Psychological Medicine (2018), **48**, 705–713. © Cambridge University Press 2017
doi:10.1017/S0033291717002859

EDITORIAL

The revolution of personalized psychiatry: will technology make it happen sooner?

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Personalized medicine (PM) aims to establish a new approach in clinical decision-making, based upon a patient's individual profile in order to tailor treatment to each patient's characteristics. Although this has become a focus of the discussion also in the psychiatric field, with evidence of its high potential coming from several proof-of-concept studies, nearly no tools have been developed by now that are ready to be applied in clinical practice. In this paper, we discuss recent technological advances that can make a shift toward a clinical application of the PM paradigm. We focus specifically on those technologies that allow both the collection of massive as much as real-time data, i.e., electronic medical records and smart wearable devices, and to achieve relevant predictions using these data, i.e. the application of machine learning techniques.

Received 27 February 2017; Revised 30 August 2017; Accepted 30 August 2017; First published online 2 October 2017

Key words: Big data, electronic medical records, machine learning, personalized medicine, precision medicine, wearable devices.

Introduction

The term personalized medicine (PM), sometimes also referred to as precision or individualized medicine, indicates a new paradigm in clinical practice. It proposes to establish clinical decisions based upon a patient's individual profile, tailoring the treatment to his/her characteristics, needs, and preferences during all phases of care including prevention, diagnosis, treatment, and follow-up (U.S. Food And Drug Administration, 2013). Although a personalized approach is characteristic of several ancient and modern non-evidence-based medical systems (Salvador-Carulla & Mezzich, 2012), PM aims to provide scientifically sound and evidence-based individual indications and predictions, fundamentally changing current clinical decision-making paradigms.

At present, evidence-based psychiatry mainly refers to practice guidelines (e.g., those from the UK National Institute for Health and Care Excellence, NICE, and the American Psychiatric Association, APA) that recommend the interventions indicated by scientific evidence as the most effective for the 'average' patients suffering from a specific DSM/ICD diagnostic class. However, high variability of treatment responses among patients with the same categorical psychiatric diagnosis is observed and clinical practice requires to tailor guidelines recommendation with each patient, exploiting recent scientific evidence and each clinician's past experience. The purpose of PM is precisely to provide reliable assistance in such customized clinical decisions.

If in other fields of medicine, particularly oncology, PM tools have already been developed and are now part of current clinical practice with considerable improvements in treatment outcomes, the development of a personalized psychiatry is particularly challenging because each psychiatric diagnosis includes very heterogeneous entities characterized by extremely complex and variable changes in the brain, which are caused by a large number of genetic and environmental factors.

A research approach guided by PM might be now feasible because of the latest improvements in technology and data analysis methods. They have made the investigation and analyses of large quantities of various types of data rapid and economically sustainable. This would have been unthinkable just a couple of decades ago (McIntosh *et al*. 2016). DNA-sequencing techniques are an example, with the cost of the human genome of single subjects reducing from $300 million in 2001 to $1000 in 2014 (Personalized Medicine Coalition, 2014); and nowadays, new techniques allowing extensive analyses of much more than genotyping opened the age of the 'ome,' i.e., genome, transcriptome,

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and proteome (Myers, 2012). Moreover, the exponential increase of the computational power and size reduction of biosensors now permit continuous and real-time analyses of physiological parameters.

Several reviews summarizing the current state-of-art of PM have already been published and all of them claim that, although it is still at an early stage, PM in psychiatry has a very promising future in improving the accuracy and relevance of predictions of both disease vulnerability and treatment outcomes (i.e. Costa e Silva, 2013; Ozomaro *et al.* 2013; McMahon, 2014). However, apart from early enthusiasm and the promising preliminary results of many theoretical papers and proof-of-concept studies, very few tools have been developed and are ready to be applied in clinical practice. They are mainly pharmacogenetic test kits (e.g. the FDA approved AmpliChip CYP450 Test from Roche, Switzerland, and GeneSight from AssureRx Health, OH, USA), but their cost-effectiveness is still debated (Howland, 2014; Chau & Thomas, 2015; Peterson *et al.* 2017).

To make the PM paradigm applicable, actionable tools are required. In this paper we will introduce some of the technological advances that can contribute to the development of such tools in psychiatry. Two fundamental steps are necessary to make a prediction: (1) to have the pertinent requisite information available regarding the phenomenon to predict and (2) to develop a model capable of making a prediction from such information. Therefore, in this commentary, we will briefly introduce two new recent tools which provide opportunity to collect relevant data, i.e. electronic medical records (EMR) and smart wearable devices, as well as analytic techniques on how to make predictions from them, i.e., machine learning. Instead, we will not cover in the current paper other advances that are rapidly contributing to the foundation of a personalized approach in psychiatry, i.e. genomics, epigenetics, transcriptomics, and proteomics, as several comprehensive papers have already been published on this topic (Myers, 2012; Geschwind & Flint, 2015; Sokolowska *et al.* 2015).

Big clinical data: EMR

The financial cost and time commitment of research has always forced researchers to make difficult decisions regarding selection of which information to study and collect, compelling them to test a limited number of hypotheses. Instead, the recent affordability and widespread availability and use of IT have made huge amounts of data easy to collect and inexpensive to store and analyze. The introduction of EMR suddenly makes all clinical information electronically storable and ready for use for potential investigations. The rate of adoption of EMR is proving to be impressive, e.g., from 18% in 2001 up to 78% in 2013 in US office-based physicians (Hsiao & Hing, 2014).

EMRs permit fast and easy acquisition of much patient data. However, EMRs usually include messy and unstandardized clinical information. The insertion of clinical data typically does not follow a standardized convention as research data does. In addition, non-homogeneous sets of data may be collected for each patient, with several missing-values broadly distributed along the different fields, particularly if records from different clinical centers are merged. Furthermore, only part of the information is coded in formats already suitable to be analyzed, while the remainder is inputted in formats such as natural language that need to be processed before any kind of analysis can be applied.

Although these and more limitations may challenge the use of such data in research, EMR also present several opportunities (Gummadi *et al.* 2014; Castaneda *et al.* 2015). Evidence indicates that the availability of huge amounts of 'noisy' data may counterbalance the absence of optimal quality, a subject of considerable debate. Promising proof exists that processing techniques can be effectively used to extract and code relevant information from unstructured data, e.g., applying natural language analytic tools to clinical notes (Perlis *et al.* 2012; Castro *et al.* 2015; McCoy *et al.* 2015; Patel *et al.* 2015*b*). For example, in a study by Perlis *et al.*, the application of natural language processing technique to information provided by EMR clinical notes allowed to classify current mood state of inpatients with a billing diagnosis of major depressive disorder and define their longitudinal outcomes (Perlis *et al.* 2012). Castro *et al.* used similar techniques to design a diagnostic algorithm for Bipolar Disorder using information included in the EMR of patients of the Partners Healthcare Research Patient Data Registry (Castro *et al.* 2015). Both studies used large samples and proved high accuracy (area under the receiving operating curve higher than 0.8) in performing diagnostic classification.

A progressive alignment of the information collected in the EMRs from all clinical centers will incrementally improve the use of EMR data in research. However diagnostic, assessment, and therapeutic procedures are far from being fully standardized in medicine in general and this is even more so in psychiatry, with substantial variation among clinicians and clinical centers. This expected heterogeneity of data coming from different EMRs might be reduced with the adoption of national and international good practice guidelines for EMR, e.g., those from the Department of Health *et al.* (2011). This would also result in the greater clinical utility of EMRs, making it easier for clinicians to

https://doi.org/10.1017/S0033291717002859 Published online by Cambridge University Press

share each other's information on their mutual patients and to retrace the whole clinical history of each patient. For such widespread data collection to be possible, EMR platforms must be fungible or at least mergeable in solitary databases, a goal unrealized in the USA with its multiple and competing platforms, e.g. Cerner, Epic, Meditech, etc.

It is important to remember that data from EMR are naturalistically collected in clinical settings. These are suitable for investigating multiple associations among different domains, a process that becomes fast and inexpensive even with large sample sizes. Also, these data may be used to develop predictive models, which may take advantage of the largeness of EMR datasets even when these are unstructured and sparse.

However, if a causal direction needs to be studied, this 'data mining' attitude to naturalistic data can only be useful in generating hypotheses, but it is unlikely that conclusive evidence can be achieved from these data. Association is a necessary but not sufficient condition to establish causation (Hume, 1739), and although advances in the field of causal inference are providing methodologies to infer causation, under specific circumstances, even from observational data (Pearl, 2010; Mooij *et al.* 2016), causation still generally requires testing in experimentally designed studies.

Real-time data collection through smart wearable devices

Another recent opportunity for the creation of a personalized psychiatry comes from the continuous miniaturization of physiological sensors, permitting them to be integrated in wearable devices. Ambulatory monitoring machines have been available for a long time, e.g. Holter monitors for electrocardiography, arterial pressure, and electroencephalography have been used since the early 1960s. However, they are suitable only for time-limited use because of their considerable inconvenience for patients. Although portable, these devices are visible, subjects perceive their weight, and they can substantially interfere with movement.

Only recently have the sensors reached a size that is suitable for investigation in smart wearable accessories, such as watches, wristbands, jewelry, clothes, smartphones, and patches (Xu *et al.* 2014). Even when the subjects are unfamiliar with them, these devices are perceived as minimally intrusive and can be worn continuously without affecting daily activities and being noticed by the wearer, with costs that are becoming increasingly affordable (Fung *et al.* 2015).

Several vital signs can now be measured with such miniaturized sensors, e.g. motion heart rate, body and skin temperature, arterial blood pressure, blood oxygen saturation, electrocardiograms, electroencephalograms (EEGs), and respiration rate (Chan *et al.* 2012). Furthermore, the capillary connection of devices to the internet and to each other, the so called 'Internet of Things' (Ashton, 2009), also allows a real-time streaming of data as much as their real-time analyses.

Smart wearable devices are one of the main current trends in non-medical consumer technology (Gilmore, 2015), but this revolution also opens up interesting possibilities in the entire medical field and particularly in psychiatry. Measurements are not only recorded continuously and in real-time, but objective physiological signals are becoming easily available to complement the assessment of symptoms, mental states, and behavior provided by patients or clinicians.

Smartphones play a fundamental role in this opportunity. Not only they provide a bridge to make wearable devices always connected to the Internet, but they also directly permit the collection of relevant data (Van Ameringen *et al.* 2017), through apps that allow users to insert information, as well as automatically collecting data via sensors that smartphones embed. For example, the motion sensors available in all smartphones, which are commonly used to track subject activities, have also been used to capture heart and respiration rates, providing preliminary promising results, at least in positions and activities without too much motion (Hernandez *et al.* 2015).

With the use of these devices, data and significant warnings can be continuously sent to clinicians, allowing them to monitor their patients' conditions and promptly intervene in case of necessity. Moreover, real-time information can also be sent directly to patients providing them with a better awareness of their condition and promoting a first-person participation in their treatment and prevention process.

This strategy has been very effective in monitoring pain, and recent proof-of-concept studies investigated the promise of such continuous monitoring in subjects with psychiatric disorder (Glenn & Monteith, 2014). For example, O'Brein *et al*. investigated the opportunity of using wrist-worn activity measurement as a real-world diagnostic biomarker for late-life depression. Results corroborated their hypotheses and specific activity parameters characterizing patients with depression compared with healthy controls were identified, such as reduction in activity in specific times of the day and slower and more repetitive fine motor movements (O'Brien *et al.* 2017). Furthermore, the European project MONARCA funded through the 7 Framework Program, developed and pilot tested a mobile technology for bipolar disorder patients with long term monitoring of physiological and behavioral information. The MONARCA system consists of four integrated elements with a sensor enabled mobile

https://doi.org/10.1017/S0033291717002859 Published online by Cambridge University Press

phone, wrist worn activity monitor, stationary EEG system for periodic measurements, and novel 'sock integrated' electrodermal activity sensor. These measures are collected with the aim of providing management, treatment, and self-treatment of the disease and to assess early warning signs and predict occurrence of episodes in an objective and timely manner (Kappeler-Setz *et al.* 2013; Faurholt-Jepsen *et al.* 2015; Haring *et al.* 2015; Osmani, 2015).

These studies led to encouraging results and were also able to identify challenges related to the application of these technologies. However, they are just early prototypes. Only further replications of these investigations on larger clinical samples will provide clear evidence of their clinical utility and cost-effectiveness, which is lacking at the moment. Moreover, a transition from proof-of-concept to fully-implemented and operating instruments is necessary before their utility will be clear.

For example, Empatica inc. (CA, USA; Italy) commercializes non-invasive wristbands that are able to continuously monitor skin temperature, skin conductance, movement, and heart rate parameters with precision. A recently released wristband and app may become an everyday application for epileptic patients, sending caregivers an alert when an epileptic seizure is occurring. Although a stress monitoring app will also be available, no specific application for patients with psychiatric disorders has been developed.

An 'era of pervasive healthcare' (Glenn & Monteith, 2014) can be envisioned as soon as the application of such systems becomes widespread. However, as for any innovative product and service, it is important that these tools are designed in a user-centric manner with a careful understanding of the patients' needs, a focus on usability and user experience, and direct involvement of patients during the development phase (Norman, 2013). This is a crucial factor to ensure that these instruments are accepted and easily adopted (Chan *et al.* 2012).

Nowadays the possession of personal digital data by private as well as governmental institutions has been generating a lot of discussion and regulations in the attempt to safeguard individuals' right to privacy. The same issue concerns medical data. A 'pervasive healthcare' necessary implies a pervasive involvement of several parties, much more than the two traditional holders of such information, that are the patients and their attending care providers. Beyond the mere risk of privacy violation, the use of EMRs and devices that continuously stream sensible data through the Internet places several issues about data protection and ethical concerns regarding the massive participation of further stakeholders other than the two previously mentioned. Data can be a source of enormous revenues for private companies and regulations should be made considering all parties' interests but without compromises in regards to patients' safety and rights.

From information to prediction: machine learning

EMR and miniaturized sensors embedded in wearable devices, as well as genomics, epigenetics, transcriptomics, and proteomics assessments, allow for the collection of a huge amount of data for every single patient. However, even when relevant information is available, making a prediction requires a model that connects this information with the outcome. Machine learning is a field at the crossroads of computer science, engineering, and statistics 'that gives computers the ability to learn without being explicitly programmed' (Samuel, 1959).

In medicine, statistical inferential analyses are commonly applied to test hypotheses and provide evidence regarding a certain population (e.g., all people suffering from a certain disorder) with data coming from limited samples. The tested hypotheses are usually about association and causation, with the final goal of achieving a better understanding of the relationships among a multitude of factors. Differently, machine learning is a data-driven approach. Such procedures use the available data as training examples to detect patterns and build algorithms that will be able to perform specific tasks.

In particular, a family of machine learning procedures referred to as 'supervised' can be used to develop predictive algorithms able to provide the best possible prediction when applied to new cases, i.e. making single-patient prediction of its expected response before a therapy is administered. Several supervised methods have been developed, e.g., artificial neural network (Bishop, 1995), support vector machine (Cristianini & Shawe-Taylor, 2012), random forest (Breiman, 2001), boosting (Breiman, 1998), but also traditional statistical methods (i.e., from linear regression to the generalized linear model) can be applied to create predictive models. The most advanced machine learning techniques can achieve excellent predictive performance considering their ability to build a complex model of the non-linear relationships and interactions that connect the set of predictors and the response variable. However, the trade-off for such a predictive performance is often a limited possibility to understand the model itself. While simpler models, such as linear models and decision trees, may allow to be easily interpreted, in the most complex ones, which are often the most performing, a clear understanding of the relationship between predictors and the predicted output is often 'blacked-boxed'.

https://doi.org/10.1017/S0033291717002859 Published online by Cambridge University Press

Instead, the so-called 'unsupervised' machine learning procedures can be used to automatically detect intrinsic structures in the data. This is different than what accomplished with the supervised ones, where the outcome to be predicted is a priori defined (Calebi & Aydin, 2016). With unsupervised techniques, one common aim is the identification of relevant subgroups (i.e. clusters) in a population of interest.

Beyond the abovementioned models, recent machine learning developments promise to help solve new and more complex problems that can be relevant in medicine. For instance, these techniques allow to update the single-subject predictions on the basis of the new measurements and information that accumulate during time (time-series techniques and especially novel methods based on Bayesian hierarchical models (Xu *et al.* 2016), to optimize a recurrent decision-making process based on rewards obtained from previous choices (reinforcement learning models (Escandell-Montero *et al.* 2014), and to identify novel drug targets exploiting the previously established drug-target associations (matrix factorization techniques, as usually applied in recommender systems (Cobanoglu *et al.* 2013)).

The rush towards the application of machine learning techniques has recently spread out into several fields, such as financial markets, marketing, artificial intelligence, fraud detection, industry control systems, and also medicine, initially principally in genetics and oncology (Yoo *et al.* 2014; Kourou *et al.* 2015). In psychiatry, the more widespread use of machine learning by now regards the application of various supervised machine learning algorithms to solve prediction problems, with an exponential increase in publications on this topic in recent years. For example, fMRI data measured during a differential fear-conditioning task were used to predict the response to a cognitive behavioral therapy in patients with panic disorder with agoraphobia, applying Gaussian process classifiers that achieved a correct classification as high as 82% (Hahn *et al.* 2015). Similarly, pre-treatment EEGs were applied to a mixture of factor analysis technique, achieving an 87.9% of correct classification in predicting the treatment response of a selective serotonin reuptake inhibitor in major depressive disorder (Khodayari-Rostamabad *et al.* 2013).

A convex hull classification algorithm achieved a 100% correct classification of later (2.5 years) psychosis in 34 high-risk youths considering semantic and syntactic features extracted from transcripts of interviews (Bedi *et al.* 2015), and suicide attempts among patients with mood disorders were predicted with a 72% accuracy with clinical and demographic information applied to a relevance vector machine algorithm (Passos *et al.* 2016). Several more examples are available in the recent literature, with the aim or early predicting response to both pharmacological and non-pharmacological treatment (Salomoni *et al.* 2009; Amminger *et al.* 2015; Mansson *et al.* 2015; Patel *et al.* 2015*a*; Chekroud *et al.* 2016), remission (Askland *et al.* 2015), relapse (Liu *et al.* 2015), severity levels of depression and suicidal ideation (Setoyama *et al.* 2016), risk for later developing a certain psychiatric disorder (Carpenter *et al.* 2016; Chuang & Kuo, 2017; Emerson *et al.* 2017), as well as to automatically perform diagnosis (Wall *et al.* 2012; Khodayari-Rostamabad *et al.* 2013; Johnston *et al.* 2014; Amminger *et al.* 2015; Askland *et al.* 2015; Liu *et al.* 2015; Mansson *et al.* 2015; Qin *et al.* 2015; Ravan *et al.* 2015; Patel *et al.* 2015*a*; Chekroud *et al.* 2016) and this field will surely expand exponentially in the years to come. Theoretically, predictive tools may be developed for nearly all clinically relevant questions, assisting clinicians when making decisions with patients.

Unsupervised machine learning techniques are becoming more popular in the psychiatric field with the aim to identify distinct subgroups within diagnostic entity. Given the aforementioned heterogeneity in psychiatry, this is advised by some Authors as a necessary initial step to develop a PM approach in psychiatry (Fraguas *et al.* 2017). To mention only a couple of interesting examples regarding Bipolar Disorder, several studies used Gaussian mixture models and found three subgroups of patients according to their age at onset, which are characterized by different phenotypical features (Azorin *et al.* 2013), while Russo *et al.* used hierarchical cluster techniques to identify three neurocognitive subtypes (Russo *et al.* 2017).

Such results are relevant because it is possible to further investigate if these homogeneous subgroups may show different responses to different treatments, thus giving the opportunity to make treatment prescriptions that have a higher expectation of efficacy in each of these groups of individuals. This is usually referred to as 'stratified medicine', a sort of half-way between the current one-diagnosis-fits-all prescription system and the final goal of developing an individual-level personalized one, an approach that has more chances to become quickly applied in psychiatry (Perlis, 2014).

However, this remarkable increase of interest of researches and publications has not been associated with an increase in the application of these models. Even when promising results are achieved and published, these models have largely been abandoned at an early-stage level of development without attempting to progress up to a clinical readiness level. This ultimately requires an investigation of

https://doi.org/10.1017/S0033291717002859 Published online by Cambridge University Press

their performance 'in the wild', i.e. when applied to different independent clinical samples.

Moreover, it is important to remember that even the best machine learning techniques cannot provide any prediction if the information that is inputted is not related to the response variable and/or other relevant predictors are missed. The identification of relevant predictors remains the most important and challenging step in prediction and precedes the application of any algorithmic tool. When predictors are unknown, the best opportunity to unearth them relies either on exploration of datasets already available or deriving them from the current scientific evidence, as much as experts' own experience.

Challenges and opportunities to make personalized psychiatry happen

The aforementioned innovations in technology might help a PM approach in psychiatry to become feasible. Considering the potential upside expected by shifting towards this approach in psychiatry and the substantial numbers of proof-of-concept studies that highlight this opportunity, what are the reasons for such a lack of commercially available tools ready for application in clinical practice? Any paradigm shift, both in science and in medical practice, always implies an initial 'critical mass' of preliminary evidence and early-adopters before the change actually gains some momentum and becomes widespread.

Personalized psychiatry has recently also become a focus of both conferences and literature, with many reviews, editorials, and thematic symposia dedicated to this topic. This is ultimately leading to a broader awareness of such an envisioned future for psychiatric clinical practice. It is time to increase these efforts to translate preliminary evidence and knowledge into clinical instruments ready to be used by clinicians.

However, several challenges need to be faced to achieve this aim. Both research and clinical practice will have to undergo several structural and procedural changes in order to allow first a development and then a widespread diffusion of such tools.

An even stronger cooperation between academic research and industry is fundamental in the years to come. Companies should work closely with academic institutions to provide sound evidence of the efficacy and cost-effectiveness of developed products, which should be available at the time of, and not after, their commercialization. Simultaneously, scientific research should also consider the translatability of the knowledge it produces. A stronger focus should be provided on increasing scientific knowledge not *per se* but with the possibility of being translated into technology, achieving a not-too-distant impact on clinical practice. An example may be the identification of a strong predictor of treatment response which, however, requires expensive techniques that not all clinical facilities may be able to adopt. Such a discovery, which is undoubtedly of important theoretical value, may not bring about any rapid improvement in clinical practice. To be of any clinical utility, any tool should just not prove to be efficacious but also efficient and cost-effective. In contrast, when a promising proof of concept has been outlined, it is necessary to pursue its final development and validation.

Governments and policy makers will play a major role in securing the progression of personalized psychiatry by their power to influence public health policies and funding. Moreover, academic institutions should identify companies as a complementary and speedier funding source than governmental institutions, with both sides partnering in the development of both commercially ready and scientifically sound personalized psychiatric tools.

A widespread adoption of the personalized approach in psychiatry will not have high chances of occurring if both its end-users, i.e., clinicians and patients, do not participate first-hand in this paradigm change and embrace this model entirely understanding its advantages. Clinicians should have an active role in the development of such tools, especially in collecting data in their everyday clinical practice. Although we mentioned above that several technological innovations can make data collection easier, at the beginning the introduction of such technologies can be experienced by clinicians as a burden in their work. They may be forced to change their routine, to follow new standardized procedures, and to collect new information that they do not usually rely on in their everyday practice. All these necessary efforts can lead to an advantage that may be experienced only in the long-term, while perceived as just time-consuming in the short-term.

Finally, data coming from multiple clinical centers have to be jointly used to reach a solid validation of these tools. As we discussed above, the opportunity to merge data from independent centers place the challenge of a higher standardization of clinical and data collection procedures among different clinical institutions, which is particularly complicated in psychiatry. Moreover, fulfilling all the requirements to safely share clinical data in compliance with the regulations that safeguard patients' rights to privacy may require substantial costs.

Only a circle that involves all the stakeholders will successfully lead to a personalized psychiatry that is no longer just a 'pie in the sky'. This implies efforts

and investments by all of them today aiming at a return that will be experienced in a not immediate future.

Considering this, the Personalized Psychiatry section of the World Psychiatric Association has recently been founded with the mission to secure, spread, and adopt the PM approach in psychiatry, promoting collaborative research among institutions and to disseminate the personalized psychiatry paradigm to both clinicians and patients. Tailoring diagnosis and treatments seem to be an ideal paradigm. A common effort to move beyond our usual practice in clinical and research endeavors, incorporating new technologies in our daily thinking, will enable to open a new era in psychiatry and behavioral sciences.

Acknowledgements

None.

Declaration of Interest

Charles Barnet Nemeroff has been founded by National Institutes of Health (NIH). He has consulted (last three years) for: Xhale, Takeda, Mitsubishi Tanabe Pharma Development America, Taisho Pharmaceutical Inc., Lundbeck, Prismic Pharmaceuticals, Bracket (Clintara), Total Pain Solutions (TPS), Gerson Lehrman Group (GLG) Healthcare & Biomedical Council, Fortress Biotech, Sunovion Pharmaceuticals Inc., Sumitomo Dainippon Pharma. He is a stakeholder in Xhale, Celgene, Seattle Genetics, Abbvie, OPKO Health, Inc., Bracket Intermediate Holding Corp., Network Life Sciences Inc. He has been a member of the scientific advisory board of American Foundation for Suicide Prevention (AFSP), Brain and Behavior Research Foundation (BBRF) (formerly named National Alliance for Research on Schizophrenia and Depression [NARSAD]), Xhale, Anxiety Disorders Association of America (ADAA), Skyland Trail, Bracket (Clintara), RiverMend Health LLC, Laureate Institute for Brain Research, Inc.. He is a member of the board of directors of AFSP, Gratitude America, ADAA. Income sources or equity of $10 000 or more for Charles Barnet Nemeroff: American Psychiatric Publishing, Xhale, Bracket (Clintara) CME Outfitters, Takeda. He holds the following patents: method and devices for transdermal delivery of lithium (US 6 375 990B1); method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7 148 027B2). Giampaolo Perna, Massimiliano Grassi and Daniela Caldirola declare no conflict of interest.

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