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GUEST EDITORIAL

The endless and frequently fallacious quest to identify biomarkers of mental disorders

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"It's déjà vu all over again."
– Yogi Berra

The precise diagnosis and prediction of disease course and outcome are the Holy Grail of clinical medicine and psychiatry. The term biological marker, or biomarker, describes an objectively measurable substance (eg, metabolite, hormone, or enzyme concentration), physiological or anatomical phenomenon/characteristic (or a combination of characteristics), or gene with which a degree of certainty and stability indicates either the presence of normal biological processes or a pathogenic state, disease, or condition. It could also be used as a marker of response to pharmacologic or other therapeutic interventions. Biomarkers could have an important role in the early efficacy and safety evaluation of treatments.[1] As outlined by the Biomarkers Definitions Working Group,[1] they could be used (a) as a "diagnostic tool for the identification of those patients with a disease or abnormal condition"; (b) as a tool for staging of disease, or extent of disease (eg, in various forms of cancer); (c) as an indicator of disease prognosis and progression; or (d) for prediction and monitoring of clinical response to an intervention.

Example of a field with many biomarkers

Cardiology is an example of a medical specialty with advanced biomarkers, specifically for cardiovascular disease (CVD).[2,3] As Vasan[2] wrote, "The overall expectation of a CVD biomarker is to enhance the ability of the clinician to optimally manage the patient." He added further definitions to the mentioned definitions/classifications[1,2]:

- Type 0 biomarker: A marker of the natural history of a disease and correlates longitudinally with known clinical indices
- Type 1 biomarker: A marker that captures the effects of a therapeutic intervention in accordance with its mechanism of action

• Surrogate end point (or type 2 biomarker): A marker that is intended to substitute for a clinical end point; a surrogate end point is expected to predict a clinical benefit or harm or a lack of benefit.

Vasan[2] also distinguishes between risk factor (associated with a disease because of a causal pathway leading to the disease) and risk marker (associated with the disease but not causally linked, because it could be a measure of the disease process itself).

There are numerous biomarkers for coronary heart disease that are cholesterol-related, inflammatory, prothrombotics, endocrine-related, vascular-related, lifestyle, and others (summarized in references 2 and 3). Not all of these markers are equally useful, but some (eg, lipid profile) are standardized, available, convenient, linked to disease prospectively, and could be tracked during disease treatment.

What about psychiatry?

Biological psychiatry has been exploring biomarkers of mental disorders almost since the beginning. Efforts to identify meaningful biomarkers have been enormous, as illustrated by a February 1, 2020 PubMed search of "biomarkers, psychiatry," which yielded 13,172 items from as far back as 1972. The search for specific biomarkers in psychiatry has at times been triggered by postulated mechanisms of a specific disease (eg, catecholamine theory of depression) or by accidental findings (eg, smooth pursuit eye movement abnormalities in patients with schizophrenia). Biomarkers have been enthusiastically welcomed, explored in numerous studies, and gradually forgotten after they fail to fulfill their early promise or meet the criteria outlined by the Biomarkers Definitions Working Group[1] or Vasan.[2]

The first group of biomarkers explored in psychiatry was the metabolites of catecholamines. During the 1970s and 1980s, many researchers investigated the role of 3-methoxy-4-hydroxyphenylglycol and other monoamine metabolites (eg, homovanillic acid, 5-hydroxyindoleacetic acid [5-HIAA]) for the prediction of treatment outcomes in depression and as a marker of suicidality (5-HIAA). Ultimately, these measures were not found to be useful in the prediction of treatment outcomes or anything else.[4] Lower levels of 5-HIAA in cerebrospinal fluid remains a well-recognized finding, but its clinical utility is questionable because "clear-cut normal" levels are not well established. Another "blockbuster" biomarker—now almost forgotten—was the dexamethasone suppression test (DST), which had utility in the prediction of treatment outcomes in mood disorders and in identifying suicidal patients. Although some clinicians found the DST valid as a marker of endogenous depression (another forgotten term in psychiatry), ultimately, after hundreds of studies, its diagnostic validity and clinical utility in depression has not been confirmed.[5] The DST has been consigned to oblivion, along with the catecholamine metabolites.

Numerous other measures and procedures have been investigated as biomarkers. Examples include the use of various EEG patterns, including quantitative EEG; provocation of anxiety/panic attack procedures (infusions of lactate, isoproterenol, infusions/injections of cholecystokinin and pentagastrin, tryptophan depletion, inhalation of CO_2); heart rate variability in various disorders and its change after treatment; brain imaging and its changes; and blockade of dopamine receptors (or percentage of occupation) by antipsychotic medications on positron emission tomography scans in schizophrenia. None of the large parade of these biomarkers seem to have clinical utility, as compared with biomarkers in some other disciplines (eg, cardiology). In a review of biomarkers and clinical markers of panic disorder, Cosci and Mansueto[6] concluded that the clinical utility, sensitivity, specificity, and predictive value of all biomarkers for panic disorder remain questionable. That seems to hold true for the rest of the biomarkers in the field of psychiatry.

The latest area promising us biomarkers of mental illness is genetics. The August 2019 issue of the *American Journal of Psychiatry* (AJP) was devoted to this topic. Editor-in-Chief Ned Kalin, MD, concluded that "… we now have a deep understanding of the molecular and genetic mechanisms underlying heritability."[7] However, the question is whether genetic markers are following the same path as other biomarkers in psychiatry, and whether they can be clinically useful. Consider this quote from another article in the same issue of AJP: "This study provides new information on genetic associations and demonstrates that genetic liability for major depression increases risk for suicide attempt across psychiatric disorders."[8] Is this not something clinicians have known? Just how does this information increase clinical utility?

What are we left with in psychiatry?

Perhaps the only valid set of biomarkers meeting criteria set in other disciplines is for narcolepsy. The diagnostic criteria for this disorder include defined hypocretin

deficiency and nocturnal sleep polysomnography showing rapid eye movement sleep latency ≤15 minutes (or multiple sleep latency test showing mean sleep latency of ≥8 minutes). In addition, approximately 99% of affected individuals carry the HLA-DQB1*06:02 antigen (vs 12% to 38% of controls).[9] Narcolepsy is well defined clinically and is a clear exception in psychiatry.

Our definitions of disease, valid diagnosis, and etiology do not reach the specificity and sensitivity of those seen in other disciplines (eg, cardiology or oncology). The brain and its functioning are too complicated, and our understanding of it is still very limited. It is not clear what we are looking for first, diagnosis or biomarker. Our diagnostic criteria are also changing frequently, which certainly does not help research into biological underpinnings and biomarkers.

We need to come to terms with the fact that in psychiatry, we do not have valid, reliable, sensitive, specific, and clinically useful biomarkers, and that we will not have them for a long time, if ever. ■

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