Fiscal Year:	FY 2017	**Task Last Updated:**	FY 01/24/2018
PI Name:	de Lemos, James Andrew M.D.		
Project Title:	Improving Cardiovascular Risk Prediction		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Cardiovascular Alterations Team		
Joint Agency Name:		**TechPort:**	Yes
Human Research Program Elements:	(1) **ExMC**:Exploration Medical Capabilities		
Human Research Program Risks:	(1) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes (2) **Medical Conditions**:Risk of Adverse Health Outcomes and Decrements in Performance Due to Medical Conditions that occur in Mission, as well as Long Term Health Outcomes Due to Mission Exposures		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:			
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Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Levine, Benjamin M.D. (The University of Texas Southwestern Medical Center) Khera, Amit M.D. (The University of Texas Southwestern Medical Center) Hundley, William M.D. (Wake Forest University Health Sciences) Wang, Thomas M.D. (Vanderbilt University Medical Center) Ballantyne, Christie M.D. (Baylor College of Medicine) Berry, Jarett M.D. (The University of Texas Southwestern Medical Center)		
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Performance Goal Text:

Task Description:

The most likely cause of a non-traumatic life- or mission-threatening medical event in astronauts would be from acute cardiovascular disease (CVD). Current risk prediction models utilize only traditional atherosclerosis risk factors and focus narrowly on coronary heart disease events rather than global cardiovascular risk, ignoring outcomes such as heart failure or atrial fibrillation that could also be potentially mission-threatening. Numerous studies have evaluated novel risk markers in an attempt to improve CVD risk prediction, with several promising imaging and blood-based biomarkers identified. Most of these studies have investigated the incremental predictive value of a single biomarker added to a traditional risk factor model, with a few reporting combinations of biomarkers. Moreover, few studies have evaluated strategies for risk prediction that cross testing modalities. Such a multi-modality approach has the potential to markedly improve CVD risk prediction among potential and existing astronauts, and would have direct relevance to the general population.
Our primary objective was to develop a consortium of biomarker and aerospace medicine leaders, with expertise in multiple different testing modalities, and with access to robust existing databases, to identify and validate novel strategies to enhance global CVD risk prediction over two time windows: 1) 10-20 years, representing the full career of the astronaut and 2) 2-5 years, representing the planning and operational phase of a manned mission to Mars. The team included many of the leading biomarker and imaging experts in the U.S. This team of collaborative investigators accessed data from multiple existing cohort studies to develop two distinct multi-modality risk prediction tools, one based on 10-year global CVD risk (Aim 2) and one based on 3-year CVD risk (Aim 3). These models evaluated novel testing modalities on top of standard risk factors, including coronary calcium (a measure of the extent of coronary atherosclerosis), multiple blood based protein biomarkers that reflect inflammation, cardiac injury, and cardiac stress, as well as ECG measurements of cardiac hypertrophy and imaging-based assessments of cardiac function. Finally, we proposed an exploratory aim to work with NASA researchers in the Human Research Program to explore the feasibility of transforming the Longitudinal Study of Astronaut Health (LSAH) into a prospective state-of-the-art cohort study of the astronaut corps.

The grant had 2 scientific aims (Aims 2 and 3). Aim 2 has been completed ahead of schedule with a major manuscript published, and Aim 3 analyses are ongoing with promising preliminary results. The primary scientific aims of the grant required pooling of data from large cohort studies. Each of these studies has a unique regulatory structure, scientific proposal system, and approval process. The goals of the first year of funding were to obtain the necessary approvals and data transfer agreements to being the data pooling process. This was accomplished during the first year, when we obtained approval for data transfer from the Dallas Heart Study (DHS), Multiethnic Study of Atherosclerosis (MESA), Atherosclerosis Risk in Communities (ARIC), and the Framingham Heart Study (FHS).

The goal for the second year of funding was to secure data transfer, and to perform harmonization of data elements. This goal was successful accomplished by the end of 2015, ahead of schedule. We then moved to analyses for Aim 2 of the grant. We derived in MESA and validation in DHS a multimodality risk prediction tool that led to marked improvement over traditional risk prediction algorithms both for predicting 10 year atherosclerotic risk as well as global and cause-specific CVD risk. Five screening tests (coronary calcium screening by CT, left ventricular hypertrophy by ECG, and elevated levels of NT-proBNP, hs-cTnT, and hs-CRP) markedly improved global CVD risk prediction compared with standard risk assessment strategies. We created a simple score, consisting of the number of abnormal CVD screening tests. In both MESA and DHS a > 25-fold gradient of risk for CVD was seen across the range of scores. Of particular relevance for NASA, participants with zero abnormal tests results have an extremely low risk for any CVD outcome over 10 years of follow-up. The findings replicate extremely well across the two distinct cohort studies. The final results were presented at the 2017 Human Research Program Investigators Workshop in Galveston, TX, and were published in Circulation in June 2017 (de Lemos et al. A Multimodality Strategy for Cardiovascular Risk Assessment: Performance in Two Population-Based Cohorts. Circulation. 2017; 135:2119-32. PMID: 28360032).

Analyses for Aim 3 are underway presently. These required data pooling due to the smaller number of events over short term follow-up. Preliminary results suggest that the multimodality strategy provides even more robust stratification of short term (3-year) risk compared with the 10-year risk models developed in Aim 2 and recently published.

Aim 4 was an exploratory aim, designed to explore the feasibility of transforming the Longitudinal Study of Astronaut Health into a prospective state-of-the-art cohort study of the astronaut corps. Although several productive discussions were held, we did not resolve whether such an ambitious study is feasible in the future.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

The outcome of this research program will have widespread benefits and Earth based applications. Identifying optimal combinations of biomarkers to improve cardiovascular risk assessment is one of the holy grails of preventive cardiology, as the vast majority of CV deaths continue to occur in individuals NOT previously considered high risk. Because the absolute number of apparently low risk individuals is so large, it is impractical to treat every person with aggressive medical therapy, not just for cost and compliance issues, but because of the possibility of side-effects of even the safest medicines. Therefore refinement of the algorithms to reclassify patients into higher risk categories is essential for optimization of medical management and reduction of morbidity and mortality from cardiovascular disease. Optimizing such scores to include modern biological assessments (biomarkers, advanced imaging, and genomics) will make such risk assessment and personalized therapy even more effective. The primary findings from this research were recently published (de Lemos et al. A Multimodality Strategy for Cardiovascular Risk Assessment: Performance in Two Population-Based Cohorts. Circulation. 2017; 135:2119-32. PMID: 28360032). The study findings provide strong evidence that a simple strategy including the most promising biomarkers from several different testing modalities substantially improves CVD risk prediction among individuals without known CVD. The tests prospectively selected included 12-lead electrocardiography for assessment of left ventricular hypertrophy (ECG-LVH), coronary artery calcium (CAC) measurement by computed tomography to identify subclinical atherosclerosis, and measurement of N-terminal pro-brain natriuretic peptide (a measure of cardiac neurohormonal activation from cardiac stress), high sensitivity cardiac troponin T (a marker of chronic myocardial injury), and high sensitivity C-reactive protein (a marker of inflammation). These tests were selected because they reflect distinct and relevant pathological processes, multiple reports from population-based studies demonstrate independent associations of these measurements with CVD outcomes, and sufficient data exist from which to generate a priori thresholds to define abnormal test results. A simple score including results from these 5 tests markedly improved the ability to identify who will (and will not) develop cardiovascular disease over a 10-year period. A simple application was developed that allows entry of test results and outputs the predicted risk.

All of the tests studied here are now available clinically in the U.S., following the U.S. FDA approved hs-cTnT assay in May

	2017. Thus, the strategy studied and reported is ready for out of the box use by NASA flight surgeons. This strategy would be appropriate for screening of potential astronauts prior to selection as well as periodic (annual for biomarkers and ECG and q 3-5 years for CAC) monitoring while training. The multimodality testing strategy may help to individualize and more efficiently target cardiovascular prevention efforts in primary care. Although current prevention guidelines recommend a risk-based approach only when implementing statin and aspirin therapy, the role for targeting therapy based on risk in primary prevention is likely to expand in the future. The risk models are widely applicable for cardiac screening in primary care clinics or cardiac prevention clinics. The findings from this project will directly inform population screening for CVD, at the same time it provides an approach that is ready immediately for implementation by NASA flight surgeons in selection and monitoring of astronaut candidates.
Task Progress:	Our primary objective was to identify and validate novel strategies to enhance global cardiovascular disease (CVD) risk prediction over two time windows: 1) 10-20 years, representing the full career of the astronaut and 2) 2-5 years, representing the planning and operational phase of a manned mission to Mars. With regard to Aim 1, the biomarker consortium had several teleconferences to 1) provide expert advice regarding a protocol for treating acute MI (myocardial infarction) in Space and 2) provide recommendations for implementing preliminary findings from this project for current astronaut screening strategies. We also had multiple conference calls to discuss protocols for managing a potential myocardial infarction in space. The primary scientific aims of the grant required combining data from large cohort studies. The goals of the first year of funding were to obtain the necessary approvals and data transfer agreements to begin the data pooling process. This was accomplished during the first year, when we obtained approval for data transfer from the Dallas Heart Study, MESA, and ARIC, the Framingham Heart Study. The goal for the second year of funding was to secure data transfer, construct the consolidated database, and perform harmonization of data elements. This goal was successful accomplished by the end of 2015, ahead of schedule. In year 3 we completed the analyses and presented and published the results for Aim 2 of our grant. The findings (described in main results in the Task Description section) demonstrate that 5 screening tests markedly improve global CVD risk prediction compared with standard risk assessment strategies. The findings of this study were published in June 2017 in Circulation (de Lemos et al. Circulation. 2017; 135:2119-32. PMID: 28360032) and have received both scientific and lay media attention. The paper already has an Altmetric Score of 105, placing it in the top 5% of all published articles, and includes reporting from 12 news media outlets. The results of these analyses are of direct relevance not only for astronaut screening but also for population screening in routine clinical practice. The analyses for Aim 3 of the grant are ongoing. Preliminary results are available and demonstrate that the multimodality approach is also of value for 3 year risk prediction. Indeed, the results look even more robust at 3 years than at 10 years. We did not make substantial progress towards Aim 4, which was an exploratory aim designed to explore the feasibility of transforming the Longitudinal Study of Astronaut Health into a prospective state-of-the-art cohort study of the astronaut corps. We held several meetings, including a face to face meeting in Dallas on May 19, 2015, that included Greg Hundley, and LSAH leadership Associate Director/Chief Scientist. A more dedicated approach will be necessary to get this off the ground if it emerges as a priority for NASA.
Bibliography Type:	Description: (Last Updated: 09/05/2020)
Articles in Peer-reviewed Journals	de Lemos JA, Ayers CR, Levine B, deFilippi CR, Wang TJ, Hundley WG, Berry JD, Seliger SL, McGuire DK, Ouyang P, Drazner MH, Budoff M, Greenland P, Ballantyne CM, Khera A. "Multimodality strategy for cardiovascular risk assessment: Performance in 2 population-based cohorts." Circulation. 2017 May 30;135(22):2119-32. Epub 2017 Mar 30. https://doi.org/10.1161/CIRCULATIONAHA.117.027272 ; PubMed PMID: 28360032; PubMed Central PMCID: PMC5486874 , May-2017
Articles in Peer-reviewed Journals	Gore MO, Ayers CR, Khera A, deFilippi CR, Wang TJ, Seliger SL, Nambi V, Selvin E, Berry JD, Hundley WG, Budoff M, Greenland P, Drazner MH, Ballantyne CM, Levine BD, de Lemos JA. "Combining biomarkers and imaging for short-term assessment of cardiovascular disease risk in apparently healthy adults." J Am Heart Assoc. 2020 Aug 4;9(15):e015410. https://doi.org/10.1161/JAHA.119.015410 ; PMID: 32698652 , Aug-2020
Awards	Ballantyne C. (Christie Ballantyne, MD) "Member, Association of University Cardiologists, January 2017." Jan-2017
Awards	de Lemos J. (James de Lemos, MD) "Member, Association of American Physicians, April 2017." Apr-2017
Awards	Wang T. (Thomas Wang, MD) "Member, Association of American Physicians, April 2017." Apr-2017