REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
6/30/2021	Interim Technical Report	August 2020 – May 2021

4. TITLE AND SUBTITLE
Development of Medical Technology for Contingency Response to Marrow Toxic Agents – Interim Technical Report with SF298 August 26, 2020 – May 31, 2021

5a. CONTRACT NUMBER
N/A

5b. GRANT NUMBER
N00014-20-1-2832

5c. PROGRAM ELEMENT NUMBER
N/A

6. AUTHOR(S)
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5d. PROJECT NUMBER
N/A

5e. TASK NUMBER
Project 1, 2, 3, 4

5f. WORK UNIT NUMBER
N/A

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N/A

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Arlington VA 22203-1995

10. SPONSOR/MONITOR'S ACRONYM(S)
ONR

11. SPONSORING/MONITORING AGENCY REPORT NUMBER
N/A

12. DISTRIBUTION AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited

13. SUPPLEMENTARY NOTES
N/A

14. ABSTRACT

1. Contingency Preparedness: 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. Immunogenic 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.

15. SUBJECT TERMS
Research in HLA Typing, Hematopoietic Stem Cell Transplantation and Clinical Studies to Improve Outcomes

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Steven Devine, MD – Chief Medical Office
U	U	U		30	19b. TELEPONE NUMBER (*Include area code*) 763-406-8239

Grant Award N00014-20-1-2832

DEVELOPMENT OF MEDICAL TECHNOLOGY

FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS

INTERIM ANNUAL REPORT

SUBMITTED June 30th, 2021

Office of Naval Research

And

The National Marrow Donor Program®

500 5th St N

Minneapolis, MN 55401

I. Heading

PI: Steven Devine, M.D.

National Marrow Donor Program

N00014-20-1-2832

Development of Medical Technology for Contingency Response to Marrow Toxic Agents

II. Scientific and Technical Objectives

The main goal of all activities funded through this grant is to develop, test and mature the ability of the NMDP Coordinating Center and NMDP contracted network sites network sites to address contingency events wherein civilian or military personnel are exposed to marrow toxic agents, primarily ionizing radiation or chemical weapons containing nitrogen mustard. As a result of prior efforts in this regard a solid foundation has been established. The proposed new activities will continue to enhance and expand our capabilities in each of the four focus areas. Contingency preparedness activities will continue to integrate NMDP's role with federal, state and local agencies.

An accident, a military incident, or a terrorist act in which a number of individuals are exposed to marrow toxic agents will result in injuries from mild to lethal. But the extent of individual injuries and the likelihood of recovery in many cases will not be apparent until days or weeks after the event. Casualties will be triaged by first responders, and those with major marrow injuries who will need aggressive medical support and may be ultimately candidates for hematopoietic cell transplantation (HCT), will need to be identified. While these patients are being supported, HCT donor identification activities will be initiated because it will not be initially clear which ones may ultimately require HCT. NMDP approved transplant centers will provide a uniform and consistent clinical foundation for receiving, evaluating and caring for casualties. NMDP Coordinating Center will orchestrate the selection and testing necessary to rapidly identify the best available donor or cord blood unit for each patient utilizing its state-of-the-art communication infrastructure, sample repository, laboratory network, and human leukocyte antigen (HLA) expertise. NMDP's on-going immunobiologic and clinical research activities promote studies to advance the science and technology of HCT transplantation to improve outcome and quality of life for the patients.

Importantly, most individuals with near-lethal marrow toxic injuries will recover their own marrow function provided they receive intensive supportive care from the medical professionals that are part of the contingency response community. These professionals can save the lives of persons with severe marrow suppression using the knowledge and skills practiced every day to treat patients undergoing HCT coordinated through the NMDP.

III. Approach

A. Contingency Preparedness

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

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

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

C. Immunogenetic Studies in Transplantation

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

D. Clinical Research in Transplantation

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

IV. Updates

A. Contingency Preparedness

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

During this year, RITN continued to develop the preparedness of its network of hospitals through the following activities:

- Reviewed the best use of RITN hospital time and effort during the SARS CoV-2 pandemic, resulting in a minimally reduced task list for the year, balancing over straining hospitals during this crisis and maintaining their readiness and engagement to radiological preparedness.

- RITN attended and represented (RITN Medical Director) at the Combined Injury Summit held January 27, 2021, bringing together a panel to discuss roles and capabilities of military medical assets for treating combined injuries, triage options for a mass casualty event with combined injuries, and to discuss and propose clinical guidelines for combined injuries. The panelists included representatives from the American Burn Association, Henry Jackson Foundation, Joint Program Committee-6, Joint Trauma System, Radiation Emergency Assistance Center/Training Site, Radiation Injury Treatment Network, Uniformed Services University and Walter Reed National Military Medical Center
- RITN and the Radiation Emergency Assistance Center/Training Site (REAC/TS) rewrote the Hematologic and Oncologic Emergency Response chapter and submitted it for publication by Springer.
- RITN attended the 16th Annual WHO REMPAN meeting held March 22-23, 2021, bringing together global experts on radiation emergency medical preparedness and assistance to discuss the latest research and current events.
- Continued its workgroup to develop a modular acute radiation syndrome treatment, a just-in-time training course for healthcare providers.
- Progressed in the development of four, virtual educational training sessions for RITN hospitals and partners; in lieu of the semi-annual RITN Workshop that would typically be held in summer 2021.
- Continued collaboration with the American Burn Association to develop advanced practice guidelines for the combined care of patients by RITN and burn centers.
- Supported Gryphon Scientific's Center for Disease Control (CDC) funded project to assess United States laboratory capabilities for ionizing radiation related testing.
- Continued to develop the Hospital Radiation Morbidity Toolkit as part of the CDC grant awarded to RITN and submitted the final form for CDC review and comment.

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

Expand the genetic diversity of the registry through continued addition of adult donors and cord blood units, utilizing high volume HLA typing methodologies.

Supported HLA typing of 23,225 newly registered volunteer donors between January 1, 2021 and June 15, 2021.

Modeling and analysis of registry coverage for the Warfighter

Forward deployed Warfighters are at a higher risk of exposure to marrow toxic injuries due to ionizing radiation or marrow toxic chemical agents. As such, it is important to model and determine the likelihood that Warfighters will have a suitably matched, unrelated donor (defined as 8/8 or 7/8 matched for HLA-A, B, C and DRB1) on the NMDP/Be The Match Registry to support lifesaving HCT or cellular therapy. Our prior results indicate that most warfighters will have suitable adult donors, though there is not an optimal match for many warfighters (below).

Adult-donor Match Likelihood for 21 populations

Table 1 lists the 8/8 and 7/8 match rates for 21 populations. The highest and lowest match rates were found for European Caucasian and African, respectively.

Table 1. Match rates of 21 populations

Race code	Description	8/8 Match (%)	7/8 Match (%)
AAFA	African American	22	74
AFB	African	18	71
AINDI	South Asian Indian	37	87
AISC	American Indian – South or Central American	52	88
ALANAM	Alaska Native or Aleut	57	89
AMIND	North American Indian	62	95
CARB	Caribbean Black	21	74
CARHIS	Caribbean Hispanic	50	91
CARIBI	Caribbean Indian	41	85
FILII	Filipino	48	89
HAWI	Hawaiian or Other Pacific Islander	37	81
JAPI	Japanese	44	89
KORI	Korean	43	88
MENAFC	Middle Eastern or N. Coast of Africa	52	92
MSWHIS	Mexico or Chicago	49	90
NAMER (EURCAU)	European Caucasian	79	99

Race code	Description	8/8 Match (%)	7/8 Match (%)
NCHI	Chinese	45	88
SCAHIS	Hispanic – South or Central American	40	85
SCAMB	Black – South or Central American	40	81
SCSEAI	Southeast Asian	32	80
VIET	Vietamese	48	86

To address the gaps in warfighter population coverage at the 8/8 or 7/8 levels, we considered the increasing body of evidence for advances in post-HCT immune modulation that allow for safe and effective HCT despite a greater number of HLA mismatches between the donor and potential patient. To this end, we have defined new scenarios to re-estimate match rates specific to different race and ethnic groups that consider HLA-A, B, C, and DRB1 high resolution matching at 8/8 7/8, 6/8, 5/8, and 4/8 HLA alleles. These will take into consideration the larger potential donor pool at higher levels of mismatches and will be adjusted for known donor age and availability statistics. These modeling efforts will evaluate less stringent HLA matching criteria to expand access for warfighters and allow for rapid identification of suitable donors for HCT and cellular therapy. The results of the analysis are pending.

Development of science and technology for rapid communication of HLA data

HLA annotation and conversion tool development

Development and improvement of tools continues for handling HLA data toward the rapid communication, identification, and evaluation of matched donors in transplantation. Updates to Py-ARD, a Python-based HLA annotation and conversion tool, were implemented. These updates allow for input of alleles based on protein and genotype groupings and for sorting of HLA nomenclature in the fourth field, loading of references to multiple allele codes in a more efficient manner and support for serological typing in genotype-list strings.

Additional improvements were made for serology mapping and expansion fixes for multiple allele codes, nomenclature version handling and genotype-list strings. These improvements facilitate the communication, integration, and handling of HLA data in general, across platforms. Immediate benefits to these improvements also include application of corrected HLA handling in the HLA frequency generation pipeline.

Further annotation and automation has been initiated for the Gene Feature Enumeration body of services to accommodate and facilitate efficient handling of sequence-level HLA data that will be important for the evaluation of key features, ligand binding affinities and match levels between subjects, and the association

to patient transplant outcomes. In addition, one hackathon was held to bring together expertise across teams to work on common objectives needed for HLA-DPB1 expression feature mapping.

HL7 FHIR Genomics Reporting

NMDP participated in a pilot project to further develop support within the HL7 FHIR Genomics Reporting Implementation Guide (IG) for complex transplant genomic data, and to use that IG to develop tooling to convert vendor-specific HLA reports to FHIR.

A report was published summarizing the results of this pilot as part of Sync for Genes Phase 3 (https://www.healthit.gov/sites/default/files/page/2021-01/Sync-for-Genes-Phase-3-Engaging-Laboratories.pdf). Launched in 2019, Sync for Genes Phase 3 explored the use of the HL7 FHIR Genomics Reporting IG (STU1) to report genomic data generated by testing labs. The goal was to identify challenges that testing labs experience when adopting health IT standards. Solutions were also identified to facilitate broad adoption of standards by generators of genomic data. Lessons learned from the demonstration project sites informed needs for the further development of the HL7 FHIR Genomics Reporting IG (STU1).

Development of HLA Reporting FHIR Implementation Guide

The NMDP previously led the development of an HLA-specific section of the FHIR Genomics Reporting IG (http://hl7.org/fhir/uv/genomics-reporting/histocompatibility.html). While this described best practices for reporting HLA using that IG, it did not have the capability of validating FHIR resources to specifically follow those practices. In this year we constrained HL7 FHIR Genomics Reporting IG (published Nov 2019) to create a full IG specifically for HLA reporting. The HLA Reporting IG includes local extensions that were necessary to support the requirements of the highly specialized HLA use case and genomic data, and it incorporates specialized business rules that were unique to the HLA domain.

These FHIR profiles include:

- HLA Summary Report
- HLA Genotype Observation
- HLA Allele Observation
- HLA Molecular Sequence

Code systems, value-sets, extensions, and examples for HLA reporting were also developed and included in this FHIR IG. The use of these artifacts allows for computational validation of FHIR resources for reporting HLA. The first draft of this IG can be found in http://fhir.nmdp.org/ig/hla-reporting.

TARR2FHIR

In addition to developing the HLA Reporting IG described above, the NMDP collaborated with Versiti, a laboratory that provides 11% of all clinical HLA typing reports in the U.S., to implement and test tooling that would enable HLA test results to be reported in FHIR format. This tooling enables the production

and exchange of FHIR-formatted, HLA genotyping reports that contain molecular sequences, a requirement that was not supported by the FHIR Genomics IG. The availability of such tooling eliminated the need to exchange HLA data using HML as an intermediate format. Versiti uses software from GenDx for HLA sequence analysis and genotype assignment. This software can export results into their XML format called TARR. For this activity, we developed a translator tool to convert this file into a FHIR bundle that conforms to the HLA Reporting FHIR IG described above. The converter is publicly available at https://github.com/nmdp-bioinformatics/tarr2fhir.

One of the key barriers that this project addressed was the difficultly for a genetic testing lab to invest the resources required to upgrade existing software to support the FHIR standard, especially when that standard is still under active development. To overcome that challenge, the development of the translator tool allowed the lab to explore the standard and evaluate its ability to render test reports without requiring a large investment of resources or a reconfiguration of software systems. This approach could help encourage early adopters to implement FHIR because it requires developing only a translator that converts existing output to FHIR format, enabling them to test the specification and provide feedback to the FHIR development teams without significant cost to or disruption of a production pipeline.

This project also demonstrated an increase in efficiency and more accurate data representation by translating results directly into FHIR format rather than performing the multiple, sequential translations that would be necessary if existing formats were utilized. The use of intermediate formats, such as HML, would result in the loss of data and/or the introduction of ambiguities that would require the recipient of the message to make assumptions when interpreting the data. The HLA Reporting IG that was created during this pilot activity captures the test results more robustly and it eliminates the need for multiple translation steps between formats.

This pilot project identified several opportunities for further development of the FHIR specification. For example, additional support is needed to capture information about organizations that act on behalf of other organizations, which is common in transplantation scenarios where one organization reports a result on behalf of another. In addition, it is necessary to develop methods that better capture novel genomic results and parameters that support organization-specific workflows. Other parameters include identifying the typing done for recipients or donors or cord blood units (information not captured in the TARR file), as well as the relationship between donor and recipient (unrelated, mother, sibling, etc.).

Use of population genetics and machine learning to automate the donor selection process

Donor Readiness Score

Data input and model preparation is under way for exploration of a new Donor Readiness score to facilitate automation of the donor selection process. Existing inputs were recorded and mapped for system of record and new input possibilities and sources are under evaluation. Existing modeling scripts were evaluated and are prepared for transition and further research and validation planned in future quarters.

Machine Learning-based prediction of overall survival

Progress was made evaluating the use of various machine learning methods applied to the US allogeneic hematopoietic cell transplantation dataset from 2014 to 2018 to improve prediction of one-year post

transplantation Overall Survival. Table 2 summarizes the results of the performance of these machine learning models. Although the MLPClassifier performed well in training, it did not perform well in testing due to issues in overfitting. The XGB extreme gradient boosting model performed the best overall and was selected for use in modeling of overall survival prediction going forward.

Table 2: Machine learning performance summaries for models applied to 1-yr post hematopoietic cell transplantation overall survival prediction.

Model	Performance			
	Training		Testing	
	Accuracy	AUC	Accuracy	AUC
Logistic regression	0.65	0.71	0.64	0.70
AdaBoost	0.76	0.72	0.77	0.72
XGB	0.79	0.81	0.77	0.73
LightGBM	0.78	0.78	0.76	0.72
SVM	0.75	0.70	0.75	0.69
KNN	0.38	0.69	0.37	0.66
MLPClassifier	0.97	0.99	0.71	0.62
GaussianNB	0.47	0.63	0.47	0.62
BernoulliNB	0.65	0.64	0.65	0.63
DecisionTreeClassifier	0.80	0.79	0.71	0.61

Throughout the year improvements were made to the machine learning pipeline for patient overall survival outcomes following allogeneic HCT. New research into the representation and interpretation of feature importance and variable encoding were pursued. Among the top ten features of importance were patient age, Karnofsky score, median household income, time from diagnosis to transplant, cytomegalovirus serostatus, conditioning intensity, and patient pre-HCT comorbidities. The contribution of molecular matching data at different levels will be added in future models. Analyses were also performed at different stages of the patient journey and for different donor types.

Machine learning models to predict Event Free Survival

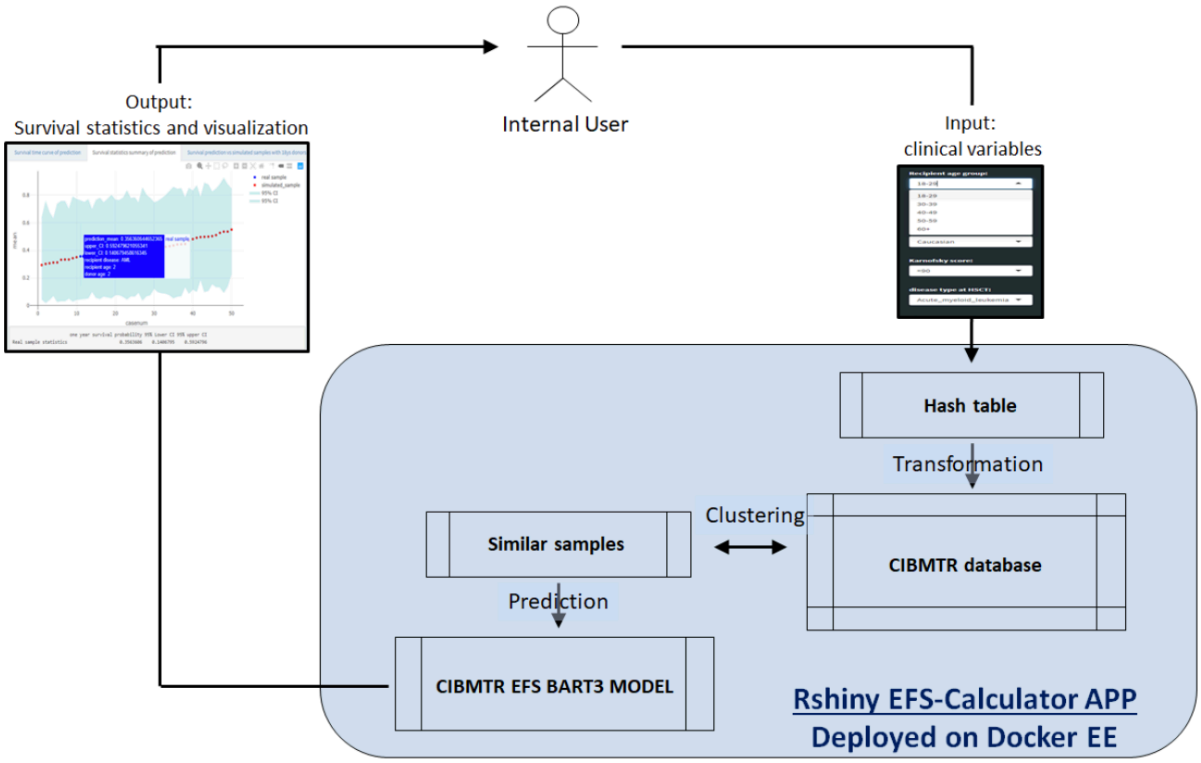
A dataset was prepared for the development of machine learning models to predict the four outcomes that constitute Event Free Survival (EFS): Death, relapse, graft rejection and moderate to severe chronic graft vs host disease. This dataset includes 9,527 matched unrelated transplants from 2016-2018 and was augmented imputation of partial genetic information. Two academic collaborators: one at the Medical

College of Wisconsin, and one at Bar Ilan University in Israel, have started working on prediction models using a variety of machine learning methods including:

- Bayesian Additive Regression Trees (BART)
- Boosted Trees (XGBoost)
- K-nearest neighbors (KNN)
- Random-Forest
- Fully connected neural network (FCNN)

A user interface prototype was created to display the existing BART-based model according to user-specified input and display simulations of patient event-free survival at 180 days post-HCT.

Figure 1 The EFS -Calculator App: A prototype tool created to calculate and display event-free survival simulations for patients after transplant. Figure 1 shows the application solution overview for this prototype.



Preliminary data analysis is in progress and additional datasets will be prepared to extend the modeling from the matched unrelated adult donor setting to:

- Mismatched unrelated adult donor transplants
- Cord blood transplants
- Matched and mismatched related transplants

C. Immunogenetic Studies in Transplantation

Evaluate HLA disparity and impact on HCT by adding selected pairs to the Donor/Recipient Pair project utilizing sample selection criteria that optimize the new data generated by the typing project.

Donor Recipient Pair Project

The study team continued to audit typing results generated in the prior grant year. To date, 8,200 of 8,600 pairs have been audited and released for use in research studies. Efforts are underway to identify pairs for testing in the current grant year with selection focused on mismatched unrelated donor transplants using novel immunomodulatory approaches to prevent GVHD. This population is critical to expanding access to donors for warfighters and civilians without an available fully-matched donor on the world-wide registries.

Full HLA Gene Matching Analysis

The manuscript for the study IB19-01: Impact of ultra-high resolution (UHR) HLA matching on the outcome of unrelated donor hematopoietic cell transplantation was published in the Journal of Clinical Oncology.

Develop and mature typing characterization of immunogenetic regions from underserved populations to improve matching and transplant outcomes for more diverse patients

A manuscript "Efficient Sequencing, Assembly, and Annotation of Human KIR Haplotypes" went to press in Frontiers in Immunology Oct 9, 2020. This study was supported under this grant and is a collaboration with industry partners to deliver a new typing protocol for the highly polymorphic KIR. During the past quarter, the method was scaled to apply it to a panel of 48 samples. Data analysis of the results is underway.

A paper "A Detailed View of KIR Haplotype Structures and Gene Families as Provided by a New Motif-Based Multiple Sequence Alignment" (https://doi.org/10.3389/fimmu.2020.58573) was published in Frontiers in Immunology on Nov 18, 2020. This paper presents data from an NMDP cohort of African American bone marrow donors and a new tool for analysis and comparison of the gene arrangements and sequencing of the KIR region. Some of the relevant finding in this study are:

- KIR haplotypes cluster by structure, not population
- KIR haplotypes from Africans or African Americans now constitute 47% of the KIR alternate references in the human genome project
- The human genome project contains more than three times as many alternative references for KIR than any part of the genome

Determine the frequency and risks associated with donor clonal hematopoiesis of indeterminate potential in HCT.

Evaluating the impact of donor clonal hematopoiesis of indeterminate potential (CHIP) on HCT outcomes

Completed the pilot analysis for the study entitled "GV19-01: Exploring the link between donor engrafted clonal hematopoiesis and adverse outcomes in allogeneic HCT: Pilot study. The study found no associations between donor CHIP and any outcomes. The lack of an association between CHIP and outcomes resulted in a reevaluation of this line of inquiry under this grant. Funds allocated for this effort have been reassigned to address the more pressing topics noted below.

Evaluation of Unrelated Donor Peripheral Blood Stem Cell (PBSC) Graft Composition and Impact on Allogeneic HCT Outcomes

While allogeneic HCT offers potentially curative therapy to patients with a variety of benign and malignant diseases, both acute and chronic GVHD continue to plague the field and often limit the longevity and quality of life for patients. The composition of PBSC grafts has been evaluated in multiple studies to attempt to discern associations between various cellular subsets and outcomes. The BMT CTN 0201 randomized trial of bone marrow versus PBSC found that PBSC grafts were associated with a higher risk of cGVHD and worse quality of life following unrelated donor HCT compared to BM. A correlative study of graft immunophenotype failed to identify any associations between PBSC graft composition and outcomes. However, the PBSC cohort included only 147 evaluable products limiting the power to evaluate various cellular subsets. The association between PBSC graft immunophenotype and outcomes remains unclear.

The primary aim of this study is to evaluate PBSC graft stem cell and associated immune cell composition and to determine at 12-months of follow-up how either the comprehensive graft cellular composition profile or specific graft composition elements influences the primary outcomes of time to neutrophil engraftment and overall survival. Secondary outcomes of interest include, but are not limited to, incidence of acute and chronic GVHD, primary disease relapse, TRM, and DFS.

Analyses include:

- Stem cell subset composition (not just number) influences time to engraftment and immune reconstitution
- Both conventional and novel unconventional T cell subsets within the graft influence GVHD, relapse, infection and immune reconstitution after transplant
- Natural killer cells have a role in transplant biology and number and phenotype in the donor graft influence GVHD, relapse, infection and immune reconstitution after transplant.
- The myeloid/antigen presenting cell compartment of the graft influences infection risk and immune reconstitution, thus play a role in long term patient outcome

The secondary aims of this study are:

- Explore potential associations of favorable PBSC graft composition features that may be predicted by analysis of peripheral blood samples at time of unrelated donor work-up such that these biomarkers could be incorporated into donor selection algorithms.
- Evaluate graft composition association with >12-month outcomes for overall survival, primary disease relapse, DFS and the incidence of late transplant effects including, but not limited to, chronic GVHD, diseases of the cardiovascular, pulmonary, and endocrine systems, dysfunction of the thyroid gland, bone diseases and the development of secondary primary malignancies.
- Establish a cohort of pre-transplant recipient and pre-donation adult unrelated donor biologic samples (whole blood, plasma, viable PBMC and viable donor PBSC graft mononuclear cells) collected prospectively from donors and patients enrolled on this study. This important biospecimen resource will be critical for the support of additional protocol team defined allogeneic HCT related correlative studies that will extend the knowledge gained from the primary study.

During the past quarter a request for quotation was distributed to the identified project testing laboratory at Roswell Park Cancer Research Institute to establish the immunophenotyping panel and finalize the sample testing strategy. Study accrual is expected to begin late next quarter.

A national framework for introducing measurable residual disease testing into the clinical care of AML patients undergoing allogeneic transplantation

While allogeneic HCT is a curative therapy for many patients with acute myeloid leukemia (AML), the risk of relapse even after achieving a cytomorphological complete remission (CR) is the most common form of treatment failure and death. Transplant-related morbidity and mortality is a major obstacle for the effective use of alloHCT, resulting in the potential under-or over-utilization of conditioning regimen intensity to prevent AML relapse. The presence of residual leukemic burden, known as measurable residual disease (MRD), prior to transplant is associated with worse outcomes after transplantation. AML MRD testing is not standardized, and no clear path to translate findings from research laboratories to clinical transplant settings currently exists.

Planning began on a project designed to address this issue by developing a coordinated national framework to 1) Allow collection of leftover initial AML diagnosis material from patients who have received alloHCT in US centers, 2) Prospectively collect samples from AML patients after unrelated donor alloHCT to determine optimal timing and method for post-alloHCT MRD monitoring and 3) Implement findings from phases 1 and 2, together with a central reference laboratory, to allow local centers to perform standardized MRD testing pre or post alloHCT. This would allow both selection of conditioning intensity, but also inform post-transplant maintenance and allow patient selection for novel clinical trials.

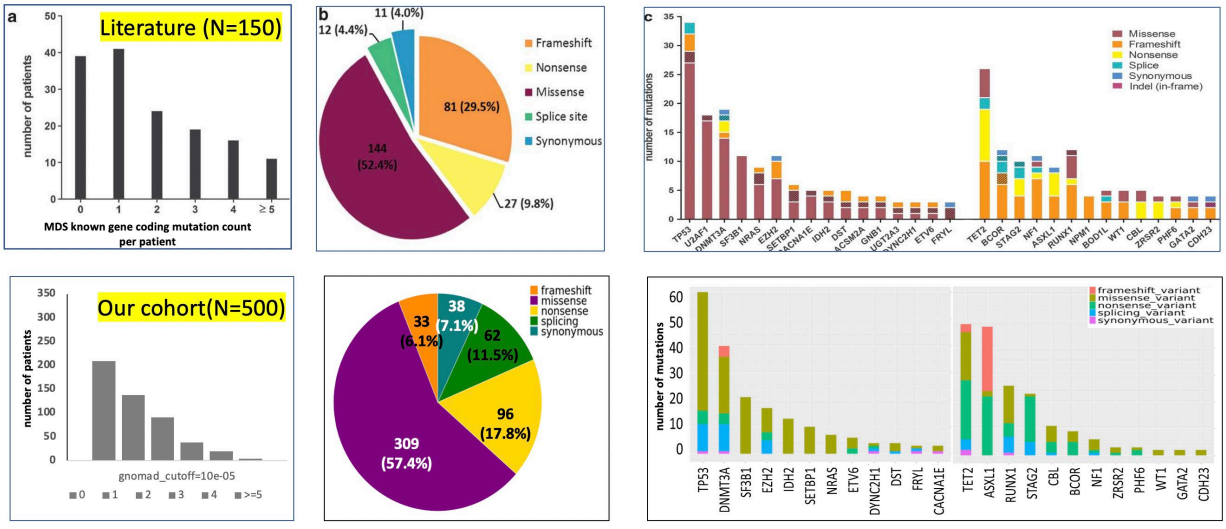
Even when patient and donor are HLA matched, post-transplant complications occur, therefore, other loci may play a role

Evaluation and identification of whole genome donor-recipient pair variation and omics patterns that affect HCT outcomes

While matching donors and transplant recipients on HLA and other well-studied loci is known to improve transplant outcomes, much remains to be explored with regards to whole genome factors and effects of mutations and other variation. We recently completed a multi-omics pilot study on a cohort of transplant recipients with Myelodysplastic Syndromes (MDS). Since then, we have followed up with the whole genome sequencing of an additional 500 pairs of donors and transplant recipients with MDS with funding from a prior Navy grant.

A manuscript was submitted from the pilot MDS study cohort and is awaiting reviews from the requested revisions. Meanwhile, somatic variation analysis has been completed on the larger cohort both for single nucleotide polymorphisms across the whole genome and for structural variants from the whole-genome sequencing data. Analysis of recurrent MDS transplant outcomes prognostic genes shows high consistency in results across cohorts as displayed in Figure 2.

Figure 2: Detection of MDS-associated genomic variants.



A subset of 27 unique mutations associated with MDS patient transplant survival and disease-free survival outcomes were selected for verification of somatic mutations in cell fractions. These mutations included coding and non-coding variants in addition to structural variant translocations, variations that less comprehensive sequence analysis strategies applied in the past were not capable of detecting. Further analyses are in progress and will be shared in future peer-reviewed publications.

D. Clinical Research in Transplantation

Conduct clinical outcomes research using the CIBMTR research database and repository.

Observational Research

- Published 38 manuscripts in peer-reviewed journals during the year.
- CIBMTR and BMTCTN presented 24 abstracts to the 2020 American Society of Hematology (ASH) annual meeting. All were accepted with 9 assigned to oral presentations and 15 as poster presentations. The study titles, presentation type and presenting author are noted below.
- CIBMTR presented 8 abstracts (5 oral and 3 poster) at the 2021 Transplant and Cellular Therapy (TCT) annual meeting. The study titles, presentation type and presenting author are noted below.

Abstracts presented at the 2020 ASH annual meeting

Study Title	***Presentation type***	***Presenting author***
A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplantation to Hypomethylating Therapy or Best Supportive Care in Patients Aged 50-75 with Advanced Myelodysplastic Syndrome: Blood and Marrow Transplant Clinical Trials Network Study 1102	**Oral**	Corey Cutler
Comparison of Outcomes after Haploidentical Relative and HLA Matched Unrelated Donor Transplantation with Post-Transplant Cyclophosphamide Containing Gvhd Prophylaxis Regimens	**Oral**	Mahasweta Gooptu
Impact of Cryopreservation of Donor Grafts on Outcomes of Allogeneic Hematopoietic Cell Transplant (HCT)	**Oral**	Jack Hsu
Bridging the Gap in Access to Transplant for Underserved Minority Patients Using Mismatched Unrelated Donors and Post-Transplant Cyclophosphamide: A National Marrow Donor Program/Be The Match (NMDP/BTM) Initiative	**Oral**	Bronwen Shaw

Study Title	*Presentation type*	*Presenting author*
Comparison of Haploidentical Donor Hematopoietic Cell Transplantation Using Post-Transplant Cyclophosphamide to Matched-Sibling, Matched-Unrelated, Mismatched-Unrelated, and Umbilical Cord Blood Donor Transplantation in Adults with Acute Lymphoblastic Leukemia: A CIBMTR Study	**Oral**	Matthew Wieduwilt
Chromosomal Aberrations in Pre-HCT Blood Samples and Outcomes after Transplantation in Patients with Myelofibrosis (Received an ASH Abstract Achievement Award)	**Oral**	Youjin Wang
Expanded Comorbidity Definitions Improve Application of the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) for Children and Young Adults with Non-Malignant Diseases Receiving Allogeneic Hematopoietic Cell Transplantation	**Oral**	Larisa Broglie
Superiority of Thiotepa-Containing Conditioning Regimens in Patients with Primary Diffuse Large B-Cell Lymphoma (DLBCL) of the Central Nervous System (CNS) Undergoing Autologous Hematopoietic Cell Transplantation (autoHCT)	**Oral**	Trent Wang
Population Distribution of GvL and GvH Minor Histocompatibility Antigens	**Oral**	Kelly Olsen
Allogeneic Hematopoietic Cell Transplantation (allo-HCT) in T-Cell Prolymphocytic Leukemia (T-PLL): An Analysis from the CIBMTR	**Poster**	Hemant Murthy
Impact of Age on the Outcomes of HCT for AML in CR1: Promising Therapy for Older Adults	**Poster**	Joseph Maakaron
Improving Donor Selection for Haploidentical Stem Cell Transplantation with Post-Transplant Cyclophosphamide through Selective HLA-Mis/Matching	**Poster**	Ephraim Fuchs
Conditioning Regimens and Outcomes after Allogeneic Hematopoietic Cell Transplant for Hyperinflammatory Inborn Errors of Immunity	**Poster**	Rebecca Marsh
Outcomes of Pediatric Patients with JMML Following Unrelated Donor Transplant: The Impact of Donor KIR Gene Content and KIR Ligand Matching	**Poster**	Hemalatha Rangarajan
Geographic Disparities of Hematopoietic Cell Transplantation in Acute Myeloid Leukemia Patients in Virginia	**Poster**	Joseph Mock
Prognostic Impact of a Modified European LeukemiaNet (ELN) Genetic Risk Stratification in Predicting Outcomes for Adults with Acute Myeloid Leukemia (AML) Undergoing Allogeneic Hematopoietic Stem Cell Transplantation (HCT). a Center for International Blood and Marrow Transplant Research (CIBMTR) Analysis for the CIBMTR Acute Leukemia Writing Committee	**Poster**	Antonio Jimenez

Study Title	*Presentation type*	*Presenting author*
Expanded Comorbidity Definitions Improve Applicability of the Hematopoietic Stem Cell Transplantation-Comorbidity Index for Children, Adolescents, and Young Adults with Hematologic Malignancies Undergoing Allogeneic Stem Cell Transplantation	**Poster**	Brian Friend
Meta-Analysis of Genome-Wide Association Studies of Acute Myeloid Leukemia (AML) Patients Identifies Variants Associated with Risk of 11q23/*KMT2A*-Translocated and Core-Binding Factor (CBF) AML and Suggests a Role for Transcription Elongation in Leukemogenesis	**Poster**	Lara Sucheston-Campbell
BMT CTN 1803: Haploidentical Natural Killer Cells (K-NK002) to Prevent Post-Transplant Relapse in AML and MDS (NK-REALM)	**Poster**	Sumithira Vasu
Associations of Clinical Outcomes after Allogeneic Hematopoietic Cell Transplantation with Number of Predicted Class II Restricted mHA	**Poster**	Othmane Jadi
Pre-Transplant Clonal Mosaicism Is Associated with Increased Relapse and Lower Survival in Acute Lymphoblastic Leukemia Patients Undergoing Allogeneic Hematopoietic Cell Transplant	**Poster**	Yiwen Wang
Non-Infectious Pulmonary Toxicity after Allogeneic Hematopoietic Cell Transplantation (HCT): A Center for International Blood and Marrow Transplant Research (CIBMTR) Study	**Poster**	Sagar Patel
Maintenance Use Is More Important Than the Choice of Bortezomib-Based Triplet Induction in Newly Diagnosed Multiple Myeloma Patients Undergoing Upfront Autologous Stem Cell Transplantation	**Poster**	Surbhi Sidana
Younger HLA-Matched Unrelated Donor Allogeneic Hematopoietic Cell Transplantation (allo-HCT) for Myelodysplastic Syndromes (MDS) Is Associated with Superior Disease-Free Survival Compared to Older HLA-Identical Sibling Donors: CIBMTR Analysis	**Poster**	Guru Murthy

Abstracts presented at the 2021 TCT annual meeting

Study Title	*Presentation Type*	*Presenting Author*
Chronic Graft-Versus-Host Disease (cGVHD), Non-Relapse Mortality (NRM) and Disease Relapse in Older Vs. Younger Adult Recipients of Matched Sibling or Unrelated Donor Allogeneic Peripheral Blood Hematopoietic Cell Transplant (alloHCT): A CIBMTR Analysis	**Poster**	Vijaya Bhatt
Hematopoietic Cell Transplant Outcomes among Medicaid and Privately Insured Patients with Sickle Cell Disease	**Poster**	Tatenda Mupfudze
Effect of Obesity on Outcomes after Alternative Donor Allogeneic Hematopoietic Stem Cell Transplant (alloHCT)	**Poster**	Mouhamed Yazan Abou-Ismail
First Late Effect in Pediatric Survivors with Chronic Graft-Versus-Host Disease Following Hematopoietic Cell Transplantation for Hematologic Malignancy	**Oral**	Catherine Lee
Impact of Chronic Graft-Versus-Host Disease on First Late Effect Among Adult Survivors of Hematopoietic Cell Transplantation: A Center for International Blood and Marrow Transplant Research (CIBMTR) Analysis	**Oral**	Catherine Lee
Utilization and Outcomes of Autologous Hematopoietic Cell Transplant in Elderly Multiple Myeloma Patients Aged 75 Years and Older in the US.	**Oral**	Pashna Munshi
HLA Class I Genotypes with Predicted Strong Binding Affinity to Mutated NPM1 Are Associated with Lower Relapse Risk in Matched Related or Unrelated Transplant for NPM1 Mutated Acute Myeloid Leukemia	**Oral**	Rupa Narayan
COVID-19 in Hematopoietic Cell Transplant Recipients: A CIBMTR Study	**Oral**	Akshay Sharma

Presentations at the 2021 TCT annual meeting

Study Title	*Presentation Type*	*Presenting Author*
Chronic Graft-Versus-Host Disease (cGVHD), Non-Relapse Mortality (NRM) and Disease Relapse in Older Vs. Younger Adult Recipients of Matched Sibling or Unrelated Donor Allogeneic Peripheral Blood Hematopoietic Cell Transplant (alloHCT): A CIBMTR Analysis	**Poster**	Vijaya Bhatt
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Impact of Chronic Graft-Versus-Host Disease on First Late Effect Among Adult Survivors of Hematopoietic Cell Transplantation: A Center for International Blood and Marrow Transplant Research (CIBMTR) Analysis	**Oral**	Catherine Lee
Utilization and Outcomes of Autologous Hematopoietic Cell Transplant in Elderly Multiple Myeloma Patients Aged 75 Years and Older in the US.	**Oral**	Pashna Munshi
HLA Class I Genotypes with Predicted Strong Binding Affinity to Mutated NPM1 Are Associated with Lower Relapse Risk in Matched Related or Unrelated Transplant for NPM1 Mutated Acute Myeloid Leukemia	**Oral**	Rupa Narayan
COVID-19 in Hematopoietic Cell Transplant Recipients: A CIBMTR Study	**Oral**	Akshay Sharma

Research data collection and systems enhancements

During the past year, CIBMTR has continued its support for electronic data submission initiatives, production FormsNet Recipient, FormsNet Donor, and AGNIS customers, as well as Data Warehouse users.

FormsNet

Continued the quarterly releases of recipient form revisions to be current with existing treatment practices, as well as implemented revisions of forms to support the cellular therapies registry. Completed in-process enhancements within Data Capture applications that include:

- The Japanese multi-language support, allowing FormsNet system and forms to display in a language other than English, was updated in January 2021 to reflect five Cellular Therapy form revisions.
- Enhancements to form capabilities to support data capture for COVID-19.
- Continued monthly security monitoring and incorporating fixes to security vulnerabilities within the month. Three vulnerabilities were fixed.

- Deployed updates to the AGNIS Mapping Tool in production that fully replaced manual processes with a semi-automated feature, producing a significant time savings (completing mappings in under 4 hours compared to 1-2 days) and increasing overall efficiency of the AGNIS mapping process while decreasing the error rate (both human and system errors).
- Enabled detailed time and date information and the automated submittal of results from a new source, EMDIS laboratories, for the Infections Disease Marker (IDM) Automation project that went live in December 2020 and which reduces the time it takes to clear a donor by automating the reporting of IDM results and improving error handling.
- Removed NMDP Donor ID (DID) from FormsNet 3 to meet Global Registration Identifier for Donors (GRID) requirements. Also updated non-NMDP Donor ID to Registry Donor ID for clarity.
- Developed an electronic process for reporting cancelled infusions in FormsNet, so that paper forms and manual system do not need to be used.
- Introduced new web-service validation for HLA data so that when data is reported on form 2005, it is validated against NMDP GRD webservice to ensure valid HLA data is entered.
- Developed and released the following data collection forms in October 2020 and January 2021.

October 2020 Release

Form	***Form Name***	***Category***
2000R6	Recipient Baseline Data	Revised recipient form
2018R6	Hodgkin and Non-Hodgkin Lymphoma (LYM) Pre-Infusion Data	Revised recipient form
2028R3	Aplastic Anemia Pre-Infusion Data	Revised recipient form
2100R6	Post-HCT Follow-Up Data	Revised recipient form
2128R3	Aplastic Anemia Post-Infusion Data	Revised recipient form
2402R6	Disease Classification	Revised recipient form

January 2021 Release

Form	*Form Name*	*Category*
2801R5	Transfer Form	Revised recipient form
2815R1	Consent Form	New recipient form
2400R8	Pre-Transplant Essential Data	Revised recipient form
3501R2	Pregnancy Form	Revised recipient form
4000R7	Pre-Cellular Therapy Essential Data	Revised recipient form
4003R4	Cellular Therapy Product	Revised recipient form
4006R5	Cellular Therapy Infusion	Revised recipient form
4100R6	Cellular Therapy Essential Data Follow Up	Revised recipient form

Electronic data submission/AGNIS

CIBMTR continued support for electronic data submission initiatives and production AGNIS customers. Effort focused on development of new AGNIS instances of CIBMTR disease specific forms, and support for CIBMTR form revision updates to existing forms. The team is in process of completing communication, educational and technical project implementations to lower AGNIS submission burden and increase the client-base including but not limited to:

- Increasing the reuse of existing AGNIS modules when supporting form revisions and other Forms Builder reports enhancements
- Investigations and pilots into the acquisition of discrete / structured data elements outside of the forms context, such as acquisition of structured laboratory data from source systems.
- Additional AGNIS reports and enhancements to the AGNIS test environments to help support external users when they are testing new AGNIS forms.

Recent AGNIS and other electronic data submission accomplishments:

- Successfully connected Oregon Health & Science University (OHSU) environment using the CIBMTR Reporting App and began exchanging:
    - Patient demographics
    - CRID assignment
- Successfully connected Duke University environment using the CIBMTR Reporting App and began exchanging:
    - Patient demographics
    - CRID assignment
    - Laboratory Observations

- The CIBMTR Reporting App was enhanced with the ability to exchange all lab results (observations), including a more focused search for observations coded to specific LOINC codes.
- Forms 4000r6, 4006r4, and 4100r5 have been released in Production for AGNIS users.
- AGNIS Auto-Population QA Testing and Development issue resolution in progress. Testing and release efforts for AGNIS maintenance release updates include:
    - 2400 - Study ID Value Added
    - 2450r5 - Updated to ensure Q50-51 can be submitted as a "multiple"
    - 2804r6 - Common validations updates
    - 2006 - Updates to ensure Non-NMDP CBU ID submissions do not automatically populate Non-NMDP unrelated donor ID values in the database.
- Forms 2402r5 and 2400r7 have been released for external testing for AGNIS users.
- Continued development of the 2815r1 for an AGNIS implementation of the Consent Tool.

Integrated Data Warehouse (IDW) and Unified Data Model (UDM)

CIBMTR continued to increase the capabilities of the IDW and UDM. Accomplishments include:

- Integrated Data Warehouse (IDW) – Operational Data Warehouse utilized for delivery of key data to stakeholders.
- Incorporated ongoing forms revisions into the warehouse.
- Added additional checks to CIBMTR's Critical Systems Dashboard to track the status of CIBMTR systems and reports.
- Implemented and enhanced processes to support CIBMTR's International CPI Processes.
- Integrated new Business Intelligence tool, Looker, to support CIBMTR Prospective Research team needs. Looker's toolsets facilitate more rapid report development for certain types of reporting.
- Enhanced pathway to capture and store survey data from CIBMTR's ePRO system.
- Completed 2020 Center Volumes Data Reporting project.
- Business Intelligence Data Sharing- Continue expansion of business intelligence tool capabilities. Adding to the existing suite of external Business Intelligence data sharing applications including the introduction of more data, dimensions and measures, stakeholder groups, and continuing data quality initiatives. Accomplishments include:
    - Introduced more data and visualizations related to Chimeric Antigen Receptor T-cells (CAR-T), enabling users to visualize CAR-T and HCT information within the same application.
    - Improvements to the user interface to maximize screen space and usability.
    - Introduction of Risk Evaluation and Mitigation Strategy (REMS) reports significantly simplifying the relationship between the centers and the CAR-T therapy vendors.
- Center Performance Analytics Dashboard
    - Executed the annual update of the data set used for this application. The update includes updated data and new data points and accompanying graphs.
- Data Operations Dashboard
    - Enhanced the DataOps self-service dashboard to include CPI (Continuous Performance Improvement) downloads for the centers.

    - Published the annual Transplant Center Specific Analysis (univariate) reports for 2020 for each center.
    - Published the annual Specific Survival Report for all centers.
- Unified Domain Model
    - Continuing the process of building this single source of truth of data that will contain high quality, validated data readily available to researchers for immunobiology, outcomes, and other types of analyses.
    - Continued delivery of monthly and quarterly CAR T-cell data sets to our Japan and pharmaceutical partners,
    - Completed the initial proof of concept for transitioning CIBMTR hematopoietic cell transplant (HCT) data from the Research Database to the Unified Domain Model
    - Began work on the next phase of transitioning HCT data from the Research Database to the Unified Domain Model. This phase is focused on Stem Cell Therapeutic Outcomes Data required for a HRSA SCTOD report.
    - Began work on adding human leukocyte antigen data (HLA) data to the Unified Domain Model

Support for the Clinical Transplant-Related Long-term Outcomes of Alternative Donor Allogeneic Transplantation (CTRL-ALT-D) trial

BMT CTN 1702: Clinical Transplant-Related Long-term Outcomes of Alternative Donor Allogeneic Transplantation (CTRL-ALT-D) trial has accrued 986 subjects through March 2021.

Publications

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* The American Society of Blood and Marrow Transplant was renamed as The American Society of Transplant and Cellular Therapy in 2020. The change led to an update to the name of the society journal from Biology of Blood and Marrow Transplant (Impact Factor: 3.9) to the Journal of Transplant and Cellular Therapy resulting in a reset of the impact factor.