Can We Design Personalized Acute Graft-*vs*-Host Disease Prevention and Treatment Strategies Using Registry Data and Sequential Multiple-Assignment Randomized Trials to Improve Disease-Free Survival of Blood and Marrow Transplant Patients?

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ABSTRACT

Objective: Graft-*versus*-host disease (GVHD) is a major complication of allogeneic hematopoietic cell transplantation (AHCT). We investigated whether the Center for International Blood and Marrow Transplant Research registry could be useful for (1) determining if the sequence of administering non-specific, highly T-lymphodepleting (NHTL) therapeutics in GVHD prophylaxis and in refractory GVHD impacts survival and (2) identifying donor- and patient-related factors that may guide individualized selection of classes of immunosuppressant agents over time, *i.e.* to develop adaptive treatment strategies (ATSs).

Method: We employed a backwards induction method derived from reinforcement learning in a large cohort of patients who underwent AHCT for acute myeloid leukemia and myelodysplasia between 1995 and 2007. We devised logistic Q-models that first estimate the optimal treatment for each patient with refractory acute GVHD and then use a pseudo-outcome approach to estimate the optimal patient-specific GVHD prophylaxis, with the goal of maximizing 2-year disease-free survival (DFS).

Results: In unadjusted analysis, NHTL prophylaxis and NHTL treatment of refractory acute GVHD were associated with inferior DFS compared to non-NHTL therapeutics. Yet, among the 9563 patients, the Q-model predicted that 4762 (50%) would have a higher probability of 2-year DFS with NHTL prophylaxis. For the 1411 patients with refractory acute GVHD, the Q-model predicted that 492 (35%) would have had a higher probability of 2-year DFS with NHTL salvage therapy. The magnitude of projected patient-specific benefit from choosing the optimal class of agent was modest. The models suggested that patient-specific combinations of characteristics could influence the choice of GVHD prophylaxis and treatment.

Conclusions: Retrospective analysis with Q-learning can be used to propose personalized ATSs for GVHD prevention and treatment, which may then be tested in sequentially-randomized clinical trials. An important limitation which threatens the validity of the registry-derived strategies is that lack of detailed information about the indication for each immunosuppressant and other salient patient characteristics may lead to residual confounding.

RÉSUMÉ

Objectif: La maladie du greffon contre l'hôte (‹‹*GVH*››) est une complication majeure de la greffe de cellules souches hématopoïétiques. Nous avons tenté de déterminer si les données du registre du Center for International Blood and Marrow Transplant Research pourraient déterminer (1) si la séquence d'administration de thérapie immunosuppressive lymphopéniante non-spécifique (‹‹*non-specific, highly T-lymphodepleting, NHTL*››) en prophylaxie et en traitement de GVH réfractaire avait un impact sur la survie et (2) si des caractéristiques des donneurs ou receveurs pourraient servir à déterminer le choix du type d'immunosuppresseurs à administrer au fil du temps, afin d'élaborer des stratégies de traitement personnalisées.

Méthode: Suivant la méthode d'induction vers l'arrière dérivée de l'apprentissage par renforcement dans une grande cohorte de patients ayant subi une greffe pour une leucémie myéloïde aigue ou des syndromes myélodysplasiques entre 1995 et 2007, nous avons mis au point un modèle de régression logistique de type Q pour déterminer le traitement optimal de la GVH réfractaire, puis avons utilisé une approche de pseudo-résultat pour estimer la prophylaxie optimale de chaque patient, cherchant à maximiser la survie sans maladie (SSM) à 2 ans.

Résultats: En analyse non-ajustée, la prophylaxie et le traitement NHTL sont associés à une SSM inferieur au traitement non-NHTL. Néanmoins, sur les 9563 patients étudiés, le modèle-Q a su prédire que 4762 (50%) d'entre eux auraient une meilleure SSM à 2 ans avec la prophylaxie NHTL. Pour 1411 patients avec GVH aigue réfractaire, le modèle-Q a démontré que 492 patients (35%) auraient eu une plus haute probabilité de SSM à 2 ans avec le traitement NHTL de sauvetage. L'ampleur du bénéfice pour les patients dans le choix optimal de classe des agents était généralement modeste. Notre modèle suggère que les caractéristiques combinées d'un patient peuvent influencer le choix de prophylaxie et de traitement de la GVH.

Conclusions: L'analyse rétrospective par l'apprentissage Q peut être utilisée pour choisir un traitement immunosuppresseur prophylactique et thérapeutique de la GVH; ceci peut subséquemment être testé dans une étude clinique randomisée en séquence. L'absence d'information précise concernant l'indication de traitement et d'autres caractéristiques des patients amène une limitation importante pouvant remettre en question la validité des résultats.

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DEDICATION

For my mother of blessed memory, who had a tender heart and generous spirit. She railed against a one-size-fits-all approach to medical treatment and demanded "personalized" medicine at a time when that idea was still in its infancy. Maybe now that idea is finally coming of age. I hope that through my career, I might help devise ways of tailoring treatment to the individual person in the most refined and rational way possible, so that future mothers like you can stay alive to realize their own dreams and to see their daughters take flight.

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LIST OF ABBREVIATIONS

AHCT	Allogeneic hematopoietic stem cell transplantation
ALG	Anti-lymphocyte globulin
AML	Acute myeloid leukemia
APC	Antigen presenting cell
ASBMT	American Society of Blood and Marrow Transplantation
ATG	Anti-thymocyte globulin
ATRA	All *trans*-retinoic acid
ATS	Adaptive treatment strategy
BCR-ABL	B-cell receptor-Abelson tyrosine kinase fusion protein
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CIBMTR	Center for International Blood and Marrow Transplant Research
cGy	Centigray
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CR	Complete remission
CRF	Comprehensive Report Form
DFS	Disease-free survival
DTR	Dynamic treatment regime
ECP	Extracorporeal photopheresis
FISH	Fluorescent *in-situ* hybridization
HLA	Human leukocyte antigen
IPCW	Inverse probability of censoring weights
IVIG	Intravenous immunoglobulin
IS	International scale
IV	Intravenous
GVHD	Graft-*versus*-host disease
GVT	Graft-*versus*-tumor
LTFU	Lost to follow-up

MDS	Myelodysplastic syndrome
MHC	Major histocompatibility complex
MiHA	Minor histocompatiblity antigen
MRD	Minimal residual disease
mRNA	Messenger ribonucleic acid
mTOR	Mammalian target of rapamycin
NCT	National Clinical Trials registry
NHTL	Non-specific highly T-lymphodepleting
NK	Natural killer
NMDP	National Marrow Donor Program
OS	Overall survival
PO	*Per os*
PTLD	Post-transplant lymphoproliferative disease
PUVA	Psoralen/ultraviolet-A
RA(RS)	Refractory anemia (with ringed sideroblasts)
RAEB(-T)	Refractory anemia with excess blasts (in transformation)
RCT	Randomized controlled trial
RR	Relative risk
SMART	Sequential multiple-assignment randomized trial
STAR*D	Sequenced Treatment Alternative to Relieve Depression
TAI	Total abdominal irradiation
TBI	Total body irradiation
TLI	Total lymphoid irradiation
TED	Transplant essential data
TKI	Tyrosine kinase inhibitor

GLOSSARY OF STATISTICAL TERMS

Action (*a*): A treatment or intervention (manipulated exposure).

Adaptive treatment strategy: A set of decision rules for choosing the optimal treatment for individuals where the input includes personal fixed and time-varying characteristics and treatment history.

Contrast function: The function used to describe the impact of an interval-specific treatment relative to some reference treatment, such as placebo or standard-of-care.

Collider stratification bias: Bias that arises when conditioning on a covariate that is a common effect (or cause) of the treatment of interest and the outcome (or one of its causes).

Counterfactual outcome: The outcome that would have been observed had a given individual received treatment *a* when in actuality some alternative treatment (or no treatment) was received. The counterfactual outcome can never be directly observed so must be estimated by studying an appropriate comparison group.

Decision rule: A rule that maps the entirety of a patient's history that is available up until the time of the treatment decision, taking account of the tailoring variables (input), to an individualized treatment recommendation (output).

Dynamic treatment regime: See *adaptive treatment strategy.*

Pseudo-outcome: The expected outcome for a patient with a given history if he or she goes on to receive optimal treatment in all subsequent stages.

Prescriptive variable: See *tailoring variable.*

Q-function: **"**Quality-of-treatment" function that estimates the total expected future outcome if starting from stage *j* with covariate history h_j, and following the set of decision rules *d* thereafter.

Q-learning: A reinforcement learning technique used to find the optimal sequence of actions from time-varying sets of possible actions by using the Q-functions to assign values to the expected outcome resulting from each possible pairing of history and treatment choice.

Reinforcement learning: The approach of fitting models to example inputs ("learning") in order to decide on the optimal action by predicting how each possible action would affect some long-term or cumulative outcome.

Sequential multiple-assignment randomized trial (SMART): A clinical trial design developed for collecting data suitable for developing adaptive treatment strategies while avoiding collider stratification bias.

Stage: The interval from the moment of treatment assignment until the next decision point or, in the case of the last stage, until observation of the final outcome.

Tailoring variable: A personal characteristic used to adapt the choice of treatment to an individual rather than merely assign a prognosis.

Trajectory: The actual (observed) longitudinal experience of a given patient including the covariates measured prior to each treatment beginning at each stage, the actual treatment assigned at each stage, the outcome of each stage (response or non-response to treatment), and the overall, long-term outcome.

1. INTRODUCTION

The primary objective of this thesis is to address a central problem where personalized medicine is at odds with traditional clinical trials methodology: How can we optimize the sequence of specific treatments for *specific* patients? This is particularly relevant to the field of blood and marrow transplantation, where immunosuppressive therapeutics are often administered sequentially, and their delayed effects, their potential synergy or antagonism, and their appropriateness given the complex and evolving characteristics of individual patients, remain poorly characterized. Moreover, because of limited monetary resources, logistic challenges, and heterogeneity (yet relative scarcity) of patients who develop the most severe post-transplant complications, such as treatment-refractory graft-*versus*-host disease (GVHD), there is a dearth of large randomized clinical trials to guide practice; registry data has likewise proved difficult to exploit for the purposes of developing "precision medicine" approaches. Therefore, the current work seeks to apply new statistical methodologies to the longstanding clinical problem of how best to prevent and treat GVHD.

The thesis is organized as follows:

(1) The first Literature Review (Section 2, pages 3 to 14) provides an overview of allogeneic hematopoietic cell transplantation and GVHD for those less familiar with the field.

(2) The second Literature Review (Section 3, pages 14 to 37) introduces adaptive treatment strategies and explores how to develop potential strategies relevant to GVHD through sequential multiple-assignment randomized trials. The end of this section considers the utility of observational data for informing the design of such trials, and serves as a bridge to the original work.

(3) The Objective section (page 37) and Methods section (pages 38 to 48) provide details on how CIBMTR data were used to propose an adaptive treatment strategy to prevent and treat GVHD.

(4) The Results section (pages 49 to 73) presents the adaptive treatment strategy.

(5) The Discussion (pages 74 to 94) elaborates on the originality and the limitations of the present work.

(6) Under Future Directions (pages 89 to 94), I explain how I plan to move this work forward and discuss legal, cultural and infrastructural challenges to widely applying machine learning in medicine, while the Conclusion (page 95) emphasizes the lessons that may be drawn at this time.

2. LITERATURE REVIEW: STEM CELL TRANSPLANTATION

2.1 Overview of the transplantation procedure

Allogeneic hematopoietic stem cell transplantation (AHCT) refers to the transplantation of self-renewing stem cells whose progeny eventually form the terminally-differentiated cellular components of the blood and the immune system – such as red cells, white cells and platelets.[1] AHCT is useful for treating both malignant and non-malignant diseases of the bone marrow, blood and lymph nodes. Approximately 25,000 allogeneic stem cell transplants are performed worldwide annually.[2]

The source of allogeneic hematopoietic stem cells (the "graft") may be a blood relative or an unrelated healthy volunteer donor. The graft may be extracted from bone marrow, from peripheral (circulating) blood, or from umbilical cord blood. In addition to stem cells, the graft usually contains an array of other types of white blood cells, each with a specialized function, such as T cells, B cells, natural killer (NK) cells, monocytes, and dendritic cells.

Human leukocyte antigens (HLAs) are glycoproteins found on most cells in the body. The genetic sequences at the HLA loci, and consequently the exact structures of the HLA proteins that are produced, vary tremendously among humans. Therefore, the HLA proteins identify cells as belonging to "self" or "non-self" and are paramount in directing the immune system to attack any foreign cells. In standard AHCT, preference is given to selecting donors who share most, if not all, key HLA proteins with the recipient.[3,4]

In standard AHCT, recipients receive a preparative "conditioning" regimen that comprises chemotherapy with or without radiation, as well as immunosuppressive drugs or antibodies (such as antithymocyte globulin, ATG). The conditioning regimen aims to prevent the recipient's immune system from rejecting the graft in the same way a functioning immune system would normally reject any foreign cells. Secondarily, it sometimes helps to eradicate any residual malignancy. Unfit or older

recipients receive milder "reduced intensity" or "non-myeloablative" rather than myeloablative conditioning regimens. While these less intense regimens minimize the risk of regimen-related toxicity, they confer a greater risk of cancer relapse.[5]

After completion of the conditioning phase, the graft is infused into the patient's bloodstream in a single session, similar to a blood transfusion. With the exception of syngeneic (identical twin to identical twin) transplantation, even where donors are "HLA-identical" to the recipients, recipients and donors still differ in many other cell-surface glycoproteins called "minor histocompatibility antigens" (MiHAs). Differences in HLA molecules or in MiHAs lead donor cells to attack both the recipient's normal tissues, resulting in graft-*versus*-host disease (GVHD), as well cancerous tissue, resulting in the graft-*versus*-tumor effect (GVT). GVT effects contribute to long-term cures.[6] The long sought-after Holy Grail in AHCT is a method for separating the GVH and GVT effects. Until such a method is developed, traditional immunosuppressive modalities will continue to be crucial to patient survival by minimizing the incidence and extent of GVHD, albeit at the expense of controlling the malignancy.

The two forms of GVHD, acute and chronic, are discussed subsequently. In order to minimize the incidence and extent of GVHD, recipients receive prolonged pharmacologic immunosuppression. Such immunosuppression entails a plethora of side effects but the goal is to gradually withdraw these drugs as the donor immune system learns to "tolerate" the foreign patient tissues. The taper schedule varies widely across centers and even among clinicians at the same center. Factors such as the aggressiveness of the underlying malignancy, the disease stage at the time of conditioning, subtle or florid evidence of post-transplant disease persistence or relapse, the degree of HLA mismatch between the recipient and the donor cells, prior manifestations of GVHD, and any medication-induced adverse effects the patient is experiencing are taken into account in determining the taper speed.

Apart from GVHD, AHCT recipients frequently suffer other short-term and delayed complications of the procedure. These include infections, medication

reactions, lung injury, cardiovascular disease, metabolic disease, and secondary malignancies.[1,7,8] The original disease might also relapse. This is especially true of acute myeloid leukemia (AML) and its precursor, myelodysplastic syndrome (MDS), which are the focus of the present study; reported relapse rates range from 10% to 40% for disease that is in first remission at the time of AHCT, but exceed 40% to 50% among patients transplanted with active leukemia.[5,9]

2.2 Alloreactivity and lymphodepletion

Alloreactivity is the immune response that leads to destruction of foreign cells (*i.e.*, cells that differ in genetic sequence from the host and that do not naturally reside in the host organism). Alloreactive responses can be divided into two broad categories: cell-mediated responses and humoral responses. Cell-mediated alloreactivity is executed by antigen-presenting cells and T cells, and in HLA-mismatched contexts, by NK cells. Humoral responses are characterized by the production of antibodies by B cells. Hyperacute rejection of solid organ grafts is a humoral response but is not relevant to AHCT. In AHCT, acute rejection of the recipient tissues by the donor immune cells – *i.e.*, acute GVHD – is mainly cell-mediated. Chronic rejection of the recipient tissues by donor immune cells – *i.e.,* chronic GVHD – entails both cellular and humoral responses. This is one reason why the strategies for immunosuppressive pharmacotherapy differ between acute and chronic GVHD.

Therapy to prevent and treat GVHD generally targets one or more steps in the cascade of alloreactivity that ultimately leads to tissue destruction.[10] For the purposes of this project, a number of therapies that non-selectively deplete both activated and resting T cells, including regulatory T cells, have been grouped together and coined "non-specific highly T-lymphodepleting" (NHTL) therapy. These include ATG, anti-lymphocyte globulin (ALG), alemtuzumab, and certain anti-CD45, anti-CD2, and anti-CD3 monoclonal antibodies, most prominently muromonab (OKT3). When given post-infusion to treat GVHD, purine analogue chemotherapy is also included in the NHTL category. The myriad of other therapies

that, for the most part, selectively target activated T cells or B cells without causing profound lymphopenia are grouped together as "standard" therapy, although the breadth of this list attests to the lack of any gold standard.

The significance of distinguishing between NHTL and standard therapy lies in the observation that profound lymphodepletion perpetuates a high risk of life-threatening opportunistic infections.[11-14] This distinction is also reasonable because NHTL therapeutics have been associated with higher relapse rates compared to standard immunosuppressants, particularly after reduced-intensity and non-myeloablative conditioning or when given in high doses, as was common practice in the era to which the CIBMTR data used in this analysis belong. For these reasons, NHTL prophylaxis and treatment are expected to impact survival-related outcomes differently than "standard" therapy. Note that the term "NHTL prophylaxis" refers to NHTL therapies administered prior to the development of GVHD, and "NHTL treatment" refers to NHTL therapies deployed in the setting of clinically-relevant, steroid-refractory GVHD.

The timing of NHTL therapies and their interaction with manipulable factors such as the intensity of the conditioning regimen might also influence their effect on overall survival. In fact, the impact of NHTL prophylaxis on AML and MDS relapse rates is an area of ongoing investigation, with many trials currently recruiting. For patients with AML in remission at the time of myeloablative AHCT, studies have generally not demonstrated an increase in relapse incidence with NHTL prophylaxis.[15-18] Those employing non-myeloablative conditioning without T cell add-back (whereby donor lymphocytes are infused in a prophylactic or pre-emptive manner post-transplant) usually,[19-22] but not universally,[23] reported unacceptably high relapse rates. Thus, we hypothesize that early in the transplant course, when minimal residual malignancy is likely to be present, NHTL prophylaxis might promote relapse by delaying GVT effects, which would decrease survival, particularly in recipients of non-myeloablative conditioning. By contrast, by the time GVHD supervenes, hopefully with accompanying GVT effects, patients might harbour less quiescent leukemia, so the impact of NHTL treatment on relapse rates

relative to standard GVHD treatment might be lessened. On the other hand, this may be offset by an increased risk of opportunistic infection in GVHD patients who have already been exposed to pharmacologic immunosuppression for a long period. The optimal sequence of NHTL therapies for patients with different time-varying characteristics is one question the present work aims to elucidate. Because of limitations detailed in Section 7.4, the present work should be viewed as an investigation into the extent to which registry data can be leveraged to answer this highly relevant clinical question. For the results to be generalizable to today's practice, the work would need to be repeated with a more modern data set that would include certain confounding variables not currently available (such as better indicators of the infirmity of patients at the time NHTL or standard treatment is deployed).

2.3 Clinical diagnosis and scoring of GVHD

GVHD is the most common short- and long-term complication of AHCT. When debilitating, it can negate the disease-curing benefit of transplantation. Diagnosis is often based on the pattern of organ involvement and timing of manifestations observed clinically because histologic confirmation from biopsies of target organs, while desirable, may be risky to obtain or falsely negative due to sampling error.

As a result of a National Institutes of Health (NIH) Consensus Conference, GVHD is now provisionally classified into acute and chronic forms based on the timing of onset, the pattern of organ involvement, and the tempo of evolution from inflammatory (acute) to fibrotic (chronic) manifestations.[24] However, prior to 2005, only the onset – arbitrarily divided at < 100 days or ≥ 100 days post-transplant – was considered.[25,26] Acute and chronic forms can be present simultaneously. Because the data available for this thesis concern transplants conducted between 1995 and 2007 and lack sufficient detail to apply the new classification retrospectively, the older classification scheme is used.

Acute GVHD usually occurs in the first 100 days after AHCT, with a median time to onset of 17 to 27 days, depending on the study, in patients who receive myeloablative conditioning and 3 months in those who receive non-myeloablative conditioning.[27-29] Acute GVHD typically involves some combination of skin, liver and gut. The manifestations of acute inflammation may be mild (*e.g.*, minimally symptomatic rashes, jaundice, or dyspepsia) or severe (*e.g.,* bullae and burn-like desquamation of the skin, liver failure, and hemorrhagic diarrhea). Due to immune dysfunction and to the pharmacologic immunosuppression used to treat GVHD, infections are also a frequent complication and may be fatal. The severity of acute GVHD is scored using the modified Seattle Glucksberg criteria accepted by the Keystone Consensus in 1994 (Appendix Section 9.1)[25,26] or International Bone Marrow Transplantation Registry (IBMTR) criteria that were developed by experienced clinicians on the basis of intuition.[30] These scoring systems are subject to substantial inter-rater variability[31] and observer bias (in that treating centers tend to assign lower scores than expert reviewers when ambiguity between grade II and grade III arises[32]) and they only account for a small proportion of the variability in overall survival.[33] Although alternative retrospective,[31,34,35] prospective,[36,37] and dynamic[38] acute GVHD scoring systems have been developed for the purpose of predicting survival, often highlighting the utility of such protean predictors as caloric intake, performance score or lymphopenia, none has been validated in multiple settings or gained widespread acceptance.

Chronic GVHD usually arises between 3 months and 2 years post-transplant. It presents similarly to an autoimmune syndrome. It may affect almost any organ and is clinically characterized by slow-brewing inflammation culminating in fibrosis and scarring. Again, infections are a frequent complication of the underlying immune dysfunction and of treatment. Chronic GVHD also predisposes to solid cancers, such as skin cancer and esophageal cancer. Chronic GVHD is scored imprecisely using the traditional criteria of "limited" *versus* "extensive" disease that were proposed in 1980 based on only 20 subjects (Appendix Section 9.2).[39] This 2-category scale is useful for distinguishing patients requiring systemic immunosuppression from

those for whom local treatment might suffice. Therefore, the heterogeneity of organ involvement, clinical severity, and prognosis within the extensive category was purposefully omitted from the scale. This scale, as well as a clinical "gestalt" of global functional impact (mild/moderate/severe) are included in the CIBMTR database. Chronic GVHD may also be scored precisely using the 2005 NIH Consensus Criteria[24] and other schemes,[40-42] but these metrics are not available for historical patients included in the registry. Even with the 2-category scale, misclassification is frequent; one large CIBMTR registry-based study noted incorrect designation of "limited" stage disease among 65% to 67% of sibling transplants and 43% of unrelated donor transplants.[43] Nonetheless, the original (misclassified) assignments performed better than the corrected assignments in predicting overall survival, suggesting that clinicians may often use "limited" and "extensive" in accordance with intuition rather than heed their strict definitions. The clinical impression of mild/moderate/severe outperformed both the (uncorrected) limited/extensive scale and an alternative scoring system developed using information available in the CIBMTR predecessor registries in predicting overall survival.[43] Because of a paucity of patients treated who received NHTL therapy for refractory chronic GVHD in the CIBMTR data set, the current project focuses only on acute GVHD treatment.

It is also worth noting that none of the scores developed for acute or chronic GVHD are specific to patients transplanted for AML or MDS. A recent meta-analysis showed that the survival trade-off between avoiding relapse *versus* incurring treatment-related mortality due to increasingly severe GVHD may vary according to the malignancy for which AHCT was performed.[44,45]

2.4 Inadequacy of GVHD prevention

The most important advances in preventing acute GVHD were improved HLA typing to aid donor selection, the development of prophylaxis containing calcineurin inhibitors and methotrexate, and limiting the toxicity of conditioning regimens such as by reducing the dose of total body irradiation (TBI).[46] Nonetheless, clinically-

significant acute GVHD affects 35% to 40% of patients who receive T cell-containing transplants from HLA-matched siblings and 40% to >50% of those whose receive transplant from unrelated donors.[46] Increased risk for developing acute GVHD is conferred by greater degrees of HLA disparity, unrelated compared to related donors, female donor to male recipient gender disparity, more intense conditioning regimens, TBI, and particular regimens for GVHD prophylaxis, while peripheral blood grafts confer a greater risk than bone marrow grafts, which in turn confer a greater risk than umbilical cord blood grafts.[29,47-51] Studies have identified other risk factors less consistently, *e.g.*, increasing recipient age[29,47,49,52] and chronic cytomegalovirus (CMV) carriage by the recipient or donor.[49,51]

With traditional conditioning and immunosuppressive regimens, chronic GVHD affects up to 80% of patients.[24] The main risk factor for developing chronic GVHD is prior acute GVHD, but chronic GVHD can occur *de novo*.[53] Other risk factors for chronic GVHD are similar to those for acute GVHD, including HLA disparity, female donor to male recipient gender disparity, graft source, and older patient and donor age.[48,52-55]

Both these conditions incur substantial morbidity and mortality.[7,56,57] However, to date, innovative methods for preventing acute and chronic GVHD, such as *ex-vivo* T cell depletion of the graft or the use of NHTL prophylaxis, entrain higher infection and (particularly with non-myeloablative conditioning) higher relapse rates so have not improved overall survival. Pre-emptive treatment of subclinical chronic GVHD found in surveillance skin and lip biopsies also proved unsuccessful in preventing overt chronic GVHD.[58] Therefore, better methods for preventing GVHD are urgently needed.

2.5 Inadequacy of first-line treatment for acute GVHD

The decision to initiate treatment depends on the certainty of the diagnosis of GVHD, the rate of progression, the organs involved and the degree of tissue damage or dysfunction, the side effects of therapy, and the risk of relapse of the underlying

malignancy. Consensus first-line treatment for acute GVHD is the use of high dose glucocorticoids, most commonly intravenous methylprednisolone or oral prednisone. A systematic review by the American Society of Blood and Marrow Transplantation (ASBMT) weighted the results from studies meeting minimal quality standards by the number of patients enrolled.[59] The authors found the complete response (CR) rate with prednisone alone was 48% (36% in 6 prospective studies and 65% in 3 retrospective studies) and the estimated probability for surviving 6-months post glucocorticoid initiation was 66%.

The optimal glucocorticoid dose remains unclear. In 1998, a randomized controlled trial (RCT) established that starting at 2 mg/kg/day methylprednisolone (equivalent to prednisone 2.5 mg/kg/day) yielded similar complete response rates, rates of progression to grade III to IV GVHD and overall survival (OS) as 10 mg/kg/day, allowing for the fact that 55% of patients in the low-dose arm switched to the higher dose after 5 days of treatment.[60] Since that publication, the methylprednisolone dose is almost universally capped at 2 mg/kg/day. A subsequent retrospective study published in 2009 indicated that in patients with grade I-II GVHD, initiating treatment with prednisone 1 mg/kg/day was sufficient.[61] A prospective trial addressing the preferred glucocorticoid dose for first-line treatment of acute GVHD has completed accrual (NCT00929695). Meanwhile, there is variability among centers and among clinicians within a given center in the dose of steroids prescribed for patients with grade I-II acute GVHD.[59]

The optimal duration of full-dose steroid therapy and the optimal rate for tapering steroid doses are likewise undefined. Because of their adverse effects, the taper is usually initiated as soon as patients show substantial improvement, but the benchmarks for successful tapering are not clearly established.[62]

As reviewed by the ASBMT, no well-designed RCT has demonstrated any benefit to combining glucocorticoids with other immunosuppressive drugs for first-line treatment.[59] These studies suffer from misclassification of acute GVHD severity, small sample size, variable timing of response assessment, variable definitions of

complete response, the inclusion of patients with mild disease (grades I-II) alongside those with severe disease (grades III-IV), and occasionally the use of historical controls or the absence of any glucocorticoid-only control arm. Moreover, overall survival is a poor marker for drug efficacy because patients who survived thanks to subsequent salvage treatments are counted as successes instead of failures, thus inflating the apparent efficacy of the investigational agent. Despite the lack of any apparent benefit to first-line multidrug therapy, in clinical practice, patients often receive combination therapy because they were already on an (often tapering) immunosuppressive drug at the time acute GVHD developed, or in order to spare steroid side effects, or as part of a clinical trial. Importantly, no trial has examined whether particular drugs used for preventing GVHD influence the efficacy of specific drugs later deployed for treating GVHD.

In summary, approximately one out of every two patients with acute GVHD fails to respond adequately to first-line treatment.

2.6 Inadequacy of treatment for refractory acute GVHD

The prognosis of patients requiring second-line therapy is poor. The aggregated CR rate among 28 studies reviewed by the ASBMT was 32%, with lower CR rates reported among the 11 prospective studies.[59] The weighted probability of OS 6-months after initiation of second-line therapy was 49%. Nearly all studies of agents to treat glucocorticoid-refractory acute GVHD were retrospective or single-arm phase II trials. In addition to the caveats noted for interpretation of studies in the first-line treatment setting, interpretation of the results of second-line trials is hampered by the lack of a uniform definition of steroid-refractory acute GVHD. Again, no trial has examined whether particular drugs used for prophylaxis or for first-line treatment of GVHD influence the efficacy of specific drugs later deployed for treating refractory GVHD.

2.7 Inadequacy of treatment for chronic GVHD

Failure to use validated criteria for diagnosing chronic GVHD and scoring its severity limit the generalizability of most reported trials in this area.[63-65] Until the 2005 NIH consensus, there were no uniform response definitions either.[66] Current consensus for first-line therapy was outlined at the 2009 Regensberg conference. First-line treatment for mild and moderate chronic GVHD should generally include systemic corticosteroids and topical immunosuppressive agents. No retrospective or controlled studies have established the optimal dose of prednisone but a starting dose of 1 mg/kg/day is extrapolated from the acute GVHD setting. Randomized controlled trials showed no benefit to incorporating azathioprine,[67] mycophenolate mofetil,[68] cyclosporine,[69] thalidomide,[70] or hydroxychloroquine[71] in first-line therapy. Nonetheless many of these and other agents, which have not been studied in the first-line setting, are often used "off-label" in an attempt to permit a lower dose of steroids (to decrease their myriad adverse effects) or because corticosteroids alone are felt to be inadequate for severe chronic GVHD (albeit no controlled trial has established the optimal treatment for severe disease).[63]

Approximately half of patients with chronic GVHD require "second-line" therapy.[64] Failure of first-line treatment was associated with a 10-year cumulative incidence of death from chronic GVHD of 62% (95% CI, 51% to 72%).[40] No controlled studies inform the choice of therapeutic agent in this population, and as noted in the Regensberg consensus document, "a 'trial-and-error' approach remains the only way to identify the drug or drug combination effective in an individual patient."[64]

Most patients require long-term treatment. Among surviving patients with chronic GVHD, less than 15% successfully discontinue immunosuppressive therapy at 1 to 2 years following transplantation, ~25% remain on therapy beyond 4 years, and ~5 to 15% are treated beyond 7 to 10 years.[56,72,73]

Recommendations for the treatment of chronic GVHD are hampered by the fact that no trial has examined whether particular drugs used for prevention and for treatment of acute GVHD influence the efficacy of specific drugs later deployed for treating chronic GVHD. Also, since the publication of the 2005 NIH Consensus definition for the diagnosis of acute and chronic GVHD that no longer relies on the arbitrary delineation at day 100, studies have reclassified 15% to 48% of "chronic GVHD" patients as actually manifesting "persistent, recurrent or late-onset acute GVHD" and 20% to 48% as manifesting "overlap syndrome," while only 5% to 57% retained a diagnosis of classic chronic GVHD.[74-77] The problem of labelling "late acute GVHD" and "overlap syndrome" as "chronic" GVHD is especially pertinent to the current project because patients who were first treated for "chronic" GVHD were not entered into the analysis of the best treatment for steroid-refractory acute GVHD. It is possible that many such patients would now be classified under "late acute GVHD" or "overlap syndrome." The Regensberg consensus document speculates that late acute GVHD and overlap syndrome with "dominating acute features" should be treated analogously to classic acute GVHD.[63]

3. LITERATURE REVIEW: ADAPTIVE TREATMENT STRATEGIES

3.1 Personalized medicine and GVHD

Individual patients respond differently to the same treatments, bearing in mind both the primary outcome and side effects. Traditional design and reporting of clinical trials aim to capture and explain the heterogeneity of responses through stratification according to baseline risk or other salient patient characteristics or through subgroup analysis. Nonetheless, the "best" treatment identified by a generic RCT might not be the "best" treatment for a particular patient because (1) the combination of characteristics that is the "signature" of a particular patient might not be captured by the coarse strata or the coarse subgroups in the RCT; (2) the effect of time-varying characteristics of the patient might dwarf the initial effect of the baseline strata or subgroup to which the patient belonged; and (3) there may be delayed synergism or antagonism between the treatment examined in the trial

and heterogeneous upstream or downstream treatments not included in the data capture or analysis. Inter-patient variability and intra-patient variability over time leading to heterogeneity of responses is the motivation for "personalized medicine" – a paradigm that emphasizes systematic use of an individual patient's ever-updated information to optimize that patient's health care.[78] Management of chronic disorders poses challenges for the personalized medicine paradigm because the personalization must be marshalled through multiple stages of intervention. These challenges obviously apply to chronic GVHD because the median duration of immunosuppression is 2 to 3 years from its initial diagnosis and ~15% of patients require more than 7 years of immunosuppression.[56,72,73] However, they apply to "acute" GVHD as well because although 35% to 50% of patients respond to first-line steroid treatment, achieving CR in a median of 3 to 7 weeks (depending on the study[79-81]), two-thirds of responders will relapse with acute GVHD,[81] and 40% to 47% of patients who experience acute GVHD will develop chronic GVHD, often within a year of initiating steroids.[29,81] Consequently, the first episode of acute GVHD is often a prelude to long-term, continuous immunosuppressive therapy.

3.2 Adaptive treatment strategies

"Dynamic treatment regimes" (DTRs) are sequences of decision rules (one per stage of intervention) for adapting treatments to the time-varying state of an individual patient, where decisions made at one stage may affect those to be made at a future stage and where the long-term effect of the current treatment may depend on the performance of future treatment choices.[82] For example, giving prednisone at a dose of 1 mg/kg to a patient newly presenting with grade II acute GVHD is a legitimate option because if it fails, evidence from a retrospective study shows that the patient can likely be salvaged with 2 mg/kg of prednisone or with other agents, and starting with the lower dose will not compromise her long-term outcome.[61] The term DTR is frequently used in the statistical literature to describe a specific instance of a personalized treatment regimen. We use the term "adaptive treatment strategy" (ATS) instead of DTR because it better communicates this intent to

clinicians. ATSs operationalize the sequential decision-making process involved in the personalized chronic care model. The decision points in a longitudinal ATS may occur at regular intervals, such as bimonthly follow-up visits, or at defined clinical events, such as remission, relapse or onset of a complication. The ATSs are considered dynamic because the recommended actions in regard to a particular patient can change based on observations made about him or her over time (such as whether the patient's GVHD responds to first-line glucocorticoids). By formalizing and studying ATSs, we hope to improve long-term outcomes. This can be done by comparing two (or more) ATSs in terms of their utility, or by identifying an optimal ATS.

3.3 Notation and data structure

For simplicity, the approach[83] will be expounded for the setting of two treatment intervals, but these methods extend naturally to any finite number of intervals. Longitudinal data on a single patient are given by the trajectory ($C_1, O_1, A_1, C_2, O_2, A_2, Y$), where C_j and O_j (j = 1, 2) denote the set of covariates measured prior to treatment beginning at the jth interval. Y is the outcome at the end of interval 2; the choice of outcomes is discussed in Section 3.8 below. A_j (j = 1, 2) is the set of actions (treatments), one of which could be assigned at the jth interval subsequent to observing O_j. The possible actions within the set are represented by a_{kj}. Two types of covariates are distinguished. Those represented by O_j interact with treatment and are called *tailoring* or *prescriptive* variables; they directly impact the optimal choice of a_{kj} from A_j. Those represented by C_j do not interact with treatment but potentially confound the relationship between treatment and outcome or may simply be risk factors for the outcome (but not predictive of treatment choices and hence not true confounders). Any variable included in O_j may also be a confounding variable, *i.e.*, a shared independent cause of both treatment and outcome.

The data set consists of a random sample of n patients. The history at each interval is defined as $H_1 = (C_1, O_1)$ and $H_2 = (C_1, O_1, A_1, C_2, O_2)$. Two possible treatments at each interval are coded as $A_j \in \{0, 1\}$.[84] However, analysis and

inference methods for 3 or more possible discrete actions at time j[85,86] or for "continuous" actions corresponding to percent changes in dose[87] have been developed. Treatment assignment from A_j may depend on the values of covariates C_j and O_j. A two-interval ATS consists of two decision rules, (d_1, d_2), with $d_j \equiv d_j(H_j) \in A_j$. Alternative notation schemes are detailed by Wallace and Moodie.[88]

3.4 Estimating optimal ATSs

Several analysis and inference methods have been developed to estimate the optimal ATS drawing on the fields of reinforcement learning (computer science) and causal inference. They include frequentist[89-91] and Bayesian[85,92,93] parametric approaches as well as semi-parametric approaches.[84,94] Two ways to distinguish among these methods are by how they handle collider stratification bias and how they estimate the contrast between different trajectories.

Collider stratification bias arises when conditioning on an intermediate observation leads to spurious correlation between the exposure (*i.e.*, treatment) and outcome of interest because of unmeasured or unknown variables that are a common cause of both the intermediate observation and outcome (Figure 1).[95-97]

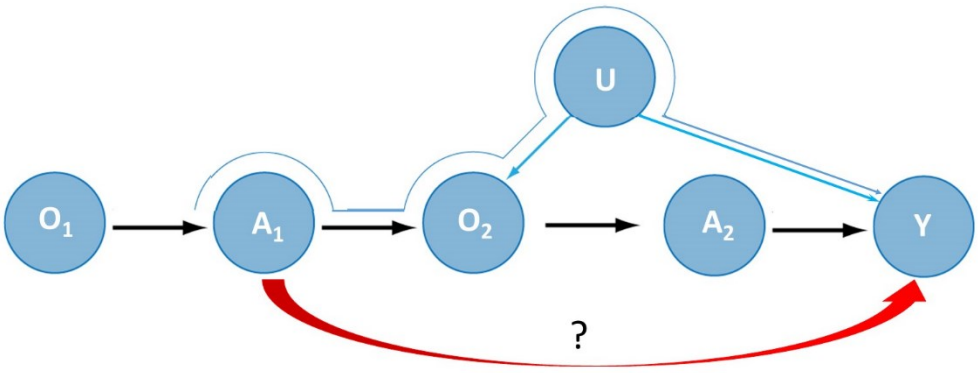

Figure 1. Collider stratification bias. *Suppose the choice of GVHD prophylaxis (A_1) truly has no effect on mortality (Y). Suppose there is an unobserved variable U, such as a pharmacogenetic polymorphism that decreases the probability of responding to prophylaxis and is positively correlated with the severity of GVHD (O_2) and with mortality (Y). If randomization to prophylaxis is successful, there should be no correlation between A_1 and U. However, there will be a conditional correlation between A_1 and U given GVHD severity: A patient with severe GVHD is more likely to harbour the deleterious polymorphism. Running a regression of Y on (O_1, A_1, O_2, A_2) necessarily conditions on the intermediate observation O_2. Conditional on O_2, there may be a non-zero effect of A_1 on Y, which is different from the true effect. Thus, all "all-at-once" regression may yield a biased assessment of the effectiveness of treatment.*

A mathematical proof how collider stratification bias arises from regressing the outcome on entire trajectories "all-at-once" is found in Chakraborty and Moodie.[98] Methods of estimating the effect of different ATSs must avoid introducing this bias by eliminating conditioning on intermediate observations (*e.g.*, with weighting techniques or stage-wise estimation), or by assuming that no such unmeasured variables on a common causal pathway exist.

Another distinguishing characteristic of approaches to estimating the best ATS is the *contrast* function that is employed, *i.e.*, the function used to describe the impact of an interval-specific treatment relative to some reference treatment, such as standard of care. For example, a regret function is loosely defined as the difference between the utility of the optimal decision for a fixed set of patient characteristics and treatment options and the actual decision taken,[99] while the welfare contrast (or blip) is the difference between the utilities corresponding to any two decisions under the same set of patient characteristics and treatment options.[84] Where one of these two decisions is the optimal decision, the welfare contrast is equivalent to the regret function. Thus, two broad approaches to designing ATSs are:

(1) Explicitly estimating parameters of the regret or blip functions and minimizing those functions; or
(2) Directly estimating the utility of different strategies and seeking to maximize the utility.

The stage-wise approach used in this thesis, Q-learning, belongs to the first category.

3.5 Decision rules

It warrants emphasizing that an ATS is a collection of decision rules, not the actual experiences of patients that result from them. Thus, under the rule "Give induction chemotherapy $A_1 = 1$ followed by maintenance chemotherapy $A_2 = 1$ if response, else if no response give second-line induction $A_2 = 0$," some patients will

realize the experience $A_1 = 1 \rightarrow$ response $\rightarrow A_2 = 1$ while others will realize the experience $A_1 = 1 \rightarrow$ no response $\rightarrow A_2 = 0$.

All treatment-relevant information from the patient's entire history, *i.e.*, tailoring variables such as responses to past treatments or lack thereof, is input into the decision rule. The decision rule in turn outputs individualized treatment recommendations. Such recommendations may include when to start treatment, when to stop treatment, when to modify or completely change treatment, and which specific treatment to deploy subsequently.

3.6 Fundamental approach to Q-learning

Q-learning is a form of dynamic programming in that estimation begins at the last interval and the optimal treatment at each interval, moving backwards in time, is then found by estimating the impact of treatment in that interval on a "pseudo-outcome." The "pseudo-outcome" is constructed by assuming all subsequent treatments are optimal; it is the patient-specific predicted (counterfactual) outcome had that patient received optimal treatment in future intervals.

In observational settings, confounding variables are typically present. In randomized trials, we assume there are no confounding variables C_j since successful balanced randomization will preclude any association between C_j and treatment assignment. However, there may be risk factors that predict outcome but are not useful for tailoring treatments, and so we retain C_j. Whatever the data source, we consider $H_1 = (C_1, O_1)$ and $H_2 = (C_1, O_1, A_1, C_2, O_2)$. The *Q-functions* are defined as follows:[100,101]

$$Q_2(H_2, A_2) = E[Y|H_2, A_2],$$
$$Q_1(H_1, A_1) = E\left[Q_2\left(H_2, a_{k2}^{opt}\right)\middle|H_1, A_1\right].$$

where a_{k2}^{opt} is the optimal treatment that could have been administered for action A_2. Put into words, the first formula yields the expected mean outcome given a particular history observed up until the start of interval 2. The second formula

yields the mean outcome given the history observed from baseline up until time 1 and given the actual treatment administered for A_1 while assuming optimal treatment is administered in the second interval. An omniscient analyst with knowledge of the true multivariate distribution of the data could therefore deduce the optimal ATS = (d_1, d_2) using backwards induction, so that

$$d_j^{opt} = \arg\max_{a_j} Q_j\left(h_j, a_{kj}^{opt}\right), \quad j = 1, 2$$

where h_j is the individual patient's history up until the start of interval j and a_{kj}^{opt} is the optimal treatment that could have been administered during interval j. In practice, the true Q-functions must be estimated from the data. Any model may be assumed for the Q-functions. For illustrative purposes, consider a linear model so that the jth interval Q-function is modelled as

$$Q_j\left(H_j, A_j; \beta_j, \psi_j\right) = \beta_j^T H_{j0} + (\psi_j^T H_{j1})A_j$$

where H_{j0} contains the collection of variables that have a predictive (prognostic) effect on the outcome and do not modify the treatment effect while H_{j1} contains the covariates that do affect the choice of treatment as they represent effect modifiers. Both H_{j0} and H_{j1} contain a constant (intercept) term. Note that $(\psi_j^T H_{j1})A_j$ describes a contrast function. The regression coefficient parameters β_j indicate the strength of the effect of the predictive variables, and those belonging to ψ_j correspond to the potential tailoring variables. The Q-learning algorithm for identifying the optimal ATS is implemented in five steps:

Table 1. Q-learning algorithm illustrated with linear Q-functions for binary treatments

<u>*Step 1:*</u> *Estimate the interval 2 parameters.* Use ordinary least squares to regress the outcome at the final date of follow-up on all confounding variables, the treatments of interest, and interactions between the treatments and potential tailoring variables:

$$\left(\hat{\beta}_2, \hat{\psi}_2\right) = \arg\min_{\beta_2, \psi_2} \frac{1}{n} \sum_{i=1}^{n} (Y_i - Q_2(H_{2i}, A_{2i}; \beta_2, \psi_2))^2$$

where $i = 1, \ldots, n$ indexes the patients.

<u>*Step 2:*</u> *Estimate the optimal interval 2 rule by substitution:*

$$\hat{d}_2^{opt}(h_2) = \arg\max_{a_2} Q_2(h_2, a_2; \hat{\beta}_2, \hat{\psi}_2).$$

<u>*Step 3:*</u> *Create the "pseudo-outcome" of interval 1 by assuming that patients had received optimal treatment for interval 2.* Patient by patient, determine which A_2 treatment would lead to the best outcome given each patient's observed values of all previous treatments and confounding variables, using the regression parameter estimates from Step 1. For each patient *i*, create a "pseudo-outcome" that is the predicted outcome for that patient under his or her own optimal treatment at the A_2 decision point:

$$\tilde{Y}_{1i} = Q_2(H_{2i}, a_2; \hat{\beta}_2, \hat{\psi}_2).$$

Note that estimation of the contrast function is inherent in finding $Q_2(H_{2i}, a_{k2}^{opt})$. That is,

$$Q_2(H_{2i}, a_2^{opt}) = \begin{cases} \hat{\beta}_j^T H_{jo} & \text{if } d_{2i}(H_{2i}) = 0 \\ \hat{\beta}_j^T H_{jo} + \left(\psi_j^T H_{j1}\right) A_j & \text{otherwise.} \end{cases}$$

<u>*Step 4:*</u> *Estimate the interval 1 parameters.* Using ordinary least squares regression, regress the pseudo-outcome from Step 2 on all confounding variables, all interval 1 treatments, and interactions between the interval 1 treatments and all potential tailoring variables:

$$\left(\hat{\beta}_1, \hat{\psi}_1\right) = \arg\min_{\beta_1, \psi_1} \frac{1}{n} \sum_{i=1}^{n} (\tilde{Y}_{1i} - Q_1(H_{1i}, A_{1i}; \beta_1, \psi_1))^2.$$

<u>*Step 5:*</u> *Estimate the interval 1 optimal rule by substitution*. Patient by patient, determine which A_1 treatment would lead to the best outcome given each patient's observed values of baseline/confounding variables, using the regression parameter estimates from Step 4:

$$\hat{d}_1^{opt}(h_1) = \arg\max_{a_1} Q_1(h_1, a_1; \hat{\beta}_1, \hat{\psi}_1).$$

Note that in Steps 3 and 5, the optimal ATS is identified for each patient given the tailoring variables included in the model. In steps 1 and 4, treatment is personalized on the variables for which interactions with treatment were included in the model. The estimated optimal ATS is given by $(\hat{d}_1, \hat{d}_2)$. From the above, it is evident that stage-wise methods like Q-learning are not vulnerable to collider stratification bias because they do not condition on any covariate that occurs after the treatment of interest in that stage.

3.7 Tailoring variables

Tailoring variables must be able to discriminate optimal treatments. That is, the effect sizes for the fixed treatment options must vary meaningfully as a function of the tailoring variables. Technically, this can be expressed as follows: Let O represent a putative tailoring variable (hence o represents specific levels of that variable), A the treatment type coded as $a = 0$ or $a = 1$, and Y the primary outcome (where a higher value is preferred). Then,

$$\begin{aligned} Y &= \beta_0 + \beta_1 o + \psi_0 a + \psi_1 o a + error \\ &= \beta_0 + \beta_1 o + (\psi_0 + \psi_1 o) a + error. \end{aligned}$$

If $(\psi_0 + \psi_1 o)$ is positive for some values of O and zero or negative for other values of O, then O is truly a tailoring variable. The magnitude of the absolute value of $(\psi_0 + \psi_1 o)$ will determine the strength of the "prescriptive" effect of the tailoring variable, *i.e.*, the impact that the variable has on the choice of therapy, as shown in Figure 2 on the following page.

The net effect of multiple covariates can also be used for tailoring treatment, even if each individual covariate does not qualitatively interact with treatment. That is, $(\psi_0 + \psi_1 O_1 + \psi_2 O_2 + \ldots + \psi_p O_n)$ may be positive for some values $(o_1, o_2, \ldots, o_p)$ and zero or negative for other values of the linear combination of predictors. This makes it possible to tailor treatment to the individual patient by accounting for many characteristics of the person simultaneously.

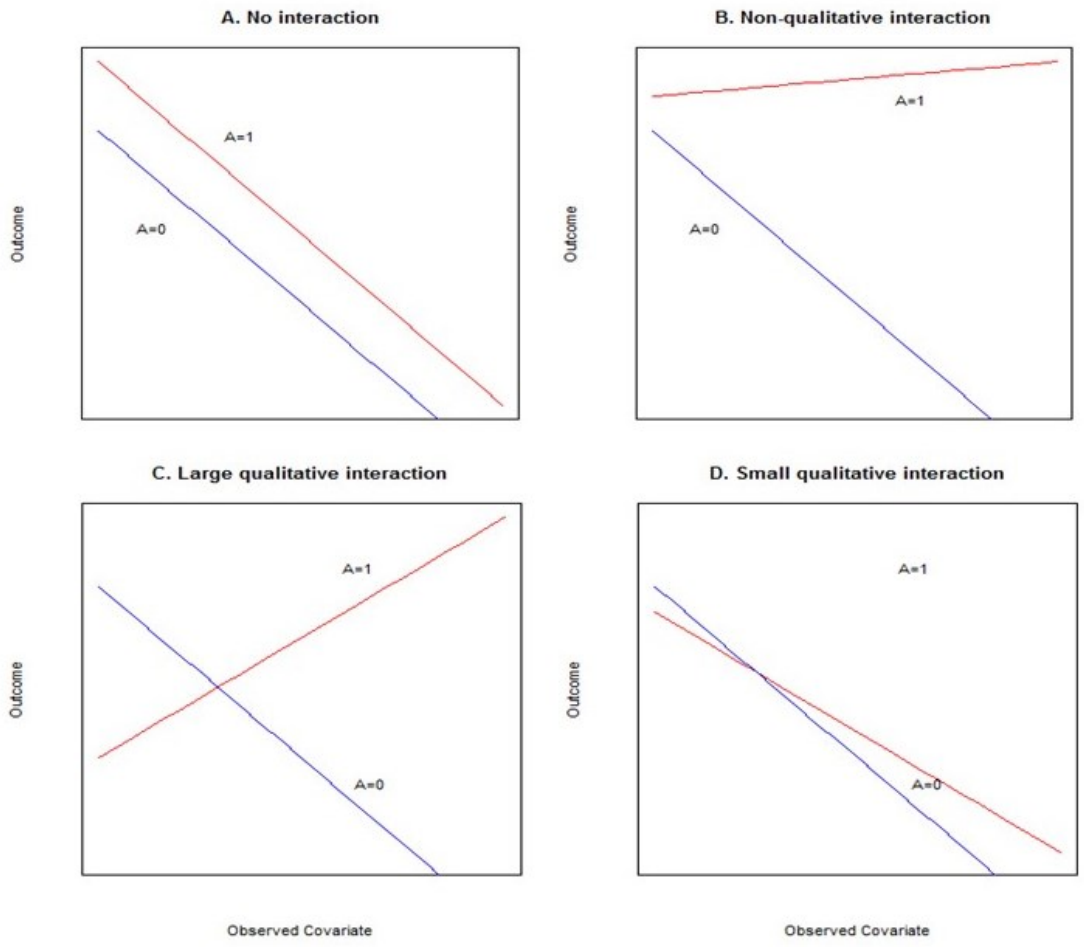

Figure 2. Some covariates are useful for individualizing treatment choice. *Assume the goal is to maximize the outcome. Panel A shows no interaction: Treatment 1 is equally and uniformly better than treatment 0 at all levels of the covariate. Panel B shows a non-qualitative interaction: The magnitude of the benefit of treatment 1 over treatment 0 differs depending on the level of the covariate. However, the covariate is not a tailoring variable because the same treatment choice would apply to all patients. Panel C shows a large qualitative interaction. Treatment 0 is better at low levels of the covariate while treatment 1 is preferred at higher levels of the covariate. The covariate is useful for tailoring treatment to the individual patient. Panel D shows a qualitative interaction of lesser magnitude, but the same conclusion as in panel C applies.*

Defining good tailoring variables is a legitimate primary or secondary objective in designing optimal ATSs. The Food and Drug Administration defines a predictive biomarker as "a baseline characteristic that categorizes patients by their likelihood of response to a particular treatment relative to no treatment" when measured prior to treatment.[102] A broader definition would acknowledge that the

predictive biomarker might predict response relative to alternative treatment choices. Many of the biomarkers that we colloquially call "prognostic" are in fact "predictive" in this sense. For example, translocation of chromosomes 15 and 17 in AML predicts response to all *trans*-retinoic acid (ATRA) and arsenic; its favourable "prognostic" implication depends entirely on the treatment we plan to give. We use the term *prescriptive* variables for information that changes what we ought to write on the prescription pad. With regard to all patients with AML, t(15;17) serves as a prescriptive variable because it identifies which patients ought to be prescribed ATRA.

Categorical and continuous covariates may be used as tailoring variables. For example, the ideal target range of a manipulable biologic variable may need to be identified in order to optimize survival. Cotton and Heagerty[103] provide an example of how to do this by considering ATSs in end-stage renal disease patients that adjust erythropoietin dose A*j* at time *j* multiplicatively based on the dose level in the previous month, A_{j-1}, and the most recent hematocrit measurement, O_j:

$$A_j \in \begin{cases} A_{j-1} \times (0, 0.75) \ \ if \ O_j \geq \varphi - 3 \\ A_{j-1} \times (0.75, 1.25) \ \ if \ O_j \in (\varphi - 3, \varphi + 3) \\ A_{j-1} \times (1.25, \infty) \ \ if \ O_j \geq \varphi + 3 \end{cases}$$

where φ is the midpoint of the target hematocrit range and hematocrit is the percentage of the total blood volume constituted by red blood cells. To find the optimal ATS that would maximize survival time, φ was varied from 31% to 40% and hence each patient's observed hematocrit at a given time point, O_j, became a tailoring variable. Estimating the ideal target hematocrit, or equivalently estimating which hematocrit upper and lower boundaries should prompt a change in erythropoietin dose, was the goal of the analysis.

In the erythropoietin example, the parameter φ does not vary over time, but rather is the same at each month *j*. This property is called *parameter sharing* (over time). One could envision situations in which it might be desirable to use time-varying values of φ. For example, in the treatment of chronic myeloid leukemia

(CML), the *rate* at which patients who initiate treatment with a tyrosine kinase inhibitor (TKI) ought to achieve particular levels of reduction in BCR-ABL mRNA transcripts detectable in the blood in order to maximize survival time can be captured by assigning φ decreasing values of transcript burden the further away from the patient is from TKI initiation (*e.g.*, ≤10% International Scale by 3 months and ≤ 0.1% IS by 12 months).[104-106] An ATS for CML might be represented by the following rule:

$$A_j \in \begin{cases} Switch\ to\ an\ alternative\ TKI\ if\ O_j > \varphi_j \\ Continue\ current\ TKI\ if\ O_j \leq \varphi_j \end{cases}$$

where A_j is the action to be taken at time j, O_j is the observed quantification of BCR-ABL transcripts at time j, and φ_j is the upper acceptable limit for O_j. Competing ATSs incorporating different time-varying values of φ_j, as well as different static parameters such as baseline Sokal risk scores, could be compared for their effect on survival. Studies that take this approach to estimating the time-varying target ranges that ought to prompt a switch of therapy would be particularly interesting in CML, acute lymphoblastic leukemia, and other malignancies where quantification of "minimal residual disease" (MRD) is being incorporated into treatment algorithms but "safe" and "dangerous" MRD levels likely depend on the initial burden of disease, on the time since initiating therapy, on the toxicity of the alternative treatments, and on patient-specific covariates, and are not yet clearly defined.

3.8 Choice of endpoints

What is an optimal ATS? The answer depends on the clinical question. Traditionally, the goal was to optimize the mean long-term outcome, *i.e.*, the outcome observed at the final stage of intervention or at the final observation time. However, any utility function can be employed as the optimization criterion. Thus, the outcome Y may be a single measurement at a uniform or patient-specific time point, or a function, $f(\cdot)$, of some or all covariates measured throughout the study. Appendix Section 9.3 offers examples of endpoints and corresponding optimization criteria that can be the focus of an ATS. The aim of the current work is to maximize

the proportion of patients alive and disease-free at 2 years post AHCT. The binary endpoint (alive and disease free *versus* dead and/or relapsed) mandates a logistic regression. (Ongoing work on maximizing disease-free survival time and minimizing the duration of immunosuppression is not presented here but is noted in Section 7.5, Future Directions.)

3.9 Form of the Q-function to accommodate the endpoint used in this thesis

With binary (Bernoulli) outcomes, the logistic model of the form

$$Q_1^{opt}\left(H_1, A_{1;\beta_1,\psi_1}\right) = Q_2(H_{2i}, a_2^{opt}; \hat{\beta}_2, \hat{\psi}_2) = \text{expit}\left(\hat{\beta}_2^T H_{20,i} + |\hat{\psi}_2^T H_{21,i}|\right)$$

can be used,[107,108] where expit(x) = $e^x/(1 + e^x)$ is the inverse logit function, bounded by [0, 1]. To find the pseudo-outcome specific to each patient *i*, the strictly-increasing logit of the probability of success in the 2nd interval under the optimal DTR, $\hat{\beta}_2^T H_{20,i} + \left(|\hat{\psi}_2^T H_{21,i}|\right)$ is maximized as in Table 1, *Step 3* because that enables the use of ordinary least squares regression to estimate the interval 1 parameters in *Step 4.* Thus, the patient-specific pseudo-outcome $\hat{Y}_{1i}$ is not the predicted value of the second-interval Q-function under optimal treatment (*i.e.*, it is not 1 = success and 0 = failure); instead, it represents a transformation of that expected outcome and can be interpreted as the probability of achieving success given optimal treatment. This is the method used for the 2-year disease-free survival analysis in this work. The Q-learning algorithm for a discrete outcome is detailed in Table 2.

Table 2. Q-learning algorithm for a discrete outcome
<u>*Step 1:*</u> *Estimate the interval 2 parameters.* Use generalized linear modelling (GLM) regression with a strictly increasing link function, $f(\cdot)$, to estimate $(\hat{\beta}_2, \hat{\psi}_2)$ of the conditional mean model for the outcome $f(\mathrm{E}[Y|H_{2i}, A_{2i}]) = Q_2\ (H_{2i}, A_{2i}; \beta_2\psi_2)$. A logistic link function satisfies the requirement for being strictly increasing.
<u>*Step 2:*</u> *Estimate the optimal interval 2 rule by substitution:* $$\hat{d}_2^{opt}(h_2) = \arg\max_{a_2} Q_2\ (h_2, a_2; \hat{\beta}_2, \hat{\psi}_2).$$
<u>*Step 3:*</u> *Create the "pseudo-outcome" of interval 1 by assuming that patients had received optimal treatment for interval 2.* Set: $$\tilde{Y}_{1i} = f^{-1}(Q_2(H_{2i}, a_2^{opt}; \hat{\beta}_2, \hat{\psi}_2)), \quad i = 1, \dots, n.$$
<u>*Step 4:*</u> *Estimate the interval 1 parameters.* Using another GLM, regress the pseudo-outcome from Step 3 on all confounding variables, all interval 1 treatments, and interactions between the interval 1 treatments and all potential tailoring variables.
<u>*Step 5:*</u> *Estimate the interval 1 optimal rule by substitution*. Patient by patient, determine which A_1 treatment would lead to the best outcome given each patient's observed values of baseline/confounding variables, using the regression parameter estimates from Step 4: $$\hat{d}_1^{opt}(h_1) = \arg\max_{a_1} Q_1\ (h_1, a_1; \hat{\beta}_1, \hat{\psi}_1).$$

3.10 Standard errors when using Q-learning

There are two difficulties in using standard methods to calculating accurate standard errors and confidence intervals for regression performed in the course of Q-learning. The first problem is that except for the last interval, the pseudo-outcome is used in the regressions. The pseudo-outcome depends on previously-

estimated parameters $\hat{\beta}_j$ and $\hat{\psi}_j$ from later intervals. The variability of those quantities needs to be taken into account. The second problem is that constructing the pseudo-outcome requires taking a maximum, and the resulting non-smoothness violates the usual large-sample assumptions. Therefore, in this work, bootstrapped analysis is used to calculate standard errors on the regression coefficients in the Q-functions.[109]

3.11 Practical development of ATSs with SMARTs

Sequential-multiple assignment randomized trials (SMARTs) entail randomizing patients to interventions each time a treatment choice must be made. SMART designs provide data that can be used to assess the comparative efficacy of the treatment options available at each isolated decision point, but they also provide data essential for comparing the effectiveness of entire strategies and for personalizing treatment over time.

SMARTs are becoming popular in the field of psychology. Published or completed studies address ATSs for drug addiction[110], attention deficit-hyperactivity disorder[111], schizophrenia[112], depression[113,114], alcoholism (NCT00115037), and Alzheimer disease.[115] Ongoing SMARTs are addressing treatment of bipolar disorder (NCT01588457), obsessive-compulsive disorder (NCT01148316), depression (NCT01880814), autism (NCT01724047), obesity (NCT1350531) and illicit drug use during pregnancy (NCT01177982). Although studies may be designed as SMARTs[115-117], the outcomes from the different randomizations (*e.g.*, initial treatment *versus* treatment for those not responding to initial treatment) are sometimes reported in separate publications, as is the case with Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)-Schizophrenia[112,118], CATIE-Alzheimer disease[119] and Sequenced Treatment Alternative to Relieve Depression (STAR*D).[120] If the goal is to identify an optimal ATS, we encourage reporting the results in a comprehensive publication to communicate the proposed optimal ATS clearly.

3.12 A SMART might address GVHD prophylaxis and treatment better than other study designs

Because of the diversity of possible prophylactic and therapeutic treatments for GVHD, the current work simplifies the choices by categorizing them as "non-specific highly T-lymphodepleting" (NHTL) or not. Based on the ASBMT systemic review,[59] suppose that the incidence of acute GVHD is 40% with standard prophylaxis and that 52% of patients who develop GVHD require salvage treatment, regardless of the type of prophylaxis received. Further suppose that NHTL prophylaxis decreases the incidence of steroid-refractory GVHD by half and that NHTL treatment improves 1-year survival among those requiring salvage treatment from 49% to 59% in patients who did not receive NHTL prophylaxis, but due to infection and relapse, decreases 1-year OS to 25% in those who previously received NHTL prophylaxis. Finally, suppose that among those without GVHD or with steroid-responsive GVHD, a rapid taper of immunosuppression improves 1-year survival compared to a slow taper, at 76% *versus* 66%, in the standard prophylaxis arm, but due to infection and relapse, a slow taper decreases survival among those who received NHTL prophylaxis to 60%. An omniscient being would know the true trajectories and survival rates of all groups of patients in the population, as depicted in Figure 3 (next page).

There are 8 possible adaptive treatment strategies, which we can consider "clinical practice guidelines." Under these assumptions, the anticipated 1-year OS for a population that followed the given practice guideline is indicated in parentheses:

1. $A_1 = 1$ followed by $A_{2\text{-}taper} = 1$ if response, else $A_{2\text{-}treatment} = 1$ (70.7%);
2. $A_1 = 1$ followed by $A_{2\text{-}taper} = 0$ if response, else $A_{2\text{-}treatment} = 0$ (58.9%);
3. $A_1 = 1$ followed by $A_{2\text{-}taper} = 1$ if response, else $A_{2\text{-}treatment} = 0$ (73.2%);
4. $A_1 = 1$ followed by $A_{2\text{-}taper} = 0$ if response, else $A_{2\text{-}treatment} = 1$ (56.4%);
5. $A_1 = 0$ followed by $A_{2\text{-}taper} = 1$ if response, else $A_{2\text{-}treatment} = 1$ (72.5%);
6. $A_1 = 0$ followed by $A_{2\text{-}taper} = 0$ if response, else $A_{2\text{-}treatment} = 0$ (62.5%);
7. $A_1 = 0$ followed by $A_{2\text{-}taper} = 1$ if response, else $A_{2\text{-}treatment} = 0$ (70.4%);
8. $A_1 = 0$ followed by $A_{2\text{-}taper} = 0$ if response, else $A_{2\text{-}treatment} = 1$ (64.5%).

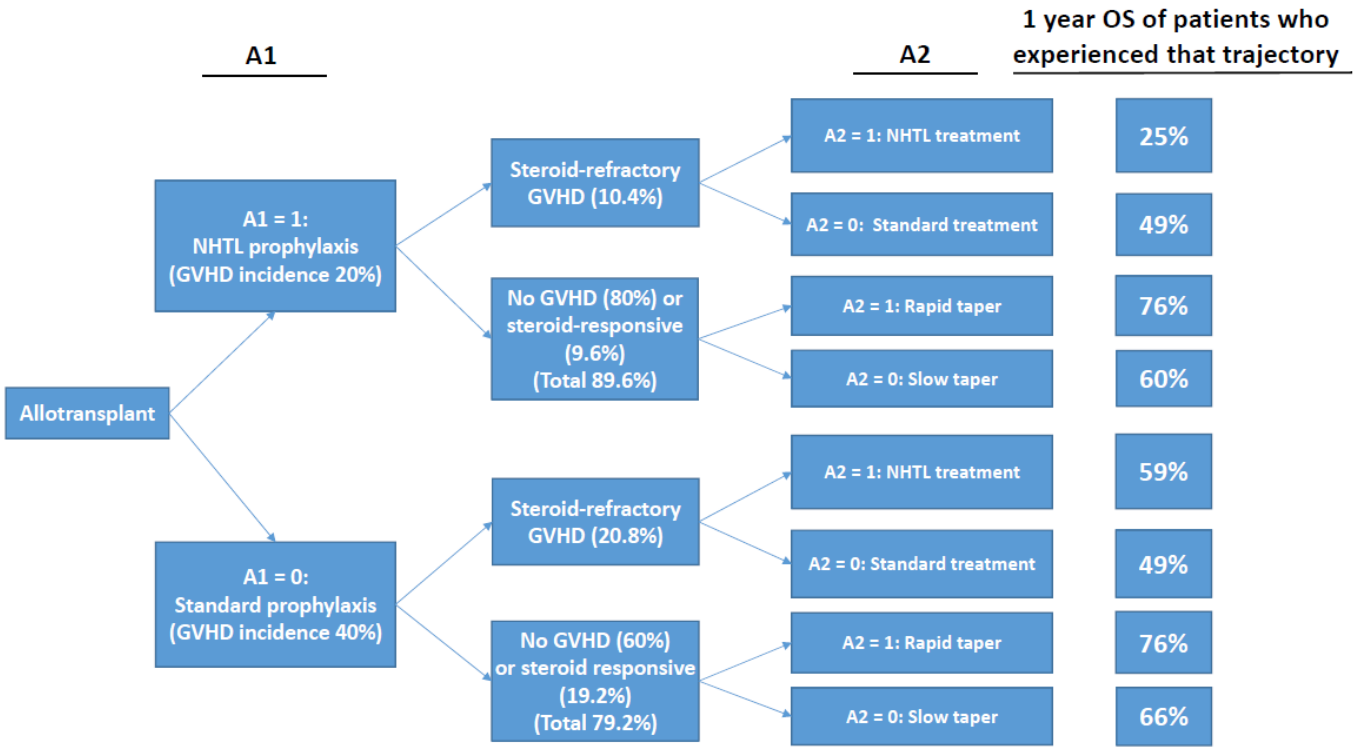

Figure 3. Trajectories post allotransplant in a population. *At the A_1 decision point, action 1 refers to non-specific highly T-lymphodepleting (NHTL) prophylaxis and action 0 to "standard" (non-NHTL) prophylaxis. At the A_2 decision point, patients with steroid-refractory GVHD may receive NHTL treatment (action 1) or "standard" treatment (action 0). Patients with no or minimal, steroid-responsive GVHD may be prescribed a rapid taper (action 1) or a slow taper (action 0) of immunosuppression. The incidence of GVHD and the true 1 year OS for each trajectory are depicted, but would only be known to an omniscient being.*

Institutional practice guidelines aimed at improving the overall survival of a population are often constructed through stringing together the results of single-stage trials. For example, at the A_1 decision point, 7 randomized trials compared highly-lymphodepleting prophylaxis (ATG) *versus* standard prophylaxis (*e.g.*, cyclosporine and methotrexate), showing a reduction in the proportion of patients developing grade II-IV acute GVHD but no benefit in terms of overall survival.[121,122] In another trial, rapid taper ($A_{2\text{-taper}} = 1$) *versus* slow taper ($A_{2\text{-taper}} = 0$) were compared in *responders*, *i.e.,* in patients without GVHD or with steroid-responsive GVHD.[60] In yet another trial among patients with acute GVHD who did not respond

to steroids alone, highly lymphodepleting GVHD second-line treatment (ATG for $A_{2\text{-}treatment} = 1$) was compared to high dose methylprednisolone ($A_{2\text{-}treatment} = 0$) on the basis of the proportion achieving complete or partial responses after 1 month, toxicity, and survival.[123] It may seem logical to piece together the results from these (and other) separate trials to figure out the "best strategy" among the 8 outlined above. For example, we could deduce the best "A_1" prophylaxis for preventing GVHD, and then the best "A_2" treatment for prolonging survival if GVHD were to occur. However, particular choices for A_1 prophylaxis might yield fewer patients with GVHD but might also have other effects that render intensification at the time GVHD develops less effective with respect to prolonging survival. Because of such delayed effects and difficult-to-predict net effects, it is preferable to study entire strategies.

One way to account for the upstream effect of prophylaxis when deciding on taper speed or GVHD treatment, and to account for the downstream effect of taper speed or GVHD treatment when deciding on prophylaxis, is to conduct a 2-stage RCT. Patients would be randomized up-front to either NHTL or standard prophylaxis. Later, those who develop no or minimal GVHD would be randomized to a rapid or a slow immunosuppression taper. Those who develop steroid-refractory GVHD would be randomized to NHTL or standard second-line treatment. However, allowing for optimal randomization probability at the prophylaxis stage, 80% power (and 5% type I error) in detecting each of the salient interactions outlined above, and no losses-to-follow-up, such a trial would require enrolling 4932 patients. Alternatively, we could design this trial with a full factorial approach where patients would be randomized up-front to one of four blocks:

AB: NHTL prophylaxis with NHTL treatment or rapid taper, depending on response.

Ab: NHTL prophylaxis with standard treatment or slow taper, depending on response.

aB: Standard prophylaxis with NHTL treatment or rapid taper, depending on response.

ab: Standard prophylaxis with standard treatment or slow taper, depending on response.

While a factorial design would be more efficient than an RTC in estimating the main effects of treatment, unfortunately, because the effect of the interactions is lesser in magnitude than the main effects, and because of the relative scarcity of patients with steroid-refractory GVHD, in this instance a factorial design would not offer any efficiency over an RCT. With the same assumptions as above, 4932 patients would still be required.

We could use SMART designs to inform the selection of the optimal treatment for each patient at each time (*i.e.*, at the prophylaxis stage, when the patient is ready for tapering, or when the patient requires augmented treatment for GVHD). The SMART would recapitulate the design of the 2-stage RCT but the analysis would be performed with Q-learning. As a simulation exercise, I created a population of 20,000 patients whom the "Omniscient Being" pre-programmed by coding their individual trajectories respecting the incidences of minimal and steroid-refractory GVHD and the 1-year survival rates depicted in Figure 3. The trajectories included the prophylaxis to which they were to be assigned, whether they would get refractory GVHD or not, if yes, then the second-line treatment to which they would be randomly assigned, and if not, then the taper speed to which they would be randomly assigned, and their outcomes. To simulate the trial, I randomly drew a sample of size n from the population of 20,000. I conducted the 2-stage RCT on this sample (with a randomization probability of 50% for each A_1 and A_2 decision) and developed Q-learning models from the trial results to predict which drug is the best prophylaxis, which is the best second-line treatment, and which taper speed is best. Then, to simulate clinical practice after the trial results are reported, I randomly sampled 300 new patients from the same 20,000 patient population, and asked the Q-learning algorithm to predict which prophylaxis and which taper speed or treatment, as applicable, was optimal for *each* of the 300 patients. Finally, for each patient, I compared the individual patient prediction to what was known by the Omniscient Being to be the true best drug for that patient at that time. I repeated this procedure of drawing random samples, running the trial, fitting the model, and out-of-sample individual patient prediction on 300 random

patients 1000 times for each trial sample size *n*, varying *n* from 40 to 996. Figure 4 shows what proportion of the 1000 times the algorithm selected the correct drug for *all* subsequent 300 non-trial patients. At sample sizes of approximately 560 trial patients, all salient interactions are detected with 100% patient-level accuracy by the models developed from at least 80% of trials. Although the confidence intervals for the estimated outcomes given alternative drug choices can overlap, the selection is made by comparing the point estimates for the outcomes. Note that this may not be reflective of the performance of an estimated ATS in the "real world," where institutions or clinical societies may be hesitant to endorse a strategy that is not "statistically significant" in some sense or other. That is, "real world" adoption of an ATS would need to be shown to be statistically superior to some alternative before it is likely to be widely adopted. Potential approaches to validating the practical utility such ATSs are discussed under Section 7.5.3.

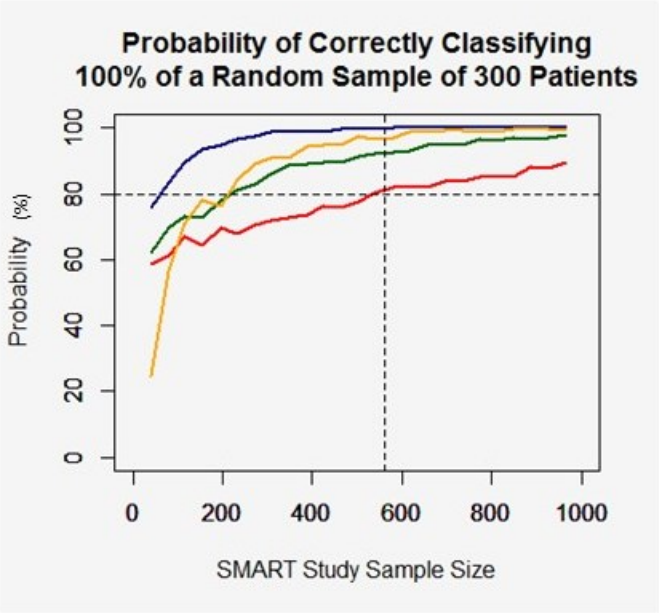

Figure 4. Simulation of a SMART. *The graph depicts the probability of correctly classifying 100% of a random sample of 300 patients with respect to the optimal prophylaxis drug, taper speed, and treatment for refractory GVHD. The blue line represents selecting a rapid taper instead of a slow taper in patients who received NHTL prophylaxis and developed no or minimal GVHD. The green line represents choosing standard second-line GVHD treatment over NHTL GVHD treatment for patients who developed refractory GVHD after NHTL prophylaxis. The red line represents choosing NHTL second-line GVHD treatment over standard GVHD treatment for patients who developed refractory GVHD after standard prophylaxis. The yellow line represents recognition that under optimal subsequent treatment or taper speed, NHTL prophylaxis is better than standard prophylaxis.*

Assessing potential tailoring variables other than the sequence of treatments would require increasing the sample size to ensure sufficient representation of all combinations of relevant covariates (*i.e.*, to have sufficient power to yield consistent estimates). Nonetheless, this example illustrates the expected efficiency gain in recruitment targets, administrative costs, and time to obtaining important results for both responding and non-responding patients associated with a SMART analysis compared to a standard 2-stage RCTs or factorial design, or to multiple individual trials with separate protocols.

A thorough discussion of sample size estimation for SMARTs when the confidence intervals of effect sizes *are* of interest is beyond the scope of this thesis. Suffice it to mention that a simple way to calculate the required sample size is to identify the primary hypothesis and apply traditional sample size formulae.[124] Thus, the SMART may be powered to detect a difference between initial treatments (controlling for later treatments) or to detect a difference between salvage treatments (controlling for the initial treatments). While that approach still allows testing hypotheses about synergistic and antagonistic effects of sequential treatments without confounding bias thanks to randomization at each decision step, it may not afford sufficient power to answer those research questions definitively and does not take advantage of the information that can be gleaned from an adequately-powered SMART.

Two potential research questions can only be answered with a SMART design.[125] These are (1) comparing effects of two entire strategies within a population and (2) choosing the single best (or worst) overall strategy for particular patients and by extension, for the population. Most researchers have considered that a SMART would aim to identify which ATSs are scientifically interesting (either because their performance seems particularly good or poor). The one or two interesting ATSs would then be tested in a traditional RCT against a suitable control arm. Such an RCT would be powered in the usual way and require fewer patients than a SMART, because the SMART would contain many trajectories that would ultimately not warrant further testing. Because SMARTs are typically viewed as

"hypothesis generating" rather than as confirmatory trials, little attention has been paid to preserving a trial-wise type I error.

3.13 SMARTs are not adaptive designs

In adaptive trials, the probability of being randomized to a particular treatment depends on the results obtained for the various treatments by patients already enrolled in the trial. Adaptive trials classically seek to minimize the number of patients exposed to inferior treatments. They can be implemented when the outcome follows fairly quickly from the time treatment is started and recruitment is slow relative to the time that typically elapses between assignment and outcome. By contrast, in SMARTs, although randomization probabilities might depend on the covariates, the randomization probabilities applicable to any given set of covariates remain constant throughout the time the study is being conducted.[82] Some researchers are developing ways to integrate adaptive trial methodology into SMARTs, but that is not yet common practice.[85,126]

3.14 Using observational data to inform SMART design

If all conceivable ATSs for a particular disease were under study, the cost, time and logistic barriers to launching a SMART in order to discover the likely optimal ATSs could be formidable. Therefore, it is advisable to choose which ATSs to test in a SMART carefully. This selection can be accomplished by turning to observational data from such sources as cohort studies, registries, administrative databases or hospital medical records. However, there are two potentially insurmountable pitfalls in using observational data to propose ATSs. The first is that if candidate tailoring variables are missing from the data set, it will be impossible to learn about their potential for improving treatment through personalization. The second is that all confounding variables *at each decision point* must be recorded; otherwise, confounding bias is likely to lead to flawed proposals. Sensitivity analyses might be able to inform us about the magnitude of potential bias when the prevalence of unmeasured confounders at each decision point and the strength of their association with the endpoint can be estimated. Sensitivity analyses have been

developed in many settings, though to date none has been proposed for any method of estimation for ATSs. Thus, although the SMART retains its status as the gold standard for ATS discovery, observational data might also provide information that is useful to developing ATSs. Moodie and colleagues recently studied four methods for handling confounders including direct adjustment and different ways of incorporating propensity scores (the predicted probability of receiving a particular treatment given a set of covariates).[83,107] Direct adjustment generally performed best.

Sample size estimation, or the corresponding power calculation, for developing ATSs from observational data has not been addressed. In practice, as in this thesis, the most common approach in observational studies is to use all available patients because the added computational costs are trivial. The adequacy of the attained power may be explored in retrospect.

3.15 Censoring

Whether in the context of a SMART or observational data, right censoring can be handled by inverse probability of censoring weights: The probability of not being censored is modeled and all observations leading to estimations of $\hat{\beta}_j$ and $\hat{\psi}_j$ are weighted by the inverse of that probability, thereby up-weighting those individuals whose events are observed to represent both themselves and individuals who are "similar" (with respect to measured covariates) but whose events are censored. This technique can also handle the situation where not all participants consent to re-randomization at the second treatment allocation point (in the case of a 2-stage SMART), where information on the second treatment is not available for a subset of patients (in the case of observational data), or where individuals are lost to follow-up for other reasons.[127]

4. OBJECTIVE

The present work seeks to answer the question of whether observational data from a particular registry are useful for discovering ATSs related to management of immunosuppression in the context of AHCT; any interesting ATSs could then be subjected to a confirmatory SMART or RCT. For example, patients could be randomized to care guided by an online application that selects the best GVHD prophylaxis and, if necessary, treatment *versus* usual physician-directed choices. Alternatively, an institution might choose to implement the online algorithm for a year, withdraw it for a year, and then re-implement it for a year. If disease-free survival is better for the patients who were transplanted and treated in the years when the algorithm was in place, and that benefit extinguished in the year the algorithm was withdrawn, that finding would serve as circumstantial evidence that personalized ATSs developed with Q-learning from observational data could add value. The path to clinical translation of this work in particular and of machine learning approaches in general is discussed in more detail in Sections 7.5.3 and 7.5.4 respectively.

This is a "feasibility study" because the registry was not originally designed for analyzing sequences of treatment. The primary aim is to propose an ATS for immunosuppressive management that would maximize disease-free survival at 2 years post AHCT performed for AML and MDS. Because the choice of GVHD treatment might be affected by the type of GVHD prophylaxis received, and the optimal GVHD prophylaxis might also vary according to individual patient and donor characteristics, this project begins to develop personalized immunosuppressive strategies at the stage of GVHD prophylaxis. Next, because glucocorticoids are established as first-line treatment and there was not a lot of variability in "first-line" treatment (the majority of patients having received steroids plus a calcineurin inhibitor), we did not create a "decision node" for first-line therapy. Because the CIBMTR does not collect information on the steroid taper speed, rapid *versus* slow taper, as envisioned in the *in silico* SMART, could not be

studied in the database. The decision at the second stage of personalization of therapy thus entailed the choice between NHTL *versus* non-NHTL salvage treatment in patients who failed to respond to systemic steroids plus one other systemic agent. We recognize that because the indication for each drug is not recorded by the CIBMTR, in reality the non-steroid systemic agent might have been instituted (1) to minimize the dose and therefore the side effects of steroids, or (2) as a concurrent steroid-potentiating agent for patients in whom steroids alone were instinctually projected to be insufficient, or (3) because of failure of GVHD to respond to steroids alone. Because patients in whom the first or second reason applies might not be as "sick" as patients for whom the third reason applies, we avoided defining "salvage treatment" as merely requiring 2 drugs. By defining salvage treatment as requiring a minimum of 3 systemic drugs, at least one of which was a systemic corticosteroid and at least 1 of which was not merely continued from prophylaxis, we sought to attain a homogeneously "sick" sample of GVHD patients who truly needed more than steroids alone. Only two stages of personalization were considered.

5. METHODS

5.1 Center for International Blood and Marrow Transplant Research

The CIBMTR was established in 2004 as a collaboration of the International Bone Marrow Transplant Registry, the Autologous Blood and Marrow Transplant Registry, and the National Marrow Donor Program (NMDP). It comprises 450 health care institutions across the globe that report longitudinal data on consecutive allogeneic and autologous hematopoietic stem cell transplants to the statistical center at the Medical College of Wisconsin (Milwaukee, WI) and the NMDP Coordinating Center (Minneapolis, MN). In accordance with Public Laws 109-129 (2005) and 111-264 (2010), American transplant centers must submit outcomes data on every allogeneic transplant to the CIBMTR. American transplant centers may voluntarily submit data on autologous transplants, and centers outside the United States voluntarily submit data on both autologous and allogeneic transplants.

The clinical database now comprises more than 330,300 transplant recipients. Data quality is ensured by computerized checks for discrepancies, physician review of submitted data, and on-site audits for the compliance of participating centers.[128,129]

The CIBMTR collects data two levels of resolution: Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data. TED include age and sex of the recipient, disease type, date of diagnosis, pre-transplantation disease stage, graft source, conditioning regimen, post-transplantation blood count reconstitution, development of GVHD, disease progression and survival, secondary malignancies, donor cell infusions, and cause of death. All contributing centers report TED. The CRFs are more extensive. They include more details regarding all the aforementioned categories of information, as well as data on infections, organ toxicity, organs involved in acute and chronic GVHD, immunosuppressant drugs, and chimerism studies. A subset of registered patients is selected for CRF submission by a weighted randomization scheme. Both TED and CRFs are collected at specified time points: before transplantation, then 100 days, 6 months and annually after transplantation or until death.[130]

5.2 Study Population

To expedite availability of a data set, the CIBMTR selected 11,141 patients transplanted between 1995 and 2007 who had been retrieved for a study on chronic GVHD.[131] Use of the registry data was approved by the CIBMTR Committee on Graft-*versus*-Host Disease (#GV13-02) and by the McGill University Research Ethics Board (#A07-E61-13A). Eligible diagnoses included AML and MDS. Exclusion criteria included lack of documented GVHD prophylaxis, *ex vivo* T cell depletion or CD34+ cell selection of the graft, lack of information about how acute GVHD was treated, and acute GVHD treatment that did not meet standard of care because multiple systemic agents without a systemic corticosteroid were administered. Early status disease was defined as AML in first complete remission (CR1), MDS subtype refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS), or MDS with <5% marrow blasts prior to AHCT. Intermediate status disease was

defined as AML in second or higher CR (≥ CR2). Advanced status disease was defined as AML in relapse or primary induction failure, refractory anemia with excess blasts (RAEB), RAEB in transformation (RAEB-T), or MDS with marrow blasts ≥ 5%. Patients with marrow blasts < 5% pre-AHCT but unspecified disease status were analyzed in the intermediate status group.[131] Patients received a variety of conditioning regimens with and without total body irradiation (TBI) and more rarely, total lymphoid irradiation (TLI) or thoraco-abdominal irradiation (TAI). Conditioning regimens were classified as "myeloablative," "reduced-intensity," or "non-myeloablative" according to the current CIBMTR directive.[132,133] Briefly, myeloablative conditioning was defined by single-dose TBI ≥ 500 cGy or ≥ 800 cGy total in fractionated doses, busulfan ≥ 9 mg/kg PO or ≥ 7.2 mg/kg IV, melphalan ≥ 150 mg/m^2, or thioptepa ≥ 10 mg/m^2. Reduced-intensity regimens included those with 200 to 500 cGy TBI in a single fraction or 800 cGy fractionated, busulfan-fludarabine with less than myeloablative doses of busulfan, fludarabine with < 150 mg/m^2 melphalan, and cyclophosphamide/etoposide. Non-myeloablative regimens included those with 200 cGy TBI and purine-analogue based regimens such as fludarabine-cyclophosphamide. Patients also received a variety of regimens for GVHD prophylaxis. These were classified as calcineurin-inhibitor (CNI) based or not, with or without mycophenolate mofetil, methotrexate, or other drugs. HLA matching was classified as well-matched, partially-matched, or mismatched according to CIBMTR criteria.[134] Well-matched pairs had either no identified HLA mismatch and informative data at four loci (*i.e.,* HLA-A, -B, -C and -DRB1) or allele matching at the four loci. Partially-matched pairs had a single locus mismatch and/or missing HLA data at a single locus. Mismatched pairs had ≥2 allele or antigen mismatches. If 2 umbilical cord grafts were administered, the worst match to the patient was entered into the analysis. Only first transplants were considered. Patients were censored at the time of second transplant, loss-to-follow-up, or when they received NHTL salvage treatment for chronic GVHD prior to or without requiring treatment for acute GVHD.

5.3 Definition of outcomes

Hematopoietic reconstitution was defined as an absolute neutrophil count ≥500 × 10^9/L that was maintained for 3 consecutive days. Acute GVHD grade was defined by consensus criteria.[26] Chronic GVHD grade was defined by the Seattle criteria.[39] Chronic GVHD severity[43] and onset[135] were defined per previously-used CIBMTR definitions. The time to acute (or chronic) GVHD was defined as the time from graft infusion (day 0) until the first recorded date-of-onset of acute (or chronic) GVHD; death without acute (or chronic) GVHD was considered a competing event. The date of relapse post AHCT was the first recorded date of relapse detected by hematological, FISH or conventional cytogenetic methods. The primary outcome was disease-free survival (DFS), defined as survival time after day 0 without confirmation of disease persistence, relapse or death. Therefore, patients not in CR at the time of transplant were included in the DFS estimate.

5.4 Simplification of GVHD prophylaxis and treatment

Because the data set contained over 11 classes of agents indicated for GVHD prophylaxis and over 22 classes of agents for treatment of acute and/or chronic GVHD, the pre-specified plan was to compare NHTL therapies to the ensemble of non-NHTL therapies. NHTL therapy included ATG and ALG, alemtuzumab, anti-CD45 antibodies, OKT-3, other anti-CD3 antibodies that do not exhibit strong selectivity for activated T cells, anti-CD2 antibodies, and (when used after day 0) purine analogue chemotherapy. Antibodies such as ATG and alemtuzumab were considered as GVHD prophylaxis even if they were administered concurrently with conditioning and not after day 0 because of their long half-life in circulation and their proven ability to induce profound lymphodepletion for months post-infusion.[136-142] The ensemble of non-NHTL therapies included drugs that inhibit but do not necessarily deplete T cells, such as calcineurin inhibitors and mTOR inhibitors, and monoclonal antibodies that more selectively deplete activated T cells, such as monoclonal antibodies directed against CD25,[143-145] the anti-CD3 visilizumab (HUM291)[146] and the anti-CD147 gavilimomab,[147] as well as

extracorporeal photopheresis. Topical treatment was defined as cutaneous, ophthalmic and inhaled corticosteroids, creams and ointments such as tacrolimus and pimecrolimus, cyclosporine eye drops (Restasis™), and psolaren/ultra-violet A (PUVA). Oral beclomethasone and budesonide were counted as a "topical treatment" of the gastrointestinal tract per CIBMTR directives[148,149] because they are poorly-absorbable and subject to high levels of first-pass metabolism.[150-152] Only immunomodulating therapies were considered; symptomatic treatments such as octreotide (for diarrhea) and anti-pruritics were ignored. Although intravenous immunoglobulin (IVIG) may be given with the intent of immunomodulation in doses of 0.8 – 2.0 g/kg, it is often given as "immune replacement therapy" in doses of 0.2 – 0.5 g/kg to prevent or treat infection. Because information on the dose of IVIG was not available and the intent of IVIG therapy could easily be misclassified, and because there is no conclusive evidence that IVIG is effective prophylaxis or treatment for GVHD,[153] IVIG was not counted in the GVHD prophylactic or therapeutic arsenal.

Because therapies given in the preceding interval are inventoried *en bloc* at the time each subsequent CRF is completed but the start and stop dates for each drug are not recorded, the CIBMTR registry affords no ability to accurately distinguish lines of therapy. Moreover, while corticosteroids usually figure in first-line therapy, they may do so alone or in combination with "steroid-sparing" agents. For the purposes of this analysis, "first-line" therapy for acute or chronic GVHD was considered to be (1) any 2 systemic therapies, which might include a systemic corticosteroid, with any number of topical treatments, or (2) continuation of a prophylaxis regimen with any number of systemic drugs without increasing their doses (*e.g.*, cyclosporine + mycophenolate), with or without a systemic corticosteroid continued from prophylaxis and with or without the addition of topical agents, or (3) any number of topical therapies. "Salvage" treatment was defined as ≥ 3 systemic therapies, at least one of which was a systemic corticosteroid, and at least one of which was new (not merely continued from prophylaxis). Note that "salvage" patients could have received any number of

topical therapies but only systemic therapies were counted towards assigning the "salvage" designation.

For the purposes of counting treatments, note that all topical corticosteroids were lumped together, such that a patient who received dexamethasone mouth rinses, fluocinonide cream and oral budesonide would have been considered to have a "topical treatment" count of 1. All systemic calcineurin inhibitors (CNIs) were lumped together as one drug for the purpose of counting the number of systemic agents used during the course of GVHD "salvage" treatment, because switching from cyclosporine to tacrolimus or *vice-versa* is usually intended to minimize adverse effects or because tacrolimus is perceived to be marginally more effective for GVHD; it does not change the therapeutic mechanisms of action. However, if a patient switched from one prophylactic CNI to the other CNI for treatment at the time GVHD was diagnosed, that patient was considered to have embarked on a new treatment and not to have simply continued prophylaxis. Twenty-five patients received NHTL treatment as first-line therapy for acute GVHD according to this definition; they were excluded from the analysis cohort. For chronic GVHD requiring treatment before acute GVHD, no patient received NHTL therapy first-line but 18 received NHTL salvage therapy. All 1382 patients who were treated for chronic GVHD before acute GVHD were ineligible to proceed to the "second decision stage" which entailed studying the effect of NHTL salvage therapy for *acute* GVHD. The original analysis plan had been to analyze acute and chronic GVHD salvage patients together, but their baseline and outcome characteristics were quite different. In the absence of detailed descriptions of their clinical presentation and in view of the fact that the distribution of drugs differed strongly for patients in whom "chronic" GVHD was treated before or without subsequent acute GVHD treatment, combining these patients with those treated first for acute GVHD was deemed non-justifiable. Indeed, the combined model "diluted" the effects of NHTL salvage therapy for acute GVHD. Therefore, separate models were created for patients with acute-GVHD-treated-first and patients with chronic-GVHD-treated-first. However, due to only 18 patients not first diagnosed with treatment-requiring acute GVHD having received

NHTL treatment as salvage therapy (and 0 as first-line therapy) for *chronic* GVHD, there were insufficient numbers to sustain the chronic GVHD second-stage decision model. Therefore, only the results for patients first treated for acute GVHD are presented here. Lastly, because each CRF only captures the maximum grade of GVHD in the interval it covers but does not provide any details of how the global or organ-specific severity changed in response to therapy, we assumed that the maximum GVHD grade recorded on the same form on which any GVHD treatment is first recorded corresponds to the grade at the time treatment-requiring GVHD was first diagnosed. The impact of this assumption is discussed under Limitations in Section 7.4.

5.5 Data management

5.5.1 Defining "first-line" versus "salvage" therapies

Several series of CRFs were used for this study because different CRFs were implemented over the years. Variable names and levels were harmonized across different CRFs. For each patient, the first CRF on which specific therapies were documented for acute GVHD yielded the list of (acute) GVHD treatments from which "first-line" and "salvage" treatments were assigned. Acute GVHD treatments trumped chronic GVHD treatments. Only if no specific treatment for acute GVHD was documented on any form, then the first form on which specific therapies were documented for chronic GVHD yielded the list of "first-line" and "salvage" (chronic) GVHD treatment. Inherent in this approach is the simplification that acute GVHD always precedes chronic GVHD in patients who develop both. Data collected by the NMDP prior to the inception of the CIBMTR had been transferred to the CIBMTR database as though derived from a single CRF, so separation of salvage treatments across multiple forms with known timing was not available for "NMDP Legacy" patients. NMDP Legacy patients comprised 23% of the entire cohort and 16% of patients at the second-stage (A_2) decision. If specific therapies for acute GVHD were indicated on "untimed" forms, then we assumed that treatment-requiring acute GVHD occurred first; otherwise, the "untimed" treatments for chronic GVHD were

extracted. For "timed" patients, treatments administered in subsequent years (*i.e.*, listed only on forms following the index form that declared the initiation of GVHD treatment) were not considered.

5.5.2 Assigning a time for making the A_2 decision

Because the date of initiation of "salvage" therapy was not collected, the date of diagnosis of acute or chronic GVHD (whichever came first) was used for the time the A_2 decision would be made. Essentially, this means that the proposed ATS recommends the choice of salvage treatment at the time of acute GVHD diagnosis, in the eventuality that front-line treatment fails. This time point will be called the "A_2 decision point." As mentioned, there were insufficient numbers of patients who received NHTL as salvage treatment for chronic GVHD (n = 18) to warrant a separate analysis of NHTL salvage *versus* standard salvage for chronic GVHD.

5.5.3 Missing Data

Patients who were missing all documentation of specific drug treatment for GVHD and had maximum acute GVHD grades of 0 or I and maximum chronic GVHD severity of "none" or "mild" over their entire post-transplant course were presumed to have needed no GVHD treatment or only first-line treatment and so were not considered "missing" from the sample of patients needing salvage treatment. By contrast, patients with maximum acute GVHD grades of II–IV or maximum chronic GVHD severity scores of "moderate" or "severe" in the post-transplant course but lacking any documentation of specific immuosuppressive treatments could possibly have needed salvage treatment. They were therefore considered "missing" from the sample of patients destined to estimate the best patient-specific salvage therapy. Because their need for salvage treatment and the specific treatments administered were impossible to glean from the data set, they were excluded from the entire analysis cohort (including analyzing the efficacy of NHTL prophylaxis).

Multiple imputation using chained equations (MICE) was used to impute missing values of covariates or outcomes where <10% of values were missing.[154]

For variables missing 10% or more values, a "missing" category was created. Creating multiple imputations with MICE, as opposed to single imputations, accounts for the statistical uncertainly in the imputations.[155] The "mice" package in R was used to implement predictive mean matching for numeric variables, logistic regression for binary variables, and multinomial logistic regression for factor variables with >2 levels.[154] Because of computational intensity, time-to-event variables were imputed using conditional random sampling. For example, time to acute GVHD was imputed by randomly sampling from a group of patients with the same conditioning intensity, graft source, donor relation, and HLA match, and survival time less than or equal to that of the target patient with missing data.

5.6 Data Analysis

5.6.1 Descriptive statistics

Covariates available in the data set and known from existing literature to be associated with outcome were tested for their univariable association with NHTL therapy at each stage (Tables 3 and acute GVHD-related variables in Table 4). None of these covariates were thought to be mediators, *i.e.*, they were considered pre-treatment factors (pre-prophylaxis or pre-salvage therapy, as appropriate) and not intermediaries in the causal pathway linking the type of therapy to relapse or survival time. Intermediate and ultimate outcomes are also described (Table 4). The Chi-squared test was used to compare categorical variables, the Fisher exact test for categorical variables with small cell size (≤5 observations), the Mann-Whitney-Wilcoxon test for continuous variables, and Gray's method for comparisons of cumulative incidence. Univariable probabilities of DFS and OS were calculated using the Kaplan-Meier estimator with Greenwald's formula for the variance. Probabilities of acute and chronic GVHD, non-relapse mortality and relapse were additionally calculated using cumulative incidence curves to accommodate competing risks.[156]

5.6.2 Q-model construction

Logistic forms of the Q-functions were used to study 2-year disease-free survival. All variables that would be useful to test for interaction with prophylaxis or treatment type were considered. Recipient and donor age were initially modelled linearly but ultimately a categorical parameterization was selected to be consistent with CIBMTR practice. This necessitated creating a combined donor age-graft categorical variable to avoid attributing a donor age to cord blood grafts yet permit a single model applicable to all graft types. (Alternatively, separate models for marrow/peripheral blood grafts and for cord blood grafts would have been needed.) As well, year of transplant (modelled linearly, categorically, and with polynomial terms) and center practice (whether the center contributed patients to the NHTL prophylaxis arm and whether the center contributed patients to the NHTL salvage arm) were tested as potential confounders without interacting them with prophylaxis or treatment type. Bidirectional model selection using the Akaike Information Criterion was abandoned because each imputation yielded a slightly different set of suggested predictors. Instead, saturated models were tested and particular variables removed if they worsened the fit as judged by plotting the observed 2-year DFS distribution within quartiles of the predicted 2-year DFS stratified by patient age and prophylaxis or treatment type. In particular, year of transplant and center practice were non-contributory (non-significant *p*-values) and in fact worsened model fit, so were removed.

Five imputed data sets were analyzed separately, and the results of the analyses were combined by averaging the model coefficients. To account for both within-imputation and between-imputation variance,[157] confidence intervals for the predictors were constructed by bootstrapping the imputations and averaging the coefficients of Q-models constructed on blocks of 5 imputed data sets (all 5 being derived from the same bootstrapped sample of patients), 570 times. A *p*-value of < 0.05 was considered significant so the 2.5%th and 97.5th% percentiles of the distribution of "bootstrapped" beta coefficients defined the confidence intervals of

the beta coefficients. Patient-specific predictions for the best intervention at each stage were made from each of the original 5 imputed data sets by predicting the outcome on the log-odds scale under each potential intervention (NHTL or salvage). The 5 predictions were then averaged to yield a final patient-specific prediction on the log-odds scale, which was then transformed into a predicted probability of 2-year DFS by applying the expit function.

Inverse probability of censoring weights (IPCW) were calculated to account for the "absence" of particular patients from the A_2 and A_1 models due to losses-to-follow-up (LTFU). Patients were deemed LTFU in the first interval if they were not known to die before 2 years or to survive to that time, and did not progress to the second treatment interval because they did not require acute GVHD salvage treatment or were "ineligible" for inclusion in the A_2 model on the basis of having first developed chronic GVHD requiring treatment. Patients were considered LTFU in the second interval if they were known to initiate salvage therapy, but their two year outcome was unknown. IPCW serves to remove the selection bias that can arise when loss to follow-up depends on measured covariates. The approach works by up-weighting those patients who remain in the study and are similar to lost patients, so that the observed patients effectively count for themselves and their equivalent, but incompletely observed, counterparts.[127] The final IPCW used in the A_2 model was the product of the IPCW for the first interval (from prophylaxis until the A_2 decision point) and the IPCW for the second interval (from the A_2 decision point until 2 years post AHCT). Variables where at least 1 level significantly predicted censoring in at least 1 imputed data set (p-value < or ≈ 0.05) were retained for constructing the models for the IPCW (Appendix Section 9.4). Type of GVHD prophylaxis or treatment were not significant predictors of censoring.

All work was performed using R, versions 3.0.1 to 3.1.2.[158]

6. RESULTS

6.1 Patient selection

A total of 11,141 records were available for analysis. After exclusion of patients who received *ex-vivo* T cell depleted (n = 807) or CD34-selected (n = 205) grafts, NHTL treatment early in the course of GVHD therapy (n = 38), GVHD treatment that was "outside the standard of care" because it entailed ≥ 3 systemic agents (not all merely continued from prophylaxis) without first or concurrently trying systemic corticosteroids (n = 116), and patients missing information about GVHD treatment (n = 412), a total of 9563 patients were retained for analysis (Figure 5, next page). These patients were contributed by 330 different centers. Five (1%) centers contributed ≥200 patients each, 16 (5%) each contributed 100 to 200 patients, 85 (26%) each contributed 25 to <100 patients, 145 (44%) each contributed 5 to <25 patients, and 78 (25%) each contributed <5 patients. A total of 21 (6%) of centers contributed patients only to the NHTL prophylaxis cohort, 100 (30%) only to the standard prophylaxis cohort, and 209 (63%) to both prophylaxis cohorts. A total of 21 (6%) of centers contributed patients only to the NHTL salvage cohort, 90 (27%) only to the standard salvage cohort, and 112 (34%) to both salvage cohorts. One hundred and seven (32%) centers did not contribute any patients to the salvage cohorts, but this is understandable in light of the bulk of centers each contributing fewer than 25 patients and the relative infrequency of acute GVHD necessitating triple systemic immunosuppression (see below).

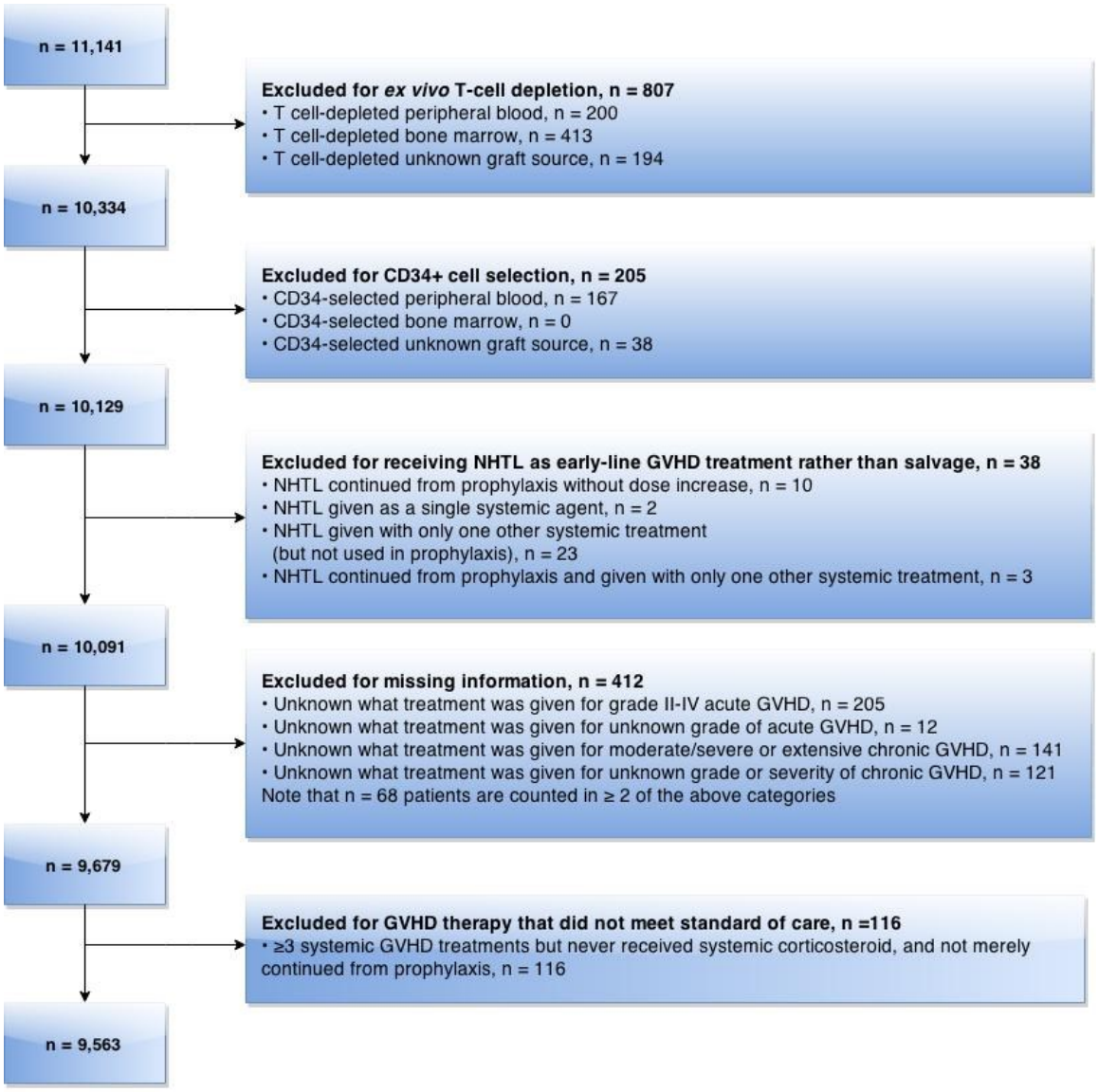

Figure 5. Selection of the analysis set. *After exclusion of patients who received* ex-vivo *T cell depleted (n = 807) or CD34-selected (n = 205) grafts, NHTL treatment early in the course of GVHD therapy (n = 38), patients missing information about GVHD treatment (n = 412), those who received GVHD treatment that was "outside the standard of care" because it entailed ≥3 systemic agents (not all merely continued from prophylaxis) without first or concurrently trying systemic corticosteroids (n = 116), and a total of 9563 patients were retained for analysis .*

6.2 Patient characteristics

6.2.1 Baseline characteristics

Table 3 describes patient-related, disease-related and transplantation-related baseline characteristics according to intervention stage.

Table 3. Baseline characteristics of the entire cohort and according to stage 1 and stage 2 intervention

Characteristic	**Entire analysis cohort** (n = 9563)		**NHTL prophylaxis** (n = 2643)		**Non-NHTL prophylaxis** (n = 6920)		p-value[1]	**NHTL salvage** (n = 347)		**Non-NHTL salvage** (n = 1064)		p-value[1]
No. of centers, (% of all centers)[2]	330	(100)	230	(43)	309	(83)	<0.001	133	(40)	202	(60)	<0.001
No. of centers reporting both NHTL and non-NHTL prophylaxis or treatment	--	--	209				--	112				--
Year of transplant, no. (%)							<0.001					<0.001
1995-1999	2892	(30)	451	(17)	2441	(35)		158	(46)	183	(17)	
2000-2003	2766	(29)	866	(33)	1900	(27)		96	(28)	365	(33)	
2004-2007	3905	(41)	1326	(50)	2579	(37)		93	(27)	527	(50)	
Recipient age at transplant												
Median age, yr (range)	40 (<1–79)		41 (<1–77)		40 (<1–79)		0.282	36 (<1–79)		42 (<1–75)		<0.001
Age category, yr, no. (%)							<0.001					0.006
0-9	913	(9)	390	(15)	523	(8)		41	(12)	93	(9)	
10-19	1101	(12)	314	(12)	787	(11)		37	(11)	93	(9)	
20-29	1296	(14)	285	(11)	1011	(15)		57	(16)	129	(12)	
30-39	1518	(16)	308	(12)	1210	(17)		68	(20)	171	(16)	
40-49	1971	(21)	436	(16)	1535	(22)		55	(16)	219	(21)	
50-59	1844	(19)	543	(21)	1301	(19)		60	(17)	230	(22)	
60+	920	(10)	367	(14)	553	(8)		29	(8)	129	(12)	
Male gender, no. (%)	5089	(53)	1414	(53)	3675	(53)	0.748	205	(59)	595	(56)	0.333
Karnofsky/Lansky score at transplant, no. (%)							0.943					0.001
<80%	899	(9)	248	(9)	651	(9)		44	(13)	85	(8)	
≥80%	8336	(87)	2314	(88)	6022	(87)		299	(86)	936	(88)	
Missing	328	(3)	81	(3)	247	(4)		4	(1)	43	(4)	
Disease for which transplant was performed, no. (%)							0.010					0.275
AML	9318	(97)	2557	(97)	6791	(98)		336	(97)	1043	(98)	
MDS	245	(3)	86	(3)	159	(2)		11	(3)	21	(2)	
Disease status at transplant, no. (%)[3]							<0.001					0.164
Early	4166	(44)	979	(37)	3187	(46)		122	(35)	409	(38)	
Intermediate	2180	(23)	710	(27)	1470	(21)		95	(27)	262	(25)	
Advanced	3155	(33)	931	(35)	2224	(32)		129	(37)	388	(36)	
NOS but <5% BM	42	(<1)	16	(<1)	26	(<1)		1	(<1)	0	(0)	

Table 3. Baseline characteristics of the entire cohort and according to stage 1 and stage 2 intervention

Characteristic	Entire analysis cohort (n = 9563)		NHTL prophylaxis (n = 2643)		Non-NHTL prophylaxis (n = 6920)		p-value[1]	NHTL salvage (n = 347)		Non-NHTL salvage (n = 1064)		p-value[1]
blasts[4]												
Missing	20	(<1)	7	(<1)	13	(<1)		0	(0)	5	(<1)	
Median % bone marrow blasts pre-HCT (range)	2 (0–100)		2 (0–100)		2 (0–100)		0.194	2 (0–100)		2 (0–100)		0.305
Bone marrow blasts pre-HCT, no. (%)							0.021					0.573
< 5%	5899	(62)	1603	(61)	4296	(62)		200	(59)	647	(61)	
6-19%	1280	(13)	374	(14)	906	(13)		51	(14)	133	(12)	
≥20%	1355	(14)	408	(15)	947	(14)		61	(17)	169	(16)	
Missing	1029	(11)	258	(10)	771	(11)		35	(10)	115	(11)	
Conditioning regimen intensity, no (%)[5]							<0.001					<0.001
Myeloablative	7312	(76)	1678	(63)	5634	(81)		286	(82)	724	(68)	
- With TBI, TAI, or TLI	3611	(38)	739	(28)	2872	(42)		167	(48)	408	(38)	
Reduced-intensity	915	(10)	437	(17)	478	(7)		22	(6)	95	(9)	
- With TBI, TAI or TLI	256	(3)	94	(4)	162	(2)		7	(2)	28	(3)	
Non-myeloblative	548	(6)	108	(4)	440	(6)		11	(3)	117	(11)	
- With TBI, TAI or TLI	380	(4)	56	(2)	324	(5)		8	(2)	84	(8)	
Unknown	788	(8)	420	(16)	368	(5)		28	(8)	128	(12)	
- With TBI, TAI or TLI	26	(<1)	20	(1)	6	(<1)		0	(0)	0	(0)	
TBI, no. (%)	4231	(44)	886	(34)	3345	(48)	<0.001	181	(52)	516	(48)	0.261
Conditioning regimens, no. (%)[5]							<0.001					<0.001
Bu-Cy based	3169	(33)	552	(21)	2617	(38)		103	(30)	262	(25)	
Cy-TBI based	3211	(34)	636	(24)	2575	(37)		144	(41)	357	(34)	
Flu-Cy (no TBI) based	211	(2)	60	(2)	151	(2)		3	(1)	37	(3)	
Flu-Mel based	582	(6)	328	(12)	254	(4)		26	(7)	105	(10)	
Bu-Flu (no Mel) based	1025	(11)	642	(24)	383	(5)		26	(7)	103	(10)	
Flu-TBI based	644	(7)	172	(7)	472	(7)		16	(5)	120	(11)	
Others[6] *without TBI*	303	(3)	152	(6)	151	(2)		7	(2)	37	(3)	
Others[6] *with TBI*	418	(4)	101	(4)	317	(5)		22	(6)	43	(4)	
Donor-recipient HLA match, no. (%)[7]							<0.001					<0.001
HLA-identical sibling	3623	(38)	313	(12)	3310	(48)		79	(23)	254	(24)	
Other relative	388	(4)	136	(5)	252	(4)		30	(9)	48	(5)	
- Well matched	81	(1)	11	(<1)	70	(1)		3	(1)	8	(1)	
- Partially matched	217	(2)	63	(2)	154	(2)		21	(6)	28	(3)	
- Mismatched	90	(1)	62	(2)	28	(<1)		6	(2)	12	(1)	
URD	4917	(51)	1744	(66)	3173	(46)		217	(63)	687	(65)	
- Well matched	2773	(29)	966	(37)	1807	(26)		84	(24)	382	(36)	
- Partially matched	1562	(16)	561	(21)	1001	(14)		81	(23)	222	(21)	
- Mismatched	582	(6)	217	(8)	365	(5)		52	(15)	69	(6)	
UCB matched (6/6)	35	(<1)	28	(1)	7	(<1)		1	(<1)	6	(1)	
UCB 1 mismatch (5/6)	110	(1)	78	(3)	32	(<1)		4	(1)	17	(1)	
UCB ≥ 2 mismatches (≤4/6)	490	(5)	344	(13)	146	(2)		16	(5)	66	(6)	
Donor age												
Median donor age, yr (range)[8]	34 (<1–85)		33 (<1–78)		35 (<1–85)		<0.001	36 (<1–71)		36(<1–72)		0.855

Table 3. Baseline characteristics of the entire cohort and according to stage 1 and stage 2 intervention

Characteristic	Entire analysis cohort (n = 9563)		NHTL prophylaxis (n = 2643)		Non-NHTL prophylaxis (n = 6920)		p-value[1]	NHTL salvage (n = 347)		Non-NHTL salvage (n = 1064)		p-value[1]
Donor age category, yr, no. (%)[8]							<0.001					0.287
0-9	298	(3)	10	(<1)	279	(4)		7	(2)	13	(1)	
10-19	527	(6)	42	(2)	485	(7)		13	(4)	19	(2)	
20-29	2066	(22)	550	(21)	1516	(22)		65	(19)	223	(21)	
30-39	2599	(27)	703	(27)	1896	(27)		110	(32)	333	(31)	
40-49	2039	(21)	524	(20)	1515	(22)		81	(23)	240	(23)	
50-59	882	(9)	207	(8)	675	(10)		33	(10)	107	(10)	
60+	324	(3)	75	(3)	249	(4)		6	(2)	24	(2)	
Missing	202	(2)	82	(3)	120	(2)		11	(3)	16	(2)	
Donor-recipient sex, no. (%)							<0.001					0.212
Female-to-male	1894	(20)	509	(19)	1385	(20)		84	(24)	221	(21)	
Other combination	7501	(78)	2062	(78)	5439	(79)		258	(74)	824	(77)	
Missing	168	(2)	72	(3)	96	(1)		5	(1)	19	(2)	
Donor-recipient CMV status, no. (%)							<0.001					0.598
Negative/negative	2287	(24)	573	(22)	1714	(25)		94	(27)	273	(26)	
One or both positive	6834	(71)	1888	(71)	4946	(71)		230	(66)	727	(68)	
Missing or inconclusive	442	(5)	182	(7)	260	(4)		23	(7)	64	(6)	
Graft type, no. (%)							<0.001					<0.001
Bone marrow	4251	(44)	904	(34)	3347	(48)		177	(51)	368	(35)	
Peripheral blood	4677	(49)	1289	(49)	3388	(49)		149	(43)	607	(57)	
Cord blood	635	(7)	450	(17)	185	(3)		21	(6)	89	(8)	
GVHD prophylaxis, no. (%)							<0.001					<0.001
FK506 + MMF ± others[9] *(except MTX)*	487	(5)	147	(6)	340	(5)		23	(7)	114	(11)	
FK506 + MTX ± others[9] *(except MMF)*	2018	(21)	571	(22)	1447	(21)		72	(21)	240	(23)	
CSA + MMF ± others[9] *(except FK506, MTX)*	644	(7)	212	(8)	432	(6)		21	(6)	160	(15)	
CSA + MTX ± others[9] *(except FK506, MMF)*	4454	(48)	849	(32)	3695	(53)		166	(48)	365	(34)	
CSA +/or FK506 + MMF + MTX ± others[9]	631	(7)	297	(11)	334	(5)		25	(4)	99	(9)	
CSA +/or FK506 ± others[9] *(except MMF, MTX)*	1112	(12)	537	(20)	575	(8)		36	(10)	74	(7)	
Only non-CNI drugs or antibodies for GVHD prophylaxis	127	(1)	30	(1)	97	(1)		4	(1)	12	(1)	
Non-NHTL GVHD prophylaxis, simplified classification, no. (%)												
Calcineurin inhibitor	9436	(99)	2613	(99)	6823	(99)	0.358	343	(99)	1052	(99)	1.000
Methotrexate	7103	(74)	1717	(65)	5486	(79)	<0.001	263	(75)	704	(66)	0.001
Mycophenolate	1762	(18)	656	(25)	1106	(16)	<0.001	69	(20)	373	(35)	<0.001
Systemic corticosteroids (not for nausea), no. (%)	1699	(18)	567	(21)	1132	(16)	<0.001	104	(30)	170	(16)	<0.001

Table 3. Baseline characteristics of the entire cohort and according to stage 1 and stage 2 intervention													
Characteristic	**Entire analysis cohort** (n = 9563)		**NHTL prophylaxis** (n = 2643)		**Non-NHTL prophylaxis** (n = 6920)		p-value[1]	**NHTL salvage** (n = 347)		**Non-NHTL salvage** (n = 1064)		p-value[1]
Anti-CD25 (e.g., basiliximab, daclizumab)	33	(<1)	25	(1)	8	(<1)	<0.001	1	(<1)	10	(1)	0.312
NHTL in conditioning or as GVHD prophylaxis, no. (%)												
Any NHTL prophylaxis	--	--	--	--	--	--	--	110	(32)	286	(24)	0.095
Any ATG[10]	2263	(24)	2263	(86)	--	--	--	102	(29)	259	(24)	0.071
- Pre-infusion	1833	(19)	1833	(69)	--	--		62	(18)	209	(20)	
- Post-infusion	187	(2)	187	(7)	--	--		23	(7)	26	(2)	
- Pre- and post-infusion	243	(3)	243	(9)	--	--		17	(5)	24	(2)	
- None	7253	(76)	377	(14)	--	--		245	(70)	805	(76)	
- Missing both pre- and post-infusion ATG information	47	(<1)	3	(<1)	--	--		0	(0)	2	(0)	
Any alemtuzumab (anti-CD52)	315	(3)	315	(12)	--	--	--	5	(1)	15	(1)	1.000
- Pre-infusion	234	(2)	234	(9)	--	--		2	(<1)	13	(0)	
- Post-infusion	50	(1)	50	(2)	--	--		2	(<1)	2	(0)	
- Pre- and post-infusion	31	(<1)	31	(1)	--	--		1	(<1)	0	(0)	
Other NHTL prophylaxis	68	(1)	68	(3)	--	--	--	3	(1)	12	(1)	1.000

1. The Chi-squared test was used to compare categorical variables, the Fisher exact test for categorical variables with small cell size (≤5 observations), and the Mann-Whitney-Wilcoxon test for continuous variables.
2. Only 223 centers contributed any patients who received GVHD salvage treatment. This is understandable in light of the fact that acute GVHD requiring "salvage" therapy is relatively uncommon and many centers each contributed few patients to the entire cohort (see text).
3. Disease status is categorized as follows: Early = AML in CR1, RA or RARS or MDS with marrow blasts pre-HCT <5%. Intermediate = AML in ≥ CR2. Advanced = relapsed AML or primary induction failure, RAEB, or RAEB-t, or MDS with marrow blasts ≥5%.
4. Classified as Intermediate for analysis purposes.
5. Myeloablative conditioning was defined by single-dose TBI ≥500 cGy or ≥800 cGy total in fractionated doses, busulfan ≥9 mg/kg PO or ≥7.2 mg/kg IV, melphalan ≥150 mg/m^2, or thioptepa ≥10 mg/m^2. Reduced-intensity regimens included those with 200–500 cGy TBI in a single fraction or 800 cGy fractionated, busulfan-fludarabine with less than myeloablative doses of busulfan, fludarabine with < 150 mg/m^2 melphalan, and cyclophosphamide/etoposide. Non-myeloablative regimens included those with 200 cGy TBI and purine-analogue based regimens such as fludarabine-cyclophosphamide. Of the "unknown" category, n = 649 patients could be assigned to one of the other categories based on examining the chemotherapeutic agents prescribed (*e.g.*, fludarabine-cyclophosphamide would be considered non-myeloablative), while n = 139 lacked sufficient information to be classified (*e.g.*, it was not possible to distinguish whether fludarabine-melphalan or busulfan-fludarabine were reduced intensity or

myeloablative if the dose of busulfan or melphalan were unknown). These 139 missing values were imputed.

6. "Fludarabine" refers to fludarabine or cladribine. "Others" includes chemotherapy drugs or monoclonal antibodies. Intrathecal chemotherapy and corticosteroids, when listed as part of conditioning, were ignored.
7. HLA match: Well-matched URD had either no identified HLA mismatch and informative data at 4 loci or allele matching at HLA-A, -B, and _DRB1. Partially matched pairs had a defined, single-locus mismatch and/or missing HLA data. Mismatched cases had ≥2 allele or antigen mismatches. "Other relative" might include non-HLA-identical siblings. "Mismatched sibling" without further specification (n = 2) was counted as "Partially matched other relative."
8. Excludes cord blood.
9. "Others" refers to other drugs, including corticosteroids, or antibodies. Keratinocyte growth factor and ursodiol were ignored. A total of 9436 (99%) patients received calcineurin inhibitor-based prophylaxis, including 257 (3%) who received both CSA and FK506 prophylaxis. No patient treated with salvage therapy for acute GVHD received both CSA and FK506 prophylaxis.
10. For analysis purposes, it was assumed that no ATG or alemtuzumab was given if no ATG or alemtuzumab was documented. Source of ATG used in the conditioning regimen ATG (horse or rabbit) was recorded for only 327 (3%) patients. Source of prophylactic ATG administered post-infusion (and source of ATG used to treat GVHD) was not available for any patient.

Most patients (97%) were transplanted for AML. A large proportion (55%) had intermediate or advanced disease status. Cytogenetic and molecular data were not available for analysis. As expected, over 60% of patients did not have an HLA-identical sibling donor. Conditioning regimens were mainly myeloblative (76%) and TBI was common (44%). GVHD prophylaxis was generally with a calcinuerin inhibitor and methotrexate (76%) but a sizable proportion of patients received mycophenolate with or without methotrexate (18%).

Of the entire cohort, 2643 (27%) patients received NHTL prophylaxis, which was mainly ATG (86%) or alemtuzumab (12%). Compared to those who received standard prophylaxis, NHTL prophylaxis patients had a higher prevalence of reduced-intensity/non-myeloablative conditioning (23% *vs.* 13%, $p < 0.001$), unrelated donors (66% *vs*. 46%, $p < 0.001$), partially-matched or mismatched non-cord blood donors (33% *vs*. 21%, $p < 0.001$), and cord blood grafts (17% *vs.* 3%, $p < 0.001$). They also had a lower prevalence of TBI (34% *vs.* 48%, $p < 0.001$) and early disease status (37% *vs.* 46%, $p < 0.001$). Thus, not surprisingly, NHTL prophylaxis was favoured in situations where the risk of GVHD was perceived to be high (*i.e.*,

unrelated and mismatched donors) and where the risk of graft rejection was perceived to be high (*i.e.*, reduced intensity conditioning and cord blood grafts). The use of NHTL prophylaxis increased over the years ($p < 0.001$).

Confounding by indication was likewise evident in the choice of salvage therapy. Younger patients were more heavily represented in the NHTL treatment group (median age 36 *vs.* 42, $p < 0.001$). Clinicians might also have been inclined to re-administer NHTL agents when patients required salvage treatment, with the prevalence of prior receipt of NHTL prophylaxis being 32% among NHTL salvage patients and 25% among standard salvage patients ($p = 0.095$), perhaps reflecting institutional bias in believing in the efficacy of NHTL agents, although this assertion is speculative because it lacks statistical significance, which might reflect an underpowered comparison. However, the most striking source of confounding is probably that NHTL salvage patients were sicker than standard salvage patients at the time salvage treatment was being decided and perhaps at the onset of GVHD, although this is conjectural (Table 4). Indeed, the prevalence of grade III-IV acute GVHD was nearly double among NHTL salvage patients than standard salvage patients (85% *vs.* 46%, $p < 0.001$) and NHTL salvage patients required more systemic acute GVHD treatments (median of 4 *vs*. 3 systemic immunosuppressant indicated for acute GVHD on their index forms, $p < 0.001$). Finally, contrary to prophylaxis, the use of NHTL salvage therapy declined over the years ($p < 0.001$).

6.2.2 Unadjusted outcomes

Median follow-up of survivors was 75.0 months (range, 3.1 to 218.6 months) in the NHTL prophylaxis group and 88.0 months (range, 3.0 to 222.7 months) in the non-NHTL prophylaxis group ($p < 0.001$). Median follow-up of survivors was 73.5 months (range, 3.2 to 186.9 months) in the NHTL salvage group and 89.5 months (range, 3.2 to 214.4 months) in the non-NHTL salvage group ($p = 0.133$).

Only 590 (6.1%) patients did not attain hematologic recovery, 111 of whom had documented persistence of disease. Chimerism data were not available for analysis.

The 2-year cumulative incidence of acute GVHD was 60% (95% CI, 59% to 61%) and was no different for patients treated with NHTL or standard prophylaxis ($p = 0.229$). The 2-year cumulative incidence of grade III-IV was very slightly lower for patients treated with NHTL prophylaxis (15%, 95% CI, 15% to 16% *vs*. 18%, 95% CI, 17% to 19%, $p < 0.001$). The median time to acute onset in those eventually developing severe acute GVHD was statistically significantly but only slightly delayed in recipients of NHTL prophylaxis; the CIBMTR does not collect the date of diagnosis of particular grades of acute GVHD, so it would not be possible to infer whether the onset of severe acute GVHD was in fact delayed.

As previously reported, the primary benefit of NHTL prophylaxis appeared to be in preventing or delaying chronic GVHD. The overall occurrence of chronic GVHD was less among recipients of NHTL prophylaxis, and the 2-year cumulative incidence of extensive chronic GVHD was 40% (95% CI, 28% to 42%) with NHTL prophylaxis *vs.* 49% (95% CI, 48% to 50%) with standard prophylaxis ($p < 0.001$).

Among those 3526 patients who received only first-line therapy for acute GVHD, 8% received systemic steroids alone, 2% topical treatment alone, 69% received systemic steroids with one other non-steroid systemic treatment, and 15% received 1 or 2 systemic non-steroid drug(s), with or without topical treatment. Among those who received salvage therapy, the median number of total treatments (systemic and topical drugs, antibodies, ECP or PUVA) was 3 (range 3 to 9), the median number of systemic treatments was 3 (range 3 to 8), and the median number of classes of topical treatments was 0 (range 0 to 2). Appendix Section 9.5 further breaks down the pattern of GVHD therapies according to acute *versus* chronic GVHD groups. Clearly patients with acute GVHD tended to receive different treatments than patients with chronic GVHD. Appendix Section 9.6 presents the various acute GVHD therapies according to “first-line” and “salvage” stages. Most

agents other than cyclosporine and topical steroids were far more likely to be deployed at the "salvage" stage than as "first-line" treatment. Duration of immunosuppression was not evaluable because a stop date was only recorded for 1761 (18%) of patients (chiefly those with chronic GVHD).

The 2-year cumulative incidence of relapse was higher among recipients of NHTL prophylaxis (37%, 95% CI, 35% to 39%) compared to those who received standard prophylaxis (33%, 95% CI, 32% to 34%, $p = 0.003$). With NHTL salvage, 2-year cumulative incidence of relapse was lower than with standard salvage (16%, 95% CI, 12% to 20% *vs*. 31%, 95% CI, 29% to 30%, $p < 0.001$) but that benefit was offset by a higher incidence of death from non-relapse causes. By the Kaplan-Meier method, the probabilities of 2-year DFS and OS for patients treated with NHTL prophylaxis were 37% (95% CI, % 34 to 41%) and 41% (95% CI, 38% to 44%) and for patients treated with standard prophylaxis they were 42% (95% CI, 40% to 43%, $p = 0.002$) and 45% (95% CI, 45 to 47%, $p = 0.002$), respectively (Figure 6). NHTL salvage treatment was associated with substantially reduced probability of 2-year DFS (12%, 95% CI, 9% to 16% *vs.* 27%, 95% CI, 25% to 30%, $p < 0.001$) and OS compared to standard salvage (13%, 95% CI, 9% to 17% *vs*. 29%, 95% CI, 26% to 32%, $p < 0.001$; Figure 6). In unadjusted analysis, there appeared to be no effect modification of salvage treatment by prior prophylaxis: OS and DFS did not differ between those who were sequentially treated with NHTL prophylaxis followed by standard salvage *vs*. standard prophylaxis followed by standard salvage ($p = 0.420$ for DFS and $p = 0.414$ for OS). OS and DFS did not differ either for those who were sequentially treated with NHTL prophylaxis followed by NHTL salvage *vs*. those who were treated with NHTL prophylaxis followed by NHTL salvage ($p = 0.744$ for DFS and 0.938 for OS). The *salvage* treatment dominated the effect on DFS and OS.

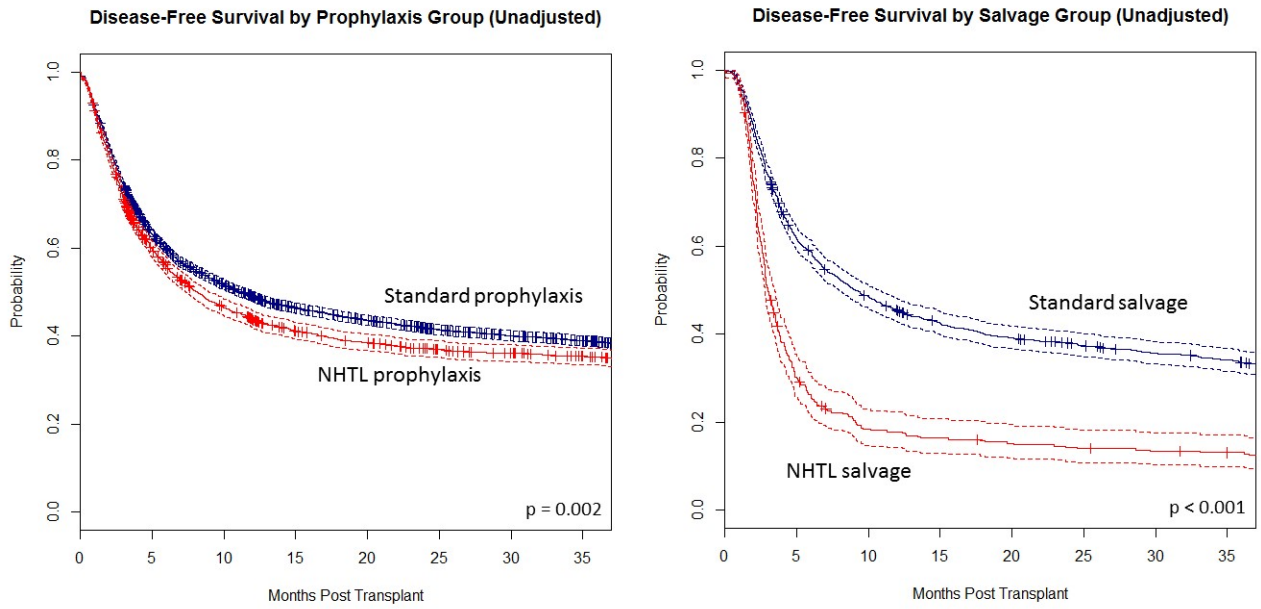

Figure 6. Kaplan-Meier estimates of disease-free survival. *Results are shown according to prophylaxis (left panel) and salvage (right panel) groups. The blue lines indicate standard drug classes. The red lines indicate NHTL therapeutics. Dashed lines show 95% confidence intervals.*

Table 4 shows additional information related to the development of GVHD, relapse, survival, and length of follow-up.

Table 4. Unadjusted outcomes of the entire cohort and according to stage 1 and stage 2 intervention

Characteristic	**Entire analysis cohort** (n = 9563)		**NHTL prophylaxis** (n = 2643)		**Non-NHTL prophylaxis** (n = 6920)		p-value[1]	**NHTL salvage** (n = 347)		**Non-NHTL salvage** (n = 1064)		p-value[1]
Acute GVHD												
Any acute GVHD, no. (%)	5719	(60)	1577	(60)	4142	(60)	0.885	--	--	--	--	--
2-year cumulative incidence of acute GVHD, % (95% CI) [2]	60	(59–61)	60	(58–61)	60	(58–61)	0.229	100	--	100	--	--
Median time from HCT to acute GVHD onset, months, (range)	0.9	(0.03–120.9)	0.9	(0.07–61.4)	0.8	(0.03–120.9)	<0.001	0.7	(0.1–5.5)	0.7	(0.1–23.6)	0.172
Maximum acute GVHD grade during follow-up, regardless of treatment, no. (% of entire cohort)[3]							<0.001					--
Grade I-II	4048	(42)	1180	(45)	2868	(41)		--	--	--	--	
Grade III-IV	1618	(17)	389	(15)	1229	(18)		--	--	--	--	
Missing	53	(1)	8	(<1)	45	(1)		--	--	--	--	
2-year cumulative	17	(16–18)	15	(15–16)	18	(17–19)	<0.001	85	(81–89)	47	(44–50)	<0.001

Table 4. Unadjusted outcomes of the entire cohort and according to stage 1 and stage 2 intervention												
Characteristic	**Entire analysis cohort** (n = 9563)		**NHTL prophylaxis** (n = 2643)		**Non-NHTL prophylaxis** (n = 6920)		p-value[1]	**NHTL salvage** (n = 347)		**Non-NHTL salvage** (n = 1064)		p-value[1]
incidence of grade III-IV acute GVHD, % (95% CI)[4]												
Indication for GVHD Treatment on Index Form, no. (%)[5,6]							<0.001					--
Acute GVHD, with or without chronic GVHD treatment	4937	(52)	1378	(52)	3559	(51)		347	(100)	1064	(100)	
Chronic GVHD, without acute GVHD treatment	1382	(14)	262	(10)	1120	(16)		0	(0)	0	(0)	
Never required GVHD treatment	3244	(34)	1003	(38)	2241	(32)		0	(0)	0	(0)	
Median no. of systemic acute GVHD treatments on the index CRF, (range)[5]	2	(0–8)	2	(0–7)	2	(0–8)	0.523	4	(3–8)	3	(3–6)	<0.001
Acute GVHD grade at "start" of acute GVHD treatment, on the index form, no. (% of n 1st treated for acute GVHD)[5]							<0.001					<0.001
Grade I-II	3336	(68)	994	(72)	2342	(66)		49	(14)	554	(52)	
Grade III-IV	1493	(30)	358	(26)	1135	(32)		296	(85)	492	(46)	
Missing	108	(2)	26	(2)	82	(2)		2	(1)	18	(2)	
Maximum grade of acute GVHD during follow-up in those 1st treated for acute GVHD, no. (% of n first treated for acute GVHD)[5]							<0.001					<0.001
Grade I-II	3356	(68)	1000	(72)	2356	(66)		50	(14)	557	(52)	
Grade III-IV	1535	(31)	370	(27)	1165	(33)		296	(85)	499	(47)	
Missing	46	(1)	8	(1)	38	(1)		1	(<1)	8	(1)	
Chronic GVHD												
Any chronic GVHD, no. (%)	4625	(48)	1112	(42)	3513	(51)	<0.001	151	(38)	556	(52)	0.005
2 year cumulative incidence of chronic GVHD, (95% CI)[7]	47	(46–48)	40	(38–42)	49	(48–50)	<0.001	43	(39–48)	52	(49–55)	<0.001
Median time from transplant to chronic GVHD onset, months, (range)	5.5	(0.1–187.2)	5.7	(0.2–142.0)	5.5	(0.1–187.2)	0.235	3.5	(0.7 – 87.3)	4.7	(0.1–146.7)	<0.001
Type of cGVHD onset, no. (% of all patients with chronic GVHD)[8]							<0.001					0.114
Progressive/ Interrupted/ Quiescent	1158	(25)	332	(30)	826	(24)		48	(31)	170	(31)	

Table 4. Unadjusted outcomes of the entire cohort and according to stage 1 and stage 2 intervention										
Characteristic	**Entire analysis cohort** (n = 9563)		**NHTL prophylaxis** (n = 2643)		**Non-NHTL prophylaxis** (n = 6920)		p-value[1]	**NHTL salvage** (n = 347)		**Non-NHTL salvage** (n = 1064)		p-value[1]
De novo	490	(11)	132	(12)	358	(10)		25	(11)	60	(11)	
Missing	2977	(64)	648	(58)	2329	(66)		78	(59)	326	(59)	
2-year cumulative incidence of extensive chronic GVHD, % (95% CI)[9]	34	(33–36)	26	(24–28)	38	(37–39)	<0.001	40	(35–45)	46	(42–49)	0.011
2-year cumulative incidence of moderate or severe chronic GVHD, % (95% CI)[10]	30		24	(22–26)	33	(32–34)	<0.001	40	(35–45)	43	(40–46)	0.058
Median no. of systemic chronic GVHD treatments on the index CRF (range)[5]	2	(0–9)	2	(0–5)	2	(0–9)	0.090	--	--	--	--	--
Chronic GVHD grade at "start" of first GVHD treatment, no. (% of n first treated for chronic GVHD)[5]							<0.001					--
Limited	478	(35)	116	(44)	362	(32)		--	--	--	--	
Extensive	836	(60)	134	(51)	702	(63)		--	--	--	--	
Missing	68	(5)	12	(5)	56	(5)		--	--	--	--	
Chronic GVHD severity at start of treatment, no. (% of n first treated for chronic GVHD)[5]							0.234					0.058
Mild	740	(53)	152	(58)	588	(52)		--	--	--	--	
Moderate	390	(28)	68	(26)	322	(29)		--	--	--	--	
Severe	148	(11)	23	(9)	125	(11)		--	--	--	--	
Missing	104	(8)	19	(7)	85	(8)		--	--	--	--	
Maximum chronic GVHD grade during follow-up in those 1st treated for chronic GVHD, no. (% of n first treated for chronic GVHD)[5]							<0.001					--
Limited	377	(27)	102	(39)	275	(25)		--	--	--	--	
Extensive	1073	(73)	159	(61)	844	(75)		--	--	--	--	
Missing	2	(<1)	1	(<1)	1	(<1)		--	--	--	--	
Maximum chronic GVHD severity during follow-up in those 1st treated for chronic GVHD, no. (% of n 1st treated for chronic GVHD)[5]							0.001					--
Mild	570	(41)	128	(49)	442	(39)		--	--	--	--	
Moderate	514	(37)	98	(37)	416	(37)		--	--	--	--	
Severe	245	(18)	26	(10)	219	(20)		--	--	--	--	
Missing	53	(4)	10	(4)	43	(4)		--	--	--	--	
DCI given prior to acute GVHD onset, no. (% of pts with acute GHVD)							0.251					0.326

Table 4. Unadjusted outcomes of the entire cohort and according to stage 1 and stage 2 intervention											
Characteristic	**Entire analysis cohort** (n = 9563)		**NHTL prophylaxis** (n = 2643)		**Non-NHTL prophylaxis** (n = 6920)		p-value[1]	**NHTL salvage** (n = 347)		**Non-NHTL salvage** (n = 1064)		p-value[1]
Yes	59	(1)	20	(1)	39	(1)		0	(0)	3	(<1)	
No, given after	397	(4)	120	(5)	277	(4)		3	(1)	24	(2)	
Missing timing of DCI relative to acute GVHD	4	(<1)	2	(<1)	2	(<1)		0	(0)	1	(<1)	
DCI given prior to chronic GVHD onset, no. (% of pts with chronic GVHD)							0.226					0.665
Yes	80	(1)	28	(1)	52	(1)		1	(<1)	6	(1)	
No, given after	373	(4)	111	(4)	260	(4)		1	(<1)	9	(1)	
Missing timing of DCI relative to chronic GVHD	7	(<1)	3	(<1)	4	(<1)		0	(0)	0	(0)	
Relapse and Survival												
Any relapse, no. (%)	3546	(37)	1030	(39)	2516	(36)	0.019	57	(16)	433	(34)	<0.001
Median time to relapse, months (95% CI)	4.4	(0.03–142.9)	3.9	(0.03–106.2)	4.6	(0.03–142.9)	<0.001	3.1	(0.03–33.1)	3.9	(0.03–103.3)	0.008
Cumulative incidence of relapse by 2 years, % (95% CI)[11]	34	(33–35)	37	(35–39)	33	(32–34)	0.003	16	(12–20)	31	(29–34)	<0.001
Alive at last follow-up, no. (%)	3422	(36)	911	(34)	2511	(36)	0.102	37	(11)	246	(23)	<0.001
Vital status at 2 years, no. (%)							<0.001					<0.001
Alive	3882	(41)	989	(37)	2893	(42)		39	(11)	293	(28)	
Dead	5215	(54)	1527	(58)	3688	(53)		300	(86)	741	(70)	
Lost-to-follow-up	466	(5)	127	(5)	339	(5)		8	(2)	30	(3)	
Disease-free survival at 2 years, no. (%)							<0.001					<0.001
Alive, relapse-free	3556	(37)	892	(34)	2664	(39)		38	(11)	273	(26)	
Dead and/or relapsed	5587	(58)	1639	(62)	3975	(57)		302	(87)	762	(72)	
Lost-to-follow-up without relapse	420	(4)	121	(5)	299	(4)		7	(2)	29	(3)	
Median disease-free survival, months (range)	8.9	(0–222.7)	7.3	(0.03–218.6)	9.8	(0–222.7)	<0.001	2.9	(0.03–186.9)	5.1	(0.03–214.4)	<0.001
Disease-free survival probability at 2 years, % (95% CI)[11]	40	(39–41)	37	(34–41)	42	(40–43)	0.002	12	(9–16)	27	(25–30)	<0.001
Median survival, months (range)	12.4	(0–222.7)	10.8	(0.03–218.6)	13.2	(0–222.7)	<0.001	3.1	(0.6–186.9)	6.6	(0.5–214.4)	<0.001
Overall survival probability at 2	44	(43–45)	41	(38–44)	45	(45–47)	0.002	13	(9–17)	29	(26–32)	<0.001

Table 4. Unadjusted outcomes of the entire cohort and according to stage 1 and stage 2 intervention											
Characteristic	**Entire analysis cohort** (n = 9563)		**NHTL prophylaxis** (n = 2643)		**Non-NHTL prophylaxis** (n = 6920)		p-value[1]	**NHTL salvage** (n = 347)		**Non-NHTL salvage** (n = 1064)		p-value[1]
years, % (95% CI)												
Median follow-up of survivors, months (range)	84.7	(3.0–222.7)	75.0	(3.1-218.6)	88.0	(3.0–222.7)	<0.001	73.5	(3.2–186.9)	89.5	(3.2–214.4)	0.133

1. The Chi-squared test was used to compare categorical variables, the Fisher exact test for categorical variables with small cell size (≤5 observations), and the Mann-Whitney-Wilcoxon test for continuous variables, and Gray's method for comparisons of cumulative incidence. Univariable probabilities of DFS and OS were calculated using the Kaplan-Meier estimator with Greenwald's formula for the variance.
2. Death without developing acute GVHD is a competing risk.
3. Regardless of whether required GVHD treatment at all, and regardless of whether treatment was first administered for acute or chronic GVHD.
4. Death without grade III-IV acute GVHD, including death with only grade I-II acute GVHD, is a competing risk.
5. The index CRF is the first CRF describing acute or chronic GVHD treatment (whichever occurred first) over the interval preceding the CRF (6 months for the first follow-up form, 12 months for subsequent follow-up forms). The grade at the "start" of treatment was considered to be the grade recorded on the index form, which is actually the maximum grade in the preceding interval. The actual grade at the start of treatment is not collected by the CIBMTR. The assumption that the maximum grade equalled the "treatment triggering" grade was made for the purpose of this proof-of-principle analysis.
6. Treatment could be topical and/or systemic. Patients who required GVHD treatment but in whom details of the drugs administered were missing were excluded from the analysis set.
7. Death without developing chronic GVHD is a competing risk.
8. The level "chronic GVHD flare" was considered as "Interrupted."
9. Death without extensive chronic GVHD, including death with only limited chronic GVHD, is a competing risk.
10. Death without moderate or severe chronic GVHD, including death with only mild chronic GVHD, is a competing risk.
11. Death without relapse is a competing risk.

6.3 Personalized treatment strategy recommendations

6.3.1 Censoring

The A_2 model included 1411 patients who received salvage treatment for acute GVHD within 2 years of AHCT. Thirty-six patients were lost-to-follow-up (LTFU) after receiving acute GVHD salvage treatment but before the 2-year mark. Inverse probability of censoring weights were calculated to account for their

absence from the A_2 model. Their pseudo-outcomes were predicted and they were included in the prophylaxis model. Four thousand one hundred and seventy-four patients died before 2 years without requiring salvage treatment for acute GVHD, including 317 who required treatment for chronic GVHD before acute GVHD and died before 2 years. These 317 patients, as well as another 1065 survivors and 34 who were LTFU before 2 years, were ineligible for the A_2 model on the basis of their treatment-requiring chronic GVHD preceding any treatment-requiring acute GVHD. Another 1047 patients were never diagnosed with treatment-requiring GVHD, and 1472 received only "first-line" treatment for acute GVHD (including 4 patients who were only diagnosed with treatment-requiring acute GVHD after the 2-year mark) while 432 were LTFU before the 2-year mark and not recorded as having required salvage therapy for acute GVHD. Thus, a total of 4333 patients were deemed ineligible for the A_2 model and were therefore assigned IPCW for the first interval (*i.e.*, from prophylaxis to the never-reached A_2 decision point). Note that relapse itself did not preclude acute GVHD salvage treatment, so the actual number of losses-to-follow-up in the prophylaxis model was 384 patients (*i.e.*, 36 who were LTFU after receiving salvage acute GVHD treatment were not LTFU for the purpose of the prophylaxis model because their pseudo-outcomes were used as the dependent variable, and 12 whose vital status was unknown at 2 years had recorded dates of relapse, so were not LTFU with respect to the A_1 model outcome of 2-year *disease-free* survival). Observed disease-free survival time (rather than time-to-acute or time-to-chronic GVHD, if applicable) was used to compute outcomes for all patients in the prophylaxis model who were not lost-to-follow-up and not requiring a pseudo-outcome. Several factors were associated with the probability of being censored in the post-A_1 interval and not proceeding to A_2 (Appendix Section 9.4). The resultant A_1 weights ranging from approximately 1.0 to 4.5 depending on the imputed data set, indicating that no individual patient was given an extreme weight. Fewer factors were associated with the probability of being censored (*i.e.*, LTFU) in the post-A_2 interval, with the resultant weights ranging from approximately 1.0 to 1.3 (Appendix Section 9.4). These yielded final weights for the A_2 model (after multiplying by the A_1 weights) that ranged from approximately 1.0 to 4.5. The small

magnitude of these weights implies that the factors considered did not strongly predict censoring. That is, censoring was apparently random with respect to measured baseline characteristics, particularly for the A_2 model.

6.3.2 Adaptive treatment strategies

From the unadjusted Kaplan-Meier estimates, NHTL prophylaxis and NHTL salvage both seem detrimental when judged by DFS and OS (Figure 6). By contrast, Tables 5 and 6 summarize the results of Q-learning applied to the decision of whether to use NHTL therapy for prophylaxis and/or for salvage treatment in multivariable analysis using a cut-point of 2 years. The relative risks of 2-year DFS estimated in the multivariable analysis using backwards stage-wise estimation suggest no effect of either NHTL prophylaxis or NHTL salvage at the population level because the confidence intervals all cross unity. However, putting aside the issue of possible lack of power for the sake of demonstrating how Q-learning makes patient-specific predictions, using the point estimates of effect we were able to identify patients who might benefit more from one intervention compared to the alternative.

The A_1 model predicted that 4762 patients (50%) would have a higher probability of 2-year DFS with NHTL prophylaxis and 4801 (50%) would fare better with standard prophylaxis. Remarkably, these proportion were stable across models employing slightly different predictors and different parameterizations of the current predictors; the proportion of patients predicted to benefit more from NHTL prophylaxis was always 49% to 50%. The magnitude of benefit was modest. Among patients predicted to benefit more from standard prophylaxis, the absolute difference in 2-year DFS probability predicted under standard prophylaxis *vs*. NHTL prophylaxis was a median of 5% (range, nearly 0% to 26%). Likewise, among patients predicted to benefit more from NHTL prophylaxis, the absolute difference in 2-year DFS probability predicted under NHTL prophylaxis *vs*. standard prophylaxis was a median of 4% (range, nearly 0% to 33%). A total of 4700 (49%) patients were predicted to have 2-year DFS differences ≥5%, and 2005 (21%) were

predicted to have 2-year DFS differences ≥10%, with the alternative prophylaxis options.

For the 1411 patients requiring salvage treatment for acute GVHD, the A_2 model predicted that 492 patients (35%) would have a higher probability of 2-year DFS with NHTL prophylaxis and 919 (65%) would fare better with standard prophylaxis. These proportions were fairly stable across models employing slightly different predictors and different parameterizations of the current predictors; the proportion of patients predicted to benefit more from NHTL salvage was always 33% to 37%. The contrast between predicted 2-year DFS for the alternative salvage choices was often substantial. Among patients predicted to benefit more from standard prophylaxis, the absolute difference in 2-year DFS probability predicted under standard prophylaxis *vs*. NHTL prophylaxis was a median of 9% (range, nearly 0% to 79%). Similarly, among patients predicted to benefit more from NHTL salvage, the absolute difference in 2-year DFS probability predicted under NHTL prophylaxis *vs*. standard prophylaxis was a median of 12% (range, nearly 0% to 65%). For 948 (67%) patients, the predicted 2-year DFS with the alternative salvage options differed by ≥5% and for 711 (50%) patients, it differed by ≥10%.

Table 5. Predictors of 2-year disease-free survival at the prophylaxis stage

Characteristic	Main Effect		Effect of NHTL *versus* Standard Prophylaxis, Given the Characteristic[1]	
	RR	95% CI	RR	95% CI
Type of prophylaxis				
Standard	1	--	NA	NA
NHTL	0.98	(0.63, 1.46)	NA	NA
Recipient age (years)				
0-10	1	--	0.98	(0.63, 1.46)
10-19	0.95	(0.84, 1.06)	0.87	(0.53, 1.35)
20-29	0.99	(0.87, 1.11)	0.68	(0.41, 1.11)
30-39	0.94	(0.82, 1.06)	0.71	(0.41, 1.18)
40-49	0.85	(0.73, 0.97)	075	(0.43, 1.32)
50-59	0.82	(0.69, 0.94)	0.69	(0.38, 1.26)
60+	0.73	(0.56, 0.89)	0.79	(0.41, 1.46)
Karnofsky/Lansky performance status at time of transplant				
≥ 80%	1	--	0.98	(0.63, 1.46)
< 80%	0.68	(0.63, 0.79)	1.00	(0.54, 1.80)

Table 5. Predictors of 2-year disease-free survival at the prophylaxis stage				
Characteristic	**Main Effect**		**Effect of NHTL *versus* Standard Prophylaxis, Given the Characteristic[1]**	
	RR	**95% CI**	**RR**	**95% CI**
Disease status at time of transplant				
Early	1	--	1	--
Intermediate	0.89	(0.82, 0.95)	1.04	(0.64, 1.60)
Advanced	0.41	(0.35, 0.48)	1.14	(0.58, 2.12)
Donor relation				
Related	1	--	0.98	(0.63, 1.46)
Unrelated	0.86	(0.80, 0.94)	1.20	(0.79, 1.78)
HLA match				
Well-matched	1	--	0.98	(0.63, 1.46)
Partially-matched	1.08	(0.97, 1.22)	1.08	(0.75, 1.47)
Mismatched	1.24	(1.09, 1.43)	1.01	(0.73, 1.30)
CMV status				
Donor or recipient positive	1	--	0.98	(0.63, 1.46)
Negative-Negative	1.08	(1.01, 1.15)	1.01	(0.69, 1.44)
Sex match (donor-recipient)				
Male-male, female-female, or male-female	1	--	0.98	(0.63, 1.46)
Female-male	1.03	(0.96, 1.11)	1.00	(0.64, 1.45)
Graft source/donor age (years)[1]				
Umbilical cord	1	--	1	1
BM, 0-19	0.96	(0.86, 1.09)	0.92	(0.66, 1.27)
BM, 20-49	0.89	(0.75, 1.11)	0.88	(0.48, 1.35)
BM, 50+	0.83	(0.69, 1.03)	1.52	(0.98, 2.16)
PB, 0-19	1.01	(0.90, 1.16)	1.04	(0.78, 1.35)
PB, 20-49	0.88	(0.74, 1.05)	1.03	(0.70, 1.49)
PB, 50+	1.14	(0.97, 1.41)	0.71	(0.52, 0.93)
Conditioning intensity				
Myeloblative	1	--	0.98	(0.63, 1.46)
RIC/NMA	0.98	(0.88, 1.07)	0.90	(0.55, 1.40)
Total body irradiation				
No	1	--	0.98	(0.63, 1.46)
Yes	0.98	(0.92, 1.03)	1.05	(0.68, 1.57)
Other Components of GVHD Prophylaxis				
Absence of drug listed below	1	--	0.98	(0.63, 1.46)
Mycophenolate	1.01	(0.90, 1.13)	0.93	(0.58, 1.44)
Methotrexate	1.04	(0.96, 1.14)	0.96	(0.64, 1.37)
Corticorsteroids (not for nausea)	0.92	(0.84, 0.99)	1.07	(0.68, 1.58)

Table 5. Predictors of 2-year disease-free survival at the prophylaxis stage				
Characteristic	**Main Effect**		**Effect of NHTL *versus* Standard Prophylaxis, Given the Characteristic[1]**	
	RR	**95% CI**	**RR**	**95% CI**
1. This column shows the combined effect of tailoring variables with NHTL prophylaxis, *i.e.*, the result of the main effects and of interactions between the characteristic and the class of prophylaxis treatment, calculated as $RR = expit(\hat{\beta}_0 + \hat{\beta}_n + (\hat{\psi}_0 + \hat{\psi}_n)a)/expit(\hat{\beta}_0 + \hat{\beta}_n)$ where $\hat{\beta}_0$ is the model intercept, $\hat{\beta}_n$ is the coefficient for the for the main effect of the candidate tailoring variable, $\hat{\psi}_0$ is the coefficient for the main effect of NHTL prophylaxis, $\hat{\psi}_n$ is the coefficient for the interaction of NHTL prophylaxis with the candidate tailoring variable, and action $a = 1$ for NHTL prophylaxis while $a = 0$ for standard prophylaxis; *n* indexes tailoring variables. Note that the impact of the reference categories is subsumed in the estimated main effect of NHTL *vs.* standard prophylaxis.				

Table 6. Predictors of 2-year disease-free survival in patients requiring treatment for acute GVHD before or without treatment for chronic GVHD, and proceeding to acute GVHD salvage treatment				
Characteristic	**Main Effect**		**Effect of NHTL *versus* Standard Salvage, Given the Characteristic[1]**	
	RR	**95% CI**	**RR**	**95% CI**
Type of salvage				
Standard	1	--	NA	NA
NHTL	0.67	(0.02, 1.47)	NA	NA
Recipient age (years)				
0-10	1	--	0.67	(0.02, 1.47)
10-19	0.79	(0.48, 0.97)	0.58	(<0.01, 2.17)
20-29	0.79	(0.48, 0.98)	0.62	(<0.01, 2.21)
30-39	0.76	(0.43, 0.96)	0.67	(<0.01, 2.55)
40-49	0.70	(0.37, 0.94)	0.35	(<0.01, 2.03)
50-59	0.67	(0.33, 0.94)	0.26	(<0.01, 1.91)
60+	0.67	(0.31, 0.93)	0.28	(<0.01, 2.48)
Karnofsky/Lansky performance status at time of transplant				
≥ 80%	1	--	1	--
< 80%	0.75	(0.31, 0.96)	0.81	(<0.01, 3.80)
Disease status at time of transplant				
Early	1	--	0.67	(0.02, 1.47)
Intermediate	0.98	(0.87, 1.06)	0.88	(0.01, 1.68)
Advanced	0.76	(0.51, 0.95)	0.69	(0.04, 2.43)
Donor relation				
Related	1	--	0.67	(0.02, 1.47)
Unrelated	0.76	(0.48, 0.95)	1.01	(0.02, 2.65)
HLA match				
Well-matched	1	--	0.67	(0.02, 1.47)
Partially-matched	1.09	(1.00, 1.43)	0.53	(0.01, 1.08)
Mismatched	1.08	(0.99, 1.41)	0.83	(0.09, 1.21)

Table 6. Predictors of 2-year disease-free survival in patients requiring treatment for acute GVHD before or without treatment for chronic GVHD, and proceeding to acute GVHD salvage treatment				
Characteristic	**Main Effect**		**Effect of NHTL *versus* Standard Salvage, Given the Characteristic[1]**	
	RR	**95% CI**	**RR**	**95% CI**
CMV status				
Donor or recipient positive	1	--	0.67	(0.02, 1.47)
Negative-Negative	1.02	(0.98, 1.15)	0.79	(0.03, 1.44)
Sex match (donor-recipient)				
Male-male, female-female, or male-female	1	--	0.67	(0.02, 1.47)
Female-male	1.00	(0.92, 1.10)	0.89	(0.07, 1.60)
Graft source/donor age (years)[1]				
Umbilical cord	1	--	0.67	(0.02, 1.47)
BM, 0-19	0.85	(0.59, 1.11)	0.50	(0.01, 1.66)
BM, 20-49	0.59	(<0.01, 0.99)	<0.01	(<0.01, 0.18)
BM, 50+	0.62	(<0.01, 1.15)	0.75	(<0.01, 5857010.45)
PB, 0-19	0.87	(0.59, 1.13)	0.56	(0.02, 1.71)
PB, 20-49	0.88	(0.58, 1.19)	<0.01	(<0.01, <0.01)
PB, 50+	0.95	(0.74, 1.42)	0.40	(<0.01, 1.25)
Conditioning intensity				
Myeloblative	1	--	0.67	(0.02, 1.47)
RIC/NMA	1.02	(0.84, 1.15)	0.98	(0.08, 1.62)
Total body irradiation				
No	1	--	0.67	(0.02, 1.47)
Yes	1.06	(1.01, 1.23)	0.70	(0.01, 1.35)
GVHD Prophylaxis				
Absence of drug listed below	1	--	0.67	(0.02, 1.47)
Mycophenolate	0.99	(0.87, 1.09)	0.54	(<0.01, 1.40)
Methotrexate	0.97	(0.84, 1.09)	0.54	(0.02, 1.51)
Corticosteroids (not for nausea)	0.90	(0.68, 1.00)	0.48	(<0.01, 1.61)
NHTL prophylaxis	1.07	(1.01, 1.30)	0.79	(0.02, 1.34)
Time from graft infusion to acute GVHD				
< 1 month	1	--	0.67	(0.02, 1.47)
≥ 1 month	0.97	(0.83, 1.03)	0.83	(0.02, 1.70)
Grade of acute GVHD at "start" of treatment (maximum grade on the index form)				
I-II	1	--	0.67	(0.02, 1.47)
III-IV	0.75	(0.47, 0.95)	0.25	(<0.01, 1.76)
Four or more immunosuppressors to treat acute GVHD on the index form				
No	1	--	0.67	(0.02, 1.47)
Yes	0.95	(0.76, 1.03)	0.51	(<0.01, 1.62)

Table 6. Predictors of 2-year disease-free survival in patients requiring treatment for acute GVHD before or without treatment for chronic GVHD, and proceeding to acute GVHD salvage treatment

Characteristic	Main Effect		Effect of NHTL *versus* Standard Salvage, Given the Characteristic[1]	
	RR	95% CI	RR	95% CI
Chronic GVHD (not needing treatment) diagnosed before acute GVHD				
No	1	--	0.67	(0.02, 1.47)
Yes	0.65	(<0.01, 0.98)	0.23	(<0.01, 32029.44)

1. This column shows the combined effect of tailoring variables with NHTL salvage, *i.e.*, the result of the main effects and of interactions between the characteristic and the class of salvage treatment, calculated as as $RR = expit(\hat{\beta}_0 + \hat{\beta}_n + (\hat{\psi}_0 + \hat{\psi}_n)a)/expit(\hat{\beta}_0 + \hat{\beta}_n)$ where $\hat{\beta}_0$ is the model intercept, $\hat{\beta}_n$ is the coefficient for the for the main effect of the candidate tailoring variable, $\hat{\psi}_0$ is the coefficient for the main effect of NHTL salvage, $\hat{\psi}_n$ is the coefficient for the interaction of NHTL salvage with the candidate tailoring variable, and action $a = 1$ for NHTL salvage while $a = 0$ for standard salvage; n indexes tailoring variables. Note that the impact of the reference categories is subsumed in the estimated main effect of NHTL *vs.* standard salvage.

6.3.3 Tailoring variables for 2-year DFS

After controlling for the factors in Tables 5 and 6, the main effects of NHTL prophylaxis (RR = 0.98, 95% CI, 0.63 to 1.46) and the main effect of NHTL salvage (RR = 0.67, 95% CI, 0.02 to 1.47) on 2-year DFS were not statistically significant. Although many candidate tailoring variables were not statistically significant (Tables 5 and 6), certain combinations of values or levels of the potential tailoring variables could "tip the balance" in favor of using NHTL prophylaxis or NHTL salvage. For example, from the point estimates of the effects, there is a suggestion that NHTL prophylaxis might benefit patients who receive TBI and those in unrelated donor settings, *i.e.*, the RR of 2-year DFS is greater than 1 with NHTL prophylaxis and below 1 with standard prophylaxis. The association of NHTL prophylaxis compared to standard prophylaxis with increased chances of 2-year DFS for patients with intermediate and advanced disease status is counterintuitive because other studies suggest that NHTL prophylaxis increases the chance of relapse, at least in non-myeloablative settings. It is important not to over-emphasize these associations that are not statistically significant and to temper

those estimates with the finding that NHTL prophylaxis might be detrimental in reduced intensity and non-myeloablative settings (RR for 2-year DFS 0.90, 95% CI, 0.55 to 1.40). Recall, however, that the RRs presented in Table 5 compare standard *versus* NHTL prophylaxis under the assumption that it will be followed by the optimal, personalized salvage therapy should it be needed. The estimates in Table 5 are not, therefore, directly comparable to results from other studies. Similarly, all other factors being equal *and assuming optimal salvage treatment for those with refractory GVHD*, NHTL prophylaxis might be more beneficial than standard prophylaxis in the unrelated, mismatched donor setting ($RR_{2\text{-year DFS}} = \frac{expit(\hat{\beta}0 + \hat{\beta}unrelated + \hat{\beta}mismatched + \hat{\psi}0 + \hat{\psi}unrelated \cdot prophylaxis + \hat{\psi}mismatched \cdot prophylaxis)}{expit(\hat{\beta}0 + \hat{\beta}unrelated + \hat{\beta}mismatched)} =$ 1.17 in favour of NHTL prophylaxis, 95% CI, 0.86 to 1.51), although this result was not statistically significant.

At the salvage stage, NHTL treatment appears detrimental for the majority of patients. In particular, there is a suggestion that NHTL treatment should not be administered to patients who received NHTL prophylaxis (RR of 2-year DFS if NHTL prophylaxis followed by standard acute GVHD salvage treatment = 1.07, 95% CI, 1.01 to 1.30, *versus* RR = 0.79, 95% CI, 0.02 to 1.34 if NHTL therapeutics are used for both prophylaxis and salvage). Also, there is a suggestion that NHTL therapy compounds the deleterious prognosis of grade III-IV acute GVHD or needing ≥4 immunosuppressant drugs. However, it would be premature to conclude that NHTL therapy should be avoided in these sickest patients because of residual confounding, as discussed below in Section 7.4.3.

6.3.4 Model fit

Figure 7 shows the model fit as assessed by first finding the mean of the quartiles of predicted 2-year survival within each combination of age group and intervention, and then finding the observed 2-year DFS proportion within each combination of age group, intervention, and quartile of predicted probability (see also Appendix Section 9.7). Overall the fit is moderately poor. Concentrating on the age categories where the bulk of the patients lie, the model substantially over-

estimated probability of 2-year DFS with both NHTL prophylaxis in the 20 to 39 year olds and in the highest quartile of 40 to 59 year olds. The model tended to underestimate 2-year DFS in those aged 60 and older across the board. The model was not useful for 0 to 19 year old patients treated with NHTL salvage, where means of the quartiles of predicted 2-year DFS and the corresponding observed 2-DFS proportion were 5% *vs*. 10%, 16% *vs*. 5%, 30% *vs*. 42%, and 56% *vs.* 10%. The reason the model fared so poorly here is that there were only 31 patients under 20 years old who received NHTL salvage treatment. In subgroups of the population with adequate representation, fit was somewhat better.

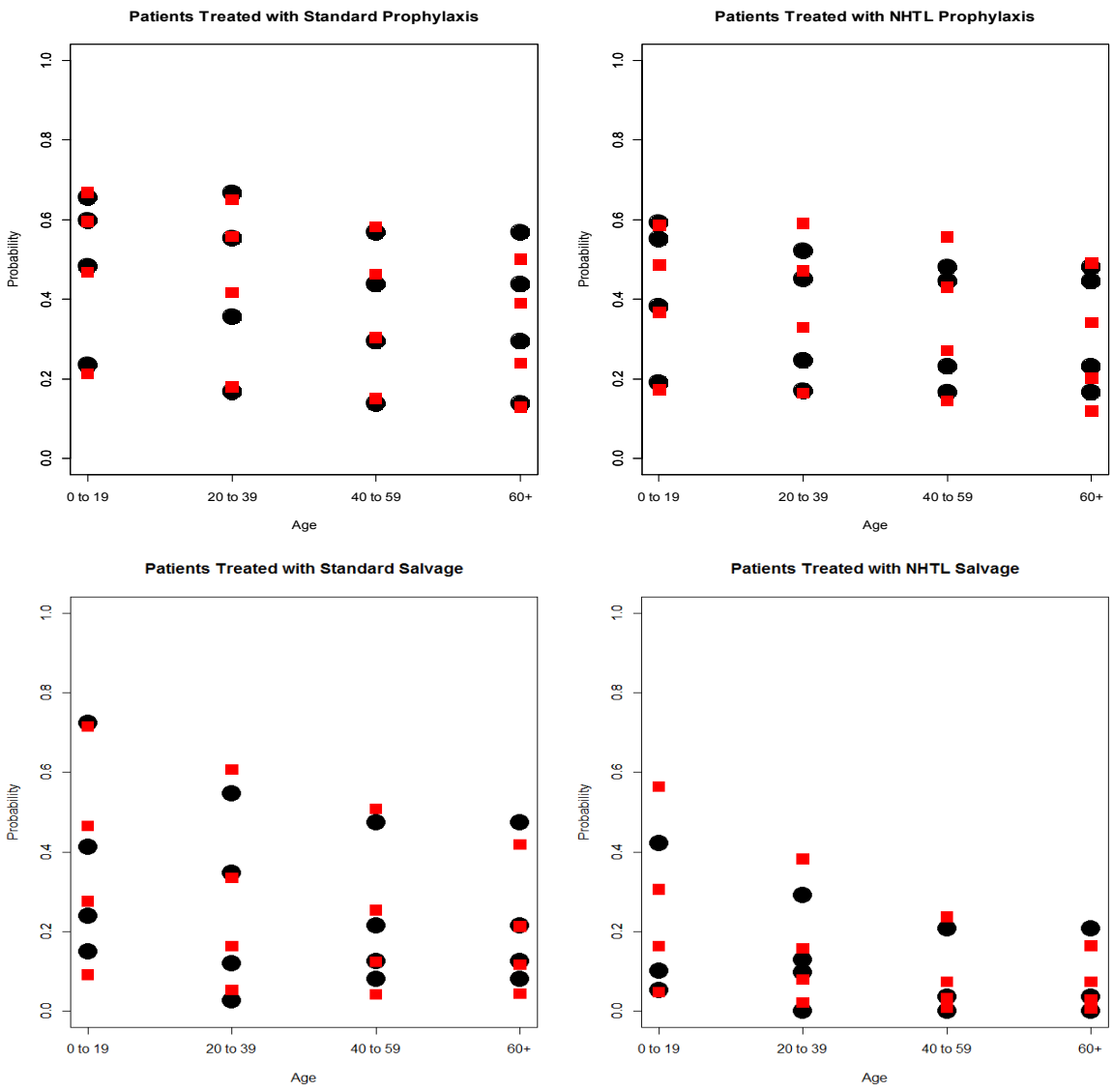

Figure 7. Assessment of model fit. *Within each age category, the mean of each quartile of predicted probability of 2-year disease-free survival is plotted as a red square. The observed proportion surviving 2-years disease-free, within each category of age and quartile of predicted probability, is plotted as a black circle.*

7. DISCUSSION

7.1 Results in the context of attainable power

It is crucial to bear in mind that the aim of this work was to see if a particular reinforcement learning strategy could be applied to CIBMTR data, and not to yield clinically-actionable algorithms. If this study were not subject to the limitations discussed below, the salient results would be that despite the apparent detrimental effect of NHTL prophylaxis and NHTL salvage on DFS at the population level, at the individual-patient level, a substantial proportion of patients are expected to actually benefit from NHTL prophylaxis (50%) and from NHTL salvage (35%). This conclusion would still need to be tempered by the realization that the model fits poorly, particularly in recipients of NHTL salvage treatment at the extremes of age. Even though the model fits were better for both prophylaxis and salvage interventions in the middle age ranges, the small magnitude of the projected survival benefit from choosing the "best" prophylaxis treatment relative to the discrepancy in the model fit raises cause for concern.

This conclusion must also be tempered by understanding that it stems from imprecise estimates. The required sample size can be estimated from the equation[159]

$$n_{total} > \left(z_{\alpha/2} + z_{\beta}\right)^2 \times \frac{1-\pi}{\pi} \times \frac{1}{Var[X]} \times \frac{1}{(1-r^2_{X\ with\ C})} \times \frac{1}{\Delta^2}$$

where n_{total} is the total sample size, $z_{\alpha/2}$ is the normal deviate for a 2-sided test with a false positive rate of α, z_{β} is the normal deviate for a false negative rate of β to yield overall power of 100(1-β)%, π is the probability of 2-year DFS for the entire cohort, X is the variable of interest – in this case receipt of NHTL instead of standard intervention, $Var[X]$ is the variance of the distribution of X, $r^2_{X\ with\ C}$ is the correlation of X with the other covariates in the model, and Δ is the difference between the non-null and null values of log(RR), and the null hypothesis is RR = 1. Keeping the assumptions already mentioned, taking the observed π = 0.23 for the

salvage cohort, and ignoring for the moment the issue of $r^2_{X\ with\ C}$, the estimated number of salvage and initial cohort patients needed to detect a $RR_{2\text{-year DFS}}$ that spans confidence interval limits of NHTL *vs.* standard salvage from 0.02 to 1.47 is shown in Figure 8. At $RR_{2\text{-year DFS}} = 0.67$, for example, a total of 863 patients would be required at the salvage stage which would imply including 5843 patients in the initial analysis cohort.

An equivalent of $r^2_{X\ with\ C}$ that holds whether regressing *X* on factor variables or continuous variables could be derived from the equation for the generalized variance inflation factor.[160] The mean $r^2_{X\ with\ C}$ for lymphodepleting salvage treatment across the 5 imputed data sets was 0.212. (This was calculated with the "car" R package[161] and interaction terms were omitted from the model for this calculation because for each patient's treatment obviously matches the treatment component of the interaction term.) This result suggests there is no strong association between receipt of NHTL salvage (or not) and one or more of the predictors. For the current model, accounting for the strength of association between salvage choice and other predictors increases the required sample size by about 27%, such that for $RR_{2\text{-year DFS}} = 0.67$, for example, a total of 1093 patients would be required at the salvage stage which would imply including 7408 patients in the initial analysis cohort. Thus, the wide confidence intervals do not simply stem from small sample size (since the sample included 9563 initial patients and 1411 salvage patients); rather, other factors influencing the behaviour of the logistic models must be considered.

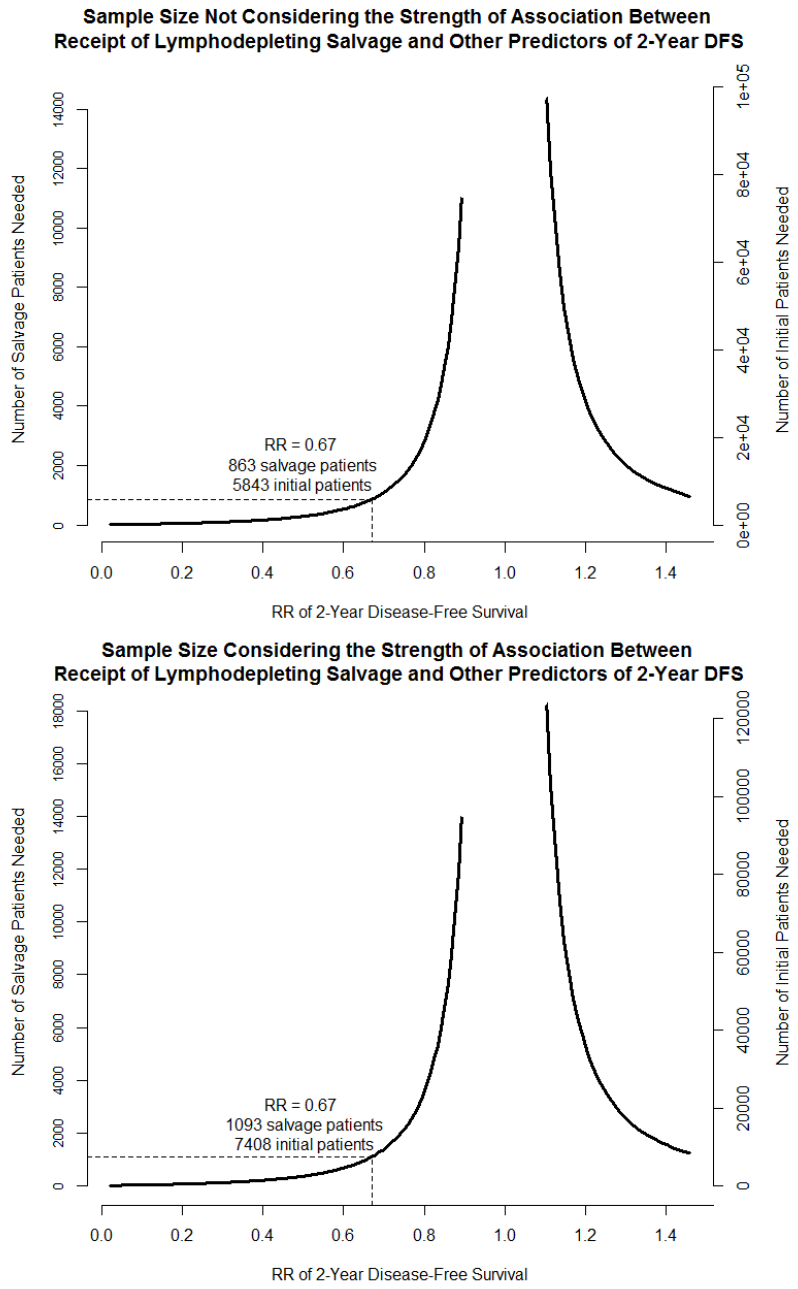

Figure 8. Post-hoc power/sample size calculation. *The horizontal axis depicts the relative risk (RR) of 2-year disease-free survival (DFS) if using NHTL salvage vs. standard salvage. The strength of association between choice of salvage intervention and other predictors does not pose a problem for the current model in the registry setting; a reasonable number of registry patients would be required to detect the clinically-relevant RRs with 80% power and a 2-sided significance of 0.05. However, these sample sizes are not feasible for a randomized trial. Salvage cohort sizes (left vertical axis) and initial cohort sizes (right vertical axis) needed to detect RRs of 0.02 to 0.90 and 1.10 to 1.47 are shown.*

A rule-of-thumb derived from an often-cited simulation study[162] is that with fewer than 10 outcome events per predictor variable in a logistic regression, variability and bias in the estimated coefficients increases and confidence interval coverage is wider than the nominal value (although the confidence intervals found from bootstrapping the data as done for the current analysis mitigate the latter problem[163]). Because the interactions between each predictor and prophylaxis or salvage choice were included as separate terms in the models and multi-level factors (including age categories) were dummy coded, the prophylaxis model contained 51 predictors and the salvage model contained 61 predictors. Considering the outcome event of disease-free survival at 2 years, the event-to-predictor ratio was 70:1 for the prophylaxis model but only 5:1 for the salvage model. Twice as many patients would need to be included in the study in order to satisfy the 10:1 event-to-predictor ratio criterion at the salvage stage, assuming the same proportion of subjects requiring acute GVHD salvage therapy and the same relapse and survival rates as in the current cohort. Increasing the event-to-predictor ratio by increasing the sample size might yield narrower confidence intervals and less biased estimates.

Lastly, some patterns of covariates were hardly represented (the most egregious examples being patients receiving NHTL salvage GVHD treatment after bone marrow transplant from donors > 50 years old, n = 12, and NHTL salvage patients with chronic GVHD not needing treatment diagnosed prior to acute GVHD, n = 1). Although R produced no explicit warnings about empty or small cells, their presence explains why the upper limit of the estimated coefficients for certain categories is exceedingly high, and these variables should be eliminated from the model in future work.[164]

7.2 Results in the context of previous studies

Conceptually, this work illustrates how observational data can be used to give highly personalized treatment recommendations. As examples: Our model predicted that an 18 year-old, CMV-positive male recipient of a female, partially-matched peripheral blood graft to treat early stage AML after cyclophosphamide-

TBI myeloablative conditioning would have an absolute 25% greater chance of DFS if given NHTL prophylaxis along with cyclosporine-methotrexate instead of solely standard prophylaxis. Our model predicted that a 48 year-old, CMV-positive woman with intermediate status AML who was conditioned with myeloablative busulfan-fludarabine, received an HLA-matched sibling peripheral blood graft after prophylaxis with tacrolimus-methotrexate, and now required a third drug to treat grade III acute GVHD that presented 1.05 months post-transplant would have an absolute 18% probability of 2-year DFS if given non-NHTL salvage but nearly 0% probability of 2-year DFS if given NHTL salvage. By contrast, a 48 year-old CMV-negative man with intermediate-risk AML who received a CMV-negative well-matched unrelated donor peripheral blood graft after reduced intensity busulfan-fludarabine conditioning and tacrolimus-methotrexate-ATG prophylaxis and now required a third drug to treat grade II acute GVHD that presented 1.8 months post-transplant was predicted to derive an absolute 55% 2-year DFS benefit from NHTL instead of standard salvage (predicted 2-year DFS 94% *vs*. 39%). As a final example, our model predicted that a 48 year-old CMV-negative man with advanced AML who received a CMV-negative, female, well-matched unrelated donor bone marrow graft after unspecified but non-TBI-containing conditioning and tacrolimus + mycophenolate prophylaxis and required a third drug to treat grade III acute GVHD with no signs of chronic GVHD presenting 2.1 months post-transplant would have a 4% probability of 2-year DFS with standard treatment and a 15% probability of 2-year DFS with NHTL salvage. (In fact, he received glucocorticoids, mycophenolate and sirolimus and died of bacterial infection and hemorrhage 3.4 months from transplant.)

The treatment recommendations above are derived from averaging the results across all 5 imputations. The stability across the different imputations provides some reassurance about the robustness of these recommendations. Only 9% of patients received a conflicting prophylaxis recommendation in at least 1 of the 5 imputations. For the 1411 refractory acute GVHD patients, 14% received a

conflicting recommendation about salvage treatment in at least 1 of the 5 imputations (Figure 9).

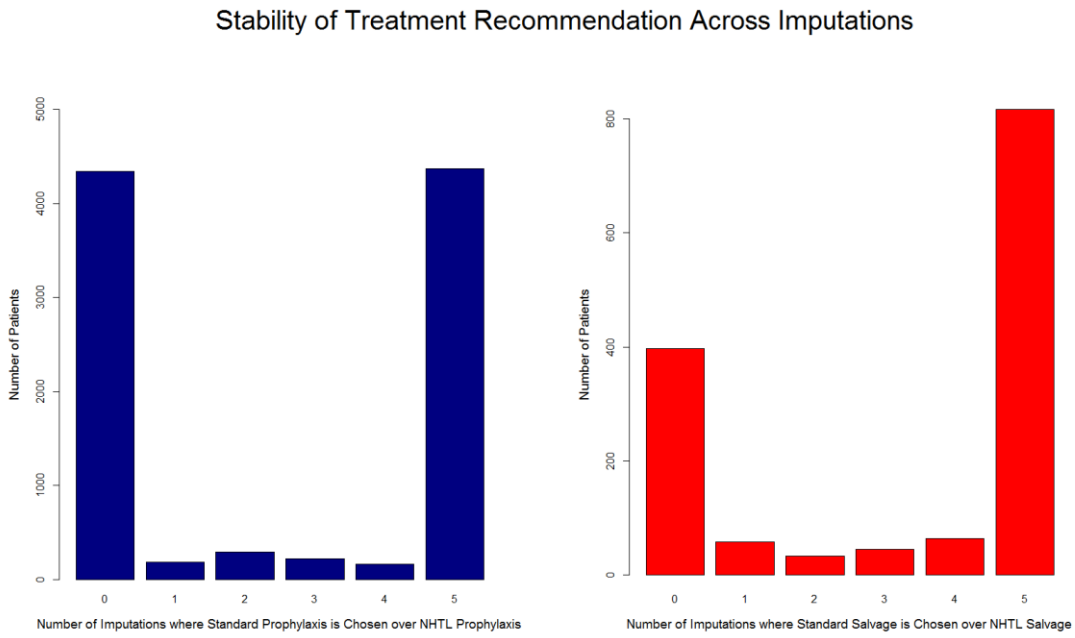

Figure 9. Stability of treatment recommendation across imputations. *For most patients, the prophylaxis or salvage recommendation was consistent across the 5 imputations such that the standard intervention was recommended in all 5 or in none of the imputations. In a minority of patients, the recommendation differed in at least 1 of the imputations.*

Randomized studies have been unable to identify any subgroup of patients who, in terms of overall, relapse-free or disease-free survival, could benefit from ATG prophylaxis,[121,165] ATG/prednisone first-line acute GVHD treatment,[166] or ATG salvage.[123,147] There is no direct evidence that particular subgroups of patients benefit from other types of NHTL prophylaxis[167] or salvage.[59] (For example, one study suggested that recipients of mismatched grafts might benefit from alemtuzumab prophylaxis, but in fact it would be impossible to conclude from this non-randomized study whether the patients with mismatched donors had better-than-expected survival or whether the patients with matched donors had worse-than-expected survival, leading to comparable 3-year survival rates.[168]) By contrast, our approach allows for highly-personalized prophylaxis and treatment recommendations. We were able to propose narrow subsets of patients for whom

NHTL prophylaxis and/or NHTL salvage may be preferable, although our patient-specific predictions must be tempered by the limitations discussed in Section 7.4. An ongoing large trial randomizing patients to rabbit ATG prophylaxis *vs*. placebo is currently being conducted by the Blood and Marrow Transplant Clinical Trials Network (NCT01295710); applying our analysis methods to that study might be appealing.

7.3 Strengths

The originality of this work lies in having used registry data in combination with a highly innovative analytic approach. This analytic approach is useful because in reality, clinicians engage in sequential treatment decision-making over time based on accruing observations about the individual patient; providing data-driven evidence to support this form of decision-making is critical. Like the CIBMTR data, clinical practice also encompasses far more diverse patient characteristics than found in the "silos" of tightly selected patient populations on which RCTs generally focus. Finally, in clinical practice, there are usually many possible treatments at each decision point, but studies usually limit these possibilities sharply and so fail to capture the complexity of real-life clinical decisions. Given the large samples afforded by registry databases, the analytic approach developed here could be extended to examine more than 2 treatment options at the prophylaxis and salvage stages, such as polyclonal NHTL therapy (ATG, ALG) *versus* therapies that primarily target activated T cells (*e.g.*, anti-CD25 antibodies) *versus* therapies that deplete neutrophils and antigen presenting cells along with activated T cells (*e.g.*, alemtuzumab).

In the dawn of the "precision medicine" era, the AHCT field is currently challenged with assessing many novel, possibly prescriptive biomarkers in the face of many traditional and novel sequentially-administered treatments. There simply are not enough patients or resources to enroll into comparative trials to answer all key questions. Using observational data to propose personalized, adaptive treatment algorithms through Q-learning or other backwards stage-wise estimation

techniques and then testing those algorithms prospectively is a credible solution. Prospective testing could be applied in a SMART that compares the most promising competing ATSs identified through retrospective analysis, or it could consist of a traditional RCT comparing the single most promising ATS to usual care. Alternatively, individual centers could be randomized to implementing or not implementing the ATS for a set period of time. Even within one center, the ATS could be implemented for a year or two, then "withdrawn," and later re-instituted. When patients would develop acute GVHD, they would be treated under the policy that was "in force" at their date of transplant (ATS or clinician-determined care). This nuance is necessary because the ATS starts at the prophylaxis stage, so if their prophylaxis was chosen according to the ATS, their acute GVHD salvage treatment ought to be chosen according to the ATS as well. If GVHD or survival indices were to improve for patients transplanted under the ATS and if the improvement were to extinguish after withdrawing the ATS, we would have strong, albeit circumstantial, evidence of benefit. The development of a web applet that operationalizes the finalized Q-learning models would allow complex results from research studies to be effectively and easily incorporated into subsequent clinical trials and clinical practice.

7.4 Limitations

7.4.1 Limitations that stem from assumptions made to structure the data

Two limitations of this work stem directly from the two assumptions that were necessary in order to generate a sequence of events for each patient. Recall that information about the exact start and stop dates of immunosuppressive drugs and the exact timing of the response to treatment are not recorded. The two assumptions were:

(1) Certain drugs or drug combinations comprise "first-line treatment" and others would be used exclusively for salvage treatment; and

(2) The grade recorded on the first form on which specific GVHD treatment was documented represents the grade that prompted treatment initiation rather than the maximum grade in the interval covered by the CRF.

7.4.1.1 Problems with the first assumption

A major limitation is the uncaptured heterogeneity of prophylactic and acute GVHD treatment practices across centers. The European Group for Blood and Marrow Transplantation conducted two surveys that span the time period of the data set available for this thesis work.[169,170] Both surveys revealed marked inter-center variability in GVHD prophylaxis and treatment strategies. Moreover, policies that appeared superficially similar often differed in key details. For example, the day on which cyclosporine is initiated pre-transplant, the loading dose, the target blood concentration, and the planned duration of prophylactic therapy all differed substantially across centers, even in the 2012 survey. When patients developed acute GVHD, 100% of centers initiated corticosteroids as first-line therapy in both time periods. However, the trigger for initiating systemic therapy differed among centers both in regard to the minimum grade of acute GVHD (with 62% and 82% initiating steroids only for grade II or higher and 34% and 17% for grade I disease, in 1994-95 and 2010 respectively) and in regard to the need for histological documentation (with 82% of centers treating based only on clinical signs and ~16% to 18% awaiting histology results, a stable finding in both time periods). Thus, over time, the tendency to treat mild GVHD using systemic therapy decreased. The dose, route and frequency of administration differed across centers and over time as well. Finally, the operational definition of steroid refractoriness differed in both the minimum time of steroid monotherapy needed and the minimum dose needed to confer this designation. Specifically, the minimum "declarative" time ranged from 2 to 21 days, with the bulk (44%) of centers waiting 6–7 days before declaring steroid refractoriness (in 2010; not directly asked in 1994–95). The minimum "declarative" dose decreased over time, with 43% of centers using a dose of ≥10 mg/kg/day (in methylprednisolone-equivalent units) in 1994–95 but only 10% using such high

doses in 2010 before declaring "refractoriness." Although a similar detailed analysis is not available from the CIBMTR, from discussions with colleagues at other centers and reading the clinical literature, it seems extremely likely that similar variability and similar time-trends would be observed in prophylactic and treatment strategies across CIBMTR member institutions. The ASBMT consensus guidelines for first-line and salvage treatment of acute GVHD[59] also attests to tremendous heterogeneity of acceptable practices. While the heterogeneity of prophylaxis and treatment options is a strength that enabled estimating ATSs, the unmeasured heterogeneity within each A_1 and A_2 option in terms of the specific drugs, their specific doses and their schedules of administration represents a source of confounding that likely biases any effect toward the null.

A second problem with the way that "first-line" and "salvage" treatments were identified is that if a patient was found to have only "first-line" treatments on his reference form, the subsequent CRFs were not automatically searched for additional treatments that could be considered "salvage." Consequently, patients who received "first-line" treatment documented on one form and salvage treatments documented on future forms would have been misclassified as having received only "first-line" treatment. Similarly, for the few patients with treatment documented on both timed and untimed forms, information from the timed forms was favoured.

Another limitation is the impossibility of distinguishing lines of salvage treatment. One reason for not combining treatments grouped on sequential forms is that we are interested in comparing patients at the same phase of GVHD illness. Ideally, we would restrict the second-stage analysis to patients receiving NHTL or non-NHTL treatment for their *first* salvage regimen. Unfortunately, in the absence of accurately-recorded start dates, it is impossible to know whether particular "salvage" treatments were deployed for first, second, third or later salvage attempts. Also, it is impossible to know whether salvage treatment was administered for failure of response to first-line therapy (as we assume to be the case) or for intolerable side effects of first-line therapy (which might not confer the same poor prognosis as non-response). The only way to surmount these problems would be

for the CIBMTR to collect more detailed data about the timing and clinical indications for each immunosuppressive treatment.

7.4.1.2 Problems with the second assumption

Some patients would obviously have worsened after the introduction of GVHD treatment, so this assumption introduces misclassification. This misclassification is expected to be non-differential with respect to receipt of NHTL or non-NHTL salvage treatment but is likely to be differential with respect to outcome. Yet the direction of the association between misclassification of GVHD grade at treatment initiation and outcome is not predictable. One possibility is that patients who died would have been more likely to have progressed from low to high grades (and hence, to have been misclassified as having a high grade at the outset) compared to patients who did not die. The other possibility is that patients who died would have been less likely to have started off with a low GVHD grade compared to survivors; under that scenario, patients who died would have been less likely to have been misclassified compared to patients who did not die. In either case, the fact that we grouped grades I-II *versus* III-IV acute GVHD mitigates the impact of the misclassification somewhat. Although the incidence of progressing from low (I-II) to high (III-IV) acute GVHD grade after initiation of treatment has not been directly estimated, extrapolating from studies where "progression" and "stability" were both grouped in the "non-response" category suggests such progression is uncommon.[79,171]

7.4.2 Limitations that stem from grouping NHTL therapies

Grouping all NHTL therapies together may be problematic because these drugs and antibodies differ in the extent to which they deplete non-T-cell populations. For example, it has been suggested that immunosuppressive treatments that selectively deplete T and NK cells but spare B cells increase the risk of post-transplant lymphoproliferative disorder (PTLD) while therapies that deplete only T cells, or all of T, NK and B cells, confer less risk of PTLD.[172,173] To overcome the problem of

diluting important effects because of treatment heterogeneity, NHTL therapies could be further divided into specific T cell depleters (*e.g.*, ATG, OKT3), T/NK cell depleters (*e.g.*, spilizumab), T/B cell depleters (e.g., purine analogues), and T/NK/B cell depleters (e.g., alemtuzumab). Alternatively, the individual treatments, particularly the most common NHTL therapy, ATG, could be examined in isolation. Another concern is that the dose of each NHTL therapy may drastically change its risk-benefit profile, pharmacodynamic effects differ unpredictably between individuals (so cannot be reliably inferred from dose or clinical patient characteristics), and NHTL therapies are frequently combined with other therapies that intentionally or inadvertently impair immune cell subsets other than T cells. To circumvent these problems, assessing the impact of the entire combination of treatments administered at their specific dosages would be necessary. The only way to do that reliably would be to directly measure the quantity and functional activity of various immune cell subsets in the peripheral blood and, ideally, in target organs. Such thorough assessments are logistically and financially difficult to orchestrate. Our work is predicated on the assumption that grouping NHTL therapies is justifiable on the basis of the added risks of these therapies, which are similar in nature and in incidence across the spectrum of NHTL therapies (being primarily opportunistic infections and PTLD). Nonetheless, we acknowledge that certain other immunosuppressants used concurrently with or following NHTL therapies, and not accounted for in this analysis, probably increase the magnitude of the additional risk by delaying post-NHTL immune reconstitution.

7.4.3 Limitations that stem from unavailability of other important covariates

The data set lacked certain covariates that, if accounted for, might alter our conclusions. For example, cytogenetic and molecular features of AML and MDS are among the strongest determinants of post-transplant survival,[174] but were not available in the data set. This information is collected by the CIBMTR so, given time and resources, it can be extracted from the database. By contrast, some types of amino acid substitutions in the HLA molecules lead to so-called "permissive"

mismatches that have no impact on the incidence of GVHD or OS[175] but such detailed HLA typing results are not available for the majority of patients in this data set. This might have led to underestimating a true detrimental effect of "mismatched" or "partially matched" donor-recipient pairs compared to well-matched pairs, because approximately 7% of supposedly mismatched transplants might actually have had permissive mismatches,[176] keeping in mind that determining the net effect of a mismatched unrelated donor with this model requires combining the estimates for 2 variables ("HLA matching" and "donor relation"). Also, the impact of NHTL therapies in non-permissively mismatched pairs might have been diluted.

Another major limitation is that the time when A_2 treatment is started is not recorded. It is likely that patients who had lower grades of GVHD at onset had a longer time to progression, and hence a longer time to needing A_2 treatment, than patients who had higher grades of GVHD at onset. Therefore, by using the time of onset of GVHD, the post-A_2 survival time estimates for patients with lower GVHD grades are likely over-estimated. This has implications for design of future CIBMTR CRFs. If studying sequential data is valuable, then future CRFs should contain the start (and stop) dates of major medications and interventions.

A third major limitation related to lack of relevant covariates is that only immunosuppressive treatments were studied for their effect on GVHD and survival, but other types of treatment might influence survival through decreasing infectious complications (*e.g.*, use of triazole antifungal medication and pre-emptive treatment of CMV and Epstein-Barr virus viremia), decreasing complications related to ABO mismatching, or altering the risk of developing intestinal GVHD (*e.g.*, use of certain antimicrobials for gut decontamination).[177] The use of such "supportive" treatments undoubtedly varied markedly across centers and over time, but details about these sorts of covariates are not available. Unmeasured concurrent antimicrobial strategies are of particular concern because they might be more important to patients receiving NHTL interventions, which naturally carry a higher risk of life-threatening infections. Controlling for antimicrobial strategies might have lessened the decrement in survival observed in the NHTL groups. Infectious complications

are less problematic with modern viral and fungal monitoring and pre-emptive treatment, and modern anti-infective prophylaxis. Indeed, a recent randomized GVHD prophylaxis trial found no increase in the incidence of serious infections in the ATG arm compared to the no-ATG arm.[122]

A fourth limitation is that we presumed that antibodies given prior to graft infusion as part of conditioning with the primary intent of preventing graft rejection were also useful for preventing GVHD. This presumption is reasonable because of their prolonged half-life in circulation[142] but sometimes that might not be the case. For instance, a subset of patients might rapidly clear NHTL antibodies due to genetic polymorphisms or if extremely low doses of antibodies were used.[178] Some researchers suggest the necessity of delivering at least one post-infusion ATG dose.[179] It is also worth considering that ATG doses higher than 7.5 mg/kg have been associated with detrimental survival outcomes because of excessive infection-related mortality.[179] Doses of NHTL therapies used for salvage therapy, their exact schedule of administration for prophylaxis and salvage, and individual-patient serum antibody levels were not available in the data set. The source of ATG administered in conditioning or as prophylaxis was available for only 3% of patients, and ATG sources was not available when administered as GVHD treatment.

Another limitation is that by excluding IVIG from prophylaxis and treatment of GVHD and by lacking information about the dose, schedule and reasons for IVIG administration, an effect on survival mediated through IVIG-induced reduction of CMV reactivation or prevention of severe CMV disease might have been missed. The effect of IVIG might have been more important in recipients of NHTL therapies because they increase the risk of CMV-related complications. While it is not necessary to adjust for CMV reactivation or disease because that is essentially a mediator on the causal pathway from NHTL exposure to death, it would be desirable to account for receipt of IVIG because IVIG could modify the effect of NHTL therapies. In particular, NHTL therapies might be safer in patients who received prophylactic IVIG.

7.4.4 Limitations that stem from unreliability of data

Any lack of reliability or systematic bias in measurement of a putative tailoring variable will impair its performance. The frequency of most misclassification likely does not differ according to exposure group (NHTL prophylaxis or NHTL salvage treatment *vs.* non-NHTL therapies) or according to outcomes and hence should bias towards the null hypotheses. One exception is the high rate of misclassification of grade II *versus* III acute GVHD, as discussed in Sections 2.3.[31,32] Because of the strong association between grade III-IV acute GVHD (*versus* grade I-II acute GVHD) and receipt of NHTL salvage therapy, misclassification of GVHD grades II and III might introduce bias. If the direction of the effect of GVHD grade is the same within each exposure group (exposure being receipt of NHTL or standard salvage), which is likely the case, the result is expected to lie between the crude and the true value on the relative risk or odds ratio scale. However, if the effect of GVHD grade is to reduce DFS in one exposure group and to increase DFS in the other exposure group, then the magnitude and direction of bias are not easily predictable.[180]

Specific treatments received for GVHD might have also been misclassified. For example, it is possible that some patients were recorded as having received "systemic steroids" when in fact all they received were "topical" beclomethasone and/or budesonide, so the use of systemic steroids might be over-estimated. Such misclassification of particular drugs is likely to be non-differential with respect to exposure and outcomes, again biasing the effect of NHTL therapy toward the null.

7.4.5 Limitations that stem from lack of representativeness

The 9563 patients analyzed this thesis represent <10% of all patients transplanted for AML and MDS in 1995 to 2007. Selection bias is introduced because only a subset of transplant centers worldwide supply data to the CIBMTR and, of those, only a subset supply the comprehensive CRFs needed for this study. Generalizability of our findings may also be limited because multiple aspects of medical practice in the mid-1990s and the first decade of 21st century are very

different compared to standard procedures employed today. Also, although it is likely that patients treated for "chronic GVHD first" actually had acute GVHD, only 18 patients received NHTL salvage treatment for "chronic GVHD first," making it impossible to offer firm conclusions for this subgroup. Whether our findings apply to patients with acute GVHD diagnosed according to the updated consensus criteria is unknown. Ultimately, the ATSs proposed herein would need to be prospectively tested in a modern multi-center study before they can be recommended.

7.5 Future Directions

7.5.1 Alternative model forms

We are currently developing a survival time model to address the same questions as the current analysis because by avoiding an arbitrary cut-off at 2 years, more relevant information about a patient's survival trajectory can be harnessed, so predictions from the survival model are expected to be more accurate than predictions from the logistic regression. In Q-learning, the outcome in the last interval and under each future treatment option in prior intervals must be predicted for each patient in order to estimate that patient's outcome under the (possibly-counterfactual) optimal treatments. It is far more convenient to use a parametric approach (such as an accelerated failure time model) to predict an individual patient's outcome than a non-parametric approach, such as a Cox proportional hazards model. This is because the Cox model readily gives a hazard ratio for death accounting for a patient's unique set of covariate values, which can be used to predict a median survival time for a population of similar patients, but does not readily provide predicted survival times as the baseline hazard rate is left unspecified in a Cox model.

Another challenge with right-censored AHCT survival data is that a group of censored patients might be immune to relapse and can be considered "cured." However, some censored patients might not, in fact, be cured. Estimating the cure

fraction and examining the effect of covariates on the cure rate can be useful for predicting the pseudo-outcome. Fortunately, this can be accomplished with parametric cure models. A common form for the cure model is

$$S(t|H) = \pi(H) + \big(1 - \pi(H)\big)S_u(t|H),$$

where T is the time-to-event (survival time), $S(t) = P(T > t)$ is the survival function of T, $S_u(t)$ is the survival function given that the patient is "uncured", H is the set of confounding and potential tailoring variables, C_j and O_j, as well as the treatments A_j received up to the point of the current decision are as already defined in Section 3.3, and $\pi(H)$ is the cure rate, which is a function of those covariates. The cure rate and covariate effects on the cure rate are often modelled parametrically with the expit function, *i.e.*, by $\pi(H) = e^{\widehat{\beta}H}/(1 + e^{\widehat{\beta}H})$, which is the "mixture cure model." Next, $S_u(t)$ can likewise be estimated with a parametric approach. To create the cure model $S(t|H)$, the model predicting the cure rate, $\pi(H)$, and the survival model restricted to patients at risk of the event, $S_u(t|H)$, are fit jointly and borrow information from each other.[181] We have chosen to use a cure model for future work, based on the strong plateau observed in the Kaplan-Meier plots (Figure 6).

7.5.2 Methodological challenges

Future work will also address how to perform sensitivity analysis within the context of Q-learning backwards interval estimation to assess the potential impact of unmeasured confounding. We are also interested in useful methods for quantifying the uncertainty in individual patient-level predictions. In situations where the confidence intervals (or prediction intervals) for the effect of some ATS *versus* an alternative ATS, or for the effect of some intervention *versus* an alternative intervention at each decision point, overlap, the sheer fact that the algorithm usually "votes" for a particular ATS or intervention given specific patient characteristics might serve to increase "confidence" in the veracity of the prediction. The ability of the algorithm to choose a particular ATS or intervention in the face of uncertainty (where uncertainty is defined as overlapping confidence intervals) is not necessarily

a weakness. On the contrary, it mirrors what clinicians do on a daily basis. Q-learning and similar approaches can be harnessed to make decisions in the face of uncertainty more rationally by making the effect of a combination of patient-specific characteristics explicit.

7.5.3 Translating the current work to clinical practice

The current analysis, as well as the Q-learning survival analysis, ought to be repeated in a modern cohort, because the relative harm or benefit of NHTL prophylaxis and acute GVHD treatment is probably very different in the current era of sensitive monitoring for viral reactivation and invasive fungal infections, pre-emptive anti-viral treatment, and broader-spectrum anti-fungal and anti-bacterial drugs. It would also be interesting to evaluate the question of prophylaxis and GVHD treatment among patients with different malignant diseases. The risk factors for acute GVHD differ somewhat according to disease, prompting the development of disease-specific GVHD risk models,[49] so it is reasonable to hypothesize that the relative harm or benefit of NHTL prophylaxis or treatment would also differ by disease. When considering disease-specific models, it bears mentioning that the choice of endpoint for a time-to-event outcome should be appropriate to the natural history of the disease under study. Because relapsed AML post AHCT is so often and so quickly fatal, the difference between relapse-free survival and overall survival is generally <3% in the setting of AHCT for AML. Therefore, in the current work, relapse and death from relapse or non-relapse causes was treated equivalently. In situations where patients may survive a long time after relapse, such as in AHCT for indolent lymphoma, a modification of Q-learning to assess failure-free time in a way that does not penalize ATSs as strongly for relapses as for deaths has been developed.[182]

7.5.4 Translating machine learning to clinical practice

On its own, physician judgment may not perform well in synthesizing a plethora of genetic, proteomic, clinical and demographic attributes – some of which

may change predictably or unpredictably over time – in order to reach the optimal treatment plan. ATSs developed using machine learning approaches on observational data or through SMARTs, and validated in traditional RCTs that test ATS-guided care *vs.* usual care, could be made available to clinicians on various platforms such as internet-accessible applications. These ATS algorithms could even be updated in real time based on a continuous input of information drawn from recent and current patients. Having more precisely generated probabilities of treatment success or failure would help us choose appropriate therapy. However, even once accessible algorithms that offer accurate patient-specific predictions are developed, how we ought to integrate that information into our practices will require additional study. For example, how is a clinician to assess whether she should follow the suggestion offered by the algorithm rather than her own judgment? We suggest greeting the uptake of machine learning-developed ATSs with cautious optimism and healthy academic skepticism. Legal, cultural and infrastructural challenges lie ahead.

7.5.4.1 Infrastructural challenges

The robustness of machine learning algorithms can only be ensured if the data used to develop them are of sufficient scale (*i.e.*, a large number of patients and events), quality (*i.e.*, measurement or classification of the predictors of response and of the responses as well as data entry must be reliable), and richness (*i.e.*, all relevant attributes including variables related to socio-economic status, lifestyle, tolerance of side effects, *etc*. would ideally be collected). These are the same challenges faced by existing patient registries.[130] The CIBMTR can aim for flexibility in data collection, for example adding detailed questions about a particular topic for a set time period (or until sufficient patients are accrued to answer the question) to allow for "prospective," relevant data collection within the registry framework. As electronic instead of paper CRFs become the norm, adding and removing supplemental questions may become logistically and financially more facile. We predict that in addition to leveraging our field's existing infrastructure for collaborative retrospective research, innovative efforts to link electronic medical records across institutions and automatically mine various sources of data such as pharmacy dispensaries and laboratory information systems will bear fruit over the

coming years.[183] Importantly, natural-language processing has matured to the point where useful information can be extracted automatically from unstructured chart notes. Patients might also wish to contribute information via social media, online portals, or wearable monitors (*e.g.*, Fitbit™). Suitable methods and software for data storage, automatic data pre-processing, handling missing data, and reducing dimensionality are already commonly applied to biomedical "big data" (dozens of terabytes to pentabytes).[184]

7.5.4.2 Cultural challenges

Many physicians and patients do not feel comfortable with opaque decision making software that does not show the reasons why a particular choice was suggested. By way of example, this sentiment was voiced by oncologists who beta-tested IBM Watson's Oncology Expert Advisor.[185] Doctors must be able to explain the choice to patients, ethics committees, review boards, and courts of law. On the other hand, our culture of scientific inquiry might facilitate adoption of ATSs into clinical practice if we treat machine learning ATS algorithms like any other experiment, treatment or risk score. (1) *Confirm reproducibility:* We expect that the results of machine learning algorithms should be reproducible with different, valid techniques. Just as our confidence that a particular cellular pathway is activated if authors not only report up-regulation of its components' gene expression but also confirm increased production of the downstream protein products, if a particular variable reliably predicts response to a particular treatment, we expect that finding to be apparent using different machine learning techniques. (2) *Confirm generalizability:* For retrospective studies, the machine learning algorithms ought to be tested in different, independent data sets. For prospective studies, the ATSs ought to be developed through SMARTs conducted across different institutions or at least verified in different institutions subsequently. This is the same standard we apply to predictive risk scores. (3) *Study the effect of their implementation:* The survival (or other) benefit of the proposed ATSs would need to be confirmed in clinical trials or in ecological studies before their adoption. By the latter, we mean that the performance of institutions that implement the ATSs could be compared to those that do not, or within a given institution the algorithm could be implemented for a year or two, then

"withdrawn," and later re-instituted. In our hypothetical example, when patients would develop acute GVHD, they would be treated under the policy that was "in force" at their date of transplant (ATS or clinician-determined care). This nuance is necessary because the ATS starts at the prophylaxis stage, so if their prophylaxis was chosen according to the ATS, their acute GVHD salvage treatment ought to be chosen according to the ATS as well. If GVHD or survival indices were to improve for patients transplanted under the ATS and if the improvement were to extinguish after withdrawing the ATS, we would have strong, albeit circumstantial, evidence of benefit. In summary, adoption of a particular ATS could only be endorsed if it was developed and evaluated with the same rigor as other prognostic and treatment approaches.

7.5.4.3. Legal challenges

Evidence that is used to reach a diagnosis or recommend a treatment plan must be archived. If an algorithm that suggests treatment is updated periodically or automatically updated continuously, a report of the algorithm's recommendation must be preserved in an unalterable format. ATSs may generate legal uncertainties. If harm results from implementing a treatment recommendation made by a computer algorithm, would the prescribing physician or the developers of the algorithm be accountable? We suggest that the current legal framework of clinical practice guidelines offers a structure in which algorithmic ATSs could be "non-litigiously" adopted.[186]

8. CONCLUSION

The danger of lacing together results from different RCTs or different "factorial comparisons" to recommend an ATS is that such an approach could fail to detect delayed effects that might enhance or abrogate the benefit of a future treatment, fail to detect side effects that preclude the use of a future treatment, and fail to elicit valuable diagnostic information, such as depth of response or adherence, that allows personalized selection of the next treatment (the so-called "prescriptive effect" or "diagnostic effect"). The approach used in this work personalizes the sequential selection of medical treatments while avoiding those pitfalls. Backwards stage-wise estimation could contribute to refining GVHD therapy as well as to improving the management of other diseases where multiple induction, consolidation, maintenance, or salvage therapies exist and the optimal combination or sequence of treatment is currently unclear.

This work also demonstrates how observational data, especially registry data, could be useful in designing adaptive treatment strategies. Prior to investing time and financial resources into a complex SMART or traditional RCT, exploitation of registry data can identify which ATSs merit prospective evaluation. Moreover, registries are useful for addressing the question of the best sequence of therapy in groups of patients who might be underrepresented in clinical trials. We successfully implemented Q-learning with a binary outcome despite the peculiarities of an AHCT registry population (such as steep initial mortality, the cure plateau, and censoring for second transplants and other reasons). Given a sufficient sample size with representation of all sorts of patients, our approaches could easily be extended to include more decision-making stages, more treatment options at any decision point, or more covariates, as well as other types of outcomes – especially survival time outcomes. To bring about "precision medicine," both retrospective analyses and prospective studies could therefore be used to develop clinically-relevant, personalized adaptive treatment strategies.

9. APPENDICES

9.1 Consensus Acute GVHD Grading[26]

Step 1: Perform staging of individual organ systems for acute GVHD

Skin Stage:

+ 1 Maculopapular eruption involving less than 25% of the body surface
+ 2 Maculopapular eruption involving 25%-50% of the body surface
+ 3 Maculopapular rash > 50% of the body surface
+ 4 Generalized erythoderma with bullous formation and often with desquamation

Liver Stage*

+ 1 Bilirubin 35-50 µmol/L
+ 2 Bilirubin 51-100 µmol/L
+ 3 Bilirubin 101-255 µmol/L
+ 4 Bilirubin > 255 µmol/L

*If the patient has documented GVHD of the liver and documented alternative cause of hyperbilirubinemia (i.e. veno-occlusive disease) then downstage liver GVHD by 1 stage.

Gut Stage**

+ 1 Diarrhea volume = 500-900 mL/day or persistent nausea (± vomiting) with histological proof of GVHD within the gut
+ 2 Diarrhea volume = 1000-1500 mL/day
+ 3 Diarrhea volume > 1500 mL/day
+ 4 Severe abdominal pain or ileus

**If the patient has documented GVHD of the gut and alternative cause of diarrhea (i.e. severe mucositis, CMV enteritis, or C.difficile infection), then downstage gut by 1 stage.

Step 2: Add organ staging together to determine overall clinical grade.

Table A1. Consensus clinical grading of severity of acute graft-*versus*-host disease

GRADE	SKIN	LIVER	GUT
0 (none)	0	0	0
I (mild)	+1 to +2	0	0
II (moderate)	0 to +3*	+1	+1
III (severe)	--	+2 to +3	+2 to +4
IV (life-threatening)**	+4	+4	--

*Skin stage 3 alone is also considered overall grade II

**Severe decrease in performance status due to GVHD should be considered grade IV irrespective of organ stages.

9.2 Traditional Chronic GVHD Grading[39]

Limited Chronic GVHD
Either or both:
1. Localized skin involvement
2. Hepatic dysfunction

Extensive Chronic GVHD
Either:
1. Generalized skin involvement or
2. Generalized skin involvement and/or hepatic dysfunction plus
    i. Liver histology showing aggressive hepatitis, bridging necrosis or cirrhosis, or
    ii. Involvement of eye: Schirmer's test with <5 mm wetting, or
    iii. Involvement of minor salivary glands or oral mucous demonstrated on labial biopsy specimen, or
    iv. Involvement of any target organ e.g. esophageal abnormalities, polymyositis.

9.3 Choice of endpoints for developing adaptive treatment strategies

Table A2. Examples of endpoints and optimization criteria for evaluating adaptive treatment strategies, and sample references

Structure of the endpoint	Clinical endpoint example	Possible optimization criteria	Derivation or application of the optimization algorithms (first author, year, reference)
1. Binary logistic	- Proportion of patients surviving at 1 year (alive *vs.* dead) - Proportion of patients achieving CR (*vs.* no CR), regardless of subsequent relapses	- Maximizing the proportion achieving "success" at a given time point, at any time during the study, or at the end of individual follow-up[1]	Wang 2012[187]
2. Trinary logistic	- Effective AML induction treatment *vs.* treatment failure due to lack of efficacy (primary refractory disease or relapse) *vs.* treatment failure due to toxicity	- Maximizing the proportion in the "success" category - Compiling utility estimates of the three-way trade-off between the likelihood of success, failure due to lack of efficacy, and failure due to treatment-related toxicity from patients and physicians and optimizing the "net projected benefit"[2]	Thall 2002[85]
3. Continuous or ordinal (assuming higher score is better)[3]	- Quality-of-life score at 1 year post AHCT - Tumor antigen-specific effector T cell titers achieved in response to vaccination with tumor-specific peptide measured serially - Platelet count in aplastic anemia patients assessed 3 months after all study treatments are withdrawn	- Maximize the group mean or median score - Maximize quantiles of a distribution - Minimize number or magnitude of deviations from a target salutary or therapeutic range	Rich 2014[87]
4. Survival time	- Overall survival from diagnosis - Disease-free survival - Survival times accounting for competing risks - Failure times with a combined endpoint of death/relapse/toxicity	- Maximize the group mean or median survival time - Maximize the median residual lifetime - Maximize quantiles of the distribution	Huang 2012[188] Wang 2012[187] Huang 2014[182] Kidwell 2014[189]
5. Count data	- Number of hospital-free days in a year - Number of multiple sclerosis relapses over a decade	- Maximize or minimize the number of in a time period	Oetting 2011[125]
6. Time-varying	- Functional level (*e.g.*, daily questionnaire on ability to accomplish activities at home) - Symptom level (*e.g.*, peripheral neuropathy in myeloma patients, bone pain in metastatic carcinoma patients)	- Maximize total functional level over time - Minimize total symptom burden over time - May incorporate a minimum threshold (*e.g.*, maximize functional level above some minimal acceptable cut-off)	Fonteneau 2008[190] Chakraborty 2009[191]
7. Cost-utility	- Quality-adjusted life years - Disability-adjusted life years	- Maximize mean, median, or quantiles of a QALY distribution - Minimize years of life lost to disability or death	Requires further development, but see Rosenheck 2006[192]

Notes: 1. "At a given time point" implies after the same length of follow-up for each patient. "At any point during the study" implies at any point before the study is administratively terminated, or at each patient's own end of study, with variable lengths of follow-up. "At the patient's own end-of-study time" likewise implies variable lengths of follow-up. 2. This also allows creation of decision-making support tools that can be used to elucidate individual patient and physician preferences. See Thall and Estey 2002.[85] 3. Since most of the literature discusses maximization, if minimizing a score is desired then one might simply maximize the difference between the maximum possible score and the attained score. Abbreviations: AHCT – allogeneic hematopoietic cell transplantation, AML – acute myeloid leukemia, CR – complete remission, QALY – quality-adjusted life year.

9.4 Inverse probability of censoring weights

Table A3. Model for the probability of censoring in the first interval		
Predictor	**Beta coefficient[1]**	**95% CI[1]**
Intercept	–92.172	(–120.791, –63.553)
Year of transplant	0.046	(0.032, 0.061)
Recipient age, years	–0.010	(–0.007, –0.013)
Karnofsky/Lanksy performance status		
≥ 80%	REF	––
< 80%	–0.708	(–0.880, –0.536)
Disease status		
Early	REF	––
Intermediate	–0.230	(–0.338, –0.122)
Advanced	–1.120	(–1.225, –1.014)
Conditioning intensity		
Myeloablative	REF	––
Reduced intensity or non–myeloablative	–0.181	(–0.301, –0.062)
Graft type		
Bone marrow	REF	––
Peripheral blood	0.018	(–0.088, 0.125)
Umbilical cord blood	–0.249	(–0.029, –0.469)
Donor relation		
Related	REF	––
Unrelated	–0.390	(–0.283, –0.497)
HLA match		
Well–matched	REF	––
Partially–matched	0.223	(0.042, 0.404)
Mismatched	0.491	(0.317, 0.666)
[1]The beta coefficients represent the average of 5 imputations. The confidence intervals were calculated from standard errors derived according to Rubin's formula.[157]		

Table A4. Model for the probability of censoring in the second interval		
Predictor	**Beta coefficient[1]**	**95% CI[1]**
Intercept	–1.870	(–2.669, –1.071)
Recipient age, years	–0.027	(–0.006, –0.048)
Conditioning intensity		
Myeloablative	REF	––
Reduced intensity or non–myeloablative	0.949	(0.067, 1.832)
Donor relation		
Related	REF	––
Unrelated	–1.333	(–0.2019, –0.647)
Grade of acute GVHD at "start" of treatment (maximal grade on the index form)		
I-II	REF	––
III-IV	–0.658	(–1.343, 0.028)
[1]The beta coefficients represent the average of 5 imputations. The confidence intervals were calculated from standard errors derived according to Rubin's method.[157]		

9.5 Distribution of GVHD therapies

Table A5. Therapeutics for acute and chronic GVHD (regardless of line of treatment)					
Drug	**Action recorded**	**Acute GVHD (n =4937)**		**Chronic GVHD (n = 1382)**	
		n	%	n	%
Systemic corticosteroids	Administered	4332	88	3244	79
	Not administered	594	12	278	20
	Missing	11	22	11	<1
Topical corticosteroids	Administered	1520	31	477	35
	Not administered	3378	68	890	64
	Missing	39	<1	15	1
ATG (or ALG)	Administered	286	6	6	<1
	Not administered	4609	93	1359	98
	Missing	42	<1	17	1
Cyclosporine (oral)	Administered	3025	61	491	35
	Not administered	1898	38	883	64
	Missing	14	<1	8	<1
Tacrolimus (oral)	Administered	1693	34	3244	39
	Not administered	2741	56	809	58
	Missing	503	10	40	3
ECP	Administered	69	1	74	5
	Not administered	1154	23	976	71
	Missing	3714	75	332	24
Anti-CD25 (including daclizumab and basilizumab)	Administered	207	4	11	<1
	Not administered	2940	59	476	34
	Missing	1790	36	895	65
Alemtuzumab	Administered	18	<1	4	<1
	Not administered	1670	34	314	23
	Missing	3249	66	1064	77
Etanercept	Administered	37	<1	12	<1
	Not administered	1475	30	198	14
	Missing	3425	69	1172	85
Infliximab	Administered	123	3	10	<1
	Not administered	56	1	36	3
	Missing	4758	96	1136	97
OKT3	Administered	25	<1	2	<1
	Not administered	1646	33	276	20
	Missing	3266	66	1104	80
In vivo immunotoxin (including denileukin defitox)	Administered	27	<1	--	--
	Not administered	4842	98	--	--
	Missing	68	1	--	--
Methotrexate	Administered	325	6	--	--
	Not administered	3147	64	--	--
	Missing	1465	30	--	--
Mycophenolate mofetil	Administered	976	20	321	23
	Not administered	1845	37	749	54
	Missing	2116	43	312	23

Table A5. Therapeutics for acute and chronic GVHD (regardless of line of treatment)					
Drug	**Action recorded**	**Acute GVHD (n =4937)**		**Chronic GVHD (n = 1382)**	
		n	%	n	%
Sirolimus	Administered	154	3	96	7
	Not administered	2464	50	952	69
	Missing	2319	47	334	24
Blinded randomized trial or unnamed investigational agent	Administered	25	<1	16	1
	Not administered	4844	98	1349	98
	Missing	68	1	17	1
Azathioprine or mizoribine	Administered	--	--	25	2
	Not administered	--	--	1341	97
	Missing	--	--	16	1
Etretinate	Administered	--	--	3	<1
	Not administered	--	--	1045	76
	Missing	--	--	334	24
Hydroxychloroquine	Administered	--	--	7	<1
	Not administered	--	--	874	63
	Missing	--	--	501	36
Clofazimine	Administered	--	--	0	0
	Not administered	--	--	1048	76
	Missing	--	--	334	24
Pentostatin	Administered	--	--	7	<1
	Not administered	--	--	873	63
	Missing	--	--	502	36
Thalidomide	Administered	--	--	13	1
	Not administered	--	--	1354	98
	Missing	--	--	15	1
Other systemic non-NHTL treatment	Administered	69	1	46	3
	Not administered	4868	99	1336	97
Other topical treatment (including PUVA)	Administered	91	2	48	3
	Not administered	4846	98	1334	97
Other highly lymphodepleting treatment (pentostatin for acute GVHD, fludarabine or cladribine for acute or chronic GVHD, certain monoclonal antibodies)	Administered	38	1	0	0
	Not administered	4899	99	1382	100

9.6 Distribution of "first-line" vs. "salvage" acute GVHD treatment

Table A6. "First-line" and "salvage" treatments for acute GVHD

Drug	Action recorded	First-line (n = 3526)		Salvage (n = 1411)	
		n	%	n	%
Systemic corticosteroids	Administered	2921	83	1411	100
	Not administered	594	17	0	0
	Missing	11	<1	0	0
Topical corticosteroids	Administered	1097	31	423	30
	Not administered	2397	68	981	69
	Missing	32	<1	7	<1
ATG (or ALG)	Administered	0	0	286	20
	Not administered	3493	99	1116	79
	Missing	33	<1	9	<1
Cyclosporine (oral)	Administered	2142	61	883	63
	Not administered	1372	69	526	37
	Missing	12	<1	2	<1
Tacrolimus (oral)	Administered	1019	29	674	48
	Not administered	2113	60	628	44
	Missing	394	11	106	8
ECP	Administered	9	<1	60	4
	Not administered	921	26	233	17
	Missing	2596	74	1118	79
Anti-CD25 (including daclizumab and basilizumab)	Administered	15	<1	192	14
	Not administered	2065	58	875	62
	Missing	1446	51	344	24
Alemtuzumab	Administered	0	0	18	1
	Not administered	1238	35	432	31
	Missing	2288	65	961	68
Etanercept	Administered	4	<1	33	2
	Not administered	860	24	615	44
	Missing	2662	75	763	54
Infliximab	Administered	9	<1	114	8
	Not administered	15	<1	41	3
	Missing	3502	99	1256	89
OKT3	Administered	0	0	25	2
	Not administered	1223	35	423	30
	Missing	2303	65	963	68
In vivo immunotoxin (including denileukin defitox)	Administered	2	<1	25	2
	Not administered	3467	98	1375	97
	Missing	57	2	11	<1
Methotrexate	Administered	66	2	259	18
	Not administered	2585	73	562	40
	Missing	875	25	590	42
Mycophenolate mofetil	Administered	172	5	804	57
	Not administered	1620	46	225	16
	Missing	1734	49	382	27

Table A6. "First-line" and "salvage" treatments for acute GVHD					
Drug	**Action recorded**	**First-line (n = 3526)**		**Salvage (n = 1411)**	
		n	%	n	%
Sirolimus	Administered	32	<1	122	9
	Not administered	1741	49	723	51
	Missing	1753	50	566	40
Blinded randomized trial or unnamed investigational agent	Administered	6	<1	19	1
	Not administered	3463	98	1381	98
	Missing	57	2	11	<1
Other systemic non-NHTL treatment	Administered	3	<1	66	5
	Not administered	3523	99	1345	95
Other topical treatment (including PUVA)	Administered	54	2	37	3
	Not administered	3472	98	1374	97
Other highly lymphodepleting treatment (pentostatin, fludarabine, cladribine, and certain monoclonal antibodies)	Administered	0	0	38	3
	Not administered	3526	100	1373	97

9.7 Internal model validation

Table A7. Internal validation: Mean of the quartile of predicted probability of 2-year disease-free survival compared to the observed 2-year disease-free survival proportion within the quartile of predicted probability

	Standard Prophylaxis		NHTL Prophylaxis		Standard Salvage		NHTL Salvage	
Age group	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed
0 to 19	0.21	0.23	0.18	0.19	0.09	0.15	0.05	0.10
	0.47	0.48	0.37	0.38	0.27	0.24	0.16	0.05
	0.59	0.58	0.49	0.55	0.46	0.41	0.30	0.42
	0.67	0.66	0.59	0.59	0.71	0.72	0.56	0.10
20 to 39	0.18	0.17	0.16	0.17	0.05	0.03	0.02	0.00
	0.42	0.35	0.32	0.24	0.16	0.12	0.08	0.10
	0.56	0.55	0.47	0.45	0.33	0.35	0.16	0.13
	0.65	0.67	0.59	0.52	0.61	0.55	0.38	0.29
40 to 59	0.15	0.14	0.15	0.17	0.04	0.08	0.01	0.00
	0.30	0.29	0.27	0.23	0.12	0.12	0.03	0.00
	0.46	0.45	0.43	0.44	0.25	0.21	0.07	0.04
	0.58	0.56	0.55	0.48	0.51	0.47	0.24	0.21
60+	0.13	0.14	0.12	0.17	0.04	0.08	0.01	0.00
	0.24	0.29	0.20	0.23	0.12	0.12	0.03	0.00
	0.39	0.45	0.34	0.44	0.21	0.21	0.07	0.04
	0.50	0.57	0.49	0.48	0.42	0.47	0.16	0.21

10. REFERENCES

1. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med.* 2006;354(17):1813-1826.
2. Worldwide Network for Blood and Marrow Transplantation. Media Fact Sheet: 1 Million Blood Stem Cell Transplants Worldwide 2013; http://www.wbmt.org/fileadmin/pdf/01_General/One_Million_Transplants_Fact_Sheet_FINAL.pdf, 2014. Accessed March 10, 2015.
3. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood.* 2007;110(13):4576-4583.
4. Woolfrey A, Klein JP, Haagenson M, et al. HLA-C antigen mismatch is associated with worse outcome in unrelated donor peripheral blood stem cell transplantation. *Biol Blood Marrow Transplant.* 2011;17(6):885-892.
5. Pavletic SZ, Kumar S, Mohty M, et al. NCI First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation: report from the Committee on the Epidemiology and Natural History of Relapse following Allogeneic Cell Transplantation. *Biol Blood Marrow Transplant.* 2010;16(7):871-890.
6. Bleakley M, Riddell SR. Molecules and mechanisms of the graft-versus-leukaemia effect. *Nat Rev Cancer.* 2004;4(5):371-380.
7. Wingard JR, Majhail NS, Brazauskas R, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *J Clin Oncol.* 2011;29(16):2230-2239.
8. Socié G, Salooja N, Cohen A, et al. Nonmalignant late effects after allogeneic stem cell transplantation. *Blood.* 2003;101(9):3373-3385.
9. Duval M, Klein JP, He W, et al. Hematopoietic stem-cell transplantation for acute leukemia in relapse or primary induction failure. *J Clin Oncol.* 2010;28(23):3730-3738.
10. Socié G, Blazar BR. Acute graft-versus-host disease: from the bench to the bedside. *Blood.* 2009;114(20):4327-4336.

11. Chakrabarti S, Mackinnon S, Chopra R, et al. High incidence of cytomegalovirus infection after nonmyeloablative stem cell transplantation: potential role of Campath-1H in delaying immune reconstitution. *Blood.* 2002;99(12):4357-4363.
12. Brunstein CG, Weisdorf DJ, DeFor T, et al. Marked increased risk of Epstein-Barr virus-related complications with the addition of antithymocyte globulin to a nonmyeloablative conditioning prior to unrelated umbilical cord blood transplantation. *Blood.* 2006;108(8):2874-2880.
13. Chakrabarti S, Mautner V, Osman H, et al. Adenovirus infections following allogeneic stem cell transplantation: incidence and outcome in relation to graft manipulation, immunosuppression, and immune recovery. *Blood.* 2002;100(5):1619-1627.
14. Kobulnicky DJ, Sabo RT, Scalora AF, et al. Immune Reconstitution In Anti-Thymocyte Globulin Conditioned Unrelated Donor Stem Cell Transplantation. Paper presented at: American Society of Hematology Abstract2013.
15. Das-Gupta EP, Russell NH, Shaw BE, Pearce RM, Byrne JL. Long-term outcome of unrelated donor transplantation for AML using myeloablative conditioning incorporating pretransplant Alemtuzumab. *Biol Blood Marrow Transplant.* 2007;13(6):724-733.
16. van Besien K, Artz A, Smith S, et al. Fludarabine, melphalan, and alemtuzumab conditioning in adults with standard-risk advanced acute myeloid leukemia and myelodysplastic syndrome. *J Clin Oncol.* 2005;23(24):5728-5738.
17. Kröger N, Zabelina T, Krüger W, et al. In vivo T cell depletion with pretransplant anti-thymocyte globulin reduces graft-versus-host disease without increasing relapse in good risk myeloid leukemia patients after stem cell transplantation from matched related donors. *Bone Marrow Transplant.* 2002;29(8):683-689.
18. Kim HJ, Min WS, Cho BS, et al. Successful prevention of acute graft-versus-host disease using low-dose antithymocyte globulin after mismatched,

unrelated, hematopoietic stem cell transplantation for acute myelogenous leukemia. *Biol Blood Marrow Transplant.* 2009;15(6):704-717.

19. Tauro S, Craddock C, Peggs K, et al. Allogeneic stem-cell transplantation using a reduced-intensity conditioning regimen has the capacity to produce durable remissions and long-term disease-free survival in patients with high-risk acute myeloid leukemia and myelodysplasia. *J Clin Oncol.* 2005;23(36):9387-9393.
20. Matthews K, Lim Z, Pearce L, et al. Rapid recovery of lymphocyte subsets is not associated with protection from relapse of myelodysplastic syndromes and acute myeloid leukaemia after haematopoietic stem cell transplantation using a reduced intensity conditioning regimen and alemtuzumab. *Br J Haematol.* 2010;149(6):879-889.
21. Siddiqi T, Blaise D. Does antithymocyte globulin have a place in reduced-intensity conditioning for allogeneic hematopoietic stem cell transplantation? *Hematology Am Soc Hematol Educ Program.* 2012;2012:246-250.
22. Soiffer RJ, Lerademacher J, Ho V, et al. Impact of immune modulation with anti-T-cell antibodies on the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies. *Blood.* 2011;117(25):6963-6970.
23. Devillier R, Crocchiolo R, Castagna L, et al. The increase from 2.5 to 5 mg/kg of rabbit anti-thymocyte-globulin dose in reduced intensity conditioning reduces acute and chronic GVHD for patients with myeloid malignancies undergoing allo-SCT. *Bone Marrow Transplant.* 2012;47(5):639-645.
24. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant.* 2005;11(12):945-956.
25. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA-matched sibling donors. *Transplantation.* 1974;18(4):295-304.

26. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant.* 1995;15(6):825-828.
27. Martin PJ, Schoch G, Fisher L, et al. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. *Blood.* 1990;76(8):1464-1472.
28. Mielcarek M, Martin PJ, Leisenring W, et al. Graft-versus-host disease after nonmyeloablative versus conventional hematopoietic stem cell transplantation. *Blood.* 2003;102(2):756-762.
29. Flowers ME, Inamoto Y, Carpenter PA, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. *Blood.* 2011;117(11):3214-3219.
30. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. *Br J Haematol.* 1997;97(4):855-864.
31. Martin P, Nash R, Sanders J, et al. Reproducibility in retrospective grading of acute graft-versus-host disease after allogeneic marrow transplantation. *Bone Marrow Transplant.* 1998;21(3):273-279.
32. Weisdorf DJ, Hurd D, Carter S, et al. Prospective grading of graft-versus-host disease after unrelated donor marrow transplantation: a grading algorithm versus blinded expert panel review. *Biol Blood Marrow Transplant.* 2003;9(8):512-518.
33. Cahn JY, Klein JP, Lee SJ, et al. Prospective evaluation of 2 acute graft-versus-host (GVHD) grading systems: a joint Société Française de Greffe de Moëlle et Thérapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI), and International Bone Marrow Transplant Registry (IBMTR) prospective study. *Blood.* 2005;106(4):1495-1500.
34. Al-Ghamdi H, Leisenring W, Bensinger WI, et al. A proposed objective way to assess results of randomized prospective clinical trials with acute graft-versus-host disease as an outcome of interest. *Br J Haematol.* 2001;113(2):461-469.

35. Arora M, Klein JP, Weisdorf DJ, et al. Chronic GVHD risk score: a Center for International Blood and Marrow Transplant Research analysis. *Blood.* 2011;117(24):6714-6720.
36. Lee KH, Choi SJ, Lee JH, et al. Prognostic factors identifiable at the time of onset of acute graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Haematologica.* 2005;90(7):939-948.
37. MacMillan ML, DeFor TE, Weisdorf DJ. What predicts high risk acute graft-versus-host disease (GVHD) at onset?: identification of those at highest risk by a novel acute GVHD risk score. *Br J Haematol.* 2012;157(6):732-741.
38. Leisenring WM, Martin PJ, Petersdorf EW, et al. An acute graft-versus-host disease activity index to predict survival after hematopoietic cell transplantation with myeloablative conditioning regimens. *Blood.* 2006;108(2):749-755.
39. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med.* 1980;69(2):204-217.
40. Akpek G, Zahurak ML, Piantadosi S, et al. Development of a prognostic model for grading chronic graft-versus-host disease. *Blood.* 2001;97(5):1219-1226.
41. Akpek G, Lee SJ, Flowers ME, et al. Performance of a new clinical grading system for chronic graft-versus-host disease: a multicenter study. *Blood.* 2003;102(3):802-809.
42. Pavletic SZ, Smith LM, Bishop MR, et al. Prognostic factors of chronic graft-versus-host disease after allogeneic blood stem-cell transplantation. *Am J Hematol.* 2005;78(4):265-274.
43. Lee SJ, Klein JP, Barrett AJ, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. *Blood.* 2002;100(2):406-414.
44. Horowitz MM, Gale RP, Sondel PM, et al. Graft-versus-leukemia reactions after bone marrow transplantation. *Blood.* 1990;75(3):555-562.

45. Stern M, de Wreede LC, Brand R, et al. Sensitivity of hematological malignancies to graft-versus-host effects: an EBMT megafile analysis. *Leukemia.* 2014;28(11):2235-2240.
46. Cutler C, Antin J. Ch. 86: Manifestations and treatment of acute graft-versus-host disease. In: *Thomas' hematopoietic cell transplantation, 4th ed.* Hoboken, NJ: Wiley-Blackwell; 2009.
47. Gale RP, Bortin MM, van Bekkum DW, et al. Risk factors for acute graft-versus-host disease. *Br J Haematol.* 1987;67(4):397-406.
48. Cutler C, Giri S, Jeyapalan S, Paniagua D, Viswanathan A, Antin JH. Acute and chronic graft-versus-host disease after allogeneic peripheral-blood stem-cell and bone marrow transplantation: a meta-analysis. *J Clin Oncol.* 2001;19(16):3685-3691.
49. Hahn T, McCarthy PL, Zhang MJ, et al. Risk factors for acute graft-versus-host disease after human leukocyte antigen-identical sibling transplants for adults with leukemia. *J Clin Oncol.* 2008;26(35):5728-5734.
50. Nash RA, Pepe MS, Storb R, et al. Acute graft-versus-host disease: analysis of risk factors after allogeneic marrow transplantation and prophylaxis with cyclosporine and methotrexate. *Blood.* 1992;80(7):1838-1845.
51. Weisdorf D, Hakke R, Blazar B, et al. Risk factors for acute graft-versus-host disease in histocompatible donor bone marrow transplantation. *Transplantation.* 1991;51(6):1197-1203.
52. Eisner MD, August CS. Impact of donor and recipient characteristics on the development of acute and chronic graft-versus-host disease following pediatric bone marrow transplantation. *Bone Marrow Transplant.* 1995;15(5):663-668.
53. Atkinson K, Horowitz MM, Gale RP, et al. Risk factors for chronic graft-versus-host disease after HLA-identical sibling bone marrow transplantation. *Blood.* 1990;75(12):2459-2464.
54. Carlens S, Ringdén O, Remberger M, et al. Risk factors for chronic graft-versus-host disease after bone marrow transplantation: a retrospective single centre analysis. *Bone Marrow Transplant.* 1998;22(8):755-761.

55. Kollman C, Howe CW, Anasetti C, et al. Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. *Blood.* 2001;98(7):2043-2051.
56. Fraser CJ, Bhatia S, Ness K, et al. Impact of chronic graft-versus-host disease on the health status of hematopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study. *Blood.* 2006;108(8):2867-2873.
57. Pidala J, Anasetti C, Jim H. Quality of life after allogeneic hematopoietic cell transplantation. *Blood.* 2009;114(1):7-19.
58. Pavletic S, Volgesang G. Ch. 87: Chronic graft-versus-host disease: Clinical manifestations and therapy. In: *Thomas' hematopoietic cell transplantation, 4th ed.* Hoboken, NJ: Wiley-Blackwell; 2009.
59. Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2012;18(8):1150-1163.
60. Van Lint MT, Uderzo C, Locasciulli A, et al. Early treatment of acute graft-versus-host disease with high- or low-dose 6-methylprednisolone: a multicenter randomized trial from the Italian Group for Bone Marrow Transplantation. *Blood.* 1998;92(7):2288-2293.
61. Mielcarek M, Storer BE, Boeckh M, et al. Initial therapy of acute graft-versus-host disease with low-dose prednisone does not compromise patient outcomes. *Blood.* 2009;113(13):2888-2894.
62. Martin PJ, Bachier CR, Klingemann HG, et al. Endpoints for clinical trials testing treatment of acute graft-versus-host disease: a joint statement. *Biol Blood Marrow Transplant.* 2009;15(7):777-784.
63. Wolff D, Gerbitz A, Ayuk F, et al. Consensus conference on clinical practice in chronic graft-versus-host disease (GVHD): first-line and topical treatment of chronic GVHD. *Biol Blood Marrow Transplant.* 2010;16(12):1611-1628.

64. Wolff D, Schleuning M, von Harsdorf S, et al. Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant.* 2011;17(1):1-17.
65. Martin PJ, Weisdorf D, Przepiorka D, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: VI. Design of Clinical Trials Working Group report. *Biol Blood Marrow Transplant.* 2006;12(5):491-505.
66. Pavletic SZ, Martin P, Lee SJ, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. *Biol Blood Marrow Transplant.* 2006;12(3):252-266.
67. Sullivan KM, Witherspoon RP, Storb R, et al. Prednisone and azathioprine compared with prednisone and placebo for treatment of chronic graft-v-host disease: prognostic influence of prolonged thrombocytopenia after allogeneic marrow transplantation. *Blood.* 1988;72(2):546-554.
68. Martin PJ, Storer BE, Rowley SD, et al. Evaluation of mycophenolate mofetil for initial treatment of chronic graft-versus-host disease. *Blood.* 2009;113(21):5074-5082.
69. Koc S, Leisenring W, Flowers ME, et al. Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone. *Blood.* 2002;100(1):48-51.
70. Arora M, Wagner JE, Davies SM, et al. Randomized clinical trial of thalidomide, cyclosporine, and prednisone versus cyclosporine and prednisone as initial therapy for chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2001;7(5):265-273.
71. Gilman AL, Schultz KR, Goldman FD, et al. Randomized trial of hydroxychloroquine for newly diagnosed chronic graft-versus-host disease in children: a Children's Oncology Group study. *Biol Blood Marrow Transplant.* 2012;18(1):84-91.

72. Arora M, Burns LJ, Davies SM, et al. Chronic graft-versus-host disease: a prospective cohort study. *Biol Blood Marrow Transplant.* 2003;9(1):38-45.
73. Stewart BL, Storer B, Storek J, et al. Duration of immunosuppressive treatment for chronic graft-versus-host disease. *Blood.* 2004;104(12):3501-3506.
74. Arora M, Nagaraj S, Witte J, et al. New classification of chronic GVHD: added clarity from the consensus diagnoses. *Bone Marrow Transplant.* 2009;43(2):149-153.
75. Vigorito AC, Campregher PV, Storer BE, et al. Evaluation of NIH consensus criteria for classification of late acute and chronic GVHD. *Blood.* 2009;114(3):702-708.
76. Jagasia M, Giglia J, Chinratanalab W, et al. Incidence and outcome of chronic graft-versus-host disease using National Institutes of Health consensus criteria. *Biol Blood Marrow Transplant.* 2007;13(10):1207-1215.
77. Cho BS, Min CK, Eom KS, et al. Feasibility of NIH consensus criteria for chronic graft-versus-host disease. *Leukemia.* 2009;23(1):78-84.
78. Chakraborty B, Moodie EEM. Ch. 1: Introduction. In: *Statistical methods for dynamic treatment regimes: reinforcement learning, causal inference and personalized medicine.* New York, NY: Springer; 2013:1-8.
79. MacMillan ML, Weisdorf DJ, Wagner JE, et al. Response of 443 patients to steroids as primary therapy for acute graft-versus-host disease: comparison of grading systems. *Biol Blood Marrow Transplant.* 2002;8(7):387-394.
80. Hings IM, Filipovich AH, Miller WJ, et al. Prednisone therapy for acute graft-versus-host disease: short- versus long-term treatment. A prospective randomized trial. *Transplantation.* 1993;56(3):577-580.
81. Weisdorf D, Haake R, Blazar B, et al. Treatment of moderate/severe acute graft-versus-host disease after allogeneic bone marrow transplantation: an analysis of clinical risk features and outcome. *Blood.* 1990;75(4):1024-1030.
82. Chakraborty B, Moodie EEM. Ch. 2: The data: observational studies and sequentially randomized trials. In: *Statistical methods for dynamic treatment*

regimes : reinforcement learning, causal inference, and personalized medicine. New York, NY: Springer; 2013:26-27.

83. Moodie EEM, Chakraborty B, Kramer MS. Q-learning for estimating optimal dynamic treatment rules from observational data. *Can J Stat.* 2012;40(4):629-645.
84. Robins J. Optimal structural nested models for optimal sequential decisions. In: Lin D, Heagerty P, eds. *Proceedings of the second Seattle symposium on biostatistics*. New York: Springer; 2004:189-326.
85. Thall PF, Sung H-G, Estey EH. Selecting therapeutic strategies based on efficacy and death in multicourse clinical trials. *Journal of the American Statistical Association.* 2002;97(457):29-39.
86. Wahed AS, Thall PF. Evaluating Joint Effects of Induction-Salvage Treatment Regimes on Overall Survival in Acute Leukemia. *J R Stat Soc Ser C Appl Stat.* 2013;62(1):67-83.
87. Rich B, Moodie EEM, Stephens DA. Simulating sequential multiple assignment randomized trials to generate optimal personalized warfarin dosing strategies. *Clin Trials.* 2014.
88. Wallace MP, Moodie EEM. Personalizing medicine: a review of adaptive treatment strategies. *Pharmacoepidemiol Drug Saf.* 2014;23(6):580-585.
89. Bertsekas DP, Tsitsiklis JN. *Neuro-dynamic programming.* Belmont, Mass.: Athena Scientific; 1996.
90. Thall PF, Millikan RE, Sung HG. Evaluating multiple treatment courses in clinical trials. *Stat Med.* 2000;19(8):1011-1028.
91. Bellman R. *Dynamic programming*. Dover ed. Mineola, N.Y.: Dover Publications; 2003.
92. Arjas E. Causal inference from observational data: A Bayesian predictive approach. In: Berzuini C, Dawid A, Bernardinelli L, eds. *Causality: Statistical perspectives and applications*. West Sussex, United Kingdom: Chichester; 2012:71-84.

93. Zajonc T. Bayesian inference for dynamic treatment regimes: Mobility, equity, and efficiency in student tracking. *Journal of the American Statistical Association.* 2012;107(497):80-92.
94. Murphy S. Optimal dynamic treatment regimes (with discussions). *Journal of the Royal Statistical Society, series B.* 2003;65(2):331-366.
95. Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology.* 2003;14(3):300-306.
96. Murphy SA. An experimental design for the development of adaptive treatment strategies. *Stat Med.* 2005;24(10):1455-1481.
97. Chakraborty B. Dynamic treatment regimes for managing chronic health conditions: a statistical perspective. *Am J Public Health.* 2011;101(1):40-45.
98. Chakraborty B, Moodie EEM. Ch. 3: Reinforcement learning. In: *Statistical methods for dynamic treatment regimes : reinforcement learning, causal inference, and personalized medicine.* New York, NY: Springer; 2013:40.
99. Wald A. Statistical decision functions. *The annals of mathematical statistics.* 1949;20(2):165-205.
100. Sutton RS, Barto AG. *Reinforcement learning : an introduction.* Cambridge, Mass.: MIT Press; 1998.
101. Murphy SA. A Generalization Error for Q-Learning. *J Mach Learn Res.* 2005;6:1073-1097.
102. Center for Drug Evaluation and Research (CDER) of the US Department of Health and Human Services Food and Drug Administration. Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools. 2014:1-35.
103. Cotton CA, Heagerty PJ. A data augmentation method for estimating the causal effect of adherence to treatment regimens targeting control of an intermediate measure. *Statistics in Biosciences.* 2011;3(1):28-44.
104. Assouline S, Lipton JH. Monitoring response and resistance to treatment in chronic myeloid leukemia. *Curr Oncol.* 2011;18(2):e71-83.
105. Cortes J, Quintás-Cardama A, Kantarjian HM. Monitoring molecular response in chronic myeloid leukemia. *Cancer.* 2011;117(6):1113-1122.

106. Mahon FX, Etienne G. Deep molecular response in chronic myeloid leukemia: the new goal of therapy? *Clin Cancer Res.* 2014;20(2):310-322.
107. Moodie EEM, Nema D, Sun. YR. Q-learning: Flexible learning about useful utilities. *Statistics in Biosciences.* 2013:1-21.
108. Chakraborty B, Moodie EEM. Ch. 7: Q-learning of DTRs for discreet outcomes. In: *Statistical methods for dynamic treatment regimes: reinforcement learning, causal inference, and personalized medicine.* New York, NY: Springer; 2013:121.
109. Chakraborty B, Moodie EEM. Ch. 8: Inference and non-regularity. In: *Statistical methods for dynamic treatment regimes : reinforcement learning, causal inference, and personalized medicine.* New York, NY: Springer; 2013:127-169.
110. Jones HE, O'Grady KE, Tuten M. Reinforcement-based treatment improves the maternal treatment and neonatal outcomes of pregnant patients enrolled in comprehensive care treatment. *Am J Addict.* 2011;20(3):196-204.
111. Pelham WE, Fabiano GA. Evidence-based psychosocial treatments for attention-deficit/hyperactivity disorder. *J Clin Child Adolesc Psychol.* 2008;37(1):184-214.
112. Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry.* 2006;163(4):611-622.
113. Gunlicks-Stoessel M, Mufson L. Early patterns of symptom change signal remission with interpersonal psychotherapy for depressed adolescents. *Depress Anxiety.* 2011;28(7):525-531.
114. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163(11):1905-1917.
115. Schneider LS, Tariot PN, Lyketsos CG, et al. National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE):

Alzheimer disease trial methodology. *Am J Geriatr Psychiatry.* 2001;9(4):346-360.

116. Stroup TS, McEvoy JP, Swartz MS, et al. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. *Schizophr Bull.* 2003;29(1):15-31.
117. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin Trials.* 2004;25(1):119-142.
118. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005;353(12):1209-1223.
119. Sultzer DL, Davis SM, Tariot PN, et al. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. *Am J Psychiatry.* 2008;165(7):844-854.
120. Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. *Am J Psychiatry.* 2006;163(7):1161-1172.
121. Theurich S, Fischmann H, Shimabukuro-Vornhagen A, et al. Polyclonal anti-thymocyte globulins for the prophylaxis of graft-versus-host disease after allogeneic stem cell or bone marrow transplantation in adults. *Cochrane Database Syst Rev.* 2012;9:CD009159.
122. Walker I, , Schultz KR, Toze CL, et al. Thymoglobulin Decreases the Need for Immunosuppression at 12 Months after Myeloablative and Nonmyeloablative Unrelated Donor Transplantation: CBMTG 0801, a Randomized, Controlled Trial. *56th American Society of Hematology Annual Meeting*. 2014, Abstract 38.
123. Van Lint MT, Milone G, Leotta S, et al. Treatment of acute graft-versus-host disease with prednisolone: significant survival advantage for day +5 responders and no advantage for nonresponders receiving anti-thymocyte globulin. *Blood.* 2006;107(10):4177-4181.

124. Cohen J. *Statistical power analysis for the behavioral sciences.* 2nd ed. Hillsdale, N.J.: L. Erlbaum Associates; 1988.
125. Shrout PE, Keyes KM, Ornstein K. *Causality and psychopathology. 98th American Psychopathological Association Meeting 2008 in New York, NY.* Oxford, UK: Oxford University Press; 2011.
126. Thall PF, Wathen JK. Covariate-adjusted adaptive randomization in a sarcoma trial with multi-stage treatments. *Stat Med.* 2005;24(13):1947-1964.
127. Hernán MA, Lanoy E, Costagliola D, Robins JM. Comparison of dynamic treatment regimes via inverse probability weighting. *Basic Clin Pharmacol Toxicol.* 2006;98(3):237-242.
128. Center for International Blood and Marrow Transplant Research. What we do. http://www.cibmtr.org/About/WhatWeDo/Pages/index.aspx. Accessed March 10, 2015.
129. Center for International Blood and Marrow Transplant Research. Stem cell therapeutics outcomes database. http://www.cibmtr.org/About/WhatWeDo /SCTOD/Pages/index.aspx. Accessed March 10, 2015.
130. Horowitz M. The role of registries in facilitating clinical research in BMT: examples from the Center for International Blood and Marrow Transplant Research. *Bone Marrow Transplant.* 2008;42 Suppl 1:S1-S2.
131. Arai S, Arora M, Wang T, et al. Increasing Incidence of Chronic Graft-versus-Host Disease in Allogeneic Transplantation: A Report from the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant.* 2015;21(2):266-274.
132. Giralt S, Ballen K, Rizzo D, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant.* 2009;15(3):367-369.
133. Pasquini MC. Reporting conditioning regimen intensity: ablative or not ablative, that is the question. http://www.cibmtr.org/Meetings/Materials/CRPDMC/Documents/2007/february/PasquiniM_DM_RIC07.pdf. Accessed March 10, 2015.

134. Weisdorf D, Spellman S, Haagenson M, et al. Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: revised definitions to predict survival. *Biol Blood Marrow Transplant.* 2008;14(7):748-758.
135. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2003;9(4):215-233.
136. Forcina A, Seitz I, Martinius H, et al. *Pharmacokinetics (PK) Study Of Antithymocyte Globulins Fresenius (ATG-F) Prior To Allogeneic Stem Cell Transplantation: Implications For Timing Of Graft and Early Adoptive Immunotherapy Infusions.* Vol 1222013.
137. Seidel MG, Fritsch G, Matthes-Martin S, et al. Antithymocyte globulin pharmacokinetics in pediatric patients after hematopoietic stem cell transplantation. *J Pediatr Hematol Oncol.* 2005;27(10):532-536.
138. Kakhniashvili I, Filicko J, Kraft WK, Flomenberg N. Heterogeneous clearance of antithymocyte globulin after CD34+-selected allogeneic hematopoietic progenitor cell transplantation. *Biol Blood Marrow Transplant.* 2005;11(8):609-618.
139. Waller EK, Langston AA, Lonial S, et al. Pharmacokinetics and pharmacodynamics of anti-thymocyte globulin in recipients of partially HLA-matched blood hematopoietic progenitor cell transplantation. *Biol Blood Marrow Transplant.* 2003;9(7):460-471.
140. Penack O, Fischer L, Stroux A, et al. Serotherapy with thymoglobulin and alemtuzumab differentially influences frequency and function of natural killer cells after allogeneic stem cell transplantation. *Bone Marrow Transplant.* 2008;41(4):377-383.
141. Rebello P, Cwynarski K, Varughese M, Eades A, Apperley JF, Hale G. Pharmacokinetics of CAMPATH-1H in BMT patients. *Cytotherapy.* 2001;3(4):261-267.
142. Morris EC, Rebello P, Thomson KJ, et al. Pharmacokinetics of alemtuzumab used for in vivo and in vitro T-cell depletion in allogeneic transplantations:

relevance for early adoptive immunotherapy and infectious complications. *Blood.* 2003;102(1):404-406.

143. Lee SJ, Zahrieh D, Agura E, et al. Effect of up-front daclizumab when combined with steroids for the treatment of acute graft-versus-host disease: results of a randomized trial. *Blood.* 2004;104(5):1559-1564.

144. Ji SQ, Chen HR, Yan HM, et al. Anti-CD25 monoclonal antibody (basiliximab) for prevention of graft-versus-host disease after haploidentical bone marrow transplantation for hematological malignancies. *Bone Marrow Transplant.* 2005;36(4):349-354.

145. Funke VA, de Medeiros CR, Setúbal DC, et al. Therapy for severe refractory acute graft-versus-host disease with basiliximab, a selective interleukin-2 receptor antagonist. *Bone Marrow Transplant.* 2006;37(10):961-965.

146. Carpenter PA, Appelbaum FR, Corey L, et al. A humanized non-FcR-binding anti-CD3 antibody, visilizumab, for treatment of steroid-refractory acute graft-versus-host disease. *Blood.* 2002;99(8):2712-2719.

147. Macmillan ML, Couriel D, Weisdorf DJ, et al. A phase 2/3 multicenter randomized clinical trial of ABX-CBL versus ATG as secondary therapy for steroid-resistant acute graft-versus-host disease. *Blood.* 2007;109(6):2657-2662.

148. Center for International Blood and Marrow Transplant Research. Instructions for six months to two years post HCT data (Form 2200). http://www.cibmtr.org/DataManagement/TrainingReference/Manuals/DataManagement/Documents/6mo-2yr%20Follow-Up%20Form%202200.pdf. Accessed March 10, 2015.

149. Center for International Blood and Marrow Transplant Research. Instructions for yearly follow-up for greater than two years post HSCT (Form 2300 - Revision 3). http://www.cibmtr.org/DataManagement/TrainingReference/Manuals/DataManagement/Documents/Greater%20Than%20Two%20Year%20Follow-Up%20Form%202300_ver1.3.pdf. Accessed March 10, 2015.

150. Martin PJ, Furlong T, Rowley SD, et al. Evaluation of oral beclomethasone dipropionate for prevention of acute graft-versus-host disease. *Biol Blood Marrow Transplant.* 2012;18(6):922-929.
151. Ibrahim RB, Abidi MH, Cronin SM, et al. Nonabsorbable corticosteroids use in the treatment of gastrointestinal graft-versus-host disease. *Biol Blood Marrow Transplant.* 2009;15(4):395-405.
152. Hockenbery DM, Cruickshank S, Rodell TC, et al. A randomized, placebo-controlled trial of oral beclomethasone dipropionate as a prednisone-sparing therapy for gastrointestinal graft-versus-host disease. *Blood.* 2007;109(10):4557-4563.
153. Sokos DR, Berger M, Lazarus HM. Intravenous immunoglobulin: appropriate indications and uses in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2002;8(3):117-130.
154. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software.* 2011;45(3).
155. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res.* 2011;20(1):40-49.
156. Scrucca L, Santucci A, Aversa F. Regression modeling of competing risk using R: an in depth guide for clinicians. *Bone Marrow Transplant.* 2010;45(9):1388-1395.
157. Rubin DB. *Multiple imputation for nonresponse in surveys.* New York ;: Wiley; 1987.
158. Team RDC. *R: A language and environment for statistical computing.* Vienna, Austria: R Foundation for Statistical Computing; 2008.
159. Hanley J, Moodie EEM. Sample Size, Precision and Power Calculations: A Unified Approach. *J Biomet Biostat.* 2011;2(124).
160. Fox J, Monette G. Generalized Collinearity Diagnostics. *Journal of the American Statistical Association.* 1992;87(417):178-183.
161. Fox J, Weisberg S. An R companion to applied regression. 2 ed. Thousand Oaks, CA: Sage; 2011.

162. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol.* 1996;49(12):1373-1379.
163. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol.* 2007;165(6):710-718.
164. Irala Jd, Fernandez-Crehuet Navajas R, Serrano del Castillo A. Abnormally wide confidence intervals in logistic regression: interpretation of statistical program results. *Revista Panamericana de Salud Pública.* 1997;2(4):268-271.
165. Theurich S, Fischmann H, Chakupurakal G, et al. Anti-thymocyte globulins for post-transplant graft-versus-host disease prophylaxis-A systematic review and meta-analysis. *Crit Rev Oncol Hematol.* 2013;88(1):178-186.
166. Cragg L, Blazar BR, Defor T, et al. A randomized trial comparing prednisone with antithymocyte globulin/prednisone as an initial systemic therapy for moderately severe acute graft-versus-host disease. *Biol Blood Marrow Transplant.* 2000;6(4A):441-447.
167. Ram R, Storb R. Pharmacologic prophylaxis regimens for acute graft-versus-host disease: past, present and future. *Leuk Lymphoma.* 2013;54(8):1591-1601.
168. Mead AJ, Thomson KJ, Morris EC, et al. HLA-mismatched unrelated donors are a viable alternate graft source for allogeneic transplantation following alemtuzumab-based reduced-intensity conditioning. *Blood.* 2010;115(25):5147-5153.
169. Ruutu T, Niederwieser D, Gratwohl A, Apperley JF. A survey of the prophylaxis and treatment of acute GVHD in Europe: a report of the European Group for Blood and Marrow, Transplantation (EBMT). Chronic Leukaemia Working Party of the EBMT. *Bone Marrow Transplant.* 1997;19(8):759-764.
170. Ruutu T, van Biezen A, Hertenstein B, et al. Prophylaxis and treatment of GVHD after allogeneic haematopoietic SCT: a survey of centre strategies by the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2012;47(11):1459-1464.

171. MacMillan ML, DeFor TE, Weisdorf DJ. The best endpoint for acute GVHD treatment trials. *Blood.* 2010;115(26):5412-5417.
172. O'Mahony D, Morris JC, Stetler-Stevenson M, et al. EBV-related lymphoproliferative disease complicating therapy with the anti-CD2 monoclonal antibody, siplizumab, in patients with T-cell malignancies. *Clin Cancer Res.* 2009;15(7):2514-2522.
173. Ambinder RF. Evaluation of T- and NK-cell-targeted therapies: is there a role for rituximab prophylaxis? *Clin Cancer Res.* 2009;15(7):2205-2206.
174. Armand P, Kim HT, Zhang MJ, et al. Classifying cytogenetics in patients with acute myelogenous leukemia in complete remission undergoing allogeneic transplantation: a Center for International Blood and Marrow Transplant Research study. *Biol Blood Marrow Transplant.* 2012;18(2):280-288.
175. Pidala J, Wang T, Haagenson M, et al. Amino acid substitution at peptide-binding pockets of HLA class I molecules increases risk of severe acute GVHD and mortality. *Blood.* 2013;122(22):3651-3658.
176. Bacigalupo A. A closer look at permissive HLA mismatch. *Blood.* 2013;122(22):3555-3556.
177. Hahn T, McCarthy PL, Hassebroek A, et al. Significant improvement in survival after allogeneic hematopoietic cell transplantation during a period of significantly increased use, older recipient age, and use of unrelated donors. *J Clin Oncol.* 2013;31(19):2437-2449.
178. Khouri IF, Albitar M, Saliba RM, et al. Low-dose alemtuzumab (Campath) in myeloablative allogeneic stem cell transplantation for CD52-positive malignancies: decreased incidence of acute graft-versus-host-disease with unique pharmacokinetics. *Bone Marrow Transplant.* 2004;33(8):833-837.
179. Bacigalupo A. Antilymphocyte/thymocyte globulin for graft versus host disease prophylaxis: efficacy and side effects. *Bone Marrow Transplant.* 2005;35(3):225-231.
180. Ogburn EL, VanderWeele TJ. On the nondifferential misclassification of a binary confounder. *Epidemiology.* 2012;23(3):433-439.

181. Jia X, Sima CS, Brennan MF, Panageas KS. Cure models for the analysis of time-to-event data in cancer studies. *J Surg Oncol.* 2013;108(6):342-347.
182. Huang X, Ning J, Wahed AS. Optimization of individualized dynamic treatment regimes for recurrent diseases. *Stat Med.* 2014;33(14):2363-2378.
183. Weber GM, Mandl KD, Kohane IS. Finding the missing link for big biomedical data. *JAMA.* 2014;311(24):2479-2480.
184. Wang W, Krishnan E. Big data and clinicians: a review on the state of the science. *JMIR Med Inform.* 2014;2(1):e1.
185. Zauderer MG, Gucalp A, Epstein AS, et al. Piloting IBM Watson Oncology within Memorial Sloan Kettering's regional network. Abtract presented at: ASCO Annual Meeting Proceedings 2014.
186. Hurwitz B. Clinical guidelines: legal and political considerations of clinical practice guidelines. *BMJ: British Medical Journal.* 1999;318(7184):661.
187. Wang L, Rotnitzky A, Lin X, Millikan RE, Thall PF. Evaluation of Viable Dynamic Treatment Regimes in a Sequentially Randomized Trial of Advanced Prostate Cancer. *J Am Stat Assoc.* 2012;107(498):493-508.
188. Huang X, Ning J. Analysis of multi-stage treatments for recurrent diseases. *Stat Med.* 2012;31(24):2805-2821.
189. Kidwell KM, Ko JH, Wahed AS. Inference for the median residual life function in sequential multiple assignment randomized trials. *Stat Med.* 2014;33(9):1503-1513.
190. Fonteneau R, Wehenkel L, Ernst D. Variable selection for dynamic treatment regimes: a reinforcement learning approach. Paper presented at: European Workshop on Reinforcement Learning 2008 (EWRL'08)2008.
191. Chakraborty B, Murphy S, Strecher V. Inference for non-regular parameters in optimal dynamic treatment regimes. *Statistical methods in medical research.* 2009.
192. Rosenheck RA, Leslie DL, Sindelar J, et al. Cost-effectiveness of second-generation antipsychotics and perphenazine in a randomized trial of treatment for chronic schizophrenia. *Am J Psychiatry.* 2006;163(12):2080-2089.