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Review

Translational potential of RNA biomarkers in mental health: A narrative review

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ABSTRACT

Schizophrenia, major depressive disorder, and bipolar disorder lack established objective diagnostic methods. Non-coding RNAs, particularly microRNAs and long non-coding RNAs, are emerging as promising biomarkers due to their involvement in gene regulation and their detectability in bodily fluids. This narrative review summarizes the translational potential of RNA biomarkers in mental health by examining the expression patterns of selected microRNAs and long non-coding RNAs associated with schizophrenia, major depressive disorder, and bipolar disorder. Particular focus is given to frequently altered species such as miR-34a, miR-181b, nuclear paraspeckle assembly transcript 1, and myocardial infarction associated transcript. These non-coding RNAs influence critical neural processes including synaptic plasticity, neuroinflammation, and stress-response pathways—domains central to neuropsychiatric pathophysiology. Circulating RNA profiles demonstrate diagnostic potential; for example, miR-4743 is elevated in schizophrenia and reduced in major depressive disorder. Diagnostic panels containing sex-specific long non-coding RNA signatures have achieved accuracies exceeding 90 %, and some RNAs, such as miR-1202, have been linked to treatment response. Therefore, RNA biomarkers show promise for non-invasive assessment and monitoring of patients with mental disorders. While clinical implementation requires further validation and standardization, continued research—supported by artificial intelligence and machine learning—offers promising new directions for integrating RNA-based biomarkers into psychiatric neuroscience.

1. Introduction

Biomarkers derived from neurobiological processes play a pivotal role in advancing neuroscience research, particularly in understanding, diagnosing, and monitoring psychiatric disorders. Major depressive disorder (MDD), schizophrenia (SCZ), and bipolar disorder (BD) have primary impacts on the global disability burden and the risk of suicide.[1] Diagnosis still relies on clinical evaluations lacking gold standard tests, and the presence of common symptoms frequently results in misdiagnosis and treatment delays.[2] This showcases the greater need for psychiatry in terms of objective biomarkers to improve diagnostic, prognostic, and treatment choices.[2]

Among various biological markers, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are emerging as the most relevant ones. MiRNAs (~22 nucleotides) decrease gene expression at the translation step by hybridizing to a specific region of the mRNA and their presence is documented in the blood as well as the brain. They are readily detected since they are stable to RNase and variations of pH, thus making them appropriate for non-invasive tests.[3] LncRNAs, which are longer than 200 nucleotides, alter the expression of genes by modulating chromatin, controlling transcription, or binding to miRNAs/proteins. Cell and brain region specificity is crucial in them since many of them target neurodevelopment, synaptic regulation, and immune pathways, which are important for psychopathology.[4] This narrative review summarizes the translational potential of RNA biomarkers in mental health by examining the expression patterns of selected miRNAs and lncRNAs associated with SCZ, MDD, and BD.

2. Search strategy

A literature search was conducted between March and May 2025 using PubMed, Scopus, Web of Science, and Google Scholar databases.

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Table 1
Representative microRNA biomarkers identified in major depressive disorder, schizophrenia, and bipolar disorder. Arrows indicate direction of dysregulation in patients relative to healthy controls (↑ upregulated or ↓ downregulated). Where applicable, the sample type (e.g., blood plasma, whole blood, brain tissue) is noted. These examples highlight some microRNAs with reported disorder-specific or overlapping changes. "—" indicates no consistent change reported or not well studied for that disorder. Blank cells do not necessarily mean no change; rather, they indicate lack of clear consensus or data for that microRNA in the given disorder. (References correspond to findings detailed in text.) BD: Bipolar disorder; MDD: major depressive disorder; miRNA: microRNA; PBMC: peripheral blood mononuclear cell; PFC: prefrontal cortex; SCZ: schizophrenia.

MicroRNA	MDD (*vs.* controls)	SCZ (*vs.* controls)	BD (*vs.* controls)	Notable findings
miR – 1202	↓ (Brain)[6]; also low in responders	—	—	Downregulated in depressed brain; low baseline levels predict positive selective serotonin reuptake inhibitor (SSRI) response. Regulates glutamate receptor (GRM4).
miR – 4743	↓ (Plasma)[9]	↑ (Plasma)	—	Opposite directions in MDD *vs.* SCZ - a potential marker to differentiate depressive vs psychotic patients.
miR – 21–3p	↓ (Whole blood)[9]	—	↑ (Whole blood)	Down in MDD but up in BD; inflammation-related miRNA, part of a differentiating panel for mood disorders.
miR – 125a – 3p	↓ (Whole blood)[3]	—	↑ (Whole blood)	Down in MDD, up in BD; shows inverse regulation in unipolar vs bipolar depression.
miR – 34a	↑ (In some studies)	↑ (Blood)[3]; ↑ (Brain) in SCZ	↑ (Plasma *vs.* MDD)[9]	Consistently elevated in psychosis[3]; part of BD *vs.* MDD signature (higher in BD)[9] Implicated in neurodevelopment.
miR – 181b	—	↑ (blood)[3]	—	Upregulated in multiple SCZ studies[3]; levels correlate with improvement of negative symptoms.[3]
miR – 137	—	(Genetic risk variant; mixed expression results)	↓ (Plasma *vs.* SCZ)[9]	Lower in BD relative to SCZ[9]; miR – 137 is a known SCZ risk gene affecting synaptic development.
miR – 124–3p	↓ (PFC brain & serum)[7]	—	—	Down in MDD cortex and blood; normalized by antidepressant treatment.[7] Regulates neurogenesis and BDNF.
miR – 134	↓ (Reported in MDD serum)	↓/↑ (Brain, context-dependent)	↑ (Plasma *vs.* MDD)[9]	Involved in synaptic plasticity. Shown to differentiate BD from MDD (higher in BD) with fair accuracy.[9]

The search covered studies published between January 2009 and April 2025. Search terms included combinations of: ("microRNA" OR "miRNA" OR "long non-coding RNA" OR "lncRNA") AND ("biomarker") AND ("depression" OR "schizophrenia" OR "bipolar disorder") AND ("neuroscience" OR "psychiatry"). Eligible articles were English-language peer-reviewed publications involving human subjects or relevant animal models that reported diagnostic, prognostic, or treatment-response roles of RNA biomarkers in major psychiatric disorders. After screening and deduplication, 72 studies were included in the final synthesis, with an emphasis on those published in the last 5–7 years for recency and clinical relevance.

3. MicroRNA biomarkers in major depressive disorder

Lopez's findings demonstrated the accelerated research pace on miRNA biomarkers by identifying miR-1202 as significantly down regulated in the ventral prefrontal cortex of MDD patients.[5] Cully observed that lower baseline levels of miR-1202 were associated with better antidepressant responses and increased during symptom improvement.[6] Cully also argued that due to miR-1202's regulation of glutamate receptor (GRM4), its reduction could indicate elevated glutamate signaling, further arguing its role as both a state and predictive biomarker.[6] This aligns with broader observations that blood-based RNA biomarkers, including miR-1202, may reflect antidepressant treatment response and symptom change.[6]

Cully also reported other miRNAs putatively linked to MDD such as miR-16 and miR-135a, both influencing serotonin transport and receptor actions, showing associations with symptom severity and treatment response.[6] In another study, Roy et al.[7] demonstrated that miR-124–3p, an important contributor to neurogenesis, shows down regulation in the prefrontal cortex and serum of non-treated MDD patients that was normalized by fluoxetine. Furthermore, Zhang et al.[8] demonstrated that miR-134, involved in synaptic plasticity, shows altered circulating levels in MDD with high sensitivity and specificity.

The miRNA profiles for MDD are intricate and often overlap with other conditions or represent inflammatory processes. As an example, some cases of MDD have miR-21 and miR-146a overexpressed, while others exhibit downregulation of mir-125a-3p. Martinez and Peplow[9] report that miR-4743 was found to be lower in MDD but higher in SCZ, and miR-125a-3p and miR-21–3p were found to be lower in MDD but higher in BD. These opposing patterns may contribute to the differential diagnosis of MDD versus BD or schizoaffective features. In general, a large number of miRNAs indicate some degree of imbalance in the neurotrophic, monoaminergic, and inflammatory pathways in MDD, with further studies expected to improve their precision in diagnosis.

4. MicroRNA biomarkers in schizophrenia and bipolar disorder

SCZ is recognized as one of the psychiatric disorders with the widest miRNA research, in part due to its genetic correlation with miRNA regulation, especially miR137 risk locus and its neurodevelopmental disturbances.[10,11] Numerous studies have been conducted to detect the widespread dysregulation of miRNA in patients, with a systematic review of 22 studies noting 55 miRNAs for which there was differential expression in the blood of people suffering from psychotic disorders, most of them being SCZ.[3] Out of these, 17 miRNAs displayed alteration in at least two studies, thus depicting cross-study reliability, and amongst those most frequently upregulated were miR-34a and miR-181b, which were found to be elevated in seven and six studies respectively.[3] These miRNAs are involved in the processes of neuroplasticity and regulation of immunity and underscore the possibility of propelling them as psychosis biomarkers.

SCZ-related miRNAs are also found to be dysregulated in post-mortem brain tissue. For instance, miR-132 is usually downregulated in cortical regions, which may hamper inflammation resolution and contribute to synapse damage.[12] SCZ-affected neurons have also

demonstrated altered expression of miR-134, which regulates the constriction of dendritic spines through Limk1.[13] Broadly, studies analyzing the profile of the brain's hemispheres emphasize disrupted networks of miRNA associated with neurodevelopment, synapse formation and activity, and communication between the brain and certain chemicals.[13]

The levels of peripheral miRNAs may relate to the stage of a disease. For instance, plasma miR-181b levels correspond with the restoration of negative symptoms, thus corroborating the treatment response hypothesis.[3] Distinct profiles have been documented for various stages of the illness and it appears that antipsychotic medication may alter the expression of some miRNAs. Diagnostic differentials also seem to be quite promising: Martinez & Peplow[9] noted increased miR-4743 expression in SCZ but decreased levels in depressive patients, furthering the notion of distinctive biological differences as BD patients were found to have higher expression of miR-34a/b/c and lower expression of miR-137 in comparison to schizophrenic patients. Collectively, these observations support the idea that some miRNAs could be helpful in distinguishing SCZ from other related disorders. Table 1 lists these candidate biomarkers along with their corresponding overlap with MDD and BD.

5. Long non-coding RNA biomarkers in mood and psychotic disorders

BD, depression, and SCZ have been found to correlate with lncRNA expression changes.[14,15] This area of research is not well established; however, a few lncRNAs with differential expression in patients might perturb biological pathways beyond the reach of miRNAs.

5.1. Nuclear paraspeckle assembly transcript 1

Nuclear paraspeckle assembly transcript 1 (NEAT1) is a paraspeckle and nuclear lncRNA associated with stress response. In the case of SCZ, NEAT1 is expressed at lower levels in cortical regions[4] and peripheral blood of patients who are not on treatment, increasing during antipsychotic treatment.[4] It also affects oligodendrocyte differentiation and myelination,[4] which may explain the changes in white matter associated with SCZ. With mood disorders, NEAT1 normally modulates stress in depression models.[4]

5.2. Myocardial infarction associated transcript

Myocardial infarction associated transcript (MIAT, Gomafu) is both neuronally enriched and downregulated in the superior temporal gyrus of SCZ patients.[4] It binds to some splicing factors with a modifying action of disrupted in SCZ 1 (DISC1) and Erb-B2 receptor tyrosine kinase 4 - those are SCZ-associated genes, and its ablation in mice most often leads to behavioral alterations.[4] MIAT was also shown to be associated with SCZ risk loci.

5.3. DiGeorge syndrome critical region gene 5

DiGeorge syndrome critical region gene 5 (DGCR5) supervises genes within the 22q11.2 deletion zone, which is a risk area for SCZ and a major site for lncRNA scars in the region. It is not a biomarker to be measured in blood circulation, but its expression demonstrates the relationship between lncRNA deregulation and cellular vulnerability in SCZ.[4]

5.4. Interferon gamma antisense RNA 1

As a neurodevelopmentally pertinent cytokine, Interferon gamma (IFN-γ) is positively regulated by interferon gamma antisense RNA 1 (IFNG-AS1). SCZ patients have been shown to exhibit lower levels of IFNG-AS1, which is associated with reduced IFN-γ concentration in the mononuclear cell fraction.[4] It is plausible that this form of epigenetic inheritance contributes to the immune imbalance observed in SCZ.[4]

5.5. Growth arrest-specific transcript 5

Growth arrest-specific transcript 5 (GAS5) is subject to negative regulation by glucocorticoid receptors. In one study, chronic SCZ patients exhibited downregulation of GAS5 in blood to a greater extent than controls, with high diagnostic accuracy in women (area under the curve (AUC) 0.93).[16] In a cohort of patients with psychosis (which included BD and SCZ), GAS5 was also downregulated and remained so even after treatment.[4] In MDD, it has been proposed that GAS5 governs the response to antidepressants through the glucocorticoid pathway, although data concerning humans suffering from MDD are scarce.

5.6. AP1AR-DT

BD is marked by enhanced expression of AP1AR-DT in postmortem brains.[17] Overexpression of the mouse medial prefrontal cortex resulted in depressive and anxiety-associated behavior, reduced synaptic activity, and downregulation of the neuronal growth regulator 1 (NEGR1) neurotrophic factor. NEGR1-mediated restoration of these alterations provided evidence linking AP1AR-DT to the pathophysiology of mood dysregulation, supporting its biomarker and therapeutic target potential.[17]

While still in its early stages, lncRNAs NEAT1, MIAT, and GAS5 show promise as potential diagnostic tools due to their altered expression in psychiatric disorders.[16] Moreover, the role of lncRNAs is multifaceted, and they might interact with miRNAs, for example, functioning as sponges, emphasizing the promise of multi-type non-coding RNA panels.

Altered levels of circulating miRNAs and lncRNAs not only mark the presence of an ailment, but also provide clues to the molecular pathways underlying depression, SCZ, and BD.[18,19] These non-coding RNA molecules frequently interact with pathways which are critical to understanding psychiatric disorders.

6. Synaptic plasticity and neurodevelopment

Some brain-specific miRNAs (such as miR-132 and miR-134, miR-138, and miR-124) regulate neuroplasticity and synapse formation by controlling ARC, CaMKIIα, Limk1, FMRP, CREB, and brain-derived neurotrophic factor (BDNF).[20] It has been demonstrated that the overexpression of miR-134 leads to dendritic spine synaptic deficits by repressing Limk1, which also alters dendritic spine structure.[20] Depressive symptoms, which are also coupled with impaired neurogenesis, can be observed due to downregulation of miR-132 or miR-124, which decreases the levels of BDNF. Other synaptic genes are regulated by the miR137 locus, which is associated with an increased risk of SCZ. LncRNAs like NEAT1 and MIAT/Gomafu control the nuclear structure and the splicing of neurodevelopmental regulators such as DISC1, affecting neuronal connectivity.[4]

7. Neurotransmitter and signal transduction

Non-coding RNAs influence neurotransmitter systems. For example, miR-16 is responsible for regulating serotonin transport and is upregulated by selective serotonin reuptake inhibitors (SSRIs), which promote serotonin release into the synapse. A low baseline level of miR-16 may help explain the deficit of serotonin in some individuals. Moreover, miR-1202 is known to affect glutamate receptor GRM4, suggesting a link to glutamatergic dysfunction in depression.[6] In SCZ, miR-199a and miR-219 target N-methyl-D-aspartate receptor subunits in accordance with the glutamate hypotheses, while miR-132 and miR-212 target the

function of dopaminergic neurons.[7] The lncRNA NONHSAT089447, expressed in SCZ, is known to be overexpressed in SCZ and is linked to the expression of dopamine receptors.[4]

8. Immune and inflammatory signaling

There is a chronic subset of psychiatric patients dealing with chronic inflammation. lncRNA IFNG-AS1 is known to regulate interferon-γ and is less expressed in SCZ, which correlates with lower levels of most cytokines.[4] Another immune-related lncRNA THRIL, controls tumor necrosis factor alpha, and is overexpressed in male SCZ patients. Depressive and schizophrenic patients seem to undergo persistent changes to immune-regulating miRNAs such as miR-146a and miR-155, which are altered in both disorders and may indicate or perpetuate an inflammatory state. Exogenous stressors such as early trauma have been shown to epigenetically alter the programming of miRNA expression.[7] Research using animal models shows enduring changes to specific miRNAs (for example, miR-124, miR-125b, and miR-29) in chronic and early-life stress models.[7]

9. The control of hormones and glucocorticoids

The overactivity of the hypothalamic-pituitary-adrenal axis in depression may be regulated by such non-coding RNAs. Wu et al.[4] describes the downregulation of GAS5 in psychosis. Furthermore, GAS inhibits activation of the glucocorticoid receptor. Changes in GAS5 expression could modulate the feedback of stress hormones and contribute to the dysregulation of cortisol. Some other examples of these sensitive miRNAs are miR-18 and miR-124, which are known to regulate corticotropin releasing hormone receptors and are sensitive to cortisol.

10. Epigenetic interactions and competing endogenous RNA networks

LncRNA can also act as competing endogenous RNA by sponging miRNA and their anti-targets. For instance, lncRNA AC006129.1 may act as a miRNA sponge that impairs immune gene regulation in SCZ as shown in discordant twin study.[21] Their findings indicate that NHSOs can alter multiple pathways in different gene networks through the solitary malfunctioning of non-coding RNA, thus exacerbating the disease.

11. Functional evidence and therapeutic implications

Supportive research exists for the role of non-coding RNAs in the pathophysiology. It has been shown that in mice, stress-induced miR-124 inhibition led to improved BDNF expression, greater spine density, and reduction of depression-like behavior.[4] It was also found that genetic blockade of miR-16 led to depressive-like behaviors, consistent with previous study.[4] Increasing expression of lncRNA AP1AR-DT in the medial prefrontal cortex of mice resulted in depression-like behaviors, reduced synaptic activity, and suppression of NEGR1, which could be reversed by restoring NEGR1. These outcomes strongly suggest that non-coding RNAs actively participate in psychiatric disorders and can be targeted for new treatments.

12. Clinical utility of RNA biomarkers: diagnosis, prognosis, and treatment response

The translation of RNA biomarkers into clinical application practices involves proving their usefulness in diagnosing conditions, predicting outcomes, and tracking treatment responses. Recent investigations have suggested that certain miRNAs and lncRNAs may be beneficial in these areas.

12.1. Diagnostic utility

RNA biomarkers can aid in differentiating between a primary diagnosis and differential diagnoses, especially when symptoms overlap and assessment is difficult. Martinez and Peplow[9] demonstrated that specific blood miRNA expression patterns enabled the differentiation of MDD, BD, and SCZ. For example, plasma miR-4743 was found to be elevated in SCZ and reduced in MDD. Also, miR-125a-3p and miR-21–3p were upregulated in BD but downregulated in MDD.[9] In addition, a panel consisting of miR-134 and miR-19b-3p and others demonstrated moderate diagnostic accuracy in differentiating bipolar depression from unipolar depression.[9] More importantly, higher levels of miR-34a and miR-34b, alongside lower levels of miR-137 and miR-34c, were instrumental in distinguishing BD from SCZ. AUC analyses also supported the border cross level of discrimination.[9]

One hybrid approach combines RNA editing marks with machine learning. A study examining RNA editing in relation to mood and immune modulation through eight editing sites reported 86.4 % sensitivity and 80.8 % specificity in distinguishing between BD and MDD, with an AUC of ~0.90.[22] Additionally, a nine-RNA panel that included lncRNAs and mRNAs demonstrated diagnostic and prognostic value in SCZ, while a specific lncRNA panel was able to detect SCZ in females with approximately 95 % sensitivity.[23] These observations pave the way towards a future where clinicians augment their evaluation processes with RNA assays.

12.2. Prognostic and monitoring value

Some RNA biomarkers are still in their infancy but have the potential to predict an individual's illness trajectory. miR-181b showed association with withdrawal of SCZ negative symptoms, which can be added in the monitoring of recovery.[3] Maternally expressed gene 3levels decreased with treatment response in psychosis, while p53-induced transcript and GAS5 remaining low may indicate persistent vulnerability.[4] In the case of depression, some inflammatory miRNAs like miR-223 or miR-29a have been connected to chronic illness courses but need further verification.

12.3. Treatment response prediction

Tailored therapies could benefit from the use of RNA biomarkers. In MDD, miR-1202 was shown to predict response to SSRIs; those with lower baseline expression who responded showed increased expression during treatment.[6] Serum miR-124–3p also changed in responding to fluoxetine and may serve as a treatment engagement biomarker.[7] In SCZ, expression of miR-128 and miR-223 delineated responders from non-responders. NEAT1 and NEAT2 expression levels dropped post-antipsychotic treatment and may serve as early markers of response to treatment.[20] In BD, lithium responders and non-responders exhibited differential expression for several candidate miRNAs, including miR-221 and miR-34a-5p,[24,25] highlighting the potential to inform treatment decisions. These, in particular, if collected longitudinally, may provide objective measures of the effectiveness of treatment. For instance, achieving a "remission signature" within ncRNA expression could strengthen or evoke changes prior to clinical assessments when patients still feel symptoms of depression and clinicians' observations precede symptom relief.[24–26]

12.4. Clinical utility of RNA biomarkers

In clinical practice, these biomarkers could be implemented in diagnostic workflows via peripheral blood panels, assisting differential diagnosis where symptom overlap is common. For example, a psychiatrist could order a serum miRNA panel to help differentiate between BD and MDD in ambiguous mood presentations, especially when rapid treatment decisions are needed.[9] Moreover, treatment algorithms

could integrate miRNA data to personalize medication choices; for instance, identifying SSRI responders in MDD via baseline miR-1202 levels.[5,6] These examples highlight how RNA biomarkers could evolve from exploratory tools to decision-support resources in psychiatric care.

13. Implementation outlook

Although the results are encouraging, the clinical utility of biomarkers use in mental health remains unconfirmed in larger trials. In this context, it is essential to prove that outcomes are better, for example, recovery is faster or relapse rates are lower, as a result of biomarker-guided decision making. That said, RNA-based diagnostics are now more viable than ever, particularly with the advancement of machine learning in multi-marker interpretation. In the future, integrated systems could potentially use symptom profile matching against RNA data as a diagnostic aid or use to tailor treatment in order to achieve the aims of precision psychiatry.[2]

13.1. Advantages of RNA biomarkers

The potential use of SCZ RNA biomarkers in tracking the illness has several advantages, including their application in psychiatry. One such benefit is the measurement's non-invasiveness and accessibility. Peripheral blood, saliva, and even cerebrospinal fluid contain several measurable RNA species, including microRNAs and long non-coding RNAs.[7,27] Blood draws are simple and straightforward procedures, not only suitable for repeated sampling, but are also minimally invasive, making them compatible with routine clinical workflows. This makes it ideal in both diagnostic and longitudinal monitoring settings.

Another one of Roy's strengths regards biofluid stability is the stability of miRNAs within biofluids.[7] Exosomes or protein complexes are protective structures that shield these molecules from enzymatic degradation. Subtle proteomic changes can also enable the use of archived samples in retrospective analyses. Unlike downstream protein markers, RNA biomarkers such as miRNAs and lncRNAs are more directly linked to underlying disease mechanisms. For instance, reductions in miR-132 or miR-124 correspond to impaired BDNF signaling depression,[28] showing the contribution of neurotrophic dysfunction to depression.

Such markers demonstrate their relevance and contribute to responsive dynamics among patients as their expression levels fluctuate during different phases of illness and treatment. Changes in the levels of NEAT1 in SCZ[4] or miR-1202 and miR-124–3p support this capability of miR-124–3p.[6,20] Throughput methodologies enable the parallel profiling of multiple RNA sets. Multi-marker panels derived from these datasets have proven valuable in diagnosis. The development of panels that differentiate complex psychiatric conditions such as BD and MDD has been advanced through machine learning techniques.[1,21]

RAN profiles assist in stratifying within a diagnosis. For example, patients with MDD and BD with inflammation-associated profiles may require specific targeted therapies.[29] This aligns with efforts toward personalized psychiatry. RNA biomarker testing also offers advantages in terms of feasibility and cost. RT-qPCR, the primary method for miRNA quantification, is already widely available in clinical laboratories.[30,31] Small, validated RNA panels can yield rapid results at relatively low cost per sample. Compared to neuroimaging or whole genome sequencing, RNA-based assays are more practical, scalable, and better suited for routine clinical use.

13.2. Limitations of RNA biomarkers

The available RNA biomarkers are still restricted in their widespread use in psychiatry due to several factors. One of the most critical limitations is the lack of specificity for particular disorders. Many RNA changes have been reported across several diseases. For example, miR-34a has confirmed dysregulation in SCZ and also in BD, while in MDD, miR-124 is also observed in SCZ.[9] This overlap limits the discriminant power of single markers for specific conditions. Custom multi-marker panels are required to resolve diagnostic precision and account for comorbidities. Focusing on variability, reproducibility remains a challenge to some degree. Studies often reach different conclusions due to variations in cohort characteristics, analysis methods, and workflows.[1] The absence of reproducible validation across independent datasets continues to undermine confidence in the proposed biomarkers and hinders their clinical adoption.[1]

Changes in clinical status and treatment can also alter the expression profile of RNA. Psychotropic medications like lithium and antipsychotics can influence the expression of neuroprotective miRNA as well as other forms of miRNA.[32,33] Sample quality, especially hemolysis, as well as variability in extraction or quantification methods, affect the outcomes. Differences in analytical platforms, such as sequencing compared to PCR, and the absence of uniform standardization procedures interfere with comparability across different studies.[1] While attempts at standardization are underway, they are not widely adopted.

In many scenarios, the impact of RNA as a biomarker is minimal. Individual markers may demonstrate modest but statistically significant differences between groups. However, most often, these small changes fall within the overlap of patients and controls, diminishing their clinical efficacy. Like polygenic risk scores, numerous RNA biomarkers inadequately explain the risk for a disease's onset or its outcomes, currently attributing less than 5 % of variance.[1] To gain clinical significance, these markers will need to be integrated with other data types, including clinical information and imaging data.

There are no clinically validated tests based on RNA biomarkers for psychiatric disorders. The route from discovery to clinical application requires validation through large datasets, demonstration of clinical utility, approval, and meeting standards, which most potential candidates fail to do.[34] The breach of ethical principles still raises practical concerns. Stigma and privacy challenges pose limitations to uptake and interpretation. Inability to analyze results may put vulnerable populations at risk and, in turn, cause harm.

Figs. 1 and 2 summarize the advantages, limitations and challenges using RNA biomarkers in psychiatric conditions. Regardless of these

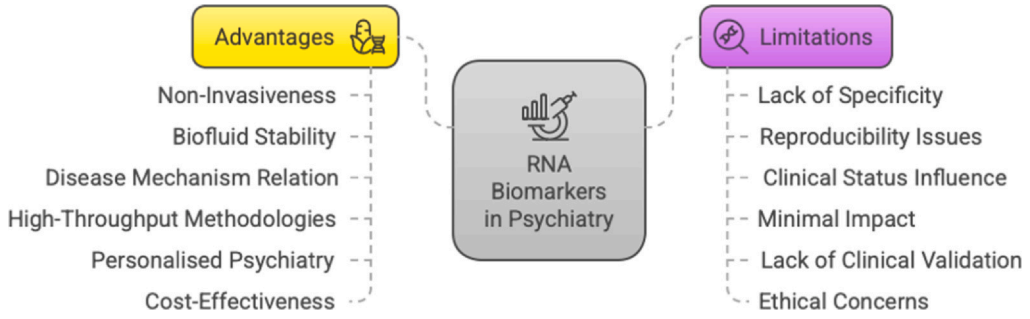

Fig. 1. RNA biomarkers in psychiatry: advantages and limitations. This figure was generated using Napkin AI (V3, 2024; beta) based on author-provided descriptions.

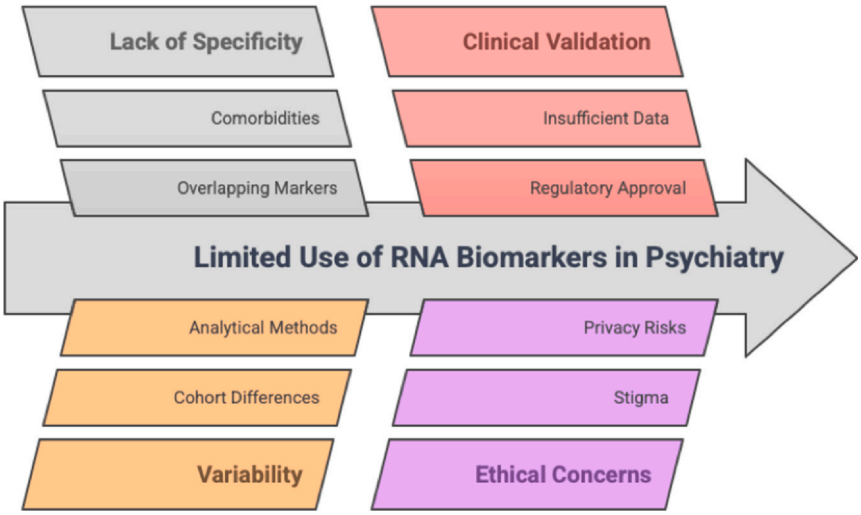

Fig. 2. Challenges in RNA biomarker application in psychiatry. This figure was generated using Napkin AI (V3, 2024; beta) based on author-provided descriptions.

issues, integrating new RNA biomarkers with other biological and clinical measurements across diverse populations could potentially yield significant benefits. The most striking prospects may be in diagnosing BD and unipolar depression where current methods still prove insufficient.

14. Future directions and emerging trends

The study of RNA biomarkers in psychiatry is expanding rapidly owing to innovations in technology and the growing understanding of the biology of mental illness. Emerging shifts in this area of study will undoubtedly change how psychiatric disorders are diagnosed and treated.

The development of multi-omic models integrates RNA biomarkers with other molecular data, including genomic, proteomic, and metabolomic information, which is one of the more significant changes.[35] These approaches are supported by large consortia, such as PsychENCODE and SCHEMA. They have improved the predictive power of biomarker panels by revealing the intricate nature of disease physiology. For example, classifiers that combine miRNA profiles and inflammatory markers, along with the genetic risk variant, can identify AP1AR-DT in BD.[17] Contemporary computational biology enables the building of machine learning models that can process multidimensional data, as seen in the case of mood disorders classification using RNA editing signatures.[21]

In parallel with these advances in computation, there has been an increase in interest in the use of extracellular vesicles, particularly neuron-derived exosomes. These vesicles are obtainable from peripheral blood and contain RNA reflective of central nervous system activities.[36] Exosomal miRNAs and lncRNAs exhibit distinct expression profiles in psychiatric cohorts,[37] providing a new direction for brain-oriented non-invasive biomarkers that surpass the capabilities of bulk plasma RNA. Their recognition and usefulness in tracking chronic illnesses have also been noted due to their stable presence in blood circulation.[38]

Circular RNAs are stable loops of RNA found in high concentration in the brain, and they play the role of gene regulators and act as miRNA sponges. Shifted circular RNA profiles have been recognized in people with depression and in people with BD.[39,40] Some of these patients respond to treatment with antidepressants. Other RNA types like piRNAs or fragments derived from tRNA are under investigation for possible involvement in neuroplasticity, synaptic signaling, stress response, and for broadening the scope of potential biomarkers.

These discoveries are now possible due to advancements in sequencing technologies. Long-read technologies, such as PacBio and Oxford Nanopore, can determine the complete length of a transcript, allowing for isoform-specific analysis of lncRNAs and the detection of editing changes in RNA molecules.[41] This is especially important for the NEAT1 gene whose multiple isoforms may be associated with some psychiatric phenotypes.[42] Such techniques also enhance the annotation of repetitively or poorly mapped genomic regions associated with mental disorders, revealing biomarker candidates that were not previously accessible.

A new frontier is opening regarding the therapeutic potential of RNA biomarkers. Beyond serving in the diagnosis, certain types of RNAs could be utilized as therapeutic targets. Other fields are developing miRNA-based therapies, e.g., antagomirs to inhibit the overexpressed miRNAs. Some preclinical work in psychiatry has demonstrated behavioral and molecular effects following RNA modulation,[43,44] suggesting psychiatric applicability. Composite clinical models in the future could use diagnostic RNA panels designed to interact with the targeted RNA-based strategies, matching the patient's expression profile.

Developing reproducibility and preparing for regulatory convergence remain top priorities. Cross-site validation projects are working to integrate protocols for sample collection, data analysis, and RNA quantification.[45] Machine learning models are increasingly being applied to independent datasets for external validation.[46] There is growing collaboration with industry spin-off companies that are enabling the commercialization of academically developed assays,[47] in conjunction with reference standards like synthetic calibrators to support consistent performance across laboratories.

Certain legislative bodies have started issuing position papers concerning the regulation of psychiatric molecular diagnostics.[48] Policies are in preparation for a consolidated informed consent, patient interaction, and data management strategy. For the clinically responsible application, additional clinical training will be required on the integration of RNA biomarker interpretation into psychiatric evaluations and care pathways.[49]

With the passage of time, it can be expected that RNA biomarker research will move from broad exploratory studies to validated clinical usage over the course of a decade. Fig. 3 illustrates the future directions and emerging trends in RNA biomarkers. Its first applications will most probably target the most challenging diagnostic problems, like differentiating BD from major depression, or recognizing treatment resistant.[50] Incorporation of these panels into electronic health records and clinical decision support systems may facilitate optimally responsive, evidence-based preemptive care.[51] Such advances would foster earlier, more precise, and advanced engagement and monitoring throughout the treatment cycle. All these developments draw psychiatry nearer to an envisaged future in which diagnostics are foundationally biological and personalized care is available for depression, SCZ, and BD.

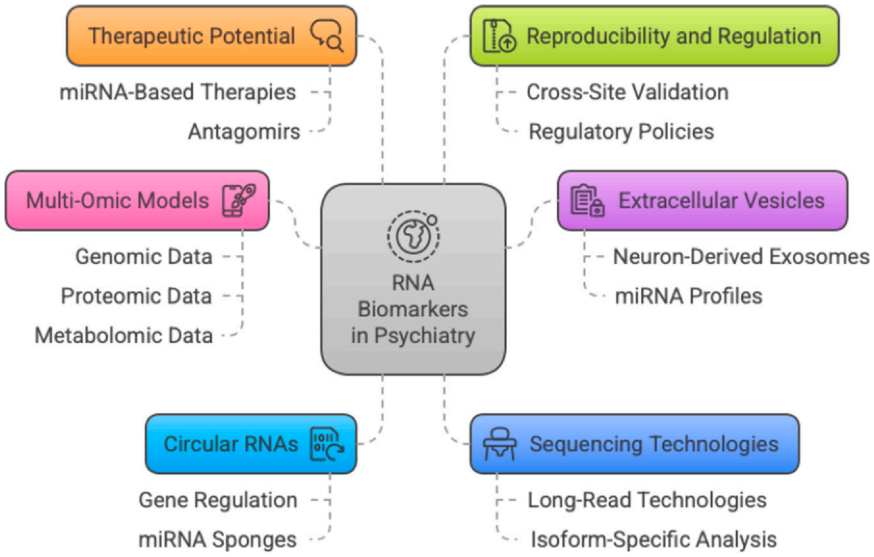

Fig. 3. Future directions and emerging trends in RNA biomarkers. This figure was generated using Napkin AI (V3, 2024; beta) based on author-provided descriptions.

15. Integration of multi-omic approaches in biomarker discovery

The convergence of transcriptomic data with proteomic, metabolomic, and genomic information enhances the discovery and validation of psychiatric biomarkers. For example, the PsychENCODE and SCHEMA consortia combine genome-wide association studies with RNA expression profiles to reveal networks underlying SCZ and BD.[35] Proteomic profiling can validate whether RNA biomarkers translate to altered protein abundance, while metabolomic data reveal downstream biochemical effects. This integrative framework helps delineate causal relationships and clarifies whether observed transcript changes are compensatory or pathogenic. Furthermore, using machine learning to combine miRNA expression with methylation marks and cytokine profiles has yielded robust classifiers to distinguish between SCZ and BD with AUCs exceeding 0.90.[22] This integrated approach is also vital for identifying disease-specific signatures, such as miR-1202 with GRM4 in MDD[5] or AP1AR-DT with NEGR1 in BD,[17] which could help distinguish overlapping syndromes.

16. Ethical, regulatory, and standardization challenges

16.1. Ethical considerations

Like other forms of testing, RNA biomarker testing in psychiatry has social ethics implications. One ethical impact center around consent and autonomy.[52] Notably, patients and individuals have to understand the consequences associated with specific marker profiles. For instance, a BD risk marker profile may have painful repercussions due to its social stigma, further exacerbating episodes when the patient's autonomy to take decisions is severely limited. Autonomy can also be better aided through accessible education and counselling resources designed for psychiatric patients. These resources have to be made available directly for effective learning.[53]

People affected by other psychiatric disorders, like SCZ, also face additional identity and stigma challenges that result from the presence of biomarker testing. The existence of such markers can subconsciously place a patient in a heightened risk category which greatly alters how one perceives themselves and results in changes from other people such as insurance and employment.[54] Although self-blame may be avoided with biomarker validation, it may inadvertently label patients and reinforce pre-existing stereotypes unless carefully communicated. Results should be communicated within a probabilistic framework, rather than a deterministic one. Justice and equity also need to be addressed. If there is a likelihood that biomarker tests become costly or are offered only at certain specialized centers, there is a danger of omitting marginalized groups.[55] Therefore, funding inclusive research involving diverse demographic groups is necessary to prevent widening gaps in healthcare inequality. Moreover, frameworks should avert the application of biomarkers in legal or employment contexts where these technologies might infringe on personal freedoms and rights.[56]

Another focus is the likelihood of misrepresentation. An abundance of reliance on biological markers could place too much focus on the biology of mental illness while ignoring the psychosocial elements, resulting in an overly clinical approach devoid of empathy and the patient's perspective.[53] The use of biomarkers in psychiatric practice should serve to improve person-centered care, rather than replace it. This includes educating clinicians to interpret and contextualize molecular information within narrative and behavioral frameworks.

DTC testing for psychiatric biomarkers has inherent risks. People may unduly panic or manage their results inappropriately without professional assistance.[57,58] The same issues noted in DTC genetic testing apply here; poorly explained or unexpected findings can cause significant harm. As such, RNA biomarker testing in psychiatry ought to be restricted to clinician orders, and thorough counselling must accompany the order to ensure that patients will not manipulate the results clinically or otherwise.[59]

16.2. Regulatory and legal frameworks

For the regulatory acceptance of RNA biomarker tests, analytical and clinical validity is a prerequisite, which in this case means the tests must be precise, accurate, and have clinical value. The formation of psychiatric disorders is currently more probabilistic rather than deterministic, which forms more challenges in cross-diagnosing clear-cut boundaries. Diagnostic biomarkers for multiple DSM-5 disorders are not that plausible; however, markers of susceptibility for the transformation of diseases and predictive markers of treatment may become possible down the line.[60] The current guidelines employed by other agencies like the FDA, TGA, and EMA perhaps require modification in order to address the uniqueness of psychiatric biomarkers which are unlike traditional diagnostics with clear yes-or-no answers.

Clinically, interpreting RNA biomarker results as a whole has its limitations. Any misclassifications, whether over- or under-optimistic, can create major legal and therapeutic ramifications. With RNA biomarkers not widely accepted, if there are no strict procedures of validation and standardization of interpretation mechanisms, clinicians

may refuse to use these tools in practice. It is telling that many psychiatrists claim feeling under prepared to analyze the data on a molecular scale,[34] signifying the need for specialists from molecular psychiatry willing to integrate molecular data into patient care.

Data privacy and governance also hold equal value, as RNA expression profiles, especially when combined with genomic information, are distinctively identifiable and may be sensitive. GINA in the USA and GDPR within the EU provide a basis for safeguarding such information[61]; however, these safeguards need to be particularly applied to RNA biomarkers. Regarding proteomics, the privacy of sensitive data and sharing of non-sensitive data must be balanced while still ensuring the deliverability of the data.[62] Morally responsible approaches to the problem require proper data management, confidentiality, and patient empowerment to control access to their biomarker data.

Current regulatory frameworks by agencies such as the FDA, TGA, and EMA require adaptation to encompass probabilistic diagnostics, stratified risk prediction, and treatment tailoring in psychiatric disorders. Clear pathways must be established for analytical validation, population-level performance evaluation, and real-world implementation studies.[63] For example, the FDA's Breakthrough Devices Program could be a potential avenue for fast-tracking high-performing RNA biomarker tests, provided they demonstrate clinical utility and safety.[63] The field must also address conceptual and structural limitations unique to psychiatry, where diagnostic categories are probabilistic, and molecular markers often lack binary thresholds.[64]

16.3. Standardization challenges

As stated, analytical consistency remains a significant concern regarding the application of clinical RNA biomarkers.[65] Differences in protocols, platforms (PCR *vs.* sequencing) and quality control across laboratories often result in variability which in turn leads to different results across various laboratories.[66] To address this issue, standardized methodologies need to be created and adopted on a wider scale. Such methods include the use of synthetic reference materials for calibration purposes, as well as the creation of inter-laboratory proficiency testing programs to ensure reproducibility and reliability.[67,68]

Data derived from RNA biomarkers require specific attention and uniformity. For example, diagnostic thresholds like a composite score depicting heightened risk for SCZ need to be pre-tested and validated by large-scale studies. Moreover, these thresholds, just like the rest, require population diversity-balanced specificity and sensitivity. Enhanced clinical utility will be provided by consensus guiding recommendations for clinicians through interpretive frameworks similar to those designed for cholesterol and cancer.

Clinical decisions of significance are what would make RNA biomarkers exceptionally useful. Take a high-risk result for BD; it must mandate a comprehensive psychiatric assessment as a follow-through. Results must be integrated into standardized clinical pathways designed to encourage ethical evidence-based decision-making while preventing misapplication or over-reliance on a predefined framework.[69]

Addressing these problems requires cooperation from different industries. Some key projects already in process include developing ethical guidelines for psychiatric biomarkers,[53] engaging patient advocacy groups for strategic communication planning, and conducting preliminary impact evaluation studies in clinical settings. In addition, some randomized trials are being planned to evaluate not only the biomarker's accuracy but also the outcomes of its use versus treatment as usual.

The overriding principle for all these activities is non-maleficence. Minimization of harm means that the use of RNA biomarkers ought to spare patients harm through misinterpretation, misdiagnosis, or wrong treatment calls. Psychiatry is now positioned to build these protective measures, learning from disciplines like oncology and neurology that have developed in molecular diagnostics.

The merits of scientific discovery alone are insufficient, however. As illustrated in Fig. 4, there is still a need for ethical, legal, and regulatory policies together with technological development before RNA biomarkers can be said to effectively revolutionize psychiatric healthcare. Some of these policies include standardized protocols for carrying out the assays, data privacy, and access to testing as well as defined clinical

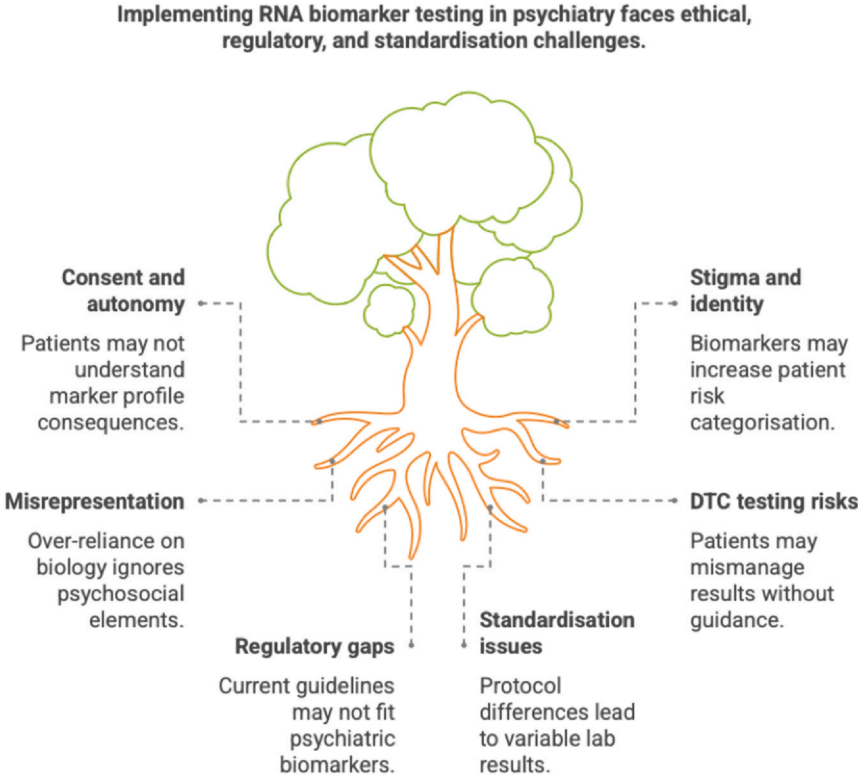

Fig. 4. Challenges in implementing RNA biomarker testing in psychiatry. This figure was generated using Napkin AI (V3, 2024; beta) based on author-provided descriptions.

Table 2
Examples of long non-coding RNAs associated with major psychiatric disorders (MDD, SCZ, BD) Arrows denote reported direction of dysregulation in patients vs. controls (↑ upregulated, ↓ downregulated). "—" indicates that clear data are not available or not consistent for that disorder. These lncRNAs illustrate various ways in which lncRNA changes are linked to pathophysiology and biomarker potential in depression, SCZ, and BD. BD: Bipolar disorder; IFN-γ: interferon-gamma; lncRNA: long non-coding RNA; MDD: major depressive disorder; PBM: peripheral blood mononuclear cell; SCZ: schizophrenia.

lncRNA	MDD	SCZ	BD	Notes and relevance
Nuclear paraspeckle assembly transcript 1 (NEAT1)	— (Upregulated in stress models)	↓ (Multiple cortical regions); ↓ (Blood of untreated SZ)[4]	—	Key stress-responsive lncRNA. Reduced in SCZ brain tissue, impacting oligodendrocyte maturation.[4] Blood NEAT1 increases with antipsychotic treatment.[4] Implicated in depression via stress pathways.
Myocardial infarction associated transcript (MIAT, Gomafu)	—	↓ (Temporal cortex)[70]	—	Synaptic lncRNA; binds splicing factors. Downregulation in SCZ disrupts splicing of genes like DISC1.[70] KO mice show behavioral abnormalities, linking MIAT to neurodevelopment.
DiGeorge syndrome critical region gene 5 (DGCR5)	—	(Genetic locus 22q11.2)[4]	—	Locus of 22q11 deletion syndrome. Regulates expression of genes in SZ-associated region.[4] Genetic variants in DGCR5 may confer SCZ risk; a biomarker for genetic subtype.
Interferon (IFN) gamma antisense RNA 1 (IFNG-AS1)	—	↓ (PBMCs)[71,72]	—	Immune-related lncRNA. Decreased in SCZ blood, correlating with lower interferon-γ levels.[71] May reflect immune dysregulation in psychosis.
Growth arrest-specific transcript 5 (GAS5)	—	↓ (Whole blood, esp. females)[16]	↓ (PBMCs in psychosis)[4]	Growth arrest lncRNA. Downregulated in SCZ and psychotic BD.[4] Showed high diagnostic accuracy for female SCZ (AUC = 0.93).[16] Tied to glucocorticoid signaling; potential stress-response marker.
AP1AR-DT	—	—	↑ (Brain)[17]	Discovered BD-associated lncRNA. Upregulated in BD cortex[17]; overexpression in mice induces depressive-like behavior and reduces synaptic function.[17] Points to causative role in mood regulation.
Maternally expressed gene 3 (MEG3)	—	—	↑ (In psychosis)[4]	Imprinted lncRNA (maternally expressed gene 3). Upregulated in psychotic disorders (SZ & BD) *vs.* controls[4]; levels decreased after treatment, suggesting state-dependence.
p53-induced transcript (PINT)	—	—	↓ (In psychosis)[4]	p53-induced non-coding transcript; down in psychotic patients' PBMCs.[4] Did not normalize with treatment, indicating a trait marker.

pathways for their use and settlement. If multidisciplinary collaboration is maintained, the application of RNA biomarkers could greatly enhance mental health care by integrating biology with compassion and person-centered care.

17. Limitations

There exists promise, but integrating them into routine clinical practice poses considerable challenges. Critical obstacles include achieving reproducibility in independent cohorts, validating in diverse populations, and standardizing methods, requiring large collaborative studies to determine true positive biomarkers and eliminate false positives. Responsible implementation is equally important. The use of psychiatric biomarkers poses risks relating to distortion, labelling, and misuse that require robust definitional boundaries, enabled because of well-defined frameworks, consent processes designed from a patient rights perspective, and integration approaches into care models crafted from a legal viewpoint.

18. Conclusion

Work has advanced on RNA biomarkers associated with psychiatric illnesses as miRNAs and lncRNAs—once disregarded as "non-coding" products—have emerged as major directors of neurodevelopmental processes, synaptic activity, immunological signaling, and stress response. Table 2 summarizes the main lncRNAs related to mood and psychotic disorders. Although more iterative testing and functional validation are required, lncRNAs constitute an emerging area for investigative paradigms in the search for biomarkers in psychiatry.[4,16,17,70–72]

The persistent underactivity of certain RNAs (miR-1202, miR-34a, miR-181b, NEAT1, MIAT, AP1AR-DT) at different "omic" levels suggests their importance to the mechanisms of illness and with many of them being peripheral blood markers, their clinical use becomes easier. Initial findings indicate that RNA panels can distinguish bipolar from unipolar depression and distinguish treatment responses. Such capabilities may reduce diagnostic dilemmas and aid in designing tailored interventions.

If the use of psychiatric biomarkers succeeds on the clinical, scientific, and ethical fronts, RNA biomarkers would be able to shift neuropsychiatry from a loose field to a precision biology-infused domain. The capability to diagnose and track mental illnesses via blood tests would support earlier interventions which improve outcomes in patients.

CRediT authorship contribution statement

Enoch Chi Ngai Lim: Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chi Eung Danforn Lim:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Formal analysis, Conceptualization.

Ethics statement

This article is a narrative review of previously published studies and does not involve any new studies with human participants or animals performed by any of the authors. Therefore, ethical approval and informed consent were not required.

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