AWARD NUMBER: W81XWH-16-1-0497

TITLE: Early Critical Care Decisions and Outcomes after SCI: Track-SCI

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CONTRACTING ORGANIZATION: University of California at San Francisco

REPORT DATE: December 2020

TYPE OF REPORT: FINAL

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

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 0704-0188*



| **1. REPORT DATE** | **2. REPORT TYPE** | **3. DATES COVERED** |
|---|---|---|
| Dec 2020 | Final | 08/15/2016-08/14/2020 |

**4. TITLE AND SUBTITLE**
Early Critical Care Decisions and Outcomes after SCI:Track-SCI

**5a. CONTRACT NUMBER**
W81XWH-16-1-0497

**5b. GRANT NUMBER**
SC150198

**5c. PROGRAM ELEMENT NUMBER**

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**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

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of California, San Francisco
1855 Folsum Street, Ste. 425
San Francisco, CA 94103

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

U.S. Army Medical Research and Development 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**

**This project was a continuation of a prospective observational study of early critical care practices and predictors of outcome in acute spinal cord injury (SCI) conducted at the UCSF campus at the Zuckerberg San Francisco General Hospital and Trauma Center and at the UCSF Fresno Medical Center. The project continues on as an expansion of this award (SC150198) which was funded beginning 08/14/2020 (SC190233). Using NINDS SCI common data elements (CDEs) and a custom REDCap database we collected detailed physiological, imaging, and treatment data on every enrollable SCI admission to these two level 1 trauma centers. Our objective was to provide a comprehensive prospective analysis of multiple variables in acute SCI that impact longterm outcomes. Most participants received follow-up interviews and ISNCSCI /ASIA neurological scores and classification at 6 and 12 months. Critical care variables included surgical timing and procedure, ICU management and physiological monitoring of blood pressure, pharmacological treatments, and all variables listed in the NINDS CDEs, with special attention to cardiovascular and autonomic variables. High resolution MR imaging was paired with a 'tool kit' of post- processing procedures that will be combined with physiological, genomic, and treatment variables to produce predictive prognostic models in the future. Guidelines based on best practices identified during the study will be communicated to both the military and civilian SCI patient care communities. White blood cells (WBC) were isolated from blood samples from acute SCI patients were used to provide WBC gene expression profiles via messenger RNA deep sequencing (RNAseq). These profiles were used to begin identification of diagnostic and prognostic biomarkers for acute SCI.**

**15. SUBJECT TERMS**

| **16. SECURITY CLASSIFICATION OF:** | | | **17. LIMITATION OF ABSTRACT** | **18. NUMBER OF PAGES** | **19a. NAME OF RESPONSIBLE PERSON** |
|---|---|---|---|---|---|
| | | | | | USAMRMC |
| **a. REPORT** | **b. ABSTRACT** | **c. THIS PAGE** | Unclassified | | **19b. TELEPHONE NUMBER** *(include area code)* |
| Unclassified | Unclassified | Unclassified | | | |

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## 1. INTRODUCTION

This project was a continuation of a prospective observational study of early critical care practices and predictors of outcome in acute spinal cord injury (SCI) conducted at the UCSF campus at the Zuckerberg San Francisco General Hospital and Trauma Center and at the UCSF Fresno Medical Center. The project continues on as an expansion of this award (SC150198) which was funded beginning 08/14/2020 (SC190233). Using NINDS SCI common data elements (CDEs) and a custom REDCap database we collected detailed physiological, imaging, and treatment data on every enrollable SCI admission to these two level 1 trauma centers. Our objective was to provide a comprehensive prospective analysis of multiple variables in acute SCI that impact long-term outcomes. Most participants received follow-up interviews and ISNCSCI /ASIA neurological scores and classification at 6 and 12 months. Critical care variables included surgical timing and procedure, ICU management and physiological monitoring of blood pressure, pharmacological treatments, and all variables listed in the NINDS CDEs, with special attention to cardiovascular and autonomic variables. High resolution MR imaging was paired with a 'tool kit' of post- processing procedures that will be combined with physiological, genomic, and treatment variables to produce predictive prognostic models in the future. Guidelines based on best practices identified during the study will be communicated to both the military and civilian SCI patient care communities. White blood cells (WBC) were isolated from blood samples from acute SCI patients were used to provide WBC gene expression profiles via messenger RNA deep sequencing (RNAseq). These profiles were used to begin identification of diagnostic and prognostic biomarkers for acute SCI.

**2. KEYWORDS.** Spinal cord injury (SCI), critical care, trauma, observational study, blood pressure, gene expression, American Spinal Injury Association (ASIA), paralysis, recovery of function, magnetic resonance imaging (MRI), spinal decompression,

## 3. ACCOMPLISHMENTS

**What were the major goals of the project?**
**Goal 1: Build a knowledge network for acute SCI** that includes critical care variables and long-term outcomes.
**Goal 2: Develop critical care diagnostic and prognostic indicators** for predicting outcomes and stratifying patients using physiological, imaging and genomics datasets. These were focused on autonomic (cardiovascular), imaging, and gene expression.
**Goal 3: Begin to optimize acute SCI treatments through** data dissemination, analysis and distribution of suggested 'best practices'.
**Goal 4: Use critical care clinical data to 'back-translate'** bedside-to-bench preclinical models.

**What was accomplished under these goals?** (References to papers form the current funding period, listed in section 6 ("Products"), are **bolded** in the accomplishments section. All of these papers are available in the appendix).

*Goal 1. A. Team building and infrastructure development.* Our first and perhaps most important accomplishment was building out the team and infrastructure necessary for this endeavor. Clinical studies of SCI are challenging in part because of the relatively low numbers of patients available for study, but also due to the difficulty of assembling clinical research teams capable of following patients and securing data across the multi-disciplinary clinical environment from the emergency department to rehabilitation. Long term follow-ups needed for assessing functional outcomes are particularly challenging. Clinical research staff need to be trained and integrated into the acute patient care setting, with buy-in from clinical stakeholders. Basic science expertise was needed to launch new directions in understanding the human biology of early SCI. Finally, multivariate approaches to big data analytics require a dedicated group of experts in data management, data curation, and statistical analysis. After more than 4 years of experience at UCSF/ZSFG in accruing patients and data, and the successful onboarding of a second center at UCSF Fresno, these challenges have been largely partially addressed. Key experts in all aspects of the study are on board and cooperating in a highly collaborative environment. Figure 1 shows the various PIs at ZSFG and their responsibilities. The team at UCSF Fresno is led by Dr. Yu-Hung Kuo who leads the neurosurgical service at Fresno. TRACK-SCI has also recruited new clinician- researchers who have contributed to both data collection and analysis, including residents (e.g. Drs. John Yue and John Burke) and attending physicians (Dr. Anthony DiGiorgio) and critical

care caregivers (e.g. RN and soon-to-be Ph.D., Debra Hemmerle). Finally, during the last part of this award, we recruited the Wexner Ohio State University Medical Center as a prospective new site for TRACK-SCI, with Drs. Frank Farhadi (Neurosurgery) and Jan Schwab (Neurology) as PIs. With the recent funding of an SCIRP expansion award (SC190233), OSUMC will be enrolling new participants beginning in late 2020 or early 2021.

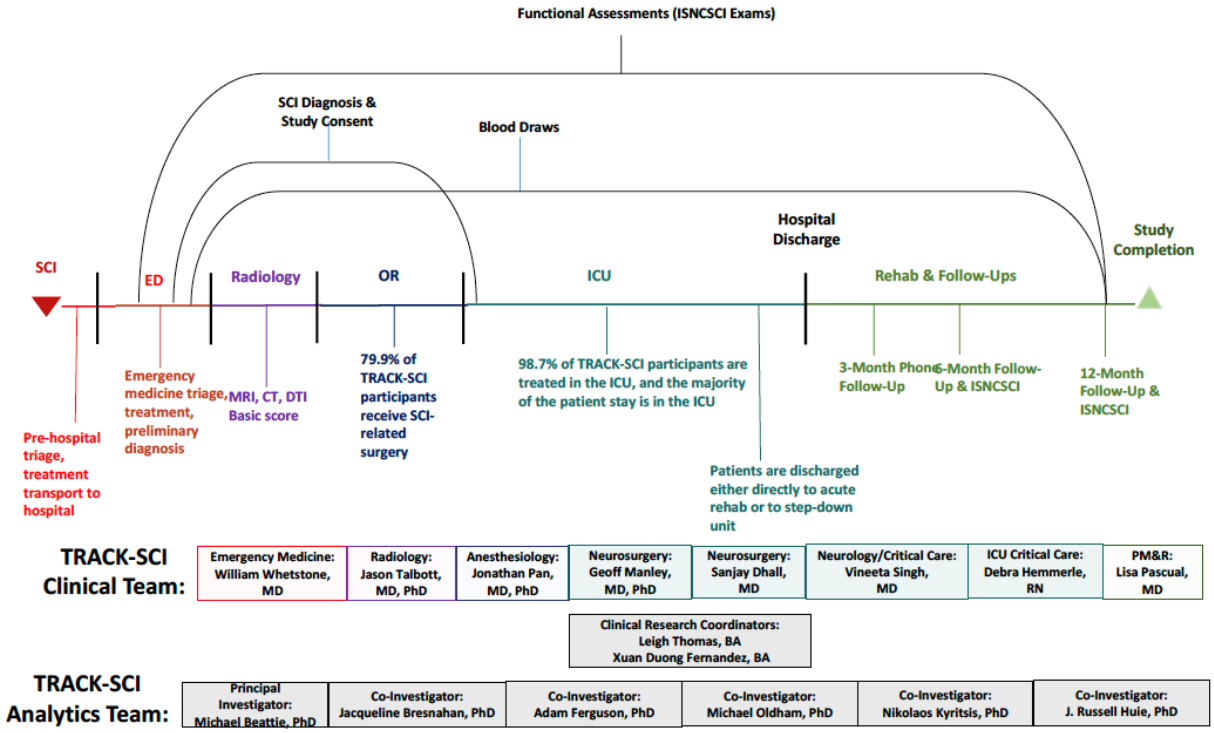


**Fig. 1. TRACK-SCI teams and data collection scheme.**

*B. Data structure, collection, and curation. Establishment of a useable data set structure that includes NINDS SCI CDEs.* A prospective RedCap dataset encompassing 20,000+ variables was established that includes over 150 acute SCI patients enrolled at UCSF/ZSFG and UCSF Fresno. This structure was initially established using data from a retrospective analysis of (218) SCI patients who were treated at ZSFG from 2008-2014. Over the course of the last 5 years (including the last years of SC120159 and the no-cost extension of this award, SC150198), some variables have been added, some deleted, and the project has been focused. We now have a core data set that can be used to get new centers up and running. Procedures for data curation and handling missing values have been established in the BASIC informatics core.

*C. Enrollment.*

*Enrollment figures as of Aug 1, 2020*: At ZSFG for this cohort (SC150198 , Aug 1, 2016 – Aug.1 2020), we have 89 subjects (28 female, 61 male) with the following characteristics: 1) mean age = 59.1 (Mdn=61; range 19-90); 2) spinal cord injuries at the cervical (84%), thoracic (12%), and lumbar (03%) levels; 3) ASIA impairment scores for this cohort at admission or first exam were A (24%), B (09%), C (12%), D (47%), E (2%) unknown/unable to assess (e.g. comatose, drug impaired, etc) (6%). 17% also had concurrent TBI. 4) mechanism of injury was assault (11%), fall (56%), transport (28%), and other (04%). 96% were categorized as blunt injuries (vs penetrating). We categorized 48% as central cord cases. The mean pre-hospital transport time was 18.2 min (median = 16.5 min; range 3-37 min; n=51); Mean time in the ED was 312 min (Mdn=235, range 37-1355 minutes, n=77). Mean time to OR was 22.7 hrs (Mdn= 7.7 hrs; range 0.7-267 hrs; n=63). ICU length of stay was a mean of 9.8days (Mdn= 5.9 d; range = 0.5-63.5 d). Mean hospital stay was 19.8 days (Mdn = 9.7 d; range 2.0-440.63 days; n =75). Subjects were discharged to an acute rehab unit (45%), another hospital (35%), home (13%), and 7% were deceased. Three-month follow-up assessments (n=44), six month follow ups (n=34), and 12 month follow-ups (n=37) have been completed; as patients move through the study, more will be completed. We also have enrolled 15 healthy, uninjured controls and 16 trauma controls, for white blood cell (WBC) RNA sequencing. (note- categories with n<89 are due to missing data).

*At UCSF/Fresno,* our second site, enrollment included 54 subjects (13 female, 41 male) with the following characteristics: 1) mean age = 46.7 (Mdn=49, range 19-87); 2) spinal cord injuries at the cervical (67%),

thoracic (20%) and lumbar (13%) levels; 3) ASIA impairment scores at admission or first exam were A (30%), B (02%), C (21%), D (36%), E (02%), & unable to determine (08%). 11% had concurrent TBI. Mechanism of injury was assault (25%), fall (44%), transport (27%), other (4%). 65% were blunt injuries (vs penetrating). 26% were categorized as central cord syndrome. Mean pre-hospital transport time was 14.8 min (Mdn= 10 min, range 3-83 min, n=34). Mean time in the ER was 538 minutes (mdn=360 min, range 29-2186, n=50). Mean time to OR was 38.4 hours (mdn 25.3 hrs, range 0.3-231.3, n=37). ICU length of stay was a mean of 6.8 days (Mdn = 4.6, range: 01- 63.5 days, n=45). Mean hospital length of

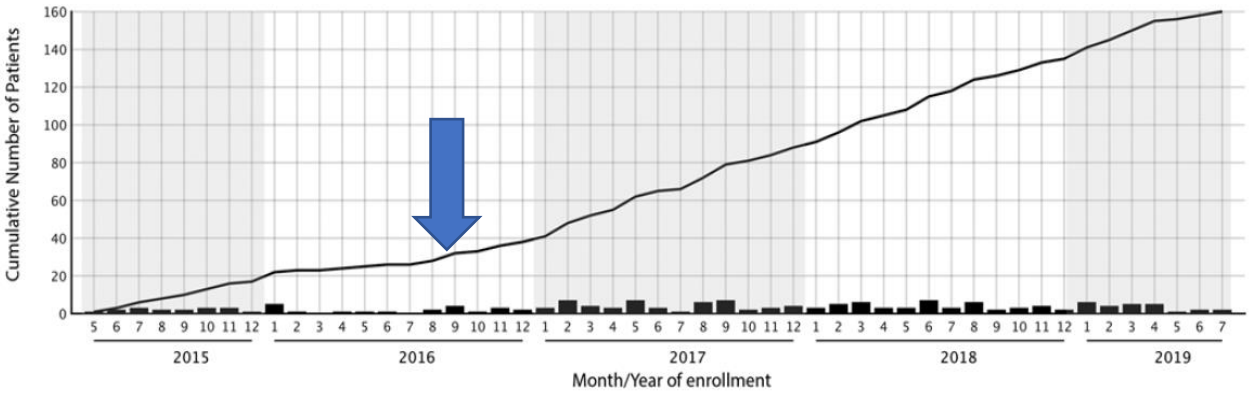


**Figure 2** shows the cumulative enrollment numbers for TRACK-SCI from 2015-2019. The period covered by SC150198 begins at the blue arrow and continues (under an NCE) until August of 2020. However, enrollment was stopped beginning in March of 2020 due to clinical research restrictions at UCSF related to COVID-19. Participant accrual was steady throughout the funding period until the recent restrictions. Note that work on the project continued in the absence of new enrollments: phone interviews for follow-up exams were conducted, and project personnel continued data curation, analysis, and dissemination of papers and protocols.(from Tsolinas et al, 2020)

stay was 14.4 days (Mdn= 10, range 2.9-63.6 days, n=50). Subjects were discharged to an acute rehab unit (52%), another hospital (31%), private residence (13%), or deceased (04%). We completed 21 three-month follow-up assessments,19 six-month, and 16 12-month assesments .

Note: TRACK-SCI prospective enrollment including the cases accrued under the prior award (SC120559) = 179 total people w SCI.

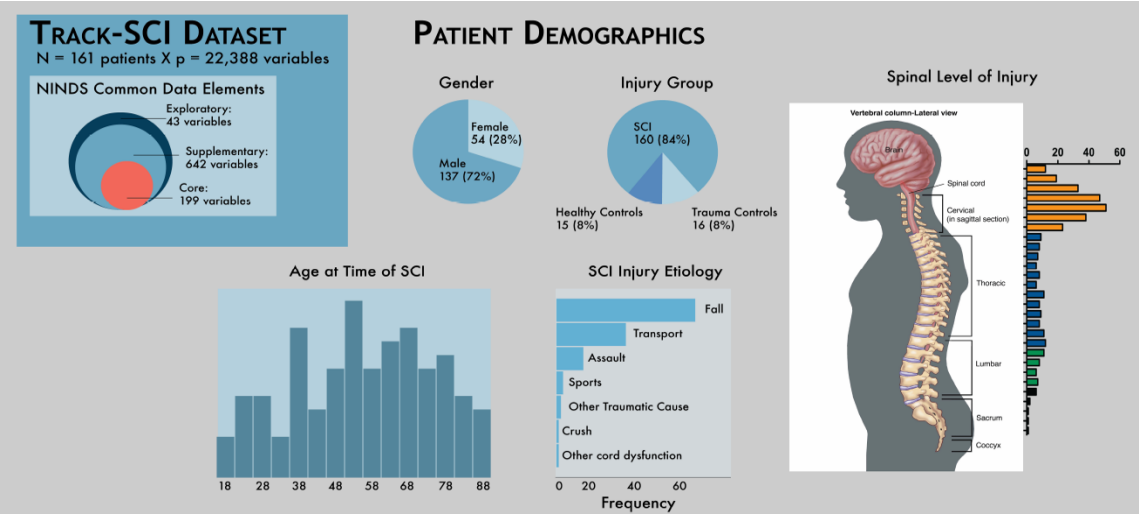


Figure 3. Patient Characteristics for TRACK-SCI prospective data as summarized for a presentation for the 2020 International Neurotrauma Symposium.

***Goal 2*. *Critical care variables that indicate severity and predict outcomes*.** The RedCap-resident dataset allows entry of thousands of data points per participant, based on NINDS CDEs for SCI, and other demographic and physiological variables. These are summarized in **Tsolinas et al. (2020)**. We have focused our published analyses to date on autonomic (cardiovascular), imaging (MRI), surgical timing, and gene expression as predictors of acute neurological status and outcomes, with most analyses limited to neuro outcomes in the subacute/subchronic time points that include the hospital stay and date of discharge. Additional analyses of predicters of outcome at later time points (3, 6, 12 months), where there are fewer data points, are ongoing and will be analyzed with higher n's as patient accrual continues in the expansion award (SC190233). Key findings include:

*Cardiovascular:* Based on several uncontrolled observational studies, as well as analogies to acute treatment of TBI, current guidelines for treatment of acute SCI suggests maintaining mean arterial pressure (MAP) above 85mm Hg in the emergency setting and in the ICU. One of the first studies of our retrospective SCI dataset at ZSFG (Hawryluk et al, 2015; **Catapano et al, 2016; Readdy et al, 2016**) lent support to that idea, and a first look at these variables in our prospective cohort has been published (**DiGiorgio et al, 2017**). High frequency recordings of MAP in the ICU showed that time spent at low MAPs (under 70 mm Hg) predicted worse outcome at discharge, and higher MAPS predicted conversion of 1 or more ASIA grades (e.g. A-C). These findings have now been extended to examine the potential impact of blood pressure management in the operating room (OR) during decompression surgery, and a detailed analysis using a machine learning approach shows robust effects of both hypo- *and* hyper-tension on probability of neurological recovery, in terms of progression from lower to higher ASIA grade at discharge (**Torres-Espin et al, submitted**). These findings are similar to those from a multidimensional analysis of recovery of locomotion in a large preclinical study of thoracic injuries in rats with systematically varied injury severities (Multicenter Animal Spinal Cord Injury Study-"MASCIS") where MAP at time of SCI surgery was the most salient predictor of outcomes (Neilsen et al, 2015). This analysis is now being extended to the intraoperative and ICU records from our prospective cohort. The importance of blood pressure management is likely to be due in part to the role of systemic BP in driving spinal cord perfusion pressure (SCPP). Our team at ZSFG has been involved in the recent CASPER observational study (Kwon et al, 2019), which provides evidence that management of SCCP using intrathecal CSF pressure as an added variable, may be particularly useful in optimizing recovery from secondary damage in human SCI. As an example of how TRACK-SCI and related studies can drive changes in clinical practice, the UCSF/ZSFG neurosurgical team is now monitoring CSF pressure in the ICU and using derived values of SCCP as an adjunct to MAP to determine use of vasopressors (**Yue et al, 2020**).

*Magnetic Resonance Imaging.* TRACK-SCI/UCSF-ZSFG neuroradiologist Jason Talbott, M.D., Ph.D., (the optional qualified collaborator on SC150198) and the team developed a useful rating scale for evaluating SCI severity from axial MRI images, the BASIC scale (**Talbott et al**, 2015, **2019**; **Mabray et al, 2016**; **Readdy et al, 2016**), which has been independently validated by our new collaborating team at the Wexner OSUMC (Farhadi et al, 2018), and is now being used to categorize all of our prospective patient cohort. The team has continued to develop new tools for evaluating acute SCI using MRI, using the Montreal "Spinal cord tool box'" and machine learning approaches to segmentation for 2D and 3D estimations of lesion size (**Haefeli et al, 2017**; **McCoy et al, 2019**), which are showing that volumetric evaluation of T2-hyperintensity can serve as predictor of outcomes in acute SCI (**Mummanneni et al, 2020**). Additional details are provided in the optional qualified collaborator's statement in section 8. The use of these new measures, and continued development of MRI features as predictors of *long-term outcomes* are being pursued as we continue TRACK-SCI in SC190233.

*Timing of decompression surgery.* ZSFG/UCSF Hospital and Trauma Center serves as the sole level 1 trauma center for high density /limited area population of San Francisco and the upper San Francisco penninsula in San Mateo County. Transport times for trauma victims are low (mean < 20 min), and recent emphases on rapid emergency department evaluation, imaging, and the availability of 24/7 surgical teams has been driving down time from admission to decompression surgery. As predicted by the results of the Canadian STASCIS study, we find that rapid decompression is associated with better outcomes (e.g. **Burke et al., 2018**). These factors have combined to drive changes in clinical standards for ZSFG that emphasize rapid imaging (available

within the emergency department in our new hospital), rapid decompression, and high resolution physiological monitoring of both BP and SCPP in the neuro ICU.

*White blood cell (WBC) gene expression patterns as predictors of severity and outcome.* We have made significant progress on the gene expression analysis feasibility studies proposed in SC150198, and we report below, and in an 'in press' publication (**Kyritsis et al, 2020,2021**) the exciting initial data that strongly supports the future possibility of obtaining blood RNAseq-based gene expression modules that predict SCI severity and long-term outcome. WBC RNA transcriptomics appear to provide a wealth of information about the effects of early SCI on white blood cells (WBC) gene expression patterns that may be useful in predicting outcomes and generating new therapeutic targets.

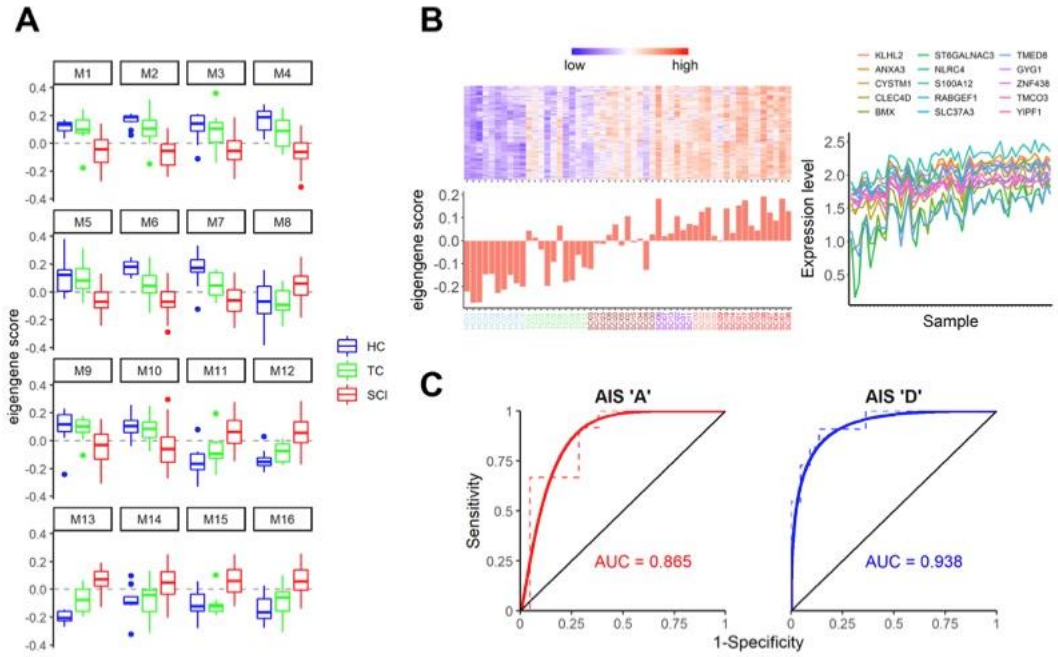


**Figure 4**. Gene co-expression network analysis reveals transcriptional modules in peripheral white blood cells that predict spinal cord injury severity. **A.** Analysis of module eigengene (PC1) scores by patient cohort reveals 16 SCI-specific gene co-expression modules following unsupervised gene co-expression network analysis. Some modules (e.g. M4) display a gradual change in gene expression, whereas in others (e.g. M1, M5) HCs and TCs are very similar to each other but different from SCIs. N = 10 for HCs and TCs and 38 for SCIs. **B –C**. The M13 module has the highest correlation to SCI severity (Spearman rho = 0.82). **B** shows the heatmap of the top-seeded genes for this module(top), and the eigengene score for each one of the patients and controls (bottom). The graph in **C** shows the expression levels of the top 15 genes of the M13 module across all 58 samples. As expected from the analysis, these top genes of the module exhibit a strong co-expression pattern. **D** shows the receiver operating characteristic (ROC) plots for the AIS 'A' against the remaining SCIs (left) and the AIS 'D' against the remaining SCIs (right). These plots show the strong predictive ability of our model for SCI patients with AIS 'A' and 'D'. The AUC is 0.865 for the 'A' and 0.938 for the 'D'. N = 12 'A' vs 21 SCIs and 11 'D' vs 22 SCIs (color scheme in x-axis labels in panel B is as follows: blue = HC, green =TC, brown = AIS 'D', purple = AIS 'C', salmon = AIS 'B', and red = AIS 'A'). **From Kyritsis et al, 2021, J. Exp. Med. (in press).**

***Goal 3. Multidimensional data analysis and dissemination of research findings and proposed 'best practices'.*** TRACK-SCI is intended, long term, to provide new data from multiple centers that impact clinical practice to enhance treatment of, and recovery from, SCI. A bioinformatics/analytics team led by Dr. Adam Ferguson was charged with helping to oversee data collection and curation standards, as well as applying their expertise in multivariate statistics and machine learning/AI technologies to the growing TRACK-SCI dataset. In addition to the original aims to collect critical care data that can be used in developing diagnostic and prognostic 'biomarkers' for SCI, the bioinformatics group provides consultation and advice to the committee of

TRACK-SCI investigators. By year 2 of the prospective collection of TRACK-SCI data, there were enough patients enrolled to begin using the prospective data set to ask questions of clinical interest generated by members of the UCSF group. Since access to the data set necessarily involves time and effort of the CRCs and advice on analytics requires time and effort from the bioinformatics team, a formal process for evaluating project proposals is in place. For example, Burke et al (2018) asked whether ultra-acute cord decompression (defined as earlier than 12 hrs after admission) could potentially enhance recovery vs later (<24hrs or >24 hrs) intervention, and requested access to the dataset, and advice and help in data curation and analysis. This was brought before the committee of research investigators that met every two weeks, and approved. This approval opened up access to help from CRCs and the bioinformatics team.

Examples of advanced multivariate analytics applied to both the retrospective and prospective datasets can be found in the publications listed in section 6 (e.g. **Haefeli et al, 2017; Kyritsis et al, 2020; Mabray et al, 2016; McCoy et al, 2019; Mummanneni et al, 2020; and Torres-Espin et al, submitted).**

A long-term goal of TRACK-SCI is to provide access to our rich dataset for qualified SCI researchers, and to provide data that is "Findable, Accessible, Interoperative, and Reproducible", i.e. that abides by the FAIR standards recently developed and recommended by NIH and other federal scientific agencies. At the end of the funding period for SC1

Emerging strategies for data sharing: Open data commons for SCI (ODC-SCI), funded by multiple sources over the past several years (NIH, VA. C.H. Neilsen Foundation).

***Goal 4: Bedside to bench translation for preclinical modeling.*** One of the stated goals of SC150198 was to use our growing evidence on acute SCI in the clinic to generate critical care treatment questions that could be tested in our preclinical models of SCI. This goal has been aided by our strong informatics group, and is reflected in parallel analysis and experiments on physiological variables that may affect outcomes including MAP and MRI studies.

**What opportunities for training and professional development has the project provided?** While training was not an explicit goal of the project, TRACK-SCI and the team of preclinical, analytics, and clinical research experts and the activities associated with the project have provided training opportunities for medical students, resident physicians, Ph.D. students, and postdoctoral fellows (e.g. TRACK-SCI authors Burke, Yue, Hemmerle, Torres-Espin, Kyritsis, Neilson, and more).

**How were the results disseminated to communities of interest?** TRACK-SCI study protocols, data, and recommendations for clinical practice have been presented by multiple members of the team at national and international professional meetings, including neurosurgical, neurology, and critical care societies, the International Spinal Cord Injury Society, the American Spinal Injury Association, and others, as well as meetings of Foundations and advocacy groups supporting people with SCI lived experience (e.g. Rick Hansen and Praxis SC Institute gatherings). Publications resulting from the work have appeared in major medical and neuroscience journals.

**4. IMPACT**

**What was the impact on the development of the principal discipline(s) of the project?** TRACK-SCI has gained an international reputation as an effort to increase data on acute SCI treatments and outcomes. The PI, Dr. Beattie has been invited to present goals and data at multiple international venues (International Spinal Cord Society-ISCoS, American Spinal Injury Association (ASIA), and the International Neurotrauma Society-INTS). Dr. Dhall, who leads the neurosurgical SCI unit and is PI on the TRACK-SCI IRB protocol, has given grand rounds at multiple academic medical research centers and introduced protocols generated during TRACK-SCI to national neurosurgical organizations. Dr. William Whetstone, TRACK-SCI emergency medicine lead, was invited to presented at the NIH-sponsored "SCI 2020" conference, emphasizing the emergency-medicine aspects of acute care of SCI. This presentation had an especially strong reception. Members of the team have been recognized by national professional organizations for their presentations of TRACK-SCI data (e.g. Dr. John Burke, "Best neurotrauma paper" at AANS neurosurgical meeting last year; Dr. Nikos Kyritsis, Best poster presentation at both the Wings for Life investigators meeting in Salzburg, and the Gordon Conference on Spinal cord injury and regeneration, 2019). Dr. Adam Ferguson, who leads the BASIC and

TRACK-SCI bioinformatics group, has been a keynote speaker at multiple international and national venues, talking about TRACK-SCI multivariate statistical methods and outcomes.

Recently, TRACK-SCI established Facebook and Twitter accounts (voluntarily managed by Dr. Kyritsis), and we are using these accounts to provide TRACK-SCI information to the social media world.

We are tracking citations to TRACK-SCI papers as well. The Hawryluk et al. (2015) report on the impact of blood pressure management on outcomes has received over 107 citations to date. The BASIC score MRI paper by Talbott et al (2016) has 71 cites to date. Perhaps more importantly, the BASIC score for MRI as a predictor of severity has been independently replicated and validated by our colleagues at OSU Medical Center, and now Drs. Farhadi and Schwab from OSU are TRACK-SCI investigator on our recent expansion award.

**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.** Our initial projections of enrollment, based on past reports of SCI incidence and on retrospective analyses, were over-estimates.

## 6. PRODUCTS

### A. Peer-reviewed full-length publications


Burke JF, Yue JK, Ngwenya LB, Winkler EA, Talbott JF, Pan JZ, Ferguson AR, Beattie MS, Bresnahan JC, Haefeli J, Whetstone WD, Suen CG, Huang MC, Manley GT, Tarapore PE, Dhall SS. Ultra-early (<12 Hours) surgery correlates with higher rate of American Spinal Injury Association Impairment Scale Conversion after cervical spinal cord injury. *Neurosurgery.* 2018;85(2):199-203. doi: 10.1093/neuros/nyy537.

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Hawryluk G, Whetstone WD, Saigal R, Ferguson AR, Talbott JF, Bresnahan JC, Dhall SS, Pan JZ, Beattie MS, Manley GT. Mean arterial blood pressure correlates with neurological recovery after human spinal cord injury: analysis of high frequency physiologic data. *J Neurotrauma*. 2015;32(24):1958-1967. doi:10.1089/neu.2014.3778. (107 cites)

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**B. Oral or Poster Presentations at National or International meetings/ Abstracts**

Beattie MS, Almeida C, Bresnahan JC, Dhall SS, Fernandez XD, Ferguson AR, Hemmerle DD, Huie JR, Kyritsis N, Manley GT, Pan JZ, Pascual LU, Singh V, Talbott JF, Thomas LH, Tsolinas R, Weinstein PR, Whetstone WD. Acute care variables at a Level 1 trauma center as predictors of outcome in SCI: TRACK-SCI progress report. Presentation at: The 3rd Joint Symposium of the International and National Neurotrauma Societies and AANS/CNS Section on Neurotrauma and Critical Care; August 11-16, 2018; Toronto, Canada.

Beattie M, Jones L, Wirth E, Fouad K. Increasing Translational Success: A Discussion on Trial Design of Animal and Human Studies to Increase the Successful Implementation of Basic Research Findings to the Clinic. Expert panel presentation at: The American Spinal Injury Association Annual Scientific Meeting, SCI Summit; April 2-5, 2019; Waikiki, HI.

Duong Fernandez X, Thomas LH. TRACK-SCI: Challenges and Solutions in Establishing an Acute Spinal Cord Injury Database*.* Presentation at: 19th Annual University of California Neurotrauma Symposium; September 23-25, 2018*;* San Jose, CA

Duong Fernandez X, Harris MH, Thomas LH. Subject retention in an acute observational spinal cord injury study: A TRACK-SCI presentation*.* Presentation at: 20th Annual University of California Neurotrauma Symposium; September 22-24, 2019*;* Santa Barbara, CA.

Ferguson, AR. Reproducibility and translation of hemodynamic predictors in SCI: Testing the limits using big-data. Presentation at Wings for Life Scientific Meeting; May 7-8, 2019; Salzburg, Austria.
Ferguson AR. Harnessing Big-Data to Drive Reproducibility and Translation in SCI. Keynote presentation at: The American Spinal Injury Association Annual Scientific Meeting, SCI Summit; April 2-5, 2019; Waikiki, HI.

Huie JR. Data-driven approaches for spinal cord injury: Insights from TRACK-SCI. Presentation at: 58th International Spinal Cord Society Annual Scientific Meeting; November 5-7, 2019; Nice, France.

Huie JR, Talbott JF, Singh V, Fernandez XD, Tsolinas RE, Pascual LU, Pan JZ, Kyritsis N, Torres D, Beattie MS, Bresnahan JC, Ferguson AF, Dhall SS, Whetstone WD. Data-driven comparison of acute imaging biomarkers for spinal cord injury: a prospective TRACK-SCI pilot study (S42.006). *Neurology.* 2018;90(15):S42.006. http://n.neurology.org/content/90/15_supplement/S42.006. Published April 20, 2018. Updated April 26, 2018. (Abstract). Presented at the 2018 American Acad. Neurology annual meeting.

Kyritsis N, Tsolinas, RE, Duong Fernandez X, Hemmerle D (nee Phillips), Pan JZ, Pascual LU, Talbott JF, Singh V, Whetstone WD, Huie JR, Manley GT, Dhall SS, Ferguson AR, Bresnahan JC, Beattie MS, TRACK-SCI investigators. Using RNASeq to discover blood biomarkers for diagnosis of SCI severity and/or prognosis of neurological recovery: TRACK-SCI. Abstract published electronically for the 17th International Symposium on Neural Regeneration; November 27-December 1, 2017; Pacific Grove, CA.

Kyritsis N, Duong-Fernandez X, Thomas LH, Hemmerle DD, Whetstone W, Singh V, Pascual LU, Talbott J, Schupp P, Dhall SS, Manley GT, Oldham M, Ferguson AR, Bresnahan JC, Beattie MS, and the TRACK-SCI Investigators. Blood RNA biomarkers for SCI: Using RNAseq and advanced analytics for discovering diagnostic and prognostic clinical tools. Presented at: 1st Gordon Research Conference on Central Nervous System Injury and Repair; June 16-21, 2019; Waterville Valley, NH.

McCoy DB, Dupont SM, Beattie MS, Ferguson AR, Talbott JF. Atlas-based MRI texture analysis with machine learning predicts motor impairment after SCI. Abstract presented at the American Roentgen Ray Society Annual Meeting; April 22-27, 2018; Washington D.C. Abstract 3090*.*

McCoy DB, Huie JR, Dupont SM, Whetstone WD, Dhall SS, Tsolinas RE, Duong-Fernandez X, Thomas LH, Singh V, Pascual LU, Narvid J, Kyritsis N, Manley GT, Ferguson AR, Beattie MS, Bresnahan JC, Talbott JF. Atlas-based volumetric assessment of T2 abnormality in acute spinal cord injury predicts motor outcomes: A transforming research and clinical knowledge in spinal cord injury (TRACK-SCI) pilot study. Abstract published electronically for the Joint Annual Meeting of the International Society for Magnetic Resonance in Medicine and the European Society for Magnetic Resonance in Medicine and Biology; June 16-21, 2018; Paris, France. Abstract 3791.

Singh V., Huie JR, Torres D, Ferguson AF, Beattie MS, Bresnahan JC, Pan JZ, Pascual LU, Talbott JF, Tsolinas RE, Fernandez XD, Whetstone WD, Dhall SS, Weinstein PR. Hypotensive episodes early after SCI associated with lower MAP in ICU: A prospective TRACK-SCI study. *Crit Care Med*. 2018;46(1):53.doi: 10.1097/01.ccm.0000528161.36203.63. (Abstract)

**7. Participants and other collaborating organizations.** While no formal agreements were included in this award, TRACK-SCI has been developed with resources from multiple funding sources.

Statement of optional contributing collaborator, Dr. Jason Talbott:

**Imaging** (Summary provided by the optional qualified collaborator, Dr. Jason. Talbott) In addition, work has commenced to access and refine a number of data types including the physiological monitoring in the OR and

ICU, including motor and sensory evoked potentials, the EMS and ER records, and work on the imaging protocols. Dr. Jason Talbott, MD, PhD (OQC, Department of Radiology) has implemented the Spinal Cord Toolbox (SCT), an open-source library of analysis tools for multi-parametric MRI of the spinal cord at UCSF. Initial study was performed to develop and validate a semi-automated image processing and analysis pipeline for axial T2-w MRI images obtained at the time of acute spinal cord injury (SCI). More than 500 texture-features were extracted for 29 acute SCI patients from our retrospective cohort, using atlas-based regions-of-interests. Five machine learning algorithms were explored to determine accuracy for predicting neurologic injury severity. Machine learning algorithms were able to accurately classify patients based on T2w texture features. This is the first study to investigate spinal cord texture features with patient clinical outcomes in spinal trauma. These data show promise for computer-aided prognosis of SCI pathology and was submitted to the ISMRM 2018 conference. Other data analytic development includes topological data analysis for the proposed multidimensional analysis. We were able to finish a retrospective cohort study to evaluate the proof-of-concept of our novel non-linear multivariate analytical workflow. The core part of this analytical workflow consists of applying non-linear principal component analysis (NL-PCA), a novel approach in the field of SCI. NL-PCA is a specialized type of statistical machine learning tool that can handle data on multiple scales: categorical, ordinal, or interval in a single multidimensional model. NL-PCA achieves this by combining logistic-link approaches similar to RASCH analysis with the power of classic multidimensional pattern detectors like principal component analysis (see Haefeli et al, 2016). Other novel analytics now being developed under the direction of Dr. Jason Talbott, uses a resampled elastic-net regression algorithm which identified top volumetric and texture features of MRIs of the SCI lesions in our prospective dataset. Tissue damage to 1) the white matter was found to be particularly associated with degree of neurological impairment ($p = 0.03$), and 2) ventral gray matter ($p = 0.02$). Inverse variance of SCI lesions was also found to be associated with neurological impairment. Several clinical factors related to associated injury, respiratory, and cardiovascular health were found to be associated with newly derived biomarkers and AIS grade during hospitalization; these included Glasgow coma scale, injury severity score, respiratory failure, mean arterial pressure, systolic blood pressure and vasopressors used in ICU. Due to the fact that clinical and MRI features are correlated and supervene from the same mechanism, severity of spinal cord trauma, modeling was conducted based on vectors of covariance rather than independent variables to predict outcomes. Multivariate regression using components from nonlinear principal component analysis showed high predictive validity for these novel quantitative biomarkers when covariance with other clinical factors is removed. Furthermore, when combined with standard qualitative metrics used to assess lesions, the addition of these new quantitative outcomes improves modeling of neurological impairments.

| **Name:** | **Michael S. Beattie, PhD** |
|---|---|
| Project Role: | Principle Investigator |
| Researcher Identifier (e.g. ORCID ID): | orcid.org/0000-0001-9463-363 |
| Nearest person month worked: | 2 |
| Contribution to Project: | He oversees the project and its organization and is responsible for all reporting and communications with the sponsor. |
| Funding Support: | N/A |
| **Name:** | **Sanjay Dhall, MD** |
| Project Role: | Co- Investigator |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 1 |
| Contribution to Project: | He is Director of Spinal Neurotrauma at UCSF/ZSFG, and leads the clinical team in caring for SCI patients and TRACK-SCI subjects. |
| Funding Support: | N/A |
| **Name:** | **Adam R. Ferguson, PhD** |
| Project Role: | Co- Investigator |

| | |
|---|---|
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 1 |
| Contribution to Project: | He is head of the Neuroinformatics Core at BASIC and an expert in statistics and multivariate analysis. He has been instrumental in establishing our current REDCap TRACK-SCI database, and is also an investigator on the TRACK-TBI project. |
| Funding Support: | N/A |
| **Name:** | **Jason Talbott, MD, PhD** |
| Project Role: | He serves as the Optional Qualified Collaborator (OQC)*. He is responsible for evaluating all MR mages for the project, for ensuring that quality controlled data are entered into the REDCap database (with access coded to the secure imaging repository at UCSF), and for processing images through the second tier SCI imaging pipeline. |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 2 |
| Funding Support: | N/A |
| **Name:** | **William Whetstone, MD** |
| Project Role: | He is Professor of Emergency Medicine at UCSF with a main appointment at ZSFG. He has a long history of both preclinical and clinical spinal cord injury research, and is a critical member of the SCI clinical research team. |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 1 |
| Funding Support: | N/A |
| **Name:** | **Carlos Almeida** |
| Project Role: | Mr. Almieda is a data analyst working on the project. |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 2 |
| Funding Support: | N/A |
| **Name:** | **Xuan Duong Fernandez** |
| Project Role: | She is the Clinical Research Coordinator for SCI at BASIC/ZSFG, reporting to Drs. Beattie and Dhall. She replaced Rachel Tsolinas. |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 10 |
| Funding Support: | N/A |
| **Name:** | **Leigh Thomas** |

| | |
|---|---|
| Project Role: | She is the Clinical Research Coordinator for SCI at BASIC/ZSFG, reporting to Drs. Beattie and Dhall. (Supported by a CH Neilsen Foundation Center of Excellence Award, but working full time on TRACK-SCI). |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 10 |
| Funding Support: | N/A |
| Funding Support: | N/A |
| **Name:** | **Nikos Kyritsis, PhD** |
| Project Role: | Post-doctoral Fellow |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 10 |
| Contribution to Project: | He provides laboratory support for the collection of blood and the preparation of DNA and RNA, RNA libraries for RNAseq, and coordinates project needs with the CAT and SABRE cores at UCSF. He also performs data analysis for the RNA seq part of this project, and presents these data at national meetings. |
| Funding Support: | N/A |
| **Name:** | Russell Huie, PhD |
| Project Role: | Dr. Huie has provided data analysis and preparation of data for presentations. |
| Nearest person month worked: | 2 |
| Funding Support: | N/A |
| **Name:** | **Yu-Hung Kuo, MD, PhD** |
| Project Role: | Dr. Kuo is the UC Fresno site PI and oversees work on the project there. |
| Nearest person month worked: | 1 |
| Funding Support: | N/A |
| **Name:** | Rebeka Garcia |
| Project Role: | UCSF Fresno clinical research coordinator |
| Nearest person month worked: | 6 |
| Funding Support: | N/A |
| | |

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?** No.

**Other organizations.**

**N/A**

**8. Special Reporting Requirements**

**N/A**

**9. Appendices. PDFs of the full-length publications listed in section 9** are presented in alphabetical order of first author.


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