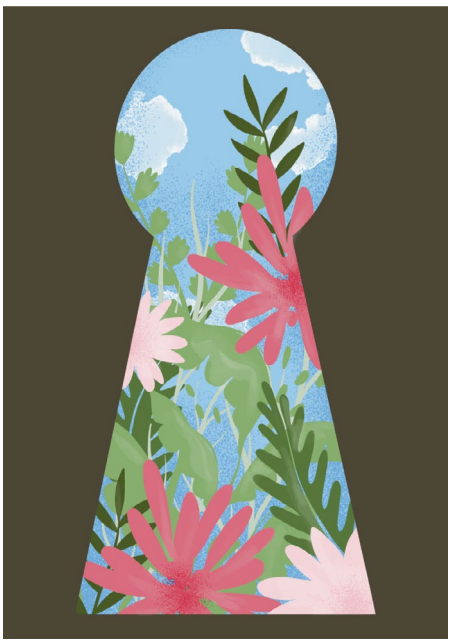
https://doi.org/10.1038/s44220-023-00131-y

The right treatment for each patient: unlocking the potential of personalized psychiatry

Personalized medicine has made substantial strides in treating cancer and rare genetic disorders by leveraging advances in genomics, yet psychiatry has lagged behind. The complexity of psychiatric disorders, owing to heterogeneity, polygenicity and environmental and epigenetic effects, calls for varied approaches in achieving personalization.

The concept of tailoring treatment for an individual patient's needs is not new. The work of Hippocrates (c. 460–370 BC) was predicated on the notion that each person possesses a unique composition of four humors or bodily fluids – black bile, yellow bile, blood and phlegm – that determine their temperament and, when imbalanced, lead to sickness. Since the days of Hippocrates, the understanding of an individual person's makeup and the concept of using so-called 'personalized medicine' to diagnose and to treat illness have evolved into a multidisciplinary engine for research and clinical application. In just the past few decades, major advances have been made in treating cancer (breast cancer, lung cancer, colorectal cancer, etc.) and rare genetic diseases (such as muscular dystrophy and spinal muscular atrophy), largely due to progress in genomic technology.

Unlike the high-profile breakthroughs made in personalized medicine, progress in psychiatry, which relies mainly on subjective methods of assessment and firsthand accounts for diagnosis, has lagged behind in delivering personalized treatments. Paradoxically, psychiatry is a field that could benefit greatly from more personalized approaches, owing to the wide heterogeneity of symptoms within individual disorders. Many psychiatric disorders are complex and can be associated with numerous, often thousands of, genetic variants, each, however, with a small effect. Polygenicity and high heterogeneity in psychiatric disorders, combined with environmental and epigenetic effects, suggest the need to apply different approaches and lines of action to shaping personalized psychiatry.



In a related way, some of the bedrock of clinical wisdom in psychiatry has begun to erode. Since the advent of monoamine-oxidase inhibitors and tricyclic antidepressants in the 1950s, these drugs have been a mainstay in psychiatric care. However, recent work has challenged long-held and widely accepted statistics about the efficacy of antidepressants. A re-analysis[1] of the patient-level dataset from the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study demonstrated that, in contrast to the previously reported cumulative remission rate of 67% (ref. 2), after examination of key methodological deviations from research protocol and related publications, the actual rate of remission was only 35.0% of participants – a precipitous drop in what has become a benchmark estimate for antidepressant efficacy.

Despite the potential need for reexamination of some of the foundational tenets of psychiatry, there continue to be areas of progress. Several contemporary approaches are moving the field forward and are providing useful insight and new directions. Brain-stimulation therapies (for example, transcranial magnetic stimulation and deep brain stimulation) used for treating various mental disorders, such as depression and obsessive–compulsive disorder, represent a rapidly evolving and promising area of personalized psychiatry. Through neuroimaging, the stimulation target sites and frequency are optimized to suit an individual patient's brain structure, function and connectivity and their clinical symptoms. For example, those patients who do not respond to brain-stimulation therapy might have a functional architecture or brain anatomy that deviates from the consensus targets, which emphasizes the importance of personalizing treatment sites. Treatment timing is also critical: stimulation of the same target region can produce different clinical responses depending on the emotional state of the patient during stimulation. To this end, there is a need for better quantification of brain–behavior interactions over shorter timescales.

Among other promising approaches is pharmacogenomics, which allows the examination of genetic attributes that may affect a patient's response to medications. For example, variations in specific genes whose products are involved in pharmacokinetics (e.g., genes encoding proteins that affect drug metabolism) and/or pharmacodynamics (e.g., genes encoding specific receptors and transporters) may affect drug exposure and response to treatments and, therefore, the likelihood of remission and risk of side effects. Despite initial enthusiasm, pharmacogenomics as a field has not yet developed to the point of accurately identifying the most appropriate psychiatric medication for a given person. At present, the utility of pharmacogenomics is restricted to narrowing down the treatment options to a safer group of psychiatric medications.

In contrast to paradigms that are focused on pinpointing treatment options, personalized psychiatry advances are also being generated through widening of the scope of measures that identify genetic and molecular functioning. Integration of multi-omics data (genomics, transcriptomics, epigenomics,

proteomics, metabolomics, etc.) into the diagnostic process enables a transdiagnostic approach by capturing the full heterogeneity and characterizing functioning within a spectrum rather than within rigid categorical diagnoses and unitary disease entities. Complementing large-scale multi-omics approaches, big data includes other modalities, such as high-density behavioral data, neuroimaging, electronic health records, data from multiple body systems and data monitored by wearables (sleep patterns, physical activity, heart rates, blood oxygen, etc.), adding more keys with which to unlock the complexities of mental disorders. Collecting and making any pragmatic use of this huge amount of data requires large-scale collaboration efforts and highlights the need for tighter cross-talk between psychiatrists and other physicians, data scientists and public health professionals.

Given the inherent complexity of big data that can interact in multiple and non-linear ways, artificial intelligence algorithms, particularly in the domains of machine learning and deep learning, are crucial to processing and interpretation. Caution must be exercised in how these data are handled and how the results are implemented in clinical settings. Data-driven insights can vary and range from identifying veiled patterns and risk factors to assisting in diagnosis, defining biomarkers and predicting treatment response. At present, however, there is no formalized actionable guidance on establishing the utility of a predictive model in a clinical setting. For instance, setting a generic performance threshold for accuracy is problematic, as specified cut-offs may be dependent on the type of clinical decision that the model aims to support. Predictive models are often built by academic researchers, yet one of the barriers to the clinical implementation of such tools is the willingness of clinicians to adopt them for use in routine care. Cost-effectiveness is another important concern. Data collection is expensive, time-consuming and often not feasible, owing to budget restrictions, lack of personnel to work with the complex data, and the reluctance or inability of patients to participate in multiple time-consuming and potentially stressful procedures. Input from patients themselves, their perspectives and lived experience should be incorporated in all stages of research and clinical implementation.

In this digital era, there has been a huge rise in the use of various digital mental health apps and interventions with claims of cost-effectiveness and personalized delivery of treatment. However, empirical evidence is often lacking and inconclusive, and there is a risk of abuse, in that private companies might exploit suffering for profit through the 'app-ification' of mental health services. It is crucial to take into account the likelihood that mental health apps may lead to overdiagnosis. Ethical and privacy concerns about the collection and analysis of sensitive data underscore the need to protect people's privacy. Data that have been anonymized can often be re-identified, and consent for non-clinical mental health data collected digitally is not standardized or comprehensively regulated. Furthermore, without greater consideration of the processes involved, personalized psychiatry may have the potential to increase disparities linked to inequities in socioeconomic status, age, gender, geography, language, disability status, citizenship status, and sexual identity and orientation. Focused work by stakeholders at community and national levels to promote equity when personalized psychiatry is brought to practice is indispensable.

In the case of psychiatry, it seems inevitable that only solutions from multi-modal and large datasets can provide a 'skeleton key' for unlocking the potential of personalized approaches that can be used in a wider population. Given the richness and immense amount of data that are becoming available and that can be processed only by artificial intelligence algorithms, practical translation of their output into clinical routine care is still not a reality. Taking into account the many potential issues that arise, including questions of ethics and inequities, this process should be treated with extreme care in order to truly follow the principle of the 'right treatment for each patient'.

Published online: 6 September 2023

References

1. Pigott, H. E., Kim, T., Xu, C., Kirsch, I. & Amsterdam, J. *BMJ Open* **13**, e063095 (2023).
2. Rush, A. J. *Am. J. Psychiatry* **163**, 1905–1917 (2006).