SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Blood-based Qualitative Colorectal Cancer Screening Test
Device Trade Name:	SimpleScreen™ CRC
Device Procode:	PHP
Applicant's Name and Address:	Freenome, LLC 3300 Marina Blvd Brisbane, CA 94005
Date(s) of Panel Recommendation:	None

Premarket Approval Application (PMA) Number: P250029

Date of FDA Notice of Approval: July 24, 2026

II. INDICATIONS FOR USE

Intended Use:

The SimpleScreen™ CRC test is a qualitative, in vitro diagnostic test intended to detect molecular signals associated with colorectal cancer. SimpleScreen CRC utilizes circulating cell-free DNA from plasma of peripheral whole blood collected in the SimpleScreen CRC blood collection kit.

SimpleScreen CRC is indicated for colorectal cancer screening in adults aged 45 years and older who are at average risk for the disease. Patients with a positive result should be followed by colonoscopy. SimpleScreen CRC is not a replacement for diagnostic colonoscopy or for surveillance colonoscopy in high-risk individuals.

III. CONTRAINDICATIONS

SimpleScreen CRC is NOT indicated for use for patients that have the following:

- Personal history of colorectal cancer (CRC), advanced precancerous lesions (APL), or other related cancers
- Family history of CRC, defined as having one or more first-degree relatives (parent, sibling, or child) diagnosed with CRC at any age
- Positive result on another CRC screening method within the last six months or

- A fecal occult blood test (FOBT) or a fecal immunochemical test (FIT) within the last 12 months
- A FIT-DNA test within the last 36 months

- Personal history of any of the following high-risk conditions for CRC:
  - Inflammatory bowel disease (IBD), including chronic ulcerative colitis (CUC) and Crohn's disease
  - Relevant hereditary cancer syndromes including but not limited to: hereditary non-polyposis colorectal cancer syndrome (HNPCC) or Lynch syndrome, familial adenomatous polyposis (FAP or Gardner's), Familial Hyperplastic Polyposis, Peutz-Jeghers syndrome, MUTYH-associated polyposis (MAP), Cowden's syndrome, Juvenile polyposis syndrome, serrated polyposis syndrome, Turcot's/Crail's syndrome, Cronkhite-Canada syndrome, or Neurofibromatosis.

IV. WARNINGS AND PRECAUTIONS

Based on data from clinical studies, SimpleScreen CRC has limited detection (57%)of Stage I colorectal cancer (64% when U.S. 2020 Census age-sex adjusted) and does not detect 87% of advanced precancerous lesions (86% when U.S. 2020 Census age-sex adjusted). One out of 10 patients with a negative SimpleScreen CRC result may have a precancer that would have been detected by a screening colonoscopy.

V. LIMITATIONS

- Providers should discuss the most appropriate screening test to use with patients depending on their medical history and individual circumstances. SimpleScreen CRC is not intended as a screening test for individuals who are at high risk for CRC.
- SimpleScreen CRC has limited ability to prevent the development of CRC from advanced precancerous lesions (APLs) and has lower detection rates for Stage I CRC, given the current data available.
  - SimpleScreen CRC has lower performance of Stage I CRC [57.1% (16/28); 95% CI: (39.1% - 73.5%)].
  - SimpleScreen CRC may fail to detect as many as 87.5% of patients with advanced precancerous lesions which can later become neoplastic because of its limited detection of advanced precancerous lesions [12.5% (321/2567); 95% CI: (11.3% - 13.8%)].
- The SimpleScreen CRC test may produce false positive or false negative results.
  - A false positive result occurs when the test produces a positive result even though a colonoscopy will not find colorectal cancer or advanced precancerous lesions. SimpleScreen CRC has a false positive rate of 10%,

meaning 1 of 10 people who do not have colorectal neoplasia (colorectal cancer or advanced precancerous lesions) will have a false positive test result.

- A false negative result occurs when the test does not detect colorectal neoplasia (colorectal cancer or advanced precancerous lesions) although a colonoscopy would identify either of these findings. SimpleScreen CRC has a false negative rate of 21% for colorectal cancer, meaning 21 of 100 people who have colorectal cancer will have a SimpleScreen CRC false negative result.

- A positive SimpleScreen CRC test result suggests patients may have colorectal neoplasia (colorectal cancer or advanced precancerous lesions). Patients with a positive result should be followed by colonoscopy.
- A negative SimpleScreen CRC test result does not guarantee absence of colorectal neoplasia (colorectal cancer or advanced precancerous lesions). Patients with a negative result should continue participating in colorectal cancer screening programs, at the appropriate guideline-recommended intervals.
    - One out of 1600 patients testing negative will be falsely reassured that they are negative for colorectal cancer, given the negative predictive value for CRC of 99.9%.
    - One out of 10 patients testing negative will be falsely reassured that they are negative for advanced precancerous lesions, given the negative predictive value for advanced precancerous lesions of 91%.
- CRC screening guideline recommendations vary for persons over the age of 75. The decision to screen patients over the age of 75 should be made on an individualized basis in consultation with a healthcare provider.
- The performance of SimpleScreen CRC has been established in a prospective, cross-sectional study with consecutively enrolled participants. The benefits and risks of programmatic colorectal screening (i.e., repeated testing over an established period of time) with SimpleScreen CRC have not been studied.
- The prospective, cross-sectional study cohort may have included participants with one first-degree relative diagnosed with colorectal cancer after age 60.
- Non-inferiority or superiority of SimpleScreen CRC sensitivity as compared to other recommended screening methods for colorectal cancer or advanced precancerous lesions has not been established.
- Cross-reactivity was observed in analytical studies using samples from subjects with non-CRC cancers, including gastric, pancreatic, liver, bladder, breast, lung, and prostate cancers.
- Consult the Freenome Blood Collection Kit (BCK) Instructions for Use for additional precautions and limitations specific to the collection and shipping of blood samples.

VI. DEVICE DESCRIPTION

The SimpleScreen CRC is performed at Freenome's CLIA-certified laboratory. SimpleScreen CRC is a qualitative in vitro diagnostic (IVD) test used to detect molecular signals (methylation) associated with colorectal cancer (CRC) from whole blood samples collected from individuals at average risk for CRC. A whole blood sample is collected by licensed healthcare providers using the Freenome blood collection kit (BCK) and is then shipped to Freenome's clinical laboratory for testing.

SimpleScreen CRC uses circulating cfDNA, from the plasma portion of peripheral whole blood collected in Streck Cell-Free DNA BCT® blood collection tubes (BCTs) that are included in the BCK, to identify DNA methylation patterns associated with CRC and typically not seen in healthy individuals. The test targets genomic regions that are highly methylated in tumor cells but show only limited methylation in cfDNA from healthy individuals.

Once laboratory processing of the blood samples is completed, molecular data are analyzed by a proprietary software platform that includes analytical pre-processing of the input data, transformation of pre-processed inputs into the numeric features used by the trained artificial intelligence/machine learning (AI/ML) classification algorithm, and generation of a binary classification.

SimpleScreen CRC yields a result that is "Positive", "Negative", or "No Result". A positive result indicates a signal was detected that may suggest the presence of CRC and should be followed by colonoscopy. A negative result indicates the test did not detect a signal associated with CRC. A negative test result does not guarantee absence of advanced colorectal neoplasia. Healthcare providers should work with individuals to continue recommended colorectal cancer screening programs. In some cases, the SimpleScreen CRC may generate a "No Result." If this happens, the ordering physician will be contacted, and the patient may be asked to provide another blood sample.

Reagents, materials, and equipment needed to perform the SimpleScreen CRC test are used exclusively in the Freenome clinical laboratory. The only components distributed outside of Freenome are contained within the Freenome BCK. The following components are required to perform the SimpleScreen CRC test:

Blood Collection Kit:

The BCK comprises all components used for the collection, stabilization, packaging, and transportation of whole blood samples. The BCK contains two BCTs and packaging materials with instructions for storage, sample collection, and shipping contents to Freenome's laboratory.

- Streck cfDNA BCTs (2)
- BCT labels
- Patient Brochure
- BCK Instructions for Use (IFU)

- Biohazard bag
- Foil pouch
- Absorbent sleeve
- Gel pack
- Shipping label and envelope

Assay:

The following reagents are required to perform the SimpleScreen CRC test and are qualified by Freenome under the Freenome Quality System:

- cfDNA extraction kit
- Library preparation kit
- DNA quantification kit
- Next generation sequencing kit and manufacturer-provided sequencer control

Controls:

- Positive control
- Negative control
- Extraction control
- No template control

Instrumentation:

The following instruments are required to perform the SimpleScreen CRC test and are qualified by Freenome under the Freenome Quality System:

- Hamilton Microlab easyBlood STARlet instrument
- Thermo Fisher Qubit® Flourometer
- Hamilton Microlab STAR instrument
- Molecular Devices SpectraMax® Plate Reader
- Agilent Bravo instrument
- Illumina NovaSeq™ 6000

Software:

SimpleScreen CRC includes software to process data from the patient's sample and return a test report to the physician. The Freenome Software Platform (FRNM-SP) uses the sequencing data from the samples processed in the laboratory. These sequencing data are transformed and processed by an AI/ML-enabled classification model which produces a

score and compares it to a pre-defined threshold in order to generate a binary result that is included in a test report.

Test Procedure:

The overall SimpleScreen CRC test is comprised of the following elements:

- Blood Collection Kit
- Pre-Analytic Process
- Genomics Workflow
- Freenome Software Platform

Blood Collection Kit

The initial step of the SimpleScreen CRC test is the collection of whole blood in two Streck cfDNA BCTs that are provided as part of the BCK. The BCK enables whole blood collection and preservation of cfDNA for downstream analytical processing. The whole blood specimen is collected from the individual by licensed healthcare providers and is then shipped at ambient temperature to Freenome's clinical laboratory. Samples are received and accessioned at Freenome's clinical laboratory.

Prior to blood draw, the Freenome BCK may be stored in conditions consistent with its labeling until the expiration date printed on the BCK label. Complete instructions for sample collection and shipping can be found in the BCK Instructions for Use.

Pre-Analytic Process

After accessioning, plasma collected from the BCTs is separated from the whole blood using automated instrumentation. The plasma is then aliquoted and frozen for future analytical processing. Whole blood specimens must be processed within 7 days of blood collection.

Genomics Workflow

The genomics workflow begins with 2 mL of plasma and assay controls which are plated together for cfDNA extraction. After the extraction process, the extraction control concentration is quantified as an in-process quality control (QC) checkpoint. Samples then proceed to library preparation.

Reagents are prepared prior to the associated library preparation steps. Reagent preparation includes the preparation of reagent master mixes used in library preparation, as well as preparation of the quantification reagent used for in-process QC steps. Library

preparation includes end repair, adapter ligation, unmethylated cytosine conversion, and polymerase chain reaction (PCR) steps.

After PCR, prepared libraries are quantified for multiplexing as an in-process QC checkpoint. Next, the multiplexing process pools a portion of each of the libraries and controls from a single plate together into an individual plate library pool, concentrates the pool, and adds the prerequisite reagents for target enrichment.

Target enrichment is performed next, followed by PCR amplification in order to ensure libraries are of sufficient concentration for sequencing. This is confirmed by a quantification step as another in-process QC checkpoint and for normalization and pooling.

After pooling, each individual library pool is quantified as an in-process QC checkpoint. A combined library pool can then be created from up to four individual plate pools using the quantification of each individual plate library pool. If a combined library pool was created, it is then quantified as an additional in-process QC checkpoint to ensure sufficient pooled library mass is present for sequencing.

Sequencing is performed and, when complete, the sequencing data are transferred to a data storage location for downstream processing by the software platform.

Freenome Software Platform (FRNM-SP)

The FRNM-SP includes proprietary cloud-based software used for analytical pre-processing and computational transformation of sequencing data, application of the trained AI/ML classification algorithm, and test report generation.

Analytical pre-processing of the sequencing data from laboratory-processed samples includes demultiplexing; sequence alignment; QC assessment of the positive control, negative control, and no template control; and sample QC. After analytical pre-processing, the pre-processed sequencing data are used to analyze cfDNA fragment nucleotide sequence and CpG methylation status, and results are computationally transformed to produce the structured quantitative values used as inputs to the AI/ML-enabled classification model. The AI/ML-enabled classification model uses this information to identify hypermethylated fragments (HMFs) across multiple regions of the genome, then aggregates information from all loci with a non-linear integrative function to generate a score.

The score is compared to a threshold, yielding a qualitative result. The learned classification threshold was selected to yield a desired specificity, based on behavior in negative samples during training. If the score is greater than or equal to the threshold, the classifier returns a positive call; if the score is less than the threshold, it returns a negative call.

Based on the call from the AI/ML classification model, a test report is generated with a diagnostic result that can be either “Positive”, “Negative”, or in some cases “No Result” for the sample.

Interpretation of Results

A test report will be returned to the ordering healthcare provider with a result of positive or negative. Patients are advised to talk with their healthcare provider about their SimpleScreen CRC results.

A positive result indicates a signal was detected that may suggest the presence of CRC or APL and should be followed by colonoscopy. A colonoscopy evaluation is necessary to determine whether CRC is present.

A negative result indicates the test did not detect a signal associated with CRC. A negative test result does not guarantee absence of CRC. Healthcare providers should work with individuals to continue guideline-recommended colorectal cancer screening programs.

In some cases, SimpleScreen CRC may generate a “No Result”. If this happens, the ordering physician will be contacted, and the patient may be asked to provide another blood sample. A “No Result” test may occur for multiple reasons, some of which include insufficient specimen volume, compromised specimen or blood collection tube, missing sample information, specimen failed QC.

Quality Control Measures

SimpleScreen CRC utilizes a number of controls as part of the genomics workflow.

- The Positive Control (PC) contains sheared genomic DNA from a cell line with a known (hypermethylated fragments) HMF ratio similar to early-stage CRC samples.
- The Negative Control (NC) contains PCR-amplified sheared genomic DNA from a cell line that should yield a negative result. (PCR amplification produces effectively unmethylated DNA.)
- The Extraction Control (EC) is used to assess cfDNA extraction success and is then removed from further processing.
- The No Template Control (NTC) is used to detect nucleic acid contamination in assay reagents, consumables, or instruments.

The controls are treated as individual samples in the workflow. As QC measures, the PC must meet a range criteria while the NC and NTC must fall below respective thresholds for reporting valid patient test results. If there is a QC failure during any of these steps, a “No Result” test report is generated for the sample.

VII. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for colorectal cancer screening. Invasive and non-invasive alternatives are available and described below. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

Recommended screening for CRC includes both invasive and non-invasive options. Invasive options include colonoscopy, flexible sigmoidoscopy, flexible sigmoidoscopy with fecal immunochemical test (FIT), and CT colonography. Non-invasive screening options include stool DNA- or RNA-based CRC screening tests, guaiac-based fecal occult blood testing (gFOBT), FIT, and blood-based plasma DNA testing.

Colonoscopy is considered to be the most accurate screening tool available, which can involve the removal of precancerous lesions to prevent cancer.

Patients who have a positive or abnormal test by an invasive or non-invasive screening method, except for colonoscopy, warrant further investigation through conventional colonoscopy. A patient should discuss these alternatives with their healthcare provider to select the method that best meets the patient's needs, expectations and lifestyle.

VIII. MARKETING HISTORY

SimpleScreen CRC has not been marketed as an IVD in the United States or any foreign country.

IX. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Due to the nature of the non-invasive blood collection process, potential adverse events (AEs) caused by or related to testing with SimpleScreen CRC are unlikely. The primary risk associated with the SimpleScreen CRC is a false test result (i.e., a false positive or a false negative result). All positive test results should lead to a colonoscopy. In the instance of a false negative result on SimpleScreen CRC, there is a possibility that a case of CRC could go undetected.

X. SUMMARY OF NON-CLINICAL STUDIES

Non-clinical studies were conducted at Freenome, LLC to evaluate the analytical performance of SimpleScreen CRC. The studies are described below

A. Algorithm Development and Cutoff Determination

The SimpleScreen CRC AI/ML- enabled classification model was developed and trained using a total of 5,168 clinical samples (negative, CRC and APL) that were

collected across numerous geographically diverse sites. Of these, 1,966 negatives were used for establishing the system score cutoff to achieve the desired specificity.

B. Analytical Sensitivity

1. C95 Establishment

The C95 (Limit of Detection (LoD)) for SimpleScreen CRC was defined as the system score (S) where the test is expected to declare a sample to be positive 95% of the time (also referred to as the C95). To establish the C95 (LoD), 18 clinical blend samples (3 clinical donors × 6 target hypermethylated fragments (4.00x10-4, 2.00x10-4, 1.00x10-4, 5.00x10-5, 2.50x10-5, and $1.25x10^{-5}$ (per donor) were tested across 2 reagent lots with 48 replicates per sample for each lot. All batches began with 4 ng cfDNA input into library preparation, an input mass below the fifth percentile of the intended use population. Testing for each reagent lot included three (3) processing runs, four (4) batches per processing run, and four (4) replicates per sample for each batch. In total, 1728 replicates were processed, of which 1698 passed QC and were used to establish the C95 (LoD).

The C95 (LoD) was determined by fitting a probit model to the percentage of replicates positive for each sample (hit rate) as the outcome and the corresponding mean system score (S) as the predictor variable. The C95 (LoD) or each reagent lot was determined as the S value corresponding to 95% positive call rate (**Table 1**).

Table 1. C95 Values per Reagent Lot for System Score S

Lot	Calculated C95 (LoD)
1	0.712085
2	0.736821

Note: Lot 2 reported an 6.71E-05 HMF for C95

The C95 (LoD) for the SimpleScreen CRC was determined to be the greater LoD value between the two reagent lots, which was system score (S) = 0.736821 (Lot 2).

A subsequent C95 study was conducted as part of the precision study, consisting of unmanipulated clinical samples (12 ACN and 12 non-ACN donors, **Table 3**) along with three clinical blends prepared from 2 CRC and 1 APL donors (the same unmanipulated donors were also run as part of the precision study). The study was conducted across 6 different days, 3 reagent lots, 2 instrument lines and for a total of 24-36 replicates per sample. The C95 (LoD) was re-established and confirmed across the combined data from unmanipulated clinical samples and clinical blends (S = 0.711697). The C95 value of 0.711697 was used as the C95 across all analytical validation studies.

2. Limit of Blank

The Limit of Blank (LoB) of SimpleScreen CRC was evaluated by confirming that the false positive rate of the assay was 0% for samples lacking HMFs. Four 0% methylated contrived samples were tested across two reagent lots with 96 replicates per lot (4 samples x 24 reps per sample). Testing for each reagent lot included 3 processing runs, 4 batches per processing run, and 2 replicates per sample for each batch. The false positive rate was 0% for both reagent lots (**Table 2**).

Table 2. False Positive Rate for Two Reagent Lots

Lot	N Positive	N Total	False Positive Rate
1	0	96	0.00%
2	0	95	0.00%

C. Precision

SimpleScreen CRC precision was evaluated across two combined studies using donors selected that had a system score (S) spanning the assay range and included 8 high positives, 7 low positives, 4 borderline, 6 high negatives and 6 low negative samples.

The initial precision study evaluated 24 individual clinical donors (12 ACN and 12 non-ACN) with ACN status confirmed by colonoscopy/pathology. The ACN donors included 9 CRC and 3 APLs. The non-ACN donors included 5 colonoscopy confirmed negatives (NEG) and 7 donors with non-advanced precancerous lesions (NAPLs). Repeated measures for each donor were taken across 12 batches that were processed across 6 different days, 3 reagent lots, 2 instrument lines, and up to 2 runs per condition. Donors were tested with 2-3 replicates per batch for a total of 24-36 replicates across the 12 batches.

A supplemental precision study was performed with 7 individual clinical donors (2 CRC and 5 APLs) with ACN status confirmed by colonoscopy/pathology. Repeated measures for each donor were taken across 8 batches that were processed across 2 different days, 1 reagent lot and 1 instrument line. Donors were tested with 3 replicates per batch for a total of 24 replicates across the 8 batches.

To evaluate the qualitative output from the SimpleScreen CRC AI/ML-enabled classification model, the majority call for each donor was reported and individual replicates were compared to the majority call for each donor. The majority call agreement for each donor is provided in **Table 3**. The majority call agreement for ACN donors ranged from 52% - 100% and the aggregate majority call agreement across all non-borderline ACN donors was 92.2%. The majority call agreement for non-ACN donors ranged from 86.1% - 100% and the aggregate majority call agreement across all non-borderline non-ACN donors was 94.3%.

Table 3. Detection Rates for Clinical Donors

Sample ID	System Score Bin	Colonoscopy Status	Majority Call	Mean System Score	Total Replicates	% Called Positive Test Result	% Called Negative Test Result
CD23	Low Negative	NEG	Negative	0.395289	36	0/36 (0%)	36/36 (100%)
CD10	Low Negative	NAPL	Negative	0.396721	36	0/36 (0%)	36/36 (100%)
CD19	Low Negative	NAPL	Negative	0.397109	36	1/36 (2.78%)	35/36 (97.22%)
CD11	Low Negative	NEG	Negative	0.398026	34	1/34 (2.94%)	33/34 (97.06%)
CD20	Low Negative	NEG	Negative	0.4024	36	1/36 (2.78%)	35/36 (97.22%)
CD18	Low Negative	NAPL	Negative	0.402839	36	2/36 (5.56%)	34/36 (94.44%)
CD12	High Negative	NEG	Negative	0.405771	34	1/34 (2.94%)	33/34 (97.06%)
CD2	High Negative	NAPL	Negative	0.408844	36	4/36 (11.11%)	32/36 (88.89%)
CD3	High Negative	NAPL	Negative	0.410831	36	4/36 (11.11%)	32/36 (88.89%)
CD6	High Negative	NAPL	Negative	0.410973	36	5/36 (13.89%)	31/36 (86.11%)
CD24	High Negative	NEG	Negative	0.411744	36	3/36 (8.33%)	33/36 (91.67%)
CD9	High Negative	NAPL	Negative	0.412533	35	2/35 (5.71%)	33/35 (94.29%)
CD8	Borderline	APL	Negative	0.425219	35	7/35 (20%)	28/35 (80%)
CD5	Borderline	APL	Negative	0.435738	33	8/33 (24.24%)	25/33 (75.76%)
CD1	Borderline	CRC	Negative	0.44109	23*	7/23 (30.43%)	16/23 (69.57%)
CD29	Borderline	CRC	Positive	0.463669	24	12/24 (50%)	12/24 (50%)
CD32	Low Positive	APL	Positive	0.49472	23**	12/23 (52.17%)	11/23 (47.83%)
CD31	Low Positive	APL	Positive	0.556103	24	22/24 (91.67%)	2/24 (8.33%)
CD13	Low Positive	APL	Positive	0.576681	36	27/36 (75%)	9/36 (25%)
CD28	Low Positive	APL	Positive	0.579151	24	18/24 (75%)	6/24 (25%)
CD33	Low Positive	APL	Positive	0.637812	24	21/24 (87.5%)	3/24 (12.5%)
CD22	Low Positive	CRC	Positive	0.677421	36	31/36 (86.11%)	5/36 (13.89%)
CD30	Low Positive	APL	Positive	0.703253	24	24/24 (100%)	0/24 (0%)

Sample ID	System Score Bin	Colonoscopy Status	Majority Call	Mean System Score	Total Replicates	% Called Positive Test Result	% Called Negative Test Result
CD34	High Positive	CRC	Positive	0.887552	24	24/24 (100%)	0/24 (0%)
CD4	High Positive	CRC	Positive	0.98949	35	35/35 (100%)	0/35 (0%)
CD16	High Positive	CRC	Positive	0.991532	34	34/34 (100%)	0/34 (0%)
CD14	High Positive	CRC	Positive	0.999227	36	36/36 (100%)	0/36 (0%)
CD7	High Positive	CRC	Positive	0.999525	36	36/36 (100%)	0/36 (0%)
CD21	High Positive	CRC	Positive	1	36	36/36 (100%)	0/36 (0%)
CD15	High Positive	CRC	Positive	1	35	35/35 (100%)	0/35 (0%)
CD17	High Positive	CRC	Positive	1	36	36/36 (100%)	0/36 (0%)

*One replicate failed the in-process QC metric "Library Concentration (ng/µL).
**One replicate failed the in-process QC metric "CHH Conversion Rate (%).

A variance component analysis was conducted on the system score (S) generated by the SimpleScreen CRC AI/ML enabled classification model. The system score mean, standard deviation (SD), and coefficient of variation (%CV) were calculated for each donor (**Table 4**). The total variability (within-laboratory) ranged from 0% CV to 27% CV.

Table 4. Variance Component Estimates for the SimpleScreen CRC System Score for each Clinical Donor. Results are Presented as: Standard Deviation (Coefficient of Variation)

Donor ID	ACN Status	Majority Call	Mean System Score	Repeatability	Within Laboratory	Between			
						Days	Lot	Instrument	Run
CD21	ACN	Positive	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CD17	ACN	Positive	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CD15	ACN	Positive	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CD7	ACN	Positive	0.999525	0.000842 (0.08%)	0.000862 (0.09%)	0 (0%)	0.000183 (0.02%)	0 (0%)	0 (0%)
CD14	ACN	Positive	0.999227	0.001347 (0.13%)	0.001362 (0.14%)	0 (0%)	0 (0%)	0 (0%)	0.000199 (0.02%)
CD16	ACN	Positive	0.991532	0.014968 (1.51%)	0.015416 (1.55%)	0 (0%)	0 (0%)	0.002014 (0.2%)	0.003091 (0.31%)
CD4	ACN	Positive	0.98949	0.032519 (3.29%)	0.032604 (3.29%)	0 (0%)	0 (0%)	0 (0%)	0.002344 (0.24%)

Donor ID	ACN Status	Majority Call	Mean System Score	Repeatability	Within Laboratory	Between			
						Days	Lot	Instrument	Run
CD22	ACN	Positive	0.677421	0.178979 (26.42%)	0.178979 (26.42%)	0.000004 (0%)	0 (0%)	0.000004 (0%)	0 (0%)
CD13	ACN	Positive	0.576681	0.155874 (27.03%)	0.155874 (27.03%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CD1	ACN	Negative	0.44109	0.077757 (17.63%)	0.077757 (17.63%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CD5	ACN	Negative	0.435738	0.052502 (12.05%)	0.055782 (12.8%)	0 (0%)	0.011989 (2.75%)	0.014539 (3.34%)	0 (0%)
CD8	ACN	Negative	0.425219	0.051409 (12.09%)	0.062409 (14.68%)	0 (0%)	0.000001 (0%)	0.000001 (0%)	0.035382 (8.32%)
CD9	non-ACN	Negative	0.412533	0.037887 (9.18%)	0.037887 (9.18%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CD24	non-ACN	Negative	0.411744	0.04148 (10.07%)	0.04148 (10.07%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CD6	non-ACN	Negative	0.410973	0.040975 (9.97%)	0.041849 (10.18%)	0.008508 (2.07%)	0 (0%)	0 (0%)	0 (0%)
CD3	non-ACN	Negative	0.410831	0.040728 (9.91%)	0.040728 (9.91%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CD2	non-ACN	Negative	0.408844	0.029132 (7.13%)	0.039957 (9.77%)	0 (0%)	0 (0%)	0.023109 (5.65%)	0.014624 (3.58%)
CD12	non-ACN	Negative	0.405771	0.027024 (6.66%)	0.027335 (6.74%)	0 (0%)	0.004117 (1.01%)	0 (0%)	0 (0%)
CD18	non-ACN	Negative	0.402839	0.021657 (5.38%)	0.022442 (5.57%)	0.005881 (1.46%)	0 (0%)	0 (0%)	0 (0%)
CD20	non-ACN	Negative	0.4024	0.014064 (3.5%)	0.014343 (3.56%)	0.002811 (0.7%)	0 (0%)	0 (0%)	0 (0%)
CD11	non-ACN	Negative	0.398026	0.010401 (2.61%)	0.011607 (2.92%)	0.002076 (0.52%)	0 (0%)	0.004715 (1.18%)	0 (0%)
CD19	non-ACN	Negative	0.397109	0.015312 (3.86%)	0.015312 (3.86%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CD10	non-ACN	Negative	0.396721	0.009417 (2.37%)	0.009417 (2.37%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CD23	non-ACN	Negative	0.395289	0.007055 (1.78%)	0.008578 (2.17%)	0.00488 (1.23%)	0 (0%)	0 (0%)	0 (0%)

Based on the clinical study, 21.6% (5846/27010) of the Prevention of Colorectal Cancer Through Multiomics Blood Testing (PREEMPT CRC) participants generated a system score within the range that will yield less than 95% concordance call.

D. Reagent Cross Reactivity (In-silico Analysis of Primers and Probes)

The specificity of the library construct primers and target capture probes used in the SimpleScreen CRC test was evaluated against the genomes of 21 species of fungi, bacteria, and viruses commonly present in human blood or on skin surfaces that may interfere with test performance, using publicly available sequences in an in-silico

analysis. The study found no potential cross reactivity to the common bacterial, fungal, and viral sources.

E. Non-CRC Cancer and Comorbid Conditions Cross-Reactivity

Cross-reactivity of SimpleScreen CRC was evaluated by determining the positivity rate in non-CRC cancers and non-cancer conditions that may share analytes with CRC and APLs. Whole blood samples collected from subjects with non-CRC cancers and non-cancer conditions were selected and processed using the SimpleScreen CRC workflow to generate a classification call, which was used to assess cross-reactivity.

These samples were collected from subjects with a known diagnosis of cancer or disease, which are not representative of an asymptomatic intended use population. As a result, the positivity rate for these samples may be overestimated. Sample size and types are listed below in **Table 5**.

Table 5. Non-CRC Cancer and Non-Cancer Cross-Reactivity Sample Size

Sample Type	Cancer or Disease	Sample Size
Non-CRC Cancers	Prostate Cancer	27
	Breast Cancer	27
	Lung Cancer	26
	Pancreatic Cancer	26
	Kidney Cancer	7
	Bladder Cancer	9
	Stomach Cancer	5
	Liver Cancer	11
Non-Cancer Conditions	Rheumatoid Arthritis	244
	Chronic Obstructive Pulmonary Disease	154
	Diabetes Type II	1442
	Inflammatory Bowel Disease	27
	Chronic Kidney Disease	117
	Systemic Lupus Erythematosus	52
	Hypertension	7769
	Dyslipidemia	3392
	Diverticulitis	98
	Diverticulosis	169
	Chronic Gastritis	105

*Other cardiovascular diseases (CVDs) categories are based on CVD prevalence (conditions involved in heart or blood vessels such as myocardial infarction, peripheral artery disease, etc.) and based on patient population data.

Sample Type	Cancer or Disease	Sample Size
Non-Cancer Conditions	Esophagitis	46
	Chronic Liver Disease	229
	Coronary Heart Disease/Coronary Artery Disease/Other Cardiovascular Diseases*	336

*Other cardiovascular diseases (CVDs) categories are based on CVD prevalence (conditions involved in heart or blood vessels such as myocardial infarction, peripheral artery disease, etc.) and based on patient population data.

Using an established analytical approach, the positive detection fraction was calculated as the number of SimpleScreen CRC positive samples out of the total number of passing samples tested per non-CRC cancer and non-cancer condition. The positivity rates in previously diagnosed non-CRC cancers and non-cancer conditions when tested with SimpleScreen CRC are listed in **Table 6** and **Table 7**, respectively. The cross-reactivity / positivity rates of non-cancer conditions were generally consistent with the false positive rate of the test.

Table 6. Cross-reactivity (Positivity) Rate for Non-CRC Cancers

Cancer	Percent Positive Call n/N (%)	Annual Incidence Rate per 10000 Subjects (45-84)*	Number of SimpleScreen CRC Positive Calls per 10000 Subjects§
Prostate Cancer†	7/27 (25.9%)	18.63	4.8
Breast Cancer	9/27 (33.3%)	17.48	5.8
Lung Cancer	16/26 (61.5%)	13.83	8.5
Pancreatic Cancer	18/26 (69.2%)	3.72	2.6
Kidney Cancer	0/7 (0.0%)	4.77	0
Bladder Cancer	3/9 (33.3%)	4.81	1.6
Stomach Cancer	4/5 (80.0%)	1.89	1.5
Liver Cancer	11/11 (100.0%)	2.84	2.8
TOTAL			27.7

* Information was obtained from National Cancer Institute (http://seer.cancer.gov; last accessed 09 July 2025)
† Value adjusted to represent sex-specific disease state.
§Calculated by multiplying positive call rates with annual incidence.

Table 7. Cross-reactivity (Positivity) Rate for Non-Cancer Conditions

Disease	Percent Positive Call n/N (%)	Prevalence Observed in PREEMPT CRC*	Number of SimpleScreen CRC positive calls per 10000 Subjects§
Rheumatoid Arthritis	24/244 (9.8%)	0.9%	8.8
Chronic Obstructive Pulmonary Disease	19/154 (12.3%)	0.9%	11.1
Diabetes Type II	176/1442 (12.2%)	5.9%	72.0
Inflammatory Bowel Disease†^	4/27 (14.8%)	1.3%	19.2
Chronic Kidney Disease	12/117 (10.3%)	0.5%	5.2
Systemic Lupus Erythematosus	2/52 (3.8%)	0.2%	0.8
Hypertension	739/7769 (9.5%)	29.5%	280.3
Dyslipidemia	303/3392 (8.9%)	12.6%	112.1
Diverticulitis	11/98 (11.2%)	0.5%	5.6
Diverticulosis	16/169 (9.5%)	0.6%	5.7
Chronic Gastritis	4/105 (3.8%)	0.4%	1.5
Esophagitis	2/46 (4.3%)	0.2%	0.9
Chronic Liver Disease	29/229 (12.7%)	0.9%	11.4

* Prevalence of non-cancer conditions was observed from PREEMPT CRC all enrolled subjects (N=48,995) with the exception of IBD.
† Data obtained from Dahlhamer et al.[1]
^Individuals with diagnosed IBD are contraindicated for SimpleScreen CRC. Prevalence estimates for undiagnosed IBD could not be determined from PREEMPT CRC.
§Calculated by multiplying positive call rates with PREEMPT CRC observed prevalence and 10000.

Disease	Percent Positive Call n/N (%)	Prevalence Observed in PREEMPT CRC*	Number of SimpleScreen CRC positive calls per 10000 Subjects[§]
Coronary Heart Disease/Coronary Artery Disease/Other Cardiovascular Diseases	44/336 (13.1%)	1.4%	18.3

* Prevalence of non-cancer conditions was observed from PREEMPT CRC all enrolled subjects (N=48,995) with the exception of IBD.
[†] Data obtained from Dahlhamer et al.[1]
^Individuals with diagnosed IBD are contraindicated for SimpleScreen CRC. Prevalence estimates for undiagnosed IBD could not be determined from PREEMPT CRC.
[§]Calculated by multiplying positive call rates with PREEMPT CRC observed prevalence and 10000.

F. Carryover and Cross-Contamination

To evaluate carryover and cross-contamination effects on the SimpleScreen CRC, alternating unmethylated contrived samples and methylated contrived samples were processed in a checkerboard layout in 6 batches, 92 samples per batch plus controls, performed consecutively on a single line of instruments and a single side of the sequencer. A total of 273 unmethylated and 279 methylated contrived sample replicates were used in this study. Of the methylated contrived samples, 279/279 (100.0%) produced valid positive results. Of the unmethylated contrived samples, 269/272 (98.8%) produced valid negative results. The three false positive results all had a DNA input of 20 ng and a system score below the C95 (Limit of Detection).

G. Interfering Substances

To evaluate the impact of potential endogenous and exogenous interfering substances on the performance of SimpleScreen CRC, 24 replicates each of clinical blend and healthy multi-donor pool plasma samples, which simulate CRC-negative samples, were tested in the absence (control) and presence (test) of nine endogenous substances (**Table 8**) and four exogenous substances (genomic DNA, magnetic beads, ethanol, and molecular index barcodes). The difference in system score drift was 0.4% - 5.1%, which was considered acceptable. No interference on the SimpleScreen CRC test was observed for any of the substances at the concentration tested.

Table 8. Endogenous Interfering Substances Tested

Interfering Substance	Level
Bilirubin, unconjugated	40 mg/dL
Bilirubin, conjugated	40 mg/dL
Hemoglobin	1,000 mg/dL
Triglycerides	1,500 mg/dL
Albumin	6 g/dL
Cholesterol	400 mg/dL
Red Blood Cells	0.4% v/v
Uric acid	23.5 mg/dL
Glucose	1,000 mg/dL

H. Robustness

1. Assay Workflow Guardbanding

The objective of the guardbanding study was to evaluate the tolerance of the SimpleScreen CRC test to variations in critical assay workflow parameters such as incubation temperatures, reagent volumes, and reagent concentrations, throughout the entire SimpleScreen CRC workflow. Guardbanding for the SimpleScreen CRC test was performed using a risk-based approach to identify assay components for guardbanding and their respective ranges (guardbands).

Three sample types, contrived high methylated, contrived low methylated, and healthy donor pooled plasma, and three controls (positive, negative, and no-template) were used to test 43 factors (guardbanded conditions) across the SimpleScreen CRC test from extraction to target enrichment.

Robustness of the test performance with respect to the 43 critical assay workflow parameters was observed. Across all guardbanded conditions, contrived high samples demonstrated 100% majority call agreement, contrived low samples maintained 81.0% - 91.3% majority call agreement, and healthy donor plasma reported majority call agreement of 91.7% - 100.0%.

2. DNA Input Mass

An input guardbanding study was conducted to evaluate the robustness of the SimpleScreen CRC assay at different cfDNA input levels. The robustness of SimpleScreen CRC to the cfDNA input level was assessed using a total of four cfDNA blends at the predicted range of cfDNA input mass of the Intended Use Population (IUP). Three cfDNA levels (3.5 ng, 11 ng, and 70 ng) covering the minimum and maximum limits of the predicted 95% intended use population (IUP) distribution were tested with a minimum of 20 replicates per sample per cfDNA input mass level for a total of 288 replicates over 4 batches. The study results demonstrated that the SimpleScreen CRC test produces a 94.5% (75/79, 95% CI: (87.5% - 98.6%) positivity rate at the minimum and a 100% (44/44, 95% CI: (92.0% - 100%) at the maximum limits of the predicted 95% IUP distribution (3.5 ng and 70 ng, respectively) comparable to the standard input mass of 11 ng.

I. Stability

1. Whole Blood Stability

Whole blood stability was assessed using whole blood samples collected in Streck cfDNA blood collection tubes (BCTs) from 25 self-identified healthy donors from the intended use population, 9 APL donors, and 35 CRC donors. Blood samples were stored at room temperature (16°C – 25°) for up to seven days before plasma separation and downstream processing with SimpleScreen CRC.

From each donor, blood was collected in BCTs from two to three lots with various ages from the date of sterilization (DOS) or date of manufacture (DOM) of the Streck cfDNA BCTs (Lot A: ≤ 30 days from DOS at study initiation, Lot B: 12-18 months from DOM, Lot C: > 18 months from DOM). From each self-identified healthy donor, 18 BCTs were collected with six BCTs from each of the three lots. From the CRC donors and APL donors, four BCTs were collected. CRC donors and APL donors were only collected with either Lot A and Lot C or Lot A and Lot B due to the limited number of BCTs that could be collected from these donor types.

For each lot, half of the BCTs from each donor were processed to plasma on the day of receipt at Freenome (Day 1 post blood draw) and the other half were stored for seven days (Day 8 post blood draw) before being processed to plasma. to support stability of whole blood specimens collected in BCTs for up to seven days (Day 8 post blood draw). The study results support whole blood samples, collected in Streck cfDNA BCTs aged up to 18 months past the DOM, are stable when stored at room temperature (16°C – 25°) for up to seven days.

An additional stability study was performed to evaluate whether whole blood processed on Day 1 post blood draw can represent the device performance for samples processed on the date of collection. Whole blood was collected in four BCTs from each of 32 unique donors (20 healthy and 12 CRC donors). For each donor, 2 BCTs were processed to plasma within 4 hours of the blood draw and 2

BCTs were processed to plasma on Day 1. The NPA and PPA were evaluated by comparing the binary SimpleScreen CRC results from the test condition (Day 1) to the control (within 4 hours) majority calls; and a PPA of 100% and NPA of 90% were observed demonstrating whole blood processed on Day 1 post blood draw represents the device performance for samples processed on the data of collection.

2. Whole Blood Transportation Stability

Whole blood stability across different shipping conditions was assessed using whole blood samples collected in Streck cfDNA BCTs from 21 self-identified healthy donors, 18 colonoscopy-confirmed negative donors, 1 non-advanced adenoma (NAA) donor, 7 APL donors, and 15 CRC donors.

Whole blood samples were either processed to plasma on the day of receipt (Day 1 post-collection, control condition) or packaged in the SimpleScreen CRC blood collection kit and exposed to winter or summer shipping conditions. Samples were then stored at room temperature (15°C – 25°C) until either Day 5 or Day 8 post-collection when plasma was isolated.

A total of seven study conditions (BCTs stored inverted Summer Day 8, upright Summer Day 8, inverted Winter Day 8, upright Winter Day 8, upright Summer Day 5, upright Winter Day 5, and Day 1 control). From each self-identified healthy donor, blood was collected into 21 BCTs with three replicates (i.e., three BCTs) for each of the seven conditions. For ACN and colonoscopy-confirmed negative/NAA donors, blood was collected into five BCTs with one BCT for each of the four conditions where plasma was isolated on Day 8 post-collection in addition to the control. The PPA was 100% for all conditions (Summer/Winter, Inverted/Upright) tested and the NPA for Winter Upright, Summer Upright, Winter Inverted, and Summer Inverted, was 95.8%, 95.7%, 93.9%, and 91.8%, respectively.

3. Plasma Stability: Freeze-Thaw

A freeze-thaw plasma stability study was conducted to evaluate the impact of plasma freeze-thaws on the performance of the SimpleScreen CRC assay. A total of 20 healthy, 10 CRC, and 4 APL samples were tested across five freeze-thaw cycles. No notable degradation in the system score in the stability study was observed over at the fifth freeze-thaw demonstrating plasma samples are stable for up to four freeze-thaw cycles.

4. **Plasma Stability: Long-Term**

A long-term plasma stability study was designed to evaluate the stability of plasma under long-term storage conditions at -80°C (-70°C to -90°C). A total of 18 healthy, 15 CRC and 13 APL samples to be tested across 5 time-points. This study is ongoing, and results were obtained for the T0, T1 (12 months), and T2 (24 months) time-points. No notable degradation in the system score the stability study was observed at 24 months. Currently, this study has demonstrated stability for at least 22 months when stored at -80ºC.

5. **Plasma Stability: On-board**

An on-board plasma stability study was conducted to evaluate the stability of plasma when stored up to eight hours at room temperature (16°C – 25°C) prior to plasma plating. Two control batches were thawed and then proceeded immediately to plasma plating and two test condition batches were held at room temperature for a total of nine hours. Each batch contained 10 replicates for each of two clinical blend samples as well as 20 replicates for one healthy multi-donor pool (HMDP), resulting in a total of 40 replicates for clinical blends and 40 replicates for HMDP for both the control and test condition. The percent difference in system scores between the control and treatment conditions was less than 2% for both the clinical blends and the HMDP. The PPA for both clinical blends was 100.0% for both the treatment and control condition. The NPA for the HMDP was 87.5% in the treatment condition and 95.0% in the control condition.

6. **cfDNA Stability**

cfDNA stability was evaluated with a total of 18 clinical blended samples (3 clinical blends x 6 hypermethylated fragment [HMF] levels), 4 unmethylated (0% methylated) contrived samples from manufacturing events, and batch controls (PC, NC, and NTC) across four timepoints (e.g., baseline, 6.5 months, 16 months, and 19 months) at -20°C. No notable differences were observed between baseline and later timepoints, demonstrating cfDNA stability for 17 months when stored at -20°C.

7. **In-Use Stability**

An in-use stability study was conducted to evaluate the stability of 4 hold-points in the SimpleScreen CRC workflow. The in-use stability study utilized two clinical blend samples and one healthy multi-donor pool plasma sample. Twenty clinical blend replicates were tested per batch per condition (10 replicates per clinical blend) and 20 healthy multi-donor pool replicates tested per batch per condition. One baseline batch and one batch stored at the corresponding condition were run. The percent change between the stored mean values and baseline mean values was calculated. The following conditions were tested:

- Samples can be stored after cfDNA extraction at -20°C for 34 days
- Samples can be stored after library preparation at -20°C for 37 days
- Samples can be stored after target capture and DNA quantification at -20°C for 32 days
- Samples can be stored after normalization and pooling at -20°C for 35 days

Test condition samples were tested at the conditions listed above and compared against the baseline values. The in-use stability study demonstrated a PPA of 100% and NPA of ≥90% for all test conditions listed .There was no notable difference in mean system score S between the control and test samples for the four tested hold conditions, supporting the use of the hold points as part of the assay process.

8. Reagent Shelf-Life Stability

A real-time reagent stability study was conducted to establish the shelf-life of SimpleScreen CRC reagents and external batch controls. Three SimpleScreen CRC reagent lots were tested across six timepoints (T0: after QC release; T1: 2 months; T2: 4 months; T3: 6 months; T4: 8 months; T5: 10 months) with 3 unique clinical blends samples at approximately 1.5 times the C95, 3 unique clinical blend samples at approximately 3 times the anticipated C95, and three healthy multi-donor pool plasma samples. A minimum of 24 replicates per sample type per reagent lot per timepoint were tested. The shelf-life stability of SimpleScreen CRC reagents and external batch controls is 10 months when stored at the appropriate conditions.

9. On Board Reagent Stability

The purpose of the on-board stability study was to determine reagent stability after using and holding reagents under different process steps including on deck (stored on the relevant instrument) of their respective automation platforms and while off deck (stored separate to instrument, e.g. on the bench) for the genomics portion of the SimpleScreen CRC test workflow. These processes include:

- cfDNA extraction kit
- Library preparation kit
- DNA quantification kit
- Next generation sequencing kit and manufacturer-provided sequencer control

A total of 60 clinical blend samples, 60 healthy multi-donor pool samples at their native systems core (correlating with ≤ C10), and three of each batch control were

tested across three batches. A total of 20 replicates per condition were tested to evaluate the tolerance of the SimpleScreen CRC assay to the final hold conditions tested. Clinical blends were blended to target C100.

The results demonstrated that the time reagents on board are stable for 2 hours.

10. Reagent Freeze-Thaw Stability

A reagent freeze-thaw stability study was conducted to evaluate the impact of freeze-thaw cycles on reagents used in the SimpleScreen CRC test that are stored at -20°C. In addition, the study evaluated the freeze-thaw stability of intermediate reagents (aged master mixes). The study tested two clinical blends (10 replicates each) and one healthy multi-donor pool (20 replicates) per batch under each test condition. One control batch and two test batches were evaluated to determine the maximum number of freeze-thaw cycles that could be tolerated without affecting assay performance. The percent change in the mean system score between the control and test conditions was evaluated, and the percent drift in the mean system score for the test condition remained within the acceptable range (<10%). The reagent freeze-thaw stability study demonstrated an overall PPA of 95% and NPA of 90%. The study results showed that the SimpleScreen CRC reagents, master mixes, and sequencing reagents are stable for up to four, three, and three freeze-thaw cycles, respectively.

11. Output Plate Freeze-Thaw Stability

An output plate freeze-thaw stability study was conducted to evaluate the freeze-thaw stability of seven out of the nine safe stopping points in the SimpleScreen CRC workflow where intermediate samples and one on-board stability condition (extraction plate on-board stability) are stored frozen. Two clinical blend samples and one healthy multi-donor pool (HMDP) were used in this study. Twenty clinical blend replicates were tested per batch per condition (10 replicates per clinical blend), and 20 healthy multi-donor pool replicates were tested per batch per condition. Twenty clinical blend replicates were tested per batch per condition (10 replicates per clinical blend) and 20 healthy multi-donor pool replicates tested per batch per condition. An overall PPA of 100% and NPA of 90% was observed. The results support intermediate samples stored at the seven stopping points are stable for up to three freeze-thaw cycles; and the extraction output plate is stabile for up to 2.5 hours when stored on-board at room temperature (16°C – 25°C).

12. Reagent Lot Interchangeability

A Reagent Lot Interchangeability study was conducted to evaluate the interchangeability of nine critical reagent groups across three reagent lots using 24 clinical blend replicates (eight replicates per three clinical blends) and 24 HMDP replicates (eight replicates per three HMDP samples). For seven of the nine critical reagent groups overall PPA of 100% and an overall NPA of 92% was observed across the nine interchangeability conditions. The remaining two reagent groups demonstrated 100% pass rate and 100% concordance with the reference condition. The overall percent drift in the mean system score for the interchangeability conditions remained within the acceptable range (<10%) for both clinical blends and healthy multi-donor pools (HMDPs).

J. Animal Studies

Not Applicable

K. Additional Studie

1. Streck cfDNA BCT Lot-to-Lot Reproducibility Study

A lol-to-lot reproducibility study was conducted to evaluate performance of the Streck cfDNA BCT across lots when used with SimpleScreen CRC. Lot-to-lot reproducibility was evaluated using whole blood samples collected across five BCTs, each from a different lot, from 21 healthy donors and 16 ACN donors from the intended use population. The PPA and NPA were evaluated by comparing the binary SimpleScreen CRC results for each lot to the majority call across lots. A PPA and NPA of 100% were observed.

2. Streck cfDNA BCT Tube-to-Tube Repeatability Study

A tube-to-tube repeatability study was conducted to evaluate performance between Streck cfDNA BCTs when used with SimpleScreen CRC. Tube-to-tube repeatability was evaluated using whole blood samples collected across five BCTs, each from the same lot, from 20 healthy donors and 19 ACN donors from the intended use population The PPA and NPA were evaluated by comparing the binary SimpleScreen CRC results for each BCT to the majority call across all BTCs. A PPA and NPA of 100% were observed.

3. Streck cfDNA BCT Preservative Guardbanding Study

A guardbanding study was performed to evaluate the performance of the SimpleScreen CRC test in the presence of excess components from the Streck cfDNA BCT preservatives. Samples were collected into standard Streck cfDNA BCTs. One standard preservative condition and four conditions containing excess amounts of preservatives were assessed. Twenty-one (21) self-identified healthy donors, 6 APL donors and 30 CRC donors were included in the study. Fifteen (15) BCTs were collected from each self-identified healthy donors with three replicates (three BCTs) for each condition. From APL donors, five BCTs were collected with one BCT for each condition. From CRC donors, three BCTs were collected with one BCT for conditions A, B, and C or for conditions A, D, and E due to the limited number of BCTs that were collected. The NPA and PPA were evaluated by comparing the binary SimpleScreen CRC results from the test conditions to the control condition majority call. The result of the guardbanding study showed underfilling the BCTs with less than 10 mL of blood may impact the SimpleScreen CRC test results (**Table 9)**.

Table 9. Streck cfDNA BCT Preservative Guardbanding Study Design

Condition (BCT Type)	Streck cfDNA BCT Preservative (Relative to the Standard)			Healthy NPA	ACN NPA	ACN PPA
	Component A	Component B	Preservative Volume			
A (Standard)	1x	1x	1x	100%	100%	100%
B (2x Component A)	2x	1x	1x	91.4%	66.7%	90.0%
C (2x Component B)	1x	2x	1x	97.2%	77.8%	90.0%
D (8 mL Short Draw)	1x	1x	1.25x	91.4%	50.0%	87.5%
E (5 mL Short Draw)	1x	1x	2x	86.1%	66.7%	87.5%

4. Streck cfDNA BCT Incomplete and Overmixing Verification Study

The purpose of the Streck cfDNA BCT Incomplete and Overmixing study was to evaluate the effect of incomplete or over mixing of blood with the anticoagulant and cell preservative in the Streck cfDNA BCTs on the SimpleScreen CRC test. Samples were collected in BCTs and subjected to three study conditions: standard mixing (10 inversion), incomplete mixing (5 inversions), and over mixing (15 inversions). Twenty-one (21) healthy donors with three replicates (three BCTs) for each condition and 16 ACN (CRC or APL) donors with one replicate (one BCT) for each condition were included in the study. The NPA and PPA were evaluated by comparing the binary SimpleScreen CRC results from the test conditions to the control condition majority call. The PPA for incomplete and over mixing was 100%; and the NPA for incomplete and over mixing was 78.8% and 90.9%, respectively. The study results demonstrate that incomplete and over mixing may impact the SimpleScreen test results.

XI. SUMMARY OF PIVOTAL CLINICAL STUDY

The Prevention of Colorectal Cancer Through Multiomics Blood Testing (PREEMPT CRC) study[2] was a prospective, multi-center study conducted to generate data to support the safety and effectiveness of SimpleScreen CRC as a blood-based screening test for the detection of markers associated with the presence of colorectal cancer (CRC) from whole blood samples. To evaluate the clinical performance of SimpleScreen CRC blood test, the test result (negative or positive) was compared with the histopathological result of the index lesion (i.e. most clinically significant lesion) identified from screening colonoscopy. The primary study objectives were sensitivity for CRC and specificity for ACN. A secondary objective was sensitivity for APLs.

Based on this evaluation, SimpleScreen CRC sensitivity (true positive fraction), was 79.2% (57/72) for subjects with a histopathological diagnosis of CRC, and 12.5% (321/2567) for subjects with a diagnosis of advanced precancerous lesion (APL, Category 2.1 – 2.5, Table 11), respectively. For subjects without a diagnosis of CRC or APL, the SimpleScreen CRC specificity (true negative fraction) was 91.5% (22306/24371).

A. Study Design

PREEMPT CRC (ClinicalTrials.gov, Identifier: NCT04369053) was a prospective study enrolling a total of 48,995 participants at 200 sites in the United States and one site in the United Arab Emirates (at a facility affiliated with a US healthcare system). Eligible participants provided signed informed consent and were enrolled from May 19, 2020, to April 1, 2022. However, to mitigate the then unknown impact of the COVID-19 pandemic on the representiveness of the study population, the pivotal clinical validation population consisted of participants consecutively enrolled on or after April 5, 2021, to April 1, 2022, for a total of 31,594 participants. Enrolled subjects were 45 to 85 years within 30 days of enrollment, asymptomatic, at average risk for CRC, and

were willing to undergo blood collection (site-based and mobile phlebotomy) and a standard-of-care (SOC) screening colonoscopy within 90 days of blood draw. The window to complete colonoscopy was increased to 120 days to account for decreased access to care due to the COVID-19 pandemic. The blood draw was completed prior to colonoscopy bowel preparation. To evaluate the performance of SimpleScreen CRC, the test results were compared to the colonoscopy results and histopathological information. All colonoscopy reports and applicable histopathology reports were reviewed by a central pathologist to assign a histopathological category. When multiple lesions were found, the most clinically significant finding was defined as the index lesion (**Table 10**). Histopathology categories were used to designate the clinical ground truth result to determine the test sensitivity and specificity, as well as positive and negative predictive values.

Table 10. Histopathological Categories and Definitions

Subcategory	Findings
CRC 1.0	All Stages (I-IV)
APL 2.1	Adenoma with carcinoma in situ or high-grade dysplasia, any size
APL 2.2	Adenoma, villous growth pattern (≥ 25%), any size
APL 2.3	Adenoma ≥ 1.0 cm in size
APL 2.4	Serrated lesion, ≥ 1.0 cm (includes sessile serrated adenoma/polyp)
APL 2.5	Traditional serrated adenoma (TSA), any size
NAPL 3.0	≥ 5 adenomas, all < 1.0 cm in size, non-advanced
NAPL 4.0	3 to 4 adenomas, all < 1.0 cm in size, non-advanced
NAPL 5.1	1 to 2 adenomas, all < 1.0 cm in size, non-advanced
NAPL 5.2	Hyperplastic polyps (HP) ≥ 1.0 cm
NAPL 5.3	All sessile serrated lesions (SSL) < 1.0 cm and HP < 1.0 cm not in sigmoid or rectum
NEG 6.1	Negative and other findings upon histopathological review
NEG 6.2	No findings on colonoscopy, no histopathological review

B. Clinical Inclusion and Exclusion Criteria

For enrollment in PREEMPT CRC, the subjects met all the following criteria:

1. 45-85 years of age (inclusive) within 30 days of enrollment
2. Willing to undergo a SOC colonoscopy within 90 days of blood collection

3. Considered by a physician or healthcare provider to be average-risk for CRC
4. Able and willing to provide blood samples per protocol
5. Able to comprehend and willing to sign and date the written informed consent document(s)

Subjects were excluded from enrolling in PREEMPT CRC if they met any of the following criteria:

1. Family history of CRC
    1.1 At least one (1) first-degree relative diagnosed with CRC before the age of 60 (Note: First degree relatives include parents, siblings, and offspring)
    1.2 At least two (2) first-degree relatives diagnosed with CRC at any age
2. Known hereditary gastrointestinal cancer syndrome including but not limited to the following:
    2.1. Hereditary non-polyposis CRC syndrome or Lynch syndrome
    2.2. Familial adenomatous polyposis (FAP)
    2.3. Cowden's syndrome
    2.4. Juvenile polyposis syndrome
    2.5. MUTYH-associated polyposis (MAP)
    2.6. Peutz-Jeghers syndrome
    2.7. Serrated polyposis syndrome
3. Personal history
    3.1. CRC or colorectal adenoma
    3.2. History of malignancy (except for non-melanomatous skin cancer) at the time of enrollment, and for the 5 years preceding enrollment
    3.3. IBD, including CUC and Crohn's disease
    3.4. Total colonic resection
    3.5. Cystic fibrosis
    3.6. Colonoscopy in the 9 years preceding enrollment with the exception of an incomplete colonoscopy, or for a poor or inadequate bowel prep
    3.7. Sigmoidoscopy or CT colonography in the 4 years preceding enrollment
    3.8. Stool DNA testing in the 2 years preceding enrollment
    3.9. Fecal occult blood testing or fecal immunochemical testing in the 6 months preceding enrollment

3.10. Requiring an immediate or emergent colonoscopy for the investigation of symptoms

3.11. Solid organ or bone marrow transplantation

3.12. Blood product transfusion in the 120 days preceding enrollment

3.13. Any trauma or surgery requiring overnight inpatient hospitalization in the 30 days preceding enrollment

4. A medical condition which, in the opinion of the investigator, should preclude enrollment into the study.
5. Participated or currently participating in a clinical research study in which an experimental medication has been administered during the 60 days leading up to and including the date of providing informed consent or may be administered through the time of the colonoscopy.
6. Known to be pregnant.

C. Follow-Up Schedule

Not Applicable

D. Clinical Performance Measures

1. Primary Objective

The primary objectives of the study were to determine the sensitivity of SimpleScreen CRC for CRC and specificity for ACN using screening colonoscopy with histopathology, as ground truth, for assessment of the target condition, within 90 days of the blood draw.

2. Secondary Objective

The secondary objective was to evaluate the sensitivity of Freenome's test for advanced precancerous lesions (APL).

E. Accountability of PMA Cohort

To mitigate the then-unknown impact of the COVID-19 pandemic on the representativeness of the study population, the pivotal clinical validation population consisted of participants consecutively enrolled on or after a cutoff date of April 5, 2021, to April 1, 2022.

- The pivotal clinical performance study included 31,594 eligible subjects (subjects who met inclusion and exclusion criteria)

- Of the 31,594 subjects, 2,497 subjects were excluded due to loss to follow-up (182 subjects) or colonoscopy not performed (2315 subjects)
- Of the remaining 29,097 subjects, 1,275 subjects were excluded due to colonoscopy/histopathology issues (e.g. unevaluable colonoscopy, unconfirmed diagnosis).
- Of remaining 27822 subjects, 812 subjects were excluded due to sample issues.

Ultimately, a total of 27,010 subjects who had confirmed clinical findings and valid SimpleScreen CRC blood test results comprised the evaluable dataset, with 72 CRC, 2,567 APLs, 8,936 NAPLs and 15,435NEGs. This population was used for the primary analysis of the clinical validation of the SimpleScreen CRC test. (**Figure 1**).

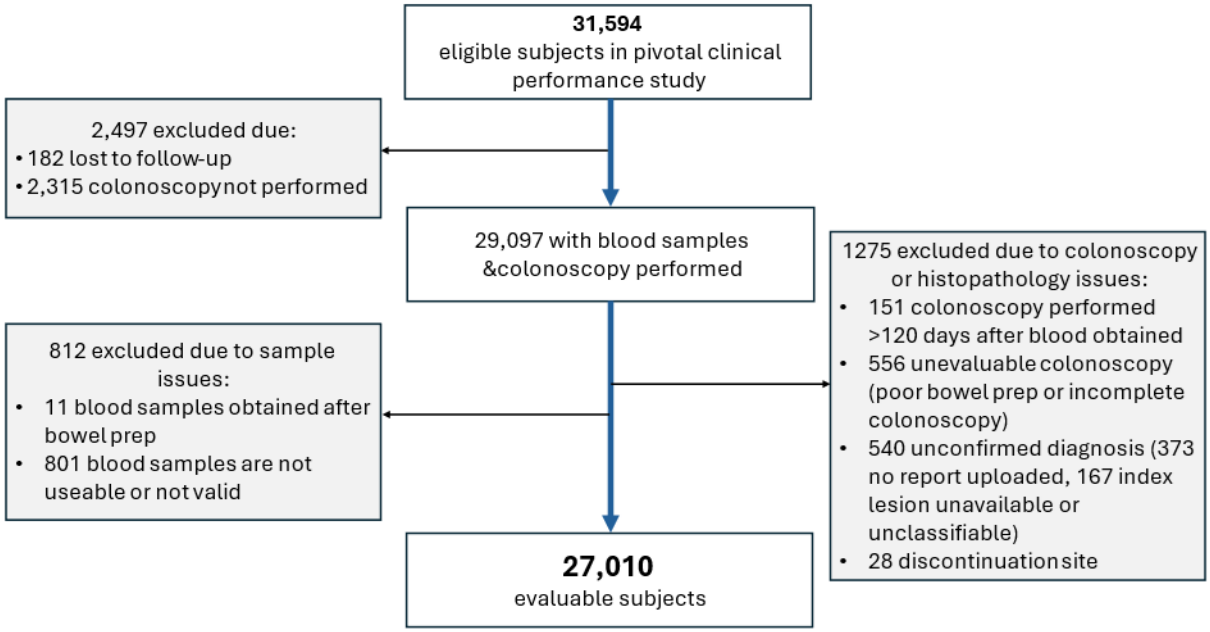

Figure 1. Accountability Flowchart

F. Study Population Demographics and Baseline Parameters

The demographic and baseline characteristics for subjects in the primary effectiveness cohort (evaluable cohort of 27,010 participants) are presented in **Table 11**. The average age was 58.1 years and 55.8% were female. Compared to the U.S. census distribution,[3] there was a higher proportion of participants aged 50 to 54 years (32.9% vs 15.6%), lower proportion of those aged 75 years and older (3.0% vs 12.5%), and a higher proportion of females (55.8% vs 51.8%). Regarding race, 8.8% were Asian, 11.2% Black or African American, 73.0% White, 0.3% Native Hawaiian or Other Pacific

Islander, and 0.3% American Indian or Alaska Native. Regarding ethnicity, 11.8% were Hispanic or Latino. The mean BMI was 29.4 kg/m^2.

Table 11. Demographic and Baseline Characteristics for the Primary Effectiveness Cohort

Characteristic	Evaluable Cohort (N=27010)[I,II]	CRC (N=72)[I,II]	APL (N=2567)[I,II]	ACN (N=2639)[I,II]	No ACN (N=24371)[I,II]
Age (Years)[III]					
n	27010	72	2567	2639	24371
Mean (SD)	58.1 (8.2)	59.9 (9.0)	58.8 (8.2)	58.8 (8.2)	58.0 (8.2)
Median	57.0	59.0	59.0	59.0	57.0
Min, Max[IV]	45.0, 86.0	46.0, 82.0	45.0, 84.0	45.0, 84.0	45.0, 86.0
Age Category (Years), n (%)					
[45 to 49]	2968 (11.0%)	7 (9.7%)	247 (9.6%)	254 (9.6%)	2714 (11.1%)
[50 to 54]	8899 (32.9%)	18 (25.0%)	769 (30.0%)	787 (29.8%)	8112 (33.3%)
[55 to 64]	8725 (32.3%)	24 (33.3%)	885 (34.5%)	909 (34.4%)	7816 (32.1%)
[65 to 74]	5604 (20.7%)	19 (26.4%)	587 (22.9%)	606 (23.0%)	4998 (20.5%)
[75 and greater]	814 (3.0%)	4 (5.6%)	79 (3.1%)	83 (3.1%)	731 (3.0%)
Sex, n (%)					
Male	11934 (44.2%)	37 (51.4%)	1413 (55.0%)	1450 (54.9%)	10484 (43.0%)
Female	15076 (55.8%)	35 (48.6%)	1154 (45.0%)	1189 (45.1%)	13887 (57.0%)
Ethnicity, n (%)					
Hispanic or Latino	3189 (11.8%)	9 (12.5%)	221 (8.6%)	230 (8.7%)	2959 (12.1%)
Not Hispanic or Latino	22421 (83.0%)	62 (86.1%)	2208 (86.0%)	2270 (86.0%)	20151 (82.7%)
Unknown	1400 (5.2%)	1 (1.4%)	138 (5.4%)	139 (5.3%)	1261 (5.2%)
Race, n (%)					
American Indian or Alaska Native	78 (0.3%)	0 (0.0%)	9 (0.4%)	9 (0.3%)	69 (0.3%)
Asian	2381 (8.8%)	14 (19.4%)	132 (5.1%)	146 (5.5%)	2235 (9.2%)
Black or African American	3038 (11.2%)	7 (9.7%)	251 (9.8%)	258 (9.8%)	2780 (11.4%)
Native Hawaiian or Other Pacific Islander	72 (0.3%)	0 (0.0%)	11 (0.4%)	11 (0.4%)	61 (0.3%)
White	19707 (73.0%)	48 (66.7%)	2023 (78.8%)	2071 (78.5%)	17636 (72.4%)
Other	543 (2.0%)	2 (2.8%)	34 (1.3%)	36 (1.4%)	507 (2.1%)
Unknown	1055 (3.9%)	1 (1.4%)	87 (3.4%)	88 (3.3%)	967 (4.0%)
More Than One Race	136 (0.5%)	0 (0.0%)	20 (0.8%)	20 (0.8%)	116 (0.5%)

Note:
[I] Percentage based on N in column heading.
[II] Columns are not mutually exclusive.
[III] Age was recorded based on year of birth; fractional age was not calculated.
[IV] Per eligibility, the study population included subjects aged 45 to 85, within one month of enrollment. Subjects outside this age range were confirmed by the respective sites to meet the age eligibility at time of enrollment.
ACN = advanced colorectal neoplasia; APL = advanced precancerous lesion; BMI = body mass index; CRC = colorectal cancer; SD = standard deviation

Characteristic	Evaluable Cohort (N=27010)[I,II]	CRC (N=72)[I,II]	APL (N=2567)[I,II]	ACN (N=2639)[I,II]	No ACN (N=24371)[I,II]
BMI (kg/m^2)					
n	26943	72	2561	2633	24310
Mean (SD)	29.4 (6.4)	30.6 (7.1)	30.6 (6.7)	30.6 (6.7)	29.2 (6.4)
Median	28.3	29.1	29.5	29.5	28.2
Min, Max	10.8, 78.6	18.7, 50.0	15.6, 75.5	15.6, 75.5	10.8, 78.6
Missing	67	0	6	6	61

Note:
[I] Percentage based on N in column heading.
[II] Columns are not mutually exclusive.
[III] Age was recorded based on year of birth; fractional age was not calculated.
[IV] Per eligibility, the study population included subjects aged 45 to 85, within one month of enrollment. Subjects outside this age range were confirmed by the respective sites to meet the age eligibility at time of enrollment.
ACN = advanced colorectal neoplasia; APL = advanced precancerous lesion; BMI = body mass index; CRC = colorectal cancer; SD = standard deviation

G. Safety and Effectiveness Results

1. Safety Results

Adverse effects that occurred in the PMA clinical study

There were no serious device-related adverse events (SAEs) observed among the 32,731 subjects enrolled for participation in the clinical validation cohort.

The SimpleScreen CRC test has the risk of a false test result (i.e. a false positive or false negative result). All positive test results should be followed by a colonoscopy. False positive SimpleScreen CRC test results could lead to an increased number of unnecessary colonoscopies and associated adverse events related to the colonoscopy procedure. A false negative SimpleScreen CRC test result could lead to colorectal cancer or precancerous lesions remaining undetected.

2. Effectiveness Results

Primary Effectiveness Evaluation

The primary clinical performance measures included sensitivity of the SimpleScreen CRC for the CRC and specificity for ACN. A secondary performance measure was sensitivity for APLs. Additional performance measures were positive predictive value (PPV) for CRC and APL, and negative predictive value (NPV) for ACN. SimpleScreen CRC clinical performance was evaluated for the 27,010 subjects meeting criteria for inclusion in the primary effectiveness clinical performance study population. The cross-tabulated results are summarized in **Table 12**.

The results are summarized in **Table 13** and **Table 14**. Sensitivity for CRC was 79.2%, specificity for ACN was 91.5%, NPV for ACN was 90.8% and PPV for ACN was 15.5%.

Table 12. Distribution of SimpleScreen CRC Result by Histopathological Category, n=27,010

SimpleScreen CRC Blood Test Result	Colonoscopy/Histopathology Lesion Category Grouping			Total
	CRC (Category 1)	APL (Category 2)	Non-ACN - NAPL or NEG (Category 3-5 and 6)	
Positive	57	321	2065	2443
Negative	15	2246	22306	24567
Total	72	2567	24371	27010

APL = advanced precancerous lesion; CRC = colorectal cancer; non-ACN = non advanced colorectal neoplasia; NAPL = non-advanced precancerous lesion; NEG = negative

Table 13. below presents measures of clinical performance of sensitivity and specificity along with two-sided 95%CIs using the Wilson score method.

Table 13: Measures of Clinical Performance: Sensitivity and Specificity

Primary Endpoint	Estimate (%), (n/N), 95% CI
CRC Sensitivity	79.2%, (57/72) 68.4%-86.9%
ACN Specificity	91.5%, (22306/24371) 91.2%-91.9%
CRC Specificity	91.1% (24552/26938) 90.8% - 91.5%371)

ACN = advanced colorectal neoplasia; CI = confidence interval; CRC = colorectal cancer

Table 14. Secondary Objective

Secondary Endpoint	Estimate (%) (n/N), 2-sided 95% CI[1]
APL Sensitivity	12.5%, 11.3%-13.8% (321/2567)

APL = advanced precancerous lesion; CI = confidence interval

Predictive Values for patients with SimpleScreen CRC test positive and negative results along with two-sided 95%CIs are presented in **Table 15**.

- The positive predictive value (PPV) for CRC is a fraction of patients with CRC among the patients with positive SimpleScreen CRC test results.
- The PPV for APL is a fraction of patients with APL among the patients with positive SimpleScreen CRC test results.
- A negative predictive value (NPV) for CRC is a fraction of patients without CRC among the patients with negative SimpleScreen CRC test results and 1-NPV is a fraction of patients with CRC among the patients with negative SimpleScreen CRC test results.
- A negative predictive value for ACN is a fraction of patients without ACN (CRC or APL) among the patients with negative SimpleScreen CRC results.

Table 15. Measures of Clinical Performance: Positive and Negative Predictive Values

	CRC	APL	Non-ACN (NAPL or Negative)
Among Patients with Positive SimpleScreen CRC test results (N = 2443)	PPV for CRC 2.3% (57/2443)	PPV for APL 13.1% (321/2443)	84.5% (2065/2443)
Among Patients with Negative SimpleScreen CRC Test results (N = 24567)	1-NPV for CRC 0.06% (15/24567) NPV for CRC 99.94% (24552/24567)	9.1% (2246/24567)	NPV for ACN 90.8% (22306/24567)

	CRC	APL	Non-ACN (NAPL or Negative)
Among All Patients in the Clinical Performance Study (N = 27010) (Prevalence)	0.27% (72/27010)	9.5% (567/27010)	90.2% (24371/27010)

In the clinical performance study,

- PPV for CRC was 2.3% (57/2443) with 95%CI: (2.0%-2.6%) and NPV for CRC was 99.94% (24552/24567) with 95%CI: (99.91%-99.96%) [1-NPV= 0.06% (15/24567) with 95%CI: (0.04%-0.09%)]. Prevalence of CRC in the pivotal clinical performance study was 0.27%.
- Among SimpleScreen CRC test positive patients, there were 13.1% (321/2443) patients with APL (PPV for APL=13.1%). Prevalence of APL in the clinical study was 9.5%.
- Among SimpleScreen CRC test negative patients, there were 90.8% (22306/24567) patients with non-ACN (NAPL or Negative).

Performance of SimpleScreen CRC Test Stratified by Age Groups

Compared to the U.S. 2020 census age and sex distribution, the evaluable dataset included a higher proportion of participants aged 50 to 54 years, a lower proportion of those aged 75 years and greater, and a higher proportion of females (**Table 16**).

Table 16. Age and Sex Distribution

Sex	Age Group	U.S. Estimate[1]	Evaluable Cohort (27,010)
Male	45 to 49	7.67%	4.74%
	50 to 54	7.78%	14.12%
	55 to 64	15.83%	14.53%
	65 to 74	11.44%	9.39%
	75 and older	5.50%	1.41%

1: U.S. census age and sex data were referenced from published data tables[3]

Sex	Age Group	U.S. Estimate[1]	Evaluable Cohort (27,010)
Female	45 to 49	7.66%	6.25%
	50 to 54	7.81%	18.83%
	55 to 64	16.50%	17.77%
	65 to 74	12.81%	11.36%
	75 and older	7.01%	1.60%

1: U.S. census age and sex data were referenced from published data tables[3]

Age-Adjusted Performance Measures

After the primary effectiveness endpoints were evaluated based on observed results, they were also evaluated by adjusting the results to reflect the U.S. census age and sex distribution (Census-adjusted). To evaluate the population-level accuracy and representativeness of observed test performance, a pre-specified analysis was conducted to adjust clinical performance to the age and sex distribution of the U.S. census population. U.S. census-adjusted sensitivity for CRC was 81.1%, specificity for ACN was 90.4%, NPV for ACN was 90.5%, and PPV for ACN was 15.5% (**Table 17).** The positive predicative value and negative predicative value by age is shown in **Table 18**.

Table 17. U.S. Census Adjusted Primary and Secondary Effectiveness Endpoints

Primary Endpoint	U.S. Census adjusted[1] %, 2-sided 95% CI[2,3], (n/N)
CRC Sensitivity	81.1%, 71.3%-88.1% (66.43/81.91)
ACN Specificity	90.4%, 90.0%-90.7% (21938.03/24280.65)
Secondary Endpoint	
APL Sensitivity	13.7%, 12.4%-15.0% (362.03/2647.44)

1: U.S. 2020 Census age and sex data were referenced from published data tables3
2: 2-sided 95% CIs for sensitivity and specificity were calculated using the Wilson score method
3: 2-sided 95% CIs for PPV and NPV were calculated based on 2-sided 95% score-based CIs for likelihood ratios (Nam 1995) with constant prevalence

Table 18. CRC and APL PPV and NPV by Age

Age	Prevalence of CRC (%)	Prevalence of APL (%)	Percent Positive SimpleScreen Results	CRC PPV (%)	CRC NPV (%)	APL PPV (%)	ACN NPV (%)
45-49	0.24	8.32	5.86	4.02	100.00	14.37	92.05
50-59	0.26	9.06	7.27	2.62	99.93	12.29	91.12
60-69	0.23	10.25	10.45	1.67	99.94	13.08	90.02
70-79	0.45	10.33	15.30	2.46	99.91	14.99	90.42
80-84	0.74	8.09	19.85	3.70	100.00	7.41	91.74
Age Adjusted	0.30	9.48	10.03	2.51	99.94	13.02	90.85

CRC = colorectal cancer; APL = advanced precancerous lesion; NPV = negative predictive value; PPV = positive predictive value

Subgroup Analysis

The SimpleScreen CRC test performance measures in the primary analysis data set were also evaluated in pre-specified subgroups, including baseline demographic characteristics, cancer stage, lesion characteristics, and histopathological subgroups.

Performance of SimpleScreen CRC test for CRC, APL, and non-advanced precancerous lesions stratified by stage and histopathological subcategories is presented in **Table 19** and lesion characteristics in **Table 20.** Results indicate a trend toward higher sensitivity with greater lesion size and severity:

- SimpleScreen CRC has lower performance of Stage I CRC [57.1% (16/28); 95% CI (39.1% - 73.5%)] than CRC Stages II – IV.
- SimpleScreen CRC has a lower performance of Stage III CRC [82.4%, (14/17); 95% CI: (59.0% - 93.8%) than CRC Stage II and IV.

Table 19. Sensitivity and Specificity of SimpleScreen CRC: Cancer Stage and Histopathological Subgroups

Colonoscopy/Histopathology	Sensitivity (2-sided 95% CI) (n/N)
Colorectal cancer	**79.2% (57/72) (68.4%-86.9%)**
Stage I	57.1% (16/28) (39.1%-73.5%)
Stage II	100.0% (15/15) (79.6%-100.0%)
Stage III	82.4% (59.0%-93.8%) (14/17)
Stage IV	100.0% (74.1%-100.0%) (11/11)
Stage unknown	100.0% (20.7%-100.0%) (1/1)
Advanced precancerous lesions	**12.5% (11.3%-13.8%) (321/2567)**
Adenoma with carcinoma in situ or high-grade dysplasia, any size (collectively HGD)	29.1% (21.4%-38.2%) (32/110)
Adenoma, villous growth pattern (≥25%), any size	15.2% (12.5%-18.4%) (86/564)
Adenoma ≥1.0 cm in size	11.5% (10.0%-13.2%) (169/1470)
Sessile serrated lesion with or without cytological dysplasia ≥1.0 cm	7.6% (5.4%-10.7%) (30/394)
Traditional serrated adenoma, any size	13.8% (5.5%-30.6%) (4/29)

Colonoscopy/Histopathology	Specificity (2-sided 95% CI) (n/N)
CRC specificity categories (category 2-6)	**91.1% (90.8%-91.5%) (24552/26938)**
ACN specificity categories (category 3-6)	**91.5% (91.2%-91.9%) (22306/24371)**
Non-advanced precancerous lesions (category 3-5)	**91.6% (91.0%-92.1%) (8184/8936)**
≥5 adenomas, all <1.0 cm in size, non-advanced (category 3)	90.8% (86.0%-94.1%) (178/196)
3 to 4 adenomas, all <1.0 cm in size, non-advanced (category 4)	91.5% (89.3%-93.2%) (696/761)
1 to 2 adenomas, all <1.0 cm in size, non-advanced or HP ≥1.0 cm (category 5)	91.6% (91.0%-92.2%) (7310/7979)
Negative (category 6)*	**91.5% (91.0%-91.9%) (14122/15435)**
No findings (category 6.2)*	**91.5% (91.0%-91.9%) (11383/12446)**

*Refer to **Table 10**
ACN = advanced colorectal neoplasia; CRC = colorectal cancer

Table 20. Sensitivity and Specificity of SimpleScreen CRC Test: Lesion Characteristics

Characteristic	CRC Sensitivity		APL Sensitivity		ACN Specificity	
	Sensitivity %, (n/N)	%Total (N/72)	Sensitivity %, (n/N)	%Total (N/2,567)	Specificity %, (n/N)	%Total (N/24,371)
Index lesion size (mm)						
≤5	20.0% (1/5)	6.9%	13.4% (9/67)	2.6%	91.5% (7584/8286)	34.0%
6-9	33.3% (1/3)	4.2%	12.1% (17/140)	5.5%	91.7% (3118/3399)	13.9%
10-19	50.0% (5/10)	13.9%	11.3% (230/2031)	79.1%	92.3% (203/220)	0.9%
20-29	90.9% (10/11)	15.3%	16.5% (37/224)	8.7%	88.2% (15/17)	0.1%
≥30	92.7% (38/41)	56.9%	25.0% (25/100)	3.9%	100.0% (3/3)	0.0%
No index lesion or no index lesion size recorded	100.0% (2/2)	2.8%	60.0 (3/5)	0.2%	91.5% (11383/12446)	51.1%
Index lesion location						
Proximal	100.0% (11/11)	15.3%	13.1% (190/1451)	56.5%	91.4% (5664/6196)	25.4%
Distal	66.7% (22/33)	45.8%	10.6% (85/804)	31.3%	92.1% (3634/3946)	16.2%
Rectum	85.7% (24/28)	38.9%	14.8% (46/311)	12.1%	91.1% (1619/1777)	7.3%
No index lesion or no index lesion location recorded	n/a (0/0)	0.0%	0.0% (0/1)	0.0%	91.5% (11389/12452)	51.1%

ACN = advanced colorectal neoplasia; APL = advanced precancerous lesion; CRC = colorectal cancer

The results from the subgroup analysis based on the demographic and baseline characteristics are shown in **Table 21**. SimpleScreen CRC performance was similar among the subgroups except for two trends. A lower CRC sensitivity in adults 50-54 (66.7%, 12/18; 95% CI: (43.7%-83.7%)) was observed; and APL sensitivity increased with age. Lower specificity ACN specificity was observed with increased age.

Table 21. Sensitivity and Specificity of SimpleScreen CRC: Demographic Characteristics

Characteristic	CRC Sensitivity %, (n/N)	APL Sensitivity %, (n/N)	ACN Specificity %, (n/N)
Sex			
Female	80.0% (28/35)	12.1% (140/1154)	92.1% (12789/13887)
Male	78.4%, (29/37)	12.8% (181/1413)	90.8% (9517/10484)
Age (years)			
45-49	100.0% (7/7)	10.1% (25/247)	94.8% (2572/2714)
50-54	66.7% (12/18)	8.6% (66/769)	93.5% (7588/8112)
55-64	83.3% (20/24)	12.7% (112/885)	91.5% (7149/7816)
65-74	78.9% (15/19)	17.7% (104/587)	87.8% (4389/4998)
≥75	75.0% (3/4)	17.7% (14/79)	83.2% (608/731)
Race			
American Indian or Alaska Native	n/a (0/0)	11.1% (1/9)	87.0% (60/69)
Asian	78.6% (11/14)	8.3% (11/132)	88.4% (1975/2235)
Black or African American	85.7% (6/7)	13.1% (33/251)	92.8% (2581/2780)
Native Hawaiian or Other Pacific Islander	n/a (0/0)	9.1% (1/11)	93.4% (57/61)
White	77.1% (37/48)	12.9% (260/2023)	91.7% (16175/17636)
More than one race	n/a (0/0)	0.0% (0/20)	87.9% (102/116)
Other/Unknown	100.0% (3/3)	12.4% (15/121)	92.0% (1356/1474)

ACN = advanced colorectal neoplasia; APL = advanced precancerous lesion; CRC = colorectal cancer

Characteristic	CRC Sensitivity %, (n/N)	APL Sensitivity %, (n/N)	ACN Specificity %, (n/N)
Ethnicity			
Hispanic or Latino	77.8% (7/9)	10.4% (23/221)	90.3% (2672/2959)
Non-Hispanic or Latino	80.6% (50/62)	12.4% (274/2208)	91.6% (18467/20151)
Unknown	0.0% (0/1)	17.4% (24/138)	92.5% (1167/1261)

ACN = advanced colorectal neoplasia; APL = advanced precancerous lesion; CRC = colorectal cancer

XII. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 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 pivotal clinical study included 265 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.

XIII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not Applicable

XIV. 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 Molecular and Clinical Genetics Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The pivotal clinical study established SimpleScreen CRC sensitivity for CRC of 79.2% (95% CI: 68.4% - 86.9%), specificity for ACN of 91.5% (95% CI: 91.2% - 91.9%), a NPV for ACN of 90.8% (95% CI: 90.7% - 90.9%), and a PPV for ACN of 15.5% (14.2% - 16.8%).

SimpleScreen CRC sensitivity for CRC was evaluated across age groups, racial/ethnic groups, and in both men and women. The observed performance correlates with subject age, CRC stage, and lesion size, reflecting the known underlying biology of colorectal neoplasia.

In conclusion, the pivotal study demonstrated that SimpleScreen CRC met the study's primary performance point estimate measures for sensitivity and specificity of the study. However, because of the limited detection for Stage I CRC and advanced adenomas (AA), Freenome will include a precaution in the SimpleScreen CRC's labeling and advertising and perform a post-approval study to gather additional information about the benefits and risks of programmatic colorectal cancer screening (i.e., repeated testing over an established period of time).

B. Safety Conclusions

SimpleScreen CRC is a non-invasive blood based in vitro diagnostic (IVD) test, and therefore risks associated with the collection of a blood sample necessary for the SimpleScreen CRC test are minimal. The risks of the device are based on data collected in the clinical study conducted to support PMA approval as described above.

Among 31,888 subjects who had blood drawn or blood collection attempted, 83 subjects reported one or more adverse events, for a total of 102 adverse events. Of those 102 adverse events, there were 46 (0.1%) reports of dizziness/fainting and 26 (0.1%) reports of bruising. These adverse events were related to phlebotomy. No device-related serious adverse events were observed among the 32,731 subjects in the clinical validation cohort.

The SimpleScreen CRC test, as with any IVD, the potential risks are associated with an incorrect test result or incorrect interpretation of results. The primary risk associated with the SimpleScreen CRC is a false positive or false negative result. Since all positive results should lead to a follow-up colonoscopy, a false positive SimpleScreen CRC test result may lead to patients being referred to an unnecessary follow-up colonoscopy. Adverse events commonly associated with colonoscopy include abdominal discomfort, dehydration, nausea, and bowel irregularity. Rare adverse events associated with colonoscopy include bleeding, intestinal perforation, and adverse reaction to the sedation resulting in respiratory arrest, cardiac arrest, arrhythmia, myocardial infarction, angina, shock, stroke, or death.

A false negative SimpleScreen CRC test result introduces the possibility that a case of CRC or advanced adenoma (AA) could go undetected, which could lead individuals with CRC or AA to forgo other recommended screening procedures such as colonoscopy.

Based on the clinical validation data for SimpleScreen CRC, there is a chance that as many as 20.8% of patients with CRC, especially stage I CRC (42.9%), and as many as 87.5% of patients with APLs may be missed by this test, given the current data available. It is recommended patients with negative results continue participating in screening programs.

C. Benefit-Risk Determination

Colorectal cancer (CRC) occurs in approximately 150,000 patients in the United States annually, and is associated with about 50,000 deaths annually, despite uptake of CRC screening via colonoscopy, and non-invasive stool-based tests. Even with the broadly recognized benefit of CRC screening and the availability of a variety of guideline-recommended screening options (including colonoscopy, non-invasive stool testing and blood-based testing), it is estimated that only an estimated 67% of eligible individuals are up to date with the guideline-recommended CRC screening. The Freenome SimpleScreen CRC test offers another blood-based alternative to acceptable screening methodologies, and has probable benefit to the public health, in particular for individuals who are noncompliant with current screening methodologies, and who are more willing to take a blood-based CRC screening test, than other modalities.

The probable benefits of SimpleScreen CRC are based on the PREEMPT CRC study, which was a prospective, blinded, multicenter, cross-sectional study designed to evaluate the clinical accuracy of the SimpleScreen CRC test. The pivotal clinical performance study included 31,594 eligible subjects (subjects who met inclusion and exclusion criteria). A total of 27,010 subjects who had confirmed clinical findings (evaluable colonoscopy) and valid SimpleScreen CRC blood test results comprised the evaluable dataset, with 72 CRC, 2,567 APLs, 8,936 NAPLs and 15,435NEGs. The evaluable cohort consisted of 27,010 asymptomatic, average-risk subjects aged 45 to 85. The study established probable benefits for CRC detection. The sensitivity of SimpleScreen CRC for CRC was 79.2% (57/72, 2-sided 95% CI 68.4-86.9%) and for APLs was 12.5% (321/2,567, 2-sided 95% CI 11.3-13.8%). For subjects without a diagnosis of CRC or APLs, the specificity of SimpleScreen CRC was 91.5% (22,306/24,371, 2-sided 95% CI 91.2-91.9%). The predictive values of the test are a direct function of specificity, sensitivity, and the disease prevalence observed in the PREEMPT CRC evaluable cohort. After a positive SimpleScreen CRC test, the chance of an advanced colorectal neoplasm (ACN: CRC or APL), or positive predictive value (PPV) for ACN was 15.5% (378/2,443, 2-sided 95% CI 14.2-16.8%). After a positive SimpleScreen CRC test positive result, the chance of CRC (PPV for CRC) was 2.3% (57/2,443, 2-sided 95% CI 2.1-2.6%) and the chance of APLs (PPV for APLs) was 13.1% (321/2,443, 2-sided 95% CI 11.9-14.4%). The chance of a subject with a negative SimpleScreen CRC test result, not having ACN (NPV for ACN) was 90.8% (2-sided 95% CI 90.4-90.7%). Finally, the chance of an individual with negative SimpleScreen CRC test, not having CRC after a result (1-NPV for CRC) was 0.061% (2-sided 95% CI 0.04%-0.10%).

The probable benefits of SimpleScreen CRC can also be described by the performance in subgroups. The sensitivity for Stage I, II, III, IV and unstaged CRC were 57.1% (16/28, 39.1-73.5%), 100.0% (15/15, 79.6%-73.5%), 82.4% (14/17, 59.0-93.8%), 100.0% (11/11, 74.1-100.0%), and 100.0% (1/1, 20.7-100.0%), respectively. The performance for Stage III CRC, missing 3/17 cases, raises some concerns; however, the performance of Stage III CRC was included in the labeling, including the Patient Information Sheet and the Physician Brochure, to help inform the Shared Decision Making between the physician and patient, regarding the decision to use this test.

The probable risks associated with the use of this device are mainly due to: 1) device performance, and 2) diversion from colonoscopy. In terms of device performance, there are key risks related to 1) false positive, 2) false negatives, or 3) a failure to provide a result. There is minimal probable risk with the phlebotomy for the use of this device. When used for screening, a positive result should be followed by colonoscopy for diagnosis. A false positive result could result in an additional invasive screening procedure, such as colonoscopy, and thus unnecessarily expose patients to the attendant risks associated with such a procedure. Rare, serious adverse events associated with colonoscopy include bleeding, intestinal perforation, and adverse reaction to sedation. A false negative result with SimpleScreen CRC could potentially delay colonoscopy and delay diagnosis of CRC or AA, which represents the more salient concern with this device. The consequences of false negatives could be quite serious, such as progression of disease, such as CRC to a more advanced, and less treatable stage. The sponsor has a post-approval study planned, to demonstrate the probable benefit of programmatic follow-up with this test. Another probable risk of this test is diversion to the SimpleScreen CRC test, in lieu of a screening colonoscopy, which more thoroughly detects CRC and AA, while at the same time intercepting disease progression by removing lesions, or tagging lesions for surgical removal.

To partially mitigate this risk, the SimpleScreen CRC Provider Brochure section on "Patient Education Through Shared Decision-Making" and Patient Labeling says:

- *Colonoscopy should be discussed with all patients, given the test's ability to detect and potentially remove colorectal lesions.*

- *As part of this shared decision-making process, it is important to communicate to patients that a negative SimpleScreen CRC test result does not preclude a CRC or APL diagnosis and that they should continue participating in CRC screening programs. Patients with a positive result should have a diagnostic follow-up colonoscopy.*

To further mitigate this risk, patient labeling has been developed, including pictograms of the performance of this test for CRC and APL detection to inform the physician patient encounter. A prominent precaution has been placed in the labeling:

- *Based on data from clinical studies, SimpleScreen CRC has limited detection (57%) of Stage I colorectal cancer (64% when U.S. 2020 Census age-sex adjusted) and does not detect 87% of advanced precancerous lesions (86% when U.S. 2020 Census age-sex adjusted). One out of 10 patients with a negative SimpleScreen CRC result may have a precancer that would have been detected by a screening colonoscopy.*

To summarize, the key probable risks of this device are the risks associated with device performance (namely sensitivity for Stage I CRC and APLs), and risks of diversion from colonoscopy. This device also missed 3/17 Stage III CRCs; this also contributes to the risks of the device – this performance should be clearly discussed in the shared decision-making process. Also, of note, there are other available modes of screening with better performance than SimpleScreen CRC in detecting APLs. With adequate

physician labeling, a pictogram of device performance for patient-physician shared decision making (in patient labeling) and prominently placed precautions, the probable risks discussed above are partially mitigated.

Additional factors to be considered in determining probable risk and benefits for the SimpleScreen CRC include data from rigorous analytical studies, which demonstrated acceptable analytical performance of this test. Post approval studies are also planned, to validate a testing interval, which may be important to help mitigate the risks of false negative results. It is important to re-emphasize that the limitations of this device clearly says that "A negative SimpleScreen CRC test result does not guarantee absence of CRC or advanced adenoma. Patients with a negative result should continue participating in CRC screening programs, at the appropriate guideline-recommended intervals." There is a similar line in the physician brochure in the section on shared decision making, that says "A negative SimpleScreen CRC test does not preclude a CRC or APL diagnosis, and patients should continue participating in CRC screening programs." The risks of a false negative results for CRC or APLs are partially mitigated by this labeling, which is intended to inform the shared decision-making process between the physicians and patients, and mitigates clinical risk, by instructing patients with negative results to continue at the appropriate longitudinally, at the guideline recommended intervals with CRC screening.

However, given that this is a blood-based test and the barriers of getting this test in a timely manner may be less than for other invasive tests, this test may have the advantage of greater uptake, which contributes to the probable benefit of this device, given the current scenario where one third of screen eligible individuals, remain unscreened for CRC.

Patient Perspective:

This submission either did not include specific information on patient perspectives, or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above and risk mitigation strategies, the data support that for the qualitative detection of CRC, the probable benefits of SimpleScreen CRC outweigh the probable risks in patients of either sex, 45 years or older, who are at average risk of the disease.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from the PREEMPT CRC study support the effectiveness of the Simple CRC to screen for the presence of CRC in adults of either sex, 45 years or older, who are at average risk for CRC.

XVI. CDRH DECISION

CDRH issued an approval order on July 24, 2026. . The final clinical conditions of approval cited in the approval order are described below.

1. The following Precaution must be prominently displayed in SimpleScreen CRC's labeling and advertising, per 21 CFR 814.82(a)(3):

   "Precaution: Based on data from clinical studies, SimpleScreen CRC has limited detection (57%) of Stage I colorectal cancer (64% when U.S. 2020 Census age-sex adjusted) and does not detect 87% of precancerous lesions (86% when U.S. 2020 Census age-sex adjusted). One out of 10 patients with a negative SimpleScreen CRC result may have a precancer that would have been detected by a screening colonoscopy."

2. Freenome. LLC must conduct a post-approval study (PAS) listed below and provide the data in PAS reports.

   The SimpleScreen CRC Post-Approval Study (PAS) is a prospective, longitudinal study supplemented with Real World Evidence (RWE) to evaluate the longitudinal performance of SimpleScreen CRC in an average risk population. If approved, the conditions of approval that will appear in the approval letter include the study requirements meeting the criteria below:

   Study Objective: The study objective is to collect longitudinal data on subjects prescribed the SimpleScreen CRC assay over the course of 3 years.

   Study Design: Subjects will be enrolled at T0 and required to complete the SimpleScreen CRC test at baseline (T0) and at year 3 (T3). Year 3 is defined as 33 months to 42 months post baseline. Subjects with a positive SimpleScreen CRC test result at T0 will undergo diagnostic colonoscopy per the standard of care and then will be discontinued from the study. Subjects with negative SimpleScreen CRC test results at T0 will remain in the study. Subjects will be offered repeat SimpleScreen CRC testing at T3 and also be expected to undergo a colonoscopy at T3. Subjects will be followed at T1 and T2 to evaluate for changes in medical history.

   Sample size: This study will enroll a sufficient number of subjects at average risk of developing colorectal cancer, between the ages of 45 and 81, to ensure at least 1,000 evaluable subjects with valid SimpleScreen CRC test results and colonoscopy results at T3 and CRC cases can be observed at T3.

Study Length: The study length will be 5 years including 3 years of longitudinal subject follow-up.

- The first subject will be enrolled within 6 months of the study protocol approval date.
- 20% of subjects enrolled within 12 months of the study protocol approval date.
- 50% of subjects enrolled within 18 months of the study protocol approval date.
- 100% of subjects enrolled within 24 months of the study protocol approval date.

Study Endpoints:

The post-approval study will include the following co-primary performance measures:

- Sensitivity for CRC, sensitivity for APL, and specificity for ACN at T3.
- Positive predictive value (PPV) and negative predictive value (NPV) for CRC, APL, and ACN at T3.

The post-approval study will include the following exploratory performance measures:

- The cumulative risk of false positive result (cFPR) and cumulative risk of a true positive result (cTPR).
- The probability that a negative SimpleScreen CRC result at baseline (T0) remains negative through 3 years.
- The probability that a negative SimpleScreen CRC result at baseline (T0) results in no CRC/AA through 3 years.
- The distribution of colorectal epithelial lesions (by Category) among positive SimpleScreen CRC subjects at T0 and at T3.
- Adherence to repeat SimpleScreen CRC at T3.
- Cumulative compliance to colonoscopy following a positive SimpleScreen CRC result.
- Cross-over to alternative screening methodologies (e.g., FOBT, colonoscopy, other) at T1 & T2.
- The rate of no SimpleScreen CRC result (e.g., invalid result).
- Supplemental real world evidence study to evaluate PPV at T0 and T3

Interim reporting: FDA tracks and evaluates the conduct of a PAS through review of study reports submitted to the Agency. Freenome Holding, Inc. must fulfill reporting requirements including Enrollment Status Reports, PAS Progress Reports which must be submitted every six months until subject enrollment has been completed, and annually thereafter, as well as a Final Report. Freenome Holding, Inc. must follow the reporting schedule, as required by the PMA approval order, until submitting the Final PAS Report.

From the date of study protocol approval, you must meet the following timelines:

- First subject enrolled within 6 months
- 20% of subjects enrolled within 12 months
- 50% of subjects enrolled within 18 months.

- 100% of subjects enrolled within 24 months

In addition, you must submit separate periodic reports on the progress of the PAS as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed, and annually thereafter, from the date of the PMA approval letter, unless otherwise specified by FDA.
- If any enrollment milestones are not met, you must begin submitting quarterly enrollment status reports every 3 months in addition to your periodic (6-month) PAS Progress Reports, until FDA notifies you otherwise.
- Submit the Final PAS Report three (3) months from study completion (i.e., last subject's last follow-up date).

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), which was in effect at the time of the inspection. As of February 2, 2026, the revised part 820, referred to as the Quality Management System Regulation (QMSR), is effective.

XVII. 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

XVIII. REFERENCES

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