Predictive Biomarker Discovery in Schizophrenia Using Advanced Machine Learning to Decode Heterogeneity: Analysis of the CATIE Schizophrenia Trial

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Methodological Issue Being Addressed The heterogeneity of clinical trials poses significant challenges for identifying predictive biomarkers and effective treatments. Traditional machine learning (ML) methods often fail to capture the complex, non-linear interactions within heterogeneous and small datasets typical of psychiatric research. This study introduces a novel ML approach that deconstructs the patient population into explainable and unexplainable subpopulations to improve clinical trial enrichment and precision medicine by identifying subsets of patients characterized by specific variables influencing treatment response.

Introduction Schizophrenia is a complex psychiatric disorder with diverse etiologies and manifestations, making treatment response highly variable among patients, complicating the identification of biomarkers for effective treatments. Traditional ML approaches struggle with this complexity due to the need for large, well-labeled datasets and the difficulty in capturing nuanced, non-linear interactions. The CATIE schizophrenia trial provides an opportunity to apply advanced ML methods to uncover biomarkers predicting treatment response, ultimately guiding precision medicine in schizophrenia.

Methods Applying a novel ML approach to analyze data from the CATIE schizophrenia trial consisting of 1600 patients with various forms of schizophrenia comparing the effectiveness of antipsychotics, our focus was on perphenazine and olanzapine. The primary outcome was time to all-cause treatment failure, indicated by discontinuation and medication change. This approach uses sub-insight learning, which deconstructs patient populations into explainable and unexplainable subpopulations. By focusing on the explainable subpopulations, it identifies subpopulations characterized by 2-4 variables that can explain treatment response. This approach is particularly effective for heterogeneous and complex psychiatric data, as it discovers high-dimensional similarities among patients concerning specific clinical questions without overfitting. Patients were categorized as perphenazine completed or olanzapine failed (PCOF) and perphenazine failed or olanzapine completed (PFOC).

Results Olanzapine preferential response: n=206 (90 PCOF, 116 PFOC) characterized by 3 variables (Cohen’s D=0.399, p=0.00519) PANSS total score between 38-81, PANSS negative score between 7-22, and PANSS hostility score of 1 (verbal and nonverbal expression of anger and resentment). These variables suggest that patients with lower to mild PANSS total and negative scores, and minimal hostility have a higher likelihood of responding to olanzapine.

Perphenazine preferential response: n=53 (26 PFOC, 27 PCOF) characterized by 3 variables (Cohen's D=0.771, p=0.0081) PANSS Difficulty in abstract thinking between 1-2 (better abstract thinking abilities), PANSS total score between 43-65, and PANSS general score between 22-37. These findings indicate that patients with higher cognitive flexibility, better abstract thinking, and better social cognition are more likely to respond to perphenazine.

Conclusion Our advanced ML approach using sub-insight learning effectively identified meaningful subpopulations within the CATIE schizophrenia trial. By focusing on subsets of variables that explain treatment response in explainable subpopulations, we overcome the limitations of traditional ML methods in handling heterogeneous psychiatric data. This approach allows for the development of comprehensive patient profiles corresponding to perphenazine or olanzapine response, offering a granular understanding of treatment effects. This study underscores the potential of innovative ML techniques in advancing precision medicine strategies in psychiatry, paving the way for more effective and personalized treatment options for patients with schizophrenia to enhance success rates.

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Guidelines I have read and understand the Poster Guidelines

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