Precision medicine in trauma: a transformational frontier in patient care, education, and research

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Abstract
Purpose Trauma is the leading cause of death before the age of 45 in the United States. Precision medicine (PM) is the most advanced scientific form of medical practice and seeks to gather data from the genome, environmental interactions, and lifestyles. Relating to trauma, PM promises to significantly advance our understanding of the factors that contribute to the physiologic response to injury.

Methods We review the status of PM-driven trauma care. Semantic-based methods were used to gather data on genetic/epigenetic variability previously linked to the principal causes of trauma-related outcomes. Data were curated to include human investigations involving genomics/epigenomics with clinical relevance identifiable early after injury.

Results Most studies relevant to genomic/epigenomic differences in trauma are specific to traumatic brain injury and injury-related sepsis. Genomic/epigenomic differences rarely encompass other relevant factors, such as coagulability and pharmacogenomics. Few studies describe clinical use of genomics/epigenomics for therapeutic intervention in trauma care, and even fewer attempt to incorporate real-time genomic/epigenomic information to precisely guide clinical decision-making.

Conclusion Considering that genomics/epigenomics, environmental exposures, and lifestyles are most likely to be of significant medical relevance in advancing the field of trauma, the lack of application of concepts and methodologies from PM to trauma education, research, practice, and community wellness is underwhelming. We suggest that significant effort be given to incorporate the tools of what is becoming the “new medicine”.

Keywords Trauma surgery · Precision medicine · Personalized medicine · Genomics · Epigenomics

Introduction
Trauma is the leading cause of death before the age of 45 and the third leading cause of death overall in the United States [1]. As trauma disproportionally affects younger people, it surpasses cancer and heart disease in terms of preventable deaths and years of life lost before the age of 70 [2]. Surveys by the National Academies of Sciences, Engineering, and Medicine reveal that approximately 30,000 deaths could be prevented each year as a consequence of inadequate trauma care [3]. High-precision methodologies would ideally provide immediate information after the trauma occurs about how an individual’s unique physiology would respond to the trauma, allowing us to improve their outcomes and reduce mortality [4–6]. This paradigm is the backbone and mission of Precision Medicine (PM). PM accounts for variation in an individual’s genes, environment, and lifestyle, allowing providers to predict which management strategies would or
would not work for specific populations with more accuracy and efficiency [7].

Implementation of PM depends on having diagnostic modalities that can accurately identify individuals that benefit from specific therapies over others in a timely fashion and allow us to more effectively tailor treatments to the individual rather than the disease [4, 5]. Such tests are sparsely used in trauma care and what does exist has not been applied in clinical practice [5]. PM studies have not resulted in alteration of clinical care because they have not been designed to yield real-time, applicable information [4–6].

The primary objective of this review is to assess the current state of various genomic, epigenomic, proteomic, and metabolomic factors in relation to traumatic injuries and associated sequela to evaluate for the existence of potentially useful PM assays in the clinical care of trauma patients. This knowledge could aid in the development of a clinical research program dedicated to PM in trauma, which would be the first of its kind.

Methods

To assure quality representation of data published, we utilized a two-tier approach. We used semantic-based algorithms to search standard databases (PubMed and Medline) to obtain articles related to PM in trauma, with a particular emphasis on epigenomics and genomics. The ontological terminology structure for our searches was “precision medicine in trauma”, “personalized medicine in trauma”, “precision trauma”, “personalized trauma”, “patient-centered trauma,” and “individualized trauma”. Curation of the articles was then carefully done by the investigators to evaluate and identify useful references found by the search methodology.

Results

Traumatic brain injury

Traumatic brain injury (TBI) has a complex pathophysiology with primary injury caused by blunt force as well as subsequent secondary injury from cerebral edema, hypoxia, and disruption of the blood–brain barrier [8]. Previous investigators have shown that patients with moderate-to-severe TBI have a meaningful chance of recovery with 25–57% reaching independence [9–11]. The clinical manifestations of TBI vary between individuals and can fluctuate over time [12]. Information yielded through PM by identification of particular genomic and epigenomic predispositions could improve overall outcomes [12].

There are at least 33 TBI genes that have been associated with various outcomes that commonly fall into two major categories: response to injury and neurocognitive reserve [13]. A major pathway affecting response to injury is variation involving the blood–brain barrier. One gene linked to this is the apolipoprotein E (ApoE) allele, which affects transport and metabolism of lipids in the central nervous system, coagulation, and neuronal membrane maintenance and repair [14]. A meta-analysis cohort study consisting of 2,527 TBI patients found that presence of an ApoE allele was associated with worse outcomes at 6 months post TBI (RR = 1.36, 95% CI 1.04–1.78) [14].

Interleukins (ILs) are a group of cytokines that play a key role in the inflammatory pathway that occurs after TBI. In a study of 69 patients with severe TBI, a strong association was seen between an IL-1β variant and poor outcomes, such as death, vegetative state, or severe disability (OR = 0.25, 95% CI 0.12–0.55; p = 0.004) [15]. One study of 77 patients with severe TBI found an IL-6 promoter to be associated with improved survival (81% v. 65%, p = 0.031) [16].

Another genetic factor linked to TBI outcomes is angiotensin-converting enzyme (ACE), which regulates both the production of angiotensin II and the degradation of bradykinin at the endothelial surface [17]. Certain angiotensin receptor subtypes can influence cerebral blood flow [18–20]. In a study of 73 patients with TBI, a variant in the ACE gene was associated with worse cognitive performance (p = 0.001), highlighting the increased susceptibility to TBI complications [17].

Among studies of genes relating TBI to outcomes, none have been investigated for use in real-time clinical decision-making [13–23]. Given the importance of minimizing secondary injury in TBI, potential treatment strategies supplemented by PM information are conceivable. These initial studies highlight that PM methodologies would be useful for evaluating risk factors and best practice guidelines for management of patients with TBI (Table 1).

Trauma-induced coagulopathy

Among those with major hemorrhage from trauma, up to one-third may exhibit trauma-induced coagulopathy, a syndrome occurring in the early stage of trauma that is caused by activation of coagulation, fibrinolytic, and anti-coagulation pathways [24, 25]. Now that more informative PM assays for evaluating coagulopathy exist, conventional tests, such as the international normalized ratio, prothrombin time and partial thromboplastin time, are proving less reliable [26–28]. Studies are now emerging that involve the identification of molecular markers associated with bleeding in coagulopathic patients (Table 1).
Thromboelastography (TEG) is a test that measures the ability of whole blood to form a clot by quantifying dynamic changes of its viscoelastic properties [29]. One study evaluated the vascular endothelial glycocalyx, which contains many substances with heparin-like properties, in relation to its degradation and TEG [30]. Elevated levels of circulating syndecan-1 protein, a marker of glycocalyx degradation, were found to be associated with hypo-coagulability, higher transfusion requirements, and worse clinical outcomes as predicted by TEG ($p=0.02$) [30]. Increased activated protein C levels, which can also lead to coagulopathy, were associated with increased transfusion requirements, multi-organ failure ($p=0.05$), and mortality ($p=0.0007$) [31].

An area of need for investigation is the role of inherited bleeding and platelet disorders (BPDs), which include diseases, such as hemophilia and von Willebrand Disease. Variations in genes associated with these diseases can have significant pathophysiological impact when faced with major injury, leading to increased morbidity and mortality [32]. Due to the lengthy time it takes to formerly diagnose BPD, the standard work-up is clinically irrelevant in patients with acute traumatic injuries [33]. There have been recent efforts to address the difficulty of diagnosing BPDs with the ThromboGenomics project [33]. A high-throughput sequencing platform classified patients into four categories: known, suspected, uncertain, or unaffected by BPD. The high-throughput sequencing platform demonstrated a 100% sensitivity for detecting genetic variants previously linked to BPDs. This study highlights using tools like the ThromboGenomics platform as a means of diagnosing coagulopathies in the acute trauma setting.

An additional area of interest is the role of genetics in determining venous thromboembolism (VTE) prophylaxis efficacy in the setting of trauma. In a study examining risk factors for VTE prophylaxis failure in acute traumatic spinal cord injury (ATSCI) patients, 22 ATSCI patients who developed new VTE were matched with 64 control ATSCI patients without VTE and tested for common thrombophilia

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### Table 1 Relevant genomic, epigenomic, proteomic, and metabolomic factors for Precision Medicine

| Authors               | Year published | Type of study | Name of factor           | Impact and association                                           |
|-----------------------|----------------|---------------|--------------------------|-----------------------------------------------------------------|
| Uzan et al. [15]      | 2005           | Prospective   | IL-1β                    | Death, vegetative state, or severe disability                   |
| Ariza et al. [17]     | 2006           | Prospective   | ACE                      | Worse cognitive performance                                     |
| Zhou et al. [14]      | 2008           | Meta-analysis | ApoE4                    | Poor long-term outcomes at 6 months                             |
| Libera et al. [16]    | 2011           | Prospective   | IL-6                     | Higher frequency in survivor group than non-survivor group       |
| Rubín-Asher et al. [34]| 2010           | Retrospective | FVL, PT, MTHFR, LAC, FVIII, Hcy | Increased risk of venous thrombembolism                        |
| Ostrowski et al. [30] | 2012           | Prospective   | Syndecan-1               | Hypocoagulability, increased transfusion requirements, and worse clinical outcomes |
| Cohen et al. [31]     | 2012           | Prospective   | aPC                      | Increased transfusion requirements, multi-organ failure, and mortality |
| Simeoni et al. [33]   | 2016           | Prospective   | BPD genes                | HTS platform with high sensitivity and specificity to detect BPD genetic variants; comprehensive method of diagnosing BPDs |
| Wypasek et al. [37]   | 2017           | Case report and literature review | PROS1 | Mutation can cause thrombosis |

IL interleukin, ACE angiotensin-converting enzyme, Apo apolipoprotein, FVL Factor V Leiden, PT prothrombin G20210A, MTHFR methylene-tetrahydrofolate reductase C677T homozygosity, LAC lupus anticoagulants, FVIII Factor VIII level, Hcy homocysteine level, aPC activated protein C, BPD bleeding and platelet disorder, HTS high-throughput sequencing, C2 complement component 2, TLR toll-like receptor, SRS sepsis response signatures, HLA human leukocyte antigen
markers [34]. In those that developed a VTE, 73% had already been on pharmacologic prophylaxis [34]. The study found that patients with VTEs had increased incidence of certain markers, demonstrating the potential of using genetic factors to predict the risk of ineffective thromboprophylaxis [34].

A number of studies have also investigated the role of protein S (PS) expression in trauma-induced VTE occurrence. PS is a vitamin K-dependent natural anticoagulant encoded by the PROS1 gene, and previous data has shown that inherited causes of PS deficiency are found in 1.5–7% of thrombophilic patients [35–37]. The presence of a heterozygous nonsense mutation is associated with PS deficiency in the setting of trauma, which creates a transient thrombotic risk. These genetic studies also provide information to identify trauma patients who may need adjustments in their VTE prophylaxis regimen.

**Sepsis and infectious complications**

A number of molecular markers and genetic variants have been studied in the setting of post-traumatic sepsis (Table 1). Cytokines, chemokines, and growth factors mediate pro- and anti-inflammatory effects, thereby playing an important role in the response to infection. Cytokine genotypes of IL-6, IL-10, IL-18, TNF-α, and IFN-γ were assayed in 68 trauma intensive care units to investigate their relationship with sepsis [38]. Findings indicate that patients with a low-producing genotype for IL-10 expressions had a two- to threefold lower risk of developing sepsis [38].

Toll-like receptor (TLR) proteins are also important when considering sepsis. TLR proteins are expressed on immune cells which recognize distinct bacterial substrates and activate a cascade of immune cell responses [39]. Studies have revealed that polymorphisms in various TLR genes appear to influence patient outcomes following trauma. It was shown that one TLR1 variant was predictive of mortality (adjusted OR = 3.16, 95% CI 1.43–6.97; p = 0.004) in a cohort of 1,498 trauma intensive care unit patients [39].

Studies have begun to identify other genetic variants that may contribute to the weakened immunologic state seen in septic patients with poor outcomes. An important study involves variant expression of transcriptional Sepsis Response Signatures (SRS) [40]. The SRS1 genetic profile characterizes an immunosuppressed phenotype, which includes endotoxin tolerance, T-cell exhaustion, and down-regulation of human leukocyte antigen (HLA) class II [40, 41]. It was reported that 41% of septic patients with the SRS1 phenotype had a 14-day mortality that was at least twice as high as other patients (22% vs 10%, hazard ratio 2.4, 95% CI 1.3–4.5, p = 0.005) [41].

Low levels of HLA-DR are associated with an immunocompromised state, placing trauma and burn patients at higher risk of morbidity and mortality from sepsis [42–45]. One study composed of 83 patients showed that HLA-DR expression differentiated between survivors and non-survivors of sepsis 3–4 days after the diagnosis [45]. Since the median onset for developing a secondary infection was determined to be 9.4 days, identifying low expression of HLA-DR earlier in the disease course could potentially aid in predicting which individuals have higher risk for secondary infection [45]. HLA variation has been one of the earliest recognized genomic variants that predispose to diseases and must be taken into consideration when treating trauma patients.

Activation of complement pathways is an important part of the acute inflammatory response. The complement system is comprised of more than 30 proteins that is important for immune defense, protecting against infection, and killing diseased cells [46, 47]. Complement component 2 (C2) is believed to be a critical factor in activating the Classical and Lectin immune pathways [46]. The effect of C2 polymorphism in 702 consecutive trauma intensive care unit admissions was studied and it was determined that its presence was associated with an increased mortality rate (OR 2.65, 95% CI 1.18–5.96; p = 0.02) and probability of developing ventilator-associated pneumonia (OR 2.0, 95% CI 1.03–3.88; p = 0.04) [46].

The autonomic nervous system (ANS) has become increasingly recognized for its role and function in sepsis, the systemic inflammatory response syndrome, and multiple organ dysfunction syndrome [48, 49]. Research has sought to determine whether patient outcomes are related to genetic differences in a patient’s ANS [48, 49]. One study evaluated how the ANS contributed to mortality risk in 1,095 trauma patients by evaluating genetic polymorphisms coding for the β2 adrenergic receptor [48, 49]. One associated polymorphism showed a protective effect against mortality (OR 0.36, p = 0.002) [48]. The mortality rates ranged from 7.6% to 15.9% depending on the specific genotypes (p = 0.02) [48].

**Conclusion**

Certain genomic, epigenomic, proteomic, and metabolomic factors can influence the response to injury. Whether any of the aforementioned examples can be translated to actionable changes in management and outcomes remains to be seen but the potential opportunity is promising. PM has the potential to not only provide an early warning indicator for complications during recovery, it also has the potential to guide management decisions of trauma patients. Existing and developing diagnostic methodologies provide us the opportunity to anticipate the physiologic response to the insult of trauma. Our review showcases the most current state of
knowledge relating to different sequela that can result from traumatic injury and genetic variations between individuals.

Application of PM in the acute trauma setting has the potential to affect outcomes and change initial management strategies. Many opportunities for individualized therapy have been identified, but there are still very few means of analyzing genomic and epigenomic differences to guide clinicians in real time. Future research is required to identify which variants are most relevant for trauma-related care and for the development of assays to rapidly detect them. Better precision in the care of our trauma patients demands it.

Author contributions All authors contributed to the manuscript design, literature search, writing, and critical revision. The table was created by CG. All authors read and approved the final manuscript.

Declarations

Conflict of interest There are no conflicts of interest to report. There was no funding obtained. Since this was a review paper, no IRB approval or consent from subjects was needed. This review meets appropriate ethical standards.

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