Irish Journal of Psychological Medicine, (2021), **38**, 163–168. doi:10.1017/ipm.2020.79

EDITORIAL

Can precision medicine advance psychiatry?

Dónal Roche* and **Vincent Russell**

Department of Psychiatry, RCSI Education and Research Centre, Royal College of Surgeons in Ireland, Beaumont, Dublin, Ireland

Precision medicine is a new approach that considers differences in genes, environment, and lifestyle in an attempt to tailor treatments for individual patients. Psychiatry, as a discipline, has historically relied on clinical judgement and phenomenology-based diagnostic guidelines and has yet to take full advantage. This editorial provides an insight into the expanding role of precision medicine in psychiatry, both in research and clinical practice. It discusses the application of genetics and subgroup stratification in increasing response rates to therapeutic interventions, mainly focusing on major depressive disorder and schizophrenia. It presents an overview of machine learning techniques and how they are being integrated with traditional research methods within the field. In the context of these developments, while emphasizing the considerable potential for moving toward precision psychiatry, we also acknowledge the inherent challenges.

Received 16 January 2020; Revised 24 April 2020; Accepted 11 June 2020; First published online 17 July 2020

Key words: Machine learning, personalized medicine, precision medicine, precision psychiatry.

Introduction

Personalized and precision medicine is at the forefront in modern healthcare. This may represent the dawn of a new way to think about and practice medicine, but what does it actually mean? Some of the concepts underlying personalized medicine have a long pedigree, but its modern father is generally considered to be Archibald Garrod, who practiced in the early 20th century (Perlman *et al.* 2016). Garrod mused that the job of a physician is not to blindly apply the knowledge they have acquired; it is to take differences into account in order to maximize benefits for each individual patient. A modern definition of personalized medicine is stated as, 'an approach to disease treatment and prevention that considers individual differences in genes, environment, and lifestyle' (Genetics Home Reference 2015).

Many researchers now prefer the term precision medicine to personalized medicine. This represents a clarification, as the word personalized tended to be misconstrued as providing completely individualized treatments for each patient, which is not the case. The National Research Council has pointed out that precision medicine 'does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease . . . or in their response to a specific treatment' (National Research Council 2011). While the term precision medicine is beginning to enter current medical parlance, 'precision psychiatry' will not come to mind for most health professionals, or for the public. Even within the medical world, precision medicine is commonly perceived as the domain of more technologically supported medical specialists, for example, oncologists who can now prescribe 'magic bullet' drugs such as Trastuzumab (Herceptin), used to treat HER2+ breast cancer, or Imatinib, the first-line treatment for Philadelphia chromosome-positive chronic myeloid leukemia (Maximiano *et al.* 2016; Sacha 2014). To a large extent, this perception may be accurate. However, there is now an increasing opportunity for psychiatry, as a specialist discipline, to embrace precision psychiatry, thereby innovating how we diagnose and treat some of the most vulnerable people in our society. Here, we will review progress to date, consider how precision medicine approaches may improve specificity, how new technologies can complement existing approaches, and the potential challenges to the field.

The story thus far

How can precision medicine be integrated into psychiatry? Several developments, separately or in combination, are likely to contribute, from the use of genetic testing to improve patient selection for treatments to the introduction of deep-learning systems. Ozomaro and colleagues, for example, have reviewed the progress of precision medicine in major depressive disorder (MDD), bipolar disorder (BP), and schizophrenia (SZ) (Ozomaro *et al.* 2013). They describe how genetics and epigenetics influence the heritability of these diseases and their role in predicting treatment response. They included data analyzed by Apud *et al.*, which studied the relationship between voltage-gated

*Address for correspondence: Mr. Dónal Roche, 118 Richmond Park, Bray, Wicklow.
(Email: donalroche@rcsi.com)

potassium channel genotypes and treatment response to atypical antipsychotics in SZ, finding significantly greater improvements in positive symptom ratings on the Positive and Negative Syndrome Scale (PANSS) for patients with the TT genotype than the TC or CC genotypes (Apud *et al.* 2012). This provides some evidence that genotyping has the potential to influence treatment choices for patients with SZ.

While still in its infancy within psychiatry, the body of research continues to expand, as reflected in the launch of a new journal, *Personalized Medicine in Psychiatry*, in March 2017.

Small but significant improvements to clinical practice have been made with the commercial availability of pharmacogenetic-based decision-support tools. Some, such as GeneSight, have a growing evidence base to support their utility in guiding treatment choices for MDD, although these have yet enter widespread usage (Hall-Flavin *et al.* 2013; Winner *et al.* 2013). The National Institute for Mental Health (NIMH) has modified the Research Domain Criteria, aiming to integrate a wider range of information such as genomics and proteomics into the field of psychiatry, supplementing the phenomenology-based DSM and ICD criteria as the current cornerstones of clinical practice (Menke 2018). There has been considerable debate surrounding the introduction of the DSM 5, much of it surrounding a perceived overmedicalization of the normal range of psychological states and a lack of evidence validating the growing list of diagnoses (Pickersgill 2014). In the context of such inevitable controversy in regard to the enduring reliance on clinical judgement in psychiatric diagnosis, psychiatry should seek to maximize the use of tools we now associate with modern medicine, including biomarkers, imaging, genetic testing, and machine learning.

The benefits of specificity

One of the terms that repeatedly appears in the precision medicine literature is specificity. While psychiatrists are usually aware of a number of treatments that may work for a range of people, they can rarely predict which patients will respond to any individual option. This conventional, top-down approach generally results in trialing different treatments and evaluating the outcome clinically. Management strategies have improved dramatically over the years, but even in highly prevalent illnesses such as depression, over 50% of patients will be non-responders to their first-line medication (Boland *et al.* 2018; Trivedi *et al.* 2006). This can negatively impact the patient's outlook on their illness and affect the doctor–patient relationship while also risking the development of an attitude of therapeutic nihilism. Any two patients may be assigned an identical diagnosis, but are likely to have distinct psychopathologies requiring different treatments, because psychiatric disorders involve multiple and varying psychosocial and neurobiological routes. By utilizing genomics, proteomics and other associated technological advances, it is possible to build more accurate models of the specific neurochemical abnormalities (Waddington *et al.* 2019). While precision psychiatry, therefore, will not be able to solve the problems of variable and unpredictable response to treatment entirely, the hope is that we can at least improve the odds.

Using the example of major depressive disorder (MDD), while we understand that neurotransmitters such as serotonin play an important role, it is clear that they do not explain the entire picture (Dell'Osso *et al.* 2016). Large cohorts of patients have limited or no response to first-line selective serotonin reuptake inhibitors (SSRIs), and while there are many proposed factors that influence response, we cannot identify those patients who will respond fully, partially, or not at all (El-Hage *et al.* 2013). Advances in precision psychiatry hope to address this challenge. Studies have shown, for example, that there is a specific subpopulation of people with MDD who have a dysfunctional cortical stress hormone response system, resulting in abnormal C-reactive protein levels (Haapakoski *et al.* 2015). When tested specifically for treatment of depression, the use of medications with anti-inflammatory effects such as infliximab and nonsteroidal anti-inflammatories was found to have significant benefits, but only for this sub-group (Kohler *et al.* 2014; Raison *et al.* 2013). In addition, a recent systematic review of randomized control trials found anti-inflammatory agents improved depressive symptoms compared to placebo both as adjunctive and monotherapies in patients with MDD (Kohler-Forsberg *et al.* 2019). While this specific abnormality may only account for a minority of patients with MDD, it makes the point that there is scope to better individualize treatments for particular subpopulations. This increased stratification of patients could, therefore, lead to improved clinical response rates and, in turn, increased patient satisfaction. Increased pharmacological specificity comes with additional benefits for future drug manufacturing as well. As it stands, for a pharmaceutical product to make it to market requires it to have significant benefits and a low side-effect profile for a large proportion of a given patient population. With precision psychiatry, there could be an aim to design psychotropic medications that may not work for everyone, but which could have large benefits for smaller groups.

There is also a wealth of exciting research into how genetic variance can influence the effectiveness of the range of treatment regimens, particularly with MDD and anxiety disorders. Variations within the promoter

https://doi.org/10.1017/ipm.2020.79 Published online by Cambridge University Press

of serotonin transporter gene (SLC6A4), one of the key regulators of antidepressant mechanisms, have been repeatedly associated with differing treatment response to antidepressants (Stevenson 2018). Patients with specific polymorphisms in this key gene display higher rates of MDD, poorer therapeutic response to serotonergic antidepressants and increased side effect profiles (Luddington *et al.* 2009). Another gene that has been implicated in MDD is MTHFR, which is involved in folate metabolism but has particular high-risk alleles that result in reduced folate production (Bjelland *et al.* 2003; Hiraoka *et al.* 2017). Studies have shown that the addition of 15mg/day of folate, as an adjunctive therapy in SSRI-resistant MDD, increases response rates and results in greater improvements in depression symptom scores when compared to SSRI + placebo, although patients were not specifically tested for the high-risk genotype or folate deficiency (Papakostas *et al.* 2012). These are just two of many examples, which show that by understanding these diseases at the level of genes and proteins, there are opportunities to identify potential targets for novel treatments and move beyond the one-size-fits-all, protocolled approaches in use today.

Utilizing new technologies

The other big change on the horizon that precision psychiatry is poised to take advantage of is the growth and integration of machine learning and big data. As technology, the internet, and social media continue to expand its influence in our lives, there is access to more data, cheaper storage, and increased computing power. In a society that is increasingly subject to the risk of our data being mishandled, it would be refreshing to see it used to improve clinical outcomes for patients with mental illness instead. Machine learning can be defined as the 'field of study that gives computers the ability to learn without being explicitly programmed' (Munoz 2014). It has a range of advantages over traditional research methods, including increases in the potential for high-quality studies. In addition, machine learning utilizes a more accurate method for model testing. It employs a prospective approach, using smaller 'training datasets' to design models then trying to validate them against 'testing datasets' to evaluate their accuracy and update based on what they find (Bzdok *et al.* 2018). By using this training and testing approach, it attempts to identify and reduce the various biases that often distort traditional models and make research findings more generalizable. Computer systems are also better suited to handling complex data that deals with multiple outcomes (Bzdok *et al.* 2018). While randomized controlled trials may determine superiority between two treatments, they tend to fail when dealing with complex interventions as the comparisons and analyses become far more difficult (Baron *et al.* 2013).

These methods are already finding their place within psychiatry. One study of consenting patients who presented to a large emergency department used a model to analyze the language in their Facebook posts and was able to identify depressed patients with accuracy similar to standard depression screening surveys (Eichstaedt *et al.* 2018). Using clinical and imaging data, machine learning algorithms have successfully been employed to predict 1 year functional outcomes for patients in clinical high-risk states for psychosis or recent-onset depression (Koutsouleris *et al.* 2018). They have also been used on large datasets from clinical trials regarding response to antidepressants in MDD. One such study applying this method looked at citalopram and was able to predict clinical remission in 65% according to self-reported Quick Inventory of Depressive Symptomatology (QIDS) scores, higher than the base rate of predicted efficacy for citalopram and the percentage of patients who should achieve remission for a given treatment (Chekroud *et al.* 2016). The model was trained using 25 variables including components of the QIDS and Hamilton Depression Rating Scale and socioeconomic factors such as employment status and years of education. By combining the use of machine learning algorithms with traditional experimental designs and statistical inference methodologies, there is much scope to improve research output and develop useful clinical tools.

Potential challenges

The integration of precision psychiatry is a unique opportunity but presents with equally unique challenges, some ethical, some technical, and some practical. It is a venture that needs extensive collaboration and sharing of knowledge, requiring an integrated approach from psychiatrists, data scientists, industry, academia, and government. This interdisciplinary approach can ensure that patients remain at the center of care. Some issues with machine learning surrounding transparency, privacy, and accountability are still unanswered. The models are often complex with some operating as 'black boxes', which can make analysis difficult. With the increase in this type of research, there are calls to create frameworks to ensure that both the methods and results are trustworthy. One such call outlines three issues, namely, explainability, transparency, and generalizability, which need to be addressed before trustworthiness can be established (Chandler *et al.* 2020). There is also the issue of applicability for researchers as these methods can be difficult to implement and interpret for non-specialists. To combat this, there is a move toward developing software that

https://doi.org/10.1017/ipm.2020.79 Published online by Cambridge University Press

reduce the requirement for advanced programming backgrounds (Dwyer *et al.* 2018). However, even with these interfaces, there will inevitably be further challenges adapting workforces and IT systems to meet these evolving requirements. If algorithms learn from the data they are trained upon then, they may develop similar issues to their human counterparts including but not limited to racial and gender biases (O'Neil 2016). Availability of the large, unbiased, and representative data sets that are required for these models is, therefore, an additional challenge. The cornerstone of psychiatric management is the biopsychosocial model. In a struggle for finite resources, we must be cautious that increased emphasis on the biological component does not distract from providing proper funding for proven interventions, both at the level of the individual and broader, public health-based initiatives. Indeed, some areas of precision psychiatry rely heavily on psychosocial inputs, for example, using electronic health records to predict suicide attempts and deaths with machine learning algorithms (Simon *et al.* 2018). Additionally, diagnosis is often complicated by the presence of overlapping and co-existing disorders. While precision psychiatry aims to determine whether there is justification for differentiating these genetically or pathophysiologically, efforts must be made to avoid research that forces 'precision' in situations where it has no clinical utility. Finally, this new approach will require an acknowledgement of its value from the psychiatric establishment and a willingness to adapt to new methods.

Conclusion

In summary, we have outlined evidence of the growing influence of precision psychiatry. We suggest that increased patient stratification and integration of genetic information can improve therapeutic response rates, allowing us to move away from one-size-fits-all, protocolled treatment approaches. We argue that machine learning algorithms are already being employed in research, to better predict and improve patient outcomes. We also acknowledge some of the potential challenges and pitfalls that may hinder the precision approach. There have been many advances in precision psychiatry thus far, and the scope for how it could change practice in mental health disciplines is vast. While there is still much to discover, we must strive to implement these new techniques, progressing from research to trials and eventually clinical practice, where it can start to benefit our patients.

Financial support

This article received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict of interest

Mr. Dónal Roche has no conflicts of interest to disclose.

Professor Vincent Russell has no conflicts of interest to disclose.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. This paper did not require ethics committee approval for publication.

References

Apud JA, Zhang F, Decot H, Bigos KL, Weinberger DR (2012). Genetic variation in KCNH2 associated with expression in the brain of a unique hERG isoform modulates treatment response in patients with schizophrenia. *American Journal of Psychiatry* **169**, 725–734. https://doi.org/10.1176/appi.ajp.2012.11081214

Baron G, Perrodeau E, Boutron I, Ravaud P (2013). Reporting of analyses from randomized controlled trials with multiple arms: a systematic review. *BMC Medicine* **11**, 84. https://doi.org/10.1186/1741-7015-11-84

Bjelland I, Tell GS, Vollset SE, Refsum H, Ueland PM (2003). Folate, vitamin B12, homocysteine, and the MTHFR 677C->T polymorphism in anxiety and depression: the Hordaland Homocysteine Study. *Archives of General Psychiatry* **60**, 618–626. https://doi.org/10.1001/archpsyc.60.6.618

Boland JR, Duffy B, Myer NM (2018). Clinical utility of pharmacogenetics-guided treatment of depression and anxiety. *Personalized Medicine in Psychiatry* **7–8**, 7–13. https://doi.org/https://doi.org/10.1016/j.pmip.2017.11.001

Bzdok D, Meyer-Lindenberg A (2018). Machine learning for precision psychiatry: opportunities and challenges. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* **3**, 223–230. https://doi.org/10.1016/j.bpsc.2017.11.007

Chandler C, Foltz PW, Elvevag B (2020). Using machine learning in psychiatry: the need to establish a framework that nurtures trustworthiness. *Schizophrenia Bulletin* **46**, 11–14. https://doi.org/10.1093/schbul/sbz105

Chekroud AM, Zotti RJ, Shehzad Z, Gueorguieva R, Johnson MK, Trivedi MH, Cannon TD, Krystal JH, Corlett PR (2016). Cross-trial prediction of treatment outcome in depression: a machine learning approach. *The Lancet Psychiatry* **3**, 243–250. https://doi.org/10.1016/S2215-0366(15)00471-X

Dell'Osso L, Carmassi C, Mucci F, Marazziti D (2016). Depression, serotonin and tryptophan. *Current Pharmaceutical Design* **22**, 949–954. https://doi.org/10.2174/1381612822666151214104826

Dwyer DB, Falkai P, Koutsouleris N (2018). Machine learning approaches for clinical psychology and psychiatry. *Annual Review of Clinical Psychology* **14**, 91–118.

https://doi.org/10.1017/ipm.2020.79 Published online by Cambridge University Press

Eichstaedt JC, Smith RJ, Merchant RM, Ungar LH, Crutchley P, Preoţiuc-Pietro D, Asch DA, Schwartz HA (2018). Facebook language predicts depression in medical records. *Proceedings of the National Academy of Sciences of the United States of America* **115**, 11203–11208. https://doi.org/10.1073/pnas.1802331115

El-Hage W, Leman S, Camus V, Belzung C (2013). Mechanisms of antidepressant resistance. *Frontiers in Pharmacology* **4**, 146. https://doi.org/10.3389/fphar.2013.00146

Genetics Home Reference (2015). What is precision medicine? [WWW Document]. *U. S. National Library of Medicine - National Institutes of Health*. URL https://ghr.nlm.nih.gov/primer/precisionmedicine/definition

Haapakoski R, Mathieu J, Ebmeier KP, Alenius H, Kivimaki M (2015). Cumulative meta-analysis of interleukins 6 and 1beta, tumour necrosis factor alpha and C-reactive protein in patients with major depressive disorder. *Brain, Behavior, and Immunity* **49**, 206–215. https://doi.org/10.1016/j.bbi.2015.06.001

Hall-Flavin DK, Winner JG, Allen JD, Carhart JM, Proctor B, Snyder KA, Drews MS, Eisterhold LL, Geske J, Mrazek DA (2013). Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. *Pharmacogenetics and Genomics* **23**, 535–548. https://doi.org/10.1097/FPC.0b013e3283649b9a

Hiraoka M, Kagawa Y (2017). Genetic polymorphisms and folate status. *Congenital Anomalies (Kyoto)*. **57**, 142–149. https://doi.org/10.1111/cga.12232

Kohler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, Krogh J (2014). Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* **71**, 1381–1391. https://doi.org/10.1001/jamapsychiatry.2014.1611

Kohler-Forsberg O, Lydholm NC, Hjorthoj C, Nordentoft M, Mors O, Benros ME (2019). Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta Psychiatrica Scandinavica* **139**, 404–419. https://doi.org/10.1111/acps.13016

Koutsouleris N, Kambeitz-Ilankovic L, Ruhrmann S, Rosen M, Ruef A, Dwyer DB, Paolini M, Chisholm K, Kambeitz J, Haidl T, Schmidt A, Gillam J, Schultze-Lutter F, Falkai P, Reiser M, Riecher-Rossler A, Upthegrove R, Hietala J, Salokangas RKR, Pantelis C, Meisenzahl E, Wood SJ, Beque D, Brambilla P, Borgwardt S (2018). Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: a multimodal, multisite machine learning analysis. *JAMA Psychiatry* **75**, 1156–1172. https://doi.org/10.1001/jamapsychiatry.2018.2165

Luddington NS, Mandadapu A, Husk M, El-Mallakh RS (2009). Clinical implications of genetic variation in the serotonin transporter promoter region: a review. *Primary Care Companion to the Journal of Clinical Psychiatry* **11**, 93–102. https://doi.org/10.4088/pcc.08r00656

Maximiano S, Magalhaes P, Guerreiro MP, Morgado M (2016). Trastuzumab in the treatment of breast cancer. *BioDrugs* **30**, 75–86. https://doi.org/10.1007/s40259-016-0162-9

Menke A (2018). Precision pharmacotherapy: psychiatry's future direction in preventing, diagnosing, and treating mental disorders. *Pharmacogenomics and Personalized Medicine* **11**, 211–222. https://doi.org/10.2147/PGPM.S146110

Munoz A (2014). Machine learning and optimization [WWW Document]. URL https://www.cims.nyu.edu/~munoz/files/ml_optimization.pdf

National Research Council Committee on a Framework for Developing a New Taxonomy of Disease (2011). *The National Academies Collection: Reports funded by National Institutes of Health. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. Washington, DC.

O'Neil C (2016). *Weapons of Math Destruction: How Big Data Increases Inequality and Threatens Democracy*. Broadway Books.

Ozomaro U, Wahlestedt C, Nemeroff CB (2013). Personalized medicine in psychiatry: problems and promises. *BMC Medicine* **11**, 132. https://doi.org/10.1186/1741-7015-11-132

Papakostas GI, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A, Baer L, Dalton ED, Sacco GR, Schoenfeld D, Pencina M, Meisner A, Bottiglieri T, Nelson E, Mischoulon D, Alpert JE, Barbee JG, Zisook S, Fava M (2012). L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. *American Journal of Psychiatry* **169**, 1267–1274. https://doi.org/10.1176/appi.ajp.2012.11071114

Perlman RL, Govindaraju DR (2016). Archibald E. Garrod: the father of precision medicine. *Genetics in Medicine* **18**, 1088–1089. https://doi.org/10.1038/gim.2016.5

Pickersgill MD (2014). Debating DSM-5: diagnosis and the sociology of critique. *Journal of Medical Ethics* **40**, 521–525. https://doi.org/10.1136/medethics-2013-101762

Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH (2013). A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* **70**, 31–41. https://doi.org/10.1001/2013.jamapsychiatry.4

Sacha T (2014). Imatinib in chronic myeloid leukemia: an overview. *Mediterranean Journal of Hematology and Infectious Diseases* **6**, e2014007–e2014007. https://doi.org/10.4084/MJHID.2014.007

Simon GE, Johnson E, Lawrence JM, Rossom RC, Ahmedani B, Lynch FL, Beck A, Waitzfelder B, Ziebell R, Penfold RB, Shortreed SM (2018). Predicting suicide attempts and suicide deaths following outpatient visits using electronic health records. *American Journal of Psychiatry* **175**, 951–960. https://doi.org/10.1176/appi.ajp.2018.17101167

https://doi.org/10.1017/ipm.2020.79 Published online by Cambridge University Press

Stevenson JM (2018). Insights and barriers to clinical use of serotonin transporter pharmacogenetics in antidepressant therapy. *Pharmacogenomics* **19**, 167–170. https://doi.org/10.2217/pgs-2017-0196

Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *American Journal of Psychiatry* **163**, 28–40. https://doi.org/10.1176/appi.ajp.163.1.28

Waddington JL, Russell V (2019). The Cavan-Monaghan First Episode Psychosis Study (CAMFEPS): arbitrary diagnostic boundaries across the gene-environment interface and within evolving models of care. *Irish Journal of Psychological Medicine* **36**, 293–303. https://doi.org/10.1017/ipm.2019.11

Winner JG, Carhart JM, Altar CA, Allen JD, Dechairo BM (2013). A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. *Discovery Medicine* **16**, 219–227.

https://doi.org/10.1017/ipm.2020.79 Published online by Cambridge University Press