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SPECIAL REPORT

A consensus roadmap for post-traumatic epilepsy: Clinical biomarkers, research priorities, policy barriers, and pathways to interventional trials

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Abstract

Understanding the mechanisms underlying post-traumatic epilepsy (PTE) following traumatic brain injury (TBI), and developing strategies to prevent or modify its progression, has been the focus of large collaborative efforts within the epilepsy and TBI research communities for over a decade. However, to date, preclinical and clinical researchers with expertise in these areas have not formally convened to discuss ways to move the field forward. To enable communication and collaboration, scientific experts as well as individuals with lived experience of PTE were gathered during the inaugural International Conference on Post-Traumatic Epilepsy (IC-PTE) held in Milan, Italy, in May 2024, to identify challenges and solutions for advancing research toward clinical trials. The IC-PTE focused on potential therapeutic approaches, clinical and preclinical biomarker discovery, and methods to predict PTE risk early following TBI, which is an important consideration in clinical trial design. In addition, conference attendees discussed animal model development with a focus on clinically relevant translational endpoints and data harmonization and sharing across the PTE research community. This article identifies recommendations for the field and outlines a strategic roadmap for interventional trials targeting PTE.

KEYWORDS
biomarkers, clinical trials, lived experience, new therapies, post-traumatic epilepsy

1 | INTRODUCTION

In this article, we present an expert consensus–informed perspective on post-traumatic epilepsy (PTE), derived from multidisciplinary discussions and recommendations emerging from the inaugural International Conference on Post-Traumatic Epilepsy (IC-PTE). Traumatic brain injury (TBI) is defined as a disruption in normal brain function caused by an external force,[1] such as blunt trauma, penetrating injuries, or blast waves, resulting in damage to cerebral tissue and impairing normal cellular function.[2] Approximately 69 million people worldwide experience TBI annually,[3,4] with more than 150 000 fatalities between Europe and the United States.[5,6] TBI severity is traditionally classified as mild, moderate, or severe, with the Glasgow Coma Scale (GCS) serving as the gold standard for assessing consciousness. Recent efforts have advocated for the development of a more comprehensive TBI classification framework based on integration of clinical data, blood-based biomarkers, neuroimaging, and neurological outcome assessments.[7,8] TBI is now recognized as a chronic and, in many cases, progressive neurological disease.[9] Beyond its immediate impact, TBI triggers progressive neuropathophysiological changes, including white matter degeneration, neuronal loss, proteinopathies, and neuroinflammation.[10,11]

Key points

- Novel therapeutic strategies, predictive modeling, and biomarker integration are essential for driving innovation in post-traumatic epilepsy (PTE) prevention research.
- Advances in preclinical models, coupled with efforts in data standardization and harmonization, are strengthening translational research.
- Collaboration with industry partners and incorporating perspectives of individuals with lived experience is central to shaping trial feasibility, the relevance of research outcomes, and dissemination.
- Devising a coordinated roadmap will accelerate clinical trials aimed at preventing PTE.

Among the potential long-term consequences is the development of PTE, defined as the occurrence of unprovoked seizures more than 7 days post-injury ("late seizures").[12,13] The International League Against Epilepsy (ILAE) defines epilepsy as having two unprovoked seizures occurring more than 24 h apart, or having one

unprovoked seizure with a probability of further seizures similar to the general recurrence risk after two unprovoked seizures, which is at least 60% over the next 10 years.[14] Because TBI greatly raises the risk of seizure recurrence, even a single unprovoked late seizure qualifies as epilepsy according to ILAE criteria. Defining the risk factors for PTE is critical; penetrating head injuries carry the greatest risk for PTE, followed by severe and moderate TBI.[15–17] Intracranial bleeding, brain contusions, cranial surgery, early seizures, and depressed skull fracture increase the likelihood of PTE.[18] PTE leads to an array of complex comorbidities that extend beyond seizures, including mental health disorders and cognitive dysfunction, as well as a higher risk of experiencing drug-resistant epilepsy. These complex comorbidities and drug resistance have significant impacts on patients and their caregivers,[18–21] calling for comprehensive studies on the burden of PTE and effective PTE prevention. Patient and public involvement remains inconsistently reported across randomized controlled trials (RCTs), including large intensive care unit (ICU) trials. Because PTE trials are burden-intensive and enroll populations with substantial comorbidity and participation barriers, stakeholder-engaged design[22] can improve feasibility, outcome relevance, and dissemination.[23,24]

Despite major collaborative efforts in PTE research, such as CURE Epilepsy's PTE Initiative, the National Institute of Neurological Disorders and Stroke (NINDS)–funded Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EPiBioS4Rx), and others, there has been no dedicated forum for preclinical and clinical experts to jointly define a path forward to developing a plan for interventional trials to prevent PTE. To address this gap, the IC-PTE was held in Milan in May 2024, convening researchers and individuals with lived experience of PTE. The individuals with lived experience of PTE, along with care-partners/advocates, participated in cross-session discussion and informed discourse of person-centered outcome selection, trial burden and acceptability, culturally responsive communication, and dissemination to address existing gaps[23,25]. We summarize and highlight key themes of the lived experience of an attendee (Box 1) and actionable engagement practices (Box 2) to support reproducible integration of stakeholder perspectives in future PTE trials.

This report reflects expert consensus on both the urgency and opportunities to advance PTE prevention through coordinated basic, clinical, and translational efforts. Although challenges remain—including trial design complexity, limited validated biomarkers, and insufficient investment (Figure 1)—recent advances in therapeutic development, predictive modeling, and biomarker discovery provide a strong foundation for progress (Table 1).

BOX 1 Illustrative Example of a Lived Experience with PTE

Summary: Capt. Somers, an individual living with post-traumatic epilepsy (PTE), described the long latency between traumatic brain injury (TBI) and the eventual diagnosis of PTE, the cumulative burden of recurrent seizures and treatment changes, and the day-to-day impacts of medication side effects, cognitive and behavioral symptoms, and social isolation. Their perspective emphasized the importance of research that prioritizes meaningful outcomes for individuals and families living with PTE, alongside earlier identification of high-risk patients and prevention-focused trials.

Curated reflective quotes (from the lived experience statement in Box S1):

- **Event impact on TBI recovery and seizure onset**: "My life was forever changed when I experienced my first seizure ... just 60 days after returning home."
- **Uncertainty of seizure burden and care journey**: "Over the years, I have endured over 100 seizures and navigated approximately 50 different treatment plans."
- **Psychosocial and treatment burden**: "The constant challenges of medication side effects, cognitive and behavioral struggles, and ... isolation ..."
- **Meaning-making, hope and vision**: "This work represents a crucial step toward ... developing life-changing treatments and support for families."

2 | ROADMAPS FOR ADVANCING INTERVENTIONAL TRIALS FOR PTE

The latency between TBI and PTE provides a critical therapeutic window during which targeted interventions may prevent or mitigate PTE development.[26,27] Several therapeutic compounds, ranging from novel agents to repurposed U.S. Food and Drug Administration (FDA)–approved drugs, have shown promise in preclinical acquired epilepsy models, particularly status epilepticus (SE) and temporal lobe epilepsy (TLE), and may be appropriate for testing in populations at risk for PTE.[28,29] However, clinical translation remains elusive due to major translational roadblocks. Herein we discuss therapeutic compounds that have demonstrated promise to date and summarize the current state of the art of therapeutic developments,

BOX 2 Key Implementation-Oriented Checklist for Engaging the Lived Experience Community in PTE Research

1) **Equitable Stakeholder Engagement:** Foster and value multi-level stakeholder collaboration from initial conceptualization through implementation and dissemination.
2) **Community-Informed, Person-Centered Design:** Solicit and incorporate community input on study design, such as randomized controlled trial (RCT) versus pragmatic trial approaches. Where feasible, person-centered outcome selection should be co-developed with lived experience stakeholders to ensure relevant measures and minimize burden. To effectively achieve this, provide tiered participation opportunities to reflect different levels of interest, expertise, and availability.
3) **Culturally Responsive Communication:** Develop clear, accessible, and culturally sensitive health education, research and clinical trial materials. Use inclusive public messaging that respects language, cultural norms, and sensitive to health literacy levels.
4) **Change Facilitation and Knowledge Sharing:** Identify and address systemic barriers, including incentives that sustain non–value-added practices by planting the seeds for change early and throughout the research lifecycle. Create and share evidence-based, actionable tools, resources, and consensus-driven design and implementation recommendations.

A recommendation from the IC-PTE 2024 proceedings is to establish panels and, where possible, a network of people with PTE, families and caregivers, to contribute their perspectives that could shape research design, outcomes, and drive greater awareness of the issues faced by those impacted by PTE.

highlighting the urgent need to overcome translational barriers and outlining consensus-driven solutions.

2.1 | State of the art

Several therapies have shown promise in standard rodent models of epileptogenesis, as anti-inflammatory and anti-oxidant drugs that have demonstrated efficacy in reducing seizure development and disease progression.[30–33] However, few studies have directly evaluated anti-seizure medications (ASMs) in PTE rodent models, although preliminary findings suggest some may have disease-modifying effects.[26,34–36] Table 2 summarizes both repurposed and novel agents tested for antiepileptogenesis, thus preventing PTE onset, as well as disease-modifying effects, including reductions in seizure burden and neurological sequelae, in rodent PTE models (with post-SE TLE models included for comparison) together with clinical data.

Levetiracetam (LEV), for example, showed a positive trend in a clinical trial,[44] supported by preclinical data,[45] and is currently under reevaluation in the fluid percussion injury (FPI) model in rats by the EpiBioS4Rx consortium.[46] Other repurposed drugs with differing mechanisms of action have also shown disease-modification effects in rodent models of PTE. Increasing evidence further supports a "network pharmacology" approach, in which combinations of drug regimens targeting complementary epileptogenic pathways might be superior in preventing epilepsy compared to monotherapies.[47] This conceptualization for treatment has led to the identification of several promising drug combinations.[48] Notably a cocktail combining LEV and atorvastatin with ceftriaxone but not with topiramate, exhibited anti-epileptogenic effects in both intrahippocampal kainate SE and FPI rodent models, and is now being tested in the controlled cortical impact (CCI) mouse and zebrafish models as a precursor to clinical trials.[43] Of note, the therapeutic effects were dose-dependent, and the drug concentrations achieved in preclinical studies were within the human therapeutic range, supporting translational feasibility.[43,49]

Beyond repurposed drugs, several new molecules are also under investigation (Table 2). These include the janus kinase/signal transducer and activator of transcription (JAK/STAT) inhibitor WP1066 and the Wnt10B modulator PP-4-one, which downregulate the mechanistic target of rapamycin (mTOR) pathway and suppress iNOS and N-methyl-D-aspartate receptor subunit-1 (NMDA-NR1) expression in PTE rats[50] by exerting disease-modifying effects in vivo. The T-type calcium channel antagonist Z944 is currently being evaluated in a rat FPI model, prompted by its disease-modifying effects observed in a post-SE model of TLE.[51]

2.2 | Challenges and solutions

Despite promising preclinical advances, therapeutic development for PTE remains complex. The field is energized by a renewed sense of urgency that is driving more coordinated efforts to overcome longstanding barriers.

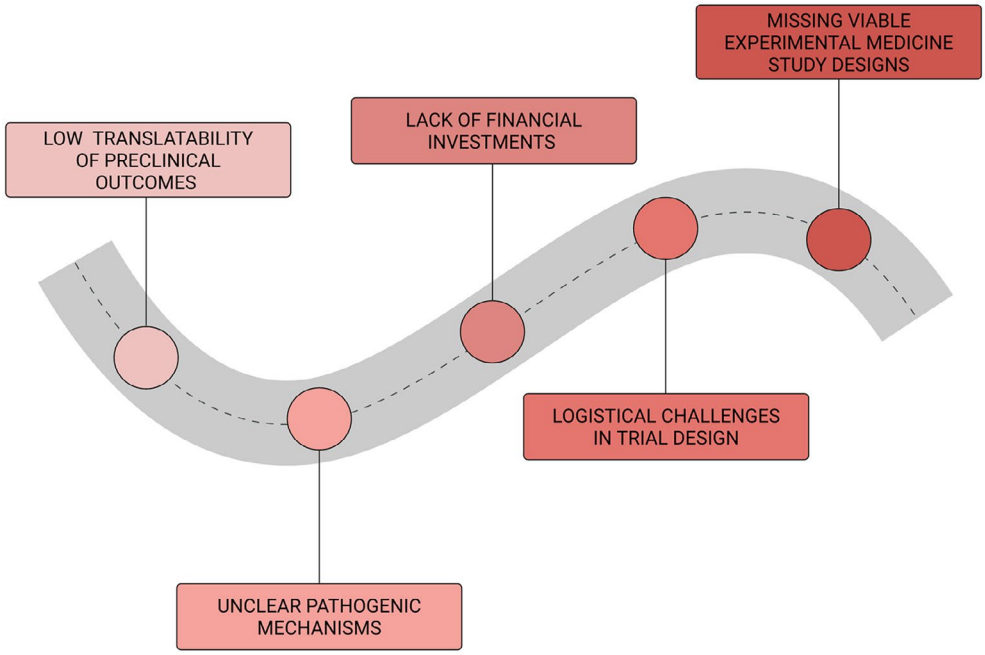

FIGURE 1 Barriers to design, execution, and translation of PTE interventional trials. Despite promising preclinical results for PTE interventions, clinical translation remains elusive. The major roadblocks to clinical translation identified in the IC-PTE conference encompass low translatability of clinical outcomes, incomplete understanding of epileptogenic mechanisms, lack of financial investments, logistical challenges in trial design linked to low PTE rate and long follow-ups required, and the lack of viable proof of concept studies paralleling biomarker discovery and therapeutic outcomes, with adaptive study design. Created with Biorender. IC-PTE, international conference on post-traumatic epilepsy; PTE, post-traumatic epilepsy.

TABLE 1 Summary of five key focus areas highlighting the current state of the art, major challenges, and consensus-driven solutions.

Key areas	State of the art	Major challenges	Consensus-driven solutions
Therapeutics	Repurposed and novel agents show disease-modifying effects in rodent PTE models; emerging evidence for combination therapies	Poor translation from preclinical models to clinical trials; limited PK/PD data; uncertainty around optimal therapeutic window; lack of proof-of-concept clinical studies	Establish coordinated preclinical testing networks; align animal models with human PTE using biomarkers; prioritize experimental medicine studies
Neuroimaging biomarkers	Classic and advanced imaging can identify structural and inflammatory changes linked to PTE	Low incidence of PTE requires long, multicenter studies; limited standardization; advanced imaging not universally available	Multimodal biomarkers integration; develop tiered, risk-based biomarker strategies and evaluate biomarkers as surrogate pharmacodynamic endpoints; prioritize mechanistic biomarkers validated in preclinical models; establish standardized, AI-enabled analyses pipelines
EEG biomarkers	Acute and subacute EEG abnormalities predict PTE risk; preclinical models identify prognostic value of HFOs, spiking activity and network-level changes	Variable methodologies; limited early EEG use; labor-intensive analysis	
Proteomic blood biomarkers	Limited information from single injury and inflammatory proteins; growing interest in multimodal biomarker panels	CNS-specificity of blood biomarkers; variability across assays and study populations; confounding factors (i.e., age, sex, injury severity, comorbidities)	
Data sharing and harmonization	FITBIR and DABI demonstrate feasibility of harmonized, multi-site data integration	Heterogeneous datasets; sustainability and interoperability barriers	Develop PTE-specific Common Data Elements; establish FAIR-compliant, cloud-based infrastructures

Note: The table synthesizes recent advances in therapeutic development, predictive modeling and biomarker discovery that together provide a strong foundation for future progress.

Abbreviations: AI, artificial intelligence; CNS; central nervous system; DABI, data archive for brain injury; EEG, electroencephalography; FITBIR, federal interagency traumatic brain injury research; HFO, high-frequency oscillation; PTE, post-traumatic epilepsy

TABLE 2 Antiepileptogenic and/or disease-modifying effects of drugs in chronic rodent models of acquired epilepsy and, if available, post-traumatic epilepsy trials in humans.

Drugs	Main mechanistic targets that could explain an antiepileptogenic effect	Post-SE models of TLE		Post-TBI models of PTE		Prevention of PTE in humans	
		Prevention of epilepsy	Disease modification	Prevention of epilepsy	Disease modification	Prevention of epilepsy	Disease modification
Repurposed ASMs							
Levetiracetam	SV2A	NE	+/−	?	+	(+)	(+)
Brivaracetam	SV2A	?	+	+	+	?	?
Gabapentin	$\alpha_2\delta$-Ca^{2+} channel	?	+	?	+	?	?
Perampanel	Glutamate (AMPA) receptor	NE	+	?	+	?[a]	?[a]
Topiramate	Multiple	+/−	+	?	+	?	?
Eslicarbazepine acetate	Na^+ and $Ca_v3.2$ Ca^{2+} channels	NE	+	?	?	?[b]	?[b]
Other repurposed drugs							
Statins (e.g., atorvastatin, simvastatin)	Multiple	?	+	?	+	?[c]	?[c]
COX inhibitors	Prostaglandin synthesis	+/−	+/−	?	+	?	?
Anakinra	IL-1	NE[d]	+[c]	?	+	?	?
Losartan	TGF-ß (and AT-1 receptor?)	+	+	+	+	?[e]	?
Isoflurane	Multiple	+	+	?	+	?	?
Sodium selenate	Tau hyperphosphorylation	?	+	NE	+	?	?
Rapamycin	mTOR	NE[e]	NE[f]	+	+	?[g]	?[g]
Atipamezole	α_2-Adrenoceptor	NE	+	NE	+	?	?
Scopolamine	Muscarinic Ach receptors	?	+	?	+	?	?
Ceftriaxone	GLT1/EAAT2	?	?	NE	+	?	?
Rimonabant	CB1 receptors	NE	NE	NE	+	?	?
Tacrolimus	Calcineurin	?	?	NE	+	?	?
Deferoxamine	Iron accumulation	?	?	?[h]	+	?	?
Dimethyl fumarate	Nrf2-Keap1	NE	+	?	+	?	?
Biperiden	mACh receptor	+	+	?	?	NE[i]	NE[i]
Rational combinations of repurposed drugs							
Levetiracetam + ceftriaxone + atorvastatin	SV2A + GLT1/EAAT2 + multiple	+	+	+[j]	+[j]	?	?
Levetiracetam + topiramate + atorvastatin	SV2A + multiple + multiple	+	+	NE[k]	NE[k]	?	?

TABLE 2 (Continued)

Drugs	Main mechanistic targets that could explain an antiepileptogenic effect	Post-SE models of TLE		Post-TBI models of PTE		Prevention of PTE in humans	
		Prevention of epilepsy	Disease modification	Prevention of epilepsy	Disease modification	Prevention of epilepsy	Disease modification
NCEs							
WP1066	JAK/STAT	NE	+	NE	+	?	?
PP-4-one	Wnt10B, mTOR, iNOS	?	?	?	+	?	?
Z944	T-type calcium channel	NE	+	?[h]	?[h]	?	?

Note: Only drugs that were tested (or are being tested) in PTE models and/or patients with TBI are shown. Data from post-SE models of TLE are shown for comparison. For epilepsy prevention, only studies in which the drug was given after the brain insult and in which spontaneous recurrent seizures were monitored after sufficiently long withdrawal of drug treatment were considered. Drug effect is indicated by: +, effective; +/−, inconsistent data; (+), retrospective clinical data or data from small trials; NE, not effective; and ?, no data available (or found by literature review). For detailed data see Kaminski et al. (2014), Saletti et al. (2019), Löscher (2020), Klein et al. (2020), Dulla and Pitkänen (2021), Pawlik et al. (2021), Löscher and Klein (2022), Pease et al. (2024), footnotes, and text.

Abbreviations: Ach, acetylcholine; AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASM, anti-seizure medication; AT-1, angiotensin 1; CB1, cannabinoid receptor 1; COX, cyclooxygenase; EAAT2, excitatory amino acid transporter 2; EpiBioS4Rx, Epilepsy Bioinformatics Study for Anti-Epileptogenic Therapy; FPI, fluid percussion injury; GLT1, glutamate transporter 1; IL-1, interleukin 1; iNOS, inducible nitric oxide synthase; JAK/STAT, Janus kinase/signal transducer and activator of transcription; Keap1, Kelch-like ECH-associated protein; mACh, muscarinic acetylcholine; mTOR, mechanistic target of rapamycin; NCE, new chemical entity; NE, not effective; Nrf2, nuclear factor erythroid 2-related factor 2; PP-4-one, pyrazolo[4,3-c]pyridine-4-one; PTE, post-traumatic epilepsy; SV2A, synaptic vesicle glycoprotein 2A; TBI, traumatic brain injury; TGF-ß, transforming growth factor ß; TLE, temporal lobe epilepsy; TSC, tuberous sclerosis complex.

[a]Currently evaluated for prevention of post-stroke epilepsy.[37]

[b]Currently evaluated for prevention of post-stroke epilepsy.[38]

[c]Large prospective trials indicate antiepileptogenic effect in post-stroke epilepsy.[39]

[d]Administered together with VX-765 (a specific non-peptide inhibitor of IL-1β cleavage and release).

[e]Antiepileptogenic effect in patients with arterial hypertension.[40]

[f]No antiepileptogenic effect when spontaneous seizures are recorded after sufficiently long withdrawal period after termination of treatment.

[g]Promising effects in tuberous sclerosis complex.[41]

[h]Currently evaluated by the EpiBioS4Rx consortium for antiepileptogenic activity in the rat FPI/PTE model.

[i]The frequency of late spontaneous seizures was higher in the biperiden group.[42]

[j]Mouse:rat dose scaling applied.[43]

[k]Mouse:rat dose scaling not applied.[43]

A key challenge lies in bridging the clinical translation gap. Preclinical TBI models provide a valuable platform for identifying clinically relevant biomarkers, uncovering new therapeutic targets, and serving as a screening tool for novel treatment strategies. Of note, experimental PTE models with clinical relevance are now available and have recently been reviewed in depth.[52] These models should be leveraged to further evaluate promising therapeutic compounds and generate robust pharmacokinetics and pharmacodynamic data to inform clinical trial design. Establishing a preclinical network capable of testing known and novel compounds in optimized animal models would help close critical data gaps and better align preclinical findings with clinical paradigms. Continued clinician–scientist collaboration will further accelerate progress. For example, under the International Initiative for Traumatic Brain Injury Research (InTBIR), a major effort is underway to improve biological and methodological alignment between animal models and human TBI by integrating clinically relevant biomarkers of acute brain injury into preclinical studies, thereby strengthening bidirectional translation across species.[53,54]

Another challenge is an incomplete understanding of human epileptogenesis and the cascade of biological changes that precede PTE. We do not know when epileptogenesis starts (and preventive treatment should commence) and when the primary epileptogenic process ends and preventive treatment is no longer effective. Mechanistic biomarkers, discovered in preclinical models and validated in patients, will aid in understanding epileptogenesis and effective treatment strategies. Incorporation of such biomarkers into predictive models that enable patient stratification may facilitate clinical trial execution.

Clinical trials for PTE prevention remain particularly challenging because only a relatively small subset of individuals with TBI ultimately develop epilepsy, necessitating very large cohorts and prolonged follow-up periods to evaluate prevention treatment effectiveness. These requirements impose substantial logistical and financial burdens that have been a barrier to study funding and implementation. For example, standard Phase III trials require a population with ~20% risk, 2-year follow-up, and large cohort size to ensure statistical significance.[28] However, this is changing. Risk-prediction models, such as those built from the TBI Model Systems National Database (TBIMS NDB), now offer a means to test our ability to enrich trial cohorts with high-risk patients based on injury characteristics (e.g., cranial surgeries as craniectomy, craniotomy, intracranial fragments, and traumatic hemorrhages), development of acute-care seizures, and other demographic and psychological health variables.[18,55] These models have been translated into an initial RShiny-based PTE Risk Calculator as a practical tool for individualized risk prediction and to guide higher-risk patient selection and streamline trial design.[18] Use of PTE risk calculator to identify and enroll higher-risk individuals, required sample sizes and trial costs could be reduced, potentially transforming the feasibility of PTE prevention trials (Figure 2).

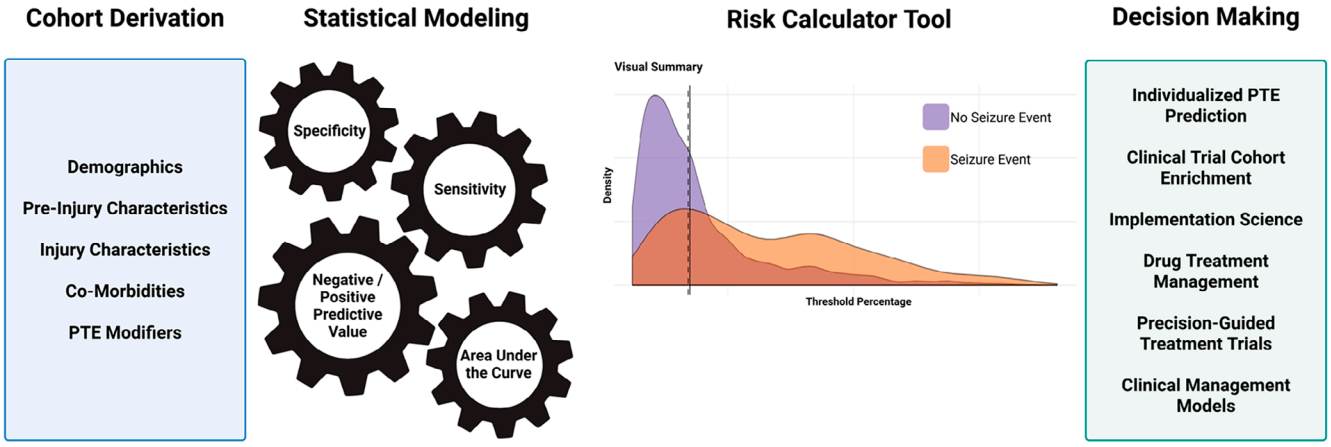

FIGURE 2 Conceptual overview of the impact of individualized PTE risk prediction for individuals with moderate to severe (ms)TBI. LASSO regression was used, with internal validation procedures, to evaluate baseline and acute care factors in their ability to predict PTE over a 2-year period after msTBI. Demographics, pre-injury variables, injury characteristics including clinical CT burden, comorbidities, and so on, were tested as predictor variables. The models yielded good sensitivity when specificity was set to 0.6. The published models correctly identified ~70%–85% of individuals with PTE and had high negative predictive values.[18] Risk-prediction thresholds (see vertical line on risk calculator tool panel) can be modified in the RShiny calculator to aid in enriching clinical trial enrollment with higher-risk enrollees. The study findings suggest that the risk calculator tool has implications for research in other aspects of PTE care, including studies aiming to test and validate clinical management models that address issues like return to driving, seizure prophylaxis duration, risk assessment for medications, and lifestyle choices that reduce seizure threshold. CT, computed tomography; PTE, post-traumatic epilepsy.

In parallel, biomarker-driven strategies with multimodal markers including imaging,[56] EEG,[57] and blood-based biomarkers,[58] as well as genomics (reviewed by[59,60]) are gaining traction. Combined biomarker approaches may improve identification of patients at risk for PTE, enable enrollment of a higher proportion of at-risk individuals,[28,61] and facilitate earlier assessment of therapeutic response.[62] Long-term EEG monitoring is now becoming feasible with wearable and home-based technologies, although studies confirming their practical deployment in people at risk of PTE are still needed. Another critical gap is the absence of reliable surrogate endpoints. Currently, PTE trials rely on the first late unprovoked spontaneous recurrent seizures as the primary outcome, resulting in prolonged Phase 1b/2a studies. Adaptive trial designs, integrating multimodal biomarker[63–68] discovery with PTE risk stratification and treatment respondership when testing early therapeutic outcomes, may offer a powerful solution. Recent and ongoing research initiatives like EpiBioS4Rx[69] and TAPTE (Team Approach to the Prevention and Treatment of Post-Traumatic Epilepsy; Department of Defense, CURE Epilepsy-funded[70]) are working on identifying biomarkers that predict the development of PTE, with the goal of enabling biomarker-informed drug screening and establishing a rigorous framework for future clinical trials.

To overcome these persistent challenges, a tightly coordinated effort between clinical and preclinical partners is essential. Working in parallel, researchers must identify clinically relevant prognostic and pharmacodynamic biomarkers to stratify patients based on TBI endotypes, provide mechanistic insight into epileptogenesis, and enable the use of surrogate outcomes in experimental medicine trial designs. This integrated approach can achieve relevant outcomes while building confidence among stakeholders—including the lived-experience and investment communities—that therapeutic breakthroughs are within reach (Figure 3). Securing dedicated funding for biomarker validation and clinical trial readiness, through federally funded mechanisms and/or public–private partnerships, will be critical to translating these advances into effective interventional trials and, ultimately, changing PTE outcome trajectories.

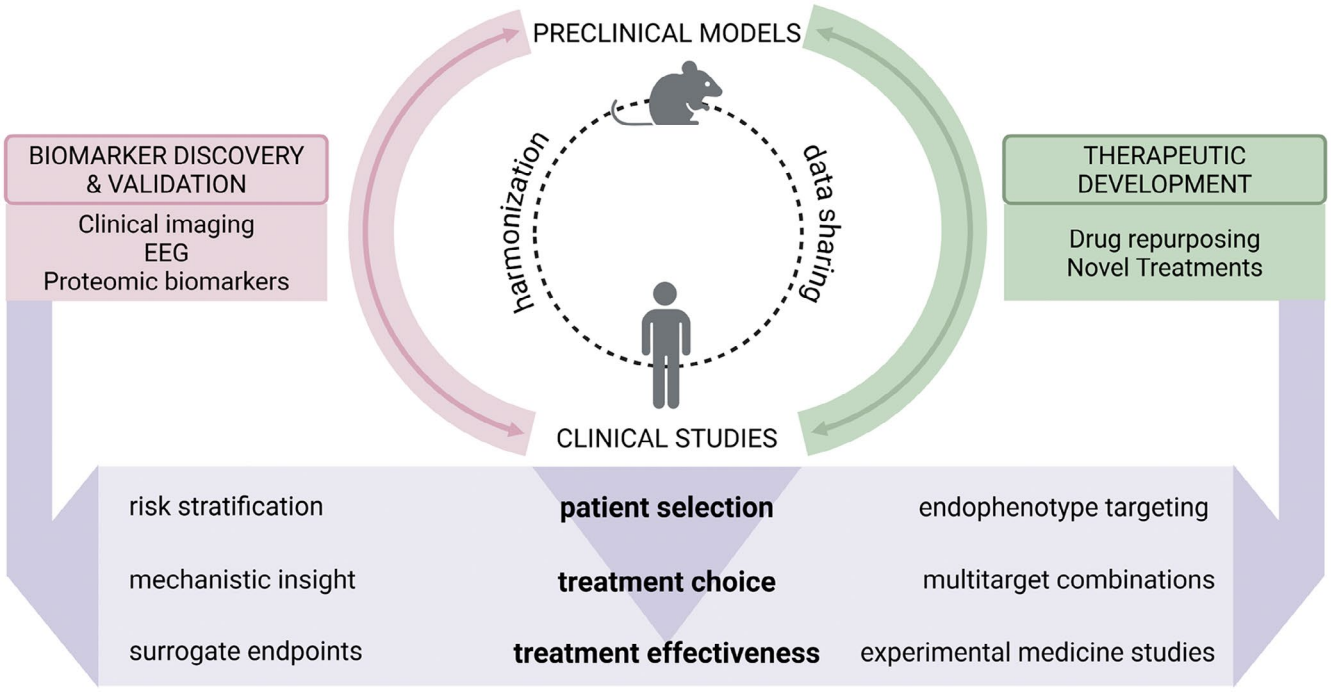

FIGURE 3 Framework for PTE intervention development. Early clinical imaging, EEG, or blood-based proteomic biomarkers can inform patient stratification, enable mechanistic insights, and serve as surrogate endpoints in clinical trials. Harmonization between preclinical models and clinical data, facilitated through data sharing, supports the validation and functional characterization of biomarkers. These insights drive personalized strategies for patient selection, treatment choice, and treatment effectiveness evaluation. Ultimately, this biomarker-informed approach enables the identification of distinct PTE endophenotypes, supports the design of individualized treatment plans including multitarget treatment combinations, and facilitates experimental medicine trials for both drug repurposing and novel therapeutic interventions. Created with Biorender. EEG, electroencephalography; PTE, post-traumatic epilepsy.

3 | CLINICAL BIOMARKERS OF PTE: FROM DIAGNOSIS TO DISEASE PROGRESSION

Readily available clinical variables, such as age, injury severity, injury mechanism, neurosurgical interventions, and acute care post-traumatic seizures, provide a functional foundation of pragmatic patient characteristics–based prognostic models. Awan et al., using only data available from the acute clinical chart in moderate to severe TBI, recently developed a prospective model able to quantify individual epilepsy risk with an area under the receiver- operator characteristic curve (AUROC) of 0.74.[18] The effect of integrating more advanced modalities to improve prognostic models in a PTE risk calculator tool should be weighed against the invasiveness and cost. Given the known biological and mechanistic heterogeneity involved with epileptogenesis, the integration of neuroimaging indices, EEG, and blood-based biomarkers in predictive models may nonetheless play a pivotal role in enhancing patient risk stratification and in assessing likely respondership for clinical trials as we discuss.

3.1 | Neuroimaging biomarkers

3.1.1 | State of the art

Brain imaging plays an important role in TBI clinical evaluation. Acute-phase computed tomography (CT) scans can provide predictive value,[18,55] with PTE risk being highest following dural penetration (60%) and biparietal contusions (44%),[71] and in pediatric patients with high Marshall scores.[72] However, although CT-measured brain volume loss is significantly associated with PTE, it is not a robust predictor in regression models.[17] Magnetic resonance imaging (MRI) can be more sensitive than CT for the detection of macro- and micro-structural changes associated with PTE.[56] In preclinical PTE models, acute thalamic damage, assessed by MRI and diffusion tensor imaging, is a prognostic biomarker of post-traumatic epileptogenesis.[73,74] However, in clinical settings, most MRI-based studies are conducted in the chronic phase following TBI, after epilepsy is established and often as part of a pre-surgical evaluation for drug-resistant epilepsy, thereby limiting the assessment of their prognostic value. Combinatorial approaches leveraging a machine learning model and including resting-state functional MRI connectivity, combined lesion burden, and amplitude of low frequency fluctuation data have been shown to predict PTE with an AUROC of 0.78.[56] There are many additional imaging modalities that might potentially provide high sensitivity and specificity for PTE. Examples include dynamic contrast-enhanced MRI to quantify blood–brain barrier (BBB) damage,[75] multidimensional MRI to measure gliosis,[76] and translocator protein positron emission tomography (TSPO PET) to monitor immune cell activation.[77] Proton magnetic resonance spectroscopy (^{1}H-MRS) adds another dimension by enabling non-invasive quantification of brain metabolites, offering insight into the biochemical and cellular mechanisms of epileptogenesis. For example, patients with structural epilepsies display increased levels of myo-inositol in the epileptic foci, which can be visualized using this technique.[78]

3.1.2 | Challenges and solutions

Although the use of advanced imaging approaches as surrogate biomarkers for predicting PTE presents some challenges, there are promising paths forward to assess their added value in materially improving prognostication, trial enrichment capability, or respondership to specific intervention. PTE has a relatively low incidence, meaning that adequately powered trials likely require multicenter collaboration over several years.[70] This raises standardization and cost concerns, particularly given the variable clinical availability of advanced imaging technologies, PET scanners, and radiotracers beyond tertiary academic sites.

Conference attendees discussed an operational approach for management of patients based on a tiered, risk-based strategy: all patients with TBI should first be screened with clinical factors and conventional imaging acutely after injury. Patients identified as moderate-to-high risk for PTE would then receive more detailed assessments, including advanced imaging, at designated specialized clinical research centers. Those at especially high risk could then be randomized to candidate antiepileptogenic agents, to both test therapeutic outcomes and serving as discovery cohorts for imaging markers as surrogate pharmacodynamic/target engagement endpoints. Alternatively, imaging-based PTE therapeutic trials could focus on the subacute to chronic phase post-injury. This would require the development of antiepileptogenic therapeutics with efficacy beyond the acute window. If this proves to be possible, patients experiencing a first post-traumatic seizure could be evaluated with advanced imaging to assess the risk of seizure recurrence or likely resistance to standard ASMs. High-risk individuals could then be randomized as candidates for ASMs. Both approaches have advantages; early stratification for acute intervention and later-phase evaluation post-seizure offer distinct advantages and should be pursued in parallel so that imaging-based clinical trial design in PTE can evolve to be both scientifically rigorous and practically achievable.

3.2 | EEG signatures

3.2.1 | State of the art

EEG, both surface and invasive electrocorticography (ECoG), remains central to epilepsy diagnosis and is increasingly advancing biomarker discovery for PTE, aided by insights from preclinical models. In patients, epileptiform abnormalities within the acute to subacute phase of TBI (<14 days post-injury)[12,72] have emerged as biomarkers of PTE susceptibility. Sporadic epileptiform discharges, lateralized or generalized periodic discharges, lateralized rhythmic delta activity, and focal slowing are associated with a threefold increased PTE risk in a retrospective case–control study of age- and injury severity-matched patients with TBI.[79] Scalp EEG abnormalities in acute brain injury also independently predict a greater than threefold risk of developing epilepsy, regardless of clinical variables (i.e., age, sex, mental status, acute brain injury etiology).[80] Given the known heterogeneity in TBI endophenotypes, the association between PTE and the above-mentioned candidate EEG biomarkers has been inconsistent.[72] Key barriers to validating these EEG signatures include variable EEG features, lack of standardization using common data elements (CDEs), variable timing of EEG recordings, and limited long-term PTE follow-up. Moreover, surface EEG recordings lack spatial resolution, making early neurophysiological changes difficult to detect. Consolidation of cross-institutional datasets depends on common data standards for neurophysiology waveform recordings and robust de-identification procedures, which have proven to be difficult to scale. Preclinical models play a vital role in this field, enabling detailed exploration of candidate EEG biomarkers under controlled conditions. Significant attention has been directed to assessing high-frequency oscillations (HFOs) and epileptiform discharges during the process of epileptogenesis. HFOs are transient EEG events in the 80–500 Hz range and have been shown to increase in the first 2 weeks in the ipsilateral cortex of rats developing PTE following FPI,[81] similar to what is observed in the kainic acid model of chronic epilepsy.[82] Spikes and sharp waves, commonly used electrophysiological markers of early epileptiform abnormalities, are transient, sharp deflections in the EEG that typically last 20–200 ms and are indicative of hyperexcitable neural circuits occurring following experimental CCI and FPI.[83,84] In recombinant inbred collaborative cross (CC) mice, the epilepsy-prone strain CCO31 exhibits increased spiking activity as early as 12 h post-injury, not observed in non–epilepsy-prone strains.[85] Advanced EEG analytical tools such as signal dimensionality and entropy analysis are also emerging as novel methods to detect early network-level changes during epileptogenesis.[85,86]

3.2.2 | Challenges and solutions

Several barriers limit the current utility of EEG as a PTE biomarker. In clinical settings, acute continuous EEG recording is not routinely pursued and usually begins after the development of the first symptomatic seizures, thereby limiting the possibility of evaluating prognostic PTE biomarkers. Studies with acute EEG recordings often result in low PTE incidences, hampering the interpretation of data.[79,87,88] Moreover, assessment of EEG features, CDE use, timing of EEG recordings, and length of follow-up is often extremely variable between studies. The presence of electrodes can also compromise other ongoing analyses, such as MRI studies. Moreover, EEG analysis is laborious and time-consuming, and depending on type of EEG and automated algorithms, it may require special expertise and extensive data processing. This data burden can be impractical if decisions based on biomarker analysis (e.g., whether to include a subject with TBI in a treatment trial or not) need to be made within a short time frame. Differences in methodologies and approaches between laboratories limit the comparison of biomarker data and support a call for increased data standardization and procedure harmonization.

To overcome these obstacles, several proactive strategies are underway. (i) Computational EEG analysis using advanced signal processing and machine learning is accelerating biomarker discovery, reducing reliance on labor-intensive manual review.[89] (ii) Invasive ECoG monitoring with depth or subdural strip electrodes allows high-resolution recordings and has revealed a fivefold increase in seizure detection compared to surface EEG in acute TBI.[90] Of note, ECoG also captures epileptogenesis-relevant features such as infra-slow oscillations and regional activity patterns.[91] (iii) Standardization and harmonization efforts across clinical and preclinical research have the potential to improve translatability across these research domains. Initiatives that focus on identifying and using CDEs, agreed statistical approaches, and uniform reporting of EEG parameters are essential to improving translatability. (iv) Integration of multimodal markers could help understand alignment between patients and experimental models. Understanding whether human ECoG features reflect mechanisms identified in animal models and structural/functional imaging will enhance translational relevance. Epileptogenesis unfolds over time[35]; thus, longitudinal neurophysiological monitoring, ideally through non-invasive or minimally invasive methods, will be key to tracking dynamic risk profiles from weeks to months post-injury. Establishing scalable, validated EEG-based tools[89] will help identify high-risk individuals earlier and more precisely, ultimately enabling targeted interventions and improved clinical trial design.

3.3 | Proteomic blood biomarkers

3.3.1 | State of the art

Fluid-based protein biomarkers have emerged as critical tools to investigate the pathophysiological mechanisms underlying secondary injury post-TBI. Among the most studied are neurofilament light chain, and glial fibrillary acidic protein (GFAP). Although no strong evidence supports the prognostic value of acute GFAP[92] or NfL[92,93] levels for PTE development in preclinical models, elevated plasma neurofilament phosphorylated heavy chains have been reported in experimental PTE after FPI.[94] These associations remain unexplored in human disease. Given the growing interest in incorporating fluid biomarkers into TBI classification systems,[53,54] further investigation is urgently needed to determine whether these classical injury markers can help identify TBI endophenotypes at risk for epileptogenesis.

Neuroinflammation is recognized as a key driver of both secondary injury in TBI[95,96] and acquired epilepsies[97,98] making circulating inflammatory proteins attractive biomarker candidates. Although the current literature directly investigating neuroinflammation and PTE is sparse, the role of the damage-associated molecular pattern (DAMP)/inflammasome/interleukin (IL)-1β pathway has been highlighted as a key candidate in both preclinical and human studies.[65,99,100] In addition, systemic inflammation and altered immune responses are well-established in both TBI and epilepsy, often correlating with worse outcomes.[101,102] These shared mechanisms underscore the potential for inflammatory biomarkers to predict and treat PTE. For example, the post-translational modifications of high-motility group Box 1 (HMGB1), a key initiator of neuroinflammation, have been identified as specific to the epileptogenic phase following SE, suggesting potential for diagnostic use.[103] Clinical findings further support this approach: elevated plasma IL-6 at hospital admission[104] and increased cerebrospinal fluid (CSF)/serum IL-1β ratios within the first week post-injury[65] have been associated with PTE development.

3.3.2 | Challenges and solutions

Measuring proteomic biomarkers, including those associated with neuroinflammation in vivo, remains a major challenge. Although techniques like 18 kDa TSPO PET, cerebral microdialysis, and CSF sampling provide insights, they each have limitations such as high cost, limited sampling frequency, and anatomic specificity.[105] Blood, although accessible and suitable for serial sampling, may reflect systemic rather than central nervous system (CNS)–specific processes; although CSF offers CNS specificity and may be warranted for the groups at highest risk, it can be impractical for routine longitudinal assessment, especially in mild-to-moderate TBI. Interpretation is further complicated by factors like BBB disruption, brain edema, and altered CSF circulation. Another major challenge lies in the variability of reported biomarkers, stemming largely from differences in study design, assay choice, biomarker definitions, and patient populations. In addition, biomarker levels are influenced by multiple factors, including injury severity, age, and sex, all of which independently impact both biomarker expression and PTE risk.[12,53,106,107] Disentangling these variables remains a fundamental challenge in the field. Moreover, PTE may develop along different trajectories, from early provoked seizures to late-onset epilepsy, each potentially driven by distinct biological processes.

To address these issues, a dual strategy is needed. (i) Mechanistic validation in preclinical models to unravel the temporal and molecular landscape of neuroinflammation during epileptogenesis and translation to the human condition. Once at-risk patients are identified through blood biomarkers, (ii) clinical trials with an experimental medicine approach can be initiated targeting the inflammation pathways. Biomarkers that reflect specific epileptogenic processes, such as HMGB1,[102] should be prioritized, especially those with the potential for early detection. Integrating fluid biomarkers with advanced imaging techniques (e.g., MRI, PET) and EEG monitoring can offer a multimodal framework to improve diagnosis, risk stratification, and monitoring of PTE progression. Ultimately, establishing validated, time-sensitive biomarker panels will enable earlier identification of high-risk individuals, support targeted therapeutic trials, and clarify the dynamic biology of epileptogenesis. The field is well positioned to advance, provided these efforts are coordinated across translational research pipelines.

3.4 | Data sharing and harmonization

Progress in PTE research requires large-scale collaborative data sharing, but limited standardization impairs reproducibility and cross-study comparisons. Harmonized protocols and reporting standards are essential for improving consistency and ensuring regulatory readiness.

3.4.1 | State of the art

The lessons learned from TBI data harmonization efforts highlight the critical importance of integrating data standards early in the planning phase of a study.

By encouraging the use of standardized data collection, analysis, and reporting methods from the outset, researchers can ensure that their findings are rigorous, reproducible, and of high quality. Existing data repositories have established standards for use and data harmonization practices that can be emulated to accelerate data sharing and harmonization practices in TBI and epilepsy research. One such example is the Federal Interagency Traumatic Brain Injury Research (FITBIR), established in 2012, which serves as a national repository for clinical TBI data, enabling data integration and sharing to accelerate research.[108] FITBIR has supported large-scale, multi-site proof-of-concept studies linking acute injury characteristics to longitudinal outcomes, including associations between TBI and sleep disturbances[109] or mental health,[110] and functional recovery, demonstrating the value of harmonized CDEs and long-term follow-up. Despite having limited data, the harmonized data approach enabled through FITBIR was able to provide relevant insights. These examples illustrate how centralized, harmonized infrastructures enable discovery and risk modeling beyond what is feasible in single-center cohorts, while reducing data duplication and encouraging scientific collaboration. Of importance to note, the same framework can be directly applied to PTE research to support risk factor identification, biomarker validation, and trial cohort enrichment as PTE-specific datasets expand. Similarly, the Data Archive for the Brain Initiative (DABI) offers a platform for managing diverse datasets across multiple institutions.[111,112] DABI's approach to data standardization and interoperability has demonstrated how large-scale collaborations can effectively share and analyze complex neurological data. Lessons learned from data management in Alzheimer's Disease Neuroimaging Initiative[113] and Parkinson's Progression Markers Initiative[114] research, such as the implementation of CDEs and standardized data collection protocols, have provided a roadmap for use with PTE datasets and may significantly improve the ability to conduct large-scale, multi-site studies, which are needed for understanding complex conditions like PTE.

3.4.2 | Challenges and solutions

Despite these advancements, managing large heterogeneous datasets remains a significant challenge in PTE research. Limited manpower, insufficient resources for storage and integration of complex data, and missing data remain obstacles to effective data curation. Large file sizes and varying formats across different imaging modalities and clinical data systems further complicate data management. Moreover, the long-term sustainability of these data resources is a pressing concern. Maintaining and updating large-scale databases and analytical tools requires substantial ongoing funding and technical support. Adhering to FAIR (Findable, Accessible, Interoperable, and Reusable) principles in data management, although important, presents its own set of challenges in implementation, particularly in terms of making diverse datasets truly interoperable across different research contexts. For harmonization to truly be effective, it is vital for researchers to "speak the same language," ensuring consistency in terms of terminology, data structure, and formats not only within individual studies but also across different disease areas and repositories.

An additional challenge for data harmonization in PTE research is the substantial heterogeneity in acute (as well as post-acute) TBI care across institutions, including sedation practices, neurosurgical timing and approaches, availability of specialized neurocritical care, and use of continuous EEG monitoring and seizure prophylaxis. Although these have been addressed in guidelines from organizations such as the Neurocritical Care Society,[115] they are largely based on low-to-moderate quality evidence. Harmonization of care management factors using CDEs and electronic health record integration is therefore needed and should be underpinned by coordinated research within controlled studies to generate more robust indicators and improve generalizability.

First, developing and adopting standardized data collection and reporting protocols specific to PTE, building existing CDE efforts in TBI and epilepsy, is essential for enhancing data harmonization and interoperability. Training on the use of CDEs should be forecasted clearly for both researchers and support staff in each lab, as it may introduce additional costs to study budgets. Implementing machine learning and AI-driven tools for automated data quality checks and preprocessing could significantly improve efficiency in managing large, heterogeneous datasets. Establishing a centralized, cloud-based infrastructure for PTE data could facilitate better data sharing and collaborative analysis of animal and human data (de-identified). To ensure sustainability, exploring public–private partnerships and developing community-driven governance models for data resources could provide more stable long-term support. Fostering closer collaborations with computer scientists and data engineers to develop PTE-specific analytical tools and data integration methods would accelerate progress in the field. Governance of shared datasets and registries should include stakeholder representation (including lived experience) to support transparency, trust, and policies for secondary use that align with PTE community priorities. When implemented collectively, these solutions could significantly advance

PTE research, enabling more efficient, large-scale studies and facilitating discoveries that may lead to better prevention and treatment strategies.

4 | DISCUSSION AND RECOMMENDATIONS TO ADVANCE TOWARD CLINICAL TRIALS FOR PTE

The IC-PTE 2024 proceedings underscored the urgency and opportunities to advance PTE prevention by aligning basic, clinical, and translational research efforts. Although considerable challenges remain, such as the complexity of trial design, limited validated biomarkers, and insufficient investment, there is growing momentum across the field. Recent advances in predictive modeling, biomarker discovery, and therapeutic development form a strong foundation for progress.

Key priorities include:

1. Establishing a coordinated translational network to accelerate testing of repurposed and novel therapeutics for PTE, including a multi-disciplinary task force to identify the most promising therapeutic candidates, trial designs, and clinical endpoints.
2. Integrating multimodal biomarkers into clinical trial design and shifting toward innovative clinical trial frameworks integrating the new TBI classification framework.
3. Enriching patient cohorts with validated risk models and surrogate biomarkers to improve feasibility, reduce costs, and maximize trial impact.

It is important to note that collaboration must extend beyond academia and industry to include people with lived experience,[22,116] who provide essential insight into relevant patient-centered priorities (e.g., cognition, mood/behavior, functional participation, treatment tolerability) and advocacy for innovations that reflect lived burden and likely influence real-world adoption (Box 2). Data harmonization and cross-institutional sharing, supported by standardized protocols, FAIR principles, and shared platforms, are equally vital to accelerate discovery and reproducibility. Perhaps the most difficult challenge is securing investment. Despite the unmet need, investors are hesitant to fund clinical trials due to past failures, creating a paradox where funding depends on clinical data that cannot be generated without support. After limited success of prior prevention trials and uncertainty about feasible endpoints, public funding agencies and the epilepsy research community have been cautious about continued investment. Although the 2000 National Institute of Neurological Diseases and Stroke (NINDS) "Curing the Epilepsies conference" prioritized PTE prevention trials, later conferences (2007, 2013, 2021) shifted focus to animal models and biomarkers, possibly contributing to the disappearance of human PTE prevention studies from funding priorities. The tide is turning, with improved models, smarter trial design, predictive tools, and strong preclinical candidates, the opportunity for breakthroughs has never been clearer. To break the cycle of limited therapeutic progress, the PTE research community must move decisively toward integrated, biomarker-driven, and patient-informed strategies. With sustained investment, multidisciplinary coordination, and proactive stakeholder engagement, accelerating effective prevention of PTE is a realistic goal, with the potential to profoundly improve outcomes for individuals living with the consequences of TBI.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Menon DK, Schwab K, Wright DW, Maas AI. Position statement: definition of traumatic brain injury. Arch Phys Med Rehabil. 2010;91:1637–40.
2. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic brain injury: an overview of epidemiology, pathophysiology, and medical management. Med Clin North Am. 2020;104:213–38.
3. Traumatic brain injury (TBI) detection: past, present, and future. https://www.mdpi.com/2227-9059/10/10/2472
4. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg. 2019;130:1080–97.
5. Majdan M, Plancikova D, Brazinova A, Rusnak M, Nieboer D, Feigin V, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. Lancet Public Health. 2016;1:e76–e83.
6. Centers for Disease Control and Prevention. National Center for Health Statistics: mortality data on CDC WONDER.
7. Bodien YG, Barra A, Temkin NR, Barber J, Foreman B, Vassar M, et al. Diagnosing level of consciousness: the limits of the Glasgow coma scale Total score. J Neurotrauma. 2021;38:3295–305.
8. Zumstein MA, Moser M, Mottini M, Ott SR, Sadowski-Cron C, Radanov BP, et al. Long-term outcome in patients with mild

traumatic brain injury: a prospective observational study. J Trauma. 2011;71:120–7.
9. Manley GT, Dams-O'Connor K, Alosco ML, Awwad HO, Bazarian JJ, Bragge P, et al. A new characterisation of acute traumatic brain injury: the NIH-NINDS TBI classification and nomenclature initiative. Lancet Neurol. 2025;24:512–23.
10. Pischiutta F, Micotti E, Hay JR, Marongiu I, Sammali E, Tolomeo D, et al. Single severe traumatic brain injury produces progressive pathology with ongoing contralateral white matter damage one year after injury. Exp Neurol. 2018;300:167–78.
11. Newcombe VFJ, Correia MM, Ledig C, Abate MG, Outtrim JG, Chatfield D, et al. Dynamic changes in White matter abnormalities correlate with late improvement and deterioration following TBI: a diffusion tensor imaging study. Neurorehabil Neural Repair. 2016;30:49–62.
12. Pease M, Mallela AN, Elmer J, Okonkwo DO, Shutter L, Barot N, et al. Association of Posttraumatic Epilepsy with Long-term Functional Outcomes in individuals with severe traumatic brain injury. Neurology. 2023;100:e1967–e1975.
13. Golub VM, Reddy DS. Post-traumatic epilepsy and comorbidities: advanced models, molecular mechanisms, biomarkers, and novel therapeutic interventions. Pharmacol Rev. 2022;74:387–438.
14. Christensen J. The epidemiology of posttraumatic epilepsy. Semin Neurol. 2015;35:218–22.
15. Caveness WF, Walker AE, Ascroft PB. Incidence of posttraumatic epilepsy in Korean veterans as compared with those from world war I and world war II. J Neurosurg. 1962;19:122–9.
16. Weiss GH, Salazar AM, Vance SC, Grafman JH, Jabbari B. Predicting posttraumatic epilepsy in penetrating head injury. Arch Neurol. 1986;43:771–3.
17. Raymont V, Salazar AM, Lipsky R, Goldman D, Tasick G, Grafman J. Correlates of posttraumatic epilepsy 35 years following combat brain injury. Neurology. 2010;75:224–9.
18. Awan N, Kumar RG, Juengst SB, DiSanto D, Harrison-Felix C, Dams-O'Connor K, et al. Development of individualized risk assessment models for predicting post-traumatic epilepsy 1 and 2 years after moderate-to-severe traumatic brain injury: a traumatic brain injury model system study. Epilepsia. 2025;66:482–98.
19. Kiraly MA, Kiraly SJ. Traumatic brain injury and delayed sequelae: a review - traumatic brain injury and mild traumatic brain injury (concussion) are precursors to later-onset brain disorders, including early-onset dementia. Sci World J. 2007;7:1768–76.
20. Jabbarinejad R, Cohen-Zimerman S, Wagner AK, Grafman J. Determinants of caregiver burden in male patients with epilepsy following penetrating traumatic brain injury. Epilepsy Behav. 2021;116:107768.
21. Juengst SB, Wagner AK, Ritter AC, Szaflarski JP, Walker WC, Zafonte RD, et al. Post-traumatic epilepsy associations with mental health outcomes in the first two years after moderate to severe TBI: a TBI model systems analysis. Epilepsy Behav. 2017;73:240–6.
22. Sheridan S, Schrandt S, Forsythe L, Hilliard TS, Paez KA. The PCORI engagement rubric: promising practices for partnering in research. Ann Fam Med. 2017;15:165–70.
23. Benizri N, Hallot S, Burns K, Goldfarb M. Patient and family representation in randomized clinical trials published in 3 medical and surgical journals: a systematic review. JAMA Netw Open. 2022;5:e2230858.
24. Estrup S, Barot E, Mortensen CB, Anthon CT, Crescioli E, Kjær MBN, et al. Patient and public involvement in contemporary large intensive care trials: a meta-epidemiological study. Acta Anaesthesiol Scand. 2023;67:256–63.
25. Kim JY, Acelas MPB, Granville CA, Getz K. Benchmarking patient engagement capabilities and preparedness of drug development sponsors. Ther Innov Regul Sci. 2023;57:1040–9.
26. Guo D, Zeng L, Brody DL, Wong M. Rapamycin attenuates the development of posttraumatic epilepsy in a mouse model of traumatic brain injury. PLoS One. 2013;8:e64078.
27. Sharma R, Leung WL, Zamani A, O'Brien TJ, Casillas Espinosa PM, Semple BD. Neuroinflammation in post-traumatic epilepsy: pathophysiology and tractable therapeutic targets. Brain Sci. 2019;9:318.
28. Klein P, Koepp M, Rotenberg A, Hameed MQ, Löscher W. Clinical trials of prevention of acquired epilepsy: new proof-of-concept approach to restart trials. Epilepsia. 2025;66:2679–89. https://doi.org/10.1111/epi.18394
29. Mula M. Treatment options for post-traumatic epilepsy: an update on clinical and translational aspects. Expert Rev Neurother. 2025;25:273–80.
30. Löscher W, Brandt C. Prevention or modification of epileptogenesis after brain insults: experimental approaches and translational research. Pharmacol Rev. 2010;62:668–700.
31. Kaminski RM, Rogawski MA, Klitgaard H. The potential of antiseizure drugs and agents that act on novel molecular targets as antiepileptogenic treatments. Neurotherapeutics. 2014;11:385–400.
32. Terrone G, Pauletti A, Pascente R, Vezzani A. Preventing epileptogenesis: a realistic goal? Pharmacol Res. 2016;110:96–100.
33. Terrone G, Frigerio F, Balosso S, Ravizza T, Vezzani A. Inflammation and reactive oxygen species in status epilepticus: biomarkers and implications for therapy. Epilepsy Behav. 2019;101:106275.
34. Saletti PG, Ali I, Casillas-Espinosa PM, Semple BD, Lisgaras CP, Moshé SL, et al. In search of antiepileptogenic treatments for post-traumatic epilepsy. Neurobiol Dis. 2019;123:86–99.
35. Pease M, Gupta K, Moshé SL, Correa DJ, Galanopoulou AS, Okonkwo DO, et al. Insights into epileptogenesis from post-traumatic epilepsy. Nat Rev Neurol. 2024;20:298–312.
36. Dulla CG, Pitkänen A. Novel approaches to prevent Epileptogenesis after traumatic brain injury. Neurotherapeutics. 2021;18:1582–601.
37. Nicolo J-P, Chen Z, Moffat B, Wright DK, Sinclair B, Glarin R, et al. Study protocol for a phase II randomised, double-blind, placebo-controlled trial of perampanel as an antiepileptogenic treatment following acute stroke. BMJ Open. 2021;11:e043488.
38. Koepp MJ, Trinka E, Mah YH, Bentes C, Knake S, Gigli GL, et al. Antiepileptogenesis after stroke-trials and tribulations: methodological challenges and recruitment results of a phase II study with eslicarbazepine acetate. Epilepsia Open. 2023;8:1190–201.
39. Hufthy Y, Bharadwaj M, Gupta S, Hussain D, Joseph PJS, Khan A, et al. Statins as antiepileptogenic drugs: analyzing the evidence and identifying the most promising statin. Epilepsia. 2022;63:1889–98.

40. Doege C, Luedde M, Kostev K. Association between angiotensin receptor blocker therapy and incidence of epilepsy in patients with hypertension. JAMA Neurol. 2022;79:1296–302.
41. Shen Y-W, Wang YY, Zhang MN, Xu Y, Lu Q, He W, et al. Sirolimus treatment for tuberous sclerosis complex prior to epilepsy: evidence from a registry-based real-world study. Seizure. 2022;97:23–31.
42. Foresti ML, Garzon E, de Moraes MT, Valeriano RPS, Santiago JP, dos Santos GM, et al. Initial clinical evidence on biperiden as antiepileptogenic after traumatic brain injury-a randomized clinical trial. Front Neurol. 2024;15:1443982.
43. Hameed MQ, D'Ambrosio R, Eastman C, Hui B, Lin R, Vermudez SAD, et al. A comparison of the antiepileptogenic efficacy of two rationally chosen multitargeted drug combinations in a rat model of posttraumatic epilepsy. Exp Neurol. 2024;382:114962.
44. Klein P, Herr D, Pearl PL, Natale J, Levine Z, Nogay C, et al. Results of phase 2 safety and feasibility study of treatment with levetiracetam for prevention of posttraumatic epilepsy. Arch Neurol. 2012;69:1290–5.
45. Yang L, Afroz S, Valsamis HA, Michelson HB, Goodman JH, Ling DSF. Early intervention with levetiracetam prevents the development of cortical hyperexcitability and spontaneous epileptiform activity in two models of neurotrauma in rats. Exp Neurol. 2021;337:113571.
46. Coles LD, Saletti PG, Lisgaras CP, Casillas-Espinosa PM, Liu W, Li Q, et al. Levetiracetam pharmacokinetics and brain uptake in a lateral fluid percussion injury rat model. J Pharmacol Exp Ther. 2023;386:259–65.
47. Löscher W, Klitgaard H, Twyman RE, Schmidt D. New avenues for anti-epileptic drug discovery and development. Nat Rev Drug Discov. 2013;12:757–76.
48. Löscher W, Klein P. New approaches for developing multitargeted drug combinations for disease modification of complex brain disorders. Does epilepsy prevention become a realistic goal? Pharmacol Ther. 2022;229:107934.
49. Welzel L, Bergin DH, Schidlitzki A, Twele F, Johne M, Klein P, et al. Systematic evaluation of rationally chosen multitargeted drug combinations: a combination of low doses of levetiracetam, atorvastatin and ceftriaxone exerts antiepileptogenic effects in a mouse model of acquired epilepsy. Neurobiol Dis. 2021;149:105227.
50. Jin J, Shen X, Tian L, He G, Zhang Y. Pyrazolo[4,3-c]pyridine-4-one (PP-4-one) exhibits anti-epileptogenic effect in rat model of traumatic epilepsy by mammalian target of rapamycin (mTOR) signaling pathway downregulation. Med Sci Monit. 2020;26:e923919.
51. Casillas-Espinosa PM, Shultz SR, Braine EL, Jones NC, Snutch TP, Powell KL, et al. Disease-modifying effects of a novel T-type calcium channel antagonist, Z944, in a model of temporal lobe epilepsy. Prog Neurobiol. 2019;182:101677.
52. Reddy DS, Golub VM, Ramakrishnan S, Churn SB, Shapiro LA, Iannucci J, et al. Advances and challenges in experimental models of post-traumatic epilepsy for therapeutic interventions. Pharmacol Rev. 2025;77(55):100080. https://doi.org/10.1016/j.pharmr.2025.100080
53. Lisi I, Moro F, Mazzone E, Marklund N, Pischiutta F, Kobeissy F, et al. Exploiting blood-based biomarkers to align preclinical models with human traumatic brain injury. Brain. 2025;148:1062–80.
54. Newcombe V, Zanier ER. Highlights in traumatic brain injury research in 2024. Lancet Neurol. 2025;24:10–1.
55. Ritter AC, Wagner AK, Szaflarski JP, Brooks MM, Zafonte RD, Pugh MJV, et al. Prognostic models for predicting posttraumatic seizures during acute hospitalization, and at 1 and 2 years following traumatic brain injury. Epilepsia. 2016;57:1503–14.
56. Akrami H, Cui W, Kim PE, Heck CN, Irimia A, Jerbi K, et al. Prediction of post traumatic epilepsy using MRI-based imaging markers. Hum Brain Mapp. 2024;45:e70075. https://doi.org/10.1101/2024.01.12.575454
57. Pyrzowski J, Kałas M, Mazurkiewicz-Bełdzińska M, Siemiński M. EEG biomarkers for the prediction of post-traumatic epilepsy – a systematic review of an emerging field. Seizure. 2024;119:71–7.
58. Necula D, Paz JT. A drop of insight: blood-based clues to posttraumatic epilepsy. Epilepsy Curr. 2025;25:203–6.
59. Cotter D, Kelso A, Neligan A. Genetic biomarkers of posttraumatic epilepsy: a systematic review. Seizure. 2017;46:53–8.
60. Kazis D, Chatzikonstantinou S, Ciobica A, Kamal FZ, Burlui V, Calin G, et al. Epidemiology, risk factors, and biomarkers of post-traumatic epilepsy: a comprehensive overview. Biomedicine. 2024;12:410.
61. Simonato M, Agoston DV, Brooks-Kayal A, Dulla C, Fureman B, Henshall DC, et al. Identification of clinically relevant biomarkers of epileptogenesis — a strategic roadmap. Nat Rev Neurol. 2021;17:231–42.
62. Bruckhaus AA, Asifriyaz T, Kriukova K, O'Brien TJ, Agoston DV, Staba RJ, et al. Exploring multimodal biomarker candidates of post-traumatic epilepsy following moderate to severe traumatic brain injury: a systematic review and meta-analysis. Epilepsia. 2025;66:6–32.
63. Kumar RG, Breslin KB, Ritter AC, Conley YP, Wagner AK. Variability with Astroglial glutamate transport genetics is associated with increased risk for post-traumatic seizures. J Neurotrauma. 2019;36:230–8.
64. Ritter AC, Kammerer CM, Brooks MM, Conley YP, Wagner AK. Genetic variation in neuronal glutamate transport genes and associations with posttraumatic seizure. Epilepsia. 2016;57:984–93.
65. Diamond ML, Ritter AC, Failla MD, Boles JA, Conley YP, Kochanek PM, et al. IL-1β associations with posttraumatic epilepsy development: a genetics and biomarker cohort study. Epilepsia. 2014;55:1109–19.
66. Diamond ML, Ritter AC, Jackson EK, Conley YP, Kochanek PM, Boison D, et al. Genetic variation in the adenosine regulatory cycle is associated with posttraumatic epilepsy development. Epilepsia. 2015;56:1198–206.
67. Darrah SD, Miller MA, Ren D, Hoh NZ, Scanlon JM, Conley YP, et al. Genetic variability in glutamic acid decarboxylase genes: associations with post-traumatic seizures after severe TBI. Epilepsy Res. 2013;103:180–94.
68. Wagner AK, Miller MA, Scanlon J, Ren D, Kochanek PM, Conley YP. Adenosine A1 receptor gene variants associated with post-traumatic seizures after severe TBI. Epilepsy Res. 2010;90:259–72.
69. Vespa PM, Shrestha V, Abend N, Agoston D, Au A, Bell MJ, et al. The epilepsy bioinformatics study for anti-epileptogenic therapy (EpiBioS4Rx) clinical biomarker: study design and protocol. Neurobiol Dis. 2019;123:110–4.

70. Iyengar SS, Lubbers LS, Harte-Hargrove L, CURE Epilepsy Post-Traumatic Initiative Advisors, and Investigators. A team science approach for the preclinical and clinical characterization and biomarker development for post-traumatic epilepsy. Epilepsia Open. 2023;8:820–33.
71. Schneider ALC, Law CA, Gottesman RF, Krauss G, Huang J, Kucharska-Newton A, et al. Posttraumatic epilepsy and dementia risk. JAMA Neurol. 2024;81:346–53.
72. Appavu BL, Temkit MH, Kensicki JF, Kuwabara M, Burrows BT, Adelson PD. Acute physiologic prediction of pediatric posttraumatic epilepsy. Epilepsy Res. 2022;183:106935.
73. Manninen E, Chary K, Lapinlampi N, Andrade P, Paananen T, Sierra A, et al. Acute thalamic damage as a prognostic biomarker for post-traumatic epileptogenesis. Epilepsia. 2021;62:1852–64.
74. Manninen E, Cabeen R, Immonen R, Ndode-Ekane XE, Andrade P, Harris NG, et al. Damage in thalamic projection to perilesional cortex as a prognostic biomarker for experimental post-traumatic epilepsy. Epilepsia. 2025;66(8):2830–41. https://doi.org/10.1111/epi.18408
75. Ware JB, Sinha S, Morrison J, Walter AE, Gugger JJ, Schneider ALC, et al. Dynamic contrast enhanced MRI for characterization of blood-brain-barrier dysfunction after traumatic brain injury. NeuroImage Clin. 2022;36:103236.
76. Benjamini D, Priemer DS, Perl DP, Brody DL, Basser PJ. Mapping astrogliosis in the individual human brain using multidimensional MRI. Brain. 2023;146:1212–26.
77. Ramlackhansingh AF, Brooks DJ, Greenwood RJ, Bose SK, Turkheimer FE, Kinnunen KM, et al. Inflammation after trauma: microglial activation and traumatic brain injury. Ann Neurol. 2011;70:374–83.
78. Matsuo N, Imamura A, Ito R, Sugawara K, Takahashi Y, Kondo N. The correlation between 1H-MR spectroscopy and clinical manifestation with tuberous sclerosis complex. Neuropediatrics. 2007;38:126–9.
79. Kim JA, Boyle EJ, Wu AC, Cole AJ, Staley KJ, Zafar S, et al. Epileptiform activity in traumatic brain injury predicts post-traumatic epilepsy: EEG abnormalities predict post-traumatic epilepsy. Ann Neurol. 2018;83:858–62.
80. Chen DF, Kumari P, Haider HA, Ruiz AR, Lega J, Dhakar MB. Association of Epileptiform Abnormality on electroencephalography with development of epilepsy after acute brain injury. Neurocrit Care. 2021;35:428–33.
81. Bragin A, Li L, Almajano J, Alvarado-Rojas C, Reid AY, Staba RJ, et al. Pathologic electrographic changes after experimental traumatic brain injury. Epilepsia. 2016;57:735–45.
82. Bragin A, Engel J, Wilson CL, Fried I, Mathern GW. Hippocampal and entorhinal cortex high-frequency oscillations (100–500 Hz) in human epileptic brain and in kainic acid–treated rats with chronic seizures. Epilepsia. 1999;40:127–37.
83. Statler KD, Scheerlinck P, Pouliot W, Hamilton M, White HS, Dudek FE. A potential model of pediatric posttraumatic epilepsy. Epilepsy Res. 2009;86:221–3.
84. Bolkvadze T, Pitkänen A. Development of post-traumatic epilepsy after controlled cortical impact and lateral fluid-percussion-induced brain injury in the mouse. J Neurotrauma. 2012;29:789–812.
85. Shannon T, Levine N, Dirickson R, Shen Y, Cotter C, Rajjoub N, et al. Early hippocampal high-amplitude rhythmic spikes predict post-traumatic epilepsy in mice. Front Neurosci. 2024;18:1422449.
86. Di Sapia R, Rizzi M, Moro F, Lisi I, Caccamo A, Ravizza T, et al. ECoG spiking activity and signal dimension are early predictive measures of epileptogenesis in a translational mouse model of traumatic brain injury. Neurobiol Dis. 2023;185:106251.
87. Tubi MA, Lutkenhoff E, Blanco MB, McArthur D, Villablanca P, Ellingson B, et al. Early seizures and temporal lobe trauma predict post-traumatic epilepsy: a longitudinal study. Neurobiol Dis. 2019;123:115–21.
88. Chen T-S, Huang T-H, Lai M-C, Huang C-W. The role of glutamate receptors in epilepsy. Biomedicine. 2023;11:783.
89. Slama K, Yahyaouy A, Riffi J, Mahraz MA, Tairi H. Comprehensive review of machine learning and deep learning techniques for epileptic seizure detection and prediction based on neuroimaging modalities. Vis Comput Ind Biomed Art. 2025;8:27.
90. Foreman B. Disorders of electrophysiology following severe traumatic brain injury. Neurosurg Clin N Am. 2025;36:411–21.
91. Mercier MR, Dubarry AS, Tadel F, Avanzini P, Axmacher N, Cellier D, et al. Advances in human intracranial electroencephalography research, guidelines and good practices. NeuroImage. 2022;260:119438.
92. Saletti PG, Mowrey WB, Liu W, Li Q, McCullough J, Aniceto R, et al. Early preclinical plasma protein biomarkers of brain trauma are influenced by early seizures and levetiracetam. Epilepsia Open. 2023;8:586–608.
93. Heiskanen M, Jääskeläinen O, Manninen E, das Gupta S, Andrade P, Ciszek R, et al. Plasma neurofilament light chain (NF-L) is a prognostic biomarker for cortical damage evolution but not for cognitive impairment or Epileptogenesis following experimental TBI. Int J Mol Sci. 2022;23:15208.
94. Heiskanen M, Banuelos I, Manninen E, Andrade P, Hämäläinen E, Puhakka N, et al. Plasma neurofilament heavy chain is a prognostic biomarker for the development of severe epilepsy after experimental traumatic brain injury. Epilepsia. 2024;65:3703–16.
95. Zanier ER, Fumagalli S, Perego C, Pischiutta F, De Simoni M-G. Shape descriptors of the "never resting" microglia in three different acute brain injury models in mice. Intensive Care Med Exp. 2015;3:7.
96. Loane DJ, Kumar A, Stoica BA, Cabatbat R, Faden AI. Progressive neurodegeneration after experimental brain trauma: association with chronic microglial activation. J Neuropathol Exp Neurol. 2014;73:14–29.
97. Vezzani A, Ravizza T, Bedner P, Aronica E, Steinhäuser C, Boison D. Astrocytes in the initiation and progression of epilepsy. Nat Rev Neurol. 2022;18:707–22.
98. Vezzani A, Balosso S, Ravizza T. Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy. Nat Rev Neurol. 2019;15:459–72.
99. Semple BD, O'Brien TJ, Gimlin K, Wright DK, Kim SE, Casillas-Espinosa PM, et al. Interleukin-1 receptor in seizure susceptibility after traumatic injury to the pediatric brain. J Neurosci. 2017;37:7864–77.
100. Ping X, Chai Z, Wang W, Ma C, White FA, Jin X. Blocking receptor for advanced glycation end products (RAGE) or toll-like receptor 4 (TLR4) prevents posttraumatic epileptogenesis in mice. Epilepsia. 2021;62:3105–16.
101. Yue JK, Kobeissy FH, Jain S, Sun X, Phelps RRL, Korley FK, et al. Neuroinflammatory biomarkers for traumatic brain

injury diagnosis and prognosis: a TRACK-TBI pilot study. Neurotrauma Rep. 2023;4:171–83.
102. de Vries EE, van den Munckhof B, Braun KPJ, van Royen-Kerkhof A, de Jager W, Jansen FE. Inflammatory mediators in human epilepsy: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2016;63:177–90.
103. Walker LE, Frigerio F, Ravizza T, Ricci E, Tse K, Jenkins RE, et al. Molecular isoforms of high-mobility group box 1 are mechanistic biomarkers for epilepsy. J Clin Invest. 2019;129:2166.
104. Choudhary A, Varshney R, Kumar A, Kaushik K. A prospective study of novel therapeutic targets interleukin 6, tumor necrosis factor α, and interferon γ as predictive biomarkers for the development of posttraumatic epilepsy. World Neurosurg X. 2021;12:100107.
105. Zeiler FA, Thelin EP, Czosnyka M, Hutchinson PJ, Menon DK, Helmy A. Cerebrospinal fluid and microdialysis cytokines in severe traumatic brain injury: a scoping systematic review. Front Neurol. 2017;8:379.
106. Pease M, Gonzalez-Martinez J, Puccio A, Nwachuku E, Castellano JF, Okonkwo DO, et al. Risk factors and incidence of epilepsy after severe traumatic brain injury. Ann Neurol. 2022;92:663–9.
107. Moro F, Lisi I, Tolomeo D, Vegliante G, Pascente R, Mazzone E, et al. Acute blood levels of neurofilament light indicate one-year White matter pathology and functional impairment in repetitive mild traumatic brain injured mice. J Neurotrauma. 2023;40:1144–63.
108. Enhancement of the FITBIR data science platform analysis tools to advance traumatic brain injury (TBI) research (NINDS/DON). https://datascience.nih.gov/data-scholars-2023/enhancement-of-the-fitbir-data-science-platform-analysis-tools
109. O'Neil ME, Krushnic D, Walker WC, Cameron D, Baker-Robinson W, Hannon S, et al. Increased risk for clinically significant sleep disturbances in mild traumatic brain injury: an approach to leveraging the Federal Interagency Traumatic Brain Injury Research Database. Brain Sci. 2024;14:921.
110. O'Neil M, Cameron D, Clauss K, Krushnic D, Baker-Robinson W, Hannon S, et al. A proof-of-concept study demonstrating how FITBIR datasets can be harmonized to examine posttraumatic stress disorder-traumatic brain injury associations. J Behav Data Sci. 2024;4:45–62.
111. Duncan D, Garner R, Brinkerhoff S, Walker HC, Pouratian N, Toga AW. Data archive for the BRAIN initiative (DABI). Sci Data. 2023;10:83.
112. Subash P, Gray A, Boswell M, Cohen SL, Garner R, Salehi S, et al. A comparison of neuroelectrophysiology databases. Sci Data. 2023;10:719.
113. https://adni.loni.usc.edu/.
114. https://www.ppmi-info.org/.
115. Frontera JA, Gilmore EJ, Johnson EL, Olson DW, Rayi A, Tesoro E, et al. Guidelines for seizure prophylaxis in adults hospitalized with moderate–severe traumatic brain injury: a clinical practice guideline for health care professionals from the neurocritical care society. Neurocrit Care. 2024;40:819–44.
116. Staniszewska S, Brett J, Simera I, Seers K, Mockford C, Goodlad S, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. BMJ. 2017;358:j3453.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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