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Review

# Clinically meaningful biomarkers for psychosis: A systematic and quantitative review

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ABSTRACT

Despite five decades of search for clinically meaningful 'biomarkers' in schizophrenia there are still no common tests to inform diagnosis or treatment. Our aim was to understand why it has been so difficult to convert biological findings into clinical tests. We categorized all PubMed-indexed articles investigating psychosis-related biomarkers to date (over 3200). Studies showed an evident publication bias, a confusing array of terminology, and a few systematic efforts at longitudinal evaluation or external validation. Fewer than 200 studies investigated biomarkers, longitudinally, for prediction of illness course and treatment response. These biomarkers were then evaluated in terms of their statistical reliability and clinical effect size. Only *one* passed our *a priori* threshold for clinical applicability. This is a modest record. In order to promote real progress, the field needs: (a) consistent use of terminology so that studies can be compared; (b) a system of standardized universal reporting to overcome the existing publication bias; and (c) practical criteria [a prototype is suggested here] for assessing the clinical applicability of the findings.



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## 1. Introduction

A search of the scientific literature for 'biomarkers' in psychosis brings up a few thousand articles spanning over half a century. Despite this large body of research, the use of biomarkers in drug development or clinical practice is still extremely limited. In theory, biomarker research should enhance the biological understanding of the illness, which should lead to better mechanism-driven biological therapeutics. However, the main purpose is the finding of biomarkers that can serve as clinical 'tests' that diagnose the disorder or predict outcome (be it prognosis or treatment response or monitoring). This review is focussed on that aim: the use of biomarkers to develop meaningful clinical tests, in the context of psychosis. This focus is further narrowed to biomarkers that predict outcome, which we hereby designate by 'outcome' markers.

Our emphasis on outcome markers derives from them potentially being more useful to a clinician, more cost-effective to a health system, and more impactful in the patient's wellbeing, than diagnostic ones, in psychosis. There is great and unpredictable variability in psychosis patients' response to the same treatment, with devastating consequences, from persistence of symptoms, even after several drug treatment courses, to irreversible and/or life-threatening side effects, such as hyperlipidaemia, weight gain, diabetes, movement disorders, tardive dyskinesia, agranulocytosis and hyperprolactinemia, and, not surprisingly, high treatment discontinuation rates (Lieberman, 2007). Among the outcome biomarkers, 'predictive' biomarkers predict a response to a specific therapy, be it psychological or pharmacological, to help determine the optimal treatment in a stratified or personalized manner before it is commenced. This has the much-awaited potential to reduce incidence of side effects and the often hit-and-miss efficacy of psychiatric treatments (an example in breast cancer has been the BRCA1/2 genetic type). 'Prognostic' biomarkers predict the natural course of the disease (Oldenhuis et al., 2008), ideally without any intervention (e.g. in cancer, it is tumour size or degree of metastasis). Thirdly, 'monitoring' markers, rather than measuring a particular endpoint, tag the current disease state, which is useful to monitor side effects and efficacy of ongoing treatments and infer expected progression (e.g. HbA1C in diabetes, or CD4 cell counts in chronic HIV). 'Diagnostic' biomarkers have another purpose – they are biological tests used to ascertain the nature or presence of an illness. However, using biomarkers as 'diagnostic' tests poses particular challenges in psychiatry. The gold standard for a psychiatric diagnosis remains the DSM or ICD set of clinical signs and symptoms, but these criteria neither hypothesize a precise biological cause nor require a biological measure. When one combines this with the relatively modest inter-rater reliability of most diagnostic criteria in clinical practice (Goodman et al., 1984; Kitamura et al., 1989; Grove et al., 1981), it is not surprising that finding a one-to-one correspondence between a biological abnormality and a psychiatric diagnosis has been difficult. The literature is then replete with studies where a diagnostic biomarker shows a statistical difference between a group of patients with the ICD/DSM illness and some well characterized normal controls – but such a differentiation is of little clinical utility. Insofar as the traditional clinically-defined diagnostic systems are used to identify and validate biological markers, it is unlikely that these could improve the existing diagnostic classification. Nevertheless, as discussed elsewhere (Kapur et al., 2012), it is plausible that diagnostic biomarkers themselves could be used to identify meaningful clinical sub-phenotypes. Such enhanced precision, if sustained on biological measures, could then make the search for outcome markers easier, with a given diagnostic sub-phenotype directly corresponding to a particular treatment outcome or prognosis. A successful example again in oncology has been in breast cancer: lumps were categorized based on different symptoms, until histopathological differentiation and molecular markers turned them into distinct illnesses subtypes (Luminal A, Luminal B, Triple negative/basal-like and the HER2+) (Arteaga et al., 2012) Now, besides of guiding diagnosis and untreated prognosis, this distinction also guides treatment decisions. There are indeed new exciting attempts, such as the NIMH Research Domain Criteria (RDoC) (Simmons and Quinn, 2013), at designing new multimodal dimensional biomarkers for mental illnesses, stemming from basic behavioural neuroscience research and disregarding current ICD/DSM categorization.

The search for biomarkers in psychosis has involved several areas of expertise, as shows a review by Lawrie et al. (2011). As diagnostic markers, the genetic ones, such as copy number variations (e.g. 22q11 deletion), chromosomal translocations (e.g. DISC1, COMT or NRG) and SNPs (e.g. ZNF804A) are objective, cheap, reliable and some have been replicated, but their applicability is low, given the small individual effect sizes and/or low prevalence. Brain imaging has been the most promising tool, identifying high effect sizes and replicability for the volume of hippocampus, ventricles and other areas, and white matter integrity and hypofrontality. The use of machine learning algorithms on this data has provided high prediction accuracies but their generalizability is still to be established. Electroencephalography of mismatch negativity has been found to have both high sensitivity and specificity, and is relatively inexpensive but not sufficiently replicated. In terms of treatment response, structural imaging however does not seem to help predict response to treatment as well, although functional imaging, such as reduced basal ganglia metabolism and increased striatal D2 receptor occupancy, has been repeatedly shown – however, clinical usefulness is still to be evaluated. As for metabolic markers, higher antipsychotic drug plasma levels and raised homovanillic acid (HVA) and other peripheral markers in plasma (and CSF) have been repeatedly related to treatment response, but replicability and accuracy is still unclear. Genetic markers in COMT, the 5-HT2A receptor, the DRD3 or the DRD2 gene have been implicated but only the latter has been consistent and, still, of small effect size. These qualitative reviews give a good feel for a breadth of investigations, with several potential leads – but do not provide a good sense of potential effect sizes, strength of association and clinical applicability.

A review of this field throws up a complex array of terminology: besides the precise above-defined biomarker types, the general term 'biomarker' is often but inconsistently interchanged with 'intermediate phenotype', 'endophenotype' and 'surrogate endpoint'. We here provide their formal definitions. A '*biomarker*' is a biologic characteristic objectively measured and evaluated as an indicator of normal or pathogenic processes; or of response to a treatment or challenge (Group, 2001). It can be identified at the molecular, cellular, organ or system levels. In a psychiatric biomarker definition, the 'processes' would be psycho-pathogenic, and the treatment generally either psychotropic medication or psychotherapy. (Specifically, in psychosis, pathogenic processes are still under scrutiny but there is the common stance that a common final pathway of different causes leads to an increased striatal dopamine tone. In terms of treatment, the one usually applicable to psychosis is antipsychotics administration, all consisting of, at least, D2 receptor blockage.) An '*intermediate phenotype*' tends to be a systems-level biomarker and is termed an '*endophenotype*' if it shows 5 well-defined pre-requisites that give indications of a strong genetic basis (Gottesman and Gould, 2003): (1) it is statistically associated with the illness, (2) it is heritable, (3) it is primarily state-independent, manifesting in an individual whether or not illness is active, (4) it segregates with the illness within families and (5) it is found in non-affected family members at a higher rate than in the general population. A '*surrogate endpoint*' is an outcome that can substitute for (because it is so highly correlated with) the usual

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