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TITLE: A Precision Medicine Approach Based on Discrete Time Windows for Predicting Outcomes of Polytrauma Patients

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

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

We propose to leverage Precision Medicine approaches in a three-phase study of military and civilian trauma, incorporating 1) Phase I- (Narrow-Window Diagnostic): A novel, time window-based trauma patient stratification scheme will be refined with genomic and admission clinical/inflammation biomarkers using both retrospective and prospective data on patients with polytrauma. We will define the admission variables that most accurately prognosticate for these adverse outcome categories. We can report that a unified Master dataset of retrospective data has been created and the Narrow-Windows patient stratification model has been initiated.

2) Phase 2- (Wide-Window Diagnostic): The stratification algorithm from Phase 1, which is based on single time point data, will be compared against a wide-window algorithm involving multiple initial readings in the first 24h post-injury, using the dataset obtained in Phase 1. We will test the hypothesis that widening the time window for data acquisition will increase the precision of the prognostication.

3) Phase 3- (Optimized Patient Stratification): a prospective study testing the optimal stratification algorithm in patients with polytrauma ± TBI. In addition, UPITT has begun its recruitment of patients; 109 eligible patients to date

15. SUBJECT TERMS
Precision Medicine, polytrauma, stratification, narrow window

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1. INTRODUCTION:

This study proposes to deliver, within 3 years, precision medicine methods that will predict each patient's risk for adverse outcomes using patient specific metrics that quantify genetic and demographic signatures combined with individualized injury and injury response signals to accurately stratify expected clinical trajectories

2. KEYWORDS:

Precision medicine, polytrauma, narrow-window, stratification, biomarkers, SNP, WGA, time to recovery, model comparison

3. ACCOMPLISHMENTS:

What were the major goals of the project?

This project is focused on developing a time window-based scheme that could serve as a diagnostic and prognostic platform for early outcome stratification of trauma patients. We will leverage Precision Medicine approaches in a three-phase study of military and civilian trauma to accomplish our goals. An overview of the Major Tasks is below.

Phase I – Narrow-Window Diagnostic
- Major Task 1.1 – Administrative Tasks
  - Milestone 1 – Obtain IRB and HRPO approval for patient enrollment
  - Milestone 2 – Register with FITBIR
  - Milestone 3 – All progress reports s ubmitted to CDMRP
  - Milestone 4 – All data submitted to FITBIR
- Major Task 1.2 – Genomic analyses from archival tissues
  - Milestone 5 – Completion of genomics analyses on archived Narrow Window samples
- Major Task 1.3 – Biomarker studies on prospectively recruited polytrauma +/- TBI patients
- Major Task 1.4 – Statistical and computational modeling of Narrow-Window data

Phase II – Wide-Window Diagnostic
- Major Task 2.1 – Biomarker studies on polytrauma +/- TBI patients prospectively recruited in Phase I

Phase III – Optimized Patient Stratification

What was accomplished under these goals?

Our goals for the third year were to continue to continue recruitment, sample testing, and launch the long-term outcomes collection protocol.

Major Task 1.1 – Administrative Tasks
- Maintenance of IRB and HRPO approval at all sites
- Maintenance of FITBIR DUA
- 5 monthly all-site PI conference calls
- 24 Site 1 weekly internal coordination meetings
- 12 monthly all-site regulatory/clinical coordinators call
- 1 Face to Face / virtual conference held in Bethesda on 11 April 2023

Major Task 1.2
- Completed in Y2

Major Task 1.3
  - Completed in Y4

- Enrolled 2 at Site 1, 0 at Site 2, and 7 at Site 3 in past year, for a total of 9
- Total enrollment is 103 at Site 1, 11 at Site 2, and 82 at Site 3, for a total of 196

Major Task 1.4
- Identified key predictor and outcome variables for modeling
- Modelers received retrospective and prospective data and are currently developing a Dynamic Profiling Method that will classify new subjects based on the database

Phase III
- Enrollment closed at all 3 sites

Data Management
- Redcap database complete, now includes all clinical, physiological and biochemical data for a total of 262 patients
- Modeling database in process to include 260 patients

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

Nothing to Report

How were the results disseminated to communities of interest?

Nothing to Report

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

1. Validation of Narrow Window modeling
2. Completion of Wide Window predictive modeling
3. Submit all data to FITBIR

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

The initial imposition of COVID-19 restrictions led to a reduction in activities conducive to traumatic injuries, thereby facilitating participant enrollment into the study. The study subsequently adopted a hybrid operational model, combining in-person and remote work modalities.

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

The initial imposition of COVID-19 restrictions led to a reduction in activities conducive to traumatic injuries, thereby facilitating participant enrollment into the study. The study subsequently adopted a hybrid operational model, combining in-person and remote work modalities. It is noteworthy that the enrollment phase has since concluded. However, it is imperative to acknowledge that the initial disruptions caused by the aforementioned restrictions have engendered a persisting delay in the study's timeline, resulting in a backlog of work.

Changes that had a significant impact on expenditures

Due to both aforementioned events, recruitment, and thus expenditures, were less than anticipated.

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

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS:

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications.

For this reporting period: None to report

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

For this reporting period:
None to report

Other publications, conference papers and presentations.

El-Dehaibi, Fayten & Zamora, Ruben & Radder, Josiah & Yin, Jinling & Shah, Ashti & Namas, Rami & Situ, Michelle & Zhao, Yanwu & Bain, William & Morris, Alison & Mcverry, Bryan & Barclay, Derek & Billiar, Timothy & Zhang, Yingze & Kitsios, Georgios & Vodovotz, Yoram. (2023). A Common Single Nucleotide Polymorphism is Associated with Inflammation and Critical Illness Outcomes. 10.2139/ssrn.4414866.

- **Website(s) or other Internet site(s)**

Nothing to Report

- **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Provisional patent as outlined in the previous annual report.

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Timothy Billiar, MD
Project Role: Principal Investigator
Nearest person month worked: 2
Funding Support: This grant

Name: Yoram Vodovotz
Project Role: Co-Principal Investigator
Nearest person month worked: 2
Funding Support: This grant

Name: Rami Namas
Project Role: Co-Investigator
Nearest person month worked: 4
Funding Support: This grant

Name: Derek Barclay
Project Role: Lab Manager
Nearest person month worked: 2
Funding Support: This grant

Name: Jinling Yin
Project Role: Molecular Biologist Technician
Nearest person month worked: 5
Funding Support: This grant

Name: Michelle Situ
Project Role: Data Extractor
Nearest person month worked: 5
Funding Support: This grant

Name: Zachariah Hoydich
Project Role: Clinical Research
Nearest person month worked: 1
Funding Support: This grant

Name: Lilith Bailey-Kroll
Project Role: Clinical Research Coordinator
Nearest person month worked: 5
Funding Support: This grant

Name: Dr. David Okonkwo
Project Role: Co-Investigator
Nearest person month worked: 1
Funding Support: This grant

Name: Dr. Ava Puccio
Project Role: Co-Investigator
Nearest person month worked: 1
Funding Support: This grant

Name: Allison Borrasso
Project Role: Clinical Research Coordinator
Nearest person month worked: 3
Funding Support: This grant

Name: Gregory Constantine
Project Role: Professor of Mathematics and Statistics
Nearest person month worked: 4
Funding Support: This grant

Name: Marius Buliga
Project Role: Co-Investigator
Nearest person month worked: 1
Funding Support: Institutional

Name: Eric Elster
Project Role: Co-Investigator
Nearest person month worked: 1
Funding Support: Institutional

Name: Seth Schobel-McHugh
Project Role: Bioinformatician
Nearest person month worked: 2
Funding Support: This grant

Name: Kim McLaughlin
Project Role: Bioinformatician Nearest person month worked: 5 Funding Support: This grant

Name: Henry Robertson
Project Role: Biostatistician
Nearest person month worked: 1
Funding Support: This grant

Name: William Patino
Project Role: IT Database Administrator
Nearest person month worked: 3
Funding Support: This grant

Name: Dr. Todd McKinley
Project Role: Co-Investigator
Nearest person month worked: 1
Funding Support: This grant

Name: Dr. Roman Natoli
Project Role: Co-Investigator
Nearest person month worked: 1
Funding Support: This grant

Name: Courteney Fentz
Project Role: Research Coordinator
Nearest person month worked: 2
Funding Support: This grant

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

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: