Advancing Toward Precision Medicine in Trauma

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Physicians and scientists have long aspired to identify ways to stratify patients into groups that would predict their outcomes and clinical trajectories. In the late 1990s, the technology of human sequencing and genomic analysis entered the scientific world and opened a plethora of exciting and novel insights to explore how the human body and genome respond to the environment or stress from trauma or exogenous factors. The technology emerged and substantially changed over the subsequent 10 to 20 years. By the beginning of the 2000s, gene chip analysis became a tool that analyzed thousands of genes in a reliable and reproducible manner. The first real focused effort to determine the effects of trauma or burns on the genome, supported by the National Institutes of Health, was the ''Inflammation and the Host Response to Injury,'' otherwise known as the Glue Grant. This large-scale collaborative research program was championed by the Investigators of the Inflammation and the Host Response, listed at www.gluegrant.org/, many leaders in their fields. The Glue Grant started in 2000 and was undertaken over 10 years.[1–5] The hypothesis of the Glue Grant was to determine the effects of major trauma or burns on the human genome and whether genomic variation can predict outcomes of trauma or burn patients. The idea was by understanding the genomic effect of these stresses that new predictive tools or drugs or intervention could be defined to improve the outcome and therefore change the trajectory of a patient from their predicted death to survive.

Over 10 years, the Glue Grant enrolled more than 2800 trauma and burn patients.[5] The Glue Grant investigators found various effects of trauma on the genome; for example, the investigators showed that in the circulating white blood cells of 167 patients that were studied compared with 35 normal volunteers that more than 80% of the white blood cell gene changed significantly during the first 28 days postinjury and the term ''genomic storm'' was associated with this reorganization of the human genome after severe injury.[3] The investigators then associated many signaling pathways that were up and downregulated after severe blunt trauma. They found that various pathways were up-regulated, including integrin, leukocyte extravasation, IL-10, and IL-6, and some were down-regulated, including T-cell apoptosis, CD8 T-cell signaling, and CD8 mediated apoptosis.[4] The next step was to associate true genomic changes with outcomes or patients that rapidly recover compared with those who have prolonged hospital stays. This is what the current paper Raymond et al[6] set out to do. The idea is that early prediction of patients genetically predisposed for complicated recovery would be identified and biological interventions applied to change the trajectory to an uncomplicated recovery.

In this issue of *Annals of Surgery*, Raymond et al[6] report the findings of a prospective observational study that aimed to validate a transcriptomic metric of blood leukocyte gene expression at 24 hours in trauma patients. This genomic score is based on a set of 63 blood leukocyte genes (S163) performed using NanoString technology. The authors tested the genomic score that was derived in a previous study from the same group.[4]. Among their cohort of 127 trauma patients, the S63 transcriptomic metric differentiated between patients who rapidly recovered (discharged < 5 d) and patients that had complicated clinical trajectories. The authors then utilized this transcriptomic metric by applying it to a publicly available dataset to discriminate among 26 critically ill trauma patients and 6 controls. The authors showed that a single transcriptomic metric of blood leukocyte gene expression can be used in blunt trauma cohorts at 24 hours to distinguish patients who rapidly recover from those with complicated clinical trajectories.[6]

The advantage of the technology utilized in this study is that the results are available in less than 24 hours and, unlike some other risk stratification algorithms, it does not require provider input. Additionally, advances in technology allow for decreasing costs and increasing feasibility. As the authors pointed out, the transcriptomic metric was discovered and validated in a population of primarily male Caucasians.[6] It would be valuable to see further validation in a cohort of patients with diverse gender/sex/race/ethnicity and, notably, age.

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Additional uses of this scoring metric are many. One potential use for the transcriptomic metric in this study is the allocation of resources based on time to recovery (TTR). The TTR outcome utilized in this study was developed by the Glue Grant investigators.[5,7] TTR not only reflects that an organ failed but it has a dynamic component to include the time that transpired before the organ recovered. TTR has a frequency component and a temporal dynamic influence. In this study, the patients were categorized using TTR based on the absence or resolution of organ injury: uncomplicated was a TTR < 5 days; intermediate was a TTR 5 to 14 days; and "complicated" was a TTR > 14 days, a TTR > 5 days with discharge to another facility with organ dysfunction, or in-hospital death.[6] In theory, the transcriptomic metric could be applied to resource allocation; including everything from staffing to supplies. Another possible use could be to ensure a diverse population in clinical trials.

As with any great study, the work of Raymond et al[6] opens new avenues for research and generates questions that need answers: how can we enable the conversion of the knowledge of rapid recovery to improved care and outcomes to patients and what are these therapeutic interventions that would change clinical management? In other words, how can a trajectory be altered with interventions? We do not think that this is a unique question specific to this study but rather a question for all studies looking at precision medicine and/or personalized medicine.

The validation of the transcriptomic metric in severe trauma is an important and fascinating step forward for precision medicine in trauma. It is now incumbent on us to focus on targeting the mechanisms or perturbations to change detrimental trajectories to beneficial trajectories, ultimately improving outcomes and "cheating death."

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