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

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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					
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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, wide-window, stratification, biomarkers

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 listed below-

- **Phase 1**

Major task 1: To meet the regulatory approvals necessary to allow the sites to share data and material; as well as secure IRBs/ HRPO approval at all sites in preparation for patient enrollment.

Major Task 2: To refine the narrow-window-based stratification algorithm using both retrospective and prospective genomic, clinical and inflammation biomarkers of military and civilian trauma patients.

- **Phase 2**

Major task 1: To complete the genomic and biomarker assays of prospective patients to allow for the optimization of a wide diagnostic window (Wide-Window)-based patient stratification platform. The Phase 1 Narrow Window algorithm (based on 1 time point) will be compared against multiple time points collected under the Wide Window Phase to prognosticate for meaningful in-hospital outcomes.

Major task 2: Generation of optimized Wide-Window diagnostic and validation based on the enriched, outcome-stratified analysis of prior studies in both military and civilian blunt trauma

- **Phase 3**

Major task 1: Optimization of a window-based patient stratification platform based on data obtained from Phases 1 and 2.

Major task 2: A prospective, observational clinical study of polytrauma \pm TBI aimed at validating a streamlined set of variables, obtained at key time points post-injury, with respect to prognosticating adverse outcomes of patients with polytrauma \pm TBI.

Major task 3: Validation of optimized, windows-based predictive models against 6-month outcomes data.

What was accomplished under these goals?

Major Task 1.1- Administrative Tasks

1.2 The objectives of this task were for the 3 sites, within 6 months, to obtain the necessary approval to conduct a clinical study.

- **Site 1-UPITT**
 - UPITT Master IRB approved
 - UPITT HRPO approved
 - Coordinating Center IRB approved
 - Coordinating HRPO approval received.
 - CRADA approval received inclusive for all sites for data sharing: UPITT, USUHS, HJF and IU
 - UPITT opened patient enrollment 7/1/2019
- **Site 2- USUHS and SC2i Consortium**
 - USUHS/Walter Reed has approved IRB covering SC2i Consortium
 - CRADA approval
 - HRPO approval pending
- **Site 3- Indiana University**
 - IRB approval received 9/18/19
 - CRADA approval
 - HRPO submission pending

1.3 The key outcomes to report are:

- UPITT met Task 1.1 and approvals were received by 3/31/19.
- USUHS / SC2i Consortium has not fully met Task 1.1 as they encountered delays with the HRPO approval process related to the SC2i infrastructure. Several communications via email and phone with Captain Elster, Dr. Billiar, our HRPO scientist and Program Officer, resulted in a path forward on May 31, 2019. USUHS submitted their HRPO application on August 2, 2019 and follow up responses were submitted on October 3, 2019.
- Indiana University has experienced internal approval delays and have not fully met Task 1.1 as their HRPO submission is pending.

Major Task 1.2 -Data Optimization and Genomic Analysis:

2.2 The objectives of this task were to develop the Narrow Windows model by beginning with the construction of datasets, logistics of data and sample sharing amongst the 3 participating sites, to stratify patients by outcomes and perform SNP analysis on retrospective samples.

- UPITT, USUHS and IU have harmonized retrospective data fields as a first step to create a unified dataset of retrospective data; in addition, a REDcap database was built.
- All sites have identified their retrospective patient cohort who met I/E criteria for analysis and based on the clinical and biomarker parameters, a Master Data spreadsheet was developed.
- A Narrow-Windows patient stratification model was initiated using the Master Data spreadsheet. Dr. Greg Constantine, a Co-Investigator on this study, received the dataset on 9/27/19 to begin the development of a statistical data-driven model.
- UPITT, has completed 30% of the SNP analysis of the 453 archived genomic DNA from Subtask 1.2.1, and 100% of the inflammatory biomarkers via LuminexTM and ELISA assays.

- A Data Platform was finalized for an all site accessible data storage platform; UPITT Network Operations System has built a virtual server, Storage Explorer, for storage and backup. UPITT scheduled for training 10/17/19 to work through any potential issues. Then rollout to sites will follow.

2.3 The key outcomes to report are:

- Harmonization of data fields using the SC2i Data Dictionary
- Consensus on biomarkers for Narrows- Window model
- SNP analysis of retrospective samples is 30% completed on UPITT archived samples and analysis continues. We anticipate USUHS shipment of their archived cohort within the next month.

Major Task 1.3 – Biomarker Studies on prospectively recruited patient

3.2 The objective of this task is recruitment and analysis of prospectively recruited patients.

- UPITT began its recruitment 7/1/2019; with 12 eligible patients enrolled through 14-OCT-2019

3.3 The key outcomes to report are:

- UPITT launched its recruitment within 10 months
- Neither USUHS/ SC2i or IU have met task 1.3 and continue to work towards regulatory approval.
- Anticipate additional site recruitment to open in this quarter.

Major Task 1.4 – Statistical and Computational modeling of Narrow Windows data

4.2 The objective of this task is to generate an optimized narrow-window diagnostic

- Statistical analysis has begun at UPITT on the Master Data spreadsheet that was finalized in Major Task 1.2.

4.3 The key outcomes to report are:

- Initiation of Narrow-Windows patient stratification model
Goals have not been met under this task due to the delay of regulatory approvals at Sites 2 and 3 and we anticipate that these sites will begin recruitment in this quarter.

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?

Our expectations for the next reporting period are;

1. UPITT will add another enrollment site, UPMC Mercy Hospital after IRB modification and HRPO notification. Expected December 2019
2. Finalize Site 2 and 3 HRPO approvals.
3. Open recruitment at Site 2 and 3.
4. Complete 45% of UPITT archived genomic DNA for SNP analysis
5. For site 2, ship retrospective archived cohort samples to UPITT for SNP analysis.
6. Progress towards completion of the Narrow-Windows platform.

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:

Nothing to Report

Changes in approach and reasons for change

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

1. UPITT has enrolled 12 trauma patients in the prospective study as of 19 OCT 2019. To accelerate enrollment at UPITT, we are modifying our IRB to include another UPMC Level1 Trauma hospital, UPMC Mercy and anticipate, with 2 enrollment sites, we will meet our enrollment goal of 50 eligible trauma patients within the next 10 months.
2. Site 2 has experienced delays with achieving HRPO submission as well as approval. A new HRPO scientist has been assigned and we expect HRPO approval in the next 2- 3weeks.
3. Site 2- the SC2i Consortium has experienced delays with the launch of enrollment due to differences in their sample quality control methods and are working towards aligning their current SOPs with the Master UPITT site.
4. Site 3-Indiana University- this site is also experiencing delays with the launch of enrollment due to internal delays that affected their IRB submission and approval. Their IRB was recently approved and HRPO submission is pending.
5. Awaiting shipment of Site 2's retrospective trauma patients' samples. All samples are needed to complete the genomic analysis at UPITT. Site 2 informed UPITT that they are making progress and anticipate approval to ship within the current quarter.

Changes that had a significant impact on expenditures

As Site 2 is experiencing delays regarding regulatory approvals, their expenditures for Phase 1 were far below the budget. With the expected resolution of Site 2's issues in the next month, an increase in their expenditures in the coming months is anticipated, as they bring their various components together and open enrollment.

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

Not Applicable

Significant changes in use of biohazards and/or select agents

Not Applicable

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

1. Almahmoud K, Abboud A, Namas RA, Zamora R, Sperry J, Peitzman AB, Truitt MS, Gaski GE, McKinley TO, Billiar TR, Vodovotz Y; Computational evidence for an early, amplified systemic inflammation program in polytrauma patients with severe extremity injuries; *PLoS One* 2019 Jun 4; 14(6):e0217577 doi: 10.1371/journal.pone.0217577. eCollection 2019. PMID: PMC6548366; Yes, acknowledgement of Federal Support
2. Lamparello A, Namas RA, Constantine G, McKinley TO, Elster E, Vodovotz Y, Billiar TR; A conceptual time window-based model for the early stratification of trauma patients; *J Intern Med.* 2019 Jul;286(1):2-15 PMID: 30623510; Yes acknowledgement of Federal Support
3. Billiar IM, Guardado J, Abdul-Malak O, Vodovotz Y, Billiar TR, Namas RA; Elevations in circulating sST2 levels are associated with in-hospital mortality and adverse clinical outcomes after blunt trauma; *J Surg Res.* 2019 Jul 3;244:23-33 PMID: 31279260; Yes acknowledgement of Federal Support
4. Lamparello AJ, Namas RA, Schimunek L, Cohen M, El-Dehaibi F, Yin J, Barclay D, Zamora R, Billiar TR, Vodovotz Y; An aging-related single-nucleotide polymorphism is associated with altered clinical outcomes and distinct inflammatory profiles in aged blunt trauma patients; *Shock.* 2019 Jul 16. doi: 10.1097/SHK.0000000000001411.
5. Cohen M, Lamparello AJ, Schimunek L, El-Dehaibi F, Namas RA, Xu Y, Kaynar AM, Billiar TR, Vodovotz Y; Quality control measures and validation in gene association studies: Lessons for acute illness; *Shock.* 2019 Jul 30. doi: 10.1097/SHK.0000000000001409. [Epub ahead of print] PMID: 31365490; Yes, acknowledgement of Federal Support

6. Schimunek, L.; Namas, R.A.; Yin, J.; Liu, D.; Barclay, D.; El-Dehaibi, F.; Abboud, A.; Cohen, M.; Zamora, R.; Billiar, T.R.; Vodovotz, Y. MPPED2 polymorphism is associated with altered systemic inflammation and adverse trauma outcomes. *Frontiers in Genetics*. 2019 (In Press).

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

Nothing to Report

Other publications, conference papers and presentations.

Ashley Lamparello, Shock Society New Investigator Competition Finalist (New Investigator Competition, 42nd Annual Conference on Shock, San Diego, CA; June 2019)
Presented “An Aging-Related Single Nucleotide Polymorphism is Associated with Distinct Inflammatory Profiles in Aged Blunt Trauma Patients”

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

Nothing to Report

• **Technologies or techniques.**

Nothing to Report

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

Nothing to Report

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Timothy Billiar, MD
Project Role:	Principal
Nearest person month worked:	Investigator 1
Contribution to Project:	Dr. Billiar has directed all aspects of this project, in close collaboration with the Co-PIs.
Funding Support:	This grant
Name:	Yoram Vodovotz, PhD
Project Role:	Co-Principal
Nearest person month worked:	Investigator 1
Contribution to Project:	Dr. Vodovotz plays a key role in SNPs typing and analyzing data across all the sites.
Funding Support:	This grant

Name: Rami Namas, MD
Project Role: Co-Investigator
Nearest person month worked: 2
Contribution to Project: Dr. Namas has been instrumental in working through the logistics of the harmonization of data fields amongst all sites for the build of REDCap
Funding Support: This grant

Name: Debra Williams
Project Role: Project Coordinator
Nearest person month worked: 6
Contribution to Project: Ms. Williams provides the project coordination of the study amongst the 3 sites for the administrative tasks; post-award, logistics of regulatory and compliance; project lead to move agenda forward.
Funding Support: Other Support

Name: Stacy Stull
Project Role: Study Clinical Coordinator
Nearest person month worked: 3
Contribution to Project: Ms. Stull provides the regulatory coordination amongst all sites.
Funding Support: Other Support

Name: Derek Barclay
Project Role: Assay Specialist
Nearest person month worked: 3
Contribution to Project: Mr. Barclay has extensive experience with cytokine Luminex™ and ELISA assays, and will be responsible for performing the analysis.
Funding Support: This grant

Name: Jinling Yin
Project Role: Molecular Biology Specialist
Nearest person month worked: 3
Contribution to Project: Ms. Yin is responsible for the SNP analysis at UPITT
Funding Support: This grant

Name: Greg Constantine, PhD
Project Role: Co-Investigator
Nearest person month worked: 1
Contribution to Project: Dr. Constantine
Funding Support: This grant

Name: Jaspreet Seth, PhD
Project Role: Regulatory Specialist
Nearest person month worked: 1
Contribution to Project: Dr. Seth provides regulatory oversight for USUHS and the SC2i consortium
Funding Support: Other Support

Name: Seth Schobel, PhD
Project Role: Bioinformatician
Nearest person month worked: 2
Contribution to Project: Dr. Schobel will manage the data and drive the analytics process to generate useful biological knowledge.
Funding Support: This grant

Name: Arnaud Belard
Project Role: Research Operations Director
Nearest person month worked: 1
Contribution to Project: Mr. Belard serves as the Project Director and provides oversight of various components.
Funding Support: Other Support

Name: Todd McKinley, MD
Project Role: Site 3 PI
Nearest person month worked: 1
Contribution to Project: Dr. McKinley directs the study at Indiana University.
Funding Support: This grant

Name: Krista Brown
Project Role: Research Coordinator
Nearest person month worked: 1
Contribution to Project: Ms. Brown will facilitate regulatory approvals.
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: Attached

9. APPENDICES: Attached