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Version 2.2

Title: REBOUND: REsiliency in older adults UNDergoing BOne marrow transplant - A pilot study of resiliency measures in older patients undergoing allogeneic blood and marrow transplant

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Schema

Prior to D-6

Pre-BMT Assessments

Study Assessments



Day -6 to -1

Non-myeloablative stem cell conditioning
(fludarabine, cyclophosphamide, total body irradiation)



Day 0

Allogeneic T-cell replete stem cell infusion



Day +3-60

GVHD prophylaxis
(cyclophosphamide Day 3,4
MMF Day 5-35
Calcineurin Inhibitor Day 5-60)

Collection of research data
Study Assessments on Day 30



Day 60

Disease Assessment, GVHD, chimerism



Day 180

Disease Assessment
Study Assessments

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1. OBJECTIVES

1.1 Primary Objective

- 1.1.1 To pilot test candidate indicators of physical resiliency to include static and dynamic, as well as global and stressor-specific, measures.

1.2 Secondary Objectives

- 1.2.1 For each indicator, to gather data on feasibility, reliability, and biological mechanism, and for the collection of indicators, to explore construct validity.

2. BACKGROUND

2.1 Study Diseases

Allogeneic blood and marrow transplantation (alloBMT) is the only potentially curative therapy for many forms of leukemia, lymphoma, and other hematologic malignancies. As with many forms of cancer, many of the most common indications for alloBMT (including but not limited to acute myelogenous leukemia [AML], myelodysplastic syndrome [MDS], non-Hodgkins lymphoma [NHL]) disproportionately affect older people. Although treatments have improved for older adults undergoing therapies for these diseases, the outcomes are variable and there is little biological knowledge to help identify specific factors that would predict why some people do well with treatment and others develop functional and cognitive decline and other adverse health outcomes.

2.2 Rationale

Conceptualization of Resiliency to Physical Stressors: Resilience is defined as the dynamic ability to maintain or recover appropriate function in response to a stressor. Although much recent attention has been given to this area of investigation, minimal progress has been made in part because of the lack of a viable framework from which to study resiliency to physical stressors. In order to meet the goals of this study, we have built on our long-standing investigations into complex dynamical systems in older adults. Within this framework, we define resilience as the capacity of an organism to absorb significant shocks (stressors) and respond so as to still retain the same function and structure. Said intuitively, resilience is the capacity to change in order to maintain the same identity, i.e. “to bend rather than break”. In the language of dynamical systems, resiliency is the capacity to retain the same control parameters. The greater the residual impacts of a stressor, in terms of long-lasting physiological changes, the less resilient the biological system with regards to that particular stressor. Thus, resilience is a dynamical property not only of the biological system but also depends upon the type and intensity of the stressor: An individual may be resilient to chemotherapy but vulnerable to infections. We hypothesize that resilience can be identified through identification of pre-existing determinants as well as phenotypic, physiologic, and molecular signatures of resiliency related to outcomes after a physical stressor. The figure displays the conceptual framework from which we have developed our approach. Here, pre-existing determinants provide a baseline for organismal resiliency, and physical stressors influence phenotypic, physiological, and molecular processes within these domains which in sum drive resilient or non-resilient outcomes. Our prior work in

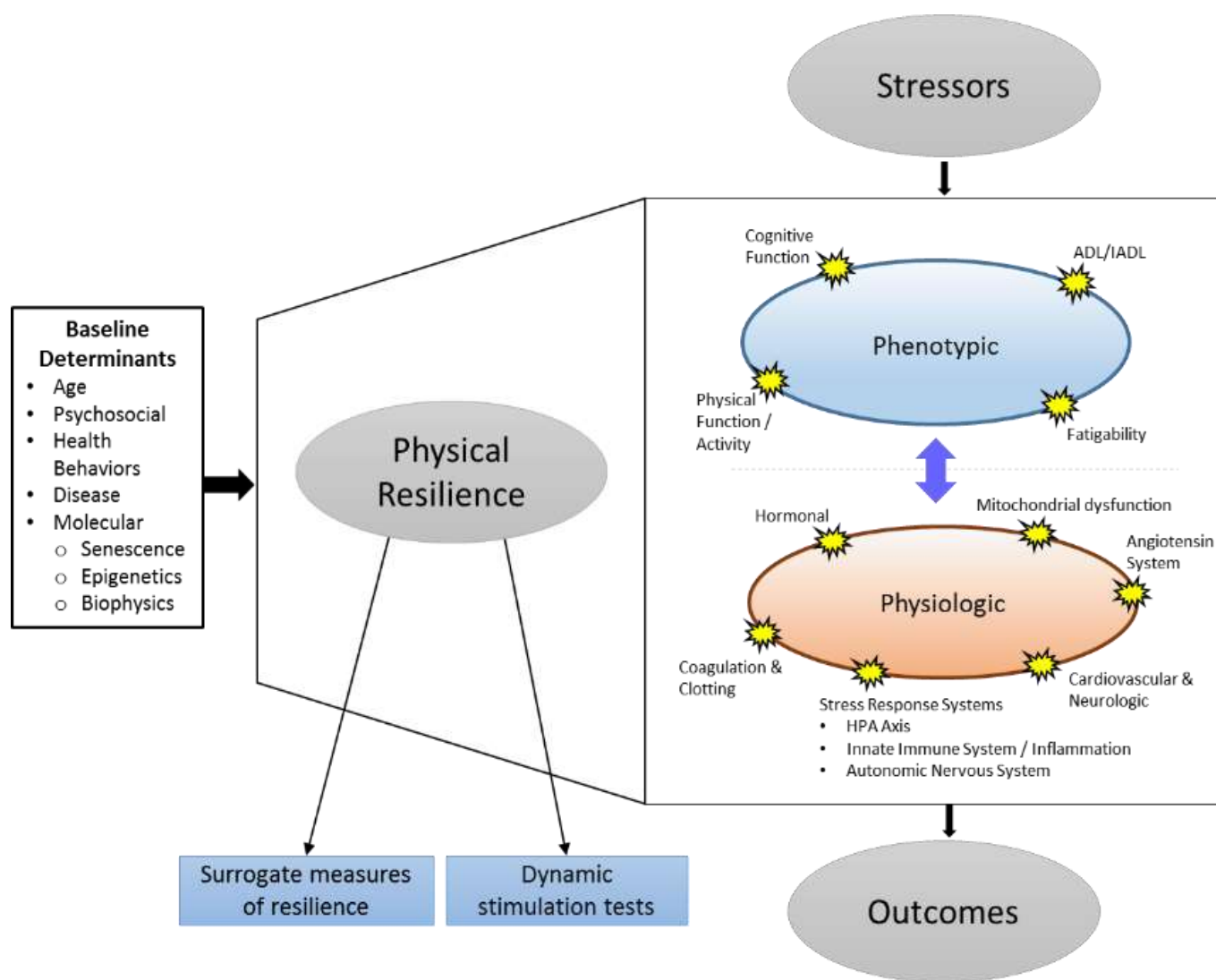


Figure 1: Conceptual framework of resilience

measurement within these domains, especially dynamic physiological measures related to stress response systems, has greatly informed sub-domains (figure 1) hypothesized to drive resiliency and provide an organizational framework for the measures proposed in this study.

Prior Work as Rationale for Approach and Measures: Our research team has performed a series of stimulation tests of stress response systems and evaluated dynamical responses in human subjects. We have long focused on developing study designs and modeling approaches for characterizing the physiology underlying the loss of global robustness and resilience in connection with our work on the geriatric syndrome of frailty[1-3]. Our group conceptualized frailty as “a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes”[1]. We have characterized and refined numerous “static” physiological measures in conjunction with frailty: nonlinear multisystem dysregulation[4]; allostatic load[5]; resting metabolic rate[6]; insulin resistance and inflammation[7]; coagulation and inflammation[3];

hormonal deficiencies[8]; white blood cells[9]. Moreover we were the first to propose the classical dynamical systems approach to the study of stimulation tests to characterize the loss of global resilience associated with frailty[10]. This framework was deployed in a series of hallmark studies of physiological stimulation tests in participants aged 83-92 years in the Women's Health and Aging Studies. These included: oral glucose tolerance test to evaluate glucose metabolism[11, 12], ACTH stimulation test for HPA axis, magnetic resonance spectroscopy for studying muscle energetics, and characterizing immune response to influenza vaccination. In addition, we have also utilized a variety of autonomous (unstimulated) dynamical response data to examine the physiology of impaired global resilience: diurnal cycle of cortisol[13], control of autonomic nervous system and complexity of heart rate variability[13, 14], and inflammatory signaling[15].

This body of knowledge supports our hypothesis that stress response systems lie at the center of physiology that either promotes resilience when functioning optimally, or prevents rapid recovery after stressors when damaged or senescent. These systems can be measured through obtaining levels of inflammatory molecules, hormones, autonomic nervous system tone, energy metabolism, cellular composition and function, as well as higher level organ function. Resilience may be defined as an ability to restore optimal function of these systems after encountering a stress. Finally, because age is so crucial to declines in resiliency, we propose to explore important features related to molecular aging in these studies.

2.3 Relevance of Resilience in bone marrow transplantation

Older patients who undergo allogeneic BMT to cure their hematologic malignancy are already a select group: they have largely recovered from the toxicities of induction chemotherapy; their disease has been put into remission; and their organs function well after decades of use. The use of the hematopoietic cell transplantation-specific comorbidity index (HCT-CI), a refinement of the Charleston Comorbidity Index, allows an estimate of non-relapse mortality, and incorporates 15 variables that span the major organ systems. The HCT-CI was developed on a cohort of patients aged 0-70, with few patients older than 60; a score of 0 means no major organ dysfunction, and higher scores indicate more preexisting organ damage. It has been validated in patients older than age 50[16], and in 372 patients aged 60-75 treated between 1998 and 2008 across 19 institutions[17]; in both cases, HCT-CI scores of 0 predicted better overall survival. In the latter study, non-relapse mortality was 8% at 3 years with an HCT-CI score of 0, but 25% with a score of 3 or more.

Transplant outcomes at Johns Hopkins Hospital are superior to this historical data in older patients[18], with 1 year non-relapse mortality of 12% in 271 patients older than age 50. These outcomes are likely related to the use of non-myeloablative conditioning and post-transplant cyclophosphamide for GVHD prophylaxis. Furthermore, while HCT-CI scores greater than 5 seem to predict increased non-relapse mortality, lower scores do not appear to raise this risk appreciably. Data specific to patients older than 65 are sparse. In none of these studies have geriatric assessment measures in domains such as cognition and function been evaluated. Given the low incidence of non-relapse mortality in our older patients, we have a unique opportunity to study the factors that influence not only mortality but function after hematopoietic stem cell transplantation. We aim to be able to counsel patients more specifically about likely outcomes

after transplant.

3. PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Undergoing allogeneic bone marrow transplant at Johns Hopkins Hospital, the indication for which is a hematologic malignancy
- 3.1.2 Age ≥ 60 years
- 3.1.3 Ability to walk without human assistance
- 3.1.4 Enrollment in concomitant clinical research is permitted but not required
- 3.1.5 English-speaking
- 3.1.6 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

- 3.2.1 Unwillingness or inability to return at 6 months after transplantation for repeated evaluation
- 3.2.2 Non-English-speaking

3.3 Inclusion of Women and Minorities

Men and women of all races and ethnicities will be recruited without prejudice, and consistent with the population in our catchment.

4. REGISTRATION PROCEDURES

4.1 Recruitment

Potential participants will be identified during initial consultation for bone marrow transplantation. They will be given a copy of a consent form at this visit, and be asked by their attending physician if they are interested in learning more about the study or it will be sent to them. Research staff will contact the patient by phone to address any questions.

In addition, potential participants may contact the study team directly. This contact may be in the form of telephone, email, etc. Initial discussions regarding study participation may take place by phone, email, etc., and individuals may be provided with the IRB approved consent form and other IRB reviewed and approved materials (e.g., Patient Handout), as applicable.

In all cases, as much time as is needed to consider study participation will be allowed to possible participants; resulting in multiple phone calls, visits, emails, or other communication, as necessary. For individuals who choose to take part, informed consent will happen as per the consent process.

4.2 Screening

- Ensure eligibility: PHI will be retained to justify screen failures, and will be stored under the same secure conditions as all study-related data for the length of the trial.
- Collect registration data [age, diagnosis]

4.3 Obtaining Consent

Those members of the research team (principal investigator, co-investigator, research nurses) who consent patients have been trained in informed consent procedures, are familiar with the protocol, and are listed as a consentor in the application document. Patients are given adequate time and privacy to consider the research study. Before the patient signs the consent, the consentor must be satisfied that the participant understands the information provided, has had an opportunity to discuss the information and ask questions, and is aware that he/she may withdraw from the study at any time. Non-English speaking participants will be unable to participate.

5. TREATMENT

Bone marrow transplantation will be conducted according to our institution's standard of care, or else according to research protocol (if applicable). Decisions regarding clinical care before, during, and after bone marrow transplantation will be the sole responsibility of the subject's attending physician.

6. STUDY PROCEDURES

Study visits that include the performance of assessments in sections 6.1 and 6.2 will occur prior to the start of conditioning chemotherapy and at 1 month and 6 months post-BMT. All dates are +/- 7 days. The initial study visit will take place during standard of care pre-transplant evaluations, which typically span 3-4 days. The post-BMT visits will take place before or after regularly-scheduled BMT follow up. The clinical coordinator will organize the research study measures listed below around necessary clinical studies.

In addition, baseline clinical factors will be collected from the electronic medical record. These data include characteristics of the recipient, donor, disease, disease status and treatment received, HCT-CI and DRI risk assessments, all of which are collected as routine clinical care. We will also utilize many clinical measurements that are taken as part of the pre-transplantation work up and incorporate them into the research database. These measures include all laboratory values, spirometry, echocardiogram, and CT scans.

6.1 Assessment of Physical Function

Both performance-based (e.g. SPPB) and self-reported measures (e.g. mobility, ADL, IADL) will be collected.

- Short Physical Performance Battery (SPPB)[19]: a performance-based assessment comprising 3 tasks: 1) repeated chair stands; 2) standing balance; and 3) a 4-meter usual paced walk in those with and without a walk aid (meters/second [m/s]).

- Instrumental Activities of Daily Living/Activities of Daily Living (IADL/ADL)[20, 21]: used by other studies of the aging population to measure disability in the context of restrictions in ability to carry out daily tasks such as bathing and taking medications. The IADL/ADL involves a series of questions about ability to perform activities of daily living such as bathing, dressing, and walking.
- Accelerometry (Toosizadeh et al., 2017a; Toosizadeh, Joseph, et al., 2016a; Toosizadeh, Mohler, & Najafi, 2015a; Toosizadeh, Mohler, Wendel, & Najafi, 2015b; Toosizadeh, Najafi, et al., 2016b; Toosizadeh, Wendel, Hsu, Zamrini, & Mohler, 2017b): A newly developed validated measure of upper extremity function that can be easily utilized in all stressor populations that involves moving the arm with a wand like device that records the number of movements that an individual makes over a timed period. Accelerometry will be assessed using the Actigraph Link accelerometer, a water-resistant, wrist-worn device that can be worn 24 hours a day (except during swimming), measuring physical activity and sedentary behaviors continuously. Participants will be fitted with the device during pre-transplant evaluations and wear it for 7 consecutive days at three points during the study, once during pre-BMT evaluations, once at day +30 post-BMT, and again at day +180 post-BMT.
- Overnight catecholamines: Subjects will be given a plastic collection jug and urine collection device that fits into the toilet seat to ease collection for female participants. They will be given instructions for at-home overnight urine collection. They will be asked to store the collection jug with urine in refrigerator until submitted. Sample will be delivered to the laboratory for processing, freezing, and future measurement of catecholamines by ICTR core chemistry laboratory.
- Frailty Assessment: We will measure frailty using the Frailty Phenotype instrument, developed by Fried, Walston and colleagues (2001) in the Cardiovascular Health Study, and validated by Bandeen-Roche and colleagues (2006) in the Women's Health and Aging Studies. The frailty assessment measures participants' walking speed and grip strength, and includes questions about exhaustion, physical activity, weight loss. The 4-meter walk is measured at comfortable pace in a normal hallway on a marked course and recorded using stopwatch (2 trials); this will be completed as part of the SPPB (described above). Grip strength is recorded using a handheld dynamometer (3 trials). Standardized self-reported questionnaires will be used to capture exhaustion, physical activity, and weight loss. The algorithm from the Hopkins Frailty Assessment Calculator (<http://hopkinsfrailtyassessment.org/>) will be used to determine a participant's frailty status.
- Pittsburgh Fatigability Scale for Older Adults (PFS) (Glynn et al., 2015): a validated self-report tool that normalizes activities in terms of intensity and duration.
- Fatigability in response to physical demand: a novel measure of perceived fatigability in response to physical demand will be assessed immediately after a slow-paced 5-minute treadmill walk (1.5 mph; 0.67 m/s; 0% grade) using the Borg Rating of Perceived Exertion (RPE) scale (42;43).

6.2 Health History

Self-Report of Health - two item questionnaire on the participant's self-report of their general health, and their current health compared to health one year ago

- Medical History and Diseases/Conditions - Questionnaire of past medical history of diseases and health conditions.
- Health Behaviors Questionnaire - documents current and past health behaviors of each participant, which permits the assessment of overall health
- Hospitalizations, Surgeries, and Falls - Questionnaire with two items on hospitalizations; 9 items (with sub-questions) on surgeries; and 3 items (with sub-questions) on falls.
- Pain Assessment - Overall bodily pain measurements will be taken using 2 questions on pain intensity/frequency and pain-related function/interference
- Anxiety Questionnaire: 8 questions to assess feelings of anxiety; this questionnaire assesses both the presence and severity of anxiety-related feelings.
- Trauma Questionnaire: 6 questions to assess any past experiences of several kinds of traumas. This includes assessment of trauma experienced by the participant and by a close loved one.

6.3 Cognitive function

- The Modified Mini-Mental State Examination (3MS): the best validated measure of global cognitive function (range 0-100; higher scores represent better function) is frequently used in studies of cognition. It captures a broad array of cognitive domains and is easily administered in clinical settings.
- Montreal Cognitive Assessment (MoCA): an alternative to 3MS and measures global cognitive function across the cognitive impairment continuum and is more sensitive to mild cognitive impairment (106). A brief, iPad-based protocol using sensitive component measures from the NIH Toolbox (46;47) will be collected to assess levels of executive inhibitory function (Flanker task; 3 min.), episodic memory (picture sequence test; 7 min.), and processing speed (Pattern Comparison; 3 min.).
- Flanker Inhibitory Control and Attention Test: Measures attention and inhibitory control. Participant focuses on a given stimulus while inhibiting attention to stimuli flanking it.
- Digit Symbol Substitution Test (DSST) - The DSST requires that the participant fill in a series of symbols correctly coded within 90 seconds. In this test the higher the score the better the person's performance.

6.4 Psychosocial measures:

- Coping Self-Efficacy Scale: 11-point Likert scale measures perceived ability to cope effectively with life challenges, has 3 domains (problem-focused coping, stop unpleasant emotions & thoughts, get support)

- Purpose in Life: Subscale of Ryff Psychological Well-being Scales: 7-item Likert type scale (from strongly disagree to strongly agree) Measures sense of direction and perception of purpose for the future
- Meaning in Life Questionnaire (MLQ): Presence of Meaning Subscale (adaptation): 3 items on Likert-type scale measuring perception of meaning and satisfaction with life
- Ten Item Personality Inventory (10 items): 7-point Likert-type scale of disagree to agree with various aspects of personality (e.g. extraverted, enthusiastic), measuring: extraversion, agreeableness, Neuroticism, Openness, Conscientiousness
- Life Orientation Test-Revised (3-items): 5 point Likert scale, assessing optimism
- Loneliness Scale- 3 item: Based on evaluation and factor analysis of Revised UCLA Loneliness Scale; can be administered via telephone, survey or interview
- U.S. comparison of socio-economic status: uses a 10-rung ladder to assess a participant's perception of their status in society, strongly linked to health status^f
- Financial Strain: 2-item measure evaluating difficulty and anxiety about money
- Social Cohesion: 3-item adapted for use in NHATS to accommodate multiple residential settings, rating statements about the community by rate of agreement (e.g. People in your community know each other well. Agree a lot, a little, do not agree)
- Social Isolation/Engagement: 7-item measure evaluating social isolation, participation and engagement in the last week and year including visiting friends/ family, attending religious services and participation in clubs
- Religion/Spirituality: 5-Item measure for use in epidemiological studies regarding spirituality.
- Patient Health Questionnaire (PHQ-8): Measures depressive symptoms in the last 2 weeks, can influence IL-6 levels and self-efficacy indices. Has been successfully used in older adults with chronic disease.
- Adverse Childhood Events (ACE) Scale: 10-item measure of Yes/No style questions assessing childhood abuse and household dysfunction's relationship to leading causes of mortality in adults.
- Perceived Stress Scale: 5-point Likert scale measures the cognitive appraisal and perceptions of stress in life over the last month, used successfully in older adults

6.5 Physiological Indicators

Physiologic, cellular, and molecular markers suspected to be involved in the re-establishment of homeostasis will be collected. Many physiological measures are captured in routine clinical and laboratory assessments. Others were chosen in part because of a previously identified relationship with frailty.

Blood tests will be performed according to the table below. Twenty (20) mL of bone marrow aspirate will be collected during standard of care bone marrow biopsies pretransplant and at day 180 for research as well. These tests will be performed twice: during pre-BMT evaluations, and at 6 months after BMT. The research portion of the blood tests will account for 160 mL of blood during evaluations, and 90mL of blood at the day 180 visit. If a patient has required a red blood cell transfusion in the past week, he or she will not be eligible for the research blood draw portion of the study.

In addition to the phlebotomy required, an MRI will be performed in a subset of 10 subjects in order to characterize cerebral white matter disease and alterations that may contribute to adverse cognitive outcomes after BMT. MRI will be assessed at baseline and six months in a subset of 10 subjects. In brief, sixty-five transverse slices will be acquired with no slice gap and 2.2 mm nominal isotropic resolution. Diffusion weighting will be applied along 96 directions with a b-value of 1,000-3,000 s/mm². Five minimally weighted images will be acquired. MRI data analysis to derive anatomical states and functional connectivity features will be performed using state of the art methods including a segmentation tool.

The MRI will be reviewed by a qualified neuroradiologist in order to screen for clinically relevant findings. These will be reported according to JHH policy. The principle investigator in consultation with the neuroradiologist will talk to the subject if there is an incidental finding. The subject does not have the option to decline information about an incidental finding.

- Salivary cortisol: Subjects will be asked to collect saliva at home at 4 time points (7am, 11am, 4pm, and 11pm) during a single 24 hour period before BMT for a measure of cortisol.
- ACTH Stimulation Test: After the baseline blood draw is taken, 1mcg (low dose) Cosyntropin (synthetic ACTH) will be given intravenously over 1-2 minutes by research nursing staff. Serum samples will be collected at 0 (pre ACTH), 30, and 60 minutes, and cortisol and DHEA levels will be measured in the samples. The test assesses reactivity of HPA axis.
- Oral Glucose Tolerance Test (OGTT): Participants will be asked to fast overnight and will be given the 75 gram glucose oral load after arrival in the ICTR in the form of an orange flavored sweet beverage (Metter et al, Diabetes Care, 2008). Blood draws will occur at 0 (prior to the administration of the glucoal drink as described above), and then again at 30, 60, and 120 minutes after glucose administration (Kalyani, et al, J Gerontol, 2012). Rationale: Older adults with abnormal glucose status may represent a vulnerable subset at high risk for adverse outcomes. Dysregulation in response to glucose challenge may signal a physiologic vulnerability associated with a lack of resiliency.
- Holter monitor: A myPatch Holter recorder, a small, lightweight digital device that records and stores electrocardiogram on a continuous basis, will be placed on the subject at the beginning of the visit and removed at the end of the visit as described below. This will allow us to capture heart rate variability data. The Holter recorder fits into an adhesive backed

patch, like a very large Band-Aid, that will be attached to the middle of the subject chest, just below the collarbone.

After the recorder is removed, at the end of the clinic visit, the datafile from the recorder will be downloaded to a PC. The file will be identifiable only by a unique deidentified ID. The file will be sent to the Washington University School of Medicine in Saint Louis Heart Rate Variability Laboratory where it will be loaded only special Holter scanning software in order to derive measures of heart rate variability and counts of abnormal beats (if any). If any suspected abnormality is seen on the Holter analysis, the PI will be notified of any abnormalities that could impact health, and the subject would be notified and informed to contact their physician.

Bone Marrow Aspirate: Bone marrow aspirate will be studied for clonal hematopoiesis in hematopoietic cells. Bone marrow stromal cells will be studied for structure and function as well.

Table 1: Proposed physiologic studies – Table 1 lists tests we are planning. Most involve a single routine phlebotomy with exceptions listed under "Research":

Part of Routine Clinical Care	Research
<ul style="list-style-type: none"> • Vital signs • ECOG/Karnofsky PS (71,72) • HCT-CI[22] • Complete blood counts and metabolic panels that assess renal and hepatic function • free T4 and TSH, vitamin D3, cholesterol, fibrinogen, D-dimer 	<ul style="list-style-type: none"> • Hormones: IGF-1, free and total testosterone (men), DHEA-S and bioavailable estradiol (women), total ghrelin, 24 hour salivary cortisol, overnight urinary catecholamine • ACTH stimulation test (250_μg cosyntropin) • OGTT[23] • Inflammatory markers <ul style="list-style-type: none"> ○ IFN-γ, IL-10, IL-12p70, IL-1β, IL-2, IL-4, IL-5, and TNF-α • Immune cell phenotype characterization: <ul style="list-style-type: none"> ○ CD3, CD4, CD8, CD28, CD45RA, CCR7, CD56, and CD57, TNFα R1 • Immune cell functional assays • Factor VIII, and tissue plasminogen activator • Holter monitor • Brain MRI

6.6 Definition of Endpoints

One purpose of this pilot study is to understand the relationship between putative markers of resiliency and clinical outcomes after alloBMT. The following are clinical endpoints of interest and their definition.

Our aim in this phase 1 portion of our project is to characterize resilience. Changes in any measure may or may not be clinically meaningful and may not contribute to our understanding of resilience. We are interested in describing, via quantitative methods, homeostatic equilibrium for an entire organism across multiple domains. In the face of a stressor, three responses are possible: a robust phenotype, wherein no perturbation is discernible; a resilient phenotype, where a shock is discernible but the system returns quickly to normal function; and a non-resilient phenotype, wherein the organism does not recover from the shock, and either reaches a new substandard baseline or indeed ceases functioning. Take weight as an example during bone marrow transplant: some patients will maintain their weight through diet and light exercise throughout the transplant; others will lose weight because they are not eating but will gain it back, with the attendant muscle mass; and others will never regain the weight they had pre-transplant. The latter manifests itself as decreased muscle mass and increased frailty.

We will collect clinically meaningful data to characterize resilience of older adults to the stressor

of BMT. These will include: relapse of leukemia, days hospitalized from day 60-365, infectious episodes requiring specific therapy, any stays in rehab or nursing facilities, measures of patient activity (such as independent activities of daily living), and patient wellbeing.

We hypothesize that many indicators of resilience will decrease in the time during and immediately following transplant, but that in the robust and resilient populations, they will return to their pre-transplant baseline at the 6-month visit. By collecting this data, we will be able to look for two types of relationships. First, which indicators of resiliency correlate with more clinically meaningful outcomes of resilience listed before? Second, which pre-stressor characteristics are able to identify patients as being robust, resilient, or not resilient?

6.7 Duration of Follow Up

Subjects will be followed through their 6-month assessment or until death, whichever comes first.

7. CORRELATIVE METHODS

Descriptions of selected correlative assays are recorded here. Other correlative assays are performed either per clinical standard or per widely accepted techniques.

7.1 Ex vivo responses in PBMCs

Isolated PBMCs will be stimulated with phorbolmyristate acetate (PMA) plus ionomycin, lipopolysaccharide (LPS) or CMV antigen peptide pools and cell proliferation. Intracellular cytokine production responses to stimulation will be collected as functional readouts, using methods developed by Dr. Leng's group[9]. Rationale: We hypothesize that immune system functioning is central to stress response physiology, and hence resiliency. The test described here probes stress response in the immune system. We have shown that strong response to LPS stimulation predicts less resilient outcomes.

7.2 Performance of Assessments

Details and time spent on assessments are listed in the table below.

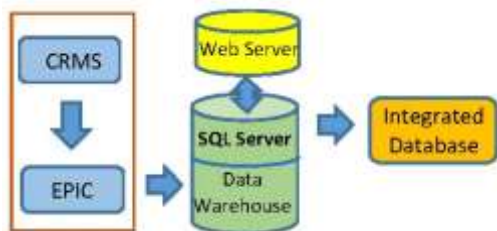
Assessment Measures	Collection Type	Location	Prep + admin time (minutes)
Blood and urine (biomarkers, dynamic ex vivo response of immune cells, physiologic markers)	Blood draw	Weinberg Phlebotomy	5
Adrenocorticotrophic Hormone (ACTH) stimulation	Blood draw, followed by ACTH injection, then 2 nd and 3 rd blood draw	IPOP	60
Fatigability (objective): Slow-paced 5-minute treadmill walk, followed by Borg Rating of Perceived Exertion	Performance test and questionnaire	Onsite	7

Assessment Measures	Collection Type	Location	Prep + admin time (minutes)
SPPB	Performance measure	Onsite	5
MMSE / MOCA / DSST	Questionnaire	Onsite	10
Phenotypic frailty	Standardized assessment	Onsite	10
MRI	Standard	Onsite	60
Oral Glucose Tolerance Test (OGTT)	Blood samples; Glucose load.	Onsite	120
24-hour salivary cortisol profile	Saliva samples	Home	15
Accelerometry	Actigraph Link Wearable technology	Home	10
Psychosocial measures	Questionnaires	Onsite	20
Self-reported: Health; Mobility function	Self-reported questions	Onsite	3
Pittsburgh Fatigability Scale for Older Adults (self-report)	Questionnaire	Onsite	5
ADLs/IADLs	Self-reported function	Onsite	10
			340

8. DATA MANAGEMENT

Management of Study Data – In a complex scenario in which data will be collected in multiple locations and extant data also will be utilized, we must implement systems and procedures to assure the highest standard of data quality, security, confidentiality, coherence and accessibility for analysis. To achieve this, we propose to create a centralized data management system on a dedicated MS SQL server, equipped

Figure 1 Integrated Data Warehouse Architecture.



with warehouse architecture to manage the multi-source origins of our data (Figure 1). Specifically, data integration will be accomplished into four steps: (1) we will use the existing Clinical Research Management System (CRMS) to streamline management of electronic eligibility checklists, eIRB approvals, consent form tracking and subject enrollment; clinical care-relevant data collected by CRMS will be transmitted to EPIC via a real time interface; (2) data extracted from EPIC and CRMS and data from our stressor-specific partners captured using existing systems (e.g., REDCap) will be integrated into the SQL server through the Data Warehouse; (3) a web interface between the SQL server and end users will be built and housed on a web server to facilitate data entry and real-time data reporting; (4) data from different source will then be merged via the SQL server to form an integrated database. Our SQL database will build in features to prevent, detect and correct data entry and omission errors automatically. We will build assurances for data security into our system, for instance, by maintaining audit trails for data changes, implementing role-based authorization rules; restrictive views

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allowing users to access only authorized data with rigorous password protection; encryption to mask personally identifiable data; and transaction logs recording all access. To prevent accidental loss of data we manage, our production system resides on the JHU Department of Medicine (DOM) computer server under a secure and HIPAA compliant environment. The server is managed by DOM IT professionals. Full and incremental data file backup are implemented multiple times daily. Study data will be collected on study-specific encrypted iPads with strong passwords, though no study data will be stored on these devices.

9. STUDY CALENDAR

NB: All dates are \pm 3 days.

	Pre- Study	Pre- BMT	Start of Conditioning through D56	D30	D180
Informed consent	X				
Demographics	X				
Medical history		X			
Physical exam		X	X	X	
Measures in Table 1 (not including MRI)		X			X
Medications		X	X	X	X
Vital Signs		X	X	X	
Performance status (ECOG/Karnofsky)	X	X		X	X
Assessments of Physical Function (section 6.1)		X		X	X
Assessments of Cognitive Function (section 6.3)		X	X ¹	X	X
Psychosocial measures (section 6.4)		X			X
Physiologic measures (section 6.5)		X			X
Flanker Test		X	X ²	X	X
MRI		X			X

- 1— Blood tests will not be performed on Day 30 due to expected anemia.
The flanker test will be performed once a week during days 0-60

10. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

10.1 Study Oversight

Data and safety monitoring will follow SKCCC Data and Safety Monitoring Plan. Additionally, scheduled meetings will take place monthly and will include the protocol principal investigator, research nurse, data manager, and, when appropriate, the collaborators, sub-investigators, and biostatistician involved with the conduct of the protocol.

During these meetings the investigators will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objectives.

The grant will be monitored by an National Institute on Aging (NIA) appointed board. The research governing body for the UH2/UH3 project consists of the leadership of the UH2/UH3 project and NIA staff (one voting member). The research governing body will be chaired by one of the UH2/UH3 PDs/PIs (Jeremy Walston). The research governing body members will meet regularly to review and monitor progress, plan and design research activities, and establish priorities. Meetings may occur as regularly scheduled teleconferences and include at least 1 in-person meeting each year in Bethesda, MD over the course of the UH2/UH3 project period. The PI(s)/PD(s) will be responsible for scheduling the teleconferences and in-person meetings, as well as for preparing concise minutes from teleconferences and in-person meetings. The meeting minutes will be distributed to the NIA Program Office and to research team members within one week of the meeting.

An independent Data and Safety Monitoring Board (DSMB), will be established by the NIA, since the research activities may involve use of novel test measures in vulnerable populations. The DSMB will review research progress and the safety of the study participants based on a safety monitoring plan and report to the NIA Program Office. The DSMB's approval will be required before initiation of the UH2 phase of the project and prior to transition to the UH3 phase. The PD(s)/PI(s) of the UH2/UH3 will assume responsibility for reporting of the DSMB recommendations to their respective Institutional Review Board(s). The NIA DSMB will generate reports concerning observations, deviations, and safety concerns on a yearly basis.

10.2 Protocol Amendments

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB before implementation.

11. STATISTICAL CONSIDERATIONS

Primary Objectives: 1) To generate data to develop the phenotype of resiliency in the face of clinical stressors. 2) To identify indicators of resiliency, including dynamic stimulation tests of

physiologic response.

Note that these two objectives may consist of overlapping data. For example, superior performance *after* transplant on the SBBP may be part of our proposed definition of resiliency that is carried forward to our phase 2 study; superior performance on the SBBP *prior* to transplant may predict a resilient phenotype. The following analyses will be conducted to attempt to describe resilience in this population.

The clinical outcome of interest in this pilot study will be the achievement of pre-transplant functioning. This means that their pre-and post-transplant weight will not differ significantly (within 5% of pre-transplant weight), they will not be hospitalized after engraftment, and they will not experience grade 3-4 adverse events. This composite clinical outcome will be assessed at the 6 month visit. This endpoint is provisional, since the thrust of this project is in fact to characterize resilience.

Objective 1: Please refer to Section 6.5 for a definition of the phenotype of resilience. We will collect clinically meaningful data to characterize resilience of older adults to the stressor of BMT. These will include: survival, relapse of disease, days hospitalized from day 60-180, any grade 3-4 non-hematologic adverse events during the study period, any stays in rehab or nursing facilities, measures of patient activity (such as independent activities of daily living), and patient wellbeing. [Since the study period lasts only until day 180 after transplant, only a minority of patients will have achieved the clinically meaningful endpoints of relapse or death.] The resilient patient will be defined as not having died during transplant, having recovered from major organ toxicities, and having been free of adverse events since the initial period of aplasia. The occurrence of expected events such as graft versus host disease will not be deemed sufficient to categorize a subject as not resilient; rather, the experience of side effects from therapy, or a decrement in function from GVHD, for example, will count against a subject's resilience.

There are two main analyses: (i) to characterize the measures' reliability, change over time, variation and covariation, and (ii) to evaluate univariate (marginal) associations of each measure with the resiliency phenotype. We will consider both measurement properties and strength of univariate associations to select candidate measures of resiliency for the larger, Phase 2 study.

Beginning with (i): Reliability and precision of single measures will be assessed through laboratory standard or published information; by empirical measures such as variance, intra-class correlation, and Kappa statistics; or longitudinally as mean change/variability ratio (in mixed effects models, as the ratio of random effect variability to overall variability). Rates of change in measured outcomes, their heterogeneity, and measures' variability about persons' long-term trends (reliabilities) will be analyzed using mixed-effects (continuous outcomes) and generalized estimating equation (GEE; categorical outcomes) analyses, allowing nonlinearity by polynomials or splines. Extent of association between connected phenotypes (e.g. magnitude of stressors and short- and long-term outcomes) will be considered: Distributions will be visualized using plots to identify proneness to outliers, skewness / need for transformation, and nonlinearity versus linearity of time trends. Analyses will be tailored to the scale of the outcome measure: Binary outcomes (e.g. delirium occurrence) will be characterized by proportions experiencing the event and their extent of association with predictors via logistic and log-linear regression; continuous

outcomes (e.g. usual pace walking speed) by mean and variance estimates and their extent of association with predictors via linear regression; times to events (e.g. falling) by cumulative incidence rates and curves (allowing recurrence / treating death as a competing risk) and their extent of association with predictors via Cox proportional hazards or subdistribution models. Recognizing the small sample size, the number of predictor variables in regression models at any one time will necessarily be restricted to a very few (e.g. age as a key covariate; other hypothesized determinants taken 1-2 at a time; stressor magnitude and interactions of this with single resilience measures). A key analysis will be to explore the relationship between the magnitude of the stressor and the extent of pre-post change. To maximize analytic precision, we will take the ANCOVA approach in which status before and after the stressor are considered as two outcomes in a single regression analysis, and an interaction between “time” (post versus pre) and the stressor magnitude assesses the effect of stressor magnitude on status change.

Objective 2: The second primary objective is to identify short- and long-term physical resiliency indicators, including dynamic stimulation tests of physiologic response. Indicators of resiliency have been previously described in Sections 6.1 – 6.4. We hypothesize that many indicators of resilience will decrease in the time during and immediately following transplant, but that in the robust and resilient populations, they will return to their pre-transplant baseline at the 6-month visit. By collecting this data, we will be able to look for two types of relationships. First, which indicators of resiliency correlate with more clinically meaningful outcomes of resilience listed before? Second, which pre-stressor characteristics are able to identify patients as being robust, resilient, or not resilient?

Here again, there are two types of analyses: (i) exploration of the construct validity of the various resiliency indicators (static and dynamic), taken as a group, for representing a shared construct of resiliency and (ii) univariate associations of static and dynamic indicators with outcomes. For (i), construct validity analyses must be simple due to small sample sizes. We will use multi-trait multi-method (MTMM) matrices which show reliabilities on the diagonal and correlations on the off-diagonal. Here the static measure domains or stimulation tests constitute “traits” and individual measures constitute different “methods.” MTMM analyses should provide guidance for simple summaries, such as averaging, for example, by suggesting sub-domains of particularly highly related measures for scaling. For dynamic stimulus-response indicators, we will follow the approach proposed in Varadhan et al. (2008), where a stimulus-response modeling paradigm was detailed using a dynamical systems approach for deriving summary “parameters” of system functioning. There are five essential elements: (1) stimulation testing to elicit response(s) from the physiological system of interest (e.g., ACTH stimulation of HPA axis), (2) formulation of a mathematical model that describes the response (typically these are differential equations), (3) estimation of model parameters using response data (e.g. maximum likelihood estimation for nonlinear models), (4) model criticism (e.g. goodness of fit, residual diagnostics), and (5) systems identification (determination of model parameters, e.g., amplitude or rate constants, that most clearly distinguish resilient versus non-resilient phenotypes). For (ii), we will evaluate the ability of resiliency measures to predict outcomes, one at a time, using appropriate regression analyses, adjusting for age and stressor severity. Additionally, we aim to build preliminary composites of resiliency indicators and assess these for their effectiveness in predicting outcomes.

11.1 Sample Size/Accrual Rate

This BMT-specific resiliency protocol is part of a larger study across JHMI looking at resiliency during stressors. We plan to recruit $n=35$ participants in total. Conservatively using a sample size of $n=30$ for calculations: This will give us precision of $(0.80s, 1.34s)$ to estimate population standard deviation of a resiliency measure to within 95% confidence, where s is the sample standard deviation. The design allows for the estimation of means to within $\pm 0.36\sigma$ with 95% confidence.

11.2 Subject Disposition

This is not a clinical trial and therefore no treatment failure or removal criteria are specified. As an observational study, data will be collected before and after a planned and clinically-indicated bone marrow transplant. No subjects will be removed from the study after we obtain informed consent unless they expressly request that their measures not be utilized for the study. Even if subjects are lost to follow up or are unable to complete subsequent evaluations due to morbidity or mortality and do not come back for subsequent follow up visits, partial data can be utilized to assess feasibility and/or predictive value of the chosen measures.

12. APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (<i>e.g.</i> , light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

REFERENCES

References

1. Fried, L.P., et al., *Frailty in older adults: evidence for a phenotype*. The journals of gerontology. Series A, Biological sciences and medical sciences, 2001. **56**(3): p. M146-56.
2. Newman, A.B., et al., *Associations of subclinical cardiovascular disease with frailty*. The journals of gerontology. Series A, Biological sciences and medical sciences, 2001. **56**(3): p. M158-66.
3. Walston, J., et al., *Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study*. Archives of internal medicine, 2002. **162**(20): p. 2333-2341.
4. Fried, L.P., et al., *Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment*. The journals of gerontology. Series A, Biological sciences and medical sciences, 2009. **64**(10): p. 1049-1057.
5. Szanton, S.L., et al., *Allostatic load and frailty in the women's health and aging studies*. Biological research for nursing, 2009. **10**(3): p. 248-256.
6. Weiss, C.O., et al., *Resting metabolic rate in old-old women with and without frailty: variability and estimation of energy requirements*. Journal of the American Geriatrics Society, 2012. **60**(9): p. 1695-1700.
7. Barzilay, J.I., et al., *Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study*. Archives of internal medicine, 2007. **167**(7): p. 635-641.
8. Cappola, A.R., Q.-L. Xue, and L.P. Fried, *Multiple hormonal deficiencies in anabolic hormones are found in frail older women: the Women's Health and Aging studies*. The journals of gerontology. Series A, Biological sciences and medical sciences, 2009. **64**(2): p. 243-248.
9. Leng, S.X., et al., *Associations of neutrophil and monocyte counts with frailty in community-dwelling disabled older women: results from the Women's Health and Aging Studies I*. Experimental gerontology, 2009. **44**(8): p. 511-516.
10. Varadhan, R., et al., *Stimulus-response paradigm for characterizing the loss of resilience in homeostatic regulation associated with frailty*. Mechanisms of ageing and development, 2008. **129**(11): p. 666-670.
11. Kalyani, R.R., et al., *Frailty status and altered glucose-insulin dynamics*. The journals of gerontology. Series A, Biological sciences and medical sciences, 2012. **67**(12): p. 1300-1306.
12. Kalyani, R.R., et al., *Frailty status and altered dynamics of circulating energy metabolism hormones after oral glucose in older women*. The journal of nutrition, health & aging, 2012. **16**(8): p. 679-686.
13. Varadhan, R., et al., *Higher levels and blunted diurnal variation of cortisol in frail older women*. The journals of gerontology. Series A, Biological sciences and medical sciences,

2008. **63**(2): p. 190-195.
14. Chaves, P.H.M., et al., *Physiological complexity underlying heart rate dynamics and frailty status in community-dwelling older women*. Journal of the American Geriatrics Society, 2008. **56**(9): p. 1698-1703.
 15. Leng, S., et al., *Total and differential white blood cell counts and their associations with circulating interleukin-6 levels in community-dwelling older women*. The journals of gerontology. Series A, Biological sciences and medical sciences, 2005. **60**(2): p. 195-199.
 16. Keller, J.W., et al., *Hematopoietic cell transplantation comorbidity index (HCT-CI) is predictive of adverse events and overall survival in older allogeneic transplant recipients*. Journal of geriatric oncology, 2014. **5**(3): p. 238-244.
 17. Sorrow, M.L., et al., *Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies*. JAMA, 2011. **306**(17): p. 1874-1883.
 18. Kasamon, Y.L., et al., *Outcomes of Nonmyeloablative HLA-Haploidentical Blood or Marrow Transplantation With High-Dose Post-Transplantation Cyclophosphamide in Older Adults*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2015. **33**(28): p. 3152-3161.
 19. Guralnik, J.M., et al., *A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission*. Journal of gerontology, 1994. **49**(2): p. M85-94.
 20. Katz, S., et al., *STUDIES OF ILLNESS IN THE AGED. THE INDEX OF ADL: A STANDARDIZED MEASURE OF BIOLOGICAL AND PSYCHOSOCIAL FUNCTION*. JAMA, 1963. **185**: p. 914-919.
 21. Lawton, M.P. and E.M. Brody, *Assessment of older people: self-maintaining and instrumental activities of daily living*. The Gerontologist, 1969. **9**(3): p. 179-186.
 22. Sorrow, M.L., et al., *Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT*. Blood, 2005. **106**(8): p. 2912-2919.
 23. Metter, E.J., et al., *Glucose and insulin measurements from the oral glucose tolerance test and mortality prediction*. Diabetes care, 2008. **31**(5): p. 1026-1030.