WHITE PAPER

Blood-Based Biomarkers for Neurological Disorders

- Discover how blood-based biomarkers (BBBs) provide a scalable, less invasive alternative to cerebrospinal fluid in neurological research
- Explore case studies using protein, autoantibody and single-cell profiling across neurological disorders
- Learn how to integrate SomaScan™, KREX™ and CyTOF™ platforms into your biomarker discovery workflow
- Examine the challenges of developing and implementing BBBs in clinical practice

Introduction

Neurological disorders are biologically and clinically diverse, with symptoms and progression varying widely between individuals[1]. Blood-based biomarkers (BBBs) offer a minimally invasive, scalable and cost-effective approach for early detection, monitoring and patient stratification. Stratification is particularly valuable in rare neurological diseases, where enriched cohorts can power smaller, more efficient clinical trials.

Once considered too nonspecific to reflect central nervous system (CNS) pathology, peripheral biomarkers gained credibility in the early 2010s when plasma concentrations of key neurodegenerative proteins – neurofilament light chain (NfL) and β-amyloid (Aβ) – strongly correlated with levels in cerebrospinal fluid (CSF)[2]. A pivotal step came in 2025, when the United States Food and Drug Administration (FDA) approved the first *in vitro* diagnostic blood test to aid early detection of Alzheimer's disease in symptomatic adults over age 55[3].

Table 1. Proteomic technologies at Standard BioTools

Technology	Analytical Focus	Sample Type	Description
SomaScan Assay	Protein profiling	Biological fluid*	Quantifies up to 11,000 unique human proteins with approximately 5% coefficient of variation (CV)
KREX microarrays	Antibody profiling	Biological fluid*	Profiles 1,800-plus antibodies with a false discovery rate (FDR) below 1%
CyTOF technology	Single-cell proteomics	Cells**	Measures 50-plus surface and intracellular proteins per cell, the highest multiplexing capability on the market

* Pre-validated biological fluids include plasma and serum. CSF is also validated for use with the SomaScan 11K and 7K Assays. For information on additional compatible sample types, please **contact us**.

** Includes the analysis of cells in whole blood

This white paper highlights how high-throughput proteomic technologies are enabling the discovery of novel BBBs across neurological conditions (Table 1). Through case studies using SomaScan (protein), KREX (autoantibody) and CyTOF (cellular) platforms, we explore the current landscape and discuss the challenges and opportunities shaping the future of BBBs (Tables 2–4).

Protein profiling

Protein biomarkers predict 20-year dementia risk

Current biomarkers for dementia largely focus on Alzheimer's disease (AD) pathology and short-term risk, leaving a need for broader, long-term prognostic tools. Using the SomaScan Assay, approximately 5,000 proteins were measured in plasma from over 11,000 participants in a longitudinal study, identifying a 25-protein signature predictive of 20-year and five-year risk of dementia[4]. The panel outperformed current AD plasma biomarkers and was validated in two independent cohorts. This signature forms the basis of the research-use-only (RUO) Dementia SomaSignal™ Test (dSST), offering a scalable solution for early risk stratification.

Proteogenomic studies uncover candidate causal proteins and therapeutic leads

Proteogenomic tools like Mendelian randomization (MR) allow researchers to identify candidate proteins causally linked to disease through correlating protein levels with genetic variants[5]. In a 2025 study, MR applied to SomaScan Assay data from over 35,000 participants uncovered five plasma proteins associated with AD (GSTP1, BIN1, Siglec-3, SERPINF2, GRN)(p <0.05)[6]. Protein–protein interaction networks and drug target databases further highlighted GSTP1 and BIN1 as promising, underexplored therapeutic candidates.

A similar approach in Parkinson's disease identified 25 proteins linked to onset or progression (p <0.05)[7]. One protein, TPST1, was linked to cognitive decline and enriched in specific neuronal subtypes, demonstrating the ability of BBBs to reflect localized neural biology.

In schizophrenia, MR integrated SomaScan Assay data from over 3,000 individuals with large-scale genetic datasets[8]. Several mitochondrial proteins were found to modify disease risk: SOD appeared protective, while ETHE1, CALU3 and

Table 2. Case studies leveraging the SomaScan Assay for protein-based BBB profiling

Disorder	Key Insight(s)	Potential Application	Representative Study
Dementia	25-protein plasma signature predicts 20-year risk	Long-term risk prediction; early intervention	Duggan (2025)
Alzheimer's disease	5 plasma proteins linked to disease; GSTP1 and BIN1 flagged as therapeutic targets	Prevention; targeted therapy	Sun (2025)
Parkinson's disease	25 circulating proteins linked to onset or progression; TPST1 enriched in neurons	Subtype identification; therapy development	Gao (2025)
Schizophrenia	Mitochondrial proteins modify risk; some are druggable	Risk biomarkers; drug repurposing	Sun (2025)

C1QBP increased susceptibility (p <0.03). Some proteins from related genes are already targeted by approved drugs, presenting repurposing opportunities, while others are untargeted, pointing to new therapeutic candidates.

Antibody profiling

Early detection AAb biomarkers of glioblastoma

Glioblastoma (GBM) is a rare cancer that lacks minimally invasive, specific biomarkers, limiting early detection strategies. To address this, researchers screened serum from grade IV GBM patients (n=20) and healthy controls using the KREX i-Ome™ Discovery microarray[9]. Sixteen AAbs were differentially expressed (p <0.05), with anti-COL4A3BP and anti-HSP90AA1 showing the greatest fold changes. COL4A3BP is a ceramide transporter linked to intellectual disability, while HSP90AA1 is a heat-shock protein associated with multiple cancers and a known autoantigen in other diseases. Despite the small cohort, findings suggest GBM triggers a detectable immune response, and AAb profiling could support early detection and patient stratification.

AAb biomarkers correlate with disease severity in autism spectrum disorder

Autism spectrum disorder (ASD) lacks approved biomarkers for diagnosis or stratification. Researchers applied the KREX i-Ome microarray to profile plasma AAbs from children with ASD (n=93) and neurotypical controls (n=28)[10]. They identified 29 significantly altered AAbs (p <0.05) targeting proteins involved in metabolism, immune signaling and synaptic regulation. Notably, anti-PSIP1 and anti-NAP1L3 were upregulated, targeting proteins linked to neurogenesis and epigenetic control. One of the most downregulated AAbs targeted β-catenin, a key Wnt signaling protein encoded by CTNNB1, a gene with known ASD-related mutations.

Several AAb levels correlated with age and autism severity, as measured by the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2), indicating their potential as tools for disease staging or progression monitoring. These results support a role for AAbs as either protective or pathological, depending on expression patterns, and highlight their promise as biomarkers for ASD diagnosis, severity assessment and therapeutic development.

AAb signatures reveal immune dysregulation in mild cognitive impairment (MCI) and dementia

Immune system dysfunction is increasingly linked to dementia. Researchers profiled plasma from 98 individuals – cognitively normal, with MCI or with dementia – using the KREX i-Ome microarray[11]. They identified 33 and 38 dysregulated AAbs in dementia versus normal and MCI groups, respectively, with nine consistently altered. Five AAbs (CAMK2A, CKS1B, ETS2, MAP4, NUDT2) were dysregulated in both dementia and MCI.

Many of these AAbs targeted proteins involved in neurodegenerative pathways such as neurotrophin signaling, axon guidance and glycolysis. AAb levels of anti-ODF3, anti-E6, anti-S100P and anti-ARHGDIG also correlated with cognitive scores, suggesting utility as progression biomarkers. These results indicate the role of autoimmunity in cognitive decline and highlight AAb profiling as a promising strategy for biomarker discovery and identifying new targets for intervention.

Table 3. Case studies leveraging KREX technology for AAb-based BBB profiling

Disorder	Key Insight(s)	Potential Application	Representative Study
Glioblastoma	16 AAbs differentially expressed in GBM	Early detection; stratification	Wei (2024)
Autism spectrum disorder	29 dysregulated AAbs linked to neurogenesis and severity	Diagnostic support; staging	Mesleh (2023)
Mild cognitive impairment, dementia	AAbs altered in early and late disease; correlate with cognition	Progression markers; immune-targeted therapy	Ehtewish (2023)

Immune cell profiling

Disease-specific myeloid signatures in multiple sclerosis

Multiple sclerosis (MS) is characterized by chronic CNS inflammation, partly driven by infiltration of peripheral immune cells. Using CyTOF technology, researchers profiled myeloid cells from CNS tissue and blood in a mouse model of MS (i.e., experimental autoimmune encephalomyelitis; EAE)[12]. Peripheral monocytes expressed high levels of inflammatory marker pSTAT3 at disease onset and peak. They also expressed adhesion molecules CD49d and CD49e, which are typically absent in resident CNS cells. Blocking α5 integrin (CD49e) significantly reduced disease severity, positioning it as a viable treatment candidate.

A separate study profiled blood from newly diagnosed relapsing-remitting MS patients (n=60) and healthy controls (n=29), identifying a CD206hi CD209hi monocyte subset in 22% of patients[13]. These cells expressed pro-inflammatory markers (for example, CCR5, CCR2, CD106) (p = 0.01) and were associated with significantly worse outcomes, including relapses, new T2 lesions and higher EDSS scores (p <0.02). These studies show how CyTOF systems can uncover disease-specific immune signatures, potentially informing early prognosis and targeted interventions in neuroinflammatory diseases like MS.

> "These studies illustrate the power of [CyTOF] mass cytometry." – Ajami et al. (2018)

Inflammation linked to major depressive disorder

Major depressive disorder (MDD) is a stress-related psychiatric condition, with over one-third of patients failing to achieve full remission with current treatments. This has driven interest in uncovering its underlying biology. Researchers used CyTOF systems to profile peripheral immune cells in stressed mice and human MDD patients[14].

Chronic stress in both mice and humans led to increased levels of inflammatory monocytes and neutrophils, and reduced B cells in circulation. In humans, these immune shifts correlated with perceived stress levels. In the brain, monocyte infiltration occurred only in stress-susceptible mice. RNA sequencing of these monocytes revealed a pronounced pro-inflammatory profile, including an elevated protease (MMP8) that crosses the blood-brain barrier and alters brain function and behavior. These results suggest peripheral inflammation as a driver of MDD and a target for future therapies.

Senescent cell signatures in amyotrophic lateral sclerosis for diagnosis, stratification and prognosis

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease marked by variable progression and poor prognosis. To characterize the immunophenotype of ALS patients, peripheral immune cells from patients with ALS (n=21) and healthy controls (n=10) were analyzed with CyTOF technology[15]. ALS patients had more senescent CD4+CD27–CD57+ T cells, fewer naïve B cells and reduced CD57+CD86 monocytes. Differences were also observed: Limb-onset ALS

Table 4. Case studies leveraging CyTOF platforms for cell-based BBB profiling

Disorder	Key Insight(s)	Potential Application	Representative Study
Multiple sclerosis	Blood monocytes predict severity; α5 integrin as a target	Prognosis; therapeutic targeting	Ajami (2018), Rodriguez (2025)
Major depressive disorder	MMP8-expressing monocytes linked to stress and behavioral changes	Immune biomarkers; drug target identification	Cathomas (2024)
Amyotrophic lateral sclerosis	Senescent T/B cells correlate with progression and subtype	Prognosis; immune modulation	Yildiz (2022)

showed more CD4 effector T cells, while bulbar-onset ALS had more CCR4+ CD4 T cells. CD4 central memory T cells negatively correlated with survival (p=0.01). These immune profiles suggest senescent lymphocyte populations could serve as BBBs for diagnosis, stratification and prognosis, and may inform trials targeting immune senescence in ALS.

The future of BBBs in neurology

BBBs are emerging as powerful tools for diagnosing, monitoring and stratifying neurological conditions. As illustrated in the case studies above, blood can meaningfully reflect CNS biology when measured with high-resolution technologies (Tables 2–4).

Advances in multi-omics are accelerating discovery. Integrating proteomic and genomic data helps uncover hidden biomarker signatures often missed by single-modality approaches, making subtype-specific, stage-aware and response-guided biomarkers more achievable[6–8].

Still, the path from discovery to clinical implementation is complex (see "Challenges in BBB development" box at right)[16]. For example, preanalytical factors such as time to spin, time to decant, time to freeze and freeze-thaw cycles can significantly affect protein integrity and data quality. To help address these issues, Standard BioTools offers RUO SomaSignal Tests designed to evaluate and mitigate the impact of these variables.

Ultimately, BBBs must show real-world clinical value: improving diagnosis, informing treatment or accelerating intervention. Broader adoption will require clinical validation, insurance reimbursement, integration into clinical guidelines and cross-disciplinary education.

Challenges in BBB development

- **CNS specificity**
  Isolating brain-derived signals remains difficult due to systemic noise and the blood-brain barrier.
- **Sensitivity and specificity**
  Detecting low-abundance CNS proteins requires high assay precision. False positives from cross-reactivity or technical variation can limit reliability.
- **Cohort diversity**
  Many studies use small cohorts. However, more inclusive, representative studies are needed to identify how biomarker performance can differ based on confounding variables like comorbidities, which are often underrepresented.
- **Pre-analytical effects**
  Variations in sample handling and storage can significantly affect the quality, consistency and interpretability of protein biomarker data. Harmonization of methodologies is necessary.
- **Analytical effects**
  Diverse assay platforms can yield variable results. Cross-platform calibration is key for clinical adoption.
- **Regulatory hurdles**
  Clinical adoption requires rigorous validation, longitudinal outcome data and compliance with evolving regulatory frameworks [for example, FDA, lab-derived tests (LDT) pathways].

Conclusion

Peripheral blood can reflect CNS pathology in ways that are quantifiable, biologically meaningful and clinically actionable. Across the case studies presented, a consistent theme is the central role of immune dysregulation, emphasizing that peripheral immune changes can reflect and potentially influence CNS pathology. While many findings remain in early stages, larger and more diverse studies will be critical to clinical translation.

The SomaScan, KREX and CyTOF platforms each offer distinct yet complementary insights that deepen our understanding of neurological disorders and accelerate translational research. Standard BioTools™ Omics Services provides access to these technologies, along with expert support for study design, execution and analysis.

With regulatory milestones like the recent approval of plasma-based Alzheimer's diagnostics, the momentum behind BBB discovery has never been stronger.

Talk to an expert

Contact our scientific team to learn how to apply these platforms to your neuro research.

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