2021 STATUS REPORT
GRAFT VERSUS HOST DISEASE WORKING COMMITTEE

Working Committee Leadership	
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INTRODUCTION

a. Minutes and overview plan from 2020 TCT meeting (Attachment 1)

PROPOSALS MOVING FORWARD FOR SCORING (click here to cast your score)

a. PROP 2010-58 Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation: A validation study (Joseph Pidala/ Brent Logan/ Michael Martens). (Attachment 2)

b. PROP 2010-180 Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease (Nosha Farhadfar/ John R. Wingard/ Zeina Al-Mansour/ Stephanie J. Lee). (Attachment 3)

PROPOSALS DROPPED BECAUSE THEY OVERLAP WITH EXISTING STUDIES OR ARE NOT FEASIBLE DUE TO LIMITATIONS OF AVAILABLE PATIENTS OR DATA

a. PROP 2010-61 Compare outcomes of calcineurin-inhibitor verses sirolimus- based GVHD prophylaxis among the recipients of haploidentical hematopoietic cell transplant with post-transplant cyclophosphamide (Bhagirathbhai Dholaria/ Bipin Savani). *Sample size issue.*

b. PROP 2010-90 Risk factors and outcomes of acute and chronic graft-versus-host disease in haploidentical hematopoietic cell transplantation using post-transplantation cyclophosphamide in pediatric patients (Akshay Sharma/ Neel S. Bhatt). *Sample size issue.*

c. PROP 2010-92 Comparison of post-transplant cyclophosphamide and conventional GVHD prophylaxis in 7/8 HLA-mismatched unrelated donor allogeneic stem cell transplantation (Dipenkumar Modi/ Joseph Uberti/ Bipin Savani). *Overlap with BMT CTN study 1703.*

d. PROP 2010-143 Trends in chronic graft versus host disease in recipients of allogeneic stem cell transplant recipients: a contemporary analysis (Hemalatha Rangarajan/ Prakash Satwani). *Overlap with published CIBMTR study GV06-04.*

e. PROP 2010-193 Influence of combination of ATG +Tacro +Mtx as GVHD prophylaxis in matched related donor (MRD) PB SCT (Shatha Farhan). *Sample size issue.*

f. PROP 2010-194 Risk of acute and chronic graft versus host disease in patients with hematologic malignancies treated with venetoclax – based therapies prior to allogeneic stem cell transplantation (Taha Al-Juhaishi/ Leonard C. Alasfeld/ Issa Khouri). *Sample size issue.*

g. PROP 2010-237 Influence of COVID-19 on graft-versus-host disease in allogeneic hematopoietic cell transplant recipients (Sagar S. Patel/ Hannah N. Imlay). *Follow-up data not available.*

h. PROP 2010-253 Post-transplant cyclophosphamide (PTCY) or anti-thymocyte globulin (ATG) in the prevention of graft versus host disease (GvHD) for matched (related/unrelated) and mismatched (unrelated) allogeneic hematopoietic cell transplantations (HCT) (Pashna N. Munshi, Scott D. Rowley, Medhi Hamadani). *Sample size issue.*

i. PROP 2010-264 Impact of post-transplantation cyclophosphamide (PTCy) on graft-versus-host disease and relapse after subsequent donor lymphocyte infusion (Christopher G. Kanakry/ Jennifer A. Kanakry/ Meredith J. McAdams). *Sample size issue.*

j. PROP 2010-266 The impact of female donor to male recipient (FDMR) on risk of graft-versus-host disease (GVHD) after allogenic hematopoietic stem cell transplantation regardless of HLA disparity with post-transplant cyclophosphamide as GVHD prophylaxis (Karamjeet S. Sandhu/ Monzr M. Al Malki/ Ryotaro Nakamura). *Overlap with published CIBMTR study GS15-01.*

k. PROP 2010-286 Clinical outcomes in matched related donor (MRD) allogeneic stem cell transplant (alloSCT) patients using post-transplant cyclophosphamide (PTCy) based graft versus host disease prophylaxis regimen (Naveen Yarlagadda/ Muthu Veeraputhiran/ Akash Mukherjee). *Sample size issue.*

l. PROP 2010-288 Clinical outcomes in matched unrelated donor (MUD) allogeneic stem cell transplant (alloSCT) patients using post-transplant cyclophosphamide (PTCy) based graft versus host disease prophylaxis regimen (Naveen Yarlagadda/ Muthu Veeraputhiran/ Akash Mukherjee). *Overlap with CIBMTR study GS18-01.*

m. PROP 2010-289 The effect of IBD on the incidence and severity of acute GVHD (Usama Gergis). *Sample size issue.*

n. PROP 2010-292 Chronic graft versus host disease in children: Incidence and outcomes over the past 10 years (Pooja Khandelwal/ Kirsten M. Williams/ Paul Carpenter). *Overlap with published CIBMTR study GV06-04.*

o. PROP 2010-309 Role of post-allogeneic hematopoietic cell transplant hypomethylating agents on the incidence and severity of graft-versus-host disease in patients with myelodysplastic syndrome and acute myeloid leukemia (Naveed Ali/ Leland Metheny/ Marcos de Lima). *Sample size issue.*

p. PROP 2010-336 Graft versus host disease mitigation: Lessons learned from patients with pre-existing diabetes mellitus (Lohith Gowda/ Brian Engelhardt/ Nataliya Buxbaum). *Sample size issue.*

PROPOSALS NOT ACCEPTED FOR CONSIDERATION AT THIS TIME DUE TO RELATIVE SCIENTIFIC IMPACT COMPARED TO ONGOING STUDIES AND/OR OTHER PROPOSALS

a. PROP 2010-96 Comparing patterns, outcomes and organ involvement with acute and chronic graft-versus-host disease between patients with non-malignant diseases undergoing haploidentical transplantation using post-transplantation cyclophosphamide vs. matched unrelated donor transplantation using calcineurin inhibitors (Akshay Sharma/ Neel S. Bhatt).

b. PROP 2010-259 Age-specific presentation of chronic graft-versus-host disease in ALL and AML. (Jacob Rozmus/ Kirk R. Schultz/ Geoff DE Cuvelier/ Amanda Li).

c. PROP 2010-206 Role of post-transplant cyclophosphamide in prevention of graft versus host disease in recipients of HLA-DPB1 non-permissively mismatched unrelated donor allogeneic hematopoietic cell transplantation (Brian C. Shaffer/ Amanda Blouin/ Miguel-Angel Perales).

d. PROP 2010-279 Impact of post-transplant cyclophosphamide (PTCY) based GVHD prophylaxis regimens on outcomes of 8/8 HLA-matched unrelated donor allogeneic transplantation with DPB1 mismatch (Ariel Perez/ Joseph Pidala/ Taiga Nishihori).

Though these proposals address important clinical questions, we will unfortunately not be able to take them forward to the TCT meeting. These studies are very interesting, but given the unique circumstances of this year, as well as a backlog of unfinished existing studies, the working committees were asked to select 0-2 total proposals from each committee to be considered further by the CIBMTR this year. This change from prior years significantly limited our ability to bring proposals to the meeting.

STUDIES IN PROGRESS

a. **GV17-03** Alterations in the characteristics and outcomes of GVHD following post-transplant cy for haploidentical HCT and in patients over 60 at high risk for GVHD. Status: Manuscript Preparation**.** An initial manuscript has been received and the plan is to submit for publication by July 2021.

b. **GV18-01** Comparison of late effects among allogeneic hematopoietic cell transplantation survivors with and without chronic graft-versus-host disease. Status: Manuscript Preparation. The initial results were presented at the CIBMTR Statistical Meeting in September 2020. Two abstracts were submitted for TCT. The plan is to have the manuscript prepared and submitted by July 2020.

c. **GV18-02** Comparison of antibacterial prophylaxis strategies and outcomes in allogeneic stem cell transplantation patients with acute graft vs host disease. Status: Data File Preparation. The protocol was presented at the CIBMTR Statistical Meeting in August 2020. The plan is to complete the data file and analysis by July 2021.

d. **GV18-03** Impact of chronic graft-versus-host disease on non-relapse mortality and disease relapse in transplant recipients. Status: Manuscript Preparation. The initial results were presented at the CIBMTR Statistical Meeting in September 2020. An abstract was submitted for TCT. The plan is to have the manuscript prepared and submitted by July 2021.

e. **GV19-01** Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic transplants recipients. Status: Analysis. Analysis of the sample sequencing results and clinical outcomes is underway. The plan is to finalize the analysis and have the manuscript prepared and submitted by July 2021.

f. **GV20-01** Machine learning models and clinical decision support tool for acute and chronic graft-versus-host disease in patients with acute myelogenous leukemia undergoing allogeneic transplants. Status: Protocol Development. The draft protocol was received in August 2020. The plan is to present the protocol at the CIBMTR Statistical Meeting in early Spring 2020. Following approval, the protocol will be forwarded to form a Writing Committee and the data file will be prepared for analysis by July 2021.

g. **GV20-02** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq. Status: Protocol Development. The draft protocol was received in August 2020. The plan is to present the protocol at the CIBMTR Statistical Meeting in early Spring 2020. Following approval, the protocol will be forwarded to form a Writing Committee and the data file will be prepared for analysis by July 2021.

PUBLICATIONS, SUBMITTED PAPERS, PRESENTATIONS

a. **GV17-02** Im A, Rashidi A, Wang T, Hemmer M, MacMillan ML, Pidala J, Jagasia M, Pavletic S, Majhail NS, Weisdorf D, Abdel-Azim H, Agrawal V, Al-Homsi AS, Aljurf M, Askar M, Auletta JJ, Bashey A, Beitinjaneh A, Bhatt VR, Byrne M, Cahn J-Y, Cairo M, Castillo P, Cerny J, Chhabra S, Choe H, Ciurea S, Daly A, Perez MAD, Farhadfar N, Gadalla SM, Gale R, Ganguly S, Gergis U, Hanna R, Hematti P, Herzig R, Hildebrandt GC, Lad DP, Lee C, Lehmann L, Lekakis L, Kamble RT, Kharfan-Dabaja MA, Khandelwal P, Martino R, Murthy HS, Nishihori T, O'Brien TA, Olsson RF, Patel SS, Perales M-A, Prestidge T, Qayed M, Romee R, Schoemans H, Seo S, Sharma A, Solh M, Strair R, Teshima T, Urbano-Ispizua A, van der Poel M, Vij R, Wagner JL, William B, Wirk B, Yared JA, Spellman SR, Arora M, Hamilton BK. Risk factors for graft-versus-host disease in haploidentical hematopoietic cell transplantation using post-transplant cyclophosphamide. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. 2020 Aug 1; 26(8):1459-1468. doi:10.1016/j.bbmt.2020.05.001. Epub 2020 May 17. PMC7391266.

b. **GV16-01a** Mehta RS, Holtan SG, Wang T, Hemmer MT, Spellman SR, Arora M, Couriel DR, Alousi AM, Pidala J, Abdel-Azim H, Agrawal V, Ahmed I, Al-Homsi AS, Aljurf M, Antin JH, Askar M, Auletta JJ, Bhatt VR, Chee L, Chhabra S, Daly A, DeFilipp Z, Gajewski J, Gale RP, Gergis U, Hematti P, Hildebrandt GC, Hogan WJ, Inamoto Y, Martino R, Majhail NS, Marks DI, Nishihori T, Olsson RF, Pawarode A, Diaz MA, Prestidge T, Rangarajan HG, Ringden O, Saad A, Savani BN, Schoemans H, Seo S, Schultz KR, Solh M, Spitzer T, Storek J, Teshima T, Verdonck LF, Wirk B, Yared JA, Cahn J-Y, Weisdorf DJ. Composite GRFS and CRFS outcomes after adult alternative donor HCT. Journal of Clinical Oncology. 2020 Jun 20; 38(18):2062-2076. doi:10.1200/JCO.19.00396. Epub 2020 May 4. PMC7302955.

c. **GV17-01** Investigating antibiotic exposure and risk of acute graft versus host disease in children undergoing hematopoietic stem cell transplantation for acute leukemia. *Accepted in BBMT.*

d. **GV18-01a** 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 presentation at the TCT 2021 Annual Meeting.*

e. **GV18-01b** First Late Effect in Pediatric Survivors with Chronic Graft-Versus-Host Disease Following Hematopoietic Cell Transplantation for Hematologic Malignancy. *Oral presentation at the TCT 2021 Annual Meeting.*

f. **GV18-03** 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 presentation at the TCT 2021 Annual Meeting.*

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
Orlando, FL
Saturday, February 22, 2020 2:45 – 4:45 PM

Co-Chair:	**Joseph Pidala, MD, PhD, H. Lee Moffitt Cancer Center and Research Institute; Telephone: 813-745-2556; E-mail: joseph.pidala@moffitt.org**
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1. Introduction

Dr. Joseph Pidala called the meeting to order and introduced the current GVWC leadership members and the incoming GVWC Co-Chair, Dr. Carrie Kitko, who will replace Dr. Pidala in the upcoming year. The attendees were reminded to have their badges scanned to be included in the working committee email list. Dr. Pidala discussed the goals, expectations, and limitations of the GVWC and gave an overview of the active study status. Dr. Madan Jagasia explained the voting process, how current and future studies will be prioritized, criteria that must be met in order to be considered for authorship on a manuscript. Additionally, the differences between TED and CRF sources of data were briefly reviewed. Dr. Jagasia thanked Dr. Pidala for his contributions over the last five years as part of the GVWC leadership and presented him with a gift.

2. Accrual summary

Stephen Spellman gave an overview of the CIBMTR, BMT CTN, and Chronic GVHD Consortium research sample repositories and discussed the sample usage policy.

3. Presentations, published or submitted papers

Details regarding presentations and publications were mentioned and made available to attendees as an attachment. There were 4 manuscripts that were submitted or published, and 2 presentations in national meetings.

4. Studies in progress

Dr. Pidala presented a graphic illustrating the status of current studies. There were 2 studies in the phase of manuscript preparation, one in data file preparation (sample typing) and 3 in protocol development.

5. Future/proposed studies

Drs. Pidala, Jagasia, and Margaret MacMillan led this session. Presenters were reminded to limit their presentations to 5 minutes to ensure time for discussion (5 minutes).

a. **PROP 1911-80/1911-175** Determining the optimal anti-thymocyte globulin dosing in patients with hematologic malignancies (N Sharma/L Metheny/M Byrne/M de Lima/Y Efebera)

Dr. Nidhi Sharma presented the proposal. The aim of the proposed study is to identify optimal ATG dose for myeloablative (MAC) and reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplant (RIC allo-HCT). Given the increasing use of RIC allo-HCT for treating malignant hematologic conditions, optimized dosing of ATG will have an impact across the centers in improving transplantation outcomes.

Members of the GVWC asked several questions regarding availability of the following data: timing of ATG administration, absolute lymphocyte count (ALC) at time ATG is given, and if G-CSF was given. The GVWC leadership informed them that information on timing is not available for the majority of the patients and that G-CSF information is available, but not collected specifically at the time of ATG administration. A member of the GVWC asked how the MAC and RIC categorizations are defined to which the GVWC leadership responded that the conditioning intensity classifications are based on CIBMTR standards. Two members asked about the primary endpoint of acute GVHD, since the incidence of GVHD correlates with ATG dose, and suggested changing it to disease free survival or GRFS, since ATG may impact other outcomes. Dr. Sharma agreed, but mentioned that previous studies did not show an association between ATG dose and GRFS. Another member brought up the concern about the heterogeneity of the patient population due to the multiple different donor types and graft sources included.

b. **PROP 1911-52** HLA-DQ2/DQ8 and GVHD risk in pediatric patients undergoing hematopoietic stem cell transplant (A Seif)

Dr. Alix Seif presented the proposal. The hypothesis is that HLA DQ2/8 haplotypes will have a dose-dependent protective effect against GVHD. The proposed study aims to establish the predictive value of HLA DQ2/8 haplotypes for acute and chronic GVHD in pediatric transplants and to evaluate the effect of these haplotypes on transplant outcomes. Clinical impacts of this study include the potential for targeted interventions and personalized GVHD prophylaxis.

A GWVC member asked about the possible biological mechanisms behind the association of DQ2/DQ8 and GVHD that was found in the preliminary data. Dr. Seif speculated that these HLA haplotypes may modify the microbiome and suggested a potential future project to investigate this interaction. Another member asked why the study is limited to pediatric patients; Dr. Seif responded that she would be open to expanding the population to include adult patients. An additional suggestion was to limit the study to gut GVHD.

c. **PROP 1911-81** Investigate the association of HLA-A*0101 allele expression and risk for acute cutaneous GVHD (A Markova/A Jakubowski/D Ponce)

Dr. Alina Markova presented the proposal. The hypothesis is that HLA-A*0101 expression is associated with increased risk of severe acute cutaneous GVHD. The specific aims are to investigate whether HLA-A*0101 expression is associated with increased risk of grade II-IV and III-IV cutaneous aGVHD after allo-HCT, to assess if HLA-A*0101 expression in patients has an impact on transplant-related mortality (TRM) and overall survival (OS), to determine the effect of T-cell depletion on associations between HLA-A*0101 expression and cutaneous aGVHD, TRM, OS, and to determine association between CMV, HHV6, Adenovirus, and EBV viremia and cutaneous

aGVHD onset in patients with and without HLA-A*0101. These findings would have practical implications for allogeneic transplant recipients, both in the development of prophylactic therapies to reduce their risk for cutaneous aGVHD, and of early therapeutic strategies targeting the skin in this high-risk HLA-A*01:01 population.
A GVWC member asked if the extended HLA-A*0101 haplotypes were examined in their preliminary data analysis. A member of the GVWC leadership asked how the proposed study will address non-skin GVHD and whether that would be a competing risk for their outcome of interest. Dr. Markova responded that the preliminary analysis presented did not include either the extended haplotype or non-skin GVHD and would consider those factors in the proposed study. Another member inquired about the ability to differentiate between late acute and chronic skin GVHD; one of the leadership members clarified which variables related to skin GVHD are collected on the forms.

d. **PROP 1911-252** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq (K Sandhu/J Altin/M Askar/R Nakamura)
Dr. Karamjeet Sandhu presented the proposal. The hypothesis is that the risk score derived from the MHC-PepSeq assay is associated with the incidence and severity of acute and chronic GHVD. The proposed study aims to evaluate the performance of the MHC-PepSeq model in predicting acute and chronic GVHD in recipients of allo-HCT from a 8/8 matched donor with a mismatch in HLA-DP and from a 7/8 HLA mismatched donor. This risk score could be used to personalize selection of donors and GVHD prophylaxis.
A member of the GVWC leadership asked for a description of the distribution of the risk scores from the model; Dr. Sandhu responded that preliminary data illustrating the score distribution is available, but not included in the proposal.

e. **PROP 1911-102** Machine learning models and clinical decision support tool for acute and chronic graft versus host disease (GvHD) in patients with acute myeloid leukemia (AML) undergoing allogeneic hematopoietic cell transplant (HCT) (T Kindwall-Keller/B Lobo)
Dr. Tamila Kindwall-Keller presented the proposal. The hypothesis is that pre- and post-HCT data collected for AML patients undergoing allogeneic HCT can be used in statistical and machine learning models to develop a clinical decision support tool (DST) providing more precise information regarding the likelihood of developing GvHD along with type and severity of GvHD. The proposed study aims to enhance the understanding of how clinical risks interplay with development of GVHD, improve outcomes, and enhance personalized care.
Two members of the GVWC pointed out that CIBMTR data has been analyzed extensively by traditional statistical methods and questioned the advantages of using machine learning; Dr. Kindwall-Keller responded that unlike other statistical methods, machine learning does not make any assumptions about the data and will not need to restrict to specific variables. Another member asked about grouping grade II-IV acute GVHD together as the endpoint since clinicians would be unlikely to change the transplant plan if grade II acute GVHD was predicted. Dr. Kindwall-Keller explained that it was chosen as an outcome because it is most commonly reported by current studies but is willing to include grade III-IV as an outcome as well. Another member suggested including pediatric patients and using age as a continuous variable in the machine learning model. Another member asked about type of information that would be outputted by the DST; Dr. Kindwall-Keller clarified that the model will compute a risk score based on patient specific factors that clinicians can take into consideration when comparing treatment options.

f. **PROP 1911-270** Clinical significance of pediatric late acute GVHD and chronic GVHD: why does it matter to differentiate? (T Takahashi/M MacMillan)

Dr. Takuto Takahashi presented the proposal. The hypothesis is that risk factors and outcomes of pediatric late aGVHD and cGVHD differ from each other. The proposed study aims to identify the incidence, risk factors, and presentation of late aGVHD and cGVHD and to assess non-relapse mortality, overall survival, and presentation of late aGVHD and cGVHD.
A member of the GVWC asked how the proponents will address patients who recover from late aGVHD and then develop cGVHD in the analysis; Dr. Takahashi responded that they will work with the study statisticians on the analysis plan for these patients. A leadership member raised the concern that late aGVHD patients may be misreported as having cGVHD to which another leadership member responded that clinical presentation including organ involvement at diagnosis as reported in the forms, is reviewed in detail for these patients to minimize misclassification, however, its likely that not all misclassifications can be corrected.

g. **PROP 1911-25** Influence of combination of GVHD prophylaxis and stem cell source on GRFS (S Farhan)
Dr. Shatha Farhan presented the proposal. The hypothesis is that peripheral blood stem cell source with in-vivo T-cell depletion or post-transplant cyclophosphamide (PT-Cy), used as risk adapted GVHD prophylaxis, is non-inferior to bone marrow stem cell source regarding GRFS in transplant for malignant hematological disorders. If the hypothesis is proven, this would expand the source of stem cells from unrelated donors.
A member of the GVWC leadership asked if it was reasonable to group together patients who received ATG/Campath and PT-Cy to which Dr. Farhan responded that they would be open to separating the two populations for homogeneity. Another question asked was if there were differences in any variables, aside from graft source and GVHD prophylaxis, provided in the demographics table; Dr. Farhan indicated that there were no differences.

h. **PROP 1912-01** Exploring the impact of allogeneic stem cell transplant volume on GRFS: a matched cohort study in contemporary era (R Shallis/L Gowda/A Zeidan/B Betts)
Dr. Rory Shallis presented the proposal. The hypothesis is that the outcomes of patients with AML or MDS proceeding to allo-HSCT in first complete remission at higher-volume centers will have favorable GVHD/relapse-free survival (GRFS) compared to those treated at lower-volume centers. The results of this proposed study can potentially be used to help patients choose their transplant centers, establish volume guidelines for human resource development and creating training programs, increase access to trials at low volume centers, and seek further NIH funding in expanding GVHD/infection mitigation consortium work.
A member of the GVWC asked at which time point post-transplant would GRFS be evaluated; Dr. Shallis responded that they have not yet decided on the time point but indicated that 100 days post-transplant would be one of the possibilities. This member also suggested including presence of a survivorship clinic within the center as a variable if long term outcomes will be evaluated. Several members asked if the study questions are already addressed by the center-specific outcomes report generated by the SCTOD; a leadership member clarified that this report only includes overall survival, while the proposed study will focus on GRFS. Two members raised the concern that focusing on only center volume would be too simplistic and suggested including social risk factors as well. Another member suggested including GVHD prophylaxis in the analysis.

i. **PROP 1906-03/1911-31/1911-139/1911-169/1911-196** Comparison of outcomes with post-transplant cyclophosphamide in haploidentical donor transplant versus 8/8 HLA-matched related and unrelated, and 7/8 mismatched unrelated donor allogeneic stem cell transplantation for acute leukemia and myelodysplastic syndrome (D Modi/F Socola/K Caldwell)
Dr. Dipenkumar Modi presented the proposal. The hypothesis is that clinical outcomes of patients receiving transplants from HLA-MRD, MUD, and 7/8 MMUD with post-transplant cyclophosphamide (PT-Cy) are similar to those of haploidentical donor transplants. If this

hypothesis is proven, the potential donor pool can be expanded for patients who currently do not have an available matched donor and will reduce the time required for the donor search process. A member of the GVWC questioned whether the small number of MRD, MUD, and 7/8 MMUD transplants with PT-Cy would be adequate to perform the study; Dr. Modi responded that those groups may be combined for comparison with the haploidentical donor group. Another member asked if the study could be expanded to include more diseases so that the results can be more generalizable; Dr. Modi explained that they restricted the proposal to AML, ALL, and MDS for a more homogeneous population, but is willing to include additional diseases. Another member raised the concern about sufficient follow-up for matched donor PT-Cy transplants and that it may be better to do the study at a later point; Dr. Modi disagreed and mentioned an ASH plenary comparing PT-Cy and cyclosporine use in conventional transplants.

Dropped proposed studies

Dr. Mukta Arora briefly discussed the reasons for dropping the proposals that were not accepted for presentation and emphasized that most of them could not proceed due to feasibility issues.

j. **PROP 1909-07** Matched control dataset from CIBMTR for an FDA requested phase II expansion cohort study on CD24Fc in prophylaxis of acute GVHD in myeloablative matched unrelated donor HCT. *Forwarded to CIBMTR Corporate Program.*

k. **PROP 1911-21** Use of therapeutic agents for treatment of steroid-refractory GVHD before and after FDA approval of ruxolitinib and ibrutinib. *Data for steroid refractory GVHD is unavailable.*

l. **PROP 1911-152** Is age an independent risk factor in younger age allogeneic stem cell transplant recipients with hematological malignancies (age 0.1-29.99 years) for grade II-IV acute GVHD and chronic GVHD? *Overlap with CIBMTR study GV14-02.*

m. **PROP 1911-154** Validating predictive biomarkers of aGVHD from a humanized mouse model of HSCT. *Post-transplant samples not available in CIBMTR sample repository.*

n. **PROP 1911-183** Graft-versus-host-disease (GVHD) relapse-free survival (GRFS) and chronic GVHD relapse free survival (CRFS) following haploidentical transplant for hematological malignancies: a comparison of T cell replete vs ex vivo T cell depletion approaches in a contemporary cohort of patients. *Sample size issue.*

o. **PROP 1911-212** Can calcineurin inhibitors be avoided for GVHD prophylaxis for umbilical cord transplant recipients in the era of anti-thymocyte globulin (ATG)? *Sample size issue.*

p. **PROP 1911-219** Role of post-allogeneic hematopoietic cell transplant hypomethylating agents on the incidence and severity of graft-versus-host disease in patients with myeloid neoplasms. *Sample size issue.*

q. **PROP 1911-233** Mesenchymal stem cells (MSC) as therapy for steroid refractory acute graft versus host disease (SRaGVHD) in patients undergoing allogenic stem cell transplant. *Data for steroid refractory GVHD and response to GVHD therapy is unavailable.*

r. **PROP 1911-240** Impact of cryopreservation versus fresh donor lymphocyte infusions on non-relapse and relapse mortality/morbidity. *Data on cryopreservation status is unavailable.*

s. **PROP 1911-241** Comparison of graft versus host disease (GVHD) and survival outcomes in alternate mismatched graft sources for allogeneic transplant. *Sample size issue.*

6. Other Business

Dr. Jagasia adjourned the meeting at 4:30 PM and reminded the attendees that the leadership would remain at the table for 10-15 minutes after the meeting to accept questions and comments.

After the new proposals were presented, each participant in the meeting had the opportunity to rate each proposal using paper ballots. Based on the voting results, scientific merit, available number of

relevant cases, and the impact of the study on the field, the following studies will move forward as a part the committee's research portfolio for the upcoming year:

- **PROP 1911-102** Machine learning models and clinical decision support tool for acute and chronic graft versus host disease in patients with acute myeloid leukemia undergoing allogeneic hematopoietic cell transplant (T Kindwall-Keller/B Lobo)
- **PROP 1911-252** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq (K Sandhu/J Altin/M Askar/R Nakamura)

Working Committee Overview Plan for 2020 – 2021

a. **GV18-01** Comparison of late effects among alloHCT survivors with and without cGVHD (C Lee/ D Couriel)
This study will test whether the cumulative incidence rate of late effects is greater among alloHCT survivors with cGVHD versus those without cGVHD.
We anticipate circulating the protocol to the GVWC in April 2020 and having the data file prepared for analysis by July 2020. The goal is to submit an abstract to ASH by August 2020. We expect to finalize the analysis and have the manuscript written and submitted by July 2021. 240 statistical hours have been allocated to accomplish these goals.

b. **GV18-02** Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD (W Wallis/ A Alousi/ A Gulbis)
This study will evaluate the cumulative incidence of bacterial blood stream infections in patients with aGVHD grade II-IV and compare patients between centers that give antibiotics for antibacterial prophylaxis versus those centers that do not.
We anticipate circulating the protocol to the GVWC in April 2020 and having the data file prepared for analysis by July 2020. We expect to finalize the analysis and have the manuscript written and submitted by July 2021. 200 statistical hours have been allocated to accomplish these goals.

c. **GV18-03** Impact of chronic GVHD on non-relapse mortality and disease relapse (V Bhatt/S Lee)
This study will evaluate the cumulative incidence of non-relapse mortality and relapse between patients who have cGVHD versus those without cGVHD, as well as between older versus younger patients.
We anticipate circulating the protocol to the GVWC in April 2020 and having the data file prepared for analysis by July 2020. We expect to finalize the analysis and have the manuscript written and submitted by July 2021. 310 statistical hours have been allocated to accomplish these goals.

d. **GV19-01** Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (N Gillis/ E Padron/ A Lazaryan)
This study will investigate the incidence of clonal hematopoiesis among matched sibling and unrelated donors, as well as determine if clonal hematopoiesis is associated with an increased rate of acute and chronic GVHD.
We anticipate having the analysis completed by July 2020 with the goal of submitting an abstract to ASH by August 2020. We expect to have the manuscript written and submitted by July 2021. 190 statistical hours have been allocated to accomplish these goals.

e. **GV20-01** Machine learning models and clinical decision support tool for acute and chronic GVHD in patients with AML undergoing allogeneic HCT (T Kindwall-Keller/ B Lobo)
This study aims to develop machine learning models and evaluate their efficacy in predicting the probability of a patient developing acute or chronic GVHD based on reported characteristics.
We anticipate receiving the draft protocol by July 2020 and finalizing the protocol by July 2021. 100 statistical hours have been allocated to accomplish these goals.

f. **GV20-02** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly multiplexed proteomics assay: MHC-PepSeq (K Sandhu/ J Altin/ A Medhat/ R Nakamura)
This study will evaluate the effectiveness of MHC-PepSeq derived risk scores in predicting acute and chronic GVHD in recipients of allo-HCT from 8/8 HLA matched donors with mismatch in HLA-DP and from 7/8 HLA matched donors.
We anticipate receiving the draft protocol by July 2020 and finalizing the protocol by July 2021. 100 statistical hours have been allocated to accomplish these goals.

Oversight Assignments for Working Committee Leadership (March 2020)

Carrie Kitko	**GV18-01** Comparison of late effects among alloHCT survivors with and without cGVHD **GV20-01** Machine learning models and clinical decision support tool for acute and chronic GVHD in patients with AML undergoing allogeneic HCT
Madan Jagasia	**GV18-02** Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD **GV18-03** Impact of chronic GVHD on non-relapse mortality and disease relapse
Margy MacMillan	**GV19-01** Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients **GV20-02** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly multiplexed proteomics assay: MHC-PepSeq

Study number and title	Current status	Goal with date	Total hours to complete	Total hours to goal	Hours allocated to 6/30/2020	Hours allocated 7/1/2020-6/30/2021	Total Hours allocated
GV18-01: Comparison of late effects among alloHCT survivors with and without cGVHD	Protocol development	Submitted – July 2021	240	**240**	110	130	**240**
GV18-02: Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD	Protocol development	Submitted – July 2021	200	**200**	70	130	**200**
GV18-03: Impact of chronic GVHD on non-relapse mortality and disease relapse	Protocol development	Submitted – July 2021	310	**310**	180	130	**310**
GV19-01: Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients	Data file preparation	Submitted – July 2021	190	**190**	60	130	**190**
GV20-01: Machine learning models and clinical decision support tool for acute and chronic GVHD in patients with AML undergoing allogeneic HCT	Protocol pending	Data file prep – July 2021	330	**100**	0	100	**100**
GV20-02: Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly multiplexed proteomics assay: MHC-PepSeq	Protocol pending	Data file prep – July 2021	330	**100**	0	100	**100**

Proposal: 2010-58

Title:
Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation: A validation study

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Research hypothesis:
We have previously conducted a large multi-state modeling-based analysis of immune suppression discontinuation (ISD) and ISD failure using data from the BMT CTN 0201 and 0402 trials supplemented with long-term follow up data from CIBMTR. In our current proposal, we anticipate that we can both (1) validate the findings from the prior study, and (2) characterize ISD in a broader cohort that includes alternative donor transplant recipients and other subject who were not well represented in the prior study.

Specific aims:
- **Aim 1**: Validate prediction models for ISD and ISD failure developed in our previous ISD study in the setting of matched sibling and 7-8/8 unrelated donors using either bone marrow or peripheral blood grafts.
- **Aim 2**: Explore determinants of ISD and ISD failure in a more diverse and recent cohort that will include alternative donor transplantation (<7/8 unrelated donors, umbilical cord blood, and haploidentical transplants) in addition to the matched related and 7-8/8 unrelated donor transplants included in our previous study.
- **Aim 3**: Construct and validate dynamic prediction models of ISD and ISD failure for this expanded patient population.

Scientific impact:
Allogeneic hematopoietic cell transplantation (HCT) can be curative for hematologic malignancies and disorders but is complicated by the potential occurrence of graft vs. host disease (GVHD) and need for prolonged immune suppressive (IS) therapy. In the current state, clinicians can't tailor a specific duration of IS therapy for individual patients to optimize outcome. Accordingly, IS taper and discontinuation practice is empiric and risks both GVHD emerging on attempted taper and conversely over-treatment for those that could safely liberate from IS. We have begun to address this issue through the study of clinical factors associated with ISD and ISD failure; however, validation is needed to confirm these findings. As well, our prior study did not include certain patient/disease/transplantation groups, limiting widespread application to current practice. The completion of our currently proposed project would address these needs, thereby providing a major advance in IS management after HCT.

Scientific justification:
Immune suppression discontinuation (ISD) is commonly attempted after HCT based on the expectation that immune tolerance develops and that earlier ISD will provide optimal outcome. However, the required duration of IS for individual patients is not known,[1 2-6] and clinical or biologic determinants of immune tolerance are lacking. This results in empiric ISD practice with

adverse consequences.[7,8] To address this issue, we previously conducted a multi-state modeling based analysis to examine the major outcomes of ISD and ISD failure.
Patients included in that analysis (N=827) were those originally enrolled in BMT CTN 0201 and 0402 trials using the trial data and additional long-term follow up data secured from the CIBMTR. These two trials were originally chosen for this study because they cover largely the major variables of sibling vs. unrelated donors and marrow vs. peripheral blood grafts, among other key patient, disease, and HCT variables. However, there were major gaps in this population that limited application to current practices, such as larger pediatric patient representation, alternative donor types (e.g. haploidentical, umbilical cord blood, <7/8 matched unrelated donors), the combination of marrow grafts in sibling donor transplants, and reduced intensity conditioning, among others.
In the multi-state model, there were 6 distinct health states: 1. initial immune suppression (IS)/no GVHD, 2. acute GVHD, 3. chronic GVHD, 4. off IS without GVHD, 5. resumed IS for GVHD, and 6. death/relapse/second HCT (combined absorbing state). The likelihood of being in each state over time was described using differences in Kaplan-Meier estimators for transient states and the cumulative incidence estimator for the absorbing state.[9] The likelihood of being off IS without GVHD as a function of baseline covariates was modeled using pseudo-value regression with results summarized using odds ratios (OR).[10-13] Baseline variables included patient age, disease and CIBMTR disease risk, donor-recipient HLA match, donor type (sibling, unrelated), donor-recipient gender match, graft source (bone marrow, PBSC), GVHD prophylaxis (cyclosporine/methotrexate, tacrolimus/methotrexate, tacrolimus/sirolimus), and anti-thymocyte globulin (ATG) use. For transitions from acute and chronic GVHD states to ISD, acute and chronic GVHD overall grade/score and organ-specific involvement and severity were examined. GVHD variables were assessed both as fixed covariates (value at GVHD diagnosis) and time-dependent covariates (prior history, and current state). Dynamic prediction models for a patient's likelihood of being off IS without GVHD at post-HCT horizon time points given their current status utilized landmarking supermodels with pseudo-value regression.[14]

- ISD: With a median follow up of 72 months, 20% of patients were alive and off immune suppression at 5 years (Figure 1). Peripheral blood grafts (OR=0.46, 99% CI 0.26-0.82, p<0.001) and mismatched unrelated donors (OR=0.37, 99% CI 0.14-0.97, p=0.008) were associated with lower odds of being off IS without GVHD. Increasing age and advanced disease were also associated with lower odds of being off IS without GVHD. ATG use did not impact ISD probability (OR = 1.26, 99% CI: 0.73 – 2.18, p = 0.27). In multivariable analysis, discontinuation

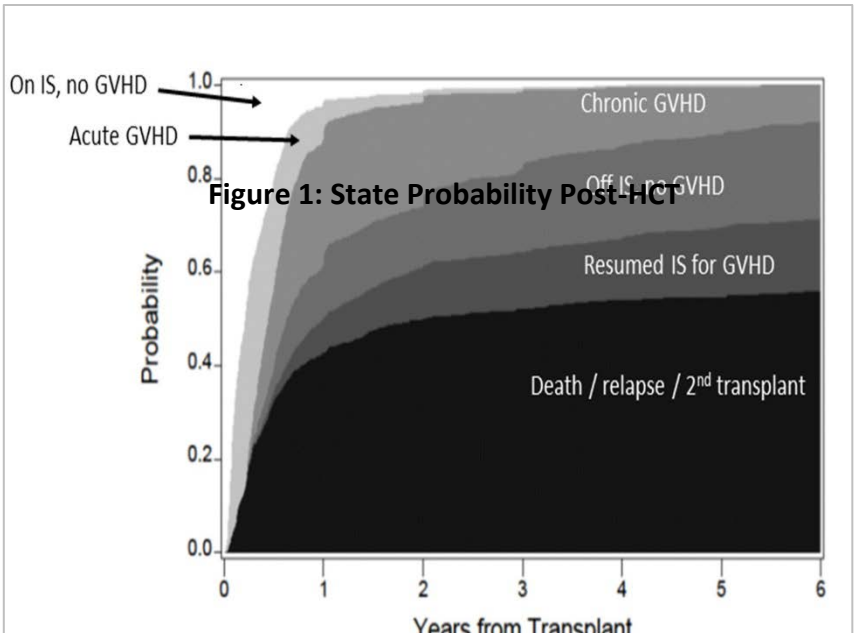


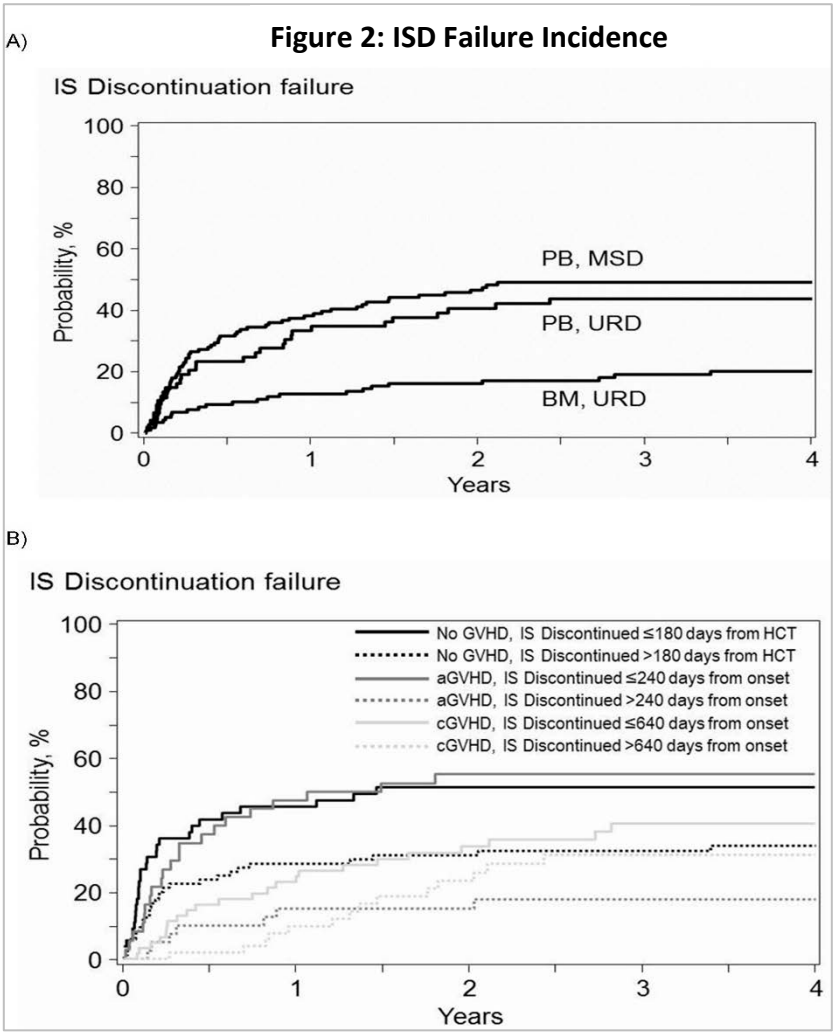
Figure 1: State Probability Post-HCT

On IS, no GVHD	4%	1%	1%	0%	0%	0%
Acute GVHD	6%	1%	0%	0%	0%	0%
Chronic GVHD	27%	21%	16%	12%	10%	8%
Off IS, no GVHD	13%	15%	18%	20%	20%	21%
Resumed IS for GVHD	7%	11%	12%	13%	15%	16%
Death / relapse / 2nd transplant	43%	50%	52%	54%	55%	56%

of IS was not significantly associated with decreased risk of relapse (HR for off IS vs. on IS as time-varying covariate among patients without the competing event of GVHD was 1.95, 99% CI 0.88-4.31, p=0.03). Separate models were considered to examine the impact of GVHD-related variables on the transition from either prior acute GVHD or chronic GVHD to ISD. No acute GVHD variables significantly affected the time to ISD after development of acute GVHD. Current (active) skin involvement (HR=0.33, 99% CI 0.14-0.80, p=0.001) and unrelated donors (unrelated well matched vs. matched sibling donor (MSD): HR=0.29, 99% CI 0.10-0.79, p=0.001; unrelated, mismatched vs. MSD: HR=0.17, 99% CI 0.03-0.95, p=0.008) were associated with lower likelihood of ISD after chronic GVHD in a multivariable model.

- ISD failure: Overall 127 patients (37%) resumed IS for GVHD after initial ISD (ISD failure). The median (IQR) time from ISD to subsequent GVHD was 113 days (42-371). The time from ISD to subsequent GVHD varied by whether patients discontinued IS without prior GVHD (n=60, Median 56 days (28-181)), had prior acute GVHD (n=28, Median 107 days (55-284)) or chronic GVHD (n=39, Median 366 days (135-643)) (p<0.001). In a multivariable Cox model, use of PBSC vs. BM (Figure 2A) in unrelated donor HCT was associated with greater likelihood of ISD failure (HR=2.62, 99% CI 1.30-5.29, p<0.001). GVHD history prior to ISD, namely the presence and timing of any acute or chronic GVHD onset prior to ISD, was also associated with ISD failure (Figure 2B). Overall, the risk of resuming IS for GVHD is highest (about 50%) for patients who discontinued IS with no prior GVHD ≤ 180 days from HCT or who discontinued IS after acute GVHD at ≤ 240 days from acute GVHD onset. By 5 years after ISD failure, only 25% successfully again reached ISD (99% CI 15.4%-34.6%), while 41% remained on IS (99% CI 28.6%-53.4%), and 27% experienced death/relapse/second HCT (99% CI 16.9%-38.1%).

Figure 2: ISD Failure Incidence



- Dynamic prediction modeling: Dynamic prediction models for the probability of being off IS without GVHD were developed with 1, 3, and 5 year time horizons, and a web application was developed to compute the probability of ISD from these prediction models at the point of care, hosted at: https://discis.shinyapps.io/discis/.

Patient eligibility population:

Inclusion criteria:

- Patients with hematologic malignancy who received allogeneic HCT from matched sibling donor (MSD), matched or mismatched unrelated donor (URD), or umbilical cord blood, or haploidentical donor
- All ages (inclusive of adult and pediatric subjects)
- Myeloablative or reduced intensity conditioning
- Any GVHD prophylaxis
- Bone marrow, peripheral blood stem cells, or umbilical cord blood as a graft source
- Transplant era of 2009-2018 (to provide at least 2 years of follow up)
- Comprehensive Research Form reporting track

Note: Aim 1 will use the subgroup of MSD and 7-8/8 URD for a validation cohort of our prior model, while Aims 2 and 3 will use all patients in the cohort. These criteria are intentionally broad to examine risk factors for ISD and ISD failure and build and validate a new model for ISD and ISD failure that is fully applicable to the range of patient, disease, and HCT features in routine practice.

Data requirements:

Patient-related data will include:

- Age at transplant
- Patient gender: male vs. female
- Race
- Ethnicity
- Karnofsky performance status at transplant: ≥ 90 vs. < 90 vs. missing
- HCT comorbidity index at transplant: 0 vs 1-2 vs ≥ 3 vs. missing

Disease-related data will include:

- Diagnosis
- Disease risk index (DRI)

Transplant-related data will include:

- Graft source: peripheral blood vs. bone marrow (Aim 1), multiple (Aim 2)
- Transplant donor type: sibling, haploidentical, unrelated, umbilical cord blood
- Donor-recipient HLA matching
- Donor-recipient gender match
- GVHD prophylaxis: Will need to define GVHD prophylaxis groups based on observed distribution across donor/HCT types, in particular separating out ATG-based, or post-transplant cyclophosphamide-based approaches
- Donor-recipient CMV status
- Transplant date
- Conditioning intensity: Myeloablative (MAC) vs. reduced intensity conditioning (RIC)
- Conditioning regimen
- ATG use

Other data elements (endpoints) include:

- Acute GVHD: date of onset, organ involvement, overall grade
- Chronic GVHD: date of onset, organ involvement, overall grade

- Disease relapse, death, second HCT dates
- Date of complete IS discontinuation (ISD)
- GVHD onset, IS resumption after initial ISD event
- Last follow-up date

Feasibility considerations: We have experience working together with CIBMTR in our previous project to amass data including the events of interest (i.e. acute GVHD, chronic GVHD, ISD, death/relapse/2nd HCT). Our prior work included manually reviewing this data to note time points of health state transitions for the model. As the dataset for the current proposal is likely to be substantially larger than our prior one, we plan to develop algorithms for coding the time points of health state transitions needed for the analysis, and validating these against manual review as was previously conducted. If we are unsuccessful in developing such an algorithm, an alternative strategy would be to randomly sample a subset of patients from the cohort, conduct a manual review of the data in this subset to determine the transition time points, and then use only those patients in the analysis. Finally, as analysis of ISD and ISD failure require good long-term follow-up, we will also consider restricting the analysis population to centers that have good completeness of long-term follow-up form submission. This will increase the likelihood that a more complete and thorough picture of GVHD and ISD is available to determine the health state transition times.

Sample requirements:
None

Study design:

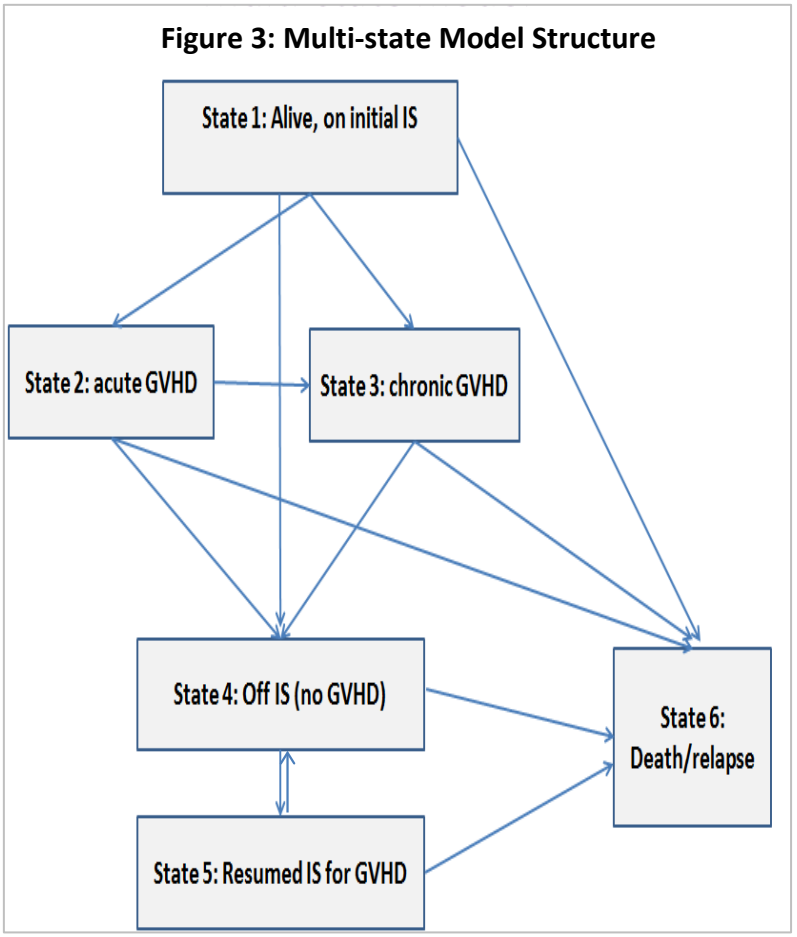
Aim 1:

- Our prior study constructed dynamic prediction models for a patient's likelihood of being off IS without GVHD at horizon times of 1, 3, and 5 years into the future given their current status at a post-HCT landmark time point. In Aim 1 of this study, we will validate these models using CIBMTR data from patients with HLA matched sibling or 7-8/8 matched unrelated donors providing either bone marrow or peripheral blood grafts. This validation will be performed by computing the time-varying area under the ROC curve (AUC) at the horizon time using pseudo-values computed from the CIBMTR cohort patients and their risk scores from the prior study's prediction models, employing a similar approach as detailed in [14]. To give a comprehensive assessment of each prediction model's performance, this AUC will be evaluated at multiple horizon times corresponding to a grid of landmark time points.

Aim 2:

- **Multi-state model:** We propose to use a multistate model to study the ISD process.[15-17] In a multistate model, the state X(t) represents a patient's clinical status at a particular time t post-HCT, from among a set of possible states. See (Logan, 2013) for a review for a clinical audience.[18] The proposed model is shown in Figure 3, where the lines indicate possible transitions. Patients start in a GVHD-free state on initial GVHD prophylaxis (state 1). Patients can stop GVHD prophylaxis (state 4) prior to development of any GVHD (directly from state 1), or they can experience aGVHD or cGVHD (state 2 or 3). Once they develop GVHD, they must discontinue both GVHD prophylaxis and GVHD treatment in order to be considered off IS and enter state 4. Subsequent development of GVHD and initiation of IS after discontinuation may also occur (state 5). At any time, patients can experience a competing event of death, relapse, or second HCT (state 6). Should IS be resumed to treat GVHD following an initial discontinuation (state 5), a patient could discontinue IS again once the GVHD resolves (return to state 4); therefore, transitions between states 4 and 5 can occur in either direction. Multistate models typically focus on understanding the impact of covariates on either the (instantaneous) transition rates between states, or on the state probabilities. We will examine the probability of being off IS at serial time points post-HCT (state 4 probability), as well as the rate of initial discontinuation of IS (transitions between states 1->4, 2->4, or 3->4). For the study of ISD failure, we will consider models for the rates of development of GVHD after initial IS discontinuation (transition from state 4 to 5) and of second ISD in patients who experience an initial ISD failure (transition back to state 4 from 5).

Figure 3: Multi-state Model Structure



- **ISD analysis:** Dates of transition between states will be determined. Analysis of ISD will include modeling of the likelihood of being in state 4 (off IS) at serial time points, as well as the transition intensities into state 4 from aGVHD or cGVHD states (2 or 3) or directly from state 1. Analysis of objective ISD failure will focus on modeling of the rate of development of GVHD subsequent to initial discontinuation of IS. Primary baseline characteristics of interest include stem cell source, donor/HLA type, donor-recipient gender match, GVHD prophylaxis, and ATG use. Other patient, disease, and transplant characteristics including age and disease/disease risk will also be examined in the models but are considered of secondary interest a priori. For transitions from GVHD states to off IS, we will also explore the impact of GVHD characteristics (aGVHD severity grading, cGVHD organ involvement and severity).

The time to discontinuation of IS among those who enter state 4 will be described using median (range). The numbers of patients undergoing each transition will be described. We will estimate the probability of being alive and off IS (state 4) as a function of time from transplant using a difference in Kaplan-Meier estimators,[9] which is valid for non-Markov models. This estimator considers whether individuals both stop IS and remain off IS, rather than only focusing on whether IS was stopped. Pseudo-values for this state probability at t=6, 12, 18, 24, 30, 36, 48, and 60 months will be determined for each patient using the leave one out estimator.[10-13] Note that pseudo-values simplify to an indicator of whether the patient is off IS (in state 4) at time t in the absence of censoring before t, so that pseudo-values are used to account for the presence of censoring. Pseudo-value regression models will be constructed to directly model the impact of baseline patient, disease, and transplant variables on the probability of being alive and off IS at each time point t. Generalized estimating equations will be used to account for the correlation across time points. An interaction between time and each covariate will be explored to see if the impact of the covariate is consistent across time. We will also conduct an analysis of the rate of initial discontinuation of IS in two ways. First, separate Cox Markov models for each transition into the off IS state will be constructed to examine the impact of covariates on each transition. These models will be left truncated at the time of entry into the preceding state (if state 2 or 3). Transitions into state 4 after development of GVHD will be checked for the Markov model assumption by considering the effect of a covariate representing the time until development of GVHD. Characteristics of aGVHD or cGVHD will be incorporated into these models to examine their impact on discontinuation of IS. Second, we will model direct transitions into the off IS state (state 4) with a time dependent Cox model, treating their state prior to discontinuation of IS as a time dependent covariate. This model will facilitate direct comparison of the impact of development of aGVHD or cGVHD on the rate of discontinuation of IS. Since these models assume that the transition intensities from states 1, 2, or 3 into state 4 are proportional to one another, we will assess this proportional hazards assumption and if needed include early and late effects of the preceding state.

- **ISD failure analysis:** The number of patients experiencing GVHD after discontinuation of IS will be described, along with the median (range) of the time to develop GVHD, and the characteristics of the GVHD. The probability of developing GVHD (entering state 5) will be estimated using the cumulative incidence technique, treating death, relapse, or 2nd HCT as a competing risk. This will be done both using the population of patients at transplant, as well as restricting to the population of patients who discontinue IS, resetting the clock at the time of discontinuation. The rate of development of GVHD after discontinuation of IS will be modeled using a left truncated Cox regression model, using date of discontinuation of IS as the left truncation date. The Markov model assumption will be checked by considering the effect of time to develop IS on the subsequent rate of GVHD. Prior GVHD history and GVHD characteristics will be considered in the model, in addition to baseline patient, disease, and transplant characteristics.
  A similar analysis will be performed to assess the number of patients and the likelihood of resuming ISD after an initial ISD failure (returning to state 4 after entering state 5). We expect that the CIBMTR cohort will have enough of these patients to permit this investigation, which could not be performed in the previous study due to limited numbers.

<u>Aim 3:</u>

- Using the entire CIBMTR cohort, dynamic prediction models will be developed for the likelihood of being off IS and GVHD-free at post-HCT horizon time points of 1, 3, and 5 years in the future given

their current status. This will be done using landmarking supermodels with pseudo-value regression[14], which allow the prediction of the probability of being off IS at a future time point based on the patient's status as it changes dynamically over time. The cohort will be split into two subsets of patients, a training set and a validation set, with the training set used for the development of the prediction models. Covariates that are found in Aim 2 to be predictive of being off IS and GVHD-free (in state 4) will be included in during the analysis. These landmarking supermodels will consider linear and quadratic effects of the landmark time, as well as interactions both between covariates and of the landmark time with covariates. The regression coefficients will be utilized to develop a scoring system for the likelihood of being off IS without GVHD at a future horizon time given a patient's current status.

These dynamic prediction models will also be internally validated by computing the time-varying area under the ROC curve (AUC) at the horizon time using pseudo-values computed from the validation set[14]. To give a comprehensive assessment of each prediction model's performance, this AUC will be evaluated at multiple horizon times corresponding to a grid of landmark time points. In an additional analysis, these validation measures will be evaluated only in validation patients who received matched related or 7-8/8 matched unrelated, bone marrow or peripheral blood graft transplants, the target population from our previous study. This will allow comparison of the new models' predictive ability for these patients to that of the previous study's models, assessed in Aim 1.

Non-CIBMTR data source:
None

Conflicts of interest:
None

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Characteristics of patients receiving first allo-HCT for hematologic malignancy in 2009-2019, CRF track

Characteristic	N (%)
No. of patients	20031
No. of centers	264
Age at HCT	
Median (min-max)	52.42 (0.3-87.77)
<10	1513 (8)
10-17	1145 (6)
18-29	1946 (10)
30-39	1843 (9)
40-49	2698 (13)
50-59	4411 (22)
60-69	5280 (26)
≥70	1195 (6)
Recipient sex	
Male	11784 (59)
Female	8247 (41)
Disease	
AML	7506 (37)
ALL	3183 (16)
OL	400 (2)
CML	669 (3)
MDS	4967 (25)
OAL	223 (1)
NHL	1104 (6)
HD	349 (2)
PCD	216 (1)
MPN	1414 (7)
Donor type	
HLA-identical sibling	5159 (26)
Haploidentical	1982 (10)
Well-matched unrelated (8/8)	8044 (40)
Partially-matched unrelated (7/8)	1570 (8)
Cord blood	3276 (16)
Graft type	
Bone marrow	3048 (15)
Peripheral blood	13707 (68)
Cord blood	3276 (16)
Conditioning regimen intensity	
MAC	12342 (62)

Characteristic	N (%)
RIC	7689 (38)
GVHD prophylaxis	
Ex-vivo T-cell depletion	187 (1)
CD34 selection	539 (3)
Post-CY + other(s)	2207 (11)
Post-CY alone	77 (0)
TAC + MMF ± other(s) (except post-CY)	2987 (15)
TAC + MTX ± other(s) (except MMF, post-CY)	8090 (40)
TAC + other(s) (except MMF, MTX, post-CY)	1212 (6)
TAC alone	419 (2)
CSA + MMF ± other(s) (except post-CY)	2029 (10)
CSA + MTX ± other(s) (except MMF, post-CY)	1430 (7)
CSA + other(s) (except MMF, MTX, post-CY)	264 (1)
CSA alone	162 (1)
Other(s)	172 (1)
Missing	256 (1)
ATG/Campath	
ATG + Campath	6 (0)
ATG alone	5358 (27)
Campath alone	462 (2)
No ATG or Campath	14043 (70)
Missing	162 (1)
Year of HCT	
2009	2185 (11)
2010	1606 (8)
2011	1021 (5)
2012	1088 (5)
2013	1968 (10)
2014	2507 (13)
2015	2328 (12)
2016	2183 (11)
2017	2022 (10)
2018	1859 (9)
2019	1264 (6)
Median follow-up of survivors (range), months	49.05 (0.03-131.68)
Post-transplant variables	
Grade 2-4 acute GVHD	
No	11581 (58)
Yes	8247 (41)

Characteristic	N (%)
Missing	203 (1)
Chronic GVHD	
No	11587 (58)
Yes	8404 (42)
Missing	40 (0)

Abbreviations: AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, OL=Other leukemia, CML=Chronic myelogenous leukemia, MDS=Myelodysplastic disease, OAL=Other acute leukemia, NHL=Non-Hodgkin lymphoma, HD=Hodgkin disease, PCD=Plasma cell disorder/multiple myeloma, MPN=Myeloproliferative disease, Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine

Proposal: 2010-180

Title:
Racial, Ethnicity and Socioeconomic Disparity in Outcome of Patients with Chronic Graft versus Host Disease

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Hypothesis:
We hypothesized that racial/ethnic and socioeconomic status disparities exists in clinical manifestations, severity, and outcome of patients with chronic graft versus host disease (GVHD).

Specific aims:
- To determine whether clinical manifestations and severity of chronic GVHD differ based on racial/ethnic and socioeconomical status (SES) differences.
- To determine whether treatment patterns of chronic GVHD differ based on racial/ethnic and SES differences
- To evaluate whether chronic GVHD treatment outcomes differ based on racial/ethnic and SES differences.

Scientific impact:
This study will characterize the role that race/ethnicity and SES plays in the incidence, clinical presentation, and outcomes of HCT recipients with chronic GVHD. This will guide future studies to identify possible reasons for any differences and highlight interventions needed to mitigate the differences. Identification of disparities in chronic GVHD clinical presentation (organ involvement) can help educate providers and may lead to tailored treatment regimens.

Scientific justification:
Profound race and ethnicity associated disparities in the prevalence of several chronic diseases has been well documented. Genetic, physiological, and anatomic differences exist between races [1]. Structural cardiac differences and variations in pulmonary vasculature have been reported between difference races[2]. Based on the Multi-Ethnic study of Atherosclerosis (MESA), left ventricular mass is lowest in Asian and Caucasians and highest in Blacks[3]. Changes in vascular endothelium and impaired nitric oxide balance is also noted in black patients leading to higher predisposition to vasculopathy[4-5]. Data also suggest racial differences in pulmonary arterial hypertension (PAH) severity and response to PAH-directed therapy[6]. Many fibroproliferative diseases including systemic scleroderma[7], nephrosclerosis[8] and sarcoidosis are also more prevalent in African-derived populations than in European populations. Racial disparities in solid tumor presentation, histology, stage at diagnosis and response to therapy have also been well documented. African Americans have the highest death rate and shortest survival of any racial and ethnic groups in the United States for most cancers[9-10]. The causes of these inequalities are thought to be multifactorial, and likely reflect racial differences in cancer biology in addition to SES disparities and racism.
Racial/ethnicity disparities have also been noted in outcomes of allogeneic stem cell transplant. An earlier CIBMTR study comparing transplant outcomes between ethnic populations who underwent MRD allo-HCT between 1990 and 1999 revealed a higher acute but not chronic GVHD risks for adult U.S.

Whites compared with adults of Japanese descent[11]. However, among children, both acute and chronic GVHD risks were higher in U.S. Whites compared with the Japanese. More recent study comparing transplant outcomes after umbilical cord blood transplant (UCBT) between Japanese and White children with acute leukemia did not observe significant differences in acute GVHD or overall mortality[12]. Ballen et al,[13] also evaluated transplant outcomes in 612 White, 145 Black, and 128 Hispanic patients receiving a single UCBT for acute leukemia, MDS or CML between 1995 and 2006. In multivariate analysis, Black patients had worse overall survival. However, it is worth noting that higher mortality in Blacks was attributed to HLA disparity and suboptimal cell dose.

Chronic GVHD remains one of the major causes of late morbidity and mortality after allo-HCT affecting up to 70% of survivors. Corticosteroid treatment, the mainstay of therapy, is often not fully effective. Approximately 60% of patients do not have complete response[13]. Although several second line treatment options are available, currently the "trial-and-error system" is the only way to identify the treatment effective in the individual patient. With the armamentarium of treatment options available, identification of unique phenotypes can help to identify the likelihood of response to a drug in advance. Genetic, physiological, physical and SES differences between races may significantly alter the disease phenotype of chronic GVHD. Further, racial and ethnic minorities may have fewer resources and less access to follow up care that could influence outcomes. Therefore, studies are needed to characterize the role that race and ethnicity plays in the prevalence, presentation, and outcomes of chronic GVHD. Unfortunately, minority groups are underrepresented in chronic GVHD clinical trials. Whether this difference in the ethnic and racial makeup of trial populations is due to differences in the background risk for the development of chronic GVHD, unequal access to medical care and resultant lower likelihood for members of racial minority groups to be diagnosed early in the course of GVHD , less access to follow up care to management immunosuppressive therapy or GVHD complications, or differences in willingness to participate in treatment trials is unknown.

To our knowledge, the impact of racial disparity on the clinical features and the clinical course of patients with chronic GVHD has not been reported. Better understanding of racial disparities will minimize inequities, inform health policy, and guide development of interventions targeted to eliminate disparities

Patient eligibility population:

- Patients aged 18 years or older who have received first allogeneic transplant for hematologic malignancy (AML, ALL, MDS) from 2006 – 2019
- Based on the number of patients available will decide whether include Haploidentical and umbilical cord transplant

Outcomes:

- To determine the impact of race/ethnicity and SES on clinical characteristics of chronic GVHD at presentation (organ involvement).
- Severity of chronic GVHD at presentation (limited vs extensive or if NIH criteria available mild, vs moderate vs severe)

<u>Secondary outcome</u>

- Incidence of sclerotic GVHD (defined when cutaneous sclerosis, fasciitis, or joint contracture) at first presentation
- Proportions of patients treated initially with a single drug as opposed to 2 or more drugs
- Time to withdrawal of systemic immunosuppressive therapy (IST)
- Overall survival after the diagnosis of chronic GVHD

Data requirements:

Main effect:

- Race/ethnicity: Non-Hispanic white vs. Non-Hispanic black vs. Hispanic vs. Asian
- SES (median annual household income based on ZIP code of residence): < 48,000 vs. 48,000-60,999 vs. 61,000-79,000 vs. ≥ 80,000

Patient-related:

- Age at HCT, years: by decades
- Sex: male vs female
- Karnofsky performance score: ≥90% vs. <90%
- Recipient CMV seropositivity (positive vs. negative vs. not reported)
- HCT comorbidity index at transplant 0 vs. 1-2 vs vs. ≥ 3
- Insurance Status: disability insurance +/-others vs. private health insurance +/- others
- Marital status: single vs. married vs. separated vs. divorced vs. widowed

Disease-related:

- Diagnosis: AML vs ALL vs MDS
- Disease-Risk Index (low vs. intermediate vs. high/very high; and low/intermediate vs. high/very high)

Transplant-related:

- Donor type: HLA-identical sibling vs. matched URD vs haplo vs cord
- Donor race: see above
- Year of HCT: continuous
- Conditioning regimen intensity: MAC vs. NMA
- TBI dose in conditioning regimen (none vs. ≤450 cGy vs. >450 cGy)
- Prior grade 2-4 acute GVHD (Yes vs No)
- Graft source Bone marrow vs PBSC vs umbilical cord
- GVHD prophylaxis
- Acute GVHD: yes vs no

Study design:

Race will be broken down into groups based on race and ethnicity: White non-Hispanic, white Hispanic, Black non-Hispanic, Black Hispanic, and Asian. Patient, disease-, and transplant-related variables for the study cohorts will be described. The incidence of chronic GVHD will be calculated using the cumulative incidence estimator, adjusting for clinical variables with race/ethnicity forced into each model. The prevalence of organ involvement at the initial diagnosis of chronic GVHD will be calculated among the groups. The χ^2 or Fisher exact test will used to evaluate the significance of differences in proportions, and Wilcoxon rank sum tests were used to compare continuously valued outcomes and to evaluate the significance of differences in distributions among ordered categories for patients who develop chronic GVHD. The log-rank test will be used to compare subsequent survival among the racial/ethnic groups after development of chronic GVHD, adjusting for time since transplant.

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Table 1. Characteristics of patients receiving first allo-HCT for AML, ALL, MDS in US in 2008-2019, CRF track

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other*
No. of patients	14131	1282	1385	867	217
No. of centers	161	133	125	108	63
Age at HCT					
Median (min-max)	59.68 (18.01-87.77)	51.34 (18.01-76.99)	46.16 (18.01-80.78)	51.97 (18.06-79.03)	50.63 (18.04-74.52)
18-29	956 (7)	180 (14)	342 (25)	118 (14)	40 (18)
30-39	975 (7)	181 (14)	220 (16)	132 (15)	23 (11)
40-49	1737 (12)	239 (19)	238 (17)	150 (17)	43 (20)
50-59	3566 (25)	333 (26)	262 (19)	200 (23)	54 (25)
60-69	5479 (39)	302 (24)	278 (20)	217 (25)	52 (24)
≥70	1418 (10)	47 (4)	45 (3)	50 (6)	5 (2)
Recipient sex - no. (%)					
Male	8352 (59)	624 (49)	745 (54)	449 (52)	118 (54)
Female	5779 (41)	658 (51)	640 (46)	418 (48)	99 (46)
Zip code available - no. (%)					
No	5979 (42)	423 (33)	656 (47)	296 (34)	86 (40)
Yes	8152 (58)	859 (67)	729 (53)	571 (66)	131 (60)
Median household income available - no. (%)					
No	6077 (43)	442 (34)	662 (48)	304 (35)	88 (41)
Yes	8054 (57)	840 (66)	723 (52)	563 (65)	129 (59)
Recipient marital status - no. (%)					
Single, never married	1559 (11)	366 (29)	367 (26)	132 (15)	47 (22)
Married	9972 (71)	630 (49)	774 (56)	587 (68)	135 (62)

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other*
Separated	130 (1)	25 (2)	29 (2)	8 (1)	2 (1)
Divorced	1158 (8)	130 (10)	106 (8)	37 (4)	17 (8)
Widowed	404 (3)	29 (2)	26 (2)	20 (2)	4 (2)
Missing	908 (6)	102 (8)	83 (6)	83 (10)	12 (6)
Highest educational grade completed - no. (%)					
No primary education	9 (0)	1 (0)	6 (0)	4 (0)	0
Less than primary or elementary education	9 (0)	3 (0)	19 (1)	3 (0)	0
Primary or elementary education	18 (0)	3 (0)	51 (4)	6 (1)	0
Lower secondary education	241 (2)	41 (3)	80 (6)	19 (2)	9 (4)
Upper secondary education	3339 (24)	402 (31)	423 (31)	124 (14)	80 (37)
Post-secondary, non-tertiary education	1208 (9)	117 (9)	111 (8)	48 (6)	16 (7)
Tertiary education, Type A[a]	3516 (25)	243 (19)	198 (14)	243 (28)	36 (17)
Tertiary education, Type B[b]	774 (5)	73 (6)	62 (4)	39 (4)	14 (6)
Advanced research qualification	648 (5)	46 (4)	31 (2)	72 (8)	8 (4)
Missing	4369 (31)	353 (28)	404 (29)	309 (36)	54 (25)
Health insurance type - no. (%)					
No insurance	64 (0)	13 (1)	25 (2)	13 (1)	4 (2)
Disability insurance +/-others	284 (2)	39 (3)	24 (2)	22 (3)	6 (3)
Private health insurance +/- others	7637 (54)	619 (48)	607 (44)	473 (55)	115 (53)
Medicaid +/-others	1208 (9)	292 (23)	437 (32)	151 (17)	45 (21)
Medicare +/-others	3885 (27)	200 (16)	186 (13)	116 (13)	33 (15)
Other	328 (2)	44 (3)	43 (3)	28 (3)	6 (3)
Missing	725 (5)	75 (6)	63 (5)	64 (7)	8 (4)
Primary disease for HCT - no. (%)					
AML	6334 (45)	687 (54)	576 (42)	476 (55)	108 (50)

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other*
ALL	1437 (10)	236 (18)	491 (35)	157 (18)	44 (20)
MDS	6360 (45)	359 (28)	318 (23)	234 (27)	65 (30)
Donor type - no. (%)					
HLA-identical sibling	3265 (23)	254 (20)	383 (28)	224 (26)	38 (18)
Other related	1528 (11)	398 (31)	268 (19)	137 (16)	29 (13)
Well-matched unrelated (8/8)	6714 (48)	206 (16)	268 (19)	245 (28)	66 (30)
Partially-matched unrelated (7/8)	1083 (8)	140 (11)	147 (11)	71 (8)	27 (12)
Mis-matched unrelated (≤ 6/8)	57 (0)	18 (1)	11 (1)	3 (0)	5 (2)
Multi-donor	25 (0)	2 (0)	3 (0)	2 (0)	0
Unrelated (matching TBD)	29 (0)	1 (0)	3 (0)	2 (0)	1 (0)
Cord blood	1297 (9)	243 (19)	288 (21)	173 (20)	49 (23)
Missing	2 (0)	0	2 (0)	0	0
Missing	131 (1)	20 (2)	12 (1)	10 (1)	2 (1)
Graft type - no. (%)					
Bone marrow	1868 (13)	189 (15)	166 (12)	109 (13)	25 (12)
Peripheral blood	10966 (78)	850 (66)	931 (67)	585 (67)	143 (66)
Cord blood	1297 (9)	243 (19)	288 (21)	173 (20)	49 (23)
Conditioning intensity - no. (%)					
MAC	6597 (47)	709 (55)	851 (61)	441 (51)	110 (51)
RIC	4883 (35)	271 (21)	299 (22)	220 (25)	61 (28)
NMA	1672 (12)	198 (15)	143 (10)	126 (15)	25 (12)
TBD	233 (2)	12 (1)	14 (1)	18 (2)	10 (5)
Missing	746 (5)	92 (7)	78 (6)	62 (7)	11 (5)
GVHD prophylaxis - no. (%)					
Ex-vivo T-cell depletion	78 (1)	13 (1)	8 (1)	4 (0)	2 (1)

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other*
CD34 selection	234 (2)	17 (1)	15 (1)	12 (1)	0
Post-CY + other(s)	1866 (13)	425 (33)	286 (21)	156 (18)	33 (15)
Post-CY alone	67 (0)	1 (0)	1 (0)	2 (0)	1 (0)
TAC + MMF ± other(s) (except post-CY)	2287 (16)	208 (16)	164 (12)	113 (13)	30 (14)
TAC + MTX ± other(s) (except MMF, post-CY)	5989 (42)	349 (27)	501 (36)	282 (33)	80 (37)
TAC + other(s) (except MMF, MTX, post-CY)	857 (6)	48 (4)	101 (7)	74 (9)	7 (3)
TAC alone	296 (2)	22 (2)	30 (2)	16 (2)	5 (2)
CSA + MMF ± other(s) (except post-CY)	1138 (8)	99 (8)	159 (11)	126 (15)	43 (20)
CSA + MTX ± other(s) (except MMF, post-CY)	403 (3)	16 (1)	40 (3)	16 (2)	3 (1)
CSA + other(s) (except MMF, MTX, post-CY)	40 (0)	5 (0)	6 (0)	2 (0)	0
CSA alone	40 (0)	4 (0)	7 (1)	3 (0)	2 (1)
Other(s)	160 (1)	4 (0)	6 (0)	10 (1)	2 (1)
Missing	676 (5)	71 (6)	61 (4)	51 (6)	9 (4)
In-vivo T-cell depletion (ATG/alemtuzumab) - no. (%)					
No	10300 (73)	1011 (79)	1098 (79)	701 (81)	167 (77)
Yes	3692 (26)	251 (20)	275 (20)	156 (18)	48 (22)
Missing	139 (1)	20 (2)	12 (1)	10 (1)	2 (1)
Year of HCT - no. (%)					
2008	1350 (10)	82 (6)	151 (11)	47 (5)	17 (8)
2009	1250 (9)	67 (5)	109 (8)	47 (5)	13 (6)
2010	902 (6)	77 (6)	104 (8)	57 (7)	17 (8)
2011	721 (5)	55 (4)	74 (5)	39 (4)	12 (6)
2012	721 (5)	51 (4)	77 (6)	28 (3)	7 (3)
2013	1271 (9)	90 (7)	125 (9)	79 (9)	27 (12)
2014	1599 (11)	133 (10)	120 (9)	78 (9)	17 (8)

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other*
2015	1456 (10)	152 (12)	122 (9)	94 (11)	21 (10)
2016	1360 (10)	151 (12)	130 (9)	104 (12)	18 (8)
2017	1276 (9)	133 (10)	129 (9)	100 (12)	24 (11)
2018	1221 (9)	157 (12)	125 (9)	104 (12)	25 (12)
2019	1004 (7)	134 (10)	119 (9)	90 (10)	19 (9)
Chronic GVHD - no. (%)					
No	8035 (57)	783 (61)	779 (56)	506 (58)	132 (61)
Yes	5934 (42)	477 (37)	594 (43)	350 (40)	83 (38)
Missing	162 (1)	22 (2)	12 (1)	11 (1)	2 (1)
Median follow-up of survivors (range), months	58.91 (0.03-149.51)	45.89 (1.55-144.11)	51.74 (2.86-145.53)	46.48 (1.58-143.16)	47.66 (3.26-120.63)

Abbreviations: AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, MDS=Myelodysplastic-myeloproliferative diseases, Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine.

* Includes Pacific Islander, American Indian, and multiracial.

[a] Programs that provide education that is largely theoretical, lasting 3-4 years.

[b] Programs that focus on practical, technical or occupational skills with a minimum duration of 2 years of full-time enrollment.

Table 2. Characteristics of patients receiving first allo-HCT for AML, ALL, MDS in US in 2008-2019, who developed chronic GVHD

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other*
No. of patients	5934	477	594	350	83
No. of centers	130	95	99	75	34
Age at HCT					
Median (min-max)	58.9 (18.01-80.58)	51.43 (18.2-74.64)	45.1 (18.07-76.47)	52.44 (19.49-74.21)	53 (19.09-74.52)
18-29	395 (7)	59 (12)	146 (25)	38 (11)	14 (17)
30-39	452 (8)	70 (15)	102 (17)	54 (15)	7 (8)
40-49	782 (13)	94 (20)	112 (19)	73 (21)	16 (19)
50-59	1555 (26)	121 (25)	114 (19)	79 (23)	25 (30)
60-69	2216 (37)	116 (24)	111 (19)	83 (24)	19 (23)
≥70	534 (9)	17 (4)	9 (2)	23 (7)	2 (2)
Recipient sex - no. (%)					
Male	3510 (59)	232 (49)	313 (53)	175 (50)	45 (54)
Female	2424 (41)	245 (51)	281 (47)	175 (50)	38 (46)
Zip code available - no. (%)					
No	2712 (46)	155 (32)	326 (55)	124 (35)	34 (41)
Yes	3222 (54)	322 (68)	268 (45)	226 (65)	49 (59)
Median household income available - no. (%)					
No	2745 (46)	161 (34)	329 (55)	129 (37)	35 (42)
Yes	3189 (54)	316 (66)	265 (45)	221 (63)	48 (58)
Recipient marital status - no. (%)					
Single, never married	639 (11)	139 (29)	148 (25)	45 (13)	19 (23)
Married	4338 (73)	244 (51)	352 (59)	246 (70)	47 (57)

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other*
Separated	64 (1)	8 (2)	13 (2)	5 (1)	1 (1)
Divorced	483 (8)	50 (10)	44 (7)	19 (5)	9 (11)
Widowed	141 (2)	6 (1)	5 (1)	11 (3)	1 (1)
Missing	269 (5)	30 (6)	32 (5)	24 (7)	6 (7)
Highest educational grade completed - no. (%)					
No primary education	3 (0)	0	4 (1)	3 (1)	0
Less than primary or elementary education	4 (0)	1 (0)	9 (2)	1 (0)	0
Primary or elementary education	7 (0)	1 (0)	23 (4)	2 (1)	0
Lower secondary education	102 (2)	17 (4)	40 (7)	7 (2)	5 (6)
Upper secondary education	1394 (23)	159 (33)	177 (30)	56 (16)	33 (40)
Post-secondary, non-tertiary education	515 (9)	40 (8)	41 (7)	14 (4)	6 (7)
Tertiary education, Type A[a]	1565 (26)	97 (20)	88 (15)	92 (26)	9 (11)
Tertiary education, Type B[b]	333 (6)	35 (7)	26 (4)	17 (5)	4 (5)
Advanced research qualification	286 (5)	22 (5)	14 (2)	35 (10)	5 (6)
Missing	1725 (29)	105 (22)	172 (29)	123 (35)	21 (25)
Health insurance type - no. (%)					
No insurance	23 (0)	6 (1)	10 (2)	5 (1)	3 (4)
Disability insurance +/-others	127 (2)	17 (4)	11 (2)	11 (3)	2 (2)
Private health insurance +/- others	3426 (58)	239 (50)	271 (46)	198 (57)	47 (57)
Medicaid +/-others	504 (8)	96 (20)	181 (30)	63 (18)	12 (14)
Medicare +/-others	1550 (26)	82 (17)	73 (12)	50 (14)	14 (17)
Other	132 (2)	18 (4)	26 (4)	11 (3)	2 (2)
Missing	172 (3)	19 (4)	22 (4)	12 (3)	3 (4)
Primary disease for HCT - no. (%)					
AML	2611 (44)	245 (51)	254 (43)	187 (53)	44 (53)

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other*
ALL	597 (10)	94 (20)	202 (34)	66 (19)	16 (19)
MDS	2726 (46)	138 (29)	138 (23)	97 (28)	23 (28)
Donor type - no. (%)					
HLA-identical sibling	1553 (26)	128 (27)	218 (37)	105 (30)	20 (24)
Other related	421 (7)	131 (27)	87 (15)	33 (9)	9 (11)
Well-matched unrelated (8/8)	3089 (52)	91 (19)	126 (21)	121 (35)	29 (35)
Partially-matched unrelated (7/8)	492 (8)	56 (12)	71 (12)	37 (11)	10 (12)
Mis-matched unrelated (≤ 6/8)	27 (0)	4 (1)	3 (1)	1 (0)	3 (4)
Multi-donor	5 (0)	0	2 (0)	0	0
Unrelated (matching TBD)	10 (0)	1 (0)	2 (0)	2 (1)	0
Cord blood	336 (6)	66 (14)	84 (14)	51 (15)	12 (14)
Missing	1 (0)	0	1 (0)	0	0
Graft type - no. (%)					
Bone marrow	585 (10)	54 (11)	60 (10)	34 (10)	10 (12)
Peripheral blood	5013 (84)	357 (75)	450 (76)	265 (76)	61 (73)
Cord blood	336 (6)	66 (14)	84 (14)	51 (15)	12 (14)
Conditioning intensity - no. (%)					
MAC	2998 (51)	291 (61)	396 (67)	205 (59)	42 (51)
RIC	2130 (36)	112 (23)	126 (21)	92 (26)	26 (31)
NMA	523 (9)	54 (11)	46 (8)	35 (10)	9 (11)
TBD	108 (2)	4 (1)	6 (1)	8 (2)	3 (4)
Missing	175 (3)	16 (3)	20 (3)	10 (3)	3 (4)
GVHD prophylaxis - no. (%)					
Ex-vivo T-cell depletion	13 (0)	4 (1)	0	1 (0)	0
CD34 selection	38 (1)	3 (1)	4 (1)	3 (1)	0

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other*
Post-CY + other(s)	492 (8)	129 (27)	94 (16)	38 (11)	10 (12)
Post-CY alone	28 (0)	0	1 (0)	1 (0)	0
TAC + MMF ± other(s) (except post-CY)	1005 (17)	72 (15)	57 (10)	41 (12)	11 (13)
TAC + MTX ± other(s) (except MMF, post-CY)	2902 (49)	180 (38)	262 (44)	153 (44)	40 (48)
TAC + other(s) (except MMF, MTX, post-CY)	475 (8)	22 (5)	67 (11)	42 (12)	2 (2)
TAC alone	116 (2)	11 (2)	11 (2)	12 (3)	2 (2)
CSA + MMF ± other(s) (except post-CY)	430 (7)	28 (6)	51 (9)	43 (12)	15 (18)
CSA + MTX ± other(s) (except MMF, post-CY)	190 (3)	9 (2)	13 (2)	3 (1)	0
CSA + other(s) (except MMF, MTX, post-CY)	16 (0)	1 (0)	2 (0)	2 (1)	0
CSA alone	16 (0)	1 (0)	4 (1)	2 (1)	0
Other(s)	36 (1)	1 (0)	5 (1)	2 (1)	0
Missing	177 (3)	16 (3)	23 (4)	7 (2)	3 (4)
In-vivo T-cell depletion (ATG/alemtuzumab) - no. (%)					
No	4679 (79)	390 (82)	496 (84)	301 (86)	72 (87)
Yes	1250 (21)	87 (18)	98 (16)	49 (14)	11 (13)
Missing	5 (0)	0	0	0	0
Year of HCT - no. (%)					
2008	613 (10)	30 (6)	73 (12)	19 (5)	8 (10)
2009	568 (10)	27 (6)	51 (9)	27 (8)	4 (5)
2010	446 (8)	30 (6)	52 (9)	26 (7)	8 (10)
2011	316 (5)	12 (3)	35 (6)	15 (4)	5 (6)
2012	316 (5)	21 (4)	42 (7)	11 (3)	3 (4)
2013	538 (9)	36 (8)	62 (10)	31 (9)	12 (14)
2014	714 (12)	52 (11)	54 (9)	37 (11)	7 (8)
2015	632 (11)	60 (13)	44 (7)	45 (13)	9 (11)

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other*
2016	598 (10)	68 (14)	53 (9)	42 (12)	8 (10)
2017	521 (9)	58 (12)	46 (8)	36 (10)	8 (10)
2018	474 (8)	58 (12)	53 (9)	42 (12)	8 (10)
2019	198 (3)	25 (5)	29 (5)	19 (5)	3 (4)
Median follow-up of survivors (range), months	60.89 (3.32-149.51)	48.36 (5.59-144.11)	60.79 (5.99-145.53)	48.49 (5.76-143.16)	50.2 (5.92-108.72)

Abbreviations: AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, MDS=Myelodysplastic-myeloproliferative diseases, Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine.

* Includes Pacific Islander, American Indian, and multiracial.

[a] Programs that provide education that is largely theoretical, lasting 3-4 years.

[b] Programs that focus on practical, technical or occupational skills with a minimum duration of 2 years of full-time enrollment.