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PREdiction and Diagnosis using Imaging and Clinical biomarkers Trial in Traumatic Brain Injury (PREDICT-TBI) study protocol: an observational, prospective, multicentre cohort study for the prediction of outcome in moderate-to-severe TBI

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ABSTRACT

Introduction Traumatic brain injury (TBI) is a heterogeneous condition with a broad spectrum of injury severity, pathophysiological processes and variable outcomes. For moderate-to-severe TBI survivors, recovery is often protracted and outcomes can range from total dependence to full recovery. Despite advances in medical treatment options, prognosis remains largely unchanged. The objective of this study is to develop a machine learning predictive model for neurological outcomes at 6 months in patients with a moderate-to-severe TBI, incorporating longitudinal clinical, multimodal neuroimaging and blood biomarker predictor variables.

Methods and analysis A prospective, observational, cohort study will enrol 300 patients with moderate-to-severe TBI from seven Australian hospitals over 3 years. Candidate predictors including demographic and general health variables, and longitudinal clinical, neuroimaging (CT and MRI), blood biomarker and patient-reported outcome measures will be collected at multiple time points within the acute phase of injury. The predictor variables will populate novel machine learning models to predict the Glasgow Outcome Scale Extended 6 months after injury. The study will also expand on current prognostic models by including novel blood biomarkers (circulating cell-free DNA), and the results of quantitative neuroimaging such as Quantitative Susceptibility Mapping and Dynamic Contrast Enhanced MRI as predictor variables.

Ethics and dissemination Ethical approval has been obtained by the Royal Brisbane and Women’s Hospital Human Research Ethics Committee, Queensland. Participants or their substitute decision-maker/s will receive oral and written information about the study before providing written informed consent. Study findings will be disseminated by peer-review publications and presented at national and international conferences and clinical networks.

Trial registration number ACTRN12620001360909.

STRENGTH AND LIMITATIONS OF THIS STUDY

⇒ This study incorporates extensive serial measures of clinical data, novel blood biomarkers and longitudinal quantitative MRI measures that will interrogate the dynamic nature of traumatic brain injury.

⇒ To our knowledge, this will be the first longitudinal trial to measure blood brain barrier leakiness by acquiring Dynamic Contrast Enhanced MRI (DCE-MRI) data.

⇒ The value of circulating cell-free DNA for long-term functional outcome will be investigated.

⇒ The acquisition of advanced MRI sequences including DTI (Diffusion Tensor Imaging), Quantitative Susceptibility Mapping, DCE-MRI and resting-state functional MRI at three time points.

⇒ The application of the deep learning artificial intelligence model that can deal with missing data is a strength of this study.

INTRODUCTION

Background and rationale Traumatic brain injury (TBI) is a growing public health problem1 and a leading cause of death and disability globally, with a pooled population incidence rate of 295 cases per 100 000 worldwide,2 and ranges between 1003 and 4153 per 100 000 in Australia. Approximately 44% of hospitalised moderate-to-severe
TBI survivors (after the initial hospitalisation) suffer some form of long-term disability, with a subsequent mortality rate post-hospitalisation of 16.5 deaths per 100 persons per year. For the clinician, TBI presents not only a diagnostic challenge, but a considerable prognostic challenge. While prognostic models have been developed they are not clinically useful because they only account for about 30% of the variance in outcomes. The reasons for this are unclear, but may relate to the selection/measurement of predictor and outcome variables, or the limitations in trying to model highly complex and heterogeneous phenomena with conventional regression techniques.

The 5-level Glasgow Outcome Scale (GOS) and the 8-level extended GOS (GOSE), which provides some added statistical discriminant ability, have been the preferred primary outcomes in TBI research for many years. Most early prognostic models for TBI (including those from the largest studies: International Mission for Prognosis and Clinical Trial (IMPACT) and Corticosteroid Randomisation After Significant Head Injury (CRASH-1)) typically included predictor variables such as injury and patient characteristics, and physiological measurements at a single time point (admission). Their predictive precision is marginally improved by including CT findings or laboratory tests (blood glucose, pH, prothrombin time, haemoglobin and sodium). More recent work has demonstrated the potential utility of serial or longitudinal measurements of biomarkers, the trajectories of which may be useful as either predictors of patient outcomes or as outcome indicators. Multivariate logistic regression techniques, typical of most existing models, have a limited ability to handle longitudinal data, but are further limited by the need to dichotomise outcome (dependent) variables. The highly heterogeneous predictor data and multidimensional outcome data that are characteristic of TBI, may be better analysed by modern machine learning techniques, such as convolutional neural networks.

Images obtained by MRI are more sensitive than CT for detecting brain injuries, and may be useful for prognosis in TBI. Several large cohort studies have incorporated MRI neuroimaging, specifically diffusion tensor imaging, into outcome prediction models for mild TBI. In moderate–severe TBI, patterns of causally located lesions, detected on MRI, correlate with greater severity and poorer long-term neurocognitive outcome. However, despite preliminary evidence of the value of MRI for prognosis, and showing utility of images acquired soon after injury, there is yet to be widespread clinical uptake of MRI for moderate–severe TBI for routine prognostication. In multicentre research, studies such as TRACK-TBI (Transforming Research and Clinical Knowledge in TBI) and CENTER-TBI (Collaborative European NeuroTrauma Effectiveness Research in TBI) have shown that standardisation of MRI techniques across centres is essential. However, to our knowledge all trials to date have focused on admission characteristics without accounting for evolving secondary injury or treatment response in patients with TBI.

In the current study, we will develop a deep learning (DL) model to determine the predictors of neurological outcomes 6 months after injury in patients with TBI. The predictor variables will include non-clinical and longitudinal clinical, CT and MRI neuroimaging and blood biomarker data. The findings of this study will help us better understand the value of longitudinally collected data, including clinical information, imaging and blood-based biomarker information, in the prediction of neurological outcomes. The findings will directly inform the design of future work to validate the machine learning model and determine its impacts on clinical decision-making and patient outcomes. A useful predictive model has the potential to help clinicians more accurately predict the course of recovery, better tailor existing treatments to individual patients and test the effectiveness of new treatments and models of care.

### Objective

The objective of the study, in adults with moderate-to-severe TBIs, is to develop a machine learning predictive model for neurological outcomes at 6 months post-injury, incorporating longitudinal clinical, multimodal neuroimaging and blood biomarker predictor data.

### METHODS AND ANALYSIS

The development of the protocol was conducted in accordance with the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis—https://www.tripod-statement.org/) guidelines. The same will also be employed at the time of reporting results of the completed study.

#### Patient and public involvement

PREDICT-TBI is built on active engagement with consumer representatives who have lived experience with TBI from geographically represented areas of Australia. Patients with lived experience from TBI and clinical nurses and consultants who care for patients with TBI provided direct input into the development of this research question and the development of the study protocol and design.

#### Study design

The study comprises a prospective, observational, cohort design. For all enrolled participants, routinely-collected information related to their hospital admission for TBI will be extracted from prehospital, emergency department (ED) and hospital electronic clinical and administrative information systems. This information will include patient demographics (age, sex, Indigenous status, relationship status), socioeconomic information (postcode, employment status), medical history including comorbidities, prior (significant)
TBI, current medications, injury characteristics (date/time of injury, type, mechanism, severity, isolated or multi-trauma, loss of consciousness), prehospital information (time to arrival on-scene, duration on-scene, treatment on-scene, prehospital medications/fluids, time to arrival to ED), ED information (date/time of arrival, mode of arrival, waiting time, physical observations, investigations/assessments details, radiological findings, diagnosis, treatment time, exit/admission delay time, total ED length-of-stay, treatment details, medications/fluids, departure destination), in-hospital information (serial/repeat physical observations and other physiological/laboratory investigations, neurological outcome measures, clinically-indicated CT and MRI findings and acute complications for up to 14 days after injury, total in-hospital length-of-stay). Information that exists as free text or is otherwise not codified in clinical information systems will be extracted via manual clinical data abstraction by the study nurses. Study-specific blood samples for measurement of novel biomarkers (see below section for details) will be collected at 36 hours, 48–72 hours, days 4, 7, 14, on discharge from intensive care unit (ICU) and on day 90 after injury. Study-specific MRI of the brain scans will be performed after discharge from ICU and at 90 (±14) and 180 (±21) after injury. Other follow-up data including clinical information will be collected from clinical information systems and directly from patients at 3 and 6 months after injury, by the study nurses.

All participants’ data will be de-identified and assigned a unique study identification number, and entered by the study nurses into electronic case report forms via the REDCap, an electronic data capture tool hosted by The University of Queensland and managed by the Queensland Clinical Trials & Biostatistics Centre. A trial master file will be securely stored at each site, which will contain recruitment logs and original signed Patient Information Consent Forms. All data from participating sites will be stored, in-de-identified format, at The University of Queensland’s Research Data Manager system (RDM). The Australian Access Federation (AAF) credentials will ensure local, state, national and international secure collaboration. All data on the RDM will be backed up following local policies and procedures.

De-identified MRI data and side band meta-data (ie, clinical data, textual annotation, survey data, spreadsheets) will be collated into the UQ-managed XNAT repository. The UQ XNAT uses AAF for user authentication and stores the files on the RDM. The UQ XNAT will be integrated with the REDCap system via soft links in both systems linking the imaging data and study data to achieve a shared and collaborative, but structured and secure approach. The final, de-identified study data set will be made available according to the UQ Research Data Management Policy PPL4.20.06 (https://ppl.app.uq.edu.au/content/4.20.06-research-data-management).

Study setting
The study will be coordinated by the Jamieson Trauma Institute (Brisbane, Queensland) and the Queensland Brain Institute, The University of Queensland (Brisbane, Queensland). Participant recruitment and data collection will occur at seven Australian acute care hospitals verified as level 1 trauma centres (or equivalent): the Royal Brisbane and Women’s Hospital, the Princess Alexandra Hospital (Brisbane, Queensland), the Townsville University Hospital (Townsville, Queensland), the Gold Coast University Hospital (Gold Coast, Queensland), the Liverpool Hospital (Liverpool, New South Wales), the Royal Darwin Hospital (Darwin, Northern Territory) and the Alfred Hospital (Melbourne, Victoria). Recruitment will occur between June 2021 and December 2024. Data collection (including follow-up data) will commence in June 2021 and conclude 6 months after the last participant is enrolled. The MRI of the brain scans will be performed using MRI scanners located at each recruiting site. Blood biospecimens will be processed at pathology services within each hospital, stored and further quantified at The University of Queensland. Circulating cell-free DNA (ccfDNA) will be quantified and assayed at the Commonwealth Scientific and Industrial Research Organisation.

The study will be regularly updated on the PREDICT-TBI website: https://qbi.uq.edu.au/PREDICT-TBI.

Participants
Patients will be eligible to participate if, during the recruitment period, they are 18 years of age or older and they are admitted to the ICU at one of the participating hospitals with a diagnosis of either moderate or severe TBI (either in isolation or with other injuries). TBI will be classified as either moderate or severe according to the post-resuscitation and/or pre-intubation Glasgow Coma Scale (GCS) score up to 24 hours after ICU admission, where a GCS score of 9–12 indicates moderate TBI and a score of 3–8 indicates severe TBI. Patients will be ineligible to participate if they meet any of the following exclusion criteria:

- Have had a previous major stroke.
- Are pregnant or may be pregnant.
- In the opinion of the treating team, the GCS deficit is solely due to intoxication, sedation or extracranial injury.
- In the opinion of the investigators, the participant would be unlikely to comply with all study procedures, including follow-up.
- Have an underlying disease with a life expectancy of less than 6 months.
- Have a pre-existing contraindication to MRI.
- Have suffered a devastating TBI with either progression toward brain death at the time of recruitment or why they were declined admission to the ICU.
where the treating medical team are not committed to ongoing full supportive care.

Recruitment
Consecutive eligible patients will be recruited and enrolled by a dedicated study nurse on ICU admission. These patients will not have capacity to provide their own consent during acute care, therefore written and/or verbal informed consent will be sought from a substitute decision-maker if possible. Individual consent and consent to continue processes at each recruiting site will be guided by each jurisdiction.

Treatments
Participants will undergo usual clinical care by their treating clinicians throughout their participation in the study. Study-specific radiology (MRI) scans will be reviewed by the radiology team and clinical team for any urgent action that would be required. The study-specific blood biomarkers will not inform usual clinical care. In Australia, usual care for moderate-to-severe TBI may typically consist of clinical examination supported by intracranial pressure monitoring and imaging, mainly CT. All study patients were managed in tertiary neurosurgical centres with protocolised critical care.

Study-specific measures

Study-specific MRI brain scans: Will be acquired on 3 Tesla whole-body MRI scanners (Siemens and Philips, Healthcare, Germany) using a 32-channel head coil. The full scanning session will last approximately 45 min. The MRI acquisition protocol with detailed information on the sequences is provided in table 1. The data acquired from the MRI of the scans will be processed through several steps using Advanced Normalisation Tool (ANTS, http://stnava.github.io/ANTs/), and FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Diffusion MRI fitting will be performed using FSL’s DTIFIT tool with the diffusion-weighted data from the b=1500 s/mm² shell while the Neurite Orientation Dispersion and Density Index (NODDI) model fitting for the full multi-shell diffusion index will be done using the NODDI MATLAB toolbox (https://www.nitrc.org/projects/noddi_toolbox). All images will be registered using ANTS’s antsRegistrationTemplateConstruction2.sh. The registered functional MRI (fMRI) data will be analysed using the fMRI toolbox (GIFT, https://www.nitrc.org/projects/gift). The Dynamic Contrast Enhanced MRI images combined with the T1 map will be analysed using the ROCKET-SHIP toolbox. The multi-echo gradient echo image will be fitted for susceptibility-weighted imaging using an in-house MATLAB code and processed for Quantitative Susceptibility Mapping measures.

Study-specific blood biospecimens: Will be collected from each participant, consisting of 25 mL of blood (two 10 mL K2 EDTA tubes and one 5 mL serum-separating tube) at each time point. The biospecimens will be used to measure brain-origin cfDNA via droplet digital PCR, and the protein biomarkers glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal hydrolase isoyyme L1 (UCH-L1), total Tau and neurofilament light (NFL) via the Neurology 4-Plex ELISA assay on the Quanterix Simoa platform. Other neurological biomarkers of relevance for consideration include amyloid β 1–40 (Aβ40), amyloid β 1–42 (Aβ42) and various phospho-Tau species, such as Tau phosphorylated at threonine 231. Any remaining samples will form a biobank for future investigations. The two K2 EDTA tubes will undergo laboratory processing within 4 hours of biospecimen collection, consisting of centrifugation at 1900 g for 10 min at 4°C with intermediate deceleration, then transfer of plasma for a second centrifugation. For the EDTA tube dedicated for cfDNA analysis, this second centrifugation is at 14–16 000 g for 10 min at 4°C with full deceleration, then aliquoting into a 6 mL P6 serology tube and storage at −80°C until quantification. For the second EDTA tube, platelet-poor plasma is generated by centrifugation at 1900 g for 10 min at 4°C with full deceleration and aliquoting into 1.5 mL Nunc cryogenic vials, and storage at −80°C until future use. Erythrocytes will be collected from both EDTA tubes and stored in 1.5 mL Nunc cryogenic vials at −80°C for future use. The serum-separating tube, delivered to the pathology laboratory at room temperature, will undergo laboratory processing within 8 hours of collection, consisting of: centrifugation at 1900 g for 10 min at 4°C with intermediate deceleration; aliquoting into one 3.5 mL c cryogenic vial; and storage at −80°C until quantification.

Figure 1 illustrates the expected pathway of a typical patient through the study, illustrating the touch points with study investigators including instances of data collection and follow-ups.

Outcome measures
The predictive model will be designed to predict several neurological outcome measures (NOMs) at two timepoints: 3 and 6 months after injury. The primary outcome is the prediction of the GOSE score, 6 months after injury. The GOSE-TBI, focusing on the specific effects of the TBI, will be administered by research staff who have been trained according to the GOSE manual. The GOSE score will be entered into the machine learning models as an ordinal variable for prediction of outcome based on the eight classes of the GOSE scoring. Secondary outcomes will include the prediction of other NOMs such as the cognitive function on the Cognitive Function 8a scale, and the protein biomarkers glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal hydrolase isoyyme L1 (UCH-L1), total Tau and neurofilament light (NFL) via the Neurology 4-Plex ELISA assay on the Quanterix Simoa platform. Other neurological biomarkers of relevance for consideration include amyloid β 1–40 (Aβ40), amyloid β 1–42 (Aβ42) and various phospho-Tau species, such as Tau phosphorylated at threonine 231. Any remaining samples will form a biobank for future investigations. The two K2 EDTA tubes will undergo laboratory processing within 4 hours of biospecimen collection, consisting of centrifugation at 1900 g for 10 min at 4°C with intermediate deceleration, then transfer of plasma for a second centrifugation. For the EDTA tube dedicated for cfDNA analysis, this second centrifugation is at 14–16 000 g for 10 min at 4°C with full deceleration, then aliquoting into a 6 mL P6 serology tube and storage at −80°C until quantification. For the second EDTA tube, platelet-poor plasma is generated by centrifugation at 1900 g for 10 min at 4°C with full deceleration and aliquoting into 1.5 mL Nunc cryogenic vials, and storage at −80°C until future use. Erythrocytes will be collected from both EDTA tubes and stored in 1.5 mL Nunc c cryogenic vials at −80°C for future use. The serum-separating tube, delivered to the pathology laboratory at room temperature, will undergo laboratory processing within 8 hours of collection, consisting of: centrifugation at 1900 g for 10 min at 4°C with intermediate deceleration; aliquoting into one 3.5 mL c cryogenic vial; and storage at −80°C until quantification.

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<th>SWI-QSM</th>
<th>DWI*</th>
<th>rs-fMRI†</th>
<th>T1 mapping</th>
<th>DCE-MRI‡</th>
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<td>38 measures; 16 s temporal resolution.</td>
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AP, anterior–posterior phase encoding direction acquisition; DCE, Dynamic Contrast Imaging; DWI, Diffusion Weighted Imaging; fMRI, functional MRI echo-planar imaging; FLAIR, Fluid Attenuated Inversion Recovery; FOV, Field of View; 3D mGRE-MRI, 3D multi-echo gradient echo MRI; 3D T1w MPRAGE, three-dimensional T1-weighted Magnetisation-Prepared Rapid Acquisition with Gradient Echo; PA, posterior–anterior phase encoding direction acquisition; rs-fMRI, resting state functional Magnetic Resonance Imaging; SWI, susceptibility-weighted imaging; TE, Time to Echo; TI, Inversion Time; TR, Repetition Time; 3D T2w TSE, 3D T2-weighted turbo spin echo; VIBE, Volumetric interpolated breath-hold examination.
Sample size
A total of 300 participants will be enrolled in the study. This sample size is based on the expected data required for building the DL generative models using structural MRI data. Data augmentation of Magnetisation-Prepared 180 degrees radio-frequency pulses and Rapid Acquisition Gradient-Echo structural MRI volumes will be performed to generate a balanced set of at least 1200 three-dimensional (3D) volumes per imaging time point. Slice-based analysis of this 3D data (100 slices per volume) will ensure that at least 120 000 two-dimensional images will be available for use in the DL models. The numbers are on par for a previous study on manifold learning for MR image reconstruction,49 which is conceptually similar because it modelled the intensities of structural MRI volumes although in k-space. Our model will directly be applied in image space, while using more modern methods that allow resulting manifolds to be manipulated50 for our tasks (see initial work51). Data augmentation will also be applied to all other modalities included in the model.

Data analysis and modelling
The DL generative model will characterise the spatial-temporal relationships between predictors and outcomes at 3-month and 6-month follow-ups. Thus, the important predictive features in the data will be extracted automatically, avoiding any a priori assumptions. This includes the efficacy and optimal combinations of MR sequences, CT images, clinical measures and blood biomarkers. The DL generative model will map the relationships between predictors and outcomes within the data as a ‘manifold’. A manifold is an interconnected higher dimensional surface created by the DL model as it learns the underlying relationships within the data. Once trained, the DL model parameterises the distribution of the data as a differentiable surface, where the local neighbourhoods on the surface represent similar samples. The trends in the data representing outcomes and progression will then have more global structure across this manifold. The types of DL models will include a variational autoencoder (VAE) that will provide a multidimensional probability distribution to represent the TBI manifold across the time points with the predictors being used as ‘priors’ in these models. Recent work in VAEs has shown that it can be used to successfully understand and segment anomalies within MRIs of the brain52 by encoding the imaging information. The priors, such as GCS, GOSE (from previous visits) and biomarkers, will be used as conditions/labels to train the network and construct the manifold, that is, the VAE will learn to model the spatio-temporal data while interpreting the condition to which it belongs. The data from multiple modalities will be handled via multimodal learning, where imaging information and clinical data will be encoded separately and the resulting compressed representations combined using powerful general DL models such as transformers to predict outcomes.53 Once the manifold is constructed, we will interrogate the model through visualisation techniques such as the Uniform Manifold Approximation and Projection54 to reduce its dimensions and view the manifold learnt. This will allow the validation of the findings and model by directly viewing the clustering of said measures. A standard n-fold cross validation will be used to split the imaging data into training and validation sets. Novel methods for dealing with missing data will be implemented as part of the model development. This method has been preliminarily tested on data from the Alzheimer’s disease Neuroimaging Initiative Data set.55

Figure 1  Schematic representation of the study workflow. ICU, intensive care unit; NOM, neurological outcome measures; TBI, traumatic brain injury.
The main hypothesis is that a DL generative model using non-clinical and longitudinal clinical data inputs, including advanced imaging and blood biomarkers, can predict neurological outcomes in patients 6 months after suffering a moderate-to-severe TBI.

Moreover, we hypothesise that the multimodal assessment will enable the identification of integrated mechanisms that are associated with outcome. More specifically, by integrating multiple modalities longitudinally such as imaging, several blood biomarkers and clinical data, this study will provide unprecedented insights into how the brain evolves over time and how such dynamics associate with outcome. These integrated approaches are also hypothesised (or anticipated) to increase prognostic power.

Specific hypotheses
Specific hypothesis related to the individual measures include: (1) Cerebral white matter and grey matter alterations due to structural changes (leading to a degree of irreversible damage) or functional changes (which may have a degree of reversibility) will correlate with patients’ neurological outcome. (2) Brain-origin ccfDNA as markers of structural damage, in combination with other markers such as Tau and amyloid, can objectively define and stratify patients with TBI’s neurological sequelae. (3) Advanced neuroimaging combined with blood biomarkers will be able to better prognosticate patient outcomes compared with the measures used in isolation.

DISCUSSION
TBI is a complex disease with an uncertain clinical course and prognosis. The investigation of TBI produces large quantities of different types of data, the clinical usefulness of which is yet to be fully realised. Machine learning methods may help to ‘unlock’ the potential of these data to strengthen our understanding of TBI and allow for enhanced characterisation, diagnosis and prognosis. Trials such as the IMPACT66 and CRASH-117 represent the best available and externally validated8 models for moderate-to-severe TBI prognosis. However, these data sets contained only simple imaging parameters and virtually no longitudinal or monitoring data, thus greatly limiting the use of available information.

Following the recommendations of IMPACT, several large projects were initiated, including the landmark CENTER-TBI56 and TRACK-TBI57 studies which form part of the International Initiative for Traumatic Brain Injury Research (https://intbir.incf.org/). The aim of this initiative is to develop treatment strategies including precision medicine for the application of individualised therapies and personalised management, healthcare policy, economy and improved health.56 Such task forces have been collaboratively creating large data repositories and applying multidimensional approaches to TBI characterisation and classification. Within this paradigm of integrative research, advanced neuroimaging techniques, mainly diffusion tensor imaging and resting state functional connectivity, have been successfully adopted in mild TBI,18,57 yet the application of neuroimaging and temporal monitoring data at large scale is still required in moderate-to-severe TBI. Preliminary evidence supports the value of advanced MRI for predicting outcomes following TBI50 especially early following the injury.21

The present study is original in many ways: (1) it will capture serial clinical data acutely following injury and at multiple subsequent time points in patients with moderate-to-severe TBI, (2) it will acquire and integrate quantitative brain imaging techniques: Diffusion imaging, dynamic contrast enhanced MRI images which will enable the assessment of dysfunction of the blood brain barrier, cerebral perfusion and cerebral volume; and quantitative susceptibility mapping MRI for the quantitative assessment of the bulk magnetic susceptibility distribution in brain tissue that can give insight into iron concentrations estimates38 and intracranial calcification,39 (3) it will determine the value of ccfDNA as a specific marker of brain injury in moderate-to-severe TBI as a marker of Blood Brain Barrier (BBB) integrity, (4) it will assess the prognostic value of other markers such as GFAP, UCH-L1, NfL, Aβ40, Aβ42 and various phospho-Tau species, markers which have previously shown an association with brain injury severity and progression and (5) it will apply state-of-the-art manifold learning for integration of all data. The biorepository created from this study will allow future investigation of complementary important biomarkers such as S100 and Neuron-Specific Enolase (NSE)60 and novel neurological biomarkers.

Under the main hypothesis of the integration of multimodal data for TBI prognosis, this combination of novel techniques has the potential to improve our understanding of the clinical course for patients with TBI. The study will also improve our understanding of the basic neural mechanisms behind TBI. The rich multimodal data set has the potential to establish new metrics to evaluate brain injury. The completion of this study and its derived developments may potentially provide evidence in a clinical area of unmet needs and support future recommendations with a positive impact on clinical practice and patients’ outcome.

ETHICS AND DISSEMINATION
Ethics
The project received ethical approval by the Royal Brisbane and Women’s Hospital Human Research Ethics Committee (approval number HREC/2020/QRBW/66058). Research coordinators will perform measurements on patients. Any adverse events will be reported to the ethics committee as required by standard protocol. In the early stages of the study, informed consent will be obtained from a substitute-decision-maker or the patient. Informed consent will then be sought from the included patient as soon as they are capable to reliably perceive and understand information themselves about

the purpose of the study, side effects and discomfort associated with procedures. However, all measurements are known to have minimal risk on healthy participants and patients with neurological disorders.

Dissemination plan
The results have the potential to have considerable societal relevance, being highly connected to the outcome of patients with TBI and their families and in turn to a better monitoring and prediction of recovery. The results may also lead to valuable neuroimaging and blood biomarkers that can be used to assess the efficacy of therapeutic interventions and inform precision medicine. The results will be reported as original research articles in peer-reviewed journals as well as in international conferences. The final results will be widely dispersed within the clinical sphere given the significant clinical network nationally and internationally involved in this work. Publications will follow open-access policies in order to increase the extent of the results outreach. Due to the data protection agreement, as well as ethical consent restrictions, individual data will not be made publicly accessible.

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