Towards Objective Diagnostics in Psychiatry: Integrating Volatilomics, Multi-Omics, and AI

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ABSTRACT

Psychiatry remains one of the few areas of medicine where diagnosis and clinical decision-making rely almost entirely on symptom-based assessment. Despite decades of research, there are still no clinically validated biomarkers for early detection, disease stratification, or longitudinal monitoring in disorders such as schizophrenia.

At the same time, converging evidence from multi-omics research indicates that psychiatric disorders are not confined to the brain but reflect systemic biological processes, including immune dysregulation, oxidative stress, and metabolic imbalance. While these insights have significantly advanced our understanding of disease mechanisms, they have yet to translate into practical clinical tools.

Volatilomics, the analysis of volatile organic compounds (VOCs) in breath, skin, and other biofluids, offers a complementary and scalable approach. VOCs represent downstream metabolic outputs and provide a dynamic window into ongoing physiological processes. Importantly, they can be measured non-invasively, repeatedly, and at low cost.

Recent studies suggest that multivariate VOC signatures, particularly when combined with machine learning approaches, may differentiate psychiatric patient groups from controls with promising performance in exploratory research settings.

This white paper argues that volatilomics should be positioned not as a standalone biomarker modality, but as a non-invasive monitoring layer, integrated with multi-omics and AI to support a tiered precision psychiatry framework. We outline the scientific rationale, clinical applications, implementation challenges, and the role of the VOLABIOS project in advancing this field.

I. The Diagnostic Gap in Psychiatry

Psychiatric diagnosis remains fundamentally phenomenological and based on clinical criteria. Contemporary treatment of schizophrenia includes division into 4 stages, based on risk (including genetic load) measurement, clinical symptom characteristics, and recurrence of psychotic episodes (1). Psychiatric disorders such as schizophrenia are currently diagnosed primarily through clinical phenomenology and behavioral assessment rather than objective biological criteria. While these approaches remain essential, they are associated with several well-recognized limitations, including diagnostic uncertainty in early stages, substantial heterogeneity between patients, and limited ability to predict disease trajectories or treatment response (2).

These limitations are particularly relevant during the early phases of illness, when symptoms may be subtle, overlapping, or nonspecific. Delayed recognition and prolonged duration of untreated psychosis have consistently been associated with poorer clinical and functional outcomes, including increased hospitalization rates and reduced long-term recovery potential.

At the same time, growing evidence suggests that psychiatric disorders are associated with measurable biological alterations involving inflammatory pathways, oxidative stress, metabolic dysregulation, and broader systemic changes (3). The challenge increasingly lies not only in identifying such biological signals, but in translating them into clinically interpretable and practically usable tools that can support diagnosis, monitoring, and decision-making in real-world psychiatric care.

II. Multi-Omics: Biological Insight and Translational Limitations

Multi-omic approaches have substantially expanded our understanding of psychiatric disorders by enabling the investigation of molecular pathways, systemic dysregulation, and biologically distinct patient subgroups. Genomic, transcriptomic, proteomic, and metabolomic studies have provided important insights into the complex and heterogeneous nature of conditions such as schizophrenia and related disorders (4).

At the same time, the translation of these approaches into routine psychiatric practice remains limited. Many multi-omic methods require specialized infrastructure, resource-intensive laboratory workflows, and analyses that are difficult to scale for repeated or longitudinal clinical use. In addition, many biological measurements represent relatively static snapshots that may not adequately capture the temporal fluctuations and dynamic trajectories characteristic of psychiatric illness.

As a result, a significant gap remains between biological discovery and clinically practical implementation. Bridging this gap will likely require complementary approaches capable of providing accessible, scalable, and longitudinally informative biological signals that can be integrated into real-world psychiatric care. This has stimulated growing interest in non-invasive and continuously accessible biomarker modalities.

III. Volatilomics: A Dynamic Metabolic Interface

Volatilomics offers a potentially complementary approach by capturing volatile organic compounds (VOCs) released through breath, skin, and other biological matrices. Because VOC profiles are influenced by ongoing metabolic and physiological processes, they may provide a dynamic and non-invasive window into systemic biological states (5).

Several characteristics make volatilomics particularly attractive for psychiatric research and longitudinal monitoring. VOC sampling is generally non-invasive, rapid, repeatable, and potentially adaptable to point-of-care settings. In contrast to many conventional biomarker approaches, repeated measurements may allow assessment of temporal fluctuations and evolving disease trajectories over relatively short time scales.

Biologically, VOCs are thought to reflect downstream processes associated with oxidative stress, mitochondrial dysfunction, inflammatory activation, microbiome-related metabolism, and broader metabolic dysregulation. For example, increased levels of hydrocarbons such as ethane and pentane have been linked to lipid peroxidation and oxidative stress, while altered acetone concentrations may reflect changes in energy metabolism. Sulfur-containing compounds and other VOC subclasses have additionally been associated with inflammatory and microbiome-related processes (6).

At the same time, VOC signatures should not be interpreted as disease-specific markers in isolation. Multiple physiological and environmental factors, including diet, smoking status, medication exposure, comorbidities, and sampling conditions, may influence volatilomic profiles. The challenge, therefore, lies not only in signal detection but in the interpretation and integration of complex VOC patterns within clinically meaningful contexts. Accordingly, the value of volatilomics may lie less in individual compounds and more in multivariate biological patterns.

The accessibility and tolerability of breath-based assessment make volatilomics particularly attractive for repeated and longitudinal measurements, potentially enabling closer monitoring of biological dynamics over time.

IV. From Single Biomarkers to Multivariate Signatures

One of the major lessons emerging from biomarker research in psychiatry is that complex disorders are unlikely to be adequately characterized by single molecules or isolated biological variables. Conditions such as schizophrenia involve heterogeneous and interacting biological processes, making reductionist biomarker models difficult to generalize across patients and clinical stages (4, 7).

In this context, volatilomics may be particularly suited to pattern-based interpretation. Rather than relying on individual VOCs as disease-specific indicators, current approaches increasingly focus on multivariate signatures that reflect combinations of metabolic, inflammatory, oxidative, and physiological processes operating simultaneously.

Several studies have demonstrated that combinations of VOC-derived features, when analyzed using machine learning and multivariate statistical approaches, can differentiate psychiatric patient groups from controls with promising levels of performance (8, 9). Importantly, the potential value of these approaches may lie less in individual compounds and more in the broader biological patterns captured through integrated signal analysis.

This conceptual shift, from isolated biomarkers toward composite biological signatures, aligns with broader developments in systems medicine, precision psychiatry, and AI-assisted diagnostics. At the same time, substantial challenges remain regarding validation, reproducibility, interpretability, and clinical generalizability across populations and real-world settings.

V. A Tiered Framework for Precision Psychiatry

The integration of volatilomics, multi-omic profiling, and AI-based analysis may support the development of a layered framework for precision psychiatry, in which different biological modalities contribute complementary forms of information across clinical contexts.

Within such a model, volatilomics could function as an accessible and repeatable interface for longitudinal assessment, potentially supporting early signal detection, symptom monitoring, and dynamic tracking over time. Because VOC-based approaches are non-invasive and relatively scalable, they may be particularly suitable for repeated measurements and real-world monitoring applications.

Multi-omic approaches may provide a deeper level of biological characterization, including investigation of molecular pathways, mechanistic heterogeneity, and biologically distinct patient subgroups. These approaches may be especially valuable in research settings and in more detailed stratification frameworks.

Artificial intelligence and multivariate computational methods could then serve as integrative layers capable of combining clinical, volatilomic, and multi-omic information into probabilistic models intended to support, rather than replace, clinical interpretation and decision-making.

Such a framework reflects a broader transition from static and symptom-centered diagnostic models toward more dynamic, longitudinal, and data-informed approaches in psychiatry.

VI. Potential Clinical Use Cases

Although volatilomics-based approaches remain at an early translational stage, several potential clinical applications are increasingly being explored within psychiatric research.

1. **Early Detection and Risk Assessment**

Non-invasive and repeatable biological monitoring may eventually contribute to the identification of individuals at increased risk for psychiatric disorders or transition to psychosis. Such approaches are unlikely to function as standalone diagnostic tools, but may complement clinical assessment and longitudinal observation in high-risk populations.

2. **Longitudinal Monitoring and Relapse Detection**

Because VOC profiles may reflect dynamic physiological and metabolic changes, repeated measurements could potentially support longitudinal monitoring over time. In some contexts, biological alterations may precede overt clinical deterioration, raising the possibility that volatilomic changes could contribute to earlier reassessment or intervention strategies.

3. **Disease Stratification and Biological Subtyping**

Psychiatric diagnoses encompass highly heterogeneous patient populations. Multivariate volatilomic signatures, particularly when combined with clinical and multi-omic information, may help identify biologically distinct subgroups or support differentiation between overlapping clinical presentations.

4. **Treatment Response Monitoring**

Repeated VOC-based measurements may also provide complementary information regarding treatment response and physiological change during therapy. Such approaches could potentially support more dynamic monitoring strategies alongside conventional clinical evaluation and patient-reported outcomes.

Despite these promising directions, substantial challenges remain regarding validation, reproducibility, standardization, and clinical generalizability before routine implementation can be considered.

5. Clinically Meaningful Outputs and Decision Support

For volatilomics-based approaches to become clinically relevant, generated outputs must be interpretable within real-world psychiatric workflows. The primary value of such systems is unlikely to emerge from isolated biomarker detection, but rather from probabilistic and longitudinal decision-support functions integrated with conventional clinical assessment.

Potentially meaningful outputs may include:

i. dynamic relapse risk estimation
ii. identification of clinically significant physiological change
iii. support for longitudinal monitoring
iv. biological stratification of heterogeneous patient populations
v. support for treatment-response assessment

Importantly, such systems should be viewed as complementary tools intended to assist clinical interpretation rather than replace psychiatric evaluation or diagnostic judgment.

VII. Challenges, Translation, and Responsible Implementation

Despite the growing interest in volatilomics and AI-assisted psychiatry, substantial scientific, technical, and ethical challenges remain before these approaches can be integrated into routine clinical care.

From a technical perspective, the field continues to face important limitations related to standardization of sampling procedures, variability across sensing platforms, and interoperability with existing clinical data infrastructures. Reproducibility across laboratories, populations, and real-world clinical settings remains a central translational challenge.

Biologically, VOC profiles are influenced by numerous physiological and environmental factors, including smoking status, diet, medication exposure, microbiome composition, physical activity, and comorbid medical conditions. As a result, careful study design, longitudinal assessment, and robust multivariate modeling strategies are essential to reduce confounding and improve interpretability.

Scientific limitations must also be acknowledged. Many existing studies remain exploratory in nature, frequently involving relatively small cohorts and limited external validation. In addition, machine learning approaches introduce risks related to overfitting, data leakage, and limited generalizability across heterogeneous psychiatric populations.

Ethical considerations are particularly important in psychiatric applications. The possibility of early risk estimation raises complex questions regarding stigma, predictive uncertainty, informed consent, communication with patients and families, and potential misuse of sensitive biological information. These concerns reinforce the importance of transparent governance frameworks and clinically responsible interpretation.

Future implementation of volatilomics-based clinical support systems will additionally require alignment with evolving European regulatory frameworks, including the Medical Device Regulation (MDR/IVDR) and the EU AI Act. Key requirements are likely to include robust clinical validation, algorithmic transparency, reproducibility across populations, and probabilistic rather than deterministic interpretation models.

VIII. The Role of VOLABIOS and the European Strategic Context

The VOLABIOS project was designed to address several of the major barriers currently limiting translation of volatilomics into psychiatric research and clinical application. Through multi-centre collaboration, harmonized protocols, integration of clinical and biological data, and longitudinal assessment strategies, the project aims to contribute to the development of clinically relevant and methodologically robust frameworks for volatilomics-based psychiatry.

Importantly, the objective is not the identification of a single diagnostic biomarker, but the development of probabilistic and clinically interpretable models capable of supporting areas such as relapse risk estimation, biological stratification, longitudinal monitoring, and treatment-response assessment.

More broadly, volatilomics and AI-assisted precision psychiatry align closely with several emerging European strategic priorities, including the European Health Data Space (EHDS), AI-enabled healthcare, interoperable clinical data ecosystems, and personalized medicine initiatives. The integration of scalable and non-invasive biological monitoring approaches may eventually support earlier intervention strategies, improve longitudinal patient management, and facilitate the responsible integration of data-driven tools into psychiatric practice.

At the same time, successful implementation will require continued collaboration between clinicians, researchers, engineers, patients, families, regulators, and health systems in order to ensure that emerging technologies remain clinically meaningful, ethically grounded, and centered on patient care.

IX. Conclusion

Psychiatry is gradually moving toward more biologically informed and data-driven models of care. However, translating biological insight into clinically meaningful practice remains one of the central challenges of modern psychiatric research.

Volatilomics offers a potentially valuable complementary interface between complex biological processes and accessible longitudinal monitoring. Its non-invasive nature, scalability, and sensitivity to dynamic physiological change make it particularly attractive for repeated assessment and real-world clinical applications.

At the same time, volatilomics should not be viewed as a standalone diagnostic solution. Its greatest potential may emerge through integration with clinical assessment, multi-omic approaches, and AI-assisted interpretation within probabilistic and clinically responsible decision-support frameworks.

If validated rigorously and implemented responsibly, such approaches may contribute to earlier detection, improved longitudinal monitoring, more personalized intervention strategies, and a gradual transition toward precision psychiatry grounded in both biological understanding and human-centered care.

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