Despite extensive research and deliberation, the diagnoses of schizophrenia and other psychiatric disorders remain enigmatically difficult and the established diagnostic criteria, even after several critical reviews, are continually ill-defined. Indeed, the widely used ICD-10 guidelines are in fact derived from the observations reported by Schneider in the early part of the last century. Recent advances in a wide-spectrum of technologies have enabled investigators to utilize robust, highly sensitive and specific biomarkers for accurate diagnoses, for example, troponin levels for the diagnosis of an acute myocardial infarction. With the absence of any biochemical tests, psychiatric disorders and schizophrenia in particular, are one of the few groups of illnesses that are clinically evaluated in their entirety.

Current diagnosis of schizophrenia relies on subjective tests which often result in varying interpretations by different clinicians for the same patient. This is further compounded by the fact that the margins used to categorize psychiatric illnesses clinically can be blurry. For example, hallucinations can be a part of bipolar disorder, schizophrenia as well as psychotic depression. This overlap in symptomatology has made it challenging to classify and distinguish these diseases.

Amongst the various identified risk factors for schizophrenia, (e.g., obstetric complications and neonatal infections), family history remains the most consistent finding, suggesting that genetics contributes to its etiology in a significant way. Based on familial linkage analyses, the estimated heritability for schizophrenia is approximately 80%, which is significantly higher than that of Parkinson's disease (13% to 30%) and breast cancer (5% to 60%), both of which have several established genetic risk factors. However, these studies inherently suffer from a low power and a recent meta-analysis failed to implicate a chromosomal region conclusively. Attention is now being focused towards case-control based association studies that investigate specific allelic variations or single nucleotide polymorphisms (SNPs) within possible 'candidate genes'. Whilst these studies have provided greater statistical power, they lack consistency in the precise genetic regions and SNPs that have been implicated when compared to other hereditable disorders such as diabetes. However, a few genes including Disrupted in Schizophrenia 1 (DISC1), Neuregulin 1 and Dystrobrevin binding protein 1 (DTNBP1) have been implicated in multiple population models of schizophrenia. In addition they have supportive neurobiological data that links the functions of these genes to the various cellular processes thought to be disrupted in schizophrenia. There is a need to study these genes in more diverse ethnic populations to further validate their roles as bona fide biomarkers for schizophrenia.
The various biochemical theories of schizophrenia that have emerged as a result of the available therapeutic interventions have prompted a vigorous search for putative biochemical biomarkers. These include glycine, serine and homocysteine that are mediators of the NMDA pathway, the dysfunction of which is currently the most strongly postulated theory of schizophrenia.\textsuperscript{8,9} Other chemical biomarkers include dehydroepiandrosterone (DHEA) and cortisol that are involved in regulating the hypothalamic pituitary-adrenal (HPA) axis and inflammatory markers such as selectins, tumour necrosis factor α (TNF-α) and nuclear factor-kappa B (NF-kB). Perhaps the most promising of these are the recently discovered neurotrophic factors, such as brain derived neurotrophic factor (BDNF) that are involved in neuronal growth and regulation.\textsuperscript{10-13} Additionally, peripheral expression of the schizophrenia candidate gene, NRG1, has been studied in the blood of schizophrenic patients and this may serve as a robust biomarker for the disease.\textsuperscript{14}

Whilst schizophrenia appears to be a polygenic disorder, it is plausible that the defects might lie beyond the level of the genome; it is well known that dysfunctional epigenetic mechanisms such as DNA methylation and histone modification during early development and later in life may contribute to its onset. Although probing such abnormalities to identify chemically useful biomarkers may be challenging, structural changes in schizophrenia could serve as reliable indicators of the disease. Reduced cortical volumes and enlarged ventricles are long-established findings in schizophrenia with early gray matter loss, particularly associated with first-episode psychosis.\textsuperscript{15} Though radiological findings have been relatively consistent, they are by no means specific to schizophrenia and hence have limited applicability as screening or prognostic tools. Advances in functional MRI may allow identification of permanent disease-specific changes in the schizophrenic brain which could in turn serve as reliable "image-based" markers for early detection of disease.

Psychiatry seems to be experiencing a fundamental shift in its approach to dealing with the complexity of diseases that fall within its spectrum. Recent advances in molecular and cellular biology and imaging technology could enable psychiatrists to diagnose cases at a much earlier stage. However, the apathy with which policy makers address the issue of mental health and the general discrimination between physical and mental disorders amongst medical practitioners is a matter of great concern. Lack of recognition of psychiatric disorders and of their severity is central to this problem as cost-effective treatment modalities are already in existence.

Schizophrenia in particular, carries an enormous economic and social burden and this is especially pertinent in the developing world where the prevalence rates are thought to be higher than previously expected.\textsuperscript{16} The authors feel that clinicians in Pakistan need to continually keep themselves abreast of the latest developments in neuropsychiatry in an effort to learn more about the disease and its management. Research that helps identify accurate, precise and cost-effective biomarkers is now crucial and this will undoubtedly result in significantly reduced morbidity and mortality by early identification of the disease process. Failure to do so will continue to deprive vast swathes of population within developing countries that suffer from undetected mental health disorders, such as, schizophrenia from appropriate healthcare and this is likely to exacerbate existing financial hardship and economic instability.

The authors are currently part of a research group that aims to study genetic biomarkers in the Pakistani population.

References