Food and Drug Administration
Center for Devices and Radiological Health

Brief Summary of the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee Meeting
October 20, 2022

Introduction:

On, October 20, 2022, the committee discussed, made recommendations, and voted on the clinical information related to the *De Novo* request for the "AvertD" test sponsored by SolvD, Health. The device is a genetic test that detects 15 single nucleotide polymorphisms that are associated with the brain reward pathway. The device is intended to identify individuals at risk for developing opioid use disorder (OUD). The panel meeting focused on the clinical study and requested panel member commentary on the study design, study population, and interpretability of the study results.

Panel Deliberations/FDA Questions

1. 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 that subjects met the inclusion/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/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 make-up of the study population with regard to race, ethnicity, age, and sex

    Panel Consensus Summary:

    a. *The panel had reasonable confidence that subjects in the clinical study met the inclusion/exclusion criteria and that use of different CRF versions made little to no*

difference on subject enrollment. However, the panel had concerns regarding the study design and recruitment procedures.

b. *The panel had reasonable confidence that subjects whose index oral opioid exposure was illicit and/or for treatment of chronic pain were excluded from the study. However, there were concerns regarding the study design and recruitment procedures.*
c. *The panel thought that recruitment from treatment sites may have introduced bias, which was reflected in the data which showed that the majority of subjects had severe OUD.*
d. *The panel thought that use of subject recollection to establish date of index exposure appeared to enrich for patients with notable experiences and resulted in a study population that is not consistent with the general population.*
e. *The panel expressed some concerns regarding how substance use disorders (SUDs) were identified for use in the study enrichment of patients at higher risk of OUD via risk pool assignment. The panel discussed how the company used comorbidity information in the medical record of patients which may miss some patients with SUDs versus performing a clinical assessment during enrollment. The panel also discussed that the study did not capture sufficient information to allow for an understanding of the number and types of comorbidities in the study population (e.g., tobacco use disorder was not assessed) and did not provide information on how SUDs were diagnosed to help give confidence in any diagnoses used in the study's enrichment process.*
f. *The panel discussed that the study population was comprised of >90% white participants and that other demographics that are present in the general population were not adequately included in the study population. Lack of diversity in the study population raised concerns for the panel about potential for health inequity. The panel did not think that the demographics of the study population adequately represented the general population that the device is intended to be used in.*

2. 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 (i.e., Form 3) clarify whether the device may be detecting comorbidities in the clinical study population?

Panel Consensus Summary:

a. *The panel discussed that the sample size was too small to allow for an understanding of the relationship between OUD and other comorbidities in the clinical study population and noted that important comorbidities (such as tobacco use disorder) were not accounted for. Despite these concerns, the panel felt that the device is detecting risk of OUD rather than risk of OUD in addition to other comorbidities. The panel felt that the results of the study were promising (in this regard), but confirmation of the study results is needed.*

b. *The panel was comfortable that the device was not detecting other comorbidities in the clinical study population.*

3. 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 discuss 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.

Panel Consensus Summary:

a. *The panel was uncertain about whether the device performance in the clinical study represented the probable performance of the device in the intended use population. The panel discussed that, without information about the risk of the potential for underuse of opioids in patients receiving a high risk result and the potential for overuse of opioids in patients receiving a low risk result, it is unknown how the test would work in the intended use population. The panel also discussed that the study population was not sufficiently powered for important subgroups (for example women 65 years old and older) to assess the performance in a significant way in those subgroups.*
b. *Some panelists expressed concern that results from a genetic test may be thought of as more objective than the other subjective risk tools that are currently used and therefore given more weight in clinical decision making. The panel also discussed that current opioid sparing strategies for all physicians should minimize opioid prescription in all patients, and it was therefore unclear how a genetic risk would impact the opioid sparing treatment practices that should already be in practice. The panel discussed that the prevalence rate of 5% used to calculate positive predictive value (PPV) and negative predictive value (NPV) may not be appropriate, since the prevalence in the general population may range from 1-10%.*
c. *The panel agreed that the predictive power should be better and that genetic risk is only one component of risk and should be treated as such. The panel was uncertain on a level of clinical performance that would be acceptable.*

4. 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.

Panel Consensus Summary:

The panel discussed that results of a genetic test could lead to over reliance on the result to change prescribing behaviors. Patients receiving a "high risk" result may not be prescribed much needed opioids, and patients receiving a "low risk" result may be over-prescribed opioids based on a sense of security. The panel also discussed that

there is conflicting information regarding the role and predictive value of the 15 SNPs used in the device. The panel agreed that the test could be of great benefit if it were accurate, but the information is not sufficient to show that the test is accurate. The panel also had concerns about real world use. Since the results may take 48-72 hours to return, it is unclear whether the test would be used as intended (i.e., for use prior to a first prescription for acute pain) in emergent situations; there's a risk of a prescription being delayed while waiting for the test results and use of ineffective pain management instead of opioids in that time. The panel was concerned that results of a genetic test could increase the stigmas around opioid prescription and use.

5. 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.

Panel Consensus Summary:

The panel felt that it was not possible to assess the clinical validity of AvertD with the current information. The panel was concerned that the 15 SNPs used in the device may not be accurately differentiating patients at high or low risk for developing OUD. The panel was also uncertain about how the test would be used in combination with other tools and clinical information, and therefore were uncertain about the clinical validity of the test when it is used as intended.

6. If you believe that additional information in the labeling (e.g., warnings, limitations) would be appropriate to mitigate some risks for this test, please describe the specific risks and the labeling mitigations that should be included to minimize those risks associated with use of the device. Are there other mitigations to consider to minimize risk associated with use of the device?

Panel Consensus Summary:

The panel proposed several modifications to the labeling that could help minimize risk. These included: 1) strong and plain language that states the test is not to be used alone, but instead to be used with other tools as one component of risk prediction, 2) addition of a limitation that the test should not be used in children, and 3) clear labeling that opioid sparing techniques should be used in all patients regardless of the result of the test. Additionally, some members of the panel were concerned that the device's output is limited to binary results (high risk or low risk) and proposed a revised device in which the results are provided results on a continuum, where literature for each of the 15 SNPs and their relationship to OUD is provided as informational. The panel also proposed additional studies to better understand test performance in subpopulations that were not included in the clinical study population.

Panel 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?

Panel Summary:

There were 13 voting members, and the panel voted:

- *2 yes*
- *11 no*

Summary of votes:

- *The 2 panel members who voted yes felt that the test would add some benefit and that modifications to the output of the device from a polygenic risk score with two results (low risk or high risk) to a continuous measure of each SNP and its ability to predict risk of OUD separately could mitigate risks.*
- *The 11 panel members who voted no generally felt that there was continuing uncertainty regarding the validity of the test given that it is unclear whether the 15 SNPs used in the device are predictive of OUD. The panel members who voted no provided a variety of reasons for their vote related to the design of the study including, 1) the study was not powered to assess important subgroups in the general population, 2) the enrollment strategy enriched for subjects with notable index exposures, thereby not capturing the full spectrum of subjects within the intended use population, 3) the enrollment strategy enriched for subjects of a certain demographic background who have more severe OUD (i.e., subjects with sufficient means to seek treatment for OUD at treatment sites), 4) the study population does not reflect the intended population, and 5) no information was provided regarding how the results of the test impact potential for over-use of opioids in low risk population and potential for under-use of opioids in the high risk population. The panel members who voted no were also concerned that the risks of the device outweigh the benefits. Specifically, 1) the binary results of "high" and "low" risk could result in stigmatization of patients, and, given that subpopulations present in the general public were not adequately represented in the study population, results from this test could further exacerbate health disparities, 2) potential for over-reliance of the genetic information may lead to over- or under-prescribing of opioids, 3) the current strategy for opioid prescription should be one that minimizes exposure to opioids for all patients, it is unclear whether results from a genetic test could alter opioid sparing strategies. A small number of panelists noted that they would have considered voting yes if a result on a continuum rather than binary test result were available.*

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