**Project Title: An Efficient, high-Quality, Unbiased, Interpretable Pipeline for Overcoming Barriers in the Translational Research using Real-World Data**

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## PROJECT SUMMARY

Randomized controlled trials (**RCTs**) are the gold standard for evaluating medical interventions, but they are often impractical, slow, or costly. Modern causal inference methods, coupled with real-world data (RWD), provide a faster, well-powered alternative for estimating treatment effects across diverse patient populations. Despite this potential, several barriers hinder their effective use in translational research. A key challenge is aligning "time zero," the point at which a patient cohort is defined, eligibility, and treatment assignment, which leads to intractable bias. Other barriers include biases induced from data preprocessing, confounding, or strong modeling assumptions. Target trial emulation (**TTE**) is a major innovation that addresses these barriers by emulating RCT protocols using RWD. The TTE framework has proven especially useful in fostering improved communication between statisticians and clinicians to align sound study design, incisive data analysis and clinical insight to improve the quality of research. Currently, the Translational Research: Implementation, Analysis, & Design (**TRIAD**) team supports multiple research groups in evaluation of causal inferences using RWD, but the work is piecemeal and we must frequently “reinvent the wheel”. In addition, resource constraints often prevent us from using the most effective methods. Our proposal aims to develop innovative solutions to overcome these barriers using TTE and rigorous causal inference methods as the foundation, systematizing and expanding the workflow to enhance the efficiency, quality, and impact of the translational research process. The specific aims are to build on TRIAD’s ongoing work on causal inference and TTE to stand up the Efficient, high-Quality, Unbiased, Interpretable Pipeline (**EQUIP**) and develop a research tool for unbiased and robust estimation of average causal effects (Aim 1). To support precision medicine, we will expand EQUIP by developing two additional research tools for estimating heterogeneous treatment effects and optimal dynamic treatment regimens (Aim 2). We will also create a public, user-friendly code hub to provide off-the-shelf implementations for the three research schemas in EQUIP (Aim 3). By providing three comprehensive, scalable, and reproducible research tools, EQUIP will empower clinicians and researchers across multiple disciplines and institutions to conduct high-quality observational studies, bridging the gap between methodology and broader applications. We will collaborate with TRIAD’s survey design core to continuously collect user feedback via surveys on the clarity, usability, and reproducibility of these tools and improve them accordingly. EQUIP will be a unified, generalized solution to streamline workflow in observational studies, enable us to answer relevant and rigorous research questions, and facilitate external collaborations.

## PROJECT NARRATIVE

Randomized controlled trials (RCTs) are the gold standard for evaluating treatment efficacy but they are often infeasible, impractical, too slow, or too expensive. Real-world data (RWD), combined with causal inference methods, can inform patient care practices across diverse populations. However, several critical barriers hinder their effective use in translational research, leading to intractable biases. The Translational Research: Implementation, Analysis, & Design (TRIAD) team currently applies target trial emulation (TTE) to address these barriers by emulating RCT protocols using RWD, but the work is piecemeal and limited by resource constraints. Our proposal aims to develop innovative solutions to overcome these barriers using TTE and rigorous causal inference methods as the foundation, systematizing and expanding the workflow to enhance the efficiency, quality, and impact of the translational research process. We aim to build on TRIAD’s ongoing work on causal inference and TTE to stand up the Efficient, high-Quality, Unbiased, Interpretable Pipeline (EQUIP). We will deliver three comprehensive, scalable, and reproducible research schemas and deployment tools for estimating average casual effects, heterogeneous treatment effects, and optimal dynamic treatment regimens. We will continuously assess and improve the clarity, usability, and reproducibility our tools based on user feedback collected via surveys. EQUIP will empower clinicians and researchers across multiple disciplines and institutions to conduct high-quality observational studies, ultimately driving advancements in human health.

## A. SPECIFIC AIMS.

The gold standard for evaluating the efficacy and safety of medical interventions is the randomized controlled trial (RCT). However, RCTs are often infeasible, impractical, too slow, or too expensive. Innovations in modern causal inference methods[1], coupled with the availability of large volumes of real-world data (RWD), provide a viable alternative for estimating treatment effects outside of RCTs. These innovations enable faster and more feasible estimation of effects of treatment, while also offering insights into patient health and care practices across diverse populations. The large sample sizes often provided by RWD, combined with extended follow-up of health characteristics, medications, and outcomes, often supports well-powered evaluation of treatment effect heterogeneity and dynamic treatment regimens which is not feasible for RCTs. RWD also often includes detailed clinical characteristics to account for confounding and capture health outcomes often absent in RCTs.

Despite these advantages, critical barriers impede the effective use of causal inference methods in RWD, hindering essential translational research. One major barrier is aligning "time zero," the point at which a patient cohort is defined, eligibility, and treatment assignment, which leads to intractable bias[2]. Another challenge is handling confounding factors—differences in patient characteristics between treatment groups—which can bias results. Biases can also be induced by strong modeling assumptions and misspecification. Additionally, many research questions are restricted to fixed-point treatments that may have limited relevance to patients and clinicians. The vast amount of RWD, including diverse and unstructured data sources, further complicates data preprocessing and analysis. Addressing these barriers is essential for the broader adoption of RWD in clinical research, thereby accelerating the translation of discoveries into improved human health outcomes.

Target trial emulation (TTE) is a major innovation in the past decade with the main idea of emulating RCT protocols using RWD to clearly define the time zero of an analysis and minimize various types of biases. The TTE framework has proven especially useful in fostering improved communication between statisticians and clinicians to align sound study design, incisive data analysis and clinical insight to improve the quality of research using RWD. Prior work has shown that observational studies that applied the TTE framework with the support of modern causal inference methods can accurately replicate findings from RCTs. Currently, the Translational Research: Implementation, Analysis, & Design (TRIAD) team supports multiple research groups in evaluation of causal inferences using RWD, <u>but the work is piecemeal and we must frequently “reinvent the wheel”. In addition, resource constraints often prevent us from using the most effective methods.</u> Our proposal aims to develop innovative solutions to overcome these barriers using TTE and rigorous causal inference methods as the foundation, systematizing and expanding the workflow to enhance the efficiency, quality, and impact of the translational research process. We will create three <u>comprehensive</u>, <u>scalable</u>, and <u>reproducible</u> research tools to empower clinicians and researchers to conduct high-quality observational studies, bridging the gap between methodology and broader applications. We will collaborate with TRIAD’s survey design core to collect user feedback on the clarity, usability, and reproducibility of these tools. The specific aims are:

1. **Stand up an Efficient, high-Quality, Unbiased, Interpretable Pipeline (EQUIP) for implementing TTE, including development of EQUIP’s research tool for estimating average causal effects.**
   **Approach**: Build on TRIAD’s ongoing work in causal inference and TTE to develop a comprehensive, easy-to-follow research schema that will enable statisticians to work with translational researchers to align research questions with available data and apply flexible doubly robust methods for unbiased estimation.
   **Expected Outcomes**: EQUIP will streamline TRIAD’s workflow and improve the quality, efficiency, interpretability, and reproducibility of RWD-based studies.
2. **Expand EQUIP to support precision medicine by developing two additional research tools for evaluating heterogeneous treatment effects (HTEs) and dynamic treatment regimens (DTRs).**
   **Approach**: Create two research schemas for estimating: (1) HTEs using S-, T-, M-, X-, and R-metalearners and (2) optimal therapies across multiple treatment stages (DTRs) using Q-, A-, and O-learning.
   **Expected Outcomes**: This expanded EQUIP will be generalizable to broad applications across multiple projects, disease states, and clinical domains to improve scientific knowledge and inform clinical practice.
3. **Provide a public, user-friendly code hub for implementing the three research schemas in EQUIP.**
   **Approach:** Create GitHub repositories for each research schema with validated, well-annotated code.
   **Expected Outcomes:** The code hub will facilitate widespread adoption of EQUIP and collaborations.

This project will deliver a unified, generalizable solution, EQUIP, that leverages the TTE framework and advanced causal inference methods to address critical barriers in observational studies. By providing three comprehensive research schemas and public deployment tools, EQUIP will enhance the rigorous and efficiency of translational research, ultimately driving advancements in human health.

## B. BACKGROUND, SIGNIFICANCE, PRELIMINARY RESULTS

**B.1. The use of TTE and causal inference methods in the medical literature has surged over the past decade.** The TTE framework facilitates effective communication between statisticians and clinical experts with domain knowledge, allowing for the integration of sound study design principles, incisive data analysis, and clinical insight. This improves the specificity and clinical relevance of both research questions and the methods used. For example, in designing emulated trials, directed acyclic graphs (DAGs) help statisticians and domain experts to contextualize subject matter understanding of biological pathways, improving the identification of confounding variables. In addition, TTE enhances the alignment between research questions and existing data, making the results more relevant and interpretable for informing clinical decision making. This includes comparing realistic treatment strategies, valid assignment of time zero, and thorough adjustment for baseline and time-varying confounding. Due in part to these benefits, TTE has become a standard approach in hundreds of observational studies in medical research publications, as well as grant applications.

**B.2. There is a pressing need for systematic research tools that can be generalized to multiple projects and clinical domains.** In our previous collaborations, we have used TTE and causal inference methods in areas such as oncology, cardiology, nephrology, mental health, metabolic diseases, and infectious diseases. However, we often conducted the analysis from scratch due to the lack of comprehensive, reusable research plans and deployment tools. Several of our collaborators, including, for example, Drs. Adam Bress, Srini Beddhu, and Barbara Jones, routinely apply the TTE framework and causal inference methods in their respective projects. Yet, each team builds its own research plans and analysis code, limiting productivity. Reusable and scalable research tools applied across multiple research teams would improve efficiency. Our project aims will consolidate the expertise and resources of these teams, along with TRIAD, to create a comprehensive, scalable, and reproducible platform—EQUIP—that will dramatically enhance the efficiency and quality of translational science using RWD.

**B.3. High-quality RWD-based studies can complement findings from RCTs and provide actionable evidence when conducted robustly.** RCTs are typically powered to measure overall treatment effects but often lack the power to assess whether treatment effects vary across different patient subgroups. Large datasets, such as electronic health records from Veterans Health Administration, Kaiser, Cosmos, and FlatIron; claims data such as Optum; survey data such as NHANES; and wearable data such as Fitbit, offer rich information on patient populations. These data sources should be leveraged to answer more rigorous and clinically relevant research questions. However, many researchers stay away from RWD since they are messy due to the non-systemic data collection within the healthcare system. Bias can arise from irregular assessment times, which are often related to the patients' evolving health status, and from greater rates of loss-to-follow-up and intermittent missing data in nonadherent patients. Successful completion of our project will address these challenges by implementing TTE and advanced causal inference methods, providing a generalizable solution to overcome these barriers and make RWD more accessible for research that informs clinical care.

**B.4. Standard research questions may fail to address the most relevant and informative questions to clinical practice.** To illustrate this point, cancer therapies are typically administered in phases, with each phase depending heavily on patient's response to the prior treatment. This is a classic DTR problem where the goal is to identify the optimal sequence of treatments over time to achieve the best final outcomes. However, due to methodological barriers, over 95% of the studies restricted themselves to point treatments —simpler to study, but less relevant and informative for real-world patient care. Successful completion of our project will expand TRIAD's existing resources by creating detailed research plans and analysis codes for advanced statistical methods, including doubly robust and machine learning

**Table 1. Current State, Short- and Long-Term Goals**

| | Current State | One-Year Goal* | Long-Term Goal |
|---|---|---|---|
| Research Plans | With pre-designed forms, statistical analysis plans are written separately for each specific project from scratch | **Deliverable 1**: One comprehensive, reproducible, easy-to-follow research schema for each of the following aims: (1) doubly robust estimation of average treatment effects, (2) heterogeneous treatment effects, and (3) optimal dynamic treatment regimens | Continue to update and expand the research schemas to keep up with methodological advances |
| Implementation | Most programming codes are written from scratch; some codes are shared between projects | **Deliverable 2**: Three off-the-shelf implementation tools (i.e., GitHub repositories) and three step-by-step tutorials (i.e., vignettes) corresponding to each of the research schemas in Deliverable 1 | Continue to improve and expand the code hub according to users' feedback and interests |
| Dissemination | Best practices and advanced methods are disseminated mainly through consulting service, usually involving a small group | **Deliverable 3**: Three seminars or discussion sessions will be held to disseminate EQUIP, each focusing on a specific aim in Deliverable 1 | Continue to hold seminars or discussion sessions to exchange ideas for paper publications or grant applications |

methods to handle large-scale RWD and estimate HTEs and optimal DTRs, ultimately leading to more relevant and impactful findings for clinical care.

**B.5. Existing resources and current workflow in TRIAD are outlined in the 1st column of Table 1**. Over the past three years, TRIAD has applied the TTE framework and causal inference methods for point treatment comparisons. In many of Drs. Bress, Jones, and Beddhu's projects, TRIAD performed intention-to-treat and per-protocol analyses using propensity score methods, such as weighting or matching, where baseline propensity scores were estimated using machine learning approaches and censoring weights and adherence weights were modeled as functions of baseline and time-varying covariates. Right-censored outcomes with competing events were also appropriately handled using a competing risk framework. However, resource constraints on each project limited TRIAD's ability to conduct all recommended analyses, resulting in quality disparity across projects. See **§B.2.** for a detailed explanation of the limitations in TRIAD's current workflow.

## C. TRANSLATIONAL SCIENCE JUSTIFICATION

### C.1. Common recurring barriers in studies using RWD can lead to biased results, uninterpretable findings, and reduced or delayed impact on improving patients' health outcomes.

**1. Unclear and infeasible research questions**: It is not uncommon that researchers ask associational questions but eventually interpret the results in a causal way. Associational questions are often posed in diffuse ways, leading to unclear definitions of study cohort, treatment strategy, and study period, leading to biased or uninterpretable results. Eligibility criteria that use information unavailable in RWD are infeasible and those that use post-baseline information induce selection bias. Defining treatment strategies that include current users may introduce prevalent user bias. Unclear start of follow-up (i.e., time zero) often leads to misalignment of patients' eligibility and treatment assignment, which can lead to selection bias and immortal time bias[2].

**2. Confounding by indication bias**: Unlike RCTs where treatment is randomized, in RWD, imbalance in patient characteristics between treatment groups may be substantial and confound associational estimates of treatment effects. Without thinking through the underlying causal relationships between variables, one may fail to identify all confounders.

**3. Biased results due to strong model assumptions, misspecification, and low power**: RWD often contains high-dimensional patient information that can be used to improve estimation accuracy if modeled appropriately. However, using all the data impulsively without careful variable selection[3] and timing of measurements may increase, rather than reduce bias. In addition, positing naïve models, e.g., linear additive models, may misspecify complex and nonlinear relationships between variables and induce bias. A further challenge is that estimating HTEs using conventional subgroup analysis that may produce false positive results due to multiple testing and false negative results due to insufficient power in small-sized subgroups[4]. Failing to identify effect modifiers when exist or publishing false discoveries may mislead personalized care practice.

**4. Research questions are restricted to point treatment comparisons**: Over 90% of the CER compares fix-point treatment regardless of the treatment procedures used in clinics. For example, most cancer therapies are administered over several stages so finding the optimal initial treatment may not improve patient outcomes effectively. Instead, identifying the best DTR[5,6], a sequence of treatments tailored to patient characteristics and time-varying responses to treatment, is more relevant and impactful on patients' health. Due to the complicated study design and statistical methods required for learning DTR, investigators tend to avoid asking such rigorous but more meaningful research questions.

**5. Computational complications of large-scale, diverse data sources in RWD**: Large-scale and high-dimensional RWD (e.g., Veterans Administration (VA) data contains >10 million patients) often pose computational challenges, particularly when analyzing longitudinal data (e.g., 20 years of patient records), performing time-consuming analytic procedures (e.g., 1,000 bootstrap sampling, multiple imputation for missing data), or using remote virtual machines (e.g., VA VINCI workspaces). These practical computational issues reduce the efficiency of the research process, thus prolonging the time to important discoveries.

**C.2. EQUIP offers a generalizable solution to overcome the translational research barriers identified above by providing three versatile research tools applicable to multiple research areas.** *First*, EQUIP <u>will be the first formal effort</u> to systematize and improve the workflow for RWD-based research in TRIAD. It provides a principled way to devise clear and feasible causal questions, carefully align research questions with available data through TTE, identify confounders using domain expertise communicated via DAGs, and control confounding using unbiased and robust modeling strategies. <u>By standardizing these critical processes, EQUIP</u>

will empower not only TRIAD but also clinicians and researchers across disciplines to conduct high-quality, impactful observational studies with greater efficiency. In addition, the use of EQUIP will provide us the bandwidth to perform advanced statistical methods (e.g., doubly robust and machine learning methods) which are currently beyond our reach due to resource constraints. *Second*, EQUIP provides a comprehensive, reproducible, and easy-to-follow research schema for estimating average treatment effects, including detailed guidance on defining research questions, study design, data preprocessing, statistical modeling, and reporting and interpreting results. We will clearly lay out the required data, *what to do* and *how to do it* for every step of the process. *Third*, we will go beyond conventional research questions and statistical methods by expanding EQUIP to answer more relevant and informative questions in personalized medicine with rigorous data analysis. We will develop two additional research schemas for the estimation of HTEs and optimal DTRs by incorporating a wide range of state-of-the-art statistical methods and machine learning approaches. To support widespread adoption, we will also create off-the-shelf implementation tools and step-by-step tutorials for each research schema. EQUIP's generalizability will allow it to be applied across diverse scientific disciplines and projects, promoting external collaborations and increasing opportunities for extramural funding.

**C.3. The tools we propose for EQUIP offers are replicable and reuseable by research groups across institutions.** Our research schemas are flexible and not limited to a particular source of observational data, intervention, outcome, or disease. They can be applied to any studies when the goal is to estimate the average treatment effects, HTEs, or optimal DTRs. Each research schema includes step-by-step instructions to ensure users stay aligned with the research plan. While every study has its own unique challenges, we will make our research schemas comprehensive by including alternative methods for handling anticipated special cases. We also outline the advantages and disadvantages of each method to help analysts choose the most appropriate approach for their study. In addition, we provide validated and well-annotated statistical programming codes and easy-to-follow tutorials for deploying the procedures described in the research schemas. Therefore, the EQUIP is generalizable to a wide range of study types and research questions, can be easily shared via GitHub with any nationwide collaborators, and aids in developing advanced ideas for grant applications.

## D. RESEARCH DESIGN AND PROPOSED METHODS

### Aim 1. Stand up EQUIP for implementing TTE, including development of EQUIP's research tool for estimating average causal effects.

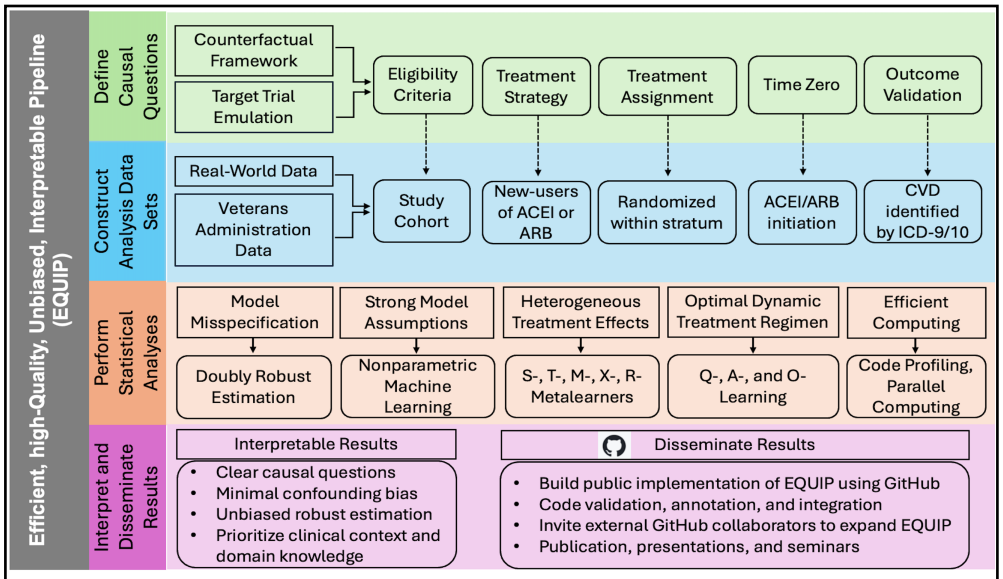

**Figure 1.** Overview of the proposed Efficient, high-Quality, Unbiased, Interpretable Pipeline

**D.1.** We will adopt the best practices currently used in TRIAD and those widely endorsed in the literature to ensure robust and efficient analyses. This includes defining clear and feasible causal questions, employing TTE to construct analysis data with well-defined eligibility criteria, treatment assignment, time zero, and outcomes, and conducting appropriate statistical modeling. We will systematize these procedures to enhance the quality of data analysis and analytical efficiency. We will propose the use of doubly robust approaches[7] since they provide unbiased results when either the treatment model for controlling confounding or the outcome model is correctly specified. Additionally, we will leverage machine learning models [3,8–12] to capture the complex, nonlinear relationships between high-dimensional variables and employ code profiling and parallel computing to reduce computation time. **Figure 1** displays the overall infrastructure of EQUIP. We will apply EQUIP to new projects and compare their quality and efficiency to TRAID's previous projects. We will collect user feedback through surveys with questions tailored to this tool and modify accordingly.

### Aim 2. Expand EQUIP to support precision medicine by developing two additional research tools for estimating HTEs and DTRs, separately.

**D.2.** We will incorporate five metalearners, namely, S-, T-, M-, X-, and R-learners[4,13,14], for estimating HTEs. These metalearners are compatible with a wide range of machine learning methods and can estimate HTEs as

a function of multiple effect modifiers simultaneously. M-, X-, and R-learners provide direct estimation of HTEs, i.e., no need to model main effects, and R-learner has the double robustness property. In addition, we will include Q-, A-, and O-learning to identify the optimal DTRs[15–17]. These methods use backward induction to sequentially determine the optimal treatment rule at current stage assuming that optimal therapies are taken for future stages. Q- and A-learning are fully parametric approaches while O-learning are policy-based approach that leverages nonparametric machine learning to solve it as a classification problem. We will summarize new projects conducted using our tools, highlighting the investigators' background and disease types. We will also gather user feedback on tools' clarity and usability via surveys and modify accordingly.

**Aim 3. Provide a public, user-friendly code hub for implementing the three research schemas in EQUIP.**

**D.3.** We will leverage GitHub as the central platform for validating, annotating, and synchronizing our programming code. We will create dedicated repositories for each research schema and assign a designated manager for ongoing maintenance. All repositories will be publicly accessible, allowing clinicians and researchers to easily download, use, or share the tools. We will also hold regular meetings to discuss best practices for conducting research using RWD and writing efficient, reproducible code. To ensure continuous improvement, we will collect user feedback on reusability of our code hub using surveys. We will summarize the number of new projects used our code hub and the number of potential additional collaborations fostered.

**D.4. Anticipated problems and alternative strategies.** Each observational study is unique, with varying data sources, interventions, outcomes, disease types, and research questions. **This diversity can make it difficult to establish universal best practices across all projects**. To address this, we will design our research schemas to be flexible and generalizable, minimizing dependency on specific factors. While users are encouraged to follow our research schemas and deployment codes, they will need to adapt them to the particular needs of their studies. **How to reconcile when there are multiple approaches to handle the same issue?** In this situation, analysts should choose the most suitable method based on the specific research questions and available data. To facilitate this decision-making process, we will outline the pros and cons of each approach in our research schemas. **Will the research tools be too technical to be useful?** We will design these research tools for a board audience rather than just well-trained statisticians. The instructions will be written in plain language, avoiding unnecessary jargon, to ensure clarity and ease of use. In addition, we will refine our research tools based on real-time user feedback to ensure accessibility and usability. **Is the proposed work too ambitious for one-year timeline?** We aim to develop three research schemas, three off-the-shelf implementation tools, and hosting three seminars or discussion sessions for dissemination. Completing these tasks within a year is feasible and realistic since EQUIP will build on existing analysis procedures, methods, and codes already developed by TRIAD and collaborators' teams. In addition, we will allocate most of the funding to analyst time, ensuring efficient progress within the set timeframe.

**Table 2. Preliminary Design of Evaluation Surveys***

| | Clarity | Useability | Reproducibility |
|---|---|---|---|
| Research Schemas | 1. How well can you follow the procedures in schemas?<br>2. How often do you encounter jargons or need additional details?<br>3. Specific recommendations and comments. | 1. How easy to find the suitable schema for your study?<br>2. How well does the research schema fit your study?<br>3. How much do you need to tailor the research plan to your project?<br>4. Specific recommendations and comments | 1. How easy to replicate one research schema for several similar projects?<br>2. How robust are the schemas to changes in data or research questions?<br>3. Specific recommendations and comments. |
| Implementation Tools | 1. How well can you follow the code?<br>2. How often do you find coding errors?<br>3. How helpful are the tutorials?<br>4. Specific recommendations and comments. | 1. How easy is it to find the programming code for your study?<br>2. How much additional coding do you need to do with our code hub?<br>3. How much does the code hub help to speed up your project?<br>4. Specific recommendations and comments. | 1. How much more confident are you about sharing the code of your project after using our code hub?<br>2. How well can you replicate the study results that you generated using our code hub?<br>3. Specific recommendations and comments. |
| Seminars | 1. How clearly were the seminars presented?<br>2. Did the seminars help you understand EQUIP?<br>3. Were the seminars too technical? | 1. How useful are the seminars to your research?<br>2. How often do you gain insights or new ideas from the seminars? | 1. Were you able to acquire presentation slides or recordings of the seminars?<br>2. Were you able to discuss questions or network? |

*These are ONLY preliminary concepts and will be refined and revised based on relevant literature and supplemented with validated instruments where available for designing user feedback survey.

## E. EXPECTED RESULTS AND METRICS

**Table 1** details our objective for the year in the 2nd column, with the project considered complete once we provide the three deliverables by its end. *First*, we will create three comprehensive, reproducible, and easy-to-follow research schemas, including detailed guidance on study design, data preprocessing, statistical modeling, and reporting and interpreting results. *Second*, we will develop an off-the-shelf implementation tool for each research schema, accompanied by step-by-step tutorials. Each GitHub repository will be made public once fully validated and

annotated. *Third*, we will host seminars for dissemination by demonstrating the benefits of using our research pipeline in several Co-Is' projects. The EQUIP will be fully operational after the research schemas and code hub are reviewed and approved by senior faculties. In collaboration with TRIAD's survey design core (see Millar letter of support), we will develop customized questionnaires for EQUIP users to report their experience and provide suggestions for further improvement. Our evaluation will begin during the project and operate at two tiers: within TRIAD where most researchers are familiar with causal inference and quantitative analysis and across various research teams within the University of Utah. Feedback will be collected over a year through brief online surveys that assess the clarity, usability, and reproducibility of the three research tools, with multiple questions and free-text options for additional suggestions. **Table 2** outlines proposed measures of these three outcomes, which will be refined and revised based on relevant literature and supplemented with validated instruments where available. Survey results will be continuously reviewed and used to make iterative improvements, enhancing the performance of our tools. In the long term, we will also seek feedback from external collaborators to further strengthen EQUIP and broaden its applicability.

## F. PROJECT MILESTONES AND TIMELINE

Dr. Xu will ensure completion of study benchmarks on schedule as indicated in **Table 3**. In summary, we plan to deliver one research tool every 3-4 months, including a research schema and a set of deployment tools (GitHub repository + tutorial). Every quarter, we also plan to have a seminar or discussion session for dissemination and collect user feedback using online surveys. See **§E. EXPECTED RESULTS AND METRICS** for a more detailed overview of the planned activities and benchmarks over the award period.

**Table 3. Milestones and timeline**

| Aim | Project component | Study Month | | |
|---|---|---|---|---|
| | | 3 | 6 | 12 |
| **Aim 1** | Integrate resources in TRIAD | | | |
| | Develop research schema for applying doubly robust and machine learning methods | | | |
| | Seminars and Discussions | | | |
| | User feedback collected via surveys | | | |
| **Aim 2** | Develop research schema for heterogeneous treatment effect estimation (2a) | | | |
| | Develop research schema for heterogeneous treatment effect estimation (2b) | | | |
| | Seminars and Discussions | | | |
| | User feedback collected via surveys | | | |
| **Aim 3** | GitHub repository for Aim 1 | | | |
| | GitHub repository for Aim 2a | | | |
| | GitHub repository for Aim 2b | | | |

## G. SPECIFIC PLAN FOR EXTRAMUTAL FUNDING

This Utah CTSI pilot funding will enable us to initiate the development of EQUIP with three research tools. However, many other building blocks are needed such as best practices of comparing time-varying treatments and conducting dose-response analysis. To ensure continuous development and expansion of EQUIP, we will pursue extramural funding after demonstrating the gains in efficiency, quality, and impact of translational science from our initial work. Our target is the Clinical and Translational Science Award (PAR-24-272) from the National Center for Advancing Translational Sciences (NCATS), as our goal of developing and expanding EQUIP aligns closely with their mission. We plan to submit our application by January 28th, 2026, and may involve biostatistics teams from other institutions to further scale up EQUIP by building additional innovative solutions and implementation tools to enhance research quality and speed up research process.

## H. SCIENTIFIC ENVIRONMENT

We have assembled a multidisciplinary team led by early-career investigator (ESI) Dr. Yizhe Xu, PhD, MSTAT, and supported by six experienced scientists from different disciplines, some with longstanding collaborations, ideally suited to complete this project. Our team has substantial expertise in designing various types of studies, analyzing different sources of data, developing and applying advanced approaches in survival data analysis, longitudinal data analysis, TTE, and causal inference, and translating research findings to inform patient care. We have abundant experience in observational studies across a wide range of clinical domains including cardiovascular disease (CVD), dementia, kidney disease, metabolic disorders, and cancer. Dr. Xu specializes in modern causal inference, machine learning, and estimating HTEs. Dr. Greene contributes expertise in survival and multilevel data analysis. Dr. Presson provides expertise in principled statistical analyses, effective communication with clinicians, and interpreting research findings. Dr. Chen contributes expertise in cancer research and single-cell gene expression studies; Drs. Bress, Beddhu, and Sborov bring clinical knowledge in CVD, cognitive health, metabolic syndromes, and hematologic cancer. Drs. Xu, Greene, and Bress have established a productive partnership, resulting in many published papers and NIH grant applications under review. All the Co-Is have high interest in developing systematic and reproducible research tools. In particular, Drs. Bress and Beddhu have been using TTE and causal inference methods frequently in their research groups. This collaboration, supported by expertise across several statistical, methodological, and clinical disciplines, positions our team to successfully complete the proposed project.

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13. Nie, X. & Wager, S. Quasi-oracle estimation of heterogeneous treatment effects. Biometrika 108, 299–319 (2021).
14. Künzel, S. R., Sekhon, J. S., Bickel, P. J. & Yu, B. Metalearners for estimating heterogeneous treatment effects using machine learning. Proceedings of the national academy of sciences 116, 4156–4165 (2019).
15. Schulte, P. J., Tsiatis, A. A., Laber, E. B. & Davidian, M. Q-and A-learning methods for estimating optimal dynamic treatment regimes. Stat Sci 29, 640 (2014).
16. Zhang, B. & Zhang, M. C-learning: A new classification framework to estimate optimal dynamic treatment regimes. Biometrics 74, 891–899 (2018).
17. Hager, R., Tsiatis, A. A. & Davidian, M. Optimal two-stage dynamic treatment regimes from a classification perspective with censored survival data. Biometrics 74, 1180–1192 (2018).

**PI response to reviewer comments.** We thank the reviewers for their thoughtful comments. We retained the reviewers' noted strengths, and in response to their critiques, we have made the following improvements:

Reviewer I. Concerns on proposed work does not address "understanding a scientific or operational principle". Thank you. A key objective of the TTE framework is to foster communication between statisticians and clinical domain experts to better integrate sound study design principles, incisive data analysis and clinical insight to improve the specificity and clinical relevance of research questions and the methods used to answer those questions. In designing emulated trials, directed acyclic graphs help statisticians and domain experts to contextualize subject matter understanding of biological pathways to better identify confounders. Accordingly, in collaboration with TRIAD's survey design core, we have extended our proposal to collect feedback from EQUIP users for continuous improvement. Our proposal also tackles operational bottlenecks in translational research. Many researchers stay away from RWD sine it is often messy and bias may be induced by irregular assessment times and from greater rates of loss-to-follow-up and intermittent missing data in nonadherent patients. We will address these challenges by applying advanced causal inference methods.

Question about why this Utah CTSI TIP program pilot fund is necessary for this work to be successful. The Utah CTSI TIP funding is essential for developing processes to extend tools for implementing TTE with RWD and repurpose them beyond specific one-off collaborations, while ensuring ongoing evaluation. Resource constraints on analysts' time for each project lead to corner-cutting in TRIAD's deployment of state-of-the-art methods which would otherwise be possible within the TTE framework, and limits TRIAD's ability to develop reusable research plans and deployment tools that can be adopted by broader research groups. We hope to use the pilot funds to synchronize resources on best practices and consolidate programming code to avoid redundant efforts. In addition, we will expand TRIAD's workflow by creating detailed research schemas and codes for advanced statistical methods, including doubly robust and machine learning methods to handle large-scale RWD and estimate HTEs and optimal DTRs. **Table 1** summarizes our short- and long-term goals.

Concerns about the project evaluation metrics are all post facto and don't inform the proposed work. We agree that our initial metrics focused on long-term success. To address this, we now target three key deliverables from this project. *First*, we will create 3 comprehensive, reproducible, and easy-to-follow research schemas, including detailed guidance on defining research questions, study design, data preprocessing, statistical modeling, and reporting and interpreting results. *Second*, we will develop an off-the-shelf deployment tool for each research schema, along with a step-by-step tutorial. We will make each GitHub repository public once it is validated and well-annotated. *Third*, we will hold seminars to disseminate EQUIP and gather user feedback via surveys (**Table 2**) and improve the clarity, usability, and reproducibility of our tools iteratively.

Questions about how much of the work has been done and how to tell the work is done and ready. We summarize the existing resources and work in TRIAD in **Table 1** (column 1) and **§B.5.** The 2nd column details our aim for the year, which will be considered complete upon providing the three deliverables. The EQUIP will be ready to use after the research schemas are reviewed by senior faculties and the code hub is validated.

Concerns about whether EQUIP is replicable and useful to other institutions or the NIH in general. EQUIP is a translational science tool that ensures rigorous and reproducible research using RWD by providing step-by-step instructions and programming codes. EQUIP is generalizable to various disease domains and research questions, easily shared via GitHub with any nationwide collaborators, and aids in developing advanced concepts and methods for grant applications. EQUIP bridges various methodologies with broader applications.

Reviewer II. Recommendations for metrics for evaluating the usability or ease of use. We appreciate the point. Our evaluation of EQUIP will begin during the project and occur in two tiers – within TRIAD where most researchers are familiar with causal inference and quantitative analysis and across various research teams within the University of Utah. We will collect user feedback on the clarity, usability, and reproducibility of our research tools through online surveys with multiple questions and free-text options for suggestions (**Table 2**).

Concerns on challenges in determining "best practices" across the entire TRIAD team and how to reconcile when there are multiple approaches to the same issue. Thank you. We want to clarify that our best practices will be defined in a general way, e.g., using imputation if missing data exceeds 10%. Users are expected to follow our research schemas and codes yet have the flexibility to adapt them to their specific studies. When multiple methods are available, analysts should choose the most suitable one based on their study questions and data. To aid decision-making, we will outline the pros and cons of each approach in our schemas.

Concerns on the ambitious goal of the proposed work. Thank you. We now clarify our short- and long-term goals in **Table 1**. Our one-year goal is summarized as three deliverables in Column 1, including 3 research schemas, 3 off-the-shelf implementation tools, and 3 seminars or discussion sessions for dissemination. These goals are feasible and can be accomplished within a year as we will leverage existing resources of TRIAD.

# BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Xu, Yizhe

eRA COMMONS USER NAME (credential, e.g., agency login): XU.YIZHE

POSITION TITLE: Assistant Professor, University of Utah

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Liaoning Medical University, China | BS | 07/2012 | Nursing |
| University of Utah, SLC, Utah, US | MStat | 12/2016 | Biostatistics |
| University of Utah, SLC, Utah, US | PhD | 08/2020 | Population Health Sciences |
| Stanford University, Stanford, CA, US | Postdoctoral Fellow | 04/2023 | Biomedical Informatics |

## A. Personal Statement

I am well positioned for my role as an Early-Career principal investigator on our proposal titled “An Efficient, high-Quality, Unbiased, Interpretable Pipeline for Overcoming Barriers in the Translational Research using Real-World Data”. This project aims to establish a principled pipeline to define clear and feasible research questions, construct data sets that are well-aligned with the questions, and perform robust estimation to answer the questions while maximizing analytical efficiency. We aim to develop innovative solutions to overcome these barriers, enhancing the efficiency, quality, and impact of the translational research process. We propose a comprehensive, generalizable, and reproducible framework that will enable clinicians and researchers to design and conduct high-quality studies using real-world data (RWD). This project will develop three research tools to bridge the gap between methodology and broader applications, overcoming identified translational roadblocks and improving the efficiency and effectiveness of the research process. Our project will integrate best practices in data preprocessing, study designs, and statistical methods to estimate average and heterogeneous treatment effects, as well as identify the optimal dynamic treatment regimens.

I have training in biostatistics and data science from the University of Utah and the Stanford University. I also have a comprehensive understanding of patient care and medical systems from my registered nurse background. I am a formally trained PhD biostatistician with a high research interest in modern causal inference and my dissertation was on developing causal methods for estimating the optimal personalized treatment rule that considers the tradeoff between treatment effectiveness and treatment-related costs (both are survival outcomes). I have abundant experience in comparative effectiveness research and strong ability of analyzing large-scale observational data. My analytic skills include patient charts review, data retrieval and preprocessing, statistical modeling and programming, and so on.

As a postdoc fellow at Stanford, I worked with clinicians, computer scientists, biomedical informaticists, and other statisticians, and developed my knowledge in the areas of machine learning and longitudinal healthcare data. I learned how to manage and process large databases using BigQuery/SQL and virtual machine instances, respectively, in Google Cloud Platform; I learned how to build cohorts using the Observational Medical Outcomes Partnership Common Data Model with standard concepts such as SNOMED, ICD9/10, and LONIC codes. With these new skills, I eventually developed cardiovascular disease risk stratification tools using large claims datasets and several machine learning approaches, proposed an evaluation metric for estimated heterogeneous treatment effects (HTEs), and characterized the empirical performance of metalearners for estimating HTEs on survival outcomes.

As a junor faculty at the University of Utah, my current research focuses on leveraging wearable data to predict the survival of patients with non-small cell lung cancer and using survey data weights to estimate the HTEs for a target population by transferring the HTEs estimated from randomized controlled trials. I am also leading a statistical team for Dr. Adam Bress to analyze over 3 million trial emulated electronic health records

(EHRs) from Veterans Healthcare Administration (VHA). Our goals are to estimate the intention-to-treat and per-protocol effects of antihypertensive medications on various outcomes such as cardiovascular disease, all-cause dementia, and cancer. In addition to my responsibility of conducting data analysis, I manage the workflow between three PhD biostats students, one statistician, and several other researchers and across eight projects. I help to answer and resolve questions related to the VINCI infrastructure, VHA data, and statistical methods.

My leadership experience, clinical background, experience in analyzing various types of data such as large-scale, large claims data, wearable data, and survey data, my statistical expertise in modern causal inference, target trial emulation, HTE estimation, and machine learning, and my analytical skills in statistical programming and manage and process large databases position me well to serve as the PI for the current proposal. I also have plenty of experience working with multidisciplinary research teams and leading statistical teams. My long-term goal is to improve patient health outcomes by applying state-of-the-art statistical methodologies and practices to provide evidence-based scientific knowledge and inform the development of effective, safe, and cost-effective treatment plans that are tailored to patient-level characteristics.

Ongoing and recently completed projects that I would like to highlight include:

R01AG074989
Bress, Adam and Cohen, Jordana (MPI); Role: **Co-Investigator**
03/01/2022–12/31/2025
*Informing optimal first-line antihypertensive therapy: A rigorous comparative effectiveness analysis of ARBs vs. ACEIs on long-term risk of dementia, cancer, heart disease, and quality of life.*

5R01HL144555
Shah, Nigam H (PI); Role: **Co-Investigator**
04/01/2019–02/28/2023
*Applying statistical learning tools to personalize cardiovascular treatment.*

Selected Relevant Publications:

a. **Xu, Y.**, Greene, T.H., Bress, A.P., Sauer, B.C., Bellows, B.K., Zhang, Y., Weintraub, W.S., Moran, A.E. and Shen, J. (2022). Estimating the optimal individualized treatment rule from a cost-effectiveness perspective. Biometrics, 78(1), pp.337-351.
b. **Xu, Y.**, Greene, T.H., Bress, A.P., Bellows, B.K., Zhang, Y., Zhang, Z., Kolm, P., Weintraub, W.S., Moran, A.S. and Shen, J. (2022). An Efficient Approach for Optimizing the Cost-effective Individualized Treatment Rule Using Conditional Random Forest. Statistical Methods in Medical Research.
c. **Xu, Y.** and Yadlowsky, S. (2022). Calibration Error for Heterogeneous Treatment Effects. In International Conference on Artificial Intelligence and Statistics (pp. 9280-9303) (AISTAT 2022)
d. **Yizhe Xu**, Nikolaos Ignatiadis, Erik Sverdrup, Scott Fleming, Stefan Wager, Nigam Shah (2023). Handbook of Matching and Weighting Adjustments for Causal Inference. Chapter 21: Treatment Heterogeneity with Survival Outcomes. Edited by JosÅLe R. Zubizaretta, Elizabeth A. Stuart, Dylan S. Small, Paul R. Rosenbaum. Chapman & Hall/CRC Press.
e. **Xu Y**, Bechler K, Callahan A, et al. Principled estimation and evaluation of treatment effect heterogeneity: A case study application to dabigatran for patients with atrial fibrillation. *J Biomed Inform*. 2023 Jul;143:104420. PMID 37328098.
f. **Xu Y**, Foryciarz A, Steinberg E, et al. Clinical utility gains from incorporating comorbidity and geographic location information into risk estimation equations for atherosclerotic cardiovascular disease. *J Am Med Inform Assoc*. 2023 Apr 19;30(5):878-887. PMID 36795076; PMCID PMC10114071.
g. Ethan Steinberg, Jason Fries, **Yizhe Xu**, and Nigam Shah (2023). A Time-to-Event Foundation Model for Structured Medical Records. Accepted by the Twelfth International Conference on Learning Representations (ICLR 2024).

## B. Positions, Scientific Appointments, and Honors

**Positions and Scientific Appointments**

| | |
|---|---|
| 2023–present | Assistant Professor, University of Utah, Utah |
| 2020–2023 | Postdoc Scholar, Stanford University, CA |
| 2016–2020 | Graduate Assistant, University of Utah, Utah |
| 2014–present | Member, American Statistical Association |
| 2014–2016 | Research Assistant, University of Utah, Utah |
| 2011–2012 | Registered Nurse, Feng Tian Hospital, Shenyang, LN, China |

**Honors**

| | |
|---|---|
| 2022 | Poster presentation at American Causal Inference Conference, Berkeley, CA |
| 2022 | Poster presentation at Artificial Intelligence and Statistics, 2022, virtual conference. |
| 2021 | Award for Student Paper Competition at Journal of Statistical Meetings (JSM) Health Policy Statistics Section, Seattle, USA |
| 2019 | Award for Student Paper Competition at American Statistical Association (ASA), Biopharmaceutical Section Regulatory-Industry Statistics Workshop Program, Washington DC |
| 2017 | Poster presentation in Association for Clinical and Translational Science, Washington DC |
| 2016 | Student of the Year, University of Utah |
| 2011 | Student of the Year, Liaoning Medical University |

## C. Contributions to Science

1. **Developed Statistical Methods for Estimating the Optimal Individualized Treatment Rule (ITR) from A Cost-Effectiveness Perspective.**
   My early work in the field of comparative effectiveness research focused on the estimation of average treatment effects. Recently, several statistical methods have been developed to identify the treatment that maximizes patients' health outcomes but without considering medical expenditure, which is a pressing issue in the U.S. healthcare system. While health economic evaluations conduct a cost-effectiveness (CE) analysis to balance treatment efficacy and treatment-related incremental costs, they typically inform treatment decisions at a population level, which may be suboptimal for patients who deviate from the 'average' participants. The gaps in the above two fields motivated me to develop statistical tools that jointly consider the impact of effectiveness and cost on treatment decisions and identify the most cost-effective treatment rule that accounts for individual heterogeneity. I conducted comprehensive simulation studies to show the validity of my proposed methods and applied them to the Systolic Blood Pressure Intervention Trial (SPRINT) to demonstrate the CE gains from utilizing a personalized and cost-effective blood pressure control strategy. In the follow-up work, I improved my method by further proposing partitioned classification weight estimators and applying a more advanced machine learning method, which led to a more accurate and efficient estimation of the optimal CE-ITR. The data, statistical methods, and software implementations resulting from my dissertation work, funded by an NHLBI R01 award, are cited and applied by several other studies to improve decision-making in various fields.
   a. **Xu Y**, Greene TH, Bress AP, et al. Estimating the optimal individualized treatment rule from a cost-effectiveness perspective. *Biometrics*. 2022;78(1):337-351. doi:10.1111/biom.13406. PMID: 33215693; PMCID: PMC8134511.
   b. **Xu Y**, Greene TH, Bress AP, et al. *CEAOptimalITR* for estimating the optimal individualized treatment rule from a cost-effectiveness perspective [R package/function]. 2020. Hosted at Github.com, under CrystalXuR
   c. **Xu Y**, Greene TH, Bress AP, et al. An efficient approach for optimizing the cost-effective individualized treatment rule using conditional random forest. Stat Methods Med Res. 2022 Nov;31(11):2122-2136. PMID: 35912490.
   d. **Xu Y**, Greene TH, Bress AP, et al. *EfficientCEITR*, an efficient approach for optimizing the cost-effective individualized treatment rule using conditional random forest [R function]. 2021. Hosted at Github.com, under CrystalXuR

2. **Developed An Evaluation Metric for Heterogeneous Treatment Effect (HTE) Estimates.**

During my doctoral training, I learned many advanced data-driven methods for modeling heterogeneous treatment effects (HTEs). Even still, estimation of HTEs is a difficult task as these methods frequently over- or under-estimate the treatment effects, leading to poor calibration of the resulting models. However, while many methods exist for evaluating the calibration of prediction and classification models, formal approaches to assess the calibration of HTE models are limited to the calibration slope. In this work, I defined an analogue of the $l_2$ expected calibration error for HTEs and proposed a robust estimator. My approach is motivated by doubly robust treatment effect estimators, making it unbiased, and resilient to confounding, overfitting, and high-dimensionality issues. Furthermore, my method is straightforward to adapt to many structures under which treatment effects can be identified, including randomized trials, observational studies, and survival analysis. I also illustrated how to use my proposed metric to evaluate the calibration of learned HTE models through the application to the CRITEO-UPLIFT Trial. This work, funded by NHLBI 5R01HL144555, has attracted several researchers' attention during and after my poster presentation at the 2022 Artificial Intelligence and Statistics Meeting (AISTAT). With the software implementation I provided, and after the publication on AISTAT proceedings is available, I anticipate this metric to become a standard and popular evaluation tool for assessing the performance of HTE methods.

a. **Xu Y**, Yadlowsky S. Calibration error for heterogeneous treatment effects. Paper and poster presented at: Artificial Intelligence and Statistics Virtual Conference 2022; March 28-30, 2022; Virtual. Paper arXiv:2203.13364. Accessed January 26, 2024. doi:10.48550/arXiv.2203.13364.
b. **Xu Y**, Yadlowsky S. *ECETH*, estimated calibration error for treatment heterogeneity [R functions]. 2022. Hosted at Github.com, under CrystalXuR
c. **Xu Y**, Yadlowsky S. Calibration error for heterogeneous treatment effects [Video]. 2022. Hosted at SlidesLive.com

3. **Benchmarked State-of-the-art Metalearners for Heterogeneous Treatment Effects on Survival Outcomes.**

My research in the past four years focused on the estimation of conditional average treatment effects (CATEs). Recently, several metalearners have been proposed to estimate CATEs in an effective and flexible way; however, their performance varies across a number of characteristics of a given study and also depends on the base learners used for executing each metaalgorithm. The lack of characterization of each CATE learner's performance and instructions on how to estimate CATEs appropriately become the barrier that prevents practitioners from applying these advanced statistical tools in their research. To fill this gap, I conducted comprehensive simulation studies to assess the performance of CATE estimation methods in the presence of right censoring. I compared 14 estimation approaches from combining five state-of-the-art metalearners (S-, T-, X-, F-, and R-learners) with two advanced machine learning methods (lasso and generalized random forest) as the base learners. I considered several data generating processes that create data with varied complexity of response and CATE functions, censoring rates, effective sample sizes, and amounts of heterogeneity in treatment effects, as well as under unbalanced design. I provided a flowchart to summarize the main takeaways based on my findings from the simulation study. I also created a software package *survlearner* that includes the implementation of all the metalearners we compared, along with tutorial webpages, to teach practitioners the proper ways of estimating CATEs and further improve the quality of quantitative research in personalized medicine.

a. **Xu Y**, Ignatiadis N, Sverdrup E, et al. Treatment Heterogeneity with Survival Outcomes. In: Zubizarreta JR, Stuart EA, Small DS, et al, eds. *Handbook of Matching and Weighting Adjustments for Causal Inference*; 2023:chap21. doi:10.1201/9781003102670
b. **Xu Y**, Ignatiadis N, Sverdrup E, et al. *survlearners*, Metalearners for heterogeneous treatment effects on survival outcomes [R package]. 2022. Hosted at Github.com, under som-shahlab

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/yizhe.xu.1/bibliography/public/

# BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Beddhu, Srinivasan

eRA COMMONS USER NAME (credential, e.g., agency login): SRINIBEDDHU

POSITION TITLE: Professor of Internal Medicine and DRF Presidential Endowed Chair

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Stanley Medical College, Chennai, India | MBBS | 06/1989 | Medicine |
| Bangalore University, Bangalore, India | Resident | 12/1992 | Internal Medicine |
| St. Mary's Hospital, Rochester, NY | Resident | 06/1996 | Internal Medicine |
| University of Pittsburgh, Pittsburgh, PA | Fellow | 06/1999 | Nephrology |

## A. Personal Statement

My research on Cardiovascular, Kidney and Metabolic (CKM) Syndrome focuses on cardiovascular disease, hypertension, obesity, diabetes and lifestyle factors in CKD. I serve as a founding Co-Director of Cardio-Renal and Metabolism Center (CRMC) at the University of Utah. I was actively involved for 9 years in the NIH funded Systolic Blood Pressure Intervention Trial (SPRINT) as the Co-Director of the Utah Clinical Center Network (CCN) and the Utah site- PI. I also served as Utah clinical site PI. We randomized 200 participants in SPRINT at the Utah clinical site. I lead SPRINT- Factors affecting Atherosclerosis Study (FAST) (R01DK091437), a multi-center SPRINT ancillary study of 503 participants examining the role of CKD in carotid MRI measured progression of atherosclerosis in 8 SPRINT sites across the country. I am PI (R01DK128640 and R01AG074592 ) or site PI (VA CSP-2008) of federally funded projects with current federal total funding of ~$1.2 million a year. I lead a strong research team that currently includes Dr. Amara Sarwal, Assistant Professor of Medicine and Dr. Sydney Hartsell, third-year nephrology CV T32 fellow in addition to the research personnel (1 Sr. clinical research coordinator, 2 clinical study assistants, 1 master level statistician, 1 senior research scientist, 3 post-docs and 3 graduate research assistants). I have mentored junior faculty, post-docs, fellows, residents, graduate students and medical students some of whom have become independent, funded investigators.

Some of my projects and papers relevant to the current proposal are listed below.

**R01DK128640** (Beddhu) 05/15/2021 – 04/30/2026
NIH/NIDDK
Sit Less, Interact and Move More (SLIMM) 2 Study
Role: PI
The objective of this RCT is to examine whether co-intervention with semaglutide/ resistance training improves adherence to an intervention targeting sedentary behavior (prolonged sitting/ laying down) in CKD.

**R01AG074592-01** (Beddhu) 07/015/2021- 03/31/2026
NIH/NIA
Objectively Measured Sedentary Behavior and Physical Activity in PREVENTABLE Study
Role: PI

The objective of this ancillary study to PREVENTABLE Trial is to examine the associations of sedentary behavior with the risk of cognitive impairment/ dementia.

**T35DK103596** (Beddhu, Round) 03/01/2015 - 02/28/2026
NIH/NIDDK
Role: PI
MSRP in Metabolism, Diabetes, Digestive and Kidney Diseases
The objective of this grant is to provide summer training program for medical students in cutting edge research projects across the translational research spectrum in areas of interest to KUH branch of NIDDK.

**ORH-14398** (Beddhu)
10/01/2023-09/30/2024
VA Office of Rural Health
Automatic E-Consults for Evidence Based Use of SGLT-2 Inhibitors in Rural Veterans with Chronic Kidney Disease
Role: PI
The project evaluates the racial and ethnic disparities in the use of SGLT2i in a cohort of rural Veterans.

The following publications highlight my prior work related to CKM Syndrome.

1. ***Beddhu S***, Shen J, Cheung AK, Kimmel PL, Chertow GM, Wei G, Boucher RE, Chonchol M, Arman F, Cambell RC, Contreras G, Dwyer JP, Freedman BI, Ix JH, Kirchner K, Papademetriou V, Pisoni R, Rocco MV, Whelton PK and Greene T. Implications of early decline in estimated glomerular filtration rate due to intensive blood pressure control for cardiovascular outcomes in SPRINT. *J Am Soc Nephrol.* 2019 Aug;30(8):1523-1533.
2. ***Beddhu S*,** Chertow GM, Cheung AK, Cushman, WC, Rahman M, Greene T, Wei G, Campbell RC, Conroy M, Freedman BI, Haley W, Horwitz E, Kitzman D, Lash J, Papademetriou V, Pisoni R, Riessen E, Rosendorff C, Watnick SG, Whittle J, Whelton PK for the SPRINT Research Group. Influence of baseline diastolic blood pressure on effects of intensive compared to standard blood pressure control. *Circulation.* 2018 Jan9; 137(2): 134-143. PMCID: PMC5760457
3. ***Beddhu S***, Greene T, Boucher R, Cushman WC, Wei G, Stoddard G, Ix JH, Chonchol M, Kramer H, Cheung AK, Kimmel PL, Whelton PK, Chertow GM. Intensive systolic blood pressure control and incident chronic kidney disease in people with and without diabetes mellitus: secondary analyses of two randomised controlled trials. *Lancet Diabetes Endocrinol*. 2018 Jul;6(7):555-563. doi: 10.1016/S2213-8587(18)30099-8. Epub 2018 Apr 21.PMID: 29685860; PMCID: PMC6071316.
4. SPRINT Research Group, Lewis CE, Fine LJ, ***Beddhu S***, Cheung AK, Cushman WC, Cutler JA, Evans GW, Johnson KC, Kitzman DW, Oparil S, Rahman M, Reboussin DM, Rocco MV, Sink KM, Snyder JK, Whelton PK, Williamson JD, Wright JT Jr, Ambrosius WT. Final Report of a Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med.* 2021 May 20;384(20):1921-1930. doi: 10.1056/NEJMoa1901281.PMID: 34010531; PMCID: PMC9907774.

**B. Positions and Honors**

**Positions and Employment**

| | |
|---|---|
| 1989-1990 | House Officer, Internal Medicine, Stanley Medical College, Madras, India. |
| 1991-1992 | Internal Medicine Resident, Bangalore University, Bangalore, India. |
| 1993-1996 | Internal Medicine Resident, St. Mary's Hospital, Rochester, NY. |
| 1996-1998 | Renal Fellow, University of Pittsburgh, Pittsburgh, PA. |
| 1998-1999 | Clinical Research Fellow, Renal Division, University of Pittsburgh, Pittsburgh, PA. |
| 1999-2006 | Director, End-Stage Renal Disease Program, VAMC, Salt Lake City, UT. |
| 1999-2002 | Assistant Professor of Clinical Medicine, University of Utah, Salt Lake City, UT. |
| 2002-2006 | Assistant Professor of Medicine, University of Utah, Salt Lake City, UT. |
| 2006-2012 | Associate Professor of Medicine, University of Utah, Salt Lake City, UT |
| 2012- | Professor of Medicine, University of Utah, Salt Lake City, UT |

| | |
|---|---|
| 10/2019- | Chief, Renal Section, Salt Lake VA Healthcare System |
| 2020 –2024 | Clinical Research Medical Director, Department of Internal Medicine, University of Utah |
| 7/2024 - | Co-Director, Cardio-Renal & Metabolism Center, University of Utah, Salt Lake City, UT |

**Honors**

| | |
|---|---|
| 1985 | Sankunnie Marar Gold medal for Proficiency in Physiology |
| 1986 | Microbiology Prize Examination, Second Prize. |
| 1987 | Merit Certificate of Honor in Pathology |
| 1996 | Best Outgoing Resident. Senior leadership award for excellence in knowledge, teaching and leadership qualities as a resident . |
| 2005 | William Odell Young Investigator Award. University of Utah |
| 2006 | Award of Tenure, University of Utah |
| 2009-2011 | Amundsen Endowed Chair in Medicine |
| 2011 | Univ of Utah Alumni Association Golden Anniversary Prize for Distinguished Clinical Investigation |
| 2018 | Dialysis Research Foundation Presidential Endowed Chair in Medicine |

**Professional Memberships**

Member – American Society of Nephrology, National Kidney Foundation, International Society of Nephrology

**Professional or Scientific Review Committees**

| | |
|---|---|
| 1999-2002 | Member, Outcomes Committee, NIH sponsored HEMO trial |
| 2000-2003 | Member, Institutional Review Board, University of Utah, Salt Lake City, Utah |
| 2001-2004 | Member, National Kidney Foundation K/DOQI Committee on Cardiovascular Disease in Hemodialysis |
| 2003 | Abstract reviewer, American Society of Nephrology |
| 2006 | Abstract reviewer, American Society of Nephrology |
| 02/2006 | Reviewer, NIDDK (ZRG1 KNOD-N(01)Q) panel |
| 06/2006 | Reviewer, NIDDK SEP (ZRG1 RUS-A 51) |
| 10/2006 | Reviewer, NIDDK SEP (ZDK1 GRB-G J2) |
| 03/2007 | Reviewer, NIDDK SEP (ZRG1 RUS-A (51) (1) |
| 04/2007 | Member, National Kidney Foundation 2008 Clinical Meeting Program Committee |
| 06/2007 | Reviewer, NIDDK SEP (ZDK1 GRB-G J2) |
| 02/2008 | Member, National Kidney Foundation Grant Review Committee |
| 03/2008 | Reviewer, NIDDK SEP (ZDK1 GRB-O1) O'Brien Center |
| 04/2008 | Reviewer, NIDDK SEP ZDK1 GRB-7 (M1) |
| 05/2008 | Member, National Kidney Foundation 2008 Clinical Meeting Program Committee |
| 06/2008 | Reviewer, NIDDK (ZRG1 KNOD-N(01)Q) |
| 06/2008 | Member, NKF Kidney Learning System Editorial Board |
| 11/2008 | Reviewer, NIDDK SEP ZRG1 RUS-F (51) S |
| 02/2009 | Member, National Research Committee, NKF |
| 10/2009 | Reviewer, NIDDK ZDK1 GRB-S (O1) 2 |
| 10/2009 | Reviewer, NIDDK ZRG1 EMNR-E (10) B |
| 01/2010 | Chair, NIDDK ZDK1 GRB-7 (J4) 1 |
| 02/2010 | Member, National Research Committee, NKF |
| 02/2010 | Member, NIDDK ZDK1 GRB-G (M1) 1 |
| 06/2010 | Abstract Category Chair (for the abstract category: Dialysis: Epidemiology, Outcomes, and Clinical Trials: Cardiovascular), American Society of Nephrology Annual Meeting |
| 03/2011 | Reviewer, ZRG1 DKUS-C (81) S |
| 05/2011 | Reviewer, ZDK1 GRB-S (O5) 1 |
| 03/2012 | Reviewer, ZDK1 GRB-6 (M3) |
| 07/2012 | Reviewer, ZDK1 GRB-7 (O3) S |
| 10/2012 | Ad-hoc reviewer, NIH PBKD Study section |
| 05/2013 | Reviewer, ZKD1 GRB-C (M1) 1 |
| 10/2010 | Member, SPRINT Utah Hub Executive Committee, Member, SPRINT Ancillary Sciences Committee |

01/2012 Member, ASN Grants Review Committee
06/2012 Member, Editorial Board, Journal of Renal Nutrition
01/2014 Member, Editorial Board, Clinical Journal of American Society of Nephrology
10/20- 6/24 Standing Member, NIDDK DDK-D Study Section

## C. Contributions to Science

1. My early work as a renal fellow was on identifying a tool that could be used to quantify comorbidity on dialysis patients. The impetus for these studies was to identify an easy to use case-mix adjustment in dialysis patients that was more than the then prevailing 4 variable tool of age, gender, race and diabetes used by USRDS but much less complicated than the Index of Coexistent Diseases (ICED) used in the HEMO Study. Hence, we used the modified Charlson Comorbidity Index. These publications played a significant role in widespread adoption of Charlson Comorbidity Index in the CKD and dialysis population studies.
   a. ***Beddhu S,*** Zeidel ML, Saul M, Seddon P, Samore MH, Stoddard GJ, Bruns FJ. The effects of comorbid conditions on the outcomes of patients undergoing peritoneal dialysis. Am J Med. 2002 Jun 15;112(9):696-701.
   b. ***Beddhu S***, Bruns FJ, Saul M, Seddon P, Zeidel ML. A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. Am J Med. 2000 Jun 1;108(8):609-13.

2. When I was a junior faculty, I developed a keen interest in obesity and lifestyle factors in CKD/ dialysis patients. I have been pursuing this area for the past several years and this remains an active area of my research.
   a. ***Beddhu S***, Pappas LM, Ramkumar N, Samore M. Effects of body size and body composition on survival in hemodialysis patients. J Am Soc Nephrol. 2003 Sep;14(9):2366-72.
   b. Martinson M, Ikizler TA, Morrell G, Wei G, Almeida N, Marcus RL, Filipowicz R, Greene TH, ***Beddhu S***. Associations of body size and body composition with functional ability and quality of life in hemodialysis patients. Clin J Am Soc Nephrol. 2014 Jun 6;9(6):1082-90. Do 10.2215/CJN.09200913. Epub 2014 Apr 24. PMCID: PMC4046730
   c. ***Beddhu S***, Wei G, Marcus RL, Chonchol M, Greene T. Light-intensity physical activities and mortality in the United States general population and CKD subpopulation. Clin J Am Soc Nephrol. 2015 Jul 7;10(7):1145-53. doi:10.2215/CJN.08410814. Epub 2015 Apr 30. PMID: 25931456; PMCID: PMC4491291.
   d. Lyden K, Boucher R, Wei G, Zhou N, Christensen J, Chertow GM, Greene T, ***Beddhu S***. Targeting Sedentary Behavior in CKD: A Pilot and Feasibility Randomized Controlled Trial. Clin J Am Soc Nephrol. 2021 May 8;16(5):717-726. doi: 10.2215/CJN.12300720. Epub 2021 Apr 22. PMID: 33888536; PMCID: PMC8259480.

3. My work related to hypertension, cardiovascular events, metabolic complications and cognitive function decline in type 2 diabetes are highlighted by the following publications.
   a. Rathi N, Whelton PK, Chertow GM, Cushman WC, Cheung AK, Wei G, Boucher R, Kimmel PL, Bress AP, Kramer HJ, Al-Marji C, Greene T, ***Beddhu S***. Influence of Prediabetes on the Effects of Intensive Systolic Blood Pressure Control on Kidney Events. Am J Hypertens. 2019 Nov 15;32(12):1170-1177. doi: 10.1093/ajh/hpz105. PMID: 31257407; PMCID: PMC6856623.
   b. Ilkun OL, Greene T, Cheung AK, Whelton PK, Wei G, Boucher RE, Ambrosius W, Chertow GM, ***Beddhu S***. The Influence of Baseline Diastolic Blood Pressure on the Effects of Intensive Blood Pressure Lowering on Cardiovascular Outcomes and All- Cause Mortality in Type 2 Diabetes. Diabetes Care. 2020 Aug;43(8):1878-1884. doi: 10.2337/dc19-2047. Epub 2020 May 4. PMID: 32366577; PMCID: PMC7372050.
   c. Grube D, Wei G, Boucher R, Abraham N, Zhou N, Gonce V, Carle J, Simmons DL, ***Beddhu S***. Insulin use in chronic kidney disease and the risk of hypoglycemic events. BMC Nephrol. 2022 Feb 21;23(1):73. doi: 10.1186/s12882-022-02687-w. PMID: 35189851; PMCID: PMC8862360.
   d. Gupta A, Boucher R, Wei G, Gronseth G, Parks A, ***Beddhu S***. Influence of Baseline Diastolic Blood Pressure on the Effects of Systolic Blood Pressure Lowering on Cognitive Function in Type 2 Diabetes Mellitus. Am J Hypertens. 2023 Feb 13;36(2):120-125. doi: 10.1093/ajh/hpac118. PMID: 36227718; PMCID: PMC9922945.

4. As mentioned in the personal statement section, I played a leadership role in SPRINT publications. This work resulted in several high impact publications.
   a. ***Beddhu S***, Rocco MV, Toto R, Craven TE, Greene T, Bhatt U, Cheung AK, Cohen D, Freedman BI, Hawfield AT, Killeen AA, Kimmel PL, Lash J, Papademetriou V, Rahman M, Rastogi A, Servilla K, Townsend RR, Wall B, Whelton PK; SPRINT Research Group. Effects of Intensive Systolic Blood Pressure Control on Kidney and Cardiovascular Outcomes in Persons Without Kidney Disease: A Secondary Analysis of a Randomized Trial. Ann Intern Med. 2017 Sep 19;167(6):375-383. doi: 10.7326/M16-2966. Epub 2017 Sep 5. PMID: 28869987; PMCID: PMC8545525
   b. Bress AP, Bellows BK, King JB, Hess R, ***Beddhu S***, Zhang Z, Berlowitz DR, Conroy MB, Fine L, Oparil S, Morisky DE, Kazis LE, Ruiz-Negrón N, Powell J, Tamariz L, Whittle J, Wright JT Jr, Supiano MA, Cheung AK, Weintraub WS, Moran AE; SPRINT Research Group. Cost-Effectiveness of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2017 Aug 24;377(8):745-755. PMCID: PMC5708850
   c. ***Beddhu S***, Chertow GM, Greene T, Whelton PK, Ambrosius WT, Cheung AK, Cutler J, Fine L, Boucher R, Wei G, Zhang C, Kramer H, Bress AP, Kimmel PL, Oparil S, Lewis C, Rahman R and Cushman WC. Effects of intensive systolic blood pressure lowering on cardiovascular events and mortality in persons with type 2 diabetes on standard glycemic control and in persons without diabetes: reconciling results from ACCORD BP and SPRINT. *J Am Heart Assoc*. 2018 Sep 18;7(18):e009326. doi: 10.1161/JAHA.118.009326.PMID: 30371182; PMCID: PMC6222943.
   d. Pajewski NM, ***Beddhu S***, Bress AP, Chang TI, Chertow GM, Cheung AK, Cushman WC, Freedman BI, Greene T, Johnson KC, Jaeger BC, Tamura MK, Lewis CE, Rahman M, Reboussin DM, Rocco MV, Williamson JD, Whelton PK, Wright JT Jr, Drawz PE, Ix JH. The Legacy Effect of Intensive versus Standard Blood Pressure Control on the Incidence of Dialysis or Kidney Transplantation. J Am Soc Nephrol. 2024 Jul 30. doi: 10.1681/ASN.0000000000000459. Epub ahead of print. PMID: 39078712.

**Link to publications: https://pubmed.ncbi.nlm.nih.gov/?term=beddhu&sort=pubdate**

# BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Bress, Adam

eRA COMMONS USER NAME (credential, e.g., agency login): ADAMBRESS

POSITION TITLE: Associate Professor with Tenure, Vice Chair of Research, Department of Population Health Sciences, University of Utah School of Medicine; and Associate Investigator, VA Salt Lake City Health Care System

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of Maryland, Baltimore | PharmD | 05/2009 | Pharmacy |
| Yale-New Haven Hospital, New Haven | Resident | 06/2010 | Pharmacy Practice Residency |
| University of Illinois at Chicago, Chicago | Resident | 06/2011 | Cardiology Residency |
| University of Illinois at Chicago, Chicago | MS | 05/2013 | Clinical and Translational Science |
| University of Illinois at Chicago, Chicago | Fellow | 06/2013 | Cardiovascular Pharmacogenomics |

## A. Personal Statement

I am well positioned for my role as Co-I on our Utah CTSI Pilot grant proposal titled "An Efficient, high-Quality, Unbiased, Interpretable Pipeline for Overcoming Barriers in the Translational Research using Real-World Data." This project builds a platform for systemizing and expanding translational research using real-word data (RWD). We will work with other clinicians and researchers closely to define clear and feasible research questions, conduct target trial emulation to align available data to the question, and apply unbiased and robust modern causal inference methods to answer the question. The results of this project will provide three sets of research tools to enable high-quality estimation of average treatment effects, heterogeneous treatment effects, and optimal dynamic treatment regimens using observational data. Within each research tool, we will provide a comprehensive research schema that includes step-by-step instructions for study design, data preparation, and data analysis, accompanied by alternative strategies for anticipated issues and guidance of accurately reporting and interpreting results in the schema. In addition, we will provide a public deployment tool for each research schema. EQUIP will enable clinicians and researchers across diverse disciplines to apply cutting-edge methods with enhanced efficiency.

I have training in cardiovascular clinical pharmacy, causal inference, and epidemiology from Yale, the University of Illinois at Chicago, and the University of Utah. I am a formally trained cardiovascular clinical pharmacist and population scientist with a record of NIH funding, leading successful collaborations, and productive publication with evidence of impact. My 5-year NHLBI Career Development Award (K01HL133468) produced 12 lead-authored original research publications, including 1 in the *New England Journal of Medicine*, 2 in *Circulation*, and another in *Diabetes Care*.

I am currently MPI or PI on 2 active R01s and 1 active K24 through the National Institute on Aging (NIA). NIA R01AG074989, for which I am MPI with Jordana Cohen uses national Veterans Health Administration and Kaiser Permanente Southern California data to determine the long-term comparative effects of two specific antihypertension medication classes (ARBs and ACEIs) on the risk of several clinical outcomes, including dementia, accounting for level of illness and quality of life. My other NIA R01 (R01AG065805), for which I am PI, examines effects of ARBs vs. ACEIs on adjudicated cognitive outcomes in the SPRINT MIND randomized trial data. My NIA K24 mentoring award (K24AG080168) further enables me to broaden and deepen my mentorship program.

My experience and expertise with applying causal inference methods to study anti-HTN medication use, responses, and outcomes in large clinical and administrative databases positions me well to serve as Co-I for the current pilot proposal. I have successfully designed, led, and published several manuscripts investigating medication use and effects using VHA data. I have substantial experience in building high-quality analysis-

ready VHA data sets and implementing rigorous causal inference methods accounting for time-varying treatment and confounding, out-of-system healthcare utilization, and intercurrent events directly relevant to the current proposal. I also have a history of productive collaborations with the PI Dr. Xu.
Of note, I have not published research under any other name.

Ongoing and recently completed projects that I would like to highlight are as follows:

K24AG080168 NIH / NIA
Bress, Adam (PI)
02/01/2023–01/31/2028
*Using pharmacoepidemiology to optimize antihypertensive medication use to prevent aging-related multimorbidity: Midcareer investigator award in patient-oriented research and mentoring.*

R01AG074989 NIH / NIA
Bress, Adam (MPI)
03/15/2022–12/31/2025
*Informing optimal first-line antihypertensive therapy: A rigorous comparative effectiveness analysis of ARBs vs. ACEIs on long-term risk of dementia, cancer, heart disease, and quality of life*

R01AG065805 NIH / NIA
Bress, Adam (PI)
08/01/2020–04/30/2025 (No-cost Extension)
*Guiding next steps for SPRINT-MIND implementation: Identifying high-benefit subgroups and comparative effects of ARB- vs. ACEI-based regimens*

R01HL139837 NIH / NHLBI
Bress, Adam (MPI)
12/15/2017–11/30/2023
*Patient level prediction of clinical outcomes and cost-effectiveness in SPRINT (Optimize-SPRINT)*

Citations:

1. King JB, Berchie RO, Derington CG, Marcum ZA, Scharfstein DO, Greene TH, Herrick JS, Jacobs JA, Zheutlin AR, **Bress AP**, Cohen JB. New Users of Angiotensin II Receptor Blocker-Versus Angiotensin-Converting Enzyme Inhibitor-based Antihypertensive Medication Regimens and Cardiovascular Disease Events: A Secondary Analysis of ACCORD-BP and SPRINT. *J Am Heart Assoc*. 2023;12(17):e030311. PMID: 37646208; PMCID: PMC10547357.
2. Marcum ZA, Gabriel N, **Bress AP**, Hernandez I. Association of New Use of Antihypertensives that Stimulate vs Inhibit Type 2 and 4 Angiotensin II Receptors with Dementia among Medicare Beneficiaries. *JAMA Netw Open*. 2023;6(1):e2249370. PMID: 36598787; PMCID: PMC9856661.
3. Cohen JB, Marcum ZA, Zhang C, Derington CG, Greene TH, Ghazi L, Herrick JS, King JB, Cheung AK, Bryan N, Supiano MA, Sonnen JA, Weintraub WS, Scharfstein D, Williamson J, Pajewski NM, **Bress AP**. Systolic Blood Pressure Intervention Trial (SPRINT) Research Group. Risk of Mild Cognitive Impairment or Probable Dementia in New Users of Angiotensin II Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors: A Secondary Analysis of Data from the Systolic Blood Pressure Intervention Trial (SPRINT). *JAMA Netw Open*. 2022;5(7):e2220680. PMID: 35834254; PMCID: PMC9284332.
4. Marcum ZA, Cohen JB, Zhang C, Derington CG, Greene TH, Ghazi L, Herrick JS, King JB, Cheung AK, Bryan N, Supiano MA, Sonnen JA, Weintraub WS, Williamson J, Pajewski NM, **Bress AP**. SPRINT Research Group. Association of Antihypertensives that Stimulate vs Inhibit Types 2 and 4 Angiotensin II Receptors with Cognitive Impairment. *JAMA Netw Open*. 2022;5(1):e2145319. PMID: 35089354; PMCID: PMC8800076.


**B. Positions, Scientific Appointments, and Honors**

**Positions and Scientific Appointments**

2020–present Vice Chair of Research, Department of Population Health Science, University of Utah School of Medicine, Salt Lake City

| | |
|---|---|
| 2020–present | Associate Professor with Tenure, Department of Population Health Science, University of Utah School of Medicine, Salt Lake City |
| 2016–2020 | Assistant Professor, Department of Population Health Science, University of Utah School of Medicine, Salt Lake City |
| 2016–present | Investigator, George E. Whalen Veterans Health Administration Salt Lake City Health Care System, Salt Lake City |
| 2015–present | Member, Million Veterans Program Genotype Quality Control Working Group |
| 2014–present | Member, Jackson Heart Study: Hypertension Working Group |
| 2014–2016 | Research Assistant Professor, Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City |
| 2012–present | Member, American College of Cardiology |
| 2009–present | Member, American Heart Association |

**Honors**

| | |
|---|---|
| 2022 | Research Impact Award, University of Illinois Chicago College of Pharmacy |
| 2022 | Mentoring Award, Department of Internal Medicine, University of Utah School of Medicine |
| 2020 | Fellow in Pharmacy, National Academy of Medicine |
| 2018 | New Investigator Award, American College of Clinical Pharmacy (ACCP) |
| 2018 | Vitae Speaker, University of Utah Health Sciences |
| 2016 | Outstanding Paper of the Year Award, ACCP Cardiology Practice and Research Network (PRN) |
| 2016 | Junior Investigator Award, ACCP Cardiology PRN |
| 2015 | New Investigator Research Presentation Podium Award, International Society of Pharmacoeconomics and Outcomes Research (ISPOR) |
| 2015 | Vice President's Clinical and Translational (VPCAT) Research Scholar Program, University of Utah |
| 2013 | Best Cardiac Care Associate Poster, American College of Cardiology |
| 2013 | Fellowship Research Award, UIC College of Pharmacy |
| 2012 | Research Day Poster Competition, First Place, UIC College of Pharmacy |

## C. Contributions to Science

**1. Disentangling the comparative effects of antihypertensive medication class on cognitive outcomes.** Mechanistic data show that anti-HTN medications that stimulate angiotensin II type 2/4 receptors (AT2/AT4R) confer beneficial effects on the brain. I have led causal inference studies in SPRINT MIND showing that prevalent users of anti-HTN medications that stimulate (ARBs) vs. inhibit (ACEIs) AT2/AT4R have 25% lower risk of mild cognitive impairment or dementia. Although not strong, we also found evidence of lower risk of amnestic MCI or probable dementia among new users of an ARB vs. ACEI in the standard systolic blood pressure (SBP) treatment arm, suggesting that the benefits of intensive BP control may have diminished any potential beneficial effects of ARBs over 4.9 years' follow-up. In a follow-up study of Medicare beneficiaries, we found that new use of AT2/AT4R-stimulating agents was associated with a 16% lower risk of Alzheimer's disease and related dementias (ADRD) compared to inhibiting agents over a median follow-up of 6.9 years. Using the SPRINT MIND data and standards, we also prepared several models to predict the net cognitive benefit of intensive vs. standard BP control

a. Ghazi L, Shen J, Ying J, Derington CG, Cohen JB, Marcum ZA, Herrick JS, King JB, Cheung AK, Williamson JD, Pajewski NM, Bryan N, Supiano M, Sonnen J, Weintraub WS, Greene TH, **Bress AP.** Identifying Patients for Intensive Blood Pressure Treatment Based on Cognitive Benefit: A Secondary Analysis of the SPRINT Randomized Clinical Trial. *JAMA Netw Open*. 2023;6(5):e2314443. PMID: 37204788; PMCID: PMC10199351.
b. Marcum ZA, Gabriel N, **Bress AP**, Hernandez I. Association of New Use of Antihypertensives that Stimulate vs Inhibit Type 2 and 4 Angiotensin II Receptors with Dementia among Medicare Beneficiaries. *JAMA Netw Open*. 2023;6(1):e2249370. PMID: 36598787; PMCID: PMC9856661.
c. Cohen JB, Marcum ZA, Zhang C, Derington CG, Greene TH, Ghazi L, Herrick JS, King JB, Cheung AK, Bryan N, Supiano MA, Sonnen JA, Weintraub WS, Scharfstein D, Williamson J, Pajewski NM, **Bress AP**. SPRINT Research Group. Risk of Mild Cognitive Impairment or Probable Dementia in New Users of Angiotensin II Receptor Blockers and Angiotensin-converting Enzyme Inhibitors: A Secondary Analysis of Data from the Systolic Blood Pressure Intervention Trial (SPRINT). *JAMA Netw Open*. 2022;5(7):e2220680. PMID: 35834254; PMCID: PMC9284332.

d. Marcum ZA, Cohen JB, Zhang C, Derington CG, Greene TH, Ghazi L, Herrick JS, King JB, Cheung AK, Bryan N, Supiano MA, Sonnen JA, Weintraub WS, Williamson J, Pajewski NM, **Bress AP**. SPRINT Research Group. Association of Antihypertensives that Stimulate vs Inhibit Types 2 and 4 Angiotensin II Receptors with Cognitive Impairment. *JAMA Netw Open*. 2022;5(1):e2145319. PMID: 35089354; PMCID: PMC8800076.

**2. Mentored research.** I take great pride in the mentoring of early-stage investigators (ESIs) in the fields of pharmacoepidemiology, HTN and CVD research. My mentored research has led to important policy implications for HTN management. The role I take as a mentor is to build a foundation for my mentees to learn how to lead independent research studies and mount productive research efforts. This starts with close hands-on collaboration and evolves into an independent role for the mentee. Despite recently entering my mid-career, I have already developed a successful track record of mentoring (n=30). I recently was awarded a NIA K24 mentoring award. Many of my mentees have published articles in high-impact peer-reviewed scientific journals and developed into federally funded, independent researchers with positions in prestigious research institutions, government, and non-profit organizations.

a. Jacobs JA, Addo DK, Zheutlin AR, Derington CG, Essien UR, Navar AM, Hernandez I, Lloyd-Jones DM, King JB, Rao S, Herrick JS, **Bress AP**, Pandey A. Prevalence of Statin Use for Primary Prevention of Atherosclerotic Cardiovascular Disease by Race, Ethnicity, and 10-Year Disease Risk in the US: National Health and Nutrition Examination Surveys, 2013 to March 2020. *JAMA Cardiol*. 2023;8(5):443-52. PMID: 36947031; PMCID: PMC10034667.
b. King JB, Berchie RO, Derington CG, Marcum ZA, Scharfstein DO, Greene TH, Herrick JS, Jacobs JA, Zheutlin AR, **Bress AP**, Cohen JB. New Users of Angiotensin II Receptor Blocker- versus Angiotensin-converting Enzyme Inhibitor-based Antihypertensive Medication Regimens and Cardiovascular Disease Events: A Secondary Analysis of ACCORD-BP and SPRINT. *J Am Heart Assoc*. 2023;12(17):e030311. PMID: 37646208; PMCID: PMC10547357.
c. Zheutlin AR, Mondesir FL, Derington CG, King JB, Zhang C, Cohen JB, Berlowitz DR, Anstey DE, Cushman WC, Greene TH, Ogedegbe O, **Bress AP**. Analysis of Therapeutic Inertia and Race and Ethnicity in the Systolic Blood Pressure Intervention Trial: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Netw Open*. 2022;5(1):e2143001. PMID: 35006243; PMCID: PMC8749480.
d. Derington CG, King JB, Herrick JS, Shimbo D, Kronish IM, Saseen JJ, Muntner P, Moran AE, **Bress AP**. Trends in Antihypertensive Medication Monotherapy and Combination Use among US Adults, National Health and Nutrition Examination Survey 2005-2016. *Hypertension*. 2020;75(4):973-81. PMID: 32148129; PMCID: PMC7398637.

**3. Optimizing CV treatment to reduce aging-related morbidity and mortality.** We have used several secondary data sources (eg, VHA, NHANES, SPRINT) to evaluate polypharmacy, therapeutic inertia, and effects of using specific medication classes (eg, statins, PCSK9 inhibitors) on aging-related morbidity and mortality.

a. Jacobs JA, Derington CG, Zheutlin AR, King JB, Cohen JB, Bucheit J, Kronish IM, Addo DK, Morisky DE, Greene TH, **Bress AP**. Association between Self-reported Medication Adherence and Therapeutic Inertia in Hypertension: A Secondary Analysis of SPRINT (Systolic Blood Pressure Intervention Trial). *J Am Heart Assoc*. 2024;13(3):e031574. PMID: 38240275; PMCID: PMC11056166.
b. Zheutlin AR, Jacobs JA, Derington CG, Chaitoff A, Navar AM, **Bress AP**. Age-based Disparities in Statin Use for Primary Prevention in US Adults: National Health and Nutrition Examination Surveys 2013-2020. *J Clin Lipidol*. 2023;17(5):688-93. PMID: 37599197.
c. Zheutlin AR, Derington CG, Herrick JS, Rosenson RS, Poudel B, Safford MM, Brown TM, Jackson EA, Woodward M, Reading S, Orroth K, Exter J, Virani SS, Muntner P, **Bress AP**. Lipid-lowering Therapy Use and Intensification among United States Veterans Following Myocardial Infarction or Coronary Revascularization between 2015 and 2019. *Circ Cardiovasc Qual Outcomes*. 2022;15(12):e008861. PMID: 36252093; PMCID: PMC10680021.
d. Derington CG, Colantonio LD, Herrick JS, Cook J, King JB, Rosenson RS, Poudel B, Monda KL, Navar AM, Mues KE, Stevens VW, Nelson RE, Vanneman ME, Muntner P, **Bress AP**. Factors Associated with PCSK9 Inhibitor Initiation among US Veterans. *J Am Heart Assoc*. 2021;10(8):e019254. PMID: 33821686; PMCID: PMC8174184.

**4. Population health impact, implementation, and cost-effectiveness of intensive BP treatment.** Using participant-specific SPRINT data, we developed a model to predict patient-specific risks for benefit (all-cause mortality and CVD events) and harm with intensive vs. standard SBP control. Higher baseline CVD risk was associated with greater benefit (ie, larger absolute CVD risk reduction). Predicted CVD benefit and predicted increased treatment-related adverse event (AE) risk were correlated (Spearman correlation coefficient =-0.72), and 95% of participants who fell into the highest tertile of predicted benefit also had high or moderate predicted increases in treatment-related AE risk. We estimated that approximately 16.8 million US adults are eligible for SPRINT intensive BP treatment or treatment intensification. We also estimated that another 8 million adults are eligible if SPRINT results are generalized to patients with diabetes, history of stroke, or age <50 years. In a third study, we linked NHANES participants to the National Death Index to estimate annual mortality risk and projected that implementation of intensive SBP treatment in all eligible US adults could prevent approximately 107.5K deaths per year (95%CI 93.3K-121.2K).

a. Derington CG, **Bress AP**, Berchie RO, Herrick JS, Shen J, Ying J, Greene T, Tajeu GS, Sakhuja S, Ruiz-Negrón N, Zhang Y, Howard G, Levitan EB, Muntner P, Safford MM, Whelton PK, Weintraub WS, Moran AE, Bellows BK. Estimated Population Health Benefits of Intensive Systolic Blood Pressure Treatment among SPRINT-eligible US Adults. *Am J Hypertens*. 2023;36(9):498-508. PMID: 37378472; PMCID: PMC10403972.
b. **Bress AP**, Greene T, Derington CG, Shen J, Xu Y, Zhang Y, Ying J, Bellows BK, Cushman WC, Whelton PK, Pajewski NM, Reboussin D, Beddu S, Hess R, Herrick JS, Zhang Z, Kolm P, Yeh RW, Basu S, Weintraub WS, Moran AE, Systolic Blood Pressure Intervention Trial (SPRINT) Research Group. Patient Selection for Intensive Blood Pressure Management Based on Benefit and Adverse Events. *J Am Coll Cardiol*. 2021;77(16):1977-90. PMID: 33888247; PMCID: PMC8068761.
c. **Bress AP**, Bellows BK, King JB, Hess R, Beddhu S, Zhang Z, Berlowitz DR, Conroy MB, Fine L, Oparil S, Morisky DE, Kazis LE, Ruiz-Negron N, Powell J, Tamariz L, Whittle J, Wright JT, Jr., Supiano MA, Cheung AK, Weintraub WS, Moran AE, Group SR. Cost-effectiveness of Intensive versus Standard Blood Pressure Control. *N Engl J Med*. 2017;377(8):745-55. PMID: 28834469; PMCID: PMC5708850.
d. **Bress AP**, Kramer H, Khatib R, Beddhu S, Cheung AK, Hess R, Bansal VK, Cao G, Yee J, Moran AE, Durazo-Arvizu R, Muntner P, Cooper RS. Potential Deaths Averted and Serious Adverse Events Incurred from Adoption of the SPRINT (Systolic Blood Pressure Intervention Trial) Intensive Blood Pressure Regimen in the United States: Projections from NHANES (National Health and Nutrition Examination Survey). *Circulation*. 2017;135(17):1617-28. PMID: 28193605; PMCID: PMC5404971.

**5. Evaluation of HTN management in African Americans.** Using observational cohorts and survey data (REGARDS, JHS, and NHANES), our team investigated the associations between self-reported African American race and, separately, genetic ancestry, with HTN-related morbidity and mortality. We evaluated disparities in clinical trials for HTN interventions specific to African Americans as well as trends and factors associated with anti-HTN monotherapy among patients with uncontrolled BP.

a. Rao S, Segar MW, **Bress AP**, Arora P, Vongpatanasin W, Agusala V, Essien UR, Correa A, Morris AA, de Lemos JA, Pandey A. Association of Genetic West African Ancestry, Blood Pressure Response to Therapy, and Cardiovascular Risk among Self-reported Black Individuals in the Systolic Blood Pressure Reduction Intervention Trial (SPRINT). *JAMA Cardiol*. 2020;6(4):388-98. PMID: 33185651; PMCID: PMC7666434.
b. Zheutlin AR, Caldwell D, Anstey DE, Conroy MB, Ogedegbe O, **Bress AP**. Trends in Hypertension Clinical Trials Focused on Interventions Specific for Black Adults: An Analysis of ClinicalTrials.gov. *J Am Heart Assoc*. 2020;9(24):e018512. PMID: 33280494; PMCID: PMC7955386.
c. Colvin CL, King JB, Oparil S, Wright JT, Jr., Ogedegbe G, Mohanty A, Hardy ST, Huang L, Hess R, Muntner P, **Bress AP**. Association of Race/Ethnicity-specific Changes in Antihypertensive Medication Classes Initiated among Medicare Beneficiaries with the Eighth Joint National Committee Panel Member Report. *JAMA Netw Open*. 2020;3(11):e2025127. PMID: 33206191; PMCID: PMC7675104.
d. Langford AT, Akinyelure OP, Moore TL, Jr., Howard G, Min YI, Hillegass WB, **Bress AP**, Tajeu GS, Butler M, Jaeger BC, Yano Y, Shimbo D, Ogedegbe G, Calhoun D, Booth III JN, Muntner P. Underutilization of Treatment for Black Adults with Apparent Treatment-resistant Hypertension: JHS and the REGARDS Study. *Hypertension*. 2020;76(5):1600-7. PMID: 32924633; PMCID: PMC7685176.

**Complete List of Published Work in My Bibliography:**
https://www.ncbi.nlm.nih.gov/myncbi/adam.bress.1/bibliography/47745024/public/

# BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Chen, Y. Ann

eRA COMMONS USER NAME: ANNCHEN

POSITION TITLE: Professor, Divisions of Epidemiology and Biostatistics, Departments of Internal Medicine and Population Health Sciences, University of Utah

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| National Taiwan University, Taiwan | BS | 06/1995 | Zoology |
| University of Charleston, SC | MS | 06/2001 | Marine Biology |
| Medical Univ. of South Carolina, SC | PhD | 12/2005 | Biostatistics and Bioinformatics |
| Texas A&M University, TX | Postdoc | 07/2008 | Statistics |

## A. Personal Statement

Dr. Chen's research has been focused on developing statistical methods and computational tools for incorporating multiple omics data sources, selecting biologically relevant markers, and predicting clinical outcomes in an integrated manner. She has the expertise in statistical modeling of single cell analyses, proteomics, metabolomics, gene expression, microRNA, genome-wide sequencing data and cancer immunology. In recent years, her group has developed integrated multiomics analytical framework to identify combination therapy strategies targeting targeting tumor-immune microenviroments using bulk and single cell samples. Her group has developed several omics computational tools for this purpose, including SinCHet, SinCHet-MS, DRepMel, and ISCVAM. As a co-Investigator on multiple NIH-funded grants, she has also been a productive collaborator for various fields of cancer research, ranging from genome-wide association studies, survival analyses, biomarker selection, to clinical trials. Her wide-range of collaboration spans from basic science, translational work, and epidemiological studies to clinical trials. She will work with the Dr. Xu closely on the proposed work, and she has the expertise needed to carry out the work successfully.

**Ongoing and recently completed projects that I would like to highlight include:**

Active:

P30CA042014
Ulrich, C. (PI) Role: Co-leader Cancer Biostatistics Shared Resource
05/01/2020-04/30/2025
*Huntsman Cancer Institute Cancer Center Support Grant*

R01CA256193
Smalley, K. (PI), Role: Co-I
08/09/2021 - 07/31/2026
*Characterization and targeting of the epigenetic state underlying uveal melanoma liver metastasis*

R01CA262483
Smalley, K./Licht, J. (MPIs), Role: Co-I
07/15/2022 - 06/30/2027
*Defining and targeting epigenetic plasticity-driven drug resistance and immune escape in melanoma*

Completed:

R21CA267141
Smalley, K. (PI), Role: Co-I
01/01/2022 - 12/31/2023
*Defining and targeting the epigenetic programs involved in melanoma development*

Moffitt Cancer Center, Team Science
Smalley, I., Chen, A. (MPIs), Role: Co-PI
03/01/2022 - 02/28/2023
*Effect of exogenous carnitines and lipids on astrocyte metabolism*

Moffitt Cancer Center, Quantitative Science Discovery Accelerator Award
Chen, A. (PI), Role: PI
01/01/2022 - 12/31/2022
*An efficient and scalable Interactive single cell multiomics visual analytics, ISCMVA*

P30CA076292
Cleveland, J. (PI), Role: Co-I
02/01/2022 - 09/22/2023
*Moffitt Cancer Center Support Grant Years 24-27*

R01CA258089
Tsai, K./Brown, J. (PI), Role: Co-I
04/01/2021 - 09/22/2023
*Eco-Evolutionary Drivers of Clonal Dynamics During UV-Induced Skin Carcinogenesis (PQ3)*

R01CA259046
Karreth, F. (PI), Role: Co-I
05/01/2021 - 09/22/2023
*Chromosome 1q ceRNAs in melanoma progression and metastasis*

R21CA256289
Smalley, K. (PI), Role: Co-I
08/01/2021 - 07/31/2023
*Targeting the suppressive immune microenvironment in leptomeningeal melanoma metastases*

R21CA256141
Karreth, F. (PI), Role: Co-I
08/01/2021 - 07/31/2023
*Exploring miR-29 in melanoma progression and prevention*
R21CA274060
Smalley, I. (PI), Role: Co-I
09/01/2022 - 08/31/2023
*Defining and targeting the immune-suppressive metabolic microenvironment of leptomeningeal melanoma metastases*

W81XWH-19-10-675
Czerniecki, B. (PI), Role: Co-I
09/01/2019 - 09/22/2023
*Novel Immunotherapy for Brain-Metastatic Breast Cancer*

R01CA207456
Kanetsky, P. (PI), Role: Co-I
09/01/2016 - 08/31/2021
*Epidemiology and Biology of lnc RNAs in Ovarian Cancer*

University of South Florida/Anna D. Valentine Research Award
Fridley, B./Chen, A. (PI), Role: Co-PI
02/01/2020 - 07/31/2021
*Analytical Interpretation of Unknown Metabolites in Untargeted Mass Spectrometry Cancer Studies*

Chen, A./Teer, J. (PI), Role: Co-PI
07/01/2020 - 06/30/2021
*Detecting and visualizing mutational and transcriptional heterogeneity in scRNA-seq data*

579030
Smalley, K./Karreth, F./Chen, A./Koomen, J./Messina, J./Teer, J. (PI), Role: Co-PI
06/01/2018 - 05/31/2021
*Defining and Targeting Driver Events in Acral Melanoma*

8BC03
Smalley, K. (PI), Role: Co-I
04/02/2018 - 03/31/2021
*Defining and therapeutically targeting HDAC8-driven reprogramming in melanoma brain metastasis development*

## B. Positions, Scientific Appointments, and Honors

### Positions and Scientific Appointments

| | |
|---|---|
| 2023 Sept. – Present | Director of Cancer Biostatistics Shared Resource, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT |
| 2023 Sept. – Present | Professor, Division of Epidemiology, Department of Internal Medicine, University of Utah, Salt Lake City, UT |
| 2023 Sept. – Present | Adjunct Professor, Division of Biostatistics, Department of Population Health Sciences, University of Utah, Salt Lake City, UT |
| 2021 – 2023 Sept. | Senior Member, Biostatistics and Bioinformatics, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL |
| 2021 – 2023 Sept. | Professor, Oncologic Sciences, University of South Florida, Tampa, FL |
| 2015 - 2020 | Associate Professor, Oncologic Sciences, University of South Florida, Tampa, FL |
| 2015 - 2020 | Associate Professor, Biostatistics and Epidemiology, University of South Florida, Tampa, FL |
| 2015 - 2020 | Associate Member, Biostatistics and Bioinformatics, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL |
| 2012 - 2015 | Assistant Professor, Biostatistics and Epidemiology, University of South Florida, Tampa, FL |
| 2008 - 2015 | Assistant Professor, Oncologic Sciences, University of South Florida, Tampa, FL |
| 2008 - 2015 | Assistant Member, Biostatistics and Bioinformatics, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL |

### Honors

| | |
|---|---|
| 2022 | Team Science Publication Award, Moffitt Cancer Center |
| 2022 | Bio-Data Club Hackathon 2022 winning team: A web-based visualization tool for proteomics and metabolomics data. Moffitt Cancer Center |
| 2018 | Faculty Biostatistician of the Year, Biostatistics and Bioinformatics Shared Resource, Moffitt Cancer Center |
| 2018 | Quantitative Science Division Faculty Outstanding Achievement Award, Moffitt Cancer Center |
| 2016 | Population Science Division Faculty Outstanding Achievement Award, Moffitt Cancer Center |
| 2013 | Team Publication Award, Moffitt Cancer Center |
| 2007 | Travel Fellowship 15th International Conference on Intelligent Systems for Molecular Biology (ISMB 2007), Vienna, Austria |
| 2005 | Travel Award, The Plant & Animal Genomics XIII meeting, San Diego, CA |
| 2005 | Travel Fellowship 13th International Conference on Intelligent Systems for Molecular Biology (ISMB 2005), Detroit, MI |

| | |
|---|---|
| 2004 | Travel Fellowship, 12th International Conference on Intelligent Systems for Molecular Biology (ISMB 2004), Glasgow, Scotland |
| 2003 | Travel Award, 4th Georgia Tech and International Conference on Bioinformatics |
| 2003 | Informatics Award, Student Research Day, Medical University of South Carolina |
| 2001 | Student Award, International Conference on Distance Sampling, St. Andrews, Scotland |
| 1999 | Joanna Foundation Scholarship |
| 1991 | President's Award, National Taiwan University |

C. **Contributions to Science** (underly indicating correspoinding author).

1. My work has always been motivated by the evolving computational challenges of genomics and proteomics technologies. In the early stage of my research career, I participated in the Marine Genomics Project building a web-based data warehouse and developing probe selection algorithm for microarrays using multiple machine learning methods to model cross-hybridization for cDNA microarrays. These methods and tools have enabled the design of the custom-design microarrays in early days.
    a. **Chen YA**, McKillen DJ, Wu S, Jenny MJ, Chapman R, Gross PS, Warr GW, Almeida JS. Optimal cDNA microarray design using expressed sequence tags for organisms with limited genomic information. *BMC Bioinformatics*. Dec 7 2004;5:191. PMCID: PMC539232.
    b. McKillen DJ, **Chen YA**, Chen C, Jenny MJ, Trent HF, 3rd, Robalino J, McLean DC, Jr., Gross PS, Chapman RW, Warr GW, Almeida JS. Marine genomics: a clearing-house for genomic and transcriptomic data of marine organisms. *BMC Genomics*. 2005;6:34. PMCID: PMC1079820.
    c. Almeida JS, McKillen DJ, **Chen YA**, Gross PS, Chapman RW, Warr G. Design and calibration of microarrays as universal transcriptomic environmental biosensors. *Comp Funct Genomics*. 2005;6(3):132-7. PMCID: PMC2447521.
    d. **Chen YA**, Chou CC, Lu X, Slate EH, Peck K, Xu W, Voit EO, Almeida JS. A multivariate prediction model for microarray cross-hybridization. *BMC Bioinformatics*. 2006;7:101. PMCID: PMC1409802.

2. I took on computational challenges in the post-genomics era by developing methods to investigate multi-scale correlation and omics integration. To integrate multiple omics signals, we develop integrated Bayesian variable selection methods to predict clinical outcomes in a unified statistical framework.
    a. **Chen YA**, Almeida JS, Richards AJ, Muller P, Carroll RJ, Rohrer B. A nonparametric approach to detect nonlinear correlation in gene expression. *J Comput Graph Stat*. Sep 1 2010;19(3):552-68. PMCID: PMC2945392 **(Featured Article).**
    b. Li Q, Fisher K, Meng W, Fang B, Welsh E, Haura EB, Koomen JM, Eschrich SA, Fridley BL, **Chen YA**. GMSimpute: a generalized two-step Lasso approach to impute missing values in label-free mass spectrum analysis. *Bioinformatics*. 2020 Jan 1;36(1):257-263. PMCID: PMC6956786.
    c. Stingo FC, **Chen YA**, Vannucci M, Barrier M, Mirkes PE. A Bayesian Graphical Modeling Approach to MicroRNA Regulatory Network Inference. *Ann Appl Sta t*. 2010;4(4):2024-48. PMCID: PMC3740979.
    d. Stingo FC, **Chen YA**, Tadesse MG, Vannucci M. Incorporating Biological Information into Linear Models: A Bayesian Approach to the Selection of Pathways and Genes. *Ann Appl Stat*. Sep 1 2011;5(3):1978-2002. PMCID: PMC3650864.

3. With a team of collaborators, I conducted SNP- and gene-level statistical association tests for large scale genome-wide association studies. In addition, I also performed pathway analyses and integrated Omics analyses to identify functional susceptibility loci for ovarian cancer and other cancers. I have co-authored several high quality research papers published in high impact journals (including 4 Nature Genetics papers). These integrated molecular analyses are not only complementary to the experimental investigational work but also effectively prioritize the candidates in follow-up experiments when a large number of downstream targets are potentially involved.
    a. Permuth-Wey J, Lawrenson K, Shen HC, Velkova A, Tyrer JP, Chen Z, Lin HY, **Chen YA**, et al. Identification and molecular characterization of a new ovarian cancer susceptibility locus at 17q21.31. *Nat Commun*. 2013;4:1627. PMCID: PMC3709460.
    b. Pharoah PD, Tsai YY, Ramus SJ, Phelan CM, Goode EL, Lawrenson K, Buckley M, Fridley BL, Tyrer JP, Shen H, Weber R, Karevan R, Larson MC, Song H, Tessier DC, Bacot F, Vincent D, Cunningham JM, Dennis J, Dicks E, Aben KK, Anton-Culver H, Antonenkova N, Armasu SM, Baglietto L, Bandera EV, Beckmann MW, Birrer MJ, Bloom G, Bogdanova N, Brenton JD, Brinton LA, Brooks-Wilson A,

Brown R, Butzow R, Campbell I, Carney ME, Carvalho RS, Chang-Claude J, **Chen YA**, …, Sellers TA. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. *Nat Genet*. Apr 2013;45(4):362-70, 70e1-2. PMCID: PMC3693183.

4. Translating scientific discoveries into diagnostic approach or therapeutic strategies is crucial for curing cancer. My statistical work has direct translational impacts on developing therapeutic strategies for melanoma patients. As the senior author and primary statistician for two recent papers regarding immunotherapies, I identified biomarkers associated with treatment response for melanoma patients in immunotherapy trials. As the primary statistician for numerous melanoma studies, I have furthered the understanding of tumor immune microenvironments and mechanisms for resistance induced by therapies.
    a. Weber JS, Kudchadkar RR, Yu B, Gallenstein D, Horak CE, Inzunza HD, Zhao X, Martinez AJ, Wang W, Gibney G, Kroeger J, Eysmans C, Sarnaik AA, **Chen YA**. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. *J Clin Oncol*. Dec 1 2013;31(34):4311-8. PMCID: PMC3837092.
    b. Weber J, Gibney G, Kudchadkar R, Yu B, Cheng P, Martinez AJ, Kroeger J, Richards A, McCormick L, Moberg V, Cronin H, Zhao X, Schell M, **Chen YA**. Phase I/II Study of Metastatic Melanoma Patients Treated with Nivolumab Who Had Progressed after Ipilimumab. *Cancer Immunol Res*. 2016 Apr;4(4):345-53. PMCID: PMC4818672.
    c. Eroglu Z, **Chen YA**, Gibney GT, Weber JS, Kudchadkar RR, Khushalani NI, Markowitz J, Brohl AS, Tetteh LF, Ramadan H, Arnone G, Li J, Zhao X, Sharma R, Darville LNF, Fang B, Smalley I, Messina JL, Koomen JM, Sondak VK, Smalley KSM. Combined BRAF and HSP90 inhibition in patients with unresectable *BRAF* V600E mutant melanoma. *Clin Cancer Res*. 2018 Apr 19. pii: clincanres.0565.2018. PMCID: PMC6195480.
    d. Smalley I, Chen Z, Phadke M, Li J, Yu X, Wyatt C, Evernden B, Messina JL, Sarnaik A, Sondak VK, Zhang C, Law V, Tran N, Etame A, Macaulay RJB, Eroglu Z, Forsyth PA, Rodriguez PC, **Chen YA**, Smalley KSM. Single-Cell Characterization of the Immune Microenvironment of Melanoma Brain and Leptomeningeal Metastases. *Clin Cancer Res*. 2021 Jul 15;27(14):4109-4125. PMCID: PMC8282775.

5. Single-cell technologies allow characterization of transcriptomes and epigenomes for individual cells under different conditions and provide unprecedented resolution for researchers to investigate cellular heterogeneity and tummor-timmue microenvironment in cancer. We have developed the computational approaches and tools, including ISCVAM, SinCHet, and SinCHet-MS to analyze single cell data, quantify tumor heterogeneity, and enabled the development of novel therapeutic strategies via interactive visual analytics.
    a. Li J, Smalley I, Schell MJ, Smalley K, **Chen, YA**. SinCHet: a MATLAB toolbox for single cell heterogeneity analysis in cancer. *Bioinformatics*. 2017 Sep 15;33(18):2951-2953. PMCID: PMC5870537.
    b. Smalley I, Kim E, Li J, Spence P, Wyatt CJ, Eroglu Z, Sondak VK, Messina JL, Babacan NA, Maria-Engler SS, De Armas L, Williams SL, Gatenby RA, **Chen YA**, Anderson ARA, Smalley KSM. Leveraging transcriptional dynamics to improve BRAF inhibitor responses in melanoma. *EBioMedicine*. 2019 Oct;48:178-190. PMCID: PMC6838387.
    c. Li J, Smalley I, Chen Z, Wu JY, Phadke MS, Teer JK, Nguyen T, Karreth FA, Koomen JM, Sarnaik AA, Zager JS, Khushalani NI, Tarhini AA, Sondak VK, Rodriguez PC, Messina JL, **Chen YA**, Smalley KSM. Single cell characterization of the cellular landscape of acral melanoma identifies novel targets for immunotherapy. *Clin Cancer Res*. 2022 May 13;28(10):2131-2146. PMID: 35247927.
    d. Liu R, Li J, Lan Y, Nguyen TD, **Chen YA**, Yang Z. Quantifying Cell Heterogeneity and Subpopulations Using Single Cell Metabolomics. *Anal Chem*. 2023 May 9;95(18):7127-7133. PMID: 37115510.

**Complete List of Published Work in MyBibliography:**

https://www.ncbi.nlm.nih.gov/myncbi/yian.chen.1/bibliography/public/

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Greene, Tom H.

eRA COMMONS USER NAME (credential, e.g., agency login): TOMGREENE

POSITION TITLE: Professor, Division of Epidemiology, Department of Internal Medicine, University of Utah / Professor, Division of Biostatistics, Department of Population Health Sciences, University of Utah / Director, Translational Science, Implementation, Analysis and Design (TRIAD) Team

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of Kentucky, Lexington, KY | B.S. | 05/1980 | Mathematics and Psychology |
| Cornell University, Ithaca, NY | M.S. | 05/1983 | Statistics |
| Cornell University, Ithaca, NY | Ph.D. | 05/1985 | Statistics/ Mathematics and Operation Research Minor |

**A. Personal Statement**

I currently serve as an H. A. and Edna Benning Professor in the Division of Epidemiology in the Department of Internal Medicine and as a Professor in the Division of Biostatistics in the Department of Population Health Sciences. I was the founding Director of the Study Design and Biostatistics Center (SDBC) in the Utah Center for Clinical and Translational Science (now the Clinical and Translational Science Institute) in 2008. Under my leadership, the SDBC grew to become the Translational Research: Implementation, Analysis and Design (TRIAD) Team with over 50 methodologists in biostatistics and related disciplines who provide integrated collaborations across the University of Utah and partner institutions. The full expertise of the SDBC will be available to support this project. My methodological work includes advances in clinical trial design, longitudinal data analysis, validation of surrogate endpoints, and modern causal inference including emulated clinical trials. During my career, I have authored more than 500 peer-reviewed publications in the medical and statistical literatures, many with high impact as reflected in more than 154,000 citations in the Google Scholar abstract and citation database, with an h-index of 143.

The proposed research will create scalable research tools to empower TRIAD team members to collaborate with researchers to conduct high-quality observational studies, bridging the gap between methodology and broader applications. This work has a strong potential to be disseminated broadly across other CTSIs. I will connect the research team with members of TRIAD to support the project, and will provide guidance regarding important research questions, methods, and implementation tools to build into the research pipeline. In carrying out these tasks, I will draw upon 30 years of experience directing the design and statistical analyses of large-scale clinical trials, observational cohort studies and other projects.

Some of my publications relevant to this work include:

a. Li L, **Greene T**. A weighting analogue to pair matching in propensity score analysis. *The International Journal of Biostatistics*. 2013 Jul 31;9(2):215-34.
b. Bress A, Dodson J, King J, Sauer B, Reese T, Crook J, Radwanski P, Knippenberg K, **Greene T**, Nelson R and Munger M. Clinical and economic outcomes of ranolazine versus conventional

antianginals users among veterans with chronic stable angina pectoris. *The American Journal of Cardiology*, 122(11), pp.1809-1816, 2018.

c. Mao H, Li L, **Greene T**. Propensity score weighting analysis and treatment effect discovery. *Statistical methods in medical research*, *28*(8), 2439-2454, 2019.
d. Xu Y, **Greene T**, Bress A, Sauer B, Bellows B, Zhang Y, Weintraub W, Moran A, Shen J. Estimating the optimal individualized treatment rule from a cost-effectiveness perspective. *Biometrics*. DOI: 10.1111/biom.134062020, 2020.

**Current or recent external support relevant to this application includes:**

UM1TR004409
Dere/Hess (MPI)
04/1/23-03/31/30
University of Utah Center for Clinical and Translational Science (CCTS)
Role: Chief of CCTS Population Health Research Foundation for Discovery

P30CA042014
Ulrich (PI)
05/01/97-04/30/25
Cancer Center Support Grant – Biostatistics Center (CB)
Role: Co-Investigator

**B. Positions, Scientific Appointments, and Honors**

**Positions and Scientific Appointments**

| | |
|---|---|
| 2016-present | *H.A. and Edna Benning* Presidential Endowed Chair in Biostatistics, University of Utah |
| 2015-2019 | Chief, Division of Biostatistics, Department of Population Health Science, University of Utah |
| 2015-present | Director, Population Health Research Foundation for Discovery (Now Translational Science: Research, Analysis and Design Team), Utah CTSI, Univ. of Utah |
| 2014-2015 | Interim Chair, Department of Population Health Science |
| 2013-2018 | Chief, Biostatistics Section, Division of Epidemiology, Dept. of Internal Medicine, Univ. of Utah |
| 2008-present | Co-Director, Study Design and Biostatistics Center, Utah CCTS, University of Utah |
| 2006-present | Professor, Division of Epidemiology, Department of Internal Medicine, University of Utah, Salt Lake City, UT |
| 2002-2006 | Full Staff Biostatistician, Cleveland Clinic Foundation, Department of Biostatistics and Epidemiology, Cleveland, OH |
| 1995-2002 | Associate Staff Biostatistician, Cleveland Clinic Foundation, Department of Biostatistics and Epidemiology, Cleveland, OH |
| 1991-1995 | Assistant Staff Biostatistician, Cleveland Clinic Foundation, Department of Biostatistics and Epidemiology, Cleveland, OH |
| 1989-1991 | Assistant Professor, MetroHealth Medical Center and Case Western University, Departments of Psychiatry, Epidemiology, and Biostatistics, Cleveland, OH |
| 1985-1989 | Assistant Professor, University of Kentucky, Department of Statistics, Lexington, KY |

**Professional Societies and Public Advisory Committees**

| | |
|---|---|
| 2012-present | Member, American Statistical Association |
| 2000-2006 | Member, Promotions and Appointment Committee, Cleveland Clinic Foundation |
| 2000-2005 | Member, Editorial Board, *Journal of the American Society of Nephrology* |

**Honors**

| | |
|---|---|
| 2008 | Recipient, *Shaul G. Massry* Distinguished Lecture for Contributions to the Kidney Health Care Community and the National Kidney Foundation (NKF), NKF |

**C. Contribution to Science**

1. Much of my methodological research focuses on problems in comparative effectiveness research, including the development of novel methods to assess the validity of surrogate endpoints, new approaches to data analyses using propensity scores, and on the application of methods from modern causal inference to estimation of effects of exposures and treatments in clinical trials and observational studies.
    a. Joffe MM, **Greene T**. Related causal frameworks for surrogate outcomes. *Biometrics*. 2009 Jun;65(2):530-538.
    b. **Greene T**, Joffe M, Hu B, Li L, Boucher K. The balanced survivor average causal effect. *Int J Biostat.* 2013 May 7;9(2):291-306.
    c. **Greene T**, Teng CC, Inker LA, Redd A, Ying J, Woodward M, Coresh J, Levey AS. Utility and validity of estimated GFR-based surrogate time-to-event end points in CKD: a simulation study. *Am J Kidney Dis*. 2014 Dec;64(6):867-79.
    d. Zhang Z, Li M, Lin M, Soon G, **Greene T**, Shen C. Subgroup selection in adaptive signature designs of confirmatory clinical trials. *J R Stat Soc Ser C Appl Stat*. 2017 Feb;66(2):345-361.
2. For over 3 decades, I have served as the lead statistician for the design, conduct and analysis of many of the major NIH sponsored multi-center clinical trials and cohort studies in nephrology. These trials include the Modification of Diet in Renal Disease Study, which evaluated the effect of a low protein diet on the progression of chronic kidney disease; the African American Study of Kidney Disease and Hypertension, which evaluated the effects of alternative treatment strategies in African Americans with hypertensive nephroscerlosis; the Hemodialysis Trial, which showed that increasing dialysis dose fails to reduce mortality in the setting of 3 times per week hemodialysis; and the Frequent Hemodialysis Study, which demonstrated a benefit of 6-times per week hemodialysis on physical function and left ventricular mass. More recently, I contributed to the design and analysis of the Systolic Blood Pressure Intervention Trial (SPRINT), which established benefits of treatment of systolic blood pressure to less than 120 mm Hg on cardiovascular and all-cause death, and the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Trial, which established that the SGLT2 inhibitor Canagliflozin slows decline of renal function.
    a. Wright JT Jr, Bakris G, **Greene T**, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG; African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK Trial. *JAMA*. 2002 Nov;288(19):2421-31.
    b. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, **Greene T**, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R; Hemodialysis (HEMO) Study Group. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med*. 2002 Dec 19;347(25):2010-9.
    c. Dixon BS, Beck GJ, Vazquez MA, Greenberg A, Delmez JA, Allon M, Dember LM, Himmelfarb J, Gassman JJ, **Greene T**, Radeva MK, Davidson IJ, Ikizler TA, Braden GL, Fenves AZ, Kaufman JS, Cotton JR Jr, Martin KJ, McNeil JW, Rahman A, Lawson JH, Whiting JF, Hu B, Meyers CM, Kusek JW, Feldman HI; DAC Study Group. Effect of Dipyridamole plus Aspirin on Hemodialysis Graft Patency. *N Engl J Med*. 2009 May 21;360(21):2191-201. PMCID: PMC3929400
    d. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, **Greene T**, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW, CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019 Jun 13;380(24):2295-2306.

3. In my role as lead statistician for clinical trials and cohort studies, I confronted challenging methodological problems in the analysis of longitudinal outcomes with complex trajectories in cohorts with high rates of attrition due to death and other clinical conditions. In collaboration with statistical colleagues, I developed new statistical methods for the analysis of longitudinal data, which address these issues.
    a. **Greene T**. A model for a proportional treatment effect on disease progression. *Biometrics*. 2001 Jun;57 (2):354-360.
    b. Vonesh EF, **Greene T**, Schluchter MD. Shared Parameter Models for the Joint Analysis of Longitudinal Data and Event Times. *Stat Med*. 2006 Jan 15;25(1):143-63.
    c. Li L, Hu B. **Greene T**. A Semiparametric Joint Model for Longitudinal and Survival Data with Application to Hemodialysis Study. *Biometrics*. 2009 Sep;65(3):737-45.
    d. Li L, Luo S, Hu B, **Greene T**. Dynamic Prediction of Renal Failure Using Longitudinal Biomarkers in a Cohort Study of Chronic Kidney Disease. *Stat Biosci*. 2017 Dec;9(2)357-378. PMCID: PMC5726783
4. I have played a leading role in the development of modern equations for estimation of glomerular filtration rate (GFR). I designed and carried out the data analyses for development and validation of the Modification of Diet in Renal Disease (MDRD) equation, which has been the primary method for estimation of GFR in clinical and research settings for more than a decade. I also supported the development and validation of the CKD-EPI equation, which is now being adopted as the primary method for estimation of GFR (updated in 2021 to include calculations without race).
    a. Levey AS, Bosch JP, Lewis JB, **Greene T**, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999 Mar 16;130(6):461-70.
    b. Levey AS, Coresh J, **Greene T**, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006 Aug 15;145(4):247-54.
    c. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, **Greene T**, Coresh J. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009 May 5;150(9):604-12.
    d. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M, Grams ME, **Greene T** et al, for the Chronic Kidney Disease Epidemiology Collaboration. New England Journal of Medicine 2021;385:1737-1749.
5. My early work focused on analyses of cohort studies investigating effects of pre-natal alcohol exposure and of low-level lead exposure on cognitive development in children. This work included statistical analyses to address multiple sources of confounding and measurement error complicate the determination of which of several correlated exposures contribute to adverse outcomes
    a. **Greene T**, Ernhart CB, Martier S, Sokol RJ, Ager J. Prenatal alcohol exposure and language development. Alcohol Clin Exp Res. 1990 Dec;14(6):937-45. PMID: 2088132.
    b. **Greene T**, Ernhart CB. Prenatal and preschool age lead exposure: Relationship with size. Neurotoxicol Teratol. 1991 Jul-Aug;13(4):417-27. PMID: 1921921.
    c. **Greene T**, Ernhart CB. Controlling for measurement error in investigations of the effects of lead on development. Proceedings of the International Conference on Heavy Metals in the Environment, JG Farmer (ed). Edinburgh, Scotland: 1991;131-134.
    d. **Greene T**, Ernhart CB. Adjustment for cofactors in pediatric research. J Dev Behav Pediatr. 1991 Dec;12(6):378-85. PMID: 1723985.

**Complete List of Published Work in MyBibliography**
https://www.ncbi.nlm.nih.gov/sites/myncbi/1N_xjzxHLg35T/bibliography/45868846/public/?sort=date&direction=ascending

# BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Sborov, Douglas

eRA COMMONS USER NAME (credential, e.g., agency login): sborov01

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE (if applicable) | END DATE MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of Wisconsin, Madison, WI | BS | 05/2000 | Biology, Psychology |
| American University of the Caribbean School of Medicine, Cupecoy, St. Maarten | MD | 04/2009 | Medicine |
| The Ohio State University, Columbus, OH | MS | 08/2015 | Clinical Investigation |
| University of Utah, Salt Lake City, UT | Resident | 06/2012 | Internal Medicine |
| The Ohio State University, Columbus, OH | Fellow | 12/2015 | Hematology/oncology |
| The Ohio State University, Columbus, OH | NIH training grant | 06/2015 | T32 Clinical Research Fellowship |

## A. Personal Statement

I am an Associate Professor at the University of Utah (UU) – Huntsman Cancer Institute (HCI), Department of Internal Medicine - Division of Hematology and Hematologic Malignancies - Bone Marrow Transplantation (BMT). I am the Director of the HCI Hematology Disease Center and the Plasma Cell Dyscrasias (PCD) Program. I am a member of the HCI Experimental Therapeutics Program, Physician Leader of the HCI Hematology Clinical Trials Office, active member of the International Myeloma Working Group (IMWG), and the SWOG and Alliance Cooperative Group Myeloma Committees, Board Member of the Society of Utah Medical Oncology (SUMO), and member of the American Society of Hematology (ASH) Foundation and Communication Committees. Based on the breadth of my research, I was selected to participate in the University of Utah Vice President's Clinical and Translational Scholars Program, was later elected as a Huntsman Translational Scholar in 2021, and most recently accepted into the HCI Leadership, Excellence, Advancement, and Development (LEAD) Program. The overall goal of my research is to investigate novel targeted and immunologic therapies for patients with multiple myeloma and I have a concentrated interest in the development of first-in-man and early phase clinical trials for the treatment of patients with relapsed and refractory multiple myeloma (RRMM) and plasma cell leukemia (PCL). The ultimate mission of our HCI Hematology Disease Center and the PCD Program are to improve care access and delivery and education alongside cutting-edge research across the Mountain West region.

Overall, my contributions to science are described in detail below, but include the development of viral oncolytics as a safe and effective novel therapeutic option for patients with RRMM, development of a personalized melphalan calculator to optimize the efficacy and minimize adverse toxicities associated with autologous transplantation, establishment of a drug repurposing investigator-initiated clinical trial platform, and the preclinical development of a novel antibody-drug conjugate for the treatment of patients with RRMM. These contributions to science have earned international awards through ECCO-AACR-EORTC-ESMO. I have authored over 100 manuscripts including publication in high-impact and relevant journals including Clinical Cancer Research, Blood, Lancet Haematology, and Clinical Pharmacology & Therapeutics. Additionally, I have presented my research at prestigious national and international conferences including the American Society of Hematology (ASH) Annual Meetings, American Society of Clinical Oncology (ASCO) Annual Meetings, International Myeloma Society (IMS) International Myeloma Workshops, and the Summit on Lymphoid Malignancies & Multiple Myeloma. My research and career development have primarily been funded through intramural funding mechanisms, start-up funds, as a Co-Investigator on R01 CA194742-0141 (PI: Hofmeister, Picchiori), and a member of the HCI ETCTN Executive Committee associated with grant 60075822 (PI:

Carson). Clinically, I lead a team of over 60 individuals responsible for > 7500 patient visits and > 30 clinical trial accruals annually. I am currently the local Principal Investigator of over 10 different phase 1 – 3 clinical trials for patients with MM and have built the HCI MM clinical trial portfolio to include investigation of numerous exciting novel immunotherapeutic constructs including CAR-T cells and T-cell redirecting bispecific antibodies.

In my role as the Director of the HCI Hematology Disease Center, I am determined to expand the collaborations across the spectrum of investigators in malignant and classical hematology. In doing so, I have committed significant resources to building bridges across disciplines, promoting novel research through pilot award funding, and growing programs to support and facilitate high-impact research. Examples of this include starting a non-interventional clinical trial program called ADAPT, expanding our robust annotated biorepository, and supporting a group of hematology-focused biostatisticians. As such, I am well positioned as a leader in our hematology program, expert in the field of multiple myeloma, and close collaborator with a broad spectrum of investigators, to support Dr. Xu's work. I enthusiastically support her current project and overall career development.

1. Li J, Cho YK, Sborov DW, Phelps MA, Hofmeister CC, Poi MJ. Evaluating the Impacts of CYP3A4*1B and CYP3A5*3 Variations on Pharmacokinetic Behavior and Clinical Outcomes in Multiple Myeloma Patients With Autologous Stem Cell Transplant. Cancer Genomics Proteomics. 2023 Jan-Feb;20(1):9-17. PubMed Central PMCID: PMC9806672.
2. Li J, Persaud AK, Johnson JA, Sborov DW, Phelps MA, Hofmeister CC, Poi MJ. A Single Nucleotide Polymorphism (SNP) in the SLC22A3 Transporter Gene Is Associated With the Severity of Oral Mucositis in Multiple Myeloma Patients Receiving Autologous Stem Cell Transplant Followed by Melphalan Therapy. Anticancer Res. 2022 Jan;42(1):385-395. PubMed PMID: 34969749.
3. Cho YK, Irby DJ, Li J, Sborov DW, Mould DR, Badawi M, Dauki A, Lamprecht M, Rosko AE, Fernandez S, Hade EM, Hofmeister CC, Poi M, Phelps MA. Pharmacokinetic-Pharmacodynamic Model of Neutropenia in Patients With Myeloma Receiving High-Dose Melphalan for Autologous Stem Cell Transplant. CPT Pharmacometrics Syst Pharmacol. 2018 Nov;7(11):748-758. PubMed Central PMCID: PMC6263666.
4. Cho YK, Sborov DW, Lamprecht M, Li J, Wang J, Hade EM, Gao Y, Tackett K, Williams N, Benson DM, Efebera YA, Rosko AE, Devine SM, Poi M, Hofmeister CC, Phelps MA. Associations of High-Dose Melphalan Pharmacokinetics and Outcomes in the Setting of a Randomized Cryotherapy Trial. Clin Pharmacol Ther. 2017 Sep;102(3):511-519. PubMed Central PMCID: PMC5821248.

## B. Positions, Scientific Appointments and Honors

### Positions and Scientific Appointments

| | |
|---|---|
| 2024 - | Chair, Cancer Biostatistics Shared Resource Faculty Advisory Committee, Huntsman Cancer Institute, Salt Lake City, UT |
| 2023 - | Director, Hematology Disease Center, Huntsman Cancer Institute, Salt Lake City, UT |
| 2023 - | Hematology Expert Representative, ETCTN Executive Committee, Huntsman Cancer Institute, Salt Lake City, UT |
| 2023 - | Member, Institutional Protocol Development Committee, Huntsman Cancer Institute, Salt Lake City, UT |
| 2022 - | Associate Professor, University of Utah - Huntsman Cancer Institute, Salt Lake City, UT |
| 2022 - | Member, Population Science Trials Office Leadership Committee, Huntsman Cancer Institute, Salt Lake City, UT |
| 2021 - 2023 | Director, Division of Hematology Biorepository, University of Utah - Huntsman Cancer Institute, Salt Lake City, UT |
| 2020 - | Member, Division of Hematology Leadership Council, Department of Internal Medicine - University of Utah, Salt Lake City, UT |
| 2020 - | Member, Experimental Therapeutics Program, Huntsman Cancer Institute, Salt Lake City, UT |
| 2019 - | Member, Protocol Review and Monitoring Committee, Huntsman Cancer Institute, Salt Lake City, UT |

| | |
|---|---|
| 2018 - | Physician Leader, Hematologic Malignancies Clinical Trials Research Group, Huntsman Cancer Institute, Salt Lake City, UT |
| 2018 - | Director, Plasma Cell Dyscrasia Programs, University of Utah - Huntsman Cancer Institute, Salt Lake City, UT |
| 2017 - 2022 | Assistant Professor, University of Utah - Huntsman Cancer Institute, Salt Lake City, UT |
| 2016 - 2017 | Clinical Instructor, University of Utah - Huntsman Cancer Institute, Salt Lake City, UT |
| 2016 - 2016 | Clinical Instructor, The Ohio State University, Columbus, OH |
| 2012 - 2015 | Clinical Fellow, The Ohio State University, Columbus, OH |

## Honors

| | |
|---|---|
| 2021 - 2024 | Huntsman Translational Scholar, Huntsman Cancer Institute |
| 2016 - 2020 | Extramural Loan Repayment Program Recipient, National Institutes of Health |
| 2018 - 2019 | Vice President's Clinical & Translational Scholars Program, University of Utah |
| 2024 | University of Utah Department of Internal Medicine Annual Resident Mentor Award, University of Utah |
| 2015 | Ambassador Special Fellowship - Methods in Clinical Cancer Research, American Society of Clinical Oncology (ASCO) |
| 2012 | William D. Odell Housestaff Award - Senior Resident of the Year, University of Utah Department of Internal Medicine |
| 2007 | Alpha Omega Phi, American University of the Caribbean School of Medicine Honor Society |

## C. Contribution to Science

1. VENOUS THROMBOEMBOLISM IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA. Patients with multiple myeloma have increased risk of venous thromboembolism (VTE) related to their underlying malignancy and this risk increases with exposure to anti-myeloma therapies, most notably immunomodulatory drugs and conventional chemotherapeutics. Historically, patients without prior history of VTE or other significant co-morbidities that increase clotting risk, have been treated with aspirin (ASA) prophylaxis based on the International Myeloma Working Group (IMWG) recommendations. We have recently shown that patients treated with contemporary multi-drug treatment regimens have a 10-15% risk of VTE even despite use of ASA and that overall, VTE prophylaxis is inadequate in a significant number of patients treated on clinical trials. As a member of the National Comprehensive Cancer Network (NCCN) Multiple Myeloma, Waldenström Macroglobulinemia, and Amyloidosis Committee, I have worked closely with my colleagues around the country to update the national guidelines for VTE prophylaxis and prospectively collect data regarding treatment patterns and rates of VTE on the randomized phase 3 Eastern Cooperative Oncology Group (ECOG) EQUATE (Effective Quadruplet Utilization after Treatment Evaluation) trial.

    a. Kumar SK, Callander NS, Adekola K, Anderson LD Jr, Baljevic M, Baz R, Campagnaro E, Castillo JJ, Costello C, D'Angelo C, Derman B, Devarakonda S, Elsedawy N, Garfall A, Godby K, Hillengass J, Holmberg L, Htut M, Huff CA, Hultcrantz M, Kang Y, Larson S, Lee H, Liedtke M, Martin T, Omel J, Robinson T, Rosenberg A, Sborov D, Schroeder MA, Sherbenou D, Suvannasankha A, Valent J, Varshavsky-Yanovsky AN, Snedeker J, Kumar R. Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2024 Jan;22(1D):e240001. PubMed PMID: 38244272.

    b. Baljevic M, Sborov DW. Understanding risks and refining strategies for thromboembolism prophylaxis in hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 2023 Nov;58(11):1177-1178. PubMed PMID: 37626266.

    c. Sborov DW, Baljevic M, Reeves B, Laubach J, Efebera YA, Rodriguez C, Costa LJ, Chari A, Silbermann R, Holstein SA, Anderson LD Jr, Kaufman JL, Shah N, Pei H, Patel S, Cortoos A, Bartlett JB, Vermeulen J, Lin TS, Voorhees PM, Richardson PG. Daratumumab plus lenalidomide, bortezomib and dexamethasone in newly diagnosed multiple myeloma: Analysis of vascular thrombotic events in the GRIFFIN study. Br J Haematol. 2022 Nov;199(3):355-365. PubMed Central PMCID: PMC9825872.

d. Baljevic M, Sborov DW, Lim MY, Hillengass J, Martin T, Castillo JJ, Streiff MB, Kumar SK, Callander NS. Optimizing Thromboembolism Prophylaxis for the Contemporary Age of Multiple Myeloma. J Natl Compr Canc Netw. 2022 Jan;20(1):91-95. PubMed PMID: 34991076.

2. NOVEL THERAPEUTIC CONSTRUCT DESIGN. The treatment landscape of MM is rapidly evolving and the standard armamentarium including traditional chemotherapy, immunomodulatory drugs, steroids, and proteosome inhibitors has now expanded to include a new generation of immunotherapeutics. These immune-directed therapies include monoclonal antibodies, including the anti-CD38 monoclonal antibodies daratumumab and isatuximab, bispecific T-cell engagers, chimeric antigen receptor (CAR) T-cells, and antibody-drug conjugates (ADC). In collaboration with Dr. Jane Yang, our team has designed a novel ADC, Daratumumab-Polymer-GDC0980 (SY120418), that consists of daratumumab and multiple GDC-0980, a dual PI3K/mTOR pathway inhibitor. Our group is currently testing the in vitro activity of this ADC on blocking MM cell proliferation, PI3K/mTOR pathway inhibition, and myeloma cell sensitization to GDC0980. Additionally, we are validating SY120418 on a preclinical mouse model. My role on this project is the Principal Investigator responsible for the overall project direction, design coordination of experiments, and data analysis. This is an interdepartmental collaboration with Co-PI, Dr. Jiyuan (Jane) Yang, PhD, a Research Professor in the Department of Pharmaceutics and Pharmaceutical Chemistry.

   a. Gambles MT, Li S, Kendell I, Li J, Sborov D, Shami P, Yang J, Kopeček J. Multiantigen T-Cell Hybridizers: A Two-Component T-Cell-Activating Therapy. ACS Nano. 2024 Aug 27;18(34):23341-23353. PubMed PMID: 39149859.
   b. Gambles MT, Sborov D, Shami P, Yang J, Kopeček J. Obinutuzumab-Based Drug-Free Macromolecular Therapeutics Synergizes with Topoisomerase Inhibitors. Macromol Biosci. 2024 Mar;24(3):e2300375. PubMed PMID: 37838941.
   c. Tommy Gambles M, Li J, Christopher Radford D, Sborov D, Shami P, Yang J, Kopeček J. Simultaneous crosslinking of CD20 and CD38 receptors by drug-free macromolecular therapeutics enhances B cell apoptosis in vitro and in vivo. J Control Release. 2022 Oct;350:584-599. PubMed Central PMCID: PMC9561060.
   d. Gambles MT, Li J, Wang J, Sborov D, Yang J, Kopeček J. Crosslinking of CD38 Receptors Triggers Apoptosis of Malignant B Cells. Molecules. 2021 Jul 31;26(15) PubMed Central PMCID: PMC8348492.

3. ONCOLYTIC VIRUSES IN MULTIPLE MYELOMA. Oncolytic viruses preferentially kill malignant cells via direct cytotoxicity and immune-mediated cell death and have primarily been studied in patients with solid tumors. In collaboration with Drs. Craig Hofmeister (Emory University) and Flavia Pichiorri (City of Hope), we are the first group to clinically investigate viral oncolytics in any hematologic malignancy. Our work investigates Pelareorep (Reolysin), a dsRNA virus that preferentially enters cancer cells, either alone or in combination with other anti-myeloma drugs in heavily pretreated patients with relapsed and refractory multiple myeloma. Collectively, we have 4 peer reviewed publications resulting from our viral oncolytics projects and I was the first author of our publication in Clinical Cancer Research that highlighted the clinical and correlative results from our NCI-CTEP sponsored phase 1 trial investigating single-agent reolysin in patients with relapsed multiple myeloma (NCT01533194). In this project, we showed that reovirus preferentially entered MM cells but did not sufficiently replicate to result in objective clinical responses. Based on unpublished preclinical data indicating synergistic MM cell killing when combined with an effective anti-myeloma drug called carfilzomib (proteosome inhibitor), we initiated two follow-up phase 1b clinical trials investigating Pelareorep in combination with carfilzomib (NCT02101944) and in combination with carfilzomib and nivolumab (checkpoint inhibitor) (NCT03605719). Our preliminary data thus far indicates that combining Reolysin with these other drugs leads to enhanced MM cell killing and objective clinical responses. Since joining the faculty at the UU-HCI, I have developed independent projects focused on optimizing viral oncolytics for the treatment of RRMM and these projects have been supported by pilot award funding through the UU-Division of Hematology and Hematologic Malignancies (Optimization of direct and immune mediated multiple myeloma cell killing utilizing a viral oncolytic based treatment approach) and the American Cancer Society supported HCI Institutional Research Grant (Utilizing oncolytic virotherapy to optimize CAR-T cell mediated multiple myeloma cell killing); both projects are ongoing.

   a. Ghose J, Dona A, Murtadha M, Gunes EG, Caserta E, Yoo JY, Russell L, Jaime-Ramirez AC, Barwick BG, Gupta VA, Sanchez JF, Sborov DW, Rosen ST, Krishnan A, Boise LH, Kaur B, Hofmeister CC,

Pichiorri F. Oncolytic herpes simplex virus infects myeloma cells in vitro and in vivo. Mol Ther Oncolytics. 2021 Mar 26;20:519-531. PubMed Central PMCID: PMC7940704.

b. Mezache L, Magro C, Hofmeister C, Pichiorri F, Sborov D, Nuovo GJ. Modulation of PD-L1 and CD8 Activity in Idiopathic and Infectious Chronic Inflammatory Conditions. Appl Immunohistochem Mol Morphol. 2017 Feb;25(2):100-109. PubMed Central PMCID: PMC5247427.

c. Stiff A, Caserta E, Sborov DW, Nuovo GJ, Mo X, Schlotter SY, Canella A, Smith E, Badway J, Old M, Jaime-Ramirez AC, Yan P, Benson DM, Byrd JC, Baiocchi R, Kaur B, Hofmeister CC, Pichiorri F. Histone Deacetylase Inhibitors Enhance the Therapeutic Potential of Reovirus in Multiple Myeloma. Mol Cancer Ther. 2016 May;15(5):830-41. PubMed Central PMCID: PMC4873335.

d. Sborov DW, Nuovo GJ, Stiff A, Mace T, Lesinski GB, Benson DM Jr, Efebera YA, Rosko AE, Pichiorri F, Grever MR, Hofmeister CC. A phase I trial of single-agent reolysin in patients with relapsed multiple myeloma. Clin Cancer Res. 2014 Dec 1;20(23):5946-55. PubMed Central PMCID: PMC4253985.

4. PERSONALIZED MELPHALAN DOSING. In collaboration with Craig Hofmeister, MD MPH (Emory University), Mitch Phelps PhD (Ohio State University), and Ming Poi (Ohio State University), we have established a novel method of personalizing high dose melphalan dosing for multiple myeloma patients undergoing autologous transplantation. We have published our observational trial experiences and together with Dr. Hofmeister, I have designed a prospective clinical trial that is now IRB-approved. Development of this novel personalized dosing approach is based on identification of PK/PD covariates that influence duration of severe neutropenia. During the initial phases of this project, I worked alongside the Phelps laboratory team to assist in the identification of these variables, co-wrote the clinical trial protocol, and was co-first author on the below listed publications with Dr. Yu Kyoung Cho.

a. Li J, Cho YK, Sborov DW, Phelps MA, Hofmeister CC, Poi MJ. Evaluating the Impacts of CYP3A4*1B and CYP3A5*3 Variations on Pharmacokinetic Behavior and Clinical Outcomes in Multiple Myeloma Patients With Autologous Stem Cell Transplant. Cancer Genomics Proteomics. 2023 Jan-Feb;20(1):9-17. PubMed Central PMCID: PMC9806672.

b. Li J, Persaud AK, Johnson JA, Sborov DW, Phelps MA, Hofmeister CC, Poi MJ. A Single Nucleotide Polymorphism (SNP) in the SLC22A3 Transporter Gene Is Associated With the Severity of Oral Mucositis in Multiple Myeloma Patients Receiving Autologous Stem Cell Transplant Followed by Melphalan Therapy. Anticancer Res. 2022 Jan;42(1):385-395. PubMed PMID: 34969749.

c. Cho YK, Irby DJ, Li J, Sborov DW, Mould DR, Badawi M, Dauki A, Lamprecht M, Rosko AE, Fernandez S, Hade EM, Hofmeister CC, Poi M, Phelps MA. Pharmacokinetic-Pharmacodynamic Model of Neutropenia in Patients With Myeloma Receiving High-Dose Melphalan for Autologous Stem Cell Transplant. CPT Pharmacometrics Syst Pharmacol. 2018 Nov;7(11):748-758. PubMed Central PMCID: PMC6263666.

d. Cho YK, Sborov DW, Lamprecht M, Li J, Wang J, Hade EM, Gao Y, Tackett K, Williams N, Benson DM, Efebera YA, Rosko AE, Devine SM, Poi M, Hofmeister CC, Phelps MA. Associations of High-Dose Melphalan Pharmacokinetics and Outcomes in the Setting of a Randomized Cryotherapy Trial. Clin Pharmacol Ther. 2017 Sep;102(3):511-519. PubMed Central PMCID: PMC5821248.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/douglas.sborov.1/bibliography/public/

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES**.

NAME: Presson, Angela

eRA COMMONS USER NAME (credential, e.g., agency login): APRESSON2

POSITION TITLE: Research Professor, Division of Epidemiology, University of Utah

EDUCATION/TRAINING

| INSTITUTION AND LOCATION | DEGREE | Completion Date | FIELD OF STUDY |
|---|---|---|---|
| University of California, Los Angeles, CA | MS | 05/2004 | Statistics |
| University of California, Los Angeles, CA | PhD | 05/2007 | Statistics |
| University of California, Los Angeles, CA | Postdoctoral Fellow | 07/2007 | Human Genetics |

**A. Personal Statement**

I am pleased to serve as a Co-Investigator on Dr. Yizhe Xu's submission titled, *An Efficient, high-Quality, Unbiased, Interpretable Pipeline for Overcoming Barriers in the Translational Research using Real-World Data*. I am a Research Professor of Epidemiology within the Department of Internal Medicine, as well as the Director of the Study Design and Biostatistics Center (SDBC) and Co-Director of the Translational Research Implementation Analysis and Design (TRIAD) in the University of Utah Clinical and Translational Sciences Institute (Utah CTSI) at the University of Utah. I hold multiple University of Utah adjunct appointments within the Department of Pediatrics' Division of Pediatric Critical Care, Department of Orthopaedics, and Department of Population Health Sciences' Division of Biostatistics. In these roles, I commonly provide study design consultation and statistical support on medical studies. For the current proposal, I will help with facilitation of communicating the EQUIP resources to clinicians who collaborate with the SDBC.

Relevant to the current proposal, I have overseen the analysis on several projects involving causal inference and machine learning methods. We regularly receive requests through the SDBC for projects involving these methods. I commit to meeting regularly with Dr. Xu and her study team to support the development and deployment of the EQUIP research schema and resources. My experience with causal inference and machine learning methods and leadership in the SDBC uniquely qualify me to support Dr. Xu's proposal.

The following are ongoing and recently completed projects I would like to highlight:

9-01_PAC-12-UTAH-FINO-23-01 Fino (PI) 06/01/23-05/31/25
Pac-12 Athletic Conference | Student-Athlete Health & Wellbeing (SAHW) Grant Program
Smartphone-based Assessment of Reactive Balance and Balance Phenotypes after Concussion
Relevance to Current Proposal: I am collaborating with Dr. Fino to determine the clinical consequences of reactive vs. static balance deficits after concussion.
Role: Co-Investigator

AARG-21-846414 Supiano (PI) 11/01/2021-10/31/2024
Pre-Loss Group Therapy for Dementia Family Care Partners at Risk for Complicated Grief
Relevance to Current Proposal: I am collaborating with Dr. Supiano to study the feasibility of providing training via telehealth to social workers in nursing homes. We will study the impact of this intervention in family care partners experiencing complicated grief.
Role: Co-Investigator

HSR&D 22-062-2 Brooke (PI) 03/01/24-02/28/28
The Impact of a Transitional Pain Service on Reducing Chronic Opioid Use Among Veterans Using Community Care for Orthopedic Surgery
Relevance to Current Proposal: I am collaborating with Dr. Brooke to investigate whether a telehealth transitional pain service is a cost-effective strategy to improve safety of post surgery opioid use.
Role: Co-Investigator

1K23NS105920-01A1 Cortez (PI) 04/15/2020-03/31/2025
NIH / NINDS
Photophobia and Pupillary Autonomic Dysfunction as Biomarkers of Post-Traumatic Headache

Relevance to Current Proposal: I am collaborating with Dr. Cortez to use a multimodal approach to sensory and autonomic testing to identify clinically meaningful biomarkers for use in PTH diagnosis, disease monitoring, and the development of non-addictive treatments with the goal of reducing the overall health burden of PTH.
Role: Co-Investigator

1I01CX002571-01A1 Tashjian (PI) 04/01/2024-03/31/2027
NIH / NINDS
Determining Genetic Variants Associated with Rotator Cuff Tearing
Relevance to Current Proposal: The goal of this proposal is to use machine learning methods to develop a polygenic risk calculator to predict rotator cuff tearing, tear progression and tendon repair healing.
Role: Co-Investigator

1R61NS125153-01A1 Brennan (PI) 04/15/2023-03/31/2026
NIH / NINDS
Sensory Amplifications as Biomarkers of Migraine Progression
Relevance to Current Proposal: The goal of this proposal is to use machine learning methods to develop a prognostic sensory biomarker signature to predict progression of patients from high-frequency episodic migraineurs (HFEM) to chronic migraineurs (CM).
Role: Co-Investigator

UL1TR004409-01 Hess/Majersik (PI) 04/01/2023-03/31/2030
NIH/NCATS
University of Utah Clinical and Translational Science Institute (CTSI)
Relevance to Current Proposal: The Utah CTSI serves as the major infrastructure and home for clinical and translational research in the state of Utah.
Role: CTSI Translational Research: Implementation, Analysis and Design Co-Director

1R01HS029482-01 Vaughn/Szymczak (MPI) 09/01/2023-08/31/2028
Reducing Overuse of Antibiotics at Discharge: The ROAD Home Trial
Relevance to Current Proposal: Conduct a 40-hospital parallel cluster randomized trial to test the effectiveness of the ROAD Home Intervention on days of antibiotic overuse at discharge in hospitalized adults with CAP and UTI. Concurrently, conduct a mixed-methods concurrent process evaluation to identify contextual factors influencing implementation of the ROAD Home Intervention. Finally, we will create and refine a ROAD Home discharge stewardship toolkit to facilitate dissemination of the ROAD Home Intervention.
Role: Co-Investigator

5I01RX003442-03 (IPA Contract #10057212) Pugh (PI) 01/01/2019-09/30/2024
VA Salt Lake City Healthcare System | Veterans Affairs
Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC): Data and Biostatistics Core
Relevance to Current Proposal: I am collaborating with Dr. Pugh to assess the impact of mild traumatic brain injury on measures of wellness, including cognitive, sleep, employment, and psychological characteristics.
Role: Co-Investigator

The following are publications that highlight my experience and qualifications for this proposal:

1. Abou-Ismail MY, Zhang C, **Presson AP**, Chaturvedi S, Antun AG, Farland AM, Woods R, Metjian A, Park YA, de Ridder G, Gibson B, Kasthuri RS, Liles DK, Akwaa F, Clover T, Kreuziger LB, Sridharan M, Go RS, McCrae KR, Upreti HV, Gangaraju R, Kocher NK, Zheng XL, Raval JS, Masias C, Cataland SR, Johnson AD, Davis E, Evans MD, Mazepa M, Lim MY. A machine learning approach to predict mortality due to immune-mediated thrombotic thrombocytopenic purpura. *Res Pract Thromb Haemost*. 2024 Mar 19;8(3):102388. PMCID: PMC11033197

2. Huang LC, Bleicher J, Torre M, Johnson JE, **Presson A**, Millar MM, Gordon AJ, Brooke BS, Kaphingst KA, Harris AHS. Evaluating a health system-wide opioid disposal intervention distributing home-disposal bags. Health Serv Res. 2023 Dec;58(6):1256-1265. Epub 2023 Sep 12. PMID: 37700549

3. Olson J, Franz-O'Neal E, Cipriano FA, Ou Z, **Presson AP**, Thorell EA. Impact of Early Oral Antibiotic Therapy in Infants With Bacteremic Urinary Tract Infections. Hosp Pediatr. 2022 Jul 1;12(7):632-638. PMID: 35726551

4. Dy CJ, Osei DA, Maak TG, Gottschalk MB, Zhang AL, Maloney MD, **Presson AP**, O'Keefe RJ. Safety of Overlapping Inpatient Orthopaedic Surgery: A Multicenter Study. *J Bone Joint Surg Am.* 2018 Nov 21;100(22):1902-1911. PMCID: PMC6636802

## B. Positions, Scientific Appointments, and Honors

### Positions and Scientific Appointments

| | |
|---|---|
| 2020-Present | Research Professor, Division of Epidemiology, Dept of Internal Medicine, University of Utah, Salt Lake City, UT |
| 2017-Present | Director of the Study Design and Biostatistics Center (SDBC), University of Utah, Salt Lake City, UT |
| 2017-Present | Adjunct Associate Professor, Dept. of Orthopaedics, University of Utah, Salt Lake City, UT |
| 2016-Present | Adjunct Associate Professor, Dept. of Population Health Sciences, University of Utah, Salt Lake City, UT |
| 2015-Present | Co-Director, Population Health Research Foundation for Discovery, Center for Clinical and Translational Science, University of Utah, Salt Lake City, UT |
| 2015-2020 | Research Associate Professor, Division of Epidemiology, University of Utah, Salt Lake City, UT |
| 2015-2016 | Member, International Society for Quality of Life Research (ISOQOL) |
| 2015-Present | Adjunct Associate Professor, Dept. of Family and Preventive Medicine, University of Utah, Salt Lake City, UT |
| 2012-2015 | Research Assistant Professor, Division of Epidemiology, University of Utah, Salt Lake City, UT |
| 2012-2013 | Member, International Genetic Epidemiology Society (IGES) |
| 2012-Present | Adjunct Assistant Professor, Dept. of Pediatrics, University of Utah, Salt Lake City, UT |
| 2007-2010 | Adjunct Assistant Professor, Dept. of Pediatrics, University of California, Los Angeles, CA |
| 2007-2007 | Postdoctoral Scholar, Dept. of Human Genetics, University of California, Los Angeles, CA |
| 2007-2019 | Adjunct Assistant Professor, Dept. of Biostatistics, University of California, Los Angeles, CA |
| 2003-2006 | Graduate Student Researcher, Dept. of Human Genetics, University of California, Los Angeles, CA |
| 2002-2007 | Member, American Statistical Association (ASA) |
| 2002-2011 | Member, American Society of Human Genetics (ASHG) |
| 2002-2003 | Programmer Analyst, Dept of Human Genetics, University of California, Los Angeles, CA |
| 2002-2002 | Teaching Assistant, Dept. of Statistics, University of California, Los Angeles, CA |
| 2000-2000 | Intern, Dept of Genomics, Bristol Meyers Squibb, Princeton, NJ |
| 1998-1998 | Research Assistant, Dept. of Molecular Genetics, Wichita State University, Wichita, KS |

### Honors

| | |
|---|---|
| 2009 | Travel Award, International AIDS Society (IAS), 5th Annual Conference, Capetown, South Africa |
| 2007 | Genomic Analysis Training Grant (GATG), University of California, Los Angeles |
| 2006 | Best Presentation Award, Critical Assessment of Microarray Data Analysis (CAMDA) |
| 2000 | Eugene V Cota Robles Fellowship, University of California, Los Angeles |

## C. Contribution to Science

1. **Patient reported outcomes and comparative effectiveness in surgical studies**. I work extensively with surgeons on studies that evaluate the success of operative techniques using patient reported outcomes. Success may be defined in terms of improved function, often measured by Patient-Reported Outcomes Measurement Information System (PROMIS), or patient satisfaction, often measured by the Ganey® Outpatient Medical Practice Survey. Patient satisfaction is of particular interest given that institutional, departmental and provider level support are tied to patient satisfaction scores. We recently studied the

psychometric properties of the Press Ganey® satisfaction survey and found that while it generally had good validity and reliability measures, it had a notable ceiling effect (29.3%) and variability in quarterly percentile scores. We have also found evidence of non-response bias in the Press Ganey® survey and that satisfaction is associated with non-modifiable patient characteristics.

a. **Presson AP**, Zhang C, Abtahi AM, Kean J, Hung M, Tyser AR. Psychometric properties of the Press Ganey® Outpatient Medical Practice Survey. Health Qual Life Outcomes. 2017 Feb 10;15(1):32. PMID:28183312, PMCID: PMC5301343, doi: 10.1186/s12955-017-0610-3.
b. Robins RJ, Anderson MB, Zhang Y, **Presson AP**, Burks RT, Greis PE. Convergent Validity of the Patient-Reported Outcomes Measurement Information System's Physical Function Computerized Adaptive Test for the Knee and Shoulder Injury Sports Medicine Patient Population. Arthoscopy. 2016 Dec. PMID: 27964968
c. Tyser AR, Abtahi AM, McFadden M, **Presson AP**. Evidence of non-response bias in the Press-Ganey patient satisfaction survey. BMC Health Serv Res. 2016 Aug;16(a):350. PMID: 27488567, PMCID: PMC4972948, doi: 10.1186/s12913-016-1595-z
d. Abtahi AM, **Presson AP,** Zhang, C Saltzman CL, Tyser AR. Association Between Orthopaedic Outpatient Satisfaction and Non-Modifiable Patient Factors. J Bone Joint Surg Am. 2015 Jul 1;97(13):1041-8. PMID: 26135070, PMCID: PMC4574907, doi: 10.2106/JBJS.N.00950

2. **Multi-institutional studies in bladder research.** In collaboration with Dr. Myers in Urology, I have provided study design and statistical support for several studies from the Trauma and Urologic Reconstruction Network of Surgeons (TURNS) and Neurogenic Bladder Research Group. TURNS includes data from six institutions, with small sample sizes due to the rarity of the conditions studied. We used Firth's penalized-likelihood logistic regression to control for and handle the sparsity introduced by institutional strata. The Neurogenic Bladder Research Group focuses on outcomes for bladder management strategies in a spinal cord injury population. In particular, we are interested in the comparative effectiveness of the different management strategies. Due to the longitudinal nature of the data, we will utilize marginal structural models to examine efficacy in the presence of time-dependent confounding.

a. Patel DP, Lenherr SM, Stoffel JT, Elliot SP, Welk B, **Presson AP**, Jha A, Rosenbluth J, Myers JB; Neurogenic Bladder Research Group. Study protocol: patient reported outcomes for bladder management strategies in spinal cord injury. *BMC Urol.* 2017 Oct 10;17(1):95. PMCID: PMC5635498
b. Bassett MR, Santiago-Lastra Y, Stoffel JT, Goldfarb R, Elliott SP, Pate SC, Broghammer JA, Gaither T, Breyer BN, Vanni AJ, Voelzke BB, Erickson BA, McClung CD, **Presson AP**, Tward JD, Myers JB; Neurogenic Bladder Research Group; Trauma and Urologic Reconstructive Network of Surgeons. Urinary Diversion for Severe Urinary Adverse Events of Prostate Radiation: Results from a Multi-Institutional Study. *J Urol.* 2017 Mar;197(3 Pt 1):744-750.
c. Redshaw JD, Broghammer JA, Smith TG 3rd, Voelzke BB, Erickson BA, McClung CD, Elliott SP, Alsikafi NF, **Presson AP**, Aberger ME, Craig JR, Brant WO, Myers JB. Intralesional injection of mitomycin C at transurethral incision of bladder neck contracture may offer limited benefit: TURNS Study Group. *J Urol*. 2015 Feb;193(2):587-92. PMCID: PMC4307389
d. Patel DP, Elliott SP, Voelzke BB, Erickson BA, McClung CD, **Presson AP**, Zhang C, Myers JB. Patient-Reported Sexual Function After Staged Penile Urethroplasty. *Urology*. 2015 Aug;86(2):395-400.

3. **Weighted Correlation Network Analysis (WCNA).** One of my earlier contributions to science is in the area of WCNA or Weighted Gene Co-expression Network Analysis (WGCNA) developed by one of my dissertation mentors at UCLA, Dr. Steve Horvath. This methodology was originally developed as a dimension reduction strategy to study large-scale gene expression data sets. The rationale behind WGCNA is to identify clusters of genes that have similar expression profiles and then relate these clusters rather than the individual genes to clinical traits of interest. The thought is that these gene clusters represent biological pathways, and by identifying a disease related pathway, one can then narrow the focus to genes within that pathway. My work here has focused on integrating WGCNA gene clusters with other genetic and protein level data. More recently I proposed WCNA methods in collaboration with Dr. Samuel Brown for an R21 proposal (funded July 2014) as an analytic strategy to identify novel Acute Respiratory Distress Syndrome (ARDS) phenotypes from a large-scale clinical data set.

a. **Presson AP**, Sobel EM, Papp JC, Suarez CJ, Whistler T, Rajeevan MS, Vernon SD, Horvath S. Integrated weighted gene co-expression network analysis with an application to chronic fatigue syndrome. *BMC Syst Biol*. 2008 Nov 6;2:95. PMID: 20663702, PMCID: PMC2625353, doi: 10.1186/1752-0509-2-95
b. Henderson-Maclennan NK, Papp JC, Talbot CC Jr, McCabe ER, **Presson AP**. Pathway analysis software: annotation errors and solutions. *Mol Genet Metab*. 2010 Oct-Nov;101(2-3):134-40. PMID: 20663702, PMCID: PMC2950253, doi: 10.1016/j.ymgme.2010.06.005
c. Maresh EL, Mah V, Alavi M, **Presson A**, Bagryanova L, Yoon NK, Chang G, Elshimali Y, Shevlin L, Zhang L, Hong L, Schatz S, Li A, Maoyong FU, Wadehra M, Chia D, Horvath S, Goodglick L. Development and Application of Tissue Microarrays for Biomarker Studies. *Forum Immunopath Dis Therap*. 2011;2(2):104.
d. **Presson AP**, Yoon NK, Bagryanova L, Mah V, Alavi M, Maresh EL, Rajasekaran AK, Goodglick L, Chia D, Horvath S. Protein expression based multimarker analysis of breast cancer samples. *BMC Cancer*. 2011 Jun 8;11:230. PMID: 21651811, PMCID: PMC3142534, doi: 10.1186/1471-2407-11-230.

4. **Bayesian change-point methods for identifying viral vector integration patterns.** Successful gene therapy research relies on a combination of an effective therapeutic vector and a vector that can safely and effectively integrate into the host genome. The integrated vector's genetic sequence is then expressed and translated into therapeutic products that can potentially cure the host's disease. In collaboration with Dr. Irvin Chen, the director of the UCLA AIDS Institute, I developed a novel statistical method to study the safety of gene therapy vector integration for the goal of curing AIDS. The purpose was to evaluate the safety of different gene therapy vectors by studying where in the genome they preferred to integrate, as some genomic regions are susceptible to insertional mutagenesis leading to cancer over the long term. I used Bayesian change-point methods to identify genomic locations that were preferred by HIV lentiviral vectors and other gene therapy vectors. Using animal models, we continue to monitor the safety and efficacy of potential therapeutic vectors via their integration patterns and expression profiles.
   a. Kim S, Kim N, **Presson AP**, An DS, Mao SH, Bonifacino AC, Donahue RE, Chow SA, Chen IS. High-throughput, sensitive quantification of repopulating hematopoietic stem cell clones. *J Virol*. 2010 Nov;84(22):11771-80. PMID: 20844053, PMCID: PMC2977897, doi: 10.1128/JVI.01355-10
   b. **Presson AP**, Kim N, Xiaofei Y, Chen IS, Kim S. Methodology and software to detect viral integration site hot-spots. *BMC Bioinformatics*. 2011 Sep 14;12:367. PMID: 21914224, PMCID: PMC3203353, doi: 10.1186/1471-2105-12-367 .
   c. Kim S, Kim N, **Presson AP**, Metzger ME, Bonifacino AC, Sehl M, Chow SA, Crooks GM, Dunbar CE, An DS, Donahue RE, Chen IS. Dynamics of HSPC repopulation in nonhuman primates revealed by a decade-long clonal-tracking study. *Cell Stem Cell*. 2014 Apr 3;14(4):473-85. PMID: 24702996, PMCID: PMC4009343, doi: 10.1016/j.stem.2013.12.012

**Complete List of Published Work in MyBibliography**
https://www.ncbi.nlm.nih.gov/myncbi/angela.presson.1/bibliography/public/

# PHS 398 OTHER SUPPORT

*Name: **Xu, Yizhe**

Commons ID: XU.YIZHE

## PROJECT/PROPOSAL OTHER SUPPORT

## ACTIVE

***Title: CTSA UM1 Program at the University of Utah**

*Major Goals: The vision of the Utah Clinical & Translational Science Institute (CTSI) is to strategically and ethically develop and apply generalizable and reproducible clinical and translational science (CTS) innovations to increase science equity and health equity, and promote social justice. The Utah CTSI collaborates with local, regional, and national partners and collaborators to achieve this vision through four specific aims: (1) Serve as a well-recognized hub for clinical and translational science that promotes science and health equity in a measurable, reproducible, and sustainable manner. (2) Design, develop, and test innovative translational science methods, tools, techniques, and best practices to increase efficiency and reproducibility. (3) Support the implementation and dissemination of translational science innovations and the education and development of the translational science and research workforce. (4) Catalyze the advancement of translational research discoveries from bench to bedside to populations to improve the health of individuals and communities, reducing health disparities and improving health equity.

*Status of Support: Active

Project Number: 1UM1TR004409-01

Name of PD/PI: Hess, Rachel and Majersik, Jennifer

*Source of Support: NIH/NCATS

Primary Place of Performance: University of Utah

Project Start and End Date: 04/01/2023 – 03/31/2030

*Total Award Amount (including Indirect Costs): $38,699,588

*Person Months per budget period:

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 2024 | 1.08 |
| 2025 | 0.00 |
| 2026 | 0.00 |
| 2027 | 0.00 |
| 2028 | 0.00 |
| 2029 | 0.00 |

*Title: Guiding next steps for SPRINT-MIND implementation: Identifying high-benefit subgroups and comparative effects of ARB- vs. ACEI-based regimens
Major Goals: In this study, we will use machine learning and predicting modeling and modern causal inference methods to determine which patients derive the greatest cognitive and net (overall) benefit from intensive systolic blood pressure treatment and if angiotensin II receptor blocker (ARB)- vs. angiotensin-converting enzyme inhibitor (ACEI)-based antihypertensive medication regimens have greater beneficial effects on cognitive and brain structure outcomes, independent of their similar BP lowering effects.
*Status of Support: Active

Project Number: 5R01AG065805-04
Name of PD/PI: Bress, Adam P
*Source of Support: National Institute on Aging
*Primary Place of Performance: University of Utah
Project/Proposal Start and End Dates: 08/01/2020 – 04/30/2024
*Total Award Amount: $2,715,187
*Person Months (Calendar/Academic/Summer) per budget period:

| Year (YYYY) | Person Months (##.## Type) |
|---|---|
| 3. 2023 | 3.0 |
| 4. 2024 | 3.0 |

## PENDING

None

## IN-KIND

None

## OVERLAP

None

## STATEMENT CERTIFICATION

I, Yizhe Xu, certify that the statements herein are true, complete, and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Signature: YIZHE XU

Date: Feb 22, 2024

# Xu, Yizhe OS_01.2024

Final Audit Report 2024-02-22

| | |
|---|---|
| Created: | 2024-02-22 |
| By: | Matthew Quigley (u0574536@utah.edu) |
| Status: | Signed |
| Transaction ID: | CBJCHBCAABAAbsACdAcWQHbDhnKCX4P2qi_yDE4niBVq |

## "Xu, Yizhe OS_01.2024" History

Document created by Matthew Quigley (u0574536@utah.edu)
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**For New and Renewal Applications – DO NOT SUBMIT UNLESS REQUESTED**
**PHS 398 OTHER SUPPORT**

*There is no "form page" for reporting Other Support. Information on Other Support should be provided in the format shown below.*

*Name of Individual: Srinivasan Beddhu, MD
Commons ID: SRINIBEDDHU

**Other Support – Project/Proposal**

**Title: Sit Less, Interact and Move More (SLIMM) 2 Study**

Major Goals: This is a RCT to examine the effects of a sedentary behavior intervention along with two cointerventions on sedentary duration, stepping duration and the number of steps/day in CKD.

*Status of Support: ACTIVE

Project Number: 1RO1DK128640

Name of PD/PI: Beddhu, Srinivasan

*Source of Support: NIH/NIDDK

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: (MM/YYYY) (if available): 05/15/2021 – 04/30/2026

* Total Award Amount (including Indirect Costs): $3,299,008

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2021 -2022 | 1.38 calendar months |
| 2. 2022-2023 | 1.38 calendar months |
| 3. 2023-2024 | 2.16 calendar months |
| 4. 2024-2025 | 2.16 calendar months |
| 5. 2025-2026 | 2.16 calendar months |

**Title: Objectively Measured Sedentary Behavior and Physical Activity in PREVENTABLE Study**

Major Goals: The goals of this ancillary study to PREVENTABLE are to examine the associations of sedentary behavior with cognitive decline and the effects of a statin intervention on physical activity levels in older adults

*Status of Support: ACTIVE

Project Number: 1RO1AG074592-01

Name of PD/PI: Beddhu, Srinivasan

*Source of Support: NIH/NIA

*Primary Place of Performance: University of Utah

Name of Individual: Srinivasan Beddhu, MD
Commons ID: SRINIBEDDHU

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/15/2021-3/31/2026

* Total Award Amount (including Indirect Costs): $3,390913

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2021-2022 | 1.35 calendar Months |
| 2. 2022-2023 | 1.80 calendar months |
| 3. 2023-2024 | 2.28 calendar months |
| 4. 2024-2025 | 2.28 calendar months |
| 5. 2025-2026 | 2.28 calendar months |

**Title: MSRP in Metabolism, Diabetes, Digestive and Kidney Diseases**
Major Goals: Summer research program for medical students in NIDDK areas of research
*Status of Support: Active

Principal Investigators: Srinivasan Beddhu, June Round
NIH National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
T35 DK103596
Role: Principal Investigator
Total Award Amount (including Indirect Costs): $321,910
*Source of Support: NIH/NIA

*Primary Place of Performance: University of Utah

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2021-2022 | 0.24 calendar Months |
| 2. 2022-2023 | 0.24 calendar months |
| 3. 2023-2024 | 0.24 calendar months |
| 4. 2024-2025 | 0.24 calendar months |
| 5. 2025-2026 | 0.24 calendar months |

**Pending:**

**R01DK1392021 Pharmacotherapies to Improve Hypoglycemia Awareness**
Major Goals: To conduct a RCT to test pharmacotherapies to improve hypoglycemia awareness
Principal Investigators: Owen Chan, Srinivasan Beddhu, Mathew Wall
04/01/2025 - 03/31/2030 (Project Period)
Total costs $3,341,584

*Primary Place of Performance: University of Utah

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2025-2026 | 1.2 calendar Months |
| 2. 2026-2027 | 1.2 calendar months |
| 3. 2027-2028 | 1.2 calendar months |
| 4. 2028-2029 | 1.2 calendar months |
| 5. 2029-2030 | 1.2 calendar months |

Name of Individual: Srinivasan Beddhu, MD
Commons ID: SRINIBEDDHU

**R01HL179586 A multi-faceted intervention to reduce sedentary time and improve physical and vascular function in cardiovascular-kidney-metabolic syndrome**
Major goals: To conduct RCT to reduce sedentary time and improve physical and vascular function in cardiovascular-kidney-metabolic syndrome
Principal Investigators: Diana Jalal (PI) Srinivasan Beddhu (MPI)
04/01/2025 - 03/31/2029 (Project Period)
Total costs $3,024,075.00
*Primary Place of Performance: University of Iowa and University of Utah

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2025-2026 | 1.2 calendar Months |
| 2. 2026-2027 | 1.2 calendar months |
| 3. 2027-2028 | 1.2 calendar months |
| 4. 2028-2029 | 1.2 calendar months |

**R01 Emulated Trials of Point and Dynamic Treatment Regimens for Cardiovascular, Kidney and Metabolic Health in Type 2 Diabetes**
Major goals; To conduct emulated trials using two large national datasets of T2D
Principal Investigators: Beddhu, Srinivasan (PI), Drakos, Stavros (MPI), Shen, Jincheng (MPI)
04/01/2025 - 03/31/2029 (Project Period)
Total costs $3,061,310.00

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2025-2026 | 1.2 calendar Months |
| 2. 2026-2027 | 1.2 calendar months |
| 3. 2027-2028 | 1.2 calendar months |
| 4. 2028-2029 | 1.2 calendar months |

***Overlap** (summarized for each individual): Pending R01HL179586 and the current proposal have substantial overlap. If both are funded, we will decline the R01HL179586

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

*Signature: _____

Date: _____08/26/24_____

# OTHER SUPPORT

**BRESS, Adam**
**Commons ID:** ADAMBRESS

Dr. Bress has joint appointments as an Associate Investigator for the VA Salt Lake City Health Care System, and as an Associate Professor at the University of Utah School of Medicine, Department of Population Health Sciences, Salt Lake City, UT. Calendar months are calculated separately based on each appointment.

## ACTIVE

**Title: Understanding the Interplay of Aspirin and Other Commonly Used Medication and the Potential for Ovarian Cancer Chemoprevention**

Major Goals: To identify novel and modifiable ovarian cancer risk factors. Building on our success demonstrating that aspirin should be considered for use in ovarian cancer chemoprevention, particularly for higher-risk groups, we will use an integrated population-based approach that directly addresses research questions about whether the aspirin-ovarian cancer risk reduction is enhanced or reduced by the use of other common medications and if prescription medications that inhibit the mevalonate pathway could also be used to reduce the burden of ovarian cancer alone or in combination with other drugs.

Status of Support: Active

Project Number: HT94252310247

Name of PD/PI: Trabert, PI

Source of Support: Department of Defense, U.S. Army Medical Research and Materiel Command, Congressionally Directed Medical Research Programs, Ovarian Cancer Research Program, Teal Expansion Program

Grants official: N/A

Primary Place of Performance: University of Utah, Salt Lake City

Project/Proposal Start and End Date: 9/30/23–9/29/26

Total Award Amount (including Indirect Costs): $592,228

Person Months (Calendar/Academic/Summer) per budget period:

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2023-2024 | 0.6 calendar |
| 2. 2024-2025 | 0.6 calendar |
| 3. 2025-2026 | 0.6 calendar |

Overlap: There is no scientific, budgetary, or commitment overlap between this support and the application under review.

**Title: Using pharmacoepidemiology to optimize antihypertensive medication use to prevent aging-related multimorbidity: Midcareer investigator award in patient-oriented research and mentoring**

Major Goals: Our goals are to investigate the mechanisms (including social determinants of health) of the use, underuse, and unsafe use of antihypertensive medications to prevent aging-

related multimorbidity, including Alzheimer's disease and related dementias and cardiovascular disease, as well as to train the next generation of diverse, patient-oriented, aging-related research scientists in hypertension pharmacoepidemiology.

Status of Support: Active

Project Number: 1K24AG080168–02

Name of PD/PI: Bress, PI

Source of Support: NIH-NIA

Grants official: Marcel Salive (marcel.salive@nih.gov)

Primary Place of Performance: University of Utah, Salt Lake City

Project/Proposal Start and End Date: 2/1/23–1/31/28

Total Award Amount (including Indirect Costs): $991,065

Person Months (Calendar/Academic/Summer) per budget period:

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2023-2024 | 6.0 calendar |
| 2. 2024-2025 | 6.0 calendar |
| 3. 2025-2026 | 6.0 calendar |
| 4. 2026-2027 | 6.0 calendar |
| 5. 2027-2028 | 6.0 calendar |

Overlap: There is no scientific, budgetary, or commitment overlap between this support and the application under review.

**Title: Informing optimal first-line antihypertensive therapy: A rigorous comparative effectiveness analysis of ARBs vs. ACEIs on long-term risk of dementia, cancer, heart disease, and quality of life**

Major Goals: In this study, we will use national Veterans Health Administration and Kaiser Permanente Southern California data to determine the long-term comparative effects of ARBs versus ACEIs on the risk of dementia, cardiovascular disease, cancer, frailty, and life expectancy accounting for level of illness and quality of life.

Status of Support: Active

Project Number: 1R01AG074989-03

Name of PD/PI: Cohen, Bress, MPIs

Source of Support: NIH / NIA

Grants official: Susan Zieman (ziemans@nia.nih.gov)

Primary Place of Performance: University of Utah, Salt Lake City

Project/Proposal Start and End Date: 3/15/22–12/31/25

Total Award Amount (including Indirect Costs): $3,103,174

Person Months (Calendar/Academic/Summer) per budget period:

BRESS, Adam
Commons ID: ADAMBRESS

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2022 | 3.0 calendar |
| 2. 2023 | 1.2 calendar |
| 3. 2024 | 1.2 calendar |
| 4. 2025 | 1.2 calendar |

Overlap: There is no scientific, budgetary, or commitment overlap between this support and the application under review.

**Title: Incorporation of a hypertension working group into the Jackson Heart Study**

Major Goals: The Jackson Heart Study Hypertension Working Group (JHS-HWG) will conduct research to identify approaches to prevent hypertension and improve blood pressure control in African Americans. The JHS-HWG will also provide career development opportunities for early-stage investigators conducting hypertension research.

Status of Support: Active

Project Number: R01HL117323

Name of PD/PI: Muntner

Source of Support: University of Alabama (NIH)

Grants official: Sharon Smite (smithsh1@mail.nih.gov)

Primary Place of Performance: University of Utah, Salt Lake City

Project/Proposal Start and End Date: 7/1/21–6/30/25

Total Award Amount (including Indirect Costs): $274,500

Person Months (Calendar/Academic/Summer) per budget period:

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2021-2022 | 1.2 calendar |
| 2. 2022-2023 | 1.2 calendar |
| 3. 2023-2024 | 1.2 calendar |
| 4. 2024-2025 | 1.2 calendar |

Overlap: There is no scientific, budgetary, or commitment overlap between this support and the application under review.

**Title: Development, testing, and implementation of virtual statin associated muscle symptom (SAMS) management**

Major Goals: The goal of this project is to develop and evaluate a novel, multicomponent technology embedded within a team-based health service to empower patients with SAMS to self-manage their statin therapy to ultimately increase statin adherence and persistence and, thereby, ultimately reduce atherosclerotic cardiovascular disease risk among patients with SAMS.

Status of Support: Active

Project Number: 1R01HL157439-03

Name of PD/PI: King

Source of Support: NHLBI

Grants official: Mary Yaa Sedegah Masterson (mary.masterson@nih.gov)

BRESS, Adam
Commons ID: ADAMBRESS

Primary Place of Performance: University of Utah, Salt Lake City

Project/Proposal Start and End Date: 4/1/21–3/31/26

Total Award Amount (including Indirect Costs): $497,179

Person Months (Calendar/Academic/Summer) per budget period:

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2021-2022 | 0.36 calendar |
| 2. 2022-2023 | 0.36 calendar |
| 3. 2023-2024 | 0.36 calendar |
| 4. 2024-2025 | 0.36 calendar |
| 5. 2025-2026 | 0.36 calendar |

Overlap: There is no scientific, budgetary, or commitment overlap between this support and the application under review.

**Title: Guiding next steps for SPRINT-MIND implementation: Identifying high-benefit subgroups and comparative effects of ARB- vs. ACEI-based regimens**

Major Goals: In this study, we will use SPRINT-MIND data and apply machine learning and predictive modeling and modern causal inference methods to determine which patients derive the greatest cognitive and net (overall) benefit from intensive systolic blood pressure treatment, and whether angiotensin II receptor blocker (ARB)- vs. angiotensin-converting enzyme inhibitor (ACEI)-based antihypertensive medication regimens have greater beneficial effects on cognitive and brain structure outcomes, independent of their similar blood pressure-lowering effects.

Status of Support: Active

Project Number: 1R01AG065805-04

Name of PD/PI: Bress

Source of Support: NIH / NIA

Grants official: Dallas Anderson (andersda@nia.nih.gov)

Primary Place of Performance: University of Utah, Salt Lake City

Project/Proposal Start and End Date: 8/1/20–4/30/24

Total Award Amount (including Indirect Costs): $3,493,580

Person Months (Calendar/Academic/Summer) per budget period:

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2020-2021 | 3.6 calendar |
| 2. 2021-2022 | 3.6 calendar |
| 3. 2022-2023 | 1.2 calendar |
| 4. 2023-2024 | 1.2 calendar |

Overlap: There is no scientific, budgetary, or commitment overlap between this support and the application under review.

**Title: Effects of a behavioral sleep extension intervention on cardiometabolic risk factors among patients with elevated BP/hypertension**

Major Goals: The goal of this study is to conduct a randomized controlled trial to test the effects of our technology-assisted behavioral sleep extension intervention compared to a health

education control on 24-hour ambulatory blood pressure among individuals with short sleep duration and prehypertension/stage 1 hypertension.

Status of Support: Active

Project Number: 1R01NR018891-04

Name of PD/PI: Baron

Source of Support: NIH

Grants official: Karen Huss (hussk@mail.nih.gov)

Primary Place of Performance: University of Utah, Salt Lake City

Project/Proposal Start and End Date: 9/1/20–5/31/25

Total Award Amount (including Indirect Costs): $3,218,124

Person Months (Calendar/Academic/Summer) per budget period:

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2020-2021 | 1.8 calendar |
| 2. 2021-2022 | 1.8 calendar |
| 3. 2022-2023 | 1.2 calendar |
| 4. 2023-2024 | 0.6 calendar |
| 5. 2024-2025 | 0.6 calendar |

Overlap: There is no scientific, budgetary, or commitment overlap between this support and the application under review.

## PENDING

**Title: A Target Trial Emulation of ANGIOTENSIN II TYPE 2 and 4 Receptor Stimulating vs Inhibiting Antihypertensive Regimens to Guide Optimal First-choice Treatment Selection for Dementia Prevention**

Major Goals: To analyze data from over 3 million patients from the national Veterans Health Administration and Kaiser Permanente Southern California to compare the long-term effects of antihypertensive medications that stimulate vs. inhibit potential beneficial receptors in the brain on risk of dementia and identify who benefits the most from the stimulating agents to guide personalized therapy.

Status of Support: Pending; Not Yet Reviewed

Project Number: 1R01AG090715-01

Name of PD/PI: Bress, Cohen, An, MPIs

Source of Support: NIH/NIA

Grants official: TBD

Primary Place of Performance: University of Utah, Salt Lake City

Project/Proposal Start and End Date: 10/1/24–9/30/29

BRESS, Adam
Commons ID: ADAMBRESS

Total Award Amount (including Indirect Costs): $7,582,486

Person Months (Calendar/Academic/Summer) per budget period:

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2024-2025 | 3.0 calendar |
| 2. 2025-2026 | 3.0 calendar |
| 3. 2026-2027 | 3.0 calendar |
| 4. 2027-2028 | 3.0 calendar |
| 5. 2028-2029 | 3.0 calendar |

Overlap: There is no scientific, budgetary, or commitment overlap between this support and the application under review. If this project is funded, currently Active person-months will be reduced to accommodate it.

**IN-KIND**

Dr Bress has no in-kind contributions to report.

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

*Signature: DocuSigned by: ADAM BRESS 950F764C1EA148C...

Date: _____

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|---|---|---|

# PHS OTHER SUPPORT

Name of Individual: Chen, Y. Ann
Commons ID: ANNCHEN

## Other Support – Project/Proposal

ACTIVE

*__Title:__ Cancer Center Support Grant

*Major Goals: This grant supports the research infrastructure of the Cancer Center. It promotes scientific excellence through coordinated, broad-based interdisciplinary programs and support of state-of-the-art shared research resources. Cancer Center research programs include: Nuclear Control of Cell Growth and Differentiation; Cell Response and Regulation; Experimental Therapeutics; and Cancer Control and Population Sciences.

*Status of Support: Active

Project Number: P30CA042014

Name of PD/PI: Ulrich, Cornelia

*Source of Support: NCI

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 05/01/2020 - 04/30/2025 (Pending extension to 04/30/2027)

*Total Award Amount (including Indirect Costs): $20,999,790

*Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 35. 2025 | 2.40 calendar |
| 36. 2026* | 2.40 calendar |
| 37. 2027* | 2.40 calendar |

*Pending the award of the extension of the grant

***Title:** Characterization and Targeting of the Epigenetic State Underlying Uveal Melanoma Liver Metastasis

*Major Goals: We will perform epigenomic, transcriptional and proteomic analyses to define how BAP1 loss overcomes the Gaq-associated senescence and stimulates the metastatic phenotype. We will elucidate the mechanisms by which mutant Gaq cooperates with BAP1 loss to allow UM cells to activate HSCs, and then in turn, how HSCs contribute to UM progression and therapeutic resistance in the liver. Finally, we will investigate the HDAC1-dependency of the dedifferentiated state driven by Gaq and BAP1-loss and its role in liver metastasis.

*Status of Support: Active

Project Number: R01CA256193

Name of PD/PI: Smalley, Kieran; Harbour, James William; Licht, Jonathan D.

Name of Individual: Y. ANN CHEN
Commons ID: ANNCHEN

*Source of Support: NCI

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 08/09/2021 - 07/31/2026

*Total Award Amount (including Indirect Costs): $82,975 (subcontract)

*Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 4. 2025 | 0.78 calendar |
| 5. 2026 | 0.78 calendar |

***Title:** Defining and Targeting Epigenetic Plasticity-Driven Drug Resistance and Immune Escape in Melanoma

*Major Goals: We expect these studies to provide the rationale for future clinical trials to reverse/limit the emergence of new cell states that underlie drug resistance in melanoma.

*Status of Support: Active

Project Number: R01CA262483

Name of PD/PI: Smalley, Keiran; Licht, Jonathan

*Source of Support: NCI

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 07/15/2022 - 06/30/2027

*Total Award Amount (including Indirect Costs): $76,728 (subcontract)

*Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 3. 2025 | 0.55 calendar |
| 4. 2026 | 0.55 calendar |
| 5. 2027 | 0.55 calendar |

PENDING

***Title:** Intestinal Stem Cells, Metabolism, and Cancer

*Major Goals: To address how intestinal stem cell (ISC) metabolism impacts stem cell function during gut homeostasis, regeneration and tumor development. To identify new nutritional, probiotic, pharmacologic, and genetic approaches for the prevention, diagnosis, and treatment of gastrointestinal malignancies, most notably colon cancers.

*Status of Support: Pending

Project Number: P01CA295496

Name of PD/PI: Edgar, Bruce

*Source of Support: NCI

Name of Individual: Y. ANN CHEN
Commons ID: ANNCHEN

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 12/01/2024-11/30/2029

*Total Award Amount (including Indirect Costs): $16,745,893

*Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2025 | 1.20 calendar |
| 2. 2026 | 1.20 calendar |
| 3. 2027 | 1.20 calendar |
| 4. 2028 | 1.20 calendar |
| 5. 2029 | 1.20 calendar |

***Title:** Frailty and Biomarkers of Biologic Aging in Older Adults with Colorectal Cancer

*Major Goals: To evaluate whether frailty and circulating biomarkers of biological aging, including telomere length, mitochondrial DNA copy number, and inflammation, are associated with clinical and quality of life outcomes in older colorectal cancer patients.

*Status of Support: Pending

Project Number: R01AG090497

Name of PD/PI: Hardikar, Sheetal

*Source of Support: NIA

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 12/01/2024-11/30/2029

*Total Award Amount (including Indirect Costs): $2,876,073

*Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2025 | 1.20 calendar |
| 2. 2026 | 1.20 calendar |
| 3. 2027 | 1.20 calendar |
| 4. 2028 | 1.20 calendar |
| 5. 2029 | 1.20 calendar |

**IN-KIND**

None

***Overlap** (summarized for each individual):

None

Name of Individual: Y. ANN CHEN
Commons ID: ANNCHEN

I, Ann Chen, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Signed by:
*Signature: Yian ann chen
EBA5B600630C485...

Date: 10/3/2024

**PHS OTHER SUPPORT**
**For All Application Types – DO NOT SUBMIT UNLESS REQUESTED**

*There is no "form page" for reporting Other Support. Information on Other Support should be provided in the format shown below.*

Name of Individual: Tom Greene, PhD
Commons ID: TOMGREENE

**Other Support – Project/Proposal**

**CURRENT**

***Title: Partnerships to Reduce Obesity in Community Health Center Patients**

Major Goal(s): SMARTLife Utah is a state-wide, pragmatic clinical trial conducted with 9 Community Health Centers and 27 clinics. The long-term goal of the project is to increase reach of existing digital evidence-based interventions for obesity among historically marginalized populations and in safety-net healthcare settings.

*Status of Support: Active

Project Number: R01CA283950

Name of PD/PI: Schlechter/Wetter/Del Fiol

*Source of Support: NIH/NCI

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 04/2024 – 03/2029

* Total Award Amount (including Indirect Costs): $3,849,961

* Person Months per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2025 | 0.40 calendar |
| 2. 2026 | 0.40 calendar |
| 3. 2027 | 0.40 calendar |
| 4. 2028 | 0.40 calendar |
| 5. 2029 | 0.60 calendar |

***Title: Multilevel RCT of Rural Community Sun Safety for Young Children in Sports**

*Major Goals: This project will evaluate the efficacy of a multilevel sun safety intervention for young children living in rural and underserved areas. Additional goals include examining the mechanisms of the intervention and influence of intervention fidelity and uptake on intervention outcomes.

*Status of Support: Active

Project Number: 1R01CA282219-01A1

Name of PD/PI: Yelena Wu

*Source of Support: NIH/NCI

*Primary Place of Performance: University of Utah/Huntsman Cancer Institute

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/2024-03/2029

* Total Award Amount (including Indirect Costs): $3,860,820

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2024 | 0.36 |
| 2. 2025 | 0.60 |
| 3. 2026 | 0.60 |
| 4. 2027 | 0.60 |
| 5. 2028 | 0.60 |

***Title: CTSA UM1 Program at the University of Utah**

*Major Goals: The vision of the Utah Clinical & Translational Science Institute (CTSI) is to strategically and ethically develop and apply generalizable and reproducible clinical and translational science (CTS) innovations to increase science equity and health equity, and promote social justice. The Utah CTSI collaborates with local, regional, and national partners and collaborators to achieve this vision through four specific aims: (1) Serve as a well-recognized hub for clinical and translational science that promotes science and health equity in a measurable, reproducible, and sustainable manner. (2) Design, develop, and test innovative translational science methods, tools, techniques, and best practices to increase efficiency and reproducibility. (3) Support the implementation and dissemination of translational science innovations and the education and development of the translational science and research workforce. (4) Catalyze the advancement of translational research discoveries from bench to bedside to populations to improve the health of individuals and communities, reducing health disparities and improving health equity.

*Status of Support: Active

Project Number: 1UM1TR004409-01

Name of PD/PI: Hess, Rachel and Majersik, Jennifer

*Source of Support: NIH/NCATS

Primary Place of Performance: University of Utah

Project Start and End Date: 04/01/2023 – 03/31/2030

*Total Award Amount (including Indirect Costs): $38,699,588

*Person Months per budget period:

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2023 | 1.2 |
| 2. 2024 | 1.2 |
| 3. 2025 | 1.2 |
| 4. 2026 | 1.2 |
| 5. 2027 | 1.2 |
| 6. 2028 | 1.2 |
| 7. 2029 | 1.2 |

***Title: SMART LBP Trial: Optimized Multidisciplinary Treatment Programs for Nonspecific Chronic Low Back Pain**

Major Goals: The SMART LBP Trial, addresses the dilemma faced by patients with chronic LBP searching for a treatment that will work for them. The presence of a large number of marginally beneficial interventions strongly suggests treatment effects are heterogeneous; with some patient benefiting greatly from a treatment while others are nonresponsive. Unfortunately, there is little evidence on how an individual patent can select a treatment, or how to effectively combine individual options into more effective multi-disciplinary care. Our project addresses these important questions. In addition, even with better targeting of initial treatments, some patients will not benefit. For these patients there is presently no information on strategies to sequence treatments in a manner to optimize outcomes.

*Status of Support: Active

Project Number: OTS-LBP-2017C1-6486

Name of PD/PI: Fritz, Julie

*Source of Support: PCORI

*Primary Place of Performance: University of Utah Health Care

Project/Proposal Start and End Dates: 9/2018 – 3/2026

*Total Award Amount: $9,453,662.00

*Person Months (Calendar/Academic/Summer) per budget period:

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2023 | 1.2 |
| 2. 2024 | 1.2 |
| 3. 2025 | 1.2 |
| 4. 2026 | 1.2 |

***Title: Nonpharmacologic Pain Management in FQHC primary care clinics**

*Major Goals: Chronic pain is at the heart of the opioid epidemic and back pain is the most common condition leading to chronic pain. Improving back pain management and reducing disparities are important considerations in reducing the opioid crisis and improving the lives of impacted individuals. The goal of this project to identify effective strategies for providing nonpharmacologic alternatives to opioid pain management for patients with back pain in low income and rural communities using telehealth solutions.

Specific Aims: Specific Aims: 1) compare the effectiveness of a pain teleconsult intervention with or without phone-based physical therapy for patients with chronic back pain in FQHCs, 2) compare the effectiveness of different 2-phase treatment strategies in which phone-based physical therapy is considered either a first-line or second-line option, 3) examine the results for Aims 1 & 2 in pre-specified sub- groups of patients based on baseline characteristics, and 4) examine implementation outcomes of the pain teleconsult including acceptability, adoption, feasibility and fidelity.

*Status of Support: ACTIVE

Project Number: 4UH3NR019943-02

Name of PD/PI: FRITZ, JULIE

*Source of Support: NIH/NINR

*Primary Place of Performance: UNIVERSITY OF UTAH

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/2020 – 08/2025

* Total Award Amount (including Indirect Costs): $1,392,901

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 3. 2023 | 0.60 |
| 4. 2024 | 0.60 |
| 5. 2025 | 0.60 |

***Title: Nonpharmacologic Pain Management for Lumbar Surgery**

*Major Goals: Lumbar spine surgeries are increasing in frequency for patients with chronic back pain. Many patients undergo surgery after years of chronic pain, often managed with long-term opioid use. Despite optimism that surgery will eliminate the need for opioids, evidence shows this is not the case. The majority of pre-operative, long-term opioid users continue use after surgery. In addition, the clinical outcomes of spine surgery are highly variable and many patients experience persistent pain and disability. Being a pre-operative long-term opioid user is associated with worse clinical outcomes after surgery including risk that opioid use will continue or even increase. The goal of this project to improve outcomes and reduce risk for opioid use following lumbar spine surgery by providing better pain management pathways from the pre-operative preparation into the post-surgery rehabilitation period.

Specific Aims: 1. Compare the effectiveness of two pain management pathways (standard vs. enriched) for patients undergoing lumbar spine surgery in the MHS. Effectiveness will be based on post-surgery patient-centered outcomes and opioid use. We hypothesize the enriched pathway will provide superior outcomes vs. the standard pathway. 1a. Explore trial results in pre-specified sub-groups based on pre-surgical risk for persistent opioid use (high or low). We hypothesize that the enriched pathway will show larger effects for high risk patients. 2. Explore mediating effect of pain self-efficacy, catastrophizing and hyper-vigilance on post-surgery opioid use and outcomes. We hypothesize mediators will be identified that can improve pain management strategies. 3. Explore implementation outcomes of pain management pathways (acceptability, fidelity and feasibility).

*Status of Support: ACTIVE

Project Number: 3UH3AT009763-06S1

Name of PD/PI: FRITZ, JULIE

*Source of Support: NIH/NCCIH

*Primary Place of Performance: UNIVERSITY OF UTAH

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/2017 – 8/2024

* Total Award Amount (including Indirect Costs): $247,617

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 6. 2023 | 0.60 |
| 7. 2024 | 0.60 |

***Title: SMART Stepped Care Management for Low Risk Pain in Military Health System**

Major Goals: While Stepped Care is advocated for pain management, and has been beneficial for improving care in other chronic conditions, many questions remain about which treatments to use within each Step, and the importance of sequences of care decisions. The SMART Stepped Care Management Project will support an innovative Sequential Multiple Randomization Trial specifically designed to address these key questions.

Specific Aims: 1) Conduct a SMART trial comparing effectiveness and cost- effectiveness of Step 1 and 2 treatments in a Stepped Care approach for patients with LBP in the MHS with patient-centered and healthcare cost outcomes. Sub-aims will compare main effects of Step 1 and 2 treatment options and the sequencing effects of different treatment combinations; and 2) Examine SMART trial results in pre-specified sub-groups based on sex/gender, age, and pain-related co-morbidities (PTSD, sleep disturbance, post-concussive symptoms).

*Status of Support: Active

Project Number: 5UH3AT009763-06

Name of PD/PI: Fritz

*Source of Support: NCCIH

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/2017 – 08/2024

* Total Award Amount (including Indirect Costs): $5,750,827

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 6. 2023 | 0.6 |
| 7. 2024 | 0.6 |

***Title: Informing optimal first-line antihypertensive therapy: A rigorous comparative effectiveness analysis of ARBs vs. ACEIs on long-term risk of dementia, cancer, heart disease, and quality of life**

Major Goals: In this study, we will use national Veterans Health Administration and Kaiser Permanente Southern California data to determine the long-term comparative effects of ARBs versus ACEIs on the risk of dementia, cardiovascular disease, cancer, frailty, and life expectancy accounting for level of illness and quality of life.

Specific Aims: The specific aims are to determine long-term comparative effects, including duration of use, of ARB- vs. ACEI-based anti-HTN medication regimens on (Aim 1) the incidence of ADRD, CVD (stroke, myocardial infarction, coronary revascularization, or heart failure), and cancers, separately and (Aim 2) the patient-centered outcome of frailty and the population-centered outcome of HALE.

*Status of Support: Active

Project Number: 1R01AG074989-01

Name of PD/PI: Cohen, Bress

*Source of Support: NIH / NIA

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: (MM/YYYY) (if available): 03/2022–12/2025

* Total Award Amount (including Indirect Costs): $1,487,758

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2023 | 0.36 |
| 2. 2024 | 0.36 |
| 3. 2025 | 0.36 |

***Title: Multi-Level Interventions for Increasing Tobacco Cessation at FQHCS**

Major Goals: Three phase, Sequential Multiple Assignment Randomized Trial (SMART) to increase the reach and impact of tobacco cessation treatment.

Specific Aims: Multi-Level Interventions for Increasing Tobacco Cessation at FQHCs Three phase, Sequential Multiple Assignment Randomized Trial (SMART) to implement and evaluate practical, feasible, scalable intervention strategies at the clinic and patient level to increase the reach and impact of evidence based tobacco cessation treatment among FQHC patients.

*Status of Support: Active

Project Number: PCS-2017C2-7613

Name of PD/PI: Wetter

*Source of Support: Patient-Centered Outcomes Research Institute (PCORI)

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: (MM/YYYY) (if available): 10/2018 – 10/2025

* Total Award Amount (including Indirect Costs): $1,109,550.00
* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 5. 2023 | 0.60 |
| 6. 2024 | 0.60 |
| 7. 2025 | 0.60 |

***Title: Optimizing Rehabilitation InterventiONs (ORION) for Cognition Following Complex Traumatic Brain Injury**

Major Goals: The overall objective of the proposed research is to utilize a prospective, longitudinal observational practice-based evidence (PBE) study design to identify the components of complex TBI treatment and evaluate their effectiveness on health outcomes of service members with mTBI.

Specific Aims: The overall objective of the proposed research is to utilize a prospective, longitudinal observational practice-based evidence (PBE) study design to identify the components of complex TBI treatment and evaluate their effectiveness on health outcomes of service members with mTBI.

*Status of Support: Active

Project Number: PT170087

Name of PD/PI: Kean

*Source of Support: DOD

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/2018 – 08/2024

* Total Award Amount (including Indirect Costs): $3,999,996

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 6. 2024 | 0.36 |

***Title: Cancer Center Support Grant – Biostatistics Center (CB)**

Major Goals: The Cancer Center Support Grant's CB Shared Resource provides state-of-the-art biostatistics and research design support to, translational, clinical, and population sciences investigators at Huntsman Cancer Institute.

Specific Aims: 1) to provide state-of-the-art biostatistics and research design support to HCI clinical, translational, laboratory, and population sciences investigators; and 2) to support the scientific research objectives of the Cancer Center by applying biostatistical methods for team science grants, high-impact research, and clinical trials in a high- quality, cost-effective manner.

*Status of Support: Active

Project Number: 5P30CA042014-32

Name of PD/PI: Ulrich

*Source of Support: NCI

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: (MM/YYYY) (if available): 05/1997 – 04/2025

* Total Award Amount (including Indirect Costs): $63,968,964

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 26. 2023 | 0.48 |
| 27. 2024 | 0.48 |
| 28. 2025 | 0.48 |

***Title: Development of Prognostic Algorithms to Identify Subjects at High Risk of ESKD in Type 2 Diabetes**

*Major Goals: We aim to develop improved algorithms for the estimation of ESKD risk in Type 2 diabetes (T2D) by adding newly identified biomarkers to established clinical predictors such as GFR and albuminuria. A more precise estimation of ESKD risk would be beneficial in several respects: it would improve the cost-benefit ratio of currently available ESKD-preventive therapies, it would help optimize clinical care by allowing referral of patients to nephrologists early in the trajectory to ESKD, and it would increase the efficiency of clinical trials aimed at

testing new therapies by facilitating the enrollment of patients with a high likelihood of experiencing significant kidney function loss within the limited timeframe of the trial.

Specific Aims: 1: To identify the most informative of the 21 biomarkers in the Joslin Kidney Panel and evaluate their performance, when added to GFR and albuminuria, in predicting ESKD risk among subjects with T2D and chronic kidney disease. We will measure the 21 proteins of the JKP in baseline serum specimens from ~1,500 CRIC participants with T2D, and will use these data together with GFR and albuminuria to develop and internally validate multi-marker prognostic algorithms predicting the risk of ESKD (primary outcome) or the composite of ESKD and/or 50% loss of kidney function (secondary outcome) during 10 years of follow-up. 2: To evaluate the generalizability of findings from CRIC to T2D individuals with a broader spectrum of kidney function. We will assay the JKP in baseline serum specimens from a case- cohort sample of ~2,000 ACCORD/ACCORDION participants and will use these data to investigate the generalizability of the predictive algorithms built in CRIC to diabetic patients with different characteristics. The prognostic models developed in Aim 1 and externally validated in Aim 2 will be used to build a web-based Kidney Risk Calculator for the estimation of the 10-year risk of ESKD in a clinical setting. 3: To evaluate the transferability of the Kidney Risk Calculator from diabetic to non-diabetic kidney disease. We will measure the 21 JKP biomarkers in baseline serum samples from ~1,700 non-diabetic subjects from the CRIC study and will assess the performance of the Kidney Risk Calculator developed in Aim 2 in predicting the risk of ESKD and ESKD/50% kidney function loss in patients with non-diabetic kidney disease.

*Status of Support: Active

Project Number: 1R01DK126799-01A1

Name of PD/PI: KROLEWSKI, ANDRZEJ S

*Source of Support: NIH/NIDDK

*Primary Place of Performance: Joslin Diabetes Center, Boston, MA

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/2021 – 07/2025

* Total Award Amount (including Indirect Costs): $775,138

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 2. 2023 | 0.60 |
| 3. 2024 | 0.54 |
| 4. 2025 | 0.54 |

***Title: Promoting Real World Implementation of an Evidence-Based Weight Management Intervention in Primary Care**

*Major Goals: Many people struggle not only to lose weight through changes in diet and physical activity, but also to maintain weight loss once they have achieved it. In a previous study, our team designed and deployed a weight maintenance intervention that was delivered through the patient portal of an electronic health record (EHR) and found that patients who tracked their weight, diet, and physical activity and also received coaching had better success with maintaining recent intentional weight loss than patients who tracked but did not receive coaching. We propose to repeat the intervention in a new health care system and train routine health care staff (e.g., medical assistants and nurses) to be coaches, a more sustainable model that will allow ongoing intervention delivery after the proposed study ends.

Specific Aims: 1) pre-implementation, in which we will do collaborative implementation design with clinic and IT teams and vanguard implementation mapping; 2) implementation, in which we will conduct a pragmatic clinical trial with weight change at 24 months as the primary outcome; and 3) post-implementation, in which we will evaluate the success of MAINTAIN PRIME, including barriers, facilitators, and costs that will inform future sustainability and be summarized in a “toolkit” to foster dissemination.

*Status of Support: ACTIVE

Project Number: 1R18DK123372-01A1

Name of PD/PI: CONROY, MARGARET

*Source of Support: NIH/NIDDK

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/2020 – 06/2025

* Total Award Amount (including Indirect Costs): $1,924,550

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 3. 2023 | 0.30 |
| 4. 2024 | 0.30 |
| 5. 2025 | 0.30 |

***Title: Sit Less, Interact and Move More (SLIMM) 2 Study**

*Major Goals: Narrative Sedentary behavior (engaging in activities in seated/ lying posture) is very common and associates with increased mortality in people with chronic kidney disease. Current interventions in moderate to advanced chronic kidney disease have focused only on physical inactivity (lack of achieving moderate/ vigorous activity goals) rather than sedentary behavior. The current proposal will examine a novel intervention targeting sedentary behavior in chronic kidney disease.

Specific Aims: We propose the addition of guided resistance training to increase physical function and semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist that has been shown to decrease adiposity and inflammation and improve health related quality of life. Herein we seek to implement SLIMM intervention alone for the first three months followed by a 9 month RCT of three equal groups of SLIMM + standard of care RT + placebo, SLIMM + guided RT + placebo and SLIMM + guided RT + oral semaglutide in 156 overweight or obese patients with moderate to advanced CKD. The designated primary endpoint is decrease in sedentary duration and the key secondary endpoint is six- minute walk distance. We will also explore the effects of the interventions on body-fat%, patient reported outcomes, lower extremity performance battery and markers of inflammation. There is a large pool of potential participants in the two institutions. The study is adequately powered to detect meaningful decrease in sedentary duration and other endpoints. This multi-disciplinary team of experienced investigators have a proven track record of successfully conducting RCTs. This proposal is feasible, innovative, and likely to yield results that will be informative. If the interventions decrease sedentary behavior in CKD, this trial will pave the way for larger RCTs of sedentary behavior interventions on hard endpoints.

*Status of Support: ACTIVE

Project Number: 1R01DK128640-01

Name of PD/PI: BEDDHU, SRINIVASAN

*Source of Support: NIH/NIDDK

*Primary Place of Performance: UNIVERSITY OF UTAH

Project/Proposal Start and End Date: (MM/YYYY) (if available): 05/2021 – 04/2026

* Total Award Amount (including Indirect Costs): $1,351,634

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 2. 2023 | 0.60 |
| 3. 2024 | 0.60 |
| 4. 2025 | 0.60 |
| 5. 2026 | 0.60 |

***Title: Objectively Measured Sedentary Behavior and Physical Activity in PREVENTABLE Study**

*Major Goals: This ancillary study by adding objective measures of sedentary behavior and physical activity levels will improve the scientific yield of the parent PREVENTABLE trial to test 1. Whether sedentary behavior is a risk factor for dementia and 2. Whether statins improve/ decrease physical activity levels in adults aged 75 years or older.

Specific Aims: The first specific aim, in a longitudinal, prospective analysis, we will examine the hypothesis that longer sedentary duration increases risk of incident mild cognitive impairment (MCI)/ probable ADRD; whereas, trade-off of sedentary duration for stepping duration is associated with lower risk of these outcomes. Second, there are conflicting data on the associations of statins with physical disability/ physical activity. PREVENTABLE is examining the possible role of atorvastatin in preventing disability (but not physical activity). We propose to add objective measures of physical activity. In the second aim, we will examine the hypothesis that decrease in physical disability and preservation of functional ability with randomization to atorvastatin compared to placebo will result in higher physical activity levels and lower sedentary duration. The investigators on this multi-disciplinary team have the experience and expertise to carry out all aspects of the project. The proposed ancillary study will be well integrated into the pragmatic design of the parent trial and place minimal burden on participants and parent study staff. By adding rigorous measures of sedentary behavior and physical activity, this ancillary study will create synergy with the parent trial to enhance scientific yield by addressing an important gap in the parent study. If sedentary behavior is associated with incident MCI/ ADRD in older adults, the results of the current study will aid in the design of a future RCT to examine the effect of a sedentary behavior intervention to prevent ADRD in older adults.

*Status of Support: ACTIVE

Project Number: 1R01AG074592-03

Name of PD/PI: BEDDHU, SRINIVASAN

*Source of Support: NIH/NIA

*Primary Place of Performance: UNIVERSITY OF UTAH

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/2021 – 03/2026

* Total Award Amount (including Indirect Costs): $740,106

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 2. 2023 | 0.60 |
| 3. 2024 | 0.60 |
| 4. 2025 | 0.60 |
| 5. 2026 | 0.60 |

***Title: Multi-sector, multi-level interventions for improving cancer prevention and control addressing persistent poverty**

Major Goals: The major goal of HC2 is to increase the reach of evidence-based cancer prevention and control interventions in areas of persistent poverty. The two research projects will work in persistent poverty census tracts and in partnership with Community Health Centers in Utah, and with Cooperative Extension Systems and American Indian communities in Montana, Oregon, South Dakota, and Wisconsin, to mitigate adverse impacts of the social determinants of health, increase tobacco cessation, and prevent obesity.

Specific Aims: AIM 1. Develop HC2 as a robust and sustainable cross-institutional center for cancer prevention research in areas and populations characterized by persistent poverty both regionally and nationally. AIM 2. Foster and implement innovative, multi-sector, multi-level cancer prevention research programs in areas of persistent poverty. AIM 3. Develop and maintain a cadre of cancer prevention researchers across institutions that incorporate persistent poverty into their work to better serve the region. AIM 4. Build on existing partnerships to expand and maintain a Health Equity Network to Address Cancer Prevention in Areas of Persistent Poverty (HC2 Network).

*Status of Support: Active

Project Number: 1U54CA280812-01

Name of PD/PI: Wetter

*Source of Support: NC

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: (MM/YYYY) (if available): 05/2023 – 4/2028

* Total Award Amount (including Indirect Costs): $11,385,926

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2024 | 0.60 |
| 2. 2025 | 0.60 |
| 3. 2026 | 0.60 |
| 4. 2027 | 0.60 |
| 5. 2028 | 0.60 |
| 6. 2029 | 0.60 |

**Title: Improving Kidney Function Assessment in Health and Disease**
Major Goals: Methodological development to support identification of parsimonious subsets of metabolites which are highly predictive of GFR and construction of accurate GFR estimating approaches
which are generalizable across a spectrum of patient populations.

*Status of Support: Active

Project Number: 1R01DK116790

Name of PD/PI: Inker, Lesley Ann

*Source of Support: National Institutes of Health

*Primary Place of Performance: Tufts Medical Center

Project/Proposal Start and End Date: 12/15/2020 – 11/30/2024

*Total Award Amount (including Indirect Costs): $1,444,294

*Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2023 | 0.34 |
| 2. 2024 | 0.34 |

***Title: ELEVATE Center: Reduction of Maternal Morbidity from Substance Use Disorder in Utah**

Major Goals: Accidental drug overdose and suicide were the leading causes of pregnancy-associated death in Utah from 2015-2020, accounting for nearly 40% of all pregnancy-associated deaths over that time period. At-risk populations, including those in rural settings and those who identify as American Indian or Alaska Native are disproportionately affected by maternal morbidity. We bring together a transdisciplinary team with expertise in obstetrics, addiction medicine, simulation training, experiential learning, bias and disparity reduction, community engagement and implementation science. Together, this collaborative team will establish the ELEVATE Maternal Health Center of Excellence.

Specific Aims: (1) provide integrated and efficient leadership of the three proposed projects, maximizing coordination with community partners and incorporating research training across all elements of the ELEVATE Center; (2) mature our existing community partnerships and statewide networks in order to facilitate future implementation science and effectiveness trials to reduce maternal morbidity and mortality in Utah, and (3) reduce maternal morbidity in Utah and nationally through implementation of community-driven interventions and training of health care practitioners.

*Status of Support: ACTIVE

Project Number: 1U54HD113169

Name of PD/PI: Metz

*Source of Support: NIH

*Primary Place of Performance: UNIVERSITY OF UTAH

Project/Proposal Start and End Date: (MM/YYYY) (if available): 08/2023 – 07/2030

* Total Award Amount (including Indirect Costs): $1,949,666

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2023 | 1.2 |
| 2. 2024 | 1.2 |
| 3. 2025 | 1.2 |
| 4. 2026 | 1.2 |
| 5. 2027 | 1.2 |
| 6. 2028 | 1.2 |
| 7. 2029 | 1.2 |
| 8. 2030 | 1.2 |

**PENDING**

***Title: Scaling up Building Healthy Families in Rural Areas and Small Towns**
*Major Goals: This project addresses the lack of access to evidence-based childhood obesity interventions (EBI-CO) in rural areas where both poverty and obesity is prevalent. Building Healthy Families (BHF) is an adapted EBI-CO designed for, and implemented in, rural areas and has successfully achieved clinically and statistically significant reductions in child BMI z-score (-0.27±0.22)—a similar magnitude of effect relative to previous efficacy trials. We propose to expand our pilot into a fully powered Hybrid Type 3 effectiveness-implementation, cluster RCT to test the utility of the BHF Program Resources Only (BHF-PO) with and without a BHF Learning Collaborative (BHF-LC). We will scale up a bundled adoption strategy we used successfully in our pilot to engage 30 micropolitan and rural communities across the 6-state region served by the Mountain West Family Healthy Weight Collaborative and Huntsman Cancer Institute (NM, ID, MT, NV, WY, UT; See Letters of Support). We will randomly assign communities to either the BHF-PO (n=15) or in combination with the BHF-LC (n=15) to determine the relative effects on RE-AIM outcomes of reach, effectiveness (secondary outcome), implementation (primary outcome), and program maintenance. In addition, we will assess potential mechanisms of change across RE-AIM outcomes using the Integrated Promoting Action on Research in Health Sciences (iPARIHS) framework. Finally, economic evaluation will be conducted to determine costs and benefits across RE-AIM outcomes.

*Status of Support: Pending

Project Number: 1R01DK137992-01A1

Name of PD/PI: Hill, Jennie (contact) and Heelan, Kate (MPI)

*Source of Support: NIH

*Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/2024 - 06/2029

* Total Award Amount (including Indirect Costs): $3,731,616

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2024 | 0.60 |
| 2. 2025 | 0.60 |

| | |
|---|---|
| 3. 2026 | 0.60 |
| 4. 2027 | 1.20 |
| 5. 2028 | 1.20 |

***Title: Community-Engaged Action for Research on Health Equity Hub at the University of Utah (CARE-Utah)**

*Major Goals: Health Equity Hub at the University of Utah (CARE-UTAH), within the Community Partnerships to Advance Science for Society (ComPASS) Program, will collaborate with the ComPASS Coordination Center (CCC), Health Equity Research Assemblies (HERAs), and the other Health Equity Research Hubs to provide support and technical assistance, capacity building, and training to assigned Community-Led, Health Equity Structural Intervention (CHESI) projects. CARE-UTAH is built upon the shared vision of supporting communities and community-based organizations throughout the nation to achieve health equity through multilevel and multisectoral structural interventions addressing social determinants of health (SDOH) among historically marginalized communities.

*Status of Support: Pending

Project Number: 1UC2CA293848-01

Name of PD/PI: Sara J. Knight PhD, JD Smith, PhD

*Source of Support: Common Fund, Office of the Director; National Cancer Institute (Primary)

*Primary Place of Performance: University of Utah, Department of Internal Medicine, School of Medicine

Project/Proposal Start and End Dates: 07/01/24 – 6/30/29

*Total Award Amount (including Indirect Costs): $6,749,999.00

*Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2024 | 1.0 |
| 2. 2025 | 1.0 |
| 3. 2026 | 1.0 |
| 4. 2027 | 1.0 |
| 5. 2028 | 1.0 |

***Title: Avenues for protein carbamylation prevention and therapy**

*Major Goals: The objectives of this project are to: 1) Quantify CKD factors that associate with longitudinal carbamylation levels and test if carbamylation trajectories predict CKD outcomes; 2) Establish the impact of key ESKD exposures on changes in carbamylation and employ longitudinal carbamylation measures to predict clinical outcomes; 3) Determine the association between existing blood carbamylation measures and dietary intake.

*Status of Support: Pending

Project Number: TBA

Name of PD/PI: Sahir Kalin, MD

*Source of Support: NIH

*Primary Place of Performance: Mass Brigham Hospital to University of Utah

Project/Proposal Start and End Dates: 04/01/2025-3/31/2029

*Total Award Amount (including Indirect Costs): $117,040

*Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2025 | 0.60 |
| 2. 2026 | 0.60 |
| 3. 2027 | 0.60 |
| 4. 2028 | 0.60 |

*Title: A novel approach to determine clinical benefit in trials of CKD progression

*Major Goals: Aim 1: Develop and validate methods to integrate trial level information from multiple surrogate endpoints and early clinical events to estimate clinical benefit Aim 2: Develop and validate patient-level models for CKD progression to determine optimal designs andto forecast long-term clinical benefit

*Status of Support: Pending

Project Number: TBA

Name of PD/PI: Inker/Greene (MPI)

*Source of Support: NiH NIDDK

*Primary Place of Performance: Tufts Medical Center subaward to University of Utah

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/2025 – 03/2030

* Total Award Amount (including Indirect Costs): $1,372,798

* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 1. 2026 | 01.80 Calendar |
| 2. 2027 | 01.80 Calendar |
| 3. 2028 | 01.80 Calendar |
| 4. 2029 | 01.80 Calendar |
| 5. 2030 | 01.80 Calendar |

**IN-KIND**

NONE

**OVERLAP** (summarized for each individual)

If the current application is funded, effort will be adjusted within allowable limits so that it does not exceed 12.0 calendar months.

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

*Signature: Tom Greene

Date: _06/20/2024_____

# PHS 398 OTHER SUPPORT

*Name: **Presson, A.**

Commons ID: APRESSON2

## APPOINTMENTS/POSITIONS (CURRENT):

Research Professor, Division of Epidemiology, Department of Internal Medicine, University of Utah, Salt Lake City, UT

Director of the Study Design and Biostatistics Center (SDBC), University of Utah, Salt Lake City, UT

Adjunct Associate Professor, Department of Orthopaedics, University of Utah, Salt Lake City, UT

Adjunct Associate Professor, Department of Population Health Sciences, University of Utah, Salt Lake City, UT

Co-Director, Population Health Research Foundation for Discovery, Center for Clinical and Translational Science, University of Utah, Salt Lake City, UT

Adjunct Associate Professor, Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT

Adjunct Assistant Professor, Department of Pediatrics, University of Utah, Salt Lake City, UT

## PROJECT/PROPOSAL OTHER SUPPORT

*Title: **The Impact of a Transitional Pain Service on Reducing Chronic Opioid Use Among Veterans Using Community Care for Orthopedic Surgery**

Major Goals: Here we propose the following specific aims to establish whether a telehealth TPS approach to perioperative pain management can serve as a scalable, cost-effective strategy to ensure safe opioid use among Veterans undergoing orthopedic joint surgery at non-VA hospitals. Veterans undergoing orthopedic joint surgery are at increased risk for COU and serve as an ideal population in which to evaluate the effectiveness of perioperative care processes designed to promote safe opioid use and mitigate risks of chronic opioid use. Our transdisciplinary team will use a sequential mixed-methods study design to assess whether telehealth TPS can reduce risks for COU among Veterans undergoing orthopedic surgery at non-VA hospitals throughout VISN-19, and assess whether this strategy is cost-effective from the perspective of both the patient and the VA.

*Status of Support: Active

Project Number: HSR&D 22-062-2

Name of PD/PI: Ben Brooke, MD, PhD

*Source of Support: VA Salt Lake City Healthcare System

*Primary Place of Performance: VA Salt Lake City Healthcare System, Salt Lake City, UT

Project/Proposal Start and End Dates: 03/01/2024 – 02/28/2028

*Total Award Amount: $1,043,696

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 1. 2024 | 1.2 Calendar |
| 2. 2025 | 1.2 Calendar |
| 3. 2026 | 1.2 Calendar |
| 4. 2027 | 1.2 Calendar |

*Title: **Pre-Loss Group Therapy for Dementia Family Care Partners at Risk for Complicated Grief**

Major Goals: Given the restrictions due to the ongoing COVID-19 pandemic, the researchers will pivot to a virtual support group model. This project will build on preliminary research by studying the feasibility of providing training via telehealth to social workers in nursing homes. Dr. Supiano's team will then study the impact of the intervention administered via telehealth to 6 PLGS groups in 6 nursing homes. The study setting includes 3 veteran homes, and 3 nursing homes both in urban and rural areas. Finally, the researchers will study the impact of the intervention in family care partners experiencing complicated grief.

*Status of Support: Active

Project Number: AARG-21-846414

Name of PD/PI: Katharine Supiano

*Source of Support: Alzheimer's Association Research Grant (AARG)

*Primary Place of Performance: University of Utah, Salt Lake City, UT

Project/Proposal Start and End Dates: 11/01/2021 – 10/31/2024

*Total Award Amount: $150,000

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 2. 2023 | 00.30 Calendar |
| 3. 2024 | 00.30 Calendar |

*Title: **A New Biomarker for Frontotemporal Lobar Degeneration with TDP-43 Proteinopathy and Alzheimer's Disease**

Major Goals: The purpose of this study is to elucidate a novel toxic TDP-43 species and its association with pathology and neurodegeneration. The long-term goal is to develop a biomarker that can predict the presence of TDP-43 in living frontotemporal lobar degeneration and Alzheimer's disease patients, which will have a significant impact on future therapies for both diseases.

*Status of Support: Active

Project Number: 1R21AG080502-01

Name of PD/PI: Qinwen Mao

*Source of Support: NIH/NIA

*Primary Place of Performance: University of Utah, Salt Lake City, UT

Project/Proposal Start and End Dates: 01/01/2023 – 12/31/2024

*Total Award Amount: $454,013

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 1. 2024 | 00.60 Calendar |

*Title: **Photophobia and Pupillary Autonomic Dysfunction as Biomarkers of Post-Traumatic Headache**

Major Goals: This proposal will us a multimodal approach to sensory and autonomic testing to identify clinically meaningful biomarkers for use in PTH diagnosis, disease monitoring, and the development of non-addictive treatments with the goal of reducing the overall health burden of PTH.

*Status of Support: Active

Project Number: 1K23NS105920-01A1

Name of PD/PI: Melissa Cortez

*Source of Support: NIH/NINDS

*Primary Place of Performance: University of Utah, Salt Lake City, UT

Project/Proposal Start and End Dates: 04/15/2020 - 03/31/2025

*Total Award Amount: $200,676

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 3. 2023 | 00.30 Calendar |
| 4. 2024 | 00.30 Calendar |
| 5. 2025 | 00.30 Calendar |

*Title: **Sex Hormone Supplementation and Rotator Cuff Repair: A Preliminary Randomized Trial**

Major Goals: Sex hormone deficiency can be treated with hormone therapy, which is widely utilized, well-tolerated, inexpensive, and FDA approved. For this project we propose a phase II study to test preliminary efficacy and feasibility of hormone therapy to reduce re-tears following rotator cuff repair surgery.

*Status of Support: Active

Project Number: 1R21AR081006-01A1

Name of PD/PI: Peter Chalmers

*Source of Support: NIH

*Primary Place of Performance: University of Utah, Salt Lake City, UT

Project/Proposal Start and End Dates: 12/01/2022 – 11/30/2025

*Total Award Amount: $169,079

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 2. 2023 | 00.84 Calendar |
| 3. 2024 | 00.84 Calendar |
| 4. 2025 | 00.84 Calendar |

*Title: **Sensory Amplifications as Biomarkers of Migraine Progression**

Major Goals: The goal of this proposal is to develop a prognostic sensory biomarker signature to predict progression of patients from high-frequency episodic migraineurs (HFEM) to chronic migraineurs (CM).

*Status of Support: Active

Project Number: 1R61NS125153-01A1

Name of PD/PI: Kevin Brennan

*Source of Support: NIH

*Primary Place of Performance: University of Utah, Salt Lake City, UT

Project/Proposal Start and End Dates: 04/15/2023 – 03/31/2026

*Total Award Amount: $750,148

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 1. 2023 | 1.10 Calendar |
| 2. 2024 | 1.10 Calendar |
| 3. 2025 | 1.10 Calendar |
| 4. 2026 | 1.10 Calendar |

*Title: **Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC): Data and Biostatistics Core**

Major Goals: To assess the impact of mild traumatic brain injury on measures of wellness, including cognitive, sleep, employment, and psychological characteristics.

*Status of Support: Active

Project Number: 5I01RX003442-03

Name of PD/PI: Mary Jo Pugh

*Source of Support: VA Salt Lake City Healthcare System

*Primary Place of Performance: VA Salt Lake City Healthcare System, Salt Lake City, UT

Project/Proposal Start and End Dates: 10/01/2019 – 09/30/2024

*Total Award Amount: $194,829

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 3. 2023 | 1.2 Calendar |
| 4. 2024 | 1.2 Calendar |

*Title: **CTSA UM1 Program at University of Utah**

Major Goals: The vision of the Utah Clinical & Translational Science Institute (CTSI) is to strategically and ethically develop and apply generalizable and reproducible clinical and translational science (CTS) innovations to increase science equity and health equity, and promote social justice. The Utah CTSI collaborates with local, regional, and national partners and collaborators to achieve this vision through four specific aims: (1) Serve as a well-recognized hub for clinical and translational science that promotes science and health equity in a measurable, reproducible, and sustainable manner. (2) Design, develop, and test innovative translational science methods, tools, techniques, and best practices to increase efficiency and reproducibility. (3) Support the implementation and dissemination of translational science innovations and the education and development of the translational science and research workforce. (4) Catalyze the advancement of translational research discoveries from bench to bedside to populations to improve the health of individuals and communities, reducing health disparities and improving health equity.

*Status of Support: Active

Project Number: 1UM1TR004409-01

Name of PD/PI: Hess/Majersik

*Source of Support: NIH/NCATS

*Primary Place of Performance: University of Utah, Salt Lake City, UT

Project/Proposal Start and End Dates: 04/01/2023 – 03/31/2030

*Total Award Amount: $38,699,588

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 1. 2024 | 1.5 Calendar |
| 2. 2025 | 1.5 Calendar |
| 3. 2026 | 1.5 Calendar |
| 4. 2027 | 1.5 Calendar |
| 5. 2028 | 1.5 Calendar |
| 6. 2029 | 1.5 Calendar |
| 7. 2030 | 1.5 Calendar |

*Title: **Analysis of the Pediatric Heart Network Echocardiogram Database to Establish Left Ventricular Strain Z-scores**

Major Goals: The objective is to establish Z-scores using the PHN Echo Database. This database includes all images needed for LV strain measurements from 3526 echoes obtained in a well-characterized population of healthy children ranging in age from birth to 18 years. Z-scores account for the effects of maturation and growth by considering body size, age, gender, and/or race when evaluating whether measurements are normal or, if abnormal, how many standard deviations they deviate from the mean.

*Status of Support: Active

Project Number: 1R21HL159629-01A1

Name of PD/PI: Luann Minich

*Source of Support: National Heart, Lung and Blood Institute

*Primary Place of Performance: University of Utah, Salt Lake City, UT

Project/Proposal Start and End Dates: 07/01/2023 – 06/30/2024

*Total Award Amount: $114,375

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 1. 2024 | 00.49 Calendar |

*Title: **Do cochlear implants mitigate the risk of Alzheimer's disease dementia and improve neuropsychological well-being in older adults?**

Major Goals: This proposal is significant to public health because of the high prevalence of severe-profound age-related hearing loss in older adults. Little is known about the collateral effects of this degree of hearing loss on non- hearing aspects of life, such as hearing loss causing Alzheimer's disease dementia. By understanding the cognitive and quality of life impact of cochlear implantation in older adults, there is the potential to decrease Alzheimer's disease in this patient population.

*Status of Support: Active

Project Number: 1R21AG067403-01A1

Name of PD/PI: Richard Gurgel

*Source of Support: NIH/NIA

*Primary Place of Performance: University of Utah, Salt Lake City, UT

Project/Proposal Start and End Dates: 09/15/2020 – 08/31/2024

*Total Award Amount: $419,375

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 3. 2023 | 00.80 Calendar |
| 4. 2024 | 00.60 Calendar |

*Title: **Smartphone-based Assessment of Reactive Balance and Balance Phenotypes after Concussion**

Major Goals: Smartphone-based Assessment of Reactive Balance and Balance Phenotypes after Concussion

Relevance to Current Proposal: I am collaborating with Dr. Fino to determine the clinical consequences of reactive vs. static balance deficits after concussion.

*Status of Support: Active

Project Number: 9-01_PAC-12-UTAH-FINO-23-01

Name of PD/PI: Peter Fino

*Source of Support: Pac-12 Student Athlete Health and Well-being

*Primary Place of Performance: University of Utah, Salt Lake City, UT

Project/Proposal Start and End Dates: 06/01/2024 – 05/31/2025

*Total Award Amount: $399,282

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 1. 2025 | 00.00 Calendar |
| 2. 2026 | 00.60 Calendar |

*Title: **Biomarkers of Habitual Short Sleep and Related Cardiometabolic Risk**

Major Goals: Examine plasma ceramides as biomarkers that link habitual short sleep duration with increased risk of T2D and assess how sleep extension impacts such risk. This project is focused on people with habitual short sleep duration and overweight or obesity.

*Status of Support: Active

Project Number: R01HL166733-01A1

Name of PD/PI: Christopher Depner

*Source of Support: NIH/NHLBI

*Primary Place of Performance: University of Utah, Salt Lake City, UT

Project/Proposal Start and End Dates: 07/01/2023 – 06/2028

*Total Award Amount: $3,815,463

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 1. 2024 | 00.80 Calendar |
| 2. 2025 | 00.80 Calendar |
| 3. 2026 | 00.80 Calendar |
| 4. 2027 | 00.80 Calendar |
| 5. 2028 | 01.20 Calendar |

*Title: **Reducing Overuse of Antibiotics at Discharge: The ROAD Home Trial**

Major Goals: Conduct a 40-hospital parallel cluster randomized trial to test the effectiveness of the ROAD Home Intervention on days of antibiotic overuse at discharge in hospitalized adults with CAP and UTI. Concurrently, conduct a mixed-methods concurrent process evaluation to identify contextual factors influencing implementation of the ROAD Home Intervention. Finally, we will create and refine a ROAD Home discharge stewardship toolkit to facilitate dissemination of the ROAD Home Intervention.

*Status of Support: Active

Project Number: 1R01HS029482-01

Name of PD/PI: Vaughn/Szymczak (MPI)

*Source of Support: AHRQ

*Primary Place of Performance: University of Utah, Salt Lake City, UT

Project/Proposal Start and End Dates: 09/01/2023 – 08/31/2028

*Total Award Amount: $2,497,926

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 1. 2024 | 00.60 Calendar |
| 2. 2025 | 00.60 Calendar |
| 3. 2026 | 00.60 Calendar |
| 4. 2027 | 00.60 Calendar |
| 5. 2028 | 00.60 Calendar |

*Title: **Determining Genetic Variants Associated with Rotator Cuff Tearing, Tear Progression, and Tendon Repair Healing**

Major Goals: The goal of this proposal is to identify genetic variants and environmental factors associated with rotator cuff tearing, tear enlargement, and revision repair using the million veteran's program data. We will directly translate the information from the study to clinical care of veterans by creating a risk calculator with and without the genetic factors identified as being associated with rotator cuff revision and tear progression. A machine learning approach will be used to develop the prediciton models used in the risk calculators. *Status of Support: Active

Project Number: CX-23-001

Name of PD/PI: Robert Tashjian

*Source of Support: VA Salt Lake City Healthcare System

*Primary Place of Performance: VA Salt Lake City Healthcare System, Salt Lake City, UT

Project/Proposal Start and End Dates: 10/01/2024 – 9/30/2027

*Total Award Amount: $879,516

*Person Months (Calendar/Academic/Summer) per budget period:

| Year | Person Months |
|---|---|
| 1. 2024 | 00.60 Calendar |
| 2. 2025 | 00.60 Calendar |
| 3. 2026 | 00.60 Calendar |
| 4. 2027 | 00.60 Calendar |

## PENDING

*Title: Shining Light on Trauma: Treatment of Chronic TBI to Improve Psychological Health using Photobiomodulation in Service Members, Veterans, and First Responders
*Major Goals: Using a multi-arm RCT to assess the effectiveness of using photobiomodulation (PBM) and computerized cognitive rehabilitation (CCR) to improve psychological and brain health in SMVs and FRs (including police and firefighters) with a history of mTBI and persistent symptoms. Specific aims are: 1) To evaluate the effectiveness of PBM in improving psychological and cognitive functioning in SMVs and FRs with a history of mTBI and persistent symptoms; 2) To evaluate the effectiveness of PBM in improving structural and functional neuroimaging markers in SMVs and FRs with a history of mTBI and persistent symptoms; 3) To evaluate the effectiveness of combined PBM+CCR in improving psychological and cognitive functioning in SMVs and FRs with a history of mTBI and persistent symptoms; 4) To evaluate the effectiveness of combined PBM+CCR in improving structural and functional neuroimaging markers in SMVs and FRs with a history of mTBI and persistent symptoms.
*Status of Support: **Pending**
Project Number: TBD
Name of PD/PI: Wilde, Elisabeth
*Source of Support: Department of Defense (Western Institute for Veterans Research and VASLCHCS (PTE)
*Primary Place of Performance: The University of Utah, Salt Lake City, UT
Project/Proposal Start and End Date: (MM/YYYY) (if available): 9/1/2025 – 8/31/2029
* Total Award Amount (including Indirect Costs): $4,613,328 (Total)
* Person Months (Calendar/Academic/Summer) per budget period.

| Year (YYYY) | Person Months (##.##) |
|---|---|
| 2025 | 0.6 |
| 2026 | 0.6 |
| 2027 | 0.6 |
| 2028 | 0.6 |

## IN-KIND

None

## OVERLAP

None

## RESOURCES

None

## STATEMENT CERTIFICATION

I, Angela Presson, certify that the statements herein are true, complete, and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Signature: Angela Presson Digitally signed by Angela Presson
Date: 2024.07.03 08:48:09 -06'00'

Date: _____

**PHS OTHER SUPPORT**
**For All Application Types – DO NOT SUBMIT UNLESS REQUESTED**

Name of Individual: Sborov, Douglas
Commons ID: sborov01

**Other Support – Project/Proposal**

**ACTIVE**

**Title: Huntsman Bispecific Collaborative Access and Referral Network (HCI biCARE) Education Initiative**

Major Goals: This education grant is focused on educating non-academic providers and collaborators across the Mountain West region about novel immunotherapeutics with a focus on T-cell redirecting bispecific antibodies. The approved grant has two primary specific aims including strengthening regional academic-community partnerships to increase identification of eligible patients with multiple myeloma that can benefit from treatment with bispecific antibodies and to establish a multi-disciplinary treatment team that assists patients in receiving and community teams in providing safe delivery of bispecific therapy following treatment initiation.

Status of Support: Active

Project Number: 90640619

Name of PD/PI: Sborov, Douglas (contact); Godara, Aman

Source of Support: Pfizer

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 12/27/2023 – 12/26/2024

Total Award Amount (including Indirect Costs): $150,000

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 2. 2024 | 0.01 calendar |

**Title: DARA-2552 Longitudinal Multi-Center Chart Review Study and Consortium for Multiple Myeloma (EMMPOWER)**

Major Goals: Given the clinical use of approved novel regimens and the upcoming launches of investigative therapies, the treatment journey for patients with newly diagnosed (NDMM) and relapsed and refractory multiple myeloma (RRMM) are fundamentally changing. As such, it is critical to understand the real-world impact of this changing treatment landscape to ensure that patients are receiving evidence-based optimal care. To gather the most current and insightful real-world evidence, this project aims to collect robust, longitudinal, high-quality real-world chart-review data for NDMM and RRMM patients in collaboration with multiple institutional medical centers and community health centers.

Status of Support: Active

Project Number: 2552

Name of PD/PI: Sborov, Douglas

Source of Support: Analysis Group Incorporated

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 05/01/2024-05/01/2031

Name of Individual: Sborov, Douglas
Commons ID: sborov01

Total Award Amount (including Indirect Costs): $89,408

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 1. 2025 | 0.01 calendar |
| 2. 2026 | 0.01 calendar |
| 3. 2027 | 0.01 calendar |
| 4. 2028 | 0.01 calendar |
| 5. 2029 | 0.01 calendar |
| 6. 2030 | 0.01 calendar |
| 7. 2031 | 0.01 calendar |

**Title: Real-World Effectiveness of Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone (DVRd) and Bortezomib, Lenalidomide, and Dexamethasone (VRd) as First-Line Treatment Among Transplant Eligible Newly Diagnosed Multiple Myeloma Patients**

Major Goals: While the efficacy of standard of care treatment regimens including RVd and DRVd has been observed in clinical trials in patients with newly diagnosed multiple myeloma, data from the real-world clinical practice setting are not yet available. This is the first real-world study aimed to describe and compare outcomes among newly diagnosed transplant eligible patients treated with one line of therapy including either RVd or DRVd. Assessment of characteristics and outcomes in patients receiving these regimens will add to our understanding of the potential benefit of daratumumab in the real-world setting.

Status of Support: Active

Project Number: NONE

Name of PD/PI: Sborov, Douglas

Source of Support: RJM Group

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 02/01/2024-02/08/2025

Total Award Amount (including Indirect Costs): $15,626

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 1. 2025 | 0.01 calendar |

**Title: The Ohio State University as a Lead Academic Organization (LAO) for the Experimental Therapeutics Clinical Trials Network**

Major Goals: The goal of this consortium, comprised of the Ohio State University (OSU) as the lead academic organization, the University of Kentucky Markey Cancer Center (MCC), and the Huntsman Cancer Institute (HCI) of the University of Utah, is to further the cooperative drug development efforts of the National Cancer Institute Cancer Therapy Evaluation Program for Investigational New Drugs by contributing to the design and implementation of ETCTN early phase therapeutic studies in solid tumors and hematologic malignancies, robust accrual of patients including from underserved populations to all ETCTN trials, facilitating the development of early career investigators in early phase clinical trial design, conduct and analysis, and by establishing the optimal dose and schedule of new treatments for efficient progress to phase 2 clinical trials.

Status of Support: Active

Project Number: UM1 CA186712

Name of PD/PI: MPI: Carson, III / Arnold / Garrido-Laguna

Name of Individual: Sborov, Douglas
Commons ID: sborov01

Source of Support: NCI

Primary Place of Performance: The Ohio State University

Project/Proposal Start and End Date: 05/2020 – 02/2026

Total Award Amount (including Indirect Costs): $1,722,607 / year

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 5. 2025 | 0.60 calendar |
| 6. 2026 | 0.60 calendar |

**Title: A Phase 2, Open-Label, Multi-Center Study of Venetoclax in Combination with Carfilzomib and Dexamethasone in Subjects with Relapsed or Refractory Multiple Myeloma**

Major Goals: A Phase 2, open-label, dose escalation study to evaluate the safety and efficacy of venetoclax in combination with carfilzomib-dexamethasone (Kd) in participants with relapsed or refractory MM and have received 1 to 3 prior lines of therapy.

Status of Support: Active

Project Number: C91149; M15-538; 2019-004340-30

Name of PD/PI: Sborov, Douglas

Source of Support: AbbVie, Inc.

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 07/1/2016 - 12/31/2025

Total Award Amount (including Indirect Costs): $816,528.39

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 9. 2025 | 0.12 calendar |

Title: **A Phase III, Randomized, Placebo-Controlled, Multi-Centre Study Evaluating the Safety, Tolerability and Efficacy of Combination Treatment of BL-8040 and G-GSF as Compared to Placebo and G-CSF for the Mobilization of Hematopoietic Stem Cells for Autologous Transplantation in Subjects with Multiple Myeloma - The GENESIS Study**

Major Goals: A total of 122 subjects were randomized into the study and investigated in the double-blind placebo-controlled setting to assess the efficacy and safety of G-CSF + BL-8040 as compared to G-CSF + placebo.

Status of Support: Active

Project Number: BL-8040-GCSF

Name of PD/PI: Sborov, Douglas

Source of Support: BioLineRx, Ltd.

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 01/01/2018 - 12/31/2025

Total Award Amount (including Indirect Costs): $151,341

Person Months (Calendar/Academic/Summer) per budget period.

Name of Individual: Sborov, Douglas
Commons ID: sborov01

| Year | Person Months |
|---|---|
| 8. 2025 | 0.86 calendar |

**Title: A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of bb2121 Versus Standard Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3)**

Major Goals: This is a multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of bb2121 versus standard regimens in subjects with relapsed and refractory multiple myeloma (RRMM).

Status of Support: Active

Project Number: BB2121-MM-003

Name of PD/PI: Sborov, Douglas

Source of Support: Celgene

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 09/01/2018 - 09/01/2026

Total Award Amount (including Indirect Costs): $670,909

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 7. 2025 | 0.12 calendar |
| 8. 2026 | 0.12 calendar |

**Title: A Phase 1/2 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 701 Monotherapy, or in Combination with Pomalidomide, With and Without Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma (ParadigMM-1B)**

Major Goals: The primary purpose of the phase 1 part of the study is to evaluate safety and tolerability of AMG 701 monotherapy to identify the RP2D for AMG 701 monotherapy followed by a dose-confirmation part to gather further safety data for AMG 701 monotherapy at the RP2D in adult subjects with relapsed/refractory multiple myeloma (RRMM). In addition, this study will include a sequential dose exploration part to identify the RP2D of AMG 701 in combination with pomalidomide, with and without dexamethasone (AMG 701-P+/-d). Phase 2 will consist of the dose-expansion part to gain further efficacy and safety experience with AMG 701 monotherapy in adult subjects with RRMM.

Status of Support: Active

Project Number: 20170122

Name of PD/PI: Sborov, Douglas

Source of Support: Amgen

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 12/31/2018 - 12/31/2026

Total Award Amount (including Indirect Costs): $884,660

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 7. 2025 | 0.12 calendar |
| 8. 2026 | 0.12 calendar |

Name of Individual: Sborov, Douglas
Commons ID: sborov01

**Title: Long-Term Follow-up Protocol for Subjects Treated with Gene-Modified T Cells**

Major Goals: This is a prospective study for the long-term follow-up (LTFU) of safety and efficacy for all pediatric and adult participants exposed to Gene-modified (GM) T cell therapy participating in a previous Celgene sponsored or Celgene alliance partner sponsored study.

Status of Support: Active

Project Number: GC-LTFU-001

Name of PD/PI: Sborov, Douglas

Source of Support: Celgene

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 03/01/2019 - 03/01/2026

Total Award Amount (including Indirect Costs): $190,640

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 6. 2025 | 0.12 calendar |
| 7. 2036 | 0.12 calendar |

Title: **A Randomized Study of Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Treatment in Patients with Newly Diagnosed Multiple Myeloma Who Are Minimal Residual Disease Positive After Frontline Autologous Stem Cell Transplant**

Major Goals: The purpose of this study is to evaluate conversion rate to minimal residual disease (MRD) negativity following the addition of daratumumab to lenalidomide relative to lenalidomide alone, when administered as maintenance treatment to anti-cluster of differentiation 38 (CD38) treatment naive participants with newly diagnosed multiple myeloma who are MRD positive as determined by next generation sequencing (NGS) at screening, following high-dose therapy (HDT) and autologous stem cell transplant (ASCT).

Status of Support: Active

Project Number: 54767414MMY3021

Name of PD/PI: Sborov, Douglas

Source of Support: Janssen Research & Development, LLC

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 04/01/2019 - 04/01/2026

Total Award Amount (including Indirect Costs): $555,703

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 6. 2025 | 0.12 calendar |
| 7. 2026 | 0.12 calendar |

**Title: Expanded Access Protocol (EAP) for Patients Receiving Idecabtagene Vicleucel That is Nonconforming for Commercial Release**

Name of Individual: Sborov, Douglas
Commons ID: sborov01

Major Goals: This study is designed to evaluate the safety and efficacy of nonconforming idecabtagene vicleucel (ide-cel) in participants with multiple myeloma per the approved prescribing information. This is an expanded access protocol (EAP) to be conducted at Risk Evaluation and Mitigation Strategies (REMS) qualified sites approved for commercial administration of idecabtagene vicleucel and where the EAP is authorized to be conducted for use of nonconforming idecabtagene vicleucel.

Status of Support: Active

Project Number: BB2121-EAP-001

Name of PD/PI: Sborov, Douglas

Source of Support: Celgene

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 05/01/2021 - 05/01/2028

Total Award Amount (including Indirect Costs): $56,991

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 4. 2025 | 0.12 calendar |
| 5. 2026 | 0.12 calendar |
| 6. 2027 | 0.12 calendar |
| 7. 2028 | 0.12 calendar |

**Title: Phase 2, Open-Label Randomized Study of Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone vs Carfilzomib, Lenalidomide, and Dexamethasone vs Bortezomib, Lenalidomide, and Dexamethasone in Patients with Newly-Diagnosed Multiple Myeloma (ADVANCE)**

Major Goals: This study is being done to find out whether carfilzomib, lenalidomide, and dexamethasone (KRD) or KRD and Daratumumab (KRD+DARA) might be safer and more effective ways of controlling multiple myeloma than the stand or care treatment, which is lenalidomide, bortezomib, and dexamethasone (VRD).

Status of Support: Active

Project Number: SPC-002334

Name of PD/PI: Sborov, Douglas

Source of Support: University of Miami

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 05/01/2021 - 05/01/2028

Total Award Amount (including Indirect Costs): $197,922

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 4. 2025 | 0.12 calendar |
| 5. 2026 | 0.12 calendar |
| 6. 2027 | 0.12 calendar |
| 7. 2028 | 0.12 calendar |

Name of Individual: Sborov, Douglas
Commons ID: sborov01

**Title: A Phase 1/2, Open-Lable, Multicenter Study to Evaluate a Dosing Regime with Two Ste-up Priming Doses and Longer Dosing Intervals of Elranatamab (PF-06863135) Monto therapy in Participants with Relapsed/Refractory Multiple Myeloma**

Major Goals: The purpose of Part 1 and Part 2 is to evaluate the safety of a step-up dosing approach (starting with low doses followed by higher doses) of the study medicine (elranatamab) in participants with multiple myeloma that has come back after responding to treatment or has not responded to treatment (relapsed/refractory multiple myeloma). The purpose of Part 3 of the study is to evaluate the safety and efficacy of elranatamab in combination with dexamethasone during the first 6 cycles followed by elranatamab monotherapy. This study will also look at the safety and efficacy of different doses of elranatamab, as well as different intervals between doses.

Status of Support: Active

Project Number: C1071009

Name of PD/PI: Sborov, Douglas

Source of Support: Syneos Health (Pfizer)

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 08/01/2021 - 08/01/2028

Total Award Amount (including Indirect Costs): $247,026

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 4. 2025 | 0.72 calendar |
| 5. 2026 | 0.70 calendar |
| 6. 2027 | 0.68 calendar |
| 7. 2028 | 0.66 calendar |

**Title: A Phase 2 Multi-Arm Study of Magrolimab Combinations in Patients with Relapsed/Refractory Multiple Myeloma**

Major Goals: The goal of this clinical study is to learn more about the safety and dosing of the study drug, magrolimab, in combination with other anticancer therapies in participants with relapsed/refractory multiple myeloma.

Status of Support: Active

Project Number: GS-US-558-5915

Name of PD/PI: Sborov, Douglas

Source of Support: Pharmaceutical Research Associates; Gilead Sciences

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 09/01/2021 - 09/01/2028

Total Award Amount (including Indirect Costs): $95,438

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 4. 2025 | 1.10 calendar |
| 5. 2026 | 1.06 calendar |
| 6. 2027 | 1.03 calendar |
| 7. 2028 | 1.00 calendar |

Name of Individual: Sborov, Douglas
Commons ID: sborov01

**Title: A Phase 1b/2 Dose-Escalation and Cohort-Expansion Study to Determine the Safety and Efficacy of BGB-11417as Monotherapy, in Combination With Dexamethasone and Carfilzomib/Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma and t(11;14)**Major Goals: Enter

Status of Support: Study consists of two parts, a part 1 dose escalation and a part 2 cohort expansion in combination with dexamethasone and carfilzomib intravenously across two cohorts with a monotherapy component as well.

Project Number: BGB-11417-105

Name of PD/PI: Sborov, Douglas

Source of Support: BeiGene

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 01/01/2022 - 01/01/2029

Total Award Amount (including Indirect Costs): $367,946

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 3. 2025 | 1.10 calendar |
| 4. 2026 | 1.06 calendar |
| 5. 2027 | 1.03 calendar |
| 6. 2028 | 1.00 calendar |
| 7. 2029 | 0.97 calendar |

**Title: A Phase II Study of CART-ddBCMA for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma**

Major Goals: A Phase II study of CART-ddBCMA for patients with relapsed or refractory multiple myeloma. CART-ddBCMA is a BCMA-directed CAR-T cell therapy.

Status of Support: Active

Project Number: ARC-112A

Name of PD/PI: Sborov, Douglas

Source of Support: Arcellx, Inc.

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 07/01/2022 - 07/01/2029

Total Award Amount (including Indirect Costs): $312,497

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 3. 2025 | 1.10 calendar |
| 4. 2026 | 1.06 calendar |
| 5. 2027 | 1.03 calendar |
| 6. 2028 | 1.00 calendar |
| 7. 2029 | 0.97 calendar |

Name of Individual: Sborov, Douglas
Commons ID: sborov01

**Title: A Phase I/II, Open-Label, Multi-Cohort Study to Evaluate the Efficacy and Safety of Cevostamab in Prior B Cell Maturation Antigen-Exposed Patients with Relapsed/Refractory Multiple Myeloma**

Major Goals: This study will evaluate the efficacy, safety, and pharmacokinetics of cevostamab in participants with refractory multiple myeloma (R/R MM) via intravenous (IV) infusion.

Status of Support: Active

Project Number: CO43476

Name of PD/PI: Sborov, Douglas

Source of Support: Hoffmann-La Roche

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 08/01/2022 - 08/01/2029

Total Award Amount (including Indirect Costs): $296,897

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 3. 2025 | 1.10 calendar |
| 4. 2026 | 1.06 calendar |
| 5. 2027 | 1.03 calendar |
| 6. 2028 | 1.00 calendar |
| 7. 2029 | 0.97 calendar |

**Title: A Phase 1, Multicenter, Open-Label Study of CB-011, a CRISPR-Edited Allogeneic Anti-BCMA CAR-T Cell Therapy in Patients with Relapsed/Refractory Multiple Myeloma (CaMMouflage Trial)**

Major Goals: This is a Phase 1 study to evaluate the safety of CB-011 (the study treatment), an allogeneic chimeric antigen receptor (CAR-T) cell therapy that targets the B cell maturation antigen (BCMA), to determine the best dose of CB-011, and to assess the effectiveness of CB-011 in treating multiple myeloma that has come back (relapsed) or that is no longer responding to other treatment (refractory).

Status of Support: Active

Project Number: CB11A (CAMMOUFLAGE)

Name of PD/PI: Sborov, Douglas

Source of Support: Caribou Biosciences, Inc.

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 03/01/2023 – 03/01/2030

Total Award Amount (including Indirect Costs): $180,808

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 2. 2025 | 1.10 calendar |
| 3. 2026 | 1.06 calendar |
| 4. 2027 | 1.03 calendar |
| 5. 2028 | 1.00 calendar |
| 6. 2029 | 0.97 calendar |
| 7. 2030 | 0.94 calendar |

Name of Individual: Sborov, Douglas
Commons ID: sborov01

**Title: Post-Autologous Transplant Maintenance with Isatuximab and Lenalidomide in Minimal Residual Disease Positive Multiple Myeloma**

Major Goals: This is a phase II study where patients will undergo isatuximab and lenalidomide maintenance if they are MRD-positive after Autologous Stem Cell Transplant (ASCT).

Status of Support: Active

Project Number: HEME-18; 2021-1101

Name of PD/PI: Sborov, Douglas

Source of Support: University of Illinois at Chicago

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 04/01/2023 – 04/01/2030

Total Award Amount (including Indirect Costs): $413,516

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 2. 2025 | 0.12 calendar |
| 3. 2026 | 0.12 calendar |
| 4. 2027 | 0.12 calendar |
| 5. 2028 | 0.12 calendar |
| 6. 2029 | 0.12 calendar |
| 7. 2030 | 0.12 calendar |

**Title: A Study to Evaluate Long-Term Safety of CAR-T Cell Therapy in Patients with Hematologic Malignancies**

Major Goals: This is a non-interventional, long-term safety study of allogeneic CAR-T cell therapy in patients with hematologic malignancies. Its purpose of is to collect long-term observational data to identify and understand potential late side effects in patients who have received CAR-T cell therapies.

Status of Support: Active

Project Number: CB-LTSS

Name of PD/PI: Sborov, Douglas

Source of Support: Caribou Biosciences, Inc.

Primary Place of Performance: University of Utah

Project/Proposal Start and End Date: 05/01/2023 - 05/01/2030

Total Award Amount (including Indirect Costs): $51,501

Person Months (Calendar/Academic/Summer) per budget period.

| Year | Person Months |
|---|---|
| 2. 2025 | 0.12 calendar |
| 3. 2026 | 0.12 calendar |
| 4. 2027 | 0.12 calendar |
| 5. 2028 | 0.12 calendar |
| 6. 2029 | 0.12 calendar |
| 7. 2030 | 0.12 calendar |

Name of Individual: Sborov, Douglas
Commons ID: sborov01

PENDING
None.

**IN-KIND**

None.

**Overlap** (summarized for each individual):
There is no scientific, budgetary or commitment overlap between the grants listed on this document.

I, **Douglas Sborov**, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

DocuSigned by:
Douglas W. Sborov, MD MS
DB5F626F2D5445A...
Signature: _____

Date: _____ 10/10/2024

HEALTH
UNIVERSITY OF UTAH

Division of Nephrology and Hypertension
Department of Internal Medicine
421 Wakara way, Suite 360
Salt Lake City, UT 84108
801.581.2772

Yizhe Xu, PhD, MSTAT
Division of Epidemiology
Department of Internal Medicine
University of Utah
295 Chipeta Way, Salt Lake City, UT 84108

September 23, 2024

Dear Dr. Xu,

I am writing to confirm my participation as a co-investigator for your Utah CTSI TIP pilot grant titled “An Efficient, high-Quality, Unbiased, Interpretable Pipeline for Overcoming Barriers in the Translational Research using Real-World Data.” I am an expert in cardiovascular disease, nutritional status and lifestyle factors in chronic kidney disease and dialysis patients. I lead a strong research team conducting studies on large national databases using cutting-edge statistical methods. I am also the Co-Director of the Cardio-Renal and Metabolism Center.

Several of my current research have applied the target trial emulation and causal inference methods, which are extremely helpful for handling various sources of bias in real-world data. I believe many research groups, including ours, will benefit from this reproducible research pipeline, EQUIP, as we will be able to access all the reliable resources and enhance the efficiency of our work. Tailoring treatment decision-making to patients’ characteristics is essential for advancing patients’ health, so expanding the implementation tools to enable answering research questions related to treatment heterogeneity and adaptive intervention is crucial. My role will be to help you explore meaningful clinical applications and ensure high utility of EQUIP to clinicians and researchers. I will also help with disseminating the work.

This project will be a wonderful opportunity to continue our collaboration. I am absolutely committed to the success of this very important project, and I hope the study section shares my enthusiasm. Wishing you all the best!

Sincerely,

Srinivasan Beddhu, MD
Professor and Dialysis Research Foundation Presidential Endowed Chair
Department of Internal Medicine
University of Utah School of Medicine

HEALTH
UNIVERSITY OF UTAH

Division of Biostatistics
Department of Population Health Sciences
295 Chipeta Way, Room 1C448
Salt Lake City, UT 84108
801.213.3741

Yizhe Xu, PhD, MSTAT
Division of Epidemiology
Department of Internal Medicine
University of Utah
295 Chipeta Way, Salt Lake City, UT84108

September 23, 2024

Dear Dr. Xu,

I am writing to confirm my participation as a co-investigator for your Utah CTSI TIP pilot grant titled "An Efficient, high-Quality, Unbiased, Interpretable Pipeline for Overcoming Barriers in the Translational Research using Real-World Data." I am an expert in clinical trial design, modern causal inference, longitudinal and time-to-event data analysis, and evaluating surrogate endpoints. I am also the Director of the Translational Science: Implementation, Analysis and Design (TRIAD) team.

I have substantial experience implementing the target trial emulation and advanced causal inference methods that you propose to improve translational research. Your proposal to synthesize existing resources and systemize the workflow of TRIAD for target trial emulation is very timely and has exceptionally high value to TRIAD and the translational researchers that TRIAD supports, and more broadly for reach across the Utah CTSI and, eventually, other institutions as well. My chief role will be to connect you with members of the TRIAD team and to provide recommendations regarding important research questions, methods, and implementation tools to build into the research pipeline. In addition, if the proposal is funded, TRIAD will allocate an additional $15,000 to ramp up the efforts on this project.

I look forward to contributing to this important project given our history of productive collaborations. I anticipate a great deal of benefit to come from this project as we work toward improving the quality and interpretability of translational research. Best luck with the grant submission.

Sincerely,

Tom Greene

Tom Greene, PhD
H.A. and Edna Benning Endowed Presidential Professor
Division of Biostatistics, Department of Population Health Sciences
Division of Epidemiology, Department of Internal Medicine
Director, Translational Research: Implementation, Analysis and Design (TRIAD) Team
University of Utah

Division of Epidemiology
Department of Internal Medicine
295 Chipeta Way, Room 1N216
Salt Lake City, UT 84108
801.587.0242

October 2, 2024

Yizhe Xu, PhD, MSTAT
Division of Epidemiology
Department of Internal Medicine
University of Utah
295 Chipeta Way, Salt Lake City, UT 84108

Dear Dr. Xu,

I am pleased to collaborative as a consultant for your Utah CTSI TIP pilot grant titled "An Efficient, high-Quality, Unbiased, Interpretable Pipeline (EQUIP) for Overcoming Barriers in the Translational Research using Real-World Data."

This proposal holds substantial translational science significance, especially in addressing crucial barriers and urgent needs in conducting efficient and high-quality research. As the ultimate goal is to deliver several research tools that can be generalized to boarder applications, the evaluation of their clarity, usability, and reproducibility is paramount.

As you know, I am an Assistant Professor in the Department of Internal Medicine at the University of Utah and an expert in survey methodology. As the Director of the Clinical and Translational Sciences Institute's Survey Design and Measurement Core and a team scientist, I have extensive experience collaborating with investigators to ensure sound methodology in survey study design, questionnaire development and assessment, and survey recruitment and retention.

I am very excited to collaborate on this project and provide my expertise in designing questionnaires for assessing EQUIP. I will offer guidance on the development of surveys to maximize the response rate and feedback quality. I look forward to the impactful outcomes this project will yield.

Sincerely,

Morgan M. Millar, PhD
Director, Clinical and Translational Sciences Institute's Survey Design and Measurement Core
Department of Internal Medicine
University of Utah School of Medicine

Program Director/Principal Investigator (Last, First, Middle): Yizhe Xu

| DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY | FROM 04/01/2025 | THROUGH 04/01/2026 |
|---|---|---|

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

| NAME | ROLE ON PROJECT | Cal. Mnths | Acad. Mnths | Summer Mnths | INST.BASE SALARY | SALARY REQUESTED | FRINGE BENEFITS | TOTAL |
|---|---|---|---|---|---|---|---|---|
| Yizhe Xu | PD/PI | 2.4 | | | | 0 | 0 | 0 |
| Tom Greene | Co-I | 0.6 | | | | 0 | 0 | 0 |
| Adam Bress | Co-I | 0.6 | | | | 0 | 0 | 0 |
| Angela Presson | Co-I | 0.6 | | | | 0 | 0 | 0 |
| Ann Chen | Co-I | 0.6 | | | | 0 | 0 | 0 |
| Srinivasan Beddhu | Co-I | 0.6 | | | | 0 | 0 | 0 |
| Douglas Sborov | Co-I | 0.6 | | | | 0 | 0 | 0 |
| Blessing Ofori-Atta | Master-level Biostatistician | 6 | | | 39,000 | 19,500 | 5,730 | 25,230 |
| **SUBTOTALS** → | | | | | | 19,500 | 5,730 | 25,230 |

| | |
|---|---|
| CONSULTANT COSTS<br>0 | 0 |
| EQUIPMENT *(Itemize)*<br>0 | 0 |
| SUPPLIES *(Itemize by category)*<br>Computer - $1,000<br>Software – backup storage, technical supplies, and especially statistical and other software renewals (e.g., Stata, SAS, Copilot for R) - $200<br>Publication cost - $1,000 | 2,200 |
| TRAVEL<br>2,500 | 2,500 |
| INPATIENT CARE COSTS 0 | 0 |
| OUTPATIENT CARE COSTS 0 | 0 |
| ALTERATIONS AND RENOVATIONS *(Itemize by category)*<br>0 | 0 |
| OTHER EXPENSES *(Itemize by category)*<br>0 | 0 |

| | | |
|---|---|---|
| CONSORTIUM/CONTRACTUAL COSTS | DIRECT COSTS | 0 |
| **SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD** *(Item 7a, Face Page)* | | $ 29,930 |
| CONSORTIUM/CONTRACTUAL COSTS | FACILITIES AND ADMINISTRATIVE COSTS | 0 |
| **TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD** | | $ 29,930 |

**BUDGET JUSTIFICATION**

**A. KEY PERSONNEL**

**Yizhe (Crystal) Xu, PhD, MSTAT**, Contact Principal Investigator (2.4 calendar months). Dr. Xu will serve as the lead biostatistician and will be responsible for collaborating with the Co-Investigators and staff on the administration and overall direction of the project. As a member of both the Study Design and Biostatistics Center (SDBC) and the Cancer Biostatistics Center (CBC), she is familiar with the workflows and researchers in both groups. Dr. Xu has extensive experience in comparative effectiveness research, particularly in the areas of cardiovascular disease (CVD), dementia, and cancer. She also possesses advanced training in modern causal inference methods and large observational data analysis. Her research interests include analyzing large electronic health records, claims data, and wearable data using machine learning techniques, estimating heterogeneous treatment effects on time-to-event outcomes, and identifying optimal fixed-point and dynamic treatment regimens. Furthermore, Dr. Xu has significant experience processing large databases and coding in various statistical programming languages (R, SAS, Stata, Python, PASS, Visual Studio Code, SQL). She also utilizes high-performance computing and software tools (GitHub, Putty, WINSCP, Google Cloud Platform), all of which are critical to the successful development of the Efficient, high-Quality, Unbiased, Interpretable Pipeline (EQUIP). Dr. Xu's methodological expertise, combined with her considerable experience in study design and analysis, will make her a key hands-on contributor to all three Aims of the project. In addition, she will take direct responsibility for the project's overall success, leading and coordinating the design and execution of the study's Aims and ensuring the timely and high-quality completion of the work. Collaborating closely with Senior Statistician Dr. Greene, Dr. Xu will lead the drafting and critical revision of research schemas and will supervise the analytical team in building implementation tools through daily interactions and monthly conference calls with the full study team. Dr. Xu will also oversee the budgetary and administrative aspects of the project and coordinate with the Co-Investigators.

**Tom Greene, PhD,** Co-Investigator (0.6 calendar months). With over 30 years of experience in designing and analyzing longitudinal and observational data, he brings invaluable expertise to the team. Dr. Greene has served as Dr. Xu's primary mentor since she joined the University of Utah last year. His expertise spans clinical trial design, modern causal inference, longitudinal and time-to-event data analysis, and surrogate endpoint evaluation. As the Director of the Translational Research: Implementation, Analysis, & Design (TRIAD) team, Dr. Greene will oversee the methodological and practical aspects of the project, providing critical guidance throughout.

**Adam Bress, PharmD, MS,** Co-Investigator (0.6 calendar months). Dr. Bress has advanced training in cardiovascular disease epidemiology and pharmacoepidemiology, with a particular focus on causal inference, hypertension, and antihypertensive medication use. He has been collaborating with Dr. Xu since joining the University of Utah last year. Dr. Bress brings extensive experience in analytical methods and study design and will offer key insights into data management, the development of analytical cohorts, and the formulation of complex statistical analysis plans. Additionally, he will apply the EQUIP, once available, to his projects and share experience and feedback.

**Angela Presson, PhD,** Co-Investigator (0.6 calendar months). Dr. Presson will assist in all aspects of the EQUIP construction including systemizing existing analytical resources in TRIAD and building easy-to-use implementation tools. She is particularly well suited for this role as she is the Co-Director of TRIAD and she has 20 years of experience in study design and statistical consultations. Dr. Presson will help with connecting existing resources generated from past projects in TRIAD and provide recommendations on designing statistical analysis plans and statistical software packages.

**Ann Chen, PhD,** Co-Investigator (0.6 calendar months). Dr. Chen is the Director of Cancer Biostatistics Center at the Huntsman Cancer Institute. Dr. Chen is a formally trained biostatistician with expertise in single-cell and genetic studies. She has over 25 years of experience in cancer research. Dr. Chen will provide insights on the design of EQUIP so that it can be effectively used in cancer studies. She will also assist in identifying important applications of EQUIP in cancer research.

**Srinivasan Beddhu, PhD, Co-Investigator** (0.6 calendar months). Dr. Beddhu is the Co-Director of the Cardio-Renal and Metabolism Center and an expert in cardiovascular disease, nutritional status and lifestyle factors in chronic kidney disease and dialysis patients. He also leads a strong research team that is conducting studies of large national databases using cutting-edge statistical techniques including modern causal inference

methods. Dr. Beddhu will assist with exploring meaningful clinical applications in the CVD, kidney disease, and metabolic disease. He will also provide recommendations to ensure the EQUIP has high utility to clinicians and researchers.

**Douglas Sborov, MD, MS** (0.6 calendar months). Dr. Sborov, is the Director of the HCI Hematology Disease Center and Plasma Cell Dyscrasias (PCD) Program. Dr. Sborov's research is focused on investigating novel targeted and immunologic therapies for patients with multiple myeloma and he is the principal investigator of a multiple of trials in patients with plasma cell dyscrasias and is actively involved in early drug development and other translational collaborations. Dr. Sborov will provide useful applications in multiple myeloma research that estimate optimal single-stage or multi-stage treatment regimens.

## B. OTHER PERSONNEL

**Blessing Ofori-Atta, MS** (6.0 calendar months). Blessing Ofori-Atta is a master-level biostatistician in the SDBC at the University of Utah. She has several years of experience working under Drs. Angela Presson and Tom Greene on various projects. Blessing is an experienced statistical programmer and she will build implementation tools for the analysis procedures described in the research schemas drafted by Dr. Xu and other Co-Is. Blessing will touch base with Dr. Xu on a daily to weekly basis throughout the year.

**BENEFITS.** The fringe benefit rate is 14% for the PhD student with an additional $3,000 for health insurance annually.

## C. EQUIPMENT

None

## D. TRAVEL ($2,500/yr)

$2,500 is requested for domestic travel to professional conferences and meetings to present findings associated with the proposed research.

## E. PARTICIPANT/TRAINEE SUPPORT COSTS

None

## F. OTHER DIRECT COSTS

### Materials and Supplies ($1,200/yr)

*Computer and Software ($1200/yr)***.** Updates of equipment, backup storage, technical supplies, and especially statistical and other software renewals (e.g., Stata, SAS, GitHub, Copilot for R, PASS) will be needed for the PhD student.

### Publication Costs ($1,000/yr)

We are requesting a total of $1,000, for costs required by open-access journals to defray publication costs.

## INDIRECT COSTS

None