

AWARD NUMBER: W81XWH-18-2-0051

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

PRINCIPAL INVESTIGATOR: Timothy R. Billiar, MD

CONTRACTING ORGANIZATION: University of Pittsburgh, Pittsburgh, PA

REPORT DATE: October 2021

TYPE OF REPORT: Annual Summary

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

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

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REPORT DOCUMENTATION PAGEForm Approved
OMB No. 0704-0188

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1. REPORT DATE October 2021		2. REPORT TYPE Annual		3. DATES COVERED 30Sep2020 – 29Sep2021	
4. TITLE AND SUBTITLE A Precision Medicine Approach Based on Discrete Time Windows for For Predicting Outcomes of Polytrauma Patients				5a. CONTRACT NUMBER W81XWH-18-2-0051	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Timothy R. Billiar E-Mail: billiartr@upmc.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) UNIVERSITY OF PITTSBURGH THEJENNIFER E WOODWARD3520 FIFTH AVEPITTSBURGH PA 15213-3320				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
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 1- (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-Window patient stratification model has been initiated. In addition, UPITT has begun its recruitment of patients; 12 eligible patients to date. 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 .					
15. SUBJECT TERMS Precision Medicine, polytrauma, stratification, narrow window					
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	13	19b. TELEPHONE NUMBER (include area code)

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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 submitted 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
- 7 monthly all-site PI conference calls
- 27 Site 1 weekly internal coordination meetings
- 7 monthly all-site regulatory/clinical coordinators call
- 1 Face to Face / virtual conference held in Pittsburgh on 24 February 2021

Major Task 1.2

- Completed in Y2

Major Task 1.3

- In progress
 - 70 patients total, each with 3-4 time points per patient and 265 patient/time point permutations total, 46 cytokines/chemokines assayed per sample
 - 108 whole-blood samples are being processed for whole-genome DNA isolation, DNA quality control, and SNP assays
- Enrolled 54 at Site 1, 7 at Site 2, and 23 at Site 3 in past year, for a total of 87
- Total enrollment is 112 at Site 1, 10 at Site 2, and 37 at Site 3, for a total of 159

Major Task 1.4

- Identified key predictor and outcome variables for modeling
- Modelers received retrospective and prospective data and are currently drafting and validating initial predictive models

Phase III

- USAMRDC exercised the option to begin Phase III, releasing additional funding
- Received IRB and HRPO approval to begin Phase III enrollment at Site 1

Data Management

- We streamlined the Phase I-II database to facilitate easier data entry and decrease redundant and unused fields
- Developed the Phase III database, automatically sorting participants based on TBI status and automatically distributing long-term outcomes surveys, using feedback from a consultation session with FITBIR

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. Begin Phase III recruitment at Site 1
2. Continue Phase I-II recruitment at Site 2
3. Receive IRB and HRPO approval for Phase III and begin recruitment at Site 3
4. Continue SNP and biomarker assay of prospectively enrolled patients
5. Continue Narrow- and Wide-Window modeling
6. Submit additional No Cost Extension

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

While COVID-19 restrictions were reduced during the last reporting year, we continued to use a hybrid in-person/remote work protocol. Additionally, due to the slowed recruitment, we plan to keep Site 2 on Phase I-II recruitment, and initiate Phase III at Sites 1 and 3 only.

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

1. COVID-19 restrictions caused a decrease in activities that may result in traumatic injuries and facilitate enrollment into the study. Site 1 continued to enroll Phase I-II subjects beyond the originally planned recruitment cap to make up for slowed recruitment at the other sites. In order to make-up for the recruitment slowdown, we are keeping Site 2 on Phase I-II recruitment for the duration of the study.
2. Site 1 reached its regulatory recruitment cap on 19 July, and could not enroll more patients until the Phase 3 modification was approved. Simultaneously, the Site 1 IRB was undergoing personnel changes and process review, ultimately resulting in an ongoing delay to recruitment. We plan to mitigate this delay in two ways: first, by increasing the anticipated window required for IRB review and approval of future modifications; second, by requesting a NCE in the future to meet enrollment goals.

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**

Journal publications.

Publications for this reporting period.

1. Schimunek, L.; Lindberg, H.; Cohen, M.; Namas, R.A.; Yin, J.; Barclay, D.; El-Dehaibi, F.; Abboud, A.; Zamora, R.; Billiar, T.R.; Vodovotz, Y. Computational derivation of core, dynamic human blunt trauma inflammatory endotypes. *Frontiers Immunol.* 2021. <https://doi.org/10.3389/fimmu.2020.589304>
2. McKinley, T.O.; Gaski, G.E.; Zamora, R.; Shen, Li; Sun, Q.; Namas, R.A.; Billiar, T.R.; Vodovotz, Y. Early dynamic orchestration discriminates between multiply injured patients who are tolerant or sensitive to hemorrhage. *J. Trauma Acute Care Surg.* 2021. 90:441 – 450.
3. Azhar, N.; Namas, R.A.; Almahmoud*, K.; Zaaqoq, A.; Barclay, D.; Yin, J.; El-Dehaibi, F.; Abboud, A.; Simmons, R.L.; Zamora, R.; Billiar, T.R.; Vodovotz, Y. A Putative “chemokine switch” that regulates systemic acute inflammation in humans. *Sci. Rep.* 2021. 11:9703. doi: 10.1038/s41598-021-88936-8

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

For this reporting period:
None to report

Other publications, conference papers and presentations.

Two abstracts that were submitted to the 2020 MHSRS and accepted for oral presentations:
None to report

- **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
Project Role: Principal Investigator
Nearest person month worked: 1
Funding Support: This grant

Name: Yoram Vodovotz
Project Role: Co-Principal Investigator
Nearest person month worked: 3
Funding Support: This grant

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: 1
Funding Support: This grant

Name:
Project Role:
Nearest person month worked:
Contribution to Project:
Funding Support:

Name: Bradley Krivitz
Project Role: Research Assistant
Nearest person month worked: 12
Funding Support: This grant

Name: Kim McLaughlin
Project Role: Bioinformatician
Nearest person month worked: 6
Funding Support: This grant

Name:
Project Role:
Nearest person month worked:
Funding Support:

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

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

Name: Krista Brown
Project Role: Lead Research Coordinator
Nearest person month worked: 6
Funding Support: This grant

Name: Courtney Fentz
Project Role: Research Assistant
Nearest person month worked: 4
Funding Support: This grant

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

Name: Jinling Yin
Project Role: Molecular Biologist Technician
Nearest person month worked: 6
Funding Support: This grant

Name: Derek Barclay
Project Role:
Nearest person month worked:
Funding Support:

Name: Michele Situ
Project Role: Data Extractor
Nearest person month worked: 6
Funding Support: This grant

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

Name: Henry Robertson
Project Role: Biostatistician
Nearest person month worked: 3
Funding Support: This grant

Name: Alexander Limkakeng
Project Role: Co-Investigator
Nearest person month worked: 1
Funding Support: Institutional

Name: Grace Hall
Project Role: Lead Clinical Research
Coordinator
Nearest person month worked: 6
Funding Support: Institutional

Name: Olivia TumSuden
Project Role: Clinical Research Coordinator
Nearest person month worked: 4
Funding Support: Institutional

Name: Maddie Frazier
Project Role: Clinical Research Coordinator
Nearest person month worked: 4
Funding Support: Institutional

Name: Debra Williams
Project Role: Administrator
Nearest person month worked: 3
Funding Support: This grant

Name: Christopher Joy
Project Role: Research Associate
Nearest person month worked: 1
Funding Support: This grant

Name: Richard Sloan
Project Role: Research Associate
Nearest person month worked: 1
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: