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Abstract: The field of psychiatry is facing an important paradigm shift in the provision of clinical care and mental health service organization toward personalization and integration of multimodal data science. This approach termed precision psychiatry aims at identifying subgroups of patients more prone to the development of a certain phenotype, such as symptoms or severe mental disorders (risk detection), and/or to guide treatment selection. Pharmacogenomics and computational psychiatry (CP) are two fundamental tools of precision psychiatry, which have seen increasing levels of integration in clinical settings. Here we present a brief overview of these two applications of precision psychiatry in clinical settings.

- **Keywords:** pharmacogenetics, personalized psychiatry, risk prediction, computational psychiatry, drug metabolism, stratification

The field of psychiatry is facing an important paradigm shift in the provision of clinical care and mental health service organization [1]. Traditionally, clinical management and selection of treatment has aimed to develop methodologically robust, standardized and reproducible, but universal, evidenced based approaches. Whereas, in the last decade there has been a slow but incremental focus on developing personalized approaches to care [2]. In its last iteration, the advancement in omics technology, digital monitoring and analytical pipelines [3] have led to the development of *precision psychiatry* [4]. Briefly, precision psychiatry aims at implementing advanced multimodal data science based on clinical, neuroimaging, proteomic, genomic and digital biomarkers to identify subgroups of patients more prone to the development of a certain phenotype, such as symptoms or severe mental disorders (risk detection), and/or to guide treatment selection [5]. Ideally, in precision psychiatry, those individuals with a specific biological make-up that predisposes to treatment resistance would be targeted with early intensive trials of those drugs that are effective in severe clinical forms (e.g. clozapine in treatment resistant schizophrenia). Similarly, people with treatment responsive signatures could be prescribed early in the course of the disorder with the drug best matching their biological fingerprint. Regrettably, however, precision psychiatry is not bereft of limitations and several barriers might impede its full implementation in clinical practice. The first set of obstacles relates to inherent properties of precision psychiatry algorithms which are still characterized by variable level of accuracy [6,7]. Generally, the more diverse data sources are integrated into models (e.g. genetic and environmental), the higher accuracy is achieved [8]. Also, precision psychiatry paradigms may still lack neurobiological interpretability, explainability, and generalizability [9]. For example, risk disclosure of estimates derived by precision psychiatry algorithms might be beneficial but also entail some risks [10]. It is plausible that the communication of risk estimates to an individual might lead to modify the risk itself based on their consequent decisions (i.e. starting a treatment program) but also on the development of personal and public stigma associated with a mental disorder risk label [10]. This should lead to the development of specific roadmaps for the implementation of precision psychiatry that should account for interdisciplinary recommendations from funders, healthcare providers, clinicians, patients, families and caregivers [10]. A major obstacle on the road to precision psychiatry is the inadequate characterization of mental disorders, in terms of their etiology, pathophysiology and correspondence with clinical features. To accurately predict diseases, and to treat each individual with sufficient specificity requires we first learn about the causes and mechanisms that differentiate the illness in one person's from another. This is especially true when

different individuals share the same clinical presentation or "phenotype": it is in fact clear that the relatively high clinical and pathophysiological heterogeneity of mental disorders is not adequately captured by current diagnostic categories. Further diversity is brought about by subjectivity of clinical observation, social and environmental factors [11]. In this context, the development of precision psychiatry needs to be based on solid bases that can be identified in those applications successfully tested in clinical scenarios. Indeed, as in any other transformative phase in healthcare (and especially in psychiatry), there is always asymmetry in the development and implementation of specific aspects of the new model of care, with some tools being applied more easily and rapidly than others. This is the case of two essential components of precision psychiatry, and specifically pharmacogenomics and computational psychiatry (CP), which have seen increasing levels of integration in clinical settings.

Pharmacogenomics is a powerful tool of precision psychiatry. It consists in the analysis and the application of genomic information to develop targeted therapies through identification of those individuals likely to respond (or non-respond) to a specific drug or to develop adverse drug reactions related to the same given drug (safety pharmacogenomics) [12]. Indeed, pharmacogenomics applications in psychiatry are now multiple and often fully integrated into clinical practice [13–15]. For instance, meta-analytical evidence of 10 randomized clinical trials and 3 open label trials, showed that patients who received pharmacogenomics-guided antidepressant therapy were more likely to achieve remission compared with those that received unguided antidepressant therapy [16]. Another study showed that the application of a Pharmacogenomic Panel in a healthcare setting with patients managed by primary care providers or by psychiatrists led to a faster improvement of depressive symptoms if administered earlier (4 weeks) compared to a later time (12 weeks) [17]. These successes are the results of more than a decade of efforts in the development of guidelines to support practitioners selecting the appropriate genetic tests for a given medication and using test results to adjust its modality of use or its dose [18,19]. Interestingly, there are also data supporting the cost effectiveness of pharmacogenomic testing in psychiatry [20], making this tool suitable for coverage within public health systems. In fact, there are indications that panels with a minimum gene and allele set 16 variant alleles within five genes (CYP2C9, CYP2C19, CYP2D6, HLA-A, HLA-B) could be useful to use pharmacogenomic testing as a standard protocol and companion tool for psychotropic medication selection and dosing [21]. In parallel with these pragmatic and clinically oriented application of pharmacogenomics, there has been a fertile area of research using pharmacogenomic phenotypes for the dissection of the genomic complexities of psychiatric disorders. For instance, the genomic analysis of lithium responsive patients with bipolar disorder, in the context of the Consortium on Lithium Genetics (ConLiGen) [22], has identified significant association signals in chromosome 21 [23] creating a dataset suitable for follow-up analyses. The predictive power of models based on genomic data alone for the a priori identification of lithium responsive patients may still be inadequate [24], but there is evidence that the integration of phenotypic and genomic data can distinguish patients with bipolar disorder who are more likely to respond to lithium from those who are not [25].

CP may also contribute to make significant advances in precision psychiatry. CP is an emergent transdisciplinary field that uses mathematical tools to explain the pathophysiology of psychiatric disorders, with particular attention to the mechanisms that govern the processing of information in the brain. One major strategy of "theory driven" CP is the development of mathematical models that seek to explain specific mental or brain processes underlying behavior [26,27]. Usually, CP exploits computerized task where the "environment" is controlled in stochastic or mechanistic way, while the proband choices and reaction times are recorded. For instance, an individual may be asked to select which (virtual) slot machines to activate based on the observed winning rate, across a number of trials. Such models are often termed "generative" as they reflect what the researchers assume about the brain/mental computations underlying behavior: they do not just describe behavior in terms of "raw" data (e.g. percentage of wins), but as a set

of latent parameters which express latent individual features (i.e. trial by trial expectations, levels of uncertainty, prediction errors, learning rates and others) [28]. Essentially, CP sees researchers build precise simulation of how a brain / mental function leads to behavior; to do so, it forces them to formally and unequivocally define such functions, as well as testing them. Thus, CP models are rather complex to build and evaluate, but they are becoming increasingly sophisticated and powerful to dissect, measure and explain the variability of human behavior at different timescales and levels. This may notably relate to specific cognitive functions, diagnoses or individual clinical features, i.e. "symptoms" [29]. Notable examples include models of perception, cognition, reinforcement learning, (Bayesian) updating of internal values or beliefs, inference and action [26,30,31]. CP model parameters are specifically promising to reconcile the subjective perspective of psychopathology with objective measurements , as well as improving the precision of the correspondence between behavior, neurobiology [32] and neuroimaging data [33]. In some cases, attempts are made to consider CP parameters as intermediate phenotypes and prompt the genetic dissection of normative brain processes or disease [34].

In light of this brief description it may become apparent that CP may be a stepping stone in the climb towards precision psychiatry and normative modeling [35]. Reliable and precise measurements of latent processes have the potential to uncover how multiple neural mechanisms potentially lead to developing similar symptoms (e.g. auditory hallucinations) in different subjects [36,37], or across different disorders (e.g. anhedonia in depression or schizophrenia) [38] with notable implications for treatment choice. Other studies, for instance, have shown that specific parameters from a reward-effort model of depression were able to predict clinical relapse after antidepressant discontinuation [39]. Another stream of CP studies, namely "data-driven" investigations often based on Artificial Intelligence, can leverage diverse data sources to classify or stratify individuals for clinical purposes [40]. Clearly, the very issue of reliability is being re-conceptualized to account for this specific framework [41,42].

In summary, we have shown that precision psychiatry is becoming a reality in psychiatry especially if founded on tools that are already being validated in clinical practice and/or are extensively investigated in clinical research settings. To make psychiatry more precise means to reduce the latency to the most effective treatment, to increase the efficacy of preventive strategies, to clarify the pathophysiological underpinnings of psychiatric disorders and to reduce the stigma, all aspects that will ultimately decrease the suffering of people living with a mental disorder and promote well-being and good quality of life.

References

1 Craske MG, Herzallah MM, Nusslock R, Patel V. From neural circuits to communities: an integrative multidisciplinary roadmap for global mental health. *Nature Mental Health* 1(1), 12–24 (2023).
2 Manchia M, Pisanu C, Squassina A, Carpiniello B. Challenges and Future Prospects of Precision Medicine in Psychiatry. *Pharmgenomics Pers Med* 13, 127–140 (2020).

3 Denny JC, Collins FS. Precision medicine in 2030—seven ways to transform healthcare. *Cell* 184(6), 1415–1419 (2021).
4 Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M. The new field of 'precision psychiatry'. *BMC medicine* 15(1), 1–7 (2017).
5 Kambeitz-Ilankovic L, Koutsouleris N, Upthegrove R. The potential of precision psychiatry: what is in reach? *The British Journal of Psychiatry* 220(4), 175–178 (2022).
6 Belvederi Murri M, Cattelani L, Chesani F, Palumbo P, Triolo F, Alexopoulos GS. Risk Prediction Models for Depression in Community-Dwelling Older Adults. *Am J Geriatr Psychiatry* 30(9), 949–960 (2022).
7 Guan F, Ni T, Zhu W *et al.* Integrative omics of schizophrenia: from genetic determinants to clinical classification and risk prediction. *Mol Psychiatry* 27(1), 113–126 (2022).
8 Chekroud AM, Bondar J, Delgadillo J *et al.* The promise of machine learning in predicting treatment outcomes in psychiatry. *World Psychiatry* 20(2), 154–170 (2021).
9 Baldwin H, Loebel-Davidsohn L, Oliver D *et al.* Real-world implementation of precision psychiatry: a systematic review of barriers and facilitators. *Brain Sciences* 12(7), 934 (2022).
10 Fusar-Poli P, Manchia M, Koutsouleris N *et al.* Ethical considerations for precision psychiatry: A roadmap for research and clinical practice. *European Neuropsychopharmacology* 63, 17–34 (2022).
11 Gómez-Carrillo A, Paquin V, Dumas G, Kirmayer LJ. Restoring the missing person to personalized medicine and precision psychiatry. *Front Neurosci* 17, 1041433 (2023).
12 Squassina A, Manchia M, Manolopoulos VG *et al.* Realities and expectations of pharmacogenomics and personalized medicine: impact of translating genetic knowledge into clinical practice. *Pharmacogenomics* 11(8), 1149–1167 (2010).
13 Hicks JK, Bishop JR, Sangkuhl K *et al.* Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clinical Pharmacology & Therapeutics* 98(2), 127–134 (2015).
14 Hicks JK, Swen JJ, Thorn CF *et al.* Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clinical Pharmacology & Therapeutics* 93(5), 402–408 (2013).
15 Beunk L, Nijenhuis M, Soree B *et al.* Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6, CYP3A4 and CYP1A2 and antipsychotics. *Eur J Hum Genet* (2023).
16 Brown LC, Stanton JD, Bharthi K, Maruf AA, Müller DJ, Bousman CA. Pharmacogenomic Testing and Depressive Symptom Remission: A Systematic Review and Meta-Analysis of Prospective, Controlled Clinical Trials. *Clinical Pharmacology & Therapeutics* 112(6), 1303–1317 (2022).
17 Bohlen KN, Kittelsrud JM, Nelson ME *et al.* Clinical utility of pharmacogenetics in a psychiatric and primary care population. *Pharmacogenomics J* 23(1), 21–27 (2023).
18 Relling MV, Klein TE, Gammal RS, Whirl-Carrillo M, Hoffman JM, Caudle KE. The clinical pharmacogenetics implementation consortium: 10 years later. *Clinical Pharmacology & Therapeutics* 107(1), 171–175 (2020).
19 Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clinical Pharmacology and Therapeutics* 89(3), 464–467 (2011).
20 Carta A, Del Zompo M, Meloni A *et al.* Cost–Utility Analysis of Pharmacogenetic Testing Based on CYP2C19 or CYP2D6 in Major Depressive Disorder: Assessing the Drivers of Different Cost-Effectiveness Levels from an Italian Societal Perspective. *Clinical Drug Investigation* 42(9), 733–746 (2022).
21 Bousman C, Al Maruf A, Müller DJ. Towards the integration of pharmacogenetics in psychiatry: a minimum, evidence-based genetic testing panel. *Current opinion in psychiatry* 32(1), 7–15 (2019).
22 Manchia M, Adli M, Akula N *et al.* Assessment of Response to Lithium Maintenance Treatment in Bipolar Disorder: A Consortium on Lithium Genetics (ConLiGen) Report. *PLoS One* 8(6), e65636 (2013).
23 Hou L, Heilbronner U, Degenhardt F *et al.* Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study. *Lancet* 387(10023), 1085–1093 (2016).
24 Stone W, Nunes A, Akiyama K *et al.* Prediction of lithium response using genomic data. *Scientific Reports* 11(1), 1155 (2021).

25 Nunes A, Stone W, Ardau R *et al.* Exemplar scoring identifies genetically separable phenotypes of lithium responsive bipolar disorder. *Transl Psychiatry* 11(1), 36 (2021).
26 Friston KJ, Stephan KE, Montague R, Dolan RJ. Computational psychiatry: the brain as a phantastic organ. *The Lancet Psychiatry* 1(2), 148–158 (2014).
27 Adams RA, Huys QJM, Roiser JP. Computational Psychiatry: towards a mathematically informed understanding of mental illness. *J Neurol Neurosurg Psychiatry* 87(1), 53–63 (2016).
28 Smith R, Friston KJ, Whyte CJ. A step-by-step tutorial on active inference and its application to empirical data. *Journal of Mathematical Psychology* 107, 102632 (2022).
29 Ossola P, Pike AC. Editorial: What is computational psychopathology, and why do we need it? *Neuroscience & Biobehavioral Reviews* 105170 (2023).
30 Petzschner FH, Weber LAE, Gard T, Stephan KE. Computational Psychosomatics and Computational Psychiatry: Toward a Joint Framework for Differential Diagnosis. *Biol Psychiatry* 82(6), 421–430 (2017).
31 Huys QJM, Maia TV, Frank MJ. Computational psychiatry as a bridge from neuroscience to clinical applications. *Nat Neurosci* 19(3), 404–413 (2016).
32 Humpston CS, Adams RA, Benrimoh D *et al.* From Computation to the First-Person: Auditory-Verbal Hallucinations and Delusions of Thought Interference in Schizophrenia-Spectrum Psychoses. *Schizophrenia Bulletin* 45(Supplement_1), S56–S66 (2019).
33 Frässle S, Yao Y, Schöbi D, Aponte EA, Heinzle J, Stephan KE. Generative models for clinical applications in computational psychiatry. *Wiley Interdiscip Rev Cogn Sci* 9(3), e1460 (2018).
34 Montagnese M, Knolle F, Haarsma J *et al.* Reinforcement learning as an intermediate phenotype in psychosis? Deficits sensitive to illness stage but not associated with polygenic risk of schizophrenia in the general population. *Schizophr Res* 222, 389–396 (2020).
35 Rutherford S, Kia SM, Wolfers T *et al.* The Normative Modeling Framework for Computational Psychiatry, Neuroscience, (2021).
36 Benrimoh D, Parr T, Adams RA, Friston K. Hallucinations both in and out of context: An active inference account. *PLoS ONE* (2019).
37 Adams RA, Vincent P, Benrimoh D, Friston KJ, Parr T. Everything is connected: Inference and attractors in delusions. *Schizophr Res* 245, 5–22 (2022).
38 Husain M, Roiser JP. Neuroscience of apathy and anhedonia: a transdiagnostic approach. *Nat Rev Neurosci* 19(8), 470–484 (2018).
39 Berwian IM, Wenzel JG, Collins AGE *et al.* Computational Mechanisms of Effort and Reward Decisions in Patients With Depression and Their Association With Relapse After Antidepressant Discontinuation. *JAMA Psychiatry* 77(5), 513–522 (2020).
40 Paulus MP, Thompson WK. Computational approaches and machine learning for individual-level treatment predictions. *Psychopharmacology (Berl)* 238(5), 1231–1239 (2021).
41 Karvelis P, Paulus MP, Diaconescu AO. Individual differences in computational psychiatry: A review of current challenges. *Neurosci Biobehav Rev* 148, 105137 (2023).
42 Benrimoh D, Fisher V, Mourgues C, Sheldon AD, Smith R, Powers AR. Barriers and solutions to the adoption of translational tools for computational psychiatry. *Mol Psychiatry* (2023).