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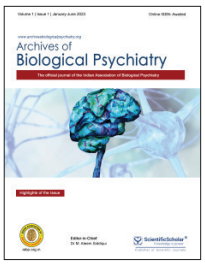

Presidential Address

Precision medicine in psychiatry

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Good evening everybody. It is great privilege and honor for me to present the presidential address in the 17th Annual National Conference of the Indian Association of Biological Psychiatry.

What is Precision Medicine in Psychiatry? And why should we go for precision medicine in Psychiatry? This is the main aim of my lecture on Precision psychiatry.

INTRODUCTION

It can be argued that among the disciplines of modern medicine, psychiatry is perhaps the most "personalized or précise" with patients at the center. However, even in psychiatry, with a wide array of interventions available and patients coming from a constellation of personal factors, a lot of scope arises to further tailor the treatments offered. The central principle of personalized medicine is the notion that an individual's unique physiologic traits have a vital role in both disease susceptibility and responsiveness to certain therapies.

Term "Precision medicine" is used in preference to "personalized" to avoid implying that each technology or technique is developed for an individual patient, rather, it depends on using such techniques for exact measurements that are most suited for each person.

Precision psychiatry, therefore, attempts to address the two outstanding quandaries that are widely accepted to be undermining the scientific legitimacy of "evidence-based" psychiatry practice:

1. About performing treatment studies on the grounds of ill-defined phenotypes that do not represent valid stratification
2. Able to successfully work with patients at the predetermined idiographic level using non-empirical data.[1]

While the most current description of "personalized medicine" is stated as, "an approach to disease treatment and prevention that takes into account individual differences in genes, environment, and lifestyle."[2] Based on the understanding that factors like the intricate interplay of personal characteristics, for example, (sub)culture, genetic culture, the bacteria in the mouth and gut, the personalities of both parents, the role one plays in the family, and the attachment to both parents, etc. these all are physically represented as biomarkers to a large extent. Personalized medicine's main goals are therefore to assess an individual's vulnerability to developing a disorder, establish an accurate diagnosis, and carry out the most efficient and favorable response to therapy.[3] Personalized in psychiatry can entail:

- Levels of healthcare delivery and access
- Implementing treatment plans based on the personal characteristics of patients:
  - Psychopathology
  - Personal history
  - Premorbid functioning
  - Family history
  - Physical comorbidities
  - Cognitive function
  - Environment and lifestyle

THE NEED IN PSYCHIATRY

To an extent, the high burden of psychiatric morbidity in the general population is contributed to our limited understanding of the etiopathogenesis of psychiatric disorders.[4] Moreover, this is compounded by the fact that symptoms overlap significantly between different disorders while varying dramatically across persons with the same disorder. The response to medications and therapy is also similarly variable, affected by multiple factors. An amalgamation of biomarkers and clinical factors is currently the most promising strategy that has been proposed for a valid individualization of disease management.[4]

THE EXPECTATIONS

Precision psychiatry model will lead to the identification of biomarkers that may assist with treatment selection and predict treatment outcome but will differ from personalized medicine. A particular patient would receive currently existing therapy modalities according to the individual's medical illness category, and not an intervention that would be specifically designed for that individual following the acknowledgment of their unique characteristics, which is the scenario in "personalized psychiatry."

THE MULTI-STRATEGY APPROACH

- Biomarkers – these are pathophysiological markers, risk factors for disease, or predictors of therapeutic response. Although, there is not a single marker that can explain a psychiatric diagnosis entirely[3]
- Data-driven discovery – needed to outline the multivariate and combinatorial profiles of biomarkers. They shed light on the myriad of clinical presentations of psychiatric disorders [Figure 1].

The emergence of "omics" strategies has been instrumental in comprehending the neurobiology of various psychiatric illnesses. OMICS disciplines are systems biology-related areas that include various studies like genome studies and other related fields of genome analysis such as metagenomics, epigenomics, transcriptomics, metabolomics,

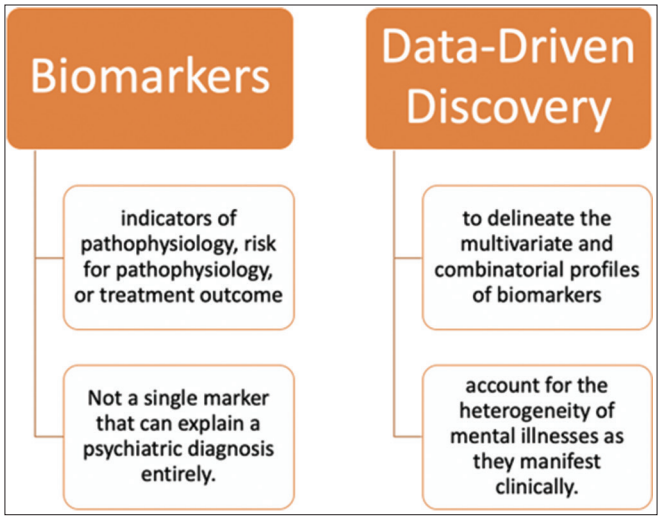

Figure 1: Flowchart for multi-strategy approach explaining biomarkers and data-driven approaches.

and its subfields like lipidomics. They individually give vital information regarding the neurobiology of mental disorders and as a result are viewed as a data-based strategy for mental disorders.[5]

Some examples: Genetics and imaging

- Ozomaro *et al.* have examined the growth of precision medicine in the treatment of depression, bipolar mood affective disorder, and schizophrenia. They discuss the ways genetics and epigenetic impact the hereditary aspects of these particular disorders and their significance in predicting mental health treatment response.[3]
- Apud *et al.* study evaluated the association between voltage-gated potassium channel genotypes and the therapeutic response to atypical antipsychotics in Schizophrenia. It demonstrated that patients with a certain genotype, the TT genotype had significantly improved much more than the patients with the TC or CC genotypes. It, therefore, provides some evidence that genotype can guide the method of interventions chosen for patients with Schizophrenia.[6]
- A positron emission tomography research found that treatment-resistant schizophrenia patients do not have drug-induced modifications in the pre-synaptic dopamine transmission receptors, like the patients who showed a positive response to antipsychotic treatment.[7,8]

Some examples of the machine learning

- On extremely convoluted datasets, numerous machine learning tools, namely, k-means clustering, random forests, linear discriminant analysis, and support vector

machines have been utilized. These aforementioned techniques can predict the treatment response and clinical outcomes, in addition to grouping patients based on biological or behavioral factors. For example, a tool that assesses an individual's susceptibility to a psychiatric disorder, and accordingly designs a neurofeedback session that focuses on enhancing their functional connectivity[9]

- A previously published meta-analysis reviewed successful working models utilizing machine learning to predict treatment responses in unipolar and bipolar depression subjects[10]
- In another study, the researchers recognized three genetic mutational signatures associated with treatment outcomes: rs6265 in the gene encoding the brain-derived neurotrophic factor; rs7430 and rs6313 in the Protein Phosphatase 3 Catalytic Subunit Gamma (PPP3CC) and the serotonin transporter receptor 2A (HTR2A) encoding gene, respectively. These genetic mutations combined with the absence of melancholic depression were associated with a decrease in the HAMD score <17, that is, around 62% of the patients with this combination in comparison to 34% in the whole study population, which showed significant improvement with the treatment.[11,12]

Some examples: other biological markers

- There are studies investigating biomarkers other than genotypic data, like peripheral messenger RNA (mRNA) levels of chosen genes which may feed machine learning-derived models.
- Through this approach, a study found that baseline expression levels of six genes, namely, IFITM3, RPL5, GZMA, RPL24, MATR3, and RPL17, which were identified from genome-wide transcriptome data, had a 0.76 accuracy in predicting non-remission after 8 weeks of citalopram therapy[13]
- A model encompassing clinical traits, resting-state fMRI, and 13 specifically chosen single-nucleotide polymorphisms which were utilized to accurately estimate early response to antidepressants[14]
- A study developed a tool from genetic information based on the high heritability of antipsychotics-induced side effects (0.60-0.80) to anticipate extrapyramidal symptoms induced by antipsychotics.[15]

On balance, the above examples show that, despite coming short on the clinical significance threshold, predictive models, relying on solely biological data, or combined with clinical data available, are as follows:

- Beginning to reach the precision necessary for clinical implementation
- Exhibiting low sensitivity, but high specificity in general.

Thus, this suggests that, at least for treatment response predictive models, it may be important to avoid premature discontinuation of drug trials, as a definitive response is more likely to occur.

Some examples: Clinical predictive models

- These also form a major tool in our arsenal. Identified and well-taught phenomena are observed in clinical spaces, for example – response to lithium, prediction of resistance to antidepressants, stratification of the risk, and prognosis in psychoses.

GUIDELINES

- The first criterion is the prior response: if an individual has previously benefited from a certain molecule, this is the most compelling criterion to prescribe the same drug again.[4]
- Secondly, if this information is not present, we can depend on the data regarding responses within the same family.[4]

These are the things we do in our clinics without second thoughts, on a regular basis.

Among the pharmacokinetics and pharmacodynamics interactions, all compounds present different degrees of modification of CYP enzymes, which can lead to potential changes in the plasma levels of concomitant drugs or of the compound itself, which may cause toxicity by synthetic reduction or increase in plasma level.[3,4] Some compounds in the presence of medical comorbidities may be contraindicated. Prediction modeling can be used to predict the likelihood of a particular condition being present through diagnostic models, the outcomes through prognostic models, or the response to an intervention as in predictive models at the individual subject level.

APPLICATIONS

All these observations and studies mean little if they are not applied on a wider scale. This is salient as psychiatry is traditionally not reliant on technologies or medical investigations. To ensure the last translational step, clinical guidelines outlining how such novel technologies should be used and assessed in clinical practice will be required [Figure 2].

- Research applications – Further identification and characterization of tests and markers that carry consistency in what they measure
- Clinical applications – Use in clinics, integration in EPR/notes, and part of training
- Regulation applications – Clear guidelines on what to use and how much to use, incentivizing, and regulating at the same time.

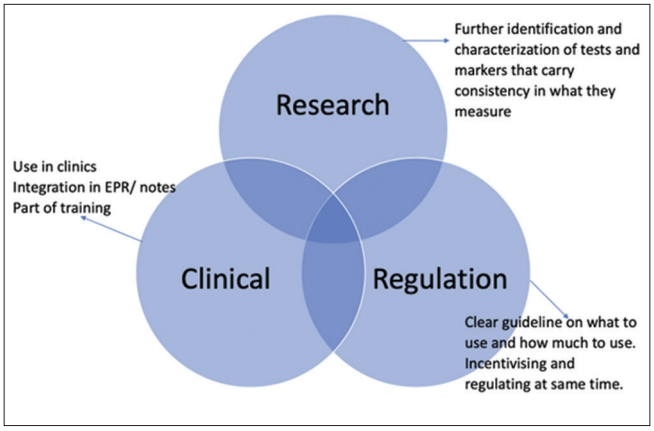

Figure 2: Applications of precision psychiatry.

BARRIERS

Multiple areas to consider, including limitations on utility, cost-effectiveness, and stigma. There are ethical considerations as well, finding a balance between patient autonomy and dictation by clinicians/"holy grail tests." Furthermore, seeing that precision psychiatry is so closely linked to the interpretation of huge databases whether phenotypic, neuroimaging, or neurobiological, with this confidentiality and discretion concerns are becoming evermore pertinent. Stigma driven by being associated with an identifiable "defect" and patients being "blamed," has been a concern in other branches of medicine, and a social example could be recent cases of stigma associated with people with COVID-19.

Equally important is the other challenges which can prevent the adoption of precision psychiatry in clinical settings. Among concerns include physicians' and mental health professionals' lack of awareness of precision techniques such as pharmacogenetics/pharmacogenomics and their compliance with precision medicine techniques.[12] Adequate knowledge and training will be the key to achieving successful results. Most importantly, the biopsychosocial framework remains the backbone of psychiatric care management.[2] We must exercise caution to ensure greater focus on the biological aspects that does not divert the attention away from delivering suitable and effective evidence-based interventions, either at the individual level or as a part of wider public health endeavors, both at the level of the individual and broader, public health-based initiatives.

CONCLUSION

Overall, the goal of any paradigm in medicine, including precision medicine in psychiatry, has to be an alleviation of morbidity and improvement in patients' lives. For this, a constant move toward newer, better, and more readily accessible tools has to be sustained. This is to have a diagnosis that is more reliable in determining the prognosis, guiding treatment, and predicting the outcome of the treatment, hoping to aid the creation of new and improved pharmacological and non-pharmacological interventions. Precision psychiatry suggests the need for better categorization of patients, along with the incorporation of their biological (genetic) data which will enhance the treatment success rates and thus enable us to transition beyond the one-size-fits-all protocolled approaches in psychiatric illness management.

It is of paramount importance that one differentiates "precision psychiatry" from "personalized psychiatry." As personalized psychiatry explores the intricate relations between biology, behavior, environment, cognitive, and social dynamics, as well as patients' perceptions, whereas precision psychiatry emphasizes primarily the biological (and arguably phenomenological) processes in psychiatric disorders. Precision psychiatry seeks to personalize treatment modalities and supplement clinical judgment by integrating biological and environmental data. The pharmacogenetic biomarkers in cytochrome genes have been incorporated in prescription recommendations, which were a significant advancement in the direction of precision psychiatry. The integration of pharmacogenetic services with health-care delivery systems is a complicated and multi-step process, focusing on the education of health-care providers, promotion by organizations, institutions, and other regulatory agencies, and overcoming the commercial and ethical hurdles are the biggest concerns. In summation, it is a complex interplay of multiple factors, each with its own salience.

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Declaration of patient consent

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Conflicts of interest

There are no conflicts of interest.

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