Pressure injures (PrI) are a major secondary complication for many people with spinal cord injury (SCI). Development and/or recurrence of a PrI limits activities of daily living, often leading to hospitalization and even death. This has a devastating impact on affected individuals and their caregivers. The economic cost burden of PrI remains significant [1,2]. PrI management has a significant effect on Veterans Heath Administration healthcare costs, which provides lifetime care for our Veterans with SCI. This research will build on the model developed by the Bogie lab of **B**iomarkers for **E**arly **I**dentification of **P**ressure **I**njury **R**isk (BEIPIR) for persons with SCI [3]. BEIPIR integrates hierarchical relationships between clinical factors, health behaviors and muscle composition. We have shown that intramuscular adipose tissue (IMAT) is a critical clinically significant risk factor for PrI development [4,*R2*]. *The preliminary repeated measures study has also found that IMAT accumulation rate varies greatly, with some individuals exhibiting rapid IMAT accumulation following SCI, while others do not. It is important to explain what is driving these changes.* These findings provide the basis for the **central hypothesis:** ***DNA variants predispose some individuals to increased deposition of IMAT following spinal cord injury, and resultant increased PrI risk.*** The study will address the conundrum of why some Veterans with SCI suffer from a continuous cycle of recurring PrI, while others remain PrI free. We propose two specific aims to refine the BEIPIR model by examining IMAT in conjunction with investigation of genetic profiles associated with accelerated and/or higher levels of IMAT deposition. *DNA variant data* will be integrated with the current BEIPIR model and the model validated to enable identification of intervention pathways.

SPECIFIC AIM 1: **DETERMINE THE ASSOCIATION OF MUSCLE COMPOSITION WITH GENETIC PROFILES:** The primary hypothesis will be investigated through genetic assay of circulatory biomarkers in existing samples from *38* persons with complete or incomplete SCI (AIS A-D) for whom gluteal muscle composition over time has already been evaluated. DNA will be extracted from previously collected whole blood samples, currently stored in a -80º freezer. The TruSight™ One Expanded Sequencing panel (Illumina, San Diego CA) will be applied for *Next Generation Sequencing (NGS) of samples, covering multiple genes associated with fatty metabolism and inflammation*. *FastQC and TrimGalore! (Babraham Institute, Cambridge, UK) will be used for quality control of NGS output data. Acceptable reads will be processed using the Genome Analysis Toolkit (GATK) pipeline (Broad Institute, Cambridge, MA) and annotated using AnnoVar. Candidate genes and DNA variants* which are differentially active between persons with and without a history of PrI *at a statistically significant level of p<0.05 will be selected* and *incorporated into the multi-scalar BEIPIR model for early identification of PrI risk.*

SPECIFIC AIM 2: UPDATE AND **VALIDATION OF THE BEIPIR MODEL OF PERSONALIZED PRESSURE INJURY RISK:** A longitudinal repeated measures study with stratified recruitment will be employed to achieve a study cohort of *100 Veterans with SCI* (AIS A-D) including participants with and without a history of PrI. Exclusion criteria will include having an open pelvic region PrI at the time of recruitment, presence of systemic disease and/or known sensitivity to contrast. Whole blood will be collected from study participants and DNA extracted prior to processing using the TruSight™ One Expanded Sequencing panel and *GATK pipeline with AnnoVar.*

Very low dose transverse pelvic region CT scans with contrast will be carried out based on our established protocol [5]. A single-phase CT will be performed with the study participant lying supine. An anterior-posterior scout image of the pelvis will be obtained to define the scan limits from the inferior aspect of the sacroiliac joints to the inferior margins of the femoral heads. 0.4mm axial slices will be obtained between the midpoint of the S2/S3 sacral vertebrae and the inferior aspect of the ischial tuberosities. Muscle composition and cross-sectional area (CSA) will be determined using our established Hounsfield Unit scale classification protocol to determine relative lean muscle and IMAT content [5]. 3D reconstruction will also be applied to show IMAT distribution throughout the muscle.

Study participants will be surveyed monthly by phone using our standardized skin status questionnaire to determine tissue health status. Incidences of tissue compromise or breakdown will be monitored and data applied to update the BEIPIR model. Blood draw and CT scans will be repeated annually or when a PrI occurs.

Our current BEIPIR model indicates that the IMAT is a critical and clinically significant PrI risk factor. The incorporation of relevant genetic profile information will facilitate earlier identification of individuals predisposed to rapid and higher levels of IMAT deposition. Development and validation of the BEIPIR model will provide a clinical tool to optimize personalized care, recognizing that every person with SCI is an individual. Our proposed study has great potential to improve PrI development risk assessment, enhance health status and quality of life for Veterans with SCI and reduce VHA costs. In the longer term, the BEIPIR model may provide the basis for development of a blood test kit for PrI risk.

This research will also expand the de-identified genetic data publicly available for this underrepresented population. *We will leverage our findings against larger cohorts by comparison with the Million Veteran Program (MVP).*

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