AWARD NUMBER: W81XWH-19-1-0318

TITLE:

Using Affinity-Based Proteomics to Identify Diagnostic and Plasma Biomarkers for Endometriosis

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CONTRACTING ORGANIZATION: Brigham and Women's Hospital, Boston, MA

REPORT DATE: October 2021

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2021	Annual Report	01Sep2020-31Aug2021

4. TITLE AND SUBTITLE

Using Affinity-Based Proteomics to Identify Diagnostic and Plasma Biomarkers for Endometriosis

5a. CONTRACT NUMBER
W81XWH-19-1-0318

5b. GRANT NUMBER
GRANT12711884

5c. PROGRAM ELEMENT NUMBER
PRMRP PR181444

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release, Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

During the past year, we evaluated the association between 1,305 proteins in blood samples from 142 confirmed endometriosis cases and 74 controls participating in the Women's Health Study: From Adolescence to Adulthood (A2A) and identified 63 proteins significantly associated with endometriosis with an absolute fold change of greater than 1.2. Furthermore, we identified biological pathways associated with endometriosis, including cell migration and angiogenesis that were upregulated in endometriosis compared to controls ($p<6.0x10^{-9}$). Furthermore, we observed that few proteins overlapped across lesion colors, suggesting different etiologic pathways. These findings were presented in an oral presentation at the World Congress of Endometriosis in March 2021. Among the cases we also evaluated proteins and pathways associated with persistent pain. These results were accepted for an oral presentation at the annual ASRM meeting to be held in October 2021. Finally, proteomics data was recently received on NHSII samples and quality control analyses are currently under way.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	29	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

	Page
1. Introduction	4
2. Keywords	4
3. Accomplishments	3
4. Impact	9
5. Changes/Problems	9
6. Products	10
7. Participants & Other Collaborating Organizations	11
8. Special Reporting Requirements	12
9. Appendices	12

1. INTRODUCTION:

Endometriosis, which is characterized by pain and infertility, is the most frequent reproductive health diagnosis among female veterans along with menstrual disorders. Notoriously difficult to diagnose, the time between symptom onset and endometriosis diagnosis averages seven years, resulting in prolonged pain symptoms leading to decreased activity and poor mental health, greatly impacting women physically, psychologically, and economically over the life-course. Identifying diagnostic and prognostic biomarkers would enable earlier intervention and prevent progression to severe pain and infertility. However, identification of endometriosis biomarkers has been limited by the heterogeneity of the disease, inappropriate control groups, and lack of prospectively collected samples. Furthermore, progression of endometriosis is not well understood. Discovery of non-invasive diagnostic and prognostic biomarkers for endometriosis has the potential to revolutionize current medical practice, leading to earlier diagnosis and interventions as well as better clinical care that could significantly impact improvement in clinical outcomes of endometriosis. We hypothesize that endometriosis development and progression will lead to altered circulating protein profiles related to systemic inflammation and immunity years before emergence of symptoms and the clinical diagnosis of endometriosis that will be detectable through the novel proteomics technology, SOMAscan, enabling early diagnosis of endometriosis. In addition, alteration of inflammation and immune proteins in systemic environments will be greater among women who do not experience pain remediation after surgical treatment. We will utilize data and specimens from the two population-based cohort studies, the Nurses' Health Study II (NHSII), a prospective cohort study with blood samples collected months to years before endometriosis diagnosis, and the Women's Health Study: Adolescent to Adulthood (A2A), a deeply phenotyped longitudinal cohort of endometriosis patients, to identify non-invasive diagnostic and prognostic protein biomarkers for endometriosis. We urgently need endometriosis biomarkers to reduce the delay to treatment and reveal new potential therapeutic targets to improve treatment outcomes and quality of life in these patients. Our unique resources will enable us to identify novel diagnostic and prognostic blood protein biomarkers for endometriosis. In the **short-term**, the proteomic data generated in our study will provide clinically applicable non-invasive diagnostic and prognostic biomarkers for endometriosis and improve treatment outcomes. **Long-term**, our study will provide biological insight to the heterogeneity and different pathogenesis by types of endometriosis and progression from the aspect of inflammation, immune dysregulation, and angiogenesis, which could lead to potential prevention strategies and development of novel therapeutic targets including immunotherapies.

2. KEYWORDS:

Endometriosis, proteomics, biomarkers, plasma, SOMAscan, diagnosis, predictor, risk model, pain

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1. Generating proteomics data

a. Local IRB Approval: IRB Approved 11/14/19 and 12/23/19
b. Milestone #1: HRPO Approval obtained 4/3/20

Specific Aim 1: In prospectively collected samples from 200 NHSII participants with laparoscopically confirmed endometriosis and 200 without, identify proteins that differentiate women who will be diagnosed with laparoscopically confirmed endometriosis from controls.

Major Task 2. Generating proteomics data on NHSII samples

a. Subtask 1. Identify appropriate cases and controls in NHSII. Retrieve and aliquot plasma samples: Due to the Covid-19 pandemic all labs were shut down for 4 months which delayed the identification and retrieval of samples from NHSII. Nevertheless, the samples were identified, retrieved from storage, aliquoted, and delivered to the Libermann lab by 8/31/20.
b. Subtask 2. Create quality control (QC) samples and plan how to align the blinded QCs and samples for proteomics assay: Samples with integrated QCs were delivered to the Libermann lab on 08/31/20.
c. Subtask 3. Measure 1,305 proteins and check quality control for variation within and between plates on NHSII samples: Assays are complete as of 9/10/21 and quality controls metrics have been calculated as of 9/17/21.
d. Milestone #2: Generating proteomics NHSII data. Completed as of 9/10/21.

Major Task 3. Identify proteins that differentiate endometriosis cases from controls using proteomics data from 200 cases and 200 controls in the NHSII

a. Subtask 1. Identify proteins that differentiate endometriosis cases from controls using the prospective samples in NHS: Planned completion by 06/01/22
b. Subtask 2. Manuscript preparation: Planned completion by 8/31/22
c. Milestone #3: Publish proteomics data predictive of endometriosis

Specific Aim 2: In plasma from 150 deeply phenotyped cases and 50 matched controls from the A2A study, determine whether proteins differ between subtypes.

Major Task 4. Identify proteins that differentiate endometriosis subtypes using proteomics data from 150 cases and 50 controls in the A2A

a. Subtask 1. Identify proteins that differentiate endometriosis cases from controls in A2A: Completed SOMAscan run on 7/20/20. Data analysis is complete, results were presented as oral presentation at the World Congress of Endometriosis on 03/07/21, and manuscript has been drafted. The manuscript is currently under review by coauthors, and we expect to have it submitted by 10/31/21.
b. Subtask 2. Evaluate whether proteins identified perform better than CA125 to discriminate cases from controls: Planned completion by 3/31/22
c. Subtask 3. Manuscript preparation: We expect this task to yield two manuscripts. The first has been drafted and will be submitted this calendar year (2021). We have completed data analyses for the second and we expect to have that manuscript drafted by the next progress report (September 2022).
d. Milestone #4: Publish protein performance compared to CA125 and by endometriosis subtype

Specific Aim 3: In preoperative samples from 100 women with endometriosis from the A2A study, identify proteins and pathways that discriminate between those who have progressive disease, characterized by chronic pain and poor quality of life, and those who improve after surgery.

Major Task 5. Identify proteins associated with progression of endometriosis

a. Subtask 1. Identify proteins associated with persistent pain and/or poor quality of life after surgical treatment of endometriosis in the A2A progression study: Completed SOMAscan run on 7/20/20. Data analyses were completed in August 2021.
b. Subtask 2. Use systems biology to identify pathways relevant to progression of endometriosis: Pathway analyses have been completed and an abstract was submitted to the American Society for Reproductive Medicine (ASRM) conference and invited for an oral presentation on 10/20/21
c. Subtask 3. Manuscript preparation: Planned completion by 10/31/22
d. Milestone #5: Publish proteins associated with endometriosis progression

What was accomplished under these goals?

1) Major activities

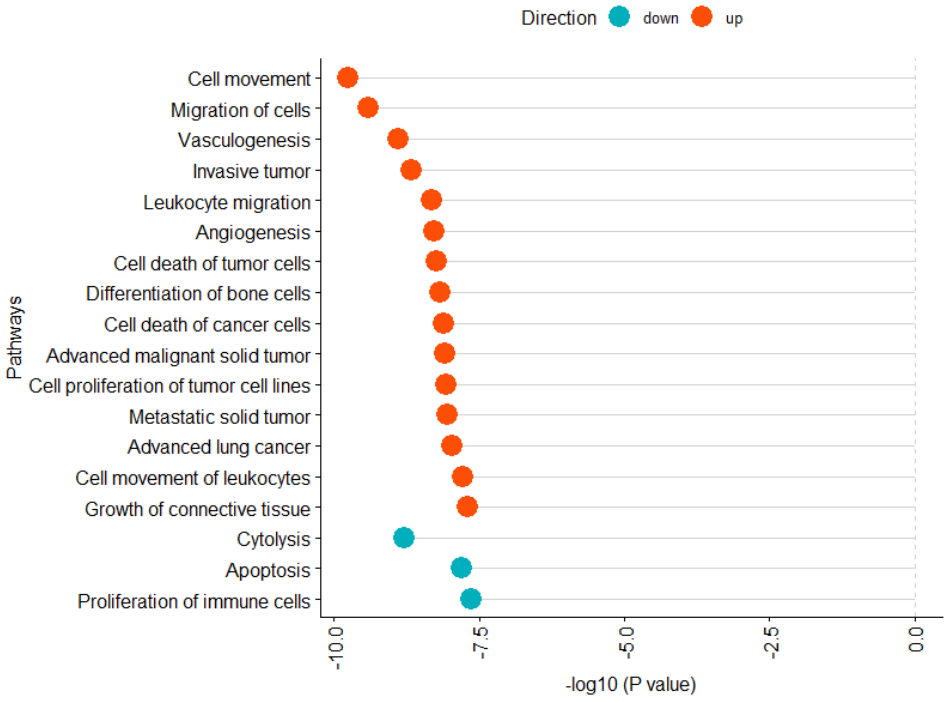
Over the past year, we accomplished the following major activities. For Aim 1, we successfully generated proteomics data on 1,305 proteins using the SOMAscan platform on 200 cases and 200 control samples from the Nurses' Health Study II cohort. Data analyses to evaluate the reproducibility of blinded quality control samples demonstrated high quality and reproducibility of the SOMAscan data. For Aim 2, we completed our data analyses evaluating individual proteins and proteomic pathways that differentiate cases and controls and the manuscript draft is currently under review by coauthors. In addition, we completed analyses on proteins and pathways associated with different endometriosis subtypes. For Aim 3, we have successfully completed data analyses and submitted an abstract to the ASRM conference which was selected for an oral presentation which will be delivered by Dr. Naoko Sasamoto on 10/20/21 in Baltimore, Maryland.

2) Specific Objectives

a. Identify proteins that differentiate endometriosis cases from controls in prospectively collected samples from the Nurses' Health Study II.
b. Identify proteins that differentiate cases and controls in A2A.
c. Evaluate whether proteins identified perform better than CA125 to discriminate cases from controls.
d. Identify proteins associated with persistent pain and/or poor quality of life after surgical treatment of endometriosis in the A2A progression study.

3) Significant results or key outcomes, including major findings, developments, or conclusions

Figure 1. Top pathways associated with endometriosis based on 63 proteins with p<0.05 and absolute fold change >1.2



This year we were able to move our research to discover diagnostic and prognostic biomarkers for endometriosis forward on several fronts. First, in the discovery of diagnostic biomarkers, we successfully measured 1,305 protein levels on 200 endometriosis cases and 200 matched controls from the Nurses' Health Study II (Aim 1). Although we have not had a chance to analyze these results yet (the stated goal in our original grant was to complete this by the end of year 2), the proteins levels have been measured and the quality control metrics with regard to normalization and calibration are good, suggesting the results are valid and reliable. Analyses of the blinded quality control samples demonstrated that 90% (1182/1305) of the proteins have a CV<25% and an ICC>0.4, adding strong evidence that the SOMAscan data for these NHS II samples are highly reproducible. Given delays due to the pandemic, leading to a late receipt of the samples by the lab, we are pleased with our progress on this front.

In Aim 2, we sought to evaluate case control differences in proteins by analyzing baseline data cross sectionally from the A2A. Using proteomics data generated from the A2A specimens in year 1, we analyzed data with Dr. Long Ngo performing the statistical analyses and all investigators contributing in real time to the analysis plan and interpretation of results through weekly Zoom meetings. Through these analyses we identified 63 proteins associated with endometriosis with a nominal p-value <0.05 and absolute fold change >1.2. Furthermore, we identified biological pathways that were associated with endometriosis. As illustrated in **Figure 1**, pathways related to cell migration and angiogenesis were upregulated in endometriosis compared to controls (p-value<6.0×10^{-9}). Furthermore, when we examined proteins associated with lesion colors, there were few proteins that overlapped across lesion colors, suggesting different pathways of pathogenesis as illustrated by the Venn diagram in **Figure 2**. A manuscript has been drafted by Dr. Sasamoto and is currently being reviewed by coauthors.

Figure 2. Venn diagram of overlapping proteins by lesion colors among endometriosis cases

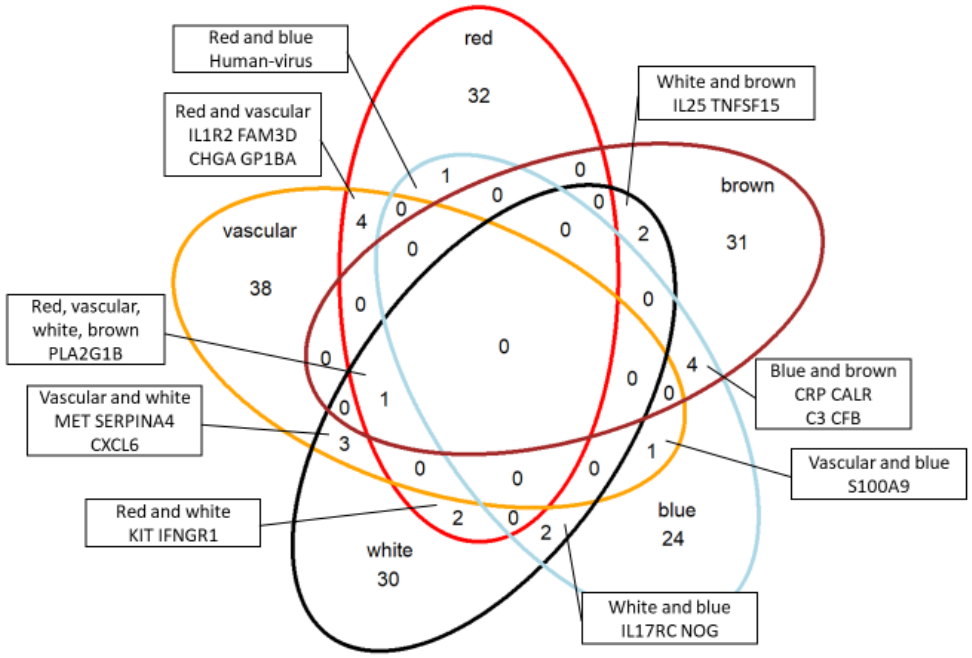
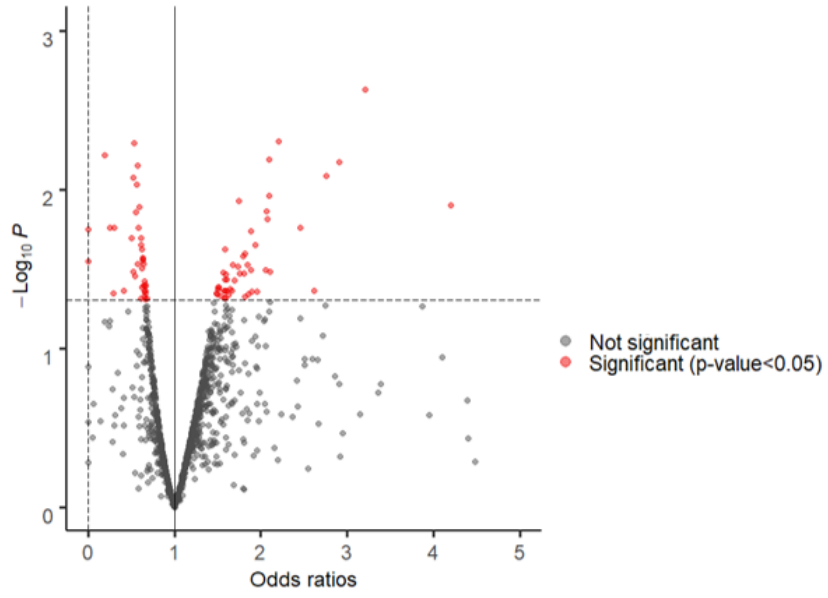


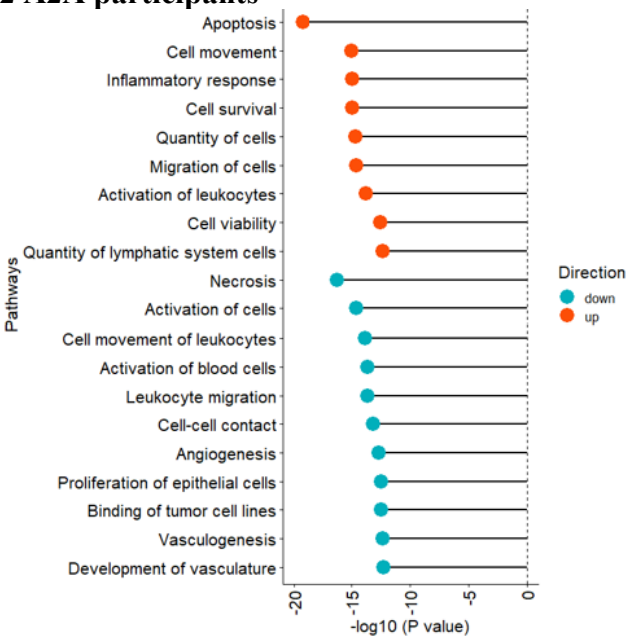
Figure 3. 94 proteins measured at baseline are associated with persistent pain after endometriosis surgery among 142 A2A participants (p<0.05)



Although the objectives in Aim 3 are scheduled for year 3 we were able to get started on these analyses this year while we were waiting for the NHSII data needed for Aim 1. Specifically, we evaluated proteins measured at baseline and persistent pelvic pain after surgery. Again, statistical analyses were led by Dr. Ngo with discussion among the investigators at our weekly meetings. Our analyses included 142 laparoscopically confirmed endometriosis cases from the A2A study. All endometriosis cases had superficial peritoneal lesions only and underwent excision and ablation of all visible disease. One-year post-surgery, pelvic pain worsened for 51 (36%) endometriosis

cases, while pelvic pain stayed the same for 25 (18%) and improved for 66 (46%). We identified 94 proteins (**Figure 3**) associated with worsening pelvic pain one-year post-surgery (nominal p<0.05). Compared to those with improved pelvic pain one year post-surgery, those with worsening pelvic pain had higher plasma levels of CD63 antigen (OR=3.21, 95% CI:1.52-6.81), N-acetyl-D-glucosamine kinase (OR=2.21, 95% CI:1.27-3.84) and lower levels of parathyroid hormone (OR=0.54, 95% CI: 0.35-0.83), soluble angiopoietin-1 receptor (OR=0.20, 95% CI: 0.06-0.63). Pathways related to cell movement and inflammatory response were upregulated and pathways related to angiogenesis were downregulated in endometriosis cases with worsening post-surgical pelvic pain compared to those with improved pain (**Figure 4**). Dr. Sasamoto submitted an abstract on this work and was invited to give an oral presentation at the ASRM annual meeting in Baltimore on October 20, 2021.

Figure 4. Top 20 pathways associated with worsening pain at 12 months after endometriosis surgery among 142 A2A participants



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

A high school summer student, Alexa Poremba, shadowed our group for the summer and submitted an abstract on a related pilot project using the same proteomic platform used in our project to measure 1,305 proteins in peritoneal fluid samples to the Discover Brigham meeting which is a local meeting at Brigham and Women's Hospital that allows trainees and junior faculty to present ongoing work to the local academic and public community. Alexa will be preparing a poster presentation of this work on November 3, 2021.

How were the results disseminated to communities of interest?

Results of the cross-sectional analysis was selected as oral presentation at the 14th World Congress of Endometriosis on March 07, 2021 and will be submitted for publication in a scientific journal in the next few months and results of the persistent pain analyses will be presented at the ASRM annual meeting in October 2021.

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

In the next reporting period, we will analyze the proteomics data from the prospectively collected Nurses Health Study II to identify proteins associated with endometriosis risk and we will continue our analyses of proteomics data in the A2A participants, including the evaluation of how change in protein levels over time relate to prognosis and persistent pain. Finally, in the next funding period we will prepare and submit a manuscript related to proteins measured in the A2A study and persistent pain.

4. **IMPACT:**

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

Nothing to report

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

We continue to feel the impact of lab closures and delays on the lab queues which resulted in delayed retrieval and aliquoting of the NHSII samples. We expected to have analyzed these results over the past year, but we just received the data this month. Consequently, we will analyze the results in the upcoming year.

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

Since we have all our proteomics data in hand, we do not anticipate and further delays.

Changes that had a significant impact on expenditures

No changes were made that impacted expenditures.

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 in 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**

Journal publications.

We do not have any publications so far. We anticipate one or two publications in the next grant year.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Results on proteomic profiles associated with endometriosis compared to controls were presented as selected oral presentation at the international World Congress of Endometriosis on 03/07/21. Results on proteomics profiles by endometriosis lesion color was presented at the local Connors Brigham Research Institute Symposium on 05/24/21.

- **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: Kathryn L. Terry, ScD - No Change

Name: Naoko Sasamoto, MD MPH
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0002-4526-2181
Nearest person month worked: 2
Contribution to Project: Dr. Sasamoto is leading the development and implementation of the study protocol, analysis plans, statistical programming, data interpretation and manuscript preparation.
Funding Support:

Name: Allison Vitonis, MS – No Change

Name: McKenzie Goodwin
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): ----------
Nearest person month worked: 1
Contribution to Project: As the research assistant, Ms. Goodwin, retrieves samples from storage, aliquots them, and transports samples to the DF/HCC proteomics core. After the proteomics assays are complete, she retrieves and restores the remainder of the samples in the BCE biorepository freezers.
Funding Support:

Name: Christopher Murphy - No Change

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

Other Support Changes for Key Personnel is attached

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

DOD - OTHER SUPPORT

Kathryn L. Terry, ScD
***New funding since YR1 Report**

Title: The Boston Center for Endometriosis: A First-in the World Care and Research Program for Women of all Ages
Time Commitment: 1.2 CM
Supporting Agency: J. Willard and Alice S. Marriott /The Boston Center for Endometriosis
Grant Number: NA
Role: Co-Investigator
Grants Specialist: Jenny Sadler Gallagher, MPH
Phone:
Email: Jenny.Sadler@childrens.harvard.edu
Performance Period: 07/01/2012-12/31/2021
Level of funding: (TC)
Project Goals: Design and conduct for study enrollment and data and biologic sample collection within Brigham and Women's Hospital and Boston Children's Hospital
Specific Aims: Establish a longitudinal cohort of girls and women with endometriosis and appropriate comparison girls/women with detailed life course data and extensive biologic samples storage.
Overlap: None

*Title: Relating molecular subgroups of endometriosis-associated ovarian cancers to survival and risk factors Time Commitments: 1.20 CM
Supporing Agency: National Institutes of Health
Grant Number: R01-CA248288
Grant Specialist: Ashley Salo
Phone number:
Email: ashley.salo@nih.gov
Performance Period: 01/13/2021-12/31/2025
Level of funding: (TC)
Project Goals: Aim 1. To characterize molecularly defined subgroups of ENOC and CCOC, we will statistically integrate sequencing and array data from gene expression, somatic mutations, and differentially methylated regions from 523 ENOC and 344 CCOC. Clustering approaches will use samples divided into training and test sets.
Aim 2. To identify subgroup-specific survival associations, we will relate molecular subgroups defined in Aim 1 to overall survival using Cox regression models.
Aim 3. To identify subgroup-specific risk factor associations, we will relate molecular subgroups defined in Aim 1 to lifestyle risk factors.
Aim 4. To identify opportunities for overlapping treatments in patient care, we will statistically compare the patterns of molecular features of the ENOC and CCOC subgroups with various TCGA cancer subgroups. Overlap: None

*Title: Changing contraceptive patterns and ovarian cancer risk
Time Commitments: 2.4 CM
Supporting Agency: National Institutes of Health 1R01CA258679
Address: NIH/NHLBI Information center
P.O Box 30105

Bethesda, MD 20824-0105
Contracting/Grants Officer: Goli Smimi; email: goli.smimi@nih.gov
Tel:
Performance Period: 07/01/2021-06/30/2026
Level of funding:
Project Goals: To examine the impact of changing contraceptive patterns of intrauterine device on ovarian cancer risk and to examine its impact on the local immune mechanisms.
Specific Aims: Aim 1. Estimate the association between IUD use and risk of ovarian cancer, including by histotype, in 17 case-control studies (20,314 cases, 26,099 controls) and 7 cohort studies (678,650 participants, 1,891 cases) with prospectively collected data. We hypothesize that:

a. IUD use is associated with a decreased risk of invasive ovarian cancer, particularly low grade serous and clear cell histotypes.
b. Secondarily, we will evaluate these associations by race and birth cohort.

Aim 2. Describe how timing and type of IUD use influence ovarian cancer risk in 13 case-control and 4 cohort studies. We hypothesize that:

a. IUD use before oral contraceptive use, particularly in nulliparous women, attenuate the inverse association or even increase ovarian cancer risk.
b. Progesterone-releasing IUDs decrease the risk of ovarian cancer more than other IUD types.

Aim 3. Evaluate whether the association between IUD use and ovarian cancer risk differs by the tumor immune microenvironment, utilizing 3,530 cases on tissue microarrays. We hypothesize that:

a. IUD use is associated with an increased risk of ovarian tumors with low stromal expression of CD163.
b. IUD use versus OC use alone will be differentially associated with ovarian cancer risk by the proportion of immune cell types in the tumor, including cytotoxic T cells, Tregs, or macrophages, identified by expression of CD3, CD8, CD4, CD69, FOXP3, and CD163.

Overlap: None

*Title: Identifying early detection metabolomics biomarkers for high-grade serous ovarian cancer
Time Commitments: .6 CM
Supporting Agency: Sperling Family Foundation (Broad Institute/BWH)
Address: 415 Main Street
Cambridge, MA
75 Francis Street, Boston, MA 02115
Contracting/Grants Officer: Ashlin Bolton
Phone:
Performance Period: 03/01/2021-02/28/2022
Level of funding:
Project Goals: To discover novel early detection metabolomic biomarkers for ovarian cancer and elucidate the systemic metabolomic profiles in the early phase of ovarian cancer development.
Specific Aims: The primary objective of this innovative application aims to discover novel early detection metabolomic biomarkers for ovarian cancer and elucidate the systemic metabolomic profiles in the early phase of ovarian cancer development utilizing the biospecimens and clinical data at the Brigham and Women's Hospital and applying the world-class innovative technology of the highly reproducible, high-throughput, multiplex metabolomics technology at the Broad Institute.
Overlap: No scientific or budgetary overlap

Title: Mucins and immune cell interactions in ovarian cancer pathogenesis & progression
Supporting Agency: National Institutes of Health
Grant Number: R35 CA197605
Role: Co-Investigator (PI: Cramer)

Grants Specialist: Neeraja Sathyamoorthy Ph.D.
Email: ns61r@nih.gov
Phone:
Time Commitment: 1.8 CM
Performance Period: 04/01/2016-03/31/2023
Level of funding: (TC)
Goals: The goal of this proposal is to study the inflammatory pathway leading to the development ovarian cancer and to further understanding mechanisms of risk that may lead to early detection.
Specific Aims: Review obstacles to cancer prevention and early detection including the needs:

1) to reconcile individual risk factors for ovarian cancer with the totality of epidemiologic evidence
2) to find unifying explanations for risk factors common to different cancers
3) to demonstrate that mucin tumor antigen levels are changed not only by the tumor but also by risk factors for the tumor
4) to be able to consider serum biomarkers in the context of the white blood count (WBC).

Overlap: None

Title: What is Endometriosis? Deep Phenotyping to Advance Diagnosis and Treatment
Supporting Agency: National Institutes of Health
Grant Number: R01HD094842
Role: Subcontract PI (PI: Missmer at Michigan State University)
Grants Specialist: Margaret Young
Phone:
Email: Margaret.young@nih.gov
Time Commitment: 1.2 CM
Performance Period: 08/01/2018 - 04/30/2023
Level of funding:
Goals: We will utilize three existing diverse studies of adolescents and women for whom surgical, clinical and participant data as well as blood and tissue samples have been harmonized via the WERF EPHect tools. The goal of our study will be to identify unique classifications of endometriosis patients that inform non-invasive diagnostics, response to current treatments, and novel treatment pathways - stratifying discoveries by participant symptom presentation, and for the cases, by surgical and imaging visualized disease characteristics to capture the full heterogeneity of endometriosis.
Specific Aims: Aim 1: Identify plasma markers of endometriosis across independent and synergistic pathways; Aim 2: Quantify informative heterogeneity in associated transcriptomic and milieu-related plasma markers by disease phenotype; Aim 3: Further identify informative disease phenotypes by symptom presentation; Aim 4: Evaluate heterogeneity in plasma markers, disease phenotype, and symptom presentation by participant characteristics
Overlap: None

Title: Inflammation and the Malignant Transformation of Endometriosis
Supporting Agency: Department of Defense
Grant: W81XWH18PRMRPDA / PR181241
Role: Co-Investigator (PI: Harris at Fred Hutchinson Cancer Center)
Grants Specialist: Patricia Modrow, Ph.D.
Phone:
Email: patricia.modrow@amedd.army.mil.
Time Commitment: 0.60 CM
Performance Period: 02/01/19-01/31/22

Level of funding: (TC)
Goals: We will examine the association between inflammatory markers in peritoneal fluid and cancer driver mutations (ARID1A, PIK3CA, PPP2R1A, CTNNB1, PTEN, KRAS, BRAF, ERBB2) and immunohistochemical (IHC) markers of cell proliferation (Ki67) and invasiveness (E-cadherin, α- and ß-catenin) in endometriosis tissue. We hypothesize that women with higher levels of peritoneal fluid inflammatory markers will have endometriosis tissue with higher numbers of cancer driver mutations and increased invasive/proliferative activity. We will evaluate whether inflammation-related factors (ovulatory cycles, NSAID use, BMI, dysmenorrhea, tubal ligation, IUD use, pelvic infections) and systemic inflammation (e.g., CRP, IL-6 plasma levels) are associated with inflammatory markers in peritoneal fluid, taking into account menstrual cycle phase.
No Overlap

*Title: Using genetic predictors of CA125 to improve personalized ovarian cancer screening
Time Commitments: .6 CM
Supporting Agency: Marsha Rivkin Center for Ovarian Cancer Research
Address: 801 Broadway, Suite 701, Seattle WA 98122
Contracting/Grants Officer: Jackie Lang, PhD Tel:
Performance Period: 04/01/2021-03/31/2023
Level of funding:
Project Goals: To identify genetic predictors of CA125 and examine whether adding genetic predictors of CA125 will improve the discriminatory performance of personalized CA125 cutpoints in blood collected months prior to diagnosis in prospective cohorts of PLCO, EPIC, and NHS/NHSII.
Specific Aims: Aim 1. Identify genetic predictors of CA125 using data on 4,391 women without ovarian cancer in PLCO, EPIC, NHS/NHSII, and NEC.

a. Identify novel genetic variants associated with blood CA125 levels by menopausal status.
b. Determine whether genetic variants associated with blood CA125 levels differ by race.
c. Secondarily, identify genetic predictors associated with change in CA125 over time.

Aim 2. Examine whether adding genetic predictors of CA125 to our model of personalized CA125 cutpoints will improve the discriminatory performance in blood collected months prior to diagnosis in prospective cohorts of PLCO, EPIC, and NHS/NHSII.
Overlap: None

*Title: Identifying proteomic profiles and biological networks of early-stage ovarian cancer
Time Commitment: .60 CM
Supporting Agency: DOD W81XWH2110320
Role: Mentor (PI: Sasamoto)
Grant Specialist: ABIGAIL STROCK
Phone number:
Email: abigail.l.strock.civ@mail.mil
Time Commitment: .6 CM
Performance Period: 04/01/2021 - 03/31/2025
Level of funding: (TC)
The overarching goal of this proposal is to elucidate molecular profiles associated with endometriosis symptom progression with a multi-omics approach (i.e. gene expression and proteomics), using data on post-surgical outcomes and paired tissue and peritoneal fluid samples from repeated surgeries, which will further our understanding of the pathophysiology of symptom progression.

Current Funding
Title: Using affinity based proteomics to identify diagnostic and plasma biomarkers for endometriosis
Supporting Agency: Department of Defense

Grant Number: W81XWH1910318
Role: Principal Investigator (Partnering PI: Libermann at Beth Israel Deaconess Medical Center)
Grants Specialist: Ms. Catherine Sanchez Phone:
Email: catherine.n.sanchez.civ@mail.mil
Time Commitment: 1.8 CM
Performance Period: 09/01/2019-08/31/2022
Level of funding:
The major goals of this project are to identify proteomic markers associated with early detection and progression of endometriosis using data and specimens from the Nurses' Health Study II cohort and the Boston Center for Endometriosis Women's Health Study: Adolescence to Adulthood.

Title: Harnessing biomarker and phenotypic diversity among adolescents and women with endometriosis to advance personalized medicine for diagnosis and pain remediation
Supporting Agency: National Institutes of Health
Grant Number: R21HD096358
Role: Co-Investigator (PI: Missmer at Michigan State University)
Grant Specialist: Unknown at this time
Phone number: Unknown at this time
Email: Unknown at this time
Time Commitment: 0.48 CM
Performance Period: 01/01/19 - 12/31/22 NCE
Level of Funding:
Goals: Within the Women's Health Study: from Adolescence to Adulthood (A2A; a prospective cohort of >1200 adolescents and young women, oversampled for those with surgically-confirmed endometriosis, followed for >4 years), we will combine WERF EPHect compliant data from participant surveys, electronic medical records, and stored blood samples collected annually. These data will capture informative changes in pain experience, inflammatory and oxidative stress milieu, and central sensitization to advance our understanding of phenotypic diversity among adolescents and women with endometriosis –the foundation for successful personalized, precision medicine to shorten diagnostic delay and maximize successful pain remediation.

*Title: Identifying Proteomic Profiles and Biological Networks of Early-Stage Ovarian Cancer
Time Commitments: .6 CM
Supporting Agency: Department of Defense W81XWH2110320
Address: 1120 Fort Detrick – CDMRP
Frederick MD 21702
Contracting/Grants Officer: Abigail Strock email: abilgail.l.strock.civ@mail.mil
Tel:
Performance Period: 05/01/2021-04/30/2025
Level of funding: (TC)
Project Goals: To identify circulating proteins and biological networks associated with ovarian cancer in blood collected 1 to 7 years before diagnosis of overt invasive disease
Specific Aims: We propose to leverage existing samples and data from the Nurses' Health Studies (NHS/NHSII), a prospective cohort of women, and the Preoperative Pelvic Mass (PreOP) Study, a clinic-based study of women who donated blood samples before surgery for a suspicious pelvic mass, and apply next generation proteomics technology that has excellent reproducibility and reliability.
Aim 1. In prospectively collected plasma samples obtained up to 7 years before diagnosis of overt invasive disease, identify proteins associated with preclinical disease in the NHS/NHSII.
Aim 2. In pre-surgical plasma samples, identify proteins associated with early stage disease in the PreOP.
Aim 3. Identify biological networks related to early stage disease and disease progression.

Overlap: None

*Title: Defining Endometriosis Physiologic Sub-Phenotypes and Subsequent Cancer and Comorbidities Risk Through Discovery of Novel Genetic Variants
Supporting Agency: National Institutes of Health
Role: Subaward PI (PI: Missmer)
Grant Number: Unknown at this time
Grants Specialist: Unknown at this time
Phone: Unknown at this time
Email: Unknown at this time
Time commitment: 1.20 CM
Performance Period: 09/01/2021-08/31/2025
Level of funding: (TC)
Goals: The overall hypothesis of this study is to identify novel germline genetic variants associated with subphenotypes in endometriosis and examine how these genetic variants relate the subsequent risk of gynecologic and non-gynecologic comorbidities including cancer, as well how they interact with the inflammatory context. These goals will be achieved using data from an international consortium, and separately, three longitudinal studies. We hypothesize that subphenotypes in endometriosis are associated with unique genetic loci above and beyond those identified in prior studies of endometriosis as a homogenous entity. We further hypothesize that some loci may be shared between specific subphenotypes and comorbidities, suggesting either a common etiology, or progression via endometriosis which we hope to elucidate in our study. Finally, we hypothesize that the disease progression from the genetic risk factor to the long-term high risk-sub phenotypes and comorbidities may be modified by the inflammatory context. To advance the two areas targeted in in FY 2020 PRMRP, we will use cross-sectional data from the International Endometriosis Genome Consortium (IEGC), and three ongoing prospective cohort studies—Nurses' Health Study II (NHS II), Women Health Study (WHS), and Women's Health Study Adolescence to Adulthood (A2A). We will leverage genomic and phenotypic data collected in multiple well-established cohort populations as well as more recent case-control studies that launched with harmonized data and sample collection via the Endometriosis Phenome and Biobanking Harmonization Project (WERF-EPHect) tools.53 For longitudinal analysis we will include three ongoing cohorts with existing whole-genome, phenotypic and comorbidity data (1) Nurses' Health Study II, a cohort of 116,429 female nurses aged 25-42 years in 1989 among whom 2,230 endometriosis cases have been genotyped, (2) Women's Health Study, including 23,294 female health professionals ≥45 years at enrollment among whom 1494 have been diagnosed with endometriosis, (3) Women's Health Study: from Adolescence to Adulthood (A2A), a cohort of 1,650 adolescents and young women with median age of 22 at enrollment. A2A is a deeply-phenotyped cohort with detailed assessment of symptoms including pain types, severity, other life-impacting symptoms, and other disease diagnoses.
Overlap: None

*Title: Defining the Role for Descending Pain Modulation and Reward-Aversion Processes Towards the Development of Chronic Pain in Endometriosis
Time Commitments:
Grant#: W81XWH1910560
Sponsor: DOD / Boston Children's Hospital (PI: Seidberg)
Contracting/Grants Officer: Jenny Sadler
Performance Period: 8/15/2021-08/14/2022
Level of funding:
Project Goals: The goals are to define changes in brain structure and function as a correlate of subjective measures of pain and psychophysical functioning in adolescent, young adult and adult women with surgically confirmed endometriosis vs. healthy controls; to correlate psychophysical measures and brain changes with levels of Offset

Analgesia (OA) and to compare brain metrics of adolescents, young adults, and adult women with endometriosis with female patients ages 12-44 with migraines.

COMPLETED

++Funding ended/moved to Completed since Progress report YR1

++ Title: PREDICT: The Prospective Early Detection Consortium for Ovarian Cancer
Supporting Agency: Department of Defense
Grant Number: Unknown at this time
Role: Subcontract PI (PI: Kaaks at German Cancer Research Center)
Grant Specialist: Unknown at this time
Phone number: Unknown at this time
Email: Unknown at this time
Time Commitment: .36 CM
Performance Period: 01/01/2019-08/31/2021
Level of funding: (BWH TC)
Goals: To develop a worldwide collaboration to assemble a sufficient number of EOC cases, with blood samples collected relatively shortly before diagnosis, to enable the development of accurate diagnostic algorithms for multi-marker panels. The aim of this consortium is to identify and cross-validate biomarker panels that, combined with TVUS and CA125, will allow diagnosis of EOC in earlier stages of disease. To achieve this aim, we propose to:

1. Establish an international consortium of large-scale prospective cohort studies and biobanks with blood samples collected prior to diagnostic surgery—"PREDICT", the Prospective Early Detection Consortium for Ovarian Cancer—for the application of state-of-the-art "omics" technologies for biomarker discovery and validation. Prospective cohorts will contribute more than 450 EOC cases with blood samples collected ≤18 months prior to diagnosis, and from cancer-free controls, for biomarker discovery and validation. Cohorts contributing to the consortium include the European Prospective Investigation into Cancer [EPIC], Women's Health Initiative [WHI], Nurses' Health Studies [NHS and NHSII], Finnish Maternity Cohort [FMC], Norwegian Janus Serum Bank cohort, and Prostate, Lung, Colorectal and Ovarian Cancer screening trial [PLCO]. Pre-operative blood samples from a large, established biorepository at the Brigham and Women's Hospital [BWH], including patients with invasive EOC (n=548) and borderline tumors (n=131), and benign pelvic disease, plus population-based based controls, will be available for additional cross-validation.
2. Leverage existing data in individual cohorts to provide preliminary data for future studies. *In silico* cross-validation of miRNA patterns with diagnostic potential (discovery studies ongoing or recently completed by individual consortium members).
3. Initiate a "proof of concept" study validating a set of candidate tumor associated autoantibodies (TAAbs) identified in an immuno-proteomics scan for antibodies against 768 candidate proteins. Preliminary data are being generated in the EPIC cohort, with findings to be validated in the consortium.

No Overlap

++Title: Integrative analysis of genomic, epigenomic and phenotypic data for disease stratification of endometriosis
Supporting Agency: National Institutes of Health
Grant Number: R01 HD089511-01
Role: Subcontract PI as of 05/01/19 (PI: Guidice at University of California San Francisco)
Grant Specialist: Candace M Tingen

Email: tingencm@mail.nih.gov
Phone:
Time Commitment: 0.24 CM
Performance Period: 09/26/2016 – 04/30/2021
Level of funding:
Goals: This global project that includes collaborative sites in the US, UK, and Australia proposes to perform genome-wide DNA methylation analyses and genotyping of nearly 1000 existing, phenotypically well-annotated eutopic endometrium tissue samples of women with endometriosis and controls, collected by standard operating procedures, to test the hypothesis that environmental and genetic influences contribute to endometriosis and leave long-term signatures in the DNA methylome in the uterine endometrium contributing to disease pathogenesis and pathophysiology, with promise for translational diagnostics and therapeutic target development. Specifically, we will address the hypotheses that 1) environmental and genetic influences contribute to endometriosis and leave long-term signatures in the DNA methylome in the eutopic endometrium that contribute to disease pathogenesis and pathophysiology, and 2) these can serve to stratify disease risk and inform new avenues for drug target discoveries and diagnostic development.
No Overlap

Sasamoto, Naoko
Active Support

*Title: Relating molecular subgroups of endometriosis-associated ovarian cancers to survival and risk factors Time Commitments: 3 CM
Supporing Agency: National Institutes of Health
Grant Number: R01-CA248288
Grant Specialist: Ashley Salo
Phone number:
Email: ashley.salo@nih.gov
Performance Period: 01/01/2021-12/31/2026
Level of funding: (TC)
Project Goals: Aim 1. To characterize molecularly defined subgroups of ENOC and CCOC, we will statistically integrate sequencing and array data from gene expression, somatic mutations, and differentially methylated regions from 523 ENOC and 344 CCOC. Clustering approaches will use samples divided into training and test sets.
Aim 2. To identify subgroup-specific survival associations, we will relate molecular subgroups defined in Aim 1 to overall survival using Cox regression models.
Aim 3. To identify subgroup-specific risk factor associations, we will relate molecular subgroups defined in Aim 1 to lifestyle risk factors.
Aim 4. To identify opportunities for overlapping treatments in patient care, we will statistically compare the patterns of molecular features of the ENOC and CCOC subgroups with various TCGA cancer subgroups. Overlap: none

*Title: Identifying early detection metabolomics biomarkers for high-grade serous ovarian cancer
Time Commitments: 1.2CM
Supporting Agency: Sperling Family Foundation (Broad Institute/BWH)
Address: 415 Main Street
Cambridge, MA
75 Francis Street, Boston, MA 02115
Contracting/Grants Officer: Ashlin Bolton

Phone:
Performance Period: 03/01/2021-02/28/2022
Level of funding: TC
Project Goals: To discover novel early detection metabolomic biomarkers for ovarian cancer and elucidate the systemic metabolomic profiles in the early phase of ovarian cancer development.
Specific Aims: The primary objective of this innovative application aims to discover novel early detection metabolomic biomarkers for ovarian cancer and elucidate the systemic metabolomic profiles in the early phase of ovarian cancer development utilizing the biospecimens and clinical data at the Brigham and Women's Hospital and applying the world-class innovative technology of the highly reproducible, high-throughput, multiplex metabolomics technology at the Broad Institute.
Overlap: none

Title: Using affinity based proteomics to identify diagnostic and plasma biomarkers for endometriosis
Time Commitments: .36
Supporting Agency: Department of Defense W81XWH1910318 (Partnering PI's: Terry at Brigham and Women's Hospital and Libermann at Beth Israel Deaconess Medical Center)
Contracting/Grants Officer: Chris Baker
Tel:
Email: christopher.l.baker132.civ@mail.mil
Performance Period: 09/01/2019-08/31/2022
Level of funding:
Project Goals: To identify proteomic markers associated with early detection and progression of endometriosis using data and specimens from the NHS II and the Women's Health Study: From Adolescence to Adulthood.
Specific Aims: We will utilize data and specimens from the two population-based cohort studies, the Nurses' Health Study II (NHSII), a prospective cohort study with blood samples collected months to years before endometriosis diagnosis, and the Women's Health Study: Adolescent to Adulthood (A2A), a deeply phenotyped longitudinal cohort of endometriosis patients, to identify non-invasive diagnostic and prognostic protein biomarkers for endometriosis. Using these unique resources, we will evaluate the following specific aims: Aim 1. In prospectively collected plasma samples obtained up to 6 years before diagnosis, identify proteins that differentiate women who will be diagnosed with endometriosis from controls in the NHSII.
Aim 2. Determine whether proteins differ between endometriosis subtypes in the A2A.
Aim 3. In pre and post-operative samples, identify proteins and pathways that discriminate between those who continue to be impacted by the disease, characterized by continued chronic pain and poor quality of life, and those who improve after surgery in the Progression Study,
Overlap: None

*Title: Identifying Proteomic Profiles and Biological Networks of Early-Stage Ovarian Cancer
Time Commitments: 6 CM
Supporting Agency: Department of Defense W81XWH2110320
Address: 1120 Fort Detrick – CDMRP
Frederick MD 21702
Contracting/Grants Officer: Abigail Strock
email: abilgail.l.strock.civ@mail.mil
Tel:
Performance Period: 05/01/2021-04/30/2025
Level of funding: (TC)
Project Goals: To identify circulating proteins and biological networks associated with ovarian cancer in blood collected 1 to 7 years before diagnosis of overt invasive disease

Specific Aims: We propose to leverage existing samples and data from the Nurses' Health Studies (NHS/NHSII), a prospective cohort of women, and the Preoperative Pelvic Mass (PreOP) Study, a clinic-based study of women who donated blood samples before surgery for a suspicious pelvic mass, and apply next generation proteomics technology that has excellent reproducibility and reliability.
Aim 1. In prospectively collected plasma samples obtained up to 7 years before diagnosis of overt invasive disease, identify proteins associated with preclinical disease in the NHS/NHSII.
Aim 2. In pre-surgical plasma samples, identify proteins associated with early stage disease in the PreOP.
Aim 3. Identify biological networks related to early stage disease and disease progression.
Overlap: None

*Title: Using genetic predictors of CA125 to improve personalized ovarian cancer screening
Time Commitments: 3.84
Supporting Agency: Marsha Rivkin Center for Ovarian Cancer Research
Address: 801 Broadway, Suite 701, Seattle WA 98122
Contracting/Grants Officer: Jackie Lang, PhD Tel:
Performance Period: 04/01/2021-03/31/2023
Level of funding:
Project Goals: To identify genetic predictors of CA125 and examine whether adding genetic predictors of CA125 will improve the discriminatory performance of personalized CA125 cutpoints in blood collected months prior to diagnosis in prospective cohorts of PLCO, EPIC, and NHS/NHSII.
Specific Aims: Aim 1. Identify genetic predictors of CA125 using data on 4,391 women without ovarian cancer in PLCO, EPIC, NHS/NHSII, and NEC.

a. Identify novel genetic variants associated with blood CA125 levels by menopausal status.
b. Determine whether genetic variants associated with blood CA125 levels differ by race.
c. Secondarily, identify genetic predictors associated with change in CA125 over time.

Aim 2. Examine whether adding genetic predictors of CA125 to our model of personalized CA125 cutpoints will improve the discriminatory performance in blood collected months prior to diagnosis in prospective cohorts of PLCO, EPIC, and NHS/NHSII.
Overlap: None

*Title: Changing contraceptive patterns and ovarian cancer risk
Time Commitments: 3.12 CM
Supporting Agency: National Institutes of Health 1R01CA258679
Address: NIH/NHLBI Information center
P.O Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Goli Smimi; email: goli.smimi@nih.gov
Tel:
Performance Period: 07/01/2021-06/30/2026
Level of funding: (TC)
Project Goals: To examine the impact of changing contraceptive patterns of intrauterine device on ovarian cancer risk and to examine its impact on the local immune mechanisms.
Specific Aims: Aim 1. Estimate the association between IUD use and risk of ovarian cancer, including by histotype, in 17 case-control studies (20,314 cases, 26,099 controls) and 7 cohort studies (678,650 participants, 1,891 cases) with prospectively collected data. We hypothesize that:

a. IUD use is associated with a decreased risk of invasive ovarian cancer, particularly low grade serous and clear cell histotypes.
b. Secondarily, we will evaluate these associations by race and birth cohort.

Aim 2. Describe how timing and type of IUD use influence ovarian cancer risk in 13 case-control and 4 cohort studies. We hypothesize that:

a. IUD use before oral contraceptive use, particularly in nulliparous women, attenuate the inverse association or even increase ovarian cancer risk.
b. Progesterone-releasing IUDs decrease the risk of ovarian cancer more than other IUD types.

Aim 3. Evaluate whether the association between IUD use and ovarian cancer risk differs by the tumor immune microenvironment, utilizing 3,530 cases on tissue microarrays. We hypothesize that:

a. IUD use is associated with an increased risk of ovarian tumors with low stromal expression of CD163.
b. IUD use versus OC use alone will be differentially associated with ovarian cancer risk by the proportion of immune cell types in the tumor, including cytotoxic T cells, Tregs, or macrophages, identified by expression of CD3, CD8, CD4, CD69, FOXP3, and CD163.

Overlap: None

Stacey A. Missmer ScD (Changes Highlighted)

Active Support

Title: The Boston Center for Endometriosis

Time Commitments: 0.09 Academic – 0.03 Summer
Supporting Agency: J.Willard and Alice S. Marriott Foundation
Address: J. Willard and Alice S. Marriott Foundation10400
Fernwood Road, Department 925 Bethesda, MD 20817
Contracting/Grants Officer: Margaret Buckley
Performance Period: 07/01/2012-12/31/2021
Level of funding:
Project Goals: Design and conduct for study enrollment and data and biologic sample collection within Brigham and Women's Hospital and Boston Children's Hospital
Specific Aims: Establish a longitudinal cohort of girls and women with endometriosis and appropriate comparison girls/women with detailed life course data and extensive biologic samples storage.
Overlap: None

Title: Subfertility and Assisted Conception Study of Parent and Child Health Outcomes
Time Commitments: 0.72 Academic – 0.24 Summer
Supporting Agency: Dartmouth College **(prime award:** NIH 5R01HD067270-07)
Dartmouth College
Office of Sponsored Projects
11 Rope Ferry Road #6210
Hanover, NH 03755
Contracting/Grants Officer: Aarron Clough
Performance Period: 06/23/2016-09/30/2021 (No Cost Extension started 4/1/2021)
Level of funding: No Cost Extension
Project Goals: The project will provide expertise in developing an understanding of the subfertility-related diagnoses by performing analyses of women's and children's health outcomes as part of the project team.
Specific Aims: Aim 1: To evaluate the effect of maternal subfertility diagnoses on long-term health; Hypothesis: Women with a history of subfertility diagnoses, independent of treatment, have higher risks of compromised health outcomes compared to women without indicators or treatment of subfertility; Aim 2: To evaluate the health of children born to women and men with subfertility diagnoses; Hypothesis: Children born to women and/or men with subfertility diagnoses, independent of treatment, have a higher risk of compromised health outcomes compared to children born to women without indicators of subfertility; and Aim 3: To develop a cost-of-subfertility measure for women and their children; Hypothesis: Women with a history of subfertility-

related diagnoses and their children have higher healthcare costs compared to their counterparts without indicators or treatment of subfertility.
Overlap: None

Title: Integrative Analysis of Genomic, Epigenomic and Phenotypic Data for Disease Stratification of Endometriosis

Time Commitments: 1.08 Academic - .36 Summer
Supporting Agency: University of California San Francisco (**prime award:** NIH 1R01HD089511-01)
UCSF Box
0850
3333 California Street 485R
San Francisco, CA 94143
Contracting/Grants Officer: Nicole Gaisbauer
Performance Period: 09/26/2016 - 04/30/2022 (No Cost Extension started 5/1/2021)
Level of funding: No Cost Extension
Project Goals: This global project that includes collaborative sites the US, UK, and Australia proposes to perform genome-wide DNA methylation analyses and genotyping of nearly 1000 existing, phenotypically well-annotated eutopic endometrium tissue samples of women with endometriosis and controls, collected by standard operating procedures, to test the hypothesis that environmental and genetic influences contribute to endometriosis and leave long-term signatures in the DNA methylome in the uterine endometrium contributing to disease pathogenesis and pathophysiology, with promise for translational diagnostics and therapeutic target development.
Specific Aims: To address the hypotheses that 1) environmental and genetic influences contribute to endometriosis and leave long-term signatures in the DNA methylome in the eutopic endometrium that contribute to disease pathogenesis and pathophysiology; and 2) these can serve to stratify disease risk and inform new avenues for drug target discoveries and diagnostic development.
Overlap: None

Title: MSU Women's Outcomes Research and Knowledge (WORK) Cohort
Time Commitments: 0.72 Academic – 0.24 Summer
Supporting Agency: AbbVie Inc.
1 N Waukegan Road
North Chicago, IL 60064
Contracting/Grants Officer: Michelle Parks
Performance Period: 04/01/2018 - 05/31/2023 (No Cost Extension started 6/1/2021)
Level of funding: No Cost Extension
Project Goals / Specific Aims: This observational longitudinal cohort study will evaluate the clinical, medical and surgical journey from pelvic pain onset and identify diagnostic paths that lead to a shorter time to diagnosis and initiation of successful pain remediating treatment. Adolescent and young women, ages 12-30, who have ever reported chronic pelvic pain will be invited to enroll.
Overlap: None

Title: What is Endometriosis? Deep Phenotyping to Advance Diagnosis and Treatment
Time Commitments: 0.67 Academic – 0.23 Summer
Supporting Agency: NIH R01HD094842
National Institutes of Health
6710B Rockledge Drive, Room 3219C, MSC 7004
Bethesda, MD 20892-7004

Contracting/Grants Officer: Vicky Haines
Performance Period: 08/01/2018 - 04/30/2023
Level of funding:
Project Goals: We will utilize three existing diverse studies of adolescents and women for whom surgical, clinical and participant data as well as blood and tissue samples have been harmonized via the WERF EPHect tools. The goal of our study will be to identify unique classifications of endometriosis patients that inform non-invasive diagnostics, response to current treatments, and novel treatment pathways - stratifying discoveries by participant symptom presentation, and for the cases, by surgical and imaging visualized disease characteristics to capture the full heterogeneity of endometriosis.
Specific Aims: Aim 1: Identify plasma markers of endometriosis across independent and synergistic pathways; Aim 2: Quantify informative heterogeneity in associated transcriptomic and milieu-related plasma markers by disease phenotype; Aim 3: Further identify informative disease phenotypes by symptom presentation; Aim 4: Evaluate heterogeneity in plasma markers, disease phenotype, and symptom presentation by participant characteristics.
Overlap: None

Title: Menstrual health during the Covid-19 pandemic: A longitudinal study among young people with and without endometriosis (Supplement to project listed above)
Time Commitments: 0.45 Academic – 0.15 Summer
Supporting Agency: NIH (R01 HD094842-04S1)
National Institutes of Health
6710B Rockledge Drive, Room 3219C, MSC 7004
Bethesda, MD 20892-7004
Contracting/Grants Officer: Vicky Haines
Performance Period: 08/27/2021-04/30/2022
Level of Funding:
Project Goal / Specific Aims: The impact of SARS-CoV-2 infection or vaccination on menstrual health is unknown, despite anecdotal reports of post-vaccination change in menstruation. We will utilize an ongoing prospective study (A2A cohort; N=1569) comprised primarily of adolescents and young adults who have already answered the first in a planned series of COVID-19 focused questionnaires and have in-hand pre- and peri-pandemic menstrual characteristics data. Accounting for change in menstruation impacting medications, medical conditions, or pandemic-related psychosocial upheaval, we will determine if infection or vaccination affect menstrual characteristics compared to pre-pandemic characteristics or to those neither infected nor vaccinated.
Overlap: None

Title: Translation in Pelvic Pain (TriPP)
Time Commitments: 0.09 Academic – 0.03 Summer
Supporting Agency: University of Oxford (European Union)
University of Oxford
Women's Centre, John Radcliffe Hospital
Oxford, OX3 9DU England
Contracting/Grants Officer: Tom Ibbotson
Performance Period: 1/01/2018-3/31/2022
Level of Funding:
Project Goal / Specific Aims: The ultimate aims of this multi-center international project are to develop: • Tools that allow the stratification of chronic pelvic pain patients on the basis of the underpinning pathophysiological mechanisms. • Refined preclinical models of endometriosis-associated pain and bladder pain symptoms to allow rapid, efficient and relevant screening of novel therapeutic compounds with a high chance of

clinical success.
Overlap: None

Title: An AHEI Dietary Intervention to Reduce Pain in Women with Endometriosis
Role: MSU subcontract PI (Overall PI: Holly Harris)
Time Commitments: 0.45 Academic – 0.15 Summer
Supporting Agency: Fred Hutchinson Cancer Research Center (**prime award:** 5 R01 NR017951-02)
1100 Fairview Ave N.
Seattle, WA 98109
Contracting/Grants Officer: Alexandria Nagel
Performance Period: 02/11/2019-12/31/2022
Level of Funding:
Project Goal / Specific Aims: The overall goal of this study is to evaluate the effects of a 12-week dietary intervention among premenopausal women aged 18-45 years, with laparoscopically-confirmed endometriosis, recruited from the Seattle area, who had a pain score of at least 5 out of 10 on the Visual Analog Scale (VAS) in the month prior to baseline. 100 women will be randomized to a 3-month dietary intervention (n=50) or a wait-list control group (n=50). The intervention will consist of a diet based on the AHEI-2010 guidelines.
Overlap: None

Title: Infertility History and Chronic Disease Profile
Time Commitments: 1.35 Academic – 0.45 Summer
Supporting Agency: NIH 5R01HD096033-02
National Institutes of Health
6710B Rockledge Drive, Room 3219C, MSC 7004
Bethesda, MD 20892-7004
Contracting/Grants Officer: Vicky Haines
Performance Period: 05/15/2019-04/30/2024
Level of Funding:
Project Goal / Specific Aims: In response to PA-17-091, within the Nurses' Health Study II (a prospective cohort of 116,430 women followed for >30 years), we will combine data from women's infertility and infertility treatment history, stored blood samples collected at two time points during follow-up (1st and 2nd collection, 10 years apart), and genome wide data to evaluate the relationship between infertility and the risk of cardiovascular diseases (myocardial infarction and stroke), type 2 diabetes, and breast cancer, including inflammatory, cardiometabolic, hormonal, and genetic profiles.
Overlap: None

Title: COVID-19 vaccination and menstrual health (Supplement to project listed above)
Time Commitments: 0.18 Academic – 0.06 Summer
Supporting Agency: NIH (R01 HD096033-03S1)
National Institutes of Health
6710B Rockledge Drive, Room 3219C, MSC 7004
Bethesda, MD 20892-7004
Contracting/Grants Officer: Vicky Haines
Performance Period: 08/27/2022-04/30/2022
Level of Funding:
Project Goal / Specific Aims: The impact of SARS-CoV-2 infection or vaccination on menstrual health is unknown, despite anecdotal reports of post-vaccination change in menstruation. We will utilize two ongoing prospective cohorts (NHS3 and GUTS) with combined 17,000 female participants who have already answereda

year-long series of COVID-19 focused questionnaires and have in-hand pre- and peri-pandemic gynecologic characteristics data. Accounting for change in menstruation impacting medications, medical conditions, or pandemic-related psychosocial upheaval, we will determine if infection or vaccination affect menstrual characteristics compared to pre-pandemic characteristics or to those neither infected nor vaccinated.
Overlap: None

Title: Inflammation and the Malignant Transformation of Endometriosis
Role: MSU subcontract PI (Overall PI: Holly Harris)
Time Commitments: 0.45 Academic – 0.15 Summer
Supporting Agency: Fred Hutchinson Cancer Research Center (**prime award:** DoD W81XWH18PRMRPDA)
1100 Fairview Ave N.
Seattle, WA 98109
Contracting/Grants Officer: Alexandria Nagel
Performance Period: 04/01/2019-09/30/2021
Level of Funding:
Project Goal / Specific Aims: The overall goal of this project is to better understand how inflammatory exposures, both local and systemic, influence cancer driver mutations in endometriosis lesions, allowing us to gain better insight into the natural history of endometriosis and its potential for malignant transformation.
Overlap: None

Title: Harnessing biomarker and phenotypic diversity among adolescents and women with endometriosis to advance personalized medicine for diagnosis and pain remediation
Time Commitments: 0.9 Academic – 0.3 Summer
Supporting Agency: NICHD R21HD096358
National Institutes of Health
6710B Rockledge Drive
Bethesda, MD 20892-7004
Contracting/Grants Officer: Vicky Haines
Performance Period: 04/01/2019-03/31/2022 (No Cost Extension started 4/1/2021)
Level of Funding: No Cost Extension
Project Goal / Specific Aims: Within the Women's Health Study: from Adolescence to Adulthood (A2A; a prospective cohort of >1200 adolescents and young women, oversampled for those with surgically-confirmed endometriosis, followed for >4 years), we will combine WERF EPHect compliant data from participant surveys, electronic medical records, and stored blood samples collected annually. These data will capture informative changes in pain experience, inflammatory and oxidative stress milieu, and central sensitization to advance our understanding of phenotypic diversity among adolescents and women with endometriosis – the foundation for successful personalized, precision medicine to shorten diagnostic delay and maximize successful pain remediation.
Overlap: None

Title: Using affinity-based proteomics to identify diagnostic and prognostic plasma biomarkers for endometriosis
Time Commitments: 0.72 Academic – 0.24 Summer
Supporting Agency: Brigham & Women's Hospital (**prime award:** DoD W81XWH1910318)
399 Revolution Drive, Suite 745
Somerville, MA 02145

Contracting/Grants Officer: Kevin Moore
Performance Period: 09/01/2019-8/31/2022
Level of Funding:
Project Goal / Specific Aims: The major goals of this project are to identify proteomic markers associated withearly detection and progression of endometriosis using data and specimens from the Nurses' Health Study II cohort and Women's Health Study: Adolescence to Adulthood (A2A). Elucidating the proteome with critical consideration for reliable measurement, advanced statistical analyses, and population sampling that embraces rather than ignores endometriosis heterogeneity - may solve this critical issue of non-invasive diagnosis for girlsand women with endometriosis.
Overlap: None

Title: Defining the role for descending pain modulation and reward-aversion processes towards thedevelopment of chronic pain in endometriosis
Time Commitments: 0.72 Academic – 0.24 Summer
Supporting Agency: Boston Children's Hospital (**prime award:** DoD W81XWH18PRMRPIIRA)
300 Longwood Avenue
Boston, MA 02115
Contracting/Grants Officer: Stephanie Davis
Performance Period: 08/15/2019-08/14/2022
Level of Funding:
Project Goal / Specific Aims: A neuroimaging study that examines changes in brain structure and function andcorrelates these findings with psychological functioning, and pain sensitivity across three aims: (1) Age-RelatedChanges: Examining differences across 3 age cohorts of women with surgically confirmed endometriosis (12- 17; 18-25; 26-44) compared to healthy controls. (2) Surgical Treatment Responsivity: Comparing the same brain and psychological and pain sensitivity tests in adolescent and young adult women presenting for surgery for endometriosis; comparing those that have and those that do not have pain at 3 months post-surgery. (3) Comparison with Existing Data: Comparing data from Aim 1 to existing databases of matched patients across the same age groups with migraines who have undergone the same type of testing.
Overlap: None

Title: Endometriosis, Infertility, and Risk of Stroke
Time Commitments: 0.67 Academic – 0.23 Summer
Supporting Agency: University of Arizona (**prime award**: NICHD R21HD099623-01A1)
Arizona Board of Regents, University of Arizona
888 North Euclid Avenue, Room 510
Tucson, AZ 85719-4824
Contracting/Grants Officer: Melissa Kramer
Performance Period: 07/01/2020-06/30/2022
Level of Funding:
Project Goal / Specific Aims: Leveraging existing data from the Nurses' Health Study II, this proposal will fill important gaps in knowledge of the association between incidence of stroke and endometriosis and infertility. This proposal is well powered to evaluate three categories of exposure: women with endometriosis but not infertility, women with infertility but not endometriosis, and women with both endometriosis and infertility.
Overlap: None

Title: Defining Endometriosis Physiologic Sub-Phenotypes and Subsequent Cancer and Comorbidities Risk Through Discovery of Novel Genetic Variants

Time Commitments: 0.9 Academic – 0.3 Summer
Supporting Agency: Department of Defense USMRAA (W81XWH2110744)
820 Chandler Street
Fort Detrick, MD 21702-5014
Contracting/Grants Office: Kathryn Argue
Performance Period: 08/15/2021-08/14/2025
Level of Funding: (Year 1 Direct Costs) Total Direct Costs:
Project Goal / Specific Aims: This study will: 1) identify novel genetic variants associated with specific endometriosis sub-phenotypes defined by symptom and macro-surgically visualized presentation; 2) determine the common and unique genetic variants that are associated with the higher risk of subsequent development of cancers, autoimmune and cardiovascular diseases among women with endometriosis. We will capitalize upon our ongoing International Endometriosis Genome Consortium (IEGC) investigations and 3) in exploratory analyses, delve more deeply into the Women's Health Study: from Adolescence to Adulthood (A2A), which has measured an array of blood chemokine and cytokine markers.
Overlap: None

Title: Epigenetic regulatory mechanisms and therapeutic opportunities in endometriosis
Time Commitments: 0.9 Academic – 0.3 Summer
Supporting Agency: NIH (HD103617-01A1)
National Institutes of Health
6710B Rockledge Drive, Room 3219C, MSC 7004
Bethesda, MD 20892-7004
Contracting/Grants Officer: Not Assigned
Performance Period: 08/15/2021-08/31/2026
Level of Funding: Total
Project Goal / Specific Aims: This proposal will advance research relevant to the health of women by expanding the genomic and phenotypic characterization of endometriosis, a disease that affects 10% of women. The primary objectives of this proposal are to identify the genetic and epigenetic regulatory mechanisms that contribute to endometriosis etiology and pathogenesis in efforts to find new ways to therapeutically target abnormal endometrial cells.
Overlap: None