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Authors
Huie, J Russell
Mondello, Stefania
Lindsell, Christopher J
et al.

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Biomarkers for Traumatic Brain Injury: Data Standards and Statistical Considerations

J. Russell Huie,[1] Stefania Mondello,[2] Christopher J. Lindsell,[3] Luca Antiga,[4] Esther L. Yuh,[1] Elisa R. Zanier,[5] Serge Masson,[5] Bedda L. Rosario,[6] and Adam R. Ferguson,[1,7]; The Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Investigators*; Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Participants and Investigators**

Abstract

Recent biomarker innovations hold potential for transforming diagnosis, prognostic modeling, and precision therapeutic targeting of traumatic brain injury (TBI). However, many biomarkers, including brain imaging, genomics, and proteomics, involve vast quantities of high-throughput and high-content data. Management, curation, analysis, and evidence synthesis of these data are not trivial tasks. In this review, we discuss data management concepts and statistical and data sharing strategies when dealing with biomarker data in the context of TBI research. We propose that application of biomarkers involves three distinct steps—discovery, evaluation, and evidence synthesis. First, complex/big data has to be reduced to useful data elements at the stage of biomarker discovery. Second, inferential statistical approaches must be applied to these biomarker data elements for assessment of biomarker clinical utility and validity. Last, synthesis of relevant research is required to support practice guidelines and enable health decisions informed by the highest quality, up-to-date evidence available. We focus our discussion around recent experiences from the International Traumatic Brain Injury Research (InTBIR) initiative, with a specific focus on four major clinical projects (Transforming Research and Clinical Knowledge in TBI, Collaborative European NeuroTrauma Effectiveness Research in TBI, Collaborative Research on Acute Traumatic Brain Injury in Intensive Care Medicine in Europe, and Approaches and Decisions in Acute Pediatric TBI Trial), which are currently enrolling subjects in North America and Europe. We discuss common data elements, data collection efforts, data-sharing opportunities, and challenges, as well as examine the statistical techniques required to realize successful adoption and use of biomarkers in the clinic as a foundation for precision medicine in TBI.

Keywords: biomarkers; data sharing; traumatic brain injury

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability, especially among children and young adults. Each year over 50 million TBIs occur worldwide with an estimated overall cost of upwards of U.S. $400 billion.[1] Despite our enhanced understanding and advances in research and clinical management, there remains a critical need for more accurate diagnostic and prognostic tools in TBI.[1] The development and validation of genomic, proteomic, and imaging biomarkers will be essential for tackling TBI heterogeneity and moving towards precision medicine. The heterogeneous nature of traumatic brain injury presents a major challenge to biomarker identification, validation, and clinical application. To optimize success in biomarker discovery and implementation into the clinic, it is crucial for the TBI research community to deal with heterogeneity in data collection, perform rigorous dimension reduction, and achieve robust statistical analysis and validation.

The aim of this review is to present recent innovations in biomarker data collection and analysis for TBI diagnosis, characterization, outcome, and precision therapeutic targeting. We address data management and statistical considerations inherent in the iterative

[1]Brain and Spinal Injury Center, Department of Neurological Surgery, University of California San Francisco, San Francisco, California, USA.
[2]Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy.
[3]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA.
[4]Orobix Srl, Bergamo, Italy.
[5]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy.
[6]Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, USA.
[7]San Francisco Veterans Affairs Medical Center (SFVAMC), San Francisco, California, USA.
*TRACK-TBI Investigators are listed at the end of the article.
**CENTER-TBI participants and investigators are listed at the end of the article.

process of biomarker identification, validation, and demonstration of medical utility, and provide an overview of large-scale discovery platforms, data reduction techniques, and strategies for development of biomarker–based signatures for TBI. We also outline the utility of these results in improving outcome prediction and clinical decisions. Further, along the way, we discuss the recent application of these issues from the International Traumatic Brain Injury Research (InTBIR) initiative, focusing on role and future directions of four current multi-center clinical studies: Transforming Research and Clinical Knowledge in TBI (TRACK-TBI), Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI), Collaborative Research on Acute Traumatic Brain Injury in Intensive Care Medicine in Europe (CREACTIVE), and the Approaches and Decisions in Acute Pediatric TBI Trial (ADAPT).

Importance of Common Data Elements

The first, fundamental step in biomarker development involves identifying and establishing standardized and rigorous methods for sample and data collection. In partnership with the National Institutes of Health, U.S. National Institute of Neurological Disorders and Stroke (NIH/NINDS), the TBI Biospecimens and Biomarkers Working Group put forth a series of recommendations for the handling, storage, and preprocessing of biospecimens from blood and cerebrospinal fluid for use in genomic and proteomic biomarker discovery and validation.[2] Moreover, this inter-agency initiative further codified a comprehensive list of common data elements (CDEs) for TBI that cover the broad range of factors and definitions in TBI research and treatment.[3] Adherence to these CDEs is essential for standardizing data collection, permitting comparisons, and establishing the replicability of findings across multi-center studies in the InTBIR initiative.

While the recent findings in TBI biomarker identification reported here were facilitated, powered, and contextualized by the use of TBI CDEs for the collection of biomarkers, further time, resources, and work will be needed to build collaborations, share data, and agree on how these data will be managed and analyzed.

Neuroimaging Biomarkers

Swift and accurate diagnosis of TBI is important for determining health management decisions, including hospital admission and surgical intervention. Thus, acute neuroimaging provides the current best opportunity to visualize the type, location, and extent of injury. But the various imaging technologies each provide unique benefits and limitations and their application depends on a number of factors, including time since injury, severity of injury, and the patient's physical state. No less important, cost and specific neuroimaging availability/capability of the different centers may limit the impact of imaging biomarkers.

In this section, we will review the strengths and weaknesses of neuroimaging techniques, and discuss the data management and statistical considerations that must be addressed in order to optimize the diagnostic, prognostic, and predictive validity of using imaging as a TBI biomarker.

The long-held standard for acute neuroimaging after TBI is computed tomography (CT). A CT scan can rapidly provide three-dimensional information regarding the anatomical localization of biological materials of varying degrees of density, the abnormal or anomalous presence of which can be used to determine possible pathologies. As a CT scan can sensitively identify bone and blood abnormalities, it is especially useful for the detection of skull fractures and intracranial hemorrhage. In contrast to the rapid broad pathological assessment of the CT scan, magnetic resonance imaging (MRI) is a more time-intensive procedure, but provides greater resolution of small focal lesions and diffuse axonal injury (DAI). MRI findings are quantified using voxel-based methods, generating large amounts of quantitative data from throughout the entire brain as well as focal regions of interest. From an analytical standpoint, MRI data may appear to lend itself more easily to data analysis standardization, but as discussed below, the wide variety of MRI measurements and analytical tools may present some difficulties. Moreover, no standardized units for magnetic resonance (MR) acquisition exist, and harmonization of MR sequences across different vendors and platforms poses substantial challenges in multi-center studies.

CT and MRI have been demonstrated to possess a relevant diagnostic and prognostic value, but most of the research on the diagnostic and prognostic validity of these techniques has been conducted in moderate and severe cases of TBI. As the vast majority ($\sim$90%) of TBI cases are mild (defined as a Glascow Coma Scale score of 13–15), there is a strong need for a rapid imaging biomarker that can detect acute mild TBI (mTBI). Although CT is the standard imaging modality for acute assessment, it is largely insensitive to axonal injury, which has been shown to occur in mTBI cases.[4,5] On the other hand, MRI is uniquely sensitive to white matter injury, but is rarely used as an acute predictive tool. In 2008, Lee and colleagues conducted a prospective study to directly compare the efficacy of acute CT and MR to identify mTBI.[6] They found that 3 Tesla (3T) MR was twice as sensitive to focal contusions and four times as sensitive to traumatic axonal injury as was CT. Interestingly, despite the greater sensitivity of MR to detect these pathologies, they found that neither CT nor MR correlated with neurocognitive outcome measures. Thus, imaging tools with greater resolution for subtle white matter abnormalities have been suggested as a more accurate alternative for identifying mTBI and predicting neurocognitive outcome.

Among the various MRI techniques, diffusion tensor imaging (DTI) has emerged as one of the foremost approaches for detecting mTBI. DTI provides a quantitative measure of water diffusivity in the form of the apparent diffusion coefficient and fractional anisotropy index, and has been shown to be more sensitive than either CT or standard MRI to the microstructural changes in water movement that is associated with DAI. Kraus and colleagues used fractional anisotropy (FA) measures to assess DAI in multiple brain regions after severe and mTBI.[7] They found that while FA values were lowered throughout all 13 of the brain regions measured in severe TBI patients, only three regions of interest showed decreased FA values after mTBI. They also showed that DTI could be used to provide an objective measure of global white matter neuropathology that was correlated with impaired neurocognition. Niogi and colleagues further sought to strengthen the specificity of DTI as a predictor of cognitive impairment after mTBI by using targeted DTI measures in specific brain regions known to be associated with particular cognitive domains.[8] They found that lowered FA values in the left hemisphere anterior corona radiata were highly correlated with decreased attentional control, and lowered FA values in the uncinate fasciculus were highly correlated with memory impairments. These and other studies helped to characterize how mild TBI produces cognitive deficits through subtle localized microstructural changes in white matter, and the ability for DTI to accurately measure these changes.

The findings from both Kraus and colleagues and Niogi and colleagues were demonstrated in chronic mTBI patients; continued

research on the use of MRI will be needed in the acute phase to determine the efficacy of this approach as an early prognostic biomarker for mTBI. Likewise, due to the heterogeneity of injury and the sensitivity of each imaging technique to different aspects of injury, a multi-modal approach has been proposed.[9,10] To that end, the TRACK-TBI group has recently completed a set of studies to assess whether early CT and MRI (12 ± 3.9 days from emergency department presentation) is predictive of cognitive outcome in patients with mTBI.[11] They found that 27% of patients with normal admission CT had positive findings on early brain MRI, and overall, the combined assessment of CT and MRI accounted for a significant portion of the variability in 3-month outcome, as measured by the Extended Glasgow Outcome Scale (GOS-E). In another study, Yuh and colleagues assessed whole–brain and region of interest DTI measures in addition to traditional CT and MRI within the first 2 weeks after mTBI in a patient population of varied demographic/socioeconomic backgrounds. They found that in patients lacking neuropsychiatric and/or substance abuse history, MRI (including DTI) was a significant predictor of cognitive outcome at both 3 months and 6 months post-injury.[12]

Imaging data and statistical considerations

The varied nature of imaging modalities means that the data generated from these approaches is also quite disparate, and even within a particular imaging type, there may exist a number of ways to synthesize, analyze, and interpret these data. Classification systems such as the Marshall Scale and later the Rotterdam Scale have been developed to standardize and operationalize CT findings, but these systems still rely on subjective assessment of imaging findings and may be prone to inter-observer variability.[13] Further, these scales were developed for cases of severe TBI, and have not been validated for mild TBI. Computer-aided assessment tools have recently been developed that use quantitative data to automate the determination of key clinical features (e.g., presence or absence of subdural hematoma, subarachnoid hemorrhage, and basal cistern effacement).[14–17] Automated image analysis was shown to sensitively and specifically determine CT negative findings, and thus could be used to minimize the false-negative error rate, which has been shown to be as high as 11%.[18]

MRI data are produced using voxel-based morphometry and can produce a variety of quantitative measures. Each voxel can provide granular values for mean diffusivity, axial diffusivity, and radial diffusivity in addition to FA values. A number of image analysis systems have been developed to handle these large amounts of data, each of which handle statistical comparisons in slightly different ways. For instance, comparison of FA and trace values across whole brain images are often made by normalizing to a white matter mask, and then performing unpaired t-tests, with multiple comparisons accounted for by Bonferroni's correction. Bazarian and colleagues have suggested that this approach may make inappropriate parametric assumptions about the normal distribution of FA values across white matter areas of different brain regions, and has advocated the use of other non-parametric tests, such as the novel-quantile approach, using the Westfall and Young step-down method to adjust for multiple comparisons.[19,20] Other statistical inference tools are often used on MRI data, such as the threshold-free cluster enhancement tool, used for permutation testing corrections on multiple-voxel comparisons,[21] and tract-based spatial statistics in which FA values are mapped onto a white matter skeleton in order to improve the sensitivity of analysis when comparing MRI data across patients.[22]

The development and maintenance of standardized neuroimaging protocols would greatly mediate a number of analytic challenges inherent with imaging data. These include comparing data across studies that used different imaging acquisition and interpretation methods, and challenges in analyzing data from this highly heterogenous patient population. Finally, absent standardized tools, it will not be possible to generate normative data across the range of population characteristics, it will be important to develop and maintain standardized neuroimaging protocols.[23] Such an effort has been undertaken in workshops bringing together NIH-NINDS, neuroradiologists, and industry representatives, and by the InTBIR Neuroimaging Work Group. The ultimate goal to create consensus-based best practice guidelines and recommendations on the development and maintenance of a normative neuroimaging data repository and associated metadata.[23,24] This database will improve transparency, standardization, and comparison of TBI patients to controls, thereby aiding in the interpretation of results across multiple sites and optimizing clinical utility.

To this end, Palacios and colleagues across the network of TRACK-TBI neuroradiologists recently investigated the reproducibility of DTI data from 13 different 3T scanners, representing three imaging vendors across 11 hospital sites.[25] Using a diffusion phantom standard that was developed by the National Institute of Standards and Technology, they demonstrated an overall low variability ($< 4\%$) across machines and centers, and determined that it would be feasible (and recommended) to undertake efforts to standardize DTI data throughout the neuroradiology field.

Taking this forward, CENTER-TBI (Icometrix) has examined the effects of confounding factors on FA and evaluated the feasibility of statistical methods to model and reduce multi-center variability. DTI phantom scans from 13 European imaging centers were acquired every 6 months and whenever maintenance or upgrades to the system were performed. A total of 64 scans were acquired in 2 years, obtained from three scanner vendors, using six individual head coils and 12 software versions. Their findings suggest that specific statistical models (LMEM; Linear Mixed Effect Models) hold promise to model the variability in quantitative imaging biomarkers for clinical routine and multi-center studies.

CENTER-TBI and TRACK-TBI have pioneered efforts towards harmonization of DTI acquisition and processing in a multi-center setting. While we recognize that complete standardization will never be possible in the absence of a fixed standard (such as Hounsfield units for CT), harmonization has now been proven to be feasible and broader implementation will facilitate more multi-center TBI trials in the future.

High Throughput Discovery Pipeline Issues

High throughput discovery approaches (genomics, transcriptomics, proteomics, and metabolomics) have special problems involving distinct analytical stages for exploratory mechanistic work, and individual biomarker evaluation as a prognostic, efficacy response and/or diagnostic tool. Below we present general and specific features of these types of approaches. Multilevel, precision integration of biological information is a far-reaching goal of this type of work, and at the current time there are very few examples of multi-omics for TBI. The goal of our discussion is to focus on general analytic concerns as well as to highlight special considerations within each domain.

Approaches to genetic biomarker discovery: Data handling and statistical considerations

Genetic screening techniques have become an invaluable tool in deciphering the underlying mechanisms of disease, and are

increasingly used in the search for reliable biomarkers for TBI. Genetic data may be analyzed at a number of levels: from the genome-wide scale, to gene pathways and networks, down to single nucleotides that may be tested to explain variation among patients. Advances in microarray technology and the advent of whole–genome mapping have now made it possible to acquire massive amounts of data for each subject or patient. While probing the entire genome for injury or disease-related variation may lead to revolutionary discoveries, proper experimental design and management of large datasets accumulating enormous amounts of data will be imperative to ensure validity and reproducibility of findings. Here, we review the many scales on which genetic testing and association can be performed, and consider some of the varied statistical approaches to synthesizing and analyzing large genetic datasets.

The development and refinement of chip-based microarrays now allows researchers the ability to assess up to 1 million nucleotides on a single chip for a single patient. Responsible data management and interpretation of such large datasets is essential. There are a number of methods for microarray data reduction, and each requires careful iterative analyses in order to make biologically-relevant inferences from the data. In genome wide association studies, the differential expression of genes (or often single nucleotide polymorphisms [SNPs] within genes) must first be determined. This is often achieved using some variation of t-test or analysis of variance to generate a separate *p* value for each gene. With up to 1 million measures, such an approach involves an extremely large number of multiple comparisons, and as such is highly susceptible to type I errors (declaring ''significant'' differences in gene expression that are due to random chance). To account for multiple testing, a family-wise error control procedure such as Bonferroni's correction is often used, but may not be the best way to control for multiple tests in such a large number of comparisons as it inflates type II error (failing to detect significant differences in gene expression that truly exist). Recently, more sophisticated methods have been developed that are built upon Benjamini and Hochberg's false discovery rate (FDR) procedure.[26] These nonparametric mixture-models estimate FDRs for genes that have been identified as differentially expressed using a different approach compared with the traditional Benjamini and Hochberg method, which controls the FDR below a certain level.[27-29] Specifically, these methods are designed to generate the Bayesian probability of a false positive for each gene. It is believed that this ''gene specific'' FDR provides a much more powerful estimate of false discovery rate.[27]

Once a set of genes has been ranked and a cutoff has been determined as to which genes are differentially expressed in TBI patients, the task of determining a meaningful biological context can begin. The most ubiquitous tool for gene annotation is the Gene Ontology (GO) database,[30] in which genes have been grouped into functional categories (by biological process, molecular function, and cellular location). The experimental gene set can be annotated according to GO in order to harness existing knowledge about gene function to help interpret observed differences in TBI gene expression. The gene clusters aligned to GO can then be further contextualized using a pathway analysis toolkit, where groups of differentially expressed genes can be mapped onto curated pathways. Most of these pathway analysis packages provide significance testing of these ranked pathways using a Fisher's exact test or hypergeometric distribution test. One limitation to this method is that it requires the prior selection of a subset of genes determined to be differentially expressed, and thus the pathway analysis is biased toward these genes that meet assumptions of statistical criteria such as Bonferroni's, Benjamini-Hochberg, or non-parametric mixture models.

In contrast, Gene Set Enrichment Analysis (GSEA) considers the entirety of gene expression values, not just those that have been deemed differentially expressed.[31] This method produces maximum enrichment scores for all ranked genes within an annotated category, successively uses a Kolmogorov-Smirnov test to iteratively compare against curated gene sets to determine differentially expressed gene groups, rather than individual genes. While this ''no cut-off'' approach ensures that genes with low expression values are not discounted or overlooked, it has been noted that GSEA is still biased toward genes with high expression values, and may not be sensitive to the potential biological relevance of genes that are not highly-regulated by TBI but still predict outcome.[32]

While these well-established methods approach gene discovery from a data-driven perspective, they still require human supervision and make assumptions and inferences about biological processes that may introduce inaccuracies and/or bias. All pathway analyses must rely on prior findings and expert curation, which steers these analyses toward well-known and well-studied genes and pathways. Thus, novel discoveries in under represented pathways are difficult to make using traditional gene discovery approaches. The development of weighted gene co-expression network analysis by Horvath and colleagues has provided an alternative to some of the limitations of traditional genomic association analyses, by avoiding the grouping of genes by expert-annotation altogether.[33,34] Instead, this approach uses the complex correlations between all genes to generate modules and network nodes, and then eigengenes are expressed in terms of a given gene's membership in a particular module. This produces module eigengenes that can then be correlated with a particular phenotypic trait of interest. Inherent researcher bias is greatly minimized because decisions are made by machine learning tools, and all human-based hypothesis testing is done in a post hoc fashion. This machine-driven approach comes at the expense of interpretability and simplicity required for rapid diagnostic decision-making, and requires very large sample sizes for reliable results. Eigengenes represent weighted multi-dimensional sets of biomarkers rather than a single biomarker, requiring a shift in clinical diagnostic and regulatory thinking that may be difficult to implement and widely use in routine clinical practice (Fig. 1). Other data-driven approaches, such as topological data analysis (TDA) have also been used recently within TRACK-TBI to discover novel relationships between genes and post-injury phenotypes.[35] Data driven approaches like TDA show great promise for future biomarker discovery.

Single gene analysis

Despite the technological advances in genomic screening, the ''bottom-up'' approach of data-driven genome-scale association analyses for identifying TBI biomarkers has yet to gain traction over the ''top-down'' approach, in which single candidate biomarkers are chosen based on traditional hypothesis-testing from a preconceived conceptual model. Regardless of the method by which a candidate biomarker is identified, appropriate testing and validation is crucial to accurately assess a biomarker's predictive/diagnostic potential. Although single gene hypothesis testing may appear rather straightforward compared with more complex whole genome-scale analyses, a number of statistical factors must be considered. Possible differences in the target gene or allele across demographic/clinical descriptors (e.g., injury etiology) must be determined, and appropriate statistical tests used, depending on

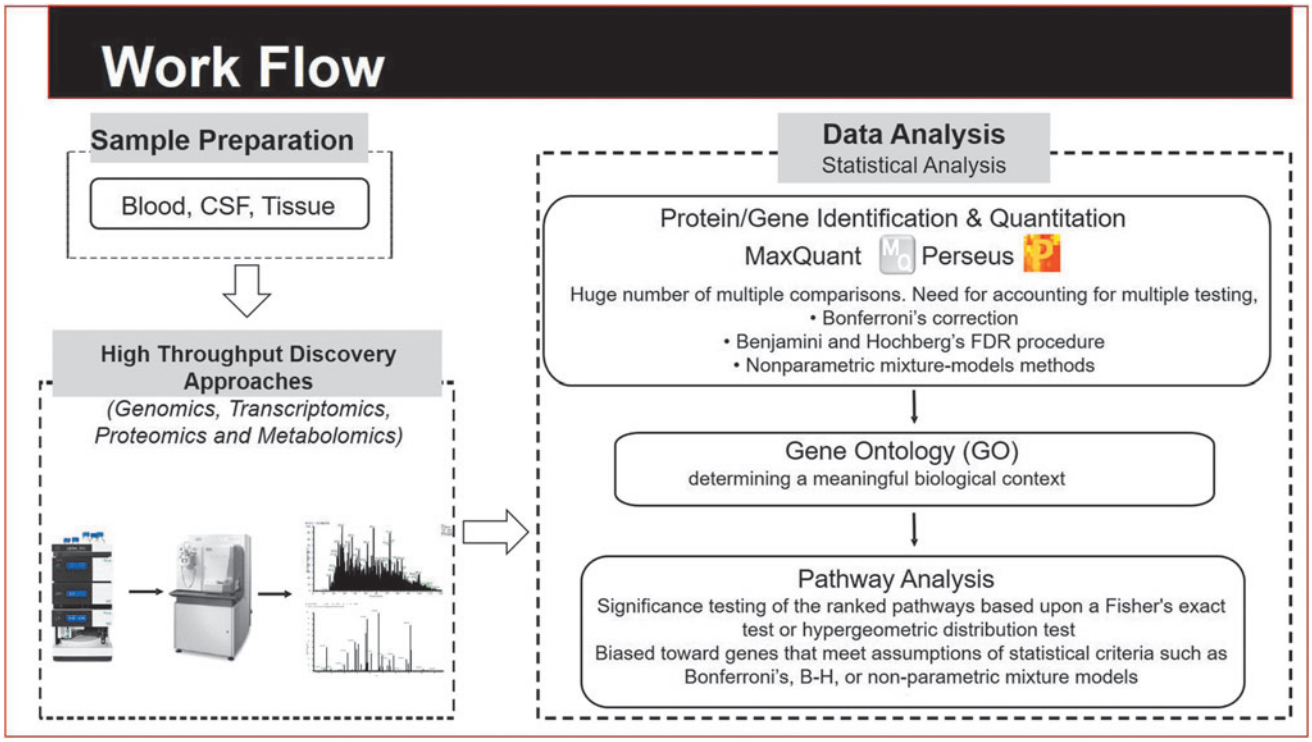

FIG. 1. Representative analytical workflow for traumatic brain injury biomarker discovery. Color image is available online.

the particular format of each variable. If, for example, the distribution of a gene of interest is found to be unequal across demographic groups, a nonparametric sensitivity analysis such as Fisher's permutation test or bootstrap resampling, can help control for such a confound. These approaches consist of iteratively performing random draws from the patient population to build numerous (sometimes thousands of) different versions of the dataset, and rerunning the statistical analyses on each of these subsamples. The resulting analyses are then pooled to estimate the variance in a much larger, more heterogeneous patient population.

TRACK-TBI utilized these statistical methods to investigate the association between a SNP of the ankyrin repeat and kinase domain-containing 1 (ANKK1) and cognitive performance after TBI in a large multi-center cohort.[36] Using the California Verbal Learning Test as the primary cognitive outcome measure, Yue and colleagues showed that TBI patients with a homozygous T allele on the ANKK1 gene performed worse than those with the homozygous C allele, or the T/C heterozygous allele.[37] A number of possible confounds including demographic differences in patient populations with different SNPs were addressed and, when necessary, statistically controlled for. This study was conducted using both the TRACK-TBI pilot data and the Citicoline Brain Injury Treatment (COBRIT) cohort, which allowed assessment of 492 patients and enabled explicit testing of statistical robustness and reproducibility. This patent population for genetic analysis is large (unprecedented in TBI), yet remains insufficient to make generalizable and robust claims about the broad and heterogeneous TBI population. It nevertheless serves as an example of the successful pooling data of across multiple centers, and the seamless integration of these data could only be accomplished through the use of NIH-NINDS TBI CDEs.

As CDEs standards are increasingly adopted, increased sample sizes will enable new studies of genetic biomarker discovery, validation, and cross-validation by pooling data from multiple sources and sites. To that end, it is important to test for the possible main effects of site/data source on the primary outcome measure, as well as the possible interaction between site/data source and the predictor (candidate biomarker). Controlling for such confounds will help to ensure validity and reproducibility of genetic biomarkers in the future.

Circulating protein biomarkers

Another promising avenue for biomarker discovery from blood and cerebral spinal fluid (CSF) is the identification of key proteins that can provide diagnostic/predictive/prognostic information in the acute phase of TBI to help guide treatment decisions. The complex and heterogeneous nature of TBI, as well as the pathophysiological progression through primary and secondary injury cascades, makes it difficult to identify a single protein that can represent a ''signature'' of TBI complexity. Despite this challenge, a number of promising candidate proteins have been put forth based on mechanistic animal studies in TBI. For example, astrogliosis is a major component of the neural injury process,[37] and astrocyte-related proteins can leak into the CSF and blood in TBI. Proteins highly-specific to astroglial overexpression and injury, S100B and glial fibrillary acidic protein (GFAP) are logical choices for investigation. S100B is a calcium-binding protein found in astrocytes, the levels of which are elevated in response to neural injury or inflammation. A number of clinical studies have shown that elevated serum levels of S100B correlate with poor outcome after TBI, but S100B has also been shown to be elevated in response to other inflammatory/traumatic processes in the absence of TBI.[38] This highlights one of the major issues in proteomic candidate biomarker selection: the balance of specificity and sensitivity for a particular measure (i.e., predictive, diagnostic, or prognostic) for any given protein must be considered, in order to determine an appropriate context of use for that biomarker.

In the case of S100B, although it has been shown to be highly sensitive to brain trauma, it lacks specificity for TBI because it is also released from extracerebral tissue and can be elevated in response to numerous other non-CNS injuries.[38-40] GFAP, a protein associated with astroglial damage and released after injury-induced breakdown of the astroglial cytoskeleton, is gaining momentum in TBI research. It has been suggested that it may serve as a marker of focal lesions and intracranial bleeding,[39,40] but may not be adequately sensitive to axonal injury. Unlike GFAP, the protease ubiquitin C-terminal hydrolase-L1 (UCH-L1) has been shown to be suggestive of diffuse injuries,[41] and appears to be a promising TBI biomarker candidate in its own right. Taken together, these observations suggest that simultaneous assessment of biomarkers reflecting different pathophysiological mechanisms and injury types would provide complementary information and might increase diagnostic and prognostic accuracy, hence enabling clinicians to stratify risk more effectively among TBI patients. Consequently, one of the key questions has now become how best to determine and quantify the improvement in risk prediction offered by the combination of different markers.

The receiver-operating-characteristic (ROC) curve is typically used to evaluate clinical utility for both diagnostic and prognostic models; thus, researchers have proposed as main criterion the improvement in the area under the receiver-operating-characteristic curve (AUC) or c-statistic, To this end, recently, Diaz-Arrastia and colleagues in the TRACK-TBI team investigated the relationship between GFAP and UCH-L1, to determine whether the combined use of these biomarkers provides greater predictive value than using them alone.[42] They found that each biomarker alone had sufficient specificity to differentiate TBI patients from healthy controls (AUC 0.91 for GFAP; AUC 0.87 for UCH-L1). When assessed in combination, the sensitivity and specificity was even greater (AUC 0.94). Additionally, assessment of UCH-L1 and GFAP together was able to predict poor outcome (as measured by the GOS-E) at 3 months better than either biomarker alone (UCH-L1 only, AUC 0.80; GFAP only, AUC 0.74, UCHL1+GFAP, AUC 0.83). A recent study from TRACK-TBI using a multiplexed blood-based protein assay also demonstrated the feasibility to use a large number of markers (72 proteins) in a data-driven, multivariate fashion. This study revealed that a composite biomarker ''score'' derived from a pattern of acute inflammatory markers was able to predict cognitive recovery up to 12 months after injury.[43]

In February of 2018, the U.S. Food and Drug Administration (FDA) authorized GFAP and UCH-L1 as the first blood-based biomarkers for evaluation of mild TBI,[44] highlighting the emerging value of biomarkers and the pressing need for analytical tools to integrate biomarkers into clinical decision making. The added value of this combined marker compared with clinical decision rules, however, still needs to be proven. Newer tools to assess improvement in predictive model performance include the reclassification calibration (RC) statistic, the net reclassification improvement, and the integrated discrimination improvement (IDI).[45-47] While widely applied in other fields these methods are still underexplored in TBI. Although promising, the appropriate use and interpretation of these tools has been called into question,[48,49] and proving added value of biomarkers may well depend more on numbers than on statistical methods.

In addition, novel bio-statistical tools such as stepwise penalized logistic regression and model-based classification and regression trees can be used to determine improved algorithms incorporating biomarkers and relevant clinical variables. Nonetheless, to have an impact on widespread medical practice, single markers and/or biomarker combinations should first demonstrate their unequivocal clinical utility, showing increased predictive value over and above standard predictors and existing clinical decision rules.[50]

Considering temporal biomarker profiles and kinetics

The biomarker work discussed thus far has focused on static 'snapshots' that aim to provide information for diagnosis and/or prognosis. However, neurotrauma is a dynamic syndrome, and the insights we gain are highly dependent on the timing of biomarker study. Thus, a greater focus on the temporal resolution in future biomarker studies will be essential in order to contextualize the progression of injury and obtain trajectories of late neurodegenerative processes and/or injury resolution. To this end, a number of recent biomarker studies have taken the time-course of neurotrauma into account.[51-53] Including repeated time-series measures into a biomarker study introduces a new set of statistical considerations, and different fields have addressed these issues in different ways.

Modeling repeated blood-based biomarkers over time presents its own statistical challenges. Biomarker studies that take repeated measures have traditionally summarized or transformed the data, taking single-point estimates (e.g., mean expression, peak expression, etc.).[54] But just as the injury itself develops and changes over time, so too does the biomarker; thus, a number of groups are now focusing on ''biomarker kinetics'' to better understand how biomarker expression changes along with the progression of secondary injury processes.[55–58] Differences in bioavailability, clearance, degradation, and release over time after injury, as well as injury severity-dependent differences in biomarker expression must all be considered. A number of studies have recently used serial serum samples to characterize the temporal profile of top candidate TBI blood biomarkers, including S100B, GFAP, neuron-specific enolase, and UCHL1—many of which were recently subjected to meta-analysis.[59] To optimally assess repeated measures, researchers have increasingly opted for hierarchical or mixed model approaches that allow for the covariance structure across time-points to be specified, rather than relying on the assumptions of independence made by methods such as repeated measures analysis of variance.[60-62] Some biomarker studies also have employed group-based trajectory analyses, where temporal biomarker profiles are being used to cluster patients based on similar patterns of expression over time.[54,63]

Similarly, longitudinal imaging studies have been used for a number of years to track progression of TBI. Functional MRI (fMRI) studies in particular have required more accurately quantifying and modeling spatiotemporal brain changes. By tracking blood oxygen level dependent (BOLD) signal across brain regions and through time, fMRI after TBI can model changes in connectivity and track recovery.[64] But a primary challenge for statistical modeling of these network changes has been reconciling contemporaneous and time-dependent sequential BOLD signals across brain regions. Traditionally, approaches such as structural equation modeling have been used to model contemporaneous signals, whereas models such as vector autoregression (VAR) could capture time-dependent changes, but not contemporaneous signals. More integrated techniques, such as latent growth models, dynamic Bayesian networks, and linear dynamical systems, allow for the integration of static and dynamic information.[65,66] For example, unified structural equation models, combining traditional standard error of the mean with VAR to model both simultaneous and sequential signals, have been used to analyze spatiotemporal brain imaging features.[67] While these unified approaches have their

limitations, they largely mitigate the biases inherent in either individual method alone.[68]

While these time-series approaches have provided insight into the dynamic processes after TBI, future TBI biomarker time-course analytics will likely continue to be informed by other fields. In metabolomics for example, non-parametric modeling techniques such as smoothing spline mixed-effects models and functional data analysis are used, wherein time-series data is viewed as a random curve, and these models use repeated measures to infer the shape of the curve, and then test for group differences between temporal profiles.[69,70] Handling time-series data in this way may allow for further exploration of multivariate TBI blood-based biomarker profiles across injury progression to more accurately predict outcome trajectories.

Moving from estimates to living evidence for health care practice

The field of TBI biomarkers has witnessed an incessant surge in attention and number of publications. Strikingly, upward of 50% of articles on TBI biomarkers in PubMed were published in the last 5 years (Fig. 2). This deluge of published information often shows conflicting or variable results for individual biomarkers. Trying to make clinical sense and obtain guidance on clinical decision-making is neither a trivial nor an immediate task.

High-quality systematic reviews and meta-analyses, based on a rigorous approach and methodology, can help to identify, appraise, and synthesize relevant research across an entire field of enquiry, thereby enabling health decisions informed by the best available evidence.[71,72] Yet, they are extremely time- and labor-intensive and difficult to keep up to date.[73] In areas in which innovations in primary research are emerging rapidly, such as TBI biomarkers, traditional systematic reviews may fail to deliver current, and therefore, accurate and useful evidence.[72,73] In response to this, the ''living systematic review'' initiative has been launched, pioneered by CENTER-TBI[75] and the Cochrane Collaboration (www.center-tbi.eu/publications/LSR; https://community.cochrane.org/review-production/production-resources/living-systematic-reviews). Living systematic reviews are high quality summaries that through a continuous systematic review workflow—from search to assessment, meta-analysis and report—are updated in real-time, incorporating relevant new evidence as it becomes available.

In the context of the CENTER-TBI project four Living Systematic Reviews have already been published,[75–78] one of which comprehensively and critically evaluates and meta-analyzes the existing body of evidence for the use of blood protein biomarkers following mild TBI. This systematic review and meta-analysis of diagnostic test accuracy (DTA) published in 2018 is under a critical updating process owing to the changes in evidence. Importantly, continually or frequently updating meta-analyses can inflate rate of false-positive findings and affect estimates and their precision (i.e., confidence interval).[79] Methods to overcome some of these statistical problems have been proposed (e.g., law of the iterated logarithm and sequential meta-analysis), but they have limitations and are not appropriate for meta-analysis of DTA studies. Further work is necessary and much remains to be developed and evaluated.

Moreover, it will be necessary to take the living systematic review approach one step further and enable ''living knowledge translation,'' by integrating in a rigorous, efficient, and timely manner evidence with guideline development platforms, living recommendations, policies, and clinical decision support systems. InTBIR and associated Working Groups (https://intbir.nih.gov/node/39) may play an instrumental role of the success and sustainability of this process, towards the common goal to create a new evidence ''ecosystem,'' which permit a seamless transition from research innovations and outputs to health care practice to precision medicine and improved outcomes of patients with TBI.

Data sharing in TBI biomarker research: ready for practice?

In addition to systematic reviews and meta-analyses, it is now increasingly possible to perform ''participant-level meta-analyses'' on the raw, unpublished data (''dark-data'') that undergirds the published literature.[80] As Common Data Elements standards are increasingly adopted, the opportunity to harmonize and share data across centers and trials is greater than ever. A set of data sharing principles has emerged to ensure that data is curated and

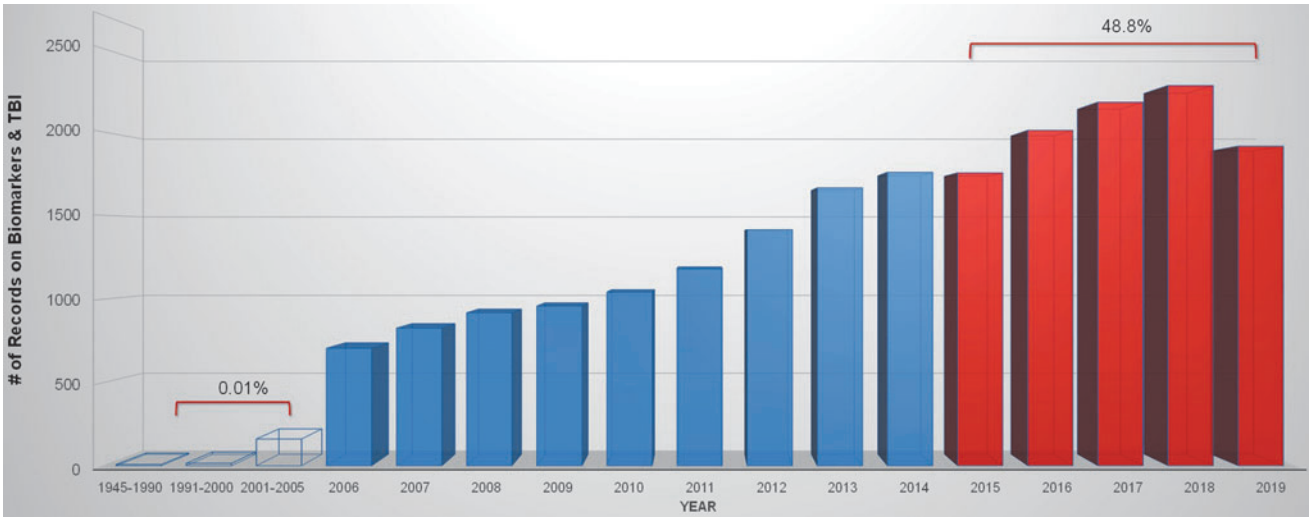

FIG. 2. The significant increase in interest in traumatic brain injury biomarkers as demonstrated by the number of articles published on the topic. Color image is available online.

democratized in a way that optimizes the value of the data and benefits the most data-users. The goal is for shared data to be FAIR: Findable, Accessible, Interoperable, and Reusable.[81] Current data repositories, such as the NIH-Federal Interagency Traumatic Brain Injury Research database and the pre-clinical spinal cord injury repository the Open Data Commons for Spinal Cord Injury (http://ODC-SCI.org) are operating under these principles. The spirit of collaboration and resource pooling are at the heart of the InTBIR initiative to translate data to knowledge. Thus, a data-sharing pipeline that facilitates sharing and accelerates findings will be key to the future of InTBIR. Both TRACK-TBI and CENTER-TBI are committed to data sharing and encourage researchers from both within and beyond the participating research centers to submit study plans for access and use of the data. From a statistical standpoint, data sharing will allow for much-needed replication analyses, as well as sufficient sample sizes to enable new studies of biomarker discovery, validation, and cross-validation by pooling data from multiple sources and sites. Given this, it will be important to test for the possible main effects of site/data source on the primary outcome measure(s), as well as the possible interaction between site/data source and candidate biomarkers.

Additional substantive advances, new insights, and ideas in TBI biomarker research can be derived from data sharing. Having access to complete global large-scale data provides an avenue for more efficiently conducting analyses, addressing confounding factors and combinations of multiple biomarkers and biomarker modalities, exploring different lines of analysis and new questions would improve our understanding and interpretation of biomarker findings and accelerate clinical translation.

Other benefits of sharing data include independent verification of results, meta-analyses of patient-level data deriving from different sources, transparency maximization, and a potential guardrail against conflicts of interest and influence from study sponsors. This would raise the bar for rigor and integrity, and enhancing reproducibility and reliability/validit.[82-84]

As such, the InTBIR initiative along with the associated clinical projects, CENTER-TBI, TRACK-TBI, CREACTIVE, and ADAPT are firmly committed to implementing an effective, efficient and global strategy for sharing TBI-related data. This direction presents a few early successes as well as daunting challenges. Early successes include development of CDEs[85] and the creation of the first standardized TBI ontology—a machine-readable set of defined descriptors of clinical manifestations—and their adoption has established the fundamental framework for data amalgamation and interoperable data-harmonization. Yet, there are still important legal, ethical, and regulatory barriers that hamper effective data sharing across borders. As a consequence, the InTBIR clinical projects (CENTER-TBI, CREACTIVE, TRACK-TBI and ADAPT), have different data policies and protocols (and requirements) for sharing data hinging on existing laws and regulations (www.center-tbi.eu/data/sharing; https://tracktbi.ucsf.edu/collaboration-opportunities).

In addition, storing, administering, and sharing data are expensive and time consuming, and the affordability/financial sustainability of international data sharing is not a trivial aspect to be considered.[86] Part of the InTBIR initiative's responsibility is to respond to these challenges. Federated cloud-based models may represent a solution, as they are financially efficient and provide assurance of data privacy and security for individual projects. At the same time, they permit access for outside researchers and organizations and across multiple platforms for increased scientific productivity. Incentives will need to be aligned toward the creation of such infrastructure and the implementation of powerful and specific data mining methods and analytic tools capable of integrating multi-modal data, visualizing multivariable interactions and quantifying biomarker variability and patterns.

Conclusions

The time has come for effective transatlantic ''TBI knowledge network and data sharing cooperation.'' This holds unique potential for the development of innovative biomarker-driven care pathways that will deliver on the promise of precision medicine and personalized treatments for patients with TBI. The search for sensitive and specific TBI biomarkers and powerful multi-marker and multimodal strategies represents an ongoing and iterative process, and candidate biomarkers must be evaluated on a number of key factors. In the process of biomarker validation, the assay methodology, protocol standardization, feasibility, and cost must all be taken into consideration. Above all, the ''optimal'' biomarker will depend on its ultimate clinical use. The use of a biomarker as a surrogate clinical endpoint requires constant reevaluation, as our understanding of biological processes underlying pathology evolve.[87]

In this review, we have covered the biological and statistical considerations relevant to identifying valid and reliable biomarkers. In each category of biomarker assessment (neuroimaging, proteomic, and genomic), recent work has shown that in the discovery phase of biomarker evaluation, a multivariate approach appears to have greater predictive/prognostic efficacy than a single biomarker. Unsupervised, data-driven genomic and proteomic screens may provide a start for future hypothesis testing, and ultimately minimize bias. Imaging techniques are highly sensitive and specific for certain neuropathologies, but in cases of mild TBI where standard CT is likely to be negative, a combined imaging approach that utilizes both standard and advanced MRI techniques in conjunction with CT may provide more prognostic resolution.

Biomarkers also will play a critical role in our advancement toward personalized medicine. Biomarkers can act not only as a surrogate for a clinical outcome measure, but also as a tool for therapeutic decision-making. When used to aid predictive enrichment in clinical trials, biomarkers can help to identify whether patients have a biological predisposition to respond to a particular therapy.

To realize the potential for biomarkers to aid in diagnosis, prognosis, and therapeutic decision-making will ultimately require well-established data standards and consensus recommendations for context-dependent use. Promising strides have been made to this end, including the establishment of the TBI Common Data Elements standards. Likewise, large multi-center trials that collecte, curate, and analyze data under common standards are also key to generating the necessary statistical power needed to determine biomarker efficacy and validation. The studies conducted by CENTER-TBI, TRACK-TBI, CREACTIVE, and ADAPT have shown promise that such large undertakings can provide fruitful findings. Continued and expanded efforts along these lines will be essential for TBI biomarker discovery, validation, and implementation.

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The TRACK-TBI Investigators

Opeolu Adeoye, University of Cincinnati, Cincinnati, OH; Neeraj Badjatia, University of Maryland, College Park, MD; Kim Boase, University of Washington, Seattle, WA; Yelena Bodien,

Massachusetts General Hospital, Boston, MD; M. Ross Bullock, University of Miami, Miami, FL; Randall Chesnut, University of Washington, Seattle, WA; John D. Corrigan, Ohio State University, Columbus, OH; Karen Crawford, University of Southern California, Los Angeles, CA; Ramon Diaz-Arrastia, University of Pennsylvania, Philadelphia, PA; Sureyya Dikmen, University of Washington, Seattle, WA; Ann-Christine Duhaime, Massachusetts General Hospital, Boston, MA; Richard Ellenbogen, University of Washington, Seattle, WA; V. Ramana Feeser, Virginia Commonwealth University, Richmond, VA; Brandon Foreman, University of Cincinnati, Cincinnati, OH; Raquel Gardner, University of California, San Francisco, San Francisco CA; Etienne Gaudette, University of Southern California, Los Angeles, CA; Joseph Giacino, Spaulding Rehabilitation Hospital, Boston, MA; Dana Goldman, University of Southern California, Los Angeles, CA; Luis Gonzalez, TIRR Memorial Hermann, Houston, TX; Shankar Gopinath, Baylor College of Medicine, Houston, TX; Rao Gullapalli, University of Maryland, College Park, MD; J. Claude Hemphill, University of California, San Francisco, San Francisco, CA; Gillian Hotz, University of Miami, Miami, FL; Sonia Jain, University of California, San Diego, San Diego, CA; Frederick Korley, University of Michigan, Ann Arbor, MI; Joel Kramer, University of California, San Francisco, San Francisco, CA; Natalie Kreitzer, University of Cincinnati, Cincinnati, OH; Harvey Levin, Baylor College of Medicine, Houston, TX; Christopher J. Lindsell, Vanderbilt University, Nashville, TN; Joan Machamer, University of Washington, Seattle, WA; Christopher Madden, UT Southwestern, Dallas,TX; Geoffrey T. Manley, University of California, San Francisco, San Francisco, CA; Alastair Martin, University of California, San Francisco, San Francisco, CA; Thomas McAllister, Indiana University, IN; Michael McCrea, Medical College of Wisconsin, Milwaukee, WI; Randall Merchant, Virginia Commonwealth University, Richmond, VA; Pratik Mukherjee, University of California, San Francisco, San Francisco, CA; Lindsay Nelson, Medical College of Wisconsin, Milwaukee, WI; Laura B. Ngwenya, Univesity of Cincinnati, Cincinnati, OH; Florence Noel, Baylor College of Medicine, Houston, TX; David Okonkwo, University of Pittsburgh, Pittsburgh, PA; Eva Palacios, University of California, San Francisco, San Francisco, CA; Daniel Perl, Uniformed Services University, Bethesda, MD; Ava Puccio, University of Pittsburgh, Pittsburgh, PA; Miri Rabinowitz, University of Pittsburgh, Pittsburgh, PA; Claudia Robertson, Baylor College of Medicine, Houston, TX; Jonathan Rosand, Massachusetts General Hospital, Boston, MA; Angelle Sander, Baylor College of Medicine, Houston, TX; Gabriella Satris, University of California, San Francisco, San Francisco, CA; David Schnyer, University of Texas, Austin, TX; Seth Seabury, University of Southern California, Los Angeles, CA; Murray Stein, University of California, San Diego, San Diego, CA; Sabrina Taylor, University of California, San Francisco, San Francisco, CA; Nancy Temkin, University of Washington, Seattle, WA; Arthur Toga, University of Southern California, Los Angeles, CA; Alex Valadka, Virginia Commonwealth University, Richmond, VA; Mary Vassar, University of California, San Francisco, San Francisco, CA; Paul Vespa, University of California, Los Angeles, Los Angeles, CA; Kevin Wang, University of Florida, Gainsville, FL; John K. Yue, University of California, San Francisco, CA; Ross Zafonte, Harvard Medical School, Boston, MA.

The CENTER-TBI Participants and Investigators

Cecilia Ackerlund, Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden; Hadie Adams, Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital and University of Cambridge, Cambridge, UK; Vanni Agnoletti, Department of Anesthesia and Intensive Care, M. Bufalini Hospital, Cesena, Italy; Judith Allanson, Department of Clinical Neurosciences, Addenbrooke's Hospital and University of Cambridge, Cambridge, UK; Krisztina Amrein, János Szentágothai Research Centre, University of Pécs, Pécs, Hungary; Norberto Andaluz, University of Cincinnati, Cincinnati, Ohio; Nada Andelic, Division of Surgery and Clinical Neuroscience, Department of Physical Medicine and Rehabilitation, Oslo University Hospital and University of Oslo, Oslo, Norway; Lasse Andreassen, Department of Neurosurgery, University Hospital Northern Norway, Tromso, Norway; Audny Anke, Department of Physical Medicine and Rehabilitation, University Hospital Northern Norway; Azasevac Antun, Department of Neurosurgery, Clinical Centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia; Anna Antoni, Trauma Surgery, Medical University Vienna, Vienna, Austria; Hilko Ardon, Department of Neurosurgery, Elisabeth-Tweesteden Ziekenhuis, Tilburg, the Netherlands; Gérard Audibert, Department of Anesthesiology and Intensive Care, University Hospital Nancy, Nancy, France; Kaspars Auslands, Riga Eastern Clinical University Hospital, Riga, Latvia; Philippe Azouvi, Raymond Poincare Hospital, Assistance Publique–Hopitaux de Paris, Paris, France; Maria Luisa Azzolini, Department of Anesthesiology and Intensive Care, S Raffaele University Hospital, Milan, Italy; Camelia Baciu, NeuroIntensive Care, Niguarda Hospital, Milan, Italy; Rafael Badenes, Department Anesthesiology and Surgical-Trauma Intensive Care, Hospital Clinic Universitari de Valencia, Spain; Ronald Bartels, Department of Neurosurgery, Radboud University Medical Center, Nijmegen, the Netherlands; Pál Barzó, Department of Neurosurgery, University of Szeged, Szeged, Hungary; Ursula Bauerfeind, Institute for Transfusion Medicine (ITM), Witten/-Herdecke University, Cologne, Germany; Romuald Beauvais, International Projects Management, ARTTIC, Munchen, Germany; Ronny Beer, Department of Neurology, Neurological Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria; Francisco Javier Belda, Department Anesthesiology and Surgical-Trauma Intensive Care, Hospital Clinic Universitari de Valencia, Spain; Bo Michael Bellander, Department of Neurosurgery and Anesthesia and Intensive Care Medicine, Karolinska University Hospital, Stockholm, Sweden; Antonio Belli, NIHR Surgical Reconstruction and Microbiology Research Centre, Birmingham, UK; Rémy Bellier, Intensive Care Unit, CHU Poitiers, Poitiers, France; Habib Benali, Anesthesie-Réanimation, Assistance Publique–Hopitaux de Paris, Paris, France; Thierry Benard, Intensive Care Unit, CHU Poitiers, Poitiers, France; Maurizio Berardino, Department of Anesthesia and ICU, AOU Città della Salute e della Scienza di Torino- Orthopedic and Trauma Center, Torino, Italy; Luigi Beretta, Department of Anesthesiology and Intensive Care, S Raffaele University Hospital, Milan, Italy; Christopher Beynon, Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany; Federico Bilotta, Department Anesthesiology and Surgical-Trauma Intensive Care, Hospital Clinic Universitari de Valencia, Spain; Harald Binder, Trauma Surgery, Medical University Vienna, Vienna, Austria; Erta Biqiri, NeuroIntensive Care, Niguarda Hospital, Milan, Italy; Morten Blaabjerg, Department of Neurology, Odense University Hospital, Odense, Denmark; Hugo den Boogert, Department of Neurosurgery, Radboud University Medical Center, Nijmegen, the Netherlands; Pierre Bouzat, Department of Anesthesiology and Intensive Care, University Hospital of Grenoble, Grenoble, France; Peter

Bragge, BehaviourWorks Australia, Monash Sustainability Institute, Monash University, Victoria, Australia; Alexandra Brazinova, Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia; Vibeke Brinck, Quesgen Systems Inc., Burlingame, CA; Joanne Brooker, Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia; Camilla Brorsson, Department of Neurosurgery, Umea University Hospital, Umea, Sweden; Andras Buki, Department of Neurosurgery, Hungarian Brain Research Program and Janos Szentagothai Research Centre, Medical School, University of Pecs and MTA-PTE Clinical Neuroscience MR Research Group, Pecs, Hungary; Monika Bullinger, Department of Medical Psychology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; Manuel Cabeleira, Brain Physics Lab, Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Emiliana Calappi, Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; Maria Rosa Calvi, Department of Anesthesiology and Intensive Care, S Raffaele University Hospital, Milan, Italy; Peter Cameron, ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Australia; Lozano Guillermo Carbayo, Department of Neurosurgery, Hospital of Cruces, Bilbao, Spain; Marco Carbonara, Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; Elsa Carise, Intensive Care Unit, CHU Poitiers, Poitiers, France; K. Carpenter, Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, the Netherlands; Ana M. Castaño León, Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain; Francesco Causin, Department of Neuroscience, Azienda Ospedaliera Università di Padova, Padova, Italy; Giorgio Chevallard, NeuroIntensive Care, Niguarda Hospital, Milan, Italy; Arturo Chieregato, NeuroIntensive Care, Niguarda Hospital, Milan, Italy; Giuseppe Citerio, NeuroIntensive Care, ASST di Monza, Monza, Italy and School of Medicine and Surgery, Università Milano Bicocca, Milano, Italy; Maryse Cnossen, Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, the Netherlands; Mark Coburn, Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany; Jonathan Coles, Department of Anesthesia and Neurointensive Care, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK; Lizzie Coles-Kemp, Movement Science Group, Oxford Institute of Nursing, Midwifery and Allied Health Research, Oxford Brookes University, Oxford, UK; Johnny Collett, Movement Science Group, Oxford Institute of Nursing, Midwifery and Allied Health Research, Oxford Brookes University, Oxford, UK; Jamie D. Cooper, School of Public Health and PM, Monash University and the Alfred Hospital, Melbourne, Australia; Marta Correia, Radiology/MRI Department, MRC Cognition and Brain Sciences Unit, Cambridge, UK; Amra Covic, Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany; Nicola Curry, Oxford University Hospitals NHS Trust, Oxford, UK; Endre Czeiter, Department of Neurosurgery, Hungarian Brain Research Program and Janos Szentagothai Research Centre, Medical School, University of Pecs and MTA-PTE Clinical Neuroscience MR Research Group, (Grant No. KTIA 13 NAP-A-II/8), Pecs, Hungary; Marek Czosnyka, Brain Physics Lab, Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Claire Dahyot Fizelier, Intensive care Unit, CHU Poitiers, Poitiers, France; François Damas, Intensive Care Unit, CHR Citadelle, Liège, Belgium; Pierre Damas, Intensive Care Unit, CHU, Liège, Belgium; Helen Dawes, Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK; Véronique De Keyser, Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium; Francesco Della Corte, Department of Anesthesia and Intensive Care, Maggiore Della Carità Hospital, Novara, Italy; Bart Depreitere, Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium; Godard C.W. de Ruiter, Department of Neurosurgery, Leiden University Medical Center, Leiden, the Netherlands, and Department of Neurosurgery, Medical Center Haaglanden, the Hague, the Netherlands; Dula Dilvesi, Department of Neurosurgery, Clinical Centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia; Shenghao Ding, Department of Neurosurgery, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; Diederik Dippel, Department of Neurology, Erasmus MC, Rotterdam, the Netherlands; Abhishek Dixit, Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Emma Donoghue, ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Australia; Jens Dreier, Neurologie, Neurochirurgie und Psychiatrie, Charité—Universitätsmedizin Berlin, Berlin, Germany; Guy Loup Dulière, Intensive Care Unit, CHR Citadelle, Liège, Belgium; Heiko Engemann, Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany; Ari Ercole, Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Patrick Esser, Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK; Erzsébet Ezer, Department of Anaesthesiology and Intensive Therapy, University of Pécs, Pécs, Hungary; Martin Fabricius, Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark; Valery L. Feigin, National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand; Junfeng Feng, Department of Neurosurgery, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; Kelly Foks, Department of Neurology, Erasmus MC, Rotterdam, the Netherlands; Francesca Fossi, NeuroIntensive Care, Niguarda Hospital, Milan, Italy; Gilles Francony, Department of Anesthesiology and Intensive Care, University Hospital of Grenoble, Grenoble, France; Ulderico Freo, Department of Medicine, Azienda Ospedaliera Università di Padova, Padova, Italy; Shirin Frisvold, Department of Anesthesiology and Intensive Care, University Hospital Northern Norway, Tromso, Norway; Alex Furmanov, Department of Neurosurgery, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; Pablo Gagliardo, Fundación Instituto Valenciano de Neurorrehabilitación (FIVAN), Valencia, Spain; Damien Galanaud, Anesthesie-Réanimation, Assistance Publique–Hopitaux de Paris, Paris, France; Dashiell Gantner, ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Australia; Guoyi Gao, Department of Neurosurgery, Shanghai Renji Hospital, Shanghai Jiaotong University/School of Medicine, Shanghai, China; Karin Geleijns, Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, the Netherlands; Pradeep George, Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden; Alexandre Ghuysen, Emergency Department,

CHU, Liège, Belgium; Lelde Giga, Pauls Stradins Clinical University Hospital, Riga, Latvia; Benoit Giraud, Intensive Care Unit, CHU Poitiers, Poitiers, France; Ben Glocker, Department of Computing, Imperial College London, London, UK; Jagos Golubovic, Department of Neurosurgery, Clinical Centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia; Pedro A. Gomez, Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain; Benjamin Gravesteijn, Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, the Netherlands; Francesca Grossi, Department of Anesthesia and Intensive Care, Maggiore Della Carità Hospital, Novara, Italy; Russell L. Gruen, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, and Monash University, Australia; Deepak Gupta, Department of Neurosurgery, Neurosciences Centre and JPN Apex Trauma Centre, All India Institute of Medical Sciences, New Delhi, India; Juanita A. Haagsma, Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, the Netherlands; Asta Kristine Håberg, Division of Psychology, University of Stirling, Stirling, UK; Bram Jacobs, Department of Neurology, University Medical Center Groningen, Groningen, the Netherlands; Iain Haitsma, Department of Neurosurgery, Erasmus MC, Rotterdam, the Netherlands; Jed A. Hartings, Department of Neurosurgery, University of Cincinnati, Cincinnati, OH; Raimund Helbok, Department of Neurology, Neurological Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria; Eirik Helseth, Department of Neurosurgery, Oslo University Hospital, Oslo, Norway; Daniel Hertle, Department of Neurology, Odense University Hospital, Odense, Denmark; Astrid Hoedemaekers, Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, the Netherlands; Stefan Hoefer, Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany; Lindsay Horton, Division of Psychology, University of Stirling, Stirling, UK; Jilske Huijben, Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, the Netherlands; Peter J. Hutchinson, Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital and University of Cambridge, Cambridge, UK; Stefan Jankowski, Neurointensive Care, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; Mike Jarrett, Quesgen Systems Inc., Burlingame, CA; Bojan Jelaca, Department of Neurosurgery, Clinical Centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia; Ji yao Jiang, Department of Neurosurgery, Shanghai Renji Hospital, Shanghai Jiaotong University/School of Medicine, Shanghai, China; Kelly Jones, National Institute for Stroke and Applied Neurosciences of the AUT University, Auckland, New Zealand; Konstantinos Kamnitsas, Department of Computing, Imperial College London, London, UK; Mladen Karan, University of Cincinnati, Cincinnati, OH; Ari Katila, Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital and University of Turku, Turku, Finland; Maija Kaukonen, Helsinki University Central Hospital, Finland; Thomas Kerforne, Intensive Care Unit, CHU Poitiers, Poitiers, France; Riku Kivisaari, Helsinki University Central Hospital, Finland; Angelos G. Kolias, Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital and University of Cambridge, Cambridge, UK; Bálint Kolumbán, Hungarian Brain Research Program-Grant No. KTIA 13 NAP-A-II/8, University of Pécs, Pécs, Hungary; Erwin Kompanje, Department of Intensive Care and Department of Ethics and Philosophy of Medicine, Erasmus Medical Center, Rotterdam, the Netherlands; Ksenija Kolundzija, Department of Psichiatry, Clinical Centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia; Daniel Kondziella, Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark; Lars Owe Koskinen, Department of Neurosurgery, Umea University Hospital, Umea, Sweden; Noémi Kovács, Hungarian Brain Research Program-Grant No. KTIA 13 NAP-A-II/8, University of Pécs, Pécs, Hungary; Alfonso Lagares, Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain; Linda Lanyon, Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden; Steven Laureys, Cyclotron Research Center, University of Liège, Liège, Belgium; Fiona Lecky, Emergency Medicine Research in Sheffield, Health Services Research Section, School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK; Christian Ledig, Department of Computing, Imperial College London, London, UK; Rolf Lefering, Institute of Research in Operative Medicine (IFOM), Witten/Herdecke University, Cologne, Germany; Valerie Legrand, VP Global Project Management CNS, ICON, Paris, France; Jin Lei, Department of Neurosurgery, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; Leon Levi, Department of Neurosurgery, Rambam Medical Center, Haifa, Israel; Roger Lightfoot, Department of Anesthesiology and Intensive Care, University Hospitals Southhampton NHS Trust, Southhampton, UK; Hester Lingsma, Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, the Netherlands; Dirk Loeckx, icoMetrix NV, Leuven, Belgium; Angels Lozano, Department Anesthesiology and Surgical-Trauma Intensive Care, Hospital Clinic Universitari de Valencia, Spain; Andrew I.R. Maas, Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium; Stephen MacDonald, Cambridge University Hospitals, Cambridge, UK; Marc Maegele, Cologne-Merheim Medical Center (CMMC), Department of Traumatology, Orthopedic Surgery and Sportmedicine, Witten/Herdecke University, Cologne, Germany; Majdan Marek, Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia; Sebastian Major, Centrum für Schlaganfallforschung, Charité—Universitätsmedizin Berlin, Berlin, Germany; Alex Manara, Intensive Care Unit, Southmead Hospital, Bristol, Bristol, UK; Geoffrey Manley, Department of Neurological Surgery, University of California, San Francisco, CA; Didier Martin, Department of Neurosurgery, CHU, Liège, Belgium; Leon Francisco Martin, icoMetrix NV, Leuven, Belgium; Costanza Martino, Department of Anesthesia and Intensive Care, M. Bufalini Hospital, Cesena, Italy; Hugues Maréchal, Intensive Care Unit, CHR Citadelle, Liège, Belgium; Armando Maruenda, Department Anesthesiology and Surgical-Trauma Intensive Care, Hospital Clinic Universitari de Valencia, Spain; Alessandro Masala, Department of Anesthesia and Intensive Care, M. Bufalini Hospital, Cesena, Italy; Julia Mattern, Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany; Charles McFadyen, Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Catherine McMahon, Department of Neurosurgery, the Walton Centre NHS Foundation Trust, Liverpool, UK; Béla Melegh, Department of Medical Genetics, University of Pécs, Pécs, Hungary; David Menon, Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Tomas Menovsky, Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium; Cristina Morganti Kossmann, National Trauma Research Institute, the

Alfred Hospital, Monash University, Melbourne, Australia; Davide Mulazzi, Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; Holger Mühlan, Department Health and Prevention, University Greifswald, Greifswald, Germany; Visakh Muraleedharan, Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden; Lynnette Murray, ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Australia; Nandesh Nair, Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium; Ancuta Negru, Department of Neurosurgery, Emergency County Hospital Timisoara, Timisoara, Romania; David Nelson, Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden; Virginia Newcombe, Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Daan Nieboer, Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, the Netherlands; Quentin Noirhomme, Cyclotron Research Center, University of Liège, Liège, Belgium; József Nyirádi, János Szentágothai Research Centre, University of Pécs, Pécs, Hungary; Mauro Oddo, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; Annemarie Oldenbeuving, Department of Intensive Care, Elisabeth-Tweesteden Ziekenhuis, Tilburg, the Netherlands; Matej Oresic, Department of Systems Medicine, Steno Diabetes Center, Gentofte, Denmark; Fabrizio Ortolano, Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; Aarno Palotie, Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland, Analytic and Translational Genetics Unit, Department of Medicine, and Psychiatric and Neurodevelopmental Genetics Unit, Department of Psychiatry; Department of Neurology, Massachusetts General Hospital, Boston, MA, and Program in Medical and Population Genetics, the Stanley Center for Psychiatric Research, the Broad Institute of MIT and Harvard, Cambridge, MA; Paul M. Parizel, Department of Radiology, Antwerp University Hospital and University of Antwerp, Edegem, Belgium; Adriana Patruno, NeuroIntenisve Care Unit, Department of Anesthesia and Intensive Care, ASST di Monza, Monza, Italy; Jean François Payen, Department of Anesthesiology and Intensive Care, University Hospital of Grenoble, Grenoble, France; Natascha Perera, International Projects Management, ARTTIC, Munchen, Germany; Vincent Perlbarg, Anesthesie-Réanimation, Assistance Publique–Hopitaux de Paris, Paris, France; Paolo Persona, Department of Anesthesia and Intensive Care, Azienda Ospedaliera Università di Padova, Padova, Italy; Wilco Peul, Department of Neurosurgery, Leiden University Medical Center, Leiden, the Netherlands and Department of Neurosurgery, Medical Center Haaglanden, the Hague, the Netherlands; Anna Piippo-Karjalainen, Helsinki University Central Hospital, Finland; Floury Sébastien Pili, Intensive Care Unit, CHRU de Besançon, Besançon, France; Matti Pirinen, Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland; Horia Ples, Department of Neurosurgery, Emergency County Hospital Timisoara, Timisoara, Romania; Maria Antonia Poca, Department of Neurosurgery, Vall d'Hebron University Hospital, Barcelona, Spain; Suzanne Polinder, Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, the Netherlands; Inigo Pomposo, Department of Neurosurgery, Hospital of Cruces, Bilbao, Spain; Jussi Posti, Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Injury Centre, Turku University Hospital and University of Turku, Turku, Finland; Louis Puybasset, Department of Anesthesiology and Critical Care, Pitié-Salpêtrière Teaching Hospital, Assistance Publique, Hôpitaux de Paris and University Pierre et Marie Curie, Paris, France; Andreea Radoi, Department of Neurosurgery, Vall d'Hebron University Hospital, Barcelona, Spain; Arminas Ragauskas, Department of Neurosurgery, Kaunas University of Technology and Vilnius University, Vilnius, Lithuania; Rahul Raj, CHECK University Central Hospital, Finland; Malinka Rambadagalla, Rezekne Hospital, Latvia; Ruben Real, Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany; Veronika Rehorčíková, Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia; Jonathan Rhodes, Department of Anaesthesia, Critical Care and Pain Medicine NHS Lothian and University of Edinburg, Edinburgh, UK; Samuli Ripatti, Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland; Saulius Rocka, Department of Neurosurgery, Kaunas University of Technology and Vilnius University, Vilnius, Lithuania; Cecilie Roe, Department of Physical Medicine and Rehabilitation, Oslo University Hospital/University of Oslo, Oslo, Norway; Olav Roise, Division of Surgery and Clinical Neuroscience, Oslo University Hospital, Oslo, Norway; Gerwin Roks, Department of Neurology, Elisabeth-TweeSteden Ziekenhuis, Tilburg, the Netherlands; Jonathan Rosand, Broad Institute, Cambridge MA Harvard Medical School, Massachusetts General Hospital, Boston MA; Jeffrey Rosenfeld, National Trauma Research Institute, the Alfred Hospital, Monash University, Melbourne, Victoria, Australia; Christina Rosenlund, Department of Neurosurgery, Odense University Hospital, Odense, Denmark; Guy Rosenthal, Department of Neurosurgery, Hadassah-Hebrew University Medical center, Jerusalem, Israel; Rolf Rossaint, Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany; Sandra Rossi, Department of Anesthesia and Intensive Care, Azienda Ospedaliera Università di Padova, Padova, Italy; Daniel Rueckert, Department of Computing, Imperial College London, London, UK; Martin Rusnák, International Neurotrauma Research Organisation, Vienna, Austria; Marco Sacchi, NeuroIntensive Care, Niguarda Hospital, Milan, Italy; Barbara Sahakian, Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Juan Sahuquillo, Department of Neurosurgery, Vall d'Hebron University Hospital, Barcelona, Spain; Oliver Sakowitz, Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany, University Hospital Heidelberg, Heidelberg, Germany; Francesca Sala, NeuroIntenisve Care Unit, Department of Anesthesia and Intensive Care, ASST di Monza, Monza, Italy; Renan Sanchez Porras, Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany; Janos Sandor, Division of Biostatistics and Epidemiology, Department of Preventive Medicine, University of Debrecen, Debrecen, Hungary; Edgar Santos, Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany; Luminita Sasu, Department of Anesthesia and Intensive Care, Maggiore Della Carità Hospital, Novara, Italy; Davide Savo, NeuroIntenisve Care Unit, Department of Anesthesia and Intensive Care, ASST di Monza, Monza, Italy; Nadine Schäffer, Cologne-Merheim Medical Center (CMMC), Department of Traumatology, Orthopedic Surgery and Sportmedicine, Witten/Herdecke University, Cologne, Germany; Inger Schipper, Department of Traumasurgery, Leiden University Medical Center, Leiden, the Netherlands; Barbara Schlößer, Institute for Transfusion Medicine (ITM) , Witten/Herdecke University, Cologne, Germany; Silke Schmidt, Department Health and Prevention, University Greifswald, Greifswald, Germany; Herbert Schoechl, Department of Anaesthesiology and Intensive Care, AUVA Trauma Hospital, Salzburg, Austria; Guus Schoonman,

Department of Neurology, Elisabeth-TweeSteden Ziekenhuis, Tilburg, the Netherlands; Rico Frederik Schou, Department of Neuroanesthesia and Neurointensive Care, Odense University Hospital, Odense, Denmark; Elisabeth Schwendenwein, Trauma Surgery, Medical University Vienna, Vienna, Austria; Michael Schöll, Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany; Charlie Sewalt, Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, the Netherlands; Özcan Sir, Department of Emergency Care Medicine, Radboud University Medical Center, Nijmegen, the Netherlands; Toril Skandsen, Department of Physical Medicine and Rehabilitation, St. Olavs Hospital and Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway; Lidwien Smakman, Department of Neurosurgery, Leiden University Medical Center, Leiden, the Netherlands and Department of Neurosurgery, Medical Center Haaglanden, the Hague, the Netherlands; Dirk Smeets, icoMetrix NV, Leuven, Belgium; Peter Smielewski, Brain Physics Lab, Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Abayomi Sorinola, Department of Neurosurgery, University of Pécs, Pécs, Hungary; Emmanuel Stamatakis, Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Simon Stanworth, Oxford University Hospitals NHS Trust, Oxford, UK; Nicole Steinbüchel, Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany; Ana Stevanovic, Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany; Robert Stevens, Division of Neuroscience Critical Care, John Hopkins University School of Medicine, Baltimore, MD; William Stewart, Department of Neuropathology, Queen Elizabeth University Hospital and University of Glasgow, Glasgow, UK; Ewout W. Steyerberg, Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, the Netherlands, and Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands; Nino Stocchetti, Department of Pathophysiology and Transplantation, Milan University, and Neuroscience ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy; Nina Sundström, Department of Neurosurgery, Umea University Hospital, Umea, Sweden; Anneliese Synnot, Quesgen Systems Inc., Burlingame, CA, and Cochrane Consumers and Communication Review Group, Centre for Health Communication and Participation, School of Psychology and Public Health, La Trobe University, Melbourne, Australia; Fabio Silvio Taccone, Department Anesthesiology and Surgical-Trauma Intensive Care, Hospital Clinic Universitari de Valencia, Spain; Riikka Takala, Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital and University of Turku, Turku, Finland; Viktória Tamás, Department of Neurosurgery, University of Pécs, Pécs, Hungary; Päivi Tanskanen, Helsinki University Central Hospital, Finland; Mark Steven Taylor, Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia; Braden Te Ao, National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand; Olli Tenovuo, Division of Clinical Neurosciences, Turku Brain Injury Centre, Turku University Hospital, and Department of Neurology, University of Turku, Turku, Finland; Ralph Telgmann, Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany; Guido Teodorani, Department of Reahabilitation, M. Bufalini Hospital, Cesena, Italy; Alice Theadom, National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand; Matt Thomas, Intensive Care Unit, Southmead Hospital, Bristol, Bristol, UK; Dick Tibboel, Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, the Netherlands; Christos Tolias, Department of Neurosurgery, Kings College London, London, UK; Jean Flory Luaba Tshibanda, Radiology/MRI Department, CHU, Liège, Belgium; Tony Trapani, ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Australia; Cristina Maria Tudora, Department of Neurosurgery, Emergency County Hospital Timisoara, Romania; Peter Vajkoczy, Neurologie, Neurochirurgie und Psychiatrie, Charité—Universitätsmedizin Berlin, Berlin, Germany; Shirley Vallance, Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain; Egils Valeinis, Pauls Stradins Clinical University Hospital, Riga, Latvia; Gregory Van der Steen, Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium; Mathieu van der Jagt, Department of Intensive Care, Erasmus MC, Rotterdam, the Netherlands; Joukje van der Naalt, Department of Neurology, University Medical Center Groningen, Groningen, Netherlands; Jeroen T.J.M. van Dijck, Department of Neurosurgery, Leiden University Medical Center, Leiden, the Netherlands, and Department of Neurosurgery, Medical Center Haaglanden, the Hague, the Netherlands; Thomas A. van Essen, Department of Neurosurgery, Leiden University Medical Center, Leiden, the Netherlands, and Department of Neurosurgery, Medical Center Haaglanden, the Hague, the Netherlands; Wim Van Hecke, icoMetrix NV, Leuven, Belgium; Caroline van Heugten, Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK; Dominique Van Praag, Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium; Thijs Vande Vyvere, Department of Radiology, Antwerp University Hospital and University of Antwerp, Edegem, Belgium; Julia Van Waesberghe, Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany; Audrey Vanhaudenhuyse, Anesthesie-Réanimation, Assistance Publique–Hopitaux de Paris, Paris, France, and Cyclotron Research Center, University of Liège, Liège, Belgium; Alessia Vargiolu, NeuroIntenisve Care Unit, Department of Anesthesia and Intensive Care, ASST di Monza, Monza, Italy; Emmanuel Vega, Department of Anesthesiology-Intensive Care, Lille University Hospital, Lille, France; Kimberley Velt, Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, the Netherlands; Jan Verheyden, icoMetrix NV, Leuven, Belgium; Paul M. Vespa, Director of Neurocritical Care, University of California, Los Angeles, CA; Anne Vik, Department of Neurosurgery, St. Olavs Hospital and Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway; Rimantas Vilcinis, Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania; Giacinta Vizzino, NeuroIntensive Care, Niguarda Hospital, Milan, Italy; Carmen Vleggeert Lankamp, Department of Neurosurgery, Leiden University Medical Center, Leiden, the Netherlands, and Department of Neurosurgery, Medical Center Haaglanden, the Hague, the Netherlands; Victor Volovici, Department of Neurosurgery, Erasmus MC, Rotterdam, the Netherlands; Daphne Voormolen, Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, the Netherlands; Peter Vulekovic, Department of Neurosurgery, Clinical Centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia; Zoltán Vámos, Department of

Anaesthesiology and Intensive Therapy, University of Pécs, Pécs, Hungary; Derick Wade, Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK; Kevin K.W. Wang, Department of Psychiatry, University of Florida, Gainesville, FL; Lei Wang, Department of Neurosurgery, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; Lars Wessels, Interdisciplinary Neuro Intensive Care Unit, Charité—Universitätsmedizin Berlin, Berlin, Germany; Eveline Wiegers, Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, the Netherlands; Eno Wildschut, Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, the Netherlands; Guy Williams, Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Lindsay Wilson, Division of Psychology, University of Stirling, Stirling, UK; Maren K.L. Winkler, Centrum für Schlaganfallforschung, Charité—Universitätsmedizin Berlin, Berlin, Germany; Stefan Wolf, Interdisciplinary Neuro Intensive Care Unit, Charité—Universitätsmedizin Berlin, Berlin, Germany; Peter Ylén, VTT Technical Research Centre, Tampere, Finland; Alexander Younsi, Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany; Menashe Zaaroor, Department of Neurosurgery, Rambam Medical Center, Haifa, Israel; Frederik Zeiler, Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Yang Zhihui, University of Florida, Gainesville, FL; Agate Ziverte, Pauls Stradins Clinical University Hospital, Riga, Latvia; Fabrizio Zumbo, Department of Anesthesia and Intensive Care, M. Bufalini Hospital, Cesena, Italy.

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Address correspondence to:
Adam R. Ferguson, PhD
Brain and Spinal Injury Center
University of California, San Francisco
1001 Potrero Avenue
Building 1, Room 101
San Francisco, CA 94110
USA

E-mail: Adam.ferguson@ucsf.edu