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. 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.

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. 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

---

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 the decision to approve AvertD was a mistake, and that the approval should be rescinded.

Sincerely,

(In alphabetical order)

Michael T. Abrams, M.P.H., Ph.D.
Senior Health Researcher
Health Research Group
Public Citizen

G. Caleb Alexander, M.D., M.S.
Professor
Department of Epidemiology
Bloomberg School of Public Health
Johns Hopkins University

Allison Ashley-Koch, Ph.D.
Professor
Departments of Medicine, Biostatistics and Bioinformatics and Molecular Genetics and Microbiology
Duke Molecular Physiology Institute
Duke University Medical Center

Jane C. Ballantyne, MD, FRCA
Professor, Anesthesiology and Pain Medicine
University of Washington

Peter B. Barr, PhD
Assistant Professor
Department of Psychiatry and Behavioral Sciences

SUNY Downstate Health Sciences University

**Tim B. Bigdeli, Ph.D.**
Assistant Professor of Psychiatry & Behavioral Sciences
SUNY Downstate Health Sciences University

**Hilary Coon, PhD**
Professor, Department of Psychiatry
University of Utah School of Medicine

**Jean Crowell Beckham, Ph.D.**
Professor in Psychiatry and Behavioral Sciences
Co-Division Director of Behavioral Medicine and Neurosciences
Duke University School of Medicine

**Danielle M. Dick, Ph.D.**
Director, Rutgers Addiction Research Center
Greg Brown Endowed Chair in Neuroscience
Professor, Department of Psychiatry, Robert Wood Johnson School of Medicine

**Anna R. Docherty, PhD, LP**
Associate Professor, Department of Psychiatry
Associate Course Director, NINDS R25 Advanced Statistical Workshop
Faculty, Center for Genomic Medicine
Assistant Director, Clinical and Translational Research Institute
University of Utah School of Medicine
Huntsman Mental Health Institute

**Gary Franklin, MD, MPH**
Research Professor
School of Public Health
University of Washington

**Adriane Fugh-Berman MD**
Professor of Pharmacology and Physiology
Georgetown University Medical Center

**David N. Juurlink, MD, PhD, FRCPC, FAACT, FACMT**
Professor of Medicine, Pediatrics and Health Policy, Management and Evaluation
Division Director, Clinical Pharmacology & Toxicology, Department of Medicine
University of Toronto

**Anna Lembke, MD**
Professor of Psychiatry and Addiction Medicine
Stanford University School of Medicine
Alexander S. Hatoum, Ph.D
Research Assistant Professor
Psychological & Brain Sciences
Washington University in St. Louis

Rachel L. Kember, Ph.D.
Assistant Professor of Psychiatry
University of Pennsylvania

Nathan A. Kimbrel, PhD
Associate Professor & Clinician Investigator
Department of Psychiatry and Behavioral Sciences
Duke University School of Medicine & Durham VAHCS
Clinical Core Co-Director & Assistant Director, Genomics Research Laboratory
Mid-Atlantic Mental Illness Research, Education, and Clinical Center

Andrew Kolodny, MD
Medical Director, Opioid Policy Research Collaborative
Institute for Behavioral Health
Schneider Institutes for Health Policy & Research
Heller School for Social Policy & Management
Brandeis University

Henry R. Kranzler, MD
Professor of Psychiatry
University of Pennsylvania Perelman School of Medicine

J. John Mann MD
Paul Janssen Professor of Translational Neuroscience in Psychiatry and Radiology
Director, Molecular Imaging and Neuropathology Division
Department of Psychiatry
Co-Director Columbia Center for Prevention and Treatment of Depression
Columbia University/New York State Psychiatric Institute

Daphne Martschenko, Ph.D.
Assistant Professor
Stanford Center for Biomedical Ethics
Stanford University

Eric Monson, MD, PhD
Child and Adolescent Psychiatry Fellow
Department of Psychiatry
University of Utah

Rohan H.C. Palmer, Ph.D.
Associate Professor, Department of Psychology
Emory University

Renato Polimanti, PhD, MSc
Associate Professor of Psychiatry and of Chronic Disease Epidemiology
Yale University Schools of Medicine and of Public Health

Reshma Ramachandran, MD, MPP, MHS
Assistant Professor
Yale School of Medicine
Co-Director, Yale Collaboration for Regulatory Rigor, Integrity, and Transparency (CRRIT)

Sandra Sanchez-Roige, Ph.D.
Associate Professor
Department of Psychiatry, School of Medicine, UCSD
Department of Medicine, Division of Genetic Medicine, VUMC

Jon Streltzer, MD
Professor Emeritus, Department of Psychiatry
John A. Burns School of Medicine, University of Hawaii

Mark D. Sullivan, MD, PhD
Professor, Psychiatry and Behavioral Sciences
University of Washington

Patrick Sulllivan, MD, FRANZCP
Yeargan Distinguished Professor
UNC Departments of Genetics & Psychiatry
Director, UNC Suicide Prevention Institute
Professor, Karolinska Institutet, Stockholm

Michael VonKorff, ScD
Senior Investigator Emeritus, Kaiser Permanente
Washington Health Research Institute

Diana Zuckerman, Ph.D.
President
National Center for Health Research

CC:
Sen. Bernie Sanders, Chair, Senate HELP Committee
Sen. Bill Cassidy, Ranking Member, Senate HELP Committee
Sen. Ron Wyden, Chair, Senate Finance Committee
Sen. Mike Crapo, Ranking Member Senate Finance Committee
Rep. Cathy McMorris Rodgers, Chair, House Energy & Commerce Committee
Rep. Frank Pallone, Jr., Ranking Member, House Energy & Commerce Committee
Rep. Jason Smith, Chair, House Ways & Means Committee
Rep. Richard Neal, Ranking Member, House Ways & Means Committee
Sen. Mike Braun
Sen. Maggie Hassan
Sen. Joe Manchin
Sen. Edward Markey
Hon. Xavier Becerra, Secretary, HHS
Hon. Miriam E. Delphin-Rittmon, Assistant Secretary HHS, SAMHSA
Hon. Chiquita Brooks-LaSure, Administrator, CMS
Hon. Nora Volkow, Director, NIDA