

From Genetics to Functional Neuronal Biology: Emerging Paths in Precision Psychiatry for Depression

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Abstract

Major depressive disorder (MDD) is a common and disabling condition with highly variable treatment response. Despite the availability of multiple antidepressant therapies, treatment selection remains largely empirical, resulting in prolonged trial-and-error care. Precision psychiatry seeks to improve outcomes by aligning treatment decisions with patient-specific biology. In this commentary, we expand on recent advances in precision approaches to depression, focusing on the role of genetics and its integration with functional brain biology. Pharmacogenetic (PGx) testing is the most established precision tool in clinical psychiatry and provides clear clinical value by informing antidepressant metabolism, exposure, and tolerability. By reducing avoidable adverse effects and guiding dose optimization, PGx represents an essential first step toward more individualized treatment. However, PGx alone does not directly address the neurobiological mechanisms that determine antidepressant efficacy. We discuss emerging complementary approaches, including neuroimaging, electrophysiologic biomarkers, and computational models, and highlight shared challenges in achieving robust, patient-level prediction. We then consider patient-derived neuronal assays as a functional extension of genetic information. These systems enable direct assessment of antidepressant effects on neuroplasticity, the capacity of neurons to modify structure and function, in human neurons, while preserving the patient's inherited genetic background. We propose that integrating established genetic tools with functional neuronal readouts offers a promising path toward accelerating treatment selection and advancing precision psychiatry in depression.

Context

Major depressive disorder (MDD) remains one of the most prevalent and disabling conditions worldwide. Despite a broad armamentarium of approved medications, most patients do not respond to a first treatment, and a substantial proportion cycle through multiple trials before achieving sufficient clinical response, contributing to prolonged illness and societal burden¹⁻³. This lack of effective disorder management can be largely attributed to the trial and error nature of treatment choice. In our recent review, "Toward Precision Psychiatry: Innovations and Prospects in Treating Depression," we examined emerging approaches aimed at addressing this long-standing limitation by aligning treatment with patient-specific biology⁴.

In this commentary, we expand on the implications of that review with a genetics focus in mind, clarify what current precision approaches can and cannot deliver, and articulate key conceptual and translational questions that remain open, with the goal of fostering further discussion.

Major depressive disorder is a biologically heterogeneous, brain-centered condition, yet prescribing decisions are typically made without direct insight into the biological processes that determine whether a given drug will improve symptoms in an individual patient. As a result, treatment effectiveness is often established only retrospectively, after weeks or months of exposure to a given medication. The inefficiency of current depression treatment reflects the absence of a precision medicine approach despite patient heterogeneity, and the lack of tools capable of translating disease biology into clinically actionable guidance to drive therapeutic efficacy. Progress in this realm has been constrained by limited access to the target organ and by the complexity of disease mechanisms. Understanding what existing approaches can—and cannot—address is therefore essential for defining the next phase of precision psychiatry.

Pharmacogenetic Approaches to Precision Medicine

At present, the only widely deployed precision approach in clinical psychiatry is pharmacogenetic (PGx) testing. PGx has achieved clinical uptake because it addresses a concrete and frequent problem: interindividual variability in antidepressant metabolism and tolerability. Genetic variation in cytochrome P450 enzymes such as CYP2D6, CYP2C19, CYP2C9, and CYP3A4 can substantially alter systemic drug exposure^{5,6}. If metabolism is too rapid, therapeutic concentrations may never be achieved in the brain; if metabolism is too slow, excessive exposure may lead to adverse effects and treatment discontinuation⁵. In both scenarios, treatment failure can occur for reasons that are mechanistically upstream of efficacy.

At the same time, PGx is often misunderstood as a method for selecting the “right” antidepressant. As emphasized in the review, PGx more often constrains prescribing—indicating which drugs may require dose adjustment or avoidance—than it predicts which treatment is most likely to be effective⁹. Some panels include pharmacodynamic variants, such as those in SLC6A4 or HTR2A, that have been associated with response or side-effect liability, but their effect sizes are generally modest and inconsistent, limiting clinical actionability^{7,8}. PGx is therefore necessary and should be used, but it provides only a partial view of antidepressant response.

The limitations of PGx have driven the expansion of complementary precision psychiatry approaches, including neuroimaging, electrophysiologic biomarkers, peripheral assays, and machine learning models based on clinical data. These modalities differ substantially in biological resolution, feasibility, and clinical applicability (a comparative overview of key modalities is provided in Table 1). Neuroimaging and EEG approaches provide circuit- and systems-level correlates of treatment response, whereas

peripheral and computational models largely capture associative patterns across populations. Recent studies have applied multi-omic integration to antidepressant response prediction, combining transcriptomic, epigenomic, and genetic profiles to derive composite biomarkers associated with clinical response versus non-response in MDD patients, demonstrating improved biological interpretability over single-omic models. While each of the various approaches has yielded valuable scientific insight, persistent challenges recur across modalities, including modest individual-level predictive performance, infrastructure requirements, and difficulty translating outputs into actionable clinical decisions¹⁰⁻¹⁶. This landscape underscores the need for approaches that can directly interrogate patient-specific neural biology rather than infer response from correlational markers alone.

A fair reading of the field is that many current approaches remain correlational rather than mechanistic. As in other areas of complex human genetics, correlational predictors can be informative without being sufficient for individual-level decision-making.

Functional Neuronal Assays as a Treatment Guide Extending Pharmacogenetics

Against this backdrop, patient-derived neuronal assays represent a qualitatively different proposal. Rather than inferring response from static markers, these systems aim to observe functional response directly in human neurons that carry the patient’s genetic background. The reviewed work emphasized neuroplasticity, the capacity of neurons and synapses to modify structure and function, as a plausible mechanistic nexus for antidepressant efficacy, supported by converging evidence linking synaptic dysfunction and restoration of neuroplasticity to depressive phenotypes and therapeutic response¹⁷.

Patient neuronal testing using blood-derived cells is being implemented in translational as well as routine clinical contexts. These assays enable direct measurement of antidepressant effects on neuroplasticity in human neurons that retain the patient’s inherited genetic background. Importantly, this approach does not rely on indirect inference from correlational biomarkers, but instead provides an experimentally tractable functional readout of drug response in disease-relevant cell types. While the field continues to evolve, functional neuronal assays now represent a practical extension of precision psychiatry beyond purely predictive or associative frameworks.

• Derived neuronal assays enable prediction of treatment efficacy

Blood-derived neuronal models make this approach tractable by enabling access to disease-relevant neural biology in a patient-specific and potentially scalable manner. In addition to biological relevance, cellular

Table 1. Comparative Overview of Precision Psychiatry Tools for Antidepressant Treatment Selection

Modality	Mechanistic insight	Practical feasibility (infrastructure / time / cost)	Key limitations	Best-fit role in an integrated workflow
Pharmacogenetics (PGx)	Pharmacokinetics/ drug metabolism (exposure, interactions, tolerability); very limited pharmacodynamic relevance	High: blood/saliva; turnaround days; low infrastructure; widely available	Guides dosing and potential safety concerns, not clinical efficacy	Front-end safety/optimization layer: constrain options (dose/avoid) and reduce exposure-driven failures before adding pharmacodynamic stratification
Neuroimaging (structural/functional MRI, PET)	Mapping symptom dimensions to network dysfunction	Low: specialized scanners, acquisition standardization, cost; analysis pipelines; limited scalability	Cannot guide treatment choice at baseline. Translation gap from group-level predictors to patient-level decisions	Second-line stratification in specialized settings / research networks; potentially useful when combined with clinical + EEG + functional assays for convergent validity
EEG (resting-state / task-based)	Neural physiology and response to perturbation	Low: cheaper than imaging and portable but requires specialized equipment and standardized acquisition + artifact handling; turnaround can be short	Limited mechanistic specificity (biomarker ≠ mechanism)	Scalable physiologic layer: add objective CNS physiology; can triage candidates for deeper phenotyping and complement cellular functional readouts
Multi-omics (AI/ML-integrated genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiome)	Convergent biological processes associated with antidepressant response	Low to moderate: requires specialized assays, substantial computational infrastructure, cross-platform harmonization, and extended turnaround times relative to clinical decision windows	High dimensionality and cohort-specific signatures, limited replication and standardization, difficulty translating probabilistic outputs into actionable prescribing decisions	Biological stratification layer: identify mechanistically informed subgroups and generate hypotheses; complementary to PGx and functional neuronal assays
Patient-derived neuronal assays	Mechanistic functional consequences of specific treatment on neuronal plasticity-related phenotypes	Moderate–high feasibility: turnaround and cost depend on platform scaling	Turn-around-time, real-world validation	Efficacy ranking layer after PGx constrains safety/exposure: functional assay compares candidate treatments within-patient; best used with PGx + clinical phenotype

systems offer a practical advantage: multiple candidate treatments can be evaluated in parallel within the same patient-specific biological context. This contrasts with the sequential, months-long trial-and-error process that characterizes clinical care and reframes precision as the ability to compare functional effects directly^{4,18}.

Patient-derived neurons preserve inherited genetic variation that influences both drug handling and neuronal biology. Although reprogramming resets many epigenetic marks, substantial evidence indicates that disease-relevant regulatory programs and epigenetic signatures can persist or re-emerge during neuronal differentiation, shaping transcriptional and functional states^{19–22}. As a result, blood-derived neurons integrate inherited genetic variation with downstream regulatory effects, providing a functional readout of how genetic risk is expressed in disease-relevant neural cell types²³.

In this sense, neuronal assays are not a detour around genetics but an extension of it—from genetic association to functional consequence.

• **Implementation considerations and evidence needs**

Although blood-derived functional neuronal assays are already operational as clinical tests, key implementation considerations will drive clinical maturity. These include scalability (throughput and reproducibility across sites), cost and reimbursement pathways, turnaround time relative to treatment decision windows, prospective validation with longitudinal clinical outcomes, and integration into routine prescribing workflows. As with pharmacogenetics in its early adoption, broader uptake will depend on accumulating prospective and real-world evidence clarifying where these assays add measurable value beyond standard care.

An Integrative Framework to Precision Psychiatry

A realistic precision psychiatry framework is likely to involve integration rather than replacement of existing tools. In such a model, pharmacogenetic testing can be used early (pre-prescribing/at first prescription) to minimize exposure-related failures and adverse effects, while

functional neuronal assays provide additional information about relative biological response among tolerated treatment options. Neuroimaging or electrophysiologic measures may further contribute at the level of circuit engagement or symptom-specific targeting. Continued prospective studies are needed to define how these data streams can be combined into clinically interpretable decision-support frameworks and to establish evidence thresholds for broader implementation.

Conclusion

Our review argued that precision psychiatry will not mature by refining trial-and-error alone. Pharmacogenetics remains essential for avoiding preventable failures driven by exposure and tolerability, but it does not address the core question of efficacy in a brain-centered disorder. Patient-derived neuronal assays aim to fill this gap by enabling functional, patient-specific interrogation of neuroplasticity in human neurons. By integrating genetic background with functional brain biology, this approach offers a plausible path toward reducing the time and burden associated with ineffective antidepressant treatment trials. Continued collaboration between basic neuroscience, genetics, and clinical psychiatry will be essential to define best-use cases, establish evidence standards, and ensure optimal integration of functional approaches into real-world care.

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