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NCT02394769
ASPirin Intervention for the REDuction of Colorectal Cancer Risk (ASPIRED)

DF/HCC IRB Protocol #14-496
STATUS UPDATED: 14FEB2019 - CLOSED TO NEW ACCRUAL
FINAL PROTOCOL VERSION DATE: 04MAR2017

STATUS PAGE
PROTOCOL **14-496**

Closed To New Accrual

Closure Effective Date: 02/14/2019
Reason: Study Accrual Goal Met

No new subjects may be enrolled in the study- as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

NCI Protocol #: NCT02394769

DF/HCC Protocol #: 14-496

DF/HCC Biomedical Protocol Template: June 30, 2014

TITLE: ASPIRED: **ASP**irin **I**ntervention for the **RED**uction of Colorectal Cancer Risk.

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NCI-Supplied Agent(s): N/A
Other Agent: Aspirin, commercial, various manufacturers

Study Exempt from IND Requirements per 21 CFR 312.2(b). Notice of formal exemption received 11/12/14.
Protocol Type / Version # / Version Date: Amendment 11/ Version 13 / 03/24/2017

SCHEMA
Randomized Clinical Trial:

ASPIRED: ASPirin **I**ntervention for the **RED**uction of Colorectal Cancer Risk

Adults (18-80 years) who have had a colonoscopy within the last 9 months at Massachusetts General Hospital AND at least 1 adenoma was removed.

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Participants have no diagnosis of inherited colorectal cancer syndromes (i.e. FAP), no ASA use w/in last 6 months, no regular use of non-aspirin NSAIDs, no current anti-coagulant or other antiplatelet drug use, no medical contraindications, and are not pregnant/breastfeeding.

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Determine Eligibility (see phone script)

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Eligibility Confirmation
LMR review of most recent blood work, endoscopy report, and accompanying pathology report.

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Registration/Randomization by QACT (Double Blinded)
Investigating physician receives written informed consent from participant

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Initial (Baseline/Pre-treatment) Visit
1. Diet & lifestyle questionnaire; 2. Flexible sigmoidoscopy (24 biopsies of normal colorectal mucosa, one cytology brushing, stool sample) 3. Urine; 4. Blood; 5. Saliva

↓

Intervention
Duration: minimum = 8 weeks, maximum = 12 weeks
ARM A: Aspirin low-dose or
ARM B: Aspirin standard-dose or
ARM C: Placebo

↓

Final (Post-treatment) Visit
1. Diet & lifestyle questionnaire; 2. Flexible sigmoidoscopy (24 biopsies of normal colorectal mucosa, one cytology brushing, stool sample) 3. Urine; 4. Blood; 5. Saliva

↓

Primary Endpoint:
Dose-dependent Urinary PGE-M level
Secondary Endpoints: Dose-dependent effects on colorectal cancer biomarkers:
a.) Plasma MIC-1; b.) TCF7L2/TCF4 binding at the 8q24 risk locus (tissue); c.) Wnt signaling genes and 15-hydroxyprostaglandin dehydrogenase gene expression by RNA-seq (tissue); d.) Microbiome alterations (saliva & stool); e.) Spectral biomarkers (cytology brushing)

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1. OBJECTIVES

1.1 Study Design

Within the gastroenterology practice of Massachusetts General Hospital (MGH), we will conduct a prospective, double-blind, placebo-controlled, randomized clinical trial to measure the effects of daily low-dose (81 mg/day) and standard-dose (325 mg/day) aspirin on urine, plasma, stool, and tissue biomarkers associated with colorectal cancer.

1.2 Primary Objectives

To measure the effect of low-dose and standard-dose aspirin treatment on urinary prostaglandin metabolites (PGE-M).

1.3 Secondary Objectives

To measure the dose-dependent effects of aspirin on the following colorectal cancer-associated biomarkers:

- Plasma macrophage inhibitory cytokine-1 (MIC-1), an inflammatory biomarker;
- TCF7L2/TCF4 binding at the 8q24 colorectal cancer risk locus in colonic epithelium;
- Wnt signaling genes (i.e. ß-catenin, *AXIN-2* and *MYC*) and 15-hydroxyprostaglandin dehydrogenase (*15-PGDH*) gene expression as measured by RNA-seq on sorted colonic epithelial cell populations.
- Bacterial populations and products associated with colorectal cancer in saliva and stool.
- Spectral biomarkers of colorectal carcinogenesis from cytology brushings.

2. BACKGROUND

2.1 Study Disease(s)

Colorectal cancer, or cancer of the large intestine, is currently the third most common cancer in the United States. In 2014, it is estimated 136,830 individuals will be diagnosed with colorectal cancer resulting in approximately 50,000 deaths. Age is strongly associated with colorectal cancer incidence, with more than a third of all colorectal cancer deaths occurring in the population aged 80 years or older. The death rates are higher in black populations and lowest in Asian individuals. Men have a slightly higher lifetime probability of receiving a colorectal cancer diagnosis (5.0%) compared to women (4.7%).[1]

Nationally, incidence rates have been declining over the past two decades; and at a slightly higher rate over the last 10 years compared to the 1990s. This is largely believed to be due to improved access to screening methods and widespread-use of detailed surveillance guidelines. Still the public health concern remains as colorectal cancer ranks third among all cancer deaths with only an approximate 65% five-year survival rate, necessitating further advances in cancer screening and early detection.[1]

2.2 IND Agent(s)

N/A; Exempt.

This study will investigate the effects of low and standard dose aspirin. We have applied for formal exemption status from the FDA, through the Division of Oncology Products 2 (DOP2), regarding our investigational use of aspirin. In consultation with Monica L. Hughes of DOP2, the DOP2 has provided guidance that the study meets the five exemption criteria as laid out by 21 CFR 312.2:

- The study is not intended to support FDA approval of a new indication or a significant change in the product labeling.
- The study is not intended to support a significant change in the advertising for the product.
- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risk (or decreases the acceptability of the risks) associated with the use of the drug product.
- The study is conducted in compliance with institutional review board (IRB) and informed consent regulations set forth in parts 56 and 50 (21 CFR parts 56 and 50)
- The study is conducted in compliance with § 312.7 (promotion and charging for investigational drugs).

If requested by the IRB, notice of formal exemption will be provided once it is received.

2.3 Other Agent(s)

Aspirin

Aspirin (also known as Acetylsalicylic Acid, ASA, or Salicylic Acid Acetate) is an analgesic, antipyretic (fever-reducing), antirheumatic, central nervous system agent, and platelet aggregation inhibitor drug. It is highly lipid soluble and slightly soluble in water. It is a more potent inhibitor of prostaglandin synthesis and platelet aggregation than other salicylic acid derivatives. At low (81 mg/day) and standard (325 mg/day) doses, aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclooxygenase (COX) preventing the formation of thromboxane A_2, a platelet aggregating factor. At standard and high doses, aspirin also has an anti-inflammatory effect due to inhibition of inflammatory mediators via COX inhibition in peripheral tissues.

2.4 Rationale

Colorectal cancer (colorectal cancer) is the third leading cause of cancer-related deaths in the US[1], with substantial evidence supporting the use of aspirin to reduce risk of colorectal neoplasia[2-13] Nonetheless, the U.S. Preventive Services Task Force (USPSTF) recommended "against the routine use of aspirin to prevent colorectal cancer" in part due to uncertainty regarding its mode of action.[2] A greater understanding of the biological mechanism by which aspirin inhibits colorectal carcinogenesis may lead to the development of molecular biomarkers to improve risk stratification of patients for aspirin therapy. Thus, before aspirin chemoprevention can be translated into clinical

practice, there is a critical need to advance mechanistic understanding of aspirin's anti-cancer effect with the goal of identifying individuals most likely to benefit.

2.5 Correlative Studies Background

Aspirin, established to reduce the risk of cardiovascular disease events in the general population and among high-risk groups,[14] has emerged as the agent with the most consistently observed chemopreventive effect on cancer, particularly of the colorectum.[11,12] Prospective studies (including several by our group)[9,10,13,15-17] and randomized clinical trials of polyp recurrence,[3,8] hereditary colorectal cancer syndromes,[4,6] cardiovascular disease prevention,[5] and cancer as a pre-specified outcome,[7] have shown that aspirin reduces incidence of colorectal neoplasia. Recently, these benefits have been extended to other cancers in 8 randomized clinical trials.[18] Taken together with studies (including those by our group)[16] showing benefits of aspirin on overall, cancer-specific, and cardiovascular-specific mortality, there is now convincing evidence that aspirin may prevent the two leading causes of death in the U.S., thereby widening its population-wide impact.[19] A systematic review estimated that aspirin significantly reduced all-cause mortality by 6%, major cardiovascular events by 10%, and cancer death by 18%.[20] Recent work by our group and others also supports activity of aspirin against metastases and death after cancer diagnosis.[17,21-23]

Despite these benefits, aspirin is associated with hemorrhage, particularly gastrointestinal bleeding for which risk is associated with increasing age as well as dose and duration of aspirin use.[24-27] The field is now at a critical juncture to translate these findings into the clinic. Specifically, there is a high unmet need for data in humans regarding the optimal dose, and its mode of action, which may help identify individual subgroups for which aspirin use may have greater chemopreventive efficacy.[12]. These knowledge gaps have precluded clinical recommendations for use of aspirin for prevention of colorectal cancer[2] or other cancers.[28] According to a USPSTF member, "further research is required to increase our confidence in the true effects of aspirin on cancer."[29]. Moreover, a recent review emphasized the importance of "research into the mechanistic basis of efficacy of aspirin….[since] in the era of targeted therapy that is increasing health care costs, aspirin is an inexpensive and well-tolerated drug that may prove to be an effective agent."[11] Thus, this study is highly timely and significant in filling critical knowledge gaps needed to recommend wider use of aspirin for chronic disease prevention.

3. PARTICIPANT SELECTION

Patients that meet the eligibility criteria will be identified through investigators during their routine clinical practice, supplemented by a periodic query of the MGH endoscopy (Provation) and pathology database. Patients also may be identified using Natural Language Processing clinical software that queries medical records. The MGH gastroenterologist that performed the procedure or saw the patient for outpatient care as follow-up to the patient's colonoscopy procedure will be notified and asked for permission to contact their patient. We plan to recruit patients who have undergone a colonoscopy within the last nine months who are seen by an MGH gastroenterologist either in the ambulatory clinic or for an endoscopic procedure. In some cases, these physicians may not be members of the study team. However, non-study physicians will not perform study-related procedures.

Appropriate patients will be contacted by a letter (attached recruitment letter). If the colonoscopy was performed at MGH, after an adenoma is resected from a patient at MGH, all gastroenterologists routinely contact their patients by mail with the results of their pathology. The recruitment letter will be included with the pathology results when possible, or it will be sent separately after the pathology report. If the colonoscopy and polypectomy was performed, at another hospital, the MGH gastroenterologist will confirm the prior diagnosis of an adenoma through review of pathology reports. Their treating MGH gastroenterologist, regardless of whether the physician is study personnel, will sign the letter. If no response is received to this recruitment letter within two weeks (10 business days) a follow-up phone call or email will be placed by a research assistant/study coordinator (phone script/sample email attached). In some cases, the treating gastroenterologist may approach the patient following the colonoscopy that identified a polyp if he/she feels the patient would be a good candidate for the study. In these cases, the patients may not receive a recruitment letter as the primary method of contact. Instead, they will be directly contacted by phone or email (see call script/sample email) from a member of the research team prior to mailing the letter (if requested). Potential participants will have additional opportunities to ask any questions by contacting an investigator or a trained research coordinator. If the participant is interested in participating, eligibility will be assessed by the study coordinator (see script) and confirmed by the investigator through additional check of the patients medical record (see "Investigator Representation for Review of Protected Health Information Preparatory to Research" form). If eligibility is confirmed, the patient will be scheduled for their initial study visit and registered with QACT. The informed consent form will be mailed to the patient prior to the initial visit so that he or she can read it in detail, if requested by the participant. Eligible participants will provide written informed consent at the baseline visit prior to participation in the study. The consenting process will be performed by the clinical investigator who is responsible for patient care.

3.1 Eligibility Criteria

3.1.1 Underwent screening or surveillance colonoscopy with removal of at least one adenoma within the last 9 months;

3.1.2 Age 18-80 years.

This study will only include adult participants because colorectal carcinogenesis in children is more likely to be related to a cancer predisposition syndrome with distinct biological mechanisms compared with sporadic colorectal cancer in adults. Patients over age 80 will not be enrolled since the benefits and risks of a daily aspirin regimen over the age of 80 have not yet been well-characterized.

3.1.3 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)

3.1.4 Not currently taking aspirin (any dose) within the last 6 months.

3.1.5 The effects of aspirin on the developing human fetus are unknown. For this reason, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

3.1.6 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Use of any non-aspirin non-steroidal anti-inflammatory drug (NSAID) at any dose at least three times a week during the two months prior to randomization..

3.2.2 Diagnosis of inflammatory bowel disease, liver or kidney disease, bleeding diathesis

3.2.3 Any prior diagnosis of gastrointestinal cancer (including esophageal, small intestine, colon, pancreatic), or any diagnosis of other cancers (with the exception of non-melanoma skin) in which there has been any active treatment within the last three years.

3.2.4 Participants who are receiving any other investigational agents.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to aspirin.

3.2.6 Known diagnosis of Familial Adenomatous Polyposis (FAP) or Hereditary Non-Polyposis Colorectal Cancer (HNPCC, Lynch Syndrome).

3.2.7 Any adenoma that was not completely removed during previous colonoscopy.

3.2.8 History of aspirin intolerance, bleeding diathesis, peptic ulcer or gastrointestinal bleed, endoscopic complications, or contraindication to colonoscopy.

3.2.9 Inability or unwillingness to abstain from non-protocol use of aspirin or NSAIDs or to provide blood, urine, or stool samples or colon biopsies during the study.

3.2.10 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.11 Pregnant or breastfeeding.

3.2.12 Pregnant women are excluded from this study because aspirin is an FDA Category D agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with aspirin, breastfeeding should be discontinued if the mother is treated with aspirin.

3.2.13 Participant must be able to swallow pills.

3.2.14 Participant is taking any anticoagulant agent (e.g. warfarin) or antiplatelet agent (e.g. clopidogrel).

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol study drug administration begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the QACT protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Notify the QACT Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

4.3 General Guidelines for Other Investigative Sites

N/A

4.4 Registration Process for Other Investigative Sites

N/A

5. TREATMENT PLAN

5.1 Treatment Regimen

Participants who are eligible to participate in the study will be randomized to a treatment group by QACT. The investigator will contact the MGH Research Pharmacy for drug dispensation. The MGH Research Pharmacy will provide blinded aspirin capsules at 81 mg, 325 mg, or placebo in blinded capsules and assign treatment. The assigned dosage will not change over the course of the study. The first dose of the study medication will be given to patients after the initial flexible sigmoidoscopy (start of randomization). Participants will be expected to take one capsule orally at the blinded dose, once daily, until the return for their final visit (minimum 8 weeks, maximum 12 weeks). The final visit, 8-12 weeks from the baseline visit, will be scheduled during the baseline visit. The MGH Research Pharmacy will assign the participant one bottle of aspirin or placebo containing 84 blinded capsules (12 weeks, one capsule/day) and participants will return any unused capsules and the bottle to the study staff at their final visit. The bottle will be labeled with their participant ID. The participant number must be recorded on the aspirin dispensation form held by QACT and in the participants case report form (CRF). These numbers are unique to each participant and must not be re-assigned. Remaining capsules will be counted as a measure of compliance, the number recorded and then the remaining capsules will be immediately destroyed. Weekly calls will be used to monitor adherence and adverse events. Patients who initiate a NSAID or aspirin during the study will be withdrawn and an exit visit performed. The key to the unblinded treatment codes will be maintained by QACT. All personnel involved with the clinical conduct of the study will remain blinded until all participants have completed the intervention period and all biospecimens have been collected (post-treatment/final visit). The study database (InForm) will remain unfrozen until the last participant is taken “off-study” and is no longer in long-term follow-up.

Neither the participant nor the study physician will know which of the three treatments (low or standard dose of aspirin or placebo) the participant is receiving. Blinded capsules will be provided by the MGH Research Pharmacy to maintain blinding. The randomization schedule will not be

disclosed to the investigator or any personnel involved in the conduct of the study before the final participant completes the intervention period except as described below.

The investigator or treating physician may unblind a participant's treatment assignment only in the case of an emergency, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant. Whenever possible, the investigator must first discuss options with the Medical Safety Monitor before unblinding the participant's treatment assignment. If this is impractical, the investigator must notify the study physician, as soon as possible, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study. The date and reason for the unblinding must be recorded in the appropriate CRF. The data safety monitor may unblind the treatment assignment for any participant with a serious adverse event (SAE). If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to clinical investigators in accordance with local regulations.

If the blind is broken by the investigator, the participant will be permanently discontinued from the study and an Early Termination assessment will be completed. If unblinding is necessary, study staff should contact QACT to request unblinding for a participant.

5.2 Agent Administration

5.2.1 Aspirin

Blinded aspirin or placebo capsules should be taken orally once every 24 hours. The capsules should not be crushed, chewed or dissolved. The dose should be taken with food and a full glass of water. If a daily dose is missed, the dose should be skipped. A dose is considered missed if more than 24 hours has elapsed since the prior dose.

5.2.2 Other Agent(s)

N/A

5.2.3 Other Modality(ies) or Procedures

N/A

5.2.4 Investigational Imaging Agent Administration

N/A

5.3 General Concomitant Medication and Supportive Care Guidelines

During the study, participants may not consume any other non-steroidal anti-inflammatory drug (NSAID), anticoagulant (e.g. warfarin) or antiplatelet agent (e.g. clopidogrel). To assist participants with maintaining study compliance by informing patients which drugs are classified as NSAIDs, an informative index card ("NSAID List Reference") outlining generic and brand names of common NSAIDs will be given with the capsules at the baseline visit with instructions for the participants to call the study staff if there are any questions. In adults, aspirin is contraindicated for use in individuals with NSAID hypersensitivity. A case report form will capture the concurrent use of all other drugs, over-the-counter medications, or herbal supplements. A list of potential drug-drug interactions is listed in **Appendix B**.

5.4 Criteria for Taking a Participant Off Protocol Therapy

Duration of study drug administration will be at minimum 8 weeks and no more than 12 weeks from the initial visit. Duration of administration will equal the number of days between initial and final visit. Study drug administration will continue until the final visit or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of study drug
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or compliance requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Participant self-administers any additional non-study aspirin or NSAID.
- Participant begins treatment with an oral anticoagulant agent

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Andrew T. Chan at Partners pager 31100.

5.5 Duration of Follow Up

Participants will be monitored closely until they complete the study. Participants who have completed the study will be those that have returned for the final visit and returned all necessary study materials including unused capsules, pill bottle and questionnaires. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. We may contact participants routinely by phone (1-2 times annually) to follow up on additional information including any continued aspirin use and results of any follow-up colonoscopies. Periodically, we may examine their LMR to determine diagnosis of any new digestive diseases or alterations in aspirin use. In the event of an adverse event (AE, see section 7), we will follow-up with the participant within one month after the AE has resolved.

5.6 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Participant consumes a non-study aspirin or NSAID.
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or compliance requirements
- Participant begins therapy with an oral anticoagulant or anti-platelet agent
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A QACT Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the QACT website or obtained from the QACT registration staff.

6. DOSING DELAYS/DOSE MODIFICATIONS

There are no dosing delays or modifications.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

According to Micromedex, salicylic acid is widely distributed to all tissues and bodily fluids.

Highest concentrations are observed in the plasma, liver, renal cortex, heart and lungs. Early signs of salicylic overdose (salicylism) include tinnitus (ringing of the ears) and occur at plasma concentrations of 200 ug/mL with plasma concentrations over 300 ug/mL being clearly toxic. Severe toxic effects are observed at 400 ug/mL. Death may be expected at a single lethal dose of 30 g. Daily doses of either 81 mg/day or 325 mg/day yield plasma concentrations much below these levels, with 325 mg/day peak serum concentrations not exceeding 150 ug/mL.

7.1.1 Adverse Events List

7.1.1.1 Adverse Event List(s) for aspirin

As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables including dosage, concurrent use of multiple agents that alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity. Accurate estimation of frequencies is not possible.

The following adverse events have been reported for aspirin as listed in Micromedex:

- Cardiovascular: Cardiac arrhythmia, edema, hypotension, tachycardia
- Central nervous system: Agitation, cerebral edema, coma, confusion, dizziness, fatigue, headache, hyperthermia, insomnia, lethargy, nervousness, Reye's syndrome
- Dermatologic: Skin Rash, urticaria
- Endocrine & metabolic: Acidosis, dehydration, hyperglycemia, hyperkalemia, hypernatremia (buffered forms), hypoglycemia (children)
- Gastrointestinal: Gastrointestinal ulcer (6% to 31%), duodenal ulcer, dyspepsia, epigastric distress, gastritis, gastrointestinal erosion, heartburn, nausea, stomach pain, vomiting
- Genitourinary: Postpartum hemorrhage, prolonged gestation, prolonged labor, proteinuria, stillborn infant
- Hematologic & oncologic: Anemia, blood coagulation disorder, disseminated intravascular coagulation, hemolytic anemia, hemorrhage, iron deficiency anemia, prolonged prothrombin time, thrombocytopenia
- Hepatic: Hepatitis (reversible), hepatotoxicity, increased serum transaminases
- Hypersensitivity: Anaphylaxis, angioedema
- Neuromuscular & skeletal: Acetabular bone destruction, rhabdomyolysis, weakness
- Otic: Hearing loss, tinnitus

- Renal: Increased blood urea nitrogen, increased serum creatinine, interstitial nephritis, renal failure (including cases caused by rhabdomyolysis), renal insufficiency, renal papillary necrosis

- Respiratory: Asthma, bronchospasm, dyspnea, hyperventilation, laryngeal edema, noncardiogenic pulmonary edema, respiratory alkalosis, tachypnea

- Miscellaneous: Low birth weight

- Postmarketing and/or case reports: Anorectal stenosis (suppository), atrial fibrillation (toxicity), cardiac conduction disturbance (toxicity), cerebral infarction (ischemic), cholestatic jaundice, colitis, colonic ulceration, coronary artery vasospasm, delirium, esophageal obstruction, esophagitis (with esophageal ulcer), hematoma (esophageal), oral mucosa ulcer (aspirin-containing chewing gum), periorbital edema, rhinosinusitis

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above will be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators must report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.3.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
N/A					

7.4 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 Aspirin

8.1.1 Description

The systematic (IUPAC) name for aspirin is 2-acetyloxybenzoic acid. It is also known as acetylsalicylic acid (ASA) and is a salicylate drug. It is a part of the group of medications called

nonsteroidal anti-inflammatory drugs (NSAIDs). The molecular formula is C9H8O4 and the molecular weight is 180.16.

Orally administered immediate release aspirin is well and completely absorbed from the gastrointestinal tract. It is rapidly metabolized in the plasma to salicylic acid and then primarily conjugated in the liver for form salicyluric acid, a phenolic glucuronide, an acyl glucoronide. Elimination follows zero order pharmacokinetics. Salicylic acid and metabolite concentrations excreted in the urine are 10% salicylic acid, 75% salicyluric acid, 10% phenolic glucuronide, and 5% acyl glucoronide. Peak plasma concentrations occur within 1-2 hours of dosing. Half-life for elimination of the parent drug is approximately 20 minutes. For salicylates the half-life is dose-dependent with a standard-dose (300-600 mg) half-life of approximately 3 hours and high-dose (1 g) half-life of approximately 6 hours.

In adults, aspirin is contraindicated for use with ketorolac or ketorolac tromethamine (enhanced gastrointestinal adverse effects such as peptic ulcers, gastrointestinal bleeding, and/or perforation). Aspirin and NSAID use with anti-coagulants (i.e. warfarin or heparin) or selective serotonin reuptake inhibitors (SSRIs; i.e. zimeldine, fluoxetine, paroxetine, nefazodone, citalopram, clovoxamine, escitalopram, flesinoxan, femoxetine) may lead to an increased risk of bleeding. Aspirin use is cautioned in those individuals that have bleeding disorders, consume 3 or more alcoholic drinks per day, are pregnant, or are experiencing gastrointestinal symptoms (peptic ulcer disease), renal failure, or sever hepatic insufficiency.

8.1.2 Form

Aspirin is an odorless, white, need-like crystalline or powdery substance. Generic aspirin is provided as an oral tablet at 81 mg or 325 mg dose. For the study, these tablets will be crushed by the MGH research pharmacy into a powder. The powder at the appropriate dose is then placed in an appropriate size gel capsule with lactose filler. In the case of placebo, an identical size capsule filled only with lactose will be used. The capsules will be packaged in a pill bottle containing 84 capsules (12-week daily supply).

8.1.3 Storage and Stability

Aspirin can be stored at room temperature; protected from moisture. Hydrolysis of aspirin occurs upon exposure to water or moist air, resulting in salicylate and acetate, which possess a vinegar-like odor. Do not use if a strong odor is present.

8.1.4 Compatibility

N/A

8.1.5 Handling

N/A

8.1.6 Availability

Aspirin is commercially available from various manufacturers and will be supplied by the MGH Research Pharmacy free of charge to the participants.

8.1.7 Preparation

For the study, these tablets will be crushed by the MGH research pharmacy into a powder. The powder at the appropriate dose is then placed in an appropriate size gel capsule with lactose filler. In the case of placebo, an identical size capsule filled only with lactose will be used.

8.1.8 Administration

Participants will orally administer one study capsule per day. Each participant will be randomized into a dosage arm (81 mg/day, 325 mg/day, or placebo)

8.1.9 Ordering

Aspirin will be provided by the MGH Research Pharmacy and paid for with NCI research funding.

8.1.10 Accountability

The MGH Research Pharmacy will maintain careful record of the inventory and disposition of study aspirin using their protocols for drug accountability.

8.1.11 Destruction and Return

Participants will return the pill bottle with any remaining capsules at their final visit to measure daily compliance. Any remaining capsules will be destroyed immediately.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

9.1.1 Background

We hypothesize that aspirin, by reducing risk of multiple cancers and cardiovascular disease, has a favorable risk-benefit profile for most individuals and influences several neoplastic pathways which can be exploited as biomarkers of chemopreventive efficacy. The following study will provide dose-dependent effects of aspirin treatment on specific biomarkers of colorectal carcinogenesis. In doing so, we aim to provide causality for aspirin's overall risk-benefit established by other studies. We and others have put forth considerable effort to determine measurable biomarkers implicated in colorectal carcinogenesis. A discussion of these biomarkers and their significance is provided below:

9.1.1.1 Urinary PGE-M

We have previously shown that aspirin's influence on colorectal cancer is mediated at least in part through inhibition of COX-2,[15,17] which catalyzes production of prostaglandin E2 (PGE2), leading to induction of proliferation, migration, and invasiveness, promotion of angiogenesis, resistance to apoptosis, and modulation of cellular and humoral immunity. We have estimated overall prostaglandin tone by accurately measuring its major metabolite, PGE-M (11alpha-hydroxy,9,15-dioxo-2,3,4,5-tetranor-prostane-1,20-dioic acid), in urine.[30] This assay is widely accepted as the "best way to quantify systemic PGE2 production in vivo."[31] Prediagnostic levels of PGE-M are associated with risk of colorectal cancer and adenoma.[32-34] PGE-M has also been associated with gastric and breast cancer.[35-37] In the Nurses' Health Study (NHS), women in the highest quartile PGE-M had a multivariate odds ratio (OR) of 1.66 (CI, 1.04-2.66) for high-risk adenoma compared to women in the lowest.[38] Moreover, aspirin/NSAIDs was associated with a significant reduction in adenoma risk among women with high (OR, 0.61; CI, 0.43-0.87) but not low PGE-M (OR 1.05; CI, 0.50-2.19). These results support the potential for PGE-M to define subsets of the population who may obtain differential chemopreventive benefit from aspirin. Moreover, in a study of 10 individuals, two doses of 650 mg of aspirin 14 hours apart reduced PGE-M by 44%.[39] Thus, PGE-M may also serve as a biomarker to assess the effectiveness of aspirin in reducing risk of adenoma. However, randomized studies are needed to determine if aspirin at typical doses of either 81 mg/d or 325 mg/d inhibits generation of PGE-M to a level associated with low adenoma risk. Our experience in measuring PGE-M and successful execution of a four-arm randomized clinical trial to determine the dose-response relation between oral vitamin D and plasma 25(OH)D supports our ability to pursue a similar randomized clinical trial of aspirin.[40,41]

9.1.1.2 Plasma MIC-1

The circulating inflammatory cytokine macrophage inhibitory cytokine-1 (MIC-1), also known as growth differentiation factor 15 (GDF-15),[42] and placental bone morphogenetic protein (PLAB),[43] prostate derived factor (PDF),[44] may be an important mediator in the systemic inflammatory response.[45] [46] Elevated levels of MIC-1 have been associated with risk of atherosclerosis and arthritis.[46,47] MIC-1 has also been linked to cancers, including those of the prostate, thyroid, pancreas, and colon,[48,49] and recurrent adenoma.[50] Experimental evidence suggests that MIC-1, as a member of the human transforming growth factor-β (TGFβ1) superfamily, may play a specific role in carcinogenesis.[51-53] We recently reported that the multivariate relative risk (RR) for colorectal cancer was 1.93 (CI, 1.27–2.94) comparing extreme quintiles of MIC-1 (p_{trend}=0.004) and among individuals with high MIC-1, aspirin/NSAIDs are associated with a lower risk of COX-2 positive (multivariate RR=0.60; CI, 0.41-0.88) but not COX-2 negative colorectal cancer (multivariate RR=1.21; CI, 0.71–2.07).[54] Taken together, these results support the potential for plasma MIC-1 to serve as a biomarker to define subsets of the population who may obtain differential chemopreventive benefit from aspirin. Thus, randomized studies are needed to determine if aspirin (81 mg/d or 325 mg/d) specifically reduces levels of MIC-1. Our experience in measuring MIC-1 and successful execution of a randomized clinical trial of oral vitamin D that assessed the effect of treatment on inflammatory markers supports our ability to pursue a similar randomized clinical trial of aspirin.[55]

9.1.1.3 ChIP-seq in colonic epithelium, Wnt/ß-catenin

Activation of the *Wnt*/β-catenin signaling pathway plays a critical role in colon tumorigenesis.[56-58] ß-catenin is a key effector in *Wnt*-signaling since T cell factor (TCF) family members transcribe their target genes only when bound to ß-catenin. Several studies have shown that aspirin may directly suppress *Wnt* signaling through COX-independent pathways.[59-62] In addition, compelling evidence supports a critical interaction between prostaglandin pathways and *Wnt* signaling such that aspirin may inhibit *Wnt* signaling through suppression of COX-mediated synthesis of PGE2.[63-68] Although these experimental data are compelling, human studies in support of an effect of aspirin mediated through *Wnt* are limited. In a case-control study of 76 patients, aspirin or ibuprofen use was associated with decreased nuclear staining of ß-catenin and the *Wnt* target gene cyclin D1 in sporadic adenoma.[61] Consistent with these findings, we found that the benefit of regular aspirin use on colorectal cancer risk was most pronounced in individuals with T alleles of rs6983267,[69] a 8q24 colorectal cancer susceptibility SNP [70-72] that we have shown is associated with impaired ß-catenin binding to TCF4 adjacent to *MYC*.[73] In a murine model, rs6983267 influences *MYC* expression and intestinal tumorigenesis.[74] We corroborated these results by ChIP-seq showing that aspirin influenced binding of TCF4 in colorectal cancer cell lines heterozygous for rs6983267.[69] The next important step will be to determine if, *in vivo,* aspirin results in differential binding of TCF4 in regulatory sites adjacent to key cancer-associated genes such as 8q24 within colonic epithelium.

9.1.1.4 Gene expression in colonic epithelium - 15-PGDH and Wnt signaling

The synthesis of tumor-promoting prostaglandins is regulated not only by COX-2, but also by the PGE2-catabolizing enzyme hydroxyprostaglandin dehydrogenase 15-(NAD) (15-PGDH), which acts as COX-2's physiological antagonist (**Fig 1**).[75,76] This function has led to characterization of *15-PGDH* as a tumor suppressor in several human cancers, including colorectal, gastric, breast, prostate and lung.[77-87] 15-PGDH is highly expressed in normal colon and is ubiquitously downregulated in colorectal cancer.[78,81,87-90] In a mouse model, knock out of *15-PGDH* (*HGPD*) increased colonic PGE2, markedly increased colon tumor numbers, and conferred resistance to the anti-tumor effect of the COX-2 inhibitor celecoxib. In a pilot analysis of the APC Trial, low *15-PGDH* expression in normal colon mucosa was associated with lack of response of response to celecoxib for the prevention of recurrent adenomas.[88] We recently extended this finding to aspirin in the Nurse's Health Study and the Health Professionals Follow-up Study.[91] Using a validated RT-qPCR assay to quantify *15-PGDH* mRNA expression in normal colonic mucosa,[92] we found that the multivariate hazards ratio associated with aspirin use was 0.49 (CI, 0.34-0.71) among those with high *15-PGDH* within normal colon but 0.90 (CI, 0.63-1.27) among subjects with low expression of *15-PGDH* ($p_{heterogeneity}$=0.02). These results suggest that the anticancer activity of aspirin in colonic mucosa is dependent on high *15-PGDH* expression, with low levels of *15-PGDH* expression conferring resistance to aspirin's tumor preventive effects. Despite these findings, however, it is unclear if aspirin directly alters *15-PGDH* levels. A prior study showed that ß-catenin/TCF4 binds the *15-PGDH* promoter to downregulate *15-PGDH* expression.[93] This would suggest that if aspirin treatment functions through inhibition of ß-catenin/TCF4 binding, *15-PGDH* expression should also be upregulated, which would lower PGE2 levels, potentially serving as negative feedback by further weakening ß-catenin function. However, in a pilot study of 45

patients, we found that aspirin (325 mg/d) was associated with a 10% increase in colonic *15-PGDH* expression but the sample size was too small to determine statistical significance (p=.12).[92] Thus, a larger randomized treatment study is needed to determine if aspirin (81 mg/d or 325 mg/d) specifically inhibits gene expression in colonic cells associated with *Wnt* signaling pathway (*CTNNB1*, *AXIN-2* and *MYC)* and *15-PGDH.*

9.1.1.5 Nanomorphological alterations in colorectal cancer

Cell nanoscale architecture (e.g. fundamental building blocks such as ribosomes, nucleosomes, etc.) is inherently linked to biochemical and genomic processes[94-96]. The alteration of nanomorphology of nuclear chromatin is one of the earliest events in carcinogenesis and a common denominator of multiple molecular pathways. The nanomorphological alterations are a continuum of microscale nuclear atypia and chromatin clumping—also known as rough chromatin texture—that are the gold-standard histopathological markers of dysplasia and neoplasia across most cancer types including colon cancer. In comparison to the micromorphological markers of dysplasia and malignancy, nanomorphological events occur at an earlier stage of carcinogenesis, field carcinogenesis. Our collaborator, Dr. Vadim Backman, has observed the alterations in chromatin nano-architecture using transmission electron microscopy (TEM) in animal models of colon carcinogenesis (AOM-treated rat) as well as in humans. The major alterations in chromatin distribution occurred for length scales under 250 nm.[97-99] The altered chromatin was "clumped", more heterogeneous, and had an increased heterochromatin content.

Although TEM provided the first insight into the chromatin nanoscale alterations, it is not practical for clinical studies. In order to reproducibly and quantitatively study chromatin and other cellular alterations in cancer a practical and quantitative technique that would not require contrast agents is needed. Optical microscopy offers clear advantages. However, the resolution of microscopic histopathology is limited to ~200 nm. In order to assess the nanoscale, the Backman laboratory has developed partial wave spectroscopic (PWS) microscopy, which couples spectroscopy with microscopy[100]. The principles of PWS are discussed in detail in multiple publications[100-112]. PWS became the technological basis for a highly sensitive clinical test, nanocytology, which allows for the detection of nanomorphological markers of colon field carcinogenesis.[108]. PWS can also be used to measure the benefit of potential chemopreventive agents, but more studies are needed. Using PWS on rectal swabs obtained from the participants of this study, we can measure early nanocytological changes that occur in response to aspirin treatment.

9.1.1.6 Aspirin, the oral and gut microbiome, and colorectal cancer

Colorectal cancer incidence rates are rapidly rising in less-developed nations as they adopt features of a Western lifestyle such as diet[113] and altered microbial[114,115]. This rise in colorectal cancer incidence[116] implicates non-genetic factors such as diet[117-120], gene-environment interactions[121], and alterations in the microbiome and associated immune responses[122-125]. Unlike human genetic risk factors, microbial contributors to colorectal cancer risk and progression are modifiable, making their identification for risk assessment and mitigation particularly critical. There is growing recognition of the association between the oral and gut microbiota and colorectal carcinogenesis. The oral and gut microbiome plays critical roles in epithelial cell proliferation and

differentiation, intestinal immunity, nutrient processing and metabolite production, and resistance to infection by pathogenic organisms[126,127]. Although there have been few detailed studies, specific microbes may be associated with colorectal carcinogenesis[128-133]. To date, no studies have determined the biomolecular mechanisms by which oral or gut microbial activity may be altered or respond to aspirin treatment implicated in colorectal cancer risk and progression.

9.1.2 Study Design

Using our gastroenterology practice population, we will implement a prospective randomized clinical trial to measure dose-dependent effects of aspirin on urine, saliva, plasma, stool, and tissue biomarkers of colorectal carcinogenesis. At MGH, we will target 180 individuals over a three year period. Eligible patients will have had a previous colonoscopy within the last 9 months at MGH and had at least one adenoma removed during the previous procedure. Eligible patients must meet all eligibility requirements and none of the exclusion criteria as outlined in Section 3: Eligibility criteria.

9.1.2.1 Prior to the initial visit

No bowel preparation will be necessary for the procedure since the sigmoidoscope will only be advanced to the distal sigmoid colon.

9.1.2.2 Initial (baseline) Visit

At the initial visit, the study physician will obtain written, informed consent for the study as well as a standard clinical consent for a flexible sigmoidoscopy. While waiting for confirmation of registration from QACT, the participants will complete a brief lifestyle and dietary questionnaire with a study coordinator. Following confirmation of registration, patients will undergo measurements of height, weight, waist and hip circumference and provide a blood (30 mL in vaccutainer), saliva and urine specimen. If requested, patients will be able to provide urine and saliva samples while waiting for confirmation for the sake of time and participant comfort. In the event that the patient is not able to be registered by QACT, the questionnaire and any urine, or saliva specimens will be destroyed immediately. A study gastroenterologist will then perform a flexible sigmoidoscopy, advancing to the level of the distal sigmoid colon. No more than a total of 24 mucosal biopsies will be taken from the rectum and sigmoid and immediately placed in collection tubes. In the MGH GI Unit, we routinely perform endoscopic biopsies regardless of concurrent aspirin use, a practice consistent with recommended guidelines.[134] A study of the safety of multiple endoscopic biopsies in research subjects from a National Institutes of Health series found that performing large numbers of endoscopic biopsies (mean number = 38.2 ± 15.6 biopsies per procedure) are "well tolerated and appears to have no more than minimal risk without appreciably increasing the risk of otherwise routine endoscopy."[135] Furthermore, there are no statistically significant association between risk of complications and the number of biopsies, type of procedure (flexible sigmoidoscopy vs. colonoscopy), colonic location of biopsy, operator, polypectomy, or, importantly, the use of non-steroidal anti-inflammatory drugs[135]. The number of biopsies is also consistent with our existing study protocols and has never been associated with any adverse events (See: "Endoscopy Protocol: Tissue Specific Immunity Against HIV-1"; PI: Kwon, Ragon Institute). We have estimated that 24 biopsies will be necessary to complete the

proposed analyses. The ChIP-seq experiments proposed require a minimum of 500,000 epithelial cells for each sample. We estimate that from a single pinch biopsy we will recover approximately 30-50,000 epithelial cells following cell sorting. Using the most conservative estimates we would require at least 17 pinch biopsies for these ChIP-seq experiments alone. The additional biopsies will be required for RNAseq/RT-PCR experiments (i.e. 15-PGDH) as well as for validation experiments based on the results of genomic and metagenomic analyses using targeted sequencing approaches. Due to the small number of cells obtained from pinch biopsies and the input requirements for these assays, we may use tissue culture techniques to expand cell populations. This will allow us to perform these comprehensive analyses without additional burden to the participants (i.e. increasing tissue yields by using larger or more biopsies). During flexible sigmoidoscopy, stool will be aspirated through the endoscope or using a Roth net and stored in glycerol and a solution to preserve nucleic acids. Also, the gastroenterologist will collect rectal cellular material using an endoscopic cyto-brush. The gastroenterologist will find an area of the rectum, clear of any stool, and apply the cytology brush with gentle pressure across the region of interest. The brush heads will then be cut off from their plastic handle and placed immediately in a tube containing 25% ethanol and stored at -4°C. Following the visit, questionnaire data will be transferred to the Partners secure REDCap electronic database system. Also, REDCap will be used to store data from the study including endoscopy data, medical history information, sample collection, and more.

Participants will be provided with $200 (US) compensation and free parking for up to 4 hours for this initial visit. The final visit will be scheduled with the patient at his or her convenience.

9.1.2.3 Final Visit

Participants will return for a second and final visit between 8 and 12 weeks from their initial visit. An abbreviated diet and lifestyle questionnaire will be administered to update information from the baseline questionnaire. Participants will also provide blood, saliva and urine samples and undergo a second flexible sigmoidoscopy procedure with mucosal biopsies. A bowel preparation will not be necessary for the follow-up flexible sigmoidoscopy. Up to 24 mucosal biopsies will be taken, as described for the baseline visit. A rectal brushing and stool specimen will also be collected, as previously described. An abbreviated diet and lifestyle questionnaire will be administered to update information from the baseline questionnaire.

Participants will be provided with an additional $300 (US) compensation and free parking for up to 4 hours for this final visit. Total compensation will equal $500 (US) for successful completion of the study. Starting with patients who underwent their qualifying colonoscopy in March 2017, these patients will instead be provided with $200 (US) compensation and free parking for up to 4 hours for this final visit. For these participants, the total compensation will equal $400 (US) for successful completion of the study.

9.1.3 Processing of Biospecimens

Immediately following each flexible sigmoidoscopy, urine specimens will be aliquoted into 1.2

mL aliquots and blood specimens will be centrifuged into plasma and buffy coat. Stool specimens will be stored in a cryovial and immediately frozen. Saliva will be collected in specialized saliva collection tubes and immediately frozen. Saliva samples and an aliquot of stool (~200mg) will be sent in batches to the Broad Institute, for processing and analysis. Colon biopsies will be shipped to Dr. Douglas Kwon (MGH/Ragon Institute) who will supervise immediate enzymatic disaggregation of colon biopsies with collagenase to isolate mucosal mononuclear cell (MMC) single cell suspensions. MMCs will then be stained with fluorescent antibodies and sorted by fluorescent activated cell sorting (FACS). Epithelial cells that are lineage negative (CD3-, CD14-, CD56-, CD19-, CD66b-) CD326+ will be isolated by FACS and sorted directly into RLT lysis buffer. Collected cell populations will be lysed and genetic material (DNA and RNA) isolated for future ChIP-seq and RNA-seq. Yield from these procedures typically exceeds requirements for both ChIP-seq and RNA-seq. Thus, any excess colon tissue will be banked for future studies. All aliquots of stool, saliva, urine, plasma, buffy coat, and epithelial cells will be frozen at -80°C until analysis. Rectal brushings will be stored at -4°C until shipment. We may access FFPE blocks of polyps/adenomas removed during the participant's qualifying colonoscopy with accompanying pathology reports to correlate our findings with tissue-specific markers in the original adenoma.

9.1.4 Analysis of Urinary PGE-M (primary efficacy endpoint)

We will use mass spectroscopy to measure PGE-M (in single batches of pre- and post-treatment urine in the Eicasonoid core laboratory of Dr. Ginger Milne at Vanderbilt University.[30,38].

9.1.4.1 Collection of Specimens

Urine samples will be collected at both the initial and final visit.

9.1.4.2 Handling of Specimens

Samples will be placed in a refrigerator within 2 hours of collection, and transferred to -80°C within 4 days of collection. Urine will be split into 1.2 mL aliquots in eppendorf tubes prior to freezing. Samples will be stored at -80°C until analysis.

9.1.4.3 Shipping of Specimens

A 1.2 mL aliquot of each urine sample will be shipped on dry ice overnight to Dr. Ginger Milne at the following address:

Attn: Ginger L. Milne, Ph.D.
Vanderbilt University Medical Center
561 Preston Research Building
Nashville, TN 37232-6602 USA

9.1.4.4 Site Performing Study

Eicasonoid Core Laboratory (Ginger Milne), Vanderbilt University

9.1.5 Analysis of Plasma MIC-1

We will use an ELISA to measure MIC-1 (CV=8%) in a single batch of pre- and post-treatment plasma in the core clinical laboratory of Dr. Nader Rifai at Children's Hospital.[38,54]

9.1.5.1 Collection of Specimens

30 mL of whole blood will be collected at both the initial and final visit in blood vial vaccutainers.

9.1.5.2 Handling of Specimens

Upon the day of collection, blood specimens will be centrifuged into plasma and buffy coat. Whole blood will be centrifuged into plasma and buffy coat the same day as procedure. Samples will be aliquoted into 1.2 mL aliquots and frozen. Plasma samples will be stored at -80°C until analysis. For buffy coat handling, see 9.1.6.2

9.1.5.3 Shipping of Specimens

A 1.2 mL aliquot will be shipped on dry ice overnight to Dr. Nader Rifai at Children's Hospital at the following address:

Attn: Gary Bradwin
Boston Children's Hospital
300 Longwood Ave.
Farley 705
Boston, MA 02115

9.1.5.4 Site Performing Study

Core Clinical Laboratory of Dr. Nader Rifai at Children's Hospital.

9.1.6 Genotyping of Patients for rs6983267

Using methods described in Nan et al, we will genotype all trial participants for rs6983267 using DNA derived from buffy coat.

9.1.6.1 Collection of Specimens

30 mLs of whole blood will be collected at the initial and final visit. Buffy coat will be used to genotype each patient once.

9.1.6.2 Handling of Specimens

Whole blood will be centrifuged into plasma and buffy coat the same day as procedure. Buffy coat samples will be stored at -80°C until analysis. Buffy coat will be aliquoted into 500 uL aliquots

and frozen. For plasma handling, see 9.1.5.2. 500 uL of buffy coat, in batches, will be sent to the Harvard-Partners Center for Genetics Core Genotyping Service.

9.1.6.3 Shipping of Specimens

500 uL of buffy coat per patient will be delivered in person or via Fed Ex on ice to the Partners HealthCare Personalized Medicine Translational Genomics Core genotyping service at the following address:

Attn: Patrice Soule
Harvard School of Public Health
655 Huntington Ave.
Building II, Room 226
Boston, MA 02115

9.1.6.4 Site Performing Study

DNA extraction and genotyping for rs6983267 will be performed by the Partners HealthCare Personalized Medicine Translational Genomics Core.

9.1.7 ChIP-seq Analysis of Colonic Epithelium

Dr. Matthew Freedman at the Dana Farber Cancer Institute will employ a ChIP-seq protocol for TCF4 in sorted colonic epithelial cells [69,136]. All tissue samples from all cohorts will be sent, coded, to the Ragon Institute for cell sorting. Sorted cell populations will then be sent to the Dana Farber Cancer Institute. Dr. Huttenhower and Dr. Freedman will supervise analyses.

9.1.7.1 Collection of Specimens

Mucosal biopsy samples will be collected at both the initial and final visit.

9.1.7.2 Handling of Specimens

Mucosal biopsy specimens will be stored frozen and sent in batches to the Ragon Institute for cell sorting by Dr. Kwon. Sorted colonic epithelial cells will then be sent from the Ragon Institute to Dr. Matthew Freedman at DFCI.

9.1.7.3 Shipping of Specimens

Mucosal biopsy specimens will be sent on dry ice to Dr. Kwon's laboratory at the Ragon Institute:

Attn: Eric Safai
Ragon Institute of MGH, MIT and Harvard
400 Technology Square, Room 830
Cambridge, MA 02139

Sorted colonic epithelial cells will be sent on dry ice from Dr. Kwon to Dr. Matthew Freedman at DFCI.

9.1.7.4 Site Performing Study

Dr. Douglas Kwon's laboratory at the Ragon Institute will perform FACS to isolate sorted colonic epithelial cells.

Dr. Matthew Freedman's laboratory at DFCI will perform ChIP-seq analyses through the DFCI core laboratory.

9.1.8 RNA-seq Analysis of Colonic Epithelium

Dr. Freedman will also process cell lysates from aliquots of the sorted epithelial cells for RNA extraction using the RNAeasy micro kit. Total RNA will be converted into a cDNA library using Illumnia TruSeq RNA sample preparation kit followed by paired end 50 cycles sequencing on a Illumina HiSeq 2500 platform.[137] RNA/cDNA samples will be sent to Dr. Sanford Markowitz for qRT-PCR analysis. All tissue samples from all cohorts will be sent, coded, to the Ragon Institute for cell sorting. Sorted cell populations will then be sent to the Dana Farber Cancer Institute. Dr. Huttenhower, Dr. Freedman, and Dr. Markowitz will supervise analyses.

9.1.8.1 Collection of Specimens

As described in 9.1.7.1.

9.1.8.2 Handling of Specimens

As described in 9.1.7.2 For this endpoint, extracted RNA from 9.1.7 will also be sent to Dr. Markowitz at Case Western Reserve University.

9.1.8.3 Shipping of Specimens

Mucosal biopsy specimens will be sent on dry ice to Dr. Kwon at the Ragon Institute and Dr. Freedman from the Broad Institute as described in 9.1.7.3.

Extracted total RNA will be sent on dry ice overnight to Dr. Markowitz at Case Western Reserve University:

Attn: Stephen Fink
Case Comprehensive Cancer Center
Wolstein Research Building, 3-101
2103 Cornell Road
Cleveland, Ohio 44106-7285
216-368-5657

9.1.8.4 Site Performing Study

As described in 9.1.7.4 qRT-PCR assays will be carried out at Case Western Reserve University in the Markowitz laboratory.

9.1.9 Analysis of spectral biomarkers of chemoprevention

We will use PWS microscopy to measure nanocytology in pre- and post-treatment rectal tissue brushings in the laboratory of Dr. Vadim Backman at Northwestern University[108]. All samples from all cohorts, coded, will be sent to Northwestern for processing and analysis.

9.1.9.1 Collection of Specimens

Rectal cytology brushings will be taken during flexible sigmoidoscopy from a rectal region of interest that is free of any stool at both the initial and final visit. Brush heads will be clipped from their plastic handle and immediately placed in 25% ethanol and refrigerated at 4°C.

9.1.9.2 Handling of Specimens

Frozen cytology brush heads will be stored in tubes containing 25% ethanol at -4°C and shipped on dry ice to Northwestern University where rectal cells will be transferred onto a glass slide and ethanol-fixed for PWS analysis.

9.1.9.3 Shipping of Specimens

Rectal brushes will be sent every 2 weeks to Dr. Vadim Backman at Northwestern University overnight on dry ice:

Attn: Seth Feder
Biomedical Engineering Department
McCormick School of Engineering and Applied Science, Northwestern University
2145 Sheridan Rd, Room # E311
Evanston IL 60208

9.1.9.4 Site Performing Study

Laboratory of Dr. Vadim Backman at Northwestern University.

9.1.10 Microbiome analysis

We will perform a “multi’omics” analysis (16S sequencing, metagenomics, transcriptomics, see Section 13) of microbial DNA and RNA on pre- and post-treatment stool and saliva samples to examine the biomolecular mechanisms by which gut microbial activity may be altered or respond to aspirin treatment. Stool and saliva samples from all cohorts will be sent, coded, to the Broad Institute for processing and analysis.

9.1.10.1 Collection of Specimens

Stool will be collected using a Roth net or aspirated through the endoscope during flexible sigmoidoscopy at both the initial and final visit. Participants will be asked to spit into a saliva collection tube at both the initial and final visit.

9.1.10.2 Handling of Specimens

An aliquot (~200 mg) of stool will be put in tubes provided by the Broad Institute. The remaining stool will be frozen in a 15 mL conical tube at -80°C. Saliva samples will be collected and stored frozen in collection vials until analysis. The entire saliva sample and the stool aliquot will be sent to the Broad Institute for processing and analysis.

9.1.10.3 Shipping of Specimens

Stool specimens will be shipped on dry ice overnight to:

Broad Institute
Attn: BSP platform
301 Binney Street Lab 5076
Cambridge, MA 02142
617-714-8952

9.1.10.4 Site Performing Study

The Broad Institute

9.1.11 *In vitro* assessment of aspirin treatment on epithelial derived colon organoids.

We will perform parallel *in vitro* studies of aspirin treatment on organoid tissue cultures derived from untreated (baseline) and treated (follow-up) pinch biopsy specimens. By doing so, we aim to validate other *in vitro* models (CRC cell lines) of aspirin chemoprevention and/or innovate beyond these established methods. Tissue culture experiments will include exposure to aspirin and its derivatives, as well as other host environmental factors (e.g. diet-derived factors, alcohol, other medications/supplements, etc.). Genomic, transcriptomic, and proteomic assays will be used to characterize these lines and assess the effects of these exposures on cellular signaling processes. Additionally, genome-editing tools (i.e. CRISPR/Cas9) may be used to manipulate the genomic background of organoid lines to recapitulate genetic environments associated with sensitivity or resistance to aspirin treatment determined by the previously described assays.

9.1.11.1 Collection of Specimens

Pinch biopsies will be collected during the flexible sigmoidoscopy in collection media and immediately dissociated in to single crypts. Single crypts will be plated and grown into organoid cultures using methods developed by Miyoshi & Stappenback (*Nature Methods*, 2013).

9.1.11.2 Handling of Specimens

4 pinch biopsies will be collected during the flexible sigmoidoscopy in collection media and immediately dissociated in to single crypts. Single crypts will be plated and grown into organoid cultures using methods developed by Miyoshi & Stappenback (*Nature Methods*, 2013). After serial passaging and expansion, aliquots of established organoid cultures will be cryogenically frozen in liquid nitrogen and stored at MGH until needed for *in vitro* experiments. Some of these lines may be sent to established collaborators. To date, we have identified the following collaborators: Dr.

Graham Casey (University of Virginia). Any collaborator receiving stocks of cells will be sent organoid lines only after a Materials Transfer Agreement is processed. To preserve our biobank of organoid cell lines and maintain quality control, all collaborators will be instructed to return two cryopreserved vials of organoids after initial expansion at their institution.

9.1.11.3 Shipping of Specimens to Collaborators

Cryovials of organoid cultures may be shipped to the following collaborators:

Casey Lab – University of Virginia
c/o Sarah Plummer
101 Hospital Drive, Davis Wing, RM3275
Charlottesville, VA 22908
434-282-7657

9.1.11.4 Site Performing Study

Massachusetts General Hospital; University of Virginia

9.2 Laboratory Correlative Studies

N/A

9.3 Special Studies

N/A

10. STUDY CALENDAR

(Next Page)

	Initial Visit	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Final Visit[b]
Aspirin or Placebo Daily		a	a	a	a	a	a	a	a	Taken daily until final visit				Return unused aspirin
Informed consent	X													
Demographics	X													X
Lifestyle and Diet Questionnaire	X													X
Height	X													
Weight	X													
Waist & Hip Circumference	X													
Performance status	X													X
Flexible Sigmoidoscopy	X													X
Tissue Biopsy Specimens Collected	X													X
Blood Samples	X													X
Saliva Samples	X													X
Stool Samples	X													X
Urine Samples	X													X
Rectal cytology brushing	X													X
Drug Compliance Calls[c]		X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event evaluation[c]		X	X	X	X	X	X	X	X	X	X	X	X	X

a: Aspirin or Placebo: Dose and Arm as assigned, post-randomization. *See drug administration.*
b: Final visit will be scheduled during the initial visit and will occur a minimum of 8 weeks and maximum of 12 weeks after the initial visit.
c: Once weekly, participants will be contacted by phone to monitor adherence to drug administration and check for adverse events.

11. MEASUREMENT OF EFFECT

This study only uses laboratory-based endpoints to measure the effect of aspirin treatment. There are no clinically observable metrics (i.e. tumor size) that will be used as a primary endpoint or primary effect measure in this study. The primary efficacy endpoint will be levels of urinary PGE-M. A detailed discussion of this primary laboratory endpoint is included in section 9.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and perform quality checks on the data for this study.

> **Note**: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the QACT according to the schedule set by the QACT.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

N/A

13. STATISTICAL CONSIDERATIONS

This study is a randomized clinical trial that will provide measurements of dose-dependent effects of aspirin treatment on specific biomarkers of colorectal carcinogenesis. In doing so, we aim to provide causality for aspirin's overall risk-benefit established by other studies. We and others have put forth considerable effort to determine measurable biomarkers implicated in colorectal carcinogenesis. A comprehensive discussion of these biomarkers and their significance is provided in Section 9.

Because experimental models may not reflect the true biological anti-cancer activity of aspirin in humans. *In vitro* models often employ aspirin doses that are not achievable *in vivo* and cannot capture the influence of the tissue microenvironment [138]. Animal models are inherently limited in their ability to recapitulate the complexity of human colorectal cancer. Thus, this study will uniquely offer additional *human* evidence of a causal association between aspirin and carcinogenesis and biomarkers that can be used to define populations most likely to benefit.

We will recruit 180 participants who recently underwent removal of their adenomatous polyps at MGH to conduct a double blind three-arm randomized controlled trial of placebo, low-dose (81 mg/d) and standard-dose (325 mg/d) aspirin treatment for 2 months. The rationale for selection of this population is to be 1) consistent with prior randomized clinical trials of aspirin;[3]2) include patients that are more motivated to participate; 3) include patients with colonic mucosa predisposed to future neoplasia[139] The rationale for selection of our aspirin doses is that these are the most common formulations available in the U.S.

13.1 Study Design/Endpoints

The primary aim of this study is to estimate the effect of aspirin on levels of urinary PGE-M. A detailed discussion of the background of this biomarker is provided in Section 9.1.1.1. Briefly, we will determine the effect of aspirin at two doses on urinary PGE-M, compared to placebo. The rationale for selection of change in PGE-M as the primary efficacy endpoint is: 1) our experience in assaying PGE-M, which is highly stable in stored biospecimens; 2) compelling evidence from our cohort and others that PGE-M is associated with risk of colorectal cancer and adenoma;[32-34,38] 3) pilot data that aspirin directly reduces PGE-M[39] Additional endpoints will include plasma MIC-1, TCF4 binding in ChIP-seq assays of colonic epithelium, expression of genes associated with *Wnt* signaling (*CTNNB1, AXIN2* and *MYC*) and *15-PGDH* in colonic epithelium. Additional effects of aspirin on spectral biomarkers of colorectal carcinogenesis and on the oral/gut

microbiome will also be investigated. Our study design for each of these endpoints is comprehensively discussed in Section 9. Statistical considerations relating to these endpoints are provided in the following sections.

13.2 Sample Size, Accrual Rate and Study Duration

Patients will be accrued in one stage with no early stopping rules. The total sample size is 180 patients (60 per arm) and we expect accrual to be approximately 60 patients per year for 3 years. This accrual rate is based upon accruals under our existing IRB-approved protocol (Protocol # 2007P002102; Drs. Chan and Kwon, PIs) to obtain endoscopic biopsies from a cohort of healthy volunteers that consent to colonoscopy with a total of 24 mucosal biopsies for research purposes. Volunteers were reimbursed ~$500, as described here. Each patient will be followed for at minimum 8 weeks and at maximum 12 weeks. This total sample size accounts for participant drop out, as endoscopy studies typical experience a drop out rate of approximately 20%.[140].

We calculated the sample size required to detect this effect in the placebo group vs. the two aspirin groups combined. The null hypothesis is H_0: $\Delta_{aspirin} - \Delta_{placebo} = 0$ versus H_A: $\Delta_{aspirin} - \Delta_{placebo} \neq 0$, where $\Delta_{aspirin}$ and $\Delta_{placebo}$ are the mean changes in urine PGE-M level from baseline to end of treatment for the intervention and placebo groups, respectively. Based on prior studies [30,38,39] we assumed a standard deviation (SD) of 5.0 for a single measurement of PGE-M and an intra-class correlation (ICC) of 0.1. With 45 participants in the placebo group and 90 participants in the combined aspirin group, we have 90% (80%) power to detect a mean change of PGE-M level in the aspirin group of 4.0 (3.5) ng/mg, compared with no change in the placebo group, assuming a Type I error rate of 0.05. This minimum detectable difference in mean change is consistent with the difference in the median level of PGE-M among individuals at high risk for adenoma compared with low risk.[38] To account for possible drop out of participants, we conservatively plan to enroll 60 participants in each group.

Our accrual target rates for ethnic and racial minorities will likely be consistent with the rate at which we see these minorities in the gastroenterology practice at MGH. (See table on next page)

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	8	+	8	=	16
Not Hispanic or Latino	82	+	82	=	164
Ethnic Category: Total of all subjects	90	+	90	=	180
Racial Category					
American Indian or Alaskan Native	1	+	1	=	2
Asian	4	+	4	=	8
Black or African American	5	+	5	=	10
Native Hawaiian or other Pacific Islander	1	+	1	=	2
White	79	+	79	=	158
Racial Category: Total of all subjects	90	+	90	=	180

13.3 Stratification Factors

Randomization will be carried out by QACT into three arms: placebo, 81 mg/day, or 325 mg/day of aspirin, as previously described. These will be the only stratification factors in the study design.

13.4 Interim Monitoring Plan

N/A

13.5 Analysis of Primary Endpoints

Analysis of Urinary PGE-M (primary efficacy endpoint): Our primary biostatistician, Dr. Spiegelman, will supervise intent-to-treat analyses comparing the effect of each treatment on 2-month end-of-treatment change in PGE-M compared to the change in the place group, using a two-sample t-test. In secondary analyses, we will use multivariate linear regression models to adjust for other covariates in case there exists imbalances in determinants of change in PGE-M levels between arms. A robust variance estimate will be used to eliminate any normality assumptions for the residuals.

13.6 Analysis of Secondary Endpoints

Analysis of Plasma MIC-1: Our biostatistician, Dr. Spiegelman, will supervise intent-to-treat analyses comparing the effect of each treatment group on 2-month end-of-treatment change in MIC-1 using

the two-sample t test. In secondary analyses, we will determine if these changes differ according to baseline urinary PGE-M using a multivariate linear regression analysis including an interaction term of the baseline urinary PGE-M and change in MIC-1. We will also use multivariate linear regression models for the change scores to adjust for other determinants of change in MIC-1 levels in case there are imbalances between the arms

ChIP-seq Analysis of Colonic Epithelium: Dr. Freedman and Dr. Curtis Huttenhower, our computational biologist (HSPH) will lead analysis of the ChIP–seq data (>60 million reads, 50-bp paired end) using the publicly available Cistrome Analysis Pipeline.[76] Short-read sequences from ChIP-seq data will be aligned to the reference genome (hg19) using the Burrows-Wheeler Aligner to create BAM files.[141] BAM files will be uploaded to Cistrome and peak calling will be performed using an automated pipeline implementing the Model-based Analysis of ChIP-seq (MACS2) tool, which will output peak regions, peak summits, fold enrichment, *p* value, and false discovery rate (FDR < 0.01).[142] Biological replicates among cases and controls will be aggregated using the Model-based Meta-analysis of ChIP-seq data (MMChIP-seq) tool to account for batch effects.[143] Normalization and differential peak calling of ChIP-seq data between experimental conditions will be performed using MAnorm (threshold $p < 0.05$).[144] Our main analysis will quantify the differential fold enrichment at the TCF4 promoter adjacent to rs6983267 associated with aspirin. In a secondary analysis, we will assess if this binding is particularly enhanced among those with germline GT/TT rs6983267 genotypes and according to baseline PGE-M using cross-product terms for aspirin with genotype or PGE-M level and assess for significance using the Wald test.

Gene Expression Analysis of Colonic Epithelium: Dr. Freedman and Dr. Huttenhower will supervise gene expression analysis. RNA-seq sequence data (> 50 million reads) will be mapped to hg19 through use of TopHat2.[145] Cufflinks will be used to assemble the transcriptome, and Cuffdiff will be used to identify differentially expressed genes between cases and controls with a fold change of 1.2 or greater with a p-value <.05.[146] Our main analysis will examine if aspirin results in differential fold changes in expression of the *Wnt* signaling genes (ß-catenin, *AXIN-2* and *MYC*) and *15-PGDH.* In secondary analyses, we will determine if these changes differ according to baseline level of urinary PGE-M. To identify additional potential effectors of the *Wnt* signaling pathways regulated by aspirin, we will utilize the Broad Institute's publicly available gene-set enrichment analysis tools (GSEA) that contain regularly updated pathway components. We will confirm our findings for *15-PGDH* using our previously described RT-qPCR protocol in Dr. Sandy Markowitz's laboratory (Case Western Reserve).[92] [91] Briefly, RNA from colonic epithelium will undergo RT-qPCR assays for *15-PGDH* following the MIQE guidelines.[147] Villin (VIL1) and E-Cadherin (CDH1) will be used as the reference gene set for normalization using established software.[148-150] Demonstrating consistent results using RNA-seq with our validated RT-qPCR assay for 15-PGDH reported in prior studies[88,91,92] will additionally validate our findings and establish a RT-qPCR pipeline to confirm novel targets derived from RNA-seq.

Microbiome Analysis: Our collaborators at the Broad Institute will oversee 16S marker gene profiling from microbial RNA extracted from saliva and stool. Aspirin use and dose will be associated with microbial operational taxonomic units (OTUs) as quantified by 16S sequencing, using one of the microbial community biomarker discovery tests developed by the Huttenhower lab: LEfSe (LDA Effect Size), a univariate class comparison method; MaAsLin (Multivariate Analysis by Linear models), a multivariate association test analogous to Singular Value Decomposition for microbial

relative abundances; and an HAllA, a Hierarchical All-against-All association test taking into account the hierarchical structure of a community's microbial phylogeny.[151,152] We expect to find that study participants taking placebo have decreased oral and gut bacterial diversity and experience perturbations in normal microbiota composition that have been previously correlated with an increased risk for colorectal cancer compared to those receiving aspirin treatment.

To study how aspirin affects the functionality of the intestinal microbiota, we will perform metagenomic and metatranscriptomic analysis of stool specimens based on MicroPITA. Samples identified by MicroPITA Systematic integration of 16S and metagenomic sequencing will be done by PICRUSt, a computational approach to predict the functional composition of a metagenome using marker gene data and a database of ~7,000 currently-sequenced microbial genomes, as well as over 10 million metagenomically identified genes.[153,154] Then, using the MaAsLin sparse regression we will associate aspirin use with high metagenomic or metatranscriptomic enzymes. We expect that study participants taking aspirin will have increased microbial genomic richness, and a decrease in transcriptional activity and inflammatory pathways associated with colorectal cancer.

Spectral Biomarkers of Carcinogenesis: The cells collected from the cytology brushings will be utilized for the spectral biomarker (Partial Wave Spectroscopy; PWS) analysis. Since this study proposes novel biomarker analysis, a power and sample size calculations are based on detecting conservative medium size effect (Cohen's d of 0.66 expected difference between endpoint means from treated and control groups divided by expected standard deviation). To be able to detect this desired effect size, a sample size of C=45 (control) and A=45 (low dose aspirin) or sample size of C=45 (control) and B=45 (high dose aspirin) is expected to yield a statistical power of 80% using a two-sample t-test assuming a Type I error rate of 0.025 for each of the comparisons between C and A and between C and B, ensuring an overall Type I error rate of below 0.05. Since these two tests are not independent, the actual detectable standardized mean difference (i.e., mean difference between groups divided by standard deviation) will be smaller than 0.66. Therefore, a total number of 135 subjects will be sufficient for the three dose comparison studies for the spectral biomarkers before and after six month of aspirin treatment (n=45 for the study groups A, B and C). The PWS measurement (L_d) will be made in triplicates and mean$\pm$ S.E. calculated and subjected to standard Student's t test for statistical differences.

13.7 Reporting and Exclusions

Participants who never start protocol therapy or do not return for final flexible sigmoidoscopy and sample collection will be considered inevaluable and will be excluded from all analyses.

13.7.1 Evaluation of Toxicity

N/A

13.7.2 Evaluation of the Primary Efficacy Endpoint

The primary efficacy analysis will be performed on an intention-to-treat basis, with primary endpoints determined for all patients who complete the final flexible sigmoidoscopy and sample collection, regardless of whether the patient complied with study drug use.[155]

13.7.3 Evaluation of the Secondary Endpoints

The secondary endpoint analyses will be performed on an intention-to-treat basis, with secondary endpoints determined for all patients who complete the final flexible sigmoidoscopy and sample collection, regardless of whether the patient complied with study drug use.[155]

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. We plan to publish in a peer-reviewed journal; thus, the initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B POSSIBLE DRUG-DRUG INTERACTIONS WITH ASPIRIN

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Agents with Antiplatelet Properties (e.g., P2Y12 inhibitors, NSAIDs, SSRIs, etc.): May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Agents with Antiplatelet Properties (e.g., P2Y12 inhibitors, NSAIDs, SSRIs, etc.): May enhance the antiplatelet effect of other Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Ammonium Chloride: May increase the serum concentration of Salicylates. *Risk C: Monitor therapy*

Anticoagulants: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Apixaban: Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Apixaban. Specifically, the risk for bleeding may be increased. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. **Exceptions:** Bepridil [Off Market]. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. **Exceptions:** Brinzolamide; Dorzolamide. *Risk D: Consider therapy modification*

Carisoprodol: Aspirin may increase serum concentrations of the active metabolite(s) of Carisoprodol. Specifically, Meprobamate concentrations may be increased. Aspirin may decrease the serum concentration of Carisoprodol. *Risk C: Monitor therapy*

Collagenase (Systemic): Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Collagenase (Systemic). Specifically, the risk of injection site bruising and/or bleeding may be increased. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Dabigatran Etexilate: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Dabigatran Etexilate. Agents with Antiplatelet Properties may increase the serum concentration of Dabigatran Etexilate. This mechanism applies specifically to clopidogrel. Management: Increase monitoring for signs/symptoms of bleeding. The dabigatran Canadian product monograph specifically recommends avoiding concomitant use with GPIIb/IIIa inhibitors or ticlopidine, or with aspirin used for stroke prevention in atrial fibrillation. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Floctafenine: May enhance the adverse/toxic effect of Aspirin. An increased risk of bleeding may be associated with use of this combination. Floctafenine may diminish the cardioprotective effect of Aspirin. *Risk X: Avoid combination*

Ginkgo Biloba: May enhance the anticoagulant effect of Salicylates. Management: Consider alternatives to this combination of agents. Monitor for signs and symptoms of bleeding (especially intracranial bleeding) if salicylates are used in combination with ginkgo biloba. *Risk D: Consider therapy modification*

Glucosamine: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Agents with Antiplatelet Properties. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Hyaluronidase: Salicylates may diminish the therapeutic effect of Hyaluronidase. Management: Patients receiving salicylates (particularly at larger doses) may not experience the desired clinical response to standard doses of hyaluronidase. Larger doses of hyaluronidase may be required. *Risk D: Consider therapy modification*

Hypoglycemic Agents: Salicylates may enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Ibritumomab: Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Ibrutinib: May enhance the adverse/toxic effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Influenza Virus Vaccine (Live/Attenuated): May enhance the adverse/toxic effect of Salicylates. Specifically, Reye's syndrome may develop. *Risk X: Avoid combination*

Ketorolac (Nasal): May enhance the adverse/toxic effect of Aspirin. An increased risk of bleeding may be associated with use of this combination. Ketorolac (Nasal) may diminish the cardioprotective effect of Aspirin. *Risk X: Avoid combination*

Ketorolac (Systemic): May enhance the adverse/toxic effect of Aspirin. An increased risk of bleeding may be associated with use of this combination. Ketorolac (Systemic) may diminish the cardioprotective effect of Aspirin. *Risk X: Avoid combination*

Loop Diuretics: Salicylates may diminish the diuretic effect of Loop Diuretics. Loop Diuretics may increase the serum concentration of Salicylates. *Risk C: Monitor therapy*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Multivitamins/Fluoride (with ADE): May enhance the antiplatelet effect of Aspirin. Aspirin may decrease the serum concentration of Multivitamins/Fluoride (with ADE). Specifically, aspirin may decrease the absorption of ascorbic acid. *Risk C: Monitor therapy*

Multivitamins/Minerals (with ADEK, Folate, Iron): May enhance the antiplatelet effect of Aspirin. Aspirin may decrease the serum concentration of Multivitamins/Minerals (with ADEK, Folate, Iron). Specifically, aspirin may decrease absorption of ascorbic acid. *Risk C: Monitor therapy*

Multivitamins/Minerals (with AE, No Iron): May enhance the antiplatelet effect of Aspirin. Aspirin may decrease the serum concentration of Multivitamins/Minerals (with AE, No Iron). Specifically, aspirin may decrease the absorption of ascorbic acid. *Risk C: Monitor therapy*

NSAID (COX-2 Inhibitor): Aspirin may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). Management: Concurrent use of aspirin at doses beyond cardioprotective levels is not recommended. While concurrent use of low-dose aspirin with a COX-2 inhibitor is permissible, patients should be monitored closely for signs/symptoms of GI ulceration/bleeding. *Risk D: Consider therapy modification*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). *Risk D: Consider therapy modification*

Obinutuzumab: Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Obinutuzumab. Specifically, the risk of serious bleeding-related events may be increased. *Risk C: Monitor therapy*

Omacetaxine: Aspirin may enhance the adverse/toxic effect of Omacetaxine. Specifically, the risk for bleeding-related events may be increased. Management: Avoid concurrent use of aspirin with omacetaxine in patients with a platelet count of less than 50,000/uL. *Risk X: Avoid combination*

Omega-3 Fatty Acids: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Agents with Antiplatelet Properties. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Pentoxifylline: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Potassium Acid Phosphate: May increase the serum concentration of Salicylates. *Risk C: Monitor therapy*

PRALAtrexate: Salicylates may increase the serum concentration of PRALAtrexate. Salicylate doses used for prophylaxis of cardiovascular events are unlikely to be of concern. *Risk D: Consider therapy modification*

Probenecid: Salicylates may diminish the therapeutic effect of Probenecid. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Rivaroxaban: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Rivaroxaban. Management: Avoid concurrent use of antiplatelet medications with rivaroxaban unless the anticipated benefits outweigh the risks of bleeding. *Risk D: Consider therapy modification*

Salicylates: Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Thrombolytic Agents: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Ticagrelor: Aspirin may enhance the antiplatelet effect of Ticagrelor. Aspirin may diminish the therapeutic effect of Ticagrelor. More specifically, the benefits of ticagrelor relative to clopidogrel may be diminished in patients receiving daily aspirin doses greater than 100-150 mg daily. Management: Avoid daily aspirin doses greater than 100 mg in patients receiving ticagrelor. Canadian recommendations are to avoid daily aspirin doses greater than 150 mg. Daily low-dose aspirin (U.S.: 75-100 mg; Canada: 75-150 mg) is recommended. *Risk D: Consider therapy modification*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tipranavir: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Urokinase: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Urokinase. *Risk X: Avoid combination*

Valproic Acid and Derivatives: Salicylates may increase the serum concentration of Valproic Acid and Derivatives. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin E: May enhance the antiplatelet effect of Agents with Antiplatelet Properties. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

ASPIRED – Invitation / Eligibility Review Phone Call Script

FOR COORDINATOR INITIATED CALLS:

Before calling the patient look them up in LMR – Check eligibility using inclusion/exclusion checklist and note any questions you need to ask regarding eligibility. If they are not eligible, STOP do not contact the patient.

Hello my name is (caller name), is this (participant name)?

IF THE PATIENT IS NOT HOME AND SOMEONE ELSE ANSWERS:

Tell them you will call back later or leave a message with your name and phone number if the offer to take one. DO NOT MENTION DFCI OR MGH OR THEIR MEDICAL CARE WHEN TALKING TO ANYONE BUT THE PATIENT. If they ask what the call is in reference to just say "*I'm calling about a study that they are interested in hearing about.*" If they keep pressing say you are "*Sorry but it is a confidential study and you can not give them anymore information*".

IF NO ONE ANSWERS:

Leave a message on the answering machine or voicemail with your name and phone number saying: "*Hello, this message is for (participant's name). My name is (caller name) and I am contacting you about a research study that you may be interested in. I will call back another time or you can call me at (caller number) between (available hours and days). Thank you."*

IF YES:

I am calling today because I would like to talk to you about the study titled "ASPIRED: ASPirin Intervention for the REDuction of Colorectal Cancer Risk" being conducted at Massachusetts General Hospital as a part of the Dana Farber/Harvard Cancer Center. You might have received a letter regarding this study from Dr. (doctor's name). Is this a good time for you to talk? The call should take about ten minutes.

IF NO:

When would be a better time to call you? **Note the preferred contact time and number.**

IF YES **-OR- IF PARTICIPANT INITIATED PHONE CALL, START HERE**

The letter sent by Dr. (doctor's name) provides a detailed overview of our research study, but briefly, the ASPIRED study is funded by the National Cancer Institute and is a cancer prevention study to investigate the mechanism by which aspirin, an over-the-counter NSAID or Non-steroidal anti-inflammatory drug commonly used for pain and fever relief, can prevent colon cancer. We plan to evaluate the effect of aspirin in reducing markers of individual risk for colon cancer development. Before we discuss more details about what the study involves, I would like to ask you a few questions to confirm you are eligible for

the study. Then if you are eligible, I will explain the study in more detail and then you can decide if you are interested in participating. Feel free to interrupt me at any point in the next few minutes with any questions you might have, or if you do not fully understand a question. Are you ready to begin?

REVIEW THE ELIGIBILIGY CHECK LIST WITH THE PARTICIPANT; be sure to ask any questions regarding eligibility status picked up from pre-screening medical records.

IF PATIENT IS INELIGIBLE:

"Sorry, but it appears as if you are not eligible for this particular study." Thank them for their time and, if they initiated the call, their interest in the study.

IF PATIENT IS ELIGIBLE:

Great it appears you are eligible for this study. Please understand that participation in this study is completely voluntary and if you decide not to participate it will not affect your medical care in any way. The letter sent by Dr. (doctor's name) provides an overview of what your participation would entail. Have you had a chance to read the letter?

IF NO, OR IF THEY ONLY LOOKED AT IT BRIEFLY:

That's ok I'll provide you with an overview of the study now. You are invited to take part in a randomized clinical trial, because you have previously undergone a colonoscopy at Massachusetts General Hospital and had an adenoma removed during this procedure. This research study is a chemoprevention clinical trial, where we are investigating the use of aspirin as a potential chemopreventive agent to reduce the risk of colorectal cancer.

If you agree to participate in this study, your role would be to provide samples of your blood, urine, saliva and fill out a brief dietary and lifestyle questionnaire. Participation also involves biopsy and stool collection during two separate flexible sigmoidoscopies. A flexible sigmoidoscopy is an abbreviated endoscopic procedure where only the lowest parts of your colon including the rectum are screened using the endoscope. Because of this you will not need to undergo a bowel preparation routine as you may have done for your previous colonoscopy. We will collect these samples at an initial flexible sigmoidoscopy that you will schedule with Dr. (doctor's name) at your earliest convenience. After this visit you will be randomized into one of three different groups: aspirin at low or standard dose or a non-drug placebo. You will receive a twelve-week supply of blinded drug capsules, meaning neither you, nor your doctor will know if you are receiving aspirin or placebo. As a part of the study, you will be responsible for taking one capsule daily until your second flexible sigmoidoscopy. At your initial visit you will schedule your second and final flexible sigmoidoscopy with Dr. (doctor's name) between 8 and 12 weeks later. During the second flexible sigmoidoscopy visit we will again collect blood, urine, saliva, stool, and biopsy samples. Again you will not need to undergo a bowel preparation routine. Your

participation in this study will help us understand the actions by which aspirin may prevent colorectal cancer.

IF YES:

If you agree to participate in this study, we will put you in contact with Dr. (doctor's name)'s assistant to schedule your initial study visit. As you have read in the letter, during your initial visit Dr. (doctor's name) will perform a flexible sigmoidoscopy, during which we will collect biopsies and a stool specimen. You will also need to provide a urine, blood, and saliva sample and complete a brief diet and lifestyle questionnaire. You will then be randomized to receive either low or standard dose aspirin or a placebo daily. You will take a blinded capsule daily until your second and final visit, which you will schedule with Dr. (doctor's name) during your initial visit for between 8 and 12 weeks after your initial visit. The flexible sigmoidoscopy will be repeated at the final visit and we will again collect urine, blood, saliva, stool and biopsy samples.

ASK FOR PARTICIPATION

Given this information, would you like to participate in the study?

IF NO:

If you have a moment, I would like to document the reason or reasons that you do not want to participate. This will help our research team in the design of future studies. I am going to read you a list of options, and you can respond yes or no to any or all of them.

-Participating in this study will take too much time
-The procedures for this study seem too complicated
-I am worried about the confidentiality of the results
-I don't feel comfortable giving biopsies
-I don't feel comfortable giving blood, urine, or saliva

Are there any other reasons that you don't want to participate?

Thank you for your time and have a nice day!

If YES:

In order to enroll you in the study, I'd like to provide you more details about the study and answer any questions you may have. Again, please feel free to interrupt me at any point in the next few minutes with any questions you might have, or if you do not fully understand a detail of the study. Are you ready to begin?

DETAILS OF CONSENT FORM

First and foremost, your participation in the study is voluntary. You can withdraw your participation from this study at any time. We hope to enroll 180 participants in this study, all of whom will be recruited from Massachusetts General Hospital.

The anticipated duration of the study is at least 8 weeks and no more than 12 weeks. Your time on the study will depend on when you and your doctor are able to schedule your follow up flexible sigmoidoscopy. We expect that these visits will last between 2 and 4 hours each.

Your initial visit will begin with a meeting with your physician include time for you to review the consent documents with your physician. Only after you provide written informed consent to participate in this study will any study procedures be completed. If you consent to participate, you will fill out a lifestyle and diet questionnaire with one of our research staff. Prior to the flexible sigmoidoscopy, you will be asked to provide a saliva, urine, and blood sample. During the flexible sigmoidoscopy, we will collect up to 24 tissue biopsies, take a brushing sample of colon tissue, and collect a stool sample. You will not need to undergo a bowel preparation procedure. Following the procedure, you will schedule your follow-up flexible sigmoidoscopy for 8-12 weeks later with your physician before you leave. You will also be provided with a bottle of blinded placebo or aspirin capsules. We will contact you weekly to ensure you take these capsules as directed. For completing this initial visit you will receive $200 (US) in compensation and up to 4 hours of free parking to be used the day of your visit.

At your final visit, we will again collect blood, saliva, urine and you will undergo an identical flexible sigmoidoscopy procedure. We will administer a second diet and lifestyle questionnaire. You will return any unused medication to the study staff at this visit. You will be compensated $200 (US) for completing this visit and receive up to 4 hours of free parking to be used the day of your visit.

To protect your privacy, all of your samples will be labeled with an alias identification number. Coded samples and/or data may be sent by MGH/DFHCC to other researchers who are also studying aspirin chemoprevention and/or collaborating with the MGH/DFHCC including but not limited to the National Institutes of Health, the Ragon Institute, the Dana Farber Cancer Institute, Children's Hospital, Vanderbilt University, the Broad Institute, Northwestern University, and the Harvard School of Public Health. Affiliated researchers or laboratories outside of MGH/DFHCC will never know who you are nor have access to the code linking the samples to you.

We believe that the risks involved in participating in this study are low. The risk of taking biopsies (1/8 of an inch samples from the lining of your colon) is very low. Among the over 10,000 colonoscopies in which a biopsy was performed over the last seven years at Massachusetts General Hospital, only two medically important problems occurred as a result of the biopsy. One patient experienced bleeding from a biopsy that led to hospitalization. A second patient experienced

less than 24 hours of fever and abdominal pain that did not require hospitalization. In addition, many patients like yourself, will have biopsies during their colonoscopy as part of routine care. Other possible risks and side effects include skin irritation from inadvertently coming in contact with preservatives in the specimen collection materials, breach of confidentiality involving your protected health information, and that information about taking part in a genetic study could influence insurance companies or employers regarding your health.

There are no direct benefits from participating in this sub-study. However, your participation will help our team gather valuable information on aspirin's chemopreventive mechanism of action. This study may help identify individuals in the future who would likely benefit from aspirin treatment in the prevention of colon cancer.

Do you have any further questions?

Thank you so much for your time and interest in our study. We look forward for your participation

Thanks again and have a nice day!

MASSACHUSETTS GENERAL HOSPITAL

ASPIRED: **ASP**irin **I**ntervention for the **RED**uction of Colorectal Cancer Risk

>Date<

>Patient Name
>Address
>City State

Dear Mr. /Ms. Patient,

I am writing to tell you about a research study we are conducting at Massachusetts General Hospital that is being led by our physicians in the Gastrointestinal Unit. I am letting my adult patients who have had an adenoma removed during their last colonoscopy know about this research project, in case they would like to participate.

We are studying the mechanism by which aspirin may prevent colorectal cancer. A growing body of evidence suggests that aspirin, a non-steroidal anti-inflammatory drug (NSAID) commonly used for fever and pain relief, may act to reduce the risk of colorectal cancer in some people. The risk of developing colorectal cancer over your lifetime varies between individuals due to a number of different dietary and lifestyle factors. This implies that there are a number of biological differences between individuals who may respond to aspirin as a chemopreventive (a drug regimen designed to reduce the risk of developing cancer) measure. Our research project is designed to measure the effect aspirin has on certain biological mechanisms that have been demonstrated to be associated with colorectal cancer risk in a randomized clinical trial setting. This study may help researchers identify individuals who would benefit from an aspirin chemopreventive treatment.

We would like to include individuals such as you who have recently had a colonoscopy during which an adenoma was removed. Participation would involve coming to MGH for two study visits spaced 8-12 weeks apart. Participation includes filling out a dietary and lifestyle questionnaire and the collection of a blood, saliva, and urine sample at both visits. You also will undergo a flexible sigmoidoscopy, an abbreviated endoscopic approach that advances only to the lowest parts of the colon and rectum, during which we will collect a stool sample, a cytological brushing and tissue biopsies at both visits. You will not need to undergo a bowel preparation regimen, as you may have had to do in the past with other endoscopic procedures. Participants will be randomly selected to receive either aspirin (low or standard dose) or placebo in double-blinded capsules, meaning neither you nor any of the research staff will know if your capsules contain aspirin or placebo. Starting at your first visit, you will take one blinded capsule daily until your second and final visit, which you will schedule with your physician during initial appointment.

Please note that **you do not have to participate in this study**. You should feel no obligation to participate in this research study and whether you participate or not will have no effect on your current standard of care.

There is no cost to joining this study. You will be compensated a total of $400 (US) for participating in this trial: $200 (US) after your initial visit, and the remainder, $200 (US) after the completion of your final visit. You will also be provided with 4 hours of free parking at each of your study visits.

You may or may not receive any personal health benefits as a result of your participation in this research study. However, we hope that the results will help us understand how aspirin acts to prevent colorectal cancer and who may benefit from aspirin treatment in the future.

Please contact our study coordinators Jennifer Mackinnon Krems at 617-724-1326 or Dylan Zerjav at 617-726-4807 M-F 9AM-5PM if you would like to learn more about the study. Your participation is voluntary. If you definitely do not want to participate or be contacted about the study, please inform our study coordinator by calling the phone number mentioned above. If we do not hear from you within 2 weeks, we may phone you to see if you might wish to hear more about the study.

Thank you in advance for considering this request

Sincerely,

Signature of Physician-Investigator (←delete)
>Printed Name of Physician
>Physician Title
>Physician Department
Massachusetts General Hospital

Study ID#: | | | | | Initials: | | |

Date: M M / D D / Y Y Y Y

ASPIRED: ASPirin Intervention for the REDuction of Colorectal Cancer Risk
Patient Registry Questionnaire

Baseline Visit

GENERAL INFORMATION

The information in this section is used only to help us better describe the general demographics of our patients. It will have no direct bearing on patient care.

Where were you born?

City State Country

Current Marital status: ○Married ○Never married ○Widowed ○Separated ○Divorced

Are you of Spanish/ Hispanic origin? ○ Yes ○ No ○ Unknown

You may choose more than one race (see below):
☐ White/Caucasian
☐ Black/African-American
☐ American Indian/Alaskan Native
☐ Native Hawaiian or other Pacific Islander
☐ Asian

American Indian or Alaskan Native	Have origins in any of the original peoples of North and South America (including Central America) and maintain tribal affiliation or community attachment
Asian	Have origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam
Black or African American	Have origins in any of the original peoples of Africa: includes Haitian
Native Hawaiian or Other Pacific Islander	Have origins in any of the original peoples of Hawaii, Guam, Somoa, or other Pacific Islander
White	Have origins in any of the original peoples of Europe, the Middle East or North Africa

What is your parent's ethnic background (please describe it in terms other than "American")?
By Ethnic Background we mean: Polish, German, etc.

Mother:

Father:

PERSONAL MEDICAL HISTORY

Have you ever been diagnosed with cancer? ○ Yes ○ No

If Yes, in what year were you diagnosed? _____ (year)

If Yes, what was your diagnosis: _____

Did you undergo treatment for your cancer? ○ Yes ○ No

If Yes, when was your last treatment? _____(month,year)

In the space below, please describe the nature of your treatment (i.e. surgery, chemotherapy [if you know drug names please provide], radiation):

Have you ever had a heart attack? ○ Yes ○ No

Have you ever been treated for heart failure? (you may have been short of breath or the doctor may have told you that you had fluid in your lungs or that your heart was not pumping.) ○ Yes ○ No

Have you ever had an operation to unclog or bypass the arteries in your legs?	O Yes	O No
Have you had a stroke, cerebrovascular accident, blood clot or bleeding in the brain, or transient ischemic attack (TIA)?	O Yes	O No
If yes, do you have difficulty moving an arm or leg as a result of a stroke or a cerebrovascular accident?	O Yes	O No
Do you have asthma, emphysema, chronic bronchitis or chronic obstructive lung disease?	O Yes	O No
If yes, do you take medication for your condition (either regular basis or for flare-ups)?	O Yes	O No
Do you have rheumatoid arthritis?	O Yes	O No
If yes, do you take medications for it regularly?	O Yes	O No
Do you have lupus (systemic lupus erythematosus) or polymyalgia rheumatica?	O Yes	O No
Have you ever been told you had a Helicobacter pylori or H. pylori infection by blood test or an endoscopy? (This is the bacteria that causes stomach ulcers)	O Yes	O No
If yes, were you treated for Helicobacter pylori?	O Yes	O No
Have you ever had problems with your kidneys?	O Yes	O No
If yes, have you had poor kidney function with blood tests showing high creatinine levels?	O Yes	O No
Have you used hemodialysis or peritoneal dialysis?	O Yes	O No
Have you received a kidney transplant?	O Yes	O No
Do you have any of the following conditions:		
Alzheimer's Disease or another form of dementia?	O Yes	O No
Cirrhosis of the liver?	O Yes	O No
HIV/AIDS? (This question is optional.)	O Yes	O No
Do you have Type I Diabetes (also known as juvenile diabetes)?	O Yes	O No
Do you have Type II Diabetes (also known as adult onset diabetes)?	O Yes	O No
If yes to either, answer all of the following five questions:		
Is it treated by modifying your diet?	O Yes	O No
Is it treated by medications taken by mouth?	O Yes	O No
Is it treated by insulin injections?	O Yes	O No
Has your diabetes caused problems with your kidneys or problems with your eyes treated by an ophthalmologist?	O Yes	O No
When were you first diagnosed with diabetes?	_____	month/year

Have you ever had radiation treatments for any reason other than cancer? ○ Yes ○ No

If Yes, why did you get radiation and to which body part? _____

_____

When? _____ month/year

If you are female, at what age did you start menstruation? _____ Age

Check which applies:
○ Pre-menopausal – Still menstruating.
○ Peri-menopausal – Has been less than 1 year since I stopped menstruating
○ Post-menopausal – Has been more than 1 year since I stopped menstruating

Please list any other surgeries or operations you have had on your abdomen or gastrointestinal tract – this includes an appendectomy (removal of appendix) or a cholecystectomy (removal of gallbladder).

Type of surgery or operation	Date (Month/Year)

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IMMUNE MEDIATED DISEASES

Have you ever been told by a physician that you have any immune diseases?

☐ none ☐ other: _____

☐ Alopecia areata
☐ Ankylosing spondylitis
☐ Arthritis (uncertain diagnosis)
☐ Autoimmune hemolytic anemia
☐ Autoimmune hepatitis
☐ Bechet's syndrome
☐ Celiac Disease
☐ Dermatitis herpetiformis
☐ Familial Mediterranean fever
☐ Grave's disease
☐ Guillian-Barre Syndrome
☐ Hashimoto's thyroditis
☐ Idiopathic pulmonary fibrosis
☐ Idiopathic thrombocytopenia purpura
☐ Microscopic Colitis (collagenous or lymphocytic)
☐ Myocarditis
☐ Neuropathy
☐ Pemphigus vulgaris
☐ Pernicious anemia
☐ Polymyositis / dermatomyosis
☐ Primary biliary cirrhosis
☐ PSC
☐ Psoriasis
☐ Sarcoidosis
☐ Scleroderma
☐ Sjogren's syndrome
☐ Systemic lupus
☐ Vitiligo

ORAL HEALTH

The last time you saw a dentist (generalist, prosthodontist, periodontist, etc.) was within the past:
Month ☐ 6 months ☐ Year ☐ Two years ☐ More than 2 years ☐

The last time you had a professional dental cleaning (dentist, hygenist, etc.) was within the past:
Month ☐ 6 months ☐ Year ☐ Two years ☐ More than 2 years ☐

How often do you use the following oral hygiene products (Check one frequency box for each product):

	Never	Rarely	1-5/ week	Daily	More than 1/day
Manual toothbrush	☐	☐	☐	☐	☐
Electric toothbrush	☐	☐	☐	☐	☐
Alcohol-based mouthwash	☐	☐	☐	☐	☐
Non-alcoholic mouthwash	☐	☐	☐	☐	☐
Floss	☐	☐	☐	☐	☐
Water-based pick/jet	☐	☐	☐	☐	☐
Tongue cleaner	☐	☐	☐	☐	☐
Tooth-whiteners	☐	☐	☐	☐	☐

If you wear dentures, how often do you clean them?
Don't own ☐ Rarely ☐ 1-5 times a week ☐ Daily ☐ More than daily ☐

MEDICATIONS: ASPIRIN

Did you ever take "BABY" or low dose aspirin (162 mg or less)?

- includes Bufferin, Bayer Aspirin, ASA, Acetylsalicylic Acid, Alka Seltzer (Do NOT include aspirin-free products such as Tylenol or acetaminophen).

○ Yes, regularly (≥2 tablets/week)
○ Yes, but intermittently (>1 tablet/month but less than 2 tablets/week)
○ No

If you answered yes to <u>regular use</u> (≥2 tablets/week) of <u>BABY aspirin</u>, please answer these additional questions:

When you regularly used BABY aspirin, how many

Days per week did you typically use:
☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+ days → Tablets per week did you typically use:
☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+ tablets

When did you first start using BABY aspirin? _____month/year

When did you stop using BABY aspirin? _____month/year

For how many years did you use BABY aspirin? Please add up all different periods. ☐ Years (can be approximate)

Why did you use BABY aspirin regularly (please choose all that apply)?
☐ Prevention of heart attacks or stroke ☐ Prevention of cancer ☐ Prevention of other diseases
☐ Headaches ☐ Joint aches or arthritis ☐ Back pain
☐ Menstrual cramps ☐ Other: _____

Did you ever take STANDARD/ADULT aspirin (325mg or more/tablet) or aspirin-containing products?

- includes Bufferin, Bayer's Aspirin, ASA, Acetylsalicylic Acid, Alka Seltzer (Do NOT include aspirin-free products such as Tylenol or acetaminophen).

○ Yes, regularly (≥2 tablets/week)
○ Yes, but intermittently (>1 tablet/month but less than 2 tablets/week)
○ No

If you answered yes to <u>regular use</u> (≥ 2 tablets/week) of <u>STANDARD aspirin</u>, please answer these additional questions:

When you regularly used STANDARD aspirin, how many

Days per week did you typically use:
☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+ days → Tablets per week did you typically use:
☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+ tablets

When did you first start using STANDARD aspirin? _____month/year

When did you stop using STANDARD aspirin? _____month/year

For how many years did you use STANDARD aspirin? Please add up all different periods. ☐ Years (can be approximate)

Why did you use STANDARD aspirin regularly (please choose all that apply)?
☐ Prevention of heart attacks or stroke ☐ Prevention of cancer ☐ Prevention of other diseases
☐ Headaches ☐ Joint aches or arthritis ☐ Back pain
☐ Menstrual cramps ☐ Other: _____

MEDICATIONS: NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Did you ever take Non-Steroidal Anti-inflammatory Drugs (NSAIDS)?
- includes Ibuprofen, Advil, Motrin, Aleve, Nuprin, Naprosyn, Naproxen, Indomethacin, Sulindac, Clinoril, Piroxicam, Feldene, Celecoxib, Celebrex, Relafen, Indocin, Ketoprofen
(Do NOT include aspirin-free products such as Tylenol/acetaminophen).

- ○ Yes, regularly (≥2 tablets/week)
- ○ Yes, but intermittently (>1 tablet/month but less than 2 tablets/week)
- ○ No

Which NSAID(s) have you taken at least 2 times per month? (check all that apply)

- ☐ Ibuprofen (Advil, Motrin, Nuprin, etc.)
- ☐ Celecoxib (Celebrex)
- ☐ Sulindac (Clinoril)
- ☐ Naproxen (Aleve, Naprosyn)
- ☐ Indocin (Indomethacin)
- ☐ Other(s) _____

If you answered yes to <u>regular use</u> (≥ 2 tablets/week) of <u>NSAIDS</u>, please answer these additional questions:

When you regularly used NSAIDS, how many

Days per week did you typically use:
☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+ days

Tablets per week did you typically use:
☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+ tablets

When did you first start using NSAIDS? _____month/year

When did you stop using NSAIDS? _____month/year

For how many years did you use NSAIDS? Please add up all different periods. ☐ Years (can be approximate)

Why did you use NSAIDS regularly (please choose all that apply)?

- ☐ Prevention of heart attacks or stroke
- ☐ Prevention of cancer
- ☐ Prevention of other diseases
- ☐ Headaches
- ☐ Joint aches or arthritis
- ☐ Back pain
- ☐ Menstrual cramps
- ☐ Other: _____

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MEDICATIONS: GASTROINTESTINAL HEALTH

Please note that all questions in this section pertaining to regular use of a medication define regular use as greater than twice per week

Have you used or do you use Antacids?
-Maalox, Rolaids, Mylanta, TUMS, etc.

- O Yes, currently and regularly
- O Yes, regularly but only in the past
- O No, never regularly

Estimate the number of years you have used antacids regularly: ____ years

---

Have you used or do you use H-2 blockers?
Zantac (Ranitidine), Tagamet (Cimetidine),
Pepcid (Famotidine), Axid (Nizatidine)

- O Yes, currently and regularly
- O Yes, regularly but only in the past
- O No, never regularly

Estimate the number of years you have used these drugs regularly: ____ years

Have you used or do you use Proton-pump inhibitors?
Prilosec (Omeprazole), Prevacid (Lansaprasole)
Nexium (Esomeprazole), Protonix (Pantoprazole),
AcipHex (Rabeprazole), Dexilant (dexlansoprazole), etc.

- O Yes, currently and regularly
- O Yes, regularly, but only in the past
- O No, never regularly

Estimate the number of years you have used these drugs regularly: ____ years

In the past 2 months, have you had any acute diarrheal illnesses?

- O Yes
- O No

Have you used or do you use anti-diarrheal medications?
Lomotil, Imodium, Kaopectate, tincture of opium (DTO), etc.

- O Yes, currently and regularly
- O Yes, regularly, but only in the past
- O No, never regularly

Have you used any medications modifying bile production?
Questran, Prevalite, Lochelst (Cholesytramine), Colestid (Colestiplo),
Welchol (Colesevelam), CDCA (Chenodeoxycholic Acids),
Ursodiol, Actigall (UDCA, Ursodeoxycholic Acid)

- O Yes, currently and regularly
- O Yes, regularly but only in the past
- O No, never regularly

Estimate the number of years you have used these drugs regularly: ____ years

MEDICATIONS: CHOLESTEROL LOWERING MEDICATIONS / STATINS

Have you ever been prescribed statin medications for high cholesterol? ○Yes ○No

Lipitor (Atorvastatin), Zocor (Simvastatin), Pravachol (Pravastatin)
Mevacor (Lovastatin), Lescol (Fluvastatin), Crestor (Rosuvastatin)

If yes, **Please provide dates of use of ANY statin drug** (include all dates if you switched from one statin drug to another)

	year to		year
	year to		year
	year to		year
	year to		year

Did you take the prescribed statin regularly?

○ Exactly as prescribed
○ Most of the time (>50% of the time)
○ Sometimes (<50% of the time)
○ Never

Please check off all types of statin medications that you took for at least one month:

☐ Lipitor (Atorvastatin) ☐ Zocor (Simvastatin) ☐ Pravachol (Pravastatin)
☐ Mevacor (Lovastatin) ☐ Lescol (Fluvastatin) ☐ Crestor (Rosuvastatin)
☐ Other: _____

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MEDICATIONS: Others

In the past 3 months, please check if you have received any of the following medications in pill or intravenous (IV) form (DO NOT INCLUDE INHALERS OR TOPICAL CREAMS). Please approximate the last date of use for these medications (month/year):

☐ Antibiotics Type : _____ Last date of use: _____/_____
☐ Immunosuppressants (e.g. oral corticosteroids) Type : _____ Last date of use: _____/_____
☐ Immunomodulators (6-MP, imuran, azathioprine) Last date of use: _____/_____

For each of the following periods of your life, please add up the TOTAL amount of time you used antibiotics. (exclude skin creams, mouthwash, or isoniazid). Please only complete the table up to your current age.

	Total Time Using Antibiotics							
	None	Less than 15 Days	15 Days to 2 Months	2-4 Months	4 Months to 2 Years	2-3 Years	3-5 Years	5+ Years
Age 20-29								
Age 30-39								
Age 40-49								
Age 50-59								
Age 60 to the present								

What was the most common reason that you used an antibiotic?

☐ Respiratory infection ☐ Urinary Tract Infection ☐ Acne/Rosacea
☐ Chronic bronchitis ☐ Dental ☐ Other : _____

Please list the medications (including antibiotics, chemotherapy, or immunosuppressants) you have taken regularly for at least **1 month** at any time in the past (table continues onto the next page).

Medication name	Duration of use *(number of months)*	Last date of use *(please approximate)*

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FAMILY CANCER HISTORY

Please answer the following questions. Include only blood relatives, both living and deceased (i.e. Do not include adopted or foster children, step-brothers, step-sisters, or in-laws).

How many full sisters do you have? ☐ **Half-sisters?** ☐

How many full brothers? ☐ **Half-brothers?** ☐

Are you a twin? ○ No ○ Fraternal-twin, same sex ○ Identical-Twin ○ Fraternal-twin, opposite sex

How many daughters do you have? ☐

How many sons do you have? ☐

Please check one of these boxes.

- ○ No, I have no blood-related relatives with cancer
- ○ No, I have no info about my blood relatives (e.g. I am adopted)
- ○ Yes, I have at least one known blood-relative with cancer

If you answered yes above, **complete the following table.** If there are several family members with cancer, please start with the closest ones: parents, children, siblings. Do not include step-siblings, step-children, adopted children, in-laws or individuals not related to you by blood.

Blood Relatives that you should consider when you fill in the boxes below:

Mother	Sister	Half-sister	Daughter	Aunt	Grandmother	Cousins
Father	Brother	Half-brother	Son	Uncle	Grandfather	

Example:

For example if your half-sister Sally was diagnosed with stomach cancer at age 74, had smoked at some point in her life, and she is still living, you would fill in the boxes as in the example below. Note that your half-sister does not need to be identified by whether she is on your maternal or paternal side of the family, but aunts, uncles, grandparents and cousins do. If you only know that she was diagnosed sometime in her 70's, you would print 70 in the Age at Diagnosis column and check off Yes in the "Is age an estimate?" column.

First name or initial	Blood relation	Sex	Maternal/ paternal	Type of cancer	Age at diagnosis	Is age an estimate?	Is person still alive?	Did person ever smoke?
Sally	Half-sister	F	-	Stomach	74	○ Yes ◉ No	◉ Yes ○ No ○ Unk	◉ Yes ○ No ○ Unk
						○ Yes ○ No	○ Yes ○ No ○ Unk	○ Yes ○ No ○ Unk
						○ Yes ○ No	○ Yes ○ No ○ Unk	○ Yes ○ No ○ Unk
						○ Yes ○ No	○ Yes ○ No ○ Unk	○ Yes ○ No ○ Unk
						○ Yes ○ No	○ Yes ○ No ○ Unk	○ Yes ○ No ○ Unk

						○ Yes ○ No	○ Yes ○ No ○ Unk	○ Yes ○ No ○ Unk

Is there any additional information about cancer in your family that you think may be important?

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CIGARETTE SMOKING HISTORY

Have you ever smoked cigarettes? ○Yes ○No
Check "yes" if you have smoked more than 100 cigarettes in your lifetime.

If yes…

How old were you when you started smoking cigarettes? [ ] Age started (years)

Throughout the time you smoked cigarettes, what was the average number of cigarettes per day that you smoked? [ ] # of cigarettes/ day (1 pack = 20 cigarettes)

Do you currently smoke cigarettes (within the past month)? ○Yes ○No

If no, what was the date you stopped smoking cigarettes? [ ] mm/yyyy

During the time you've smoked, were there periods of time (lasting **six months** or more) that you **temporarily** stopped smoking cigarettes? ○Yes ○No

How many years did you temporarily quit (add up all periods) [ ] years

CIGAR SMOKING HISTORY

Have you ever smoked cigars? ○Yes ○No
Check "yes" if you have smoked at least 1 cigar a week for at least 1 year

If yes…How old were you when you started smoking cigars? [ ] Age started (Years)

PIPE SMOKING HISTORY

Have you ever smoked a pipe? ○Yes ○No
Check "yes" if you have smoked at least 12 oz of tobacco in a pipe during your lifetime

If yes…How old were you when you started smoking a pipe [ ] Age started (years)

GREEN TEA DRINKING HISTORY

Have you ever consumed green tea? ○Yes ○No
Check "yes" if you have had at least 10 cups of green tea in your lifetime?

Did you ever drink green tea more than once per week on a regular basis? ○Yes ○No

If yes…How old were you when you started drinking green tea regularly? [ ] Age started (years)

What was the average number of cups of green tea per day that you drank? [ ] cups per day

Do you currently drink green tea (within the past month)? ○Yes ○No

If no, what was the date you stopped drinking green tea? [ ] mm/yyyy

BLACK TEA DRINKING HISTORY

Have you ever consumed black tea? ○Yes ○No
Check "yes" if you have had at least 10 cups of black tea in your lifetime

Did you ever drink black tea more than once per week on a regular basis? ○Yes ○No

If yes…How old were you when you started drinking black tea regularly? ____ Age started (years)

What was the average number of cups of black tea per day that you drank? ____ cups per day

Do you currently drink black tea (within the past month)? ○Yes ○No

If no, what was the date you stopped drinking black tea? ____ mm/yyyy

COFFEE (CAFFEINATED) DRINKING HISTORY

Have you ever consumed caffeinated coffee? ○Yes ○No
Check "yes" if you have had at least 10 cups of coffee in your lifetime

Did you ever drink caffeinated coffee more than once per week on a regular basis? ○Yes ○No

If yes…How old were you when you started drinking coffee regularly? ____ Age started (years)

What was the average number of cups of coffee per day that you drank? ____ cups per day

Do you currently drink caffeinated coffee (within the past month)? ○Yes ○No

If no, what was the date you stopped drinking coffee? ____ mm/yyyy

DECAFFEINATED COFFEE DRINKING HISTORY

Have you ever consumed decaffeinated coffee? ○Yes ○No
Check "yes" if you have had at least 10 cups of decaffeinated coffee in your lifetime

Did you ever drink decaffeinated coffee more than once per week on a regular basis? ○Yes ○No

If yes…How old were you when you started drinking decaffeinated coffee regularly? ____ Age started (years)

What was the average number of cups of decaffeinated coffee per day that you drank? ____ cups per day

Do you currently drink decaffeinated coffee (within the past month)? ○Yes ○No

If no, what was the date you stopped drinking decaffeinated coffee? ____ mm/yyyy

ADDITIONAL DIET AND LIFESTYLE

In the past 2 months, have you ingested a contrast agent for a CT scan or x-ray?

Yes ☐ No ☐

In the past 2 months, have you had chronic diarrhea?

Yes ☐ No ☐

In the past 2 months, have you consumed any probiotics (other than yogurt; see below) at least once per week?

Yes ☐ No ☐

In the past 2 months, how often have you consumed yogurt or other foods containing active bacterial cultures (kefir, sauerkraut, etc.)?

Never ☐ Rarely ☐ 1-5 times a week ☐ Daily ☐ More than daily ☐

What are your dietary preferences with respect to meat?

Standard diet ☐ Standard diet with poultry and/or fish (no red meat) ☐
Vegetarian (no meat) ☐ Vegan (no meat, dairy, or animal products) ☐

How often do you consume alcoholic beverages?

Never ☐ Rarely ☐ 1-5 times a week ☐ Daily ☐ More than daily ☐

RECENT DIET HISTORY

	DID YOU EAT THIS PRODUCT IN THE LAST 24 HOURS? (Check if Yes)	HOW OFTEN DID YOU EAT OR DRINK THE FOLLOWING PRODUCTS IN THE LAST WEEK							
		Never or not in the last week	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
Tea or coffee no sugar and no sugar replacement									
Soft drinks, tea or coffee with sugar (corn syrup, maple syrup, cane sugar, etc.)									
Diet soft drinks, tea or coffee with sugar substitute (Stevia, Equal, Splenda, etc.)									
Fruit juice (orange, apple, cranberry, prune, etc.)									
Water									
Alcohol (beer, brandy, spirits, hard liquor, wine, aperitif, etc.)									
Dairy (milk, cream, ice cream, yogurt, cheese, cream cheese)									
Fruits (no juice) (Apples, raisins, bananas, oranges, strawberries, blueberries, etc. (frozen or fresh)									
Vegetables (salad, tomatoes, onions, greens, carrots, peppers, green beans, etc.)									
Beans (tofu, soy, soy burgers, lentils, Mexican beans, lima beans, etc.)									
Starch (bread, pizza, potatoes, yam, rice, wheat, cereals, pancakes, etc.)									
Eggs									
Red meat (beef, hamburger, pork, lamb)									
White meat (chicken, turkey, etc.)									
Processed meats (lunch meat, sandwich meat, ham, salami, bologna, sausage, kielbasa, hotdog, bacon, etc.)									
Shellfish (shrimp, lobster scallops, etc.)									
Fish (fish nuggets, breaded fish, fish cakes, salmon, tuna, etc.)									
Sweets (pies, jam, chocolate, cake, cookies, etc.)									

PHYSICAL ACTIVITY

What is your normal walking pace outdoors?

- ○ Slow (less than 2 mph)
- ○ Normal, average (2 to 2.9 mph)
- ○ Brisk pace (3 to 3.9 mph)
- ○ Very brisk, striding (4 mph or faster)
- ○ Unable to walk

How many flights of stairs (not steps) do you climb daily?

- ○ No flights
- ○ 1-2 flights
- ○ 3-4 flights
- ○ 5-9 flights
- ○ 10-14 flights
- ○ 15 or more flights

DURING THE PAST 2 MONTHS, what was your average time **PER WEEK** spent at each of the following recreational activities?

	TIME PER WEEK									
	Zero	1-4 Min	5-19 Min	20-59 Min	One Hour	1-1.5 Hrs	2-3 Hrs	4-6 Hrs	7-10 Hrs	11+ Hrs
Walking for exercise or walk to work (including golf)										
Jogging (slower than 10 minutes/mile)										
Running (10 minutes/mile or faster)										
Bicycling (including stationary machine)										
Tennis, squash, racquetball										
Lap swimming										
Other aerobic exercise (calisthenics, ski or stair machine, etc)										
Lower intensity exercise (yoga, stretching, toning)										
Other vigorous activities (e.g., lawn mowing)										
Weight training or resistance exercises										

Name of person who completed this survey: Date:

Version Date: 5/20/2016

Sample Email for ASPIRED (14-496)

Dear Mr. /Ms. Patient,

I am emailing you today because I would like to inform you about a study titled "ASPIRED: ASPirin Intervention for the REDuction of Colorectal Cancer Risk" being conducted at Massachusetts General Hospital, a founding member of the Dana Farber/Harvard Cancer Center. You might have received a letter regarding this study from Dr. (doctor's name) or you might have spoken with your physician about this study previously. You are receiving this email because your physician has identified you as a potential participant based on the results of your recent colonoscopy.

Briefly, the ASPIRED study, supported by the National Cancer Institute, is investigating the mechanism by which aspirin can prevent colon cancer. We plan to evaluate the effect of aspirin in reducing markers of individual risk for colon cancer development. This study may help researchers identify individuals who would most benefit from aspirin as a long-term treatment for cancer prevention.

Participation would involve coming to MGH for two study visits spaced 8-12 weeks apart in which you will undergo a flexible sigmoidoscopy – basically a short colonoscopy -- that advances only a few inches into the rectum. During the sigmoidoscopy, we will collect a stool sample and tissue samples. You will not need to undergo a bowel preparation regimen, as you may have had to do in the past with your colonoscopy. Because we are only going a few inches with the instrument, you will also not require any sedatives, which means you do not need an escort for the procedure. Participation also will include filling out a dietary and lifestyle questionnaire and the collection of a blood, saliva, and urine sample. Participants will be randomly selected to receive either aspirin (low or standard dose) or placebo in double-blinded capsules, meaning neither you nor any of the research staff will know if your capsules contain aspirin or placebo. Starting at your first visit, you will take one blinded capsule daily until your second and final visit.

Please note that **you do not have to participate in this study**. You should feel no obligation to participate in this research study and whether you participate or not will have no effect on your current care.

There is no cost to joining this study. You will be compensated a total of $500 (US) for participating in this trial: $200 (US) after your initial visit, and the remainder, $300 (US) after the completion of your final visit. You will also be provided with 4 hours of free parking at each of your study visits.

You may or may not receive any personal health benefits as a result of your participation in this research study. However, we hope that the results will help us understand how aspirin acts to prevent colorectal cancer and who may benefit from aspirin treatment in the future.

If you are interested in learning more about this study or if you do not want to be contacted further about this study, kindly respond to this email or call our research coordinator, Katherine Gilpin at 617-724-1326.

Sincerely,
Name
Study Role
Massachusetts General Hospital
Gastrointestinal Unit

Aspirin Use

Since completing the ASPIRED trial, have you taken aspirin?

O Yes
O No

When did you start taking aspirin? _____ (mm/yyyy)

Have you taken any aspirin within the last two months?

O Yes
O No

When did you stop taking aspirin? _____ (mm/yyyy)

How frequently do/did you take aspirin?

O Daily
O Frequently (2 or more times per week)
O Occasionally (<2 times per week

What dose of aspirin do you typically take?

O "Baby" or low-dose aspirin (100 mg or less/tablet)
O Aspirin or aspirin-containing products (325mg or more/tablet)
O Unknown
O Other

What other dose of aspirin do you take? _____

How many tablets per week?

O 1-2 tablets
O 3-5 tablets
O 6-14 tablets
O 15+ tablets

What time of day do you typically take aspirin?

O Morning
O Mid-day
O Evening
O Varies

Why do you take aspirin?

[ ] Prevention of heart disease or stroke
[ ] Prevention of cancer

[ ] Doctor's recommendation
[ ] ASPIRED Trial
[ ] Previous heart attack
[ ] Previous stroke
[ ] Pain/headache
[ ] Arthritis and/or musculoskeletal pain
[ ] Other
(Check all that apply)Please describe other _____

Bleeding Events
Have you had any significant bleeding events in the past year? _____
(For example, GI bleed, stroke, etc.)
What was determined to be the source of the bleed?
[ ] Digestive system (Esophagus, stomach, colon, rectal)
[ ] Brain (Stroke)
[ ] Nasal (Nosebleed)
[ ] Other
[ ] Could not be determined
[ ] Unknown
(Check all that apply)Please describe other _____
Did you require a blood transfusion or hospitalization?
[ ] No, neither
[ ] Yes, hospitalization
[ ] Yes, transfusion
[ ] Unknown
(Check all that apply)How was your bleeding investigated?
[ ] Abdominal bleeding scan (tagged red blood cell scan)
[ ] Capsule endoscopy (pill camera)
[ ] Surgery
[ ] Angiography
[ ] CT/MRI scan of the brain
[ ] Upper endoscopy (EGD)
[ ] Lower endoscopy (colonoscopy)
[ ] Other
(check all that apply)Please describe other _____
Where along the digestive tract was the bleed?
[ ] Esophagus
[ ] Stomach
[ ] Small intestine (duodenum, jejenum, ileum)
[ ] Colon (Large intestine)
[ ] Unknown
[ ] Could not be found
(Check all that apply)Were you ever diagnosed with a Helicobacter pylori (H. pylori) infection?
O Yes
O No
O Unknown

(A type of bacteria)When were you first diagnosed with an H. pylori infection? _____ (mm/yyyy)
Have you received treatment for this H. pylori infection?

O Yes
O No
O Unknown

When were you last treated for H. pylori? _____ (MM/YYYY)
Did you receive any of the following for treatment of the gastrointestinal bleeding?

[ ] H2 Blockers (e.g. Pepcid, Zantac, Axid, Tagamet)
[ ] Proton Pump Inhibitors (e.g. Prilosec, Nexium, Protonix, Prevacid, Aciphex)
[ ] H. Pylori Treatment (antibiotics usually with a proton pump inhibitor)
[ ] Endoscopy with cautery, clipping, or banding to stop the bleeding
[ ] Surgery
[ ] Other

(Check all that apply)Please describe other: _____
What type of stroke did you have?

[ ] Non-bleeding (ischemic) stroke
[ ] Bleeding (hemorrhagic) stroke
[ ] Mini-stroke/transient ischemic attack
[ ] Unknown

(Check all that apply)Were you taking any of the following the week prior to your bleed?

[ ] Baby Aspirin (< 100 mg)
[ ] Adult Aspirin (>100 mg)
[ ] NSAID (e.g. Ibuprofen, Motrin, Naproxen, Aleve)
[ ] Coumadin (Warfarin)
[ ] Plavix (Clopidogrel)
[ ] Pradaxa (Dabigatran)
[ ] Brilinta (Ticagrelor)
[ ] Ticlid (Ticlopidine)
[ ] Effient (Prasugrel)
[ ] Xarelto (Rivaroxaban)
[ ] Eliquis (Abixaban)
[ ] Other

(Check all that apply)Please describe other: _____
Did you experience recurrent bleeding within one month of the initial bleeding episode?

O Yes
O No
O Unknown

Recent Endoscopic History
Have you had any endoscopic procedures since your second ASPIRED procedure? _____
How many endoscopic procedures have you had in the last year?

Please record Upper endoscopy (Esophagogastroduodenoscopy) and Lower endoscopy (Colonoscopy or Sigmoidoscopy) separately even if they occurred on the same day or at the

same time. _____

First Endoscopic Procedure
What type of Endoscopic Procedure?
- O Upper Endoscopy
- O Colonoscopy
- O Sigmoidoscopy

Why did you have your procedure?
- [ ] Follow-up of my polyps
- [ ] Family history
- [ ] Occult fecal blood
- [ ] Cologuard
- [ ] Diarrhea/Constipation
- [ ] Anemia
- [ ] Visible blood
- [ ] Reflux
- [ ] Barrett's esophagus monitoring
- [ ] Difficulty swallowing or speaking
- [ ] Abdominal pain
- [ ] Abnormal X-ray, CT scan, or MRI
- [ ] Other

(Check all that apply)Please describe other: _____
Date of Endoscopic Procedure _____ (mm/yyyy)
Was the procedure done at MGH? _____
Where was your procedure done? _____ (Name of Hospital, City, State)
Were any polyps found or removed?
- O Yes
- O No
- O Unknown

Second Endoscopic Procedure
What type of Endoscopic Procedure?
- O Upper Endoscopy
- O Colonoscopy
- O Sigmoidoscopy

Why did you have your procedure?
- [ ] Follow-up of my polyps
- [ ] Family history
- [ ] Occult fecal blood
- [ ] Cologuard
- [ ] Diarrhea/Constipation
- [ ] Anemia
- [ ] Visible blood
- [ ] Reflux
- [ ] Barrett's esophagus monitoring
- [ ] Difficulty swallowing or speaking

[ ] Abdominal pain
[ ] Abnormal X-ray, CT scan, or MRI
[ ] Other

(Check all that apply)Please describe other: _____

Date of Endoscopic Procedure _____ (mm/yyyy)

Was the procedure done at MGH? _____

Where was your procedure done? _____ (Name of Hospital, City, State)

Were any polyps found or removed?

O Yes
O No
O Unknown

Third Endoscopic Procedure

What type of Endoscopic Procedure?

O Upper Endoscopy
O Colonoscopy
O Sigmoidoscopy

Why did you have your procedure?

[ ] Follow-up of my polyps
[ ] Family history
[ ] Occult fecal blood
[ ] Cologuard
[ ] Diarrhea/Constipation
[ ] Anemia
[ ] Visible blood
[ ] Reflux
[ ] Barrett's esophagus monitoring
[ ] Difficulty swallowing or speaking
[ ] Abdominal pain
[ ] Abnormal X-ray, CT scan, or MRI
[ ] Other

(Check all that apply)Please describe other: _____

Date of Endoscopic Procedure _____ (mm/yyyy)

Was the procedure done at MGH? _____

Where was your procedure performed? _____ (Name of hospital, city, state)

Were any polyps found or removed?

O Yes
O No
O Unknown

Fourth Endoscopic Procedure

What type of Endoscopic Procedure

O Upper Endoscopy
O Colonoscopy
O Sigmoidoscopy

Why did you have your procedure?

[ ] Follow-up of my polyps
[ ] Family history
[ ] Occult fecal blood
[ ] Cologuard
[ ] Diarrhea/Constipation
[ ] Anemia
[ ] Visible blood
[ ] Reflux
[ ] Barrett's esophagus monitoring
[ ] Difficulty swallowing or speaking
[ ] Abdominal pain
[ ] Abnormal X-ray, CT scan, or MRI
[ ] Other

(Check all that apply)Please describe other: _____
Date of Endoscopic Procedure _____ (mm/yyyy)
Was your procedure done at MGH? _____
Where was your procedure done? _____ (Name of hospital, city, state)
Were any polyps found or removed?

O Yes
O No
O Unknown

Please list additional endoscopic procedures with approximate date of procedure, location, and reason for the procedure. Skip a line between procedures

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Cancer Diagnosis

Have you received a cancer diagnosis or had a recurrence of cancer since your second ASPIRED visit? _____
Did you receive a new cancer diagnosis or recurrence of cancer?

O New cancer diagnosis
O Recurrence

How many types of cancer? _____
What type?

[ ] Esophageal

[ ] Gallbladder
[ ] Stomach
[ ] Liver
[ ] Pancreas
[ ] Breast
[ ] Leukemia or Lymphoma
[ ] Prostate
[ ] Ovarian
[ ] Skin
[ ] Uterine
[ ] Lung
[ ] Colorectal
[ ] Other

(Check all that apply)Please describe other: _____

Did your cancer spread or metastasize to other organs?

O Yes
O No
O Not sure

To which organs did your cancer spread to? _____

Esophageal Cancer

When were you diagnosed with esophageal cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

[ ] Surgery
[ ] Cryotherapy
[ ] Chemotherapy
[ ] Immunotherapy
[ ] Radiation
[ ] None
[ ] Other

(Check all that apply)Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Gallbladder Cancer

When were you diagnosed with gallbladder cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

[ ] Surgery
[ ] Cryotherapy
[ ] Chemotherapy
[ ] Immunotherapy
[ ] Radiation
[ ] None
[ ] Other

(Check all that apply)Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's

date. _____ (mm/yyyy)

Stomach Cancer
When were you diagnosed with stomach cancer? _____ (mm/yyyy)
What kind of treatment did you receive?

- [ ] Surgery
- [ ] Cryotherapy
- [ ] Chemotherapy
- [ ] Immunotherapy
- [ ] Radiation
- [ ] None
- [ ] Other

(Check all that apply)Please describe other: _____
When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Liver Cancer
When were you diagnosed with liver cancer? _____ (mm/yyyy)
What kind of treatment did you receive?

- [ ] Surgery
- [ ] Cryotherapy
- [ ] Chemotherapy
- [ ] Immunotherapy
- [ ] Radiation
- [ ] None
- [ ] Other

(Check all that apply)Please describe other: _____
When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Pancreatic Cancer
When were you diagnosed with pancreatic cancer? _____ (mm/yyyy)
What kind of treatment did you receive?

- [ ] Surgery
- [ ] Cryotherapy
- [ ] Chemotherapy
- [ ] Immunotherapy
- [ ] Radiation
- [ ] None
- [ ] Other

(Check all that apply)Please describe other: _____
When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy/)

Breast Cancer
When were you diagnosed with breast cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

- [ ] Surgery
- [ ] Cryotherapy
- [ ] Chemotherapy
- [ ] Immunotherapy
- [ ] Radiation
- [ ] None
- [ ] Other

(Check all that apply)Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Leukemia/Lymphoma

When were you diagnosed with leukemia/lymphoma? _____ (mm/yyyy)

What kind of treatment did you receive?

- [ ] Surgery
- [ ] Cryotherapy
- [ ] Chemotherapy
- [ ] Immunotherapy
- [ ] Radiation
- [ ] None
- [ ] Other

(Check all that apply)Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Prostate Cancer

When were you diagnosed with prostate cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

- [ ] Surgery
- [ ] Cryotherapy
- [ ] Chemotherapy
- [ ] Immunotherapy
- [ ] Radiation
- [ ] None
- [ ] Other

(Check all that apply)Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Ovarian Cancer

When were you diagnosed with ovarian cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

- [ ] Surgery
- [ ] Cryotherapy

[ ] Chemotherapy
[ ] Immunotherapy
[ ] Radiation
[ ] None
[ ] Other

(Check all that apply)Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Skin Cancer

What type of skin cancer were you diagnosed with?

[ ] Melanoma
[ ] Basal cell
[ ] Squamous cell
[ ] Other

(Check all that apply)Please describe other: _____

When were you diagnosed with skin cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

[ ] Surgery
[ ] Cryotherapy
[ ] Chemotherapy
[ ] Immunotherapy
[ ] Radiation
[ ] None
[ ] Other

(Check all that apply)Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Uterine Cancer

When were you diagnosed with uterine cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

[ ] Surgery
[ ] Cryotherapy
[ ] Chemotherapy
[ ] Immunotherapy
[ ] Radiation
[ ] None
[ ] Other

(Check all that apply)Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Lung Cancer

When were you diagnosed with lung cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

[ ] Surgery
[ ] Cryotherapy
[ ] Chemotherapy
[ ] Immunotherapy
[ ] Radiation
[ ] None
[ ] Other

(Check all that apply)Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Colorectal Cancer

When were you diagnosed with colorectal cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

[ ] Surgery
[ ] Cryotherapy
[ ] Chemotherapy
[ ] Immunotherapy
[ ] Radiation
[ ] None
[ ] Other

(Check all that apply)Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Cancer Type - Other

When were you diagnosed with cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

[ ] Surgery
[ ] Cryotherapy
[ ] Chemotherapy
[ ] Immunotherapy
[ ] Radiation
[ ] None
[ ] Other

(Check all that apply)Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Cancer Screening

Have you had any cancer screening in the past year aside from procedures done for ASPIRED? _____ (e.g., Physical Exam, Skin Exam, Mammogram, etc.)

What type of screening procedure?

[ ] Pap Smear
[ ] Mammogram
[ ] Prostate Exam/PSA Testing

[ ] Skin Exam
[ ] Physical Exam
[ ] Colonoscopy
[ ] Eye Exam
[ ] Chest X-ray
[ ] Chest CT
[ ] Abdominal Sonogram
[ ] Other
(Check all that apply)Please describe other: _____

Other Digestive Issues
Have you been diagnosed with any digestive disorders since your second ASPIRED procedure? _____
What digestive disorder?
[ ] GERD (Gastroesophageal reflux disease)
[ ] Celiac
[ ] Irritable Bowel Syndrome
[ ] Barrett's esophagus
[ ] Diverticulitus
[ ] Inflammatory Bowel Disease (Crohn's/Ulcerative colitis)
[ ] Microscopic colitis
[ ] Other
(Check all that apply)Please describe other: _____
Name of person completing the survey: _____

Identifiers

Study ID _____
First Name _____
Last Name _____
* Patient Email _____
* Medical Record Number (MGH) _____
* QACT Code _____
* Date of Birth _____
Date of Second ASPIRED Procedure _____

Call Log

Was the patient called? _____
Why not?
O Phone number did not work
O Patient passed away since last contact

O Other

Lost to Follow-up Date _____

When did the patient die? _____ (mm/dd/yyyy)

What is the cause of death?

Other:

Date of Phone Call _____ (mm/dd/yyyy)

Phone Notes

Medical Record Review

Date of Record Review _____
Has patient passed away? _____
Date of death _____
Cause of Death _____

Endoscopy Review
Did the patient have any recent endoscopic procedures? _____
How many endoscopic procedures are in the record in the past year? _____ (Please count Upper and Lower seporately)
Have all endoscopic procedures and findings recorded in the appropriate RedCap forms? _____

Recent Cancer History
Was the patient diagnosed with cancer or have a recurrence of cancer in the past year? _____
New cancer diagnosis or recurrence?
- O New cancer diagnosis
- O Recurrence

How many types of cancer? _____
What type of cancer was the patient diagnosed with?
- [ ] Esophageal
- [ ] Gallbladder
- [ ] Stomach
- [ ] Liver
- [ ] Pancreas
- [ ] Breast
- [ ] Leukemia or Lymphoma
- [ ] Prostate
- [ ] Ovarian
- [ ] Skin
- [ ] Uterine
- [ ] Lung
- [ ] Colorectal
- [ ] Other

What type of skin cancer?
- [ ] Melanoma
- [ ] Basal cell
- [ ] Squamous cell
- [ ] Other

Identify other type of skin cancer _____
Identify the site of the other cancer type _____
When was the patient diagnosed? _____
What type of treatment was administered?
- [ ] Surgery

[ ] Cryotherapy
[ ] Chemotherapy
[ ] Immunotherapy
[ ] Radiation
[ ] None
[ ] Other

What other treatment? _____

Cancer Screening

Did the patient have any recent cancer screenings? _____

Type of cancer screening performed

[ ] Pap Smear
[ ] Mammogram
[ ] Prostate Exam/PSA Testing
[ ] Skin Exam
[ ] Physical Exam
[ ] Colonoscopy
[ ] Eye Exam
[ ] Chest X-ray
[ ] Chest CT
[ ] Abdominal Sonogram
[ ] Other

Other: _____

Aspirin Use in Record

Did the patient begin an aspirin regimen since last ASPIRED contact? _____

When was aspirin regimen prescribed? _____

What dose was prescribed?

O "Baby" or low dose (100mg or less)
O Standard aspirin (325 mg or more)

Bleeding Events

Did patient have a bleeding event for which they were hospitalized? _____

Did patient require a blood transfusion?

O Yes
O No
O Not Sure

Date of Admission _____

Date of Discharge _____

Specify the source of the bleeding

[ ] Digestive system (Esophagus, stomach, colon, rectal)
[ ] Brain (Stroke)
[ ] Nasal (Nosebleed)
[ ] Other

[ ] Could not be determined
[ ] Unknown

What other bleeding event? _____

Location of the Source of Bleeding?

[ ] Esophagus
[ ] Stomach
[ ] Duodenum
[ ] Other small bowel (e.g.Jejenum/Ileum
[ ] Colon
[ ] Could not be found
[ ] Not clear

What was the type of stroke?

O Non-bleeding (ischemic) stroke
O Bleeding (hemorrhagic) stroke
O Mini-stroke/transient ischemic attack
O Unknown

Diagnostic Tests Performed

[ ] Abdominal bleeding scan (tagged red blood cell scan)
[ ] Capsule endoscopy (pill camera)
[ ] Surgery
[ ] Angiography
[ ] CT/MRI scan of the brain
[ ] Upper endoscopy (EGD)
[ ] Lower endoscopy (colonoscopy)
[ ] Other

(may choose more than one option)Please describe other _____

Was there an episode of recurrent bleeding within a month of discharge?

O Yes
O No
O Unknown

Digestive Disorders

Has patient been diagnosed with a digestive disorder in the past year? _____

What digestive disorder was diagnosed? _____

Information Sheet: For ASPIRED participants who underwent their qualifying endoscopy before March 1, 2017.

The informed consent document you have been given describes on page 13, in section I "Will I be paid to take part in this research study", that participants who complete the baseline visit and protocol will receive $200.00 (US) compensation and those that complete the end visit and protocol will receive $200.00 (US). Because you had your qualifying endoscopy (prior colonoscopic procedure that resulted in adenoma detection and removal) *BEFORE* March 1, 2017, you will receive an additional $100.00 (US) if you complete the end visit and protocol. This means that you will receive a total of $300.00 (U.S.) for completing the end visit and protocol. If you successfully complete both visits and protocol, the total compensation for being on the trial will equal $500.00 (US) as described in your recruitment letter and subsequent conversations with study staff.

Why does the consent document say I will be paid $200 after each visit?

The current consent document describes a change that has had to be implemented due to budgeting constraints. Due to these constraints, we have had to change the compensation provided to any participant who had their qualifying endoscopy *ON* or *AFTER* March 1, 2017. It is required that we use a single informed consent document for all participants on the study. Because you received your qualifying endoscopy prior to March 1, 2017 and were recruited to the study under different circumstances, we intend to honor our original quoted compensation, as described above. All other parts of the consent document are accurate and apply as written. You are reminded again at this time that your participation is voluntary.

Questionnaire, Subsequent Years

Record ID _____

Aspirin Use

In the past year, have you taken aspirin?
- ◯ Yes
- ◯ No

When did you start taking aspirin?
_____
(mm/yyyy)

Are you currently taking aspirin?
- ◯ Yes
- ◯ No

(Within the past two months)

When did you stop taking aspirin?
_____
(mm/yyyy)

How frequently do you take aspirin?
- ◯ Daily
- ◯ Frequently (2 or more times per week)
- ◯ Occasionally (< 2 times per week

What dose of aspirin do you typically take?
- ◯ "Baby" or low-dose aspirin (100 mg or less/tablet)
- ◯ Aspirin or aspirin-containing products (325mg or more/tablet)
- ◯ Unknown
- ◯ Other

What other dose of aspirin do you take?
_____

How many tablets per week?
- ◯ 1-2 tablets
- ◯ 3-5 tablets
- ◯ 6-14 tablets
- ◯ 15+ tablets

What time of day do you typically take aspirin?
- ◯ Morning
- ◯ Mid-day
- ◯ Evening
- ◯ Varies

Why do you take aspirin?
- ☐ Prevention of heart disease or stroke
- ☐ Prevention of cancer
- ☐ Doctor's recommendation
- ☐ ASPIRED Trial
- ☐ Previous heart attack
- ☐ Previous stroke
- ☐ Pain/headache
- ☐ Arthritis and/or musculoskeletal pain
- ☐ Other

(Check all that apply)

Please describe other
_____

Bleeding Events

Have you had any significant bleeding events in the past year?
- ◯ Yes
- ◯ No

(For example, GI bleed, stroke, etc.)

What was determined to be the source of the bleed?
- ☐ Digestive system (Esophagus, stomach, colon, rectal)
- ☐ Brain (Stroke)
- ☐ Nasal (Nosebleed)
- ☐ Other
- ☐ Could not be determined
- ☐ Unknown

(Check all that apply)

Please describe other _____

Did you require a blood transfusion or hospitalization?
- ☐ No, neither
- ☐ Yes, hospitalization
- ☐ Yes, transfusion
- ☐ Unknown

(Check all that apply)

How was your bleeding investigated?
- ☐ Abdominal bleeding scan (tagged red blood cell scan)
- ☐ Capsule endoscopy (pill camera)
- ☐ Surgery
- ☐ Angiography
- ☐ CT/MRI scan of the brain
- ☐ Upper endoscopy (EGD)
- ☐ Lower endoscopy (colonoscopy)
- ☐ Other

(check all that apply)

Please describe other _____

Where along the digestive tract was the bleed?
- ☐ Esophagus
- ☐ Stomach
- ☐ Small intestine (duodenum, jejenum, ileum)
- ☐ Colon (Large intestine)
- ☐ Unknown
- ☐ Could not be found

(Check all that apply)

Were you ever diagnosed with a Helicobacter pylori (H. pylori) infection?
- ◯ Yes
- ◯ No
- ◯ Unknown

(A type of bacteria)

When were you first diagnosed with an H. pylori infection?

_____

(mm/yyyy)

Have you received treatment for this H. pylori infection?
- ◯ Yes
- ◯ No
- ◯ Unknown

When were you last treated for H. pylori?

_____

(MM/YYYY)

Did you receive any of the following for treatment of the gastrointestinal bleeding?

- ☐ H2 Blockers (e.g. Pepcid, Zantac, Axid, Tagamet)
- ☐ Proton Pump Inhibitors (e.g. Prilosec, Nexium, Protonix, Prevacid, Aciphex)
- ☐ H. Pylori Treatment (antibiotics usually with a proton pump inhibitor)
- ☐ Endoscopy with cautery, clipping, or banding to stop the bleeding
- ☐ Surgery
- ☐ Other

(Check all that apply)

Please describe other: _____

What type of stroke did you have?

- ☐ Non-bleeding (ischemic) stroke
- ☐ Bleeding (hemorrhagic) stroke
- ☐ Mini-stroke/transient ischemic attack
- ☐ Unknown

(Check all that apply)

Were you taking any of the following the week prior to your bleed?

- ☐ Baby Aspirin (< 100 mg)
- ☐ Adult Aspirin (>100 mg)
- ☐ NSAID (e.g. Ibuprofen, Motrin, Naproxen, Aleve)
- ☐ Coumadin (Warfarin)
- ☐ Plavix (Clopidogrel)
- ☐ Pradaxa (Dabigatran)
- ☐ Brilinta (Ticagrelor)
- ☐ Ticlid (Ticlopidine)
- ☐ Effient (Prasugrel)
- ☐ Xarelto (Rivaroxaban)
- ☐ Eliquis (Abixaban)
- ☐ Other

(Check all that apply)

Please describe other: _____

Did you experience recurrent bleeding within one month of the initial bleeding episode?

- ◯ Yes
- ◯ No
- ◯ Unknown

Recent Endoscopic History

Have you had any endoscopic procedures in the past year?

- ◯ Yes
- ◯ No

How many endoscopic procedures have you had in the last year? _____

Please record Upper endoscopy (Esophagogastroduodenoscopy) and Lower endoscopy (Colonoscopy or Sigmoidoscopy) separately even if they occurred on the same day or at the same time.

First Endoscopic Procedure

What type of Endoscopic Procedure?

◯ Upper Endoscopy
◯ Colonoscopy
◯ Sigmoidoscopy

Why did you have your procedure?

☐ Follow-up of my polyps
☐ Family history
☐ Occult fecal blood
☐ Cologuard
☐ Diarrhea/Constipation
☐ Anemia
☐ Visible blood
☐ Reflux
☐ Barrett's esophagus monitoring
☐ Difficulty swallowing or speaking
☐ Abdominal pain
☐ Abnormal X-ray, CT scan, or MRI
☐ Other
(Check all that apply)

Please describe other: _____

Date of Endoscopic Procedure _____
(mm/yyyy)

Was the procedure done at MGH?

◯ Yes
◯ No

Where was your procedure done? _____
(Name of Hospital, City, State)

Were any polyps found or removed?

◯ Yes
◯ No
◯ Unknown

Second Endoscopic Procedure

What type of Endoscopic Procedure?

◯ Upper Endoscopy
◯ Colonoscopy
◯ Sigmoidoscopy

Why did you have your procedure?

☐ Follow-up of my polyps
☐ Family history
☐ Occult fecal blood
☐ Cologuard
☐ Diarrhea/Constipation
☐ Anemia
☐ Visible blood
☐ Reflux
☐ Barrett's esophagus monitoring
☐ Difficulty swallowing or speaking
☐ Abdominal pain
☐ Abnormal X-ray, CT scan, or MRI
☐ Other
(Check all that apply)

Please describe other: _____

Date of Endoscopic Procedure

_____
(mm/yyyy)

Was the procedure done at MGH?

◯ Yes
◯ No

Where was your procedure done?

_____
(Name of Hospital, City, State)

Were any polyps found or removed?

◯ Yes
◯ No
◯ Unknown

Third Endoscopic Procedure

What type of Endoscopic Procedure?

◯ Upper Endoscopy
◯ Colonoscopy
◯ Sigmoidoscopy

Why did you have your procedure?

☐ Follow-up of my polyps
☐ Family history
☐ Occult fecal blood
☐ Cologuard
☐ Diarrhea/Constipation
☐ Anemia
☐ Visible blood
☐ Reflux
☐ Barrett's esophagus monitoring
☐ Difficulty swallowing or speaking
☐ Abdominal pain
☐ Abnormal X-ray, CT scan, or MRI
☐ Other
(Check all that apply)

Please describe other:

_____

Date of Endoscopic Procedure

_____
(mm/yyyy)

Was the procedure done at MGH?

◯ Yes
◯ No

Where was your procedure performed?

_____
(Name of hospital, city, state)

Were any polyps found or removed?

◯ Yes
◯ No
◯ Unknown

Fourth Endoscopic Procedure

What type of Endoscopic Procedure

◯ Upper Endoscopy
◯ Colonoscopy
◯ Sigmoidoscopy

Why did you have your procedure?

- ☐ Follow-up of my polyps
- ☐ Family history
- ☐ Occult fecal blood
- ☐ Cologuard
- ☐ Diarrhea/Constipation
- ☐ Anemia
- ☐ Visible blood
- ☐ Reflux
- ☐ Barrett's esophagus monitoring
- ☐ Difficulty swallowing or speaking
- ☐ Abdominal pain
- ☐ Abnormal X-ray, CT scan, or MRI
- ☐ Other

(Check all that apply)

Please describe other: _____

Date of Endoscopic Procedure _____ (mm/yyyy)

Was your procedure done at MGH?

- ◯ Yes
- ◯ No

Where was your procedure done? _____ (Name of hospital, city, state)

Were any polyps found or removed?

- ◯ Yes
- ◯ No
- ◯ Unknown

Please list additional endoscopic procedures with approximate date of procedure, location, and reason for the procedure. Skip a line between procedures _____

Cancer Diagnosis

Have you received a cancer diagnosis or had a recurrence of cancer in the last year?

- ◯ Yes
- ◯ No

Did you receive a new cancer diagnosis or recurrence of cancer?

- ◯ New cancer diagnosis
- ◯ Recurrence

How many types of cancer? _____

What type?

- ☐ Esophageal
- ☐ Gallbladder
- ☐ Stomach
- ☐ Liver
- ☐ Pancreas
- ☐ Breast
- ☐ Leukemia or Lymphoma
- ☐ Prostate
- ☐ Ovarian
- ☐ Skin
- ☐ Uterine
- ☐ Lung
- ☐ Colorectal
- ☐ Other

(Check all that apply)

Please describe other: _____

Did your cancer spread or metastasize to other organs?

◯ Yes
◯ No
◯ Not sure

To which organs did your cancer spread to? _____

Esophageal Cancer

When were you diagnosed with esophageal cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

☐ Surgery
☐ Cryotherapy
☐ Chemotherapy
☐ Immunotherapy
☐ Radiation
☐ None
☐ Other
(Check all that apply)

Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Gallbladder Cancer

When were you diagnosed with gallbladder cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

☐ Surgery
☐ Cryotherapy
☐ Chemotherapy
☐ Immunotherapy
☐ Radiation
☐ None
☐ Other
(Check all that apply)

Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Stomach Cancer

When were you diagnosed with stomach cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

- ☐ Surgery
- ☐ Cryotherapy
- ☐ Chemotherapy
- ☐ Immunotherapy
- ☐ Radiation
- ☐ None
- ☐ Other

(Check all that apply)

Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Liver Cancer

When were you diagnosed with liver cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

- ☐ Surgery
- ☐ Cryotherapy
- ☐ Chemotherapy
- ☐ Immunotherapy
- ☐ Radiation
- ☐ None
- ☐ Other

(Check all that apply)

Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Pancreatic Cancer

When were you diagnosed with pancreatic cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

- ☐ Surgery
- ☐ Cryotherapy
- ☐ Chemotherapy
- ☐ Immunotherapy
- ☐ Radiation
- ☐ None
- ☐ Other

(Check all that apply)

Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy/)

Breast Cancer

When were you diagnosed with breast cancer?
_____
(mm/yyyy)

What kind of treatment did you receive?
☐ Surgery
☐ Cryotherapy
☐ Chemotherapy
☐ Immunotherapy
☐ Radiation
☐ None
☐ Other
(Check all that apply)

Please describe other:
_____

When did you last receive treatment? If you are still undergoing treatment, please use today's date.
_____
(mm/yyyy)

Leukemia/Lymphoma

When were you diagnosed with leukemia/lymphoma?
_____
(mm/yyyy)

What kind of treatment did you receive?
☐ Surgery
☐ Cryotherapy
☐ Chemotherapy
☐ Immunotherapy
☐ Radiation
☐ None
☐ Other
(Check all that apply)

Please describe other:
_____

When did you last receive treatment? If you are still undergoing treatment, please use today's date.
_____
(mm/yyyy)

Prostate Cancer

When were you diagnosed with prostate cancer?
_____
(mm/yyyy)

What kind of treatment did you receive?
☐ Surgery
☐ Cryotherapy
☐ Chemotherapy
☐ Immunotherapy
☐ Radiation
☐ None
☐ Other
(Check all that apply)

Please describe other:
_____

When did you last receive treatment? If you are still undergoing treatment, please use today's date.
_____
(mm/yyyy)

Ovarian Cancer

When were you diagnosed with ovarian cancer?
_____
(mm/yyyy)

What kind of treatment did you receive?
☐ Surgery
☐ Cryotherapy
☐ Chemotherapy
☐ Immunotherapy
☐ Radiation
☐ None
☐ Other
(Check all that apply)

Please describe other:
_____

When did you last receive treatment? If you are still undergoing treatment, please use today's date.
_____
(mm/yyyy)

Skin Cancer

What type of skin cancer were you diagnosed with?
☐ Melanoma
☐ Basal cell
☐ Squamous cell
☐ Other
(Check all that apply)

Please describe other:
_____

When were you diagnosed with skin cancer?
_____
(mm/yyyy)

What kind of treatment did you receive?
☐ Surgery
☐ Cryotherapy
☐ Chemotherapy
☐ Immunotherapy
☐ Radiation
☐ None
☐ Other
(Check all that apply)

Please describe other:
_____

When did you last receive treatment? If you are still undergoing treatment, please use today's date.
_____
(mm/yyyy)

Uterine Cancer

When were you diagnosed with uterine cancer?
_____
(mm/yyyy)

What kind of treatment did you receive?

- ☐ Surgery
- ☐ Cryotherapy
- ☐ Chemotherapy
- ☐ Immunotherapy
- ☐ Radiation
- ☐ None
- ☐ Other

(Check all that apply)

Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Lung Cancer

When were you diagnosed with lung cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

- ☐ Surgery
- ☐ Cryotherapy
- ☐ Chemotherapy
- ☐ Immunotherapy
- ☐ Radiation
- ☐ None
- ☐ Other

(Check all that apply)

Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Colorectal Cancer

When were you diagnosed with colorectal cancer? _____ (mm/yyyy)

What kind of treatment did you receive?

- ☐ Surgery
- ☐ Cryotherapy
- ☐ Chemotherapy
- ☐ Immunotherapy
- ☐ Radiation
- ☐ None
- ☐ Other

(Check all that apply)

Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date. _____ (mm/yyyy)

Cancer Type - Other

When were you diagnosed with cancer?
_____
(mm/yyyy)

What kind of treatment did you receive?
- ☐ Surgery
- ☐ Cryotherapy
- ☐ Chemotherapy
- ☐ Immunotherapy
- ☐ Radiation
- ☐ None
- ☐ Other

(Check all that apply)

Please describe other: _____

When did you last receive treatment? If you are still undergoing treatment, please use today's date.
_____
(mm/yyyy)

Cancer Screening

Have you had any cancer screening in the past year?
- ◯ Yes
- ◯ No

(e.g., Physical Exam, Skin Exam, Mammogram, etc.)

What type of screening procedure?
- ☐ Pap Smear
- ☐ Mammogram
- ☐ Prostate Exam/PSA Testing
- ☐ Skin Exam
- ☐ Physical Exam
- ☐ Colonoscopy
- ☐ Eye Exam
- ☐ Chest X-ray
- ☐ Chest CT
- ☐ Abdominal Sonogram
- ☐ Other

(Check all that apply)

Please describe other: _____

Other Digestive Issues

Have you been diagnosed with any digestive disorders in the past year?
- ◯ Yes
- ◯ No

What digestive disorder?
- ☐ GERD (Gastroesophageal reflux disease)
- ☐ Celiac
- ☐ Irritable Bowel Syndrome
- ☐ Barrett's esophagus
- ☐ Diverticulitus
- ☐ Inflammatory Bowel Disease (Crohn's/Ulcerative colitis)
- ☐ Microscopic colitis
- ☐ Other

(Check all that apply)

Please describe other: _____

Name of person completing the survey: _____