Journal of Psychiatric Research 143 (2021) 572–579

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Review article

Methodological and clinical challenges associated with biomarkers for psychiatric disease: A scoping review

Ryan H. Kirkpatrick [a,b,*], Douglas P. Munoz [a,b,c,d], Sarosh Khalid-Khan [a,b,d,e], Linda Booij [d,f,g,h,**]

[a] Centre for Neuroscience Studies, Queen's University, Kingston, Canada
[b] School of Medicine, Queen's University, Kingston, Canada
[c] Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Canada
[d] Department of Psychology, Queen's University, Kingston, Canada
[e] Department of Psychiatry, Queen's University, Kingston, Canada
[f] Department of Psychology, Concordia University, Montréal, Canada
[g] CHU Sainte-Justine Hospital, University of Montréal, Montréal, Canada
[h] Department of Psychiatry, McGill University, Montréal, Canada

ARTICLE INFO

Keywords:
Psychiatry
Biomarker
Translational research
Mental health
Genetics
Brain-imaging

ABSTRACT

Over the past decade, psychiatric research has been on an important hunt for biomarkers of psychiatric disease. In psychiatry, the term "biomarker" is a broad umbrella term used to identify any biological variable that can be objectively measured and applied to a diagnosis; this includes genetic and epigenetic assessments, hormone levels, measures of neuro-anatomy and many other scientific modalities. However, despite hundreds of studies on the topic being published yearly and other medical specialties having success in discovering biomarkers, clinical psychiatric practice has not had the same success. This paper aims to consolidate the many opinions on the search for psychiatric biomarkers to suggest key methodological and clinical challenges that psychiatric biomarker research faces. Psychiatry as a specialty has many fundamental differences compared to other medical specialties in methods of diagnosing, underlying etiology and disease pathologies that may be limiting the success of biomarker research in itself and puts strict requirements on the research being conducted. The academic and clinical environment in which the research is being conducted also heavily influences the translation of the findings. Finally, once biomarkers are identified, more often than not they are inapplicable to clinical settings, unable to integrate into clinical practice and fail to outperform current diagnostic practices and guidelines. We also make six recommendations for more promising future research in psychiatric biomarkers.

1. Introduction

There is an urgent need for biomarkers of disease in various areas of medicine including pharmacology, oncology and, especially, psychiatry. Although the first reference to "biomarker psychiatry" occurred in 1966, the search for a biomarker in psychiatric research has skyrocketed in the last decade (Fig. 1). The vast number of studies seeking biomarkers alone suggests that the term "biomarker" is broad; on its own even the topic of what constitutes a biomarker has prompted numerous publications and working groups (e.g., Atkinson et al., 2001; Strimbu and Tavel, 2010). What does "biomarker" actually mean? By dictionary definition, it is "a distinct biochemical, genetic or molecular characteristic or substance that is an indicator of a particular biological condition or process" (Biomarker Definition, n.d.). By definition, a biomarker is an objective measurement of a specific psychiatric diagnosis. This use of the term biomarker may be in contrast to the historically subjective nature of psychiatry. Biomarker candidates currently being investigated include (but are not limited to) genotypes, epigenetic modifications, brain connectome characteristics, hormone levels and saccadic eye movement patterns. While there is no shortage of research aimed at identifying biomarkers, their clinical efficacy is, however, currently extremely limited (e.g., Carvalho et al., 2020; Schwarz et al., 2010; Lozupone et al., 2019).

Once identified, not all biomarkers have the same degree of impact

* Corresponding author. Botterell Hall, 18 Stuart St., Queen's University, Kingston, Ontario, K7L 3N6, Canada.
** Corresponding author. 7141 Sherbrooke St. West, Concordia University, Montréal, H4B 1R6, Canada.
E-mail addresses: ryan.kirkpatrick@queensu.ca (R.H. Kirkpatrick), linda.booij@concordia.ca (L. Booij).

https://doi.org/10.1016/j.jpsychires.2020.11.023
Received 11 July 2020; Received in revised form 20 September 2020; Accepted 9 November 2020
Available online 11 November 2020

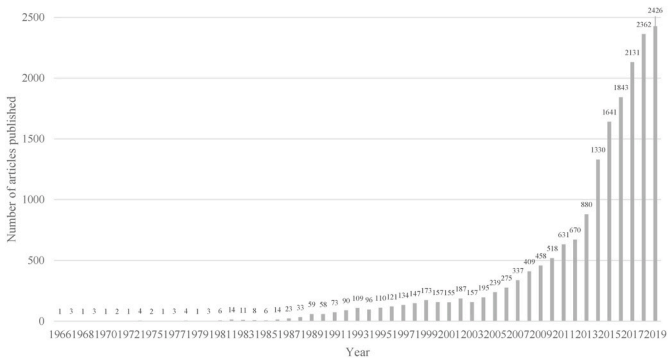

Fig. 1. PubMed "Biomarker Psychiatry" publications since 1966.
Note. The number of published articles in a PubMed search of the terms "biomarker" and "psychiatry". Data was generated using PubMed's internal analytics tools September 19, 2020.

on their respective clinical field. An ideal biomarker can be illustrated in the context of Huntington's Disease, which has a clear genetic cause. The presence of an elongated triple nucleotide repeat (36 or greater) in the Huntingtin gene indicates with certainty that the individual will develop Huntington's Disease (MacDonald et al., 1993). This genetic biomarker is ideal as there is no subjectivity associated with its interpretation. In contrast, when looking at cancer, the presence of *BRCA1* and *BRCA2* gene mutations confer an increased risk of developing breast cancer by approximately 65% and ovarian cancer by approximately 39% (Antoniou et al., 2003). The presence of either mutation alone does not definitively indicate the development of cancer (Antoniou et al., 2003).

Psychiatric conditions are inherently complex and often difficult to diagnose. For example, when an individual presents with symptoms of psychosis, it could be due to a number of disorders such as schizophrenia, bipolar disorder, major depressive disorder (MDD) with psychotic features or a reaction to illicit drugs. Furthermore, for most diagnostic categories, symptom presentation is highly heterogenous. For instance, to receive a diagnosis of MDD, an individual must meet five of nine listed symptoms with one symptom being either a depressed mood or anhedonia (American Psychological Association, 2013). The diagnostic challenges are further enhanced by a lack of objective, laboratory-based tests for psychiatric diagnoses. A clinician must therefore use clinical interviews to distinguish between these different diagnoses. All of these examples not only reinforce the immense drive but also highlight the need to search for psychiatric biomarkers.

Further support for the development of biomarkers is found with the American National Institute of Mental Health's (NIMH's) establishment of a strategic plan to develop evidence-based mental health care through the Research Domain Criteria (RDoC). The RDoC is a framework that aims to generate research in human function and behaviour from the micro (e.g., genetic) to the macro (e.g., self-reported symptoms) level and provides an ideal opportunity to discover biomarkers (Cuthbert, 2014). Biomarkers appear to be quite versatile; they seek to identify individuals at high-risk of diagnosis development, distinguish those with or without a diagnosis and predict patient treatment response.

Despite many research findings concerning biomarkers, results of individual empirical studies often remain unreplicated, and findings that were replicated have yet to impact any stage of clinical engagement. For example, in 2014, a blood test was scheduled for release on the market with the promise of being able to objectively aid in the diagnosis of MDD. MDDScore (Bilello et al., 2015) is an assay of nine MDD-associated biomarkers and controls for gender and body mass index. However, when considering the success of MDDScore, it is crucial to note that from 2015 to September 2020, no further studies have been published, there are no known psychiatric clinics utilizing MDDScore and it is not available for purchase.

The lack of utilization and acceptance of MDDScore illustrates the difficulty for psychiatric biomarker research to make a meaningful difference clinically. The goal of this paper is to highlight some of the key methodological and clinical challenges that impact biomarker research in terms of identification and successful implementation of biomarkers within the medical field. To the authors' knowledge, this paper is the first to provide an extensive review of methodological and practical challenges facing biomarker research in psychiatry at various points in the research translation process. Outlining the challenges at both the methodological and practical levels could help the design, interpretation and implementation of psychiatric biomarker research.

2. Method

For this scoping review, a literature search was conducted for articles published until September 19, 2020 using Web of Science. Search terms were "biomarker" and "psychiatry" and did not include any diagnosis specific terms. The articles reviewed in this scoping review were not selected systematically and cannot be classified as all-inclusive. Relevant and recent articles were reviewed for key findings and overarching ideas were consolidated and summarized within this paper. The common themes of the selected articles were classified into methodological or clinical challenges.

3. Results

3.1. Methodological challenges

3.1.1. Missing links

The biomarker search has had success in other medical specialties such as neurology, as in the case of Huntington's Disease, but there are some critical differences between fields that may underlie the lack of successful biomarker identification and integration into psychiatric clinical care (Berdasco and Esteller, 2019).

Animal Models. There are very few valid and reliable animal models of psychiatric diagnoses in which biomarker identification can begin. While the literature includes numerous references to animal models of psychiatric diagnoses (e.g., MDD, schizophrenia), their validity has yet to be demonstrated. Articles published in high impact journals such as *Cell* claimed to have rescued cognitive dysfunction associated with schizophrenia in mice (Mukherjee et al., 2019). However, certain behaviours and diagnoses are uniquely human. In the study of oncology, the ability of cells to metastasize may be similar in animal models and in humans, but the inability of animal models to display complex human emotions, cognitions and behaviours (e.g., hallucinations) may be a limiting factor (Of Mice and mental health, 2019). For example, the dorsolateral prefrontal cortex, a brain region implicated in high level cognitive functioning, is not present within rodents, suggesting a lack of applicability of rodent models for psychiatric diagnoses and their associated behaviours (Petrides et al., 2012; Preuss, 1995). While non-human primates may be a model organism that is closer to humans, many differences in key brain regions must still be considered (Petrides and Pandya, 2002). Without having true all-encompassing animal models, researchers are limited in ways they may study psychiatric biomarkers.

Postmortem Brain Tissue. The use of postmortem brain tissue has been suggested as a promising route to effective psychotropic drug discovery and as a method for connecting genetic and neurobiological information of psychiatric diagnoses (Jaffe, 2016; Kim and Webster, 2009; McCullumsmith et al., 2014). Studying postmortem brain tissue allows for the addition of a translational link between animal models of psychiatric diagnoses and studies in living humans (McCullumsmith et al., 2014). However, there is a lack of available postmortem brain tissue from individuals with psychiatric diagnoses (Venkatasubramanian and Keshavan, 2016). This lack of access may be minimized through optimizing high-level cooperation between clinicians, pathologists performing the autopsies, patients and families. Further, the

quality and usability of data obtained from the brains is critical and requires strict adherence to a timeline between death and tissue collection (McCullumsmith et al., 2014). When examining brain tissue, it is also crucial to match patient and control groups on tissue-related parameters such as age, storage time and pH level or add these parameters as covariates within analyses (Hercher et al., 2009). There are multiple ongoing efforts to increase availability of such tissues (e.g., the JAPAN Brain Bank Network (Iritani et al., 2018), the Douglas-Bell Canada Brain Bank (Almeida and Turecki, 2016); Netherlands Brain Bank for Psychiatry (Rademaker et al., 2018)). Lastly, it is also important to note that postmortem brain tissues cannot answer all biomarker questions as information is retrospective and certain processes are challenging, if not impossible (e.g., brain activity), to identify in such tissues.

Pathological Features. In psychiatry, systems often appear "normal" on the surface but have a pathological phenotype within their functioning, thereby adding an additional layer of complexity to identifying psychiatric diagnoses (Abi-Dargham and Horga, 2016). Linden (2012) highlights that the increased presence of a biomarker in individuals with a psychiatric diagnosis compared to a control group does not exclude that same trait from still having a large presence in healthy populations; oftentimes this overlap prevents the biomarker from having diagnostic utility.

Furthermore, whereas a cancerous tumor may be relatively easily visible within imaging modalities (e.g., MRI) prompting further medical testing, in psychiatry, there is rarely one pathological feature that can be easily seen or identified. Therefore, with regard to brain biomarkers, as symptoms are produced by a network of brain areas rather than one region alone, examining brain connectivity may provide more promise for biomarkers than studying specific brain regions. Likewise, in genetic research, genome-wide association studies (GWAS) or polygenic risk score approaches may be able to provide more fruitful biomarkers than candidate-gene studies, as behaviours, and likely psychiatric diagnoses, are impacted by multiple genes rather than a single gene. Yet, conducting such research in large sample sizes that allows for such comprehensive analyses is deemed essential.

The aforementioned issues need to be considered in light of proper research protocols. When developing a new diagnostic test or treatment, it is critical that the newly investigated method be compared to the highest standard of care. For example, in oncology, a new chemotherapy drug is compared to the currently approved top-of-the-line chemotherapy drug. This is not as clear-cut within psychiatry. Diagnostic criteria within psychiatry are always evolving. The Diagnostic and Statistical Manual (DSM) and International Classification of Diseases (ICD) have undergone many revisions since their establishment. Both the DSM and psychiatric guidelines within the ICD are primarily based on symptom presentation rather than the underlying neurobiology of a diagnosis. Therefore, there is no gold standard test that can be used for biomarker comparison. Also, as these guides are revised, diagnoses become further stratified and, without a neurobiological basis, make it more difficult to identify biomarkers that fully encompass a diagnosis (Kapur et al., 2012). Of note, Kapur et al. (2012) highlight that breast cancer faced a similar difficulty until histological evidence was able to classify lumps. This suggests that overcoming a diagnostic system without a biological bias is not impossible, rather it requires large effect sizes to allow for meaningful analyses.

3.1.2. Research requirements

Systematic. The term biomarker has been applied very broadly within psychiatry, encompassing everything from gene variants to structural brain changes. While this may seem to be a positive factor for the search, the lack of structure may lead to missed biomarkers. Abi-Dargham and Horga (2016) emphasize the need for systematic biomarker identification initiatives. As research into biomarkers has increased exponentially over the past decade, it has resulted so far in few, if any, clinically applied findings. Therefore, something about the search method must change. During his State of the Union Address in 2015, former American President, Barack Obama, highlighted the need to approach medical research differently and announced a research initiative with that aim (Collins and Varmus, 2015). While this initiative specifically named oncology as a target, it also emphasized the need to utilize recent scientific advances to improve identification, diagnosis and treatment of other medical conditions (Collins and Varmus, 2015). Essentially, this initiative encourages a more holistic approach to the search for biomarkers. This suggests that biomarker research should encompass various biomedical fields and has oftentimes been referred to as "precision psychiatry" (Fernandes et al., 2017). This approach has been embodied by several large-scale research initiatives such as the Canadian Biomarker Integration Network on Depression (CAN-BIND). CAN-BIND collects clinical information (e.g., course of the depressive episodes) and connects this information with neuroimaging (e.g., brain structure), molecular (e.g., genetic, hormonal) and electrophysiological (e.g., response to transcranial magnetic stimulation) data from across the country (MacQueen et al., 2019). Research initiatives comparable to CAN-BIND that approach biomarker identification in a comprehensive and systematic way are less likely to miss potential biomarkers and, therefore, have increased chances for success. However, there is also a strong need for cross-disorder analysis as biological processes underlying a given psychiatric disorder appear to be not truly distinct (e.g., Antilla et al., 2018).

Sample Size. Many research studies described in the literature are characterized by small sample sizes. This may be challenging as some psychiatric diagnoses have a relatively low prevalence. For example, bipolar disorder type II was estimated to have a lifetime prevalence of 0.57% (McDonald et al., 2015). Collaborations between different research groups to obtain collaboratively large sample sizes is therefore important.

Without a sufficient sample size, and therefore adequate statistical power, data-analyses may not identify significant findings when a clinically significant association actually exists. Conversely, small sample sizes may also lead to false positive unreplicable findings. To overcome these limitations, collaborative interinstitutional initiatives and consortia that utilize standardized methodologies are necessary. These efforts not only provide more statistical power but also allow for complex data-analysis (e.g., machine learning) to be conducted reliably. Indeed, various international efforts have recently been developed to promote generation of large datasets such as the Psychiatric Genomics Consortia and the Connectomes Related to Human Disease studies of the Human Connectome Project (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Glasser et al., 2016).

Standardization. One of the most important aspects of identifying and utilizing biomarkers is ensuring their accuracy and reproducibility. With that in mind, strict standardization is required both within individual studies and within replication studies. In individual studies, it is necessary that all data-collection procedures are identical. In studies using for example clinical interviews or neuropsychological testing, it is critical that instructions given to each participant are identical. For studies involving biological materials, collection procedures and supplies must be consistent. When blood is collected, factors such as time of day, length of time since last meal and caffeine consumption are known to impact the presence of certain biomarkers (e.g., cytokines, gene expression, cortisol; Dean, 2011; Leonardson et al., 2010; Lovallo et al., 2008). When complementary and replication studies are being conducted, methods should ideally also be closely matched with previous studies.

Without standardization of study procedures, firm conclusions on the validity of biomarkers are difficult to make. A lack of standardization between and within studies is likely to be an important reason why there have been few successful psychiatric biomarkers in clinical settings (Scarr et al., 2015). It is clear that when replication or multi-site studies are being planned, standardization is essential, particularly if there are multiple data collection sites. However, it is also important to note that a

robust finding should still be present across studies despite small variations in experimental procedures.

Longitudinal. Once biomarkers are identified, their temporal relationship with the diagnosis should be determined. In other words, it is important to know if a biomarker is a state (only present at one stage of the disorder) or trait (present throughout the course of the disease) biomarker. For example, an individual that will develop Huntington's Disease will have the genetic biomarker for the Disease throughout their life. This knowledge is critical to the applicability of the biomarker to ensure it can be properly used within clinical settings.

In an ideal research environment, the temporal relationship between all proposed biomarkers and their disease characteristic would be studied. However, this is not always feasible, and a recent systematic review found that only 34% of studies on peripheral biomarkers for major psychiatric diagnoses were longitudinal (Pinto et al., 2017). The availability of this information is limited by research funding (longitudinal studies are typically more expensive than for example cross-sectional studies) and participant attrition rate.

Non-Representative Samples. Many research studies exclude patients with the most severe symptomatology within the diagnosis of interest. For example, it is common for studies, including the CAN-BIND study, to exclude patients with a high suicide risk (Lam et al., 2016). While such exclusion criteria is beneficial to isolating true findings in a heterogeneous clinical group and ensuring participant safety throughout the research study, this lack of heterogeneity in the study group may widen the translation gap between the identification of the biomarker and how well it can be used within a clinical setting.

Approximate Replications. An approximate replication is a follow-up study that uses a similar, but not identical, protocol to the original that neither confirms nor disputes the findings of the original study (Kapur et al., 2012; Scarr et al., 2015). These studies can often be an attempt to account for a previously underpowered study by the same research group (Kapur et al., 2012). While they may seem beneficial on the surface when considering the need for replication studies, in reality they are not. Approximate replication studies cloud research by inadequately providing a clear conclusion on the validity of a previous finding, while also suggesting another potential finding to pursue. Given the current academic climate, the tendency of journals to favour the publication of positive results (Fanelli, 2012) and papers to cite positive results (Duyx et al., 2017), the commonality of approximate replications is unsurprising. Perhaps it may be particularly evident in psychiatric biomarker literature, as protocols are often not strictly adhered to, which does not allow for strict support or disputation of previous findings.

3.1.3. Academic environment

Advancements in medicine often depend on the work of researchers, and the majority of research is conducted within academic institutions (National Science Board, 2014). While this can be conducive to collaborations between departments and research specialties, it also impacts the advancement of biomarker research into clinical practice.

Novel Findings. When describing the academic setting, the phrase "publish or perish" is often used (Rawat and Meena, 2014). The phrase describes the emphasis placed on researchers to continually publish their findings in peer-reviewed academic journals, suggesting that those who fail to do so will become irrelevant within their field. This phrase is further supported by recruitment methods often used by hiring institutions where number of publications and other metrics based around publications (e.g., H-index) are used to determine the top candidates (Rawat and Meena, 2014). This harsh reality has influenced the academic climate. To achieve scientific relevance and prestige, researchers must conduct the research that journals want to publish and, unfortunately, replication studies often do not fit within that criterion (Grimes et al., 2018). Replication is necessary to ensure the validity of scientific findings. Indeed, the validity of published findings and soundness of current scientific practices have been called into question more than once within literature (e.g., Moore et al., 2017; Young et al., 2008). Fanelli, Costas and Ioannidis (2017) found that highly cited peer-reviewed papers that were small and older had a higher likelihood to overestimate effects. However, with the recent increase in open science practices, there may be an optimistic change in practice that may reduce the proliferation of false findings (Smaldino et al., 2019).

For biomarkers to be successful in their transition from an academic finding to a clinical tool, they must be true and valid. Without an environment that supports and encourages widespread replication studies, it is less likely that biomarker replication studies will be conducted, thereby widening the gap in time between a finding being made, replicated and applied. Alternatively, proposed biomarkers may transition from academics to clinic without replication. While this may speed along the process when true biomarkers are found, it will result in added cost and time spent on false findings.

3.2. Clinical challenges

Once the aforementioned methodological challenges are addressed, the most pertinent question becomes whether the biomarker can be used clinically. Often, so far, the answer is no. The limited ability of biomarker research to change practice in psychiatry can be the direct result of inapplicability to clinical settings, inability to integrate and inability to outperform current diagnostic practices and clinical guidelines. Some of these aspects are reviewed below.

3.2.1. Inapplicability

Sensitivity and Specificity. To be useful in a clinical setting, it is important that any biomarkers that are used have both a high sensitivity and specificity. In the case of a diagnostic biomarker, it must be able to correctly identify those with the diagnosis (sensitivity) while being able to correctly identify those who do not have the diagnosis (specificity). There are various factors that limit the ability of biomarkers in psychiatry to have high sensitivity and specificity.

In psychiatry, there is a high degree of symptom overlap between diagnoses. For example, obsessive behaviours are a core feature of obsessive-compulsive disorder, anorexia nervosa and obsessive-compulsive personality disorder. As well, certain proposed biomarkers appear in multiple diagnoses. For example, brain-derived neurotrophic factor (BDNF; a neurotrophin implicated in neurodevelopment and neuronal function) has been found to have decreased serum levels in depression, bipolar disorder and schizophrenia (Buckley et al., 2007; Fernandes et al., 2015; Gorski et al., 2003; Terracciano et al., 2011). Not only can this overlap cause difficulties when diagnoses are made using traditional symptom-centric diagnostic guides, but these commonalities may result from overlap in underlying pathologies. To the contrary, there is high heterogeneity in psychiatric diagnoses (Feczko et al., 2019). This high heterogeneity occurring in psychiatric diagnoses makes it difficult for a biomarker to be able to have high sensitivity and specificity and without both, the biomarker would be unsuccessful when applied to a clinical setting. Similarly, with many diagnostic criteria stating that only a specific number of symptoms of all listed symptoms must be present in order to meet full diagnostic criteria, there are many differing ways in which the same diagnosis can present and manifest. Whereas research so far showed that the identification of a biomarker for a specific psychiatric diagnosis have not been very fruitful, further investigation of neurobiological factors that underlie the clinical heterogeneity commonly seen in individuals with mental disorders is desperately needed. Biomarkers in psychiatry might eventually guide the principled assignment of individuals to distinct clinical subgroups and, further, the clinical application of treatments tailored to individual differences in a precision medicine type of approach.

Confounders. The success of clinical research studies is dependent on the rate at which individuals with a certain diagnosis actually present to a treatment clinic. Although psychiatric diagnoses have a global high prevalence, only specific subpopulations present to a psychiatric clinic

(e.g., individuals with more severe concerns or comorbidities). This may lead to an overall skew in the individuals recruited for clinical biomarker research studies.

Another source of bias is selection bias. For example, rates of MDD are historically higher in women than men (Albert, 2015). While there may be biological reasons for this (e.g., Albert, 2015), sociological differences in mental health treatment engagement between men and women must also be considered. Men identify psychiatric symptoms much less frequently within themselves which may result in their decreased presentation to psychiatric treatment settings, in turn resulting in lower availability of men to contact for participation in psychiatric research studies-a phenomenon called gender-related selection bias (Seidler et al., 2016). Selection biases may also occur in relation to ethnicity (Akinhanmi et al., 2018). For example, various studies indicate that racial/ethnic minorities have less access and are less likely to use mental health services (Maura and de Mamani, 2017). There is also research showing that certain minority groups are more likely to be misdiagnosed and less likely to be recruited for genomic biomarker studies (Akinhanmi et al., 2018). Consequently, biomarkers may run the risk of having little generalizability.

Research studies also aim to control for external factors that may influence or confound the results (e.g., age, sex). This allows for the direct relationship between the diagnosis and biomarker to be teased out. However, these factors cannot be removed in a clinical setting. One of the most important confounders in psychiatric research is comorbidity. It is not uncommon for individuals with the diagnosis of interest to be excluded from a study if they have more than one psychiatric diagnosis. By limiting the inclusion of individuals with multiple diagnoses or controlling for any and all potential confounders, the results of most biomarker research may be less generalizable to the clinical setting in which they would be used.

Diagnosis Stability and Reliability. In psychiatry, diagnosing disorders is further complicated by the lack of diagnostic stability within an individual. For example, when an individual presents to a psychiatric clinic, they may meet all criteria of MDD and therefore receive such a diagnosis. However, this individual may truly have a bipolar disorder and simply sought help before they had experienced a manic or hypomanic episode. Therefore, after this episode occurs, their diagnosis may be changed to bipolar disorder. With psychiatric diagnoses and symptom presentation frequently evolving, it can become difficult to determine the correct diagnosis and therefore difficult to ensure that the biomarker identified is associated with the correct diagnosis.

Additionally, inter-rater reliability of psychiatric diagnoses poses a constraint. Few et al. (2013) examined inter-rater reliability of DSM-5 personality disorder constructs in trained graduate interviewers. Inter-rated reliability on Levels of Personality Functioning scales fell within the “fair agreement” range. This lack of consistent agreement between clinicians increases difficulty with ensuring that the diagnosis for which a biomarker is being sought is accurate.

3.2.2. *Inability to integrate*

Provided a biomarker is able to account for or avoid the common issues discussed above, it must then be able to be used clinically. The healthcare system is incredibly complex, involving government, clinicians, patients and other stakeholders. Therefore, there are many barriers that must be overcome before a biomarker can be implemented clinically.

Costs. It is anticipated that the Canadian government spent $264 billion CAD on the healthcare system in 2019 alone (Canadian Institute for Health Information, 2019). National Hospital associated costs, pharmaceuticals and physician services alone account for approximately 67% of the health care expenditures, with remaining funds covering everything from the purchasing of public and private health plans and funding of long-term care facilities, medications and patient food to equipment (Canadian Institute for Health Information, 2019). Comparatively, in the USA, hospital care, physician and clinical services account for 53% of their $3.6 trillion USD health care expenditures (Centre for Medicare and Medicaid Services, 2019). This leaves little for implementing new tests, especially those that are costly. For example, a routine Magnetic Resonance Imaging (MRI) scan costs on average $895 CAD and it costs approximately $3 million CAD to install a new scanner into a hospital (Canadian Magnetic Imaging, n.d.; GE Healthcare, 2016). However, not all methodologies and equipment used to identify biomarkers may be as costly. Differences in eye movements, pupil response and blinks are being examined as potential biomarkers (e.g., Yep et al., 2018). Based on a quote provided directly to the authors from SR Research, a comprehensive, high speed (2000 Hz), high fidelity ($<0.01^{\circ}$ error) EyeLink 1000 eye-tracker costs $40 000-$50 000 CAD. When biomarkers are ready to be implemented into a clinic, it is important that a cost-benefit analysis be made comparing not only the cost of the associated equipment and running each individual test, but also the reduction to the disease burden that would occur with the said biomarker’s implementation and the success of the biomarker compared to the cost of its implementation.

Practical Implementation Issues and Challenges. Once a biomarker has been deemed cost-effective for implementation, it is then important to consider how it will be integrated into the circle of care. Do the clinicians have access to the necessary equipment? Will the clinician be administering the test themselves or will they be referring the patient to an external clinic (e.g., an MRI facility)? Will the test’s output be received by the clinician for a final decision or will the output be sent to an analysis lab and subsequently returned to the clinician? All of these decisions and their associated feasibility must be considered in the cost-benefit analysis as well as when determining the most efficient way to implement the biomarker’s test. As it may not be realistic to expect clinicians to learn how to read the output from an eye-tracking test, unprocessed genetic analysis or functional MRI scan, but it may be more practical to send the results to an external analysis technician and have a final, unambiguous report sent to the clinician for subsequent clinical care decisions. If the means of relaying the output to clinicians are ambiguous, it is unlikely that a biomarker will be successful in the clinical setting.

3.2.3. *Inability to outperform*

Finally, it is paramount that the proposed biomarker performs better than current methods and has a clear benefit. For example, less than one fifth of individuals with Huntington’s Disease in their family choose to have a genetic test administered (Meiser and Dunn, 2001). Without a promising treatment or benefit to identifying risk earlier, there is little incentive or benefit of finding out whether an individual will go on to develop the disease. This highlights the need for clinically relevant research questions to underlie biomarker research and the need for researchers and clinicians to work together to ensure their continued clinical relevance throughout the process.

3.3. *An example*

In 2010, Rules Based Medicine rolled out a blood-based test for schizophrenia aimed at assisting clinicians in forming the initial diagnosis (Schwarz et al., 2010). The test boasted a specificity and sensitivity of 84% and 85%, respectively (Schwarz et al., 2010). However, the test was later withdrawn from commercial production. It is speculated that the high cost and clinically low sensitivity and specificity played large roles in this decision (Scarr et al., 2015).

The preceding example illustrates the complexities engaged in successfully implementing a biomarker into psychiatric settings. Despite the test seemingly overcoming many of the methodological challenges reviewed in this paper, it was still ultimately shown to be clinically unsuccessful. The test fell victim to insufficient sensitivity and specificity levels, extreme comparisons and a high cost (Scarr et al., 2015; Schwarz et al., 2010).

4. Discussion

Overall, research aiming to identify biomarkers in psychiatry has many barriers to success. Methodologically, researchers must work to fill or overcome missing links (animal models, postmortem brain tissue and pathological features) while ensuring their research meets strict recommendations (systematic and standardized longitudinal studies with large sample sizes) in an academic environment not always entirely supportive of the research needed (exact replication studies). Additionally, the psychiatric biomarker must be studied in the context of various clinical realities such as heterogeneity within existing diagnostic categories, psychiatric comorbidities, as well as various clinician and referral biases. However, these potential roadblocks are not unsurmountable. Once a test is ready to move into the clinic, it must apply directly to the clinical setting in which it will be used with high sensitivity and specificity, be able to integrate into the current healthcare system and, most importantly, have a clinical benefit.

The use of biomarkers may provide many advantages to individuals with psychiatric disorders. A reliable and valid biomarker could allow personalized medicine and precision treatment. Individual patients may receive the proper diagnosis, and therefore proper treatment, more quickly. Additionally, biomarkers may be able to more accurately match patients with treatments they are more likely to respond to. This may allow treatment to commence before symptoms reach a severe level and increase the likelihood of expedited recovery. Furthermore, biomarkers may help clinicians to identify who is most at risk for relapse and recurrence, which would in turn also benefit individual treatment guidance.

That being said, it is important to note the potential impact biomarkers may have on mental illness and its related stigma. By providing support for a biological rather than a psychosocial basis for mental illness, it could be argued that the stigma surrounding mental illness may increase. This shift towards a biological basis of mental illness has been found to increase the public's desire for social distance from individuals with a mental illness and increase the public's notion of uncontrollability associated with mental illness (Haslam and Kvaale, 2015). On the other hand, by providing a more objective method for identifying mental illness, biomarkers may validate an individual's mental illness and therefore decrease their personal stigma and prevent individuals from placing the blame on themselves. For example, when genetic counselling, aimed at identifying any shame, guilt, stigma, fear or blame a patient may be experiencing as a result of the heritability associated with their diagnosis, is provided to individuals with a psychiatric diagnosis, they report an increased sense of empowerment, acceptance and management surrounding their diagnosis (Semaka and Austin, 2019; Steiger and Booij, 2020).

Going forward, we propose six main recommendations for biomarker research:

1. Achieve clinically meaningful specificity and sensitivity. Large sample sizes that consider population and environmental diversity are a necessary first step to achieve this.
2. Once a sufficiently large sample size has been obtained to allow for more complex analyses, integrate multiple biomarker classes or various methods of the same modality. For example, combine polygenic risk scores determined from GWAS studies with connectome data to inform an objective, rather than subjective, measure of a psychiatric diagnosis. Alternatively, GWAS studies should be used to develop polygenic risk scores, that determine common variants, as well as rare variants to create a more complete picture of the genetic components.
3. Build collaborative research networks and consortia involving individuals at every stage of the research and implementation process: basic scientists, clinician-scientists, physicians and government stakeholders. Patients, caregivers and patient advocacy groups should be involved in defining research questions and to ensure that relevant research questions are being addressed (e.g., Breault et al., 2018).
4. Utilize and expand existing collaborative networks (e.g., Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) and develop new networks to continually ensure the validity and clinical applicability of proposed biomarkers using standardized techniques. Collaboration between networks/consortia is also essential to allow for cross-disorder analyses in order to learn more about disease-specificity of a proposed biomarker.
5. Improve research methodologies that allow for reliable combination of data from varying sources (e.g., neuroimaging, genetics) at different collection sites. Computational neuroscience methodologies, particularly machine learning, have shown potential as a reliable method for data combination and comparison for large-datasets within various psychiatric diagnoses (Nielsen et al., 2019; Rutledge et al., 2019).
6. Following RDoC recommendations, future biomarker research should not be limited by current psychiatric diagnostic label. Since the distinction between diagnoses was not originally made based on biological data, researchers must be open to the likelihood of two diagnoses being biologically similar therefore indicating the presence of one diagnosis rather than two. On the other hand, a single diagnosis may have subsets of diverging data suggesting more than one diagnosis.

With these points in mind, many groups around the world have begun to address the challenges and recommendations stated above. Various collaborative efforts have commenced that incorporate multiple data collection sites with standardized methodologies. The Psychiatric Genomic Consortium (PGC) is a collaboration between over 800 investigators in over 40 countries collecting genetic data from patients with eleven psychiatric diagnoses aimed at identifying genetic differences between the genes of individuals with a diagnosis compared to controls (Ripke et al., 2011; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Similarly, the ENIGMA consortium is an international effort to identify characteristic pathologies in over ten diagnoses and traits associated with psychiatric diagnoses (e.g., irritability; Thompson et al., 2020). ENIGMA connects structural, functional and diffusion tensor imaging with genetic and electroencephalogram data to identify biomarkers (Thompson et al., 2020). Finally, the previously mentioned collaboration, CAN-BIND, connects Canadian researchers and clinicians to collect longitudinal clinical information (e.g., medication and medical history), demographics, electroencephalogram, social background, blood and urine samples as well as structural and functional neuroimaging using standardized protocols and timelines in patients with depression to identify biomarkers of depression (Lam et al., 2016).

While there are countless challenges to identifying meaningful biomarkers in psychiatry, their use has invaluable potential to validate psychiatric diagnoses and neurobiological conditions, thereby advancing the practice of psychiatry into modern medical practice. Dr. Kenneth Kendler has stated that "our strongly held desires to find *the* explanation for individual psychiatric disorders are misplaced and counterproductive" due to the complexity of psychiatry diagnoses (Kendler, 2005). While it is unlikely that one individual biomarker will be able to explain each psychiatry diagnosis, the integration of multiple modalities or different methods of the same modality through large-scale transdiagnostic research efforts may have more promise at developing biomarkers for psychiatric diagnoses.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Acknowledgements

Author RHK was supported by an Ontario Graduate Scholarship and Susan E. Phillips Scholarship from Queen's University. Author DPM was supported by the Canada Research Chair Program. Author LB was supported by a career award from the Fonds de Recherche du Québec Santé.

References

Abi-Dargham, A., Horga, G., 2016. The search for imaging biomarkers in psychiatric disorders. Nat. Med. 22, 1248–1255. https://doi.org/10.1038/nm.4190.

Akinhanmi, M.O., Biernacka, J.M., Strakowski, S.M., McElroy, S.L., Balls Berry, J.E., Merikangas, K.R., et al., 2018. Racial disparities in bipolar disorder treatment and research: a call to action. Bipolar Disord. 20, 506–514. https://doi.org/10.1111/bdi.12638.

Albert, P.R., 2015. Why is depression more prevalent in women? J. Psychiatry Neurosci. 40, 219–221. https://doi.org/10.1503/jpn.150205.

Almeida, D., Turecki, G., 2016. A slice of the suicidal brain: what have postmortem molecular studies taught us? Curr. Psychiatr. Rep. 18, 98. https://doi.org/10.1007/s11920-016-0736-8.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. https://doi.org/10.1176/appi.books.9780890425596

Antoniou, A., Pharoah, P.D., Narod, S., Risch, H.A., Eyfjord, J.E., Hopper, J.L., et al., 2003. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am. J. Hum. Genet. 72, 1117–1130. https://doi.org/10.1086/375033.

Anttila, V., Bulik-Sullivan, B., Finucane, H.K., Walters, R.K., Bras, J., Duncan, L., et al., 2018. Analysis of shared heritability in common disorders of the brain. Science 360, 1–40. https://doi.org/10.1126/science.aap8757.

Biomarkers Definitions Working Group, Atkinson Jr., A.J., Colburn, W.A., DeGruttola, V. G., DeMets, D.L., Downing, G.J., et al., 2001. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin. Pharmacol. Ther. 69, 89–95. https://doi.org/10.1067/mcp.2001.113989.

Berdasco, M., Esteller, M., 2019. Clinical epigenetics: seizing opportunities for translation. Nat. Rev. Genet. 20, 109–127. https://doi.org/10.1038/s41576-018-0074-2.

Bilello, J.A., Thurmond, L.M., Smith, K.M., Pi, B., Rubin, R., Wright, S.M., et al., 2015. MDDScore: confirmation of a blood test to aid in the diagnosis of major depressive disorder. J. Clin. Psychiatr. 76, 199–206. https://doi.org/10.4088/JCP.14m09029.

Biomarker Definition. Dictionary.com. n.d. https://www.dictionary.com/browse/biomarker?s=t. (Accessed 6 February 2020).

Breault, L.J., Rittenbach, K., Hartle, K., Babins-Wagner, R., de Beaudrap, C., Jasaui, Y., et al., 2018. People with lived experience (PWLE) of depression: describing and reflecting on an explicit patient engagement process within depression research priority setting in Alberta, Canada. Res Involv Engagem 4, 37. https://doi.org/10.1186/s40900-018-0115-1.

Buckley, P.F., Mahadik, S., Pillai, A., Terry Jr., A., 2007. Neurotrophins and schizophrenia. Schizophr. Res. 94, 1–11. https://doi.org/10.1016/j.schres.2007.01.025.

Canadian Institute for Health Information, 2019. National health expenditure trends, 1975 to 2019. https://www.cihi.ca/sites/default/files/document/nhex-trends-narrative-report-2019-en-web.pdf. (Accessed 30 April 2020).

Canadian Magnetic Imaging, n.d. Scans + rates. https://www.canmagnetic.com/scans-rates/. (Accessed 24 April 2020).

Carvalho, A.F., Solmi, M., Sanches, M., Machado, M.O., Stubbs, B., Ajnakina, O., et al., 2020. Evidence-based umbrella review of 162 peripheral biomarkers for major mental disorders. Transl. Psychiatry 10, 1–13. https://doi.org/10.1038/s41398-020-0835-5.

Centre for Medicare and Medicaid Services, 2019. National health expenditure 2018 highlights. https://www.cms.gov/files/document/highlights.pdf. (Accessed 30 April 2020).

Collins, F.S., Varmus, H., 2015. A new initiative on precision medicine. N. Engl. J. Med. 372, 793–795. https://doi.org/10.1056/NEJMp1500523.

Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 381, 1371–1379. https://doi.org/10.1016/S0140-6736(12)62129-1.

Cuthbert, B.N., 2014. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatr. 13, 28–35. https://doi.org/10.1002/wps.20087.

Dean, B., 2011. Understanding the role of inflammatory-related pathways in the pathophysiology and treatment of psychiatric disorders: evidence from human peripheral studies and CNS studies. Int. J. Neuropsychopharmacol. 14, 997–1012. https://doi.org/10.1017/S1461145710001410.

Duyx, B., Urlings, M.J., Swaen, G.M., Bouter, L.M., Zeegers, M.P., 2017. Scientific citations favor positive results: a systematic review and meta-analysis. J. Clin. Epidemiol. 88, 92–101. https://doi.org/10.1016/j.jclinepi.2017.06.002.

Fanelli, D., 2012. Negative results are disappearing from most disciplines and countries. Scientometrics 90, 891–904. https://doi.org/10.1007/s11192-011-0494-7.

Fanelli, D., Costas, R., Ioannidis, J.P., 2017. Meta-assessment of bias in science. Proc. Natl. Acad. Sci. U. S. A. 114, 3714–3719. https://doi.org/10.1073/pnas.1618569114.

Feczko, E., Miranda-Dominguez, O., Marr, M., Graham, A.M., Nigg, J.T., Fair, D.A., 2019. The heterogeneity problem: approaches to identify psychiatric subtypes. Trends Cognit. Sci. 23, 584–601. https://doi.org/10.1016/j.tics.2019.03.009.

Fernandes, B.S., Molendijk, M.L., Köhler, C.A., Soares, J.C., Leite, C.M.G., Machado-Vieira, R., et al., 2015. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. BMC Med. 13, 289. https://doi.org/10.1186/s12916-015-0529-7.

Fernandes, B.S., Williams, L.M., Steiner, J., Leboyer, M., Carvalho, A.F., Berk, M., 2017. The new field of 'precision psychiatry'. BMC Med. 15, 80. https://doi.org/10.1186/s12916-017-0849-x.

Few, L.R., Miller, J.D., Rothbaum, A.O., Meller, S., Maples, J., Terry, D.P., et al., 2013. Examination of the Section III DSM-5 diagnostic system for personality disorders in an outpatient clinical sample. J. Abnorm. Psychol. 122, 1057–1069. https://doi.org/10.1037/a0034878.

Glasser, M.F., Smith, S.M., Marcus, D.S., Andersson, J.L.R., Auerbach, E.J., Behrens, T.S. C., et al., 2016. The human connectome project's neuroimaging approach. Nat. Neurosci. 19, 1175–1187. https://doi.org/10.1038/nn.4361.

GE Healthcare. 2016. MRI buyer's guide 2017. https://www3.gehealthcare.com/~/media/documents/us-global/products/magnetic-resonance-imaging/resource%20center%20awareness/2017%20mri%20buyers%20guide.pdf (accessed 13 November 2020).

Gorski, J.A., Zeiler, S.R., Tamowski, S., Jones, K.R., 2003. Brain-derived neurotrophic factor is required for the maintenance of cortical dendrites. J. Neurosci. 23, 6856–6865. https://doi.org/10.1523/JNEUROSCI.23-17-06856.2003.

Grimes, D.R., Bauch, C.T., Ioannidis, J.P., 2018. Modelling science trustworthiness under publish or perish pressure. R Soc Open Sci 5, 171511. https://doi.org/10.1098/rsos.171511.

Haslam, N., Kvaale, E.P., 2015. Biogenetic explanations of mental disorder: the mixed-blessings model. Curr. Dir. Psychol. Sci. 24, 399–404. https://doi.org/10.1177/0963721415588082.

Hercher, C., Turecki, G., Mechawar, N., 2009. Through the looking glass: examining neuroanatomical evidence for cellular alterations in major depression. J. Psychiatr. Res. 43, 947–961. https://doi.org/10.1016/j.jpsychires.2009.01.006.

Iritani, S., Habuchi, C., Sekiguchi, H., Torii, Y., 2018. Brain research and clinical psychiatry: establishment of a psychiatry brain bank in Japan. Nagoya J. Med. Sci. 80, 309–315. https://doi.org/10.18999/nagjms.80.3.309.

Jaffe, A.E., 2016. Postmortem human brain genomics in neuropsychiatric disorders—how far can we go? Curr. Opin. Neurobiol. 36, 107–111. https://doi.org/10.1016/j.conb.2015.11.002.

Kapur, S., Phillips, A.G., Insel, T.R., 2012. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? Mol. Psychiatr. 17, 1174–1179. https://doi.org/10.1038/mp.2012.105.

Kendler, K.S., 2005. Toward a philosophical structure for psychiatry. Am. J. Psychiatr. 162 (3), 433–440. https://doi.org/10.1176/appi.ajp.162.3.433.

Kim, S., Webster, M.J., 2009. Postmortem brain tissue for drug discovery in psychiatric research. Schizophr. Bull. 35, 1031–1033. https://doi.org/10.1093/schbul/sbp106.

Lam, R.W., Milev, R., Rotzinger, S., Andreazza, A.C., Blier, P., Brenner, C., et al., 2016. Discovering biomarkers for antidepressant response: protocol from the Canadian biomarker integration network in depression (CAN-BIND) and clinical characteristics of the first patient cohort. BMC Psychiatr. 16, 1–13. https://doi.org/10.1186/s12888-016-0785-x.

Leonardson, A.S., Zhu, J., Chen, Y., Wang, K., Lamb, J.R., Reitman, M., et al., 2010. The effect of food intake on gene expression in human peripheral blood. Hum. Mol. Genet. 19, 159–169. https://doi.org/10.1093/hmg/ddp476.

Linden, D.E., 2012. The challenges and promise of neuroimaging in psychiatry. Neuron 73, 8–22. https://doi.org/10.1016/j.neuron.2011.12.014.

Lovallo, W.R., Farag, N.H., Vincent, A.S., Thomas, T.L., Wilson, M.F., 2006. Cortisol responses to mental stress, exercise, and meals following caffeine intake in men and women. Pharmacol. Biochem. Behav. 83, 441–447. https://doi.org/10.1016/j.pbb.2006.03.005.

Lozupone, M., La Montagna, M., D'Urso, F., Daniele, A., Greco, A., Seripa, D., et al., 2019. The role of biomarkers in psychiatry. Adv. Exp. Med. Biol. 1118, 135–162. https://doi.org/10.1007/978-3-030-05542-4_7.

MacDonald, M.E., Ambrose, C.M., Duyao, M.P., Myers, R.H., Lin, C., Srinidhi, L., et al., 1993. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72, 971–983. https://doi.org/10.1016/0092-8674(93)90585-E.

MacQueen, G.M., Hassel, S., Arnott, S.R., Addington, J., Bowie, C.R., Bray, S.L., et al., 2019. The Canadian biomarker integration network in depression (CAN-BIND): magnetic resonance imaging protocols. J. Psychiatry Neurosci. 44, 223–236. https://doi.org/10.1503/jpn.180036.

Maura, J., de Mamani, A.W., 2017. Mental health disparities, treatment engagement, and attrition among racial/ethnic minorities with severe mental illness: a review. J. Clin. Psychol. Med. Settings 24, 187–210. https://doi.org/10.1007/s10880-017-9510-2.

McCullumsmith, R.E., Hammond, J.H., Shan, D., Meador-Woodruff, J.H., 2014. Postmortem brain: an underutilized substrate for studying severe mental illness. Neuropsychopharmacology 39, 65–87. https://doi.org/10.1038/npp.2013.239.

McDonald, K.C., Bulloch, A.G., Duffy, A., Bresee, L., Williams, J.V., Lavorato, D.H., Patten, S.B., 2015. Prevalence of bipolar I and II disorder in Canada. Can. J. Psychiatr. 60, 151–156. https://doi.org/10.1177/070674371506000310.

Meiser, B., Dunn, S., 2001. Psychological effect of genetic testing for Huntington's disease: an update of the literature. West. J. Med. 174, 336–340. https://doi.org/10.1136/ewjm.174.5.336.

Moore, S., Neylon, C., Eve, M.P., O'Donnell, D.P., Pattinson, D., 2017. "Excellence R Us": university research and the fetishisation of excellence. Palgrave Commun 3, 1–13. https://doi.org/10.1057/palcomms.2016.105.

Mukherjee, A., Carvalho, F., Eliez, S., Caroni, P., 2019. Long-lasting rescue of network and cognitive dysfunction in a genetic schizophrenia model. Cell 178, 1387–1402. https://doi.org/10.1016/j.cell.2019.07.023.

National Science Board, 2014. Science and Engineering Indicators 2014. National Science Foundation, Arlington VA (NSB 14-01).

Nielsen, A.N., Barch, D.M., Petersen, S.E., Schlaggar, B.L., Greene, D.J., 2019. Machine learning with neuroimaging: evaluating its applications in psychiatry. Biol Psychiatry Cogn Neurosci Neuroimaging. https://doi.org/10.1016/j.bpsc.2019.11.007.

Of Mice and mental health, 2019. Lancet Psychiatry 6, 877. https://doi.org/10.1016/S2215-0366(19)30407-9.

Petrides, M., Pandya, D.N., 2002. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. Eur. J. Neurosci. 16, 291–310. https://doi.org/10.1046/j.1460-9568.2001.02090.x.

Petrides, M., Tomaiuolo, F., Yeterian, E.H., Pandya, D.N., 2012. The prefrontal cortex: comparative architectonic organization in the human and the macaque monkey brains. Cortex 48, 46–57. https://doi.org/10.1016/j.cortex.2011.07.002.

Pinto, J.V., Moulin, T.C., Amaral, O.B., 2017. On the transdiagnostic nature of peripheral biomarkers in major psychiatric disorders: a systematic review. Neurosci. Biobehav. Rev. 83, 97–108. https://doi.org/10.1016/j.neubiorev.2017.10.001.

Preuss, T.M., 1995. Do rats have prefrontal cortex? The Rose-Woolsey-Akert program reconsidered. J. Cognit. Neurosci. 7, 1–24. https://doi.org/10.1162/jocn.1995.7.1.1.

Rademaker, M.C., de Lange, G.M., Palmen, S.J., 2018. The Netherlands brain bank for psychiatry. Handb. Clin. Neurol. 150, 3–16. https://doi.org/10.1016/B978-0-444-63639-3.00001-3.

Rawat, S., Meena, S., 2014. Publish or perish: where are we heading? J. Res. Med. Sci. 19, 87–89.

Ripke, S., Sanders, A.R., Kendler, K.S., Levinson, D.F., Sklar, P., Holmans, P.A., et al., 2011. Genome-wide association study identifies five new schizophrenia loci. Nat. Genet. 43, 969–976. https://doi.org/10.1038/ng.940.

Rutledge, R.B., Chekroud, A.M., Huys, Q.J., 2019. Machine learning and big data in psychiatry: toward clinical applications. Curr. Opin. Neurobiol. 55, 152–159. https://doi.org/10.1016/j.conb.2019.02.006.

Scarr, E., Millan, M.J., Bahn, S., Bertolino, A., Turck, C.W., Kapur, S., et al., 2015. Biomarkers for psychiatry: the journey from fantasy to fact, a report of the 2013 CINP think tank. Int. J. Neuropsychopharmacol. 18 https://doi.org/10.1093/ijnp/pyv042 pyv042.

Schwarz, E., Izmailov, R., Spain, M., Barnes, A., Mapes, J.P., Guest, P.C., et al., 2010. Validation of a blood-based laboratory test to aid in the confirmation of a diagnosis of schizophrenia. Biomark. Insights 5. https://doi.org/10.4137/bmi.s4877. BMI-S4877.

Seidler, Z.E., Dawes, A.J., Rice, S.M., Oliffe, J.L., Dhillon, H.M., 2016. The role of masculinity in men's help-seeking for depression: a systematic review. Clin. Psychol. Rev. 49, 106–118. https://doi.org/10.1016/j.cpr.2016.09.002.

Semaka, A., Austin, J., 2019. Patient perspectives on the process and outcomes of psychiatric genetic counseling: an "Empowering Encounter". J. Genet. Counsel. 28, 856–868. https://doi.org/10.1002/jgc4.1128.

Smaldino, P.E., Turner, M.A., Contreras Kallens, P.A., 2019. Open Science and Modified Funding Lotteries Can Impede the Natural Selection of Bad Science, vol. 6. Royal Society Open Science, p. 190194. https://doi.org/10.1098/rsos.190194.

Steiger, H., Booij, L., 2020. Eating disorders, heredity and environmental activation: getting epigenetic concepts into practice. J. Clin. Med. 9, 1332. https://doi.org/10.3390/jcm9051332.

Strimbu, K., Tavel, J.A., 2010. What are biomarkers? Curr. Opin. HIV AIDS 5, 463–466. https://doi.org/10.1097/COH.0b013e32833ed177.

Terracciano, A., Lobina, M., Piras, M.G., Mulas, A., Cannas, A., Meirelles, O., et al., 2011. Neuroticism, depressive symptoms, and serum BDNF. Psychosom. Med. 73, 638–642. https://doi.org/10.1097/PSY.0b013e3182306a4f.

Thompson, P.M., Jahanshad, N., Ching, C.R., Salminen, L.E., Thomopoulos, S.I., Bright, J., et al., 2020. ENIGMA and global neuroscience: a decade of large-scale studies of the brain in health and disease across more than 40 countries. Transl. Psychiatry 10, 1–28. https://doi.org/10.1038/s41398-020-0705-1.

Venkatasubramanian, G., Keshavan, M.S., 2016. Biomarkers in psychiatry-a critique. Ann. Neurosci. 23, 3–5. https://doi.org/10.1159/000443549.

Yep, R., Soncin, S., Brien, D.C., Coe, B.C., Marin, A., Munoz, D.P., 2018. Using an emotional saccade task to characterize executive functioning and emotion processing in attention-deficit hyperactivity disorder and bipolar disorder. Brain Cognit. 124, 1–13. https://doi.org/10.1016/j.bandc.2018.04.002.

Young, N.S., Ioannidis, J.P., Al-Ubaydli, O., 2008. Why current publication practices may distort science. PLoS Med. 5, 1418–1422. https://doi.org/10.1371/journal.pmed.0050201.