

## **Machine learning-assisted treatment selection for smoking cessation**

John J. Curtin<sup>aff-1</sup>

<sup>aff-1</sup>Department of Psychology, University of Wisconsin-Madison

### **Author note**

Correspondence concerning this article should be addressed to .

### **Abstract**

This study found some pretty cool results that have both high impact and important clinical implications. For example ...

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## Introduction

### Precision mental health

Precision mental health is the application of the precision medicine paradigm to mental health conditions.<sup>1</sup> It addresses an important problem in traditional treatment selection: what works best at a population level does not necessarily work best for a given patient. Rather than relying on population-level efficacy, precision mental health seeks to guide treatment selection using individual difference characteristics that are likely to predict treatment success for each patient.<sup>2</sup> Successful precision mental health would increase the likelihood of treatment success for each patient because each patient receives the treatment predicted to work best for them. It would also improve treatment effectiveness rates across the population because each treatment is administered only to the patients for whom that treatment is expected to be their best option.

Researchers have pursued precision mental health – and precision medicine broadly – for decades. In medicine, emphasis on personalizing treatments has grown rapidly with the ascendancy of advanced genetic methods. Complex clinical disorders tend to be polygenic; methods like genome-wide association studies permit identifying all common genetic variants associated with a trait to create an aggregate polygenic score that incorporates a wealth of genetic information simultaneously<sup>3,4</sup>. Within precision mental health, an early example comes from the substance use disorder (SUD) domain: the Project MATCH Research Group attempted to match people with alcohol use disorder to a particular treatment based on individual differences such as gender, social support, or symptom severity<sup>5,6</sup>. Many researchers have followed in their

footsteps as the understanding has grown that neither mental health diagnoses nor treatments are one-size-fits-all<sup>7</sup>. Efforts thus far have often focused on tailoring treatments at the group level; in other words, identifying a (single) factor that divides individuals within a single diagnostic category into subgroups that can be treated differently<sup>7</sup>.

Despite these opportunities for advances, however, precision mental health research has progressed with limited success. Extant research has not yet enabled reliable recommendations for treatment selection at the level of individual patients (vs. groups). These patient-level predictions are required for clinical implementation; our goal in clinical science is to predict behavior such that we can apply findings to a new patient.

One reason for this slow progress is that many factors influence a complex clinical phenomenon like treatment success. Thus, any single feature (i.e., predictor variable) cannot account for more than a small portion of the variance in treatment success. Unfortunately, traditional analytic techniques have often limited the ability to consider more than one or a few features simultaneously. These limitations have also prevented considering concurrently features across constructs (e.g., demographics, psychological traits, environmental variables). Therefore, models have failed to capture that real-world complexity.

Moreover, because researchers using traditional analytic techniques typically develop and evaluate their precision mental health models in a single sample, the models may become very overfit to that sample. Consequently, they do not generalize well to new patients that were not used for model development. This problem is particularly concerning because clinical

implementation of precision mental health requires that these models provide accurate recommendations about treatment selection for new patients.

These pitfalls interact with each other. To capture sufficient complexity to predict treatment success, we need to increase the total number of features in precision mental health models. Incorporating more features, however, makes overfitting the data more likely. Thus, successful precision mental health requires an analytic approach that can handle high-dimensional data without becoming too overfit to generalize to new patients.

### **Applying machine learning approaches**

Applying machine learning to precision mental health research can address these limitations of traditional analytic techniques. Machine learning is an alternative analytic technique that uses statistical algorithms trained on high-dimensional arrays (hundreds or even thousands) of features<sup>8</sup>. Flexibly considering many features simultaneously means these models can tap the tangled web of constructs that comprise complex clinical phenomena. Critically, this allows researchers to consider many features in the same model – unlike previous precision mental health research that was limited to considering very few features simultaneously. This high dimensionality across and within sets of related features is necessary to explain a high portion of variance in person-level treatment success.

Although machine learning models can handle very large numbers of features, this capacity comes at a cost, referred to as the “bias-variance trade-off”<sup>9</sup>. Too many features (particularly correlated features) yield unstable models that vary strongly based on the data used

to develop them. High variance compromises model generalizability because a high variance model may not predict very accurately in new data. However, too few features (as well as other constraints on model characteristics) yield biased models that also do not predict well because they miss important predictive patterns and relationships. Machine learning uses various techniques (e.g., regularization, hyperparameter tuning, simultaneous consideration of many statistical learning algorithms) to optimize this bias-variance trade-off to accommodate high-dimensional sets of features while reducing overfitting<sup>8,9</sup>. Thus, machine learning methods allow for precision mental health models that both capture clinical complexity and generalize accurately to new data.

Finally, machine learning provides rigorous resampling techniques to fit and evaluate models in separate data<sup>9</sup>. Consequently, models generalize well to new patients because they are evaluated on out-of-sample prediction. In a simplest case, data can be divided into held-in and held-out samples. More sophisticated resampling techniques such as cross-validation involve dividing the data many times to create multiple held-in and held-out samples. These approaches offer significant advantages for 1) accurately selecting a best model among multiple model configurations, and 2) estimating how well that model will perform when applied to new data (e.g., new patients in a clinical setting). Applying machine learning can accomplish the goal in precision mental health of accurate, robust treatment selection for new patients.

## **Cigarette smoking as a critical PMH target**

Cigarette smoking could benefit greatly from combining precision mental health and machine learning. Smoking remains an enormous public health burden. Fourteen percent of U.S. adults smoke cigarettes daily, and smoking is the leading cause of preventable death, accounting for 480,000 deaths annually<sup>10–12</sup>. Despite the severity of the problem, the best available smoking cessation treatments are only modestly effective, with 6-month abstinence rates hovering around 30–35% for smoking cessation medications combined with psychosocial counseling<sup>13,14</sup>. These rates represent a best-case scenario in that clinical trial data involve treatment regimens that are rigorously followed and optimized for adherence. Additionally, because several first-line (i.e., FDA-approved) smoking cessation treatments have comparable population-level effectiveness rates, population effectiveness alone cannot guide selection among smoking cessation treatments. These facts suggest a critical need for machine learning-assisted treatment selection in the cigarette smoking domain.

To select among treatments for smoking cessation, features must exist that differentiate treatment success. Smoking cessation medications have distinct pharmacological mechanisms of action at nicotinic acetylcholine receptors (nAChRs), which may affect how helpful they are for different smokers. Nicotine replacement therapy (NRT) provides nicotine, a full agonist at nAChRs. Different NRTs provide nicotine differently. Some cigarette smokers may rely on a low, steady nicotine level from a NRT patch to replace nicotine from cigarettes. Other NRTs like gum or lozenges provide oral administration with more rapid onset, which could help individuals who

need a quick boost during craving. Other individuals who smoke may benefit from a medication like varenicline. As a nAChR partial agonist, varenicline's effect depends on surrounding neurotransmitter levels such that it can act like a NRT in the absence of other nicotine but can reduce nicotine's effects when it is present<sup>15</sup>.

Features across several behavioral or environmental domains may also guide treatment selection, alone or in combination with medication mechanisms of action. For example, some cigarette smokers may have strong cravings with good self-monitoring. These characteristics may make treatments such as nicotine lozenges or gum more effective for those people because they can get a quick "hit" of nicotine when needed. Some smokers may be prone to side effects from a specific treatment, reducing adherence and subsequent likelihood of treatment success, though they may not have had the same adverse reactions to a different treatment. Environmentally, an individual who lives with other smokers may benefit from a partial agonist treatment like varenicline because any secondhand smoke would produce less effect.

Any of these characteristics, among others, could powerfully inform treatment selection for cigarette smoking cessation. These examples illustrate the potential clinical benefit of using a precision mental health paradigm to inform treatment selection for smoking cessation. They point to the value of analytic techniques that can incorporate complex interactions among features. Although these examples were selected because they are more intuitive, there are likely other unexpected ways that treatment success differs across people. Machine learning models are not limited to intuitive or theoretically derived features. Thus, machine learning may reveal



unanticipated features that could meaningfully guide treatment selection for cigarette smoking cessation.

## **Specific Aims? / Purpose**

## **Methods**

### **Transparency & Openness**

21-word solution everything posted publicly on website preregistered aim 2 analyses CV as a way to help mitigate concerns about model building process all analyses were: 1) preregistered, 2) based on CV approaches, and/or 3) following previous work from our lab and others'

### **Data**

info on original trial/sample/treatments & cite baker et al 2016 inclusion criteria for trial, analysis inclusion criteria original trial procedure here? predictors - detailed accounting of different domains, table likely helpful outcomes

### **Analytic strategy**

#### ***Feature engineering and dimensionality reduction***

incl mmissing data

#### ***Model training and evaluation***

**Model configurations. Performance matrix. cross-validation.**

### *Evaluation of model performance*

model performance & comparisons across outcomes bayesian approach following tidymodels team recs & our previous work (ema paper), explain posterior probability distributions & credible intervals

### *Feature importance with SHAP?*

### *Evaluation of clinical benefit*

reminder preregistered primary analysis: effect of best vs. other treatment (from model) on observed abstinence (from rct) possible exploratory analyses re: comparing to grand mean (effects coding), 1/2/3 rank

## **Results**

### **Model performance**

4-week & 26-week models absolute performance (vs. 0.5) model comparison (4 v 26)

### **Feature importance?**

### **Clinical benefit**

## **Discussion**

## **References**

## **Bibliography**