NETRAMARK Preferential Drug Response Model in a Schizophrenia Trial via an Alternative AI Method: Revisiting the CATIE Schizophrenia Trial

camh Centre for Addiction and Mental Health

SCAN ME

Joseph Geraci[1,2,3,4,5], Bessi Qorri[1], Mike Tsay[1], Christian Cumbaa[1], Paul Leonczyk[1], Larry Alphs[1], Luca Pani[6,7], James Kennedy[5]

[1]NetraMark Corp., Toronto, Canada, [2]Department of Pathology & Molecular Medicine, Queen's University, [3]Centre for Biotechnology & Genomic Medicine, Medical College of Georgia, Augusta University, [4]Arthur C. Clarke Center for Human Imagination, School of Physical Sciences, University of California San Diego, [5]Tanenbaum Centre for Pharmacogenetics, Molecular Brain Science Department, Centre for Addiction and Mental Health, [6]Miller School of Medicine, University of Miami, [7]University of Modena and Reggio Emilia

INTRODUCTION

Schizophrenia is a multifaceted psychiatric disorder with diverse etiologies and manifestations. This variability leads to widely divergent responses to antipsychotic treatments, further complicating the discovery of reliable predictive biomarkers.

Psychiatric datasets are often small and consist of highly heterogeneous patient populations, posing a significant challenge for traditional machine learning (ML) approaches, which struggle with the complexity of capturing nuanced, non-linear interactions.

OPPORTUNITY

Advances in ML techniques offer the potential to overcome these limitations by uncovering high-effect-size patient subpopulations within a clinical trial. By focusing on robust insight generation in small, heterogeneous subpopulations, these approaches can identify distinct groups of schizophrenia patients who exhibit differential responses to specific medications.

OBJECTIVES

1. Apply a novel ML approach to the CATIE schizophrenia trial dataset to identify specific patient subpopulations with differential response to specific antipsychotics.
2. Identify biomarkers and clinical features that can be used to predict drug response, laying the groundwork for precision-guiding antipsychotic selection in future clinical practice.

METHODS

DATASET

CATIE schizophrenia trial dataset (n=1600) evaluating several antipsychotics with respect to tolerability and efficacy. We utilized the perphenazine, olanzapine, and risperidone arms to build response models.

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

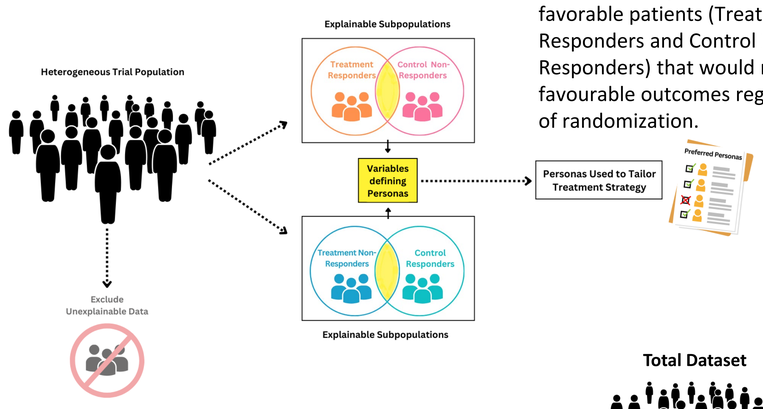
NETRAAI APPROACH

NetraAI is an advanced, mathematically-augmented AI/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. This approach doesn't attempt to explain everyone in a clinical trial – focusing only on those subpopulations that can be explained, avoiding overfitting and minimizing disease biases through a unique long range memory mechanism.

For each analysis between trial arms, NetraAI categorizes the patient population into:

- Treatment Responders and Control Non-Responders
- Treatment Non-Responders and Control Responders

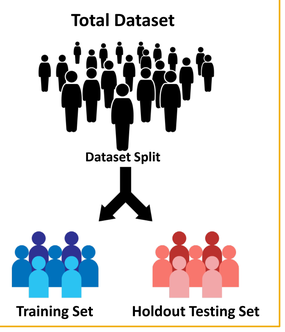
Goal: Identify variables that ***simultaneously*** characterize the favorable patients (Treatment Responders and Control Non-Responders) that would result in favourable outcomes regardless of randomization.



NetraAI is run on the Testing Set to identify subpopulations that characterize preferential response to each arm.

Surviving Personas that meet the thresholds ($p<0.05$, Cohen's $D>0.5$) are validated in the Holdout Testing Set (representing a pool of patients to replicate a clinical trial). Variable distributions are checked for normality and tests are adjusted accordingly.

This dataset splitting validates the reproducibility of these subpopulations, highlighting robustness and clinical relevance.

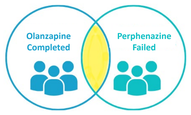


RESULTS

1 CHARACTERIZING SUBPOPULATIONS OF PREFERENTIAL RESPONSE TO OLANZAPINE OR PERPHENAZINE

Using the olanzapine and perphenazine arms (**n=597**; 336 Olanzapine, 261 Perphenazine), the patient subpopulation was characterized as Perphenazine Failed/Olanzapine Completed (PFOC; n=316) or Perphenazine Completed/Olanzapine Failed (PCOF; n=281) with respect to time to failure, to identify variables that characterize preferential response.

OLANZAPINE PREFERENTIAL RESPONSE

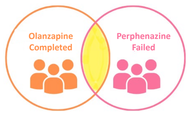


Persona 1: n= 220 (100 Perphenazine, 120 Olanzapine)
p=0.0031, Cohen's D=0.577, characterized by:

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

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

PERPHENAZINE PREFERENTIAL RESPONSE



Persona 2: n=60 (20 Perphenazine, 40 Olanzapine)
p=0.037, Cohen's D=0.948, characterized by:

- PANSS Hallucinatory Behavior between 1-3 (Ref Range 1-7)
- PANSS Suspiciousness/Persecution between 3-4 (Ref Range 1-6)
- PANSS Marder Factor Negative Symptoms between 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 IDENTIFYING EXPLAINABLE SUBPOPULATIONS WITH PREFERENTIAL RESPONSE TO PERPHENAZINE OR OLANZAPINE

In the CATIE schizophrenia trial, olanzapine showed the strongest overall response and longest time to treatment failure. Our models identified multiple replicating personas associated with olanzapine response, which will be detailed in forthcoming publications. Here, we focus on identifying subpopulations responsive to perphenazine or risperidone, defined by specific variable sets. Although these arms had shorter times to failure, some patients did benefit. To validate findings, the dataset was split: 50% for training, surviving personas were tested in a 50% holdout set, and the full dataset was used to estimate the total number of responsive patients.

PERPHENAZINE & OLANZAPINE

n=597 (336 Olanzapine, 261 Perphenazine)
Olanzapine: 120 completed, 216 failed
Perphenazine: 65 completed, 196 failed

Persona 3: Side effect mitigation

- **Training Set (n=298)**: n= 29
  13 Perphenazine [CI 198.77-423.69]
  16 Olanzapine [CI 76.81-210.14]
  p=0.0104, Cohen's D=1.0391, characterized by:
  - Heart Rate 46-70 (Ref Range: 46-132)
  - Prolactin 0-13.1 (Ref Range 0-197.9)
  - Systolic Blood Pressure – Sitting 3 min (mmHg) 82-116 (Ref Range 82-190)
- **Holdout Testing Set (n=299):** n=17
  5 Perphenazine [CI 190.80-505.40]
  12 Olanzapine [CI 62.41-241.30]
  p=0.0129 Cohen's D=1.6923
- **Total Dataset (n=597):** n=29
  13 Perphenazine [CI 197.46-423.42]
  16 Olanzapine [CI 76.68-213.61]
  p=0.0112 Cohen's D=1.0533

PERPHENAZINE & RISPERIDONE

n=602 (261 Perphenazine, 341 Risperidone)
Perphenazine: 65 completed, 196 failed
Risperidone: 88 completed, 253 failed

Persona 4: Lower health burden & dopaminergic aspects

- **Training Set (n=301):** n=49
  18 Perphenazine [CI 179.22-369.66]
  31 Risperidone [CI 88-195.57])
  p=0.0138, Cohen's D=0.7639, characterized by:
  - # Active Medical Diagnoses 0-1 (Ref Range: 0-6)
  - Major Depression Present in Past 5 Years 0 (Ref Range 0-1)
  - Drug Abuse 1 (Ref Range 0-1)
- **Holdout Testing Set (n=301):** n=23
  10 Perphenazine [CI 159.42-420.10]
  13 Risperidone [CI 71.38-237.20]
  p=0.0440 , Cohen's D=0.9132
- **Total Dataset (n=602):** n=49
  18 Perphenazine [CI181.11-369.88]
  31 Risperidone [CI 87.79-196.48]
  p=0.0104, Cohen's D=0.8085

RISPERIDONE & OLANZAPINE

n=677 (341 Risperidone, 336 Olanzapine)
Risperidone: 88 completed, 253 failed
Olanzapine: 120 completed, 216 failed

Persona 5: Lower health burden & serotoninergic aspects

- **Training Set (n=338)**: n=21
  10 Risperidone [CI 180.1-409.47]
  11 Olanzapine [CI 35.45-131.09])
  p=0.0024, Cohen's D=1.3795, characterized by:
  - # Active Medical Diagnoses 0-1 (Ref Range: 0-8)
  - Major Depression Present 1 (Ref Range 0-1)
  - Diastolic Blood Pressure – Sitting 3 min (mmHg) between 50-72 (Ref Range 50-118)
- **Holdout Testing Set (n=339): n=9**
  5 Risperidone [CI 298.80-513.20]
  4 Olanzapine [CI 14.00-155.00]
  p=0.0158 , Cohen's D=3.6969
- **Total Dataset (n=677):** n=21
  10 Risperidone [CI 179.76-411.69]
  11 Olanzapine [CI 35.54-131.08]
  p=0.0042, Cohen's D=1.5241

Persona 6: Antipsychotic benefits without the need for emotional blunting

- **Training Set (n=338)**: n=20
  10 Risperidone [CI 277.40-474.72]
  10 Olanzapine [CI 89.40-277.58]
  p=0.0050, Cohen's D=1.3741, characterized by:
  - Major Depression Present in Past 5 Years 0 (Ref Range: 0-1)
  - PANSS Total Score 95-133 (Ref Range 35-133)
  - PANSS Lack of Judgement & Insight 4-6 (Ref Range 1-6)
- **Holdout Testing Set (n=339): n=26**
  11 Risperidone [CI 92.36-381.38]
  15 Olanzapine [CI 173.92-388.93]
  p=0.5052 , Cohen's D=0.2677 favoring Olanzapine
- **Total Dataset (n=677):** n=46
  21 Risperidone [CI 208.21-389.86]
  25 Olanzapine [CI 157.24-315.45]
  p=0.2628, Cohen's D=0.3345

3 Enhancing Feature and Subpopulation Learning with NetraAI vs LLMs

To investigate whether small schizophrenia subpopulations can be separated using explainable AI-guided feature selection, we evaluated: several LLM based classification performance distinguishing PCOF vs PFOC, improvements gained by using NetraAI-derived variables, and performance using NetraAI findings tested across multiple ML algorithms. 5-fold stratified cross-validation was used, each time holding out a different 20% of the data.

Dataset: n=52 (21 PCOF, 31 PFOC) **NetraAI Relabelling:** n=10 (7 PCOF, 3 PFOC); n=11 (1 PCOF,10 PFOC); 31 No Call

Full Feature Set (Baseline): 292 clinical and behavioral features
NetraAI-Selected 4 Variables: COWAT # Correct Words Generated in Category S, QOL Curiosity, QOL Moderate Vocational Activity, QOL Extremely Restrictive Residence
NetraAI-4 Variables + Subpopulation Relabelling: Clinical trial patient acquisition is very expensive and thus small patient populations are the norm. NetraAI utilizes a novel paradigm to find the explainable subpopulations.

Model	AUC			Accuracy		
	Baseline	NetraAI 4 Var	NetraAI 4 Var + Subpop	Baseline	NetraAI 4 Var	NetraAI 4 Var + Subpop
Random Forest	0.242	0.704	1.000	0.65	0.70	0.95
Naïve Bayes	0.456	0.694	1.000	0.55	0.68	1.00
Gradient Boosting	0.297	0.574	1.000	0.40	0.56	1.00
Neural Net	0.516	0.594	0.990	0.60	0.62	0.95

NetraAI-guided feature selection and explainable subpopulation discovery significantly improved model performance across all classifiers, especially when the subgroups were relabelled and 4 variables were used.

CONCLUSIONS AND SIGNIFICANCE

OVERCOMING HETEROGENEITY: Successfully uncovered clinically meaningful subpopulations within the CATIE schizophrenia trial by isolating variable combinations that drive treatment response to overcome traditional ML limitations on small, heterogeneous psychiatric datasets.

HIGH-EFFECT=SIZE, REPLICABLE MODELS: 3 variable personas predicting preferential response to specific antipsychotics were validated via holdout.

NETRAAI-POWERED DATA LIFTING: Incorporating NetraAI variables and labeling (No Call) produced significant data lifting, improving both AUC and classification accuracy.

PRECISION PSYCHIATRY: Detailed patient profiles in the schizophrenia population, offering insights into different perspectives of the patient population that can result in differential treatment effects, providing a framework for precision psychiatry.

CLINICAL IMPACT: Offers a path to reduce trial failures and accelerate the identification of responders, guiding more successful, individualized antipsychotic selection.

POWER OF EXPLAINABLE ML FOR PSYCHIATRY: Explainable, subpopulation ML techniques have the potential to advance psychiatric research and therapeutic development.

DISCLOSURES

J.G is the founder of NetraMark and is a significant shareholder of NetraMark Holdings, which is a publicly traded company. B.Q., L.P., M.T, C.C.,P.L., and L.A. are employed by NetraMark. L.P.'s disclosures: AbbVie, USA; Acadia, USA; Alexion, Italy; BCG, Switzerland; Boehringer Ingelheim International GmbH, Germany; Compass Pathways, UK; EDRA-LSWR Publishing Company, Italy; Ferrer, Spain; Gedeon-Richter, Hungary; GLG-Institute, USA; Immunogen, USA; Inpeco SA, Switzerland; Ipsen-Abireo, France; Johnson & Johnson USA; NeuroCog Trials, USA; Novartis-Gene Therapies, Switzerland; Sanofi-Aventis-Genzyme, France and USA; NetraMark, Canada*; Otsuka, USA; Pfizer Global, USA; PharmaMar, Spain; Relmada Therapeutics, USA*; Takeda, USA; Vifor, Switzerland; WCG-VeraSci/Clinical Endpoint Solutions, USA (*options/shares).