ASSESSING THE EFFECT OF OFFERING A BLOOD-BASED COLORECTAL CANCER SCREENING TEST ON SCREENING ADHERENCE AND COLONOSCOPY COMPLETION IN PATIENTS WHO HAVE REFUSED COLONOSCOPY AND FIT

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1) **Protocol Title**

Assessing the effect of offering a blood-based colorectal cancer screening test on screening adherence and colonoscopy completion in patients who have refused colonoscopy and FIT

2) **Objectives**

Despite multiple options for colorectal cancer (CRC) screening, including several proven to reduce CRC mortality, population-level participation rates are suboptimal. In 2015, it was estimated that only 62% of Americans aged 50-75 were up to date with screening, which is substantially lower than the 80% by 2018 screening goal set by the National Colorectal Cancer Roundtable and endorsed by the American Society of Gastrointestinal Endoscopy.[1] The US Multi-Society Task Force (USMSTF) recommends colonoscopy and fecal immunochemical testing (FIT) as Tier 1 screening tests,[2] but barriers to completing these tests have been well-characterized.[3] For colonoscopy, patient barriers include an aversion to the bowel preparation process, loss of a workday, and the invasive nature of the procedure. For FIT, the main patient barrier is a reluctance to handle stool samples. Although blood-based tests are not currently recommended in the screening guidelines, they overcome all of these known barriers and may substantially improve adherence to screening. Epi proColon is an FDA-approved blood test that detects methylated Septin9 DNA, which is increased in individuals with CRC. The test is indicated for average-risk individuals who have declined guideline-recommended screening options, such as colonoscopy and FIT. Guidelines suggest that patients who decline these Tier 1 options should be offered Tier 2 or 3 options such as sigmoidoscopy, stool-DNA, CT colonography, and capsule colonoscopy. However, since these lower-tier tests face the same patient barriers as the Tier 1 tests and are less widely available, individuals who have declined both colonoscopy and FIT constitute the *de facto* target population for the blood test. Studies have shown that patients who are offered a choice between the blood test and FIT prefer and have higher compliance to the blood test,[4,5] but it is unknown what proportion of "screen-resistant" patients who have declined *both* colonoscopy and FIT will accept the blood test. This is the crucial question that will determine the potential role of the blood test in the CRC screening landscape.

The VA New York Harbor Health Care System (VA NYHHCS) offers both colonoscopy and FIT for CRC screening and has achieved a screening rate of 80%, but efforts to further improve the screening rate by promoting these two tests have resulted in limited success. Since the stability of the screening rate likely indicates a saturation of individuals who are willing to undergo either colonoscopy or FIT, this is an ideal clinical environment to test the ability of a blood test to further improve the screening rate. The convenience of the blood test may expand the number of patients who are willing to undergo screening, and patients with positive test results will likely be more motivated to undergo potentially cancer-detecting diagnostic colonoscopy. Therefore, the introduction of the blood test may effectively convert a proportion of individuals who have previously declined colonoscopy to undergo this important procedure. In this study, we will assess the effect of the Septin9 blood test on screening rates among screen-resistant veterans who have declined both colonoscopy and FIT at the VA NY Harbor Health Care System, as well as their follow-through with diagnostic colonoscopy. Our Specific Aims are as follows:

Aim 1: To measure screening uptake with a blood test in screen-resistant patients who have declined both colonoscopy and FIT at the VA New York Harbor Health Care System (VA NYHHCS)

Sub-Aim 1a: To assess the proportion of those with a positive blood-based screening test who undergo diagnostic colonoscopy

Sub-Aim 1b: To describe the endoscopic findings on diagnostic colonoscopy

Aim 2: To survey screen-resistant patients to understand their beliefs and attitudes about CRC screening and testing options

3) **Background**

In 2017, over 135,000 people in the US will be diagnosed with CRC and more than 50,000 will die from this disease—making it the third most common cancer in both men and women and the second leading cause of cancer death.[6] A preponderance of data show that both colonoscopy and fecal occult blood testing substantially reduce CRC incidence and mortality.[7–10] Despite these compelling statistics, only 62% of Americans were up to date with CRC screening in 2015, which is substantially below our national goal of 80% by 2018 and also falls short of screening rates achieved for breast (72%) and cervical (83%) cancer.[1] Of the two Tier 1 screening options recommended by the USMSTF, colonoscopy is by far the predominant screening modality; 96% of individuals who were up to date with screening reporting that they received lower endoscopy, compared to 11% for a stool-based test.[11] Yet from a patient perspective, neither of these two options is ideal. Colonoscopy requires dietary modification, bowel preparation, an invasive procedure, time off from work, and an escort for the majority of individuals who receive sedation. Despite the gastroenterology community's continuous efforts to improve the patient experience through innovations such as low residue diet, split dose and smaller volume bowel preparation, and carbon dioxide, the suboptimal screening rate is proof that a substantial proportion of the population still refuses colonoscopy. Similarly, a segment of the population refuses FIT because they find the idea of providing a stool sample unhygienic and unappealing. Therefore, despite the existence of many CRC screening options, there is still an unmet need for a test that is non-invasive, does not require a bowel preparation, and does not involve handling stool. The Septin9 DNA blood test is the only FDA-approved test that fits this description. Septin9 is currently not recommended by the USMSTF as a screening option, but it is not intended to be offered to patients in place of the recommended options. Rather, the blood test is intended for patients who have declined the available options—usually for the reasons cited above—for whom a blood test would be an acceptable alternative. Thus, it is not a competitor to colonoscopy but may motivate more patients to participate in screening and ultimately undergo diagnostic colonoscopy after a positive test. Both national and VA screening rates have plateaued over the last few years, which suggests that a new strategy may be needed to further improve screening uptake. The Septin9 blood test may address an unmet need for patients and provide a much-needed boost to screening efforts. In this study, we will offer Septin9 to individuals who have previously declined both colonoscopy and FIT, which will allow us to measure the effect of the test in the real-world clinical situation in which it is indicated.

Our prior work has shown that adherence to fecal testing declines rapidly with successive rounds of screening,[12] which highlights the potential of a blood-based test with high-compliance for capturing non-adherent individuals. The performance of the Septin9 blood test was first studied in 7941 asymptomatic individuals, which found an age-standardized 48% sensitivity and 92% specificity for CRC.[13] These results were based on an assay that defined test positivity as one of two samples with a positive result. A subsequent study has shown that redefining test positivity as one of three samples with a positive result yielded 68% sensitivity and 79% specificity for CRC.[14] The current FDA-approved Epi proColon assay uses three samples. In a trial that compared the blood test to FIT in individuals who were either recently diagnosed with

CRC or were undergoing screening colonoscopy, the blood test was found to be non-inferior to FIT with respect to sensitivity (73% vs. 68%) for CRC but had lower specificity (82% vs. 97%).[15] Two studies have evaluated uptake of the blood test compared to FIT. In a German study of 109 individuals who refused screening colonoscopy, 83% chose the blood test and 15% chose FIT. In a multi-center randomized controlled trial conducted in the US, patients who were overdue for screening were assigned to either the blood test or FIT. Test completion rate was 99.5% for the blood test and 88% for FIT. Of the 30 individuals who had a positive blood test, 20 (67%) scheduled or completed a diagnostic colonoscopy within 3 months.

4) **Inclusion and Exclusion Criteria**

Inclusion criteria (based on review of the electronic health record):
-Age 50-75
-Declined CRC screening (both colonoscopy and FIT) in the previous 6 months, which must be documented in the electronic health record

Exclusion criteria (based on review of the electronic health record data and self-reported questionnaire data):
-Personal history of colonic adenomas (including sessile serrated adenomas), proximal hyperplastic polyps, CRC, inflammatory bowel disease, or hereditary gastrointestinal cancer syndrome
-First degree relative with CRC diagnosed at <60 years of age; family history of hereditary gastrointestinal cancer syndromes.
-Patients with severe comorbidities who may not benefit from CRC screening due to limited life expectancy (e.g. poorly controlled or end-stage neurologic, cardiac, pulmonary, renal, or oncologic disease).
-Vulnerable populations
    -Adult unable to consent
    -Individuals who are not yet adults (infants, children, teenagers)
    -Pregnant women
    -Prisoners

5) **Study-Wide Number of Subjects**

This is a single site study with a total enrollment of 360 patients. 180 patients each will be in the intervention and control groups, respectively.

6) **Study-Wide Recruitment Methods**

All participants will be primary care patients within the VA NY Harbor Health Care System. We will perform an updated CRC screening audit at the beginning of the study to obtain the entire pool of eligible patients who are not up to date with screening. Eligible patients will then be randomized 1:1 to either an intervention group or a control group. All patients will receive a letter noting that they are not up to date on screening and encouraging them to contact a study number if they choose to screen with colonoscopy or FIT. Patients who call will speak to a research assistant who is trained in patient navigation and can facilitate referrals for colonoscopy or FIT. Following the sequential testing approach, letters addressed to the intervention group will also include an option to participate in the blood test, with instructions to call the study number to schedule the blood draw. In addition to the letter, both groups will also receive a follow-up telephone call that reiterates information in the letter. The research assistant will make and receive all calls using a standard script.

7) Study Timelines

Each individual who is enrolled in this study will participate for a maximum of 6 months. We anticipate enrollment will take approximately 9 months. From the time that the study is approved, we estimate that it will take 18 months to complete the primary analysis.

8) Study Endpoints

Aim #1: *To measure screening uptake with a blood test in screen-resistant patients who have declined both colonoscopy and FIT at VA NY Harbor Health Care System*. Using the approach outlined above, we will identify and randomize 360 eligible patients, with 180 patients each in the intervention and control groups (see Sample Size Calculations).
Primary outcome: Screening rate in the intervention group vs. control group after 6 months.
Secondary outcomes:
A) Complete screening rate in both groups, which is defined as completion of the entire screening strategy. For colonoscopy, this requires cecal intubation and an adequate bowel preparation. For individuals who took Septin9 and FIT, positive results must be followed by a colonoscopy with cecal intubation and adequate bowel preparation.
B) Among individuals in the intervention group who had a positive blood test, proportion who completed a follow-up colonoscopy within 6 months.
C) Endoscopic and pathologic findings among individuals in the intervention group who had a diagnostic colonoscopy.

Aim #2: *To survey screen-resistant patients to understand their beliefs and attitudes about CRC screening and testing options*. Both intervention and controls groups will be invited to complete a brief questionnaire. Questionnaire questions are shown in the Table and are adapted from a previous study that offered both the blood test and FIT to patients who had refused screening colonoscopy.[4] All response options will be presented in a multiple-choice format. The full questionnaire is shown in the Appendix.
Primary outcome: Demographic and health-related predictors of accepting the blood test in the intervention group.
Secondary outcomes:
A) Proportion of both groups who answered that they would be willing to take a blood test for colorectal cancer screening
B) The most commonly cited advantages of a blood test compared to colonoscopy and stool test in both groups
C) The most commonly cited reasons for not taking the blood test in the intervention group. In an exploratory analysis, we will stratify results by race/ethnicity, self-reported health, frequency of healthcare access, and self-perceived risk of CRC.

Table. Select Questionnaire Questions

Demographics
What is your age?
What is your race?
What is your ethnicity?
Health status and medical history
How would you rate your overall health?
How many visits have you had with your primary care doctor in the past year?
What do you think is your own risk of getting colorectal cancer?
Colorectal cancer testing
Have you ever had a colonoscopy? If so, when?
Have you ever had a stool-based test? If so, when?

Why did you decide not to do a colonoscopy when offered in the past 6 months?
What would make you change your mind and get a colonoscopy?
Why did you decide not to do a stool test (fecal immunochemical test/FIT) when offered in the past 6 months?
What would make you change your mind and take a stool test?
Why did you decide to take a blood test?
What are the advantages of a blood test compared to colonoscopy and stool test?
Why did you decide not to take a blood test?
What would make you change your mind and take a blood test?

9) **Procedures Involved**

The proposed study is a randomized controlled trial that will 1) assess the uptake of a CRC screening blood test among patients who have declined both colonoscopy and FIT in the previous 6 months, including diagnostic evaluation of positive results and 2) survey patients about their beliefs and attitudes regarding CRC screening and testing options. All participants will be primary care patients at the VA NY Harbor Health Care System. Based on a recent internal audit, there were 1502 patients who had at least one primary care visit from August 2016 through August 2017 and were not up to date with CRC screening. Up to date CRC screening is defined as either 1) a colonoscopy within the past 10 years or 2) FIT within the past year. We will perform an updated CRC screening audit at the beginning of the study to obtain the entire pool of eligible patients who are not up to date with screening. Eligible patients will then be randomized 1:1 to either an intervention group or a control group. All patients will receive a letter noting that they are not up to date on screening and encouraging them to contact a study number if they choose to screen with colonoscopy or FIT. Patients who call will speak to a research assistant who is trained in patient navigation and can facilitate referrals for colonoscopy or FIT. Following the sequential testing approach, letters addressed to the intervention group will also include an option to participate in the blood test, with instructions to call the study number to schedule the blood draw. In addition to the letter, both groups will also receive a follow-up telephone call that reiterates information in the letter. The research assistant will make and receive all calls using a standard script. All patients will also be asked to complete a questionnaire about their beliefs and attitudes regarding CRC screening (see Appendix). The questionnaire will be mailed with the invitation letter and will also be administered over the telephone by the research assistant. The study team will notify patients and their primary care physicians of blood test results and will facilitate a colonoscopy referral for those with positive tests. Primary care physicians will not be asked to notify the patients or make the colonoscopy referral because most will not have adequate knowledge of the Septin9 test to provide appropriate patient education.

Participants who are randomized to the blood test arm will undergo phlebotomy, which will be performed by the study research assistant. The blood sample will be temporarily stored on-site and then transported to an off-site commercial laboratory to run the assay.

Clinical outcomes for both the intervention and control group participants will be measured as a secondary outcome. This includes timing and result of a screening colonoscopy or FIT for individuals in the controls group as well as diagnostic colonoscopy for participants who had a positive blood test.

10) **Data and Specimen Banking**

Blood specimens for individuals in the intervention group will be assayed but not stored. No data other than what is described the sections above will be stored.

11) **Data Management**

Blood specimens will be transported and assayed by an outside commercial laboratory. Result will then be uploaded to the electronic medical record.

All personnel who will be working on this project will have completed the necessary CITI and TMS training for research involving patient data. Data will be collected from the electronic medical record, which only individuals credentialed by the VA can access using password-protected accounts. All data collected will be compiled in a password-protected spreadsheet, and sharing of data will be restricted to the study personnel listed on the proposal using VA email. After data has been collected from the electronic health record, the data will be de-identified prior to analysis.

Data Analysis

Aim 1: Screening rates in the intervention vs. control groups will be compared using the chi-squared or Fisher's exact test. Clinical outcomes of individuals who took the blood test will be reported as descriptive statistics.
Aim 2: We will use a multivariable logistic regression model to assess demographic and health-related predictors of accepting the blood test. We will perform descriptive statistics to assess the secondary outcomes. Results for secondary outcomes will also be reported stratified by race/ethnicity, self-reported health, frequency of healthcare access, and self-perceived risk of CRC.

Sample Size Calculations

Aim 1: Two prior studies that have measured uptake of the Septin9 blood test have found very high rates of 84% and 99%, respectively.[4,5] The study that found 84% uptake involved patients who had previously declined colonoscopy and were subsequently given a choice between the blood test and FIT. Since our study population has previously declined both colonoscopy and FIT, their uptake of the blood test will likely be lower. We estimate that uptake in our population will be 50% and will power our study to detect a 15% absolute difference in screening rate. With alpha = 0.05 and 80% power, the required sample size in each group is 170. To account for drop-out, we will include 180 patients in each group.
Aim 2: Assuming a 50% uptake in the intervention group of 170 individuals, there will be an estimated 85 individuals who take the blood test. We will select variables with the strongest association with blood test completion on bivariate analysis, which will be entered into the final multivariable logistic regression model. The number of variables in the final model will be limited to ensure that there are at least 10 events per variable, which is the conventional minimum standard to preserve model validity.[16]

12) **Provisions to Monitor the Data to Ensure the Safety of Subjects**

We believe this study poses no more than Minimal Risk to study participants, and therefore there are no plans to establish a data monitoring committee. However, any unexpected adverse events will be reported immediately to the PI, who will report to the IRB on an ad-hoc basis.

13) **Withdrawal of Subjects**

There are no anticipated circumstances under which subjects will be withdrawn from the research without their consent. Participants may choose to withdraw from the study at any point by giving notification to the study team. Patients who withdraw from the study will no longer be tracked in the electronic medical record after the time of withdrawal.

14) **Risks to Subjects**

The proposed study contains minimal risk. All participants in the study are due for colorectal cancer screening and will receive a letter stating this and encouraging them to screen with either colonoscopy or FIT. These are considered standard of care clinical tests. For the intervention group, the blood-based screening test is also presented as an alternate option. This is a FDA-approved test, although it is currently not available in the VA. Individuals in the intervention group who choose to undergo the blood test would undergo a single blood draw. A final risk is that of breach in patient confidentiality.

15) **Potential Benefits to Subjects**

Nearly 20% of age-eligible veterans cared for at the VA NY Harbor Health Care System are not up-to-date on colorectal cancer screening. The introduction of a non-invasive test that also does not involve handling stool may increase participation in screening in this refractory population.

16) **Vulnerable Populations**

Vulnerable populations will not be enrolled.

17) **Sharing of Results with Subjects**

The study team will share the results of the blood test with patients by telephone or mail and notify their primary care physicians using a CPRS note.

18) **Setting**

Study recruitment and phlebotomy will be performed at the VA NY Harbor Health Care System. The lab assay will be performed offsite at a commercial laboratory because the equipment is not available onsite.

19) **Resources Available**

The Principal Investigator (PI) is a board-certified gastroenterologist and clinical researcher with expertise in colorectal cancer screening. He has master's level training in epidemiology and biostatistics and is able to perform all of the planned analysis.

The research assistant will be credentialed in phlebotomy and trained by the PI in principles of patient navigation.

The PI has the full support of the Epigenomics, which makes the blood-based test. Epigenomics has agreed to cover the cost of the study.

20) **Confidentiality**

Patients will be informed of the potential risks as part of the informed consent process. All efforts will be made to ensure patient confidentiality and assurance of HIPAA compliance. Participant data will be de-identified using a protocol-specific unique code that will be used for all further data management. A list matching the patient medical record number to the protocol specific unique code will be maintained in a password-protected file in the PI's private drive on the VA network. There will be no data entry or interpretation outside of the VA NY Harbor Health Care System. The names of the patients will not be revealed in written reports or publications detailing the research findings.

21) **Provisions to Protect the Privacy Interests of Subjects**

The study team will take every possible precaution to protect the privacy of study participants. Only study team members who have been trained by the PI will be allowed to access patient data. Participants data will be de-identified for analysis and only aggregate data will be presented for publication. In addition, participants will not be required to answer any questionnaire question that may make him/her not at ease.

22) **Compensation for Research-Related Injury**

N/A

23) **Consent Process**

We are requesting waiver of HIPAA and informed consent for the purpose of screening patients who are eligible for participating in the study. For the control arm, we are requesting waiver of HIPAA and informed consent to access their medical record and determine whether they undergo a colonoscopy for FIT within 6 months of the initial invitation letter. For participants in the intervention arm who elect to undergo the blood test, written informed consent and HIPAA authorization will be obtained onsite prior to phlebotomy. All patients will also be invited to participate in a short anonymous questionnaire by mail and if needed, by phone. A one-page description of the questionnaire and how to contact the research team will be provided in the mailing and reiterated in the phone call. However, we are requesting waiver of documentation of consent for the anonymous questionnaire.

24) **Drugs or Devices**

N/A

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APPENDIX

Dear Veteran,

We are conducting a research study to understand people's thoughts about colorectal cancer and colorectal cancer screening. We would greatly appreciate it if you would be willing to participate by filling out the enclosed questionnaire. It should take *less than 5 minutes*.

If you choose to participate by completing the questionnaire and mailing it back to us in the addressed stamped envelope, please rest assured that it is anonymous and we will not connect your answers to you. We will combine your answers with that of other study participants before analyzing the results. Whether or not you choose to participate will not affect your clinical care in any way.

If you have any questions about the study, please call 212-686-7500 x5745 and ask to speak with a member of the study team.

Sincerely,

Peter S. Liang, MD MPH
Division of Gastroenterology
VA New York Harbor Health Care System Manhattan Medical Center

Demographics

1) What is your age?
☐ 50-60 ☐ 61-75

2) What is your race?
☐White ☐Black ☐Asian ☐Other

3) What is your ethnicity?
☐Hispanic ☐non-Hispanic

4) What is your employment status?
☐Employed ☐Not employed

5) What is the highest level of education that you've completed?
☐High school/GED ☐College ☐Graduate degree

Health status and medical history

6) How would you rate your overall health?
☐Very poor ☐Poor ☐Good ☐Very Good

7) How many visits have you had with your primary care doctor in the past year?
☐0-1 ☐2-5 ☐6-10 ☐>10

8) Do you know anyone who has been diagnosed with colorectal cancer?
☐Yes ☐No

9) What do you think is your own risk of getting colorectal cancer?
☐Low ☐Below Average ☐Above Average ☐High

10) Have you ever been diagnosed with any of the following conditions: pre-cancerous colon polyp (adenoma), colorectal cancer, ulcerative colitis, Crohn's disease, hereditary gastrointestinal cancer syndrome (e.g. Lynch syndrome or FAP)?
☐Yes ☐No

11) Do you have a parent or sibling who was diagnosed with colorectal cancer before age 60?
☐Yes ☐No

12) Do you have a family history of a hereditary gastrointestinal cancer syndrome (e.g. Lynch syndrome or FAP)?
☐Yes ☐No

Colorectal cancer screening

13) Have you ever had a colonoscopy?
☐Yes ☐No (SKIP to 14)

13a) How long ago was your last colonoscopy?

☐Less than 10 years ☐More than 10 years

14) Have you ever had a stool-based test (e.g. fecal occult blood test/FOBT or fecal immunochemical test/FIT)?
☐Yes ☐No (SKIP to 15)

14a) How long ago was your last stool-based test?
☐Less than 12 months ☐More than 12 months

15) Why did you decide not to do a colonoscopy when offered in the past 6 months?
☐I don't want to take the bowel prep
☐I don't want to know if I have colorectal cancer
☐Colonoscopy is painful
☐I don't have time
☐I don't have an escort
☐I'm at low risk and don't need screening
☐Other
☐I wasn't offered the test in the past 6 months

16) What would make you change your mind and get a colonoscopy?
☐If the bowel prep were easier
☐If I knew colonoscopy can prevent cancer by removing pre-cancerous polyps
☐Overcoming my fears about colonoscopy
☐If my doctor recommended it
☐If I knew it wasn't going to hurt
☐If I had time/could get time off from work
☐If I could find an escort
☐Other
☐Nothing would change my mind

17) Why did you decide not to do a stool test (fecal immunochemical test/FIT) when offered in the past 6 months?
☐I don't want to handle stool
☐I don't want to know if I have colorectal cancer
☐The directions for the stool test was too complicated
☐I don't think a stool test is accurate
☐I don't have access to a toilet that's suitable for collecting the stool sample
☐Other
☐I wasn't offered the test in the past 6 months

18) What would make you change your mind and take a stool test?
☐If the directions for the stool test was easier to understand
☐If I knew the stool test was accurate
☐If I had access to a toilet that's suitable for collecting the stool sample
☐Other
☐Nothing would change my mind

19) Would you take a blood test to screen for colorectal cancer?
☐Yes ☐No (SKIP to 22)

20) Why would you take the blood test?
☐A blood test is easy/convenient
☐A blood test is not painful
☐A blood test is accurate
☐Other

21) What do you think are the advantages of a blood test compared to colonoscopy and stool test?
☐It's more convenient than a colonoscopy or a stool test
☐I don't have to do any special preparation to take the test
☐I'm used to getting blood tests
☐I think blood tests are more accurate than other tests
☐The test is done by a medical professional and I don't have to do anything myself
☐Other

22) Why would you not take a blood test?
☐I don't like getting my blood drawn
☐I don't think a blood test is as accurate as a colonoscopy or stool test
☐I don't want to know if I have colorectal cancer
☐Other

23) What would make you change your mind and take a blood test?
☐If I knew the blood test is better than colonoscopy and the stool test
☐If my primary care physician recommended the test
☐Other
☐Nothing would change my mind