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Commentary on Kohne and van OS view on precision psychiatry

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Precision psychiatry is indeed an exciting and fashionable concept since its inception (Vieta, 2015). Kohne and van Os (Kohne & van Os, 2020) raise the question whether there will be any diagnostic, prognostic or therapeutic usefulness of the efforts of precision psychiatry for clinical practice. While they express their concern about the future impact of precision psychiatry, we believe that it has already started to shake up the present.

Precision psychiatry aims to tailor pharmacological and psychological treatments to subgroups of patients (or, ideally, individual patients) sharing similar characteristics in terms of their susceptibility to a particular disease, outcome or their probability to respond to a specific treatment (Vieta, 2015). Hence, it seeks to move away from the 'one size fits all' mentality by understanding the underlying mechanisms that drive patients' heterogeneity in clinical presentation or treatment response with the final goal of providing early and adapted solutions. To this end, research is changing and increasingly moving its focus towards those patients who do not seem to be guided by the rules that apply to the majority, since this 'deviation from the norm' can just translate differential biological traits that could help to discover new therapeutic targets or help to refine current psychiatric nosology. Drug development has also been transformed by the new paradigm of precision psychiatry and there is a growing interest to find drugs that treat particular symptoms within broad DSM diagnoses. Antidepressants specially oriented to patients with cognitive disturbances, antipsychotics with new receptor-binding profiles that benefit patients with predominant negative symptoms or treatments specifically designed for postpartum depression are examples of this turnaround. Hence, clinicians can already refine their treatment selection to better adapt to patients' clinical needs beyond their DSM diagnosis. Nevertheless, perhaps the clearest example of the impact of precision medicine in clinical practice is pharmacogenomics. Although pharmacogenetic tests are still not routinely implemented, selected patients with unusual patterns of drug response or unexpected adverse reactions can benefit from testing whether they present a polymorphism in the cytochrome P450 genes CYP2D6 and CYP2C19, for instance, that affects the way they metabolize particular psychiatric drugs (Perez et al., 2017). This procedure can save them a potentially lengthy trial-and-error process – which is costly and burdensome for both patients and clinicians – until the right medication is found, since psychiatrists can use this personalized information to select treatment accordingly.

Psychiatry is not only about biology, but it is getting progressively precise

Despite the reservations of Kohne and van Os (Kohne & van Os, 2020) about the relationship between biology and the phenomena of the mind, we believe that, when it comes not to social psychological constructs like falling in love, but specifically to severe mental disorders (that are indeed the target of psychiatry), biology plays a determinant role. So far, genome-wide association studies (GWAS) from international collaborative consortia have led to great advances in the knowledge of the genetic underpinnings involved in the genetic vulnerability to develop a psychiatric disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019), in the biological differences between psychiatric disorders (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018), in treatment response variability (Hou et al., 2016), and even in suicide attempts (Mullins et al., 2019). These studies are also helping to understand the biological basis of individual symptoms shared across psychiatric diagnosis, which might, in the future, make reconsider current psychiatric nosology (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019).

And although, as Kohne and van Os (Kohne & van Os, 2020) point out, these biological advances have not reach the bedside yet, we believe that it is not possible to infere that this is an end road. Diabetes, especially diabetes type 2, is also struggling through the search for realiable biomakers, without that meaning that there are no biological alterations underlying insulin resistance. And the same is true for a long list of somatic diseases. The fact is that, despite the sequencing of the human genome held great promise for precision medicine (in fact, genomics helped to initiate the era of precision medicine), now we are realizing that its direct benefit is limited in complex and/or heterogeneous diseases, like diabetes type 2 or psychiatric

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disorders. Although some psychiatric disorders are highly heritable (Carvalho, Firth, & Vieta, 2020a), they are clearly multifactorial, and therein lies the challenge of precision psychiatry.

In consequence, in order to be precise in patients' stratification or in clinical predictions, psychiatry will most surely need to integrate different levels of biological and non-biological information, and in an increasingly sophisticated way (Salagre et al., 2018; Vieta, 2015). That might include clinical and environmental factors, genetic, molecular and neuroimaging biomarkers, epigenetic modifications and even information on the individuals' microbiome. Luckily enough, precision psychiatry relies on some important allies. Machine learning methods will be key to build such predictive models, which can be incorporated in clinical practice, for instance, through web-based risk calculators (Silva Ribeiro et al., 2020). They can be used to integrate all these multiple measurements of different nature and to select – even without a prior hypothesis – the most relevant ones in order to build prediction models to estimate the probability of a particular outcome at an individual level. They can also be used to design optimal dynamic treatment regimens by combining the individual clinical evolution and the treatment history of each patient. The application of new analytical approaches is already helping to identify clusters of patients more similar in terms of a particular characteristic, such as response to particular treatments or cognitive performance (Mas et al., 2020; Varo et al., 2020). This information can be used for clinical prediction or to design tailored pharmacological and psychological interventions for subgroups of patients that are expected to benefit the most from these treatments. The digital transformation is also boosting precision psychiatry. Wearables or smartphones can be used to collect behavioral biomarkers (like sleep patterns, geolocation or use of social media) for continuous health monitoring. This is already being tested in research to identify, for instance, early signs of relapse (Hidalgo-Mazzei, Young, Vieta, & Colom, 2018). Potentially, this would allow for earlier interventions that would save patients more aggressive treatments and minimize the negative outcomes of a relapse (e.g. hospital admission, long work leaves, etc.).

All these objective tools will sum up to the personal skills of the treating clinician. That will create a synergy that is expected to increase the probabilities of establishing the right diagnosis or choosing the right treatment for patients from the start. Even if precision psychiatry is envisaged to be highly data-driven, this does not exclude the need for a good therapeutic relationship between patients and their treating clinicians. An effective communication will be needed to make comprehensible for the patient the information about complementary test and treatments that might be increasingly complex. Moreover, patients (with their context, their values, their personalities, etc.) will be in the center of the decision-making process, so physicians need to be aware of patients' reality, opinions and preferences and make sure they are active participants in their health delivery.

In the light of all the aforementioned, we cannot help but firmly believe that the concept of precision psychiatry has the potential to bring obvious benefits for patients, albeit some will come in due course.

Rome was not built in a day

Precision psychiatry is still developing. Although some question its value on the basis that it has not accomplished all its promises yet, major changes require time.

Novel clinical trial designs focusing more on specific phenotypes than on diagnoses, targeting patients in particular illness stages, using innovative analysis paradigms and including a wide range of variables of different nature will be required to advance in precision psychiatry. There are already some examples of longitudinal cohort studies that simultaneously acquire data across different behavioral and biological domains at different time points, such as the R-LiNK Study (Scott et al., 2019). The establishment of a standardized methodology is also needed, which will help to overcome the problem of replicability faced, for instance, by the biomarker field (Carvalho et al., 2020b). Moreover, investing in collaborative studies to increase sample size and to ensure that data is diverse enough to be also representative of minority groups will improve the generalizability of the results. More patients will benefit from research findings. Finally, for new advances in precision psychiatry to reach the clinic, they must be cost-effective, ethical, useful for the patient and easy to implement. This is timely, but will require funding for translational health research and advancing in the regulatory frameworks for precision medicine tests.

With time, though, precision psychiatry is envisaged to enhance our understanding of psychiatric diseases and symptoms and enrich current psychiatric practice. For that, the focus not only needs to be made on technology and biology; in fact, the weak link at present time is, in our opinion, the clinical phenotype. Notice that for most large biomarker datasets (Psychiatric Genomics Consortium for genetics, or ENIGMA for neuroimaging, as for many brain banks, for example) the available phenotype mostly consists on age, sex and DSM diagnosis, lacking many key potential clinical endophenotypes, such as psychopathological dimensions, age at onset, pre-natal data and so on. Why one would expect biological markers to be aligned with consensus-based constructs such as DSM or ICD conditions? In that sense, we agree with Kohne and van Os (Kohne & van Os, 2020): DSM/ICD classification is in need of renewal. But we believe that we need to move towards 'molecular psychopathology' (Vieta, 2014) to enrich the datasets that connect clinically relevant dimensions, such as impulsivity and suicidality, for example, with genomics, proteomics, transcriptomics and metabolomics, as well as neuroimaging data. And it makes little sense to us to limit the search to pure neuroscience-based phenomena, as the research domain criteria (Insel, 2014). By integrating rich clinical, biological and environmental information, thanks to the incorporation of technology in psychiatry, new diagnostic, prognostic, preventive and therapeutic strategies increasingly adapted to each patient's requirements are expected to be created, ensuring that patients get the right treatment at the right dose at the right time so that outcomes are improved, adverse effects minimized and treatment effectiveness maximized. Despite the obstacles, that goal is worth pushing for.

Precision psychology

Precision psychiatry will eventually deliver because there is no question, in our opinion, that mental disorders are disorders of the brain, and as such, can be tracked through biological clues, which can be complex, but are still there, awaiting discovery. What is indeed arguable is to what extent biology will eventually explain all mental processes. This is what Kohne and van Os (Kohne & van Os, 2020) describe as a challenge to biological psychiatry: what are the biomarkers of falling in love, for example? Indeed, this gets into philosophical grounds even though we still

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believe that all natural phenomena are subject to scientific scrutiny. But the symbolic and cultural aspects of human behavior, despite being relevant to psychiatry, are not the target of precision psychiatry, but something we could call 'precision psychology'. In our view, it would be a mistake to interpret that psychological processes, such as those that Kohne and van Os (Kohne & van Os, 2020) describe in their paper, need to be fully understood from a biological perspective before we can work on precision psychiatry. In oncology, many questions remain unsolved as regards to normal cell reproduction, genetic expression, and the role of environmental factors, and nevertheless genetic biomarkers have become indispensable for treatment selection and improved relevant outcomes, such as mortality. Let us admit it, even though falling in love, as Kohne and van Os (Kohne & van Os, 2020) say, is difficult to track through biomarkers, we have to confess that we are deeply in love with the concept of 'precision psychiatry'!

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