Name: Christal Davis
PI Name: Henry Kranzler
Email: christal.davis@va.gov
PI Email: kranzler@pennmedicine.upenn.edu

Candidate Genes from an FDA-Approved Algorithm Fail to Predict Opioid Use Disorder Risk in Over 450,000 Veterans

Christal N. Davis, Zeal Jinwala, Alexander S. Hatoum, Sylvanus Toikumo, Arpana Agrawal, Christopher T. Rentsch, Howard J. Edenberg, James W. Baurley, Emily E. Hartwell, Richard C. Crist, Joshua C. Gray, Amy C. Justice, Joel Gelernter, Rachel L. Kember, & Henry R. Kranzler

Mental Illness Research, Education, and Clinical Center, Crescenz VA Medical Center, Philadelphia, PA, USA
Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
Department of Psychological and Brain Sciences, Washington University School of Medicine, St. Louis, MO, USA
Department of Psychiatry, Washington University, St. Louis, MO, USA
Veterans Affairs Connecticut Healthcare System, West Haven, CT, USA
Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA
Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK
Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, USA
BioRealm LLC, Walnut, CA, USA
Department of Medical and Clinical Psychology, Uniformed Services University, Bethesda, MD, USA
Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
Departments of Genetics and Neuroscience, Yale University School of Medicine, New Haven, CT, USA

As the opioid epidemic evolves, reliable, clinically relevant tools are needed to predict opioid use disorder (OUD) risk. Recently, the U.S. Food and Drug Administration (FDA) approved an algorithm designed to predict OUD risk using 15 genetic variants; however, their clinical utility has not been independently validated. Using data from the Million Veteran Program, we examined the performance of these variants in a sample of 452,664 opioid-exposed individuals (33,669 OUD cases). Participants were on average 61.2 years old (SD = 13.4), and 90.5% were male. In a logistic regression model, the 15 variants collectively explained 0.4% of the variation in OUD risk. An ensemble machine learning model using the variants correctly predicted OUD status 52.8% of the time (95% CI: 52.1 - 53.6%). Without accounting for global genetic similarity, there was consistent evidence that the algorithm distinguished OUD status based on patterns of population stratification rather than true disorder risk. Findings from this large, independent test sample suggest the candidate variants in the FDA-approved algorithm do not adequately predict OUD risk. The low predictive power of an algorithm based on these genetic variants indicates that many false positives and false negatives are expected, which could compromise care and increase stigma towards patients. Given that genetic risk models are increasingly being incorporated to guide clinical decision making, stringent validation and oversight is needed before their approval for clinical use. Improved regulatory frameworks for genomic algorithms could ensure that only robust and reliable prediction models are used to guide medical decision-making.