SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Opioid Use Disorder Genetic Risk Assessment Tool
Device Trade Name:	AvertD™ AvertD™ Buccal Sample Collection Kit
Device Procode:	QZH
Applicant's Name and Address:	AutoGenomics, Inc. 1600 Faraday Avenue Carlsbad, CA 92008
Date(s) of Panel Recommendation:	October 20, 2022[1]

Premarket Approval Application (PMA) Number: P230032

Date of FDA Notice of Approval:	December 19, 2023
Breakthrough Device:	Granted breakthrough device status on March 29, 2018

II. INDICATIONS FOR USE

AvertD™ is a prescription, qualitative genotyping test used to detect and identify 15 genetic polymorphisms in genomic DNA isolated from buccal samples collected from individuals 18 years of age and older. The test may be used as part of a clinical evaluation and risk assessment to identify patients who may be at elevated risk for developing opioid use disorder (OUD). The test is indicated for use only in patients prior to receiving a first prescription of oral opioids for 4-30 days for acute pain, such as in patients scheduled to undergo a planned surgical procedure and who consent to having the test performed.

The AvertD™ Buccal Sample Collection Kit is intended for use in the non-invasive collection, transport and storage of buccal specimens. DNA from the buccal sample will be suitable for use in AvertD. Buccal samples are collected by a qualified healthcare professional. For use only in individuals 18 years or older.

[1] A public advisory committee meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee was held on October 20, 2022, to discuss the AvertD Test associated with DEN220036. The Advisory Committee's recommendations were considered in the review of this PMA.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the AvertD labeling and in the AvertD Buccal Sample Collection Kit labeling.

The AvertD labeling contains a black box warning stating the following:

- Opioid sparing techniques should be used when prescribing oral opioids for all patients, regardless of test result.
- Not for use in patients receiving treatment for chronic pain.
- An Elevated Genetic Risk test result does not mean that a patient will develop OUD or does not already have OUD. Results from this test are not intended for the diagnosis of OUD.
- A Non-Elevated Genetic Risk test result does not mean that a patient will not develop OUD.
- Results of the test should not be used alone to make any decisions regarding treatment. Results may be used as part of a complete clinical evaluation and risk assessment to determine appropriate pain management strategies.
- This test is intended for voluntary use. It is not intended for use as part of a mandated testing program.

V. DEVICE DESCRIPTION

AvertD is a multiplex, genotyping (hybridization capture microarray gene expression analysis) assay intended for use in testing human deoxyribonucleic acid (DNA) collected from buccal swab specimens. AvertD detects the presence or absence of 15 single nucleotide polymorphisms (SNPs) involved in the brain reward pathways that are associated with Opioid Use Disorder (OUD). It is designed to distinguish between two groups: patients at elevated genetic risk of OUD and patients who are not at elevated genetic risk of OUD and intended to be used in combination with a clinical evaluation and assessment of the patient. The 15 single nucleotide polymorphisms (SNPs) tested are listed below:

Table 1: Single nucleotide polymorphisms (SNPs) 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	rsl800497
DRD4 T>C	Dopamine D4 Receptor	rs3758653

Allelic Variants	Gene Name	rs Number
DAT1 A>G	Dopamine Transporter	rs6347
DBH C>T	Dopamine Beta Hydroxylase	rsl611115
MTHFR C>T	Methylene Tetrahydrofolate Reductase	rsl801133
OPRKI G>T	Kappa Opioid Receptor	rsl051660
GABA C>A	Gamma-Aminobutyric Acid (GABA)	rs211014
OPRM1 A>G	Mu Opioid Receptor	rsl799971
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 I (ABCB1)	rs1045642

AvertD is designed to be used with the INFINITI PLUS Analyzer (a class 2, 510(k) cleared medical device, sold separately). The AvertD is comprised of the following components:

Table 2: List of AvertD components

Component Name
AvertD™ Buccal Sample Collection Kit
AvertD™ Amplification Mix
AvertD™ Intellipac Reagent Module
AvertD™ BioFilmChip Microarray
AvertD™ Assay Specific Software

The AvertD™ Buccal Sample Collection Kit is designed for the collection, stabilization, transportation, and room temperature storage of buccal samples. The collection kit is non-invasive and consists of the following components:

- 2 single-use, sterile flocked swabs with plastic shaft
- 2 vials each containing 550 µL DNA stabilizing solution
- Instructions for Use
- 1 Biohazard Bag with Absorbent Pad
- Packing materials to protect and secure the components

The PCR Amplification Mix consists of the reagents needed for the PCR amplification step of the purified DNA. The AvertD BioFilmChip® Microarray consists of a polyester film coated with proprietary multi-layer components designed for DNA analysis. The AvertD Intellipac® Reagent Module acts as a communication link and contains four reservoirs that house the test reagents and has an integrated memory chip. Reagent information such as lot number, expiration date, and the number of available tests is stored in the memory chip. The Intellipac® Reagent Module contains the ASPE master mix and the Hybridization Buffer.

The AvertD utilizes hybridization capture microarray technology and is designed to be run on the AutoGenomics INFINITI® PLUS Analyzer. Testing involves the following processes:

a) Buccal swab specimen collection using the AvertD Buccal Sample Collection Kit
b) DNA extraction from the buccal sample
c) Multiplex PCR amplification of DNA
d) SAP/EXO processing for combined amplified products
e) Fluorescent label incorporation using analyte specific primer extension (ASPE)
f) Hybridization of the ASPE primers to a microarray followed by washing.
g) Scanning of the microarray
h) Signal detection and analysis

Steps (e) through (h) are automated on the INFINITI® PLUS Analyzer.

The intensity of the signal indicates the presence or absence of the target SNPs in the specimen. This information is processed by an algorithm that that generates a result of either "Elevated Genetic Risk" or "Non-Elevated Genetic Risk. The algorithm was developed using data from known patients with OUD and known patients with no OUD. The AvertD™ test report will state "Elevated Genetic Risk" or "Non-Elevated Genetic Risk," and it will also include a listing of more detailed information including a quantitative score, interpretation of the results, a description of the test, a listing of the 15 single nucleotide polymorphisms that are genotyped, information about the clinical study, and limitations associated with the test.

Expiration dating for this device has been established and approved at 12 months at 2-8°C for the AvertD BioFilmChip Microarray and AvertD Intellipac Reagent Module, 12 months at -15 to -30°C for the AvertD Amplification Mixture, and 1 year at ambient temperature for the AvertD Buccal Sample Collection Kit

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no alternative genetic risk assessment devices for opioid use disorder (OUD) commercially available in the United States. The current standard of care for OUD risk prediction includes structured clinician interviews. The current standard of care for diagnosing OUD is generally made by clinical assessment, either via psychiatric evaluation or by using a structured or semi-structured interview (which are labeled for use in chronic pain patients but are often used broadly when opioids are used or being considered) administered by a trained administrator in a clinical research setting.

VII. MARKETING HISTORY

The AvertD Buccal Sample Collection Kit has been marketed in Europe.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

There were no known adverse events that occurred during the clinical trial.

IX. SUMMARY OF NONCLINICAL STUDIES

1. Laboratory Studies

1. Precision/Reproducibility

AvertD

Two reproducibility studies were conducted. The first reproducibility study was conducted at 3 sites using the AvertD™. Twelve samples were tested in the reproducibility study. The 12 samples underwent bidirectional sequencing to confirm their genotype. From each of these 12 samples, three aliquots were sampled and sent to the 3 sites to test using AvertD™. The sites were blinded to the sample genotype. DNA was extracted from the buccal samples, using a different extraction method for each site. The concentration and absorbance ratio A_{260}/A_{280} were determined for the DNA samples.

Three lots of the reagents were used in the study. Each study site received 2 lots of reagents. Three INFINITI® PLUS Analyzers were used, 1 at each site. Each site had 2 operators and each operator, using 1 reagent lot each, tested all 12 samples in duplicate on 5 non-consecutive days. Site 2 and Site 3 performed 240 tests each (12 samples x 5 days x 2 operators x 2 lots = 240 tests). Site 1 performed 245 tests. Each of the 15 analytes was tested 725 times. No repeats were allowed for the reproducibility study. The genotype for each analyte reported by AvertD was compared to the genotype obtained using Sanger bidirectional sequencing. All tests with a No Call (NC) or an Indeterminate Call (IND) failed to meet the built-in assay specifications, i.e., test failed to qualify (FTQ) and therefore these samples were invalid and excluded from analyses. The reproducibility study results are summarized below.

Table 3: AvertD Reproducibility Study Results by Genotype for All Reagent Lots, Instruments, and Sites (Study 1)

Analytes	Replicates Tested	Replicates with Invalid Tests	Replicates with Valid Tests	Valid Replicates with Incorrect Calls	Valid Replicates with Correct Calls	% Valid Replicates with Correct Calls
5-HTR2A	725	30	695	0	695	100%
COMT	725	30	695	0	695	100%
DRD1	725	30	695	0	695	100%
DRD2	725	30	695	0	695	100%
DRD4	725	30	695	0	695	100%
DAT1	725	30	695	0	695	100%
DBH	725	30	695	0	695	100%
MTHFR	725	30	695	0	695	100%
OPRK1	725	30	695	0	695	100%

Analytes	Replicates Tested	Replicates with Invalid Tests	Replicates with Valid Tests	Valid Replicates with Incorrect Calls	Valid Replicates with Correct Calls	% Valid Replicates with Correct Calls
GABA	725	30	695	0	695	100%
OPRM1	725	30	695	0	695	100%
MUOR	725	30	695	0	695	100%
GAL	725	30	695	0	695	100%
DOR	725	30	695	0	695	100%
ABCB1	725	30	695	0	695	100%
Total	**10,875**	**450**	**10,425**	**0**	**10,425**	**100%**

A second reproducibility study was conducted to demonstrate reproducibility with samples at concentrations near the limit of detection (LoD). The study was conducted at one site. Fifteen (15) samples were tested once by 1 operator on 3 instruments on 5 non-consecutive days over an 8 day period. One DNA extraction method was used to isolate DNA from the buccal samples. The second reproducibility study results compared to bidirectional sequencing are summarized below.

Table 4: AvertD Reproducibility Study Results by Genotype (Study 2)

Analytes	Replicates Tested	Replicates with invalid tests	Replicates with Valid Tests	Replicates with Incorrect calls	Valid Replicates with all Correct Calls	% Correct calls
5-HTR2A	225	10	215	0	215	100%
COMT	225	10	215	0	215	100%
DRD1	225	10	215	0	215	100%
DRD2	225	10	215	0	215	100%
DRD4	225	10	215	0	215	100%
DAT1	225	10	215	0	215	100%
DBH	225	10	215	0	215	100%
MTHFR	225	10	215	0	215	100%
OPRK1	225	10	215	0	215	100%
GABA	225	10	215	0	215	100%
OPRM1	225	10	215	0	215	100%
MUOR	225	10	215	0	215	100%
GAL	225	10	215	0	215	100%
DOR	225	10	215	0	215	100%
ABCB1	225	10	215	0	215	100%
Total	3,375	150	3,225	0	3,225	100%

AvertD Buccal Sample Collection Kit

Site-to-Site Reproducibility: An inter-laboratory reproducibility study was conducted at 3 sites to demonstrate the site-to-site reproducibility of the AvertD Buccal Sample Collection Kit. Seven buccal samples were collected using the AvertD Buccal Sample collection kit (The 7 samples underwent bidirectional sequencing to confirm their genotype) and 2 aliquots of each of the seven samples were sent to each site. At each site two operators each extracted DNA from the buccal samples (each site used a difference extraction method). The concentration and absorbance ratio A_{260}/A_{280} were determined for the DNA samples.

Three lots of the reagents were used in the study. Each study site received 2 lots of reagents. Three INFINITI® PLUS Analyzers were used, 1 at each site. At each site, the 2 operators each used 1 reagent lot to test all 7 samples in duplicate on 5 non-consecutive days for a total of 140 tests (70 tests per operator), resulting in each of the 15 alleles being tested 420 times. The site-to-site reproducibility study results compared to bidirectional sequencing are summarized below.

Table 5: AvertD Buccal Sample Collection Kit Site-to-Site Reproducibility Results

Site	Analytes Tested	Analytes from Invalid Tests	Analytes from Valid Tests	Discordant Calls from Valid Tests	Concordant Calls from Valid Tests	% Concordant Calls from Valid Tests (95% Confidence Interval)
1	2,100	0	2,100	0	2,100	100.0 (99.8 – 100.0)
2	2,100	15	2,085	0	2,085	100.0 (99.8 – 100.0)
3	2,100	15	2,085	0	2,085	100.0 (99.8 – 100.0)
Total	6,300	30	6,270	0	6,270	100.0 (99.9 – 100.0)

Day-to-Day, Lot-to-Lot, Operator-to-Operator, and Right/Left Cheek Reproducibility: To evaluate reproducibility between days, collection kit lots, operators, and right/left cheek collection sites, twelve subjects generated a total of 60 buccal samples, two per subjects per day (once from each side cheek) across three days, using a different AvertD buccal swab lots per day. A different extraction method was used each of the three days. The 60 buccal swabs tested in duplicate using two genotyping assays. All samples (120/120) tested using the first assay (duplicate samples of day-to-day runs using a combination of days, kit lots, operators, and right/left cheek collection site) were concordant with the bidirectional sequencing results. 98.3% (118/120) of samples tested with the second assay (duplicate samples of day-to-day runs using a combination of kit lots, operators, and right/left cheek collection site) were concordant with bidirectional sequencing results. Two (2) of the 120 samples did not yield a valid test result with the second assay and were tested for a second time. On repeat testing, both samples were concordant with the bidirectional sequencing results.

2. Detection Limit/Analytical Sensitivity

AvertD

The limit of detection (LoD) was assessed by testing 4 previously characterized DNA samples (Coriell DNA samples) and 4 buccal DNA samples at 8 serial dilutions at 60, 30, 15, 7.5, 3, 1, 0.3 and 0.1 ng/µL. Using 2 µL/test, as described in the device labeling, the total DNA input was 120, 60, 30, 15, 6, 2, 0.6 and 0.2 ng/test. Buccal samples were collected using the AvertD Buccal Sample Collection Kit and DNA was extracted using the Roche MagNa Pure extraction method. The genotypes of all 8 samples were confirmed by bidirectional sequencing.

The study was conducted by 1 operator on 5 instruments. A total of 1280 tests (8 samples x 8 dilutions x 20 replicates) were performed. The limit of detection study demonstrated that 100% correct call rates were attained at concentrations between 1 ng/µL and 60 ng/µL. This study established that the lowest concentration of DNA that can be detected by the device is 1 ng/µL.

3. Analytical Specificity/Interference

AvertD and the AvertD Buccal Sample Collection Kit

A study was conducted to evaluate the effect of potential endogenous and exogenous interfering substances on the performance of AvertD. Buccal samples were collected using the AvertD Buccal Sample Collection Kit by three study staff following the instructions for use before and after exposure to exogenous substances. Subjects did not have anything to eat or drink for at least 1 hour prior to buccal collection and rinsed twice with water immediately prior to buccal collection. Two (2) buccal samples were collected from each subject, one from the left cheek and one from the right cheek. Samples were collected from individuals without (control) and with direct exposure to the potential exogenous interferents:

- Antiseptic mouthwash
- Toothpaste
- Baking soda solution
- Cough syrup
- Cranberry juice
- Salt water
- Sugar water
- Meat
- Chewing gum
- Hard candy
- Cigarette or tobacco smoking
- Denture paste
- Coffee
- Blood (endogenous)

For endogenous interference testing, individuals were not directly exposed to whole blood. Instead, whole blood was added directly to the tube containing the stabilizing solution immediately prior to insertion of the buccal swab sample. The genotype of each sample was confirmed by Sanger sequencing. No interference with AvertD was observed.

4. Stability

a. Specimen Stability

AvertD Buccal Sample Collection Kit

Specimens collected using the AvertD Buccal Sample Collection Kit were stored at ambient temperatures to evaluate specimen stability in the DNA stabilizing solution. A total of 352 specimens were tested within 90 days of collection using AvertD. Performance was compared to Sanger bidirectional sequencing. The level of agreement to Sanger bidirectional sequencing for the 352 specimens extracted within 90 days of collection was >99%. DNA was also extracted from a specimen stored at room temperature for 1 year. For those samples which met the DNA requirements for purity and concentration to run the AvertD assay and were retested following 1 year of storage, there was 100% agreement with bidirectional sequencing. The results support the labeling claim that samples should be tested within 1 year of collection.

b. Shipping Stability Study

AvertD Buccal Sample Collection Kit

Samples collected using the AvertD Buccal Sample Collection Kit were stored at -20°C or 50°C for 8-16 days, or through three cycles of freeze-thaw between these temperatures. All samples met the DNA quality requirements for the AvertD assay ($A_{260}/A_{280} \geq 1.2$ and DNA concentration $\geq$ 1ng/µL). Absorbance values ranged from 1.2-1.9 and DNA concentrations ranged from 2.2 to 62.8 ng/uL. The downstream performance of the DNA samples were evaluated using two previously cleared molecular assays. All samples tested with both assays had 100% agreement with bidirectional sequencing results. These results support the overnight shipping claim at ambient temperature on the AvertD Buccal Sample Collection kit labeling.

5. Method Comparison (Analytical Accuracy)

AvertD

A method comparison study was conducted comparing AvertD to Sanger bidirectional sequencing. 442 deidentified patient samples were collected using the AvertD Buccal Sample Collection Kit and 8 samples were excluded for a total of 434 patient samples tested. Testing was performed according to the instructions for use at 3 sites, where laboratory personnel were blinded to the results of Sanger bidirectional sequencing. Each site tested a different set of de-identified patient

samples and used a different DNA extraction method. The accuracy of AvertD was >99.95% (6507/6510 alleles) and the results are summarized below.

Table 6: Accuracy between AvertD and Bidirectional Sequencing

Allelic Variants	Number of Samples	Discordant Samples		Concordant Samples	
		Number	Percentage	Number	Percentage
5-HTR2A (rs7997012)	434	0	0%	434	100%
COMT (rs4680)	434	0	0%	434	100%
DRD1 (rs4532)	434	0	0%	434	100%
DRD2 (rs1800497)	434	1	0.23%	433	99.77%
DRD4 (rs3758653)	434	0	0%	434	100%
DAT1 (rs6347)	434	1	0.23%	433	99.77%
DBH (rs1611115)	434	0	0%	434	100%
MTHFR (rs1801133)	434	0	0%	434	100%
OPRK1 (rs1051660)	434	0	0%	434	100%
GABA (rs211014)	434	0	0%	434	100%
OPRM1 (rs1799971)	434	0	0%	434	100%
MUOR (rs9479757)	434	0	0%	434	100%
GAL (rs948854)	434	0	0%	434	100%
DOR (rs2236861)	434	0	0%	434	100%
ABCB1 (rs1045642)	434	1	0.23%	433	99.77%
Total	**6510**	**3**	**0.05%**	**6507**	**99.95%**

6. Sample Carry Over

AvertD

A study was conducted to evaluate the potential effect of sample carry-over on the performance of the AvertD using 4 Coriell DNA samples and PCR grade water. Sample carry-over was evaluated by testing 120 ng of a positive sample, followed by 6 ng of a second positive sample, and 120 ng of a positive sample followed by a "No Template Control (PCR grade water)." This series of sample testing was repeated 12 times varying the Coriell DNA samples used. A total of 48 tests were performed.

All results were 100% concordant with bidirectional sequencing except for two samples which did not yield a valid test result. No carry-over contamination was observed.

7. Sample Volume Study

AvertD Buccal Sample Collection Kit

The AvertD Buccal Sample Collection Kit is intended for DNA collection with one buccal swab in 500 µL of transportation medium. This study was designed to collect 2 pooled buccal swabs in 1 mL of transportation medium from 30 subjects and subsequently use 50 µL, 100 µL, 200 µL and 400 µL aliquots from each

pooled swab transportation solution for DNA extraction to evaluate DNA concentration and A_{260}/A_{280} ratio and to determine performance of the extracted DNA with two molecular tests. The sample volume tolerance study results demonstrated that DNA extracted from buccal swabs for volumes between 100 µL and 400 µL had 100% concordant calls compared to bidirectional sequencing when analyzed using two molecular tests.

8. Sample Tolerance Study

AvertD Buccal Sample Collection Kit

A study was conducted using the AvertD Buccal Sample Collection Kit to evaluate the effect of under-sampling. The instructions specify that the healthcare provider should swab firmly across the surface of the inside of the cheek approximately 20 times. The study evaluated the effect of:

- Number of passes (10 passes, 20 passes, or 40 passes)
- Location of sampling in the mouth: tongue surface, under the tongue, upper gum, lower gum, upper palate
- Contamination of the buccal swab and stabilizing solution (e.g., touching the swab tip to the surface of a table, touching the swab tip to the operator's fingers, dropping the vial cap of the stability solution on the floor)
- Failure to use the swab breakpoint (i.e., cutting swab with scissors)
- Failure to rinse mouth before sample collection

This study demonstrated that 20 strokes on the inner cheek is optimal for DNA buccal collection, although 10 strokes on the inner cheek produced the same results. Sampling was not sensitive to contamination or use of alternative break points.

9. Specimen Preparation

Four (4) DNA extraction kits from two different manufacturers were used for analytical and comparison studies. Each kit used a different method to extract DNA: magnetism, spin column, fast spin-column, and precipitation. Buccal samples collected using the AvertD Buccal Sample Collection Kit were extracted using these extraction methods and the genotypes were confirmed by Sanger bidirectional sequencing. The data supported the use of all of these DNA extraction methods.

2. Animal Studies

No animal studies were conducted.

3. Additional Studies

1. Biocompatibility (Flocked Swab)

The flocked swab of the AvertD Buccal Sample Collection Kit has transient contact with mucosal tissue. Biocompatibility studies were performed to show the device materials are safe, biocompatible, and suitable for their intended use. Both

ISO 10993 and FDA Guidance "Use of International Standard ISO 10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing within a Risk Management Process" were utilized to guide the biocompatibility testing. The following biocompatibility studies were successfully completed with the flocked swab; see Table 7 below.

Table 7: Summary of the Biocompatibility Tests and Results

Test Performed	Test Method	Test Results
MEM Elution Assay (Cytotoxicity)	ISO 10993-5:2009	Pass
Intracutaneous Reactivity	ISO 10993-10:2010	Pass
Guinea Pig Maximum Sensitization	ISO 10993-10:2010	Pass

2. Sterilization (Flocked Swab)

The flocked swab is provided sterile for single patient use. The device is sterilized using ethylene oxide (EO) to a sterility assurance level (SAL) of 10^{-6}. The sterilization validation was performed in conformance to ISO 11135:2014 Sterilization of Health-Care Products - Ethylene Oxide - Requirements for the Development, Validation and Routine Control of a Sterilization Process for Medical Devices using the overkill approach. Ethylene oxide residue levels were evaluated to demonstrate that the device meets the tolerable contact limit (TCL) for limited use (< 24 hours) for residues according to ISO 10993-7.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of AvertD in the US. A summary of the clinical study is presented below.

1. Study Design

A clinical study was conducted using buccal samples collected from subjects enrolled at 10 sites across the United States of America between February 2, 2019 and February 19, 2020. The clinical study design and results were previously described in the October 20, 2022 Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee Meeting. All study specimens were collected by a healthcare provider and were stored at ambient temperature prior to testing using the AvertD test by a central laboratory that was masked to the subject information. Buccal samples were stored between 24 to 393 days at ambient temperature prior to testing. Enrollers at each site approached potentially eligible patients and, after the patient agreed to participate in the study and signed the informed consent document, the patient was enrolled using one of four different case report forms (all four versions were used to enroll patients). The sponsor stated that patients were enrolled as part of a routine visit to the sites. Most of the subjects enrolled in the clinical study were identified by practitioners that were familiar with the clinical history of the patients.

Subjects enrolled in the study were to have had a minimum exposure of 4 consecutive days to oral opioids and a maximum exposure of 30 consecutive days to be consistent with acute use of prescription oral opioids rather than chronic use (i.e., treatment for chronic pain). The subject's index exposure to prescription oral opioids should have happened at least 1 year prior to enrollment in the clinical study. Each patient was administered a clinical evaluation to determine OUD status based on DSM-5 criteria. Each patient provided two buccal swab samples for de-identified genetic testing with AvertD at a central laboratory. All buccal samples were collected by a healthcare professional using the AvertD Buccal Sample Collection Kit. One central College of American Pathologists (CAP) certified and Clinical Laboratory Improvement Amendments (CLIA) accredited laboratory tested all study specimens. 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 investigators and participants were blinded to the AvertD test results.

A total of 812 subjects were enrolled into the clinical study. Subjects were required to meet a set of inclusion and exclusion criteria in order to be enrolled into the clinical study. None of the 812 subjects withdrew and no subject was lost to follow-up. Information from 689 of the subjects were forwarded to a statistician who used a predefined sampling plan to select 385 subjects for inclusion in the clinical study analysis. The clinical study evaluated subjects who had experienced a 4-30 day exposure to prescription oral opioids 1-51 years prior to study enrollment to determine risk of developing OUD following such opioid exposure. The OUD status of each subject was determined by clinical evaluation. To assign subjects to a risk pool, information collected during enrollment (i.e., clinical history) from each subject was reviewed for history of any substance use disorder (SUD). If a history of any SUD, including OUD, was present, the subject was classified as high-risk (HR). If no history of any SUD, including OUD, was present, the subject was classified as low-risk (LR). HR and LR pools were used to enrich the study population to ensure an adequate number of OUD-positive patients were enrolled. Sensitivity and specificity estimates were calculated by comparing the OUD status (determined by clinical evaluation during enrollment) to the results of the AvertD test.

Sample Size

Sample sizes were determined for a single binomial test against a constant rate for the binomial parameter. The power was computed at 90.00% because both endpoints (sensitivity and specificity) and the joint power for both is 0.9*0.9=0.81. As determined by PASS 14 software for 90.00% power at alpha = 0.025, 154 completed OUD subjects and 159 completed non-OUD subjects were required to achieve a lower confidence limit above 0.595 for sensitivity and above 0.555 for specificity. The recruited numbers were upweighted by approximately 10.00% from the minimally required sample sizes to account for invalid test results and the fact that some subjects who were grouped in the high-risk group may ultimately be OUD-negative. Thus, the minimum goals for the recruited populations were set at

154/0.90=171 OUD-positive subjects and 159/0.90=177 OUD-negative subjects, for a total sample size of 348 subjects in both groups combined.

A total of 385 subjects were evaluated in the clinical study, with 210 ultimately being OUD-negative and 175 ultimately being OUD-positive.

Performance Goals
The sponsor defined the sensitivity performance goal 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%.

The pre-specified performance goals for sensitivity and selectivity were selected by the sponsor based on 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%, the sponsor set lower boundaries in the point estimate minus 11% to 15% range. Preliminary results from AvertD indicated estimates of sensitivity and specificity resulting from an algorithm testing set were 76% and 72%, respectively. The estimate of the study was assumed to be about 4% lower, 72% for sensitivity and 68% for specificity. Therefore, the sponsor set the performance goal for both endpoints to be the point estimate minus 12.5%:

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

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

Selection of the Study Analysis Population
In order to ensure a sufficient number of OUD-positive subjects were enrolled in the study, the sponsor employed an enrichment strategy. One way the study population was enriched was to recruit subjects from sites with at least 1 prescriber who held a waiver to prescribe buprenorphine; patients at that site are more likely to be OUD-positive. OUD-positive subjects were also recruited from sites that offer clinical care as well as participate in research. In order to provide the statistician with data to complete the stratified sampling, “risk” pools were incorporated.

Subjects were assigned to a LR pool or a HR pool based on the clinical evaluation and demographic information collected on the case report forms. Risk pooling was conducted to create 1 pool with a lower frequency of OUD (“low-risk”) and another pool with a higher frequency of OUD (“high-risk”). Pool assignment occurred after enrollment (enrollment is defined as being included in the study and eligible to be picked for the clinical analysis group), was not performed by the sites, and the sites remained blinded to the risk pool to which each was assigned. The following describes how both LR and HR groups were enriched based on OUD and SUD status.

- Low-risk category subjects had no evidence of alcohol or drug SUD at the time of enrollment. Specifically, these subjects had no:
    - DSM-5 diagnosis of OUD documented as of the day of enrollment
    - Alcohol use disorder

    - Other drug use disorder (cocaine, cannabinoids, sedatives, stimulants, etc.)
- High-risk category subjects, on the other hand, had evidence of SUD at the time of enrollment. Specifically, these subjects had one or more of the following:
    - DSM-5 diagnosis of OUD documented as of the day of enrollment
    - Alcohol use disorder
    - Other drug use disorder

By design, no OUD-positive subjects were included in the LR pool; therefore, no sensitivity analyses are available for the LR pool. All OUD-positive subjects were grouped in the HR group. Risk pools, along with demographic information, were used by an independent statistician to determine which subjects to include in the clinical study analysis group. Of the 812 total enrolled subjects, the statistician reviewed 689 and judged that an adequate pool was available to select the study analysis population. Using subject demographics and risk pool assignment, the statistician employed a stratified sampling plan to select a subset of enrolled subjects to analyze test performance. From the statistician's assessment, a study population of 385 subjects who populated 32 subgroups was analyzed. The subgroups are 2 genders (male and female), 4 age groups (18-34, 35-49, 50-64, and 65+), 2 time-since-index-exposure bins (<3 years and 4 years or more), and 2 risk pools ("high-risk" pool or "low-risk" pool).

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the AvertD clinical study was limited to patients who met the following inclusion criteria:

    1. Subject is at least 18 years old
    2. Subject or legal representative has consented to participate in the study
    3. Subject has provided consent for DNA testing (either by signing the informed consent for 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. Subject has consented to buccal sample collection in accordance with this study protocol or subject has a DNA sample that meets the DNA requirements of the study as documented by signing the study-specific informed consent
    5. Subject was exposed to prescription oral opioids for a duration of 4-30 consecutive days or a psychiatrist has diagnosed the subject 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

Patients were not permitted to enroll in the AvertD clinical study if they met any of the following exclusion criteria:

1. Subject has never received medical care that included taking oral opioids for more than 30 consecutive days unless a psychiatrist has diagnosed the subject as having OUD according to DSM-5 criteria
2. Subject or legal representative is not able to provide informed consent to participate in the study.

2. Follow-up Schedule

Subject participation consisted of a clinical evaluation to determine OUD status based on DSM-5 criteria and buccal swab sample collect during a single visit. OUD status was determined by clinical assessment as well as, as available, medical history. At this visit, a clinical assessment was performed to diagnose OUD at the time of enrollment at least 12 months (on average 10 years) following a self-reported index exposure to prescription oral opioid use.

3. Clinical Endpoints

The study had two co-primary endpoints:

- Sensitivity, which is defined as the proportion of subjects with OUD who are correctly identified by the AvertD™ as positive.
- Specificity, which is defined as the proportion of subjects without OUD who are correctly identified by the AvertD™ as negative.

The study had two co-secondary endpoints:

- Positive likelihood ratio (LR+) of AvertD™
- Negative likelihood ratio (LR-) of AvertD™

2. Accountability of PMA Cohort

At the time of enrollment, after subjects were determined to have met a set of inclusion and exclusion criteria and signed the consent form, a clinical evaluation was performed by a clinician at the site. The clinical evaluation, which included a patient interview and clinical history, assessed whether the subject met the DSM-5 criteria for OUD. Of the 812 total enrolled subjects, at which time subject enrollment ceased, a study population of 385 subjects, who populated 32 distinct subgroups, was analyzed. Subjects were selected so that the risk pools were balanced across strata. See Table 8 below for a description of the 385 subjects who were selected to populate the strata and form the study population.

Table 8: Distribution of Selected Participants by Strata

Age (years)	Sex	Follow-up (years)	HR Pool	LR Pool
18–34	Female	1–3	4	4
		4+	25	24

Age (years)	Sex	Follow-up (years)	HR Pool	LR Pool
	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

3. Study Population Demographics and Baseline Parameters

See Table 9 below for a description of the study population demographics and characteristics.

Table 9: 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)

Category	N=385
Follow-up Time Since Index Exposure, %	
1–3 years	85 (22.1)
4+ years	300 (77.9)

The medical records and medical histories at each enrolling site for all 385 subjects were retroactively queried after the clinical study was completed for any information indicating the presence of the following comorbidities: alcohol use disorder, anxiety, bipolar disorder, cannabis use disorder, depression, schizophrenia, or other SUD that is not alcohol or cannabis use disorder. This retroactive query did not assess how the identified comorbidities were diagnosed or where the diagnosis was made. Patients for whom no information describing a comorbidity could be identified are described as "No Information Avaliable" in Tables 10 and 11 below (this includes 8 patients, 7 OUD-negative and 1 OUD-positive who had no medical records avaliable. See Tables 10 and 11 below for a description of the study population comorbidities that were identified at the time of index exposure as well as at the time of enrollment into the clinical study.

Table 10: History of Comorbidities in Clinical Study Population at the Time of Self-Reported Index Exposure (385 subjects)

		By OUD Status	
Comorbidity	**Response Category**	**OUD Negative Subjects (N=210)**	**OUD Positive Subjects (N=175)**
History of Alcohol Use Disorder	No Information Avaliable	193 (91.9%)	165 (94.3%)
	Comorbidity Identified	17 (8.1%)	10 (5.7%)
History of Anxiety	No Information Avaliable	194 (92.4%)	155 (88.6%)
	Comorbidity Identified	16 (7.6%)	20 (11.4%)
History of Bipolar Disorder	No Information Avaliable	208 (99.0%)	164 (93.7%)
	Comorbidity Identified	2 (1.0%)	11 (6.3%)
History of Cannabis Use Disorder	No Information Avaliable	209 (99.5%)	169 (96.6%)
	Comorbidity Identified	1 (0.5%)	6 (3.4%)
History of Depression	No Information Avaliable	193 (91.9%)	154 (88.0%)
	Comorbidity Identified	17 (8.1%)	21 (12.0%)
History of Schizophrenia	No Information Avaliable	210 (100%)	175 (100%)
	Comorbidity Identified	0 (0.00%)	0 (0.00%)
History of Substance Use Disorder Other than Opioids Alcohol or Cannabis	No Information Avaliable	210 (100%)	175 (100%)
	Comorbidity Identified	0 (0.00%)	10 (5.71%)

Table 11: History of Comorbidities in Clinical Study Population at the Time of Enrollment (385 subjects)

		By OUD Status	
Comorbidity	**Response Category**	**OUD Negative Subjects (N=210)**	**OUD Positive Subjects (N=175)**
History of Alcohol Use Disorder	No Information Avaliable	178 (84.8%)	133 (76.0%)
	Comorbidity Identified	32 (15.2%)	42 (24.0%)
History of Anxiety	No Information Avaliable	184 (87.6%)	116 (66.3%)
	Comorbidity Identified	26 (12.4%)	59 (33.7%)
History of Bipolar Disorder	No Information Avaliable	208 (99.0%)	161 (92.0%)
	Comorbidity Identified	2 (1.0%)	14 (8.0%)
History of Cannabis Use Disorder	No Information Avaliable	206 (98.1%)	147 (84.0%)
	Comorbidity Identified	4 (1.9%)	28 (16.0%)
History of Depression	No Information Avaliable	177 (84.3%)	99 (56.6%)
	Comorbidity Identified	33 (15.7%)	76 (43.4%)
History of Schizophrenia	No Information Avaliable	209 (99.5%)	175 (100%)
	Comorbidity Identified	1 (0.5%)	0 (0.00%)
History of Substance Use Disorder Other than Opioids Alcohol or Cannabis	No Information Avaliable	210 (100%)	117 (66.9%)
	Comorbidity Identified	0 (0.0%)	58 (33.1%)

Subjects were enrolled at 10 sites in the United States. Two of the sites, Caron Treatment Center and Seven Hills Hospital, are opioid treatment program sites listed on the Substance Abuse and Mental Health Services Administration's (SAMHSA) Opioid Treatment Program Directory. The patient population at these sites includes individuals seeking treatment for substance use disorders (SUDs), including OUD, or other mental health disorders. The aforementioned sites also had at least 1 healthcare provider who held a waiver to prescribe buprenorphine (which is used to treat opioid dependency) at the time the study was performed. One other site, Clinical Research Associates, also had at least 1 healthcare provider who held a waiver to prescribe buprenorphine at the time the study was performed. None of the remaining 7 sites had a healthcare provider that held a waiver to prescribe buprenorphine. No information was provided regarding the medical services subjects were seeking when enrolled at the 8 sites that are not opioid treatment program sites, and since most (7/8) of these sites provide clinical care as well as participate in research or are research only sites, it is unknown what types of medical services are available at these sites. See Table 12 below for a list and description of the clinical study sites and number of OUD-positive and OUD-negative subjects enrolled at each site.

Table 12: List of Clinical Study Sites, Site Locations, Site Grouping, Patient Population at Each Site, and Number of Subjects Enrolled at Each Site

Site #	Site Name	Site Location (City, State)	Site with at least one prescriber who holds a waiver to prescribe buprenorphine	Number of Subjects (OUD status based on clinical evaluation)	Prescription records available for some subjects at this site
1	Healthstar Physicians	Morristown, TN	No	Total = 77 OUD-positive = 0 OUD-negative = 77	Yes
2	Clinical Research Associates	Altoona, PA	Yes	Total = 57 OUD-positive = 29 OUD-negative = 2	Yes**
3	Continental Research Network	Miami, FL	No	Total =35 OUD-positive = 8 OUD-negative = 27	Yes
4	Florida Research Center	Miami, FL	No	Total = 1 OUD-positive = 0 OUD-negative = 1	Yes
5	Vista Health Research	Miami, FL	No	Total = 29 OUD-positive = 4 OUD-negative = 25	Yes
6	Vital Pharma Research	Hialeah, FL	No	Total = 16 OUD-positive = 0 OUD-negative = 16	No
7	Medical Research Networx Diagnostics	Franklin, MA	No	Total = 7 OUD-positive = 0 OUD-negative = 7	No
9*	Community Clinical Research Center	Anderson, IN	No	Total = 19 OUD-positive = 0 OUD-negative = 19	Yes
10	Caron Treatment Center	Wernersville, PA	Yes	Total = 58 OUD-positive = 48 OUD-negative = 10	No**
11	Seven Hills Hospital (Acadia)	Henderson, NV	Yes	Total = 86 OUD-positive = 86 OUD-negative = 0	No**

**Note: Site 8 did not obtain IRB approval, did not enroll any subjects, and was not included in the clinical study.*

*** Note: Documentation of the actual prescriptions (e.g., physical copy, electronic copy, scan or photograph) was not available from the 2 opioid treatment program sites but were available for the other site with at least 1 provider who held a waiver to prescribe buprenorphine (site 2).*

4. Safety and Effectiveness Results

1. Safety Results

   No adverse events were reported due to the buccal sample collection. Investigators and subjects were blinded to the AvertD results.

2. Effectiveness Results

   A total of 385 subjects were analyzed in the clinical study. Of the 385 subjects, 210 were OUD-negative and 175 were OUD-positive, as determined by the DSM-5 clinical evaluation. All 175 OUD-positive subjects were present in the HR group and 180/210 OUD-negative subjects were present in the LR group. Of the 385 samples (from 385 subjects), 4 resulted in invalid test results and were not included in final analyses; therefore 381 samples were evaluated in the clinical study. The sensitivity and specificity results and the likelihood ratios are summarized in Tables 13 and 14 below.

Table 13: Sensitivity and Specificity Estimates for 381 Subjects in the Clinical Study

		OUD Diagnosis (per DSM-5 clinical evaluation)		
		Positive	**Negative**	**Total**
AvertD test result	**Positive**	144	43	187
	Negative	30	164	194
	Total	174	207	381
Sensitivity = 100*(144/174) = 82.76% (95% CI: 76.31, 88.05) Specificity= 100*(164/207) = 79.23% (95% CI: 73.06, 84.54)				

Table 14: Likelihood Ratios for the 381 Subjects in the Clinical Study

Statistic	Negative Likelihood Ratio	Positive Likelihood Ratio
Estimate	0.22	3.98
95% Confidence Limits	(0.17%, 0.33%)	(3.26%, 6.87%)

3. Subgroup Analyses

   The following preoperative characteristics were evaluated for potential association with outcomes: Age Group, Sex, Race, Ethnicity, Time Since Index Exposure, Tier, Opioid Treatment Program Sites, and Site with at Least One Prescriber Who Holds a Waiver to Prescribe Buprenorphine.

   Slightly more than half of the study population were male (N=219; 57.48%) and slightly less than half were female (N=162; 42.51%). Subjects were selected to ensure that an adequate number of subjects in each age group (18-34, 35-49, 50-64, and 65+) were represented. Device performance (sensitivity and specificity) by Age Group and Sex are summarized below.

Table 15: Sensitivity and Specificity by Age Group and Sex

Sex	Age Group	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Female	18-34	25	5	5	22	57	81.48% (61.92%, 93.70%)	83.33% (65.28%, 94.36%)
Female	35-49	22	4	3	21	50	87.50% (67.64%, 97.34%)	84.62% (65.13%, 95.64%)
Female	50-64	23	6	1	10	40	90.91% (58.72%, 99.77%)	79.31% (60.28%, 92.01%)
Female	65+	5	6	1	3	15	75.00% (19.41%, 99.37%)	45.45% (16.75%, 76.62%)
Female	Total	75	21	10	56	162	84.85% (73.90%, 92.49%)	78.13% (68.53%, 85.92%)
Male	18-34	26	6	8	39	79	82.98% (69.19%, 92.35%)	81.25% (63.56%, 92.79%)
Male	35-49	29	s	6	31	72	83.78% (67.99%, 93.81%)	82.86% (66.35%, 93.44%)
Male	50-64	17	5	4	10	36	71.43% (41.90%, 91.61%)	77.27% (54.63%, 92.18%)
Male	65+	17	5	2	8	32	80.00% (44.39%, 97.48%)	77.27% (54.63%, 92.18%)
Male	Total	89	22	20	88	219	81.48% (72.86%, 88.31%)	80.18% (71.54%, 87.14%)
Both Sex	18-34	51	11	13	61	136	82.43% (71.83%, 90.30%)	82.26% (70.47%, 90.80%)
Both Sex	35-49	51	10	9	52	122	85.25% (73.83%, 93.02%)	83.61% (71.91%, 91.85%)
Both Sex	50-64	40	11	5	20	76	80.00% (59.30%, 93.17%)	78.43% (64.68%, 88.71%)
Both Sex	65+	22	11	3	11	47	78.57% (49.20%, 95.34%)	66.67% (48.17%, 82.04%)

Sex	Age Group	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Both Sex	Grand Total	164	43	30	144	381	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)
Sensitivity across age groups within females: Two-sided exact Kruskal-Wallis test p-value 0.81. Specificity across age groups within females: Two-sided exact Kruskal-Wallis test p-value 0.048. Sensitivity across age groups within males: Two-sided exact Kruskal-Wallis test p-value 0.77. Specificity across age groups within males: Two-sided exact Kruskal-Wallis test p-value 0.94. Sensitivity across age groups for both sexes combined: Two-sided exact Kruskal-Wallis test p-value 0.90. Specificity across age groups for both sexes combined: Two-sided exact Kruskal-Wallis test p-value 0.24. Sensitivity across females and males: Two-sided Fisher's exact test p-value 0.68. Specificity across females and males: Two-sided Fisher's exact test p-value 0.73.								

The majority of the clinical study population (92.13%, 351/381) identified their race as White and their ethnicity as non-Hispanic (74.80%, 285/381). Fourteen (14) of the total study population identified as Black/African American and 2 identified as Asian/Pacific Islander. Tables 16 and 17 below summarize AvertD sensitivity and specificity by race and ethnicity.

Table 16: Sensitivity and Specificity by Race

Race	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
White	155	39	30	127	351	80.89% (73.86%, 86.72%)	79.90% (73.56%, 85.30%)
Non-white	9	3	0	12	24	100.00% (73.54%, 100.00%)	75.00% (42.81%, 94.51%)
No information*	0	1	0	5	6	N/A	N/A
Total	164	43	30	144	381	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)
Sensitivity across race categories: Two-sided Fisher's exact test p-value 0.13. Specificity across race categories: Two-sided Fisher's exact test p-value 0.71.							

*A total of 375 subjects provided information about their race. Information was not available for 6 subjects. Of the 24 “non-white” subjects, 1 was “White/African American”, 2 were “Asian/Pacific Islander”, 14 were “Black/African American”, 1 was “East Indian”, and 6 were “other”.

Table 17: Sensitivity and Specificity by Ethnicity

Ethnicity	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Hispanic	47	19	2	22	90	91.67% (73.00%, 98.97%)	71.21% (58.75%, 81.70%)
Non-Hispanic	117	24	28	116	285	80.56% (73.14%, 86.67%)	82.98% (75.74%, 88.78%)
No information*	0	0	0	6	6	N/A	N/A
Total	164	43	30	144	381*	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)
Sensitivity across ethnicity: Two-sided Fisher's exact test p-value 0.26. Specificity across ethnicity: Two-sided Fisher's exact test p-value 0.066.							

*Ethnicity information was not available for 6 of the subjects.

During enrollment in the AvertD clinical trial, a minimum time of 1 year was required to have passed between the self-reported index exposure date and enrollment (defined as "time since index exposure") for the subject to meet the inclusion and exclusion criteria. No maximum time since self-reported index exposure was implemented. For the subjects enrolled in the AvertD clinical trial, the maximum time since self-reported index exposure was 51 years, the median time since self-reported index exposure was 8 years and the mean time since self-reported index exposure was 10 years. Tables 18 and 19 below summarize AvertD sensitivity and specificity by time since index exposure and the percentage of subjects with OUD (per the DSM-5 clinical evaluation) as the time since index exposure increases.

Table 18: Sensitivity and Specificity by Time Since Index Exposure

Self-reported Time Since Exposure (years)	True Negative	False Positive	False Negative	True positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
1-3	47	13	5	19	84	79.17% (59.53% - 90.76%)	78.33% (66.38% - 86.88%)
4-7	48	15	3	31	97	91.18% (77.04% - 96.95%)	76.19% (64.36% - 85.01%)
8-10	31	8	4	23	66	85.19%	79.49%

Self-reported Time Since Exposure (years)	True Negative	False Positive	False Negative	True positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
						(67.52% - 94.09%)	(64.47% - 89.22%)
11-13	10	3	2	19	34	90.48% (71.09% - 97.35%)	76.92% (49.74% - 91.82%)
14-16	11	3	7	12	31	63.16% (41.04% - 80.85%)	91.67% (52.41% - 92.43%)
17-24	11	2	4	24	41	85.71% (68.51% - 94.30%)	84.62% (57.77% - 95.68%)
25+	6	1	5	16	28	76.19% (54.91% - 89.37%)	85.71% (48.69% - 97.44%)
				Total	381		

Table 19: Percentage of subjects with OUD based on time since index exposure

Time since exposure (years)	Percent of OUD-positive Subjects
1-3	28.57%
4-7	35.05%
8-10	40.91%
11-13	61.76%
14-16	61.29%
17-24	68.29%
25+ (25-51 years)	75.00%

After the clinical study was completed and analyses based on self-reported index exposure dates were conducted, additional information on the subjects enrolled in the clinical study was collected from the clinical sites. All information was collected from medical records or medical histories available at the enrollment site. No information from outside the enrollment site was used and the subjects were not contacted to obtain the information. The medical records and histories were queried for information within a year (plus or minus 1 year) to support the accuracy of the self-reported index exposure date. Medical records and medical histories were defined as: "*Information that includes but is not limited to the reason for visit (chief complaint), past surgical history, past medical history, prescription history, review of systems, procedure and operative notes, radiology reports, consults, current medications, and summary of findings*." This information was collected in tiers according to the following approach:

- **Tier 1**: All subjects who meet the inclusion and exclusion criteria
- **Tier 2**: Subjects who have documentation of 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 3**: Subjects who have a description in the medical records of an oral opioid prescription for acute pain within a calendar year before or after the self-reported index exposure, but may or may not have documentation of the actual prescription (e.g., a record that states "a patient was prescribed 7 days of hydrocodone for knee surgery" but the prescription may or may not be documented)
- **Tier 4**: Subjects who have documentation of an oral opioid prescription for acute pain within a calendar year before or after the self-reported index exposure (e.g., physical copy, electronic copy, scan, or photograph)
- **Tier 5**: Subjects for whom the available medical records indicate neither a procedure (e.g., surgery) or event (e.g., accident) where opioids may be prescribed for acute pain nor any indication in the available medical records and history that an oral opioid was prescribed.
- **Tier 6**: Subjects who have documentation of 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 AND who have documentation of an oral opioid prescription for acute pain within a calendar year before or after the self-reported index exposure (e.g., physical copy, electronic copy, scan, or photograph).

Tables 20 and 21 below summarize the number of subjects with information in each tier and AvertD sensitivity and specificity by each tier.

Table 20: Summary of Number of Subjects with Information in Each Tier

Category	Observed n (%)
Tier 1	381 (100.00%)
Tier 2	361 (94.75%)
Tier 3	318 (83.46%)
Tier 4	133 (34.91%)
Tier 5	20 (5.25%)

Tier 6 is not summarized in the table above as the same subjects in Tier 4 are in Tier 6

Table 21: Sensitivity and Specificity by Tier

Category	True Negative	False Positive	Total OUD-negative	False Negative	True Positive	Total OUD-positive	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Tier 1	164	43	207	30	144	174	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)
Tier 2	157	42	199	28	134	162	82.72%	78.89%

Category	True Negative	False Positive	Total OUD-negative	False Negative	True Positive	Total OUD-positive	Sensitivity Exact 95% CI	Specificity Exact 95% CI
							(76.00%, 88.20%)	(72.56%, 84.35%)
Tier 3	144	37	181	24	113	137	82.48% (75.06%, 88.44%)	79.56% (72.94%, 85.18%)
Tier 4	78	14	92	12	29	41	70.73% (54.46%, 83.87%)	84.78% (75.79%, 91.42%)
Tier 5	7	1	8	2	10	12	83.33% (51.59%, 97.91%)	87.50% (47.35%, 99.68%)
Tier 6	78	14	92	12	29	41	70.73% (54.46%, 83.87%)	84.78% (75.79%, 91.42%)

Subjects were enrolled at 10 sites. Two of the sites are listed as opioid treatment programs (sites 10 and 11). The patient population at sites 10 and 11 are people seeking treatment for SUDs, including OUD, and other mental health disorders. The majority of OUD-positive subjects were enrolled at opioid treatment program sites (76.44%, 133/174). The remaining 23.56% (41/174) were enrolled at sites that are not opioid treatment program sites. Of the OUD-positive subjects recruited at opioid treatment program sites (sites 10 and 11) with information available regarding the severity of their OUD (132/133), 126 were severe (94.73%, 126/133), 2 were moderate (1.50%, 2/133), and 4 were mild (3.00%, 4/133). Therefore, the majority (94.73%) of OUD-positive subjects enrolled at opioid treatment program sites had severe OUD. Table 22 below summarizes AvertD sensitivity and specificity by opioid treatment program sites.

Table 22: Sensitivity and Specificity by Opioid Treatment Program Sites

Opioid Treatment Program Site	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
No (Sites 01/02/03/04/05/ 06/07/09)	156	41	12	29	238	70.73% (55.52%, 82.39%	79.19% (72.99%, 84.27%
Yes (Sites 10/11)	8	2	18	115	143	86.47% (79.62%, 91.27%)	80.00% (49.02%, 94.34%)
Total	164	43	30	144	381	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)
Sensitivity across site specialization categories: Two-sided Fisher's exact test p-value 1.00.							

Opioid Treatment Program Site	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Specificity across site specialization categories: Two-sided Fisher's exact test p-value 0.12.							

Three of the sites have at least 1 healthcare provider who holds a waiver to prescribe buprenorphine (sites 2, 10, and 11). The majority of OUD-positive subjects were enrolled at sites with at least 1 prescriber who holds a waiver to prescribe buprenorphine (93.10%, 162/174). The remaining 6.89% (12/174) were enrolled at sites that do not have a healthcare provider with a waiver. Of the OUD-positive subjects recruited at sites with at least 1 waiver (sites 2, 10 and 11) with information available regarding the severity of their OUD (160/162), 129 were severe (79.63%, 129/162), 27 were moderate (16.67%, 27/162), and 4 were mild (2.47%, 4/143). Therefore, the majority (79.63%) of OUD-positive subjects enrolled at sites with at least 1 waiver had severe OUD. Table 23 below summarizes AvertD sensitivity and specificity by site with at least one prescriber who holds a waiver to prescribe buprenorphine.

Table 23: Sensitivity and Specificity by Site with at Least One Prescriber Who Holds a Waiver to Prescribe Buprenorphine

Site with at least one prescriber who holds a waiver to prescribe buprenorphine	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
No (Sites 01/03/04/05/06/07/09)	130	39	2	10	181	83.33% (51.59%, 97.91%)	76.92% (69.83%, 83.05%)
Yes (Sites 02/10/11)	34	4	28	134	200	82.72% (76.00%, 88.20%)	89.47% (75.20%, 97.06%)
Total	164	43	30	144	381	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)
Sensitivity across site specialization categories: Two-sided Fisher's exact test p-value 1.00. Specificity across site specialization categories: Two-sided Fisher's exact test p-value 0.12.							

In total, there were 174 OUD-positive subjects in the clinical study, the majority of which, 74.13% (129/174), had severe OUD and the majority of which were enrolled at specialized sites (76.44% at opioid treatment program sites or 93.10% at sites with at least 1 waiver).

The medical records and medical histories at each enrolling site for all 385 subjects were queried for any information indicating the presence of the following comorbidities: alcohol use disorder, anxiety, bipolar disorder, cannabis use disorder, depression, schizophrenia, or other SUD that is not alcohol or cannabis use disorder. Subjects were not contacted and only information available at the

site was used. It is not known whether the enrollment site that held the medical record or medical history was also the site where the diagnosis was made. Of the 377 subjects with information available, 200 (53.05%, 200/377) subjects had at least one of the queried comorbidities (at any time). The remaining 177 (46.95%, 177/377) did not have a record of any of the queried comorbidities. A greater percentage of subjects with OUD also had a comorbidity (67.00% versus 22.59%) at any time.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population of <18 years old.

5. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR Part 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The clinical study included ten investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in Sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices, an FDA advisory committee, for review and recommendation because the information in the PMA is substantially similar to information reviewed by this panel on October 20, 2022 when the panel met to discuss the AvertD test[2].

The panel was asked whether the probable benefits to health from use of the AvertD device outweigh the probable risks for the proposed indications, considering the probable risks and benefits of currently available alternative forms of detecting risk of developing OUD. The panel voted 2 (yes) to 11 (no).

The panel discussed specific mitigations that may be appropriate to address the risks of the device discussed at the panel meeting including:

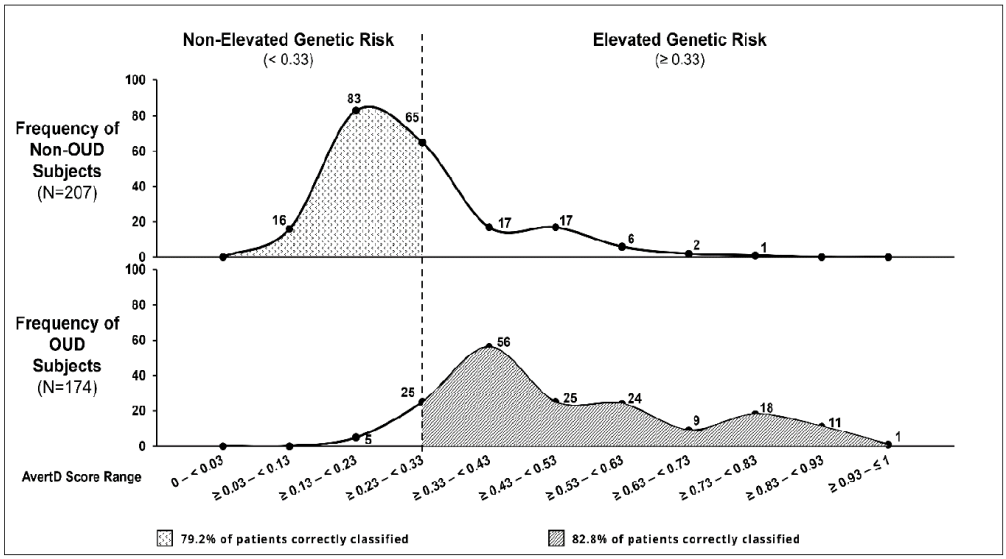
- Presentation of the device results along a continuum rather than as a binary result.
- Strong and plain language that makes clear the test is not intended to be used alone but instead with other tools to evaluate risk.

[2] *See* October 20, 2022 Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee Meeting Announcement and related materials, available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/amended-information-october-20-2022-clinical-chemistry-and-clinical-toxicology-devices-panel-medical.

- Clear labeling that opioid sparing techniques should be used in all patients regardless of the results of the test.
- Additional studies to better understand test performance in subpopulations that were not included in the clinical study population.

- Following the Advisory Committee meeting, the sponsor conducted additional analyses, provided additional information, and made numerous modifications to address advisory committee feedback including:Additional data analyses demonstrating device performance on a continuum as displayed in Figure 1 below. The higher the AvertD score, the more likely the subject is a true positive. The lower the AvertD score, the more likely the subject is a true negative.

Figure 1: AvertD Scores for Non-OUD and OUD subjects



- Reframed the Test Report to describe and display AvertD results along a continuum rather than as a binary result only.
  - Results/score is now provided quantitatively.
  - A cutoff at 0.33 is used (i.e., if the result is ≥0.33 then the patient has "elevated" risk; if the result is <0.33 then the patients has "non-elevated" risk)
- Providing additional information about the training data set.
- Modifications to the Indications for Use making clear the test is to be used only as part of a clinical evaluation and risk assessment, not as a stand-alone test to assess OUD risk.
- Specific labeling revisions, including addition of a boxed warning with specific statements to emphasize appropriate use of the device, and expansion of the limitations section discussing additional limitations of the elevated/non-elevated AvertD test results, non-genetic factors associated with development of OUD, warnings that the device should not be used in patients with chronic pain or

individuals under 18, results should be used by a qualified healthcare provider in conjunction with a clinical evaluation, and the clinical study only assessed the device performance in a subset of the general population.

- Creation of Fact Sheets for health care providers and patients, and a FAQ document for patients that clearly explains how to interpret the AvertD test result.
- Proposal for a mandated training program for healthcare providers who prescribe the test.
- Proposal for a required post-approval study to assess real-world AvertD test performance in a racially and ethnically diverse population representative of the U.S. population.

FDA evaluated the additional information and the modified device and considered the recommendations of the Advisory Committee during the PMA review.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

1. Effectiveness Conclusions

The clinical study showed AvertD had clinical performance with a sensitivity of 82.8% (95% CI 76.3% - 88.1%), a specificity of 79.2% (95% CI 73.1% - 84.5%), a positive likelihood ratio of 3.98 (95% CI 3.26 - 6.87) and a negative likelihood ratio of 0.22 (95% CI 0.17 – 0.33).

A sensitivity of 82.8% means that 82.8% of subjects with OUD were identified as having an elevated risk for developing OUD. There was a 18.2% False Negative Rate, meaning that 18.2% of the subjects were incorrectly identified as having non-elevated risk of developing OUD.

A specificity of 79.2% means that 79.2% of subjects without OUD were identified as having non-elevated risk for developing OUD. There was a 20.8% False Positive Rate, meaning that 20.8% of the subjects were incorrectly identified as having an elevated risk of developing OUD.

A positive result with AvertD is 18 times more likely (3.98/0.22) to occur in a patient who will develop OUD than it would in a patient who will not develop OUD. To understand the interpretation of Likelihood Ratios, consider two patients, Patient A and Patient B, who both have a pre-test probability of developing OUD of 5% (i.e., assuming a population prevalence of OUD 5%). If Patient A has a positive AvertD test and Patient B has a negative AvertD test, then the post-test probability of developing OUD is 18 times higher for Patient A than Patient B.

See the summary of the clinical study above in Section X for more detailed information regarding the effectiveness of the device.

2. Safety Conclusions

There were no known adverse events that occurred during the clinical study. The analytical validation of the device was determined to be acceptable.

3. Benefit-Risk Determination

Benefits

The probable benefits of the device are based on data collected in clinical and nonclinical studies conducted to support PMA approval as described above.
The probable benefit of AvertD is that it provides a measurement that could be used to identify people who may be at elevated genetic risk of developing OUD when they are first prescribed oral opioids for acute pain management. The benefits of AvertD include the following:

- Results from AvertD may be used as part of a complete clinical evaluation and risk assessment to make pain management prescribing decisions
- Patients and healthcare providers may be better informed of possible genetic contribution to risk of developing OUD.
- People at elevated genetic risk may be identified and additional precautions can be taken when prescribing opioids.
- Results from AvertD may minimize undue exposure to oral opioids.

Risks

The risks of the device are based on data collected in the clinical study described above. Risks associated with use of the device include the following:

- Incorrect test result: False Positive or False Negative
    - A false positive result incorrectly identifying a patient as being at elevated risk of developing OUD may prevent patients from receiving opioid therapies that would relieve pain. False positive results may also incur an emotional burden on the patient. In addition, prescribers may have concerns with the responsibility of treating an "at risk" patient with opioids.
    - A false negative result incorrectly identifying a patient as being at non-elevated risk of developing OUD may result in exposure to opioids that may not have otherwise been prescribed. Healthcare providers may base prescribing decisions on a false negative laboratory test result, resulting in a patient who is at an elevated risk for OUD receiving opioids for medical care for acute pain. Patient may also participate in risky behavior that would otherwise have been avoided

based on a false sense of security that they are not at risk for developing OUD.

The risks of false negative and false positive results can be mitigated, in part, through accurate, transparent product labeling and a health provider training program. It is critical that users of the test (health care providers and patients) understand how to interpret the test result and use it not in isolation, but as part of a comprehensive clinical evaluation and risk assessment. The product labeling includes:

- An Indications for Use that makes clear the test is to be used only as part of a clinical evaluation and risk assessment, not as a stand-alone test to assess OUD risk
- A boxed warning to emphasize that:
    - Opioid sparing techniques should be used when prescribing oral opioids for all patients, regardless of test result.
    - An Elevated Genetic Risk test result DOES NOT mean that a patient has or will develop Opioid Use Disorder (OUD).
    - Results from the test are not intended for the diagnosis of OUD.
    - A Non-Elevated Genetic Risk test result DOES NOT mean that a patient does not have and will not develop OUD.
    - Results of the test should not be used alone to make any decisions regarding treatment. Results may be used as part of a complete clinical evaluation and risk assessment to determine appropriate pain management strategies.
    - The test is intended for voluntary use. It is not intended for use as part of a mandated testing program.
- A limitations section that discusses the limitations of the AvertD test and the role of non-genetic factors associated with the development of OUD.
- Clear warnings that the device should not be used in patients with chronic pain or individuals under 18, and that results should be used by a qualified healthcare provider in conjunction with a clinical evaluation.
- A clear description of the clinical study, emphasizing that device performance has been assessed in a subset of the general population.
- A table showing the negative and positive predictive values of AvertD at 1% and 5% OUD prevalence rate.
- Creation of Fact Sheets for health care providers and patients, and a FAQ document for patients that clearly explains how to interpret the AvertD test result.

Additionally, FDA is requiring as a PMA condition of approval, a mandated training program for healthcare providers who prescribe the test to ensure that the test's strengths and limitations are well understood by those health care providers who choose to use it.

Uncertainty

The extent of uncertainty of the benefits and risks of a device is a factor considered when making benefit-risk determinations. One source of uncertainty for AvertD is that some sociodemographic groups of patients were underrepresented in the clinical validation study. Further, inferences based on selected clinical sampling contribute to the uncertainty in performance of the device in a broader, more diverse population. In determining the appropriate extent regarding the benefits and risks of the AvertD, FDA considered the following:

- The public health need for tools to address the opioid crisis remains extremely urgent, and the device fills an unmet medical need related to the treatment or diagnosis of life-threatening or irreversibly debilitating human disease/conditions. There are no FDA authorized genetic tests available that may be used as part of a clinical evaluation and risk assessment to identify patients who may be at elevated genetic risk for developing OUD.
- The ability exists to reduce or resolve remaining uncertainty of a device's benefit-risk profile through postmarket data collection. As a condition of PMA approval, a large post-approval study is required to further assess real world device performance; performance in a broader representative patient population, including across racial and ethnic subgroups; impact of device results on provider prescribing practices; and patient and health care labeling comprehension.
- Mitigations, such as labeling, and other tools, such as training, are likely to be effective in addressing uncertainty. As a condition of PMA approval, the manufacturer will be required to implement a robust training program for health care providers prior to prescription of AvertD to patients. Fact Sheets for health care providers and patients and a FAQ document for patients must also be provided by the manufacturer.

FDA also considered patient perspectives during the review of the PMA as outlined below:

Given the ongoing opioid epidemic, the general population has learned of the addictive effects of opioids and the high potential for developing opioid use disorder. While many are affected, those who are not may be worried about potential addiction and prefer not to take opioids for treatment of acute pain even if prescribed. It is likely that information indicative of elevated or non-elevated risk of developing OUD would decrease patient apprehension and allow for a better decision-making process for prescription (by the healthcare provider) and for taking the drug (by the patient). In this case, the patient perspective may be that the results of device are beneficial and useful for situations in which opioids may be prescribed.

The open public hearing (OPH) portion of the Advisory Committee Meeting held on October 20, 2022, allowed for real patients to provide their perspectives. Patients generally saw benefit for a test that could predict genetic risk, but patients also highlighted an important risk for the device. Most patients indicated that the test

would be used to identify genetic risk in children when opioids would be considered for pain relief for a procedure (e.g., a dental surgery) despite the intended use for patients 18 years or older. Patients also highlighted the risk of over-reliance on the result of the test to determine behaviors.

4. Overall Conclusions

Given the available scientific evidence on the safety and effectiveness of the AvertD and AvertD Buccal Sample Collection Kit, the FDA determined that the probable benefits outweigh the probable risks for the intended use and that there is a reasonable assurance of safety and effectiveness for this device when considering available alternatives, patients' perspectives, the public health need (e.g., urgent need for devices that can make a positive impact in addressing opioid use and misuse), and the ability to reduce or resolve remaining uncertainty postmarket. The PMA approval order includes conditions of approval that mitigate concerns raised during FDA's review of the PMA and those raised in the advisory committee meeting. For example, AutoGenomics Inc. is required to 1) conduct a post-approval study, 2) provide mandatory training for health care providers, 3) provide fact sheets for health care providers and patients, and additional resources for patients to facilitate an understanding of interpretation of results and limitations.

XIII. CDRH DECISION

CDRH issued an approval order on December 18, 2023. The final conditions of approval cited in the approval order are described below.

1. AutoGenomics, Inc. (AGI) must mandate and facilitate robust training for health care providers prior to prescription of AvertD to patients. The purpose of this training is to ensure healthcare providers understand how to use the results from AvertD, understand the limitations associated with the test, and mitigate the risk of incorrect interpretation of test results. This training must include a description of the following:
    - AvertD (including sample collection and handling and the clinical workflow)
    - The AvertD indications for use (as well as patient populations it is not indicated for)
    - AvertD results, their interpretation, and how to use the results
    - The AvertD clinical study and results
    - Limitations with AvertD results

    As part of the training program, AGI must provide training on the informed consent process and obtain concurrence from healthcare providers that they will consent patients and provide the Fact Sheet for Patients and Other Recipients to the patient prior to collection of a sample for use with the genetic test.

2. AGI must provide a Fact Sheet (in addition to the AvertD package insert) to all health care providers prior to prescription of AvertD to patients. The Fact Sheet must inform

healthcare providers of the probable benefits and risks of use of AvertD. This fact sheet for healthcare providers must be provided at the time of training.

3. AGI must provide a Fact Sheet to be given to all patients prescribed AvertD. The Fact Sheet must advise patients of the probable benefits and risks of use of AvertD.

4. AGI must provide all healthcare providers a document with Frequently Asked Questions (and answers) that must be given to all patients prescribed AvertD. This document must include information on how the AvertD test works, how to interpret the results of AvertD, limitations with AvertD results, and what patient populations AvertD should not be used with.

5. AGI must conduct a post-approval study of AvertD to assess the following:
    a. Device performance in the "real world" in the intended use population.
    b. Device performance across representative demographic subgroups (racial and ethnic).
    c. Impact of device results on provider prescribing practices (i.e., What do providers do when they have this result? How do prescribing habits change?)
    d. Patient and health care provider labeling comprehension to 1) ensure patients can understand on their own the meaning of the information they are given and 2) ensure providers understand indicated patient population, how to interpret test result and what to do with it.

    To address the post-approval study requirements cited above, AGI must complete a prospective study of patients tested by AvertD prior to receiving a first prescription of oral opioids for 4-30 days for acute pain, such as in patients scheduled to undergo a planned surgical procedure, and who consent to participate and have the test performed. The study must enroll a minimum of 3000 patients and be statistically powered to assess AvertD performance in demographically relevant subgroups in the United States population. Study participants must be followed for 5 years or until at least 50 OUD-positive patients are diagnosed per relevant demographic subgroup. Study participants must be clinically assessed at baseline and annually thereafter. Results of the AvertD must be compared to DSM-V based OUD diagnosis annually to assess device sensitivity and specificity in each subgroup and overall.

    i. AGI must develop and submit a complete post-approval study plan within 30 calendar days of the date of this order.
    ii. AGI must have an FDA approved post-approval study plan within 60 calendar days of this order.
    iii. AGI must provide interim reports to FDA every six months for the first two years of the post-approval study, and annually thereafter, from the date of the post-authorization study plan approval. By marketing your product, AGI agrees that the interim test performance data may be made public by FDA.
    iv. If any enrollment milestones are not met, AGI must submit a root cause analysis and a plan for completing the study on-time. In addition, AGI must begin

submitting quarterly enrollment status reports every 3 months in addition to AGI's periodic (6-month) interim reports, until FDA notifies AGI otherwise.

v. AGI must submit a final report to the agency within 3 months from study completion (i.e., last subject's last follow-up date).

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.