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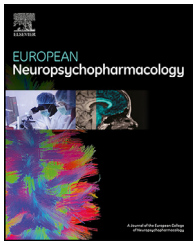

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REVIEW

Ethical considerations for precision psychiatry: A roadmap for research and clinical practice

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Abstract
Precision psychiatry is an emerging field with transformative opportunities for mental health. However, the use of clinical prediction models carries unprecedented ethical challenges, which must be addressed before accessing the potential benefits of precision psychiatry. This critical review covers multidisciplinary areas, including psychiatry, ethics, statistics and machine-learning, healthcare and academia, as well as input from people with lived experience of mental disorders, their family, and carers. We aimed to identify core ethical considerations for precision psychiatry and mitigate concerns by designing a roadmap for research and clinical practice. We identified priorities: learning from somatic medicine; identifying precision psychiatry use cases; enhancing transparency and generalizability; fostering implementation; promoting mental health literacy; communicating risk estimates; data protection and privacy; and fostering the equitable distribution of mental health care. We hope this blueprint will advance research and practice and enable people with mental health problems to benefit from precision psychiatry.

1. Introduction

Precision medicine is defined as an approach for treatment and prevention, which allows healthcare providers to make clinical choices based on the characteristics of a given individual (Panel 1) (Ashley, 2016; Denny and Collins, 2021; *Toward Precision Medicine*, 2011). Therefore, precision medicine ultimately aims at developing individualised healthcare approaches (Ahadi et al., 2020; Yates et al., 2018). This term was introduced to replace "personalised" medicine to avoid miscommunicating that each patient will be treated completely differently from any other patient (*Toward Precision Medicine*, 2011). At the core of precision medicine are individualised clinical prediction models that are developed and validated for screening, prognostic, diagnostic or therapeutic stratification purposes (see Panel 1) (Adams and Leveson, 2012; Moons et al., 2009; Steyerberg, 2009) at the individual (precision medicine) or subgroup level (stratified medicine). Precision or stratified medicine using these models can be used for identifying people with or at risk of a disorder, predicting their clinical outcomes and informing treatment strategies (e.g. standalone or combined treatments,

such as medication, psychological interventions and/or brain stimulation) therefore improving cost effectiveness (Arns et al., 2022).

Psychiatry is in itself personalised, relying on descriptive psychopathology and phenomenology (Häfner, 2015; Stanghellini et al., 2019) of symptoms and signs, which cannot be properly understood or identified apart from an appreciation of their "subjective" and, therefore, personalised nature (Parnas et al., 2013). However, while psychiatry has always had a personalised approach (Maj et al., 2021, 2020; Stein et al., 2021), it is not completely precise, or at least not precise enough. Psychiatric personalisation is typically based on the physician's clinical impression rather than on "objective" measures, which can be delivered by precision psychiatry (Vieta, 2015). Over the past decade (Fernandes et al., 2017), several clinical prediction models have been published to screen large populations (Fusar-Poli et al., 2017; Raket et al., 2020), detect individuals at-risk of developing mental disorders (Lalousis et al., 2021), improve diagnostic workflow (Koutsouleris et al., 2021a) or predict treatment response (Koutsouleris et al., 2018; Nunes et al., 2021).

While precision psychiatry has gained momentum and promises to be transformative, in particular if combined with preventive psychiatry (Fusar-Poli et al., 2021), its translation into clinical practice is still in its infancy. A core set of barriers relates to broader ethical implications of precision psychiatry that may impede its adoption by researchers, clinicians, and policymakers. There is also an associated lack of an empirical ethical blueprint shared across different stakeholders to guide future research and clinical practice (Salagre and Vieta, 2021). This collaborative study fills these gaps of knowledge by critically addressing core ethical challenges of precision psychiatry and proposing a roadmap to find solutions to current issues. The ultimate aim is to provide a novel, culturally sensitive and participatory ethical framework that can become the reference benchmark for the next generation of precision psychiatry research and clinical practice.

2. Methods

Consensus exercise conducted through a two-day workshop on the ethical barriers to precision psychiatry held in February 2021. The workshop was organized by the Prevention of Severe Mental Disorders (PSMD) Cluster and funded by the European Brain Research Area (EBRA),(Morris et al., 2016) building on two existing Networks of the European College of Neuropsychopharmacology ECNP (Prevention of Mental Disorders & Mental Health Promotion and Bipolar Disorders). Workshop participants were selected to reflect a multidisciplinary professional background, including key leaders from psychiatry, oncology, big data research, genomics, imaging, clinical implementation, ethics, philosophy, and healthcare policies. Individuals with lived experiences of mental disorders or their carers/family members [from the Global Alliance of Mental Illness Advocacy Networks-Europe (GAMIAN, https://www.gamian.eu) (Brohan et al., 2011) and European Federation of Associations of Families of People with Mental Illness (EUFAMI, http://eufami.org)] (Steffen, 2011) actively participated in the workshop. During the workshop, core themes were summarised (day 1) and then presented to individuals with lived experiences of severe mental illness (day 2) who fed into the orientation of the ethical analysis. The material produced in the workshop was complemented by a non-systematic review of the literature related to ethical barriers of precision psychiatry (see search strategy and selection criteria). All workshop participants, including individuals with lived experiences of mental disorders, were invited to contribute to the current manuscript and were directly involved in the final consensus. Although this study will frequently refer to severe mental disorders (psychosis and bipolar disorders) as use-case scenarios, the core findings can be transported to other mental disorders.

2.1. Search strategy and selection criteria

A multistep literature search was performed for articles published from inception until January 1st, 2022. First, the Web of Science database (Clarivate Analytics) was searched, incorporating the Web of Science Core Collection, BIOSIS Citation Index, KCI Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index. Independently, PubMed was searched. Several combinations of the following key words and their acronyms were used: ethic*, precision psychiatry, artificial intelligence, bipolar disorders, psychosis.

Key papers were critically (non-systematically) selected based on the topic covered and the quality of research. We supplemented these publications with earlier landmark papers and studies conducted in developing countries. The resulting literature covered a wide range of empirical constructs and populations representative of global research.

3. Results

3.1. Ethics of precision psychiatry: Key concepts

Broadly speaking, ethical issues concern the development of 'practical ought claims' (Sheehan and Dunn, 2013) (i.e. normative claims that are practical in nature), which arise when we face ethical uncertainty in precision psychiatry. These practical claims come schematically like this: how should somebody or a group of people act in relation to a particular issue when they face certain circumstances? For example, how should researchers inform patients about their individualised risk estimates after running a novel clinical prediction model? To address these questions, four overarching ethical principles have been suggested (by Beauchamp and Childress) (Beauchamp and Childress, 2019), which include autonomy, beneficence, non-maleficence and justice. These can be applied to precision psychiatry, complemented by an extra principle of "explainability/interpretability" (Panel 1) which has been specifically introduced for artificial intelligence (Floridi et al., 2018) (for a more detailed discussion of ethical platforms for big data analytics see eSupplementary 1).

Although these four principles have become the cornerstones of biomedical ethics in healthcare practice, they have been criticised as they are often conflicting with no clear hierarchy and are not very specific (i.e. these principles are somewhat implicit, representing general moral values), leading to "imprecise ethics" that may not fit the needs of precision psychiatry (Table 1). Rather we should ask ourselves "why" a certain act may be harmful or beneficial. For example, let's imagine having a risk assessment; what would that mean for the individual, their family planning, workplace, choosing their studies, or their period of life? Alternatively, let's imagine that the risk assessment is

Table 1 Ethical challenges of precision psychiatry and proposed solutions

Ethical challenge	Proposed solution
Autonomy, beneficence, non-maleficence and justice criteria are imprecise	Refer to the fundamental rights of the European Union: dignity, freedom, equality, solidarity, citizens' rights and justice (European Union, 2012)
Clinical prediction models may not be accurate enough to capture the complexity of mental disorders	Refine multimodal clinical prediction models across high-dimensional data
Clinical prediction models lack neurobiological interpretability	Refine candidate prediction models towards neurobiological and mechanistic interpretability (e.g. computable knowledge graphs)
Clinical prediction models may be too complex and poorly explainable (black-box)	Adopt glass-box, explainable machine-learning methods to increase the model's transparency and trustworthiness (e.g. FAST Track Principles) (Leslie et al., 2021)
Generalisability of precision psychiatry models is poorly tested, in particular in specific/vulnerable subgroups	Foster collaborative replication science against deeply-phenotyped federated databases with a specific focus on vulnerable groups
The real-world value of precision psychiatry is unclear because a few models are currently implemented	Foster implementation research (early identification of implementation barriers, demonstrated cost-effectiveness and scalability, establishing an integrated infrastructure for model refinement, updating and comparability)
Citizens are not well prepared to deal with risks for mental disorders	Fostering mental health literacy in order to consolidate self-determination and the alliance between stakeholders
People vary in terms of disclosure preferences	Ask whether/how much the users want to be shared the results of precision psychiatry; conduct interpretive research; address the issue of reporting incidental findings.
Communicating a mental health risk estimate to an individual might impact behaviours and the risk itself	Establish a multidisciplinary governance framework to promote ongoing reflection and discourse on the interaction between risk prediction and human reaction
Methods of disclosure of mental health risk states are poorly investigated	Promote research on varying disclosure models and stakeholder perceptions
Health professionals are not well prepared for communication about the futures of individual health	Develop risk-disclosure guidelines, educate healthcare providers and train clinicians on precision psychiatry
High-risk of data leakage and privacy concerns, Big Data and actors from outside the healthcare system	Implementation of robust data governance and security that comply with the local regulations
Observational health data are used in precision psychiatry without accounting for context blindness bias	Promote interdisciplinary bias-aware research and innovation practices with clinicians and patients being included at all stages (problem formulation, data pre-processing, models selection, testing, validation, and implementation)
The impact of precision psychiatry on the inequitable distribution of mental health resources is unknown	Conduct cost-effectiveness research of precision psychiatry and test generalisability in vulnerable groups
Access to precision psychiatry is still limited in particular for vulnerable groups	Implement policies aimed at prioritizing the technological accessibility of the marginalized populations.

not performed; what would be the results in a few years' time? To address these sorts of questions, this study will consider ethical values in a broader sense, for example, by taking into account some of the different principles present in the charter of fundamental rights of the European Union – starting from dignity, freedom, equality, solidarity, citizens' rights and justice (Table 1) (European Union, 2012; Hallinan, 2021). In particular, human dignity and human flourishing are the most crucial elements from an ethical point of view that are tightly linked to autonomy and self-determination (which is modulated by several factors such as physical health, psychological state, sociocultural environment, as well as values and beliefs). The loss of insight associated with some psychiatric disorders may incapacitate the individual to make autonomous decisions. For example, autonomy emerged as the driving decision component for undergoing risk prediction testing among young populations (Mantell et al., 2021a), regardless of whether a person would decide for or against risk profiling. Finally, it is important to highlight that unique ethical considerations may be associated with the historically complex socio-political perceptions and attitudes towards severe mental disorders and psychiatry (Ball et al., 2020a; Manchia et al., 2020a).

3.2. Learning from somatic medicine – Progress in oncology

Examples of how precision approaches can ethically lead to a paradigm shift can be seen in modern precision oncology

(Le Tourneau et al., 2019; National Cancer Institute, n.d.). While the challenges that can be addressed with precision medicine methodologies are substantially distinct between oncology and psychiatry, understanding the scope of application of these methods may be useful when considering future development and implementation of similar tools within psychiatry, particularly in terms of the ethical implications (e.g. the impact of genetic counselling). Relevant technological breakthroughs in this discipline have allowed the development of new treatments capable of pointing to singular molecular targets. For example, based on clinical trial findings (von Minckwitz et al., 2017), the Food and Drug Administration (FDA) approved the use of pertuzumab in addition to adjuvant trastuzumab in patients with HER2-positive early breast cancer (Howie et al., 2019) and pembrolizumab to target specific microsatellite genome instability (Marcus et al., 2019). Furthermore, the implementation of extensive molecular profiling such as transcriptomics, tumour DNA and genome sequencing has informed therapeutic decision making in more severe forms of cancers (Rodon et al., 2019; Rothwell et al., 2019; Sicklick et al., 2019). In addition, risk stratification using polygenic hazard scores has reached levels of accuracy to translate into clinical applicability in the case of prostate cancer (Huynh-Le et al., 2020; Seibert et al., 2018). The development of next-generation sequencing, combined with the availability of electronic health records (EHRs) and decision support applications, has provided tools that can improve outcomes and quality of life (Kato et al., 2020). For example, treatments recommended by a molecular tumour board, compared with 'physician choice' treatments, resulted in significantly longer progression-free survival and overall survival for patients to the point that the need for randomised clinical trials in patients with progressed cancer has been questioned (Lassen et al., 2021). Furthermore, precision oncology has shifted toward transdiagnostic targeting of actionable mutations that can be found across multiple cancer types (Lassen et al., 2021).

This represents a major difference with respect to precision psychiatry, which still operates detached from molecular understanding in a mechanism-agnostic fashion, in the lack of established "objective" biomarkers (e.g. genomics, neuroimaging) (Manchia et al., 2020b). Illustrative examples are polygenic models that predict only a limited amount of the known heritability. Hundreds of common variants are associated with psychiatric conditions such as schizophrenia (Trubetskoy et al., 2022), individually contributing small effects (polygenic disorders). Still, in combination they explain a significant fraction of variance, which is the basis of polygenic risk scores (Landi et al., 2021; Martin et al., 2019). However, the common variants are often pleiotropic (i.e. associated with more than one diagnostic category) (Smeland et al., 2019). While polygenic risk score predictions are improving, they still lack clinical utility (Smeland and Andreassen, 2021), raising ethical concerns (Daws, 2017; Landi et al., 2021). Therefore, precision psychiatry may be more interpretive (Panel 1) than an exact science, requiring consideration of symptoms and categories of people living in society rather than objective biomarkers. The proposed solution is to implement core methodological innovations that can support the ethical acceptability of precision psychiatry, as discussed below.

3.3. Refining multimodal, neurobiologically-informed precision psychiatry

An overarching ethical concern is that prediction accuracy may be too poor to be clinically useful. For example, a recent meta-analysis has shown that individuals at clinical high-risk for psychosis could be classified against healthy control subjects with 78% sensitivity and 77% specificity using different types of prediction methods (Sanfelici et al., 2020), representing sub-optimal performance. Clinical prediction models' performance in psychiatry may specifically increase when theory or expert knowledge constrains input data to disorder-relevant features (Bharadwaj et al., 2017; Raghu et al., 2017). For example, by integrating machine-learning estimates with clinician judgment on the prognosis, the accuracy of the prediction raised to 86% from 73% when based on clinician judgment alone (Koutsouleris et al., 2021a). This "cybernetic" version of artificial-intelligence models would also allow keeping the "human in the loop" (Jotterand and Bosco, 2020) of precision psychiatry, maintaining the essential human connection with suffering individuals and mitigating the bias of excessive automation, hyper-personalisation, decision-automation, which in turn trigger automation-distrust bias (Panel 2). However, this level of accuracy might represent an upper ceiling effect, as severe mental disorders represent such a complex system of illnesses, with high rates of heterogeneity, both phenotypic and biological, that it might not be possible to resolve without high-dimensional (i.e. multimodal) data. This approach better captures the multifactorial origin of psychiatric disorders, which extends from the underlying genetic and environmental risk factors to neurobiology (Arango et al., 2021; McCarthy and Birney, 2021) relating to individuals' sociocultural backgrounds and histories. Clinical and environmental metrics collected longitudinally can help supplement biological and genetic information to better model the individual trajectories of patients from good health to disorder onset (McCarthy and Birney, 2021). However, multimodal models have ethical implications: increased patient burden (due to more extensive assessments), increased costs for society (paying for additional examinations), and increased risk for inequalities between patients as only a minority of service users will have access to the different tests required to reach useful clinical yield while retaining significant diagnostic uncertainty (e.g. about 15%) (Koutsouleris et al., 2021a).

At the same time, as noted above, features analysed by psychiatric clinical prediction models are typically complex derivatives of the original data, such as connectivity matrices derived from functional MRI signal fluctuations, not enriched by information on disorder mechanisms and their causal links to targeted outcomes. The lack of a neurobiological mechanistic reference frameworks impacts substantially on the utility of clinical prediction models: mechanism-agnostic models cannot be linked with personalised strategies, and their inability to back-project predictions to a person's biomarker signatures reduces trustworthiness and ethical acceptability. This problem is further amplified by the overall lack of normative biological data that can be used as benchmark references (Dima et al., 2021; Frangou et al., 2021).

However, evidence is emerging for neurobiological-based biomarkers leading to stratification and individualized prognosis/diagnosis strategies for individuals at clinical high-risk for psychosis (Chan et al., 2015; Dickens et al., 2020; Mongan et al., 2020; Perkins et al., 2015) and individuals in the early phases of psychosis (Khadimallah et al., 2021). Furthermore, a potential solution is to refine candidate prediction models towards neurobiological interpretability by using new computational methods (Khanna et al., 2018). These encode complex disease pathways comprising biological entities (e.g. genes, proteins), clinical outcomes or normative data and their causal relationships (Slater, 2014). Although multimodal models have been used to support putative disease mechanisms via brain simulation (Stefanovski et al., 2021; Triebkorn et al., 2021), decision support based on patient 'avatars' (Emon et al., 2020; Khatami et al., 2020; Schultz et al., 2021), drug repurposing (Lars V. Kessing et al., 2019; L.V. Kessing et al., 2019) or the development of novel modes of action (Rivas-Barragan et al., 2020), they are not yet clinically validated for implementation in precision psychiatry.

3.4. Enhancing methodological transparency and generalizability to pre-empt ethical concerns

Nevertheless, multimodal clinical prediction models come with higher complexity, and poor explainability, to end-users and regulators (Beam et al., 2020), which raises ethical concerns. This applies in particular to machine-learning ("black-box", Panel 2) methods that do not allow for back-tracing of the key patterns that produced a specific prediction (e.g. nonlinear data transformations) (Lipton et al., 2019). While clinicians rightly crave actionable insights at the time of decision making in line with the five rights of decision support; the right information, delivered to the right person, in the right intervention format, through the right channel, and at the right time in the workflow (Osheroff and Healthcare Information and Management Systems Society, 2012), black-box models are uninterpretable (Radua and Carvalho, 2021). Furthermore, the more complicated the models become, the higher the risk of operator error, reinforcement of structural biases, overoptimism, and algorithmic biases (Panel 2). These limitations may eventually reduce the models' trustworthiness and ethical acceptability, impede clinical adoption (Kundu, 2021), and raise discriminatory harms (Jobin et al., 2021). Transparent, glass-box alternatives (explainable/interpretable machine learning as detailed in the initiative "AI4people" (Floridi et al., 2018) and FAST track principles: Fairness, Accountability, Sustainability, Transparency, eSupplementary 1) that complement these models with interpreters (e.g. "*why/how did the model produce this prediction in my case?*") (Molnar et al., 2020) and detail the rationale behind the decisions (Burgos and Colliot, 2020; Leslie et al., 2021) should be considered to increase the transparency of individual predictions and in turn the models' trustworthiness and ethical acceptability (Nori et al., 2019).

The additional ethical concern is that the generalisation capacity of most precision or stratification psychiatry methods is currently suboptimal. A recent meta-analysis has identified that about six hundred individualised clinical prediction models have been published in psychiatry, but only 10% have been internally validated, and only 5% externally validated (Salazar de Pablo et al., 2021b). Unknown generalisability due to lacking external validation in representative samples may raise ethical concerns because the utility of a prediction algorithm is highly dependent on the quality and relevance of the data on which it is trained. For example, a prediction model built on genetic risk factors of disorders in a population with European ancestry currently will not work well in individuals of African descent (Koutsouleris et al., 2021a; Olde Loohuis et al., 2021), though this is addressed in advances in trans-ancestry genetics (Huynh et al., 2021), which is currently a focus in the psychiatry field (e.g. (Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2019)). Similarly, a model predicting psychosis in secondary care patients may not perform well in primary care (Fusar-Poli et al., 2017).

These concerns are particularly serious for the heterogeneous and changing societal, cultural, and healthcare contexts of vulnerable people (e.g. ethnic or sexual minorities) (Millman et al., 2019). Health disparities contribute to algorithmic biases (Walsh et al., 2020): datasets used to train, test, and validate the models are too often insufficiently representative, under/oversampling individuals with diverse ancestries or vulnerable subgroups (e.g. the disproportionate number of diagnoses of schizophrenia in ethnic minorities) (Leslie et al., 2021) (Panel 2), leading to higher error rates for members of marginalized communities (Leslie, 2020). Care should be taken to ensure that clinical prediction models do not discriminate in risk assessment, in particular with respect to sociodemographic data (e.g. ethnicity is a socially constructed set of categories), which are much more interpretive.

Another issue relates to the so far neglected dimension of generalisation capacity is the between-sex applicability and age-dependency of prediction models. These concerns apply particularly to clinical prediction models based on biophysical data, such as geolocation (Capon et al., 2016), social media data (Nicholas et al., 2020), smartphone data (Roy, 2017; Torous et al., 2021) or EHR data (Fernández-Alemán et al., 2013) (e.g. non-binary gender is typically not recorded), which might be much more subject to these biases (Leslie et al., 2021). Future collaborative research should vet current prediction models against deeply-phenotyped and large scale clinical samples and epidemiologically valid registry cohorts through the establishment of a platform for federated, harmonised data access. Examples of these initiatives are brought forward by the ECNP Networks collaborations referenced above or the replication of an individualised risk calculator for predicting the onset of psychosis across different research consortia (Koutsouleris et al., 2021b).

3.5. Fostering implementation science of precision psychiatry

A recent systematic review found that less than 1% (only one pilot implementation study of a risk calculator screening EHRs to detect young people at-risk of psychosis) (Fusar-Poli et al., 2019; Oliver et al., 2020; Wang et al., 2020) of clinical prediction models published in psychiatry was

considered for real-world implementation in clinical practice (Salazar de Pablo et al., 2021b). This highlights major gaps in the translational cascade of precision psychiatry. The 'valley of death' between promising innovation and clinical implementation (Scangos et al., 2021) is a main source of serious ethical concerns relating to the real-world beneficence of precision psychiatry for the life of the patients. Overall, implementation barriers should be considered in the very early phases of model development. Although implementation frameworks and templates for precision medicine are poorly established, the only available implementation study for psychosis risk adopted the Consolidated Framework for Implementation Research during an in-vitro phase to identify implementation factors and plan practical solutions to address them early in advance to model validation (Oliver et al., 2020). Notably, implementation research is participatory and necessitates a strong alliance between users and healthcare providers (see below).

The factors described above (suboptimal accuracy, neurobiological interpretability, explainability, generalisability) have been demonstrated to amplify ethical barriers to implementing precision psychiatry (Baldwin et al., 2022). Other factors may include undemonstrated cost-effectiveness and scalability related to algorithmic complexity: digital phenotypes as generated by mobile devices or EHRs are particularly attractive solutions in this respect (see below).(Fusar-Poli, 2021) A greater research focus on the economic modelling of high-cost precision medicine methodologies is needed. Furthermore, while improving and updating existing models represents a better way to maximise cost-efficiency (Fusar-Poli et al., 2018) over the wasteful overabundance of *de novo* model development (Adibi et al., 2020), there are no feedback systems to iteratively improve them based on empirical insights into their clinical utility. Moreover, the rapidly growing number of prediction models is exacerbating existing issues: which models should be combined to produce optimal predictions? How should models be aligned along care pathways to be maximally useful? How do complex models compare to fast and frugal heuristics (e.g. clinicians' judgement) (Djulbegovic et al., 2018; Goldstein and Gigerenzer, 2009; Nagendran et al., 2020; Wilkinson et al., 2020)? An exciting possibility would be to create models that consider sparsity and parsimony (*"why do we need to conduct all these examinations?"*) and that are constantly being updated and recalibrated, in a continuously learning health system (McGinnis et al., 2021), to adapt to incoming data, new settings, and new clinical practices (Adibi et al., 2020), although these models would be more complex to interpret and implement. This would require establishing an integrated infrastructure to facilitate selecting and testing the best clinical prediction models for their clinical utility (Adibi et al., 2020).

3.6. Promoting mental health literacy to consolidate the alliance between users and health care providers

The alliance between patients, their families/carers and healthcare providers is weak, threatening patients' self-determination in society. Self-determination and autonomy are highly dependent on the degree of mental health literacy, a core domain of good mental health (Fusar-Poli et al., 2020b; Fusar-Poli and Santini, 2022), incorporating knowledge, competence and motivation of individuals to meet the demands of mental health in modern society (Sørensen et al., 2012). Mental health literacy of key situations of risk awareness, the understanding of disease risk, and risk-related agency plays an essential role in the process of understanding the individual's risk threshold, of how the individual copes with it, and how they are able to integrate it into their identity, health-related behaviour and life plan (Harzheim et al., 2020). Therefore, fostering mental health literacy is essential to consolidate self-determination, autonomy and the alliance between stakeholders. For example, community mental health services for the prevention of psychosis offer mental health literacy packages around vulnerability to the disorder and its implication on the individual as family, thus supporting the active alliance between patients, their families and clinicians (Estradé et al., 2022; Fusar-Poli et al., 2020c; Kotlicka-Antczak et al., 2020; Salazar de Pablo et al., 2021a). There is also evidence that educating teenagers about gene-environment interactions facilitates the translational efforts of precision psychiatry (Sabatello et al., 2021a). To address these issues, future research should carefully assess how precision psychiatry models reconfigure the alliance between patients, families and healthcare providers.

3.7. Communicating risk estimates and understanding implications

While the traditional medical research model is largely one-directional where participants contribute data that is analyzed by researchers to yield generalizable knowledge (Nebeker et al., 2019), precision psychiatry requires sharing information with the users. Communicating the outcome of risk prediction is a complex and perilous task. There is an air of paradox: while patients are supposed to be the key beneficiaries of precision psychiatry, their preferences are currently underarticulated (Kettner, 2014). As people may vary in terms of their disclosure preferences (e.g. *"wanting to hear about risk/prediction")* (Mittal et al., 2015). and ability to understand the impact of the information given, it is imperative to first ask patients whether and how much they would like to be shared about precision psychiatry results in order to make an autonomous decision. Future interpretive research should also better understand the role of sociomedical marginalization in decisions about sharing precision psychiatry results. For example, some surveys found ethnic minority groups (Halbert et al., 2016) and disabilities groups (Sabatello et al., 2020) were less interested in receiving precision medicine results than the general population. There is also an ongoing dialogue among researchers, research policy specialists, and ethicists about obligations to communicate certain kinds of individual results (e.g. incidental findings) to participants that could usefully inform debates in the clinical context (Fiore and Goodman, 2016).

Individuals express concerns on how risk prediction can potentially be career-altering and life-altering (Mantell et al., 2021b), fearing loss of autonomy and self-determination (Mantell et al., 2021b): the simple act of

defining risk may foster stigmatization and discrimination (Ratheesh et al., 2017). For example, providers and clinicians may feel compelled to respond to a "high-risk" designation (e.g. for suicide) through readmission. At the same time, public (prejudice held by the general population toward patients) and self-stigma (prejudice internalized by the patient) (Manchia et al., 2020b) may be greater for symptoms and behaviours than for risk labels (Yang et al., 2015).

Communicating a risk estimate to an individual might also change the risk itself, based on their consequent decisions (e.g. perform clinical assessments) but also on actionable modifiable risk factors and behaviours and, in turn, on the underlying biology. This back and forth between risk prediction and human reaction may raise ethical concerns, for example, accountability gaps (Panel 2), in particular given that risk communication typically is an accompaniment of the patient during the whole course of their being at-risk. The solution is to establish a governance framework taking into account a multidisciplinary approach involving the clinicians, psychosocial workers, legal experts, or different professionals.

The associated ethical issue is "how" to disclose risk estimates. In general, healthcare operators should focus on patients' preferences and priorities on the level of knowledge that they would like to receive. Methods of disclosing at-risk designations (Mittal et al., 2015; Sisti and Calkins, 2016; Woods et al., 2021) that match cultural preference toward the type of disclosure of risk should be better developed elucidating the variable stakeholder perceptions (Mittal et al., 2015). For example, pilot studies showed that sharing results with clinicians and not with the patients can allow for nuanced and personalised communication of risk in the context of clinical care (Oliver et al., 2020). Therefore, the ability to communicate the results of a risk prediction analysis ethically relies heavily on the competence, level of knowledge and training, and skills of the health professionals (Betancourt et al., 2002). This appears particularly crucial for sharing behavioural genetics findings (Palk et al., 2019), given that the risk of misinterpreting results might increase the potential for discrimination and stigma (Sabatello et al., 2021b). Communicating risk estimates properly should also include an adequate knowledge of the limitations of the methodology used to produce them and their discussion with the service users and their families (Smeland and Andreassen, 2021). For example, studies show a need to educate healthcare providers regarding approaches to facilitate sharing of genetic results within families (Wynn et al., 2021). This is particularly pertinent as genetic results may have implications for more than one family member. Considering how to best communicate risk is also relevant in light of the continuous (and not categorical) nature of several precision psychiatry results returned, and for the varying degree of severity of the eventual prognosis, and the appropriate indicated intervention, corresponding to the increasing risk (eSupplementary 2) (Lawrie et al., 2019).

The core solution is, therefore, to develop practical risk-disclosure guidelines, educate healthcare providers and train clinicians to adequately operate prediction models, interpret and communicate predictions ("*Could you explain to me how this model works?*"). A recent systematic review confirmed that the availability of adequate competence and skills training for staff is the most important facilitator of precision psychiatry implementation (Baldwin et al., 2022).

3.8. Protecting sensitive data and privacy issues in the era of digital medicine

Digital technology is already changing the paradigm of care in mental health (Bauer et al., 2019; Torous et al., 2021), offering a convenient and flexible approach for sharing precision psychiatry results with participants (Nebeker et al., 2019). At the same time, there are ethical concerns related to privacy, cybersecurity, confidentiality and device dependability (Aboujaoude, 2019; Klugman et al., 2018; Weber et al., 2018), in particular given the presence of Big Data and actors from outside the healthcare system. For example, leaking of private information can affect personal lives, including bullying, high insurance premiums, and loss of jobs due to medical and psychiatric history (Thapa and Camtepe, 2021). These concerns should be addressed by the implementation of strict data governance and security policies that comply with the local regulations (eSupplementary 3), and can be achieved through early and sustained multidisciplinary interactions with individuals and regulatory bodies. These best methods and techniques to achieve data security and privacy, informed consent management, maintaining the trustworthiness of data and adhering to legal regulations are common to other areas of precision medicine and have already been discussed (eSupplementary 4) (Thapa and Camtepe, 2021).

Specific ethical concerns apply to EHR databases, which often report indirect measures; the data often do not directly reflect the health of the patient but also clinicians' and patients' interactions with the system. For example, financial incentives for screening for a particular condition, various other billing and treating codes influencing reimbursements may be significant contextual elements that should be considered (contextual bias, Panel 2) (Agniel et al., 2018). The speed by which technology is making Big Data available to biomedical researchers is outpacing the development of new analytical techniques to understand the implicit processes that lead to their generation (Agniel et al., 2018). Thus, bias-aware interdisciplinary research and innovation practices will be needed across clinicians and other stakeholders in the development, validation and implementation of precision psychiatry models (see also below).

3.9. Fostering the equitable distribution of mental health care through precision psychiatry

Despite the high potential of precision psychiatry, there is also some risk for these methods to perpetuate existing patterns of inequities that pervade the healthcare industry. These may include discriminatory healthcare processes due to unequal access (e.g. disadvantaged economies are less likely to access costly biological and/or neuroimaging scanning) and resource allocation (e.g. limited number of special care programs, particularly for prevention) (Figure 2). These inequalities may feed discriminatory data

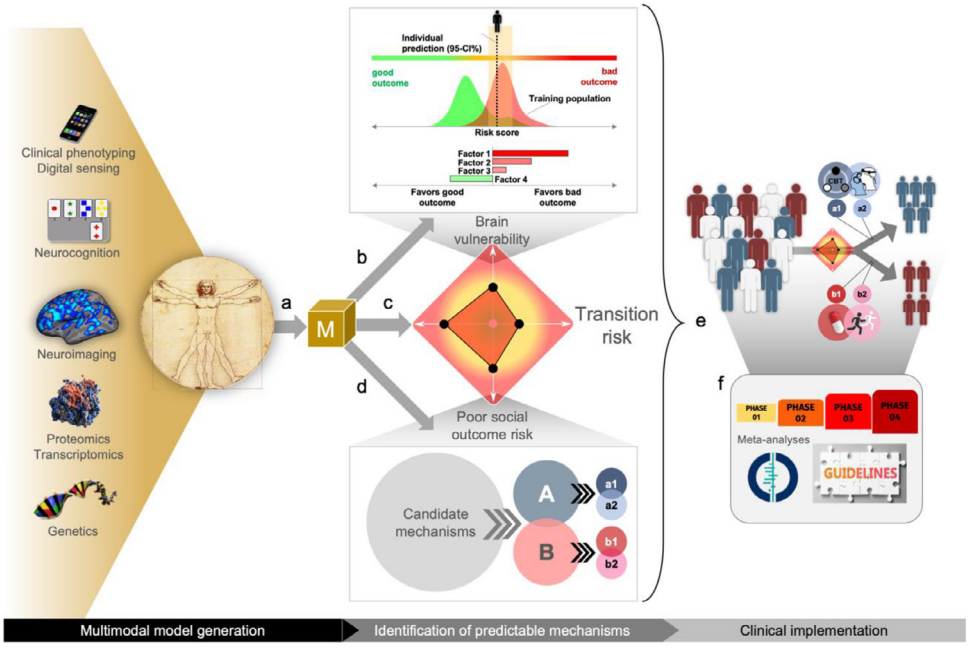

Figure 1 Components of the precision psychiatry ecosystem. A precision psychiatry ecosystem ideally links patients, providers, clinical laboratories and researchers through the use of screening, prognostic, diagnostic and therapeutic clinical prediction models. a = modelling; b = transparent prediction; c = heterogeneity analysis & deconvolution; d = guided mechanistic research; e = stratified clinical trials; f = clinical knowledge embedding.

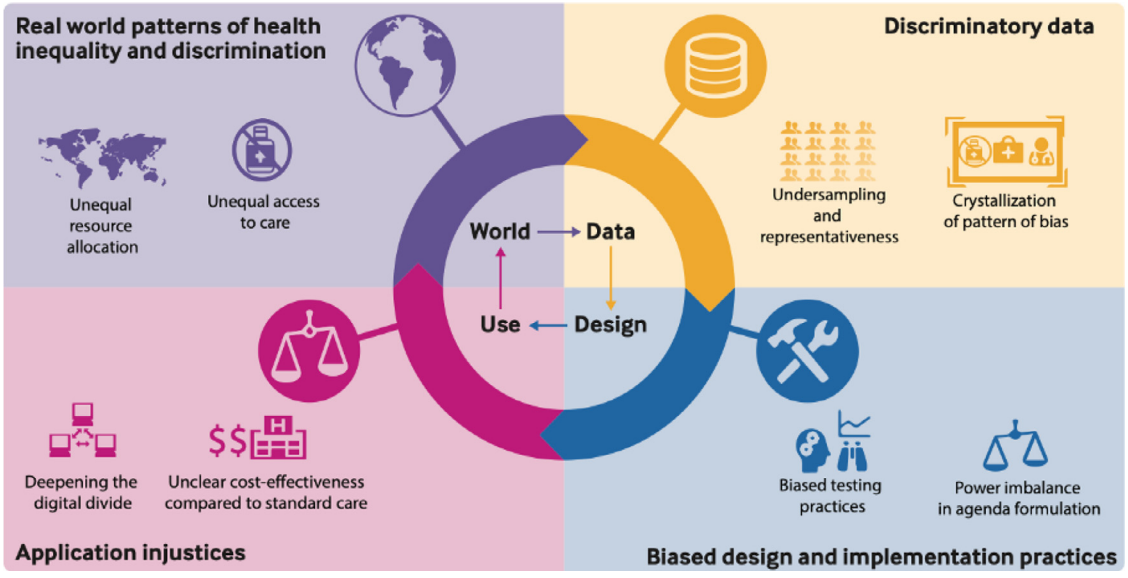

Figure 2 Potential cascading effects of precision psychiatry on the equitable distribution of mental health care. Adapted from (Leslie et al., 2021)

through representativeness biases and crystallisation of patterns of inequalities that are baked in the data distribution (e.g. a successful model has to reproduce the patterns of social and demographics data) (Figure 2). Power and balances can then show up in the design phase (e.g. *which clinical questions should be reformulated as statistical problems?*), for example, who is deciding to pursue designing precision psychiatry models (Figure 2). For example, an industrial-grade machine-learning clinical prediction model released by the insurance industry was demonstrated to systematically discriminate millions of black patients because it had equated healthcare costs with the status of ill health (Obermeyer et al., 2019). Additional ethical concerns may involve the testing practices that come in the implementation of systems and at the user level. These ethical concerns may ultimately lead to application

inequalities (Figure 2). While more precise prognoses and tailored interventions might result in more cost-effective approaches (Starke et al., 2020) and convince policymakers to implement evidence-based preventative approaches (Arango et al., 2018; Fusar-Poli et al., 2020a; Salazar de Pablo et al., 2021b), there is not yet a solid demonstration of the cost-effectiveness of precision psychiatry over standard approaches. Growing digital divides can also amplify disparities in the accessibility of clinical prediction models in economically disadvantaged or marginalized populations, as it has also been highlighted during the COVID-19 pandemic, where many people did not have an adequate internet connection to access digital medicine models (Leslie, 2020). The proposed solutions, beyond those already discussed, call for more extensive cost-effectiveness research of precision psychiatry and policies aimed at prioritizing the technological accessibility of the marginalized populations.

In conclusion, while precision psychiatry is at the forefront of mental health innovations, it also raises unprecedented ethical concerns at the individual, healthcare and whole societal level (Ball et al., 2020b). The current roadmap opens up the possibility to identify and question these ethical concerns and mitigate them through recommended strategies. We propose that these findings will represent a core benchmark for future multidisciplinary research and clinical practice in this area, stimulating an ongoing discussion among funders, healthcare providers, clinicians, patients, families and caregivers, to support the real-world potential of precision psychiatry.

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Ethics declarations

.**Panel 1** Core concepts in precision psychiatry

- Precision medicine — "an emerging approach for treatment and prevention that takes into account each person's variability in genes, environment, and lifestyle"(Toward Precision Medicine, 2011)
- Clinical prediction model — an algorithm (screening, prognostic, diagnostic, therapeutic) employing a number of predictors to provide risk estimates of a clinical outcome.
- Prognostic model — An algorithm that forecasts outcomes independent of treatments.
- Predictive model — An algorithm that forecasts treatment-dependent outcomes.
- Autonomy — The right for an individual to make his or her own choice.
- Beneficence - The principle of acting with the best interest of the other in mind.
- Non-maleficence - The principle that "above all, do no harm".
- Justice - Fairness and equality among individuals.
- Interpretability—Why a clinical prediction model arrives at an output/prediction
- Explainability—How a clinical prediction model arrives at an output/prediction
- Interpretive science/research—Consider the subjective viewpoints or experiences of the individual and how they have a bearing on facts that are being considered.

. **Panel 2** Common precision psychiatry biases and errors that should be mitigated to prevent ethical concerns

- **Excessive automation**—The reduction of the need for human-to-human interaction leading to isolation.
- **Hyper-personalisation**—Limiting our exposure to worldviews different from ours might polarise social relationships and disintegrate social connections built on relations of trust, empathy, and mutual understanding.
- **Decision-automation bias/Technological-Halo Effect**—Users of automated precision psychiatry model may become hampered in their critical judgment as a result of their faith in the perceived certainty or superiority of the artificial-intelligence system.
- **Automation-distrust bias**—Users of an automated precision psychiatry model may disregard its salient contributions because of distrust, skepticism, over-prioritisation of common sense/human experience, aversion to the "amoral" character of artificial-intelligence.
- **Black-box bias—**Artificial-intelligence-based clinical prediction models whose inputs and operations are not visible to the user or another interested party may lead to low ethical and scientific acceptability.
- **Representativeness bias—**Underrepresentation or overrepresentation of disadvantaged or vulnerable groups (e.g. ethnic or sexual minorities) in the data sample may lead to discriminatory harm.
- **Operator error—**Unintended errors (invalid data) caused by humans who programme/operate clinical prediction models may reduce trustworthiness.

- **Reinforcement of structural bias**—Complex algorithms not properly validated may reinforce pre-existing errors (e.g. representativeness bias) and lead to discriminatory harm.
- **Overoptimism** —Overfitting a clinical prediction model to training data without testing it in unseen data (external validation) produces inaccurate predictions and low ethical acceptability.
- **Algorithmic bias**—Errors in data generation (historical bias), population selection (representation bias), measurement, model specification, validation, implementation.
- **Privacy leakages**—Use of health data without consent.
- **Contextual bias**—Observational health data used in precision psychiatry without accounting for underlying healthcare practices, domain-specific norms, learning processes, and patient/environment interactions.
- **Digital divide**—Inability to use the new technologies (e.g., by senior or socially emargined citizens) for the services delivered through the new technologies.
- **Accountability gaps**—The designation of individual responsibility may be complicated in algorithmically generated decisions, predictions or classifications, harming the autonomy and violating the rights of the affected individuals.

Competing interests

The authors declare no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2022.08.001.

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