SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

GENERAL AND PLASTIC SURGERY DEVICES PANEL

October 20, 2022

9:00 a.m. EST

Webcast via Zoom

Attendees:

Chairperson

Karol E. Watson, M.D.
Professor of Medicine/Cardiology – Geffen School of Medicine at UCLA

Voting Members

Wang, Ping, Ph.D., DABCC
Professor of Pathology and Laboratory Medicine – Hospital of the University of Pennsylvania

Temporary Voting Members

Wilson Compton, M.D., MPE
Deputy Director – National Institute on Drug Abuse (NIDA) – National Institutes of Health

Adam J. Gordon, M.D., MPH, FACP, DFASAM
Salt Lake City Health Care System
Professor of Medicine and Psychiatry – University of Utah School of Medicine

Timothy J. Ness, M.D., Ph.D.
Clinical Professor Emeritus – University of Alabama at Birmingham
Senior Scientist – UAB Center for Palliative and Supportive Care

Sherif Zaafran, M.D., FASA
President – Texas Medical Board
FDA Advisory Committee Member
Vice-Chair – US Anesthesia Partners Gulf Coast

Walter S. Dunn, M.D., Ph.D.
Director of Mood Disorders Clinic and Interventional Psychiatry Clinic – Greater Los Angeles, VA Healthcare Center

John T. Farrar, M.D., Ph.D.
Professor of Epidemiology, Anesthesiology and Critical Care – Hospital of the University of Pennsylvania

Anne-Michelle Ruha, M.D.
Professor of Emergency Medicine and Internal Medicine – University of Arizona College of Medicine

Brian T. Bateman, M.D.
Professor of Anesthesiology, Perioperative, and Pain Medicine – Stanford
Chair of the Department of Anesthesiology, Perioperative, and Pain Medicine – Stanford

Laura J. Bierut, M.D.
Vice Chair for Faculty Development, Psychiatry Department – Washington University School of Medicine

Lawrence S.B. Goldstein, Ph.D.
Distinguished Professor, Chairman of the Department of Neurology, Co-Director of the Kentucky Neuroscience Institute – University of Kentucky

Cheryl Walker, Ph.D.
Director – Center for Precision Environmental Health
Baylor College of Medicine

Colleen Gallagher, M.D.
Chief and Executive Director – Section of Integrated Ethics in Cancer Care
Professor, Department of Critical Care – MD Anderson Cancer Center

Industry Representative

Elijah Wreh, M.S.
Senior Manager Regulatory Affairs at Boston Scientific

Consumer Representative

Jennifer Higgins Ph.D., M.B.A
CommonWealth GrantWorks, Owner

Patient Representative

Elizabeth A. Joniak-Grant, Ph.D
Sociologist and Qualitative Research Consultant, Raleigh-Durham

Food and Drug Administration

Kellie Kelm Ph.D.
Food and Drug Administration – Silver Spring, MD
Director, Division of Chemistry and Toxicology Devices

James Swink, Designated Federal Officer

CALL TO ORDER
INTRODUCTIONS

Panel Chairperson Dr. Karol E. Watson called the meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel to order at 9:00 a.m. She noted the presence of a quorum and stated that present members have received training in FDA device law and regulations. She stated the day's agenda: to discuss, make recommendations, and vote on clinical information related to the de novo request for the AvertD test, sponsored by SOLVD Health.

Chairperson Watson then asked members of the Committee and the FDA Staff to introduce themselves.

CONFLICT OF INTEREST STATEMENT
PANEL MEMBER MEMOS
APPOINTMENT TO TEMPORARY VOTING STATUS MEMO
INTRODUCTORY REMARKS

James Swink, Designated Federal Officer, reported that no Conflict of Interest Waivers were issued for this meeting. He announced that Mr. Elijah Wreh would serve as the Industry Representative and that Doctors Brian Bateman, Laura Bierut, Walter Dunn, John Farrar, Lawrence Goldstein, Adam Gordon, Timothy Ness, Michelle Ruha, Sharif Zaafran, and Cheryl Walker were appointed to serve as Temporary Voting Members. He introduced Dr. Jennifer Higgins as the Temporary Non-Voting Consumer Representative and Dr. Elizabeth Joniak-Grant as the Temporary Non-Voting Patient Representative. He gave an overview of the Special Government Employee participants and their affiliations, noting that all appointments to the Committee were authorized by Russell Forney on September 21, 2022.

James Swink read the Appointment to Temporary Voting Status Memo and appointed Dr. Wilson Compton and Dr. Colleen Gallagher as Temporary Voting Members, the decision for which was signed by Dr. Jeffrey Sheerin on September 27, 2022. He introduced Laura J. McCarthy as the meeting's press contact and noted FDA's receipt of one written comment.

Dr. Watson acknowledged the Panel's and FDA's receipt of several additional comments submitted to the docket.

FDA PRESENTATIONS – TRAINING ON DE NOVO PROGRAM

Peter Yang, Program Lead for the De Novo Program**,** presented context on the de novo process. He distinguished between Class I, Class II, and Class III devices, underscoring that Class II devices require general and special controls and are cleared through substantial equivalents and the 510K process. He further defined a de novo request: a request that FDA formally classify the device into Class I or, most likely, Class II, based on a determination of reasonable assurance of safety and effectiveness. He clarified that if FDA grants a de novo request, new classification regulations are written for the device as a first of its kind, and it becomes the predicate device for regulating future, similar devices. To be eligible for a de novo

request, a device must be a medical device that is new and does not fit into an existing classification regulation.

Three goals must be met to grant a de novo request: to determine whether the probable benefits of the device outweigh the probable risks when the device is used as intended; to identify what the probable risks to health are for the device or product; and, based on the health risks, to determine the level of control that is needed to mitigate those risks. FDA's benefit/risk assessment acts as a basis for these determinations, which explores probable benefits and probable risks, as well as uncertainty, patient perspectives, and unmet medical needs. Also crucial is the risk mitigation table, where each identifiable risk to health is paired with specific mitigation measures. Additionally, special controls, which the device must meet to be considered for the approval, which may include analytical validation requirements, clinical validation requirements, labeling requirements, and post-market authorities, can be implemented for a device type.

Granting a de novo request allows the device to be legally marketed and serve as a predicate for future devices. FDA publishes decision summaries for transparency and also publishes any new regulations created for the device. Examples of highly specific special controls related to the 2018 de novo request for the GSP Neonatal Creatine Kinase MM Kit were provided.

Peter Yang concluded by informing the Panel that FDA is asking questions about the benefits and risks of the AvertD device and will use input from this meeting to help decide whether to grant SOLVD Health's de novo request.

FDA PRESENTATIONS – BREAKTHROUGH DEVICE DESIGNATION PROGRAM

Ouided Rouabhi, Assistant Director for Policy and Operations Team 1, provided an overview of the Breakthrough Devices Program, reviewed criteria for breakthrough device designation, and identified features of the Program. She stated that the intention of the Program is to provide patients and healthcare providers with timely access to devices that provide for more effective treatment or diagnosis of life threatening or irreversibly debilitating diseases or conditions. For certain devices that meet the program eligibility criteria, FDA expedites their development assessment and review. This:

- Facilitates interactive and timely communication between sponsors and FDA
- Prioritizes the review of marketing applications for designated devices, and
- Provides efficient and flexible approaches during review.

Criterion 1: The sponsor must demonstrate:

- A reasonable expectation of technical success, and
- A reasonable expectation of clinical success, and
- Evidence that the device will serve a representative population for an indicated life-threatening or debilitating condition.

Criterion 2:

- The device must be breakthrough technology, or

- No approved alternatives exist, or
- The device offers significant advantages over existing alternatives, or
- The availability of the device is in the best interest of patients

Upon meeting eligibility criteria and being designated a breakthrough device,

- A Data Development Plan is instituted that monitors all progress,
- Sprint Discussions occur to rapidly reach agreements on singular development issues
- Regular status updates are sent in between submissions to facilitate planning.

CLARIFYING QUESTIONS FROM THE PANEL

Dr. Goldstein asked: are the data standards for quality the same as those which would be used in drug development? **Peter Yang** answered that participants should consider standards relevant to their clinical experience and perspectives, and FDA will sort though any applicable differences in standards applied by the Committee.

Dr. Farrar asked: has the FDA approved chip technology or a combined genetic testing of some sort previous to this particular product? And if so, why doesn't this one fit into that category? **Peter Yang** responded that he cannot speak to that, but the device is considered based on a combination of the intended use and the technology, as well as the application space, and this product differs in those areas. **Dr. Farrar** followed up: are there specifications for sensitivity and specificity in genetic testing? **Peter Yang** answered that a Center-wide policy for metrics can be limiting, and solicited **Kellie Kelm**'s perspective, who relayed that there is no hard fast standard or requirement for this.

Dr. Bierut asked if, at a later time, FDA could provide examples of genetic testing guidelines as applied to other, non-OUD risk assessment tools.

Dr. Watson ensured there were no other clarifying questions or comments and prompted the Sponsor presentation.

SPONSOR PRESENTATION

Dr. Keri Donaldson, CEO of SOLVD Health, presented on his company's device, AvertD, which is designed to be used in conjunction with clinical evaluation to facilitate informed decision making regarding the prescription of oral opioids to treat acute pain. His key points included:

- Reduced prescribing of opioids has not slowed the opioid epidemic, indicating a need for more effective risk assessments.
- There are no FDA approved tools to assess genetic risk of developing Opioid Use Disorder (OUD).

- AvertD uses genetic polymorphisms involved in the brain reward pathways to detect, identify, and analyze genetic risk of developing Opioid Use Disorder after taking prescription oral opioids for acute pain.
- The machine learning algorithm followed best practices to classify individuals with OUD versus those without OUD and did not include detection of other substance use disorders or comorbidities.
- AvertD testing is simple and only requires a cheek swab and DNA extraction followed by PCR amplification performed at a CLIA-certified laboratory.
- The AvertD report indicates whether a patient has a high or low genetic risk for Opioid Use Disorder.
- The device meets pre-specified performance goals for sensitivity and specificity, and the test is 80% accurate at identifying the genetic risk.
- Identified "high-risk" patients have 18 times the odds of developing OUD after taking an oral opioid for between 4 and 30 days, suggesting AvertD is an appropriate and beneficial tool.

Dr. Donaldson also provided an overview of his company's interactions with the FDA:

- In 2018, AvertD received breakthrough device designation.
- Clinical studies were conducted in 2019.
- In 2020, the sponsor submitted a de novo request to classify AvertD as a Class II medical device with special controls; this request was declined in 2021.
- Additional analyses were performed to address FDA's remaining questions regarding study population uncertainty and applicability of results to the intended use population. Following this, the de novo request was resubmitted in June 2022.

Dr. Garbely spoke next on the sponsor's behalf. His main points included:

- Oral opioids fuel the epidemic and often open a door towards fentanyl use and drug overdose.
- Current practices involve assessing addiction risk before opioid prescription, but interviews, medical records, and questionnaires have significant limitations.
- The CDC has stated that current risk stratification tools are not sufficiently accurate to classify patients as high or low risk for abuse/misuse.
- Genes account for approximately 50% of a person's risk for addiction, in combination with environmental and developmental factors.
- Genetic mutations in the brain's reward pathway result in substance seeking behavior and often substance use disorders.
- An accurate genetic risk assessment test will better inform safe prescribing practices.

Dr. Donaldson reviewed the study design and efficacy data:

- The study was prospective with retrospective data collected on the participant's self-reported index exposure to prescription oral opioids.
- OUD diagnoses were issued in accordance with the DSM-5.
- The study incorporated sensitivity, specificity, and likelihood ratios as performance endpoints, all of which were successfully met.
- A blinded, independent statistician randomly selected participants who met predefined eligibility criteria, including an OUD diagnosis by the SOLVD Health Chief Medical Officer, ensuring random sampling of strata and participation of enough OUD-positive patients.
- 385 of 812 enrolled participants were selected to fill the strata and ensure sufficient study power.
- Sex and age stratification is consistent with patients prescribed oral opioids in the United States.
- Results showed no difference based on subgroup analyses, were consistent with the overall population, and exceeded performance goals.
- The diagnostic odds ratio for AvertD is 18.1, showing significant clinical value.
- Labeling and educational materials will clearly communicate that AvertD has limitations and is for use in informing decision making, not as a test to diagnose OUD, and should only be used in conjunction with a complete clinical evaluation.
- AvertD will require prescription and be administered by a healthcare professional.
- AvertD will be launched through a few select Centers of Excellence, whose feedback will support further development of product until it is sufficiently safe to roll out to more Centers of Excellence prior to market availability.

Christine Brower, a regulatory affairs consultant for SOLVD Health, addressed additional analyses performed to address FDA's questions from prior years. On the impact of using multiple versions of case report forms, she asserted that changes to the forms were minor and had no impact on enrollment or study outcome. On the uncertainty of self-reporting in capturing oral opioid exposure, she stated that published literature has shown that prescription records are often inaccurate, as many patients may not fill or take their prescription. To further address that concern, SOLVD collected medical records for one year before and after the self-reported index exposure to corroborate testimonies, finding 95% of participants had a procedure/event and 83% had record of a prescription. Towards uncertainty in applicability to the intended use population, especially pertaining to study site results and prevalence and impact of comorbidities. Regarding site specialization, she mentioned that three sites provided OUD treatment and most of the OUD positive participants were recruited at these sites. She presented that there were no statistically significant differences in sensitivity or specificity between study site types, indicating applicability to the intended use population. She presented data on comorbidities and confounding factors in the study population and reinforced that data showed no statistically significant differences for mental health conditions or other substance use disorders, and that AvertD is not indicated for the detection of such conditions.

Dr. Zacko provided a clinical perspective and advocated for the usefulness of AvertD. He mentioned that current risk assessments do not incorporate predisposition to addiction, are subjective, and do not incorporate genetics. As a provider, he wants access to information on genetic risk in the name of precision medicine. If he determines a patient to be low risk, he stated, he follows current standard of care; but, if a patient is high risk, he would develop a more personalized pain management plan to minimize or eliminate the use of opioids. AvertD would help him have a more informed conversation with his patients.

SPONSOR Q&A

Dr. Higgins expressed doubts about sample size and diversity in age and race within the study population, also inquiring about any age-based variation amongst comorbidities. **Chris Mullen,** a SAMHSA statistician speaking on the sponsor's behalf, responded that variations in age and comorbidity were due to change. **Dr. Higgins** also requested answers from the sponsor on what safeguards they would put in place to avoid insurance companies revoking or denying prescription coverages, for which **Dr. Brauer** cited the Genetic Information Non-Discrimination Act of 2008, adding that educational materials will make clear to patients, providers, and insurers that AvertD is non-diagnostic and does not absolutely predict OUD development.

Dr. Joniak-Grant wondered about how long it takes results to get back to the provider; **Dr. Brauer** answered 24 to 48 hours. **Dr. Joniak-Grant** asked if AvertD will be used in primary care or ERs and/or other settings; **Dr. Brauer** answered that AvertD is for use in primary care, surgery centers, surgery consultations, for dental procedures, or potentially even emergency rooms. **Dr. Joniak-Grant** also inquired about demographic data for race, ethnicity, and sex for high risk versus low risk persons, and **Dr. Brauer** responded she will work on getting that data for her. **Dr. Joniak-Grant** also wondered about who evaluated study participants and whether participants were aware that their self-reported index exposure needed to be from a prescription written to them. To these, **Dr. Brauer** responded that clinical evaluations were provided by on-site providers trained in DSM-5 criteria during the study initiation process, and that participants were aware that their index exposure had to be a prescription. **Dr. Joniak-Grant** expressed concerns about sample size and algorithm weight and bias and asked for clarification on the "18 times more likely to develop OUD" statistic. **Dr. Donaldson** weighed in that larger data sets introduce ambiguity, and their patient population size of 1300 was deliberate to permit validation for both exposure as well as standardized DSM-5 outcomes, as well as validating individual genetics. **Dr. Donaldson** displayed graphics on the pre- and post-test probabilities to clarify, and he also mentioned that out of the 1300 patients, certain groups, such as African Americans and Hispanics, were overrepresented in the weighting to make sure the algorithm's training accounts for greater genetic diversity.

Concerned about biased memories, **Dr. Dunn** asked: was information collected about how or why patients recall the use of these index exposures? **Dr. Brauer** responded that most patients had their exposure following a surgery, injury, or dental procedure. **Dr. Dunn** also asked for a review about their methods for diagnosing comorbidities, to which **Dr. Brauer**

responded that providers at the study sites were trained to review medical records closely to identify comorbidities. **Dr. Dunn** also asked whether OUD-positive patients were asked if they had any insight into the factors that caused their use disorder. In response, **Dr. Garbely** commented that opioids are likable and legal prescriptions often turn to prescription-seeking, looking in others' medicine cabinets, and eventually the use of illicit substances.

Dr. Gordon requested clarification on what constitutes mild, moderate, versus severe OUD, to which **Dr. Brauer** said she would re-present the slide after lunch and clarified that no sensitivity differences occurred between mild versus moderate and severe and mild/moderate versus severe. **Dr. Gordon** also wondered whether OUD diagnostic criteria was modified for patients currently on prescription opioids for therapy, as is standard practice. **Dr. Donaldson** responded that participants on opioid therapy chronically were excluded from the study protocol, and **Dr. Garbely** added that participants that were OUD-positive were abusing opioids, not using them as prescribed, and that those with chronic pain were excluded from the study.

Dr. Compton asked if tobacco use was incorporated into the comorbidity evaluations as it often coincides with OUD; **Dr. Brauer** responded it was not. **Dr. Compton** further inquired what a clinical evaluation would look like using AvertD, to which **Dr. Garbely** responded that the AvertD classification would be used along with the Prescription Drug Monitoring Program, medical record review, and subjective questionnaires.

Dr. Farrar asked about the rate of false positives and raised a concern about small positive predictive values, and also asked for comment on the tendency of medical professionals to rely on objective versus subjective testing, posing a risk for over-reliance on AvertD. **Dr. Donaldson** and **Chris Mullen** clarified the statistical calculations, argued that sensitivity and specificity are preferable to predictive values in this case, and re-stated that educational materials will help avoid over-reliance on AvertD. **Dr. Farrar** wondered what difference AvertD test results will make when the standard is already to prescribe as little opioid as possible; **Dr. Zacko** responded that it can help educate the patient and potentially inform the extent of surgeries ordered. **Dr. Brauer** reminded the Panel of their plans for a controlled launch through Centers of Excellence to ensure users use the product correctly.

Dr. Zaafran posed concerns about under-representation of racial minorities, to which **Dr. Brauer** said that there was no difference in test performance based on race or ethnicity amongst the small sample size and announced the company's commitment to further evaluating AvertD in African Americans in the post-market setting. **Dr. Zaafran** also wondered if a "high risk" indication could develop stigma and lead to under-treatment of acute pain; he also asked if there was any delineation between different types of or amounts of opioids used by study participants, to which **Dr. Brauer** responded there was not an investigation into those delineations.

Time ran out, but **James Wang** gave Committee members an opportunity to ask their questions for response after the Open Public Hearing. **Dr. Ness** wondered if any information was collected on first-degree relatives to determine if the test is better than clinical history or may be missing genes; **Dr. Brauer** responded no. **Dr. Wang** requested more specific

information on how AvertD can be combined with clinical information and on future studies in development. **Dr. Zacko** restated clinical implications and added that two pieces of data are more powerful than one, and **Dr. Garbely** said this does not replace the standard of care, but rather adds to it by allowing for a more nuanced conversation. **Dr. Walker** noted that the study was underpowered to see differences between race and ethnicity; **Dr. Brauer** confirmed this. **Dr. Bierut** found that the intended use population seems to be the general population but pointed out that the study population is not representative of the general population; **Dr. Brauer** disagreed on the basis that patients were enrolled during regular clinical visits. **Dr. Goldstein** requested the exact number of African Americans in the study and the frequency of those who declined to participate. **Dr. Brauer** responded 14 African Americans were included and no data was collected on those who declined to participate. **Dr. Bateman** wondered why the sponsors did not use already-developed methods to account for genetic admixture in their algorithm, and also wondered why Genome-Wide Association Studies have not identified the 15 SNPs used by AvertD; **Dr. Donaldson** provided literature in support of the 15 SNPs and outlined their unsupervised dimensionality reduction approach to attempt to account for admixture. **Dr. Donaldson** also responded that mean allele frequencies were used to try to balance the algorithm.

FDA PRESENTATION

Dr. Keisha Gussow presented a summary of the device, of the regulatory review process and device's regulatory history, and of Opioid Use Disorder. She also summarized data from the sponsor in support of the de novo requests. Overall, she cited several factors that contribute to the uncertainty in whether the observed clinical study results accurately represent the device's performance in the intended use population for the test: uncertainty in how the study was designed, including the enrichment strategy of enrolling subjects from opioid treatment program site and grouping subjects into high and low risk pools based on evidence of an SUD or OUD prior to selection of the subjects for inclusion in the study; uncertainty in the study population due to use of inconsistent inclusion and exclusion criteria; use of subject recall to determine index exposure as well as the enrollment of subjects who had a previous relationship with the enroller; uncertainty in the device design due to use of SNPs that are associated with comorbidities that are common in OUD positive subjects; and uncertainty in the clinical performance.

She concluded with an overview of the question for the Panel: does the clinical study population adequately represent the intended use population such that the estimates derived from the clinical study are representative of the expected performance of the device when it is marketed and used in the intended use population?

Dr. Gussow responded to two written questions. First, were performance goals of 59.5% for sensitivity and 55.5% for specificity cited by the sponsor, pre-specified by, or agreed upon by the FDA, as the minimum threshold for the device to be clinically useful? In response: the company proposed the stated performance goals prior to the submission of the de novo classification request. FDA did not have sufficient information at the time to assess the proposed goals. FDA is now seeking the panel's input on the clinical significance of the study, results in

performance, including the sensitivity and specificity estimates. Secondly, does the FDA have concerns about the study design and what type of patients were enrolled by the inclusion criteria of retrospective self-reported opioid exposure? In response: FDA is seeking the panel's input on questions along these lines. That is, the study design and the representativeness of the clinical study population of the intended use population.

Dr. Gussow also explained FDA thinking on polygenic risk scores, saying that FDA does not have a singular expectation for performance in this area and assesses based on intended use. She finished by responding to an earlier question about the REMS, Risk Evaluation and Mitigation Strategy, Program, asserting that this is not in scope for the day's discussion.

FDA Q&A

Dr. Walker asked if FDA took into consideration the possibility that predictive capacity was negatively influenced by genetic ancestry; **Dr. Gussow** responded the Panel is to consider this question. **Dr. Goldstein** asked if FDA determined the number of patients that declined to be tested; **Dr. Gussow** said no. **Dr. Goldstein** asked if approval of AvertD could likely lead to genetic testing requirements prior to prescribing opioids; **Dr. Kelm** said the FDA declines to comment in this area.

Dr. Dunn asked if a patient's second time receiving prescription opioids would be considered off-label use of AvertD; **Dr. Gussow** responded yes. **Dr. Dunn** requested more information on the breakdown of research versus clinical duties performed at the test sites; **Dr. Gussow** said FDA does not have that information.

Dr. Farrar asked if FDA calculated positive predictive values for the estimated prevalence of the disorder in the group, and whether it uses positive predictive value in its assessment of the potential benefits of particular diagnostic tests; **Dr. Gussow** and **Dr. Kelm** both responded that this information was not reliably obtainable, so sensitivity and specificity were chosen as performance metrics.

Dr. Bateman referenced a study suggesting that AvertD is highly confounded by genetic ancestry that also found the 15 SNPs do not predict risk better than chance, soliciting FDA thoughts. **Dr. Gussow** responded that she hopes the Panel will weigh in on this.

Dr. Watson announced a lunch break after the conclusion of the FDA Q&A.

LUNCH BREAK
OPEN PUBLIC HEARING

Dr. Watson reconvened the meeting at 1:15 p.m. **James Swink** read the Open Public Hearing Disclosure Process Statement. 19 requests to speak were heard.

Dr. Andrew Kolodny expressed his belief that the problem with opioids is not that there are some risky patients, it is that the drugs themselves are inherently addictive, and genetic

screening tools are essentially useless when exposure to the drug is the problem. He ambiguously cited a paper saying that NSAIDs are as effective as opioids for emergency room acute pain treatment. Finally, he pointed out that many other countries don't prescribe opioids at all.

Dr. Michael Abrams pointed out flaws in the predictive modeling for AvertD, largely related to confounds in ancestry, urging FDA to deny the de novo request on the basis that the device's benefits are poorly established and the device suggestion is scientifically implausible.

Dr. Suzet McKinney expressed a desire for novel ways to approach the opioid epidemic and advocated for the potential usefulness of AvertD.

Dr. Brand Newland also believes a pre-therapy risk assessment would be clinically beneficial, as genetics play a role in addiction, and an informed decision is always preferable to an uninformed one. He also stated there is no stigma associated with this device, purely patient empowerment.

Dr. Kamran Hamid spoke on how addiction is suffering and this technology can help prevent suffering.

Dr. Eric Fox expressed his belief that, especially in Florida, and especially as a maxillofacial surgeon, he would find this test clinically useful to alleviate the opioid crisis.

Dr. Guillermo Chacon relayed that this device could potentially be useful for teens receiving wisdom teeth extraction and/or orthodontics and advocated for device approval.

Rich Jones gave his account of recovering from his own OUD, asserting that patient education before reaching the point of dependency is crucial in preventing misuse of opioids. He finds AvertD to be useful in facilitating pre-emptive conversations between patients and physicians.

Ken Kaufman described his son's journey with prescription opioids, eventually causing his death from heroin. He said that if AvertD had identified his son as high risk, he would have never allowed him to take prescription opioids, and his son might still be alive.

Jodi Barber also lost her son and other acquaintances to overdoses, none of whom were asked about their genetic predisposition to addiction prior to prescription. She highlighted an immediate need for AvertD technology in clinicians' repertoire.

Ken Daniels also lost his son to fentanyl and would have had his son tested if AvertD had been available, saying that knowledge would have been priceless.

Megan Barry lost her son to overdose and, as a parent, would see AvertD approved in order to give her child every fighting chance when it comes to fighting disease.

Whitney Kannaka had her family destroyed by opioid addiction and feels her story may have ended differently if a cheek swab could have told her husband he was prone to addiction. She asserted that all tactics to prevent abuse should be utilized, calling AvertD approval a 'no brainer.'

Chris Fox, from an insurer's perspective, wants to make sure patients with predisposition to OUD get special access to non-opioid based therapies.

Joe Janasek touted AvertD as a patient-centered approach that will empower patients with knowledge to facilitate better healthcare choices.

Cal Beyer recounted his journey misusing opioids, and he expressed that an easy-to-use swab device can help prevent addiction, especially for opioid-naïve patients.

Brett Large advocated for construction workers who often do not get a choice in their pain management plan after being injured on the job. He finds AvertD low-risk and said the device will allow for better decision-making via its proactive approach.

Bradley Sorte urged FDA to authorize AvertD in the name of awareness and early intervention.

Jeff Horwitz touted the major advantage of AvertD as patient education and empowerment, stating that his organization, Safe Project, strongly urges FDA to approve the use of AvertD.

Dr. Watson announced the Open Public Hearing portion of the meeting to be officially closed and began Panel Deliberations.

PANEL DELIBERATIONS

Dr. Walker requested clarification on the number of African Americans. **Dr. Donaldson** said that 14 African Americans were in the clinical study population, but 30% of the training and learning data set was African American.

Dr. Compton raised concerns about potential risks of over-prescribing in the face of low-risk patients, touting this as much bigger than a patient issue. **Dr. Donaldson** simply responded that, in a survey of physicians, 40% of prescribers are not performing risk assessments prior to prescribing, and this is where he sees AvertD fitting in.

Dr. Dunn posed a question to his colleagues: should there not be a greater incidence of comorbidities even at time of opiate exposure. **Dr. Bierut** agreed that comorbidities are incredibly common in people with substance use disorders, and **Dr. Compton** agreed and assumed that the sponsor's low detection of comorbidities is due to a simple medical history review rather than a comprehensive patient evaluation. **Dr. Brauer** presented additional data showing that in the OUD-positive subpopulation, comorbidity rates were indeed quite high for depression, alcohol use disorder, and anxiety.

Dr. Bateman cited a paper by Hatoum et al. stating that the 15 SNPs do not predict OUD better than chance, and he expressed significant concerns about confounding by ancestry exacerbating racial and ethnic differences and opioid prescribing.

Dr. Wang still wondered if the enriched study population is actually representative of the intended use population. She also commented she still does not know how other clinical tools can be combined with AvertD. She also noted that negative results may lead to a false sense of security. **Dr. Joniak-Grant** agreed strongly about the risk of "low risk" test results providing a false sense of security and causing people to go down the wrong path with opioids.

Dr. Farrar pointed out the negative predictive values are very, very high, saying that "not doing the test is a pretty good test."

Dr. Ness suggested that the language "low-risk" be taken out and replaced with "within normal limits" to mitigate false sense of security. **Dr. Donaldson** stated he is open to this and other wording changes.

Dr. Goldstein asked the sponsor why the clinical study population did not look like the American population, and **Dr. Donaldson** replied that the study population was modeled after CDC consensus documents on the population that is prescribed oral opioids in the US. **Dr. Goldstein** was skeptical of the number of people of color being that low. **Dr. Donaldson** responded that it is about half and that despite their best efforts, they were unable to achieve the target goal of 6% African American enrollment. **Dr. Mullen** reiterated that they are committed to addressing this in post-approval studies.

Dr. Zaafran also found the number of African Americans to be unacceptably low. He also pointed out that there are many ethnicities that underlie "white" and was very concerned by this lack of variability in the sample size. He expressed concerns about stigma associated with a positive result causing prescribers to frown on what is actually an appropriate use of medication, be it under-treatment or over-treatment.

Dr. Ruha, too, worried that patients will be under-treated for pain and suffer as a result.

Dr. Walker stated that the onus is on the sponsor to do corrections for genetic ancestry and prove the test is still valid before going forward with approval. **Dr. Brauer** made a counter-point that over 90% of prescribers use some form of risk assessment prior to prescribing opioids, and over 50% of surgeons are not satisfied with the tools available for risk assessment for OUD, making it of great benefit to patients to approve now. **Dr. Donaldson** reiterated that their dimensionality reductions do not cause differences in classification by ancestry across huge in silico data sets and that they have validated their data, exposures, populations, and results.

Dr. Bierut expressed doubts about the validity of the study and the implementation of the study. She is concerned that physician and patient behavior will change unpredictably in the face of test results, and she would like to see their proprietary combination for weighting the SNPs validated in a second data set.

Dr. Gallagher wondered if there is overlap between these 15 SNPs and other conditions; she does not think it can be known with certainty that AvertD is using the correct 15 SNPs. She also asked the sponsor when they expect to have enough data that they will know the test has to change in some way. **Dr. Donaldson** answered that the data sets are big enough to be representative but small enough to be validated, and that is where the confidence in the 15 SNPs

arises; he also noted that the 15 genes are combined in around 1600 ways to give differential divisions between populations, and he showed how the 15 relate to each other. **Dr. Donaldson** also commented that this is a work in progress and, at this stage, needs market approval to further refine the algorithm and predictive capacity.

Dr. Joniak-Grant wondered how positive results may translate to assumptions that people have addictive personalities, so to speak, and wonders what impact that may have beyond just opioid procurement, such as future medical decisions for children of a positive test holder and altered prescribing behavior for other medicines. She expressed concerns for the safety of those who refuse the genetic test. She seconded the use of alternate language rather than high risk/low risk, as this suggests the test can definitively predict risk, but it cannot. Finally, she noted that if 20% of cases can be expected to be an error, that this does not constitute an informed decision.

Dr. Higgins wondered why the sponsor used subjects who were with practitioners that knew them; **Dr. Brauer** responded that patients were asked to participate during routine visits in an effort to eliminate potential bias in patient selection. **Dr. Higgins** expressed a further concern regarding geographical bias towards the eastern part of the country.

Dr. Walker seconded **Dr. Bierut**'s earlier point about discrimination potential upon being labeled high risk. **Dr. Walker** also wondered if the sponsor agreed that since the study was underpowered to look at race and ethnicity, it is unlikely it could have been challenged by genetic ancestry. **Dr. Donaldson** again reinforced their weighted model to account for this and that the study also employed large in silico data sets derived from consensus allelic frequencies worldwide to avoid excessive confounding from ancestry.

Dr. Farrar said having a test would be wonderful, but that this is not the test because of the low positive predictive value. Upon request from **Dr. Walker**, **Dr. Farrar** clarified his calculations for the positive predictive value and emphasized that sensitivity/specificity are not adequate measures when a test is looking for something that is relatively rare. **Dr. Farrar** also reinforced that opioid sparing techniques should always be employed, so the most likely change in physician behavior will be stigmatizing people with positive results.

Dr. Dunn reiterated that this tool is too nuanced to be emitting a readout that simply says "high risk" or "low risk", and that significant physician education would need to occur in order for the test to not be harmful.

Dr. Bateman mentioned the contradictory GWAS study, again, and **Dr. Donaldson** reiterated that their study was different in methodology and veracity, and it should not be expected that the same results would be reported. **Dr. Bateman** wondered if there are examples of machine learning approaches applied to candidate genes with high predictive values for other complex traits; **Dr. Donaldson** said yes and gave schizophrenia as a example.

Dr. Higgins asked, rhetorically, if the uninsured would have access to the test, and, if so, if public benefits would pay for this.

Dr. Farrar remained concerned that this test, with a seemingly more objective presentation, will gain too much traction over subjective testing, leading it to be adopted where it shouldn't be.

Dr. Joniak-Grant expressed her final concern that there has been a lot of talk about the importance of training and education, but no explicit details have been provided at all.

Dr. Watson ensured that all participants had spoken their questions, comments, and concerns before prompting the FDA to pose their questions to the Panel.

FDA QUESTIONS

Question One

As described in the FDA and sponsor executive summaries and Panel presentations, there are several factors that contribute to the uncertainty in whether the observed clinical study results accurately represent the device's performance in the intended use population. For the test, for each of the following factors, please discuss its impact on a) Clinical study subject enrollment and the resulting clinical study population, b) Clinical study test performance interpretation, c) Applicability of the study results to the intended use population.

> **A:** Use of different CRF versions during the study to collect the data, including completion of an additional CRF after study completion to support the subjects met the inclusion and exclusion criteria specified in the protocol.
> **B:** Confidence with which the study excluded subjects whose index oral opioid exposure was illicit and or for treatment of chronic pain.
> **C:** Recruitment of subjects both from treatment sites and from non-treatment sites.
> **D:** Determination of index oral opioid exposure based on subject recollection and the additional information available in the medical records and histories at enrollment sites.
> **E:** Assignment to a risk pool based on SUD and OUD status, absence of OUD positive subjects in the low risk pool, and subsequent use of risk pools to select study participants.
> **F:** Demographic makeup of the study population with regard to race, ethnicity, age, and sex.

Towards A, **Dr. Farrar** found the CRF differences, while not ideal, make little difference to study design and quality; **Dr. Dunn, Dr. Gordon,** and **Dr. Compton agreed.**

Towards B, **Dr. Joniak-Grant** stated that she feels fairly confident in the study's exclusion criteria but would feel more confident with additional data collected outside the enrollment sites. **Dr. Zaafran** expressed his concerns that there is too much selection bias in the study design and is not confident. **Dr. Farrar** and **Dr. Gallagher** are also concerned about the validity of exclusion criteria. **Dr. Compton** felt reasonably confident because of the sponsor's corroboration of medical and prescription records, and **Dr. Watson** agreed with this.

Towards C, **Dr. Farrar** worries about potential bias introduced by the need to enrich the population with OUD patients. **Dr. Wang** felt very unconfident about the study design and the populations of mild/moderate/severe being unable to mirror the intended use population. **Dr. Gordon** echoed this, as did **Dr. Watson. Dr. Compton** added that the recruitment strategy should have the number of mild/moderate outnumber the severe cases to mirror intended use population.

Towards D, **Dr. Higgins** noted that family members can corroborate an opioid use patient's experience. **Dr. Dunn** does not worry about patient recall but finds the study design to inherently favor patients with strongly biasing experiences, drawing parallels to the rewards pathway. He is very concerned this retrospective component may confound AvertD's applicability in clinical use. **Dr. Joniak-Grant** thinks that while minor details may be mis-recalled by the patients, it is likely in more nuanced areas such as number of days pills were taken. She also noted that historically, opioids, like codeine, may not have been considered opioid-like by patients. **Dr. Farrar** worries that the short index oral opioid exposure period favors people who have unusually distinct memories of their experience, which is problematic. **Dr. Watson** and **Dr. Dunn** reinforced that there was considerable variability in range of past exposures. The Panel overall is concerned about biases introduced from subject recollection.

Towards E, **Dr. Dunn** feels uncertain about the categorization of high risk patients, especially pertaining to other SUDs and comorbidities that may not have been diligently collected, thus influencing categorization. He noted, however, that he does not know how to interpret this risk pooling concern with respect to study outcomes. **Dr. Compton** noted the overlap between this concern and the Panel's general concern about enrichment from using treatment sites, as that is confounded with OUD status. **Dr. Watson** and **Dr. Wang** back this observation.

Towards F, **Dr. Higgins** wants to see better subgroup analyses to be generalizable to the overall population in any future studies from the sponsor. **Dr. Joniak-Grant** finds 92% white to be unacceptable, emphasizing that the tool may be perceived to provide racial equity in treatment, but with a non-diverse study population, this would be problematic. **Dr. Gallagher** noted that the demographic was skewed by using patients at treatment centers, who are inherently more likely to be privileged racially and financially, which **Dr. Watson** noted ties into problems with recruitment procedures. **Dr. Farrar** expressed his surprise that social determinants of health were not collected for the study and that other social factors, like sexual preference, were inappropriately excluded from the consideration of an individual's risk of developing OUD. **Dr. Zaafran** expressed concerns about the ambiguity of the "white" classification, stating that there are many different ethnicities that classify as white, but the study failed to distinguish heritage to that extent. He seconded the concerns about neglecting social determinants of health.

Dr. Watson summarized the Panel's contributions to Question One.

Question Two

Given the device design, in which 15 SNPs that are associated with OUD as well as other mental health and SUDs are evaluated, and the clinical study design, please discuss the following:
A) Does the clinical study provide sufficient information to understand whether the device is detecting risk of OUD specifically or risk of OUD in addition to other comorbidities?
B) Does the information collected following initial study completion, for example, Form 3, clarify whether the device may be detecting comorbidities in the clinical study population?

Towards A, **Dr. Dunn** said the study did not provide sufficient information to conclude anything about the relationship between comorbidities and OUD. **Dr. Compton** discerned that some important comorbidities known to correlate with OUD, such as Tobacco Use Disorder, were not considered in the study; however, he is convinced that the study detected OUD accurately. **Dr. Farrar** agreed but reiterated his concern about overall bias in the study due to under-detection of comorbidities, emphasizing that the study is underpowered. **Dr. Bierut** concurred that the study detects OUD, but she is not confident that it exclusively detects OUD, as there is genetic overlap between many SUDs.

Towards B, **Dr. Ruha** and **Dr. Gallagher** expressed confidence that OUD was detected, not just comorbidities, to which no one objected.

Dr. Watson summarized the Panel's contributions: overall, OUD is detected acceptably, with some concerns about under-detection of comorbidities. **Dr. Kelm** requested the Panel's clarification on whether, given the insufficient study power they noted, it is still reasonable to conclude sufficient numbers of OUD patients. **Dr. Farrar** stated that the study should be repeated in a larger population for full confidence.

Question Three

The reported sensitivity and specificity of the AvertD test, when tested in the clinical study population, is 82.76% and 79.23%, respectively. The negative likelihood ratio is 0.22 and the positive likelihood ratio is 3.98.
A) Does the reported device performance in the clinical study population represent the probable performance of the device in the intended use population?
B) Please discuss the clinical significance of the study results including sensitivity, specificity, positive and negative likelihood ratios.
C) With the consideration that genetics is only one contributor to the overall risk of developing OUD, please describe the level of sensitivity and specificity that would be clinically acceptable for a genetic risk test for helping to identify individuals at increased risk of developing OUD.

Towards A), **Dr. Goldstein** stated it is impossible to know since the trial does not represent the long-term intended use population. **Dr. Farrar** emphasized the inadequacy of the positive predictive value, which **Dr. Walker** clarified that this value is problematic because the prevalence is so low but voiced a concern that if the high positive predictive value cannot be

good enough, then perhaps the goal is unattainable on this scale, suggesting another measure could be more appropriate. **Dr. Bateman** asked **Dr. Farrar** if, given that AvertD is for screening and not a hard fast diagnostic test, he would consider lowering his acceptable threshold for the predictive values. **Dr. Farrar** responded that screening tests must be held to a higher bar than diagnostic test and stood firm on his stance: a 99% specificity achieves 84% prediction, and a 95% sensitivity and 95% specificity achieves 50% prediction. He notes it is a difficult bar to meet. **Dr. Wang** agreed with **Dr. Farrar** and suggested using secondary tests to validate the screening test to make a screening test clinically applicable. **Dr. Compton** added that language used to interpret test results could help with some of the ambiguity around predictive values. **Dr. Compton** also expressed that he finds the study performance to be in accordance with real-world performance; he also questioned the sponsor on why they chose to power their device to detect 50-60% sensitivity and specificity, finding that value low.

Dr. Donaldson took this opportunity to reiterate that AvertD is a risk assessment test, not a screening test. He urged the Committee to understand the early stage of this technology, emphasizing that risk assessment tools start with genotyping tests in order to build predictive phenotyping models over time using information from clinical practice before an accurate predictive model can be established. **Dr. Donaldson** answered **Dr. Compton**'s question, stating that their dual performance goal was set at a threshold estimated from earlier studies to give a reliable sensitivity/specificity combination. **Dr. Donaldson** also reiterated that observed performance was much higher than the set performance goal.

Dr. Kelm reminded the Panel that AvertD is a risk assessment tool. **Dr. Farrar** worries that because of the popularity of opioid dependence prevention, the risk assessment tool will be interpreted by doctors and patients as a diagnostic or screening tool. **Dr. Kelm** solicited the Panel's thoughts on how to present this information so that it's used appropriately as a risk prediction tool rather than a screening test or a diagnostic tool, to be addressed under question six.

Dr. Dunn asserted that this device will not work in the intended use population and does not think the conversation about sensitivity/specificity necessarily applies to this type of test. **Dr. Grant** expressed concerns about large confidence intervals for data pertaining to older individuals, non-white individuals, and women, giving her significant doubts about applicability to the intended use population.

Dr. Watson summarized the contributions to part A by saying that the Panel does not know how the device will be used in real life, nor does the Panel know if the performance in the study population represents the probable performance in the intended use population.

Dr. Gordon added that the intended use population will not necessarily be seeing providers with experience treating OUD like the providers used in the study, lending further to sensitivity/specificity issues.

Dr. Farrar inquired about how AvertD could improve the over-prescribing of opioids when the solution is to prescribe as few as possible regardless of circumstances, finding test

results irrelevant to prescribing initiatives. He worries that a positive test result could prevent patients who need opioids from getting them. **Dr. Watson** found this point especially pertinent.

Towards C, **Dr. Joniak-Grant** stated she would like predictive power to be more than a coin toss. **Dr. Bierut** said she does not know but it is good to have the discussion as the technology's eventual implementation seems inevitable. **Dr. Ness** stated sensitivity/specificity cannot be adequately stated while categorizing patients into overly simplified high risk/low risk classifications. **Dr. Zaafran** stated that regardless of the numbers, the results should only be taken as risk stratification, and objective numbers could be harmful by lending too much perceived certainty to the device output. **Dr. Gordon** echoed concerns that AvertD may be given inappropriate weight because it is a genetic test, especially with more naïve providers. **Dr. Higgins** concurred, adding that the expedient nature of the test may make it prone to overuse compared to more in-depth clinical assessments. **Dr. Farrar** seconded **Dr. Ness**'s point about conveyance of results, suggesting an output for risk on a 0-10 scale, rather than a categorical high/low risk classification strategy, and mentioned this output could help facilitate clinicians' conversations with patients. **Dr. Ness** mentioned that referencing literature in the device output itself allows for flexibility over time as research advances and may bypass unnecessary regulatory issues in the future.

Dr. Watson and **Dr. Kelm** noted the eclectic opinions of the Panel and prompted Question Four.

Question Four

Please discuss the benefits and risks of genetic testing as an aid in assessing the risk of developing OUD following exposure to prescription oral opioids for acute pain.

Dr. Joniak-Grant asked the Panel for their thoughts on whether genes actually contribute 50% of the risk of developing OUD. **Dr. Bierut** contributed that this percentage is highly variable at the individual level and primarily applies at the population level. **Dr. Farrar** finds 50% to be a decent biological estimate for genetic weight in most broad considerations. **Dr. Bateman** explained that, just because 50% of the population level is explained by genetics, that's not to say that 15 SNPs account for 50% of the inter-individual variability. He cited a GWAS study to mention that only 3.8% of inter-individual variability is explained by SNPs genome wide. **Dr. Watson** underscored **Dr. Bateman**'s point.

Dr. Gallagher reiterated her concerns about patient and physician behavioral changes as a result of test interpretations and reinforced that genetic information is empowering as long as it is not relied upon too heavily. **Dr. Dunn** observed a risk that patients may feel genetic testing is necessary for precision medicine and appropriate case management, though that is not necessarily true; he also expressed a desire for test results to be erased from a patient's medical record, lest doctors use the results in an off-label manner to inform their treatment of patients who have been evaluated previously for opioid use. **Dr. Compton** praised **Dr. Bierut**'s point

and added that post-marketing evaluation will be necessary to understand the real-world behavioral changes of physicians and patients that may occur due to the use of this device.

Dr. Joniak-Grant voiced several concerns, asserting that, while contextualized information is empowering, there is a risk of under-prescribing. She worries about physician liability in the context of positive results, OUD stigma impacting future clinician interactions, and the uncertainty around institutional responses from hospitals and professional organizations. **Dr. Bateman** furthered the point that a failure to account for genetic admixture in the algorithm could create inequitable care. He urged the FDA to get input from statistical geneticists to account for admixture to ensure racial bias is mitigated.

Question Five

Taking into consideration the current methods for assessing the risk of developing OUD after exposure to prescription oral opioids for acute pain, please discuss the clinical validity of AvertD.

Dr. Bierut expressed she needs more information to have any idea about the clinical validity of AvertD.

Dr. Dunn asked the Panel members what other methods exist for assessing risk of developing OUD after obtaining an opiate prescription. **Dr. Farrar** answered that standard practices vary dramatically between institutions. **Dr. Compton** added that retrospective studies are a main, though limited, approach, and made a specific reference to the Monitoring the Future study from University of Michigan. **Dr. Gordon** mentioned that the VA has very good predictive tools for opioid-related adverse events, but not for OUD. **Dr. Farrar** noted that conflating OUD with chronic opioid use hinders study abilities. **Dr. Zaafran** voiced concerns over the risk of under-prescribing opioids to patients who need them but test at-risk, and he noted that the test would be used ambiguously in acute pain situations for patients with preexisting chronic pain.

Dr. Watson summarized the Panel's attitude towards question five: total uncertainty regarding the clinical validity of AvertD for its proposed use.

Question Six

If you believe that additional information in the labeling, like warnings limitations, would be appropriate to mitigate some risk for this task, please describe the specific risks and the labeling mitigations that should be included to minimize those risks associated with the use of the device.

Dr. Higgins proposed four facets: communication should focus on educating both prescribers and patients; it should be communicated that this is only one tool and not for

standalone use; the tool is to assess risk of OUD; and a disclaimer about the ongoing development of the PDMP should be included. **Dr. Kelm** requested clarification about her mention of the PDMP. **Dr. Higgins** responded that prescription monitoring needs to be tightened up.

Dr. Compton posed that the labels of high risk and low risk should be reconsidered to allow for more nuanced interpretation of results, ideally preventing overreliance on the test for a yes/no answer about adverse outcomes. He also suggested post-marketing studies to fill the data gaps for certain subpopulations.

Dr. Ruha found it imperative that labeling include the information that opioid-sparing strategies are recommended for all patients, and that test results should not be used to withhold opioids from those who are otherwise candidates for their prescription. She also asserted that it should be clear to physicians that they avoid making determinations based solely on the test's results. **Dr. Joniak-Grant** concurred and advocated for extremely clear language to that effect that is not muddied by statistical language, suggesting bullets and/or brief fact sheets to clarify the important disclaimers.

Dr. Ness reiterated that categorical yes/no answers should not be provided by the test's language, and he repeated concerns about under-prescribing. **Dr. Walker** agreed that a scale is more useful than a yes/no output. **Dr. Zaafran** suggested that something akin to, "This test is one of many possible risk factors for Opioid Use Disorder that must be used with clinical correlation, and it's only for aiding in managing patients in acute pain" be included at the very top of device information sheets. **Dr. Farrar** backed all of these notions and reiterated that categorical yes/no presentation of results could be catastrophic. **Dr. Kelm** asked the Panel to keep their comments to the device in front of them, which, for better or worse, does present results in a categorical yes/no manner. **Dr. Farrar** is strongly opposed to the device as-is and would need it to provide a continuous scale to consider approving the device.

Dr. Bierut brought up the concern that there would be a strong push to utilize the device on patients under 18 receiving opioids for, for example, wisdom teeth extractions. She does not know how to mitigate this risk. **Dr. Walker** shared this concern and suggested specific marking that the device is for use only on patients 18 and older.

FDA AND SPONSOR SUMMATIONS

For the FDA Summation, **Dr. Kelm** thanked the participants for their time.

For the Sponsor Summation, **Dr. Donaldson** thanked the participants and praised their useful input on question six. He reiterated that AvertD is a genetic risk stratification test, not a screening test, and it's intended to be used in conjunction with a clinical evaluation in acute non-emergent pain. He emphasized that the company is committed to improving their algorithm through post-market studies that he believes are ready to commence, and he underscored a willingness to alter labeling as suggested. **Dr. Donaldson** finally posited that the benefits of AvertD to provide genetic risk information outweighs potential risks of device use.

Dr. Higgins, the consumer representative, thanked the participants and the FDA.

Dr. Wreh, the industry representative, thanked the participants and made two points: he does not find the CRF changes to compromise the study, and he supports the data enrichment process the study employed.

Dr. Joniak-Grant, the patient representative, thanked the participants and FDA. She stated that she does not believe this test is appropriate to provide genetic risk information, at least not at present, due to clinical design issues. She cited risks related to delayed treatment, under-treatment, stigma, incorrect results, low predictive power, and lack of context for device usage as main reasons she does not support the approval of AvertD.

VOTE

James Swink, Designated Federal Officer, read the definitions of safety and effectiveness and prompted the Panel members to place their votes on the question: Do the probable benefits to health from use of the AvertD device outweigh the probable risk for the proposed indications, taking into account the probable risks and benefits of currently available alternative forms of detecting risk of developing OUD?

The final vote was 2 "yes" and 11 "no".

Dr. Watson prompted each Panel member to state their vote and rationale, and whether changes to labeling, use restrictions, or other controls would make a difference in their answer.

Dr. Compton voted yes because there are no other currently available genetic tests to this end.

Dr. Ness voted no because of the categorical nature of the device. The risk of the device lies in the false positives/negatives, in his thinking. If the device reported continuous data with associated information, he would have voted in favor.

Dr. Gallagher voted no because of the high risk/low risk categorization output. More descriptive information provided by the device could make her reconsider.

Dr. Walker voted yes and her uncertainty about test validity was alleviated by the question and answer sessions.

Dr. Farrar voted no due to the categorical nature of the device, uncertainty around how much of the genetic component is attributed to each individual SNP, and lack of environmental and socioeconomic information as it pertains to OUD.

Dr. Bateman voted no, citing uncertainty about algorithm performance across different populations, confounding my ancestry, lack of understanding of the 15 SNPs and their predictive values, and uncertainties about the device's impact on prescribing behaviors.

Dr. Dunn voted no on the basis of the trial's design. He contended that the selection process enriches for a type of patient that is not representative of the intended use population.

He also cited concerns about the ability to communicate to physicians appropriate and commensurate ways to incorporate test information to their treatment plan and reiterated concerns regarding over-reliance on test results. He would mitigate this with dimensional outcomes rather than categorical outcomes from device use. Dr. Dunn also voiced that there is no way to tell how this would change management of patients and that the study did not systematically collect information about potential risks, such as the risk of inadequate pain control.

Dr. Bierut voted no because there is no information on how clinicians will practically use the device and interpret its results. She also found efficacy data to be limited and felt risks outweigh benefits. She would like to see the study replicated in silico for assurance.

Dr. Gordon voted no for four reasons: inadequate study design and analysis; lack of safety evaluation towards altered prescribing patterns and patient behaviors; high risk of false positives; and the generation of stigma from an OUD-positive result.

Dr. Zaafran voted no because the intended use population does not match the study population and because of the categorical nature of the device. He stated concerns about over- and under-treatment and about targeting from regulatory agencies as a result of positive results.

Dr. Wang voted no on the basis that the clinical study design does not reflect the target patient population, with secondary concerns about safety and real-world usage. She would like to see more information on how the test results can be used in combination with clinical information to avoid its off-label use as a standalone assessment.

Dr. Goldstein voted no because of the binary readout, the clinical trial population, inadequate power behind the machine learning algorithm for racial subgroups, and due to concerns regarding Genetic Non-Discrimination Act laws.

ADJOURNMENT

Dr. Watson thanked the Panel and adjourned the meeting.

I certify that I attended this meeting on October 20, 2022 and that these minutes accurately reflect what transpired.

James P. Swink -S Digitally signed by James P. Swink -S Date: 2022.11.04 14:15:39 -04'00'

James Swink
Designated Federal Officer

I approve the minutes of this meeting as recorded in this summary.

Karol E. Watson M.D.,

Chairperson

Summary Prepared By:

Debbie Dellacroce
Translation Excellence
3300 South Parker Road, Suite 200
Aurora, CO 80014
(720-325-0459)
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