AvertD Qualitative Genotyping Test From SOLVD Health To Predict Opioid Use Disorder Risk Does Not Seem Plausible

Testimony Before the Food and Drug Administration's Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee

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Public Citizen opposes Food and Drug Administration (FDA) marketing authorization of the AvertD test (hereafter AvertD) for identifying patients at increased genetic risk of opioid use disorder (OUD) prior to the first prescription of oral opioids for acute pain.

We share the following concerns expressed by the FDA:

> [N]umerous factors impact the interpretation of the test performance and raise uncertainty about the applicability of the observed clinical trial study test results in the intended population.[1]

We agree, for example, that there are concerns about the standardization of data collection across study sites, and the reliance on years-past self-reports and medical record abstractions. We also note that the study population was racially homogenous (92% white).[2]

However, our main concern about this test's effectiveness is its reliance on flawed predictive modeling, flawed because of the limits of genetic markers to predict OUD risk and because it was highly confounded by genetic ancestry.

These concerns were summarized in comments submitted to this committee by researchers Alexander Hatoum and colleagues, who stated the following:

> Current knowledge about OUD genetics is strong enough for it to be clear that [predicting a patient's risk of OUD using AvertD] is impossible, because there are

[1] Food and Drug Administration. FDA executive summary: Prepared for the October 20, 2022 meeting of the Clinical Chemistry and Clinical Toxicology Panel, DENxxxxxx, AvertD, SOLVD Health. https://www.fda.gov/media/162373/download. Accessed October 19, 2022. PDF p. 42.
[2] *Id.* PDF p. 28.

> no variants with large enough effect size to make a set of 15 [genetic markers] predictive of risk for OUD.[3]

They further noted that "even a full genome's worth of markers (roughly 6,000,000) are not sufficient to predict OUD in a clinically useful way."[4]

Notably, Hatoum et al. directly analyzed an earlier, similar version of AvertD with 16 markers and found:

(1) Only one of the 15 markers were supported by current well-powered gene discovery studies.
(2) None of the five machine-learning algorithms used for AvertD predicted OUD any better than chance once ancestry of the subjects was balanced.
(3) The markers showed large differences in allele frequency in different populations.
(4) Due to these population differences, the machine-learning algorithms used for AvertD predicted race/ethnicity rather than OUD.[5,6]

Accordingly, these researchers concluded that tests like the AvertD "are not only of no predictive utility and give false sense of confidence; they could lead to widespread harm by biasing decisions about the treatment of pain."[7]

In conclusion, we agree, and thus we encourage the committee to vote "no" on voting question 1 and urge the FDA to deny the De Novo request to obtain marketing authorization for AvertD because the device's benefits are poorly established and scientifically implausible.

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[3] Hatoum AS, Agrawal A, Edenberg HJ, Gelernter J. Comments to the FDA Clinical Chemistry and Clinical Toxicology Devices Panel, Re: AvertD™ genetic test for OUD risk, from SOLVD Health. https://www.fda.gov/media/162374/download. Accessed October 19, 2022.
[4] *Ibid.*
[5] *Ibid.*
[6] Hatoum AS, Wendt FR, Galimberti M, et al. Ancestry may confound genetic machine learning: Candidate-gene prediction of opioid use disorder as an example. *Drug Alcohol Depend*. 2021;229(Pt B):109115. PDF p. 3.
[7] Hatoum AS, Agrawal A, Edenberg HJ, Glernter J. Comments to the FDA Clinical Chemistry and Clinical Toxicology Devices Panel, Re: AvertD™ genetic test for OUD risk, from SOLVD Health. https://www.fda.gov/media/162374/download. Accessed October 19, 2022.