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PRINCIPAL INVESTIGATOR: Duygu Tosun-Turgut, PhD

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Duygu Tosun-Turgut, Ph.D.

E-Mail: duygu.tosun@ucsf.edu

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14. ABSTRACT

The overall goal is to cost-efficiently harness the newly available wealth of nationwide clinical neuroimaging data and merge with our existing cohort of 1.6 million TBI-exposed and unexposed veterans with up to 12 years of follow-up in order to (1) create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data; (2) predict which TBI-exposed veterans will go on to develop dementia; and (3) identify prevalence of specific sub-types of dementia among TBI-exposed versus unexposed veterans. We expect that we will (1) produce the largest military-relevant MRI dataset with expertly curated TBI exposure and dementia outcome and up to 12 years of follow-up (with option of continued follow-up via VHA EMR); (2) develop a method for predicting 5+-year risk of post-TBI dementia using routinely collected clinical MRI. This work may directly inform public health planning within the DoD and VHA and generate testable hypotheses regarding underlying etiology of post-TBI dementia.

15. SUBJECT TERMS

Traumatic brain injury (TBI); veterans; dementia; magnetic resonance imaging (MRI); deep learning; brain atrophy; endophenotyping

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1. **INTRODUCTION:** An estimated 10 to 20% of Veterans from the wars in Iraq and Afghanistan have suffered traumatic brain injury (TBI). Many Veterans from prior conflicts have experienced TBI as well. Some studies have reported a link between TBI and increased risk of cognitive impairment and dementia even after years of active life post injury, but few have studied Veterans. Many people with TBI do not develop dementia; however, we have no tools to predict which individuals are at highest risk and would benefit from careful follow-up and recruitment into clinical trials to prevent post-TBI dementia. Practical biomarkers for identifying patients at highest risk for dementia after TBI are desperately needed to inform individual patient management, dementia prevention strategies, and clinical trials. Furthermore, understanding the underlying etiology of post-TBI dementia (clinical dementia sub-types) could further inform clinical care and prevention for Veterans with TBI. Measures of structural brain changes rapidly measured on neuroimaging modalities, particularly structural brain magnetic resonance imaging (MRI), are well-established predictors of cognitive decline and risk for dementia in the general population. Large population-based samples of TBI-exposed veterans are needed in order to leverage advances in neuroimaging and biomarker discovery via artificial intelligence approaches to develop robust and generalizable models to predict post-TBI dementia and to discover neuroimaging biomarkers to characterize dementia subtypes among TBI-exposed individuals. The Veterans Health Administration (VHA) has recently made the nationwide VHA imaging data available to researchers; we have the unprecedented opportunity to merge this nationwide structural MRI with our existing nationwide VHA cohort of 1.6 million TBI-exposed and unexposed veterans to create the largest military-relevant TBI MRI data-set that has (to our knowledge) ever been created and directly address the major knowledge gaps described. We have assembled a team of experts in dementia, TBI, neuroimaging, and prognostic modeling with track records of successful completion of high impact research. The propose a 3-year project will cost-efficiently harness the newly available wealth of nationwide clinical neuroimaging data and merge with our existing cohort of 1.6 million TBI-exposed and unexposed veterans with up to 12 years of follow-up in order to (1) create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data; (2) predict which TBI exposed veterans will go on to develop dementia; and (3) identify prevalence of specific sub-types of dementia among TBI-exposed versus unexposed veterans. We expect that we will (1) produce the largest military relevant MRI dataset with expertly curated TBI exposure and dementia outcome and up to 12 years of follow up (with option of continued follow-up via VHA EMR); (2) develop a method for predicting 5+-year risk of post-TBI dementia using routinely collected clinical MRI. This work may directly inform clinical care of veterans and identify a high-risk subset that may be ideal for further studies of underlying mechanisms of post-TBI dementia and clinical trials for prevention; and (2) facilitate discovery of the nationwide epidemiology of neuroimaging biomarker-supported dementia sub-types in TBI-exposed versus unexposed veterans receiving care within VHA. This work may directly inform public health planning within the DoD and VHA and generate testable hypotheses regarding underlying etiology of post-TBI dementia.

2. **KEYWORDS:** Traumatic brain injury (TBI); veterans; dementia; magnetic resonance imaging (MRI); deep learning; brain atrophy; endophenotyping;

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction*

- **What were the major goals of the project?**

	Timeline
Major Task 1: Obtain local and HRPO IRB approval	Months
Subtask 1: Submit document for local IRB review. • Submitted: UCSF CHR & SFVAMC R & D; 07 AUG 2019 • Approved by: UCSF CHR; 25 NOV 2019; • Approved by: SFVAMC R & D 06 DEC 2019	1-3

Subtask 2: Submit IRB approval and necessary documents for HRPO review: • Submitted: DOD HRPO; 06 DEC 2019 o Approval: 21 FEB 2020	3-5
Milestone #1: HRPO approval • *DOD HRPO; Approval Achieved; 100% Complete*	5-6
Specific Aim 1:	
Major Task 2: To create a large, nationwide, high- quality cohort of ~200,000 TBI-exposed and un- exposed veterans with MRI imaging data.	Months
Subtask 1: Identify veterans diagnosed with TBI in the VHA system • *100% Complete*	1-5
Subtask 2: Build MRN list for relevant neuroimages in VHA system • *100% Complete*	5-7
Subtask 3: Retrieve MRI data via PACS-AIR • *100% complete within VISN21*	7-9
Subtask 4: Import MRI data to research DICOM database • *100% complete within VISN21*	9-10
Subtask 5: Sort/clean MRI data at research DICOM database • *100% complete*	10-11
Subtask 6: Perform MRIQC rating to identify excellent and acceptable quality MRI datasets • *100% complete*	10-12
Milestone #2: Clinical and MRI Data curation completed • *100% complete within VISN21*	12
Specific Aim2:	
Major Task 3: Develop and internally validate an MRI- based algorithm for predicting 5+ year risk of post-TBI dementia N>70,000 veterans with TBI (N>33,000 with mild TBI) • In progress	
Subtask 1: Robust processing of MRIs to estimate regional tissue volume metrics, following the priority ordering based on MRIQC rating and VISN • *100% complete within VISN21*	11-24
Subtask 2: Statistical ComBat harmonization of MRI volumetric estimates, within and across the dataset subsets based on MRIQC rating and VISN • *100% complete within VISN21*	16-24
Subtask 3: White matter hyperintensity lesions burden in T2-weighted MRIs • *100% complete within VISN21*	15-24
Subtask 4: Machine Learning of Structural MRI Data to build prognostic models on training data, following the priority ordering based on MRIQC rating and VISN • *100% complete within VISN21*	18-24
Subtask 5: Deep Learning of Structural MRI Data to build prognostic models on training data, following the priority ordering based on MRIQC rating and VISN • In progress	22-28

Subtask 6: Assess performance of prognostic models on independent validation data, within the dataset subsets based on MRIQC rating and VISN and the entire dataset • In progress	23-25
Subtask 7: Determine whether MRI data predicts post- TBI dementia, within the dataset subsets based on MRIQC rating and VISN and the entire dataset • N/A study has not yet started	24-27
Milestone #3: Developed practical prognostic model of risk for post-TBI dementia using readily available clinical MRI • N/A study has not yet started	28
Specific Aim 3:	
Major Task 4: Build dementia phenotype relevance scores capturing individual patients' dementia MRI endophenotypes Veterans with post-TBI dementia (N=3,677) versus those with dementia without preceding TBI (N=8,435)	
Subtask 1: Create intrinsic functional connectivity map templates for 6 disease-specific NOIs • *100% complete*	18-20
Subtask 2: Generate individual dementia atrophy signature based on voxel-based W-score estimates • *100% complete within VISN21*	18-24
Subtask 3: Estimate dementia phenotype relevance scores • N/A study has not yet started	24-30
Milestone #4: Objectively quantified NOI-based dementia-subtypes (MRI dementia endophenotyping) • N/A study has not yet started	30
Major Task 5: Build frequency maps capturing individual patients' white matter disease topographies Veterans with post-TBI dementia (N=3,677) versus those with dementia without preceding TBI (N=8,435)	
Subtask 1: Generate white matter lesion frequency maps • N/A study has not yet started	28-32
Subtask 2: Generated W-score maps as quantitative representation of spatial distribution of white matter lesion burden • N/A study has not yet started	28-32
Subtask 3: Bin individuals by the predominant regional pattern of white matter disease • N/A study has not yet started	30-34
Subtask 4: Identify similarities and differences in burden/distribution of white matter lesions in TBI exposed vs. unexposed veterans with dementia • N/A study has not yet started	30-36
Milestone #5: Investigated vascular contributions to post-TBI dementia • N/A study has not yet started	36

- **What was accomplished under these goals?**

A. All regulatory approvals for the local UCSF/SFVAMC and HRPO were obtained.

B. Following our proposed multi-layer tier approach, we curated a data set for our initial conservative tier focusing on images from local repository at SFVAMC. The conservative tier allows us to test the hypotheses with minimal impact of imaging heterogeneity.

Dr. Yaffe is the PI of the CENC Epidemiology Project in which her team has assembled a state-of-the-art data repository of all veterans followed by VHA with a TBI diagnosis and a random sample of veterans without TBI for a cohort of 1.6 million veterans. TBI exposure is defined either by having a diagnosis of TBI after a comprehensive neurological assessment (CTBIE) or by having at least one inpatient or outpatient TBI diagnosis (NPCD) from a comprehensive list of ICD-9 codes used by the Defense and Veterans Brain Injury Center (DVBIC) and the

Armed Forces Health Surveillance Branch (AFHSB) for TBI surveillance.46 ICD-9 codes are used as these were available during the study period ending in 2015. Dementia is defined using a comprehensive list of ICD-9 codes recommended by the VA Dementia Steering Committee (2016 version).

Within this large veteran's cohort, we created a cohort of all SFVAMC cases (selected based on having STA3N = 662, indicating parent VA hospital is San Francisco) with TBI, with and without dementia from FY2013 through FY2015 and had at least one clinical brain magnetic resonance imaging (MRI) (N=740). Fiscal year criterion allows us to minimize scanner software/hardware upgrade related imaging heterogeneities. MRI studies was compiled by searching procedures with Current Procedural Terminology (CPT) code 70551 for MRI brain without contrast or 70553 for MRI brain with and without contrast in the VHA Computerized Patient Record System (CPRS). Geographic distribution of residency within this imaging cohort is illustrated in Fig 1, as expected large portion of cases are Bay Area and California based.

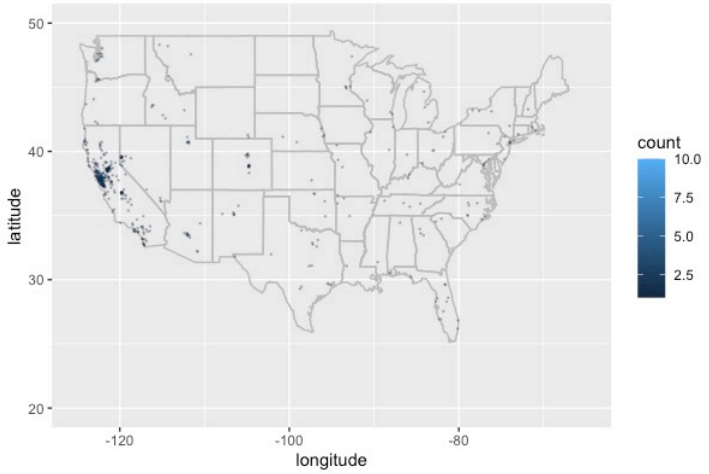


Fig 1. Geographic distribution of residency.

Distribution of clinical MRI over the fiscal years 2012-2015 were similar between cases with and without dementia (p=0.98). As expected, our cohort is mostly male veterans and there was no significance difference in prevalence of female cases with and without dementia (p=0.15).

We observe a bimodal distribution of age at TBI exposure within cases without dementia, where early exposure cases clustering around age 30 and later exposure cases around age 60 (Fig 2). Cases with dementia diagnosis had TBI exposure at age 61.6 ± 13.6 years. Among cases with dementia diagnosis, 40% of them had early onset dementia (dementia diagnosis before age 65). It is important to study early-onset

dementia cases as these present a unique opportunity to study impact of TBI in isolation as late-onset individuals may have comorbid pathologies.

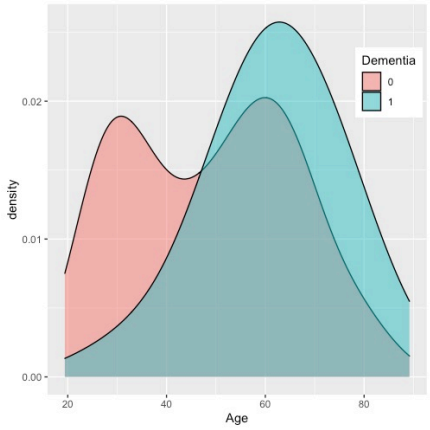


Fig 2. Age at TBI exposure for veterans with (1) and without (0) dementia.

As illustrated in Fig 3, time from TBI exposure to dementia diagnosis was 3.9 ± 3.1 years (median of 3.6 years), independent of the age of TBI exposure (correlation = 0.02; p = 0.91). Furthermore, 40% of the cases had at least one clinical brain MRI within a year of TBI exposure (Fig 4), and cases with dementia diagnosis after TBI exposure on average had a clinical brain MRI within 0.9 ± 2.1 years of their clinical dementia diagnosis (Fig 5). Considering the demographic and clinical characteristics of this conservative tier cohort as well as timing of the available clinical brain MRIs relative to time of TBI exposure and dementia diagnosis matches fits well the proposed analyses to test the hypotheses with minimal impact of imaging heterogeneity.

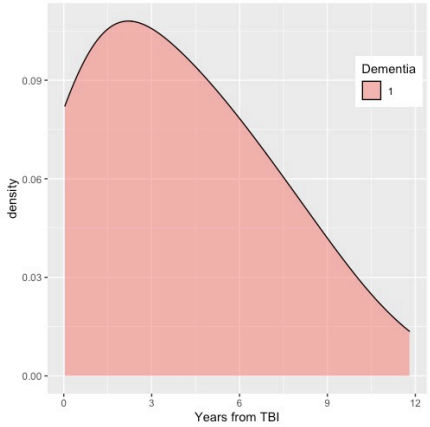


Fig 3. Time from TBI exposure to dementia diagnosis.

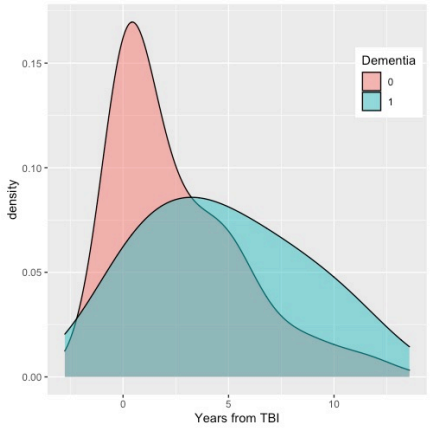


Fig 4. Time from TBI exposure to clinical MRI of veterans with (1) and without (0) dementia.

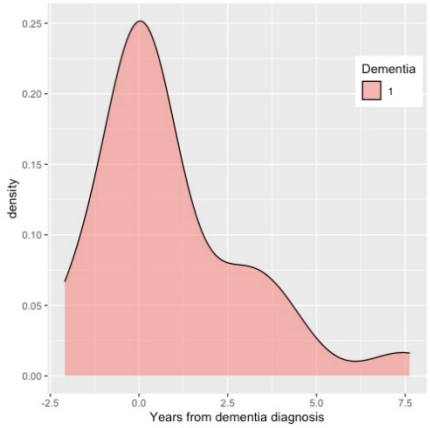


Fig 5. Time from dementia diagnosis to clinical MRI acquisition.

C. We retrieved clinical brain MRI images from SFVAMC Clinical PACS archives. Each image was coded and deidentified. One of our objectives is to show how well the harmonized image processing will work for the VHA clinical MRI data, as success of this step is important for success of Aims 2 and 3 of our proposal. We implemented and tested an MRI quality control pipeline using MRIQC tool which is developed and distributed as an open-source software by OpenNeuro, Stanford Center for Reproducible Neuroscience.

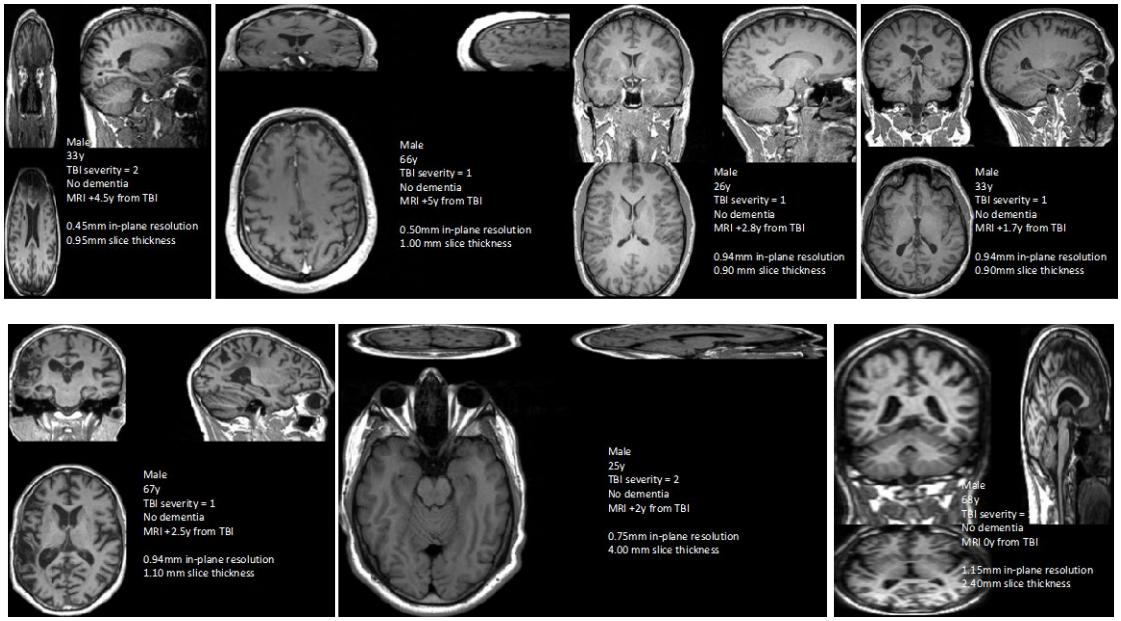


Fig 6. Expected heterogeneity in MRI data quality in clinical setting is illustrated through sample cases with varying demographic and clinical characteristics.

Influence of scanner differences on MR image contrast and their effect on tissue segmentation is well documented. Expected heterogeneity in MRI data quality in clinical setting is illustrated through sample cases with varying demographic and clinical characteristics in Fig 6. This leads to biased cortical morphometry metrics due to field strength, scanner platform (e.g., different vendors/models, hardware/software upgrades over time), and imaging protocol difference in multi-site and longitudinal studies. As most of the neuroimaging tools are developed and validated on research quality MRIs, indeed it is important to understand the intrinsic quality differences between clinical MRIs and research MRIs for a true clinical translation of biomarker studies. Therefore, to better understand the differences between clinical quality and research quality MRI acquisition from quantification of imaging markers of neurodegeneration, we leveraged imaging data from another DoD funded project, namely Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder and Alzheimer's Disease on Brain Tau in Vietnam Veterans using ADNI (ADNI-DoD; W81XWH-12-2-0012), which recruited Vietnam Veterans who meet criteria for normal cognition or mild cognitive impairment with history of TBI only, PTSD only, or both TBI and PTSD or with no history of TBI and/or PTSD.

Compared to ADNI-DoD structural MRIs, clinical MRIs of veterans had significantly greater coefficient of joint variation (CJV; β=0.46; p=0.0006), suggesting presence of greater head motion and/or large intensity non-uniformity artifacts. Clinical MRIs presented with significantly lower contrast-to-noise ratio (CNR; β=-0.78; $p<10^{-4}$) compared to ADNI DoD MRIs, indicating weaker separation between the tissue distributions of GM and WM in clinical quality MRIs, therefore inferior quality. Yet, no significant difference was observed between clinical MRIs and ADNI-DoD MRIs in terms of overall signal-to-noise ratio (SNR; β=0.18; p=0.2; Fig 7), although tissue specific SNR varied between clinical and research quality MRI datasets (gray matter tissue SNR β=2.66; $p<10^{-4}$; white matter tissue SNR β=-2.01; $p<10^{-4}$; Fig 7).

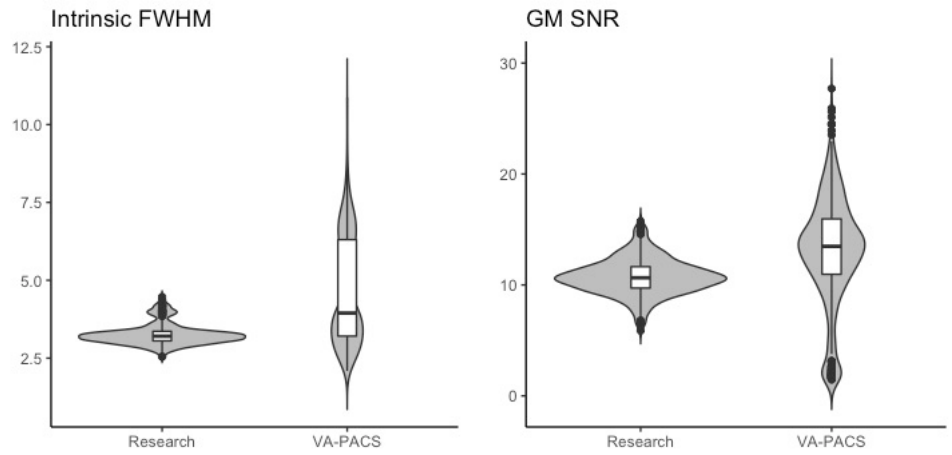


Fig 7. Clinical versus research MR image quality metric distributions

D. Given the expected greater heterogeneity in MRI data quality in this study, we adapted a multi-atlas segmentation framework to achieve a consistent parcellation of anatomical brain structures in our MRI dataset where we expect high levels of inter-scanner and imaging protocol differences. Multi-atlas segmentation framework uses a rich ensemble of warped atlases, rather than a model-based average that shares the same regional labels. This approach allows us to optimally estimate regional tissue volumes in a given structural MRI regardless of image acquisition parameters (e.g., slice thickness and spatial resolution) and quality, by imposing the consistency of segmentations, while each atlas set preserves the image intensity characteristics of the specific field strength/scanner platform/imaging protocol. Resulting robust anatomical segmentation of a sample clinical brain MRI is shown in Fig 8.

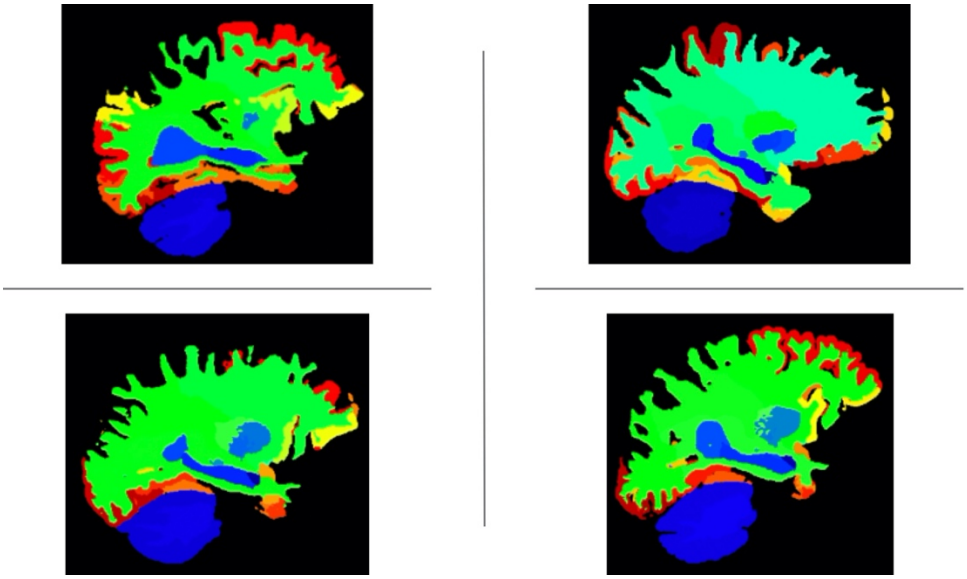


Fig 8. Multi-atlas anatomical segmentation of a sample clinical brain MRI.

Furthermore, when compared to data from a multicenter research neuroimaging cohort of ADNI-DoD, estimated hippocampal volume distribution from clinical brain MRIs was comparable to hippocampal estimates from research MRI data (p=0.32; Fig 9) despite the clinical vs research MRI quality differences as reported above, further supporting the robust application of harmonized image processing to clinical quality MRI data.

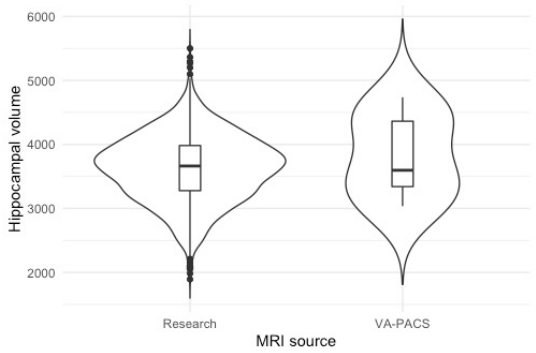


Fig 9. Distribution of hippocampal volume within a multicenter research imaging cohort (Research) and within clinical brain MRI cohort (VA-PACS)

E. We have been further building upon our previous developments on robust processing of clinical quality MRIs of veterans with and without TBI and dementia. Particularly, our recent results showed wide-spread cortical atrophy in Male Veterans with TBI+Dementia compared to ones with TBI only, after controlled for age at MRI, TBI severity at MRI, and time from Dementia diagnosis. As illustrated in the glass-brain maps shown in Fig 10, predominantly frontotemporal atrophy was associated to dementia in veterans with TBI. The extend of atrophy was more pronounced in temporal regions for veterans with TBI and dementia after age of 60 years. As illustrated in the glass-brain maps shown below, predominantly frontotemporal atrophy was associated to dementia in veterans with TBI. The extend of atrophy was more pronounced in temporal regions for veterans with TBI and dementia after age of 60 years.

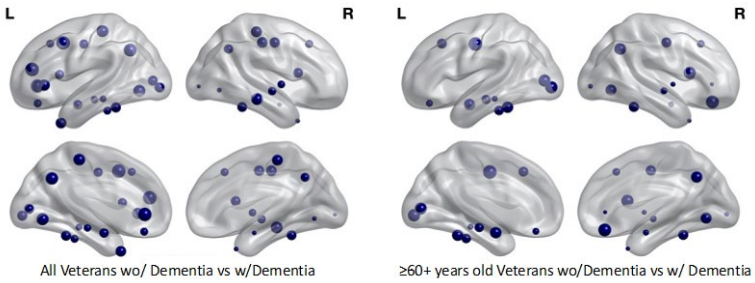


Fig 10. Wide-spread cortical atrophy in Male Veterans with TBI+Dementia compared to ones with TBI only, after controlled for age at MRI, TBI severity at MRI, and time from Dementia diagnosis

Furthermore, when compared to lower TBI severity (1) cases, veterans with TBI severity of 2 and 3 presented with greater frontotemporal and parietofrontal atrophy, respectively (Fig 11). These latent atrophy signatures were used to inform the machine learning predictive models to test the primary hypotheses as described below.

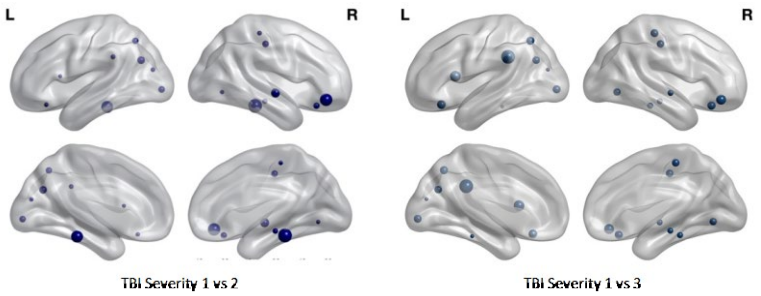


Fig 11. Compared to lower TBI severity (1) cases, veterans with TBI severity of 2 and 3 presented with greater frontotemporal and parietofrontal atrophy, respectively

F. Multilabel machine learning based phenotypical classification: Based on the unique anatomical signatures of TBI and dementia in veterans (Fig 12), we have developed multi-label learning classification techniques. Multi-label classification is an important approach as each veteran's data is associated with multiple labels (e.g., exposed to TBI or not and developed dementia or not) and these are not mutually exclusive phenotypical labels (e.g., exposure to TBI increasing risk for development of dementia). Instead of considering each phenotypic label independently, the multi-label technique learns a single model for all phenotypical outcomes and makes a prediction at the sample level. We believe that this method is closer to the clinical reality, where clinical/cognitive phenotypes are not typically independent of one another.

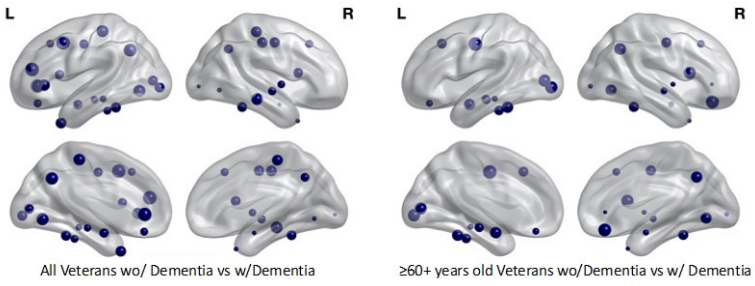


Fig 12. Compared to Veterans without Dementia diagnosis, Veterans with Dementia presented with greater parietotemporal and frontal atrophy

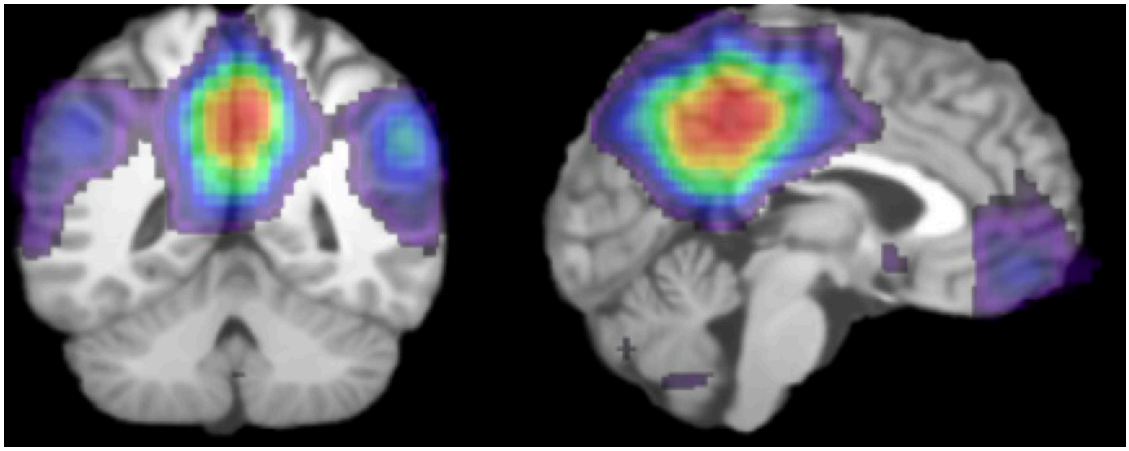
In the context of this study, we started implementation of a multi-label random forest (MLRF) classifier. The RF is an ensemble method that is based on building several independent decision tree classifiers on different subsets of the dataset. It considers the combination (often the average) of the output of each independent classifier to improve performance in producing overall predictions.

G. Multi-label learning is a supervised problem in which several labels are learned simultaneously. For all experiments, model construction and evaluation has been performed over 10 iterations of five-fold multi-label stratified cross-validation. Feature space includes harmonized estimates of regional atrophy measures from T1 MRIs, age at T1 MRI acquisition, and sex. The outcome phenotype labels are TBI vs no-TBI exposure and Cognitively Normal vs Dementia. Our preliminary implementation had a multi-label classification performance of 69% ± 25% accuracy. We are currently performing sensitivity analyses and an analysis to assess to what extent multi-label classifier perform better than single-label classifiers for different optimization criteria including overall accuracy, positive predictive value, and false negative rates.

H. To determine network-based neurodegeneration sub-types of dementia while preserving the information of individual effects, we have been working on establishing a 6-dimensional dementia phenotype relevance score. This phenotype relevance

score aims to quantify topographic similarity between atrophy signature of each individual and networks of interest from intrinsic brain connectivity, including default mode network, executive network, frontoparietal network, visual network, auditory network, and motor network (Fig 13). Each of these networks of interest has been associated with distinct dementia subtypes [1,2].

Default mode network



Frontoparietal network

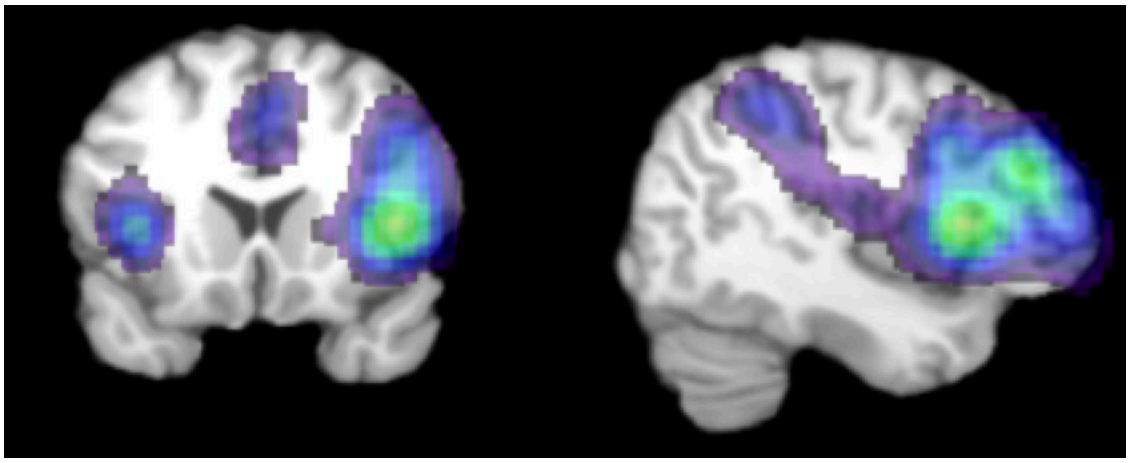
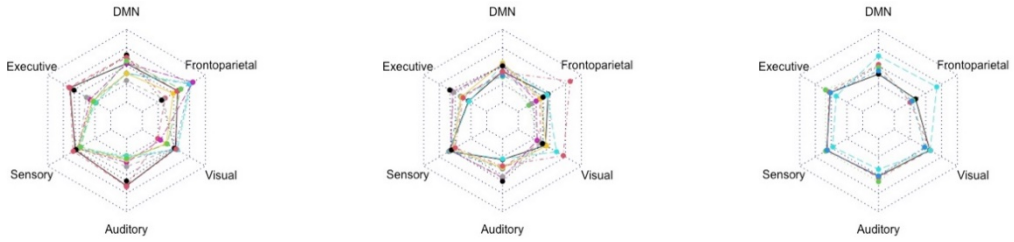


Fig 13. Example estimated networks of interest illustrating default mode network and frontoparietal network.

Individual atrophy signature based on harmonized MUSE parcellation has been estimated as W-scores by regressing out normal confounding effects of age and sex differences in No-TBI/No-Dementia age-matched cohort. Specifically, a W-score map provides spatial distribution where individulas's gray matter probability would fall on the normal grey matter probability distribution[3]. We have been developing an approach that explicitly avoids pairwise registrations between individual brain MRIs, but instead focuses on modeling and discriminating between the cortical topographic patterns with the following computational framework. First, for each network of interest, a connectivity density vector of dimensionality equal to the number of MUSE ROI parcellations was created based on established intrinsic functional connectivity map templates[4]. This involved estimating average functional connectivity within each MUSE ROI and vector normalization, using established intrinsic functional connectivity map templates. A ROI-based W-score feature vector was then created for each individual by averaging W-scores within each MUSE anatomical ROI parcellations. W-score feature vector was normalized, yielding a W-score density vector capturing topography of atrophy signature independent of the severity of atrophy. This is important because our aim is to assign biomarker-supported dementia sub-types, regardless of the magnitude/severity of the disease. Subject specific cortical atrophy topographic

patterns within each network of interest are illustrated using radar plots in Fig 14, for sample individuals with post-TBI dementia diagnosis and different levels of TBI severity, capturing expected heterogeneity in atrophy patterns across individuals.

Among all networks of interest, the greatest association of cortical atrophy topographic patterns with post-TBI dementia was observed within executive and auditory network while association with TBI severity was strongest within the sensory network. Furthermore, frontoparietal network presented the greatest association with cortical atrophy topographic patterns and post-TBI dementia and TBI severity interaction. These observations will be further assessed for MRI-based dementia endophenotyping.



TBI severity of 1 *TBI severity of 2* *TBI severity of 3*

Fig 14. Cortical atrophy topographic patterns within each network of interest for sample individuals with post-TBI dementia

1. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron.* 2009;62(1):42-52
2. Gardner RC, Boxer AL, Trujillo A, et al. Intrinsic connectivity network disruption in progressive supranuclear palsy. *Annals of neurology.* 2013;73(5):603-616.3732833
3. Suk HI, Lee SW, Shen D. Hierarchical feature representation and multimodal fusion with deep learning for AD/MCI diagnosis. *Neuroimage.* 2014;101:569-582.PMC4165842
4. Smith SM, Fox PT, Miller KL, et al. Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences.* 2009;106(31):13040-13045

- **What opportunities for training and professional development has the project provided?**
  - *Keynote presentation at Artificial Intelligence in NMR, MRI and Neuroscience, Gruppo Italian Discussione Risonanze Magnetiche (GIDRM), Jan 2021*
  - *Invited lecture at Advanced epidemiology course on dementia prevention, Imperial College, Sep 2021*
- **How were the results disseminated to communities of interest?**
  - *Keynote presentation at Machine Learning in Clinical Neuroimaging (MLCN / MICCAI), Oct 2020*
  - *Invited presentation at ADRC Directors Meeting, May 2021*
- **What do you plan to do during the next reporting period to accomplish the goals?**
  - We plan to direct our efforts in four areas as follows:

1. Deep Learning of Structural MRI Data to build prognostic models on training data;

2. Developed practical prognostic model of risk for post-TBI dementia using readily available clinical MRI

3. Objectively quantified NOI-based dementia-subtypes (MRI dementia endophenotyping)

4. Investigated vascular contributions to post-TBI dementia

- The primary goal is to use machine-learning to develop and internally validate an MRI-based algorithm for predicting 5+ year risk of post-TBI dementia.

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

- **What was the impact on the development of the principal discipline(s) of the project?**

  - When compared to data from a multicenter research neuroimaging cohort of ADNI-DoD, estimated cortical atrophy distribution from clinical brain MRIs was comparable to estimates from research MRI data despite the clinical vs research MRI quality differences as reported above. This finding has a significant impact on clinical translational value of methods developed in this project, further supporting the robust application of harmonized image processing to clinical quality MRI data.

  - Among all networks of interest, the greatest association of cortical atrophy topographic patterns with post-TBI dementia was observed within executive and auditory network while association with TBI severity was strongest within the sensory network. Furthermore, frontoparietal network presented the greatest association with cortical atrophy topographic patterns and post-TBI dementia and TBI severity interaction. These observations will be further assessed for MRI-based dementia endophenotyping.

- **What was the impact on other disciplines?**

  - *Nothing to Report.*

- **What was the impact on technology transfer?**

  - *Nothing to Report.*

- **What was the impact on society beyond science and technology?**

  - *"Nothing to Report."*

5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

  - *Nothing to Report.*

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  - Shelter-in-place order due to Covid-19 pandemic has been in effect in San Francisco since March 13th 2020. Since then, the research team has been practicing social

distancing and working remotely from home via VPN and Citrix connections. We expect that the pandemic is likely to have effects on research team members' academic performance and productivity during this period and upcoming months. We also recognize that the disruptions of shelter-in-place ordinances, both direct (e.g., an inability to access laboratories, etc.) and indirect (e.g., childcare issues, a need to devote time to adjust to remote work), will have an impact on our productivity. Although, we have been working on this project as outlined in the approved SOW table, the extend of the disruptions remains unclear.

- **Changes that had a significant impact on expenditures**
    - Due to a Covid-19 pandemic related research shut-down both at SFVAMC and UCSF, recruit of a data scientist had been delayed. We were delayed in initiating spending. Therefore, the expenditures for this period is lower than originally proposed. The project and spending are now on track and we plan to complete the project as originally designed.
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
    - Not applicable.
- **Significant changes in use or care of human subjects**
    - Not applicable.
- **Significant changes in use or care of vertebrate animals**
    - Not applicable.
- **Significant changes in use of biohazards and/or select agents**
    - Not applicable.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award
    - **Journal publications.** Nothing to Report.
    - **Books or other non-periodical, one-time publications.** Nothing to Report.
    - **Other publications, conference papers, and presentations.** Nothing to Report.
- **Website(s) or other Internet site(s)**
    - *Nothing to Report.*
- **Technologies or techniques**.
    - Nothing to Report.
- **Inventions, patent applications, and/or licenses**
    - Nothing to Report.

- **Other Products**
    - Nothing to Report.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

Name:	Duygu Tosun-Turgut
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	ORCID ID 0000-0001-8644-7724
Nearest person month worked:	1.47
Contribution to Project:	Dr. Tosun-Turgut is the contact Principal Investigator and oversees all aspects of the project.

Name:	Kristine Yaffe
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	KYAFFE
Nearest person month worked:	0.6
Contribution to Project:	Dr. Yaffe is Co-Principal Investigator. In coordination with Dr. Tosun-Turgut, provides scientific leadership and input on the analyses and interpretation of results

Name:	Raquel Gardner
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	ORCID ID 0000-0003-4028-440X
Nearest person month worked:	1.8
Contribution to Project:	Dr. Gardner is Co-Principal Investigator. In coordination with Dr. Tosun-Turgut, provides scientific leadership and input on the analyses and interpretation of results

Name:	W. John Boscardin
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	N/A

Nearest person month worked:	0.6
Contribution to Project:	Dr. Boscardin is Co-Investigator. In coordination with Dr. Tosun-Turgut, provides scientific leadership and input on the analyses and interpretation of results

Name:	Alison Myoraku
Project Role:	Staff Research Associate
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	3.12
Contribution to Project:	Ms. Myoraku works on dataset creation and management.
Name:	Alison Myoraku

Name:	Feng Xia
Project Role:	Epi Programmer
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1.2
Contribution to Project:	Responsible for management of all VHA non-imaging data.

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
    - In the appendix, please find the Other Support of the PI and all senior/ key personnel.
- **What other organizations were involved as partners?**
    - *"Nothing to Report."*

8. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:** *For collaborative awards, independent reports are required from **BOTH** the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to https://ebrap.org for each unique award.*
- **QUAD CHARTS:** *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. **APPENDICES:**

- PI & Key Personnel Other Support

Neuroimaging Endophenotypes and Predictors of Post-Traumatic Brain Injury Dementia in a Nationwide Cohort of Veterans

#E00952.1a Yr 2 Annual Report
W81XWH-19-1-0669

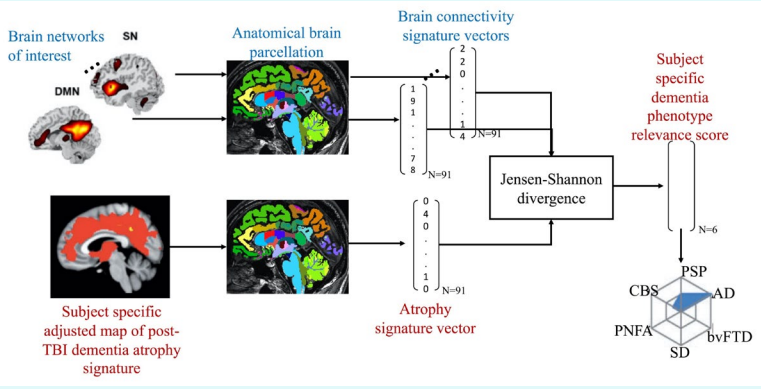
PI: Tosun-Turgut **Org:** Northern California Institute for Research (NCIRE) **Award Amount:**$1,299,638.00

Study/Product Aim(s)

A1: To create a large, nationwide, high-quality cohort of TBI-exposed and unexposed veterans with MRI imaging data.
A2: To use machine-learning to develop and internally validate an MRI-based algorithm for predicting 5+ year risk of post-TBI dementia.
A3a: Identify TBI-associated patterns of atrophy within previously established neurodegenerative disease-specific neural networks (a proxy for clinical dementia sub-types)
A3b: Identify TBI-associated burden and distribution of WM disease.

Approach

The propose a 3-year project will cost-efficiently harness the newly available wealth of nationwide clinical neuroimaging data and merge with our existing cohort of TBI-exposed and unexposed veterans with up to 12 years of follow-up in order to (1) predict which TBI-exposed veterans will go on to develop dementia and (2) identify prevalence of specific sub-types of dementia among TBI-exposed versus unexposed veterans.



Subject stratification to network-based neurodegeneration sub-types of post TBI-dementia by quantifying topographic similarity between dementia atrophy signature and networks of interest implied in related neurodegenerative diseases.

Accomplishment: Curated a large, nationwide, cohort of TBI-exposed and unexposed veterans with MRI data; Showed robust application of harmonized image processing to clinical MRIs to estimate metrics of neurodegeneration, Build dementia phenotype relevance scores

Timeline and Cost

Activities CY	2019	2020	2021	2022
Institutional approval				
Clinical and MRI data curation				
Prognostic model of risk for post-TBI dementia				
MRI endophenotyping				
Vascular contributions				
Estimated Budget ($K)	132	458	440	260

Updated: 11 October 2021

Goals/Milestones

CY19 Goal – Institutional approval
☑ Obtain local and HRPO IRB approval
CY20 Goals – Clinical and MRI Data curation
☑ Identify veterans diagnosed with TBI in the VHA system
☑ Retrieve MRI data via PACS-AIR
☑ Sort/clean MRI data at research DICOM database
CY21 Goal – Develop prognostic model of risk for post-TBI dementia
☑ Machine Learning of structural MRI data (*in progress for further development*)
☑ Build prognostic models on training data (*in progress for further development*)
☑ MRI dementia endophenotyping (*in progress for further development*)
CY22 Goal – Vascular contributions
☐ Generate white matter lesion frequency maps

Comments/Challenges/Issues/Concerns

- Nothing to report

Budget Expenditure to Date
Projected Expenditure: $857,455
Actual Expenditure: $277,578

RPPR OTHER SUPPORT

TOSUN-TURGUT, D.

ACTIVE

5U19AG024904-15 (Weiner) 09/15/16-07/31/22 0.60 CM
NIH $46,780,250
Alzheimer's Disease Neuroimaging Initiative 3
The Alzheimer's Disease Neuroimaging Initiative is a large multisite public private partnership that will validate brain imaging, blood tests, and other diagnostics. The overall goal is to discover, standardize, and validate biomarkers for AD clinical treatment trials.

5R01AG058676-03 (PI: Masters) 09/30/18-05/31/23 0.60 CM
NIH $3,646,420
Investigating Alzheimer's dementia onset and progression in international Cohorts
The overall goal of this project is to leverage the power of five leading well characterized Alzheimer's cohorts to clarify risk and protective factors for Alzheimer's disease and related dementias. This application will establish and validate the impact of demographics, genotype and comorbidities on the onset and progression rates of Alzheimer's dementia. This work will enable us to establish and validate hazard scores for disease onset and severity using clinical markers across the domains of cognition, neuroimaging, and biomarkers. The datasets of these cohorts will be combined to enable an improved understanding of the risk and protective factors for Alzheimer's dementia.

W81XWH1910669 (PI: Tosun-Turgut/Gardner/Yaffe) 09/01/19-08/31/22 1.44 CM
DOD $847,774
Neuroimaging Endophenotypes and Predictors of Post-Traumatic Brain Injury Dementia in A Nationwide Cohort of Veterans
The proposed 3-year project will cost-efficiently harness the newly available wealth of nationwide clinical neuroimaging data and merge with our existing cohort of 1.6 million TBI-exposed and unexposed veterans with up to 12 years of follow-up in order to (1) create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data; (2) predict which TBI-exposed veterans will go on to develop dementia; and (3) identify prevalence of specific sub-types of dementia among TBI-exposed versus unexposed veterans. We expect that we will (1) produce the largest military-relevant MRI dataset with expertly curated TBI exposure and dementia outcome and up to 12 years of follow-up (with option of continued follow-up via VHA EMR); (2) develop a method for predicting 5+-year risk of post-TBI dementia using routinely collected clinical MRI. This work may directly inform clinical care of veterans and identify a high-risk subset that may be ideal for further studies of underlying mechanisms of post-TBI dementia and clinical trials for prevention; and (2) facilitate discovery of the nationwide epidemiology of neuroimaging biomarker-supported dementia sub-types in TBI-exposed versus unexposed veterans receiving care within VHA. This work may directly inform public health planning within the DoD and VHA and generate testable hypotheses regarding underlying etiology of post-TBI dementia.

U01AG068057 (Thompson/Shen/Davatzikos/Saykin/Huang) 08/01/20-07/31/25 0.90 CM
NIH/USC Subcontract $99,566
Ultrascale Machine Learning to Empower Discovery in Alzheimer's Disease Biobanks

The goal of this proposal is to develop transformative AI approaches for high throughput analysis of next generation sequencing (NGS) and related AD biomarker and cognitive data. Our collective effort in this proposal will sieve extensive genomic, biomarker, and cognitive data to extract and prioritize the features that are essential to address fundamental barriers to AD prevention and drug discovery.

R01MH115020-01 (PI: Neylan; Role: Co-Investigator) 01/01/2019-10/31/23 1.20 CM
NIH $2,810,877
Individual Variation in Effects of Traumatic Stress on Gray Matter Myelin
The project will test the hypothesis that maladaptive myelin development in response to traumatic stress is a critical mechanism in the brain's response to trauma. The project involves both animal and human subjects and helps fill key gaps in our understanding of how trauma adversely impacts the brain.

U19AR076737 (Lotz); Sub PI: Strigo 10/01/19 – 09/30/24 2.40 CM
NIH-NIAMS $1,543,551
UCSF Core Center for Patient-centric Mechanistic Phenotyping in Chronic Low Back Pain (UCSF REACH"
The major goal of this project is to define chronic low back pain (cLBP) phenotypes and pain mechanisms that can lead to effective, personalized treatments for patients across the population.

RF1AG062196 (Raj) 03/01/2019 – 12/31/2023 0.90 CM
NIH $472,391
Network Modelling of Multimodal Dynamics in Alzheimer's Disease and Dementia
The major goals of this project are to learn, test and apply biophysical models of networked spread in AD.

COMPLETED IN THE LAST THREE YEARS

A129485 (PI: Grinberg) 07/01/17-06/30/20
BrightFocus Foundation $300,000
Diagnosing and monitoring prodromal Alzheimer's Disease (AD) using novel locus ceruleus-based imaging volumetry
The main goal of this project is to advance the technological platform by introducing ultra-high field 7T MR, and comparing it directly with lower field-strength 3T MR, which is more widely used for clinical MR.

P50 AG23501 (PI: Miller) 03/31/14-03/31/19
NIH/NIA $10,257,645
New Approaches to Dementia Heterogeneity: Alzheimer's Disease Research Centers, Core F
The main goal of this project is to integrate science and clinical resources to investigate Alzheimer's disease (AD), non-AD dementias, and mild cognitive impairment.

W81XWH-12-2-0012 (Weiner) 02/21/12-09/29/19
DOD $6,000,000
Effects of Traumatic Brain Injury (TBI) and Post Traumatic Stress Disorder (PTSD) on Alzheimer's Disease (AD) in Veterans Using Imaging and Biomarkers in the AD Neuroimaging Initiative (ADNI)
This study will provide novel data to test the hypothesis that Combat associated TBI and/or PTSD increase the risk for AD, and decrease cognitive reserve, determined with imaging/biomarkers, in Veteran subjects, after accounting for age and APOE genotype.

R01 NS092802 (PI: Tosun-Turgut/Raj) 07/15/16 – 04/30/21

NIH $182,970

Predictive Model Spread of Parkinson's Pathology Using Network Diffusion

The overarching goal of this project is to develop an imaging-based prognostic computational biomarker of Parkinson's disease (PD), based on the idea that PD pathology propagates along fiber tracts, and hence its progression and topography can be captured using mathematical models of networks spread.

W81XWH-14-1-0462 (Weiner; Role: Co-Investigator) 09/22/14-09/21/21 (NCE)

DOD $5,281,404

Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder and Alzheimer's Disease on Brain Tau in Vietnam Veterans using ADNI

The overall goal of this project is to determine the effects of prior traumatic brain injury (TBI), and ongoing post-traumatic stress disorder (PTSD) on brain tau, and the longitudinal change of brain tau, measured with the tau specific ligand [18F]-T807 and positron emission tomography (PET) scanning.

OVERLAP:

There is no scientific or budgetary overlap amongst the projects listed above.

OTHER SUPPORT

Dr. Gardner has a 100% appointment with University of California, San Francisco. Dr. Gardner has a 1/8th (12.5%) appointment at the SFVAMC. Her combined effort may not exceed 150%.

University of California, San Francisco – Associate Professor – 100% appointment

GARDNER, RAQUEL

ACTIVE

Title of the Project: *Transforming Research and Clinical Knowledge in Geriatric Traumatic Brain Injury (TRACK-GERI)*
Grant number: R01NS110944-01
Principal Investigator: Gardner
Time commitment: 3.7 calendar months
Supporting Agency: NIH Center for Scientific Review
Grants Management Specialist: Yvonne C. Talley; talleyy@mail.nih.gov
Performance Period: 09/01/2019 – 05/31/2024
Level of Funding: $162,000 direct/yr
Projects Goals: The goals of this career development award are to assemble a new prospective longitudinal cohort study of acute geriatric traumatic brain injury (TBI) that will establish the natural history and neuropathology, identify age-appropriate blood-based biomarkers, and develop an optimized set of tools for capturing geriatric TBI predictors and outcomes for use in large-scale geriatric TBI clinical trials.
Specific Aims: **Aim 1**: Assemble a prospective cohort of patients age ≥65y presenting to the Emergency Department ≤72h after TBI who underwent CT. Enroll 270 TBI patient/study-partner dyads and 90 controls; perform baseline assessments and blood draws, and assess longitudinal outcomes at 2wk, 3mo, 6mo (primary endpoint) and 12mo; offer enrollment in a brain donation program. **Aim 2:** Develop and validate optimized geriatric TBI predictor and outcome assessments: 2a: Systematically measure apolipoprotein E allele and pre-injury comorbidities/polypharmacy, physical frailty, and multi-domain functional status via detailed patient and study partner interviews using validated geriatric instruments and assess association of these predictors with outcome after TBI. 2b: Describe the natural history of geriatric TBI using validated TBI and geriatric outcomes and then use data-driven analytics to identify the most parsimonious set of measures for longitudinal outcome assessment in this population. 2c (exploratory): Measure pre-injury brain structure (atrophy/white matter disease of uninjured brain visualized on baseline CT) and explore association with outcome after TBI. **Aim 3:** Identify age-appropriate diagnostic and prognostic blood-based biomarkers. This work will directly inform design of large-scale age-appropriate geriatric TBI clinical trials that are urgently needed to improve care and outcomes in this vulnerable population.
Role: PI
Project Overlap: None

Title: A Novel Visually Graded CT Biomarker of Preinjury Brain Structure to Improve Prediction of Cognitive Decline After Mild Traumatic Brain Injury
Grant number*: W81XWH-18-1-0514*
Principal investigator: Gardner
Time Commitment: 3.0 calendar months
Supporting agency: Dept of Defense (DoD)
Performance period: 09/30/2018 - 09/29/2021
Level of funding: $34,138 direct/yr
Project Goals: The overarching goal of this project center is to determine if evaluation of preinjury brain structure can identify heterogeneity in preinjury brain health that directly contributes to heterogeneity in cognitive recovery after mild traumatic brain injury.
Specific Aims: 1) To develop and internally validate a practical prognostic model using only TBI common data elements (CDEs) that are routinely collected in the acute trauma setting. 2) To develop and validate the PBS score in the same cohort of well-characterized adults with mTBI and to determine whether PBS score independently predicts cognitive function and cognitive decline 1 year after mTBI. 3) To determine whether the PBS score improves the prognostic value of the model developed in Aim 1 and to create a

final, optimized, open-access, Web-based clinical risk calculator appropriate for use in an acute trauma setting to predict cognitive decline 1 year after mTBI in individual patients.
Role: PI
Project Overlap: None

Title: Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC): Epidemiological Study
***Grant number**:* W81XWH-18-PH/TBIRP-LIMBIC
Principal investigator: Yaffe
Time Commitment: 1.8 calendar months
Supporting agency: Dept of Defense (DoD)
Performance period: 09/30/2019 - 09/29/2024
Level of funding: $34,138 direct/
yr
Project Goals: The goal of this project is to leverage a large nationwide cohort of TBI-exposed veterans and the latest machine learning techniques to understand the phenotype and neuropathology of post-TBI dementia.
Specific Aims: Aim 1: To create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data. Aim 2: To use machine-learning to develop and internally validate an MRI-based algorithm for predicting 5+ year risk of post-TBI dementia in all veterans nationwide with a diagnosis of TBI and a MRI as well as specifically among those with mild TBI. Aim 3: To compare neuroimaging features on structural MRI in veterans with post-TBI dementia versus those with dementia without preceding TBI. Specifically, we will identify: TBI-associated patterns of atrophy within previously established neurodegenerative disease-specific neural networks (a proxy for clinical dementia sub-types), and TBI-associated burden and distribution of white matter disease.
Project Role: Co-PI
Project Overlap: None

Title: Neuroimaging Endophenotypes and Predictors of Post-Traumatic Brain Injury Dementia in a Nationwide Cohort of Veterans
***Grant number**: Pending* W81XWH-19-1-0669, AZ180117
Principal investigator: Tosun-Turgut/Gardner/Yaffe
Time Commitment: 1.80 calendar months
Supporting agency: Dept of Defense (DoD)
Performance period: 09/01/2019-08/31/2022
Level of funding: $1,299,638 direct/yr
Project Goals: The proposed 3-year project will cost-efficiently harness the newly available wealth of nationwide clinical neuroimaging data and merge with our existing cohort of 1.6 million TBI-exposed and unexposed veterans with up to 12 years of follow-up in order to (1) create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data; (2) predict which TBI-exposed veterans will go on to develop dementia; and (3) identify prevalence of specific sub-types of dementia among TBI-exposed versus unexposed veterans. We expect that we will (1) produce the largest military-relevant MRI dataset with expertly curated TBI exposure and dementia outcome and up to 12 years of follow-up (with option of continued follow-up via VHA EMR); (2) develop a method for predicting 5+-year risk of post-TBI dementia using routinely collected clinical MRI. This work may directly inform clinical care of veterans and identify a high-risk subset that may be ideal for further studies of underlying mechanisms of post-TBI dementia and clinical trials for prevention; and (2) facilitate discovery of the nationwide epidemiology of neuroimaging biomarker-supported dementia sub-types in TBI-exposed versus unexposed veterans receiving care within VHA. This work may directly inform public health planning within the DoD and VHA and generate testable hypotheses regarding underlying etiology of post-TBI dementia.
Specific Aims: 1) To create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data. 2) To use machine-learning to develop and internally validate an MRI-based algorithm for predicting 5+ year risk of post-TBI dementia in all veterans nationwide with a diagnosis of TBI and an MRI available for analysis (N>70,000) as well as specifically among those with mild TBI (N>33,000). 3) To compare neuroimaging features on structural MRI in veterans with post-TBI dementia (N=3,677) versus those with dementia without preceding TBI (N=8,435). Specifically, we will identify:

a. TBI-associated patterns of atrophy within previously established neurodegenerative disease-
+1.specific neural networks (a proxy for clinical dementia sub-types), and

b. TBI-associated burden and distribution of white matter disease.

Project Role: Co-PI
Project Overlap: None

Title: New Approaches to Dementia Heterogeneity in Veterans
Grant Number: UCSF ADRC (P30-AG062422) Supplement
PI: Bruce Miller
Time Commitment: 1.2 calendar months
Supporting agency: NIH
Grants Management Specialist Jennifer Edwards; edwardsj@mail.nih.gov
Performance Period: 10/01/20-09/30/21
Level of funding: $13,502 directs/yr
Project Goals: Identify and implement effective and sustainable strategies to increase recruitment and retention of Veterans in the UCSF Alzheimer's Disease Research Center (ADRC), to improve efficient technology-based characterization of military-relevant risk factors for dementia, to expand the deep phenotyping performed at our ADRC to individuals at high risk of vascular contributions to cognitive impairment and dementia (VCID), to measure novel biomarkers of vascular cognitive impairment and dementia, and to provide rigorous training opportunities in Veteran-focused research.
Specific Aims:
Aim 1: Explore the heterogeneous features of healthy aging, MCI, AD, FTD-spectrum disorders, and CJD *in Veterans* to better understand their clinical, genetic, and molecular underpinnings.
Aim 2: Leverage the valuable ADRC cohorts and the talented neuroscience communities at UCSF, *the SFVAMC*, and beyond to "enhance the performance of innovative research" around diagnosis and treatment of dementia.
Aim 3: Increase understanding of the unique cultural and biological features of aging Chinese and Latino Americans *and U.S. Military Veterans*, while educating these communities with outreach lectures and web-based presentations.
Aim 4: Develop innovative approaches to data management and biostatistics *– including efficient capture of military relevant risk factors –* to support easy access and analysis of ADRC-related data while offering statistical support to our investigators.
Aim 5: Train new leaders in dementia research *including unique considerations for successful research on veterans*. with innovative education approaches and educate medical and lay communities about the heterogeneity of dementia with conferences, web-based presentations, and films.
Aim 6: Create a new Biomarker Core to enhance the genomic, proteomic, and transcriptomic data captured from our extensive biospecimen collection*, including targeted collection in veterans and expanded focus on biomarkers of vascular contributions to cognitive impairment and dementia.*
Aim 7: Transition to a more gender and ethnically diverse ADRC leadership by 2024.
Project Role: Co-Investigator
Project Overlap: None

PENDING:

Title: Long-Term Vascular-Related Cognitive Decline after Traumatic Brain Injury (PI: Schneider)
Time Commitment: 1.8 calendar-months (15% effort)
Funding Agency: DoD/USAMRAA - AZ200044
Point of Contact at Funding Agency: Nicholas Heroux
Performance Period: Estimated 09/01/2021 – 8/31/2024
Level of Funding: $500,000
Goals of Project: The overall objective of this study is to use rigorously developed sophisticated biostatistical and epidemiological methods that account for study attrition to model cognitive trajectories assessed at multiple time-points over 5 years of follow-up and to determine if individuals with TBI and vascular risk factors have less cognitive recovery in the first year post-TBI and have greater cognitive decline over years 1-5 post-TBI compared to individuals with comparable TBI without vascular risk factors and to controls.
Specific Aims:
Aim 1: To collaboratively use cutting-edge, rigorous, biostatistical and epidemiological methods to generate 5-years of analysis-ready cognitive trajectory models that account for study attrition.
Aim 2: To investigate if vascular risk factors are associated with unfavorable cognitive outcomes after TBI.

Aim 3: To evaluate if markers of modifiable vascular risk severity are associated with unfavorable cognitive outcomes after TBI.
Overlap: Current project

Title: Modular Design-Accelerated Development of Minimally Invasive Dried Plasma and Saliva Tests for Detecting TBI Sequelae for AD Dementia
Grant number*:* P0547961
Principal investigator: Gardner
Time Commitment: 0.60 calendar months
Supporting agency: Dept of Defense (DoD), Gryphon Bio, Inc. (GRYNPHONBIO)
Performance period: 09/01/2021 - 08/31/2025
Level of funding: $88,213.0/yr
Project Goals: to identify novel minimally-invasive blood-based biomarkers of post-TBI cognitive decline and Alzheimer's dementia across the spectrum of age and time since injury
Specific Aims:
Aim 1: Operationalize a TBI Patient Type Module with multiple sites
Aim 2: Develop an adaptive post-TBI cognitive decline module.
Aim 3: Simplify biofluid sampling procedure within the biofluid sampling module.
Aim 4: Identify and verify dried plasma/saliva-based detection of putative protein and miRNA biomarkers
Aim 5: Optimize a multiplexing method in the Diagnostic Assay Platform Module.
Aim 6: Apply an adaptive modular assembly principle to identify one or more TBI-AD/ADRD test assemblies that are optimized to address the different post-TBI cognitive phenotypes at risk for developing AD dementia. Develop an adaptive Post-TBI-Cognitive Decline Module
Project Role: Co-PI
Project Overlap: None

INACTIVE:
Title of the Project: *Traumatic Brain Injury and the Aging Brain: Predictors of Clinical Trajectories*
Grant number: K23NS095755
Principal Investigator: Gardner
Time commitment: 6.00 calendar months
Supporting Agency: NIH/National Institute of Neurological Disorders and Stroke
Grants Management Specialist: Yvonne C. Talley; talleyy@mail.nih.gov
Performance Period: 07/01/2015 – 08/31/2020
Level of Funding: $162,000 direct/yr
Projects Goals: The goals of this career development award are to provide protected time and dedicated training for the PI to study the effects of traumatic brain injury (TBI) on the aging brain. The PI's long-term career goal is to become a leader in TBI and brain aging research with a focus on clinical predictors and mechanisms of post-TBI neurodegeneration. The specific long-term goal of this research program would be to uncover novel targets for treatment and prevention of post-TBI cognitive, behavioral, motor, and functional decline in high-risk, vulnerable, aging adults. Training goals include (1) advanced training in research methods and biostatistics, (2) advanced training in epidemiology of aging with a focus on inter-disciplinary neurological and geriatric predictors and outcomes, and (3) TBI-focused research. The scientific goals of this project are to describe multi-domain clinical trajectories after acute and remote traumatic brain injury in older adults and also to define clinical predictors of these trajectories.
Specific Aims: (1) to define detailed clinical trajectories and predictors of trajectories after *acute* TBI in older adults, (2) to define detailed clinical trajectories and predictors of trajectories after *remote* TBI in older adults.
Project Overlap: None

OVERLAP
If Dr. Gardner, U.Penn sub is award, she will reduce her effort on the Dod.

San Francisco Veterans Affairs Medical Center, Staff Physician, 12.5% appointment

ACTIVE
None

PENDING:

Title: *Transforming Research and Clinical Knowledge in Older Veterans with Acute Traumatic Brain Injury (TRACK-VA)*
Grant Number: CX002346-01 (CSRD Merit)
Principal Investigator: Gardner
Time commitment: 4.5 calendar months.
Supporting Agency: Department of Veterans Affairs
Grants Management Specialist: Rebecca Yu; rebecca.yu@va.gov
Performance Period: 09/2021 - 08/2022
Level of Funding: $300,000 direct/year
Projects Goals:. This project will focus on two VA Clinical Science Research and Development priority research areas: (1) traumatic brain injury (TBI) diagnosis and (2) diseases with a high healthcare burden in Veterans. Over the 4-year timeline of this project, it is expected that the total number of acute TBIs sustained by older Veterans residing in the U.S. (N>520,000) will exceed the total number of TBIs sustained by active duty service members in the past 20 years (N=413,858). Geriatric TBI is a massive epidemic within Veterans Health Administration (VHA) with high associated morbidity, mortality, and cost. Yet, acute geriatric TBI has never been prospectively studied by VHA. This pioneering project will comprehensively characterize baseline and longitudinal endophenotypes of older Veterans presenting with acute TBI to our VA. Findings will inform precision medicine approaches to age-appropriate diagnosis, treatment, and disease-monitoring that are urgently needed to improve outcomes in this large and burdened population of Veterans.
Specific Aims:
Aim 1: Characterize baseline and 12-mo longitudinal clinical features using TBI Common Data Elements (CDEs) among Veterans age ≥65y who enrolled in the TRACK-TBI study with acute TBI.
Aim 2: Assemble a new prospective cohort of Veterans age ≥65y presenting to SFVA ED ≤72h after TBI who received CT ("TRACK-VA") and deeply phenotype clinical and biological features over 12-months using TBI CDEs.
Aim 3: Characterize neuroimaging features of acute geriatric TBI in Veterans using TBI CDEs and quantitative structural and functional MRI.
Aim 4: Determine accuracy of blood-based GFAP, p-tau, abeta, and NFL for TBI diagnosis, outcome prediction, and disease-monitoring in older Veterans.
Project Overlap: None

INACTIVE
None

OVERLAP
None. SFVA received the notice of award for Dr. Gardner's Merit Review Grant on 07/23/21. Dr. Gardner has requested a 5/8th appointment waiver so that combined UCSF + VA effort will not exceed 150% when the Merit is awarded.

Aim 4: Develop prognostic models to determine which Veterans decline versus sustain/improve after mTBI
Role: PI

U24AG065204 (Yaffe/Van der Willik/Gill/Watson) 09/19 – 04/24 1% (0.12 cal mos)
NIH: National Institute on Aging $4,594,015 TDC
Clin-STAR Coordinating Center
Goals: The goal of this project is to build a robust, multi-faceted and highly-networked national platform for clinician-scientists in aging research from diverse disciplines across the US.
Aim 1: To develop an organizational structure that will facilitate the exchange and dissemination of scientific and research knowledge on aging and the care of older persons.
Aim 2: To provide mentoring and career development support for emerging investigators committed to pursuing aging research in their clinical discipline
Aim 3: To stimulate aging research, foster networking and collaborations across disciplines, and identify and support high priority and understudied areas of aging research.
Aim 4: To develop and implement strategies for assessing the effectiveness of the Clin-STAR program and to use this information to guide future directions and report outcomes to stakeholders.
Role: Multiple- PI

R01AG063887 (Yaffe/Sidney) 9/19 – 5/23 6% (0.72 cal mos)
NIH: National Institute on Aging $3,090,949 TDC
Lifecourse CVD Risk and Midlife Cognitive Trajectories and Brain Aging: Implications for Alzheimer's and Dementia Prevention
Goals: The goal of the project is to determine the cardiovascular risk factors for cognitive aging in the mid to late-life transition and to investigate how these are related to structural brain changes.
Aim 1: To determine the independent associations of 10-year midlife cognitive decline with timing, level and trend in CVD risk factors including body mass index, blood pressure, and fasting glucose, assessed over 35 years from early adulthood to midlife.
Aim 2: To determine the association of 10-year midlife cognitive decline with subclinical CVD markers (over 10-25 years) including carotid artery intima thickness, coronary artery calcification and cardiac function.
Aim 3: To determine whether CVD risk factors and subclinical CVD markers are associated with brain aging indices in midlife, derived by the application of machine-learning neuroimaging pattern analysis to brain MRI and diffusion tensor imaging data obtained on nearly 700 CARDIA participants at Year 30.
Role: Multiple-PI

R01AG066137 (Yaffe/O'Bryant) 09/19 – 06/24 4% (0.48 cal mos)
NIH: National Institute on Aging $4,313,915 TDC
Sleep Quality and Mechanistic Links to Alzheimer Disease and Related Disorders among older Mexican Americans and Non-Hispanic Whites (HABLE Dormir)
Goals: The goal of this project is to investigate the relationship between sleep quality/disorders and Alzheimer's disease and related dementias in older Mexican American and Non-Hispanic Whites.
Aim 1: To characterize objective and subjective sleep quality among older MAs and NHWs across the cognitive spectrum.
Aim 2: To examine the association of sleep quality with cognitive function and 2-3 year cognitive decline across the spectrum of baseline cognitive status.
Aim 3: To assess the association between sleep quality and vascular and inflammatory pathways to ADRD.
Aim 4: To investigate the association between sleep quality and a neurodegeneration pathway to ADRD.
Role: Multiple-PI.

(Multiple PI: Yaffe/O'Bryant) 09/17 – 05/22 1% (0.12 cal mos)
NIH: National Institute on Aging $12,317,460 TDC
Nina Silverberg, Program Officer

Other Support

YAFFE, KRISTINE

Dr. Yaffe has a 100% appointment with University of California, San Francisco and a 4/8th appointment at the SFVAMC.

PREVIOUS (Past 5 years)

W81XWH-16-0507 (Yaffe) 08/16 – 08/20 1% (0.12 cal mos)
Department of Army $419,245 TDC
Anthony Pacifico, Science Officer
820 Chandler Street, Fort Detrick, MD 21702-5014
Risk and Resiliency for Dementia: Comparison of Male and Female Veterans (WAVE)
Goals: The goal of this project is to identify factors that are associated with risk and resiliency for cognitive impairment and dementia in older Veterans and determine how they differ by gender.
Aim 1: We will compare age-standardized prevalence rates of mild cognitive impairment and dementia among older male and female Veterans receiving VHA healthcare and identify key health-related risk factors for developing cognitive impairment.
Aim 2: We will examine the associations and magnitude of effect between key military related factors and diagnoses of mild cognitive impairment and dementia among older female and male Veterans.
Aim 3: We will determine whether the risk of nursing home placement and mortality differs between older female and male Veterans with a documented diagnosis of dementia, and examine whether there are gender specific associations between military and health-related factors and nursing home placement and mortality.
Role: PI

2P01 AG019724 (Miller/Yaffe) 06/12 – 05/17 1% (0.12 cal mos)
NIH: National Institute on Aging $663,642 TDC (Core)
John Hsiao, Director, Diagnosis and Biomarkers Program, Dementias of Aging Branch
31 Center Drive, MSC 2292, Bethesda, MD 20892
Frontotemporal Dementia: Genes, Images, and Emotions: Data Management and Biostatistics Core
Goals: The goal of this program project is to test new international research criteria for frontotemporal dementia and to determine the value of imaging and biomarkers for diagnosis.
Aim 1: To develop and maintain centralized, integrated data management systems and procedures that ensure the accuracy, availability, and confidentiality of administrative, clinical, and research data from PPG cores and projects.
Aim 2: To provide high-quality biostatistical consultation to all PPG cores and projects in order to systematically unify and focus research design and statistical analysis.
Aim 3: To promote research methods integration and collaboration among PPG cores, projects, and related research protocols through efficient data sharing, coordinated data analysis plans, and regular meetings to discuss research process and data integration.
Role: Dr. Yaffe is the PI of the Data Management and Biostatistics Core

5R01 DK069406 (Multiple PI: Yaffe/Kurella) 09/11-05/17 14% (1.68 cal mos)
NIH: NIDDK $2,867,726 TDC
John Kusek, Program Director, Division of Kidney, Urologic and Hematologic Diseases, NIDDK
6707 Democracy Boulevard, MSC 5450, Bethesda, MD 20892-5450
Cognitive Decline in Chronic Renal Insufficiency
Goals: The goal of this project (a competitive renewal of R01-DK069406) is to investigate cognitive trajectories of individuals transitioning from CKD to ESRD.
Aim 1: To determine the long-term trajectory of cognitive function in adults with CKD.
Aim 2: To determine the clinical significance of cognitive decline among adults with CKD by evaluating its association with CKD management strategies and geriatric outcomes.
Aim 3: To characterize the trajectory of cognitive function during the transition from advanced CKD to ESRD.

Aim 4: To determine if several novel biomarkers associated with CKD and aging may also predict cognitive decline, thereby informing about mechanisms linking these disorders.
Role: Multiple-PI

R01 AG005407 (Multiple PI: Yaffe/Cummings) Yrs26-30 09/11 – 05/18 2% (0.24 cal mos)
NIH: National Institute on Aging $3,706,144 TDC
Sherry Sherman, Project Officer
31 Center Drive, MSC 2292, Bethesda, MD 20892
Study of Osteoporotic Fractures
Goals: The goal of this multicenter prospective study is to investigate aging outcomes.
Aim 1: Determine the association of age-related parameter trajectories with longevity and active lifespan in older women.
Aim 2: Determine the association of age-related parameter trajectories with exceptional healthspan in older women.
Aim 3: Among older women, determine the association of age-related parameter trajectories with inpatient and residential health care use. 4. Sustain and actively use the extensive SOF biologic repository of serum, urine and DNA specimens.
Role: Multiple-PI

R01 AG026720 (Multiple PI: Stone/Yaffe) 10/12 – 03/19 1% (0.12 cal mos)
NIH: National Institute on Aging $2,068,666 TDC
Miroslaw Mackiewicz, Program Director
31 Center Drive, MSC 2292, Bethesda, MD 20892
Change in Sleep & Cognition in Older Women
Goals: The goal of this renewal is to determine the association between sleep dysfunction and cognitive impairment in a large ongoing prospective study.
Aim 1: To identify candidate -regions, -genes, and -pathways for both sleep characteristics and cognitive outcomes using recently obtained phenotypic and genome-wide genetic data from the SOF cohort.
Aim 2: To test the hypothesis that poor sleep is associated with metabolic dysfunction among older women, and that metabolic dysfunction mediates associations between poor sleep and cognitive outcomes.
Aim 3: To determine the associations of sleep characteristics (among older women with and without cognitive impairment) with incident age-related outcomes assessed every six months during 5 years of follow-up.
Role: Multiple-PI

P50 AG023501 (Miller/Yaffe) 04/14 – 03/19 1% (0.12 cal mos)
NIH: National Institute on Aging $528,482 TDC (Core)
Creighton Phelps, Deputy Director
31 Center Drive, MSC 2292, Bethesda, MD 20892
Alzheimer's Disease Research Centers: Data and Statistical Core
Goals: The goal is to integrate science and clinical resources to investigate Alzheimer's disease (AD), non-AD dementias, and mild cognitive impairment.
Aim 1: Explore the heterogeneous features of AD, FTD-spectrum disorders, and CJD in the early stages with the goal of predicting their physiological, genetic, and molecular underpinnings. This aim will be facilitated via our Clinical; Data Management and Statistical (DMS); Neuropathology, Biospecimens, and Genetics (Neuropath); Education and Imaging Cores.
Aim 2. Leverage the valuable cohorts in the ADRC and the powerful neuroscience community at UCSF and beyond to stimulate new diagnostic and treatment efforts for AD, FTD and CJD. Drs. Mucke and Miller from the Administrative Core will lead the ADRC's effort for this aim.
Aim 3. Increase understanding of the unique cultural and biological features of aging Chinese-Americans with neurodegenerative disease, while educating this community with lectures and web-based presentations.
Aim 4. Develop innovative approaches to data management and biostatistics that we will share across the ADRC infrastructure and will use to better understand our own cohorts. The DMS will accomplish these aims.
Aim 5. The Education Core will be responsible for training new dementia leaders, while educating the medical and lay communities regarding the non-AD dementias and non-amnestic subtypes of AD with conferences and web-based presentations.
Role: PI of Data and Statistical Core C

W81XWH-12-PHTBI-CENC 02/15-09/19 12% (1.44 cal mos)
DoD/VA $2,442,885 TDC
COL Dallas Hack, Director of Combat Casualty Care Research Program/ Stuart Hoffman (VA), Scientific Program Manager for the Brain Injury Portfolio
810 Vermont Avenue, NW, Washington, DC 20420
Chronic Effects of Neurotrauma Consortium: Epidemiology Project
Goals: The goals of this study are to capitalize on a variety of existing data sources by integrating and analyzing them in novel ways to examine trajectories and neurosensory outcomes of mild traumatic brain injury (mTBI) in Veterans over time.
Aim 1: Among OEF/OIF/OND Veterans, to determine the association of mTBI and mental health disorders with adverse clinical outcomes with the goal of understanding why some Veterans with mTBI are more resilient than others.
Aim 2: Among Veterans from any era, to determine whether mTBI is independently associated with adverse neurosensory outcomes and mortality across the life course and whether treatment of comorbid conditions reduces risk.
Aim 3: Among OEF/OIF/OND Veterans with mTBI who received five or more years of VA care, we will identify trajectories of neurosensory, psychiatric, and pain comorbidity.
Role: PI

R01HL122658 (Yaffe/Sidney) 12/14 – 11/19 5% (0.60 cal mos)
NIH: NHLBI $2,608,740 TDC
Jared Reis, Program Officer
31 Center Drive, MSC 2292, Bethesda, MD 20892
Determinants of Midlife & Longitudinal Change in Cognitive Function: CARDIA Study
Goal: The goal of this project is to determine the cardiovascular, metabolic, and lifestyle risk factors for cognitive aging in midlife and to investigate how these are related to structural brain changes and genetic risk factors.
Aim 1. To determine the rate and correlates of 5-year change in cognitive function at mid-life with regard to gender, education, literacy, socio-economic status and race among approximately 3100 black and white adults.
Aim 2. Using carefully collected repeated measures over 30 years, to determine the association between cardiovascular and metabolic risk factors (such as diabetes, insulin, dyslipidemia, blood pressure, adiposity, inflammation) in young adulthood and cognitive function and its 5- year change at mid-life with consideration of whether there are “critical windows” and cumulative effects of exposure.
Aim 3: Using carefully collected repeated measures over 30 years, to determine the association between measures of “modifiable” behavioral and psychosocial risk factors (such as physical activity, diet, depression, social support) on cognitive function and 5-year change at mid-life with consideration of whether there are “critical windows” and cumulative effects of exposure.
Aim 4: To use already collected genome-wide genetic data from CARDIA to investigate the association of genetic variants, which are known to influence the cardiovascular, metabolic and behavioral risk factors (Aims 2 and 3), with cognitive outcomes and to further investigate causal associations for these risk factors.
Role: Multiple-PI

W81XWH-14-2-0176 (Yaffe) 10/14-09/19 1% (0.12 cal mos)
Department of Defense $593,534 TDC
Wendy Clevenger, Grants Officer
MRPRA CSRA
820 Chandler Street, Fort Detrick, MD 21702-0514
Blood Biomarker Profile of TBI-associated Cognitive Impairment Among Old and Young Veterans
Goals: The goal of this project is to define the biomarker profile of late-life cognitive impairment in eterans who have been exposed to TBI.
Aim 1: To establish a unique new cohort of older veterans with AD, TBI-associated CI and healthy controls living in veterans homes at two sites.
Aim 2: We will conduct a state-of-the-art study of the blood biomarker profile of TBI-associated CI compared to that of AD and normal aging
Role: PI

2013624 (Multiple PI: Yaffe/Zeki Al-Hazzouri) 06/18 - 5/20 1% (0.12 cal mos)
Alzheimer Drug Discovery Foundation $100,000 TDC
Heather Moore, Operations Contact
57 W 57th Street, Suite 904, New York, NY 10019
Connection Between Depressive Symptoms and Dementia: When Best to Intervene?
Goals: The goal of this project is to create a pooled cohort of four prospective studies to determine depressive symptoms as a risk factor for Alzheimer's disease and dementia.
Aim 1: To estimate sex and race-specific trajectories of depressive symptoms over the adult life-course.
Aim 2: To determine whether the associations between depressive symptoms and cognitive decline and risk of Alzheimer's disease and other dementias differ by the timing (e.g. young adulthood, midlife, vs. later-life) of depressive symptom exposure.
Aim 3: To determine when is best to intervene.
Role: Multiple-PI.

(Multiple PI: Yaffe/Kenney) 06/18 – 12/20 2% (0.24 cal mos)
Global Brain Health Institute $248,217 TDC
Leveraging New Data on Cognitive Aging & Dementia from Around the World
Goals: The goal of this project is to establish a platform of longitudinal aging datasets to investigate brain health.
Aim 1: To develop a platform of HRS studies for GBHI fellows to conduct research.
Aim 2: To develop methods to harness data from HRS international partner studies that will inform GBHI on dementia prevalence, risk factors and care world-wide.
Aim 3: To pilot investigate harmonized variables pertinent to novel risk factors for cognitive aging by indexing meta data from the extended HRS family of international surveys and creating key harmonized variables on demographics, physical and cognitive health, social engagement and health and social care utilization.
Aim 4: To link GBHI Fellows and Faculty to HRS and Harmonized Cognitive Assessment Protocol (HCAP) partners especially in GBHI targeted regions.
Aim 5: To foster UCSF-Trinity collaborations focused on novel risk factors and prevention strategies for dementia.
Role: Multiple-PI.

5K24 AG031155 (Yaffe) 06/13 – 6/21 NCE 25% (3.0 cal mos)
NIH: National Institute on Aging $796,095 TDC
Molly Wagster, Chief, Behavioral and Systems Neuroscience Branch
31 Center Drive, MSC 2292, Bethesda, MD 20892
Predictors of Cognitive Aging across the Lifecourse
Goals: This K24 Midcareer Investigator Award renewal is being used for aging-related patient-oriented research as well as mentorship. The goal of this project is to identify the predictors of cognitive aging and structural brain integrity across the lifecourse among a biracial cohort of adults.
Aim 1: To perform rigorous patient-based research studies in a new direction aimed at the identification of the predictors of cognitive aging and structural brain integrity across the lifecourse among biracial adults.
Aim 2. To use the applicant's research as a platform for the mentorship of patient-oriented researchers in the epidemiology of cognitive aging.
Aim 3. To enable the applicant to pursue new research directions and to continue to support her development as an internationally recognized mentor for trainees from a wide range of disciplines interested in cognitive aging.
Role: PI

CURRENT

R35AG071916 (Yaffe) 07/01 – 06/26 50% (6.0 cal mos)
NIH: National Institute on Aging $4,726,675 TDC
Cerise Elliot, Program Officer
31 Center Drive, Bethesda MD 20892
UCSF Population Based Research for Alzheimer's Innovation (POP BRAIN)

Goals: The goal of this leadership award is to create a multidisciplinary, groundbreaking research program focused on the exposome for ADRD, its effects over the life-course, and interactions with health disparities in ADRD risk. Pop-BRAIN will investigate new avenues for prevention and foster the careers of junior investigators in population health for ADRD.
No Aims
Role: PI.

1R01AG069120 (Yaffe/Bacarelli/Hou) 07/20 – 04/25 1% (0.12 cal mos)
NIH: National Institute on Aging $3,953,132 TDC
Yuan Luo, Program Officer
31 Center Drive, Bethesda MD 20892
Age-related mitochondrial DNA mutations as blood-based biomarkers of preclinical decline and structural brain changes in mid-life
Goals: The goal of the project is to identify a panel of blood-based biomarkers associated with cognitive and structural brain changes in pre-clinical stages.
Aim 1: Determine whether higher levels of mtDNA mutations and their accumulation over time are associated with greater cognitive decline in midlife.
Aim 2: Determine whether mtDNA mutations are associated with structural, physiological, and functional MRI phenotypes of preclinical ADRD as well as with sensitive MRI-based markers of accelerated brain aging and preclinical ADRD constructed by our team using contemporary machine learning techniques.
Aim 3: Test the clinical utility of these mtDNA mutation biomarkers in identifying individuals at risk of future ADRD in four older cohorts
Role: Multiple-PI.

W81XWH-18-PH/TBIRP-LIMBIC 10/19 – 09/24 6% (0.72 cal mos)
I01CX002096 $2,993,341 TDC
DoD/VA
Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC): Epidemiological Study
Goals: The goals of this study are to maintain and build upon our nearly 2 million veteran data repository and to examine neurodegenerative outcomes of mild traumatic brain injury (mTBI) in Veterans over time.
Aim 1: Maintain, augment, and refine the 1.6 million Veteran data repository of all era Veterans
Aim 2: Identify subgroups at greatest risk and resilience for mental health and neurodegenerative outcomes after mTBI
Aim 3: Examine and elucidate complex associations between mTBI and comorbidities
Aim 4: Develop prognostic models to determine which Veterans decline versus sustain/improve after mTBI
Role: PI

U24AG065204 (Yaffe/Van der Willik/Gill/Watson) 09/19 – 04/24 1% (0.12 cal mos)
NIH: National Institute on Aging $4,594,015 TDC
Clin-STAR Coordinating Center
Goals: The goal of this project is to build a robust, multi-faceted and highly-networked national platform for clinician-scientists in aging research from diverse disciplines across the US.
Aim 1: To develop an organizational structure that will facilitate the exchange and dissemination of scientific and research knowledge on aging and the care of older persons.
Aim 2: To provide mentoring and career development support for emerging investigators committed to pursuing aging research in their clinical discipline
Aim 3: To stimulate aging research, foster networking and collaborations across disciplines, and identify and support high priority and understudied areas of aging research.
Aim 4: To develop and implement strategies for assessing the effectiveness of the Clin-STAR program and to use this information to guide future directions and report outcomes to stakeholders.
Role: Multiple- PI

R01AG063887 (Yaffe/Sidney) 9/19 – 5/23 6% (0.72 cal mos)
NIH: National Institute on Aging $3,090,949 TDC
Lifecourse CVD Risk and Midlife Cognitive Trajectories and Brain Aging: Implications for Alzheimer's and Dementia Prevention

Goals: The goal of the project is to determine the cardiovascular risk factors for cognitive aging in the mid to late-life transition and to investigate how these are related to structural brain changes.
Aim 1: To determine the independent associations of 10-year midlife cognitive decline with timing, level and trend in CVD risk factors including body mass index, blood pressure, and fasting glucose, assessed over 35 years from early adulthood to midlife.
Aim 2: To determine the association of 10-year midlife cognitive decline with subclinical CVD markers (over 10-25 years) including carotid artery intima thickness, coronary artery calcification and cardiac function.
Aim 3: To determine whether CVD risk factors and subclinical CVD markers are associated with brain aging indices in midlife, derived by the application of machine-learning neuroimaging pattern analysis to brain MRI and diffusion tensor imaging data obtained on nearly 700 CARDIA participants at Year 30.
Role: Multiple-PI

R01AG066137 (Yaffe/O'Bryant) 09/19 – 06/24 4% (0.48 cal mos)
NIH: National Institute on Aging $4,313,915 TDC
Sleep Quality and Mechanistic Links to Alzheimer Disease and Related Disorders among older Mexican Americans and Non-Hispanic Whites (HABLE Dormir)
Goals: The goal of this project is to investigate the relationship between sleep quality/disorders and Alzheimer's disease and related dementias in older Mexican American and Non-Hispanic Whites.
Aim 1: To characterize objective and subjective sleep quality among older MAs and NHWs across the cognitive spectrum.
Aim 2: To examine the association of sleep quality with cognitive function and 2-3 year cognitive decline across the spectrum of baseline cognitive status.
Aim 3: To assess the association between sleep quality and vascular and inflammatory pathways to ADRD.
Aim 4: To investigate the association between sleep quality and a neurodegeneration pathway to ADRD.
Role: Multiple-PI.

(Multiple PI: Yaffe/O'Bryant) 09/17 – 05/22 1% (0.12 cal mos)
NIH: National Institute on Aging $12,317,460 TDC
Nina Silverberg, Program Officer
31 Center Drive, MSC 2292, Bethesda, MD 20892
Health Disparities in Alzheimer's Disease and Mild Cognitive Impairment among Mexican Americans (HABS-HD)
Goals: The goal of the project is to study the differential pathological mechanisms and biomarkers of MCI and AD among Mexican Americans.
Aim 1: Examine the impact of higher rates of diabetes and depressive symptomatology on MCI and AD among community-dwelling Mexican Americans.
Aim 2: Examine neuroimaging and blood-based biomarkers associate with MCI and AD among Mexican Americans.
Aim 3: Validate our blood-based AD screening tool as the first-step in a multi-stage diagnostic process among Mexican Americans.
Role: Multiple PI

R01AG057508 (Multiple PI: Yaffe/Larson) 09/17 – 11/21 4% (0.48 cal mos)
NIH: National Institute on Aging $5,984,339 TDC
Kristina McLinden, Program Officer
31 Center Drive, MSC 2292, Bethesda, MD 20892
Multi-domain Alzheimer's Risk Reduction Study (SMARRT)
Goals: The goal of this project is to conduct the first multi-domain Alzheimer's disease risk reduction intervention in a U.S. integrated healthcare system.
Aim 1: To compare the efficacy of SMARRT to Health Education (HE) for our primary outcome of one year cognitive change.
Aim 2. To compare retention rates and changes in Alzheimer's risk factors over one year in those randomized to SMARRT vs HE.
Aim 3. To gather preliminary data on the impact of SMARRT vs HE on secondary outcomes of physical performance, functional ability, quality of life and incidence of mild cognitive impairment (MCI) and Alzheimer's disease.

Role: Multiple PI

1RF1AG054443 (Yaffe/Zeki Al-Hazzouri) 05/17 – 04/22 NCE 2% (0.24 cal mos)
NIH: National Institute on Aging $1,384,845 TDC
Dallas Anderson, Program Officer
31 Center Drive, MSC 2292, Bethesda, MD 20892
Healthy Heart, Healthy Brain? A Pooled Life-course Cohort for Dementia Risk Assessment (HARMONY)
Goals: The goal of this study is to create a pooled cohort from four prospective studies to investigate cardiovascular risk factors over the lifecourse.
Aim 1: To estimate sex and race-specific trajectories of cardiovascular risk factors over the adult life-course. We hypothesize that cardiovascular burden across the life-course will be greater in blacks and will show different peak exposure times or ages in women and men.
Aim 2: To estimate the association between trajectories of cardiovascular risk factors and cognitive decline, Alzheimer disease and other dementias. We hypothesize that greater risk factor exposure as well as greater cumulative burden of exposure over the life-course will be associated with increased risk of cognitive decline, Alzheimer disease, and other dementias.
Aim 3: To determine whether the associations between exposure to cardiovascular risk factors and cognitive decline, Alzheimer disease, and other dementias differ by the timing of exposure (e.g. midlife vs. late-life). We hypothesize that young adult and midlife exposure to cardiovascular risk factors will be more strongly associated with cognitive decline, Alzheimer disease, and other dementias than late-life exposure.
Role: Multiple PI

1R01AG058537(Multiple PI: Yaffe/O'Bryant) 06/18 – 05/22 NCE 1% (0.12 cal mos)
NIH : National Institute on Aging $6,532,245 TDC
John Hsiao, Program Officer
31 Center Drive, MSC 2292, Bethesda, MD 20892
An Alzheimer's Blood Test for Primary Care
Goals: The goal of the project is to administer the first-ever examination of an AD blood test within a primary care setting.
Aim 1: Validate the Alzheimer's Blood Test in Primary Care Settings.
Aim 2: Validate the Alzheimer's Blood Test for the Detection of Prodromal AD in Primary Care Settings.
Role: Multiple-PI

W81XWH-18-0692 (Yaffe/Plassman) 09/18 – 09/22 NCE 1% (0.12 cal mos)
Department of Army $1,299,907 TDC
Anthony Pacifico, Science Officer
820 Chandler Street, Fort Detrick, MD 21702-5014
Genetics, comorbidities, and ethnicity: Effects of TBI on Dementia
Goals: The goal of this research collaboration is to leverage two established epidemiological datasets to investigate factors associated with adverse cognitive outcomes among veterans with head injuries.
Aim 1: To determine the contribution of sociodemographic factors such as race, ethnicity, education, and socioeconomic status (SES) to the association between TBI and dementia in the VA TBI cohort.
Aim 2: To determine the contribution of medical and psychiatric conditions to the association between TBI and dementia in the VA TBI cohort.
Aim 3: Capitalizing on the twin design, to determine the contribution of sociodemographic factors (e.g., SES and education) to the association between TBI and cognitive decline/dementia in the Twin Registry.
Aim 4: Using the Twin Registry, to determine the contribution of medical and psychiatric conditions to the association between TBI and cognitive decline/dementia.
Aim 5. Estimate the attributable risk of TBI on dementia among Veteran and non-Veteran populations and the portion of that risk attributable to each of the contributing variables including medical and psychiatric comorbidities.
Role: Multiple-PI.

2015211 (Yaffe) 01/21 – 12/23 1% (0.12 cal mos)
Doris Duke Charitable Foundation $540,000 TDC
Katrina Bandong, Program Officer

650 5th Avenue, 19th fl, New York, NY 10019
Doris Duke Fund to Retain Clinical Scientists
Goals: The goal of this project is to provide supplemental, flexible funding to young faculty members working on clinical research projects and facing extraprofessional demands of caregiving.
Aim 1: Provide competitive funding to help retain junior physician-scientists who have obtained NIH-funding (or the equivalent), are on a clear trajectory to a successful independent research career and are facing significant caregiving responsibilities.
Aim 2: Help the junior faculty member not only survive but thrive academically despite caregiving challenges by providing mentorship and the support of a Doris Duke community of clinical researchers who have experienced extraordinary caregiving responsibilities. Expand the community of DDSFA-funded faculty, mentors and leaders to include other Doris Duke programs by comparing activities, measuring similar outcomes, and developing best-practices.
Role: PI

ACTIVE (Dr. Yaffe as Co-Investigator)

RF1AG056331 (Wallace) 04/21 – 03/24 1% (0.6 cal mos)
NIH: National Institute on Aging $276,420 TDC
Basil Eldadah, Program Officer
31 Center Drive, MSC 2292, Bethesda, MD 20892
Sleep Health Profiles Predicting Impaired Cognition and Depressive Symptoms in Older Adults: Extending Novel Statistical Models in Multi-Cohort Applications
Goals: The goal of this study is to examine multivariate sleep health as a predictor of changes in depressive symptoms and cognitive impairment across multiple cohorts.
Aim 1: Examine multivariable sleep health for predicting changes in global cognition (primary) and Incident Clinically Significant Cognitive Impairment (secondary) in a high-dimensional ML context.
Aim 2. Examine multivariable sleep health for predicting changes in depressive symptoms (primary) and Incident Clinically Significant Depressive Symptoms (secondary) in a high-dimensional ML context.
Aim 3. Examine temporal pathways among sleep health, cognitive function, and depressive symptoms.
Role: Co-Investigator.

R01AG063946 (Xiao) 04/20 – 03/24 1% (0.12 cal mos)
NIH: Natl Institute on Aging $2,603,388 TDC
Mackiewicz Miroslaw, Program Officer
31 Center Drive Bethesda, MD 20892
Circadian Rest-Activity Rhythms, Metabolic Profiles, and Incidence of Alzheimer's Disease and Related Dementia in older Men and Women
Goals: The goal of this project is to investigate the relationship between age-related impairment in circadian rhythms and Alzheimer's disease and related dementias.

Aim 1: Determine the gender-specific relationships between rest-activity rhythms and long-term cognitive outcomes including ADRD in older men and women.
Aim 2: Identify metabolomics signatures that are associated with characteristics of rest-activity rhythms and incident ADRD, respectively.
Aim 3: Test whether common metabolites and pathways mediate relationships between rest-activity rhythms and incident ADRD.
Role: Co-Investigator

1R01AG062531 (Himali) 04/20 – 03/24 1% (0.12 cal mos)
NIH: National Institute on Aging $2,983,824 TDC
Mackiewicz Miroslaw, Program Officer
31 Center Drive Bethesda, MD 20892
Contributions of sleep to preclinical and clinical Alzheimer's disease
Goals: The goal of this project is to investigate the relationship between sleep and Alzheimer's disease.
Aim 1: To examine the aspects of sleep that relate to a higher risk of incident Alzheimer's disease (AD) dementia

Aim 2: To examine the aspects of sleep (defined in Aim 1) that relate cross-sectionally to dementia endophenotypes.
Aim 3: To examine whether changes in sleep neurophysiology over ~6 years predict incident dementia
Role: Co-Investigator

P30 AG062422 (Miller) 04/19 – 03/24 2% (0.24 cal mos)
NIH: National Institute on Aging $12,633,948 TDC
New Approaches to Dementia Heterogeneity (ADRC)
Goals: The overall goal for this project is to define and detect the subtypes of healthy aging, MCI, AD, FTD, PSP, CBS, and CJD that predict specific molecular and physiological causes for dementia; improve early recognition and tracking of transitions from normal aging to dementia; and stimulate drug development and clinical trials.
Aim 1: Explore the heterogeneous features of healthy aging, MCI, AD, FTD-spectrum disorders, and CJD to better understand their clinical, genetic, and molecular underpinnings.
Aim 2: Leverage the valuable cohorts in the ADRC and the talented neuroscience communities at UCSF and beyond to “enhance the performance of innovative research” around diagnosis and treatment of dementia.
Aim 3: Increase understanding of the unique cultural and biological features of aging Chinese and Latino Americans, while educating these communities with outreach lectures and web-based presentations.
Aim 4: Develop innovative approaches to data management and biostatistics to support easy access and analysis of ADRC-related data while offering statistical support to our investigators. Aim 5: Train new leaders in dementia research with innovative education approaches and educate medical and lay communities about the heterogeneity of dementia with conferences, web-based presentations, and films.
Role: REC Lead, CO-I Data Core

PENDING

None

OVERLAP
Dr. Yaffe has a joint UCSF/VA appointment. There is no budgetary or scientific overlap with the pending grant.

OTHER SUPPORT

BOSCARDIN, W.J.

ACTIVE

RF1MH117604 (Byers/Barry) 09/01/18-08/31/22 0.60 calendar months
NIH – National Institute of Mental Health $250,000
Precursors of Suicide in Older Adults Transitioning from Prison to Community
Denise M. Juliano-Bult; Program Officer; National Institute of Mental Health; 6001 Executive Boulevard, Room 7144, MSC 9631, Bethesda, MD 20892; 301-443-3364
The goal of this study is to determine precursors and health care use patterns that may increase or mitigate risk of suicide, suicide attempts, and death by unintentional injury (e.g., drug overdose) transitioning from prison to community in late life
Aims:

1) To determine rates and precursors (e.g., need factors such as psychiatric and general medical diagnoses) of suicide, death by unintentional injury, and suicide attempt in two groups of veterans.
2) To determine health care services use patterns (e.g., timing; number of visits) that are related to increased risk of suicide, death by unintentional injury, and suicide attempt.
3) To investigate if associations between health care services use patterns and suicide, death by unintentional injury, and suicide attempt differ according to predisposing, enabling, and need factors, including health care system (i.e., using both Medicare and VA's health services vs. Medicare only), reason for Medicare eligibility, and other key precursors.

Role: Co-Investigator

R01AG057751 (Lee & Smith) 08/15/18-04/30/22 1.20 calendar months
NIH / NIA $434,671
Prognostic calculators for patients with Alzheimers disease and related dementias
Marcel Salive – Program Official
National Institute on Aging, Building 31, Room 5C27, 31 Center Drive, MSC 2292, Bethesda, MD 20892: 301-496-5278
Goals:
The goal of this project is to create prognostic tools for estimating life expectancy, time to the nursing home placement, and 6-month mortality for persons with Alzheimer's disease and related dementias.
Aims:

1) Develop and internally validate a family of life-expectancy prediction models for older adults with ADRD enrolled in HRS using LASSO survival regression allowing for unavailable predictors
2) Develop and internally validate a family of time to nursing home placement prediction models for older adults with ADRD enrolled in HRS using LASSO and competing risks survival regression allowing for unavailable predictors
3) Develop and internally validate a family of 6-month mortality risk prediction models for older adults with ADRD enrolled in HRS using LASSO logistic regression allowing for unavailable predictors
4) Externally validate these prognostic models with data from older adults with ADRD in NHATS

Role: Co-Investigator

KL2TR001870 (Bauer) 07/18/16-05/31/22 1.20 calendar months
NIH / NCATS $2,026,503
Clinical and Translational Science Institute
David B. Wilde, MD, PhD – Program Official
Division of Clinical Innovation National Center for Advancing Translational Sciences National Institutes of Health, 31 Center Drive, Suite 3B11, Bethesda, Maryland 20892-2128: 301-435-0790
Goals:
The overarching goal of the Clinical and Translational Science Institute (CTSI) is to create an integrated academic home that transforms research and education in clinical investigation and translational science at UCSF and throughout the community.
Aims:

1) To enhance the highly successful activities of the UCSF CTSI, including the development of new initiatives in the areas of Training, Infrastructure/Services, and Advocacy/Culture Change;
2) To develop crosscutting initiatives using the knowledge, skills, and infrastructure developed by multiple CTSI programs in the first funding period to accelerate clinical and translational research and its impact on health, well beyond the institutions collaborating in the UCSF CTSI

Role: Co-Investigator

R01AG058616 (Suskind) 06/15/18-05/31/22 0.96 calendar months
National Institutes of Health $339,678
Optimizing surgical decision-making for nursing home residents undergoing surgery for bladder and bowel dysfunction
Marcel Salive; Health Scientist Administrator; Division of Geriatrics and Clinical Gerontology (DGCG) National Institute on Aging, 31 Center Drive, Bethesda, MD 20892; 301-496-6761
Goals: The main goal is to improve our knowledge to develop more effective ways to prevent, diagnose, and treat common diseases and conditions of aging like bladder and bowel dysfunction in this underserved and vulnerable population

Aims:
1) To compare short-term (30-day mortality, surgical complications, length of stay, readmission) and long-term (1-year mortality and intensity of care) surgical outcomes between nursing home residents and age-, sex- and comorbidity-matched community-dwelling older adults undergoing elective surgery for bladder and bowel dysfunction.
2) To determine longitudinal changes in functional status, cognition, and bladder and bowel function among nursing home residents following elective surgery for bladder and bowel dysfunction.
3) To develop and internally validate a prognostic tool for nursing home residents considering elective surgery for bladder and bowel dysfunction to predict surgical morbidity, mortality and postoperative function, cognition and bladder and bowel function.

Role: Co-Investigator

W81XWH-18-PRARP-RPA (Tosun-Turgut/Gardner/Yaffe) 09/01/19-08/31/22 0.60 calendar months
Department of Defense $1,299,638
Neuroimaging Endophenotypes and Predictors of Post-Traumatic Brain Injury Dementia in a Nationwide Cohort of Veterans
The proposed 3-year project will cost-efficiently harness the newly available wealth of nationwide clinical neuroimaging data and merge with our existing cohort of 1.6 million TBI-exposed and unexposed veterans with up to 12 years of follow-up in order to (1) create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data; (2) predict which TBI-exposed veterans will go on todevelop dementia; and (3) identify prevalence of specific sub-types of dementia among TBI-exposed versus unexposed veterans.
Aims:
1) Create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data;
2) Predict which TBI-exposed veterans will go on to develop dementia;
3) Identify prevalence of specific sub-types of dementia among TBI-exposed versus unexposed veterans.

Role: Co-Investigator

P30AG044281 (Covinsky) 07/01/18-06/30/23 2.16 calendar months
NIH / NIA $1,589,963
UCSF Older Americans Independence Center
Amy Gipson; Grants Management Officer; National Institute on Aging; Building 31, Room 5C27, 31 Center Drive, MSC 2292, Bethesda, MD 20892
Goals: The goal of this project is to improve the health care and quality of life of vulnerable older adults with or at risk for disability.
Aims:

1) Catalyze research on disability in vulnerable older persons at UCSF by serving as a hub that brings together scholars and leverages resources.
2) Provide core access to data resources, statistical support, and expertise enrolling and retaining vulnerable older subjects in order to stimulate new research on disability.
3) Support pilot studies that accelerate science and lead to research funding in late life disability.
4) Identify the future leaders of geriatrics research and catalyze their development with career development funding and exceptional mentoring.
5) Develop a leadership and administrative structure that spurs interdisciplinary collaboration, making the OAIC greater than the sum of its parts.

Role: Core Leader (Data Analysis Core)

K24HL141354 (Fang) 07/01/18-06/30/23 0.48 calendar months
NIH $609,170
Use and outcomes of anticoagulants for the treatment and prevention of thrombosis among hospitalized patients
Andre D Walker, Grants Management Specialist; (301) 827-8061
Goals: The overall objectives of this K24 proposal are to (1) expand Dr. Fang's continuing research program of describing the use and outcomes of antithrombotic treatment strategies to help mitigate the morbidity and mortality associated with thrombotic conditions; and (2) leverage this research program as a platform to train junior investigators in patient-oriented outcomes research.
Aims:

1) To describe the use and outcomes of pharmacologic venous thromboembolism (VTE) prophylaxis in patients undergoing hip or knee arthroplasty
2) To describe periprocedural management and outcomes in patients on therapeutically-dosed oral anticoagulants undergoing surgery
3) To describe treatment satisfaction, quality-of-life, and medication adherence in patients taking oral anticoagulants

Role: Co-Investigator

W81XWH-18-0692 (Yaffe) 10/01/2019 – 09/30/2024 1.80 calendar months
Dept of Defense/Department of Veterans Affairs $2,993,341
Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC), Epidemiology Study
Goals:
The objective of this project is to follow veterans in our previously established dataset prospectively and investigate both the course and long-term outcomes of TBI. We will investigate how mTBI is often interwoven with other comorbidities especially mental health factors and how these other factors may be synergistic or additive. We will translate our findings to develop prognostic models that will guide clinician and researchers toward better care and prevention of mTBI and associated outcomes.
Aims:

1) Aim 1: Maintain, augment, and refine the 1.6 million Veteran data repository of all era Veterans
2) Aim 2: Identify subgroups at greatest risk and resilience for mental health and neurodegenerative outcomes after mTBI
3) Aim 3: Examine and elucidate complex associations between mTBI and comorbidities
4) Aim 4: Develop prognostic models to determine which Veterans decline versus sustain/improve after mTBI

Role: Co-Investigator

R24AG071456 (Portacolone, Hill, Perez) 6/01/21 – 3/31/24 0.60 calendar months
NIH/NIA $2,426,913
Leveraging the national infrastructure of trusted organizations to increase representation of Latinos dementia research
Ryan Blakeney, Grants Management Officer, National Institute on Aging. Building 31, Room 5C27, 31 Center Drive, MSC 2292, Bethesda, MD 20892; 301-451-9802
The aim of this grant is to develop and test a culturally appropriate and scalable nationally intervention to facilitate recruitment of Latino communities into dementia research studies.

Aims:

1. Define consensus to establishing an effective recruitment Consortium
2. Build and complete the needed components of a novel Consortium-based recruitment intervention
3. Establish and evaluate the Consortium recruitment intervention

Role: Co-Investigator

No grant # (Spetz) 7/1/19 - 6/30/22 1.20 calendar months
UCSF Strategic Initiatives $1,446,945
Infrastructure to advance health services research at UCSF
The goal of this project is to expand the capacity to jumpstart the career of young investigators interested in building a Health Services Research (HSR) career at UCSF through increasing the acquisition, visibility and use of needed data sets and analytics that will lead to increased opportunities and collaborations across UCSF and UC Health, leading to a greater impact of the UCSF HSR community both here and nationally.
Role: Co-Investigator

R21AG067463 (Schwartz/Fang) 04/15/20-03/31/22 0.24 calendar months
NIH $160,259
Direct-Acting Oral Anticoagulants: Anticoagulant Activity in Understudied Older NVAF Patients
Susan Zieman – Program Official
Division of Geriatrics and Clinical Gerontology (DGCG), 7201 Wisconsin Ave. 3W200, Bethesda, Maryland 20892: 301-496-6949
Goals:
The overarching goal of this project is to determine Direct-acting Oral Anticoagulant (DOAC) concentrations in previously unstudied groups of very old patients with non-valvular atrial fibrillation. We hypothesize that plasma DOAC levels are higher than expected in these patients and this could result in higher bleeding complications. The work will also identify factors in addition to age contributing to high concentrations .
Aims:
1) Determine steady-state apixaban concentrations, assessed by clinical anti-Factor Xa inhibition assay, in patients receiving recommended and lower than recommended dosing.
2) Determine steady-state rivaroxaban concentrations, assessed by clinical anti-Factor Xa inhibition assay, in patients receiving recommended dosing
Role: Co-Investigator

P01AG066605 (Morrison/Covinsky) 09/30/20-05/31/25 0.60 calendar months
NIH $1,856,848
Deploying High Value Longitudinal Population-Based Data in Dementia Research (DEVELOP AD Research)
Elena Fazio – Program Official
Division of Behavioral and Social Research (DBSR) 7201 Wisconsin Ave. 3W200, Bethesda, Maryland 20892: 301-496-3136
Goals:
The goals of this project are to employ rich population-based data to develop a comprehensive longitudinal understanding of dementia that will better inform clinical and policy interventions and improve healthcare for persons with dementia and their families.
Aims:
1) Create a research program guided by a shared conceptual model that considers the longitudinal context of co-existing medical, social, and health system factors that affect outcomes for PWD and their families.
2) Undertake research that: a) examines the complex interaction of dementia and other serious illness-RP1; b) identifies the impact of clinical and social disruptive events on disease trajectory and outcomes-RP2; c) explores medication prescribing in the context of dementia-RP3; and d) examines how models of community-based care (home-based clinical care-RP4 and hospice-RP5) meet the needs of PWD and their families
3) Establish two new resource cores that support the complex analytics required of each research project, integrate and coordinate research activities, disseminate findings and data resources including programming code and data dictionaries, create a platform of research to support early-stage investigators, and identify future directions and research collaborations.
Role: Co-Investigator

R01NS110944 (Gardner) 09/01/19-05/31/24 0.36 calendar months
NIH $536,742
Transforming Research and Clinical Knowledge in Geriatric Traumatic Brain Injury (TRACK-GERI)
Linda Louise Bambrick – Program Official
National Institute of Neurological Disorders and Stroke: 301-496-1447
Goals:
To assemble a new prospective longitudinal cohort study of acute geriatric traumatic brain injury (TBI) that will establish the natural history and neuropathology, identify age-appropriate blood-based biomarkers, and develop an optimized set of tools for capturing geriatric TBI predictors and outcomes for use in large-scale geriatric TBI clinical trials.
Role: Co-Investigator

PENDING SUPPORT

CX002346-01 (Gardner) 10/2021-09/2025 0.30 calendar months
Department of Veterans Affairs $300,000
Transforming Research and Clinical Knowledge in Older Veterans with Acute Traumatic Brain Injury (TRACK-VA)
Goals:
This project will focus on two VA Clinical Science Research and Development priority research areas: (1) traumatic brain injury (TBI) diagnosis and (2) diseases with a high healthcare burden in Veterans. Over the 4-year timeline of this project, it is expected that the total number of acute TBIs sustained by older Veterans residing in the U.S. (N>520,000) will exceed the total number of TBIs sustained by active duty service members in the past 20 years (N=413,858). Geriatric TBI is a massive epidemic within Veterans Health Administration (VHA) with high associated morbidity, mortality, and cost. Yet, acute geriatric TBI has never been prospectively studied by VHA. This pioneering project will comprehensively characterize baseline and longitudinal endophenotypes of older Veterans presenting with acute TBI to our VA. Findings will inform precision medicine approaches to age-appropriate diagnosis, treatment, and disease-monitoring that are urgently needed to improve outcomes in this large and burdened population of Veterans.

Role: Co-Investigator

OVERLAP:
Should the pending project be awarded, Dr. Boscardin will decrease his effort on P30AG044281 so that total effort does not exceed 12 calendar months

INACTIVE

CDR-1306-01500 (Sudore) 04/01/14-03/31/17 0.30 calendar months
Patient-Centered Outcomes Research Institute $500,000
Preparing Spanish-speaking Older Adults for Advance Care Planning and Medical Decision Making
Ayodola Anise, MHS – Program Officer
1828 L St., NW, Suite 900 Washington, DC 20036: 202-827-7700
Goals:
Our study goals are to refine and adapt a Spanish translation of PREPARE and to test the efficacy of a novel ACP paradigm and website to prepare older Latinos with multi-morbidity for communication and decision making.
Aims:
1) to adapt and refine PREPARE in Spanish through cognitive interviews with Spanish-speaking Latinos and stakeholders;
2) to conduct an RCT to compare the efficacy of PREPARE plus a previously-tested, easy-to-read AD (intervention) versus the AD alone (control), and;
3) to disseminate PREPARE with input from patients, surrogates and stakeholders.

Role: Co-Investigator

60770272-104939 (Dudley) 09/30/14-09/30/16 0.48 calendar months
Agency for Healthcare Research and Quality $64,148
Inventory and Prioritization of Measures to Support the Growing Effort in Transparency Using All-payer Claims Databases (APCD)
Maushami Desoto – Program Officer
540 Gaither Road, Rockville, MD 20850: (301) 427-1546
Goals:
The major goal of this project is to create tools that will help sponsors of all-payer claims databases (APCDs) decide what data to collect, what can be measured form APCDs, and how to present information in order to support consumer choice, improve transparency, drive value-based care, and improve health.
Aims:

1) To conduct a literature review and environmental scan
2) To develop an inventory of APCD-based measures.

Role: Statistician

RRP 13-420 (Keyhani) 12/01/13-09/30/15 0.90 calendar months
VA HSR&D $100,000
De-implementing Unnecessary Medications in Stroke and Cardiovascular Prevention
Seth Eisen, MD, MSc – Director, HSR&D
Department of Veterans Affairs, Office of Research and Development, HSR&D (10P9H): 202-443-5707
Goals:
This is a study designed to conduct the research necessary as the first step in the process of developing two overuse measures that can be tracked and reported for the purposes of reducing unnecessary ambulatory care in the VA.
Aims:

1) To examine the unnecessary use of Statins for cardiovascular or stroke prevention. Hypothesis: Many patients who are ineligible for Statins based on Framingham risk score or limited life expectancy receive Statins in the VA.
2) To examine the unnecessary use of dual antiplatelet therapy in secondary stroke prevention. Hypothesis: Use of dual antiplatelet agents is fairly common as expert opinion used to support the dual use of these medications in secondary stroke prevention.

Role: Co-investigator

R01MD007019 (Byers) 04/01/12-12/31/15 0.60 calendar months
NIH / NIMHD $87,750
Epidemiology of Suicidal Behavior in Racially/Ethnically Diverse Older Americans
Jennifer Alvidrez – Program Official
National Institute on Minority Health and Health Disparities, National Institutes of Health, 6707 Democracy Boulevard, Suite 800, Bethesda, MD 20892-5465: 301-594-9567
Goals:
The primary goal of this study is to determine the prevalence and key predictors of suicide-related behaviors in ethnically-diverse older Americans using data from three nationally representative studies. A secondary goal is to determine racial disparities in receipt of mental health services in older adults at increased risk of suicide. Findings from this study will be important for identifying those older Americans most at risk of suicide and with great need of care.
Aims:

1) To determine the prevalence and socio-demographic predictors of suicidal behavior in older racially and ethnically diverse Americans (i.e., non-Hispanic Whites, non-Hispanic Blacks, Hispanics, and Asians);
2) To determine whether psychiatric disorders, chronic medical conditions, and disability are associated with suicide-related behavior over the lifetime in older racially and ethnically diverse Americans;
3) To determine if the prevalence and factors related to suicidal behavior in older racially and ethnically diverse Americans differ by gender; and
4) To determine if there are racial disparities in the prevalence and predictors of mental health services use for older adults at increased risk of suicide.

Role: Co-Investigator

R01CA134425 (Walter) 07/01/09-04/30/14 0.50 calendar months
NIH / NCI $142,499
Prostate-Specific Antigen Practices and Outcomes in the Elderly
Veronica Chollette, RN, MS - Program Official
9609 Medical Center Drive, GB 9609 MSC 9760, Bethesda, MD 20892-9760: 240-276-6969
Goals:
Project goal is to determine the factors associated with PSA screening decisions and the downstream consequences over the next 5 years that follow PSA screening in men aged 65 years and older.
Aims:

1) to determine the health-system, provider, and patient factors associated with PSA screening in elderly men across a spectrum of advancing age and comorbid illness;
2) to quantify the real world downstream consequences (e.g., PSA testing, prostate biopsies, cancer diagnosis, treatment, and complications) during the 5 years following PSA screening in elderly men across a spectrum of advancing age and comorbid illness; and
3) To identify health-system, provider, and patient factors associated with these downstream consequences.

Role: Co-Investigator

No grant # (Lee) 09/16/11-09/15/14 1.20 calendar months
S.D. Bechtel, Jr. Foundation $200,000
Computational Science and the Biology of Alzheimer's Disease
Marcia Argyris – Program Director
P.O. Box 193809, San Francisco CA 94119-3809: 415-284-8675
Goals:
To conduct basic research in AD through the novel integration of computational biology, laboratory-based neuroscience, and neuroimaging to advance our understanding of the predictors of AD to determine how the test should influence treatment for those at risk for AD.
Aims:

1) Synthesize current evidence regarding the biologic changes of AD and their imaging and laboratory correlates test characteristics of each marker for preclinical Alzheimer's pathology (CSF Ab1-42, PET amyloid tracer retention, FDG uptake, CSF tau and hippocampal atrophy) to determine the risk of progressing to the next stage of pathology given an abnormal test result.
2) To apply novel/advanced methods of computational biology to develop a Markov chain model incorporating the stages of Alzheimer's Disease as well as the competing risk of other causes of mortality to identify the patients who are most likely to benefit from screening and subsequent treatment.

Role: Co-Investigator

W81XWH-11-2-0189 (Barnes) 10/01/11-06/30/14 0.60 calendar months
Department of Defense $125,000
Identification of Key Dementia Risk Factors in Older Veterans
David Cifu, MD – Consortium Director
Department of PM&R, Virginia Commonwealth University, 1233 East Marshall Street, Richmond, VA 23298-0677: 804-628-2902
Goals:
The goal of the project is to perform detailed analyses of existing Veterans Health Administration (VHA) databases to identify the key risk factors for dementia in older veterans.
Aims:

1) To determine whether traditional risk factors such as demographics, cardiovascular disease and depression are associated with increased risk of dementia in older veterans.
2) To determine whether non-traditional and combat-related risk factors such as substance abuse, radiation, Agent Orange and prisoner of war status will be associated with increased risk of dementia in older veterans

Role: Co-Investigator

71138 (Dudley) 08/15/13-08/14/14 0.56 calendar months
Robert Woods Johnson Foundation $259,402
The Process and Quality of Virtual Doctor Visits for Urgent Care Issues—An Initial Study
Nancy Barrand – Program Official
Route 1 and College Road East, P.O. Box 2316, Princeton, NJ 08543-2316: (609) 627-5943
Goals:
The major goal of this project is to give us a better understanding of the processes of virtual care and generates baseline data about the sites' performance.
Aims:

3) Given the recent increase in interest in telemedicine, this project informs the discussion among patients, doctors, payers, and policymakers about whether to pay for and how to monitor virtual care.

Role: Statistician

R01NR013347 (Covinsky) 09/27/11-07/31/15 0.30 calendar months
NIH / NINR $237,000
Needs and Outcomes of Elders with Hip Fracture: Supportive, Functional, Palliative
Lynn Adams, MD – Program Official
6701 Democracy Blvd., 7th Floor, One Democracy Plaza, Bethesda, MD 20892-4870: 301-594-8911
Goals:
The goal of this project is to learn about the palliative and supportive needs of elders who have hip fracture. It aims to develop the knowledge base that will be make it possible to better attend to the needs of elders who die or become disabled in the year after hip fracture.
Aims:

1) Describe the need for personal assistance in basic and instrumental activities of daily living in the two years before and the two years after hip fracture;
2) Determine which elders are at highest risk for death and disability following hip fracture;
3) Among those who die in the year after hip fracture, describe patterns of resource use (hospital, ICU, and hospice), location of death, advance care planning, and quality of symptom control.

Role: Co-Investigator

R01HL111032 (Steinman) 08/22/12-06/30/16 0.60 calendar months
NIH / NHLBI $409,611
Outcomes of beta blockers following myocardial infarction in nursing home residents
Patrice Desvigne-Nickens - Program Official
P.O. Box 30105, Bethesda, MD 20824-0105: 301-435-0515
Goals:
In this study, we propose using existing data to evaluate the impact of beta blockers given after myocardial infarction on important clinical outcomes in nursing home residents.
Aims:

1) to describe patterns of beta blocker use in nursing home residents after myocardial infarction and to characterize individual and facility-level determinants of use;
2) to determine the impact of beta blockers on functional outcomes, repeat hospitalization, and death in older nursing home residents after myocardial infarction; and
3) to determine the impact of beta blockers on repeat hospitalization and death in older nursing home residents after myocardial infarction

Role: Co-Investigator

K24AR052667 (Chren) 07/01/05-08/31/16 0.60 calendar months
NIH / NIAMS $169,004
Patient-Oriented Research in Skin Diseases
Carl Baker, MD, PhD – Program Director
Keratinocyte Biology and Diseases Program, Division of Skin and Rheumatic Diseases, NIAMS, NIH, DHHS
One Democracy Plaza, 6701 Democracy Blvd., Ste. 800, Bethesda, MD 20892-4872: 301-594-5017
Goals:

The goal of this Midcareer Investigator Award in Patient-Oriented Research is to enhance the PI's research in outcomes of patients with chronic diseases, and to mentor beginning investigators in patient-oriented research.
Aims:

1) To compare recurrence rates at five years after different therapies for nonmelanoma skin cancer
2) To compare skin-related quality of life at five years after different therapies for nonmelanoma skin cancer

Role: Co-Investigator

130831A-Interagency Agreement (Dudley) 06/23/14-09/30/16 1.20 calendar months
State of California Department of Insurance $2,431,729
Price Transparency Cycle III Data Center Project
Sheirin Ghoddoucy – Program Official
300 Capitol Mall Fl 17, Sacramento, CA 95814: (916) 492-3591
Goals:
The major goal of this project is to work with CDI to obtain and analyze health care cost and quality data and make the results available via consumer-friendly website(s), thereby increasing health care price transparency, so that Californians may compare health care cost and quality information by geographic region.
Aims:

1) During the Project Period, Contractor will work with CDI to obtain medical claims data, develop and convene a stakeholder process to engage with stakeholders, leverage available health care quality and appropriateness measures, and analyze health care cost and quality information. Contractor will increase the transparency of health care prices by making information available on a consumer-friendly website regarding the cost and quality of medical services or episodes of care to allow Californians to compare health care costs and quality by geographic region and provider.

Role: Co-Investigator

No grant # (Ritchie) 07/01/14-06/30/16 0.60 calendar months
National Palliative Care Research Center $70,000
Development of a Health tool to assess the Impact of Opioids in Older Adults
Catherine Maroney, MA, MPH – Deputy Director
One Gustave L. Levy Place, New York, NY 10029: 212-241-7447
Goals:
The major goal of this project is to develop a tool that integrates computer-administered symptom assessments with real-time monitoring of function and cognition to improve our understanding of the efforts of analgesics in older adults with chronic pain. We will develop and test this mHealth tool with 30 study participants in a pilot study.
Aims:

1) Develop a mobile health (mHealth) application that monitors the impact of opioids on pain, function, and cognition, and assess its usability and clarity in older adults.
2) Pilot test this mHealth application in older adults with multiple chronic conditions, both on opioids and not on opioids, in order to understand usability and feasibility and to gain preliminary response data, effect sizes, and effect variation

Role: Statistician

IIR 11-110 (Sudore) 07/01/12-06/30/16 0 calendar months
VA HSR&D $287,166
Preparing Older Veterans with Serious and Chronic Illness for Decision Making
Seth Eisen, MD, MSc – Director, HSR&D
Department of Veterans Affairs, Office of Research and Development, HSR&D (10P9H): 202-443-5707
Goals:
Our goal is to conduct a randomized control trial (RCT) to determine the efficacy of PREPARE to engage Veterans in ACP
The primary aims of this study are:

1) to determine the efficacy of PREPARE to engage diverse, older Veterans with chronic illness in advance care planning (ACP) by performing an RCT with follow-up interviews;

2) to determine the efficacy of PREPARE to activate diverse, older Veterans and their clinicians within clinical encounters utilizing audio recordings
3) to explore the barriers to and facilitators of implementation and dissemination of PREPARE within the VHA through individual interviews with Veterans, Surrogates, and VA Clinic

Role: Co-Investigator / Biostatistician

R01AG044425 (Finlayson) 09/01/13-03/31/18 0.96 calendar months
NIH/ NIA $447,389
Use and Outcomes of Elective Colonoscopy in Nursing Home Residents
Robin A. Barr, D. Phil. – Program Official
National Institute on Aging, Building 31, Room 5C27, 31 Center Drive, MSC 2292, Bethesda, MD 20892: 301-496-9322
Goals:
To inform nursing home residents, their providers, and policy-makers with information about realistic risks, benefits, and costs of elective colonoscopy and to inform individualized decision-making in this population in order to optimize care and potentially reduce costs by informing individualized decision-making for elective diagnostic colonoscopy among nursing home residents.
Aims:

1) The aim of the proposed research is to examine the use and outcomes of surgery and nonsurgical treatment for acute cholecystitis (infection of the gallbladder) among elder nursing home residents in the United States.

Role: Co-Investigator

130831A-Interagency Agreement (Dudley) 06/23/14-09/30/17 0.60 calendar months
State of California Department of Insurance $2,431,729
Price Transparency Cycle III Data Center Project
Sheirin Ghoddoucy – Contracts Manager
300 Capitol Mall, Suite 1300, Sacramento, CA 95814: 916-492-3363
Goals:
The major goal of this project is to work with CDI to obtain and analyze health care cost and quality data and make the results available via consumer-friendly website(s), thereby increasing health care price transparency, so that Californians may compare health care cost and quality information by geographic region.
Aims (*there are no specific aims for this project, just the following 10 tasks/deliverables*):

1) Product Solution
2) Data Sources
3) Data Center
4) Methodology
5) Reportable Results Website
6) Consumer Content
7) Consumer Marketing
8) Stakeholder and CDI Services
9) Copyright, Data Ownership and Data Use Agreement
10) Contractor Work Plan

Role: Co-Investigator

R01HL116522 (Keyhani) 07/01/13-05/31/18 0.60 calendar months
NIH / NHLBI $417,108
An Evaluation of Novel Domains for Predicting 30-day readmission
Patrice Desvigne-Nickens - Program Official
P.O. Box 30105, Bethesda, MD 20824-0105: 301-435-0515
Goals:
The goal of this project is to improve prediction of 30-day readmission through use of data on social risk factors and functional status available in national VA databases including data extracted using natural language processing (NLP) from the medical record.
Aims:

1) To develop and evaluate NLP algorithms to support the automatic identification of measures of social risk and functional status that may influence patient-level readmission rates. Hypothesis: automated NLP can accurately identify most measures of social risk and functional status.
2) To compare the performance of current patient-level readmission models which include measures of demographics and health status to a model that also includes social risk factors and functional status extracted using automated NLP algorithms for four conditions (CHF, AMI, pneumonia and stroke). Hypothesis: social risk factors and functional status are critical domains for predicting 30-day readmission.
3) To compare the performance of 30-day readmission models which include social risk factors and functional status extracted using automated NLP algorithms to a model in which variables were extracted by humans using NLP-assisted chart review. Hypothesis: automated extraction of social risk factors and functional status from the EHR is sufficient for improving readmission risk prediction across multiple diseases.

Role: Co-investigator

No Grant # (Dudley) 07/18/17-06/30/18 1.14 calendar months
UCSF REAC $50,000
Analysis of the Association between Adoption of Commercial EMR Systems and Clinical Outcomes
Linsey Criswell, MD, MPH, Program Officer, Chair, REAC Committee
University of California, San Francisco
400 Parnassus Ave. San Francisco, CA 94122
Goals:
The UCSF Clinical and Translational Science Institute (CTSI) at the University of California, San Francisco (UCSF) was established in 2006 to accelerate the pace of research that improves the health of the public. The overall mission of CTSI is to improve and transform clinical and translational research infrastructure and training at UCSF and partner institutions.
Aims:

1) Determine whether the widespread adoption of EHRs in the US has improved standard measures of clinical care

Role: Co-Investigator

R21HS24553 (Bardach) 09/01/16-08/31/18 0.36 calendar months
Agency for Health Care Research and Quality $114,137
Novel IT to Create Patient-Integrated Hospital QI and Improve Patient Safety
Derrick Wyatt – Program Official
Department of Health and Human Services/ AHRQ OMS/Division of Grants Management 5600 Fishers Lane, Mail Stop 07N13 Rockville, MD 20857: 301-427-1569
Goals:
The overall goal is to create and evaluate a tool that gathers patient and family member feedback and makes it rapidly available to providers, enabling nimble and responsive safety and quality improvement efforts.
Aims:

2) Determine feasibility and acceptability of the patient data collection and provider dashboard tool (Use and Implementation). We will conduct usability testing prior to study start, measure user (patients and providers) engagement over time, and gather feedback about the tool at study end. We hypothesize that patient and caregiver characteristics will predict tool use.
3) Assess whether reporting patient- and caregiver- observed processes of care to providers leads to changes over time (Implementation). We hypothesize that performance on structured items of interest will improve over time with rapidly available data presented to providers.
4) Estimate tool implementation effect sizes, using a pre/post design, on medical errors (Impact on outcomes).

Role: Co-Investigator

R03AG056342 (Tang) 08/01/17-05/31/20 0.15 calendar months
NATIONAL INSTITUTE ON AGING $75,000
Geriatric Factors and Outcomes after High Risk Surgery in Older Adults

Susan Zieman; Program Official; 31 Center Drive, Bethesda, MD 20892; 301-496-6949
Goals:
The long-term goal is to broaden our understanding of the quality of life in the geriatric population and to direct surgical care towards this aim.
Aims:
1) Describe the long-term (up to 2-year) survival rate following high-risk elective surgery, and to identify individual patient characteristics associated with mortality.
2) Determine long-term functional recovery outcomes following high-risk elective surgery and determine factors associated with functional decline.

Role: Biostatistician

CER-1507-31834 (Cohen) 07/01/16-05/31/20 0.81 calendar months
Patient-Centered Outcomes Research Institute $315,351
Improving Care for Veterans with PTSD: Comparative Effectiveness of Medications to Augment First-line Pharmacotherapy
This contract has no assigned Program Officer
1828 L St., NW, Suite 900 Washington, DC 20036: 202-827-7700
Goals:
The goal of this project is to investigate and compare the effectiveness of various medications to augment first-line pharmacologic therapy in treating Posttraumatic Stress Disorder in Veterans.
Aims:
1) To create a retrospective cohort to compare the effectiveness of augmentation of SRI therapy with several commonly used medications.
2) In addition, as several of the medications used in this setting have deleterious effects on cardiovascular risk factors, we will also compare metabolic and cardiovascular outcomes.

Role: Co-Investigator

R01AG047897 (Smith & Lee) 05/15/15-01/31/20 0.48 calendar months
NIH / NIA $328,580
Developing prognostic models for life expectancy and geriatric outcomes
Georgeanne E. Patmios, MA – Program Official
National Institute on Aging, Building 31, Room 5C27, 31 Center Drive, MSC 2292, Bethesda, MD 20892: 301-402-0051
Goals:
The major goal of this project is to create prognostic tools for estimating life expectancy and time to the onset of disability, difficulty managing finances or medications, and mobility impairment.
Aims:
1) Develop and internally validate a predictive model incorporating demographics, behaviors, comorbidities, and functional limitations to estimate median life expectancy.
2) Develop and internally validate predictive models that estimate time to geriatric outcomes.
3) Externally validate our life expectancy and time to geriatric outcomes models.

Role: Co-Investigator

R01AG052041 (Steinman) 08/01/16-04/30/20 1.56 calendar months
NIH / NHLB $241,156
Secondary Analyses of Existing Data Sets and Stored Biospecimens to Address Clinical Aging Research Questions
Marcel Salive – Program OfficialR01AG
National Institute on Aging, Building 31, Room 5C27, 31 Center Drive, MSC 2292, Bethesda, MD 20892: 301-402-1784
Goals:
The goal of this proposal is to create a toolbox of measures that can be used to measure multimorbidity in community-dwelling older adults using claims data.
Aims:
1) To develop and validate claims-based measures of multimorbidity that predict decline in ability to perform basic and instrumental activities of daily living (ADLs, IADLs);

2) Using an expanded range of disease characteristics measurable in claims data, to develop and validate measures of multimorbidity that predict hospitalization and death;
3) To compare the predictive validity of our measures for functional decline, hospitalization, and death with existing measures of multimorbidity such as the Charlson Index.

Role: Co-Investigator

ADRA 16-10054 (Brennan) 07/01/16-06/30/19 0.12 calendar months
California Department of Public Health $74,074
Late Life-Span Use of Alcohol: Prospective Effects on Dementia Risk and Cognitive Functioning
Julie Hohn – Program Coordinator
P.O. Box 997377, MS 7210, Sacramento, CA 95899: 916-552-9869
Goals:
The goal of this project is to examine how late-middle-aged adults' longitudinal patterns of alcohol consumption and drinking problems during earlier old age influence their risk of dementia and changes in cognitive functioning during later old age.
Aims:

1) Determine the key 10-year longitudinal patterns of alcohol consumption and drinking problems among older adults following their baseline assessment in late-middle-age, at about age 60;
2) Establish how these 10-year patterns predict older adults' incidence of dementia, and level and rate of change in cognitive functioning, over the next 8 to 10 years;
3) Determine whether older women differ from older men in:
   a) Their 10-year longitudinal patterns of alcohol use past the age of 60, and
   b) The impacts of these patterns on subsequent incidence of dementia, and level and rate of change in cognitive function, for the next 8 to 10 years; and
4) Determine whether older African Americans differ from older non-Hispanic Whites, in
   a) Their 10-year longitudinal patterns of alcohol use past the page of 60, and
   b) Impacts of these patterns on subsequent incidence of dementia and level and rate of change in functioning for the next 8 years.

Role: Co-Investigator

I01CX001119 (Byers) 07/01/15-09/30/19 1.20 calendar months
Department of Veterans Affairs $315,099
Suicidal Behavior and Suicide in Older Veterans
Sumitra Muralidhar – Scientific Review Administrator and Grants Management Specialist
U.S. Department of Veterans Affairs | 810 Vermont Avenue, NW Washington DC 20420: 202-443-5679
Goals:
The major goal of this project is to determine the prevalence and key predictors of suicide-related behaviors and suicide in older Veterans using four national databases, the Suicide Prevention and Application Network (SPAN) database, the Veteran Suicide Archive data, the National Patient Care Database (NPCD), and the Centers for Medicare and Medicaid Services (CMS) database.
Aims:

1) To identify the predictors of suicidality in older Veterans (age 50 years or older), including socio-demographic factors, psychiatric disorders, and medical conditions.
2) To determine dynamic risk factors associated with suicidality in older Veterans and whether addition of these dynamic factors in the predictor model improve the assessment of risk.
3) To determine whether associations found for key static and dynamic predictors of suicidality in older Veterans differ across prominent health disparity groups (age, gender, and race/ethnicity).
4) To determine the most important predictors and clusters of risk factors (i.e., highest risk subgroups) associated with developing suicidal behavior and completing suicide over the long term in older Veterans.

Aims:

1) To develop and internally validate eRADAR using 'gold standard' ACT dementia diagnosis data and linked EMR data.
2) To craft optimal strategies for testing and delivering eRADAR, heavily informed by input from patients, caregivers, clinicians and key healthcare system stakeholders from diverse cultural perspectives.

Role: Co-Investigator

W81XWH-12-PHTBI-CENC (Yaffe) 07/01/13-09/30/19 1.20 calendar months
DOD: Department of Defense $937,572
Chronic Effects of Neurotrauma Consortium (CENC) Award
David Cifu, MD – Consortium Director
Department of PM&R, Virginia Commonwealth University, 1233 East Marshall Street, Richmond, VA 23298-0677: 804-628-2902
Goals:
The goals of consortium are to identify and characterize the anatomic, molecular and physiological mechanisms associated with neurotrauma and identify appropriate treatment strategies.
Aims:

1) Among OEF/OIF/OND Veterans, to determine the association of mTBI and mental health disorders with adverse clinical outcomes with the goal of understanding why some Veterans with mTBI are more resilient than others.
2) Among Veterans from any era, to determine whether mTBI is independently associated with adverse neurosensory outcomes and mortality across the life course and whether treatment of comorbid conditions reduces risk.

Role: Co-Investigator on Study 4: Integrating Dataset Study

R56AG056417 (Barnes) 09/15/17-02/29/20 0.17 calendar months
NIH/NIA $201,531
Development and Validation of the EMR Risk of Alzheimer's and Dementia Assessment Rule (eRADAR)
Partha Bhattacharyya, Program Director
Division of Behavioral and Social Research
31 Center Drive, MSC 2292
Bethesda, MD 20892
Goals:
The major goal of this project is to develop and prospectively validate the EMR Risk of Alzheimer's and Dementia Assessment Rule (eRADAR), a simple, automated tool that will use information in the electronic medical record (EMR) to identify patients likely to have current, undiagnosed dementia. We will conduct focus groups and interviews with patients, caregivers, clinicians and health care system leaders to seek guidance about best practices for implementing eRADAR in clinical practice.
Aims:
1) To develop and internally validate eRADAR using 'gold standard' ACT dementia diagnosis data and linked EMR data. Rationale. Based on our preliminary data, we hypothesize that patients with undiagnosed dementia will have a unique EMR 'fingerprint' that can be used to identify them including evidence of difficulty managing comorbid medical conditions, chaotic healthcare utilization, and visits for dementia-related symptoms.
2) To craft optimal strategies for testing and delivering eRADAR, heavily informed by input from patients, caregivers, clinicians and key healthcare system stakeholders. Rationale. In order to successfully test and, ultimately, implement eRADAR in the healthcare system, it is critical to obtain input on sensitive issues such as how best to contact high-risk patients, communicate assessment results, and work effectively with the primary care team.
3) To prospectively assess accuracy, clinical test characteristics, feasibility and acceptability of eRADAR in Group Health to inform a larger clinical trial of impact on patient care and clinical outcomes. Rationale. This 'real world' test of eRADAR will lay the groundwork for a future clinical trial by determining positive and negative predictive values and identifying barriers and facilitators to healthcare delivery.

Role: Co-Investigator

IIR 15-434 (Lee) 02/01/17-01/31/21 1.20 calendar months
Department of Veterans Affairs $223,378
Development and Validation of 10-Year Life Expectancy Calculators to Individualize Veterans' Prevention Decisions
Miho Tanaka, PhD, Scientific Portfolio Manager

U.S. Department of Veterans Affairs Health Services Research and Development (10P9H) | 810 Vermont Avenue, NW Washington DC 20420: 202-443-5759
Goals:
Our long-term goal is to link our life expectancy (LE) calculator with the existing colorectal (CRC) screening clinical reminders so that 1) reminders are suppressed for Veterans with limited LE (even if they fall within the recommended age for screening) and 2) reminders are triggered for Veterans with an extended LE (even if they are beyond the recommended age range for screening).
Aims:

1) Develop and validate a LE calculator for Veterans over age 50 (LE50) using 2005 VA electronic data (demographics, diagnoses, laboratory results and pharmacy records) in a national cohort of Veterans seen in primary care clinics.
2) Using 2009 data from a national cohort of Veterans over age 75 seen in primary care, develop and validate a LE calculator with functional data (LE75function) or Medicare data (LE75Medicare) in addition to the other risk factors considered in Aim 1. To determine whether functional or Medicare data leads to more accurate LE predictions, develop a LE calculator ignoring functional and Medicare data (LE75standard) and compare discrimination (Harrell's c-statistics) and diagnostic test characteristics (sensitivity, specificity, positive and negative predictive values) between the augmented (LE75function and LE75Medicare) and LE75standard calculators.
3) Using actual 5-year and 10-year survival of our 2005 cohort as the gold standard, compare the Elixhauser index and the Care Assessment Need (CAN) score to our calculators (LE50, LE75function and LE75Medicare) across a variety of metrics including discrimination, reclassification indexes and diagnostic test characteristics (c-statistic, sensitivity, specificity and positive and negative predictive values). Quantify the number of Veterans seen in VA primary care clinics in 2015 who were likely overscreened (CRC screening in age-appropriate Veterans 50-75 years old with <25% likelihood of LE 10+ years) and underscreened (no CRC screening in Veterans beyond recommended age of 75 with >75% likelihood of LE 10+ years).

Role: Co-Investigator

1085.7 (Jacoby) 05/20/20-05/19/21 0.78 calendar months
CDC Foundation $464,564
PRIORITY: Supporting the Public Health Response to COVID-19
Turquoise Sidibe – Emergency Response Director
CDC Foundation, 600 Peachtree St, NE, Suite 1000, Atlanta, Georgia 30308: 404-653-0790
Goals:
The analyses from PRIORITY will fill a major gap in our knowledge about how pregnant people are affected by COVID-19. This data will serve to inform clinical care and national guidelines during and after this global pandemic.
Aims:

1) To understand the course of infection for pregnant people infected with COVID-19
2) To determine if infection with COVID-19 causes pregnancy-related complications
3) To resolve heath inequities and understand how social determinants of health may be associated with worse health outcomes for self-identified Black, Indigenous, and People of Color (BIPOC) pregnant people infected with COVID-19
4) To learn how the newborns of people with COVID-19 are impacted by the infection
5) To understand how coronavirus may be transmitted between pregnant people and their newborns either directly through the placenta during pregnancy, during the birth process, or after birth.

Role: Biostatistician

19RD029 (Reynolds) 06/01/20-05/31/21 0.12 calendar months
California Air Resources Board $105,943
The Impact of Air Pollution on COVID-19 Case and Death Risk
Lori Casias; Contract/Procurement Analyst; California Air Resources Board; 1001 I Street, Sacramento, CA
A geographic information system project to assess the role of ambient air pollution on COVID-19 outcomes in California adjusting for population characteristics associated with both air quality and COVID-19 risks.
Role: Co-Investigator

R01HS027369 (Auerbach) 09/30/19-09/29/21 0.30 calendar months
PHS AHRQ $338,589
Utility of Predictive Systems to Identify Inpatient Diagnostic Errors: The UPSIDE Study
David Meyers; Center for Primary Care, Prevention, and Clinical Partnerships, AHRQ, 540 Gaither Rd. Rockville, MD 20850; 301-427-1634
Goals:
The main goal is to improve our knowledge to develop more effective ways to prevent, diagnose, and treat common diseases and conditions of aging like bladder and bowel dysfunction in this underserved and vulnerable population
Aims:
1) To determine the incidence of diagnostic errors among patients who die in hospital or are transferred to the ICU two days or more after admission through a structured, standardized adjudication process of cases identified at medical centers affiliated with HOMERuN
2) To combine adjudication data from HOMERuN sites with administrative data from Vizient to determine the degree to which specific factors contribute to the risks of diagnostic errors among our patient cohort, and to use risk estimates to calculate adjusted incidence and impact of factors contributing to diagnostic errors.
3) To apply machine-learning methods to our data to create models that can be used to retrospectively identify patients in whom a diagnostic error was likely to have taken place.
Role: Co-Investigator

NOACs-1510-32651 (Fang) 11/01/16-01/31/22 1.08 calendar months
Patient-Centered Outcomes Research Institute $980,724
The comparative effectiveness of warfarin and new oral anticoagulants for the extended treatment of venous thromboembolism
No assigned program officer
1828 L Street NW, Suite 900, Washington, DC 20036
Goals:
The goal of this project is to compare the benefits and harms of different treatment options for the extended treatment of VTE.
Aims:
1) compare the effectiveness and safety of extended anticoagulation vs. no extended anticoagulation for VTE;
2) compare the effectiveness and safety of NOACs vs. warfarin for the extended treatment of VTE; and
3) describe the effectiveness and safety of different NOACs for the extended treatment of VTE.
Role: Co-Investigator