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Biomarkers of treatment outcome in schizophrenia: Defining a benchmark for clinical significance

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Abstract
Emerging data from on imaging and genetic studies have generated interest in "clinically significant" biomarkers to predict response and prognosis. What constitutes "clinical significance" and how a biomarker would reach that threshold are unclear. To develop a benchmark we reviewed different approaches for defining "clinical significance" applied in schizophrenia research and identified that an improvement of 15 points on the PANSS Total is considered meaningful in clinical settings. Using this benchmark and we simulated thousands of schizophrenia trials, using characteristics derived from the NEWMEDS database with over 8000 patients with schizophrenia, to the kind of imaging, genetic, and other biomarkers that could attain clinical significance. We plotted the interaction between frequency-of-occurrence, the effect size of biomarkers and their relationship to the clinical significance threshold. Results show that categorical biomarkers are likely to attain clinical significance when they occur in 20-50% of the clinical population, and can predict at least a 8–10 point PANSS scale difference. Genetic markers are likely to have clinical significance when they occur in 20–50% of the population and can predict 7–9 points on the PANSS scale. A marker with a lower frequency or lesser effect size would find it hard to meet clinical significance thresholds for schizophrenia. The assumptions and limitations of this approach are discussed. Compared with standards in the rest of medicine, biomarkers that can attain this benchmark will be cost-effective and are likely to be adopted by clinical systems.

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1. Introduction

For nearly half a century scientists have pursued the biological causation of psychiatric diseases with the objective of identifying objective tests and markers that would enhance clinical response. Given the new technologies applied to genetics, proteomics and imaging adding to the traditional armamentarium of electrophysiology and biochemistry, the opportunities for identifying such markers have exponentially increased. Few biomarkers, however, have made the transition from the research laboratory to the clinic, the reasons for which have been documented in recent reviews (Kapur et al., 2012; Simon and Perlis, 2011; Prata et al., 2014). Reasons given by these reviews are that "while several biomarkers meet statistical significance" they lack evidence for clinical practice. Furthermore, few, if any biomarker meets the stringent criterion of "clinical significance". Clinical significance is defined as the " extent to which therapy moves someone outside the range of the dysfunctional population or within the range of the functional population", and so differs to statistical significance (Jacobson and Truax, 1991).

Tests of statistical significance of a biomarker are relatively clear-cut, since they are based on attaining an accepted threshold value (e.g., $p<0.01$). The concept of clinical significance, however, is more complex than statistical significance and cannot be divorced from the disorder under consideration. For example, a biomarker that correctly predicts at least a 20% increase in suicide attempts is of much more clinical significance than one that correctly predicts a 20% increase in the symptoms of anxiety. Similarly, a biomarker that accurately predicts at least a 20% exacerbation in the positive symptoms of schizophrenia may be more clinically significant than one that predicts a worsening in negative symptoms - just because there are more effective psychopharmacological interventions available for positive than negative symptoms. Thus, unlike statistical significance for which there is a single standardized metric, the issues of clinical significance will always be contextual to the nature of the disorder and current treatment options.

The purpose of the current study is to examine how clinical significance could be approached in the context of a prototypical psychiatric instance - the psychopharmacological treatment of the positive symptoms of schizophrenia. Since schizophrenia has attracted arguably the greatest attention in terms of biomarker development, it serves as a good exemplar to highlight the issues (Prata et al., 2014). To examine clinical significance in the context of schizophrenia we first examined studies that used different approaches to identify clinical significance. Second, we calculated the performance characteristics that the different kinds of biomarkers: continuous (e.g. brain imaging, electrophysiological); categorical (e.g., biochemical and immune assays); and genetic markers (e.g., single nucleotide polymorphisms) would need to cross this evidence-based clinically significant threshold. To make this practically useful for clinicians and treatment studies, we provide a set of graphical figures that can be easily applied to assess whether a particular biomarker would meet the criteria of clinical significance.

1.1. The concordance between change and 'clinical significance' in schizophrenia

Systematic and randomized psychopharmacotherapy trials have now been in practice for nearly 60 years. However, concern as to the 'clinical significance' of statistically significant findings is relatively recent. In the 1980s "clinically significant change" was defined in the context of psychotherapy as the extent to which a particular treatment moves an individual outside the range of the patient population and within the range of the norm (Jacobson et al., 1984). They (Jacobson and Truax, 1991) developed analytic methods to give statistically-based cut off values a clinical meaning. Part of the reason that the methods had little impact is that they use two not multiple assessments, as typically found in RCTs. Hence these analytic methods, such as the "reliable change index" could have been applied to pharmacotherapy trials but not cross over to clinical trials of schizophrenia (McGlinchey et al., 2008).

Generally, pharmacotherapy trials in schizophrenia use continuous scales, such as the BPRS or PANSS to measure improvement. Using change scores on these scales arbitrary cutoffs are applied (from 20% to 50%) to indicate "clinical response" to convey clinical significance (Frank et al., 1991; McGlinchey et al., 2008). Most trials, however, do not formally address "clinical significance" or justify their choice of "response" cutoffs.

Jaescheke and colleagues have defined clinical significance from a health outcomes perspective (Jaeschke et al., 1989). They define clinical significance as "the smallest difference in a score in the domain of interest which patients or providers perceive as beneficial and which … in the absence of troublesome side-effects and excessive costs [would lead to] a meaningful change in the patient's management". Two systematic approaches have been used to identify the "minimal clinically important difference" (Crosby et al., 2003) in schizophrenia.

The approach to an evidence-based clinically meaningful change in schizophrenia is termed 'anchor-based'. This approach asks clinicians to rate the clinical impression of their patient's improvement on an ordinal scale. For example, the Clinical Global Impression (CGI; Guy, 1970) has two versions each consisting of one item rated on a seven point scale by symptom severity or change to provide a clinical impression. Hence, the CGI provides an overall index of symptom severity or change (i.e., improvement). To rate improvement it has seven anchors ranging from "no improvement" to "very much improved") and on the continuous scale (e.g. the PANSS, which has 30 items, with possible improvement of a 180 points). These scores are linked the two to find the level of improvement in the PANSS scale that corresponds to minimal improvement (Lydick and Epstein, 1993). Using such methods Leucht et al. (2006) ($n=4091$) have suggested that a 15 point improvement on a PANSS score corresponds to a minimal improvement; a finding that has been replicated. This has been corroborated by Hermes et al. (2012) who used a similar method and found that an improvement of 15.3 points ($n=1442$) corresponded to a minimal improvement. Others have attempted to capture this difference in terms of percentage change from baseline severity and reported that changes of 17-34%

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