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Precision psychiatry in depression *via* mechanism based stratification and therapy

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Abstract

Major depressive disorder (MDD) exhibits such pronounced heterogeneity that conventional symptom-based diagnoses and monoamine-focused treatments have proven largely inadequate, pushing the field toward what we now call precision psychiatry. In this review, we map out stratification approaches rooted in mechanisms spanning neural circuits, immune function, metabolic regulation, and the gut-brain axis. We also discuss how multi-omics, neuroimaging, and digital phenotyping can be integrated to construct continuous, biological grounded disease subtypes. Building from this groundwork, precision drug development has increasingly turned its attention to targets with genetic validation, therapeutics tailored to specific biological profiles, and adaptive trial designs that leverage biomarker-guided patient selection. Making this vision operational demands more than scientific insight as it requires weaving predictive algorithms into closed-loop care systems and everyday clinical practice, all while keeping health equity front and center so that technological progress does not end up widening gaps in access and outcomes. Real progress in MDD care will only emerge when we manage to blend deep mechanistic understanding with intelligent data analysis and genuinely inclusive implementation.

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Introduction

Major depressive disorder (MDD) stands as one of the most devastating conditions faced globally, wreaking havoc on patients' emotional lives, thinking abilities, relationships, and basic daily functioning[1,2]. Despite advances in the diagnosis and treatment of depression over recent decades, major gaps remain in both mechanistic understanding and clinical effectiveness[3–7]. Current diagnostic systems like the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, published by the American Psychiatric Association) and the International Classification of Diseases, 11th Revision (ICD-11, issued by the World Health Organization) provide a shared clinical language. However, they are built around observable symptoms rather than the underlying biological complexity that actually drives this disorder[8–11].

The central limitation is that current diagnostic criteria are fundamentally descriptive rather than mechanistic. DSM-5 requires at least five symptoms from a checklist, lasting two weeks or more, with either low mood or loss of interest being present[10,12,13]. In practice, this diagnostic framework allows for hundreds of different symptom combinations to meet criteria for the same diagnosis[14,15]. As a result, patients with identical diagnoses might have completely different biological problems driving their depression. Increasing evidence supports the view that MDD is a heterogeneous syndrome rather than a single disease entity[16–18]. This creates a real headache for researchers trying to find biological markers, because they end up averaging across what are likely distinct disease processes, which makes it nearly impossible to find clear signals[19–22].

The dominant therapeutic paradigm has evolved only marginally from its mid-20th century origins. The monoamine hypothesis, formulated in the 1950s, remains influential in clinical practise and continues to guide first-line pharmacotherapy targeting serotonin, norepinephrine, and dopamine systems[23,24]. This led to the development of selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), which continue to constitute the cornerstone of first-line agents[25–28]. However, treatment responses vary wildly among patients, and clinical benefit often emerges only after 4–8 weeks[26,29,30]. This delayed onset strongly implies that these agents may modulate downstream neurobiological changes rather than directly addressing primary etiological drivers. Real-world data show that only 30%–40% of patients achieve remission after their first antidepressant trial. Among patients with treatment-resistant depression, 50%–67% still do not experience adequate relief despite multiple treatment attempts[6,31–33]. Some medications like duloxetine have a Number Needed to Treat (NNT) of nine, indicating that a substantial proportion of treated patients experience side effects and delayed symptom relief without meaningful benefit beyond placebo[29,34,35].

More fundamentally, the current framework fails to recognize depression as a whole-body, multi-system disorder[36,37]. Evidence increasingly indicates that MDD involves complex, interconnected disruptions across brain circuits, hormone systems, immune function, metabolism, gut bacteria, and social environment[37–39]. Approximately 30% of patients show chronic low-grade inflammation with elevated markers such as C-reactive protein (CRP) and IL-6. This inflammation correlates with specific symptoms, particularly loss of pleasure and cognitive problems, and predicts poor response to standard antidepressants[31,40–42]. Other subgroups show disrupted stress hormone systems, cellular energy problems, altered gut microbes, and changes in gene expression[43–45]. Yet despite all this

evidence, routine clinical practice rarely incorporates any objective biological measures, and treatment decisions remain largely disconnected from mechanistic understanding[36,44].

In addition, clinical monitoring is another unmet need. The current clinical framework lacks good ways to monitor how patients are doing over time and adjust treatments accordingly based on their ongoing response patterns[46,47]. Follow-up visits still rely mainly on patients' subjective reports, which can miss clinically important changes in symptom severity[48]. New technologies like digital monitoring platforms, wearable sensors, and genetic testing for drug metabolism show real promise, but they are barely being used in routine clinical practice yet[49–53].

Collectively, these limitations indicate the need to move beyond symptom-based categories toward mechanism-informed diagnosis and treatment. This means developing what researchers call precision psychiatry, an approach rooted in the principles of precision medicine. While often used interchangeably with personalized medicine, precision psychiatry is distinct: it does not aim to create unique treatments for each individual, but rather leverages multimodal data such as genetic, imaging, immunological, and metabolic data to stratify patients into biologically defined subgroups that share a common disease mechanism. This stratification enables more targeted and effective interventions than the current one-size-fits-all approach, moving beyond the descriptive categories of traditional psychiatry by linking specific pathophysiological pathways to tailored treatments[16,54]. In this context, artificial intelligence (AI) and machine learning show particular promise here, offering ways to identify biologically meaningful subtypes, predict which treatments will work for whom, and potentially enable real-time treatment adjustments[50,55]. This review summarizes key advances enabling this transition and provides both the conceptual foundation and practical considerations for implementing truly mechanism based, individualized depression care.

Mechanism-based patient stratification in depression

Over the past decade, MDD research has been moving away from symptom-based classification and toward stratifying patients by underlying mechanisms (Table 1). The goal here is to identify biotypes (such as monoamine neurotransmitter imbalance, abnormal neural plasticity, dysregulation of the HPA axis and stress system, inflammation and immune activation, abnormal neural circuits, and brain networks, genetic and epigenetic factors, imbalance of glutamate/GABA and other excitatory-inhibitory systems, circadian rhythm and sleep mechanism abnormalities, gut-brain axis, and metabolic factors), (Fig. 1), that reflect shared pathophysiological pathways and can inform treatment selection[56–58]. This shift depends on a more nuanced grasp of the multisystem origins of MDD, and recent advances in high-dimensional data capture, multi-omics platforms, and AI-powered analytics. Together, these developments support subtype identification that is more flexible and clinical informative than traditional categorical approaches[50,59].

The rise of biological biotypes

Early efforts to stratify MDD patients relied on single biomarkers like serum cortisol, CRP, or brain-derived neurotrophic factors (BDNF). While these flagged certain subgroups, such as inflammatory depression or HPA axis overactivity, they provided limited explanatory power due to their neglect of interactions across biological systems[31,41,60,61]. The real turning point came when researchers started combining data types. Drysdale et al. used resting state functional magnetic resonance imaging (fMRI) alongside machine learning to pinpoint four reproducible neural circuit biotypes in MDD, each with its own prefrontal limbic connectivity signature, and each predicting whether patients would respond to transcranial magnetic stimulation (TMS)[62]. In parallel, other groups built MDD models that pulled together inflammation, metabolism, and neuroendocrine activity, sorting patients into categories like high inflammation/insulin resistant, HPA axis hyperactive, or autonomic dysregulated, and each subtype (typically a category defined by clinical, biological, or combined features) responded differently to factors like anti-inflammatories, lifestyle interventions, or glucocorticoid modulators[63,64]. These studies support a model in which MDD comprises overlapping yet distinguishable biological syndromes. For clinical utility, such subtypes must be linked to reproducible mechanisms, measurable markers, and actionable treatment strategies[21,65,66].

From discrete categories to continuous dimensions

The concept of continuous subtyping is increasingly replacing traditional discrete classification[67–69]. The mechanisms driving MDD do not fit neatly into separate boxes; however, they are better thought of as existing along multiple sliding scales, such as inflammatory load, neural plasticity, stress reactivity, microbiome diversity, monoamine system integrity, and so on[56,70,71]. In this model, every patient becomes a point in multidimensional space, positioned according to how much each mechanism contributes to their condition. For example, patients with high neuroinflammatory activity but normal monoamine function (normal CSF 5-HIAA) may plausibly benefit more from immune-targeted interventions than from SSRIs alone[70]. Patients with pronounced glutamatergic dysfunction and severe anhedonia may be more likely to respond to ketamine or similar agents[68,72]. This dimensional approach not only maps onto biology more accurately, but it also gives clinicians a quantitative framework for matching treatments to patients. It sidesteps the awkwardness of forcing people into mutually exclusive boxes and acknowledges what we see all the time in practice; mixed presentations are the norm, not the exception[16,56].

Multi-omics integration and AI-driven subtyping

The core technologies driving the transition toward mechanism-based, multidimensional patient stratification in depression are multi-omics integration and machine learning[73]. Combined analysis of genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microbiomic data, which some call the six-omics layers, can reveal the full arc from genetic risk through environmental exposures to downstream physiological changes[49,74]. A multicenter study illustrates this nicely: researchers found that certain gut microbiota profiles (like depleted Faecalibacterium) correlated with disrupted plasma tryptophan metabolism (higher kynurenine-to-tryptophan ratios) and weaker functional connectivity in the anterior cingulate cortex, essentially defining a gut-brain axis subtype[75,76]. Modern algorithms, including graph neural networks and deep autoencoders can extract latent structures from heterogeneous datasets and support unsupervised or semi-supervised biotype discovery[50,77]. Causal inference tools such as Mendelian randomization and mediation analysis can help distinguish drivers from downstream correlates[74,78]. For example, Mendelian randomization studies have implicated IL-6 as causally contributing to MDD rather than just being a byproduct of the illness[31], strengthening the rationale for anti-inflammatory interventions in appropriately selected patients[79,80].

Table 1. Recent advances in major depressive disorder research: multi-omics, digital phenotyping, and precision psychiatry approaches.

Category	Key approach/method	Main finding or contribution	Implication for MDD	Ref.
Multi-omics and causal inference	Mitochondrial multi-omics integration	Identified mitochondrial-related causal genes for MDD	Links cellular energetics to depression pathogenesis	[74]
	Gut microbiome + metabolomics	Revealed bacterial/metabolic signatures in MDD	Supports gut-brain axis as therapeutic target	[75]
	Proteome-transcriptome integration (brain/blood)	Prioritized causal genes for depression	Enables cross-tissue biomarker discovery	[81]
	Single-nucleus ATAC-seq	Mapped chromatin accessibility in MDD-relevant cell types	Identifies regulatory variants in excitatory neurons	[82]
	Bulk and single-nucleus transcriptomics	Convergent synaptic dysregulation in excitatory neurons	Highlights shared molecular pathology across cohorts	[83]
	Cross-disorder systems biology (MDD/PTSD)	Shared and distinct molecular signatures across brain regions	Suggests transdiagnostic mechanisms	[84]
	Two-sample Mendelian randomization	IL-6 and plasma proteins causally linked to MDD	Validates immune-inflammatory pathway as causal	[78,79]
Digital phenotyping and AI	Graph neural networks on fMRI	Detected functional connectivity features of MDD	Offers data-driven neuroimaging biomarkers	[77]
	Survey of ML/DL in psychiatry	Reviewed AI applications in depression detection/treatment	Maps current landscape of computational psychiatry	[50]
	Smartphone/wearable digital phenotyping	Demonstrated feasibility of passive mood monitoring	Enables real-time symptom tracking	[50,85]
	Wearable sensors + ML modeling	Predicted depression severity from behavioral data	Supports scalable screening tools	[86,87]
	Retrospective mHealth analysis	Highlighted challenges in data quality/prediction	Calls for standardized digital biomarker validation	[88]
Novel therapeutics	Preclinical/clinical review	Ketamine may benefit TRD in Alzheimer's/elderly	Expands ketamine's applicability beyond typical TRD	[89]
	fMRI + glutamate spectroscopy	Linked S-ketamine's acute network effects to delayed glutamate changes	Clarifies mechanism of rapid-acting antidepressants	[90]
	KOR antagonist (anticipant) in UCMS mice	Reversed stress-induced depressive behaviors	Supports kappa opioid system as drug target	[91]
Precision psychiatry and EHR	EHR-based stratification	Showed EHR can enable patient subtyping and treatment prediction	Bridges real-world data to precision care	[92,93]
	Pharmacogenomics + CDS in EHR	Implemented PGx-guided prescribing with clinical impact	Proves feasibility of genomic medicine in psychiatry	[94–96]
Patient-centered care and equity	Decision aids for depression/TRD	Improved shared decision-making in RCTs	Enhances patient autonomy in complex treatment choices	[97,98]
	Conceptual framework	Argues for 'person-centered' over purely biological precision psychiatry	Calls for integrating lived experience	[99]
	Health equity frameworks	Highlight disparities in genomic/ digital mental health access	Urges inclusive design and intersectional research	[100–102]
Detection and prediction	DNA methylation risk scores (MRS)	MRS significantly discriminated MDD cases from controls	Enhancing MDD prediction from PRS and environmental traits	[103]
	Examine surrogate measures of insulin resistance	Three measures positively predicted incident MDD in a 9-year follow-up period	Useful for evaluating the risk of MDD among patients with metabolic pathology	[104]
	Machine learning to identity multivariate MDD biomarkers	Mean accuracies for diagnostic classification ranged between 48.1% and 62.0%	Improved predictive capability compared with univariate neuroimaging markers	[105]
	Volatile organic compounds (VOCs) from breath	76.8% accuracy to distinguish MDD patients from healthy controls	Promising for use of biomarkers in gas samples of human breath as a diagnostic measure	[106]

Digital phenotyping enables dynamic subtyping

Conventional subtyping provides a static profile and may miss fluctuations in symptoms and biology over time[88]. Digital phenotyping supports more dynamic stratification by enabling longitudinal, real-world measurement[85,107]. Smartphones and wearables can capture speech features, activity patterns, sleep metrics, and social interaction frequency, generating behavioral signatures that may change with treatment[86–88]. Someone with anhedonia-predominant depression might show sharply reduced activity and flatter speech, while an anxious patient could have fragmented sleep and low heart rate variability. Time-series models can flag these patterns as they emerge[55,107,108]. In the EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care) study, combining baseline fMRI with eight weeks of digital behavioral tracking yielded a dynamic prediction model that beat static baseline only models for forecasting long-term remission[109,110].

Challenges and future directions

Despite its promise, mechanism-based stratification faces challenges[111]. First, reproducibility across cohorts has been spotty, as many biotypes work well in specific populations or with one data type but do not generalize[56,111]. The next is about feasibility: multi-omics is expensive and slow, hardly practical for primary care[112]. Regulatory and ethical guardrails for AI-derived subtypes remain underdeveloped, including questions of validation, accountability, and clinical responsibility[113]. These issues require urgent attention[54]. A further layer of complexity arises from the frequent overlap and co-occurrence of multiple biotypes within the same individual. For example, a patient may simultaneously exhibit elevated inflammatory markers, disrupted prefrontal-amygdala connectivity, and reduced BDNF signaling. Such multimodal pathophysiology is not merely additive as it can create emergent interactions that confound treatment selection. Should clinicians prioritize anti-inflammatory agents, neuromodulation, or plasticity-enhancing drugs first? The lack of evidence on how to sequence or combine

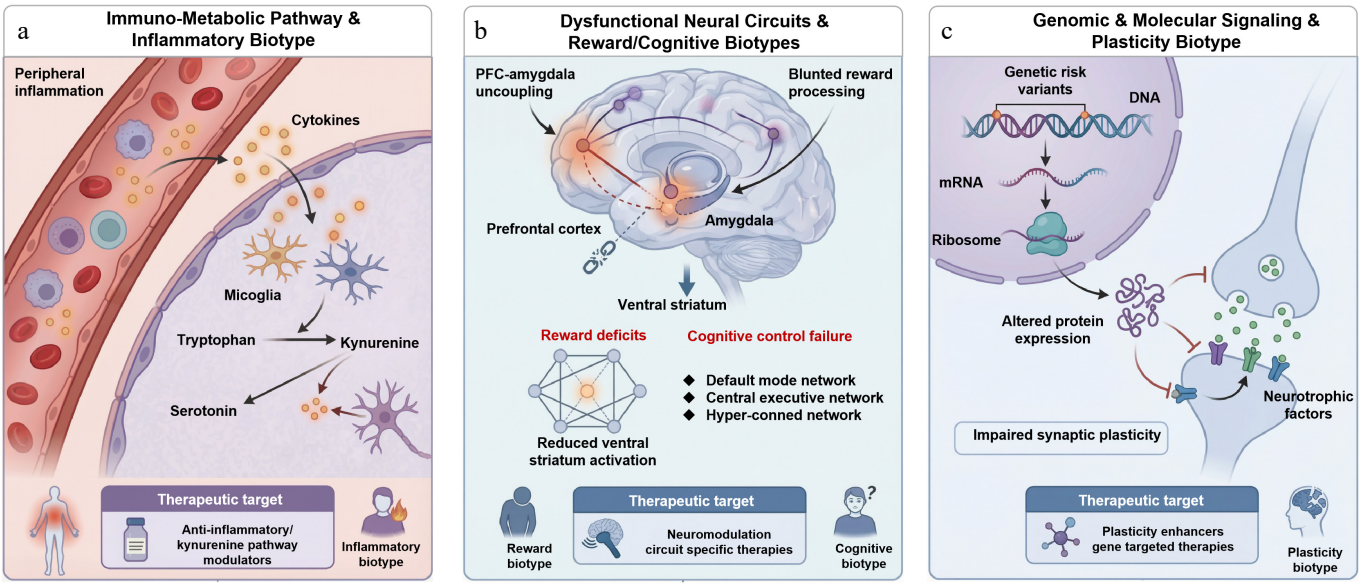

Fig. 1 Integrated biological biotypes of depression and their underlying mechanistic pathways. (a) Immuno-metabolic/inflammatory biotype, where peripheral inflammation drives microglial activation, and shifts tryptophan metabolism toward neurotoxic kynurenine metabolites, reducing serotonin; (b) neural circuit/reward-cognitive biotype, characterized by disrupted prefrontal amygdala connectivity, blunted ventral striatum response, and impaired default mode executive network interactions; and (c) genomic/plasticity biotype, marked by genetic risk variants that impair neurotrophic signaling and synaptic plasticity. Each biotype maps to specific therapeutic strategies, anti-inflammatory/kynurenine modulators, circuit targeted neuromodulation, and plasticity enhancing agents, respectively, illustrating a mechanism-based framework for precision treatment in depression.

mechanism-targeted therapies in patients with mixed biotypes remains a major barrier to clinical implementation[62,114].

The path forward probably involves closed-loop precision care platforms. Imagine starting with baseline multi-omics, neuroimaging, and digital phenotyping to create a detailed biopsychosocial snapshot for each patient; using that profile to select targeted interventions such as anti-inflammatories, neuromodulation, probiotics, and cognitive training, then continuously adjusting based on real-time monitoring and feedback[49,115]. Early pilots are encouraging. For example, machine learning models have shown potential for predicting antidepressant response with impressive accuracy[116]. Making this scalable will require simpler biomarker approaches, like dried blood spots for CRP or salivary cortisol, and equity-minded design to ensure algorithms perform well across diverse populations, not just the groups they were trained on[117,118].

Precision drug discovery in depression

For three decades, antidepressant development has seen high failure rates and limited innovation[119]. Most new drugs amount to tweaks of existing monoaminergic compounds, and fewer than 10% succeed in clinical translation[25,120]. Contributing factors include simplified disease models and heavy reliance on animal experiments that do not really mirror human biology[121]. As the biological heterogeneity of MDD has become clearer, drug development has begun to shift towards approaches grounded in human genetics and mechanism-defined subgroups[122]. This transformation is reflected in three main trends: choosing targets validated by genetic data, designing therapies matched to the underlying biology, and running adaptive trials enriched with biomarker-defined patient subgroups[49,123].

Anchoring drug discovery in human biology

Traditional drug target selection leaned heavily on animal behavioral assays such as the forced swim test, which do not capture the cognitive and emotional complexity of human depression, so candidate drugs kept failing in human trials[83,124]. The newer strategy starts with large-scale human genetic data. Genome wide association studies have turned up hundreds of loci linked to MDD risk, pointing to pathways involved in synaptic plasticity (BDNF, DLG2), glutamate signaling (GRM7, GRIA3), immune function (IL6R, CRP), and stress reactivity[82,84] (Fig. 2). More crucially, Mendelian randomization can further test whether these targets are causally related to MDD rather than correlated, helping prioritize targets with stronger mechanistic support[125].

Studies have shown that elevated IL-6 signaling genuinely raises MDD risk[31,126], motivating efforts to repurpose anti-inflammatory drugs for certain patients[126]. A randomized trial reported that tocilizumab (an IL-6 receptor blocker) significantly eased anhedonia and fatigue in MDD patients with baseline CRP above 3 mg·L^{-1}, with minimal effects in the low inflammation group[126]. Another example is SLC6A15, a neuronal amino acid transporter associated with stress vulnerability and a smaller prefrontal cortex volume, making it an attractive target for neuroprotective drugs[127]. Overall, anchoring target selection in human causal genetics can improve the likelihood that experimental treatments address disease-relevant mechanisms[81].

From one-size-fits-all to mechanism-tailored therapeutics

The second pillar of precision drug development is biology-matched agents. Therapeutics designed, not for all patients with MDD, but for specific pathophysiological subtypes[122]. Glutamatergic modulators represent one mechanistic leap forward. Esketamine (S-ketamine), an NMDA receptor antagonist, has been approved by the FDA for treatment-resistant depression and works within hours rather than weeks like SSRIs[89]. It seems especially effective in patients with abnormal prefrontal glutamate/glutamine ratios or hyperconnectivity in the default mode network[90]. Similarly, kappa-opioid receptor (KOR) antagonists like CERC-501 are now in Phase II

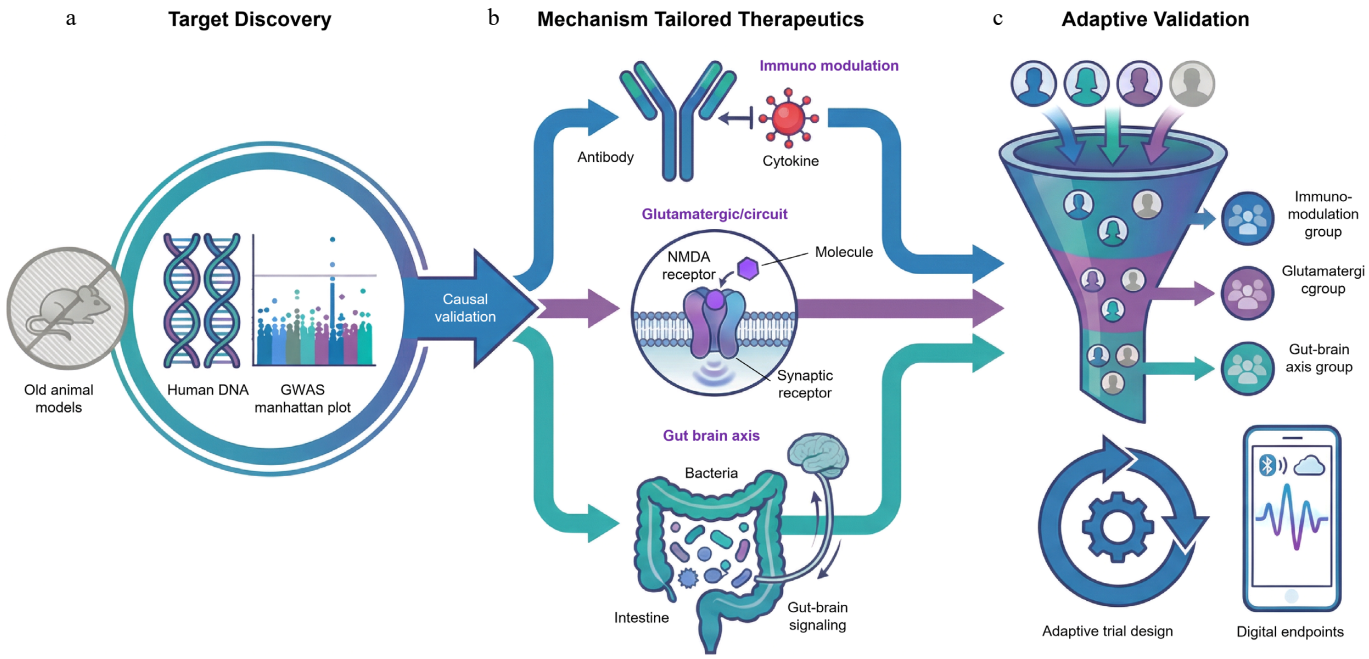

Fig. 2 The paradigm shifts toward precision drug development in depression. This framework illustrates the transition from empirical screening to a mechanism based approach across three stages: (a) human-anchored discovery, where large scale genomics (GWAS) and Mendelian randomization replace traditional animal models to identify causally valid targets; (b) mechanism tailored therapeutics, developing specific agents for distinct biotypes, such as anti-inflammatory biologics, rapid acting glutamatergic modulators, and microbiome interventions; and (c) next-generation evidence generation, utilizing biomarker enriched adaptive platform trials and digital endpoints to efficiently validate efficacy in specific patient subgroups.

trials targeting patients with high stress reactivity or severe anhedonia, trying to prevent stress induced dopamine suppression[91].

Moreover, gut-brain axis targeted therapies are becomming fertile ground. Since gut microbiota dysbiosis and disrupted tryptophan metabolism appear central to certain MDD subtypes, researchers are testing targeted interventions, such as defined probiotic mixes, postbiotics, and even fecal microbiota transplantation as an add-on therapy[128]. A preliminary trial report shows improvements in gut microbial diversity and plasma kynurenine to tryptophan ratios alongside symptom reduction in selected patients[129,130]. Such examples demonstrate that future antidepressants will not be blunt instruments trying to lift the mood across the board, they'll be precise tools aimed at particular circuits or molecular pathways gone awry[131].

Redefining evidence generation

Even with a well-validated target and a biologically tailored drug, traditional trial designs with their broad inclusion criteria and rigid protocols will still wash out efficacy signals under a flood of patient heterogeneity. Thus, precision drug development requires precision trial designs to match[132,133].

Biomarker-enriched enrollment is one solution that only brings in patients who share the relevant underlying pathology[133]. For example, trials targeting p11-mediated signaling have used baseline p11 expression to enrich samples and improve response rates[133]. Similarly, the EMBARC platform uses fMRI connectivity patterns to identify a prefrontal amygdala decoupling subtype, which sharply improved their ability to predict who would respond to SSRIs[134].

Adaptive platform trials push this further. Instead of testing one drug at a time, these protocols run multiple investigational agents simultaneously under a shared framework, adjusting allocation ratios, doses, or target populations on the fly, based on accumulating data[135]. The EU-PEARL initiative used a Bayesian adaptive design to evaluate three mechanistically different agents in treatment-resistant depression all at once, dropping ineffective arms in real time and fast tracking promising ones into Phase III[135]. It is more efficient and arguably more ethical, since fewer patients end up on ineffective treatments.

Digital biomarkers are also being explored as trial endpoints. With the help of smartphones and wearable devices, passive collected behavioral data such as voice features, typing rhythms, and activity patterns can continuously and objectively reflect disease states and treatment responses in real-life environments[136,137]. In some studies, improvements in digital activity patterns occurred earlier than improvements in traditional scales (such as HAMD) scores, suggesting that these indicators may serve as early signals of treatment response[136]. In terms of regulation, regulatory agencies such as the FDA is accelerating the layout of digital health technologies, proposing frameworks and guidelines to explain how digital indicators can be used as biomarkers or clinical outcome indicators under a clear context of use. It is required to pass the technical and clinical validation as fit for purpose[138]. The key difficulties include: variations brought about by different devices and algorithm versions, data loss, and compliance issues in real environments, bias and generalizability of algorithms in different populations, and the need to prove that these digital indicators can correspond to existing endpoints (such as HAMD/PHQ 9) in terms of reliability, sensitivity to change, and clinical significance[137,139]. Therefore, at present, most regulatory authorities position digital endpoints as exploratory or secondary/supporting evidence. Only after strict pre-setting, standardization in advance, and continuous performance monitoring and full validation can they be accepted as registered primary endpoints[138,140].

Challenges and the path forward

Precision drug development for depression shows real promise, but faces persistent challenges. Multi-omics biomarker profiling

remains expensive, regulatory frameworks have lagged in addressing complex interventions such as AI-guided drug combinations, and standardized tools for diagnosing biotypes are limited[54]. Getting past these hurdles will require: (1) building cheaper, scalable biomarker platforms, such as multiplexed protein assays from dried blood spots; (2) creating richly phenotyped, multi-institution biobanks where data and samples can actually be shared; and (3) pushing regulatory science forward so there are faster approval routes for mechanism-based therapies.

Implementing precision treatments in depression

Mechanism-based patient stratification, targeted drug development, and multimodal biomarker research have built a solid scientific base for precision treatment of depression, but implementation in routine care remains difficult[141]. Effective translation requires an ecosystem that is scalable, sustainable, patient-centered, and equitably accessible[54,142]. Key components include robust and interpretable predictive models, closed-loop care systems that support longitudinal adaptation (Fig. 3), technology that integrates seamlessly into existing clinical workflows, and a sustained commitment to equity in access and performance[49].

From research algorithms to clinically actionable predictive models

Plenty of machine learning models for predicting depression outcomes perform well in research settings, but hardly any have made it into routine use[143]. The usual culprits are insufficient external validation, distrust of black-box algorithms, expensive data collection, and a poor fit with existing electronic health record (EHR) systems[50,66,143]. To be clinically useful, models must be accurate, actionable, and usable in real time[144].

Some recent initiatives have moved toward this goal. The EMBARC consortium built a multimodal algorithm combining resting state fMRI, EEG, and blood inflammatory markers to predict SSRI response eight weeks out[66,109]. It hit an AUC of 0.78 and used circuit-level visualization to improve interpretability. The STARD*IT platform took a different route, pulling from real-world EHR data and pharmacogenomic profiles (CYP2D6/CYP2C19 metabolic types, for example) to create a decision support tool for choosing antidepressants, and in a prospective pilot, it increased initial remission rates by 22%[25,145].

However, deploying these models brings regulatory and ethical headaches. The FDA-issued AI/Machine Learning Software as a Medical Device (SaMD) Action Plan now requires algorithms to be transparent, robust, and capable of continuous learning[146,147]. Ideally, future prediction tools should work as clinical decision support systems embedded right in the EHR, presenting concise recommendations and clearly indicating the data elements supporting each output (e.g., whether an inflammatory profile supports consideration of anti-inflammatory strategies or referral to a precision pathway)[148,149].

Toward closed-loop, dynamic precision care

Depression is dynamic: symptoms fluctuate, biological states shift, and treatment responses change over time[49]. Therefore, precision treatment can not rely on a single baseline subtype assignment. Closed-loop care integrates continuous monitoring, real-time analysis, and adaptive intervention strategies[49,150].

Digital phenotyping gives us the tools to do this. Smartphones can passively track things like voice tone, typing speed, and how often someone interacts with others, while wearables capture heart rate variability, sleep structure, and activity levels[151,152]. These metrics become behavioral biomarkers that objectively reflect emotional changes. For example, one study in treatment-resistant depression found that drops in voice fundamental frequency showed up as much as five days before HAMD scores worsened, essentially an early warning system for relapse[49,153]. AI agents can act on these signals automatically as nudging someone toward mindfulness exercises, tweaking light therapy intensity, or alerting the clinical team to step up follow-up[153].

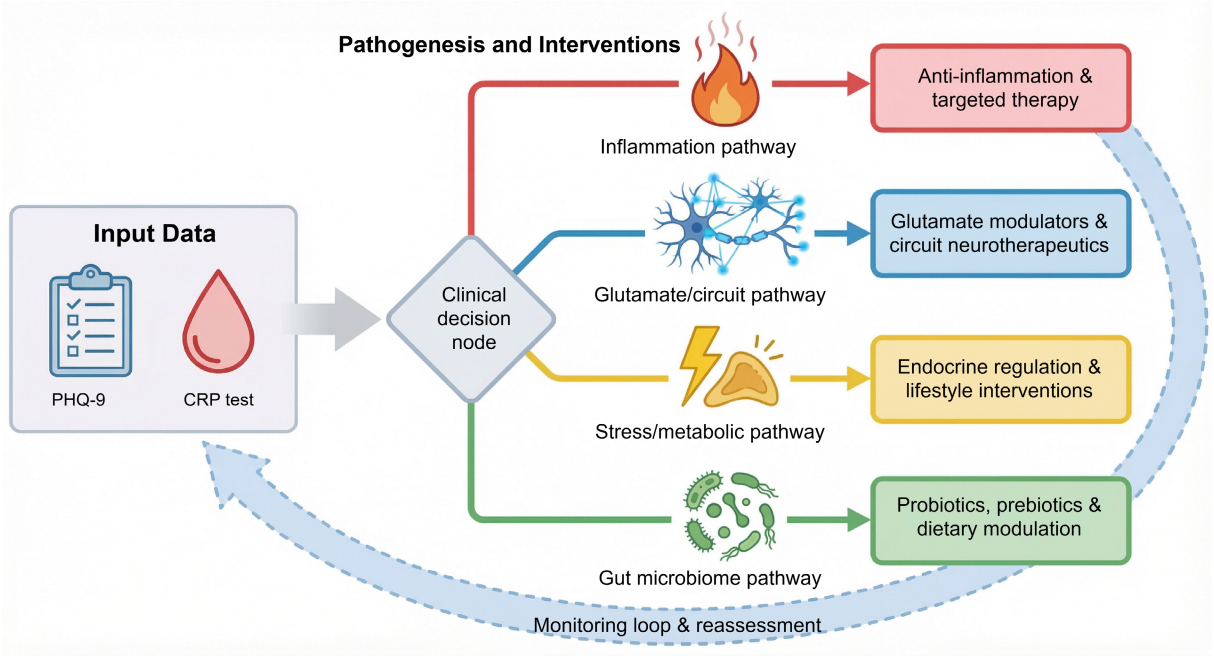

Fig. 3 Mechanism-based clinical decision framework for precision treatment in depression.

Importantly, the accuracy of assessment should not rely solely on biological or digital signals. Patient-reported outcomes (PROs) and quality of life (QoL) indicators can directly reflect symptoms, functions, health status, and treatment burden, which are often overlooked by doctors' ratings or sensor data[154]. PROs are widely regarded as the gold standard for assessing subjective symptoms and health-related quality of life, complementing traditional clinical endpoints such as survival rate or biomarker changes[155,156]. Embedding short, validated PRO/QoL tools (such as PHQ-9 for depressive symptoms, as well as functional and quality of life scales) into electronic or closed-loop monitoring systems has been proven feasible and readily accepted, which helps improve symptom monitoring, doctor-patient communication, and timely treatment adjustments[157]. Integrating this data into electronic health records through digital health technologies and feeding them back to patients and doctors can support collaborative decision-making and patient value-oriented healthcare, ensuring that technological progress truly enhances the quality of patients' daily lives, rather than merely optimizing a single biological or digital metric[154,158].

The next logical step involves closed-loop systems that may combine physiological markers, behavioral patterns, and treatment response data to refine mechanistic profiling over time. For instance, co-occurring signals such as more frequent nighttime awakenings, elevated cortisol levels and decreased social media engagement may support an HPA-axis hyperactivity profile with social withdrawal tendencies. It can then recommend a targeted approach combining cognitive behavioral therapy with a melatonin receptor agonist[159,160]. What's particularly interesting is that if physical activity levels do not show an improvement after a couple of weeks of this treatment, the system can flag this and suggest moving to TMS while arranging follow-up neuroimaging to better understand what is happening[55]. Such adaptive pathways represent a shift away from fixed, one-size-fits-all treatment protocols toward interactive, data-informed care[150,159].

Seamless integration into clinical workflows

Even the most sophisticated technology will get shelved if it does not align with the realities of clinical practise. Frontline psychiatrists typically juggle 15 to 20 patients a day, with limited time per visit, which constrains tolerance for complex interfaces or lengthy reports[161]. Therefore, precision tools should minimize clinician burden while providing clear value[93]. Smart defaults turn out to be crucial. The Mayo Clinic, for example, built pharmacogenomic test results straight into the EHR prescribing interface. When a clinician pulls up venlafaxine, the system automatically shows the patient's CYP2D6 metabolizer status as ultrarapid, normal, or poor, and flags the recommended dosing range[94,95]. That simple design drove a notable uptick in genotype-guided prescribing[49,96]. At the VA Health System, predictive models use baseline PHQ-9 scores, EHR data, and patient self-reports to estimate the probability of response to antidepressant medication, psychotherapy, or both, with the aim of eventually supporting shared decision-making in everyday practice[162,163].

In addition, natural language processing (NLP) may further reduce the burden by extracting information from unstructured clinical notes, cutting down on manual data entry. A system might automatically spot phrases like diurnal mood variation (worse in the morning), appetite loss, or suicidal ideation, then map them onto DSM-5 criteria or research biotypes[92]. For scale-up, a consistent principle is to automate data processing in the background while keeping point-of-care outputs simple, transparent, and actionable[92].

Centering health equity in precision implementation

The most concerning risk is that precision psychiatry could widen existing health disparities instead of narrowing them. Current multi-omics databases are heavily skewed toward specific demographic groups, with underrepresentation of racial and ethnic minorities, low-income communities, rural populations, and older adults[54,99]. Predictably, algorithms trained on these lopsided datasets often perform worse and can even introduce harmful biases in marginalized groups.

Avoiding this requires deliberate inclusive design from the start. That means enrolling diverse cohorts across race, ethnicity, and socioeconomic status when building models to enhance data representativeness. It also requires affordable alternatives (e.g., dried blood spot CRP tests, salivary cortisol) to prevent biomarker access from becoming a financial barrier. Digital inclusion matters too: phone follow-ups, text-based interventions, and support from community health workers can all reach people with limited smartphone access or digital literacy. Digital platforms need to be culturally tailored, such as language, visual design and context, so they make sense to the communities using them[99,101,102].

As emphasized by the WHO in 2023, precision medicine should support improved care at the population level rather than concentrating benefits among a small subset of patients. If precision psychiatry does not put health equity at the center of its implementation strategy, it will not live up to its promise of meaningfully reducing the global burden of mental illness[99,142].

Future perspectives and research priorities

Precision diagnosis and treatment of depression have made real headway, but turning mechanistic insights into standard clinical practice demands a coordinated push across technology, collaboration, and implementation[50]. Over the next decade, research should be aiming for the breakthrough integration of emerging tools, building institutionalized ecosystems for cross-disciplinary work, and creating concrete roadmaps for clinical translation (Fig. 4). These efforts are all directed toward accelerating the generation and equitable rollout of high-impact innovations[164,165].

Emerging technological frontiers

Next-generation technology platforms will further sharpen our ability to untangle depression's complexity[166]. Single cell multi-omics can map transcriptomic, epigenomic, and proteomic variation within specific brain regions such as the prefrontal cortex and amygdala, across neurons, glia, and immune cells, revealing disease linked cellular subtypes and their regulatory circuits[18,49]. Paired with human induced pluripotent stem cells (iPSCs), researchers can grow patient-specific brain organoids or organ-on-chip models that mimic functional disruptions at key interfaces like the gut-brain axis or blood-brain barrier, streamlining drug screening and toxicity testing[167].

In drug development, generative AI is reshaping molecular design. By learning structure activity patterns from existing antidepressants, these systems can propose entirely new molecular scaffolds with better pharmacokinetics and target selectivity, and predict how they will perform in particular biological subtypes[168]. Meanwhile, *in silico* clinical trials use digital twin technology to simulate treatment responses in thousands of virtual patients, cutting development timelines and reducing late-stage failure risk[50,169].

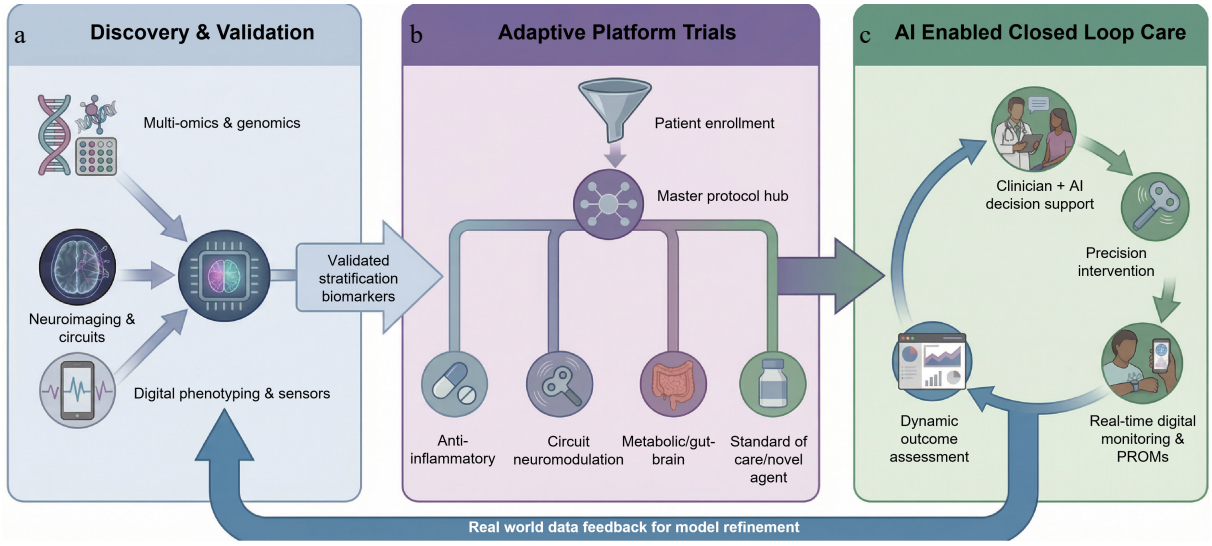

Fig. 4 An integrated roadmap for a precision psychiatry ecosystem. This framework illustrates the translational pathway from; (a) discovery and validation, where multi-omics and digital data inform AI-driven biotype identification; to (b) adaptive platform trials, utilizing master protocols to dynamically assign patients to mechanism-based treatments; and finally to (c) AI enabled closed loop care, where real-world clinical outcomes continuously refine predictive models, creating a learning health system that bridges research and clinical practice.

For interventions, precision neuromodulation is moving toward closed-loop systems. Next-generation brain-computer interface (BCI) platforms decode mood-related neural activity in real time, such as theta oscillations in the anterior cingulate, and automatically fire TMS or deep brain stimulation (DBS) pulses when pathological states are detected, delivering intervention exactly when needed[166]. This kind of technology looks especially promising as a mechanism-matched, non-drug option for treatment-resistant symptoms like anhedonia or cognitive rigidity[166].

Interdisciplinary collaboration frameworks

A technological breakthrough alone is insufficient without the right collaborative infrastructure. A major priority is building deeply phenotyped, comprehensive depression biobanks that pull together genomic data, multi-omics profiles, neuroimaging, digital behavioral metrics, environmental exposures, and longitudinal follow-up, all while making sure the populations represented are diverse enough to prevent algorithmic bias[54,170]. These resources need to be shared openly through data ecosystems that follow FAIR principles (findable, accessible, interoperable, reusable) to enable independent validation and global collaboration[171].

Furthermore, sustained partnerships across industry, academia, and clinical care are also essential. Pharmaceutical companies bring compound libraries and trial networks, academic institutions contribute mechanistic understanding and methodological innovation, clinical centers make sure patients are engaged and findings hold up in the real world[172]. Initiatives like PsychENCODE and the EU-AIMS consortium show this kind of partnership can really speed up the journey from biomarker discovery to validation[1]. Looking ahead, patient advocacy groups and policymakers should also be incorporated to ensure that research priorities reflect patient needs and implementation constraints[173].

Clinical translation roadmap

To prevent innovations from remaining confined to academic journals, a translational roadmap is needed. While any timeline is inherently speculative, the following scenario-based projections outline what could be achievable under favorable conditions of continued research investment, regulatory innovation, and healthcare system adaptation. Short-term horizon (1–3 years), assuming successful completion of ongoing validation studies, could see the prospective validation of three to five mechanism-based depression subtypes, with selected biomarkers incorporated into clinical guidelines. Concurrently, if regulatory science keeps pace, we might witness the first FDA-authorization of an AI-powered clinical decision support tool classified as a medical device (SaMD) for depression treatment selection.

Medium-term targets (3–7 years) are predicated on broader health system adoption and infrastructure development. Should multimodal stratification platforms demonstrate cost-effectiveness in diverse healthcare settings, they could begin roll out across major health systems. Adaptive platform trials, assuming regulatory and payer alignment, might become a standard route for new drug approvals in depression. Digital phenotyping metrics could gain formal acceptance as regulatory endpoints if ongoing validation studies confirm their reliability and clinical utility.

The long-term vision (7–10 years) rests on the cumulative realization of these earlier milestones. If the preceding conditions are met, we could envision a future where every newly diagnosed MDD patient walks out of their initial assessment with an individualized biopsychosocial profile that guides first-line treatment selection.

None of this happens without fundamental policy shifts and strategic funding. Regulatory agencies would need to establish approval pathways designed for complex interventions, such as AI paired with medications and behavioral therapies. Insurers have to move toward value-based reimbursement that rewards precision matching, not just volume. Governments and foundations should funnel resources into high-risk, high-reward interdisciplinary work, especially implementation research focused on closing equity gaps. The timeline presented here is therefore contingent on these parallel developments occurring in synchrony.

Conclusions

The clinical management of MDD stands at a historic inflection point. For decades, symptom-based diagnosis and

monoamine-focused treatments have provided a framework to work with, but they have been hobbled by a blind spot, the biological heterogeneity underlying depression. The result has been stubbornly high prevalence, disappointing remission rates, and frequent relapses[174]. This review systematically lays out why and how we need to shift toward precision psychiatry. The core pieces include weaving together multi-omics, neuroimaging, immunometabolic data, digital phenotyping, and environmental exposures to carve out biologically coherent subtypes with shared disease mechanisms; designing therapeutics matched to those mechanisms, built on genetically validated targets; speeding up translation through biomarker-enriched and adaptive trial designs, and deploying closed-loop care systems embedded in clinical workflows that allow for dynamic, individualized treatment adjustments[122].

However, technological sophistication does not automatically translate into clinical benefit. Without an explicit focus on health equity, precision approaches could exacerbate disparities. Moving forward, inclusivity, accessibility, and cultural fit need to be baked in from the start, algorithms have to perform reliably across diverse populations, biomarker testing needs to be affordable and widely available, and digital tools have to actually reach the marginalized groups.

Ultimately, precision psychiatry should aim to improve the speed, safety, and effectiveness of depression care for all patients. This is both a scientific shift and an ethical obligation. Only by braiding together mechanistic depth, intelligent data analysis, and genuine human compassion can we find our way out of the fog surrounding MDD diagnosis and treatment for so long, and step into an era that is truly patient centered, evidence based, and grounded in equity.

Ethical statements

Not applicable.

Author contributions

The authors confirm their contributions to the work as follows: draft manuscript preparation: Wang M, Jiang Y, Wu C; performing the graphmapping: Liao J; data collection and manuscript revision: Zhou B, Yuan Y, Sun J. All authors reviewed the results and approved the final version of the manuscript.

Data availability

Data sharing is not applicable to this review as no datasets were generated or analyzed.

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Conflict of interest

The authors declare no competing financial interest.

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References

[1] Corrivetti G, Monaco F, Vignapiano A, Marenna A, Panarello E, et al. 2025. Precision medicine for depression: improving treatment response and remission. *Asian Journal of Psychiatry* 110:104585

[2] Bottaccioli AG, Bologna M, Bottaccioli F. 2025. Rethinking depression—beyond neurotransmitters: an integrated psychoneuroendocrineimmunology framework for depression's pathophysiology and tailored treatment. *International Journal of Molecular Sciences* 26:2759

[3] Guidi J, Fava GA. 2025. The clinical inadequacy of the concept of treatment-resistant depression: innovative strategies in assessment and psychotherapeutic management. *Clinical Psychology Review* 120:102616

[4] Njenga C, Ramanuj PP, de Magalhães FJC, Pincus HA. 2024. New and emerging treatments for major depressive disorder. *BMJ* 386:e073823

[5] Rush AJ, Sackeim HA, Conway CR, Bunker MT, Hollon SD, et al. 2022. Clinical research challenges posed by difficult-to-treat depression. *Psychological Medicine* 52:419–432

[6] Cui L, Li S, Wang S, Wu X, Liu Y, et al. 2024. Major depressive disorder: hypothesis, mechanism, prevention and treatment. *Signal Transduction and Targeted Therapy* 9:30

[7] Walter HJ, Abright AR, Bukstein OG, Diamond J, Keable H, et al. 2023. Clinical practice guideline for the assessment and treatment of children and adolescents with major and persistent depressive disorders. *Journal of the American Academy of Child & Adolescent Psychiatry* 62:479–502

[8] Akil H, Gordon J, Hen R, Javitch J, Mayberg H, et al. 2018. Treatment resistant depression: a multi-scale, systems biology approach. *Neuroscience & Biobehavioral Reviews* 84:272–288

[9] Maes M. 2022. Precision nomothetic medicine in depression research: a new depression model, and new endophenotype classes and pathway phenotypes, and a digital self. *Journal of Personalized Medicine* 12:403

[10] Sofocleous A. 2025. Major depressive disorder: from accurate diagnosis to effective treatment. *Journal of Humanistic Psychology* 2025:00221678251385600

[11] Patten SB. 2023. Problematic features of episode-based definitions of depression and a preliminary proposal for their replacement. *Frontiers in Psychiatry* 14:1121524

[12] Thakur S, Tadwalkar S. 2021. Comparative epidemiology analysis of major depressive disorder with DSM-5 and DSM-IV criteria in high-income countries. *International Journal of Epidemiology* 50:dyab168.657

[13] Nussbaum AM. 2020. Questionable agreement: the experience of depression and DSM-5 major depressive disorder criteria. *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine* 45:623–643

[14] Athira KV, Bandopadhyay S, Samudrala PK, Naidu VGM, Lahkar M, et al. 2020. An overview of the heterogeneity of major depressive disorder: current knowledge and future prospective. *Current Neuropharmacology* 18:168–187

[15] Zhu H, Tong X, Carlisle NB, Xie H, Keller CJ, et al. 2024. Contrastive functional connectivity defines neurophysiology-informed symptom dimensions in major depression. *Cell Reports Medicine* 6:102151

[16] Comai S, Manchia M, Bosia M, Miola A, Poletti S, et al. 2025. Moving toward precision and personalized treatment strategies in psychiatry. *International Journal of Neuropsychopharmacology* 28:pyaf025

[17] Wang X, Su Y, Liu Q, Li M, Zeighami Y, et al. 2025. Unveiling diverse clinical symptom patterns and neural activity profiles in major depressive disorder subtypes. *eBioMedicine* 116:105756

[18] Yao S, Harder A, Darki F, Chang YW, Li A, et al. 2025. Connecting genomic results for psychiatric disorders to human brain cell types and regions reveals convergence with functional connectivity. *Nature Communications* 16:395

[19] Young JJ, Silber T, Bruno D, Galatzer-Levy IR, Pomara N, et al. 2016. Is there progress? An overview of selecting biomarker candidates for major depressive disorder. *Frontiers in Psychiatry* 7:72

[20] Nobis A, Zalewski D, Waszkiewicz N. 2020. Peripheral markers of depression. *Journal of Clinical Medicine* 9:3793

[21] Dadkhah M, Jafarzadehgharehziaaddin M, Molaei S, Akbari M, Gholizadeh N, et al. 2023. Major depressive disorder: biomarkers and biosensors. *Clinica Chimica Acta* 547:117437

[22] Mähler R, Reichenbach A. 2025. Beyond the label "major depressive disorder" —detailed characterization of study population matters for EEG-biomarker research. *Frontiers in Neuroscience* 19:1595221

[23] Boku S, Nakagawa S, Toda H, Hishimoto A. 2018. Neural basis of major depressive disorder: beyond monoamine hypothesis. *Psychiatry and Clinical Neurosciences* 72:3–12

[24] Liu B, Liu J, Wang M, Zhang Y, Li L. 2017. From serotonin to neuroplasticity: evolvement of theories for major depressive disorder. *Frontiers in Cellular Neuroscience* 11:305

[25] Singh MK, Thase ME. 2025. Current progress in targeted pharmacotherapy to treat symptoms of major depressive disorder: moving from broad-spectrum treatments to precision psychiatry. *CNS Spectrums* 30:e16

[26] Jiang Y, Zou D, Li Y, Gu S, Dong J, et al. 2022. Monoamine neurotransmitters control basic emotions and affect major depressive disorders. *Pharmaceuticals* 15:1203

[27] Perez-Caballero L, Torres-Sanchez S, Romero-López-Alberca C, González-Saiz F, Mico JA, et al. 2019. Monoaminergic system and depression. *Cell and Tissue Research* 377:107–113

[28] Dale E, Bang-Andersen B, Sánchez C. 2015. Emerging mechanisms and treatments for depression beyond SSRIs and SNRIs. *Biochemical Pharmacology* 95:81–97

[29] Gao K, Oruc EB, Koparal B. 2025. Pharmacological monotherapy for depressive disorders: current and future—a narrative review. *Medicina* 61:558

[30] Pastis I, Santos MG, Paruchuri A. 2024. Exploring the role of inflammation in major depressive disorder: beyond the monoamine hypothesis. *Frontiers in Behavioral Neuroscience* 17:1282242

[31] Kajumba MM, Kakooza-Mwesige A, Nakasujja N, Koltai D, Canli T. 2024. Treatment-resistant depression: molecular mechanisms and management. *Molecular Biomedicine* 5:43

[32] Nuñez NA, Joseph B, Pahwa M, Kumar R, Resendez MG, et al. 2022. Augmentation strategies for treatment resistant major depression: a systematic review and network meta-analysis. *Journal of Affective Disorders* 302:385–400

[33] Feng Y, Lv Y, Yang J, Xu L, Chen J, et al. 2025. Quantitative evaluation of multiple treatment regimens for treatment-resistant depression. *International Journal of Neuropsychopharmacology* 28:pyaf007

[34] Cookson J, Gilaberte I, Desaiah D, Kajdasz DK. 2006. Treatment benefits of duloxetine in major depressive disorder as assessed by number needed to treat. *International Clinical Psychopharmacology* 21:267–273

[35] Jakobsen JC, Katakam KK, Schou A, Hellmuth SG, Stallknecht SE, et al. 2017. Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. *BMC Psychiatry* 17:58

[36] van Baalen M, van der Velden L, van der Gronde T, Pieters T. 2025. Developing a translational research framework for MDD: combining biomolecular mechanisms with a spiraling risk factor model. *Frontiers in Psychiatry* 15:1463929

[37] Maes M, Almulla AF, You Z, Zhang Y. 2025. Neuroimmune, metabolic and oxidative stress pathways in major depressive disorder. *Nature Reviews Neurology* 21:473–489

[38] Kouba BR, de Araujo Borba L, Borges de Souza P, Gil-Mohapel J, Rodrigues ALS. 2024. Role of inflammatory mechanisms in major depressive disorder: from etiology to potential pharmacological targets. *Cells* 13:423

[39] Kunugi H. 2021. Gut microbiota and pathophysiology of depressive disorder. *Annals of Nutrition and Metabolism* 77:11–20

[40] Varela RB, MacPherson H, Walker AJ, Houghton T, Yates C, et al. 2025. Inflammation and metabolic dysfunction underly anhedonia-like behavior in antidepressant resistant male rats. *Brain, Behavior, and Immunity* 127:170–182

[41] Orsolini L, Pompili S, Valenta ST, Salvi V, Volpe U. 2022. C-reactive protein as a biomarker for major depressive disorder? *International Journal of Molecular Sciences* 23:1616

[42] Mac Giollabhui N, Slaney C, Hemani G, Foley ÉM, van der Most PJ, et al. 2025. Role of inflammation in depressive and anxiety disorders, affect, and cognition: genetic and non-genetic findings in the lifelines cohort study. *Translational Psychiatry* 15:164

[43] Lowe VM, Chaplin M, Sgambato D. 2023. Major depressive disorder and the gut microbiome: what is the link? *General Psychiatry* 36:e100973

[44] Xia X, Li K, Zou W, Wang L. 2025. The central role of microglia in major depressive disorder and its potential as a therapeutic target. *Frontiers in Behavioral Neuroscience* 19:1598178

[45] Foster JA, Baker GB, Dursun SM. 2021. The relationship between the gut microbiome-immune system-brain axis and major depressive disorder. *Frontiers in Neurology* 12:721126

[46] Huckvale K, Venkatesh S, Christensen H. 2019. Toward clinical digital phenotyping: a timely opportunity to consider purpose, quality, and safety. *npj Digital Medicine* 2:88

[47] Sameh A, Rostami M, Oussalah M, Korpelainen R, Farrahi V. 2024. Digital phenotypes and digital biomarkers for health and diseases: a systematic review of machine learning approaches utilizing passive non-invasive signals collected *via* wearable devices and smartphones. *Artificial Intelligence Review* 58:66

[48] Zhang Y, Wang J, Zong H, Singla KR, Ullah A, et al. 2025. The comprehensive clinical benefits of digital phenotyping: from broad adoption to full impact. *npj Digital Medicine* 8:196

[49] Gao QL, Chen X, Castellanos FX, Lu B, Yan CG. 2025. Towards closed-loop precision psychiatry: integrating MRI biomarkers for individualized care of major depressive disorder. *Psychoradiology* 5:kkaf024

[50] Squires M, Tao X, Elangovan S, Gururajan R, Zhou X, et al. 2023. Deep learning and machine learning in psychiatry: a survey of current progress in depression detection, diagnosis and treatment. *Brain Informatics* 10:10

[51] Oudin A, Maatoug R, Bourla A, Ferreri F, Bonnot O, et al. 2023. Digital phenotyping: data-driven psychiatry to redefine mental health. *Journal of Medical Internet Research* 25:e44502

[52] Baumgartner R. 2021. Precision medicine and digital phenotyping: digital medicine's way from more data to better health. *Big Data & Society* 8:20539517211066452

[53] Liu JJ, Borsari B, Li Y, Liu S, Gao Y, et al. 2024. Digital phenotyping from wearables using AI characterizes psychiatric disorders and identifies genetic associations. *medRxiv* 188:515–529

[54] Maj M, Stein DJ, Parker G, Zimmerman M, Fava GA, et al. 2020. The clinical characterization of the adult patient with depression aimed at personalization of management. *World Psychiatry* 19:269–293

[55] Cohen ZD, DeRubeis RJ. 2018. Treatment selection in depression. *Annual Review of Clinical Psychology* 14:209–236

[56] Tang L, Tang R, Zheng J, Zhao P, Zhu R, et al. 2025. Dissecting biological heterogeneity in major depressive disorder based on neuroimaging subtypes with multi-omics data. *Translational Psychiatry* 15:72

[57] Kashiwagi Y, Tokuda T, Takahara Y, Masaki Y, Sakai Y, et al. 2026. Generalizable stratification based on thalamo-somatomotor functional connectivity predicts responses to antidepressants in patients with depression. *Molecular Psychiatry* 31:270–281

[58] Yin L, Lin Y, Qiu J, Xiang Y, Li M, et al. 2025. Integrating brain imaging features and genomic profiles for the subtyping of major depression. *Psychological Medicine* 55:e158

[59] Tang L, Wu L, Dai M, Liu N, Liu L. 2025. Integrative analysis of signaling and metabolic pathways, immune infiltration patterns, and machine learning-based diagnostic model construction in major depressive disorder. *Scientific Reports* 15:13519

[60] Kennis M, Gerritsen L, Van Dalen M, Williams A, Cuijpers P, et al. 2020. Prospective biomarkers of major depressive disorder: a systematic review and meta-analysis. *Molecular Psychiatry* 25:321–338

[61] Rimti FH, Shahbaz R, Bhatt K, Xiang A. 2023. A review of new insights into existing major depressive disorder biomarkers. *Heliyon* 9:e18909

[62] Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, et al. 2017. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nature Medicine* 23:28–38

[63] Lamers F, Milaneschi Y, Vinkers CH, Schoevers RA, Giltay EJ, et al. 2020. Depression profilers and immuno-metabolic dysregulation: Longitudinal results from the NESDA study. *Brain, Behavior, and Immunity* 88:174–183
[64] Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman ATF, et al. 2013. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Molecular Psychiatry* 18:692–699
[65] Paganin W, Signorini S. 2024. Inflammatory biomarkers in depression: scoping review. *BJPsych Open* 10:e165
[66] Jiao Y, Zhao K, Wei X, Carlisle N, Keller C, et al. 2025. Deep graph learning of multimodal brain networks defines treatment-predictive signatures in major depression. *Molecular Psychiatry* 30:3963–3974
[67] Li J, Long Z, Ji GJ, Han S, Chen Y, et al. 2025. Major depressive disorder on a neuromorphic continuum. *Nature Communications* 16:2405
[68] Dunlop K, Grosenick L, Downar J, Vila-Rodriguez F, Gunning FM, et al. 2024. Dimensional and categorical solutions to parsing depression heterogeneity in a large single-site sample. *Biological Psychiatry* 96:422–434
[69] Zhang B, Li Y, Shen Y, Zhao W, Yu Y, Tang J. 2023. Dimensional subtyping of first-episode drug-naïve major depressive disorder: a multisite resting-state fMRI study. *Psychiatry Research* 330:115598
[70] Miller AH. 2025. Advancing an inflammatory subtype of major depression. *The American Journal of Psychiatry* 182:516–524
[71] Woelfer M, Kasties V, Kahlfuss S, Walter M. 2019. The role of depressive subtypes within the neuroinflammation hypothesis of major depressive disorder. *Neuroscience* 403:93–110
[72] Wang Y, Tang S, Zhang L, Bu X, Lu L, et al. 2021. Data-driven clustering differentiates subtypes of major depressive disorder with distinct brain connectivity and symptom features. *The British Journal of Psychiatry* 219:606–613
[73] Mokhtari A, Ibrahim EC, Gloaguen A, Barrot CC, Cohen D, et al. 2025. Using multiomic integration to improve blood biomarkers of major depressive disorder: a case-control study. *eBioMedicine* 113:105569
[74] Li H, Liu Q, Shan Q, Xu H, Wang J, et al. 2025. Identification of mitochondrial-related causal genes for major depression disorder *via* integrating multi-omics. *Journal of Affective Disorders* 382:540–548
[75] Yang J, Zheng P, Li Y, Wu J, Tan X, et al. 2020. Landscapes of bacterial and metabolic signatures and their interaction in major depressive disorders. *Science Advances* 6:eaba8555
[76] Gao K, Mu CL, Farzi A, Zhu WY. 2020. Tryptophan metabolism: a link between the gut microbiota and brain. *Advances in Nutrition* 45:623–643
[77] Zhang Y, Liu X, Tang P, Zhang Z. 2025. AFMDD: analyzing functional connectivity feature of major depressive disorder by graph neural network-based model. *Journal of Computational Biology* 32:156–163
[78] Jia R, Nie M, Wang X, Yang Y. 2026. Immunophenotype-mediated effects of plasma proteins on major depressive disorder: a two-step Mendelian randomization study. *European Archives of Psychiatry and Clinical Neuroscience* 276:379–389
[79] Kelly KM, Smith JA, Mezuk B. 2021. Depression and interleukin-6 signaling: a Mendelian Randomization study. *Brain, Behavior, and Immunity* 95:106–114
[80] Ting EY, Yang AC, Tsai SJ. 2020. Role of interleukin-6 in depressive disorder. *International Journal of Molecular Sciences* 21:2194
[81] Deng YT, Ou YN, Wu BS, Yang YX, Jiang Y, et al. 2022. Identifying causal genes for depression *via* integration of the proteome and transcriptome from brain and blood. *Molecular Psychiatry* 27:2849–2857
[82] Chawla A, Cakmakci D, Fiori LM, Zang W, Maitra M, et al. 2025. Single-nucleus chromatin accessibility profiling identifies cell types and functional variants contributing to major depression. *Nature Genetics* 57:1890–1904
[83] Goes FS, Collado-Torres L, Zandi PP, Huuki-Myers L, Tao R, et al. 2025. Large-scale transcriptomic analyses of major depressive disorder reveal convergent dysregulation of synaptic pathways in excitatory neurons. *Nature Communications* 16:3981
[84] Daskalakis N, Iatrou A, Chatzinakos C, Jajoo A, Snijders C, et al. 2024. Systems biology dissection of PTSD and MDD across brain regions, cell types, and blood. *Science* 384:eadh3707
[85] Camargo A, Tagliaferri SD, D'Alfonso S, Zhang T, Munoz Z, et al. 2025. SmartSense-D: a safety, feasibility, and acceptability pilot study of digital phenotyping in young people with major depressive disorder. *Digital Health* 11:20552076251330509
[86] Rykov Y, Thach TQ, Bojic I, Christopoulos G, Car J. 2021. Digital biomarkers for depression screening with wearable devices: cross-sectional study with machine learning modeling. *JMIR MHealth and UHealth* 9:e24872
[87] Wang R, Wang W, DaSilva A, Huckins JF, Kelley WM, et al. 2018. Tracking depression dynamics in college students using mobile phone and wearable sensing. *Proceedings of the ACM on Interactive, Mobile, Wearable and Ubiquitous Technologies* 2:1–26
[88] Sun S, Folarin AA, Zhang Y, Cummins N, Garcia-Dias R, et al. 2023. Challenges in using mHealth data from smartphones and wearable devices to predict depression symptom severity: retrospective analysis. *Journal of Medical Internet Research* 25:e45233
[89] Mario A, Ivana L, Claudia MM, Antonello B, Francesco P, et al. 2025. Can ketamine therapy overcome treatment-resistant depression in Alzheimer's disease and older adults? Preclinical and clinical evidence. *Biomedicine & Pharmacotherapy* 188:118199
[90] Danyeli LV, Sen ZD, Colic L, Kurzweil L, Gensberger-Reigl S, et al. 2023. Association of the delayed changes in glutamate levels and functional connectivity with the immediate network effects of S-ketamine. *Translational Psychiatry* 13:60
[91] Jacobson ML, Wulf HA, Browne CA, Lucki I. 2020. The kappa opioid receptor antagonist aticaprant reverses behavioral effects from unpredictable chronic mild stress in male mice. *Psychopharmacology* 237:3715–3728
[92] Oliver D, Arribas M, Perry BI, Whiting D, Blackman G, et al. 2024. Using electronic health records to facilitate precision psychiatry. *Biological Psychiatry* 96:532–542
[93] Grzenda A, Widge AS. 2024. Electronic health records and stratified psychiatry: bridge to precision treatment? *Neuropsychopharmacology* 49:285–290
[94] Hicks JK, Dunnenberger HM, Gumpper KF, Haidar CE, Hoffman JM. 2016. Integrating pharmacogenomics into electronic health records with clinical decision support. *American Journal of Health-System Pharmacy* 7323:1967–1976
[95] Wang L, Scherer SE, Bielinski SJ, Muzny DM, Jones LA, et al. 2022. Implementation of preemptive DNA sequence-based pharmacogenomics testing across a large academic medical center: the Mayo-Baylor RIGHT 10K study. *Genetics in Medicine* 24:1062–1072
[96] O'Donnell P, Wadhwa N, Danahey K, Borden B, Lee S, et al. 2017. Pharmacogenomics - based point - of - care clinical decision support significantly alters drug prescribing. *Clinical Pharmacology & Therapeutics* 102:859–869
[97] Perestelo-Perez L, Rivero-Santana A, Sanchez-Afonso JA, Perez - Ramos J, Castellano-Fuentes CL, et al. 2017. Effectiveness of a decision aid for patients with depression: a randomized controlled trial. *Health Expectations* 20:1096–1105
[98] Shillington AC, Langenecker SA, Shelton RC, Foxworth P, Allen L, et al. 2020. Development of a patient decision aid for treatment resistant depression. *Journal of Affective Disorders* 275:299–306
[99] Gómez-Carrillo A, Paquin V, Dumas G, Kirmayer LJ. 2023. Restoring the missing person to personalized medicine and precision psychiatry. *Frontiers in Neuroscience* 17:1041433
[100] Brown JEH, Young JL, Martinez-Martin N. 2022. Psychiatric genomics, mental health equity, and intersectionality: a framework for research and practice. *Frontiers in Psychiatry* 13:1061705
[101] Robinson A, Flom M, Forman-Hoffman VL, Histon T, Levy M, et al. 2024. Equity in digital mental health interventions in the united states: where to next? *Journal of Medical Internet Research* 26:e59939
[102] Stiles-Shields C, Cummings C, Montague E, Plevinsky JM, Psihogios AM, et al. 2022. A call to action: using and extending human-centered design methodologies to improve mental and behavioral health equity. *Frontiers in Digital Health* 4:848052
[103] Barbu MC, Shen X, Walker RM, Howard DM, Evans KL, et al. 2021. Epigenetic prediction of major depressive disorder. *Molecular Psychiatry* 26:5112–5123

[104] Watson KT, Simard JF, Henderson VW, Nutkiewicz L, Lamers F, et al. 2021. Incident major depressive disorder predicted by three measures of insulin resistance: a dutch cohort study. *The American Journal of Psychiatry* 178:914–920

[105] Winter NR, Blanke J, Leenings R, Ernsting J, Fisch L, et al. 2024. A systematic evaluation of machine learning–based biomarkers for major depressive disorder. *JAMA Psychiatry* 81:386–395

[106] Henning D, Lüno M, Jiang C, Meyer-Lotz G, Hoeschen C, et al. 2023. Gut–brain axis volatile organic compounds derived from breath distinguish between schizophrenia and major depressive disorder. *Journal of Psychiatry and Neuroscience* 48:E117–E125

[107] Aledavood T, Luong N, Baryshnikov I, Darst R, Heikkilä R, et al. 2025. Multimodal digital phenotyping study in patients with major depressive episodes and healthy controls (mobile monitoring of mood): observational longitudinal study. *JMIR Mental Health* 12:e63622

[108] Cai Y, Wang H, Ye H, Jin Y, Gao W. 2023. Depression detection on online social network with multivariate time series feature of user depressive symptoms. *Expert Systems with Applications* 217:119538

[109] Poirot MG, Ruhe HG, Mutsaerts HMM, Maximov II, Groote IR, et al. 2024. Treatment response prediction in major depressive disorder using multimodal mri and clinical data: secondary analysis of a randomized clinical trial. *The American Journal of Psychiatry* 181:223–233

[110] Nguyen KP, Fatt CC, Treacher A, Mellema C, Cooper C, et al. 2022. Patterns of pretreatment reward task brain activation predict individual antidepressant response: key results from the EMBARC randomized clinical trial. *Biological Psychiatry* 91:550–560

[111] Hickie IB, Berk M, Scott J, Crouse J, Scott E, et al. 2024. What are the best strategies for stratification of clinical cohorts with depression and other mood disorders? *Research Directions: Depression* 1:e18

[112] Rengasamy M, Moriarity D, Price R. 2025. On the pursuit of reproducibility: the importance of large sample sizes in psychoimmunology. *Translational Psychiatry* 15:29

[113] McCradden M, Hui K, Buchman DZ. 2023. Evidence, ethics and the promise of artificial intelligence in psychiatry. *Journal of Medical Ethics* 49:573–579

[114] Pinzi M, Fagiolini A, Koukouna D, Gualtieri G, Rescalli MB, et al. 2025. Inflammatory and immune biomarkers in mood disorders: from mechanistic pathways to clinical translation. *Cells* 14:1558

[115] Chen ZS, Kulkarni PP, Galatzer-Levy IR, Bigio B, Nasca C, et al. 2022. Modern views of machine learning for precision psychiatry. *Patterns* 3:100602

[116] Kautzky A, Möller HJ, Dold M, Bartova L, Seemüller F, et al. 2021. Combining machine learning algorithms for prediction of antidepressant treatment response. *Acta Psychiatrica Scandinavica* 143:36–49

[117] Li W, Koethe JR, Gabriel CL, Silver HJ, Garrett TJ. 2025. Multiomics analysis of dried plasma spots using stable isotope internal standards for biomarker discovery. *Analytical Chemistry* 97:20724–20733

[118] Hernandes VV, Zeyda M, Wisgrill L, Warth B. 2025. Dried blood spots analysis for targeted and non-targeted exposomics. *Environment International* 205:109814

[119] Hendrie C, Pickles A. 2013. The failure of the antidepressant drug discovery process is systemic. *Journal of Psychopharmacology* 27:407–416

[120] Khan A, Brown WA. 2015. Antidepressants versus placebo in major depression: an overview. *World Psychiatry* 14:294–300

[121] Borbély É, Simon M, Fuchs E, Wiborg O, Czéh B, et al. 2022. Novel drug developmental strategies for treatment - resistant depression. *British Journal of Pharmacology* 179:1146–1186

[122] Drevets WC, Wittenberg GM, Bullmore ET, Manji HK. 2022. Immune targets for therapeutic development in depression: towards precision medicine. *Nature Reviews. Drug Discovery* 21:224–244

[123] Le-Niculescu H, Roseberry K, Gill SS, Levey DF, Phalen PL, et al. 2021. Precision medicine for mood disorders: objective assessment, risk prediction, pharmacogenomics, and repurposed drugs. *Molecular Psychiatry* 26:2776–2804

[124] Castagné V, Moser P, Roux S, Porsolt RD. 2011. Rodent models of depression: forced swim and tail suspension behavioral despair tests in rats and mice. *Current Protocols in Neuroscience* 55:8.10A.1–8.10A.14

[125] Storm CS, Kia DA, Almramhi MM, Bandres-Ciga S, Finan C, et al. 2021. Finding genetically-supported drug targets for Parkinson's disease using Mendelian randomization of the druggable genome. *Nature Communications* 12:7342

[126] Perry BI, Upthegrove R, Kappelmann N, Jones PB, Burgess S, et al. 2021. Associations of immunological proteins/traits with schizophrenia, major depression and bipolar disorder: a bi-directional two-sample mendelian randomization study. *Brain, Behavior, and Immunity* 97:176–185

[127] Santarelli S, Wagner KV, Labermaier C, Uribe A, Dournes C, et al. 2016. SLC6A15, a novel stress vulnerability candidate, modulates anxiety and depressive-like behavior: involvement of the glutamatergic system. *Stress* 19:83–90

[128] Lukić I, Ivković S, Mitić M, Adžić M. 2022. Tryptophan metabolites in depression: Modulation by gut microbiota. *Frontiers in Behavioral Neuroscience* 16:987697

[129] Schaub AC, Schneider E, Vazquez-Castellanos JF, Schweinfurth N, Kettelhack C, et al. 2022. Clinical, gut microbial and neural effects of a probiotic add-on therapy in depressed patients: a randomized controlled trial. *Translational Psychiatry* 12:227

[130] Kazemi A, Ali Noorbala A, Azam K, Eskandari MH, Djafarian K. 2019. Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: a randomized clinical trial. *Clinical Nutrition* 382:522–528

[131] Menni AE, Theodorou H, Tzikos G, Theodorou IM, Semertzidou E, et al. 2025. Rewiring mood: precision psychobiotics as adjunct or standalone therapy in depression using insights from 19 randomized controlled trials in adults. *Nutrients* 17:2022

[132] Angus DC, Alexander BM, Berry S, Buxton M, Lewis R, et al. 2019. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nature Reviews Drug Discovery* 18:797–807

[133] Gadad BS, Jha MK, Czysz A, Furman JL, Mayes TL, et al. 2018. Peripheral biomarkers of major depression and antidepressant treatment response: Current knowledge and future outlooks. *Journal of Affective Disorders* 233:3–14

[134] Prompiengchai S, Dunlop K. 2025. Breakthroughs and challenges for generating brain network-based biomarkers of treatment response in depression. *Neuropsychopharmacology* 50:230–245

[135] Freitag MM, Zocholl D, Meyer EL, Gold SM, Roig MB, et al. 2025. Design considerations for a phase ii platform trial in major depressive disorder. *Pharmaceutical Statistics* 24:e70025

[136] Dockendorf MF, Hansen BJ, Bateman KP, Moyer M, Shah JK, et al. 2021. Digitally enabled, patient-centric clinical trials: shifting the drug development paradigm. *Clinical and Translational Science* 14:445–459

[137] Godfrey A, Vandendriessche B, Bakker JP, Fitzer-Attas C, Gujar N, et al. 2021. Fit-for-purpose biometric monitoring technologies: leveraging the laboratory biomarker experience. *Clinical and Translational Science* 14:62–74

[138] Bakker JP, Izmailova ES, Clement A, Hoffmann S, Leptak C, et al. 2025. Regulatory pathways for qualification and acceptance of digital health technology-derived clinical trial endpoints: considerations for sponsors. *Clinical Pharmacology & Therapeutics* 117:56–72

[139] Babrak LM, Menetski J, Rebhan M, Nisato G, Zinggeler M, et al. 2019. Traditional and digital biomarkers: two worlds apart? *Digital Biomarkers* 3:92–102

[140] Izmailova ES, AbuAsal B, Hassan HE, Saha A, Stephenson D. 2023. Digital technologies: innovations that transform the face of drug development. *Clinical and Translational Science* 16:1323–1330

[141] Kas MJH, Penninx BWJH, Knudsen GM, Cuthbert B, Falkai P, et al. 2025. Precision psychiatry roadmap: towards a biology-informed framework for mental disorders. *Molecular Psychiatry* 30:3846–3855

[142] Fusar-Poli P, Manchia M, Koutsouleris N, Leslie D, Woopen C, et al. 2022. Ethical considerations for precision psychiatry: a roadmap for research and clinical practice. *European Neuropsychopharmacology* 63:17–34

[143] Ntam VA, Huebner T, Steffens M, Scholl C. 2025. Machine learning approaches in the therapeutic outcome prediction in major depressive disorder: a systematic review. *Frontiers in Psychiatry* 16:1588963

[144] Ke H, Xu A, Zhou H, Chen J, Wu W, et al. 2025. Machine learning models of depression in middle-aged and older adults with cardiovascular metabolic diseases. *Journal of Affective Disorders* 387:119494
[145] Hines LJ, Wilke R, Myers RA, Mathews CA, Liu M, et al. 2024. Rationale and design for a pragmatic randomized trial to assess gene-based prescribing for SSRIs in the treatment of depression. *Clinical and Translational Science* 17:e13822
[146] Vokinger KN, Feuerriegel S, Kesselheim AS. 2021. Continual learning in medical devices: FDA's action plan and beyond. *The Lancet Digital Health* 3:e337–e338
[147] Shick AA, Webber CM, Kiarashi N, Weinberg JP, Deoras A, et al. 2024. Transparency of artificial intelligence/machine learning-enabled medical devices. *npj Digital Medicine* 7:21
[148] Liu YC, Lin GL, Scholl J, Hung YC, Lin YJ, et al. 2025. Evaluation of diagnostic recommendations embedded in medication alerts: prospective single-arm interventional study. *Journal of Medical Internet Research* 27:e70731
[149] Tai AMY, Kim JJ, Schmeckenbecher J, Kitchin V, Wang J, et al. 2024. Clinical decision support systems in addiction and concurrent disorders: a systematic review and meta-analysis. *Journal of Evaluation in Clinical Practice* 30:1664–1683
[150] Zrenner C, Ziemann U. 2024. Closed-loop brain stimulation. *Biological Psychiatry* 95:545–552
[151] Jung HW, Kim DY, Lee I, Kim O, Lee S, et al. 2025. Key features of digital phenotyping for monitoring mental disorders: systematic review. *Journal of Medical Internet Research* 27:e77331
[152] Shin YB, Kim AY, Kim S, Shin MS, Choi J, et al. 2025. Development of prediction models for screening depression and anxiety using smartphone and wearable-based digital phenotyping: protocol for the Smartphone and Wearable Assessment for Real-Time Screening of Depression and Anxiety (SWARTS-DA) observational study in Korea. *BMJ Open* 15:e096773
[153] Wang Y, Liang L, Zhang Z, Xu X, Liu R, et al. 2023. Fast and accurate assessment of depression based on voice acoustic features: a cross-sectional and longitudinal study. *Frontiers in Psychiatry* 14:1195276
[154] Stillman IO, Boyle B, Lencoski K, Styliadou M, Muir JM, et al. 2025. Rooting patient-reported outcomes in clinical care: a scoping review on benefits, challenges, and opportunities for patients and clinicians. *Health and Quality of Life Outcomes* 23:93
[155] Puccini A, Viscardi G, Ciani O, Efficace F, Piattelli A, et al. 2025. Patient-reported outcomes (PROs) in clinical trials and in clinical practice: report from the XXI national conference of the Italian Association of Medical Oncology (AIOM). *BMJ Oncology* 4:e000783
[156] Remick JS, Kowalski E, Samanta S, Choi S, Palmer JD, et al. 2020. Health-related quality of life and patient-reported outcomes in radiation oncology clinical trials. *Current Treatment Options in Oncology* 21:87
[157] Naqvi IA, Strobino K, Li H, Schmitt K, Barratt Y, et al. 2023. Improving patient-reported outcomes in stroke care using remote blood pressure monitoring and telehealth. *Applied Clinical Informatics* 14:883–891
[158] Jackman L, Kamran R. 2025. Transforming patient-reported outcome measurement with digital health technology. *Journal of Evaluation in Clinical Practice* 31:e70107
[159] Scangos KW, Khambhati AN, Daly PM, Makhoul GS, Sugrue LP, et al. 2021. Closed-loop neuromodulation in an individual with treatment-resistant depression. *Nature Medicine* 27:1696–1700
[160] Soleimani G, Nitsche MA, Bergmann TO, Towhidkhah F, Violante IR, et al. 2023. Closing the loop between brain and electrical stimulation: towards precision neuromodulation treatments. *Translational Psychiatry* 13:279
[161] Colle R, El Kader Ait Tayeb A, de Larminat D, Commery L, Boniface B, et al. 2020. Short-term acceptability by patients and psychiatrists of the turn to psychiatric teleconsultation in the context of the COVID-19 pandemic. *Psychiatry and Clinical Neurosciences* 74:443–444
[162] Ziobrowski HN, Cui R, Ross EL, Liu H, Puac-Polanco V, et al. 2023. Development of a model to predict psychotherapy response for depression among Veterans. *Psychological Medicine* 53:3591–3600
[163] Bossarte RM, Ross EL, Liu H, Turner B, Bryant C, et al. 2023. Development of a model to predict combined antidepressant medication and psychotherapy treatment response for depression among veterans. *Journal of Affective Disorders* 326:111–119
[164] Reddy S. 2024. Generative AI in healthcare: an implementation science informed translational path on application, integration and governance. *Implementation Science* 19:27
[165] You JG, Hernandez-Boussard T, Pfeffer MA, Landman A, Mishuris RG. 2025. Clinical trials informed framework for real world clinical implementation and deployment of artificial intelligence applications. *npj Digital Medicine* 8:107
[166] Nagy C, Maitra M, Tanti A, Suderman M, Théroux JF, et al. 2020. Single-nucleus transcriptomics of the prefrontal cortex in major depressive disorder implicates oligodendrocyte precursor cells and excitatory neurons. *Nature Neuroscience* 23:771–781
[167] Cerneckis J, Cai H, Shi Y. 2024. Induced pluripotent stem cells (iPSCs): molecular mechanisms of induction and applications. *Signal Transduction and Targeted Therapy* 9:112
[168] Du Y, Jamasb AR, Guo J, Fu T, Harris C, et al. 2024. Machine learning-aided generative molecular design. *Nature Machine Intelligence* 6:589–604
[169] Gangwal A, Lavecchia A. 2024. Unleashing the power of generative AI in drug discovery. *Drug Discovery Today* 29:103992
[170] Anderson KM, Collins MA, Kong R, Fang K, Li J, et al. 2020. Convergent molecular, cellular, and cortical neuroimaging signatures of major depressive disorder. *Proceedings of the National Academy of Sciences of the United States of America* 117:25138–25149
[171] Ugochukwu AI, Phillips PWB. 2024. Open data ownership and sharing: challenges and opportunities for application of FAIR principles and a checklist for data managers. *Journal of Agriculture and Food Research* 16:101157
[172] Forbes A, Keleher MR, Venditto M, DiBiasi F. 2023. Assessing patient adherence to and engagement with digital interventions for depression in clinical trials: systematic literature review. *Journal of Medical Internet Research* 25:e43727
[173] Sadeh Y, Denejkina A, Karyotaki E, Lenferink LIM, Kassam-Adams N. 2023. Opportunities for improving data sharing and FAIR data practices to advance global mental health. *Cambridge Prisms: Global Mental Health* 10:e14
[174] Stolfi F, Abreu H, Sinella R, Nembrini S, Centonze S, et al. 2024. Omics approaches open new horizons in major depressive disorder: from biomarkers to precision medicine. *Frontiers in Psychiatry* 15:1422939