



Blood-Based mRNA Testing for the Diagnosis of Schizophrenia and Bipolar Disorder

Mental health diagnostics have been in crisis for some time now due to increasing patient loads, lack of definitive diagnostics and adverse societal impact. This has created a huge burden on healthcare systems along with uncertainty for individuals, particularly young people who begin to exhibit symptoms in their early teens, causing anguish for families, often for many years. Recent advances in mRNA analytics and automation, along with scalable solutions, have led to improved tests that detect and differentiate schizophrenia from bipolar disorder with higher accuracy than traditional psychiatric methods. Results are reported in days, not months or years, from a simple blood test. Recently, the US FDA assigned "Breakthrough Device Designation" to a methodology in this area in recognition of its potential to change the way these two diseases are diagnosed. The methods being developed have the potential to change how psychiatry is practiced more in the next ten years than it has been practised in the past 100 years.

Schizophrenia (SZ) and bipolar disorder (BD) are severe psychiatric disorders associated with functional impairment, substantial morbidity and reduced life expectancy. SZ is characterised by psychiatric symptoms such as delusions, hallucinations and cognitive deficits that manifest as people seemingly lose touch with reality. It is usually first diagnosed between the ages of 16 and 30 following an initial psychotic episode. SZ affects millions of people with a global prevalence of 0.33%–0.75%. BD is a chronic mood disorder characterised by episodes of mania alternating with depressive episodes.¹ BD affects more than 1% of the world's population and ranks second in terms of its most significant impact for lost workdays. The clinical presentation of these disorders frequently overlaps during acute episodes. Psychosis is present in 20% to 50% of patients with acute bipolar mania and depressive symptoms occur in both conditions.² First-episode psychosis patients may present with overlapping symptoms making initial differentiation particularly challenging.³ This overlap is especially pronounced in young adults with first presenting episodes, where distinguishing features may not yet fully show.

Despite advances in understanding disease biology, diagnosis and differentiation of SZ and BD remain based almost exclusively on clinical and symptom-based criteria rather than objective biological measurements. The lack of quantitative tools to aid in early detection and differentiation between SZ and BD represents a significant unmet need for the mental health community. Misdiagnosis or delayed diagnosis can result in inappropriate treatments, including exposure to medications that may be ineffective or cause adverse effects, as well as delay of appropriate therapies. Accurate differentiation between SZ and BD is essential, as treatment selection, dosing strategies and risk–benefit profiles

differ substantially. Misdiagnosis can lead to delayed or inappropriate therapy and increased hospitalisation, leading to poorer long-term outcomes.

One USA-based organisation has developed (and patented) blood-based mRNA biomarker tests with a biological rationale for identifying mental illnesses. The hypothesis is that SZ and BD have distinct, globally differentially expressed mRNA genes in blood for each disorder; these are trait-stable biomarkers over time. This hypothesis is based, in part, on the concept that circulating blood reflects the body's changing health, i.e., the "Sentinel Principle."⁴ As blood circulates, it communicates with cells in various tissues. Changes in these cells, due to injury or disease, trigger detectable alterations in gene expression. These changes can be profiled to generate molecular biomarkers that reflect disease activity. As blood circulates through the brain, communication occurs between blood cells and the brain. Following a brain injury or disorder, circulating white blood cells alter their mRNA gene expression profiles.⁵ This allows for the identification of disease-specific gene expression signatures. This means that different diseases, including brain disorders, can be detected and monitored through these molecular biomarkers.

From a molecular biology perspective, gene expression reflects the dynamic activity of biological pathways. While DNA encodes genetic potential, mRNA represents the transcriptional output of genes that are actively expressed at a given point in time. mRNA expression therefore provides a functional measure of cellular state, reflecting ongoing physiological and pathological processes rather than static genetic risk. This distinction underpins the use of RNA-based biomarkers in diagnostics, as mRNA levels capture disease-associated biological activity that may not be detectable solely through DNA sequence analysis.

The mRNA gene biomarker test measures mRNA gene expression across 18 genes in whole blood that were selected from whole-transcriptome discovery studies. These genes represent pathways involved in immune signalling, cellular stress response, metabolic regulation and other biological processes implicated in severe psychiatric disorders.⁶ Although the assay does not directly measure brain tissue, the selected transcripts reflect biological states influenced by central neuroimmune and neuroendocrine activity.

By evaluating expression levels of these 18 genes and applying a computational model, the assay generates a molecular signature that detects and differentiates SZ and BD based on underlying biology, rather than solely on subjective symptom assessment. Furthermore, it is hypothesised that these gene signatures and the predictive accuracy of white blood cells remain robust and independent of medication status and disease progression and that the algorithm may support prediction of disease development in young people at clinically high risk.⁷



Clinical Performance Demonstrating a More Effective Diagnostic Approach

The mRNA gene biomarker test reported a more effective, faster and more accurate diagnostic approach than the current standard-of-care by evaluating disease-specific mRNA biomarkers from a standard whole-blood sample. The test delivers objective results within days, enabling earlier and more informed clinical decision-making. In contrast, current standard-of-care diagnostic pathways frequently require months to years of clinical observation before diagnostic clarity is achieved.

Across a pivotal 90 subject clinical trial (30 SZ, 30 BD, 30 NC controls) with 4 visits over 90 days and blood samples collected at visits 2, 3 and 4, with analysis of blood samples at visits 2 and 4 over 60 days, the 18-gene mRNA biomarker assay demonstrated diagnostic performance using prespecified logistic regression models applied to whole-blood RNA expression levels. Using a four-step classifier, the assay achieved a combined overall accuracy of 86% and 92% retest accuracy across visits 2 and 4, supported by class-specific metrics: bipolar disorder sensitivity 95%, schizophrenia sensitivity 90% and control specificity 72% when evaluated against clinician-assigned diagnoses using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR).

Predicted	Visit 2 Actual			Visit 4 Actual			Both Actual		
	BD	SZ	NC	BD	SZ	NC	BD	SZ	NC
BD	28	1	4	29	1	2	57	2	6
SZ	1	26	5	0	28	6	1	54	11
NC	1	3	21	1	1	22	2	4	43
Accuracy	83%			88%			86%		
Sensitivity (SZ)	87%			93%			90%		
Sensitivity (BD)	93%			97%			95%		
Specificity (NC)	70%			73%			72%		

Overall Diagnostic Classification Performance Across Visits

Collectively, these clinical data demonstrate that the 18-gene mRNA biomarker assay delivers a rapid, reliable, objective and biologically grounded diagnostic readout capable of distinguishing SZ, BD and NC with high accuracy, near-perfect Receiver Operating Characteristic (ROC) performance with stability over time. These performance metrics highlight the test's potential to provide clinicians with a reliable, objective diagnostic tool, substantially reducing the uncertainty associated with symptom-based diagnosis.

Risks and Harms of the Current Standard-of-Care for These Life-Threatening and Irreversibly Debilitating Psychiatric Diseases

Under the current standard-of-care, diagnosis of SZ and BD relies almost exclusively on a clinician's subjective assessment of patient-reported symptoms and observed behaviours during clinical encounters, guided by symptom-based diagnostic criteria. At initial presentation, clinicians typically form a provisional diagnosis based on cross-sectional clinical impressions which may evolve over time as symptoms change or additional episodes occur. This symptom-driven pathway introduces significant

clinical risks, including diagnostic uncertainty, misclassification and delayed treatment, particularly early in the disease course.

Current diagnostic pathways depend heavily on patient recall, longitudinal observation and future symptom emergence. They often require years of follow-up before achieving diagnostic certainty. Early differentiation and diagnosis are especially challenging since SZ and BD share overlapping clinical features including psychosis, mood disturbances and cognitive impairment. Early SZ symptoms are frequently misattributed to mood disorders, substance use or developmental issues, while BD is commonly misdiagnosed as major depressive disorder or schizophrenia due to symptom overlap. As a result, diagnostic delays are common and clinically significant. The average diagnostic delay for BD is estimated at 5–10 years and the duration of untreated psychosis in SZ averages 1–3 years, with longer delays strongly associated with poorer clinical and functional outcomes. Initial incorrect diagnosis rates remain high, with up to 50% of individuals with SZ and approximately 70% of individuals with BD receiving inaccurate diagnoses.

These challenges are compounded by the early age of onset of serious mental illness. Approximately 35% of lifetime mental illnesses begin by age 14, 48% by age 18 and 63% by age 25. During this vulnerable developmental period, delays in accurate diagnosis and appropriate treatment can result in irreversible functional impairment leading to further stress and anxiety for patients and their loved ones.

SZ and BD carry a high risk of suicide, particularly when left untreated or misdiagnosed, with suicide being the second leading cause of death among youths aged 10–14. Suicide accounts for approximately 15% of deaths in individuals with BD and around 10% of deaths in those with SZ. Meta-analytic evidence from early psychosis studies suggests that structured early intervention programmes can reduce suicide risk by one-third. This underscores that earlier diagnosis, combined with appropriate psychiatric care and timely initiation of treatment, could significantly reduce suicide rates. Patients with BD have a reduced life expectancy of up to 20 years, with cardiovascular disease accounting for 35–40% of deaths alongside the high suicide rate. SZ is associated with a 10–20-year reduction in life expectancy compared with the general population. In addition, the average potential years of life lost (YPLL) in US individuals with schizophrenia is estimated at 28.5 years. SZ is frequently accompanied by comorbidities such as cardiovascular disease, metabolic syndrome and substance use disorders, contributing further to mortality and functional impairment.

The rapid blood-based mRNA gene biomarker test is being evaluated as an approach for the diagnosis of severe mental illnesses. The objective of the test is to return objective results to the ordering physician within days, rather than longer clinical observation periods, to support earlier clinical decision-making. The assay has demonstrated an accuracy of 86% and a retest accuracy of 92% for these severe psychiatric disorders.

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