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14. ABSTRACT

1. Contingency Prepardness: Collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

2. Rapid Identification of Matched Donors: Increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

3. Immunogenetic Studies: Increase understanding of the immunologic factors important in HSC transplantation.

4. Clinical Research in Transplantation: Create a platform that facilitates multicenter collaboration and data management.

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Research in HLA Typing, Hematopoietic Stem Cell Transplantation and Clinical Studies to Improve Outcomes

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National Marrow Donor Program® N00014-13-1-0039
HLA Typing for Bone Marrow Transplantation
FINAL REPORT
December 1, 2012 – November 30, 2014

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ACRONYM LIST

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
AFA	African American
AFB	African
AFRRI	Armed Forces Radiobiology Research Institute
AGNIS®	A Growable Network Information System
AHA	American Hospital Association
AIM	Ancestry Informative Markers
AINDI	South Asian
AISC	American Indian South or Central
ALANAM	Alaska Native or Aleut
ALDH	Aldehyde Dehydrogenase
ALDHbr	Aldehyde Dehydrogenase bright
AMIND	North American Indian
AML	Acute Myelogenous Leukemia
AMR	American Indian
ANSI	American National Standards Institute
API	Asian Pacific Islander
AQP	Ancestry Questionnaire Project
ARC GIS	ArcGIS is a brand name: GIS = Geographical Information System
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
BGI	Beijing Genome Institute
BISC	Bioinformatics Integration Support Contract
BM	Bone Marrow
BMCC	Bone Marrow Coordinating Center
BMDW	Bone Marrow Donors Worldwide
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
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
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
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
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 Hematopoeitic Transplant Coordinator
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
COG	Children's Oncology Group
CPI	Continuous Process Improvement
CREG	Cross Reactive Groups
CRF	Case Report Forms
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
DAIT	Division of Allergy, Immunology, and Transplantation
DaSH	Data Standards Hackathon
DC	Donor Center

DCAA	Defense Contract Audit Agency
DFCI	Dana-Farber Cancer Institute
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
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
EDC	Electronic Data Capture
EFI	European Federation for Immunogenetics
EHR	Electronic Health Record
ELISA	Enzyme-linked Immunosorbant Assay
ELIspot	Enzyme-linked Immunosorbent Spot
EM	Expectation Maximization
EMDIS	European Marrow Donor Information System
EMR	Electronic Medical Records
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
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
GETS	Government Emergency Telecommunications Service
GCSF	Granulocyte-Colony Stimulating Factor (also known as filgrastim)
GDRGEN	Group (HLA)-DR Generic
GETS	Government Emergency Telecommunication Service
GIS	Geographic Information System
GL	Genotype List
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GS	General Services
GTR	Genetic Testing Registry
GUI	Graphical User Interface
GVHD	Graft vs. Host Disease
GWAS	Genome Wide Association Studies
Gy	Gray-measure of dose of irradiation
HARPs	HLA Ambiguity Resolution Primers
HAWI	Hawaiian or other Pacific Islander Unspecified
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
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
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
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
IPR	Immunobiology Project Results
IRB	Institutional Review Board
IS	Information Services
ISO	International Organization for Standardization
IT	Information Technology
JAPI	Japanese
JCHO	Joint Commission of Healthcare Organizations
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
KIR	Killer Immunoglobulin-like Receptor
KORI	Korean
LD	Linkage Disequilibrium
LEL	Low Expression Alleles
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
MENAFC	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
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
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
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
P2P	Peer-to-Peer
PA	Physicians Assistant
PBMC	Peripheral Blood Mononuclear Cells
PBSC	Peripheral Blood Stem Cell
PCR	Polymerase Chain Reaction
PI	Principle Investigator
POI	Procedures of Interaction
PP	Psudopatient
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&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
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
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
SG	Sample Group
SHF	Synthetic Haplotype Frequency
SIRE	Self Identified Race and Ethnicity
SLCBB	St. Louis Cord Blood Bank
SLW	STAR Link® Web
SNP	Single Nucleotide Polymorphism
SNS	Strategic National Stockpile
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
SVM	Support Vector Machine
SWOG	Southwest Oncology Group
TBI	Total Body Irradiation
TC	Transplant Center
TCE	T-cell Epitope
TED	Transplant Essential Data
TNC	Total Nucleated Cell
TNCC	Total Nucleated Cell Count
TRM	Transplant Related Mortality
TSA	Transportation Security Agency
TTY	Text Telephone
UCB	Umbilical Cord Blood
UCBT	Umbilical Cord Blood Transplant
UCSF	University of California – San Francisco
UI	User Interface
UML	Unified Modeling Language

UNK	Unkown
URD	Unrelated Registry Donor
US	United States
USID	Unique System Identifier
USIDNet	US Immunodeficiencies Network
USB	Universal Serial Bus
VCF	Variant Cell 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	Zertrales Knochenmarkspender – Register für die Bundesrepublik Deutchland

Executive Summary

In 1986, Congress appropriated funds to begin development of the National Bone Marrow Donor Registry. Today, 28 years later, the National Marrow Donor Program (NMDP), as the contractor for the Registry, has built a racially diverse donor registry of 12 million donors, facilitated more than 65,000 hematopoietic stem cell transplants, developed comprehensive research programs to improve post-transplant outcomes, and established a network of transplant centers (TCs) capable of treating casualties resulting from military or terrorist actions, as well as patients suffering from leukemia, aplastic anemia, and other life-threatening diseases.

Contingency Preparedness Planning

This grant funded the continued development of the Radiation Injury Treatment Network® (RITN). The RITN provides comprehensive evaluation and treatment for victims of radiation exposure or other marrow toxic injuries from exposure to chemicals such as mustard agent. Many of the casualties with radiation injury will be salvageable, but require specialized supportive care to recover. Recognizing this, the NMDP, US Navy and American Society for Blood and Marrow Transplantation (ASBMT) collaboratively developed RITN, which is comprised of medical centers with expertise in the management of bone marrow failure, stem cell donor centers and umbilical cord blood banks across the US.

The goals of RITN are:

1. Develop treatment guidelines for managing hematologic toxicity among victims of radiation exposure
2. Educate health care professionals about pertinent aspects of radiation exposure management
3. Help coordinate the medical response to radiation events
4. Provide comprehensive evaluation and treatment for victims at participating centers

During the project period, RITN expanded to 55 transplant centers (up from 53), 6 donor centers and 7 cord blood banks. RITN educated and trained medical and support staff across the nation including a 3 day workshop on the mitigation and treatment of radiation damage and performed a fullscale nuclear event exercise. Finally, RITN was made a member of the National Alliance for Radiation Readiness (NARR) a public-private partnership formed to improve radiological/nuclear disaster preparedness.

The NMDP's organizational resiliency program further improved the NMDP's ability to weather devastating operational disruptions.

Rapid Identification of Matched Donors

Donor Recruitment Typing

Published research data have clearly defined the relationship between Human Leukocyte Antigen (HLA) matching and optimal patient outcomes following unrelated adult donor transplantation. Continually working to increase the genetic diversity of the Registry helps to ensure that more patients will be able to locate a suitably matched stem cell product for a transplant**.**
NMDP donor centers (including DoD) and recruitment groups added 205,607 minority race and 191,977 Caucasian donors, for a total of 397,584 U.S. donors added to the Registry. During NMDP's 2013 Fiscal Year (10/01/12-09/30/13) grant funds supported the HLA typing of 93,790 of this culturally diverse group of new donors, including 18,813 minority donors. All donors were typed for a minimum of HLA-A, B, and DRB1.

Evaluation of the Suitability of Buccal Swabs continued along 3 lines of investigation:

- Results from the 5-year Sample Storage Research Study were shared with the scientific community as an oral abstract presentation at the November 2013 ASHI Annual Meeting and awarded the Best Stem Cell Case Study.
- Frozen buccal swab sample storage studies were initiated. Storing buccal swabs in a frozen state has been shown by others to preserve DNA integrity for SBT for longer periods than controlled room temperature storage. A controlled storage study was initiated to determine the useful lifetime of frozen swabs for HLA typing by a variety of methods: SSO, high resolution SBT, and long range amplification Next Generation Sequencing (NGS).
- Studies using alternate sample collection and storage methods. Experts in biospecimen preservation were consulted to consider the range of current approaches to room temperature sample stabilization and to analyze those that could be further explored, as an alternative to freezing buccal swab samples.

Enhancements to HLA Typing Quality Control Program

The NMDP's comprehensive quality control (QC) program has supported the successful increase in the quality of HLA typing received through the contract laboratory network. In addition, this program helps to ensure the accuracy of data obtained from research studies that support abstracts and publications.

The predominant material for QC samples is derived from NMDP Research Repository samples that are transformed into B-Lymphocytic cell lines (B-LCL) and applied to cotton-tipped swabs for inclusion as blind QC samples. B-LCL swabs are expensive and time consuming to prepare. In an effort to decrease the cost of the QC program, a pilot program was initiated to supplement the blind QC program with purified genomic DNA absorbed onto cotton-tipped swabs leading to a substantial cost savings.

ABO Rh Blood Group Data

The ABO Rh Blood Group project was initiated to increase the number of registry members with ABO/Rh information to evaluate if the presence of ABO resulted in increased donor utilization. From March 3, 2014 through April 30, 2014, 527 donors were identified through NMDP's Pre-search donor contact process who, after being on the top of a patient's potential donor list, were contacted to confirm donor interest and availability. These donors were asked if they had documentation of their ABO/Rh data. If available, it was then added to the donor's data on the registry. These donors were compared against an additional 931 who did not have this information. Donors with ABO/Rh data were requested for confirmatory typing three times more in the 1st 60 days than those donors without ABO/Rh information.

Ancestry Questionnaire Pilot

A new study was initiated to pilot a geographical ancestry and race/ethnicity questionnaire. The first round of analysis was completed, showing that the pilot questionnaire demonstrated an enhanced capability to capture race and ethnicity information on multiple race and Hispanic donors that correlate with genetically inferred information via ancestry informative markers and HLA. It was also determined that there is a significant difference between subjects' initial self-identified race and ethnicity response and those obtained from the test questionnaires.

HLA-DPB1 T Cell Epitope (TCE) Matching Study

Recent research has demonstrated potential benefit for matching at the DPB1 TCE for patients given the luxury of multiple donors to select. New patient preliminary searches entered into the NMDP with DPB1 typing were evaluated for eligibility criteria. Searches meeting the criteria were evaluated for existing DPB1 TCE donor matches or if no existing matches, HLA typing was performed to identify a match (max 10 donors per patient). During this period 183 searches were enrolled and 280 donors were HLA typed. On initial donor search results, patients carrying any DPB1 TCE group 1 allele found a match 18% of the time, 34% for group 2 and 63% for group 3. Typing donors significantly improved the identification of a DPB1 permissive mismatched donor for all three groups to 55% for TCE group 1, 71% group 2 and 97% for group 3. The results were submitted to the 2015 ASBMT/CIBMTR Tandem meeting and accepted as a poster presentation.

Rapid identification of potential donors for newly diagnosed AML patients

The Southwest Oncology Group (SWOG) has identified the time from diagnosis of 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. 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 study includes a transplant arm for patients diagnosed with high risk cytogenetics following the initiation of induction therapy. NMDP/CIBMTR is supporting the project using grant funds to provide study-specific sample collection kits for all enrolled patients, processing samples, HLA typing patients that are 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

approach developed for this project will be applicable to facilitating rapid donor searches in support of RITN in the course on an incident.
During the project period:

- 220 patients enrolled in the study
- 223 sample collection kits distributed to patients
- 198 kits were collected and returned to the repository
- 55 patients were considered high-risk or unknown risk
- 54 patients have been HLA typed
- 53 patients had a preliminary search completed

Immunogenetic Research

Donor-Recipient Pair Project
The high resolution HLA typing of paired donor and recipient samples continued to provide substantive data to increase the understanding of the impact of HLA matching on patient outcome. The high-resolution HLA data generated through the project are routinely incorporated into all outcomes analyses performed by the Center for International Blood and Marrow Transplant Research (CIBMTR) to provide the best HLA typing and matching information possible. The project has developed the largest, fully validated pool of unrelated stem cell transplant donor-recipient HLA data in the world and is an unparalleled resource for transplant research. The data generated through the project have had a major impact on the evolution of the NMDP HLA matching requirements. The following typing was completed during the grant period:

- Typing was completed on 4260 unrelated donor/recipient transplant pairs.
- Typing was completed on 662 single cord blood transplants and 503 double cord blood transplants.
- To date over 18,000 pairs have been high resolution typed and over 10,000 samples have been typed for presence/absence of 14 KIR loci (2DL1-5, 2DS1-5, 3DL1-3 and 3DS1).

Antigen Binding Domain (ABD) Alloreactivity Study
Current HLA matching guidelines for unrelated Hematopoietic Cell Transplantation (HCT) recommend avoidance of mismatches only within the ABD, i.e. exons 2 and 3 for HLA class I and exon 2 for HLA class II. This recommendation is based on the hypothesis that amino acid differences outside the antigen recognition site are not immunogenic. Initial investigations of class I non-ABD mismatches of interest (A*02:01/02:09, B*44:02/44:27 and C*07:01/07:06) were performed. Queries of the Be The Match Registry identified 140 donors for high resolution typing. The retyping did not identify any instances where the isolated class I mismatch was found on identical extended haplotypes. These results of the Class I analysis was summarized and submitted to the 2013 ASHI meeting where

it was accepted for poster presentation. The results of the previous Class II DRB1*14:01:01/14:54 analysis was also submitted to the 2013 ASHI meeting and was selected for an oral presentation.

Genetic Ancestry Outcomes Study

A study protocol was approved by the CIBMTR Immunobiology Working Committee to study the effect of matched genetic ancestry of donors and patients on transplant outcomes. A pilot group of 376 samples were genotyped using an AIMs panel, including custom assay design, oligo acquisition, assay validation. Multivariate analysis on seven outcomes suggests there are trends worth investigating further. However, most p-values were not significant as the number of donor/recipient pairs in the discovery pilot was small. A power analysis was conducted for a second larger phase of the study that is currently being planned where we will perform SNP typing on a cohort of 1000 transplantation pairs.

Clinical Research in Transplantation

Resource for Clinical Investigations in Blood and Marrow Transplantation (RCI BMT)
The RCI BMT continued to develop and mature elements of its infrastructure. The RCI BMT also made progress on a number of studies. The goal of this program is to provide an avenue for investigators to obtain statistical, study and data management support for prospective trials focusing on addressing various transplant issues. The following key elements were accomplished:

- The Clinical Trials Advisory Committee (CTAC) mission is to provide scientific review and recommendations on clinical trial proposals submitted to the RCI BMT for potential collaboration. The CTAC met a total of three times during this period. Twice in person (Tandem 2013 and 2014) and one conference call meeting during July 2014. A total of two study proposals were reviewed. One was not recommended to proceed, the second was scored favorably however the CTAC was concerned about drug compliance by the subjects and asked for additional information from the proposer regarding mechanism to reduce non-compliance.

- Completed a phase II study to establish the one year overall survival after myeloablative double unit UCBT in a multi-institution setting in patients with high-risk hematopoietic malignancy (DCB). A final dataset was completed and a manuscript submitted and accepted for publication in the British Journal of Hematology.

- Completed the Lenalidomide after allogeneic HCT for Myeloma trial. A dataset was finalized and manuscript submitted and accepted for publication to the Biology of Blood and Marrow Transplantation.

- The Long-term Donor Follow-up protocol continued to accrue. Enrollment reached just over 16,000 donors of which 6614 were enrolled prospectively and 9618 from donors who donated prior to the study being activated.

- RCI BMT staff continued to work with CIT staff to make a recommendation to CIBMTR leadership regarding building or purchasing a) comprehensive system for management of activities and studies within the SRG and b) clinical trial management system (CTMS) to coordinate operational and administrative activities within RCI BMT. .

Cord Blood Research Activity

Defining Biomarkers Associated with Cord Blood Engraftment

Duke and MD Anderson Cancer Center laboratory staff completed work on validating the assay methodologies but were unable to ensure consistent results generated at both testing sites. Initial and final statistical analysis of the validation testing results showed poor inter-laboratory reliability for all assays performed. Therefore, testing using a third laboratory was developed with St. Louis Cord Blood Bank to determine whether the poor reliability is due to center-specific or assay related issues. The study group halted the study based on the poor reliability of results and a lack of continuing interest in developing the assay by additional laboratories.

Impact of Non-inherited Maternal Antigen Mismatching on Cord Blood Transplantation

In the NMDP/Eurocord NIMA match case study it was shown that NIMA matches (NIMA+) are associated with more common HLA types and therefore more common haplotypes. More common haplotypes may lead to better allele level matching and matching at HLA-C. Work was initiated and continued on a NIMA assessment of high resolution (HR) match grades at HLA-A, B, C, and DRB1 between transplant recipients and the cord blood unit to determine whether the NIMA phenomena may be a consequence of better allele level matching in the NIMA+ group . In this small population NIMA+ 5/6 had a better high resolution level HLA matching. It remains to be seen whether the skewed HR matching is a driver of the previously observed NIMA effect. This study was presented at the 2014 ASHI National Meeting

Impact of Cord Blood Release Testing on Engraftment

A study was initiated to determine the impact of colony forming unit (CFU) testing at the time of cord blood release on transplantation outcome. Preliminary results presented at the International Cord Blood Symposium in June 2014 showed no correlation between post thaw CFU dose and neutrophil engraftment. There was a suggestion that low CFU doses were associated with delayed engraftment by day 28, but the effect disappeared by days 45 and 60 post transplant.

CIBMTR Information Technology (CIT) Activity

The CIBMTR Information Technology team manages CIBMTR data and information, implements commercial software products, develops custom software and provides technical support. Additional accomplishments were made in delivering new functionality, improving data quality, data capture and data reporting through the CIBMTR IT suite of applications.

FormsNet

The FormsNet application suite is CIBMTR's web-based application for data collection, storage, and retrieval for HCT and cellular therapy research. Key enhancements made during the project period include:

- **Auditing support**. Enhancements were made to the applications for auditing of FormsNet data against source documents at recipient and donor centers.
    - A release occurred to improve users' efficiency of the existing Audit capabilities, increasing productivity.
- **Monitoring support**. The Monitoring application was enhanced to increase productivity and create the infrastructure required to Monitor TREO Centers in support of the 11-Treo Study.
- **Research support**. Simplified selection logic for the 11-Treo research study, and added new Treo study forms.
- **Additional enhancements.** A number of enhancements were implemented as part of the above initiatives, plus additional data capture support and management reports. The enhancement to management reports included support for management oversight and clinical trials.
    - **Performance Enhancement**- a release for the Recipient functionality was implemented in August, 2013 to improve overall application performance, printing, provided key bug fixes, and support for additional internet browsers. The release was well-received by the application users.
- **Customer experience**: In 2013, 22 site visits were completed across the country. Lessons learned from these site visits as well as from the 2013 Tandem Data Manager's meeting, and a 2013 FormsNet 3 user survey were applied in the August Performance enhancement release, and served as input into remaining releases targeted for 2013.

Immunobiology Research Program

During the grant period, funds supported significant outreach efforts by the IBWC leadership to increase exposure for the IBWC to basic scientists. The IBWC leadership participated in several scientific meetings including: American Society of Hematology, BMT Tandem, European Group for Blood and Marrow Transplant and International Cord Blood Symposium meetings. Support permitted the committee to maintain a strong performance record with 14 publications (submitted or accepted) and collaboration on 3 grant proposals submitted to NIH completed in calendar year 2013. In addition, 7 new proposals were accepted by the IBWC during the BMT Tandem meetings in February 2014.

END – EXECUTIVE SUMMARY

II.A. Contingency Preparedness:

Coordination of the care of casualties who will require hematopoietic support will be essential in a contingency situation.

Aim A.1.1: Contingency Response Network

The Radiation Injury Treatment Network® (RITN) and its efforts were the focus of this Aim. The Radiation Injury Treatment Network® provides comprehensive evaluation and treatment for victims of radiation exposure or other marrow toxic injuries.

Many of the casualties with radiation injury will be salvageable but require outpatient and/or inpatient care. Recognizing this, the US National Marrow Donor Program (NMDP), US Navy and American Society for Blood and Marrow Transplantation (ASBMT) collaboratively developed RITN, which comprises of medical centers with expertise in the management of bone marrow failure, stem cell donor centers and umbilical cord blood banks across the US.

The goals of RITN are:

1. to develop treatment guidelines for managing hematologic toxicity among victims of radiation exposure,
2. to educate health care professionals about pertinent aspects of radiation exposure management,
3. to help coordinate the medical response to radiation events, and
4. to provide comprehensive evaluation and treatment for victims at participating centers.

During 2013 the RITN grew to include 68 centers comprised of:

- 55 transplant centers
- 6 donor centers
- 7 cord blood banks

Three hospitals joined RITN during 2013, these included:

1. Boston Children's (MA)
2. All Children's (FL)
3. Thomas Jefferson (PA)

One hospital left RITN during 2013:

4. Vanderbilt University (TN)

RITN centers are well distributed across the nation as shown in Figure 1.

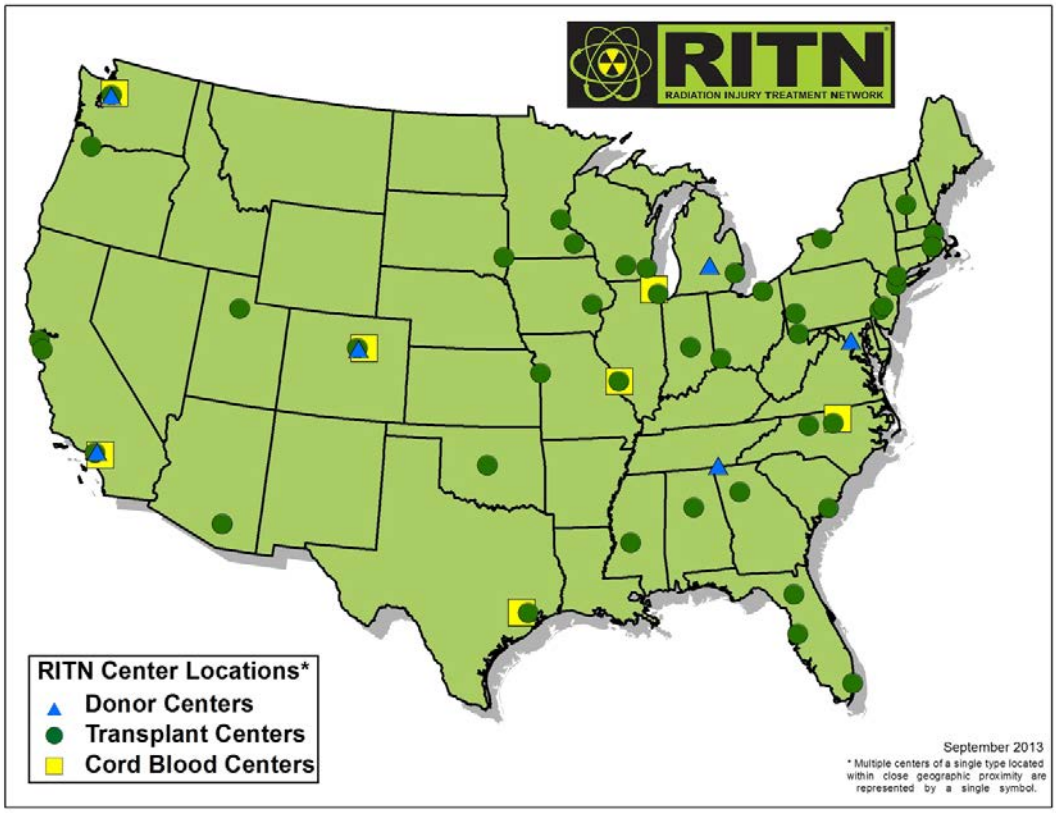


Figure 1. RITN Center Locations in the United States

The RITN is managed by the RITN Executive Committee which develops or reviews all RITN materials from the training courses to the treatment guidelines. As part of the Executive Committee the RITN Control Cell interfaces with the network of medical professionals that RITN is comprised of. Supporting the Executive Committee is a Steering Committee consisting of RITN center staff, federal advisors and partners.

The Executive Committee meets every other month (typically) through a teleconference call and the Steering Committee meets once a year in person at a meeting held during the annual ASBMT/CIBMTR BMT Tandem Meetings. Since many members of RITN already regularly attend this annual conference there is a cost savings to hold the Steering Committee meeting at the conference as well as broadcasting the strong relationship between the RITN and ASBMT. During the period of performance the Steering Committee met at the 2013 BMT Tandem Meeting in Salt Lake City, Utah in February 2013.

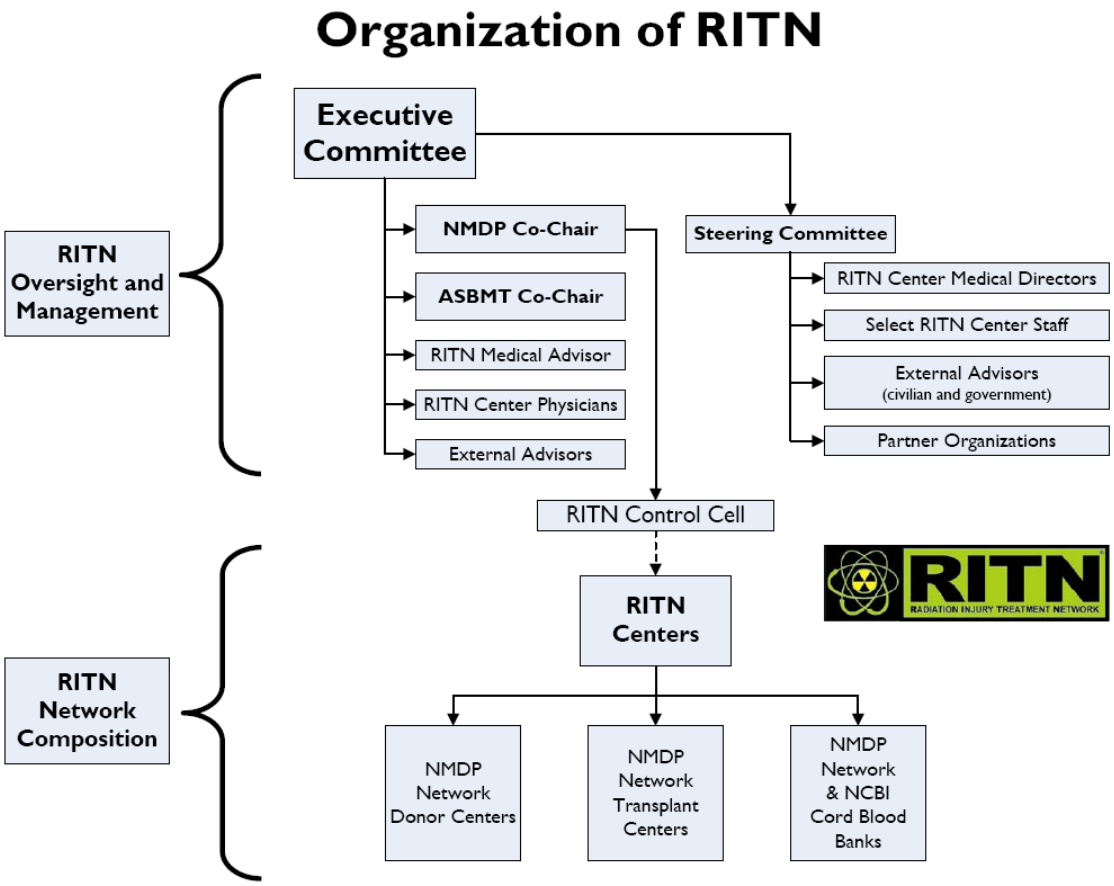


Figure 2. Organization of RITN

The RITN Executive Committee is co-chaired by a representative from the NMDP and from the ASBMT (current or past officer), and assisted by a Medical Advisor, other physicians and technical advisors that support the activities of this committee:

- Committee Chairs:
  - Co-Chair: Dennis Confer, MD
  - Co-Chair: Nelson Chao, MD (ASBMT past President)
- RITN Medical Advisor:
  - David Weinstock, MD
- Committee Members:
  - Transplant physician: Daniel Weisdorf, MD (ASBMT past President)
  - Transplant physician: John Chute, MD
  - Transplant physician: Willis Navarro, MD
  - Emergency medicine physician: David Markenson, MD

- ASBMT Advanced Practitioner representative: Julie Wilhauk, ARNP, AOCNP
- ASBMT representative: Robert Krawisz, MBA
- RITN Program Manager: Cullen Case Jr., CEM, CHEP

Some of the outcomes of Executive Committee conference calls held during this period of performance included:

- Planning for a successful RITN Conference with the NIAID-CMCRs
- Creation of six web based RITN training courses
- Implementation of web based table top exercises for RITN centers annual exercise
- Accomplishment of two resident and one mobile REAC/TS course

Much of the work done in support of the activity reviewed by the RITN Executive Committee can be attributed to the efforts of the RITN Medical Advisor, his work included:

- Increased the knowledgebase related to radiation/nuclear disaster preparedness through:
  - Authoring a chapter on Radiation Emergency Response in the: Koenig & Schultz's Disaster Medicine: Comprehensive Principles & Practice textbook
  - Updating the RITN Grand Rounds Presentation to include guidance to centers that need to obtain HLA typing
- Improved readiness of hospitals through the development of clinically realistic exercises:
  - 2013 RITN Table-Top Exercise
  - Dana-Faber/Brigham and Women's radiation emergency drill for 2014
- Increased visibility and awareness of RITN through speaking engagements:
  - Institutes of Medicine Improvised Nuclear Device Workshop in Washington, DC in January 2013
  - A clinical guidance workshop in May 2013 organized by the Office of Policy and Planning, Division of Medical Countermeasure Strategy and Requirements, Department of Health and Human Services
  - 2013 CMCR/RITN workshop entitled, "Mitigation and treatment of radiation damage" scheduled for 7/31-8/2/13
  - 2013 National Association of County and City Health Officials meeting in Dallas, TX
  - Keystone Center and CDC to draft guidelines for medical management of radiation casualties
  - FDA meeting to evaluate the preclinical data supporting approval of G-CSF for acute radiation syndrome

  - Organizing Committee for the CMCR/RITN Conference in Baltimore, MD in August 2013

- Worked with the Hospital Preparedness Program to increase awareness of RITN within the organization
- Led the RITN effort to secure a contract with BARDA to establish a user managed inventory system at RITN centers; to accomplish the proposal he organized the formation of a network of 18 RITN centers to participate in a G-CSF user managed inventory program, with a proposal to be submitted to BARDA for funding in 2013
- REMM:
  - Provided feedback for the new Acute Radiation Syndrome Interactive Management Tool for the Radiation Emergency Medical Management website supported by the National Library of Medicine
- Provided guidance to commercial entities (Cellerant, DxTerity, Sanofi) with interest in developing radiation countermeasures

Monthly all RITN center staff and partners are invited to a conference call where updates are provided on current projects, RITN center staff are afforded an opportunity to talk about implementation issues with other RITN centers. As part of this monthly conference call "Rad in the News" is reviewed, it is a summary of radiological related current events from open source media reports. In addition to these monthly meetings each December we hold a RITN Year in Review Webinar, this presentation reviews the accomplishments during the year and planned activity in the upcoming year.

RITN Annual Tasks

RITN centers are tasked each year to complete a set of tasks in exchange for a small grant. Centers had to update their standard operating procedures, conduct a tabletop exercise and conduct training of staff.

TASK 1 – Emergency Communications
- Center must update contact information for key staff.
- Participate in the monthly RITN conference call.
- Perform communications tests as directed by RITN.

TASK 2 - Standard Operating Procedure (SOP) update
- All centers must review for accuracy (update as needed) and submit a copy of their SOPs for review, even if there are no changes.

TASK 3 - Participate in RITN directed tabletop exercise
- All materials related to this exercise will be provided by RITN.
- Responses to confirm completion are submitted to RITN for review.

TASK 4 – Education of staff or response community

- **Option A - Present the RITN Overview presentation** to the Local Emergency Planning Commission, emergency preparedness group, federal emergency response planning group, county or city emergency managers, a local blood bank or similar appropriate entity. If this is selected it requires:
- **Option B – Staff training of NMDP Basic Radiation Training**: 20 staff members must successfully complete the Basic Radiation Training course. --- Staff must not have taken the BRT previously---
- **Option C - RITN Grand Rounds presentation to medical staff** using the RITN presentation titled ''Medical Response to Radiation Exposure: the Role of Hematologists'" to expand the medical knowledge of staff.
- **Option D - Physician attendance of Advanced Radiation Medical Training at the Radiation Emergency Assistance Center and Training Site (REAC/TS)**
- **Option E – Site assessment;** centers are evaluated using standard RITN checklists to assess their level of preparedness for response to a mass casualty incident resulting in marrow toxic injuries by an RITN Control Cell evaluator.

TASK 5 – IRB Approved Marrow Toxic Injury Research Consent Form

- All RITN centers must have the CIBMTR Marrow Toxic Injury Research Consent form approved by their institutions IRB or show it has been submitted for approval by their IRB

RITN Exercises:

Each year one of the tasks is to conduct a tabletop exercise with hospital staff and local/regional public health preparedness officials. RITN provides all the basic materials necessary to conduct the exercise and each hospital submits responses to standardized questions that are made available to the entire network. This allows the RITN network centers to compare their approaches to their peer organizations. Periodically, RITN Control Cell staff will observe a RITN hospital's tabletop or other exercise.

The results of each year's tabletop exercise, including each centers response to all of the questions, are posted (in a non-attributable format) on the RITN website: www.RITN.net/exercises/

In addition to the tabletop exercise, this grant funded two Web based Tabletop Exercises. Facilitators conducted the exercise via a webinar for 17 hospitals to collaborate on how they would respond in realtime. This afforded each hospital the opportunity to gleam new ways of responding as well as to highlight their best practices to the group.

Since the first RITN tabletop exercise conducted in 2006, 376 RITN exercises have been held across the country (Figure 3). These include fullscale exercises as well as the tabletop exercises. The annual tabletop exercise scenarios are detailed in table 1.

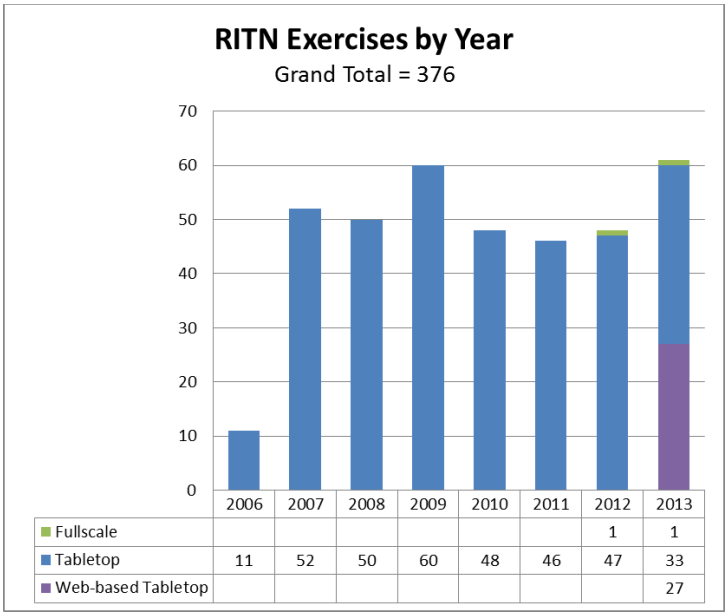


Figure 3. RITN exercises from 2006-2013.

Table 1. Annual RITN Tabletop Exercise Scenarios

Year	Situation	Max Victims
2006	Radioactive sources discovered 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 rads 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 rads 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	20 w/ limited bed availability provided
2013	Radiological Exposure Devices on mass transit at eight metropolitan cities	4,500 across the nation; 300 casualties w/ 80 that have cutaneous ARS and accompanied by 140 family members

Annual Task Completion

During this grant period 92% of the RITN centers completed all of their tasks (Figure 4), the same as the previous grant period

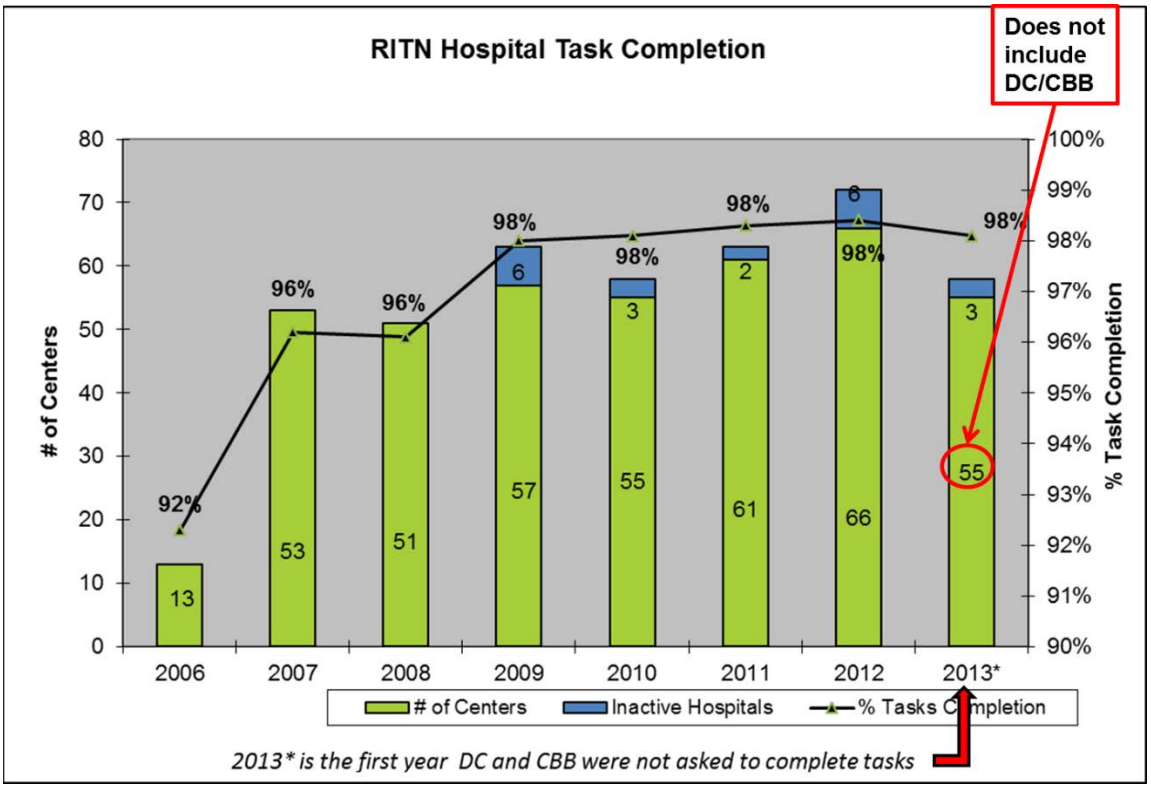


Figure 4. RITN Task Completion by Year

RITN Partnerships

RITN would not be able to successfully respond to a mass casualty incident without coordinating with partner organizations. The NMDP has carefully developed and maintained relationships with key emergency response organizations.

RITN has two types of relationships; formal relationships are documented through a Memorandum of Understanding (MOU) and informal relationships through periodic collaboration. One notable new formal relationship addition during this grant period is the inclusion of the RITN as a member of the National Alliance for Radiation Readiness (NARR).

According to the NARR website (http://www.radiationready.org): "the NARR is a coalition of public health, healthcare, and emergency management organizations. These organizations represent practitioners in the field of radiation readiness including state and local public health

practitioners; elected officials at the state and local level; and first responder and first receiver groups. Representatives of federal agencies participate as liaison members.

The NARR serves as the collective "voice of health" in radiological preparedness by:

- Participating in national dialogues on radiological emergency issues
- Providing thoughtful feedback on documents, policies, and guidelines
- Convening partners to raise awareness of and resolve radiological emergency issues"

Members of the NARR include:

- Association of State and Territorial Health Officials (ASTHO)
- American Association of Poison Control Centers (AAPCC)
- American Hospital Association (AHA)
- American Medical Association (AMA)
- American Public Health Association (APHA)
- Association of Public Health Laboratories (APHL)
- Association of Schools of Public Health (ASPH)
- Conference of Radiation Control Program Directors (CRCPD)
- Council of State and Territorial Epidemiologists (CSTE)
- Health Physics Society (HPS)
- International Association of Emergency Managers (IAEM)
- National Association of County and City Health Officials (NACCHO)
- National Association of State EMS Officials (NASEMSO)
- National Disaster Life Support Foundation (NDSLF)
- National Emergency Management Association (NEMA)
- National Public Health Information Coalition (NPHIC)
- Radiation Injury Treatment Network (RITN)
- Society for Disaster Medicine and Public Health (SDMPH)
- Centers for Disease Control and Prevention (CDC)
- Office of the Assistant Secretary for Preparedness and Response/US Department of Health and Human Services (ASPR/HHS)
- US Department of Homeland Security (DHS)
- Environmental Protection Agency (EPA)
- US Department of Energy (DOE)
- US Department of Agriculture (USDA)
- Food and Drug Administration (FDA)
- US Nuclear Regulatory Commission (NRC)
- Federal Emergency Management Agency (FEMA)

RITN has established formal partnerships with:

- Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services (ASPR-DHHS)

- American Society for Blood and Marrow Transplantation (ASBMT)
- National Alliance for Radiation Readiness (NARR)
- American Association of Blood Banks (AABB), through the AABB Inter-organizational Task Force for Disasters and Acts of Terrorism
- New England Center for Emergency Preparedness (NECEP)

RITN has developed informal relationships with the following:

- U.S. Department of Veterans Affairs (VA)
- Radiation Countermeasures Centers of Research Excellence (RadCCORE) at Duke University
- The National Institutes of Health, The National Institute of Allergy and Infectious Diseases, Division of Allergy, Immunology and Transplantation (NIH-NAIAD-DAIT)
- Radiation Emergency Medical Management web portal (NIH-NLM-REMM)
- National Cancer Institute's (NCI)
- Biomedical Advanced Research and Development Authority (BARDA)
- European Group for Blood and Marrow Transplantation (EBMT) - Nuclear Accident Committee
- The Radiation Emergency Medical Preparedness and Assistance Network of the World Health Organization (WHO-REMPAN)
- Radiation Emergency Assistance Center and Training Site (REAC/TS)
- American Hospital Association (AHA)
- American Medical Association (AMA)
- National Association of City and County Health Officials (NACCHO)
- Association of State and Territorial Health Officials (ASTHO)

Education and Awareness Training about RITN

To increase the visibility of RITN and make new connections with additional organizations and agencies, overview presentations were given to various professional groups and government agencies. The chart below (Figure 5) summarizes the number of these presentations given as well as the size of the audience:

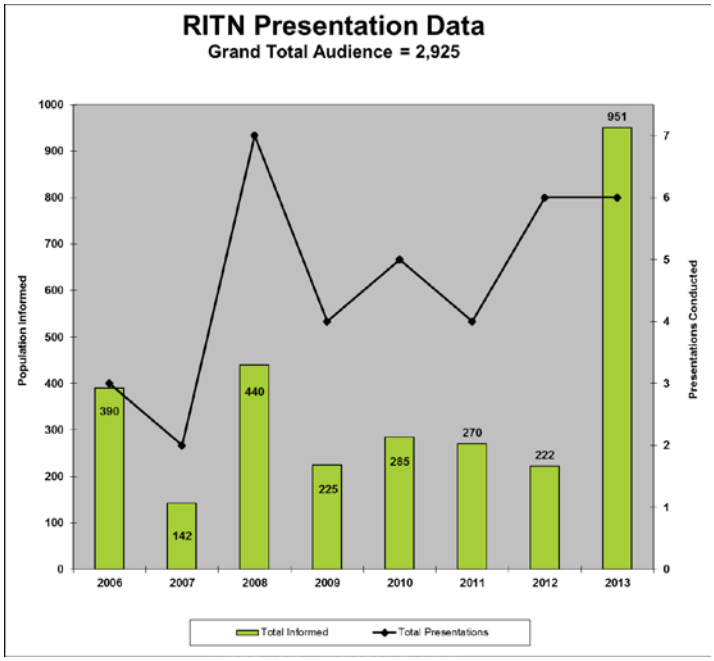


Figure 5. RITN Presentations and audience

Biennial RITN Conference

The Radiation Injury Treatment Network (RITN) and the Centers for Medical Countermeasures against Radiation (CMCR) convened a three-day workshop on the Mitigation and Treatment of Radiation Damage from July 31st to August 2nd, 2013. The workshop covered topics such as patient assessment, biomarkers and biodosimetry, suitability of animal models, small molecules, growth factors, and cells as mitigators, as well as their mechanisms of action in radiation-damaged tissues, late effects of acute and prolonged exposure, survivorship issues, and future developments. The workshop flyer and attendee meeting packet are available on the RITN website (http://www.ritn.net/meetings/) . The workshop was held at the Tremont Plaza Hotel in Baltimore, MD.

The purpose of the conference was to provide an open forum for invited speakers and discussants to assess progress on issues related to radiation injury, mitigation and treatment. Various radiation scenarios were presented along with novel approaches at multiple stages of development. This was justified due to the tremendous environmental, social, and medical cost of a large-scale release of nuclear or radiological material as a result of deliberate attack or natural disaster has led to several programs aimed at improving national and local preparedness.

175 people attended the conference, of these 95 attendees completed the evaluation, 27 physicians requested CME credits and 53 attendees requested contact hours, nursing credits or med tech credits. The conference evaluation results were very favorable (ratings were on a scale of 1 to 5, with 5 being best):

- Overall Rating of the Workshop: 4.55

- The information presented applies to my work: 4.45
- The instructional materials helped me to understand the content: 4.10
- The program was well organized: 4.55
- I learned new knowledge & skills from this session: 4.45

The Conference agenda included:

- Keynote Address: Preparedness and Response to Radiation
- Possible Radiological Incident Scenarios
- Casualty Triage and Distribution
- The RITN Response to Radiological Scenarios
- Emergency Management from the CMCR perspective
- Workshop 1: Biodosimetry and Biomarkers - assessing the need
- Animal Models of Radiation Damage and Confounders
- The Challenge underlying Radiation Mitigation
- Workshop 2: Small Molecule Radiation Mitigators
- Workshop 3: Growth Factors and Cytokines as Mitigators
- Workshop 4: Cell Replacement Approaches for Radiation Mitigation
- Workshop 5: Mitigation and Treatment of Late Effects
- Identification of the Grand Challenges in Radiation Mitigation and Treatment

Education of RITN Medical and Support Staff:

Education of physicians, medical and support staff is accomplished through multiple avenues. There are instructor lead didactic sessions and self guided web based training (http://www.ritn.net/training/). Instructor led training includes the RITN Acute Radiation Syndrome Medical Grandrounds, and the Advanced Medical Training on Radiation Emergency Medicine course. The Grandrounds training is a standardized class that RITN provides to hospitals for their implementation, each year RITN centers have tasks that they must accomplish and this is one of the options, as a result of this thousands of hospital staff have attended this training course since its original creation.

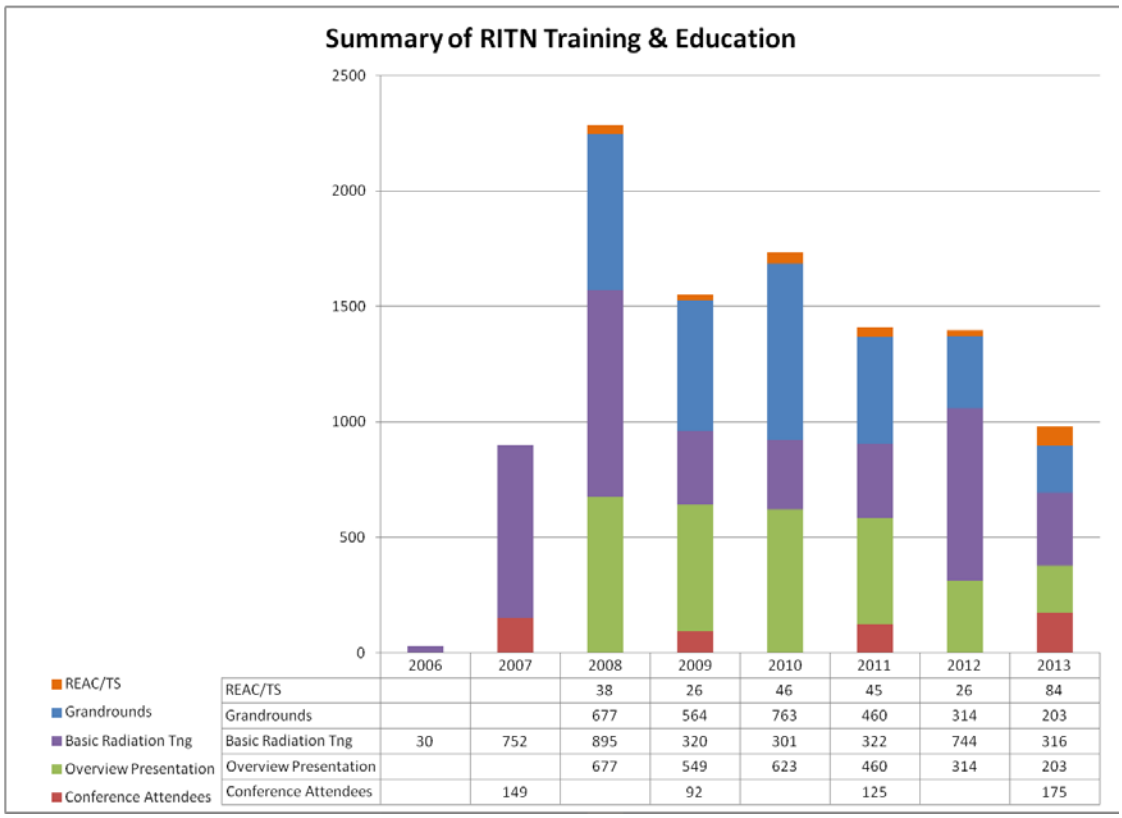
The second instructor lead course is the Advanced Medical Training on Radiation Emergency Medicine course. This is a course that is conducted by staff from the Radiation Emergency Assistance Center and Training Site (REAC/TS) in Oak Ridge, TN. During this period of performance we expanded the course offerings to include a mobile course where the REAC/TS instructors travel to an institution to provide the training. The mobile course option significantly decreases the medical staff travel and allows for much larger class sizes. The REAC/TS classroom in TN is limited to 25 students, where as the first mobile class held at Duke University in August 2013 included over 50 students.

Advanced Medical Training on Radiation Emergency Medicine is a two day course, attendees earn 14 continuing medical education credits for attending. The course covers a comprehensive set of topics including:

- Basic Health Physics & Radiation Protection: Part I
- A History of Serious Radiological Incidents: The Real Risk
- Health Physics & Contamination Control: Part II
- Radiation Detection, Monitoring & Protection Laboratory Exercise & Quiz
- Diagnosis & Management of the Acute Radiation Syndrome
- Diagnosis & Management of Internal Contamination
- Diagnosis & Management of Acute Local Radiation Injury & Case Review
- Radiation Sources & Radiological Terrorism
- Radiation Emergency Area Protocol Demonstration
- Radiation Emergency Medical Management Drill
- Radiation Dose Estimations – Problem Solving Session

This grant supported two resident courses at REAC/TS for 44 students and one mobile class for 53 students.

Figure 6 summarizes the training that RITN has provided or coordinated, since inception. Over 10,000 staff have received training through these sources since 2006.



	2006	2007	2008	2009	2010	2011	2012	2013
REAC/TS			38	26	46	45	26	84
Grandrounds			677	564	763	460	314	203
Basic Radiation Tng	30	752	895	320	301	322	744	316
Overview Presentation			677	549	623	460	314	203
Conference Attendees		149		92		125		175

Figure 6. Summary of RITN training activities and attendees from 2006-2013.

II.A. Contingency Preparedness – Hypothesis 2:

Ensure the NMDP maintains effective plans to continue critical facility and staff-related functions as a result of operations interruption events.

Aim A.2.1: Operational Continuity Planning:

The focus of this Aim is to improve organizational resiliency to severe operational disruptions through Operational Continuity Planning. In the event that the Coordinating Center is not available for an extended period of time, critical tasks will have to be conducted at an alternate location. To meet these needs the NMDP maintains a formal Operational Continuity Plan (OCP) consisting of documented procedures for guiding the organization to respond, recover, resume and restore to a predefined level of operations following disruptions. In the event that the Coordinating Center is not available for an extended period of time, critical task execution will require use of available non-contracted alternate locations.

The OCP is annually reviewed by key stakeholders to test planned response actions with current operational practices and predefined maximum tolerable periods of disruption (MTPD). MTPD is the time it takes for adverse impacts as a result of not providing services or performing activity to become unacceptable. Inputs for OCP improvement include current operational impact analyses, functional and tabletop exercises, and industry regulatory or standard changes. The OCP is adaptable and enables the organization to respond to a wide range of disruptive incidents, including those the NMDP may not have anticipated. The NMDP's formal OCP is maintained by the Manager of Operational Continuity and Emergency Preparedness.

During this period of performance the NMDP conducted two important exercises to ensure sustainability of essential donor related sample collections during operational disruptions. The two successful exercises tested the ability of the Repository staff to move KitMaker operations to a backup location in the NMDP Headquarters building in the event the Repository was not accessible. The second exercise involved implementing a Plan C where the operations are moved to the DOD Donor Center, in the event both the Repository and the NMDP Headquarters building were not available. This scenario is a likely situation if a blizzard were to hit the Twin Cities both facilities would not be available.

Additionally, a real-world implementation of Operational Continuity principles was applied when the Phoenix Phase II (IT project) was implemented. This required shutting down all operations systems for four days. The Manager of Operational Continuity and Emergency Preparedness managed the efforts of the Operations Group to prepare for the IT outage, leading teams to determine what must be done to prepare for the shutdown to include what activities could be conducted manually for a short duration and what activities could be deferred. Teams developed control reports, developed or refined manual processes for systems downtime, determined

"Operational Catchup" needs, educated staff to effectively work in the "new normal" after the implementation was complete. The project was successful and highlighted the importance of operational continuity planning across the organization.

The annual operational impact analysis was conducted by each of 21 NMDP departments to validate and update critical tasks, assigned personnel, and required applications. A low-level evaluation of throughput necessitated increasing the number of critical staff to 175. The information system applications required for the critical tasks were tiered and provided to the IT Infrastructure Team for use in IT disaster recovery planning.

To sustain communications with Network partners during a severe operational disruption, the NMDP maintains a variety of redundant channels. The NMDP has over 150 active Governmental Emergency Telecommunications Service (GETS) emergency calling cards issued to RITN centers and NMDP staff and over 60 Iridium satellite telephones assigned and distributed to external partners. Recurring tests of each of these capabilities ensured user familiarity and equipment accountability.

Site visits to NMDP operated donor centers resulted in improved preparedness for NMDP field staff. A review of the NMDP Operational Continuity Action Guide with each site manager and their staff ensured they know what to do for the major hazards applicable to their location. Processes for closing offices due to local hazards and transferring critical activity to other facilities was refined. Operated donor center site visits occurred in Santa Ana, CA and Leawood, KS.

II.B. Rapid Identification of Matched Donors – Hypothesis 1:

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

Advances in laboratory methods and supporting equipment continued to positively impact the level of quality and typing resolution for newly recruited volunteer donors. As of September 30, 2013, all newly recruited donors were being typed at a minimum of 5 loci (HLA-A, B, C, DRB1 and DQB1). Of these, 35% were being typed at 6 loci (adding HLA- DPB1), and 13% were being typed at 8 loci (adding HLA-DPA1 and DQA1). Furthermore, 87% of all donors were typed with Sequenced Based Typing (SBT), providing the highest level of resolution to date.

In order to maximize the typing resolution and ensure the optimal use of typing funds, the NMDP uses a process to allow selective typing based on donor characteristics. Samples from donors with particularly desirable demographics (male, younger age and minority) are directed to specific laboratories to ensure they are listed on the registry with the best typing possible.

Over the past 15 years, the NMDP has reduced the cost of HLA typing by over 64% while increasing typing resolution and quality (Figure 7). The vision and efforts of the Navy project officer to continually press the HLA community in this direction and to lead the advancement and development of new typing technologies has been instrumental in achieving gains in resolution and decreases in cost.

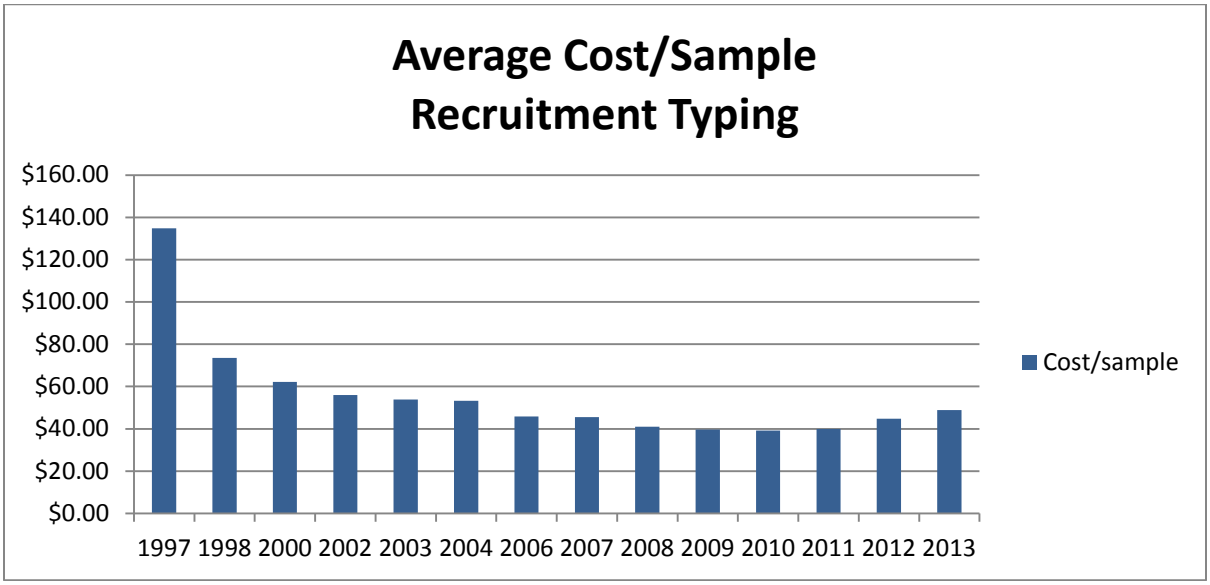


Figure 7. Cost Decreases for HLA-Recruitment Typing

Average cost per sample for HLA-A, B, DRB1 recruitment typing has decreased over time, from more than $134.00/sample to approximately $49.00/sample. While per sample costs have been relatively constant over recent years, it should be noted that the number of loci typed and the resolution of the results has continued to increase over time, thereby facilitating improvements in donor selection without increased cost.

If a patient does not find a matched donor and is in urgent need, patient-focused drives can be held and the donor registration process can be expedited, shortening the length of time to listing from about 2 months to about 1 month. This process includes time to enter demographic data, confirm financial coverage, ship and receive the samples and complete the HLA typing. Demographic data are entered within 72 hours for expedited samples, and they are shipped for HLA typing in less than 1 week. In case of a contingency event, high volumes of samples could be processed and shipped quickly using this established process.

The NMDP's exacting quality control processes have successfully increased the quality of typing received through the contract laboratory network. The method of inserting blind quality control samples into each laboratory's shipment of volunteer donor samples has provided more than 13 years of data tracking the accuracy of high volume typing. Over this time, the accuracy rates have continued to improve, as documented by decreased monthly error rates and decreased discrepancies as donors are selected for patients and retyped by other laboratories. The effectiveness of this program and the efforts of a highly qualified high-volume HLA typing

laboratory network has resulted in a combined HLA class I and class II QC accuracy rate in 2013 of greater than 99.9%.

Aim B.1.1: Increase Registry Diversity

Newly recruited donors increased diversity
During NMDP FY13, NMDP donor centers (including DoD) and recruitment groups recruited 205,607 minority race and 191,977 Caucasian donors, for a total of 397,584 U.S. donors added to the Registry. Navy funding contributed to the addition of 93,790 of this culturally diverse group of new donors, with 18,813 of these donors being minorities. All donors were typed for a minimum of HLA-A, B, and DRB1.

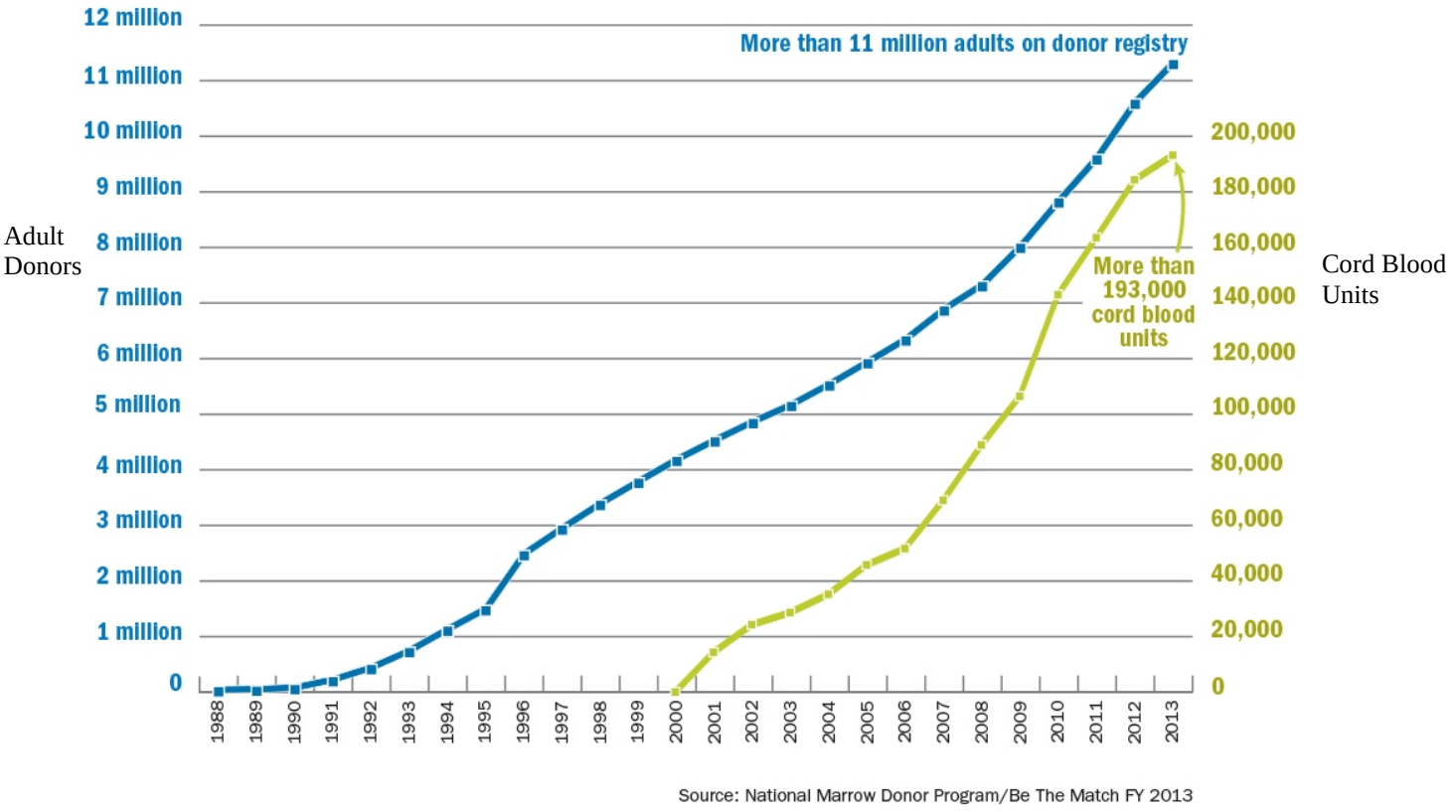


Figure 8. Be the Match Registry Growth: Adult Donors and Cord Blood Units

New Donor Queue Sorting
To maximize the utilization of the HLA recruitment typing resources, a process was developed to strategically select samples from the newly recruited donor queue and direct these samples to

specific laboratories. This process allows the NMDP to select donors, based on demographic data, and direct the testing to laboratories that provide the most complete and highest resolution HLA typing at the time of recruitment. The goal is to select the most valuable donors (young males, young females, and all minorities) and ensure they are listed on the registry with the most comprehensive typing available through the contract laboratory network.

This queue sorting process has provided a dramatic increase in the number of loci typed on the most valuable new donors joining the registry, which are male (M) and female (F) donors, 18-30 years of age. Table 2 summarizes the queue typing strategy for these most valuable donors by time period, gender and loci tested.

Table 2: Donor queue sorting strategy for high value recruits age 18-30.

Time period	% of queue	Gender	HLA Loci Typed
2011	95%	M and F	HLA-A, B, C, DRB1
2012	23%	M	HLA-A, B, C, DRB1, DQB1
	77%	M	HLA-A, B, C, DRB1, DQB1, DPB1
	83%	F	HLA-A, B, C, DRB1, DQB1
	17%	F	HLA-A, B, DRB1
2013	100%	M	HLA-A, B, C, DRB1, DQB1, DPB1
	50%	F	HLA-A, B, C, DRB1, DQB1
	50%	F	HLA-A, B, C, DRB1, DQB1, DPB1

Advancing technology improved performance and pricing
Advances in laboratory methods and supporting equipment continue to have a positive impact on lab performance and pricing.

As of September, 2013:

- 64% of new donors received HLA-A, B, C, DRB1 and DQB1 typing; 46% of new donors had these plus an additional locus tested (HLA-DPB1).
- Blind quality control testing error rate was 0.05%, exceeding the project requirement of $\leq 2.0\%$.
- On-time testing completion rate was 98.4%, meeting the project requirement of a minimum of 90% of typing results reported within 14 days of shipment of samples.
- The cost of HLA typing continued to decrease as technology improved. In FY13, the average price per sample was approximately $49.00 compared to $134.75 in 1997, which represents a decrease of over 64%. Note that in addition to decreasing average cost, there were significant increases in the number of loci typed and resolution of results over this time period.

HLA Typing Laboratory Meetings

Two NMDP staff performed a site visit to a contracted HLA typing laboratory. Operational topics were discussed including: the current scope of work, future goals for registry HLA typing, and the laboratory's future HLA testing vision. Presentations were given including an overview of the Be The Match Registry, as well as specifics of the laboratory's service agreement performance and interactions with the NMDP. Likewise, the laboratory staff gave a reciprocating presentation on the processes and workflows of their HLA typing methodologies, which included a tour of their laboratory facilities and equipment, highlighting recent changes in lab testing platforms and staffing. In the longer term, the laboratory is evaluating new and emerging technologies to decrease costs and increase resolution. These discussions are important to allow NMDP to continue to provide low cost and high quality HLA typing for patients searching the registry.

Two-Step Recruitment at Live Drive Registration

To further understanding of donor personal commitment and its effect on downstream donor availability, the NMDP investigated a new two step donor recruitment strategy. The hypothesis was that those who pro-actively take a second step will likely be more committed to being on the registry and available if called. In this pilot, a portion of live drive recruits took an additional step to activate their membership, in order to have their sample typed and to be listed on the registry. The activation step is much like that used commonly used for credit card activation, by calling in to an automated phone line, or texting in an activation confirmation, or going online to complete activation.

Some highlights of the results include:

- Activation rates vary by recruiting center and by recruiters within a center.
- The greatest frequency of activation was on the first few days after the drive. Bumps of activation occurred after reminder texts and emails.
- The distribrution of activation methods are displayed in Figure 9.
- Those members who activated via this pilot were more likely to be available when called for Confirmatory Typing requests than those who joined via the standard live drive process.

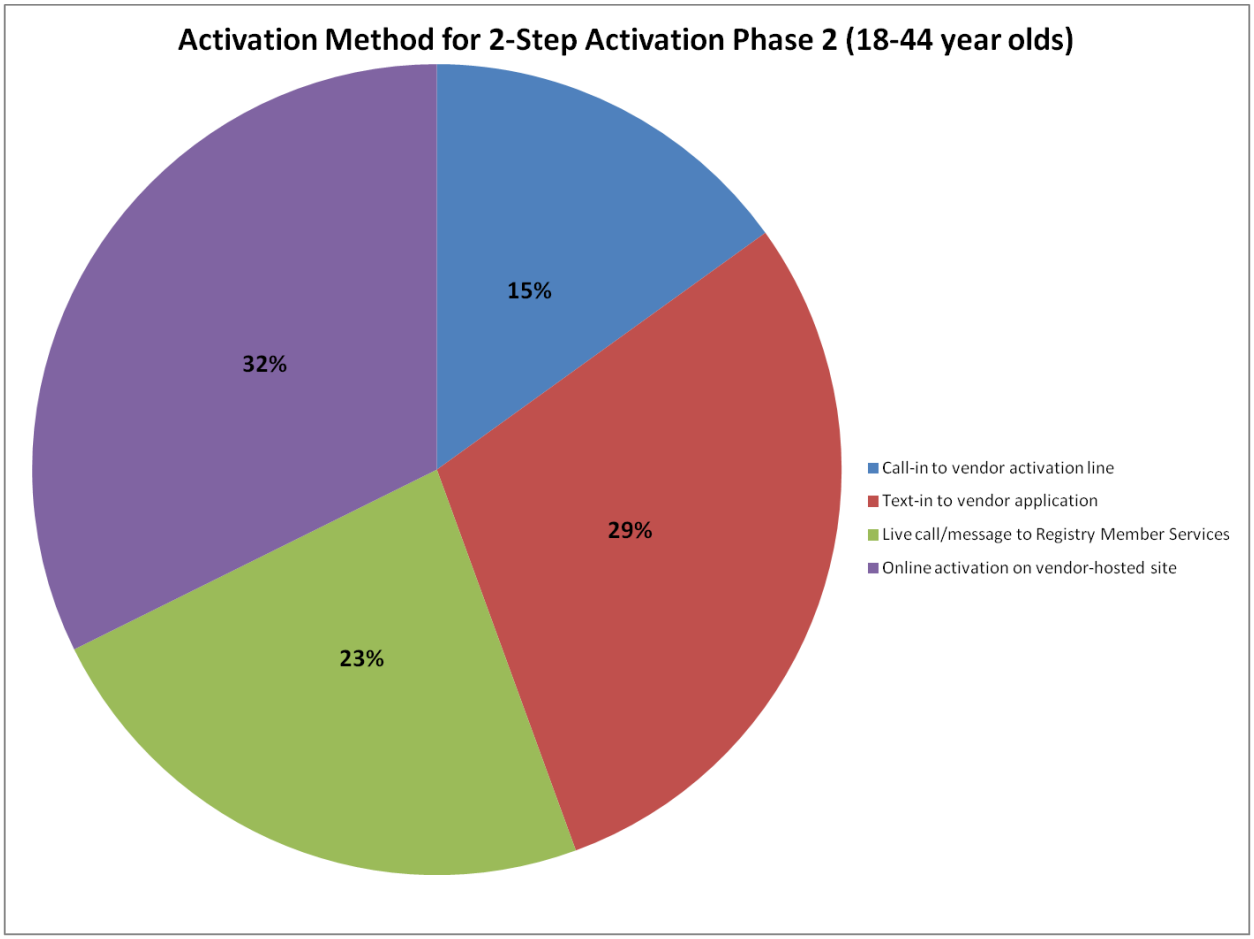


Figure 9. Distribution of 2-step activation methods used newly recruited donors in the pilot project.

Quality of HLA Typing Improved

During the grant period , the NMDP maintained and updated a list of rare alleles as a service to the American Society for Histocompatibility & Immunogenetics (ASHI). These lists were derived from HLA allele level typings of patients, adult volunteers, and cord blood units in the Be The Match Registry. In an on-going Registry data quality project, adult volunteers with reported HLA typing containing a rare allele were evaluated to determine if the results were accurate based the following rules:

1. Sample assignments showed previous corrections
2. Samples typed >four years ago and allele not subsequently observed
3. Alleles reported in a sample whose race differed from the race the allele was initially described
4. Interpreted primary data received from the laboratory not consistent with assignment
5. Rare allele consistently reported as a pair with the same second allele

6. Sample carried two rare alleles at the same locus.

A total of 1003 samples were flagged for evaluation and re-typed at intermediate or high resolution HLA-A, B, C, or DRB1. Overall, 38% of the samples were found to have a mistyping and corrected on the Registry. The results are summarized in Table 3.

Table 3: Results of HLA retyping project

	Samples Typed Using SBT		Samples Typed Using Intermediate resolution			
Locus	Confirmed	Corrected	Confirmed	Corrected	Total typed	% corrected
HLA-A	43	13	72	49	177	35.0%
HLA-B	46	0	115	85	246	34.6%
HLA-C	17	0	32	31	80	38.8%
HLA-DRB1	73	0	226	201	500	40.2%

The results of these data were presented as a poster abstract at the Americian Society of Histocompatibility and Immunogenetics (ASHI), in November 2013. Further, the data from this study provided critical information used in the Mack et al Common and Well Documented Allele manuscript.

Poster presentation at ASHI annual meeting:
Jane H. Kempenich, Elizabeth Beduhn, Gail Flickinger, Jason Dehn, John Hermanson. Alleles Problematic Through The Ages. 142-P. 39th American Society of Histocompatibility and Immunogenetics (ASHI). 2013.

Results of these re-typing projects improved the HLA typing quality of listed adult volunteers and removed erroneous typing from the registry. During this contract period, three adult volunteer whose typing had been corrected through this project were requested for additional testing on behalf of a searching patient. The re-typing project highlights the importance of technical oversight of the Registry data and the necessity to upgrade typings routinely in order to provide the most accurate HLA data for searching patients.

During this contract, efforts in re-typing projects resulted in the following accepted peer-reviewed publication:
Kempenich, J., Dehn, J., Flickinger, G. and Setterholm, M. Unrelated donor HLA re-typing effort to verify prevalence of newer alleles: HLA-A*24:23, A*30:10, DRB1*08:11, DRB1*15:03, and DRB1*15:06. Tissue Antigens. 2014 Nov;84(5):489-91. doi: 10.1111/tan.12442. Epub 2014 Sep 21.

Aim B.1.2: Evaluate HLA-DRB1 High Res Typing

No funding was requested under this Aim for the 0039 budget cycle.

Aim B.1.3: Evaluate HLA-C Typing of Donors

No funding was requested under this Aim for the 0039 budget cycle.

Aim B.1.4: Evaluate Suitability of Buccal Swabs

Sample Storage Research Study

The purpose of this 5 year research study was to evaluate, over time, the quality and quantity of the DNA derived from three stored sample types: frozen whole blood, room temperature whole blood spotted on filter paper (FP) and room temperature buccal swabs (SW). This study evaluated the ability of the testing laboratories to accurately and consistently obtain HLA typing results from each stored sample type. The data collected through this study has allowed the NMDP to determine the length of time samples are able to be stored and still be useful for HLA testing. All samples were tested annually.

- **Results:** Sequence Specific Oligonucleotide (SSO) and Sanger Sequence Based Typing (SBT) HLA results were accurate at all loci through the 4 year Time Point. At 5 years, SSO results were 100% accurate, whereas SBT results were 99.4% accurate for FP and 97.3% for SWs. One FP and 4 SWs had amplification failure, 5 SWs had one allele drop-out and 1 SW had both alleles drop out. 19 FP and SW samples required repeat testing at multiple loci to obtain accurate HLA results. Sufficient DNA for HLA testing was extracted from all samples at all time points. DNA quality from frozen whole blood remained high through year 5. DNA quality consistently decreased for the FP starting at the year 3, and at 1 year for SWs. At year 5, 33% (10/30) of the buccal swab samples could not be successfully typed at one or more loci.
- **Conclusion:** Room temperature storage of swabs and filter paper allows for DNA degradation over time, creating HLA testing inaccuracies and inefficiencies. Specifically, shorter amplicons were required to achieve accurate SBT results, which required a modification to the standard SBT procedures. DNA degradation did not affect SSO typing. Buccal swabs are a cost effective and efficient mechanism for registry DNA sample collection and storage, but shelf-life at room temperature is limited for Sanger SBT HLA typing methodology.
- **Presentation:** Results of the study were presented at the Annual ASHI Meeting held in Chicago Illinois, in November 2013. The abstract was selected for an oral presentation, and was awarded the Best Stem Cell Case Study. The study was also presented as a poster at the World Marrow Donor Association – International Donor Registry Conference in London, UK in May 2014.

Frozen Buccal Swab Storage Study

Storing buccal swabs in a frozen state has been shown by others to preserve DNA integrity for SBT for longer periods than controlled room temperature storage. A controlled storage study was initiated to determine the useful lifetime of frozen swabs for HLA typing by a variety of methods: SSO, high resolution SBT, and long range amplification Next Generation Sequencing (NGS). A limited feasibility study was completed in a previous grant period. In this grant period, the long term study was initiated, with timepoints extending to 40 years.

- The study compares buccal swabs stored at room temperature and -30°C, for quality of DNA, quantity of DNA, and high resolution HLA characterization.
- IRB approval of the study was completed, and volunteer QC donors enrolled. The sample collection from volunteer donors was completed, and all samples were segregated to their assigned storage conditions. The initial collection period to obtain a sufficient number of samples from all volunteer QC donors spanned several months, therefore baseline samples were collected last.
- Testing laboratories were identified to cover the typing methodologies noted above.
- Baseline testing of room temperature and frozen swabs was in process.
    - The sample cohort consisted of freshly collected room temperature samples, and frozen samples that were collected and stored at -30°C for a range of 4-7 months, from 30 previously HLA typed volunteers.
    - The data show comparable DNA quantity and quality measures.
        - DNA quantity of the room temperature swabs compared to the frozen swabs showed no substantial differences in the concentrations of DNA [Room temperature: 12.6 ng/ul (±9.0), Frozen: 17.4 ng/ul (±16.0)].
        - DNA quality comparisons (subjective measure, scale of 1-4) also indicated no substantial differences between room temperature and frozen samples [Room temperature: 2.7 (±1.1), Frozen: 2.0 (±0.9)].
    - The evaluation of baseline HLA typing is ongoing:
        - SSO methodology (96.7% successful). No (or minimal) issues for SSO, with only one locus from a frozen sample failing amplification.
        - SBT methodology (100% successful). No issues for SBT.
        - NGS methodology with swabs shipped at ambient temperature (94.4% successful). Four samples with issues were encountered: 2 frozen samples completely failed amplification and 2 frozen samples each had a single locus HLA typing discrepancy. A second set of freshly-collected blinded samples were sent for re-testing. The follow-up samples from the same volunteers, all had successfully typed results, but with 2 samples requiring the lab to alter the amplification primers used. The issues encountered with the NGS approach were all unique volunteer samples.To address concerns regarding the impact of freeze/thaw cycles on the samples, another evaluation of NGS methodology was initiated with swabs shipped frozen. This study segment will investigate whether the need for altered reagents was potentially due to the degradation of the

samples following the transition from a frozen to thawed state during transit.

Alternate Sample Collection and Storage Methods

Research into methods for preserving the long-term integrity of DNA within the biological samples collected from registry members is an ongoing focus of the NMDP, in order to provide the highest quality samples when needed for patient or contingency needs. NMDP research focuses on the evaluation of alternate sample collection and storage methods, including possibilities for storage formats that offer increased sample lifetime, more compact storage, and greater downstream sample utility for either further typing or for research use.

In a previous grant period, three collection methods (current cotton swab, ejectable-tip swab, and saliva) were evaluated for high resolution HLA typing, plus evaluation of extracted DNA stored in a dry, room-temperature stable state. Initial results have indicated that both of the new methods (ejectable-tip and saliva) have significant limitations with respect to cost, would require extensive adaptation to a high-throughput environment, and would not provide enough benefits over the current methodology.

While long-term storage of buccal swabs at -30°C provides a near term approach (see Frozen Swab Storage Study, above), continuing investigation of more innovative approaches to sample collection and storage continue in parallel, focusing on those that have the potential to be simple, cost-effective, and scalable.

Experts in biospecimen preservation were consulted to consider the range of current approaches to room temperature sample stabilization and to analyze those that could be further explored, as an alternative to freezing buccal swab samples. Overall findings and potential new approaches include:

- The four main room temperature stabilization methods (isothermal vitrification, lyophilization, precipitation, and solution state stabilization) rely on beginning with a liquid sample and are not directly applicable to buccal swab samples.
- Potential Approach 1: Addition of agents to buccal swab samples after sample collection. Agents could include pH stabilizing agents, chelating agents, detergents, anti-oxidants, protease/nuclease inhibitors, anti-microbial agents, lyo-protectant sugars.
- Potential Approach 2: Collect saliva onto a highly porous carbohydrate matrix. Cells would be stabilized within the matrix as it dries during transit.

Aim B.1.5: Enhancing HLA Data for Selected Donors

ABO Rh Blood Group Data

The ABO Rh Blood Group project was initiated to increase the number of registry members with ABO/Rh information to evaluate if the presence of ABO resulted in increased donor utilization. If ABO Rh information was important to Transplant Centers for donor selection and was available on the registry, it could increase the speed of the donor selection and progression to

transplant. The results of the study could be used to modify recruitment testing strategies to include these important data.

From March 3, 2014 through April 30, 2014, 527 donors were identified through NMDP's Pre-search donor contact process who, after being on the top of a patient's potential donor list, were contacted to confirm donor interest and availability. These donors were asked if they had documentation of their ABO/Rh data. If available, it was then added to the donor's data on the registry. These donors were compared against an additional 931 who did not have this information.

The donors were then evaluated at 30 and 60 days to see if a confirmatory typing (CT) request was made for them during that time.

Table 4. CT requests for donors enrolled in the ABO/Rh data collection pilot project.

		0-30 day CT's	31-60 day CT's	All 0-60 day CT's	Total DID's
With ABO typing		32 (6%)	15 (2.8%)	47 (8.9%)	527
Without ABO typing		18 (2%)	9 (1%)	27 (2.9%)	931

Results show that those donors with ABO/Rh data were requested for CT three times more in the 1st 60 days than those donors without ABO/Rh information. Logistic regression analysis was also performed to control for other donor factors in the selection and results showed donors with ABO/Rh typing have a utilization rate approximately 3.5 times higher than those without ABO/Rh. This information was then used to support the process of typing new recruited donors for ABO/Rh data at the highest volume recruitment laboratory using NGS based methodologies.

Aim B.1.6: Maintain a comprehensive quality control program

The NMDP's comprehensive quality control (QC) program has supported the successful increase in the quality of HLA typing received through the contract laboratory network. In addition, this program helps to ensure the accuracy of data obtained from research studies that support abstracts and publications.

Goals of the program include, but are not limited to:

- When possible, maintain coverage (n=2) of all alleles listed in "Common and well-documented HLA alleles: 2012 update to the CWD catalogue, Mack, et al. Tissue Antigens, 2013, 81, 194–203."
- Retire existing QC Master lots and introduce novel QC Master lots, in order to continually challenge labs with new combinations of alleles.
- Maintain an inventory large enough to challenge the highest volume lab with a unique QC Master every 8 weeks.
- Confirmatory type master lots by high resolution SBT prior to incorporation into the program to ensure accuracy of HLA.

Purified Genomic DNA as a QC Sample Type: Pilot Study and Implementation
The predominant material for QC samples is derived from NMDP Research Repository samples that are transformed into B-Lymphocytic cell lines (B-LCL) and applied to cotton-tipped swabs for inclusion as blind QC samples. B-LCL swabs are expensive and time consuming to prepare. In an effort to decrease the cost of the quality control (QC) program, a pilot program was initiated to supplement the blind QC program with purified genomic DNA absorbed onto cotton-tipped swabs ("DNA-swabs").

Pilot study:

- **Successful Phase 1 Pilot (1 laboratory):** Ten frozen blood aliquots from NMDP volunteer QC donors were selected from existing inventory for DNA extraction and dilution to 2ng/ul. Quantitative (DNA yield) and qualitative (spectrophotometric reading and agarose gel photo of genomic DNA and one amplicon) analysis of the purified DNA was performed. The purified DNA was subsequently applied to cotton-tipped swabs and shipped with existing frozen blood aliquots and fresh buccal swabs obtained from the same donors to a contracted Registry recruitment donor laboratory for HLA typing of the purified DNA and fresh buccal swabs, as well as quantitative and qualitative analysis on all sample types.
    - The laboratory was able to successfully HLA type all but one specimen in an identical manner to the current HLA typing of their Registry Donors Agreement. The failed result for the purified DNA swab was due to low DNA yield. One additional sample was removed from the pilot study due to a sample identity issue.

- **Successful Phase 2 Pilot (5 laboratories):** Expanded pilot to all laboratories that routinely receive QC samples through registry and/or customized HLA typing contracts. In all, 5 labs (encompassing 4 customized and 4 recruitment agreements) participated in phase 2 of the pilot study.
    - Four of the 5 labs were able to successfully type the purified DNA swabs through their normal processes without issues. None of the labs were able to detect a difference between the purified DNA and buccal swab QC sample types. An additional set of purified DNA swabs was shipped to the lab that experienced problems with sample repeats in order to gather additional information on the technical issues. Results of the investigation suggested an increase in the DNA concentration on the cotton-tipped swabs from 2 to 3ng/ul may eliminate further sample repeats.

- **Successful Phase 3 Pilot (evaluate DNA extraction options):** Five distinct frozen blood aliquots from NMDP volunteer QC donors were selected from existing inventory and shipped to 2 DNA extraction laboratories identified as alternative vendors for purified DNA extraction and dilution to 3ng/ul. The purified DNA swabs were incorporated into the regular recruitment and customized shipments to confirm all the contract HLA laboratories could accurately type blind purified QC samples from both alternative DNA extraction laboratories.
    - All labs successfully typed the purified DNA QC samples from both extraction labs without repeats. The technical analysis revealed the laboratory originally selected to perform the DNA extractions on the stored frozen whole blood during phase I of the pilot study had superior DNA yields, as well as the most competitive price.

- **Successful Phase 4 Pilot (evaluate fresh and frozen blood):** Five distinct NMDP volunteer QC donors with existing frozen blood aliquot inventory were selected to assess whether DNA yield is impacted by sample age or freeze/thaw cycles. Five ml of fresh blood, fresh frozen blood, and existing frozen blood inventory were sent to the DNA extraction lab for quantitative and qualitative DNA analysis.
    - Based on a small sample size (n=5), no significant difference in yield between the 3 blood sample types for any donor was observed.

- **Pilot Conclusions**
    - DNA swabs can successfully replace B-LCL swabs as an alternative QC sample source.
    - Significant cost savings were achieved by switching from B-LCL initiations/cultures/expansions to DNA extracted from frozen whole blood, enhancing long-term sustainability of the QC program.
    - In addition, this alternative QC sample type has the potential to expand allelic coverage and HLA diversity of QC buccal swabs by expanding the sample selection pool into existing NMDP volunteer QC donor blood inventory and to Registry donors with desirable HLA types.

Implementation of Purified Genomic DNA as a QC Sample Type

Based on the successful results of the Pilot Study, the routine use of DNA Swabs was implemented into the normal blind QC process.

- 10 DNA QC Masters extracted during the pilot phase of the study were incorporated into the blind QC program. No issues were reported by any of the laboratories.
- 233 existing QC volunteer blood samples with a minimum of 10 frozen aliquots in inventory were shipped for DNA extraction. These will represent a 45% increase in overall buccal swab QC inventory, and help achieve a minimum 7.5 week unique QC master shipment rotation.
    - The purified DNA was received by the Biorepository and aliquots from these samples were shipped for high resolution confirmatory typing of HLA-A, B, C, DRB1, DRBX, DQA1, DQB1, DPA1, and DPB1 prior to incorporation in the NMDP QC buccal swab program.
- At the writing of this report, nine purified DNA QC Masters were validated and added to the regular blind buccal QC program, increasing the number of purified DNA QC Masters to 19; 219 masters await validation prior to inclusion.

Additional QC Program Activities:

- Nineteen B-LCL cell lines received from the cell processing laboratory were confirmatory typed by high resolution SBT at HLA-A, B, C, DRB1, DQB1, DPB1, DQA1, and DPA1 to ensure accuracy, prior to adding the new lots to active circulation.
- **Cord Blood QC Master lots added:** An agreement was established with a cord blood bank to obtain preferentially selected unregistered research inventory based on available HLA typing. Twenty-two research cord blood units were acquired for expansion of the NMDP Cord QC Program. High resolution confirmatory typing was performed. These new CBU masters were incorporated into the cord QC program, adding 10 unique A alleles, 16 unique B alleles, 3 unique C alleles, 5 unique DRB1 alleles, and 4 unique DPB1 alleles, as well as providing previously lacking QC CBU allelic coverage at DRB3/4/5, DQA1, and DPA1. In addition, acquisition of these units increased the current cord QC inventory by 45%, and provides the framework for the eventual implementation of a blind cord QC program.
- The abstract "HLA MUTATIONS OBSERVED IN EBV-TRANSFORMED AND EXPANDED B-LYMPHOBLASTOID CELL LINES, (BLCLS)" was accepted for poster presentation at the 2014 ASHI Annual Meeting. The study documented mutation as a cause of HLA typing discrepancies observed in 2 BLC QC lines. The conclusion was that the discrepancies arose as the result of mutations that occurred during the transformation of PBMC to BLCL and/or during the expansion of existing BLCLs. As a result of this work, B*49:15 was deleted from the IMGT/HLA database in 6/2014. C*02:09 was typed by 2 labs using DNA from the same cell, but should be confirmed by

SBT on a second subject. Purified DNA extracted from whole blood has begun to replace BLCL swabs in the QC program.

Table 5. HLA allele mutation following B-LCL expansion or transformation.

Cell Type	Original HLA	Cell Culture Technique	Post-Culture HLA
B-LCL	B*49:01	B-LCL Expansion	B*49:15
PBMC	C*02:09	PBMC to B-LCL Transformation	C*02:02

II.B. Rapid Identification of Matched Donors – Hypothesis 2:

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

Aim B.2.1: Collection of Primary Data

- An XML export of the IMGT-HLA database was developed in collaboration with Anthony Nolan Bioinformatics. The NMDP instance of IMGT-HLA database was loaded with the new XML format of the allele sequences. Quality assurance testing of the database was completed. The updated database will be used as the source of HLA reference sequences and will be a more stable platform for all downstream bioinformatics analyses that make use of HLA sequence information.
- Requirements were gathered and development was initiated on a new HML 1.0 specification to address community feedback on the current formats and incorporate new constructs for Next-Generation Sequencing.

HL7

- The HL7 Working Group Meetings in Phoenix AZ, Jan 14-18, 2013, Atlanta GA, May 6-10, 2013 & Cambridge MA, Sep 23-27, 2013 were attended; meetings were held with working groups for Clinical Genomics, Structured Documents, and Orders & Observations. Clinical Sequencing Domain Analysis Model development took place, as well as weekly Clinical Genomics Workgroup meetings.
- Development continued of a Project Scope Statement for a constrained CDA for reporting HLA typing. This constrained CDA for HLA typing was presented to the HL7 Clinical Genetics Work Group.

Genetic Testing Registry (GTR)

- Discussions continued with NCBI staff to develop use of NCBI GTR for meeting Silver Standard principles for methodology reporting of HLA typing. Agreements were signed between NCBI and One Lambda for including One Lambda data into NCBI GTR.
- Kit definitions for One Lambda RSSOH2B1 lot 008 and RSSO2B1 lot 017 were imported into dbMHC (development, non-public) by NCBI.

Aim B.2.2: Validation of Logic of Primary Data

No funding was requested under this Aim for the 0039 budget cycle.

Aim B.2.3: Reinterpretation of Primary Data

No funding was requested under this Aim for the 0039 budget cycle.

Aim B.2.4: Genotype Lists & Matching Algorithm

- Primary data reinterpretation was performed to generate GL Strings for HLA DB Versions 3.8.0 through 3.11.0. The reinterpretation pipeline has been re-engineered to re-analyze the full registry data of >20 million locus-levels results within 24 hours.
- A new version of the Silver Standard genotype list RESTful web service was developed for IMGT/HLA Database nomenclature versions up to 3.11.0 at https://gl.nmdp.org/imgt-hla/3.11.0/
- A manuscript was published in Tissue Antigens: Genotype List String: a grammar for describing HLA and KIR genotyping results in a text string.[1]
- Design continued toward a scalable Next Generation Sequencing (NGS) processing pipeline based on CloudBioLinux, Genotype Analysis Toolkit, and other bioinformatics tools.
- Progress was made on the design of a system to store and analyze variant effect predictions from NGS reads using GEMINI, SnpEff, Ensemble Variation Effect Predictor (VEP), and other bioinformatics tools.

II.B. Rapid Identification of Matched Donors – Hypothesis 3:

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.

Aim B.3.1: Phase I of Expectation Maximization (EM) Haplotype Logic

- Work continued on a draft manuscript describing the match algorithm with a target physician audience. A new series of validation experiments was initiated.
- Changes to the matching algorithm were implemented, based on approval from Histocompatibility Advisory Group, to make antigen match grade assignments based on probabilities. This paves the way for the removal of allele codes from the matching equation and the constraints on the allele code system to not allow certain allele combinations.

Aim B.3.2 Enhancement of EM Algorithm
Hispanic Donor Typing

OBJECTIVES:

- To investigate the impact of Hispanic donor race/ethnic groups on HapLogic predicted HLA haplotypes, comparing recruited self-reported race of broad Hispanic vs post-recruitment self-identified race groups from an ancestry questionnaire providing higher level of sub-Hispanic detail (e.g. Cuban, Mexican).
- To improve predictions of the EM algorithm for various Hispanic subgroups.

The goal of this task is to validate allele predictions for various minority populations using NMDP registry donors. After completing an ancestry questionnaire, where they were instructed to select a country of origin and give parental background information, 2043 donors with Mexican or Caribbean island ancestry were defined. These donors were previously defined as unspecified Hispanic. The ancestry questionnaire classified 71% of respondants as having ancestry in Mexico, 14% from Puerto Rico, 6% from Cuba, 2% from the Dominican Republic or El Salvador, 1% from Guatemala and 4% from multiple of these countries.

A total 1202 of these donors had stored samples available that were sent to an HLA typing lab for 6 locus (A-B-C-DRB1-DQB1-DPB1) high resolution typing. High resolution typing results from 1201 of these donors at all 6 loci of interest were received by the end of this project (one donor had sample failure). Each donor's haplotype, as predicted by the HapLogic III Haplotype frequency data via the Haplostats.org tool, was compared to the actual typing of the donor as

reported by the lab. The alleles were predicted based off the original recruitment typing and the population the donor self-identified as on the ancestry questionnaire. By comparing the Haplostats prediction to the actual typing, we were able to detect potential inconsistencies or variation in the Hispanic sub-populations of the Caribbean islands and Mexico.

Of the 1201 donors who were re-typed, 7 showed confirmed discrepancies with the previous HLA typing. 54 donors would have improved HapLogic allele predictions if the donor would have been listed under their self-report ancestry race as opposed to their recruitment selection of Hispanic (unspecified). Haplostats was unable to identify pairs in any race groups for 4 (<1%) donors, and no pairs were identified in the Hispanic race group for a further 21 (2%) donors. Additionally, when the the high resolution 5-locus haplotypes were compared with the haplotypes predicted by Haplogic based on the donor's original typing and Hispanic broad race, the first pair in 374 (31%) donors was not the first pair originally predicted by the algorithm. Haplogic did not show the high resoloution haplotype in Haplostats when the old typing was inputed for 47 (4%) donors. This was usually the result of one of the donor's haplotype pairs showing an uncommon B-C or DRB1-DQB1 association or an uncommon allele. This could also result from underrepresentation of haplotypes in the specific Hispanic subpopulations tested.

NMDP transplant centers requested 12 donors for CT after the retyping project, 4 of which went on to donate. The 4 donors that donated were MULTI (HIS), DEC (HIS), MSWHIS and EEURO (HIS) race groups. The new typing also improved the predictions for 6 of the 12 donors who were selected for CT because of less common associations, less common alleles and/or competing alleles predicted by the original typing. Comparably, out of 1184 donors who were recruitment typed around the same time period, 7 were requested by transplant centers, 2 of which went to transplant.

Overall, this project was successful in confirming that HapLogic frequency tables do a reasonable job in the characterization of haplotypes present in various Hispanic subpopulations but also highlights an opportunity to refine how donors self-identify and/or how Haplostats maps various donor race groups. Future projects aimed to selectively re-type minority donors on the NMDP registry may also be useful to transplant centers in helping to identify and select suitably matched, high resolution typed donors for their minority patients and so improve their patient's path and time to transplant.

Unique and less common patient haplotypes

OBJECTIVES:

- To understand the incidence of patient searches having suboptimal HapLogic predictions due to lack of haplotype frequency data overall or in patient reported race
- To understand haplotypes that are lacking from the haplotype frequency tables, yet have representation among the URD pool (i.e. 10/10 URD matches)

- To identify the proportion of difficult patient searches with suitable donors (at least 7/8)

HapLogic III offers accurate matching predictions for patients and donors with good haplotype representation in the registry, often resulting in high likelihood or low likelihood of matching. One of the reasons for highly accurate predictions by HapLogic III is that 23 race-defined haplotype frequency tables are being considered, compared to only 5 broad race groups in Hap II. Patient entry into Traxis allows TCs to report patients' race and ethnicity; however cases occur when the patient HLA entered into Traxis cannot be characterized by HapLogic. This typically happens when a patient's reported race groups fall into a sub race group under which the haplotype frequency tables were derived from a small sample size and thus the full spectrum of HLA haplotypes have not been captured. This situation also happens in multi-race patients, as HapLogic does not consider multi-race information. Close examination of these types of patient searches will help to gain a better understanding of the frequency of this event and identify how often patients' HLA can be described by another race table or when it cannot be described in any race table.

To examine these searches, from April through September 2014, all NMDP domestic preliminary search patients with HLA typing for which there were no haplotype pairs in any race group, or in the patient's self-identified race group were evaluated. The incidence of patient searches which lacked haplotype frequency data overall in *any* race groups was 1.3% (81 of 6032 preliminary searches). Of these 81 patients, 62 patients had potential donors selected for HLA typing to further characterize these under-represented haplotypes, and/or identify potentially matched donors on these difficult searches. A total of 182 donors were typed at selected HLA loci for these 62 patients. Addressing the third objective of the study stated above, 46% (37 of the 81 patients) had a suitable donor (7/8 matched or better) identified either before or after HLA typing was performed.

Several underrepresented haplotypes were further characterized among the URD pool through this HLA typing, as we typed several donors with low HapLogic matching predictions that came back a match to the patient at various loci. No patient without haplotype pair representation in *any* race group has identified an 8/8 match donor to date.

The incidence of patient searches which lack haplotype frequency data in the patient's self-reported race and/or ethnicity was 3.4% (204 of 6032 preliminary searches). Of these 204 patient searches, 36 were identified that had suboptimal HapLogic predictions due to the lack of haplotype frequency data in their self-identified race group. Communication with the transplant centers resulted in race and/or ethnicity changes for 33 of these patients, which resulted in improved and accurate HapLogic predictions for potentially matched donors and CBUs.

This project has provided valuable information and insight into these difficult patient searches. Characterizing the occurrence of these events can help target intervention in future patient searches and understand how search strategy can assist these patients in the identification of a URD. This project is continuing into the 2014 funding year to accrue larger numbers of patients and type potentially matched donors.

- Work progressed toward generating HLA Haplotype Frequencies based on the genomic allele names which will allow the identification of associations that are currently ignored for applications of this data to matching such as:

  C*16:01~B*52:01:02
  C*03:03:01G~B*52:01:02
  C*12:02:01G~B*52:01:01G
- A Haplotype Frequency manuscript was published: "Six-Locus High Resolution HLA Haplotype Frequencies Developed for Mixed-Resolution DNA Typing for the Entire US Donor Registry" [2]
- A manuscript was published summarizing IHIW project to validation haplotype estimation methods "Comparative Validation of Computer Programs for Haplotype Frequency Estimation from Donor Registry Data" [3]
- Improvements were made to the EM (Expectation Maximization) analysis Pipeline (to improve re-computing Haplotype frequencies that are used in matching). Run time of one of the modules was reduced significantly. The EM pipeline was re-factored to run with less expert user intervention and the pipeline was evaluated with control IHIW files to establish a regression test.

Aim B.3.3 Optimal Registry Size Analysis

- A meeting was held in Leiden, the Netherlands to discuss NIMA (Non-Inherited Maternal Antigen) modeling with Professor Jon van Rood, and completed modeling to a level where a manuscript is in preparation, entitled " Modeling NIMA Match Rates for Be the Match Registry® ".
- An oral abstract summarizing a series of experiments to evaluate modeled non-inherited maternal antigens (NIMA) match rates in cord blood transplantation entitled, "Modeling non-inherited maternal antigen registry match rates and effective inventory size increase", was presented as a poster presentation at the 2013 EFI meeting and also the 2013 meeting of the WMDA

Aim B.3.4: Target Under-Represented Phenotypes

- An abstract on the impact of moving typing lab ambiguity resolution standards to common and well-documented allele list version 2 (CWD2) was submitted and accepted for oral presentation at the 2013 annual ASHI meeting.

Typing ambiguity score

- A numerical "typing ambiguity score" was developed to quantify the level of ambiguity in a typing based population frequencies. Designed a measure to evaluate the ambiguity contained in HLA typing. The measure takes into account the number of possible non-ambiguous typings and the distribution of their likelihoods. The measure, termed typing ambiguity score, ranges from zero to one, one being given to non-ambiguous typing. The typing ambiguity score was applied to a number of simulated datasets, describing various typing methodologies (sequence based typing, sequence specific oligonucleotide based typing and serology) in order to quantify the average ambiguity produced in HLA typing using each methodology. Work was initiated to integrate the measure into HaploStats, a web-tool that provides HLA imputation and a summary of ambiguous HLA data using population haplotype frequencies.
- An abstract was submitted to the 2013 ASHI meeting describing the typing ambiguity score and its performance on simulated HLA data. The abstract was accepted as a poster presentation.
- Work began on a manuscript describing the typing ambiguity score, its performance on simulated and real registry data, as well as its web-application. The manuscript should be a valuable tool for researchers in the field.

Ancestry Questionnaire Pilot

- A new study was initiated to pilot a geographical ancestry and race/ethnicity questionnaire.
- The protocol was developed, revised and submitted to IRB for approval.
- The consent and questionnaire was developed and mailed to participants of the study.
- The first round of SNP genotyping was completed and data received
- The first round of analysis was completed, showing that the pilot questionnaire demonstrated an enhanced capability to capture race and ethnicity information on MULTI and HIS donors that correlate with genetically inferred information via ancestry informative markers and HLA. It was also determined that there is a significant difference between subjects' initial self-identified race and ethnicity (SIRE) response and those obtained from the test questionnaires.

Aim B.3.5: Bioinformatics Web Site

- Work was carried out to design and develop a new web site for distribution of tools and data generated under this research grant with the goal of making it a global hub for HLA informatics and standards.
- The new full registry haplotype frequencies developed under this grant were made publically available under an academic and non-profit license (frequency.nmdp.org)
- Multimedia production was carried out for the "HLA: Making the Match" video [https://vimeo.com/67522128]

Aim B.3.6: Maximize the ability of the software to identify the best donors/cords for each patient

Search Archive

- A new "search archive" data mart was developed to store search results from the matching algorithm in a new database archive. This will allow analysis of every search of the registry by persisting the full match list and current values of all donor/CBU attributes.
- Primary software development for the implementation of a search archive was completed.

II.B. Rapid Identification of Matched Donors – Hypothesis 4:

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.

Aim B.4.1: Expand Network Communications

No activity was proposed for this Aim under the current grant.

Aim B.4.2: Central Contingency Management

The NMDP initiated a project evaluating the patient match rate of HLA-DPB1 T-cell Epitope (TCE) donors for patients with 10/10 donor matches. Recent research has demonstrated potential benefit for matching at the DPB1 TCE for patients given the luxury of multiple donors to select. New patient preliminary searches entered into the NMDP with DPB1 typing were evaluated for eligibility criteria. Searches meeting the criteria were evaluated for existing DPB1 TCE donor matches or if no existing matches, HLA typing was performed to identify a match (max 10 donors per patient). During this period 183 searches were enrolled and 280 donors were HLA typed.

If patients (n=163) are classified into condensed TCE groups, with patients being classified by their highest immunogenic TCE reactivity (*i.e.* 1>2>3) the ability to identify a DPB1 match/permissive mismatched donor are as follows. On initial donor search results, patients carrying any DPB1 TCE group 1 allele found a match 18% of the time, 34% for group 2 and 63% for group 3. Typing donors significantly improved the identification of a DPB1 permissive mismatched donor for all three groups to 55% for TCE group 1, 71% group 2 and 97% for group 3. The results to date were submitted to the 2015 ASBMT/CIBMTR Tandem meeting and accepted as a poster presentation.

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 provided support for the collection of six products (3 PBSC, 2 CBU and 1 therapeutic T cell) under current prior grant through April 2014.

Rapid identification of potential donors for newly diagnosed AML patients

The Southwest Oncology Group (SWOG) has identified the time from diagnosis of 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 is 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 includes a transplant arm for patients diagnosed with high risk cytogenetics following the initiation of induction therapy (see Figure 10 below). NMDP/CIBMTR is supporting the project using grant funds to provide study-specific sample collection kits for all enrolled patients, processing samples, HLA typing patients that are 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 is provided to the S1203 transplant arm principal investigator who shares the data with the referring physician.

April 2013 – September 2014 activity:

- 220 patients enrolled in the study
- 223 sample collection kits distributed to patients
- 198 kits were collected and returned to the repository
- 55 patients were considered high-risk or unknown risk
- 54 patients have been HLA typed
- 53 patients had a preliminary search completed

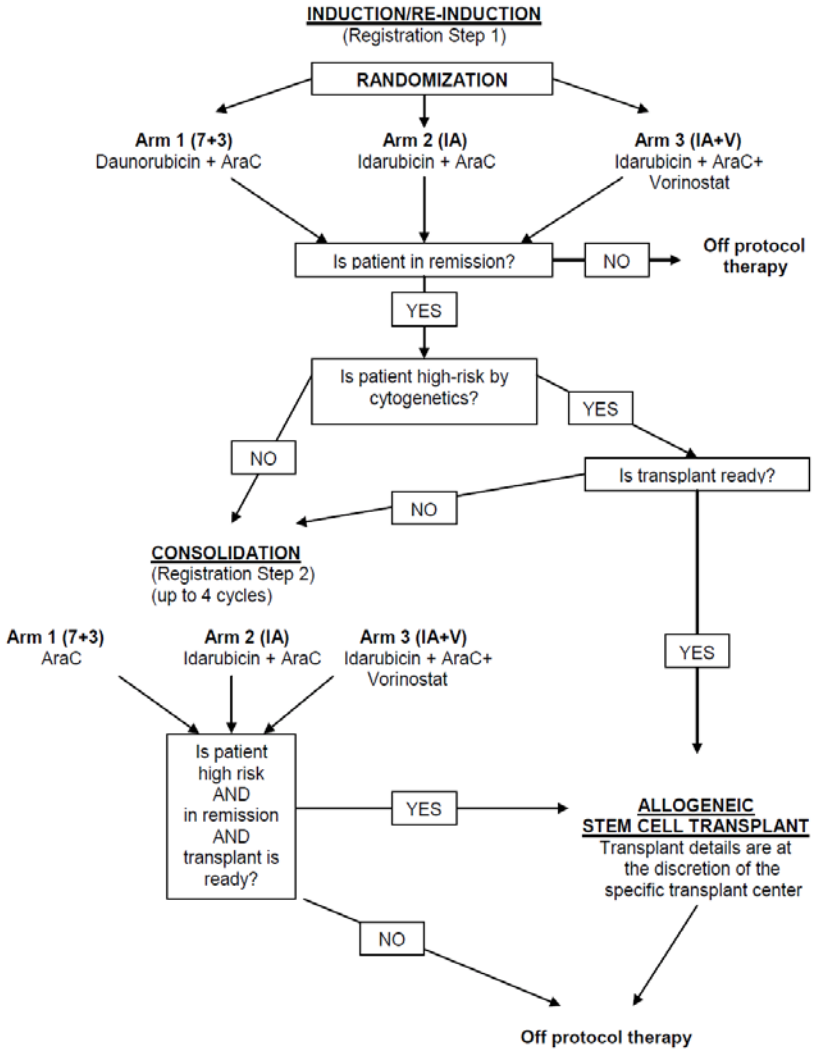


Figure 10. S1203 trial randomization and treatment schema.

Aim B.4.3 Conduct a transplant center benchmarking analysis to identify center-specific factors (e.g., quality management techniques and processes) that contribute meaningfully to superior survival outcomes. Share processes that contribute to superior outcomes with the entire TC network as best practices.

No funding was requested under this Aim for the 0039 budget cycle.

Aim B.4.4 Identify plans to expand capabilities of collection center and apheresis center network to meet increasing number of donor product requests on both a short-term and long-term basis.

No funding was requested under this Aim for the 0039 budget cycle.

II.C. Immunogenetic Studies – Hypothesis 1:

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.

Aim C.1.1: Donor Recipient Pair Project

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

In 1994 a retrospective D/R Pair HLA typing project to characterize class I and class II alleles of donor/recipient paired samples from NMDP's Repository was initiated. The goals of this ongoing research project are to assay the impact of DNA-based HLA matching on unrelated donor transplant outcome, develop strategies for optimal HLA matching, evaluate the impact of matching at alternative HLA loci on transplant outcome and finally to promote the development of DNA-based high resolution HLA typing methodologies. Presence/absence typing of 14 KIR loci (2DL1-5, 2DS1-5, 3DL1-3 and 3DS1) has been included. Cohorts of paired samples are distributed and tested as Sample Groups (SG). The following is a summary of the work completed during the grant period:

- SG 30 audit of KIR is ongoing.
- SG31 period of performance came to a close on December 31th, 2012. This sample group consisted of 168 single cord blood transplants and 33 double cord blood transplants. This is the first sample group with double cord transplants. SG 31 HLA audit has been completed and the KIR audit is ongoing.
- SG 32 consisted of 402 single cord blood transplants, 299 double cord blood transplants and 843 donor/recipient transplants was completed on September 30, 2013. Auditing of SG 32 HLA and KIR is complete and data released for use in studies.
- SG 33 consisted of 2272 adult donor/recipient pairs, 92 single cord blood/recipient pairs and 171 double cord blood triplets and was completed on September 30, 2014.
- SG 34 consisted of 1145 related donor/recipient pairs and was completed on September 30, 2014.

KIR Copy Numbert Variation (CNV) Assessment Project

Most clinical association studies of KIR have analyzed the presence/absence of each gene. Although the region has long been known to be both allelically and structurally diverse, the extent of copy number variation (CNV) has only started to be clarified. CNV data has the potential to improve, association studies by defining the gene content and increasing haplotypic resolution.

- KIR CNV typing was performed on 821 selected samples.
- An abstract describing the CNV analysis was presented at the KIR Polymorphism Workshop on June 17th, 2013.

- Analysis of the full KIR genotyped samples with CNV assignments is ongoing. Selection of future samples for CNV typing has included all haplotype variants and inclusion in two sets of minority samples. The copy number variation typing of the selected samples for CNV typing is still ongoing.

Antigen Binding Domain (ABD) Allo-Reactivity Assessment Project

Current HLA matching guidelines for unrelated HCT recommend avoidance of mismatches only within the ABD. This recommendation is based on the hypothesis that amino acid differences outside the ABD are not immunogenic. The ABD allo-reactivity assessment project will give insight into the allowable percent tolerance of matching needed outside of the ABD.

- Previously investigated data from a few Class II non-ABD mismatched samples underwent analysis and was written up and submitted to the EFI 2013 conference and was been selected for an oral presentation.

- Initial investigations of class I non-ABD mismatches of interest (A*02:01/02:09, B*44:02/44:27 and C*07:01/07:06) were performed. Queries of the Be The Match Registry identified 140 donors for high resolution typing. The retyping did not identify any instances where the isolated class I mismatch was found on identical extended haplotypes. These results of the Class I analysis was summarized and submitted to the 2013 ASHI meeting where it was accepted for poster presentation.

- The results of the previous Class II DRB1*14:01:01/14:54 analysis was also submitted to the 2013 ASHI meeting and was selected for an oral presentation.

- We initiated a second round of testing to confirm the data seen in the initial Class II DRB1*14:01:01/14:54 study. New queries for haplotypes containing both the DRB1*14:01:01/14:54 resumed to identify additional registry member that may be included in the second round.

- Analysis of the potential haplotypes provided four haplotype pair cohorts that were further typed. A total of 334 samples were high resolution typed using a with A, B, C, DRB1/3/4/5, DQB1 and DPB1 panel and a total of 140 potential donors were identified.

57 donors were approached to participate in the study and 19 donors consented and had samples drawn for peripheral blood mononuclear cell collection. Analysis of the samples collected will occur in the next grant period.

II.C. Immunogenetic Studies – Hypothesis 2:

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

Aim C.2.1: Analysis of non-HLA loci

Recent research has heightened interest in additional genetic polymorphisms which may modify the outcomes of transplantation. HLA genes, other than the major histocompatibility complex (MHC) found on chromosome 6, and non-HLA genetic factors may all influence the suitability and success of allogeneic stem cell transplants. The largest body of data with clear correlation to unrelated stem cell transplant outcome was surrounding the role of Natural Killer (NK) cells. These cells express inhibitory receptors (KIR) that specifically interact with MHC class I molecules. Genes encoding for these Ig-like ligands are found on chromosome 19. The regulatory mechanism mediated by these receptors is thought to protect normal cells from autologous NK attack, while rendering cells for which class I expression is compromised (e.g. by tumor transformation or viral infection) or incompatible (e.g. by stem cell transplant) susceptible to NK-mediated killing. This has been shown to be responsible for anti-leukemic effects and protection against GVHD following allogeneic HSC transplantation.

Immunobiology Project Results (IPR) application

- Release 2.2.2 of IPR was deployed to production and included a number of updates:
    - B/C-linkage report for samples under consideration for inclusion in sample groups
    - DRB-linkage report for auditing sample groups
    - Support for multi-donor/cord transplants

Immunobiology Integration Data Base (IIDB)

- An HLA Validation Service was developed that applies NMDP Operational rules for the validation of non-NMDP facilitated data (e.g. CIBMTR forms)
- Non-NMDP-facilitated transplant HLA typing information was added to the CIBMTR data warehouse and match grades for these transplants was computed using the NMDP HapLogic III algorithm.

Clinical Ancestry Study

- A new CIBMTR study (IB12-02) was initiated to look at the role of genetic ancestry on transplant outcomes
- Pilot analysis has been complete, two analyses have been performed:
    - Effect of donor/recipient genetic disparity on transplant outcome: Multivariate analysis on seven outcomes suggests there are trends worth investigating further. However, most p-values were not significant as the number of donor/recipient pairs in the discovery pilot was small.

  - Effect of recipient admixture on transplant outcome. Four main recipient admixtures were analyzed for all recipients in the pilot cohort: EUR, AFR, NAM and ASI. Again there were trends which require a larger sample to show statistical significance.
- A power analysis was conducted for a second larger phase of the study that is currently being planned where we will perform SNP typing on a cohort of 1000 transplantation pairs in support of the CIBMTR study IB12-02.

IMMPUTE project – to validate algorithms to impute HLA typings from MHC region SNP data

- Experimental plan and the data was distributed to the external participants for SNP-based imputation of HGDP (Human genome diversity project) SNPs based on KG (1000 Genomes) training data. While the participants were generating the results, the NMDP team performed test runs on KG data only using publicly accessible methods. Data checks were completed to identify any issues in the data and code was prepared to evaluate results returned by the participants. Test experiments were performed. An initial set of imputation results was received and validated. Participants completed a Method survey table that describes methodological and practical characteristics of their approach. The survey results were compiled into a comprehensive review table for publication with final results.
- The experimental plan for this project was developed in conjunction with collaborators at UCSF and CHORI. A methodological survey was developed and distributed to all IMMPUTE collaborators. Results of this study will be reported in the next grant period.

Immunobiological test results generated through NMDP/CIBMTR approved studies and reported to the NMDP are summarized in Table 6. These data will be used for testing, validation, and population of the IPR database.

Table 6. 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[4,5]	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

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data Submitted
Candidate Gene Study to Examine the Impact of Chemokine and Chemokine Receptor Gene Polymorphisms on the Incidence and Severity of Acute and Chronic GVHD[6]	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[7]	B. Dupont, K. Hsu	2000 pairs	KIR	SSP	Yes
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[8,9]	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[10]	T. Ellis	730 pairs	mHAg	Allele-specific Primer Extension	Yes
Genetic Polymorphisms in the Genes Encoding Human Interleukin-7 Receptor-a: Prognostic significance in Allogeneic Stem Cell Transplantation[11]	K. Muller	851 pairs	IL-7	Taqman PCR	Yes
The Effect of Non-Inherited Maternal Antigens in Cord Blood Transplantation[12]	M. Eapen	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

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[13]	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	In process
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	In process
To Develop and Test a Prognostic Index for Survival in CML URD HCT[14]	A. Dickinson	1100 pairs	TNF, IL-1RA and IL-10	Taqman	Yes
Evaluation of TGF-β1 Promoter and Signal Peptide Polymorphisms as Risk Factors for Renal Dysfunction in HCT Patients Treated with Cyclosporine A [15]	R. Shah	400 samples	TGF-β1	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	In process
Development of a GVHD Prevention Biodiagnostic Test	R. Somogyi	450 samples	Gene Expression Array	Array	In process
Genetic polymorphisms and HCT related mortality Re: Pre-HCT conditioning in matched unrelated donor HCT	T. Hahn	>4,000 pairs	GWAS	Array	In process

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data Submitted
Impact of CTLA4 SNPs on outcome after URD transplant	M. Jagasia	1,200 pairs	CTLA-4 SNPs	Taqman	In process
KIR genotyping and immune function in MDS patients prior to unrelated donor transplantation	A. E.Warlick and J. Miller	970 samples	KIR genotype, expression and cellular function	SSP, flow cytometry and cellular assays	In process
Plasma YKL-40 anc CHI3LI genotype to predict mortality after unrelated donor HCT	B. Kornblit	800 pairs	YKL-40 plasma levels and CHI3LI SNPs	ELISA and Taqman	In process
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	In process
Effect of genetic ancestry matching on HSCT outcomes	A Madbouly, M. Maiers and N. Majhail	1100 pairs	Ancestry Informative Markers	Taqman	In process
Impact of MHC Class I chain related polymorphisms on HCT outcomes	M. Askar and R. Sobecks	700 pairs	MICA genotypes	Taqman	In process
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
Prognostic impact of somatic mutationand 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	In process
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

II.D. Clinical Research in Transplantation – Hypothesis 1:

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

Aim D.1.1: Observational Research, Clinical Trials, and NIH Transplant Center

Prospective Research

During this grant, the Resource for Clinical Investigations in Blood and Marrow Transplantation (RCI BMT) continued to develop and mature elements of its infrastructure. The RCI BMT also made progress on a number of studies. The goal of this program is to provide an avenue for investigators to obtain statistical, study and data management support for prospective trials focusing on addressing various transplant issues. The following key elements were accomplished:

- The Clinical Trials Advisory Committee (CTAC) mission is to provide scientific review and recommendations on clinical trial proposals submitted to the RCI BMT for potential collaboration. The CTAC met a total of three times during this period. Twice in person (Tandem 2013 and 2014) and one conference call meeting during July 2014. A total of two study proposals were reviewed. One was not recommended to proceed, the second was scored favorably however the CTAC was concerned about drug compliance by the subjects and asked for additional information from the proposer regarding mechanism to reduce non-compliance. At the end of this grant period a response had not yet been received.

- Completion of a phase II study to establish the one year overall survival after myeloablative double unit UCBT in a multi-institution setting in patients with high-risk hematopoietic malignancy (DCB). During this grant, follow up was completed on the 56 enrolled patients. Staff continued to coordinate study activities, manage data and perform on site monitoring. A final dataset was completed and a manuscript submitted and accepted for publication in the British Journal of Hematology.
    - Br J Haematol. 2014 Oct 1. doi: 10.1111/bjh.13136. [E-pub ahead of print] Results of a prospective multicentre myeloablative double-unit cord blood transplantation trial in adult patients with acute leukemia and myelodysplasia.

- During this grant period, staff completed the Lenalidomide after allogeneic HCT for Myeloma trial also known as REV. Follow up on the 30 enrolled subjects was completed. A dataset was finalized and manuscript submitted and accepted for publication.

- Biol Blood Marrow Transplant 20(8):1183-1189, 2014 Lenalidomide maintenance for high-risk multiple myeloma after allogeneic hematopoietic cell transplantation.

- The Long-term Donor Follow-up protocol continued to accrue donors both from the previous donated group and prospectively as donors participated in the standard work-up process. As part of this grant enrollment reached just over 16,000 donors of which 6614 were enrolled prospectively and 9618 from donors who donated prior to the study being activated. The Survey Research Group is responsible for completing the follow up time points for the NMDP Operated Donor Centers and a few non-operated centers. During the time labor was expended on this grant, the SRG completed 4,599 follow up forms. The SRG also facilitate the follow up process for any reported events on the study. This includes requesting a release of medical records from the donors, obtaining the records and preparing them for review by the Medical review team. The team sent out 280 medical record release forms to donors that had reported and event during the labor period on this grant. During this same period 260 records were received and prepared for medical review.

- During this grant period staff from the RCI BMT continued to work with CIT staff to make a recommendation to CIBMTR leadership regarding building or purchasing a) comprehensive system for management of activities and studies within the SRG and b) clinical trial management system (CTMS) to coordinate operational and administrative activities within RCI BMT. After a presentation in May 2013, staff were asked to refine the build estimates and gather more information on two of the purchase options which was worked on during this grant.

- During this grant period one new project was initiated where staff manage the participation of unrelated donors to a trial for an external group. Logistical elements were established and the study opened.

Cord Blood Research Activity

Defining Biomarkers Associated with Cord Blood Engraftment

For the study investigating biomarkers associated with cord blood engraftment, the Duke and MD Anderson laboratory staff completed work on validating the assay methodologies but were unable to ensure consistent results generated at both testing sites. Initial and final statistical analysis of the validation testing results showed poor inter-laboratory reliability for all assays performed. Therefore, testing using a third laboratory was developed with St. Louis Cord Blood

Bank (SLCBB) to determine whether the poor reliability is due to center-specific or assay related issues.

Duke and SLCBB created and finalized plans for training and validating the assay methodologies. The data analysis for the results of the training phase met the acceptable threshold for the inter-laboratory reliability coefficient of variation (CV); however, the validation phase data analysis did not. An investigation into the cause of the poor reliability was conducted and included the following:

- The two laboratories swapped raw flow cytometry data and re-analyzed based on the study protocol. These data indicated more consistent reliability for most of the ALDHbr measurements than previously recorded when each center used their own flow data. Once re-gating was complete, histograms from each lab were compared side-by-side to look for variance in gating strategies. From this comparison, it was noted that the gating strategies were different between Duke and SLCBB pertaining to live/dead cells.

The results of the investigation suggested that the gating strategies introduced much of the variability. The study group halted the study based on the poor reliability of results and a lack of continuing interest in developing the assay by additional laboratories.

A white paper detailing recommendations/guidelines for the assessment of new assays (potency or other assays) relevant to cord blood banking and/or transplantation was published in Cytotherapy[16]. As a result, in 2012 the NMDP was contacted by Hemogenix regarding a collaborative validation study for their potency assay (HALO). The proposal was reviewed by the Cord Blood Advisory Group (CBAG) and the Cord Research Sub-advisory Group. The subsequent protocol was develop and reviewed and approved by the CBAG. The protocol was developmed. Members of the CBAG expressed interest in the validation; however, upon solicitation of member banks for completion of the validation none could commit to the effort due to other priorities. The cord blood banks expressed a need to focus on FDA licensure efforts.

In 2014, the protocol was once again reviewed by the CBAG, and once again, the group indicated no interest in proceeding with the validation. The reasons cited by the CBAG regarded concerns about various aspects of the assay.

Impact of Non-inherited Maternal Antigen Mismatching on Cord Blood Transplantation

An analysis evaluating the likelihood of finding a non-inherited maternal antigen/allele (NIMA) match for HLA mismatched cord blood unit for transplant when upfront maternal typing is not

available was completed. The retrospective analysis compared the frequencies of the NIMA matched and mismatched HLA- A, B antigens or DRB1 alleles found in the Eurocord/NMDP/CIBMTR study to determine any significant differences. Results were incorporated into a manuscript which was published in Biology of Blood and Marrow Transplantation.[12]

In the NMDP/Eurocord NIMA match case study it was shown that NIMA matches (NIMA+) are associated with more common HLA types and therefore more common haplotypes. More common haplotypes may lead to better allele level matching and matching at HLA-C. Work was initiated and continued on a NIMA assessment of high resolution (HR) match grades at HLA-A, B, C, and DRB1 between transplant recipients and the cord blood unit to determine whether the NIMA phenomena may be a consequence of better allele level matching in the NIMA+ group . HR typing was imputed for loci with intermediate or low resolution typing. Typing ambiguity scores were included to determine the confidence of the imputations. HR match grades were then determined between the recipient and the cord blood unit. Analysis indicated significant skewing in the 5/6 NIMA+ group to better HR matching. There was no significant difference in the 4/6 subset between the NIMA+/- groups. In this small population NIMA+ 5/6 had a better HR level matching. It remains to be seen whether the skewed HR matching is a driver of the previously observed NIMA effect. This study was presented at the 2014 ASHI National Meeting

Impact of Cord Blood Release Testing on Engraftment

Work continued on the study titled, “Cord blood unit release testing criteria and impact on the transplantation outcome.” to determine the impact of CBU CFU testing at the time of release on transplantation outcome. The focus of the study was on the CFU assay because post-thaw growth is indicative of overall unit suitability and approximately 50% of NMDP network CBBs perform the assay pre-release. The study proposal was presented to the Graft Sources and Manipulation Working Committee meeting during Tandem 2013. The committee members assigned a low priority score and were unable to accept the proposal. The Cord Research Sub-advisory Group met to discuss the future of the study and determined to continue without the support of the Graft Sources and Manipulation Working Committee. Further protocol development based on suggestions made by the Graft Sources and Manipulation Working Committee as well as defined data points to capture were determined and incorporated into the study protocol. The study proposal was presented to the Cord Blood Advisory Group in June 2013. The Group members voted unanimously to move forward with the study. The study protocol, data collection forms, and population were finalized. The lists of cases distributed for data capture to participating cord blood banks. Data was returned to the CIBMTR and analyzed. Preliminary results presented at the International Cord Blood Symposium in June 2014 showed no correlation between post thaw CFU dose and neutrophil engraftment. There was a suggestion that low CFU doses were associated with delayed engraftment by day 28, but the effect disappeared by days 45 and 60 post transplant.

CIBMTR IT Activity

The CIBMTR Information Technology team manages CIBMTR data and information, implements commercial software products, develops custom software and provides technical support. Additional accomplishments were made in delivering new functionality, improving data quality, data capture and data reporting through the CIBMTR IT suite of applications.

FormsNet

The FormsNet application suite is CIBMTR's web-based application for data collection, storage, and retrieval for HCT and cellular therapy research. Key functionality includes:

- Electronic data submission from center to CIBMTR for both TED forms and CRFs, including real-time error validation and forms due listings
- Support for all aspects of prospective research, including clinical trials and survey research
- Collection of donor clearance/suitability and follow-up data to ensure donor safety
- Support for data collection, quality control, and clinical studies via the Management Reporting tool

To accommodate future data collection and management needs, FormsNet is being upgraded based on an "Agile Software Development" model that successively refines software at each development stage to address functionality, usability, and end user requirements. Requirements for FormsNet3 include a more user-friendly design, improved navigation, and customization capability, as well as a new tools and forms with enhanced validation checks. The Recipient functionality was upgraded to the FormsNet 3 platform in 2012. Donor functionality is in the process of being upgraded for FormsNet 3, with a targeted 2014 release date.

- Released a major upgrade, FormsNet3, in December 2012. This upgrade improved user experience, data capturing and validation. This was a significant 2012 milestone. Some overall benefits of the FormsNet 3 application include:
  - Provides greater flexibility to improve data quality and responsiveness to user needs.
  - Enhanced performance by improving speed, usability, consistency and usefulness of forms access, user data entry, and validations
  - Improved user experience/usability by offering real-time data validations, rules, control of data entry "flow", error handling and messaging, and "smart navigations" (from form-to-form or from field-to-field on the same form), auto population of key fields

- Improved data quality- by enabling data entry to be as easy, consistent, accurate, and fast as possible

Some key features of the FormsNet 3 application include:

- New Site features
  - Flexibility, site search, expanded browser support
- Forms Entry improvements
  - Faster loading of pages, improved layout, and navigation
  - Auto-population, field (rather than form) level saving
- Validation improvements
  - Display validation rules, over-ride improvements, validation across forms

- **Auditing support**. Enhancements were made to the applications for auditing of FormsNet data against source documents at recipient and donor centers.
  - A release occurred to improve users' efficiency of the existing Audit capabilities, increasing productivity.
- **Monitoring support**. The Monitoring application was enhanced to increase productivity and create the infrastructure required to Monitor TREO Centers in support of the 11-Treo Study.
- **Research support**. Simplified selection logic for the 11-Treo research study, and added new Treo study forms.
- **Additional enhancements.** A number of enhancements were implemented as part of the above initiatives, plus additional data capture support and management reports. The enhancement to management reports included support for management oversight and clinical trials.
  - **Performance Enhancement**- a release for the Recipient functionality was implemented in August, 2013 to improve overall application performance, printing, provided key bug fixes, and support for additional internet browsers. The release was well-received by the application users.
- **Customer experience**: In 2013, 22 site visits were completed across the country. Lessons learned from these site visits as well as from the 2013 Tandem Data Manager's meeting, and a 2013 FormsNet 3 user survey were applied in the August Performance enhancement release, and served as input into remaining releases targeted for 2013.
- **AGNIS Integration release**: A release was implemented in March to synchronize AGNIS to FormsNet 3, at which time AGNIS users were fully supported in the FormsNet 3 application. AGNIS services were fully supported during the interim period by utilizing the FormsNet 2 recipient module for editing AGNIS submitted forms.

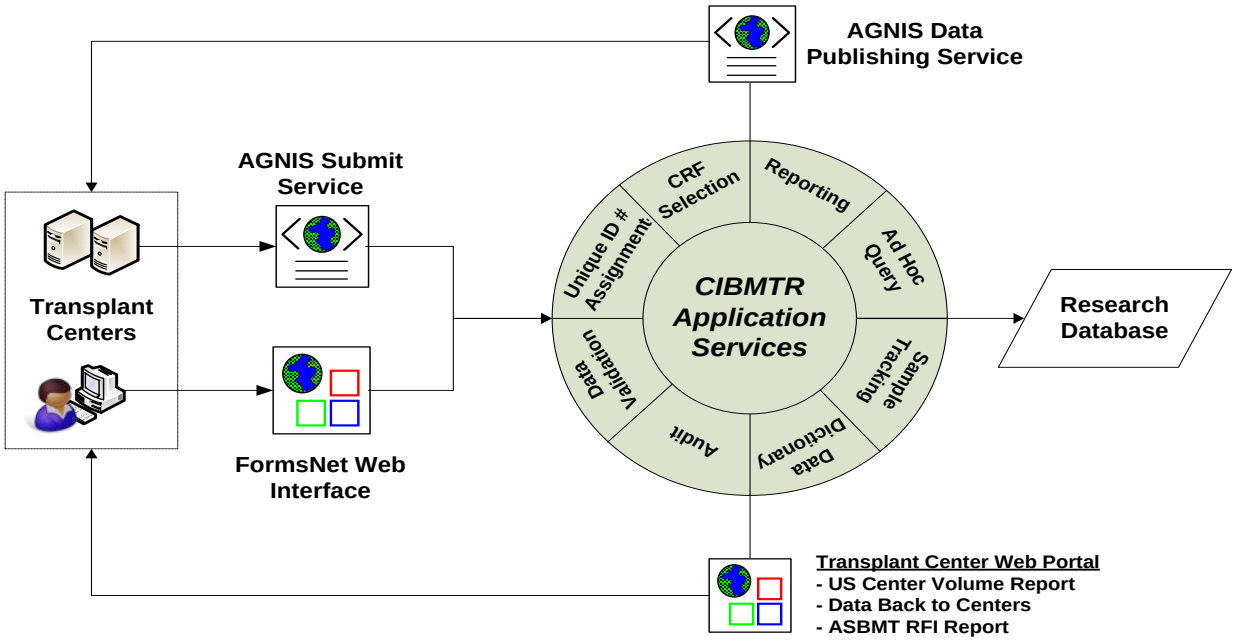


Figure 11. AGNIS data sharing schema

AGNIS

A Growable Network Information System (AGNIS)

To assist transplant centers in collecting data for internal research, patient care requirements, and reporting purposes, CIBMTR and NMDP BioInformatics created A Growable Network Information System (AGNIS). AGNIS supports secure data sharing across diverse database systems. It is an open-source Web service developed with tools from the NCI caBIG® effort and other well-established projects, such as the Globus Toolkit. AGNIS software, distributed under a public license at www.agnis.net, is available to any interested center.
AGNIS allows participating centers to collect and share data with CIBMTR and others who link to AGNIS (Figure 11). Data are entered once and then distributed and synchronized among databases. Data transmitted via AGNIS are stored in a metadata repository operated by the NCI Center for Biomedical Informatics and Information Technology (NCI CBIIT), known as the Cancer Data Standards Registry and Repository (caDSR). This repository is compliant with government standards for electronic data transmission.
Forms supported with AGNIS

- Form 2000 - Recipient Baseline Data
- Form 2004 - Infectious Disease Markers

- Form 2005 - Confirmation of HLA Typing
- Form 2006 – HSCT Infusion Form
- Form 2018 - Hodgkin and Non-Hodgkin Lymphoma Pre-HSCT data
- Form 2007 - Cord Blood Unit – SCTOD Data Requirements
- Form 2100 - 100 Days Post-HSCT Follow-up Form
- Form 2118 - Hodgkin and Non-Hodgkin Lymphoma Post-HSCT data
- Form 2200 - Six Months to Two Years Post-HSCT Data
- Form 2300 - Yearly Follow-Up for Greater Than 2 Years Post-HSCT data
- Form 2400 - Pre-Transplant Essential Data
- Form 2450 - Post-Transplant Essential Data
- Form 2451 - Chimerism Studies
- Form 2455 - Selective Post-Transplant Essential Data
- Form 2804 – Unique ID form
- Form 2900 - Recipient Death Data

Current AGNIS status:

- Data elements for CIBMTR forms are in NCI caDSR library
- CIBMTR has facilitated development and testing efforts with the European Group for Blood and Marrow Transplantation (EBMT) to support Production data submission from EBMT systems to CIBMTR. The forms currently being submitted in production include the PRE-TED form (2400), Unique ID Assignment Form (2804), POST-TED 100 Day (2450 -100 day) and the HSCT Infusion Form (2006).
- Other users submitting data through AGNIS:
    - 4 centers making direct submissions
    - 1 registry supporting 50 centers
    - 6 vendors certified for production submission
- Other users retrieving data from FormsNet through AGNIS:
    - 2 centers doing direct retrieval
    - 4 vendors supporting center retrieval

Progress:

- EBMT-CIBMTR and CIBMTR-Eurocord AGNIS connections in progress
    - EBMT has submitted >8,000 initial forms and is beginning to send follow-up forms for those transplants . This represents an increase in 6000 forms over the past year.
- The number of AGNIS production users has increased from 4 to 6. Two of the production users are vendors who support multiple clients. One production user is a registry which supports 48 centers.

Aim D.1.2: Research with NMDP Donors

No funding was requested under this aim for the 0142 budget cycle.

Aim D.1.3: Expand Immunobiology Research

During the grant period, 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 International Cord Blood Symposium meetings. Support permitted the committee to maintain a strong performance record with 14 publications (submitted or accepted) and collaboration on 3 grants completed in calendar year 2013. In addition, 7 new proposals were accepted by the IBWC during the BMT Tandem meetings in February 2014.

IBWC 2013 manuscripts (submitted/accepted):

- Petersdorf EW, Malkki M, Horowitz MM, Spellman SR, Haagenson MD, Wang T. Mapping MHC haplotype effects in unrelated donor hematopoietic cell transplantation. Published. Blood. 2013 Mar 7; 121(10):1896-1905.
- Dobbelstein C, Ahn KW, Haagenson M, Hale GA, van Rood JJ, Miklos D, Waller EK, Spellman SR, Fernandez-Vina M, Ganser A, Aljurf M, Bornhaeuser M, Gupta V, Marino SR, Pollack MS, Reddy V, Eder M, Lee SJ. Birth order and transplant outcome in HLA-identical sibling stem cell transplantation – an analysis on behalf of the Center for International Blood and Marrow Transplantation (CIBMTR). Published. Biology of Blood & Marrow Transplantation. 2013 May 1; 19(5):741-745.

- Hurley CK, Woolfrey A, Wang T, Haagenson M, Umejiego J, Aljurf M, Askar M, Battiwalla M, Dehn J, Horan J, Oudshoorn M, Pidala J, Saber W, Turner V, Lee SJ, Spellman SR. The impact of HLA unidirectional mismatches on the outcome of myeloablative hematopoietic stem cell transplantation with unrelated donors. Published. Blood. 2013 Jun 6; 121(23):4800-4806.

- Shamim Z, Spellman S, Haagenson M, Wang T, Lee SJ, Ryder LP, Müller K. Polymorphism in the interleukin-7 receptor-alpha and outcome after allogeneic hematopoietic cell transplantation with matched unrelated donor. Published. Scandinavian Journal of Immunology. 2013 Aug 1; 78(2):214-220.

- Morishima Y, Kawase T, Malkki M, Morishima S, Spellman S, Kashiwase K, Kato S, Cesbron A, Tiercy JM, Senitzer D, Verlardi A, Petersdorf EW. Significance of ethnicity in the risk of acute graft-versus-host disease and leukemia relapse after unrelated donor haematopoietic cell transplantation. Published. Biology of Blood & Marrow Transplantation. 2013 Aug 1; 19(8):1197-1203.

- Venstrom JM, Pittari G, Gooley TA, Chewning J, Spellman S, Haagenson M, Gallagher MM, Malkki M, Petersdorf E, Dupont B, Hsu KC. HLA-C dependent prevention of leukemia relapse by donor activating KIR2DS1. Published. N Engl J Med, 2013 August 30, 367(9):805-816.

- Fernández-Viña MA, Klein JP, Haagenson M, Spellman SR, Anasetti C, Noreen H, Baxter-Lowe LA, Cano P, Flomenberg N, Confer DL, Horowitz MM, Oudshoorn M, Petersdorf EW, Setterholm M, Champlin R, Lee SJ, de Lima M. Multiple mismatches at the low expression HLA loci DP, DQ, and DRB3/4/5 associate with adverse outcomes in hematopoietic stem cell transplantation. Published. Blood. 2013 May 30; 121(22):4603-4610.

- Pidala J, Wang T, Haagenson M, Spellman SR, Askar M, Battiwalla M, Baxter-Lowe LA, Bitan M, Fernandez-Viña M, Gandhi M, Jakubowski AA, Maiers M, Marino SR, Marsh SG, Oudshoorn M, Palmer J, Prasad VK, Reddy V, Ringden O, Saber W, Santarone S, Schultz KR, Setterholm M, Trachtenberg E, Turner EV, Woolfrey AE, Lee SJ, Anasetti C. Amino acid substitution at peptide- binding pockets of HLA class I molecules increases risk of severe acute GVHD and mortality. Published, Blood. Epub 2013 Aug 27, DOI:10.1182/blood-2013-05-501510.

- Eapen M, Klein JP, Ruggeri A, Spellman S, Lee SJ, Anasetti C, Arcese W, Barker JN, Baxter-Lowe LA, Brown M, Fernandez-Vina MA, Freeman J, He W, Paola Iori A, Horowitz MM, Locatelli F, Marino S, Maiers M, Michel G, Sanz GF, Gluckman E, and Rocha V. Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy. Published. Blood. 2013 October 18; Epub, DOI:10.1182/blood-2013-05-506253

- Cooley S, Weisdorf DJ, Guethlein LA, Klein JP, Wang T, Marsh SGE, Spellman S, Haagenson MD, Saeturn K, Ladner M, Trachtenberg E, Parham P, Miller JS. Recipient HLA-C1 enhances the clinical advantage of killer-cell immunoglobulin-like receptor B haplotype donors in unrelated transplantation for acute myelogenous leukemia. Submitted.

- Fleischhauer K, Fernandez-Viña MA, Wang T, Haagenson M, Battiwalla M, Baxter-Lowe LA, Ciceri F, Dehn J, Gajewski J, Hale GA, Heemskerk MBA, Marino SR, McCarthy PL, Miklos D, Oudshoorn M, Pollack MS, Reddy V, Senitzer D, Shaw BE, Waller EK, Lee SJ, and Spellman SR. Risk-associations between HLA-DPB1 T cell epitope matching and outcome of unrelated hematopoietic cell transplantation are independent from HLA-DPA1. Submitted.

- Sengsayadeth S, Wang T, Lee SJ, Haagenson MD, Spellman S, Fernandez-Viña MA, Muller CR, Verneris MR, Savani BN, Jagasia M. Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) Single Nucleotide Polymorphisms Do Not Impact Outcomes after Unrelated Donor Transplant: A Center for International Blood and Marrow Transplant Research Analysis. Submitted.

- Gleason MK, Ross JA, Warlick ED, Lund TC, Verneris MR, Wiernik A, Spellman S, Haagenson MD, Lenvik AJ, Litzow MR, Epling-Burnette PK, Weiner LM, Weisdorf DJ, Vallera DA, Miller JS. CD16xCD33 bispecific killer cell engager (BiKE) activates NK cells from MDS patients against primary MDS and MDSC CD33+ targets. Submitted.

- Fernandez-Vina M, Wang T, Lee S, Haagenson M, Aljurf M, Askar M, Battiwalla M, Baxter-Lowe LA, Gajewski J, Jakubowski A, Marino S, Oudshoorn M, Marsh S, Petersdorf E, Schultz K, Turner EV, Waller E, Woolfrey A, Umejiego JB, Spellman S, and Setterholm MI. Identification of a Permissible HLA Mismatch in Hematopoietic Stem Cell Transplantation. Submitted.

IBWC 2014 proposals:

- The prognostic impact of somatic mutations and levels of CXC chemokine ligands on post hematopoietic cell transplantation (HCT) outcomes in patients with myelodysplastic syndromes (MDS). PIs: Wael Saber, Coleman Lindsley, Benjamin Ebert

- Donor-Specific anti HLA antibodies, Allele and Antigen level HLA mismatches in the outcomes of Transplantation of Non-Malignant Diseases with Unrelated Donors. PIs: Marcelo Fernandez-Vina and Ann Woolfrey

- Structural/Functional Models of HLA for Data Mining of Permissive Mismatching in Allogeneic Hematopoietic Stem Cell Transplantation. PI: Loren Gragert

- Indirectly recognizable HLA epitopes (PIRCHES): a retrospective validation study on the role of indirect recognition of mismatched HLA in hematopoietic stem-cell transplantation outcome. PI: Eric Spierings

- A Retrospective Assessment of Outcomes of Follicular Lymphoma Patients who have Undergone Allogeneic Stem Cell Transplant Based on Human Leukocyte Antigen (HLA) Type. PIs: Basem William, Marcos de Lima, Marcelo Fernandez-Vina and Brian Hill

- Assessing the similarity of the T cell receptor repertoire in allogeneic hematopoietic stem cell recipients with the same single human leukocyte mismatches. PI: Everett Meyer

- mtDNA haplotypes and unrelated donor transplant outcomes. PIs: Michael Verneris and Julie Ross

Attachment A – References

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2. Gragert L, Madbouly A, Freeman J, et al. Six-locus high resolution HLA haplotype frequencies derived from mixed-resolution DNA typing for the entire US donor registry. Hum Immunol. 2013 Oct;74(10):1313-20. doi: 10.1016/j.humimm.2013.06.025. Epub 2013 Jun 24.

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11. Shamim Z, Spellman S, Haagenson M, et al. Polymorphism in the Interleukin-7 Receptor-alpha and Outcome after Allogeneic Hematopoietic Cell Transplantation with Matched Unrelated Donor. Scand J Immunol 2013; 78(2): 214-220.

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Attachment B – Published Manuscripts and Abstracts Associated with this Grant

Manuscripts and Book Chapters

1. Logan BR, Zhang M-J. The use of group sequential designs with common competing risks tests. Statistics in Medicine. 2013 Mar 15; 32(6):899-913. doi:10.1002/sim.5597. Epub 2012 Sep 4.

2. Danner-Koptik KE, Majhail NS, Brazauskas R, et al. Second malignancies after autologous hematopoietic cell transplantation in children. Bone Marrow Transplantation. 2013 Mar 1; 48(3):363-368. doi:10.1038/bmt.2012.166. Epub 2012 Sep 10.

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2013 Jan 1; 9(1):19-32. doi:10.1007/s10985-012-9229-1. Epub 2012 Sep 12.

4. Keating A, DaSilva G, Pérez WS, et al. Autologous blood cell transplantation versus HLA-identical sibling transplantation for acute myeloid leukemia in first complete remission: a registry study from the Center for International Blood and Marrow Transplantation Research. Haematologica. 2013 Feb 1; 98(2):185-192. doi:10.3324/haematol.2012.062059. Epub 2012 Sep 14.

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HLA Typing for Bone Marrow Transplantation
FINAL REPORT
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Abstracts

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