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PERSPECTIVES

From Personalized Medicine to Precision Psychiatry?

Eva Češková [1–4]
Petr Šilhán [1,2]

[1]Department of Psychiatry, University Hospital Ostrava, Ostrava, Czech Republic; [2]Department of Clinical Neurosciences, Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; [3]Department of Psychiatry, University Hospital Brno, Brno, Czech Republic; [4]Department of Psychiatry, Faculty of Medicine, Masaryk University, Brno, Czech Republic

Abstract: Personalised medicine aims to find an individualized approach for each particular patient. Most factors used in current psychiatry, however, depend on the assessment made by the individual clinician and lack a higher degree of reliability. Precision medicine bases decisions on quantifiable indicators available thanks to the tremendous progress in science and technology facilitating the acquisition, processing and analysis of huge amounts of data. So far, psychiatry has not been benefiting enough from the advanced diagnostic technologies; nevertheless, we are witnessing the dawn of the era of precision psychiatry, starting with the gathering of sufficient amounts of data and its analysis by the means of artificial intelligence and machine learning. First results of this approach in psychiatry are available, which facilitate diagnosis assessment, course prediction, and appropriate treatment choice. These processes are often so complex and difficult to understand that they may resemble a "black box", which can slow down the acceptance of the results of this approach in clinical practice. Still, bringing precision medicine including psychiatry to standard clinical practice is a big challenge that can result in a completely new and transformative concept of health care. Such extensive changes naturally have both their supporters and opponents. This paper aims to familiarize clinically oriented physicians with precision psychiatry and to attract their attention to its recent developments. We cover the theoretical basis of precision medicine, its specifics in psychiatry, and provide examples of its use in the field of diagnostic assessment, course prediction, and appropriate treatment planning.

Keywords: personalised medicine, personalised psychiatry, precision medicine, precision psychiatry

Introduction

Psychiatry is a basic field of medicine, which focus and approaches largely differ from most other medical fields. It relies primarily on subjective methods of assessment, based either on the symptoms described by the patient or their evaluation by the physician. While the treatment approaches may be more personalized compared to other medical fields due to large interindividual differences, the use of objective markers in clinical decision-making is significantly less frequent. Traditional education in psychiatry emphasizes the critical assessment of subjectively skewed information, and a large proportion of psychiatrists use it as the only alternative to the lack of objective markers. Therefore, the aim of this article is to attract interest of clinically oriented physicians in the field of personalized psychiatry, which is inevitably linked with the future of the field, and to provide a brief overview of the theoretical basis of precision medicine and its applications in diagnostic assessment, course prediction and treatment planning. The authors do not aim to provide a comprehensive and fully balanced overview of the issue as more in-depth and focused reviewed of the topic are provided elsewhere.[1–5]

Correspondence: Petr Šilhán
Department of Psychiatry, University Hospital Ostrava, 17. listopadu 1790, Ostrava, 708 52, Czech Republic
Tel +420 597 373 145
Fax +420 597 373 314
Email petr.silhan@fno.cz

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Personalized Medicine

Personalized medicine is a term describing the tailoring of treatment to each patient's individual characteristics and needs. Nowadays, physical examination and medical history remain the cornerstones (and, sadly, the only means) of such individualization in clinical practice. However, the concept of personalisation is broader and dates back at least to the time of Hippocrates (460–377 BC), who is considered the father of modern medicine based on clinical observation and rational conclusions.[6] Hippocrates aimed to find the cause of the patient´s symptoms, regarded each patient as unique, and paid particular attention to their characteristics and habits. He also emphasized the importance of disease prevention and prediction, which may be another link between Hippocrates and modern P4 (predictive, preventive, personalized, participatory) Medicine.[7]

Personalized Psychiatry

The current psychiatric diagnosis and treatment are based on symptoms presumed to be very similar (or even identical) in all individuals with a particular diagnosis. This approach using classification criteria helped to solve justified concerns about the reliability of psychiatric diagnosis in the past; nevertheless, at the same time, the disease classifications reflect neither the psychobiological mechanisms of the psychopathology nor the complex interplay of the genetic and environmental factors.[2] Patients evaluated by a psychiatrist using the phenomenological classification are then first-line treated according to the diagnosis (ie, psychosis including schizophrenia is treated with antipsychotics, a depressive disorder with antidepressants, etc.) and relevant guidelines are designed for the "universal" patient. Where the personalised approach is used, the clinician choosing a particular medication takes into account the patients' history and circumstances of the disease, symptom profile, gender, weight, known metabolic abnormalities, smoking, previous therapeutic adherence and many other aspects including, for instance, more frequent therapeutic drug monitoring. However, even if the personalized approach is used, the response to treatment is poor or even not observable in many patients, which highlights the importance of the transition to truly precision psychiatry.

Precision Medicine

The terms personalized medicine and precision medicine are often used interchangeably, depending on the emphasis placed on the partial procedure. While medicine has always had, to a certain extent, a personalised character, it cannot be considered sufficiently precise.[4] Precision medicine, as a kind of personalised medicine, facilitates decision-making by introducing measurable biomarkers, ie, indicators of normal biological processes, pathogenic processes, or responses to the exposure or intervention.[8] Such biomarkers are available thanks to the tremendous progress in science and technology enabling the acquisition and processing of huge amounts of information and identification of associations between individual patients' characteristics on the one hand, and diagnosis, prognosis and treatment methods and success on the other.

The completion of the Human Genome Project, which provided the complete sequence information for the human genome in 2003, was a critical landmark in genetics. The development of genome-wide association studies (GWAs) enabled the construction of polygenic risk scores providing a genetic risk summary of the disorder based on the number of risk alleles in an individual patient. In the current clinical practice, polygenic risk scores are rather used for the confirmation of the diagnosis in the early stages of the disease than for the identification of the individuals who are at a high genetic risk of a particular disease from the general population.[9] However, there are some areas of medicine, where polygenic risk scores already help to determine the risk of a specific disease and allow for patient stratification (eg, for prostate cancer, breast cancer, cardiovascular disease, and type 2 diabetes mellitus).[10]

A fast growing field of genetics in the real-world practice is pharmacogenetics, which aims to elucidate the genetic basis for drug response and adverse events development in individual patients. According to a study of more than 7.7 million US veterans, it was estimated that 99% of them used medications associated with at least 1 pharmacogenic variant.[11] In medicine, pharmacogenomics is perhaps most established in oncology. Several oncological drugs are associated with gene's variations that contribute to clinical outcome and so the pre-emptive testing is not only recommended but, in some instances, also mandated.[12] Tumour sequencing is standardly used for diagnostic purpose and also to determine optimal treatment (according to FDA, genetic testing is required in one half of drugs with annotated pharmacogenetic information). Likewise, the pharmacogenomic assessment of pharmacokinetically important enzymes is recommended for optimizing dosing and minimizing toxicities.[13]

To map brain structure and function, the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) program was initiated in the USA in 2013. Since then, cooperation has been established with similar projects in many other countries, including European Union countries. To reach the goal, optimization of existing tools such as magnetic resonance imaging (MRI) and physiological recording are needed, which necessitates multidisciplinary cooperation of diverse disciplines from engineering through medicine to computational science.[14,15] Other new technologies, such as systems biology, sophisticated portable analytical equipment (biosensors), and others, enable gathering of large amounts of other types of data, the analysis of which uses artificial intelligence and machine learning.[16]

Systems biology is a biology-based interdisciplinary field of study that focuses on complex interactions within biological systems. This systemic approach reduces the risk of inaccurate interpretation of isolated findings and integrates new scientific subspecialties analysing complex data collected at different levels of the organism and its functions. These subspecialties are also called "-omics" according to the suffix used in their designation that indicates "completeness". The most studied omics include the cascade of 1) genomics (focusing on the identification of genes and genetic variants in an entire genome), 2) epigenomics (complex study of epigenetic modifications affecting gene expression without altering the DNA), 3) transcriptomics (which aims to identify the qualitative and quantitative mRNA in the genome), 4) proteomics (studies the cellular proteome), 5) metabolomics (metabolome comprises all metabolites present in a cell, thus representing the final product of gene transcription) and others.[4]

Modern computer technologies and, in particular, artificial intelligence constitute crucial support to the above-mentioned sciences. Artificial intelligence is a computer science that mimics and extends human intelligence. Its subspecialty – machine learning – uses a system of algorithms that analyses data based on the experience obtained from structured training data, learns from it and answers predefined questions. It possesses the ability to learn from provided data (with some human intervention or supervision) without previous explicit programming. One of the machine learning methods, deep learning, uses artificial neural networks capable of simulating human multi-layer analytical learning. It does not necessarily require labelled datasets and can, to a degree, evaluate the accuracy of its conclusion on its own and, if not, improve its performance without interventions. This way, using unsupervised learning, it can be applied to more complex cases.[17,18] If trained on large enough amounts of data, these technologies are able to find links and sets of predictors that may not be detected by more conventional approaches; at the same time, however, such links may be difficult to understand and interpret, which can limit the acceptance of the results and their transfer to clinical practice.[16]

There are also other possible pitfalls and objections to the idealisation of machine learning. Firstly, training data are often chosen based on statistically proven group differences, which may lack the discriminatory character sufficient for decision making on the level of individual subjects. Sometimes, there is a risk of overfitting when results fit very well the training data but perform poorly on the test data. Many studies use the overall accuracy of classification as the metric for evaluation of the results, which, however, may not be informative enough, especially when taking into account unequal sample sizes.[19]

Precision Psychiatry

The same new precision methods that are gradually finding their way into the field of medicine can be applied to psychiatry as well and nowadays, we are witnessing the beginnings of a new era in psychiatry – precision psychiatry. Till now, psychiatry has not been benefiting enough from the advanced diagnostic technologies, perhaps because of the heterogeneity in the presentation and symptoms of mental disorders and because the current psychiatric classification does not consider underlying psychobiological mechanisms.[2]

It is increasingly unlikely that a single biomarker would be able to correctly identify all cases of a particular mental disorder. This is obvious, among others, in the field of genetic studies. There are growing amounts of reproducible findings in the genetics of psychiatric disorders that confirm their underlying polygenic basis, ie, the existence of many contributing genetic loci with small effect sizes. The 10 basic psychiatric disorders have association with 241 loci and many of them increase the risk for several disorders. They may be considered as non-specific risk factors with an overlap outside the field of psychiatry.[10] To be able to use the existing partial indicators with limited clinical value in practice, it seems necessary to combine clinical characteristics with genetic profiling, omics results, structural and functional brain

imaging, other laboratory findings, data from new mobile devices, electronic health records.

Such an immense amount of data can be processed again only by artificial intelligence. However, the complexity of brain physiological and pathological processes relevant in psychiatry require not only to standardise and control the quality of the data, but also to integrate raw information with underlying neurobiology theories. In other words, "to turn big data into smart data".[20] This is also the way how to give a sense of precise psychiatry to clinically oriented physicians. Even so, as mentioned above, the established connections may be so complex that the analysis may resemble a "black box" solution with input data on the one hand and (more or less unexpected) outputs on the other, which can be perceived as a limitation by some. Even more so in the field of psychiatry, where the main source of diagnostic information and therapeutic considerations is still based on the direct contact with the patient.

Diagnosis Assessment and Course Prediction

While the progress in general medicine with its "precision tools" is expected to be rather quantitative, such tools may, in the case of psychiatry and its nomenclature, lead to a qualitative shift. In other words, data gathered from different diagnostic sources and analysed by artificial intelligence would give us "biosignatures", ie, a set of biomarkers that would yield a more appropriate diagnosis, treatment and prognosis. This would expand and specify the current symptom-based diagnostic system (or even possess a potential of replacing it).[4]

The number of works using artificial intelligence for the construction of multivariate predictive models for the diagnosis and/or prognosis of certain psychiatric disorders grows. Most of the promising studies focus on distinguishing patients with mental disorders from healthy controls. However, the long-term goals should include differential diagnosis of overlapping disorders, such as schizophrenia, schizoaffective and mood disorders, the importance of which is at least equally high.[19]

Nowadays, many examples of the benefits of this approach can be found. For instance, Jo et al reviewed 16 studies and found that the application of deep learning has yielded accuracies of up to 96.0% for classification of Alzheimer disease and 84.2% for the prediction of mild cognitive impairment conversion. The best classification performance was obtained combining multimodal neuroimaging and fluid biomarkers.[21] Schnack et al tried to separate schizophrenia and bipolar patients using machine learning and MRI structural scans. Schizophrenia subjects could be separated from healthy ones with an average accuracy of 90% and from bipolar ones with an average accuracy of 88%.[22] However, the accuracy of distinguishing bipolar patients from healthy controls was lower. Schmaal et al used a machine learning approach processing neuroimaging data and clinical characteristics to predict three trajectories of the course of major depressive disorders (chronic, gradually improving and fast remitting). Chronic patients could be distinguished from patients with more favourable trajectories with as much as 73% accuracy.[23] The contribution of proteomics is demonstrated in the study by Mongan et al. In individuals at risk of psychosis, proteomic biomarkers, together with clinical features, predicted the individualized prognosis of transition to psychotic disorder with high accuracy when used machine learning algorithms (AUC, 0.95).[24]

Appropriate Treatment Choice

Classification of the patient population into relevant diagnostic subgroups using specific biomarkers would not promote only better diagnosis but, perhaps even more importantly, it would also lead to better treatment. Ultimately, the goal of precision medicine adopted also by the Food and Drug Administration is "to fit the right treatment to the right patient at the right time".[25]

One of the most important research fields in precision psychiatry is pharmacogenomics, the science studying the influence of genes on an individual's response to medications.[17] Pharmacogenomics has already succeeded in detecting genetic factors that predict clinical response and side effects, such as genetic variations that impact drug-metabolizing enzymes, neurotransmitter transporters or drug targets.[26] Recent advances have resulted in several generations of testing approaches. The first-generation pharmacogenomic testing of individual genes encoding cytochromes P450 (CYP) has limited utility. The second-generation tests comprise more genes; nevertheless, even with this multigene testing, mixed results were reported.[27] The third-generation testing accounts for the combined effect of multiple genotypes that may impact the pharmacokinetics and pharmacodynamics of a drug. This combinatorial approach using machine-learning methods achieved accurate and replicable prediction of specific serotonin

reuptake inhibitors (SSRI) therapy response.[28] One of the important and illustrative step was very recently done by Le-Niculescu et al. His group assessed 26 blood gene expression biomarkers with the ability to objectify diagnosis of mood disorders, predict its clinical course, and match patients to pharmacogenetically appropriate medications.[1]

Pharmacogenomics-guided treatment is a promising approach, especially given the rapidly decreasing costs of genetic testing. Further progress may be expected from combining genetic information with other omics and neuroimaging.[29]

Translational Medicine

As can be obvious from above, the amount of available data arising, on the one hand, from modern sciences and, on the other hand, from the routine clinical practice keeps growing. To bridge the gap between science and practice and/or to bring the knowledge from bench to bedside, a new field called translational medicine has been established. According to Wehling, translational medicine mediates the transition of in vitro and experimental research to human applications.[30] This process consists of several steps, sometimes summarily termed as 3T's model where T indicates translation and numbers 1 to 3 represent the 3 major translational steps. T1 represents the translation from basic science into clinically useful hypotheses, T2 from this stage into recommendations for practice and T3 seeks to bring this knowledge into the healthcare system's rules.[31]

Conclusions

Precision psychiatry promises to provide novel objective approaches in this traditionally subjective field of medicine and has the potential to become a tool for real personalized treatment. What will start as an analysis of a large amount of anonymized data may lead to the production of algorithms useful for individualized diagnostics and treatment. Bringing precision medicine including psychiatry to the reality of clinical practice is a big enterprise that will most likely require synergy between academic environment, industry and government. Opening the door (and mind) to these new opportunities is a major challenge to the current and future psychiatrists and offers almost unlimited research opportunities.

Disclosure

The authors report no conflicts of interest in this work.

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