

Rethinking Mental Health Diagnosis Through Emerging Biomarkers and Intelligent Technologies: A Review

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Abstract: *Psychiatric disorders, including depression, bipolar disorder, schizophrenia, anxiety, PTSD, eating disorders, and disruptive behaviour disorders, are a major global health burden that reduces life expectancy, impairs quality of life, and increases healthcare costs. Diagnosing mental health conditions can be really tough because symptoms often overlap or get complicated by other conditions. That's why biomarkers are becoming very important; they are like measurable signs that can help doctors figure out the main problem. Researchers are exploring multiple biomarker domains: molecular, neuroimaging, biochemical and even digital data. For instance, some biomarkers can show how stress is affecting someone's mental health, or indicate if someone has a specific condition like depression or schizophrenia. While no biomarker is yet clinically validated. With the help of AI and advanced technology, researchers are focusing on combining these biomarkers to create personalised treatment plans. It is really a promising area of research that could lead to more accurate diagnoses and effective treatment.*

Keywords: Psychiatric disorder, Biomarkers, Neuroimaging, Omic technologies, Artificial intelligence, Precision Psychiatry

1. Introduction

Although understanding of the causes of mental disorders has advanced and access to specialised treatment and therapy has improved, the number of people affected by these conditions remains high.^[1] Impaired psychomotor, cognitive and volitional domains are hallmarks of complex multisystem conditions such as major depression, bipolar disorder, schizophrenia, generalised anxiety, and other major psychiatric disorders. Complex interactions between immune dysregulation, environmental exposures, neuroendocrine stress responses, genetic predisposition, and abnormalities of the gut-brain axis contribute to their development.^[2]

Mental illness poses a major global burden, with a 13-32 years reduction in life expectancy, as well as an increase in mortality, disability and healthcare costs (~4%). Major trials (CATIE, STAR*D, STEP-BD) have reported low adherence and remission, showing the limited success of current drug treatment. Overlapping symptoms and comorbidities can make the diagnosis challenging. However, advances in brain research and omic technologies may lead to biomarker-based prediction, diagnosis and personalised treatment.^[3]

Biomarkers in psychiatry are measurable signs that reflect the functioning and malfunctioning of the brain and body. The DSM-5 and ICD-10 systems, the main basis of current diagnosis, have trouble with overlapping classifications. To fill this gap, the NIHM's RDOC (Research Domain Criteria) framework links mental disorders to biological markers and the brain system. Despite the shortage of clinically approved biomarkers, advances in proteomics and genomics continue

to bring us closer to better personalised and accurate mental health care.^[4]

Schizophrenia is still an incurable condition, with little change in prevalence or outcomes over the past century. Fewer than 14% of people recover within five years, and long-term recovery remains uncommon due to a limited understanding of its pathophysiology. To make real progress, there must be a greater, coordinated effort to advance the science and greater transparency regarding the difficulties faced by researchers.^[5]

The growing use of biomarkers in psychiatry holds great potential for better mental health care, but it also raises important questions about ethics, law, and society, especially when it comes to using these tools in young people. Biomarker research must be monitored closely as it moves from the laboratory to clinical practice, education and society. This ensures that its applications are ethically and practically sound in addition to advancing science.^[6]

Early research in schizophrenia found metabolic abnormalities, which were initially overlooked. Mitochondrial dysfunction, oxidative stress, and hypometabolism in major psychiatric disorders are confirmed by modern research. These pathways affect oxidative stress, inflammation, and brain energy. These led to the exploration of new therapeutic strategies, including antioxidants, metabolic modulators, and ketogenic diets.^[7]

Loss of Control (LOC) is when someone feels like they can't stop or control what they are eating, even if they want to. This

Volume 15 Issue 3, March 2026

Fully Refereed | Open Access | Double Blind Peer Reviewed Journal

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can be a big part of eating disorders like bulimia, but it can also affect people who don't have a specific diagnosis, especially those who are overweight or have a higher body mass index (BMI). LOC is linked to inflammation, stress, anxiety, depression, and body image issues. During pregnancy, it is the most common disordered eating behaviour, particularly in women with a BMI ≥ 25 , and is associated with excess weight gain and poorer heart health.^[8]

The HPA axis controls stress via cortisol. While a typical rapid rise and fall in cortisol is adaptive, excessively high or low reactivity makes a person more susceptible to stress. Chronic stress changes the brain and increases the risk of mental health issues like schizophrenia, bipolar disorder, depression, and anxiety. Thus, HPA axis reactivity links stress and mental illness.^[9]

Due to trauma and displacement, refugees and internally displaced people in low- and middle-income countries face significant mental health challenges, including PTSD, depression, and anxiety, with women being disproportionately affected. There is limited research on critical mental health issues like substance abuse, psychosis, and suicidality. There are so many obstacles, like staff shortage, persistent stigma, and a lack of funding. Some common tools used to assess mental health include the Hopkins Symptoms Checklist-25, the Harvard Trauma Questionnaire, the Composite International Diagnostic Interview, the Mini-International Neuropsychiatric Interview, and the Structured Clinical Interview for DSM Disorders.^[10]

The Impact of the COVID-19 pandemic is severe, with increased cases of PTSD, depression, anxiety, and grief. Staying at home has increased family violence, and overuse of the internet and social media during lockdown may also harm mental health. For adolescents, their personal strengths, family support, and social environment play a big role in how they cope. More research is needed because such pandemics can continue or happen again.^[11]

Social media strongly shapes the brain, behaviour, and mental health of young people, but research is limited and often confused with "internet addiction." New habits like nomophobia (fear of being without a phone) and FoMO (fear of missing out) show risks, while online activity could also serve as a tool to track and support mental health.^[12]

2. Psychiatric Disorder

2.1 Definition of Mental Disorder

The first formal definition of mental disorder appeared in DSM-III, drafted by Spitzer's committee, to provide an atheoretical, evidence-based classification. It aimed to remove homosexuality from diagnosis and respond to antipsychiatry claims that psychiatry was more about social control than medical science.^[13] Debates over misclassification led the DSM to refine its definitions of mental disorders. DSM-III (1980) stressed that cultural or political deviations are not diseases, while later editions (DSM-IV, DSM-V) acknowledged blurred boundaries. Stein et al. (2010) proposed the term *psychobiological*, warning that vague criteria risk over-medicalisation, and emphasised that new diagnoses must show clinical utility and empirical validity.^[14]

2.1.1 DSM-V definition of mental disorder

A condition known as a mental disorder is defined by a clinically significant disruption in a person's behaviour, emotion control or thought processes that indicates a malfunction in the biological, psychological or developmental processes that underlie mental functioning. Significant suffering or impairment in social, professional or other crucial tasks is typically linked to mental problems. A typical stressor event, such as the death of a loved one, might elicit an expected or socially acceptable reaction that is not a mental illness. Socially aberrant conduct (such as political, religious or sexual) and disputes that mostly arise between an individual and society are not mental illnesses unless the individual is dysfunctional.^[14]

2.2 Types of psychiatric disorder

According to the WHO, 1 in every 8 people in the world lives with a psychiatric disorder. It involves disturbed thinking, emotional regulation and behaviour. There are different types of psychiatric disorders as follows:

- 1) Anxiety Disorders
- 2) Depression
- 3) Bipolar Disorder
- 4) Post-Traumatic Stress Disorder
- 5) Schizophrenia
- 6) Eating Disorder
- 7) Disruptive behaviour and dissocial disorders^[15]

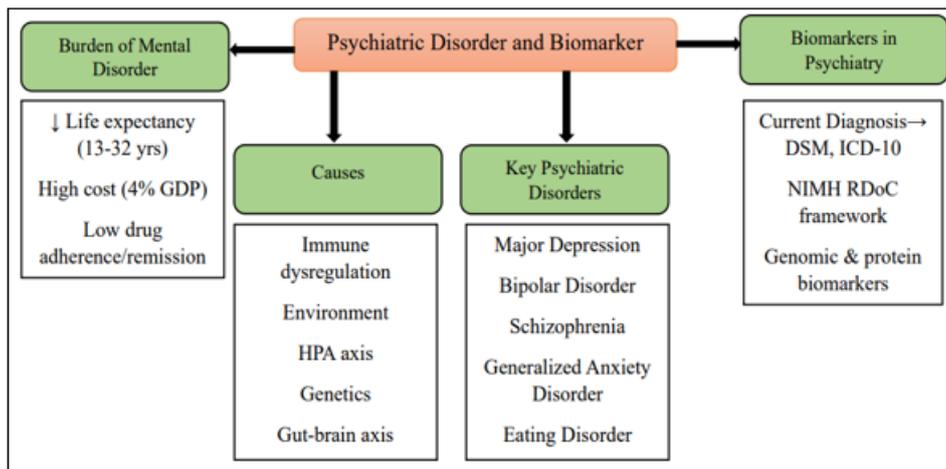


Figure 1: Psychiatric Disorder and Biomarker

2.2.1 Anxiety Disorder

Generalised anxiety disorder is marked by excessive worry lasting at least six months, with symptoms like motor tension (fatigue, trembling, restlessness), autonomic hyperactivity (palpitations, shortness of breath, dizziness), and increased vigilance (feeling on edge, easily startled, poor concentration).^[16] Fear triggers an instinctive fight-or-flight response, while anxiety- closely related to fear- is a future-focused state involving cognitive, emotional, physiological, and behavioural changes. Pathological anxiety occurs when threats are misjudged or exaggerated, causing excessive and inappropriate reactions.^[17]

Self-help (especially bibliotherapy) and complementary therapies (relaxation, exercise, kava) show some benefit in anxiety, though kava is restricted due to hepatotoxicity. Computerised CBT (Cognitive Behavioural Therapy) is effective, cost-saving, and a practical solution for primary care where therapist demand is unmet.^[18] Generalised Anxiety Disorder (GAD) affects about 5% (DSM-III/III-R) and 6.5% (ICD-10) of the population. In primary care, its prevalence is around 8%, making it the most common anxiety disorder and the second most frequent psychiatric disorder after depression.^[19]

2.2.2 Depression

Depression affects about 350 million people around the world. It's the leading cause of disability and ranks 9th in terms of overall disease burden when disability and death are combined. Despite this, depression goes undiagnosed and untreated due to stigma and limited treatment. The situation is especially tough in areas with very few psychiatrists.^[20] Stressful life events are strongly linked to major depression. Earlier studies focused on stress as a cause of depression, but recent views emphasise a two-way cycle where stress increases depression risk, and depression heightens vulnerability to new stressors.^[21] Depressive disorders are heterogeneous and classified by DSM-IV and ICD-10. The DSM-IV provides a framework for understanding mood disorders. According to severity or characteristics, the DSM-IV categorised depression into major depression and dysthymia. ICD-10 has similar categories. Both use structured criteria but are complex and partly inconsistent.^[22]

2.2.3 Bipolar Disorder

Bipolar disorder affects about 1% of people worldwide, and it's a complex condition. Bipolar disorder causes mood swings, from mania to depression, which can lead to serious problems like suicide, disability and cardiovascular disease. Diagnosing it can be challenging because it often comes with conditions, and it is hard to distinguish from depression. As bipolar disorder is complex, it is driven by the combination of genetic, environmental, and neurological factors. For the treatment of bipolar disorder, mood stabilisers, antipsychotics, and psychological therapy are used. It is challenging to find the right approach due to the complexity and limited biomarkers.^[23]

According to recent studies, pharmacotherapy and focused psychotherapy are essential for the best management of bipolar disorder. Psychotherapies (CBT, family-focused, interpersonal & social rhythm therapy, psychoeducation, care management) help by reducing stress, identifying relapse signs, improving lifestyle regularity, and enhancing medication adherence.^[24]

2.2.4 Post-Traumatic Stress Disorder

PTSD is a mental illness triggered by trauma, affecting mood, behaviour, and cognition, with risks of suicide, comorbidities, and disability. Recognised in DSM-III (1980), the diagnosis includes trauma, intrusive symptoms, avoidance, mood/cognitive changes, and hyperarousal. Treatment involves a combination of personalised medications and therapy, with early support and intervention being really important.^[25] PTSD is a trauma-related disorder; it can appear years later and often occurs with depression or anxiety.^[26]

PTSD can affect anyone, but it is more common in young people. Depending on the severity and intensity of the trauma, symptoms may vary in everyone. Women are more likely to develop PTSD than men. It is frequent in high-risk professions (healthcare, military, police, journalists, and emergency workers). Trauma severity, demographics, and temperament strongly influence its development.^[27]

2.2.5 Schizophrenia

Schizophrenia is a complex condition that affects about 1% of the global population, impacting men and women equally, though later onset in women. Symptoms can be characterised into positive (hallucinations, delusions) and negative (social withdrawal, flat affect). Research suggests that EEG and MRI

can accurately predict the treatment response and understand brain changes. AI models are also showing promise, but need more standardisation.^[29] Epigenetic changes, like DNA methylation, may underlie individual differences in symptoms and treatment response. It offers potential for personalised treatment approaches.^[30]

2.2.6 Eating Disorder

Eating disorders affect 2-5% of people, mostly females, causing physical issues like weight changes, low bone density, electrolyte imbalance, hormonal problems, and bradycardia. It also causes mental health issues like depression, anxiety, and suicide attempts.^[31] People with eating disorders often have poor sleep quality.^[32] Binge Eating Disorder is the most common disorder that occurs with depression, anxiety, and other mood disorders.^[33] Eating disorders are quite serious but often under-recognised. Most of the patients don't get better care. Therapies, like family-based therapy, are most effective, while pharmacotherapy has a limited role.^[34]

2.2.7 Disruptive behaviour and dissocial disorder

Disruptive Behaviour Disorders (DBD) are conditions marked by problems with self-control and aggression, usually starting in childhood and sometimes continuing into adulthood.^[35] Irritability in adults has both mood and behavioural parts. Mood is seen in mild cases and strongly linked to impairment, while behavioural outburst shows up in severe cases. This shows the need to improve how irritability is diagnosed in adults.^[36] A personality disorder marked by impulsivity, aggression, lack of empathy and poor emotional regulation. Strongly linked with conduct disorder in youth and commonly comorbid with ADHD, anxiety, depression and substance use, leading to high risk of crime and poor treatment outcomes.^[37]

3. Biomarkers

The term "biomarker" evolved from biochemical/biological markers (1949–1957) to its first use in 1973. In 2000, NIH (National Institute of Health) defined it as "a characteristic that is objectively measured and evaluated as an indication of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention".^[3] In psychiatry, biomarkers can be developed by four steps. First of all, choose an important clinical question where a biomarker can really help. Next, make sure the biomarker truly reflects the disease itself and is not affected by other factors. Then, test it on new groups of patients to check if it works the same way for everyone and provides reliable results. Finally, show that the biomarker improves the treatment decision, is easy to use in hospitals, and is worth the cost.^[38] Psychiatric disorders are too complex for a single biomarker to guide diagnosis or treatment. Current research focuses on combining biological, clinical, and environmental data to create "biomarker signatures," as seen in Alzheimer's and depression initiatives. The main challenge is to simplify these into a few reliable, standardised, and cost-effective biomarkers that can improve outcomes over current clinical methods.^[39]

3.1 Types and Role of Biomarker in Clinical Practice

Biomarkers serve different purposes in medicine. Diagnostic biomarkers help to find or confirm a disease, like how amyloid-beta is involved in Alzheimer's Disease. Monitoring biomarkers tracks how the disease is progressing or how treatment is working over time. Response biomarkers help to identify the biological changes in the body from specific treatment. Predictive biomarkers help to identify which patients will respond best to certain treatments. Prognostic biomarkers predict how a disease will progress in the future. Finally, risk (susceptibility) biomarkers indicate the likelihood of developing a disease before symptoms appear, making them useful for prevention.^[3]

4. Biomarkers in Major Psychiatric Disorders

4.1 Major depressive disorder

Major Depressive Disorder (MDD) is clinically and biologically heterogeneous, and no single biomarker has adequate sensitivity or specificity. A combined biomarker panel approach integrating genetic, epigenetic, biochemical, and imaging factors (e.g., BDNF, HPA axis changes) is more promising for improving diagnosis, treatment, and understanding of subtypes.^[40] Current evidence for most proposed biomarkers of MDD is limited, with little prospective support for factors like neuroimaging, neurotransmitters, or immunity. Cortisol shows some predictive value but is confounded by study quality and baseline depression. High-quality prospective studies combining biomarkers with psychosocial factors are needed to clarify MDD's causes and course.^[41] C-reactive protein (CRP) shows consistent associations with MDD, with elevated levels linked to greater severity, poorer treatment response, and a distinct inflammatory subgroup affecting about one-third of patients. Monitoring CRP may guide personalised treatment and highlight potential benefit from anti-inflammatory interventions.^[42]

4.2 Bipolar Disorder

In bipolar disorder (BD), pro-inflammatory cytokines are increased and BDNF is decreased during acute episodes. Preliminary evidence suggests these biomarkers change over time and with treatment.^[43] Biomarkers in bipolar disorder remain complex, but they may help track disease activity, progression, and guide targeted therapies.^[44] In bipolar disorder (BD), several biomarkers have been proposed, mainly linked to neuroplasticity, neuroinflammation, intracellular signalling pathways, bioenergetics, oxidative/nitrosative stress, apoptosis, proteolysis, calcium signalling, and membrane/vesicular transport. These biomarkers may help in early diagnosis and treatment.^[45] In bipolar disorder, blood-brain-barrier (BBB) leakage is found in about 28% of patients and is linked to more severe and chronic illness. Detected through DCE-MRI, BBB dysfunction is emerging as a potential biomarker for disease progression.^[46]

4.3 Schizophrenia

In schizophrenia, certain brain changes can act as biomarkers. Key candidates like dopamine hyperactivity, Hippocampal hyperactivity, immune system imbalance and loss of gray matter in the cortex. These biomarkers could help to identify people at risk, improve diagnosis and track how well treatments are working. Their development could guide personalised therapies and validate new treatment pathways.^[47] Computational language analysis is a powerful emerging biomarker in schizophrenia, showing 80–90% accuracy and even 94% sensitivity/specificity in difficult clinical distinctions. It can aid in early detection, relapse monitoring, and treatment prediction. In the future, using multiple methods, long-term tracking, and studies across the world in different languages could make biomarkers more powerful for detecting diseases early and predicting their progression.^[48] In schizophrenia, important biomarkers like genetic variations, elevated IL-6, the immune system and inflammatory changes, changes in proteins like FCN3 and APO proteins, and white matter differences. By combining multi-omics approaches with AI could make it possible to detect the disease and improve diagnosis accuracy.^[49]

4.4 Anxiety Disorder

In anxiety disorders, hippocampal theta rhythms (especially type II theta) are key biomarkers linked to freezing and avoidance behaviours. In humans, EEG-based Goal Conflict-Specific Rhythmicity (8-9 Hz) has emerged as a measurable biomarker that responds to anti-anxiety medications.^[50] In depression, anxiety, and chronic stress, salivary biomarkers like cortisol, α -amylase, etc., reflect the body's stress response, inflammation, and neuroplasticity changes. These markers provide a non-invasive and simple way to help with diagnosis and guide personalised treatment.^[51] Blink pattern also acts as a simple and non-invasive marker for detecting anxiety. Changes in blink pattern during emotions like sadness and disgust may indicate anxiety.^[52]

4.5 Post-traumatic stress disorder

In PTSD, promising biomarkers include elevated serum BDNF (Brain-derived Neurotrophic Factor) and VEGF-A (Vascular Endothelial Growth Factor A), both linked to platelet release and neuroplasticity, as well as reduced brain volumes in the hippocampus, grey matter, and white matter. These markers reveal changes in brain growth and blood vessels, while the results for cytokines are still inconclusive.^[53] PTSD biomarkers can be grouped into different types:

Susceptibility markers (GR sensitivity, BDNF, heart rate, and skin conductance), Diagnostic markers (amygdala hyperactivity, hippocampal loss, cortisol, monoamine, Inflammatory markers, NPY, miRNA), and therapeutic markers (rACC activity, blood flow changes, 5HTTLR, BDNF levels). Using a combination of biomarkers is more reliable than depending on single biomarker.^[54] miRNA could be more useful biomarker for PTSD, but requires more clinical validation to confirm reliability.^[55] Multimodal brain imaging helps identify biomarkers for PTSD diagnosis and management, providing a deeper understanding of the brain's

changes. When compared with the single-method approaches, it gives more accurate and clear information. When combined with AI, it could enhance the clinical use.^[56]

4.6 Eating Disorder

Ghrelin (\uparrow in AN, \downarrow /altered in obesity & BED) reflects hunger drive, stress response, and predicts treatment outcomes, while leptin (\downarrow in AN, \uparrow with resistance in obesity & BED) reflects fat stores, satiety, and treatment progress. Together, their dysregulation patterns serve as diagnostic and prognostic biomarkers in eating disorders.^[57] In Anorexia Nervosa, researchers found 673 genes that behave differently, and one of them is VNN1 (vanin 1) on chromosome 6q23.2, showing reduced expression. This gene may be linked to the body's unusual metabolic response to food restriction, but larger studies are required to confirm it.^[58] In AN, eye movement alterations such as saccadic intrusions (SWJs) and inhibitory control errors have been proposed as digital biomarkers, mainly evident during the active phase of the illness. Eye-tracking technology offers a non-invasive and easy method to detect eating disorders early and monitor changes over time.^[59]

5. Advances in Biomarker Discovery Technology

5.1 Proteomics

Mass spectroscopy-based proteomics (such as DIA-MS) is a powerful technique that can identify protein biomarkers in neuropsychiatric disorders from blood, brain tissue, or saliva, helping with early diagnosis and personalised treatment.^[60] By using DIA-MS (Data-Independent Acquisition Spectroscopy) plasma proteomics, researchers have identified specific protein patterns like ACTBL2, PFN1, PKM and YWHAZ, that can differentiate between bipolar disorder, major depressive disorder and healthy individuals. These proteins are linked to processes such as cell structure, mitochondrial function, oxidative stress, and platelet activity. Together, they form a biomarker panel that could improve diagnosis and help guide personalised treatment for mood disorders.^[61]

5.2 Transcriptomics

Transcriptomic studies explore how genes behave in depression at both the single-cell and bulk level, showing the specific pathways and processes involved. By combining data from the brain and blood with advanced multi-omics techniques, researchers can discover better biomarkers.^[62] Measuring extracellular vesicle mRNAs in blood offers a non-invasive way to monitor brain-specific gene activity, while single-cell sequencing, organoids, and tissue-specific databases help identify important neural transcripts more accurately. By combining transcriptomics, cell-free DNA, and proteomics helps researchers discover better biomarkers and develop more personalised treatments for psychiatric disorders.^[63]

5.3 Metabolomics

AI and machine learning enhance psychiatric metabolomics by analysing complex datasets, identifying biomarkers, and reconstructing metabolic pathways. They enable integration with multi-omics data, improve diagnostic precision, and support early prediction and personalised treatment of disorders like SCZ, MDD, BD, and PTSD.^[64] Research on late-life depression shows that changes in amino acids and fatty acids could serve as potential biomarkers, revealing how the body's metabolism is altered in this condition.^[65]

5.4 Epigenetics

Epigenetics helps explain how genes and the environment work together in schizophrenia. Studies have found changes such as DNA methylation, histone modifications, and regulatory networks that influence how the disorder develops and responds to treatment.^[66] Epigenetic analysis using RNA editing biomarkers in blood (EDIT-B test) is being explored to differentiate bipolar disorder from major depressive disorder. RNA sequencing evaluates these epigenetic RNA signatures for diagnostic accuracy.^[67]

6. Recent trends

The number of people with mental health conditions continues to increase: more than 1 billion people worldwide are affected by mental disorders, according to the WHO in 2025. Anxiety and depressive disorders remain the most common.^[68] The disability-adjusted life years (DALYs) for mental disorders have increased over the past decades across many regions.^[69] Post-COVID, there has been an uptick in diagnoses (or at least in detection) of depression/anxiety, especially among adolescents.^[70] In schizophrenia, research shows that higher CRP levels and lower BDNF are linked to poorer thinking and memory abilities. Similarly, research from the ALSPAC cohort shows that inflammatory and metabolic markers like IL-6, neutrophil count, and insulin are linked to symptoms of depression and anxiety.^[71] A large study from the ALSPAC cohort found that certain inflammatory and metabolic markers like IL-6, neutrophil count, and insulin are connected to depression and anxiety symptoms.^[72]

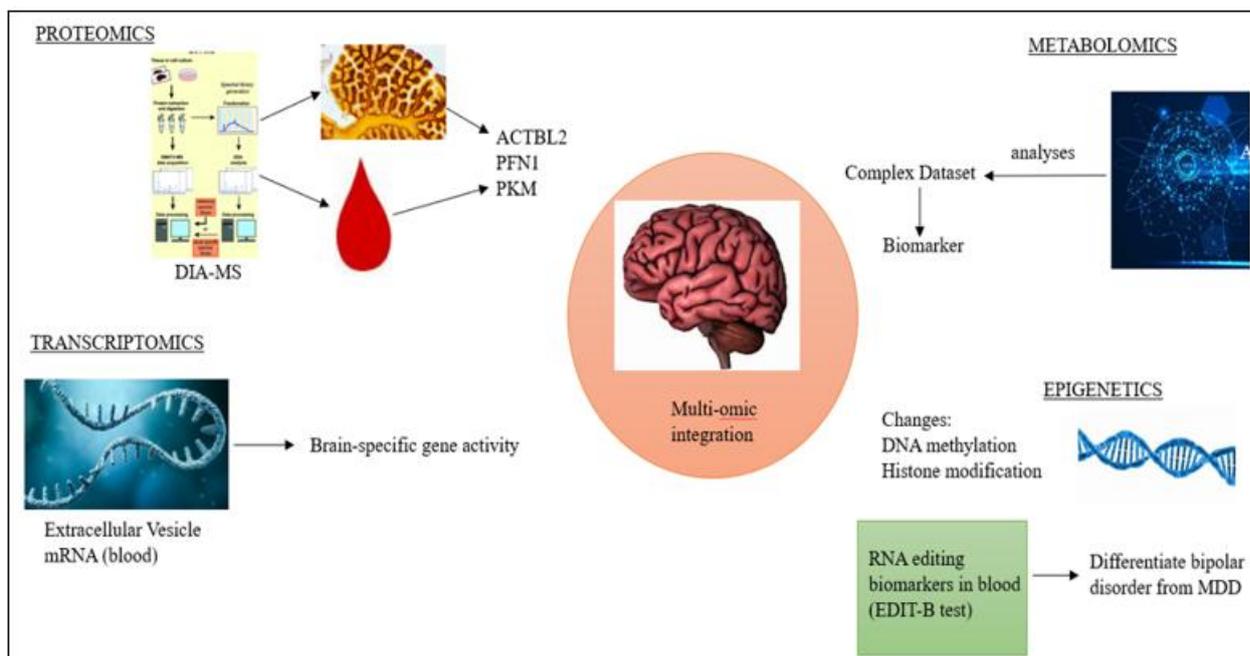


Figure 2: Advances in Biomarker Discovery Technology

7. Conclusion

Mental disorders are complex and influenced by many factors, including genes, environment, hormones, the immune system, and gut-brain interactions. Even with advances in research and treatment, these conditions remain common worldwide, causing significant health, social, and economic burdens. Currently, diagnosis mainly relies on symptoms, which can be challenging because symptoms often overlap, and multiple disorders can occur together. Biomarkers offer a promising way to make more accurate diagnoses, better predictions, and personalised treatment in psychiatric care.

New research is highlighting various potential biomarkers for mental health, from genes and molecular changes to

hormones, brain imaging, and digital markers. By combining these approaches with AI and machine learning, researchers can find biomarkers more efficiently, which could allow early detection, continuous monitoring, and more personalised treatments.

Although no single biomarker can diagnose a mental health condition on its own, combining multiple biomarkers, and with technologies like proteomics, transcriptomics, metabolomics, and epigenetics, has the potential to transform psychiatric care. Future research needs to validate these biomarkers, ensure ethical use, and make them practical and affordable in clinics, ultimately helping people with mental disorders get better, more personalised care.

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