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Precision in Psychiatry Trials: A Novel Mathematically-Augmented Machine Learning Approach for Identifying Patient Personas for Tailored Antipsychotic Therapy for the CATIE Schizophrenia Trial

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SCAN ME

KEY FINDINGS

- **OVERCOMING HETEROGENEITY:** NetraAI successfully uncovered meaningful subpopulations by isolating variable combinations that drive differential treatment response to olanzapine or perphenazine to overcome traditional ML limitations on small heterogeneous psychiatric datasets.
- **HIGH-EFFECT-SIZE, REPLICABLE MODELS:** NetraAI-identified 3-variable personas predicting preferential response to olanzapine or perphenazine were validated in a Holdout Testing Set.

CLINICAL IMPACT

- **EXPLAINABLE ML FOR PSYCHIATRY:** Explainable ML offers a path to reduce trial failures and accelerate the identification of responders.
- **PRECISION PSYCHIATRY:** Detailed patient profiles in the schizophrenia population, offer insights into various perspectives of the patient population that can result in differential treatment effects, providing a framework for precision psychiatry.

INTRODUCTION

Precision psychiatry requires innovative methodologies that can unravel patient heterogeneity and enhance personalized treatment strategies.

THE CHALLENGE

Like many psychiatric disorders, schizophrenia presents with diverse symptomatology and treatment responses. Conventional machine learning (ML) approaches often struggle to identify robust biomarkers in these small, complex datasets.

THE OBJECTIVE

Apply NetraAI, a mathematically-augmented ML technology leveraging sub-insight learning to stratify patient populations into explainable and unexplainable subgroups to reveal high-effect-size "Personas" linked to differential treatment responses.

METHODS

DATASET

CATIE schizophrenia trial dataset (n=1600) evaluating the efficacy and tolerability of several antipsychotics, focusing on the perphenazine and olanzapine arms (n=597).

Primary Outcome: Time to all-cause treatment failure, indicated by discontinuation and medication change.

Data Types: Symptom Severity (PANSS, CGI, CDRS), Functional Outcome Measures (SF-12, QLS), Side Effects and AEs (AIMS, SAEPS, BAS, metabolic effects), Neurocognitive Assessments, Labs
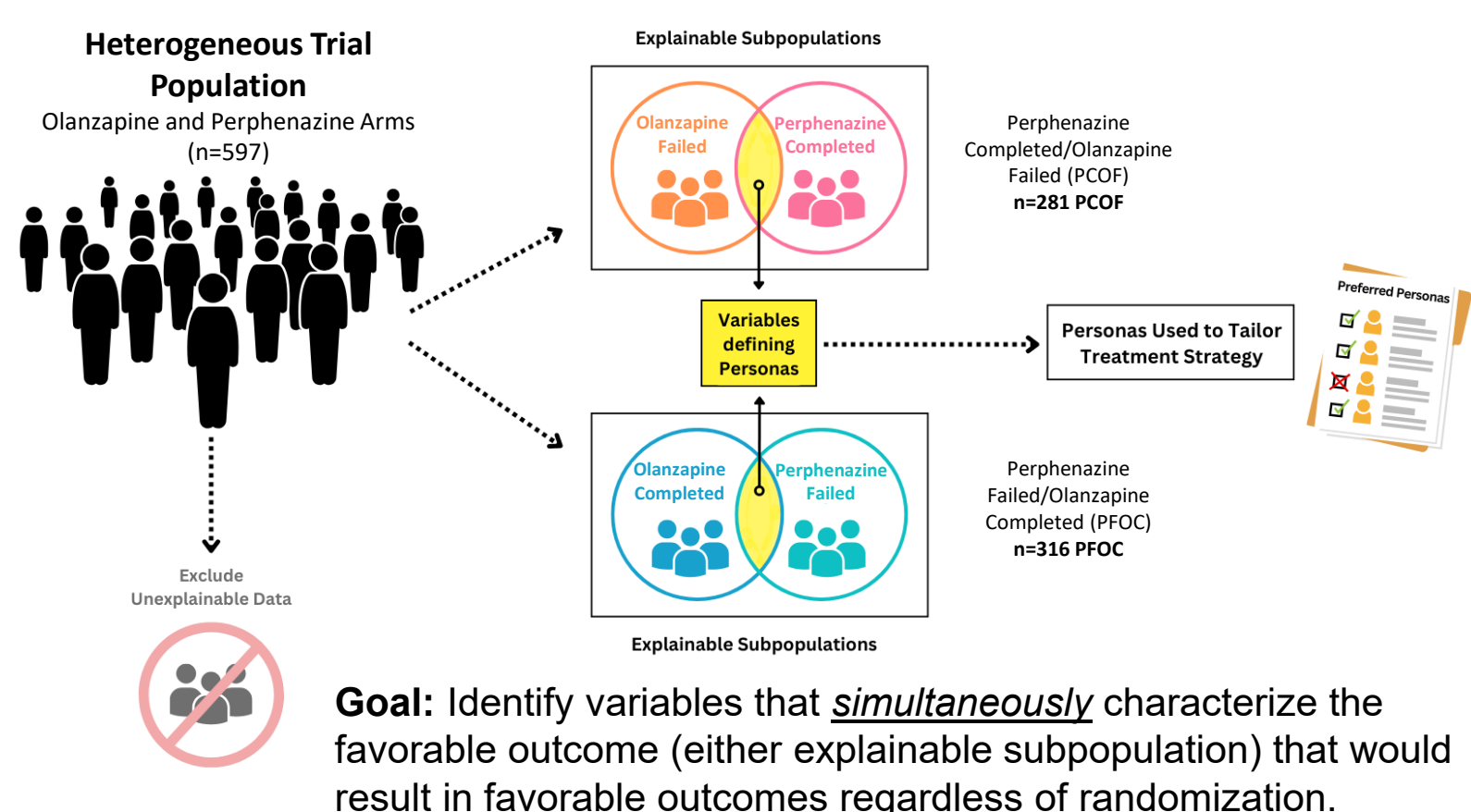
NETRAAI APPROACH

NetraAI is an advanced, mathematically-augmented ML technology developed to identify explainable patient subpopulations by distinguishing causal, high-effect-size "Personas" defined by 2-4 variables and specific ranges with respect to the endpoint, that are linked to differential treatment responses, leading to more robust models.

NetraAI leverages sub-insight learning to stratify patients into explainable and unexplainable subpopulations. By not attempting to explain everyone in a clinical trial, and focuses only on those subpopulations that can be explained, NetraAI avoids overfitting and minimizes disease biases through a unique long-range memory mechanism. This approach ensures generalizability and reproducibility in hold-out validation sets.

RESULTS

1 SEPARATING THE PATIENT POPULATION FOR PREFERENTIAL RESPONSE

Heterogeneous Trial Population Olanzapine and Perphenazine Arms (n=597)

Explainable Subpopulations: Olanzapine Failed, Perphenazine Completed — Perphenazine Completed/Olanzapine Failed (PCOF) **n=281 PCOF**

Variables defining Personas → Personas Used to Tailor Treatment Strategy

Olanzapine Completed, Perphenazine Failed — Perphenazine Failed/Olanzapine Completed (PFOC) **n=316 PFOC**

Exclude Unexplainable Data

Goal: Identify variables that _simultaneously_ characterize the favorable outcome (either explainable subpopulation) that would result in favorable outcomes regardless of randomization.

OLANZAPINE PREFERENTIAL RESPONSE PERSONA

n=220 (100 P, 120 O) p=0.003, Cohen's D=0.577

- PANSS Total Score: 69-132 (Ref Range: 32-132)
- CGI Severity: 4-7 (Ref Range: 1-7)
- PANSS Mannerisms & Posturing: 1-2 (Ref Range 1-7)

Patients with moderate-to-severe overall symptom burden with mild behavioral disturbances despite their illness severity would have a higher likelihood of responding to olanzapine.
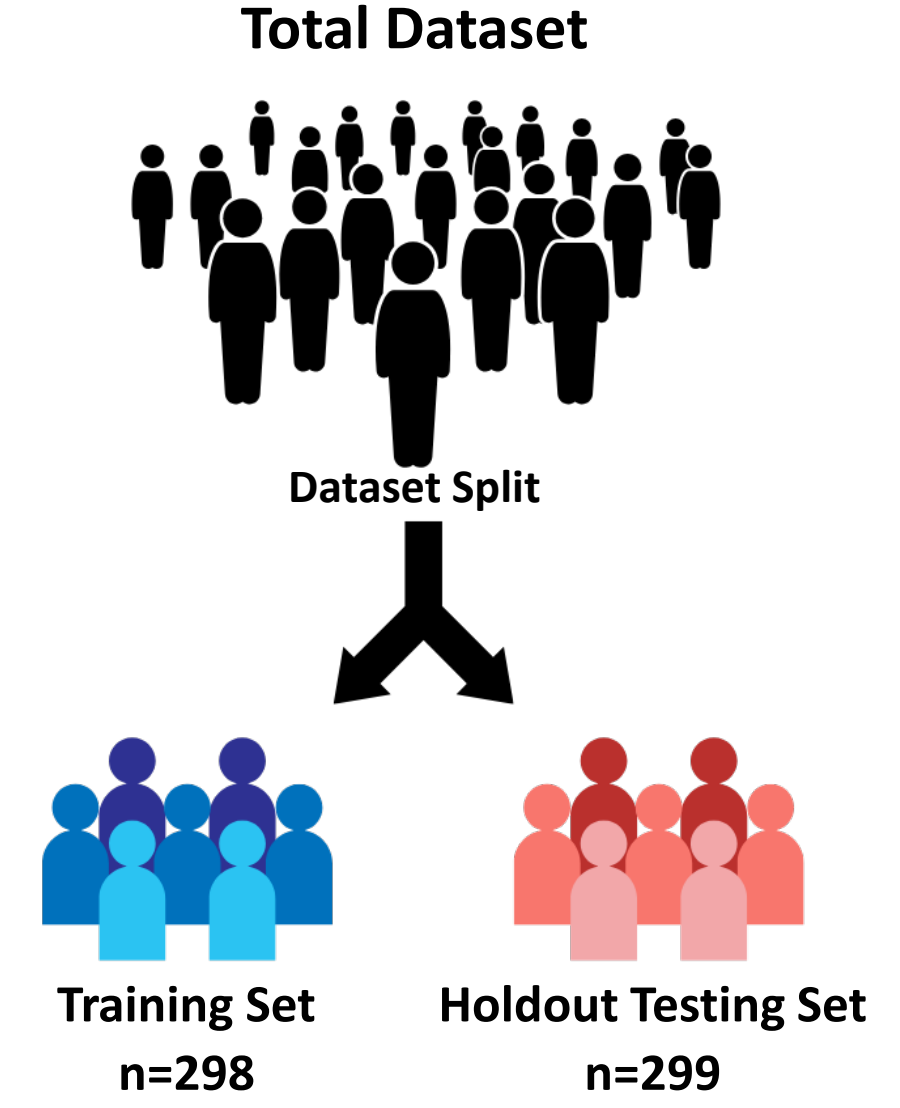
PERPHENAZINE PREFERENTIAL RESPONSE PERSONA

n=60 (20 P, 40 O) p=0.037, Cohen's D=0.948

- PANSS Hallucinatory Behavior: 1-3 (Ref Range 1-7)
- PANSS Suspiciousness/Persecution: 3-4 (Ref Range 1-6)
- PANSS Marder Factor Negative Symptoms: 16-21 (Ref Range 7-40)

Patients with moderate negative symptoms and mild-to-moderate hallucinations and delusions are more likely to respond to perphenazine.

2 VALIDATION OF ANTIPSYCHOTIC PREFERENTIAL RESPONSE PERSONAS

Total Dataset

Dataset Split

Training Set n=298   **Holdout Testing Set n=299**

To validate Personas, the dataset is split into a Training and Holdout Testing Sets. Personas from the Training Set that meet statistical thresholds (p<0.05, Cohen's D>0.5) are validated in the Holdout Test Set for reproducibility and feasibility.

Total: n=597 (336 Olanzapine, 261 Perphenazine)

Olanzapine: 120 Completed, 216 Failed   **Perphenazine:** 65 Completed, 196 Failed

OLANZAPINE RESPONSE

Persona 1:

Training Set: n=171
71 P [CI 147.3-231.1]; 69 O [CI 232.3-315.4]
p=0.004 , Cohen's D=0.459, characterized by:

- QOL Total Score: 0.5-3.32 (Ref Range 0.5-5.8)
- QOL Interpersonal Relations Subscale: 0-3.13 (Ref Range 0-6)
- QOL Level of Social Activity: 0-2 (Ref Range 0-6)

Holdout Testing Set: n=153
63 P [CI 177.0-265.7]; 90 O [CI 257.1-345.7]
p=0.018, Cohen's D=0.408

PERPHENAZINE RESPONSE

Persona 2: Side effect mitigation

Training Set: n=29
13 P [CI 198.7-423.7]; 16 O [CI 76.8-210.1]
p=0.010, Cohen's D=1.039, characterized by:

- Heart Rate: 46-70 (Ref Range: 46-132)
- Prolactin: 0-13.1 (Ref Range 0-197.9)
- Sitting Systolic Blood Pressure (mmHg): 82-116 (Ref Range 82-190)

Holdout Testing Set: n=17
5 P [CI 190.8-505.4]; 12 O [CI 62.4-241.3]
p=0.013, Cohen's D=1.692

CONCLUSIONS

NetraAI identifies explainable, treatment-responsive subpopulations by leveraging early-stage clinical data to optimize treatment selection. Through sub-insight learning, this approach enhances clinical trial enrichment strategies and precision psychiatry applications.