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

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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.