Review

From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care

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From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care

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Abstract: Background/Objectives: The dual forces of structured inquiry and serendipitous discovery have long shaped neuropsychiatric research, with groundbreaking treatments such as lithium and ketamine resulting from unexpected discoveries. However, relying on chance is becoming increasingly insufficient to address the rising prevalence of mental health disorders like depression and schizophrenia, which necessitate precise, innovative approaches. Emerging technologies like artificial intelligence, induced pluripotent stem cells, and multi-omics have the potential to transform this field by allowing for predictive, patient-specific interventions. Despite these advancements, traditional methodologies such as animal models and single-variable analyses continue to be used, frequently failing to capture the complexities of human neuropsychiatric conditions. **Summary:** This review critically evaluates the transition from serendipity to precision-based methodologies in neuropsychiatric research. It focuses on key innovations such as dynamic systems modeling and network-based approaches that use genetic, molecular, and environmental data to identify new therapeutic targets. Furthermore, it emphasizes the importance of interdisciplinary collaboration and human-specific models in overcoming the limitations of traditional approaches. **Conclusion:** We highlight precision psychiatry's transformative potential for revolutionizing mental health care. This paradigm shift, which combines cutting-edge technologies with systematic frameworks, promises increased diagnostic accuracy, reproducibility, and efficiency, paving the way for tailored treatments and better patient outcomes in neuropsychiatric care.

Keywords: precision medicine; artificial intelligence; neuropsychiatric disorders; induced pluripotent stem cells; multi-omics integration; mental health care; machine learning; dynamic systems analysis; biomarkers; personalized medicine

1. Introduction

Medical research often relies on two pillars: systematic data collection and the unpredictable nature of serendipity [1–3]. While structured data collection provides a solid empirical foundation, many significant medical breakthroughs have occurred by chance [4,5]. For example, Alexander Fleming's discovery of penicillin resulted from accidental mold contamination, and Wilhelm Röntgen discovered X-rays while experimenting with cathode rays. In psychiatry, serendipitous findings have been particularly impactful, such as the use of lithium for bipolar disorder and ketamine for depression—both discovered unexpectedly [6,7]. These instances underscore how unplanned observations have historically led to major advancements in medical science [8–11] (Table 1). In psychiatric treatment, where new therapies are desperately needed, relying on chance is inadequate and risks stagnation [12,13]. To accelerate progress, we must integrate innovative procedures and technologies that streamline research, enhance predictive accuracy, and broaden discovery scopes [14–17]. However, depending on chance is increasingly inadequate, especially in psychiatric treatment, where new therapies are urgently needed [8,18]. Mental health disorders like depression,

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anxiety, and bipolar disorder are rising globally, affecting millions and straining healthcare systems [19,20]. The unpredictability of serendipitous discoveries means that breakthroughs may not happen promptly, potentially leading to stagnation in therapeutic advancements [21–23]. Relying solely on chance overlooks the benefits of proactive, systematic exploration using modern scientific tools [21,24,25]. In an era of escalating mental health challenges, there is a pressing need for more efficient and predictable research methodologies to accelerate the development of new treatments [21,22,26].

Integrating innovative procedures and emerging technologies into medical research is essential to address this need. Advanced analytical tools such as artificial intelligence (AI) and machine learning (ML) algorithms can analyze vast datasets efficiently, uncovering patterns and correlations that might remain hidden with traditional method [27–29]. For instance, AI can assist in identifying biomarkers for psychiatric disorders by analyzing genetic, neuroimaging, and clinical data, leading to more personalized treatment approaches [30–32]. One notable example of this is in oncology, where AI has been used to analyze tumor genetic profiles to guide immunotherapy, significantly improving treatment outcomes for cancers such as melanoma [33–35]. Similarly, in cardiology, ML algorithms have enhanced early detection of atrial fibrillation through wearable devices, allowing timely intervention and reducing the risk of stroke [36,37]. These successes underscore the transformative potential of precision-based methods in other fields and highlight the promise they hold for psychiatry. Adaptive trial designs allow modifications based on interim results without compromising integrity, making clinical studies more flexible and cost-effective [38–40]. Interdisciplinary collaboration brings together experts from neuroscience, genetics, pharmacology, computer science, and bioinformatics, fostering a holistic approach to problem-solving and yielding more robust solutions [41–43].

Emerging strategies like induced pluripotent stem cells (iPSCs) and organoids offer human-specific models for deeper insights into disease mechanisms at the cellular level [44–46]. iPSCs derived from patients can be differentiated into various cell types, enabling researchers to study disease pathology and test potential treatments in environments closely mimicking human biology [47–49]. Organoids—three-dimensional cell cultures replicating organ structures—allow the examination of complex interactions within human tissues [46,50,51]. These models overcome the limitations of traditional animal studies, which often lack relevance to human biology and fail to capture the complexity of human disease interactions.

Multi-omics approaches—integrating genomics, transcriptomics, proteomics, metabolomics, and other 'omics' data—provide a comprehensive understanding of biological systems and disease processes [52–54]. By analyzing multiple layers of biological information simultaneously, researchers can identify novel therapeutic targets and biomarkers with greater precision [55–57]. AI tools further enhance precision and reproducibility by automating data analysis, reducing human error, and handling complex, high-dimensional datasets [53,58,59]. Network-based modeling reveals intricate interactions within biological systems, identifying pathways critical for precision medicine. These models simulate how alterations in one system component affect others, offering insights into disease mechanisms and potential interventions [52,54,58]. An illustrative case is in diabetes management, where precision modeling of glucose-insulin dynamics has informed personalized insulin therapy, improving blood sugar control and reducing complications [60–62]. Similarly, in rheumatoid arthritis, biomarkers have been used to predict patient response to biologic treatments, ensuring that individuals receive the most effective therapy with minimal delay [63–65]. These applications highlight how integrating system-level insights can optimize both diagnosis and treatment strategies.

Despite these advancements, a significant research gap remains due to continued reliance on traditional models and serendipity [21,66,67]. One major obstacle in adopting precision-based approaches in neuropsychiatric research is the complexity and heterogeneity of psychiatric disorders themselves [68–70]. Unlike diseases with clear biological markers, psychiatric conditions often manifest through a combination of genetic, environmental, and behavioral factors, making it challenging to identify universally applicable biomarkers [71–73]. Additionally, the lack of standardized protocols for integrating multi-omics data with clinical phenotypes creates

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inconsistencies in research outcomes [73–75]. Another barrier lies in the ethical and logistical challenges associated with large-scale data collection [75–77]. Privacy concerns, particularly when dealing with sensitive neuroimaging and genetic data, hinder widespread adoption [76,78,79]. Moreover, ensuring diverse representation in datasets is critical but often difficult, as many studies disproportionately include participants from developed regions [78,80,81]. Addressing these challenges will require robust frameworks for data sharing, advances in explainable AI to interpret complex datasets, and international collaboration to ensure findings are globally relevant and equitably implemented [75,76,79]. Conventional research paradigms often isolate single variables, failing to account for the dynamic interactions between genes, proteins, and the environment that characterize complex diseases like psychiatric disorders [67,82,83]. Dynamic systems analysis contributes by tracking temporal changes in disease progression, providing predictive insights to tailor interventions more effectively [67,82,84]. Understanding how diseases evolve over time enables clinicians to develop treatment plans that address specific patient needs at different stages [66,85].

Given these challenges, it is imperative for the research community to embrace innovation as a necessity rather than an option. This review aims to highlight the importance of emerging strategies in transforming medical research—particularly in psychiatry—into a field driven by design rather than chance. We will explore how adopting innovative technologies and collaborative approaches can foster an ecosystem where breakthrough treatments are discovered more predictably and efficiently. By emphasizing predictive accuracy, efficiency, and human relevance, we can accelerate the discovery of new treatments and ultimately improve patient outcomes. The review will focus on evaluating the limitations of traditional models and the continued reliance on serendipity, exploring the potential of emerging technologies like iPSCs, organoids, multi-omics, and AI in revolutionizing psychiatric research. It will identify research gaps that hinder the efficient discovery of new therapies and a comprehensive understanding of complex disease mechanisms. Additionally, the review will propose integrative strategies to incorporate innovative procedures and interdisciplinary collaboration into current research frameworks while addressing ethical considerations and policy changes necessary to support these advancements responsibly. By systematically examining these areas, we aim to provide a roadmap for transitioning from chance-driven discoveries to deliberate, design-focused research. This shift is essential for meeting the urgent need for new psychiatric treatments and enhancing the overall effectiveness of medical research. Embracing these innovations will not only reduce our dependence on serendipity but also pave the way for more predictable and efficient discovery of breakthrough therapies, ultimately improving outcomes for patients worldwide.

Table 1. Historical serendipity in drug discovery for mental illnesses.

Year	Drug Name	Primary Targets	Expected Diseases to Treat	Mental Illnesses Treated	Ref.
1940s-1950s	Iproniazid	Monoamine Oxidase	Tuberculosis	Depression	[9,22]
1950s	Lithium	Unknown	N/A	Bipolar Disorder	[8]
1950s	Chlorpromazine	Dopamine Receptors	Sedation	Schizophrenia	[10,22,86]
1950s	Imipramine	Serotonin/Norepinephrine Reuptake	N/A	Depression	[9,22]
1950s	Chlordiazepoxide	GABA Receptors	N/A	Anxiety	[22]
1960s	Psilocybin	Serotonin Receptors	N/A	Depression	[10]
2000s	Ketamine	NMDA Receptors	Anesthesia	Depression	[9–11]
2010s	Minocycline	Unknown	Infection	Schizophrenia	[10]
2010s	Warfarin	Blood Clotting Factors	Blood Clotting Disorders	Schizophrenia	[10]

N/A: Not applicable.

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2. Integrative Models of Wet and Dry Research

The integration of wet and dry research is crucial for advancing treatments of neuropsychiatric disorders. Wet research, involving experimental and clinical studies, provides empirical data, while dry research, encompassing computational models and data analysis, offers predictive insights [87–92]. Combining these approaches enhances the understanding of complex neuropsychiatric conditions and improves treatment strategies [88,93,94].

In cardiac research, integrating experimental data into computational models has refined treatments and predicted outcomes [95]. Similarly, partnerships between AI and neurology have advanced neuroimaging biomarkers for Alzheimer's disease (AD), enabling earlier and more accurate diagnoses [95–98]. The triadic relationship between vascular dysfunction, muscle atrophy, and cognitive decline underscores the necessity for multidisciplinary approaches that address these interconnected mechanisms [99–101]. For instance, integrative medicine approaches have shown promise in treating post-stroke depression by combining traditional Chinese medicine, Western medicine, and rehabilitation techniques, leading to improved patient outcomes [95,102]. Integrative psychotherapy models for conditions like psychogenic nonepileptic seizures and anxiety disorders have demonstrated significant efficacy by incorporating cognitive-behavioral techniques, psychoeducation, and individualized treatment protocols [103–105]. Furthermore, integrative care models for Parkinson's disease (PD) and AD emphasize multidisciplinary approaches, combining pharmacotherapy with allied health therapies to effectively manage both motor and neuropsychiatric symptoms [106–110]. These examples underscore the necessity of integrative approaches that leverage both empirical data from wet research and predictive models from dry research to develop comprehensive treatment plans, ultimately enhancing patient care in neuropsychiatric disorders. iPSC technologies are valuable for modeling disease mechanisms and testing potential treatments in vitro, they are limited by high costs, labor intensity, and expertise requirements, highlighting the need for automation and cost reduction [108,111–113]. AI predictions, although promising, face validation issues due to biases, limited generalizability, and opacity, necessitating diverse datasets, explainable AI, and multi-site validation [111,114,115].

Wet research employs advanced techniques like genome-wide association studies (GWAS) to identify genetic loci associated with neuropsychiatric disorders, providing insights into their genetic basis [116–118]. The integration of wet and dry research has proven effective in fields such as cardiac mechano-electric function studies, where experimental data build and validate computational models, enhancing our understanding of cardiac behavior [119–121]. In toxicology, combining high-throughput wet lab techniques with computational methods addresses the challenges of analyzing high-dimensional data, translating complex data into actionable insights. Innovative educational programs are also incorporating both wet and dry lab experiences, such as using CRISPR/Cas9 for gene editing in mouse stem cells alongside computer simulations to generate transgenic mouse models, enriching learning and reducing animal testing.

Computational models play a pivotal role in dry research by integrating and analyzing extensive datasets from wet research. They are essential for understanding complex biological systems and predicting the effects of various factors [122,123]. Systems-level integrative pathway analyses have been instrumental in elucidating the polygenic contributions of risk variants to neuropsychiatric disorders, guiding the development of targeted therapies [123–126]. Computational models in cardiac research have evolved over decades, enhancing our understanding of cardiac function and predicting outcomes [127–129]. Similarly, computational fluid dynamics has revolutionized the modeling of drying processes, optimizing technologies across multiple scientific domains [130,131].

3. Cyclic Data Processing

To provide a multidimensional view of biological systems and disease mechanisms, the cyclic data processing framework begins with the systematic collection of various data types—genetic, epigenetic, transcriptomic, proteomic, and clinical datasets [132–134]. Integrative multi-omics

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approaches, such as combining GWAS with epigenetic and transcriptomic data, facilitate the identification of novel genetic loci and potential therapeutic targets [135,136]. For example, integrating single-cell RNA sequencing with chromatin accessibility data has revealed cell-type-specific regulatory elements in neuropsychiatric disorders, which is critical for understanding complex diseases like schizophrenia or bipolar disorder [116,136–139].

ML and statistical methods are used to create predictive models from integrated datasets. These models enable forecasting of disease progression, patient stratification, and treatment outcomes [140,141]. To ensure clinical reliability, these predictions undergo rigorous validation through experimental techniques such as CRISPR-based functional genomic studies or in vitro neural organoids derived from patient-specific induced iPSCs [140,142]. This iterative process of prediction and validation refines models and enhances their clinical applicability, advancing precision medicine [140,142,143].

The transition from micro to macro in cyclic data processing allows for breakthroughs in complex biological systems, connecting molecular insights to large-scale applications [144,145]. Micro-level research focuses on fundamental molecular and cellular mechanisms, such as the role of G protein-coupled receptors (GPCRs) and their modulation in neuropsychiatric disorders [144,146–148]. These receptors are crucial in neurotransmission, offering potential for targeted therapeutic interventions. Similarly, epigenetic mechanisms like histone modification and non-coding RNA regulation provide insight into how cellular processes adapt to environmental changes [149,150]. Dysregulation of non-coding RNAs (ncRNAs), such as microRNAs, which regulate gene expression and neural plasticity, has been linked to conditions such as schizophrenia and depression. Therapies aimed at ncRNAs, such as microRNA mimics, show promise in modulating synaptic function and neuroinflammation.

Understanding emergent properties and using advanced computational tools such as ML to model system-wide effects are required for translating these findings into macro-level applications [151–155]. Integrating genomic and proteomic data with deep clinical phenotyping has enabled the development of precision medicine strategies [156–159]. Patient-specific models derived from iPSCs are used to simulate disease progression and test therapeutic responses [160–162]. This strategy has been used in oncology, where genetic profiling informs targeted treatments, and in neurodegenerative diseases such as AD, where cellular models predict patient-specific drug efficacy [160,162–167].

To summarize, the cyclic data processing framework connects micro-level molecular insights to macro-level applications by integrating diverse datasets and predictive modeling. This approach promotes a thorough understanding of complex diseases and advances precision medicine, allowing for the development of targeted therapies for neuropsychiatric and other complex disorders.

4. Interpreting Experimental Results

Interpreting experimental results in neuropsychiatric research is challenging due to the complexity of these disorders. Animal models, while valuable, cannot fully replicate human conditions, necessitating cautious interpretation and validation in human models [168–170]. Overreliance on statistical significance, particularly P values, can lead to misinterpretations; treating nonsignificant results as evidence of no effect confuses the absence of evidence with evidence of absence [171,172]. Variability in diagnostic accuracy using different interpretive approaches can yield inconsistent outcomes [173,174]. The complexity of neuroimaging data adds further challenges [174,175]. ML-based predictive models in neuroimaging frequently lack interpretability and require extensive validation across multiple datasets to ensure reliability [176–178]. Presenting only significant results can obscure the full picture, leading to biases and reproducibility issues [173,179,180]. Furthermore, AI-powered neuroimaging analyses may introduce bias if algorithms are trained on non-representative datasets, reducing clinical utility [178,179]. The use of sensitive imaging and genomic data necessitates stringent privacy protections [181–183]. As a result, a

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comprehensive approach—including careful statistical analysis, validation in human models, and transparent reporting—is required for accurate interpretation in neuropsychiatric research.

Table 2. Challenges and solutions in translating artificial intelligence (AI) models to clinics.

Challenge	Description	Example/Context	Proposed Solution	Future Implications
Data Bias	Limited diversity in datasets leads to models that perform poorly across populations.	Neuroimaging datasets over-represent individuals from developed countries.	Collect data from underrepresented populations and build balanced datasets.	Improved model generalizability and equitable healthcare.
Lack of Interpretability	AI models, particularly deep learning, are often "black boxes," making decisions hard to explain.	Clinical decisions influenced by opaque ML predictions.	Implement Explainable AI (XAI) techniques, such as SHAP or LIME frameworks.	Builds clinician trust and facilitates regulatory approval.
Scalability	High computational demands and infrastructure requirements restrict widespread adoption.	Training advanced models like GPT-based NLP systems.	Optimize algorithms and leverage cloud computing or edge AI technologies.	Reduces costs and enhances accessibility for smaller clinics.
Regulatory Barriers	Slow adaptation of regulatory frameworks for AI integration in clinical workflows.	FDA approval processes for AI tools in diagnostics.	Develop standardized guidelines and real-world evidence collection protocols.	Accelerates AI implementation in healthcare systems.
Data Privacy Concerns	Sensitive patient information is vulnerable to misuse or breaches during data collection and analysis.	Sharing genomic data for psychiatric biomarker research.	Use federated learning and encrypted data-sharing protocols.	Ensures secure collaboration without compromising privacy.
Validation and Reproducibility	AI models often lack external validation and reproducibility across clinical settings.	AI-based neuroimaging biomarkers not validated in multi-site trials.	Conduct multi-site, cross-population validation studies.	Increases confidence in clinical utility and robustness.
Integration with Existing Systems	AI tools often face challenges integrating with legacy electronic health record (EHR) systems.	AI models for patient stratification requiring manual data input.	Develop interoperable APIs and adopt standardized data exchange formats.	Seamless AI adoption into routine clinical workflows.
Ethical Concerns	Potential for AI misuse, such as bias amplification or unfair treatment recommendations.	Disparities in AI-driven mental health treatment outcomes.	Implement ethical AI design principles and multidisciplinary oversight boards.	Ensures ethical and responsible deployment of AI.

AI, artificial intelligence; API, Application Programming Interface; HER, legacy electronic health record; FDA, United States Food and Drug Administration; GPT, Generative Pre-trained Transformer; LIME, Local Interpretable Model Agnostic Explanation; NLP, Natural language processing; SHAP, SHapley Additive exPlanations; XAI; explainable artificial intelligence;.

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Translational research bridges the gap between experimental findings and clinical applications by converting laboratory discoveries into practical treatments [184,185]. This process is crucial for developing effective therapies for diseases like neuropsychiatric disorders. For example, novel therapies targeting neuroinflammatory pathways in glial cells are being investigated using insights from induced iPSC-derived models [171,186,187]. Integrating high-throughput experimental data with existing knowledge and automated inference tools, as seen in GWAS, demonstrates the power of translational research frameworks [188–190]. Ensuring robustness across genetically diverse populations improves the translational potential of preclinical findings, leading to better prediction of treatment responses in heterogeneous patient groups [191,192]. Blinded interpretation of study results reduces bias and enhances reliability [191,193]. Translational research, aided by initiatives such as the National Institutes of Health's Center for Advancing Translational Sciences, emphasizes the importance of collaborative efforts among researchers, clinicians, and funders in effectively translating laboratory findings into clinical applications [194–196]. By addressing uncertainties and ensuring rigorous, reproducible methodologies, translational research continues to play a pivotal role in advancing medical science and improving patient care [197,198].

5. Towards Patient-Specific Models

Precision medicine is the future of neuropsychiatric disorder treatment, as it combines genetic, clinical, and environmental data to create patient-specific models that predict disease risk and treatment response [199–201]. This personalized approach aims to improve patient outcomes by tailoring care to individual needs [200,202,203]. To find underlying biological drivers and enable targeted drug development in neuropsychiatric disorders, precision medicine uses patient stem cell models, deep clinical phenotyping, and genomics [56,204]. These conditions require thorough functional genomic annotation and experimental validation using in vivo or in vitro model systems due to their highly polygenic and pleiotropic nature [57].

Environmental and socioeconomic factors like stress, diet, and access to care significantly affect neuropsychiatric outcomes [205,206]. Including these factors in predictive models enhances accuracy and addresses health disparities, enabling more personalized interventions. For example, in schizophrenia, precision medicine involves using biological markers to individualize treatment, predict future illness, and determine outcomes over the disease course [202,207–209]. Precision clinical trials for neurobehavioral disorders use adaptive treatments and precise measurement techniques to improve personalized care [210]. In epilepsy, precision medicine extends beyond genetics to include a broader array of personalized factors, aiming to address both seizures and associated comorbidities [202,211].

AI and ML have the potential to transform neuropsychiatry by predicting disease progression, aiding patient stratification, and identifying biomarkers [210,212]. However, challenges such as overfitting due to limited datasets, biases in training data, and lack of interpretability hinder clinical adoption [213–215]. These issues highlight the need for explainable AI frameworks, diverse datasets, and rigorous validation to ensure reliable and equitable applications.

Clinical trials and case studies are required to validate patient-specific models. Integrative psychotherapy models for psychogenic nonepileptic seizures have demonstrated promising outcomes in terms of seizure frequency reduction and improved patient functioning [216]. Patient-derived xenograft models have been used in clinical trials to evaluate the efficacy of anticancer drugs, providing a strong foundation for personalized cancer treatment [216]. Patient-specific computational models in congenital heart disease have aided in planning medical procedures and predicting clinical outcomes [216]. Involving patients and the public in clinical trials improves study design, recruitment, and communication, enhancing the relevance and impact of research [216,217].

Developing patient-specific models requires balancing the use of detailed personal data with ethical considerations [218–220]. Privacy concerns must be addressed through transparent consent processes and secure data management systems [218,221,222]. Furthermore, biases in computational

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frameworks may impede the equitable implementation of precision medicine, emphasizing the importance of algorithms that are both accurate and fair across diverse patient populations [223,224].

6. Discussion

The field of neuropsychiatric research stands at a critical crossroads, navigating between traditional methodologies and the burgeoning potential of precision-based approaches [71,225]. Historically, many significant advances in this domain have emerged serendipitously, driven by unexpected discoveries [21,226]. Examples such as the therapeutic use of lithium for bipolar disorder and the antidepressant effects of ketamine underscore the transformative impact of chance findings [225–228]. These breakthroughs, while revolutionary, often came at the expense of time and systematic predictability [21,229]. Serendipity, by its very nature, lacks reproducibility and scalability, limiting its ability to address the rapidly growing global burden of mental health disorders [10,21,230]. Disorders like depression, anxiety, and schizophrenia are increasing in prevalence, necessitating more reliable and efficient strategies to uncover effective treatments [13,16,231]. In this context, the limitations of serendipitous discoveries have become apparent, prompting the research community to seek innovative methods that align with the demands of modern medicine [22,232,233].

The shift from serendipity to precision-based approaches represents a paradigm change in neuropsychiatric research [71,234,235]. Precision medicine emphasizes tailored treatments, leveraging patient-specific data to improve diagnostic accuracy and therapeutic outcomes [201,236,237]. This approach builds on advancements in technologies such as AI, induced iPSCs, and multi-omics integration [234,237,238]. For instance, in cystic fibrosis, precision medicine has revolutionized treatment through the identification of genetic mutations like *F508del*, enabling the development of targeted therapies such as CFTR modulators [239–241]. These treatments have dramatically improved lung function and quality of life for patients with specific genetic profiles. In hematology, genomic analysis has allowed for the precise classification of leukemia subtypes, guiding personalized chemotherapy regimens that enhance survival rates [242,243]. These examples illustrate how precision-based approaches have redefined therapeutic paradigms in diverse areas of medicine and emphasize their potential applicability to neuropsychiatric disorders. The innovations enable researchers to identify disease mechanisms at unprecedented levels of detail, offering insights into complex biological interactions [71,235,244]. The evolution toward precision is not merely a technological shift; it reflects a broader commitment to systematic, reproducible, and predictive science [234,245,246]. By transitioning to data-driven methodologies, the field aims to replace chance with design, fostering an era of intentional discovery and targeted intervention [247–249]. This evolution underscores the urgency of integrating cutting-edge tools to address the challenges of neuropsychiatric disorders effectively [250–252].

A paradigm shift in psychiatric research calls for moving beyond traditional, primarily categorical diagnostic systems toward frameworks grounded in neurobiology and observable behaviors [253–255]. While DSM-5 and ICD-11 predominantly rely on categorical classifications (with DSM-5 incorporating only minimal dimensional features), the Research Domain Criteria (RDoC) framework and the Hierarchical Taxonomy of Psychopathology (HiTOP) adopt a dimensional, integrative approach to understanding mental health [256–258]. Rather than grouping disorders solely by clinical symptom clusters, RDoC and HiTOP focus on core domains of functioning—such as cognition, emotion, and arousal—linked to measurable biological constructs, behavioral data, and neural circuits [258,259]. For instance, RDoC's cognitive systems domain examines processes like attention and memory, illuminating the mechanisms that bridge symptoms and underlying neurobiology [260–262]. Incorporating these dimensional frameworks into research and diagnostic practices has the potential to unify disparate approaches, reduce heterogeneity in patient populations, and improve reproducibility across studies [253,261,263]. Ultimately, RDoC and HiTOP offer a scientifically grounded path to personalized interventions, tailoring treatments to individual biological and behavioral profiles [263–265].

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This review highlights the transformation of neuropsychiatric research, emphasizing the transition from traditional, chance-driven discoveries to deliberate, precision-based methodologies. The paper outlines the limitations of conventional approaches, such as serendipitous findings and animal models, which often fail to capture the complexity of human neuropsychiatric conditions. In response, it underscores the necessity of integrating advanced technologies and interdisciplinary methods to uncover novel therapeutic targets and improve patient outcomes. Key insights include the importance of dynamic systems analysis, which tracks temporal changes in disease progression, and network-based modeling that identifies critical biological pathways. By focusing on predictive and personalized strategies, the review positions precision medicine as the cornerstone of future neuropsychiatric research, aiming to achieve greater accuracy, reproducibility, and efficiency in treatment development.

The review also details the integration of transformative technologies that are reshaping the field. AI and ML provide unparalleled capabilities for analyzing large, complex datasets, uncovering patterns that traditional methods often overlook. iPSCs and organoids offer human-specific models to study disease mechanisms and test potential therapies in environments that closely mimic human biology. Multi-omics approaches combine genomics, transcriptomics, proteomics, and metabolomics to deliver a comprehensive view of disease processes, enabling the identification of biomarkers and therapeutic targets with precision. Collectively, these innovations represent a unified framework for advancing neuropsychiatric research, bridging gaps between basic science, translational studies, and clinical applications. This review underscores the synergistic potential of these tools in addressing the unmet needs of neuropsychiatric disorders.

The ultimate goal of neuropsychiatric research is to transition from generalized, trial-and-error treatment approaches to predictive, patient-specific treatments tailored to individual biological, environmental, and clinical profiles [71,235,236]. This shift aligns with the broader objectives of precision medicine, which seeks to enhance therapeutic efficacy and minimize adverse effects by accounting for the unique characteristics of each patient [244,266,267]. In neuropsychiatric care, where disorders like depression, bipolar disorder, and schizophrenia are heterogeneous and multifaceted, this approach holds transformative potential [116,268,269]. Patient-specific treatments can better address the diverse manifestations of these disorders, which are often influenced by genetic predispositions, environmental exposures, and lifestyle factors [270–272]. Predictive tools such as biomarkers, advanced imaging, and personalized diagnostic algorithms offer the promise of identifying at-risk individuals and intervening early, potentially altering the trajectory of illness and improving quality of life [273–275].

Table 3. Key artificial intelligence (AI) applications in neuropsychiatric research.

Application	Methodology	Outcome	Challenges	Future Directions	Reference
Neuroimaging Biomarkers	Deep Learning Models	Early detection and diagnosis of Alzheimer's and schizophrenia	Data bias and limited generalizability	Use diverse training datasets; implement explainable AI	[276–280]
Drug Discovery	Predictive Modeling	Identification of novel compounds and drug repurposing	Lack of experimental validation pipelines	Develop AI-driven validation platforms using human-derived organoids	[281–284]
Personalized Therapy	Patient Stratification Models	Tailored treatment recommendations for depression and bipolar disorder	Difficulty in accounting for multi-modal patient data	Integrate multi-omics and real-time patient monitoring data	[244,285–288]

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Disease Progression Prediction	Temporal ML Models	Forecast disease stages and response to treatments	Overfitting due to limited long-term datasets	Establish longitudinal cohort studies with wearable sensors	[91,276,289–291]
Mental Health Screening	Natural Language Processing (NLP)	Automated analysis of patient speech and text for early mental illness detection	Privacy concerns and interpretability	Develop privacy-preserving algorithms and user-consent frameworks	[292–296]

AI, artificial intelligence; ML, machine language; NLP, natural language processing.

The early detection of psychiatric disorders, including schizophrenia, bipolar disorder, and depression, is fundamental to improving outcomes and advancing precision medicine [32,297,298]. Biomarkers derived from neuroimaging, genetics, and multi-omics data are particularly valuable, as they reveal biological and physiological changes that often occur long before clinical symptoms appear [32,298,299]. For instance, subtle shifts in brain volume or abnormal connectivity patterns observed through functional magnetic resonance imaging (fMRI) have been associated with heightened risk for these conditions [40,300,301]. Similarly, genetic variations can indicate a predisposition to mental health issues, making these tools indispensable in identifying at-risk individuals [302–304]. Behavioral changes are another critical component of early diagnosis [302,304]. Sleep disturbances, cognitive deficits, and emotional dysregulation frequently emerge during the initial stages of psychiatric disorders [302–304]. In the case of schizophrenia, mild hallucinations, social withdrawal, or declining functionality often signal the prodromal phase, yet these symptoms frequently go unnoticed [304–306]. Combining behavioral insights with biological markers enhances diagnostic precision, enabling timely interventions to alter disease trajectories and improve quality of life [302,304,306].

AI is transforming the landscape of early psychiatric diagnosis by introducing unprecedented analytical capabilities [307,308]. Unlike traditional methods, AI-powered models can process large, multi-modal datasets to uncover intricate patterns among biomarkers, behaviors, and environmental factors [308,309]. These tools are especially effective in identifying subtle changes that might otherwise be overlooked [310–312]. For example, ML algorithms have demonstrated remarkable success in predicting the onset of psychosis by analyzing speech patterns, neuroimaging findings, and genetic data [309,310,313]. The implications of early intervention extend beyond individual health benefits. Preventive strategies, such as cognitive-behavioral therapy or pharmacological treatments administered during the prodromal phase, can delay or mitigate the progression of psychiatric conditions [308,314]. This, in turn, reduces hospitalizations, alleviates the strain on healthcare systems, and lowers associated societal costs [292,315]. AI-driven insights, when combined with interdisciplinary collaboration and a focus on prevention, represent a paradigm shift [292].

Integrating objective measures such as biomarkers and structured frameworks like the RDoC into psychiatric diagnostics could transform the field by standardizing diagnostic criteria [253,254,263,316–318] . Current methods, which often rely on subjective clinical observations and self-reports, introduce variability that hampers research cohesion and clinical reproducibility [32,254,260,319,320]. By contrast, biomarkers provide measurable and consistent data points that capture the underlying biological mechanisms of disorders, reducing ambiguity in diagnosis [32,260,318–320]. Standardized diagnostic criteria would create more homogeneous research cohorts, ensuring that studies are conducted on well-defined and comparable patient populations [253,254,260,263,316,317]. This uniformity would enhance the reproducibility of findings across different studies and improve the translatability of preclinical and clinical research into practical treatments [321–323]. Moreover, it would enable more accurate stratification of patients for targeted therapies, paving the way for precision medicine in psychiatry [201,202,324]. A shift toward such integrative, biomarker-driven approaches holds the potential to unify the field, addressing long-

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standing challenges of heterogeneity and variability in psychiatric research and improving outcomes for patients globally [201,325,326].

Precision methodologies are vital to realizing this goal, as they enable a deeper understanding of complex neuropsychiatric conditions [71,201,235]. Traditional diagnostic methods and treatment paradigms often fail to capture the nuanced interplay of genetic, molecular, and environmental factors, resulting in variable outcomes and limited progress [327–329]. Precision approaches leverage cutting-edge technologies, including multio-mics, AI, and patient-derived models like iPSCs [330–332]. By integrating these tools, researchers can identify specific disease mechanisms, predict individual responses to therapies, and tailor interventions with greater accuracy. The necessity of these methodologies is underscored by the rising prevalence and societal impact of neuropsychiatric disorders, which demand innovative strategies to address unmet clinical needs [333–336].

The transition to predictive, patient-specific treatments is hindered by several challenges, including the limitations of traditional models and reliance on serendipity. Historically, many neuropsychiatric therapies have emerged unexpectedly, highlighting the unpredictability of chance-driven discoveries [16,337,338]. While such breakthroughs have been valuable, they often lack the scalability and reproducibility required to address modern healthcare demands [16,339,340]. Conventional research methods, particularly those relying on animal models, fail to adequately mimic human neuropsychiatric conditions, limiting their translational value [338,341,342]. These limitations underscore the need for human-specific models and systematic, hypothesis-driven approaches that prioritize reproducibility and precision. In addition to methodological challenges, there are significant gaps in knowledge and infrastructure. The complex interplay of genetic, molecular, and environmental factors in neuropsychiatric disorders remains poorly understood, impeding the development of targeted interventions [271,272,343]. Insufficient integration of interdisciplinary expertise further hinders progress, as effective solutions require collaboration among neuroscientists, geneticists, data scientists, and clinicians [344–346]. Infrastructure challenges include limited access to advanced technologies, fragmented datasets, and the lack of standardized frameworks for data sharing and analysis [346–348]. Addressing these gaps is crucial for building a robust foundation for precision neuropsychiatry.

Achieving the goal of predictive, patient-specific neuropsychiatric care necessitates the integration of essential innovations such as AI, ML, and multio-mics. AI and ML technologies are transformative in their ability to process and analyze large, complex datasets, uncovering patterns and relationships that traditional methods cannot [244,349,350]. These tools are instrumental in identifying biomarkers, stratifying patients, and predicting treatment outcomes with unprecedented accuracy [214,349,351]. Multi-omics approaches—combining genomics, transcriptomics, proteomics, and metabolomics—provide a comprehensive understanding of the molecular underpinnings of neuropsychiatric disorders [298,352,353]. Together, these technologies enable the development of precise, individualized interventions. Dynamic systems analysis and network-based modeling are critical for understanding the intricate interactions within biological systems. Dynamic systems analysis captures temporal changes in disease progression, offering insights into the timing and efficacy of interventions [354–356]. Network-based modeling reveals the complex relationships between genes, proteins, and environmental factors, identifying key pathways and nodes that can serve as therapeutic targets [354,357,358]. These approaches shift the focus from isolated components to holistic, system-level insights, providing a more accurate representation of disease mechanisms. The successful application of these technologies requires a supportive research ecosystem. This includes access to diverse, high-quality datasets, collaboration across disciplines, and investments in training programs to equip researchers with the skills needed to utilize these tools effectively. By addressing these technological and knowledge requirements, the field of neuropsychiatry can move closer to achieving its ultimate goal of predictive, patient-specific care.

Advancing neuropsychiatric research is crucial for addressing the global mental health crisis, as disorders such as depression, anxiety, and schizophrenia rank among the leading causes of disability worldwide [334,359]. These conditions impose substantial social and economic burdens, yet

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traditional diagnostic and treatment methods often fall short of addressing their complexity [360–362]. Precision psychiatry provides a transformative solution by tailoring care to individual biological, genetic, and environmental profiles [363–365]. This approach enhances diagnostic accuracy, enables early interventions, and optimizes therapeutic outcomes, shifting the focus from generalized treatments to personalized care [187,362,363]. Technologies like multi-omics and AI drive this transition, identifying biomarkers and predicting treatment responses with unprecedented precision. Beyond innovation, this shift fulfills an ethical imperative to provide equitable and effective healthcare. By addressing these challenges through precision psychiatry, the field can significantly reduce the burden of mental health disorders and improve patient outcomes.

This review synthesizes recent advancements in neuropsychiatric research, integrating technologies like AI, multi-omics, and patient-derived models such as iPSCs and organoids. It builds on prior frameworks, which often relied on serendipity or animal models that lack human-specific relevance and scalability. By bridging traditional methodologies with contemporary approaches, this review outlines a roadmap for precision-based research and therapeutic strategies. It highlights the importance of interdisciplinary collaboration and robust infrastructure to support these innovations. By situating these advancements in the broader scientific context, the review demonstrates how emerging tools can overcome historical limitations, paving the way for transformative breakthroughs in neuropsychiatric care.

Precision psychiatry has profound clinical implications, driven by AI-powered diagnostics and personalized interventions. AI and ML can identify complex patterns in patient data, enhancing diagnostic accuracy and predicting treatment outcomes. These tools enable personalized care plans tailored to individual needs, improving therapeutic efficacy while minimizing side effects. Meanwhile, patient-derived iPSCs and organoids provide human-specific models to study disease mechanisms and test therapies, mimicking biological conditions with exceptional fidelity. Together, these innovations herald a new era of targeted, efficient, and effective mental healthcare, addressing unmet clinical needs and transforming patient outcomes.

This review's key strength lies in its comprehensive integration of technological and biological insights, forming a robust foundation for advancing neuropsychiatric research. By synthesizing innovations such as AI, multi-omics, and patient-derived models like induced iPSCs and organoids, it highlights tools addressing long-standing challenges in understanding and treating complex disorders. Additionally, the inclusion of dynamic systems analysis and network-based modeling demonstrates the potential for uncovering intricate disease mechanisms, offering a system-level perspective on neuropsychiatric conditions. This emphasis on human-specific models bridges critical gaps left by traditional animal models and serendipitous findings. The review also underscores the importance of multidisciplinary approaches, emphasizing collaboration across neuroscience, genetics, bioinformatics, and clinical psychiatry. This cross-disciplinary focus is crucial for tackling the complexity of mental health disorders, which demand diverse expertise. Furthermore, the review provides actionable strategies for integrating advanced technologies into clinical and research frameworks, offering a roadmap for implementing precision psychiatry. By combining theoretical insights with practical directions, it serves as a valuable resource for advancing the field. By synthesizing advanced methodologies and promoting interdisciplinary collaboration, this review not only addresses existing gaps in neuropsychiatric research but also sets the stage for transformative breakthroughs, benefiting researchers, clinicians, and patients alike.

7. Outlook

Future research in neuropsychiatric disorders should prioritize refining integrative models and fostering collaboration between experimental ("wet") and computational ("dry") labs. By combining computational modeling, AI, multi-omics, and experimental methods like CRISPR technology, researchers can advance precision medicine. Interdisciplinary training programs that merge ML with experimental techniques prepare scientists to tackle complex neuropsychiatric challenges. Techniques such as single-cell and deep learning in neuroimaging can identify cell-type-specific

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mechanisms multi-omics and biomarkers in disorders like schizophrenia and autism, leading to more precise therapeutic targets [366]. Interpretability tools enhance clinical trust by clarifying AI model predictions. Collaboration among researchers, clinicians, and patients ensures that research remains patient-centered and clinically relevant. Adapting advanced techniques for resource-limited settings through simplified workflows, open-source tools, and portable technologies democratizes access. Engaging local centers and training programs in underrepresented regions ensures diverse data and globally relevant findings.

Patient and public involvement (PPI) aligns research priorities with patient needs, enhancing relevance and impact [367]. For example, PPI in epilepsy trials highlighted overlooked mental health comorbidities [368]. Addressing scaleability and inclusivity requires substantial investment and global collaboration. International consortiums like ENIGMA and the Human Brain Project exemplify the value of large-scale collaborations [369,370]. Enhancing reproducibility and clinical relevance necessitates strong validation structures and better integration of diverse datasets. Establishing standardized pipelines for model validation can streamline the use of advanced tools like AI. Investments in low-cost iPSC platforms and AI-based computational models can democratize access to cutting-edge research tools. By synergizing computational and experimental approaches and cultivating strong collaborative frameworks, the field is poised to deliver more effective and personalized interventions, revolutionizing neuropsychiatric care [371].

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Abbreviations

AD	Alzheimer's disease
AI	artificial intelligence
GWAS	genome-wide association studies
iPSCs	pluripotent stem cells
ML	machine learning
ncRNAs	non-coding RNAs
PD	Parkinson's disease[118]
PPI	patient and public involvement
RDoC	Research Domain Criteria

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