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TITLE: Development and Validation of Predictive Models for Transition from Acute to Persistent Pain After Major Surgery

PRINCIPAL INVESTIGATOR: Simon Haroutounian

CONTRACTING ORGANIZATION: Washington University, St. Louis, MO

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> The transition from acute to pathological persistent pain is complex and is dependent on multiple biological, psychological, and social-environmental factors that change across the surgical care continuum. Current approaches for predicting PPSP are primarily based on risk factors assessed at a single time point, most often - preoperatively. Moving beyond a one-time baseline assessment to a multifactorial and temporal measurement approach is a relatively unexplored research avenue that has a substantial potential. A temporal approach, accounting for multiple factors across the care continuum can afford opportunities for ascertaining the impact of time-varying patient and clinical events across the surgical care continuum. Our central hypothesis is that advanced machine learning models that account for individual biological, cognitive, and psychological factors across the surgical care continuum will allow personalized prediction of PPSP. In this context, pragmatic prediction models for precise PPSP prediction will allow appropriate resource allocation in mitigating PPSP and long-term disability in high-risk individuals. From a research standpoint, such models will allow the efficient testing of perioperative interventions or rehabilitation programs, by implementing appropriate risk stratification to improve assay sensitivity in future clinical trials. We have two specific aims: Aim 1: Collect longitudinal prospective data for a comprehensive biological, psychological, cognitive, and psychophysical characterization of a surgical patient cohort. Aim 2: Develop, validate, and test advanced machine learning models for predicting PPSP.					
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## 1. Introduction

Persistent postsurgical pain (PPSP) is the most common long-term postoperative complication, affecting approximately one in eight patients undergoing surgery. PPSP substantially affects patients' functioning, quality of life, and ability to return to work or service. Associations between several individual or perioperative factors and increased risk of PPSP have been reported, but current methodological approaches are ill-equipped to predict an individual patient's risk. Our proposal will determine whether machine learning methods, applied to analyzing longitudinal multifactorial perioperative data, will result in robust prediction models, that will allow the identification of patients at risk for PPSP after major surgery. In this context, pragmatic prediction models for PPSP prediction will (a) allow appropriate resource allocation in mitigating PPSP and long-term disability in high-risk individuals, and (b) allow the efficient testing of perioperative interventions or rehabilitation programs, by implementing appropriate risk stratification in future clinical trials.

## 2. Keywords

Acute pain, persistent post-surgical pain, surgery, risk prediction, chronic pain, machine learning, prediction modeling

## 3. Accomplishments

### What were the major goals of the project?

**CY22 Goal** – Prospective data collection and follow-up

- Obtaining all regulatory approvals, establishing recruitment and data collection framework, troubleshooting processes, initiating and maintaining recruitment and data collection.

**CY23 Goals** – Model training and feature engineering

**CY24 Goal** – Model validation and testing

**CY25 Goal** – Manuscript preparation

### What was accomplished under these goals?

1. Study has continued to successfully enroll, staff training has been maintained, and new team members have been onboarded to the study, as necessary.
2. Patient enrollment to the study ongoing. We have currently consented and enrolled 1680 participants as of September 12, 2023, above the planned target.
3. We continue to collect follow-up data (3 months and 6 months postoperatively).
4. We are developing pipelines for data synchronization (data collected to REDCap, EMAs, and data extracted from the electronic health record (Epic), and developing initial Machine Learning models, based on about 30% of the eventually planned data
5. We have initiated the development of certain manuscripts, such as validating the EMA-based pain catastrophizing assessment.

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

The project has provided opportunities for professional development to a number of trainees and junior faculty. Among these are Teniya Lewis – an undergraduate student accepted to Washington University Department of Anesthesiology's ASSURE program (<https://assure.wustl.edu/>).

The project has provided professional development opportunities for a post-doctoral fellow, Jakayla Hart, MD (now left Washington University and is currently in Residency training in Psychiatry).

The project has provided opportunities for professional development for Lingshu (Lily) Liu MD – an

Anesthesiology resident on the Scholar's track at Washington University (now successfully completed residency).

### **How were the results disseminated to communities of interest?**

So far, the results from our work in progress have been disseminated through peer-reviewed publication (PMID: 37019164, and a conference presentation at the IASP 2022 World Congress on Pain. Toronto, Canada. Sep 2022.

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

1. Our recruitment is going according to the plan.
2. During the next reporting period, we will continue to enroll subjects prospectively, and collect perioperative and follow-up data.
3. We will continue collecting the 3 and 6-months outcomes data.
4. We expect to complete the data synchronization and setup for building prediction models based on the combination of data collected to REDCap, EMAs, and data extracted from the electronic health record (Epic).
5. We expect to generate 2 manuscripts focusing on preoperative characterization of pain and mental health in about 50% of the patient cohort, and describing relationship between acute pain and mental health (anxiety and depression) trajectories. This work will not tap into prediction modeling for PPSP, i.e., is not expected to interfere with primary analysis.

## **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?**

Disseminating our approach through conferences has initiated conversations about the design of perioperative data collection and reporting in longitudinal studies focusing on persistent postsurgical pain

### **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

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

Nothing to report.

### Changes that had a significant impact on expenditures

Participant recruitment in line with our plan still requires higher %FTE effort from research coordinators than initially expected.

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

Nothing to report.

### Significant changes in use or care of human subjects

Nothing to report.

### Significant changes in use of biohazards and/or select agents

Nothing to report.

## 6. Products

### Publications, conference papers, and presentations

#### Journal publications

[Madelyn R Frumkin](#) , [Jacob K Greenberg](#) , [Preston Boyd](#) , [Saad Javeed](#), [Bulenda Shayo](#), [Jin Shin](#), [Elizabeth A Wilson](#), [Justin K Zhang](#), [Michael J L Sullivan](#), [Simon Haroutounian](#), [Thomas L Rodebaugh](#) . *Establishing the Reliability, Validity, and Prognostic Utility of the Momentary Pain Catastrophizing Scale for Use in Ecological Momentary Assessment Research*. J Pain 2023 Aug;24(8):1423-1433 (PMID: **37019164**)

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

Nothing to report.

#### Other publications, conference papers and presentations

Simon Haroutounian. *Risk Factors and Clinical Predictors of Chronic Pain After Surgery and Acute Injury*. Workshop presentation at the IASP 2022 World Congress on Pain. Toronto, Canada. Sep 2022.

#### 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?**

**Simon Haroutounian, MSc. Pharm, PhD**, Principal Investigator 1.44 calendar months. Dr. Haroutounian is responsible for the overall study design, and will provide general oversight and management of the project, ensuring timely progression to meet milestones.

**Thomas Rodebaugh, PhD**. Co-Investigator; 0.6 calendar months, Dr. Rodebaugh is responsible for incorporating EMA into the study protocol, and developing the platform for data collection, cleaning and harmonization, in preparation for modeling.

**Chenyang Lu, PhD**; Co-Investigator; 0.6 calendar months; Dr. Lou is responsible for development and validation of the advanced machine learning models for prediction clinical outcomes.

**Denise Head, PhD**; Co-Investigator; 0.36 calendar months, Dr. Head contributes to optimizing cognitive and psychological assessment in the proposed study, and will assist with cognitive and psychological data analysis and interpretation.

**Thomas Kannampallil, PhD**; Co-Investigator; 1.14 calendar months; Dr. Kannampallil contributes to study design, oversees electronic data collection, and contribute to data analysis and interpretations.

Ben Swan, Research Administrator; 1.2 calendar months. Assists in patient recruitment, data collection, and maintain the appropriate study documentation.

Karen Frey, Research Specialist; 0.6 calendar months. Assists in patient recruitment, data collection, and maintain the appropriate study documentation.

Cristina Bowman, Research Nurse; 5.5 calendar months. Assists in patient recruitment, data collection, and maintaining the appropriate study documentation.

Joel Hanns, Research Assistant; 6.5 calendar months. Assists with study recruitment, consenting, blood processing, and remuneration, as necessary.

Haley Bernstein; Research Assistant 12.0 calendar months. Assists with study recruitment, consenting, blood processing, and remuneration.

Joel Brown, Research Nurse; 0.5 calendar months; Assists with study recruitment, consenting, blood processing, and remuneration, as necessary.

Liz Wilson, Research Coordinator; no longer on study team as of 03 Feb 2023. Assisted in patient

recruitment, data collection, and maintaining the appropriate study documentation.

Bulenda Shayo, Research Coordinator; no longer on study team as of 11 Aug 2023. Assisted in patient recruitment, data collection, and maintaining the appropriate study documentation.

Preston Boyd; Student; no longer on study team as of 05 May 2023. Assisted with study recruitment, consenting, blood processing, and remuneration.

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

Nothing to report.

**What other organizations were involved as partners?**

Nothing to report.

## **8. Special Reporting Requirements**

Quad Report attached

## **9. Appendices**

Nothing to report