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# How not to think about biomarkers in psychiatry: Challenges and conceptual pitfalls

## Introduction

Throughout the centuries, scientists, philosophers, and physicians alike, have endeavored to identify and classify afflictions of human thought, emotions and behaviors. In fact, the ability to identify patterns of symptoms for the purposes of diagnosis and identification of appropriate treatment form a central tenet of medical sciences as a whole. Advances in medical sciences and technology have allowed us to create high resolution images of the whole body, and sequence the entire human genome, heralding the promise of personalized and precision medicine. Although the importance of biomarkers has been recognized across medical specialties for several decades now, biomarkers have assumed even greater prominence in research investigations pertaining to diagnosis and treatment in recent years, and psychiatry is no exception. A biomarker is, according to the FDA-NIH Biomarker Working Group, "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions."[14]. A quick keyword search on PubMed reveals that the number of papers published exploring biomarkers in psychiatry increased from about 229 papers in the year 2000 to 3617 papers in 2019. While this is partly reflective of the increased adoption and popularity of the specific term "biomarker", it is also likely that this corresponds to an actual increase in the number of research studies investigating biomarkers for psychiatric disorders.

As is evident from the FDA-NIH working group definition, biomarkers can be utilized for a wide variety of different goals and targets. Some examples include:

- *Susceptibility/risk biomarker*: Reduced mismatch negativity (an early event related potential) has been associated with increased risk of transitioning to psychosis in individuals considered to be clinically at high risk for psychosis [5].
- *Diagnostic biomarkers*: PET scan using amyloid radiotracers such as Pittsburgh Compound B (Amyloid PET scans) have been used for the diagnosis of Alzheimer's Disease [18].
- *Monitoring biomarkers*: MicroRNA based biomarkers have shown early promise in monitoring treatment response in depression [6].
- *Prognostic biomarkers*: Digital phenotyping has been used for predicting onset of mood episodes in individuals with major depressive disorder and bipolar disorder [10,23].
- *Response prediction biomarkers*: Men diagnosed with Major Depressive Disorder with smaller N100 amplitude have been shown to be less likely to respond to Venlafaxine [13].

In this commentary we will focus primarily on diagnostic biomarkers, and we will discuss some of the inherent challenges associated with the identification of diagnostic biomarkers and some of the conceptual pitfalls regarding how we may interpret potential diagnostic biomarkers.

## Challenges

The quest to identify diagnostic biomarkers in psychiatry faces several challenges. This is because biomarkers need to be identified with reference to a particular construct (whether it is a formal diagnostic construct based on DSM/ICD or an informal one, such as suicidality), which adds an additional layer of complexity subjecting candidate biomarkers to the uncertainty surrounding the validity of that particular construct. Much of the research in this area has been conducted using DSM or ICD diagnoses, although the trend has changed over the last decade after the introduction of the Research Domain Criteria and its emphasis on transdiagnostic constructs [4]. Consensus-based diagnostic categories that utilize clinical descriptions of psychiatric syndromes do not appear to align with findings from clinical neuroscience and genetics research. Research findings do not validate the boundaries of DSM constructs in a way we would expect if these constructs represented distinct disease processes. All this suggests that the DSM categories are unlikely to capture fundamental mechanisms of dysfunction and etiology [1,17]. Additionally, there are high levels of co-morbidities and individuals are often diagnosed as having more than one DSM based psychiatric disorders. For example, individuals diagnosed as having a depressive disorder are at 30–40% increased risk of being diagnosed with an anxiety disorder as well [22]. There is a growing consensus that psychiatric disorders are better understood as spectra/dimensional constructs rather than as categorical, discrete disorders as outlined in DSM and ICD based classification systems. This has been borne out in recent studies that found that major psychiatric disorder have shared genetic risk and alterations of brain networks [9,11,25]. All these considerations necessitate that we should be mindful of the limits of diagnostic biomarkers when it comes to conventional descriptive diagnoses, and that diagnostic markers will need to be continually revisited as our nosology evolves.

## Conceptual pitfalls

In the discussion below, we will examine some of the ways in which diagnostic biomarkers may prompt erroneous assumptions regarding etiology and reductionism, and we illustrate ways in which biomarkers can be approached in a more conceptually robust manner.

### *Etiology*

It is important to recognize that diagnostic biomarkers, even if they have high sensitivity and specificity in diagnosing a particular condition,

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may not be causally informative. This is because of the wide variety of ways in which biomarkers can aid in diagnosis. At one end of the spectrum, a biomarker may be directly involved in the causal process (for instance, markers of tau pathology in Alzheimer's disease) but at the other end of the spectrum, a biomarker may simply a physical sign of the illness, a consequence of the disease processes [7].

For instance, attempts are being made to use electroencephalogram (EEG) for diagnosis of major depressive disorder [21]. However, assuming that such efforts are successful and EEG patterns can aid in the identification of individuals with MDD, there would be little reason to suspect that EEG patterns are involved in the etiology of MDD in a manner that is different from other signs of MDD, say psychomotor retardation. This is not to say that biomarkers *cannot* be causally informative. The presence of anti-NMDA receptor antibodies in an individual with psychosis or elevated TSH in an individual with depression, for instance, are potentially causally informative. The conceptual point is that the default explanation for diagnostic biomarkers should not be in causal terms, and great caution is needed before a causal role is assumed.

*Reification of psychiatric diagnoses*

There is a tendency to think that a diagnostic biomarker validates the disorder as a discrete disease entity or establishes the disorder as more "real". If such thinking is left unchecked, a biomarker can lead to a false sense of validity of the construct under study and in the context of psychiatric nosology may further contribute to the already rampant reification of DSM diagnoses. A biomarker or a certain set of biomarkers may be associated with a specific construct, but it is quite possible that a different set of biomarkers would emerge if we were to alter the definition of our construct.

This is particularly important when machine learning algorithms are used to detect the presence of diagnostic constructs. For instance, machine learning algorithms may be trained to differentiate between individuals with MDD and normal controls based on EEG data [21]. However, the success of such an algorithm should not, by itself, be seen as evidence of the validity of the construct, since it is our *pre-defined construct* that is driving the learning process. That is, we could very well begin with a *different* diagnostic construct of depression, and successfully train the machine learning algorithm to detect *that* construct using EEG data. Douglas Adams, at one point in his writings, imagines a puddle of water becoming conscious and thinking, "This is an interesting world I find myself in — an interesting hole I find myself in — fits me rather neatly, doesn't it? In fact it fits me staggeringly well . . . " [2]. Machine-learning biomarkers may turn out to fit psychiatric diagnoses *staggeringly well*, but that is not necessarily evidence that we are carving nature at its joints.

*Confounding role of medications*

Biomarkers may relate to diagnosis but may also be related to the effects of medications. A recent umbrella review of potential diagnostic biomarkers for obsessive-compulsive disorder (OCD) examined evidence for 73 potential biomarkers [16]. The authors reported that a number of biochemical, neurophysiological, and neuroimaging biomarkers showed statistically significant, albeit weak, associations with OCD. Interestingly, however, analyses in unmedicated samples (123 studies) weakened the strength of the evidence for most biomarkers or rendered them non-significant. This is an important and informative finding. Most biomarker studies are conducted in medicated individuals; however, psychiatric medications have effects of their own on brain functioning, and it is quite possible that we may interpret a biomarker association as evidence of association with the disorder when in fact it may simply be an association with the biological effects of the intervention. Biomarkers in medicated patients therefore cannot simply be assumed to be related to the psychiatric disorder. As another example, reduced volume of brain matter and increased volume of ventricles (on average) in individuals with schizophrenia has been reported in multiple studies, but there has been increasing recognition that use of antipsychotic medications may contribute in part to this reduction of brain volume [20].

The broader point about confounding role of medications also applies to other correlates or consequences of the condition in question. Factors which are conventionally understood to be "non-biological", such as social isolation or marginalization, can be proximate explanations of "biomarkers" given their influence on the brain and may therefore show association with psychiatric disorders.[1] This highlights the need to understand biomarkers from an integrative perspective that also includes psychosocial variables and their interactions with biological variables.

*Biomarkers from an integrative perspective*

Biological and psychological variables can be two different aspects or dimensions of the same phenomenon. This is particularly true when it comes to functional neuroimaging studies, where the distinction between neuroscience and psychology is effectively blurred [3]. For instance, resting amygdala activity and perceived stress are associated with each other. However, it would likely be inaccurate to say that increased activity of the amygdala *causes* the stress or vice versa that the stress *causes* the increased activity of the amygdala [24]. Rather, both amygdala activity and perceived stress represent two different aspect of a phenomenon, related to each other through an organizational form of causality [12]); amygdala activity and perceived stress are not identical, but they are also not *distinct processes* with a linear causal relationship.

The mind-brain-environment systems from which psychopathology emerges encompass multiple components across different levels of analysis, involving a web of complex interactions. It is important to keep in mind that biomarkers for psychiatric disorders will inevitably be embedded in this complex causal web. For instance, biomarkers of accelerated aging have been proposed as mediators of the effect of childhood trauma and transdiagnostic psychopathology [19], however, this relationship exists in a complex and dynamic model which also includes measures of social information processing and emotional processing as other mediators. It is to be expected that majority of psychiatric biomarkers will exist within causal networks that span the biological, psychological, and social domains [15]. In other words, biomarker associations should not be seen as evidence of bioreductionism.

Chronic stress is another example where no explanatory reduction to the biological level alone is possible. This is because chronic stress emerges from the complex interaction between psychological agency, social task demands and social resources, and biological fight-flight-fright arousal systems. As Bolton and Gillett put it, "chronic stress as the key hypothesized mechanism linking psychosocial factors with poor physical and mental health outcomes is—as to be expected—a mechanism that explicitly addresses criss-crossing biological, psychological and social processes" [8]. Any biomarker of chronic stress would necessarily exist in the web of top-down and bottom-up causal influences.

## Conclusion

Despite several challenges, the past few decades have seen significant advances in our neuroscientific understanding of psychiatric disorders. We are just beginning to scratch the surface of the complexity of the brain and the manner in which brain functions need to be understood, not simply in isolation, but also in the context of environmental interactions. More importantly we have to guard against overly simplified reductionist approaches, reification of psychiatric diagnoses, and uncritical assumptions of causality.

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## Declaration of competing interest

The authors report no declarations of interest.

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## References

[1] A. Aboraya, C. France, J. Young, K. Curci, J. Lepage, The validity of psychiatric diagnosis revisited: the clinician's guide to improve the validity of psychiatric diagnosis, Psychiatry Edgmont (Edgmont) 2 (9) (2005) 48–55http://www.ncbi.nlm.nih.gov/pubmed/21120108.

[2] D. Adam, The Salmon of Doubt: Hitchhiking the Galaxy One Last Time, McMillan Books, 2002.

[3] A. Aftab, Scepticism of the gentle variety: interview with derek Bolton PhD, International Review of Psychiatry, (2020) , pp. 1–5, doi:http://dx.doi.org/10.1080/09540261.2020.1800600.

[4] A. Aftab, J.G. Csernansky, Diagnosis and conceptualization of mental illness, in: E. Ryznar, A.B. Pederson, M.A. Reinecke, J.G. Csernansky (Eds.), Landmark Papers in Psychiatry, Oxford University Press, 2020, pp. 3–26.

[5] C. Andreou, S. Borgwardt, Structural and functional imaging markers for susceptibility to psychosis, Mol. Psychiatry 25 (11) (2020) 2773–2785, doi:http://dx.doi.org/10.1038/s41380-020-0679-7.

[6] R. Belzeaux, R. Lin, G. Turecki, Potential use of MicroRNA for monitoring therapeutic response to antidepressants, CNS Drugs 31 (4) (2017) 253–262, doi:http://dx.doi.org/10.1007/s40263-017-0418-z.

[7] D. Bolton, Classification and causal mechanisms: a deflationary approach to the classification problem, in: K.S. Kendler, J. Parnas (Eds.), Philosophical Issues in Psychiatry II: Nosology, Oxford University Press, 2012, pp. 6–11.

[8] D. Bolton, G. Gillet, Biopsychosocial conditions of health and disease, The Biopsychosocial Model of Health and Disease.New Philosophical and Scientific Developments, Palgrave Mcmillan, 2019, pp. 109–145.

[9] Brainstorm Consortium, V. Anttila, B. Bulik-Sullivan, H.K. Finucane, R.K. Walters, J. Bras, L. Duncan, V. Escott-Price, G.J. Falcone, P. Gormley, R. Malik, N.A. Patsopoulos, S. Ripke, Z. Wei, D. Yu, P.H. Lee, P. Turley, B. Grenier-Boley, V. Chouraki, et al., Analysis of shared heritability in common disorders of the brain, Science 360 (6395) (2018) , doi:http://dx.doi.org/10.1126/science.aap8757.

[10] C.-H. Cho, T. Lee, M.-G. Kim, H.P. In, L. Kim, H.-J. Lee, Mood prediction of patients with mood disorders by machine learning using passive digital phenotypes based on the circadian rhythm: prospective observational cohort study, J. Med. Internet Res. 21 (4) (2019) e11029, doi:http://dx.doi.org/10.2196/11029.

[11] Cross-Disorder Group of the Psychiatric Genomics Consortium, Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis, Lancet (London, England) 381 (9875) (2013) 1371–1379, doi:http://dx.doi.org/10.1016/S0140-6736(12)62129-1.

[12] S. de Haan, An enactive approach to psychiatry, Philos. Psychiatry Psychol. 27 (1) (2020) 3–25, doi:http://dx.doi.org/10.1353/ppp.2020.0001.

[13] Rvan Dinteren, M. Arns, L. Kenemans, M.L.A. Jongsma, R.P.C. Kessels, P. Fitzgerald, K. Fallahpour, C. Debattista, E. Gordon, L.M. Williams, Utility of event-related potentials in predicting antidepressant treatment response: An iSPOT-D report, Eur. Neuropsychopharmacol. 25 (11) (2015) 1981–1990, doi:http://dx.doi.org/10.1016/j.euroneuro.2015.07.022.

[14] FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and Other Tools) Resource, Silver Spring (MD): Food and Drug Administration (US) & National Institutes of Health (US), 2016https://www.ncbi.nlm.nih.gov/books/NBK402285/pdf/Bookshelf_NBK402285.pdf.

[15] E.I. Fried, D.J. Robinaugh, Systems all the way down: embracing complexity in mental health research, BMC Med. 18 (1) (2020) 205, doi:http://dx.doi.org/10.1186/s12916-020-01668-w.

[16] M.A. Fullana, A. Abramovitch, E. Via, C. López-Sola, X. Goldberg, N. Reina, L. Fortea, A. Solanes, M.J. Buckley, V. Ramella-Cravaro, A.F. Carvalho, M. Tortella-Feliu, E. Vieta, C. Soriano-Mas, L. Lázaro, D.J. Stein, L. Fernández de la Cruz, D. Mataix-Cols, J. Radua, Diagnostic biomarkers for obsessive-compulsive disorder: A reasonable quest or ignis fatuus? Neurosci. Biobehav. Rev. 118 (2020) 504–513, doi:http://dx.doi.org/10.1016/j.neubiorev.2020.08.008.

[17] S. Kawa, J. Giordano, A brief historicity of the Diagnostic and Statistical Manual of Mental Disorders: issues and implications for the future of psychiatric canon and practice, Philos. Ethics Humanit. Med. 7 (2012) 2, doi:http://dx.doi.org/10.1186/1747-5341-7-2.

[18] V.J. Lowe, E. Lundt, D. Knopman, M.L. Senjem, J.L. Gunter, C.G. Schwarz, B.J. Kemp, C.R. Jack, R.C. Petersen, Comparison of [18 F]Flutemetamol and [11 C]Pittsburgh Compound-B in cognitively normal young, cognitively normal elderly, and Alzheimer's disease dementia individuals, Neuroimage Clin. 16 (2017) 295–302, doi:http://dx.doi.org/10.1016/j.nicl.2017.08.011.

[19] K.A. McLaughlin, N.L. Colich, A.M. Rodman, D.G. Weissman, Mechanisms linking childhood trauma exposure and psychopathology: a transdiagnostic model of risk and resilience, BMC Med. 18 (1) (2020) 96, doi:http://dx.doi.org/10.1186/s12916-020-01561-6.

[20] J. Moncrieff, J. Leo, A systematic review of the effects of antipsychotic drugs on brain volume, Psychol. Med. 40 (9) (2010) 1409–1422, doi:http://dx.doi.org/10.1017/S0033291709992297.

[21] W. Mumtaz, L. Xia, S.S.A. Ali, M.A.M. Yasin, M. Hussain, A.S. Malik, Electroencephalogram (EEG)-based computer-aided technique to diagnose major depressive disorder (MDD), Biomed. Signal Process. Control 31 (2017) 108–115, doi:http://dx.doi.org/10.1016/j.bspc.2016.07.006.

[22] O. Plana-Ripoll, C.B. Pedersen, Y. Holtz, M.E. Benros, S. Dalsgaard, P. de Jonge, C.C. Fan, L. Degenhardt, A. Ganna, A.N. Greve, J. Gunn, K.M. Iburg, L.V. Kessing, B.K. Lee, C.C.W. Lim, O. Mors, M. Nordentoft, A. Prior, A.M. Roest, et al., Exploring comorbidity within mental disorders among a danish national population, JAMA Psychiatry 76 (3) (2019) 259–270, doi:http://dx.doi.org/10.1001/jamapsychiatry.2018.3658.

[23] J.P. Stange, J. Zulueta, S.A. Langenecker, K.A. Ryan, A. Piscitello, J. Duffecy, M.G. McInnis, P. Nelson, O. Ajilore, A. Leow, Let your fingers do the talking: passive typing instability predicts future mood outcomes, Bipolar Disord. 20 (3) (2018) 285–288, doi:http://dx.doi.org/10.1111/bdi.12637.

[24] A. Tawakol, A. Ishai, R.A. Takx, A.L. Figueroa, A. Ali, Y. Kaiser, Q.A. Truong, C.J. Solomon, C. Calcagno, V. Mani, C.Y. Tang, W.J. Mulder, J.W. Murrough, U. Hoffmann, M. Nahrendorf, L.M. Shin, Z.A. Fayad, R.K. Pitman, Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study, Lancet (London, England) 389 (10071) (2017) 834–845, doi:http://dx.doi.org/10.1016/S0140-6736(16)31714-7.

[25] M. Xia, F.Y. Womer, M. Chang, Y. Zhu, Q. Zhou, E.K. Edmiston, X. Jiang, S. Wei, J. Duan, K. Xu, Y. Tang, Y. He, F. Wang, Shared and distinct functional architectures of brain networks across psychiatric disorders, Schizophr. Bull. 45 (2) (2019) 450–463, doi:http://dx.doi.org/10.1093/schbul/sby046.

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