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December 7, 2022

Robert Califf, M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Jeffrey Shuren, M.D., J.D.
Director
Center for Devices and Radiological Health
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Opposition to marketing authorization of AvertD (SOLVD Health) for identifying patients at increased risk of opioid use disorder prior to use of opioids for acute pain.

Dear Drs. Califf and Shuren:

We write to you to strongly oppose marketing authorization of SOLVD Health's AvertD device — and any similar genetic tests — to identify patients who are claimed to be at increased genetic risk of opioid use disorder (OUD) prior to the first prescription of oral opioids for acute pain because the AvertD device fails to demonstrate reasonable effectiveness for its intended use. Most importantly, AvertD relies on the dangerously flawed assumption that there is a subset of patients at high risk of developing OUD who can be readily identified and protected by using treatment strategies to minimize or avoid the use of opioids, when in fact, because opioids themselves are inherently highly addictive, *all* patients must be considered at risk of developing OUD whenever these drugs are prescribed.

AvertD uses a proprietary machine-learning algorithm to purportedly calculate OUD risk based on the observed variation in 15 single nucleotide polymorphisms (SNPs) that the sponsor claims are "involved in the brain reward pathways that are associated with [OUD]."[1] However, AvertD does not reliably predict future OUD. AvertD's empirical sensitivity, specificity, and positive predictive value show that it fails to differentiate between individuals who subsequently develop OUD and those who do not. Moreover, to assume such risk assessments are attainable contradicts several prior genome-wide association studies (GWAS) demonstrating that simplistic genetic assays are unlikely to yield OUD risk results that are clinically useful.

[1] SOLVD Health. AvertD™: A genetic risk assessment tool for opioid use disorder (OUD). Sponsor executive summary, Clinical Chemistry and Clinical Toxicology Devices Panel meeting. October 20, 2022. https://www.fda.gov/media/162377/download. Accessed November 28, 2022. PDF pp. 11, 35.

Written comments submitted by a team of researchers from Yale University, Indiana University, and Washington University (hereafter Hatoum et al) — who had expertise spanning psychology, psychiatry, neuroscience, and genetics — for the October 20, 2022, meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel (CCCTDP) regarding the *de novo* application for AvertD authorization, highlighted serious problems with AvertD.[2] Hatoum et al's knowledge regarding GWAS focusing on substance use disorders is particularly germane for the review of AvertD because the convened membership of the CCCTDP appeared to lack such necessary expertise as was evident from their professional titles, as well as their comments and questions during the public meeting on October 20, 2022.[3]

Despite the apparent absence of genetic and computational scientists on the CCCTDP, the panel membership did appear to have deep clinical and epidemiological experience regarding the management of pain and expertise regarding brain science, including substance use disorder prevention, diagnosis, and treatment. The panel voted negatively on the following question posed to them by the FDA:

> **Voting question:** Do the probable benefits to health from use of the AvertD device outweigh the probable risks for the proposed indications, taking into account the probable risks and benefits of currently available alternative forms of detecting risk of developing OUD?[4]

The final vote on this question was 2 YES and 11 NO, strongly signaling that the panel did not believe AvertD should be marketed at this time.[5] The arguments of two advisory committee members who opposed marketing authorization of AvertD seemed especially important and were also related to the comments of Hatoum et al.

The first set of such arguments came from John Farrar, M.D., Ph.D., Professor of Epidemiology at the Hospital of the University of Pennsylvania. Dr. Farrar expressed deep concern that the sensitivity and specificity of AvertD, which were the co-primary effectiveness endpoints of the AdvertD clinical study,[6] were insufficient to establish the utility of the test as a risk indicator for OUD at the individual patient level. In particular, Dr. Farrar said the following at the October 20, 2022, meeting:

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[2] 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 November 28, 2022.

[3] Food and Drug Administration. Panel Roster. Clinical Chemical and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee. October 20, 2022. https://www.fda.gov/media/162371/download. Accessed November 28, 2022.

[4] Food and Drug Administration. Clinical Chemical and Clinical Toxicology Devices Panel questions. October 20, 2022. https://www.fda.gov/media/162372/download. Accessed November 28, 2022.

[5] Food and Drug Administration. Summary minutes. Center for Devices and Radiological Health. Medical Devices Advisory Committee. Clinical Chemistry and Clinical Toxicology Devices Panel. October 20, 2022. https://www.fda.gov/media/162982/download. Accessed November 28, 2022. PDF p. 24.

[6] SOLVD Health. AvertD™: A genetic risk assessment tool for opioid use disorder (OUD). Sponsor executive summary, Clinical Chemistry and Clinical Toxicology Devices Panel meeting. October 20, 2022. https://www.fda.gov/media/162377/download. Accessed November 28, 2022. PDF p. 16.

> [T]he positive predictive value [of AvertD] means that…when a positive test is achieved, you're going to be wrong 96% of the time — between 92 and 96[%], depending on what you think the prevalence is… [7]
>
> And the large negative predictive value, as I said, really is no better than not doing the test — we know already that 95 to 99% of patients are not likely to have OUD… And we need to keep that in mind, related to the fact that there are 40 to 50 million surgeries in the US every year, and so the number of possible incorrect answers is huge...[8]
>
> This test is not going to improve what should be our standard of clinical care, and it's going to end up with stigmata of positives when they shouldn't be, it's going to raise risks about what happens to people who are negative…[9]

With such poor positive and negative predictive values, AvertD clearly would provide no meaningful clinical utility.

The second set of key advisory committee arguments critiquing AvertD was voiced by Brian Bateman, M.D., Professor of Anesthesiology, Perioperative and Pain Medicine and Chair of the Department of Anesthesiology, Perioperative, and Pain Medicine at Stanford University. Dr. Bateman was particularly concerned about the criticisms articulated by Hatoum et al, as reflected in the following statements that he made during the advisory committee deliberations:

> So, I just want to draw the panel's attention to some of the points made in the letter we received in our briefing packet from [Hatoum et al]. These investigators are some of the leading human geneticists working on opioid use disorder and they make the point in their letter that they've conducted some of the largest well-powered and state-of-the-art genome wide association studies of opioid use disorder to date. And they say that current knowledge about…opioid use disorder genetics is strong enough for it to be clear that it is not possible for patients' risks for opioid use disorder to be predicted from the 15 SNPs that are included in the assay. And they point out that it's very likely that the associations that are observed in the sponsor's studies are highly confounded by genetic ancestry, and they found that when they did an evaluation of these SNPs that if ancestry is balanced, [the AvertD array of SNPs] does not predict opioid use disorder risk any better than chance alone.
>
> They cited a recent genome wide association study [published in *Molecular Psychiatry*, 2022] of individuals of both European and African ancestry looking at opioid use disorder [in which]…they pulled together seven large cohorts resulting

[7] Food and Drug Administration. Video recording of the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee meeting. October 20, 2022. https://www.youtube.com/watch?v=xwkeKYOOTZo. Accessed November 28, 2022. See approximately 6:48:06 to 6:48:29.
[8] *Id*. See approximately 6:50:19 to 6:50:47.
[9] *Id*. See approximately 6:51:43 to 6:51:57.

> in over 20,000 cases and 600,000 controls. And despite …doing a genome wide association study across all SNPs in this very large cohort and correcting for ancestry, single nucleotide polymorphisms accounted for only 3.8% of opioid use disorder variance. So, you know, I think… that study and the points [Hatoum et al] make about the potential for confounding by ancestry really calls into question…the performance of this test… If in fact their explanation is correct, which it seems likely that it is, this confounding by ancestry could exacerbate racial and ethnic differences in opioid prescribing. So, it carries really significant risks. So, I just wanted to make sure everyone had noted those points. To me they're really quite compelling.[10]

Public Citizen also emphasized in its testimony before the advisory committee on October 20, 2022, the compelling critique of AvertD provided by Hatoum et al.[11] Among the key points made by Hatoum et al were the following:

- "It is not merely this set of 16 markers [SNPs composing the original AvertD, 15 of which compose the current AvertD] 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."[12]
- "Only one of the 15 SNPs [composing AvertD] is supported by current well-powered gene discovery studies."[13]
- None of five different machine-learning algorithms used by Hatoum et al to independently test AvertD "predicted OUD any better than chance when the ancestry of the subjects was balanced" between the OUD and non-OUD groups.[14] Five different machine algorithms were tested by Hatoum et al because these algorithms represented machine-learning approaches that have been used in industry and academia and because the actual algorithm used for the AvertD is proprietary.[15]
- "The SNPs [composing AvertD] all showed large differences in allele frequency in different populations."[16]
- 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."[17]

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[10] *Id.* See approximately 6:00:05 to 6:03:05.
[11] 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 November 28, 2022.
[12] *Ibid.*
[13] *Ibid.*
[14] *Ibid.*
[15] 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 Dec 1;229(Pt B):109115.
[16] 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 November 28, 2022.
[17] *Ibid.*

These concerns led Hatoum et al to conclude that genetic 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."[18]

The empirical research conducted by Hatoum et al and others indicates that AvertD fails as a clinical test for OUD risk, and moreover, it further suggests pursuit of such a test is a "fools' errand" that flies in the face of the complexity of the OUD phenotype and its known nongenetic antecedents, and the powerful potential of opioids to trigger abuse/dependence in most people.

As one of us — Andrew Kolodny, M.D., a psychiatrist and expert on the treatment of OUD — explained at the advisory committee on October 20, 2022,[19] AvertD relies on the dangerously flawed assumption that there is a subset of patients at high risk of developing OUD who can be readily identified and protected from developing OUD by implementing personalized pain-management plans to minimize or avoid the use of opioids, when in fact, because opioids themselves are inherently highly addictive, *all* patients must be considered at risk of developing OUD whenever these drugs are prescribed.

In the early 2000s, prompted by troubling upward trends in opioid sales, opioid-related treatment admissions, and opioid-related deaths, pharmaceutical manufacturers shifted their messaging away from false claims that it is rare for their prescription opioids to trigger addiction to instead encouraging the use of risk assessment tools to allow opioid prescribing trends to continue upward while reducing OUD and overdose deaths. Those efforts failed to mitigate the negative public health effects of opioid overprescribing. That failure was based on the flawed assumption that there are some risky patients who are prone to addiction and can be readily identified and protected from bad treatment outcomes.

But that does not work. The problem with opioids is not that there are some risky patients but that the drugs themselves are inherently addictive.

A 2017 review by Bonnet and Scherbaum considered the abuse and dependence risks of opioids alongside those of alcohol and benzodiazepines (tranquilizers) and found that for every abuse/dependence characteristic reviewed, research exists showing that opioids are as or more addictive than either of these other highly addictive substances.[20]

Importantly, opioids are not like alcohol. Most of the population can be repeatedly exposed to alcohol without becoming addicted to it. There is a subset of the population that becomes addicted to alcohol; therefore, genetics are likely to play a significant role. In contrast, opioids are more like nicotine. With highly addictive drugs like nicotine and opioids, genetics play much less of a role, and exposure to the drug plays the most significant role in the development of addiction.

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[18] *Ibid.*

[19] Food and Drug Administration. Video recording of the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee meeting. October 20, 2022. https://www.youtube.com/watch?v=xwkeKYOOTZo. Accessed November 28, 2022. See approximately 4:34:28 to 4:40:59.

[20] Bonnet U, Scherbaum N. How addictive are gabapentin and pregabalin? A systematic review. *Eur Neuropsychopharmacol*. 2017;27(12):1185-1215.

Accordingly, developing a purported genetic test for assessing OUD risk is an irrational approach to address the risks associated with opioid use to treat acute pain. Instead, the appropriate public health response should be to reduce opioid use in the clinic as much as possible, and much research exists supporting that approach.

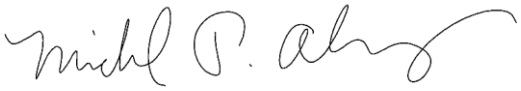
For example, a 2022 meta-analysis published in the *Annals of Internal Medicine* found that opioids were not clinically or statistically more effective in reducing pain than nonsteroidal anti-inflammatory drugs in emergency department patients with musculoskeletal pain.[21] In a separate international study of medical records from 2016-2017 related to the treatment of postsurgical pain (following appendectomy, cholecystectomy, or inguinal hernia repair), it was found that 91% of U.S. patients were prescribed opioids, whereas only 5% of non-U.S. patients received an opioid prescription. The median number of opioid pills dispensed to U.S. patients at discharge following surgery was 20, whereas in all other countries (Brazil, China, Columbia, Lebanon, Mexico, Netherlands, and Thailand) the median number of opioid pills dispensed to patients at discharge was zero.[22] These observations suggest that OUD risk in the U.S. in many cases is largely driven by unnecessary use of opioids for acute pain management.

Preventing OUD does not require a genetic test; it requires more cautious opioid prescribing. Whenever possible — which is most of the time — opioids should be avoided for treatment of acute pain. When opioids are needed for treatment of acute pain, the lowest possible dose should be prescribed for the shortest duration possible.

In closing, we urge the FDA to deny marketing authorization for AvertD — and any future marketing applications for similar genetic tests for assessing OUD risk — because the device has no clinical utility for predicting the risk of developing OUD, and it relies on the false and dangerous assumption that there is a subset of patients at high risk of developing OUD who can be readily identified.

We appreciate your attention to this important public health matter.

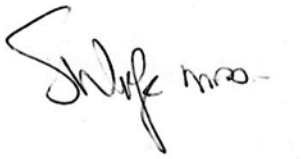
Sincerely,



Michael T. Abrams, M.P.H., Ph.D.
Senior Health Researcher
Public Citizen's Health Research Group

[21] Jones CMP, Lin CC, Jamshidi M, et al. Effectiveness of opioid analgesic medicines prescribed in or at discharge from emergency departments for musculoskeletal pain: A systematic review and meta-analysis. *Ann Intern Med.* 2022 Nov;175(11):1572-1581.
[22] Kaafarani HMA, Han K, El Moheb M, et al. Opioids after surgery in the United States versus the rest of the world: The International Patterns of Opioid Prescribing (iPOP) Multicenter Study. *Ann Surg.* 2020;272(6):879-886.

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group

Andrew Kolodny, M.D.
Medical Director, Opioid Policy Research Collaboration
Brandeis University
President, Physicians for Responsible Opioid Prescribing