AVERTD™: A GENETIC RISK ASSESSMENT TOOL FOR OPIOID USE DISORDER (OUD)

SPONSOR EXECUTIVE SUMMARY

CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES PANEL MEETING

MEETING DATE: 20 OCTOBER 2022

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List of Abbreviations

Abbreviation	Definition
ASPE	Allele Specific Primer Extension
CI	Confidence interval
CRF	Case Report Form
CMO	Chief Medical Officer
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FDA	Food and Drug Administration
FD&C Act	Food Drug and Cosmetics Act
IVD	In vitro diagnostic
LR-	Negative likelihood ratio
LR+	Positive likelihood ratio
OUD	Opioid use disorder
PCR	Polymerase chain reaction
PDMP	Prescription Drug Monitoring Program
RFU	Relative fluorescence units
SAP	Statistical Analysis Plan
SUD	Substance use disorder
SNPs	single nucleotide polymorphisms
US	United States

Glossary

Class I device: low risk device; subject to General Controls

Class II device: moderate risk device; subject to General Controls and Special Controls

Class III device: high risk device; intended to be used in supporting or sustaining human life or preventing impairment of human health, or that may present a potential unreasonable risk of illness or injury for which General Controls and Special Controls are insufficient to provide reasonable assurance of the safety and effectiveness of a device, or for which there is insufficient information to make such a determination.

Devices that are not within a type marketed before the date of the Medical Device Amendments of 1976 – referred to pre-amendments devices – are classified into Class III automatically under federal law unless and until reclassified by FDA as Class I or Class II (e.g., through the De Novo process).

General Controls: regulatory requirements authorized by the Federal Food, Drug, and Cosmetic Act (FD&C Act), under sections 501, 502, 510, 516, 518, 519, and 520. General controls apply to all medical devices, unless exempted by regulations. Examples: registration requirements (device registration and listing), notification requirements (such as repairs and replacements), records and reporting requirements (such as medical device reporting).

Special Controls: regulatory requirements for Class II devices; Special Controls are usually device-specific and include: performance standards, post-market surveillance, patient registries, special labeling requirements, pre-market data requirements, guidelines.

Prognostic Enrichment Strategies: choosing patients with a greater likelihood of having a disease-related endpoint event (for event-driven studies) or a substantial worsening in condition (for continuous measurement endpoints). These strategies would increase the absolute effect difference between groups but would not be expected to alter relative effect.

De Novo: regulatory pathway for market authorization and classification for novel, low to moderate risk medical devices for which General Controls alone or General and Special Controls provide a reasonable assurance of safety and effectiveness, but for which there is no legally marketed predicate device.

Premarket Approval: approval pathway for Class III devices

Acute pain: a sudden onset of pain that lasts no longer than 30 days

Chronic pain: pain that lasts for longer than 90 days

1 DE NOVO REGULATORY FRAMEWORK

Through the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 513, federal law established the risk-based classification system for medical devices. Each device is assigned to one of three regulatory classes — Class I, Class II, or Class III — based on the level of controls necessary to provide reasonable assurance of its safety and effectiveness. As device class increases from Class I to Class II to Class III, the regulatory controls also increase, with Class I devices subject to the least regulatory control, and Class III devices subject to the most stringent regulatory control. The regulatory controls for each device class include:

- Class I (low risk): General Controls
- Class II (moderate risk): General Controls and Special Controls
- Class III (high risk): General Controls and Premarket Approval

Novel medical devices (i.e., those of a new type that the Food and Drug Administration [FDA] has not previously classified) are automatically classified into class III (requiring premarket approval) regardless of the level of risk they pose or the ability of General and Special Controls to assure safety and effectiveness.

The De Novo classification process (Section 513(f)(2)) provides a regulatory pathway for market authorization and classification for novel, low to moderate risk medical devices for which General Controls or General and Special Controls provide a reasonable assurance of safety and effectiveness, but for which there is no legally marketed predicate device.

SOLVD Health (SOLVD) submitted a De Novo request to classify AvertD as a Class II medical device subject to Special Controls as SOLVD believes General and Special Controls provide a reasonable assurance of safety and effectiveness. The proposed device type is “Opioid Use Disorder Genetic Risk Assessment System.” The Special Controls proposed by SOLVD (described in Section 5.2 and 12.1), rely upon well-accepted methods common to many genotyping tests and are modeled after several Class II genetic risk assessment tests, including– Cancer Predisposition Risk Assessment Systems (21 CFR 866.6090), Genetic Health Risk Assessment Systems (21 CFR 866.5950) and Pharmacogenetic Assessment Systems (21 CFR 862.3364), as well other in vitro tests.

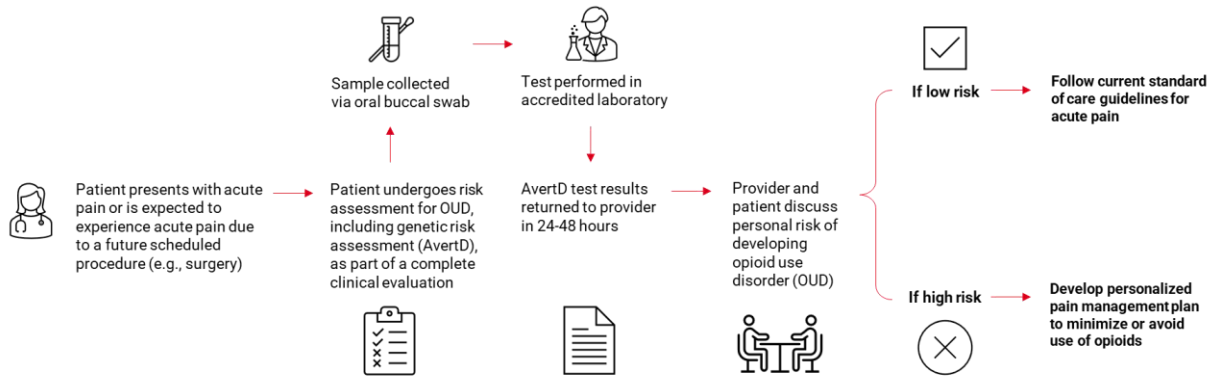
2 SYNOPSIS

2.1 Introduction

The opioid epidemic is a public health emergency in the United States (US) with no sign of slowing down. While the opioid crisis is multi-faceted, research shows that the use of prescription opioids when prescribed by physicians and used appropriately by patients may lead to addiction. Despite government and private efforts to reduce prescription opioid use, people are still becoming addicted, indicating that additional measures are needed to lower the prevalence of opioid use, to develop safer prescribing practices, and to prevent opioid use disorder (OUD) (CDC).

SOLVD is seeking market authorization for AvertD™, a genetic risk assessment tool for OUD that identifies patients who may be at higher genetic risk of addiction resulting from prescription opioids prior to prescribing. AvertD uses proprietary film-based microarray technology to detect and identify 15 single nucleotide polymorphisms (SNPs) involved in brain reward pathways that are associated with OUD. The results from AvertD provide physicians and patients objective information about a patient's potential genetic risk for OUD, which can be used in conjunction with other available risk assessment tools and a full clinical evaluation to facilitate informed decision-making regarding prescription of oral opioids to relieve acute pain (Figure 1).

Figure 1: AvertD Clinical Workflow for Acute Pain



In early 2018, the FDA granted AvertD Breakthrough Device designation. A device is eligible for breakthrough designation if it provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; and one of the following criteria is met:

- (1) it represents a breakthrough technology;

- (2) no approved or cleared alternatives exist;
- (3) it offers significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies; or
- (4) the availability of which is in the best interest of patients.

In the case of AvertD, there are no cleared or approved alternatives to identify genetic risk for developing OUD; making such a device available is, therefore, in the best interest of patients (FDA Breakthrough Device Designation Criteria).

SOLVD completed a clinical study validating the device in April 2020 and subsequently submitted a De Novo request for AvertD. The FDA declined the request but encouraged SOLVD to re-submit a De Novo request with additional information. Following multiple interactions with the FDA, SOLVD submitted a second De Novo request for AvertD in June 2022 to address the FDA's open issues.

The current De Novo includes new data and analyses that address the FDA's remaining questions regarding the clinical performance and the applicability of results from the study population to the intended use population. This additional information further demonstrates that the benefits of AvertD for its proposed intended use outweigh its risks, that the study results are applicable to the intended use population, and that the proposed risk mitigations provide a reasonable assurance of device safety and effectiveness, thus meeting the requirements for De Novo authorization.

2.2 Background and Unmet Need

Oral prescription opioids are a primary source of opioid addiction in the US. In 2020, 13.4 million people self-reported misused prescription opioids in the previous year (SAMHSA 2021), and overdose deaths involving prescription opioids increased nearly five times from 1999 to 2020 (CDC 2021). In addition to mortality, there are serious morbidities associated with opioid use and OUD.

OUD is characterized by a desire to obtain and take opioids despite social and professional consequences. Individuals with OUD experience an overpowering desire to use opioids, have an increased opioid tolerance, and will experience withdrawal syndrome when opioid use is discontinued.

OUD risk assessment prior to prescribing opioids is a cornerstone of clinical practice, Physicians use a variety of approaches to assess the risk OUD including interviewing patients, reviewing medical records, and using risk questionnaires. However, these tools do not assess the genetic risk of patients, and no tools currently exist to assess genetic risk. The CDC states that "currently available risk stratification tools…show insufficient accuracy for classification of patients as at low or high risk for abuse or

misuse" (Dowell et al 2016). Patients and physicians need more information, including information regarding a patient's genetic risk, to assess an individual's risk of developing OUD prior to the decision to prescribe oral opioids for acute pain management.

When patients are identified to be at increased risk related to the use of prescription oral opioids, non-opioid alternatives for pain management can be considered. Decisions regarding pain management should be approached through a shared decision-making process including the clinician and patient and an evaluation of all known benefits and risks. The goal of this informed decision-making is to select a pain management strategy that optimizes benefits while minimizing risks. The pain management strategy may include opioids prescribed according to the current standard of care or an opioid minimization or elimination approach (e.g., multi-modal analgesics) for patients deemed to be at higher risk (CDC 2022; Echeverria-Villalobos et al 2020; Wick et al 2017).

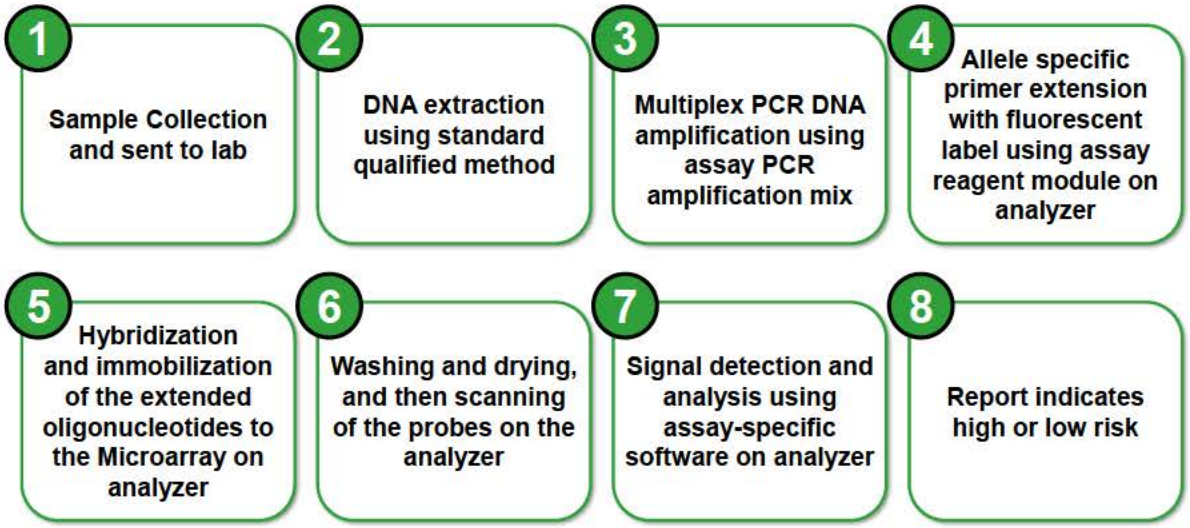
Understanding a patient's genetic risk is a critical component of an informed, decision-making process. Collectively genetics have been associated with approximately 50% of the risk of developing OUD (Berrettini 2017). Numerous genomic studies across ancestries (both candidate gene and genome-wide association approaches) have identified genetic markers associated with addiction. Genetic markers have been identified that are specific to OUD including the mu opioid receptor (OPRM1), the delta opioid receptor (OPRD1), as well as genetic markers seen across substance use disorders (SUDs) including the dopamine D2 receptor (DRD2) (Crist et al 2019; Deak et al 2022). However, despite the advances in genetic research and technology, there are currently no FDA cleared or approved in vitro diagnostic (IVD) devices to identify individuals who are at greater genetic risk for developing opioid dependence.

2.3 Product Overview

AvertD is an IVD that distinguishes between individuals who may be at increased genetic risk of OUD from those who may not be at increased genetic risk by identifying the presence or absence of 15 single SNPs involved in the brain reward pathways that are associated with OUD (see Table 4). The 15 SNPs are then analyzed, and a result (high or low risk) is reported.

AvertD, which is used in combination with the INFINITI PLUS Analyzer, comprises a polymerase chain reaction (PCR) Amplification Mix, Intellipac® Reagent Module, BioFilmChip® Microarray, and assay-specific software. Each of these components is described in detail in Table 5. Figure 2 depicts the key steps of the AvertD test process.

Figure 2: Overview of AvertD and its Key Steps



2.3.1 Proposed Intended Use

The proposed intended use is as follows:

> AvertD™ is a prescription, qualitative genotyping test used to detect and identify 15 clinically relevant genetic polymorphisms in genomic DNA isolated from buccal samples collected from adults. The 15 detected genetic polymorphisms are involved in the brain reward pathways that are associated with opioid use disorder (OUD) and identify patients who may be at increased genetic risk for OUD. Information from AvertD™ provides patients 18 years of age or older and healthcare providers with objective information to be used for informed decision-making prior to the first prescription of oral opioids for acute pain. The information from AvertD™ is intended to be used in combination with a clinical evaluation and assessment of the patient.

2.3.2 Analytical Validation

Analytical validation testing of AvertD included accuracy compared to sequencing, precision/reproducibility, sensitivity (limit of detection), interfering substances, and specimen and reagent stability.

- The accuracy of AvertD was compared to Sanger bidirectional sequencing in 434 de-identified patient samples. Of the 6,510 analytes tested, there was > 99.9% agreement between AvertD and bidirectional sequencing.
- The precision of AvertD was determined by comparing the genotype for each analyte reported by AvertD to the genotype obtained using bidirectional sequencing. The concordance rate was 100% with a 95% one-sided confidence limit of 100.0%.

- The limit of detection was defined as the lowest level of genomic DNA (ng DNA input per test) that would give a ≥ 95% correct call rate. The lower limit of detection was using DNA at a concentration of 1 ng/µl. At this lower limit, the percent correct call rate was 100.0%
- No interference with AvertD was observed for any of the tested substances.
- All specimen and reagent lot tests passed the acceptance criteria supporting the shelf life.

Detailed results of the validation studies are provided in Section 4.5.

2.4 AvertD Clinical Study

2.4.1 Design Overview

AvertD was clinically validated through a blinded, multi-center study evaluating participants at least 1 year after their initial exposure to prescription oral opioids. This study had both prospective and retrospective aspects to the design (i.e., retrospective reporting of opioid exposure). Enrollment occurred on an all-comers basis (i.e., all participants who met the inclusion/exclusion criteria were enrolled). This approach minimizes subject selection bias. Participants were approached during their normal clinical care at 9 sites, including 6 general practice sites and 3 sites that specialize in treating SUD, including OUD. One research-only site enrolled participants.

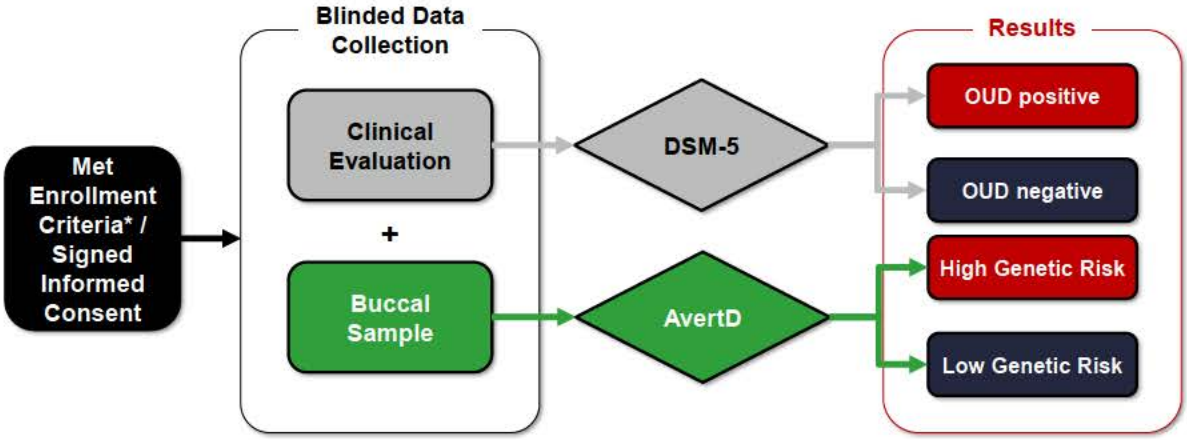
Because the prevalence of OUD is low, enrichment with sites that specialize in treating SUD, including OUD, was used to increase the likelihood of enrolling enough OUD-positive participants and complete the clinical study in an efficient and least burdensome means. This approach was used to provide robust estimates of the test's performance, particularly for sensitivity.

Adults 18 years of age or older were interviewed by study site personnel to determine if they had been prescribed and taken oral opioids a minimum of 1 year prior to the interview. In addition, to qualify for the study, the index (initial) exposure to prescription oral opioids was required to be between 4 and 30 consecutive days, which is consistent with prescription opioid use for acute pain and, by definition, excludes patients taking opioids for > 30 days for indications including chronic pain. Opioid exposure was self-reported, an approach which is used widely in research, and commonly forms the basis of measurement of medication use in clinical trials, including the approvals of opioids and other analgesics. Studies have shown that self-reporting is an accurate method of determining prescription use given that prescriptions may not be filled or filled but not taken (Cramer et al 1989; Drieling et al 2016; Hafferty et al 2018).

Following the study, additional data were collected and analyzed to ensure that the study population met the enrollment criteria and therefore represented the intended use population.

After informed consent was provided, a clinician at the site conducted a clinical evaluation of the patient to determine if the participant ever met the criteria for a DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) diagnosis of OUD, described in Appendix Section 12.2. The presence or absence of DSM-5 OUD served as the basis for comparison to the AvertD test result (Figure 3).

Figure 3: AvertD Clinical Study Design



*Enrollment Criteria
- ≥ 18 years of age
- Prior prescription opioid use
  - ≤ 12 months prior
  - for ≥ 4 - ≤ 30 days

Study staff collected two buccal swabs from each participant for testing with AvertD. All buccal samples were collected using the INFINITI Buccal Sample Collection Kit. One central laboratory tested all study specimens; the laboratory personnel were blinded to participant source, demographics, and clinical information including OUD status. Investigators and participants were also blinded to the test results.

The two co-primary effectiveness endpoints of the study included:

- Sensitivity — the proportion of participants with OUD correctly identified by AvertD as OUD-positive
  - Performance goal: lower limit of 95% confidence internal (CI) > 59.5%
- Specificity — proportion of participants without OUD correctly identified by AvertD as OUD-negative
  - Performance goal: lower limit of 95% CI > 55.5%

Co-secondary effectiveness endpoints included:

- Positive likelihood ratio (LR+)

$$LR+= \frac{Sensitivity}{1 - Specificity}$$

- Negative likelihood ratio (LR-)

$$LR-= \frac{1 - Sensitivity}{Specificity}$$

Description of the selection of the performance goals can be found in Section 6.1.7.2. Additional sensitivity and subgroup analyses were conducted to support the primary and secondary endpoints.

2.4.2 Random Representative Sampling Process

A pre-specified random, representative sampling using strata was employed to ensure the study analysis population from the enrolled participants mirrored the demographics of the intended use population of adults in the US who are prescribed oral opioids. This process minimizes selection bias and the impact of unmeasured confounders while ensuring a sufficient number of OUD-positive participants were included (see Section 6.1.4).

As per the pre-specified Statistical Analysis Plan (SAP), a blinded, independent statistician randomly selected participants post-enrollment who met predefined categories (sex, age, time from index exposure to enrollment, likelihood of OUD) to ensure an adequate number of participants in each strata was included for statistical analyses. The statistician used a prognostic enrichment strategy in which evidence of any SUD (as assessed by SOLVD's Chief Medical Officer [CMO]) was used to choose patients with a higher likelihood of having an OUD. This allowed the random sampling of the strata while ensuring that the study population had enough OUD-positive participants. Of note, the statistician was blinded to test results as well as OUD status during this process; the CMO was blinded to the AvertD test result.

2.4.3 Participants

A total of 812 participants were enrolled. The blinded statistician reviewed the demographic composition of the enrollees and determined that 689 participants were sufficient to meet the stratification criteria. Of the 689, 385 participants were selected at random to fill the strata to ensure the study population represented the US population that takes prescription oral opioids and based on a statistical calculation that 385 participants would be sufficient to assess the product's performance.

Participant demographics are shown in Table 1.

Table 1: Summary of Participant Demographics

Category	N=385
Mean age at exposure, years (SD)	33 (17.7)
Sex, n (%)	
Male	222 (57.7)
Female	163 (42.3)
Race, n (%)	
White	351 (91.2)
Non-white	17 (4.4)
Ethnicity, n (%)	
Hispanic	91 (24)
Non-Hispanic	288 (76)

Clinical Truth (OUD Status)

Participants were assessed by a clinician at the study site at enrollment (after signing the informed consent form) for the presence or absence of DSM-5 OUD using a clinical evaluation, which consisted of a conversation with the patient to gather clinical information (clinical history) relevant to a diagnosis of OUD. Participants for whom a DSM-5 OUD diagnosis was established were assigned an outcome of OUD positive for the study.

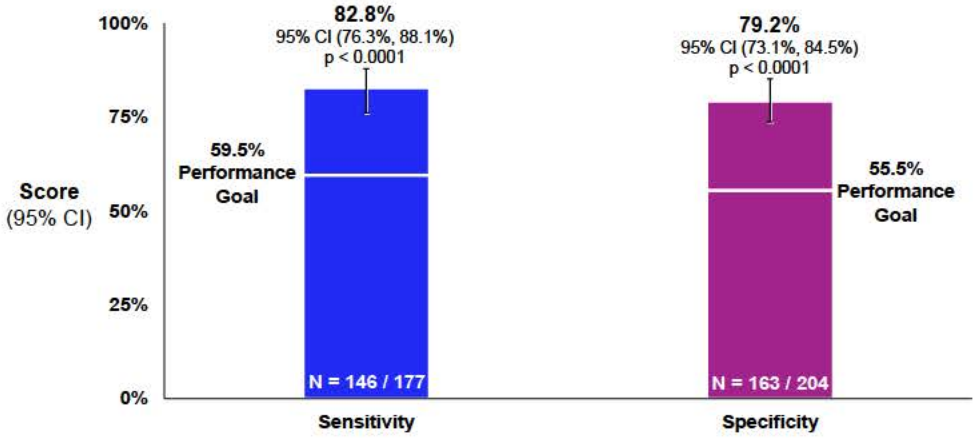
A total of 175 participants had a DSM-5 diagnosis of OUD (i.e., were OUD positive), and 210 participants did not have an OUD diagnosis (i.e., were OUD negative).

2.4.4 Results

AvertD had a sensitivity of 82.8% and specificity of 79.2% (Figure 4). The lower bound of the 95% CI for sensitivity was 76.3, greater than the performance goal of 59.5% and the lower bound of the 95% CI for specificity was 73.1, greater than the performance goal of 55.5%; therefore, both co-primary endpoints were successfully met.

Exact tests of proportions for both sensitivity and specificity against the corresponding performance goals resulted in p-values < 0. 0001.

Figure 4: AvertD Sensitivity and Specificity Co-Primary Endpoint Results



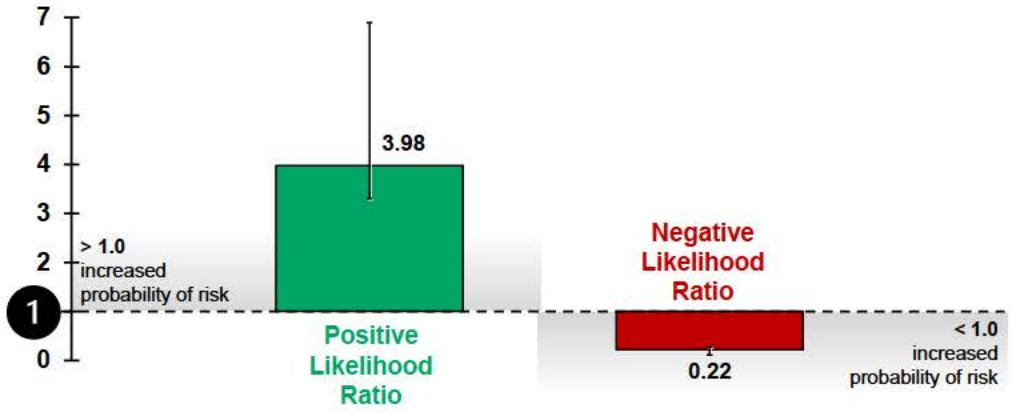
AvertD test results were not available for 4 participants (1 was OUD-positive; 3 were OUD-negative). In a sensitivity analysis of this missing data, under the worst-case assumptions that all 4 missing test results were either false negative or false positives, the sensitivity was 82.3% (95% CI: 75.8 – 87.6) and specificity was 78.1% (95% CI: 71.9 – 83.5), still achieving statistical significance and exceeding the performance goals.

In the subgroup analyses by sex, age, race, ethnicity, and length of time since initial opioid use, all point estimates were above the performance goal thresholds. No statistically significant differences were observed for any of the variables, demonstrating robust test performance in all tested subgroups (see Figure 11 through Figure 15).

The positive and negative likelihood ratios were both favorable. The positive likelihood ratio showed a strong increase in the probability of having OUD with a positive test result, and the converse was true for the negative likelihood ratio which showed a strong decrease in the probability of having OUD with a negative test result (Figure 5).

The diagnostic odds ratio, which is ratio of the positive and negative likelihood ratios, was 18.1 (3.98/0.22). This results means that a positive result with AvertD is 18 times more likely to happen in a patient who will develop OUD than it would in a patient who will not develop OUD. Pre- and post-test probability, also calculated using the likelihood ratios, also help explain the clinical relevance of the results. Based on an OUD prevalence of 5%, approximately 1 in 6 patients identified as high genetic risk may develop OUD, whereas 1 in 100 patients identified as low genetic risk may develop OUD (further described in Section 6.4.2).

Figure 5: Positive and Negative Likelihood Ratios



2.4.5 Clinical Study Conclusions

The data collected and analyzed support the use of AvertD test results to assist in the detection of individuals who may have a higher risk for OUD. The co-primary endpoint analyses demonstrate that sensitivity and specificity are high and not sensitive to age, sex, time from index exposure, race or ethnicity. The diagnostic likelihood ratios support the primary endpoint results. Today, clinicians have no tools to assess whether a patient may be at greater risk of OUD due to genetics. Overall, these results support the use of AvertD as a valuable risk assessment tool by providing physicians and patients with currently unavailable insights into genetic susceptibility to OUD prior to prescribing prescription oral opioids for acute pain.

2.5 Summary of Applicability of Study Population to Intended Use Population

SOLVD designed the clinical study to ensure that the study population represented the intended use population. During the FDA review process, SOLVD collected and analyzed additional data to directly address questions related to the applicability of the study population to the intended use population. The data collected by SOLVD supports that the study population reflects the intended use population ensuring that the results are applicable to the intended use population.

2.5.1 Ensuring All Participants Met Inclusion Criteria

2.5.1.1 Case Report Forms

As is common in clinical studies, the case report forms (CRFs) evolved throughout the study to more accurately capture study data. Prior to enrolling any participants, sites were trained using the study protocol, which included the inclusion/exclusion criteria, and the inclusion/exclusion criteria from the study protocol, not the CRFs, were used to enroll participants.

To address the use of multiple CRF versions during the study and to ensure data collection consistency, after the study completion, study sites documented and ensured all eligibility criteria for each participant using a single, new CRF. Using the new CRF data and the instructions specified in the SAP, all participants (N=385) were confirmed to meet the study eligibility criteria. These new data demonstrate the sites consistently applied the study-specific enrollment criteria across all participants and did not introduce any uncertainty in the clinical study population.

2.5.1.2 Exclusions of Participants Taking Oral Opioids for Treatment for Chronic Pain

To be enrolled in the study, the index exposure to prescription oral opioids was required to be between 4 and 30 consecutive days, which is consistent with prescription opioid use for acute pain. By definition, this excludes patients taking opioids for > 30 days for indications including chronic pain.

2.5.1.3 Exclusion of Illicit use of Opioids

To meet the inclusion criteria, the index exposure had to be prescribed by a healthcare professional for that participant. During the site initiation process, the term “prescription oral opioids” was discussed in detail when reviewing the inclusion/exclusion criteria. The discussion included specifying that the prescription oral opioids were to have been prescribed by a healthcare provider (e.g., physician or dentist) for that patient and taken by that patient (i.e., the taking of the oral opioids was “doctor-directed” and not illicit use).

2.5.2 Self-Reported Data of Index Exposure to Prescription Oral Opioids

Under the inclusion criteria, participants needed to report that they had taken prescription oral opioids for 4 to 30 days at least one year ago. Self-reporting for the index exposure was selected for the study design as studies have shown that self-reporting is an accurate method for confirming that a patient took a medication given that prescriptions may not be filled and can be filled but not taken (Cramer et al 1989; Drieling et al 2016; Hafferty et al 2018). Authors have described that self-report is particularly accurate when associated with a significant pain event, such as those indicating a prescription for oral opioids for acute pain in the AvertD study, that would stand out to the patient (Stull et al 2009).

To corroborate the self-reported opioid exposure, the available participants’ medical records at the site at which they were enrolled were examined by study site personnel. Based on the type of supporting evidence found in the records, participants were classified into tiers, as described in Table 2. Tier 1 consisted of participants who met the enrollment criteria (self-reports of index exposure of 4–30 days more than a year prior to enrollment). All 381 participants fell into this tier. For 361 participants (95%), medical records documented a procedure (e.g., surgery) or event (e.g., accident) where oral opioids may be prescribed for acute pain as part of medical care within a calendar year before or after the self-reported index exposure (Tier 2). For 318 participants, the

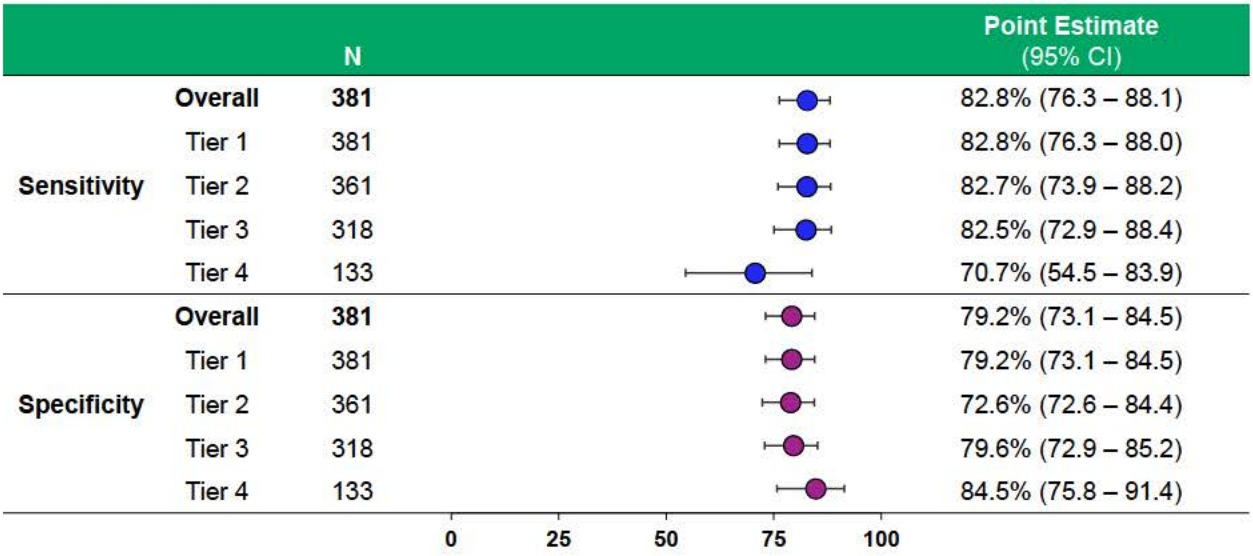
medical records established that a prescription had been written (Tier 3). Finally, an actual copy of the prescription was available for 133 participants (Tier 4). This result was expected and is driven by 2 primary contributing factors. First, most of the participants had their index procedure prior to 2015, which is when the Prescription Drug Monitoring Program (PDMP) began to be widely adopted. Prior to the PDMP, medical records may not have had physical copies of actual prescriptions. Second, it is not common for sites that did not prescribe an oral opioid to have physical copies of prescriptions from other prescribers in their records. Therefore, certain sites in the study would not have this type of information available for the index exposure.

Table 2: Tier Classification Based on Additional Opioid Exposure Data

Tier	Key Criteria to Meet Classification	Observed n (%)
Tier 1	Met inclusion exclusion criteria	381 (100)
Tier 2	Tier 1 + Documentation of surgery, procedure, or accident in medical record where opioids could be prescribed	361 (95)
Tier 3	Tier 2 + Medical records noted opioid prescription written	318 (83)
Tier 4	Tier 3 + Medical records included a physical copy, electronic copy, scan or photograph of actual prescription	133 (35)

The analyses by tiers support the sensitivity and specificity of AvertD (Figure 6). Tier 3 includes all participants that met the enrollment criteria, had documentation in the medical records of a surgery or an event where opioids could be prescribed, and had documentation in the medical records that an opioid was indeed prescribed. Tier 3 includes 83% of the participants and shows consistent performance with the overall study population for both sensitivity and specificity and exceeds the performance goals as pre-specified in the addended SAP. Tier 4, as defined included only patients where the medical records included a physical copy, electronic copy, scan or photograph of the actual prescription. At the time of the index exposure, it was uncommon in clinical practice to include copies of prescriptions in medical records. Therefore, it is not surprising that Tier 4 has fewer patients to analyze. This resulted in a lower point estimate and wider confidence intervals for the sensitivity results for Tier 4. Overall, the sensitivity and specificity data, regardless of the subset of participants analyzed, support the conclusion that AvertD is a sensitive and specific genetic test and a useful tool for health care providers in assessing the risk of OUD.

Figure 6: Sensitivity and Specificity of AvertD by Tier of Additional Opioid Exposure Data



2.5.3 Enrollment Sites

Participants were enrolled at 10 sites including 3 sites (Sites 2, 10 and 11) that provided OUD treatment and had providers holding waivers to prescribe buprenorphine. Sites 10 and 11 were mental healthcare practices that provided OUD treatment and Site 2 was a general practice site that provided OUD treatment. These 3 sites were grouped together in sub-analyses as all three sites offer OUD treatment; i.e., they had providers with special accreditation to treat OUD and prescribe buprenorphine (Substance Abuse and Mental Health Services Administration Drug Addiction Treatment Act of 2000 waiver certifications). The remaining sites were general practice that participated in research studies, but there were no healthcare providers at these sites who held a waiver to prescribe buprenorphine. Most of the OUD-positive participants were recruited at the sites where OUD treatment was available.

To address the question about whether AvertD test performance differed by type of study site, SOLVD compared AvertD performance in participants who were enrolled from sites that offered OUD treatment (defined as providing specialized clinical care for OUD treatment that requires specific accreditation, Sites 2, 10 and 11) to participants who were enrolled at sites who do not offer specialized OUD treatment (general practice that participate in research studies).

There were no statistically significant differences in AvertD sensitivity or specificity between OUD-specialized and non-specialized sites, providing confidence in the study results and the applicability of the study results to the intended use patient population (Figure 7).

Figure 7: AvertD Sensitivity and Specificity by OUD-Specialized Site and Non-Specialized Sites

2.5.4 Prospective Prognostic Enrichment (Prevalence "Risk" Pools)

Enrichment is a scientifically and statistically valid clinical study design option. For AvertD, prospective enrichment was critical to complete the clinical study in an efficient and least burdensome means and to provide robust estimates of the test's performance, particularly for sensitivity

More specifically, the clinical study utilized an enrichment strategy known as Prognostic Enrichment. In a Prognostic Enrichment Strategy, patients are selected who had a greater likelihood of having a disease-related endpoint event – in this case, being OUD positive. Prognostic Enrichment Strategy is recognized as a valid approach in the FDA guidance document entitled "Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products," March 2019. While the guidance document was intended for therapeutic products and risk reduction, the principles of study design apply equally well to assays, such as AvertD.

Given the sensitivity analyses across subgroups demonstrated a lack of statistically significant impact on test performance, it is reasonable to conclude that bias and confounding have been minimized with the study design (including more broadly any unmeasured or residual confounders), providing confidence in the validity of the study results and their generalizability.

2.5.5 Effect of Mental Health Comorbidities on AvertD Performance

A comparison of the mental health and non-opioid substance use comorbidities present in the study population with prevalence data in the literature show that the study population is not enriched for mental health disorders, is consistent with the US

prevalence rates and similar between OUD-positive and OUD-negative participants (Table 3).

Table 3: Comparison of History of Mental Health Comorbidities at Index Exposure to US Prevalence Data

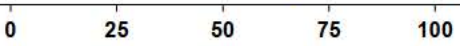
	Study Participants at Index Exposure N = 377			
History of:	Overall Population n (%)	DSM-5 OUD Negative N=210 n (%)	DSM-5 OUD Positive N=175 n (%)	US Prevalence Data
Depression	38 (10.1)	17 (8)	21 (12)	8.1%[1]
Anxiety	36 (9.5)	16 (8)	20 (11)	3.1–9.1%[2]
Alcohol Use Disorder	27 (7.2)	17 (8)	10 (6)	6.2%[3]
Bipolar Disorder	13 (3.4)	2 (1)	11 (6)	2.8%-4.4%[4]
Other SUD	10 (2.7)	0 (0)	10 (6)	3.9%[5]
Cannabis Use Disorder	7 (1.9)	1 (0)	6 (3)	1.5%[6]

1. https://www.cdc.gov/nchs/covid19/pulse/mental-health.htm
2. https://adaa.org/understanding-anxiety/facts-statistics
3. https://www.apa.org/topics/substance-use-abuse-addiction/alcohol-disorders
4. https://www.nimh.nih.gov/health/statistics/bipolar-disorder
5. https://www.samhsa.gov/data/sites/default/files/reports/rpt29393/2019NSDUHFFRPDFWHTML/2019NSDUHFFR090120.htm
6. https://pubmed.ncbi.nlm.nih.gov/31586809/

In addition, regardless of the presence or absence of a given mental health disorder at the time of index exposure, the sensitivity and specificity of results are generally consistent with the overall population (Figure 8 and Figure 9).

Figure 8: AvertD Sensitivity Results by Mental Health Status at Time of Index Exposure

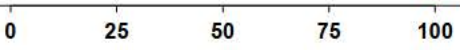
	History of Use	N	Sensitivity	Point Estimate (95% CI)	P-value
Depression	No	335		80.9% (73.8 – 86.8)	0.28
	Yes	38		95.2% (76.2 – 99.9)	
Anxiety	No	337		83.0% (76.1 – 88.6)	0.80
	Yes	36		80.0% (56.3 – 94.3)	
Alcohol Use Disorder	No	347		82.8% (76.1 – 88.3)	0.74
	Yes	26		80.0% (44.4 – 97.5)	
Bipolar Disorder	No	360		84.0% (77.4 – 89.2)	0.26
	Yes	13		63.6% (30.8 – 89.1)	
Other SUD	No	363		82.2% (75.5 – 87.8)	1.00
	Yes	10		90.0% (55.5 – 99.8)	
Cannabis Use Disorder	No	366		83.2% (76.7 – 88.6)	0.40
	Yes	7		66.7% (22.3 – 95.7)	



Data not available (n=8)

Figure 9: AvertD Specificity Results by Mental Health Status at Time of Index Exposure

	History of Use	N	Specificity	Point Estimate (95% CI)	P-value
Depression	No	335		79.2% (72.6 – 84.9)	0.91
	Yes	38		76.5% (50.1 – 93.2)	
Anxiety	No	337		78.3% (71.6 – 84.0)	0.76
	Yes	36		87.5% (61.7 – 98.5)	
Alcohol Use Disorder	No	347		79.9% (73.4 – 85.4)	0.57
	Yes	26		68.8% (41.3 – 89.0)	
Bipolar Disorder	No	360		79.3% (73.0 – 84.7)	0.59
	Yes	13		50.0% (1.3 – 98.7)	
Other SUD	No	363		79.0% (72.7 – 84.4)	1.00
	Yes	10		--	
Cannabis Use Disorder	No	366		78.9% (72.6 – 84.4)	1.00
	Yes	7		100.0% (2.5, 100.0)	



Data not available (n=8)

AvertD was specifically designed and trained for opioid use disorder by including genes/SNPs established to be associated with opioid dependency, such as the mu opioid receptor gene (2 SNPs), the delta opioid receptor gene and the kappa opioid receptor gene. In addition, the machine learning algorithm was specifically trained to classify individuals with OUD from individuals without OUD, not to classify individuals with or without other SUDs or other mental health comorbidities.

To explore if AvertD is classifying other comorbidities (mental health conditions or other SUDs) not OUD, the performance of AvertD for classifying these comorbidities in OUD-negative participants was evaluated. The analyses removed OUD-positive patients to avoid this confounding factor. The performance of AvertD in other comorbidities is shown in Figure 20. The sensitivity and specificity of AvertD in classifying each comorbidity is essentially the same as the prevalence of these comorbidities in the underlying study population demonstrating that AvertD performance seen in the study is for OUD classification not these comorbidities.

2.5.6 Applicability Conclusions

The clinical study as designed, and its resulting data demonstrate that the study population reflects the intended use population ensuring the results are applicable to the intended use population. Additional data have been collected, as discussed with the FDA prior to the submission of this De Novo, and analyzed and further support the applicability of the results. All participants in the study met the inclusion and exclusion criteria and took opioids at their index exposure for 4 to 30 days (acute pain relief). Self-reported index exposure most accurately defines whether a participant took an oral opioid as it is known that many patients do not fill or take their prescriptions for oral opioids. Medical record documentation corroborates the self-reported index exposure providing additional certainty in the study methodology and results. Prospective prognostic enrichment used in the study is a recognized valid study design for low prevalence conditions such as OUD. When prognostic enrichment is prospectively defined in the study protocol bias is mitigated and does not affect performance estimates. The additional data also suggest that that the study did not enrich for mental health comorbidities at the time of index exposure and that AvertD performs well in patients with and without mental health comorbidities.

2.6 Benefit-Risk Summary

Opioid use and OUD are serious, ongoing public health problems, yet physicians have no tools to assess a patient’s genetic risk of OUD prior to being prescribed prescription oral opioids. There is a critical unmet need for objective tools including those that assess genetics to assist physicians and their patients in the decision-making process for acute pain management.

AvertD demonstrated 82.8% sensitivity and 79.2% specificity in the clinical study. The results showed that a positive result with AvertD is 18 times more likely to happen in a patient who will develop OUD than it would in a patient who will not develop OUD. When used in conjunction with a complete clinical evaluation, results from AvertD test provide individual, genetic data for decision-making regarding opioid use and can be integrated into the pain management treatment paradigm.

As supported through additional analyses conducted in response to FDA concerns, remaining uncertainty regarding the clinical study population, interpretation of the study

results, and the applicability of the results to the intended use population have been sufficiently mitigated to enable a benefit-risk assessment.

Potential risks of AvertD include false negatives, false positives, and the possibility for physicians to over rely on results. These risks can be mitigated through proper use, which will be reinforced through labeling and education. AvertD is intended for use in conjunction with a clinical evaluation and the labeling will emphasize the importance of following opioid prescribing guidelines, even in the presence of a negative test result. A false positive could mean a patient that is at low genetic risk of developing OUD, still avoids an opioid prescription and is prescribed an analgesic alternative. Finally, with any risk assessment tool, there is the potential for overreliance on the results. Labeling and education will further reinforce that AvertD is intended to be used in combination with a clinical evaluation and assessment of the patient.

In summary, AvertD will enable patients and providers to make more informed choices about prescribing opioids for acute pain, differentiating patients who are at genetic risk for developing of OUD from those who are not, and allowing the prescription of opioids in a manner consistent with recommended guidelines. The benefits of providing additional, currently unavailable, genetic risk information outweigh the potential risks of false negative/positive results and over reliance on test results, which can be mitigated through labeling and Special Controls (see Appendix Section 12.1). Therefore, AvertD should be granted marketed authorization via granting of the De Novo request.

3 BACKGROUND ON OPIOID USE DISORDER AND UNMET NEED

Summary

- The opioid epidemic is a public health emergency in the United States (US) with no sign of slowing down.
- Opioid overdose is estimated to cause approximately 185,000 emergency room visits annually for patients 15 years of age and older.
- Opioid misuse and abuse disproportionately impact young Americans, with the highest percentage of self-reported prescription pain reliever misuse and abuse reported among adults 26–34 years old.
- OUD is characterized by a desire to obtain and take opioids despite social and professional consequences.
- Individuals with OUD frequently start by misusing prescription opioids.
- Currently there are no FDA cleared or approved risk assessment tools to differentiate patients a genetic risk for developing OUD and suffering the long-term consequences eventually arising from opioids initiated under a provider's care.
- Research has shown that genetics can account for approximately 50% of the risk of developing OUD (Berrettini 2017).
- Patients and physicians need better decision-making tools to assess individual risk of OUD prior to the decision to use opioids for acute pain management.

3.1 Epidemiology of Opioid Use Disorder

There is a critical unmet need to reduce the harmful effects of opioids, which constitute a serious, ongoing US public health problem associated with significant mortality, morbidity and costs:

- Drug overdose is the leading cause of death for Americans under 50, and opioids account for the majority of overdose deaths (Drug Policy Aliance 2022).
- Every day more than 130 Americans die from opioid addiction (CDC).
- Overdose deaths involving prescription opioids increased nearly five times from 1999 to 2020 (CDC 2021).
- Opioid overdose is estimated to cause approximately 185,000 emergency room visits annually for patients ages 15 years and older (Rui P 2016).

- Opioid misuse and abuse disproportionately impact young Americans in the primeof their lives, with highest percentage of self-reported prescription pain reliever misuse and abuse reported among adults 26–34 years old (CDC 2019).
- The total US economic burden of opioid use disorder has increased from an estimated $78 billion in 2013 (Florence et al 2016) to a staggering $179 billion in 2018 (Davenport et al 2019), of which approximately one-third are healthcare costs.
- In 2018, 15.0% of the US population filled one or more opioid prescriptions with the self-reported prevalence of opioid misuse at 3.7% in the past year (CDC 2019).

While there is variability in the estimates in the precise scope of the ongoing harm caused by oral opioids, one fact remains clear – a proportion of persons prescribed oral opioids will subsequently develop OUD.

3.2 Clinical Condition

OUD is characterized by a desire to obtain and take opioids despite social and professional consequences. Individuals with OUD experience an overpowering desire to use opioids, have an increased opioid tolerance, and will experience withdrawal syndrome when opioid use is discontinued.

3.3 Role of Genetics

While estimates vary, the degree of addiction that is due to genetics (i.e., heritability), ranges from 20% to 60% (Crist et al 2019; Deak and Johnson 2021). A reasonable approximation of a complex genetic model to predict the genetic component of OUD is represented by twin studies, which show heritability of approximately 50% (Berrettini 2017). Numerous genomic studies across ancestries (both candidate gene and genome-wide association approaches) have identified genes specific to OUD including the OPRM1, OPRD1, as well as genes seen across SUDs including the DRD2 (Crist et al 2019; Deak et al 2022).

Fundamentally, genetic predisposition for OUD occurs in the meso-limbic system, sometimes called the “reward center.” In this area, chemical messages release dopamine, and genes that control these messages and subsequent release are referred to as the “Brain Reward Cascade.” Genetic mutations affecting the Brain Reward Cascade can result in substance seeking behavior.

3.4 Gap in Opioid Risk Assessment: Lack of Incorporation of Genetics

The CDC states that “currently available risk stratification tools…show insufficient accuracy for classification of patients as at low or high risk for abuse or misuse” (Dowell et al 2016). While OUD risk assessment prior to prescribing opioids is a cornerstone of

clinical practice to help prevent opioid misuse, abuse, and overdose, genetic risk of patients is not available to help make this decision.

3.5 Unmet Need

New options for the prevention of OUD and for promoting safer prescribing practices by healthcare professionals are critically needed. Given that genetics make up a significant portion of the risk for addiction, it is critical for physicians and patients to understand the individual, genetic risk of addiction to be considered in the context of the patient's overall risk of addiction prior to prescribing opioids. Yet, no genetic risk assessment tool exists today to meet this need.

4 AVERTD PRODUCT DESCRIPTION

Summary

- AvertD is a genetic risk assessment tool that provides objective information about a patient's potential genetic risk for OUD.
    - Used in combination with a clinical evaluation, AvertD results can facilitate informed decision-making regarding the prescription of oral opioids to relieve acute pain.
- AvertD detects, identifies, and analyzes 15 SNPs in brain reward pathways that are associated with OUD.
- AvertD brings the benefits of personalized medicine to understanding a patient's risk for OUD, addressing an important public health need.

4.1 Overview of AvertD

The AvertD genetic risk assessment tool is designed to provide healthcare professionals and patients with objective information about a patient's potential genetic risk for OUD to facilitate informed decision-making regarding prescription oral opioids to relieve acute pain.

AvertD utilizes proprietary film-based microarray technology to detect, identify, and analyze 15 SNPs involved in the brain reward pathways that are associated with OUD (Table 4). These SNPs are analyzed and used to determine genetic opioid risk through a proprietary algorithm within the multiplex analyzer instrument. AvertD produces a binary test result of high or low genetic risk for OUD.

Table 4: The Fifteen Genetic Polymorphisms Detected by AvertD

Allelic Variants	Gene Name	rs Number
5-HTR2A C>T	Serotonin 2A Receptor	rs7997012
COMT G>A	Catechol-O-Methyltransferase	rs4680
DRD1 A>G	Dopamine D1 Receptor	rs4532
DRD2 G>A	Dopamine D2 Receptor	rs1800497
DRD4 T>C	Dopamine D4 Receptor	rs3758653
DAT1 A>G	Dopamine Transporter	rs6347
DBH C>T	Dopamine Beta Hydroxylase	rs1611115
MTHFR C>T	Methylene Tetrahydrofolate Reductase	rs1801133
OPRK1 G>T	Kappa Opioid Receptor	rs1051660
GABA C>A	Gamma-Aminobutyric Acid (GABA)	rs211014
OPRM1 A>G	Mu Opioid Receptor	rs1799971
MUOR G>A	Mu Opioid Receptor	rs9479757
GAL T>C	Galanin	rs948854
DOR G>A	Delta Opioid Receptor	rs2236861
ABCB1 C>T	ATP Binding Cassette Transporter 1 (ABCB1)	rs1045642

4.1.1 AvertD Components and Instrument Requirements

AvertD is designed to be used with the INFINITI PLUS Analyzer (a class 2, 510(k) cleared medical device, sold separately). Components of AvertD are listed and described in Table 5.

Table 5: Components of AvertD

Component Name	Description/Use
INFINITI® Buccal Sample Collection Kit	• Collection, stabilization, transportation and room temperature storage of buccal samples for molecular diagnostic applications
AvertD Amplification Mix	• Provides the reagents for the multiplex PCR amplification step • Consists of Multiplex Primer Mix, dNTPs, PCR Buffer
AvertD Intellipac® Reagent Module	• Communicates with the INFINITI PLUS Analyzer and provides the reagent information • Contains four reservoirs that house the test reagents and has an integrated 64K bit memory chip • Provides the reagents needed to run the test (ASPE master mix and Hybridization Buffer)
AvertD BioFilmChip® Microarray	• Test film-based microarray consisting of multiple layers of porous hydrogel matrix (8–10 µm in thickness) coated on a polyester solid support. • The top layer is designed for the immobilization of biomolecules (capture probes) to enable the genomic analysis on the same platform. • The allele specific primer is tagged at 5' end with a sequence complementary to a specific capture probe. • The Zipcode (capture probe) and Anti-zipcode (ASPE) technology make the BioFilmChip Microarray assay-specific.
AvertD Assay-Specific Software	• Algorithm specifically designed, developed and tested to determine the genotype call for each gene and the patient's genetic risk for OUD • Formats assay results report for the AvertD user

4.1.2 Test Principle

Steps of the testing principle process are as follows:

1. Sample Collection and Shipment to the Lab

   A buccal sample is collected by a healthcare professional using the INFINITI Buccal Sample Collection Kit, which includes a collection device (a flocked swab which is registered and listed for marketing in the US), a vial with DNA stabilizing solution and materials for transportation. The sample is shipped to the lab overnight under ambient conditions.

2. DNA Extraction

   DNA is extracted from the buccal sample using standard laboratory methods and then undergoes amplification using the AvertD Amplification Mix. The DNA extraction is performed manually using standard laboratory equipment.

   Extracted DNA samples must meet the following criteria for purity and concentration for use:

   - Purity: an ultraviolet light absorbance ratio of $A_{260}/A_{280} \geq 1.2$ and
   - Concentration: ≥ 1 ng of DNA per uL

3. Sample Amplification

   The extracted DNA from the buccal sample undergoes amplification using the Amplification Mix, which provides the necessary reagents for the multiplex PCR amplification steps for the 15 genes detected by the assay. The PCR amplification is performed manually using standard laboratory equipment.

4. Allele Specific Primer Extension Reaction

   The sample is loaded onto the sample plate of the INFINITI PLUS Analyzer and the remainder of the processes are automated by the analyzer. The Intellipac Reagent Module provides the assay-specific reagents needed for the Allele Specific Primer Extension (ASPE) and subsequent steps. The ASPE reaction progresses by subjecting the sample to repeated cycles of a temperature profile that denatures, anneals and extends the PCR products with all steps automated by the analyzer.

   The ASPE reagent contains a fluorescent nucleotide (DY648-dCTP) that is incorporated into the primer-extended, PCR products during the extension step of reaction. Both wildtype and mutant extension primer-extended products are labeled with DY648-dCTP and are detected using separate spots on the BioFilmChip Microarray.

5. Application to the Microarray Chip and Hybridization

   After the ASPE reaction is complete, the hybridization buffer, which is included in the Intellipac Reagent Module, is added to the sample by the analyzer.

   The sample is then automatically applied to the AvertD BiofilmChip Microarray by the analyzer. The microarray chip has spots for the assay-specific capture probes, negative control, and registration.

6. Scanning of the Microarray

   The BioFilmChip Microarray is scanned by the INFINITI PLUS Analyzer.

7. Signal Detection and Analysis

   A specific algorithm is utilized to determine the genotype for each gene and then a risk classification for OUD.

8. A report is produced by the instrument at the end of the run.

4.2 Mechanism of Action/Determination of Risk for OUD

AvertD uses an algorithm that was specifically designed, developed, and tested to classify patients with OUD versus patients without OUD. When this test is performed prior to oral opioid prescription it allows the clinician and the patient to understand if the patient's genetics are similar to the group who developed OUD, based upon the genotype call for each gene.

The algorithm was developed from machine learning on genotypes from more than 1,700 individuals with and without OUD at a case to control ratio of approximately 1:1. The modeling was performed within a proprietary data analytical tool where 80% of the dataset was used for leaning and 5-fold cross validation, and 20% was reserved for a holdout. Logloss of various models was compared, and the most accurate model was selected for blinded test deployment into a large feasibility dataset. The data for both the holdout and the feasibility data were not part of the training data set. After the feasibility testing, the algorithm was version controlled and "locked".

The AvertD OUD algorithm from learning environment above is deployed in the genotype results from the 15 gene genotype test results (HTR2A, COMT, DRDI, DRD2, DRD4, DATI, DBH, MTHFR, OPRKI, GABA, OPRMl, MUOR, GAL, DOR, ABCBl). The algorithm uses the genotype to formulate the value (0.000000000–1.000000000). The value is set to 1 for all OUD scores ≥ 0.33 and to 0 for all OUD score < 0.33. A value of 1 indicates high risk for OUD.

4.2.1 Determination of Genotype Calls

Three spots for each analyte and three background control spots are used to determine genotype. The background control spots are used to adjust for background relative fluorescence units (RFUs). The signals (RFU) from the three analyte spots are averaged and the CV and SD are calculated.

4.3 Intended Use

SOLVD is seeking the following intended use for AvertD:

> AvertD™ is a prescription, qualitative genotyping test used to detect and identify 15 clinically relevant genetic polymorphisms in genomic DNA isolated from buccal samples collected from adults. The 15 detected genetic polymorphisms are involved in the brain reward pathways that are associated with opioid use disorder (OUD) and identify patients who may be at increased genetic risk for OUD. Information from AvertD™ provides patients 18 years of age or older and healthcare providers

with objective information to be used for informed decision-making prior to the first prescription of oral opioids for acute pain. The information from AvertD™ is intended to be used in combination with a clinical evaluation and assessment of the patient.

4.4 Proposed Classification

The De Novo request seeks to classify, under Section 513(f)(2) of the FD&C Act, AvertD as a Class II medical device subject to Special Controls because General and Special Controls are believed to provide a reasonable assurance of safety and effectiveness. A proposed classification regulation for this generic type of device – Opioid Use Disorder Genetic Risk Assessment System – is provided.

A series of Special Controls is proposed for AvertD and any other test classified as an Opioid Use Disorder Genetic Risk Assessment System followed by an analysis of why General and Special Controls are adequate to provide a reasonable assurance of safety and effectiveness. The proposed Special Controls rely upon well-accepted methods common to many genotyping tests and are modeled after several Class II genetic risk assessment tests, including 21 CFR 866.6090 – Cancer Predisposition Risk Assessment System, 21 CFR 866.5950 – Genetic Health Risk Assessment System and 21 CFR 862.3364 – Pharmacogenetic Assessment System, as well other in vitro tests.

See Appendix Section 12.1.

4.5 Analytical Performance

Rigorous analytical testing was performed to determine the analytical sensitivity (limit of detection), precision/reproducibility, accuracy compared to sequencing, interfering substances and specimen and reagent stability. The data demonstrate that AvertD has sufficient analytical performance characteristics to provide reliable results to healthcare providers and patients.

4.5.1 Method Comparison (Accuracy)

AvertD was compared to Sanger bidirectional sequencing to evaluate its accuracy in determining the genotype of the target analytes. Three laboratories participated in the study. Each laboratory evaluated a different set of de-identified patient samples with AvertD. A total of 453 samples were included in the study, but 19 did not qualify (11 samples did not meet DNA quality specifications and 8 samples did not have sequencing complete for all analytes). A total of 434 samples had complete bidirectional sequencing and AvertD test results. All 45 genotypes were included in the study (Table 6). Concordant results were obtained for 6,507/6,510 analytes. The results from the comparison study demonstrated that AvertD had an accuracy of > 99.95%.

Table 6: Agreement between AvertD and Bidirectional Sequencing

Allelic Variants	Genotype	Accuracy of AvertD	
		Number of Alleles with Concordance	Percentage of Alleles with Concordance
5-HTR2A (rs7997012) C>T	Wild Type	138/138	100.00%
	Heterozygous Mutant	236/236	100.00%
	Homozygous Mutant	60/60	100.00%
COMT (rs4680) G>A	Wild Type	119/119	100.00%
	Heterozygous Mutant	208/208	100.00%
	Homozygous Mutant	107/107	100.00%
DRD1 (rs4532) A>G	Wild Type	176/176	100.00%
	Heterozygous Mutant	196/196	100.00%
	Homozygous Mutant	62/62	100.00%
DRD2 (rs1800497) G>A	Wild Type	268/269	99.63%
	Heterozygous Mutant	151/152	99.34%
	Homozygous Mutant	13/13	100.00%
DRD4 (rs3758653) T>C	Wild Type	274/274	100.00%
	Heterozygous Mutant	146/146	100.00%
	Homozygous Mutant	14/14	100.00%
DAT1 (rs6347) A>G	Wild Type	235/236	99.58%
	Heterozygous Mutant	167/168	99.40%
	Homozygous Mutant	30/30	100.00%
DBH (rs1611115) C>T	Wild Type	276/276	100.00%
	Heterozygous Mutant	138/138	100.00%
	Homozygous Mutant	20/20	100.00%
MTHFR (rs1801133) C>T	Wild Type	197/197	100.00%
	Heterozygous Mutant	193/193	100.00%
	Homozygous Mutant	44/44	100.00%
OPRK1 (rs1051660) G>T	Wild Type	340/340	100.00%
	Heterozygous Mutant	88/88	100.00%
	Homozygous Mutant	6/6	100.00%
GABA (rs211014) C>A	Wild Type	260/260	100.00%
	Heterozygous Mutant	154/154	100.00%
	Homozygous Mutant	20/20	100.00%
OPRM1 (rs1799971) A>G	Wild Type	320/320	100.00%
	Heterozygous Mutant	100/100	100.00%
	Homozygous Mutant	14/14	100.00%

Allelic Variants	Genotype	Accuracy of AvertD	
		Number of Alleles with Concordance	Percentage of Alleles with Concordance
MUOR (rs9479757) G>A	Wild Type	370/370	100.00%
	Heterozygous Mutant	60/60	100.00%
	Homozygous Mutant	4/4	100.00%
GAL (rs948854) T>C	Wild Type	229/229	100.00%
	Heterozygous Mutant	167/167	100.00%
	Homozygous Mutant	38/38	100.00%
DOR (rs2236861) G>A	Wild Type	250/250	100.00%
	Heterozygous Mutant	159/159	100.00%
	Homozygous Mutant	25/25	100.00%
ABCB1 (rs1045642) C>T	Wild Type	91/92	98.91%
	Heterozygous Mutant	218/219	99.54%
	Homozygous Mutant	123/123	100.00%%

4.5.2 Precision/Reproducibility Study

A precision/reproducibility study was conducted at three laboratories. Twelve (12) samples were tested in the reproducibility study: 7 buccal samples collected from volunteers and 5 DNA samples from well characterized cell lines. The buccal samples were collected using the INFINITI Buccal Sample Collection Kit. The 12 samples underwent bidirectional sequencing to confirm their genotype.

Aliquots from each of the 12 samples were sent to each laboratory for evaluation using AvertD. The laboratory was blinded to the genotyping results from bidirectional sequencing. Each laboratory used 2 operators and each operator performed the test on 5 non-consecutive days. Three (3) lots of the reagents were used (Lot 1, Lot 2, and Lot 3) with each laboratory receiving 2 lots of reagents. Three INFINITI PLUS Analyzers were used, one at each site. The study was designed to evaluate a total of 10,800 analytes (12 samples × 3 laboratories × 2 operators/site × 5 days × 2 lots/site × 1 instrument/site × 15 analytes/test = 10,800 analytes). One operator at one site tested an extra set of the 5 DNA samples on one day (5 samples x 15 analytes/test = 75 analytes), resulting in a total of 10,875 analytes evaluated in the study.

The genotype for each analyte reported by AvertD was compared to the genotype obtained using bidirectional sequencing. The concordance rate was 100% with a 95% one-sided confidence limit of 100.0% (Table 7).

Table 7: AvertD Reproducibility by Genotype

Analytes	Samples Tested	Samples with Invalid Tests	Samples with Valid Results	Valid Samples with Discordant Calls	Valid Samples with Concordant Calls	Percent Concordant Calls
5-HTR2A	725	30	695	0	695	100.00%
COMT	725	30	695	0	695	100.00%
DRD1	725	30	695	0	695	100.00%
DRD2	725	30	695	0	695	100.00%
DRD4	725	30	695	0	695	100.00%
DAT1	725	30	695	0	695	100.00%
DBH	725	30	695	0	695	100.00%
MTHFR	725	30	695	0	695	100.00%
OPRK1	725	30	695	0	695	100.00%
GABA	725	30	695	0	695	100.00%
OPRM1	725	30	695	0	695	100.00%
MUOR	725	30	695	0	695	100.00%
GAL	725	30	695	0	695	100.00%
DOR	725	30	695	0	695	100.00%
ABCB1	725	30	695	0	695	100.00%
Total	**10,875**	**450**	**10,425**	**0**	**10,425**	**100.00%**

4.5.3 Limit of Detection (Analytical Sensitivity)

The analytical sensitivity (limit of detection) of AvertD was determined by testing 8 samples (4 patient buccal samples and 4 DNA samples from well-characterized cell lines). Each sample was tested at 8 serial dilutions with 20 replicates: 60 ng/µl, 30 ng/µl, 15 ng/µl, 17.5 ng/µl, 63 ng/µl, 1 ng/µl, 0.3 ng/µl, and 0.1 ng/µl of DNA. The study included 1,280 tests (8 samples × 8 dilutions × 20 replicates). The genotypes were confirmed by bidirectional sequencing.

The limit of detection was defined as the lowest level of genomic DNA (ng DNA input per test) that would give a ≥ 95% correct call rate. The lower limit of detection was using DNA at a concentration of 1 ng/µl. At this lower limit, the percent correct call rate was 100.0% (Table 8).

Table 8: Limit of Detection of AvertD

DNA concentration (ng/µl)	Number of samples tested	Number of samples with valid test results	Number of samples with correct results	Percentage of samples with correct results
1	160	160	160	100%
3	160	160	160	100%
7.5	160	160	160	100%
15	160	160	160	100%
30	160	160	160	100%
60	160	160	160	100%

4.5.4 Interference Study

A study was conducted to evaluate the effect of potential endogenous and exogenous interfering substances on AvertD performance. Buccal swab samples were collected using the INFINITI Buccal Sample Collection Kit. Samples were collected from individuals before exposure to the potential interference substance and then following direct exposure to the potential exogenous interferents were tested using AvertD. If direct exposure to endogenous substances was not possible, the potential endogenous substance was added directly to the tube containing the stabilizing solution immediately prior to insertion of the buccal swab sample.

Unexposed samples (control) and exposed samples were tested using AvertD. Fifteen (15) individuals participated in the study, and their genotypes were determined by bidirectional sequencing of the controls.

Thirteen (13) potential interferents were studied: antiseptic mouthwash, toothpaste, baking soda, cough syrup, cranberry juice, table salt, sugar, meat, chewing gum, hard candy, cigarette, coffee, and whole blood.

No interference with AvertD was observed for any of the tested substances.

4.5.5 Stability and Shelf Life

The stability of the buccal specimens was evaluated from patient collected specimens from the method comparison study. Collected specimens were evaluated to determine how long they may be stored at room temperature prior to DNA extraction. The quality of the extracted DNA was evaluated by absorbance ratio and concentration. Samples stored for up to 90 days at room temperature met the DNA quality requirements.

The stability of AvertD reagents was evaluated using the 3 lots of reagents. To support a shelf life of 1 year, the reagents were tested at least 12 months after their manufacture date. DNA samples from well characterized cell lines were used during the stability testing. All lots passed the acceptance criteria supporting the shelf life.

5 PRODUCT DEVELOPMENT HISTORY

Summary

- The FDA granted AvertD Breakthrough Device designation in 2018.
- In April 2020, SOLVD submitted a De Novo application for AvertD (formerly known as LifeKit Predict). The FDA denied the request in August 2021 and the decision was upheld on appeal in January 2022.
- SOLVD worked with the FDA to address the uncertainties of the performance of AvertD in the intended population and a De Novo application to classify AvertD as a Class II device was re-submitted in June 2022.

5.1 Regulatory History

The FDA granted AvertD Breakthrough Device designation on 29 March 2018. There are no FDA cleared or approved alternatives to identify genetic risk for developing OUD; making such a device available is, therefore, in the best interest of patients (FDA Breakthrough Designation Criteria).

In April 2020, SOLVD submitted a De Novo application for AvertD (formerly known as LifeKit Predict) under Section 513(f)(2) of the Federal Food, Drug and Cosmetic Act. The FDA denied the request in August 2021 and the decision was upheld on appeal in January 2022.

SOLVD worked collaboratively with FDA through an interactive process to identify a data collection and analysis plan that could address the open questions. All aspects of that plan were documented and reviewed by FDA prior to initiation of the data collection and analysis. Upon completion of data collection and analysis, a new De Novo was submitted by SOLVD in June 2022.

A 510(k) notification for the buccal swab collection device used to collect samples for analysis using AvertD is currently under review by FDA.

5.2 2022 De Novo Request Proposed Classification

The current De Novo request seeks to classify under Section 513(f)(2) of the FD&C AvertD as a Class II medical device subject to Special Controls because General and Special Controls provide a reasonable assurance of safety and effectiveness. A proposed classification regulation for this generic type of device – Opioid Use Disorder Genetic Risk Assessment System – is provided (see Appendix Section 12.1).

The proposed Special Controls rely upon well-accepted methods common to many genotyping tests and are modeled after several Class II genetic risk assessment tests, including 21 CFR 866.6090 – Cancer Predisposition Risk Assessment System, 21 CFR

866.5950 – Genetic Health Risk Assessment System and 21 CFR 862.3364 – Pharmacogenetic Assessment System, as well other in vitro tests.

The first proposed Special Control concerns the sample collection device and specifies that the sample collection device must be legally marketed (either FDA-cleared, FDA-approved or 510(k) exempt) as a standalone device or part of a test system or the sample collection device must be cleared as part of the device. This Special Control is common among many Class II in vitro tests given the importance of collecting a patient specimen to test safety and accuracy.

The second proposed Special Control concerns the device labeling to ensure that healthcare providers have adequate information available regarding how to collect a sample and perform the test, as well as the expected test performance and interpretation of the test results. This Special Control helps provide a reasonable assurance of safety and effectiveness by enabling healthcare providers to have ready access to important information about how to collect patient specimens to ensure accurate test results, and by providing users with sufficient information regarding the expected performance of test in the laboratory and the anticipated accuracy of the results.

The second Special Control also proposes that the labeling provide a detailed explanation of the interpretation of the test results and its limitations. This Special Control helps provide a reasonable assurance of device safety and effectiveness by providing comprehensive information to healthcare professionals about the test result, its meaning and limitations, thereby facilitating an informed decision-making discussion with the patient regarding prescription oral opioid use.

The third Special Control concerns design verification and validation testing, including analytical validation and clinical validation. This Special Control identifies required performance metrics, such as accuracy and sensitivity and specificity, as well as study design elements to ensure the quality and reliability of the completed studies. This Special Control helps provide a reasonable assurance of device safety and effectiveness by ensuring that the test meets clinically acceptable requirements for accuracy and performance to provide clinically meaningful information to healthcare providers and patients.

6 AVERTD CLINICAL STUDY

Summary

- The clinical performance of AvertD was evaluated in individuals with a history of exposure to prescription oral opioids for acute pain.
- Stratified random sampling and prognostic enrichment were used to study a population that mirrored the intended use of population of adults in the US who are prescribed oral opioids and to enrich the sample for OUD-positive participants.
- AvertD had a sensitivity of 82.8% (95% CI: 76.3 – 88.1) and specificity of 79.2% (95% CI: 73.1 – 84.5), meeting the pre-specified performance goals.
- Robust test performance was observed in all tested subgroups.
- The 3.98 positive likelihood ratio showed a strong increase in the probability of having OUD with a positive test result; the converse was true for the negative likelihood ratio (0.22).
- A patient who will develop OUD is 18 times more likely to receive a positive result than a patient who will not develop OUD.

6.1 Study Design

6.1.1 Overview

The AvertD clinical study was a multi-center, prospective study of participants with a history of exposure to prescription oral opioids. The objective of the study was to evaluate the clinical performance of AvertD in identifying individuals who may be at increased genetic risk for developing OUD after short-term exposure to prescription oral opioids for acute pain relief.

Enrollment included all participants who met the inclusion/exclusion criteria. At 9 of the sites, participants were approached during their normal clinical care, including 6 general practice sites and 3 sites that specialize in treating SUD, including OUD. Seven participants were enrolled at one site that performed research only. This approach minimizes subject selection bias as all participants who met the enrollment criteria were enrolled in the study.

To allow for sufficient time for OUD to develop, the index exposure to oral opioids was retrospective. Opioid exposure needed to occur at least 1 year before enrollment. After enrollment, each participant's confirmed OUD status was compared to the presence or absence of a genetic predisposition for OUD as determined by AvertD.

Each participant provided two buccal swabs for testing with AvertD. All buccal samples were collected by a healthcare professional using the INFINITI Buccal Sample Collection Kit.

One central College of American Pathologists (CAP) certified and Clinical Laboratory Improvement Amendments (CLIA) accredited laboratory (Prescient Lab Services) tested all study specimens, which contained study participant ID as the only identifier. The laboratory personnel (including laboratory technicians, supervisors and medical director) were blinded to participant source, participant demographics, and participant clinical information including OUD status. The statistician was blinded to the OUD status and the laboratory results during the conduct of the study. The investigators and participants were blinded to the test results.

6.1.2 Enrichment Approach

6.1.2.1 Rationale for Enrichment Approach in AvertD Clinical Trial

Enrichment is a scientifically and statistically valid clinical study design option. In the case of the AvertD study, enrichment was critical to complete the clinical study in an efficient and least burdensome means and to provide robust estimates of the test's performance, particularly for sensitivity.

If the prevalence of OUD is 1%, then the study would require at least 150 / 0.01 = 15,000 participants to obtain 150 OUD+ participants. This number could be much higher in a prospective study due to loss of follow-up and deaths of affected individuals over the study period. The study period would also need to be long (e.g., several years) to allow OUD to develop. Thus, enrichment was added to the design.

The clinical study utilized an enrichment strategy known as Prognostic Enrichment. Using a Prognostic Enrichment strategy, patients who had a greater likelihood of having a disease-related endpoint event – in this case, being OUD positive were selected. Prognostic Enrichment Strategy is recognized as a valid approach in the FDA guidance document entitled "Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products" (FDA 2019). While the guidance document was intended for therapeutic products and risk reduction, the principles of study design apply equally well to assays, such as AvertD.

The guidance document stated that strategies for enrichment that are prospectively planned and that "generally do not compromise the statistical validity of the trials or the meaningfulness of the conclusions reached for the population actually studied." In the case of the AvertD clinical study, the enrichment strategy was prospectively planned and executed. The likelihood groups (i.e., "risk pools") were assigned after patients were enrolled in the study, assignment was not known by site study personnel, and assignment was performed by an individual blinded to patients AvertD results. Further the statistician using the likelihood groups was blinded to the participant outcome (OUD

positive or negative) and AvertD test results. The Agency concurred that enrichment was needed to obtain a sufficient number of OUD-positive participants.

6.1.2.2 Ensuring Sufficient OUD-positive Participant Recruitment

Prospective prognostic enrichment was included in the study design facilitated in part by recruiting participants at sites that offered OUD treatment to increase the likelihood of enrolling enough participants with OUD.

6.1.3 Enrollment Criteria

Participant selection was based on the inclusion and exclusion criteria provided in Table 9 and Table 10.

Table 9: Inclusion Criteria

	Study Inclusion Criteria
1	Individual is at least 18 years old
2	Individual or legal representative has consented to participate in the study
3	Individual has provided consent for DNA testing (either by signing the informed consentfor this study or by past consent). In the latter case, the DNA sample collected in a prior study must meet all requirements for this study
4	Individual has consented to buccal sample collection in accordance with this study protocol or has a DNA sample that meets the DNA requirements of the studyas documented by signing the study-specific informed consent
5	a. Individual was exposed to prescription oral opioids for a duration of 4–30 consecutive days
	b. A psychiatrist has diagnosed the individual as having OUD according to DSM-5 criteria
6	The index exposure to prescription oral opioids began at least 1 year prior to enrollment in this study

Table 10: Exclusion Criteria

	Study Exclusion Criteria
1	Individual has ever received medical care that included taking oral opioids for more than 30 consecutive days unless a psychiatrist has diagnosed the individual as having OUD according to DSM-5 criteria
2	Individual or legal representative is not able to provide informed consent to participate inthe study

The study inclusion and exclusion criteria were designed to mirror the intended use population and incorporate the current research and clinical knowledge about the development of OUD:

- Qualifying individuals were to have a minimum exposure of 4 consecutive days to oral opioids because this duration has been shown to precede persistent opioid use and is consistent with clinical prescribing patterns in the US (Shah et al

2017a; Shah et al 2017b). This minimum exposure period was agreed upon with FDA during the Pre-Submission process.

- A minimum follow-up period of 1 year after oral opioid exposure was specified to allow sufficient time to transition from first opioid exposure to developing OUD. This minimum period of follow-up was agreed upon with FDA during the Pre-Submission process.

The retrospective element of the study was that participants self-reported their index exposure to opioids. Self-reporting of index exposure is required, as merely obtaining a prescription from a physician does not necessarily indicate that patients filled or used (i.e., took) the medication (Cramer et al 1989).

6.1.4 Stratified, Random Sampling of the Study Analysis Population

A pre-specified random, representative sampling using strata was employed to ensure the study analysis population from the enrolled participants mirrored the intended use of population of adults in the US who are prescribed oral opioids and to ensure a sufficient number of OUD-positive participants were included while minimizing bias. The sample size was statistically powered to test sensitivity and specificity (see Section 6.1.7.1).

Participants were stratified by sex, age (four age groups), length of follow-up since oral opioid exposure, and higher or lower likelihood of having OUD (determined by presence of SUD) to produce 32 strata for randomization. As the study enrolled participants, demographic data and the likelihood of having OUD were forwarded to a blinded statistician for review to determine whether an adequate pool was available to randomly populate the 32 pre-specified strata.

After the statistician reviewed a total of 689 participants for whom all requisite data had been obtained, the statistician judged an adequate pool was available to randomly sample the study analysis population. A total of 812 participants were enrolled, at which time enrollment ceased. The statistician's random sampling of the study analysis population identified 385 participants who populated 32 distinct subgroups (strata). It should be noted that the independent statistician was blinded to the AvertD test result throughout this process.

6.1.5 Clinical Truth

Participants were assessed by a clinician at the study site at enrollment (after signing consent forms) for the presence or absence of DSM-5 OUD using a clinical evaluation, which consisted of a conversation with the participant to gather clinical information (clinical history) relevant to a diagnosis of OUD. Participants for whom a DSM-5 OUD diagnosis was established were assigned an outcome of OUD positive for the study.

6.1.6 Study Endpoints

6.1.6.1 Primary Endpoints

The study had two co-primary endpoints:

- Sensitivity, defined as the proportion of participants with OUD who arecorrectly identified by AvertD as positive
- Specificity, defined as the proportion of participants without OUD who arecorrectly identified by AvertD as negative

Sensitivity and specificity were selected as the co-primary endpoints because these measures are familiar to healthcare providers and will help to identify two patient subpopulations of interest:

- Patients who are at genetic risk to develop OUD (Sensitivity)
- Patients who are not at genetic risk to develop OUD (Specificity)

This information informs the decision-making process as healthcare providers and patients may judge whether the benefits of short-term opioid pain relief outweigh the risks of harmful side effects.

6.1.6.2 Secondary Endpoints

Based on Pre-Submission discussions with the FDA, the study included likelihood ratios as the secondary endpoints. In evidence-based medicine, likelihood ratios commonly are used to assess the value of performing a test, particularly a risk assessment test.

The study had two co-secondary endpoints:

- Positive likelihood ratio (LR+)

$$LR+= \frac{Sensitivity}{1 - Specificity}$$

- Negative likelihood ratio (LR-)

$$LR-= \frac{1 - Sensitivity}{Specificity}$$

The secondary endpoints are estimated with 95% confidence limits which maintains nominal alpha if the co-primary endpoints are both successful.

6.1.7 Statistical Methods

6.1.7.1 Determination of Sample Size

Sample sizes were determined for a single binomial test against a constant rate for the binomial parameter. The power was computed at 90% because both endpoints must pass for the primary endpoint to be successful and the joint power for both is 0.9*0.9=0.81. As determined by PASS 14 software

(https://www.ncss.com/software/pass/) for 90% power at alpha = 0.025, 154 completed OUD-positive participants and 159 completed OUD-negative participants were required to achieve a lower confidence limit above 0.595 for sensitivity and above 0.555 for specificity. The participant numbers were increased by approximately 10%, resulting in a target sample size of 171 OUD-positive participants and 177 OUD-negative participants, for a total sample size of 348 participants in both groups combined.

6.1.7.2 Performance Goals

The sensitivity performance goal was defined as a lower bound of the 95% CI greater than 55.9%. The specificity performance goal was defined as the lower bound of the 95% CI greater than 55.5%.

In the absence of comparator data or a predicate device, the pre-specified performance goals for sensitivity and selectivity were selected based on experience interacting with regulatory institutions and preliminary testing of AvertD. These pre-specified goals were established prior to the initiation of the clinical study. For point estimates in the range of 70% to 80%, experience indicates that lower boundaries in the point estimate minus 11% to 15% range are acceptable. Preliminary results from AvertD indicated estimates of sensitivity and specificity resulting from an algorithm testing set were 76% and 72%, respectively. As a conservative assumption, the estimate of the study was assumed to be about 4% lower, 72% for sensitivity and 68% for specificity. Therefore, the performance goal for both endpoints was set to be the point estimate minus 12.5%:

Performance goal sensitivity = 72% - 12.5% = 59.5%

Performance goal specificity = 68% - 12.5% = 55.5%

6.1.7.3 Analysis Populations

The Study Analysis Population included all participants randomly selected to populate the 32 strata.

The primary and secondary analyses required paired evaluations (an AvertD test result and clinical truth) and therefore were conducted in the Completed Cases Population, which included all participants with AvertD test results.

6.1.7.4 Missing Data

A worst-case scenario sensitivity analysis was performed for missing data (i.e., missing test results).

6.2 Study Participants

6.2.1 Descriptive Statistics of Study Population

6.2.1.1 Participant Demographics

Of the 689 enrolled participants, 385 participants from 10 sites were randomly selected to populate the 32 strata and formed the Study Analysis Population. The number eligible and the number selected in this array are presented in Table 11.

Table 11: Distribution of Selected Participants by Strata

Age (years)	Sex	Follow-up (years)	Had an SUD (High Likelihood of OUD)	Did not have an SUD (Low Likelihood of OUD)
18–34	Female	1–3	4	4
		4+	25	24
	Male	1–3	7	7
		4+	41	25
35–49	Female	1–3	2	2
		4+	25	22
	Male	1–3	3	6
		4+	43	21
50–64	Female	1–3	4	7
		4+	12	16
	Male	1–3	3	4
		4+	14	17
65+	Female	1–3	4	6
		4+	2	3
	Male	1–3	11	11
		4+	5	5

Table 12 shows the participant demographics and characteristics.

Table 12: Participant Demographics and Characteristics

Category	N=385
Mean age at exposure, years (SD)	33 (17.7)
Age, %	
18–34	137 (35.6)
35–49	124 (32.2)
50–64	77 (20.0)
65+	47 (12.2)
Sex, n %	
Male	222 (57.7)
Female	163 (42.3)
Race, n %	
White	355 (92.2)
African American	14 (3.6)
Asian/Pacific Islander	2 (0.3)
Biracial	1 (0.3)
Other	7 (1.8)

Unknown	6 (1.0)
Ethnicity, n %	
Hispanic	91 (24)
Non-Hispanic	288 (76)
Follow-up Time Since Index Exposure, %	
1–3 years	85 (22.1)
4+ years	300 (77.9)

The vast majority of participants (98.2%; 378 out of 385) in the study population were recruited and enrolled as they came to the sites for clinical care which was unrelated to the study. Nine (9) of the 10 sites, although participating in research studies, have clinical practices that patients visit as part of their standard clinical care. Three hundred and seventy-eight (378) participants from these 9 sites were enrolled while visiting the site for regular clinical visits. Only one site (Site 7) enrolled 7 participants who were not recruited during regular clinical visits. Participants were recruited and enrolled from these sites in a manner that mitigated the risk of selection bias. Additional details are provided in Appendix Section 12.3.

6.2.2 Clinical Truth: OUD Status at Time of Enrollment

A total of 175 (45.4%) participants had a DSM-5 diagnosis of OUD.

For longer time since index exposure, there is more time an individual is at risk for development of OUD. The data in the study supports this concept, with a higher percentage of participants being OUD positive based on stratification of time since initial exposure (Table 13). Capturing exposure retrospectively allowed the study to capture a greater length of time since index exposure, and a higher rate of OUD incidence.

Table 13: Percentage of Participants with OUD by Time Since Index Exposure

Time Since Exposure (Years)	Percent of OUD-positive participants
1–3	28.9%
4–7	35.0%
8–10	40.9%
11–13	61.8%
14–16	61.3%
17–24	68.3%
25+	75.0%

6.2.3 Available AvertD Test Results for Participants

AvertD test results were available for 99% of participants (381/385). Test results were not available for 4 participants due to inadequate DNA extraction from the buccal specimen.

6.3 Safety Results

No adverse events were reported as a result of the buccal sample collection.

6.4 Effectiveness Results

6.4.1 Co-Primary Endpoint Results

The AvertD had a sensitivity of 82.8% (95% CI: 76.3 – 88.1) and specificity of 79.2% (95% CI: 73.1 – 84.5) and met the pre-specified performance goals (Figure 4 and Table 14).

Table 14: Sensitivity and Specificity of AvertD

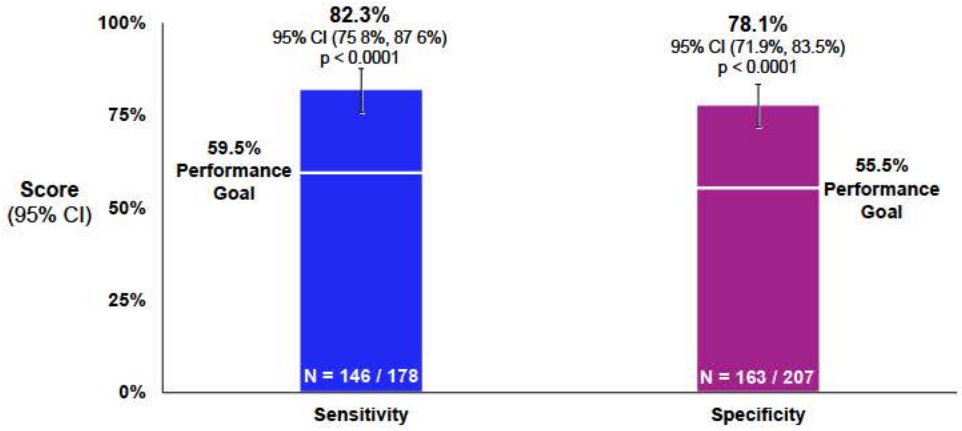
		OUD Diagnosis		Total
		-	+	
AvertD assay results	**-**	164	30	194
	+	43	144	187
Total		207	174	381

Sensitivity=100*(144/174) = 82.8% (95% CI: 76.3 – 88.1); p < 0.0001
Specificity=100*(164/207) = 79.2% (95% CI: 73.1 – 84.5); p < 0.0001

6.4.1.1 Co-Primary Endpoint Sensitivity Analyses

A sensitivity analysis was performed for the 4 participants without a test result. In the sensitivity analysis, 1 of the 4 participants was OUD positive and imputed as a negative test result (assuming this is a false negative) and 3 participants were OUD negative and imputed as false positives. Under these worst-case assumptions that all 4 missing test results are assumed to be false negative or false positives, the sensitivity was 82.3% and specificity was 79.1%, still achieving statistical significance (Figure 10).

Figure 10: Sensitivity Analysis–Worst-Case Imputation for Missing Data



6.4.1.2 *Co-Primary Endpoint Subgroup Analyses*

A series of sensitivity analyses was performed to determine whether sex, age, length of follow-up from opioid exposure, race or ethnicity affected sensitivity or specificity. No statistically significant differences were observed demonstrating robust test performance in the subgroups (Figure 11 through Figure 14).

Figure 11: Subgroup Analysis for Sensitivity by Age Group and Sex in the OUD-Positive Population (N=174)

		n / N	Sensitivity	Point Estimate (95% CI)	Subgroup p-value
Overall		**144 / 174**		**82.8%** (76.3 – 88.1)	
Sex	**Females**	**56 / 66**		**84.9%** (73.9 – 92.5)	**0.68**
	Males	**88 / 108**		**81.5%** (72.9 – 88.3)	
Age	**18-34**	**61 / 74**		**82.4%** (71.8 – 90.3)	**0.90**
	35-49	**52 / 61**		**85.3%** (73.8 – 93.0)	
	50-65	**20 / 25**		**80.0%** (59.3 – 93.2)	
	65+	**11 / 14**		**78.6%** (49.2 – 95.3)	

Figure 12: Subgroup Analysis for Sensitivity by Length of Follow-up from Opioid Exposure, Race, and Ethnicity in the OUD-Positive Population (N=174)

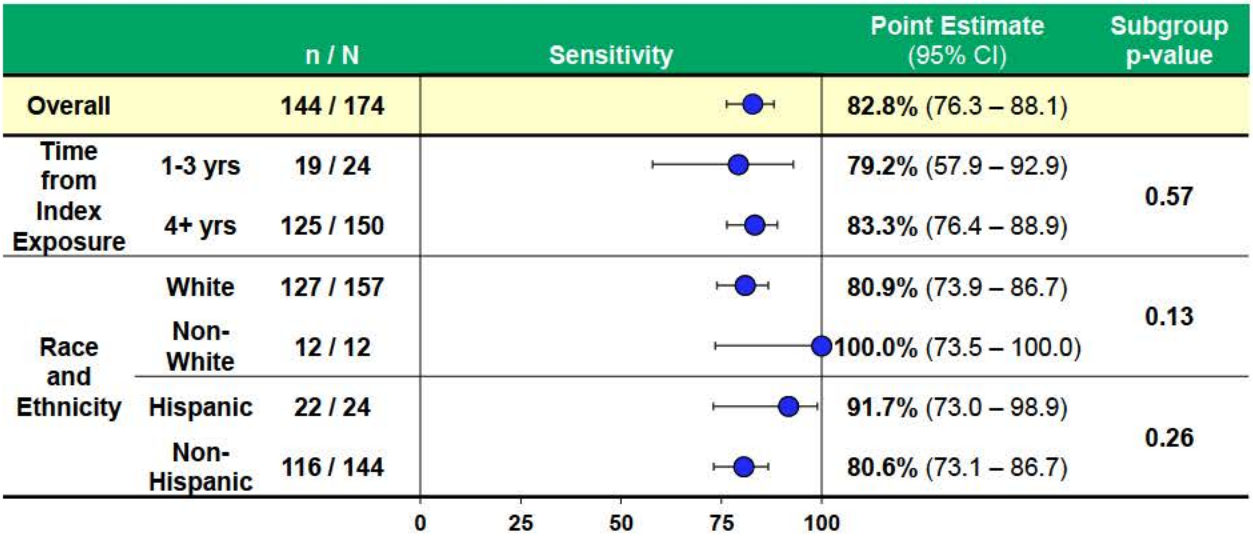


Figure 13: Subgroup Analysis for Specificity Results Based on Sex and Age in the OUD-Negative Population (N=207)

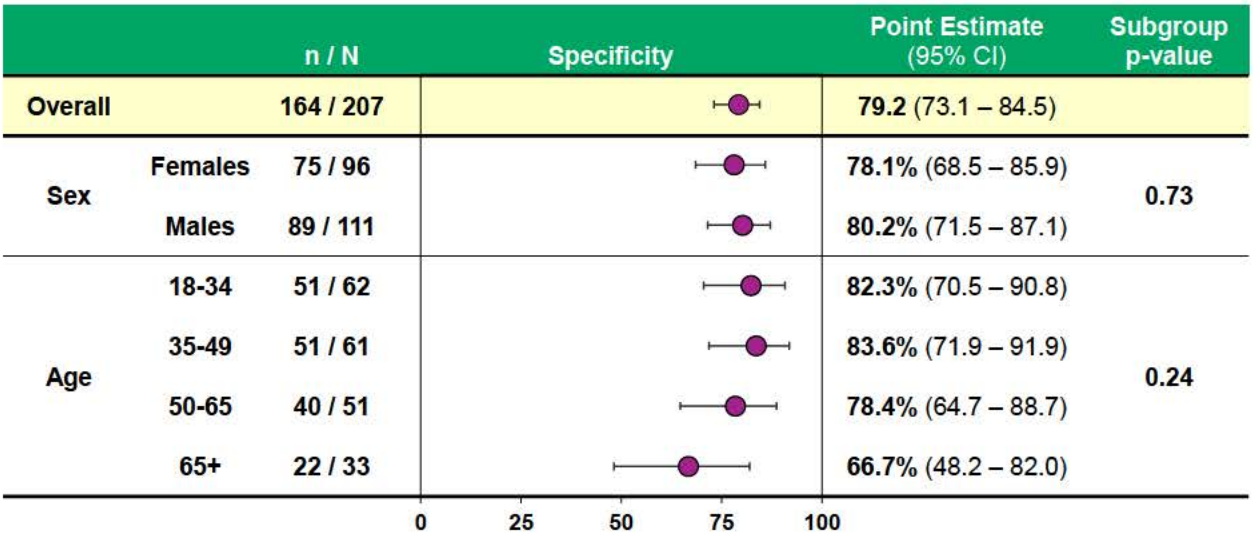
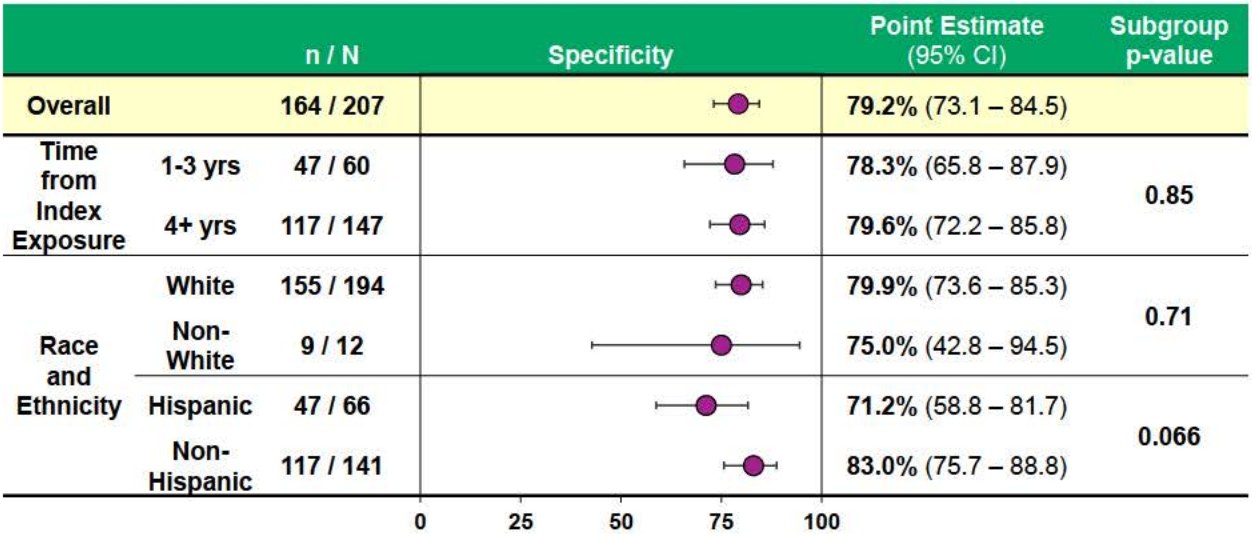
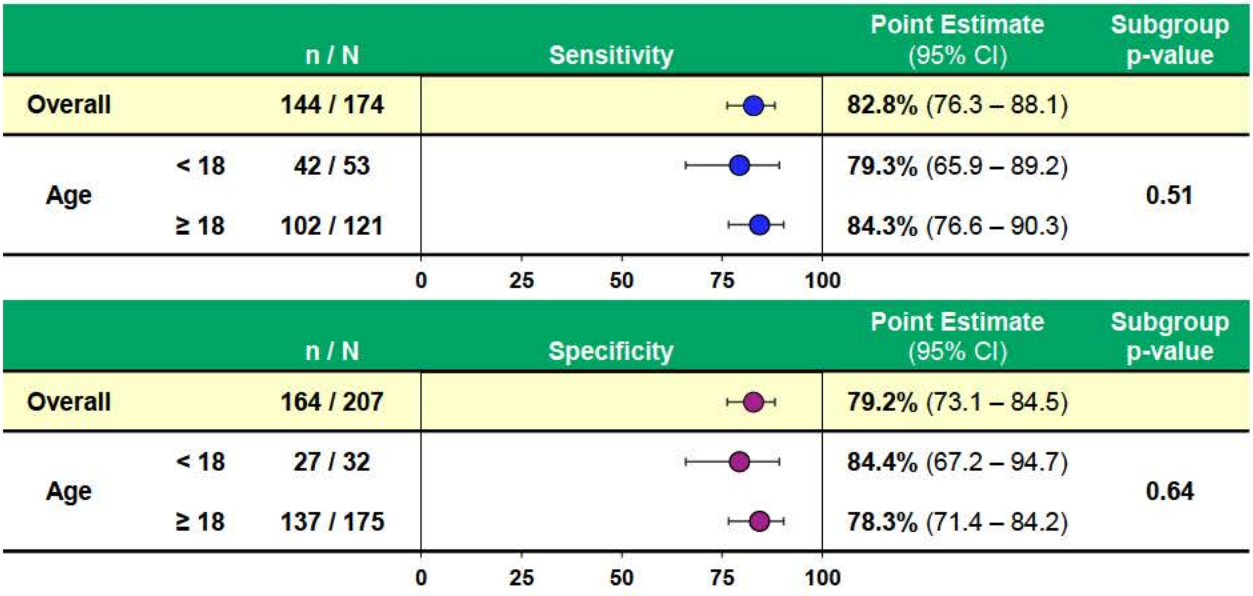


Figure 14: Subgroup Analysis for Specificity Results Related to Opioid Exposure, Race, and Ethnicity in the OUD-Negative Population (N=207)



Although all participants were ≥ 18 years old at the time of enrollment, age at the time of initial exposure could have been < 18 years. A total of 86 participants were under the age of 18 at their initial exposure (mean [SD]: 14.8 [2.4]). Therefore, subgroup analyses were also performed for participants ≥ 18 years old (n = 296) and < 18 years old (n=85). Sensitivity and specificity in each age subgroup were consistent with the overall population and exceeded the performance goal (Figure 15).

Figure 15: Sensitivity and Specificity by Age (≥ 18 and < 18 years)



6.4.2 Co-Secondary Endpoint Results

The positive likelihood ratio (3.98) showed a strong increase in the probability of having OUD with a positive test result (Table 15). The reverse was true for the negative likelihood ratio (0.22). The negative likelihood ratio showed a strong decrease in the probability of having OUD with a negative test result.

Table 15: Likelihood Ratios with Two-Sided 95% Confidence Limits

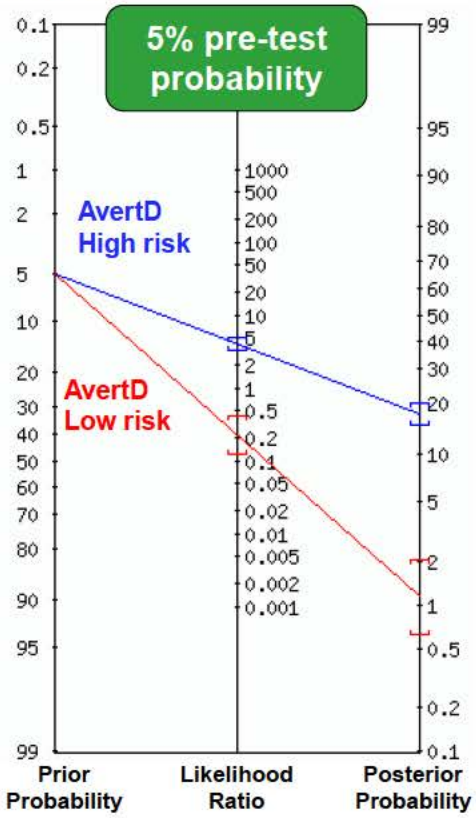
Variable	Negative Likelihood Ratio	Positive Likelihood Ratio
Estimate	0.22	3.98
95% Confidence Limits	0.174 – 0.334	3.264 – 6.874

One way to describe the diagnostic performance in terms of a single number that is based on all results is the diagnostic odds ratio. For AvertD, the diagnostic odds ratio, which is ratio of the positive and negative likelihood ratios, was 18.1 (3.98/0.22). The results showed that a positive result with AvertD is 18 times more likely to happen in a patient who will develop OUD than it would in a patient who will not develop OUD.[1]

The likelihood ratios can also be used to calculate post-test probabilities. Assuming a 5% prevalence, the high-risk post-test probability is 17% and the low-risk post-test probability is 1% (Figure 16). Pre-test probability and post-test probability are the probabilities of the presence of a condition (such as a disease) before and after a diagnostic test, respectively. Post-test probability, in turn, can be positive or negative, depending on whether the test falls out as a positive test or a negative test, respectively. In some cases, it is used for the probability of developing the condition of interest in the future. Post-test probabilities may also be referred to as positive and negative predictive values. These measures tell us how likely it is that a person has a disease of interest based on test results and prevalence of the disease within the community. In this case, the pre-test probability is 5% and changes: with a high-risk test result to (represented by the blue line in Figure 16) to approximately 17%, and with a low-risk test result to (represented by the red line in Figure 16) to approximately 1%. In this example, approximately 1 in 6 patients identified as high genetic risk may develop OUD, whereas 1 in 100 patients identified as low genetic risk may develop OUD.

[1] Analysis has not been submitted and reviewed by the FDA.

Figure 16: Pre-test and Post-test Probability



6.4.2.1 Co-Secondary Endpoint Subgroup Analyses

A series of subgroup analyses was performed to determine whether sex, age, length of follow-up from opioid exposure, race or ethnicity affected the positive and negative likelihood ratios. No differences were observed for any of the variables as evidenced by the overlapping 95% confidence levels for all groups, demonstrating robust test performance in all tested subgroups (Table 16).

Table 16: Positive and Negative Likelihood Ratios for Subgroups

Subgroup		Negative Likelihood Ratio Estimate (95% CI)	Positive Likelihood Ratio Estimate (95% CI)
Sex	Female	0.19 (0.11, 0.35)	3.88 (2.62, 5.74)
	Male	0.23 (0.15, 0.35)	4.11 (2.80, 6.04)
Age	18–34	0.21 (0.13, 0.35)	4.65 (2.69, 8.02)
	35–49	0.18 (0.10, 0.33)	5.20 (2.92, 9.25)
	50–64	0.26 (0.11, 0.57)	3.71 (2.12, 6.49)
	65+	0.32 (0.11, 0.90)	2.36 (1.35, 4.10)
Race	White	0.24 (0.17, 0.33)	4.02 (3.01, 5.38)
	Non-White	0.00 -	4.00 -
Ethnicity	Non-Hispanic	0.23 (0.17, 0.33)	4.73 (3.26, 6.87)
	Hispanic	0.12 (0.03, 0.45)	3.18 (2.14, 4.74)
Follow-up Group	1–3 Years	0.27 (0.12, 0.59)	3.65 (2.17, 6.16)
	4+ Years	0.21 (0.15, 0.30)	4.08 (2.94, 5.66)

7 APPLICABILITY OF STUDY POPULATION TO INTENDED USE POPULATION

7.1 Sponsor Approach

SOLVD designed the clinical study to ensure that the study population represented the intended use population. To address the FDA's questions regarding the uncertainty in the study population and the applicability of the study results to the intended use population, SOLVD collected new information for the participants in the pivotal clinical study of AvertD and performed additional statistical analyses.

Specifically, modifications to the CRFs and processes, additional training of the clinical study sites, and the addended SAP were made in consultation with the FDA review team.

7.1.1 Ensuring All Participants Met Inclusion Criteria

7.1.1.1 Case Report Forms

Throughout the study multiple versions of CRFs were used to capture study data. To ensure data collection consistency, study sites documented all eligibility criteria for each participant were met using a single, new CRF. Using the new CRF data and the instructions specified in the SAP, all participants (N=385) were confirmed to meet the study eligibility criteria. These new data demonstrate the sites consistently applied the study-specific enrollment criteria across all participants and did not introduce any uncertainty in the clinical study population.

7.1.1.2 Exclusions of Participants Taking Oral Opioids for Treatment for Chronic Pain

To be enrolled in the study, the index exposure to prescription oral opioids was required to be between 4 and 30 consecutive days, which is consistent with prescription opioid use for acute pain. By definition, this excludes patients taking opioids for > 30 days for indications including chronic pain.

7.1.1.3 Exclusion of Illicit use of Opioids

To meet the inclusion criteria, the index exposure had to be prescribed by a healthcare professional for that participant. During the site initiation process, the term "prescription oral opioids" was discussed in detail when reviewing the inclusion/exclusion criteria and was part of the site training process. The discussion included specifying that the prescription oral opioids were to have been prescribed by a healthcare provider (e.g., physician or dentist) for that patient and taken by that patient (i.e., the taking of the oral opioids was "doctor-directed" and not illicit use).

7.2 Self-Reported Data of Index Exposure to Prescription Oral Opioids

Under the inclusion criteria, participants needed to report that they had taken oral opioids for 4 to 30 days at least one year ago. Self-reporting for the index exposure was selected for the study design as studies have shown that self-reporting is the most

accurate method for confirming that a patient took a medication given that prescriptions, and prescription oral opioids in particular, may not be filled and can be filled but not taken (Cramer et al 1989).

FDA expressed concern about the accuracy of using self-reported index exposure to prescription oral opioids for qualifying individuals for enrollment in the clinical study and any uncertainty that using self-reported index exposure may raise. To provide corroborative documentation of the index exposure in this study, SOLVD collected new information about self-reported index exposure.

Study site personnel examined medical records dated 1 calendar year before and after the self-reported index exposure. Based on the type of information available such as a documented procedure (e.g., surgery or dental procedure) or event (e.g., accident) that could result in oral opioid prescriptions, documentation in medical record of oral opioid prescription, and/or presence of prescription itself, participants were then assigned to tiers (see Table 2). The tiers were defined in collaboration with the FDA as a method to evaluate the level of corroborating evidence of opioid exposure to address FDA's concern regarding the self-reported index exposure.

An analysis of sensitivity and specificity by tier supported the overall study findings (Figure 6). Fewer participants met the criteria for Tier 4 (physical copy of the prescription), which was expected and is driven by 2 primary contributing factors. First, most of the participants had their index procedure prior to 2015, which is when the PDMP began to be widely adopted. Prior to the PDMP, medical records may not have physical copies of actual prescriptions. Second, it is not common for sites that did not prescribe an oral opioid to have physical copies of prescriptions from other prescribers in their records. Therefore, certain sites in the study would not have this type of information available for the index exposure.

Overall, these data confirm the accuracy of the self-reported index exposure and resolve uncertainty relating to the self-reported index exposure for qualifying study participants and the applicability of the study results to the intended use population.

7.3 Applicability of the Results of the Study Population to the Intended Use Population

7.3.1 Study Enrollment Sites

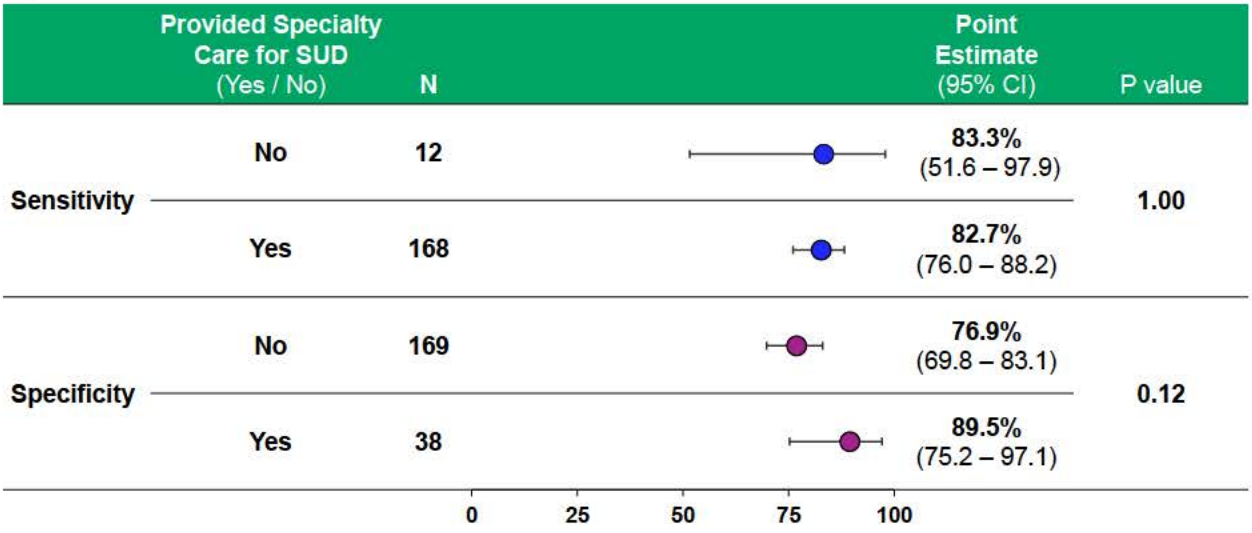
Participants were enrolled at 10 sites including 3 sites (Sites 2, 10 and 11) that provided OUD treatment and had providers holding waivers to prescribe buprenorphine. Sites 10 and 11 were mental healthcare practices that provided OUD treatment and Site 2 was a general practice site that provided OUD treatment. These 3 sites were grouped together in sub-analyses as all three sites offer OUD treatment (i.e., they had providers with special accreditation to treat OUD and prescribe buprenorphine [Substance Abuse and Mental Health Services Administration Drug Addiction Treatment Act of 2000 waiver certifications]). The remaining sites were general practice who participated in research

studies, but there were no healthcare providers at these sites who held a waiver to prescribe buprenorphine; i.e., they did not provide OUD treatment. Most of the OUD-positive participants were recruited at the sites where OUD treatment was available.

To address the question about whether AvertD test performance differed by type of study site, SOLVD compared AvertD performance in participants who were enrolled from sites that offered OUD treatment (defined as providing specialized clinical care for OUD treatment that requires specific accreditation, Sites 2, 10 and 11) to participants who were enrolled at sites who do not offer specialized OUD treatment (general practice that participate in research studies).

There were no statistically significant differences in AvertD sensitivity or specificity between OUD-specialized and non-specialized sites, providing confidence in the study results and the applicability of the study results to the intended use patient population (Figure 17).

Figure 17: Sensitivity and Specificity by SUD-Specialized Site and Non-Specialized Sites



7.3.2 Prevalence of Mental Health Comorbidities

The FDA requested additional information concerning the prevalence of mental health and non-opioid substance use disorder comorbidities at the time of index exposure to prescription oral opioids to examine if the study population was enriched for these comorbidities and potential confounding factors in the study population to better understand the applicability of the study population to the intended use population.

The most common comorbidities at the time of index exposure were alcohol use disorder, anxiety and depression (see Table 3). Importantly, the prevalence of the comorbidities between OUD-negative and OUD-positive participants was very similar at

the time of index exposure (Table 17). For less common mental health comorbidities (such as bipolar disorder or schizophrenia), the sample sizes are small with the total number of affected participants low.

These data demonstrate that the prevalence of mental health and non-opioid substance use disorder comorbidities was similar between participants who did and who did not ultimately develop OUD at the time of the index exposure. Additionally, these data do not indicate that there was any enrichment of mental health and non-opioid substance use disorder comorbidities at the time of index exposure.

Table 17: Prevalence of Mental Health and Non-opioid Substance Use Disorder Comorbidities at the Time of Index Exposure in OUD-negative and OUD-Positive Participants

Comorbidity at the Time of Index Exposure	DSM-5 OUD Negative N=210 n (%)	DSM-5 OUD Positive N=175 n (%)
History of Alcohol Use Disorder		
No	186 (89)	164 (94)
Yes	17 (8)	10 (6)
Data not available	7 (3)	1 (1)
History of Anxiety		
No	187 (89)	154 (88)
Yes	16 (8)	20 (11)
Data not available	7 (3)	1 (1)
History of Bipolar Disorder		
No	201 (96)	163 (93)
Yes	2 (1)	11 (6)
Data not available	7 (3)	1 (1)
History of Cannabis Use Disorder		
No	202 (96)	168 (96)
Yes	1 (0)	6 (3)
Data not available	7 (3)	1 (1)
History of Depression		
No	186 (89)	153 (87)
Yes	17 (8)	21 (12)
Data not available	7 (3)	1 (1)
History of Schizophrenia		
No	203 (97)	174 (99)
Yes	0 (0)	0 (0)
Data not available	7 (3)	1 (1)
History of Substance Use Disorder Other than Opioids, Alcohol or Cannabis		
No	203 (97)	164 (94)
Yes	0 (0)	10 (6)
Data not available	7 (3)	1 (1)

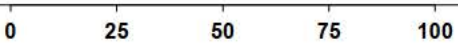
7.3.3 Performance in the Presence or Absence of Mental Health and Non-Opioid Substance Use Disorder Comorbidities

To understand how AvertD performs in the intended use population, sensitivity and specificity were analyzed in participants with and without mental health and non-opioid substance use disorder comorbidities at the time of index exposure. There were no statistically significant differences in test performance between OUD-positive and OUD-negative participants at the time of index exposure (Figure 18 and Figure 19).

These data further remove uncertainty of the test performance in the intended use population (the test is intended to be used to help determine OUD risk prior to prescribing oral opioids for acute pain) as no statistically significant difference in AvertD performance was observed across participants with and without mental health and non-opioid substance use disorder comorbidities at the time of index exposure (prior to prescribing opioids).

Figure 18: Sensitivity Results for AvertD by Mental Health Status at Time of Index Exposure

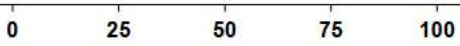
	History of Use	N	Sensitivity	Point Estimate (95% CI)	P-value
Depression	**No**	**335**		**80.9%** (73.8 – 86.8)	**0.28**
	Yes	**38**		**95.2%** (76.2 – 99.9)	
Anxiety	**No**	**337**		**83.0%** (76.1 – 88.6)	**0.80**
	Yes	**36**		**80.0%** (56.3 – 94.3)	
Alcohol Use Disorder	**No**	**347**		**82.8%** (76.1 – 88.3)	**0.74**
	Yes	**26**		**80.0%** (44.4 – 97.5)	
Bipolar Disorder	**No**	**360**		**84.0%** (77.4 – 89.2)	**0.26**
	Yes	**13**		**63.6%** (30.8 – 89.1)	
Other SUD	**No**	**363**		**82.2%** (75.5 – 87.8)	**1.00**
	Yes	**10**		**90.0%** (55.5 – 99.8)	
Cannabis Use Disorder	**No**	**366**		**83.2%** (76.7 – 88.6)	**0.40**
	Yes	**7**		**66.7%** (22.3 – 95.7)	



Data not available (n=8)

Figure 19: Specificity Results for AvertD by Mental Health Status at Time of Index Exposure

	History of Use	N	Specificity	Point Estimate (95% CI)	P-value
Depression	**No**	**335**		**79.2%** (72.6 – 84.9)	**0.91**
	Yes	**38**		**76.5%** (50.1 – 93.2)	
Anxiety	**No**	**337**		**78.3%** (71.6 – 84.0)	**0.76**
	Yes	**36**		**87.5%** (61.7 – 98.5)	
Alcohol Use Disorder	**No**	**347**		**79.9%** (73.4 – 85.4)	**0.57**
	Yes	**26**		**68.8%** (41.3 – 89.0)	
Bipolar Disorder	**No**	**360**		**79.3%** (73.0 – 84.7)	**0.59**
	Yes	**13**		**50.0%** (1.3 – 98.7)	
Other SUD	**No**	**363**		**79.0%** (72.7 – 84.4)	**1.00**
	Yes	**10**		--	
Cannabis Use Disorder	**No**	**366**		**78.9%** (72.6 – 84.4)	**1.00**
	Yes	**7**		**100.0%** (2.5, 100.0)	

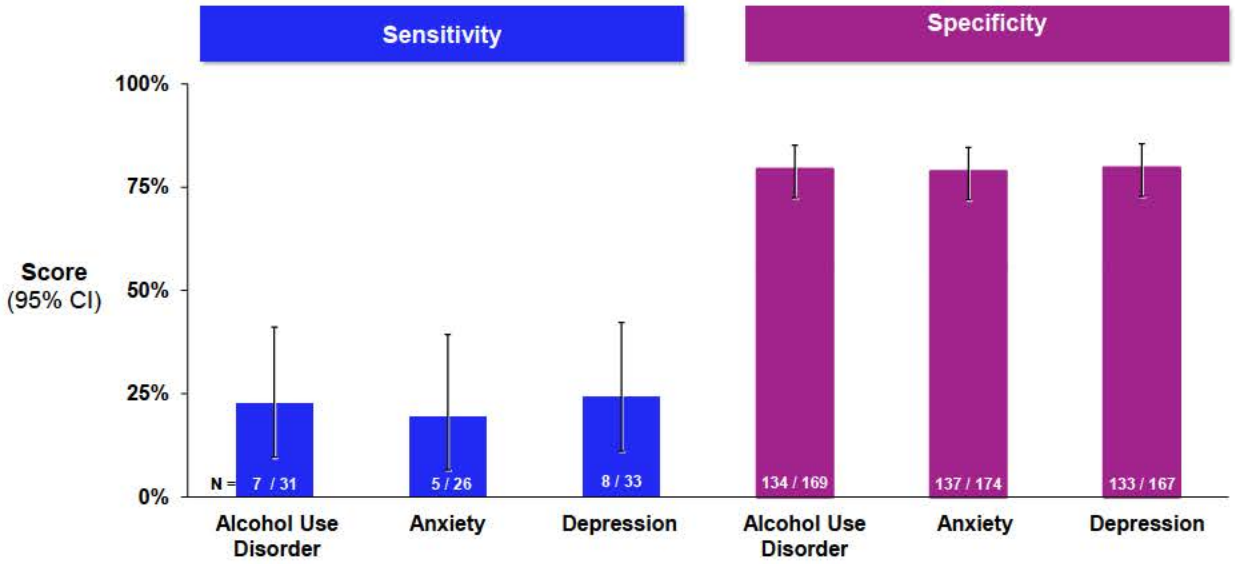


Data not available (n=8)

AvertD was specifically designed and trained for opioid use disorder by including genes/SNPs established to be associated with opioid dependency, such as the mu opioid receptor gene (2 SNPs), the delta opioid receptor gene and the kappa opioid receptor gene. In addition, the machine learning algorithm was specifically trained to classify individuals with OUD from individuals without OUD, not to classify individuals with or without other SUDs or other mental health comorbidities.

To explore if AvertD is classifying other comorbidities (mental health conditions or other SUDs) not OUD, the performance of AvertD for classifying these comorbidities in OUD-negative participants was evaluated. The analyses removed OUD-positive patients to avoid this confounding factor. The performance of AvertD in other comorbidities is shown in Figure 20. The sensitivity and specificity of AvertD in classifying each comorbidity is essentially the same as the prevalence of these comorbidities in the underlying study population demonstrating that AvertD performance seen in the study is for OUD classification not these comorbidities.

Figure 20: Sensitivity and Specificity of AvertD for Mental Health Conditions other than OUD in Participants without OUD



Note: Data have not been reviewed by FDA.

7.3.4 Severity of OUD

Individuals with varying levels of OUD seek treatment. The DSM-5 criteria categorize OUD into three severity levels: mild, moderate and severe. In the clinical study, 28% of the OUD-positive participants were classified as mild or moderate and 72% were classified as severe. While more severe cases were present, all levels of severity were represented in the study population including those with no disease (non-OUD patients). Importantly, AvertD performed equally well in all levels of severity as evidenced by the lack of statistical significance in test sensitivity across the OUD-positive severity subgroups (note, specificity cannot be measured because all participants are OUD positive in this analysis).

Table 18 describes AvertD test sensitivity for participants by level of OUD severity. The severity (i.e., mild, moderate, severe) are defined per the DSM-5 criteria. The numbers below include all OUD-positive participants for whom OUD severity was documented and had a valid test result.

Table 18: AvertD Results for Participants of Each OUD Severity

	AvertD Result		
OUD severity	**NO**	**YES**	**Total**
Mild	1	12	**13**
Moderate	10	21	**31**
Severe	18	111	**129**
Total	**29**	**144**	**173**

Using one-tailed Fisher's exact test, analyses were performed to evaluate whether test sensitivity was affected by OUD severity. No statistically significant differences were found (Table 19 and Table 20).

Table 19: Sensitivity for Mild OUD vs. Severe OUD

	Sensitivity			
Measure	**Mild**	**Severe**	**Difference**	**1-tailed p-value**
Sensitivity	0.9231	0.8605	0.0626	0.4552

Table 20: Sensitivity for Mild OUD vs. Moderate or Severe OUD

	Sensitivity			
Measure	**Mild**	**Moderate or Severe**	**Difference**	**1-tailed p-value**
Sensitivity	0.9231	0.8250	0.0981	0.3226

7.4 Conclusions

SOLVD designed the clinical study to ensure that the study population represented the intended use population. The additional analyses further ensured the applicability of AvertD results in the intended use population. Specifically,

- Consistency between participants' self-reporting oral opioid exposure and the corroborating documentation in the medical record over time, further establishing the use self-reported index exposure within the study design and AvertD performance in the intended use population.
- No statistically significant differences in AvertD sensitivity or specificity between sites that did and did not offer OUD treatment, providing confidence in the study results and the applicability of the study results to the intended use patient population.
- Similar prevalence of mental health and non-opioid substance use disorder comorbidities between participants at the time of the index exposure, who did and who did not ultimately develop OUD, demonstrating that the study population is not enriched for mental health disorders and reflects the intended use population.

- No statistically significant differences in AvertD performance in participants with or without mental health comorbidities and non-opioid substance use disorder comorbidities at the time of index exposure.

8 IDENTIFIED POTENTIAL RISKS TO HEALTH AND PROPOSED MITIGATIONS

SOLVD analyzed the risks and mitigations and believes the study results provide reasonable assurance of safety and effectiveness to demonstrate that the benefits of AvertD outweigh the potential risks. The potential risks have been mitigated through multiple means taking into consideration the intended use, design, and technological characteristics of AvertD.

The intended use of AvertD inherently helps to mitigate patient risk. AvertD is intended for use as a risk assessment tool – not a standalone diagnostic screening test – that should be used in combination with the healthcare provider's assessment and evaluation of a patient. While genetics play a substantial role in the development of OUD, other factors contribute to the development of OUD as well. For these reasons, AvertD is intended to be used by healthcare providers in conjunction with other patient information, including the healthcare provider's clinical evaluation and assessment, for informed decision-making regarding oral opioid use to treat acute pain. The intended use of AvertD, including its limitations, is clearly described in the indication for use and device labeling to mitigate risk.

Table 21 provides an overview of the risks associated with false positives and false negatives.

Table 21: Discussion of False Positives and False Negatives

Type	Potential Patient Impact	Discussion/Mitigation
False Positives	Patient is under-treated for pain by minimizing or avoiding opioids	• Prescribing guidelines for acute pain recommend opioid minimizing or eliminating strategies to manage acute pain (e.g., multi-modal analgesia), which have been shown to be effective (CDC 2022; Echeverria-Villalobos et al 2020; Wick et al 2017).
	Patient experiences emotional harm thinking he/she is at increased risk of OUD when they are not	• For some genetic risk tests when the patient receives a high-risk result and there is no specific intervention to prevent the disease, emotional stress may occur. • In contrast, AvertD empowers patients with information that is actionable (i.e., the disease can be prevented because patients can avoid taking opioids). • Patients who are concerned about emotional harm from a positive test result can choose not to take the test.
False Negatives	Patient is prescribed oral opioids according to standard of care even though he/she is at higher risk of OUD	• If the patient does not take the test, he/she will receive the standard of care for pain management which includes minimizing the use of opioids. • A patient receiving a false negative will also receive the same standard of care and therefore is no worse off than he/she would have been if they did not take the test.
	Patient is prescribed oral opioids with a longer duration or higher dosage than the standard of care because the physician believes the patient is at low risk	• Opioid prescribing guidelines minimizing the use of opioids are well known and established. • Training will be provided to physicians so that they understand that genetics contribute only a portion of the addiction risk, that other factors could lead to addiction, and prescribing opioids beyond the current prescribing guidelines puts all patients at increased risk.

Additional potential risks for AvertD shown in Table 22 are common to many in vitro tests, are well understood based upon the product's design, and well-established test methods are available to mitigate the risks. AvertD shares many similar technological characteristics with other in vitro tests that are regulated as Class II medical devices, and the controls applied to these devices are similarly applicable to this new generic type of device. General and the Special Controls that incorporate well-established test methods are sufficient to mitigate the risks from the device when combined with Special Controls regarding the device labeling.

Therefore, General and Special Controls are adequate to provide a reasonable assurance of device safety and effectiveness.

Table 22: Identified Potential Risks to Health and Mitigations

Potential Risk	Identified Mitigations – Special Controls
Incorrect Test Result (False Positive or FalseNegative)	Sample Collection Device Labeling Design Verification and Validation
No Test Result	Sample Collection Device Labeling Design Verification and Validation
Incorrect Interpretation of Test Results	Device Labeling Education Program and Training Materials
Incorrect Action Based on Test Results	Device Labeling Education Program and Training Materials
Overreliance on Test Results	Device Labeling Education Program and Training Materials

9 EDUCATION PROGRAM AND TRAINING MATERIALS

SOLVD will develop physician and patient educational materials regarding key points specific to AvertD test, including:

- Discussion that genetics are only one factor in understanding risk of developing OUD from using oral opioids. Consequently, test results should be used in conjunction with complete clinical evaluation to determine appropriateness of opioids in pain management plan and not be the only tool used in the decision process.
- Guidance on the clinical interpretation of test results, including the limitations of AvertD (i.e., that the test is a risk assessment tool that separates the population between low and high-risk groups, that it is not a diagnostic test, and that it does not predict OUD will develop).
- The importance of following opioid prescribing guidelines even for negative tests to prevent incorrect action based on test results.
- Direction to resources that provide information on non-opioid alternatives.

10 BENEFIT-RISK ASSESSMENT

Healthcare providers prescribed opioids to approximately 50 million US adults in 2018, providing pain relief but also contributing to the current opioid crisis that causes more than 45,000 overdose deaths annually (CDC 2019). Since individuals with OUD frequently start by misusing prescription opioids, prescribing guidelines call for providers to assess each patient's risks before initiating opioid therapy. However, current risk assessment tools cannot provide a patient's complete personalized OUD risk profile to physicians as no tools assess genetic risk, and approximately 50% of OUD can be tied to genetics (Berrettini 2017).

10.1 Benefits

AvertD offers objective, personalized genetic information about OUD risk that is not currently available. This information can help complete a patient's personalized OUD risk profile and inform provider-patient decision-making regarding oral opioid prescribing for acute pain.

AvertD assesses a patient's genetic risk to develop OUD and while genes are only one factor contributing to OUD, this test's combination of sensitivity (82%) and specificity (79%) provide useful information that is not currently available to healthcare providers. Prescribing guidelines call for individual benefit-risk assessments to determine the appropriateness of opioids to manage acute pain. Thus, AvertD would fit into current clinical flow, with the principal benefits being providing information to patients and providers to make more informed choices about prescribing opioids for acute pain.

10.2 Risks

Since genetic makeup is only one factor contributing to the development of OUD, no genetic test will be a perfect predictor. Key potential risk of false positives, false negatives, and overreliance on test results have been examined by SOLVD (Table 21). Importantly, the potential risks of AvertD can be mitigated through proper use, which will be reinforced through labeling and education.

10.3 Conclusions

If granted authorization, AvertD will be the first and only clinically validated test for genetic risk assessment prior to the prescribing of oral opioids for acute pain. The benefits of AvertD outweigh its potential risks when assessed in accordance with FDA guidance concerning factors to consider in benefit-risk determinations. AvertD will enable patients and providers to make more informed choices about prescribing opioids for acute pain.

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12 APPENDIX

12.1 Proposed Classification Regulation and Special Controls

SOLVD is proposing a classification regulation with a series of Special Controls for AvertD and other devices classified within the Opioid Use Disorder Genetic Risk Assessment System:

Device Type: Opioid Use Disorder Genetic Risk Assessment System

Class: II (Special Controls)

(a) Identification: An opioid use disorder genetic risk assessment system is a qualitative in vitro molecular test used for detecting variants in genomic DNA isolated from human specimens that provides information about the genetic risk of developing opioid use disorder to provide healthcare providers and patients with risk information for informed decision-making regarding prescription oral opioid use. The test results are intended to be used in conjunction with other patient information, including clinical presentation, patient history, family history, patient demographics, and other test results.

(b) Identification: An opioid use disorder genetic risk assessment system is a qualitative in vitro molecular test used for detecting variants in genomic DNA isolated from human specimens that provides information about the genetic risk ofdeveloping opioid use disorder to provide healthcare providers and patients with risk information for informed decision-making regarding prescription oral opioid use. The test results are intended to be used in conjunction with other patient information, including clinical presentation, patient history, family history, patientdemographics, and other test results.

(c) Classification: Class II (Special Controls): An opioid use disorder genetic riskassessment system must comply with the following Special Controls:

(d) Classification: Class II (Special Controls): An opioid use disorder genetic risk assessment system must comply with the following Special Controls:

(1) Any sample collection device used must be FDA-cleared, FDA-approved or classified as 510(k) exempt (standalone or as part of a test system) for the collection of human specimens; alternatively, the sample collection device must be cleared in a 510(k) submission as part of this device.

(2) The labeling required under CFR 809.10 must include:

(i) An intended use with a detailed description of what the device detects and measures, the type of results provided to the user, the specimen type(s), theclinical indications for the test use, and the specific population(s) for whichthe device is intended.

(ii) A detailed description of the performance characteristics of the device forall intended specimen type(s) from the analytical and clinical studies (as applicable) required under paragraphs 3(ii) and 3(iii).

(iii) A detailed explanation of the interpretation of the test results, including acceptance criteria for evaluating the validity of individual runs (eg, assessment of internal and/or external controls, as applicable).

(iv) A limiting statement that any diagnosis, counseling, or treatment decisions should use the test results in conjunction with other patient information, including clinical presentation, patient history, family history, patient demographics, and other test results, and that test results should not be thesole determinant in diagnosing, counseling, or making prescribing decisions.

(3) Design verification and validation must include:

(i) A detailed device description, including as appropriate, all device parts or components; control elements incorporated into the test procedure; instrument requirements; reagents or other materials required but not provided; the principle of device operation and test methodology, including pre-analytical methods for processing of specimens and the methodology from obtaining a sample to the result; design of the primer/probe sequences; rationale for target analyte section; description of the method for establishing and validating the algorithm to generate the test result; and computational path from collected raw data to reported result (eg, how collected raw signals are converted into a reported result).

Detailed documentation of analytical validation studies, including analytical sensitivity (eg, limit of detection), precision, reproducibility, accuracy compared to sequencing, interfering substances and specimen andreagent stability.

a. Accuracy must be evaluated by comparison to bidirectional Sanger sequencing or other methods identified as appropriate by FDA for each genetic variant identified by the test. Performance criteria for both the comparator method (eg, bidirectional Sanger sequencing) and the device must be predefined. The accuracy as measured by percent concordance between the device and the comparator methodmust be ≥ 99% (both per reported variant and overall). Sufficient specimens must be tested per genotype and all genotypes

must be included in the accuracy study. Results should be generated from clinical specimens.

b. Precision and reproducibility testing must be conducted using multiple sites, multiple instruments and multiple operators, on multiple days and using multiple reagent lots. The sample panel must include specimens from the claimed sample type (eg, buccal specimen) and represent genotypes for the variants (eg, wild type, heterozygous and homozygous mutants). Results should be preferentially generated from clinical specimens when feasible, but other samples or cell lines that represent clinical specimens may be utilized if needed to include all genetic variants.

(ii) Detailed documentation of a clinical study(ies) to demonstrate clinical performance through a clinically valid protocol. Clinical validation testing must be performed on a patient population set separate from which the algorithm was established and trained (ie, the training data set must be separate and distinct from the validation data set). This detailed documentation must include the following information: results must demonstrate appropriate clinical performance and accuracy of the device output for each specimen type for the intended use population.

a. Clinical performance must include an assessment of sensitivity and specificity for opioid use disorder, as well as an assessment of likelihood ratios and positive and negative predictive values.

b. The clinical truth for each subject (opioid use disorder positive or negative) must be established by a validated clinical diagnostic standard or method consistent with medical practice in the US to allow for an evaluation of the clinical performance of the device.

c. Sufficient positive and negative samples must be included in the clinical study to provide statistically robust point estimates of sensitivity and specificity. The point estimates must be at least 82% for sensitivity and 80% for specificity based upon the test results alone.

d. All samples must be tested with the subject device by study personnel masked to the opioid use disorder status of the subject.

12.2 DSM-5 Criteria for Diagnosis of OUD

Participants were assessed by a clinician at the investigational site after enrollment for the presence or absence of DSM-5 OUD using a clinical evaluation, which consisted of a conversation with the patient to gather clinical information (clinical history) relevant to a diagnosis of OUD (Table 23). Participants for whom a DSM-5 OUD diagnosis was established were assigned an outcome of OUD positive for the study.

Table 23: DSM-5 Criteria for Diagnosis of OUD

Item	DSM-5 Criterion
1	Opioids are often taken in larger amounts or over a longer period of time than was intended.
2	There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3	A great deal of time is spent in activities to obtain the opioid, use the opioid, or recover from its effects.
4	Craving, or a strong desire or urge to use opioids.
5	Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of opioids.
7	Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8	Recurrent opioid use in situations in which it is physically hazardous.
9	Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that's likely to have been caused or exacerbated by the substance.
10	Tolerance, as defined by either of the following: A need for markedly increased amounts of opioids to achieve intoxication or desired effect A markedly diminished effect with continued use of the same amount of an opioid
11	Withdrawal, as manifested by either of the following: The characteristic opioid withdrawal syndrome The same—or a closely related—substance is taken to relieve or avoid withdrawal symptoms

Severity: Mild: 2–3 symptoms. Moderate: 4–5 symptoms. Severe: 6 or more symptoms *Criteria from American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Washington, DC, American Psychiatric Association page 541.

12.3 Study Sites

To adequately describe the performance of AvertD in the intended use population, participants were recruited from ten geographically distinct sites as shown in Table 24. At all sites, participants were recruited and enrolled according to the inclusion/exclusion criteria.

Furthermore, 9 of the 10 sites, although participating in research studies, have clinical practices that patients visit as part of their standard clinical care. Participants at these 9 sites were enrolled as the came to the sites for their clinical care which was unrelated to the study. One site (Site 7) enrolled 7 participants who were aware of the study at the research center and were enrolled following standard good clinical practices but were not recruited during regular clinical visits.

Table 24: Details on the Clinical Study Sites

Site #	Site Name	Patient Population	N
1	Healthstar Physicians	General Practice	77
2	Clinical Research Associates of Central PA	General Practice, Addiction Specialty	57
3	Continental Research Network	General Practice	35
4	Florida Research Center	General Practice, Specialty	1
5	Vista Health Research	General Practice, Specialty	29
6	Vital Pharma Research	General Practice	16
7	Medical Research Networx Diagnostics	General Practice/Other	7
9	Community Clinical Research Center	General Practice	19
10	Caron Treatment Center	Mental Health and SUD patients	58
11	Seven Hills Hospital (Acadia)	Mental Health and SUD patients	86