure 12. Screen shot of the ignite platform version of the Search Application.

Readiness Score

Availability of donors at the CT request stage continues to be a barrier to the rapid identification of a suitable donor. During the past year we have developed a donor “Readiness” score by applying a machine learning method for statistical modeling of historical requests and validated this score against a validation set of donors. The model utilizes donor center, donor demographics and donor response action information such as Post Recruitment Survey results, e-mail responses from donors renewing their commitment, responses to health-history questionnaires, donor-initiated updates to contact information and other factors.

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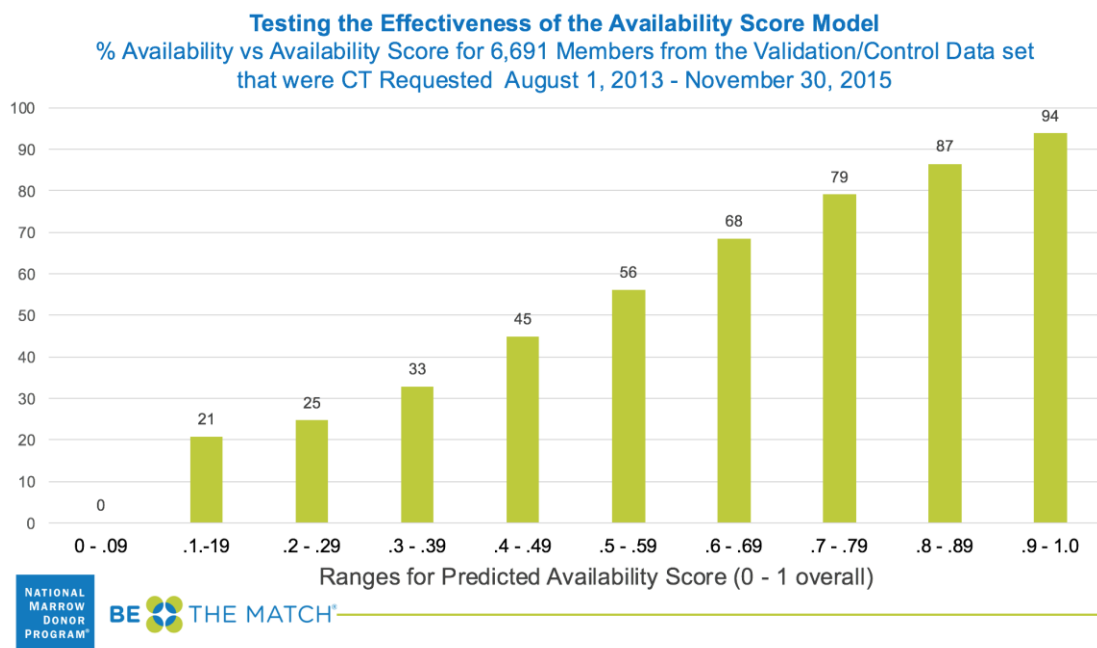


Figure 13. Donor availability correlation with the predicted availability score

This model was applied to 6,691 requests and the predictions agreed with the observed availability across nearly the full spectrum of predictions (Figure 13). This predictor has been applied to the entire NMDP database and has also been incorporated into the R-Shiny Search Application for internal use.

Search Prognosis - Genotype Frequency Study

The goal of this project was to develop a simple scoring system that uses a patient's genotype frequency to determine whether the patient is likely to have a 10/10 donor (good search), a 9/10 donor (fair search), or neither (poor search). The genotype frequency boundaries for the three prognosis categories were defined in each of the four broad race groups - African American (AFA), Hispanic (HIS), White (WH), and Asian/Pacific Islander (API) - and an unknown race group (UNK) using a proportional odds model on a training data set of over 2400 patients.

A validation analysis was conducted to assess the precision of using genotype frequency to predict search prognosis. A second cohort (n= 2411) was used to calculate the concordance for

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each race group in all three categories: Good: WH: 94%, AFA: 58%, API: 89%, HIS: 74%, and UNK: 83%; Fair: WH: 61%, AFA: 91%, API: 72%, HIS: 84%, and UNK: 71%; and Poor: WH: 83%, AFA: 44%, API: 61%, HIS: 44%, and UNK: 70%. Additionally, a validation was performed against an independent cohort previously resolved as having a 10/10, 9/10, or no such matched donor, which demonstrated the genotype frequency categories defined here provide differential likelihood of donor matching. A prototype online tool that can output a search prognosis (good, fair, or poor) by simply entering a patient's HLA has also been developed. This manuscript was accepted for publication in Bone Marrow Transplantation¹⁴.

Presented one abstract at the ASHI annual meeting in St. Louis, MO in September 2016.

- Halagan MS, Gragert L, Hurley CK, et al. Imputation of DPB1 for donor selection in the major US race groups

Haplotype Frequency Curation

A small international meeting was hosted at NMDP to improve the international sharing and curation of global haplotype frequencies. This meeting resulted in a set of technical requirements for a Haplotype Frequency Curation Service.

Reducing the time and effort required to identify closely matched donors for patients in urgent need of HSC transplants will improve access to transplantation and patient survival in the context of a contingency response and routine patient care.

Genotype Frequency Project

The aim of this project was to determine the impact of proactive intervention by the NMDP on searches with poor prognosis as defined by patient genotype frequency. These searches were characterized as having limited donor options, where even finding a 9/10 matched donor may not be possible.

Between April and October 2015, patients from domestic transplant centers with a search determined to have poor prognosis using the Genotype Frequency Tool were randomized into two groups, intervention (399 patients) and non-intervention (389 patients) for comparative purposes. The project provided proactive donor contact, typing and/or search strategy advice early in the search process for patients enrolled in the intervention group. The goal was to

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determine if this type of intervention helps cases with limited donor options proceed forward from the preliminary stage, decrease the time to transplant and influence the product (donor or cord blood unit) pursued. Search strategy advice and 9/10 or better donors who were identified were messaged to transplant centers through their respective case managers.

A total of 147 9/10 donors and four 10/10 donors were identified for patients enrolled in the intervention group. Overall patient data show a larger number of younger donors were contacted and/or typed through this project for API and HIS patients, suggesting improved donor typing for these groups could be beneficial. The number of total donor/cord blood transplants between groups was similar (65 intervention and 70 non-intervention), but a greater number of donors were utilized in the intervention group (35% cord) whereas a greater number of cords were utilized in the non-intervention group (44%) (Figure 14).

At 90 days post project, the greatest benefit in terms of case progression was observed in the cases where patients identified as API. There were 11% more cases at the formal search stage and twice as many cases at the collection/shipment stage (8% vs 4%) in the intervention group compared to the non-intervention group (Figure 15).

Preliminary data at 90 Days show slight improvements in case progression and case progression time between groups with the greatest benefit observed in API searches. Proactive intervention also appears to be helping transplant centers ability to proceed with a suitably matched donor at this time point.

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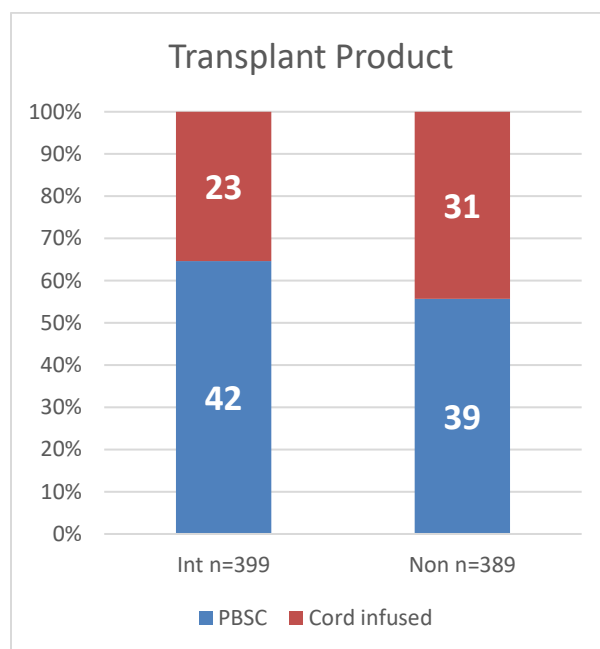


Figure 14. Product type selected for patients proceeding to transplant in the genotype frequency intervention project.

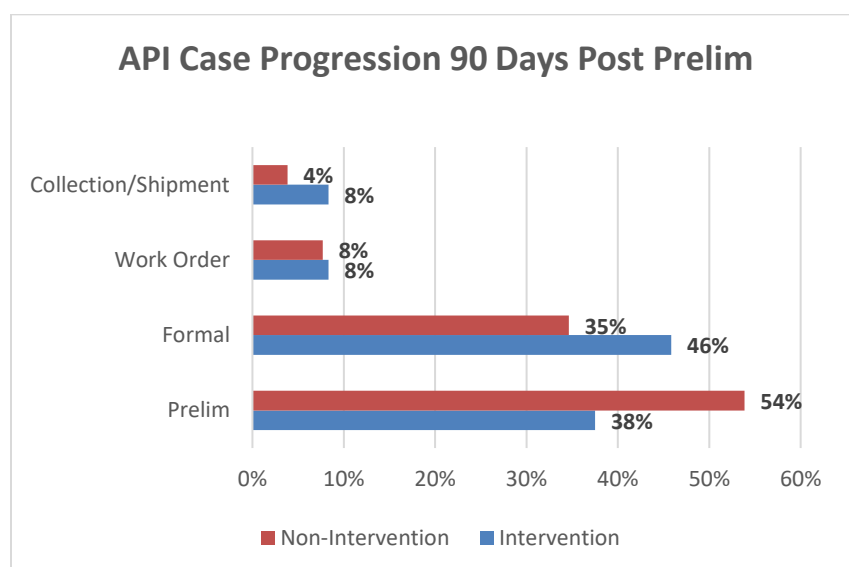


Figure 15. Case progression in the API subgroup enrolled in the genotype frequency intervention project.

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DPB1 TCE Donor Selection Study

HLA-DPB1 permissive matching based on T-cell epitope (TCE) groups should be considered when selecting among donors equally matched at HLA-A, B, C and DRB1 to improve survival. Previous studies have defined three TCE groups based on functional assays of alloreactivity. Combinations of donor and recipient DPB1 alleles with low immunogenic potential identify permissive donors, who provide no increased risk of mortality compared to DPB1 matched donors. In order to determine the likelihood of identifying a DPB1 permissive matched (includes both allele matched and DPB1 permissive mismatched) unrelated donor for patients with high resolution matches at HLA-A, B, C, DRB1 and DQB1 in the Be The Match Registry®, preliminary search requests from US transplant centers for 595 DPB1-typed patients were evaluated. The baseline DPB1 permissive match rate was 69% and improved to 80% after additional donor DPB1 typing (median, 4 donors per patient). When seeking a 10/10 matched, young (18-32 years old) donor in the registry, the probability to find a DPB1 permissive matched donor started lower at 59% and improved to 70% after additional DPB1 testing. Our results show that most patients with a 10/10 match can find a DPB1 permissive matched donor. The results of the study were published.

NIH Search Support

The National Institutes of Health (NIH) has been accepted as an NMDP transplant center since 2007. Prior to that time, the NIH, representing our Nation's premier medical research endeavor, was not applying their considerable problem-solving skills to issues surrounding unrelated donor transplantation. The NMDP, with ONR support, set out to remedy that deficiency by entering into collaboration with NIH. This collaboration has been extremely successful.

The NMDP is collaborating with intramural NIH transplant programs from the National Cancer Institute, the National Heart Lung and Blood Institute and the National Institute of Allergy and Infectious Diseases. These programs are investigating alternative approaches in unrelated donor transplantation to improve patient outcomes. The actual transplants and the investigational portions of each transplant (i.e., the research protocols) are supported entirely with NIH funds. Navy funding supplies support for donor identification, selection and collection. NMDP donors are not research subjects on these protocols because the donors are making standard donations for accepted transplant indications. The research component of these transplants is conducted entirely by NIH intramural program staff and funded entirely with NIH dollars. The NMDP

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provided support for the collection of 19 products (10 PBSC, 1 CBU, 5 marrow and 3 therapeutic T cells) under the current grant.

Rapid identification of potential donors for newly diagnosed AML patients

The Southwest Oncology Group (SWOG) has identified the time from diagnosis of Acute Myelogenous Leukemia (AML) to transplant as critical for successful treatment of patients with cytogenetically defined high risk disease. Proceeding to transplant within four months of diagnosis for patients with high risk disease in first chronic remission could potentially improve the overall disease free survival rates. Currently, these patients are referred for transplant following cytogenetic screening and several lines of therapy. The initial diagnosis and treatment phase can take several months significantly delaying the initiation of an unrelated donor search and making transplant within four months highly unlikely. NMDP/CIBMTR up front involvement would permit the rapid identification and pre-search screening of potential donors, so patients will be well along in the search process when/if ultimately referred for HCT.

In April 2013 SWOG initiated the clinical trial entitled, [“S1203: A Randomized Phase III Study of Standard Cytarabine plus Daunorubicin \(7+3\) Therapy or Idarubicin with High Dose Cytarabine \(IA\) versus IA with Vorinostat \(IA+V\) in Younger Patients with Previously Untreated Acute Myeloid Leukemia \(AML\)”](#). The trial was a randomized phase III trial of cytarabine and daunorubicin hydrochloride or idarubicin and cytarabine with or without vorinostat to see how well they work in treating younger patients (18-60 years old) with previously untreated acute myeloid leukemia. Drugs used in chemotherapy, such as cytarabine, daunorubicin hydrochloride, idarubicin, and vorinostat, work in different ways to stop the growth of cancer cells, either by killing the cells or stopping them from dividing. Giving more than one drug (combination chemotherapy) and giving the drugs in different doses and in different combinations may kill more cancer cells. It is not yet known which combination chemotherapy is more effective in treating acute myeloid leukemia. The study included a transplant arm for patients diagnosed with high risk cytogenetics following the initiation of induction therapy (see Figure 16 below). NMDP/CIBMTR supported the project using grant funds to provide study-specific sample collection kits for all enrolled patients, processing samples, HLA typing patients that were diagnosed as cytogenetic high-risk and generating preliminary search strategy reports to assist in the identification of donors and/or CBUs through the NMDP. The resulting search information was provided to the S1203 transplant arm principal investigator who shared the data with the referring physician.

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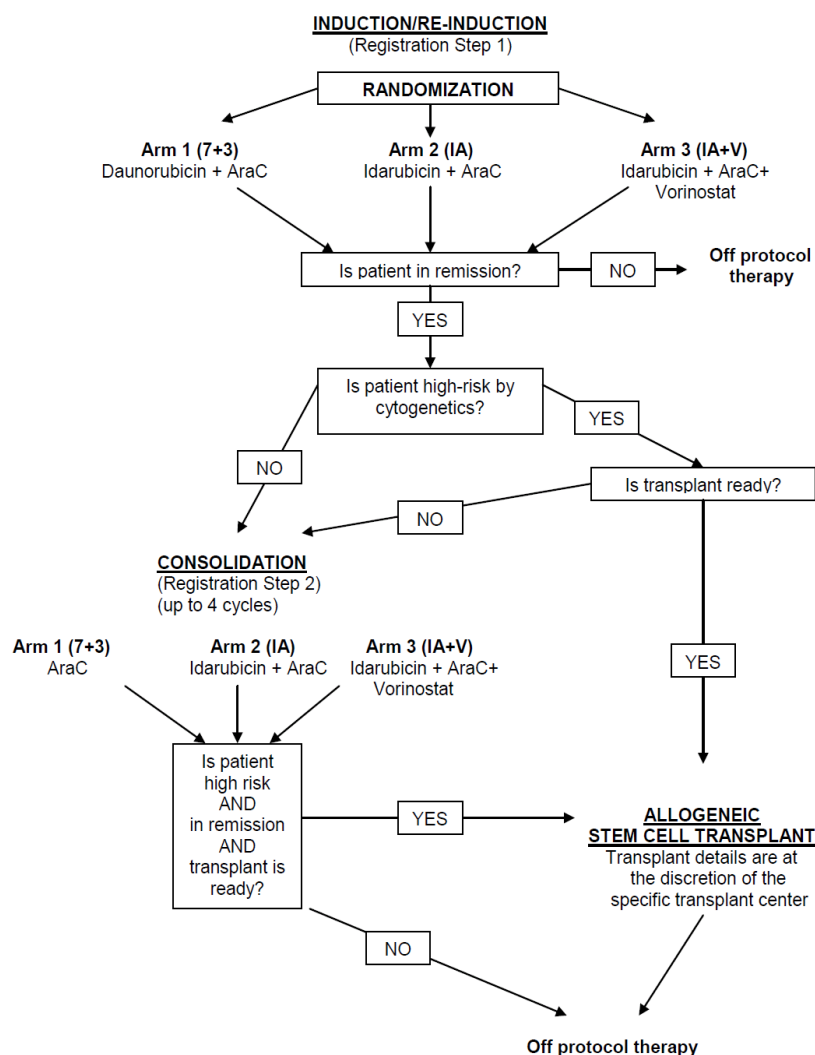


Figure 16. S1203 trial randomization and treatment schema.

The study opened in April 2013 and accrual was completed November 2015. The results of the transplant cohort was presented as an oral abstract the 2016 ASH annual meeting. Of 738 eligible patients (median age, 49 years; range, 18-60), 159 (22%) had high-risk cytogenetics, of whom 60 (38%), 61 (38%), and 38 (24%) received induction with 7+3, IA, or IA+V, respectively. A total of 107 of the 159 high-risk patients achieved complete remission (CR1) (67%). HCT was performed in 317 of all 738 patients (43%) and 68 (64%) of the high-risk patients received a transplant in CR1 ($p < 0.001$ compared to historical rate of 40%). Twenty-five (37%) had a matched related donor, 31 (45%) had a matched unrelated donor, 3 (4%) had a mismatched

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related donor, 8 (12%) had a mismatched unrelated donor, and 1 (1%) received an umbilical cord blood transplant. Median time to HCT from CR1 was 76 days (range, 20-365). Fifty-seven patients (86%) received a myeloablative regimen and 9 (14%) reduced-intensity conditioning. Reasons for 39 high-risk CR1 patients not receiving a transplant in CR1 were: co-morbidities (n=1), death (n=6), no insurance (n=1), no donor (n=1), physician decision (n=3), patient decision (n=3), relapse (n=6), other (n=10), or unknown (n=8). The 2-year relapse-free (RFS) estimate in the entire high-risk cohort is 32%, significantly higher than the 22% historical rate (p=0.05). Median RFS in the high-risk CR1 cohort (n=107) was 10 months [range, 1-32* (censored) months]. RFS and overall survival (OS) were similar among HCT patients using matched related [1 year estimates: 40% (95% confidence interval (CI) 27%, 74%) and 56% (37%, 74%), respectively] and matched unrelated [1 year estimates: 52% (37%, 75%) and 56% (37%, 74%), respectively] donors in CR1. The HR (reference = unrelated) for RFS was 0.67 (0.32, 1.37) and for OS was 0.88 (0.41, 1.90). Median overall survival (OS) among all patients in the high-risk cohort (n=159) was 12 months [range, 1-33* (censored) months] and was 18 months [range 3-33* (censored) months] for those transplanted in CR1 (Figure 17). The study clearly demonstrated that in newly diagnosed adults with AML age 18-60, early cytogenetic testing with an organized effort to identify a suitable allogeneic HCT donor led to a CR1 transplant rate of 64% in the high-risk group, which in turn led to a significant improvement in RFS over historical controls. Better outcomes in poor prognosis AML patients may be achieved simply by rapidly finding unrelated donors and performing allogeneic HCT in CR1 as soon as possible.

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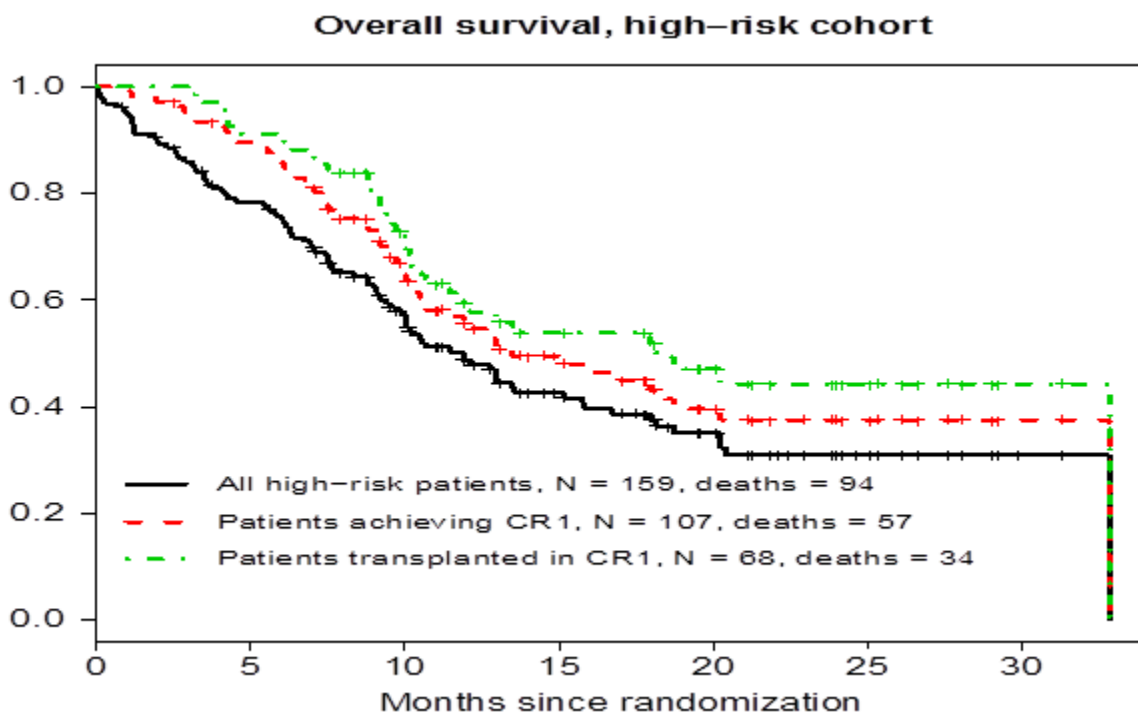


Figure 17. Overall survival of high risk cytogenetic AML patients enrolled in SWOG 1203.

Immunogenetic Studies in Transplantation

HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantify the influence of specific HLA mismatches. In contingency situations, it will not be possible to delay transplant until a perfectly matched donor can be found.

Donor/Recipient Pair Project

A retrospective Donor/Recipient Pair HLA typing project to characterize class I (HLA-A, B and C) and class II (HLA-DRB, DQB1, DQA1, DPA1 and DPB1) alleles of stored donor/recipient paired samples was initiated in 1994. To date, over 24,000 unrelated paired samples and more than 1,500 related paired samples from the Repository have been fully characterized and the resultant data are available for research use. The data are stored in an NMDP developed database and is available to any researcher with a CIBMTR approved study wishing to analyze

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the impact of matching as either the focus of, or as a variable in a research study. To date, 160 published research studies (not including abstracts) have used these data, including the seminal publication from Lee et al, describing the importance of high resolution HLA matching in unrelated donor transplantation that formed the basis for NMDP's updated guidelines for unrelated adult donor HCT HLA matching.

In 2016, the typing strategy for the donor/cord and recipient samples being tested was significantly changed to take advantage of high quality results of whole gene and extended gene typing for HLA-A, B, C, DRB1, DQB1, and DPB1 and presence/absence of 16 KIR loci at the reduced cost of full panel high resolution typing secured by using the Registry typing contract. High resolution panel typing allows for sample identity confirmation thus resulting in the discontinuation of intermediate resolution typing. The project has continued to not type the DQA1 locus due to the greater than 98% linkage seen with DQB1 and continues high resolution DPB1 typing. Recent studies have demonstrated significant impact of permissive and non-permissive DPB1 matching on mortality.

The grant supported the typing of 5,210 unrelated and 613 related adult donor transplant pairs for the project. With the utilization of the Registry typing contract, the cost per sample was reduced from approximately \$60 for HLA and KIR to \$47 per sample. All samples were typed using NGS methodologies at a minimum of G group resolution. After successful completion of the typing, each pair was audited for use in analyses. All samples were selected in collaboration with the CIBMTR Statistical Center to ensure the additional cases would benefit ongoing and future analyses. Transplantation practices are constantly evolving and the project will continue to enroll the most recent transplant pairs to ensure that changes in practice can be evaluated with fully quality controlled high resolution HLA data. With the implementation of the IPR database, we continue to audit sample groups that contain both KIR and high resolution HLA to allow for inclusion in studies.

HLA-DPB1 crossover frequency analysis of HLA matched sibling Donor (MSD)/Recipient pairs
Previous studies have demonstrated a significant impact of DPB1 matching on aGVHD. The large genetic distance between the HLA-DPB1 locus and the remainder of the HLA loci may result in high rates of genetic crossover. Previously, the NMDP has not had access to samples to evaluate this phenomenon. The collection of a large cohort of HLA matched sibling donor transplant pairs through the CIBMTR Related Donor Repository provided the opportunity to explore the role of HLA-DPB1 crossover and resultant mismatch in allogeneic HCT.

A cohort of 1199 presumed MSD pairs, from 55 centers, collected by the CIBMTR Research Repository from 2007–2015 were analyzed. All pairs were reported to the CIBMTR as HLA

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identical siblings and received a transplant for either AML (44%), ALL (24%), MDS (26%) and 6% other diseases. The median patient age was 52, 59% were male, 86% received PBSC and 14% bone marrow. To determine the crossover frequency the subjects were typed by targeted exon NGS of exons 2 and 3 for both Class I and Class II yielding G group or better results, at HLA-A, B, C, DRB1, DRB3/4/5, DQA1, DQB1, DPA1 and DPB1. The majority (97.25%) of MSD pairs were identical at all loci tested. A small subset (2.75%) of the pairs contained a mismatch impacting either DPA1, DPB1 or both. The majority of the 33 mismatches, 26 (78.79%) were DPB1, 6 (18.18%) included both DPA1 and DPB1 and 1 (3.03%) only DPA1. Analysis of the TCE groups found that 28% of the DPB1 mismatches were not permissive (Table 4). All were presumed crossover events, but family typing was not available to confirm. Six (18%) of the DPB1 mismatches included a homozygous recipient with a heterozygous donor suggesting a potential loss of heterozygosity.

Table 4. T cell epitope group matching in matched sibling donors with DPB1 mismatches.

	TCE v1*		TCE v2*	
	N	%	N	%
All DPB1 MM known or unknown				
Total DPB1 crossover events	32	100.00%	32	100.00%
Permissive MM	23	71.88%	23	71.88%
Non-Permissive GvH	6	18.75%	6	18.75%
Non-Permissive HvG	3	9.38%	3	9.38%
Non-Permissive HvG	3	9.38%	3	9.38%

*DPB1 T-Cell Epitope Algorithms found on the [IPD-IMGT/HLA website](http://www.impgt.org/HLA).

The mismatch frequency at the DP loci in MSD pairs was relatively low at 2.75% and 28% were not TCE permissive. The impact of DP mismatching on MSD HCT outcomes are unclear and warrant further study. This study was presented as an oral abstract at the 2016 ASHI meeting in St Louis. Manuscript preparation is in process.

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Full HLA Gene Typing Match Assessment

The impact of amino acid differences outside of the antigen recognition domain (ARD) have not been previously evaluated in a retrospective analysis. During a prior grant period, a collaborative project was launched with the research laboratory at the Georgetown University Medical Center to generate complete HLA gene sequencing at HLA-A, B, C, DRB1, DQB1 and DPB1 on a cohort of previously characterized ARD identical at HLA-A, B, C, DRB1 and DQB1 unrelated donor/recipient pairs from the CIBMTR Research Repository.

A pilot cohort of 360 pairs were analyzed to assess the frequency of sequence disparities outside of the ARD and facilitate a sample size calculation for the final study cohort. The majority of the population was self-identified Caucasian (80%). NGS was performed on the Illumina MiSeq platform and interpreted with Connexio Assign MPS. Class I gene sequences covered 5'UTR-3'UTR; DRB1, intron 1-intron 3; DQA1 5'UTR-exon 4; DQB1, intron 1-3'UTR. DQ noncoding regions were not evaluated. The majority (98.1%) of the pairs were matched for sequences outside the ARD exons: 0.5% differed in non-ARD exons, 1.9% differ in noncoding regions (Fig. 18). A small number (0.2%) differed within ARD exons. Mismatches in non-ARD exons varied from 0.7% for HLA-C and DQA1 to 0% DQB1; noncoding variation ranges from 2.8% for HLA-C to 1.3%, HLA-B and DRB1. Within non-ARD exons, both nonsynonymous (16 allele pairs) and silent (2) variation were present. Intron variation was minor and usually impact only a single nucleotide.

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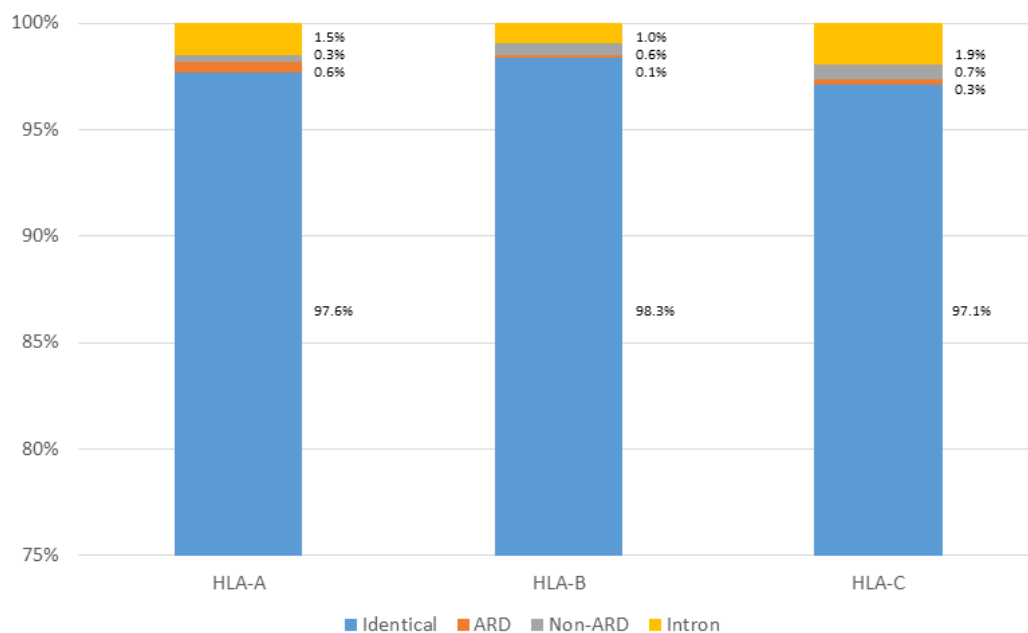


Figure 18. Summary of HLA class I matching between unrelated donor and recipient by locus. The four categories include: (1) donor and recipient carry identical alleles (exons and introns); (2) donor and recipient exhibit a difference in the exons encoding the ARD; (3) donor and recipient exhibit a difference in the non-ARD encoding exons; and (4) donor and recipient exhibit a difference in an intron. Each pie chart represents 720 allele comparisons.

This was the first study to evaluate the genetic variation and characterize mismatching outside of the ARD in a cohort of HLA-matched donor-recipient pairs. The paucity of exonic mismatches outside of the ARD is striking. Intronic variation was more common but would not contribute to an alloreactive mismatch as these variants are not present in the final protein. At present, it does not appear to be necessary to increase the resolution of HLA typing beyond the ARD in selecting a matched donor except in cases of common non-expressed variants within G-group assignments. The impact of amino acid sequence variation caused by substitutions in exons outside ARD regions in donor-recipient pairs will be difficult to assess in HCT outcome studies since it does not occur very frequently. Further study is warranted to confirm these findings in

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larger and more diverse cohorts. The results of the study were presented as oral abstract and received an ASHI Scholar award during the 2016 ASHI annual meeting. The results were summarized in a manuscript and published in the journal HLA.

Production of the KIR SAVE dataset

In 2016 production of a dataset containing all available KIR data received from research projects or through the DRPP on both donors and recipients was initiated. The KIR data contained within this dataset ranges from allelic, copy number variation to presence absence of the KIR2DL1-5, 2DS1-5, 3DL1-3, 3DS1, 2DP1 and 3DP1. This dataset includes variables that define KIR ligand match grades, the assignments of the haplotypes into A and B containing regions as well as the Cooley KIR-B content scores and assignments. This data set was produced to allow for further analysis and inclusion into further studies and will be updated as new KIR data is received.

KIR Copy Number Variation (CNV) Analysis

Our collective knowledge of structural diversity at the KIR gene level is still coarse, especially for unrelated and non-European populations. Dozens of structural haplotypes have been described for the KIR region. Although informative and functional haplotype patterns have been reported, most genotyping has been performed at resolutions that are structurally ambiguous. In order to leverage structural information given low-resolution genotypes, we performed experiments to quantify the effects of population variations, reference haplotypes, and genotyping resolutions on population-level haplotype frequency estimations as well as predictions of individual haplotypes.

We genotyped 10,157 unrelated individuals in 5 populations (518 African American[AFA], 258 Asian or Pacific Islander [API], 8,245 European[EUR], 1,073 Hispanic[HIS], and 63 Native American[NAM]) for KIR gene presence/absence (PA), and additionally half of the AFA samples for KIR gene copy number variation (CNV). A custom EM algorithm was used to estimate haplotype frequencies for each population by interpretation in the context of three sets of reference haplotypes. The algorithm also assigns each individual the haplotype pairs of maximum likelihood (Fig. 19 and 20).

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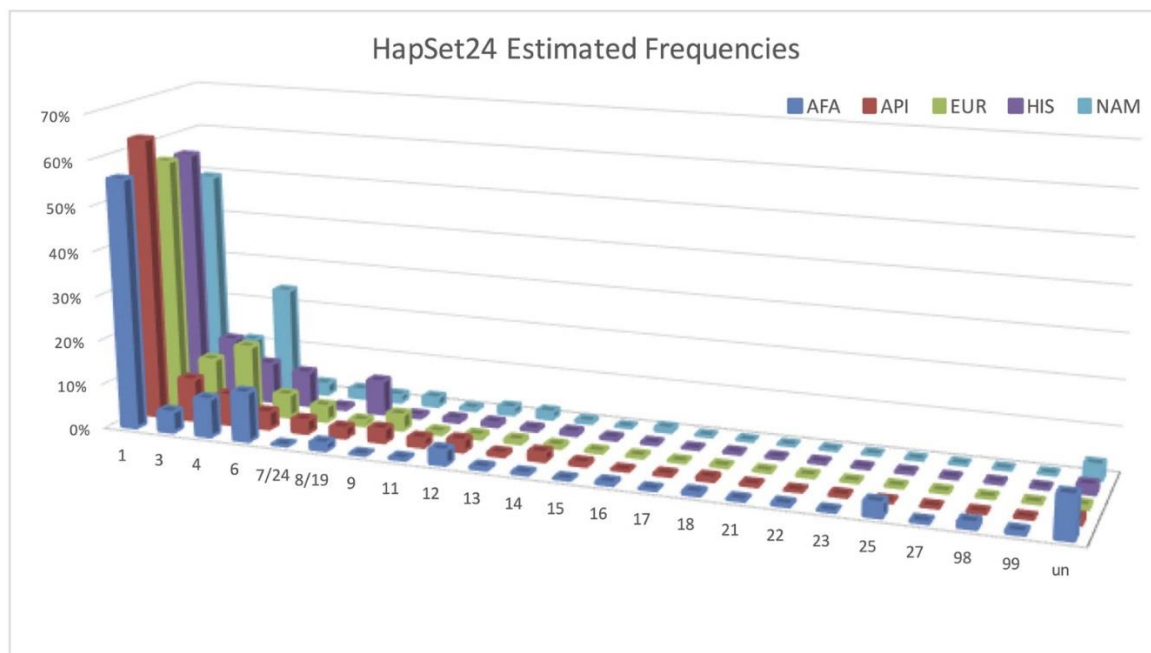
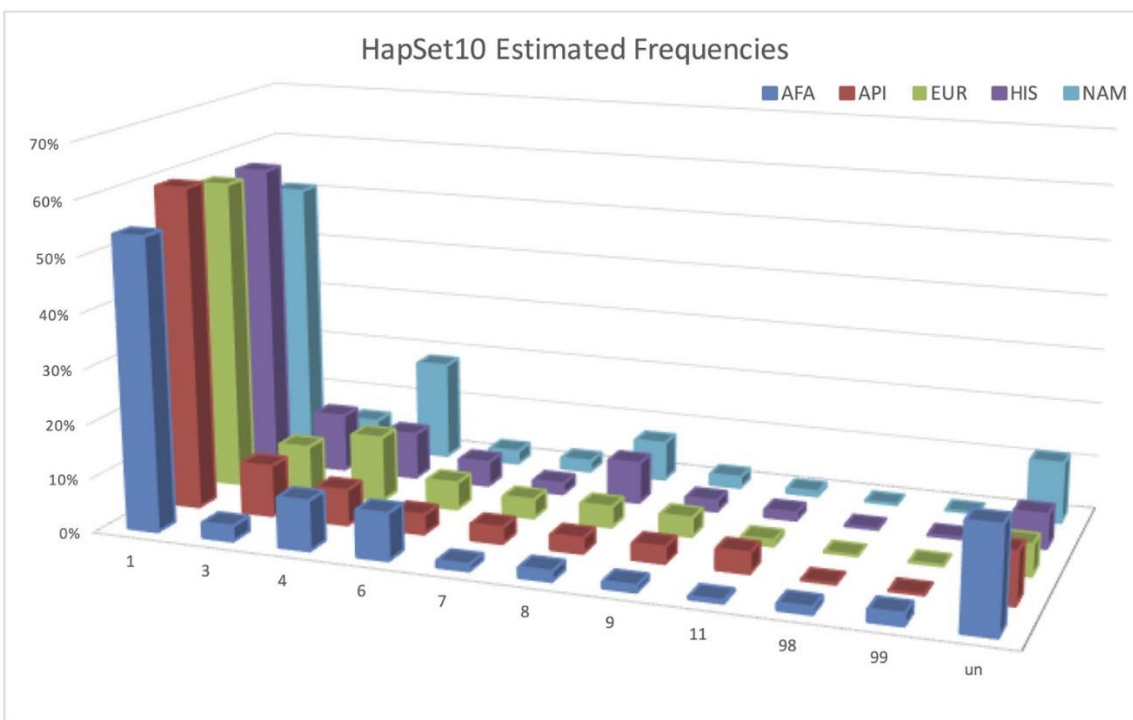


Fig 19. Estimated PA haplotype frequencies for HapSet10 (a) and HapSet24 (b). Frequencies

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are displayed by population and reference haplotype set. Haplotypes are on the x-axis, frequencies on the y, and populations on the z. For clarity and distinction, the chart displays a maximum frequency of 70%. 'un' haplotype represents the frequency of individuals that could not be interpreted.

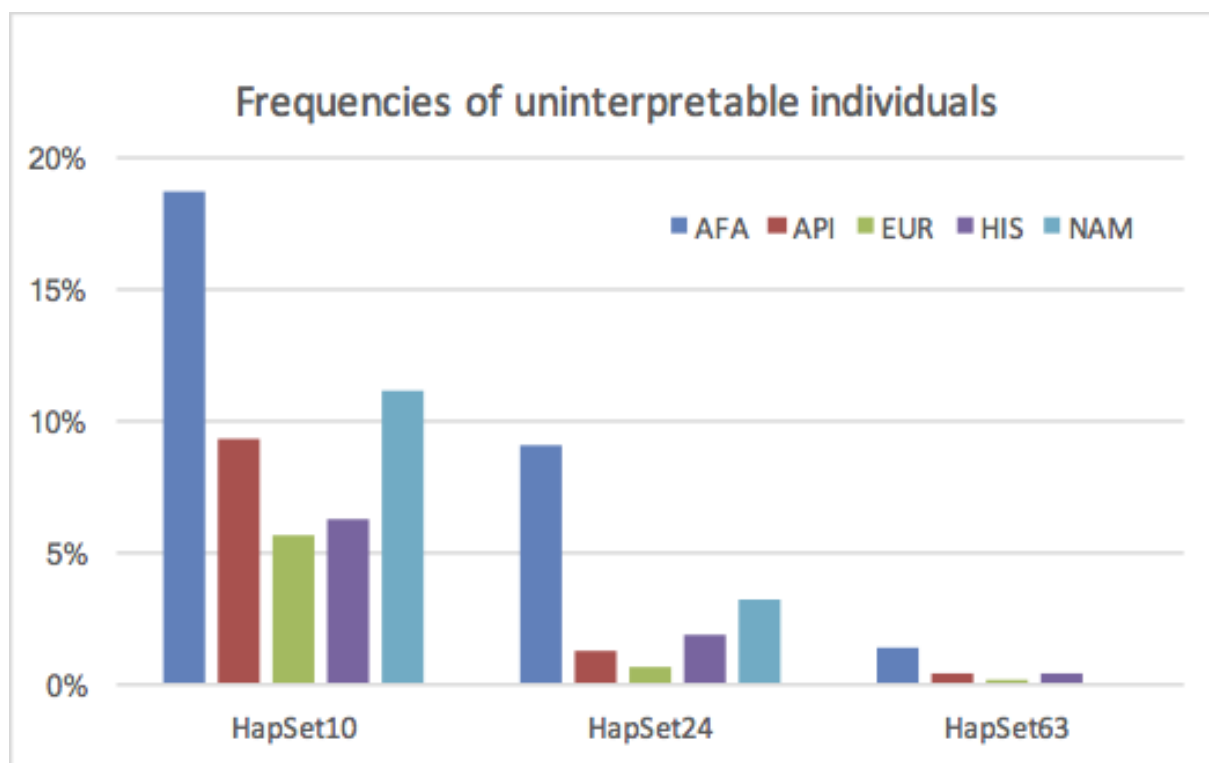


Figure 20. Each bar represents the percentage of a population that cannot be explained by one of three reference sets of haplotypes. For clarity and distinction, the chart displays a maximum frequency of 20%. Five populations are represented: African American (AFA), Asian Pacific Islander (API), European (EUR), Hispanic (HIS), and Native American (NAM).

Generally, our haplotype frequency estimates agree with similar previous publications to within <5% difference for all haplotypes. The exception is that estimates for NAM from the U.S. showed higher frequency association of cB02 with tA01 (+14%) instead of tB01 (-8.5%) compared to a previous study of NAM from south of the U.S. The higher resolution CNV

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genotyping on the AFA samples allowed unambiguous haplotype-pair assignments for the majority of individuals, resulting in a 22% higher median typing resolution score (TRS), which measures likelihood of self-match in the context of population-specific haplo- and geno-types. The use of TRS to quantify reduced ambiguity with CNV data clearly revealed the few individuals with ambiguous genotypes as outliers. It is observed that typing resolution and reference haplotype set influence haplotype frequency estimates. For example, PA resolution may be used with reference haplotype sets up to the point where certain haplotypes are gene-content subsets of others. At that point, CNV must be used for all genes. Preliminary results were presented at the 2015 KIR Workshop in Southampton, England and a manuscript was submitted to and published in 2016 in PLoS One.

Full KIR region sequencing

The most informative way to characterize the full KIR region is to sequence it from long single molecules. These whole region sequences provide the ability to experiment, discover, and annotate at highest resolution. They also provide indirect value as references, evolutionary informers, and source material for imputation.

Therefore, a collaboration was started between NMDP, Daniel Geraghty at Scisco Genetics and Pacific Biosciences with the aims of fosmid library construction, including content mapping and fosmid isolation, DNA sequencing of the fosmid clones using Pacific Biosciences long read technology, and determination of phase and full haplotype sequences.

We generated full-length sequences of the KIR region for 8 diploid individuals using a fosmid-based library preparation and sequencing on Pacific Bioscience's Single Molecule, Real-Time (SMRT™) sequencing.

Individuals had previously been typed at presence/absence, copy number, and SSO/SSP in the exons. The group was chosen for a balance of known/unknown haplotypes, insertion/deletion events, A/B content, and representation of the centromeric and telomeric regions. Fifteen of the sixteen haplotypes have been typed and submitted to GenBank. One individual was fully homozygous across both KIR haplotypes. These data were presented at the 2015 KIR Workshop in Southampton, England in September 2015. The data was also selected to be included in the 2016 summer release updates for the Human Genome Project. Manuscript preparation has begun and publication in a peer reviewed journal will be completed in the next grant period.

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17th IHIW collaboration

The NMDP collaborated with the IHIW KIR component to produce multiple replicates of a panel of 10 KIR defined reference samples from the pool of previously expanded high resolution KIR typed cell lines at the CIBMTR Research Repository. This panel was used to qualify laboratories for participation in the IHIW KIR sequencing project. Laboratories received either DNA or viable cell lines as requested. The samples were selected for haplotypic diversity and alleles with large insertions and/or deletions. To date, we have received presence absence typing from 7 of the 9 typing labs and CNV typing from 4. We have also started a collaboration with the DKMS typing laboratory in Dresden to confirm the allelic typing on 40 NMDP KIR high resolution typed reference cell lines. The results will be analyzed and presented at the 17th IHIW in September 2017.

Antigen Recognition Domain (ARD) study

Amino acid mismatches outside the ARD (i.e., exons 2 and 3 for HLA class I and exon 2 for class II) are ignored under current HLA matching guidelines with the assumption that these differences are irrelevant. There is little data to confirm or refute this assumption; furthermore, the amount of data needed to form a conclusion is unattainable.²⁴ In order to provide more information, the ARD allo-reactivity assessment project will provide insight into the allowable percent tolerance of matching needed outside of the ARD. It is collaboration between the NMDP and Europdonor under the direction of Machteld Oudshoorn and Franz Claas from Leiden, Netherlands.

Initial investigation of the Class II ARD mismatch of DRB1*14:01 and DRB1*14:54 and DRB3*02:01 and 02:02 respectively have produced preliminary results demonstrating two weakly positive and one positive result. Interestingly, all positive results occurred in one direction only, which is DRB1*14:01 / DRB3*02:01 against DRB1*14:54 / DRB3*02:02. This data from the Class II analysis was presented in an oral abstract²⁷ at the 2013 EFI conference in Maastricht, Netherlands. To confirm these results, we identified 135 additional donors via registry queries. Fresh blood draws were collected from 22 donors and peripheral blood mononuclear cells cryopreserved for evaluation. All combinations tested showed no responses in the mixed lymphocyte culture whereas 4 out of 10 combinations were positive in the Elispot against the combined DRB1/DRB3 mismatch and only in one direction; DRB1*14:01/DRB3*02:01 against DRB1*14:54/DRB3*02:02. Positive responses were confirmed by primed lymphocyte testing (PLT) that was more sensitive than the Elispot.

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Furthermore, the PLT results suggested that the DRB1* mismatch was responsible for the response. In conclusion, mismatches involving positions outside the ARD are not very immunogenic. However, some mismatches can lead to T cell reactivity in vitro. The impact of these mismatches on clinical outcome of HCT remains to be established. The study results were published in Bone Marrow Transplantation.

Analysis of four HLA Class I ARS mismatches; A*02:01 and 02:09, B*44:02 and 44:27, C*07:01, 07:06 and 07:18 have demonstrated that the selected pairs do not travel on the same haplotypes. A manuscript is under development.

Even when patient and donor are HLA matched, GVHD occurs, therefore, other loci may play a role.

We completed the analysis of 16 KIR genomic haplotypes which resulted in over 130 new KIR alleles described, 15 GenBank submissions (1 homozygote) and 10 new ALT_LOCI alternate genome structures have been submitted for inclusion in future human genome patches.

Abstract presentations:

- ASHG October 6 – 10, Baltimore, MD
 - Madbouly A, Paunic V, Albrecht M, et al. A pairwise genomic distance measure to evaluate the effect of donor/recipient genomic proximity on unrelated stem cell transplantation.
- ASH 5-8 December, 2015, Orlando, FL
 - Madbouly A, Wang T, Albrecht M, et al. Investigating effect of genetic admixture and donor/recipient genetic disparity on transplant outcomes.

Table 5 lists currently active and completed CIBMTR/NMDP-supported studies that are conducted on NMDP samples. The CIBMTR/NMDP encourages such collaborative projects and closely monitor them. Such studies are instrumental to understanding the role of non-HLA loci in HCT. The data is obtained and generated via NMDP donor and recipient research samples, along with their outcomes and demographics. The researchers are required to submit the interpreted results of all assays performed on the samples. The data submission requirement ensures that all sample testing yields information that is readily available to the HCT research community for subsequent analysis and eliminates or reduces duplicative testing to preserve resources and sample inventory. These results are stored in the IPR and IIDB databases, and associated with their samples in the CIBMTR Research Repository database.

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Non-HLA data is available for use in research studies in a fashion analogous to the Donor/Recipient Pair Project generated HLA data and is made available, when possible, via the NMDP Bioinformatics web site. Data origin will be noted for all information stored, along with relevant citations. Access to the detailed data will be subject to the existing NMDP/CIBMTR data request procedures.

Table 5. Immunobiology typing projects utilizing NMDP samples and contributing data to the IPR database

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
NK Cells, Their Receptors and Unrelated Donor Transplant	J. Miller	2300 pairs	KIR	RT-PCR, FACS, SSO, MALDI-TOF	Yes
Survey of Diversity of Immune Response Genes in Unrelated Hematopoietic Stem Cell Transplantation	C. Hurley	40 Pairs	cytokine and KIR	SBT	Yes
Candidate Gene Study to Examine the Impact of Chemokine and Chemokine Receptor Gene Polymorphisms on the Incidence and Severity of Acute and Chronic GVHD	R. Abdi	1300 pairs	CCL1, CCL2, CCR5, CCR2, CX3CR1	Taqman PCR	Yes
Functional Significance of Killer Ig-like Receptor (KIR) Genes in HLA Matched and Mismatched Unrelated HCT	B. Dupont, K. Hsu	2000 pairs	KIR	SSP	Yes

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Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Functional Significance of Cytokine Gene Polymorphism in Modulation Risk of Post-Transplant Complications	E. Petersdorf	2500 pairs	>30 Immune response genes	Taqman PCR	Yes
Identification of Functional SNPs in Unrelated HCT	E. Petersdorf	3500 pairs	Entire MHC region	Taqman PCR	In Process
Use of Female Donors with Pre-existing Antibody to H-Y Antigen will Result in Robust Serologic Response to H-Y Antigens in Male HSC transplantation Recipients	D. Miklos	288 pairs	H-Y Antigen	ELISA, protein array	Yes
Multiplexed Genotyping of Human Minor Histocompatibility Antigens (mHAg): Clinical Relevance of mHAg Disparity in Stem Cell Transplantation	T. Ellis	730 pairs	mHAg	Allele-specific Primer Extension	Yes
Genetic Polymorphisms in the Genes Encoding Human Interleukin-7 Receptor- α : Prognostic significance in Allogeneic Stem Cell Transplantation	K. Muller	851 pairs	IL-7	Taqman PCR	Yes
The Effect of Non-Inherited Maternal Antigens in Cord Blood Transplantation	L. Baxter-Lowe	102 pairs	HLA	SBT	Yes
Detection of HLA Antibody in Single Antigen HLA-Mismatched Unrelated Donor Transplants	S. Arai, D. Miklos	200 pairs	Anti-body	ELISA, Protein array	Yes

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Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Detection of Donor-Directed, HLA-Specific Alloantibodies in Recipients of Unrelated Stem Cell Transplantation and Their Relationship to Graft/Patient Outcome	R. Bray	111 pairs	Anti-bodies	Flow cytometry	Yes
Genome-wide Association in Unrelated Donor Transplant Recipients and Donors: A Pilot Study	R. Goyal	858 pairs	> 600,000 Genome wide SNPs	Human 610 - Quad V1 arrays	Yes
SNPs in the p53 Pathway and Outcomes in URD HCT	B. DuPont	1500 pairs	p53, ATM, MDM2 and p21/Waf1	Taqman	In process
Association of Donor and Recipient Gene Polymorphisms of Drug and Innate Immune Response with Outcomes after URD HCT	V. Rocha	725 pairs	GSTP, GSTT, GSTM, UGT CD14, TIRAP, and NALPs	Taqman	Yes
To Develop and Test a Prognostic Index for Survival in CML URD HCT	A. Dickinson	1100 pairs	TNF, IL-1RA and IL-10	Taqman	Yes
Evaluation of TGF- β 1 Promoter and Signal Peptide Polymorphisms as Risk Factors for Renal Dysfunction in HCT Patients Treated with Cyclosporine A	R. Shah	400 samples	TGF- β 1	Taqman	Yes
Donor and Recipient Telomere Length as Predictors of Outcomes after Hematopoietic Stem Cell Transplant in Patients with Acquired Severe Aplastic Anemia	S. Gadalla	650 samples	Telomere length and Telomerase Polymorphisms	Taqman	Yes

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Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Development of a GVHD Prevention Biodiagnostic Test	R. Somogyi	450 samples	Gene Expression Array	Array	Yes
Genetic polymorphisms and HCT related mortality Re: Pre-HCT conditioning in matched unrelated donor HCT	T. Hahn	>4,000 pairs	GWAS	Array	In process
Impact of CTLA4 SNPs on outcome after URD transplant	M. Jagasia	1,200 pairs	CTLA-4 SNPs	Taqman	Yes
KIR genotyping and immune function in MDS patients prior to unrelated donor transplantation	E. E. Warlick and J. Miller	970 samples	KIR genotype, expression and cellular function	SSP, flow cytometry and cellular assays	In process
Plasma YKL-40 and CHI3LI genotype to predict mortality after unrelated donor HCT	B. Kornblit	800 pairs	YKL-40 plasma levels and CHI3LI SNPs	ELISA and Taqman	Yes
Natural killer cell genomics and outcomes after allogeneic transplantation for lymphoma	V. Bachanova, J. Miller, D. Weisdorf and L. Burns	800 pairs	KIR genotype, expression and cellular function	SSP, flow cytometry and cellular assays	Yes
Effect of genetic ancestry matching on HCT outcomes	A. Madbouly, M. Maiers and N. Majhail	2300 pairs	Ancestry Informative Markers	Taqman GWAS	Yes
Impact of MHC Class I chain related polymorphisms on HCT outcomes	M. Askar and R. Sobecks	700 pairs	MICA genotypes	Taqman	Yes
Impact of donor signal-regulatory protein alpha polymorphism on HCT outcome	A. Gassas, J. Danska and S. Rajakumar	400 pairs	SIRP- α SNPs	Taqman	In process
Discrepancy analysis of microsatellite loci as a proxy measure for ancestral differentiation	J. Harvey, C. Steward and V. Rocha	800 pairs	Microsatellites and STR	Taqman	In process

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Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Prognostic impact of somatic mutation and the levels of CXC chemokine ligands in MDS	W. Saber, R.C. Lindsley and B. Ebert	1300 pairs	Chemokine levels Somatic mutations	ELISA Sequence capture	Yes
Mitochondrial DNA haplotypes and outcome	M. Verneris and J. Ross	4000 pairs	SNPs	Taqman	In process
Assessing T cell repertoire similarity in HLA mismatched HCT	E. Meyer	50 samples	TCR repertoire sequence	NGS	In process
Impact of SNPs in the Gamma Block of the MHC	M. Askar and R. Sobecks	700 pairs	SNPs	Taqman	In process
Clinical outcomes among HCT recipients as a function of socioeconomic status and transcriptome differences	J. Knight, J.D. Rizzo and S. Cole	252 samples	Gene expression array	Array	In process
Natural killer cell genomics and outcomes after HCT for CLL	V. Bachanova, J. Miller, D. Weisdorf and S. Cooley	600 samples	KIR genotype	SSP	Yes
Donor telomere length and outcomes after HCT for acute leukemia	S. Gadalla, S. Savage, D. Loftus and E. Hytopoulos	1145 samples	Leukocyte telomere length	qPCR	Yes
KIR gene content and pediatric acute leukemia HCT outcome	M. Verneris, J. Miller and S. Cooley	500 samples	KIR genotype	SSP	In process
Functional genetic variants of the ST2 gene in pairs of recipient and donors for risk stratification of GVHD and TRM outcomes.	S. Paczesny and S. Spellman	1000 pairs	sST2	Taqman	Yes

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Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
The role of HLA-E compatibility in the prognosis of acute leukemia patients undergoing 10/10 HLA matched HCT	C. Tsamadou, D. Furst and J. Mytilineos	3300 pairs	HLA-E	NGS	In process

Clinical Research in Transplantation

Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.

Clinical Outcomes Research

Clinical Outcomes Research using the CIBMTR Research Database is a core activity of the organization. These studies address a wide range of issues, focusing on questions that are difficult or impossible to address in single center studies or randomized trials because diseases treated with HCT are uncommon, single centers treat few patients with a given disorder, and not all important questions are amenable to a randomized research design. The majority of the clinical outcomes research is conducted through the CIBMTR Working Committee structure, which incorporates many highly successful researchers in clinical transplantation. The Working Committees perform retrospective studies to identify the most promising transplant approaches, and by identifying the patients most likely to benefit from this therapy. In addition, research in immunobiology was conducted to better understand how transplantation works including how to harness the power of the immune system to control cancer.

The CIBMTR collects data for approximately 22,000 new transplant recipients annually as well as a continually increasing volume of follow-up data on previously reported recipients and donors. Figure 21 shows cumulative accession of transplants since 1970 when the International Bone Marrow Transplant Registry began collecting these data and figure 22 shows the distribution of the patients by transplant type and graft source. These data are the basis for the CIBMTR Clinical Outcomes Research program and are accessed by the Working Committees to conduct studies.

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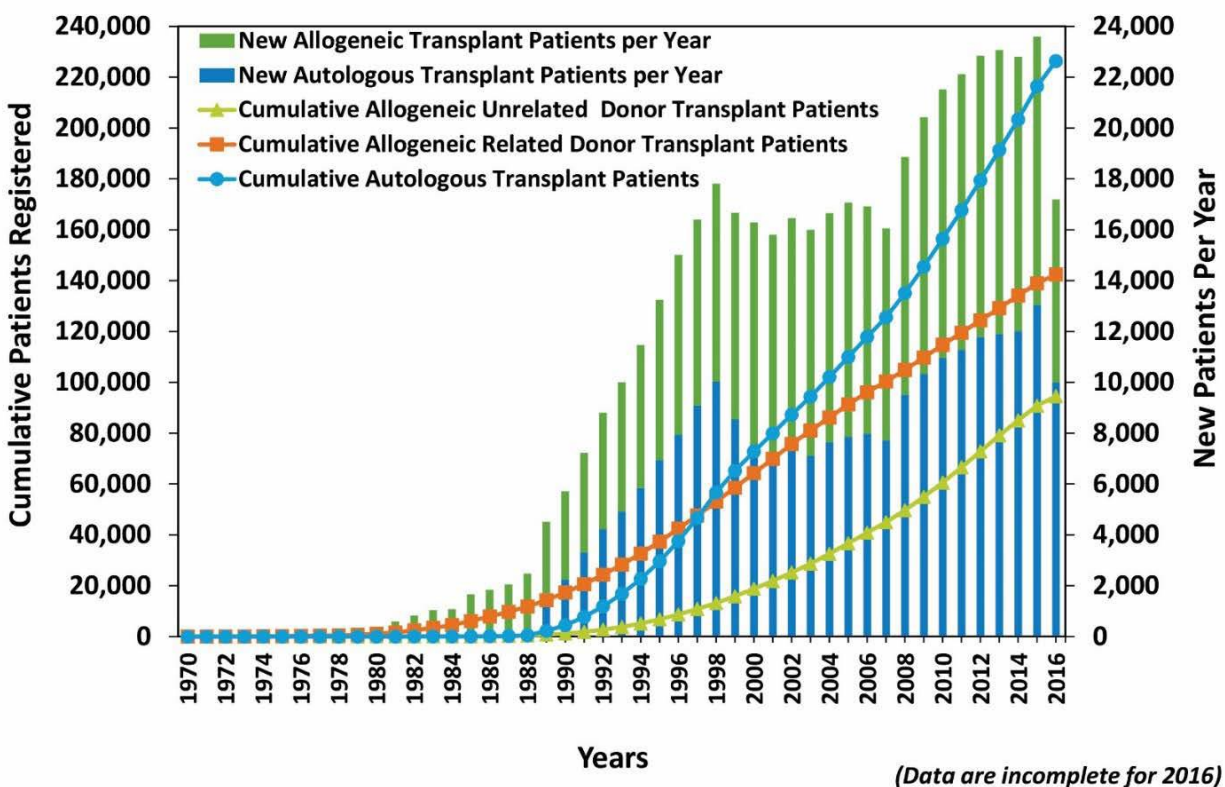


Figure 21. Accession of Transplant Recipients Registered with the CIBMTR

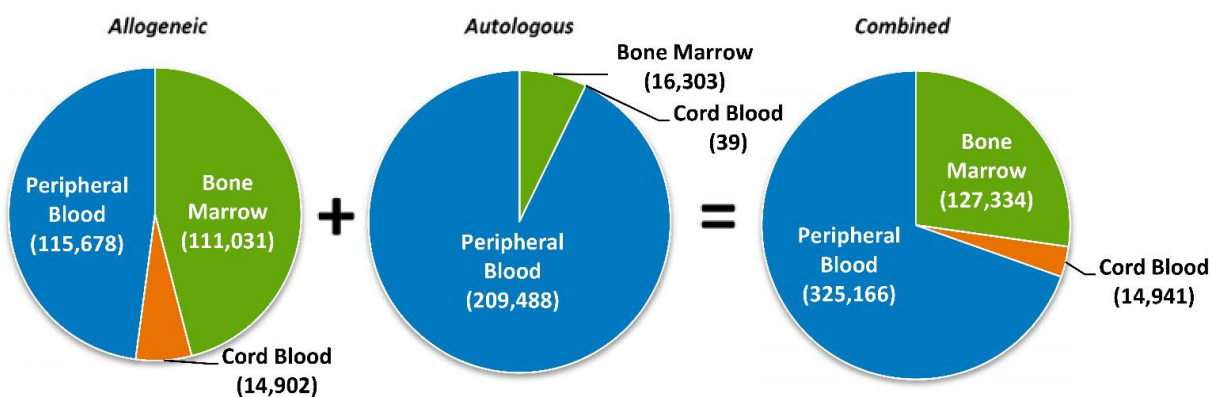


Figure 22. Distribution of Patients in the CIBMTR Research Database by Graft Source

Currently, there are 15 Working Committees within the CIBMTR with 176 active studies in progress (Table 56). In 2016, the CIBMTR published a total of 95 mostly peer-reviewed

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publications (66 working committee studies, 1 Health Services Research, 14 BMTCTN, 5 Statistical Methods and 9 Bioinformatics) (Figure 23). Sources of funding for these studies vary by investigator, but the majority use NMDP resources and CIBMTR statistical support.

Table 6. 2016 CIBMTR Working Committee portfolio and productivity

Working Committee	Studies in Progress	Publications	Presentations
Acute Leukemia	14	5	2
Autoimmune Diseases and Cellular Therapies	5	0	0
Chronic Leukemia	12	5	1
Donor Health and Safety	11	2	2
Graft Sources and Manipulation	7	5	1
Graft-versus-Host Disease	10	1	2
Health Services and International Studies	11	7	3
Immunobiology	39	12	13
Infection and Immune Reconstitution	7	5	0
Late Effects and Quality of Life	11	8	3
Lymphoma	9	4	1
Pediatric Cancer	5	0	1
Plasma Cell Disorders and Adult Solid Tumors	9	5	4
Primary Immune Deficiencies, Inborn Errors of Metabolism, and Other Non-Malignant Marrow Disorders	14	2	0
Regimen-Related Toxicity and Supportive Care	12	5	2
TOTAL	176	66	35

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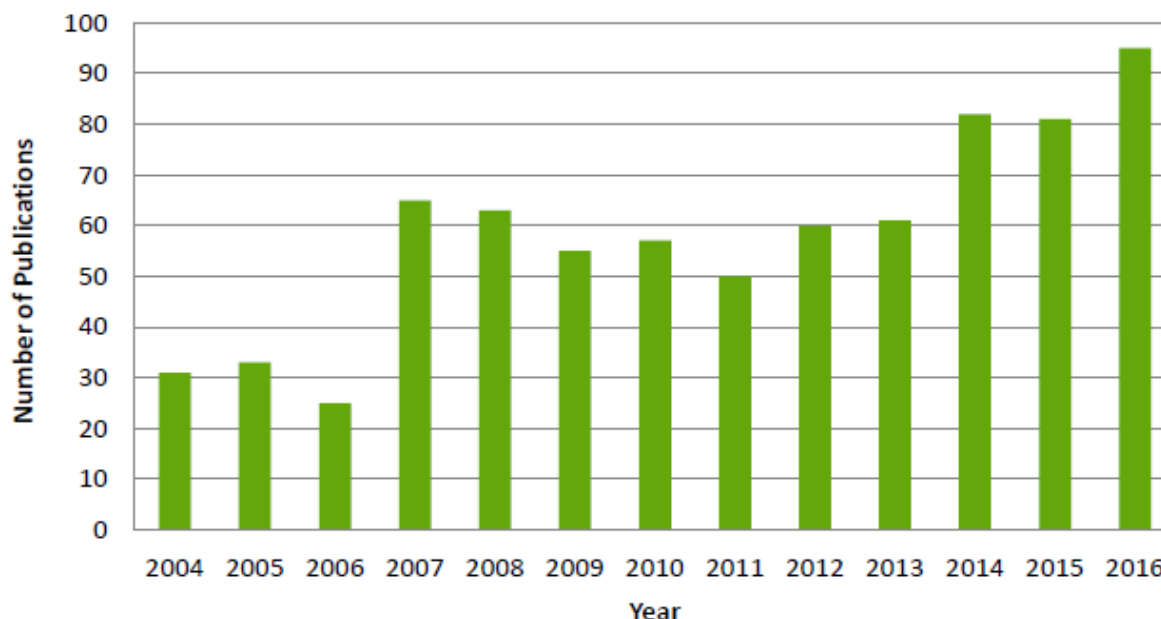


Figure 23. CIBMTR peer-reviewed publications by year.

Clinical Trials

In October 2010, RCI BMT activated a study referred to as the Long Term Donor Follow up study. The primary goal of this study is to evaluate the hypothesis that the incidence of targeted malignant, thrombotic and autoimmune disorders after unrelated hematopoietic stem cell donation are similar between unstimulated BM and filgrastim-mobilized PBSC donors. Once the donor has consented to participate, the donor is contacted and asked study specific questions every other year. This will continue until study completion which is estimated to be 2020. If the donor reports an incidence of interest, a request for their medical records is made. Cases of targeted disorders are reviewed by the medical monitors to confirm the veracity of the report.

In October 2015, accrual to this study was closed however, follow-up assessments will continue until the end of 2020. Table 7 below summarizes the accrual by cohort and product. The SRG team is responsible for the follow up assessments of just over 63% of the enrolled donors. To date the SRG has completed a total of 27,387 assessments of which 5,691 were during this past year.

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Table 7. Long Term Donor Follow-up Study accrual summary

	Marrow	PBSC	Both	Total
Prospective Cohort	3016	8911	157	12084
Retrospective Cohort	3855	5478	157	9711
Totals	6871	14389	535	21795

Electronic Data Capture (EDC) and Clinical Trials Management System (CTMS)

In December 2015, RCI BMT completed the transition to [Medidata RAVE®](#). RAVE is a leading web-based EDC which allows us to optimize our study data collection, data management and implement our studies in a more efficient and effective manner. In addition, RCI BMT completed the implementation of Medidata's CTMS. The addition of a CTMS will eliminate the duplication, delays and errors caused by manual data entry and multiple, disconnected data management systems that are not integrated. As of this report we have two studies utilizing RAVE and a third in process of being created. All active studies have been uploaded into CTMS for staff management.

Patient Reported Outcomes (PRO) Data Collection

Explored options for implementing a PRO system within SRG. Numerous studies now recognize the value of measuring PROs as the most accurate measure of the patient's experience with disease and treatment, primary and secondary outcomes in clinical trials, and 'biomarkers' of disease activities. Several studies in HCT show that pre-HCT PROs can predict survival and post-HCT health related quality of life (HRQoL). Collecting PRO data will allow CIBMTR to conduct research in HCT outcomes that are important to patients and their caregivers. Collecting PRO with an electronic system will allow for the most direct, cost effective and efficient way to collect this important data. During this past grant period the team determined the requirements of a system and explored potential solutions. It is important to the organization to include the use of PROMIS® (Patient-Reported Outcomes Measurement Information System) measures. PROMIS is a set of person-centered measures that evaluate and monitor physical, mental and social health in adults and in children. It is important for the selected system to also allow other

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measures to be incorporated into the surveys and be flexible and easy access for patients, donors and research subjects. A recommendation was presented to CIBMTR leadership and an initial proof of concept is currently in process. Next steps will be identified following the outcome of the proof of concept analysis.

Cord Blood Research Initiatives

During the project period, the Cord Blood Research Sub-advisory Group met semi-monthly to discuss study priorities and plan analyses for the following:

Cord Blood Bank Proficiency Testing

The NMDP facilitates a proficiency testing (PT) program for network cord blood banks (CBB) through Stem Cell Technologies (SCT). The purpose of this program is to monitor and evaluate the accuracy of a CBB's assay performance and analysis through inter-CBB comparisons. The program was initiated in 2004 and distributes one testing panel annually. Initially, the program reflected the local testing of individual CBBs who performed the assays according to their internal protocols. Due to the highly subjective nature of the colony forming unit (CFU) assay, this resulted in very little inter-CBB consensus of results. To address the poor consensus for the CFU assay, the program was modified to require that the participants use a standardized protocol and reagents distributed by SCT, thereby controlling the introduction of variability in testing results from the use of different CFU protocols. In the current form of the program, participants are instructed to perform, analyze, and report results for the following assays: total nucleated cell count (TNCC), %CD34+ cells gated on viable cells, %CD34+/CD45+ gated on viable cells, and colony forming unit enumeration and identification. Throughout the years of the program, the inter-CBB coefficient of variation (CV) has remained high for the enumeration of CFUs, despite efforts to control for this, as evidenced by the PT data analysis from 2014 summarized in table 8.

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Table 8. Aggregate results of the 2014 cord blood Proficiency Testing program

	N	Mean	SD	CV	Median	Range
BFU-E	30	17.77	6.88	38.69	16.88	10.90-24.65
CFU-GM	31	18.31	5.74	31.37	17.75	12.57-24.05
CFU-GEMM	29	2.26	1.72	76.18	2.50	0.54-3.98
Total Colonies	33	35.33	14.23	40.28	37.50	21.10-49.56

The NMDP Cord Blood Advisory Group (CBAG) raised concerns about the current program because the SCT CFU protocol used by participants does not reflect the CBB's standard methodologies. The results of the SCT CFU protocol testing only assesses the participants proficiency in performing an assay on an annual basis in a manner that is not consistent with the methodologies used to report product characteristics through Emtrax for use in CBU selection algorithms by TCs.

The College of American Pathologists (CAP) administers a PT program where the CFU assay is performed using local CBB protocols. However, the data analysis provided through the CAP program is limited and does not capture sufficient information to compare differences between testing methodologies, reagents, and instruments used by the various participants. In addition, very few CBBs participate in the CAP program making consensus analyses difficult to perform.

The Cord Blood Research Sub-advisory group started work on a re-design of the 2015 administered PT program to compare testing results generated using CBB in-house methodologies, reagents, and instruments (Study Arm) compared to the use of the standardized SCT protocol and reagents (PT Arm) on a standardized sample. The standardized sample was red blood cell depleted, which was not characteristic of all previous send-outs. A survey was created and sent to CBBs participating in the study to capture characteristics of the in-house testing methods. The survey results will facilitate an evaluation inter-CBB differences in testing approaches in general and any data consensus issues that may be the result of these differing approaches. Data was analyzed by SCT and returned to the sub-group late summer of 2015. The sub-group reviewed the results and created a detailed analysis that was shared with the CBAG in January of 2016 and summarized below.

Forty three individuals from 24 different institutions submitted data for the PT Arm. Twenty five individuals from 14 different institutions submitted data for the Study Arm. Fifteen institutions

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completed the Study Arm survey. The variability in CFU counts was analyzed within a subgroup of participants who submitted data for both the Study and PT Arms (N=25).

Results of the survey, depicted in the table 8 below, indicate most institutions plate total nucleated cells (87%), as opposed to white blood cells. 53% use 35mm Dish to plate, while 20% use 6 well plates. 53% use a 1 to 10 dilution when adding cells to the media tube. Most responders (73%) reported identifying and counting blast forming unit-erythrocytes (BFU-E), colony forming unit granulocyte macrophage (CFU-GM), and colony forming unit-gran erythrocyte macrophage monocyte (CFU-GEMM). The survey revealed some variability between participants' in house methods; however, the effect of variables could not be assessed due to small size of specific cohorts.

Table 8. Results of 2015 Proficiency Testing program survey

Question	Response	% Response
Type of cells plated	WBC	13
	TNC	87
Viability assessment method	Trypan Blue	40
	7-AAD	40
	NA	20
Type of plates/wells for CFU assay	35mm Dish	53
	6 Well Plates	20
	SmartDish	13
	24 Well Plates	13
	1	7

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Number of replicates plated per sample	2	60
	3	27
	4	7
Volume of cells inoculated into MethoCult	1/10 of media	53
	Variable/Other	47
Method to mix the cells into the semi-solid media	Vortex	93
	Pipetting	7
Method for dispensing the semi-solid medium into well/plate	Needle/Syringe	100
Cord blood processing method	Sepax	47
	AXP	20
	PrepaCyte	13
	Manual	7
Day of colony enumeration	14d	100
CFU counting method	Manual	80
	Automated	20
CFU colony types identified and counted	BFUE/GM/GEMM	73
	Total CFU	7
	Other	20

Analysis of the results of the PT Arm are shown in Table 9. All parameters measured showed a percent CV lower than 25% except for enumeration of CFU-GM (33.73% CV) and CFU-GEMM (58.50% CV). The % coefficient of variations were the lowest for total CFU, TNC, and CD34+

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assessments within the past eight years and may be explained by the use of the RBC-depleted sample.

Table 9. Results of the 2015 Proficiency Testing program evaluation using the standardized protocol (PT Arm)

	N	Mean*	Standard Deviation*	% Coefficient of Variation	Median
Total Nucleated Cells (x10⁶ cells)	42	10.89	0.51	4.71	10.86
Viability (%)	42	95.95	2.00	2.08	96.28
Viable Nucleated Cells (x10⁶ cells)	42	10.44	0.41	3.94	10.39
%CD34⁺ Gated on Viable Cells	13	0.22	0.022	10.09	0.23
%CD34⁺+CD45⁺ Gated on Viable	25	0.24	0.036	14.72	0.25
BFU-E	40	16.56	4.10	24.76	16.50
CFU-GM	41	17.45	5.89	33.73	17.00

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CFU-GEMM	39	2.77	1.62	58.50	2.75
Total Colonies	41	38.02	8.64	22.73	37.00

*Robust analysis

The total colony enumeration results of the participants of the PT and Study Arms are detailed in the table 10 below. Of note is the difference in percent CV between the two arms: 18.67% and 40.49%, PT Arm and Study Arm, respectively. However, the difference between the CFU results from the two arms is not statistically significant when analyzing the normalized total CFU (p-value = 0.9467).

Table 10. Comparison of results between the PT and Study arms

	N	Mean*	Standard Deviation*	% Coefficient of Variation	Median
PT Arm	25	117.18	21.88	18.67	109.17
Study Arm	25	104.21	42.20	40.49	98.39

*Robust analysis

The Cord Research Sub-advisory Group determined that more evaluation is required before recommendations can be made regarding the CFU assay.

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Dextran Shortage Response

In late 2014 the CBAG was informed of an impending shortage of clinical grade Dextran solution that was caused by a manufacturing issue at the primary supplier. Dextran is utilized by TCs during the thaw and wash preparation of CBUs prior to infusion and is a critical component of the thaw protocols developed by CBBs. The Cord Research Sub-advisory Group was tasked with seeking alternatives to standard dextran solution that would meet FDA requirements.

A sample of TCs were surveyed to determine their process to compare these alternatives. The TCs were then asked to share their comparability protocols for review. The 12 TCs that responded to the survey studied various types of alternative reagents and manufacturers of the standard Dextran 40 in 0.9% NaCl. Four TCs submitted their protocols to the Sub-advisory group from which a model comparability protocol was created for centers who need assistance. Whether comparing Dextran 40 in 0.9% NaCl to that of a different manufacturer or a different reagent, the results of the comparability studies submitted by the TCs indicated equivalency. During a shortage, the model comparability study protocol can be used as a reference to establish an alternative to Dextran 40 in 0.9% NaCl. This information was disseminated to NMDP network partners by a network announcement and can be currently found at the link:

<https://network.bethematchclinical.org/WorkArea/DownloadAsset.aspx?id=13620>.

To reach a wider audience, the Sub-advisory group developed the information into a brief report that was published in Transfusion.

Cord blood unit release testing criteria and the impact on transplantation outcome

Cryopreservation and storage can affect the quality of CBU. There is growing evidence to suggest that post-cryopreservation quality assessment should be conducted prior to release of CBU for use in HCT. The 4th edition of NetCord-FACT International Cord Blood Standards recommends an additional post-cryopreservation CFU test to assess these affects. It is therefore, important to study the role of post-cryopreservation CBU CFU characteristics on transplant outcomes. A study was developed to evaluate the association of the post-thaw CFU assay results and neutrophil engraftment.

An initial cohort of 297 CBU HCT cases was evaluated in 2014 and the cohort was expanded to 563 cases in 2016. Patients receiving a first allogeneic myeloablative minimally manipulated single cord blood transplantation facilitated by the NMDP between 2005 and 2015 for which

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there is recipient consent for research were included. The participating cord blood banks of Duke, MD Anderson Cancer Center (MDACC), and St. Louis Cord Blood Bank (SLCBB) submitted pre- and post- cryopreservation CFU data to the CIBMTR to merge with the clinical data and perform the analysis. The cumulative incidence of neutrophil engraftment was evaluated based on pre and post-cryopreservation CFU recovery ratios split by quartiles with the lowest quartile split to attempt to define a minimal recovery threshold (Table 11). There were no significant differences observed between any of the CFU recovery groups suggesting that the post thaw CFU recovery thresholds already in place at the participating CBBs ensures high quality CBU are being released. What cannot be assessed is whether CBBs that do not have similar practices in place run the risk of releasing lower quality CBU. The group will continue to evaluate methods to qualify unit quality and engraftment potential post-cryopreservation.

Table 11: Cumulative Incidence of engraftment by pre- and post-cryopreservation CFU recovery in quartiles for all CBBs, quartiles combined (N=557)

Outcome	<u>Q1.1</u>	<u>Q1.2</u>	<u>Q2</u>	<u>Q3</u>	<u>Q4</u>	Pointwise p-value
	N Prob (95% CI)	N Prob (95% CI)	N Prob (95% CI)	N Prob (95% CI)	N Prob (95% CI)	
Engraftment	69	70	140	141	137	
@ 28 days	75 (65-85)	67 (56-78)	78 (71-84)	82 (76-88)	77 (70-84)	0.212
@ 45 days	88 (80-95)	79 (68-87)	88 (82-93)	89 (84-94)	87 (81-92)	0.403
@ 60 days	90 (82-96)	80 (70-88)	90 (85-94)	89 (84-94)	91 (86-95)	0.314

Immunobiology Research

During a previous grant period, the NMDP developed the Immunobiology Research grant request and award procedures for use by the IBWC and developed the IBWC Web site (http://www.cibmtr.org/COMMITTEES/Working_Committees/Immunobiology/index.html). The content was further refined and migrated to the CIBMTR.org Web site in 2010 and is refreshed quarterly.

During the grant period, grant funds supported significant outreach efforts by the IBWC leadership to increase exposure for the IBWC to basic scientists. The IBWC leadership attended several scientific meetings including: American Society of Hematology, BMT Tandem, European Group for Blood and Marrow Transplant and American Society for Histocompatibility and Immunogenetics meetings. In addition, the Assistant Scientific Director made a webinar presentation to the Foundation for the Accreditation in Cellular Therapy highlighting research from the IBWC and data sharing capabilities of the CIBMTR. Support permitted the committee to maintain a strong performance record with 9 publications (submitted or accepted),

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collaboration on 4 grant submissions and accepted 2 new proposals during the performance period.

IBWC 2016 manuscript summaries (submitted/accepted):

1. **IB08-06** Rocha V, Ruggeri A, Spellman S, Wang T, Sobecks R, Locatelli F, Askar M, Michel G, Arcese W, Iori AP, Purtill D, Danby R, Sanz GF, Gluckman E, Eapen M. Killer cell immunoglobulin-like receptor ligand matching and outcomes after unrelated cord blood transplantation acute myeloid leukemia. ***Published in BBMT***
 - i. A collaborative retrospective study between the CIBMTR, Eurocord and EBMT evaluating the role of Killer Immunoglobulin-Like Receptor (KIR) ligand matching in unrelated cord blood transplantation. There were no significant differences in non-relapse mortality (NRM), relapse, and overall mortality by KIR-ligand match status. However, among recipients of 3-5/8 HLA-matched transplants, NRM and overall mortality were higher with KIR-ligand mismatched compared with KIR-ligand matched transplants. These data do not support selecting cord blood units based on KIR-ligand match status for transplants mismatched at 1 or 2 HLA loci. Although transplants mismatched at 3 or more HLA loci are not recommended, avoiding KIR-ligand mismatching in this setting lowers mortality risks.
2. **IB08-08** Goyal RK, Lee SJ, Wang T, Trucco M, Haagenson M, Spellman SR, Veneris M, Ferrell RE. Novel HLA-DP region susceptibility loci associated with severe acute GvHD. ***Published in BMT***
 - i. A retrospective genome-wide association study (GWAS) using samples from the CIBMTR Repository to identify recipient and donor genes associated with the risk of acute GvHD. Three novel susceptibility loci in the HLA-DP region of recipient genomes that were associated with III-IV acute GvHD. This report contributes to emerging data showing clinical significance of the HLA-DP region genetic markers beyond structural matching of DPB1 alleles.
3. **IB10-01b** Gadalla SM, Khincha PP, Katki HA, Giri N, Wong JYY, Spellman S, Yanovski JA, Han JC, De Vivo, Alter BP, Savage SA. The limitations of qPCR telomere length measurement in diagnosing dyskeratosis congenita. ***Published in Molecular Genetics & Genomic Medicine***

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- i. A retrospective study using biospecimens from the CIBMTR Repository to compare qualitative real-time polymerase chain reaction (qPCR) assessment of telomere length versus the current gold standard test using flow cytometry fluorescence in-situ hybridization (Flow FISH) for the diagnosis of dyskeratosis congenital (DC), a telomere biology disorder characterized by very short telomeres. The qPCR assay failed to identify 60% of patients with known DC. Flow FISH remains the gold standard for DC diagnosis.
4. **IB10-01c** Gadalla SM, Wang T, Dagnall C, Haagenson M, Spellman SR, Hicks B, Jones K, Katki HA, Lee SJ, Savage SA. Effect of recipient age and stem cell source on the association between donor telomere length and survival after allogeneic unrelated hematopoietic cell transplantation for severe aplastic anemia. ***Published in BBMT***
 - i. A retrospective validation analysis using samples from the CIBMTR Repository to evaluate the association between donor leukocyte relative telomere length (RTL) and post- HCT survival in patients with severe aplastic anemia. Data from the validation cohort found no association between donor RTL and patient survival, but further analysis identified differences by recipient age and stem cell source. Analyses using data from the discovery and validation cohorts showed a statistically significant survival benefit only in <40-year-old patients receiving bone marrow grafts. The study suggested that the association between donor RTL and post-HCT outcomes may vary by recipient age and stem cell source. A larger study is needed to account for multiple comparisons and to further test the generalizability of the findings.
5. **IB10-04** Arora M, Lee SJ, Spellman SR, Weisdorf DJ, Guan W, Haagenson M, Wang T, Horowitz MH, Verneris MR, Fleischhauer K, Hsu K, Thyagarajan B. Validation study failed to confirm an association between genetic variants in the base excision repair pathway and transplant-related mortality and relapse after hematopoietic cell transplantation. ***Published in BBMT***
 - i. A retrospective study using biospecimens from the CIBMTR Repository to validate findings from a single institution study that identified an association between genetic polymorphism in DNA repair genes and transplant outcome. The results of the study were negative with no associations found in the larger CIBMTR cohort. The manuscript stressed the importance of validating associations between genetic variants and transplant outcomes in independent datasets prior to implementing in clinical practice.

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6. **IB12-05/RT10-01** Kornblit B, Wang T, Lee SJ, Spellman SR, Zhu X, Fleischhauer K, Müller C, Johansen JS, Vindelov L, Garred P. YKL-40 in allogeneic hematopoietic cell transplantation after AML and myelodysplastic syndrome. *Published in BMT*
 - i. A retrospective study using plasma samples from the CIBMTR Repository to evaluate the prognostic value of recipient and donor pre-transplant levels of YKL-40, an inflammatory biomarker, on transplant outcomes. Patient YKL-40 levels did not aid in the risk stratification, but elevated donor levels were associated with a trend towards higher rates of grades II-IV acute graft versus host disease (aGvHD). This suggests that YKL-40 may aid donor selection when multiple, otherwise equal, donors are available.
7. **IB12-06** Bachanova V, Weisdorf DJ, Wang T, Marsh SGE, Trachtenberg E, Haagenson MD, Spellman SR, Ladner M, Guethlein LA, Parham P, Miller JS, Cooley SA. Donor KIR B genotype improves progression-free survival of non-Hodgkin lymphoma patients receiving unrelated donor transplantation. *Published in BBMT*
 - i. A retrospective analysis using biospecimens from the CIBMTR Repository. Donor killer immunoglobulin-like receptor (KIR) genotypes are associated with relapse protection and survival after HCT for acute myelogenous leukemia, but had not been evaluated in non-Hodgkin lymphoma (NHL). In 10/10 HLA matched HCT for NHL, use of KIR B/x haplotype donors was associated with significantly reduced relapse risk and improved PFS. The relapse protection was not observed in HLA-mismatched HCT.
8. **IB13-02** Marino SR, Lee SM, Binkowski TA, Wang T, Haagenson M, Wang H-L, Maiers M, Spellman S, van Besien K, Lee SJ, Karrison T, Artz A. Identification of high-risk amino-acid substitutions in hematopoietic cell transplantation: a challenging task. *Published in BMT*
 - i. A retrospective validation analysis of 19 previously identified amino-acid substitution and position types (AASPT) conferring higher risks of transplant related mortality and GvHD following HLA mismatched unrelated donor HCT. When tested in an independent validation cohort of 3530 patients, none of the AASPT were validated as high risk, however. The analysis does not support avoidance of any specific class I AASPT for unrelated donor HCT.

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9. **IB13-03** Lazaryan A, Wang T, Spellman SR, Wang H-L, Pidala J, Nishihori T, Askar M, Olsson R, Oudshoorn M, Abdel-Azim H, Yong A, Gandhi M, Dandoy C, Savani B, Hale G, Page K, Bitan M, Reshef R, Drobyski W, Marsh SGE, Schultz K, Müller CR, Fernandez-Viña M, Verneris MR, Horowitz MM, Arora M, Weisdorf DJ, Lee SJ. Human leukocyte antigen supertype matching after myeloablative hematopoietic cell transplantation with 7/8 matched unrelated donor allografts: A report from the Center for International Blood and Marrow Transplant Research. *Published in Haematologica*
 - i. A retrospective analysis on the impact of matched and mismatched HLA-A -B, -C and -DRB1 superotypes on clinical outcomes following unrelated donor HCT for acute leukemias or myelodysplasia/myeloproliferative disorders. The analysis found no associations between supertype mismatching and survival. However, HLA-B supertype mismatches were associated with increased risk of grade II-IV acute GvHD.

IBWC 2016 proposals:

1. Impact of HLA-disparity on graft-versus-lymphoma effects in patients with and without graft-versus-host-disease after allogeneic stem cell transplantation. PIs: F Ayuk and U Bacher. **Declined**
2. The role of HLA-E compatibility in the prognosis of acute leukemia patients undergoing 10/10 HLA matched unrelated HSCT. PIs: C Tsamadou, D Fürst, J Mytilineos). **Accepted**
3. Use of HLA structure and function parameters to understand the relationship between HLA disparity and transplant outcomes. PI: LA Baxter-Lowe. **Accepted**
4. Investigating influence of minor histocompatibility antigens/alleles and previously uncharacterized KIR interacting factors on outcomes after HLA matched HSCT. PIs: CH Roberts and A Madbouly. **Declined**

CIBMTR Information Technology (CIT) Minneapolis Initiatives

The scope of the work performed by the CIBMTR IT department in Minneapolis includes collecting and reporting outcomes data on all allogeneic transplantations performed in the U.S. (for the SCTOD, as required by U.S. law). U.S. transplant centers also voluntarily submit autologous transplantation data, and transplant centers worldwide voluntarily submit both autologous and allogeneic transplantation data. As a result, and as reported in the CIBMTR 2015 Annual Report, the CIBMTR Research database now contains information on more than 425,000

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patients. CIT strives to provide applications that will reduce center burden for government mandated forms and provide high quality data on demand.

CIT Application Suite:

- FormsNet: Recipient – Donor
- AGNIS
- Management Reporting
- Sample Tracking
- Auditing

FormsNet

Since its original release in Dec 2007, the Recipient Module of the FormsNet application has been used at more than 418 centers to register 183,198 patients and collect over 1,242,313 forms with more than 10 million data elements. This program was developed for both local data entry from paper forms and web-based entry by clinical centers. Currently over 94.9% of the data are being entered by clinical centers via the web. In the last six months, NMDP derived 99% by calculating forms submitted electronically divided by those forms eligible for electronic submission. Two forms (2801 – log of appended documents and 2802 – transfer forms) can only be submitted on paper to ensure audit standards. The Form 2801 – log of appended documents, is in process of being decommissioned as a new feature has been added to FormsNet3 proving the ability to attach electronic documents directly to a form.

FormsNet is a secure, Web-based application for submission of outcomes data to CIBMTR (Recipient module), support for Auditing and Event Reporting, and support for Donor clearance, follow-up and safety (Donor module). The original features of real-time error validation and override capabilities, and the option to generate a Forms Due Report to track all forms due for every patient have been improved and enhanced. The original deployment in December 2007 was built in 126,000 lines of code supporting 90 Recipient forms and no user tools. Today there are over 500,000 lines of code supporting 249 forms, tools, web services, email, and two user-based modules. The application is fully integrated with the CIT applications suite supporting CIBMTR. The application was converted from its original website to a web application with an enhanced object oriented code structure. Service Oriented Architecture integration services were created to provide flexibility and extensibility for future enhancements. In 2012, the planned upgrade to FormsNet replaced the technical foundation of the current FN2 application, with more agile, efficient & effective systems. It improved the user experience by providing enhanced functionality (defined by the network users). In 2014, the Donor module was upgraded to the FormsNet 3 platform, providing the same benefits for Donor module users as realized by Recipient module users. In 2015, CIBMTR evaluated and determined that an external Clinical Trials product will be purchased and integrated with the CIBMTR platform to meet the

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electronic data capture business need, as opposed to an upgrade of the FormsNet application to support this need. Utilizing non-Navy funding, in 2016 the Medidata RAVE package was implemented for use as the web-based electronic data capture system for Clinical Trials and other prospective research projects. RAVE also is the system used for monitoring of the data submitted.

In 2016, FormsNet was upgraded to include additional tools to support efficiencies at the centers and for internal staff. One implemented tool is the Attachments tool, which enables users to attach electronic documents directly to a form. Another new feature implemented, the query management tool, was added to enable the Data Quality Team to electronically notify centers within FormsNet when a question exists on an individual field within a form. This enhances data quality by eliminating manual processes such as emails and phone calls.

FormsNet was updated monthly during the grant period to enhance the Recipient, Donor, and Audit modules to apply enhancements and ensure optimal performance, flexibility and efficiency of applications.

RITN Data Collection Forms

As part of the RITN preparedness efforts, Institutional Review Board-approved protocols are in place at multiple RITN centers for the collection of demographic, situational and clinical data from radiation casualties who are sent to RITN hospitals and provide informed consent. The CIBMTR is uniquely positioned to collect this data, based on the existing data collection system and the program's long track-record of collecting similar data on more than 22,000 blood and marrow transplant recipients annually. Importantly, the data collection approach for radiation casualties will differ from that which is collected daily in CIBMTR centers since only those who receive a transplant are tracked in the current system. This data collection process will not only capture those who undergo blood and marrow transplantation but also all radiation casualties treated at RITN centers and provide informed consent. The data obtained from the RITN Data Collection Interface will be an invaluable resource for subsequent efforts to improve triage, treatment and monitoring approaches for individuals exposed to radiation.

In 2014, CIBMTR performed analysis and design to support the RITN data collection needs. This included confirming the overall scope, interviewing key stakeholders, identifying business needs/requirements, defining required forms and other key design elements essential to begin development early in 2015. RITN development and testing continued during 2015. In early 2016, the production rollout of the Contact, Baseline, and Follow-up Forms necessary to collect the required data points took place. To be able to fully validate that the system is ready for use, in 2016 CIBMTR collaborated with RITN on one of its tabletop exercises. The successful mock

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test of the workflow and data gathering capabilities involved testing the forms at a cross-section of centers.

A Growable Network Information System (AGNIS)

AGNIS is a system for electronic messaging of standard Common Data Elements (CDEs) between participating nodes. Messaging can occur between transplant centers, registries, investigators or any combination of entities willing to map relevant data elements and install the software/messaging system. The system relies on two key components, data standards in the form of common data elements (CDEs), and software for transferring the data, providing audit trails, conveying error messages, etc.

- **CDE Development:**
CIBMTR has invested substantial effort defining CDEs for CIBMTR forms. All CDEs are defined in the Cancer Data Standards Repository (caDSR) of the NCI. This leverages a strong national system of standards regarding the definitions and related metadata. Additionally, a substantial portion of the CDEs have also been defined in the Biomedical Research Integrated Domain Group (BRIDG) model, which is compatible with HL7, the most prevalent ‘language’ used in biomedical informatics.

- **caDSR:**
 - Definitions have been created for nearly 2,500 CDEs associated with 14,000 data points on more than 90 forms.

The following 16 recipient outcome forms have been released in the caDSR and are available for electronic data exchange via AGNIS: seven mandated forms (pre- and post-TED, HLA, IDM, Infusion, Chimerism, and Selected Post-TED), five Comprehensive Forms (Baseline, 100 day Follow-Up, 6 mo. to 2 yr. Follow-up, Annual Follow-Up, and Death), Unique ID Assignment, Indication for CRID Assignment, and two disease specific inserts (Pre- and Post-HSCT Hodgkin and Non-Hodgkins Lymphoma).

- **System Users:**
 - Independent Transplant Centers:

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- 4 centers actively submitting and retrieving data through AGNIS: H. Lee Moffitt, MD Anderson, Cleveland Clinic, and Stanford
- 1 center actively retrieving through AGNIS: Seidman Cancer Center
- 4-6 centers actively developing solutions, including Mayo (planning to move to production in 2016) and Memorial Sloan Kettering Cancer Center (MSKCC)
- 1 center currently testing and planning to move to production in 2016 with a RED cap database solution. They plan to share their mapping and development strategies with 2-3 centers other centers that utilize RED cap and are interested in AGNIS capabilities, including Cornell and Chicago.
- Transplant centers using Vendor solutions:
 - Over 40 centers working with StemSoft to submit or receive AGNIS supported forms from CIBMTR
 - 12 centers actively utilizing AGNIS for submission
 - Other centers authorized, but some are only retrieving and not all active at this time
 - 2 centers authorized to submit and retrieve all AGNIS supported forms via OTTR® software: Barnes Jewish and St. Louis Children's
 - 2 more planning to move to production in 2016
 - 3 centers authorized to submit and retrieve all AGNIS supported forms via Medidata software and center testing is in progress: Hackensack, Georgetown and Kentucky
 - 4 centers authorized Liaison Technologies to develop capability to submit and retrieve all AGNIS supported forms (formerly Remedy Informatics. Remedy had 18 centers authorized)
 - 7 centers in the Sarah Cannon consortium working with Velos to develop capability to submit and retrieve all AGNIS supported forms
 - 1 center submitting in production via LabCentrix(StemTrek) software
 - 1-2 additional vendors developing software: Title21 and others
- System Enhancements:

In the last year, the AGNIS team accomplished the following:

- The AGNIS platform was used for over 30,000 submissions to FormsNet
- Provided ongoing support for EBMT-CIBMTR and CIBMTR-Eurocord AGNIS connections
- Released the new CIBMTR Recipient ID Assignment Form (2804r5) and Indication for CIBMTR Recipient Identification (CRID) Assignment Form (2814r1) to support the Flexible CRID project

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- Released AGNIS translator rewrite project in January 2016. This software update will include enhancements to performance, error reporting and the core AGNIS processing engine.
- Registry connections:
 - EBMT has been working with the CIBMTR to develop a pathway to share TED-level data from EBMT centers that also participate in the CIBMTR. Mapping has occurred for the Pre-TED, Post-TED at 100 days, Unique ID, and Infusion forms. Data submission, initially manually and now with automation, has occurred for participating centers who have not submitted forms to CIBMTR since 2008 for new transplants.
 - This approach has provided over 34,000 new form records.
 - With automation, expect to receive about 40,000 Pre-TED, Post-TED, Unique ID and Infusion forms
- EMR connections:
CIBMTR worked with EPIC to integrate 51 standard CDEs into the BMT registration form in EPIC (BMT smartform).

Information Management

The CIBMTR Information Management Strategy (IMS) project's main objective is to establish a comprehensive program for the management of data across the enterprise, turning the large volumes of data into a strategic asset supporting high value, sophisticated analyses. The Integrated Data Warehouse is the primary deliverable for this project. At delivery, the Integrated Data Warehouse will contain high quality, validated data readily available to researchers for immunobiology, outcomes, and other types of analyses. It will be the single source of truth of data that supports the diverse administrative and scientific needs of internal and external stakeholders. The team is building a unified domain to house multiple sources and dimensions of data. CIBMTR operational teams will be able to dramatically reduce the amount of time they spend on data consolidation, preparation, and validation of datasets and instead focus on the analysis. As a result, analyses will be completed in a timely manner facilitating decision-making based on these data assets.

This effort is aligned with NMDP enterprise architectural standards, and incorporates selective use of industry standards, including BRIDG (Biomedical Research Integrated Domain Group) and HL-7 FHIR (Fast Healthcare Interoperability Resources). The first deliverable implemented an Integrated Data Store (IDS) which serves as the foundation for the long-term data warehouse.

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Using the IDS as the unified data source, the first phase of the Data Warehouse was completed by integrating data used for immunobiology analyses into the Data Warehouse. In 2016, the team continued designing the unified domain and built the conceptual model. Table 12 below shows the types of data stored in the Data Warehouse and their data sources, including data sources added since the original release of the IDS:

Table 12. Types of sources of data in CIBMTR Data Warehouse

Focus area	Description	Source
IDM	Donor IDMs information for NMDP facilitated HCTs	Legacy (Formsnet1) & current FormsNet3
Infusion data	50 most Requested Variables for ad-hoc and center volumes reporting requests from FN3 - Clinical outcome data tied to each infusion event (future)	FormsNet, SIP
Research Specimen Data	- Research Repository Specimen Inventory data on related and unrelated cords, donors, and recipient samples - Data on Research Repository Specimen submission and compliance - Integration with 3rd party vendor, Labvantage, to provide Research Sample data - Provides self-service environment for analysis through Business Intelligence tool. (OBIEE) - Provides end user defined reports utilized to complete HRSA reporting requirements.	BIO Res (IPR/RR) Lab Vantage vendor application
NMDP Source Data	- Cord Blood Unit Data - Double Cord (Multi)	StarLink CordLink (SyBase) Emtrax through Reg ODS

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Focus area	Description	Source
HLA/KIR Match Data	- Transformed CIBMTR Legacy HLA data - HLA data for donor/recipient for NMDP facilitated HCTs, legacy and current (STAR/SIP) (form 2005) - HLA data transformation on new form 2005/non-NMDP Tx SCTOD data - Donor-Recipient Match Grade results (HLA Save) - KIR data - Re-Evaluate current data sources	- CIBMTR OBS DB - STAR - FormsNet3 - IPR - HLA Save
Donor & Recipient data	- Transformed Donor and Recipient data - Provides self-service environment for analysis through pre-defined joins (business view of the metadata), calculations and generating adhoc data sets - Capability for near real time(~ 5 minutes) data sharing and analytics across forms through combined and unified virtualization layer (views) - Faster turnaround on visibility to data quality fixes.	- FormsNet - NMDP Legacy
Metadata	Provides data lineage, impact analysis and FormsNet metadata analysis	FormsNet Metadata, BODI metadata, OBIEE metadata
Center volumes	- Provides metrics around the number of infusions by center/donor type/product type/disease/age group/race variables - Replaces existing manual process	FormsNet, NMDP

In addition to the referenced source data consolidated in the Data Warehouse, CIT has also implemented operational improvements to the warehouse, and developed, in the last 12 months, the following functionality:

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- Implementation of the Data Quality Mart and associated reports will allow for early detection of questionable data in an effort to proactively identify and correct discrepant data, thus reducing the time spent preparing datasets
- Completed Data Warehouse Operational Improvements, including upgrades to the latest version of development tools and completion of automation of the Center Volumes Reporting Dashboard Data set.

- Delivering two Business Intelligence applications to share data with centers
 - Enhanced Data Back to Centers (eDBtC), enabling visualization of center trends and descriptive statistics as well as ad hoc querying capabilities
 - Center Performance Analytics (CPA), enabling a center to analyze center trends related to other centers in data set, create selective queries, and export filtered data for analysis.
- Automation of the calculation of HLA and match grade variables for use in studies
- Support of Research Repository Sample data transfer from LabVantage to the Integrated Data warehouse. This includes operational reports capturing HRSA requirements and enrollment data.

- Integration with Clinical Trials vendor software, Medidata Rave, to transfer Clinical Trials data to the Integrated Data Warehouse. This transfer includes operational access to complete reporting requirements.

VI. Publications

1. Nakasone H, Sahaf B, Tian L, et al. Presensitization to HY antigens in female donors prior to transplant is not associated with male recipient post-transplant HY antibody development nor with clinical outcomes. *Haematologica*. 101(1):e30-e33. doi:10.3324/haematol.2015.134551. Epub 2016 Jan 1. PMC4697905.

2. Williams KM, Ahn KW, Chen M, et al. The incidence, mortality and timing of *Pneumocystis jirovecii* pneumonia after hematopoietic cell transplantation: a CIBMTR analysis. *Bone Marrow Transplantation*. 2016 Apr 1; 51(4):573-580. doi:10.1038/bmt.2015.316. Epub 2016 Jan 4. PMC4823157.

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3. Kanda J, Brazauskas R, Hu ZH, et al. GVHD after HLA-matched sibling BMT or PBSCT: comparison of North American Caucasian and Japanese populations. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*. 2016 Apr 1; 22(4):744-751. doi:10.1016/j.bbmt.2015.12.027. Epub 2016 Jan 4. PMC4801761.
4. Yoshimi A, Baldomero H, Horowitz M, et al. Global use of peripheral blood vs bone marrow as source of stem cells for allogeneic transplantation in patients with bone marrow failure. *JAMA: The Journal of the American Medical Association*. 2016 Jan 12; 315(2):198-200. doi:10.1001/jama.2015.13706. Epub 2016 Jan 12. NA.
5. Al Malki MM, Horowitz M, Handgretinger R, et al. Proceedings from the Second Haploidentical Stem Cell Transplantation Symposium - Haplo2014, San Francisco, California, December 4, 2014. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*. 2016 Apr 1; 22(4):594-604. doi:10.1016/j.bbmt.2016.01.001. Epub 2016 Jan 13. NA.
6. Kumar R, Kimura F, Ahn KW, et al. Comparing Outcomes with Bone Marrow or Peripheral Blood Stem Cells as Graft Source for Matched Sibling Transplants in Severe Aplastic Anemia across Different Economic Regions. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*. 2016 May 1; 22(5):932-940. doi:10.1016/j.bbmt.2016.01.012. Epub 2016 Jan 18. PMC4826285.
7. Sparapani RA, Logan BR, McCulloch RE, et al. Nonparametric survival analysis using Bayesian additive regression trees (BART). *Statistics in Medicine*. 2016 Jul 20; 35(16):2741-2753. doi:10.1002/sim.6893. Epub 2016 Feb 7. PMC4899272.
8. van Besien K, Hari P, Zhang M-J, et al. Reduced intensity haplo plus single cord transplant compared to double cord transplant: improved engraftment and graft-versus-host disease-free, relapse-free survival. *Haematologica*. 2016 May 1; 101(5):634-643. doi:10.3324/haematol.2015.138594. Epub 2016 Feb 11. PMC5004373.
9. Teira P, Battiwalla M, Ramanathan M, et al. Early cytomegalovirus reactivation remains associated with increased transplant related mortality in the current era: a CIBMTR analysis. *Blood*. 2016 May 19; 127(20):2427-2438. doi:10.1182/blood-2015-11-679639. Epub 2016 Feb 16. PMC4874224.

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VIII. Acronyms

AABB	American Association of Blood Banks
AAFA	African American (NMDP race code)
AAR/IP	After Action Review/Improvement Plan
ABA	American Burn Association
ABD	Antigen Binding Domain
ABMTR	Autologous Blood and Marrow Transplant Registry
AC	Apheresis Center
ACT	Allele Calling Tool
AFA	African American
AFR	African
AFRRI	Armed Forces Radiobiology Research Institute
AGNIS®	A Growable Network Information System
AHA	American Hospital Association
AHLS	Advanced HAZMAT Life Support

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AIM	Ancestry Informative Markers
AINDI	South Asian
AISC	American Indian South or Central
ALANAM	Alaska Native or Aleut
ALD	Asymmetric Linkage Disequilibrium
ALDH	Aldehyde Dehydrogenase
ALDHbr	Aldehyde Dehydrogenase bright
ALT-LOCI	Alternate Loci
AMIND	North American Indian
AML	Acute Myelogenous Leukemia
AMR	American Indian
ANSI	American National Standards Institute
API	Application Programming Interface
AQP	Ancestry Questionnaire Project
ARC GIS	ArcGIS is a brand name: GIS = Geographical Information System
ARD	Antigen Recognition Domain
ARRA	The American Recovery and Reinvestment Act of 2009
ARS	Acute Radiation Syndrome (also known as Acute Radiation Sickness)
ARS	Antigen Recognition Site
ASBMT	American Society for Blood and Marrow Transplantation
ASEATTA	Australian and South East Asian Tissue Typing Association
ASH	American Society for Histocompatibility
ASHG	American Society of Human Genetics
ASHI	American Society for Histocompatibility and Immunogenetics
ASI	Asian American
ASPR	Assistant Secretary for Preparedness and Response
ASTHO	Association of State and Territorial Health Officials
AUC	Area Under Curve
B-LCLs	B-Lymphocytic Cell Lines
B2B	Business to Business
BAA	Broad Agency Announcement
BARDA	Biomedical Advanced Research and Development Authority
BBMT	Biology of Blood and Marrow Transplantation
BCP	Business Continuity Planning
BCPeX	Business Continuity Plan Exercise
BFU-E	Burst Forming Unit-Erythrocytes
BGI	Beijing Genome Institute
BISC	Bioinformatics Integration Support Contract
BM	Bone Marrow
BMCC	Bone Marrow Coordinating Center
BMDW	Bone Marrow Donors Worldwide

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BMT	Bone Marrow Transplant/Transplantation
BMT CTN	Blood and Marrow Transplant - Clinical Trials Network
BODI	Business Objects Data Integrator
BRAGG	Bioinformatics Research Advisory Ginger Group
BRIDG	Biomedical Research Integrated Domain Group
BRT	Basic Radiation Training
BTM	Be The Match
caBIG	NIH/NCI Cancer Biomedical Informatics Grid
caDSR	Cancer Data Standards Repository
C&A	Certification and Accreditation
CAP	College of American Pathologists
CARB	Black Caribbean
CARHIS	Caribbean Hispanic
CARIBI	Caribbean Indian
CATI	Computer Assisted Telephone Interviewing
CAU	Caucasian
C&A	Certification and Accreditation
CB	Cord Blood
CBA	Cord Blood Association
CBAG	Cord Blood Advisory Group
CBITT	Center for Biomedical Informatics and Information Technology
CBMTG	Canadian Blood and Marrow Transplant Group
CBB	Cord Blood Bank
CBC	Congressional Black Caucus
CBS	Canadian Blood Service
CBT	Cord Blood Transplantation
CBU	Cord Blood Unit
CC	Collection Center
CCD	Continuity of Care Document
CD	Cluster of Differentiation
CDA	Clinical Document Architecture
CDC	Centers for Disease Control
CFU	Colony Forming Unit
CDE	Common Data Elements
CDISC	Clinical Data Interchange Standards Consortium
CEM	Certified Emergency Manager
CEO	Chief Executive Officer
CFO	Chief Financial Officer
CEP	Collect Eject Protect
CFU	Colony Forming Unit
CFU-GM	Colony Forming Unit-Granulocyte Macrophage

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CFU-GEMM	Colony Forming Unit-Gran Erythrocyte Macrophage Monocyte
CG-WG	Clinical Genomics Work Group
cGy	CentiGrey
CHORI	Children's Hospital of Oakland Research Institute
CHOP	The Children's Hospital of Philadelphia
CHS	Certified Histocompatibility Specialist
CHTC	Certified Hematopoietic Transplant Coordinator
CI	Confidence Interval
CIBMTR®	Center for International Blood & Marrow Transplant Research
CIO	Chief Information Officer
CIT	CIBMTR Information Technology
CLIA	Clinical Laboratory Improvement Amendment
CMCR	Centers for Medical Countermeasures Against Radiation
CMDP	China Marrow Donor Program
CME	Continuing Medical Education
CMF	Community Matching Funds
CML	Chronic Myelogenous Leukemia
CMO	Chief Medical Officer
CMS	Center for Medicare and Medicaid Services
CMV	Cytomegalovirus
CNV	Copy Number Variation
COG	Children's Oncology Group
CPA	Center Performance Analytics
CPI	Continuous Process Improvement
CREG	Cross Reactive Groups
CRF	Case Report Forms
CRI	Complete Remission
CRID	CIBMTR Recipient ID
CRIS	Computerized Repository Inventory System
CRO	Chief Recruitment Officer
CSF	Colony Stimulating Factors
CSO	Chief Strategy Officer
CSS	Center Support Services
CSS	Custom Search Support
CT	Confirmatory Testing
CTA	Clinical Trial Application
CTLp	Cytotoxic T Lymphocyte Precursor
CTMS	Clinical Trial Management System
CUPC	Cisco Unified Personal Communicator
CV	Co-efficient of Variations
CWD	Common Well Documented

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DAIT	Division of Allergy, Immunology, and Transplantation
DaSH	Data Standards Hackathon
DC	Donor Center
DCAA	Defense Contract Audit Agency
DFCI	Dana-Farber Cancer Institute
DFS	Disease Free Survival
DHHS	Department of Health and Human Services
DIY	Do It Yourself
DKMS	Deutsche Knochenmarkspenderdatei
DMSO	Dimethylsulphoxide
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DOE	Department of Energy
DP	Domain Prediction
DQ	Data Quality
DR	Disaster Recovery
D/R	Donor/Recipient
DRPP	Donor Related Pair Project
DSA	Donor specific anti-HLA antibody
DSMB	Data Safety Monitoring Board
DSTU	Draft Standard for Trial Use
DVD	Digital Video Disc
EBMT	European Group for Blood and Marrow Transplantation
EC	Ethics Committee
ED	Emergency Department
eDBiC	Enhanced Data Back to Centers
EDC	Electronic Data Capture
EFI	European Federation for Immunogenetics
EHR	Electronic Health Record
ELISA	Enzyme-linked Immunosorbent Assay
ELIsport	Enzyme-linked Immunosorbent Spot
EM	Expectation Maximization
EMDIS	European Marrow Donor Information System
EMR	Electronic Medical Records
EMS	Emergency Medical System
ENS	Emergency Notification System
ERSI	Environment Remote Sensing Institute
ESRI	Environmental Systems Research Institute
EUR	European American
E-utilities	Entrez Programming Utilities
FACS	Fluorescent Activated Cell Sorting

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FBI	Federal Bureau of Investigation
FDA	Food and Drug Administration
FDR	Fund Drive Request
FGM	France Greffe de Moelle
FHCRC	Fred Hutchinson Cancer Research Center
FHIR	Fast Healthcare Interoperability Resources
FILII	Filipino
FLOCK	Flow Cytometry Analysis Component
FN	FormsNet
FN3	FormsNet3
Fst	Fixation Index
FWA	Federal-wide Assurance
FY	Fiscal Year
GEMM	Granulocyte, Erythrocyte, Monocyte/macrophage, Megakaryocyte
GETS	Government Emergency Telecommunications Service
GCSF	Granulocyte-Colony Stimulating Factor (also known as filgrastim)
GDRGEN	Group (HLA)-DR Generic
GETS	Government Emergency Telecommunication Service
GFE	Gene Feature Enumeration
GIS	Geographic Information System
GL	Genotype List
GM	Granulocyte Macrophage
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GS	General Services
GTR	Genetic Testing Registry
GUI	Graphical User Interface
GVHD	Graft vs. Host Disease
GVL	Graft-Versus-Leukemia
GWAS	Genome Wide Association Studies
GWASH	Genome-Wide Association Scan for Histocompatibility Antigens
Gy	Gray-measure of dose of irradiation
HAPI	HL7 Application Programming Interface
HARPs	HLA Ambiguity Resolution Primers
HAWI	Hawaiian or other Pacific Islander Unspecified
HAZMAT	Hazardous Material
HBCU	Historical Black Colleges and University
HC	Hematopoietic Cell
HCS®	Health Care Standard
HCT	Hematopoietic Cell Transplantation
HEPP	Hospital Emergency Preparedness Program
HHQ	Health History Questionnaire

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HHS	Health and Human Services
HIEDFS	HLA Information Exchange Data Format Standards
HIPAA	Health Insurance Portability and Accountability Act
HIS	Hispanic
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HML	Histoimmunogenetics Mark-up Language
HR	High Resolution
HRSA	Health Resources and Services Administration
HSC	Hematopoietic Stem Cell
HSCT	Hematopoietic Stem Cell Transplant
HSR	Health Services Research
HTML	HyperText Markup Language
HUGO	Human Genome Organization
HWE	Hardy-Weinberg Equilibrium
IBMDR	Italian Bone Marrow Donor Registry
IBMTR	International Bone Marrow Transplant Registry
IBWC	Immunobiology Working Committee
ICRHER	International Consortium for Research on Health Effects of Radiation
ID	Identification
IDAWG	Immunogenetics Data Analysis Working Group
IDM	Infectious Disease Markers
IDS	Integrated Data Store
IDW	Integrated Data Warehouse
Ig	Immunoglobulin
IHIW	International Histocompatibility and Immunogenetics Workshop
IHIWS	International Histocompatibility Work Shop
IHWG	International Histocompatibility Working Group
IIDB	Immunobiology Integration Database
IIMMS	International Immunomics Society
IMGT	ImMunoGeneTics
IMStrategy	Information Management Strategy
ImmPort	Immunology Database and Analysis Portal
IND	Investigational New Drug
IND	Improvised Nuclear Device
IPD	Immuno Polymorphism Database
IPR	Immunobiology Project Results
IRB	Institutional Review Board
IS	Information Services
ISO	International Organization for Standardization
IT	Information Technology

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JAPI	Japanese
JCHO	Joint Commission of Healthcare Organizations
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
JMML	Juvenile Myelomonocytic Leukemia
KIR	Killer Immunoglobulin-like Receptor
KORI	Korean
KT	Kiloton
LD	Linkage Disequilibrium
LEL	Low Expression Alleles
LOINC	Logical Observation Identifiers Names and Codes
LSSG	Life Sciences Strategy Group
LTA	Lymphotoxin Alpha
M	Million
MALDI-TOF	Matrix-Assisted Laser Desorption/Ionization – Time Of Flight
MBS	Masters of Biological Science
MCW	Medical College of Wisconsin
MD	Medical Doctor
MDACC	MD Anderson Cancer Center
MDHT	Model Driven Health Tools
MDS	Myelodysplastic Syndrome
MENAF	MidEast/North Coast of Africa
mHAg	Minor Histocompatibility Antigen
MHC	Major Histocompatibility Complex
MICA	MHC Class I-Like Molecule, Chain A
MICB	MHC Class I-Like Molecule, Chain B
MiHAs	Minor Histocompatibility Antigens
MIRING	Minimal Information for Reporting Immunogenomic NGS Genotyping
MKE	Milwaukee
MLC	Mixed Lymphocyte Culture
MLR	Mixed loss Ratio
MOU	Memorandum of Understanding
MRD	Minimal Residual Disease
MSD	Matched Sibling Donor
MSKCC	Memorial Sloan-Kettering Cancer Center
MSP	Minneapolis
MSWHIS	Mexican or Chicano
MUD	Matched Unrelated Donor
NAC	Nuclear Accident Committee
NACCHO	National Association of County and City Health Officials
NAM	Native American
NAMER	North American

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NARR	National Alliance for Radiation Readiness
NCBI	National Center for Biotechnology Information
NCBM	National Conference of Black Mayors
NCHI	Chinese
NCI	National Cancer Institute
NDMS	National Disaster Medical System
NECEP	New England Center for Emergency Preparedness
NEMO	N-locus Expectation-Maximization using Oligonucleotide typing data
NGS	Next Generation Sequencing
NHLBI	National Heart Lung and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIMA	Non-inherited maternal antigen
NIMS	National Incident Management System
NK	Natural Killer
NL	Netherlands
NLE	National Level Exercise
NLM	National Library of Medicine
NMDP®	National Marrow Donor Program
NNSA	National Nuclear Security Administration
NRP	National Response Plan
NST	Non-myeloablative Allogeneic Stem Cell Transplantation
NYC	New York City
OB	Obstetrician
OB/GYN	Obstetrics & Gynecology
OCP	Operational Continuity Planning
OCR/ICR	Optical Character Recognition/Intelligent Character Recognition
OHRP	Office of Human Research Protections
OIT	Office of Information Technology
OMB	Office of Management and Budget
ONR	Office of Naval Research
OPA	Office of Patient Advocacy
OS	Overall Survival
P2P	Peer-to-Peer
PA	Presence/Absence
PBMC	Peripheral Blood Mononuclear Cells
PBSC	Peripheral Blood Stem Cell
PCR	Polymerase Chain Reaction
PED	Pedigree
PI	Principle Investigator
POI	Procedures of Interaction

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PP	Pseudopatient
PRO	Patient Reported Outcomes
PROMIS®	Patient-Reported Outcomes Measurement Information System
PSA	Public Service Announcement
PT	Proficiency Testing
QAMS	Quality Assurance Membership Services
QARM	Quality Assurance and Risk Management
QC	Quality control
QR	Quick Response
R	Race Pair
R&D	Research and Development
RCC	Renal Cell Carcinoma
RCI	Resource for Clinical Investigations
RCI BMT	Resource for Clinical Investigations in Blood and Marrow Transplantation
RD Safe	Related Donor Safety
REAC/TS	Radiation Emergency Assistance Center/Training Site
RED	Radiological Exposure Devices
REDMO	Spanish Bone Marrow Donor Registry
REMM	Radiation Event Medical Management
REMPAN	Radiation Emergency Medical Preparedness and Assistance
REST	Representational State Transfer
RFA	Request for Application
RFP	Request for Proposal
RFQ	Request for Quotation
RG	Recruitment Group
Rh	Rhesus
RITN	Radiation Injury Treatment Network
ROC	Receiver Operating Characteristics
RSSA	R-Shiny Search Application
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SAA	Severe Aplastic Anemia
SAP	Single Amino-Acid Polymorphisms
SBT	Sequence Based Typing
SCAHIS	South/Central American Hispanic
SCAMB	Black South or Central America
SCD	Sickle Cell Disease
SCSEAI	Southeast Asian
SCT	Stem Cell Transplantation
SCTOD	Stem Cell Therapeutics Outcome Database
SEARCH	Page 10
SFVT	Sequence Feature Variant Type

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SG	Sample Group
SHF	Synthetic Haplotype Frequency
SIRE	Self Identified Race and Ethnicity
SLCBB	St. Louis Cord Blood Bank
SLW	STAR Link® Web
SMRT	Single Molecule, Real-Time
SNOMED CT	Systematized Nomenclature of Medicine – Clinical Terms
SNP	Single Nucleotide Polymorphism
SNS	Strategic National Stockpile
SO	Sequence Ontology
SOA	Service Oriented Architecture
SOP	Standard Operating Procedure
SQL	Structured Query Language
SRA	Sequence Read Archive
SRB	Survey Research Group
SRG	Survey Research Group
SSA	Search Strategy Advice
SSO	Sequence Specific Oligonucleotides
SSP	Sequence Specific Primers
SSOP	Sequence Specific Oligonucleotide Probes
SSRS	Sample Storage Research Study
STAR®	Search, Tracking and Registry
STaT	Selection, Typing and Transplant
SVM	Support Vector Machine
SWOG	Southwest Oncology Group
TBI	Total Body Irradiation
TC	Transplant Center
TCE	T-cell Epitope
TCR	T-cell Receptor
TED	Transplant Essential Data
TNC	Total Nucleated Cell
TNCC	Total Nucleated Cell Count
TRM	Transplant Related Mortality
TRS	Typing Resolution Score
TSA	Transportation Security Agency
TTY	Text Telephone
TU	Temporarily Unavailable
UCB	Umbilical Cord Blood
UCBT	Umbilical Cord Blood Transplant
UCSF	University of California – San Francisco
UI	User Interface

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UML	Unified Modeling Language
UNK	Unkown
URD	Unrelated Registry Donor
US	United States
USAID	United States Agency for International Development
USID	Unique System Identifier
USIDNet	US Immunodeficiencies Network
USB	Universal Serial Bus
UTR	Untranslated Region
VCF	Variant Call Format
VIET	Vietnamese
VP	Vice President
VPN	Virtual Private Network
WBMT	Worldwide Network for Bone Marrow Transplantation
WC	Working Committees
WebEOC®	Web-based Emergency Operations Center
WGA	Whole Genome Amplification
WH	White
WHO	World Health Organization
WMDA	World Marrow Donor Association
WU	Work-up
XML	Extensible Markup Language
ZKRD	Zentrales Knochenmarkspender – Register für die Bundesrepublik Deutschland
7 AAD	7-Aminoactinomycin D