Re: AvertD™ genetic test for OUD risk, from SOLVD Health

To FDA Clinical Chemistry and Clinical Toxicology Devices Panel:

We understand that your panel will be evaluating the AvertD™ genetic test for OUD risk from SOLVD Health. This is a genetic test that claims to predict a patient's risk for opioid use disorder (OUD) from 15 common single nucleotide polymorphisms (SNPs). Current knowledge about OUD genetics is strong enough for it to be clear that this is impossible, because there are no variants with large enough effect size to make a set of 15 predictive of risk for OUD. Based upon the SOLVD Health website (https://solvdhealth.com/news-solvd-health-launches-genetic-risk-assessment-for-opioid-use-disorder/) the AvertD™ test appears to be the same test published Donaldson et al. in 2021, a very slightly modified version of one originally published by Donaldson et al. in 2017. We evaluated that test in detail in a scholarly, peer reviewed publication (Hatoum et al. 2021). Our evaluation demonstrated that the test was highly confounded by genetic ancestry, and that if ancestry was balanced it did not predict risk any better than chance. We have studied the genetics of OUD, and have conducted some of the largest well-powered and state-of-the-art genome-wide studies of OUD to date. The results show that among the variants on this panel, only one is supported by those studies, and that has a small effect size. That one variant's risk effect required a sample size of >80,000 for detection. Therefore, based on the best current genetic studies, any test of a few variants cannot predict OUD. Furthermore, because our analysis of the test showed a strong confound with ancestry, there is the potential that use of the test could exacerbate racial/ethnic differences in opioid prescribing.

We present some key issues below. They are more fully developed in our published, peer-reviewed manuscript, Hatoum et al. 2021.

AvertD™ is described on the SOLVD Health website as based upon "15 genetic markers involved in the brain reward pathways" and tested on "patients after their initial exposure to prescription oral opioids (n=385)." It references Donaldson et al. 2021. Essentially the same test was originally published in 2017 by Donaldson et al. The difference is that the more recent test eliminates 1 of the original 16 SNPs.

We carefully analyzed the original test (16 markers) in a larger, independent dataset, using multiple approaches parallel to the one in the Donaldson et al. papers. Key findings of our analyses (Hatoum et al. 2021) were:

- Only one of the 15 SNPs is supported by current well-powered gene discovery studies (e.g. Deak et al., 2022; Kember et al., 2022; Sanchez-Roige et al., 2021).
- None of 5 different machine learning algorithms we tested predicted OUD any better than chance when ancestry of the subjects was balanced.
- The SNPs all showed large differences in allele frequency in different populations.
- Due to the population differences in allele frequency, when given mixtures of European Americans and African Americans the machine learning algorithms predicted race/ethnicity rather than OUD.
- 8 random sets of 16 variants, chosen to have similar allele frequencies in those populations, produced similar biases. i.e. any SNPs at the same allele frequencies would in

fact predict race/ethnicity rather than OUD, and only appear to predict OUD if the disorder was highly confounded by race/ethnicity.

- It is not merely this set of 16 markers that was not sufficient to the task; based on the largest genome-wide studies to date – led by ourselves and our colleagues (e.g. Deak et al., 2022; Kember et al., 2022; Sanchez-Roige et al., 2021) -- even a full genome's worth of markers (roughly 6,000,000) are not sufficient to predict OUD in a clinically useful way.

For more information on this work, you can see the papers cited in our bibliography. In addition, Dr. Alexander S. Hatoum will be speaking at an FDA workshop on November 8th entitled "Risk Prediction Devices of Opioid Use and Opioid Use Disorder – Opportunities and Challenges", where he will demonstrate many of the issues discussed herein and engage in broader discussion.

We urge your panel to carefully review the consensus on the genetics of OUD and the published work on algorithmic bias in genetic prediction of opioid use disorder. Given that the original training procedures seem to preferentially predict membership in subpopulations of minoritized populations rather than OUD, such tests are not only of no predictive utility and give a false sense of confidence; they could lead to widespread harm by biasing decisions about the treatment of pain.

Sincerely,

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*Note: The opinions expressed are our own, and do not necessarily represent those of any affiliated group, institution, or organization.*

**Bibliography**


Deak JD, Zhou H, Galimberti M, Levey DF, Wendt FR, Sanchez-Roige S, Hatoum AS, Johnson EC, Nunez YZ, Demontis D, Børglum AD, Rajagopal VM, Jennings MV, Kember RL, Justice AC, Edenberg HJ, Agrawal A, Polimanti R, Kranzler HR, Gelernter J. 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. Molecular Psychiatry. 2022 Jul 25: doi: 10.1038/s41380-022-01709-1. Online ahead of print. PMID: 35879402.

Donaldson K, Cardamone D, Genovese M, Garbely J, Demers L. Clinical Performance of a Gene-Based Machine Learning Classifier in Assessing Risk of Developing OUD in Subjects Taking Oral Opioids: A Prospective Observational Study. Ann Clin Lab Sci. 2021 Jul;51(4):451-460. PMID: 34452883.

Donaldson K, Laurence D, Taylor K, Lopez J, Chang S, 2017. Multi-variant genetic panel for genetic risk of opioid addiction. Ann. Clin. Lab. Sci. 47, 452–456. PMID: 28801372

Hatoum AS, Wendt FR, Galimberti M, Polimanti R, Neale B, Kranzler HR, Gelernter J, Edenberg HJ, Agrawal A. Ancestry may confound genetic machine learning: Candidate-gene prediction of opioid use disorder as an example. Drug and Alcohol Dependence. 2021 Dec 1;229:109115. PMID: 34710714

Kember RL, Vickers-Smith R, Xu H, Toikumo S, Niarchou M, Zhou H, Hartwell EE, Crist RC, Rentsch CT, Million Veterans Program, Davis LK, Justice AC, Sanchez-Roige S, Kampman KM, Gelernter J, Kranzler HR. Cross-ancestry meta-analysis of opioid use disorder uncovers novel loci with predominant effects in brain regions associated with addiction. Nature Neuroscience. 2022 Sep 28:1-9. PMID: 36171425

Sanchez-Roige S, Fontanillas P, Jennings MV, Bianchi SB, Huang Y, Hatoum AS, Sealock J, Davis LK, Elson SL, Palmer AA. Genome-wide association study of problematic opioid prescription use in 132,113 23andMe research participants of European ancestry. Molecular psychiatry. 2021 Nov;26(11):6209-17. PMID: 34728798