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EDITORIAL

Improving prognosis research: examples from psychiatry

Diagnosis, treatment, and prognosis are the central tenets of clinical practice where diagnosis and prognosis inform clinical decision-making regarding treatment (Croft, P. *et al*., *BMC Med*., 2015, **13**, 20). Prognosis predicts health outcomes in people with a given disease following the treatment. This can vary depending on the outcome in question – recovery from the disease, likelihood of its recurrence, or response to a specific treatment. This prediction is based on current clinical knowledge. The accuracy of prognosis is often related to the certainty or validity of the diagnosis. Diseases with specific known causal mechanisms tend to have an accurate prognosis, often contingent upon successful implementation of treatment based on a thorough knowledge of the cause of the disease. In contrast, disorders with unknown or multiple causes (e.g., severe mental disorders like schizophrenia) tend to have heterogeneous outcomes. Here, the ambit of prognosis is essentially in the realm of the clinicians, who make estimates based on clinical intuition shaped by domain expertise and experience after reviewing the signs, symptoms and laboratory reports. Clinicians are largely accurate in their prognosis only when they are very confident (e.g., <10% error margin). However, prognosis, even in such cases, comes out to be accurate in a minority of the patients, leaving many 'indeterminate' patients with unknown prognostication. Prognostic aids can be useful in such scenarios through prognostic scoring models built on a combination of clinical and disease-mechanistic parameters.

In our perpetual quest for the elusive biomarkers of mental health conditions or diagnoses, prognosis research has received relatively less attention. Prognosis research can offer crucial evidence for translating the findings from the laboratory to humans and from clinical research to clinical practice (Steyerberg, E. W. *et al.*, *PLoS Med*., 2013, **10**, e1001381). Such research includes *describing* the course and outcome of a disorder, identifying *associations* between candidate prognostic factors and outcomes, estimating the probability of a particular clinical outcome at an individual level based on a *model* with multiple prognostic factors, investigating the *clinical utility* of such models, and ultimately informing *stratified treatment approaches* to improve patient outcomes. In the field of mental health, this is particularly relevant to schizophrenia, a complex, heterogeneous, severely disabling brain disorder affecting large-scale brain networks with high heritability and substantial environmental risk factors. Today, we stand at the cusp of a dualistic reality: (i) tremendous scientific progress in our ability to investigate brain function and our genetic architecture, and (ii) the disquietingly vast mental health gap.

Despite a low point prevalence (~0.3–0.4%), schizophrenia is amongst the top ten most disabling conditions globally. This is more so in low- and middle-income countries, given the population growth and ageing, and in the most productive age group of 25–49 years. While antipsychotic medications are effective in controlling symptoms of schizophrenia, between 20% (two-drug failure) and 40% (one-drug failure) of those with schizophrenia, do not show sufficient improvement with antipsychotic medications (Mueser, K. T. and McGurk, S. R., *The Lancet*, 2004, **363**, 2063–2072). These patients are resistant to treatment. Resistant schizophrenia comes with higher healthcare utilization costs, higher disability, greater caregiver burden, and potentially higher physical morbidity and mortality. Much of the burden of illness in schizophrenia is due to treatment resistance; hence, despite its low prevalence, schizophrenia remains very disabling. Perhaps this is why improving the treatment outcomes of resistant schizophrenia is the top priority for schizophrenia research according to patients and their caregivers (Lloyd, K. and White, J., *Nature*, 2011, **474**, 277–278). This is all the more important in a country like India, where there is a much lower contact coverage for schizophrenia (~40–50%) than in China or the western world (Patel, V. *et al*., *The Lancet*, 2016, **388**, 3074–3084). In summary, schizophrenia is extremely disabling; a substantial proportion is attributable to resistant schizophrenia. Scientifically informed, efficient utilization of resources to intervene early in resistant schizophrenia may reduce the burden of this debilitating disorder.

Clinical characteristics are perhaps the oldest attempts to prognosticate outcomes in schizophrenia. However, pooled quantitative analyses indicate that several initially promising clinical prognostic markers (e.g., duration of untreated psychosis) do not get replicated in subsequent studies. However, younger age at onset, male gender and poor premorbid adjustment are perhaps the most replicated findings that provide information about poor prognosis. Brain structure and function characterization (Mehta, U. M. *et al*., *Schizophrenia Res*., 2021, **237**, 153–165), along with genotyping and gene sequencing, DNA methylation and proteomic data, have shown promising results as isolated predictors of treatment response. Further, refined individual-level characterization of thought, using computational linguistics and behaviour, using digitally captured mobility and circadian rhythm metrics, provide novel real-world phenotyping avenues that can

be used as clinical predictors of treatment response. However, while increasing associations are being found between candidate prognostic factors and treatment response in schizophrenia, there have been limited efforts so far to examine how these factors can be combined in one prediction model to assist in (i) estimating the probability of treatment resistance in everyone with schizophrenia, and (ii) improving the accuracy of treatment resistance prediction beyond what can be achieved using clinical markers only. Such an approach could have potentially greater prediction accuracy. It will also enable the identification of a parsimonious model that can take the best predictors from specific streams of baseline data to be tested and implanted in a clinical set-up.

Despite early diagnosis and treatment of schizophrenia, to possibly prevent the development of resistant schizophrenia, it has remained a challenge to implement this knowledge in clinical practice. Here, a preventive medicine paradigm supported by prognosis research can potentially bridge this wide gap. Traditionally, preventive paradigms include risk mitigating strategies that are applied at different stages in the natural course of a disease: primordial (universally), primary (susceptible individuals), secondary (sub-clinical disease-states), and tertiary (after disease onset to prevent disability). While this is a critical aspect of preventive medicine, it may not always translate to be of public health relevance. When there are limited resources to treat those who are already ill, it may not be prudent to spend more resources on what appears to be a not-so-effective and expensive path to prevent illness. In this light, we propose the application of a different prevention paradigm, i.e. early identification and treatment of resistant schizophrenia. The *resistance prevention* paradigm has three components: (i) consider all individuals with the first episode of schizophrenia as being susceptible to developing resistant schizophrenia; (ii) intensify science funding into the systematic study of prognosis research in schizophrenia with an aim to identify parsimonious and clinically useful prediction models; and (iii) clinically use evidence-based prediction models to identify potentially resistant schizophrenia early in the illness course; scientifically study alternative treatments using randomized controlled experiments, and implement effective therapeutic alternatives. Recent strategic frameworks (e.g., PROGnosis RESearch Strategy (PROGRESS framework)) and reporting guidelines (e.g., the Transparent Reporting of a multivariable prediction model of Individual Prognosis or Diagnosis-TRIPOD guidelines (Collins, G. S. *et al*., *BMC Med*., 2015, **13**, 1)) to support such work are welcome initiatives that can expedite high-quality research outputs with translational value.

The primary goal of such a paradigm would be to foster a clinical neuroscience ecosystem within the country and elsewhere that works towards improving outcomes and reducing disability due to schizophrenia by using a prognosis research approach that informs clinical care and a learning healthcare system that uses real-world multimodal clinical and bio-behavioural data to improve population-level mental health outcomes. As a parallel deliverable, this approach will also be suited to study the *etiopathogenesis* and the *trajectories* of resistant schizophrenia. The field is currently trying to understand if resistant schizophrenia lies on the extreme end of the schizophrenia spectrum, with shared but accentuated genetic risk or if it has independent genetic risk factors with unique pathophysiology. The trajectories to resistant schizophrenia will advance our understanding of its etiopathogenesis and vice-versa. While some may have a pernicious form of illness that rapidly progresses to resistant schizophrenia within a few months of onset, others may develop it later in its course, partly due to frequent relapses owing to poor adherence or substance use and partly due to the slowly worsening course of the illness itself (i.e. those who relapse despite being on treatment that worked earlier for them). Multiple relapses owing to psycho-social adversities can trigger a cascading series of *neurotoxic*, *psychotoxic* (shame, demoralization) and *sociotoxic* (breaks in work, relationships) consequences leading to resistant schizophrenia. Therefore, a careful and nuanced recording of the individual's psycho-social environment will be crucial in taking this approach forward.

This leads us to deliberate on how early identification of treatment non-responders alters our current clinical practices. Early identification of potential treatment resistance will enable channelizing more resources to facilitate a comprehensive clinical management approach for these patients. This will be particularly relevant in tertiary care centres which focus on managing resistant psychiatric disorders with already available multidisciplinary treatment teams and neuroimaging and genetic analysis infrastructure. Adjuvant therapies that are generally implemented after treatment resistance emerges, may be initiated early. These include cognitive training, nutritional therapies (e.g., vitamin B12, folic acid, vitamin D), yoga or aerobic exercises, and non-invasive brain stimulation therapies like transcranial magnetic and direct current stimulation. Another potential strategy that could be implemented is the early initiation of clozapine, the drug of choice in treatment-resistant schizophrenia. This is even more critical since one of the strongest determinants of clozapine refractoriness is delayed initiation of clozapine.

In summary, identifying those at risk for resistant schizophrenia has the potential to inform strategies akin to primary and secondary prevention of treatment resistance by channelizing more resources for their management. Developing composite, bio-behavioural, pragmatic predictive biomarkers of treatment resistance in first-episode schizophrenia will enable identifying a unique subset of schizophrenia that might benefit from different pharmaco-therapeutic and psycho-social treatment strategies. This could also pave the way for potential mechanistic biomarker discovery that can have diagnostic and prognostic relevance.

Urvakhsh Meherwan Mehta*
Jagadisha Thirthalli

Department of Psychiatry,
National Institute of Mental Health & Neuro Sciences,
Bengaluru 560 029, India
*e-mail: urvakhsh@nimhans.ac.in