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Endotypes and the Path to Precision in Moderate and Severe Traumatic Brain Injury

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Abstract

Heterogeneity is recognized as a major barrier in efforts to improve the care and outcomes of patients with traumatic brain injury (TBI). Even within the narrower stratum of moderate and severe TBI, current management approaches do not capture the complexity of this condition characterized by manifold clinical, anatomical, and pathophysiologic features. One approach to heterogeneity may be to resolve undifferentiated TBI populations into endotypes, subclasses that are distinguished by shared biological characteristics. The endotype paradigm has been explored in a range of medical domains, including psychiatry, oncology, immunology, and pulmonology. In intensive care, endotypes are being investigated for syndromes such as sepsis and acute respiratory distress syndrome. This review provides an overview of the endotype paradigm as well as some of its methods and use cases. A conceptual framework is proposed for endotype research in moderate and severe TBI, together with a scientific road map for endotype discovery and validation in this population.

Keywords: Traumatic brain injury, Phenotype, Endotype, Machine learning, Enrichment, Precision medicine, Heterogeneity of treatment effect

Introduction and Context

Traumatic brain injury (TBI) is the most common trauma-related cause of death and disability worldwide. An estimated 69 million individuals experience TBI each year, and up to half of the global population will experience TBI in their lifetime [1, 2]. Across the world TBI represents a major economic burden, with global TBI-related expenditures exceeding 400 billion dollars annually [1]. Within the United States, there are approximately 2.8 million emergency department visits, 250,000 hospitalizations, and 50,000 deaths related to TBI each year [3].

Patients with moderate and severe TBI (msTBI) represent less than one fifth of all TBI cases, yet these individuals carry the highest risk of mortality and long-term neurologic disability. Research on msTBI has focused on novel diagnostic strategies and therapeutic interventions to enhance patient recovery [4–9]. For example, therapeutic hypothermia and decompressive craniectomy have each been considered as potential approaches to improve survival and recovery probabilities in this group. However, randomized clinical trials (RCTs) evaluating these treatment modalities (and a number of others) have not conclusively demonstrated that they improve outcomes [7, 9–11].

Heterogeneity

One theory regarding the challenges in developing effective therapies for TBI is the biological heterogeneity of the disorder [1]. We use TBI as an overarching term to describe a disruption of brain function or other brain pathology caused by a physical force, yet it represents a broad range of severities, traumatic insults (e.g., skull fracture, contusion, parenchymal laceration, intracranial hemorrhage, diffuse axonal injury), and secondary pathophysiological mechanisms (e.g., ischemia, excitotoxicity,

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inflammation, mitochondrial dysfunction, apoptosis, cortical spreading depression, vasospasm) whose individual and collective effects are not fully understood [12, 13]. Fundamentally, TBI may be considered more as a class of disorders rather than a specific pathology [14]. Biological heterogeneity is the mechanistic basis for heterogeneity of treatment effects, according to which the type and magnitude of responses to a treatment within a defined population represent a distribution, with individuals (or subgroups) exhibiting differentiable levels of efficacy or harm or no effect [15].

Heterogeneity in many cases may be a latent attribute, concealed (or unrecognized) within phenotype-based methods of detection, diagnosis, stratification, treatment selection, and prognostication. Patients with msTBI may be stratified and treated by clinical and/or radiological severity indices or scores, such as the Glasgow Coma Scale (GCS) [16], International Mission for Prognosis and Analysis of Clinical Trials in TBI [17], or Corticosteroid Randomisation after Significant Head Injury scores [18]. For example, the Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury (POLAR) trial evaluating therapeutic hypothermia included only patients with severe TBI, defined as those with a GCS score of < 9 and imminent intubation, and the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST:TRIP) trial evaluating intracranial pressure monitoring included patients with severe TBI defined as those with a GCS score of < 9 within the first 48 h of presentation [9, 11]. Overall, although severity-based stratification provides a convenient way to assess and classify patients, individuals with similar TBI severity may vary widely in underlying pathophysiology and recovery probabilities [19–21].

Nomenclature

An alternative method of stratifying patients with msTBI, one that has demonstrated promise in other heterogenous clinical disorders, is to segregate them into subclasses (Table 1). If a phenotype is the ensemble of observable characteristics exhibited by a patient with a given diagnosis or condition, a subphenotype refers to a subclass of patients who share a set of characteristics or features (e.g., biomarker level, imaging feature, treatment response) that distinguish the subclass from other patients with the same diagnosis [22]. If a common biologic mechanism is identified among patients within a given subphenotype, the term "endotype" can be used to designate this subgroup; an endotype is thus a subphenotype that has a distinct mechanistic basis [23, 54]. A subset of endotype is the endophenotype, which refers to patients who share a measurable indicator or pattern of disease that lies along the causal pathway between gene expression and the phenotype. Endophenotypes were initially proposed in psychiatry as a strategy to anchor disease features as the expression of a biological sequence that mandatorily was driven by gene expression [24]. The difference between endotype and endophenotype is that the latter must have a clear genetic linkage.

The endotype paradigm is widely regarded as a conceptual building block in precision medicine, as it could enable the integration of subclass-specific disease mechanisms and characteristics in selecting patients and targeting therapies tailored to a particular individual (Fig. 1) [25]. Although patients with a similar phenotype may have vastly different underlying disease mechanisms and thus differential responses to the same therapy, treatment effects within the same endotype would theoretically be more consistent and predictable because of a common pathophysiology. As the biological mechanisms of TBI are elucidated, the discovery of TBI endotypes may enable enrichment strategies to be in biomarker development, randomized controlled trials, and targeted therapeutic approaches [26].

Endotypes in Medicine: The Asthma Paradigm

Early work on endophenotypes centered on psychiatric disorders, yet the broader endotype paradigm has been explored and developed in many domains, including oncology, cardiology, neurology, and pulmonology. In the study of asthma, for example, it was discovered that the asthmatic syndrome, unified by a cluster of

Table 1 Nomenclature

Nomenclature	Definition
Phenotype	1. Observable characteristic(s) of an individual 2. A subset of individuals who share a phenotype
Subphenotype	A subset of individuals who share a constellation of linked features
Endotype	A subclass of individuals who share features anchored in a specific biological mechanism or pathophysiological process
Endophenotype	A subclass of individuals who share features that are on the causal pathway between the phenotype and gene expression

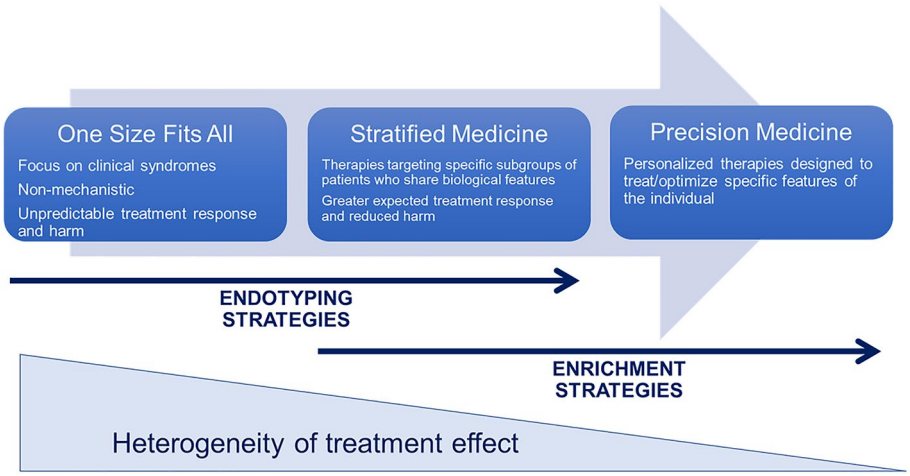

Fig. 1 The path to precision medicine begins with existing paradigms in which uniform therapeutic approaches are applied to heterogeneous populations, with the goal of achieving personalization in which treatments are directed to the specific needs of the individual. An intermediate step is stratified medicine, in which mechanistically based disease subclasses are identified via endotyping. Key steps in precision medicine are enrichment strategies that identify patients most likely to achieve a specific outcome (prognostic enrichment) or respond to a specific intervention (predictive enrichment)

common symptoms, is actually caused by a number of distinct pathologic mechanisms [27]. Endotypes of asthma include type 2 T helper cell (T2)-high asthma, which is characterized by predominantly eosinophilic inflammation, and non-T2 asthma, which is associated with predominantly neutrophilic and granulocytic inflammation [28]. This stratification has enabled the development of targeted therapies. For example, T2-high asthma may be selectively responsive to therapies that target interleukin 5 (IL-5) signaling, a key component of the eosinophilic inflammatory pathway. Currently, three humanized monoclonal antibodies targeting IL-5 or IL-5-receptor signaling (mepolizumab, benralizumab, and reslizumab)- are approved for use in Europe and the United States in patients with eosinophil-predominant T2 asthma [29]. Trials using these drugs have demonstrated therapeutic efficacy when used in patients who have the T2 endotype (despite significant variability in asthma phenotype), including reductions in the number of severe episodes per year, scores on standardized questionnaires, and daily dose of maintenance glucocorticoids [30]. Targeted therapies have also been developed for other signaling pathways implicated in the pathogenesis of T2 asthma, such as immunoglobulin E, prostaglandin D2 type 2 receptor, and interleukin 4. These successes in the domain of asthma research are an instance of disease endotyping that is emerging as a generalizable paradigm across medical research [31–34]. For example, first-line chemotherapy and immunotherapy in patients with cancer are increasingly determined by genetic characterization, and endotyping in tuberculosis offers promise in shortening treatment duration and curing resistant disease [35, 36].

Endotypes in Intensive Care Medicine

Conditions commonly encountered in intensive care have also been the object of endotype classification. Although the application to critically ill patients presents a unique set of challenges, findings in acute respiratory distress syndrome (ARDS) and sepsis suggest how endotypes could be used to advance precision medicine for these heterogenous and difficult-to-treat diseases.

ARDS is a heterogenous syndrome that has been investigated in a number therapeutic clinical trials, many of which have been inconclusive [37]. Recent research has led to the identification of two ARDS endotypes, hyperinflammatory and hypoinflammatory, characterized by differential expression of inflammatory biomarkers. These endotypes have been identified in five RCTs of ARDS, and patients from the two subclasses have demonstrated differential responses to positive end-expiratory pressure and fluid therapy [38, 39]. Furthermore, retrospective application of these subphenotypes to prior negative RCTs has allowed researchers to identify subgroups of patients who may actually respond positively to pharmacological therapy. For example, although treatment with the hydroxymethylglutaryl-Coenzyme A reductase inhibitor simvastatin did not significantly improve clinical outcomes in an undifferentiated sample of patients enrolled in the Hydroxymethylglutaryl-Coenzyme A Reductase

Inhibitor With Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction trial, a stratified analysis did demonstrate improved survival for treated patients with the hyperinflammatory endotype when compared with placebo [40, 41]. Thus, rethinking clinical trial design to incorporate the endotype framework may allow for more effective treatment discovery and validation [42, 43].

Sepsis is a dysregulated host response to infection involving a number of pathophysiologic changes, including immune overactivation, immunosuppression, altered metabolism, and coagulopathy [44]. Although the phenotype is described by a widely accepted uniform nomenclature [45], clinical trajectories of sepsis and responses to treatment vary considerably, suggesting a high level of underlying biological heterogeneity and heterogeneity of treatment effects and an opportunity for subphenotyping and endotyping [46]. For example, the Genomic Advances in Sepsis study used transcriptomics to identify two distinct types of sepsis response signatures, SRS1 and SRS2, in 265 patients with sepsis [47]. SRS1 individuals had a relatively immunosuppressive profile, including human leucocyte antigen II downregulation and T-cell exhaustion. Beyond association with clinical outcomes (e.g., 14-day mortality of 22% for SRS1 vs. 10% for SRS2, $p=0.005$), these endotypes also demonstrated a differential response to steroid therapy [48, 49]. A more recent study used advanced informatics to analyze data from 700 patients in 14 bacterial sepsis transcriptomic data sets and revealed three endotypes: inflammopathic, adaptive, and coagulopathic [50]. This initial endotyping provides the foundation for the future application of targeted therapy within this patient population. For example, it was suggested that immunotherapies targeting the adaptive immune system may be more likely to provide significant therapeutic benefit in the adaptive cluster and that cytokine antagonists targeting innate immunity may achieve greater success in the inflammopathic cluster.

Approaches to Endotype Discovery

Two possible approaches for endotype research are model-driven (or hypothesis-driven) discovery and model-free (or data-driven) discovery (Fig. 2). In hypothesis-driven discovery, the primary features of the endotype are determined a priori on the basis of clinical and/or biologic insights, whereupon the task is to validate the endotype in terms of differential treatment response or prognostic trajectory. In model-free endotype discovery, complex data sets are explored agnostically using unsupervised methods, such as clustering or latent class analysis (LCA), with the goal to identify subclasses with similar features or characteristics.

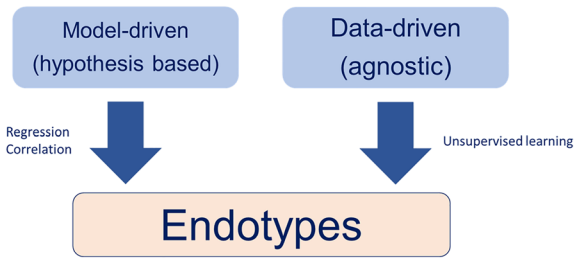

Fig. 2 Methodologies for endotype discovery include a model-driven approach, in which clinical insights or biological hypotheses are used to predefine endotype subclasses, which are then validated (or not) by exploring associations with treatment responses or recovery trajectories. This contrasts with a model-free approach, in which data are explored agnostically using unsupervised machine learning techniques, such hierarchical clustering, with the goal of discovering new, previously unrecognized subclasses of patients who are biologically plausible and clinically meaningful

An example of hypothesis-driven subphenotype discovery can be observed in a recent multicenter prospective cohort study of delirium in patients with critical illness [51]. The authors defined four delirium subphenotypes prior to initiating the study on the basis of expert clinical opinion and prior research regarding delirium risk factors. They outlined specific clinical, physiologic, and laboratory parameters for inclusion into each subphenotype and prospectively assigned intensive care unit (ICU) patients who met these criteria to one or more subphenotype group. They found significant differences between delirium subphenotypes and the likelihood of long-term cognitive impairment, suggesting these clinically defined groups may have clinical significance.

In contrast, a recent study of ARDS implemented data-driven discovery using LCA to identify two subphenotypes of ARDS (hypoinflammatory and hyperinflammatory) [52]. LCA is a statistical technique used to find subclasses in multivariate categorical data [53]. These inflammation-based ARDS subphenotypes had been previously identified in RCTs with carefully selected patient populations. The authors applied LCA to clinical and biological data from two prospective observational patient cohorts, recapitulating these known subphenotypes in a nonselected patient population and suggesting their generalizability. Without a priori class assignment, the same subphenotypes emerged using the data-driven approach.

Endotypes in msTBI

TBI, like ARDS and sepsis, is a heterogeneous syndrome; however, endotype research is in a very early phase. The expectation is that endotype research will ultimately increase precision in msTBI detection and diagnosis, contribute to more accurate prognostic models

(prognostic enrichment), help predict response to therapy, and enable the design of more effective clinical trials (predictive enrichment). A conceptual framework for endotypes in patients with severe brain injury was proposed in a recent overview [54]. The authors suggested that endotypes could be distinguished from phenotypes not only because endotypes are anchored in biological mechanisms but also because they integrate dynamic temporal information (state transition, clinical trajectory) rather than focusing on a single instance (clinical snapshot).

In considering strategic directions for research in this space, three methodological domains need consideration. First, one will need to precisely define the data sources from which endotype features can be derived. Second, studies will need to be designed to enable effective modeling and validation. Last, effective strategies are needed to demonstrate how endotypes are to be implemented in real-world clinical and operational workflows.

Data Types and Sources

Because many patients with msTBI are managed without surgery, tissue sampling is not consistently available, and consideration of nontissue feature sets is necessary (Table 2). These might include neuroimaging [55, 56], blood and cerebrospinal fluid biomarkers [57, 58], biometric data (e.g., quantitative pupillometry) [59], and continuous physiological signals. Consideration will also need to be given to environmental and treatment features in addition to intrinsic patient data. Continuous physiological signals include data from invasive intracranial monitoring or less invasive approaches, such as electroencephalography [60, 61]. One promising direction in msTBI endotype characterization was recently demonstrated by Jha et al. [62]. They used group-based trajectory modeling of intracranial pressure monitoring to define six subphenotypes associated with differentiable 6-month clinical outcomes [62].

TBI endotyping will require large rich data sets composed of the diverse data types discussed above. Three general categories of available data sets may be amenable to endotyping. First, are deidentified publicly available electronic health records data sets. Prominent examples of this include the Philips eICU Collaborative Research Database [63], a multicenter data set of 200,859 patient encounters for 139,367 unique ICU patients, and the Medical Information Mart for Intensive Care–III [64], which contains 55,000 encounters for 38,597 patients admitted to ICUs of a single tertiary care medical center over more than 10 years. Second are prospective multicenter TBI-specific observational studies, such as Transforming Research and Clinical Knowledge in TBI [65] and Collaborative European Neurotrauma Effectiveness

Table 2 Sources of features for moderate and severe TBI endotype discovery

	Description
Neuroimaging and brain mapping	Cranial CT modalities (noncontrast CT, CT angiography, CT perfusion)
	Brain MRI (structural, functional)
	Digital subtraction angiography
	Near-infrared spectroscopic modalities
	Transcranial Doppler
	Magnetoencephalography
Intracranial neuromonitoring	Intracranial pressure
	Brain tissue oxygen partial pressure
	Cerebral microdialysis
	Cerebral blood flow
Neurophysiologic studies	EEG
	Electrocorticography
	Depth EEG
	Evoked potentials
Extracranial physiological time series	Photoplethysmography
	Arterial blood pressure waveform
	Electrocardiography
	Ventilator-derived pulmonary physiology
Biological data	Gene expression, genomics
	Transcriptomics
	Epigenetic modifications
	Protein expression, proteomics
	Metabolomics
	Lipidomics
Quantitative biometric features	Quantitative pupillometry
	Accelerometry
	Extraocular movements

CT computed tomography, *EEG* electroencephalography, *MRI* magnetic resonance imaging, *TBI* traumatic brain injury

Research in TBI [26, 66]. Finally, a yet unrealized data source is the concept of an integrated learning health system. Recommended specifically in a recent National Academies of Sciences, Engineering, and Medicine report [67], a learning health system would integrate longitudinal linked patient records with clinical, molecular, physiologic, and radiographic data.

Study Design

TBI endotype study design considerations include feature space exploration and specification, designation of clinically meaningful ground-truth labels, and selection of the appropriate statistical methods to be used in modeling. Model-driven endotype research will be largely reliant on supervised classifiers (e.g., generalized

linear models, tree-based models, and neural networks), whereas model-free endotype discovery will require unsupervised learning techniques (e.g., k-means, hierarchical, spectral, and density-based spatial clustering algorithms; principal components analysis; and t-distributed stochastic neighbor embedding). Another key step in endotype study design is clinical validation. Endotypes have limited significance unless they can enable more effective therapy and more meaningful outcomes for patients with msTBI. A natural venue for validation is to leverage endotypes as a strategy for predictive enrichment in RCTs (Fig. 1). In the intensive care domain, this approach has been successfully tested in patients with ARDS and acute kidney injury [39, 41, 68]. Biologically based and meaningful endotypes must also demonstrate robust generalizability across msTBI populations in different practice settings, health systems, regions, and countries.

Implementation

Several factors will be pivotal for any consideration of real-world implementation of msTBI endotypes. The proposed endotypes must be recognizable as biologically plausible and clinical meaningful. They will need to be quantifiable, and the time scales for endotype derivation and assignment should be commensurate with clinical decision-making. It will be critical to demonstrate how and when endotypes can be integrated in diagnostic, prognostic, and treatment workflows. Most important will be to demonstrate that TBI endotypes improve the prediction of recovery and treatment response in comparison to existing phenotype-driven approaches or isolated biomarkers.

Concluding Remarks

msTBI is intrinsically heterogeneous, yet this quality is overlooked in existing phenotype-driven paradigms of msTBI management. The inability to measure and account for this complexity is a major barrier to effective treatment of patients with this condition. The endotype paradigm represents a powerful methodological approach that can help mitigate heterogeneity and enable higher levels of precision and personalization in the care of these patients.

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Author contributions
TDA created the article outline, performed the literature review, and wrote the manuscript. PPS participated in the literature review and drafting of the manuscript. HBK reviewed and edited the manuscript. RDS conceptualized the article and reviewed and edited the manuscript. The final manuscript was approved by all authors.

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