CITY OF HOPE NATIONAL MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF OUTCOMES RESEARCH

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PRINCIPAL INVESTIGATOR:
Saro Armenian, DO, MPH

COLLABORATING INVESTIGATORS:

Stephen Forman, MD	Kyuwan Lee, PhD	June-Wha Rhee, MD
Faizi Jamal, MD	Rusha Bhandari, MD	Sonal Khemani, MD
Brittany Echevarria	Hannah Komai, NP	Molly Thornock, RN
Itaua Leston Araujo, MD	Andri Lemarquis, MD, PhD	Natalie Smith
Jayvi Villamin	Louiselle David	Avigail Dolleton
Vanessa Mendoza	Biraj Bista, MD	Deniz Urgun, MD
Carol Canete	Keimya Sadeghi	Lee Jones, PhD

PARTICIPATING CLINICIANS:

Vaibhav Agrawal, MD	Len Farol, MD	Salman Otoukeshi, MD
Monzr Al Malki, MD	James Godfrey, MD	Anna Pawlowska, MD
Ibrahim Aldoss, MD	Scott Goldsmith, MD	Tycel Phillips, MD
Haris Ali, MD	Alex Herrera, MD	Leslie Popplewell, MD
Joseph Alvarnas, MD	Myo Htut, MD	Hoda Pourhassan, MD
Idoroenyi Amanam, MD	Murali Janakiram, MD	Vinod Pullarkat, MD
Ahmed Aribi, MD	Avyakta Kallam, MD	Michael Rosenzweig, MD
Shukaib Arslan, MD	Swetha Kambhampati, MD	Firoozeh Sahebi, MD
Andrew Artz, MD	Nicole Karras, MD	Amandeep Salhotra, MD
John Baird MD	Niloufer Khan, MD	Yazeed Samara, MD
Brian Ball, MD	Paul Koller, MD	Karamjeet Sandhu, MD
Pamela Becker, MD, PhD	Amrita Krishnan, MD	Geoffrey Shouse, DO
Amanda Blackmon DO	Larry Kwak, MD	Tanya Siddiqi, MD
Azra Borogavac, MD	Peter Lee, MD	Eileen Smith, MD
Elizabeth Budde, MD	Joshua Mansour, MD	Ricardo Spielberger, MD
Ji-Lian Cai, MD	Guido Marcucci, MD	Anthony Stein, MD
Thai Cao, MD	Matthew Mei, MD	Forrest Stewart, MD
Peter Curtin, MD	Ryotaro Nakamura, MD	Leo Wang, MD, PhD
Alexey Danilov, MD, PhD	Nitya Nathwani, MD	Jasmine Zain, MD
Amrita Desai, MD	Liana Nikolaenko, MD	

STUDY STATISTICIAN:
Lennie Wong, PhD
Sitong Chen
Xinyi Du

NON PHYSICIAN CONSENTER:

Liezl Atencio, CCRP, CRC	Claudia Herrera, CRA
Meagan Echevarria, CRC	Lanie Lindenfeld, CCRP
Caitlyn Estrada, CRA	Derek Lance, CRA
Stephanie Rodarte, CRA	Emma Grigorian, CRA

ABSTRACT

There are currently 200,000 hematopoietic cell transplantation (HCT) survivors in the U.S. today, a number that will exceed 500,000 by 2030. Despite improvements in overall survival, long-term HCT survivors remain at high risk for chronic health complications such as cardiovascular disease (CVD). Cardiovascular complications, such as myocardial infarction and cardiomyopathy/heart failure, are not only more common in HCT survivors, but they occur earlier than in the general population; in essence, HCT is associated with accelerated cardiovascular aging. However, as highlighted by the recent NIH HCT Late Effects Consensus Conference, the biological mechanisms underlying this problem remain unknown. Our *overall hypothesis* is that multiple sequential organ system and metabolic impairments sustained prior to, during, or after HCT accelerates depletion of cardiovascular physiologic reserves (cardiovascular reserve capacity), predisposing to early onset CVD. To test this hypothesis, we will measure cardiovascular reserve capacity in a group of HCT survivors over time. Peak oxygen consumption (VO_{2peak}), as derived from cardiopulmonary exercise testing, is the gold standard measure of cardiovascular reserve capacity, because it represents the integrative efficiency with which multiple organ systems deliver and use oxygen for ATP resynthesis. Using a longitudinal study design, we will evaluate VO_{2peak} at baseline (prior to HCT), 6 months, one year and two years post-HCT, allowing us to determine its trajectory over time. We will also determine the impact VO_{2peak} on self-reported physical functioning, and identify populations at high risk for accelerated VO_{2peak} decline after HCT. Importantly, we will use novel diagnostic strategies to define the organic-specific determinants of VO_{2peak} and its impairment after HCT. By the end of our study, we will have: 1) established initial VO_{2peak} in patients undergoing HCT and characterized its post-HCT trajectory over time, identifying patients at highest risk for decline after HCT; 2) informed the screening for subclinical CVD, using strategies that are readily applicable in the clinical setting; and 3) identified mechanisms by which organ-specific impairments, alone and in combination, contribute to abnormalities in VO_{2peak} after HCT. This study builds on our previous successful research and will address important knowledge gaps about cardiovascular complications in HCT survivors. Information obtained from this study will support development of evidence-based interventions to decrease the risk of CVD after HCT. The growing population of long-term HCT survivors makes development of prevention strategies imperative, to ensure that these survivors live long and healthy lives well after completion of HCT.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
2MSPT	2-Minute Step in Place Test
30STS	30-second sit to stand test
ACLS	Advanced Cardiovascular Life Support
ACC	American College of Cardiology
ADL	Activities of Daily Living
AHA	American Heart Association
AR(1)	Autoregressive one
ASE	American Society of Echocardiography
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
BP	Blood Pressure
CAPA	Corrective and Preventative Action
CBC	Complete Blood Count
COH	City of Hope
CPET	Cardiopulmonary exercise testing
CVD	Cardiovascular disease
CS	Compound Symmetry
CSA	Cross-Sectional Area
CRA	Clinical Research Assistant
DL/VA	DLCO/Volume
DLCO	Carbon monoxide diffusing capacity of the lungs
ECG	Electrocardiogram
EF	Ejection fraction
ESP	End-Systolic Pressure
FEV1	Forced expiratory volume in 1 second
FSH	Follicular stimulating hormone
FVC	Forced vital capacity
GEE	Generalized Estimating Equation
GLM	Generalized Linear Models
GvHD	Graft vs. Host Disease
HRQOL	Health-Related Quality Of Life
HCT	Hematopoietic cell transplantation
IRB	Institutional Review Board
KPS	Karnofsky performance scale
LH	Luteinizing hormone
LV	Left ventricular
MOS	Medical outcomes study
MRI	Magnetic Resonance Imaging
O2	Oxygen
OR	Odds Ratio

PMM	Pattern Mixture Models
SAE	Serious adverse event
SV	Stroke Volume
T4	Free thyroxin
TUG	Timed Up and Go
TBI	Total body irradiation
TLC	Total lung capacity
TSH	Thyroid stimulating hormone
UP	Unanticipated problem
US	Ultrasound
VA	Ventricular-Arterial
VO2peak	Peak oxygen consumption
VTI	Velocity Time Integral

1.0 PURPOSE OF STUDY

Advances in hematopoietic cell transplantation (HCT) have led to a 10% improvement in survival each decade since the 1980's.[1] As a result, there are currently 200,000 HCT survivors in the U.S today, a number that will exceed 500,000 by 2030.[2] Despite these improvements in survival, long-term HCT survivors remain at high risk of chronic health complications such as cardiovascular disease (CVD).[3] Indeed, cardiovascular complications, including cardiomyopathy/heart failure and myocardial infarction, are not only more common (2-fold to 4-fold higher risk),[4] but also occur significantly earlier in HCT survivors than in the general population;[4] in essence, HCT is associated with accelerated cardiovascular aging. However, the pathophysiology and mechanisms underlying this phenomenon remain unknown. To improve the lives of HCT survivors, it is of critical importance to address these knowledge gaps. This will catalyze future strategies to more effectively monitor and treat HCT patients, and ultimately decrease the burden of CVD in this population.

The cardiovascular system has an inherent reserve capacity maintained by integrative cross-organ function among the pulmonary, cardiac, hematologic/vascular, and musculoskeletal systems. Collectively, these systems possess tremendous ability to withstand and adapt to physiologic perturbations.[5] However, reserve capacity is finite, and continued organ injuries can lead to cardiovascular aging.[5] Our overall hypothesis is that repeated direct and indirect perturbations to these organ systems prior to, during, and shortly after HCT accelerate depletion of cardiovascular reserve capacity, resulting in premature onset of CVD in HCT survivors.

Peak oxygen consumption (VO_{2peak}), as derived from cardiopulmonary exercise testing, is the gold standard measure of cardiovascular reserve capacity, because it represents the integrative efficiency with which multiple organ systems (pulmonary, cardiac, hematologic/vascular, musculoskeletal) deliver and use oxygen for ATP resynthesis.[6,7] VO_{2peak} is inversely and independently correlated with cardiovascular and all-cause mortality in a broad range of adult populations.[6-9] Accordingly, it is used as a reliable endpoint to measure treatment efficacy for interventions designed to reduce CVD risk.[6,8] However, there is virtually no information on initial VO_{2peak} in patients undergoing HCT, its post-HCT trajectory over time, or whether its decline has a measurable impact on health-related quality of life (HRQOL) and CVD risk after HCT. Importantly, very little is known regarding organ-specific contributions to depletion of VO_{2peak} after HCT.

2.0 SPECIFIC AIMS

2.1 **AIM 1:** Evaluate cardiovascular reserve capacity, as measured by $VO_{2peak,}$ in HCT survivors. We will measure initial VO_{2peak} in patients prior to HCT and its post-HCT trajectory over time; compare VO_{2peak} in HCT survivors at baseline (pre-HCT), 6m, 1Y, and 2Y post-HCT to established age- and sex-normative data; and define the association between VO_{2peak} and self-reported health-related quality of life (HRQOL) at baseline/over time.

2.2 **AIM 2:** Define the determinants of VO_{2peak} impairment in HCT survivors. We will use advanced imaging and functional measures to examine the organ-specific contributions to VO_{2peak} at baseline, 6m, 1Y, and 2Y post-HCT.

3.0 BACKGROUND AND RATIONALE

3.1 BURDEN OF CVD IN HCT SURVIVORS

Cardiovascular disease (CVD) and cardiovascular aging are important problems in long-term hematopoietic cell transplantation (HCT) survivors. Despite improvements in long-term outcomes, HCT survivors continue to have substantially higher mortality rates compared with the general population.[10-12] In particular, the risk of cardiovascular-related mortality is more than twice that of the general population,[11-13] and the magnitude of risk increases with time from HCT.[13] However, examining CVD-associated mortality alone underestimates the true burden of CVD morbidities after HCT. HCT survivors have a 4-fold higher risk of developing CVD compared to the general population,[14] adding to the already high burden of chronic health-related conditions in these survivors.[15] Among HCT survivors, median age at first cardiovascular event such as myocardial infarction is 53 years (range 35–66 years),[16] much lower than would be expected in the general population (67 years).[17] The markedly increased risk of CVD, coupled with the development of complications earlier than would be expected in the general population, suggests the presence of an accelerated cardiovascular aging phenotype in HCT survivors.

3.2 COMPLEX MECHANISMS OF ACCELERATED CARDIOVASCULAR AGING

Complex mechanisms contribute to accelerated cardiovascular aging. Biologic aging involves multiple complex changes in structure and function that lead to decreased reserve capacity across virtually all organ systems, with increased vulnerability to age-related diseases.[5] Similarly, we can envision CVD as being induced by sequential and concurrent pathologic perturbations to the organ systems that maintain cardiovascular reserve: pulmonary, cardiac, hematologic/vascular, and musculoskeletal. Injury to one or more of these systems is initially offset by a compensatory response in others (e.g. activation of the renin-angiotensin system to enhance stroke volume (SV) during cardiac dysfunction, or increase in hemoglobin during chronic hypoxemia), a process termed coordinated adaptation. **However, continued direct or indirect injuries to these systems over time results in a decline in cardiovascular reserve capacity (Figures 1-2), which in turn drives accelerated cardiovascular aging.[5,18]**

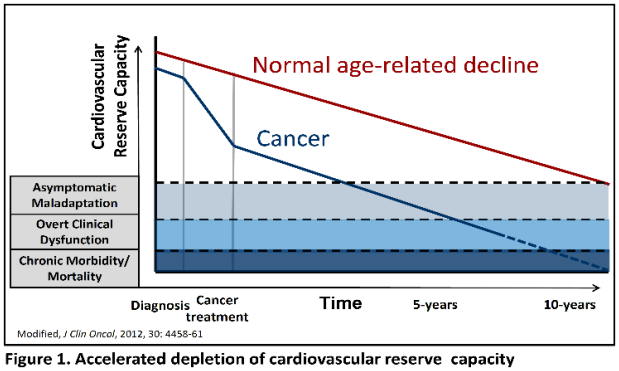

Figure 1. Accelerated depletion of cardiovascular reserve capacity

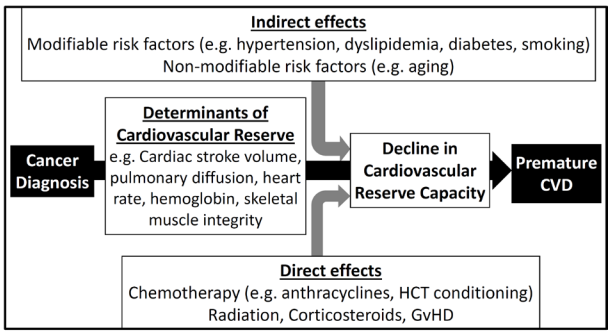

Figure 2. *Direct* and *indirect* "hits" result in ↓cardiovascular reserve after HCT

The following preliminary studies provide the scientific premise for studying impaired

cardiovascular reserve and accelerated cardiovascular aging in HCT survivors

3.2.1 *Multiple organ systems contribute to cardiovascular reserve capacity maintenance*

Pulmonary: Nearly half of all patients undergoing allogeneic HCT will develop acute pulmonary toxicity, and pulmonary complications account for up to 40% of transplant-related deaths within the first year after HCT.[19,20] Pulmonary complications can be due to injuries sustained during HCT (conditioning chemotherapy, total body irradiation [TBI], infection) or non-infectious complications that develop after HCT (e.g. bronchiolitis obliterans, idiopathic pneumonia syndrome).[20] In a recently completed study, we showed a high prevalence (35%) of diffusion capacity defects in HCT survivors, corresponding to a greater than five-fold risk compared to age-matched non-cancer controls (OR: 5.2, p<0.01).[21]

Cardiac*:* It is well-established that cancer treatments involving the heart can lead to physiologic alterations in the heart and its blood vessels.[4] *Anthracycline cardiotoxicity* is related to myocardial injury through generation of damaging free radicals and intracardiac metabolic derangements.[22] For HCT survivors treated with anthracyclines prior to HCT, additional exposures such as high-dose cyclophosphamide during conditioning may further compromise cardiomyocyte architecture and function.[4] We have shown that cumulative anthracycline dose ≥250 mg/m^2 is associated with a ten-fold risk of heart failure in HCT survivors (odds ratio [OR]=9.9, p<0.01),[23] a dose threshold that is markedly lower than conventionally recognized cutoffs (350–450 mg/m^2) in non-HCT cancer populations.[24] *Radiation* can cause direct myocardial injury, or result in endothelial cell proliferation and atherosclerosis.[25] Among allogeneic HCT patients, *graft versus host disease* (GvHD) can lead to additional microvessel disease, due to endothelial infiltration of alloreactive cytotoxic T lymphocytes,[26] suggesting an immunological mechanism for accelerated arterial disease.[26]

Musculoskeletal: Chronic corticosteroid exposure, TBI, prolonged inactivity, or poor nutritional status can lead to abnormal body composition that manifests as an increase in total percent fat mass and a reduction in muscle mass (sarcopenia).[27] We have shown that pre-HCT sarcopenia is associated with increased risk of CVD-related and non-relapse mortality in HCT survivors.[28] Moreover, patients who survive HCT often do not adhere to national exercise recommendations, and have significant declines in physical activity levels from pre-to-post HCT.[29] Patients with GvHD are more likely to demonstrate physical inactivity due to the disproportionate muscle atrophy seen in lower extremity and back extensor muscles. In HCT survivors, physical inactivity combined with reduction in muscle mass can compromise the efficiency of capillary transport and utilization of oxygen (O_2), contributing to additional impairments in cardiovascular reserve.[29]

Hematologic: Persistent post-HCT abnormalities such as myelodysplastic syndrome, myelofibrosis, or bone marrow failure,[20] while rare, may further contribute to decline in cardiovascular reserve over time.

3.2.2 *Comorbidities indirectly contribute to depletion of cardiovascular reserves.*

Traditional cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia are important modifiers of CVD risk in the general population.[17] We have shown that nearly one-third of HCT survivors (32%) have multiple (≥2) cardiovascular risk factors, compared to only 21% in the general population,[30] and that each risk factor confers an incremental risk of CVD over time (10-year incidence of CVD: 4% [no risk factor], 7% [one], 11% [at least two]; p<0.01). CVD

incidence is highest (15%) among HCT survivors with multiple risk factors who had also been exposed to cardiotoxic therapies. Other health conditions such as thyroid dysfunction, chronic kidney disease, and gonadal dysfunction are established CVD risk factors in the general population,[17] and are highly prevalent in HCT survivors.[3] There is a paucity of information regarding the contribution of these conditions to long-term CVD risk in HCT patients, a knowledge gap we will address in the current study.

Taken together, these findings support our **overall hypothesis** is that repeated *direct* and *indirect* perturbations to these organ systems prior to, during, and shortly after HCT accelerate depletion of cardiovascular reserve capacity, resulting in premature onset of CVD in HCT survivors.

3.3 CARDIOPULMONARY EXERCISE TESTING (CPET) TO MEASURE CARDIOVASCULAR RESERVE CAPACITY

VO_{2peak} is an optimal measurement of cardiovascular reserve capacity. In clinical practice, cardiovascular function is almost exclusively determined via resting assessment of cardiac left ventricular ejection fraction (EF). However, resting EF provides only a snapshot of the heart's performance under optimal circumstances, and is a poor prognosticator of future cardiovascular events or mortality in patients undergoing HCT.[18,31] Importantly, EF does not provide information on the functional integrity of other organ systems involved in maintaining cardiovascular reserve.[32-34] A better measure of cardiovascular reserve is VO_{2peak}, a measurement of cardiopulmonary function that represents maximal O_2 uptake capacity. Indeed, *VO_{2peak} derived from cardiopulmonary exercise testing (CPET) is the gold standard measure of cardiovascular reserve* because it represents the integrative efficiency with which multiple organ systems (pulmonary, cardiac, hematologic/vascular, and musculoskeletal) deliver and use O_2 for ATP synthesis.

VO_{2peak} is reduced in cancer patients. VO_{2peak} was evaluated in *colorectal cancer (CRC)* patients without CVD and matched controls.[35] In CRC patients, mean VO_{2peak} was 23% below that of controls, despite the presence of comparable resting EF (EF: 59% [CRC] vs. 62% [controls]).[35] Interestingly, even chemotherapy-naïve patients with CRC had significantly lower VO_{2peak} when compared to controls (23.4 ml/kg/min vs. 28.0 ml/kg/min, $p<0.01$),[35] underscoring the message that *reduced VO_{2peak} may be a hallmark of both the cancer and the treatments used for curative intent.* In *breast cancer* patients, anthracycline chemotherapy, chest radiation, and anti-Her2 therapy contribute to an increased risk of CVD, compared to women without cancer.[36-38] In fact, CVD is now the leading cause of mortality in older women (>50 years) with early stage disease.[37] In a study of 248 breast cancer patients with normal resting cardiac function (EF ≥50%), VO_{2peak} was on average 27% less than that of age-matched *sedentary* women without a history of cancer.[9] Remarkably, the study found that patients with breast cancer reached a predicted VO_{2peak} for a particular age group (e.g. 40 years) approximately 20 to 30 years earlier than healthy women without a history of breast cancer.[9]

4.0 ELIGIBILITY

4.1 INCLUSION CRITERIA

The subject must meet all criteria below to qualify for a screening visit:

- Age at HCT ≥ 18 years

- Diagnosis of Acute Leukemia (myeloid, lymphoid), Lymphoma (non-Hodgkin, Hodgkin), Multiple Myeloma or Myelodysplastic Syndromes.
- Planning to undergo first autologous or allogeneic transplant.
- Able to read, understand and write in English or Spanish.
- Able to understand and sign the study specific Informed Consent Form (ICF)
- Physically able and willing to complete all study procedures.

4.2 EXCLUSION CRITERIA

The following are absolute contraindications to cardiopulmonary exercise testing:

- Unstable bone lesions per electronic medical record review and/or notification from patient's primary physician
- Unstable angina or history of acute myocardial Infarction (< 5 days of any planned study procedures)
- Recurrent syncope
- Acute myocarditis or pericarditis
- Symptomatic severe aortic stenosis
- Uncontrolled arrhythmia causing symptoms
- Pulmonary embolus < 3 month of study procedures
- Thrombosis of lower extremities
- Moderate or Severe Persistent asthma (National Asthma Education & Prevention)
- Room air desaturation at rest ≤ 85%
- Non-cardiopulmonary disorders that may affect exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis)
- Anemia (Hgb <8 g/dL) on the day of the cardiopulmonary exercise test

5.0 SUBJECT RECRUITMENT

5.1 SUBJECT IDENTIFICATION AND RECRUITMENT

Eligible patients will be identified and recruited at COH from existing databases, referrals and EMR reports, using the inclusion criteria outlined in Section 4.1. Study staff will pre-screen each individual by reviewing the medical charts and will exclude anyone with conditions or reasons that may prohibit study entry. To ensure that participants enrolled on the current study reflect the demographics of all eligible patients, we will recruit patients stratified by key variables (age at recruitment, sex, diagnosis, HCT type [auto/allo]). After preliminary determination of eligibility, the patient's primary physician will be contacted for permission to approach the patient.

5.2 INFORMED CONSENT PROCESS

After identifying a patient, informed consent will be obtained in person or via mail, electronic mail, or other electronic applications (i.e. DocuSign™,) to obtain electronic signatures from each patient per standard practice. At the time of consent, the study will be reviewed with the subject either by a study investigator or clinician or by a specially trained clinical research staff member who will answer any questions that the subject may have prior to signing consent. Informed consent will be obtained from each subject who agrees to participate. The investigational nature and objectives of the study, the procedures involved, and their possible risks and discomforts will be carefully explained while obtaining informed consent. Subjects that agree to participate will be

given a signed copy of the consent form and experimental subjects' bill of rights to keep. The Principal Investigator will be available to speak to the subject in the event that the subject asks a question that the consenter is unable to answer or if the subject requests to speak with the Principal Investigator.

6.0 METHODS

The screening process will begin after the subject signs the informed consent and bill of rights. The research team will review the physical examinations conducted by the participants primary hematologist prior to each CPET to access physical ability. The study participants will be asked a few questions focusing on signs and symptoms outlined in Section 4.2.

Participants who do not pass the screening procedure will be deemed as "screen fail" and will not be enrolled to the study.

Participants that do pass the screening procedure will be enrolled to the study and will complete the following study procedures:

1) Echocardiographic evaluation (Section 6.1)
2) Symptom-limited cardiopulmonary exercise test w/ 12-lead electrocardiography (Section 6.2)
3) Pulmonary function evaluation (Section 6.3)
4) Musculoskeletal ultrasound (Section 6.4)
5) Bioelectrical impedance analysis (BIA) (Section 6.5)
6) Blood draw for CBC and study evaluations (Section 6.6)
7) Functional Testing (Section 6.7)
8) Study questionnaire packet to assess/obtain information on (Section 6.8)
    a. Quality of life (SF-36)
    b. Fatigue (FACIT-fatigue scale)
    c. Exercise (Godin Leisure-Time Exercise Questionnaire)
    d. Demographics, family history, comorbidities, and lifestyle behavior
    e. Activities of Daily Living (ADL)
9) Karnofsky Performance Scale (KFS) (Section 6.9)

All study measurements and assessments do not need be in sequential order nor be completed on the same day. All pre-HCT testing should be performed ≤ 60 days from the start of conditioning therapy. In the case that a participant completes study procedures and their transplant is subsequently delayed, the participant will be asked to repeat the study procedures if the first set of procedures are outside the 60-day window. If repeating study procedures is not feasible based on physician discretion, then we will utilize the most recent set of study procedures for analysis. For subsequent 6M, 1Y and 2Y post-transplant time points study participants will be allowed ±6 weeks from the expected date to complete the time point. In addition, if the participant is physically unable or unwilling to complete all study procedures at the subsequent time points, we will ask

them to complete as many study measurements and assessments listed above as possible. For the post-HCT timepoint, the subjects may be asked to repeat any of the study procedures within that timepoint if the physician determines it is necessary for safety and screening purposes. If the participant tests positive for COVID-19 or has a medical condition that has to be resolved during the ±6 week window, an extension of 4 weeks will be added to the end of the procedure window to allow time for the participant to fully recover and to be compliant with all City of Hope policy and procedures for testing.

Study Calendar:

		Visit 1	Visit 2	Visit 3	Visit 4
	Screening*	Pre-HCT	6 mo Post-HCT	1 yr Post-HCT	2 yr Post-HCT
Sign Consent	X	-	-	-	-
Screening Questions	X	X	X	X	X
Pulse Oximeter Reading		X	X	X	X
Blood Test		X	X	X	X
Echocardiogram		X	X	X	X
Musculoskeletal Ultrasound		X	X	X	X
Bioelectrical Impedance Analysis (BIA)		X	X	X	X
Pulmonary Function Test		X	X	X	X
Electrocardiogram		X	X	X	X
Vitals and Physical Examination**		X	X	X	X
Cardiopulmonary Exercise Test (CPET)****		X***	X	X	X
Functional Testing		X	X	X	X
Questionnaires-Overall health, fatigue and physical activity		X	X	X	X

*Screening procedures may be completed on the same day as Visit 1 Pre-HCT.
** Physical examination will be completed by the patient's primary oncologist.
*** If PI requested, Hemoglobin Test will be done prior to beginning the CPET.
**** If PI requested, any study procedure may be repeated within a timepoint for safety and screening purposes.

6.1 ECHOCARDIOGRAPHIC EVALUATION

We will assess **cardiac function and mechanics** using comprehensive 2D echocardiography with Doppler imaging. Cardiac structure and function will be quantified at rest and peak stress as recommended by the American Society of Echocardiography (ASE).[39,40] For consistency and reproducibility, we will acquire and perform all measurements using an established research protocol. We successfully used this research protocol to evaluate cardiac function in cancer survivors (R01CA196854, R21CA178344 [S. Armenian]) and demonstrated excellent inter-observer correlation (range 0.94–0.97).[41] We will record heart rate, quantify LV volumes in systole and diastole in the apical 4- and 2-chamber views in triplicate using the biplane method of discs to calculate EF, as recommended by the ASE.[42] At rest and peak stress, we will estimate SV using the equation: SV = (LV outflow tract diameter/2)^2 × LV outflow tract velocity time integral (VTI). We will also derive effective arterial elastance (E_a), end-systolic elastance (E_{es}), and E_a/E_{es}. E_a, which is a measure of systemic arterial stiffness, will be estimated as end-systolic pressure (ESP)/SV, and ESP will be estimated as 0.90 x systolic pressure, obtained by blood pressure (BP) cuff at the time of the echo. E_{es} is a measure of LV contractility, and will be derived using a modified single-beat algorithm using BP, SV, pre-ejection and total systolic ejection timing intervals.[43] VA coupling provides insight into chamber efficiency and is also predictive of cardiac dysfunction and will be indexed by the ratio E_a/E_{es}. Quantifying these parameters while concomitantly measuring VO_{2peak} permits dissection of each component of the Fick Equation (VO_{2peak} = AVO_2D X Cardiac Output; Cardiac Output = Heart rate x SV). We will also obtain detailed measures of *LV diastolic function*, including pulsed Doppler measurement of mitral valve inflow, peak velocities of early filling (E-wave) and filling during atrial systole (A-wave), mitral annular myocardial e' and a' velocities, mitral E/A and E/e' ratios, and mitral deceleration time. We will evaluate *peak systolic strain* using commercially available analysis software (EchoPAC vBT08; GE Healthcare, USA). Measurements will include peak longitudinal (global and all LV segments), as well as regional and global circumferential strain.[44] These will be used in secondary analyses to determine their relationships with VO_{2peak}.

6.2 SYMPTOM-LIMITED CARDIOPULMONARY EXERCISE TEST (CPET)

Evaluate peak O_2 consumption (VO_{2peak}) using an electronically braked cycle ergometer with breath-by-breath expired gas analysis. If PI requested, prior to beginning the test for the pre-HCT visit, a member of the study team will check the patients' hemoglobin using the Germaine™ Hb Hemoglobin (Hb) Test System analyzer and blood will be collected via a finger stick. After recording resting metabolic data, participants will begin a 1-minute period of unloaded exercise, followed by a continuous incremental ramp increase of 5-30 W/min until volitional exhaustion or until a symptom limitation is achieved.[6] VO_{2peak} will be defined as the highest VO_2 value for a given 30-second interval within the last 60 seconds of exercise.[45] During exercise, we will monitor O_2 saturation continuously, while blood pressure will be measured using an automated sphygmomanometer.[6] Acceptable test criteria for this assessment will include any of the following: 1) a plateau in O_2 consumption concurrent with increased power output, 2) an RER >1.1, 3) 85% predicted maximal HR is achieved, or 4) peak exercise ventilation approaches or exceeds maximal ventilatory capacity.[6,46] Tests in which these parameters are not achieved will be excluded. VO_{2peak} will be defined as the highest VO_2 value for a given 30-second interval within the last 60 seconds of exercise.[45,46] Gas exchange, HR, and ECG monitoring will continue for 5 minutes of recovery (2 minutes active recovery followed by 3 minutes passive recovery) to permit derivation of exercise recovery patterns that have recently been shown to be highly prognostic in patients with established CVD.[47] This protocol has been demonstrated to be appropriate for

measuring VO_{2peak} in studies of early- and advanced-stage cancer patients,[8,48] and has been successfully implemented in our recent feasibility trial in HCT survivors.[49] Participants will be monitored continuously with an electrocardiogram (ECG) during exercise and recovery.

All COH personnel who administer the test are trained to read exercise ECGs and are trained in Advanced Cardiovascular Life Support.If we observe any ECG abnormalities either prior to, during, or after the exercise test, suggestive of ischemia or malignant arrhythmia, all procedures will be stopped. At this point, a staff cardiologist will review the ECG to determine the appropriate course of action. The participant will not be allowed to leave the facility until such an examination has been performed. We will define severe adverse events (SAEs) as the occurrence of: (1) sustained ventricular tachycardia, (2) myocardial ischemia, (3) syncope, (4) provision of cardiac life support medications, (5) direct admission to emergency room/equivalent, or (6) death. Of note, the reported incidence of SAEs during CPET ranges from 0.001% to 0.01%.[6] Criteria for ischemic changes in ECG will include 0.1 mV deviation of the ST segment horizontal to/away from the baseline isoelectric line at 0.08 seconds after the J-point in the absence of significant resting ST-T abnormalities.

CPET-derived measures to be obtained*:* We will apply an integrative approach that includes (1) assessment of the overall quality of the test, subject effort, and reasons for stopping, (2) tabulation and graphical depiction of the key data to determine whether obtained data is normal or abnormal, with comparison to appropriate reference values,[46] (3) use CPET measures to determine causes of exercise limitation and patterns of exercise response; this will be done by plotting the cardiopulmonary response of each patient using outcomes per established guidelines.[46] The plots will include but are not limited to: 1) VO_2 (x-axis) versus: V_T, f_R, HR, V_{CO2}; V_E/VO_2; P_{ETO2} and P_{ETCO2}; 2) WR (x-axis) versus VO_2; 3) V_E (x-axis) versus WR, VO_2, VCO_2. We will use information obtained from arterial blood gas analysis (e.g. pH, arterial oxygen pressure (PaO_2) and oxygen saturation (SaO_2), alveolar-arterial difference for O_2 pressure ($P[_{A-a}]O_2$), ratio of physiologic dead space to tidal volume (V_D/V_T) to examine efficiency of pulmonary gas exchange, as well as for potential underlying acid-base imbalance.[46]

6.3 PULMONARY FUNCTION EVALUATION

Pulmonary function testing (PFT) will be per American Thoracic Society recommendations.[50,51] Measurements will include spirometry; lung volumes; diffusion capacity; total lung capacity (TLC); forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and FEV_1/FVC ratio; diffusing capacity of the lungs corrected for hemoglobin content (DLCOcorr), and DLCO/volume of air (DL/VA). We will calculate percent of predicted normal values using reference values for adults ≥18y.[50,51] For each patient we will integrate PFT data with measurements of minute ventilation and ventilator efficiency to determine breathing reserve and whether subjects encroach on a pulmonary mechanical limit to exercise.

6.4 MUSCULOSKELETAL ULTRASOUND (US) EVALUATION

Quantification of lower extremity skeletal muscle cross-sectional area (CSA) and volume will be assessed by musculoskeletal ultrasound. The decision to use musculoskeletal ultrasound was founded on concerns regarding the prohibitive costs of magnetic resonance imaging (MRI) for population-based screening, and to remove the radiation exposure from a dual energy x-ray absorptiometry. The skeletal muscle cross-sectional area will be evaluated using an ultrasound machine and probe (GE LOGIQ E, USA). The device will be calibrated prior to each use to ensure accuracy. Additionally, we will use standard of care CT scans obtained as part of pre-HCT

treatment response assessment to retrospectively measure body muscle quantity and quality using a validated software (Data Analysis Facilitation Suite (DAFS).[52]

6.5 BIOELECTRICAL IMPEDANCE ANALYSIS (BIA)

Body composition (total lean body mass and percent body fat) will be measured using bioelectrical impedance analysis (BIA). Participants stand on the bioelectrical impedance scale with bare feet in contact with the electrode foot pads and hands holding the hand electrode. Body weight will be measured by the device followed by body composition. The device will be calibrated prior to each analysis to ensure accuracy. Participants will be asked to remove any wearable metal prior to each assessment. Participants with an implantable defibrillator or pacemaker will not undergo the BIA procedure.

6.6 BIOLOGICAL SAMPLE COLLECTION AND PROCESSING

6.6.1 *Peripheral blood collection*

Peripheral blood collection, processing, and reporting

Approximately 15 mL of peripheral blood will be procured at baseline and during the subsequent 6M, 1Y and 2Y post-transplant time points. Within a timepoint, an additional draw of approximately 15 mL of peripheral blood will be requested if the physician determines it is necessary for safety and screening purposes prior to the CPET. For each study-related lab draw, the following tests will be run in real time: complete blood count (CBC), lipid panel, hemoglobin A1-C, thyroid stimulating hormone (TSH), free thyroxin (T4), luteinizing hormone (LH), follicular stimulating hormone (FSH) and testosterone. We recognize that emerging blood biomarkers of aging (e.g. clonal hematopoiesis, DNA methylation)[53-56] may provide additional insight into the trajectory of cardiovascular aging in these patients. As such, approximately 5 mL of blood will be drawn during each study-related blood collection into a 6-mL lavender-top tube for future correlative and exploratory analyses. Further details below:

To better understand serum markers correlating with cardiotoxicity and/or depletion of CVRD in HCT survivors, we plan to conduct multiomics analysis (e.g. proteomics, metabolomics) of the longitudinally collected plasma samples in this study. De-identified plasma samples of the participants eligible for the analysis will be shipped to the Sapient laboratory (10421 Wateridge Circle, Suite 100, San Diego, CA 92121) for metabolomic profiling and the Pfizer/Azenta Life Sciences laboratory (2910 Fortune Circle West, Suite E, Indianapolis, IN, 46241, USA) for proteomics profiling. The results will be returned to City of Hope and will be analyzed and interpreted to identify novel sensitive serum markers for cardiotoxicity. Leftover samples will be destroyed or returned to City of Hope.

To better understand delayed T-cell immune reconstitution and/or lack of T-cell production correlating with depletion of CVRD and accelerated cardiovascular aging in HCT survivors, we plan to measure T Cell Receptor Excision Circles (TRECs) pre and post-HCT. TRECs are byproducts of the rearrangement of the DNA at the T cell receptor locus, as a result of combining TCR chains (Alpha & beta). In addition to using the TREC multi-step technique in measuring TCR combination, a highly sensitive digital PCR (dPCR) will be used to detect low concentrations of DNA target within a single analysis. Lastly, a newly designed tool combining these 2 metions using 96 TREC prbes labeled with FAM, Cy5, Cy5.5, ATTO590, ROX, or HEX reporter

fluorophores using the Integrated DNA Technologies (IDT) OligoAnalyzer™ 3.1 program and the Bio-Rad QX600 ddPCR recommendations will be used as well.

If sufficient biological material for anything mentioned above is not obtained for any reason, a leftover sample will be requested and obtained from linked study, IRB#00029 Long-term follow-up following Hematopoietic cell transplanation and cellular therapy, if available.

6.6.2 *Blood sample handling, processing and storage*

Immediately after blood collection, the 6-mL lavender-top tube should be inverted 8-10 times to gently mix the blood in EDTA. Study staff will transport the blood within approximately 24 hours of collection at room temperature to the Outcomes Research laboratory for processing and storage. Plasma and buffy coat samples will be prepared by spinning the tube in a balanced centrifuge at 1200 x g for 10-15 min. Plasma is aliquoted into up to 5 study-labeled cryovials with approximately 0.5 mL in each aliquot and the buffy coat will be collected in 1 study-labeled cryovial. If there is not enough plasma to store 0.5 mL in each aliquot, 3 aliquots will contain approximately 0.5 mL and the remaining 2 aliquots will contain approximately 0.25mL. Aliquots will be labeled with study IRB number, study specific participant ID, date of blood draw, “Plasma EDTA” or “Buffy Coat EDTA”, and aliquot number (1-5) using permanent marker or preprinted freezer-ready labels. Samples will be stored in a -80 freezer located in Furth Lab immediately after processing.

6.7 FUNCTIONAL TESTING

6.7.1 30 Second Sit to Stand Test (30STS)

The 30-second sit to stand test is a test that has been used to indicate functional status of patients with cancer, cardiovascular diseases as well as chronic obstructive pulmonary disease patients. It is highly correlated with VO_{2peak} obtained via CPET. This test will be performed with a stable chair that is prevented from sliding backwards. Participants will be instructed to sit in the middle of the chair, with their hands on the opposite shoulders, crossed at the wrists. Participants will be instructed to keep their feet flat on the floor and to keep their back straight, with arms against the chest. On “ready, go” the participants will be asked to rise to a full standing position and then sit back down, repeating this standing-sitting action for as many times as possible in 30 seconds. The number of repetitions of full sit-to-stand motions completed in 30 seconds will be recorded.

6.7.2 2-Minute Step in Place Test (2MSPT)

The 2-minute step in place test is a test that measures aerobic endurance. The participants will be asked to stand up straight next to the wall while a mark is placed on the wall at the level corresponding to midway between the patella (kneecap) and iliac crest (top of the hip bone). The participants then march in place for two minutes, lifting the knees to the height of the mark on the wall. The number of steps in which the participants reach the marked level on the wall in 2 minutes will be recorded.

6.7.3 Timed Up and Go (TUG)

Timed Up and Go is a performance test of physical mobility. The test measures how many seconds it takes an individual to stand up from a standard armchair (approximate seat height of 46 cm), walk a distance of 10 ft, turn, walk back to the chair, and sit down again. The time it takes for participants to perform this test will be recorded.

6.8 STUDY QUESTIONNAIRE PACKET

The questionnaires will be self-administered or administered by the study staff.

6.8.1 ***SF-36*** is a patient-reported outcome measure that quantifies health status and measures health-related quality of life.

6.8.2 ***FACIT-fatigue scale*** is a 13-item instrument designed to assess fatigue/ tiredness and its impact on daily activities and functioning.

6.8.3 ***Godin Leisure-Time Exercise Questionnaire*** will assess physical activity level by asking “During a typical 7-Day period, how many times on average do you do the following kinds of exercise for more than 15 minutes during your free time?”

6.8.4 ***Study-specific questionnaire*** will obtain data on demographics, family history, current medications, lifestyle behaviors (exercise [Godin Leisure-Time Exercise Questionnaire][57], alcohol and tobacco use), and history of other cardiovascular risk factors and other comorbidities (hypertension, diabetes, dyslipidemia, chronic renal disease, thyroid disorder, hypogonadism.

6.8.5 Activities of Daily Living (ADL) is a subscale of the Medical Outcomes Study (MOS) Physical Health. The MOS Physical Health Scale measures a broad range of physical functioning, with questions ranging from “Can you bathe and dress yourself?” to “Can you perform vigorous activities, such as running or lifting heavy objects?” Items are rated on a 3-point Likert scale measuring independence in performing the activity.

6.9 KARNOFSKY PERFORMANCE RATING SCALE (KPS)

KPS is a general measure of patient independence in carrying out normal activities and self-care needs (score: 0-100) and is a global indicator of functional status.

7.0 DATA COLLECTION

Additional data, such as therapeutic exposures and related variables, will be collected through medical record abstraction and gathered by completing a Therapeutic Summary form. Information will be recorded up to the completed 2-year time point or the date of the first relapse post-HCT.

Data may also be obtained from linked studies. Only data variables approved for collection under these linked studies will be obtained. Study linkages are specified under the "Research Site and Linkage to Other Studies" section of the study application.

8.0 HUMAN SUBJECTS ISSUES

8.1 POTENTIAL BENEFITS

Subjects will not receive any additional benefit from participating in the current protocol. The knowledge gained from the current study may be used to develop more comprehensive screening strategies in at-risk populations, as well as assist in the development of novel endpoints to be used in intervention studies to improve cardiovascular reserve capacity.

8.2 POTENTIAL RISKS

The eligibility criteria and screening procedures for the current study have been established to exclude individuals for whom graded exercise testing, echocardiography, pulmonary function testing, and blood collection, and are not appropriate. Next, the primary physician at City of Hope will be contacted to obtain approval to approach their patients and to potentially identify patients who may not be eligible for any other reasons. Finally, in-person assessments will be performed by the study staff to screen/verify participants for cardiovascular or ECG contraindications on a symptom-limited graded exercise test. This multi-gated comprehensive approach should systematically identify and screen out any individual for whom this study is contraindicated.

For the subsequent visits (6M, 1Y, 2Y), study participants will be re-screened to look for any conditions or reasons that may prohibit them from undergoing study diagnostics.

Anticipated (expected) side-effects associated with symptom-limited CPET include (5-10% of individuals)[6,58] fatigue, muscle soreness, joint pain, lower back pain, and leg cramps. Unanticipated but possible side-effects that are rare (0.001%-0.01%),[6,59] *but serious* include: angina, arrhythmias, myocardial ischemia, sudden cardiac death, and cerebrovascular accident. As detailed above, all study participants will be closely monitored by experienced personnel who have received training in ACLS, or Pediatric Advanced Life Support (PALS). Both of these American Heart Association certifications are designed to give you the knowledge, skills, and confidence needed to successfully provide life-saving interventions in emergency situations. If any ECG abnormalities are observed either prior to, during, or after the exercise test, all procedures will be immediately stopped. At this point, the staff cardiologist will be asked to review the ECG to determine the appropriate course of action. The participant will not be allowed to leave the facility until such an examination has been performed by a cardiologist.

Additional protection against risk: Strategies to protect against risk are discussed above (**Potential Risks**), as part of a preemptive strategy to address participant safety. Of note, we previously evaluated the feasibility of CPET, along with resting measures cardiovascular and pulmonary health in twenty (10 allogeneic, 10 autologous) HCT survivors at COH (P30 CA33572, [Project PI: S. Armenian]). Participation rate was 87%, median time from HCT: 9.8 years (range 2-20 years), median age at assessment: 57 years (range 38-75 years), and median Karnofsky Performance: 90 (range 70–100). All participants successfully completed the study tests including CPET, echocardiogram with strain, PFT, neuromuscular and functional assessment (, 30 second sit to stand test, 2 minute step in place test, timed up and go), and patient-reported outcomes (activities of daily living subscale, fatigue, sleep, quality of life*)*. Importantly, there were no adverse events reported during CPET testing, and all studies were considered adequate for interpretation (reached 80% of maximal heart rate and respiratory exchange ratio >1.1 in all participants). We recently completed feasibility testing in 14 additional consecutive patients planning to undergo

HCT; 86% of participants successfully completed *both* baseline (pre-HCT) and 6-month measures outlined in the current study, including arterial blood gas testing.[60] No unanticipated adverse events were reported in our most recent feasibility study.

In order to protect participants from any potential risks associated with the current study, the following assurances will be adhered to: (1) participation is voluntary and consent to participate can be withdrawn at any point within the study without penalty, (2) prospective participants who do not wish to volunteer for the current study will not lose their access to medical services at COH, (3) all participants will be informed of foreseeable benefits and risks, (4) all data collected from participants or via medical chart review will be stored in a secure computer network folder and/or locked file cabinet(s), (5) participants will be informed that they have the right to refuse to continue their participation without penalty if they experience significant emotional discomfort, or for any other personal reason. If significant distress is evident during the course of the study, participants will be encouraged to seek appropriate treatment, and a list of referrals will be provided as needed.

8.3 ALTERNATIVES

The subject may choose not to participate in the study.

8.4 CONFIDENTIALITY

All data collection will remain confidential. All database records require a password in order to access data. Only personnel directly involved with the study will have access to the database. Any paper records will be kept in a secure locked cabinet in an access-controlled building. All study electronic files will be kept in access-controlled files on the COH server. Subject data in published study results will not include personal identifiers.

8.5 FINANCIAL COMPENSATION AND OBLIGATION

There is no charge for participation in this study; all procedures will be covered through grant funding. All study participants will receive a $200 gift card at each time point, which will be provided following completion of study testing procedures. In the event that a participant is asked to repeat study procedures for a specific time point, they will receive an additional $200 as compensation for their time and effort. In addition, if a participant lives more than 30 miles from the Duarte campus they will also receive a $25 gas card to compensate for the distance traveled. The participant may opt out of receiving the financial compensation; however, this option will not be offered to the participant unless he or she requests not to receive any compensation. If the participant is unable or unwilling to complete all study procedures for a time point, but completes at least one of the study procedures listed in Section 6.0, the participant will still receive the study compensation.

8.6 INCLUSION OF WOMEN AND MINORITIES

The study will be open to all individuals meeting the eligibility criteria regardless of gender or ethnicity.

9.0 STATISTICAL CONSIDERATIONS AND POWER CALCULATIONS

9.1 STATISTICAL ANALYSES

We will generate descriptive statistics for participants' demographics (age, sex, race/ethnicity), lifestyle behaviors (physical activity, tobacco use), family history of CVD, and history of cardiovascular risk factors and other comorbidities (hypertension, diabetes, dyslipidemia, chronic renal disease, thyroid disorder, hypogonadism). We will obtain tobacco use history, collect a lipid panel and blood pressure, and calculate the American College of Cardiology/American Heart Association (ACC/AHA) CVD Risk Score for all participants. We will perform analyses to describe pre-HCT and HCT-related therapeutic exposures and complications (e.g. GvHD). We will assess *participation bias* by comparing demographic (age, gender, race/ethnicity) and treatment-related exposures (diagnosis, pre-HCT and HCT-related therapeutic exposures, type of HCT) among participants and non-participants. A two-sided Type I error=0.05 will be used in general; however, a Bonferroni adjustment will be used for testing multiple specific hypotheses in the Aims.

AIM 1: Evaluate cardiovascular reserve capacity, as measured by VO_{2peak}, in HCT survivors.

Our *working hypotheses* are that: **1.1)** there will be distinct trajectories of VO_{2peak} after HCT, as determined by pre-HCT cardiotoxic exposures (≥250 mg/m^2 anthracycline exposure), CV risk profile (≥intermediate risk [ACC/AHA]), HCT conditioning intensity (myeloablative), and post-HCT complications such as GvHD; **1.2)** HCT survivors will have significantly worse VO_{2peak} compared to normative data at all three time points; and **1.3)** VO_{2peak} will be strongly correlated with key domains of HRQOL (SF-36 PF scale), after adjusting for fatigue, demographics (age, sex), and clinical risk factors (HCT type, conditioning intensity, physical activity).

Interpretation of CPET-derived measures: We will apply an integrative approach that includes (1) assessment of the overall quality of the test, subject effort, and reasons for stopping, (2) tabulation and graphical depiction of the key data to determine whether obtained data is normal or abnormal, with comparison to appropriate reference values,[46] (3) use CPET measures to determine causes of exercise limitation and patterns of exercise response; this will be done by plotting the cardiopulmonary response of each patient using outcomes per established guidelines.[46] The plots will include but are not limited to: 1) VO_2 (x-axis) versus: V_T, f_R, HR, V_{CO2}; V_E/VO_2; P_{ETO2} and P_{ETCO2}; 2) WR (x-axis) versus VO_2; 3) V_E (x-axis) versus WR, VO_2, VCO_2. We will use information obtained from arterial blood gas analysis (e.g. pH, arterial oxygen pressure (PaO_2) and oxygen saturation (SaO_2), alveolar-arterial difference for O_2 pressure ($P[_{A-a}]O_2$), ratio of physiologic dead space to tidal volume (V_D/V_T) to examine efficiency of pulmonary gas exchange, as well as for potential underlying acid-base imbalance.[46] These data will be compiled for each patient and correlated with clinical data to generate a comprehensive picture of cardiopulmonary status. Our investigative team has utilized the proposed protocol for numerous CPETs performed in patients with[8,48] and without cancer,[61,62] and has successfully implemented it in our feasibility studies for patients prior to[60] and after HCT.[49]

Analyses: We will calculate descriptive statistics (mean, standard deviation, median, range, quartiles) for CPET-derived measures in all participants and by sex and HCT subtype at each time point: baseline, 6m, 1Y, and 2Y post-HCT. We will determine the percentage of HCT survivors with VO_{2peak} impairment at each of the four time points, Symptom-limited cardiopulmonary exercise testing per established parameters (e.g. VO_{2peak} required for functional independence).[6,63] We will also examine the distribution of VO_{2peak} by sex and HCT subtype and determine the appropriate transformation to normalize the distribution as necessary for

subsequent analyses.

Aim 1.1: Determine the initial VO_{2peak} in patients undergoing HCT and its post-HCT trajectory over time.

Our longitudinal study design will allow us to determine the impact of certain pre-HCT variables (cumulative lifetime anthracycline dose, ACC/AHA CVD score) as well as HCT-related risk factors (myeloablative conditioning, GvHD) on the trajectory of VO_{2peak} shortly after HCT (baseline to 6m) as well as the long-term change after HCT (6m to 1Y, 2Y). Specifically, we will conduct a longitudinal analysis to examine the trajectories of VO_{2peak} by fitting a Generalized Estimating Equation (GEE) model, with VO_{2peak} as the dependent variable and three indicators of time as independent variables. We will also describe time trends parametrically using time since HCT, with a join-point at 6m to connect the baseline and post-HCT time periods. We will primarily use compound symmetry (CS) working covariance matrix to account for within-person correlation over time, but will also examine the use of the autoregressive one [AR(1)] covariance structure. We selected the GEE approach with the empirical sandwich estimator because it has been shown to provide robust parameter estimates under mis-specified correlation structure in repeated measurements.[64] We will examine the effects of selected risk factors on longitudinal trends of VO_{2peak} by including them as main effects and interactions with indicators of time (or time since HCT) to allow for varying effects over time, and testing their significance. Continuous measurements will be treated as such or dichotomized (categorized) appropriately per thresholds for increased risk (e.g. cumulative anthracycline dose ≥ 250 mg/m^2).

We are especially interested in understanding change in VO_{2peak} as it pertains to pre-HCT (anthracycline dose), HCT-related (conditioning, GvHD) exposures, and baseline CV risk profile (ACC/AHA CVD risk) after adjusting for race/ethnicity (non-Hispanic white, Hispanic, African American, other), HCT type (autologous/allogeneic), physical activity level (Godin Questionnaire), and comorbidities (e.g. hypogonadism, thyroid disease, renal dysfunction). We recognize that the expected proportion of individuals varies in each of the four risk categories to be examined (myeloablative conditioning [estimated proportion, 40%]; ≥intermediate risk ACC/AHA [30%]; cumulative anthracycline dose ≥250 mg/m^2 [20%]; acute GvHD [10%]). Therefore, we powered this study to enable identification of factors that affect VO_{2peak} trajectories using a range of proportions (40%–10%).

Power calculations: Aim 1.1 is powered to detect differences between two groups (cumulative anthracycline dose <250 mg/m2 vs. >=250 mg/m2; reduced intensity vs. myeloablative conditioning; no/grade I GvhD vs. grades II-IV GVHD; low vs. intermediate/high ACC/AHA CVD risk) at 2Y post-HCT. Assuming a Type I error=0.0125 (accounting for 4 hypothesis tests, for an overall Type I error=0.05); three time points post-HCT; attrition rates of 20% from pre-HCT to 6m, 14% from 6m to 1Y, and 14% from 1Y to 2Y (a retention rate of 60% at 2Y); and a correlation range of 0.5 to 0.8 for within-person measurements across time,[48,65] 350 HCT survivors at pre-HCT will achieve 80% power to detect an effect size of at least 0.70 at 2Y, given the sample size in group 1 is 10% of the total sample. An effect size of 0.7 is equivalent to an absolute mean difference of 3.5 ml/kg/min for VO_{2peak} between groups, assuming a standard deviation (SD) of 5.0 ml/kg/min.[63,66] A difference in VO_{2peak} of one metabolic equivalent (3.5 ml/min/kg) has been associated with a 10–15% increase in all-cause mortality in the general population,[67,68] and represents a clinically meaningful difference. If the group 1 sample is 20% or 40% of the total sample size, then under the same assumptions, a pre-HCT total sample size of 185 and 153, respectively, will be sufficient to detect an effect size of 0.7 at 2Y. To assess the specific impact

of HCT on the trajectory of VO_{2peak} after HCT, we will compare baseline VO_{2peak} to 6m. Assuming 20% attrition (pre-HCT to 6m), 280 subjects with VO_{2peak} values at both time points, there is 80% power to detect an effect size of 0.17 at Type I error=0.05, assuming a correlation in VO_{2peak} ranging from 0.5 to 0.8.

Aim 1.2: Compare measured VO_{2peak} in HCT survivors at baseline (pre-HCT), six months, one year, and two years after HCT to established age- and sex- normative data.

We will calculate expected VO_{2peak} for each subject using published VO_{2peak} age-specific equations for sedentary men/women [63,66] we will also calculate difference between observed and expected for each person. We will fit a GEE model with indicator variables of time to test whether the mean differences differ significantly from zero at all time points using CS and/or AR(1) working covariance structures to account for within-person correlation across time. If the overall test is significant, we will test if the mean difference at each time point differs from zero using the one-sample t-test to examine the extent to which VO_{2peak} worsens over time.

Power calculations: Assuming equal numbers of men and women, the expected overall normative VO_{2peak} values at baseline, 6m, 1Y, and 2Y are 29.0, 28.6, 28.4, 28.0 ml/kg/min, respectively, with an estimated SD=5.0 ml/kg/min.[63,66] Assuming a Type I error=0.0125 (accounting for 4 hypothesis tests at four time points, for an overall Type I error=0.05), 350 HCT survivors at baseline, 280 at 6m (80% retention), 240 at 1Y (68% retention), and 210 at 2Y (60% retention) will achieve 80% power to detect a significant minimum difference of 0.9, 1.0, 1.1, and 1.2 ml/kg/min at the respective time points, compared to the expected normative values for sedentary men and women using the one-sample t-test. *Longitudinal trend over time*: With these sample sizes, assuming a correlation of 0.5 to 0.8 between two time points, we will have 80% power to detect a significant minimum reduction in mean VO_{2peak} of 0.8 to 1.3 ml/kg/min between pre-HCT and 6m, 0.9 to 1.4 ml/kg/min between 6m and 1Y, and 0.9 to 1.5 ml/kg/min between 1Y and 2Y, using the two-sample paired t-test at Type I error of 0.017 (accounting for 3 tests [6m *vs* pre-HCT; 1Y *vs* 6m; 2Y *vs* 1Y], for an overall Type I error=0.05).

Aim 1.3: Define the association between VO_{2peak} and self-reported HRQOL at baseline and over time.

We will measure patient-reported outcomes and correlate them with VO_{2peak} at baseline and at 6m, 1Y, and 2Y post-HCT. We will collect patient-reported HRQOL, using the SF-36 PF scale, specifically, to assess activity limitation.[69] The PF scale is composed of 10 items encompassing a hierarchical range of difficulties. Each item is scored (1–3) on the basis of the limitations perceived by surveyed individuals, and total score is derived via summation of responses. This scale has good internal consistency (Cronbach $\alpha \geq 0.81$),[69] and has been used as a "stand-alone" instrument in research describing activity limitation in HCT survivors[70] and patients with CVD.[71] *Fatigue* will be assessed using the FACIT-fatigue scale for assessment of fatigue in cancer patients.[72]Initially, we will use multivariable linear regression to examine the association between VO_{2peak} and SF-36 PF cross-sectionally at baseline, 6m, 1Y, and 2Y. We will treat VO_{2peak} as the independent and PF as the dependent variable, and adjust for potential confounding variables such as age, sex, race/ethnicity, body mass index (BMI), physical activity level, fatigue, and tobacco use. We will evaluate the effect of VO_{2peak} on PF by estimating the regression coefficient and testing its significance. We will also calculate the change in VO_{2peak} and change in PF from baseline to 6m, 6m to 1Y, 1Y to 2Y, as well as from baseline to 2Y. A positive difference indicates a decline in values over time. For each time-pair difference, we will use multivariable linear

regression to assess the relationship between the difference in VO_{2peak} levels, treated as independent variable, and the difference in PF scores, treated as dependent variable, adjusted for covariates. The significance of the relationships will be evaluated for each time-pair comparison. Finally, we will use GEE analysis to examine the relationship between VO_{2peak} and PF longitudinally. We will model PF using three indicator variables of time, adjusted for covariates, and test the significance of VO_{2peak} as an independent variable.

Power calculations: With sample sizes of 350 (baseline), 280 (6m), 240 (Y1), and 210 (Y2), in multivariate regression, we will have 80% power to show a significant correlation (r) between VO_{2peak} and PF ranging: 0.14-0.17 at baseline, 0.14-0.17 at 6m, 0.17-0.20 at Y1, 0.17-0.22 at Y2 (**Table 6**), assuming a Type I error=0.0125 (accounting for 4 tests, Type I error=0.05) and that the covariates in the regression model have a square of the partial correlation coefficient (r^2) of 0.1-0.4 with VO_{2peak}.

Aim 1 Anticipated results, potential pitfalls, and alternative approaches: We anticipate that the trajectory of VO_{2peak} will differ by subgroups, with a significant difference between survivors treated with high-dose anthracyclines or myeloablative conditioning, or having high ACC/AHA CVD risk scores or grades II-IV acute GvHD, when compared to HCT survivors without these exposures or conditions. These differences will be clinically meaningful, and will inform future strategies for risk-based screening. Overall, HCT survivors will have significantly lower mean VO_{2peak} when compared to age- and sex-predicted normative data at each of the assessment time points, and there will be a strong correlation between VO_{2peak} and self-reported PF, after accounting for age, sex, race/ethnicity, BMI, physical activity level, tobacco use, and fatigue.

Attrition during the study period: Given our previous experiences with longitudinal studies in HCT patients,[73-75] we anticipate ~20% attrition per year. This takes into consideration patient death, recurrence of malignancy, illness, or loss to follow-up. Note, our recent longitudinal study included comprehensive neurocognitive function testing (3–4 hours), brain MRI (1–2 hours), and HRQOL questionnaires at baseline, 6m, 1Y, and 2Y post-HCT.[75] At the 2Y time point, 268 out of 429 (63%) participants who underwent baseline (pre-HCT) testing completed all study time points.[75] HCT recipients who completed testing at all time points did not differ from those who did not complete testing at one or more time points by HCT type (autologous vs. allogeneic, p=0.78), age at HCT (p=0.10), gender (p=0.06), race/ethnicity (p=0.42), or household income (p=0.21).[75] That said, we acknowledge that there may be differential loss to follow-up according to participant attributes and prognosis, which may contribute to selection or participation bias and/or survival bias. To minimize participation bias we will incorporate many of the strategies (e.g. reminder phone calls, minimizing multiple visits) that we have successfully used to maintain excellent participation rates in our studies to date. Attrition will be monitored in real time, allowing us to address obstacles in a timely manner. Differential loss to follow-up due to prognosis, death, and missing data, which could potentially invalidate the results, will be addressed using the methods of pattern mixture models (PMM)[76] and multiple imputation (MI) (below).

Selection of appropriate VO_{2peak} normative data: We will derive expected VO_{2peak} using age-specific equations for sedentary men/women[63,66], a strategy successfully used in patients with breast[8,9,77] and lung[59,78,79] cancer. Alternatively, we will compare our CPET-obtained results to those from the ongoing Framingham Heart Study Offspring Cohort in which ~3,500 individuals are undergoing CPET (PI: G Lewis). There is no normative data for patients with hematologic malignancies who have not undergone HCT, limiting our ability to directly compare cardiovascular reserve in our patients to conventionally treated cancer patients. However, each participant will

have a baseline (pre-HCT) VO_{2peak} to which post-HCT VO_{2peak} will be compared, allowing us to examine change in trajectory over time by multiple risk factors, including pre-HCT and HCT-specific exposures.

Interpretation of VO_{2peak}: We acknowledge that certain study participants will not meet the criteria for maximum effort on which the interpretation of VO_{2peak} depends. In these individuals, we will work in conjunction with the investigative team to determine indices of cardiorespiratory fitness that are independent of volitional effort but highly correlated with peak VO_{2peak}, such as O_2 uptake efficiency slope. We will also adjust for RER to account for differences in volitional effort, while providing standardized encouragement. Additionally, we recognize that CPET measurements obtained prior to HCT may not reflect the true physiologic baseline of study participants, as some will still be recovering from salvage therapy for relapsed/refractory disease. Nevertheless, we believe the measures obtained prior to and shortly after HCT may provide important information regarding the effect of HCT on cardiovascular reserve capacity, independent of pre-HCT treatment exposures. This would in turn facilitate the development of primary preventions (e.g. consideration of alternatives to HCT or reduction of conditioning intensity) in patients deemed to be at highest risk *prior* to HCT. Of note, the current study is powered to examine three trajectories of VO_{2peak} (pre-HCT to 6m; 6m to 2y; and pre-HCT to 2y), which would allow us to examine change in VO_{2peak} across different physiologic baselines over time.

AIM 2: Define the determinants of VO_{2peak} impairment in HCT survivors.

As discussed previously, VO_{2peak} represents the integrative efficiency with which O_2 is delivered to tissues for ATP synthesis. O_2 delivery and utilization are in turn determined by a series of steps akin to a bucket brigade, which transport O_2 from the mouth to respiring mitochondria in the muscle. The main steps in this O_2 cascade include alveolar ventilation, diffusion from alveolar gas into pulmonary capillary blood and loading onto hemoglobin, convective transport by the heart (cardiac output) and vasculature, and diffusion into skeletal muscle. We will use measures obtained from CPET along with advanced organ-specific imaging and functioning studies to deconstruct the O_2 cascade in patients at baseline, 6m, 1Y, and 2Y post-HCT. Our *working hypothesis* is that cardiac systolic function, pulmonary diffusion capacity, and lean muscle mass will be important contributors to VO_{2peak}, and that comprehensive interrogation of determinants of VO_{2peak} will provide both quantitative and qualitative information for the development of interventions to improve VO_{2peak} after HCT.

We will use GEE and generalized linear models (GLM) to examine the relationship between VO_{2peak} and measures of: a) *cardiac* (LV function/ contractility [systolic, diastolic, cardiac output, strain], ventricular-arterial (VA) coupling, arterial elastance); b) *pulmonary* (obstructive, restrictive lung disease, diffusion capacity); c) *musculoskeletal* (body composition [% lean muscle mass], muscle quality,, 30 second sit to stand test, timed up and go); and d) *hematologic* function, adjusting for potential confounding variables (e.g. age, sex) and time since HCT.

Analyses: We will assess the influence of the variables considered in each of the physiologic domains (pulmonary, cardiac, hematologic/vascular, and musculoskeletal) on the variability in VO_{2peak} by initially using GLM at each time point to estimate their relationship with VO_{2peak}, adjusted for potential confounding variables (e.g. age, sex, physical activity, CV risk factors). For each physiologic domain, measures will be examined individually in GLM, adjusted for

confounding factors, to identify those that are significantly associated with VO_{2peak}, using Type I error=0.05. Linear and quadratic terms (and higher order as appropriate) of continuous variables will be considered. The identified measures will then be examined together in multiple regression to identify those that are independently significantly associated with VO_{2peak} within the domain. All measures thus identified across domains will be considered simultaneously in step-wise multiple regression to determine the independently significant variables associated with VO_{2peak}. Step-wise regression was selected because want to obtain an unbiased estimate of the effects of specific organ-function measures on VO_{2peak}, and examine the strength of their relationship (e.g. using r^2) with VO_{2peak}, with an emphasis on explanatory analysis. Since the dynamics of organ-function measures may change with time, evaluating the relationship by time point could uncover varying relationships with VO_{2peak}. We will use r^2 of the measures included in the multivariate models to assess the percent of variance in VO_{2peak} explained by each variable, holding other measures constant.

We will also use GEE to fit a *longitudinal model* of VO_{2peak} with time since HCT, using CS and/or AR(1) working covariance matrix, adjusted for clinically relevant variables, to identify variables in the four physiologic domains significantly associated with VO_{2peak}. The univariate and multivariate approaches described above for cross-sectional analysis will be applied. Longitudinal (or repeated measures) equivalent of r^2 between VO_{2peak} and each variable of interest can be calculated using the formula $R_k = (Z_k/\sqrt{N})/\sqrt{(1+Z_k^2/N)}$, where Z_k = Wald statistic for the k^{th} variable estimated from the GEE analysis and N = total number of subjects.[80] The magnitude of R_k can inform the relative importance of the variables in the model. We will also compute the repeated measures equivalent of the coefficient of determination R^2 (the percent of total variation explained by all the variables in the model).[80] By computing R^2 with successive inclusion of each variable in the model, one can see the incremental change in R^2 due to that variable, thus informing the relative importance of that variable in explaining the total variation in VO_{2peak}. This approach has been successfully used to gain insight into phenotypically heterogeneous cardiopulmonary conditions,[81-83] optimizing their screening and management.

Power calculations: Sample sizes of 350 (baseline/pre-HCT) and 280 (6m) will provide 80% power at Type I error=0.05 to detect a correlation (r) of 0.10 to 0.14 between VO_{2peak} and a variable of interest when adjusted for additional covariates in the model, with r^2 ranging from 0.05 to 0.5. A sample size of 240 at 1Y post-HCT will enable detection of an r of 0.14 to 0.17, and a sample size of 210 at 2Y post-HCT will enable detection of an r of 0.14 to 0.20, for the same assumptions made for pre-HCT.

Missing data will be addressed by applying PMM[76] and MI.[84] Non-ignorable missing data from death or study dropout could potentially invalidate GEE results. We will define three missing-data patterns based on survival and study completion status: 1) deceased before 2Y (deceased/non-completer), 2) alive at 2Y but dropped out before 2Y (alive/non-completer), and 3) alive and participated at 2Y (alive/completer). Pattern 1 has missing data at all time points after death, with possible intermittent missingness prior to death. Pattern 2 has missing data at 2Y, with possible intermittent missingness prior to 2Y. Pattern 3 has non-missing data at 2Y, with possible intermittent missingness prior to 2Y. Intermittent missing data will be multiply imputed (e.g. 20 times) to generate monotone missing-data patterns (i.e. missing data occurring only at consecutive time points for which patients were alive).[76] For each resulting MI data set, the data at preceding time points will then be used in the regression method for MI to singly impute the missing data at subsequent consecutive time points for which the patients were alive but did not

participate. We will use the three missing-data patterns as stratification factors in the PMM analysis of the MI data sets using GEE to assess the effects of missing-data patterns on the estimated exposure factors using Rubin's rule.[84] We will include interactions between strata indicators and parameters of exposure factor effects in the GEE model. A significant interaction indicates that treatment effects vary by missing-data patterns and that they should be reported by pattern/strata. We will also calculate an averaged exposure effect (over missing-data patterns) to examine the overall effects.

10.0 DATA SAFETY AND MONITORING

10.1 DEFINITION OF RISK LEVEL

This is a Risk Level 2 study, as defined in the "City of Hope Data and Safety Monitoring Plan", City of Hope Institutional Data and Safety Monitoring Plan [policy effective date: 08/23/17], because it involves obtaining blood samples, undergoing CPET, echocardiography, and pulmonary function testing, where the risk of harm is low.

The study team has previous experience conducting similar research studies namely IRB15073 Assessment of cardiovascular reserve capacity in hematopoietic cell transplant survivors: a pilot feasibility study. There were no serious adverse events during CPET, which is important, since CPET requires exercise to symptom limitation (volitional exhaustion).[49]

10.2 MONITORING AND PERSONNEL RESPONSIBLE FOR MONITORING

The Principal Investigator (PI) is responsible for monitoring protocol conduct and reporting to the City of Hope (COH) Data and Safety Monitoring Committee (DSMC) and Institutional Review Board (IRB) as indicated in the sections below.

10.3 UNANTICIPATED PROBLEMS (UP) INVOLVING RISKS TO SUBJECTS OR OTHERS

An unanticipated problem is any incident, experience or outcome that **meets all three** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures that are described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**

2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the procedures involved in the research); **AND**

3. Suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Any UP that occurs during the study conduct will be reported to the DSMC and IRB in accordance with the City of Hope's Institutional policy [policy effective date: 05/14/14] using the electronic submission system, iRIS.

10.4 DEVIATIONS

A deviation is a divergence from a specific element of a protocol and that occurred without prior IRB approval. Deviations from the approved protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. A Corrective and Preventative Action (CAPA) plan should be developed by the study staff and implemented promptly to avoid similar issues in the future. All deviations from the protocol must be documented in study source documents and promptly reported to the DSMC and IRB.

10.5 REPORTING DEVIATIONS

Investigators may deviate from the protocol to eliminate immediate hazards for the protection, safety, and well-being of the study subjects without prior IRB approval. For any such deviation, the PI will notify the DSMC and IRB, within 5 calendar days of its occurrence by electronic submission of a Deviation Notice via iRIS.

10.6 PLANNED PROTOCOL DEVIATION (PPD AMENDMENT REQUEST

Deviations from the written protocol that are not done to eliminate an immediate hazard(s) for the protection, safety and well-being of study subjects but may increase risk and/or alter the protocol integrity require prior IRB approval. The deviation is submitted as a Planned Protocol Deviated (PPD) amendment request. An IRB approved PPD does not need to be submitted as a protocol deviation to the DSMC. The PPD should be submitted according to the IRB guidelines and COH Institutional Deviation Policy [policy effective date: 11/02/11] and submitted via iRIS.

A deviation that is not an PPD (i.e., discovered after the occurrence) must be reported to the COH DSMC and IRB according to the COH Institutional Deviation Policy [policy effective date: 11/02/11] and submitted via iRIS.

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