2018-10 Statistical Analysis Plan V.2

An Evaluation of a Multi-Target Stool DNA (mt-sDNA) Test, Cologuard, for CRC Screening in Individuals Aged 45-49 and at Average Risk for Development of Colorectal Cancer: Act Now

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AN EVALUATION OF A MULTI-TARGET STOOL DNA (mt-sDNA) TEST, COLOGUARD, FOR CRC SCREENING IN INDIVIDUALS AGED 45-49 AND AT AVERAGE RISK FOR DEVELOPMENT OF COLORECTAL CANCER: ACT NOW

Statistical Analysis Plan

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1.0	19Nov2018	Initial Version	[redacted]
2.0	05Jul2019	V 2.0 – Clarification of ITS and PP populations	[redacted]

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1 OVERVIEW

This analysis plan describes the planned data analyses.

2 STATISTICAL AND ANALYTICAL PLANS

2.1 Study Parameters

- This prospective, cross-sectional, multi-center study will enroll subjects 45-49 years of age at average risk for development of colorectal cancer.
- Cologuard is intended for the qualitative detection of colorectal neoplasia-associated DNA markers and for the presence of occult hemoglobin in human stool.
- A positive Cologuard result may indicate the presence of colorectal cancer or advanced adenoma (AA) and should be followed by diagnostic colonoscopy; Cologuard is intended for adults of either sex, 50 years or older, who are typical average-risk candidates for colorectal cancer (CRC) screening.
- Subjects will be required to complete the mt-sDNA (Cologuard) test followed by a screening colonoscopy.
- Exact Sciences Laboratory will perform the Cologuard test.
- Cologuard results will be recorded as 'positive', 'negative', 'no result obtained' or 'sample could not be processed' for each individual corresponding to a specific stool sample.
- A valid mt-sDNA (Cologuard) test is defined as a result that is recorded as either 'positive' or 'negative.'
- A usable mt-sDNA (Cologuard) test is defined as a result that is recorded as either 'positive' or 'negative' (i.e. valid) and is received within 72 hours of sample collection.
- A colonoscopy must follow a Cologuard test.
- In the event of an additional colonoscopy due to inadequate preparation, the colonoscopy with the most significant findings will be considered the study colonoscopy and will be used as the reference test result in the analysis.
- A reportable colonoscopy is defined as one where the procedure was attempted, and a procedure report is available.
- A complete colonoscopy procedure will be considered and defined as: reaching the cecum (or) reaching the junction between the small and large intestine (in the event the cecum has been resected) or a colonoscopy wherein a CRC or AA was identified regardless of any limiting factors experienced during the colonoscopy.
- A subject is considered to be Per Protocol following a usable mt-sDNA (Cologuard) test and complete colonoscopy
- Subjects who have a colonoscopy following a Cologuard sample collection will be considered completed subjects and the date of completion will be the date that the last colonoscopy was performed.
- Colonoscopy findings with pathology samples submitted for histopathology are interpreted by independent central pathologist(s) who will be responsible for determining the lesion histopathology.
- [redacted]

2.2 General Considerations Impacting the Data Analysis

- This Statistical Analysis Plan (SAP) is based on Clinical Trial Protocol 2018-10 Version 2.0 dated October 16, 2018.

- All calculations will be performed using Statistical Analysis Software (SAS 9.2 and JMP Version 12 or higher both from SAS Institute, Cary, NC).
- The enrollment target is 731non-advanced neoplasia and negative evaluable subjects with the maximum enrollment to be set at approximately 942 subjects to account for subject discontinuation.
- This study will be performed at approximately 35 clinical sites to be pooled for analysis; no individual sites will be analyzed separately.
- Analyses will be conducted at the subject level with the most clinically significant lesion category used for analyses when multiple lesions are found during colonoscopy.
- Final analyses will be conducted after the last subject completes their colonoscopy or discontinues the study.
- Effectiveness analyses include a primary endpoint and all other defined exploratory endpoints for Intent-to-Screen (ITS) population.
- One-sided p=0.025 or two-sided p=0.05 will be required to achieve statistical significance; no p-value adjustment will be made for testing multiple effectiveness endpoints.
- This analysis may be used to support use of Cologuard tests in subjects 45-49 years of age.
- There is 1 primary endpoint
- There are additional exploratory endpoints of interest (see Section 2.8.1).
- The effect of early withdrawals will be assessed using sensitivity analyses for just the primary effectiveness endpoint.
- All effectiveness analyses will be performed using the ITS Population with confirmation in a Per Protocol (PP) Population.

2.3 Study Objective

The study objective is to confirm the specificity of the multi-target stool DNA (mt-sDNA), Cologuard, test in an average risk population, ages 45-49.

2.4 Lesion Classification

A colonoscopy that was limited in any way but wherein a colorectal cancer or advanced adenoma was identified or wherein a partially obstructing colorectal cancer or advanced adenoma was identified will be included in the analyses. Colonoscopic findings will be recorded on the colonoscopy reports per site-specific standard of practice. Histopathology interpretation of tissue samples will be conducted according to standard practice of each clinical site. [redacted].

Lesion classification is based on the most significant lesion. The location within the colorectum (site) and size (mm) is recorded for all index lesions. TNM stage and overall CRC Stage (I-IV) will be recorded for all CRCs. If a subject has CRC(s), the subject will be classified as category (1.0) regardless of the presence of any other adenomas or hyperplastic polyps. In the presence of multiple (synchronous) CRCs, a subject will be classified by the most advanced CRC stage.

Similarly, in the absence of CRC, a subject with AA will be categorized as category (2.0) regardless of the presence of any other adenomas or hyperplastic polyps. With category (2.0), subjects will be categorized by the most clinically significant AA subcategory. For this study, the hierarchy of clinical significance in descending order of significance is Subcategory 2.1 (highest clinical significance), then Subcategory 2.2, then Subcategory 2.3, and then Subcategory 2.4 (lowest clinical significance). In summary, subjects will

be placed in the lowest applicable Subcategory for this study, based on the most clinically significant lesion confirmed on histopathologic analysis. The presence of multiple advanced adenomas will not change the classification of a subject as category 2.0. The most clinically significant lesion is hereafter referred to as the index lesion and is the lesion upon which the subject categorization will be made.

Subjects with pathologically confirmed non-advanced adenoma(s) but without CRC (1.0) or advanced adenoma (2.0), subjects will be classified by the reviewing pathologists into category 3.0, 4.0, or 5.0 based on the size and number of lesions. The largest of the non-advanced adenomas will be the index lesion for the case. In the scenario a subject has both small (<10 mm) non-advanced adenomas and hyperplastic polyps < 10mm, the subject will be classified based on the non-advanced adenoma(s) only and will be classified into category 3.0, 4.0, or 5.0.

All subjects who do not have CRC (1.0), advanced adenoma (2.0), small or non-advanced adenomas (3.0, 4.0, or 5.0) will be classified as negative (6.0). Category (6.0) includes subjects with any number of hyperplastic polyps <10mm and subjects with no index lesion. or tissue removed for analysis during colonoscopy.

Sites will submit the colonoscopy reports for all subjects. Subjects who have lesions identified on colonoscopy that are neither biopsied initially nor excided subsequently or that are lost during lesion retrieval and, therefore, not submitted for histopathological analysis, will not be included in the ITS or PP data analysis because they cannot be categorized for the study analysis.

Below is the listing of categories that the central pathologist will use when assessing and determining final categorization. Final categorization will be based on the most significant index lesion. The order of significance is presented below.

1.0: Adenocarcinoma of colorectum, Stage I-IV (Colorectal Cancer, CRC)

2.0 Advanced Adenoma (AA)

- 2.1: Adenoma with HGD/CIS, any size
- 2.2: Adenoma with villous growth pattern (≥25%), any size
- 2.3: Adenoma, ≥10 mm in size
- 2.4: Serrated lesion, ≥10 mm (SSA/SSP/HP)

3.0: Adenoma, non-advanced, >5, <10 mm in size, 1 or 2 adenomas

4.0: Adenomas, non-advanced, ≥3 adenomas, < 10 mm in size

5.0: Adenoma, non-advanced, ≤ 5 mm in size, 1 or 2 adenomas

6.0: Negative: No colorectal adenocarcinoma: no adenomas or SSA/SSP; no HP ≥10 mm

- 6.1 Negative, no colorectal neoplasia upon histopathological review
- 6.2 No findings on colonoscopy, no biopsy(s) taken

2.5 mt-sDNA test (Cologuard)

Exact Sciences Laboratories (ESL) will receive and process all stool samples. Assay results will be recorded as ‘Positive’, ‘Negative’, ‘Sample Could Not Be Processed’, or ‘No Result Obtained’. The mt-sDNA (Cologuard) test result will not be provided to investigators for clinical management of

study subjects. All mt-sDNA test results will remain blinded to investigators and study subjects. ESL is blinded to all clinical (colonoscopy and pathology) outcomes.

2.6 Analysis Populations

The following database components will be used to determine analysis population inclusion:

- mt-sDNA test (Cologuard) exposure data
- mt-sDNA test (Cologuard) results including compliance
- Colonoscopy, biopsy, and pathology reports
- Safety data.

Each data source will be reviewed by the Contract Research Organization (CRO) with specialized input from Exact Sciences for the mt-sDNA (Cologuard) test samples and reflecting input from appropriate medical, clinical, data management, and statistical personnel.

2.6.1 Safety (SS) Population

The safety population is described at the subject level. All subjects attempting to use the mt-sDNA (Cologuard) test kit will be included in the Safety Population. This safety analysis set (SS) will be used for the description of safety.

2.6.2 Intent-to-screen (ITS) Population

The ITS population is described at the subject level. A subject may have

- a valid mt-sDNA (Cologuard) test and a reportable colonoscopy, OR
- a valid mt-sDNA (Cologuard) test and a complete colonoscopy, OR
- a usable mt-sDNA (Cologuard) test and a reportable colonoscopy

to be included in the ITS population. The ITS analysis set will be used for assessment of effectiveness.

2.6.3 Per-Protocol (PP) Population

The Per Protocol population is described at the subject level. A subject must have a usable mt-sDNA (Cologuard) test and a complete colonoscopy to be included in the PP population. A subject will be excluded from the PP population if there is a major protocol violation or deviation that would compromise the integrity of effectiveness evaluations.

Population	mt-sDNA Test (Cologuard) Kit Attempted	Valid mt-sDNA Test (Cologuard)	Usable mt-sDNA Test (Cologuard)	Reportable Colonoscopy	Complete Colonoscopy	No Major Protocol Deviations
SS	X					
ITS		X		X		
ITS		X			X	
ITS			X	X		

PP			X		X	X

Rules regarding ITS exclusion decisions will be prospectively established prior to database lock.

2.7 Subject Disposition

All enrolled subjects will be included in summaries of disposition and evaluation for analysis sets. Accounting will be provided for the following parameters:

1. Number of subjects enrolled
2. Number of subjects with a mt-sDNA test (Cologuard).
3. Number of subjects with a complete colonoscopy.
4. Number of subjects with available colonoscopy findings.
5. Study completion status and reasons for discontinuation.

Subject exclusions from analysis sets and associated reasons will be tabulated.

2.7.1 Demographic and Other Baseline Characteristics

Gender, age, race, ethnicity, and smoking status will be presented using descriptive statistics by sites and by category for the overall ITS and PP populations. Results will also be presented to show inter-relationships between lesion location, lesion size, ethnicity, and gender.

2.7.2 Subject Replacement Rules

Subjects who are withdrawn due to no stool sample provided within 30 days of enrollment or due to colonoscopy procedure not done may be replaced.

2.8 Effectiveness Analysis

2.8.1 Effectiveness Parameters and Hypotheses

The primary effectiveness endpoint of this study is the specificity to advanced neoplasia of the mt-sDNA (Cologuard) test in the 45-49 age group in an average risk population, using colonoscopy with histopathology (if appropriate) as the reference method. The primary effectiveness analysis requires the one-sided 97.5% confidence lower bound of the specificity of mt-sDNA (Cologuard) test to exceed 85.0%.

Subjects with colonoscopic findings in categories 3-6 will be included in the specificity analysis as disease status negative outcomes for the primary endpoint calculation. Thus, specificity to advanced neoplasia (AN) will be calculated for the primary endpoint evaluation. The colonoscopically 'negative' population (category 6) will include those subjects with a colonoscopy showing no findings of colorectal neoplasia, non-neoplastic disease, and/or hyperplastic polyps $\leq$ 1 cm in diameter.

Subjects with no findings on the colonoscopy, no photographic evidence of cecal intubation and no documentation of cecal intubation in the report, will be excluded from Per Protocol analyses. Subjects found to have occult inflammatory bowel disease (IBD) on colonoscopy will be excluded from all analyses. Subjects with an invalid mt-sDNA (Cologuard) test will be excluded from the ITS and Per Protocol population. All excluded cases will be assessed for bias.

Subjects with colonoscopic/histopathologic findings in category 1 (confirmed colorectal cancer cases) will be considered to have a positive outcome and will be included in the CRC sensitivity calculations. Note:

Due to the low prevalence of CRC in the Age 45-49 group, there will likely be no CRC prospectively enrolled in the study, so no primary endpoints will be designed around CRC sensitivity. CRC sensitivity (if any CRC cases are present) will be analyzed as an exploratory endpoint.

Similarly, due to the low prevalence of AA in the Age 45-49 group, there may only be approximately 29 subjects* with colonoscopic/histopathologic findings in category 2 (advanced adenomas) prospectively enrolled in the study, so no primary endpoints will be designed around AA sensitivity. AA sensitivity will be calculated as an exploratory endpoint. To determine sensitivity for histopathologically-confirmed advanced adenomas, subjects with colonoscopic findings in Category 2 will be considered to have a positive outcome (for the AA sensitivity calculation) and, as above, subjects with colonoscopic findings in categories 3-6 will be considered to have a negative outcome.

*Advanced adenoma prevalence among never-screened individuals aged 45-49 years may be derived, based on simulation results, to be 3.92%. 731*3.92%= 29 [1].

The primary effectiveness endpoint analysis for mt-sDNA (Cologuard) test specificity will be performed using an exact binomial (Clopper-Pearson) test to compute the one-sided 97.5% confidence lower bound; the lower bound must exceed 85.0%. Specificity will be assessed for a random sample of approximately 731 subjects with non-advanced neoplasia and negative colonoscopies.

Rejecting the null hypothesis will demonstrate the Specificity in the Age 45-49 group is no worse than the pre-specified lower bound limit established in the DeeP-C protocol.

The parameters below are all single point in time following last subject enrolled and all study procedures complete. This is not meant to be an exhaustive list: additional exploratory analyses may be performed.

Parameter	Hypothesis/ Analysis*
Endpoint 1 (Primary):	Evaluation of Specificity (Category 3-6) in the Age 45-49 group. H0: P ≤ P0 (85.0%) H1: P = P1 > P0 (85.0%)
Endpoint 2 (Exploratory):	Analysis of sensitivity for CRC (if applicable)
Endpoint 3 (Exploratory):	Analysis of Sensitivity for AA. [redacted]
Endpoint 4 (Exploratory):	[redacted]
Endpoint 5 (Exploratory):	[redacted]
Endpoint 6 (Exploratory):	[redacted]
Endpoint 7 (Exploratory):	[redacted]
Endpoint 8 Exploratory):	[redacted]

	[redacted]
Endpoint 9 (Exploratory):	[redacted]
Endpoint 10 (Exploratory):	[redacted]
Endpoint 11 (Exploratory):	The Odds Ratio, NLR, PLR, NPV, PPV and diagnostic yield for the mt-sDNA test will be estimated. [redacted]
Endpoint 12 (Exploratory):	[redacted]
Endpoint 13 (Exploratory):	[redacted]
Endpoint 14 (Exploratory)	[redacted]
Endpoint 15 (Exploratory)	[redacted]
Other Outcome 1:	[redacted]
Other Outcome 2:	[redacted]

	[redacted]
Other Outcome 3:	The rate of no valid mt-sDNA (Cologuard) test result
Other Outcome 4:	[redacted]
Other Outcome 5:	[redacted]

*Hypothesis tests will be limited to the primary effectiveness endpoint.

Additionally, baseline demographic information will be presented for all enrolled, and by specificity and sensitivity subsets.

The measures of screening accuracy are defined as follows:

mt-sDNA (Cologuard) Test	Reference Test (Colonoscopy)	
	CRC+	CRC-
sDNA +	A (TP)	B (FP)
sDNA -	C (FN)	D (TN)

Definitions	
Advanced Neoplasia (AN)	Colonoscopic findings that include colorectal cancer (CRC) (category 1) and advanced adenoma (AA) (category 2).
Non-advanced neoplasia (NAN)	Colonoscopic findings ≤ 1.0 cm that exclude colorectal cancer (CRC) and advanced adenoma (AA) and include categories 3 – 5.
Sensitivity (Se)	TP/(TP + FN)
Specificity (Sp)	TN/(TN+FP)
False positive fraction (FPF)	FP/(TN+FP)
Odds ratio	(TP/FP)/(FN/TN)
Negative likelihood ratio	(1-Se)/(Sp)
Positive likelihood ratio	Se/(1-Sp)
Negative Predictive Value	TN/(FN+TN) and/or [Sp*(1-Prevalence)]/[(1-Se)*(Prevalence+Sp*(1-Prevalence)].
Positive Predictive Value	TP/(TP+FP) and/or (Se*Prevalence)/[Se*Prevalence+(1-Sp)*(1-Prevalence)]

2.9 Subject Accounting

All subjects will be followed from enrollment to study completion or withdrawal. A correction will be made for the number of subjects lost to follow-up during the study. Age, gender, race, smoking status and ethnicity will be assessed as explanatory covariates in exploratory analyses. These analyses include sensitivity and specificity, negative and positive likelihood ratio (NLR, PLR), and cumulative risk of a false or true positive (cFPR, cTPR). As noted in section 2.8.1, the prevalence of CRC and AA in the study

population is expected to be low, so certain exploratory analyses may not be performed due to this limitation.

2.9.1 Handling of Missing Data

All subjects will be used for all analyses, when possible, with the caveat of limitations existing due to eligibility considerations, the availability of a valid mt-sDNA test result, and the availability of a reportable colonoscopy reference test result. Additional considerations follow:

- If a subject is found to have occult inflammatory bowel disease (IBD) on colonoscopy, the subject will be excluded from all analyses; this may not be known in advance of performing the colonoscopy.
- It is possible for the mt-sDNA (Cologuard) test to not be valid for multiple reasons; this results in the need to exclude such subjects from analysis because it will not be known if the subject was positive or negative—there is no way to infer or impute the outcome.
- The colonoscopy needs to be complete prior to data base lock and it must be reportable. If the colonoscopy is not reportable, the subject cannot be used for any analyses; calculations of sensitivity and specificity require a reference-test result.

Performance estimates from this study can be adjusted for missing mt-sDNA results by assuming that within each histologic category, the distribution of mt-sDNA results, when available, would be expected to have the same distribution as mt-sDNA non-missing results (i.e. missing at random).

2.9.2 Study Completion

Subjects who have a mt-sDNA (Cologuard) test and complete colonoscopy will be considered complete with respect to study procedure requirements. The date of study completion is the date of colonoscopy.

The study will end when all subjects have completed or discontinued including withdrawals.

2.9.3 Handling of Withdrawals

Subjects may be withdrawn from the study by any of the following mechanisms:

1. Voluntary withdrawal of consent to participate by the subject at any time during the study.
2. Determination by the clinical investigator that it is in the best interest of the subject.
3. Determination by the Sponsor it is in the best interest of the subject or study.
4. Stool sample not provided.
5. Colonoscopy procedure is not performed.

All data available from enrollment to subject withdrawal will be collected unless the subject withdraws consent from the study. Data for all study visits will be collected for subjects who discontinue participation but who do not withdraw consent. Withdrawal of consent must be documented by site personnel in the subject source record.

2.10 Data Monitoring

Once subject enrollment is initiated and data become available, data review will be completed on a monthly basis by the statistical and clinical affairs teams to provide ongoing monitoring feedback and continuous data cleaning. Due to the low prevalence of CRC in the Age 45-49 group, there will likely be no CRC prospectively enrolled in the study, so no endpoints will be designed around CRC sensitivity. Similarly, due to the low prevalence of AA in the Age 45-49 group there may only be approximately 29 subjects [1] with colonoscopic/histopathologic findings in category 2 (advanced adenomas) prospectively enrolled in the study, so no endpoints will be designed around AA sensitivity.

The study will not be stopped for efficacy under any circumstances so no alpha-spend is planned.

The study will be further monitored to assure appropriate clinical management of subjects and rigor of study conduct in the following ways:

- Independent central pathologist(s) may review surgery and histopathology reports.
- The Investigator or the Investigator's designees are required to complete all data entry into the EDC system. Every effort should be made to respond to all monitoring and/or data management questions in the EDC system, as completion of the data is required by the protocol. A unique ID number (site specific) will identify each subject along with subject's initials. Completed data is needed in order to provide statistical analysis for each subject. All data should be promptly entered once obtained by the site. The Principal Investigator is responsible for reviewing and signing the EDC system as required and ensuring 21 CFR Part 11 adherence.
- A designated study Clinical Research Associate (CRA) will periodically inspect relevant study records at the clinical site to ensure the study is being conducted in accordance with FDA regulations, the signed investigator agreement, and the approved investigational plan/protocol. The CRA will also ensure the EDC system is being completed accurately. The designated CRA assigned to the site will perform visits as per the Study Monitoring Plan.
- A representative of Exact Sciences will monitor the study at regular intervals throughout the course of the trial, per the Monitoring Plan. On-site monitoring of the Investigator's facilities will aid in assuring compliance to the protocol and applicable laws and regulations. Any deficiencies noted during the monitoring visits will be discussed with the Investigator, and the corrective action(s) to be taken will be agreed upon and documented.

2.10.1 Multiple Comparisons / Multiplicity

No p-value adjustments will be performed for multiple testing. A p-value will be computed for the primary effectiveness endpoint. The other effectiveness endpoints may include p-values in their evaluation but are considered exploratory endpoints.

2.10.2 Examination of Subgroups

Results for exploratory effectiveness endpoints include analyses by gender, age, race, ethnicity and smoking status.

2.10.3 Supplementary Analyses

Supplementary, emergent, and exploratory analyses may be conducted.

3 SAFETY EVALUATION

3.1 Extent of Exposure

Summary of exposure is by subject according to the number of Cologuard tests performed. Exposure will be characterized as the total number of mt-sDNA (Cologuard) tests. Exposure will not be characterized by start/stop dates or days on study.

3.2 Adverse Events

An adverse event (AE) is any unfavorable or unintended sign, symptom, or disease temporally associated with the use of an investigational product or protocol-imposed intervention, regardless of attribution.

[redacted]

[redacted]. [redacted] The liquid buffer/liquid preservative in the quantities provided is non-toxic. An AE may be investigated as an Unanticipated Adverse Device Effect (UADE), if applicable.

Adverse events commonly associated with colonoscopy will not be collected. Such events include: Abdominal discomfort, bowel irregularity, bleeding, intestinal perforation, and adverse reaction to the sedation.

Surgical intervention, such as, but not limited to, colectomy and sub-mucosal resection are part of routine patient care for subjects with CRC or AA; therefore, adverse events commonly associated with surgeries will not be collected. Such events include: Bleeding, blood clots in the legs (deep vein thrombosis) and lungs (pulmonary embolism); infection; injury to organs near the colon, such as the bladder and small intestines; and tears in the sutures that reconnect the remaining parts of the digestive system.

AEs will be coded in MedDRA. Type, timing (onset and resolution), relationship, and severity will be of primary interest. In addition to adverse events, related AEs, Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs) will be summarized separately.

3.3 Clinical Laboratory Evaluation

No clinical laboratory evaluations are made for this study.

3.4 Vital Signs, Physical Findings, and Other Safety-related Observations

Weight and height will be collected. No other vital signs, physical findings, or other safety observations are made for this study.

4 STUDY DESIGN

Refer to the study protocol Section 7 for the specific hypotheses to be tested.

4.1 Determination of Sample Size

Refer to the study protocol Section 12.3 for a comprehensive justification for the final sample size.

5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

No changes have been made to the planned analysis delineated in the study protocol.

6 REFERENCES

1. Rutter C, Miglioretti D, Savarino J, Bayesian Calibration of Microsimulation Models. J Am Stat Association 2009, 104(488): 1338-1350.

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3. Master Clinical Protocol 2018-10: An Evaluation of a Multi-target Stool DNA (mt-sDNA) Test, Cologuard, for CRC Screening in Individuals Aged 45-49 and at Average Risk for Development of Colorectal Cancer (Act Now). Identification No. NCT03728348