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Seminar series on Anti-Racism in Data and Analysis

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OBJECTIVES/GOALS: The mission of our new Anti-racism in Data and Analysis seminar series is to provide a forum for researchers to discuss the ways that race and racism show up in data and analysis so that we as scientists may work together to advance racial equity and justice in society. METHODS/STUDY POPULATION: Our CTSA's Biostatistics, Epidemiology, and Research Design (BERD) Program has initiated a seminar series that focuses on the ways that race and racism show up in all phases of the research process. We have hosted guest speakers who have shared their cutting-edge research as well as their reflections on race in research, and have facilitated breakout discussions to provide a forum for researchers to discuss specific questions. Our seminars are intended for practicing clinicians, clinical and population researchers, basic scientists, students, and others. RESULTS/ANTICIPATED RESULTS: We have sponsored three discussion-based seminars and two guest speaker seminars, and have several seminars of each type in the planning stages. We have collaborated with another CTSA to sponsor a discussion-based seminar at their institution, thus outfitting them with the tools to initiate a seminar series of their own. Our seminars have been extremely well attended, attracting researchers from a broad base of departments at our institution, from students to full professors. Feedback has been very positive; complaints cluster around paucity of similar opportunities, and students have asked why such material is not included as a required part of their respective training programs. DISCUSSION/SIGNIFICANCE: Race and racism permeate research, and failure to recognize and address the issues involved perpetuates racism in our society. Researchers want to learn more, but there are few opportunities for them to do so. Our seminar series provides one such forum to researchers at our institution and beyond.

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Senolytic Therapy Transiently Reduces Inflammatory Markers in Primary Blood Mononuclear Cells of Individuals with Early Alzheimer's Disease: Exploring the Conserved Transcriptional Response to Adversity as a Biomarker for Disease State*

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OBJECTIVES/GOALS: Determine if the Conserved Transcriptional Response to Adversity transcriptomic profile established in primary blood mononuclear cells (PBMC) of chronically stress caregivers, is present in individuals with early Alzheimer's disease. Chronic stress is a risk factor for Alzheimer's, and may be an untapped biomarker for disease risk and pathology. METHODS/STUDY POPULATION: To collect preliminary data on the Conserved Transcriptional Response to Adversity profile in individuals with Alzheimer's disease, we were able to utilize primary blood mononuclear cell samples from a small open label pilot study called Senolytic Therapy to Modulate the Progression of Alzheimer's Disease, designed to clear stressed senescent cells. We hypothesized senolytics may beneficially reverse this stress profile. We developed a NanoString assay (measuring 19 inflammatory, 31 type-1 interferon, and 3 antibody synthesis genes) to compare these transcriptomic changes within 4 individuals measured at baseline, post-treatment with an intermittent 12-week senolytic therapy, and at an optional extended post-treatment follow-up time point > 3 months after their post treatment visit. RESULTS/ANTICIPATED RESULTS: There was relative downregulation of expression in transcription in 7 of 19 measured inflammatory genes (FOS, PTGS2, IL8, FOS, Il1b, JUNB, and JUN) in Alzheimer's disease participants after receiving senolytic treatment (baseline vs. post-treatment). This is consistent with a decrease in the inflammatory arm of the Conserved Transcriptional Response to Adversity profile. These differences were not significant between baseline and the extended follow-up, indicative of a transient effect of senolytic. There were no changes in type 1 interferon or antibody synthesis genes. This data provides preliminary evidence for larger controlled studies to further establish this profile in Alzheimer's disease, providing exciting evidence for transcript changes that may be reproducible with senolytic therapy. DISCUSSION/SIGNIFICANCE: Literature relevant to Alzheimer's disease indicates global increases in inflammation paired with deficits in immune response, capturing some genes associated with the Conserved Transcriptional Response to Adversity. This profile may be a useful biomarker for prediction of disease severity or risk of dementia due to chronic stress.

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Shrinking Coarsened Win Ratio and Testing of Composite Endpoint

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OBJECTIVES/GOALS: Win ratio (WR) is an increasingly popular composite endpoint in clinical trials. A typical set up in cardiovascular trials is to use death as the first and hospitalization as the second layer. However, the power of WR may be reduced by its strict hierarchical structure. Our study aims to release the oracular hierarchical structure of the standard WR. METHODS/STUDY POPULATION: Addressing the power reduction of WR when treatment effects lie in the subsequent layers, we propose an improved method, Shrinking Coarsened Win Ratio (SCWR), that releases the oracular hierarchical structure of the standard WR approach by adding layers with coarsened thresholds shrinking to zero. A weighted adaptive approach is developed to determine the thresholds in SCWR. We conducted simulations to compare the performance of our improved method and the standard Win Ratio (WR) under different scenarios of follow-up time, association between events, and treatment effect levels. We also illustrate our method by re-analyzing real-world cardiovascular trials. RESULTS/ANTICIPATED RESULTS: First, the developed Shrinking Coarsened Win Ratio (SCWR) method preserves the good statistical properties of the standard WR and has a greater capacity to detect treatment effects on subsequent layer outcomes. Second, the SCWR method outperforms the

https://doi.org/10.1017/cts.2023.136