Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR NON-MALIGNANT DISEASES WORKING COMMITTEE
Honolulu, HI
Friday, February 14, 2025, 1:00 – 3:00 PM HST

Co-Chair:	**Ashish Gupta, MD, MPH; University of Minnesota, Minneapolis, MN; Telephone: 612-626-2691; Email: gupta461@umn.edu**
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Co-Chair:	**Kasiani Myers, MD; Cincinnati Children's Hospital Medical Center, Cincinnati, OH Telephone: 513-636-4943; E-mail: kasiani.myers@cchmc.org**
Page Scholar:	**Brian Ball, MD; City of Hope, Duarte, CA; E-mail: brball@coh.org**
Scientific Director:	**Larisa Broglie, MD, MS; CIBMTR® (Center for International Blood and Marrow Transplant Research), Milwaukee, WI; Telephone: 414-955-4108; Email: lbroglie@mcw.edu**
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Statistician:	**Yongzi Yu, MS; CIBMTR® (Center for International Blood and Marrow Transplant Research), Milwaukee, WI; Telephone: 414-805-0700; E-mail: yoyu@mcw.edu**

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1. **Introduction**
   a. Minutes from February 2024 meeting (Attachment 1)
2. **Accrual summary** (Attachment 2)
3. **Presentations, Published or Submitted papers**
   NM20-01 Hematopoietic stem cell transplantation for Fanconi anemia (S Rotz/H Eissa). **Presented at ASH 2024.**
4. **Studies in progress** (Attachment 3)
   a. **NM15-01** Outcome of allogeneic Hematopoietic Cell Transplant (HCT) in Erythropoietic Porphyria (A Saad/H Abdel-Azim/J Bloomer). **Manuscript Preparation.**
   b. **NM17-01** Late effects after hematopoietic stem cell transplantation in patients with **HLH** (A Horne/ KS Baker/K Beutel). **Protocol Development.**
   c. **NM18-01** Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/D Wall/K Paulson). **Protocol Development.**
   d. **AC18-02** Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis (G Georges/K Sullivan). **Manuscript Preparation.**

e. **NM20-01** Hematopoietic stem cell transplantation for Fanconi anemia (S Rotz/H Eissa). **Manuscript Preparation**
f. **NM22-01** Outcomes after second or greater allogeneic stem cell transplants in patients with severe aplastic anemia: A contemporary analysis (H Rangarajan/P Satwani). **Protocol**
g **Development.**
NM23-01 Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant (A Rayes/ S Otoukesh/ R Nakamura/ M Pulsipher). **Protocol Development.**
h. **NM24-01** The outcomes of PTCY based GVHD prophylaxis for allogeneic stem cell transplantation in patients with severe aplastic anemia patients who lack a HLA-matched sibling donor (N Khaire/ L Gowda/ A Mirza/ R Kumar/ B Ball). **Protocol Development.**
i. **NM24-02** Impact of somatic mutations in aplastic anemia after allogeneic stem cell transplantation (B Ball/ R Nakamura). **Protocol Development.**

5. Proposed studies

a. **PROP 2408-01; 2409-26; 2410-217** Outcomes after Allogeneic Hematopoietic Stem Cell Transplant in Diamond-Blackfan Anemia: A contemporary CIBMTR analysis (J Koo/ N Gloude/ N Hossain/ P Munshi/ H Rangarajan/ N C Shah) (Attachment 4)
b. **PROP 2409-17; 2410-218; 2410-251** Outcomes of Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis (E Ayala/ M Iqbal/ S Mirza/ T Nishihori/ S Hosahalli Vasanna/ J Dalal) (Attachment 5)
c. **PROP 2410-11** Impact of mixed chimerism post stem cell transplantation on the long term outcome of patients with Fanconi anemia (M Ayas) (Attachment 6)
d. **PROP 2410-246** The Impact of Donor-derived Clonal Hematopoietic Mutations in children and patients less than 18 years of age following allogeneic Hematopoietic Stem Cell Transplantation for non-hematological and non-malignant hematological Conditions (M Kulasekaran/ G Hildebrandt) (Attachment 7)

Proposed studies; not accepted for consideration at this time

e. **PROP 2410-27** Effect of age, donor source and preparative regimen on outcome of hematopoietic cell transplantation in patients with Glanzmann Thrombasthenia (D Citla-Sridhar/ J Dalal). ***Dropped due to small sample size.***
f. **PROP 2410-56** Effect of mixed host-donor chimerism on graft failure/rejection after hematopoietic cell transplantation for non-malignant hematological disorders (A Lipsitt/ A Sharma). ***Dropped due to heterogeneous population and overlap with current study.***
g. **PROP 2410-160** Post-transplant cyclophosphamide vs. TCR αβ/CD19 deplete Haploidentical Transplant in Inborn Errors of Immunity: A CIBMTR Analysis (H Rangarajan/ M Albert). ***Dropped due to supplemental data needed.***
h. **PROP 2410-169** Evaluating hematopoietic cell transplant outcomes in patients with HbSC sickle cell disease: A CIBMTR Study (S Hosahalli Vasanna/ J Dalal). ***Dropped due to small sample size.***
i. **PROP 2410-192** Evaluating Outcomes of Autologous Hematopoietic Cell Transplantation in patients with Severe Systemic Sclerosis (Scleroderma) in the contemporary era (M Iqbal/ E Ayala). ***Dropped due to overlap with current study.***
j. **PROP 2410-205** Real-world gene therapy experience for sickle cell disease and comparing it with allogeneic stem cell transplant for toxicities (K Chetlapalli/ L Gowda). ***Dropped due to small sample size.***

k. **PROP 2410-212** Allogeneic transplant outcomes in Vexas Syndrome (S R Cingam/ J M Lewis-Gonzalez). ***Dropped due to small sample size.***
l. **PROP 2410-233** Evaluating outcomes of Hematopoietic Cell Transplantation in VEXAS syndrome (H Murthy/ Y Moreno Vanegas). ***Dropped due to small sample size.***
m. **PROP 2410-264** Transplant-Related Outcomes in Patients Undergoing Allogeneic Stem Cell Transplant vs. Gene Therapy for Sickle Cell Disease and Thalassemia (M Gallogly/ L Metheny). ***Dropped due to small sample size.***

6. Other business

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR NON-MALIGNANT DISEASES
San Antonio, TX
Friday, February 23, 2024, 1:00 – 3:00 PM CT

Co-Chair:	**Andrew Gennery, MD; Newcastle General Hospital/The Royal Victoria Infirmary, Newcastle, UK; E-mail: andrew.gennery@newcastle.ac.uk**
Co-Chair:	**George Georges, MD; Fred Hutchinson Cancer Research Center, Seattle, WA; E-mail: ggeorges@fredhutch.org**
Co-Chair:	**Kasiani Myers, MD; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Telephone: 513-226-4948; Email: kasiani.myers@cchmc.org**
Scientific Director:	**Larisa Broglie, MD; CIBMTR® (Center for International Blood and Marrow Transplant Research), Medical College of Wisconsin, Milwaukee, WI; Telephone: 414-955-4108; E-mail: lbroglie@mcw.edu**
Statistical Director:	**Soyoung Kim, PhD; CIBMTR® (Center for International Blood and Marrow Transplant Research), Medical College of Wisconsin, Milwaukee, WI; Telephone: 414-955-8271; E-mail: skim@mcw.edu**
Statistician:	**Yongzi Yu, MS; CIBMTR® (Center for International Blood and Marrow Transplant Research), Medical College of Wisconsin, Milwaukee, WI; E-mail: yoyu@mcw.edu**

1. Introduction

The Non-Malignant Disease Working Committee (NMWC) met on Friday, February 23, 2024, at 1:05 p.m. Attendees were asked to have their name badges scanned at the front gate for attendance purposes and members attending the meeting virtually will be part of the committee membership roster.
As scientific director of the NMWC, Dr. Kristen Page called the meeting to order and welcomed the attendees on behalf of the working committee leadership.
Dr. Page started the welcome presentation by introducing each member of the working committee leadership. Dr. Page introduced new leadership members of the non-malignant working committee, including incoming chairs Ashish Gupta and Carmen Bonfim. The committee also acknowledged the contributions of outgoing members, George and Andy, who have been with the committee for five years.
Dr. Page also introduced the working committee's new statistician, Yongzi Yu.

Dr. Brian Ball, then walked the audience through the sources of data and the difference between TED and CRF data. Additionally, cellular therapy data is collected and available.
Dr. Ball talked about the CIBMTR's Patient-Reported Outcome (PRO) data collection effort. It collects survey data from HCT/CT patients who have agreed to be contacted by CIBMTR. We are currently collecting data from adult patients at 17 partnering centers, with plans to expand to pediatric patients in the future.

Dr. Page shared that there are publicly available datasets for secondary analysis on the organization's website, including those specifically from the Non-Malignant Diseases Working Committee, and highlighted the website as a resource for additional information on the committee. Dr. Page then shared with the audience the new initiative called CIBMTR Working Committee Training and Leadership (CTL)

Program. The program is offered to early career investigators who are interested in expanding their observational research skills as well as gaining exposure to CIBMTR and its Working Committee study portfolios.

Dr. George Georges shared the goals, limitations, and expectations of the committee, the rules for working committee membership and the rules of authorship. Dr. Georges emphasized all in person attendees that had the name badges scanned at the front gate for attendance purposes and members attending the meeting virtually will be part of the committee membership roster.

2. Accrual summary

Dr. Andrew Gennery presented the accruals summary. In non-malignant diseases, the highest accrual is in acquired aplastic anemia, followed by primary immune deficiencies, hemoglobinopathies, and bone marrow failure syndrome. Most patients with inherited bone marrow are under Fanconi Anemia, with half of the patients having CRF data available. Sickle Cell Anemia, Thalassemia, and Beta Thalassemia comprised the majority of patients with hemoglobinopathies. In metabolic diseases, Hurler Syndrome, Osteopetrosis, MLD, and ALD have the highest proportions with high percentages on the CRF track. Among histiocytic diseases, the highest accrual is familial HLH. In Immune Deficiencies, the highest proportions are in SCID and CGD.

3. Presentations, Published or Submitted Papers

Dr. George Georges provided updates on the committee. The two committee publications from 2023 are below:

a. **NM16-03b:** Gale RP, Hinterberger W, Young NS, Gennery AR, Dvorak CC, Hebert KM, Heim M, Broglie L, Eapen M. What causes aplastic anaemia? ***Leukemia. 2023 Jun 1; 37(6):1191-1193. doi:10.1038/s41375-023-01892-2. Epub 2023 Apr 27. PMC10353698.***

b. **NM19-01:** Nakamura R, Patel BA, Kim S, Wong FL, Armenian SH, Groarke EM, Kessler DA, Hebert KM, Heim M, Eapen M, Young NS. Conditional survival and standardized mortality ratios of patients with severe aplastic anemia surviving at least one year after hematopoietic cell transplantation or immunosuppressive therapy. ***Haematologica. 2023 Dec 1; 108(12):3298-3307. doi:10.3324/haematol.2023.282781. Epub 2023 Jun 1. PMC10690917.***

4. Studies in progress

Dr. George Georges shared the studies in progress including two manuscripts in progress and other ongoing studies in protocol development. The following is the full list of the current status of the active committee studies:

a. **NM15-01:** Outcome of Allogeneic Hematopoietic Cell Transplant in Erythropoietic Porphyria (A Saad/ H Abdel-Azim/ J Bloomer) **Manuscript Preparation.**
b. **NM17-01:** Late effects after hematopoietic stem cell transplantation in patients with HLH (A Horne/ KS Baker/ K Beutel) **Protocol Development.**
c. **NM18-01:** Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/ D Wall/ K Paulson) **Protocol Development.**
d. **NM20-01:** Hematopoietic stem cell transplantation for Fanconi anemia (S Rotz/ H Eissa) **Manuscript Preparation.**
e. **AC18-02:** Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis (G Georges/ K Sullivan) **Manuscript Preparation.**

f. **NM22-01:** Outcomes after second or greater allogeneic stem cell transplants in patients with severe aplastic anemia: A contemporary analysis. **Protocol Development.**

g. **NM23-01:** Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant. **Protocol Development.**

5. Future/proposed studies

Dr. Kasiani Myers introduced the five proposals that were presented. Dr. Myers emphasized that each proposal had 5 minutes for presentation and ~10 minutes for discussion. Dr. Myers outlined the voting process for the attendees, explaining that voting should be based both on scientific impact and feasibility using the CIBMTR data.

a. **PROP 2309-09:** Outcomes of second allogeneic-HSCT for graft failure in patients with inherited bone marrow failure syndromes (J Koo/ A Sabulski)
The proposal was presented by Dr. Anthony Sabulski. The objective is to evaluate outcomes of children or adults with IBMFS who completed second allogeneic HSCT for primary or secondary graft failure.
   1. *A question was made that DKC and FA are 2/3 of the patients, how to divide the patients? Those questions highlighted the suggestion to consider dividing the data into two manuscripts, DKC and FA, and rest of other disease. However, there are comments made that we need to be cautious in these disorders because it is FA and approaches in Europe and US are different.*
   2. *A comment was made that if we want to have a good data, we need to join the EBMT and CIBMTR. There was a second transplant outcome in FA patients and published the data. There was a good paper about cause of death in the patients who underwent a second transplant was another graft failure event.*
   3. *A comment was made that CIBMTR does not have data on donor-specific antibodies. Dr. Page commented that she does not believe so for this disease, but we do collect it for other diseases.*

b. **PROP 2309-12:** A comparative study of the use of myeloablative or reduced-intensity/non-myeloablative conditioning regimens in hematopoietic stem cell transplant outcomes for the treatment of Telomere Biology Disorders (J Koo/ K Myers)
The proposal was presented by Dr. Jane Koo. The objective is to describe and evaluate outcomes of children and adults with TBD undergoing HSCT (OS, EFS, GVHD) comparing myeloablative and reduced intensity/non-myeloablative regimens.
   1. *A question was made that there are 60 patients had received their transplant with myeloablative conditioning. It speculated that these patients could be older. Dr. Georges explained that 68% of myeloablative patients were between 2010 and 2021 and they may be the MDS AML patients.*
   2. *A recommendation was made to look at chimerism as an outcome since we do not know the implications of having mixed chimerism in the long term. Dr. Page added that chimerism data will be restricted to CRF so there is only a subset of patients with chimerism.*
   3. *Does CIBMTR collect the gene defects data from 2000 to 2010? Dr. Page commented that we rely on center to report data correctly. We can send query to center to ask for more information about genetic testing to show the mutation. But it requires some time and not fully sure we can get the center of data.*

4. *How to define TBD for this study? Dr. Koo explained that there are some specific questions on CRF forms, such as do they have a genetically defined mutation? And questions like telomere length.*
5. *Why there are few numbers of patients in accruals for DC? Dr. Page explained that because Dr. Broglie and statistician added patients from other specify category for DKC patients.*
6. *A comment was made that the conditioning regimen classification should be reconsidered like separate RIC and non-myeloablative. Dr. Page added that CIBMTR will clean the date and make sure the assignment is appropriate for the study in terms of conditioning regimen.*

c. **PROP 2310-143:** Outcomes of allogeneic stem cell transplant for Hurler's syndrome in a contemporary era: Analyzing the Impact of conditioning regimens (H Rangarajan/ RA Arja/ J Kurtzberg/ P Satwani)

The proposal was presented by Hema Rangarajan. The objective is to estimate the 2-year OS of patients with HS who have received BuCY vs BuFlu-based conditioning regimens for allogeneic HCT.

1. *A comment was made that it should restrict the population to 2010 onwards and combing with European data.*
2. *Does CIBMTR collect PK data because it can make a difference related to graft failure? Dr. Rangarajan replied that there are some data but not sure about the amount of it.*
3. *Does the study collect enzyme data? Dr. Page commented that CIBMTR do collect the patient enzyme level, but only half of the patients have those CRF data.*
4. *Can CIBMTR provide some guides for regiments? Dr. Page responded that CIBMTR will have the planned conditioning regimen. But we will not make too many changes. We may not define a conditioning regimen that has the outcome of optimal enzyme or chimerism since it requires too much registry data.*
5. *A comment was made that newborn younger than 6 months should be selected.*

d. **PROP 2310-205:** Impact of somatic mutations in aplastic anemia (AA) after allogeneic stem cell transplantation (B Ball)

The proposal was presented by Dr. Brian Ball. The objective is to determine the impact of CH, CH variant allele fraction ≥ 10%, and CH number of mutations on OS after alloHCT in adult patients with AA and determine the impact of AA unfavorable mutations on OS after alloHCT in adult patients with AA.

1. *Does the study have any funding? Dr. Brian and his collaborators replied that yes they have funding support with several organizations such as AAMDSIF, Leukemia Research Foundation, NHLBI.*
2. *A comment was made that concerns about the challenges of interpreting data from patients dating back to 2000 due to changes in diagnosis methods.*
3. *A suggestion was made that considering collaboration with the NIH, which has a larger patient population and longitudinal data.*

e. **PROP 2310-213/2310-255:** Comparison of Haploidentical Donor transplantation using post-transplant cyclophosphamide platform versus Matched Unrelated Donor transplantation in Severe Aplastic Anemia patients who lack a Matched Sibling Donor (Revision 1) / Assess impact of Post Transplant Cyclophosphamide as GVHD prophylaxis in aplastic anemia (N Khaire/ R Kumar/L Gowda/ S Mirza)
The *proposal was presented by Dr. Niranjan Carey. The research team wants to answer those research questions: Outcomes of PTCY based SCT across donor types in real world setting (Haplo, MUD, MMUD)? Does PTCY make Haplo donor comparable to MUD? Does PTCY make MUD and MMUD SCT even safer that conventional SCT?*

1. *A question was asked about PTCY and non PTCY for haplo in table since the overall percentage is over 100%. Dr. Niranjan replied that that the percentage should be 73.7% instead of 83.1%.*
2. *A question was asked about whether to make a comparison for the earlier versus later since the tbi dosing is now recommended to 400? Dr. Niranjan replied that current table don't have the exact breakdown of the conditioning.*
3. *A question was asked about are you planning to report whether they were transplanted for relapsed versus refractory? Dr. Niranjan replied that yes, 25% of more than 40 years will be refractory, so we hope that data is available.*

6. Dropped proposed studies

a. **PROP 2309-06:** The impact of Transplant Conditioning Intensity (TCI) score on the prognosis of allogeneic hematopoietic cell transplantation for aplastic anemia and Fanconi anemia in children. *Dropped due to overlap with current ongoing study (NM 23-01).*

b. **PROP 2310-26:** Second transplantations for severe aplastic anemia. *Dropped due to overlap with current ongoing study (NM 22-01).*

c. **PROP 2310-90:** HSCT for DADA2 - Real World Experience from the CIBMTR. *Dropped due to low sample size.*

d. **PROP 2310-88:** Allogeneic Hematopoietic Stem Cell Transplant in non-SCID Rare Inborn Errors of Immunity: Leukocyte Adhesion Deficiency (LAD) Type I and III and Cartilage Hair Hypoplasia (CHH).
Dropped due to recent EBMT publication of LAD.

e. **PROP 2310-109:** Outcomes following Allogeneic Hematopoietic Stem Cell Transplant in patients with hemophagocytic lymphohistiocytosis (HLH) and oculocutaneous manifestations (Chediak Higashi Syndrome and Griscelli syndrome). *Dropped due to low sample size.*

f. **PROP 2310-126:** Pain and Physical Function post-HCT for SCD. *Dropped due to low sample size and only recent addition of questions to capture chronic pain on recent forms.*

7. Concluding Notes

a. Meeting adjourned at 2:20pm.

b. After the new proposals were presented, each participant in the meeting had an opportunity to score each proposal electronically using the Tandem app or website. Based on the voting results, current scientific merit, available number of relevant cases, and the impact of the study on the field, the following proposal was accepted to move forward to be added to the committee's active studies:

1. ***PROP 2310-213/2310-255 and PROP 2310-205:*** *The outcomes of PTCY based GVHD prophylaxis for allogeneic stem cell transplantation in patients with severe aplastic anemia patients who lack a HLA-matched sibling donor*
    a) *We had ranked this along with the other SAA study as 1a/1b. We discussed combining the two studies since the other one is dependent on funding.*
2. ***PROP 2309-12****: A comparative study of the use of myeloablative or reduced-intensity/non-myeloablative conditioning regimens in hematopoietic stem cell transplant outcomes for the treatment of Telomere Biology Disorders*
    b) *This we had tentatively ranked #2*

The following proposals were not accepted as studies:

3. ***PROP 2309-09:*** *Outcomes of second allogeneic-HSCT for graft failure in patients with inherited bone marrow failure syndromes*
4. ***PROP 2309-143:*** *Outcomes of allogeneic stem cell transplant for Hurler's syndrome in a contemporary era: Analyzing the impact of conditioning regimens.*

Working Committee Overview Plan 2024-2025		
Study Number and Title	**Current Status**	**Chairs Priority**
NM15-01: Outcome of allogeneic Hematopoietic CellTransplant (HCT) in Erythropoietic Porphyria	Manuscript Preparation	**3**
NM17-01: Late effects after hematopoietic stem celltransplantation in patients with HLH	Protocol Development	**3**
NM18-01: Impact of choice of serotherapy in pediatricstem cell transplantation for non-malignant disease	Protocol Development	**2**
AC18-02: Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for SystemicSclerosis	Manuscript Preparation	**1**
NM20-01: Hematopoietic Stem Cell Transplantation forFanconi anemia	Manuscript Preparation	**2**
NM22-01: Outcomes After Second or Greater AllogeneicStem Cell Transplants in Patients with Severe Aplastic Anemia: A Contemporary Analysis	Protocol Development	**2**
NM23-01: Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant	Protocol Development	**3**

Allogeneic Transplants for Immune Deficiencies reported to the CIBMTR from 2000-2024

Characteristic	TED N	CRF N	Total
No. of patients	4574	3192	7766
No. of centers	286	194	318
ALL subdisease (2400 Q174) - no. (%)			
acute megakaryoblastic leukemia (M7):	0 (0.0)	1 (0.0)	1 (0.0)
Immune Deficiencies (ID)	106 (2.3)	29 (0.9)	135 (1.7)
SCID ADA deficiency:	76 (1.7)	123 (3.9)	199 (2.6)
SCID absence of T and B cells:	166 (3.6)	204 (6.4)	370 (4.8)
SCID absence of T, normal B cell SCID:	153 (3.3)	245 (7.7)	398 (5.1)
Omenn syndrome:	87 (1.9)	104 (3.3)	191 (2.5)
Reticular dysgenesis:	7 (0.2)	11 (0.3)	18 (0.2)
MHC Class II Deficiency (Bare lymphocyte syndrome)	108 (2.4)	42 (1.3)	150 (1.9)
SCID, NOS:	154 (3.4)	174 (5.5)	328 (4.2)
SCID other, specify:	236 (5.2)	365 (11.4)	601 (7.7)
Wiskott Aldrich syndrome:	330 (7.2)	333 (10.4)	663 (8.5)
DiGeorge anomaly:	9 (0.2)	8 (0.3)	17 (0.2)
Chronic granulomatous disease:	421 (9.2)	361 (11.3)	782 (10.1)
Chediak-Higashi syndrome:	81 (1.8)	32 (1.0)	113 (1.5)
Common variable immunodef:	79 (1.7)	35 (1.1)	114 (1.5)
SAP deficiency (XIAP-1)	129 (2.8)	71 (2.2)	200 (2.6)
Leukocyte adhesion deficiencies:	67 (1.5)	52 (1.6)	119 (1.5)
Kostmann agranulocytosis:	127 (2.8)	57 (1.8)	184 (2.4)
Neutropenia with combined immune deficiency (MKL1 deficiency, Actin deficiency)	1 (0.0)	0 (0.0)	1 (0.0)
Cartilage hair hypoplasia:	51 (1.1)	27 (0.8)	78 (1.0)
Immune deficiency plus neutropenia	1 (0.0)	0 (0.0)	1 (0.0)
CD40 ligand deficiency:	92 (2.0)	28 (0.9)	120 (1.5)
Griscelli syndrome type 2:	26 (0.6)	13 (0.4)	39 (0.5)
Combined immunodef dis (CID), NOS:	5 (0.1)	7 (0.2)	12 (0.2)
CID other, specify:	1 (0.0)	16 (0.5)	17 (0.2)
Other immunodeficiencies, specify:	799 (17.5)	220 (6.9)	1019 (13.1)
Histiocytic disorder	29 (0.6)	7 (0.2)	36 (0.5)
FELH Familial erythrohemophagocytic lymphohis:	896 (19.6)	443 (13.9)	1339 (17.2)
Langerhans Cell Histiocytosis:	65 (1.4)	34 (1.1)	99 (1.3)
Hemophagocytosis:	112 (2.4)	82 (2.6)	194 (2.5)

Characteristic	TED N	CRF N	Total
Malignant histiocytosis:	15 (0.3)	2 (0.1)	17 (0.2)
Other histiocytic disord:	52 (1.1)	56 (1.8)	108 (1.4)
SCID, T- B+ NK-, JAK3 mutation (2411)	3 (0.1)	0 (0.0)	3 (0.0)
SCID, T- B+ NK-, IL2RG mutations, X-linked SCID (2412)	12 (0.3)	0 (0.0)	12 (0.2)
SCID, T- B- NK+, RAG 1/2 deficiency (2413)	11 (0.2)	0 (0.0)	11 (0.1)
SCID, T- B- NK+, DCLRE1C (Artemis) deficiency (2414)	4 (0.1)	1 (0.0)	5 (0.1)
SCID, T- B- NK-, NOS (2415)	1 (0.0)	1 (0.0)	2 (0.0)
DOCK8 Deficiency (2416)	9 (0.2)	0 (0.0)	9 (0.1)
ZAP-70 deficiency (2417)	1 (0.0)	0 (0.0)	1 (0.0)
NEMO Deficiency Syndrome (2418)	1 (0.0)	0 (0.0)	1 (0.0)
Activated PI3 Kinase Delta Deficiency Syndrome (APDS1 or PIK3CD) (2419)	2 (0.0)	0 (0.0)	2 (0.0)
XIAP-2 deficiency (2420)	2 (0.0)	0 (0.0)	2 (0.0)
Autoimmune Lymphoproliferative Syndrome (ALPS) (2422)	0 (0.0)	1 (0.0)	1 (0.0)
CTLA4 deficiency (2423)	1 (0.0)	1 (0.0)	2 (0.0)
IPEX, Immune Dysregulation Polyendocrinopathy, enteropathy X-linked (FOXP3 deficiency) (2424)	3 (0.1)	0 (0.0)	3 (0.0)
LRBA Deficiency (2425)	2 (0.0)	0 (0.0)	2 (0.0)
STAT3 Gain of Function (2426)	1 (0.0)	0 (0.0)	1 (0.0)
GATA2 deficiency (2427)	5 (0.1)	0 (0.0)	5 (0.1)
STAT1 Gain of Function (2428)	2 (0.0)	2 (0.1)	4 (0.1)
Familial Hemophagocytic Lymphohistiocytosis, Perforin deficiency (FHL2) (2511)	8 (0.2)	0 (0.0)	8 (0.1)
Familial Hemophagocytic Lymphohistiocytosis, UNC13D (FHL3) (2512)	9 (0.2)	1 (0.0)	10 (0.1)
Familial Hemophagocytic Lymphohistiocytosis, STX11 (FHL4) (2513)	3 (0.1)	0 (0.0)	3 (0.0)
Familial Hemophagocytic Lymphohistiocytosis, STXBP2 (FHL5) (2514)	6 (0.1)	1 (0.0)	7 (0.1)
Familial Hemophagocytic Lymphohistiocytosis, no mutation identified (2515)	2 (0.0)	2 (0.1)	4 (0.1)
Familial Hemophagocytic Lymphohistiocytosis, other mutations (2516)	5 (0.1)	0 (0.0)	5 (0.1)

Allogeneic Transplants for Inborn Errors of Metabolism reported to the CIBMTR from 2000-2024

Characteristic	TED N	CRF N	Total
No. of patients	1188	1107	2295
No. of centers	183	128	212
ALL subdisease (2400 Q174) - no. (%)			
Inherited disorders of metabolism, NOS	23 (1.9)	4 (0.4)	27 (1.2)
Osteopetrosis	242 (20.4)	135 (12.2)	377 (16.4)
Lesch-Nyhan(HGPTR defic)	0 (0.0)	2 (0.2)	2 (0.1)
Neuronal ceroid lipofuscinosis	3 (0.3)	5 (0.5)	8 (0.3)
Other inherited metabolism disorders, specify	74 (6.2)	40 (3.6)	114 (5.0)
Mucopolysaccharidosis, NOS	12 (1.0)	7 (0.6)	19 (0.8)
IH Hurler syndrome	264 (22.2)	355 (32.1)	619 (27.0)
IS Scheie syndrome	2 (0.2)	0 (0.0)	2 (0.1)
II Hunter syndrome	27 (2.3)	26 (2.3)	53 (2.3)
III Sanfillippo	7 (0.6)	26 (2.3)	33 (1.4)
IV Morquio	5 (0.4)	1 (0.1)	6 (0.3)
VI Maroteaux-Lamy	21 (1.8)	25 (2.3)	46 (2.0)
VII B-glucuronidase deficiency	2 (0.2)	1 (0.1)	3 (0.1)
V Mucopolysaccharidosis	7 (0.6)	3 (0.3)	10 (0.4)
Other mucopolysaccharidosis	1 (0.1)	3 (0.3)	4 (0.2)
Mucolipidoses, NOS	1 (0.1)	3 (0.3)	4 (0.2)
Gaucher disease	10 (0.8)	4 (0.4)	14 (0.6)
Metachromatic leukodystrophy(MLD)	104 (8.8)	86 (7.8)	190 (8.3)
Adrenoleukodystrophy(ALD)	267 (22.5)	245 (22.1)	512 (22.3)
Globoid leukodystrophy/Krabbe disease	52 (4.4)	85 (7.7)	137 (6.0)
Neiman-Pick disease	11 (0.9)	12 (1.1)	23 (1.0)
I-cell disease	9 (0.8)	15 (1.4)	24 (1.0)
Wolman disease	7 (0.6)	6 (0.5)	13 (0.6)
Glucose storage disease	1 (0.1)	0 (0.0)	1 (0.0)
Other mucolipidoses	0 (0.0)	1 (0.1)	1 (0.0)
Asparty1 glucosaminuria	3 (0.3)	1 (0.1)	4 (0.2)
Fucosidosis	4 (0.3)	5 (0.5)	9 (0.4)
Mannosidosis	29 (2.4)	11 (1.0)	40 (1.7)

Allogeneic Transplants for non-malignant disorders reported to the CIBMTR from 2000-2024

Characteristic	TED N	CRF N	Total
No. of patients	10480	8612	19092
No. of centers	461	347	496
ALL subdisease (2400 Q174) - no. (%)			
PNH Proxysmal nocturnal hemoglobinuria:	274 (2.6)	206 (2.4)	480 (2.5)
NHL diffuse, large B-cell:	0 (0.0)	1 (0.0)	1 (0.0)
Severe aplastic anemia	555 (5.3)	27 (0.3)	582 (3.0)
SAA idiopathic:	5200 (49.6)	4576 (53.1)	9776 (51.2)
SAA secondary to hepatitis:	275 (2.6)	215 (2.5)	490 (2.6)
SAA secondary to toxin-other:	71 (0.7)	92 (1.1)	163 (0.9)
Amegakaryocytosis(not congenital):	18 (0.2)	17 (0.2)	35 (0.2)
Schwachmann-Diamond:	42 (0.4)	36 (0.4)	78 (0.4)
Acquired Pure Red Cell Aplasia:	70 (0.7)	51 (0.6)	121 (0.6)
Telomere Biology Disorders including Dyskeratosis congenita (DKC1, TERT, TERC, and other mutations)	37 (0.4)	43 (0.5)	80 (0.4)
Other acquired cytopenic syndrome, specify:	175 (1.7)	159 (1.8)	334 (1.7)
Inherited abnormal of erythrocyte differ.	8 (0.1)	10 (0.1)	18 (0.1)
Fanconi anemia:	728 (6.9)	771 (9.0)	1499 (7.9)
Diamond-Blackfan anemia (pure red cell aplasia):	192 (1.8)	148 (1.7)	340 (1.8)
Acquired AA secondary to chemotherapy (313)	3 (0.0)	1 (0.0)	4 (0.0)
Acquired AA secondary to immunotherapy or immune effector cell therapy (314)	2 (0.0)	7 (0.1)	9 (0.0)
Other constitutional anemia (not THALs):	114 (1.1)	64 (0.7)	178 (0.9)
Thalassemia, NOS:	1206 (11.5)	487 (5.7)	1693 (8.9)
Type B+ Thalassemia major	6 (0.1)	1 (0.0)	7 (0.0)
Type B0 Thalassemia major	0 (0.0)	1 (0.0)	1 (0.0)
Sickle Thalassemia major:	44 (0.4)	70 (0.8)	114 (0.6)
Sickle cell anemia:	1006 (9.6)	926 (10.8)	1932 (10.1)
Beta thalassemia major:	399 (3.8)	660 (7.7)	1059 (5.5)
Other hemoglobinopathy, specify:	55 (0.5)	43 (0.5)	98 (0.5)

Autologous Transplants for autoimmune diseases reported to the CIBMTR from 2000-2024

Characteristic	TED N	CRF N	Total
No. of patients	1818	114	1932
No. of centers	123	47	137
ALL subdisease (2400 Q174) - no. (%)			
Autoimmune disease unclassified	24 (1.3)	0 (0.0)	24 (1.2)
Myasthenia gravis	21 (1.2)	1 (0.9)	22 (1.1)
Multiple sclerosis	1231 (67.7)	54 (47.4)	1285 (66.5)
Rheumatoid arthritis	9 (0.5)	3 (2.6)	12 (0.6)
Psoriatic arthritis or psoriasis	0 (0.0)	1 (0.9)	1 (0.1)
Systemic lupus erythematosis (SLE)	51 (2.8)	9 (7.9)	60 (3.1)
Polymyositis-dermatomyositis	6 (0.3)	0 (0.0)	6 (0.3)
System Scleroderma	301 (16.6)	33 (28.9)	334 (17.3)
Other vasculitis	1 (0.1)	0 (0.0)	1 (0.1)
Antiphospholipid syndrome	7 (0.4)	0 (0.0)	7 (0.4)
Other autoimmune disease, specify	26 (1.4)	0 (0.0)	26 (1.3)
Other arthritis, spec	2 (0.1)	0 (0.0)	2 (0.1)
Other Connective tissue dis	10 (0.6)	0 (0.0)	10 (0.5)
Churg-Strauss	1 (0.1)	0 (0.0)	1 (0.1)
Behcets Syndrome	4 (0.2)	0 (0.0)	4 (0.2)
JIA systemic	2 (0.1)	0 (0.0)	2 (0.1)
JIA Other, specify	1 (0.1)	0 (0.0)	1 (0.1)
Other neuro disorder, spec	56 (3.1)	7 (6.1)	63 (3.3)
ITP- Idiopathic thrombocytopenic purpura	2 (0.1)	2 (1.8)	4 (0.2)
Hemolytic anemia	1 (0.1)	0 (0.0)	1 (0.1)
Evan syndrome	1 (0.1)	0 (0.0)	1 (0.1)
Crohns disease	59 (3.2)	3 (2.6)	62 (3.2)
Other bowel disorder, spec	1 (0.1)	1 (0.9)	2 (0.1)
Diabetes mellitustype I	1 (0.1)	0 (0.0)	1 (0.1)

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A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

TO: Non-Malignant Diseases Working Committee Members

FROM: Larisa Broglie, MD, MS; Scientific Director for the Non-Malignant Diseases Working Committee

RE: Studies in Progress Summary

NM15-01: Outcome of allogeneic Hematopoietic Cell Transplant (HCT) in Erythropoietic Porphyria (A Saad/H Abdel-Azim/J Bloomer) The aim of the study is to describe the population of children or adults with Erythropoietic Porphyria who have undergone HCT and examine the outcomes post-transplant. Analysis has been completed. **Manuscript has been prepared by our EBMT colleagues and being prepared for circulation.**

NM17-01: Late effects after hematopoietic stem cell transplantation in patients with HLH (N Bhatt/KS Baker/R Marsh/J Talano) The purpose of this study is to investigate the long-term outcomes and late effects of patients with hemophagocytic lymphohistiocytosis (HLH) who are survivors after hematopoietic cell transplantation (HCT). The main hypothesis is that HLH survivors will be at risk for significant long term medical and neuropsychological late effects, which is dependent upon pre-transplant disease related factors and post-transplant chimerism. **Protocol development is underway and we are preparing chimerism data.**

NM18-01: Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/D Wall/K Paulson) The purpose of this study is to compare outcomes following allogeneic HCT for pediatric patients with non-malignant disease based on the specific serotherapy used. Post-transplant outcomes, including overall survival, acute and chronic GVHD, graft failure, and graft-failure free survival will be compared between patients given alemtuzumab and patients given ATG. The focus will be on non-malignant diseases for which transplant is most commonly used as treatment to establish as much homogeneity as possible in the comparison. **Protocol development is underway and demographics tables finalized after expanding the population and years.**

NM20-01: Hematopoietic stem cell transplantation for Fanconi anemia (S Rotz/H Eissa) This study aims to assess the impact of prognostic factors and describe the outcomes of patients undergoing transplant for Fanconi anemia, including overall survival, non-relapse mortality, and acute and chronic GVHD. Additionally, the study's goal is to obtain information on late effects including the rate of solid tumors and the association with radiation and GVHD. The study has completed analysis and the results presented at the American Society of Hematology Conference this past December. **The study is in manuscript preparation and will be submitted for publication soon.**

AC18-02: Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis (G Georges/K Sullivan) The objective of this study is to explore patient characteristics and post-transplant outcomes of patients undergoing autologous transplant for systemic sclerosis. Supplemental data collected and analysis complete. Study presented in 2021 and **Manuscript preparation is in progress.**

Aplastic Anemia Studies:
Protocol development and datafile preparation have been delayed due to data availability with the recent transition in the CIBMTR database. Protocols have been reviewed and demographics tables will be developed soon.

NM22-01: Outcomes after second or greater allogeneic stem cell transplants in patients with severe aplastic anemia: A contemporary analysis (H Rangarajan/P Satwani) This study aims to evaluate outcomes of a contemporary cohort of patients with aplastic anemia who require second allogeneic transplantation.

NM23-01: Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant (R Ahmad/O Salman). The study has 2 aims: 1) to assess rates of graft failure in patients receiving upfront alternative donor transplant, compared to those who receive transplant as salvage therapy, and 2) to assess outcomes using increased intensity regimens (Flu/Cy/ATG/TBI) for mismatched (related and unrelated) alternative donor transplantation.

NM24-01: The outcomes of PTCY based GVHD prophylaxis for allogeneic stem cell transplantation in patients with severe aplastic anemia patients who lack a HLA-matched sibling donor. (N Khaire/ L Gowda/ A Mirza/ R Kumar/ B Ball). The study has 2 aims: 1）: Assessing outcomes of PTCY in SAA across all donor types (Haploidentical, MUD, MMUD) 2): Comparing outcomes of haplo-PTCY transplants for SAA with MUD transplants for SAA.

NM24-02： Impact of somatic mutations in aplastic anemia after allogeneic stem cell transplantation (B Ball/ R Nakamura). The study has 2 aims: 1) To evaluate if the presence of somatic mutation detected in AA recipients is associated with overall survival after alloHCT 2) To evaluate if the presence of high-risk somatic mutations (DNMT3A, ASXL1, TP53, RUNX1, CSMD1) detected in AA recipients is associated with overall survival after alloHCT.

CIBMTR Study Proposal: Non-malignant diseases

Study Title: Outcomes after Allogeneic Hematopoietic Stem Cell Transplant in Diamond-Blackfan Anemia: A contemporary CIBMTR analysis

Principal Investigators: Jane Koo MD, Nicholas Gloude MD, Nasheed Hossain MD, Pashna Mushni MD, Hemalatha Rangarajan MD, Niketa Shah MD

1. **Research Question**

   Do the clinical outcomes for patients with Diamond-Blackfan Anemia (DBA) undergoing allogeneic hematopoetic stem cell transplant (allo-HSCT) differ based on donor source and/or conditioning regimen?

2. **Research Hypothesis**

   Advancements in allogeneic hematopoietic stem cell transplantation (HSCT), including the use of alternative donors and optimized conditioning regimens, have improved outcomes for patients with DBA. We *hypothesize* that overall survival (OS) has increased over time, with reduced-intensity conditioning (RIC) regimens providing comparable outcomes to myeloablative conditioning (MAC). However, event-free survival (EFS) may vary based on donor type, with matched sibling donors (MSD) offering superior outcomes and a potential hierarchy among alternative donors, favoring -matched unrelated donors (MUD) over mismatched unrelated donors (MMUD).

3. **Specific Aims**

   Primary Aims:

   - Estimate the 2-year OS for patients with DBA who have undergone an allogeneic HSCT (allo-HSCT) from 2000 to 2022

   Secondary Aims

   - **Donor Outcomes:** To assess the impact of donor type on transplant outcomes, specifically comparing MSD to alternative donors, including MUD, and MMUD.
   - **Conditioning Regimen Comparisons:** To determine whether outcomes with RIC regimens are equivalent to MAC regimens in terms of OS, EFS, and transplant-related complications.
   - **Temporal Trends:** To evaluate changes in survival outcomes (OS and EFS) over time, considering advancements in HSCT approaches and supportive care.
   - **Donor Hierarchy:** To explore and establish a hierarchy among alternative donors based on transplant-related outcomes, hypothesizing superior outcomes with MUD compared to MMUD.
   - **Complication Analysis:** To characterize the incidence and severity of transplant-related complications (e.g., graft-versus-host disease, veno-occlusive disease, graft failure, CMV reactivation based on donor type and conditioning regimen.

4. **Scientific Impact**

This study will provide critical insights into the evolving outcomes of allogeneic hematopoietic stem cell transplantation (HSCT) in DBA, highlighting the role of alternative donors and conditioning regimens. By establishing evidence-based donor hierarchies and evaluating the

efficacy of reduced-intensity conditioning, the findings will guide optimized transplant strategies, improve patient survival, and advance the standard of care for DBA and other rare bone marrow failure syndromes.

5. Scientific Justification

DBA is an inherited bone marrow failure syndrome (IBMFS) resulting from a defect of ribosomal proteins characterized by red cell aplasia, congenital anomalies and increased risk for malignancy[1-4]. Red cell transfusions and corticosteroids are the mainstay of first line treatment for the anemia observed in DBA. Approximately 80% of patients usually respond to corticosteroids with continued sufficient hemoglobin levels and achieve red blood cell (RBC) transfusion independence[1,5].

For the subset of patients who do not respond to corticosteroids, allo-HSCT is the only cure available for the hematologic manifestations of this disease[5-9]. With allo-HSCT, the OS is reported to be between 74-91%[8,10,11]. In an earlier report from the DBA registry in North America of 20 patients who underwent HSCT, MSD recipients had an 87% OS, whereas alternative donor recipients had only a 14% OS[10]. The last study from CIBMTR on outcomes of HSCT in DBA (n=61) analyzed outcomes of patients with DBA who underwent HSCT from 1984-2000[7]. The majority of patients (67%) received BM from a matched-related door. Also the 5-year OS for HLA matched sibling donor transplant was far superior (87.5%) compared to the use of alternative donor transplant (14.1%).

However, since the publication of these studies, there have been several registry-based studies from Europe that have reported improved outcomes over time especially in patients who received transplants from MUD donors. The Franco-German DBA registry data demonstrated comparable OS between MRD and MUD HSCT DBA recipients (91% vs 92%)[8]. However, in patients that underwent HSCT after the year 2000, recipients of MUD HSCT had slightly lower chronic graft-versus-host disease (cGVHD)-free survival compared to MRD HSCT recipients (87% vs. 100%, p=0.06).

Furthermore, a recent EBMT study included 106 DBA patients who underwent HSCT from 1985-2016[9]. Donor sources included matched sibling (57%), unrelated (36%) or other related donor sources (7%). Marrow was the most common graft source (68%). The 3-year OS and EFS were 84% and 81%, respectively and was similar between MSD and MUD HSCTs. An Italian study included 30 patients with DBA s who received transplant form 1990-2012[11]. Most patients (83%) were transplanted after 2000. Sixteen patients (53%) received MSD HSCTs, while the remaining 14 patients (47%) received MUD HSCTs. The 5-year OS ad TRM were 74% and 25%, respectively. Patients younger than 10 years as well as those transplanted after 2000 showed a significantly higher OS and lower risk of TRM. There was no difference between donor type was observed.

In the abovementioned studies, the majority of these transplants had been performed typically include a MAC regimen which usually includes the use of alkylators such as busulfan and cyclophosphamide. Such alkylators have an adverse side effect profile including reduced fertility and the development of secondary cancers – especially given the inherent ribosomathy driving DBA[12-16]. The use of reduced toxicity/RIC regimens have been introduced more recently in order to mitigate some of the adverse outcomes associated with myeloablative chemotherapy regimens. Studies which used reduced toxicity/RIC regimens have reported overall positive

outcomes within DBA allo-HSCT recipients[9,17-22]. More specifically, treosulfan is a less toxic form of its close relative busulfan and has been incorporated as part of a reduced intensity condition regimen for the treatment of patients with DBA and other IBMFS. Multicenter trials which used treosulfan demonstrated an overall 100% engraftment at day 100 post-HSCT with minimal toxicity. Furthermore, this study reported an overall survival rate of 90% at 2-years post-HSCT[20]. Reduced toxicity/RIC regimens have the potential to lessen transplant-related morbidity and mortality (TRM) for bone marrow failure patients; however, their use also increases the potential risk for undesirable outcomes such as graft failure necessitating subsequent transplants.

However, all of these previous studies have not fully elucidated the outcomes with alternative donor sources and conditioning regimens for patients with DBA. As varying modalities are seeing increased utilization in other disease groups, it will be of utmost importance to evaluate their outcomes in the DBA population. Given the rarity of the disease, a prospective trial would face the challenges of slow accrual and risk of patient withdrawals and in such a space a retrospective study leveraging the CIBMTRs database and statistical expertise would be well poised to full in this knowledge gap and may be practice-defining for the transplant physicians' approach to a DBA patient who does not have a fully matched related donor.

6. Patient Eligibility Population:

Inclusion Criteria:

- Patients who received allo-HSCT for DBA as diagnosed by their treating physician transplanted between 2000 and 2022

Exclusion Criteria:

- Patients with less than 2 years of follow up data.
- Recipients of non-myeloablative transplant
- Patients with incomplete data
- Non-consented patients
- Previous allogeneic or autologous stem cell transplant
- Patients with other constitutional bone marrow failure syndromes
- Patients with diagnosis of congenital sideroblastic anemia
- Patients with diagnosis of congenital dyserythropoietic anemia

1. Data Requirements

1.1. Primary objectives

- 2-year Overall Survival for patients with DBA who have undergone an allogeneic HCT from 2000 to 2022

1.2. Secondary Objectives

- Days to neutrophil and platelet engraftment
- Incidence of primary and secondary graft failure
- Incidence of CMV reactivation by day 100
- Incidence of veno-occlusive disease
- Incidence of acute GVHD, grades I-IV
- Incidence of chronic GVHD
    - Maximum grade of cGVHD
    - Maximum overall severity of cGVHD
- 2-year EFS

- Events including death from transplant-related cause, graft failure, 2nd or subsequent HSCT, Donor lymphocyte infusion or CD34 selected boost
- Graft failure free, cGVHD free Event Free survival (events being Graft failure both primary and secondary, moderate to severe chronic GVHD needing systemic therapy)

1.3. <u>Patient-related variables</u>

- Age at transplant (continuous)
- Sex: male vs. female
- Race
- Obesity (BMI > 35 kg/m2) at transplant
- Karnofsky score ≥ 90 vs < 90 vs unknown or missing
- Sorror Co-morbidity index: 0 vs 1-2 vs ≥ 3 or pediatric non-malignant CI index if available
- Time from diagnosis to HSCT
- Disease status at time of HSCT
    - Number of red blood cell transfusions received
- Baseline recipient ferritin
    - Surrogate marker for transfusional iron overload
- Baseline liver iron concentration (LIC) if available
    - As measured by liver MRI (if performed)

1.4. <u>Transplant related variables</u>

- Year of transplant
- Donor type: HLA-matched sibling, haploidentical relative, unrelated donor
- Degree of HLA match
- Sex-match, recipient-donor: female-female, female-male, male-female, male-male
- CMV status, recipient donor: -/-; -/+; +/-; +/+
- Stem cell source: bone marrow, peripheral blood, cord blood
- GVHD prophylaxis
- Conditioning regimen: myeloablative or reduced intensity. Use of TBI in conditioning - yes/no, dose of TBI if available
- ATG/Campath: yes vs. no
- Ex vivo T cell depletion (Yes no), if yes what type (CD34 selection, TCRAB, or CD45RA etc)
- Chimerism: at definied time points D 100, 1 year and 2 year and last follow up
- Organ toxicity: VOD (Yes/No) and severity status if available.
- Follow-up time (months)
- Survival status at the end of the reporting period
- Incidence of secondary malignancies post-transplant
- Cause of death if applicable

What types of Cellular Therapy data does this proposal include? Please check all that apply:

Hematopoietic Cell Transplantation (HCT)

Feasibility: Based on the 2024 meeting materials from the NMD working group, a total of 314 patients have undergone HCT for Diamond-Blackfan Anemia (DBA) between 2000 and 2022. This includes 196 patients in the TED track and 145 in the CRF track. Therefore, our proposed study on a contemporary analysis of DBA patients who have undergone

HCT would represent the largest cohort of patients reported to date.

PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS. For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Committees/wc/LateEffects/Pages/default.aspx

Not applicable

MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions. More information about our bioinformatics program can be found here: https://cibmtr.org/CIBMTR/Studies/Research-Programs/Bioinformatics-Research

Not applicable

SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions. More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index.aspx

Not applicable

NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

Not applicable

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Table 1. combined proposal 1: 2408-01/2409-26/2410-217

Characteristic	N (%)
No. of patients	272
age at transplant - no. (%)	
<10	155 (57.0)
10-18	62 (22.8)
>=18	55 (20.2)
Conditioning intensity reported by center - no. (%)	
MAC	191 (70.2)
NMA	18 (6.6)
RIC	40 (14.7)
Not MAC, either RIC or NMA	21 (7.7)
Not reported	2 (0.7)
Donor type - no. (%)	
HLA identical sibling	76 (27.9)
Haploidentical donor	20 (7.4)
Other related	9 (3.3)
Well-matched unrelated (8/8)	95 (34.9)
Partially-matched unrelated (7/8)	12 (4.4)
Multi-donor	3 (1.1)
Unrelated (matching cannot be determined)	24 (8.8)
Cord blood	33 (12.1)
Conditioning regimen - no. (%)	
TBI/Cy/Flu	26 (9.6)
TBI/Cy/Flu/TT	3 (1.1)
TBI/Mel	4 (1.5)
TBI/Flu	1 (0.4)
Bu/Cy	80 (29.4)
Bu/Mel	1 (0.4)
Flu/Bu/TT	23 (8.5)
Flu/Bu	52 (19.1)
Flu/Mel/TT	20 (7.4)
Flu/Mel	20 (7.4)
FCR	2 (0.7)
Cy/Flu	5 (1.8)
Treosulfan	30 (11.0)
Other(s)	1 (0.4)
None	1 (0.4)
Missing	3 (1.1)
Year of current transplant - no. (%)	

Characteristic	N (%)
2008	8 (2.9)
2009	12 (4.4)
2010	12 (4.4)
2011	14 (5.1)
2012	20 (7.4)
2013	21 (7.7)
2014	19 (7.0)
2015	17 (6.3)
2016	26 (9.6)
2017	11 (4.0)
2018	27 (9.9)
2019	17 (6.3)
2020	16 (5.9)
2021	20 (7.4)
2022	32 (11.8)
Follow-up of survivors - median (range)	58.7 (3.2-188.8)

CIBMTR Combined Study Proposal

Study Title: Outcomes of Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis

PI Information:

Smitha Hosahalli Vasanna MD, Jignesh Dalal MD, Sayeef Mirza MD MPH, Taiga Nishihori MD, Ernesto Ayala MD, Madiha Iqbal MD

Working group committee: non-malignant conditions

Research Question:

1. What is the impact of conditioning regimen in patients with MS undergoing auto-HCT?
2. What is the impact of auto-HCT on quality of life in patients with MS?

Research Hypothesis:

1. We hypothesize that intensity of conditioning (myeloablative vs non-myeloablative) has no impact on post auto-HCT outcomes in MS.
2. Auto-HCT leads to overall improvement in quality of life in patients with MS

Specific Aims:

1. Primary aims: Compare progression free survival after auto-HCT for patients with MS receiving myeloablative vs non-myeloablative conditioning chemotherapy

2. Secondary aims:

a. Overall Survival (OS)

b. To study impact of auto HCT in terms of “No Evidence of Disease Activity” defined by clinical (EDSS score or any equivalent functional score) and/or MRI lesions

c. To assess the impact of auto-HCT in Health-related quality of life (HRQoL) and patient related outcomes

Rationale and Background:

Multiple sclerosis (MS) is the leading cause of non-traumatic neurologic disability in young adults. It is characterized by B-cell mediated auto-antibodies causing chronic inflammatory demyelination in the brain and spinal cord. While over 80% of patients experience remission after the initial active phase, further course can be relapsing-remitting or progressive, with the relapsing form often transitioning into progressive disease overtime. Current treatments, such as disease-modifying therapies (DMTs), target the immune system to reduce relapses but require lifelong administration and have significant side effects, including infection risks and high costs.

Autologous hematopoietic stem cell transplantation (auto-HCT) is a promising alternative, using high-dose chemotherapy to reset the immune system and halt the autoimmune attack on the nervous system. Growing evidence supports auto-HCT as the standard of care for treatment of resistant relapsing-remitting MS. Auto-HCT has shown impressive results in preventing relapses, achieving long-term remission, and even reversing some disability, particularly in patients with aggressive relapsing-remitting MS. By inducing long-term remission, auto-HCT may allow patients to avoid the need for lifelong DMTs and their associated risks, offering a better quality of life. However, the intensity of conditioning regimens used in auto-HCT, especially myeloablative protocols, carries significant risks, including treatment-related morbidity and mortality. This raises the question of whether non-myeloablative conditioning could provide a safer alternative while maintaining efficacy, seeking long term remission without the toxicities of more aggressive regimens.

Analyzing CIBMTR data, Pasquini et al. (2012) reported the outcomes of 149 MS patients treated with auto-HCT. While overall survival (OS) was documented in that study, there was limited data on progression-free survival (PFS), disability scores, and outcomes for specific MS subtypes. Additionally, there are limited studies that define the impact of auto-HCT on patient related outcomes (PRO) and health related quality of life (HRQoL) in MS.

Given the increasing number of auto-HCTs for MS patients over the past decade and the lack of real-world evidence in the modern era, this study is warranted to analyze patient selection, prognostic features, and outcomes of auto-HCT, particularly concerning the intensity of conditioning regimens and PRO/HRQoL.

Significance:

Most clinical trials have primarily focused on high intensity/myeloablative conditioning regimens, with non-myeloablative regimens being less commonly studied. Additionally, these two approaches have not been prospectively evaluated in randomized clinical trials. Several retrospective studies, case series and one prospective comparative study suggest that reduced-intensity conditioning (RIC) regimens may result in low transplant-related mortality and reduced toxicity, while maintaining efficacy in the treatment of MS. Concerns persist regarding higher rates of disease recurrence compared to more aggressive myeloablative conditioning.

Additionally, studies have shown superior progression-free survival (PFS) after auto-HCT compared to currently available DMTs. While alleviating physical symptoms is often seen as reducing disease burden, the significant impact of chronic illnesses like MS on psychological and social well-being, which can lead to considerable disability, is gaining recognition. Considering this, experts now advocate for incorporating health-related quality of life (HRQoL) assessments into post-transplantation care in MS, highlighting a gap in this area.

Patient Eligibility Population:

Any patient (any age) with the diagnosis of Multiple Sclerosis who received auto-HCT.

Study Period:

January 1st, 1996 to June 30, 2024 to include all patients with at least 6 months of follow up.

Data Requirements:

1. Pre-transplant:
    - Indication for HCT: relapsing/remitting, primary progressive, or secondary progressive MS
    - Disease Modifying Therapies (DMT) prior to HCT
    - HCT-CI index
    - Mobilization: Chemotherapy based or not.
    - Mobilization: any use of G-CSF: Yes or no.
    - CD34+ selection in the graft: Yes or no.
    - CD34+ cells/kg collected/infused.
    - EDSS score in the preceding 6-12 months
    - MRI findings typically are done within 1 to 3 months before transplant.
    - Date of diagnosis and date to transplant to establish duration of disease before transplant.
2. Transplant:
    - Conditioning regimens used
    - Use of serotherapy: ATG vs alemtuzumab
    - Use of radiation: Yes or no (with or without shielding)
    - Time to engraftment
    - Progression free survival
    - EDSS or any other functional MS score data collected

- Evidence of NEDA “No evidence of disease activity”: No new neurological deficits, no new MRI lesions and no evidence of worsening disability.
- Transplant related mortality
- Regimen related toxicity
- Late outcomes hematologic disorders (MDS/AML) or secondary malignancies (if available)
- Secondary autoimmune condition in patients receiving alemtuzumab as a part of conditioning
- Need for disease modifying therapies post HCT

3. QOL:
    - PROMIS data (We understand CIBMTR adopted it recently and likely have 4-5 years of data).

Conflicts of Interest:

All other authors have no conflict of interest or relevant/non-relevant disclosures.

References:

1. Burt, Richard K., et al. "Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients with Relapsing-Remitting Multiple Sclerosis: A Randomized Clinical Trial." *JAMA*, vol. 321, no. 2, 2019, pp. 165–174. doi:10.1001/jama.2018.18743. (MIST Trial)

2. Pasquini MC et al. Transplantation for Autoimmune Diseases in North and South America: A Report of the Center for International Blood and Marrow Transplant Research. Biol Blood Marrow Transplant 2012; 18: 1471-1478. Transplant 2019; 25: 845-854.

3. Burt RK et al. Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis A Randomized Clinical Trial.

JAMA 2019; 321:165-174.

4. Atkins, H. L., et al. "Immunoablation and Autologous Haematopoietic Stem-Cell Transplantation for Aggressive Multiple Sclerosis: A Multicentre Single-Group Phase 2 Trial." *The Lancet*, vol. 388, no. 10044, 2016, pp. 576–585. doi:10.1016/S0140-6736(16)30169-6. (ASSIST Trial)

5. Nash, Richard A., et al. "High-Dose Immunosuppressive Therapy and Autologous Hematopoietic Cell Transplantation for Relapsing-Remitting Multiple Sclerosis (HALT-MS): A 3-Year Interim Report." *JAMA Neurology*, vol. 72, no. 2, 2015, pp. 159–169. doi:10.1001/jamaneurol.2014.3780. (HALT-MS Trial)

6. Mancardi, Gianluigi, et al. "Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis: A Phase II Trial." *Neurology*, vol. 84, no. 10, 2015, pp. 981–988. doi:10.1212/WNL.0000000000001329. (BEAM-MS Trial)

7. Saiz, Albert, et al. "Prospective Multicenter Study of Autologous Stem Cell Transplantation in Relapsing-Remitting and Secondary Progressive Multiple Sclerosis: The ASTIMS Trial." *JAMA Neurology*, vol. 68, no. 8, 2011, pp. 954–960. doi:10.1001/archneurol.2011.41. (ASTIMS Trial)

Table 1. combined proposal 2: 2409-17/2410-251/2410-218

Characteristic	N (%)
No. of patients	738
No. of centers	33
age at transplant - no. (%)	
<18	4 (0.5)
>=18	734 (99.5)
transplant type - Auto/Allo - no. (%)	
Autologous	738 (100)
Conditioning regimen - no. (%)	
Bu/Cy	34 (4.6)
Cy/Flu	13 (1.8)
Cy alone	596 (80.8)
BEAM	80 (10.8)
BEAM like	4 (0.5)
Other(s)	11 (1.5)
HCT-CI - no. (%)	
0	592 (80.2)
1	68 (9.2)
2	32 (4.3)
3	25 (3.4)
4	13 (1.8)
5+	2 (0.3)
Not reported	6 (0.8)
Year of current transplant - no. (%)	
2008	4 (0.5)
2009	11 (1.5)
2010	15 (2.0)
2011	7 (0.9)
2012	2 (0.3)
2013	9 (1.2)
2014	4 (0.5)
2015	38 (5.1)
2016	5 (0.7)
2017	5 (0.7)
2018	55 (7.5)
2019	116 (15.7)
2020	148 (20.1)
2021	114 (15.4)
2022	205 (27.8)

Characteristic	**N (%)**
TED or RES (RF) track determined for this event - no. (%)	
TED	718 (97.3)
CRF (RES)	20 (2.7)
Follow-up of survivors - median (range)	12.0 (0.3-173.0)

Field	Response
Proposal Number	2410-11-AYAS
Proposal Title	impact of mixed chimerism post stem cell transplantation on the long term outcome of patients with Fanconi anemia
Key Words	Fanconi anemia, mixed chimerism, stem cell transplantation
Principal Investigator #1: - First and last name, degree(s)	Mouhab Ayas
Principal Investigator #1: - Email address	mouhab@kfshrc.edu.sa
Principal Investigator #1: - Institution name	King Faisal Specialist Hospital & Research Center
Principal Investigator #1: - Academic rank	Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	-
Principal Investigator #2 (If applicable): - Email address:)	-
Principal Investigator #2 (If applicable): - Institution name:	-
Principal Investigator #2 (If applicable): - Academic rank:	-
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:	-
If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:	-
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	-
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Non-Malignant Diseases
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	Yes
If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:	I have not
RESEARCH QUESTION:	how does mixed chimerism in FA patients affect their long term outcome? Does increase the risks of graft failure? do the residual FA cells contribute to an increased risk of myelodsyplasia, leukemia after long term follow up
RESEARCH HYPOTHESIS:	Mixed chimerism in FA patients may adversely affect their outcome after long-term follow up
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	In FA patients who have mixed chimerism, we will examine the following: 1. Rate of delayed graft failure 2. Rate of leukemia, MDS or abnormal clones 3. Rate of solid tumors as a secondary objective.

Field	Response
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Currently, FA patients who have mixed chimerism, there are no recommendations as how to proceed, particularly if they have adequate hematopoiesis. If indeed, mixed chimerism is shown to increase the risk of leukemia post transplant; then recommendations like DLI, follow up bone marrow examinations could be implemented. Furthermore, there are some emerging data that Haplo-identical HCT (particularly with PT-CY) may be associated with better chances for full chimerism raising the question regarding who is the best donor for FA patients
SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.	Does Mixed Chimerism After Allogeneic Hematopoietic Cell Transplantation in Pediatric Patients With Fanconi Anemia Impact on Outcome? Ayas M, Siddiqui K, Al-Jefri A, Al-Ahmari A, Ghemlas I, Al-Saedi H, Al-Anazi A, Khan S, El-Solh H, Al-Seraihi A. Transplant Cell Ther. 2021 Mar;27(3):257.e1-257.e6. doi: 10.1016/j.jtct.2020.11.024. Epub 2020 Dec
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	1. All patients with fanconi anemia post stem cell transplant with mixed chimerism 2. Mixed chimerism could be defined as any donor cells (lymphoid or myeloid) on chimerism studies. This is subject to discussion when presented 3. A minimum follow up time of 2 years; again this is subject to discussion
Does this study include pediatric patients?	Yes
If this study does not include pediatric patients, please provide justification:	-
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Patients demographics Type of transplant Graft failure GVHD Secondary leukemias/solid tumors post transplant Follow up time Chimerism datanot
Types of cellular therapy data this proposal includes:	Hematopoietic Cell Transplantation (HCT)
PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis speci	no
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	no
SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous e	None
NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required.	none

Field	Response
REFERENCES:	Does Mixed Chimerism After Allogeneic Hematopoietic Cell Transplantation in Pediatric Patients With Fanconi Anemia Impact on Outcome? Ayas M, Siddiqui K, Al-Jefri A, Al-Ahmari A, Ghemlas I, Al-Saedi H, Al-Anazi A, Khan S, El-Solh H, Al-Seraihi A. Transplant Cell Ther. 2021 Mar;27(3):257.e1-257.e6. doi: 10.1016/j.jtct.2020.11.024. Epub 2020 Dec
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal
If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.	-

Characteristics of patients undergoing first allogeneic HCT for Fanconi anemia, 2000-2018

Characteristic	Total
No. of patients	646
No. of centers	91
Age at transplant, years - no. (%)	
Median (min-max)	9.0 (0.7-46.1)
< 1 to 9	371 (57.4)
10 to 18	220 (34.1)
18 or older	55 (8.5)
Sex - no. (%)	
Male	323 (50.0)
Female	323 (50.0)
Karnofsky score prior to HCT - no. (%)	
90-100	518 (80.2)
< 90	118 (18.3)
Not reported	10 (1.5)
Graft source - no. (%)	
Bone marrow	370 (57.3)
Peripheral blood	138 (21.4)
Umbilical cord blood	133 (20.6)
BM + PB	1 (0.2)
BM + UCB	4 (0.6)
Donor type - no. (%)	
Matched related and related CB	223 (34.5)
Haploidentical	44 (6.8)
Other mismatched related	12 (1.9)
Unrelated	244 (37.8)
Unrelated CB	123 (19.0)
GVHD prophylaxis - no. (%)	
Ex-vivo T-cell depletion	97 (15.0)
CD34 selection	82 (12.7)
PtCy + other(s)	33 (5.1)
PtCy alone	2 (0.3)
TAC + MMF +- other(s) (except PtCy)	17 (2.6)
TAC + MTX +- other(s) (except MMF, PtCy)	11 (1.7)
TAC + other(s) (except MMF, MTX, PtCy)	5 (0.8)
TAC alone	12 (1.9)
CSA + MMF +- other(s) (except PtCy,TAC)	78 (12.1)

Characteristic	Total
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	132 (20.4)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	79 (12.2)
CSA alone	91 (14.1)
Other(s)	7 (1.1)
Conditioning regimen group - no. (%)	
Fludarabine	509 (78.8)
non-Fludarabine	137 (21.2)
Year of HCT	
2000-2007	353 (54.6)
2008-2018	293 (45.4)
Any Chimerism result available	
Yes	168 (26.0)
No	250 (38.7)
Missing	228 (35.3)
Follow-up of survivors - median (range)	73.5 (2.7-241.5)

Field	Response
Proposal Number	2410-246-KULASEKARAN
Proposal Title	The Impact of Donor-derived Clonal Hematopoietic Mutations in children and patients less than 18 years of age following allogeneic Hematopoietic Stem Cell Transplantation for non-hematological and non-malignant hematological Conditions
Key Words	allogeneic, Hematopoietic, Stem Cell Transplantation, sickle cell disease, immunodeficiency diseases
Principal Investigator #1: - First and last name, degree(s)	Monika Kulasekaran, MD,
Principal Investigator #1: - Email address	mky55@health.missouri.edu
Principal Investigator #1: - Institution name	University of Missouri, Columbia
Principal Investigator #1: - Academic rank	Junior Investigator
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Gerhard Hildebrandt, MD, FACP
Principal Investigator #2 (If applicable): - Email address:)	gchhrb@health.missouri.edu
Principal Investigator #2 (If applicable): - Institution name:	University of Missouri, Columbia
Principal Investigator #2 (If applicable): - Academic rank:	Professor of Medicine
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:	Dr. Monika Kulasekaran and Dr. Gerhard Hildebrandt
If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:	Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	-
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Non-Malignant Diseases
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:	-

Field	Response
RESEARCH QUESTION:	Do younger patients under the age of 18 who undergo allogeneic transplantation for non-hematological and non-malignant conditions have an increased risk of acquiring donor-derived clonal hematopoiesis mutations?
RESEARCH HYPOTHESIS:	We hypothesize that donor-derived CH mutations are transferred into young patients during allogeneic HSCT for non-hematological conditions and that these mutations significantly contribute to late effects/long-term complications (eg: Cardiovascular, secondary MDS/AML, Clonal cytopenia) after allogeneic HCT.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Objectives: To evaluate the incidence and clinical impact of donor CH mutations in patients who have undergone HSCT for non-hematological and non-malignant hematological conditions at a young age, including but not limited to Hemoglobinopathies, Immunodeficiency diseases, Aplastic anemia, Bone marrow failure syndromes, Storage disorders. Primary Outcome: To determine the incidence of secondary MDS/AML in children and AYA patients who underwent allogeneic HSCT for non-hematological and for non-malignant hematological conditions. Secondary outcome: To correlate the presence of donor CH mutations and the development of late effects/long-term complications after allogeneic HSCT.
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Our study aims to improve donor screening protocols for clonal hematopoiesis, particularly when the donor's stem cells are used to treat young and adolescent/young adult (AYA) patients.

Field	Response
SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.	The prevalence of clonal hematopoietic (CH) mutations increases with age, reaching as high as 20% in older populations. Research indicates that donor CH mutations can be transferred to recipients during allogeneic hematopoietic stem cell transplantation (HSCT) and may influence graft-versus-host disease (GVHD) and engraftment outcomes. Currently, there are no clear guidelines for screening donors for CH mutations, particularly in young patients undergoing HSCT from matched siblings or haploidentical, unmatched donors. While congenital condition donors are screened for disease-related mutations, the implications of CH mutations remain underexplored. In clonal hematopoiesis genetically altered clones dominantly expand, which can lead to ineffective hematopoiesis and can be considered a premalignant condition. Premalignant clonal cytopenia carries the risk of progression to myeloid neoplasm. Commonly involved pathways are epigenetic regulators (DNMT3A, TET2, IDH1, IDH2), chromatin modifiers (KDM6A, PHF6, ASXL1), RNA splicing (SF3B1, SRSF2, U2AF1, ZRSR2), genes involved in DNA repair (TP53, PPM1D, ATM), signaling (JAK2, GNAS, GNB1, CBL, KIT, PTEN) and transcription regulation (RUNX1, BCOR, BCORL). Among these variants, TP53, IDH1 and, IDH2 carries high risk of progression to myeloid malignancy. DNMT3A mutations are the most commonly noted mutations in individuals over 40 years old. Among young patients who receive HSCT from donors with CH mutations, there is a potential risk for these mutations to engraft in the recipient. Such mutations may lead not only to hematological conditions like secondary myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) but also independently increase the risk of cardiovascular diseases and thrombosis. Given that young recipients with non-hematological conditions often have a life expectancy greater than 10 years, the likelihood of complications arising from CH mutations becomes a significant concern. These can be initial steps to propose screening for CH mutations in donors.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion criteria: - Age < 18 years - Patients with Nonmalignant conditions who underwent allogeneic HSCT between 2015 and 2024 - Diagnoses included are Hemoglobinopathies, Sickle cell disease, thalassemia Immunodeficiency diseases, Aplastic anemia, Bone marrow failure syndromes, and Storage disorders. Exclusion criteria: - Patients who underwent HSTC for Malignant conditions (ALL, AML, Juvenile myelomonocytic leukemia)

Field	Response
Does this study include pediatric patients?	Yes
If this study does not include pediatric patients, please provide justification:	-

Field	Response
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Recipient related - Age at allogenic HCT - Gender: Male vs. Female - Ethnicity: Caucasian, Hispanic, African American, Asian Pacific Islander - Performance Status: Karnofsky score (³90% vs. 80-80% vs. <80%) for adults HSCT variables: Type of HCT (allogenic related HCT, allogenic unrelated HCT, alternative donor source (haplo / cord blood)) - Product type (bone marrow, peripheral blood stem cell, cord blood) - Degree of donor/recipient match (8/8 matched sibling, 8/8 matched unrelated donor, 7/8 or less mismatched unrelated donor, haploidentical donor, cord blood donor - Conditioning regimen (myeloablative, RIC, non-myeloablative (mini) and regimen type/drugs) - GVHD prophylaxis: - Calcineurin inhibitor (CNI) plus mini MTX - CNI plus MMF - Post-transplant cyclophosphamide plus CNI plus MMF - ATG yes/no - Campath yes/no - TBI yes/no - TBI dose - Donor gender - Donor age - Donor and Patient CMV serostatus - Donor blood group - Donor CH mutation analysis based on donor blood sample availability - Donor / Patient gender mismatch: male into female/female into female/female into male/male into male) - Presence of donor HLA-directed antibodies for HLA mismatched donor/recipient pairs - Post-allo transplant maintenance y/n - Post-allo transplant donor lymphocyte infusion y/n Disease-related: - Pre-transplant molecular mutations if available - Post-transplant molecular mutations if available - Indication for transplant - Pretransplant cardiovascular condition (Ejection fraction) - Pre transplant H/o Hypertension - Pre-transplant liver dysfunction. Post HSCT: - Acute GvHD >/= grade 2 - Acute GVHD grade 3 or grade 4 - Chronic GVHD -Limited versus extensive - NIH consensus grading criteria - mild - moderate – severe - Time to platelet engraftment - Time to neutrophil engraftment - Engraftment failure yes/no. - Donor chimerism. - Loss of Donor chimerism - Secondary AML/MDS - Time of Secondary AML/MDS - Date of last contact - Alive or dead - Cause of death
Types of cellular therapy data this proposal includes:	Hematopoietic Cell Transplantation (HCT)

Field	Response
PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis speci	-
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	-
SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous e	To gather data on donor clonal hematopoiesis (CH) mutations, we will collaborate with the Center for International Blood and Marrow Transplant Research (CIBMTR) immunology working group. Our goal is to test paired donor samples for CH mutations and correlate these findings with the development of late effects, complications, and patient outcomes. The University of Missouri will provide funding to facilitate this donor testing. This proposal represents an initial step toward understanding donor CH mutations as a potential factor influencing outcomes in this young patient population, which typically has a favorable long-term prognosis. We will utilize next-generation sequencing libraries prepared and enriched by the FoundationOne Heme laboratory to conduct random donor sample testing for clonal hematopoiesis. Peripheral whole blood samples from donors will be collected, stored, and tested according to established recommendations. Sequencing will be performed on the FoundationOne Heme platform, following the manufacturer's suggested protocols. My mentor and primary investigator, Dr. Hildebrant, will guide and supervise sample testing. He is a member of national and international committees, such as the Center for International Blood and Marrow Transplant Research as well as a good-standing member of the American Society of Hematology, American Society of Stem Cell Transplant and Cellular Therapy, American College of Physicians, American Society of Clinical Oncology and American Association for Cancer Research. He is actively involved in multiple preclinical studies for graft versus host disease, with a primary focus on Graft versus host disease involving lungs.
NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required.	-

Field	Response
REFERENCES:	1. Nawas MT, Schetelig J, Damm F, Levine RL, Perales MA, Giralt SA, VanDenBrink MR, Arcila ME, Zehir A, Papaemmanuil E, Klussmeier A. The clinical implications of clonal hematopoiesis in hematopoietic cell transplantation. Blood reviews. 2021 Mar 1;46:100744. 2. Steensma DP. Clinical implications of clonal hematopoiesis. InMayo Clinic Proceedings 2018 Aug 1 (Vol. 93, No. 8, pp. 1122-1130). Elsevier. 3. Gibson CJ, Kennedy JA, Nikiforow S, Kuo FC, Alyea EP, Ho V, Ritz J, Soiffer R, Antin JH, Lindsley RC. Donor-engrafted CHIP is common among stem cell transplant recipients with unexplained cytopenias. Blood, The Journal of the American Society of Hematology. 2017 Jul 6;130(1):91-4. 4. Gillis N, Padron E, Wang T, Chen K, DeVos JD, Spellman SR, Lee SJ, Kitko CL, MacMillan ML, West J, Tang YH. Pilot Study of Donor-Engrafted Clonal Hematopoiesis Evolution and Clinical Outcomes in Allogeneic Hematopoietic Cell Transplantation Recipients Using a National Registry. Transplantation and Cellular Therapy. 2023 Oct 1;29(10):640-e1.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal
If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.	-

Table 1.proposal 4: 2410-246

Characteristic	N (%)
No. of patients	1312
age at transplant - no. (%)	
<5	461 (35.1)
5-10	358 (27.3)
10-18	493 (37.6)
Autologous HSCT? (2400 Q17) - no. (%)	
Allogeneic	1312 (100)
Indicate the primary disease for which the HSCT was performed: (2400 Q173) - no. (%)	
Aplastic anemia	438 (33.4)
Inherited abnormal of erythrocyte differ.	261 (19.9)
Inherited bone marrow failure syndromes	34 (2.6)
Hemoglobinopathies	115 (8.8)
Immune Deficiencies (ID)	406 (30.9)
Inherited disorders of metabolism	58 (4.4)
conditioning intensity - no. (%)	
Myeloablative	597 (45.5)
RIC	687 (52.4)
TBD/Missing	28 (2.1)
Donor type - no. (%)	
HLA-identical sibling	424 (32.3)
Twin	2 (0.2)
Other related	230 (17.5)
8/8 matched URD	445 (33.9)
7/8 mismatched URD	129 (9.8)
<= 6/8 mismatched URD;	6 (0.5)
Multi-donor	4 (0.3)
Unrelated (matching TBD)	41 (3.1)
Cord blood	31 (2.4)
GVHD prophylaxis - no. (%)	
None	25 (1.9)
Ex-vivo T-cell depletion alone	13 (1.0)
Ex-vivo T-cell depletion + other(s)	57 (4.3)
CD34 selection alone	28 (2.1)
CD34 selection + other(s)	42 (3.2)
PtCy + other(s)	167 (12.7)
TAC + MMF +- other(s) (except PtCy)	142 (10.8)
TAC + MTX +- other(s) (except MMF,PtCy)	323 (24.6)
TAC +- other(s) (except MMF,MTX,PtCy)	34 (2.6)

Characteristic	N (%)
TAC alone	32 (2.4)
CSA + MMF +- other(s) (except PtCy,TAC)	156 (11.9)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	201 (15.3)
CSA +- other(s) (except PtCy,TAC,MMF,MTX)	41 (3.1)
CSA alone	22 (1.7)
Other	24 (1.8)
None, Twin donor	1 (0.1)
Missing	4 (0.3)
TX year - no. (%)	
2015	162 (12.3)
2016	171 (13.0)
2017	189 (14.4)
2018	192 (14.6)
2019	160 (12.2)
2020	90 (6.9)
2021	168 (12.8)
2022	180 (13.7)
URD adult donor transplant sample types available - no. (%)	
Not unreltaed donor type	690 (52.6)
Samples avaliable for both recipient and donor	622 (47.4)
Related donor transplant sample types available - no. (%)	
Not reltaed donor type	622 (47.4)
Samples avaliable for both recipient and donor	690 (52.6)
Follow-up of survivors - median (range)	25 (2-77)