Academic and Community Cancer Research United (ACCRU)

ACCRU-GI-1611 **COLOMATE: COlorectal Cancer Liquid BiOpsy Screening Protocol for Molecularly Assigned ThErapy**

Amendment 2– January 28, 2021

Summary of Changes	
Protocol section updated	**Nature of change**
Title Page	• Stat personnel change – Joseph Larson • Updated Document History
Section 3.0, Patient Eligibility	• Section 3.19 updated to clarify that one of two conditions must be met
Section 4.0, Test Schedule	• 28 days prior to registration changed to 60 days prior to registration • Tumor assessment test removed • Footnote 1 Removed • Footnotes renumbered
Section 6.0, Registration/Randomization Procedures	• Added Exemption: Guardant360 tests completed ≤60 days prior to registration will be accepted
Section 14.0, Body Fluid Biospecimens	• Instructional text updated throughout for ordering Guardant 360 kits
Section 16.0, Statistical Considerations and Methodology	• Edit of primary endpoint for actionable genomic profile and trial recommendations • Edit of secondary endpoint for companion trial enrollment • Addition of confidence interval table in sample size section • Analysis plan edit for primary endpoint, goal of 20% of patients with actionable genomic profiles. • Addition of secondary endpoint analysis, subsequent screening, goal of 75% patients with actionable genomic profiles.
Appendix I: ACCRU Informed Consent	• Removed the need for CT or MRI of tumor • Added information regarding the protocol selection process based off of the Guardant360 blood test
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

A replacement protocol is provided. Please replace the current copy with the one attached.
Please keep this summary of changes with your protocol

Academic and Community Cancer Research United (ACCRU)

COLOMATE: COlorectal Cancer Liquid BiOpsy Screening Protocol for Molecularly Assigned ThErapy

For any communications regarding this protocol, please contact the person indicated on the Protocol Resource Page. This is a stand-alone document found on the ACCRU website [redacted]

Study Chairs

ACCRU: [redacted]

Study Co-chairs: [redacted]

Statistician: [redacted]

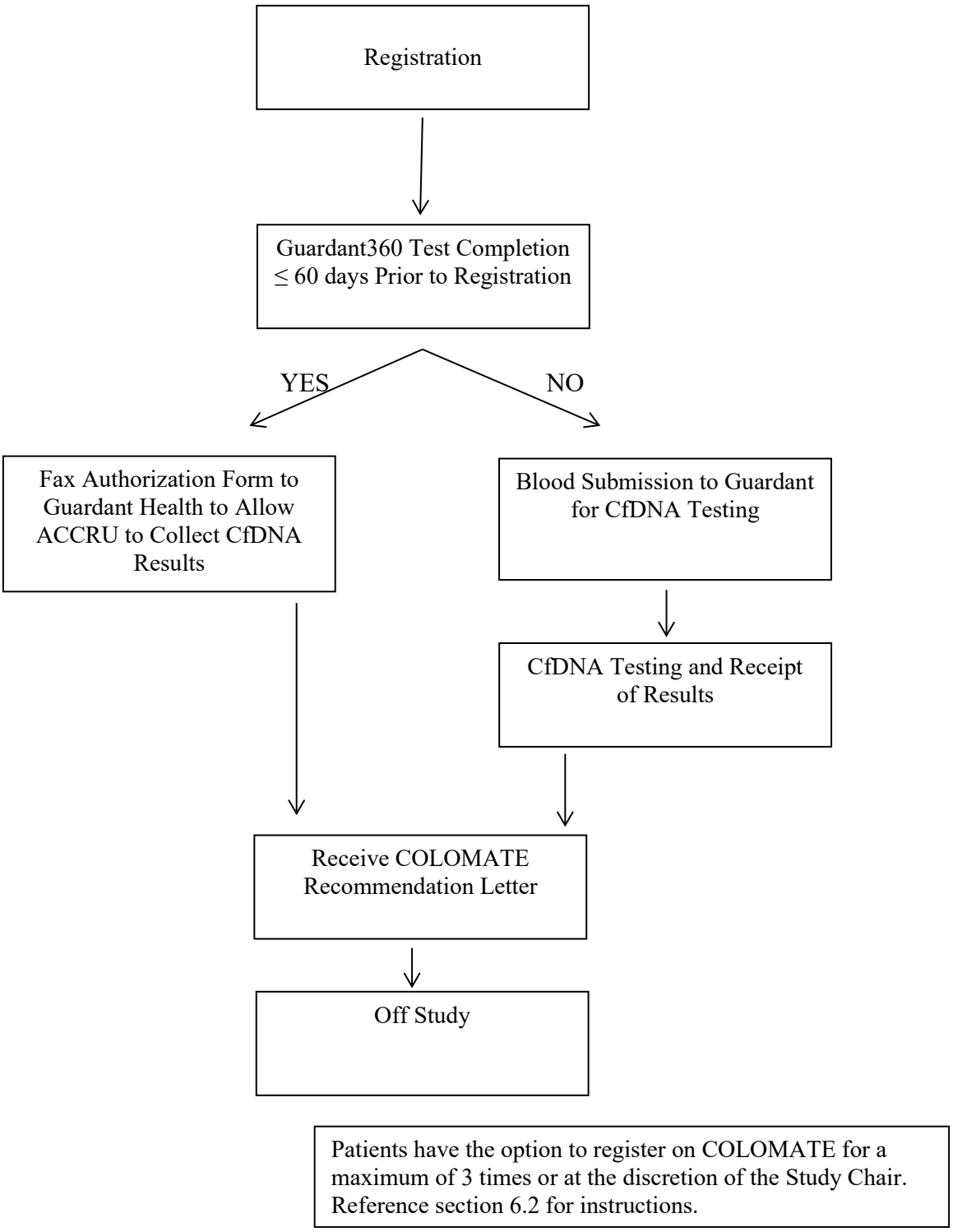
√ Study contributor(s) not responsible for patient care.

Research Coordinating Center
Academic and Community Cancer Research United
[redacted]

Document History	**(effective date)**
Version 1	May 15, 2017
Preactivation Amendment	November 8, 2018
Activation	November 1, 2019
Amendment 1	March 4, 2020
Amendment 2	January 28, 2021

Index

Schema


Registration
Guardant360 Test Completion
≤ 60 days Prior to Registration
YES
NO
Fax Authorization Form to Guardant Health to Allow ACCRU to Collect CfDNA Results
Blood Submission to Guardant for CfDNA Testing
CfDNA Testing and Receipt of Results
Receive COLOMATE Recommendation Letter
Off Study
Patients have the option to register on COLOMATE for a maximum of 3 times or at the discretion of the Study Chair. Reference section 6.2 for instructions.

1.0 Background

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States (Jemal, Siegel et al. 2010). Over the past two decades, overall survival for patients with metastatic disease has steadily improved. To build on this progress, comprehensive efforts are needed to identify and treat actionable molecular alterations. Already, this approach has been used to enhance the benefit of anti-EGFR (Oliner, Douillard et al. 2013) and anti-PD-1 (Le, Uram et al. 2015) monoclonal antibodies. This screening protocol is designed to identify actionable genomic alterations, and then facilitate accrual to molecularly assigned therapies.

Several basket trials are ongoing to match tumor genotype with targeted therapies. Nonetheless, the impact of these trials thus far has been limited by operational and technical challenges. For example, at MD Anderson Cancer Center large-scale genomic testing was performed on 2,000 consecutive patients. Of these, 39% of patients had a potentially actionable tumor mutation, but only 11% were enrolled on a genotype-matched clinical trial (Meric-Bernstam, Brusco et al. 2015). This experience identified several barriers to trial enrollment, including use of non-investigational treatments off trial, excessive delays in receiving test results, declining performance status, and lack of available tumor tissue for testing. To capture the value of mutational testing, it is critical to have an efficient screening process, provide convenient access to clinical trials, and offer treatments with a high probability of clinical benefit.

1.1 Study Rationale

Precision medicine is predicated on the notion that therapeutic strategies can be tailored to a tumor's unique molecular profile. Nonetheless, in practice most targeted therapeutic strategies provide limited clinical benefit. There are several reasons that many targeted therapies fail to provide durable disease control. First, tumor heterogeneity allows rapid outgrowth of resistant subclones (Gerlinger, Rowan et al. 2012). Second, molecular targets that are actionable in one tumor type may not be actionable in another tumor type (Kopetz, Desai et al. 2015). Finally, targeted therapies may induce feedback re-activation of upstream receptors and alternate signaling pathways (Corcoran, Ebi et al. 2012, Mao, Tian et al. 2013). To understand the drivers of sensitivity and resistance, it is critical to understand a tumor's molecular profile before therapy, during therapy, and at progression.

Access to tumor tissue hinders the ability to understand and treat the molecular drivers of resistance. In recent years, technology has emerged to identify genomic alterations from a routine blood draw. In a series of simultaneously obtained blood and tissue biopsies, concordance between circulating cell free tumor DNA (cfDNA) and tissue mutation profiles approached 90% (Kim, Lee et al. 2015, Janku, Huang et al. 2016, Sacher,

Paweletz et al. 2016). For patients with treatment refractory disease, sampling cfDNA for genomic alterations may be particularly valuable. A peripheral blood draw spares a patient an invasive tissue biopsy, and offers rapid, safe, and cost-effective genomic profiling. In addition, blood-based biopsies offer anatomically unbiased genomic profiling, allowing detection of both dominant clones and resistant sub-clones.

The use of cfDNA in treatment-refractory metastatic CRC is feasible, with tumor DNA detected in most patients (Bettegowda, Sausen et al. 2014). Among patients who have progressed on anti-EGFR therapy, cfDNA is already being used to identify molecular drivers of resistance. Some of these drivers, such as *ERBB2* amplification, are often present in original diagnostic tumor tissue, and likely represent a primary driver of EGFR resistance (Strickler, Zhang et al. 2015). Other genomic alterations, including *KRAS*, *NRAS*, *BRAF* and *EGFR* somatic mutations may emerge under the selective pressure of anti-EGFR therapy (Diaz, Williams et al. 2012, Morelli, Overman et al. 2013, Morelli, Overman et al. 2014, Arena, Bellosillo et al. 2015). Additionally, cfDNA profiling often reveals concurrent gene mutations and copy number alterations. In a case series of 56 patients with *RAS* WT/ *MET* non-amplified tumors treated with anti-EGFR therapy, 14% of patients developed *MET* amplification upon progression (Morelli, Overman et al. 2013). Of these patients with acquired *MET* amplification, half also had concurrent *RAS* mutations (Morelli, Overman et al. 2014). These results have been reproduced in an ongoing clinical trial of cabozantinib plus panitumumab (NCT02008383). Among the first 26 patients with EGFR-refractory metastatic CRC receiving cfDNA profiling, 5 patients (19%) had *MET* amplified tumors (Strickler, Zhang et al. 2015). Concurrent *BRAF* and *KRAS* somatic mutations were detected in 2 out of 5 (40%) of these patients. These results illustrate the genomic complexity of acquired resistance.

Approximately 30-40% of patients with EGFR-refractory metastatic CRC have an "actionable" molecular alteration. These actionable alterations include, but are not limited to *MET* amplification (10-15%), *EGFR* somatic mutations (10%), and *ERBB2* amplification or somatic mutations (7%). Additionally, patients with metastatic CRC may have other actionable alterations, including *FGFR* amplifications or translocations (5%), *RET* fusions (1%), and *TRK* fusion (<1%). This protocol will utilize blood-based genomic profiling to identify and treat actionable genomic alterations.

2.0 Goals

2.1 Primary

2.11 To perform blood-based genomic profiling on patients with treatment refractory metastatic CRC to facilitate accrual to molecularly assigned therapies.

2.12 To facilitate clinically annotated genomic analyses.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥ 18 years.

3.12 Histological confirmation of adenocarcinoma of the colon or rectum that is metastatic and/ or unresectable.

3.13 Progression, intolerance, or contraindication to a fluoropyrimidine (e.g., 5-fluorouracil or capecitabine), oxaliplatin, irinotecan, an anti-VEGF monoclonal antibody (bevacizumab, ziv-aflibercept, or ramucirumab), and an anti-PD-1 monoclonal antibody (nivolumab or pembrolizumab) if tumor has deficient mismatch repair proteins (dMMR) or is microsatellite instability-high (MSI-H).

3.14 For patients with *KRAS* and *NRAS* wild-type tumors, progression, intolerance, or contraindication to an anti-EGFR monoclonal antibody (cetuximab or panitumumab). Note: If tissue is known to be positive for HER2 expression (IHC 3+) or the tumor has *ERBB2* (HER2) amplification detected by a CLIA-certified assay, prior treatment with anti-EGFR therapy is not required.

3.15 At least one site of disease that is measurable by RECIST criteria (version 1.1) that has not been previously irradiated; if the patient has had previous radiation to the target lesion(s), there must be evidence of progression since the radiation (see section 11).

3.16 Life expectancy ≥3 months per estimation of investigator.

3.17 ECOG Performance Status (PS) 0, 1, or 2 (Form is available on the ACCRU web site [redacted]

3.18 Capable of understanding and complying with the protocol requirements and has signed the informed consent document.

3.19 Satisfy at least one of the following two conditions:

- Willing and able to provide blood sample for screening purposes (See Section 14.0).

- Guardant360 testing completed ≤ 60 days prior to registration is available for COLOMATE steering committee to review.

3.2 Exclusion Criteria

3.21 Evidence within the last 3 years of another malignancy which required systemic treatment. EXCEPTIONS: Non-melanotic skin cancer, carcinoma-in-situ of the cervix, or localized prostate cancer with a current PSA of < 1.0mg/dL on 2 successive evaluations, at least 90 days apart, with the most recent evaluation no more than 4 weeks prior to registration.

3.22 Unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.

3.23 History of solid organ transplantation.

3.24 Pregnant or planning to become pregnant within the next 12 months.

4.0 Test Schedule

Tests and Procedures	Active Monitoring		
	≤60 days prior to registration	Registration/ Baseline	30 Days after Registration (±3 days)
Informed Consent	X		
Demographics	X		
Medical and Cancer History	X		
Physical Examination	X		
Height	X		
Weight	X		
Vital Signs	X		
ECOG Performance Status	X		
Cell-Free DNA Analysis[1,R]		X[2]	
COLOMATE Companion Trial Recommendation Form		X[3]	
Nurse/CRA phone contact			X[4]

1 Kits are required for this collection. Please reference Section 14 for instructions. Sites will access results through the Guardant Health portal: [redacted] Sites will be notified by Guardant Health via email when results are available in the portal. Following receipt of results, sites must email the de-identified results to [redacted] See detailed instructions on the ACCRU website under Manuals and Forms.

2 If the patient has received Guardant360 testing ≤ 60 days of registration, these test results will be accepted for study and cell-free DNA analysis will not be repeated (no blood drawn at baseline). To receive test results, if not already available, the patient will fill out the Authorization to Use and Disclose Health Information form found on the ACCRU website under Manuals and Forms. Guardant will send the results to the site contacts they list on the authorization form. Sites will then email the de-identified results to [redacted] See detailed instructions on the ACCRU website under Manuals and Forms.

3 Complete top portion of COLOMATE Companion Trial Recommendation Form and email to [redacted] The COLOMATE steering committee will complete the form and send to treating physician and CRA within 5 business days of receipt of Guardant360 results. The treating physician/CRA will provide this form to the appropriate companion trial study team.

4 Nurse/CRA to call patient 30 days after the date of registration to collect status of registration to companion trial needed to complete On-Study Form.

R Research funded (see Section 19)

5.0 Grouping Factors

NONE

6.0 Registration Procedures

6.1 Initial Registration

6.11 To register a patient, access the ACCRU web page at [redacted] go to the Remote Application section, click on "Registration" and enter the registration/ randomization application. The registration application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration application are available on the above web page under the Remote Application section, "Remote Application Training."

Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted] If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.

- Refer to "Remote Registration, Installation & Entry Instructions" under "Training Material Manuals."

6.2 Subsequent Registrations

6.21 To register a patient, fax ([redacted]) a completed eligibility checklist to the Academic and Community Cancer Research United (ACCRU) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

NOTE: Patients have the option to register on COLOMATE for a maximum of 3 times or at the discretion of the Study Chair. Patients must reconsent and meet eligibility criteria in section 3 and will receive a new patient ID.

6.3 At the time of registration, the following will be recorded:

- Patient has given permission to share his/her data for future research to learn about, prevent, or treat cancer or other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has given permission for ACCRU to share his/her data to outside researchers.

6.4 Documentation of IRB approval must be on file with ACCRU before an

investigator may register any patients. Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file with ACCRU no less than annually. Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals to ACCRU is required until the study is closed through your IRB*.

*Please note, if the study site IRB determines that the study meets requirements for a minimal risk study, per the Revised Common Rule, any study approved after January 21, 2019, is not required to provide continuing/annual reviews.

6.5 Prior to accepting the registration, the registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.6 Study-specific activities cannot begin prior to registration and must begin ≤30 days after registration.

NOTE: Guardant360 testing completed ≤ 60 days prior to registration will be accepted.

6.7 Pretreatment tests/procedures (see Section 4) must be completed within the guidelines specified on the test schedule.

6.8 Study-specific activities on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

6.9 Blood draw kits are available on site.

EXEMPTION: Guardant360 tests completed ≤ 60 days prior to registration will be accepted.

7.0 Protocol Treatment

This is a screening protocol to identify genomic alterations via cfDNA and facilitate enrollment onto COLOMATE companion clinical trials. Standard genomic profiling will be performed using the Guardant360 assay in Guardant Health's CLIA-certified laboratory. Guardant360 is a commercially available cfDNA genotyping assay; the genomic results from Guardant360 may be used in conjunction with other data to guide patient care. Guardant360 is not being used as an investigational device in this study, nor is the purpose to validate its use in patient selection for study treatments.

7.1 Guardant 360 test

7.11 Patients who had Guardant360 test completed ≤60 days prior to registration.

If the patient has received Guardant 360 testing ≤60 days prior to registration, these test results will be accepted for study and cell-free DNA analysis will not be repeated.

To receive test results, if not already available, the patient will fill out the Authorization to Use and Disclose Health Information form found on the ACCRU website under Manuals and Forms that the treating physician/CRA will fax to Guardant Health.

7.12 Patients who do not have Guardant360 results or Guardant360 results completed >60 days prior to registration.

Follow section 14 to submit blood samples to Guardant Health.

7.2 Site access to Guardant360 testing results

7.21 Patients who had Guardant360 results completed ≤60 days prior to registration.

Guardant will send the results to the site contacts they list on the authorization form. Sites will then email the de-identified results (including ACCRU patient ID) to [redacted]

7.22 Patients who do not have Guardant360 results or Guardant360 results completed >60 days prior to registration.

Sites will access Guardant360 results through the Guardant Health portal: [redacted] Following receipt of results, sites must email the de-identified results (including ACCRU patient ID) to [redacted] See detailed instructions on the ACCRU website under Manuals and Forms.

7.3 COLOMATE Committee Recommendation

7.31 At the time of Guardant360 kit submission or at the time of faxing authorization form to Guardant Health, sites will complete the top portion of the COLOMATE Companion Trial Recommendation Form and email to [redacted] The COLOMATE steering committee will complete the form and send the treating physician/CRA the COLOMATE Companion Trial Recommendation form with companion trial recommendations within 5 business days of receipt of Guardant360 test results. If a patient qualifies to be screened for a companion clinical trial, the treating physician/CRA will provide this form to the appropriate companion trial study team.

COLOMATE recommendations are not binding and the local investigator and/or

treating physician may determine the preferred companion trial taking into consideration best clinical evidence and the patient's clinical circumstances.

If additional assistance with companion trial recommendations are needed, local investigators and/or treating physicians may contact the COLOMATE steering committee at [redacted]

7.32 Actionable alteration is defined as a genomic alteration/mutation profile that qualifies a patient to be screened for one companion trial.

7.4 Patients for whom 1 actionable alteration is identified

If an actionable alteration is identified, the treating physician will be notified of any available COLOMATE companion trials on the COLOMATE Companion Trial Recommendation Form.

7.41 Patients who choose to enroll in a COLOMATE companion trial and meet eligibility criteria will be treated according to that companion trial protocol.

7.42 Patients who decline participation on the COLOMATE companion trial or do not meet eligibility criteria can subsequently register with COLOMATE ≥60 days after previous registration for a maximum of 3 times or at the discretion of the Study Chair.

7.5 Patients for whom ≥2 actionable alterations are identified

If more than one actionable alteration is identified, COLOMATE companion trial recommendations will be prioritized according to the following algorithm: 1) fusions; 2) amplifications; 3) all other alterations. If the algorithm does not assign a patient to one companion clinical trial, the report will be referred to the COLOMATE PI and/or a COLOMATE steering committee designee and statistician for adjudication.

7.51 Patients who choose to enroll in a COLOMATE companion trial and meet eligibility criteria will be treated according to that companion trial protocol.

7.52 Patients who decline participation on a COLOMATE companion trial or do not meet eligibility criteria can re-register with COLOMATE ≥60 days after previous registration for maximum of 3 times or at the discretion of the Study Chair.

7.6 Patients for whom no actionable alteration is identified

If no actionable alteration is identified, the treating physician will be notified of any other COLOMATE companion trials for which the patient may be eligible on the COLOMATE Companion Trial Recommendation Form. The patient can re-register with COLOMATE ≥60 days after previous registration for maximum of 3 times or at the discretion of the Study Chair.

7.7 Evaluation procedures

7.71 Each patient will be contacted by telephone 30 days (± 3 days) after registration to document the patient's status of registration to a companion study. This

information is needed to complete the On-Study form.

8.0 Dosage Modification Based on Adverse Events

None for this screening protocol.

9.0 Ancillary Treatment/Supportive Care

None for this screening protocol.

10.0 Adverse Event (AE) Reporting and Monitoring

Adverse Events will not be collected for this screening protocol.

11.0 Treatment Evaluation Using RECIST Guideline

NONE

12.0 Descriptive Factors

12.1 Microsatellite instability (MSI)/Mismatch repair (MMR) status (MSI-H/deficient MMR vs. MSS/ proficient MMR)

12.2 KRAS (mutated vs. wildtype)

12.3 NRAS (mutated vs. wildtype)

12.4 BRAF V600E (mutated vs. wildtype vs. unknown)

12.5 Primary tumor site: Cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, rectum vs. unknown vs. multiple

13.0 Treatment/Follow–up Decision at Evaluation of Patient

This is a screening protocol and patients will not receive any treatment.

13.1 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient will go directly to off study.

- If the patient had cfDNA testing, all data up until the point of confirmation of ineligibility must be submitted

13.2 A patient is deemed a *cancel* if he/she is removed from the study for any reason other than ineligibility before any study-specific activities take place. On-study material must be submitted. No further data submission is necessary.

- If the patient never had cfDNA testing, only on-study material must be submitted

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood/Blood Products for This Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted by participating site	Baseline	Storage /shipping conditions[4]
Mandatory	Streck tube	10 mL (2)	Whole blood	X	Room temperature

NOTE: If the patient has received Guardant360 testing ≤60 days of registration, these test results will be accepted for study and cell-free DNA analysis will not be repeated; no blood drawn at baseline. To receive test results, see section 7.0.

14.2 Kits are required for this study.

14.21 In order to receive an initial kit shipment and access to the Guardant portal, fill out the Guardant Site Setup form for each treating location and email it to ACCRU at [redacted]

14.22 ACCRU will notify Guardant Health once each site is activated and will help facilitate portal access requests and the initial kit shipment. Guardant Health will provide portal access [redacted] and will ship the initial supply of kits to each site. Following the initial shipment, each site can request that kits be refreshed/replaced by completing the "Kit Reorder Form" and emailing it to Guardant Health Client Services Team at [redacted]

14.3 Shipping and Handling

14.31 Guardant360 (Streck Tube)

14.311 Complete the Test Requisition Form and barcode labels.

14.312 Ship tubes the same day as collection with properly prepared gel packs. Do not freeze gel packs. Use as is.

14.313 Place the kit into the preprinted FedEx Clinical Pak and call FedEx for a pickup to be shipped to Guardant Health.

14.314 Detailed Blood Draw and Shipping Instructions are located on the ACCRU website under Manuals and Forms.

14.4 Return of Genetic Testing Research Results

Results of CLIA-certified assays (e.g., Guardant360) are permitted to be shared with

patients and their treating physicians. The return of genetic testing research results do not apply to patients who completed Guardant360 testing outside of the COLOMATE trial.

15.0 Drug Information

Patients will be treated according to companion treatment protocol or clinical standard of care.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a screening protocol that is designed to identify patients with actionable genomic alterations and recommend them to an appropriate companion trial. A patient who has an actionable genomic profile is defined as a patient with one or more actionable alteration where the patient qualifies to be screened for a COLOMATE companion trial based on the information recorded on the COLOMATE companion trial recommendation form.

16.2 Primary Endpoints

There are two primary endpoints for this trial:

- The first primary endpoint is "actionable genomic profile" defined as a patient who received a trial recommendation per the COLOMATE companion trial recommendation form.

- The second primary endpoint is "companion trial enrollment" defined as a patient who has an actionable genomic profile that enrolls in their recommended companion trial.

16.3 Statistical Design

This is a screening protocol and is not designed to test a specific hypothesis. All analyses will be done in descriptive fashion only.

16.4 Sample Size

The total sample size of COLOMATE will be approximately 500 patients. The sample size for each individual companion trial will depend on the prevalence of the actionable genomic alterations and availability of companion trials.

For ACCRU-GI-1611, there is no formal hypothesis testing.

Given 500 patients, assume X% of patients can be assigned to a companion trial, the corresponding 95% confidence interval is shown in the table below. The sample size of 500 allows us to have good precision (i.e. confidence interval width less than 10%) in estimating the proportion of patients recommended into a companion trial.

Assumed proportion of patients can be recommended to a companion trial (X%)	Confidence interval
10%	(7.37%, 12.63%)
20%	(14.49%, 23.51%)

30%	(25.98%, 34.02%)
40%	(35.71%, 44.29%)
50%	(45.62%, 54.38%)
60%	(55.71%, 64.29%)

Assume 40% of the patients will be recommended to a companion trial (i.e. N=200) and further assume X% of patients would enrolled into the recommended trial, the corresponding 95% confidence interval is shown in the table below. With a sample size of 500 and 40% of patients recommended, we also have decent precision (i.e. confidence interval width less than 15%) in estimating the proportion of patients enrolled into the recommended trials among those recommended. Given the fact that ACCRU-GI-1611 is actively opening additional companion trials, we do not expect less than 40% of patients will be recommended to a companion trial.

Proportion of patients enrolled into the recommended companion trial (X%)	Confidence interval
5%	(1.98%, 8.02%)
10%	(5.84%, 14.16%)
15%	(10.05%, 19.95%)
20%	(14.46%, 25.54%)
25%	(19.00%, 31.00%)
30%	(23.65%, 36.35%)

16.5 Analysis Plan

16.51 Primary Endpoints

- For the analysis of the first primary endpoint, the proportion of patients who have an actionable genomic profile will be calculated. This is defined as the total number of eligible patients who have an actionable genomic profile divided by the total number of eligible patients whose genomic profile is available for COLOMATE steering committee review.

  A patient may come back to ACCRU-GI-1611 for subsequent screening (see sections 7.5, 7.5, and 7.6); therefore, a patient can contribute information to the first primary endpoint more than once.

- Our goal is to have at least 20% of patients have actionable genomic profile. The endpoint will be presented as a point estimate along with a 95% confidence interval (by Wald asymptotic confidence limit).

- For the analysis of the second primary endpoint, the proportion of patients that enroll in the companion trial recommended by the COLOMATE committee will be calculated. This is defined as the total number of eligible patients that enroll in the recommended companion trial divided by the total number of eligible patients who have an actionable genomic profile.

  A patient may come back to ACCRU-GI-1611 for subsequent screening (see sections 7.4, 7.5, and 7.6); therefore a patient can contribute information to

the second primary endpoint more than once.

- Our goal is to enroll at least 75% of patients who have an actionable genomic profile. The endpoint will be presented as a point estimate along with a 95% confidence interval (by Wald asymptotic confidence limit).

17.0 Pathology Considerations/Tissue Biospecimens

As specific future analyses are identified, this protocol may be amended and IRB approval obtained.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4)
Institutional Contacts	30 days (±3 days) after registration
On-Study	
Supporting Documentation: Baseline[1]	
Specimen Submission: Blood - Baseline (see Section 14)[2]	
Patient Status: Baseline	

1. Pathology report confirming adenocarcinoma, all available tumor molecular testing reports (KRAS, NRAS, BRAF, MSI-H, etc.), Guardant360 test results, and COLOMATE Companion Trial Recommendation Form.
2. Submit if Guardant360 (cfDNA) test is done after registration to COLOMATE.

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4)	
	At Receipt of Guardant360 Testing	At any occurrence
Consent Withdrawal[1]		X
Consent Withdrawal: Specimen Only[1]		X

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4)	
	At Receipt of Guardant360 Testing	At any occurrence
Deviation Form[1]		X
DNA Testing Dates (Internal Use Only-ACCRU Office)		X

1. Submit only if applicable.

19.0 Budget

19.1 Each site should review the test schedule (Section 4), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded:

- Guardant360 cfDNA testing at baseline

19.3 Other budget concerns: Refer to the payment synopsis for funding provided for covering any costs, as well as any additional invoiceables that may be allowed.

20.0 References

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Appendix I: ACCRU Informed Consent Template for ACCRU-GI-1611

(English Language)

***NOTES FOR LOCAL INVESTIGATORS:**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

* *These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.*

This model informed consent form has been reviewed by the ACCRU and is the official consent document for this study. Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the Academic and Community Cancer Research United (ACCRU) Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

Study Title: *COLOMATE: COlorectal Cancer Liquid BiOpsy Screening Protocol for Molecularly Assigned ThErapy*

IRB#: *{institutional IRB number}*

Principal Investigator: *{Site PI}* and Colleagues

Please read this information carefully. It tells you important things about this research study. A member of our research team will talk to you about taking part in this research study. If you have questions at any time, please ask us.

Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision.

To help you decide if you want to take part in this study, you should know:

- Taking part in this study is completely voluntary.
- You can choose not to participate.
- You are free to change your mind at any time if you choose to participate.
- Your decision won't cause any penalties or loss of benefits to which you're otherwise entitled.
- Your decision won't change the access to medical care you get at *{institution}* now or in the future if you choose not to participate or discontinue your participation.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you a copy of this form to keep. A copy of this form will be put in your medical record.

If you are signing this consent form for someone else, "you" in the consent form refers to the participant.

CONTACT INFORMATION

{Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.}

You can contact …	At …	If you have questions about …
Principal Investigator(s): **Study Team Contact:**	**Phone:** **Phone:** **Institution Name and Address:**	▪ Study tests and procedures ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints ▪ Withdrawing from the research study ▪ Materials you receive ▪ Research-related appointments
Institutional Review Board (IRB)	**Phone:** **Toll-Free:**	▪ Rights of a research participant
Research Subject Advocate (The RSA is independent of the Study Team)	**Phone:** **Toll-Free:** **E-mail:**	▪ Rights of a research participant ▪ Any research-related concerns or complaints ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information
Research Billing		▪ Billing or insurance related to this research study

Other Information:

A description of this clinical trial will be available on [redacted] as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

1. Why are you being asked to take part in this research study?

You are being asked to take part in this research study because you have adenocarcinoma of the colon or rectum that is spreading to other parts of the body and/or cannot be removed completely through surgery.

2. Why is this research study being done?

The purpose of this research study is to use a blood test to find out what mutations your cancer cells might have. We would like to use this information to see if there is a research study available that may target these mutations.

3. Information you should know

Who is Funding the Study?

This study is funded by an anonymous philanthropic donor, a foundation grant from Mayo Clinic, and by Guardant Health.

Information Regarding Conflict of Interest:

{Insert any institution- /investigator-specific financial conflict language}

Your healthcare provider may be referring you to this research study. If your healthcare provider is also an investigator on this study, there is the chance that his or her responsibilities for the study could influence his or her recommendation for your participation. If you prefer, your healthcare provider will be happy to refer you to another investigator on the research study team for you to decide if you want to participate in the study and to see you for the research study activities while you are in the study

How Many People Will Take Part in the Research Study?

About 500 people will take part in this study.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

[redacted]

You may also visit the NCI Web site at [redacted]

- For NCI's clinical trials information, go to: [redacted]
- For NCI's general information about cancer, go to [redacted]

You will get a copy of this form. If you want more information about this study, ask your study doctor.

4. How long will you be in this research study?

You will only be in this research study for the time it takes to have the research blood test drawn and for the results to come back. Your study team will contact you by phone 30 days after the date you go on study to ask you which, if any, research trial you enrolled on after receiving the recommendations given to you based on your blood test results.

5. What will happen to you while you are in this research study?

Before you begin the study:

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated.

- Demographics
- Medical and cancer history
- Physical examination
- Height
- Weight
- Vital signs
- ECOG performance status

During the study:

You will need the following test and evaluation.

- Cell-free DNA blood test (Guardant360 testing). If you have completed this blood test ≤60 days prior to this study, you can fill out an authorization form to release the results to the study team and will not need to complete this test again. Your demographic information will be collected on the form to send in the blood test and also on the authorization form to release previous results. Your demographic information will be sent to Guardant Health, Inc. and will only be used for the purposes of the Guardant360 blood test. Your demographic information will not be used to conduct this study nor will it be shared outside of Guardant Health, Inc.
- Follow-up phone call 30 days after you enroll on this study.

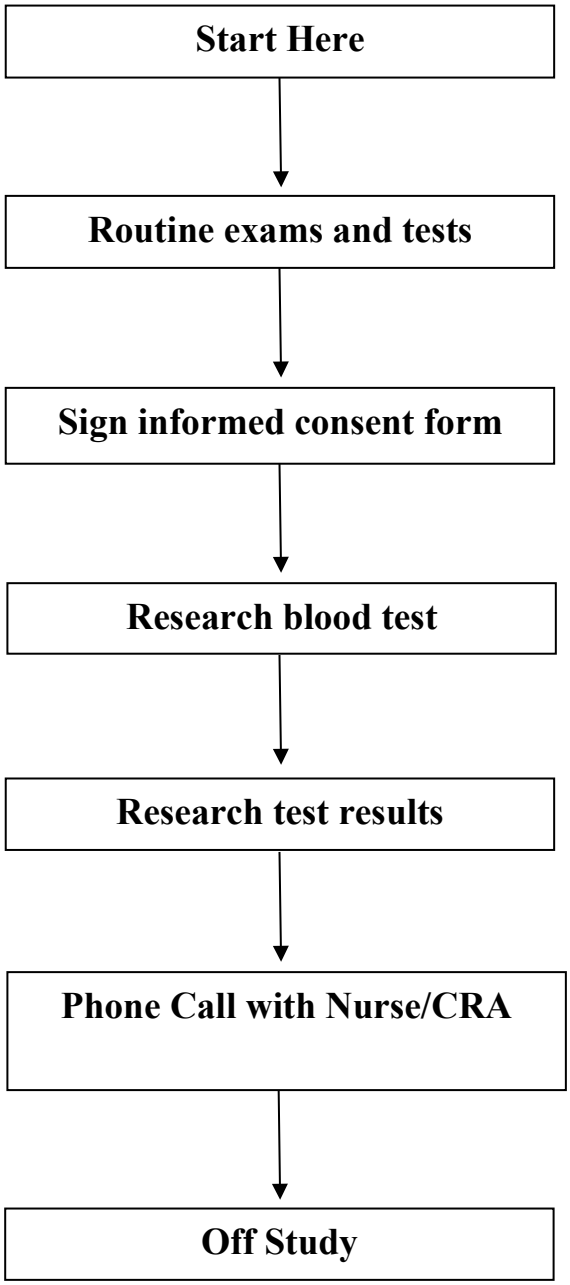
Study Chart

Day	**What you do**
Before starting study	• Get routine exams and testing
Day 1	• Sign consent
Between Day 1 and Day 30	• Get research blood test
Within 2-3 weeks	• Get blood test results and list of any available trials

30 days after starting study	• You will receive a follow-up phone call from your study team

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



Selection Process

The results of your Guardant 360 blood test will be reviewed by the COLOMATE review committee. The committee will review any mutations found by the test and provide recommendations to which companion trial you may be eligible for based on these mutations. The associated companion trials involve receiving drug regimens that target different mutations, including but not limited to, RAS wild-type, FGFR alterations, or HER 2 positive tumors. If you are found to be a match to one these trials, your treating physician will be notified and will provide your information to the appropriate companion trial study team. You will then be provided information on the trial you matched with and be provided the option to begin screening for the trial if you so choose.

6. What are the possible risks or discomforts from being in this research study?

Blood draw risk

The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.

Confidentiality risk

As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

Genetic testing risk

This study involves testing your DNA, which is the genetic information you inherited from your parents (also known as genetic testing). The risks of learning genetic test results may include emotional upset, insurance or job discrimination, and/or changes in family relationships because test results may affect other blood relatives.

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

- Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law.

Be aware that this new Federal law doesn't protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

7. Are there reasons you might leave this research study early?

Yes, you can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop.

It is important to tell the study doctor if you are thinking about stopping so any risks can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

8. What if you are injured from your participation in this research study?

Where to get help:

It is important that you tell your study doctor, *{investigator's name(s)},* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at *{telephone number}*.

Who will pay for the treatment of research related injuries?

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

9. What are the possible benefits from being in this research study?

Taking part in this study may not make your health better. However, the doctors hope that results of the research test will help identify other research trials that you might be eligible for to treat your cancer.

10. What alternative do you have if you choose not to participate in this research study?

This study is only being done to gather information. You may choose not to take part in this study.

11. What tests or procedures will you need to pay for if you take part in this research study?

You and/or your health plan/ insurance company will need to pay for some of the costs of screening for your cancer prior to enrolling in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Guardant Health is covering the cost of the research blood test.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at [redacted] coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call [redacted] and ask them to send you a free copy.

12. Will you be paid for taking part in this research study?

You will not be paid for taking part in this study.

13. What will happen to your samples?

Your samples will be used for this study to perform cell-free DNA testing. When the testing is done, any remaining sample will be kept for quality assurance but no further research testing will be performed.

If you choose to be evaluated for a research study available that may target the mutations your cancer might have, the data that we receive from the blood test results will be sent to the appropriate study team.

The data that we receive from the blood test results may be used for future research that may help people who have cancer and other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

In the future, people who do research outside of ACCRU may need to know more about your health. While ACCRU may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

The data will be used only for research and will not be sold. The research done with your data may help to develop new products in the future.

14. How will your privacy and the confidentiality of your records be protected?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The local and/or central IRB that oversees the research
- Other *{institution}* physicians involved in your clinical care
- Duke University
- Mayo Clinic
- Guardant Health
- National Cancer Center Hospital
- Yokohama City University
- National Cancer Hospital East, Japan
- University of Chicago
- Government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

{Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.}

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission.

Health information may be collected about you from:

- Past, present and future medical records
- Research procedures, including research office visits, tests, interviews and questionnaires

Why will this information be used and/or given to others?

- To do the research
- To report the results
- To see if the research was done correctly

If the results of this study are made public, information that identifies you will not be used.

Is your health information protected after it has been shared with others?

{Institution} asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside *{Institution}*, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Privacy Rights

You do not have to sign this form, but if you do not, you cannot take part in this research study.

If you cancel your permission to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

If you choose not to take part or if you withdraw from this study, it will not harm your relationship with your own doctors or with *{Institution}*.

You can cancel your permission to use or share your health information at any time by *{note instructions for canceling consent}*:

Your permission lasts until the end of this study, unless you cancel it. Because research is an ongoing process, we cannot give you an exact date when the study will end.

ENROLLMENT AND PERMISSION SIGNATURES

Your signature documents your permission to take part in this research.

	/ /	: AM/PM
Printed Name	Date	Time

Signature

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

	/ /	: AM/PM
Printed Name	Date	Time

Signature