Review

Biological Psychiatry

Novel Multimodal Precision Medicine Approaches and the Relevance of Developmental Trajectories in Bipolar Disorder

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ABSTRACT

There is a pressing need to establish objective measures to improve diagnosis, prediction, prevention, and treatment of bipolar disorder (BD). Multimodal artificial intelligence (AI) tools could provide these means by incorporating various layers of data orthogonally related to BD, including genomics and other omics, environmental exposures, imaging measures, electronic health records, cognition, sensing devices, and clinical variables. These rapidly evolving AI models hold promise to capture the multidimensional complexity of BD and delineate clinically relevant developmental trajectories that could guide clinical care and therapeutic strategies. In this review, we describe the potential of mapping developmental trajectories that underlie BD, outline how novel multimodal models could improve the prediction of BD and related outcomes, and discuss specific clinical use cases and key ethical and practical challenges regarding the development and potential implementation of these multimodal AI solutions to advance precision medicine approaches in BD.

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Bipolar disorder (BD) is a recurrent mood disorder that often persists throughout an individual's lifetime (1) and exerts a substantial clinical and socioeconomic toll (2). Importantly, the burden of BD increases substantially during adolescence and young adulthood (2), during which its highest peak of age of onset occurs (17.6 years) (3). BD is associated with premature all-cause mortality and specific-cause mortality, including suicide, the risk of which is 11 times higher in people with BD (4). However, while mortality from somatic comorbidities typically increases in later life, suicide risk is particularly high during adolescence and young adulthood (5,6). In this context, early identification of BD is critical.

Longitudinal studies of individuals living with BD and individuals at high risk for developing the disorder have identified clinical (7,8) and neurobiological (9,10) antecedents. However, the clinical heterogeneity of BD has hampered research on risk prediction of BD and related outcomes (suicidality, treatment response) (11). While this heterogeneity calls for precision medicine approaches, addressing it requires careful consideration, and methods such as ecological biodiversity analysis (12) or study designs that focus on more homogenous patient subgroups could be helpful (13,14). While studies of particular subgroups [e.g., lithium responsive (15,16) or early onset (17)] have advanced our understanding of genetic and neurobiological mechanisms (15–19), the generalizability of these findings to patients with less typical presentations remains uncertain. The heterogeneity of developmental trajectories between identifiable subgroups (i.e., narrowly defined BD vs. psychotic disorders) may significantly influence risk prediction/treatment and prognosis (20). Replicated evidence from longitudinal familial at-risk studies has shown clear differences in cognitive, motor, and psychosocial development in children at familial risk for psychosis compared with children at risk for BD (21–24). Developmental trajectories of BD can be stratified by phenotypic features such as response to treatment or adverse effects. For example, there is evidence that lithium-responsive patients with BD and their offspring have a distinct clinical course and prodromal stages that clearly distinguish them from lithium-nonresponsive patients with BD (25). Moreover, offspring of lithium-nonresponsive patients with BD have shown developmental trajectories similar to those observed in children at familial risk for psychosis (8,26–28). Additionally, the capricious course of BD leads to ample fluctuations in clinical symptoms, with phases of elevated syndromal activity alternating with spontaneous (or treatment-induced) remission (25).

While disentangling the complexity of BD remains a considerable challenge, particularly in its early course, novel theoretical frameworks support the application of integrated approaches that can address heterogeneity and lead to more precise diagnostic and treatment decision making (29). These frameworks may leverage the development of artificial intelligence (AI) and multiomics technologies to produce predictive and prognostic models that are able to estimate the risk of illness, thereby aiding the design of specific preventive interventions and ultimately reducing disease burden (30). Precision approaches in BD are still in their infancy, but they are promising, including risk prediction during developmental phases such as adolescence (10,31,32).

In this review, we examine how mapping of developmental trajectories may inform novel precision medicine approaches

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for BD, with a focus on premorbid developmental processes. We explore the potential utility of multimodal AI models that integrate complementary types of data and discuss specific clinical use cases, as well as ethical and practical challenges regarding the development and potential implementation of novel precision approaches for BD.

DEVELOPMENTAL TRAJECTORIES IN BD

There is consistent evidence that BD develops during certain neurodevelopmental stages. A series of studies conducted with offspring of parents with BD has shown that these stages are characterized by symptoms that precede its full-blown onset (33). The development of specific tools such as the Semistructured Interview for Bipolar At-Risk States has enabled mapping of these antecedents and improved the prediction accuracy of BD illness status (34). These antecedents may carry a diverse degree of specificity and indicate a homotypic rather than a heterotypic trajectory (35). For example, affective lability (36–41) and subthreshold mood symptoms, especially of depressive nature (42–44), tend to precede the manifestation of BD. High-risk studies have consistently shown higher rates of anxiety disorders in offspring of affected parents than in those with unaffected parents (7,36,38,39,41,43,45,46), and anxiety disorders show predictive value for subsequent BD diagnosis (7,40,43). Alteration of sleep patterns similarly appears to predict the development of BD in high-risk offspring (47,48). Recently, the presence of a neurodevelopmental subphenotype of BD was validated in ∼5000 patients with BD (49), including features such as advanced parental age, childhood maltreatment, specific learning disorders, and other psychiatric disorders (49). Patients with a higher neurodevelopmental load showed a worse prognosis, increased neurological soft signs, poorer response to lithium, and correlated genetic signal with attention-deficit hyperactivity disorder (49). While these neurodevelopmental factors currently have insufficient clinical predictive value, the findings suggest that multimodal characterization of neurodevelopmental phenotypes for BD may be a potential facilitator of precision approaches for prognosis and preventive interventions.

DATA MODALITIES RELEVANT FOR PRECISION MEDICINE IN BD

Combined with novel insights into the developmental trajectories of BD, multiple data sources could be leveraged to enable personalized risk assessment of BD, delineate clinical subgroups, and predict relevant outcomes. Here, we describe key modalities selected based on their clinical relevance, availability, and potential for capturing distinct aspects of BD. Apart from genomics, which represents stable risk factors, it will be critical to acquire multimodal data across different time points to disentangle trait- and state-specific variations and construct robust longitudinal models.

Molecular/Biological Measurements (Omics)

Genomics. The substantial heritability of BD emphasizes the potential of leveraging genomics data for precision medicine approaches (50). The genetic architecture of BD mostly comprises common variants with very small effects (51), with recent analyses implicating more than 10,000 causal variants (52). Rare variants with larger effect sizes may also influence BD risk, but they play a lesser role than in other psychiatric disorders such as autism spectrum disorder (51). Common variants collectively explain a significant fraction of phenotypic variation (i.e., the single nucleotide polymorphism [SNP] heritability), with an estimate of 9% in the latest genome-wide association study (GWAS) sample and approximately 20% in subgroups (52). The discrepancy between the SNP heritability and reported twin-family heritability estimates [60%–80% (50,53)] may reflect nonadditive genetic effects or gene-by-environment interactions (54).

Polygenic risk scores (PRSs) are the standard approach for out-of-sample prediction and estimating an individual's genetic susceptibility to illness or outcome, which is calculated by aggregating the sum of risk alleles with weights typically determined in GWASs (55). While PRSs are nearing clinical implementation in other complex medical conditions (56), they do not provide sufficient clinical predictive accuracy in BD, with a median area under the receiver operating characteristic curve (AUC) of 0.70 using the latest GWAS data across 10 random samplings of training and testing sets (52). PRSs perform worse when they are applied to ancestries other than that of the original GWAS (57), which are still overrepresented by individuals of European ancestry.

In addition to predicting innate susceptibility to BD, integrating genetic data on other phenotypes could help delineate patterns of clinical features and comorbidities. For example, genetic risk appears to transcend diagnostic categories, with higher levels of schizophrenia PRSs being associated with psychotic symptoms among individuals with BD (58). Genomic data on related phenotypes such as brain imaging (59), cardiovascular diseases (60), and cognition (61) are now available, while data on treatment response remain insufficiently powered (62,63).

Other Omics Sources. Other large-scale sources of omics data are increasingly becoming available, such as metabolomics (64) and proteomics (65) data from the UK Biobank cohort. Information from these modalities may capture environmental factors and potentially modifiable disease-related processes that provide information orthogonal to genomics data.

Environmental Exposures

A variety of lifestyle and environmental exposures are associated with increased risk of BD, including childhood maltreatment, traumatic experiences, drug use, socioeconomic status, and certain infections, which may be related to different clinical trajectories and subgroups of patients (66). The predictive ability of PRSs is sensitive to environmental context, as indicated by a recent study that demonstrated that PRSs for BD explained less phenotypic variance in subgroups of patients with a history of sexual trauma (67).

Clinical Assessments

Clinical Features. Deep phenotyping and accurate clinical characterization of patients with BD will be key to disentangling the heterogeneity of BD and facilitating precision medicine approaches. Clinical data may also help predict other outcomes

such as such as lithium response (68), with better prognostic performance when combined with genetic data (69).

Cognitive Ability. Cognitive impairment is associated with worse outcomes in BD (70,71) and is often assessed in routine clinical care. Both euthymic and symptomatic individuals with BD display cognitive deficits across a wide range of domains, including processing speed, memory, attention, learning, and executive functioning (72–74). However, there is considerable heterogeneity in cognitive performance within the patient group (70), and both higher and lower premorbid cognitive performance have been linked to increased BD risk (75). Cognitive deficits are more severe in patients with a history of psychosis (73) and in patients with bipolar I disorder compared with patients with bipolar II disorder (74).

Technical Measurements

Imaging Measures. Magnetic resonance imaging studies of BD have implicated widespread but subtle structural abnormalities in cortical (76) and subcortical (77) regions, including excessive cerebral cortical thinning, smaller subcortical volumes, and larger lateral ventricles. These abnormalities are smaller than those that have been associated with schizophrenia but greater than those found in major depressive disorder (59). Diffusion tensor imaging studies have demonstrated white matter microstructural abnormalities in multiple regions of interest in BD, indicative of altered structural connectivity integrity (78). Longitudinal analyses have indicated an inverse association between the number of mood episodes and greater cortical thinning (79,80), while various localized neuroimaging associations have been linked to clinically relevant phenotypes such as illness duration and lithium usage (76–78). Currently, neuroimaging analysis does not have a role in clinical care of BD except for ruling out neurological illness owing to small effect sizes and considerable heterogeneity across patients. Extending imaging analyses to other tissues may provide prognostic information about the likelihood of developing somatic adverse effects or comorbidities.

Sensing Devices and Digital Phenotyping. Sensing devices and digital phenotyping represent untapped sources of data for enabling BD precision medicine and cost-effective strategies for deep phenotyping of samples (81,82). Smart phones and wearables can be used to collect a variety of relevant longitudinal information including physical measurements, sleep rhythms, movement patterns, and social media usage, all of which are phenotypes that could be relevant for detecting the development of mood episodes early on (83,84).

Electronic Health Records

Electronic health records (EHRs) represent an extensive source of information that may contain data on all types of modalities relevant to BD. These digital repositories can include both structured (diagnostic codes, laboratory tests, medication prescriptions, appointments, and hospitalization records) and unstructured data (clinical notes, discharge summaries, imaging reports, patient self-reports), which may span over several decades. Longitudinal EHRs with repeated measures and comorbid conditions are especially valuable for precision medicine approaches as they can aid in defining clinical trajectories and predicting progression and development of illness. Natural language processing methods have been developed to help extract information from unstructured text from medical notes and facilitate analysis of free text data (85).

MULTIMODAL PRECISION MEDICINE OPPORTUNITIES FOR BD

Multimodal AI algorithms may transform various BD-related data into clinically useful precision medicine tools across health care systems (86). The potential of the models lies in their capacity to process and integrate different layers of data that capture orthogonal aspects of illness, ranging from nonmodifiable innate susceptibility to dynamic pathogenic processes (Figure 1). Multimodal AI algorithms may thus help account for the considerable clinical and etiologic variability within the diagnostic group and delineate longitudinal clinical trajectories that could guide clinical decision making.

Central to these possibilities is the rapid technological innovation that is currently taking place (87–92). Machine learning and deep-learning methodologies have enabled models that can detect patterns and relationships within and across datasets that are not readily recognizable by humans and that automatically improve without explicit programming. In particular, the advent of transformers has revolutionized the AI field by allowing for efficient paralleled computations that do not rely on sequential data analysis (93). This has led to novel tools like generative pretrained transformers (94), originally designed for natural language processing, but can also be applied to other forms of data like DNA (89,90) or proteins (91). The applicability of these prediction models depends on 2 key elements: transfer learning and their scale (95). Transfer learning refers to the ability of pretrained models to yield strong predictive performance in smaller target datasets with matched properties, although the models have not been specifically trained on that specific task (96). The scale of the models depends on the size of the training datasets, the specific architecture of the transformer model, and the computational hardware (95). Accordingly, while technological innovation is expected to continue at an accelerating pace, it is paramount to obtain and harmonize large-scale datasets across a range of modalities relevant to BD to enable the development of efficient multimodal prediction tools in this field. Here, large-scale cohorts with rich phenotypic and biological data such as the UK Biobank will play a key role (Table 1), in combination with existing EHR repositories, which are now widely adopted across health care systems.

As markers of innate susceptibility, individual genomic data will likely play a central role in multimodal precision tools for BD. However, the standard PRS approach does not leverage the potential of genomic prediction tools. Evidently, only a minority of the genetic architecture of BD and its subtypes has been uncovered (52), which underscores the need for larger GWAS samples to improve performance, including better representation of ancestries worldwide. In addition, other genomic features could be exploited to improve the utility of genomic prediction tools. First, the standard PRS approach builds on an additive model, with the assumption that each variant contributes independently to disease risk (55).

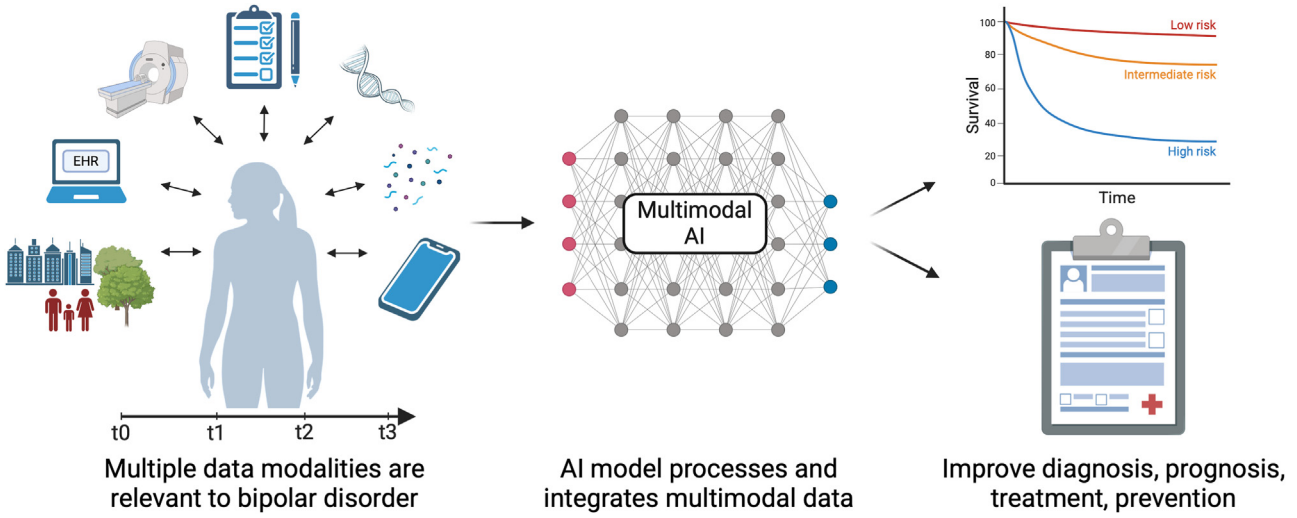

Figure 1. Multimodal biomedical artificial intelligence (AI) for bipolar disorder. Simplified illustration of the concept of multimodal AI for enabling precision medicine approaches for bipolar disorder. Multimodal AI algorithms can process and integrate a variety of data across different modalities to improve diagnosis, prognosis, treatment, and prevention. Data types of predictive and prognostic relevance to bipolar disorder include family history, environmental exposures, electronic health records (EHR), imaging measures, clinical and cognitive features, genomics, other omics sources, and phenotypes from sensing and screen devices. While genomics represents stable risk factors, it will be critical to acquire multimodal data over time to disentangle trait- and state-specific variations and construct robust longitudinal models. (Figure created with https://BioRender.com.)

Therefore, it does not consider nonadditive effects, i.e., combinations of genetic variants affecting the same gene or biological pathways in a synergistic manner (97,98). Hypothetically, integrating nonadditive genetic effects could improve phenotypic variance explained and capture biological differences within the patient group. Second, including principal components (PCs) in predictive modeling may further improve performance by capturing additional genetic variation, both within and across populations. In contrast, in the standard GWAS approach, PCs are used to correct for population stratification and avoid spurious findings driven by ancestral differences in linkage disequilibrium structures (99). However, for prediction, maximizing the explained variance will improve performance. To our knowledge, including PCs for prediction remains an unexplored area and is a subject of ongoing research. This approach requires raw individual-level data, whereas current PRS algorithms are predominantly generated from GWAS summary statistics. Third, the large extent of shared genetic signal between BD and clinically related complex phenotypes (100–104) indicates that individual genetic differences may contribute to variability in patterns of multimorbidities (105). Integrating genomic data across multiple traits and disorders may aid in predicting clinically meaningful trajectories and enable stratification of patients into subgroups of individuals who are more likely to develop adverse effects or comorbid illness (106,107). Here, mathematical modeling approaches designed for polygenic architectures may be valuable, like MOSTest (108) or the MiXeR suite of tools (109,110), which can take advantage of the high degree of shared genetic signal across complex phenotypes to improve predictive performance. Finally, genetics may be leveraged to improve the predictive utility of potential biomarkers for BD. By accounting for genetic factors that contribute to variability in biomarker levels, their specificity and predictive ability can be increased. For example, genetically adjusted prostate-specific antigen levels have been shown to improve the detection of aggressive prostate cancer (111). In BD, this approach could be used to quantify personalized ranges for potential biomarkers like neuroimaging measures, electrocardiogram parameters, or cognitive performance. This would generate an individual's expected trajectories of various clinically relevant features and provide a more accurate framework for evaluating biomarker values and facilitate earlier detection of abnormalities in neurodevelopmental or disease trajectories.

Because patients exhibit varying risk factor profiles (67), and distinct longitudinal trajectories may correspond to different biological signatures over time, incorporating multiple data modalities will likely be necessary to achieve sufficiently strong predictive performance, which implies increasing model complexity and costs. Already, multiple multimodal prediction and prognostic algorithms have been developed across different medical fields (87), many of which outperform polygenic risk tools (112–115). The integration of temporal data into multimodal models may facilitate the prediction of time-specific events. A multimodal hazard score that incorporated genomics, neuroimaging, clinical, and cognitive data enabled the prediction of time to develop Alzheimer's disease among older adults with mild cognitive impairment (114), with the difference in predicted conversion time exceeding 5 years between the 80th and 20th risk-percentile groups. Another study found that changes in plasma proteomic profiles were predictive of the future onset of dementia (AUC $>$ 0.8; internal cross-validation) when combined with demographic information (116). Analysis of longitudinal cohorts will be key to enable time-sensitive prediction models in BD and delineate developmental trajectories (117) (Table 1).

Table 1. Large-Scale Datasets With Multimodal Data Relevant for Advancing Precision Medicine in BD

Dataset	Country	Data Modalities	Sample Size	Ancestry	Age	Design
PGC	Global	Genomics Clinical, community, self-reports	~158,000 BD cases	Mostly European	–	Case-control
ENIGMA	Global	Clinical Imaging Genomics	~3500 BD cases	Mostly European	–	Case-control
MoBa	Norway	Questionnaires Genomics Biosamples EHR/medical records Environmental exposures	~114,000 children ~95,000 mothers ~75,000 fathers ~1000 BD cases	Mostly European	Recruited during pregnancy	Prospective, population-based
DNBC	Denmark	Questionnaires/interviews Biosamples EHR/medical records	~96,000 children ~93,000 mothers Unknown number of BD cases	Mostly European	Recruited during pregnancy	Population-based pregnancy cohort
iPSYCH	Denmark	EHR/medical records Genomics Blood samples Environmental exposures	~130,000 participants ~3000 BD cases	Mostly European	From birth	Population-based case-cohort sample
FinnGen	Finland	EHR/medical records Genomics Laboratory measures Omics (underway)	~500,000 participants ~9000 BD cases	Mostly European	>18 years	Longitudinal, nationwide biobank
UK Biobank	United Kingdom	Questionnaires EHR/medical records Cognition Genomics Metabolomics/laboratory measures Proteomics Imaging Sensing devices Environmental exposures	~500,000 participants ~3000 BD cases	Mostly European	40–69 years at recruitment	Prospective, population-based
ABCD	United States	Questionnaires/interviews Genomics Cognition Health care data Biosamples Imaging Environmental exposures Social media and sensing devices	~12,000 participants ~250 BD cases	Diverse	9–10 years at recruitment	Prospective longitudinal cohort
MVP	United States	Questionnaires EHR Genomics Omics (underway)	~1 million participants ~52,000 BD cases	Diverse	>18 years	Prospective cohort
All of Us Research Program	United States	Questionnaires EHR/clinical Genomics Biosamples Sensing devices Environmental exposures	1 million participants (target) >20,000 BD cases	Diverse	>18 years	Prospective, population-based
23andMe	United States	Questionnaires Genomics	>3 million participants ~90,000 BD cases	Mostly European	>18 years	Direct-to-consumer genetic testing

While most of these datasets include some longitudinal data, the extent and frequency of temporal sampling varies considerably between the resources.

ABCD, Adolescent Brain Cognitive Development; BD, bipolar disorder; DNBC, Danish National Birth Cohort; EHR, electronic health record; ENIGMA, Enhancing Neuro Imaging Genetics through Meta Analysis; MoBa, Norwegian Mother, Father and Child Cohort Study; MVP, Million Veteran Program; PGC, Psychiatric Genomics Consortium.

POSSIBLE USE CASES FOR MULTIMODAL PREDICTION APPROACHES

Broadly, novel prediction tools for psychiatry could be useful in 4 main settings (55,118): 1) community screening, 2) testing undiagnosed individuals who present with signs or symptoms of illness (premorbid), 3) guiding clinical decisions for patients with BD, and 4) enriching clinical trials (Figure 2).

Currently, the lack of satisfactory therapeutic interventions to prevent onset of BD among high-risk individuals does not warrant screening for BD in the general population. To effectively identify individuals before the onset of BD, wide-scale screening of children and adolescents would be necessary, which raises several ethical issues. However, improving the possibility of influencing illness trajectory in early adulthood would have a major impact on the lives of affected individuals, because this is a formative period for education, work, and starting a family. While antecedents and prodromal symptoms increase the risk of BD, not all high-risk individuals develop mental illness. Thus, increasing the prediction specificity of BD is crucial. Novel precision medicine tools may have greater predictive utility when applied to individuals at higher background risk of developing BD (119), e.g., undiagnosed individuals who present with mood symptoms or individuals with increased familial risk or other signs of psychiatric illness. However, it should be noted that the correlated genetic signal across psychiatric disorders, which likely also extends to other data modalities, represents a considerable challenge for differential diagnostic assessments, because a person with increased genetic susceptibility for BD would also be expected to have higher genetic risk of other mental disorders such as schizophrenia or major depressive disorder (51). Nevertheless, multimodal tools that integrate a variety of modalities may help capture patterns within data and further improve prediction of correct diagnostic categories. Existing precision approaches have shown some promise in the premorbid phase of BD. Prediction of BD diagnosis in a cohort of 227 at-risk offspring achieved an AUC of 0.81 (internal cross-validation) when both clinical information and a BD-PRS were included in the model (10). Furthermore, a disorder-specific PRS for BD predicted risk of progression to BD (hazard ratio of 1.11) in a cohort of patients with unipolar depression, although with smaller effects than parental history (120). While this is a promising area of research, more accurate tools are needed to obtain clinically relevant predictions.

Prognostic models may be useful for delineating clinical subgroups among individuals diagnosed with BD for stratification by risk of developing certain clinical outcomes, therapeutic response, and adverse effects or for predicting the course of illness. Here, the most readily available application may be to predict which individuals are most likely to develop comorbid illness, either endogenously or due to adverse effects (103), incorporating risk of other complex disorders such as cardiovascular illness (56) or cognition (121). Finally, multimodal prediction tools may be used to enrich clinical trials by facilitating selection of participants who are most likely to experience certain outcomes and reduce sample heterogeneity. Improved selection strategies may substantially lower the sample size needed for clinical trials, thus reducing the number of participants exposed to a certain treatment and the total cost involved (114).

ETHICAL CHALLENGES AND CONSIDERATIONS

The advent of more precise prediction tools for BD will necessarily have profound ethical impacts. First, estimates of risk prediction have the potential to transform the developmental trajectory of BD, and these could be optimized by the application of multimodal approaches that can capture neurobiological, genetic, and environmental variation (86,122). This has relevant clinical implications because a better comprehension of one's own health risks can empower and motivate families and individuals to engage in self-management by reducing modifiable risk exposures

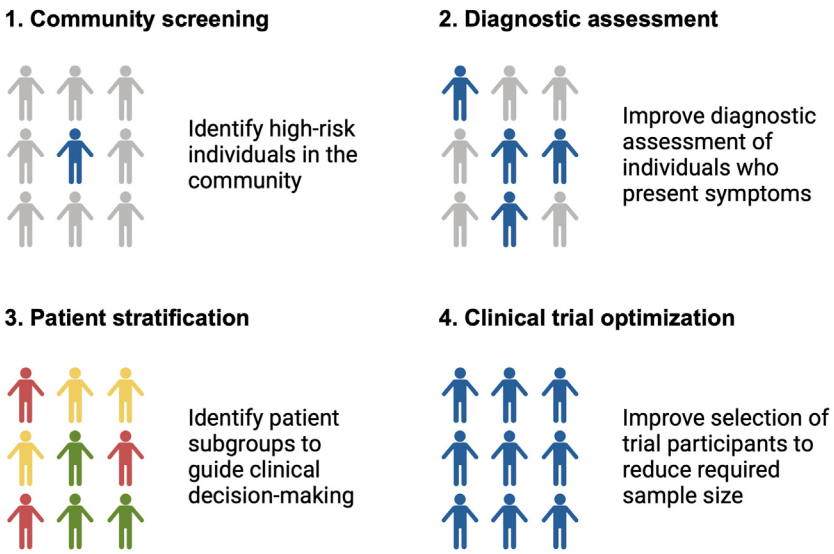

Figure 2. Possible use cases of multimodal artificial intelligence (AI) tools for bipolar disorder. The utility of multimodal AI tools depends on context and population. 1) In the community setting, multimodal AI tools may improve screening strategies to facilitate early detection, intervention, and prevention. In the clinical setting, multimodal AI may 2) improve diagnostic accuracy and 3) help stratify patients into clinical subgroups to guide clinical decision making. 4) Multimodal AI may also enrich clinical trials through refined participant selection to reduce sample heterogeneity and improve signal detection while minimizing costs. Blue color denotes individuals with high risk of bipolar disorder, while gray color denotes individuals without a high risk of developing bipolar disorder. The colors yellow, red, and green denote putative clinical subgroups underlying bipolar disorder. (Figure created with https://BioRender.com.)

(123,124). However, in a disorder with a highly heterogeneous clinical course (i.e., episodic vs. chronic vs. rapid cycling), risk prediction should not be limited to the onset of the disorder and should also include estimates on the type of trajectory more likely to occur in a given individual. This is crucial to increase the quality of prediction, which is positively associated with better ethical decision making (125,126). Secondly, risk disclosure should be tailored to the patient's preference, considering both the patient's willingness to receive information and the health care professional's ability to effectively communicate risk estimates, including a transparent explanation of the methods used and their inherent limitations (127,128). Risk estimates of BD should also be communicated under a high standard of privacy and safety of data used for their calculation to avoid the risk of predatory predictions (129). Third, BD risk varies substantially according to ethnicity (130) and environmental conditions, such as insolation (131,132). Thus, risk calculators should include these determinants of variations in models including genomic (133) and exposomal data to allow unbiased estimates and promote equitable access to the results of precision approaches in BD. Finally, modifications of clinical practice informed by risk estimation could produce performative predictions, which may lead to consequent underestimation of risk in new calculations (134). Using holdout sets, in which a set of patients do not receive model-derived risk scores, could ensure stability of predictions provided that specific ethical safeguards are maintained (134). In sum, the ethical challenges of precision psychiatry in BD are substantial, and some may not yet be completely envisioned because only full implementation of models will clarify their exact ethical implications.

CHALLENGES AND FUTURE DIRECTIONS

Despite significant advances in biological psychiatry in the past decade (51,59), there is a pressing need to establish objective measures to reduce unwanted variability in diagnostic assessment, treatment, and management of BD (135). Multimodal AI tools could provide these means, which clearly hold transformative potential for health care (86,136). With the remarkable ongoing progress in the development of AI models (88–92), which co-occurs with the expansion of comprehensive longitudinal datasets with relevant data for BD (Table 1), novel precision medicine tools may eventually have real-world applicability in psychiatry. By incorporating orthogonal layers of data, these AI solutions may help capture the multidimensional complexity of BD; delineate clinically relevant trajectories to guide clinical care; and improve prediction, prevention, and treatment strategies (Figure 1).

To realize the potential of multimodal precision medicine solutions in BD, several major challenges need to be addressed. Sufficiently powered datasets are needed to ensure adequate training and testing of the prediction models. Here, large-scale nationwide or international cooperation will be key, including taking measures to ensure data harmonization across cohorts. Robust external independent validation in diverse populations is essential to establish the clinical advantage and utility of novel predictive and prognostic models before they can be integrated into health care systems and screening programs (137). In clinical settings, the application of novel AI solutions must be combined with evidence-based knowledge, which can also be embedded within the technical framework. However, user-friendly front-end solutions are needed for practical implementation of the decision support tools, and clinicians are required to be on board with the new precision medicine approach. To avoid inadequate communication and interpretation of the results, there is a need to improve education of clinicians regarding the probabilistic and faulty nature of prediction models. Other critical issues include ensuring portability across ancestries and addressing privacy and security concerns. Given the complexity and transformative potential of multimodal AI tools, successful development and implementation require collaborative efforts between academia, policymakers, user groups, health care systems, and technological companies (138).

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