

Biomarkers in Psychiatry – A Critique

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In the past decades, cutting-edge research techniques have facilitated better understanding of the bi-directional ‘vectors of influence’ that link the genes, brain and social behavior. This, in turn, has led to remarkable progress in biological research principles, paradigms and processes, having rendered critical insights on the pathogenesis of various psychiatric disorders.

For instance, neuroimaging has revolutionized the research on understanding the biological underpinnings of several psychiatric disorders [1]. Coupled with the immense expansions on the computational techniques and resources to handle ‘big-data’, the neuroimaging procedures have facilitated non-radioactive, non-invasive research to examine the *in vivo* brain aberrations in patients with psychiatric manifestations [2]. These techniques attempt to profile the ‘panorama’ of brain dysfunction involving structural, neurohemodynamic, neurochemical as well connectivity aspects. One is hopeful that these significant advances in neuroimaging techniques will pave the way for insights about the disruption of neural networks in neuropsychiatric disorders (pathoconnectomics) [3].

In tandem with vast advances in neuroimaging research, the progress in molecular biology involving genomics, proteomics and several other related fields have been astonishing. Noteworthy among such advances is the feasibility of utilizing ‘stem cell models’ to characterize the complex pathogenetic interactions that underlie the genesis of complex psychiatric disorders [4]. These exciting advances have generated immense hope and novel avenues for identifying biomarkers for psychiatric disorders.

A biomarker is defined as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes or biological responses to a therapeutic intervention’ (Biomarkers Definition Working Group [5]); a biomarker can involve a gene or a set of genes, proteins/other biomolecules, morphological characteristic. In terms of application, biomarkers can be used for diagnosis or prognosis [6]. Thus, bio-

markers are critically needed for diagnosis, predicting treatment response and follow-up outcomes of medical ailments [7].

Although, ‘concerted’ research efforts in the ‘decade of the brain’ and the years that followed have unravelled critical insights on the pathogenesis of psychiatric disorders, clinically translatable biomarkers in psychiatry are yet to be identified. For instance, a recent publication which performed a systematic and qualitative review of clinically meaningful biomarker for psychosis by examining 3,200+ studies could identify just one study that passed the author’s threshold of clinical applicability [8]. A ‘snap-shot’ review on the status of biomarkers in certain major psychiatric disorders reiterates this lag. For instance, in Alzheimer’s disease, current research studies suggest that about 8 biochemical measurements (amyloid proteins and their A-beta precursors or tau proteins) or brain imaging procedures (advanced structural/functional/neurochemical imaging techniques) are considered as potential biomarkers [9]. However, there are none that might qualify for the ‘rigorous’ definition of biomarker [8]. Recent findings needing further confirmation suggest that reductions in plasma phospholipid levels might be useful in accurate prediction of the development of Alzheimer’s dementia within 2 years [9]. The status of biomarkers is almost the same in another important psychiatric disorder of significant public health implication – autism. In autism, while there are promising leads for potential biomarkers that involve parameters of mitochondrial function, oxidative stress, immune system or certain gene clusters, a clinically translatable biomarker is yet to be identified [10]. All these reiterate the fact that the current status of biomarkers in psychiatry has significantly lagged behind in comparison with other medical specialties.

In most of the existing studies on biological abnormalities of psychiatric disorders, patients are distinguishable as a group from healthy controls; however, these differential biological correlates have not been transformed into clinically useful biomarkers. The following are some of the critical reasons for this lacuna [7, 11]: (a) cur-

rent classificatory and diagnostic systems in psychiatry are primarily symptom based, (b) methodological limits of the existing studies on biological abnormalities in psychiatry, (c) lack of valid 'in-vitro' models for psychiatric disorders and (d) issues related to conceptualizations of pathogenetic paradigms for psychiatric disorders.

Lack of Gold Standard Diagnostic Criteria

For establishing a coherent and convergent evidence base for biological abnormalities in a specific disorder, one needs to have a stable set of criteria that defines the diagnosis; unfortunately, psychiatric nosological systems have undergone constant changes. Thus, psychiatry has been in an unenviable 'catch-22' situation, that is, on one hand, the current classificatory systems are not specifically designed to pave the way for identifying valid biological markers and on the other hand, despite the vast amount of biological studies, a clinically viable alternative system based on robust neurobiological parameters is yet to be developed [11]; this, in turn, has led to an unbreakable chain of circularity. To complicate this further, the fundamental tenet of 'categorical approach' to classify psychiatric disorders has been questioned and a dimensional approach is offered as an alternative [12]. To address these problems, research domain criteria (RDoC) has been proposed as an alternative with an aim to 'develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures' [13]. One is hopeful that the expected 'goal of the RDoC project for treatment development is to identify particular symptoms that can be related strongly to dysfunction in a particular neurobehavioral system' [14] with a dimensional approach [15].

Methodological Limits of the Existing Studies

Some of the common methodological limits of the existing studies that explore the biological basis of psychiatric disorders include use of small sample sizes, low power and frequent non-replication, use of single modality parameter (in contrast with multiple modalities), single biomarker of small effect and related factors [7]. The suggested alternatives to address these methodological limits include multi-site studies, data sharing, multi-modal imaging studies, multivariate biomarker studies, use of 'omic' data (such as genome-wide, transcriptome and proteome data) and pattern classification algorithms [7]. Another important limitation is the paucity in studies that have used rigorous methods as well as large sample size to elucidate robust biomarkers that reliably differentiate one disorder from another by concurrently examining both patient groups – for example, such efforts can lead to potential 'disorder-specific' signatures [16].

Lack of Valid 'in-vitro' Models for Psychiatric Disorders

One of the unique limitations in studying psychiatric disorders is the difficulty in testing or developing animal models for complex, multi-dimensional psychopathological syndromes with mul-

tifactorial causation. To compensate for this, it has been recommended that testing for biomarkers in conditional knockout models as well as identifying translational cognitive domains for testing in animal models is a promising avenue for further pursuit [7]. It has been suggested that such unbiased approaches have to be integrated with stem cell models; this might help to fully understand the neuroepigenome, its myriad interaction and impact toward the pathogenesis of psychiatric disorders in the context of the extraordinarily complex nature of the human brain [17].

Issues Related to Conceptualizations of Pathogenetic Paradigms for Psychiatric Disorders

In the current context, neurotransmitter aberrations in the genesis of psychiatric manifestations continue to be one of the cornerstone research paradigms. For instance, glutamatergic as well as GABA-ergic dysfunction is considered important contemporary 'hot-spot' areas in biological psychiatry with immense pathogenetic and potential treatment implications in schizophrenia [18]. However, it is increasingly being uncovered that these neurotransmitter interactions are complex in terms of their interaction with other neurotransmitter systems (in this context of schizophrenia – dopamine) [19] with certain other biological systems involving neurotrophic factors (like brain-derived neurotrophic factor) [20] as well as immune parameters [20, 21]. Thus, future studies need to adopt a wider perspective in terms of testing 'informed models' that have multi-level interactions within a 'systems biology approach'. Such approaches may even have to incorporate distal factors that might be of importance in the context of evolutionary neuroscience [22].

Biomarkers in Psychiatry – The Way Ahead

Over the past decades, while substantial research efforts have provided promising leads toward understanding the biological basis of psychiatric disorders, clinically translatable biomarkers in psychiatry have been elusive. Adding to the enormous complexity of brain, the study of the biological basis of psychiatric disorders is further compounded by the symptom overlap among disorders, inaccessibility of brain tissue, failure of several cutting-edge techniques to identify robust biological correlates as well as related major factors as described above. Majority of the research efforts have been 'reductionist', in a sense that they were implicated with the hope that single brain region/circuit or a particular gene or a specific neurotransmitter might unravel one-to-one relationship with a disorder. To facilitate further understanding about the pathobiological basis of these complex disorders, while the 'neurotransmitter-based approach' has offered clinically useful therapeutic options (although most often serendipitously), it is time to expand this to incorporate the more inclusive 'systems biology-based approach' to unravel the complexities of neurobiological interactions in psychiatry [23].

Systems biology paradigm facilitates the analysis of relationships within a biological system to elucidate interactions among different components of that system [24]. Indeed, there have been noteworthy efforts that have applied systems biology paradigm to

an extent yielding preliminary leads. For instance, studies that have examined schizophrenia and psychotic bipolar disorder identified 3 genetic components comprising multiple genes mediating neurophysiological aberrations as measured by event-related potential subcomponent abnormalities in schizophrenia and psychotic bipolar disorder. These observations suggest a possible polygenic structure comprising genes influencing key neurodevelopmental processes, neural circuitry and brain function mediating biological pathways plausibly associated with psychosis [25]. Similarly, integrated analyses of genome-wide association data from schizophrenia, major depression and bipolar disorder have identified several overlapping as well as differentiating pathways that involve histone methylation, immune and neuronal signaling (The Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium [26]). Along the same lines, in autism, gene-ontology enrichment analyses have uncovered sets of genes involved in diverse biological processes that included pyruvate metabolism, transcription factor activation, cell signaling and cell cycle regulation [27]. Future studies to identify clinically translat-

able biomarkers should apply robust principles of systems biology by combining mathematical models with experimental molecular information derived from studies based on *in silico*, *in vivo* and *in vitro* models with high-throughput data sets obtained from cutting-edge techniques that involve genomics, proteomics, metabolomics and transcriptomics [23] in the context of clinical manifestations as well as potential epigenetic factors that map gene-environment interactions [28].

Finally, as stated earlier, a major road block in the development of actionable biomarkers in psychiatry has been the reliance on symptom-based categories for validation of any putative biomarker. By analogy, if we were to classify chest pain patients into those with and without cough and wanted to test the latest test that had come along (e.g., cardiac enzyme elevations), we would get nowhere. Alternatively, if we tested whether the enzyme elevations differed between those with versus without ST segment changes in ECG, we are more likely to see a clinical meaningful difference. This approach, which can be called ‘stratified psychiatry’, has served well in the rest of medicine and is likely to be fruitful [29].

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