

April 4, 2024

Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Recent FDA approval of AvertD

Dear Commissioner Califf:

We, the undersigned, including experts in the fields of genetics, addiction, psychiatry, public health and device regulation, respectfully request that the FDA revoke its recent approval of AvertD, a genetic test that claims it can predict risk for opioid use disorder (OUD). Current scientific knowledge about OUD genetics is strong enough for us to state that AvertD does not predict genetic risk of OUD.

AvertD detects 15 common single nucleotide polymorphisms (SNPs). This test is based on an approach that has been abandoned by mainstream genetics.¹ The largest well-powered and state-of-the-art genome-wide studies of OUD to date demonstrate that even a full genome's worth of markers (roughly 6,000,000) is not sufficient to predict OUD in a clinically useful way.²

The claim that the gene markers underlying AvertD can predict OUD was independently evaluated by geneticists who published their findings in a scholarly peer-reviewed journal.³ This independent evaluation, using a methodology resembling the one used by AvertD's sponsor, found that the algorithm used for AvertD fell into known pitfalls of genetic prediction that give the appearance of predicting genetic risk, without being a true measure of genetic risk. With proper controls for ancestry, genetic predictors from the 15 variants used in AvertD did not predict risk of OUD any better than chance.

The harmful consequences of an invalid genetic test for OUD are clear. Patients who test negative, and their clinicians, may have a false sense of security about use of opioids.

Positive test results may also result in harmful consequences. For example, clinicians might refrain from prescribing opioids to patients who test positive, even in situations where opioids are beneficial. This problem may be magnified in minoritized populations because the gene markers underlying AvertD also show ancestral confounding (i.e., effects associated with

¹ Duncan LE, Keller MC. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry*. 2011 Oct;168(10):1041-9.

² Deak, J.D., Zhou, H., Galimberti, M. *et al.* Genome-wide association study in individuals of European and African ancestry and multi-trait analysis of opioid use disorder identifies 19 independent genome-wide significant risk loci. *Mol Psychiatry* **27**, 3970–3979 (2022); Kember, R. L., *et al.* (2022). Cross-ancestry meta-analysis of opioid use disorder uncovers novel loci with predominant effects in brain regions associated with addiction. *Nature Neuroscience*, 25(10), 1279-1287.

³ Hatoum AS, *et al.* Ancestry may confound genetic machine learning: Candidate-gene prediction of opioid use disorder as an example. *Drug Alcohol Depend*. 2021 Dec 1;229(Pt B):109115.

familial geographic origins, not OUD risk). Moreover, a substantial number of people may be wrongly labeled as prone to OUD, a highly stigmatized medical condition. These patients may face discrimination and other negative health and social consequences. Concern about false positives was one of the reasons that the FDA's own scientific advisors voted 11-2 against approval of AvertD.⁴

FDA's decision to approve AvertD despite opposition from geneticists, other experts, and from its own advisory committee, was surprising. Ironically, FDA has touted its approval of AvertD as a step toward addressing the opioid crisis. We believe AvertD may make the opioid crisis worse by contributing to overprescribing in patients who falsely test negative.

We urge you to personally review the peer reviewed publications cited in this letter. We are hopeful that after careful review you will agree with the expert consensus that that the decision to approve AvertD was a mistake, and that the approval should be rescinded.

Sincerely,

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⁴ George, J. (2022). Thumbs down for genetic test for opioid use disorder, FDA advisors say. *Medpagetoday*.
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