Objective tests for schizophrenia: window to the future

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Lawrie et al review findings from phenomenological, epidemiological, proteomic, genomic, and brain imaging studies of patients with or at risk for schizophrenia, addressing the question whether these findings provide an objective basis for prediction, diagnosis, and/or prognosis. The field has advanced significantly over the past 20 years, such that the associations of schizophrenia with many risk factors and markers are "beyond a reasonable doubt". At the same time, however, translating findings in these domains into objective algorithms for prediction/diagnosis/prognosis is likely to remain a promise rather than reality for the foreseeable future. Several considerations motivate this somewhat more dour perspective.

First, at the present time, no particular risk factor is known to be sufficient to cause the disorder, and it remains unknown what aggregations of risk factors are sufficient. In other words, how much, or what combinations, are enough? Given the multiplicity of the causes of schizophrenia and other mental disorders, it seems likely that there will be several combinations, making it highly unlikely that we will ever have a simple heuristic, or single diagnostic test, for use in the clinic. However, multivariate algorithms may eventually prove feasible. It would seem likely that the most parsimonious algorithms would include markers of pathophysiology (e.g., glutamatergic and/or dopaminergic signaling) rather than etiologic risk factors, since there are likely to be many causal combinations or routes into such final common pathways.

Second, efforts to surface such multivariate classification algorithms would be greatly enhanced if all studies began considering their data within the rubric of classification/prediction (i.e., sensitivity and specificity, positive and negative predictive power, etc.), in addition to the traditional group comparisons of means. Currently, very few studies even consider the issue of classification, despite the fact that there is a general interest in investigations of "biomarkers" and despite the availability of many elegant mathematical and statistical approaches (e.g., machine learning). In this sense, the efforts of Lawrie et al are commendable and timely, representing perhaps the opening "salvo" in calls for such a sea change.

Third, for any predictive/diagnostic/prognostic algorithm to be successful,

we must define the conditions under which it is expected to perform best. In their review, Lawrie et al appear to hold the segregation of schizophrenia and bipolar disorder as the ultimate litmus test that most markers have yet to achieve. Yet, at their genomic roots, these two syndromes may have more in common than not, in which case such segregation at the level of biomarkers would not necessarily be expected. At the very least, future classification approaches should model syndromal outcomes both within and outside of the lenses provided by our current diagnostic classification systems.

Clearly there are many other points of interest in the debate about objective tests for schizophrenia. The issues noted above represent a few suggestions for an emerging field that carries the hopes and dreams of millions of patients and family members on its shoulders.