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Review

Chemo-Omics Integration of the Gut-Brain-Liver Triad in Hepatic Encephalopathy: A Multi-Omics Trans-Integrated Bio-Intelligence Network Framework for Molecular Biomarkers and AI-Driven Precision Therapeutics

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Abstract

Hepatic encephalopathy (HE) is a multifactorial neuropsychiatric comorbidity that develops as a result of hepatic dysfunction, and its pathogenesis is determined by a complex of interactions of gut dysbiosis, hepatic metabolic failure, and neuroinflammation. This study presents the multi-omics framework called Trans-Integrated Bio-Intelligence Network (TIBIN), which explains the gut-brain-liver triad of molecular and microbial interactions based on the combination of metagenomic, metabolomic, proteomic, and epigenomic data with artificial-intelligence-based analytics. This review will fill the gap between systems biology and computational modelling to outline mechanistic pathways between ammonia dysmetabolism, bile-acid signalling and neuroimmune cross-talk in HE pathogenesis by synthesising evidence systematically between 2020 and 2025. The TIBIN model also suggests an AI-written diagnostic algorithm to be used in accurate stratification, which involves microbial signatures, serum-CSF biomarkers, and predictive metabolite panel. This transdisciplinary philosophy highlights a paradigm change in symptom-based management to predictive and personalized hepatoneurology, and provides a guide to clinical translation in the future. Through the combination of omics convergence and machine learning (ML), the paper results in a scalable platform of biomarker discovery, real-time integration of biosensors, and adaptive optimisation of therapeutics.

Keywords

Hepatic encephalopathy, Gut-brain-liver axis, Multi-omics, Artificial intelligence, Precision hepatoneurology

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1. Introduction

Hepatic encephalopathy (HE) is a serious neuropsychiatric complication of liver disease, ranging from minimal hepatic encephalopathy (MHE) with mild cognitive impairments to overt coma and increased mortality [1]. The central feature of HE pathophysiology is the liver's inability to detoxify gut-derived neurotoxins, with hyperammonemia as a key mediator. Ammonia causes astrocytic edema, glutamine accumulation, oxidative stress, and disturbances in glutamatergic and gamma-aminobutyric acid (GABA) neurotransmission, impairing cognitive and motor function. Comorbid factors including neurosteroids, endogenous benzodiazepine-like molecules, and manganese deposition in the basal ganglia exacerbate synaptic dysfunction, microglial activation, and motor-cognitive deterioration [2,3].

Current diagnostic tools, such as the West Haven criteria, psychometric testing, and episodic ammonia measurements, are limited in sensitivity for MHE and inadequately predict progression, as they fail to capture subtle neurocognitive fluctuations [4]. Recurrence of HE often persists despite standard therapies lactulose for osmotic catharsis, rifaximin for selective gut decontamination, and L-ornithine L-aspartate for ammonia scavenging because these treatments achieve only partial symptomatic control [5]. Interventions like transjugular intrahepatic portosystemic shunt (TIPS) may paradoxically increase HE risk by redirecting gut-derived metabolites into systemic circulation, as post-TIPS metabolomic profiling demonstrates heightened exposure to neurotoxic intermediates [6]. Single-target strategies also fail to counter the neuroinflammatory cascades of MHE, including elevated Interleukin-1 beta (IL-1β), interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), reactive oxygen species, and shifts in neuroactive metabolites such as GABA, which continue to drive cognitive impairment even when ammonia is controlled [7].

The gut microbiota modulates host homeostasis via neuronal signaling through the vagus nerve [8], endocrine regulation via the hypothalamic-pituitary-adrenal axis, metabolic mediators such as short-chain fatty acids (SCFAs) and bile acids, and immunological signaling including cytokines and pathogen-associated molecular patterns (PAMPs) [9-11]. Dysbiosis promotes increased ammonia production, intestinal permeability, systemic endotoxemia, and hepatic inflammation through Toll-like receptor 4 signaling [8,9]. Circulating microbial products and altered bile-acid profiles further disrupt blood-brain barrier integrity, activate central microglia, and promote neuroinflammation linked to cognitive and motor dysfunction in HE [10-12].

Addressing HE's complexity requires multi-omics approaches, including 16S rRNA sequencing, metatranscriptomics, metabolomics, and proteomics to define microbial composition, temporal host-microbiome interactions, and functional metabolic pathways [13,14]. Machine learning (ML), graph neural networks (GNNs), and genome-scale metabolic modeling enable the integration of high-dimensional datasets to identify predictive biomarkers and interaction networks [15,16]. Longitudinal datasets allow modeling of disease trajectories and therapeutic responses, supporting early intervention in subclinical stages and reducing reliance on reactive ammonia-lowering measures [16-19].

The trans-omics integrative bioinformatics for interconnected networks (TIBIN) model compiles multi-omics data to define key microbial taxa, bile acid conjugates, and inflammatory nodes, guiding individualized interventions such as microbiome modulators, anti-cytokine biologics, or bile acid receptor agonists alongside conventional therapy [10,20]. Despite extensive studies, most HE research has focused on single-layer analyses of clinical features, microbiome composition, or metabolomic/proteomic signatures without integration. Consequently, the dynamic interactions across the gut-brain-liver axis and their translational potential for predictive biomarkers and targeted therapies remain underexplored.

This study addresses these gaps by applying a chemo-omics TIBIN framework, which integrates multi-omics datasets (metagenomics, metatranscriptomics, metabolomics, and proteomics) with AI-driven analyses to identify molecular biomarkers, therapeutic nodes, and predictive networks. By linking microbial, metabolic, and inflammatory features to clinical phenotypes, this approach offers actionable insights for precision medicine, including stratified prophylactic interventions, targeted microbiome modulation, and individualized therapy selection, thereby moving beyond descriptive summaries toward mechanistic and translational guidance for HE management.

2. Methodology

2.1 Study Design and Reporting Framework

This study was conducted as a systematic and integrative review of literature examining the gut-brain-liver interactions in HE, emphasizing multi-omics integration and AI-driven analyses. The review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, reproducibility, and methodological rigor.

Given the heterogeneity of omics platforms, computational approaches, and study designs, a hybrid methodology combining systematic mapping with structured narrative synthesis was applied. This approach allowed comprehensive evidence integration while maintaining consistency across diverse datasets, supporting the construction of the TIBIN framework for mechanistic and translational interpretation.

2.2 Data Sources and Search Strategy

A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar, covering studies published from January 2020 to November 2025 to capture recent advances in multi-omics and AI-driven research relevant to HE.

The search strategy used Boolean operators and controlled vocabulary with the following string:

("HE" OR "liver dysfunction") AND

("gut-brain-liver axis" OR "microbiome") AND

("multi-omics" OR "metabolomics" OR "metagenomics" OR "proteomics" OR "transcriptomics" OR "epigenomics") AND

("artificial intelligence (AI)" OR "ML" OR "deep learning (DL)")

Searches were conducted independently by two reviewers.

Reference lists of included studies were manually screened for additional relevant publications.

A log of search dates, keywords, and database hits was maintained to ensure reproducibility and transparency.

2.3 Study Selection and Screening

All retrieved records were exported to EndNote X10 for management, and duplicates were removed. Study selection was conducted in two stages:

Title and abstract screening to remove irrelevant studies.

Full-text review for eligibility based on predefined inclusion/exclusion criteria.

Screening was performed independently by two reviewers, with discrepancies resolved through discussion, and a third reviewer arbitrated unresolved conflicts.

The PRISMA 2020 flow diagram was used to document the selection and exclusion process.

Each excluded study was tagged with a reason for exclusion to enhance transparency.

2.4 Inclusion and Exclusion Criteria

Inclusion criteria:

Studies investigating gut-brain-liver interactions in HE.

Use of one or more omics platforms (metagenomics, metabolomics, proteomics, transcriptomics, or epigenomics).

Application of computational, network-based, or AI/ML methods for data integration or analysis.

Peer-reviewed studies published in English between 2020 and 2025.

Exclusion criteria:

Non-peer-reviewed literature (preprints, editorials, conference abstracts).

Studies unrelated to HE or the gut-brain-liver axis.

Articles lacking methodological details sufficient for extraction.

Studies with inadequate statistical or computational rigor.

2.5 Data Extraction and Thematic Synthesis

Data were extracted using a standardized, piloted template to ensure consistency. Key variables included:

Study design, population characteristics, and sample type.

Omics platform(s) employed and molecular targets analyzed.

Identified microbial, metabolic, or molecular biomarkers.

Computational or AI-based integration methods (e.g., Random Forest (RF), Support Vector Machine (SVM), deep neural networks (DNNs).

Diagnostic, prognostic, or therapeutic relevance to HE.

Quality and reproducibility indicators (e.g., cross-validation, independent cohorts).

Data were synthesized into five thematic domains:

Gut microbiome metabolism and ammonia-related pathways.

Astrocyte dysfunction and neuroinflammatory mechanisms.

Multi-omics biomarker discovery.

AI-driven integration and predictive modeling.

Translational and clinical implications.

Findings were then mapped onto the TIBIN conceptual framework, integrating biological, computational, and clinical dimensions of HE.

2.6 Quality Assessment and Risk of Bias

Methodological quality was evaluated using Joanna Briggs Institute (JBI) Critical Appraisal Checklists, adapted to study type (observational, experimental, or computational). Assessment focused on:

Methodological transparency and reproducibility.

Adequacy of statistical and computational approaches.

Validity of omics integration.

Appropriateness of AI/ML model evaluation (e.g., cross-validation, training/testing splits).

Studies with low quality or substantial bias were flagged, and sensitivity analyses were performed to assess their influence on overall conclusions. Exploratory computational studies with conceptual relevance were included but annotated as low-certainty evidence.

2.7 Data Integration and Visualization

Omics-derived features were linked with clinical phenotypes using a knowledge-graph-based computational framework.

Feature selection and biomarker prioritization employed Random Forest, SVM, and DNNs with rigorous cross-validation.

Inter-omics networks were visualized using Cytoscape v3.10, Python libraries (Scikit-learn, TensorFlow, NetworkX).

All workflows were documented with code snippets and parameters to maximize reproducibility.

3. The Triad of Gut-Brain-Liver Systems Biology

The gut-brain-liver triad is a complex neuroimmune-biochemical communication network that regulates metabolism, cognition, and detoxification. This system operates through dynamic feedback loops involving microbial metabolites, cytokine signaling, and neuroendocrine mediators. Systems biology studies indicate that disturbances in any node gut, liver, or brain can trigger multidirectional cascades affecting the other components, positioning HE as a systems-based disorder rather than a purely hepatic pathology [3,10,21].

3.1 Gut Microbiome Dysbiosis and Ammonia Metabolism

The gut microbiome represents the metabolic frontline of the gut-brain-liver triad, orchestrating nutrient fermentation, ammonia metabolism, and immune tolerance. Dysbiosis, characterized by reduced microbial diversity and the depletion of butyrate-producing taxa, promotes the expansion of urease- and glutaminase-expressing bacteria, accelerating ammonia generation and increasing systemic toxicity. Loss of butyrate-producing species further compromises epithelial barrier integrity, facilitating microbial translocation. Concurrently, the enrichment of urease-positive organisms increases luminal ammonia, which disrupts epithelial structure and enters the portal circulation, rapidly exceeding hepatic detoxification capacity and contributing to neurotoxicity [3,10,20].

Beyond ammonia, dysbiosis disrupts additional metabolic networks critical for neurocognitive function. Altered ratios of SCFAs are linked to impaired astrocytic signaling, while dysregulated bile-acid pools modulate microglial activation. Disturbances in tryptophan-derived metabolites, including indoles and kynurenines, further affect neuroinflammatory pathways relevant to cognitive decline in HE. These observations indicate that microbial dysregulation has both ammonia-dependent and ammonia-independent consequences on central nervous system function [5,21,22].

Metatranscriptomic analyses provide mechanistic insight, showing that depletion of microbial genes encoding ammonia-trophic enzymes correlates with cognitive dysfunction in MHE, supporting a direct link between microbial metabolic potential and neurobehavioral outcomes [9,23]. AI-driven network-mapping studies reveal the broader interaction landscape of microbial genes, metabolites, and host physiology. Hub species such as Enterococcus faecalis dominate nitrogen metabolism under dysbiotic conditions, while Klebsiella pneumoniae significantly contributes to

urease-mediated ammonia production. Collectively, these data underscore that ammonia is not merely a metabolic by-product but a central regulatory node within an interconnected microbial-hepatic-cerebral network [24].

3.2 Intestinal Barrier Dysfunction and Leakage of Endotoxins

The dysfunction of the gut-liver-brain axis, when the barrier fails at the gateway, is referred to as barrier dysfunction. This barrier is a complex biophysical filter composed of the intestinal epithelium, tight junction proteins (occludin, ZO-1), and mucus layers that prevent microbial translocation [8]. Dysbiosis and hyperammonemia degrade this barrier, leading to the leakage of endotoxins and systemic inflammation.

Endotoxemia activates hepatic Kupffer cells, triggering cytokine storms that increase oxidative stress and mitochondrial dysfunction in hepatocytes. This process also reduces ammonia clearance, perpetuating a vicious cycle of intestinal permeability and systemic toxicity. Systems biology simulations indicate that microbial-derived lipopolysaccharide (LPS) acts as a cross-organ signalling molecule, reprogramming liver metabolic genes and initiating inflammatory cascades in astrocytes via TLR4 and NF-kB signalling [25-27].

Recent studies show that gut epithelium regeneration through photobiomodulation and metabolic interventions can restore mucosal homeostasis and prevent hepatic inflammation caused by endotoxins. Such models are derived by integrating metabolomics and transcriptomics to quantify barrier functionality as an emergent property of host-microbe interactions.

3.3 Neuroinflammation, Astrocyte Swelling and Cognitive Impairment

The vulnerability of the brain in HE results from the synergistic effects of ammonia neurotoxicity, neuroinflammation, and impaired energy metabolism. Astrocytes, the main ammonia detoxifiers through glutamine synthetase, undergo osmotic swelling under chronic hyperammonemia. This swelling disrupts neuronal communication and impairs cognitive processing [15,16].

Proteomic studies of hippocampal lysates have shown that hyperammonemia alters the expression of neuroprotective enzymes. Inflammatory cytokines derived from peripheral sources exacerbate excitotoxicity in neurons. Microglial sources of cytokines, such as IL-6 and TNF-a, increase oxidative damage. Dysbiosis impairs microbiota-brain signalling. Reduced microbial synthesis of neuroactive metabolites, including GABA and serotonin, contributes to astrocyte and neuronal dysfunction [7,28,29].

HE is now recognized as a network-level neurodegenerative disorder in systems neuroscience. Metabolic stress in the liver propagates synaptic reprogramming via bile acids. SCFAs and kynurenine metabolites also act as molecular mediators connecting the liver and brain. Integrative multi-omics approaches, such as transcriptomics, proteomics, and metabolomics, allow mapping of neuroinflammatory signatures associated with specific microbial taxa. These signatures and metabolite fluxes can serve as predictive biomarkers for early cognitive impairment in HE [13,22].

3.4 Hepatic Detoxification and Mitochondrial Stress and Immune Crosstalk

The liver serves as the biochemical filter of the gut-liver-brain triad, removing ammonia via the urea cycle and producing glutamine. Mitochondrial dysfunction, oxidative stress, and immune reprogramming in HE impair these processes. This dysfunction shifts the liver's role from a metabolic regulator to an inflammatory amplifier [6,14].

Systems modeling indicates that mitochondrial stress not only reduces adenosine triphosphate (ATP), production but also drives immunometabolic changes that favor pro-inflammatory phenotypes in Kupffer and stellate cells. Interactions between hepatic macrophages and intestinal microbiota-derived metabolites, such as indoles and secondary bile acids, regulate NLR Family Pyrin Domain Containing 3 (NLRP3), inflammasome activation. This activation promotes hepatocellular damage and contributes to systemic inflammation [26,27].

The hepatic immune milieu functions as a bidirectional signalling hub, transmitting inflammatory signals to the central nervous system via both humoral and neural pathways. This relay mechanism blurs the boundaries between organs, highlighting the need for multi-omics strategies to capture systemic effects of dysfunction in the gut-liver-brain triad [20,30].

3.5 Inter-Organ Signalling Molecules: Cytokines, Metabolites and Neurotransmitters

Gut-liver-brain molecular dialogue relies on a diverse set of mediators, including cytokines, microbial metabolites, and neurotransmitters, to regulate both homeostatic and pathological processes. Cytokines such as IL-1, IL-6, and TNF-a imediate systemic inflammation by altering neurovascular permeability. They act as primary messengers in the communication between the gut, liver, and brain [22,31].

Microbial metabolites, including SCFAs, tryptophan catabolites, and secondary bile acids, interact directly with G protein-coupled receptors on enterohepatic cells. These interactions modulate metabolic flux and influence neurotransmitter production [20].

Neurotransmitters previously thought to act solely within the central nervous system (CNS), such as GABA, glutamate, and serotonin, are now recognized as components of a distributed signalling network that coordinates gut and brain activity. They also integrate signals from microbial and immune pathways to maintain systemic homeostasis [7,28].

At the systems level, perturbations in this molecular network can shift the triadic system from adaptive to maladaptive signalling, driving the progression of HE. In this context, the gut-liver-brain triad exemplifies a distributed self-regulating circuit, in which local molecular disturbances are amplified through systemic biochemical resonance [32]. The key functional components of this triadic system, their biological roles, and representative molecular events are summarized in Table 1, providing a systems-level framework for understanding HE pathophysiology.

Table 1. Functional layers of the gut-brain-liver triad in HE.

System Component	Key Functional Role	Representative Molecular Events	References
Gut Microbiome	Regulates nitrogen metabolism and immune modulation	Dysbiosis, ammonia production, altered SCFA profiles	[3,8,10]
Intestinal Barrier	Controls permeability and endotoxin translocation	Tight junction disruption, LPS leakage, mucosal inflammation	[8,9,12]
Liver	Detoxifies ammonia and microbial metabolites	Impaired urea cycle, mitochondrial stress, inflammatory cytokines	[1,5,13]
Brain	Integrates neuroinflammatory and metabolic signaling	Astrocyte swelling, microglial activation, GABAergic dysfunction	[15,16,19]
Inter-Organ Signaling Molecules	Coordinate systemic cross-talk	Cytokines, bile acids, neurosteroids, and microbial metabolites	[9,10,17]

3.6 Cohort-Specific Variability and Conflicting Microbiome Signatures in HE

Microbiome alterations associated with HE exhibit notable heterogeneity across clinical cohorts, with no single taxonomic signature consistently replicated between studies. While some investigations report enrichment of urease-positive and ammonia-producing taxa, others describe predominant loss of autochthonous, metabolically protective microorganisms without the emergence of dominant pathogenic species. These discrepancies highlight the complexity of microbiome alterations in HE and underscore the context-dependent nature of dysbiosis [33,34].

Variability in reported microbial profiles is influenced by multiple factors, including disease severity, underlying liver disease etiology, prior exposure to antibiotics or ammonia-lowering therapies, dietary patterns, geographic differences, and methodological inconsistencies in sequencing and bioinformatic pipelines. As a result, taxonomic-level findings often lack reproducibility, limiting their standalone translational value [35-37].

Despite these inconsistencies, convergence is observed at the functional level. Independent cohorts consistently demonstrate perturbations in microbial metabolic pathways related to nitrogen metabolism, urease activity, SCFA biosynthesis, bile acid transformation, and endotoxin production. These shared functional disruptions align closely with core pathological features of HE, including hyperammonemia, intestinal barrier dysfunction, and neuroinflammation [38].

Collectively, these observations suggest that microbial functional capacity and metabolite output represent more robust and biologically meaningful markers of HE than individual taxa. Integrative multi-omics approaches that combine metagenomics, metatranscriptomics, metabolomics, and host-response profiling are therefore essential to reconcile cohort-specific variability and to identify conserved disease mechanisms with diagnostic and therapeutic relevance. Indeed, identifying these conserved mechanisms is critical for developing robust diagnostic biomarkers and targeted therapeutic strategies that overcome the challenges posed by individual variability and the complex interplay within the microbiota-gut-liver-brain axis [33,34].

4. Multi-Omics Understandings of the Gut-Brain-Liver Triad

Understanding HE requires moving beyond isolated molecular observations to a whole-systems perspective. Multi-omics technologies including metagenomics, metatranscriptomics, metabolomics, proteomics, lipidomics, and epigenomics enable the detailed exploration of complex signaling pathways that govern interactions among host physiology, microbial metabolism, and neural function. These multi-layered datasets are integrated into the TIBIN framework, a computational model that reconstructs dynamic biological interactions and identifies precision therapeutic targets [39,40].

4.1 Metagenomics and Metatranscriptomics: Cracking Microbial Functional Shifts

Metagenomics and metatranscriptomics provide complementary insights into microbial communities, revealing not only taxonomic composition but also metabolic potential and transcriptional dynamics. In HE, the gut microbiome undergoes profound alterations driven by hepatic insufficiency, bile-acid dysregulation, and systemic inflammation [41].

Metagenomic analyses show a loss of key SCFA-producing taxa, such as Faecalibacterium and Roseburia, alongside an increase in urease- and endotoxin-producing bacteria. This compositional shift promotes elevated ammonia and neurotoxin flux, contributing directly to HE pathogenesis [42,43].

Metatranscriptomics adds a dynamic layer, highlighting upregulation of urease pathways and amino-acid decarboxylases under hyperammonemic conditions [6,40]. These activity signatures demonstrate how microbial metabolism adapts to nitrogen overload and oxidative stress, linking transcriptional plasticity to disease severity. Importantly, combining metagenomics with metatranscriptomics allows differentiation between dormant and metabolically active microbial populations a distinction not achievable with 16S rRNA sequencing alone [43].

Integrative machine-learning models enhance predictive accuracy for HE progression [41]. By coupling microbial gene networks with host transcriptomic data, researchers can identify causal interactions for example, microbial expression correlates with astrocytic glutamine synthetase dysregulation. This multi-omic integration lays the foundation for precision microbiome interventions within the TIBIN framework [39,41,43].

4.2 Metabolomics: Mapping Gut-Derived Metabolites in HE

Metabolomics serves as the functional readout connecting microbial activity to host physiology. By profiling small-molecule mediators in gut-liver-brain signaling, metabolomics identifies critical biochemical changes in HE. Key mediators include SCFAs, ammonia, and bile acids [9,13].

SCFAs, such as butyrate and propionate, are produced by fermentative microbes. They support epithelial barrier integrity, modulate neuroinflammatory tone via G-protein-coupled receptors, and influence hepatic gluconeogenesis. Loss of SCFA-producing microbes in HE contributes to intestinal barrier dysfunction and endotoxemia [8,9,10].

Ammonia, generated through microbial urease activity and impaired hepatic detoxification, drives astrocytic swelling, mitochondrial dysfunction, and neurotransmission dysregulation. Hyperammonemia can be quantified in serum, urine, and cerebrospinal fluid (CFS) via metabolomic profiling, providing biomarkers for early HE detection [6,15,42].

Bile acids function as central regulators of hepatic and neural homeostasis. Altered bile-acid composition influences farnesoid X receptor (FXR) and Takeda G-protein receptor 5 (TGR5) signaling, modulating microglial activation and cognitive function. Integrating metabolomic data with transcriptomics reveals how conjugated bile acids regulate neuroinflammation and synaptic plasticity [13,42].

Network-based metabolomic analyses highlight inter-metabolite crosstalk. For instance, SCFA depletion exacerbates ammonia-induced mitochondrial stress, underscoring the interplay between microbial metabolism and host neural function. These insights support biomarker discovery and therapeutic targeting, which can be leveraged via probiotics, prebiotics, or fecal microbiota transplantation (FMT) [2,39,42].

4.3 Proteomics and Lipidomics: The Discovery of Circulating and Cerebral Biomarkers

The application of proteomic and lipidomic technologies enhances multi-omics resolution in translational studies, allowing identification of host-derived factors involved in inflammation, oxidative stress, and neural signalling [39]. Quantitative proteomic analyses of serum and CSF from HE patients reveal dysregulation of neurofilament proteins, ammonia-detoxifying enzymes, and glial fibrillary acidic protein (GFAP), reflecting astrocyte activation and neuronal damage [15,16].

Advanced lipidomic studies demonstrate alterations in phosphatidylcholine profiles and sphingolipid composition, indicating changes in neuronal membrane structure and synaptic transmission. These lipidomic changes are linked to mitochondrial stress in hepatocytes and microglia, connecting peripheral lipid metabolism with central neurodegeneration [42].

Comparisons of proteomic signatures with gut metagenomic data reveal coordinated pathways, such as microbial LPS synthesis, which associates with hepatic complement activation. These integrated biomarker panels have the potential to refine clinical stratification by identifying inflammatory subtypes of HE. Computational models incorporating protein-interaction networks enable dynamic simulation of molecular fluxes across organ systems [39].

Emerging spatial proteomics and single-cell mass spectrometry provide region-specific proteomic landscapes in liver lobules and hippocampal subfields. Together, proteomics and lipidomics serve as diagnostic and mechanistic pillars, offering unprecedented granularity in understanding HE pathogenesis [16,41].

4.4 Epigenomics: Crosstalk of MicroRNA and Histone Modifications of Gut, Liver, and Brain

Epigenomic regulation provides a dynamic link between environmental stimuli, microbial metabolites, and host gene expression. MicroRNAs (miRNAs) and histone modifications act as tightly regulated switches, encoding metabolic and inflammatory signals into long-term transcriptional alterations. These mechanisms integrate microbial and host-derived signals to shape cellular function [39,41].

In HE, ammonia detoxification, neuroinflammatory regulation, and astrocyte homeostasis are associated with differential expression of miR-122 [6], miR-155, and miR-132. Butyrate and other gut-derived SCFAs act as histone deacetylase (HDAC) inhibitors, modulating chromatin accessibility and regulating tight-junction and cytokine gene expression. Chromatin immunoprecipitation sequencing (ChIP-seq) has been used to map hepatic histone-acetylation signatures and to correlate these modifications with microbiome-derived metabolite flux.

These findings demonstrate the bidirectional influence between the microbiota and host epigenome, whereby microbial metabolites alter gene expression, and host immune responses reorganize microbial ecology. Causal inference can be strengthened by incorporating epigenomic data into the TIBIN network, revealing the mediating role of epigenetic rewiring during long-term organ crosstalk and treatment responsiveness [44,45].

4.5 Integrative Omics Modeling: Triad Network Reconstruction

Integrative multi-omics seeks to reconstruct functional networks across the gut-liver-brain axis in HE. By combining genomic, transcriptomic, proteomic, metabolomic, and epigenomic datasets, the TIBIN framework enables the creation of causal interaction maps that trace information flow from microbial metabolism to hepatic and neural outcomes [39,41].

Using Bayesian inference and network topology analysis, TIBIN identifies hub molecules such as TNF-α, glutamine synthetase, and bile-acid transporters that maintain system stability. These computationally derived insights provide a roadmap for drug target prioritization and in silico intervention design [13,15,41].

Deep-learning approaches facilitate the integration of high-dimensional datasets into adaptive models that continuously refine predictions as new clinical and molecular data are acquired. Such iterative feedback loops shift HE management from reactive interventions to proactive, precision-guided prediction. With decreasing sequencing costs and improved computational pipelines, integrative multi-omics is poised to advance personalized therapeutics [40-42].

Ultimately, TIBIN operationalizes multi-omics by capturing distinct yet interconnected molecular signatures across metagenomics, metabolomics, proteomics, lipidomics, and epigenomics. By reconstructing cross-organ signaling networks that link the gut, liver, and brain (Figure 1), this framework provides a systems-level understanding of HE, enabling the identification of robust biomarkers and the rational development of precision-guided therapeutic strategies [40,41,44].

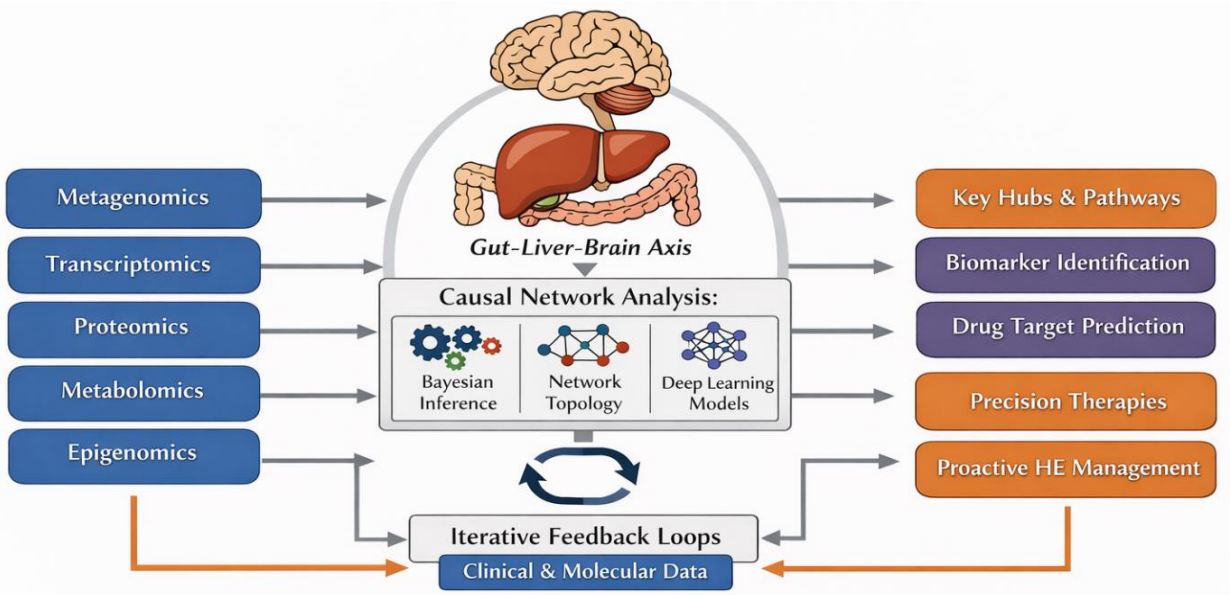

Figure 1. Integrative multi-omics network reconstruction of the gut-liver-brain axis in HE within the TIBIN framework.

4.6 Role of the Gut Microbiome in HE

The gut microbiome plays a central mechanistic role in the pathogenesis of HE by influencing systemic metabolism, immune signaling, and neural function through the gut-liver-brain axis. Accumulating evidence indicates that dysbiosis in cirrhosis and HE leads to increased production of neurotoxic metabolites such as ammonia and endotoxins, which escape hepatic detoxification due to liver dysfunction and contribute to systemic inflammation and neuroinflammation in the brain. This is compounded by increased gut permeability ("leaky gut") and bacterial translocation, which amplifies inflammation and disrupts the blood-brain barrier (BBB), exacerbating HE symptoms beyond ammonia toxicity alone [30].

Microbial alterations in cirrhotic patients typically include a depletion of beneficial taxa such as Lachnospiraceae and Ruminococcaceae, which are important producers of SCFAs that support intestinal barrier integrity and modulate

immune responses, and an increase in pathogenic bacteria associated with ammonia production and inflammation. SCFAs have been shown to decline significantly in overt HE, and reduced SCFA-producing bacteria correlate with disease severity, suggesting that microbial metabolites act as modulators of host metabolic and inflammatory pathways relevant to HE progression [30].

Beyond ammonia and SCFAs, gut microbiota also affect bile acid metabolism, immune activation, and neurotransmitter pathways, which collectively influence both liver function and brain physiology. These interactions underscore the complex network of gut-liver-brain communication that contributes to HE pathophysiology, emphasizing that microbial dysbiosis is not merely a bystander but an active player in disease development [14].

Clinically, the recognition of microbiome dysregulation in HE has therapeutic implications: microbiome-targeted interventions such as lactulose, rifaximin, probiotics, synbiotics, and FMT have shown promise in ameliorating HE symptoms, reducing ammonia levels, and improving cognitive outcomes by restoring microbial balance and reducing systemic inflammation.

Integrating gut microbiome findings into a systems biology framework like TIBIN helps elucidate how microbial signals interact with liver and brain pathways to drive HE, supports the rationale for microbiome-based biomarkers, and guides precision therapeutic strategies that extend beyond conventional ammonia-focused models.

5. The TIBIN Framework: TIBIN

5.1 Theoretical Basis of the TIBIN Model

The TIBIN is a next-generation systems biology framework designed to integrate molecular data, inter-organ communication, and AI-driven modeling to decipher gut-brain-liver interactions in HE. Traditional models often treat the gut, liver, and brain as independent systems, overlooking their dynamic, bidirectional biochemical crosstalk [25,31].

TIBIN fills this gap by combining multi-omics datasets, clinical biomarkers, and machine-learning predictions to identify emergent phenomena that single datasets cannot reveal. The framework reconceptualizes HE as a network-level disorder, where microbial dysbiosis, ammonia overload, mitochondrial dysfunction, and inflammatory cytokine release are interlinked through distributed gut-brain-liver signaling. By leveraging computational intelligence, TIBIN transforms descriptive multi-omics data into actionable systems-level insights, creating a platform for predictive diagnostics and precision therapeutics [23,41].

5.2 Layered Architecture of TIBIN

The TIBIN framework is structured into four interconnected layers, each representing a domain of biological data and computational processing. Feedback loops between layers enable adaptive learning, continuously improving predictions as new data are incorporated [25].

5.2.1 Molecular Layer: Genomic and Metabolic Inputs

The molecular layer integrates genomic, metagenomic, and metabolomic data to define individual disease susceptibility and progression. Microbial gene clusters regulating urease activity, bile-acid transformation, and SCFA production influence ammonia metabolism and hepatic load. Host-derived transcriptomic data from hepatocytes, astrocytes, and microglia provide insight into mitochondrial oxidative stress and inflammatory gene activation across organ systems [26,45].

This layer identifies molecular switches linking microbial activity to host responses. For example, Enterococcus faecalis and Clostridium difficile enhance ammonia synthesis, whereas beneficial taxa such as Lactobacillus modulate glutamine synthetase activity to suppress neurotoxicity [24,40,43].

5.2.2 Network Layer: Inter-Organ Communication Pathways

The network layer represents dynamic cross-organ interactions mediated by metabolites, cytokines, neurotransmitters, and extracellular vesicles. It quantifies communication flux within the gut-liver-brain triad [39].

For example, gut-derived LPS activate hepatic Kupffer cells, inducing systemic cytokine release including TNF-α [30] and IL-6 [41] which modulate astrocyte function and neural excitability. Conversely, neuroinflammatory mediators such as IL-1β from microglia influence vagal tone [21] and hepatic metabolism [45]. In TIBIN, these interactions are represented as directed weighted graphs, allowing computational reconstruction of inter-organ dependencies.

5.2.3 Computational Layer: Systems Modeling and AI

The computational layer embodies TIBIN's AI-driven intelligence, employing ML and causal inference to identify predictive patterns in multi-omic and clinical data. Graph-based algorithms and DNNs uncover topological motifs distinguishing healthy from pathological states [32,40].

Dynamic data assimilation enables continuous model updates from longitudinal patient data, including microbiome composition, serum metabolites, and neurocognitive assessments. Explainable AI (XAI) highlights the most clinically relevant features such as ammonia concentration, SCFA ratios, or miRNA profiles bridging the gap from computational predictions to actionable clinical decisions.

Causal graph theory extends correlation-based inferences into mechanistic models of organ-to-organ signaling. For example, hepatic mitochondrial stress precedes neuroinflammatory cascades, guiding therapeutic prioritization and biomarker discovery [26,40].

5.2.4 Translational Layer: Clinical and Biomarker Application

The translational layer connects TIBIN-derived predictions to clinical diagnostics, therapeutic targeting, and personalized medicine. Biomarkers identified through upstream multi-omics integration are mapped onto clinically measurable variables such as serum ammonia, circulating cytokines, and cognitive performance scores [27,42].

This alignment enables clinicians to interpret computational outputs in a patient-specific context, supporting biomarker-guided therapy and early intervention strategies. The translational layer thus operationalizes multi-omics discoveries into precision medicine applications for HE.

An overview of the key translational biomarkers, their associated omics origins, and corresponding clinical applications is summarized in Figure 2, illustrating how the TIBIN framework operationalizes molecular insights into patient-centered clinical outcomes.

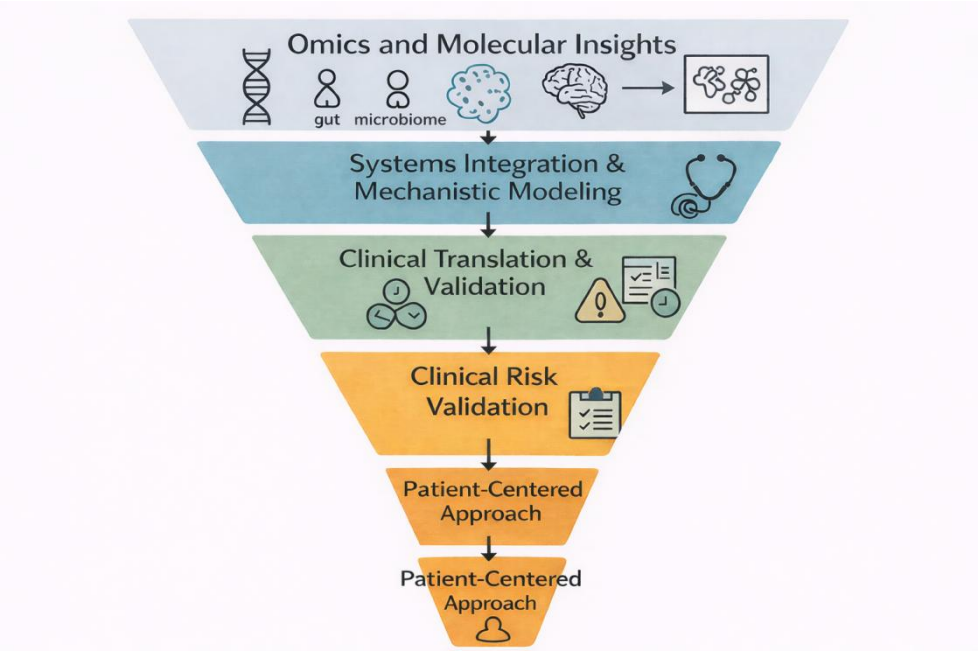

Figure 2. Translational layer: Integrating omics insights into clinical and biomarker applications.

This Figure 2 illustrates the progressive translation of omics and molecular discoveries into clinically actionable biomarkers. The framework moves from molecular and mechanistic understanding through systems integration, clinical translation, and biomarker validation, culminating in patient-centered outcomes and precision medicine.

Table 2. Multi-omics platforms in the TIBIN framework.

Omics Layer	Analytical Tools and Platforms	Major Outputs and Applications	References
Metagenomics	Whole-genome sequencing (Illumina, Nanopore), 16S rRNA profiling	Identifies microbial diversity, dysbiosis, and ammonia-producing taxa	[9,25,27]
Metatranscriptomics	RNA-Seq, qPCR arrays	Decodes microbial gene expression and metabolic pathway shifts	[2,9,26]
Metabolomics	LC-MS/MS, GC-MS, Nuclear Magnetic Resonance (NMR) spectroscopy	Profiles bile acids, SCFAs, and neuroactive metabolites	[5,28]
Proteomics/Lipidomics	MALDI-TOF, SWATH-MS, targeted mass spectrometry	Reveals plasma and CSF biomarkers of hepatic stress and neuroinflammation	[25,27,28]
Epigenomics	miRNA sequencing, ChIP-Seq, methylation analysis	Identifies histone modifications and miRNA networks regulating inflammation	[25,29,31]
AI and Computational Layer	ML (RF, CNNs), network analysis	Predicts HE progression and integrates multi-omics datasets	[25,27,30]

Clinically, TIBIN facilitates precision stratification by sorting HE patients based on individual gut-brain-liver signatures rather than general symptomatology. This enables tailored interventions, including microbiome modulation via probiotics or fecal transplantation, hepatic detoxification therapies, and neuroprotective agents, guided by the patient's systemic profile. The multi-omics platforms and analytical layers underpinning this precision stratification, along with their clinical applications, are summarized in Table 2. The framework further supports real-time feedback loops, allowing continuous improvement of the computational model using therapeutic outcomes, thereby creating a dynamic system of clinical intelligence [24,43].

5.3 Mapping the Dynamics of Feedback between the Gut, Brain, and Liver

A core strength of TIBIN is its ability to capture bidirectional feedback mechanisms that either maintain homeostasis or drive dysfunction across the gut-brain-liver triad. Unlike static network models, TIBIN employs temporal system mapping, which models how perturbations in one organ propagate over time to others through molecular signaling.

For instance, gut dysbiosis-induced ammonia overproduction increases systemic neurotoxins, impairing astrocytic glutamate uptake, causing excitotoxicity, and disrupting neurotransmission. Concurrent hepatic inflammation further increases blood-brain barrier permeability, amplifying a vicious cycle of metabolic and neural dysfunction [25,29].

TIBIN quantifies both the directionality and strength of these inter-organ interactions by integrating time-series multi-omics data into feedback-aware AI architectures. This dynamic approach is more biologically representative than traditional correlation matrices, enabling clinicians to visualize real-time interactions between microbial, hepatic, and neuronal biomarkers. Such temporal mapping represents a key milestone toward predictive pathophysiology in HE.

5.4 Predictive Intelligence: AI Learning Pathophysiology

The predictive power of TIBIN emerges from iterative AI learning, where computational models are simulated, tested, and optimized against empirical datasets [40,44]. Reinforcement learning allows virtual interventions such as modifying microbial composition or suppressing cytokine signaling to predict their downstream effects on hepatic and neural function.

TIBIN identifies critical intervention points within molecular networks where perturbations can restore homeostasis. For example, AI models can learn that restoration of Lactobacillus-derived butyrate reduces systemic inflammation and hepatic stress, indirectly improving cognitive outcomes in HE patients [39,41].

This adaptive intelligence ensures that TIBIN continuously evolves, integrating new insights from clinical trials, wearable biosensors, and longitudinal microbiome sequencing studies. By learning from real-world interventions, TIBIN supports precision-guided, dynamic management strategies for HE.

5.5 TIBIN Framework Research Strategy: Clinical Database Validation

To achieve robust translational impact, TIBIN requires a multi-tiered validation pipeline combining in silico modeling, clinical cohorts, and translational studies [29,42]. Multi-cohort validation tests the framework's performance against established HE diagnostic models across populations and disease severities, benchmarking predictive accuracy.

Clinical validation involves comparing TIBIN-predicted biomarkers with quantitative plasma, cerebrospinal, and imaging-based measures. Integration with fMRI and MR spectroscopy confirms AI-inferred connectivity between hepatic metabolism and neural activity [31,43].

Prospective interventional trials directed by TIBIN predictions can assess therapeutic efficacy. Successful validation would position TIBIN as a digital twin of the gut-brain-liver axis, providing real-time decision support to clinicians for HE management and related disorders.

5.6 TIBIN Framework: Conceptual Construction and Reported Validation in Multi-Omics

The (TIBIN) framework represents a systems-level approach to elucidate complex molecular interactions across the gut, liver, and brain axis by integrating diverse high-throughput omics datasets. Although TIBIN itself may be a novel term coined within this review, it builds upon widely used multi-omics integrative strategies that have been increasingly applied to complex disorders such as (HE). Multi-omics integration facilitates an understanding of disease pathophysiology by capturing the combined influence of microbiome, metabolome, transcriptome, proteome, and other molecular layers, which cannot be fully resolved by single-omics analyses alone [46].

5.6.1 Conceptual Construction of the TIBIN Model

(1) Multi-Omics Data Fusion Across Organs

The core of TIBIN involves vertical and horizontal data integration across three biological systems gut (including microbiota and host intestinal signals), liver (metabolic and immunological functions), and brain (neural, neuroinflammatory, and neurotransmitter pathways). This is conceptually grounded in evidence that HE pathogenesis is

shaped by metabolites originating from the gut and liver that ultimately influence brain function via systemic circulation and neural pathways.

(2) Network-Based Integration Strategies

TIBIN draws on network-based multi-omics integration methods, which represent biological entities (e.g., genes, proteins, metabolites) as nodes and their associations as edges such that complex interactions can be modeled computationally. Researchesshow that network extension methods including graphical models, similarity network fusion, and ML-driven networks are central to multi-omics frameworks for complex diseases and biomarker discovery.

(3) Layered Interaction Mapping

In TIBIN, individual omics layers (e.g., metabolome, transcriptome) are integrated first within each organ system and then cross-linked to map inter-organ crosstalk. For example, integrative analyses have linked gut microbiota metabolites to host transcriptomes in HE patients, identifying hub genes and pathways that form a multi-layer molecular network spanning gut, immune, and neural components.

(4) AI and ML Components

Emerging literature emphasizes that modern multi-omics integration increasingly incorporates AI-driven algorithms (e.g., ML classification, network feature extraction, GNNs) to discern patterns that may serve as biomarkers or mechanistic indicators. Such methods improve predictive performance and can highlight important biological features across omics layers.

5.6.2 Reported Validation and Evaluation

Because TIBIN in its full form is a conceptual integrative framework rather than a single published algorithm, validation of its components is inferred from multi-omics studies incorporating network and systems biology approaches:

(1) Cross-Dataset and Cross-Condition Corroboration

Published multi-omics investigations often validate integrative findings by verifying that molecular signatures are consistent across independent datasets or different biological conditions. Meta-analytical comparisons, pathway enrichment, and consensus network features are typical validation pathways in multi-omics reviews.

(2) Biological Plausibility Checks

Validation in multi-omics contexts frequently relies on demonstrating that integrated signals converge on known biological processes for example, systemic inflammation, oxidative stress pathways, and neuroimmune signaling in HE which reinforces the biological relevance of the inferred network [47].

(3) Benchmarking Against Known Biomarkers

Network integration results are often assessed against established biomarkers or previously reported mechanistic pathways. In HE, integration of gut microbiota-derived metabolites with host gene expression has revealed overlapping hub genes and molecular routes that align with emerging mechanistic insights beyond classical hyperammonemia paradigms [47].

(4) Robustness Through Multi-Level Analytics

Studies applying multi-omics integration typically perform robustness checks such as multi-level enrichment analysis (e.g., gene set enrichment, pathway analysis), statistical cross-validation, and sensitivity analyses to ensure findings are stable across analytical configurations.

The TIBIN framework synthesizes multi-omics integration and network modeling methods documented in the literature to bridge gut-liver-brain interactions in HE. Its construction is rooted in established multi-omics integration principles especially network-based approaches and its validation in review contexts is grounded on consistency with known biology, cross-dataset corroboration, and convergence on clinically relevant mechanisms.

6. Integrative Biomarkers of Precision Stratification

6.1 Early Diagnosis Using Microbial Signatures and Metabolite Panels

Early detection of HE relies on high-resolution biomarker systems capable of capturing its multidimensional nature. Recent evidence indicates that the structure of gut microbial communities and their metabolic output can predict HE onset even before clinical symptoms emerge. The TIBIN model redefines early diagnosis by integrating multi-omics signatures simultaneously analyzing microbial, metabolic, and host immune data to forecast pathophysiological states [23,39].

Key microbial taxa in preclinical HE include Enterococcus faecalis, Clostridium difficile, Klebsiella pneumoniae, and Bacteroides fragilis, which drive urease-mediated ammonia production and stress gut epithelial integrity. Protective species such as Lactobacillus and Faecalibacterium prausnitzii produce SCFAs like acetate and butyrate, supporting tight-junction integrity and astrocytic energy metabolism. Dysbiosis destabilizes metabolic homeostasis, weakening the gut barrier and triggering inflammatory cascades that affect both hepatic and neuronal cells [31,41,42].

Metabolite-based biomarker panels translate microbial activity into biochemical footprints, including elevated ammonia, indole derivatives, bile acids, and branched-chain amino acids. Advanced metabolomics techniques mass spectrometry and NMR spectroscopy allow simultaneous quantification, enabling construction of diagnostic indices that reflect both microbial metabolism and host detoxification efficiency [25,40,45].

Integration of microbial and metabolic measures via machine-learning classifiers (e.g., support vector machines) improves early disease detection with superior sensitivity and specificity compared to single-marker assays. These microbial-metabolite panels constitute the first diagnostic layer of TIBIN, providing a non-invasive, data-rich foundation for precision stratification [27,32].

6.2 Gut-Serum-CSF Combined Biomarkers for Stage-Specific HE Classification

Accurate diagnosis and staging of HE increasingly require multi-compartmental biomarker assessment that integrates signals from the gut, systemic circulation, and CNS. Within the TIBIN framework, CSF biomarkers complement stool and serum analyses, enabling a more comprehensive characterization of the molecular continuum linking intestinal dysbiosis, systemic inflammation, and neurochemical dysregulation [23]. The resulting gut-serum-CSF biomarker signature reflects the progressive transmission of metabolic and inflammatory disturbances from the intestinal microbiome through hepatic metabolism to the brain, providing a biologically integrated model of HE pathogenesis [23,31].

At the gut level, dysbiosis promotes excessive ammonia generation, endotoxin release, and disruption of intestinal barrier integrity. These alterations contribute to systemic inflammatory activation and metabolic stress, reflected in the serum by elevated levels of TNF-α, IL-6, IL-1β, hyperammonemia, and oxidative stress markers such as malondialdehyde. Parallel biochemical changes occur within the central nervous system, where CSF analyses reveal elevated glutamine concentrations, reduced SCFAs, and markers of neuroinflammation including S100B and GFAP. Together, these alterations reflect astrocytic swelling, impaired neurotransmitter metabolism, and microglial activation hallmarks of the neurochemical disturbances underlying HE-associated cognitive dysfunction [25,30,44].

Importantly, disturbances in neurotransmitter balance particularly involving glutamate and γ-aminobutyric acid (GABA) begin early in the disease process and progressively intensify as HE advances. Rather than emerging exclusively in late stages, these neurochemical alterations develop during minimal or covert HE and contribute to the gradual deterioration of cognitive and neuropsychological function across the disease continuum. Within the TIBIN model, cross-compartmental biomarker integration therefore enables the identification of stage-specific molecular patterns that reflect progressive amplification of interconnected gut, systemic, and neural disturbances.

Stage I-II (minimal/covert HE) are characterized by early microbial dysbiosis, moderate hyperammonemia, and mild systemic inflammation, typically reflected by modest increases in IL-6 and oxidative stress markers. At this stage, subtle alterations in neurotransmitter metabolism—including early glutamate-GABA imbalance may already be detectable, accompanied by slight elevations in CSF glutamine and early astrocytic metabolic stress.

Stage III (intermediate HE) demonstrates broader systemic inflammation and more pronounced neurochemical disruption. Elevated inflammatory mediators, increasing ammonia levels, and detectable CSF changes including higher glutamine and IL-1β concentrations reflect escalating neuroinflammatory signaling and astrocytic dysfunction. Neurotransmitter imbalance becomes more evident at this stage, contributing to worsening cognitive impairment and impaired neural network regulation.

Stage IV (overt HE) represents the culmination of these processes, marked by severe neuroinflammation, pronounced oxidative stress, and profound neurometabolic disturbance. At this stage, glutamate-GABA dysregulation becomes highly pronounced, reflecting advanced astrocytic swelling, impaired ammonia detoxification, and widespread disruption of neuronal signaling pathways.

Through this second diagnostic layer, TIBIN converts heterogeneous biochemical measurements across biological compartments into a unified disease model. By integrating gut microbial signals, systemic inflammatory markers, and CSF neurochemical changes, the framework enables differentiation between mechanistic HE subtypes, including ammonia-dominant metabolic forms, immune-driven neuroinflammatory variants, and phenotypes associated with hepatic mitochondrial dysfunction [26,39]. Such integrative classification provides a mechanistic foundation for precision diagnostics and targeted therapeutic strategies in HE.

6.3 AI-Assisted Omics Integration: Predictive Modelling and Feature Selection

AI is the analytical engine of TIBIN, capable of handling the high-dimensionality of multi-omics data, including metagenomics, transcriptomics, metabolomics, and proteomics [32,40]. Conventional biomarker pipelines cannot manage the tens of thousands of features present in such datasets.

TIBIN employs DL neural networks, particularly GNNs and variational autoencoders (VAEs), to uncover hidden interactions between gut microbial gene expression, hepatic detoxification, and neuronal mitochondrial integrity [27,40]. These iterative models assign importance-ranked weights to biomarkers (genes, metabolites, cytokines), prioritizing features that determine HE severity.

XAI modules provide clinically interpretable visualizations, showing which biomarkers drive predictions. For instance, butyrate depletion and elevated bile acids may indicate early HE, whereas TNF-a and S100B dominate late-stage disease prediction.

Cross-cohort generalization allows TIBIN-trained models to predict HE risk in diverse populations. Transfer learning further enables application to related disorders, such as Non-Alcoholic Fatty Liver Disease (NAFLD) or hepatic-Alzheimer comorbidity, demonstrating broad translational potential [39,42].

This constitutes the third diagnostic tier of TIBIN: predictive modeling with AI-enhanced biomarker prioritization, converting complex multi-omics data into actionable clinical insights [39].

6.4 Composite Index Development: TIBIN Diagnostic Risk Matrix (TDRM)

To translate predictions into clinically actionable scores, TIBIN introduces the TDRM. This composite index integrates microbial, metabolic, immunological, and neurochemical features into a single, interpretable risk profile.

The TDRM functions as both a diagnostic and prognostic tool, estimating HE likelihood, progression, or therapeutic response in real time [41]. Dynamic monitoring allows clinicians to assess treatment effects:

Protective signals: High Lactobacillus abundance and favorable bile-acid ratios lower the TDRM score, indicating restored gut-liver-brain communication [43].

Risk signals: Increases in inflammatory markers automatically update TDRM, alerting clinicians to potential relapse [39]. Thus, the TDRM operationalizes TIBIN's multi-layered outputs into a quantitative, actionable framework for precision HE management.

The TDRM also functions as a decision-support interface, combining predictive analytics, time-series visualizations, and personalized treatment recommendations. Within hospital or telemedicine environments, the TIBIN platform can continuously process incoming laboratory and sensor data to update patient risk scores every 24 hours. These adaptive stratification capabilities align with precision medicine principles, whereby interventions whether antibiotics, probiotics, lactulose therapy, or neuroprotective compounds are guided by the patient's evolving systemic profile rather than solely by clinical grading [29,44]. The integrative biomarker panels supporting these decision-making processes and their corresponding clinical applications are summarized in Table 3.

Table 3. Integrative biomarker panels and clinical applications under the TIBIN framework.

Biomarker Category	Representative Molecules	Clinical Application	References
Microbial Signatures	Faecalibacterium prausnitzii, Enterococcus faecalis, Streptococcus salivarius	Early diagnostic markers of gut dysbiosis and ammonia overproduction	[3,9,14,25]
Metabolite Panels	SCFAs, bile acids, indoles, trimethylamine-N-oxide (TMAO)	Stage-specific stratification of HE	[9,25,28,30]
Proteomic Markers	S100B, GFAP, CRP, mitochondrial enzymes	Biomarkers for neuroinflammation and oxidative stress	[5,9,16,28]
Epigenetic Biomarkers	miR-122, miR-21, histone acetylation profiles	Prognostic indicators for neurocognitive impairment and hepatic dysfunction	[25,29,31]
Composite Index TDRM	Integrated omics signature combining gut, serum, and CSF data	Precision classification and therapeutic response prediction	[25,26,30]

7. Precision Intervention Pathways Through the AI

7.1 ML in HE Progression and Therapy Response Prediction

AI has transformed HE research, enabling real-time predictive modeling of disease progression. ML algorithms particularly ensemble methods such as random forests, gradient-boosting machines, and support vector classifiers detect complex, non-linear relationships among microbiome, metabolome, and clinical variables [24,39,41].

Within the TIBIN, ML functions as the cognitive core for precision forecasting. It identifies subtle shifts in gut microbial transcription, systemic ammonia, and neuroinflammatory cytokine profiles that precede detectable cognitive decline by analyzing longitudinal datasets. This approach facilitates early warning systems capable of predicting HE exacerbations days to weeks before clinical manifestations.

Integrative multi-omics models have demonstrated high predictive accuracy for both covert and overt HE stages (AUC > 0.90), outperforming conventional prognostic scores such as Model for End-Stage Liver Disease (MELD) and Child-Pugh. ML pipelines further enable therapeutic stratification, identifying patient subgroups likely to respond to interventions including lactulose, rifaximin, or microbiota-targeted therapies [39,45].

Causal inference frameworks integrated with ML allow mechanistic exploration of HE pathophysiology, for instance, mapping how dysbiosis-driven ammonia accumulation induces astrocytic dysfunction via cytokine cascades [31,40]. This combination of predictive precision and biological interpretability enhances translational potential.

Despite extensive evidence linking gut dysbiosis to ammonia overproduction, intestinal barrier dysfunction, and neuroinflammation in HE, substantial variability exists between cohorts. Differences in cirrhosis etiology, geographic location, diet, prior therapies, and comorbidities lead to divergent taxonomic and functional microbiome profiles. Cross-sectional studies dominate the literature, providing only snapshots of microbial alterations, whereas longitudinal designs remain limited, restricting the ability to infer causal relationships or temporal dynamics. Moreover, methodological heterogeneity including sequencing platforms, bioinformatic pipelines, and metabolite quantification approaches creates reproducibility challenges, highlighting the need for standardized, multi-center, and multi-omics studies. Ultimately, functional readouts (e.g., ammonia metabolism, SCFA production) appear more consistent and clinically relevant than individual taxa, supporting a shift from descriptive taxonomic profiling to mechanistic, metabolically informed analyses.

While AI and ML have demonstrated high predictive performance for HE progression and therapy response, several critical limitations remain. Small sample sizes in most omics datasets introduce bias and reduce model generalizability, increasing the risk of overfitting. The lack of robust external validation across independent cohorts further limits clinical translation. Additionally, AI outputs often lack interpretability for clinicians, constraining their adoption in routine care. Variability in cohort demographics, geographic diversity, and disease severity complicates model reproducibility. Cross-sectional training datasets cannot fully capture longitudinal disease trajectories, emphasizing the need for prospective, multi-center studies that combine functional microbiome data with host multi-omics for validated, clinically actionable predictions.

7.2 AI-Driven Repurposing of Gut-Brain-Active Molecules

Traditional HE therapeutics focus largely on symptomatic relief, with limited attention to underlying gut-brain-liver dysregulation. AI-driven computational drug repurposing offers a sustainable alternative, integrating multi-omics and pharmacogenomic data to identify existing compounds capable of restoring key triad pathways [39].

Within TIBIN, graph-based ML models and molecular docking simulations link host-microbiome networks with drug-target databases, identifying molecules that modulate ammonia metabolism, neuroinflammation, or hepatic oxidative stress. Examples include:

Mitochondrial enhancers: metformin analogues.

Neuroinflammation modulators: minocycline derivatives.

Natural bioactives: polyphenols, SCFAs, bile acid analogues.

Cheminformatics AI predicts Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties, optimizing compound selection prior to *in vitro* validation. This paradigm shift moves HE therapeutics beyond generic ammonia-lowering agents toward multi-target, pathway-specific interventions. TIBIN accelerates the discovery of compounds capable of restoring system-level homeostasis [39].

7.3 Accuracy of Nutrition and Microbiome Modulation

Nutritional interventions offer a direct, adjustable mechanism to modulate the gut-brain-liver axis. Using multi-omics and AI-guided personalization, diet becomes a precision therapy rather than a supportive measure. AI models trained on microbiome and metabolome data can predict how specific nutrients fiber, amino acids, probiotics, polyphenols affect microbial gene expression and metabolite production [41].

For example, prebiotic fibers (inulin, galactooligosaccharides) selectively increase Lactobacillus and Bifidobacterium, enhancing SCFA-mediated epithelial integrity and reducing systemic ammonia. ML further allows adaptive diet optimization, dynamically adjusting nutrient recommendations based on real-time biomarker monitoring [42].

Integration with nutrigenomics and nutriproteomics enables modeling of diet-gene interactions on hepatic detoxification and neuronal performance. Omega-3 fatty acids reduce neuroinflammation via hepatic lipid modulation, while vitamin B6 supports ammonia clearance through urea cycle enhancement. Within TIBIN, these multilayered datasets predict

dietary effects on biomarker trends and HE progression, creating personalized nutrition dashboards. Nutrition is thus transformed into AI-guided metabolic recalibration, representing a core precision intervention strategy [43,44].

7.4 TIBIN-Based Smart Therapeutic Decision Support Systems (ST-DSS)

The culmination of TIBIN is the ST-DSS, a clinical interface translating AI-derived insights into actionable interventions [31]. ST-DSS continuously learns from patient data, integrating:

TDRM

Laboratory and imaging data

Wearable biosensor readings

Electronic medical records

Reinforcement learning algorithms simulate intervention outcomes, recommending strategies that are safe, effective, and cost-efficient. For instance, increasing probiotic therapy or rifaximin may be suggested when rising TDRM scores coincide with elevated serum ammonia and LPS, predicting biomarker normalization [26,39,43].

ST-DSS incorporates dynamic feedback loops across microbiome, hepatic, and neuronal layers, allowing real-time intervention adaptation. Clinicians can visualize network perturbations such as hepatic mitochondrial stress or neuronal glutamine accumulation on an interactive systems map [32,44].

Beyond individual care, ST-DSS aggregates anonymized cohort data to retrain predictive models, refine risk stratification, and identify new therapeutic targets, enabling lifelong learning and advancing the trans-integrated bio-intelligence paradigm. By combining AI, multi-omics integration, and real-time feedback, ST-DSS enables dynamic, precision-driven HE management, aligning with P4 medicine principles [39].

TIBIN transforms HE care into a self-optimizing, adaptive system, integrating ML, DNNs, computational pharmacology, personalized nutrition, and decision-support. This approach surpasses traditional diagnostics, enabling real-time predictions, individualized treatment plans, and long-term outcomes, while establishing a platform for next-generation digital biomedicine.

7.5 Multi-Omics Data Fusion Using Deep Neural Models

The future of gut-brain-liver research increasingly depends on computational frameworks capable of integrating heterogeneous biological datasets into coherent mechanistic insights. Within the TIBIN framework, DL architectures function as integrative engines that overcome key limitations of conventional ML approaches, including reliance on manual feature engineering, limited scalability, and restricted capacity to capture nonlinear cross-organ interactions. DNNs, GNNs, and transformer-based architectures enable the simultaneous analysis of genomics, transcriptomics, metabolomics, proteomics, and imaging data, embedding these high-dimensional datasets into biologically meaningful latent representations that reflect coordinated physiological processes across the gut, liver, and brain [40,42].

Experimental multi-omics studies in liver disease demonstrate that different molecular layers encode complementary, nonredundant biological information that cannot be captured through single-modality analysis. For example, integrative transcriptomic-proteomic modeling in alcohol-associated liver disease has shown that machine-learning-derived latent molecular signatures outperform individual biomarkers in discriminating disease states, emphasizing the clinical relevance of data-driven feature fusion for disease stratification and mechanistic interpretation [48]. These findings support the premise underlying TIBIN that meaningful gut-brain-liver interactions emerge only when heterogeneous molecular layers are jointly modeled within a shared analytical framework.

Within this integrative paradigm, multimodal autoencoders represent one of the most powerful architectures for cross-organ systems modeling. These models compress diverse biological inputs such as gut microbial gene abundance, hepatic metabolic fluxes, and brain connectivity patterns into a shared manifold that captures latent relationships among microbial metabolism, host liver function, and neural regulation. By learning compressed representations of complex molecular states, autoencoder-based frameworks can reveal previously unrecognized biological interactions, including links between microbial metabolic pathways such as urease activity or SCFA production and hepatic mitochondrial function or neuroglial metabolic regulation [39,44]. Such latent-space representations transform fragmented molecular datasets into unified system-level signatures that reflect the dynamic interplay between intestinal microbiota, hepatic metabolism, and neurological function.

Evidence from patient-based multi-omic profiling further illustrates the value of integrated modeling for identifying early disease signals in HE. Studies of cirrhotic patients demonstrate coordinated immune, metabolic, and signaling pathway alterations that occur prior to the onset of overt neurological symptoms. Rubio et al. [49], for instance, showed that the integration of transcriptomic, metabolomic, and immunological datasets revealed peripheral immune pathways associated with minimal HE that were not detectable using conventional clinical biomarkers alone. These findings reinforce the importance of multi-layer biological integration for uncovering mechanistic drivers of neurocognitive impairment in chronic liver disease.

Deep neural architectures also facilitate the identification of dominant molecular drivers within integrated biological representations. Transformer-based models incorporate attention mechanisms that assign differential importance to specific molecular features, thereby improving both predictive accuracy and biological interpretability. Within the context of HE, such models can prioritize biologically meaningful signals—including butyrate-producing microbial genes, bile acid ratios, inflammatory mediators such as TNF-α, or metabolic markers associated with ammonia detoxification—as critical determinants of disease progression. Comparable approaches in large-scale molecular datasets have demonstrated that nonlinear learning models can automatically prioritize functionally relevant genes, signaling pathways, and immune mediators associated with disease progression or therapeutic response. For example, machine-learning analyses of liver cancer immunotherapy cohorts have identified molecular features exerting disproportionate influence on treatment outcomes, illustrating how hierarchical feature learning can uncover actionable biological insights without manual feature selection [50].

An important design principle of the TIBIN framework is its ability to accommodate real-world clinical constraints through tiered implementation of multi-omics intelligence. While comprehensive multi-layer data fusion offers the highest resolution of biological insight, experimental studies demonstrate that reduced yet biologically informed feature sets can retain substantial predictive power when derived from integrated analyses. Evidence from patient-based omics investigations indicates that selective incorporation of the most informative molecular layers preserves interpretability while reducing computational and logistical burden [48,49]. This flexibility enables the deployment of simplified models in time-sensitive clinical settings while reserving full multi-omics integration for specialized research or tertiary-care environments.

Collectively, these developments position DL-driven multi-omics integration as a foundational component of the TIBIN framework. By learning cross-organ biological structure directly from experimental data, deep neural models transform fragmented molecular observations into clinically interpretable systems intelligence. Grounded in empirically validated interactions among gut microbial activity, hepatic metabolism, and neuroimmune signaling, this integrative approach provides a scalable pathway toward precision hepatology. As advances in data availability, computational efficiency, and clinical infrastructure continue to evolve, DL-based multi-omics fusion is expected to play a central role in translating complex gut-brain-liver biology into actionable diagnostic and therapeutic strategies.

Table 4. Translational positioning of DL-driven multi-omics integration within the TIBIN framework for HE management.

Dimension	Current Clinical Practice (HE Management)	Near-Term TIBIN Implementation (Experimentally Supported)	Long-Term TIBIN Vision (Scalable Extension)
Patient stratification	Symptom-based grading (West Haven), ammonia levels	Data-driven stratification using targeted multi-omics signatures derived from patient cohorts	Fully individualized gut-brain-liver phenotypes learned from continuous multi-omics data
Data modalities	Clinical exam, routine biochemistry	Selected transcriptomic, proteomic, metabolomic, and immune markers shown to be predictive in experimental studies	Integrated genomics, transcriptomics, proteomics, metabolomics, microbiome, and neuroimaging
Modeling approach	Rule-based clinical judgment	Deep neural models trained on experimentally derived multi-omics datasets	Adaptive DL models with continuous updating and cross-center generalization
Interpretability	Clinician experience	Feature prioritization highlighting dominant molecular drivers identified experimentally	Mechanism-aware AI linking molecular perturbations to functional outcomes
Time to clinical output	Immediate	Clinically actionable (hours to days) using reduced-input models	Near real-time inference enabled by automated data pipelines
Infrastructure requirements	Standard hepatology unit	Tertiary or academic centers with omics and computational capacity	Distributed digital health platforms with integrated analytics
Cost and scalability	Low and widely accessible	Moderate, limited to centers with omics capability	Currently high, expected to decrease with technological maturation
Clinical role	Symptom control and supportive care	Precision risk stratification and therapeutic guidance	Fully adaptive systems-level decision support

As summarized in Table 4, the TIBIN framework illustrates the progression from current clinical practice to near-term experimental applications and long-term scalable DL-driven multi-omics integration

8. Translational and Clinical Applications

8.1 Integration of TIBIN into Clinical Care Pathways

The (TIBIN) is designed for seamless integration into current hepatology and neuro-metabolic care pathways. As a hospital-based decision-support ecosystem, TIBIN aggregates longitudinal multi-omics data including gut microbial

sequencing, serum metabolomics, and cognitive metrics into a single clinical dashboard. This integration enables early detection of HE decompensation, allowing pre-emptive interventions rather than reactive management [22].

TIBIN stratifies patients according to individual risk trajectories by combining AI-driven pattern recognition with existing clinical scoring tools, such as the West Haven criteria and MELD, forecasting transitions between covert and overt HE stages. Multivariate visualizations help hepatologists prioritize interventions, from ammonia-lowering therapies to microbiota-targeted modulation, while neurologists monitor cortical and cognitive biomarkers in real time [25,31].

Critically, TIBIN establishes a two-way feedback loop between bedside observations and computational inference. Continuous integration of laboratory, imaging, and sensor data enhances predictive precision and enables dynamic, personalized treatment adjustments [17,26]. Linking TIBIN to electronic health records (EHRs) ensures interoperability and supports interdisciplinary decision-making across gastroenterology, neurology, and nutrition units [19,28]. This data-science-clinical interface represents a major milestone in precision medicine for HE [17,26,40].

8.2 Biosensor Monitoring of Gut-Liver-Brain Biomarkers in Real Time

Biosensing technologies bridge TIBIN's computational predictions with *in vivo* physiology. Implantable and wearable sensors now allow continuous measurement of biomarkers such as blood ammonia, lactate, volatile organic compounds (VOCs), and microbial metabolites. These sensors relay data via wireless telemetry to cloud-based analytics, enabling TIBIN's AI core to refine gut-liver-brain homeostasis models in real time [23,27,39].

In the gut compartment, microfluidic capsules monitor SCFAs and bile-acid fluxes, providing a metabolic fingerprint of microbial activity. Hepatic and neurochemical sensors track glutamine/glutamate balance, transaminases, and bilirubin dynamics, reflecting liver detoxification efficiency and cortical metabolic status [20,29].

The integration of these multidimensional streams enables a closed-loop monitoring system, alerting clinicians or adaptive-dose algorithms to deviations from predicted baselines. For example, early detection of increased ammonia alongside microbial dysbiosis allows timely probiotic or rifaximin intervention. Each biosensor reading serves as a ground-truth data point, continuously training TIBIN's AI and improving auto-learning capabilities, effectively transforming it into a living bio-intelligent system [5,18,30].

8.3 Customized Therapeutic Algorithms

TIBIN enables personalized therapeutic algorithms, optimizing interventions across microbial, metabolic, and neurological pathways. AI-driven predictive analytics recommend probiotic or synbiotic formulations tailored to a patient's baseline microbial diversity and functional gene expression [15,20,25].

Patients with low Bifidobacterium or Lactobacillus abundances receive strain-specific supplementation to restore SCFA synthesis and reduce intestinal ammonia production. Similarly, TIBIN models the effects of ammonia-lowering drugs, including lactulose, rifaximin, or L-ornithine-L-aspartate, incorporating individualized hepatic clearance values [16,23].

Integration of pharmacogenomic data with biosensor feedback enables AI-controlled dose optimization, reducing adverse events and improving efficacy. Nutrition is incorporated into this multi-axis intervention, with AI-based dietary recommendations aligned with microbial fermentation patterns and nitrogen balance. Together, these interventions operate within a single, systems-level framework, aiming to restore gut-brain-liver homeostasis [30,42].

8.4 Clinical Validation and Data Harmonization Challenges

Despite its potential, TIBIN faces practical challenges in clinical implementation. Data heterogeneity is a major hurdle: multi-omics datasets differ in scale, noise, sampling frequency, and platform, complicating integration. Harmonization requires common pipelines and interoperable metadata structures [8,31].

Ethical and privacy considerations are also paramount. TIBIN processes highly sensitive personal biological data, necessitating compliance with frameworks such as General Data Protection Regulation (GDPR) and Health Insurance Portability and Accountability Act (HIPAA). Solutions like blockchain audit trails and secure cloud infrastructure are being explored to ensure traceability and data integrity [29,32].

Robust clinical validation requires prospective, multicenter cohort studies across diverse genetic and environmental backgrounds. Without such diversity, AI models risk bias and poor generalizability.

Another barrier is interpretability: deep-learning models are often "black boxes," which can undermine clinician trust. XAI modules that visualize causal networks are essential for transparent decision-making [28,43].

Finally, real-time biosensor integration demands high-throughput computational infrastructure and rigorous *in vitro* calibration to maintain sensitivity amidst biological variability [30,44]. Addressing these challenges requires multidisciplinary collaboration among hepatologists, neurologists, bioinformaticians, data engineers, and regulatory specialists under standardized governance [39,40].

8.5 Translational Potential of TIBIN in HE

The translational implementation of TIBIN represents a major step forward in AI-assisted, microbiome-driven precision medicine for HE. By combining real-time biosensing, multi-omics modeling, and adaptive therapeutic feedback, TIBIN transforms HE management from a reactive to a pre-emptive and personalized model.

While technical and ethical hurdles remain, interdisciplinary cooperation and rigorous validation will accelerate its adoption. Once operational, TIBIN promises to deliver dynamic, data-driven care, empowering clinicians to manage patients along the gut-brain-liver axis in real time, and setting a new benchmark for precision hepatoneurology.

9. Future Directions, Gaps, and Challenges

9.1 Harmonization and Integration of Multi-Omics Data

A central challenge for TIBIN is the integration of heterogeneous multi-omics datasets metagenomics, metabolomics, proteomics, lipidomics, and transcriptomics along the gut-brain-liver axis. Variability in data acquisition, sample preparation, and sequencing platforms introduces analytical noise and biases, complicating downstream interpretation. Lack of standardized pipelines often leads to disjointed biological insights, reduced reproducibility, and difficulties in cross-study comparisons [18].

To address this, bioinformatic normalization strategies are essential for consistent feature extraction in high-dimensional datasets. Standards such as Minimum Information about any (Meta)Genome Sequence (MIxS) and Human Proteome Organisation-Proteomics Standards Initiative (HUPO-PSI), alongside Findable, Accessible, Interoperable, and Reusable (FAIR)-compliant repositories, provide foundational templates for harmonization [4]. In The International Biobank Information Network (TIBIN), federated learning architectures can process decentralized datasets jointly without compromising patient privacy [27].

Temporal asynchrony across organs adds another layer of complexity: gut microbes, liver hepatocytes, and neuronal networks exhibit distinct circadian and metabolic rhythms. Capturing these spatiotemporal dynamics requires real-time sampling and time-resolved modeling, allowing TIBIN to accurately reflect cross-organ interactions. Future progress depends on developing coherent longitudinal datasets to serve as AI-ground-truth for predictive modeling [20,28].

9.2 Ethics, Regulation, and AI-Guided Diagnostics

The deployment of AI in TIBIN raises ethical, legal, and social considerations. Multi-omics data are inherently identifiable, carrying risks of re-identification, misuse, or discrimination. Compliance with GDPR and HIPAA is critical to protect patient autonomy and consent [23].

Other ethical imperatives include transparency and explainability. Clinicians require interpretable AI outputs to guide diagnostic and therapeutic decisions. Black-box deep-learning models can obscure causal reasoning, potentially introducing diagnostic bias, especially for underrepresented populations. Implementing XAI modules within TIBIN allows clinicians to trace decision pathways and identify which omics features underpin each outcome [39].

Regulatory frameworks are evolving. Although bodies like the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are preparing adaptive pathways for AI-based medical devices, the approval process remains slow and fragmented. Establishing internationally harmonized AI validation standards is essential to enable TIBIN-guided diagnostics across borders [44].

Algorithmic fairness is equally critical. Training datasets should be socio-demographically and genetically diverse to avoid bias. Global data-sharing consortia and ethical oversight committees will be key in ensuring inclusive, transparent, and equitable deployment of TIBIN [39].

9.3 Multi-Cohort Validation and Open-Access Databases

HE biomarker research remains limited by small, single-center studies, which fail to capture geographic, dietary, and genetic diversity. To be globally effective, TIBIN must be trained on multi-ethnic, multi-environment datasets [28].

Open-access repositories that combine omics, imaging, and clinical phenomics will accelerate AI learning and reduce information silos. A Global HE Omics Repository (GHEOR) could standardize microbiome composition, ammonia metabolism, neuroinflammatory biomarkers, and treatment outcomes. Such infrastructure would support cross-validation, reproducibility, and benchmarking of TIBIN AI models [29].

Data annotation and quality control pipelines must also be standardized. Benchmarking initiatives like CAMI and HMP provide methodological templates. Applying similar protocols to the gut-brain-liver axis will facilitate uniform validation of microbial, metabolic, and neural signatures in HE [23,30].

Data democratization is another priority. Open-access policies must balance scientific collaboration with patient confidentiality, leveraging technologies such as blockchain and cryptographic tokenization to ensure transparency and security. This global shared system would accelerate the development of TIBIN's predictive intelligence [40,44].

9.4 The Future of Precision Hepatoneurology: The TIBIN Paradigm

The TIBIN paradigm represents a holistic, systems-medicine approach to the gut-liver-brain axis, moving beyond reductionist diagnostics. Future iterations will incorporate single-cell and spatial omics, offering unprecedented granularity in mapping intercellular and inter-organ interactions. Coupled with real-time biosensor feedback, these data will enable adaptive therapeutic algorithms that respond at micro-physiological timescales [41].

Emerging technologies, including quantum computing and edge AI, will allow near real-time processing of multi-terabyte clinical datasets, supporting decision-making even in resource-limited settings. This will democratize access to sophisticated diagnostic intelligence and enhance real-time HE management [24].

TIBIN's translatable framework extends beyond HE to other gut-organ axis disorders, including hepatic fibrosis, Parkinson's disease, and Metabolic Associated Fatty Liver Disease (MAFLD). Shared computational blueprints could facilitate cross-disease biomarker discovery and therapeutic repurposing [40,43].

Ultimately, TIBIN envisions a digitally augmented hepatoneurological ecosystem, where AI continuously learns from patient interactions, and clinical decisions are guided by integrated omics, biosensor data, and global knowledge networks. This paradigm shifts HE management from reactive symptom control to real-time systems optimization, setting a new benchmark for AI-based precision hepatoneurology [40].

However, translation faces practical barriers: data heterogeneity, ethical and regulatory constraints, and the need for standardized global validation. Overcoming these challenges will require international collaboration, robust data governance, and equitable technology access. The next decade will determine whether AI and multi-omics integration evolve into a clinically actionable intelligence system, transforming HE management and advancing human systems medicine.

10. Limitations

Despite providing a comprehensive synthesis of multi-omics and AI-driven insights into HE, this review has several limitations.

First, heterogeneity across studies poses a challenge. Variations in patient populations, disease severity, sample types, omics platforms, and analytical pipelines limit direct comparability and may introduce interpretative bias. Differences in sequencing depth, metabolomic coverage, and data normalization further complicate cross-study integration.

Second, publication and selection bias cannot be excluded. The review focused on peer-reviewed, English-language studies published between 2020 and 2025, potentially omitting relevant data from other sources or timeframes. Additionally, positive or statistically significant findings are more likely to be published, which may overrepresent certain biomarkers or pathways.

Third, many studies are cross-sectional, limiting causal inference between microbiome alterations, molecular signatures, and HE progression. Longitudinal dynamics of the gut-brain-liver axis and treatment-induced molecular changes remain underexplored.

Fourth, although AI and ML approaches are increasingly applied, model interpretability and external validation are inconsistent. Differences in feature selection, training datasets, and performance metrics may affect reproducibility and translational reliability.

The TIBIN framework is conceptual, synthesizing evidence rather than being experimentally validated within this review. Its clinical utility will depend on future prospective studies.

11. Conclusion

In this research, the TIBIN framework has been demonstrated as a paradigm shift in the process of decoding the gut-brain-liver triad in HE by integrating the multi-omics and AI-driven analytics. The synthesis highlights the pathophysiological complexity of HE, which is mediated by the interdependence of mechanisms of gut dysbiosis, hepatic detoxification failure, and neuroinflammatory cascades. TIBIN facilitates accurate finding of biomarkers and computational intelligence-based personalized intervention pathways through the integration of omics science with computational intelligence. The future study needs to be based on establishing open-access, multi-cohort databases to substantiate the framework and incorporating biosensor-based real-time monitoring to predictive hepatoneurology. This paradigm eventually represents a new era of data-driven, precision-based hepatic medicine, which aligns clinical decision-making with the dynamism of the biology of the gut-brain-liver axis.

Conflict of Interest

The authors declare no conflicts of interest related to this publication.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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