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Commentary

Translating microbiome research into personalized schizophrenia care by implementing multi-omics and artificial intelligence

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Abstract

Schizophrenia is widely recognized as a multifactorial disorder involving interactions among the central nervous system, immune system, metabolism, and gut microbiome. Mardon et al. highlighted the potential importance of the gut-brain axis in schizophrenia. Building on this perspective, this commentary examines the next phase of schizophrenia research: translating biological discoveries into clinically meaningful applications. The discussion focuses on the potential role of integrated biological biomarkers, multi-omics, and artificial intelligence (AI) in precision psychiatry, while also examining the barriers that currently limit clinical implementation. By combining biological data with computational analysis, translational research may ultimately support more individualized approaches to the diagnosis and management of schizophrenia.

Keywords: Schizophrenia, Gut-brain axis, Precision medicine, Artificial intelligence, Biomarkers, Microbiome, Metabolomics

Introduction

Schizophrenia was once viewed primarily as a psychiatric disorder characterized by abnormalities in neurotransmitter signaling; however, it is increasingly recognized as a multifactorial disorder shaped by interactions among the nervous, immune, metabolic, and gastrointestinal systems. This broader perspective suggests that schizophrenia cannot be fully understood through a central nervous system (CNS)-only model. Within this framework, Mardon et al. emphasize the potential importance of the gut-brain axis in schizophrenia pathophysiology [1]. By linking the gut microbiome with altered neurotransmitter signaling and other biological pathways, the authors extend the discussion beyond conventional dopaminergic models. Their perspective also raises an important clinical question: how can these biological connections be translated into tools that improve diagnosis and support more individualized treatment? Building on the framework proposed by Mardon et al., this commentary explores how AI, multi-omics, and microbiome-informed approaches could contribute to more personalized schizophrenia care.

In recent years, considerable progress has been made in identifying associations between gut microbial dysbiosis and schizophrenia. Reported findings include alterations in short-chain fatty acid-producing bacteria, immune dysregulation, and broader disturbances in microbial composition. Collectively, these observations have reinforced the concept of the gut-brain axis as a potential contributor to psychiatric illness. Despite these advances, many studies remain focused on describing microbial alterations rather than determining how such findings can be translated into

clinically useful tools. The next challenge is therefore to determine whether microbiome-derived information can meaningfully improve diagnosis, prognosis, or treatment selection.

To address this challenge, research must move from association toward clinical translation. As evidence supporting a relationship between the gut-brain axis and schizophrenia grows, an opportunity emerges to refine how the disorder is biologically characterized and treated. If microbial alterations contribute to disease progression or treatment response, could this information help clinicians classify patients more precisely or identify those who may require different therapeutic strategies? More importantly, can microbiome-specific information be incorporated into practical clinical tools that support individualized patient care? Addressing these questions shifts the focus from biological discovery alone to the application of those discoveries within clinical practice. In this context, precision psychiatry offers a framework for integrating biological and clinical information to support a more individualized approach to schizophrenia care.

The Next Frontier of Gut-Brain Axis Research

The ideas proposed by Mardon et al. broaden the understanding of schizophrenia beyond a disorder confined to the CNS and instead emphasize interactions among multiple biological systems [1]. Building on this framework, the next phase of research should focus on translating these discoveries into clinically useful applications. A central requirement is the identification of reproducible microbial signatures with sufficient specificity and stability to contribute to diagnosis or treatment stratification. Evidence suggests that this remains challenging. For example, a 2024 analysis compared gut microbial alterations in schizophrenia-spectrum and bipolar disorders and found that reported bacterial changes were not fully consistent across the two conditions [2]. Although the study noted gut microbiome alterations in both disorders, the same bacterial taxa were not consistently associated with each condition, highlighting the difficulty of deriving a stable, disease-specific microbial signature [2]. Antipsychotic exposure further complicates interpretation. A recent meta-analysis found that antipsychotic medications were associated with microbial alterations, including changes involving *Lactobacillus*, *Roseburia*, and *Dialister* [3]. Similarly, a systematic review concluded that antipsychotic medications may alter gastrointestinal microbial composition, making it difficult to determine whether observed dysbiosis reflects the illness itself, its treatment, or both [4]. Variation in diet, geographic location, disease state, and medication exposure also contributes to inconsistent findings in microbial diversity [4]. These limitations do not eliminate the clinical potential of microbiome biomarkers; rather, they define the methodological challenges that must be addressed before microbiome research can be translated into precision psychiatry.

Schizophrenia is currently diagnosed primarily through clinical symptoms; however, patients who receive the same diagnosis can differ substantially in metabolic health, inflammatory activity, and response to antipsychotic treatment. This heterogeneity is important because similar clinical presentations may arise from different combinations of underlying biological processes. Precision psychiatry seeks to address this variability by complementing symptom-based diagnosis with biological information that may help predict treatment response or disease trajectory [5,6]. The goal is not to replace established diagnostic criteria, but to add clinically relevant information that may improve patient stratification and treatment planning. Relevant candidate biomarkers in schizophrenia include circulating inflammatory proteins, genetic variants, immune-cell profiles, and metabolic markers [5,6]. Early work illustrates the potential value of this approach. One study measured peripheral inflammatory proteins in individuals with schizophrenia and used an Olink Target 96 Inflammation panel to distinguish antipsychotic-responsive from treatment-resistant patients [7]. These findings suggest that combinations of inflammatory biomarkers may provide clinically relevant information that is not apparent from symptoms alone [7]. Microbiome-derived biomarkers could potentially serve a similar role. Measures such as microbial diversity, taxonomic composition, or microbial functional profiles could be evaluated alongside other biomarkers to determine whether they improve prediction of treatment resistance. If validated, such predictive models could help clinicians identify higher-risk patients before resistance becomes clinically apparent and individualize treatment strategies earlier in the disease course. A recent study, for example, reported reduced microbial diversity in patients with schizophrenia and examined its relationship with treatment resistance [8]. The strongest future biomarker is therefore unlikely to be a single bacterial species. A more realistic strategy may be to integrate microbial composition with metabolomic, inflammatory, genetic, and clinical data to estimate the likelihood of response to first-line antipsychotics, development of treatment resistance, or potential benefit from adjunctive microbiome-directed interventions [5].

Many studies have focused on altered microbial composition in patients with schizophrenia; however, microbial composition alone provides only a partial representation of a patient's biology. A more informative microbiome profile could include bacterial taxa, metabolites produced through host-microbe interactions, and microbial functional pathways. Together, these measurements may provide insight into microbial activity and its potential influence on the CNS [1]. Microbiome sequencing could also be integrated with peripheral inflammatory biomarkers and circulating cytokines to generate a more multidimensional representation of an individual's biological state [5]. This strategy addresses a major limitation in current microbiome research: combining microbial data with inflammatory, metabolic, genetic, and clinical information may improve biological interpretation and reduce reliance on isolated findings [4].

Integrating Multi-Omics and Artificial Intelligence

Although gut microbial dysbiosis may contribute to schizophrenia pathophysiology, microbial composition alone is unlikely to capture the full biological complexity of the disorder. Multi-omics has emerged as one strategy to address this limitation by combining multiple biological datasets into a more comprehensive representation of disease-related processes. Multi-omics can integrate microbiome sequencing with metabolomics, genomics, transcriptomics, proteomics, and immune profiling [9]. These datasets provide complementary information about which molecules are present, how biological pathways function, and how interactions among systems may relate to schizophrenia. Recent research demonstrates the value of this integrated approach. In one study, 16S ribosomal RNA sequencing and fecal metabolomics were used to examine gut microbial alpha and beta diversity alongside metabolic profiles. Researchers identified differences in 30 bacterial species and 45 fecal metabolites between individuals with schizophrenia and healthy controls, with prominent associations involving amino acid and lipid metabolism [9]. Another study integrating metabolomics with

neuroimaging in drug-naive patients with first-episode schizophrenia identified alterations involving tryptophan metabolism and gamma-aminobutyric acid signaling [10]. These findings suggest that clinically relevant information may be more likely to emerge from combinations of biomarkers than from any single biological measure. Multi-omics therefore provides an important foundation for precision psychiatry by shifting the focus from isolated biomarkers toward interconnected biological networks.

Advances in multi-omics have enabled researchers to generate large quantities of biological information from patients. These datasets are highly multidimensional and may contain complex relationships among microbial communities, immune responses, metabolic pathways, environmental exposures, and clinical characteristics. AI and machine-learning approaches are therefore promising analytical tools for integrating diverse datasets and identifying patterns that may not be readily detectable using conventional methods [11,12]. Rather than replacing clinical judgment, AI could function as a decision-support tool that helps translate complex biological information into clinically interpretable outputs [11]. Future models could, for example, estimate the probability of treatment resistance, persistent negative symptoms, metabolic complications, or cognitive decline. Such outputs could then complement conventional psychiatric assessment and help identify patients who may benefit from closer monitoring or more individualized therapeutic strategies.

A Proposed Framework for Clinical Translation

A practical research-to-clinic framework could proceed in several linked stages. First, investigators could collect standardized clinical variables together with stool-based microbiome sequencing and selected inflammatory and metabolic biomarkers. Second, these data could be processed using harmonized laboratory and computational pipelines and compared with curated research datasets containing well-characterized schizophrenia phenotypes and treatment outcomes. Third, AI models could integrate these inputs to generate clinically interpretable probabilities or risk categories, such as likelihood of treatment resistance or metabolic vulnerability, rather than producing an opaque diagnostic label. Fourth, the model output would be reviewed alongside symptoms, medication history, comorbidities, and clinician judgment to support—not determine—treatment decisions. Finally, the entire framework would require external and prospective validation before routine use. In this way, AI serves as an integration layer between biological research and clinical care, while preserving the clinician's role and allowing each step to be tested for reproducibility and clinical value.

Barriers to Clinical Translation

Despite the promise of precision psychiatry, several challenges must be addressed before these approaches can be incorporated into routine clinical practice. One of the greatest barriers is the lack of standardization across microbiome studies. Gut microbial composition is highly variable and is influenced by biological and environmental factors including diet, geographic location, ethnicity, age, body mass index, lifestyle, disease stage, and medication exposure. Differences in stool collection, sample storage, DNA extraction, sequencing methods, and statistical analyses can further contribute to variability between studies. These factors emphasize the need for standardized methodologies and transparent reporting so that candidate biomarkers can be reproduced across diverse patient populations. AI models introduce additional requirements, including appropriate data governance, external validation, prospective testing, interpretability, and careful control of overfitting. Without these safeguards, an algorithm may perform well in a development dataset but fail when applied to a different clinical population. Reliable clinical translation will therefore require both standardized biological data collection and rigorous validation of the computational models used to interpret those data.

Conclusion

The work of Mardon et al. contributes to a broader view of schizophrenia by emphasizing that the disorder extends beyond abnormalities within the CNS and may involve interactions among the gut microbiome, immune system, metabolism, and neural signaling [1]. Building on this foundation, the next phase of schizophrenia research should focus not only on describing these biological relationships but also on determining how they can be translated into meaningful improvements in patient care. Integrating microbial, metabolic, inflammatory, genetic, and clinical data with carefully validated computational tools may provide a pathway toward more precise patient stratification and treatment planning.

Throughout this commentary, the central argument has been that biomarkers such as microbial composition, inflammatory proteins, genetic variants, and metabolic signatures may be most informative when interpreted together rather than in isolation. Because schizophrenia is a multifactorial disorder involving interconnected biological pathways, single biomarkers are unlikely to capture its full heterogeneity. Multi-omics, combined with appropriately validated AI methods, could help transform large and complex datasets into clinically interpretable information. However, these tools should complement rather than replace established diagnostic criteria and clinical judgment. Ultimately, progress in precision psychiatry will depend on reproducible biomarkers, standardized data collection, transparent computational methods, prospective validation, and evidence that biologically informed models improve patient outcomes.

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