HEOR 24

Detecting cancers Earlier Through Elective plasma-based CancerSEEK Testing - Ascertaining Serial Cancer patients to Enable New Diagnostic (DETECT-ASCEND)

NCT04213326

November 9th, 2020

SARAH CANNON
The Cancer Institute of HCA

HEOR 24

Detecting cancers Earlier Through Elective plasma-based CancerSEEK Testing - Ascertaining Serial Cancer patients to Enable New Diagnostic (DETECT-ASCEND)

INNOVATIONS STUDY NUMBER:	HEOR 24
SPONSOR:	Thrive Earlier Detection Corp. [redacted]
PRINICPAL INVESTIGATOR:	Dax Kurbegov, MD [redacted]
DATE FINAL:	18 October 2019
AMENDMENT 1	25 October 2019
AMENDMENT 2	27 January 2020
AMENDMENT 3	5 March 2020
AMENDMENT 4	13 March 2020
AMENDMENT 5	13 July 2020
AMENDMENT 6	9 November 2020

Clinical Study Statement of Compliance

HEOR 24

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This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards (IRBs)**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance with the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

Clinical Study Principal Investigator Signature Form

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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____	_____
Principal Investigator Name (Please Print)	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

Sarah Cannon Development Innovations, LLC
[redacted]

HEOR 24 Summary of Changes

AMENDMENT NUMBER: 6 **AMENDMENT DATE:** 9 November 2020

Additions are noted by **bolding**. Deletions are noted by ~~cross outs~~.

Throughout the protocol, enrollment of healthy subjects was changed from 3,300 to 4,300 and the total number of subjects enrolled changed from 4,300 to 5,300.

Synopsis

A total of **5,300**~~4,300~~ patients are planned to be enrolled on this study, 1,000 subjects with known or suspected cancer confirmed through pathology reports and/or clinical/radiographic data and **4,300**~~3,300~~ subjects with no known cancer.

Synopsis and Section 2.1 Primary Objective

- Up to ~~the first~~ 700 subjects with known or suspected cancer and ~~the first~~**approximately** 1,400 subjects with no known cancer collected will be used as training cases to develop a model to discriminate cancer from non-cancer cases.

Synopsis and Section 3.1 Inclusion Criteria

- Age ≥50 years **(both cancer and non-cancer cohorts)** or age 18-30 years (non-cancer cohort only).

Synopsis and Section 9 Determination of sample size

The overall study aims to consent **5,300**~~4,300~~ subjects (1,000 confirmed cancer subjects, **4,300**~~3,300~~ non-cancer). ~~The cancer cohort will limit breast and endometrial cancer to approximately 200 subjects and 50 subjects, respectively.~~

Section 2 Study Objectives and Endpoints

Thrive Earlier Detection is seeking to conduct a development and validation study for a new version of the CancerSEEK assay, in a cohort of 1,000 subjects diagnosed with cancer and a cohort of **4,300**~~3,300~~ non-cancer volunteers with no known diagnosis of cancer. The overall study aims to consent **5,300**~~4,300~~ subjects meeting eligibility criteria (1,000 confirmed **cancer** subjects and **4,300**~~3,300~~ non-cancer subjects).

Section 5.1 Overview

To ensure **inclusion of** ~~that~~ **a heterogeneous group of cancer types and that** breast and endometrial cancer patients are not overrepresented in the sample of cancer patients (N_{Total} = 1,000), we will limit enrollment of those tumor sites **as shown in Table 1. Each cancer type should include a distribution of Stage I-IV.** ~~to approximately 20% of the overall sample (N_{Breast} = 200, $N_{endometrial}$ = 50). Initial data analysis will be conducted after collecting 70% of our cancer cohort ($N_{Initial}$ = 700). Breast and endometrial cancer patients will be capped at approximately 20% and 5% of the initial sample as well (N_{Breast} = 140, $N_{Endometrial}$ = 35) (See Table 1 below).~~

Table 1 Proposed Cancer Cohort Enrollment

	Testing Analysis *First 700 Cancer Blood Samples*	Validation Analysis *Final 300 Cancer Blood Samples*	Total Requirement
Breast Cancer	**193**	**82**	**275**
Lung Cancer	**280**	**120**	**400**
Colorectal Cancer	**105**	**45**	**150**
Other Cancers	**122**	**53**	**175**
Endometrial	**(35)**	**(15)**	**(50)**
~~Breast Cancer Limit~~	~~140~~	~~60~~	~~200~~
~~Endometrial Cancer Limit~~	~~35~~	~~15~~	~~50~~

HEOR 24 PROTOCOL SYNOPSIS

Title of Study:	Detecting cancers Earlier Through Elective plasma-based CancerSEEK Testing - Ascertaining Serial Cancer patients to Enable New Diagnostic (DETECT-ASCEND)
Study Number:	HEOR 24
Sponsor:	Thrive Earlier Detection Corporation– Cambridge, MA 02139
Number of Patients:	A total of 5,300 patients are planned to be enrolled on this study, 1,000 subjects with known or suspected cancer confirmed through pathology reports and/or clinical/radiographic data and 4,300 subjects with no known cancer.
Objectives:	The primary objective of the study is to develop and validate the classification algorithm used by the CancerSEEK cancer screening test by collecting clinically annotated peripheral blood specimens from subjects with cancer and no known cancer. • Up to 700 subjects with known or suspected cancer and approximately 1,400 subjects with no known cancer collected will be used as training cases to develop a model to discriminate cancer from non-cancer cases. • The subsequent cases collected will be used as test cases to validate a model that discriminates cancer from non- cancer cases. In addition to planned analyses for the primary objective, future exploratory investigation may study histology, pathology, medical records, tissue, and other biospecimens collected as part of standard of care.
Study Design:	This is a prospective, observational study of 1,000 subjects with known or suspected cancer and 4,300 subjects with no known cancer. Potential participants will be asked questions to confirm their eligibility by a nurse navigator, study staff member, physician or via the patient web portal. Informed consent will be carried out for eligible subjects in accordance with applicable federal regulations and International Council for Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines. Subjects will then complete a survey, and either study staff will draw 60 mL of blood and measure the height and weight of the subject, or a home health visit will be scheduled to complete the blood draw and collect height and weight. Where available, data from the medical records of the cancer subjects will reviewed and collected. In addition, non-cancer subjects will be requested to allow access to their medical records as an optional portion of their informed consent.
Inclusion Criteria:	**<u>All Patients</u>** • Age ≥50 years (both cancer and non-cancer cohorts) or age 18-30 years (non-cancer cohort only). • Ability to understand the nature of this study and give written informed consent. **<u>Cancer cohort</u>** Either of the following: • Histologic diagnosis of cancer with no prior systemic or definitive therapy (any stage, inclusive of in-situ carcinoma) Or

	• Subject with high suspicion of cancer through radiological and/or clinical assessment who are scheduled for resection or biopsy within 6 weeks of study blood collection and have not received prior systemic or definitive therapy. **Non-cancer cohort** • No prior history of cancer with the exception of localized, non-melanoma skin cancer.
Exclusion Criteria:	**All Patients** • Evidence of active febrile infection prior to blood draw. • Women who are pregnant or breast-feeding. • History of an allogeneic bone marrow, stem cell transplant, or solid organ transplant. • Judgment by the Investigator or study staff of any other reason that would prohibit the inclusion of the subject in the study. **Cancer cohort** • Subjects newly diagnosed with a hematologic malignancy, primary central nervous system tumor, prostate cancer, or skin cancer (including melanoma). • History of, or currently receiving, systemic or definitive cancer treatment including curative surgical resection (with the exception of localized, non-melanoma skin cancer), chemotherapy, radiation therapy, immunotherapy, and hormone therapy. **Non-cancer cohort** • None
Statistical Methodology:	The statistical analysis will be descriptive and consist of subject listings, graphs, and summary statistics comprising geometric mean, arithmetic mean, standard deviation (SD), median, minimum (min) and maximum (max) values as appropriate. The overall study aims to consent 5,300 subjects (1,000 confirmed cancer subjects, 4,300 non-cancer).

HEOR 24 CONTACT INFORMATION

Outcomes Contact Address and Phone#:	Sarah Cannon Health Economics and Outcomes Research [redacted]
Study Chair:	Dax Kurbegov, MD [redacted]
Sarah Cannon Health Economics and Outcomes Research Enrollment email:	[redacted]

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
CFR	Code of Federal Regulations
eCRF	Electronic case report form
EDC	Electronic data capture
GCP	Good Clinical Practice
HCA	Hospital Corporation of America
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identifier
Innovations	Sarah Cannon Development Innovations
IRB	Institutional Review Board
Outcomes	Sarah Cannon Health Economics and Outcomes Research
PPV	Positive predictive value
SAE	Serious adverse event

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1. INTRODUCTION

1.1 Background and Study Rationale

Recommended screening is known to reduce the mortality and morbidity of breast, colorectal, cervix, prostate, and lung cancer. At present, a screening assessment, the prostate-specific antigen (PSA) test, can be performed with a blood sample. Cervical cancer screening involves a Pap smear test, and in countries where the test is the standard-of-care cervical cancer has nearly disappeared. Breast and colorectal cancer screenings are conducted with mammography and colonoscopy, respectively, and may detect precancerous lesions that can be removed (Kalinich et al 2018). Screening heavy smokers with low-dose chest computed tomography (CT) scans can detect lung cancer and improve cancer-specific survival (Siegel et al 2019).

Timely, less invasive, and effective screening for cancer provides the best opportunity to reduce cancer mortality and morbidity for patients. The CancerSEEK assay constitutes an important step towards early cancer detection (Cohen et al 2018). The CancerSEEK assay was characterized in a retrospective study of over 1800 subjects (1,005 previously diagnosed with cancer and 812 non-cancer subjects). A cross-validation technique was used to train and evaluate the performance of classified algorithms. Eight cancer types (ovary, liver, stomach, pancreas, esophagus, colorectal, lung, and breast) were used to demonstrate the performance of the assay. Altogether, the algorithm for detection demonstrated sensitivity of 62% and specificity of 99.14%. In cases where the CancerSEEK result was positive for presence of cancer (N=626) the algorithm for localization further predicted the 2 most likely anatomical sites (out of 8) for each assayed tumor. During cross-validation this prediction contained the actual site of origin of the tumor in a median of 83% of subjects (Cohen et al 2018).

In this study a new analytic feature of the CancerSEEK test not available in previous CancerSEEK studies will be validated. The new CancerSEEK test will measure genome-wide aneuploidy and as a result, a new version of the algorithm will be developed.

2. STUDY OBJECTIVES AND ENDPOINTS

Thrive Earlier Detection is seeking to conduct a development and validation study for a new version of the CancerSEEK assay, in a cohort of 1,000 subjects diagnosed with cancer and a cohort of 4,300 non-cancer volunteers with no known diagnosis of cancer. The overall study aims to consent 5,300 subjects meeting eligibility criteria (1,000 confirmed cancer subjects and 4,300 non-cancer subjects). Enrolled subjects will complete a brief survey and supply a sample of blood to be sent to a central laboratory where the CancerSEEK blood test is in development.

2.1 Primary Objective

The primary objective of the study is to develop and validate the classification algorithm used by the CancerSEEK cancer screening test by collecting clinically annotated peripheral blood specimens from subjects with cancer and no known cancer.

- Up to 700 subjects with known or suspected cancer and approximately 1,400 subjects with no known cancer collected will be used as training cases to develop a model to discriminate cancer from non-cancer cases.

- The subsequent cases collected will be used as test cases to validate a model that discriminates cancer from non-cancer cases.

2.2 Exploratory Objective

[redacted]

2.3 Endpoints

The primary endpoint is the ability of the CancerSEEK assay to effectively discriminate cancer from non-cancer as measured by sensitivity, specificity, and positive predictive value (PPV). Additional indicators of accuracy will be provided in a full confusion matrix, which is a table that shows the full performance of a classification model against true values.

[redacted]

3. STUDY POPULATION

3.1 Inclusion Criteria

- Age ≥50 years (both cancer and non-cancer cohorts) or age 18-30 years (non-cancer cohort only).
- Ability to understand the nature of this study and give written informed consent.

3.1.1 Cancer cohort

Either of the following:

- Histologic diagnosis of cancer with no prior systemic or definitive therapy (any stage, inclusive of in-situ carcinoma)

Or

- Subject with high suspicion of cancer through radiological and/or clinical assessment who are scheduled for resection or biopsy within 6 weeks of study blood collection and have not received prior systemic or definitive therapy.

3.1.2 Non-cancer cohort

- No prior history of cancer with the exception of localized, non-melanoma skin cancer.

3.2 Exclusion criteria

- Evidence of active febrile infection prior to blood draw.
- Women who are pregnant or breast-feeding.
- History of an allogeneic bone marrow, stem cell transplant, or solid organ transplant.
- Judgment by the Investigator or study staff of any other reason that would prohibit the inclusion of the subject in the study.

3.2.1 Cancer cohort

- Subjects newly diagnosed with a hematologic malignancy, primary central nervous system tumor, prostate cancer, or skin cancer (including melanoma).
- History of, or currently receiving, systemic or definitive cancer treatment including curative surgical resection (with the exception of localized, non-melanoma skin cancer), chemotherapy, radiation therapy, immunotherapy, and hormone therapy.

3.2.2 Non-cancer cohort

- None.

3.3 WITHDRAWAL FROM STUDY PARTICIPATION

Participation in this study is voluntary. Subjects are not required to participate and may decide to withdraw their information from the study at any time, without penalty and without affecting their medical care.

- If a subject elects to discontinue participation in the study and withdraws consent and authorization, Outcomes will make all reasonable efforts to take the following actions:
- Future use of the subject's biological sample and future access to the subject's medical information will not take place.
- Any information already obtained through study of the subject's biological sample will continue to be used as described in this protocol.
- Any information already collected from the subject's medical record or through study surveys will continue to be used as described in this protocol.
- Any remaining portion of the subject's biological sample will be destroyed.

Note: It may not be possible to retrieve and/or destroy biological sample and other information previously released; in addition, the biological sample may have already been depleted at the time of the request.

4. STUDY REGISTRATION

The subject must willingly consent after being informed of the procedures, the experimental nature

of the study, potential benefits, alternatives, side-effects, risks, and discomforts. Human protection committee approval of this protocol and associated consent form(s) is required.

Study subjects will be identified for one of the two cohorts (Cancer Cohort or Non-Cancer Cohort [healthy volunteer]) (please refer to Table 1).

In the confirmed Cancer Cohort, subjects for the study will be identified by physicians, study staff and nurse navigators. For some participants, a Natural Language Processing (NLP) machine learning algorithm will be applied to pathology reports to predict a positive cancer diagnosis and the most likely primary tumor site.

Cancer subjects will then be populated into an application where they will be assigned a nurse navigator or study coordinator who may identify them as eligible for the study.

All subjects participating in the cancer cohort will receive compensation after signing informed consent and completing the study survey (see Appendix A). Completion of the study survey is defined as an attempt at survey, and compensation will be sent regardless of any skipped or "prefer not to answer" responses present.

Navigated gateway

For sites using the navigated gateway, a nurse navigator will recruit potential participants. Because nurse navigators will only be recruiting potential participants for the study and not consenting them, their activities are limited to screening activities, entering subject demographics, tablet activation and distribution of Institutional Review Board (IRB)-approved materials. They will be trained to direct participants to the study phone line if they have questions related to the informed consent form. Patients will be supplied with the consent by the nurse navigator, but will call the study phone line if they have any questions.

Study site gateway

For sites using a study coordinator, the study coordinator will conduct the consent survey and blood draw.

In the Non-Cancer Cohort, subjects will be recruited and enrolled from several sources. Firstly, from the Hospital Corporation of America (HCA) employee base, referrals to non-HCA-employed individuals (e.g., friends, family, neighbors) and others in waves until enrollment targets are met. This approach will include messaging to create awareness of the opportunity within targeted departments/subsidiaries of HCA Healthcare. While employee email addresses may be used to inform individuals of the study opportunity, no data regarding individual employee participation will be shared with the employer, and participation will have no impact on employees' standing with their employer. A financial incentive will not be offered to HCA employees or HCA-employee referrals. Secondly, subjects will be recruited and enrolled via a study web portal. Informed consent and survey data collection will be performed via the web portal, and the blood draw performed using home health visits. A financial incentive will be offered to this non-cancer cohort for additional time and effort in participating.

Study site gateway

For sites using a study coordinator, the study coordinator will conduct the consent survey and blood draw.

5. STUDY DESIGN

5.1 Overview

This is a prospective, observational study of 1,000 subjects with known or suspected cancer confirmed through pathology reports (Table 1) and/or clinical/radiographic data and 3,300 subjects with no known cancer. De-identified blood samples and clinical data will be collected from subjects to validate a classification algorithm for a new version of the CancerSEEK assay. All subjects in the cancer cohort signing informed consent and completing the study survey will receive compensation for participating.

Potential participants will be asked questions to confirm their eligibility by a nurse navigator, study staff member, physician (see Appendix A), or via the patient web portal, to document screening including date of upcoming therapy or surgery for cancer patients if one has been scheduled, before providing informed consent to participate in the study. Study procedures outside of the pre-screening for eligibility will not be performed prior to the subject providing consent. Informed consent will be carried out in accordance with applicable federal regulations and International Council for Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines. Prior to signing the informed consent form (ICF), potential participants will confirm that they understand the study and that they have no questions about the study.

The ICF may be offered by paper, electronically, or via a secure web site, with the option to also review a paper copy provided by the nurse navigator or study coordinator either face-to-face on a tablet, via printing, or via email. Potential participants will be given a phone number to call with any study specific questions. Copies of all signed consent forms will be stored centrally in a secure environment, and signed consent forms will thereby be available for verification by Thrive or its designee at any time.

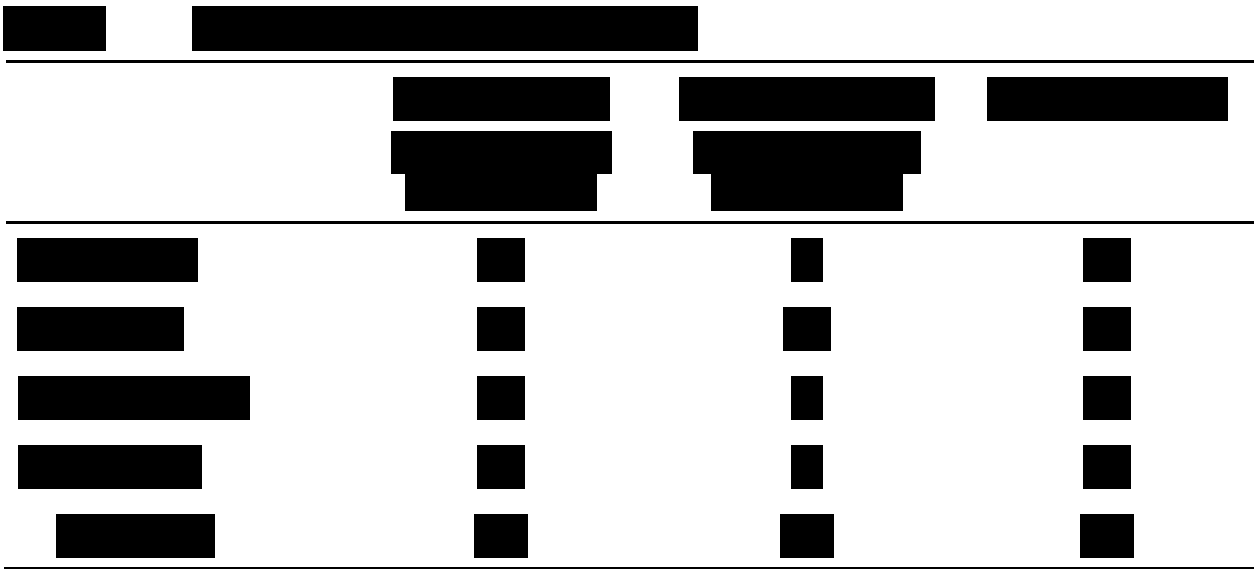
Once the subject completes the survey, study staff will complete the blood draw and collect height and weight data. For some participants, their contact information and unique study identifier (ID) will be sent securely to a third-party vendor who will contact the subject within 24 hours to schedule the blood draw and height and weight measurements at a location convenient to the subject.

For all subjects, study staff and/or the third-party vendor performing the blood collection will verify the following before performing the blood draw and height and weight measurements: participant identity and age against a form of identification, that consent to participate has been given, that the participants in the cancer arm are still treatment naïve, and that they do not have a fever that could be caused by an infection. The blood collection vendor or study staff will ensure all required data are captured and included with the blood sample, that the sample is collected and packaged according to laboratory manual specifications, and that the sample is shipped to the indicated processing lab with the required expediency. Following all study visits, study staff and third party vendor or study staff will complete a visit checklist confirming all of the study activities that occurred.

Subjects in the **Cancer cohort** will be identified via nurse navigation, study staff or oncology physicians in local offices. The nurse navigator or study staff will verify eligibility through chart

review and pre-screen, approach the subject about the study opportunity, and present the informed consent form. For participants enrolling electronically, participants will be presented with a secured tablet device on which the subject will watch a brief video about the study, read the informed consent and provide electronic consent. Some participants may also have the option of having the video, informed consent and survey emailed to them. Upon consent and enrollment, subjects will be assigned a unique subject study ID, which will be used to track the subject, their data and their biospecimen throughout study operations. Consented subjects will then be directed to complete a survey via the tablet device, email or paper. Participants will be allowed to skip questions in the survey or select the answer option "prefer not to answer." Subject data will be tracked in real-time by central study staff to ensure desired tumor type diversification and communicate enrollment strategy changes to the nurse navigators and study staff.

To ensure inclusion of a heterogeneous group of cancer types and that breast and endometrial cancer patients are not overrepresented in the sample of cancer patients (N_{Total} = 1,000), we will limit enrollment of those tumor sites as shown in Table 1. Each cancer type should include a distribution of Stage I-IV.



[redacted]

6. BLOOD SAMPLE COLLECTION

Subjects will have 6 (10 mL) biological samples (blood) collected in Streck circulating free DNA (cfDNA) tubes with a needle no larger than 21G. Tubes will be filled completely and then immediately mixed by gentle inversion 8-10 times. A temperature monitor is required to ensure the blood samples do not become too hot or cold as samples must be shipped at ambient temperature (43-99ºF, 6-37ºC). Sample shipping instructions are detailed in the study operations manual.

7. DATA COLLECTION

Data from the non-cancer subjects (healthy volunteers) and cancer subjects will be self-reported for this study. Where available, data from the medical records of the cancer subjects will reviewed and collected. In addition, non-cancer subjects will be requested to allow access to their medical records. These subjects will be asked to check and sign the optional section of the consent allowing access to their long-term outcomes data.

The following demographic data will be collected from each subject (cancer and non-cancer):

- Date of birth
- Gender
- Race
- Ethnicity
- Education
- Family history of cancer
- Family member(s) with cancer diagnosis
- Current medications
- Known comorbidities
- Recent or current flare-up of inflammatory disease
- Smoking status

This set of data demographic data may expand based on emergent data.

Additional data points will be collected from the cancer subjects. These data points will include but are not limited to the following:

- Cancer diagnosis at enrolment
- Procedure used for cancer diagnosis

- Date of any cancer diagnosis
- Cancer histology
- Clinical staging
- Pathological staging, where available

7.1 Benefit/risk and ethical assessment

There are no benefits for the subjects participating in the study.

No test results will be provided to the Investigator or subject.

Inclusion and exclusion criteria as well as study restrictions are chosen to ensure the selected subjects are exposed to minimal risk in this study.

7.2 Study timetable and end of study

The study is expected to start in 4th quarter of 2019.

The end of the study is defined as the last visit of the last subject undergoing the study.

8. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

This research study will be conducted according to the standards of GCP outlined in the ICH E6 Tripartite Guideline and Code of Federal Regulations (CFR) Title 21 part 312, applicable government regulations, institutional research policies and procedures, and any other local applicable regulatory requirement(s).

8.1 Institutional Review Board Approval

The clinical study protocol and ICF will be submitted to the IRB for review and approval prior to study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going IRB study review. The Principal Investigator/Sponsor must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Informed consent will be obtained using the method outlined above in Section 5.1.

8.2 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by Sarah Cannon Health Economics and Outcomes Research (Outcomes). All amendments require review and approval of the Principal Investigator/Sponsor supporting the study. The written amendment must be reviewed and approved by Outcomes and submitted to the IRB at the Investigator's facility for the board's approval.

8.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the electronic case report forms (eCRFs) are to be included on this document. All entries in the subjects' eCRFs are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the subjects' eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, electrocardiogram (ECG) traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, x-rays, and correspondence.

The Principal Investigator and study staff members are responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or Investigator study file [ISF]) of all essential study-related documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain at a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the Investigator's Brochure (IB) and any amendments, the protocol and any amendments, copies of completed eCRFs, IRB approval documents, subject identification lists, and enrollment logs.

8.4 Data Management

The Data Science team will work with the Sponsor and Investigator to provide operational definitions for each variable and the Data Manager will work with the appropriate subject matter experts (SME) to map these required variables to the appropriate data fields, ensuring their existence and completeness, and will design requirements for their collection. Variables to be abstracted will be outlined and collected via study staff manually entering the data into the study electronic data capture EDC system or through automated direct transfer of electronic health record (EHR) data elements to the EDC system. Requirements for the EDC eCRF will be identified, documented and developed under the oversight of Sarah Cannon Data Management.

Innovations will monitor enrolled subjects – receiving both their EMR subject ID and unique study ID – and will ensure that other required study variables are abstracted from the subject records into the EDC. A percentage of these cases will be reviewed in entirety for quality assurance, and monitoring of all collected data will be performed according to the agreed-upon Monitoring Plan.

Quality-assured abstracted subject data will be merged with quality-assured subject survey data via unique subject ID to produce a final dataset.

Electronic Case Report Form

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable Outcomes to review the subjects' status throughout the course of the study.

In order to maintain confidentiality, only study number, subject number, and year of birth will identify the subject in the eCRF. If the subject's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Outcomes and be replaced instead with the subject number and other identifier (i.e., subject initials) as allowed per institutional policy. The Investigator will maintain a personal subject identification list (subject numbers with corresponding subject identifiers) to enable records to be identified and verified as authentic. Subject data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF system must be supported by and be consistent with the subject's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the test was "Not Done" or the result was "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Investigator will electronically sign and date the subject eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that subject is final.

8.5 Confidentiality

Confidentiality of subjects' personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a subject must sign an authorization form for the study that he or she has been informed of the following:

- What protected health information will be collected from subjects in the study;
- Who will have access to that information and why;
- Who will use or disclose that information;
- The health information may be further disclosed by the recipients of the information, and that if the information is disclosed, the information may no longer be protected by federal or state privacy laws;
- Whether the authorization contains an expiration date;
- The rights of a research subject to revoke his or her authorization.

In the event that a Subject revokes authorization to collect or use his or her personal health information (PHI), the Investigator retains the ability to use all information collected prior to the revocation of authorization.

The Investigator and institution must permit authorized representatives of Outcomes, Innovations, applicable regulatory authorities and the IRB to review the subject's original medical records for verification of trial-related procedures and data.

8.6 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process.

Inclusion of the Investigator in the authorship of any multi-center publication will be based upon substantial contribution to the study design, the analysis or interpretation of data, or the drafting and/or critically revising of any manuscript(s) derived from the study.

9. STATISTICAL ANALYSIS

The primary objective of the study is to collect clinically annotated peripheral blood specimens from subjects with confirmed cancer and subjects with no known cancer (healthy volunteers) to develop and validate the classification algorithm used by the CancerSEEK cancer screening test.

The primary endpoint is the assay's ability to effectively discriminate cancer from non-cancer as measured by the full confusion matrix, including sensitivity, specificity, and PPV.

[redacted]

9.1 Determination of sample size

Given the exploratory nature, no formal statistical analysis will be performed in this study. The statistical analysis will be descriptive and consist of subject listings, graphs, and summary statistics comprising geometric mean, arithmetic mean, standard deviation (SD), median, minimum (min) and maximum (max) values as appropriate.

The overall study aims to consent 5,300 subjects (1,000 confirmed cancer subjects, 4,300 non-cancer).

9.2 Subject characteristics

Demographic and baseline characteristic data will be recorded. Demographic data will include date of birth, age, sex, race and ethnicity. Subject characteristics, cancer history, family history, and baseline data will include smoking details (quantity and duration of smoking history).

10. SAFETY REPORTING AND ANALYSES

The Principal Investigator is responsible for recognizing and reporting serious adverse events (SAEs) to the Innovations Safety Department. It is the Sponsor's responsibility to report relevant SAEs to the applicable national regulatory bodies. In addition, the Principal Investigator must report SAEs and follow-up information to the responsible IRB according to the policies of that IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

10.1 Definitions

10.1.1 Serious Adverse Events

Each SAE must be assessed for severity and intensity using the following classification guidelines:

Mild: Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae.

Moderate: Interferes with the subject's usual activity and/or requires symptomatic treatment.

Severe: Symptom(s) causing severe discomfort and significant impact on the subject's usual activity and requiring treatment.

10.1.2 Relatedness

An SAE should be considered definitely related if, in the opinion of the Investigator, the study procedure caused or contributed to the SAE. The initial assessment may be revised as new information becomes available.

Related: there is a reasonable relationship to study application

Unrelated: there is not a reasonable relationship to the study application

Unknown: there is no clear or compelling evidence that the event is **or** is not due to the study application

10.1.3 Definitions of serious adverse event

An SAE is an adverse event occurring during any study phase that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening (e.g. subject cannot breathe)
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. Examples of these would include: angioedema not severe enough to require intubation but requiring IV hydrocortisone

treatment, intensive treatment in an emergency room or at home for allergic bronchospasm, or convulsions that do not result in hospitalization.

10.2 Recording of serious adverse events

All SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through other means will be reported appropriately.

10.3 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel must inform appropriate Innovations Safety Department representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

To report a SAE, the SAE Report Form should be completed with the necessary information.

The SAE report should be sent to Innovations Safety Department via fax or e-mail using the following contact information (during both business and non-business hours):

Sarah Cannon Innovations Safety Department

Safety Dept. Fax #: [redacted]

Safety Dept. Email: [redacted]

Transmission of the SAE report should be confirmed by the site personnel submitting the report, and a copy of the confirmation should be retained with the subject's records.

The Principal Investigator must report SAEs and follow-up information to the responsible IRB according to the policies of the responsible IRB.

10.4 Recording of Serious Adverse Events

10.4.1 Diagnosis versus Signs and Symptoms

All SAEs should be recorded individually in the subject's own words (verbatim) unless, in the opinion of the Principal Investigator, the SAEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an SAE as appropriate on the SAE Report Form. If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

10.4.2 Persistent or Recurrent Adverse Events

A persistent SAE is one that extends continuously, without resolution, between subject evaluation time points. Such events should only be recorded once on the SAE Report Form. If a persistent

SAE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form.

A recurrent SAE is one that occurs and resolves between subject evaluation time points, and subsequently recurs. All recurrent SAEs should be recorded on an SAE Report Form.

11. REFERENCES

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Appendix A Screening & Survey Questions

SURVEY QUESTIONS

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Uterine cancer

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