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

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CONTRACTING ORGANIZATION: University of Pittsburgh, Pittsburgh, PA

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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. 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**
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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 listed below-

- **Phase 1 Narrow -Window Diagnostic**

Major Task 1: Administrative Tasks **– goals met**

Milestone 1: To obtain IRB and HRPO approval for patient enrollment at all 3 sites. *100% completion.*

Major Task 1.2: Genomic analysis from archival tissue **– goals met**

Milestone 5: Completion of genomic analyses on archived Narrow-Window samples. The 3 subtasks have been completed. *100% completion*.

Major Task 1.3: Biomarker studies on prospectively recruited *polytrauma* patients – **goals not met**

Milestone 6: Completion of inflammation biomarker and genomic analysis on *prospectively* obtained Narrow-Window samples. *0% completion.*

Major Task 1.4: Statistical and computational modeling of Narrow-Windows data – **goals 33% met?**

Milestone 7: Generation of optimized genomic narrow-window diagnostic and validation using *prospectively* obtained data. *0% completion*

- **Phase 2 Wide-Window Diagnostic**

Major task 2.1: 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. *0% completion as patient enrollment still in progress*.

Major task 2.2: 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. *0% completion as patient enrollment still in progress.*

- **Phase 3 Optimized Patient Stratification**

What was accomplished under these goals?

Our goals for the second-year reporting period were to continue to move the project forward while facing challenging times and here we report that we have met the following goals:

Major Task 1.1- Administrative Tasks

The objectives of this task were for the 3 sites to obtain the necessary approval to conduct a clinical study in Year 1. This task was completed in this reporting period.

In addition, UPITT Coordinating Center continues to engage all sites and investigators in several weekly and monthly conference calls, TEAMs meeting and when possible, in person meetings. For this reporting period, the key outcomes to report are:

- 9 monthly all Site PI conference calls
- 24 UPITT weekly internal meetings
- 10 monthly all Site regulatory/clinical coordinators call
- 1 Face to Face/ virtual conference held in Pittsburgh on 14-SEP-20. As the 2020 MHSRS was cancelled due to the pandemic, UPITT held an all Site 1-day conference, that was either attended in person following COVID-19 guidelines or via TEAMs.

Major Task 1.2: Genomics analyses from archival tissues

The objectives of this task were to complete single nucleotide polymorphism (SNP) analysis, perform bioinformatics of the SNP data and for all sites to determine genomic biomarkers for Narrow-Windows Diagnostic

- All 3 subtasks and Milestone 5 have been met in this reporting period.
- The key findings from Task 1.2 to report:
    - All 453 archived genomic DNA submitted for SNP analysis have been completed. In addition, we assayed a total 223 samples (129 samples from IU and 94 samples from SC2i) for SNPs (rs906790, rs10790334, and rs2065418).
    - We assayed a select set of '0' hour samples from UPITT archived biobank for Syndecan-1.
    - We have obtained retrospective data on 89 patients from Emory and patients from Duke, with a total of 31 cytokines assayed in these samples.
    - UPITT, USUHS and IU PIs have discussed the end points and have preliminarily concluded that the following should be included in Narrow-Windows:
        - Nosocomial Infections
        - Time to recovery (TTR) using <5days vs >5 days as an outcome
        - Single organ failure including lung and kidney
        - A coagulation and hematologic failure based on platelet count

      Biomarker analysis on retrospective plasma samples is complete and includes a validation run at USUHS employing 2 analysis platforms: Millipore Luminex™ and Meso Scale Discovery (MSD).

Major Task 1.3: Biomarker studies on *prospectively* recruited polytrauma patients.
The key outcomes to report:

- Subtask 1.3.1: Recruitment of polytrauma patients is underway at all 3 Sites. For this reporting period,
  - UPITT has enrolled 58 patients
  - IU has enrolled 17 patients
  - USUHS has no enrollments
  - Delay in regulatory approval delays at both Sites 2 & 3
  - COVID-19 shutdown of all workplaces and patient enrollment from 15-MAR-20 through 7-JUL-20 significantly impeded progress.

Major Task 1.4 – Statistical and Computational modeling of Narrow Windows data
The objective of this task is to generate an optimized narrow-window diagnostic. Due to the setback
in prospective patient enrollment, progress has been made only in Subtask 1.4.1. During the no cost
extension period, our goal is to meet the Phase 1, 200 patient enrollment number
The key outcomes to report are:

- UPITT and USUHS/SC2i Bioinformatics personnel meet regularly to discuss statistical analysis, various platforms for model comparison: conventional, CART, conventional + CART.

Data Management:
Data management and dataset curation activities have been ongoing to qualitatively merge the more than 11,000 TDAP variables with the datasets from IU and UPITT. Several key qualitative differences have been noted and communicated to the team at U Pitt for a comprehensive review and qualitative assessment. Specifically, despite similar variable naming conventions specific categorical terms within variables have led to some incompatibilities of the data. To address this the SC2i data management team is looking into converting all SC2i datasets to the OMOP CDM (Observational Medical Outcomes Partnership Common Data Model: https://www.ohdsi.org/data-standardization/the-common-data-model/) from the OHDSI (Observational Health Data Sciences and Informatics) group. This CDM is thought to provide a universal framework for observational health related research data and will allow us to converse in a standard and universal way between datasets when conducting analysis. We are currently investigating methods for performing a conversion of all the SC2i data to this format in parallel with efforts to convert the U Pitt and IU datasets as well. The hope is this will put all three datasets into a common qualitative data framework and accelerate explorations of the data in later stages of this project. The data were merged using software developed at U Pitt for collating clinical, biomarker, and genome-level data.

U Pitt / IU Narrow Window Modeling:
The first clinical end point to be used for statistical modeling was the development of nosocomial infection (NI). Work was performed by both U Pitt and SC2i, using distinct approaches at each performance site.
At U Pitt, we examined fitting predictive (logistic), non-parametric, and least absolute shrinkage and selection operator (LASSO) models for Infection as a function of biomarkers and clinical variables obtained from a first blood reading only, on the existing patients. This serves purposes set in the Narrow-Windows protocol. It was emphasized that data collection protocols should be homogenized between institutions, clinical interventions should be made available in the data, and biomarker readings be made at comparable time intervals throughout.

The data used were obtained within 6 hours from injury. A need to collect complete data in all variables of interest was emphasized, since considerable data are missing. We found 73 out of 221 subjects to have developed infection. The data were transformed by newdata=log(1+data) to mediate at least in part issues of Gaussian behavior.

Models were built on variables that have no more than 11% missing data. We retained 39 variables, including clinical, DNA markers, and 17 plasma cytokines. A random training set (TR) of 75% of patients was used. Relevant variables were selected by examining large number of random subsets of TR. The stepAIC in R was used to pin down logistic models. Main effects and two-factor interactions were considered. Models that emerged as useful in predicting Infection involved the following variables: the related cytokines IL-10 and IL-17E/IL-25; potassium; systolic blood pressure (SBP); creatinine; the interaction SBP:creatinine; the genetic marker rs906790; and the Injury Severity Score (ISS). ISS seems to have an overarching explanatory effect both on prediction and the ROC area under the curve (AUC). To a lesser extent, rs906790 has a similar effect. This model has AUC of 0.71 (74%), sensitivity of 0.73 (73%), and specificity 0.63 (63%) when predicting in the full data set. On the Testing set, sensitivity was 68% and specificity 58%. As we allow more data in beyond the first blood draw (Wide Windows), these statistics would improve. The Lasso and nonparametric analyses gave comparable results.

In summary, initial presence of rs906790AA is helpful, and ISS should be added on as early as possible. Some clinical variables could be exchanged for essentially identical effects. To a lesser extent, the same was found among subsets of biomarkers. We expect greater specificity in model identification as more data is gathered and a wider window is selected.

The SC2i performance site performed narrow window modeling of patients from the same combined IU and U Pitt dataset. 222 patients were considered with a total of 74 patients with a nosocomial infection (NI). Patient data was only considered if there was less than 11% incompleteness in a particular variable. A total of Random Forest imputation was used to account for missing data. Cytokine correlation analysis, Principal Component Analysis (PCA), conventional model-building with backward elimination, Classification and Regression Tree Analysis (CART), and Mahalanobis Distances were all considered for analysis. Cytokine data were log-transformed to account for absolute differences and to approximate normal data distributions. Correlation analysis revealed three clusters of correlated cytokines. PCA based on these clusters did not provide a strong separation between groups, thus requiring further analysis. Conventional modeling with backward elimination showed significant associations between ISS, MVC injury, and the rs906790 AA SNP genotype and the NI outcome. The cross-validated AUC of this model was 0.71 (71%), with a 0.7 (70%) and 0.75 (75%) sensitivity and specificity, respectively. Plasma IL-10 and IL-8 also showed some association with NI. CART analysis selected entirely cytokine-based models with IL-6 and MIG showing the highest predictive association with NI. The Mahalanobis Distance technique showed the highest predictive ability for NI when using all 17 cytokines with an AUC of 0.91 (91%), sensitivity of 0.81 (81%), and specificity of 0.88 (88%). This technique showed a cross-validated AUC of 0.54 (54%), however, implying model overfitting. Overall, the hybrid approach of the conventional technique and CART modeling combined show the best modeling performance with cross-validated results of 0.78 (78%) AUC, sensitivity of 0.68 (68%), and specificity of 0.82 (82%).

Preliminary TDAP Wide Window Modeling:

In preparation for later wide window modeling work across both the U Pitt and SC2i performance sites, we performed preliminary wide window modeling of TDAP patients from Walter Reed, Duke, and Emory to predict patient hospital lengths of stay (LOS). In this work, we took subsets of the more than 11,000 TDAP variables and focused on the specific variables with high completeness (>=90%). 33 clinical variables as well as 11 cytokine measurements from patient serum samples were used in modeling. All missing data were imputed using Random Forest imputation. All cytokine measurements were log-transformed to approximate a normal distribution and diminish the effect of absolute differences on a linear scale. Models were constructed using CART and LASSO techniques. A total of 181 trauma patients were considered for modeling and patients who died were removed from the analysis set as to not add a bias to the LOS modeling. From CART modeling, several thresholds were revealed within the predictor distributions with good linear predictive ability of length of stay. Specifically, MCP-1, IL-11RA, and SBP showed this characteristic. R^2 and cross-validated R^2 were 0.24 and 0.18 respectively, a moderate result for linear modeling. LASSO modeling showed better R^2 values at 0.40 and 0.30, respectively. MCP-1 again was selected as an accurate predictor of LOS, specifically a 10-fold increase of MCP-1 was associated with a 14.42 day increase in LOS. The combination of low SBP and increased HR was also associated with longer LOS. Finally, increased HGF also showed an association with longer LOS. Overall, MCP-1 was the best predictor of LOS seen in both modeling results, in line with previously published work from UPITT (Ziraldo et al, PLoS ONE. 2013. 8:e79804; Namas et al, Ann. Surgery. 2016.263:191), as well as some hints at other potential useful predictors from both the clinical and cytokine data.

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. Follow the No Cost Extension SOW outline; specifically
   - To reach our goal of 200 trauma patients by 31-MAR-21
   - Begin SNP assays at UPITT on patients enrolled prospectively
   - Begin inflammation biomarker assays at USUHS on patients enrolled prospectively
   - Identify prospectively enrolled patients for Whole Genome Sequencing (WGS) at UPITT.
2. Finalize subtask 1.4.1: Statistical analyses and computational modeling of Narrow-Window modeling.

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

For this reporting period, changes in our approach were necessary due to the 2020 COVID-19 pandemic and its effects on personnel, workplace shutdowns, remote work, quarantining and the everchanging and updated guidelines that continue at this time and require our constant attention and ability to progress the project. Our collaborators and team members have been very resilient during this time and have moved the SOW tasks forward.

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

During this reporting period we experienced the following challenges that resulted in the delay of the overall progress of the study and meeting SOW tasks.

1. Regulatory issues at both Sites 2 & 3 caused delays in the required approvals to initiate patient enrollment, patient data exchange as well as patient sample shipment to Site 1 for analysis. Our plans to mitigate these issues were communication based: PIs and coordinators from all sites were in constant communication to address the issues, possessing all the information needed to respond to institutional authorities accurately, thoroughly and in a timely manner. These actions resulted in Site 3 (Indiana University) receiving HRPO approval and launching patient enrollment 2-FEB-20 and Site 2 (USUHS) receiving HRPO approval 26-MAR-20. In addition, Site 1 continued their enrollment above the planned 50 patients. Unfortunately, the COVID-19 pandemic was our next challenge to overcome.
2. COVID-19 pandemic and its impact on the project.
   a. Each Site had similar institutional, local and state-wide directives implemented approximately 12-MAR-20, that resulted in the shutdown of work and patient enrollment. As expected, this caused numerous complications and delays in patient enrollment, bench work, personnel/family health issues, travel complications and remote work.
   - MITIGATION plans- in a timely manner, communication was initiated with all Site PIs to agree on a plan to move forward while these restrictions were in place. The plan agreed upon shifting the focus from patient enrollment and bench work to data analysis, model discussions and building using available data and refining/ finalizing Narrow-Window retrospective endpoints. Progress was made in subtasks 1.2.3 and 1.4.1 during this period.
   b. Subtask 1.3.6: Inflammatory Biomarkers- to address the delay in bench work, Site 2 biomarker analysis laboratory was deemed essential during the COVID-19 shutdown and remained operable. Therefore, the mitigation plan was for Site 2 to validate the biomarker platform and run 94 retrospective samples from their eligible biobanked samples. This was accomplished and the dataset shared, thus allowing progress on this subtask during the pandemic.

Changes that had a significant impact on expenditures

Due to both points mentioned above, expenditures for this reporting period were less than anticipated. Although we were able to utilize personnel by refocusing the work to computer-based analysis and accommodating the partial return to laboratories to conduct SNP analysis, we faced a significant delay in patient enrollment. This delay impacted anticipated expenditures on prospectively recruited patients as the biomarker, SNP and WGS analysis could not be initiated.
The prime PI, Dr. Billiar discussed these concerns with the Program SO, Dr. Regan in order to make the most appropriate immediate decisions, as well as for the remainder of the project. A No Cost Extension was discussed and followed up with our GOR and a determination was to request a 9month NCE through 6/30/2021 that would allow us to meet our SOW tasks of patient 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

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.

Publications for this reporting period.

- Zaaqoqq AM, Namas RA, Abdul-Malak O, Almahmoud K, Barclay D, Yin J, Zamora R, Rosengart MR, Billiar TR, Vodovotz Y; Diurnal variation in systemic acute inflammation and clinical outcomes following severe blunt trauma; Front Immunol 2019 Nov 20;10:2699 doi: 10.3389/fimmu.2019.02699. eCollection 2019. PMCID: PMC6879654; Yes, acknowledgement of Federal Support
- 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. Front Genet. 2019 Nov 8;10:1115. doi: 10.3389/fgene.2019.01115. eCollection 2019. PubMed PMID:31781170; PubMed Central PMCID: PMC6857553; Yes, acknowledgement of Federal Support
- Gruen DS, Brown JB, Guyette FX, Vodovotz Y, Johansson PI, Stensballe J, Barclay DA, Yin J, Daley BJ, Miller RS, Harbrecht BG, Claridge JA, Phelan HA, Neal MD, Zuckerbraun B, Billiar TR, Sperry JL; *Prehospital plasma is associated with distinct biomarker expression following injury;* JCI Insight 2020 Mar 31. Pii:135350 doi: 10.1172/jci.insight. 135350; PMID: 32229722

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

For this reporting period:
Complex Systems and Computational Biology Approaches to Acute Inflammation: A Framework for Model-based Precision Medicine. **Vodovotz, Y.** and An, G., eds. New York, NY: New York, NY: Springer. 2020 (In Press).

Other publications, conference papers and presentations.

Two abstracts that were submitted to the 2020 MHSRS and accepted for oral presentations:
1) Abstract 1:
Dynamic Networks and Principal Drivers of Systemic and Local Inflammation in Combat Casualties
Ruben Zamora, Jonathan Forsberg, Seth Schobel-McHugh, Desiree Unselt, Scott Grey, Timothy R. Billiar, Eric Elster, Yoram Vodovotz

2) Abstract 2:
Coordination of the Immediate Immunologic Response to Injury is Reduced in Patients Sustaining Femur Fractures Compared to Patients Sustaining Pelvis Fractures
Todd O. McKinley Indiana University; Greg E. Gaski MD INOVA Health System; Eric Elster MD Uniform Services University; Yoram Vodovotz PhD University of Pittsburgh; Timothy R. Billiar University of Pittsburgh

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

Nothing to Report

- **Technologies or techniques**

Nothing to Report

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

THERE IS A PROVISIONAL PATENT APPLICATION ON TRAUMA PATIENT STRATIFICATION (Refer to Appendix)

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Timothy Billiar:	no change
Name:	Yoram Vodovotz:	no change
Name:	Rami Namas:	no change
Name:	Debra Williams	no change
Name:	Derek Barclay	no change
Name:	Jinling Yin	no change
Name:	Greg Constantine	no change
Name:	Michelle Situ	no change
Name:	Eric Elster	no change

Name:	Seth Schobel
Project Role:	Bioinformatician
Nearest person month worked:	2.4
Contribution to Project:	Dr. Schobel is a subject-matter expert in bioinformatics, an interdisciplinary field that develops and improves upon methods for storing, retrieving, organizing and analyzing biological data.
Funding Support Name:	CDMRP

Name:	Henry Robertson
Project Role:	Biostatistician
Nearest person month worked:	3.0
Contribution to Project:	Dr. Robertson will provide biostatistical support for clinical and/or laboratory research performed under this collaborative effort.
Funding Support Name:	CDMRP

Name:	Felipe Lisboa
Project Role:	Medical Scientist
Nearest person month worked:	2.4
Contribution to Project**:**	Dr. Lisboa will coordinate patient enrollment, sample collection and handling. Dr. Lisboa will assist in keeping the team adherent to IRB protocol procedures.
Funding Support:	CDMRP
Name:	Jaspreet Seth
Project Role:	Associate Director-regulatory & laboratory compliance
Nearest person month worked:	0.36
Contribution to Project:	Dr. Seth will carry out the development and submission of all regulatory requirements for the implementation of this study
Funding Support:	CDMRP
Name:	Victoria Doseeva
Project Role:	Associate Director- laboratory science
Nearest person month worked:	0.36
Contribution to Project**:**	Dr. Doseeva is responsible for sample preparation and processing for clinical and laboratory samples
Funding Support:	CDMRP
Name:	Bradley Krevit
Project Role:	Research Assistant
Nearest person month worked:	9.6
Contribution to Project**:**	Mr. Krevit is responsible for sample preparation and processing for clinical and laboratory samples.
Funding Support:	CDMRP
Name:	Todd McKinley: no change
Name:	Krista Brown: no change
Name:	Christopher Seymour
Project Role:	Biostatistician & Assistant Professor of Critical Care
Nearest person month worked:	2.4
Contribution to Project**:**	Dr. Seymour's expertise in biomarker science and modeling methods are utilized.
Funding Support:	This funding
Name:	David Okonkwo
Project Role:	Professor of Neurological Surgery
Nearest person month worked:	1.0
Contribution to Project**:**	Dr. Okonkwo's expertise in traumatic brain injury will be utilized.
Funding:	This funding

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: