

REVIEW ARTICLE

Translating neuroscience-driven biomarkers into adult clinical practice: Challenges, opportunities, and pathways forward

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Abstract

Despite remarkable advances in neuroscience and high-throughput omics technologies, the translation of novel biomarkers into routine clinical use remains stubbornly slow and fragmented. While the volume of discovery data continues to grow exponentially, many candidate markers fail to cross the translational valley of death due to a profound clinical utility gap. This narrative review synthesizes recent progress in neuroscience biomarker discovery, evaluating the systemic bottlenecks that hinder clinical translation, ranging from pre-analytical variability and statistical overfitting to complex regulatory and reimbursement hurdles. We propose integrative, reverse-translational frameworks designed to accelerate implementation by beginning with the end clinical context in mind. Emphasis is placed on the shift toward multimodal biomarkers, including the integration of proteomic, metabolomic, advanced neuroimaging, and emerging digital phenotypic data. Through detailed, disease-specific case studies spanning Alzheimer's disease, multiple sclerosis, traumatic brain injury, and neuropsychiatry, we illustrate both translational successes and persistent methodological pitfalls. We also examine the imperative of global health equity. We argue that biomarker scalability, economic viability, and point-of-care adaptability are just as vital as biological sensitivity in the democratization of precision neurology. Over-reliance on expensive, Western-centric validation pipelines risks exacerbating existing healthcare disparities. Ultimately, we advocate for collaborative, data-driven pipelines that bridge isolated laboratory innovation with pragmatic clinical needs, ensuring that precision neuroscience translates into tangible, accessible outcomes for diverse patient populations worldwide.

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1. Introduction

The translation of basic neuroscience insights into clinically useful biomarkers represents one of the most significant opportunities, and persistent challenges, in modern medicine. Ideally, biomarkers serve as objective indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.¹

For neurological and neuropsychiatric disorders, where diagnoses have historically relied on subjective symptom clusters and post-mortem pathology, the promise of objective biomarkers is transformative. They offer the potential for pre-symptomatic diagnosis, precise patient stratification, and real-time monitoring of therapeutic efficacy.²

However, a stark disconnect exists between the burgeoning volume of discovery data and routine clinical practice. Despite the exponential growth in high-throughput technologies, such as proteomics, metabolomics, and advanced neuroimaging, the vast majority of candidate biomarkers fail to cross the translational valley of death.^{3,4} This attrition is rarely due to a lack of scientific innovation; rather, it stems from systemic failures in validation, standardization, and the alignment of discovery efforts with practical clinical needs.⁵

A critical, often-overlooked hurdle is the clinical utility gap, the distinction between a biomarker that is statistically significant in a controlled study and one that alters patient management or outcomes in a real-world setting.^{6,7} For a biomarker to be truly translational, it must not only be biologically plausible but also economically viable, scalable, and actionable for clinicians.⁸ This review synthesizes recent progress in multimodal biomarker discovery, evaluates specific barriers to their implementation, including global accessibility and pre-analytical variability, and proposes integrative frameworks to accelerate their journey from the bench to the clinic.^{9,10}

To ensure the quality and representativeness of the studies cited, this review used a structured search of the primary literature and existing meta-analyses within the PubMed, Scopus, and Google Scholar databases (January 2010–January 2025). Selection criteria focused on high-impact longitudinal cohorts, Food and Drug Administration (FDA)-cleared diagnostic assays, and consensus frameworks from international bodies such as the Global Biomarker Standardization Consortium (GBSC) and National Institute on Aging and Alzheimer's Association (NIA-AA). While this is a narrative synthesis designed to propose integrative frameworks, the selection of evidence was prioritized based on analytical validity, clinical utility, and multi-site replication.

While neurodevelopmental conditions, such as epilepsy, and pediatric stage-dependent biomarker expression are critical areas of study, this review focuses specifically on translation in adult neurodegenerative and neuropsychiatric populations. This boundary is established to maintain a focused analysis on the specific regulatory and biological hurdles of the aging or mature brain, where normal biomarker ranges are more established. However,

it is important to note that the integrative frameworks proposed in this review, particularly the World Health Organization (WHO) ASSURED (affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end-users) criteria for scalability and the AT(N) triage model, are designed to be modular. These structural pathways can be adapted by future research to bridge the gap between neonatal screening and long-term neurodevelopmental monitoring, ensuring that the principles of analytical rigor and clinical utility are applied across the entire lifespan.

2. The current state of neuroscience biomarker research

The landscape of neuroscience biomarkers has shifted from searching for single “silver bullet” proteins to capturing complex biological signatures using multimodal and high-dimensional approaches.

2.1. Fluid biomarkers: the “liquid biopsy” of the brain

While cerebrospinal fluid (CSF) remains the gold standard for neurochemical analysis due to its proximity to the brain parenchyma, the field is aggressively pivoting toward blood-based biomarkers to enable population-scale screening.¹¹

Specifically, the field is pivoting from non-specific markers of axonal injury, such as neurofilament light chain (NfL), which acts as a C-reactive protein (CRP)-like biomarker for the brain, to pathology-specific assays.^{12,13} For example, plasma p-tau181 and p-tau217 have achieved diagnostic performance rivaling CSF, distinguishing Alzheimer's disease (AD) from frontotemporal dementia with high specificity.^{14,15} This suite of fluid markers is further complemented by indicators of glial activation, such as chitinase-3-like protein 1 (YKL-40), glial fibrillary acidic protein (GFAP), and soluble triggering receptor expressed on myeloid cells 2 (sTREM2), which track the neuroinflammatory drivers of degeneration.^{16–18} Recent large-scale studies have confirmed the utility of these markers in longitudinal cohorts.^{19,20}

2.2. Neuroimaging: from structure to molecular pathology

Advanced imaging has evolved significantly, moving beyond structural magnetic resonance imaging (MRI) toward more granular molecular phenotyping. Central to this shift is the use of positron emission tomography (PET) ligands; specifically, radiotracers for beta-amyloid (A β) and tau now enable in vivo staging of AD pathology. Furthermore, newer tracers targeting synaptic density (e.g.,

synaptic vesicle glycoprotein 2A [SV2A]) and microglial activation (e.g., translocator protein [TSPO]) are providing critical insights into the earliest phases of synaptic loss and neuroinflammation.²¹⁻²³

Collectively, these technologies have been pivotal in defining and refining the amyloid cascade hypothesis. Parallel to molecular imaging, advances in functional MRI (fMRI) and connectomics are revealing network-level dysfunctions in psychiatric disorders by examining resting-state functional connectivity.²⁴⁻²⁷ Connectome-based models are increasingly being used to explore the structural-functional coupling in both healthy and diseased brains.²⁸⁻³⁰ However, the broad clinical application of these functional techniques remains currently limited by significant scanner variability. Despite these challenges, the diversification of the biomarker toolkit has led to several validated candidates that are now entering clinical workflows. These key biomarkers, along with their specific clinical contexts of use across major neurological indications, are summarized in [Table 1](#).

2.3. Genetic and epigenetic biomarkers

The integration of genomics has introduced polygenic risk scores, which aggregate the effects of thousands of common genetic variants to predict disease susceptibility.^{31,32} However, while polygenic risk scores provide a powerful statistical tool for stratification, their clinical utility is currently limited by a significant ancestry bias in the underlying genome-wide association study (GWAS) datasets. This lack of diversity means risk predictions may be less accurate for non-European populations, representing a critical challenge for global health equity.

Complementing these genetic insights, the field of

epigenetics has produced DNA methylation clocks, such as the Horvath clock. Measured in blood, these are emerging as robust markers of biological aging that correlate with brain atrophy and cognitive decline, independent of chronological age.^{33,34} These biological age estimates are gaining significant traction as surrogate endpoints in anti-aging trials.³⁵ Nevertheless, for these epigenetic and genomic markers to move beyond an optimistic portrayal toward routine practice, they must be validated against the risk of over-medicalization. Widespread deployment without a clear understanding of the psychological impact of “high-risk” labeling, particularly in the absence of preventative cures, could lead to undue patient anxiety and place an unsustainable financial burden on public healthcare systems.

2.4. The rise of digital biomarkers

A distinct and rapidly evolving category is that of digital biomarkers, which comprise high-granularity data collected via wearable sensors and smartphones.³⁶ In contrast to traditional snapshot clinical assessments, these tools offer the advantage of continuous ecological monitoring in a patient's natural environment. For example, motor phenotyping through accelerometer data can objectively quantify gait freezing in Parkinson's disease (PD) or capture the subtle reductions in physical activity associated with depression.^{37,38} Similarly, cognitive and speech metrics are gaining ground; algorithms capable of analyzing typing latency (keystroke dynamics) and voice acoustics (speech prosody) have demonstrated significant sensitivity to early cognitive decline and even prodromal psychosis.^{39,40}

However, as noted in recent critical reviews, the implementation of these tools faces a profound validation

Table 1. Validated neuroscience biomarkers and clinical context of use

Category	Biomarker(s)	Clinical utility	References
AD	p-tau217, p-tau181	Differential diagnosis of AD vs. FTD; population-scale screening/triage.	11,14,15
Neurodegeneration	NfL	Monitoring axonal injury and therapy response in MS; general neurodegeneration marker.	12,13,19
Neuroinflammation	YKL-40, GFAP, sTREM2	Tracking microglial and astrocytic activation in longitudinal cohorts.	16,17,18,23
Acute triage	GFAP & UCH-L1	“Rule-out” test for intracranial lesions in mild TBI to avoid unnecessary CT scans.	68,69
Synucleinopathy	Alpha-synuclein (RT-QuIC)	Molecular confirmation of PD and prodromal REM sleep behavior disorder.	70,71,72

Abbreviations: AD: Alzheimer's disease; CT: Computed tomography; FTD: Frontotemporal dementia; GFAP: Glial fibrillary acidic protein; MS: Multiple sclerosis; NfL: Neurofilament light chain; PD: Parkinson's disease; REM: Rapid eye movement; RT-QuIC: Real-time quaking-induced conversion; sTREM2: Soluble triggering receptor expressed on myeloid cells 2; TBI: Traumatic brain injury; UCH-L1: Ubiquitin C-terminal hydrolase L1; YKL-40: Chitinase-3-like protein 1.

challenge. Unlike fluid assays, which can be standardized across international laboratories through established standard operating procedures (SOPs), digital biomarkers often rely on proprietary black-box algorithms that lack transparency. This opacity complicates the explainable artificial intelligence (XAI) requirements necessary for clinical trust and regulatory approval.

While efforts are underway to validate these digital signals against gold-standard clinical scales^{41–45}, a significant gap remains in addressing the cultural and structural shifts required for healthcare providers to integrate such continuous data streams into daily workflows.

Beyond algorithmic opacity, digital biomarkers face additional translational hurdles. Model drift, demographic bias, device heterogeneity, and evolving software ecosystems can degrade performance over time. Algorithms trained in homogeneous populations may underperform in diverse real-world settings. Furthermore, continuously adaptive systems challenge traditional regulatory frameworks designed for static diagnostics. Addressing these issues will require multi-site validation, demographic diversity in training datasets, and ongoing post-market surveillance.

To transition digital biomarkers from experimental tools into durable clinical standards, a more proactive implementation roadmap is required. First, the field must prioritize standardized feature extraction by moving toward open-source, device-agnostic libraries that support universal calculations for typing latency or gait variability, to ensure that biomarkers remain comparable across different hardware and software ecosystems. Second, regulatory frameworks must shift from static validation models toward a dynamic lifecycle approach, leveraging real-world evidence and post-market surveillance to detect and mitigate model drift in real time. Finally, to bridge the pervasive trust gap among clinicians, these digital outputs should be integrated with XAI frameworks, such as Shapley additive explanations (SHAP), which visualize the specific behavioral features, such as altered sleep architecture or decreased social reciprocity, driving a particular risk score. By aligning digital development with these technical and regulatory pillars, these tools can move beyond simple monitoring to become actionable, utility-driven diagnostics that mirror the translational success seen in acute triage models.

3. Barriers to translation and strategic solutions

The transition from a research-grade assay to a clinical diagnostic is stalled by systemic inefficiencies.

3.1. Analytical validity *versus* clinical utility

A primary source of failure is conflating analytical validity (measuring the analyte correctly) with clinical utility (improving patient outcomes).⁴⁶ Many proteomic signatures show statistical correlation with disease but fail to demonstrate added value over standard clinical exams in heterogeneous populations.^{47,48} Bridging this gap requires prospective, outcome-based trials rather than retrospective case-control studies⁴⁹ (Figure 1).

3.2. The pre-analytical hurdle: standardization and biobanking

Pre-analytical variability remains the silent killer of biomarker validation, as neuro-specific proteins in the blood are often present in sub-femtomolar concentrations and are highly labile.⁵⁰ Because these molecules are highly fragile, minor handling deviations, such as the choice between glass and plastic tubes, delay in time-to-centrifugation, hemolysis, and multiple freeze-thaw cycles, can alter measured concentrations of p-tau or A β by more than 20%, directly leading to diagnostic errors.^{51,52} To address this, the GBSC and similar international bodies are establishing universal SOPs to ensure technical reproducibility.⁵³ To mitigate pre-analytical variability, researchers must adhere to strict SOPs that specify the use of dipotassium ethylenediaminetetraacetic acid (K2 EDTA) tubes over serum tubes to prevent protease degradation of p-tau. Furthermore, the time-to-centrifugation must be capped at 30–60 min to maintain the stability of sub-femtomolar proteins such as NfL. These technical safeguards are the prerequisite for cross-site reproducibility and eventual regulatory approval.

However, the implementation of these SOPs is not merely a technical requirement but also a structural challenge for global health equity. While high-quality biobanking with rigorous annotated metadata is essential to ensure archived samples reflect the diversity of future clinical populations^{54,55}, these stringent requirements can be difficult to maintain in resource-limited settings. If biomarker validation remains tethered to high-cost infrastructure, the resulting diagnostic tools risk being Western-centric and inaccessible to the global majority. Furthermore, a lack of ancestry diversity in biobanked samples can lead to a weak evidence base that fails to account for genetic variability in protein expression, potentially increasing the risk of false positives and subsequent over-medicalization in underrepresented populations. Bridging this gap requires moving beyond aspirational statements toward pragmatic, scalable solutions that maintain scientific rigor without sacrificing global inclusivity.

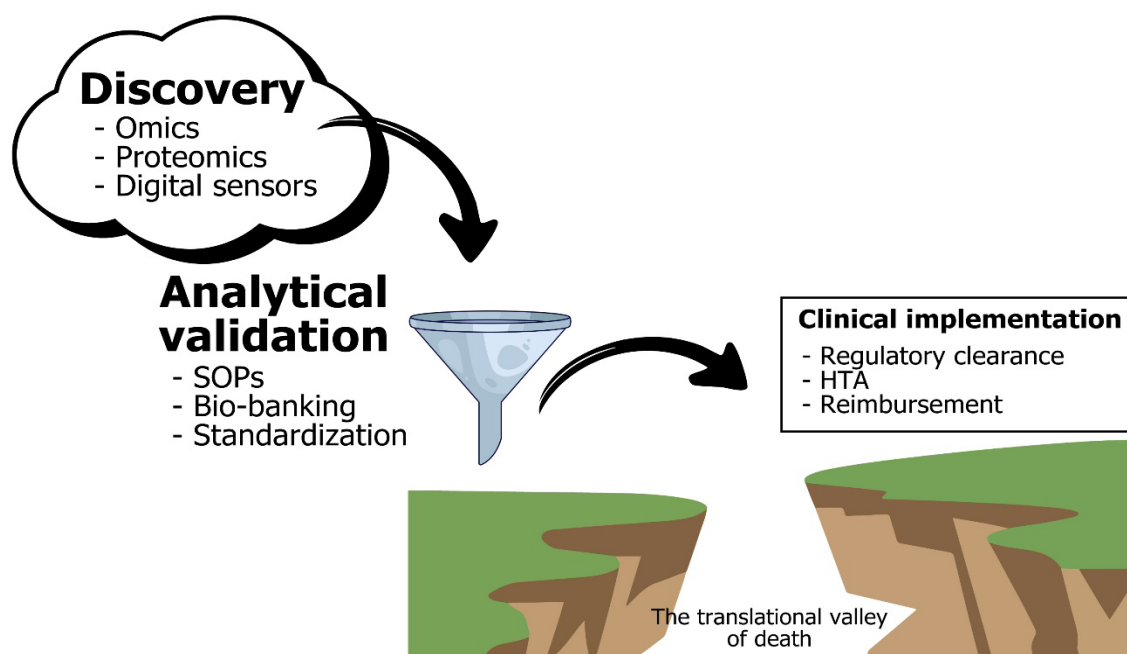


Figure 1. The neuroscience translational pipeline. This figure illustrates the translational valley of death and the path from discovery to clinical impact. It highlights where the pipeline often breaks due to lack of standardization.

Abbreviations: HTA: Health technology assessment; SOP: Standard operating procedure.

3.3. Regulatory frameworks and reimbursement

The regulatory landscape is shifting; the FDA's 2024 final rule on laboratory-developed tests significantly increases oversight of these assays, moving them toward the more rigorous *in vitro* diagnostic and companion diagnostics pathways.⁵⁶ This shift is particularly impactful for artificial intelligence (AI)-driven “software as a medical device (SaMD),” which requires dynamic validation to maintain performance. Furthermore, approval does not guarantee reimbursement. Health technology assessment bodies require evidence of cost-effectiveness.⁵⁷ For example, a blood test for AD must prove it reduces the burden of expensive PET scans or unnecessary therapies to justify payer coverage.^{58,59}

Overcoming the translational gap requires addressing specific technical and conceptual hurdles. A categorization of these barriers, alongside proposed strategic frameworks, is provided in [Table 2](#).

4. Case studies: successes, failures, and emerging models

Analyzing specific disease areas highlights the practical application of these principles.

4.1. Alzheimer's disease: The AT(N) framework

Alzheimer's disease represents the most advanced example of biomarker-driven disease redefinition. The NIA-AA's AT(N) research framework introduced a biological classification system based on amyloid (A), tau (T), and neurodegeneration (N), effectively decoupling pathological status from clinical symptom severity ([Figure 2](#)). This shift enables patient stratification according to molecular processes rather than cognitive scores alone, laying a critical foundation for precision neurology.⁶⁰

While PET imaging and CSF analysis remain the reference standards for this framework, their high cost and invasiveness limit scalability in routine clinical practice. In response, plasma p-tau217 has demonstrated strong diagnostic performance across multiple cohorts, showing high specificity for AD pathology. Large-scale studies have confirmed that plasma p-tau217 correlates highly with CSF and PET status, offering a potentially scalable screening tool for primary care.^{61,62} However, as noted by recent critiques, the current enthusiasm for p-tau217 must be tempered by significant platform variability, specifically between Lilly, ALZpath, and Fujirebio assays, and a lack of robust real-world data in diverse primary care settings.

Table 2. Barriers to translation and strategic frameworks

Barrier type	Key challenges	Proposed solutions/frameworks	References
Conceptual	The clinical utility gap; lack of ground-truth pathology in psychiatry.	Biotyping; focus on outcome-based trials rather than case-control studies.	1,3
Economic	High cost of PET/MRI; lack of reimbursement for novel assays.	Triage models; health economic modeling (proving cost-effectiveness).	10,30,56,58
Technical	Pre-analytical variability (e.g., tube type, freeze-thaw).	Universal SOPs and high-quality biobanking with metadata.	48,49,53
Regulatory	Regulating AI's black boxes and SaMD.	Explainable AI (XAI) and dynamic validation frameworks.	77,78,79

Abbreviations: AI: Artificial intelligence; MRI: Magnetic resonance imaging; PET: Positron emission tomography; SaMD: Software as a medical device; SOP: Standard operating procedure.

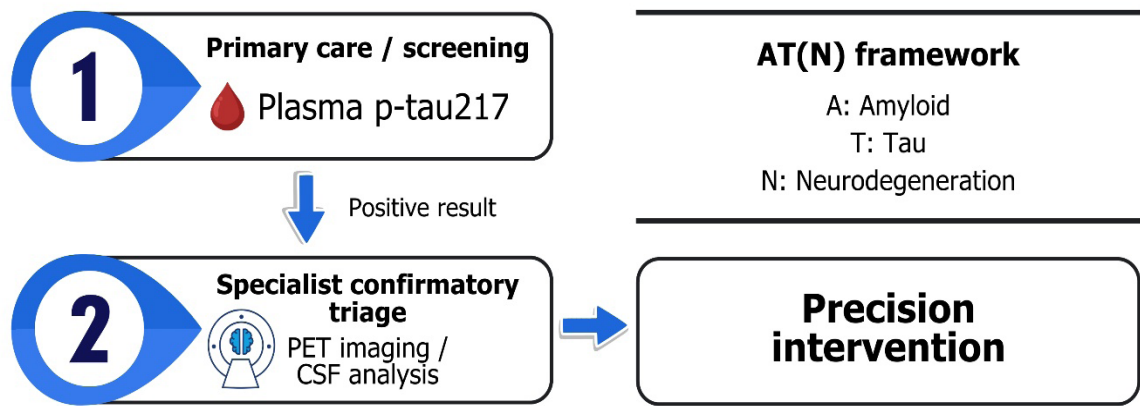


Figure 2. The AT(N) triage model for Alzheimer's disease. This figure demonstrates the pragmatic implementation of the AT(N) framework. It shows how high-performance plasma biomarkers (e.g., p-tau217) can act as a cost-effective triage step before expensive positron emission tomography (PET) or cerebrospinal fluid (CSF) confirmatory tests.

The accuracy of these fluid markers supports a pragmatic triage implementation model. Rather than screening the general population with expensive PET scans, clinicians can use accessible blood tests to filter patients, referring only those with positive results for confirmatory imaging or CSF analysis.⁶³ This approach not only improves cost-effectiveness but also addresses concerns regarding the unsustainable financial burden on public healthcare systems by avoiding over-medicalization. Longitudinal studies further suggest that these biomarkers can detect pathological changes years before overt symptoms, enabling earlier enrollment in prevention-focused clinical trials during the silent phase of the disease.⁶⁴ While this capability is revolutionizing the field, it also necessitates a critical discussion on the ethical implications of early diagnosis in the absence of accessible cures, ensuring that global health equity remains a central pillar of the translational pipeline.

4.2. Multiple sclerosis: monitoring disease activity

While AD biomarkers are revolutionizing early diagnosis, multiple sclerosis (MS) illustrates a different translational victory: the shift from reactive observation to real-time longitudinal monitoring through fluid biomarkers. Historically, monitoring MS relied on intermittent assessments of physical relapses and annual MRI scans, a snapshot approach that often missed silent disease activity occurring between clinical checks. MS now represents a premier model for how fluid biomarkers, specifically NfL, can fill this critical monitoring gap.

The translation of NfL has seen it move from a purely research-based metric to an increasingly integrated clinical adjunct in specialized centers. As a surrogate marker of subclinical axonal injury, elevated NfL levels can predict future relapses and MRI lesion load even before physical symptoms manifest.⁶⁵ This capability is now being

integrated into the clinical definition of no evidence of disease activity. In practice, a rising NFL level in a seemingly stable patient serves as an early warning system, potentially triggering a proactive re-evaluation of therapy or a switch to higher-efficacy, disease-modifying treatments.^{66,67}

This shift toward proactive management is fundamentally altering the disease trajectory for many patients. Early intervention strategies informed by these biomarker dynamics are associated with improved long-term outcomes, though the independent contribution of biomarker-guided decisions continues to be evaluated in prospective trials.⁶⁸ However, as with all high-sensitivity markers, clinicians must remain vigilant against the risk of over-medicalization. A “dry” clinical profile with a slightly elevated biomarker reading requires a nuanced, discursive discussion with the patient to avoid undue anxiety or premature treatment escalation that could place an unsustainable financial burden on the healthcare system. Furthermore, ensuring that these monitoring tools are accessible beyond high-resource settings remains a priority to avoid a Western-centric implementation of precision MS care.

4.3. Traumatic brain injury: utility-driven clearance

In contrast to the longitudinal monitoring seen in MS, the field of traumatic brain injury (TBI) provides a premier model of translational success by solving an acute logistical problem: the systemic over-utilization of neuroimaging. Historically, the standard of care for mild TBI (Glasgow Coma Scale 13–15) involved routine head computed tomography (CT) scans to screen for intracranial bleeding. However, because over 90% of these scans are negative, this practice resulted in unnecessary radiation exposure and massive healthcare costs.⁶⁹

The breakthrough in this field came from defining a pragmatic and strategic context of use. Rather than attempting to biologically diagnose the clinical syndrome of concussion, which remains physiologically elusive, researchers focused on a rule-out diagnostic: identifying patients who do not have a brain bleed and therefore do not require a scan. This was achieved through biomarker synergy, combining GFAP (a marker of astrocyte injury) with ubiquitin C-terminal hydrolase L1 (UCH-L1; a marker of neuronal cell body injury). By measuring damage to these two distinct central nervous system (CNS) cell types simultaneously, the assay maximizes clinical sensitivity.

In pivotal studies, this combination demonstrated a negative predictive value of over 99% for intracranial lesions.^{69,70} Consequently, the FDA cleared this panel specifically to predict the absence of lesions, representing a landmark achievement in pragmatic diagnostics. This

clearance has fundamentally changed the triage workflow in emergency medicine, allowing clinicians to safely discharge patients without imaging. While this success is commendable, the rule-out model also highlights the importance of the WHO ASSURED criteria; for such a tool to have a global impact, the technology must move beyond high-cost laboratory platforms toward rapid, point-of-care formats accessible in low-resource emergency settings. Furthermore, clear communication is required to prevent the risk of false negatives or patient anxiety, ensuring that the clinical focus remains on the patient's symptomatic recovery rather than just the biomarker result.

4.4. Parkinson's disease: the synuclein breakthrough

While TBI biomarkers address acute logistical gaps, PD research has achieved a different milestone: the first true molecular definition of pathology in a living patient. Historically, the field faced a significant barrier: PD lacked a definitive molecular diagnostic; diagnosis was purely clinical, based on motor symptoms, such as bradykinesia and tremor, that typically appear only after 50–70% of dopaminergic neurons are already lost.

The technological leap that overcame this barrier was the development of seed amplification assays, specifically real-time quaking-induced conversion (RT-QuIC). Functioning conceptually as a protein amplification assay, this technique exploits the prion-like ability of misfolded alpha-synuclein to induce misfolding in normal proteins, allowing for the detection of minute, previously undetectable traces of pathology in CSF or skin biopsies with over 95% specificity.^{71,72} This qualitative yes/no marker is revolutionizing early intervention by advancing the diagnostic timeline, enabling the identification of patients in the prodromal phase of rapid-eye-movement (REM) sleep behavior disorder years before motor tremors manifest.⁷³ By capturing patients at this molecular stage, the field is finally positioned to test neuroprotective drugs before neurodegeneration becomes irreversible.

However, as with the previously discussed modalities, the transition from technological leap to clinical standard requires a more critical appraisal of practical barriers. Despite high analytical specificity, RT-QuIC testing remains largely confined to specialized laboratories, and cross-center standardization is currently an ongoing hurdle. For it to reach a level suitable for broad publication and practice, the field must establish harmonized protocols and clear reimbursement pathways. Furthermore, to avoid the risk of over-medicalization or undue patient anxiety, particularly in the absence of a disease-modifying cure, the deployment of such powerful yes/no markers must be accompanied by a discursive clinical framework that

prioritizes the patient's long-term wellbeing over the mere presence of a molecular signal. Finally, ensuring these advanced amplification assays remain non-Western-centric requires a concerted effort to adapt them to the WHO ASSURED criteria for global accessibility.

4.5. Neuropsychiatry: the heterogeneity challenge

While PD research has thrived by identifying a distinct molecular target in alpha-synuclein, neuropsychiatry faces a more formidable obstacle: the absence of a defined “ground-truth” pathology. This heterogeneity trap remains a primary barrier, as psychiatric diagnoses are currently based on descriptive symptom clusters, such as those in the Diagnostic and Statistical Manual of Mental Disorders (DSM), rather than a shared etiology. Consequently, two patients diagnosed with major depressive disorder may share zero biological overlap, rendering the search for a single “troponin for depression” largely unsuccessful. Unlike AD, where amyloid plaques provide a post-mortem gold standard, psychiatry lacks a tissue-based “truth” against which to benchmark blood tests or imaging markers.⁷⁴

To bypass this, the field is pivoting toward biotyping, a strategy that clusters patients based on biological signatures rather than clinical labels. This approach often requires multimodal data integration; for example, combining fMRI measures of functional connectivity with inflammatory cytokines (e.g., CRP, interleukin [IL]-6) has helped identify distinct immunometabolic subtypes of depression where systemic inflammation drives specific alterations in brain reward circuits.^{75,76} Such precision implementation is not merely an academic taxonomy; it has shown the potential to predict treatment success, with specific connectivity biotypes identifying which patients are most likely to respond to transcranial magnetic stimulation.⁷⁷

4.5.1. An actionable framework for clinical biotyping

To move beyond the heterogeneity trap, we propose a three-tiered implementation roadmap for psychiatric biomarkers.

- (i) Tier 1 (immunometabolic triage): Utilizing low-cost, peripheral inflammatory markers (e.g., CRP >3 mg/L) to identify the inflamed depression biotype. This provides an immediate, actionable signal for clinicians to consider augmenting standard care with anti-inflammatory agents or specific lifestyle interventions.
- (ii) Tier 2 (functional connectivity mapping): For patients non-responsive to Tier 1, resting-state fMRI can identify connectivity biotypes (e.g., frontostriatal anhedonia vs. amygdala-centered anxiety subtypes). This allows for the precise anatomical targeting of

neuromodulation, such as transcranial magnetic stimulation, rather than a one-size-fits-all approach.

- (iii) Tier 3 (outcome-based longitudinal tracking): Implementing digital biomarkers (e.g., sleep patterns and speech prosody) to monitor state-dependent shifts in these biotypes. This ensures that treatment is adjusted dynamically based on objective behavioral data rather than on periodic, subjective symptom scales.

4.5.2. Deciphering the replication crisis in psychiatric biotyping

The failure of pioneering models, such as the connectivity biotypes proposed by Drysdale *et al.*⁷⁶, to replicate in independent cohorts highlights critical methodological and biological hurdles that must be addressed to achieve clinical utility. A primary technical driver of this non-replication is preprocessing variability; the lack of standardized noise-reduction pipelines in fMRI means that minor variations in how researchers handle head motion or physiological artifacts can lead to fundamentally different connectivity clusters. Furthermore, a discovery-vs.-real-world gap persists because most initial biotypes are discovered in small, homogeneous samples from tertiary research centers. When these models are applied to larger, more diverse community populations, the subtle biological signals often wash out against the background noise of comorbidities and varied medication histories. This is frequently compounded by overfitting and high dimensionality, where complex AI models learn the specific quirks of a training dataset rather than biologically robust patterns. To overcome these failures, the field must prioritize cross-site validation and the utilization of larger, open-access datasets, such as the United Kingdom (UK) Biobank, to ensure that identified biotypes are generalizable across different populations and recording environments.

However, the portrayal of biotyping must be balanced with a more rigorous critical appraisal of its current limitations. Several early biotyping frameworks, most notably the connectivity models proposed by Drysdale *et al.*⁷⁶, have encountered significant replication challenges and methodological scrutiny. Effect sizes often attenuate when these models are applied to independent, heterogeneous cohorts, underscoring the urgent need for harmonized preprocessing pipelines and large-scale prospective validation.

Furthermore, the transition to these AI-driven biotypes represents a profound cultural and structural shift for healthcare providers that is often understated. Before widespread adoption, the field must demonstrate not only statistical significance but also clear outcome superiority over the current standard of care, while remaining vigilant

against the risk of over-medicalization in populations where biological signals may not yet correlate with actionable clinical improvements.

5. Future perspectives and emerging technologies

As we look toward the next decade, the focus shifts from discovering individual markers to integrating them into holistic, predictive models and ensuring these tools reach the populations that need them most.

5.1. Artificial intelligence and multi-omics integration

The future of diagnostics lies in moving beyond single-analyte thresholds toward composite risk scores. While human clinicians cannot simultaneously process the high-dimensional interplay of proteomic, genomic, and imaging variables, machine learning excels in this domain. Machine learning algorithms can identify non-linear relationships within these complex datasets, for example, determining how a specific polygenic risk score modulates the predictive value of an MRI atrophy pattern to provide a more personalized prognosis.⁷⁸

However, the transition of AI-driven biomarkers from black-box algorithms to regulated SaMD faces a significant trust gap. Clinicians are ethically and practically hesitant to rely on opaque models, making XAI the critical bridge for clinical adoption. Methods such as SHAP are being developed to open the black box by quantifying the contribution of specific features, such as an elevated p-tau level combined with hypertension, to a specific risk score.⁷⁹ This transparency satisfies both clinical rationale and the stringent requirements of the FDA's 2024 Final Rule, which distinguishes between locked and adaptive algorithms by requiring feature-level transparency.

Ultimately, this convergence leads to high-performance medicine, where AI does not replace the clinician but augments them with data-driven precision.⁸⁰ Yet, the portrayal of XAI implementation must remain grounded in reality. Integrating these algorithms into daily clinical workflows represents a profound cultural and structural shift for healthcare providers, often understated in the current literature. Furthermore, the scientific discussion must account for the risks of ancestry bias in AI training data, which can exacerbate global health inequities if models are not validated across diverse populations. The next frontier of care requires that our statistical accuracy is matched by a robust commitment to both clinical transparency and global inclusivity.

5.2. Extracellular vesicles (exosomes)

While standard blood tests measure free-floating proteins, CNS-derived exosomes offer a protected “window into the brain.” The challenge with blood biomarkers is often the “noise” from peripheral organs (e.g., the liver). By isolating vesicles expressing neural surface markers (e.g., L1 cell adhesion molecule [L1CAM]), researchers can effectively enrich CNS-derived vesicular populations and analyze cargo proteins specifically derived from neurons. While this strategy aims to enhance CNS specificity, methodological variability in exosome isolation, particularly L1CAM-based enrichment, has generated reproducibility concerns. Large-scale, standardized validation studies are required before CNS-derived exosomal biomarkers can be considered clinically mature.⁸¹

5.3. Global health and point-of-care

Finally, translational success must be measured by accessibility. To address global health equity, the field is moving away from centralized, expensive lab equipment toward miniaturized point-of-care devices. The goal is to develop lateral flow assays (similar to COVID-19 rapid tests) for complex markers, such as NfL and p-tau. This would bring precision neurology to rural clinics and low-resource settings where MRI infrastructure is unavailable, effectively democratizing AD and MS diagnosis. To ensure these technologies are truly accessible, development should align with the WHO ASSURED criteria. Without this focus, biomarker innovation risks remaining Western-centric, limited to high-cost modalities such as PET imaging.

6. Conclusion

The future of neuroscience biomarker translation will depend less on discovery velocity and more on the structural alignment of validation, regulation, reimbursement, and implementation. Translational attrition persists not because of a lack of molecular innovation, but because discovery pipelines often remain disconnected from clinical realities. To bridge this valley of death, a shift toward reverse translation is essential, defining the specific context of use, regulatory pathways, and economic viability at the very inception of biomarker development. Ultimately, a biomarker must demonstrate more than just analytical validity; it must prove a measurable, positive impact on clinical decision-making and patient outcomes.

Equally critical is the imperative of scalability. While high-cost modalities such as PET imaging have set the gold standard, fluid biomarkers and digital tools offer

the potential to decentralize neurological diagnostics beyond tertiary centers. Ensuring this accessibility across diverse populations and global health systems is both a technical and ethical necessity. To move these goals from aspirational to actionable, development should align with the WHO ASSURED criteria, ensuring that diagnostic democratization does not remain a Western-centric endeavor.

Furthermore, the risk of false positives in large-scale deployment cannot be ignored. The adoption of biomarkers that lack near-perfect specificity, particularly in primary care settings, could lead to significant over-medicalization, causing undue patient anxiety and placing an unsustainable financial burden on public healthcare systems. This concern underscores the need for a more critical appraisal of “breakthrough” markers such as p-tau217, where platform variability and a lack of real-world data still present significant hurdles. When analytical rigor, clinical utility, and equitable implementation finally converge, neuroscience biomarkers can transition from promising discoveries into durable, global standards of care.

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Conflict of interest

The authors declare they have no competing interests.

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