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TITLE: Using affinity-based proteomics to identify diagnostic and plasma biomarkers for endometriosis

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14. ABSTRACT: 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.

15. SUBJECT TERMS: NONE LISTED

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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. **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.

KEYWORDS

Endometriosis, proteomics, biomarkers, plasma, SOMAscan, diagnosis, pathophysiology, systems biology, predictor, risk model, pain

ACCOMPLISHMENTS:

The major goals of the project are as follows:

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: 50% complete. Blinded QCs have been created and integrated into the sample. Additional laboratory QCs still need to be created. Completion by 10/1/20
c. Subtask 3. Measure 1,305 proteins, check quality control for variation within and between plates on NHSII samples: Planned to be assayed between 12/1/20-2/2/21
d. Milestone #2: Generating proteomics NHSII data

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 8/31/21
b. Subtask 2. Manuscript preparation: Planned completion by 3/31/22
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. Proteomics Data analysis will be completed 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: Planned completion by 8/31/22
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. Proteomics Data analysis will be completed by 12/31/21
b. Subtask 2. Use systems biology to identify pathways relevant to progression of endometriosis: Planned completion by 5/31/22
c. Subtask 3. Manuscript preparation: Planned completion by 8/31/22
d. Milestone #5: Publish proteins associated with endometriosis progression

What was accomplished under these goals?

1) Major Activities

In the first three months of the current funding period IRB approval was sought and obtained. The next four months the HRPO application was completed, reviewed, revised, and finally approved.

For Aim 1 (major tasks 2), we were able to identify and select samples for appropriate endometriosis cases and controls within the NHSII study, but then the biorespository was shutdown due to the Covid-19 pandemic lab. The biorepository reopenend this summer and these samples have finally been aliquoted and transferred to our lab for SOMAscan proteomics analysis.

For Aims 2 and 3 (major task 4), we identified A2A study samples and transferred to our lab for SOMAscan analysis. We completed the SOMAscan run for the A2A samples, assessed quality control metrics, and created a covariate dataset for further analyses.

2) Specific Objectives

a. Obtain IRB approval.
b. Obtain HRPO approval.
c. Identify, select, and transfer plasma samples for endometriosis cases and matched controls from the NHSII study for proteomics measurement by SOMAscan.
d. Identify, select, and transfer plasma samples for endometriosis cases and matched controls from the A2A study for proteomics measurement by SOMAscan.
e. Run A2A samples on SOMAscan proteomics platform.

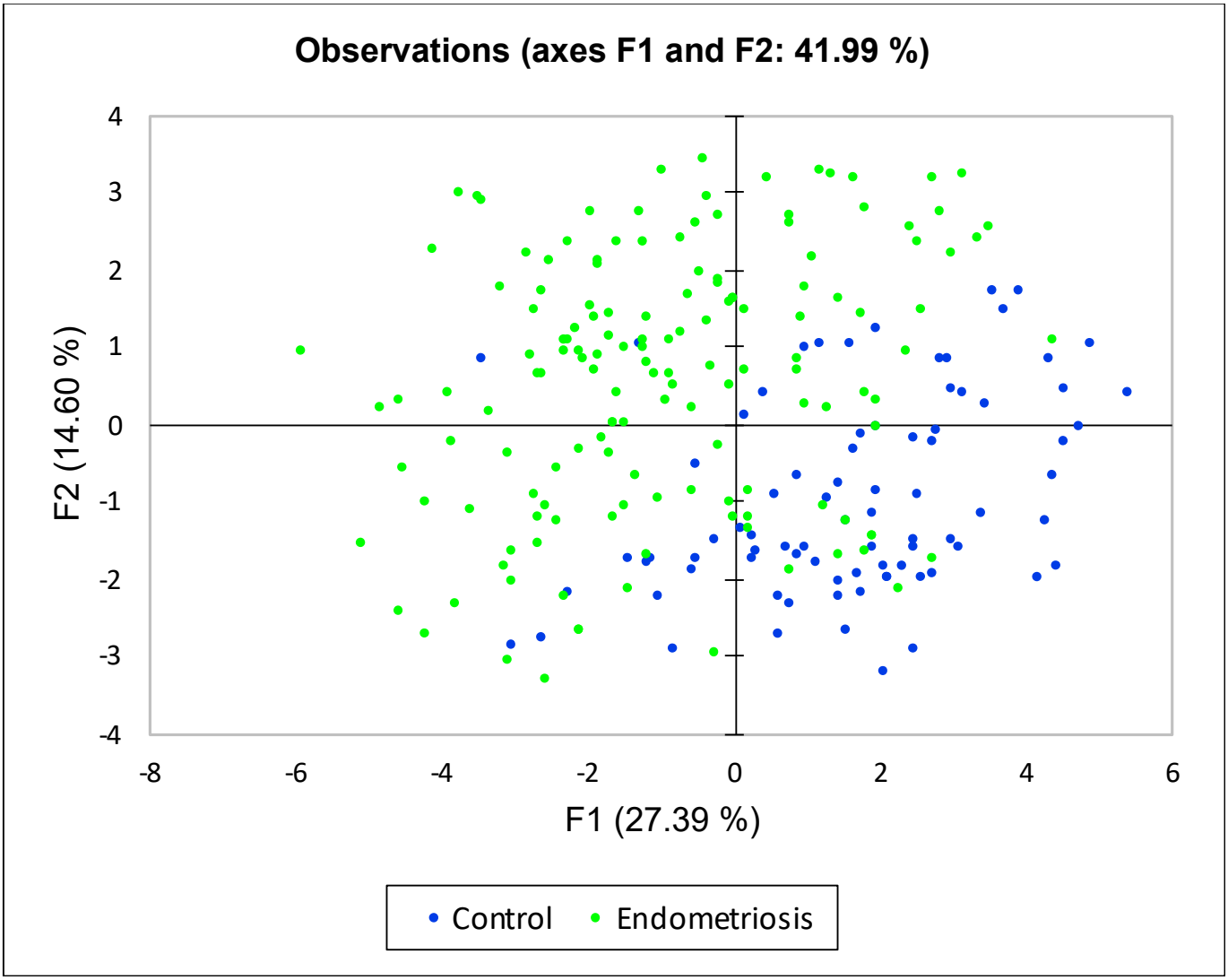
3) Significant results or key outcomes, including major findings, developments, or conclusions

While IRB and HRPO approval took longer than expected and the Covid-19 pandemic shutdown after approval slowed the selection and transfer of samples and other lab work until late June 2020, we succeeded to run the first set of samples from the A2A study on the SOMAscan platform.

We identified and selected A2A plasma samples according to our inclusion criteria (superficial peritoneal cases who has surgery at baseline, completed the baseline and year 1 questionnaire, have no/little missing data for menstrual and acyclic pain, blood drawn within 90 days prior to surgery, baseline questionnaire completed within 6 months of blood draw, no more than 3 freeze/thaw cycles, and no hemolysis). Unfortunately, we were only able to identify 139 of the 150 samples planned that met these criteria. Therefore, we increased the number of controls included from 50 to 72 samples. In total our A2A sample set included 330 EDTA samples consisting of 89 paired (preoperative/postoperative) case samples, 50 single baseline case samples, 72 control samples, and 30 blinded quality control (QC) samples.

These 330 EDTA plasma samples from the A2A study were run on the manual version of SOMAscan Assay Kit 1.3K, Human Plasma (item 900-00011). The kit provided pooled plasma controls were run 5X on each SOMAscan plate as well as a no protein buffer control. 345 out of 350 samples passed the SomaLogic standard quality control and normalization criteria.
To further evaluate the quality of the SOMAscan data we performed a Spearman correlation analysis comparing all samples with all 1,305 proteins to each other. Typically, we expect to see a correlation between samples >0.9, indicating that the majority of proteins across all samples change very little. Indeed, we observed that the correlation between all samples was typically >0.91 with only a few samples between 0.86-0.9. This analysis further confirmed that there is no significant QC problem with the samples and data and that technically everything performed as expected. In addition, we observed excellent inter- and intra-plate CVs for blinded QC aliquots of <15% for well over 90% of the proteins.

Preliminary data analysis revealed that 155 proteins are significantly differentially expressed between 139 endometriosis cases and 72 controls with a p-value <0.01. Principal Component Analysis (PCA) using the top 20 proteins separates endometriosis cases (green) from controls (blue) quite well as seen in the figure below.



In initial evaluation of specific proteins enriched in endometriosis, there are several that we identified in our analyses that have been previously linked to endometriosis in the literature such as VEGF. In the next funding period, we will further explore the A2A SOMAscan data as well as running the 400 NHSII samples on SOMAscan.

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

The project provided opportunities for professional development for Dr. Naoko Sasamoto, early career investigator, to gain hands-on training in A2A sample selection for the proposed aims. In addition, the funding provided support for Dr. Sasamoto to publish a paper on CA125 and endometriosis symptoms in the A2A cohort.

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?
During the next reporting period we will perform the detailed bioinformatics, statistics, and systems biology analysis on the SOMAscan data from the A2A participants to identify plasma proteins associated with endometriosis that may inform candidate biomarkers for early diagnosis. Among other analyses we plan to define endometriosis subtypes and its pathophysiology. We will also run the 440 NHSII prediagnostic samples on SOMAscan.

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?
We have completed running blood samples for endometriosis cases and matched controls on the SOMAscan proteomics platform that measures 1,305 proteins in the circulation. Once we have analyzed the data, we anticipate identifying blood biomarkers that discriminate between endometriosis and controls as well as identifying different subtypes of endometriosis. Such a phenotyping of endometriosis will help with differential diagnosis and improved management of patients with endometriosis and may also identify new druggable therapeutic targets. We expect that our data by the end of the funding period will have a major impact on predicting who will develop endometriosis and on how best to monitor and manage endometriosis patients.

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."

CHANGES/PROBLEMS:
We do not have any significant changes to report. The project is following the approved SOW. The only problem we have encountered in the first year is the delay in getting the proposed experiments executed in the original timeframe due to the Covid-19 related shut down of all labs for almost four months as well as due to the delay in getting the HRPO approval which we obtained only on 4/3/20. However, since getting IRB and HRPO approval and after reopening of the labs we are quickly caught up on lost time. For Aim 1 we are back on the planned timeline and for Aim 2 we are a few months ahead of the timeline.

PRODUCTS:
Journal publications
Evaluation of CA125 in relation to pain symptoms among adolescents and young adult women with and without surgically-confirmed endometriosis.
Sasamoto N, DePari M, Vitonis AF, Laufer MR, Missmer SA, Shafrir AL, Terry KL.PLoS One. 2020 Aug 24;15(8):e0238043. doi: 10.1371/journal.pone.0238043. eCollection 2020.PMID: 32833998
Acknowledgement of federal support: yes

Other products
We have generated the SOMAscan proteomics data for the A2A study samples including endometriosis cases and matched controls.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name: Kathryn L. Terry, ScD
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID): https://orcid.org/0000-0002-8540-7066
Nearest person month worked: 2
Contribution to Project: Dr. Terry oversees the study protocol, data analysis, interpretation of the data and manuscript writing.
Funding Support: Next section

Name: Naoko Sasamoto, MD MPH
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): https://orcid.org/0000-0002-4526-2181
Nearest person month worked: 4
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: Next Section

Name: Allison Vitonis, MS
Project Role: Programmer
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Ms. Vitonis identifies the appropriate PreOP Study samples to be requested, designs plate maps with appropriate distribution of case/control/quality control samples, cleans and stores data generated from this study and links data with existing questionnaire data. She calculates quality control measures such as coefficients of variation and assist modeling analyses, including linear regression, splines, development of ROC curves.
Funding Support: NA

Name: McKenzie Goodwin
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 2
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: NA

Name: Christopher Murphy
Project Role: Channing Programmer
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Mr. Murphy identifies incident endometriosis cases in the Nurses' Health Study II cohort (that is, cases that occurred after blood draw) as well as matched controls, accounting for as many matching variables as possible. In addition, he manages all proteomics data generated as a part of this project with appropriate documentation in the Channing UNIX system.
Funding Support: NA

Name: Stacey Missmer, ScD
Project Role: Subaward PI
Researcher Identifier (e.g. ORCID ID): https://orcid.org/0000-0003-3147-6768
Nearest person month worked: 1
Contribution to Project:
Dr. Missmer is responsible for scientific direction of the BCE at both Boston Children's and Brigham and Women's Hospitals, as well as overseeing all collaboration between the biorepository and external laboratories. She will continue her close working relationship with Dr. Terry, ensuring access to A2A data and samples pertinent to the proposed aims and contribute expertise regarding study design, statistical analyses, coordination with Children's and Brigham-based study staff, interpretation of results, writing manuscripts for publication in peer-reviewed journals, and scientific communication with the DOD as well as the scientific, clinical, and patient education communities.
Funding Support: Next Section

OTHER SUPPORT

Kathryn L. Terry, ScD

Current Research Support

Title: The Boston Center for Endometriosis: A First-in the World Care and Research Program for Women of all Ages
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

Time Commitment: 1.2 CM
Performance Period: 07/01/2012-06/30/2020
Level of funding: $301,644
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: 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.

Time Commitment: 1.8 CM
Performance Period: 04/01/2016-03/31/2023
Level of funding: $557,004
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: Dietary and Hormonal Determinants of Cancer in Women
Supporting Agency: National Institutes of Health
Grant Number: P01 CA87969
Role: Project 3 Leader (PI: Stampfer)
Grants Specialist: Somdat Mahabir

Time Commitment: 0.96 CM
Performance Period: 07/01/2015-06/30/2020
Level of funding: $133,534
Goals: The goal of this project is to improve ovarian cancer prevention, which is key for reducing morbidity and mortality. This proposal examines two key, but understudied putative pathways in ovarian carcinogenesis, metabolism and inflammation. We will examine several key lipid classes using a metabolomics profiling platform as well as an agnostic evaluation of all measured metabolites. For inflammation, we propose to focus on modifiable factors, such as diet, sedentary behavior, premenopausal NSAID use, as well as biomarkers of prostaglandins and chlamydia antibodies. We also will consider tumor characteristics including mRNA expression with inflammatory exposures. Finally, for the first time, we will consider post-diagnosis modifiable exposures with ovarian cancer survival.

1. Project 1. Diet, exogenous hormones, and breast cancer risk. A series of analyses is being conducted that relates specific aspects of hormone replacement therapy and diet and nutritional status to breast cancer incidence and survival among women with the disease.
2. Project 2**.** Diet hormones, and colorectal cancer risk. A series of analyses is being conducted that relates specific aspects of hormone replacement therapy and diet and nutritional status to colorectal cancer incidence and survival among women with the disease.
3. Project 3. Hormones diet, and ovarian cancer risk. Repeated measurement of diet, body weight, and hormone use are permitting evaluation of relationships between these variables and risk for ovarian cancer.
4. Project 4. Statistical innovations in risk modeling. The rich body of epidemiologic data available through the cohort and the statistical expertise of the investigators provide opportunities to develop methods for prediction of cancer risk and analysis of multiple endpoints

Overlap: None

Title: <u>What is Endometriosis? Deep Phenotyping to Advance Diagnosis and Treatment</u>
Supporting Agency: National Institutes of Health
Grant Number: R01HD094842
Role: Subcontract PI (PI: Missmer at Michigan State University)
Grants Specialist: Margaret Young

Time Commitment: 1.2 CM
Performance Period: 08/01/2018 - 04/30/2023
Level of funding: $61,163
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: <u>Inflammation and the Malignant Transformation of Endometriosis</u>
Supporting Agency: Department of Defense
Grant: W81XWH18PRMRPDA / PR181241
Role: Co-Investigator (PI: Harris at Fred Hutchinson Cancer Center)

Grants Specialist: Patricia Modrow, Ph.D.
Time Commitment: 0.60 CM

Performance Period: 02/01/19-01/31/22
Level of funding: $36,700
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: 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: 01/01/2019-12/31/2020
Level of funding: $29,802
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

***Funded since JIT was reported**

*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
Time Commitment: 0.24 CM
Performance Period: 09/26/2016 – 04/30/2021
Level of funding: $19,279
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

*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 - 12/31/20
Level of Funding: $36,722
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.

PENDING

+New Pending

+Title: Longitudinal assessment of metabolites to elucidate pathophysiology of endometriosis progression
Supporting Agency: Department of Defense

Grant Number: PR201153
Role: Partnering PI Terry/Clish
Grant Specialist: Unknown at this time
Phone number: Unknown at this time
Email: Unknown at this time
Time Commitment: 3.0 CM
Level of Funding: $293,640.00
Performance Period:09/01/2020-08/31/2025
Goal: We propose a research program which will advance our understanding and improve clinical care of endometriosis. Specifically, our proposal addresses two Areas of Encouragement of endometriosis. Results from our study will 1) further our understanding of how endometriosis disease starts, why it starts, and why it gets so bad in some women; and 2) identify blood biomarkers that can be used to optimize surgical treatment and reduce progression and symptoms of disease

+Title: Relating molecular subgroups of endometriosis-associated ovarian cancers to survival and risk factors
Supporting Agency: National Institutes of Health
Grant Number: R01-CA248288
Role: Subcontract PI (PI: Goode at Mayo Clinic)
Grant Specialist: Unknown at this time
Phone number: Unknown at this time
Email: Unknown at this time
Time Commitment: 1.2 CM
Performance Period: 09/01/2020-08/31/2025
Level of funding: $44,216.00
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.

+Title: Identifying proteomic profiles and biological networks of early-stage ovarian cancer
Supporting Agency: Department of Defense
Grant Number: Unknonwn
Role: Co-Investigator (PI: Sasamoto)
Grants Specialist: Unknown at this time
Phone: Unknown at this time
Email: Unknown at this time
Time commitment: 0.6 CM
Perforamnce Period: 04/01/2021-03/30/2025
Level of funding: $184,891
Goals: The overarching goal of this application is to identify circulating proteins and biological networks associated with ovarian cancer in blood collected 1 to 7 years before diagnosis of overt invasive disease, which will likely reflect biological changes related to progression from early to late stage disease.

+Title: Investigating the underlying mechanisms of the breastfeeding and ovarian cancer risk association
Supporting Agency: National Institutes of Health

Grant Number: 1R03CA259659-01
Role: Co-Investigator (PI: Sasamoto)
Grants Specialist: Unknown at this time
Phone: Unknown at this time
Email: Unknown at this time
Time commitment: 0.6 CM
Perforamnce Period: 04/01/2021-03/31/2023
Level of funding: $50,000
Goals: To evaluate the underlying mechanisms of the breastfeeding ovarian cancer association using circulating biomarker, tumor marker expression, and detailed questionnaire data from more than 800,000 women. Results from this study have the potential to inform new avenues for primary chemoprevention targets and/or intervention strategies and further our understanding of ovarian cancer etiology.

+Title: Characterization of the microbiome in endometriosis and its association with endometriosis-associated ovarian cancer
Supporting Agency: Department of Defense
Role: Subaward PI (PI: Harris)
Grants Specialist: Unknown at this time
Phone: Unknown at this time
Email: Unknown at this time
Time Commitment: 0.6 CM
Performance Period: 10/01/2020-09/30/2022
Level of Funding: $43,778
Goals: The goal is to understand the endometriosis to ovarian cancer transition to elucidate new opportunities for prevention and treatment.

+Title: Elucidating molecular profiles associated with endometriosis progression
Supporting Agency: Department of Defense
Role: Co-Investigator (PI: Sasamoto)
Grants Specialist: Unknown at this time
Phone: Unknown at this time
Email: Unknown at this time
Time Commitment
Performance Period: 10/1/2020-09/30/2022
Level of Funding: $103,473
Goals: 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.

+Title: Determining biomolecular mechanisms and the direct and indirect impacts of Covid-19 on the mental health, coping, and pain symptoms among women with endometriosis and chronic pelvic pain
Supporting Agency: Department of Defense
Role: Subcontract PI (PI: Missmer)
Grants Specialist: Unknown at this time
Phone: Unknown at this time
Email: Unknown at this time
Time Commitment: 1.8 CM
Performance Period: 01/01/2021-12/31/2024
Level of Funding: $99,409
Goals: The overarching goal of this proposal is to elucidate biological mechanisms and risk defining biomarkers of SARS-CoV-2 infection comparing women with and without endometriosis or chronic pelvic pain and to

explore the impact of social isolation and diminished access to healthcare on pain symptom severity and mental health progression using two longitudinal cohorts, which will further our understanding of the biological mechanisms of COVID-19 short- and long-term health in this large and oft ignored potentially high risk group.

+Title: Changing contraceptive patterns and ovarian cancer risk
Supporting Agency: National Institutes of Health
Grant Number:
Role: PI
Grant Specialist: Unknown at this time
Phone: Unknown at this time
Email: Unknown at this time
Time Commitment: 2.40 CM
Performance Period: 07/01/2021-06/30/2026
Level of Funding: $2,035,632 TDC
Changing contraceptive patterns, specifically the decline of oral contraceptives and rise intrauterine devices, could have important implications for future ovarian cancer risk. Leveraging consortium data including more than 700,000 women (>20,000 cases) as well as blood (n~1,500) and tissue (n~2,000) on women to examine systemic and local immune mechanisms with cutting-edge multiplex immunofluorescence technology, we will evaluate how this highly prevalent and modifiable risk factor may impact the population burden of this extremely fatal disease
Overlap: None

+Title: Metabolomic profiling of endometriosis in adolescents and adults
Supporting Agency: NIH K08 HD102598 Resubmission
Role: Mentor (PI: Sasamoto)
Grants Specialist: Unknown at this time
Phone: Unknown at this time
Email: Unknown at this time
Time Commitment: as needed/no salary
Performance Period: 04/01/2021-03/30/2026
Level of Funding: $102,184
Goals:The major goals of this career award are to: (1) learn advanced statistical methods to analyze and interpret high-dimensional metabolomics data through hands-on training and didactic courses; (2) learn about data generation, data cleaning, standardization, and interpretation of metabolomics data; (3) develop expertise in endometriosis-associated pain biology through literature review, didactic courses, and interactions with experts in this area; (4) gain academic experience in developing research collaborations, networking, teaching, presentations, and grant writing; (5) establish a strong research and publication record in the field of endometriosis for future successful R01 applications

COMPLETED

++Funding ended/moved to Completed since JIT

++Title: Redefining normal: Personalized CA125 cutpoints for ovarian cancer screening
Supporting Agency: National Institutes of Health
Grant number: 5R01CA193965-03
Role: Principal Investigator
Grants Specialist: Franklin, Nicole
Time Commitment: 3.6 CM

Performance Period: 06/01/2016-05/31/2020

Level of funding: $ 244,959
Goals: We propose to develop personalized CA125 cutpoints using individual characteristics to improve the sensitivity and specificity of this important ovarian cancer marker and lead the way to population screening that could save lives.
Specific Aims:

1. Develop and validate a predictive model of CA125 in women without ovarian cancer.
2. Calculate personalized cutpoints and evaluate discriminatory ability compared to a single threshold in PLCO, NHS, and EPIC.
3. Evaluate whether the addition of personalized CA125 improves ovarian cancer risk prediction by adding adjusted CA125 to established ovarian risk models.

Overlap: none

++Title: Comparing Options for Management: Patient—centered Results for Uterine Fibroids (COMPARE-UF)
Supporting Agency: PCORI
Grant Number: 1P50HS023418
Role: Co-Investigator (PI: Myers at Duke University)
Grants Specilaist: Bryan Luce PhD, MS, MBA

Time Commitment: 1.2 CM

Performance Period: 09/30/2014 – 09/29/2020 (NCE)
Level of funding: $114,828
Goals: The objective of the national collaborative project is to develop a multicenter registry that is geographically, racially, and clinically diverse that will generate high quality data that will enable women with fibroids to make informed decisions about treatment options. Specific research questions will focus on how treatment options impact symptom relief, preserving reproductive function, and other outcomes important to participants.
AIM 1: Develop the infrastructure necessary to implement large-scale observational comparative effectiveness research (CER) studies of management options for women with UF, including (a) a governance structure, policies, and procedures conducive to collaborative research involving patients, clinicians, methodologists, and other stakeholders, (b) an experienced Research and Data Coordinating Center, and (c) nine geographically diverse Clinical Centers (CCs) representing a broad range of patients and providers.
AIM 2: Use this infrastructure to implement three projects addressing high-priority evidence gaps related to the effect of different management strategies on patient-centered outcomes. These include PROJECT 1: Comparing management options for symptom relief PROJECT 2: Comparing management options for preserving reproductive function PROJECT 3: Comparing effectiveness in different subpopulations.
AIM 3: Evaluate innovative methods for the design, conduct, and analysis of observational comparative effectiveness research in this population.
AIM 4: Translate research results into improved patient care, through both traditional peer-reviewed publications and collaborations with stakeholders to integrate the research findings into evidence-based patient decision making tools, clinical practice guidelines, and quality.
No Overlap

++Title: Metabolomic signatures of pain and progression among women with endometriosis.
Supporting Agency: Marriott Family Foundation/ Peery Foundation
Grant Number: Marriott Family Foundation/Boston Center for Endometriosis Investigator Grant
Role: Principal Investigator
Grants Specialist: Jenny Sadler Gallagher, MPH

Time Commitment: 0.36 CM

Performance Period: 01/01/2018-12/31/2019
Level of funding: $ 26,087.00
Goals: The objective of this project is to identify metabolites and metabolite signatures in women with endometriosis that are associated with pain and progression which may aid in monitoring disease, lead to personalized treatment, and provide insight into the biology of the disease that may lead to new therapeutic targets.
Overlap: None

++Title: High-throughput proteomics profiling for identification of early detection biomarkers of high-grade serous ovarian cancer
Supporting Agency: Minnesota Ovarian Cancer Alliance
Grant Number: Unknown at this time
Role: Co-Investigator (PI: Sasamoto)
Grants Specialist: Unknown at this time
Phone: Unknown at this time
Email: Unknown at this time
Time Commitment: 0.24 CM
Performance Period: 05/01/2019-04/30/2020
Level of funding: $ 50,000
The major goals of this project are to identify biomarkers that predict high grade serous ovarian cancer and elucidate etiologic pathways of development. Specifically, we plan to:
Aim 1. Identify proteins associated with early stage HGSOC in prospectively collected samples. We hypothesize that Pro-inflammatory and immunosuppression-related proteins in blood drawn one to three years prior to diagnosis of late stage HGSOC will be higher compared to healthy controls. In addition, untargeted proteomics profiling considering all 1,305 proteins will identify novel candidate biomarkers for early stage HGSOC using blood drawn one to three years prior to diagnosis of late stage HGSOC compared to healthy controls. Aim 2. Elucidate potential biological pathways relevant to early stage HGSOC. We hypothesize that: Inflammatory and immunosuppression pathways are enriched among the circulating proteins associated with early stage HGSOC using blood drawn one to three years prior to diagnosis of late stage HGSOC compared to healthy controls.
No Overlap

Title: Medication Use and Ovarian Cancer Survival
Supporting Agency: Marsha Rivkin Center for Ovarian Cancer Research
Grant: NA
Role: Co-Investigator (PI: Poole)

Time Commitment: .36 CM
Performance Period: 04/01/2015-09/30/2016
Level of funding: $59,825
Goals: The goal of this application was to develop ovarian cancer survivorship research in the Nurses' Health Study cohorts. We will evaluate a signature of optimal cytoreductive surgery and apply it in a study of common medication use among ovarian cancer patients.
Specific Aims:

1. To measure and validate an immunohistochemical signature of debulking in ovarian cancer cases from the NHS, NHSII, and NECC (n=601 cases). We hypothesize that this signature predicts debulking status equally well in serous vs. non-serous cases and that it is independently associated with survival.
2. To evaluate whether use of anti-inflammatory (e.g., aspirin and other NSAIDs) and anti-stress medications (e.g., anti-depressant medications, beta blockers, anti-anxiety medications) is associated

with survival. We hypothesize that use of these medications prior to diagnosis is associated with better survival and that accounting for optimal debulking (either through surgical reports or through the immunohistochemical signature) will not affect these results.

3. As a secondary analysis, we will analyze whether post-diagnosis medication use or change in medication use pre- to post-diagnosis is associated with survival. We will also evaluate whether associations differ by tumor histology, a key predictor of survival. We hypothesize that use of these medications after diagnosis is associated with better survival.

Title: Screening and Risk Biomarkers for Ovarian Cancer in EPIC Specimens
Supporting Agency: National Institutes of Health
Grant: 5R01CA158119-04
Role: Co-Investigator (PI: Cramer)
Grants Specilaist: Jennifer Edwards

Time Commitment: 2.4 CM
Performance Period: 04/01/2012-03/31/2016
Level of funding: $293,513
Goals: Ovarian cancer morbidity and mortality could be improved by better methods of primary and secondary prevention. In turn, primary prevention would benefit from biomarkers of risk, especially those which inform disease pathogenesis and translate into strategies for intervention.

1. In aim 1, using 780 EPIC cases and 1880 controls, we planned identify key individual epidemiologic risk factors and combine them in a risk prediction model.
2. In aim 2, for the risk biomarker analysis, we planned focus on the 620 cases diagnosed more than three years after blood draw and 1240 matched (1:2) controls and measure free MUC1 and MUC16 antigen, IgG antibodies against CA125 (MUC16), CA15.3 (MUC1), and immune complexes involving these antigens and their antibodies.
3. For the early detection analysis, we planned to create test and validation sets from the 160 cases diagnosed within three years of blood draw and 640 matched (1:4) controls and measure all of the markers noted above plus CA72.2, HE4, and beta-2-microglobulin.

Overlap: There is no scientific or budgetary overlap

Title: Dietary factors and uterine fibroids
Supporting Agency: NIH
Grant Number: 1R03HD081064
Role: Co-Investigator (PI: Missmer)
Grants Management Specialist: Susan M. Parker

Time Commitment: .48 CM
Performance Period: 03/23/15-02/28/17
Level of funding: $49,965
Goals: In this project, we evaluated the association between dietary fat, dairy consumption and vitamin D with the incidence of uterine fibroids by utilizing data from the Nurses' Health Study II (NHS).

1. Aim 1. Evaluate the association between dietary fat and risk of incident uterine leiomyoma using data among 97,807 women in the NHSII cohort who completed a dietary assessment. In a subset of these women we will examine the association between circulating fatty acid levels and uterine leiomyoma.
2. Aim 2. Dairy food intake is associated with risk of uterine leiomyoma.
3. Aim 3. Vitamin D levels are associated with risk of uterine leiomyoma.

Overlap: None

Title: Serum protein biomarker discovery for early diagnosis of endoemtriosis

Supporting Agency: Marriott Family Foundation
Grant Number: NA
Role: Co-Investigator
Grants Management Specialist: Jenny Sadler Gallagher, MPH

Time Commitment: 0.18 CM
Performance Period: 1/1/2018 – 12/31/18
Level of funding: $21,739
Goals: The goal of this pilot grant was to compare proteomic profiles in 10 women with endometriosis compared to 10 without to evaluate the performance of the proteomics platform on serum and plasma from the Boston Center for Endometriosis Women's Health Study: Adolescence to Adulthood study and develop preliminary data for a larger grant application.

Stacey A. Missmer, ScD

CURRENT

Title: The Boston Center for Endometriosis: A First-in the World Care and Research Program for Women of all Ages
Role: Scientific Director for the Boston Center for Endometriosis
Time Commitments: 0.09 Academic – 0.03 Summer
Supporting Agency: J.Willard and Alice S. Marriott
Contracting/Grants Officer: Jenny Sadler Gallagher
Performance Period: 07/01/2012-12/30/2020
Level of funding: $141,548
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
Role: MSU subcontract PI (Overall PI: Judy Stern)
Time Commitments: 0.72 Academic – 0.24 Summer
Supporting Agency: Dartmouth College (prime award: NIH 5R01HD067270-07)
Contracting/Grants Officer: Aarron Clough
Performance Period: 06/23/2016-06/30/2021
Level of funding: $26,966
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 subfertilityrelated 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
Role: Multi-PI (Administrative Multi-PI: Linda Giudice)
Time Commitments: 1.08 Academic – 0.36 Summer
Supporting Agency: University of California San Francisco (prime award: NIH 1R01HD089511-01)
Contracting/Grants Officer: Eric Ormsby
Performance Period: 09/26/2016 - 04/30/2021 Level
of funding: $45,041
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
Role: PI
Time Commitments: 0.72 Academic – .24 Summer
Supporting Agency: AbbVie Inc.
Contracting/Grants Officer: Michelle Parks
Performance Period: 04/01/2018 - 03/31/2021 Level
of funding: $629,471
Project Goals: This proposed 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 (<2 years) and initiation of successful pain remediating treatment. Adolescent and young women, ages 10-30, who have ever reported chronic pelvic pain, who are unresponsive to over the counter or prescribed NSAIDS or require opioids will be invited to register in WORK (Women's Outcomes Research and Knowledge) cohort.
Specific Aims: Primary Aim – To quantify time in months/years from pelvic pain onset to confirmed diagnosis following a retrospective analysis of EMR, patient report, and 18 month prospective observational period of routine clinical practice that includes medical, imaging and surgery aspects. Secondary Aims – Measurement of response throughout time will include the Proportion of patients with different levels (e.g., mild / moderate / severe) of pelvic pain and types (e.g., dysmenorrhea, dyspareunia, non-menstrual (acyclic) pain) at enrollment and quarterly during follow-up. Pain severity will be measured using discomfort/distress terms as defined using the VAS: Discomfort is defined as a VAS of lower than 3 VAS score definition of clinically-relevant improvement is a lowering of VAS by 1.6 points or greater. Proportion of patients stratified by different pain medications (e.g., NSAIDS, opioid, other) or endometriosis treatments (e.g., OC, surgical procedure) who are treatment responders as defined by an improved pain scale (e.g. VAS scale) from baseline. Change from baseline in SF-36 physical score and mental score across three timepoints: baseline, month 9 and month 18 of follow-up.
Overlap: None

Title: What is Endometriosis? Deep Phenotyping to Advance Diagnosis and Treatment
Role: PI
Time Commitments: 0.9 Academic – 0.3 Summer
Supporting Agency: NIH R01HD094842
Contracting/Grants Officer: Margaret Young

Performance Period: 08/01/2018 - 04/30/2023 Level
of funding: $499,760
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 noninvasive 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: Translation in Pelvic Pain (TriPP)
Role: MSU subcontract PI (Overall PI: Katy Vincent)
Time Commitments: 0.09 Academic – 0.03 Summer
Supporting Agency: University of Oxford (European Union)
Contracting/Grants Officer: Tom Ibbotson
Performance Period: 1/01/2018-3/31/2021
Level of Funding: $8,923
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 sponsor: NIH)
Contracting/Grants Officer: Kelly Stewart
Performance Period: 02/01/2019-11/30/2022
Level of Funding: $10,235
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 waitlist 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
Role: PI
Time Commitments: 1.8 Academic – 0.6 Summer
Supporting Agency: NIH
Contracting/Grants Officer: Pending
Performance Period: 04/01/2019-03/31/2024
Level of Funding: $596,335
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 genomewide 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: 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 sponsor: DoD W81XWH18PRMRPDA)
Contracting/Grants Officer: Alexandria Nagel
Performance Period: 11/01/2018-04/30/2020
Level of Funding: $7,360
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
Role: Administrative Multi-PI (Multi-PI: Amy Shafrir)
Time Commitments: 0.9 Academic – 0.3 Summer
Supporting Agency: NICHD R21HD096358
Contracting/Grants Officer: Vicky Haines
Performance Period: 04/01/2019-03/31/2021
Level of Funding: $201,994
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: Determining biomolecular mechanisms and the direct and indirect impacts of COVID-19 on mental health, coping, and pain symptoms among women with endometriosis and chronic pelvic pain
Time Commitments: 1.8CM
Supporting Agency: Department of Defense Peer Reviewed Medical Research Program
Contracting/Grants Officer: Not Assigned
Performance Period: 01/01/2021-12/31/2024
Level of Funding: $99,409Project Goal/Specific Aims: The goal of this project is to explore the impact of social isolation and diminished access to healthcare on pain symptom severity, functional status, and mental health progression, and to elucidate biological mechanisms and risk defining inflammatory biomarkers of SARS-CoV-2 infection comparing women with chronic pelvic pain (with and without endometriosis) to those without pelvic pain using two longitudinal cohorts. The specific aims of this project are to: (1) confirm the psychosocial impact of the COVID-19 pandemic on chronic pelvic pain and (2) define biologic mechanisms and risk defining inflammatory biomarkers of SARS-CoV-2 infection in the context of chronic pelvic pain and endometriosis.

Overlap: None

+Title: Defining the role for descending pain modulation and reward-aversion processes towards the development of chronic pain in endometriosis
Role: MSU subcontract PI (Overall PI: Christine Sieberg)
Time Commitments: 0.72 Academic – 0.24 Summer
Supporting Agency: Boston Children's Hospital (Prime sponsor: DoD W81XWH18PRMRPIIRA)
Contracting/Grants Officer: Stephanie Davis
Performance Period: 08/15/2019-08/14/2022
Level of Funding: $15,726
Project Goal / Specific Aims: A neuroimaging study that examines changes in brain structure and function and correlates these findings with psychological functioning, and pain sensitivity across three aims: (1) Age-Related Changes: Examining differences across 3 age cohorts of women with surgically confirmed endometriosis (1217; 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

PENDING

+ +Title**:** Determining biomolecular mechanisms and the direct and indirect impacts of COVID-19 on mental health, coping, and pain symptoms among women with endometriosis and chronic pelvic pain
Time Commitments: 0.9 Academic – 0.3 Summer
Supporting Agency: Department of Defense Peer Reviewed Medical Research Program
Contracting/Grants Officer: Not Assigned
Performance Period: 01/01/2021-12/31/2024
Level of Funding: $368,262 (Year 1 Direct Costs) Total Direct Costs: $1,599,228
Project Goal/Specific Aims: The goal of this project is to explore the impact of social isolation and diminished access to healthcare on pain symptom severity, functional status, and mental health progression, and to elucidate biological mechanisms and risk defining inflammatory biomarkers of SARS-CoV-2 infection comparing women with chronic pelvic pain (with and without endometriosis) to those without pelvic pain using two longitudinal cohorts. The specific aims of this project are to: (1) confirm the psychosocial impact of the COVID-19 pandemic on chronic pelvic pain and (2) define biologic mechanisms and risk defining inflammatory biomarkers of SARS-CoV-2 infection in the context of chronic pelvic pain and endometriosis.

Overlap: None

PREVIOUS

Title: Causes & Impact of Minority Stress on Health & Development in Youth
Role: Co-investigator
Supporting Agency: NIH/NICHD R01 HD057368
Performance Period: 2009-2016
Project Goal / Specific Aims: The major goal of this work is to study the effects of violence, discrimination and other sexual minority related stressors on adolescent and young adult adjustment in youth in the Growing Up Today Study 1, a longitudinal cohort study of over 16,000 adolescents. Overlap: None

Title: Weight and Weight-related Behaviors in Youth: Influence of the Family Context
Supporting Agency: NIH R01 HL096905
Performance Period: 2011-2016
Level of Funding:

Project Goal / Specific Aims: We will use linear mixed models and generalized estimating equations to analyze data from questionnaires collected in 2004, 2006, 2008, and 2010 from 10,920 adolescents and young adults nationwide, to assess the independent association of artificially-sweetened soda, sugar-sweetened soda, sports drinks, energy drinks, and coffee drinks with subsequent weight gain and the development of obesity. In addition, we will determine whether frequency of eating prepared foods (fast food and commercially prepared takeout food) is independently predictive of weight gain, waist circumference, hypertension, and the development of obesity.
Overlap: None

Title: Sexual Orientation and Obesity: Test of a Gendered Biopsychosocial Model
Role: Co-investigator
Supporting Agency: NIH/ NICHD R01 HD066963
Performance Period: 2011-2016
Project Goal / Specific Aims: The major goal of this work is to test a conceptual model to explain sexual orientation related disparities in obesity in adolescence and young adulthood in the Growing Up Today Study 1 and 2, two longitudinal cohort studies that when combined include of over 27,000 youth, and the National Longitudinal Study of Adolescent Health, a national longitudinal cohort study of over 20,000 youth. Overlap: None

Title: Dietary Factors and Uterine Fibroids
Role: Co-investigator
Supporting Agency: NIH/NICHD R03 HD81064-01A1
Contracting/Grants Officer:
Performance Period: 2015-2017 Level
of Funding: $47,901
Project Goal / Specific Aims: This project aims to evaluate whether dietary factors such as fat intake, dairy food intake and vitamin D levels are associated with a lower incidence of uterine leiomyoma. The Nurses' Health Study II presents a unique opportunity for large-scale, prospective study of the dietary predictors of uterine fibroids. The presence of prospectively collected UL, dietary, and covariate data and stored blood samples, allows cost-efficient and valid consideration of the temporality of disease diagnosis – supporting the potential identification of modifiable risk factors
Overlap: None

Title: Shiftwork and Cognitive Function
Role: Co-investigator
Supporting Agency: NIH R01 OH010930
Performance Period: 2015-2017
Project Goal / Specific Aims: We propose to leverage existing data from the Nurses' Health Study 2 on rotating night shift work, to initiate highly novel research on rotating night shifts and cognitive function. To facilitate this research, we will administer a brief, validated, computerized cognitive battery in NHS2, providing an initial measure of cognitive function at age 48-65, and repeated measures of cognitive change. This will provide a framework for extensive future research and has the potential to substantially improve health in nurses, and other shift-workers.
Overlap: None

+New Funding

++New Pending