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TITLE: PSA Level During Midlife and Undiagnosed Prostate Cancer at Autopsy: Understanding Tumor Biology and Racial Disparities

PRINCIPAL INVESTIGATOR: Mark A. Preston, M.D., M.P.H.

CONTRACTING ORGANIZATION: The Brigham & Women's Hospital, Inc., Boston, MA

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Mark A. Preston, M.D., M.P.H.

E-Mail: mpreston@bwh.harvard.edu

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The Brigham & Women's Hospital, Inc.
75 Francis Street
Boston, MA 02115-6110

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14. ABSTRACT

Black men have a higher risk of prostate cancer diagnosis and death, but there remains a dearth of research investigations specifically focused on black populations and an inadequate evidence base for creation of screening guidelines for black men. Data from our group and others has shown that a single baseline PSA measured in midlife strongly predicts long-term risk of prostate cancer, particularly risk of aggressive disease, in both black and white men. We propose to further develop the evidence basis for a risk stratified baseline PSA screening strategy by conducting an autopsy study among black and white men to assess how PSA in midlife relates to the pre-diagnosis natural history of prostate cancer, and how this varies by race. This study is designed to explore the underlying biology by which midlife PSA predicts prostate cancer risk.

15. SUBJECT TERMS
Prostate Cancer, PSA level, autopsy, racial disparities

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1. INTRODUCTION

The study aims to develop smarter screening strategies to accurately identify men at risk for developing aggressive prostate cancer while minimizing harms by testing midlife PSA levels. PSA levels during midlife have been shown by our group and others to strongly predict long-term risk of prostate cancer, particularly risk of aggressive disease, in both black and white men. This could be used to determine which men should undergo more intensive on-going screening, and which men could safely be screened less frequently. The study will obtain blood from autopsies of black and white men to assess how PSA in midlife relates to pre-diagnosis natural history of prostate cancer and to determine when racial differences manifest in the natural history of prostate cancer.

2. KEYWORDS

High-grade prostatic intraepithelial neoplasia (HGPIN)

Kallikrein related peptidase 2 (hK2)

Prostate Specific Antigen (PSA)

SNP = Single nucleotide polymorphisms

TNM = Tumor, node, metastasis

3. ACCOMPLISHMENTS

What were the major goals of the project?

The major goals established in the approved SOW are:

Upon careful examination of the available samples, current accrual progress, and pragmatic procedures, we have conducted a comprehensive re-assessment of our overarching target. Our initial aspiration for sample size was indeed ambitious. However, aiming for even 100 subjects with associated pathology and blood biomarkers holds substantial value and aligns well with our current and enhanced pace. Moreover, the forthcoming objectives can be executed expeditiously, as Major Tasks 3 and 4 are concurrently carried out within the laboratory setting. The subsequent step involves linking these tasks with the pathology findings, streamlining the process further.

Major task 1. Specific Aim 1: - 30% complete

a) Determine the presence, volume, grade, stage, and location of latent prostate cancer and premalignant lesions (HGPIN, ASAP) present in black and white men aged 35-59 undergoing autopsy.

b) Assess how total PSA measured at autopsy predicts for presence of prostate cancer, potentially aggressive prostate cancer (>Gleason 6), HGPIN, and ASAP at autopsy.

c) Assess how the prediction of total PSA is related to volume, grade, and location of disease.
Subtask 1: Collect and clean data
Subtask 2: Develop statistical analyses and analyze data

i. Expected completion: Months 1-6

ii. Actual completion: Actual projected date, pushed out to 2024

Major task 2. Specific Aim 1b: - 30% complete

a) Explore the predictive ability of baseline PSA level in AA men for advanced (Stage>T3b, metastases or death) prostate cancer in the SCCS.
Subtask 1: Collect and clean data
Subtask 2: Develop statistical analyses and analyze data

i. Expected completion: Months 7-12

ii. Actual completion: Actual projected date, pushed out to 2024

Major task 3. Specific Aim 2: - 0% complete

a) Explore whether free PSA and other PSA isoforms, including intact PSA and kallikrein-related peptidase 2, provide additional predictive benefit over total PSA in predicting latent prostate cancer by age and race.
Subtask 1: Collect and clean data
Subtask 2: Develop statistical analyses and analyze data

i. Expected completion: Months 13-24

ii. Actual completion: Actual projected date, pushed out to 2024 to early 2025

Major task 4. Specific Aim 3: - 0% complete

a) Assess whether SNPs related to circulating PSA levels and/or SNPs related to prostate cancer risk provide additional predictive benefit over total PSA measurement in predicting incidental prostate cancer by age and race.
Subtask 1: Collect and clean data
Subtask 2: Develop statistical analyses and analyze data
Subtask 3: Prepare abstract for submission to conferences
Milestone(s) Achieves: Present findings to research groups at BWH/Chicago
Subtask 5: Prepare manuscripts for submission for peer-reviewed publication

i. Expected completion: Months 25-36

ii. Actual completion: Actual projected date, pushed out to 2024 to early 2025

What was accomplished under these goals?

A. Major task 1. Specific Aim 1: Determine the presence, volume, grade, stage, and location of latent prostate cancer and premalignant lesions (HGPIN, ASAP) present in black and white men aged 35-59 undergoing autopsy; Assess how total PSA measured at autopsy predicts for presence of prostate cancer, potentially aggressive prostate cancer (>Gleason 6), HGPIN, and ASAP at autopsy; Assess how the prediction of total PSA is related to volume, grade, and location of disease.

- The data collection process has been augmented with the participation of four selected sites. The formal agreements governing this collaboration have been successfully concluded. During our endeavor, we encountered two primary challenges. Firstly, staffing shortages exacerbated by the Covid pandemic at certain sites contributed to delays in processing pathology samples. Secondly, the previous autopsy authorization policy at Brigham & Women's Hospital (BWH) impeded the utilization of returned cases. However, our autopsy authorization policy has undergone a transformation (June 2023). While in the past, routine sampling (return organ) was solely designated for clinical purposes, the updated policy now permits the utilization of such samples by the hospital, its partners, affiliates, and for endeavors aligned with the hospital's mission, including education and approved research.
- Following a productive discussion with our Autopsy Director, it has been estimated that the new autopsy authorization protocol, would have allowed an additional 17 return cases. A review of these, yields the subsequent outcomes: 9 cases are eligible for allocation, 2 cases exceed the post-mortem interval (PMI) threshold, 3 cases surpass the age of 72.5, and 3 cases exceed both the PMI and age of 72.5. ***This key change will greatly increase eligibility for case inclusion at both BWH and MGH, our primary accruing sites.***
- In addition, kindly refer to the Figure 1 below, which delineates the distribution of the 123 autopsy cases at BWH based on the elimination criteria.

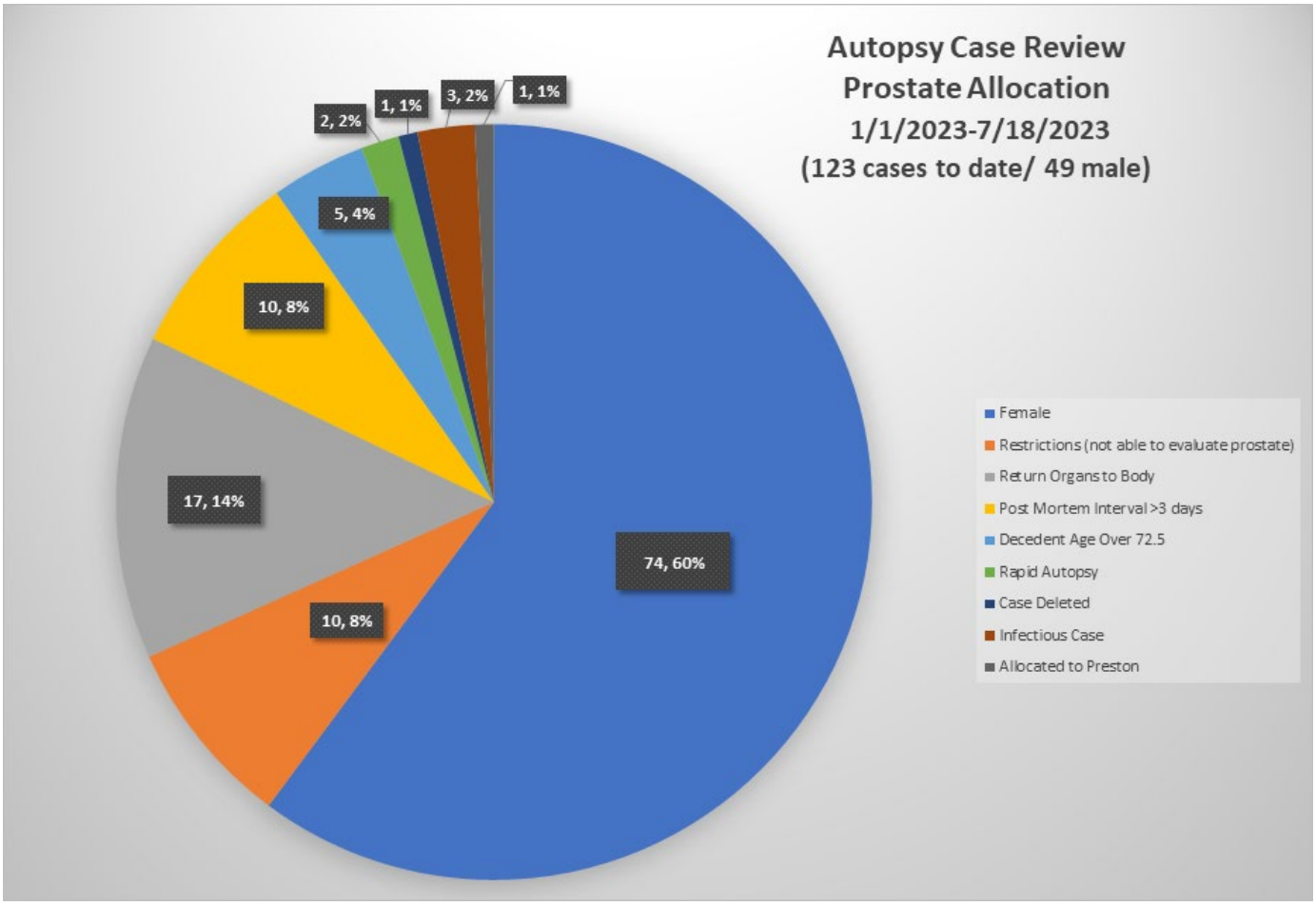

Figure 1- Autopsy Case Review Prostate Allocation

B. Major task 2. Specific Aim 1b: Explore the predictive ability of baseline PSA level in AA men for advanced (Stage>T3b, metastases or death) prostate cancer in the SCCS.

- We are presently engaged in the process of collecting and examining the data. Enclosed below is Table 1 presenting the cause of death, prostate size, and associated observations from Brigham & Women's Hospital (BWH). It's important to note that this table does not encompass a complete analysis of the entire sample pool; rather, it provides a condensed overview tailored for the content of this report. Concurrently, for the samples obtained from other participating sites, our team is actively collaborating to assess the prostate specimens. We are currently in the final stages of securing funding to conduct comprehensive analyses on each allocated sample.
- Approximately 30% of samples have had prostate cancer which is in keeping with existing estimates from literature.

Cause of Death	Prostate Size	Findings
Cardiac, Pneumonia	4.0 x 4.0 x 2.3, 26 grams	Benign prostate tissue
Myeloma, B cell LB Leukemia, Infection		?PCA in B4, stain
AML		?PCA in B14 and B16, stain
Metastatic Gastric vs pancreatic cancer	4.5 x 4.0 x 3.5, 43.6 grams	Benign prostate tissue
CLL, Richters DLBCL	4.5 x 4.3 x 3.0, 34.2 grams	Benign prostate tissue

Cause of Death	Prostate Size	Findings
Acinar Cell Ca of pancreas, Aspergillus pneumonia	5.0 x 4.5 x 4.0, 58.3 grams	PCA, 3 nodules
Ulcerative colitis with perf, abscess, sepsis and PE, CAD too	6.0 x 5.7 x 4.2; 68.3 grams	PCA, bilateral nodules, 3+3=6 on left, 3+4=7 on right, 1.0 cm each
Acute GI hemorrhage with CR failure and infection	4.5 x 4.1 x 3.8, 43.8 grams	PCA, 0.3 cm right, 3+3, pT2 (slide E16)
Mesothelioma	6.0 x 5.0 x 3.8, 85.5 grams	PCA, left up to 1.0 cm, 3+3, pT2 (slides
Small Cell CA	4.5 x 3.1 x 2.8, 29.6 grams	Benign prostate tissue
Sudden cardiac death	5.3 x 4.6 x 4.2 cm, 106 grams	ASAP vs BPT vs PCA
Non-ischemic cardiomyopathy, cardiomegaly, MI	4.7 x 4.5 x 4.5cm, 51.8 grams	Benign prostate tissue
Sepsis, Ischemic bowel, severe vascular disease	5.0 x 4.7 x 4.5 cm, 82.6 grams	Benign prostate tissue, ? Infarct ? Squam/SM
EARLY ONSET ALZHEIMER'S DISEASE (clinical diagnosis, with evidence of APOE e4 homozygosity)	4.5 x 3.8 x 1.2cm, 45.6 grams	Benign prostate tissue, Amyloid of SV
POORLY DIFFERENTIATED SQUAMOUS CELL CARCINOMA OF THE LEFT LUNG	4.7 x 4.3 x 3.4 cm, 50.7 grams	Benign prostate tissue
	4.0 x 3.0 x 2.0 cm, 44.6 grams	Benign prostate tissue
Pneumonia, Respiratory failure, DAD, MI	4.1 x 3.9 x 2.4, 52.3 grams	Benign prostate tissue
Cutaneous T-cell lymphoma, Pes	5.2 x 4.5 x 3.4cm, 40 grams	Benign prostate tissue

A. Major task 3. Specific Aim 2: Explore whether free PSA and other PSA isoforms, including intact PSA and kallikrein-related peptidase 2, provide additional predictive benefit over total PSA in predicting latent prostate cancer by age and race.

B. Major task 4. Specific Aim 3: Assess whether SNPs related to circulating PSA levels and/or SNPs related to prostate cancer risk provide additional predictive benefit over total PSA measurement in predicting incidental prostate cancer by age and race.

The commencement of Major Tasks 3 and 4 is contingent upon the shipment of all collected blood samples to Dr. Hans Lilja's laboratory in Malmo, Sweden, which is scheduled to take place at the study's conclusion for analysis.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

With the attainment of HRPO approval and the resumption of collaboration with the Pathology laboratory, our focus has shifted towards addressing the intended objectives initially outlined for Year 1-3. Our partnerships with The University of Chicago, Duke University, Boston Medical Center, and Massachusetts General Hospital in the acquisition of prostate and aortic blood samples from around 110 men who succumbed to causes unrelated to prostate cancer are progressing favorably. We are actively engaged in monthly meetings to evaluate accrual progress and exchange insights for enhanced accrual practices. Additionally, we maintain biweekly check-ins with the respective sites' Clinical Research Coordinators (CRCs) to ensure up-to-date status reports.

4. IMPACT

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

This comprehensive study aims to study how a baseline PSA can predict for future risk of prostate cancer, particularly that of aggressive disease in black and white men. Knowing this, will be beneficial and relevant to the larger population of men in determining who should undergo more intensive on-going screening and which men could safely be screened less frequently.

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

As previously indicated, a significant evolution has taken place in our autopsy authorization policy as of June 2023. Where routine sampling (return organ) was previously exclusively reserved for clinical objectives, the revised policy now grants the opportunity for the utilization of these samples by the hospital, its partners, affiliates, and for initiatives that align with the hospital's mission, encompassing education and sanctioned research pursuits. ***This will allow for an almost tenfold increase.***

Please see below *Figure 2* indicating accrual improvement from 2022-2023 for participating sites. We are accruing better now with all sites activated, and processes/logistics in place.

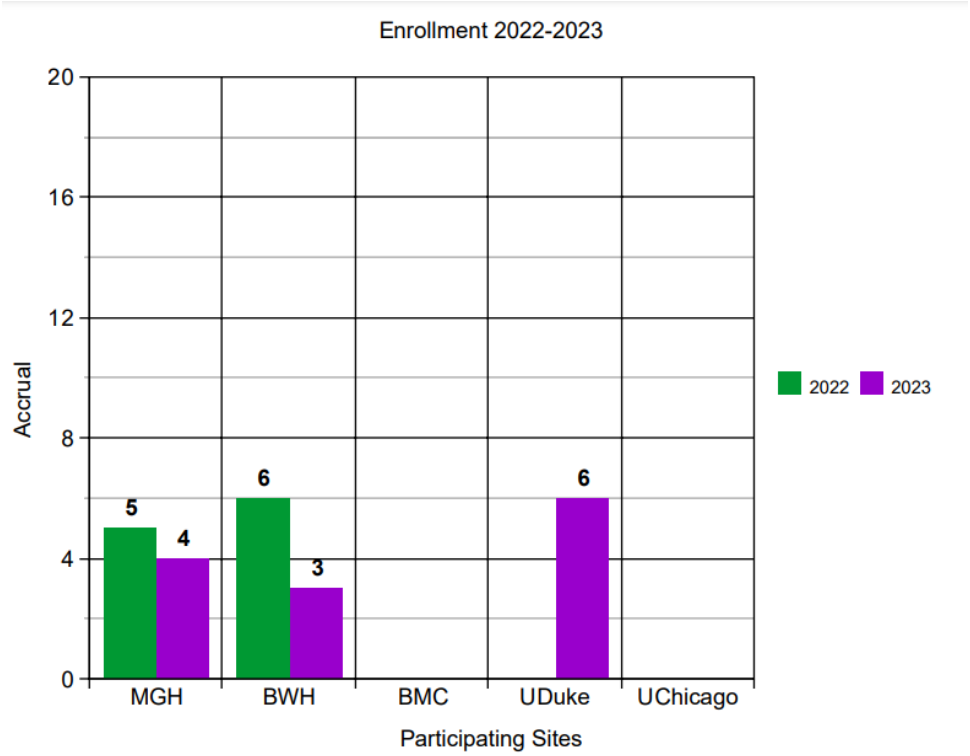

Figure 2- Site Enrollment 2022-2023

Figure 3 below illustrates the progressive rise in our total enrollment since the initiation of the study from all sites. It's important to observe that the projection presented below pertains specifically to BWH and MGH, which serve as our primary enrollment sites, given our study target of 100 cases. Furthermore, with the inclusion of Duke and UChicago, we anticipate a substantial exponential surge that will supplement the projected figures Y2024.

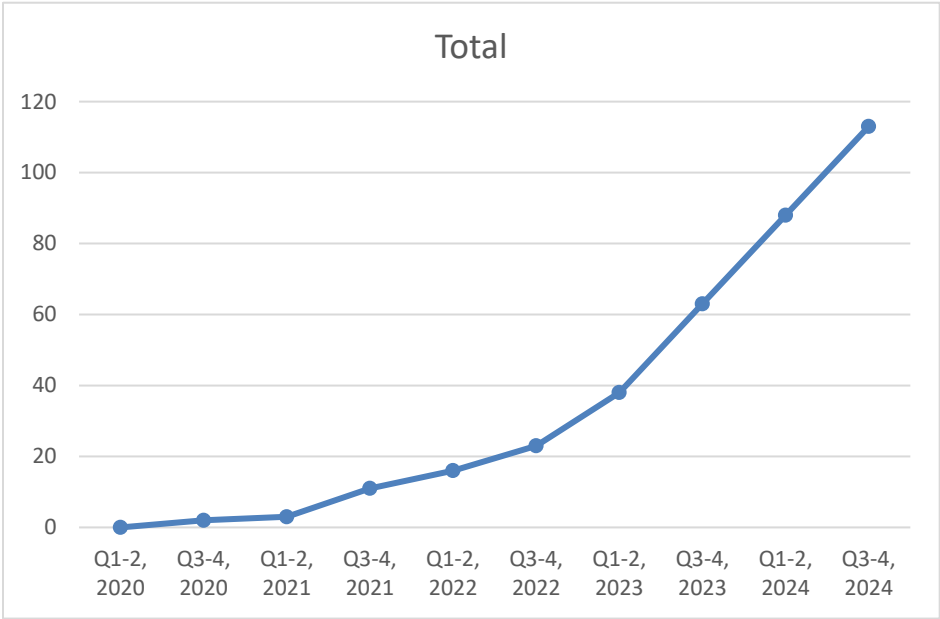

Figure 3- Overall Study Accrual 2020-2023

Actual or anticipated problems or delays and actions or plans to resolve them.

As describe above.

Changes that had a significant impact on expenditures

There was a delay in hiring staff for the pathology team, the team was stretched to their limits in terms of performing autopsies for research related tasks given this shortage.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects: No changes have been made regarding the use of care of human subjects.

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

Publications, conference papers, and presentations: Nothing to report.

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: REDCap database

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Mark A. Preston, M.D., M.P.H.*
Project Role:	PI
Nearest person month worked:	1.8 CM
Contribution to Project:	*Dr. Preston has overseen the designing, coordinating and execution of this proposed research study.*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	*Scott Eggener, M.D.*
Project Role:	Co-Investigator
Nearest person month worked:	0.6 CM
Contribution to Project:	*Dr. Eggner has overseen prostate accruement and assessment at University of Chicago.*

Funding Support:	DOD - W81XWH-19-1-0708

Name:	*Chin-Lee Wu, M.D.*
Project Role:	Co-Investigator
Nearest person month worked:	0.6 CM
Contribution to Project:	*Dr. Wu has overseen prostate accruement and assessment at MGH.*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	*Sarah Higgins, M.D*
Project Role:	Co-Investigator
Nearest person month worked:	0.6 CM
Contribution to Project:	*Dr. Higgins has overseen prostate accruement and assessment at Boston Medical Center.*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	*Michelle Hirsh, M.D.*
Project Role:	Co-Investigator
Nearest person month worked:	0.6 CM
Contribution to Project:	*Dr. Hirsch has overseen prostate accruement and assessment.*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	Brant Inman, M.D
Project Role:	Co-Investigator
Nearest person month worked:	0.4 CM
Contribution to Project:	*Dr. Wilson provided guidance on the process for data management and statistical analysis of this study. She devoted 10% effort during the period 10/1/22-present.*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	Kathryn Penney, Sc.D.
Project Role:	Co-Investigators
Nearest person month worked:	0.60 CM
Contribution to Project:	*Dr. Penney has provided guidance on the methodology related to the genotyping assays and analysis which will occur in Aim 3.*

Funding Support:	DOD - W81XWH-19-1-0708

Name:	Rieya Philip
Project Role:	Research Assistant
Nearest person month worked:	2.0 CM
Contribution to Project:	*Rieya oversaw the IRB and HRPO submissions*
Funding Support:	DOD - W81XWH-19-1-0708

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Dr. Kathryn Wilson left the Harvard T.H. Chan School of Public Health as of 01/31/2020. A replacement for her role on this project has not yet been identified.

What other organizations were involved as partners?

Organization Name:

Location of Organization:

Partner's contribution to the project

Financial support;

In-kind support: Not applicable

Facilities *(e.g., project staff use the partner's facilities for project activities)*;

Collaboration *(e.g., partner's staff work with project staff on the project)*;

Personnel exchanges *(e.g., project staff and/or partner's staff use each other's facilities, work at each other's site)*; and

Other.

8. SPECIAL REPORTING REQUIREMENTS

- **QUAD CHARTS:**

9. APPENDICES