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Review Article

Biomarkers in Schizophrenia: A Brief Conceptual Consideration

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Biomarkers have been sought after in the field of schizophrenia research for decades. In this paper, we discuss some of the concepts around developing biomarkers in an effort to understand why the use of biomarkers for schizophrenia has not been realized. In particular, we address the following 4 questions. Why would we need a diagnostic biomarker for schizophrenia? How is a biomarker typically defined and how does that influence the discovery of biomarkers in schizophrenia? What is the best use of biomarkers in schizophrenia? Do any biomarkers for schizophrenia currently exist? Thus, while we suggest that no biomarker currently exists for schizophrenia, the heterogeneity associated with schizophrenia will most likely need to be taken into account which will result in multiple biomarkers that identify the multiple underlying pathophysiological processes involved in schizophrenia. Therefore, much additional work will be required prior to obtaining any well-established biomarkers for schizophrenia.

1. Introduction

Medicine is repeatedly transformed by the discovery of biological processes and ultimately disease indicators that inform and refine clinical care. A century ago, exposure and contraction of tuberculosis were common with little ability to prevent, predict, or treat this condition. The simple and now widely available Bacillus Calmette-Guérin (BCG) vaccine, coupled with selective screening by X-ray chest examination, has transformed the disease profile of tuberculosis and almost eliminated tuberculosis in the developed world. More recently, cancer biomarkers are offering the very real capacity for early detection and for selective and targeted therapeutic strategies based on molecular markers. In contrast, the quest for cures for schizophrenia seems to be limited while our definition of the disease remains a largely opaque scientific venture where clinical diagnosis is cast and dependent upon "the quicksand of symptomatology."

2. What Is a Biomarker?

Any biological feature of living humans has the potential to be an informative indicator of schizophrenia risk, occurrence, or progression. In a narrow sense, a biomarker refers to a molecular change in body tissues and fluids that can be used as a clinical indicator. Those measures that prove to be reliable (consistent) and valid (true) predictors through research efforts can be used as clinical biomarkers. Thus, a biomarker has to have clinical utility and biomarkers will take time, money, and coordinated research to develop. To prove clinical utility in schizophrenia will take large scale and coordinated efforts of biologists, doctors, and patients and is by nature translational. In considering the effort required to identify, replicate, and validate biomarkers for clinical use, it may not be surprising that no biomarker has been accepted for use in schizophrenia, although there are some leads.

The goal of finding biomarkers for schizophrenia is not new. A PubMed search with the keywords "Biomarker and Schizophrenia" reveals a Nature paper from 1965 entitled "Phenolic and indoleamines in the urine of schizophrenics" and demonstrates biomarkers have been sought after by our field for decades [1] and a review by Professor Sabine Bahn points out that studying the blood of the "insane" was taking place as early as the mid-1800s by W. Lauder Lindsey in Scotland [2]. In more modern times, the published literature in biomarkers and schizophrenia grew slowly over the 15 years following 1965 reaching double-digit figures/year by 1980 and then undergoing a substantial increase more recently with over 100 papers/year in 2005–2012 and ~2,000 papers in total including almost 400 review articles. This increase in biomarkers research articles in schizophrenia may be due to more sensitive and sophisticated assessment tools that can provide thousands of measurements in parallel and the development of modelling approaches and computing power to store and analyse large amounts of data; however, despite the increase in research papers, there has not been a corresponding increase in clinical use of biomarkers in schizophrenia. Since the use of multiple molecular measures is a fairly recent development, and the standards against which we assess new markers are likely imperfect and evolving, the power of any proposed biological marker to predict disease or treatment response, even in some people with schizophrenia, in a real-world setting has not had adequate time to be developed, tested, modified, and implemented. When considering a nascent field with almost 20% reviews, we were challenged to consider what another review article could provide when most biomarkers for schizophrenia are still in the realm of speculation; or, said another way: "are there any schizophrenia biomarkers with unassailable data and widespread agreement for use available for review?" From our perspective, this ambitious goal has not yet been realized. In this paper, rather than review the controversial evidence for or against any one biomarker in particular, we will raise major concepts and questions regarding how biomarkers can be chosen, prioritized, and evaluated in schizophrenia.

Generally, a biomarker can be developed for three main purposes (1) diagnostic (to classify as having a disease), (2) prognostic (to make predictions on who will develop a disease), or (3) theranostic (to predict an individual response to a particular therapy). It is important to consider that the biomarkers useful for one purpose (i.e., diagnosis) do not necessarily have to be useful for the others (i.e., response to treatment). Also worth emphasizing is that when DSM5 was being developed, biomarkers were considered to be forthcoming as external validations that may help to define and group diagnoses and inform reclassifications [3]. However, this thinking seems to have been premature, as biomarkers do not feature in DSM5. In this paper, we will discuss some of the concepts around developing biomarkers in an effort to understand why the use of biomarkers for schizophrenia has not been realized.

3. Question 1: Why Would We Need a Diagnostic Biomarker for Schizophrenia?

One argument for a diagnostic biomarker for schizophrenia is that while diagnosis can be made based on clinical interviews and careful observations by trained medical staff, the diagnostic process is by nature more subjective and variable than in some other areas of medicine and thus would benefit from a more objective test. However, this basic concept is in and of itself problematic. Psychiatrists working at the turn of the last century recognized that schizophrenia was not a single entity, but that heterogeneity was present in the illness. The fact that schizophrenia has multiple causes each with distinct biological mechanisms means that attempting to find a single biomarker or group of biomarkers that would coincide with all cases of DSM-defined schizophrenia is unlikely. Perhaps it would be beneficial for the biomarker field to look for biomarkers in subsets of people with schizophrenia and, in this way, biomarkers may be developed for the most common biological underpinnings of schizophrenia, but we suggest schizophrenia researchers developing biomarkers may not want to attempt to capture all people with this diagnostic label. A diagnostic biomarker test (even if for a subgroup) may be of clinical benefit if a positive prediction can be made, as even though psychiatrists are highly trained to provide reliable diagnoses, some clinicians may have difficulty discriminating schizoaffective disorder from bipolar I disorder. Furthermore, those without extensive experience in psychiatry, such as general practitioners, may have limited experience in discriminating one major mental illness from another; for example, symptoms of major depression (particularly psychotic depression), schizophrenia, schizoaffective disorder, and bipolar I can overlap [4]. This problem is especially apparent in the "premorbid" phase, as in the prodromal phase of schizophrenia, which typically occurs during teenage years; the major symptoms of "preschizophrenia" can be loss of motivation, social withdrawal, and lack of focused attention and can overlap with the symptoms of depression [5]. A "misdiagnosis" can have treatment implications because what is considered optimal treatment for each major mental illness category currently differs. Additionally, some individuals with schizophrenia will receive multiple diagnoses throughout their life depending on the clinician, as described above, in combination with different information disclosed by the patient and variation in symptom presentation over time. These problems suggest that a diagnostic biomarker to discriminate schizophrenia from other major mental illnesses especially early in the course of the disease (a prognostic one) may be particularly helpful. Another argument in support of a prognostic biomarker for schizophrenia is that if the biomarker is present in an individual before any behavioural symptoms are present, then it could be used to initiate specific (antipsychotic) treatment early to prevent schizophrenia onset. However, another major problem with this approach is that the underlying biological root causes could cut across diagnostic boundaries and

may not be expected to be discriminate based on DSM criteria.

4. Question 2: How Is a Biomarker Typically Defined and How Does That Influence the Discovery of Biomarkers in Schizophrenia?

Prototypical biomarkers for disease are molecular and would encompass targets generated in the "omics" arena; these are DNA based (genomics), mRNA based (transcriptomics), protein based (proteomics), or metabolism based (metabolomics) [6]. However, the term biomarker as it applies to the field of schizophrenia is also used on a more macroscopic scale largely because the abnormal tissue (brain) is not easily sampled and while important biological information regarding schizophrenia can be derived from other organs or cells like liver, pituitary, fibroblasts, nasal epithelium, or blood cells [7], most schizophrenia researchers have focused on brain measures. Thus, it is typical for a schizophrenia researcher to consider MRI brain imaging or electrophysiological measures (EEG) as biomarkers as well. Further, it may be that more macroscopic markers and molecular markers need to be combined to be informative, as many individual molecular abnormalities in the brains of people with schizophrenia are often within the range of individuals without schizophrenia. If we consider the definition of a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological response" [8], then more systems-based, like fMRI and EEG, measures would be consistent with this definition. Once a potential measure or group of measures are made, be they at the molecular (micro) level or systems (macro) level, techniques (i.e., algorithms) for patient classification and disease prediction have to be devised. This requires a solid bioinformatics approach involving multivariate data analysis, mathematical modelling approaches, statistical learning techniques, and a team of experts. There are two phases of developing a prediction task (developing a rule or algorithm), one is referred to as "training" which allows the construction of the model based on available data and the second is referred to as the "testing" phase which requires that the rule is applied to an independent dataset to predict an "unknown" outcome. Thus, even when a given marker or set of markers are identified to be of high predictive value in the training phase, they may not have real-world traction in the testing phase. Most of the papers available on biomarkers in schizophrenia have been concentrating on making an initial prediction based on the training phase and often use approaches of resampling or regrouping their own data in a testing phase. This may be a reasonable first step but is not a rigorous one, and replication across laboratories with different sets of researchers and samples is required for a true test of biomarker performance.

The number of possible predictive models that could be developed and tested for biomarkers in schizophrenia is limitless. Predictive models are based on multiple measures with uncertain weighting and uncertain thresholds for making decisions at branch points used for categorization. When constructing prediction models, there are unspecified parameters on the number and/or type of biomarkers needed and there is no set guide as to how many or in what order questions with binary outcomes should be posed (in terms of construction of decision trees). While the goal seems simple, to make accurate predictions about category membership or disease risk, the construction of models can be, in fact, quite complex. Most of the diagnostic biomarker models use a two-classification scheme outcome, for example, likelihood of having/developing schizophrenia or not. However, as briefly described above, the challenge in the clinical setting is related to the notion of diagnostic specificity: separating schizophrenia from other major mental illnesses, which, as highlighted above, may be a false standard as we suggest that biomarkers should define an underlying pathophysiology and be indicators of a biological process that has gone awry rather than a DSM-defined disease category. Furthermore, the structure of the prediction models we use as clinical tools in schizophrenia will have to vary depending on what is being classified (diagnostic group, future risk, and relapse likelihood). Since the number of assumptions (factors) entering into a model is infinite and the best result will always be a probability of outcome, it is unlikely that schizophrenia will be predicted with 100% accuracy. We suggest that rather than aiming for a biomarker identifying a diagnostic category, to be most beneficial, a biomarker should provide information about the underlying pathophysiology that may in fact cut across traditional diagnostic categories. Since schizophrenia is best viewed as a syndrome [4], with various root causes, then a biomarker may be used to identify distinct biological processes involved in subsets of people with the diagnosis of schizophrenia.

One assumption often made by some schizophrenia researchers centres around the notion that for biomarkers to be useful, biomarkers need to be stable over time or need to be "trait" markers. However, when one considers the characteristics of an ideal biomarker as outlined for use in Alzheimer's disease, the main concerns are that the test measures an underlying component of the disease, is valid and specific, and would be easily and reliably measured across laboratories [9]. In the review [9], the authors point out that valuable biomarkers could be either "trait" dependant (ApoE4 genotype) or "state" dependant (CSF β-amyloid level). It may be that some individuals support the notion that an optimal biomarker needs to be consistent with an invariant diagnostic label, in a similar way that, the term "endophenotype" may be used to indicate an "intermediate" step involved in risk for schizophrenia, as being stable over time in order to aid identification of associated genes. However, it is well known that the severity of symptoms of people with schizophrenia can vary considerably over time (for multiple reasons, including but are not limited to voluntary medication withdrawal, stress, or sex hormone fluctuations in females). Thus, it may be that biological underpinnings best associated with the disease may depend on environmental conditions or other factors such as endocrine state of the individual. If one considers the biological changes in schizophrenia to be dynamic, then the concerns about the timing of sampling individuals (particularly in relevance to time since onset, the state of

acute exacerbation or remission, trajectory within the course of illness, time since last menstrual cycle (for females), and time since medication) will be important factors to consider in research designs and in clinical applications. Typically, the stability of markers over time and in relationship to symptom variation within individuals with schizophrenia is not considered in design of many biomarker discovery projects to date. The schizophrenia biomarker field does not appear to be as organized and systematic as needed in testing for and accounting for human biological variance and time of day in sampling biological markers. This adds a confounding source of methodological heterogeneity in the currently available literature on biomarkers in schizophrenia. It will be important for future studies to try to control/record as many factors as possible, that is, for example, time of day of sampling (for the MRI scan or blood draw), day of the menstrual cycle and status of oral contraceptive intake (in women), time since last dose of antipsychotic, time since last cold/flu symptoms, body composition (BMI), diet or exercise level, and degree of symptoms present. It is unclear if biomarkers assessed in a stable state or in a more actively psychotic state will be more informative for clinical application and it may be that the degree of change for a given marker over time within the same person will be the most predictive. In sum, since many biomarker studies in schizophrenia have sampled chronic patients who are typically stable, studies incorporating more dynamic sampling strategies could provide a more insight and possibly a unique set of markers to pursue.

5. Question 3: What Is the Best Use of Biomarkers in Schizophrenia?

5.1. Diagnostic. While some may argue a diagnostic biomarker for schizophrenia does not yet exist, a company originally founded by Professor Sabine Bahn, PsyNova, in collaboration with Rules-Based Medicine generated a putative blood biomarker assay for the diagnosis of schizophrenia [7, 10]. This test measured 51 blood anolytes (small molecules and proteins) and was reported to be 83% specific and sensitive. Although this test, called VeriPsych, was available in 2010, the use of this test did not gain widespread support and the assay has recently been withdrawn from the market. There is a certain amount of healthy skepticism in the field of psychiatry in relation to the use of biologically based diagnostic tests for schizophrenia mainly due to the fact that the VeriPsych early tests did not include tests of diagnostic specificity (schizophrenia versus other psychiatric disorders). Although this criticism was addressed by later studies from the same group [11], this diagnostic blood test for schizophrenia still did not become widely used. According to one of the developers of VeriPsych "there may have been at least two further reasons for the reluctance (1) market research found that most psychiatrists believe that they are very good at diagnosing schizophrenia patients using a basic clinical interview" [2] and (2) the $2500 (US) cost was considered high. Indeed, the extensive training involved in using clinical interview skills to make a differential diagnosis is considered the "gold standard" to which all bioassays should be calibrated, so it is not clear as to what additional information a blood test would provide and finding additional funds to cover serum testing for each patient is often prohibitive. It is also argued that the ~83% sensitivity and specificity reported for this proposed diagnostic blood test has not been rigorously tested with independent cohorts (predictive), by independent teams, working in independent laboratories, so the predictive power is still uncertain. It would also be the case that any newly developed diagnostic instrument (even if 100% predictive, specific, and sensitive) would take time to gain clinical use due to time required to train on site medical staff and the high initial cost involved. If the result of a biomarker test cannot provide any insight into the optimal therapeutic strategy, it will likely be of limited usefulness to psychiatrists.

Another point to consider is that using blood-based assays is going to be evolving for use in psychiatry. Any type of maker used in isolation is not likely to be as informative as using a combination of approaches including biological brain scans and "nonbiological" interviews, self reports, and cognitive testing, as is done in Alzheimer's Disease [12]. In this way, it is possible that the number of markers to be screened from blood could be reduced potentially lowering costs. Another important point worth emphasizing again is there is a large biological heterogeneity found in the brains of patients with schizophrenia at the molecular and cellular levels (in addition to the cognitive and clinical level) with many individuals with the diagnosis of schizophrenia falling into the normal range [13–15]. Also, it seems that molecular neuropathology of schizophrenia is commonly shared with bipolar disorder and/or depression [16–20]. Further, if there are definable subsets of people with a distinct neuropathological profile even within a DSM-defined illness (e.g., see [13]), then it would follow that identifying a single biomarker test that reflects the underlying disease processes with a high degree of diagnostic sensitivity and specificity should be unlikely. Rather, multiple biomarkers each reflecting various neuropathological processes or biological underpinnings in subsets of individuals would be required.

5.2. Prognostic. Another possible use for biomarkers in schizophrenia is to predict who will become ill prior to "first break" when symptoms meet current diagnostic criteria. The argument in favour of development of an early diagnostic test is that patients with schizophrenia who have a shorter duration of untreated psychosis (DUP) tend to be more treatment responsive to currently available antipsychotics and are often less symptomatic later and require lower maintenance doses of antipsychotics [21]. Thus, if the diagnosis of schizophrenia could be predicted with certainty even in some individuals, then one could theoretically reduce their DUP to zero. However, there are many clinical issues to consider when developing an ideal treatment for a prodromal person who does not clearly fit into any diagnostic category. Even in cases that present early with more severe "psychiatric" symptoms and when antipsychotics alone are used to treat those with "preschizophrenia", there is increased risk for metabolic side effects, cardiac disease, obesity, and diabetes with second-generation antipsychotics [22] and motor side effects of

akathesia, extrapyramidal symptoms, and tardive dyskinesia with first-generation antipsychotics that need to be considered. Despite the fact that no biomarker currently exists and no optimal early treatment is yet available, many psychiatrists do prescribe antipsychotics to individuals deemed to be at high risk of developing schizophrenia based on family history and functional decline [23]. At this stage, it is unclear what value a diagnostic blood test to predict schizophrenia would be when early optimal treatment has not yet been defined. One could also argue that for an early predictive test to be useful, more research into early clinical staging and treatment algorithms needs to be developed in parallel [24, 25].

5.3. Theranostics. We suggest that perhaps one of the most promising areas for investment into development of schizophrenia biomarkers is in the prediction of treatment response, not only to existing pharmacological therapies, but in particular to novel therapies. The ability to predict response to a drug (i.e., theranostics) can be subdivided into (1) beneficial symptom attenuation, (2) deleterious side effect occurrence, and (3) probability of relapse. While clinical decisions on choosing the correct antipsychotic medication are based on many variables and require clinical training and skill, there is still an element of trial and error in relation to which antipsychotic will produce symptom reduction with the least side effects for a given individual. Once a diagnosis of schizophrenia is made and antipsychotics are chosen as the drugs of choice, there is also consideration of which type (first- or second-generation antipsychotic), what dose, and which route of administration will be optimal. There are many parameters at the biological (risk of metabolic side effects), psychological (patient insight), and social (level of family support) levels that need to be considered. If a biomarker test could be used to help determine the degree of symptom reduction and potential for treatment discontinuation in a given patient with a given antipsychotic at a given dose, this could also shorten the duration of untreated psychosis, help maintain compliance, and lead to a better outcome. In fact, a blood test already exists that predicts if a high, medium, or low dose of antipsychotics drug would be most effective in a particular person. This test uses a panel of genetic polymorphisms coding for liver enzymes important for degradation of psychiatric medication (both antipsychotics and antidepressants) to predict the rate of metabolism of antipsychotics. This genetic test has been proposed as a tool to help determine treatment dose; for example, if someone is a high metaboliser, then the person would require a higher dose. However, despite the availability of this test since 2003, it has not been widely accepted possibly because only a few individuals fall into the ultrahigh metaboliser range [26]. Also, genetic factors alone may provide an incomplete picture, as, for example, smoking cigarettes can increase the activity of liver enzymes that break down clozapine resulting in a need for a higher effective dose in patients who smoke [27]. Thus, any genetic biomarker when used in isolation and in absence of critical behavioural or other "environmental" information will have limited clinical value. This is not to suggest that potential biomarkers should not be tested and eventually used, but instead they need to be understood in a context and interpreted by trained staff. The important "nonbiological" factors that should be entered into predictive programs or algorithms are still mostly undefined, suggesting that biomarker use in schizophrenia is perhaps best thought of as being in a very early, exploratory stage and may be beginning to move to the more iterative model building stage of development.

Another useful aspect of a biomarker in regard to prediction of treatment response is to inform the patient and doctor about which individuals would be at risk for deleterious side effects of available treatments. This has obvious benefits as those at high risk for metabolic side effects may be able to avoid the rapid weight gain associated with some antipsychotics. As a proof of this concept, serotonin transporter genetic polymorphisms may predict risk for the common weight gain associated with clozapine administration [28]. Unfortunately, there are not a lot of alternatives since most second-generation antipsychotics cause weight gain. Another serious, but uncommon, side effect observed with high doses of antipsychotic drugs is a lengthening of the heart's electrical cycle of activity. This can be detected by a prolonged QT interval on an electrocardiogram (ECG) and is itself a biomarker for increased risk of sudden death [29]. If a biomarker could be developed to predict risk for QT elongation, then clinicians may be able to avoid high doses of certain antipsychotics in those individuals at risk for sudden cardiac arrest and death. Another example of a dangerous side effect is agranulocytosis associated with clozapine. Increased risk of developing agranulocytosis, characterized by a decrease in white blood cells and increased risk of death, has resulted in the failure to widely prescribe clozapine, especially in the United States [29]. This is despite the claims that clozapine is believed to be one of the most efficacious clinical antipsychotics available. However, agranulocytosis occurs in about 1% of patients with schizophrenia-prescribed clozapine (without monitoring), and while significant, this suggests that 99% may be at low risk for this side effect. If a biomarker could be developed to determine those likely and unlikely to develop agranulocytosis from clozapine, then clozapine could be prescribed as a first-line treatment in more people with schizophrenia rather than just using it in treatment-resistant patients or as a "last-resort" treatment. It also may reduce the costs of having weekly or monthly blood tests in patients determined to be at very low risk of agranulocytosis. In 2007, a pharmacogenetic test was launched to measure the probability of developing agranulocytosis by examining the HLA-DQB1 gene. This test has been limited in its clinical usage possibly due to the reluctance to use clozapine in general. Another proposed use for biomarkers in schizophrenia is to predict likelihood to relapse. Discontinuation (via "drug holiday") and relapse are associated with poor prognosis, poor functional outcome, and increased disability. Prediction of relapse response could significantly reduce or avoid this problem.

6. Question 4: Do Any Biomarkers for Schizophrenia Currently Exist?

From the examples of biomarker tests in schizophrenia outlined in this paper, it is clear that in order for any

biomarker to successfully transform practice they cannot simply be identified and available. Biomarkers need to predict something of value (e.g., diagnosis when there is uncertainty, treatment response, etc.) and need to be justified in terms of cost and benefit to the patient. Once a valid and reliable biomarker has been identified, to reach full implementation will require shifts at the political and societal level such that prescribing, training, and compliance practices can be changed to successfully collect medical specimens and interpret biomarker results. Any biomarker in schizophrenia will require more clinical research to gather evidence of validity and cost effectiveness before it will be in routine use.

Thus, we would suggest that no biomarker currently exists for schizophrenia. Any biomarker measurement has varying degree of error that needs to be considered when making conclusions. Perhaps most importantly the heterogeneity associated with schizophrenia will most likely need to be taken into account resulting in multiple biomarkers that identify the multiple underlying pathophysiological processes involved in schizophrenia. Currently, uncertainty overrules the predicative ability of any biomarker assay(s) rendering them of questionable clinical value. Therefore, much additional work will be required prior to obtaining any well-established biomarkers for schizophrenia. Some of the real challenges of determining biomarkers in schizophrenia may be change over time that requires following patients longitudinally—which is challenging as followup is hard, noncompliance is high, medication change is the rule, and multiple comorbidities exist. Further, development of longitudinal assessment of schizophrenia over time with a goal of developing biomarkers will take thoughtful leadership, large multidisciplinary teams, well-organized research protocols, and grand-scale funding from government, corporate, and private sources.

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